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ABSTRACT SUPPLEMENT

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November 6–11, 2015

San Francisco, CA

American College of Rheumatology
Education • Treatment • Research

WILEY

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TUESDAY, NOVEMBER 10, 2015

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4:30 - 6:00 PM
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**Please Note: ACR Late-breaking abstracts are listed below in numberic order instead of presentation order.*

Abstract Number: 1

The Integrin Very Late Antigen-4 Plays a Key Role in the Recruitment of B Cells at the Inflammatory Foci

Estefanía Armas-González[1], Ana Díaz-Martín[2], María Jesús Domínguez-Luis[3], María Teresa Arce-Franco[2] and Federico Díaz-González[4], [1]Universidad de La Laguna, Pharmacology Department, Tenerife, Spain, [2]Hospital Universitario de Canarias, Rheumatology Service, Tenerife, Spain, [3]CIBICAN, Center of Biomedical Research of the Canary Islands, University of La Laguna, Tenerife, Spain, [4]Investigation Unit, Sociedad Española de Reumatológía, Madrid, Spain

First publication: September 29, 2015

SESSION INFORMATION

Session Date: Sunday, November 8, 2015
Session Title: Cytokines, Mediators, Cell-cell Adhesion, Cell Trafficking and Angiogenesis Poster I
Session Type: ACR Poster Session A
Session Time: 9:00AM-11:00AM

Background/Purpose:

Experimental data suggest that B cells must migrate and accumulate into the synovial membrane to exert their pathogenic role in rheumatoid arthritis (RA). Leukocyte extravasation requires a number of coordinated adhesives events between circulating leukocytes and endothelial cells, a process known as the adhesion cascade. While the molecules involved in the sequential steps of the adhesion cascade for neutrophils and T lymphocytes have been well established, little is known about this process in B cells.

Objective: To determine the adhesion molecules involved in the interactions between B cells and endothelium under dynamic condition resembling those of postcapillary venules during the inflammatory response.

Methods:

The surface expression levels of very late antigen (VLA)-4, intercellular adhesion molecule (ICAM)-1 and L-selectin were assessed by double-colour staining flow cytometry analysis in CD20 + cells from the peripheral blood (PB) and synovial fluid (SF), simultaneously obtained from 10 RA and 8 psoriatic arthritis (PsA) patients. Dynamic interactions between B cells negatively immunoselected from buffy coats, and 12h TNF-a-activated human umbilical vein endothelial cell (HUVEC) monolayers were studied in a two-parallel plate flow chamber. To study molecules involved in the B-cells-HUVEC dynamic interaction, B cells were preincubated with monoclonal antibodies (mAbs) anti-CD20 or blocking mAbs anti- L-selectin, VLA-4 and ICAM-1; and HUVEC, with anti-vascular adhesion molecule (VCAM)-1.

Results:

Flow cytometry analysis showed that the VLA-4 surface expression level in B-cells from SF in both RA (105±30%) and PsA (135±45%) patients was not significantly different with respect to PB (considered 100%). Interestingly, the surface expression level of ICAM-1 was significantly higher in SF relative to PB, in both RA (280±85%;) and PsA (300±65%) patients, while L-selectin surface expression diminished in SF compared to PB in RA (40±5%) and PsA (45±5%). In flow chamber experiments, no differences were observed in the process of rolling when B cells were incubated with anti-CD20 antibodies, or with blocking mAbs anti-L-selectin and anti-ICAM-1 with respect to cells incubated with mAb matching controls. However, the presence of blocking anti-VLA-4 mAb or anti-VCAM-1 mAbs abrogated the interaction of B cells with activated endothelial cells.

Conclusion:

These results suggest that 1) B-cells with increased ICAM-1 expression and decreased L-selectin expression are preferentially recruited in the inflamed synovial microenvironment; and 2) the integrin VLA-4, vis-à-vis its endothelial counter receptor VCAM-1, plays a key role in the initial process of B-cell extravasation to inflammatory foci.

Disclosure: E. Armas-González, None; **A. Díaz-Martín**, None; **M. J. Domínguez-Luis**, None; **M. T. Arce-Franco**, None; **F. Díaz-González**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/the-integrin-very-late-antigen-4-plays-a-key-role-in-the-recruitment-of-b-cells-at-the-inflammatory-foci

Abstract Number: 2

The Neutrophil Protein S100A12 Has Stronger Associations with a Comprehensive Ultrasound Score of Synovitis Than Vascular Endothelial Growth Factor in a Longitudinal Study of Rheumatoid Arthritis Patients

Hilde Haugedal Nordal[1,2] and Hilde Berner Hammer[3], [1]Broegelmann Research Laboratory, Department of Clinical Science, University of Bergen, Bergen, Norway, [2]Department of Rheumatology, Haukeland University Hospital, Bergen, Norway, [3]Department of Rheumatology, Diakonhjemmet Hospital, Oslo, Norway
First publication: September 29, 2015

SESSION INFORMATION
Session Date: Sunday, November 8, 2015
Session Title: Cytokines, Mediators, Cell-cell Adhesion, Cell Trafficking and Angiogenesis Poster I
Session Type: ACR Poster Session A
Session Time: 9:00AM-11:00AM

Background/Purpose:

S100A12, a neutrophil protein, has proinflammatory effects on immune cells and can activate endothelial cells. The mechanism of action suggests vascular endothelial growth factor (VEGF) as a marker of synovial neovascularization in rheumatoid arthritis (RA). S100A12 and VEGF have both been associated with disease activity in RA. We wanted to compare S100A12 and VEGF as biomarkers in a large longitudinal study of RA patients, and explore their association with inflammatory activity expressed as synovial power Doppler (PD) scores.

Methods:

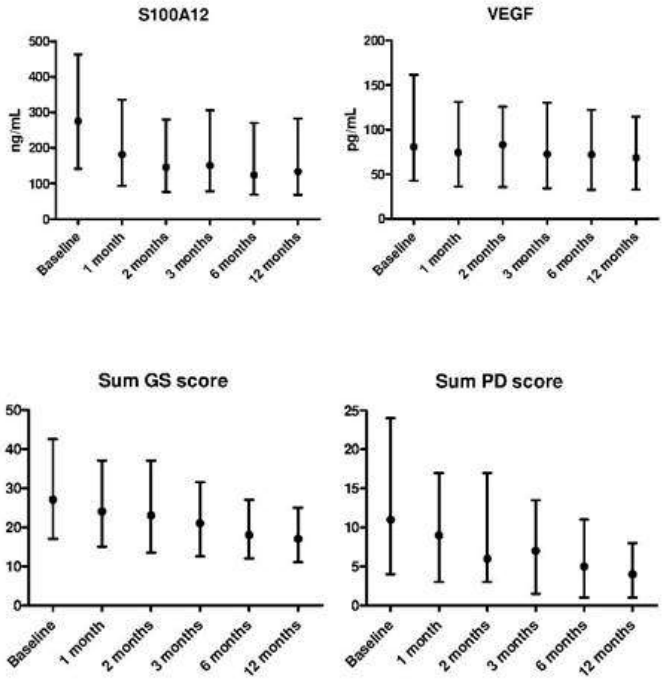
A total of 141 patients with RA (all met the ACR 1987 criteria, 81% women, mean (SD) age 52 (12) years, 79% anti-CCP positive) were examined clinically and with ultrasound (US) before starting biologic treatment (67% anti-tumor necrosis factor therapy) and after 1, 2, 3, 6 and 12 months. Inflammation of wrist (radiocarpal, intercarpal, radioulnar), metacarpophalangeals 1-5, proximal interphalangeals 2-3, elbow, knee, ankle, metatarsophalangeals 1-5, extensor carpi ulnaris and tibialis posterior tendons bilaterally, expressed as gray scale (GS) and PD scores, was scored semiquantitatively 0-3. C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) were analyzed by in-house methodology. Sera from all examinations were frozen at -80 ˚C and S100A12 was analyzed by an enzyme-linked immunosorbent assay and VEGF by multiplex analysis. A total of 141 blood donors were controls (81% women, mean (SD) age 52 (12) years). Mann-Whitney test was used to evaluate differences between patients and controls, Wilcoxon signed rank test to study changes from baseline and Spearman's rank test for correlation analysis.

Results:

At baseline, median (interquartile range) values of S100A12 were 275 (142-463) ng/mL in patients and 129 (75-222) ng/mL in controls ($p<0.0001$), while VEGF values were 81 (43-162) pg/mL in patients and 68 (46-108) pg/mL in controls ($p=0.08$). S100A12, VEGF, CRP, ESR, DAS28, sum GS and PD scores were reduced from baseline at all time points (all $p<0.0001$). S100A12 correlated with ESR and CRP at all times ($r=0.23$-0.56, $p\leq0.003$) except with CRP after 12 months. VEGF did not correlate with ESR/CRP at any examination, except with CRP at 2 months ($r=0.17$, $p=0.05$). S100A12 correlated with DAS28 at all times ($r=0.27$-0.35, $p\leq0.001$), with sum GS scores ($r=0.26$-0.39, $p\leq0.002$) except after 12 months, and with sum PD scores at all times ($r=0.17$-0.42, $p\leq0.04$). No correlations were found between VEGF and DAS28. VEGF correlated with sum GS scores ($r=0.18$-0.21, $p\leq0.03$) before 12 months and with sum PD scores ($r=0.17$-0.19, $p\leq0.05$) only before 3 months.

Conclusion:

S100A12 was a stronger biomarker than VEGF in RA patients treated with biologic medication during one year, having significant associations with clinical and US examinations. VEGF was expected to be associated with PD activity, but only weak correlations were presently found.



Figure

Median values with interquartile range (error bars) of the inflammatory markers S100A12 and vascular endothelial growth factor and sum ultrasound scores in patients during one year after starting with biologics. All values are significantly lower after baseline ($p<0.0001$)

VEGF= vascular endothelial growth factor, GS = gray scale, PD = power Doppler

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Disclosure: H. H. Nordal, None; **H. B. Hammer**, AbbVie, 2.

Abstract Number: 3

Cytokine Production Patterns in Osteoporosis Suggest a Pro-Inflammatory Bias

Khaled Al-Jarallah[1], Fawaz Azizieh[2], Diaa Shehab[3], Raj Reghupathy[4] and Renu Gupta[5], [1]Medicine, Kuwait University, Kuwait, Kuwait, [2]Gulf University for Science and Technology, Kuwait, Kuwait, [3]Faculty of Medicine, Kuwait University, Kuwait, Kuwait, [4]Microbiology, Faculty of Medicine, Kuwait University, Kuwait, Kuwait, [5]Radioliogy, Faculty of Medicine, Kuwait University, Kuwait, Kuwait

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Background/Purpose:

Considering the extent, predicted growth rates, and growing economic impact on health care, osteoporosis is a significant problem. In addition to hormones and nutrients, the immune system is suspected to play key roles in osteoporosis, primarily through the involvement of pro-inflammatory cytokines. Cytokines play important roles in the regulation of normal bone remodeling, as well as in bone resorption and formation during pathologic bone remodeling. The objective of this study was to measure levels of osteoclastogenesis stimulator cytokines TNF-a, IL-6, IL-12, IL-17 and osteoclastogenesis inhibitor cytokines IFN-g, IL-4, IL-10, IL-13 produced by peripheral blood mononuclear cells (PBMC) from postmenopausal osteoporotic women and normal healthy controls.

Methods:

The study population included 36 postmenopausal women that were grouped based on their bone mineral density (BMD) into normal (n=12), osteopenia (n=16) and osteoporosis (n=8). PBMC from these subjects were stimulated with the mitogen phytohemagglutinin and culture supernatants collected after incubation were used to measure the levels of 8 cytokines using the Multiplex system (Millipore) read on the Magpex ELISA platform.

Results:

PBMC from osteopenic women produced significantly higher levels of IL-6 and IL-17A as compared to women with normal BMD (p=0.037, 0.026), while osteoporotic women produced significantly lower levels of IL-4 and IL-13 as compared to women with normal BMD (p=0.013, 0.048) as well as women with osteopenia (p=0.049, 0.006), which is suggestive of a decreased anti-inflammatory or increased pro-inflammatory cytokine bias. Furthermore, osteoporotic women produced higher levels of the pro-inflammatory cytokine TNF-a (p=0.021), and lower levels of the anti-inflammatory cytokine IL-10 (p=0.033) compared to osteopenic women. Ratios of osteoclastogenesis stimulator cytokines to osteoclastogenesis inhibitor cytokines suggest a dominance of osteoclastogenesis stimulator cytokines in postmenopausal women with lower BMD.

Conclusion: These data are suggestive of a bias towards increased osteoclastogenesis stimulator cytokines and pro-inflammatory cytokines in women with osteoporosis.

Disclosure: K. Al-Jarallah, None; **F. Azizieh**, None; **D. Shehab**, None; **R. Reghupathy**, None; **R. Gupta**, None.

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Abstract Number: 4

The Influence of Adipokines on the Interaction of Rheumatoid Arthritis Synovial Fibroblasts with Endothelial Cells

Rebecca Hasseli[1], Klaus W. Frommer[2], Thomas Dr. Umscheid[3], Markus Prof. Dr. Schönburg[4], Stefan Rehart[5], Ulf Müller-Ladner[2] and Elena Neumann[2], [1]Justus-Liebig-University of Giessen, Kerckhoff-Klinik, Bad Nauheim, Germany, [2]Internal Medicine and Rheumatology, Justus-Liebig-University of Giessen, Kerckhoff-Klinik, Bad Nauheim, Germany, [3]William Harvey Klinik; Bad Nauheim, Germany, Bad Nauheim, Germany, [4]Department of Cardiac Surgery; Kerckhoff-Klinik, Bad Nauheim, Bad Nauheim, Germany, [5]Orthopedics and Trauma Surgery, Markus-Hospital, Frankfurt, Germany

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Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose:

Rheumatoid Arthritis (RA) is a systemic chronic inflammatory disease. Adipose tissue, being an endocrine organ, plays an important role in inflammatory processes. Adipokines are immunomodulatory factors mainly secreted by the adipose tissue. In previous studies we could show that RA synovial fibroblasts (SF) are able to migrate long distances in vivo via the vasculature. Therefore, we analysed the role of adipokines on RASF and endothelial cell (EC) adhesion and interaction. Static and dynamic adhesion as well as the expression of selected adhesion molecules on RASF and EC after stimulation with adipokines (adiponectin, visfatin, resistin), glucocorticoids and methotrexate (MTX) were evaluated.

Methods:

Primary RASF and EC were stimulated with adiponectin (10 µg/ml), visfatin (100 ng/ml) and resistin (20 ng/ml) as well as with MTX (1.5 µM) and the glucocorticoids prednisolone (1 µM) and dexamethasone (1 µM). The interaction of both cell types under static conditions using a cell-to-cell-binding assay was analyzed. RASF adhesion to E-selectin was studied in a flow adhesion assay (flow rates: 18.4/30.5/60.5 ml/h) as flow conditions are required for selectins to be obtain their active conformation. The expression of selected adhesion molecules on RASF and EC after adipokine./MTX/glucocorticoid stimulation was analyzed by real-time PCR.

Results:

Prednisolone stimulation down-regulated mRNA expression of VCAM-1 (-3.3-fold) in RASF (n=3), which was also reduced after dexamethasone stimulation (8.3 fold). TNF-α used as proinflammatory control increased ICAM-1 mRNA expression (46.5 fold), while P selectin mRNA expression (-7.7-fold) was decreased in EC (n=3).Under static conditions, the adipokines increased adhesion of RASF to EC (Ad: 37%, Vis: 23%, Res: 32%; n=6), while prednisolone and MTX caused a minor decrease (-7% for both; n=4). Dexamethasone did not change RASF adhesion to EC under static conditions. Under flow conditions, visfatin increased RASF adhesion to E-selectin (28%/87%/29%;

n=3 for each flow rate), while dexamethasone decreased their adhesion to E-selectin (-33%/-35%/-41%; n=3 for each flow rate).

Conclusion:

Adipokines have an influence on the cellular expression of adhesion molecules on RASF and EC as well as their interaction. Adipokines increase adhesion of RASF to EC and therefore influence RASF migration. Therapeutics such as glucocorticoids and MTX antagonized these effects, which may represent a mechanism of the protective effects of these drugs observed in patients. Evaluation of the immunomodulatory role of adipokines and therapeutics in the pathogenesis and progression of RA may help to understand new metabolic-inflammatory pathways active in chronic inflammatory diseases such as RA.

Disclosure: R. Hasseli, None; **K. W. Frommer**, None; **T. Dr. Umscheid**, None; **M. Prof. Dr. Schönburg**, None; **S. Rehart**, None; **U. Müller-Ladner**, None; **E. Neumann**, None.

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Abstract Number: 5

Prospective Study of the Effect of Treatment with Adalumumab in Angiogenesis in Moderate or Severe Psoriasis for a Period of 6 Months

Montserrat Santos-Gómez[1], Leyre Riancho-Zarrabeitia[1], Ricardo Blanco[1], Carmen Gonzalez-Vela[2], Jose L. Hernández[3], Susana Armesto[4], Marcos A González López[4], Javier Loricera[1], Vanesa Calvo-Río[1], María Marcellán[4], Marta Drake[5], Sandra Hermana-Ramírez[2], Enar Pons[5], Patricia Fuentevilla[1], Alfonso Corrales[1], Trinitario Pina[1], Natalia Palmou[1] and Miguel Angel Gonzalez-Gay[1], [1]Rheumatology, Hospital Universitario Marqués de Valdecilla. IDIVAL, Santander, Spain, [2]Pathology, Hospital Universitario Marqués de Valdecilla. IDIVAL, Santander, Spain, [3]Internal Medicine, Hospital Universitario Marqués de Valdecilla. IDIVAL, Santander, Spain, [4]Dermatology, Hospital Universitario Marqués de Valdecilla. IDIVAL, Santander, Spain, [5]Hospital Universitario Marqués de Valdecilla. IDIVAL, Santander, Spain

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Session Time: 9:00AM-11:00AM

Background/Purpose:

Angiogenesis plays an important role in the pathogenesis of psoriasis. TNFa is an essential mediator that induces the expression of VEGF, which activates the endothelial cells, promoting angiogenesis.

Our aims were: **a)** to quantify the angiogenesis and the VEGF expression in healthy skin and in plaque psoriasis before and 6 months after starting adalimumab (ADA), and **b)** to correlate these parameters with clinical assessment scales.

Methods:

Prospective study of a series of patients with moderate/severe psoriasis who completed 6 months of treatment with

ADA.Two biopsies of healthy skin and of plaque psoriasis were performed, one before starting ADA and the other was performed at 6 months. In each sample, an immunohistochemical study to VEGF, TNF‡ and CD31 was performed. Quantification of angiogenesis (CD31) was analyzed using an Automated Cellular Imaging sistem (DAKO).

Results:

Twenty three patients (13 W/10 M; mean age of 37±12 years) with a mean evolution of psoriasis of 19,9±13.1 years were included. Six patients also had (26%) arthritis. Comparison of clinical and histological parameters at baseline and at 6 months of treatment with ADA is shown in TABLE. At the baseline visit the following values were significantly higher in skin biopsy with psoriasis than in healthy skin: **a)** levels of angiogenesis (endothelial area positive-CD31): 2274.2±833.1 vs 810.6±425.2 ($p<0.001$); **b)** positive expression of VEGF: 87% vs 8.7% ($p<0.001$) y **c)** positive expression of TNF_: 82.6 vs 4.3% ($p<0.001$). A significant clinical and histological improvement in the expression of TNF, VEGF and angiogenesis was observed after treatment with ADA**.** The clinical parameters of psoriasis and angiogenesis (VEGF, TNF and CD31) only showed a significant correlation between the improvement in PASI and basal CD31. Thus, patients with lower baseline PASI had a greater response to therapy ($r=0.590$; $p<0.003$).

Conclusion:

In this series, ADA reduces the levels of VEGF and angiogenesis in plaque psoriasis. This fact seems to suggest that a part of their effect is due to inhibition of angiogenesis.

TABLE

	Baseline	**month 6**	**p**
Clinical improvement			
BSA (%)	37.9±16.3	3.1±5.5	<0.001
PASI (0-72)	18.9±7.8	1.3±2.1	<0.001
NAPSI hands (0-80)	5.4±10.5	1.5±3.9	0.26
PGA psoriasis (0-6)	3.9±0.6	0.7±0.6	<0.001
PASE total score (15-75)	32.5±15.9	25.2±13.0	0.007
PASE (functional) (8-40)	15.9±8.7	12.1±6.2	0.013
PASE symptoms (7-35)	16.6±7.7	13.1±7.3	0.014
BASDAI	2.61±2.77	1.26±1.31	0.11
BASFI	1.31±1.97	0.82±1.62	0.29
Patients with arthritis	26.1%	15.0%	0.004
Histological improvement in simple with psoriasis			
VEGF (% positive)	86.9%	17.4%	<0.001
VEGF (% negative)	13.1%	82.6%	<0.001
TNF‡ (% positive)	82.6%	8.6%	<0.001
TNF‡ (% negative)	17.4%	8.6%	<0.001
CD31 (median [IQR])	2117 [843-1590]	987 [684-1590]	<0.001

Disclosure: M. Santos-Gómez, None; **L. Riancho-Zarrabeitia**, None; **R. Blanco**, None; **C. Gonzalez-Vela**, None; **J. L. Hernández**, None; **S. Armesto**, None; **M. A. González López**, None; **J. Loricera**, None; **V. Calvo-Río**, None; **M. Marcellán**, None; **M. Drake**, None; **S. Hermana-Ramírez**, None; **E. Pons**, None; **P. Fuentevilla**, None; **A. Corrales**, None; **T. Pina**, None; **N. Palmou**, None; **M. A. Gonzalez-Gay**, None.

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Abstract Number: 6

The Novel Role of Corticotropin-Releasing Hormone and Urocortin1 on

Sjogren's Syndrome

Yuichi Yokoyama[1], Kiyoshi Matsui[2], Sachie Kitano[2], Tetsuya Furukawa[3], Masahiro Sekiguchi[2], Naoto Azuma[2], Masayasu Kitano[2], Shinichiro Tsunoda[2], Tsuyoshi Iwasaki[4] and Hajime Sano[2], [1]Division of Rheumatology, Department of internal medicine, Hyogo College of Medicine, Nishinomiya, Japan, [2]Division of Rheumatology, Department of Internal Medicine, Hyogo College of Medicine, Nishinomiya, Japan, [3]Division ofRheumatology Department of internal medicine, Hyogo College of Medicine, Nishinomiya, Japan, [4]Department of Pharmacy, Hyogo University of Health Sciences, Kobe, Japan

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Background/Purpose:

Corticotropin releasing hormone (CRH) is the principal regulator of hypothalamus pituitary adrenal (HPA) axis. CRH and urocortin1 (UCN1) are member of the CRH family. These biological actions are mediated via CRH type1 receptor (CRHR1) and CRH type2 receptor (CRHR2). CRH and UCN1 are expressed in the cells of the immune system. We previously reported that CRH closely connected with the pathogenesis of RA. However, the function of CRH and UCN1 are poorly understood in autoimmune disease. On the other hand, recently, it was reported that IL-21 plays an important role on Sjogren's syndrome (SS). The aim of this study is to reveal the biological function of CRH and UCN1 inducing IL-21 in SS.

Methods:

We investigated the expression of CRH, UCN1, CRHR1 and CRHR2 by immunohistochemistry (IHC) and reverse transcription with the polymerase chain reaction (RT-PCR) in the salivary gland of patients with SS. We analyzed the function of CRH and UCN1 by NS-SV-DC cell lines, which are immortalized normal salivary gland ductal cells established by transfection with SV40. We examined the mRNA expression of CRH, UCN1, CRHR1, and CRHR2 in NS-SV-DC cell lines by RT-PCR. NS-SV-DC cell lines were cultured in the absence or presence of CRH (10-100nM) or UCN1 (10-100nM). After 24h of culture,IL-21 and IL-23 levels were measured by Enzyme-linked immune Sorbent assay (ELISA). We examined the mRNA expression of IL-21, IL-21 receptor, IL-23α and IL-23 receptor in NS-SV-DC stimulated by CRH or UCN1.

Results:

We detected the expression of mRNA and the protein level of CRH, UCN1 and CRHR2 in the SS patient`s salivary gland by RT-PCR and IHC staining. Moreover we found the mRNA expression of CRH, UCN1 and CRHR2 in NS-SV-DC by RT-PCR. The culture supernatants stimulated by CRH or UCN1 in NS-SV-DC cell lines showed that IL-21 and IL-23 levels increased in a dose-dependent manner by ELISA. To stimulate NS-SV-DC cell lines by CRH and UCN1, we investigated the increasing mRNA expression of IL-21 and IL-23α by RT-PCR.

Conclusion:

The known function of IL-21 is facilitating differentiation, proliferation, survival of both B and T cells. IL-21 is elevated in the serum of patients with SS and is expressed by the lymphocytic infiltrating salivary gland. This is the first report that CRH and UCN1 were detected in salivary gland in patient with SS, and that CRH and UCN1 induce IL-21 and IL-23 production in NS-SV-DC cell lines. These results indicate that CRH or UCN1 play a crucial role of the IL-21 or IL-23 induction in salivary gland in pathogenesis of SS. Regulated IL-21 induction via CRH and UCN1 signal may be a novel therapeutic target in SS.

Disclosure: Y. Yokoyama, None; **K. Matsui**, None; **S. Kitano**, None; **T. Furukawa**, None; **M. Sekiguchi**, None; **N. Azuma**, None; **M. Kitano**, None; **S. Tsunoda**, None; **T. Iwasaki**, None; **H. Sano**, None.

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Abstract Number: 7

Influence of TNF on Anti-Inflammatory Tyrosine-Hydroxylase-Positive Synovial Cells in Rheumatoid Arthritis and Osteoarthritis

Zsuzsa Jenei-Lanzl, Markus Herrmann and Rainer Straub, Laboratory of Experimental Rheumatology and Neuroendocrine Immunology, Department of Internal Medicine, University Hospital Regensburg, Regensburg, Germany

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Session Time: 9:00AM-11:00AM

Background/Purpose:

In recent studies we demonstrated that catecholamines produced by tyrosine-hydroxylase-positive (TH+) synovial cells are able to mediate anti-inflammatory effects in rheumatoid arthritis (RA).[a] TNF has been shown to be toxic to catecholaminergic neurons in Parkinson´s disease (PD).[b] Therefore, the aim of this study was to analyze whether TNF exhibits also inhibitory effects on TH in the chronic inflamed synovium.

Methods:

Human mixed synovial cells were isolated from RA and osteoarthritis (OA) patients and “induced TH+ cells” (iTH+) were generated from human mesenchymal stem cells (MSC) as described previously.[a] Cells were cultivated under hypoxia (1% O_2), because the microenvironment of inflamed joints is hypoxic. TNF and the anti-TNF etanercept were administered in different concentrations and combinations. Expression and activity of TH was analyzed by immunofluorescence and TH activity assay. In addition, catecholamines were quantified via HPLC and the quality of catecholaminergic differentiation was investigated staining VMAT2, Nurr1, and βIII tubulin as markers.

Results:

In mixed synovial cell culture, TNF inhibited TH activity and catecholamine synthesis compared to untreated control in both OA and RA. In general, TNF did not disturb catecholaminergic differentiation of MSCs to iTH+ cells. However, TH staining of TNF-treated iTH+ cells was weaker, the TH activity and the amount of produced catecholamines lower. Similarly, expression of VMAT2, Nurr1, and βIII tubulin decreased after TNF-treatment in iTH+ cells. The effects of TNF were reversed by etanercept in both synovial cell and iTH+ cell cultures.

Conclusion:

This study shows TNF inhibition of TH expression and activity in TH+ synovial cells and differentiating iTH+ cells leading to the decrease of anti-inflammatory acting catecholamines. This might be a reason why resident synovial TH+ cells are not able to unfold their anti-inflammatory effects in RA.

Disclosure: Z. Jenei-Lanzl, None; **M. Herrmann**, None; **R. Straub**, None.

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Abstract Number: 8

Bay 11-7085 Induces Glucocorticoid Receptor Activation and Autophagy to Initiate Human Synovial Fibroblast Cell Death

Biserka Relic[1], Edith Charlier[2], Céline Deroyer[1], Olivier Malaise[1], Sophie Neuville[1], Aline Desoroux[1], Philippe Gillet[3], Michel G. Malaise[1] and **Dominique de Seny**[1], [1]Department of Rheumatology- GIGA Research - Arthropôle - University of Liège - CHU Liège, Liège, Belgium, [2]Department of Rheumatology, Department of Rheumatology- GIGA Research - Arthropôle - University of Liège - CHU Liège, Liège, Belgium, [3]Orthopaedic Surgery Department- University of Liège-CHU de Liège, Liège, Belgium

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Background/Purpose: BAY 11-7085 is an inhibitor of IκBα phosphorylation that leads to NF-κB inactivation and downregulation of inflammation in mouse model of asthma, in articular chondrocytes as well as in synovial fibroblasts. Proliferation of synovial fibroblasts is one of the major causes of cartilage destruction in rheumatic diseases that needs to be counteracted. In our previous work, we observed that BAY 11-7085 induces apoptosis by inactivating PPAR-γ in human synovial fibroblasts. In this work, we investigated if autophagy was also involved in BAY 11-7085-induced synovial fibroblast cell death.

Methods: Primary human synovial fibroblasts were isolated from synovial membrane of osteoarthritis patients after joint surgery. Cells were seeded within 0.5 ml of DMEM medium with 10% FCS or without FCS in starvation condition. Synovial fibroblasts were stimulated with 15d-PGJ2, prednisolone, mifepristone, pepstatin A, rapamycin or NH_4Cl for 24 h, then BAY 11-7085 was added for two additional hours. MTS was performed for survival assay. Proteins such as LC3B, atg3, p62, glucocorticoid receptor (GR), phospho-glucocorticoid receptor pSer211, PPAR-γ, phospho-PPAR-γ pSer112, phospho-ERK1/2 on Tyr-204, caspase 8, α-tubulin and GAPDH were analyzed by western blotting. pPPAR-γ1, pCMV-MEK1 and pEGFP were overexpressed in HEK293 cells. *P* values were obtained using the Mann-Whitney test. A value of $P < 0.05$ was considered as statistically significant.

Results: Results have shown that BAY 11-7085 could induce autophagy within 2 hours of cell treatment and that it preceded BAY 11-7085-induced apoptosis. Of interest, BAY 11-7085 induced Serine 211 phosphorylation and degradation of glucocorticoid receptor (GR), suggesting that GR activation is involved in BAY 11-7085-induced autophagy. Glucocorticoid prednisolone induced both activation and degradation of GR, as well as autophagy in synovial fibroblasts. Of interest, BAY 11-7085-induced cell death was significantly decreased with glucocorticoid inhibitor mifepristone and with inhibitors of autophagy. BAY 11-7085-induced autophagy and GR activation were both downregulated by PPAR-γ agonists such as 15d-PGJ2 and MEK/ERK inhibitor UO126. Inhibition of autophagy markedly decreased endogenous and BAY 11-7085-induced ERK phosphorylation, suggesting a positive feed back loop between ERK activation and autophagy in synovial fibroblasts. Co-transfection of MEK1 with PPAR-γ1 in HEK293 cells caused known inhibitory phosphorylation of PPAR-γ1 (Serine 112) and enhanced GR degradation, in the absence or presence of prednisolone. Furthermore, GR was phosphorylated on Serine 211 and downregulated in

synovial fibroblasts during serum starvation-induced autophagy.

Conclusion: BAY 11-7085 induced human synovial fibroblast autophagy that acts as an agonist to promote BAY 11-7085-induced apoptosis. Furthermore, our results suggest that BAY 11-7085-induced autophagy in synovial fibroblasts is mediated through GR activation and PPAR-γ inactivation. Thus, modulation of autophagy and inflammation through GR and PPAR-γ regulation is a challenging approach to be further studied in rheumatic diseases.

Disclosure: B. Relic, None; **E. Charlier**, None; **C. Deroyer**, None; **O. Malaise**, None; **S. Neuville**, None; **A. Desoroux**, None; **P. Gillet**, None; **M. G. Malaise**, None; **D. de Seny**, None.

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Abstract Number: 9

Serum Visfatin Levels in Patients with Axial Spondyloarthitis and Early Rheumatoid Arthritis: Relation to Inflammation and Bone Changes

Hana Hulejova[1], Klára Prajzlerová[2], Olga Krystufkova[2], Krystýna Grobelná[2], Maria Filkova[2], Herman F Mann[3], Karel Pavelka[4], Jiri Vencovsky[3] and Ladislav Senolt[5], [1]Institute of Rheumatology and Department of Rheumatology, Prague, Czech Republic, [2]Institute of Rheumatology and Department of Rheumatology, 1st Faculty of Medicine, Charles University, Prague, Czech Republic, [3]Institute of Rheumatology, Prague, Czech Republic, [4]Charles University, Prague, Czech Republic, [5]Institute of Rheumatology and Department of Rheumatology, 1st Faculty of Medicine, Charles University, Prague, Czech Republic, Prague, Czech Republic

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Background/Purpose:

Visfatin may represent a novel biomarker of disease severity. Serum visfatin levels are elevated in patients with early rheumatoid arthritis (ERA) and axial spondyloarthritis (AxSpA)[1,2]. Serum visfatin levels may be associated with the degree of inflammation, clinical disease activity and radiographic joint damage.

The aim of this study was to analyze serum levels of visfatin in patients with ERA and AxSpA compared to healthy controls (HC) and to investigate their relationship with disease activity and spinal involvement.

Methods:

The study included 23 patients with non-radiographic AxSpA (nr-AxSpA) according to the ASAS criteria with active sacroiliitis confirmed by MRI, 44 patients with radiographic AxSpA (with and without spinal involvement), 40 patients with ERA and age- and sex-matched healthy control (HC) for ERA (n=30) and AxSpA (n=43). Serum visfatin levels were determined by ELISA. Disease activity was assessed by the Disease Activity Score for 28 joints (DAS28) in ERA and Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) in AxSpA. For analysis of differences between groups Mann-Whitney U and for correlations of parameters Spearman's rank order tests were used.

Results:

Visfatin serum levels were significantly elevated in ERA patients compared to HC (1.92±1.17 vs. 1.36±0.93 ng/ml; p=0.034) and correlated positively with DAS28 (r=0.383, p=0.015) and CRP levels (r=0.456, p=0.003). In all patients with AxSpA, visfatin levels were significantly higher compared to HC (2.79±2.05 vs. 1.22±0.86 ng/ml; p<0.0001) and on the borderline of significance also compared to ERA patients (p=0.051). Furthermore, visfatin levels were significantly higher in patients with radiographic AxSpA compared to nr-AxSpA (3.23±2.24 vs. 1.94±1.28 ng/ml; p=0.013) and there was a borderline difference between radiographic AxSpA with and without spinal involvement (3.79±2.45 vs 2.55±1.79 ng/ml; p=0.067). Serum visfatin levels were not associated with CRP and BASDAI in AxSpA patients.

Conclusion:

Visfatin levels are elevated in both ERA as well as AxSpA patients compared to healthy controls. Although visfatin levels correlate with measures of inflammation in ERA patients, its levels rather reflect radiographic spinal involvement in AxSpA patients in this cross-sectional study. Therefore, we suggest that visfatin possibly plays a distinct role in the pathogenesis of both diseases.

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Abstract Number: 10

CD13/Aminopeptidase N Contributes to Angiogenesis and Monocyte Chemotaxis in Rheumatoid Arthritis

Rachel Morgan[1], M. Asif Amin[1], Jeffrey Ruth[1], Gautam Edhayan[2], Stephanie Rasmussen[3] and David A. Fox[1], [1]Internal Medicine, Division of Rheumatology, University of Michigan Medical Center, Ann Arbor, MI, [2]Division of Rheumatology, University of Michigan Medical Center, Ann Arbor, MI, [3]Division of Rheumatology, University of Michigan, Ann Arbor, MI

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Session Title: Cytokines, Mediators, Cell-cell Adhesion, Cell Trafficking and Angiogenesis Poster I

Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose: Aminopeptidase N (CD13, EC 3.4.11.2) is a metalloproteinase expressed on the surface of fibroblast like synoviocytes (FLS), and as a soluble protein in serum and synovial fluid. CD13 is also expressed by multiple other cell types including monocytic lineage cells and endothelial cells. We have shown that CD13 can be released from FLS in culture, and that CD13 is higher in amount and activity in rheumatoid arthritis (RA) synovial fluids compared to osteoarthritis (OA). The goals of this study are to further explore potential roles for CD13 in the synovium in relation to monocytes and endothelial cells.

Methods: Synovium samples were cyrosectioned and stained for CD13 (antibody 591.1D7.34) and von Willebrand factor (VWF, rabbit anti-human DAKO) followed by secondary immunoflourescent antibodies. Co-localization was analyzed with ImageJ. Chemotaxis was performed in a modified Boyden chamber system using human dermal microvascular endothelial cells (HMVECs) or monocytes isolated from healthy donors. Chemotaxis was measured toward PBS, recombinant human CD13 (rhCD13) or an enzymatically inactive mutant CD13. Angiogenesis was measured using a HMVEC tube formation assay and a mouse Matrigel plug assay.

Results: CD13 on endothelial cells has been linked to angiogenesis; however, endothelial CD13 has not been examined in the synovium. We show that RA synovial sections stained more strongly for CD13 and showed stronger co-localization of CD13 and VWF than either OA or normal samples. A role for soluble CD13 (sCD13) has also not been determined in endothelial cell or monocyte migration. We therefore examined whether sCD13 could contribute to angiogenesis and/or monocyte chemotaxis. We found that CD13 was significantly chemotactic for monocytes over a range from 125ng/ml-500ng/ml CD13 with a peak chemotaxis at 500ng/ml (213.86±43.42 cells/well $p=0.05$). sCD13 was strongly chemotactic for HMVECS over a range from 0.5ng/ml-2000ng/ml with peak chemotaxis at 1000ng/ml (164.25±21.13 cells/well, $p=0.000173$). The enzymatically inactive mutant of CD13 was also chemotactic for HMVECs (135.02±11.47 cells/well, $p=0.012$) but to a lesser degree than the enzymatically active form (204.06±24.02 cells/well, $p=0.0078$). Depletion of CD13 from RA synovial fluid significantly decreased HMVEC chemotaxis. Furthermore, rhCD13 significantly increased HMVEC tube formation ($p<0.05$) in Matrigel, and rhCD13 significantly increased angiogenesis in a mouse Matrigel plug assay (PBS 0.099±0.025 g/dl/mg, CD13 1.49±0.62 g/dl/mg, $p<0.05$).

Conclusion: Soluble CD13 is shed from FLS and can act as a chemoattractant for T cells and monocytes, bringing these pro-inflammatory cells to the RA joint. CD13 is present on synovial endothelial cells, but sCD13 can also act as a pro-angiogeneic factor in the synovium in a manner that is partially independent of its enzymatic activity. The concentrations of CD13 used in these experimental systems correspond to levels of CD13 in the RA joint. In summary CD13 secreted by FLS in the RA joint may contribute to a pro-inflammatory milieu and lead to increased angiogenesis and migration of monocytes and T cells to the RA synovium.

Disclosure: R. Morgan, None; **M. A. Amin**, None; **J. Ruth**, None; **G. Edhayan**, None; **S. Rasmussen**, None; **D. A. Fox**, None.

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Abstract Number: 12

Delta-like 1 Enhances the Production of Pro-Inflammatory Mediators By Fibroblast-like Synoviocytes

Chiyoko Sekine, Department of Clinical Research Medicine, Teikyo University School of Medicine, Tokyo, Japan
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Session Type: ACR Poster Session A
Session Time: 9:00AM-11:00AM

Background/Purpose: Notch signaling is known to regulate cell fate decision and differentiation during embryonic and post-natal development. I have been reported that a Notch ligand Delta-like 1 (DLL1) promoted osteoclastogenesis via Notch2 activation and DLL1 blockade in rheumatoid arthritis (RA) model mouse reduced the number of osteoclasts in the affected joints. This DLL1 blockade also suppressed the joint inflammation by suppressing the production of pro-inflammatory mediators such as IL-6, GM-CSF, and MMP-3. In arthritic mouse joint, DLL1 expressed on macrophages and stimulated Notch2 on fibroblast-like synoviocytes (FLS), which enhanced the production of IL-6 and MMP-3. In this study, the role of DLL1 on the production of pro-inflammatory mediators by RA FLS was evaluated.

Methods: The expression of Notch receptors and ligands on RA FLS was analyzed by flow cytometry. OA FLS was also analyzed. DLL1 expression was investigated by imunohistochemical analysis of synovial tissue. FLS were stimulated with anti-Notch2 monoclonal antibody or DLL1-transfected CHO cells and IL-6, GM-CSF, and MMP-3 in the supernatants were measured by ELISA.

Results: As similar to mouse joint cells, Notch2 was expressed on RA-derived FLS and DLL1 was expressed on macrophages in RA synovium but not on FLS. Meanwhile, little expression of Notch2 was detected on osteoarthritis-derived FLS. Activation of Notch2 on RA FLS enhanced the production of IL-6 and GM-CSF. DLL1 stimulation also enhanced the production of IL-6, GM-CSF, and MMP-3 by RA FLS.

Conclusion: These results suggest that DLL1 activates Notch2 on RA FLS and enhances the production of RA-related pro-inflammatory mediators similar to mouse FLS. Therefore, DLL1 blockade may be a novel strategy to treat RA by suppressing the production of pro-inflammatory mediators in the joint as well as osteoclastogenesis.

Disclosure: C. Sekine, None;

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Abstract Number: 13

Altered Soluble Mediators, Autoantibodies, and Lupus-Specific Connective Tissue Disease Questionnaire Scores Distinguish Blood Relatives with Incomplete Lupus from Unaffected Relatives and Relatives with Classified SLE

Melissa E. Munroe[1], Kendra A. Young[2], Jill M. Norris[3], Teresa Aberle[1], Virginia C. Roberts[1], Joel M. Guthridge[1], Diane L. Kamen[4], Gary S. Gilkeson[5], Michael H. Weisman[6], Mariko L. Ishimori[6], Daniel J Wallace[7], David R. Karp[8], Kathy L. Sivils[9], John B. Harley[10] and Judith A. James[11], [1]Arthritis and Clinical Immunology, Oklahoma Medical Research Foundation, Oklahoma City, OK, [2]Epidemiology, University of Colorado Denver, Aurora, CO, [3]University of Colorado Denver, Aurora, CO, [4]Medicine, Medical University of South Carolina, Charleston, SC, [5]Department of Rheumatology, Medical University of South Carolina, Charleston, SC, [6]Rheumatology, Cedars-Sinai Medical Center, Los Angeles, CA, [7]Division of Rheumatology, Cedars-Sinai Medical Center, Los Angeles, CA, [8]Internal Medicine - Rheumatic Diseases, University of Texas Southwestern Medical Center, Dallas, TX, [9]Oklahoma Medical Research Foundation, Oklahoma City, OK, [10]Center for Autoimmune Genomics and Etiology (CAGE), Cincinnati Children's Hospital Medical Center, Cincinnati, OH, [11]Arthritis and Clinical Immunology, University of Oklahoma Health Sciences Center and Oklahoma Medical Research Foundation, Oklahoma City, OK

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Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose: Blood relatives (Rel) of lupus patients have increased risk of SLE. Some have autoantibodies and SLE clinical features, but do not meet ≥ 4 ACR criteria needed to reach SLE classification (incomplete lupus, ILE). Some individuals with ILE may transition to classified SLE, yet many will remain ILE patients without major organ involvement. Using a unique resource of SLE patient family members, the goal of this study is to determine factors that distinguish ILE patients from unaffected Rel and SLE patients.

Methods: This study examined individuals enrolled in the Lupus Family Registry and Repository (LFRR) who only met 3 ACR classification criteria during medical record review and did not meet Systemic Lupus International Collaborating Clinics (SLICC) SLE classification, designated as ILE. ILE patients (n=77) were matched by race, gender, and age (± 5 years) to unaffected Rel and unrelated, unaffected controls (Ctls). We were able to subsequently match a subset of ILE patients (n=55) to medical record-confirmed SLE patients in the LFRR. Study participants provided clinical and demographic information, and completed the SLE-specific portion of the CTD Screening Questionnaire (CSQ). Plasma samples were assessed for autoantibody production and 52 soluble inflammatory mediators (BLyS, APRIL, cytokines, chemokines, and shed TNF receptors).

Results: ILE patients had significantly higher SLE-specific CSQ scores than unaffected Rel and Ctls ($p<0.0001$); CSQ scores in unaffected Rel > Ctls ($p=0.009$). Initial analysis revealed a number of soluble mediators that positively correlated with CSQ scores, including SCF ($p=0.0001$), BLyS ($p=0.0086$), MCP-3 ($p=0.0017$), and TNFRI ($p=0.0144$). Compared to unaffected Rel and Ctls, ILE patients had the highest levels of SCF ($p=0.0001$), BLyS ($p=0.0018$), MCP-3 ($p=0.0167$), and TNFRI ($p=0.0196$), as well as highest ANA titer ($p<0.01$) and number of lupus-associated autoantibodies ($p<0.01$). We subsequently examined factors that differentiated ILE patients matched to SLE patients in the LFRR (n=55). SLE patients had significantly higher rates of arthritis, serositis, and renal disease ($p<0.004$), as well as increased number of autoantibody specificities ($p<0.004$) and levels of BLyS ($p=0.0138$), IL-2Rα ($p=0.0201$), IP-10 ($p=0.0269$), and TNFRII ($p=0.0309$) compared to ILE patients. CSQ scores and SCF levels, which were elevated in ILE patients compared to Rel and Ctl, were equivalent compared to SLE patients. Yet, ILE patients had higher levels of the regulatory mediator TGF-β compared to SLE patients ($p=0.0454$).

Conclusion: ILE patients are distinguished from unaffected Rel by elevated number of autoantibodies and inflammatory mediators that correlate with SLE-specific CSQ scores, yet have fewer clinical criteria and increased levels of the regulatory mediator, TGF-β, compared to SLE patients. Identification of factors which discern relatives at increased risk of transitioning to classified SLE from relatives who remain unaffected may be beneficial to curtail inflammatory damage and identify individuals for prevention trials.

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Abstract Number: 14

The SLE Susceptibility Gene Macrophage Migration Inhibitory Factor

Serves As an Upstream Regulator of NLRP3 (NOD-like receptor family pyrin domain containing 3) Expression and Subsequent IL-1beta Production in Human Monocytes in Response to Lupus U1-snRNP Immune Complex

Min Sun Shin[1], Youna Kang[1], Elizabeth Wahl[1], Lin Leng[1], Richard Bucala[1] and **Insoo Kang**[2], [1]Yale University School of Medicine, New Haven, CT, [2]Rheumatology Section, Yale University School of Medicine, New Haven, CT
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Background/Purpose: The pathologic hallmarks of systemic lupus erythematosus (SLE or lupus) are altered immune responses to nuclear autoantigens with autoantibody production and subsequent tissue injury. Early studies suggested a critical role for adaptive immunity in the development of lupus; however, recent data have expanded this paradigm to a pathogenic role for innate immunity. For instance, TLR7/8 recognize the ssRNA of the self-antigen U1-small nuclear ribonucleorprotein (U1-snRNP) that is targeted by anti-U1-snRNP antibodies (Abs) in lupus. Indeed, we showed the production of IL-1β from human monocytes (MO) exposed to a combination of U1-snRNP and anti-U1-snRNP Abs by the activation of the caspase-1-containing NLRP3 inflammasome. Macrophage migration inhibitory factor (MIF), primarily produced from MO and macrophages, plays an important role in immune cell function by promoting the production of IL-1, IL-6 and TNF-α, which are increased in blood, skin and/or renal tissues in lupus patients. Recent data have shown an association between serum MIF levels and *MIF* gene polymorphisms with SLE-related organ damage as well as decreased glomerulonephritis in lupus-prone mice treated with MIF antagonists. However, little is known about the mechanisms underlying MIF production in SLE as well as the functional link between MIF and the NLRP3 inflammasome. We have addressed these questions using human MO.

Methods: Human primary MO were purified from peripheral blood mononuclear cells (PBMCs) of healthy donors and incubated in the presence or absence of U1-snRNP and/or anti-U1-snRNP Ab+ or healthy serum with or without the MIF inhibitor MIF098. Tissue culture supernatants and cells were analyzed for MIF, IL-1β, NLRP3 and NF-kB by ELISA, flow cytometry and Western blotting.

Results: A combination of U1-snRNP and anti-U1-snRNP Ab+ serum (hereafter snRNP immune complex or IC) induced the production of MIF and IL-1β from freshly purified human MO. However, U1-sNRNP, anti-U1-snRNP alone, or a combination of U1-snRNP and healthy serum did not induce the production of these cytokines from the same cells. The small molecule MIF inhibitor MIF098, which interferes with the binding of MIF to its receptor, decreased the production of IL-1β from MO in response to the snRNP IC, suggesting a co-stimulatory role for MIF in the activation of the NLRP3 inflammasome. Indeed, the MIF inhibitor MIF098 substantially reduced the expression of NLRP3, a critical component of the NLRP3 inflammasome, in MO in response to the snRNP IC. This phenomenon is likely mediated in part by the suppression of NF-kB activation, which can up-regulate the expression of NLRP3, since MIF098 also suppressed the activation of NF-kB. Moreover, adding exogenous MIF during the incubation of MO with snRNP IC increased IL-1β production.

Conclusion: These results are the first to demonstrate the inducible production of MIF from MO by lupus snRNP IC and support MIF action in regulating the NLRP3 inflammasome in human MO. These data also provide a functional link for an association of high expression *MIF* alleles with SLE and a rationale for targeting MIF in human disease.

Disclosure: M. S. Shin, None; **Y. Kang**, None; **E. Wahl**, None; **L. Leng**, None; **R. Bucala**, None, 9; **I. Kang**, None.

Abstract Number: 15

Regulation of Neutrophil Extravasation By Interleukin-8-Induced Intravascular Reactive Oxygen Species Production during the Inflammatory Response

María Jesús Dominguez-Luis[1], Estefanía Armas-González[2], Maria Teresa Arce-Franco[3], Francisco Sanchez-Madrid[4] and Federico Díaz-González[5], [1]CIBICAN, Center of Biomedical Research of the Canary Islands, University of La Laguna, Tenerife, Spain, [2]Universidad de La Laguna, Pharmacology Department, Tenerife, Spain, [3]Rheumatology Service, Hospital Universitario de Canarias, Tenerife, Spain, [4]Immunology Service, Hospital Universitario de La Princesa, Madrid, Spain, [5]Investigation Unit, Sociedad Española de Reumatológía, Madrid, Spain
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Background/Purpose:

The extravasation and recruitment of leukocytes in damaged tissues is an essential component of the inflammatory response. Once in the inflammatory foci, neutrophils destroy invading microorganisms by bringing them into contact with chemicals, among which reactive oxygen species (ROS) are the most important. Correct cell extravasation requires the coordinated intervention of a number of adhesion molecules, including L-selectin, a molecule that plays a key role in the initial interaction between flowing neutrophils and endothelial cells. However, the mechanisms that control the regulation of the L-selectin ectodomain processing during the inflammatory response are still not well understood. **Objectives:** In this work we study the mechanisms involved in the intravascular ROS production by neutrophils, as well as the potential implication of these oxygen derivatives in the regulation of neutrophil/endothelial cell interactions during the early events of the inflammatory response

Methods:

The effect of ROS on L-selectin and CD11b basal surface expression on human neutrophils was studied by flow cytometry analysis. Neutrophil ROS production during neutrophil-HUVEC (human umbilical vein endothelial cells) interaction was assessed in dihydroethidium-preloaded neutrophils using a flow chamber. The role of Interleukin(IL)-8 in the neutrophil ROS production was studied using lL-8 blocking mAb or a synthetic CXCR1 inhibitor (SB225002). Physiologic antioxidants such as superoxide dismutase (SOD) and catalase, as well as the NADPH-oxidase complex inhibitor diphenyleniodonium chloride (DPI), were used to determine the role of ROS in the regulation of neutrophil rolling and extravasation.

Results:

Flow cytometry experiments showed that shedding of L-selectin can be triggered in response to ROS through an autocrine-paracrine TACE-dependent mechanism in neutrophils. Flow chamber experiments showed that intracellular ROS production by neutrophils: 1) is proportional to the distance a neutrophil travelled doing rolling; and 2) requires

Interleukin (IL)-8/CXCR1 interaction. In accordance with this result, the preincubation of neutrophils with physiological antioxidants (SOD and catalase) and an inhibitor of NADPH oxidase complex (DPI) increased the number of rolling cells, reducing the transmigration capability of neutrophils through activated-HUVEC

Conclusion:

Our data indicate that, in response to IL-8, neutrophils initiate intracellular ROS production during the rolling phase of the inflammatory response. By inducing L-selectin shedding, ROS could participate in the regulation of inflammation, thereby reducing the extravasation capability of neutrophils. These data could help to define new therapeutic targets for control inflammation in diseases such as Rheumatoid Arthritis.

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Abstract Number: 16

Rantes/CCL5 Selectively Induces MMP-1 and MMP-13 Production in Rheumatoid Arthritis Synovial Fibroblasts Via PKC-Î´ and JNK Pathways

Solomon A. Agere, Nahid Akhtar and Salahuddin Ahmed, Department of Pharmaceutical Sciences, Washington State University College of Pharmacy, Spokane, WA

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Background/Purpose:

RANTES/CCL5 (RANTES) is a C-C chemokine that binds to its receptor (CCR5) and initiates inflammatory processes in rheumatoid arthritis (RA) by facilitating leukocyte infiltration. However, the role of RANTES/CCL5 beyond its chemotactic activity is not fully known. The present study was carried out to study the effect of RANTES/CCL5 on matrix metalloproteinase (MMP)-1 and MMP-13 expression using human rheumatoid arthritis synovial fibroblasts (RA-FLS).

Methods:

Human RA-FLS isolated from RA synovial tissues were serum-starved overnight followed by treatment with RANTES/CCL5 (20-100 ng/ml) for different time period. Conditioned media was collected and cells were lysed with RNA lysis buffer. Effect of RANTES/CCL5 on MMP and TIMP activation in the conditioned media from RA-FLS was evaluated using human MMPs protein array. MMP-1 and MMP-13 mRNA expression and protein synthesis was evaluated using qRT-PCR, ELISA, and Western blotting methods. Effect of RANTES/CCL5 on collagenase activity was studied using in-gel zymography. The inhibitory effect of RANTES/CCL5 antagonist, Met-RANTES (50-200 ng/ml), on RANTES/CCL5-induced MMP-1 and MMP-13 production was evaluated. RA-FLS were stimulated with

RANTES/CCL5 alone or the presence of signaling inhibitors for 5-30 mins to determine signaling mechanisms involved. Statistical value of $p<0.05$ was considered significant.

Results:

Results from human MMP antibody array showed that RANTES/CCL5 selectively induces MMP-1, MMP-13, TIMP-1, and TIMP-2 in RA-FLS ($p<0.05$; n=3). The confirmatory results using ELISA and qRT-PCR analysis showed that RANTES/CCL5 (20-100 ng/ml) significantly induced MMP-1 (~3-6-fold) and MMP-13 (~3-8-fold) expression in a dose-dependent manner ($p<0.05$ for 100 ng/ml). Collagen zymography results showed that RANTES/CCL5 induced collagenase activity in human RA-FLS dose-dependently ($p<0.05$; n=3). RA-FLS pretreatment with met-RANTES significantly reduced the ability of RANTES/CCL5 to induced MMP-1 and MMP-13 expression ($p<0.05$; n=3). Interestingly, silencing of RANTES/CCL5 gene using siRNA approach also markedly inhibited TNF-α-induced MMP-1 and MMP-13 production. Stimulation of RA-FLS with RANTES/CCL5 selectively activated PKC-δ and JNK pathways. In addition, pretreatment of RA-FLS with selective inhibitors for PKC-δ, ERK and JNK markedly inhibited RANTES/CCL5-induced MMP-1 and MMP-13 production.

Conclusion:

RANTES regulates MMP-1 and MMP-13 expression in RA-FLS via selective activation of PKC-δ, ERK, and JNK pathways and may also contribute to tissue destruction in RA.

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Abstract Number: 17

Disentangling the Role of Hypoxia-Inducible Factor 1 and 2 in the Adaption Process of Human Microvascular Endothelial Cells to Pathophysiological Hypoxia

Martin Hahne[1], Peggy Kunath[2], Mathias Mursell[3], Cindy Strehl[2], Gerd Burmester[4], Frank Buttgereit[2] and **Timo Gaber**[2], [1]Miltenyi Biotec GmbH, Berlin, Germany, [2]Department of Rheumatology and Clinical Immunology, Charité – Universitätsmedizin Berlin, Berlin, Germany, [3]German Rheumatism Research Center (DRFZ), Berlin, Germany, [4]Department of Rheumatology and Clinical Immunology, Charité - Universitätsmedizin Berlin, Berlin, Germany
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Background/Purpose: Angiogenesis is a prominent feature of the pathogenesis of RA. Although new blood vessels deliver oxygen to the augmented inflammatory cell mass, the neovascular network is dysfunctional and fails to restore tissue oxygen homeostasis, so that the inflamed joint remains markedly hypoxic. At a cellular level, hypoxia is detected by a mechanism that regulates the amount of hypoxia-inducible factor (HIF)-1α and -2α. After translocation to the nucleus, HIF-1α or HIF-2α subunit bind its partner HIF-1β to form a functional, heterodimeric transcription factor, HIF-1 and HIF-2, which activate a gene program associated with angiogenesis, glycolysis, and adaptation to pH. The

distinct functions of HIF-1 and HIF-2 in the hypoxia-induced angiogenesis and metabolic switch of endothelial cells are still unknown.

Methods: For this purpose we investigated the adaption of Human Microvascular Endothelial Cell (HMEC)-1 to pathophysiologic hypoxic conditions (1% O_2). Angiogenesis assay and cytokine analyses were conducted to describe angiogenesis. Gene expression and ATP/ADP measurements were performed to visualize the bioenergetic switch under hypoxia. shRNA-technology enabled a specific knockdown of either HIF-1α or HIF-2α or the combination of HIF-1α and HIF-2α, in order to identify distinct functions of both transcription factors, which were assessed via microarray analysis.

Results: Hypoxia induced angiogenesis and a bioenergetic switch from oxidative phosphorylation towards glycolysis. Knockdown of either HIF-1α or HIF-2α leads to a reduced angiogenesis *in vitro*. Although HIF-1α and HIF-2α show overlapping functions during adaption of HMEC-1 towards hypoxia reduction of HIF-1α resulted in a diminished cellular energy supply due to a reduction in hypoxia-induced glycolytic enzyme gene expression thereby not altering pro-angiogenic factors VEGF, VEGF receptor 1 and 2, and IL8. In contrast, reduction of HIF-2α resulted in a reduction of hypoxia induced pro-angiogenic VEGF and IL8 gene and protein expression but induction of VEGFR1 without altering glycolytic enzyme gene expression. Finally, the results of HIF-1α / HIF-2α combined knockdown demonstrate that the lack of both factors significantly reduced cell survival as compared to the scramble control thereby diminishing both gene expression of pro angiogenic factors and glycolytic enzymes.

Conclusion: Our results indicate distinct but also overlapping functions of HIF-1α and HIF-2α in ECs which are of high interest regarding the intervention of tumour growth but also the chronicity of the inflammatory process in RA. Finally we clearly demonstrate a major impact of HIF-1α and HIF-2α on angiogenesis mediated either via the expression of pro-angiogenic factors in case of HIF-2α or via the glycolytic switch in case of HIF-1α. At least both are essential for endothelial cellular function. These findings open new possibilities for therapeutic approaches by targeting the specific hypoxia induced factors.

Disclosure: M. Hahne, None; **P. Kunath**, None; **M. Mursell**, None; **C. Strehl**, None; **G. Burmester**, None; **F. Buttgereit**, None; **T. Gaber**, None.

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Abstract Number: 18

Epigallocatechin-3-Gallate (EGCG) Facilitates TAK1 Nuclear Translocation and Its Interaction with p300 to Inhibit Histone Acetylation in Human RA Synovial Fibroblasts

Anil Singh[1,2], Mukesh Chourasia[3] and Salahuddin Ahmed[4], [1]Department of Pharmaceutical Science, Washington State University, Spokane, WA, [2]Department of Pharmaceutical Sciences, Washington State University, Spokane, WA, [3]Department of Pharmacoinformatics,, National lnstitute of Pharmaceutical Education and Research, Hajipur,, India, [4]Department of Pharmaceutical Sciences, Washington State University College of Pharmacy, Spokane, WA

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Session Title: Cytokines, Mediators, Cell-cell Adhesion, Cell Trafficking and Angiogenesis Poster I

Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose:

TAK1 is one of the most important proteins in IL-1β signaling cascade that mediates downstream p38/JNK and NF-κB activation. In the present study, we evaluated the effect of EGCG, a potent anti-inflammatory compound, on TAK1 activation and its downstream consequent effects in human rheumatoid arthritis synovial fibroblasts (RA-FLS).

Methods: Human RA-FLS were treated with IL-1β for 30 minutes alone or in presence of EGCG. Cytoplasmic, nuclear, or whole cell extracts were prepared for Western blotting analysis to study the activation and cellular distribution of IL-1β signaling proteins proximal to IL-1 receptor as well as different phosphorylated forms of TAK1. Immunofluorescence was performed to study TAK1 nuclear translocation. EGCG and IL-1β-stimulated TAK1 interacting protein partners were identified using immunoprecipitation assay. *In silico* docking studies were performed using EGCG as a ligand and three-dimensional TAK1 structure was generated using ligand and protein preparation wizard of Schrodinger suit 2014.3. The ligand (EGCG) was docked using GLIDE module.

Results: Molecular docking studies on TAK1 structure *in silico* shows that EGCG occupies the binding pocket at C174 position, an ATP-binding site, which causes a reversible yet stable inhibition in TAK1 phosphorylation at Thr184/187site and kinase activity. Western blotting analysis showed that EGCG facilitates nuclear translocation of TAK1 in a dose dependent manner. Furthermore, we also observed overall reduction in cytoplasmic levels of TAK1 in response to EGCG treatment, which was further confirmed by immunofluorescence staining. Interestingly, TAK1 phosphorylation at Thr184/187 is not at all observed in the nuclear compartment while TAK1 phosphorylated at Ser439 mainly translocate to the nucleus in response to EGCG treatment. Ingenuity Pathway analysis predicted STAT3, ATM, SMAD7, and p300 (histone acetyltransferase) as the potential nuclear partners of TAK1. Further validation studies using immunoprecipitation assays in human RA-FLS confirmed the strongest interaction between TAK1 and p300 in addition to the other identified important nuclear proteins in RA-FLS. In parallel to these findings, EGCG inhibited histone H3K56 acetylation in a dose-dependent manner in RA-FLS. Additionally, these results confirmed that the interaction with p300 was significantly higher in EGCG and IL-1β treated RA-FLS, suggesting regulatory role of TAK1 in chromatin modifications.

Conclusion:

Our study provides a novel mechanism through which EGCG facilitates nuclear translocation of TAK1 and regulates transcriptional machinery involved in RA pathogenesis.

Disclosure: A. Singh, None; **M. Chourasia**, None; **S. Ahmed**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/epigallocatechin-3-gallate-egcg-facilitates-tak1-nuclear-translocation-and-its-interaction-with-p300-to-inhibit-histone-acetylation-in-human-ra-synovial-fibroblasts

Abstract Number: 19

Pentagalloyl Glucose (PGG) Exhibits Anti-Rheumatic Activity in Human RA Synovial Fibroblasts and Rat Adjuvant-Induced Arthritis

Sadiq Umar[1], Gates Roe[1], Sabrina Fechtner[1] and Salahuddin Ahmed[2], [1]Department of Pharmaceutical Science, Washington State University College of Pharmacy, Spokane, WA, [2]Department of Pharmaceutical Sciences, Washington State University College of Pharmacy, Spokane, WA

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Session Time: 9:00AM-11:00AM

Background/Purpose: Pentagalloyl glucose (PGG) is a natural polyphenolic and water-soluble gallotannin that exhibits anti-cancer and anti-inflammatory activities. In the present study, we evaluated the efficacy of PGG in regulating interleukin-1β (IL-1β) stimulated human rheumatoid arthritis synovial fibroblasts (RA-FLS) and rat adjuvant-induced arthritis (AIA) model of inflammatory arthritis.

Methods: The effect of PGG on RA-FLS viability was tested using MTT assay. Human RA-FLS were pretreated with PGG (0.1–10 μM) for 2 hours followed by IL-1β (10 ng/ml) stimulation 24 hours (for IL-6 and IL-8 production) and 30 mins to study cell signaling mechanisms. Conditioned medium was used for the quantification of IL-6 and IL-8 by ELISA and cell lysates were prepared for the analysis of IL-1β signaling network proteins like Myd88, IRAK1, p-TAK1, and TRAF6. To test *in vivo* efficacy of PGG, we performed studies in a rat AIA model. PGG was administered at doses of 12.5 and 25 mg/kg body weight once daily (starting on day 8 of AIA induction). The severity of the arthritis was quantified by ankle circumferences measurement.

Results: PGG (0.1–10 μM) had no adverse effect on the viability of RA-FLS. Pretreatment of PGG inhibited IL-1β-induced IL-6 (55 and 91% at 1 and 5 μM) and IL-8 (61 and 94 % at 1 and 5 μM) production in human RA-FLS in a dose-dependent manner ($p<0.01$; $n=4$). Evaluation of the signaling pathways using Western immunoblotting showed that PGG had no inhibitory effect on MyD88 expression, an adaptor protein in IL-1 receptor signaling pathway that mediates the innate immune responses. Similarly, among the downstream proteins proximal to IL-1β receptor such as IRAK1/TAK1/TRAF6, PGG was unable to inhibit IL-1β induced TRAF6 expression or rapid degradation of IRAK-1. However, PGG selectively inhibited the phosphorylation of TAK1 at Thr184/187, a site critical for its kinase activity and downstream activation of MAPK and NF-κB pathways in RA-FLS. In our rat AIA studies, arthritis peaked around day 19 and therapeutic administration of PGG at the daily doses of 12.5 and 25 mg/kg p.o. from day 8 markedly inhibited the severity of arthritis as evident from the reduction in ankle circumferences by ~30 and 45%, respectively, when compared to the untreated arthritic rats. In addition, there was no body weight loss observed with PGG treatment.

Conclusion: Our study provides novel evidence that PGG interferes with IL-1β signaling in RA-FLS by selectively inhibiting TAK1 activation and ameliorates rat AIA. These findings suggest PGG or its synthetic analogs may be developed for the comprehensive pre-clinical testing for their anti-rheumatic activity.

Disclosure: S. Umar, None; **G. Roe**, None; **S. Fechtner**, None; **S. Ahmed**, None.

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Abstract Number: 20

Role of the Epigenetic Regulator EZH2 in Proinflammatory Macrophage Polarization and Signaling in Rheumatoid Arthritis

Michelle Trenkmann[1], Eimear Linehan[2], Mary Canavan[3], Douglas J. Veale[4] and Ursula Fearon[1], [1]St. Vincent's University Hospital, Centre for Arthritis and Rheumatic Diseases, Dublin Academic Medical Centre, Dublin 4, Ireland, [2]St. Vincent's University Hospital Dublin, Centre for Arthritis and Rheumatic Diseases, Dublin Academic Medical Centre, Dublin, Ireland, [3]St. Vincent's University Hospital, Centre for Arthritis and Rheumatic Diseases, Dublin Academic Medical Centre, Dublin, Ireland, [4]St Vincent's University Hospital, Centre for Arthritis and Rheumatic Diseases, Dublin Academic Medical Centre, Dublin 4, Ireland

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Session Time: 9:00AM-11:00AM

Background/Purpose:

In rheumatoid arthritis (RA), synovial tissue macrophages (MΦ) are inherently involved in disease pathogenesis by producing inflammatory mediators and matrix-destructive enzymes. Depending on their polarization, MΦ show proinflammatory (classically activated M1 MΦ) or regulatory/wound-healing (alternatively activated M2 MΦ) behavior. Epigenetic mechanisms play a crucial role in the plasticity of cells and aberrant epigenetic regulation of pathogenetically relevant processes is a hallmark of many human diseases such as RA. In this study we examined if the epigenetic regulator Enhancer of Zeste Homolog 2 (EZH2) mediates differentiation and polarization of RA macrophages.

Methods:

Peripheral blood monocytes from healthy controls (HC) or RA patients were treated with M-CSF to obtain monocyte-derived MΦ (MDM). Efficient *in-vitro* MΦ differentiation was confirmed by CD68 staining (>95%). M0 MΦ were transfected with siRNA for histone 3 lysine 27 (H3K27) methyltransferase EZH2 or the H3K27 demethylase JMJD3 and/or stimulated with LPS+IFNγ or IL-4 to drive M1 or M2 polarization, respectively. Multicolor flow cytometry, quantitative real-time PCR (qPCR) and Western blot were performed to analyze MΦ polarization and gene expression.

Results: M1 MDM induced M1 markers CD40 and CD64 and the activation marker CD80 whereas M2 MDM upregulated CD206 (RA n=8 and HC n=9), thus confirming polarization. RA M0 MDM showed much higher expression of CD64 than HC MΦ (64±16% vs. 35±23% CD64+ cells; $p<0.01$) indicating skewing towards a proinflammatory M1 phenotype in RA. JMJD3 was significantly induced in both M1- and M2-polarized MDM (3.45±1.3- and 2.1±0.66-fold, $p<0.005$) whereas EZH2 was upregulated only in M1-polarized MDM (9.25±3.1-fold, $p<0.0001$)(n=9 HC) which was confirmed at the protein level by Western blot. Silencing of EZH2 (n=5 each) significantly inhibited M1 polarization (i.e. reduced numbers of $CD80^+$, $CD64^+$ and $CD40^+$cells), whereas, interestingly, unpolarized M0 MDM showed increased expression of CD40 and CD80 ($p<0.05$ all). Consistent with this, EZH2 silencing resulted in increased expression of VEGF (2.2±0.6-fold) and IL1B (3.4±2-fold) in M0 MDM, but inhibition of IL1B induction in M1 MDM (-75±15%) (all $p<0.05$). Looking for potential targets of EZH2 that might mediate the observed effects on MΦ polarization and cytokine expression, we analyzed genes involved in MΦ plasticity and interferon signaling (KLF4, STAT1, STAT3, STAT6, IRF4 and IRF5). Silencing of EZH2 increased STAT1 mRNA and STAT1 protein in M0 and M1 MDM ($p<0.05$), with no change observed for STAT1 phosphorylation. In contrast, we found reduced phospho-STAT3 in EZH2-silenced M1 MDM with levels of total STAT3 remaining unchanged.

Conclusion: Our data show an intrinsic shift of RA MDM towards a proinflammatory M1-like phenotype and induction of EZH2 in M1-polarized MΦ. We found EZH2 silencing to skew MΦ plasticity towards an inflammatory/activated phenotype under neutral conditions but attenuation of the inflammatory phenotype in a proinflammatory milieu. Mechanistically, different arms of the JAK/STAT pathway appear to be involved in these processes underpinning the importance of EZH2 in inflammatory MΦ signaling.

Disclosure: M. Trenkmann, None; **E. Linehan**, None; **M. Canavan**, None; **D. J. Veale**, None; **U. Fearon**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/role-of-the-epigenetic-regulator-ezh2-in-proinflammatory-macrophage-polarization-and-signaling-in-rheumatoid-arthritis

Abstract Number: 21

Pseudostarvation Using the AMPK Activator Metformin Downregulates Inflammation in Rheumatoid Arthritis Synovial Tissue

Lorna Gallagher[1], Ursula Fearon[2], Douglas J. Veale[3], David Kane[4], Luke A. O'Neill[5] and Ronan Mullan[4], [1]Clinical Medicine, School of Medicine, Trinity College Dublin, Dublin, Ireland, [2]St. Vincent's University Hospital, Centre for Arthritis and Rheumatic Diseases, Dublin Academic Medical Centre, Dublin 4, Ireland, [3]St Vincent's University Hospital, Centre for Arthritis and Rheumatic Diseases, Dublin Academic Medical Centre, Dublin 4, Ireland, [4]Department of Rheumatology, Tallaght Hospital, TCD, Dublin 24, Ireland, [5]Inflammation Research, School of Biochemistry and Immunology, Trinity College Dublin, Dublin, Ireland

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Session Time: 9:00AM-11:00AM

Background/Purpose: AMP-activated protein kinase (AMPK) is a highly conserved, regulator of cellular energy status. In inflammation, AMPK inactivation is associated with increased glucose consumption through aerobic glycolysis, and up-regulation of pro-inflammatory effector responses. Pseudostarvation of cells via AMPK activation by hypoglycaemic therapy, i.e. Metformin, reverses these effects. AMPK activity has a cascade effect on other mediators of cell metabolism, including Acetyl-CoA Carboxylase (ACC). Once activated, phosphorylated AMPK (P-AMPK) in turn phosphorylates ACC (P-ACC). AMPK/ACC interactions play a central role in the regulation of cellular lipid homeostasis. Here we demonstrate AMPK activation in RA synovial tissues (RAST), and inhibition of pro-inflammatory responses in stimulated primary RA synovial fibroblast cells (RASFCs) following pharmacological AMPK activation by Metformin *in vitro*.

Methods: P-AMPK, AMPK, P-ACC and ACC expression in RAST and RASFCs were analyzed by immunoblotting, normalized against β-actin. RASFCs were stimulated with LPS or TNFα (10 ng/ml) in the presence of Metformin (0 – 62.5 μM) and assessed for wound healing and invasion capabilities. Culture supernatants were evaluated for IL-6 and IL-8 production by ELISA. RAST, obtained from RA patients during arthroscopy, were stained by immunohistochemistry for Phosphorylated ACC (P-ACC) and ACC, and by Immunofluorescence for P-AMPK and AMPK.

Results: Western blot analysis showed that P-AMPK was present in RAST, and cultured RASFCs. P-AMPK expression was upregulated in the presence of Metformin (10 μM & 50 μM). Stimulating cells, with either LPS or TNFα (10 ng/ml), in the presence of Metformin (10 μM & 50 μM) increased P-AMPK, expression was greater than what was observed following LPS or TNFα stimulation alone. Additionally, LPS stimulated cells in the presence of Metformin (10 μM & 50 μM) showed P-ACC expression, which was not observed in LPS stimulated cells alone. *In vitro* immunofluorescence staining of RASFCs showed P-AMPK upregulation both in the presence of Metformin (50 μM) compared to basal and TNFα (10 ng/ml) stimulated RASFCs. Positive immunohistochemistry staining of RAST for P-ACC, indicated that AMPK is activated and in its phosphorylated state, with maximal expression localized around blood vessels. Stimulation of RASFCs with LPS or TNFα (10 ng/ml) in the presence of Metformin (15 – 62.5 μM) decreased IL-6 and IL-8 production in a dose dependent manner. RASFCs stimulated with either LPS or TNFα (10 ng/ml) in the presence of Metformin (15 – 62.5 μM) showed a dose dependent decrease in the ability of the cells to heal an induced wound or invade through matrigel.

Conclusion: Our findings indicate that RAST and RASFCs are capable of responding to pharmacological alterations in cellular metabolic pathways. Metformin both activates AMPK and downregulates pro-inflammatory effects in RA. AMPK activation occurs in concert with P-ACC around blood vessels but not in the lining layer where matrix metalloproteinase mediated joint destruction occurs, in keeping with an anti-inflammatory role for activated AMPK. AMPK activation therapy pathways may therefore be a suitable future strategy in the treatment of Rheumatoid Arthritis.

Disclosure: L. Gallagher, None; **U. Fearon**, None; **D. J. Veale**, None; **D. Kane**, None; **L. A. O'Neill**, None; **R. Mullan**, None.

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Abstract Number: 22

Expression of High Mobility Group Box 1 Protein and the Receptor for Advanced Glycation End Products in Primary Gouty Arthritis

Yu-Feng Qing[1], Quan-Bo Zhang[2], Shu-Yue Pan[3] and Jingguo Zhou[4], [1]Affiliated Hospital of North Sichuan Medical College, Sichuan 637000, China, Nanchong, China, [2]Department of geriatrics of the Affiliated Hospital of North Sichuan Medical College, Sichuan 637007, China, Nachong, China, [3]Department of Rheumatology and Immunology of the Affiliated Hospital of North Sichuan Medical College, Sichuan 637000, China, Nachong, China, [4]Department of Rheumatology and Immunology, Affliated hospital of North Sichuan Medical College, Nanchong, China

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Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose:

To investigate the role of high mobility group box 1 protein (HMGB1) and the receptor for advanced glycation end products (RAGE) in the pathogenesis of primary gouty arthritis (GA).

Methods:

(1) Enzyme-linked immunosorbent assay(ELISA) was used to determine the level of plasma HMGB1 in 68 acute gout (AG), 48 intercritical gout (IG) and 45 healthy control (HC). (2)Real-time quantitative polymerase chain reaction (RT-qPCR) was employed to study the expression of HMGB1 and RAGE mRNA in peripheral blood mononuclear cells (PBMCs) in 68 AG,48 IG and 94 HC, and the differences of gene expression in two groups were compared .(3)Western blot(WB)was used to measure HMGB1 in PBMCs from 18 AG, 13 IG and 21 HC,REGE in PBMCs from 12 GA and 8 HC, and the otherness of protein expression in two groups were compared .(4)Analysis of T test or Wilcoxon test and Spearman's correlations were used for statistical analysis.

Results:

The level of plasma HMGB1, PBMCs HMGB1, RAGE mRNA and protein were significantly higher in GA patients than those in HC (plasma HMGB1 (ng/mL): 222.00±178.32 *vs* 106.99±175.79 *vs* 23.88±34.05; PBMCs HMGB1 mRNA: 0.235±0.954 *vs* 0.044±0.117 vs 0.019±0.029; PBMCs RAGE mRAN F0.0015±0.0035 *vs* 0.0013±0.0009 *vs* 0.0005±0.0003; HMGB1 protein:3.59±2.49 *vs* 1.89±2.00 *vs* 0.74±0.78 G*P*<0.05)),while the level of plasma HMGB1 and PBMCs HMGB1 mRNA were significantly higher in AG patients than those in IG patients (*P*<0.05), the level of PBMCs RAGE protein was higher in GA patients than that in HC (2.94±0.67 *vs* 1.61±0.51; *P*<0.05), and the level of PBMCs RAGE mRNA was higher in AG patients than that in IG patients (*P*>0.05) . In the GA patients, the level of plasma HMGB1 was positively correlated with white blood cell, neutrophile granulocyte, mononuclear cell and erythrocyte sedimentation rate (r=0.34,0.44,0.39,0.33; *P*<0.05),while negatively correlated with apolipoprotein A1(r=-0.28; *P*<0.05); the level of PBMCs HMGB1 mRNA was positively correlated with RAGE mRNA, white blood cell counts, neutrophil counts, lymphocyte counts, total cholesterol, low density lipoprotein and apolipoprotein B100

(r=0.29,0.36,0.26,0.28,0.29; P<0.05),while negatively correlated with high density lipoprotein (r=-0.30;P <0.01); the level of PBMCs RAGE mRNA was positively correlated with Lymphocyte counts, total cholesterol and apolipoprotein B100 (r=0.35,0.35,0.44; P<0.05).

Conclusion:

HMGB1 and its signaling pathway might play an important role in the pathogenesis of gouty arthritis, which may also be involved in regulating the lipid metabolism of gout.

Disclosure: Y. F. Qing, None; **Q. B. Zhang**, None; **S. Y. Pan**, None; **J. Zhou**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/expression-of-high-mobility-group-box-1-protein-and-the-receptor-for-advanced-glycation-end-products-in-primary-gouty-arthritis

Abstract Number: 23

Microvesicle-Associated Hsa-Mir-223-3p Is Elevated in Rheumatoid Synovial Fluid Compared with Osteoarthritis Synovial Fluid

Nancy D. Kim[1], Robert B. Lochhead[1], Pauline Schmit[2], Minna J. Kohler[3] and Andrew D. Luster[4], [1]Division of Rheumatology, Allergy & Immunology, Massachusetts General Hospital, Harvard Medical School, Boston, MA, [2]Massachusetts General Hospital, Charlestown, MA, [3]Rheumatology, Allergy, and Immunology, Massachusetts General Hospital / Harvard Medical School, Boston, MA, [4]Rheumatology, Allergy and Immunology, Massachusetts General Hospital, Harvard Medical School, Boston, MA

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Session Time: 9:00AM-11:00AM

Background/Purpose:

Microvesicles (MVs) (100-1000 nm diameter) are subcellular particles that are enriched in nucleic acid, including microRNA (miR), which may be transferred from cell to cell as a novel form of intercellular communication. In this study, we wished to characterize the microRNA content of microvesicles purified from the synovial fluid of patients with osteoarthritis or rheumatoid arthritis. Furthermore, we wished to determine whether predominant miR species identified in RA SF MVs may be transferred to recipient fibroblast-like synoviocytes (FLS) in vitro.

Methods:

Discarded synovial fluid (SF) from patients with established diagnoses of osteoarthritis (OA) (n=5) or rheumatoid arthritis (RA) (n=5) obtained during routine clinical care was transferred into tubes containing acid-citrate-dextrose and stored at 4°C until further processing. SF was treated with thromboplastin D, centrifuged at 300 g x 10 minutes and 3000 g x 15 minutes to remove cells and cellular debris, respectively, and filtered through a 0.8 mm filter. Next, SF was placed into ultracentrifuge tubes diluted with sterile PBS in a 1:8 ratio and ultracentrifuged at 100,000 g x 90 min using a Beckman 70.1Ti rotor. Purified MV pellets were resuspended in sterile PBS at one-fifth the original volume and quantified using a Nanosight LM10 instrument. MicroRNA from purified MV pellets was purified using a miRNeasy Serum/Plasma Kit (Qiagen), reverse transcribed, and subject to miRNA analysis using miScript miRNA PCR Serum/Plasma Arrays. PCR array data were analyzed using the Qiagen GeneGlobe Data Analysis Center online

software tool, normalizing to global CT mean of expressed miRNAs, using a cutoff of CT=37. Purified RA SF MVs were incubated with OA FLS for 16 hours, and pri-miR, pre-miR, and mature miR expression by FLS was determined by qPCR.

Results: Purified RA SF MVs purified in this manner were significantly greater than OA SF MVs (OA vs. RA 24.95 vs. 53.55 million/ml, p=0.0001). A total of 39 miRs showed greater than 2-fold statistically significant differences in expression between groups ($p<0.05$). Of these miRs, hsa-mir-223-3p expression was significantly upregulated in the RA SF MV group (102.4 fold regulation, p=0.005) when compared with the OA SF MV group. Addition of purified RA SF MVs to cultured human FLS induced expression of mir-223, but not pri-miR-223 or pre-mir-223, indicating that mir-223 in FLS was of exogenous (i.e. microvesicle) origin.

Conclusion: Microvesicle numbers in RA synovial fluid are greater than in OA synovial fluid, consistent with other previously published reports. We found significantly increased expression of mir-223-3p in RA SF MV, likely reflecting myeloid cell activation in the inflamed joint, and demonstrated that mir-223 may be transferred to recipient FLS in vitro.

Disclosure: N. D. Kim, None; **R. B. Lochhead**, NIAMS (T32 AR007258-36A1), 2; **P. Schmit**, None; **M. J. Kohler**, None; **A. D. Luster**, None.

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Abstract Number: 24

Investigating the Role of Vitamin D in the Transition to Systemic Lupus Erythematosus in Individuals at Risk for the Disease

Kendra A. Young[1], Melissa E. Munroe[2], Joel M. Guthridge[2], Diane L. Kamen[3], Timothy B. Niewold[4], Gary S. Gilkeson[5], Michael H. Weisman[6], Mariko L. Ishimori[6], Daniel J Wallace[7], David R. Karp[8], John B. Harley[9], Judith A. James[10] and Jill M. Norris[11], [1]Epidemiology, University of Colorado Denver, Aurora, CO, [2]Arthritis and Clinical Immunology, Oklahoma Medical Research Foundation, Oklahoma City, OK, [3]Medicine, Medical University of South Carolina, Charleston, SC, [4]Division of Rheumatology and Department of Immunology, Mayo Clinic, Rochester, MN, [5]Department of Rheumatology, Medical University of South Carolina, Charleston, SC, [6]Rheumatology, Cedars-Sinai Medical Center, Los Angeles, CA, [7]Division of Rheumatology, Cedars-Sinai Medical Center, Los Angeles, CA, [8]Internal Medicine - Rheumatic Diseases, University of Texas Southwestern Medical Center, Dallas, TX, [9]Center for Autoimmune Genomics and Etiology (CAGE), Cincinnati Children's Hospital Medical Center, Cincinnati, OH, [10]Department of Pathology, University of Oklahoma Health Sciences Center, Oklahoma City, OK, [11]University of Colorado Denver, Aurora, CO

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Session Time: 9:00AM-11:00AM

Background/Purpose: Lower vitamin D levels are associated with increased disease activity in systemic lupus erythematosus (SLE) and individuals with SLE have increased prevalence of vitamin D deficiency. However, there

have been no prospective studies on whether vitamin D is associated with transitioning to clinical SLE. We examined whether vitamin D supplement use, 25-hydroxyvitamin D (25[OH]D) levels and single nucleotide polymorphisms (SNPs) in vitamin D genes were associated with transitioning to SLE in individuals at risk for the disease.

Methods: 436 individuals who reported having a relative with SLE but who did not have SLE themselves at baseline were followed-up an average of 6.3 (± 3.9) years later. At both visits, detailed demographic, environmental, clinical, and therapeutic information was collected by questionnaire, and a blood sample was obtained. The 56 individuals (77% ANA positive, 77% European American (EA), 88% female) who transitioned to SLE (> 4 cumulative ACR criteria) were verified by medical record review. 25[OH]D levels were measured by ELISA. Vitamin D deficiency was defined as 25[OH]D <20 ng/ml. Twelve SNPs in 7 vitamin D genes were typed by Immunochip. Ancestry was determined by principal components analysis of the full Immunochip data. Generalized estimating equations (GEE), adjusting for correlation within families, were used to test associations between the vitamin D variables and the categorical outcome of transitioning to SLE. GEE analyses examining the association between SNPs in an additive model and transitioning to SLE was limited to 294 EA, adjusting for age, sex and ancestry.

Results: Mean baseline 25[OH]D levels were not different between those who transitioned to SLE and those who did not transition to SLE (23.0 versus 24.1 ng/ml, p=0.42), nor was vitamin D supplement use (10.7% versus 12.9%, p=0.65). Adjusting for age, sex, race and season of blood draw, transitioning to SLE was not associated with baseline 25[OH]D levels (adjusted OR=0.98, 95% CI 0.95-1.02), being vitamin D deficient (adjusted OR=1.92. 95% CI 0.64-5.77), nor taking vitamin D supplements at baseline (adjusted OR=0.70, 95% CI 0.28-1.79). SNPs in *CYP27A1, GC, DHCR7/NADSYN1, CYP2R1, VDR, CYP27B1* and *CYP24A1* were also not associated with transitioning to SLE. However, significant effect modification (interaction p-value=0.02) indicated that in those not taking vitamin D supplements, each additional minor allele in rs12794714 in *CYP2R1*was associated with a decreased risk of transitioning to SLE (adjusted OR= 0.71, 95% CI 0.40-1.25); in those taking supplements, each additional allele resulted in increased risk of transitioning to SLE (adjusted OR= 5.76, 95% CI 0.73-45.75).

Conclusion: 25[OH]D levels at baseline were not associated with transitioning to SLE at follow-up. However, the large effect size of vitamin D deficiency and the interaction between supplement use and *CYP2R1* on SLE risk suggests that vitamin D may play a role that is not adequately marked by 25[OH]D levels. To our knowledge, this is the first prospective study examining the association between vitamin D and SLE disease onset, and indicates that vitamin D does not play a strong role in transitioning to SLE.

Disclosure: K. A. Young, None; **M. E. Munroe**, None; **J. M. Guthridge**, None; **D. L. Kamen**, None; **T. B. Niewold**, None; **G. S. Gilkeson**, None; **M. H. Weisman**, None; **M. L. Ishimori**, None; **D. J. Wallace**, None; **D. R. Karp**, None; **J. B. Harley**, None; **J. A. James**, None; **J. M. Norris**, None.

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Abstract Number: 25

Attrition and Participant Characteristics in a Rheumatoid Arthritis Cohort

Angela Cesta[1], Xiuying Li[1], Mark Tatangelo[2,3] and Claire Bombardier[1,4,5], [1]Toronto General Hospital Research Institute, University Health Network, Toronto, ON, Canada, [2]Clinical Decision Making and Health Care, Toronto General Hospital Research Institute, University Health Network, Toronto, ON, Canada, [3]University of Toronto, Toronto, ON, Canada, [4]Division of Rheumatology and Institute of Health Policy, Management, and Evaluation, University of Toronto, Toronto, ON, Canada, [5]Division of Rheumatology, Mount Sinai Hospital, Toronto, ON, Canada

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Background/Purpose: The generalizability and validity of in longitudinal observational studies is contingent on participant characteristics. If attrition is not random, it is important to identify any systematic differences b etween patients who continue to participate versus those who drop out. The purpose of this analysis was to compare characteristics of rheumatoid arthritis (RA) patients who continue to participate in the Ontario Best Practices Research Initiative (OBRI) to those of patients who have dropped out prior to reaching their 3 yr follow up.

Methods: Currently, 61 rheumatologists in Ontario (51% of active rheumatologists in Ontario) recruit patients into the OBRI. As of January 2015, 1533 patients had consented and were eligible to participate. 175 (11.4%) patients dropped out before reaching their 3 yr follow up assessment. Among the drop outs, 109 (7.1%) withdrew consent, 38 (2.5%) were lost to follow up, and 28 (1.8%) refused to re-consent after 2 yrs of follow up. In addition to the drop outs, 38 (2.5%) patients had died. 1320 (86.1%) patients remained active participants. Patient characteristics and disease activity at enrollment were compared in the 175 patients who dropped out versus the 1320 patients who continued to participate. A survival curve was generated to look at time of drop out over the 3 year follow up period.

Results: Patients who dropped out were similar to those who remained active with respect to age, gender, race, education, employment status, having private insurance, disease duration, number of comorbidities, and living alone. Compared to patients who dropped out, patients who continued to participate had higher household incomes, lower disease activity scores, and were more likely to be taking a biologic at the time of enrollment (Table 1). The survival curve shows that the majority of patients drop out within the first two years (Figure 1).

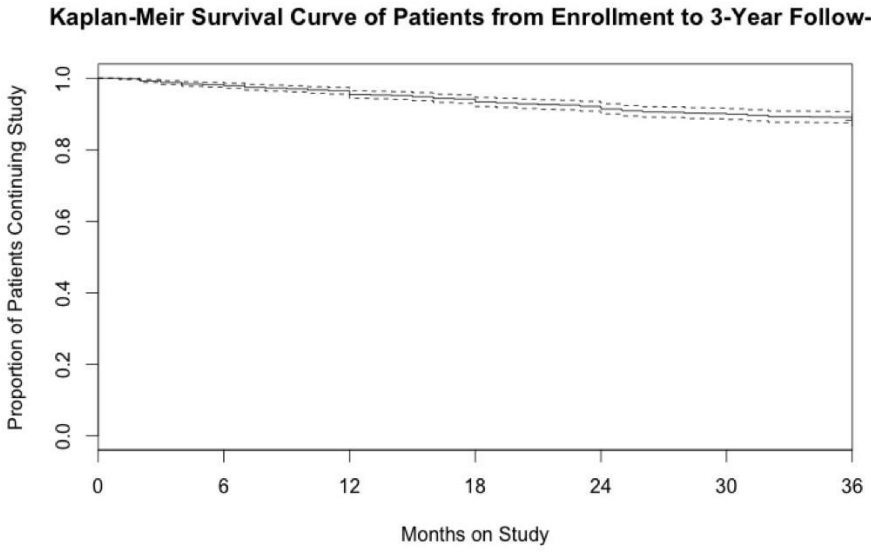
Conclusion: Patients with higher disease activity at enrollment were more likely to drop out. The OBRI attrition rate was 11.4% during the first three years of follow up, with 4.7% of patients dropping out in the first year, 3.5% in the second year and 3.2% in the third year. OBRI attrition rates were lower than those reported in the BRASS cohort (4.31% per 6 month follow up cycle) [1] and the ARAMIS cohort (6% per year) [2]. The lower number of drop outs in the OBRI cohort could be attributed to the time invested in rheumatologist site visits by our study monitors and the biannual follow-up by our OBRI telephone interviewers.

Reference:

1. Iannaccone et al., Arthritis Care &Research, Jul 2013

2. Reisine et al., ACR, Feb 2000

Table 1: Patient Characteristics and Disease Activity at Time of Enrollment into OBRI		
	Patients who Dropped Out **(N = 175)**	Active Patients **(N = 1320)**
Age, Mean (SD)	57.1 (15.4)	56.9 (12.6)
Female, N (%)	125 (75%)	1041 (79%)
White, N (%)	140 (88%)	1133 (91%)
Education, N (%)		
Less than High School	21 (13%)	106 (8%)
High School	65 (39%)	492 (38%)
College or greater	81 (49%)	699 (54%)
*Household Income, N (%)		
<20,000	15 (9%)	98 (7%)
20,000-34,999	22 (13%)	147 (11%)
35,000-49,999	18 (10%)	153 (12%)
50,000-74,999	19 (11%)	171 (13%)
³75,000	29 (17%)	344 (26%)
Missing data	72 (41%)	407 (31%)
Live Alone, N (%)	28 (17%)	178 (14%)
Employment (Full time), N (%)	75 (45%)	615 (52%)
Having Private Insurance, N (%)	101 (60%)	848 (68%)
Duration of Disease (yrs), Mean (SD)	7.8 (9.9)	9.2 (9.8)
*DAS28 (0-9.4), Mean (SD)	4.9 (4.4)	4.4 (1.6)
*CDAI (0-76), Mean (SD)	25.7 (14.7)	20.9 (14.3)
*HAQ (0-3), Mean (SD)	1.44 (0.78)	1.22 (0.76)
*Pain Score (0-3), Mean (SD)	1.76 (0.89)	1.48 (0.87)
*RADAI (0-10), Mean (SD)	4.8 (2.2)	4.0 (2.2)
Number of Co-morbidities, Mean (SD)	2.3 (1.9)	2.5 (2.1)
*RA Medications		
Biologic monotherapy, N (%)	7 (4%)	68 (5%)
Biologic combination therapy, N (%)	6 (4%)	132 (10%)
*P²0.05		



Disclosure: A. Cesta, None; **X. Li**, None; **M. Tatangelo**, None; **C. Bombardier**, None.

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Abstract Number: 26

Higher Scores of Women Compared to Men for Most Clinical Measures of Rheumatoid Arthritis (RA) Status: Greater Differences for Patient Self-Report Scores Than for Rheumatologist Estimates: A Cross-Sectional 3 Center Study from Routine Care

Isabel Castrejón[1], Martin Bergman[2], Yusuf Yazici[3], Annie Huang[1], Joel A. Block[1] and Theodore Pincus[1], [1]Rheumatology, Rush University Medical Center, Chicago, IL, [2]Division of Rheumatology, Taylor Hospital, Ridley Park, PA, [3]NYU Hospital for Joint Diseases, New York, NY

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Background/Purpose: Higher scores for women compared to men have been reported for all 7 rheumatoid arthritis (RA) Core Data Set measures (1, 2). Most of these measures predict premature RA mortality (3), but women with RA (and the general population) live 5-10 years longer than men. These findings suggest that higher scores for women may result in part from an ascertainment bias of more candid responses rather than poorer clinical status in women. We sought to probe this possibility by comparing differences between females and males in scores on a patient self-report MDHAQ/RAPID3 (multidimensional health assessment questionnaire/routine assessment of patient index data) vs physician estimates on a RheuMetric checklist.

Methods: All patients (with all diagnoses) at 3 settings complete a MDHAQ at each visit in the waiting area before seeing the rheumatologist. The 2-page MDHAQ includes physical function (FN) in 10 activities of daily living, three 0-10 visual analogue scales (VAS) for pain (PN), patient global estimate (PATGL), fatigue (FT), RADAI self-report joint count, and demographic data. RAPID3 (0-30) is the sum of 0-10 scores from FN, PN, and PATGL. In addition, the rheumatologist completes a RheuMetric checklist, which includes 4 0-10 VAS estimates for overall status, inflammation (reversible), damage (irreversible), and distress (e.g. fibromyalgia and depression). Mean differences between scores of women and men on the patient self-report MDHAQ and physician RheuMetric were compared, using t-tests to estimate statistical significance.

Results: Overall 461 patients were analyzed, 173, 147, and 141 from 3 sites. Females and males were similar in age and education level (Table). All 0-10 MDHAQ scores were ≥0.5 units higher in females than males, $p<0.05$ for pain, RAPID3, and RADAI self-report joint count. RheuMetric physician 0-10 estimates also were higher in females than males, but differences were 0.2 or less for estimates overall global status, inflammation, and damage ($p>0.05$). Only physician estimate of distress differed by 0.6 units ($p=0.02$) (Table).

Conclusion: Female RA patients have higher scores than males, with greater differences for patient self-report measures compared to physician measures other than for distress. These data suggest that higher MDHAQ scores in females may be attributable in part to an ascertainment bias of greater candor rather than clinical severity in females. Further studies of mechanisms for gender differences are needed.

References: **1)** Sokka T, et al. Arthritis Res Ther. 2009;11(1):R7. **2)** Castrejon Fernandez I, et al. Rheumatol Clin. 2010;6(3):134-40. **3)**Sokka T, et al. Clin Exp Rheumatol. 2008;26(5 Suppl 51):S35-61.

Table: MDHAQ/RAPID3 patient self-report scores and RheuMetric physician estimates in female compared to male patients with rheumatoid arthritis

	Females (N=365)	**Males (N=96)**	**p**
Demographic variables			
Age, years	56.5 (15.5)	54.9 (16.8)	0.39
Education level, years	14.2 (3.2)	14.6 (3.1)	0.31
MDHAQ/RAPID3: Patient self-report scores			
Physical function (0-10)	2.3 (2.1)	1.8 (1.8)	0.06
Pain (0-10)	**4.4 (3.1)**	**3.5 (2.6)**	**0.01**
Patient global estimate (0-10)	4.1 (3.1)	3.4 (2.5)	0.06
RAPID3 (0-30)	**10.6 (7.6)**	**8.5 (6.4)**	**0.01**
Fatigue (0-10)	4.0 (3.2)	3.4 (2.9)	0.07
RADAI (0-48)	**10.9 (10.5)**	**7.4 (8.5)**	**0.05**
RheuMetric: Physician Estimates			
Physician global estimate (0-10)	2.6 (2.1)	2.4 (1.9)	0.48
Inflammation (0-10)	1.5 (1.8)	1.4 (1.8)	0.62
Damage (0-10)	1.9 (2.0)	1.7 (1.8)	0.46
Distress (0-10)	**0.7 (1.7)**	**0.1 (0.4)**	**0.02**

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Abstract Number: 27

Self-Reported Sedentary Behavior in Patients with Rheumatoid Arthritis

Abigail Gilbert[1], Julia (Jungwha) Lee[2], Madeleine Ma[1], Pamela Semanik[3], Dorothy D. Dunlop[4] and Rowland W. Chang[5], [1]Northwestern University Feinberg School of Medicine, Chicago, IL, [2]Department of Preventive Medicine, Biostatistics Collaboration Center, Northwestern University Feinberg School of Medicine, Chicago, IL, [3]College of Nursing, Rush University, Chicago, IL, [4]Institute for Healthcare Studies, Northwestern University Feinberg School of Medicine, Chicago, IL, [5]Preventive Medicine, Northwestern University Feinberg School of Medicine, Chicago, IL
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Abstract

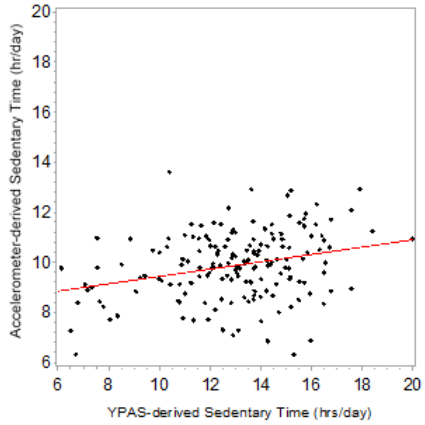
Background/Purpose: Sedentary behavior is associated with increased risk of functional decline and disability. Individuals with rheumatoid arthritis (RA) spend more time in sedentary activity than healthy adults. Despite the association of RA with other deleterious health states, the assessment of sedentary behavior in clinical settings has not been well-developed in this patient population. We examined 3 potential approaches to identify the most sedentary individuals in adults with RA using a modified version of the Yale Physical Activity Survey (YPAS).

Methods: 172 adults with RA were enrolled in IMPAACT (Improving Motivation for Physical Activity in Arthritis Clinical Trial). Participants wore an accelerometer for 7 days then completed the modified YPAS for the same 7-day accelerometer period. Daily sedentary time was estimated from YPAS in three ways: 1) a categorical estimate of hours/day spent sitting (<3, 3-6, 6-8, >8 hrs/day); 2) a subjective continuous estimate of sedentary time calculated by subtracting hours sleeping and time spent in physical activity from a 24-hour day; and 3) rank order of the subjective continuous estimate. Each estimate was compared to objective accelerometer-derived sedentary time, defined as time registering counts of less than 100/minute during waking hours.

Results: On average, the 172 participants had RA for 13 years. Mean Disease Activity Score-28 was 6.4 and mean age was 55 years. 83% were female. Accelerometer-derived sedentary time was greater than 8 hours/day in 93% of participants. The 4 sitting categories had a significant increasing linear trend with objective sedentary time but over half the participants categorized themselves as sitting more than 8 hours/day. A significant linear relationship was observed between the continuous YPAS-derived sedentary time and objective sedentary time (Pearson $r = 0.29$, $p<0.001$); but a Bland-Altman plot demonstrated systemic bias. There was a significant linear relationship between the ranked YPAS-derived continuous estimate and ranked accelerometer sedentary time (Spearman = 0.26, $p <0.001$). Rank-order was an unbiased predictor.

Conclusion: All three approaches showed a significant relationship between self-reported and objectively measured sedentary time. The self-reported sitting category might be more informative with a category to capture sitting > 10 hours/day. The continuous YPAS-derived sedentary time estimate was a biased estimator. The unbiased rank of the YPAS-derived continuous sedentary the best use of the detailed YPAS information. This patient-reported approach using the modified YPAS shows promise to be a useful tool to identify the most sedentary patients at highest risk for functional decline. Providing a practical and accurate tool to identify the most sedentary individuals could lead to increased awareness and patient monitoring of sedentary behavior by clinicians.

Figure: Subjective and objective s edentary time (n=172)



Disclosure: A. Gilbert, None; **J. Lee**, None; **M. Ma**, None; **P. Semanik**, None; **D. D. Dunlop**, None; **R. W. Chang**, None.

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Abstract Number: 28

The Decrease over Time of Orthopaedic Surgery in Patients with Rheumatoid Arthritis Is Mainly Due to Reduced Rates Among Those with Rheumatoid Factor Positive Disease – Results from a Well Defined Area

Korosh Hekmat[1,2], Lennart T.H. Jacobsson[3], Jan-Åke Nilsson[1], Minna Willim[1], Martin Englund[4,5], Ingemar F Petersson[4] and Carl Turesson[6], [1]Department of Rheumatology. Malmö University Hospital, Section of Rheumatology, Department of Clinical Sciences, Malmö, Lund University, Malmö, Sweden, [2]Karolinska University Hospital, Department of Medicine, Unit of Rheumatology, Stockholm, Stockholm, Sweden, [3]Department of Rheumatology Malmö University Hospital, Section of Rheumatology, Department of Clinical Sciences, Malmö, Lund University, Malmö, Sweden, [4]Department of Orthopedics, Clinical Sciences Lund, Lund University, Lund, Sweden, [5]Clinical Epidemiology Unit, Orthopedics, Dept of Clinical Sciences Lund, Lund University, Lund, Sweden, [6]Section of Rheumatology, Department of Clinical Sciences, Malmö, Lund University, Malmö, Sweden

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Background/Purpose : Seropositive and seronegative rheumatoid arthritis (RA) differ in course and prognostic feature. The overall incidence of orthopaedic surgery in patients with RA has previously been shown to decline over time. The purpose of this study was to investigate whether there were differences in the time trends for orthopaedic surgery in rheumatoid factor (RF) positive and RF negative RA.

Methods: A population-based dynamic cohort of all known patients with RA in a defined geographic area was investigated. The patients had a clinical diagnosis of RA made by a rheumatologist, and fulfilled the 1987 ACR criteria for RA. Data on orthopaedic surgery procedures between 1998 and 2011 were retrieved from a regional health care register. Incidence rates of orthopaedic surgery procedures after RA diagnosis during the period from 1998 through 2011 were estimated separately for RF positive and RF negative patients. The incidence rates for 1998-2001 were compared to those of 2002-2006 and 2007-2011.

Results: A cohort of 2095 patients with RA (72 % women, 69 % RF positive) was investigated. There were 1702 orthopaedic procedures during a total follow-up of 21,123 person-years (py). Patients with RF positive RA were treated more extensively with methotrexate and biologic disease modifying anti-rheumatic drugs than those with RF negative RA. The incidence of orthopaedic surgery procedures overall declined significantly over time for RF positive RA, and there was a corresponding decline in small joint surgery and large joint surgery (Table). In patients with RF positive RA, the incidence of large joint surgery was reduced already in 2002-2006 compared to 1998-2001, whereas a decline in small joint surgery was apparent only in the final period (2007-2011). The incidence rate ratio (IRR) for orthopaedic surgery overall in this subset compared to 1998-2001 was 0.83 (95% confidence interval (CI) 0.73-0.95) in 2002-2006, and 0.68 (95% CI 0.59-0.79) in 2007-2011. On the other hand there was no significant decline among patients with RF negative RA in the incidence of all orthopaedic surgery procedures, with similar findings for small joint surgery or large joint surgery (Table). In patients with RF negative RA, the IRR for surgery overall compared to 1998-2001 for 2002-2006 was 0.90 (95% CI 0.68-1.18), and for 2007-2011 0.80 (95% CI 0.60-1.06).

Conclusion: The overall incidence of orthopaedic surgery declined over time in patients with RF positive RA, with significant decreases in both large and small joint surgery. In contrast, there was no major decline in RF negative RA. Patients with seropositive RA may benefit more from improved management and modern anti-rheumatic pharmacotherapy in terms of reduction of joint damage and the need for joint surgery.

Incidence of orthopaedic surgery per 1000 py (95 % CI) in the population-based RA cohort

	1998-2001	**2002-2006**	**2007-2011**	**P**
RF positive RA				
All orthopaedic surgery	114.2 (103.6-125.5)	94.9 (86.6-103.9)	78.1 (70.0-86.8)	<0.0001
Small joint surgery	57.6 (50.2-65.8)	52.2 (46.0-58.9)	36.2 (30.8-42.3)	<0.0001
Large joint surgery	54.7 (47.5-62.7)	41.4 (35.9-47.4)	40.5 (34.8-46.9)	<0.0001
RF negative RA				
All orthopaedic surgery	61.4 (49.5-75.3)	55.0 (45.9-65.5)	49.3 (40.6-59.3)	0.12
Small joint surgery	22.0 (15.2-30.9)	21.8 (16.2-28.8)	15.0 (10.4-20.9)	0.10
Large joint surgery	36.0 (27.1-47.0)	32.3 (25.4-40.6)	31.7 (24.8-39.9)	0.49

Disclosure: K. Hekmat, None; **L. T. H. Jacobsson**, None; **J. Nilsson**, None; **M. Willim**, None; **M. Englund**, None; **I. F. Petersson**, None; **C. Turesson**, None.

Abstract Number: 29

Development of Multimorbidity in Patients with Newly Diagnosed Rheumatoid Arthritis – a Population-Based Study

Helga Radner[1,2], Rishi Desai[3], Theodore Tsacogianis[4], Daniel H. Solomon[5] and Seoyoung C. Kim[6], [1]Division of Rheumatology, Immunology and Allergy, Brigham and Women's Hospital, Boston, MA, [2]Department of Internal Medicine III; Division of Rheumatology, Medical University of Vienna, Vienna, Austria, [3]PharmacoEpidemiology & PharmacoEconomics, Brigham and Women's Hospital, Boston, MA, [4]Division of Pharmacoepidemiology and Pharmacoeconomics, Department of Medicine, Brigham and Women's Hospital, Boston, MA, [5]Rheumatology, Brigham and Women's Hospital, Boston, MA, [6]Medicine/Rheumatology, University of Pennsylvenia, Philadelphia, PA

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Background/Purpose: Limited information exists whether RA patients are likely to develop more morbid conditions after RA diagnosis compared to those without RA and the trajectory of multimorbidity over the course of RA remains unclear. We aimed to examine the accumulation of incident morbidities after onset of RA compared to patients with hypertension (HTN)- a highly prevalent chronic non-inflammatory condition.

Methods: Using claims data from a U.S commercial health plan, we identified new onset RA patients with ³2 ICD-9 codes of RA, >7 to <365 days apart, and new initiation of ³1 DMARD after ³12 months of enrollment. HTN Patients were identified similarly using ICD-9 codes of HTN and new initiation of ³1 HTN medication. The index date was defined as first prescription of a DMARD or respective HTN medication. We excluded patients with any prior use of DMARDs, HTN medication, or other chronic conditions any time prior to the index date. RA and HTN patients were 1:4 matched on age, sex, obesity status, and index date. Beginning on the index date, patients were followed for development of any of the 16 chronic conditions according to the widely used Deyo-adapted Charlson Index (Table). We calculated incidence rates (IR) per 1,000 patient-years (PY) for each condition. Cumulative percentage of patients developing at least one additional chronic condition over time was plotted separately for RA and HTN patients using Kaplan-Meier curves.

Results: We includeda total of 4,803 RA and 19,212 HTN patients. Mean age was 49 years , 71% was female, 0.5% obesity. Mean time of follow up was 25 months in the RA and 32 months in the HTN cohort. In the RA cohort the highest IR was found for chronic pulmonary disease (66.2/1,000 PY) compared to HTN (47.3/1,000 PY; $p<0.01$). The IR of cancer was higher in RA patients (RA 32.6/1,000 PY vs. HTN 25.3/1,000 PY $p<0.01$) whereas the IR for diabetes was higher in the HTN cohort (RA 27.9/1,000 PY vs. HTN 40.1/1,000 PY $p<0.01$; **table**). The cumulative incidence of patients with ³1 co-morbidity was higher for RA patients within the first two years of follow-up (FU) (16.8% vs. 14.6% up to 1 year, 24.6% vs. 21.4% up to 2 years; $p<0.01$), after 3 years of FU Kaplan Meier curves revealed no significant differences between RA and HTN patients (log rank test $p=0.35$).

Conclusion: Within the first 2 years after disease onset, a higher incidence of multimorbidity was observed in RA

patients. The highest IR was found for pulmonary disease, which might have an important impact on many outcomes including morbidity and mortality.

Table. Incidence rate of 16 different morbid conditions per 1,000 person-years for the rheumatoid arthritis (RA) and the hypertension (HTN) cohorts.

Chronic morbid condition	Rheumatoid Arthritis cohort n=4,803		Hypertension cohort n=19,212		p-value
	N	IR per 1,000 patient-years	N	IR per 1,000 patient-years	
Chronic pulmonary disease	698	66.2	2405	47.7	<0.01
Collagenosis/vasculitis	469	44.5	212	4.2	<0.01
Any tumor including leukemia/lymphoma	343	32.6	1273	25.3	<0.01
Diabetes mellitus	294	27.9	2021	40.1	<0.01
Cerebrovascular disease	199	18.9	1016	20.2	0.40
Mild liver disease	130	12.3	627	12.4	0.93
Peripheral vascular disorder	107	10.2	502	10.0	0.86
Peptic ulcer disease	92	8.7	257	5.1	<0.01
Congestive heart failure	85	8.1	400	7.9	0.89
Renal disease	84	8.0	498	9.9	0.07
Metastatic solid tumor	51	4.8	152	3.0	0.03
Myocardial infarction	45	4.3	193	3.8	0.51
Hemiplegia or paraplegia	23	2.2	50	1.0	<0.01
Dementia	14	1.3	36	0.7	0.05
Moderate to severe liver disease	11	1.0	33	0.7	0.18
HIV/AIDS	4	0.4	13	0.3	0.50

ADDIN EN.REFLIST 1. Deyo RA, Cherkin DC, Ciol MA. Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. J Clin Epidemiol. 1992;45(6):613-9.

Disclosure: H. Radner, None; **R. Desai**, None; **T. Tsacogianis**, None; **D. H. Solomon**, None; **S. C. Kim**, Pfizer Inc, 2,AstraZeneca, 2,Lilly, 2,Genentech and Biogen IDEC Inc., 2.

Abstract Number: 30

Complications of Inflammatory Arthritis in First Nations and Non-First Nations Populations of Alberta, Canada

Cheryl Barnabe[1], Gilaad Kaplan[2], J Antonio Avina-Zubieta[3], Diane Lacaille[4], Brenda Hemmelgarn[5] and JM Esdaile[6], [1]Cumming School of Medicine, University of Calgary, Calgary, AB, Canada, [2]Division of Gastroenterology,

University of Calgary, Calgary, AB, Canada, [3]Arthritis Research Canada / University of British Columbia, Vancouver, BC, Canada, [4]Arthritis Research Centre, University of British Columbia, Vancouver, BC, Canada, [5]Division of Nephrology, University of Calgary, Calgary, AB, Canada, [6]Rheumatology, Arthritis Research Canada, Richmond, BC, Canada

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Background/Purpose: With markedly improved control of the acute effects of inflammatory arthritis, the major causes of morbidity and premature death now arise from the complications of chronic inflammation. Alberta's First Nations (FN) population has an increased prevalence of rheumatoid arthritis (RA), ankylosing spondylitis (AS) and psoriatic disease (PsD includes psoriasis and psoriatic arthritis) relative to the non-FN population. These conditions are reported to be more severe in FN which may result in higher rates of inflammatory complications. Our objective was to compare incidence rates of recognized complications of inflammation, namely cardiovascular disease (CVD, including myocardial infarction, stroke, venous thrombotic events), hospitalized infections, osteoporotic hip fracture, and malignancy (lymphoma, breast, colon), and conditions newly hypothesized to be secondary to chronic inflammation (diabetes, chronic obstructive pulmonary disease, COPD) in FN and non-FN populations.

Methods: ICD-9-CA and ICD-10-CM codes from population-based healthcare administrative data (physician billing claims and hospitalizations, years 1993 to 2011) were used to define incident cohorts of patients with RA, AS, and PsD using validated definitions. FN identity was determined from the Alberta Health Care Insurance Plan Registry File. Complications were determined using validated algorithms of ICD-9-CA and ICD-10-CM codes, with prevalent cases excluded. Incidence rates of complications were calculated for each disease cohort overall (per 1,000 person-years), and stratified by FN status to calculate the incidence rate ratio.

Results: The disease cohorts include 27,587 persons with RA, 5,120 persons with AS and 4,279 persons with PsD, with FN representing 6.1%, 5.0% and 3.7% of the cohorts respectively. Persons with RA had the highest frequency of CVD, hospitalized infection, osteoporotic hip fracture, malignancy and COPD compared to persons with AS and PsD, but persons with PsD had higher incidence rates of diabetes (Table 1). FN persons with RA, AS and PsD were not at increased risk for complications of inflammation (Table 2).

Conclusion: There were no significant increases in rates of complications in FN persons compared to non-FN in our population-based cohort.

Table 1. Incidence Rate (per 1,000 person-years) of Inflammatory Arthritis Complications

Complication	**RA (n=27,587)**	**AS (n=5,120)**	**PsD (n=4,279)**
CVD	14.0	8.3	10.4
Hospitalized Infection	29.7	19.8	22.4
Osteoporotic Hip Fracture	4.7	2.2	3.0
Malignancy	6.5	4.0	5.4
Diabetes	4.8	2.9	5.9
COPD	12.0	6.6	11.2

Table 2. Incidence Rate Ratio (95% confidence interval) for Inflammatory Arthritis Complications in the First Nations relative to non-First Nations Populations			
Complication	**RA**	**AS**	**PsD**
CVD	0.7 (0.4 to 1.2)	NR	1.9 (0.5 to 8.1)
Hospitalized Infection	1.3 (0.9 to 1.8)	1.2 (0.4 to 3.8)	0.5 (0.1 to 3.8)
Osteoporotic Hip Fracture	0.8 (0.3 to 2.0)	NR	NR
Malignancy	0.6 (0.3 to 1.4)	NR	NR
Diabetes	2.2 (0.8 to 6.2)	4.6 (0.5 to 40.9)*	NR
COPD	1.1 (0.6 to 1.8)	0.8 (0.1 to 5.8)	1.1 (0.2 to 8.4)*
Results are for fiscal year 2009 unless indicated by * where fiscal year 2008 is reported NR not reported due to <5 events in the First Nations group during the entire study period			

Disclosure: C. Barnabe, None; **G. Kaplan**, None; **J. A. Avina-Zubieta**, None; **D. Lacaille**, None; **B. Hemmelgarn**, None; **J. Esdaile**, None.

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Abstract Number: 31

Risk of Chronic Obstructive Pulmonary Disease in Rheumatoid Arthritis: A Population Based Cohort Study

Katherine McGuire[1], J Antonio Avina-Zubieta[2], Eric C. Sayre[1], JM Esdaile[3] and Diane Lacaille[4], [1]Arthritis Research Canada, Richmond, BC, Canada, [2]Arthritis Research Canada / University of British Columbia, Vancouver, BC, Canada, [3]Rheumatology, Arthritis Research Canada, Richmond, BC, Canada, [4]Arthritis Research Centre, University of British Columbia, Vancouver, BC, Canada

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Background/Purpose:

A link between chronic obstructive pulmonary disease (COPD) and inflammation has been established in a number of studies. This raises the question of whether chronic inflammatory conditions, such as RA, predispose to COPD. The objective of this study was to evaluate the risk of incident COPD in RA compared to the general population.

Methods:

We conducted a retrospective cohort study of a population based incident RA cohort, identified between 1996-2006 and followed until 2010, using administrative health data. All incident RA cases in British Columbia were selected using previously published criteria. Controls were randomly selected from the general population, matched 1:1 to RA cases on birth year, gender and calendar year of inclusion. Individuals with inpatient or outpatient visits for COPD prior to index date were excluded. COPD outcome was defined as a hospitalization with a COPD code, which has been validated. All data were obtained from the Ministry of Health, including all visits to physicians, hospitalizations and dispensed medications.

Incidence rates and 95% CI were calculated for the RA cohort and controls, along with incidence rate ratios (IRR). Multivariable Cox proportional hazard models (PHM) were used to estimate the risk of COPD in RA compared to the general population after adjusting for potential confounders. Sensitivity analyses were performed to test the robustness of the results to the possible confounding effect of smoking, as it is a risk factor for both RA and COPD unavailable in administrative data, assuming a prevalence of 10% or 20% and an OR of 1.3 or 3.0, which covers the smoking rate of 16% for BC and of 12.5% observed in our prior RA survey.

Results:

The population cohorts included 24625 RA cases (67% female; mean [SD] age 57.2[17.1] years) and 25537 controls contributing 170401 and 184416 person-years of follow-up, respectively. The incidence rate of COPD was greater in RA than controls (Table 1), yielding an IRR of 1.75. After adjusting for potential confounders, RA cases had a 42% greater risk of developing COPD than controls (Table 1). The increase in risk did not differ according to age or gender. The increased risk in RA remained significant after modelling for smoking.

Conclusion:

In our population-based cohort, individuals with RA had a 42% greater risk of developing COPD compared to the general population. This has important clinical implications for clinicians and people living with RA, supporting good control of inflammation, smoking cessation, and testing for COPD, as indicated.

Table 1: Risk of COPD in RA compared to general population controls

	RA cohort (N=24625)	Controls (N=25537)
No. of incident cases of COPD	892	551
Incident rate of COPD per 1000 patient-years	5.23	2.99
Incident rate ratio (95% CI), RA vs. controls	1.75 (1.57-1.95)	
	aHR (95% CI) for COPD	
PHM adjusted for age and sex RA vs. general population	1.70 (1.53-1.89)	
PHM adjusted for baseline GC use, no. physician visits, prior hospitalizations, asthma, cardiovascular disease and hyperlipidemia, in 1 yr prior to index date RA vs. general population	1.42 (1.27-1.60)	
Multivariable PHM stratified by gender RA vs. general population	Males	1.42 (1.19-1.69)
	Females	1.45 (1.25-1.68)
Multivariable PHM stratified by age RA vs. general population	<60 years	1.53 (1.15-2.03)
	>60 years	1.37 (1.20-1.56)
PHM Sensitivity Analyses modeling potential confounding effect of smoking, RA vs. general population controls	Prev.:10% OR: 1.3	1.39 (1.23-1.56)
	Prev.:10% OR: 3.0	1.23 (1.10-1.39)
	Prev.:20% OR: 1.3	1.41 (1.26-1.59)
	Prev.:20% OR: 3.0	1.14 (1.01-1.29)

Abbreviations: GC= Gluococorticosteroids, aHR=adjusted Hazard Ratio, CI= Confidence Intervals

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Abstract Number: 32

Risk for Lung Cancer in RA and Different RA Phenotypes: Results from a Population-Based Case-Control Study

Katerina Chatzidionysiou[1], Gudrun Reynisdottir[2], Vijay Joshua[2], Thomas Frisell[3], Johan Askling[3] and Anca I Catrina[2], [1]Department of Medicine, Unit of Rheumatology, Department of Medicine Solna, Karolinska University

Hospital, Karolinska Institutet, Stockholm, Sweden, [2]Unit of Rheumatology, Department of Medicine Solna, Karolinska University Hospital, Karolinska Institutet, Stockholm, Sweden, [3]Clinical Epidemiology Unit, Department of Medicine, Karolinska Institutet, Stockholm, Sweden

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Background/Purpose: It has been shown that patients with Rheumatoid Arthritis (RA) are at increased risk for certain malignancies, among them lung cancer. We aimed to investigate the association between lung cancer and different RA phenotypes based on rheumatoid factor (RF) and anti-citrullinated peptide antibody (ACPA) status.

Methods: We used the population-based case-control study EIRA (Epidemiological Investigation of Risk factors for Rheumatoid Arthritis). Patients with RA diagnosis and controls (matched for age, sex, calendar period and area of residence) were included during 1996-2013. The data were linked to the Swedish nationwide cancer register. Cox regression was used to calculate RR. Due to the significant correlation between smoking and RA as well as presence of RF and ACPA, stratified analyses based on smoking status were performed, in order to account for effect modification.

Results: A total of 3547 RA patients and 5586 controls were included in the study**.** The mean age (SD) was 52 (13) years and the percentage of female was 72%. Significantly more RA patients than controls were diagnosed with lung cancer after RA diagnosis (58 vs. 26 per 100,000 patient-years, respectively, p=0.002). RA itself gave twice an increased risk for developing lung cancer when adjusted for age and sex (RR=1.9, 95% CI=1.2-3.2, p=0.01), but the statistical significance disappeared when smoking was included in the model. However, after stratification according to smoking status, RA was significantly associated to lung cancer development in never or ex-smokers (RR=2.4, 95% CI=1.0-6.2, p=0.05) but not in current smokers (RR=1.2, 95% CI=0.6-2.3, p=0.6).

In RA patients, higher age, smoking, RF positivity, RF and/or ACPA positivity and double seropositivity were significant risk factors for lung cancer (table 1). In a stratified by smoking status analysis RF positivity was significantly associated to lung cancer in non-smokers (table 2).

Conclusion: In this study RA, especially RF positive RA, was associated to the development of lung cancer in never or ex-smokers. Although not statistically significant, patients who developed lung cancer were more often positive for RF and/or ACPA irrespective of smoking status.

Variable	RR (95% CI)	P-value
Sex (female vs. male)	0.6 (0.3-1.2)	0.64
Age	1.1 (1.1-1.2)	<0.0001
Smoking (current vs. never/ex)	3.2 (1.6-6.6)	0.002
Smoking (ever vs. never)	3.6 (1.1-12.0)	0.03
Silica exposure (yes vs. no)	2.2 (0.7-6.9)	0.18
RF (pos vs. neg)	4.6 (1.6-13.0)	0.004
ACPA (pos vs. neg)	1.9 (0.9-4.0)	0.11
ACPA and/or RF (pos vs. neg)	7.0 (1.7-28.9)	0.008
Double pos (RF and ACPA) vs. double neg	6.8 (1.6-28.8)	0.01

Table 1. Risk factors for developing lung cancer after RA diagnosis (results of the Cox regression analysis adjusted for age and sex).

	Non-Smokers (never or ex-smokers)			Smokers (current)		
Variable	N. patients (seropositive with lung ca/total with lung ca)	RR (95% CI)	P-value	N. patients (seropositive with lung ca/total with lung ca)		
RF (pos vs neg)	11/12	7.4 (1.0-57.4)	0.06	17/20	2.4 (0.7-8.2)	0.16
ACPA (pos vs neg)	9/12	2.3 (0.6-8.7)	0.20	14/20	1.2 (0.4-3.1)	0.74
ACPA and/or RF pos vs double neg	11/12	5.5 (0.7-42.5)	0.10	19/20	5.8 (0.8-43.2)	0.09
Double pos (RF and ACPA) vs double neg	9/10	6.1 (0.8-47.9)	0.09	12/13	4.8 (0.6-36.5)	0.14

Table 2. Risk for developing lung cancer after RA diagnosis for different RA phenotypes according to the presence of RF and ACPA in non-smokers and smokers.

Disclosure: K. Chatzidionysiou, None; **G. Reynisdottir**, None; **V. Joshua**, None; **T. Frisell**, None; **J. Askling**, None; **A. I. Catrina**, None.

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Abstract Number: 33

Analysis of Incidence Rates of Pulmonary Embolism in the Rheumatoid Arthritis Population Compared with the Non-Rheumatoid Arthritis Population

Richa Rajwanshi[1], Khaled Sarsour[2], Laura Governale[2], Brandon Arnieri[2], David Oliveri[2] and Erhan Berber[2], [1]1 Dna Way, Ms 361a, Genentech, South San Francisco, CA, [2]Genentech, South San Francisco, CA
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Background/Purpose: This study was conducted in a large health care claims database to determine whether there is a difference in the incidence rate (IR) of pulmonary embolism (PE) among the bDMARD-treated rheumatoid arthritis (RA) population compared with the non–bDMARD-treated RA population and the general non-RA population.

Methods: This retrospective cohort study was performed using a large health care claims database (2001-2013). The study consisted of three cohorts: RA biologic treated, RA biologic naive, and general non-RA population. These cohorts were matched by age and sex. Patients were considered bDMARD exposed if they had one or more prescription claims for a biologic DMARD continuously for at least 90 days after the first RA diagnosis, and they were considered bDMARD naive if they had no bDMARD claims at any time after the first RA diagnosis and 365 days before the first RA diagnosis. The non-RA cohort consisted of those who did not have any exposure to bDMARDs or any arthritis diagnosis claims throughout the study period. Patients who were younger than 18 years of age or who had a history of PE were excluded. Cox regression analysis was used to derive the incidence rate ratio (IRR) comparing the 3 study cohorts, adjusting for age, sex, baseline comorbidity score, and oral steroid use.

Results: For each of the 3 cohorts, 25,373 patients were identified. Most patients were female (~70%) and 34 to 65 years of age (~75%). Certain comorbidities (CHF, CV disease, and diabetes) were seen more often in the RA population than in the general population. The IR of PE was 0.38 (95% CI, 0.33-0.44) in bDMARD-treated patients, 0.31 (95% CI, 0.27-0.34) in bDMARD-naive patients, and 0.10 (95% CI, 0.07-0.14) in the general population per 100 person-years. The adjusted IRR of PE for bDMARD-treated patients was 2.3 times that for the general population ($p < 0.0001$; 95% CI, 1.59-3.23) and 1.05 times that for non-bDMARD RA patients ($p = 0.5743$; 95% CI, 0.88-1.25). The adjusted IRR of PE for non-bDMARD RA patients was 2.2 times that for the general population ($p < 0.0001$; 95% CI, 1.53-3.04). Age ($p < 0.0001$, IRR = 1.03; 95% CI, 1.022-1.037), baseline comorbidity score ($p < 0.0001$, IRR = 1.17; 95% CI, 1.13-1.20), and baseline oral steroid use ($p< 0.0001$, IRR = 1.43; 95% CI, 1.20-1.71) were all significantly associated with the risk for PE.

Conclusion: The IR of PE was 2-fold to 3-fold higher in the RA population than in the general population. However, after adjusting for baseline covariates, we did not identify any statistical difference between bDMARD-treated and bDMARD-naive RA patients. Age, steroid use, and comorbidities are important risk factors for PE in RA patients.

Disclosure: R. Rajwanshi, Roche, 1,Roche, 3; **K. Sarsour**, Roche, 1,Roche, 3; **L. Governale**, Roche, 3,Roche, 1; **B. Arnieri**, F. Hoffmann-La Roche, 1,F. Hoffmann-La Roche, 3; **D. Oliveri**, Genentech, 3; **E. Berber**, Roche, 1,Roche, 3.

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Abstract Number: 34

The Impact of Cardiovascular and Lung Disorder Morbidities on Physical Activity in People with Inflammatory Arthritis Compared to the General Population in the UK

Michael Cook[1], Eftychia Bellou[2], Jamie C Sergeant[3], John Bowes[2], Anne Barton[4], Terence W. O'Neill[1] and **Suzanne M.M. Verstappen**[1], [1]Arthritis Research UK Centre for Epidemiology, The University of Manchester, Centre for Musculoskeletal Research, Manchester, United Kingdom, [2]Arthritis Research UK Centre for Genetics and Genomics, The University of Manchester, Centre for Musculoskeletal Research, Manchester, United Kingdom, [3]NIHR Manchester Musculoskeletal Biomedical Research Unit, Central Manchester University Hospitals NHS Foundation Trust, Manchester, United Kingdom, [4]NIHR Manchester Musculoskeletal Biomedical Research Unit, Manchester Academic Health Science Centre, Manchester, United Kingdom

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Background/Purpose: Cardiovascular and lung disorder morbidities are more common in people with inflammatory arthritis (IA) than in the general population. However, little is known about the impact of these morbidities on daily functioning including physical activity. The aim of this study was to investigate the levels of physical activity in people with and without these morbidities.

Methods: This study was conducted in a large population-based study in the UK (UK Biobank), including people aged 40 to 70. Age, gender, and smoking status were recorded at inclusion. Inflammatory arthritis (rheumatoid arthritis (RA), psoriatic arthritis (PsA) and ankylosing spondylitis (AS)) and morbidity data including cardiovascular diseases (heart attack, angina, stroke) and lung disorders (emphysema, bronchitis, and asthma) was identified on the basis of self-report and participants were categorised as follows: no IA and no morbidity (noIA-noM), no IA and morbidity (noIA-M), IA and no morbidity (IA-noM) or IA and morbidity (IA-M). Participants completed the International Physical Activity Questionnaire and were classified as doing "low physical activity (lpa)", "moderate physical activity (mpa)" or "vigorous physical activity (vpa)". Multinominal logistic regression analysis was applied to assess the association between health status group (noIA-noM=base case) and physical activity group (lpa=reference), adjusted for gender, age and smoking, and presented as relative risk ratios (adjRRR, (95%CI)). Adjusted probabilities for each activity level are presented in figure.

Results: This study included 400,261 (81.5%) people with noIA-noM, 83,246 (17.0%) people with noIA-M, 5,800 (1.2%) people with IA-noM, and 1,790 (0.36%) people with IA-M. Percentage female gender was, respectively, 55%, 51%, 63%; and 63% and mean (SD) age ranged from 56 (8) to 59 (7) years. Within each group, the percentage of participants doing lpa, mpa or vpa was, respectively: lpa (24.9%, 29.3%, 34.9%, 42.9%); mpa (38.4%, 36.9%, 35.6%, 32.0%) or vpa (36.7%, 33.8%, 29.5%, 25.1%). The expected risk for people with a cardiovascular/lung disorder morbidity and/or IA doing moderate or vigorous activity was lower than those without these diseases. Furthermore, people with IA, but no morbidity, were less likely to do mpa or vpa than people without IA, but having these morbidities. adjRRRs (95%CI) for noIA-M, IA-noM and IA-M were respectively: for mpa (0.82 (0.80-0.83); 0.66 (0.62-0.71); 0.49 (0.44-0.55)) and even lower for vpa (0.78 (0.77-0.79); 0.59 (0.55-0.63); 0.42 (0.37-0.47)). Adjusted probabilities are shown in figure.

Conclusion: In this large population-based study we observed that people with both IA and morbidities were less active compared to those without morbidities or those with no IA and morbidities. It is therefore important to evaluate morbidities in clinical studies when investigating functional ability.

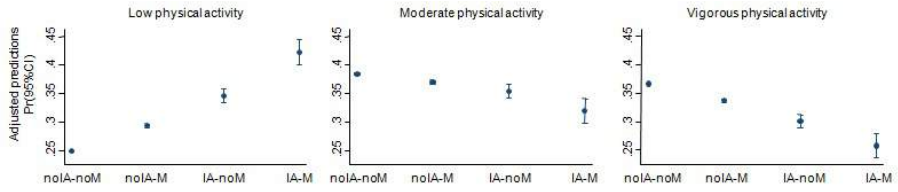

Figure. Adjusted predicted probabilities by physical activity group. Probabilities adjusted for age, gender and smoking status.

Disclosure: M. Cook, None; **E. Bellou**, None; **J. C. Sergeant**, None; **J. Bowes**, None; **A. Barton**, None; **T. W. O'Neill**, None; **S. M. M. Verstappen**, None.

Abstract Number: 35

Rheumatoid Arthritis As a Risk Factor for Cardiovascular Events Following Hospitalized Pneumonia; A Population-Based Cohort Study

Mette Holland-Fischer[1], Ulrik Tarp[2], Reimar W. Thomsen[3] and Mette Nørgaard[3], [1]Department of Rheumatology, Aalborg University Hospital, Aalborg, Denmark, [2]Department of Rheumatology, Aarhus University Hospital, AArhus, Denmark, [3]Department of Clinical Epidemiology, Aarhus University Hospital, Aarhus, Denmark

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Background/Purpose: Cardiovascular disease is a major cause of morbidity and mortality in patients with Rheumatoid Arthritis (RA). Patients with RA do also have an increased risk of infections. Previous studies suggest that recent infection may trigger myocardial infarction and stroke, and this mechanism may be particularly important in patients with underlying low-grade inflammation such as RA. Our objective was to examine whether RA-patients have increased risk of cardiovascular events (CVE) following hospitalized pneumonia compared to patients with pneumonia without RA.

Methods: We conducted this population-based cohort study of adults with a first-time hospitalization with pneumonia between 1997 and 2011 in Northern Denmark. Information on RA, comorbidity, pneumonia and CVE was obtained from medical databases. Comorbidity data included the 19 conditions in the Charlson Index, alcoholism and previous diagnosis of CVE. We defined CVE as stroke or acute myocardial infarction. Data on mortality was ascertained from the Danish Civil Registration System. Cox regression was used to compute Hazard Ratios (HR) for CVE following hospitalization comparing patients with and without RA, controlling for sex, age, level of comorbidity, prior CVE, alcoholism, and antibiotic therapy before admission.

Results: A total of 75,087 patients were hospitalized with pneumonia. Among them 1677 (2.2%) had RA. All-cause mortality after 30 or 90 days did not differ between RA- and non-RA-patients with crude 30- and 90-day MRRs of 0.98

(95% CI: 0.87-1.11) and 0.99 (95% CI: 0.89-1.10) and adjusted MRRs of 0.99 (95% CI: 0.87-1.12) and 0.98 (95% CI: 0.88-1.09), respectively (table 1). A larger proportion of the RA-patients had prior CVE 18.1% (95% CI: 16.3-20.0) vs non-RA-patients 15.3% (95% CI: 15.1-15.6). Overall, we found no substantially higher risk of CVE following pneumonia among RA patients compared with non-RA patients (table 2). However, 8 to 30 days after pneumonia CVE risk tended to be increased in RA patients, with corresponding crude and adjusted HRs for CVE of 1.41 (95%CI: 0.94-2.12) and 1.32 (95%CI: 0.88-1.98) (table 2).

Conclusion: A larger proportion of RA patients with a first time hospitalization with pneumonia had prior CVE compared to pneumonia patients without RA. The risk of new CVE 8 to 30 days after pneumonia admission tended to be increased in RA patients.

Table 1 Characteristics of 75087 patients hospitalized for pneumonia from 1997 to 2011 in Northern Denmark

	Rheumatoid Arthritis	**No Rheumatoid Arthritis**
N	1677 (2.2%)	73410 (97.8%)
Age (years), mean	72.2	69.2
Sex*		
Women	1099 (65.5%)	34306 (46.7%)
Men	578 (34.5%)	39104 (53.3%)
Comorbidity index* (Charlson index score)		
Low (0)	552 (32.9)	30829 (42.0%)
Medium (1-2)	744 (44.4%)	28335 (38.6%)
High (≥3)	381 (22.7%)	14246 (19.4%)
Prior cardiovascular event*	303 (18.1%)	11235 (15.3%)
Systemic antibiotic therapy* before admission	555 (33.1%)	21890 (29.8%)
30-day mortality*	242 (14.4%)	10773 (14.7%)
90-day mortality*	357 (21.3%)	15759 (21.5%)
Crude 30-day MRR	0.98 (CI:0.87-1.11)	
Crude 90-day MRR	0.99 (CI:0.89-1.10)	
Adjusted 30-day MRR	0.99 (CI:0.87-1.12)	
Adjusted 90-day MRR	0.98 (CI:0.88-1.09)	
*Data presented as number of patients and proportion (%)		

Table2 CVE following hospitalized pneumonia				
	RA	**Non-RA**	**Crude HR**	**Adjusted HR^**
N	1677	73410		
Patients with CVE on or 1-7 days after admission with pneumonia	105 (6.3%)*	4917 (6.7%)	1.04 (95%CI:0.86-1.26)	1.01 (95%CI:0.84-1.23)
Patients with CVE 8-30 days after admission with pneumonia	24 (1.4%)*	853 (1.2%)*	1.41 (95%CI:0.94-2.12)	1.32 (95%CI:0.88-1.98)
Patients with CVE 31-90 days after admission with pneumonia	17 (1.0%)*	832 (1.1%)*	1.00 (95% CI:0.62-1.62)	0.94 (95% CI:0.58-1.52)
Patients with CVE 91-180 days after admission with pneumonia	13 (0.8%)*	645 (0.9%)*	0.98 (95% CI:0.57-1.70)	0.92 (95% CI:0.53-1.60)
*Data presented as number of patients and proportion (%) ^ Adjusted for sex, age, level of comorbidity, prior cardiovascular events, alcoholism and antibiotics before admission CVE: cardiovascular event				

Disclosure: M. Holland-Fischer, None; **U. Tarp**, None; **R. W. Thomsen**, None; **M. Nørgaard**, None.

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Abstract Number: 36

The Incidence of Cardiovascular Events in Patients with Rheumatoid Arthritis: a 15 Years Observational Cohort Study

Koen Laan[1], Rabia Agca[1,2], Alexandre E. Voskuyl[3], Maarten Boers[2], Willem Lems[2] and Mike T. Nurmohamed[1,2], [1]Rheumatology, Amsterdam Rheumatology and immunology Center, Reade, Amsterdam, Netherlands, [2]Rheumatology, Amsterdam Rheumatology and immunology Center, VU University medical center, Amsterdam, Netherlands, [3]Rheumatology, Amsterdam Rheumatology and immunology Center, location VU University medical center, Amsterdam, Netherlands

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Background/Purpose: The increased risk for cardiovascular (CV) disease in rheumatoid arthritis (RA) is well established. However, there are relatively few contemporary cohort studies with long term follow up studying this risk.

Methods: The CARRÉ study is an ongoing prospective cohort study investigating cardiovascular morbidity and mortality in 353 patients with longstanding RA. Cardiovascular end points, defined as a verified medical history of coronary, cerebral or peripheral arterial disease, were assessed at baseline, 3, 10 and now 15 years of follow up. Incidence density rates per 100 patient years were calculated and cox regression analyses were performed to investigate the associations between baseline characteristics and incident CV disease.

Results: During 15 years of follow up 99 (28%) individuals developed at least one CV event. The mean follow up time was 9.0 ± 4.1 years with a total time at risk of 3186 patient years. This resulted in an incidence rate of 3.1 per 100 patient-years. Risk factors for developing a CV event were an elevated blood pressure, dyslipidemia and renal dysfunction after adjustment for age, gender, prevalent CVD.

Conclusion: The incidence rate was 3.1 CV events per 100 person years in RA patients approximately double that of the general population (Peters et al. 2009). Further research will include a direct comparison of these patients to a control group representative of the general population to generate hazard ratios of CV events in this study population.

Disclosure: K. Laan, None; **R. Agca**, None; **A. E. Voskuyl**, None; **M. Boers**, None; **W. Lems**, None; **M. T. Nurmohamed**, None.

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Abstract Number: 37

Cardiovascular Disease in Immune-Mediated Inflammatory Diseases: Cross Sectional Analysis of the Influence of Demographic and Traditional Cardiovascular Risk Factors

Luis Rodriguez-Rodriguez[1,2], Pedro P Perrotti[3], Adrià Aterido[3], Jesús Tornero[4], Carlos Ferrandiz[5], Juan D. Cañete[6], Antonio Fernandez-Nebro[7], Javier P Gisbert[8], Eugeni Domènech[9,10], María López-Lasanta[3], Sara Marsal[3], Benjamín Fernández-Gutiérrez[1,11] and IMID Consortium, [1]Instituto de Investigación Sanitaria San Carlos (IdISSC), Madrid, Spain, [2]Department of Rheumatology, Hospital Clinico San Carlos, Madrid, Spain, [3]Rheumatology Research Group, Vall d'Hebron Hospital Research Institute, Barcelona, Spain, [4]Rheumatology Department, Hospital Universitario Guadalajara, Guadalajara, Spain, [5]Dermatology Department, Hospital Universitari Germans Trias i Pujol, Badalona, Spain, [6]Rheumatology, Hospital Clinic and IDIBAPS, Barcelona, Spain, [7]Rheumatology, Hospital Regional Carlos Haya, Biomedical Research Institute of Malaga (IBIMA), Malaga, Spain, [8]Gastroenterology, Hospital Universitario de La Princesa. IIS La Princesa, Madrid, Spain, [9]Gastroenterology & Hepatology Department, Hospital Universitari Germans Trias i Pujol, Badalona, Spain, [10]CIBERehd, Madrid, Spain, [11]Rheumatology, Hospital Clínico San Carlos, Madrid, Spain

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Diseases

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Background/Purpose : Our aim was 1) to analyze the association between demographic and traditional cardiovascular risk factors (CVRF) and cardiovascular disease (CVD) in subjects affected with rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), psoriasis (Ps), psoriatic arthritis (PsA), Crohn's disease (CD), or ulcerative colitis (UC), and 2) to compare the standardized prevalence of CVD among these conditions.

Methods : Subjects included in this cross-sectional study were collected as part of the Immune-Mediated Inflammatory Disease Consortium between 2007-2010. Demographic and clinical data was collected using standardized questionnaires during a clinical interview with close questions and review of medical records. Multivariate logistic regression models adjusted by demographic (gender, age, educational level, elapsed time from IMID diagnosis) and traditional CVRF [dyslidepemia (DL), type 2 diabetes (T2D), obesity (OB), ever smoking] were constructed for each IMID. **Results** for each variable were combined using inverse variance weighted metaanalysis. Standardized prevalence for each IMID, adjusted by demographic and traditional CVRF [per 100 patients, with 95% confidence intervals (CI)] was calculated using marginal analysis.

Results: 9951 patients were included (**Table 1**). **Table 2** shows the association between demographic and traditional CVRF and CVD in each IMID. When results from the 6 cohorts were combined, males, lower educational level, older age and more time elapsed from disease diagnosis, and presence of DL and T2D were independently associated with a higher risk of CVD. SLE exhibited the highest standardized prevalence, followed by RA, Ps, CD, PsA and UC (**Figure 1**).

Conclusion : The contribution to CV risk of demographic and traditional CVRF is different for each IMID. SLE showed the higher standardize prevalence of CVD when compared to other IMIDs.

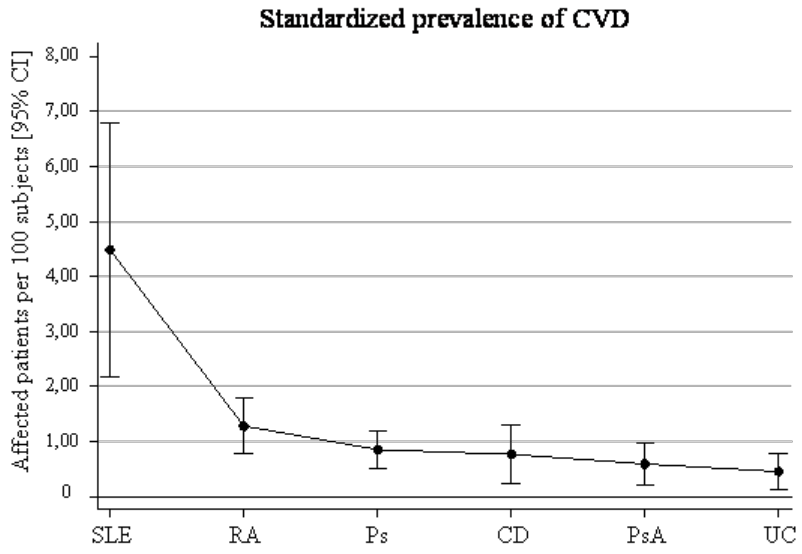
Table 1: Demographic characteristics and prevalence of CVD disease and traditional CV risk factors of the patients included in this study.

	RA (n = 2152)	PsA (n = 1147)	Ps (n = 2497)	SLE (n = 760)	CD (n = 1938)	UC (n = 1457)
Age, (n) X (IQR)	(1996) 61 (52 to 70)	(1113) 52 (41.09 to 63)	(2430) 47 (36 to 59)	(702) 44 (35 to 55)	(1913) 39 (32 to 49)	(1436) 47 (37 to 58.12)
Women, n (%)	1.567 (77.69)	522 (47.28)	1.057 (43.46)	671 (93.19)	956 (49.84)	663 (46.01)
Calendar year at IMID diagnosis, (n) X (IQR)	(2144) 1998 (1991 to 2004)	(1137) 2003 (1996 to 2007)	(2482) 1992 (1980 to 2001)	(678) 1999 (1993 to 2004)	(1314) 1998 (1993 to 2002)	(975) 1998 (1993 to 2002)
Elapsed time from IMID diagnosis to study§, in years , (n) X (IQR)	(2132) 10 (5 to 17)	(1076) 7 (3 to 13)	(2480) 17 (8 to 29)	(675) 10 (6 to 17)	(1313) 10 (6 to 15)	(975) 10 (7 to 16)
Secondary or higher education, n (%)	655 (33.73)	449 (44.46)	1278 (54.20)	378 (54.00)	1187 (62.77)	785 (55.48)
CVD, n (%)	91 (4.23)	24 (2.09)	94 (3.76)	24 (3.16)	14 (0.72)	22 (1.51)
Current/past smoker, n (%)	828 (49.49)	533 (59.55)	1.411 (69.68)	369 (62.02)	1.282 (74.62)	727 (62.08)
Arterial hypertension, n (%)	638 (29.65)	-	476 (19.06)	178 (23.42)	123 (6.35)	148 (10.16)
Dyslipidemia, n (%)	433 (20.12)	157 (13.69)	436 (17.46)	125 (16.45)	68 (3.51)	127 (8.72)
Type 2 diabetes, n (%)	172 (7.99)	92 (8.02)	203 (8.13)	24 (3.16)	28 (1.44)	55 (3.77)
Obesity, n (%)	366 (19.02)	250 (24.56)	612 (25.82)	102 (15.36)	184 (9.97)	198 (14.25)
Number of DMARDs, X [IQR]	2 (1-3)	1 (0-2)	0 (0-0)	2 (1-2)	1 (0-1)	0 (0-1)
Patients with biological drugs, n (%)	914 (42.47)	299 (26.07)	493 (19.74)	47 (6.18)	282 (14.55)	70 (4.80)

Table 2: Multivariate logistic regression models to analyze the influence of demographic and traditional cardiovascular (CV) risk factors in the prevalence of CV disease in each of our 6 cohorts.

	RA		PsA		Ps		SLE		CD		UC	
	OR [95%CI]	p	OR [95%CI]	p	OR [95%CI]	p	OR [95%CI]	p	OR [95%CI]	p	OR [95%CI]	p
Women	0.36 [0.21 - 0.64]	4.30E-04	0.04 [0.01 - 0.35]	3.20E-03	0.27 [0.15 - 0.52]	6.10E-05	0.13 [0.04 - 0.42]	5.50E-04	0.68 [0.18 - 2.50]	0.56	0.02 [0.002 - 0.27]	2.80E-03
Age	1.04 [1.02 - 1.07]	6.50E-04	1.04 [1.00 - 1.09]	0.061	1.08 [1.05 - 1.10]	1.20E-11	1.04 [1.01 - 1.08]	0.014	1.10 [1.05 - 1.15]	1.90E-04	1.05 [0.99 - 1.11]	0.080
Elapsed time from IMID diagnosis to study	1.04 [1.02 - 1.06]	2.10E-04	1.05 [1.00 - 1.1]	0.049	1.02 [1.00 - 1.03]	9.70E-03	1.08 [1.02 - 1.14]	8.80E-03	1.03 [0.97 - 1.10]	0.32	1.00 [0.95 - 1.06]	0.89
Dyslipidemia	2.68 [1.67 - 4.29]	4.30E-05	3.84 [1.32 - 11.13]	0.013	5.00 [3.1 - 8.06]	4.20E-11	1.41 [0.51 - 3.93]	0.51	7.64 [1.46 - 39.99]	0.016	10.75 [3.33 - 34.74]	7.30E-05
Type 2 diabetes	1.74 [0.95 - 3.20]	0.075	5.05 [1.79 - 14.29]	2.30E-03	1.83 [1.07 - 3.13]	0.026	0.91 [0.09 - 9.60]	0.94	1.84 [0.28 - 12.01]	0.52	8.68 [2.13 - 35.3]	2.50E-03
Obesity	1.19 [0.67 - 2.11]	0.55	1.30 [0.43 - 3.92]	0.64	1.42 [0.86 - 2.33]	0.17	1.63 [0.57 - 4.69]	0.36	2.48 [0.45 - 13.71]	0.30	1.13 [0.29 - 4.44]	0.86
Current/past smoker	2.07 [1.07 - 3.98]	0.030	0.67 [0.22 - 2.04]	0.48	1.41 [0.76 - 2.65]	0.28	0.52 [0.19 - 1.44]	0.21	0.48 [0.10 - 2.33]	0.36	0.41 [0.08 - 2.02]	0.28
Secondary or higher education	0.69 [0.39 - 1.22]	0.20	0.64 [0.18 - 2.34]	0.50	0.54 [0.31 - 0.94]	0.030	1.20 [0.44 - 3.26]	0.72	2.16 [0.49 - 9.50]	0.31	0.37 [0.09 - 1.58]	0.18

Figure 1: Standardized prevalence of cardiovascular disease, with 95% confidence intervals, for each IMID.



Disclosure: L. Rodriguez-Rodriguez, None; **P. P. Perrotti**, None; **A. Aterido**, None; **J. Tornero**, None; **C. Ferrandiz**, None; **J. D. Cañete**, None; **A. Fernandez-Nebro**, None; **J. P. Gisbert**, None; **E. Domènech**, None; **M. López-Lasanta**, None; **S. Marsal**, None; **B. Fernández-Gutiérrez**, None.

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Abstract Number: 38

Impact of Obesity on the Disease Course of Rheumatoid Arthritis

Yang (Linda) Liu[1], Gilaad Kaplan[2], Bertus Eksteen[3] and Cheryl Barnabe[1], [1]Cumming School of Medicine, University of Calgary, Calgary, AB, Canada, [2]Division of Gastroenterology, University of Calgary, Calgary, AB, Canada, [3]Division of Hepatology, University of Calgary, Calgary, AB, Canada

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Background/Purpose: Obesity results in a higher risk for the development of rheumatoid arthritis (RA) but is associated with less radiographic damage. The evidence for the effect of obesity on disease outcomes and course has not been synthesized but is important to understand as it may be a modifiable risk factor that impacts RA progression and response to treatment.

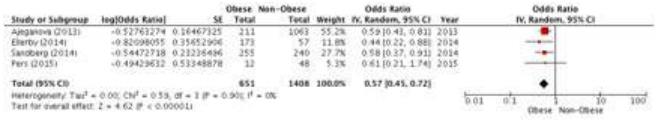
Methods: A Medline search was performed (to May 2015) using 'Obesity' and 'Body Mass Index' as MeSH terms, and with relevant terms and acronyms in the title and abstract search. The results of this search were combined with a strategy to identify rheumatoid arthritis studies. Articles were selected for inclusion if they described composite disease activity measures or states (DAS28, SDAI, CDAI), individual disease activity measures (tender and swollen

joint counts, ESR, CRP, patient global assessment), patient reported outcomes (pain, HAQ, fatigue, quality of life scales), or mortality rates, stratified by body mass index (BMI) category or in relationship to BMI on a continuous scale. Meta-analysis was completed using the generic inverse-variance approach with random effects models based on the most adjusted models presented using RevMan version 5.3.

Results: A total of 1,281 records were screened. After applying inclusion criteria, a total of 24 articles were identified that reported on a disease activity measure of interest, 3 reported on the association with obesity and mortality in RA, and 8 articles described remission by obesity status. Only 6 out of 19 studies reporting on DAS28 found higher DAS28 scores at baseline for obese patients in comparison to normal weight subjects, but 6 out of 8 studies found significantly higher scores in obese subjects during follow-up. Obese patients demonstrated lower odds of achieving remission (pooled OR 0.57, 95%CI 0.45 to 0.72, Figure 1) and sustained remission (pooled OR 0.49, 95%CI 0.32 to 0.74). Of the 12 studies that reported on ESR and CRP, only 3 found an association between BMI and baseline ESR and none found a significant association for CRP. Obese patients had a worse baseline HAQ score in 6 out of 14 studies, worse patient global assessment of health in 5 out of 11 studies, and higher levels of pain in 5 out of 8 studies. Three studies measured the total SF-36 Score, or Physical and Mental Component Scores, with obese patients having worse quality of life. There was not an increased mortality risk for obese patients (n=3 studies).

Conclusion: Obesity decreases the odds of achieving remission in RA, and is associated with increased pain, impaired functional ability, and decreased quality of life. Interventions to reduce BMI should be investigated for the ability to improve disease outcomes.

Figure 1. Meta-Analysis of the Effect of Obesity on Remission in Rheumatoid Arthritis Studies



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Abstract Number: 39

Baseline Obesity and Subsequent Weight Loss Are Independently Associated with Cardiovascular Mortality in Established Rheumatoid Arthritis

Bryant R. England[1], Joshua F. Baker[2], Harlan Sayles[3], Kaleb Michaud[4,5], Liron Caplan[6], Lisa A. Davis[6], Grant W. Cannon[7], Brian Sauer[8], E. Blair Solow[9], Andreas Reimold[10], Gail S. Kerr[11], Pascale Schwab[12] and Ted R. Mikuls[13], [1]Division of Rheumatology, Department of Internal Medicine, University of Nebraska Medical Center, Omaha, NE, [2]Rheumatology, University of Pennsylvania, Philadelphia, PA, [3]University of Nebraska Medical Center, Omaha, NE, [4]Internal Medicine, Division of Rheumatology, University of Nebraska Medical Center, Omaha, NE, [5]National Data Bank for Rheumatic Diseases, Wichita, KS, [6]Div of Rheumatology, Univ of CO Denver School of Med, Aurora, CO, [7]Division of Rheumatology, Salt Lake City VA Medical Center and University of Utah, Salt Lake City, UT, [8]Salt Lake City VA Medical Center and University of Utah, Salt Lake City, UT, [9]Rheumatology, UT Southwestern Medical Center, Dallas, TX, [10]Rheumatology, VAMC, University of Texas Southwestern Medical Center, Dallas, TX, [11]VAMC, Georgetown University, Washington, DC, [12]Div Arth & Rheum Dis, Oregon Health & Sci Univ OP09, Portland, OR,

[13]Medicine, University of Nebraska Medical Center, Omaha, NE
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Background/Purpose: In the general population, higher body mass index (BMI) is associated with cardiovascular (CV) disease. However, an obesity paradox has been observed in rheumatoid arthritis (RA), where lower BMI is associated with adverse outcomes while obesity appears to be protective. This relationship may be confounded by weight-loss among sicker individuals. We sought to comprehensively examine independent associations between baseline BMI and recent weight loss with CV mortality in RA.

Methods: Patients in the Veterans Affairs RA Registry were followed from enrollment until death or December 2013. BMI was obtained from medical records ±14 days of each visit. Enrollment BMI was categorized as underweight (<22 kg/m^2), normal (22-25 kg/m^2), overweight (25-30 kg/m^2) and obese (>30 kg/m^2). An annualized rate of BMI change was determined from the slope of BMI over time from visits in the preceding 13 months (categories: <0, 0-2, 2-3, and >3 kg/m^2 lost/year). Vital status and cause of death were determined through the National Death Index. Associations with CV mortality were examined using multivariable competing-risks regression.

Results: There were 1,652 patients with 99 CV deaths occurring over 5,851 patient-years of follow-up. Patients were predominantly male (91%), had established disease (mean 11.7±11.4 years), and were positive for RF (80%) or anti-CCP antibody (78%). Mean BMI at enrollment was 28.6±5.7 kg/m^2 with 9% underweight, 18% normal, 38% overweight, and 35% obese. Associations with CV mortality are shown in Table 1. In age- and gender-adjusted models (Model A), enrollment BMI category was not associated with CV mortality. In a multivariable model adjusting for comorbid conditions (Model B), an obese BMI at enrollment was associated with greater CV mortality (Hazard ratio [HR] 1.55, 95% confidence interval [CI] 1.05-2.27, P = 0.026). Annualized recent weight loss of more than 3 kg/m^2/year was also independently associated with CV mortality (HR 1.66, 95% CI 1.24-2.22, P = 0.001). Cumulative incidence of CV death by weight loss categories is shown in Figure 1.

Conclusion: Obesity at enrollment and greater rates of weight loss are independently associated with CV mortality in RA. These results suggest that weight loss rather than low body weight per se may drive the observed Òobesity paradoxÓ in RA with regard to CV risk. Preventive strategies for CV mortality in RA should focus on maintaining a normal BMI.

Table 1. Association of Body Mass Index and Weight Loss with Cardiovascular Mortality			
Variables	Model A	Model B	Model C
	N=1652	N=1383	N=1379
Enrollment BMI category			
Underweight	1.45 (0.78-2.70)	1.43 (0.55-3.72)	1.43 (0.54-3.82)
Normal	1.00	1.00	1.00
Overweight	1.24 (0.93-1.66)	1.46 (0.63-3.42)	1.42 (0.62-3.24)
Obese	1.23 (0.78-1.94)	1.55 (1.05-2.27)*	1.47 (1.01-2.12)
Weight loss category			
No loss or gain	-	-	1.00
<2 kg/m^2	-	-	1.02 (0.73-1.44)
2-3 kg/m^2	-	-	1.14 (0.60-2.18)
>3 kg/m^2	-	-	1.66 (1.24-2.22)ǂ

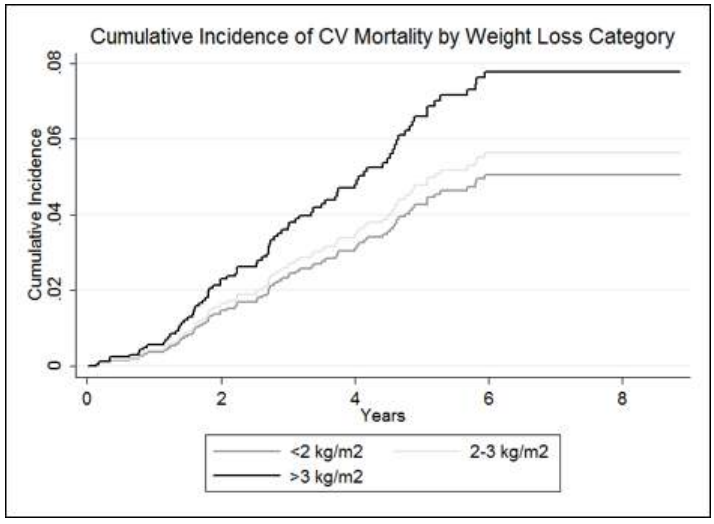
* P = 0.026; P = 0.047; ǂ P = 0.001

Abbreviations: BMI, body mass index.

Model A covariates include age and gender.

Model B & C covariates include age, gender, race, smoking status, Rheumatic Disease Comorbidity Index score, prior myocardial infarction, and prior other cardiovascular disease.

Figure 1. Cumulative Incidence of Cardiovascular Mortality by Weight Loss Category in Rheumatoid Arthritis.



*Weight loss category modeled as time varying variable

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Abstract Number: 40

Increased Mortality in Indigenous North Americans Persons with Rheumatoid Arthritis Is Partially Explained By Psychiatric and Physical Comorbidity: a Population Based Study

Carol Hitchon[1], Sazzadul Khan[2], Brenda Elias[3], Alan Katz[4] and Christine A. Peschken[5], [1]Internal Medicine, University of Manitoba, Winnipeg, MB, Canada, [2]Manitoba Centre for Health Policy and Research, University of Manitoba, Winnipeg, MB, Canada, [3]Community Health Sciences, University of Manitoba, Winnipeg, MB, Canada, [4]Manitoba Centre for Health Policy, University of Manitoba, Winnipeg, MB, Canada, [5]Arthritis Center, University of Manitoba, Winnipeg, MB, Canada

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Background/Purpose: Rheumatoid Arthritis (RA) is associated with excess mortality. Indigenous North Americans (INA) in our region have high RA prevalence rates and young age at onset yet experience disparities in arthritis treatment. We determined if comorbidity and mortality were increased in INA with RA and the factors associated with mortality in RA.

Methods: Using administrative health data from our region (years 2000-2010; population 1.1 million), a previously validated case definition for RA, and the INA identifier from Indian Affairs, we identified cohorts of incident (N=4195) and prevalent (N-8095) RA. Comorbidity was determined using a modified Charlson Comorbidity Index (mCCI) categorized as 0, 1, 2, 3 or more, and the John Hopkins mental and physical Major Adjusted Disease Groups (mADG, pADG). Regional income quintiles were used as a proxy for socioeconomic status. Death, age at death and cause of death were identified in prevalent and incident RA; duration of RA at death was determined in incident RA. Crude all-cause mortality rates were adjusted to age and sex or to age, sex and last visit mCCI. Annual mortality rates between INA and nonINA and persons with or without RA were compared using Student T tests. Cox proportional hazards models evaluated contributors to death in RA controlling for age, sex, ethnic group, income quintile, and comorbidity. Odds Ratio(OR) with 95% confidence limits (CL) are reported.

Results: In spite of a young onset age (INA 42 vs nonINA 55 yr $p<0.001$), INA were more likely to have nonRA comorbidity (mCCI >0) than nonINA at baseline (39% vs 31% OR 1.43 CL 1.25-1.64 $p<0.0001$) but equally likely to have multiple comorbidities at last visit (both 22% OR 0.99 CL 0.84-1.16). More INA than nonINA reported mADG at baseline (27% vs 19% OR 1.59 CL 1.37-1.84) and last visit (26.9% vs 22.8% OR 1.29 CL 1.12-1.49). pADG rates were similar at baseline (39% vs 42% OR 0.9 CL 0.79-1.02) and last visit (49% vs 52% OR 0.9 CL 0.79-1.02). Between 2000-2010 1068 prevalent RA patients died (96 (9%) INA; 972 (14%) nonINA including 301 incident RA (23 (4%) INA; 278 (8%) nonINA). Prevalent RA INA were much younger at death than nonINA (56 (CL 54-59)vs 77 (CL 76-77) years; $p<0.0001$), a trend seen for males and females each year even after adjusting for mCCI. Cause of death was similar for INA and nonINA with a trend to less cancer deaths and more “other” deaths in INA. Age and sex (and mCCI) adjusted mortality rates decreased in the general population yet increased for persons with RA. Age, sex

and mCCI adjusted annual mortality rates were higher in INA than nonINA with RA. In cox proportional hazards models, increasing comorbidity, both pADG (1.64 (1.29-2.08)) and mADG (1.56 (1.19-2.04)), older age, female sex and lower income predicted death, but INA ethnicity did not.

Conclusion: Persons with RA, in particular INA, have increased mortality partly explained by increasing mental and physical comorbidity. The high rate of comorbidity at an early age and young age at death in INA RA is striking. The independent influence of mental comorbidity on mortality suggests a complex social-biologic phenomenon of particular relevance to INA given their unique social stressors that needs to be addressed as an early step to improving outcomes for this vulnerable population.

Disclosure: C. Hitchon, Health Sciences Centre Foundation, 2; **S. Khan**, None; **B. Elias**, None; **A. Katz**, None; **C. A. Peschken**, None.

Abstract Number: 41

Trends in Non-Cardiovascular Mortality in Patients with Incident Rheumatoid Arthritis: Is There Room for Improvement?

Elena Myasoedova[1], Cynthia S. Crowson[2], Eric L. Matteson[3], John M. Davis III[4] and Sherine E. Gabriel[5], [1]Internal Medicine and Rheumatology, Mayo Clinic, Rochester, MN, [2]Health Sciences Research, Mayo Clinic, Rochester, MN, [3]Rheumatology, Mayo Clinic, Rochester, MN, [4]Division of Rheumatology, Mayo Clinic, Rochester, MN, [5]Rutgers Robert Wood Johnson Medical School, New Brunswick, NJ

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Background/Purpose: Rheumatoid arthritis (RA) is associated with increased all-cause and cause-specific mortality, including mortality from cardiovascular (CV) disease, respiratory causes, infections and malignancy. Evidence of improved overall mortality in RA is growing and decrease in CV mortality has been suggested in some studies including our own. Recent trends in non-CV mortality are not well understood. We aimed to assess trends in non-CV mortality including mortality from respiratory disease, neoplasms and other causes in patients with incident RA in 2000-2007 compared to the previous decades.

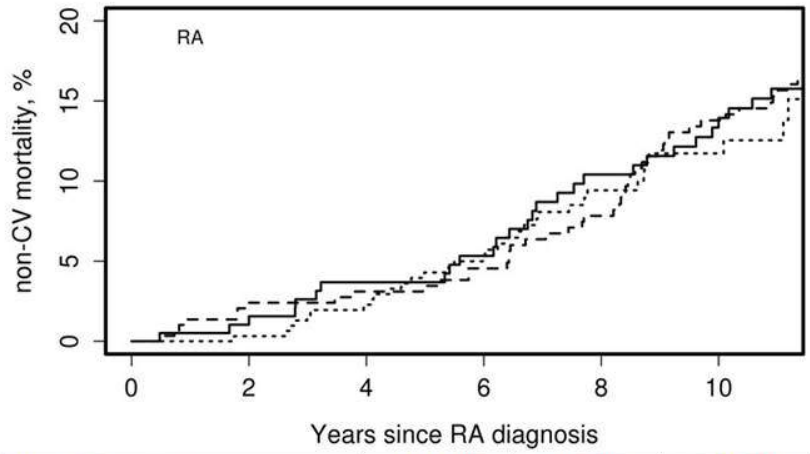
Methods: The study population comprised a retrospectively identified population-based incidence cohort of patients with RA (age>18 years, 1987 ACR criteria met in 1980-2007). All subjects were followed until death, migration, or 1/1/2014. Underlying causes of death were obtained from state and local death certificates as well as the National Death Index Plus and grouped according to ICD-9 and ICD-10 chapters. Kaplan-Meier methods were used to estimate mortality rates. Cox proportional hazards models, adjusting for age and sex, were used to compare cause-specific mortality by decade.

Results: The study included a total of 813 RA patients (mean age 55.9 years; 68% female; 66% rheumatoid factor [RF] positive). Figure shows non-CV mortality by decade of RA incidence and the table summarizes these data. In patients

with incident RA during the 2000–2007 period, there was no statistically significant difference in 10-year mortality from non-CV causes overall (hazard ratio [HR] 0.92; 95% Confidence Interval [CI] 0.60 – 1.42; p=0.71), including mortality from respiratory disease (HR 1.51; 95% CI 0.56 – 4.09; p=0.42), neoplasms (HR 0.69; 95% CI 0.36 – 1.31; p=0.25) and other causes (HR 0.84; 95% CI 0.38 – 1.86; p=0.66) compared to those with RA incidence in 1990–1999.

Conclusion: Our findings suggest that there has been no significant improvement in mortality from non-CV causes overall among patients with incident RA in 2000-2007 compared to patients with incident RA in the previous decades. However, the trends in individual non-CV causes including respiratory disease, neoplasms and other causes may be heterogeneous and require caution in interpretation due to limited statistical power in our study. Lack of improvement in non-CV mortality in RA may be contributing to the persistent excess in relative mortality in RA vs non-RA subjects, suggesting a need for improved control of non-CV comorbidities in RA. More studies are needed to understand the underlying reasons for this lack of improvement in mortality from non-CV causes in RA patients.

Figure. Mortality from Non-Cardiovascular (non-CV) causes in patients with Rheumatoid Arthritis (RA) with incidence date in 1980-89 (solid line) 1990-99 (dashed line), 2000-07 (dotted line).



Year of RA incidence	1980-1989	1990-1999	2000-2007
Number of patients	202	296	315
Mean follow-up, years	17.6	14.5	8.6
Non-cardiovascular deaths	77	79	33
- Respiratory	10	11	8
- Neoplasms	26	37	14
- Other causes	41	31	11
10-year non-cardiovascular mortality, %	13.9±2.6	13.8±2.1	11.7±2.1
- 10-year respiratory mortality, %	1.7±1.0	2.3±0.9	3.3±1.2
- 10-year neoplasm mortality, %	7.0±1.9	8.3±1.7	5.3±1.4
- 10-year other cause mortality, %	5.9±1.8	3.8±1.2	3.3±1.3

Disclosure: E. Myasoedova, None; **C. S. Crowson**, None; **E. L. Matteson**, None; **J. M. Davis III**, None; **S. E. Gabriel**, None.

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Abstract Number: 42

Does the Risk of Mortality in Patients with RA Change over Time or Disease Duration?

Kaleb Michaud[1,2], Sofia Pedro[2], Bryant R. England[3] and Frederick Wolfe[2], [1]Internal Medicine, University of Nebraska Medical Center, Omaha, NE, [2]National Data Bank for Rheumatic Diseases, Wichita, KS, [3]Division of Rheumatology, Department of Internal Medicine, University of Nebraska Medical Center, Omaha, NE

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SESSION INFORMATION

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Session Title: Epidemiology and Public Health Poster I: Comorbidities and Outcomes of Systemic Inflammatory Diseases

Session Type: ACR Poster Session A

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Background/Purpose: Observational studies have shown an increased risk of mortality in patients with RA, though none have done so with patients from all 50 US states nor is it clear how this risk may vary over time. We examined this risk since 1998 by calendar year, duration of RA, and treatment.

Methods: RA and non-inflammatory rheumatic disease (NIRD) patients were studied from 1998 through 2011 in the National Data Bank for Rheumatic Diseases (NDB), a longitudinal observational study following patients from all regions of the US through biannual questionnaires. Patients were required to have at least 2 observations or 1 observation and died before 2012; those recruited through FDA-mandated safety registries were excluded. Mortality was confirmed through National Death Index-matched death records. We calculated standardized mortality rate ratios (SMRRs) of RA vs. NIRD based on age-, race- and sex-stratified US population data (CDC.gov). Cox regression models with time varying covariates were used to investigate the risk of mortality among diagnoses.

Results: Among 15,791 RA patients, 3,531 patients died (22.4%). The mean (median) time in the study was 5.0 (4.0) years with a total of 79,841 patient-years of follow-up. For the 4,058 NIRD patients, 947 patients died (23.3%) with a mean (median) time in the study of 5.0 (3.9) years with a total of 20,500 patient-years of follow-up. The overall SMRR for RA vs. NIRD patients was 1.48 (95% CI 1.38-1.78). For RA duration ≤5 years, the SMRR was 1.35 (1.20-1.52). For earlier calendar cut-offs, the SMRR was 1.56 (1.38-1.63) for before 2008 and 1.74 (1.42-2.15) for before 2004. Adjusted for age, age^2 and sex, the hazard ratio (HR) for RA vs. NIRD was 1.40 (1.30-1.50). Adjusting for additional confounders such as HAQ, pain, patient global, employment, marital status, BMI, and smoking, resulted in an HR of 1.27 (1.17-1.38). Worse disease activity markers, higher comorbidity index, and smoking were all associated with an increased risk of mortality, as opposed to higher education, being employed, and married. When analyzing RA patients only, hierarchical DMARD/biologic treatments showed only cytotoxic DMARD use being associated with an increased risk compared to monotherapy MTX (Table).

Conclusion: In this large US cohort, the risk of mortality for RA patients remained elevated compared to NIRD patients. We found trends that the SMRRs decreased over the last 14 years, yet unlike other US studies, we found no associated mortality benefit of biologics over MTX monotherapy after adjusting for multiple confounders.

Table. Cox regression model for mortality in RA patients

	HR	[95% Conf.	Interval]	P-value
DMARDs				
Monotherapy MTX	referent			
None	1.09	0.99	1.21	0.08
Non-cytotoxic DMARDs	1.00	0.90	1.12	0.95
Cytotoxic DMARDs	1.25	1.10	1.42	<0.01
TNF biologics	1.01	0.90	1.13	0.90
Non-TNF biologics	1.12	0.81	1.55	0.49
Patient Activity Scale (PAS) (0-1)	1.13	1.11	1.15	<0.01
BMI				
Normal (18.5-26.5kg/m^2)	referent			
Underweight (<18.5 kg/m^2)	2.10	1.76	2.41	<0.01
Overweight (>26.5 kg/m^2)	0.84	0.78	0.91	<0.01
Rheumatic Disease Comorbidity Index	1.14	1.11	1.16	<0.01
Smoking status				
Never smoked	referent			
Current	1.55	1.38	1.75	<0.01
Past	1.22	1.12	1.32	<0.01

*Also adjusted for age, age^2, sex, and race

Disclosure: K. Michaud, None; **S. Pedro**, None; **B. R. England**, None; **F. Wolfe**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/does-the-risk-of-mortality-in-patients-with-ra-change-over-time-or-disease-duration

Abstract Number: 43

Prevalence and Relevance of Depressive Symptoms in Patients with Rheumatic Diseases

Stefan Kleinert[1,2], Almuth Marx[3], Hermann Faller[4], Martin Feuchtenberger[5], Christian Kneitz[6], Stefanie Lehmann[3], Hans Peter Tony[7], Christiane Angermann[3,8], Georg Ertl[8], Stefan Störk[3] and Margret Breunig[3,9], [1]Rheumatologische Schwerpunktpraxis Erlangen, Erlangen, Germany, [2]University Hospital Würzburg, Würzburg, Germany,

[3]Comprehensive Heart Failure Center, University of Würzburg, Würzburg, Germany, [4]Abteilung für Medizinische Psychologie und Psychotherapie, University of Würzburg, Würzburg, Germany, [5]Rheumatologie/Klinische Immunologie, Kreiskliniken Altötting-Burghausen, Burghausen, Germany, [6]Internal Medicine II, Hospital Südstadt, Rostock, Germany, [7]Rheumatology / Clinical Immunology, University Hospital Würzburg, Würzburg, Germany, [8]Dept. of Internal Medicine / Cardiology, University Hospital Würzburg, Würzburg, Germany, [9]Dept. of Internal Medicine / Cardiology, University Hospital Würzburg, Würzburg, Wuerzburg, Germany
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Background/Purpose:

Patients with rheumatic diseases (RD) have an increased mortality risk compared to the normal population. The current prospective follow-up study investigated the prevalence of depressive symptoms and quality of life and their impact on prognosis.

Methods:

764 consecutive patients attending the rheumatology outpatient department of the University Hospital Würzburg underwent a comprehensive cardiovascular (CV) risk assessment. Quality of life and depressive symptoms were investigated by SF-36 and PHQ-9 (range 0-27 score points), respectively. A PHQ score >14 points is considered indicative for severe depressive symptoms. Patients were followed over 5 years for incident CV events and death of any cause.

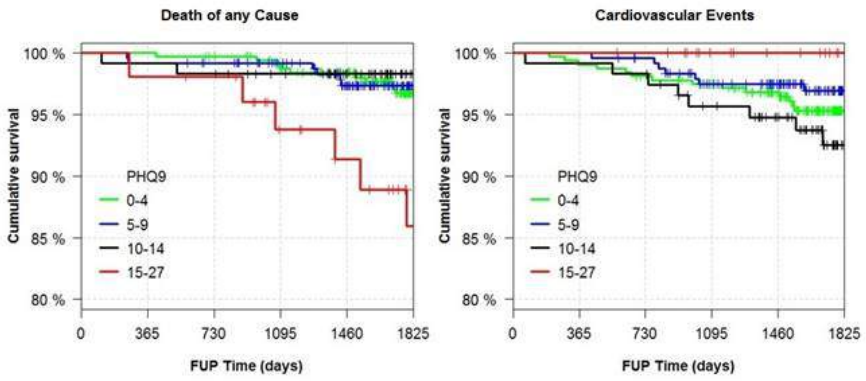
Results:

352 subjects suffered from rheumatoid arthritis (RA: 79.5% female, 64.9% RF positive, mean age 54.3 (SD 14.3)), 260 from systemic autoimmune disease including connective tissue disease and vasculitis (SAI: 76.9 % female, mean age 51.4 (SD 14.5)), and 152 patients had spondyloarthritides including psoriatic arthritis (SpA: 35.5 % female, mean age 44.7 (SD 12.3)).

Severe depressive symptoms were prevalent in 7% (tab 1) of patients. There were no significant differences in the three groups regarding PHQ-9 subgroups (χ^2-Test: p=0.214).

n (%)	PHQ9			
	0-4 (minimal)	5-9 (mild)	10-14 (moderate)	15-27 (severe)
RA	154 (46.1)	110 (32.9)	48 (14.4)	22 (6.6)
SAI	109 (44.3)	85 (34.6)	35 (14.2)	17 (6.9)
SpA	54 (36.7)	47 (32)	34 (23.1)	12 (8.2)
total	317 (43.6)	242 (33.3)	117 (16.1)	51 (7.0)

Within 5 years, 18/10/0 patients died in the 3 groups (RA/SAI/SpA). Patients with severe depressive symptoms had a hazard ratio (HR) of 5.11 (95% CI 2.01–12.97) for death of any cause compared to the patients with less severe depressive symptoms. By contrast, the risk of CV events in the severe depressive group was similar compared with the other groups (p=0.73).



IMG1: Kaplan-Meier plot: Survival and CV events in PHQ-9 groups.

The 4 physical sections of SF-36 revealed an influence on the risk of death: HR for low tertile 3.95 (95% CI 1.67–9.31) if compared versus mid and high tertile combined. The 4 non-physical sections did confer prognostic information.

Conclusion:

RD patients with severe depressive symptoms as assessed by PHQ-9 exhibit an increased mortality risk, but not an increased risk for CV events.

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Abstract Number: 44

The Prevalence of Depression and Anxiety in a Cross-Section of Rheumatological Conditions

Faith Matcham[1], Nicola J. Gullick[2], Matthew Hotopf[3], Sam Norton[4], Sophia Steer[5] and James Galloway[6], [1]Psychological Medicine Clinical Academic Group, King's College London, London, United Kingdom, [2]Rheumatology, Department of Rheumatology, King`s College Hospital NHS Foundation Trust, London, United Kingdom, [3]Department of Psychological Medicine, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, United Kingdom, [4]Institute of Psychiatry, King's College London, London, United Kingdom, [5]Rheumatology Dept, Kings College Hospital, London, United Kingdom, [6]Academic Department of Rheumatology, King´s College London, London, United Kingdom

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Background/Purpose:

Depression and anxiety have detrimental effects on quality-of-life, treatment response and disease outcomes. Whilst psychological morbidity has been described in individual rheumatic diseases, less is known about the comparative burden across the spectrum of rheumatic conditions. The prevalence of depression and anxiety in the general population is 3.8% and 5% respectively. We sought to quantify major depressive disorder (MDD), suicidal ideation, and generalised anxiety disorder (GAD), in a cross-section of rheumatology outpatients.

Methods:

All data were collected using electronic records from an inner city hospital in London, UK. MDD/GAD were identified using the Patient Health Questionnaire (PHQ9) and Generalised Anxiety Disorder questionnaire (GAD7) respectively. Suicidal ideation was identified using PHQ9 item 9: having "thoughts that you would be better off dead or of hurting yourself in some way".

Results:

Between February 2013 and February 2015, 1281 patients with a confirmed diagnosis were screened (mean age 53.6 (SD15.8); 24.6% male). Overall, 29.7% of patients reported significant psychological morbidity: 21.9% screened positive for MDD; 6% of patients reported suicidal ideation. GAD was found in 23.1% of patients; 10% reported severe anxiety symptoms (GAD7≥15). Depression correlated with increased pain (rho = 0.46, $p<0.001$) and fatigue (rho = 0.44, $p<0.001$). Anxiety correlated with increased pain (rho = 0.38, $p<0.001$) and fatigue (rho = 0.33, $p<0.001$). MDD was most prevalent in early inflammatory arthritis (EIA) (29.7%), and least prevalent in patients with vasculitis (17.5%). Fewer AxSpa reported severe MDD (8%), whilst the highest levels were reported in CTD (10.9%), EIA (10.8%) and PsA (10.8%). Severe anxiety was not significantly different across the diseases however GAD was substantially more prevalent in EIA (35.1%). Patients with PsA reported the most suicidal ideation (10%).

Conclusion:

Psychological comorbidity is highly prevalent across rheumatic diseases. The slightly higher levels of MDD and GAD in EIA may relate to the recent diagnosis, reflecting a period of adjustment to chronic illness and lifestyle and medication changes. The high prevalence of suicidal ideation in PsA may reflect the impact of visible cutaneous disease upon self-esteem and mood. Reporting suicidal ideation within the PHQ9 can imply anything from a fleeting thought of suicide, to a detailed plan. There is a need for greater awareness of mental health comorbidities in patients attending rheumatology clinics. These findings help delineate the magnitude of the problem and inform departments of the likely level of provision that will be needed. Integrating mental health services into musculoskeletal clinics offers a unique opportunity to improve clinical care, and based upon the burden of disease in our population, this approach is justifiable.

	Total	AxSpa	CTD	EIA	PsA	RA	Vasculitis	P values
Total, N (%)	1281	52 (3.6)	221 (17.3)	38 (3.0)	133 (10.4)	622 (48.6)	63 (5.40)	
Male Gender, N(%)	293 (24.6)	15 (30.6)	35 (12.6)	7 (18.4)	56 (46.3)	109 (19.8)	17 (26.6)	p<0.0001
Age , M (SD)	53.6 (15.8)	47.1 (12.6)	47.9 (13.8)	44.7 (14.4)	51.2 (13.1)	58.7 (15.4)	60.5 (17.7)	p<0.0001
Fatigue, M (SD)	50.5 (26.1)	50.7 (24.9)	50.6 (25.8)	52.8 (25.1)	53.0 (24.1)	50.5 (26.4)	45.2 (26.5)	p=0.67
Pain, M (SD)	43.8 (28.6)	45.7 (27.2)	36.4 (28.7)	48.3 (30.8)	47.3 (27.0)	46.7 (27.9)	38.4 (28.6)	p<0.01
Current Smoker N(%)^	149 (15.3)	5 (10.9)	29 (11.5)	6 (16.2)	11 (10.8)	75 (18.3)	8 (14.9)	p=0.15
MDD or GAD N(%)	358 (29.7)	14 (28.0)	78 (30.5)	17 (46.0)	45 (34.9)	162 (27.7)	13 (23.2)	p=0.12
Depression, N (%)								
Probable MDD	265 (21.9)	9 (18.0)	60 (23.3)	11 (29.7)	27 (20.8)	128 (21.8)	10 (17.5)	p=0.86
Severe Depression (PHQ9 20-27)	111 (9.2)	4 (8.0)	28 (10.9)	4 (10.8)	14 (10.8)	49 (8.3)	5 (8.8)	p=0.71
Moderate Depression (PHQ9 15-19)	101 (8.3)	4 (8.0)	24 (9.3)	6 (16.2)	6 (4.6)	52 (8.8)	2 (3.5)	
Mild Depression (PHQ9 <15)	53 (4.4)	1 (2.0)	8 (3.1)	1 (2.7)	7 (5.4)	27 (4.6)	3 (5.3)	
Suicidal Ideation	74 (6.1)	2 (4.0)	12 (4.7)	2 (5.4)	13 (10.0)	35 (6.0)	4 (7.0)	0.42
Anxiety, N (%)								
Probable GAD	278 (23.1)	12 (24.0)	63 (24.6)	13 (35.1)	37 (28.7)	121 (20.7)	11 (19.6)	p<0.001
High Anxiety (GAD7>14)	121 (10.0)	4 (8.0)	34 (13.3)	4 (10.8)	13 (10.1)	49 (8.4)	8 (14.3)	p=0.30
Psychological Multi-morbidity, N (%)								
MDD & GAD	183 (15.2)	7 (14.0)	44 (17.2)	7 (18.9)	19 (14.7)	86 (14.7)	8 (14.3)	p=0.93

AxSpa Axial Spondyloarthropathy. CTD Connective Tissue Disease. EIA Early Inflammatory Arthritis. RA Rheumatoid Arthritis. MDD Major Depressive Disorder. GAD Generalised Anxiety Disorder. ^N=903.

Disclosure: F. Matcham, None; **N. J. Gullick**, None; **M. Hotopf**, None; **S. Norton**, None; **S. Steer**, None; **J. Galloway**, None.

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Abstract Number: 45

Contributions of Social Determinants of Health on Probability of Remission in Early and Established Rheumatoid Arthritis Patients

Kangping Cui[1,2], Claire Bombardier[3,4,5], George A. Tomlinson[6,7,8] and the OBRI Investigators, [1]Toronto General Hospital Research Institute - University Health Network, Toronto, ON, Canada, [2]Faculty of Medicine, University of Toronto, Toronto, ON, Canada, [3]Division of Rheumatology and Institute of Health Policy, Management, and Evaluation, University of Toronto, Toronto, ON, Canada, [4]Toronto General Hospital Research Institute, University Health Network, Toronto, ON, Canada, [5]Division of Rheumatology, Mount Sinai Hospital, Toronto, ON, Canada, [6]Institute for Health Policy, Management and Evaluation, University of Toronto, Toronto, ON, Canada, [7]Medicine, Mount Sinai

Hospital, Toronto, ON, Canada, [8]Medicine, University Health Network, Toronto, ON, Canada
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Session Time: 9:00AM-11:00AM

Background/Purpose:

Treatment responses and outcomes vary among rheumatoid arthritis (RA) patients. There is limited evidence on the contribution of social determinants of health (SDH) to remission in RA. This study aimed to determine the contribution of socioeconomic, environmental, and behavioral factors to remission in RA patients.

Methods:

Data were collected from the Ontario Best-practices Research Initiative (OBRI) Rheumatoid Arthritis Registry, a Canadian clinical registry of early and established RA patients followed in routine care. Remission at the 6-month follow-up visit was measured by three ways, based on disease activity measures DAS28 (Disease Activity Score-28), SDAI (Simple Disease Activity Index) and CDAI (Clinical Disease Activity Index). The SDH variables assessed include age, sex, socioeconomic status, health behaviors, social support, living condition, and psychosocial factors. The association between these variables and remission was evaluated by logistic regression analyses, controlling for clinical factors such as RA duration, RA medications, baseline disease activity and functional disability. Subgroup analyses were performed on early RA, with disease duration ≤1year, and established RA patients respectively. All statistical analyses were performed in SAS9.4.

Results:

Out of the 2305 patients at cohort entry, 1291 reached the 6-month follow-up visit, at which time, 26.9% achieved CDAI remission, 40% achieved DAS28 remission, and 41% achieved SDAI remission. Among the 406 early RA patients, alcohol consumption was independently associated with CDAI (OR 1.76 95%CI 1.01-3.05), SDAI (OR 1.79 95%CI 1.01-3.17), and DAS28 remission (OR 1.77 95%CI 1.06-2.93), while depression was negatively associated with SDAI (OR 0.23 95%CI 0.08-0.65) and DAS28 remission (OR0.34 95%CI 0.15-0.80), after adjusting for confounders (Table 1). Such findings were not observed in established RA patients with >1 year of RA or in all patients (early and established RA) combined. With the exception of education in the early RA group (Table 1), none of the socioeconomic factors was significantly associated with remission.

Conclusion:

In early RA, remission at 6 months into cohort entry was positively associated with alcohol consumption and negatively associated with depression. Previous studies have found a protective effect of alcohol against developing RA[1]. This study shows in addition a protective effect of alcohol on RA remission. This highlights the potential role of health behaviors in achieving positive treatment outcomes.

1. Scott IC, Tan R, Stahl D, Steer S, Lewis CM, Cope AP. The protective effect of alcohol on developing rheumatoid arthritis: a systematic review and meta-analysis. *Rheumatology (Oxford)*. 2013;52(5):856-867.

Table 1. Summary of social determinants of health factors associated with remission at the 6-month follow-up.

		Social Determinants of Health Factors Associated with Remission[§]				
	Outcome measures	Age	Alcohol Consumption	Smoking	Depression	Higher Education
Early RA patients' (RA duration ≤1yr)	CDAI Remission		+			
	SDAI Remission		+		–	+
	DAS28 Remission		+	–	–	
Established RA patients' (RA duration >1yr)	CDAI Remission					
	SDAI Remission	–				
	DAS28 Remission	–		+		

[§] In the multivariable analysis, variables with a $p<0.2$ in univariate analyses were included for adjustments. Factors tested in the univariate analyses include SDH factors (sex, employment status, neighborhood income, private insurance status, marital status, urban/rural residency, and the frequency of interruption to social interaction due to RA) and clinical factors (RA medication type, baseline disease activity, and baseline functional disability status).
[†] $p<0.05$ for variables with a '+' or '-' sign. A '+' sign represents a positive association with remission. A '-' sign represents a negative association with remission.

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View Abstract and Citation Information Online - http://acrabstracts.org/abstract/contributions-of-social-determinants-of-health-on-probability-of-remission-in-early-and-established-rheumatoid-arthritis-patients

Abstract Number: 46

Feasibility Study of Smartphone Data Collection for Cloudy with a Chance of Pain: Sustained Engagement for Daily Self-Reporting of Disease Severity in Rheumatoid Arthritis over Two Months

Samuel Reade[1], Jamie C Sergeant[2,3], Matthew Sperrin[4], David M. Schultz[5], Karen Spencer[6], Caroline Sanders[6] and William G Dixon[7], [1]The University of Manchester, Manchester, United Kingdom, [2]NIHR Manchester Musculoskeletal Biomedical Research Unit, Manchester, United Kingdom, [3]Arthritis Research UK Centre for Epidemiology, Centre for Musculoskeletal Research, Manchester Academic Health Science Centre, University of Manchester, Manchester, United Kingdom, [4]Institute of Population Health, Health e-Research Centre, The University of Manchester, Manchester, United Kingdom, [5]Faculty of Engineering and Physical Sciences, School of Earth, Atmospheric and Environmental Sciences, The University of Manchester, Manchester, United Kingdom, [6]Institute of Population Health, Centre for Primary Care, The University of Manchester, Manchester, United Kingdom, [7]Manchester Academic Health Sciences Centre, Arthritis Research UK Centre for Epidemiology, The University of Manchester, Manchester, United Kingdom
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Background/Purpose: Previous research has attempted to study the association between weather and joint pain. Inconclusive results may be due, in part, to infrequent measures of pain and poor quality weather data. Patients' own smartphones present an opportunity for frequent data collection with parallel usage of global positioning satellite (GPS) technology to pull local weather data. This pilot study aimed to assess the feasibility and acceptability of symptom and weather data collection using a smartphone application (app).

Methods: Twenty adult patients with rheumatoid arthritis were recruited from a single rheumatology centre. The app was co-designed with 14 participants in conjunction with a pre-existing platform by uMotif. Patients were asked to report six symptom scores every evening (pain, morning stiffness, tiredness on waking, fatigue, wellbeing and overall disease severity) on a 1–5 scale for the past 24 hours, for 60 consecutive days. In addition, they reported four other factors (mood, physical activity, time spent outside and perceived influence of the weather). All ten scores were collected on a single screen using a visual 'motif' (figure). GPS data was collected hourly and weather data was pulled from the closest Met Office weather station. Weather variables were summarised for each patient-day.

Ongoing engagement was measured as: the number of study withdrawals; mean completion rate (mean proportion of days with at least one score out of time in study); and the proportion of eligible patients who completed 0–1, 2–4 or 5–7 entries per week. The completeness of weather data was measured as the proportion of days any weather data was collected.

Results: 5 male and 15 female patients were recruited (mean age 54.7). Dropout rate was 30%, (weeks 0, 1, 4, 4, 5 and 6) and reasons given were personal, technical and health issues. At the time of reporting, full eight week follow-up data were available for 11/14 patients. Mean completion rate was 73%. Patients reported scores ≥ 5 days per week 64% of the time and 86% of the time patients reported scores ≥ 2 times per week. Weather data were available for 80% of symptom reports.

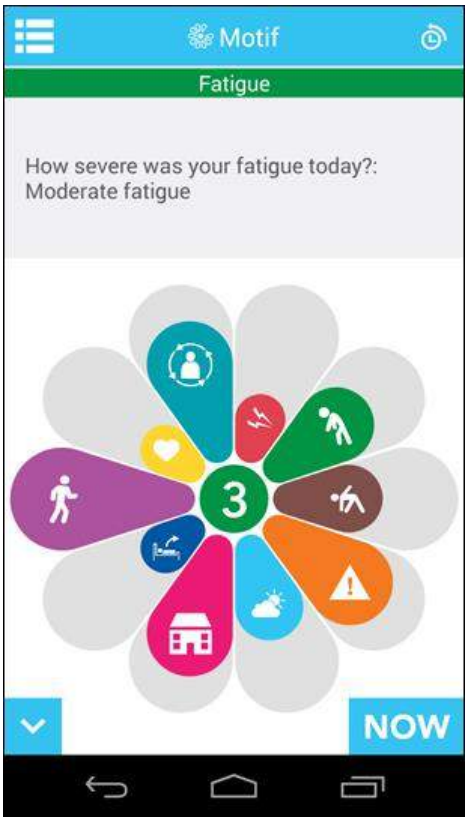
Conclusion: Patient engagement with the app was high. Although six patients withdrew from the study, the remainder regularly reported symptoms over a two-month period.Weather data were successfully extracted from GPS data. This pilot study is proof of concept that this novel mode of data collection can be used for research and will inform a future larger study. Concurrent qualitative work will assess reasons for dropout and motivators for ongoing engagement.

Table Proportion of patients with regular data entry, by week

Week number	Number of patients in study	Number of participants entering data (percentage) 0–1 times per week	2–4 times per week	5–7 times per week
1	19	0 (0%)	4 (21%)	15 (79%)
2	18	1 (6%)	3 (17%)	14 (78%)
3	18	3 (17%)	4 (22%)	11 (61%)
4	18	4 (22%)	3 (17%)	11 (61%)
5	16	3 (19%)	4 (25%)	9 (56%)
6	14	4 (29%)	4 (29%)	6 (43%)
7	12*	2 (17%)	3 (25%)	7 (58%)
8	11*	1 (9%)	2 (18%)	8 (73%)

** Shows incomplete follow-up for two and three patients respectively*

Figure uMotif app



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Abstract Number: 47

Use of Social Media Data for Comparative Effectiveness and Safety Research: An Example from Rheumatoid Arthritis

Jeffrey R. Curtis[1,2], James Willig[3], Monica Safford[1], Joseph Coe[4], Kaitlin O'Hara[5] and Rosee Sa'adon[6], [1]University of Alabama at Birmingham, Birmingham, AL, [2]Rheumatology & Immunology, University of Alabama-Birmingham, Birmingham, AL, [3]Med - Infectious Diseases, University of Alabama at Birmingham, Birmingham, AL, [4]Creaky Joints/Global Healthy Living Foundatio, Upper Nyack, NY, [5]Treato Ltd., Princeton, NJ, [6]Treato, Ltd., Or-Yehuda, Israel

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Background/Purpose:

The data sources available to answer comparative effectiveness and safety questions shortly after medication licensure may be limited. Social media may provide a unique resource to complement traditional data sources.

Methods:

We used the TREATO platform to crawl all publically-available social media data including Facebook, blogs, and discussion boards for posts mentioning inflammatory arthritis (e.g. rheumatoid, psoriatic arthritis). Safety events were self-reported by patients and mapped to medical ontologies, resolving synonyms. Disease and symptom-related treatment indications (e.g. arthritis, joint pain) were manually redacted and excluded. The unit of analysis was unique terms in posts. The focus of the analysis was more recently licensed US drugs (tofacitinib,tocilizumab).

Pre-specified conditions were selected based upon safety signals from clinical trials and reported as pairwise odds ratios (ORs); RA drugs were compared with Fisher's exact test. Empirically-identified events were analyzed using disproportionality analysis [similar to methods used to analyze FDA AERS data], and reported as relative reporting ratios (RRRs) and proportional reporting ratios (PRRs).

Results:

As of 6/2015, there were 549,939 arthritis-related posts discussing tofacitinib (n=543), etanercept (n=17,173), adalimumab (n=12,418), abatacept (n=2,776), and tocilizumab (n=821). Posts were predominantly U.S. (75%) and had patient authors (86%). The most common sources were Facebook, Arthritis Foundation, RemedySpot, Dailystrength, ArthritisCare and RA Warrior. The age distribution was <19(17%), 19-29(22%), 30-39(20%), 40-49(17%), 50-54(18%), and 65+ (6%). Common tofacitinib themes are shown as a word cloud (Figure).

For herpes zoster posts (n=888), ORs were significantly increased for tofacitinib compared to other RA therapies (Table); ORs for certolizumab-associated shingles mentions were higher as well (not shown). ORs for mentions of perforated bowel (n=11) were higher for tocilizumab vs. other therapies.

RRRs and PRRs associated with tofacitinib were highest for conditions related to baldness and hair regrowth, infections and cancer. Ongoing work is evaluating the clinical validity of the cases based upon available narratives and refining the analysis to restrict to confirmed cases.

Conclusion:

Social media is a challenging yet promising data source that may be used to complement traditional approaches for comparative effectiveness research for new medications shortly after licensure.

Table: Pairwise relative risks for posts mentioning herpes zoster and perforated bowel associated with RA-related medications in social media data sources

Outcome	Contrast	Relative Risk
Herpes Zoster	Tofacitinib vs. etanercept	2.88 (1.15 – 7.20)
	Tofacitinib vs. adalimumab	2.70 (1.07-6.79)
	Tofacitinib vs. infliximab	3.88 (1.47-10.23)
	Tofacitinib vs. methotrexate	3.24 (1.32-7.95)
	Certolizumab vs. etanercept	5.04 (3.02 – 8.41)
	Certolizumab vs. adalimumab	4.71 (2.78-7.98)
	Certolizumab vs. infliximab	6.77 (3.69-12.40)
	Certolizumab vs. golimumab	5.28 (1.56-17.82)
Perforated Bowel	Tocilizumab vs. infliximab	27.26 (5.29-140.37)
	Tocilizumab vs abatacept	18.73 (2.19-160.19)
	Tocilizumab vs. methotrexate	55.21 (16.00 – 190.42)
	Tocilizumab vs. adalimumab	26.95 (6.45-112.62)

Figure: Word cloud associated with tofacitinib discussions

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Abstract Number: 48

Polypharmacy Is a Predictor of Hospitalisation in Patients with Rheumatoid Arthritis

Maria Filkova[1], Joao Carvalho[1], Sam Norton[2], David L. Scott[1], Tim Mant[3], Andrew P. Cope[1], Mariam Molokhia[4] and James Galloway[1], [1]Academic Department of Rheumatology, King´s College London, London, United Kingdom, [2]Department of Psychological Medicine, King´s College London, London, United Kingdom, [3]Quintiles Drug Research

Unit at Guy's Hospital, London, London, United Kingdom, [4]Division of Health and Social Care Research, King´s College London, London, United Kingdom

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Background/Purpose: Multimorbidity is a major problem in rheumatoid arthritis (RA) but is difficult to measure. Polypharmacy (PP) - co-prescribing an individual multiple medications – is considered a surrogate marker for the burden of multimorbidity. We evaluated the inter-relationships between PP, disease characteristics and acute hospital admissions in a retrospective cohort study of RA patients managed at one large UK specialist centre.

Methods: Routinely captured data were retrospectively analysed. All patients under care at the centre in May 2013 with a diagnosis of RA were included. Information on PP was extracted from the electronic record. Cox proportional hazards were used compare hospitalization risk according to levels of PP over the subsequent 18-months. Follow up was censored at date of first admission or study end, whichever came first. Further analysis explored relationships between DMARD prescribing and hospitalisation risk. All acute admissions were manually reviewed by two independent clinicians and adjudicated to determine whether an adverse drug reaction (ADR) or drug interaction was implicated.

Results: 1,101 RA patients were studied; their baseline features are shown in the table. The mean number of medications was 5, 29% of patients were on 6-9 medications and 11% on ≥10 medications. PP correlated with increasing age, longer disease duration, higher disease activity and disability (Table). In total 173 patients had at least one unplanned admission during follow up (overall incidence 11/100 patient years (95% CI 9 to 13). Patients on ≥10 medications had an age and gender adjusted hazard ratio for hospitalisation of 3.1 (95% CI 2.1 to 4.5) compared to those on <6. Different DMARD prescription strategies were not significantly associated with hospitalisation risk; steroid use associated with a doubling in risk 2.3 (95% CI 1.6 to 3.1). The most common reason for hospitalisation was infection 44/173 (28%), which was not significantly different across PP strata (p= 0.242). In half of all admissions, an ADR was a possible contributing factor. However, only 4 admissions were definitely a direct result of an ADR. Of these, 2 were related to over anticoagulation, 1 in the setting of co-prescription of leflunomide with warfarin.

Conclusion: PP is prevalent in RA patients and correlates to more severe disease as well as a higher rate of hospitalisation. What is unclear is whether or not PP is harmful. Review of the individual hospitalisations revealed very few admissions definitely attributable to an adverse drug reaction. However, there were many possible relationships (e.g. in cases of infection in patients on DMARDs), making a true understanding of the causal relationship between PP and hospitalisation unclear. Irrespective, PP does appear to reflect comorbidity well and represents a useful tool to adjust for confounding in epidemiologic analyses.

Table

Baseline characteristic	All patients	0-5 medications	6-9 medications	≥10 medications	p value*
Number of subjects, n	1101	658	320	123	
Age	61.34 (16.00)	57.6 (16.3)	66.6 (14)	67.7 (13.3)	0.0001
Gender (% female)	78.8	76.8	83.1	78.1	0.07
DAS28 mean (SD)	3.65 (1.61)	3.33 (1.60)	4.06 (1.56)	4.24 (1.38)	0.0001
HAQ (SD)	1.35 (0.93)	1.02 (0.90)	1.66 (0.81)	2.04 (0.74)	0.0001
Disease duration (SD)	10.42 (9.93)	9.15 (8.66)	11.93 (10.68)	13.45 (12.92)	0.0002
DMARD prescribing strategy (%)					
Mono	45	49	42	32	0.001
Dual	26	24	29	27	0.19
Triple	8	7	8	12	0.09
Biologic	22	17	33	19	<0.000
Hospitalisation data					
Exposure (person-years)	1599	983	469	147	
Events, n	173	75	50	48	
Incidence /100 years (95% CI)		7.6 (6.1, 9.6)	10.7 (8.1, 14.1)	32.6 (24.6, 43.2)	
Unadjusted HR (95% CI)		Ref	1.4 (1.0, 2.0)	4.2 (2.9, 6.0)	
Adjusted HR (95% CI)		Ref	1.0 (0.7, 1.5)	3.1 (2.1, 4.5)	

Analysis of causal relationship between medication and admission				
Was an ADR responsible for the admission n (%)	**Definitely** 4 (2.3)	**Probably** 8 (4.6)	**Possibly** 74 (42.8)	**Unlikely** 87 (50.3)
If and ADR was implicated, was an RA drug involved, n (% of ADRs)	2 (50)	4 (50)	39 (52.7)	N/A
Corticosteroid involved, n	0	0	8	N/A
Any DMARD involved, n	2	3	26	N/A
Biologic involved, n	0	3	9	N/A
Was a major drug-drug interaction present on the admission medication, n	2	3	6	N/A
Were any minor drug-drug interactions present on the	1	5	57	N/A

admission
medication, n
**p value for significance across medication strata using either Kruskal Wallis or Chi2 (for dichotomous variables) tests*

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Abstract Number: 49

Dose Relationship Between Oral Glucocorticoids and TNF Inhibitors and the Risk of Hospitalized Infectious Events Among Patients with Rheumatoid Arthritis

Neil Accortt[1], Jennifer Schenfeld[2] and Mona Trivedi[3], [1]Amgen, Inc., Thousand Oaks, CA, [2]Docs Global, Inc, North Wales, PA, [3]Rheumatology, Amgen, Thousand Oaks, CA

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Background/Purpose: Patients with rheumatoid arthritis (RA) are at an increased risk for serious hospitalized infectious events (HIEs). Research suggests that tumor necrosis factor alpha inhibitors (TNFi), as well as oral glucocorticoids (GCs) both increase the risk of HIEs. Limited information is available regarding the contribution toward HIEs when taking into account the dose-level of oral glucocorticoids when used concomitantly among new users of TNFi.

Methods: We conducted a retrospective cohort study using an administrative claims database. Among incident and prevalent adult RA patients newly exposed to TNFi, patients were assigned to 3 fluid study cohorts: no GC exposure; low-dose GC (≤ 7.5 mg); high-dose GC (>7.5 mg). Patients were required to have at least 1 inpatient or outpatient diagnostic claim for RA (ICD-9-CM 714.0) with an accompanying claim for an incident TNFi and at least 6 months of continuous enrollment prior to TNFi initiation and 6 months after. Patients could be considered exposed to GCs multiple times during follow-up-time and may contribute time to different categories of exposure. Follow-up continued until disenrollment, HIE, discontinuation of TNFi, end of study (June 30, 2014), or 2 years after the index-date. The primary outcome was incident HIE and was attributed to the GC exposure category at the time of the outcome. Incidence rates and 95% confidence intervals per 100 person years were estimated for HIEs.

Results: The mean age and sex distribution (% of female) of RA-TNFi patients for the no GC, low-dose GC, and high-dose GC were 53.7 and 77%, 55.1 and 76%, and 55.1 and 74%. The risk of HIEs increased with increasing GC dose, with a higher incremental risk from high dose to low dose than from low dose to no dose (Table). The risk of HIEs is highest among patients ages >65 years of age but the elevated dose-related effects are comparable for those <65 and those > 65.

Conclusion: We found that both high dose and low dose steroids significantly increase the risk of HIEs. Although steroid doses under 7.5 mg are often considered to be relatively low risk for infection, physicians should bear in mind

that even low dose steroids significantly increase the risk of HIEs among patients newly initiating TNFi therapy.

Table. Incidence Rates of Hospitalized Infectious Events Among RA-TNFi¥ Patients

	Glucocorticoid Cohorts		
	None	**Low^**	**High***
		All Patients	
Total patients (n)	39,895	18,294	11,685
Number of HIE Cases	988	341	243
Total Patient-Time (yrs)	24664.84	4771.37	1302.88
IR per 100 pyrs	4.01	7.15	18.65
(95% CI)	(3.77, 4.26)	(6.45, 7.92)	(16.65, 20.89)
Rate Ratio	Ref.	1.78	4.66
(95% CI)		(1.58 , 2.02)	(4.05, 5.36)
		Ages < 65	
Total patients (n)	34,031	15,185	9,599
Number of HIE Cases	682	196	165
Total Patient-Time (yrs)	20881.49	3703.65	1052.94
IR per 100 pyrs	3.27	5.29	15.67
(95% CI)	(3.03, 3.51)	(4.60, 6.05)	(13.57, 17.96)
Rate Ratio	Ref.	1.62	4.79
(95% CI)		(1.38 , 1.89)	(4.05, 5.69)
		Ages ≥ 65	
Total patients (n)	6,103	3,293	2,170
Number of HIE Cases	306	145	78
Total Patient-Time (yrs)	3783.35	1067.72	249.94
IR per 100 pyrs	8.09	13.58	31.21
(95% CI)	(7.25, 8.99)	(11.62, 15.73)	(25.69, 37.15)
Rate Ratio	Ref.	1.68	3.86
(95% CI)		(1.38, 2.05)	(3.00, 4.95)

¥: etanercept, adalimumab, infliximab, golimumab, certolizumab pegol

^: ≤7.5 mg of a prednisone equivalent oral glucocorticoid

*: >7.5 mg of a prednisone equivalent oral glucocorticoid

Disclosure: N. Accortt, Amgen, 1,Amgen, 1; **J. Schenfeld**, Amgen, 3; **M. Trivedi**, Amgen, 1,Amgen, 3.

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Abstract Number: 50

Characteristics and Outcomes Associated with Early Corticosteroid Use in a Large Multicenter Canadian RA Cohort

Kathleen Andersen[1], Daming Lin[2], Susan J. Bartlett[3,4], Gilles Boire[5], Boulos Haraoui[6], Carol Hitchon[7], Shahin Jamal[8], Edward C. Keystone[9], Janet E. Pope[10], Diane Tin[11], J Carter Thorne[12], VP Bykerk[13,14] and CATCH Investigators, [1]Hospital for Special Surgery, New York, NY, [2]Rheumatology, Mount Sinai Hospital, University of Toronto, Toronto, ON, Canada, [3]Division of Rheumatology, Johns Hopkins School of Medicine, Baltimore, MD, [4]Medicine , Divisions of Clinical Epidemiology, Rheumatology, Respirology, McGill University, Montreal, QC, Canada, [5]Department of Medicine/Division of Rheumatology, Université de Sherbrooke, Sherbrooke, QC, Canada, [6]Institut de Rhumatologie, Montreal, QC, Canada, [7]Department of Rheumatology, University of Manitoba, Winnipeg, MB, Canada, [8]Vancouver Coastal Health, Vancouver, BC, Canada, [9]Mount Sinai Hospital, University of Toronto, Toronto, ON, Canada, [10]University of Western Ontario, London, ON, Canada, [11]The Arthritis Program, Southlake Regional Health Centre, Newmarket, ON, Canada, [12]University of Toronto, Toronto, ON, Canada, [13]Rheumatology, Hospital for Special Surgery, New York, NY, [14]Medicine, Mount Sinai Hospital/University of Toronto, Toronto, ON, Canada

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Background/Purpose: Synthetic glucocorticoids (steroids) are commonly used in RA to rapidly inhibit pro-inflammatory cytokines. They are frequently used as "bridge therapy", quickly dampening down the immune response allowing slower-acting DMARDs time to effectively reduce disease activity. Early steroid use is variable. The purpose of this study was to compare characteristics and outcomes over time of patients exposed to early steroid use in a large early RA cohort.

Methods: Data are from the first 18 months of patients entering and followed in CATCH (Canadian early ArThritis CoHort). Inclusion criteria were symptoms ≤12-months, fulfillment of ACR 1987 and/or 2010 RA criteria and steroid use was recorded. Patients were stratified based on steroid use within first 3 months of study entry. Sociodemographic and RA characteristics between groups at baseline and selected outcomes (CDAI, DAS28, MD global, RAPID III and biologic starts) at 3, 6, 12, and 18 months were compared using t-test. Outcomes for patients receiving no, intra-articular/intra-muscular (IA/IM) only, oral only (PO), or both forms of steroids were evaluated at each time point.

Results: At baseline, patients who received steroids were older and less likely to be employed but not statistically different by race, weight, or SES. Steroid users had shorter symptom duration, higher acute phase reactants, and reported more pain and fatigue (Table 1). Both patient-reported outcomes (PROs: patient global, HAQ, RAPID III, RADAI pain and VR12) as well as clinically reported observations (CLINROs: MD global, joint counts, and DAS28) were significantly worse in those who received steroids. Steroid use was more frequent in participants enrolled at large study sites (>100 enrolled) and in those concomitantly taking MTX. Composite measures are worse over time in patients receiving both forms of steroids at months 3-12, and there is a trend toward more biologic use thereafter (Table 2).

Conclusion : Patients receiving steroids within the first 3 months tend to be older, with shorter disease duration and higher indicators of disease activity. These data suggest steroids are being used to intensify treatment in patients with

poor prognostic factors to control more active disease. Despite early use of both parenteral and oral steroids, biologic use in the long term is still required in patients with more active disease at baseline.

Table 1: Characteristics of participants by steroid use in first three months.

	None	IA/IM only	Oral only	Oral + IA/IM	Sig
N	*697*	*436*	*392*	*164*	
Sociodemographics					
Age (yrs)	**51.9 (14.1)**	**52.9 (15.6)**	**56.4 (15.5)**	**56.1 (14.1)**	**<0.0001**
Female sex	**528 (76%)**	**335 (77%)**	**281 (72%)**	**106 (65%)**	**0.01**
BMI (kg/m^2)	28.0 (6.5)	28.2 (6.4)	28.3 (5.8)	29.2 (5.3)	0.492
Caucasian, n (%)	563 (81%)	349 (80%)	324 (83%)	139 (85%)	0.464
Living alone, n (%)	103 (15%)	58 (13%)	62 (16%)	19 (12%)	0.542
Employed, n (%)	**415 (60%)**	**242 (56%)**	**194 (49%)**	**73 (45%)**	**<0.0001**
Education <= HS	288 (43%)	189 (45%)	165 (44%)	84 (53%)	0.19
Income >$50,000/year	229 (47%)	125 (39%)	98 (43%)	39 (37%)	0.076
Currently Smoking	117 (17%)	76 (17%)	68 (17%)	25 (15%)	0.934
Co-morbidities	524 (76%)	332 (76%)	308 (79%)	127 (78%)	0.637
Comorbidities	2.0 (2.0)	2.1 (2.1)	2.2 (2.0)	2.3 (2.1)	0.254
Site enrolled > 100	**413 (59%)**	**383 (88%)**	**233 (59%)**	**149 (91%)**	**<0.0001**
Clinical					
Symptom duration (mo)	**6.8 (4.1)**	**5.4 (3.0)**	**5.5 (3.3)**	**5.4 (3.6)**	**<0.0001**
Tender Joints (28)	**7.6 (5.9)**	**9.7 (6.7)**	**9.5 (7.2)**	**9.7 (7.2)**	**<0.0001**
Swollen Joints (28)	**6.7 (5.4)**	**9.1 (6.2)**	**7.8 (6.3)**	**8.9 (6.5)**	**<0.0001**
Morning stiffness ≥60 min	**433 (63%)**	**237 (54%)**	**265 (68%)**	**106 (65%)**	**<0.0001**
Patient Global (0-100 mm)	**53.6 (29.1)**	**66.7 (25.8)**	**57.3 (29.6)**	**64.6 (29.8)**	**<0.0001**
MD Global (0-100 mm)	**45.4 (24.7)**	**54.8 (23.0)**	**50.6 (24.4)**	**52.9 (25.2)**	**<0.0001**
Pain (0-10 cm)	**5.0 (2.8)**	**6.5 (2.6)**	**5.5 (2.8)**	**6.1 (2.8)**	**<0.0001**
Fatigue (0-10 cm)	**4.5 (2.9)**	**6.0 (2.9)**	**5.5 (3.0)**	**6.1 (2.9)**	**<0.0001**
CDAI*	**24.1 (13.1)**	**30.9 (13.6)**	**28.1 (15.2)**	**30.2 (15.3)**	**<0.0001**
DAS28**	**4.8 (1.4)**	**5.4 (1.3)**	**5.2 (1.5)**	**5.5 (1.4)**	**<0.0001**
HAQ-DI (0-3)	**0.8 (0.6)**	**1.2 (0.7)**	**1.1 (0.7)**	**1.3 (0.8)**	**<0.0001**
RAPID3 (0-10)	**4.3 (2.3)**	**5.6 (2.2)**	**4.9 (2.4)**	**5.5 (2.5)**	**<0.0001**
RADAI Joint Area (0-48)	**11.0 (8.0)**	**15.3 (9.7)**	**13.3 (9.7)**	**15.6 (9.6)**	**<0.0001**
Erosions	148 (21%)	107 (25%)	80 (20%)	34 (21%)	0.466
ESR (mm/h)	**24.7 (19.9)**	**28.4 (21.8)**	**29.7 (25.1)**	**35.8 (28.5)**	**<0.0001**
CRP (mg/dl)	**11.5 (15.7)**	**15.5 (19.0)**	**16.5 (18.2)**	**22.6 (24.8)**	**<0.0001**
RF+	**410 (65%)**	**270 (67%)**	**195 (56%)**	**96 (64%)**	**0.006**
Anti-CCP+	**323 (63%)**	**172 (61%)**	**147 (52%)**	**68 (58%)**	**0.018**
MTX baseline	**462 (66%)**	**301 (69%)**	**290 (74%)**	**136 (83%)**	**<0.0001**
MTX dose 0 months	**19.6 (4.1)**	**20.4 (4.3)**	**18.7 (4.4)**	**19.1 (4.2)**	**<0.0001**
MTX 3 months	**496 (71%)**	**328 (75%)**	**312 (80%)**	**137 (84%)**	**0.001**
MTX dose 3 months	**20.4 (4.0)**	**21.2 (4.1)**	**19.8 (4.4)**	**20.9 (3.6)**	**0<0.0001**
Biologics (0 or 3 months)	34 (5%)	18 (4%)	18 (5%)	11 (7%)	0.618

*CDAI n=X, N=Y, N=Z, respectively; DAS n=X, N=Y, N=Z

Table 2: Change in selected outcomes over time.

	Month				
	0	**3**	**6**	**12**	**18**
CDAI (n)	*1631*	*1513*	*1321*	*1398*	*1122*
None	**24.1 (13.1)***	13.6 (11.6)	10.0 (10.0)	7.9 (8.7)	7.5 (9.2)
Oral	28.1 (15.2)	14.6 (12.4)	11.8 (11.0)	8.9 (9.6)	8.8 (9.8)
IA	30.9 (13.6)	13.9 (11.0)	12.4 (11.8)	9.5 (10.1)	8.8 (10.1)
Both	30.2 (15.3)	**17.7 (14.0)***	**14.4 (13.4)***	**11.8 (11.8)***	9.7 (9.5)
DAS28 (n)	*1532*	*1279*	*1147*	*1209*	*973*
None	**4.8 (1.4)***	3.5 (1.4)	**3.0 (1.4)***	2.8 (1.3)	2.7 (1.4)
Oral	5.2 (1.5)	3.6 (1.5)	3.3 (1.5)	3.0 (1.4)	3.0 (1.5)
IA	5.4 (1.3)	3.6 (1.4)	3.4 (1.5)	3.0 (1.5)	2.9 (1.4)
Both	5.5 (1.4)	**4.2 (1.6)***	**3.7 (1.5)***	**3.3 (1.5)***	3.1 (1.4)
RAPID3 (n)	*1662*	*1563*	*1370*	*1453*	*1190*
None	**4.3 (2.3)***	**2.7 (2.1)***	**2.3 (2.1)***	**2.1 (2.0)***	2.1 (2.0)
Oral	**4.9 (2.4)***	3.1 (2.3)	2.9 (2.2)	2.6 (2.2)	2.8 (2.4)
IA	5.6 (2.2)	3.1 (2.2)	2.8 (2.3)	2.6 (2.2)	2.5 (2.3)
Both	5.5 (2.5)	**3.8 (2.4)***	**3.5 (2.4)***	**3.1 (2.4)***	3.1 (2.4)
MD Global (n)	*1603*	*1485*	*1325*	*1410*	*1114*
None	**45.4 (24.7)***	25.3 (22.5)	**17.4 (19.4)***	14.9 (19.3)	13.3 (18.8)
Oral	50.6 (24.4)	27.7 (24.1)	22.6 (22.9)	15.3 (19.6)	14.3 (19.7)
IA	54.8 (23.0)	25.8 (21.8)	21.4 (21.8)	15.2 (19.5)	14.6 (19.4)
Both	52.9 (25.2)	30.8 (25.4)	24.2 (23.2)	17.2 (20.9)	14.3 (19.4)
Biologics (n)	*1689*	*1689*	*1689*	*1689*	*1689*
None	23 (3%)	34 (5%)	46 (7%)	61 (9%)	72 (10%)
Oral	9 (2%)	17 (4%)	35 (9%)	53 (14%)	59 (15%)
IA	6 (1%)	18 (4%)	28 (6%)	54 (12%)	62 (14%)
Both	5 (3%)	10 (6%)	27 (16%)	40 (24%)	35 (21%)

*Statistically different from any other group based on Duncan multiple comparison ($p<0.05$)

Disclosure: K. Andersen, None; **D. Lin**, None; **S. J. Bartlett**, PCORI, 2,NIH, 9; **G. Boire**, None; **B. Haraoui**, Abbott, Amgen, BMS, Janssen, Pfizer, Roche and UCB Pharma, 2,Abbott, Amgen, BMS, Janssen, Pfizer, Roche and UCB Pharma, 5,Abbott, Amgen, BMS, Janssen, Pfizer, Roche and UCB Pharma, 8; **C. Hitchon**, Health Sciences Centre Foundation, 2; **S. Jamal**, None; **E. C. Keystone**, Janssen Inc., 2,Abbott/AbbVie, 5,Amgen, 2,Bristol-Myers Squibb, 5,Janssen Inc., 5,Hoffmann-La Roche, Inc., 5,Janssen Inc., 2,Janssen Inc., 5,Merck Pharmaceuticals, 5,Merck Pharmaceuticals, 5,Pfizer Pharmaceuticals, 5,Pfizer Pharmaceuticals, 5; **J. E. Pope**, None; **D. Tin**, None; **J. C. Thorne**, Amgen, Canada, 5; **V. Bykerk**, None.

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Abstract Number: 51

Oral Glucocorticoid Use Is Associated with Osteonecrosis in Adults with Chronic Inflammatory Diseases but Not in Children: A Population-Based Cohort Study

Daniel B. Horton[1,2,3], Kevin Haynes[1,4], Michelle R. Denburg[1,5], Mihir Thacker[6], Carlos D. Rose[2], Mary E. Putt[1], Mary B. Leonard[7] and Brian L. Strom[1,3], [1]Biostatistics and Epidemiology, Center for Clinical Epidemiology and Biostatistics, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, [2]Pediatrics, Nemours A.I. duPont Hospital for Children, Division of Pediatric Rheumatology, Thomas Jefferson University, Wilmington, DE, [3]Rutgers Biomedical and Health Sciences, New Brunswick, NJ, [4]Clinical Epidemiology, HealthCore, Wilmington, DE, [5]Pediatrics, Children's Hospital of Philadelphia, Division of Nephrology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, [6]Orthopedics, Nemours A.I. duPont Hospital for Children, Thomas Jefferson University, Wilmington, DE, [7]Pediatrics, Division of Nephrology, Stanford School of Medicine, Stanford University, Palo Alto, CA

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Background/Purpose: Glucocorticoids have long been linked to the development of osteonecrosis, mostly in heavily exposed patients from specialty clinics. We tested the hypothesis that oral glucocorticoids were associated with osteonecrosis in a dose-dependent relationship in people with chronic inflammatory diseases and modified by age and inflammatory disease.

Methods: We performed a retrospective cohort study using The Health Improvement Network, a population-representative medical records database from the United Kingdom. The study population included people at least 2 years old diagnosed with asthma; inflammatory bowel disease (IBD); juvenile, psoriatic, or rheumatoid arthritis; psoriasis; or systemic lupus. Those with prevalent glucocorticoid use, prior osteonecrosis, malignancy, or other high-risk diseases were excluded. Prednisone-equivalent dose was classified in tertiles by age. The association between time-varying oral glucocorticoid exposure and incident osteonecrosis was estimated using discrete time failure models and expressed as an adjusted hazard ratio (aHR). Hypothesis testing was 1-sided, since glucocorticoids were unlikely to decrease the rate of osteonecrosis.

Results: There were 428 cases of osteonecrosis among 920,321 eligible subjects. After adjusting for age, sex, inflammatory disease, history of fracture, and number of drugs prescribed, any glucocorticoid exposure was most strongly associated with osteonecrosis among adults ages 18-49 (aHR 2.0, 90% CI 1.4, 2.8, P<0.001)(Table). A dose response with cumulative glucocorticoid exposure was seen in adults (high vs. low dose, ages 18-49: aHR 3.2, 90% CI 1.6, 6.3, P=0.003; ages 50 and older: aHR 1.6, 90% CI 1.0, 2.6, P=0.048). Models examining maximum dose, dose intensity (integrating dose and duration), and weight-based dosing were similar. No significant association was seen for children in any model. Low-dose glucocorticoid exposures, corresponding to average doses <7.5 mg daily prednisone equivalents and maximum doses <30 mg daily in adults, were not associated with osteonecrosis at any age. Arthritis, IBD, and systemic lupus were independent risk factors (Table), but disease did not modify the effects of glucocorticoid dose on osteonecrosis.

Conclusion: High dose glucocorticoids are associated with osteonecrosis in adults, most strongly in those ages 18-49, but not in children. Underlying disease is an important risk factor but does not magnify the effect of glucocorticoid dose on osteonecrosis risk.

Table. Primary multivariable analysis of oral glucocorticoid exposure and osteonecrosis, stratified by age						
Variables	**Exposed** **Unexposed**	**Outcomes (N)**	**Unadj. hazard ratio**	**Adjusted hazard ratio[a]**	**CI[b]**	**P value[c]**
Glucocorticoid exposure						
Ages 2-17 years	55,230 179,298	25 103	1.1	0.9	0.6, 1.4	0.384
Ages 18-49 years	109,388 338,829	43 80	2.3	2.0	1.4, 2.8	<0.001
Ages 50 years and older	98,419 144,157	76 101	1.6	1.2	0.9, 1.5	0.153
Chronic inflammatory disease [d]						
Asthma (reference)	212,939 501,635	92 192	-	-	-	-
Psoriasis	15,681 85,051	7 33	0.9	1.2	0.9, 1.7	0.274
Juvenile, psoriatic, or rheumatoid arthritis	16,917 40,075	22 43	2.6	2.8	2.1, 3.8	<0.001
Inflammatory bowel disease	15,739 27,173	20 12	1.8	2.1	1.4, 3.1	<0.001
Systemic lupus erythematosus	1,761 3,350	3 4	3.2	3.7	1.7, 7.9	<0.001
Other model variables						
Prior fracture	51,384 110,625	40 65	1.7	1.8	1.5, 2.3	<0.001
Other autoimmune disease[e]	9,846 9,308	12 13	3.2	2.0	1.3, 3.1	0.001
Number of drugs prescribed	-	-	1.13	1.11	1.08, 1.15	<0.001

[a] Models adjusted for all variables shown and the interaction between sex and age.

[b] 90% confidence interval is shown for the association between oral glucocorticoid exposure and osteonecrosis. All other variables are shown with a 95% confidence interval.

[c] One-sided P values are shown for the association between oral

glucocorticoid exposure and osteonecrosis. All other P values are two-sided.

[d] Individuals with two or more chronic inflammatory diseases of inclusion were categorized as having the latter disease as listed here.

[e] Autoimmune diseases include connective tissue diseases other than systemic lupus (e.g., Sjšgren syndrome, systemic sclerosis), gout, and vasculitis.

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Abstract Number: 52

Validity of Simplified Ankylosing Spondylitis Disease Activity Scores (SASDAS) in Indian As Patients

Nagma Bansal[1], Lalit Duggal[2], Neeraj Jain[2], Amit Dua[3] and Appu Patil[1], [1]Department of Rheumatology and Clinical Immunology, Sir Ganga Ram Hospital, DNB trainee, New Delhi, India, [2]Department of Rheumatology and Clinical Immunology, Sir Ganga Ram Hospital, Consultant, New Delhi, India, [3]Department of Rheumatology and Clinical Immunology, Sir Ganga Ram Hospital, Fellow, New Delhi, India

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Background/Purpose:

Ankylosing Spondylitis Disease Activity Score (ASDAS) is a complex score for monitoring disease activity and ASDAS calculator is required for estimation. This study aimed to develop a simplified version which may be useful in AS patients in India.

Methods:

Consenting AS patients (modified New York and/or Assessment in Ankylosing Spondylitis 2009 criteria) were recruited between Jan 2012 and Dec 2014; n=254. Sociodemographic data and disease characteristics (Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Bath Ankylosing Spondylitis Functional Index (BASFI), and Ankylosing Spondylitis Quality of Life (ASQoL), erythrocyte sedimentation rate (ESR) by Westergren's method, and C-reactive protein (CRP)by nephelometry were collected. Simplified ASDAS (SASDAS) was calculated as the simple sum ofpatient global assessment (using visual analogue scale), back pain (BASDAI question no. 2), peripheral pain and swelling (BASDAI question no. 3), morning stiffness (BASDAI question no. 6), and either ESR in millimeters per hour

(for SASDAS-ESR) or, CRP in mg/L (for SASDAS-CRP); this sum was divided by 10 to obtain the final score.

Results:

Most patients (224/254, 88.18 %) were males with median age of 30 years. Median disease duration was 4 years. SASDAS-ESR and SASDAS-CRP showed excellent correlation with the ASDAS-ESR and ASDAS-CRP respectively (r^2=0.78 and 0.58 respectively; p<0.0001). SASDAS-ESR showed good correlation with back pain (r=0.19), morning stiffness (r=0.21), peripheral pain (r=0.21), and CRP (r=0.50); SASDAS-CRP showed good correlation with BASFI (r=0.32), and ESR (r=0.55) (all p<0.0001). Using established ASDAS cut-off values, the corresponding cut-off points between inactive disease, moderate disease activity, high disease activity, and very high disease activitywith optimum sensitivity and specificity for SASDAS-ESR were 1.83, 2.45 and 4.45; the corresponding points for SASDAS-CRP were 0.79, 1.50, and 3.26. While SASDAS-ESR agreed with ASDAS-ESR in the extremes of the condition only, SASDAS-CRP agreed with ASDAS-CRP throughout the range of disease activity. Both the SASDAS scores showed excellent correlation with BASDAI scores.

Conclusion:

SASDAS-ESR and SASDAS-CRP are reliable scores for assessment of disease activity in Indian AS patients. These are easy to calculate and can be useful in daily clinical practice in resource constraint countries.

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Abstract Number: 53

Associations Between Race and Income Disparity on Morbidity in Juvenile Dermatomyositis

Kathryn Phillippi[1], Mark Hoeltzel[2], Angela Byun Robinson[3,4], Susan Kim[5] and CARRA investigators, [1]Pediatric Infectious Diseases and Rheumatology, Rainbow Babies and Children's Hospital / Case Medical Center, Cleveland, OH, [2]Rheumatology Division, University of Michigan Mott Children's Hospital, Ann Arbor, MI, [3]Pediatrics, Rainbow Babies & Children's Hospital / Case Medical Center, Cleveland, OH, [4]Pediatric Rheumatology, Rainbow Babies and Childrens Hospital, Cleveland, OH, [5]Division of Immunology, Boston Children's Hospital, Boston, MA

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Background/Purpose: A significant number of patients with juvenile dermatomyositis (JDM) develop long term morbidity, such as calcinosis or lipodystrophy, however, the factors contributing to the development of such morbidities are not well understood.

Methods: Data from 426 patients with JDM enrolled in the Childhood Arthritis and Rheumatology Research Alliance (CARRA) Registry were analyzed to evaluate potential risk factors for morbidity, including age at diagnosis, sex, race, ethnic status, insurance status, family income, time to treatment, disease duration, functional status measures (CHAQ, ACR functional status, CMAS, physician and patient global assessments), and a history of calcinosis or lipodystrophy.

Results: By univariate analysis, black or minority race, annual family income less than $25,000 per year, negative ANA, and delay in diagnosis greater than 12 months were associated with the development of calcinosis or lipodystrophy. Multivariate analysis demonstrated that disease duration and delay to diagnosis are independent predictors of either calcinosis or lipodystrophy. Black race (OR 2.42, 1.11-5.27), disease duration (OR 1.22, 1.12-1.33), and delayed diagnosis (OR 1.02, 1.00-1.04) were independent risk factors for the development of calcinosis alone. Minority subjects with JDM in the CARRA Registry are more likely than Caucasian subjects to have low family income and no health insurance, and this subgroup had lower scores on measures of function and disease outcome.

Conclusion: Race and socioeconomic status are associated with worse morbidity and outcomes in patients with JDM. Future studies are needed to further clarify these associations so that efforts may be developed to address health disparities in patients with JDM and improve their disease outcomes.

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Abstract Number: 54

Impact of Age at Disease Diagnosis on Clinical Manifestations, Disease Activity, and Outcomes in Patients with Systemic Lupus Erythematosus: Single-Center Prospective Cohort Study

Il Woong Sohn[1], Young Bin Joo[1], Soyoung Won[2], Seung Taek Song[1], Seung Lee[3], Hye-Jin Jeong[3] and Sang-Cheol Bae[1], [1]Department of Rheumatology, Hanyang University Hospital for Rheumatic Diseases, Seoul, South Korea, [2]Clinical Research Center for Rheumatoid Arthritis (CRCRA), Seoul, South Korea, [3]Hanyang University Hospital for Rheumatic Diseases, Seoul, South Korea

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Background/Purpose: Systemic lupus erythematosus (SLE) is an autoimmune disease that affects frequently in their 20s and 30s. However, SLE could develop in other age group such as childhood-onset or late-onset. We aimed to investigate the influence of age of disease onset on clinical features, disease activity, and outcomes in adult patients with SLE.

Methods: We analyzed 917 adult patients with SLE from 1998 to 2012. The patients were classified into two groups based on the age at disease diagnosis: adult-onset SLE (≥18 and <50 years) and late-onset SLE (≥50 years). The American College of Rheumatology (ACR) criteria for SLE classification, the SLE Disease Activity Index (SLEDAI-2K), adjusted mean SLEDAI-2K (AMS), incidence rate of SLE flares (defined by ≥4 points increase of the SLEDAI-2K compared with that of previous visit), and prescribed medication were compared between two groups. As outcomes, organ damage and mortality were compared using SLICC/ACR Damage Index (SDI) and age- and sex adjusted standardized mortality ratio (SMR), respectively.

Results: Of the 917 SLE patients, 885 (91.4%) patients were adult-onset (mean age 29.4, range 18-49 years) and 32 (3.5%) patients were late-onset (mean age 55, range 50-68 years). After the mean follow-up years of 6.4, the number of cumulative ACR criteria was significantly lower in patients with late-onset compared with adult-onset SLE (4.6±1.2 vs 5.5±1.4, p<0.001). The mean SLEDAI-2K at enrollment (3.3±2.9 vs 5.4±4.2, p<0.001) and adjusted mean SLEDAI-2K over time (2.7±2.1 vs 4.3±2.6, p<0.001) were significantly lower in patients with late-onset compared with adult-onset SLE. The incidence rate ratio of SLE flares (late-onset/adult-onset SLE patients) was 0.44. The use of glucocorticoids and immunosuppressants was similar between two groups, but the use of azathioprine was lower in late-onset SLE patients (9.4% vs 29.8%, p=0.021). The percentage of cumulative SDI≥1 was higher in patients with late-onset compared with adult-onset SLE, but none reached statistical significance (50% vs 43.4%, p=0.576). A total of 42 patients died (6 in late-onset and 36 in adult-onset SLE group). The leading cause of death in both groups was SLE-related diseases, followed by infection. As compared to general population, the age- and sex adjusted SMR in late-onset and adult-onset SLE group was 1.58 (95% CI 0.58-3.43) and 3.34 (95% CI 2.34-4.63), respectively.

Conclusion: Compared with adult-onset SLE, late-onset SLE showed significantly mild clinical features and lower disease activity during follow-up. However, the percentage of patients with organ damage in patients with late-onset SLE was similar to that of adult-onset. The mortality of late-onset SLE was not higher than general population, although the mortality of adult-onset was three times higher than general population. Our results suggest that the clinical prognosis of late-onset SLE is better than adult-onset SLE.

	ACR criteria		**AMS**		**SDI**		**Age- and sex adjusted SMR**
	mean±SD	p-value	mean±SD	p-value	mean ±SD	p-value	(95% CI)
Adult-onset	5.5±1.4	<0.001	4.3±2.6	<0.001	0.9±1.5	0.933	3.34(2.34-4.63)
Late-onset	4.6±1.2		2.7±2.1		0.9±1.2		1.58(0.58-3.43)

Disclosure: I. W. Sohn, None; **Y. B. Joo**, None; **S. Won**, None; **S. T. Song**, None; **S. Lee**, None; **H. J. Jeong**, None; **S. C. Bae**, Bristol-Myers Squibb, 2.

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Abstract Number: 55

Increased Incidence of Tuberculosis Among Systemic Lupus Erythematous Patients – Should Tuberculosis Screening at Diagnosis be the Next Step?

Ana Maria Gherghe[1], Alexandru Matei[2], Hermina Gyorfi[2], Alina Soare[1], Rucsandra Dobrota[1], Mariana Sasu[1], Liviu Macovei[2], Ioan Ancuta[1], Mihaela Milicescu[1], Mihai Bojinca[1], Victor Stoica[2] and Carina Mihai[1], [1]Carol Davila University of Medicine and Pharmacy, Internal Medicine and Rheumatology, Cantacuzino Hospital, Bucharest, Romania, [2]Internal Medicine and Rheumatology, Cantacuzino Hospital, Carol Davila University of Medicine and Pharmacy, Bucharest, Romania

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Background/Purpose: Tuberculosis (TB) represents a major global health problem, responsible for ill health among millions of people each year (1). TB has a higher incidence among patients with autoimmune rheumatic diseases than in the general population; in such patients, it frequently presents as extrapulmonary or disseminated disease. According to WHO surveillance reports, although steadily decreasing during the last years, the incidence of TB in Romania in 2005-2014 has been by far the highest among all EU countries.

Objectives: To assess the characteristics and risk factors of active TB infection in a cohort of patients with systemic lupus erythematosus (SLE).

Methods: Data of all SLE patients followed up in our clinic during 2005 – 2014 were retrospectively analyzed. Clinical and demographic characteristics and treatment before diagnosis of TB were recorded. The incidence of active TB infection was compared to data from the general population. Univariable logistic regression was used to assess the influence of various factors on the risk of developing TB.

Results: Four hundred SLE patients were evaluated in our clinic during the 10-year interval; of them, 18cases of active TB per 4291 patient-years (time of exposure, PY) were identified, accounting for an incidence of 419.5/100.000 PY, which is 4.4 times the incidence of TB in our region in the period 2005-2014.

Ten of the 18 cases had extrapulmonary or disseminated TB; delayed diagnosis and more severe forms were observed in them. Two patients repeatedly had recurrent TB infection after 2, respectively 3 years from the first TB diagnosis. High-dose glucocorticoids (hd-GC) and cyclophosphamide (CYC) treatment were significantly associated with TB: OR (95% CI) 9.6 (1.2-77.5), p=0.03 for hd-GC and 3.3 (1.2-9.1), p=0.02 for CYC. Duration from the most recent hd-GC treatment was significantly shorter in patients who developed TB, compared to those who did not: mean (range) 5.6 (0-15) months vs. 56.5 (0-321) months; (median (IQR): 0 (14) months vs. 28.5 (88) months), p=0.022 (Mann-Whitney U test), suggesting that hd-GC is the most important risk factor for TB.

Fever was the most important red-flag for the diagnosis of TB, OR (95% CI) 73.1 (15.2-352.7), p<0.001. Other frequent manifestations were weight loss and cough. No association was found between TB and age, disease duration or socio-economic status.

Conclusion: We found an increased incidence of active TB infection with a majority of extrapulmonary TB in a large cohort of Romanian SLE patients. Cyclophosphamide treatment and high dose of glucocorticoids were important determinants for the increased risk of TB in SLE patients. These results suggest that in a country with a high TB burden, TB screening and treatment of latent TB would be useful before initiation of immunosuppressive treatment.

References: 1. WHO Global tuberculosis report 2014. (http://apps.who.int/iris/bitstream/10665/137094/1/9789241564809_eng.pdf?ua=1)

Disclosure: A. M. Gherghe, None; **A. Matei**, None; **H. Gyorfi**, None; **A. Soare**, None; **R. Dobrota**, None; **M. Sasu**, None; **L. Macovei**, None; **I. Ancuta**, None; **M. Milicescu**, None; **M. Bojinca**, None; **V. Stoica**, None; **C. Mihai**, None.

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Abstract Number: 56

Utilizing City-Wide Electronic Health Record Data to Assess Care

Fragmentation in Patients with Systemic Lupus Erythematosus (SLE)

Kathryn Jackson, Theresa Walunas, Anh Chung and Rosalind Ramsey-Goldman, Northwestern University, Chicago, IL
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Background/Purpose:

Care fragmentation is associated with poor health outcomes and is hard to assess in a single-site data registry. The Chicago HealthLNK Data Repository (CHDR) is a city-wide database of de-duplicated patient Electronic Health Record data from 6 institutions in Chicago, with the capability to match patient data from outside registries to supplement registries and provide a multi-institution view of a patient population. The Chicago Lupus Database (CLD) is a registry of 880 patients meeting ≥3 of the 1982/1997 revised ACR classification criteria for SLE. CLD participant data was combined with CHDR to understand factors influencing fragmentation.

Methods:

Using a HIPAA compliant algorithm[1], patients from the CLD were hashed and matched into the CHDR to create a comprehensive set of patient visits from all institutions. Patients' demographics, insurance, fragmentation (defined as having ≥ 1 visit at ≥ 2 institutions) and visit data were pulled from the CHDR. Differences between groups were computed using chi-squared tests and odds ratios. Multivariate regression was used to assess factors contributing to percent inpatient visits and probability of death.

Results:

625 patients from the CLD matched with a CHDR patient having at least 2 visits from 2006-2012. 92% were female; 52% white and 32% black; 65% private and 21% public insurance; 29% had fragmented care. Sex had no effect on fragmentation. Blacks were more likely to have fragmented care than whites (OR: 2.52 CI: 1.68,3.79). Fragmented care was increased for both blacks (OR: 2.81 CI: 1.44,5.50) and whites (OR: 2.01 CI: 1.09,3.68) on public compared to private insurance. Overall, 6% of patient visits were inpatient. Table 1 shows percent change in inpatient visits for categories of fragmentation, race, and insurance; in the multivariate model, fragmentation, black race, public and no insurance all contributed to higher percent of inpatient visits. For each percent increase in inpatient visits, the odds of death increase by 1.05 (CI: 1.03,1.07).

Conclusion:

By combining a disease specific registry with a city-wide database, this study examines factors contributing to care fragmentation among SLE patients, and whether fragmented care impacts health outcomes in patients with a complicated chronic illness. For blacks and whites, public insurance correlated with fragmented care and increased inpatient visits, which is suggestive of more serious health impacts due to SLE. With the expansion of public insurance, patients with chronic illness seeking care at multiple sites may need improved care coordination or access to primary care to avoid more severe situations, hospitalization and increased likelihood of death.

Reference:

1. Kho AN, Cashy JP, Jackson KL et al. Design and Implementation of a Privacy Preserving Electronic Health Record Linkage Tool in Chicago. JAMIA 2015.

Table 1. Change in Percent of Inpatient Visits

Group	Percent Change	95% CI	p-value
Race	**Ref=White**		
Black	3.7	(1.6,5.9)	<0.001
Other	-0.4	(-2.9,2.1)	0.76
Insurance	**Ref=Private**		
Public	3.8	(1.8,5.9)	<0.001
No Insurance Reported	9.7	(4.9,14.6)	<0.001
Fragmentation	**Ref=Not Fragmented**		
Fragmented	2.2	(0.2,4.2)	0.03
Combinations			
Race and Insurance	**Ref=White, Private**		
Blacks w/ Public Insurance	7.6	(5.1,10.1)	<.0001
Whites w/ Public Insurance	3.8	(1.8,5.9)	<0.001
Race and Fragmentation	**Ref=White, No Fragmentation**		
Blacks w/ Fragmentation	5.9	(3.2,8.6)	<.0001
Whites w/ Fragmentation	2.2	(0.2,4.2)	0.03
Race, Insurance, and Fragmentation	**Ref= White, Private, No Fragmentation**		
Blacks w/ public and fragmentation	9.8	(7.0,12.6)	<.0001
Whites w/ public and fragmentation	6.0	(3.4,8.7)	<.0001

Disclosure: K. Jackson, None; **T. Walunas**, None; **A. Chung**, None; **R. Ramsey-Goldman**, None.

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Abstract Number: 57

Age, Gender, Racial and Comorbidity Differences Among Systemic Lupus Erythematosus Patients Hospitalized with Ischemic Stroke Compared to the General Population: A Nationwide Analysis

Tapan Mehta[1], **Khushboo Sheth**[2], Ronak Soni[3], Vishad Sheth[4], Kathan Mehta[5] and Christopher Scola[6], [1]Neurology, University of Connecticut, Farmington, CT, Farmington, CT, [2]Internal Medicine, University of Connecticut, Farmington, CT, Farmington, CT, [3]Central Michigan University, Mount Pleasant, MI, [4]Mercy Catholic Medical Center, Yeadon, PA, [5]Internal Medicine, University of Pittsburgh Medical Center, Pittsburgh, PA, Pittsburgh, PA, [6]Rheumatology, Hartford Hospital, Hartford, CT

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Session Time: 9:00AM-11:00AM

Background/Purpose: To determine if age, gender and racial discrepancies exist, and to determine the occurence of comorbidities among patients hospitalized with ischemic stroke with Systemic Lupus Erythematosus (SLE) in comparison to the general population.

Methods: We queried the Healthcare Cost and Utilization Project's (HCUP) Nationwide Inpatient Sample (NIS) between 2004 and 2010 and separated the hospitalizations due to or with ischemic stroke using ICD 9 diagnostic codes previously established by HCUP. Among this population, we identified the patients with SLE and calculated the average age of patients with and without SLE at the time of hospitalization for ischemic stroke. In addition, we calculated the gender and racial distribution of occurrence of ischemic stroke among SLE patients compared to the general population using the above database. We also looked at the Charlson comorbidity index (CCI) among these populations. Using SAS 9.2, survey procedures were used to identify univariate predictors of ischemic stroke.

Results: A total of 790,912 (weighted N=3,900,707) patients who were hospitalized with ischemic stroke were available for analysis out of which 3428 (weighted N= 16,828) had SLE. On univariate analysis, the average age of ischemic stroke in the general population was 70.9+_0.02 years, whereas in the SLE population, the average age of ischemic stroke was 56.5+-0.30 years ($p<0.0001$). Among the general population, 53.61% of all ischemic stroke population was females; whereas among the SLE population, 85.98% of the population was females ($p<0.0001$). Of the general ischemic stroke population, 55.7% were white, 22.6% were black and 21.7% belonged to other races. Among the SLE population, 44.9% were white, 35.6% were black and 19.5% belonged to other races ($p<0.0001$). The average CCI for the SLE population was 3.48+-0.03 compared to 2.67+-0.00 among the general population ($p<0.0001$).

Conclusion: There are significant discrepancies in age, gender and racial distribution among patients with SLE hospitalized with ischemic stroke compared to the general population. Patients with SLE are at increased risk of stroke approximately 13 years before the general population. The preponderance of SLE among female patients explains the increased incidence of ischemic stroke in females compared to the general population. Higher proportion of African American patients with SLE was hospitalized with ischemic stroke compared to the general population. The higher CCI is elucidated by the fact that SLE is a multisystemic disease, thus increasing the risk for comorbidities.

Disclosure: T. Mehta, None; **K. Sheth**, None; **R. Soni**, None; **V. Sheth**, None; **K. Mehta**, None; **C. Scola**, None.

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Abstract Number: 58

Attribution of Cause of End-Stage Renal Disease Among Systemic Lupus Erythematosus Patients

Laura Plantinga[1], Cristina Drenkard[1], Stephen Pastan[2] and S. Sam Lim[3], [1]Department of Medicine, Emory University, Atlanta, GA, [2]Department of Medicine, Division of Renal Medicine, Emory University, Atlanta, GA, [3]Emory University School of Medicine, Atlanta, GA

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SESSION INFORMATION

Session Date: Sunday, November 8, 2015

Session Title: Epidemiology and Public Health Poster I: Comorbidities and Outcomes of Systemic Inflammatory Diseases

Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose: The attributed cause of end-stage renal disease (ESRD) in the United States Renal Data System (USRDS) is often used to identify systemic lupus erythematosus (SLE) patients in U.S. studies of ESRD incidence and quality of care. We aimed to compare the attributed ESRD cause from the USRDS to the validated SLE status of patients in the Georgia Lupus Registry (GLR) who had progressed to ESRD.

Methods: Data from the USRDS were linked to the GLR to identify SLE patients (diagnosed through 12/04) who progressed to ESRD (through 9/12). The percentage of these SLE patients whose ESRD was subsequently attributed to SLE in the USRDS was calculated, overall and by patient characteristics.

Results: Among 251 SLE patients who progressed to ESRD, 78.9% had their ESRD attributed to SLE in the USRDS. Of the remaining 53 patients, most had their ESRD attributed to hypertension, diabetes mellitus, and non-SLE-related glomerulonephritis (Figure). Attribution of ESRD to SLE did not differ by sex or race but was lower among older vs. younger patients (P<0.001; Table). Only 20.0% of those aged ≥50 had ESRD attributed to SLE. Having Medicaid or no insurance was associated with greater attribution of ESRD to SLE than having private insurance (P=0.02), as was having two or more providers state a SLE diagnosis (P=0.008).

Conclusion: These estimates indicate that USRDS-based studies may underreport ESRD in U.S. SLE patients. However, observed patterns of differential attribution of ESRD cause, particularly by age, suggest that providers may be correctly attributing ESRD to causes other than SLE and lupus nephritis among some SLE patients.

Figure. Attributed cause of ESRD among 251 SLE patients in the Georgia Lupus Registry who progressed to ESRD (through 2012). HTN, hypertension; DMII, diabetes mellitus type II; FSGS, focal segmental glomerulosclerosis; Other GN, glomerulonephritis not attributed to SLE. Other includes tubular necrosis, IgA nephropathy, scleroderma, diabetes mellitus type I, multiple myeloma, other renal disorder, and uncertain etiology.

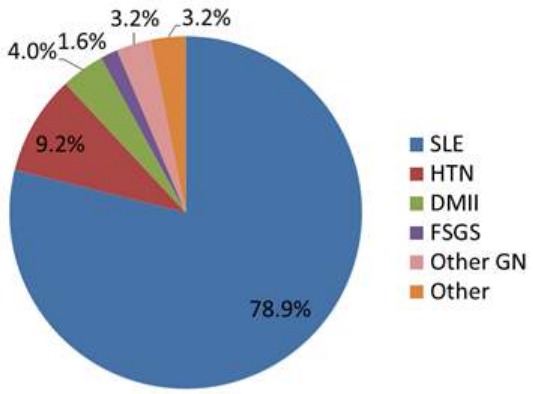

Table. Attribution of ESRD to SLE among Georgia Lupus Registry patients who initiated ESRD treatment through 2012, by selected patient characteristics

Patient subgroup	% attribution of ESRD to SLE (95% CI)
Overall	78.9 (73.3-83.8)
Demographics	
Age at SLE diagnosis	
<18	93.9 (86.3-98.0)
18-30	87.9 (79.4-93.8)
>30	52.6 (40.9-64.0)
Sex	
Male	81.6 (65.7-92.3)
Female	78.4 (72.3-83.7)
Race	
Black	79.3 (73.5-84.3)
White	72.2 (46.5-90.3)
Insurance at start of ESRD	
Private	72.5 (62.2-81.4)
Medicaid	86.2 (75.3-93.5)
Other	71.4 (55.4-84.3)
None	93.5 (78.6-99.2)
Physician stating final SLE diagnosis	
None	60.6 (42.1-77.1)
Rheumatologist	73.5 (62.7-82.6)
Dermatologist	75.0 (19.4-99.4)
Nephrologist	82.1 (66.5-92.5)
Combination	89.0 (80.7-94.6)

Disclosure: L. Plantinga, None; **C. Drenkard**, None; **S. Pastan**, None; **S. S. Lim**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/attribution-of-cause-of-end-stage-renal-disease-among-systemic-lupus-erythematosus-patients

Abstract Number: 59

Variation in Heart Failure Hospitalizations Among U.S. Medicaid

Recipients with SLE 2000-2010, By Race and Ethnicity

Medha Barbhaiya[1], Candace H. Feldman[1], Hongshu Guan[1], Jose A. Gomez Puerta[2], Michael A. Fischer[3] and Karen H. Costenbader[1], [1]Division of Rheumatology, Immunology and Allergy, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, [2]Grupo de Inmunología e Inmunogenética, GICIG, Universidad de Antioquia, Medellín, Colombia, Medellín, Colombia, [3]Division of Pharmacoepidemiology and Pharmacoeconomics, Brigham and Women's Hospital, Boston, MA

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SESSION INFORMATION

Session Date: Sunday, November 8, 2015

Session Title: Epidemiology and Public Health Poster I: Comorbidities and Outcomes of Systemic Inflammatory Diseases

Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose: Heart failure (HF) is a leading cause of hospital admissions. In the US, Blacks have higher HF prevalence than other racial/ethnic groups. Cardiovascular disease (CVD) risks are elevated in SLE, but racial/ethnic variation in HF prevalence in SLE has not been well studied. We examined rates and adjusted risks of HF admissions among SLE patients overall and by race/ethnicity within Medicaid, the US health insurance program for the poor.

Methods: Within Medicaid Analytic eXtract (MAX), containing billing claims from 2000-10 for Medicaid patients from the 29 most populated US states, we identified patients aged 18-65 with prevalent SLE (≥3 ICD-9 codes 710.0, ≥30 days apart) with ≥6 months of continuous enrollment prior to the 3rd diagnosis code (index date). Baseline data from the 6 months prior to index date included age, sex, race/ethnicity, zip code, year, SLE-related and other comorbidities (based on ICD-9 codes). Those missing race/ethnicity were excluded. Within MAX inpatient claims, ICD-9 codes identified multiple types of HF as primary or secondary discharge diagnoses (Chen J, *Circulation,* 2013). Subjects were followed from index date to first HF admission, death, Medicaid disenrollment, or end of follow-up. HF admission rates per 1000 person-years with 95% CIs were calculated overall and within subgroups. Fine and Gray proportional hazards regression models, accounting for the competing risk of death, were used to calculate subdistribution hazard ratios (HR) for HF hospitalization, adjusting for sociodemographics and comorbidities.

Results: Of 57,292 patients with prevalent SLE, 93.2% were female. Racial/ethnic breakdown was: 41% Black, 39% White, 15% Hispanic, 3% Asian, 1% Native American. Mean follow-up was 3.67 (±3.03) years, 2,596 (5%) patients had ≥1 HF hospitalization, and 3,972 (7%) patients died. The HF admission rate was 12.76 (95%CI 12.28, 13.26) per 1,000 person-years for the entire cohort. Asians and Hispanics had the lowest HF admission rates: 7.49 (95%CI 5.76, 9.73) and 8.75 (95%CI 7.78, 9.84) per 1,000 person-years. Blacks had the highest rates: 17.56 (95%CI 16.68, 18.48) per 1,000 person-years. After adjustment, the HR for HF admission was 1.84 (95%CI 1.68, 2.02) among Blacks vs. Whites, and 1.82 (95%CI 1.66, 1.99) after further comorbidity adjustment (Table). Sensitivity analyses restricting to the primary discharge diagnosis (1,560 events) yielded similar results for Blacks vs. Whites: HR 2.06 (95% CI 1.83, 2.32), and 2.10 (95%CI 1.86, 2.40) after further comorbidity adjustment.

Conclusion: Rates of HF hospitalization were high in all racial/ethnic groups of SLE Medicaid patients. In multivariable models, Black SLE Medicaid patients had nearly two-fold higher risks of HF hospitalization than Whites and higher risks than all other groups. Future analyses will seek to differentiate prevalent vs. incident HF and examine different HF etiologies.

Table. Multivariable Subdistribution Hazards Ratios for First Hospitalizations for Heart Failure* among 57,292 Medicaid Patients with SLE in the US, by Race and Ethnicity, 2000-2010				
Racial/Ethnic Group	**Events**	**Person-years**	**Model 1** **HRsd**(95% CI)**	**Model 2** **HRsd**(95% CI)**
Black, n=23,586	1,465	83,413	**1.84 (1.68, 2.02)**	**1.82 (1.66, 1.99)**
White, n=22,444	772	78,482	Ref.	Ref.
Hispanic, n=8,825	277	31,644	1.07 (0.93,1.24)	1.10 (0.92, 1.23)
Asian, n=1,779	56	7,474	0.94 (0.71,1.25)	0.92 (0.69, 1.22)
Native American, n=658	26	2,418	1.21 (0.82,1.79)	1.16 (0.78, 1.72)

*ICD-9 codes for HF: 402.01, 402.11, 402.91, 404.01, 404.11, 404.91, 404.03, 404.13, 404.93, and 428.xx, but excluding 398.91 rheumatic heart disease (Chen J, Circulation, 2013).

**HRsd= Subdistribution hazard ratios accounting for the competing risk of death.

Model 1: adjusting for age, sex, calendar year, US region, ZIP-code level socioeconomic status (Ward MM, *J Rheum*, 2007), and SLE Risk Adjustment Index (includes lupus nephritis, Ward MM, *J Rheum*, 2000) during the 6 months prior to the index date.

Model 2: additionally adjusting for Charlson comorbidity index, as well as angina, percutaneous coronary intervention, hypertension, obesity and smoking during the 6 months prior to the index date.

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Abstract Number: 60

Mortality of Systemic Lupus Erythematosus in Puerto Rico Assessed By Multiple-Cause-of-Death Analysis

Mariangelí Arroyo-Ávila[1], José G. Conde[2] and Luis M. Vilá[1], [1]Department of Medicine, Division of Rheumatology, University of Puerto Rico Medical Sciences Campus, San Juan, PR, [2]School of Medicine and Research Centers in Minority Institutions Program, University of Puerto Rico Medical Sciences Campus, San Juan, PR

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Session Date: Sunday, November 8, 2015

Session Title: Epidemiology and Public Health Poster I: Comorbidities and Outcomes of Systemic Inflammatory Diseases

Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose: Systemic lupus erythematosus (SLE) is a chronic autoimmune disorder that is associated with a high morbidity and mortality. The specific causes of death vary among ethnic groups or geographical locations. The purpose of this study was to determine the mortality profile related to SLE in Puerto Rico using multiple-cause-of-death analysis.

Methods: Public use, multiple-cause-of-death mortality files from the National Center of Health Statistics were used to select death records of residents in Puerto Rico listing SLE (International Classification of Diseases, 10th Revision, codes M32.1 or M32.9) as an underlying cause of death (UCD) or as a non-underlying cause of death (NUCD) for years 2003-2013 . Demographic data, gender-specific age-adjusted mortality rates, and associated causes of death were analyzed. Causes of death were classified into four groups: SLE-related complications, infectious diseases, cardiovascular diseases, diabetes mellitus, and malignancy. Proportionate mortalities were used to investigate associations between causes of death, calculating the ratio of observed to expected deaths (O:E ratio) for selected comorbidities. Mann-Whitney, chi-square and Fisher's exact tests were used to evaluate statistical associations.

Results: In total, 393 SLE-related deaths were identified. Median age was 52 years (53 for females and 45 for males; p=0.216). Three hundred and forty five (87.8%) deaths occurred in women, for a female to male ratio of 7.2. The age-adjusted mortality rate for SLE-related deaths for women was 166.5 deaths/million and 27.8 deaths/million for men (relative risk = 6.0; $p < 0.001$). In 308 deaths (78.37%), SLE was listed as the UCD. Those listed with SLE as the UCD were younger (median age 51 vs. 57 years, p =0.008) and were more likely to die at a medical center (82.2% vs. 68.2%, p= 0.007) compared to those listed with SLE as a NUCD. In multiple-cause of death analysis, the most common causes of SLE-related deaths (UCD and NUCD) were infectious diseases (42.5%), SLE-related complications (37.4%), cardiovascular diseases (27.9%), diabetes mellitus (12.2 %), and malignancy (5.6%). For men, SLE related complications (54.2% vs. 35.1%, p=0.016) and cardiovascular diseases (41.7% vs. 26.1%, p=0.038) were more common than in women. No significant differences were observed for infectious diseases, diabetes mellitus, and malignancy between men and women. Among infectious diseases, bacterial infections were reported in 130 death certificates and sepsis in 124. The overall O:E ratio was >1 for bacterial infections (1.86, $p < 0.001$) and renal failure (1.45, p = 0.002). The O:E ratio for malignant hypertensive disease , ischemic heart, cerebrovascular diseases and malignant neoplasms was < 1.

Conclusion: In Puerto Rico, SLE deaths were more commonly associated with infectious disorders, particularly bacterial infections and sepsis. Adhering to prevention and control measures of infection could be crucial in improving SLE survival in this population.

Disclosure: M. Arroyo-Ávila, None; **J. G. Conde**, None; **L. M. Vilá**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/mortality-of-systemic-lupus-erythematosus-in-puerto-rico-assessed-by-multiple-cause-of-death-analysis

Abstract Number: 61

Predictors of Mortality Among Patients with Sarcoidosis: A Population-Based Study

Patompong Ungprasert[1], Eva M. Carmona Porquera[2], James P. Utz[2], Jay H. Ryu[3], Cynthia S. Crowson[4] and Eric L. Matteson[5], [1]Rheumatology, Mayo Clinic, Rochester, MN, [2]Pulmonary and Critical Care Medicine, Mayo Clinic, Rochester, MN, [3]Division of Pulmonary and Critical Care Medicine, Mayo Clinic, Rochester, MN, [4]Health Sciences Research, Mayo Clinic, Rochester, MN, [5]Division of Rheumatology, Department of Internal Medicine and Department of Health Sciences Research, Mayo Clinic, Rochester, MN

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Session Title: Epidemiology and Public Health Poster I: Comorbidities and Outcomes of Systemic Inflammatory Diseases

Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose: The epidemiology and natural history of sarcoidosis is not well-characterized as only coding-based studies without detailed clinical information from individual medical record review have been reported. This study aimed to assess the predictors of mortality of sarcoidosis, using data from a population-based cohort.

Methods: An inception cohort of patients who were diagnosed with sarcoidosis in 1976-2013 in a geographically well-defined population was identified based on comprehensive individual medical record review. Diagnosis required histopathological confirmation and diagnostic radiologic features of intrathoracic sarcoidosis, compatible clinical presentation, and exclusion of other known causes of granulomatous inflammation. Histopathological confirmation required presence of non-caseating granuloma without evidence of acid-fast bacilli or fungi. The only exception to the requirement of histopathological confirmation was stage I pulmonary sarcoidosis that required only radiographic evidence of symmetric bilateral hilar adenopathy with or without mediastinal lymphadenopathy. Cases of isolated granulomatous disease of the skin without other features of sarcoidosis were not included. Data were collected on demographic, clinical presentation, laboratory investigations and mortality. Univariable Cox models were used to identify prognostic factors of death.

Results: In 1976-2013, 345 incident cases of sarcoidosis were identified. 50.4% of the cohort was female and the mean age of the cohort was 45.6 years. During follow-up (median: 12.2 years; 5002 total person-years), 50 patients died.

Age, male sex, absence of intra-thoracic disease, and hepatic, cardiac, splenic or neurological involvement in conjunction with intra-thoracic disease were predictive factors for mortality in univariable models after adjustment for age, sex and calendar year of sarcoidosis diagnosis (Table 1).

Conclusion: Age, male sex, absence of intra-thoracic disease, and hepatic, cardiac, splenic or neurological involvement in conjunction with intra-thoracic disease were prognostic factors associated with mortality in patients with sarcoidosis.

Table 1: Predictors of mortality among patients with sarcoidosis

Characteristic	Hazard ratio* (95% CI)	p-value
Age, per 10 year increase	2.48 (1.97, 3.13)	<0.001
Male sex	1.98 (1.04, 3.79)	0.038
Calendar year of diagnosis, per 1 year increase	0.98 (0.94, 1.02)	0.25
Black (vs white ethnicity)	3.16 (0.72, 13.81)	0.29
Other (vs white ethnicity)	1.33 (0.32, 5.58)	
Former smoker (vs never)	1.80 (0.76, 4.30)	0.36
Current smoker (vs never)	0.94 (0.42, 2.11)	
Presence of intrathoracic involvement	0.28 (0.08, 0.93)	0.038
Presence of parenchymal involvement	0.92 (0.51, 1.63)	0.77
Symptomatic from intrathoracic involvement	1.27 (0.705, 2.33)	0.44
Eye	0.46 (0.13, 1.57)	0.22
Nervous system	4.18 (1.44, 12.11)	0.008
Skin	0.84 (0.35, 2.03)	0.70
Liver	5.37 (1.90, 15.21)	0.002
Spleen	11.54 (4.05, 32.91)	<0.001
Heart	12.35 (2.76, 55.18)	0.001
Kidney	2.46 (0.72, 8.39)	0.15
Exocrine gland	0.43 (0.06, 3.15)	0.40

Disclosure: P. Ungprasert, None; **E. M. Carmona Porquera**, None; **J. P. Utz**, None; **J. H. Ryu**, None; **C. S. Crowson**, None; **E. L. Matteson**, Novartis/Sanofi/Centocor-Jansen/Celgene/Amgen/Roche/Genentech/Mesoblast/Pfizer, 2.

Abstract Number: 62

Patient Perception of Disease Burden in Diffuse Cutaneous Systemic Sclerosis

Dinesh Khanna[1], Yannick Allanore[2], Christopher P. Denton[3], Marco Matucci-Cerinic[4], Janet E. Pope[5], Barbara Hinzmann[6], Siobhan Briody[7], Janethe de Oliveira Pena[8] and Oliver Distler[9], [1]Division of Rheumatology, University of

Michigan, Ann Arbor, MI, [2]Immunogenetics, Cochin Institute, Paris, France, [3]Rheumatology and Connective Tissue Diseases, University College London, London, United Kingdom, [4]Department of Medicine, Division of Rheumatology, University of Florence, Florence, Italy, [5]University of Western Ontario, London, ON, Canada, [6]Bayer Pharma AG, Berlin, Germany, [7]Blueprint Partnership, Manchester, United Kingdom, [8]Bayer HealthCare Pharma, Whippany, NJ, [9]Research of Systemic Autoimmune Diseases, Center of Experimental Rheumatology, University Hospital Zurich, Zurich, Switzerland
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Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose:

Diffuse cutaneous SSc (dcSSc) is associated with high morbidity and mortality, and reduced quality of life. Patient priorities are rarely discussed, with physicians traditionally focusing on organ involvement rather than skin changes. Using discursive approaches and ethnography, a unique, qualitative research methodology, we evaluated the impact of dcSSc symptoms on patients' daily lives, and examined how disease burden shapes patient outlook.

Methods:

Patients were recruited via healthcare professionals (HCPs) or patient associations. In France, Italy, the UK and US, patients filmed daily short (~15-minute) video diaries about their lives over 7 days. On Days 1 and 7, patients took part in a moderator-led discussion of their experiences, and an observation session to understand the impact of living with dcSSc. In Germany and Spain, patients participated in 60-minute telephone interviews. Patients were also assigned tasks to encourage reflection on their feelings about dcSSc. Video footage and transcribed discussions were reviewed, and the data were categorized and assessed for themes, patterns, and indicators of emotion, ambivalence, and conflict.

Results:

Twenty-three patients (mean age 54; 83% women) were recruited. Of these, 17 made video diaries, and 6 took part in telephone interviews. The majority of video diaries and interviews took place in patients' homes, and on average 5.25 hours of video footage were collected per patient.

The results of the study show that time to diagnosis may be delayed, as patients trivialize their symptoms and HCPs often attribute symptoms to other causes. Patients also have a poor understanding of their diagnosis, and information to aid understanding is rarely provided. DcSSc is associated with a high treatment burden; on average this patient sample received 10 tablets of prescribed drugs per day. Importantly, while patients were aware of the seriousness of organ involvement, they reported that skin changes, pain, and fatigue have a dominant effect on daily life, impairing their ability to perform routine tasks. Skin tightening in the lower limbs and feet lead to deformity and loss of mobility, while Raynaud's phenomenon, calcinosis, and digital ulcers cause significant pain, as well as loss of function. Furthermore, skin tightening around the mouth impacts the ability to eat, and dental hygiene. Changes in esthetic appearance lead to embarrassment, loss of identity, withdrawal from social life, and depression. Patients experience dcSSc as a series of losses, including independence and self-esteem, and the unpredictability of the disease makes the patient journey and acceptance of the condition difficult. Moreover, patients tend to have small support networks and support services are not offered as part of standard care.

Conclusion:

Patients with dcSSc have high treatment and emotional burdens, with skin complications, pain, and fatigue profoundly impacting their daily lives. Patients place the most emphasis on these issues rather than the chance of organ

involvement. There is an unmet need for patient information at the time of diagnosis and for emotional support services throughout their journey with dcSSc.

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Abstract Number: 63

Association of Smoking and Cognitive Function in Patients with Fibromyalgia

Lin Ge[1,2], Terry H. Oh[3], Ann Vincent[4], Arya Mohabbat[5], li Jiang[6], Mary Whipple[7], Samantha McAllister[8], Zhen Wang[9] and WenChun Qu[10], [1]Physical Medicine and Rehabilitation, Mayo Clinic, Rochester, MN, [2]Rheumatology, Guang An Men Hospital, China Academy of Chinese Medical Science,, Beijing, China, [3]Physical Medicine & Rehabilitation, Mayo Clinic, Rochester, MN, [4]General Internal Medicine, Mayo Clinic, Rochester, MN, [5]Department of Medicine, Mayo Clinic, Rochester, MN, [6]Rehabilitation, The Third Affiliated Hospital，Sun Yat-sen University,China, Guangzhou, China, [7]Fibromyalgia and Chronic Fatigue Clinic, Mayo Clinic, Rochester, MN, [8]Mayo Clinic, Rochester, MN, [9]Health Sciences Research, Mayo Clinic, Rochester, MN, [10]Department Physical Medicine and Rehabilitation, Department of Anesthesiology Division of Pain Medicine, Mayo Clinic, Rochester, MN
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Background/Purpose:

To evaluate the association between smoking and cognitive function in patients with fibromyalgia (FM).

Methods:

We surveyed 668 patients with FM from May 2012 through November 2013. Patients were categorized by smoking status (non-smoker and smoker). Primary outcomes included cognitive symptoms (MASQ). Secondary outcomes include fatigue (MFI-20), sleep (MOS-sleep Scale), depression (PHQ-9), anxiety (GAD-7), overall FM symptom severity (FIQ-R), and quality of life (SF-36). Univariate and multivariate analyses were used.

Results:

Ninety-four (14.07%) patients self-identified as smokers. Smokers were associated with several demographic variables, including lower education, unmarried status, and younger age. Smokers reported worse cognitive functions, including total functional score and 4 out of 5 domains of the MASQ (all $p<0.05$) Secondary outcomes showed worse sleep (MOS-sleep scale $p=0.01$), anxiety (GAD-7 total $p=0.001$), depression (PHQ-9 $p=0.04$), FM symptom severity (FIQ-R total score $p<0.01$), and QoL in bodily pain(BP) and mental health(MCS) (SF-36: BP $p=0.03$; MCS $p=0.02$).

Conclusion:

The results of this study indicate that smokers with FM report worse cognitive function. Although the cause-effect relationship between smoking and cognition is unclear, clinicians who care for patients with FM should be aware of this association.

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Abstract Number: 64

Nociceptive Flexion Reflex Threshold: Possible Surrogate Marker of Symptom Severity in Fibromyalgia

Dennis Ang[1], Christopher France[2] and James Slaven[3], [1]Section on Rheumatology and Immunology, Wake Forest University, Winston Salem, NC, [2]Psychology, Ohio University, Athens, OH, [3]Biostatistics, Indiana University, Indianapolis, IN

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Background/Purpose: Central sensitization has been demonstrated in patients with fibromyalgia (FM) using an objective assessment of spinal nociception called the nociceptive flexion reflex (NFR). This reflex is measured (electromyographically) as the withdrawal of a proximal leg muscle (biceps femoris) in response to an electrical stimulus applied over the sural nerve. The lowest level of electrical stimulation that generates a measurable withdrawal response is called the NFR threshold. A low NFR threshold (i.e., augmented nociceptive responsivity) has been demonstrated in FM when compared to healthy controls. In this report we sought to determine the prospective association of the change in the NFR threshold with global FM severity (as measured by the Fibromyalgia Impact Questionnaire/FIQ-total score).

Methods:

This is a secondary data analysis of a 12-week randomized clinical trial of the effect of cognitive behavioral therapy (CBT) on nociceptive responsivity and global FM severity. Female subjects who met the 1990 Classification Criteria for FM were randomized to 1 of 2 treatment arms: six weekly sessions of CBT or usual care (UC). Subjects were evaluated at 3 time points: baseline, week 6 (post-intervention) and week 12. For these analyses, the predictor was the *baseline-to-week 6 change* in NFR threshold and the primary outcome was the FIQ-total at *week 12*. Linear regression analyses were controlled for treatment group assignment, baseline use of opiates, anticonvulsants and serotonin-

norepinephrine reuptake inhibitor (SNRI), and other potential confounders. We considered a variable as a potential confounder if the variable was associated with boththe predictor and the primary outcome.

Results:

The 32 female participants had a mean (± standard deviation) age of 47 ± 12 years; 81% were white, 94% had ≥ high school education, and 44% were employed. At baseline, the sample had a mean disease duration of 12 ± 6 years; 16 (50%) were on opiates; 9 (28%) were on anticonvulsant; and 7 (22%) were on SNRI. Based on the Patient Health Questionnaire-8 (score ≥ 10), 16 (50%) of the participants had probable depression. The mean FIQ-pain score was 5.0 ± 2.3, and the mean FIQ total score was 61 ± 16, suggesting a moderate-to-severely ill patient population. The mean change in NFR threshold (week 6 minus baseline) was - 1.76 ± 13.32 mA, suggesting a reduction in nociceptive responsivity for the entire group.

	Model Parameter	p-value
Unadjusted Model		
NFR threshold change	β = -0.51	0.09
Adjusted model 1		
NFR threshold change	β = -0.60	0.08
Treatment Group (CBT vs. UC)	β = -5.15	0.56
Adjusted model 2		
NFR threshold change	**β = -0.70**	**0.07**
Treatment Group (CBT vs. UC)	β = -7.39	0.44
SNRI (yes)	β = -6.94	0.53
Opiates (yes)	β = 1.53	0.86
Anticonvulsants (yes)	β = 9.17	0.37

None of the other baseline variables were associated with both the predictor and the primary outcome.

Conclusion:

Our study is the first to demonstrate that a prior change in NFR threshold predicted future global disease severity in FM. Specifically, a reduction in nociceptive responsivity was (marginally) associated with better clinical status in female FM patients. If corroborated in a larger study, the change in NFR threshold may be a surrogate marker of improvement (or worsening) of overall FM symptomatology.

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Abstract Number: 65

Disability in the Rheumatic Diseases

Robert S. Katz[1], Hannah Leavitt[2], Lauren Kwan[3] and Jessica L. Polyak[3], [1]Rush University Medical Center, Chicago, IL, [2]Suite 365, Rheumatology Associates S.C., Chicago, IL, [3]Rheumatology Associates S.C., Chicago, IL

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Background/Purpose: The number of people receiving disability payments in the United States has increased substantially. Rheumatic diseases are common causes of disability. Rheumatologists are often asked to evaluate patients for disability, even though the symptoms are often largely subjective. This situation is particularly challenging in evaluating fibromyalgia in patients.

We We evaluated our patients' claims over the past year in those applying for Social Security Disability.

Methods: A rheumatologist and a rheumatology nurse reviewed each claim sent to the Social Security Administration for disability status in 2013 and 2014 to determine how often we agreed that the claimant with fibromyalgia deserved to receive disability status. We defined disability as the inability to work at any job, indefinitely.

Results: Of the 31 Social Security applicants with fibromyalgia, the physician and the rheumatology nurse agreed that only 5 (16%) were incapable of working even in a sedentery position. Admittedly, this was a subjective determination. The evaluation process took into account the number of physical complaints, severity of pain, health assessment questionnaire, and physical examination. Sometimes patients, revealed they could perform tasks in their personal lives, but claimed incapable of doing at work. However, chronic fatigue and the level of pain can not be assessed objectively.

Of the patients with a diagnosis other than fibromyalgia, such as lupus and rheumatoid arthritis, 18 subjects requested Social Security disability, and 7 (39%) were thought by the physician and the nurse to be totally incapable of working.

Conclusion: In the majority of cases, the rheumatologist and nurse did not agree with the Social Security disability claim, especially in fibromyalgia patients. Because of the subjective nature of fibromyalgia symptoms, such as fatigue and pain, it may be difficult to render an accurate judgment regarding disability. But job modifications and periodic days off, permitted by the Family Leave Act, may be better alternatives to try before granting total disability status

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Abstract Number: 66

Fibromyalgia Patients Identify More Causes of Disease Flare Ups Than RA Patients

Robert S. Katz[1], Lauren Kwan[2], Hannah Leavitt[2] and Jessica L. Polyak[2], [1]Rush University Medical Center, Chicago, IL, [2]Rheumatology Associates S.C., Chicago, IL

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Background/Purpose: Flare-ups are a frequent and painful part of FMS and RA. We compared FMS and RA patients with respect to stresses that the patients belive may have caused their diseases to flare.

Methods: 211 office patients with FMS or RA (150 FMS:130 women and 20 men; mean age 51±12, 61 RA:45 women and 16 men; mean age 55±15) completed a questionnaire as to whether the following conditions cause their disease to flare: lack of sleep, fatigue, emotional stress, physical stress, depression, anxiety, traumatic events, overdoing it, being overworked, feeling overwhelmed, illness, personal changes, and confrontations with friends or family members. The chi-square test of association was done to compare FMS and RA patients with respect to their responses, using a 0.05 significance level.

Results: For most of the conditions, FMS patients were significantly more likely than RA patients to report that a stress caused their disease to flare, including emotional stress (58% vs. 43%, p= 0.042), physical stress (54% vs. 34%, p= 0.010), lack of sleep (53% vs. 33%, p= 0.007), illness (39% vs. 12%, p < 0.001, anxiety (31% vs. 16%, p= 0.027),depression (25% vs. 10%, p = 0.012), and traumatic events (25% vs. 12%, p = 0.026).

Conclusion: FMS patients were significantly more likely than RA patients to identify specific stresses as a cause of disease flare-ups, such as emotional and physical stress. Fibromyalgia patients are more somatically sensitive and more often recognize stresses that aggrevate their symptoms. Stress reduction strategies might help fibromyalgia patients.

Disclosure: R. S. Katz, None; **L. Kwan**, None; **H. Leavitt**, None; **J. L. Polyak**, None.

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Abstract Number: 67

Higher Levels of Pro-Inflammatory and Lower Levels of Anti-Inflammatory Cytokines Are Present in Fibromyalgia Patients

Robert S. Katz[1], Hannah Leavitt[2] and Daniel Pickrell[2], [1]Rush University Medical Center, Chicago, IL, [2]Rheumatology Associates, Chicago, IL

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Background/Purpose: Abnormalities in the central processing of pain may play a role in fibromyalgia and cytokines could be targets for new therapies. We measured cytokine levels in the blood of patients with fibromyalgia.

Methods: 35 Fibromyalgia patients followed in a rheumatology office practice had their blood analyzed for cytokine levels by the University of Miami Immunology Lab. Normal levels were established in healthy controls by the lab. The following cytokines were measured: Pro-inflammatory: TNF alpha, TNF beta, TNF receptor I, TNF receptor II, interferon gamma , IL 1 alpha, IL 1 beta, IL 6. Anti-inflammatory: IL 4, IL 5, IL 10, IL 13. IL 17, IL 23.

Results: Abnormally high and low cytokine levels were:

	Anti-inflammatory		Pro-inflammatory		
	IL-10	IL-23	Ifn-g	TNF-alpha	TNF-beta
Patient Mean	4.1	7.2	42.6	39.3	34.1
Normal Mean	13.6	17.6	1.9	9.2	14.6

Conclusion: Higher levels of certain pro-inflammatory cytokines and lower levels of anti-inflammatory cytokines were found in these fibromyalgia patients. The significance of abnormal cytokine levels in fibromyalgia is unclear but cytokines could be important in the etiology of the disorder.

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Abstract Number: 68

The Stroop Word-Naming Test in Fibromyalgia Patients

Robert S. Katz[1], Alexandra Katz Small[1,2] and Kelli Davis[3], [1]Rush University Medical Center, Chicago, IL, [2]University of Illinois College of Medicine, Chicago, IL, [3]Rheumatology Associates S.C., Chicago, IL

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Background/Purpose: The Stroop Word-Naming Test has demonstrated decreased word-naming speed in many patients with fibromyalgia who experience the symptoms of fibrofog. The slower processing of information may disturb the synchrony of other neural circuits and lead to some of the symptoms of cognitive dysfunction termed "fibrofog."

Methods: We administered this test to rheumatic disease patients in a rheumatology office practice. Impairment of concentration due to distraction is present in many fibromyalgia patients, particularly using the auditory consonant trigram of neuropsychological tests. We have attempted to treat fibromyalgia patients with fibrofog symptoms with stimulants, including methylphenidate, Adderall, and Vyvanse.

Results: 18 rheumatic disease patients in a rheumatology office practice were given the Stroop Word-Naming Test. The test was administered by a rheumatology nurse. 13 of 18 (72%) patients had a diagnosis of fibromyalgia and met the 2010 ACR criteria. 5 of 18 patients (28%) had other rheumatic diseases. Of the patients with fibromyalgia, 7 of 13 were taking stimulant medication, including methylphenidate, Adderall (amphetamine and dextroamphetamine), or Vyvanse (lisdexamfetamine). The 5 rheumatic disease controls were not taking stimulant medication. Of the fibromyalgia patients, 12 were female and 1 was male. In the control group, 3 were female and 2 were male. The mean age of the fibromyalgia group was 52 years old (32-68). The mean age of the control group was 35 years old

(32-43). The education level of the participants was 5 high school graduates, 7 had some college experience, 3 had a bachelor's degree, 2 had a master's degree, and 1 had a law degree.

In the fibromyalgia patients not taking a stimulant for fibrofog, the mean Stroop score was 70.8 (47-89). In the fibromyalgia patients taking methylphenidate, amphetamine and dextroamphetamine, or lisdexamfetamine, the mean

Stroop score was 80.7 (range 53-113). The control group without fibromyalgia, none of whom were taking an ADHD type stimulant medication, had a mean Stroop score was 93.4 (83-111).

Conclusion: Fibromyalgia patients have reduced word-naming speed based on the Stroop Word-Naming Test. This test is simple to administer. Those fibromyalgia patients taking stimulant medication usually reserved for ADHD, but used clinically for some patients with fibrofog symptoms because of a significant effect of distraction on their cognitive ability, performed better than the fibromyalgia group not taking ADHD type medication, but still performed worse than the control group.

Fibromyalgia patients appear to be a beat behind in their cognitive functioning. This slower processing of certain kinds of information can be assessed through the Stroop Word-Naming Test.

Disclosure: R. S. Katz, None; **A. Katz Small**, None; **K. Davis**, None.

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Abstract Number: 69

Fibrofog in Mild and Severe Variants of Fibromyalgia

Robert S. Katz and Frank Leavitt, Rush University Medical Center, Chicago, IL
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Background/Purpose: : A triad of symptoms defines cognitive dysfunction in fibromyalgia known as fibrofog. The set of primary signs are short-term memory loss, a general loss of mental sharpness, and a disturbance in mental clarity. The stability of this symptom triad is uncertain, in a disorder than is marked by a high degree of symptom variability. The purpose of this study is to determine if the level of disease intensity needs to be taken into account, when assessing the symptom triad that defines fibrofog.

Methods: Participants were 61 female patients with a clinical diagnosis of fibromyalgia with a mean age of 50. 7±14.0 years and a mean education of 15.2±2.2 years. Data on memory loss was collected on a 0-10 point Likert scale with anchor points of no problems to severe problems. Data on mental sharpness and mental clarity were derived from the 16 item Mental Clutter Scale. Disease intensity was measured on a 4 point scale ranging from usual symptom status to symptoms severely intensified.

Results: For analytical purposes, disease intensity was collapsed into two categories; low and high disease intensity. The percentage of high and low disease intensity was 60.7% (37/61) and 39.3% (24/61) respectively. Comparisons between low and high disease intensity on short term memory, mental sharpness and mental clarity are shown in Table 1. As can be seen, high disease intensity was related to more severe problems with memory, significant reductions in mental sharpness ($p<0.001$), and severe disturbances in mental clarity ($p<0.001$). The mental clarity score of 3.33 in the low intensity group is approximately one standard deviation below the normative range for fibromyalgia patients with cognitive dysfunction (normative mean: 5.0±2.3).

Conclusion: Patients with fibromyalgia can and do present with mild to severe symptom variants. These symptom variants are associated with marked differences in the manifestations of the cardinal features of fibrofog. In the milder

symptom variants of fibromyalgia, symptom expression of fibrofog is likely to be muted. In fibromyalgia, knowledge of disease intensity is likely critical for accurately assessing the presence of fibrofog and needs to be taken into account.

Table 1. Comparison of Female Fibromyalgia Patients with High and Low Disease Intensity on the Cardinal Features of Fibrofog.

	Fibromyalgia (n=61)			
Disease Intensity	High	Low	(n=37)	(n=24)
Short Term Memory Problems[c]	5.86±2.29***	3.37±2.58***		
Decline in Mental Sharpness[c]	6.17±1.91	3.95±2.49***		
Disturbance in Mental Clarity[c]	5.47±2.27	3.33±2.33***		

[a] Values are mean ± sd.
[b] Higher score indicates greater magnitude of disturbance
[c] Symptom triad defining fibrofog

***Significant difference between groups ($P < 0.001$)

Disclosure: R. S. Katz, None; **F. Leavitt**, None.

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Data from Brazilian Fibromyalgia Patients Registry (EPIFIBRO) in 2014

Jose Eduardo Martinez[1,2], Marcelo C. Rezende[3,4], Eduardo Paiva[4,5], Daniel Pollak[4,6], Milton Helfenstein Jr[4,7], Jose Roberto Provenza[4,8], Aline Ranzolin[4,9], Roberto E Heymann[4,10], Eduardo L. Ribeiro[4,11], Marcos Renato Assis[4,12] and Eduardo J. R. Souza[4,13], [1]Sociedade Brasileira de Reumatologia, Sorocaba, Brazil, [2]Medicine, Pontifical Catholic University of Sao Paulo, Sorocaba, Brazil, [3]Santa Casa de Campo Grande, Campo Grande, Brazil, [4]Sociedade Brasileira de Reumatologia, São Paulo, Brazil, [5]Rheumatology, Universidade Federal do Parana, Curitiba, Brazil, [6]Rheumathology, Universidade Federal de São Paulo, São Paulo, Brazil, [7]RUA JOAO DE LACERDA SOARES, 90, Unifesp, Sao Paulo, Brazil, [8]Rheumatology, Pontificia Universidade Católica de Campinas, Campinas, Brazil, [9]Hospital das Clínicas - Universidade Federal de Pernambuco, Recife, Brazil, [10]Universidade Federal de São Paulo, São Paulo, Brazil, [11]Instituto de Previdência dos Servidores do Estado de Minas Gerais, Belo Horizonte, Brazil, [12]Faculdade de Medicina de Marilia, Marilia, Brazil, [13]Santa Casa de Belo Horizonte, Belo Horizonte, Brazil
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Background/Purpose: –The Brazilian registry on fibromyalgia syndrome (EPIFIBRO) included 810 patients who satisfied the American College of Rheumatology Classification Criteria for Fibromyalgia (ACR1990) at the time of diagnosis. Objectives – 1. To determine how many patients fulfill the ACR1990 and the 2010 Preliminary Diagnostic Criteria for Fibromyalgia (ACR 2010); 2. To determine if there is correlation between the impact of FM measure by the Fibromyalgia Impact Questionnaire (FIQ) and by the Polissymptomatic Distress Scale (PDS); 3. To describe data on the follow-up evaluation of the patients enrolled in the registry.

Methods: A transversal study on a multicenter cohort of Brazilian Fibromyalgia patients. The analysis included the following evolution parameters: Pain and Fatigue Analogical Numerical Scales (PNS and FNS); FIQ and PDS at entry and at the last registered evaluation. Statistical analysis included descriptive statistics and the Pearson Correlation Scale. In order to analyze the follow-up measures 30% up or down variation was defined as the minimal clinically significant difference.

Results: The mean value observed for the PNS was 8.4 ± 1.9, for FNS was 7.9 ± 2.3, for FIQ was 68.5 ± 17.1 and for PSD was 22.19 ± 5.8. In order to establish the concordance of the ACR1990 and the ACR2010 criteria 613 patients were analyzed. The fulfillment of diagnostic criteria was observed in 386 (62.9%) patients for the ACR 1990, 529 (86.2%) for the ACR 2010 and 347 patients (56.6%) for both criteria, while 39 (6.3%) only met the ACR 1990 and 185 (30.1%) only met the ACR 2010. There is a low correlation between PNS and PDS and a moderate correlation between PNS and FIQ (r = 0.359; 0.687). There was no correlation between FNS and PDS or FIQ (r = 0.073; 0.017). It was also found a moderate correlation between the FIQ and the PDS (r = 0.576). There were 314 patients with more than one evaluation. Eighty-eight patients with less than a month from the entry were excluded resulting in 226 patients with at least one follow up parameter registered (FIQ – 222; PDS – 199; both 195). Patient registry included 221 females (97.78%) and only 5 male subjects (2.21%) with a mean age of 51.58 ± 10.56 years old. The mean time of follow up was 9.11 ± 7.47 months (1–44). The mean value of the initial FIQ score was 66.10 ± 19.59 and the final value was 67.06 ± 19.13. The mean initial score of the PDS was 22.53 ± 5.57 and the final one was 19.67 ± 6.67. There were no differences on both parameters. When considering the FIQ, 37 patients (16.6%) improved, 21 worsened (9.45%), and 164 (73.87%) were stable. Concerning the PDS, 39 patients (19.59%) improved, 9 worsened (4.52%), and 151 were unchanged (75.87 %). In 146 patients there was a concordance of the FIQ and PDS results (74.87%).

Conclusion: There was a weak correlation between the ACR1990 and ACR2010. It was observed a moderate correlation between the FIQ and the PDS used to evaluate the Fibromyalgia Syndrome impact. Most Brazilian Fibromyalgia patients from EPIFIBRO Registry did not show changes in follow up parameters over time. FIQ and PSD showed good correlation in this follow up study.

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Abstract Number: 71

Fibromyalgia Dysautonomia and Distress. Correlation Between the Newly Developed Composite Autonomic Symptoms (COMPASS-31) Questionnaire and the Fibromyalgia Polysymptomatic Distress Scale

Laura-Aline Martinez-Martinez[1], Maya Chacón Pérez[2], Paola Reyes-Loyola[3] and Manuel Martínez-Lavín[3], [1]National Institute of Cardiology. Mexico, Mexico City, TX, Mexico, [2]National Institute of Cardiology, Mexico City, Mexico, [3]National Institute of Cardiology. Mexico, Mexico City, Mexico

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Background/Purpose:

A consistent line of investigation suggests that dysautonomia may explain the multisystem fibromyalgia features, and that fibromyalgia is a sympathetically maintained neuropathic pain syndrome. The sympathetic nervous network is the main component of the stress response system (Arthritis Res Ther. 2007;9:216).

The ACR 2010 preliminary fibromyalgia diagnostic criteria is based on the Polysymptomatic Distress Scale. According to its developers, this scale is able to assess illness severity while still allowing a dichotomous diagnosis (Arthritis Care Res. 2010;62:600). We noted that Polysymptomatic Distress Scale items have clear dysautonomia connotations.

COMPASS-31 is a newly developed questionnaire to appraise dysautonomia. In contrast to the old COMPASS questionnaire, this new version has simplified scoring algorithm, and is suitable for widespread use in autonomic research and practice (Mayo Clin Proc. 2012;87:1196).

The objectives of our study were: 1) To correlate COMPASS-31 with the Polysymptomatic Distress Scale and with the Fibromyalgia Impact Questionnaire in 3 different groups of adult women: patients with fibromyalgia, patients with rheumatoid arthritis or healthy controls. 2) To compare the burden of dysautonomia symptoms in these 3 groups of individuals.

Methods: ,

To date, we have studied 25 women with fibromyalgia (ACR 1990 + ACR 2010 criteria), 19 with active rheumatoid arthritis (ACR criteria) and 24 healthy controls. All participants filled out the following questionnaires: COMPASS-31, Fibromyalgia Impact Questionnaire, and Polysymptomatic Distress Scale.

Results:

Age was similar in the 3 studied groups (mean: 41 years). In fibromyalgia patients there was correlation between COMPASS-31 scores and Polysymptomatic Distress Scale (Spearman Rho = 0.583, $p = 0.002$) and between COMPASS-31 and Fibromyalgia Impact Questionnaire (Rho = 0.525, $p = 0.007$). Remarkably, there was a strong correlation between COMPASS-31 scores and pain VAS values (Rho = 0.721, $p < 0.0001$). Patients with rheumatoid arthritis did not display such COMPASS 31 - pain VAS values correlation (Rho = - 0.024, $p = 0.92$). Patients suffering from fibromyalgia had much higher COMPASS-31 values (39.7 ± 15.3) when compared with rheumatoid arthritis patients (9.5 ± 8.5) and healthy controls (9.05 ± 8.7) $p < 0.0001$.

Conclusion:

Patients suffering from fibromyalgia have much more dysautonomia symptoms when compared to rheumatoid arthritis patients. In fibromyalgia, but not in rheumatoid arthritis, pain is closely related to autonomic dysfunction. There is correlation between the Polysymptomatic Distress Scale and COMPASS-31. Therefore, dysautonomia rather than "polysymptomatic distress" may be fibromyalgia's underlying pathogenesis. COMPASS-31 may become a useful clinical instrument to evaluate fibromyalgia's multisystem features.

Disclosure: L. A. Martinez-Martinez, None; **M. Chacón Pérez**, None; **P. Reyes-Loyola**, None; **M. Martínez-Lavín**, None.

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Performance of the New Survey Criteria for Fibromyalgia Under

Conditions of Low and High Symptom Activity

Robert S. Katz and Frank Leavitt, Rush University Medical Center, Chicago, IL
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Background/Purpose: In 2010, new criteria for fibromyalgia were proposed. In 2011, the questionnaire was adjusted so that patients provided the necessary information to satisfy the following criteria: Widespread Pain Index score (WPI) ≥ 7 and a Symptom Severity Score (SS) ≥5, or WPI of 3 to 6, and an SS score ≥ 9. In addition, a 0-31 Fibromyalgia Symptom Scale (FS) was developed by adding the 19 items of the WPI to the 12 items of the SS scale. Fibromyalgia symptoms wax and wane. The purpose of this study is to determine if the level of disease activity needs to be taken into account, when applying the new criterion sets in survey research.

Methods: The original questionnaire contained two scales; in one, patients record areas of pain and tenderness on a 19 point pain drawing; in the second, patients describe symptom severity on a 12 point range. The survey questionnaire (SQ) simplified the clinician somatic symptom report, by reducing it to yes-no answers to 3 symptoms (Lower abdominal discomfort, depression and headaches). Disease activity was measured on a 4 point scale ranging from usual symptom status to Symptoms severely intensified. The SQ was administered to 61 randomly selected women with a clinical diagnosis of fibromyalgia (FMS).

Results: The mean age of the FMS sample was 50.7±14.0 years with 15.2±2.2 years of education. The modified criteria were satisfied by 54.1% of the women who carried a clinical diagnosis of fibromyalgia. The FSS scale using a threshold score ≥ 13 was satisfied by 68.9% of the same women. For further analytical purposes, disease activity was collapsed into two categories; low and high disease activity. Performance of the modified criteria and FSS scale when disease activity is taken into account is shown in Table 1. As can be seen, sensitivity of both measures improved by over 30% when disease activity was high (67.6% versus 33.3%-modified measure; 81.1% versus 50.0%- FS scale).

Conclusion: Symptom variability is a problem for the new criterion sets for fibromyalgia and needs to be taken into account. People will engage in survey research at different levels of disease activity and are considerable more likely to satisfy the new criteria in periods or symptom exacerbation, often referred to as flare-ups. Taking symptom intensity into account is likely to generate more homogenous groupings within the fibromyalgia spectrum. In the low disease activity state, many patients are likely to function below the level of the new criteria.

Table 1. Performance of the New Modified Criteria[a] and the FSS criteria[b] in Classifying Patients with a Clinical Diagnosis of Fibromyalgia at Two Levels of Symptom Intensity.

	Modified Criteria		FSS criteria	
Symptom Intensity	Low	High	Low	High
Sensitivity[c]	8 (33.3%)	25 (67.6%)**	12 (50%)	30 (81.1%)**
False Negatives[d]	16 (66.7%)	10 (27.0%)	12 (50%)	7(18.9%)

**p<0.01

[a]Modified Criteria: Widespread Pain Index score (WPI)≥ 7 and a Symptom Severity Score (SS) ≥5 , or WPI of 3-6, and a SS score ≥ 9

[b] Fibromyalgia Symptom Scale Criteria: FS ≥ 13, with a 0-31 range.

[c]Sensitivity – test is positive for individual with clinical diagnosis of fibromyalgia.

[d]False Negative - test is negative for individual with clinical diagnosis of fibromyalgia.

Disclosure: R. S. Katz, None; **F. Leavitt**, None.

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Abstract Number: 73

Anti -N-Methyl-D-Aspartate Receptor Antibody Is Associated with Fibromyalgia in Patients with Systemic Lupus Erythematosus

Jeong-Won Lee[1], Dong-Jin Park[2], Yi-Rang Yim[1], Ji-Eun Kim[1], Kyung-Eun Lee[1], Lihui Wen[1] and Shin-Seok Lee[1], [1]Chonnam National University Medical School and Hospital, Gwangju, South Korea, [2]Rheumatology, Chonnam National University Medical School and Hospital, Gwangju, South Korea

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SESSION INFORMATION

Session Date: Sunday, November 8, 2015

Session Title: Fibromyalgia, Soft Tissue Disorders, Regional and Specific Clinical Pain Syndromes Poster I

Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose: The high concordance of systemic lupus erythematosus (SLE) with fibromyalgia (FM) suggests common underlying mechanisms related to pain and distress in both patient groups. This study was aimed to evaluate roles of NMDAR antibodies in development of FM in SLE patients.

Methods: Sera from 104 SLE patients, 112 FM patients, and 110 healthy controls were analyzed to detect titers of antibodies to N-terminus of 2B subunit of NMDAR (GluN2B). Clinical, laboratory data and concomitant diseases were found by reviewing the patient charts. We underwent clinical examination and neuropsychiatric evaluation, and interviewed SLE patients using a structured questionnaire that included FM and neuropsychiatric symptoms.

Results: 18 patients (17.3 %) of total 104 SLE patients were revealed having FM. The titer of anti-GluN2B antibodies was significantly higher in SLE patients than FM patients and healthy controls ($P < 0.001$). In SLE patients, patients with concomitant FM showed higher titers of anti-GluN2B antibodies ($P < 0.05$). The titers of anti-GluN2B antibodies were correlated with tender point count (Spearman's rho = 0.238, $P = 0.016$) and widespread pain index (Spearman's rho = 0.276, $P = 0.005$), but not with other symptom scales. Anti-GluN2B antibody-positive SLE patients were more likely to have NPSLE and concomitant FM ($P < 0.05$). In multivariate analysis, Anti-GluN2B antibody was independent predictor of concomitant FM and NPSLE.

Conclusion: This is the first study to present that antibodies to NMDAR may be associated with pathogenesis of FM in SLE patients.

Disclosure: J. W. Lee, None; **D. J. Park**, None; **Y. R. Yim**, None; **J. E. Kim**, None; **K. E. Lee**, None; **L. Wen**, None; **S. S. Lee**, None.

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Abstract Number: 74

Clinical Characteristics of Fibromyalgia in a Chronic Pain Population

Mark Gostine[1], Fred Davis[1], Bradley Roberts[2], Rebecca Risko[2], Joseph Cappelleri[3], **Michael Asmus**[4], Andrew Clair[5] and Alesia Sadosky[6], [1]Michigan Pain Consultants, PC, Grand Rapids, MI, [2]ProCare Systems, Inc., Grand Rapids, MI, [3]Biostatistics, Pfizer, Inc., Groton, CT, [4]North American Medical Affairs, Pfizer, Inc., Middleton, WI, [5]Pfizer Inc., New York, NY, [6]Pfizer Inc,, New York, NY

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Session Time: 9:00AM-11:00AM

Background/Purpose: The study's purpose was to advance the understanding and treatment of fibromyalgia (FM) for patients in a chronic pain management center. FM is a chronic disorder that causes widespread musculoskeletal pain and fatigue, as well as a number of other symptoms. FM pain ranges from mild to incapacitating. Given the many possible co-morbidities associated with FM, we set out to examine clinical characteristics of FM patients compared with those with chronic pain but without FM. We did this to identify and better match patients to appropriate therapy.

Methods: This was a retrospective study with a case-control design based on data collected from July 1999 to February 17, 2015 in multiple chronic pain clinics in the United States. Patients were assigned to the case group of FM patients based on specific inclusion criteria. Propensity-score 1:1 matching was used to match controls (non-malignant chronic pain patients without FM) to cases based on identified confounders. A final sample of 1,070 controls and 1,069 cases was obtained to investigate co-morbidities, procedures, and regions of pain associated with FM. Items from a pain health assessment were also used to investigate patient-reported measures such as impairment, pain, fatigue, and quality of sleep. Pearson's chi-square and odds ratios were used to assess the significance and magnitude of relationships, two-sample t-tests were used for patient procedures, and a mixed model with repeated measures was implemented for patient-reported outcomes. Confidence intervals and effect sizes were included for each individual analysis.

Results: Nine additional International Classification of Diseases, Clinical Modification (*ICD-9*-CM) diagnoses were found to have odds ratios with large effect sizes (Cohen's $d > 0.8$). These diagnoses included chronic pain syndrome, latex allergy, muscle spasm, fasciitis, cervicalgia, thoracic pain, shoulder pain, rheumatoid arthritis, and cervical disorders (all $p < 0.0001$). Six diagnoses were found to have a moderate effect size (Cohen's $d > 0.5$): cystitis, cervical degeneration, anxiety, joint pain, lumbago, and cervical radiculitis. Current Procedural Terminology (CPT) procedure codes for musculoskeletal pain, specifically, trigger point injections, were shown to be used to treat FM cases in 5.9 more instances than controls, on average. There was insufficient evidence to suggest that patient-reported items from the pain health assessment were significantly different between cases and controls.

Conclusion: Multiple co-morbidities, diagnoses, and procedures were associated with FM patients in this study. Pain management physicians are uniquely positioned to treat FM patients. When coding procedural work they are driven by billing codes associated with each procedure and sometimes miss the fact they are dealing with a FM patient. Our goal is develop an alert system of diagnoses and procedures that would help doctors in differentiating FM patients from other painful conditions. Doing so is more practical and realistic than the current symptom severity scale and widespread pain index, both of which are rarely obtained in the pain management clinical setting.

Disclosure: M. Gostine, Pfizer, Inc. 235 E 42nd Street, New York, NY, 2; **F. Davis**, Pfizer, Inc., 235 E 42nd St., New York, NY, 2; **B. Roberts**, ProCare Systems, Inc., 3; **R. Risko**, ProCare Systems, Inc., 3; **J. Cappelleri**, Pfizer Inc, 3; **M. Asmus**, Pfizer, Inc., 235 E 42nd Street, New York, NY, 3; **A. Clair**, Pfizer Inc, 1,Pfizer Inc, 3; **A. Sadosky**, Pfizer Inc, 3,Pfizer Inc, 1.

Abstract Number: 75

Fibromyalgia and Positional Cervical Cord Compression Differ Only By Autonomic Nervous System Consequences: A Double-Blinded, Prospective Study

Andrew Holman, Pacific Rheumatology Reseach, Seattle, WA
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Session Time: 9:00AM-11:00AM

Background/Purpose:

In 1998, C Muhle and D Resnick proposed a corollary to cervical spinal stenosis caused by intermittent abutment of the cervical spinal cord from dynamic shifting of degenerative discs with flexion and extension of the neck.[1] This positional cervical cord compression (PC3) has been documented in 54-71% of patients with fibromyalgia (FM)[2,3] and was an exclusion criterion in the pramipexole FM randomized controlled trial[4]. In animal models, PC3 is a potent sympathetic nervous system arousal[5].

In humans, PC3 is so difficult to distinguish from FM (without dynamic imaging) that its validity and impact have been questioned. Given PC3 and FM symptom overlap, a blinded study was conducted.

Methods: Patients diagnosed with fibromyalgia per American College of Rheumatology 1990 classification criteria were recruited from the Seattle area and after consent, were provided standard, non-contrast cervical spine magnetic resonance imaging (MRI) with two additional saggital flexion and extension views with spinal canal diameter measurement at each disc level. PC3 was defined by a canal narrowing below 10 mm at any level WITH clear visual abutment of the cervical spinal cord by the commensurate disc and ligamentum flavum[2].

Double-blinded to the MRI results, subjects were assessed by history, physical examination, and a variety of surveys, including the Multidimensional Health Assessment Questionnaire (MDHAQ), Fibromyalgia Impact Questionnaire (FIQ), Short Form Health Survey (SF-36), Epworth Sleepiness Scale (ESS), Fatigue Severity Scale (FSS), Health Assessment Questionnaire (HAQ), 16-item Quick Inventory of Depressive Symptoms (QIDS) as well as autonomic nervous system (ANS) assessment by 5-minute, frequency domain, heart rate variability (HRV) of parasympathetic, sympathetic and total power measures (Omegawave Ltd, Espoo, Finland). Statistical analysis was conducted using Wilcoxon rank-sum for continuous variables and Fisher's exact test for categorical variables.

Results: Fifty-four patients with FM participated in this study (92% women, mean age 45.2 years). PC3 was identified in 31 of 54 subjects (57.4%). All three ANS HRV measures demonstrated statistical significance. Consistent with animal model data, parasympathetic score was lower 0.145 ± 0.067 for PC3+ patients and higher 0.198 ± 0.098 for PC3- patients (p=0.029). Sympathetic score was higher 61.0 ± 17.5 for PC3+ patients and lower 46.2 ± 15.8 for PC3- patients (p=0.005). Total power score was lower 440 ± 492 for PC3+ patients and higher 1633 ±4232 for PC3- patients (p=0.022). No clinical, historical or survey measures distinguished PC3-FM+ patients from PC3+FM+ patients.

Conclusion: This study provides the first evidence that intermittent, positional abutment of the cervical cord is a potent sympathetic arousal in humans. It also highlights the challenge of diagnosing and addressing PC3 without imaging. Further investigation will to sort out the role of PC3 in the diagnostic conundrum of FM, its pathogenesis and its treatment algorithms.

1. Am J Neuroradiol. 1998;19(9):1763-71. 2. J Pain 2008;9(7):613-22. 3. Presented at MYOPAIN 2010, Toledo, Spain. 4. Arthritis Rheum 2005;52(8):2495-2505. 5. Neuroscience 1999;88(3):959-973.

Disclosure: A. Holman, None;

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/fibromyalgia-and-positional-cervical-cord-compression-differ-only-by-autonomic-nervous-system-consequences-a-double-blinded-prospective-study

Abstract Number: 76

Evaluating Weather's Effect on Fibromyalgia Patients Using the Revised Fibromyalgia Impact Questionnaire and the Brief Pain Inventory

Daniel Kim[1], Ruth Chan[1], Marcal Plans[2] and Kevin Hackshaw[1], [1]Rheumatology & Immunology, Ohio State University, Columbus, OH, [2]Food Science and Technology Department, Ohio State University, Columbus, OH

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Session Time: 9:00AM-11:00AM

Background/Purpose: The objective of this study was to evaluate whether weather had an affect on fibromyalgia symptoms as measured by the Revised Fibromyalgia Impact Questionnaire (FIQR) and the Brief Pain Inventory (BPI), which had not been reported previously.

Methods: 67 female patients with fibromyalgia from the Ohio State University Rheumatology clinic were recruited to participate in the study. We received survey results back from 30 patients. Patients were given questionnaires for the FIQR and BPI to fill out every day for 7 consecutive days. Data was collected from February 1, 2015 through February 7, 2015. We recorded daily weather parameters (temperature, humidity, and barometric pressure) during evening time for Columbus Ohio from the National Weather Service website beginning on January 31, 2015 to Feb 8, 2015. After the data was centered to remove the bias effect for each patient, linear correlation between temperature, humidity, and barometric pressure was done using Pearson correlation coefficient. Analysis of covariance (ANCOVA) was used to correlate each patient trend with the weather parameters. Finally, principal component analysis (PCA) was used to recognize patterns in our data.

Results: No significant effect of weather on fibromyalgia symptoms was found using ANCOVA as measured by FIQR and BPI. PCA showed weak significant correlations between the second and the third principal components with the barometric pressure (0.26) and the humidity (-0.15), respectively. They accounted for only 6.6% and 5%, respectively, of the variability in our dataset which are too low to extract strong conclusions from.

Conclusion: This study investigated whether weather parameters of temperature, humidity, and barometric pressure could affect fibromyalgia symptoms using FIQR and BPI to measure symptoms, which had not been done before. We did not find any statistically significant effect of weather on fibromyalgia symptoms as measured by FIQR and BPI.

PCA of the FIQR and BPI showed low correlation with barometric pressure and humidity but they accounted for only 6.6% and 5% of the variability in our dataset, which are too low to extract strong conclusions from.

Disclosure: D. Kim, None; **R. Chan**, None; **M. Plans**, None; **K. Hackshaw**, None.

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Abstract Number: 78

Exploratory Analysis of Somatic Symptoms in Fibromyalgia By Multidimensional Scaling and Latent Class Analysis

Marco Antivalle[1], Michele Battellino[1], Alberto Batticciotto[1], MariaChiara Ditto[1], Alessandra Mutti[1], Valentina Varisco[1], Federica Rigamonti[1], Fabiola Atzeni[1] and Piercarlo Sarzi-Puttini[2], [1]Rheumatology, L. Sacco University Hospital, Milano, Italy, [2]Rheumatology Unit, L. Sacco University Hospital, Milano, Italy

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Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose:

Attempts to individuate subsets of fibromyalgia patients based on the aggregation of different symptoms have so far produced conflicting results. The 2010 preliminary diagnostic criteria for fibromyalgia (1), with the suggestion of the symptoms to be considered in the diagnosis, offers a frame for further investigation on this topic.

Methods:

338 patients (314 F; 24 M, mean age 45.47±11.37 yrs) diagnosed with fibromyalgia (FM) according to 2010 criteria were studied. FM was evaluated by tender points (TP), Widespread Pain Index (WPI), and Symptom Severity Scale (SS). The clustering in a two-dimentional space of the 41 somatic symptoms to be considered according to 210 criteria was assessed by Multidimentional Scaling analysis (MDS) by the ALSCAL routine of IBM SSPS 20.0 package, and the existence of an undelying classificative structure was explored by Latent Class Analysis (LCA) by the R poLCA package.

Results:

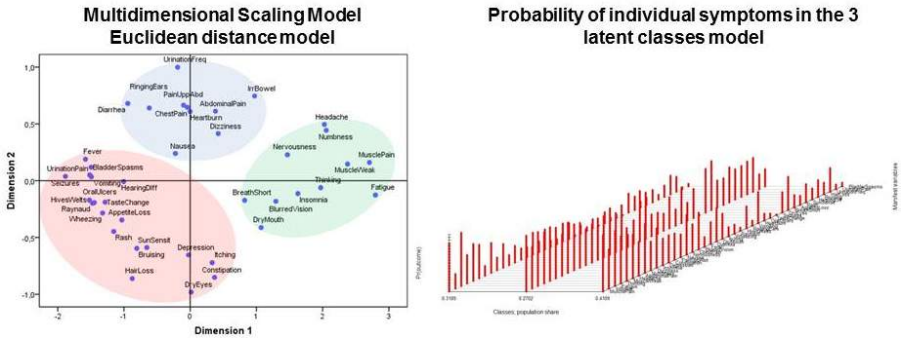
In the whole population, fibromyalgia scores were: TP 12.92±4.46, WPI 11.43±4.1 SS 9.04±2.10. Among somatic symptoms, muscle pain, muscle weakness, fatigue and thinking difficulties showed the highest similarity (Dice $\geq$ 0.8). Multidimensional scaling analysis was performed on the 41 somatic symptoms reported by the diagnostic criteria: the model was found to account for a substantial proportion of the variability of data (RSQ = 0.893); Kruskal stress was = 0.167. The Euclidean distance model (Fig. 1, left panel) showed at least 3 individualized grouping of symptoms: Group A symptoms, comprising muscle symptoms, fatigue and thinking difficulties, were prevalent in the majority (N = 225, 66.6%) of patients, while Group B (mainly digestive and urinary symptoms), and Group C (miscellaneous symptoms, including depression) symptoms were prevalent in 17.2% (N=58) and 16.3% (N=55) respectively. Group A patients reported the lowest total number of symptoms (16.8±5.4 vs 21.5±6.6 in group B and 23.0±7.9 in group C, p <0.001), and the lowest WPI (11.0±3.8 vs 11.5±4.5 and 14.1±4.6, p = 0.01); Group C showed also the highest TP count

(15.1±2.9 vs 12.9±3.9 in group A and 12.0±5.0 in group B). Fatigue, waking unrefreshed, and cognitive symptoms intensity were not different in the 3 groups ($p > 0.05$).Latent Class Analysis by poLCA showed that modeling the data from 1 to 3 latent classes produced only a small improvement in the model estimate (AIC coefficient from 15538.65 to 14578.15).

Conclusion:

The results of our study are consistent with the hypothesis of the existence of separate subsets FM patients, characterized by different clusters of symptoms stratified on the common core of altered pain sensation. The definite characterization of these subsets requires further studies, and more complex modeling of data with consideration of covariates.

References: 1) Wolfe F, et al. Arthritis Care Res. 2010;62:600-10



Disclosure: M. Antivalle, None; **M. Battellino**, None; **A. Batticciotto**, None; **M. Ditto**, None; **A. Mutti**, None; **V. Varisco**, None; **F. Rigamonti**, None; **F. Atzeni**, None; **P. Sarzi-Puttini**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/exploratory-analysis-of-somatic-symptoms-in-fibromyalgia-by-multidimensional-scaling-and-latent-class-analysis

Abstract Number: 79

Hypervigilence: Patients with Fibromyalgia Often Appear Very Sensitive to Environmental Stresses

Robert S. Katz[1], Kelli Davis[2], Lauren Kwan[2] and Jessica L. Polyak[2], [1]Rush University Medical Center, Chicago, IL, [2]Rheumatology Associates S.C., Chicago, IL

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Session Type: ACR Poster Session A

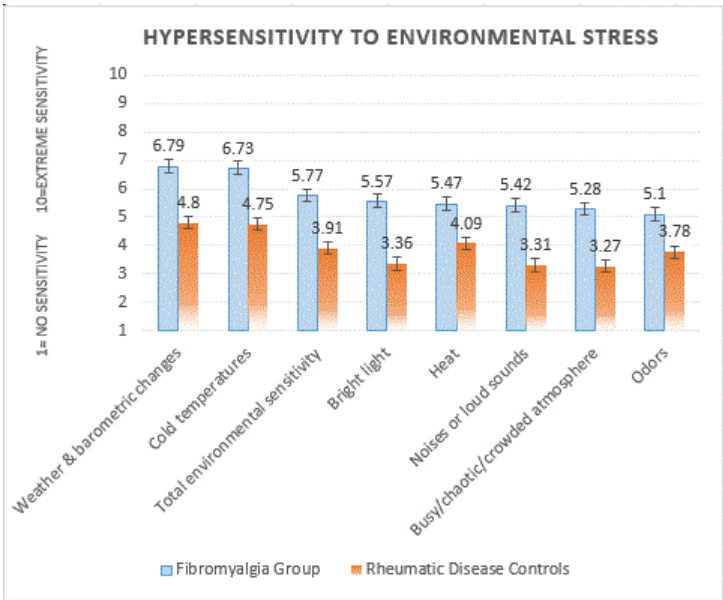
Session Time: 9:00AM-11:00AM

Background/Purpose: We inquired about hypervigilence and hypersensitivity to various environmental stresses in patients with fibromyalgia and in rheumatic disease controls.

Methods: 103 fibromyalgia patients with fibromyalgia and 124 rheumatic disease controls without fibromyalgia followed in a rheumatology office practice filled out a questionnaire regarding their sensitivity to various

environmental factors, including noises and loud sounds; light, certain artificial lighting or changes in brightness; certain odors and fragrances; cold temperatures; heat; busy, chaotic, or crowded atmospheres; weather or barometric pressure changes.

Results: See Chart



Conclusion: In every category of environmental stress, fibromyalgia patients were more sensitive than rheumatic disease controls. This supports the theory that fibromyalgia patients have a form of hypervigilence and are more sensitive to environmental stresses. Whether this hypervigilence was present before the onset of fibromyalgia is not assessed by this questionnaire, but hypervigilence and sensitivity to environmental stress potentially may play a role in both the etiology and exacerbation of symptoms in fibromyalgia.

Disclosure: R. S. Katz, None; **K. Davis**, None; **L. Kwan**, None; **J. L. Polyak**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/hypervigilence-patients-with-fibromyalgia-often-appear-very-sensitive-to-environmental-stresses

Abstract Number: 80

Paresthesias in Fibromyalgia Patients

Robert S. Katz[1], Lauren Kwan[2], Kelli Davis[2] and Jessica L. Polyak[2], [1]Rush University Medical Center, Chicago, IL, [2]Rheumatology Associates S.C., Chicago, IL

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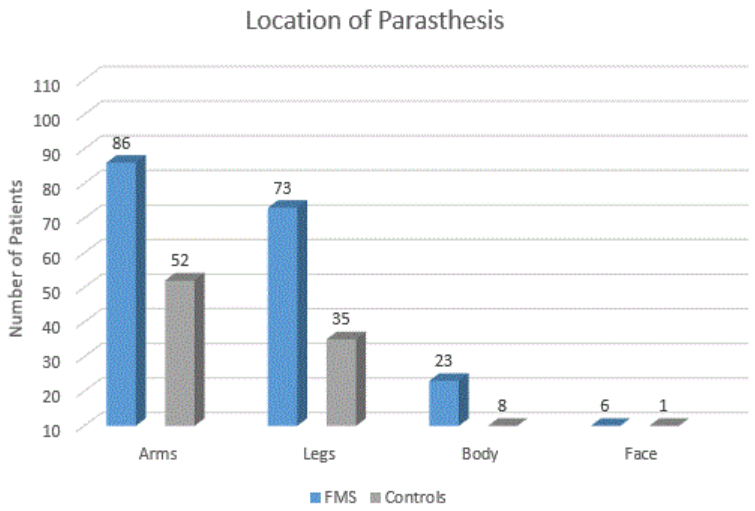
Background/Purpose: Paresthesias are common in patients with fibromyalgia. We evaluated the symptoms of numbness and tingling in fibromyalgia patients and rheumatic disease controls without fibromyalgia.

Methods: 104 fibromyalgia patients meeting the 2010 ACR criteria for fibromyalgia and 124 rheumatic disease controls without fibromyalgia answered a questionnaire regarding the presence of paresthesias. They were asked if they had numbness or tingling; whether it was constant, intermittent, or frequent; and also the location of their numbness and tingling; the intensity; whether there were color changes in the hands or feet; skin temperature changes; symptoms related to rubbing the area; symptoms related to putting on socks or gloves; and numbness and tingling related to activity.

Results: 104 fibromyalgia patients and 124 rheumatic disease controls without fibromyalgia responded to the questionnaire during an office visit in a rheumatology practice. 45% of the fibromyalgia patients compared with 19% of the controls indicated that they had frequent paresthesias, 55% of fibromyalgia patients versus 33% of the controls indicated that they had intermittent paresthesias, and 20% of fibromyalgia patients versus 9% of controls answered that they had constant paresthesias. 51% of the fibromyalgia patients versus 41% of the controls experience color changes in the hands and feet, 61% of fibromyalgia patients versus 45% of the controls had skin temperature changes, 28%.

On a 1-10 visual analog scale with 10 being very severe, fibromyalgia patients were 5.51 and controls were 4.83.



Conclusion: Fibromyalgia patients more often experience paresthesias than rheumatic disease controls. The paresthesias are more commonly frequent or constant compared with rheumatic disease controls without fibromyalgia. The paresthesias are often widespread and frequently associated with color changes in the hands and feet, skin temperature changes, symptoms when rubbing the area, symptoms with putting on socks or gloves, and paresthesias related to activity.

The subjective sensations of numbness and tingling, without a neurological deficit, appear to be a common component of the fibromyalgia syndrome. We suggest that fibromyalgia-related paresthesias be further described, such as using a term like “paresthesias of unknown etiology”or Idiopathic paresthesias (IP).

Similar to other syndromes based on subjective symptoms, such as irritable bowel syndrome and migraine, the terms “paresthesias of unknown etiology” or “idiopathic paresthesias” may describe patients with and without fibromyalgia who do not have a clear neurological basis for these symptoms.

A descriptive name might be reassuring to patients who otherwise feel that the physician thinks they are “crazy,” or that their paresthesias might be part of a more serious neurological syndrome (such as multiple sclerosis), despite reassurance from a neurologist or other practitioner.

Disclosure: R. S. Katz, None; **L. Kwan**, None; **K. Davis**, None; **J. L. Polyak**, None.

Abstract Number: 81

The Value of Routine Use of Creatine Kinase and Thyroid Stimulating Hormone Tests in Patients with Suspected Fibromyalgia: Results of a Cross-Sectional Study

Nadine Boers[1], Nathan den Broeder[1], Judith van Vliet[2], Ronald F. van Vollenhoven[3], **Nienke Lesuis**[1] and Alfons A. den Broeder[1], [1]Rheumatology, Sint Maartenskliniek, Nijmegen, Netherlands, [2]Neurology, Canisius Wilhelmina Ziekenhuis, Nijmegen, Netherlands, [3]Department of Medicine, Unit for Clinical Therapy Research, Inflammatory Diseases (ClinTRID), The Karolinska Institute, Stockholm, Sweden

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Background/Purpose:

Creatine kinase (CK) and Thyroid stimulating hormone (TSH) are frequently used tests in the diagnostic work-up of fibromyalgia (FMS) to exclude thyroid disease or myopathy. However, the diagnostic values of these tests in this clinical context are still unclear.

Methods:

All patients with suspected fibromyalgia, referred to the study hospital between November 2011 and April 2014 were asked to participate. Patients received a protocolized workup for FMS and exclusion of other disease using history, physical exam, neurological questionnaire, and additional testing when necessary. Patients with a previous diagnosis of thyroid disorder or a history of CK related disease were excluded.

Mean CK and TSH, percentage of abnormal CK and TSH values and the final diagnosis in patients with an abnormal CK or TSH value were used as outcome measures. An abnormal CK was defined as a CK >200 U/l for men and >170 U/l for women. Abnormal TSH was defined as a TSH <0.4 or >4.0 mE/l. Free Thyroid Hormone (FT4) was assessed when TSH was abnormal (reference values FT4: 8-22 pmol/l). The final diagnoses (ICD-9 code) were obtained from the patients' files.

Results:

375 patients with suspected FMS were included (patient characteristics: table 1). Mean CK and TSH in these patients were 96 ± 50 mE/L and 1.8 ± 1.4 U/L respectively.

26 (6.9%; 95%-confidence interval (95%-CI) 4.3%-9.5%) patients had a borderline abnormal CK, considered clinically irrelevant. In 2 (0.5%; 95%-CI -0.2%-1.2%) patients CK value was clearly elevated and therefore retested, resulting in a normal CK value at this second test. In none of the patients with an abnormal CK a CK-related diagnosis was made and the final diagnosis was fibromyalgia in most of them (n=25).

13 (3.5%; 95%-CI 1.6%-5.3%) patients had an elevated TSH and 5 (1.3%; 95-CI 0.2%-2.5%) a lowered TSH, with one patient also having an abnormal FT4 value. However, the latter was deemed insignificant by the treating

rheumatologist and the final diagnosis of all these patients was fibromyalgia.

Table 1 Characteristics of the patient population

Characteristic	**Study population (n = 375)**
Female sex, *n(%)*	354 *(94%)*
Mean age, *years (range)*	42 *(18-75)*
Second opinion, *n(%)*	107 *(29%)*
Previous diagnosis of fibromyalgia, *n(%)*	188 *(50%)*
ICD-9 diagnosis, *n(%)*	358 *(95)*
Fibromyalgia	17 *(5)*
Other	

Conclusion:

This study shows that abnormal CK and TSH values are rare in patients with suspected FMS referred to the hospital, and not resulting in another diagnosis as explanation for the complaints. Therefore, it seems that routine testing of CK and TSH levels, in secondary care, in all patients with suspected FMS does not contribute positively to the diagnostic process.

Disclosure: N. Boers, None; **N. den Broeder**, None; **J. van Vliet**, None; **R. F. van Vollenhoven**, None; **N. Lesuis**, None; **A. A. den Broeder**, None.

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Abstract Number: 82

Cross-Sectional Analysis of Heart Rate Variability in Patients with Fibromyalgia (FM): Correlations with Baseline Clinical Measures

Adam Dziuba[1], Nancy A. Lockhart[2], Howard Schubiner[3], Daniel J. Clauw[4], David A. Williams[5] and Mark A. Lumley[2], [1]Medical School, University of Michigan, Ann Arbor, MI, [2]Psychology, Wayne State University, Detroit, MI, [3]Wayne State University, Detroit, MI, [4]Anesthesiology, University of Michigan, Ann Arbor, MI, [5]Anesthseiology, University of Michigan, Ann Arbor, MI

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Background/Purpose: Autonomic nervous system (ANS) dysfunction is thought to play a role in the pathophysiology and symptoms of FM. Evaluation of the ANS may be done through heart rate variability (HRV) analysis. While HRV

has been shown to be abnormal in patients with FM, this is the largest study to examine relationships between HRV measures and clinical measures.

Methods: 230 patients (Age: 49.1 ± 12.2, 94% female) meeting 1990 ACR fibromyalgia criteria who were part of a randomized control trial of psychological interventions also had assessments of HRV measures at baseline prior to randomization. HRV was obtained via 30-minute Holter monitor recording which included periods of supine positioning, orthostatic challenge, and experimental pain testing. Time domain and frequency domain measures of HRV were calculated and analyzed with CardioScan Premier 12 software (DM Software, Stateline, NV). Age, sex, race, BMI, along with comorbidities diabetes mellitus and hypertension were adjusted for during analyses.

Results:

At baseline, a time domain measure of greater HRV, as reflected by the square root of the mean of the sum of the differences between adjacent N-N intervals (RMSSD), was significantly correlated with better sleep quality and lower fatigue ($\beta = -.15$, $p = .02$ and $\beta = -.129$, $p = .04$, respectively). Frequency domain measures of greater HRV, as reflected by total low-frequency power (LF) and total high-frequency power (HF) were found to be significantly correlated with lower anxiety ($\beta = -.13$, $p = .03$ and $\beta = -.14$, $p = .02$, respectively), better sleep quality ($\beta = -.13$, $p = .03$ and $\beta = -.15$, $p = .01$, respectively), lower fatigue ($\beta = -.13$, $p = .02$ and $\beta = -.14$, $p = .02$, respectively), and better mental health ($\beta = .16$, $p = .007$ and $\beta = .15$, $p = .01$, respectively). Similar associations were demonstrated in the supine positioning and orthostatic challenge periods ($p < .05$ for each), with the exception of LF component in supine positioning correlation to anxiety ($p = .11$) and HF component of orthostatic challenge correlation to fatigue ($p = .09$). LF and HF components during the pain-testing period did not reveal significant associations with clinical measures ($p > .05$ for each).

Conclusion: This study demonstrates that better clinical status is associated with greater HRV in a population of patients with fibromyalgia. Further work is needed to clarify whether changes contribute to the pathogenesis of FM, are caused by the FM, or are epiphenomena.

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View Abstract and Citation Information Online - http://acrabstracts.org/abstract/cross-sectional-analysis-of-heart-rate-variability-in-patients-with-fibromyalgia-fm-correlations-with-baseline-clinical-measures

Abstract Number: 83

Immediate Benefits of a Multidisciplinary Educational Program for Fibromyalgia on Patients' Pain Related Self-Efficacy and Health Locus of Control

Amrita Kaur Bath[1], Carmen E. Gota[2], Anabelle Morales Cavolo[3] and Sara Davin[4], [1]Internal medicine, Fairview Hospital- Cleveland Clinic, Cleveland, OH, [2]Orthopedic and Rheumatologic Institute, Cleveland Clinic, Cleveland, OH, [3]former Cleveland Clinic fellow, Cleveland, OH, [4]Neurologic Institute, Cleveland Clinic, Cleveland, OH

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SESSION INFORMATION

Session Date: Sunday, November 8, 2015

Session Title: Fibromyalgia, Soft Tissue Disorders, Regional and Specific Clinical Pain Syndromes Poster I
Session Type: ACR Poster Session A
Session Time: 9:00AM-11:00AM

Background/Purpose: To evaluate the effect of an intensive, brief, multidisciplinary educational intervention on self – efficacy and locus of control specific self-management constructs, in patients who suffer from fibromyalgia (FM).

Methods: Patients and family actively participated in a brief educational program involving discussion about clinical, pathophysiologic, and therapeutic aspects of FM; exercise instruction, orientation on the cognitive behavioral model of pain and stress, review of psychosocial contributors to chronic pain, family education, and introduction to relaxation techniques. Patients completed Pain Related Self Efficacy Questionnaire (PSEQ) and Multidimensional Health Locus of Control Scale (MHLC Form C subscale) questionnaires before and immediately after the program.

Results: From May 2014 to April 2015, 77 female patients, who met the ACR 2010 preliminary criteria for FMS, mean age 48.3 (10.9), 44.2% employed, with poly symptomatic distress score of 21.6 (5), participated in an 3.5 hour educational program. Fibromyalgia impact questionnaire revealed severe levels of symptomatology 62 (18.2), and patients had moderate depressive symptoms by patient heath questionnaire 9, 13.9 (6.5). The program was rated very or extremely helpful by 79.7% of patients, with 78.6% reporting getting answers to most or all their questions. Results showed significant increases in PSEQ ($p<0.0001$), and decreases in external locus of control MHLC "chance" ($p<0.0001$).

Conclusion: These results show that a brief multidisciplinary educational program in FM can significantly enhance self efficacy related to pain and external attributions in patients with severe FM and moderate depression. Our study supports the utility of short education programs on positive coping for FM patients.

Disclosure: A. K. Bath, None; **C. E. Gota**, None; **A. Morales Cavolo**, None; **S. Davin**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/immediate-benefits-of-a-multidisciplinary-educational-program-for-fibromyalgia-on-patients-pain-related-self-efficacy-and-health-locus-of-control

Abstract Number: 84

Sexual Dimorphism in the Association Between Multi-Site Pain and Other Fibromyalgia Features: an Analysis of Data from Three UK Population-Based Studies

Linda E. Dean[1], Lesley Arnold[2], Robert Bennett[3], Leslie J. Crofford[4], Don Goldenberg[5], Elisa Flüß[1], Daniel J. Clauw[6], Mary-Ann Fitzcharles[7], Eduardo Paiva[8], Roland Staud[9] and Gary J. Macfarlane[1], [1]Musculoskeletal Research Collaboration (Epidemiology Group), University of Aberdeen, Aberdeen, United Kingdom, [2]University of Cincinnati, Cincinnati, OH, [3]SN-Office of Research & Development, Oregon Health & Science Univ, Portland, OR, [4]Medicine, Vanderbilt University, Nashville, TN, [5]Newton-Wellesley Hospital, Newton, MA, [6]Anesthesiology, University of Michigan, Ann Arbor, MI, [7]MGH, Montreal, QC, Canada, [8]Rheumatology, Universidade Federal do Parana, Curitiba Parana, Brazil, [9]University of Florida, Gainesville, FL
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Background/Purpose:

The 2011 modification of the preliminary 2010 American College of Rheumatology criteria for fibromyalgia require the self-report of multi-site pain in addition to a number of additional symptoms: fatigue, sleep disturbance, somatic symptoms and cognitive problems. As part of the ACTTION[1]initiative - developing a new taxonomy for pain conditions, including fibromyalgia – the current study aimed to investigate whether there is sexual dimorphism between the presence of multi-site pain (MSP) and these additional features.

Methods:

Three UK-based population studies were used for the current analysis: the 1958 Birth Cohort, EpiFunD and SHAMA studies. MSP was defined as the presence of pain in at least eight body sites, (as indicated on 4-view body manikins with a total of 35 designated sites), regardless of location.

Amongst those reporting MSP, the relationship between gender and: fatigue (lowest tertile of SF-36 Vitality (VT) Scale), sleep disturbance (Estimation of Sleep Problem Scale score 12-20), presence of somatic symptoms (Somatic Symptom Scale) and poor mood (highest tertile of General Health Questionnaire, lowest tertile of SF-36 Mental Health (MH), and Hospital Anxiety and Depression Scales (HADS)), were assessed using logistic regression models including terms for gender. **Results** are presented as Odds Ratio (OR), with 95% Confidence Intervals (CI).

Results:

There were 26,452 participants across the three study populations (mean age range: 42-55 yrs, proportion male: 43-52%). The prevalence of MSP ranged between 12 and 17% and, within these groups, 35-47% were male.

Amongst those reporting MSP; females reported higher levels of sleep disturbance [OR 1.2, 95% CI 1.002-1.7] and more somatic symptoms compared to males [mean 1.8, CI 1.7-1.9 vs. 1.5, 1.3-1.6]. There was also some indication that females reported higher levels of fatigue [SF36 VT 1.7, 0.97-2.9], poorer mental health [GHQ 1.4, 1.2-1.6; SF36 MH 1.3, 0.8-2.3], in addition to higher levels of anxiety [HADs 1.2, 0.9-1.7], although differences were small and not always statistically significant. There was, however, no indication that females exhibited higher levels of clinical/borderline depression [HADS 0.8, 0.6-1.1].

Conclusion:

Amongst those with MSP, sex differences in the reporting of features typical of fibromyalgia are generally small and not always statistically significant, though females exhibit more sleep problems and higher levels of fatigue.

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[1] Analgesic, Anesthetic, and Addiction Clinical Trial Translations, Innovations, Opportunities, and Networks

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based-studies

Abstract Number: 85

Low Socioeconomic Status, High Disability Rates, and Increased Use of Health Care Resources in Fibromyalgia Patients Taking Narcotics

Carmen E. Gota[1], **Sahar Kaouk**[2] and William Wilke[3], [1]Orthopedic and Rheumatologic Institute, Cleveland Clinic, Cleveland, OH, [2]Undergraduate, John Caroll University, University Heights, OH, [3]retired Cleveland Clinic staff, Cleveland, OH

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Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose:

To determine the prevalence and characteristics of fibromyalgia patients who are prescribed opiod drugs.

Methods:

Consecutive patients who met the ACR 1990 criteria for fibromyalgia, seen in a tertiary care center, were dichotomized based on current prescription of opioid drugs (yes/no). Demographic and clinical data were compared. The following questionnaires were used: fibromyalgia impact questionnaire (FIQ), patient health questionnaire (PHQ-9), health assessment questionnaire disability index (HAQ-DI).

Results:

Of 240 patients 38.3% were prescribed opioid medications. Patients who were prescribed opiates as treatment, compared to those who were not, had significantly ($p \leq 0.05$) lower employment rates 31.5% vs 48.6%, were less college educated 23.4% vs 41.7%, had higher pain scores, FIQ pain 8.2 (1.7) vs 7.3 (2.1), depression PHQ-9 13.2 (6.3) vs 11.5 96.1), disability HAQ DI 1.4 (0.5) vs 1 (0.6), and reported severe fibromyalgia impact, FIQ 73.1 (15.1) vs 64.8 (18.3). They were also taking more medications for fibromyalgia 4.8 (1.9) vs 2.1 (1.8), had more surgeries 5.1 (3.9) vs 3.2 (3), and more doctor visits in the past 6 months 11.9 (11.5) vs 7.7 (8.4).

Conclusion:

Opioid use identifies about 1/3rd of tertiary care FM patients, a group with low socioeconomic status, and high use of medical resources. Our study suggests that clinicians prescribe opiates for FM patients who have severe disease, despite taking other drugs for FM. The high pain scores reported at the time of taking narcotic medications also raise questions about the benefit of prescribing these drugs in FM.

Disclosure: C. E. Gota, None; **S. Kaouk**, None; **W. Wilke**, None.

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Abstract Number: 86

Auxilin Is a Novel Susceptibility Gene for Congenital Heart Block Modulating Cardiac Function

Sabrina Meisgen[1], Malin Hedlund[1], Aurélie Ambrosi[1], Lasse Folkersen[2], Vijole Dzikaite-Ottosson[3], Bo Ding[1], Linn Strandberg[4], Luca Biavati[4], Daniel Ramsköld[5], David Forsberg[1], Lisa Bergin[1], Sabrina Ruhrmann[1], The Swedish Congenital Heart Block Study Group[1], Robert M. Hamilton[6], Anders Franco-Cereceda[1], Anders Hamsten[1], Tomas Olsson[7], Lois Greene[8], Per Eriksson[1], Kristina Gemzell-Danielsson[1], Stina Salomonsson[1], Vijay K. Kuchroo[9], Eric Herlenius[1], Ingrid Kockum[7], Sven-Erik Sonesson[1] and Marie Wahren-Herlenius[10], [1]Karolinska Institutet, Stockholm, Sweden, [2]Technical University of Denmark, Copenhagen, Denmark, [3]Department of Medicine, Rheumatology Unit, Centre for Molecular Medicine (CMM), Karolinska Institutet, Stockholm, Sweden, [4]Hospital for Sick Children Toronto, Toronto, ON, Canada, [5]Department of Medicine, Rheumatology Unit, Karolinska Institutet, Stockholm, Sweden, [6]Cardiology, The Hospital for Sick Children, University of Toronto, Toronto, ON, Canada, [7]Neuroimmunology, Department of Clinical Neurosciences, Karolinska Institutet, Stockholm, Sweden, [8]National Heart, Lung and Blood Institute, Bethesda, MD, [9]Center of Neurological Disease, Harvard Medical School, Boston, MA, [10]Department of medicine, Rheumatology unit, Karolinska Institutet, Stockholm, Sweden

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SESSION INFORMATION

Session Date: Sunday, November 8, 2015
Session Title: Genetics, Genomics and Proteomics Poster I
Session Type: ACR Poster Session A
Session Time: 9:00AM-11:00AM

Background/Purpose:

Congenital heart block (CHB) may affect children of women with anti-Ro/SSA and anti-La/SSB autoantibodies. The most recognized manifestation of CHB is an atrioventricular (AV) block, but atrial and ventricular arrhythmias, a prolonged isovolumetric contraction time and cardiomyopathies also affect a substantial proportion of the babies. The potentially lethal cardiac manifestations develop *in utero* during gestational weeks 18-24, and the risk of giving birth to a child with CHB is 1-2% in anti-Ro/SSA-positive pregnancies. A recurrence rate of only 12% despite persisting maternal autoantibodies suggests that additional factors influence disease development. The purpose of this study was to identify fetal genetic susceptibility factors for CHB, and to understand their functional impact on pathogenesis.

Methods:

We performed a genome-wide association study of >500,000 single nucleotide polymorphisms (SNP) in a population-based cohort of families with children diagnosed with CHB and analyzed transmission of SNPs based on genotypes of index cases (n=92) and first degree relatives (n=256). CHB-associated SNPs ($p \leq 1x10^{-4}$) were replicated in a population-based case-control analysis ($n_{controls}$=1122). Expression quantitative trait loci (eQTL) analysis was performed in cardiac tissue of genes present in the regions surrounding replicating SNPs (±500 kb) across both data sets. Human and mouse tissue expression of genes and proteins was assessed by qPCR, RNAseq, Western blot, immunohistochemistry and immunofluorescence staining. Functional analysis *in vitro* using primary cultured cardiomyoctes from genetically modified neonatal mouse pups was performed with time lapse Ca^{2+} recordings. Doppler echocardiography was used to assess cardiac disease phenotypes *in utero*.

Results: We discovered *DNAJC6* as a novel fetal susceptibility gene associated with CHB, with decreased cardiac expression of *DNAJC6* associated with the disease risk genotype. Auxilin, the putative tyrosine-protein phosphatase encoded by *DNAJC6,* was remarkably higher expressed in the fetal compared to the adult heart both before and during the risk period for CHB (>10 fold, $p < 0.001$). In human fetal cardiomyocytes we observed auxilin in the cytoplasm in a vesicular pattern, co-localized with clathrin, suggesting that the cellular function of auxilin in cardiomyocytes, as

already described for neurons, is within the clathrin-mediated endocytic process. Analysis of auxilin-deficient cardiomyocytes of neonatal mice revealed abnormal connectivity and Ca^{2+} homeostasis in culture. Doppler echocardiography of auxilin-deficient fetal mice *in utero* revealed several CHB-related manifestations *in vivo*, including AV-block, abnormal heart rhythm with atrial and ventricular ectopias and a prolonged isovolumetric contraction time as a sign of decreased myocardial performance.

Conclusion:

In conclusion, our study identifies auxilin as the first susceptibility gene in CHB modulating cardiac function, and connects the decreased auxilin expression observed for the susceptibility allele with clinical fetal CHB features.

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Abstract Number: 87

Rheumatoid Arthritis (RA) Risk Gene CCR6 Polymorphism: Drug-Induced “Reversal” of ER Binding and the Expression of Inflammatory Mediators -Potential Molecular Mechanism Links Between Estrogen and RA

Ming-Fen Ho[1], Richard M. Weinshilboum[2], Liewei Wang[2], James N. Ingle[3] and Tim Bongartz[4], [1]Department of Molecular Pharmacology and Experimental Therapeutics, Mayo Clinic Rochester, Rochester, MN, [2]Department of Molecular Pharmacology and Experimental Therapeutics, Mayo Clinic, Rochester, MN, [3]Department of Medical Oncology, Mayo Clinic, Rochester, MN, [4]Rheumatology, Mayo Clinic, Rochester, MN
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Background/Purpose: The rheumatoid arthritis (RA) risk locus *CCR6* SNP rs3093024, is in tight linkage disequilibrium with rs3093023 which has been associated with RA risk. RA is more common in females with an increased risk of disease and flares during the postpartum or postmenopausal periods—times of rapidly falling estrogen levels. We previously reported that these two SNPs in *CCR6* are associated with changes in the expression of CCR6 and, downstream, those of CCL20, IL17RA and IL17A in a SNP-dependent fashion in response to 17-β-estradiol (E2) treatment. In the present study, we set out to determine the effects of these *CCR6* SNPs on the expression of CCR6, CCL20, IL17RA and IL17A during estrogen withdrawal, which has been implicated in RA pathogenesis, as well as mechanism(s) underlying *CCR6*SNP function and estrogen-dependent gene expression regulation by functional genomic studies.

Methods: "Human Variation Panel" lymphoblastoid cell lines (LCLs) consisting of LCLs from 300 subjects were used to obtain genome-wide mRNA expression and SNP data. A panel of LCLs with six wild-type (WT; homozygous) and six variant (V; homozygous) genotypes for these SNPs, were used for functional genomic study. Cells were treated with E2 and the estrogen receptor α (ERα) antagonist fulvestrant. Changes in mRNA and protein expression after treatment were determined. ChIP assays were used to determine ERα binding to estrogen response elements (EREs) before and after ER blockade.

Results: Knockdown of CCR6 resulted in down-regulation of NF-κB p65 and phosphorylated IκB, indicating that *CCR6* plays a role in inflammatory pathways. CCR6, CCL20, IL17RA and IL17A expression was altered in a *CCR6* SNP estrogen-dependent fashion. Specifically, CCR6 and IL17RA were significantly up-regulated in response to E2 treatment, but only in cells homozygous for the *CCR6* SNP V alleles. Conversely, the expression of CCL20 and IL17A, which are the ligands for CCR6 and IL17RA respectively, were significantly increased in response to E2 treatment, but only in cells homozygous for WT alleles for the *CCR6* SNPs. However, this pattern of gene expression could be ‘’reversed’’ in a *CCR6*SNP-dependent fashion in the presence of the ERα antagonist fulvestrant, compatible with our DNA-ERα protein binding observations for two EREs near the rs3093023 SNP. When E2 was present, cells homozygous for the V allele for rs3093023 displayed elevated ERα binding compared with cells homozygous for the WT allele. However, a reversal of ERα binding was observed in the presence of fulvestrant.

Conclusion: We observed differential ERα binding before and after ER blockade which might be associated with underlying mechanisms for the SNP and estrogen-dependent variation of CCR6 expression and, downstream, the expression of CCL20, IL17RA and IL17A--all of which play roles in the pathogenesis of RA. These observations also suggest that the expression of immune mediators could potentially be pharmacologically manipulated in a SNP-dependent fashion. Our findings suggest a novel molecular mechanism that may play an important role in the interplay between estrogen and immune mediators in RA—a disease that displays striking variation in incidence and disease activity which might be related to hormonal status.

Disclosure: M. F. Ho, None; **R. M. Weinshilboum**, None; **L. Wang**, None; **J. N. Ingle**, None; **T. Bongartz**, None.

Abstract Number: 88

Integrating Evidence for Genetic Association and Natural Selection Helps Detect New Systemic Lupus Erythematosus Risk Loci in African-Americans

Paula S. Ramos[1], Satria Sajuthi[2], Jasmin Divers[3], Kenneth M. Kaufman[4], Uma Nayak[5], Wei-Min Chen[5], Kelly J. Hunt[6], Diane L. Kamen[7], Gary S. Gilkeson[8], Jyotika K. Fernandes[7], Ida J. Spruill[9], Robert P. Kimberly[10], John B. Harley[11], W. Timothy Garvey[12], Michèle M. Sale[13] and Carl D. Langefeld[2], [1]Department of Medicine, Medical University of South Carolina, Charleston, SC, [2]Biostatistical Sciences, Wake Forest School of Medicine, Winston-Salem, NC, [3]Department of Biostatistical Sciences, Wake Forest School of Medicine, Winston-Salem, NC, [4]Center for Autoimmune Genomics and Etiology, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, [5]Public Health Sciences, University of Virginia, Charlottesville, VA, [6]Public Health Sciences, Medical University of South Carolina, Charleston, SC, [7]Medicine, Medical University of South Carolina, Charleston, SC, [8]Department of Medicine, Division of Rheumatology, Medical University of South Carolina, Charleston, SC, [9]Nursing, Medical University of South Carolina, Charleston, SC, [10]Medicine, Clinical Immun & Rheumatology, University of Alabama at Birmingham, Birmingham, AL, [11]Center for Autoimmune Genomics and Etiology (CAGE), Cincinnati Children's Hospital Medical Center, Cincinnati, OH, [12]Department of Nutrition Sciences and Birmingham VA Medical Center, University of

Alabama at Birmingham, Birmingham, AL, [13]Department of Medicine and Center for Public Health Genomics, University of Virginia, Charlottesville, VA

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Background/Purpose: In many rheumatologic and autoimmune diseases African Americans (AA) have a higher prevalence and greater disease severity than other ethnicities. We posit that population-specific natural selection have influenced allele frequencies at some loci and thereby contribute to the higher prevalence and severity of systemic lupus erythematosus (SLE) in AA. The Gullah population of coastal South Carolina and Georgia has lower European admixture and higher ancestral homogeneity from the Sierra Leone (SL) area in Far-West Africa than other AA populations. The shorter genetic distance between the Gullah and SL suggests that population genetic signals, such as regions under recent selection, may be more easily detected in the Gullah than in other AA populations. The goal of this study was to leverage the evidence for recent natural selection to increase the statistical power to detect novel SLE-predisposing loci in the Gullah.

Methods: We computed a genome-wide association study (GWAS) on 151 Gullah SLE cases and 119 Gullah controls adjusting for admixture estimates. We also computed the likelihood ratio test for allelic differences between 277 Gullah population controls and 400 SL population controls adjusting for admixture. The intersection of SNPs from the case-control and test of selection that met standard quality control were 193,008 SNPs. We combined the evidence of association with SLE in the Gullah from the case-control analysis with evidence of selection by summing the chi-square statistic from a SNPs allele frequency test with its case-control association chi-square to create an overall chi-square statistic with 2 df (Ayodo et al, 2007). We used HaploReg for functional annotation of variation.

Results: Several genomic regions with multiple SNPs with suggestive evidence for association with SLE ($P<5.0E-04$) were found, including an intergenic region at 1p31.1, *TLE4*, and *PCNXL4*. When combined with the allele frequency differences, *XCR1-CCR1* showed multiple SNPs with $P<0.0005$. However, several other regions showed multiple SNPs with increased significance ($P<0.005$) when the association and selection evidence was combined, including the *HLA, PKHD1, GAS2L3* and *FHOD3*. Interestingly, the strength of significance increased for several SNPs in the *PCNXL4* region. This was also the region with the highest regulatory potential, with multiple marks of active promoters and transcription start sites in different immune-related cell lines.

Conclusion: We report novel loci with suggestive evidence for association with SLE in a genetically homogeneous AA population, by combining evidence of natural selection with association to detect SLE risk variants in Gullah AA. These loci merit focused association replication efforts in SLE and this approach is generalizable to several other rheumatic diseases with ethnic differences in prevalence. Clearly the link with evidence of selection will only increase the power for a subset of SLE-predisposing to those that may have been historically adaptive. Such distinctions help not only identify new risk loci but may help provide insight into the evolution of rheumatic and autoimmune diseases in humans.

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Abstract Number: 89

A Longitudinal Genome-Wide Association Study of Anti-Tumor Necrosis Factor Response Among Japanese Patients with Rheumatoid Arthritis

Kyoko Honne[1], Ingileif Hallgrimsdottir[2], Chunsen Wu[3], Ronnie Sebro[4], Nicholas Jewell[2], Takeo Sakurai[5], Masahiro Iwamoto[6], Seiji Minota[6] and **Damini Jawaheer**[7], [1]Division of Rheumatology and Clinical Immunology, Jichi Medical University, Shimotsuke, Japan, [2]UC Berkeley, Berkeley, CA, [3]University of Southern Denmark, Odense, Denmark, [4]University of Pennsylvania, Philadelphia, PA, [5]Inoue Hospital, Takasaki, Japan, [6]Department of Internal Medicine, Division of Rheumatology/Clinical Immunology, Jichi Medical University, Shimotsuke, Japan, [7]Children's Hospital Oakland Research Institute, Oakland, CA

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Background/Purpose: Studies of patients with rheumatoid arthritis (RA) to identify genetic biomarkers of anti-tumor necrosis factor (TNF) response have been conducted mostly in Caucasian populations. These studies have used anti-TNF response at a single follow up time point as the phenotype with which single nucleotide polymorphisms (SNP) associations have been tested. There has been little overlap in findings across studies. To identify genetic biomarkers of anti-TNF response among Japanese RA patients, we have performed a genome-wide association study (GWAS) using response at 2 follow up time-points for a more reliable clinical phenotype over time.

Methods: Disease Activity Scores based on 28 joint counts and C-reactive protein (DAS28) were assessed at baseline (before initial therapy), and after 3 and 6 months in 487 Japanese RA patients starting anti-TNF therapy for the first time or switching to a new anti-TNF agent. A genome-wide panel of 1,133,484 SNPs was genotyped and additional SNPs were imputed. Using change in DAS28 scores from baseline (ΔDAS28) at both 3 and 6 months as the response phenotype, a longitudinal genome-wide association analysis was conducted using Generalized Estimating Equations (GEE) models to accommodate the repeated measures of the outcome, adjusting for baseline DAS28, time since initiation of therapy, type of anti-TNF agent and concomitant methotrexate.

Results: A total of 4,253,138 autosomal SNPs passed quality thresholds for association analysis. Suggestive evidence of association ($p<1x10^{-6}$) with ΔDAS28 was observed at 3 chromosomal regions (6q15: rs284515, $p=6.6x10^{-7}$; 6q27: rs75908454, $p=6.3x10^{-7}$ and 10q25.3: rs1679568, $p=8.1x10^{-7}$), extending to numerous SNPs in linkage disequilibrium (LD) with the index SNPs across each region. Potential candidate genes in these regions include *MAP3K7* (6q15) a key player in TNFα-mediated inflammatory pathway signaling, *GFRA1* (10q25.3) which was associated with anti-TNF response in an independent study, and *WDR27* (6q27).

Conclusion: In this first GWAS of anti-TNF response among Japanese RA patients using a longitudinal analysis approach, three genomic regions demonstrated suggestive association with response to anti-TNF therapy. Using more than one assessment of response enhanced the power to detect these associations.

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Abstract Number: 90

Influence of Susceptible HLA-DRB1 Alleles on Clinical Subphenotypes of Systemic Lupus Erythematosus in Koreans

So-Young Bang[1], Ji-Young Choi[1], Songree Park[1], Seung Lee[2], Jeongim Choi[1], Seung-Jae Hong[3], Hye-Soon Lee[1], Chan-Bum Choi[1] and Sang-Cheol Bae[1], [1]Rheumatology, Hanyang University Hospital for Rheumatic Diseases, Seoul, South Korea, [2]Hanyang University Hospital for Rheumatic Diseases, Seoul, South Korea, [3]Kyung Hee University Hospital, seoul, South Korea

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Background/Purpose: We investigated the association between human leukocyte antigen (HLA)-DRB1 alleles and systemic lupus erythematosus (SLE) susceptibility and whether each allele has a significant effect on clinical manifestations and autoantibody profiles in a Korean population.

Methods: All SLE patients (n=1,089) and control subjects (n=2,161) were Korean. We performed a two-stage analysis in a discovery set (group 1: 475 SLE and 1,119 controls) and a replication set (group 2: 614 SLE and 1,072 controls) using high-resolution HLA-DRB1 typing. The odds ratio (OR) of risk alleles associated with SLE was calculated by a regression method, which was adjusted for age, sex, and disease duration.

Results: We found that four HLA-DRB1 alleles [two confirmed alleles; **15:01* (P=1.11×10^{-13}), **09:01* (P=1.59×10^{-5}), two novel alleles; **08:03* (P=8.80×10^{-8}), **07:01* (P=1.14×10^{-6})] and were associated with susceptibility to SLE. Double copies of these risk alleles (OR 3.38) were associated with a higher risk of developing SLE than a single copy (OR 1.95), showing additive genetic effects. In addition, three novel HLA-DRB1**12:02* (P=6.35×10^{-4}), **11:01* (P=1.24×10^{-3}), **13:02* (P=8.88×10^{-3}) alleles were significantly protective against SLE. The HLA-DRB1**15:01* allele alone (OR 2.20) and double-copies of risk alleles (OR 3.71) increased the risk for anti-Sm production. In addition, SLE patients with double-copies of risk alleles showed more diverse clinical manifestations.

Conclusion: We demonstrated that four HLA–DRB1 risk alleles were associated with SLE in a Korean population, and also promote the production of anti-Sm and diverse clinical manifestations

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Abstract Number: 91

Coevolution of a Uric Acid Transporter and Uricase: Implications for Gout

Philip K. Tan[1], Eric A. Gaucher[2] and **Jeffrey N. Miner**[3], [1]Ardea Biosciences, San Diego, CA, [2]Georgia Institute of

Technology, Atlanta, GA, [3]Discovery Biology, Ardea Biosciences, San Diego, CA
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Background/Purpose: Gout is caused by chronic hyperuricemia, leading to uric acid deposition. Humans and apes have relatively high serum uric acid (sUA) levels due to inactivating mutations in the enzyme uricase, which took place during hominid evolution, preventing the conversion of uric acid into more soluble allantoin. Uric acid is eliminated primarily by excretion through the kidneys. Most gout patients exhibit reduced renal excretion of uric acid. In the kidney, most of the uric acid is reabsorbed back into the bloodstream through URAT1, a uric acid transporter that is essential for maintaining sUA levels. From our studies on URAT inhibitors, we identified phenylalanine 365 as important for inhibitor affinity. We now find that this residue also affects the affinity of URAT1 for the substrate uric acid. Evolutionary changes in this amino acid appear to track with alterations in uricase function. Our objective was to determine whether URAT1 may have been subject to adaptive evolution for controlling and maintaining the relatively high sUA levels in humans.

Methods: Ancestral URAT1 sequences were inferred by analyzing modern transporter sequences within an evolutionary framework. Briefly, extant sequences were collected and used to infer a phylogenetic tree. Ancestral sequences were then computationally inferred from the tree and then synthesized and cloned in the laboratory. Modern and ancestral URAT1 genes were transiently expressed in HEK-293T cells to measure URAT1-dependent transport of uric acid. The affinity of each construct for uric acid was determined.

Results: Among the URAT1 orthologs, residue 365 is phenylalanine in humans, apes, and monkeys, but is tyrosine in most other mammals. Ancestral sequence analysis reveals that the tyrosine to phenylalanine replacement occurred deep in the primate lineage. Human URAT1 has a significantly higher affinity for uric acid (K_m ~ 150 μM) compared to rat URAT1 (K_m~ 800 μM). Point mutant chimeras between the 2 transporters show that human phenylalanine 365 confers a higher affinity to uric acid. The transport activities of ancestral and other modern orthologous URAT1 proteins also indicate that phenylalanine 365 is important for high uric acid affinity. Remarkably, the known decrease in primate uricase activity tracks concomitantly in evolutionary history with the alterations that increase uric acid affinity of URAT1 during primate evolution.

Conclusion: Human URAT1 phenylalanine 365 is important for high affinity transport of uric acid, while URAT1 orthologs and ancestors that carry tyrosine 365 have low affinity transport of uric acid. Evolutionary analysis shows that the tyrosine-to-phenylalanine conversion in URAT1 coincides with the inactivating mutations in uricase that took place between 45–90 million years ago, suggesting that this URAT1 mutation occurred due to adaptive positive selection for elevated uric acid levels in humans and their closest relatives. We posit that phenylalanine 365, along with other residues, plays an important role in URAT1-dependent uric acid homeostasis.

Disclosure: P. K. Tan, Ardea/AstraZeneca, 3; **E. A. Gaucher**, DuPont, 2; **J. N. Miner**, Ardea/AstraZeneca, 3,AstraZeneca, 1,ARTA Bioscience Inc., 6.

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Abstract Number: 92

Variation at Interleukin-6 Receptor Gene Is Associated to Joint Damage in

Rheumatoid Arthritis

María López-Lasanta[1], Antonio Julià[1], Joan Maymo[2], Benjamin Fernandez Gutierrez[3], Inmaculada Ureña[4], Francisco J. Blanco[5], Juan D. Cañete[6], Mercedes Alperi-López[7], Alejandro Olivé[8], Hector Corominas[9], Jesús Tornero[10], Alba Erra[11], Miriam Almirall[12], Nuria Palau[13], Ana M. Ortiz Garcia[14], Gabriela Avila[13], Luis Rodriguez-Rodriguez[15], Arnald Alonso[1], Raül Tortosa[1], Isidoro González-Alvaro[16] and Sara Marsal[1], [1]Rheumatology Research Group, Vall d'Hebron Hospital Research Institute, Barcelona, Spain, [2]Rheumatology, Hospital del Mar, Barcelona, Spain, [3]Department of Rheumatology, Hospital Clínico San Carlos, Madrid, Spain, [4]Rheumatology service, Hospital Regional Universitario Carlos Haya, Malaga, Spain, [5]Osteoarticular and Aging Research Lab, INIBIC–Complejo Hospitalario Universitario A Coruña, A Coruña, Spain, [6]Arthritis Unit. Rheumatology, Arthritis Unit. Rheumatology Department. Hospital Clínic, Barcelona, Spain, [7]Department of Rheumatology, Hospital Universitario Central de Asturias, Asturias, Spain, [8]Rheumatology, Hospital Germans Trias i Pujol, Badalona, Spain, [9]Rheumatology, Hospital de Sant Joan Despí Moisès Broggi, Barcelona, Spain, [10]Rheumatology Department, Hospital Universitario Guadalajara, Guadalajara, Spain, [11]Rheumatology, Rheumatology Hospital San Rafael, Barcelona, Spain, [12]Rheumatology Department, Hospital del Mar, Barcelona, Spain, [13]Vall d'Hebron Hospital Research Institute, Barcelona, Spain, [14]Rheumatology, H.U. La Princesa, Madrid, Spain, [15]Department of Rheumatology, Hospital Clinico San Carlos, Madrid, Spain, [16]Rheumatology, Hospital Universitario de La Princesa. IIS La Princesa, Madrid, Spain

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Background/Purpose: Interleukin-6 (IL-6) cytokine signaling is key in Rheumatoid Arthritis (RA) pathophysiology. Blocking IL-6 receptor (IL6R) has proven to be a highly effective treatment to prevent joint damage. This study was performed to investigate the association between the genetic variation at*IL6R* gene and the severity of joint damage in RA.

Methods: *IL6R* gene tagging SNPs (n=5, Figure 1) were genotyped in a discovery group of 527 RA patients from 5 different university hospitals from Spain. For each marker, a multivariate linear regression analysis was performed to test for association with joint damage and also to adjust several covariates including years disease evolution, autoantibody status and gender. Haplotypes combining the SNPs were also estimated and tested for association with the level of joint destruction. Using an independent cohort of 705 RA patients from 6 university hospitals we performed a validation study of the SNPs associated in the discovery phase.

Results: In the discovery group we found a highly significant association between *IL6R* SNP rs4845618 and the level of joint destruction in RA (*P*=0.0058, Table 1), and a moderate association with SNP rs4453032 (*P*=0.02, Table 1). The resulting haplotype from both SNPs was more significantly associated with joint damage (*P*=0.0037). Using the validation cohort, we replicated the association between the two IL-6R SNPs with the degree of joint destruction in RA (*P*=0.007 and *P*=0.04, meta-analysis *P*=0.00011 and *P*=0.0021, respectively, Table 1), and the haplotype association (*P*=0.0058, meta-analysis *P*=6.64 e-5).

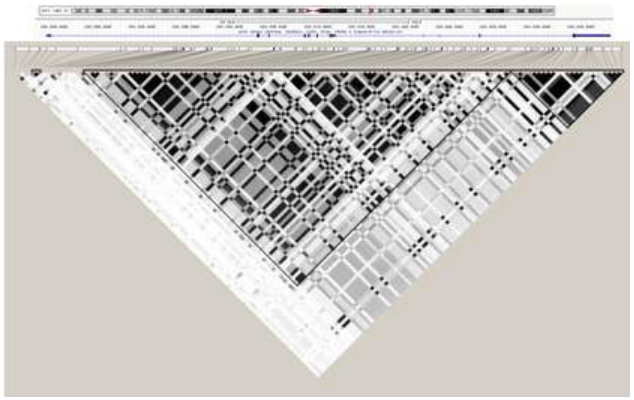

Figure 1. LD pattern at IL6R locus. The two main haplotype blocks covering most common genetic variation at *IL6R* gene (in blue) are indicated by solid line triangles.

Table 1. Association of *IL6R* markers with the severity of joint damage in RA. Significance values for *IL6R* SNPs in the discovery, replication cohorts as well meta-analysis of the two cohorts.

SNP	Basepair	MAF	*P*-Discovery	*P*-Replication	Meta-analysis *P*
rs4845618	154400015	0.44	0.0052	0.007	0.00011
rs4453032	154414086	0.4	0.51	-	-
rs4845374	154426947	0.17	0.02	0.04	0.0021
rs6698040	154432948	0.21	0.11	-	-
rs4379670	154439865	0.16	0.25	-	-

Conclusion: We show for the first time that genetic variation at *IL6R* gene is associated to joint damage in RA.

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Abstract Number: 93

An HLA-C Amino Acid Variant in Addition to HLA-B*27 Confers Risk for Ankylosing Spondylitis in the Korean Population

Kwangwoo Kim[1], So-Young Bang[2], Seunghun Lee[3], Hye-Soon Lee[2], Seung-Cheol Shim[4], Young Mo Kang[5], Chang-Hee Suh[6], Celi Sun[7], Swapan Nath[7], Sang-Cheol Bae[2] and Tae-Hwan Kim[2], [1]Hanyang University Hospital for Rheumatic Diseases, Seoul, South Korea, [2]Rheumatology, Hanyang University Hospital for Rheumatic Diseases, Seoul, South Korea, [3]Department of Radiology, Hanyang University College of Medicine, Seoul Hospital, Seoul, South Korea, [4]Division of Rheumatology, Daejeon Rheumatoid and Degenerative Arthritis Center, Chungnam National University, Daejeon, South Korea, [5]Dept of Internal Medicine, Kyungpook National University School of Medicine, Daegu, South Korea, [6]Allergy-Rheumatology, Ajou University School of Medicine, Suwon, South Korea, [7]Oklahoma Medical Research Foundation, Oklahoma City, OK

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Background/Purpose: Ankylosing spondylitis (AS) is a highly heritable rheumatic disease causing chronic inflammation of axial spine, joints and various organs. The presence of HLA-B*27 is strongly associated with development of AS, explaining most of the genetic associations between AS and the major histocompatibility complex (MHC) locus on human chromosome 6. Here, we investigated residual effects outside HLA-B within the MHC region.

Methods: We obtained high-density genotyping array Immunochip data for the extended MHC locus in 3,820 unrelated Korean subjects (comprising 654 cases of AS and 3,166 controls) who were ethnically homogeneous and showed no evidence of systemic bias or potential population substructure. The patients with AS satisfied the modified New York criteria for AS diagnosis. Using the SNP2HLA script and the Korean HLA reference panel, we imputed the two- and four-digit classical alleles and amino-acid residues of *HLA-A*, *-B*, *-C*, *-DRB1*, *-DPB1* and *-DQB1*, as well as MHC SNPs (spanning 25–35 Mb). AS associations of all markers with minor allele frequency ≥1% and imputation quality (PLINK INFO) ≥0.1 were assessed using logistic regression, adding the top ten principal components as covariates. AS associations at HLA amino-acid positions (or multiple markers) were assessed using log likelihood ratio tests (LRT).

Results: We imputed 5,658 polymorphic variations including 158 classical alleles and 663 amino-acid variants in *HLA-A*, *-B*, *-C*, *-DRB1*, *-DPB1* and *-DQB1*, as well as 4,837 MHC SNPs. The most significant associations were identified at amino-acid positions 97 ($P_{LRT}=7.20\times10^{-479}$) and 114 ($P_{LRT}=2.54\times10^{-484}$) in the epitope-binding site of *HLA-B*, highlighting the risk effect of the HLA-B*27 allele (OR=243) and the protective effects of other classical alleles (OR≤0.67). A secondary effect was located at the leucine at amino-acid position 116 in the epitope-binding site of HLA-C ($p=3.76\times10^{-15}$) in a conditional logistic regression analysis adding the two amino-acid positions 97 and 114 as covariates. This residue was highly correlated with the HLA-C*15:02 allele and had a large effect in HLA-B*27-negative patients (OR=6.6; 95% CI=3.8-11.4; $p=1.52\times10^{-11}$). After conditioning on the three AS-associated amino-acid positions, we could not find any MHC SNPs or HLA variants associated with AS susceptibility ($p>1.32\times10^{-5}$).

Conclusion: We identified associations of *HLA-C* in addition to *HLA-B* with AS susceptibility in the Korean population. This updates the list of AS susceptibility loci and provides new insight into AS pathogenesis mediated by MHC class I molecules.

Disclosure: K. Kim, None; **S. Y. Bang**, None; **S. Lee**, None; **H. S. Lee**, None; **S. C. Shim**, None; **Y. M. Kang**, None; **C. H. Suh**, None; **C. Sun**, None; **S. Nath**, None; **S. C. Bae**, None; **T. H. Kim**, None.

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Abstract Number: 94

NGS Panel for the Detection of Monogenic SLE in Children: Initial Results

Alexandre Belot[1], Gillian Rice[2], Anne-Laure Mathieu[1], Brigitte Bader-Meunier[3], Thierry Walzer[1], Tracy A. Briggs[2], James O'Sullivan[4], Simon Wiliams[5], Michael W. Beresford[6], Yanick Crow[2,7] and GENIAL Investigators, UK JSLE

Study Group, [1]INSERM U1111, Lyon, France, [2]Manchester Academic Health Science Centre, University of Manchester, Manchester, United Kingdom, [3]Pediatric Rheumatology & Immunology, Necker hospital, Imagine Institution, Paris, France, [4]University of Manchester, Manchester, United Kingdom, [5]University of Manchester, Manchester, France, [6]Paediatric Rheumatology, Alder Hey Children's NHS Foundation Trust, Liverpool, United Kingdom, [7]Neuroinflammation, Institut Imagine, Paris, France
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Background/Purpose:

Next generation sequencing (NGS) represents a revolution in the field of molecular medicine, and offers a new approach to deciphering the pathogenesis of complex diseases. Paediatric-onset SLE (pSLE) is a very rare and more severe phenotype than its adult-onset counterpart, and is possibly associated with a greater contribution of genetic aetiological factors. A few monogenic causes of SLE have been described, including: complement deficiencies, defects of apoptosis and the so-called interferonopathies. The frequency of these Mendelian subtypes in a large cohort of pSLE has not been assessed previously.

Methods:

We designed an NGS panel comprising 200 genes including proven disease-associated as well as prospective candidate genes, and analysed 85 children under 11 years of age who fulfilled ACR criteria for SLE. As a first step, we focussed on rare (ExAC database frequency of < 1% for homozygous variants and < 0.01% for heterozygous variants) null / frameshift variants, and missense substitutions predicted *in silico* as damaging by both SIFT and POLYPHEN.

Results:

We identified three patients with biallelic mutations in genes of the complement pathway - one with a homozygous missense variant (p.Gly164Ser) and one with compound heterozygous variants (p.Gly164Ser/p.Leu41CysfsTer97) in *C1QC*, and one with a homozygous frameshift variant (p.Ile15AsnfsTer7) in *C1QA*. Four further patients harboured heterozygous variants (in *C1QC*, *C2*, *C5* and *C9*) which were predicted as pathogenic. Copy number variant analysis in these genes has not yet been undertaken. A *TREX1* p.Ser82LeufsTer9 variant, previously observed in a patient with Aicardi-Goutières syndrome, was identified in one patient in combination with a missense variant of unknown significance. One patient carried a heterozygous variant in *ACP5* - predicted as pathogenic by *in silico* analysis but not seen previously in SPENCD. In total, 11 patients harboured heterozygous rare variants in 2 or 3 panel genes (8 and 3 patients respectively). No likely pathogenic variants were identified in *DNASE1*, *DNASE1L3* or *PRKCD*.

Conclusion:

This first-step analysis of candidate gene variants in a population of 85 pSLE patients revealed three cases of C1Q deficiency – associated with a 1 in 4 risk of recurrence, and which had not been diagnosed previously. The significance of heterozygous variants in other genes is difficult to determine at this stage. The association of 2 / 3 very rare heterozygous variants in a single patient raises the possibility of an oligogenic burden in the pathogenesis of pSLE. Functional experiments are mandatory to understand the impact of these rare variants. Future work will also involve increasing the number of patients analysed, and consideration of intronic and splicing variants. However, we already conclude that an NGS panel approach can diagnose unappreciated monogenic forms of pSLE.

Disclosure: A. Belot, None; **G. Rice**, None; **A. L. Mathieu**, None; **B. Bader-Meunier**, None; **T. Walzer**, None; **T. A. Briggs**, None; **J. O'Sullivan**, None; **S. Wiliams**, None; **M. W. Beresford**, None; **Y. Crow**, None.

Abstract Number: 95

Validation of Differential Methylation in Paternally Versus Maternally Transmitted Psoriatic Disease

Remy Pollock[1], Darren O'Reilly[2], Amanda Dohey[2], Dianne Codner[2], Vinod Chandran[3], Dafna Gladman[3] and Proton Rahman[4], [1]University of Toronto, Toronto Western Hospital, Toronto, ON, Canada, [2]Memorial University of Newfoundland, St. John's, NF, Canada, [3]Rheumatology, University of Toronto, Toronto Western Hospital, Toronto, ON, Canada, [4]Computer Sciences, Memorial University of Newfoundland, St. John's, NF, Canada

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Background/Purpose: Several studies have demonstrated excessive paternal transmission of psoriasis and psoriatic arthritis (PsA). This phenomenon is thought to be mediated by genomic imprinting. We previously compared whole blood methylation patterns among PsA patients from Newfoundland, Canada and identified 90 significant CpG sites that differentiate patients with paternally and maternally-transmitted disease. This study aimed to validate previously-identified CpG sites in an independent sample of PsA patients with paternally and maternally-transmitted disease from Toronto, Canada.

Methods: All PsA patients included in the study satisfied the CASPAR criteria and had a parent with either psoriasis or PsA. Forty-six (46) PsA patients with paternally-transmitted disease were compared to 48 PsA patients with maternallytransmitted disease at 136 CpG sites on 10 different chromosomes. Percent methylation was measured at each CpG site by Sequenom EpiTyper technology, which involves bisulfite conversion followed by mass spectrometric analysis. Generated β values ranging from 0% (fully unmethylated) to 100% (fully methylated) were compared between groups using the nonparametric Mann-Whitney U test. Logistic regression models adjusting for age and sex were run to confirm the unadjusted results.

Results: PsA patients with paternally-transmitted disease were 52% female, and at the time of sample collection had a mean (SD) age of 47.7 (12.6) years, psoriasis duration of 23.7 (13.3) years, PsA duration of 14.1 (9.7) years, PASI score of 5.3 (7.2) and tender joint count of 4.9 (7.8). Patients with maternally-transmitted disease were 53% female, and had a mean age of 50.3 (11.1) years, psoriasis duration of 23.1 (12.2) years, PsA duration of 14.9 (12.0) years, PASI score of 4.5 (5.3) and tender joint count of 6.8 (8.5). Three CpG sites were significantly differentially methylated in the Toronto patients with paternally and maternally-transmitted disease. The most significant site was located within an intron of the CROCC (rootelin) gene on 1p36.13 and was hypomethylated in paternally-transmitted disease (p=0.014). Two sites within the 5' UTR of the PACSIN1 gene on chromosome 6p21.3 were also significantly hypomethylated in paternallytransmitted disease (p=0.040 and p=0.047). After adjustment for age and sex, CpG methylation at CROCC remained significantly associated with paternally-transmitted disease (OR=0.77, 95% CI 0.60-0.99, p=0.04).

Conclusion: CpG methylation at the CROCC locus on chromosome 1p36.13 differentiates PsA patients with paternally and maternally-transmitted disease. Although CROCC is not known to be imprinted in humans, these data suggest it may play some role in the excessive paternal transmission of psoriatic disease. Further validation of these results in somatic and germ line cells are necessary.

Disclosure: R. Pollock, None; **D. O'Reilly**, None; **A. Dohey**, None; **D. Codner**, None; **V. Chandran**, None; **D. Gladman**, None; **P. Rahman**, None.

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Abstract Number: 96

The ABCG2 polymorphism Is Associated with Hyperuricemia in a Community-Based Korean Cohort

Jae-Bum Jun[1], Hye-Jin Jeong[2], Chang-Nam Son[3], Ji-Min Kim[3], Sang-Hyon Kim[3], So-Young Bang[4] and Sang-Cheol Bae[1], [1]Rheumatology, Hanyang University Hospital for Rheumatic Diseases, Seoul, South Korea, [2]Hanyang University Hospital for Rheumatic Diseases, Seoul, South Korea, [3]Division of Rheumatology, Department of Internal Medicine, Dongsan Medical Center, Keimyung University School of Medicine, Daegu, South Korea, [4]Department of Rheumatology, Hanyang University Guri Hospital, Guri, South Korea

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Background/Purpose: Hyperuricemia is known as a risk factor of diverse diseases such as gout, hypertension, metabolic syndrome, diabetes mellitus, and cardiovascular diseases. Recent genome-wide association studies (GWASs) have identified that 28 genetic loci are associated with hyperuricemia among individuals of European ancestry. For example, SLC2A9, ABCG2 and SLC22A12 modulate serum uric acid levels (SUAs) in the renal urate-transport system. The purpose of the present study is to find novel loci associated with hyperuricemia using data from a GWAS conducted on healthy Koreans.

Methods: We conducted a GWAS using data from a community-based cohort study where 3,647 subjects aged 40 - 69 were recruited by the Korea National Institute of Health (KNIH). The community-based cohort consisted of subjects who did not suffer from any of six major diseases (hypertension, hyperlipidemia, diabetes, heart diseases, brain diseases, and cancers). Epidemiologic information includes 249 traits such as epidemiological surveys, physical examinations, and laboratory tests. A total of 3,647 participants, including 234 hyperuricemia cases (SUA level was 7 or higher) and 3,413 controls, were genotyped by Illumina HumanOmni1-Quad BeadChip GWAS array at KNIH.

Results: In the multivariate regression analysis of clinical variables, significant variables were male gender ($P = 5.0 \times 10^{-10}$), body mass index (BMI) ($P = 1.5 \times 10^{-7}$), current alcohol ($P = 7.8 \times 10^{-7}$), fasting plasma glucose (FPG) (P = 0.035), and creatinine ($P = 2.7 \times 10^{-14}$). We identified new hyperuricemia susceptible loci (rs2054576 in ABCG2, $P = 4.7 \times 10^{-8}$) that passed a genome-wide significance threshold, adjusted by clinical variables (male, BMI, current alcohol, FPG, and creatinine).

Conclusion: It was first identified that rs2054576 in ABCG2 is associated with hyperuricemia. ABCG2 is a transporter that is located in the apical border membrane of renal proximal tubule cells and plays a role in uric acid secretion. Our results should be validated through replication studies among other Korean subjects or various ethnic groups.

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Abstract Number: 97

Genomic Sequencing of Uric Acid Metabolizing and Clearing Genes in Relationship to Xanthine Oxidase Inhibitor Dose

Matthew Carroll[1], **Kristen Cook**[2] and Thomas Shaak[3], [1]Rheumatology, Keesler Medical Center, Keesler AFB, MS, [2]Internal Medicine, Keesler Medical Center, Keesler AFB, MS, [3]Clinical Research Laboratory, Keesler Medical Center, USAF, Keesler AFB, MS

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Background/Purpose: Effective long term uric acid lowering therapy with the xanthine oxidase inhibitors (XOI) allopurinol and febuxostat exists. When compliant with therapy, it is unclear why some patients need higher or lower doses of XOI yet achieve the same serum uric acid (SUA) goal. We pursued genomic sequencing (GS) of genes related to XOI metabolism and clearance to determine if any SNVs relate to differences in dose needed.

Methods: Subjects with a diagnosis of Gout based on the 1977 American College of Rheumatology Classification Criteria for the disorder, who were on stable doses of a XOI, and who were at their goal SUA level were enrolled. When available up to 3 pre- and post-treatment SUA values were recorded. GS was performed on whole blood samples for genes related to metabolism of allopurinol, specifically *XO*, aldehyde oxidase 1 (*AOX1*), and molybdenum cofactor sulfurase (*MOCOS*). The gene *SLC22A12* was sequenced because it impacts oxypurinol clearance. For the metabolism of febuxostat, the genes uridine diphosphate glucuronsyltransferase (*UDT*) 1A1 and 1A4 were sequenced. The primary outcome was to detect any relationship between single nucleotide variants (SNVs) in any of these genes to XOI dose. The secondary outcome was to detect a relationship between SNVs and change in SUA, specifically the difference between average pre- and post-treatment values.

Results: Time and funding permitted sequencing of our first 80 subjects. The average patient age was 68.3 ± 11.2 years old. The majority were men and 76% were Caucasian. The GS error rate was 0.293 ± 0.048%. Of 1.8 ± 0.5 million base pairs mapped, 145 SNVs were identified; no indels were identified. For the primary outcome, 5 SNVs were associated with a lower XOI dose (allopurinol ≤ 300 mg daily) to reach a goal SUA (all $p < 0.05$): rs13419410, rs6760292, rs34929837, rs45612738, and rs4541294. One SNV, rs7599556 was associated with a higher XOI dose (allopurinol > 300 mg daily) to reach a goal SUA. Of these SNVs, rs34929837 is an exonic missense mutation affecting XO (Lys395Met) and lies in the Flavin adenine nucleotide (FAD) domain of the enzyme. Rs45612738 is a synonymous codon in *XO* (Gly378=). All other SNVs were intronic with the majority in *XO*. For the secondary outcome, 1 SNV was associated with a smaller change in SUA with a lower XOI dose: rs6760292 ($p < 0.05$). This SNV is intronic and located in *XO*. Four SNVs were associated with larger changes in SUA with febuxostat 80 mg daily (all $p < 0.05$): rs7599556, rs75995567, rs145877467, and rs78467837. Both rs145877467 and rs78467837 are synonymous codons in *AOX1*(Pro1245= and Ser1264= respectively).

Conclusion: Though the sample size is modest, we identified multiple SNVs that were associated with a lower XOI dose and one related to a higher XOI dose to reach a goal SUA. One of the exonic alleles detected, rs34929837, leads

to an amino acid substitution in the FAD co-factor domain of xanthine oxidase. Additional work is needed to assess the impact of this change but our data may start to explain why some patients need different doses of XOI and yet achieve the same serum uric acid (SUA) goal.

Disclosure: M. Carroll, None; **K. Cook**, None; **T. Shaak**, None.

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Abstract Number: 98

The Mitochondrial DNA (mtDNA) Haplogroups Influence the Risk of Incidence Knee OA. Replication Study Including Data from Check and OAI Cohorts

Ignacio Rego-Pérez[1], Angel Soto-Hermida[1], Juan Fernandez-Tajes[1], Mercedes Fernandez Moreno[1], Maria Eugenia Vazquez Mosquera[1], Estefanía Cortés-Pereira[1], Sonia Pertega[2], Sara Relaño-Fernandez[1], Natividad Oreiro[1], Carlos Fernandez-Lopez[1] and Francisco J. Blanco[1], [1]Servicio de Reumatología. Instituto de Investigación Biomédica de A Coruña (INIBIC). Complexo Hospitalario Universitario de A Coruña (CHUAC), Sergas. Universidade da Coruña (UDC), A Coruña, Spain, [2]Unidad de Epidemiología Clínica y Bioestadística. Instituto de Investigación Biomédica de A Coruña (INIBIC). Complexo Hospitalario Universitario de A Coruña (CHUAC), Sergas. Universidade da Coruña (UDC), A Coruña, Spain

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Background/Purpose:

Previous studies showed a significant influence of the mtDNA haplogroups on prevalence, radiographic progression and cartilage integrity of knee OA patients from different worldwide cohorts. The aim of this study is to analyze the influence of the mitochondrial variants on the risk of incident knee OA in patients from CHECK as well as in an updated cohort of OAI patients.

Methods:

We assessed the mtDNA haplogroups in 1003 DNA samples from CHECK and 3681 Caucasian samples from the OAI. Incident knee OA was defined as a KL score <2 at baseline and a KL≥2 during 8 (CHECK) and 4 (OAI) years follow-up. Patients suitable for incident knee OA study (KL≤1 at baseline) consisted in 768 and 2409 respectively. Statistical analyses included chi-square contingency tables and logistic regression models considering age, gender, body mass index (BMI), bilateral KL=1 (CHECK) or contralateral knee OA (OAI) at baseline and mtDNA variants as variables of interest.

Results:

After 8 and 4 years respectively, patients from CHECK had more radiographic change compared with the OAI group (p<0,001) so that 418 (54,4%) patients from CHECK and 326 (13,5%) patients from OAI underwent incident knee OA.

Patients carrying the haplogroups of the mitochondrial cluster TJ were significantly underrepresented in the incident knee OA group of both cohorts when compared with the most common mtDNA haplogroup H/HV (OR=0,598; CI=0,357-0,999; p=0.05 for the CHECK cohort and OR=0,658; CI=0,467-0,927; p=0.017 for the OAI cohort). In addition, bilateral KL=1 at baseline in the CHECK cohort and contralateral knee OA in the OAI cohort were risk factors to develop incident knee OA (p<0,001). For both cohorts BMI was a risk factor too (p=0,023 and p<0,001 respectively) (Tables 1 and 2). The AUC of the regression models ranged from 0,643 to 0,688.

Conclusion:

The mitochondrial genome contributes to the development of incident knee OA in two well-defined follow-up cohorts, one of them an early-stage OA cohort (CHECK). The assignment of the mitochondrial polymorphisms common to the major mtDNA clusters could be used as complementary genetic biomarkers to predict the risk of incident knee OA.

Table 1. Percentage of OA patients from the CHECK cohort that underwent incident knee OA during 8 years follow-up according to mtDNA haplogroups and results of the regression model

Variables	N (% Incidents)	OR	95% CI	p-value
Gender (female)		1,204	0,823-1,759	0,339
Age		1,025	0,995-1,056	0,107
BMI		1,047	1,006-1,089	0,023*
Bilateral KL=1 at baseline		4,943	3,347-7,301	<0,001*
mtDNA haplogroups				
H (n=320)	181 (56,6%)	1	-	-
Uk (n=176)	97 (55.1%)	0,963	0,647-1,434	0,855
J (n=65)	35 (53,8%)	0,966	0,541-1,724	0,906
T (n=87)	39 (44,8%)	0,598	0,357-0,999	0,050*
Others (n=120)	66 (55,0%)	0,939	0,595-1,481	0,787
KL: Kellgren and Lawrence; mtDNA: mitochondrial DNA; OR: odd ratio; CI: confidence interval; BMI: body mass index; (*): statistical significance declared at p≤0.05 (the most common mtDNA haplogroup H was used as reference group)				

Table 2. Percentage of OA patients from the OAI cohort that underwent incident knee OA during 4 years follow-up according to mtDNA clusters and results of the regression model

Variables	N (% Incidents)	OR	95% CI	p-value
Gender (female)		1,540	1,205-1,968	0,001*
Age		1,003	0,990-1,016	0,682
BMI		1,068	1,040-1,096	<0,001*
Contralateral (KL≥2) OA at baseline		1,830	1,434-2,336	<0,001*
mtDNA clusters				
HV (n=1123)	168 (15,0%)	1	-	-
KU (n=565)	78 (13,8%)	0,920	0,684-1,237	0,581
TJ (n=471)	50 (10,6%)	0,658	0,467-0,927	0,017*
Others (n=250)	30 (12,0%)	0,793	0,518-1,215	0,287
KL: Kellgren and Lawrence; mtDNA: mitochondrial DNA; OR: odd ratio; CI: confidence interval; BMI: body mass index; (*): statistical significance declared at p≤0.05 (the most common mtDNA cluster HV was used as reference group)				

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Abstract Number: 99

Personalised Genetic Medicine: HLA-DRB1 Amino Acid Positions 11, 71 and 74 Predict Inflammation Level, Disease Activity and Disability in Rheumatoid Arthritis

Stephanie Ling[1], Sebastien Viatte[2], Mark Lunt[3], Alper van Sijl[4], Lucía Silva Fernández[4,5], Soumya Raychaudhuri[2,6,7], Deborah P.M. Symmons[4,8], Adam Young[9,10], Alex J Macgregor[11] and Anne Barton[12], [1]Arthritis Research UK Centre for Genetics and Genomics, Centre for Musculoskeletal Research, Mancheser Academic Health Science Centre, The University of Manchester, Manchester, United Kingdom, [2]Arthritis Research UK Centre for Genetics and Genomics, Centre for Musculoskeletal Research, Manchester Academic Health Science Centre, The University of Manchester, Manchester, United Kingdom, [3]Manchester Academic Health Sciences Centre, Arthritis Research UK Centre for Epidemiology, The University of Manchester, Manchester, United Kingdom, [4]Arthritis Research UK Centre for Epidemiology, Centre for Musculoskeletal Research, Manchester Academic Health Science Centre, The University of Manchester, Manchester, United Kingdom, [5]Rheumatology, Complexo Hospitalario Universitario de Ferrol, Ferrol, Spain, [6]Divisions of Rheumatology and Genetics, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, [7]Medical and Population Genetics Program, Broad Institute of MIT and Harvard, Cambridge, MA, [8]Centre for Musculoskeletal Research, University of Manchester, Arthritis Research UK Centre for Epidemiology, Manchester, United Kingdom, [9]Rheumatology, ERAS, St Albans City Hospital, St Albans, United Kingdom, [10]School of Life & Medical Sciences, University of Hertfordshire, Hatfield, United Kingdom,

[11]School of Medicine, Health Policy and Practice, University of East Anglia, Norwich, United Kingdom, [12]Arthritis Research UK Centre for Genetics and Genomics, Centre for Musculoskeletal Research, Manchester Academic Health Science Centre, The University Of Manchester, Manchester, United Kingdom

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Background/Purpose:

Amino acid (AA) positions 11, 71 and 74 inside HLA-DRB1 confer susceptibility to rheumatoid arthritis (RA). AAs from these positions form 16 haplotypes, hierarchically classified according to their effect (risk to protective) on RA susceptibility and radiographic severity. However, the mechanism of action remains unknown. The effect of these haplotypes on non-radiographic measures of disease activity/outcomes has not yet been systematically tested.

Hypothesis: The effect of HLA-DRB1 AAs on severity is mediated via inflammation.

Aim: To test association of individual AAs with CRP, tender joint count (TJC), swollen joint count (SJC), DAS28 and HAQ score.

Methods: Genetic data from patients with inflammatory polyarthritis from the Norfolk Arthritis Register (NOAR) were analysed using Generalised Linear Latent and Mixed Modelling to incorporate multiple records per patient over time. The associations of individual AAs, individual positions and individual haplotypes were systematically tested with all outcome variables in univariate and multivariate analyses. Correction for multiple testing in univariate analysis was carried out using the Benjamini-Hochberg (false-discovery rate) method. Validation studies were carried out in the Early Rheumatoid Arthritis Study (ERAS) cohort.

Results:

2,158 patients had genetic and phenotypic data available for analysis in NOAR. Valine at position 11 showed the strongest association with CRP, SJC and DAS28, was marginally associated with HAQ, but not with TJC. The same risk hierarchy observed for susceptibility and radiographic severity was also observed with CRP levels and non-radiographic measures of RA activity/outcome at the AA and haplotype level, although not with TJC.

The valine-containing haplotypes VKA (valine 11, lysine 71, alanine 74) and VRA (valine 11, arginine 71, alanine 74) were significantly associated with increased CRP levels, whereas the serine-containing haplotype SEA (serine 11, glutamic acid 71, alanine 74) was associated with reduced levels. The multivariate haplotype model was significantly associated with CRP levels. When effect sizes for association with CRP were plotted against effect sizes for susceptibility, a significant correlation was observed. A similar pattern was also demonstrated for SJC and DAS28, but not for TJC.

The results replicated in ERAS.

Conclusion: Our findings demonstrate an association between objective disease activity measures and AAs at position 11. At diagnosis, patients with RA can be stratified into 16 genetic categories to predict levels of inflammation, SJC and DAS28 during the disease course. These findings describe a genetic basis for the increased inflammatory response leading to radiographic progression.

Disclosure: S. Ling, None; **S. Viatte**, None; **M. Lunt**, None; **A. van Sijl**, None; **L. Silva Fernández**, None; **S. Raychaudhuri**, Pfizer Inc, 2; **D. P. M. Symmons**, None; **A. Young**, None; **A. J. Macgregor**, None; **A. Barton**, Eli-Lilly, Pfizer, Abbvie, 2.

Abstract Number: 100

Validation of a Distinct Psoriatic Arthritis Risk Variant at IL23R

Ashley Budu-Aggrey[1,2], John Bowes[1], Sabine Lohr[3], Maria I. Zervou[4], Philip S. Helliwell[5], Anthony W. Ryan[6], David Kane[7], Eleanor Korendowych[8], Emiliano Giardina[9], Jonathon Packham[10], Ross McManus[6], Oliver FitzGerald[11], Neil J McHugh[8], Frank Behrens[12], Harald Burkhardt[12], Ulrike Huffmeier[3], Javier Martín[13], George Goulielmos[4], Pauline Ho[1,14], Andre Reis[3] and Anne Barton[1,2,14], [1]Arthritis Research UK Centre for Genetics and Genomics, The University of Manchester, Manchester, United Kingdom, [2]NIHR Manchester Musculoskeletal Biomedical Research Unit, Central Manchester Foundation Trust and University of Manchester, Manchester Academy of Health Sciences, Manchester, United Kingdom, [3]Institute of Human Genetics, University of Erlangen-Nuremberg, Erlangen, Germany, [4]Laboratory of Molecular Medicine and Human Genetics, Department of Internal Medicine, University of Crete, Heraklion, Greece, [5]NIHR-Leeds Musculoskeletal Biomedical Research Unit, Leeds Institute of Molecular Medicine, University of Leeds, Leeds, United Kingdom, [6]Department of Clinical Medicine, Institute of Molecular Medicine, Trinity College Dublin, Dublin, Ireland, [7]Adelaide and Meath Hospital and Trinity College Dublin, Dublin, United Kingdom, [8]Royal National Hospital for Rheumatic Diseases and Dept Pharmacy and Pharmacology, University of Bath, Bath, United Kingdom, [9]Department of Biopathology, Centre of Excellence for Genomic Risk Assessment in Multifactorial and Complex Diseases, School of Medicine, University of Rome 'Tor Vergata' and Fondazione PTV 'Policlinico Tor Vergata', Rome, Italy, [10]Rheumatology department, Haywood Hospital, Health Services Research Unit, Institute of Science and Technology in Medicine, Keele University, Staffordshire, United Kingdom, [11]Department of Rheumatology, St. Vincent's University Hospital, UCD School of Medicine and Medical Sciences and Conway Institute of Biomolecular and Biomedical Research, University College Dublin, Dublin, Ireland, [12]Division of Rheumatology and Fraunhofer IME-Project-Group Translational Medicine and Pharmacology, Goethe University, Frankfurt, Germany, [13]Instituto de Biomedicina y Parasitología López-Neyra, Granada, Spain, [14]The Kellgren Centre for Rheumatology, Central Manchester Foundation Trust, NIHR Manchester Biomedical Research Centre, Manchester, United Kingdom

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Background/Purpose: Psoriatic Arthritis (PsA) is an inflammatory arthritis that is associated with psoriasis. In the UK, it is estimated to present in approximately 14% of psoriasis patients. PsA is a complex disease that is influenced by both genetic and environmental factors. Genetic studies have aided the discovery of PsA risk loci, the majority of which also confer risk for psoriasis. We have recently reported evidence of specific loci that confer risk for PsA and not psoriasis, including a variant at *IL23R* which was also found to be independent of the psoriasis variant reported at the same locus.

Methods: In this study, we attempted to identify additional PsA-specific risk variants by genotyping 32 single nucleotide polymorphisms (SNPs) which included those found to have nominal significance in our recent Immunochip study ($P < 1x10^{-4}$) as well as SNPs selected from other studies. These were analysed in 914 PsA cases and 6945

controls from the UK, Crete, Spain and Germany which were independent from those genotyped as part of the Immunochip study. Genotyping was performed using the Life Technologies QuantStudio genotyping platform and association testing was carried out using PLINK. SNPs and samples with poor call rates (<0.9) were excluded prior to analysis.

Results: We found a significant association for the SNP rs12044149 mapping to *IL23R* ($P = 4.03x10^{-6}$). A very weak association was found with the psoriasis variant rs9988642, which has been reported at the same locus ($P = 0.04$). This supports the evidence previously reported of rs12044149 being distinct from rs9988642 and associated with PsA, as demonstrated by the conditional analysis carried out in our Immunochip study [1].

Conclusion:

For the first time we have been able to successfully validate a PsA-specific risk variant at the IL23R locus in an independent cohort. This now gives us a total of four PsA-specific associations that have been identified. Such variants could potentially provide us with a marker to identify psoriasis patients who are prone to developing PsA. IL23 is a target for the psoriasis drug ustekinumab which has also shown efficacy in PsA during clinical trials. It would be interesting to explore whether disease-specific risk variants identifies those PsA patients likely to respond to the drug.

References: 1. Bowes J, Budu-Aggrey A, Huffmeier U.*et al*. Dense genotyping of immune-related susceptibility loci reveals new insights into the genetics of psoriatic arthritis. Nat Commun 2015;6

Disclosure: A. Budu-Aggrey, None; **J. Bowes**, None; **S. Lohr**, None; **M. I. Zervou**, None; **P. S. Helliwell**, None; **A. W. Ryan**, None; **D. Kane**, None; **E. Korendowych**, None; **E. Giardina**, None; **J. Packham**, None; **R. McManus**, None; **O. FitzGerald**, None; **N. J. McHugh**, None; **F. Behrens**, AbbVie Deutschland GmbH & Co KG; Chugai; Pfizer; Roche, 5,Pfizer Inc, 8; **H. Burkhardt**, AbbVie Deutschland; Pfizer; BMS; UCB; Chugai, 5,Pfizer Inc, 2; **U. Huffmeier**, None; **J. Martín**, None; **G. Goulielmos**, None; **P. Ho**, None; **A. Reis**, None; **A. Barton**, Eli-Lilly, Pfizer, Abbvie, 2.

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Abstract Number: 101

New Technologies for Typing Self-Identifying Antigens Encoded By HLA Genes Provide Cost-Effective Alternatives to Identifying B27 Allele Status in Rheumatoid Arthritis Subjects

Kimberly Robasky[1], Jatinder Kaur[2], Jennifer Sims[1], Melissa Howard[1], Eric Earley[1] and Eric Lai[2], [1]EA|Quintiles, Durham, NC, [2]Takeda Pharmaceuticals International, Inc., Deerfield, IL

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Background/Purpose:

Human leukocyte antigen (HLA) genes code for proteins that allow the immune system to distinguish self from foreign cells. These genes have important indications in rheumatology, as well as other autoimmune disorders, transplantation, cancer, and pharmacotoxicity. The gold standards for HLA-typing are Sequence Specific Oligonucleotide Probe and

Sequence Specific Primed PCR typing (PCR-SSOP and PCR-SSP), both of which are manually-intensive and costly. Multiplexing samples with next-generation sequencing (NGS) could easily reduce costs. Unfortunately, HLA genes are the most variable in the human genome and also have high sequence similarity, each of which pose considerable challenges to new technologies. However, nascent assays and bioinformatic methods are emerging in support of more cost-effective platforms for finding new biomarkers of inflammatory disease and for typing patients in the clinic. Here we apply new and traditional methods to investigate the HLA B27 allele, which has known links to a large family of inflammatory diseases.

Methods:

We obtained 90 samples from RA patients and compared the HLA allele calls on three platforms: 1) GenDx's NGSengine for the NGSGo kit for Illumina's MiSeq, 2) SNP2HLA [1] for both the Affymetrix Axiom and the Illumina Omni 5 microarrays, and 3) the Luminex PCR process. We stratified the sample populations by principal components to identify 47 samples of European ancestry to call alleles using array genotypes against a European reference panel. We measured HLA B27-positive status in those 47 samples to check for enrichment in both the NGS-based and the array-based calls.

Results:

Alleles were called and compared to the Luminex calls for two-digit and four-digit precision, and with the exception of DRB1, NGS-based allele calls were 97-100% concordant. However, two-digit precision suffices for testing B27 status, which will be positive for all 4-digit precision alleles ranging from HLA-B*27:01-HLA-B*27:117. The microarray approach measured 19% of the RA subjects as B27-positive, and the NGS technique measured 12%. This is enriched, compared with 3.65 (+/- 1.7)% observed in typical European populations [2]. The less accurate array-based technique found the association and the NGS technique confirmed it. Notably, the NGS-based technique can assay the same number of loci as the high-throughput gold standard option but at close to half the cost and with fewer ambiguities. Some NGS-based options have already been submitted for CLIA-validated clinical use. Alternatively, the array-based techniques are offered at a cost that is an order of magnitude lower than the gold standard and can be used on legacy datasets, presenting a lower cost option for association discovery.

Conclusion:

Existing, legacy microarray data can guide exploration and hypotheses at reduced costs, and should be confirmed with gold standard or CLIA-validated NGS technologies, the latter of which poses a viable candidate for reducing costs, time and effort in a clinical setting.

References:

1. Xiaoming et al. PLoS One 2013; 8(6):e64683
2. Gonzalez-Galarza et al. NAR 2015; 28, D784-8

Disclosure: K. Robasky, EA|Quintiles, 3; **J. Kaur**, Takeda Pharmaceuticals International, Inc., 3; **J. Sims**, EA|Quintiles, 3; **M. Howard**, EA|Quintiles, 3; **E. Earley**, EA|Quintiles, 3; **E. Lai**, Takeda Pharmaceuticals International, Inc., 3.

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Abstract Number: 102

Xanthine Oxidase Gene Variants and Their Association with Blood Pressure and Incident Hypertension: A Population Based Study

Lieke E.J.M. Scheepers[1], Jan A. Staessen[2,3], Lutgarde Thijs[2], Erika Salvi[4], Annelies Boonen[5] and Ilja C.W. Arts[6], [1]Department of Internal Medicine, Division of Rheumatology, CAPHRI School for Public Health and Primary Care, Maastricht University Medical Centre, Maastricht, Netherlands, [2]Studies Coordinating Centre, Research Unit Hypertension and Cardiovascular Epidemiology KU Leuven, Department of Cardiovascular Diseases, University of Leuven, Leuven, Belgium, [3]R & D Group VitaK, Maastricht University, Maastricht, Netherlands, [4]Department of Health Sciences, University of Milan, Milan, Italy, [5]Department of Internal Medicine, Division of Rheumatology, Maastricht University Medical Center, Maastricht, Netherlands, [6]Department of Epidemiology, CAPHRI School for Public Health and Primary Care, CARIM School for Cardiovascular Diseases, and MaCSBio Maastricht Centre for Systems Biology, Maastricht University, Maastricht, Netherlands
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Session Time: 9:00AM-11:00AM

Background/Purpose:

Uric acid (UA) has been associated with blood pressure (BP) and hypertension. During the final stage of purine metabolism, xanthine oxidoreductase (XOR) breaks down hypoxanthine to xanthine, and xanthine to UA, while reactive oxygen species (ROS) are formed. These ROS inactivate the vasodilator nitric oxide. We hypothesize that variants in the XOR gene, responsible for the production of UA, are associated with elevated BP and hypertension. The aim of the present study is to investigate the association of variants in the XOR gene with BP and the development of hypertension.

Methods:

Analyses were conducted in the prospective Flemish FLEMENGHO and European EPOGH study (n=2769). 28 tagging SNPs that are in disequilibrium (r^2>0.80) with 387 SNPs covering the entire gene were selected. 24 SNPs remained after exclusion of 4 SNPs not meeting the Hardy-Weinberg equilibrium. Minor allele carriers were determined by using the European HAPMAP population as reference. The minor allele homozygotes and heterozygotes were compared with the major allele homozygotes. BP was measured by trained observers at baseline (1985-2004) and repeatedly during follow-up (1991-2013). The relation between variants of the XOR gene and changes in pulse pressure (PP) and mean arterial pressure (MAP) over time; and incidence of hypertension, were analysed using multivariable mixed models and cox-regression, respectively. Family clusters were modelled as random effect. Analyses were corrected for multiple testing by the Benjamini Hochberg correction, the false discovery rate was set at 0.25.

Results:

Follow-up data for BP were available at 1, 2, or ≥3 occasions in 2769, 1450, and 1035 participants, respectively (median follow-up: 8.79 yrs (IQR: 6.54)). The rise in PP from baseline to the last available measurement was significantly associated with SNP rs11904439, in the crude and confounder adjusted model (adjusted P=<0.01), averaging 8.55 mm Hg (SD 13.6) in minor *G* allele carriers and 6.33 mm Hg(SD 13.6) in AA homozygotes. The association remained significant after correction for multiple testing. No association with change in MAP was found. Among 2050 participants normotensive at baseline, 753 (36.7%) developed hypertension during follow-up (median follow-up: 10.7 yrs (IQR: 7.3)). Multivariably, two SNPs, rs148756340 and rs11904439, were associated with onset of hypertension. For SNP rs148756340 the minor *G* allele carriers had a higher risk of hypertension compared to AA homozygotes (adjusted HR: 1.69; 95% CI 1.11 to 2.57, p=0.01). For SNP rs11904439 minor *G* allele carriers had a higher risk of hypertension compared to AA homozygotes (adjusted HR: 1.33; 95% CI 1.04 to 1.70, p=0.02). For both SNPs the association remained significant after correction for multiple testing.

Conclusion:

Two SNPs, rs11904439 and rs148756340, of the XOR gene were associated with change in PP over time and/or the development of hypertension. This suggests that UA production may be associated with BP and the development of hypertension. Because of the exploratory nature of this study and because it is unknown if the SNP has an effect on the enzyme activity, further investigation is required.

Disclosure: L. E. J. M. Scheepers, None; **J. A. Staessen**, None; **L. Thijs**, None; **E. Salvi**, None; **A. Boonen**, None; **I. C. W. Arts**, None.

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Abstract Number: 103

Axial Disease in Psoriatic Arthritis: Genetic Biomarkers of Psoriatic Spondyloarthritis

Deepak R. Jadon[1], John Bowes[2], Anne Barton[3], Raj Sengupta[1], Alison L Nightingale[4], Mark Lindsay[5], Eleanor Korendowych[1], Graham Robinson[6] and Neil J. McHugh[7], [1]Rheumatology, Royal National Hospital for Rheumatic Diseases, Bath, United Kingdom, [2]Arthritis Research UK Centre for Genetics and Genomics, The University of Manchester, Centre for Musculoskeletal Research, Manchester, United Kingdom, [3]Arthritis Research UK Centre for Genetics and Genomics, Centre for Musculoskeletal Research, Manchester Academic Health Science Centre, The University Of Manchester, Manchester, United Kingdom, [4]Pharmacy and Pharmacology, University of Bath, Bath, United Kingdom, [5]Pharmacy & Pharmacology, University of Bath, Bath, United Kingdom, [6]Royal United Hospital, Bath, United Kingdom, [7]Rheumatology, Royal National Hospital for Rheumatic Diseases, Upper Borough Walls, United Kingdom

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Background/Purpose:

A lack of well-characterised clinical cohorts has impeded research of the genetics of axial disease in psoriatic arthritis (PsA). We sought to determine genetic biomarkers of psoriatic spondyloarthritis (PsSpA) occurrence in patients with PsA.

Methods:

A cross-sectional observational study was conducted of all PsA patients attending a teaching hospital. Axial radiographs were examined for the presence of PsSpA, defined as: sacroiliitis grade ≥3 unilaterally, or grade ≥2 bilaterally; and/or ≥1 syndesmophyte of the cervical and/or lumbar spine.

All PsA cases were genotyped using the Illumina Infinium HumanCoreExome Beadchip. In order to determine genetic risk factors for axial disease in PsA, comparisons were made between PsA cases with and without: PsSpA; sacroiliitis; and spondylitis. Multivariate modelling was adjusted for sex, age and disease duration at radiographic assessment. Associated single nucleotide polymorphisms (SNPs) within 100 kb of each other were considered as one locus, and an index SNP identified.

Results:

The study enrolled and genotyped 515 PsA cases fulfilling CASPAR criteria. Of 436/515 with complete radiographs to determine PsSpA, 144/436 (33.03%) had PsSpA and 292/436 (66.97%) did not have PsSpA. Genetic analyses were performed on these 436 cases only.

No single nucleotide polymorphisms (SNPs) passed the conventional genome-wide significance ($5x10^{-8}$); a total of seven SNPs were in tier 1 (defined as p-value $<1x10^{-5}$). Notable associations include rs11950551 with PsSpA (OR 3.03; 95%CI 1.88, 4.89; p-value $5.42x10^{-6}$) (*Table 1*) that maps close to gene *CD180,* belonging to a family of toll-like receptors important in B-cell signalling (*Figure 1*). Secondly, an insertion on chromosome 4 (rs202217778) within the *SMAD1* gene is associated with sacroiliitis (OR 3.98; 95%CI 2.18, 7.27; p-value $7.36x10^{-6}$) but not spondylitis (*Table 1*, *Figure 1*). *SMAD1*has a key role in bone morphogenesis and immune responses.

Forty eight SNPs showing association with psoriasis, PsA or AS in Genome Wide Association Studies, were specifically compared in PsA cases with and without PsSpA. Of note, none of the SNPs were associated with PsSpA.

Conclusion:

We have identified suggestive evidence for association of 24 independent loci associated with axial disease in patients with PsA (PsSpA). The genetic loci associated with sacroiliitis did not overlap either with those associated with vertebral spondylitis in PsA, or with known AS loci. The findings need investigation in validation datasets and the functional influence of confirmed variants on biological pathways may warrant further exploration.

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Abstract Number: 104

A Genome-Wide Association Study Identifies SLC8A3 As a Susceptibility Locus for ACPA-Positive Rheumatoid Arthritis

Antonio Julià[1], Isidoro González-Alvaro[2], Antonio Fernandez-Nebro[3], Francisco Blanco[4], Benjamin Fernandez Gutierrez[5], Antonio Gonzalez[6], Juan D. Cañete[7], Joan Maymo[8], Mercedes Alperi-López[9], Alejandro Olivé[10], Hector Corominas[11], Víctor Martínez Taboada[12], Alba Erra[13], Simon Sanchez Fernandez[14], Arnald Alonso[1], María López-Lasanta[1], Raül Tortosa[1], S. Louis Bridges Jr.[15], Jesús Tornero[16] and Sara Marsal[17], [1]Rheumatology Research Group, Vall d'Hebron Hospital Research Institute, Barcelona, Spain, [2]Rheumatology Department, Hospital Universitario la Princesa, IIS-Princesa, Madrid, Spain, [3]Rheumatology, Hospital Universitario Carlos Haya, Malaga, Spain, [4]Rheumatology Division, Fundación Profesor Novoa Santos, A Coruna, Spain, [5]Department of Rheumatology, Hospital Clínico San Carlos, Madrid, Spain, [6]H. Clinico Universtiario de Santiago, Santiago de Compostela, Spain, [7]Unitat d'Artritis, Servei de Reumatologia, Hospital Clínic de Barcelona and Institut d'Investigacions Biomèdiques August Pí i Sunyer, Barcelona, Spain, [8]H del Mar, Barcelona, Spain, [9]Department of Rheumatology, Hospital Universitario Central de Asturias, Asturias, Spain, [10]Hospital Germans Trias i Pujol, Badalona, Spain, [11]Servei de Reumatologia, Hospital Moises Broggi, Barcelona, Spain, [12]Rheumatology, Hospital Marqués de Valdecilla, Santander, Spain, [13]CapiCAT group (Nailfold Capillaroscopy group from the Catalan Society for Rheumatology)., Catalonia, Spain, [14]Rheumatology Department, Hospital General La Mancha Centro, Ciudad Real, Spain, [15]Clinical Immunology and

Rheumatology, University of Alabama at Birmingham, Birmingham, AL, [16]Rheumatology Department, Hospital Universitario Guadalajara, Guadalajara, Spain, [17]Rheumatology Research Unit, Vall d'Hebron Hospital, Barcelona, Spain

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Background/Purpose: Rheumatoid Arthritis (RA) patients with serum anti-citrullinated peptide antibodies (ACPA) have a strong and specific genetic background. We performed a genome-wide association study (GWAS) of ACPA-positive RA with erosive disease to identify additional disease susceptibility genes.

Methods: A total of 924 ACPA-positive RA patients with joint damage in hands and/or feet, and 1,524 healthy controls were genotyped in 582,591 single-nucleotide polymorphisms (SNPs) in the discovery phase. In the validation phase, the most significant SNPs in the GWAS representing new candidate loci for RA were tested in an independent cohort of 863 ACPA-positive patients with joint damage and 1,152 healthy controls. All individuals from the discovery and validation cohorts were Caucasian and from Southern European ancestry.

Results: In the discovery phase, 60 loci not previously associated with RA risk showed evidence for association at $P < 5e\text{-}4$ and were tested for replication in the validation cohort. A total of 12 loci were replicated at the nominal level ($P < 0.05$, same direction of effect as in the discovery phase). When combining the discovery and validation cohorts, an intronic SNP in Solute Carrier family 8 gene (*SLC8A3*) was found to be associated with ACPA-positive RA at a genome-wide level of significance RA (OR(95%CI): 1.42(1.25-1.6), $P_{combined} = 3.19e\text{-}8$, Figure 1).

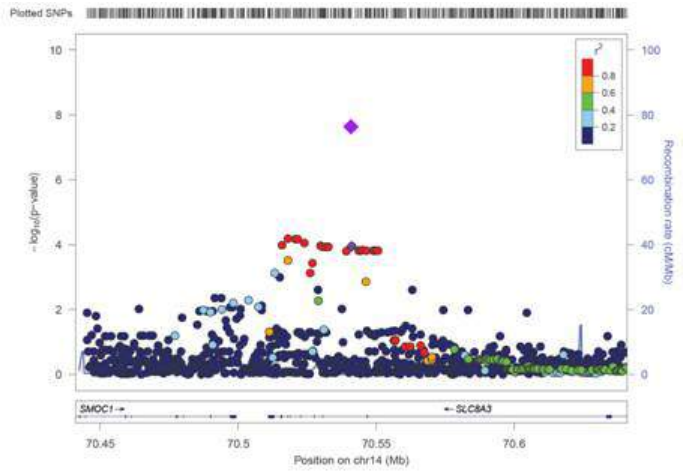

Figure 1. Association results for *SLC8A3* locus with ACPA-positive RA. Significance -log10(P-value) of association of SNPs at SLC8A3 locus with ACPA-positive RA. The genome-wide significant marker is plotted as a purple diamond, and all the remaining markers as color-coded according to their LD with this SNP.

Conclusion: *SLC8A3* was identified as new risk locus for ACPA-positive RA. This study demonstrates the advantage of analyzing relevant subsets of RA patients to identify new genetic risk variants.

Disclosure: **A. Julià**, None; **I. González-Alvaro**, None; **A. Fernandez-Nebro**, None; **F. Blanco**, None; **B. Fernandez Gutierrez**, None; **A. Gonzalez**, None; **J. D. Cañete**, None; **J. Maymo**, None; **M. Alperi-López**, None; **A. Olivé**, None; **H. Corominas**, None; **V. Martínez Taboada**, None; **A. Erra**, None; **S. Sanchez Fernandez**, None; **A. Alonso**, None; **M. López-Lasanta**, None; **R. Tortosa**, None; **S. L. Bridges Jr.**, None; **J. Tornero**, None; **S. Marsal**, None.

Abstract Number: 105

Analysis of the Association of PTGER4 Gene Variants with Radiological Joint Damage in Rheumatoid Arthritis

Luis Rodriguez-Rodriguez[1,2], J. Ivorra-Cortes[3], Francisco David Carmona[4], Javier Martín[5], Alejandro Balsa[6], H.W. van Steenbergen[7], A. H. M. van der Helm- van Mil[8], Isidoro González-Alvaro[9] and Benjamín Fernández-Gutiérrez[10], [1]Instituto de Investigación Sanitaria San Carlos (IdISSC), Madrid, Spain, [2]Hospital Clínico San Carlos, Department of Rheumatology, Madrid, Spain, [3]Rheumatology, University Hospital la Fe, Valencia, Spain, [4]Instituto de Parasitología y Biomedicina López-Neyra, IPBLN-CSIC, PTS-Granada, Granada, Spain, [5]Instituto de Parasitología y Biomedicina López- Neyra, IPBLN-CSIC, PTS-Granada, Granada, Spain, [6]Rheumatology, La Paz University Hospital-Rheumatology Department, Madrid, Spain, [7]Leiden University Medical Center, Leiden, Netherlands, [8]Rheumatology, Leiden University Medical Center, Leiden, Netherlands, [9]Rheumatology Department, Hospital Universitario la Princesa, IIS-Princesa, Madrid, Spain, [10]Department of Rheumatology, Hospital Clínico San Carlos, Madrid, Spain
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Background/Purpose: *PTGER4*(prostaglandin E receptor 4) is implicated in immune regulation and bone metabolism. The aim of this study was to analyze the role of single nucleotide polymorphisms (SNPs) located in this locus in radiological joint damage in rheumatoid arthritis (RA).

Methods: 6 independent cohorts of RA patients of European and North-American descent were included in this study, comprising 1,789 patients with 5,083 sets of X-rays. Three cohorts from Madrid (Spain) were used for identification: *Hospital Clínico San Carlos* Rheumatoid Arthritis Cohort, the *Hospital Universitario de la Princesa* Early Arthritis Register Longitudinal cohort, and the *Hospital Universitario de La Paz* early arthritis cohort. On the other hand, the Leiden Early Arthritis Clinic Cohort (The Netherlands), Wichita (US) and National DataBank (US and Canada) cohorts were used for replication. First, the *PTGER4* rs6896969 SNP was genotyped using Taqman assays and available Illumina Immunochip data. The latter was also used to obtain genotyping data from the *PTGER4* gene and adjacent regions (Chr 5: from 38,957,820 bp to 41,336,050 bp; GRCh37/hg19). The effect of the SNPs on radiological joint damage was assessed using two models: a *continuous effect model* that analyzes the overall effect of each SNP in radiological damage, assuming a stable effect over time, and a *time-varying effect model* that analyzes the effect of the SNP in the slope (progression) of the radiological damage. Linkage disequilibrium (LD) structure of the locus was assessed and for each LD block (r^2>0.9), 1 SNP with a p value <0.05, preferably located in a region with transcriptional properties, was selected for replication. **Results** from the different cohorts were pooled using inverse variance-weighted meta-analysis, and the pooled p values were adjusted using the Bonferroni method, based on the number of effectively independent SNPs tested, and in the fact that we performed a *continuous* and a *time-varying effect* analysis for each SNP (threshold p value=$1.3x10^{-4}$).

Results: The rs6896969 polymorphism showed a significant association with radiological damage in the *continuous effect* pooled analysis of the Spanish cohorts, although no significant association was observed in the replication cohorts or when the results from the 6 cohorts were pooled. In the analysis of the *PTGER4* region, 12 and 20 SNPs,

from the *continuous* and *time-varying effect* models, respectively, were analyzed in the replication cohorts. Only the rs76523431 variant showed a significant association with higher radiographic progression in the *time-varying effect* analysis (overall pooled $p=2.10x10^{-5}$, $I^2=0.13$).

Conclusion: The *PTGER4* gene could play a role in RA radiological progression.

Disclosure: L. Rodriguez-Rodriguez, None; **J. Ivorra-Cortes**, None; **F. D. Carmona**, None; **J. Martín**, None; **A. Balsa**, None; **H. W. van Steenbergen**, None; **A. H. M. van der Helm- van Mil**, None; **I. González-Alvaro**, None; **B. Fernández-Gutiérrez**, None.

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Abstract Number: 106

Does the Timing of Phenotype Assessment Influence Association Results in Pharmacogenetics Studies of Anti-TNF Response in Rheumatoid Arthritis?

Kyoko Honne[1], Nicholas Jewell[2], Takeo Sakurai[3], Masahiro Iwamoto[4], Seiji Minota[4] and **Damini Jawaheer**[5], [1]Division of Rheumatology and Clinical Immunology, Jichi Medical University, Shimotsuke, Japan, [2]UC Berkeley, Berkeley, CA, [3]Inoue Hospital, Takasaki, Japan, [4]Department of Internal Medicine, Division of Rheumatology/Clinical Immunology, Jichi Medical University, Shimotsuke, Japan, [5]Children's Hospital Oakland Research Institute, Oakland, CA

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Background/Purpose: Pharmacogenetics studies of anti-tumor necrosis factor (TNF) response among patients with rheumatoid arthritis (RA) have routinely used assessment of response at a single time-point, ranging between 3 and 12 months after initial treatment, to define the phenotype. Given the general lack of consistency in the findings from published studies, we have examined whether differences in the timing of anti-TNF response assessment in the same patients can influence the results of a genome-wide association study (GWAS) investigating associations between anti-TNF response and single nucleotide polymorphisms (SNPs).

Methods: Disease Activity Scores based on 28 joint counts and C-reactive protein (DAS28) were assessed at baseline (before initial therapy), and after 3 and 6 months in 487 Japanese RA patients starting anti-TNF therapy for the first time or switching to a new anti-TNF agent. DNA samples from these patients were genotyped using a genome-wide panel of 1,133,484 SNPs and additional SNPs were imputed. Change in DAS28 scores from baseline were evaluated at 3 months (ΔDAS28-3) and at 6 months (ΔDAS28-6). Association analyses between anti-TNF response at one follow up and each SNP were performed using 2 separate multivariate linear regression models, with ΔDAS28-3 (model 1) and ΔDAS28-6 (model 2) as the outcome (response) variable. A longitudinal Generalized Estimating Equations model (model 3) was also used to allow inclusion of response at both 3 and 6 months in the outcome variable. All models adjusted for baseline DAS28, type of anti-TNF agent and concomitant methotrexate. In model 3, time since initiation of therapy was also adjusted for.

Results: At 3 months (model 1), five SNPs were moderately associated with ΔDAS28-3 ($p<1x10^{-5}$). At 6 months (model 2), a SNP at 6q15 was associated with ΔDAS28-6 at a genome-wide significance level ($p=2.5x10^{-8}$). This SNP mapped close to the *MAP3K7* gene which is a key player in TNFα-mediated inflammatory pathway signaling. Four other chromosomal regions showed evidence of moderate association with ΔDAS28-6 ($p<1x10^{-5}$), including a SNP at 10q25.3 which mapped to the *GFRA1* gene ($p=5.3x10^{-6}$). There was no overlap between the regions of association identified when using as phenotype response at 3 months (model 1) vs. response at 6 months (model 2). On the other hand, when response at both 3 and 6 months were included in the phenotype (model 3), suggestive association with anti-TNF response was observed at two of the same loci identified in model 2: 6q15 ($p=6.6x10^{-7}$) and 10q25.3 ($p=8.1x10^{-7}$). A third region mapping to the *WDR27* gene at 6q27 showed suggestive evidence of association in model 3 ($p=6.3x10^{-7}$), but not in models 1 and 2 (ΔDAS28-3: $p=7x10^{-4}$; ΔDAS28-6: $p=5.5x10^{-5}$).

Conclusion: The timing of anti-TNF response assessment significantly influences the results of genetic association studies, especially since clinical response is known to fluctuate over time. Using more than one assessment of response provides a more reliable clinical phenotype and, in our dataset, enhanced the power to detect associations.

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Abstract Number: 107

FCGR3A-158V/F Polymorphism Is Associated with a Lower Response Rate to Tumor Necrosis FactorÂ Î± Blockers in Early Axial Spondyloarthritis: Data from the DESIR Cohort

Cécile LUXEMBOURGER[1], Anna Molto[2], Pascal Claudepierre[3], Delphine Nigon[1], Alain G. Cantagrel[1], Maxime Dougados[4], Arnaud CONSTANTIN[1] and Adeline Ruyssen Witrand[5], [1]Rheumatology, CHU Purpan - Hôpital Pierre-Paul Riquet, Toulouse, France, [2]Hopital Cochin, Paris Descartes University, Paris, France, [3]Hôpital Henri Mondor, Créteil, France, [4]Service de Rhumatologie B, GHU Cochin, F-75014 France, PARIS, France, [5]Rheumatolgy, CHU Purpan - Hôpital Pierre-Paul Riquet, Toulouse, France

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Background/Purpose:

The *rs396991* polymorphism of *FCGR3A* alters the Fcγ Receptor Type IIIA function by enhancing or diminishing the affinity to the Fc of immunoglobulins (1) by the substitution of a valine (V) for a phenylalanine (F) at amino acid position 158. *FCGR3A* polymorphism has already been associated with the biological Disease Modifying Anti-Rheumatic Drugs (bDMARDs) response in patients with rheumatoid arthritis and Psoriatic Arthritis (1,2). Our study was carried out to evaluate the influence of the *FCGR3A – 158 V/F*polymorphism on the therapeutic response to anti

TNFα in the DESIR (Devenir des SpondyloarthrItes (SpA) Récentes) cohort.

Methods:

All patients included in the DESIR cohort fulfilling the Assessment of SpondyloArthritis international Society (ASAS) diagnosis criteria for axial SpA and who received TNFα blockers at least 8 weeks were included in our study. Univariate and multivariate analyses by Chi square test and logistic regression were performed to assess whether *FCGR3A-158V/F*polymorphism was associated with ASAS 40 response after at least 8 weeks of treatment (3).

Results:

Among the 147 patients who received TNF blockers in DESIR cohort, 139 could be genotyped of whom 52 patients (37%) were responders. *FCGR3A-158V/V* polymorphism was significantly associated with a lower response rate (17% of responders for VV genotype vs 38 % of responders for VF genotype and 47 % of responders for FF genotype, p=0.016). In multivariate analysis (taking into account of the presence of radiographic sacroiliitis, abnormal VS or CRP levels, HLA–B27 positivity, peripheral arthritis, psoriasis, and smoking status at baseline), *FCGR3A-158V/V*polymorphism was independently associated with a lower response rate to TNF-α blockers (risk of response to TNF-blockers in case of V allele carriage: OR (95% CI) = 0.44 (0.20 to 0.96) (p=0.041).

Conclusion:

In the Desir cohort, *FCGR3A158 VV*genotype was associated with a lower response rate to TNF-α blockers in SpA. This association has already been described in previous publications in rheumatoid arthritis patients (1). A higher affinity to the Fc region of antiTNFα could influence their clearance from the circulation. Further studies involving more axial SpA patients should be performed to confirm this association.

This work received an institutionnal support by the French society of rheumatology.

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Abstract Number: 108

A New Susceptibility Locus for Systemic Lupus Erythematosus on Chromosome 12

F. Yesim Demirci[1], Xingbin Wang[1], Jennifer A. Kelly[2], David L. Morris[3], M. Michael Barmada[1], Eleanor Feingold[1], Amy H. Kao[4], Kathy L. Sivils[5], Sasha Bernatsky[6], Christian A. Pineau[6], Ann Clarke[7], Rosalind Ramsey-Goldman[8],

Timothy Vyse[9], Patrick M. Gaffney[10], Susan Manzi[11] and M. Ilyas Kamboh[12], [1]Department of Human Genetics, University of Pittsburgh, Pittsburgh, PA, [2]Arthritis & Clinical Immunology Research Program, Oklahoma Medical Research Foundation, Oklahoma City, OK, [3]Department of Medical & Molecular Genetics, King's College London, London, United Kingdom, [4]Lupus Center of Excellence, Department of Medicine, West Penn Allegheny Health System, Pittsburgh, PA, [5]Oklahoma Medical Research Foundation, Oklahoma City, OK, [6]Divisions of Rheumatology and Clinical Epidemiology, McGill University Health Centre, Montreal, QC, Canada, [7]Division of Rheumatology, Department of Medicine, University of Calgary, Calgary, AB, Canada, [8]Northwestern University Feinberg School of Medicine, Chicago, IL, [9]Division of Genetics and Molecular Medicine and Division of Immunology, Infection and Inflammatory Disease, King's College London, London, United Kingdom, [10]Arthritis and Clinical Immunology, Oklahoma Medical Research Foundation, Oklahoma City, OK, [11]Internal Medicine, West Penn Allegheny Health System, Pittsburgh, PA, [12]Human Genetics, University of Pittsburgh, Pittsburgh, PA
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Background/Purpose: Genome-wide association studies (GWASs) and large follow-up studies in European-descent or Asian subjects have identified a number of susceptibility loci for systemic lupus erythematosus (SLE) to date. Despite this tremendous progress, a significant portion of genetic component of SLE still remains to be uncovered. The purpose of this multi-stage study was to identify new susceptibility loci for SLE in individuals of European ancestry.

Methods: In Stage 1, a new GWAS of SLE was conducted in a North American case-control sample of European ancestry (~1,200 subjects) genotyped on Affymetrix Genome-Wide Human SNP Array 6.0. In Stage 2, the top new suggestive GWAS hits were further investigated by *in silico* evaluation in an additional dataset of European-descent subjects (>2,500 individuals) followed by meta-analysis. In Stage 3, the top meta-analysis findings were evaluated for replication in another dataset of European-descent subjects (>10,000 individuals).

Results: Our GWAS revealed the most significant associations at the major histocompatibility complex (MHC) locus on chromosome 6p21 ($P<5x10^{-8}$), followed by those on chromosomes 2q32 (*STAT4*) and 8p23 (*BLK*). Several other SLE signals/loci previously reported in Caucasians and/or Asians were also confirmed in our Stage 1 sample. Stage 2 meta-analyses identified a new genome-wide significant locus on chromosome 12q12 (meta $P=3.1x10^{-8}$), which was replicated in Stage 3.

Conclusion: We conducted a new GWAS of SLE and, through a multi-stage approach, we have discovered and replicated a new SLE locus at 12q12. Publicly available databases suggest that this new SLE signal falls within a genomic region with regulatory function and near biologically relevant genes.

Abstract Number: 109

Association of HLA-G and Leukocyte Immunoglobulin-like Receptor A3 Polymorphisms with the Susceptibility to Pulmonary Hyterpention in Systemic Sclerosis

Yuki Hachiya[1], Aya Kawasaki[1], Takashi Matsushita[2], Hiroshi Furukawa[1], Shouhei Nagaoka[3], Kota Shimada[4], Shoji Sugii[4], Keigo Setoguchi[5], Akira Okamoto[6], Noriyuki Chiba[7], Eiichi Suematsu[8], Masao Katayama[9], Shunsei Hirohata[10], Hajime Kono[11], Kiyoshi Migita[12], Takayuki Sumida[13], Shigeto Tohma[14], Minoru Hasegawa[15], Manabu Fujimoto[16], Shinichi Sato[17], Kazuhiko Takehara[18] and Naoyuki Tsuchiya[19], [1]Molecular and Genetic Epidemiology Laboratory, Faculty of Medicine, University of Tsukuba, Tsukuba, Japan, [2]Department of Dermatology, Faculty of Medicine, Institute of Medical, Pharmaceutical and Health Sciences, Kanazawa University, Kanazawa city, Japan, [3]Rheumatology, Yokohama Minami Kyosai Hospital, Yokohama, Japan, [4]Department of Rheumatic Diseases, Tokyo Metropolitan Tama Medical Center, Fuchu, Japan, [5]Department of Allergy and Immunological Diseases, Tokyo Metropolitan Cancer and Infectious Diseases Center Komagome Hospital, Tokyo, Japan, [6]Department of Rheumatology,, Himeji Medical Center, National Hospital Organization, Himeji, Japan, [7]Department of Rheumatology, Morioka National Hospital, NHO, Iwate, Japan, [8]Department of Internal Medicine and Rheumatology, National Hospital Organization, Kyushu Medical Research Center, Fukuoka, Japan, [9]Division of Rheumatology, Department of Internal Medicine, Nagoya Medical Center, National Hospital Organization, Nagoya City, Aichi, Japan, [10]Rheumatology and Infectious Diseases, Kitasato University School of Medicine, Kanagawa, Japan, [11]Department of Internal Medicine, Teikyo University, Tokyo, Japan, [12]Department of Rheumatology and Clinical Research Center, Nagasaki Medical Center, Omura, Japan, [13]Division of Rheumatology, Department of Internal Medicine, Faculty of Medicine, University of Tsukuba, Tsukuba, Japan, [14]Sagamihara Hospital, National Hospital Organization, Sagamihara, Japan, [15]Dermatology, Faculty of Medical Sciences, University of Fukui, Fukui, Japan, [16]Department of Dermatology, Faculty of Medicine, University of Tsukuba, Tsukuba, Japan, [17]Dermatology, University of Tokyo Graduate School of Medicine, Tokyo, Japan, [18]Dermatology, Department of Dermatology, Faculty of Medicine, Institute of Medical, Pharmaceutical and Health Sciences, Kanazawa University, Kanazawa city, Japan, [19]Faculty of Medicine, University of Tsukuba, Tsukuba, Japan

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Background/Purpose: Human leukocyte antigen-G (HLA-G) is a non-classical class I molecule expressed in the immune cells, the spleen, and the lungs, and plays a key role in immunosuppression. HLA-G binds to inhibitory leukocyte immunoglobulin-like receptor (LILR)B1, LILRB2, and killer cell immunoglobulin-like receptor (KIR)2DL4. LILRA3, a soluble member of the LILR family and also binds to HLA-G, has a deletion polymorphism. Although the function of LILRA3 remains elusive, some evidence suggests that LILRA3 might work as an antagonist of other LILRs including LILRB1 or LILRB2. *HLA-G* gene contains a 14bp insertion polymorphism in the 3'UTR, which has been shown to influence the splicing and affect mRNA stability, thereby leading to low expression of HLA-G. Previous studies reported association of *HLA-G* 14bp ins/ins genotype with systemic lupus erythematosus in the European and Asian populations. In this study, we examined whether *HLA-G* 14bp ins/del polymorphism is associated with systemic sclerosis (SSc), either in itself or in combination with *LILRA3* genotypes.

Methods: 379 Japanese patients with SSc and 765 healthy Japanese controls were examined. All patients fulfilled the American College of Rheumatology criteria. 127 were classified as diffuse cutaneous (dc) SSc, while 230 as limited cutaneous (lc) SSc. 45 patients as having pulmonary hypertension (PH). *HLA-G* 14bp ins/del was genotyped by PCR

with the product size of 224 or 210bp. *LILRA3* ins/del was genotyped by PCR-sequence specific primers method. This study was reviewed and approved by the ethics committees of each participating institute.

Results: The results are shown in Table 1. Although significant association of *HLA-G* ins/del polymorphism was not observed with overall SSc nor with dc/lc subsets, significant increase of *HLA-G* ins allele was observed in SSc patients with PH when compared with healthy controls (P=0.047, OR 2.32, dominant model) or with PH(-) SSc (P=0.019, OR 1.75, allele model; P=0.021, OR 2.88, dominant model). *LILRA3* ins/del was not associated with PH. However, when *HLA-G* association was examined with respect to the *LILRA3* genotypes, more striking association of *HLA-G* 14bp ins with PH was observed in the subjects with *LILRA3* del/del genotype (P=0.010, OR 2.13, allele model, and P=0.016, OR 3.36, dominant model vs healthy controls; P=0.0044, OR 2.40, allele model, P=0.033, OR 2.47, recessive model, P=0.010, OR 4.14, dominant model vs PH(-) SSc). In contrast, significant association of *HLA-G* was not detected in the patients and controls having one or two copies of *LILRA3* allele.

Conclusion: Association of *HLA-G* 14bp ins with SSc patients with PH was detected. The association was more striking in *LILRA3* null individuals, suggesting a possibility that the predispositional effect of *HLA-G* low expression allele becomes manifest when its soluble receptor LILRA3 is deficient.

Table 1. Association of *HLA-G* 14bp insertion polymorphism with pulmonary hypertension in overall SSc and controls and with respect to *LILRA3* genotypes.

	n	*HLA-G* 14bp ins/del genotype frequency			ins allele freq (%)	PH(+) SSc vs healthy controls						PH(+) SSc vs PH(-) SSc					
						allele		recessive		dominant		allele		recessive		dominant	
		del/del (%)	ins/del (%)	ins/ins (%)		P	OR (95%CI)	P	OR (95%CI)	P	OR (95%CI)	P	OR (95%CI)	P	OR (95%CI)	P	OR (95%CI)
Overall patients and controls																	
PH(+)SSc	46	22 (48.8)	17 (37.0)	7 (15.2)	33.7	0.058	1.54 (0.99-2.40)	0.20	1.46 (0.82-2.67)	0.047	2.32 (1.01-5.30)	0.019	1.75 (1.10-2.80)	0.092	1.70 (0.92-3.16)	0.021	2.88 (1.17-7.09)
PH(-)SSc	307	187 (60.9)	102 (33.2)	18 (5.9)	22.5												
HC	785	440 (57.5)	270 (35.3)	55 (7.2)	24.8												
LILRA3 del/del patients and controls																	
PH(+)SSc	25	10 (40.0)	10 (40.0)	5 (20.0)	40.0	0.010	2.13 (1.20-3.79)	0.057	2.19 (0.98-4.89)	0.016	3.38 (1.25-9.04)	0.0044	2.40 (1.31-4.38)	0.033	2.47 (1.07-5.68)	0.010	4.14 (1.40-12.19)
PH(-)SSc	188	120 (62.2)	62 (32.1)	11 (5.7)	21.8												
HC	462	274 (59.3)	156 (33.8)	32 (6.9)	23.8												
LILRA3 ins/del or ins/ins patients and controls																	
PH(+)SSc	21	12 (57.1)	7 (33.3)	2 (9.5)	26.2	0.95	1.02 (0.50-2.08)	0.93	0.96 (0.39-2.33)	0.75	1.28 (0.28-5.78)	0.88	1.17 (0.55-2.50)	0.82	1.12 (0.43-2.88)	0.58	1.58 (0.31-8.14)
PH(-)SSc	112	67 (59.8)	38 (33.9)	7 (6.3)	23.2												
HC	369	207 (56.1)	134 (36.3)	28 (7.6)	25.7												

PH: pulmonary hypertension, HC: healthy controls, The genotype frequencies of healthy controls were not significantly departed from Hardy-Weinberg equilibrium (P=0.13 in all healthy controls, P=0.14 in *LILRA3* null healthy controls).

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Abstract Number: 110

Genome-Wide DNA Epigenetic Profiling of Monozygotic Twins[L1] Discordant for ACPA or ACPA-Positive Rheumatoid Arthritis Reveals Novel Associated Genes

David Gomez[1], Malin Almgren[2], Louise Sjoholm[2], Aase Haj Hensvold[3], Andrew Feinberg[4], L. Klareskog[5], Tomas Ekstrom[2,6] and **Anca I Catrina**[5], [1]Unit of Computational Medicine Karolinska Institutet Center for Molecular Medicine Karolinska University Hospital, stockholm, Sweden, [2]Laboratory for Medical Epigenetics, Dept. of Clinical Neuroscience, Karolinska Institutet, Karolinska Hospital, Stockholm, Sweden, [3]Rheumatology Unit, Department of Medicine, Solna, Karolinska Institute, Stockholm, Sweden, Stockholm, Sweden, [4]Department of Genetics, Johns Hopkins University School of Medicine, Baltimore, MD, [5]Rheumatology Unit, Department of Medicine, Karolinska Institutet, Stockholm, Sweden, [6]Departmen of Clinical Neuroscience, karolinska Institute, Stockholm, Sweden
First publication: September 29, 2015

SESSION INFORMATION
Session Date: Sunday, November 8, 2015
Session Title: Genetics, Genomics and Proteomics Poster I
Session Type: ACR Poster Session A
Session Time: 9:00AM-11:00AM

Background/Purpose:

Occurrence and progression of complex autoimmune diseases are orchestrated by interactions between genes and environment, in part mediated by epigenetic mechanisms. It is yet unclear how these interactions operate over time for different disease sub-phenotypes. We aimed to investigate how epigenetic modifications might contribute to different development phases of an autoimmune disease, using ACPA (antibodies to citrullinated protein antigens)-positive rheumatoid arthritis (RA) as a disease model and an epigenome-wide DNA methylation analysis of two sets of monozygotic (MZ) twins.

Methods:

Five healthy twin pairs discordant for presence of ACPA but not having RA and seven twin pairs discordant for ACPA-positive RA were included in this study. The selected twin pairs belong to a population based twin cohort (Twingene) which is part of the Swedish twin register ACPA status is defined by testing sera with CCP2 ELISA assay (Immunoscan CCPlus). None of the healthy twins have reported chronic rheumatic joint disease (rheumatoid arthritis) at time point of blood donation. During a median follow up of 3 years (IQR 2-4) they all continued to lack an RA diagnosis (or other rheumatic joint disease diagnosis e.g. polyarthritis) in the Swedish National Patient Register. The ACPA positive RA twins have also tested positive for ACPA while their co-twin have tested negative for ACPA. The RA twins reported RA at the time of blood donation and this was verified by review of the medical records. Co-twins of these ACPA positive RA twins did not report RA and this was again verified by linkage to the Swedish National Patient Register. Genome wide gene specific methylation was analysed by CHARM methodology.

Results:

CHARM analysis of the healthy twin pairs, discordant for ACPA, revealed 17 genome wide significant (family wise error rate (FWER) <0.2) differentially methylated gene regions (DMRs), after cell-type distribution correction. Profiling of the seven twin pairs discordant for ACPA-positive RA identified 36 significant DMRs (where one associated with an exosome component) after cell-type distribution correction. Interestingly, one ACPA-discordant associated DMR associated to a protocadherine (PCDH) gene showed a high probability to be also found in ACPA-positive RA. None of the identified DMRs were found in the proximity of previously known genetically associated genes, including MHC, suggesting a successful neutralization of genetic influence in our design with MZ twins.

Conclusion:

We describe here novel associations between DNA methylation and different phases of ACPA-positive RA, prompting further studies to address the potential pathogenic relevance of these epigenetic modifications for RA.

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Abstract Number: 111

The Mitochondrial DNA (mtDNA) Haplogroups Influence the Risk of Radiographic OA Progression. a Meta-Analysis

Angel Soto-Hermida[1], Ignacio Rego-Pérez[1], Juan Fernandez-Tajes[1], Mercedes Fernandez Moreno[1], Maria Eugenia Vazquez Mosquera[1], Estefanía Cortés-Pereira[1], Sara Relaño-Fernandez[1], Sonia Pertega[2], Natividad Oreiro[1], Carlos Fernandez-Lopez[1] and Francisco J. Blanco[1], [1]Servicio de Reumatología. Instituto de Investigación Biomédica de A Coruña (INIBIC). Complexo Hospitalario Universitario de A Coruña (CHUAC), Sergas. Universidade da Coruña (UDC), A Coruña, Spain, [2]Unidad de Epidemiología Clínica y Bioestadística. Instituto de Investigación Biomédica de A Coruña (INIBIC). Complexo Hospitalario Universitario de A Coruña (CHUAC), Sergas. Universidade da Coruña (UDC), A Coruña, Spain

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SESSION INFORMATION

Session Date: Sunday, November 8, 2015

Session Title: Genetics, Genomics and Proteomics Poster I

Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose:

In the last years the role played by the mtDNA haplogroups in the pathogenesis of OA attracted much attention. The aim of this study is to perform a meta-analysis to investigate the association between mtDNA haplogroups and the risk of radiographic OA progression

Methods:

For this work we collected previously published and personal data involving the study of the mtDNA haplogroups on the radiographic progression of OA in terms of KL grade. Meta-analysis was performed using R 2.15.0 software with the package *meta* added. Combined effect was estimated using a random-effects model using hazard ratios (HR) with 95% confidence interval (CI) as the outcome variable.

Results:

A total of 3 studies, involving 1603 OA patients (progressors and non-progressors) were involved. All the studies were based on the analysis of the mtDNA clusters TJ and the risk of radiographic progression. A significant association with a lower risk of radiographic OA progression was found for the mtDNA cluster TJ when compared with both HV (HR=1,3063; 95% CI=1,0673-1,5989; p-value=0.0096) and KU (HR=1,3359; 95% CI=1,065-1,6757; p-

value=0.00123) considering the three cohorts combined (Figures 1 and 2)

Conclusion:

The current meta-analysis suggest that the mtDNA cluster TJ correlates with a lower risk of radiographic OA progression in terms of KL grade. The assignment of the polymorphims characteristic of the mtDNA cluster TJ could be potential complementary genetic biomarkers to predict the risk of OA progression.

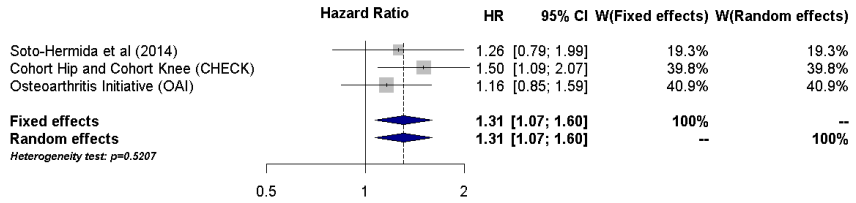

Figure 1. Forest plot showing the comparison between the mtDNA cluster HV and TJ on the risk of radiographic OA progression

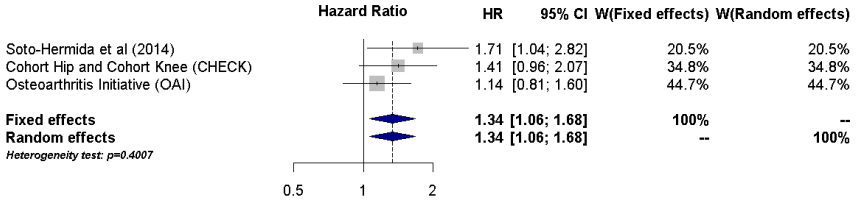

Figure 2. Forest plot showing the comparison between the mtDNA cluster KU and TJ on the risk of radiographic OA progression

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Disclosure: A. Soto-Hermida, None; **I. Rego-Pérez**, None; **J. Fernandez-Tajes**, None; **M. Fernandez Moreno**, None; **M. E. Vazquez Mosquera**, None; **E. Cortés-Pereira**, None; **S. Relaño-Fernandez**, None; **S. Pertega**, None; **N. Oreiro**, None; **C. Fernandez-Lopez**, None; **F. J. Blanco**, Pfizer, Bioiberica, and Gebro Pharma, 5.

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Abstract Number: 112

The Molecular Genetic Analysis of the Autoinflammatory Syndromes in Russian Patients with Manifestation of Systemic Juvenile Idiopathic Arthritis

Ekaterina Alexeeva[1], Alexander Baranov[2], Kirill Savostyanov[2], Alexander Pushkov[2], Tatyana Sleptsova[1], Tatyana Bzarova[1], Saniya Valieva[1], Rina Denisova[1], Kseniya Isayeva[1], Evgeniya Chistyakova[1] and Chomahidze Alexandra[1], [1]Rheumatology, Scientific Center of Children's Health, Moscow, Russia, [2]Scientific Center of Children's Health, Moscow, Russia

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SESSION INFORMATION

Session Date: Sunday, November 8, 2015
Session Title: Genetics, Genomics and Proteomics Poster I
Session Type: ACR Poster Session A
Session Time: 9:00AM-11:00AM

Background/Purpose:

Group of monogenic autoinflammatory syndromes is characterized by recurrent episodes of fever and inflammation.

Methods:

The study included 90 pts (37 boys, 63 girls) at the age from 1 to 17 y. (8.2 (4.7; 11.5) followed with a diagnosis of systemic JIA. The median age of disease onset was 3.0 (1.5; 5.1) y., disease duration – 4.4 (1.0; 7.6)y.

The commonest features were fever (100%), arthritis or arthragia (100%), rash (96%), hepato- and splenomegaly (96%), lymphadenopathy (94%), headache (62%), abdominal pain (58%), eye manifestations (21%). The patients were selected according to the clinical manifestations, with subsequent obligatory genetic counseling in the Department of Rheumatology of the Scientific Center for Children's Health. Pts' DNA was sequenced in all coding exons and intronic flanks of the TNFRSF1A and NLRP3 genes whose mutations cause autoinflammatory syndromes, TRAPS and CAPS, respectively.

Results:

In 13/90 (14.4%) pts genetic autoinflammatory syndrome was established. In 10/13 pts, we found mutations in TNFRSF1A: in 8/10 pts - the most frequent mutations *c.362G>A (p.R92Q)* located in exon 4 and associated with the mild progression of TRAPS. One TRAPS pt. had a frameshift mutation *c.792delT* (*p.Lys265Serfs*87*) in exon 9 of *TNFRSF1A* gene. Another pt. revealed a *TNFRSF1A* mutation known *c.374G>A* (C96Y).

The median age of disease onset was 5.1 years. A family history was present in 3 patients: 2 girls with R92Q variant and 1 – with C96Y mutation. 3 pts with symptomes of CAPS identified mutations in *NLRP3* gene. None of the mutations were previously described in the databases for mutations. One pt. with a clinical picture of the CINCA, had a mutation *c.796C>T* (*p.Leu266Phe*) in exon 04 of NLRP3 gene. 2 other pts had mutations *c.2861C>T* and *c.2173C>A*, respectively. Pts with *c.2173C>A* mutation has CINCA/NOMID phenotype and dramatic effect of canacinumab. In 7 (7.5%) pts we identified NLRP3 gene polymorphism *c.2113C>A,* associated with elevated levels of IL1.

Conclusion:

Our results suggests for a relatively frequent incidence of CAPS and TRAPS in Russian systemic JIA patients. The number of genetically confirmed patients with periodic fever syndromes in Russia is very low. In order to identify more patients in the future, it is important to organize educational programs for increasing the knowledge on these diseases, to establish a network for genetic testing of periodic fever syndromes and to carry out differential diagnoses.

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View Abstract and Citation Information Online - http://acrabstracts.org/abstract/the-molecular-genetic-analysis-of-the-autoinflammatory-syndromes-in-russian-patients-with-manifestation-of-systemic-juvenile-idiopathic-arthritis

Abstract Number: 113

Longitudinal, Incremental Direct Medical Costs of Giant Cell Arteritis for the First Five Years Following Diagnosis: A General Population-Based Cohort Study

Natalie McCormick[1], Carlo Marra[2] and J Antonio Avina-Zubieta[3], [1]Pharmaceutical Sciences, University of British Columbia, Vancouver, BC, Canada, [2]Pharm Sciences, Univ of British Columbia, Vancouver, BC, Canada, [3]Arthritis Research Canada / University of British Columbia, Vancouver, BC, Canada

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SESSION INFORMATION

Session Date: Sunday, November 8, 2015

Session Title: Health Services Research Poster I: Diagnosis, Management and Treatment Strategies

Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose:

Giant cell arteritis (GCA) is the most common form of adult vasculitis, but estimates of the healthcare costs of GCA are extremely scarce. We determined the incremental (extra) direct medical costs of a general population-based cohort of incident GCA for the first five years after diagnosis. We also assessed the changes in costs over calendar time (1996-2010).

Methods:

Data Source: Our administrative data captured all provincially-funded outpatient encounters and hospitalizations (1990-2010), and all dispensed medications (1995-2010), for ALL residents of the province of British Columbia, Canada.

Sample:We assembled a population-based cohort of all incident cases of GCA who satisfied the following criteria: a) ≥ 40 years of age; b) new diagnosis of GCA on at least one hospitalization or rheumatologist visit, or two non-rheumatologist visits, between January 1996 and December 2010; and c) use of oral glucocorticoids between 1 month before and 6 months after the second GCA visit (or first if from hospital or rheumatologist). Ten controls matched by age at diagnosis (±2 years), sex, and calendar year of diagnosis were selected for each case from the general population.

Cost Calculation: Costs for outpatient services and prescriptions were summed directly from billing data. Case-mix methodology was used for hospitalizations.

Statistical Analysis: We estimated the unadjusted incremental costs of GCA (difference in per-patient-year (PY) costs between cases and controls), then used generalized linear models to further adjust for socioeconomic status, urban/rural residence, and Charlson-Romano comorbidity index.

Results: We matched 797 incident GCA cases to 7,970 controls (72% female, mean age 76 ±9.2 years, median Charlson-Romano comorbidity index of 0). Unadjusted incremental costs of GCA for the first five years after diagnosis averaged $26,348 per-PY (2010 Canadian), with 78% from hospitalizations, 15% from outpatient, and 6% from medications. 59% of cases (vs. 26% of controls) were hospitalized during the first year after diagnosis, with GCA cases averaging 0.46 more admissions than controls (even after the index admission was excluded).

Following adjustment, 5-year costs for GCA cases were 1.9-times higher than matched controls (95% CI: 1.7-2.0, see **Table**). These incremental costs decreased over calendar time, even after inflation adjustment, averaging $41,113 per-PY for cases diagnosed over 1996-2002 (early period), and $19,033 per-PY for cases diagnosed over 2003-2010 (later period). Incremental hospitalization costs had the biggest change, decreasing by 61%, from $34,732/PY in the earlier period to $13,531/PY in the later

Conclusion:

The absolute costs of GCA have recently decreased, by 54%. Still, even after adjusting for pre-existing comorbidities, patients with newly-diagnosed GCA incur two-times more medical costs than age-matched individuals without GCA from the general population.

	Adjusted Cost Ratios between GCA Cases and Matched Controls (95% CI)					
	Year After GCA Diagnosis					**Total Over First Five Years**
	1	**2**	**3**	**4**	**5**	
N Cases Followed	797	553	422	305	199	
Mean Per-Patient-Year Outpatient Costs	2.3 (2.1-2.4)	1.8 (1.6-1.9)	1.7 (1.6-1.9)	1.6 (1.4-1.7)	1.5 (1.3-1.7)	1.7 (1.6-1.8)
Mean Per-Patient-Year Inpatient Hospitalization Costs (amongst hospitalized individuals)	1.1 (0.9-1.2)	1.2 (1.0-1.5)	1.3 (1.0-1.5)	1.3 (1.0-1.6)	1.4 (1.0-1.9)	1.3 (1.2-1.4)
Mean Per-Patient-Year Medication Costs	1.4 (1.3-1.5)	1.4 (1.3-1.5)	1.5 (1.3-1.6)	1.5 (1.3-1.7)	1.4 (1.2-1.6)	1.2 (1.1-1.4)
Mean Per-Patient-Year Overall Costs	2.4 (2.2-2.7)	2.0 (1.8-2.2)	2.0 (1.7-2.2)	1.9 (1.6-2.2)	1.9 (1.6-2.3)	1.9 (1.7-2.0)
	Adjusted Mean Per-Patient-Year Incremental Utilization (95% CI) of GCA Cases					
Mean Per-Patient-Year Outpatient Encounters	33.6 (31.5-35.8)	18.8 (16.7-20.9)	14.7 (12.2-17.2)	13.5 (10.6-16.4)	15.4 (11.7-19.1)	55.9 (50.3-61.6)
Mean Per-Patient-Year Inpatient Admissions (amongst hospitalized individuals)	0.72 (0.39-1.06)	0.46 (0.06-0.87)	0.59 (0.16-1.03)	0.77 (0.23-1.31)	0.40 (-0.22-1.03)	1.40 (1.05-1.76)
Mean Per-Patient-Year Dispensed Prescriptions	22.3 (17.0-28.3)	27.9 (19.8-36.0)	36.9 (27.3-46.5)	35.6 (23.0-48.2)	36.0 (18.6-53.4)	65.5 (42.9-88.2)

Disclosure: N. McCormick, None; **C. Marra**, None; **J. A. Avina-Zubieta**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/longitudinal-incremental-direct-medical-costs-of-giant-cell-arteritis-for-the-first-five-years-following-diagnosis-a-general-population-based-cohort-study

Abstract Number: 114

Surfing the Net: Patient Empowerment or Patient Deceit? Fifteen-Year Trends on the World Wide Web Information for Patients with Rheumatoid Arthritis

Jose de Jesus Valdivia-Nuno[1], Victor Brambila-Barba[1], Luis Hernandez-Sanchez[1], Jose Juan Castaneda-Sanchez[1], Carlos Gallegos-Rios[1], Gabriel Flores-Hernandez[1], Angel Suarez-Rico[1], Zalathiel Barajas-Ochoa[1], Heber Garagarza-Mariscal[1], Andrea Ramirez-Gomez[2], Jose Dionisio Castillo-Ortiz[2] and Cesar Ramos-Remus[2], [1]Servicio Social, Universidad de Guadalajara, Guadalajara, Mexico, [2]Unidad de Investigacion en Enfermedades Cronico-Degenerativas, Guadalajara, Mexico
First publication: September 29, 2015

SESSION INFORMATION

Session Date: Sunday, November 8, 2015
Session Title: Health Services Research Poster I: Diagnosis, Management and Treatment Strategies
Session Type: ACR Poster Session A
Session Time: 9:00AM-11:00AM

Background/Purpose: Considering rheumatoid arthritis (RA) is a chronic disease that lasts for decades, patient education is of upmost importance. RA patients seeking information on the web has been exponential during the last 15 years. The aim of this study was to assess the content, authorship, and scope of the information currently available on the internet in relation to this topic and compare it with a report published in 2001*.

Methods: Two internet search engines were used to perform the task: WebCrawler, to replicate the referent study published in 2001*, and Google, since it is now the most widely used search engine. We conducted the search using the phrase "rheumatoid arthritis" as an average patient would do. Information was evaluated from the first 30 pages of each search carried out. All the websites that were used to collect data from were critically assessed afterwards in relation to relevance, scope, authorship, type of publication, and financial objectives. Significant differences were assumed if 95% confidence intervals did not overlap between referent and current studies.

Results: The search returned 316 hits using WebCrawler (85% considered relevant). We found significant differences between the referent study* and ours. There was a decrease in; advertisements (48% vs. 2%), hits posted by profit industries (51% vs. 18%), financial interest regarding "primary sold products" (42% vs. 9%), and promoting alternative therapies (45% vs. 27%). While an increase was noted in; "mainly RA information" (8% vs. 58%), support groups (<1% vs. 6%) and discussing "conventional treatment" (8% vs. 49%). University and/or hospital owned Web pages remained unchanged (5% vs. 8%).

Regarding Google, the search returned 326 hits, and when compared with our WebCrawler search we found significant differences: lower relevance (58% vs. 85%), more news articles (17% vs 7%), more "only RA discussed" (73% vs. 58%), and less "alternative therapy" (18% vs. 27%). Concerning Universities and hospitals providing information for patients, the proportion is almost the same (7% vs. 8%). Yet Mayo Clinic appeared in the 1st position, Arthritis Foundation in the 3rd position, the American College of Rheumatology in the 8th position, Johns Hopkins in the 21st position, UCSF in the 77th position, and Washington University in the 197thposition.

Conclusion: It seems that surfing the net is in some ways more reliable and trustworthy now, for RA patients, than it was 15 years ago, with significantly less advertisements and less focus on only alternative therapies. Yet there is a window of opportunity for rheumatology centers and universities to have a more prominent social involvement in patient education for rheumatic diseases.

*Suarez-Almazor et al. Surfing the Net--information on the World Wide Web for persons with arthritis: patient empowerment or patient deceit? J Rheumatol 2001;28:185-91

Abstract Number: 115

Validation of a Large Rheumatoid Arthritis Cohort and Preventive Health Screening

Michael Grasso[1], **Dana Direnzo**[2], Yelena Yesha[3], Naphtali Rishe[4] and Amanda Niskar[5], [1]Emergency Medicine, University of Maryland School of Medicine, Baltimore, MD, [2]Internal Medicine, University of Maryland Medical Center, Baltimore, MD, [3]Computer Science and Electrical Engineering, Professor, Baltimore, MD, [4]Computer Science, Florida International University, Miami, FL, [5]1330 West Peachtree Street NW, Arthritis Foundation, Atlanta, GA
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Session Time: 9:00AM-11:00AM

Background/Purpose:

We extracted a large cohort of rheumatoid arthritis (RA) patients, on which we plan to apply big data analytics for earlier diagnosis of RA. To help validate this cohort, we performed an initial study to answer a health services question regarding lipid surveillance and cardiovascular risk reduction in the RA community. Cardiovascular disease is the leading cause of death among people with RA. This disease risk is double to that of the general population. Our research was supported with resources from the Department of Veterans Affairs (VA).

Methods:

We worked with clinical data from the VA. This dataset is one of the largest clinical repositories available, and provides detailed patient information for approximately 35 million patients who have received care at more than 150 medical centers over the past 15 years. Using the VA repository of 35 million patients, we identified a cohort of roughly 155,000 patients with any RA ICD code (714.x). We used a previously published algorithm by JA Sing to define a RA cohort, by selecting patients with an ICD code 714.x and either a positive rheumatoid factor or a positive anti-CCP. This resulted in a cohort of 29,713 rheumatoid arthritis patients with an estimated specificity and positive predictive value of about 90%. The RA cohort contained 3,978 women (13%) and 19,826 Caucasians (67%), with an average age of 66, and with 19,761 (67%) on a disease-modifying antirheumatic drug.

Results:

A total of 6,632 patients (22%) had their LDL cholesterol checked at least once while receiving care within the VA system. In addition, 421 (90%) of patients whose LDL was at least 190, 1,331 (85%) of patients whose LDL was at least 160, and 3,555 (72%) of patients whose LDL was at least 130 were placed on statin therapy.

Conclusion:

In this RA cohort, 22% had their LDL checked at least once during their follow-up in the VA. This suggests the need for improvements in lipid screening among rheumatoid arthritis patients in this population. However, this value is likely an underestimate, since it does not include patients who had their LDL checked outside the VA system. In addition, 78% of all people with RA and an LDL at least 130 were on statin therapy. We did not consider cardiovascular risk factors to

determine the appropriate pharmaceutical management strategy. In addition, we did not consider reasons why patients may not have been on a statin.

Our research incorporated a large and comprehensive data set, whose size and attributes create analytic and data mining issues that are beyond the capabilities of traditional software tools. We are currently working on machine learning tools for big data analytics, which we hope to use for early disease prediction of RA.

Disclosure: M. Grasso, None; **D. Direnzo**, None; **Y. Yesha**, None; **N. Rishe**, None; **A. Niskar**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/validation-of-a-large-rheumatoid-arthritis-cohort-and-preventive-health-screening

Abstract Number: 116

The Effect of the Formal Approval of Colchicine on Utilization of Emergency Department and Rheumatology Outpatient Services By Patients with Gout

Leah Krull[1,2], Erin Patton[3,4] and Harry D. Fischer[5,6], [1]Internal Medicine, Mount Sinai Beth Israel, New York, NY, [2]Medicine, Mount Sinai Icahn School of Medicine, New York, NY, [3]Rheumatology, Mount Sinai Icahn School of Medicine, New York, NY, [4]Medicine/Rheumatology, Mount Sinai Beth Israel, New York, NY, [5]Division of Rheumatology, Mount Sinai Beth Israel, New York, NY, [6]Medicine/Rheumatology, Mount Sinai Icahn School of Medicine, New York, NY

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Background/Purpose:

Although colchicine has been used in the management of gout for decades, it had never undergone the formal approval process by the Food and Drug Administration (FDA). In 2006 the FDA announced its Unapproved Drugs Initiative. This initiative encouraged manufacturers of colchicine to study the safety and efficacy of their product, and to formally apply for FDA approval. In 2009 one brand name colchicine became the sole FDA approved colchicine product in the United States. In 2010 all unapproved colchicine products were removed from the market. With the availability of only one colchicine product, the cost increased significantly. Each pill was estimated to be 50 times more expensive. Concerns were raised that this price increase would result in decreased access for patients with gout who need colchicine. The inability to afford, and therefore utilize colchicine, could result in more frequent and prolonged flares of gout. Patients with acute gout often present to an emergency department (ED) or rheumatology office for treatment. The number of visits to the ED and rheumatology outpatient office by gout patients may correlate with gout flares.

Methods:

A retrospective cohort study comparing the number of patients presenting to the ED and outpatient rheumatology practice at our institution was compared during two distinct time periods: January 1, 2008 to December 31, 2008 when unapproved inexpensive colchicine was still available, and January 1, 2012 to December 31, 2012 when only one approved more expensive colchicine was available. A diagnostic code search was performed for ICD-9 codes 274.0,

274.01, and 274.9 as the primary diagnosis. The total number of visits for both gout and non-gout diagnoses in each time period and setting were calculated for comparison.

Results:

The number of visits to the ED for gout was 73 out of 85,500 total ED visits in 2008. This increased to 91 out of 122,200 total ED visits in 2012. This was not found to be statistically significant. In the rheumatology outpatient setting there were 225 gout visits out of a total of 7,827 total office visits in 2008. This decreased to 112 out of 10,377 total office visits in 2012. In this patient population there was a statistically significant lower incidence of gout in 2012 compared to 2008 with a risk ratio of 2.66 (95% CI 2.13-3.33, p-value <0.0001). Combining ED visits and outpatient rheumatology there was again a statistically lower incidence of gout presentations in 2012 compared to 2008 with a risk ratio of 2.08 (95% CI 1.74-2.49, p-value <0.0001). These findings suggest it was about twice as likely to present with gout in 2008 compared to 2012.

Conclusion:

There have been concerns that a significant increase in cost would reduce access to colchicine for patients with gout resulting in possibly more frequent and prolonged flares of gout. Our study did not show an increase in ED utilization by patients with gout during the period of increased cost, and outpatient rheumatology visits actually decreased. This may in fact be partially due to the availability of newer medications for the long-term management of gout.

Disclosure: L. Krull, None; **E. Patton**, None; **H. D. Fischer**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/the-effect-of-the-formal-approval-of-colchicine-on-utilization-of-emergency-department-and-rheumatology-outpatient-services-by-patients-with-gout

Abstract Number: 117

Same Day Rheumatology Access Clinic in an Academic Health Care Center

Muhammad Ijaz[1,2], Alireza Meysami[1], Amita Bishnoi[1] and Bernard Rubin[3], [1]Rheumatology, Henry Ford Hospital, Detroit, MI, [2]Rheumatology, Wayne State University/Detroit Medical Center, Detroit, MI, [3]Rheumatology, Henry Ford Health System, Detroit, MI

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Session Time: 9:00AM-11:00AM

Background/Purpose:

Open access clinics have been studied extensively in the primary care setting [1], but there is limited data regarding rheumatology open access clinics. To improve rheumatology clinic access for patients, we created a same day clinic. We anticipated an improvement in access, no show rates, and a unique learning opportunity for fellows to see more acute rheumatologic conditions than in conventional academic clinic practice.

Methods:

A rheumatology fellow-based same day clinic (SDC) was created at a tertiary care academic health center. Clinic appointments were made available forty-eight hours before the appointment using an electronic scheduling system, or through a call center. Patients could also contact their PCP to refer them electronically. Same day appointments are available five days a week at one of four clinics staffed by the division of rheumatology at Henry Ford Hospital. Second year fellows were assigned to SDC, supervised by a senior staff attending, who were on call and exempted from routine clinics. To gauge improvement in access, we compared the time to third next available appointment for both follow up and new patients, before and after SDC implementation. Press-Ganey patient satisfaction surveys were used to evaluate patient satisfaction. We also compared the no-show rates in clinic before and after SDC implementation. Educational value for the fellows was assessed by a focused questionnaire.

Results:

Implementation of same day clinics improved access with a decreased time to third next available appointment from 30.9 days in June, 2014, to 20.8 days in March, 2015. Although the overall patient satisfaction score did not change; measures including the access score and the ability to get the desired appointment improved from 81.9 to 87.5, and 78.8 to 90 respectively from July, 2014, to February, 2015. The no show rate remained unchanged, and it was specifically high in February, 2015, due to brutal winter weather in Michigan, and implementation of new insurance market exchanges. The fellows reported enhanced educational value from exposure to patients with acute, non-emergent complaints. Many new consults seen by the fellows in SDC were followed in their respective continuity clinics, although many patients did not require a second visit.

Conclusion:

Implementation of a same day clinic (SDC) in an academic rheumatology practice improved access, access score, and the ability to get a desired appointment. We did not see improvement in overall patient satisfaction scores or no show rates. Further improvement and refinement is anticipated as we expand this SDC model to our other rheumatology clinic sites across several counties. A preliminary survey of the current fellows showed positive educational benefits, and as the model expands to more clinic locations in the future, we anticipate statistical improvement that can be measurable and actionable. In addition, SDC could provide some financial benefit for health care system by minimizing the number of unnecessary ER visits and hospital admissions.

1. Katherine D. Rose, MD; Joseph S. Ross, MD, MHS; Leora I. Horwitz, MD, MHS. Advanced Access Scheduling Outcomes. A Systematic Review. Arch Intern Med. 2011;171(13):1150-1159.

Disclosure: M. Ijaz, None; **A. Meysami**, None; **A. Bishnoi**, None; **B. Rubin**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/same-day-rheumatology-access-clinic-in-an-academic-health-care-center

Abstract Number: 118

Identifying the Investment Needed to Generate a Durable Prednisone Dose Decrement

Martha Delgado[1], Lorena Wilson[2], James D. Katz[3] and Ann Biehl[4], [1]the National Institute of Arthritis Musculoskeletal and Skin Diseases, the National Institutes of Health, Bethesda, MD, [2]National Institute of Arthritis and Musculoskeletal and Skin Diseases, The National Institutes of Health, Bethesda, MD, [3]Department of Medicine, Division of Rheumatology, The George Washington University, Washington, DC, [4]Department of Pharmacy, National Institutes of Health Clinical Center, Bethesda, MD

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Background/Purpose:

Assessment of the total cost of care requires clinical, epidemiological, patient-centered, and economic data. However, barriers to a value-driven outcome assessment include the resource-intensive nature of activity-based costing. One aspect of the total cost of care is direct costs. Government-based outpatient care enables an analysis that controls for all direct costs apart from medication costs. The aim of our study is to understand one aspect of the direct cost of care upon a given steroid decrement.

Methods:

We reversed the Branching Decision Tree for identification of expenses attributable to clinical care by restricting our assessment to a given steroid taper. Our analysis identifies drug costs over the preceding 10 weeks as the basis for allocating direct care costs to specific encounters. This timeframe is chosen because it is the average interval between outpatient appointments. We identified patients for analysis at the time that they were instructed by the rheumatologist to reduce prednisone dosage. Patients were enrolled over a 6-month period at a community outpatient clinic. Captured data included diagnosis, current and new prednisone dose, and other rheumatology medications. We extended our analysis to a 10-week prospective durability ascertainment of the success of the intervention. We stratified the analysis based upon a diagnosis of Rheumatoid Arthritis (RA) or Other Autoimmune diseases (OTHER).

Results:

Direct costs invested over a ten-week period for all patients tapering prednisone were $1659.30 (Table 1), which normalizes to $434.37/mg decrement (Table 1). A greater normalized cost was invested per patient for RA as compared to OTHER. There was a 97% completion rate for data collection in the prospective arm of the study. We observe a 76% durability response towards maintaining the recommended reduced steroid dose 10 weeks after the incident date in RA patients as compared to 85% for OTHER patients (Table 1). In general, a two or three-fold greater direct investment antecedent to steroid decrement was associated with a durable response over the ensuing ten weeks for either disease category.

Conclusion:

Our analysis demonstrates that outpatient drug costs for RA are most fruitful to target when looking to contain direct health care costs. On the other hand, the prospective arm of the study suggests that higher direct costs are associated with durable steroid decrement outcomes regardless of inflammatory disease classification. The advantage of this study is that reimbursement, coverage levels, and access to care are all controlled for because our protocol-based health care delivery model renders this a unique opportunity to assess relatively pure direct costs. A disadvantage of this study is that indirect costs are not analyzed. Future research is needed to ascertain whether the higher invested direct costs are offset by the drop in future indirect costs consequent to a durable steroid-sparing benefit.

Table 1. AVERAGE DRUG COST AND NORMALIZED DRUG COST INVESTED IN THE PRECEDING 10 WEEKS PER MG PREDNISONE DECREMENT AND TEN-WEEK OUTCOME OF PREDNISONE TAPER				
Category	Number of Patients	Per Patient Avg. Drug Cost	Avg. Decrement (mg)	Average Cost/mg decrement
All patients	38	$1659.30	3.82	$434.37
All RA patients	25	$2195.57	2.65	$828.52
RA patients with Durable response	19	$2543.14	2.67	$952.49
RA patients with lack of Durable response	6	$1094.93	2.58	$424.39
All Other autoimmune patients	13	$627.98	5.88	$106.80
Other autoimmune patients with Durable Response	11	$678.40	5.36	$126.57
Other autoimmune patients with lack of Durable Response	2	$350.65	8.75	$40.07

Disclosure: M. Delgado, None; **L. Wilson**, None; **J. D. Katz**, None; **A. Biehl**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/identifying-the-investment-needed-to-generate-a-durable-prednisone-dose-decrement

Abstract Number: 119

Triage in Chronic Rheumatic Diseases: Quantitative Physician Estimates for Inflammation (Reversible), Damage (Irreversible), and Distress in Patients with Rheumatoid Arthritis, Osteoarthritis, and Fibromyalgia Seen in Usual Care

Isabel Castrejón[1], Kathryn A. Gibson[2], Ruchi Jain[1], Annie Huang[1], Joel A. Block[3] and Theodore Pincus[1], [1]Rheumatology, Rush University Medical Center, Chicago, IL, [2]Liverpool Hospital, Liverpool, Australia, [3]Rush University Medical Center, Chicago, IL

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Background/Purpose: A physician estimate of a patient's global status (DOCGL) often is most often the most efficient of all 7 rheumatoid arthritis (RA) core data set measures to distinguish active from control treatments in clinical trials(1). DOCGL is designated to assess inflammatory activity. However, DOCGL may be influenced by damage, as seen in comorbid osteoarthritis (OA), and distress, as seen in fibromyalgia and chronic pain syndromes. Indeed, it may be suggested that the expertise of a rheumatologist is directed to a form of "triage" in chronic diseases, to recognize the extent to which a patient's signs and symptoms may be explained by inflammation, damage, and/or distress. Therefore,

3 new physician 0-10 visual analog scales (VAS) developed to estimate subsets of DOCGL. We analyzed physician scales for overall global status, inflammation, damage and distress in patients with RA, osteoarthritis (OA), and fibromyalgia (FM).

Methods: Patients seen in routine care at one academic clinical setting are assigned 4 0-10 VAS estimates for overall DOCGL, inflammation or reversible problems, damage (to any organ) or irreversible problems, and/or distress, as seen in fibromyalgia, depression, chronic pain syndrome, etc. A cross-sectional analysis was performed of a random visit between September and December 2014 of consecutive patients with 3 primary diagnoses: RA (n=108), OA (n=131), and FM (n=51). The medians and interquartile ranges (IQR) of non-normally distributed data and Spearman correlations were computed to estimate associations of the overall DOCGL with subscales and PATGL in the 3 diagnosis groups.

Results: Median DOCGL ranged from 3 to 5, highest for patients with FM (5.0), followed by OA (4), and RA (3.5). The highest median score for inflammation was for patients with RA (1.5), for damage in patients with OA (4.2) and for distress in patients with FM (5.2) (Table). The highest correlation with DOCGL was seen for the inflammation scale in RA, damage in OA, and distress in FM. DOCGL was correlated significantly with PATGL in RA and OA, but not in FM.

Conclusion: Physician estimates for inflammation, damage, and distress differ according to different rheumatic diagnoses. These 3 subscales supplement the overall physician global estimate as a quantitative summary of the history and physical examination, to estimate levels of inflammation, damage, and distress in an individual patient, analogous to triage function in acute injury, to support clinical decisions in patients with chronic rheumatic diseases in usual care.

Reference: **1)**Pincus T, et al. Clin Exp Rheumatol. 2014;32 Suppl 85(5):47-54.

Table: Median (IQR) for the four physician estimates and Spearman correlations between DOCGL and the three physician subscales in addition to PATGL in the three diagnostic categories

	RA N=108	**OA N=131**	**FM N=51**
Median (IQR) for four physician global estimates			
Overall DOCGL (0-10 scale)	3.5 (2-5)	4 (3.5-5)	5 (4-6)
Inflammation (0-10)	1.5 (0.5-3)	0 (0-1)	0 (0-1)
Damage (0-10)	3 (1-4)	4.2 (3-5)	1 (0-4)
Distress (0-10)	0 (0-0.7)	0 (0-3)	5.2 (4.5-7)
Spearman correlations with overall physician global estimate			
Inflammation	0.72**	0.02	-0.08
Damage	0.51**	0.64**	0.13
Distress	0.31*	0.38**	0.70**
PATGL (0-10 scale)	0.61**	0.60**	0.28*
**p<0.01; **p<0.001*			

Disclosure: I. Castrejón, None; **K. A. Gibson**, None; **R. Jain**, None; **A. Huang**, None; **J. A. Block**, None; **T. Pincus**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/triage-in-chronic-rheumatic-diseases-quantitative-physician-estimates-for-inflammation-reversible-damage-irreversible-and-distress-in-patients-with-rheumatoid-arthritis-osteoarthritis-and-fib

Abstract Number: 120

Validity of the Inpatient Diagnosis of Systemic Lupus Erythematosus: Clarifying Hospital Readmission Rates

Sadiq Ali[1], Stephen Mullis[2], Amer Al-Khoudari[1] and Dennis Ang[1], [1]Section on Rheumatology and Immunology, Wake Forest University, Winston Salem, NC, [2]Department of Internal Medicine, Wake Forest University, Winston Salem, NC
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Background/Purpose: Systemic lupus erythematosus (SLE) is assumed to be associated with one of the highest hospital readmission rates among chronic illnesses. Based on a recently published (Arth Rheumatol (2014) 66:2828) electronic database analysis of Medicare/Medicaid hospital discharges, 16.5% of patients with the ICD-9-CM code 710.0 for SLE were readmitted to any hospital within 30 days. Our long-term research goals are to determine the 30-day all-cause readmission rate for adults with SLE in our tertiary care hospital, and to identify the risk factors for readmission. The aim of the current report was to determine the validity of SLE diagnosis among our hospitalized patients with an ICD-9-CM code of 710.0.

Methods: Potential admissions were identified through the electronic medical record system (EMR). From October 1, 2012 to December 30, 2014, index admissions were defined as hospital admissions from adult patients (≥ 18 years of age) who had a primary or secondary ICD-9-CM diagnosis of 710.0. Individual charts were then manually reviewed by a single rheumatology fellow to determine if the patient fulfilled the 1997 ACR revised criteria for SLE. Chart review included analysis of all documents dated as far back as the implementation of the EMR in 1997, including clinical visits, imaging studies and laboratory results.

Results: 1003 index admissions met our inclusion criteria, obtained from 433 unique patients. Only 196 (45%) of 433 patients fulfilled criteria for SLE. 237 (55%) patients did not meet criteria: 185 (43%) patients had an inappropriate diagnosis of SLE (i.e., chart review contained sufficient data to support an alternate diagnosis), 34 (8%) patients had limited cutaneous lupus, and 18 (4%) patients had insufficient data to either confirm or refute a diagnosis of SLE.

Conclusion: Our initial result demonstrates a 55% rate of miscoding of hospital records for adult patients with a primary or secondary diagnosis of SLE designated by the ICD-9-CM code 710.0. Our result brings into question the use of ICD-9-CM coding to evaluate readmission data in SLE.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/validity-of-the-inpatient-diagnosis-of-systemic-lupus-erythematosus-clarifying-hospital-readmission-rates

Abstract Number: 121

Serum Uric Acid Levels and Gout Flares in a US Managed Care Setting

Aki Shiozawa[1], Erin Buysman[2], Stephanie Korrer[2] and Hyon Choi[3], [1]Global Outcomes and Epidemiology Research, Takeda Pharmaceuticals International, Inc, Deerfield, IL, [2]Health Economics and Outcomes Research, Optum, Eden Prairie, MN, [3]Massachussetts General Hospital/Harvard Medical School, Boston, MA
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Background/Purpose:

Gout is a common chronic inflammatory condition due to hyperuricemia. Gout patients typically have the clinical manifestation of acute painful flare attacks. While the role of lowering serum uric acid (sUA) levels in the prevention of flares is clearly recognized in recent gout care guidelines, only a limited number of published studies exist about the association. To provide further evidence on the topic, we sought to assess the risk of flares in patients with gout according to detailed categories of sUA levels in a US managed care population.

Methods:

We conducted a retrospective cohort study using administrative claims data from a large US health plan of commercially insured and Medicare Advantage enrollees. Patients were required to have evidence of gout (ICD-9-CM code 274.xx) based on medical and pharmacy claims between January 2009 and April 2012. The 12 months prior to the index gout claim were used to assess baseline sUA levels and patient characteristics. Gout flares were assessed during a variable observation period which lasted up to 2 years following the index gout claim; patients who initiated urate-lowering therapy (ULT) in the follow-up period were censored after the first claim for ULT. Flares were identified based on diagnoses for gout or joint pain followed within 7 days by claims for NSAIDs, colchicine, corticosteroids, or joint aspiration/drainage. Patients were assigned to cohorts determined by baseline sUA level. Incidence rate ratios were calculated for occurrence of first gout flare (using a sUA < 5.0 mg/dL reference cohort as denominator). A Kaplan-Meier analysis and a Cox proportional hazards model were used to assess the relationship between baseline sUA levels and risk of flares.

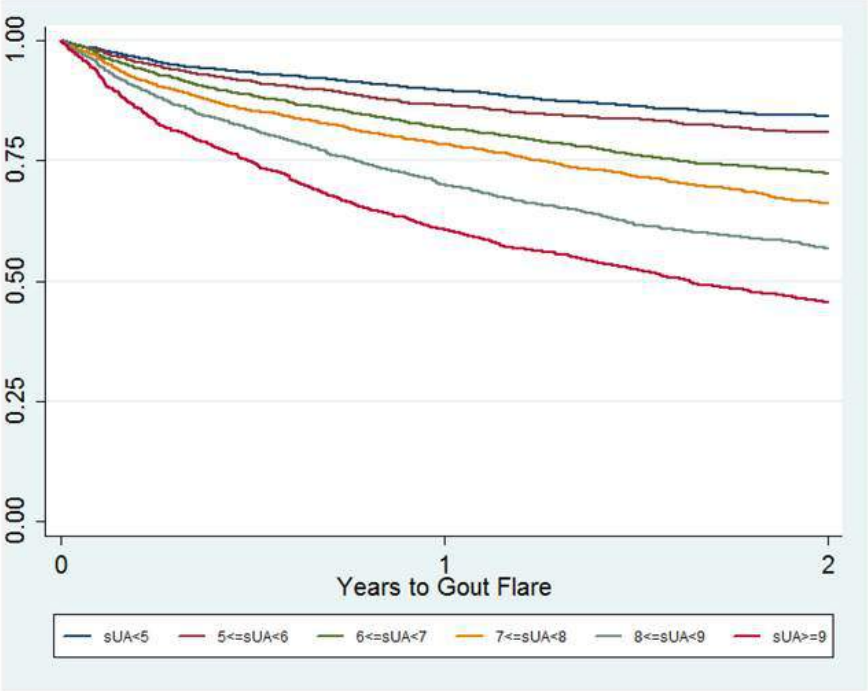
Results:

This study included 18,008 patients (mean age = 55 years; 78 % male) with gout. Patients were assigned to cohorts as follows: sUA < 5.0 mg/dL (N=1,953, reference); sUA 5.0 to 5.9 mg/dL (N=2,046); sUA 6.0 to 6.9 mg/dL (N=2,739); sUA 7.0 to 7.9 mg/dL (N=3,487); sUA 8.0 to 8.9 mg/dL (N=3,677); and sUA ≥ 9.0 mg/dL (N=4,106). The incidence rate ratios for gout flares during the observation period were 1.0 (reference), 1.3, 1.9, 2.4, 3.4, and 5.0, respectively (all $p < 0.01$ in comparison to the reference cohort). In a Cox proportional hazards model that adjusted for baseline characteristics, cohorts with baseline sUA ≥ 6.0 mg/dL had a significantly higher risk of flares (HRs ranged from 1.7 to 3.9, all $p<0.001$ in comparison to reference cohort). The time to first flare in a Kaplan-Meier analysis was shorter for cohorts with higher baseline sUA levels (Figure 1).

Conclusion:

This large contemporary study of gout patients in a managed care setting confirms that patients with sUA levels ≥ 5.0 mg/dL (unadjusted analysis) or ≥ 6.0 mg/dL (multivariate analysis) are at an increased risk of experiencing a gout flare with rising sUA levels. These findings underscore the need to treat to target as recommended by recent gout care guidelines.

Figure 1: Kaplan-Meier Curve of Time to First Gout Flare



Disclosure: A. Shiozawa, Takeda Pharmaceuticals International, Inc., 3; **E. Buysman**, Optum, 3; **S. Korrer**, Optum, 3; **H. Choi**, Takeda Pharmaceuticals International, Inc., 5,Astra-Zeneca Pharmaceuticals, 5,Astra-Zeneca Pharmaceuticals, 9.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/serum-uric-acid-levels-and-gout-flares-in-a-us-managed-care-setting

Abstract Number: 122

General Practitioners' Perceptions of Methotrexate and Anti-TNF Therapies: A Qualitative Study

Martin Soubrier[1], Sylvain Mathieu[2] and Elise Berthet[3], [1]Rheumatology department CHU Clermont-Ferrand, Clermont-Ferrand, France, [2]Rheumatology Department, CHU clermont-Ferrand, Clermont-Ferrand, France, [3]Rheumatology, CHU Gabriel Montpied, Clermont-Ferrand, France
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Background/Purpose:

Remission of disease is the primary goal in chronic inflammatory arthritis, especially in rheumatoid arthritis. Traditional disease-modifying drugs like methotrexate and anti-tumor necrosis factor (anti TNF) therapy are

increasingly prescribed. General practitioners (GP) have to be faced with these treatments. The aim of the study is to explore GPs' perceptions of using these treatments in regular day-to-day practice.

Methods:

Semi structured interviews conducted with 14 GPs following patients under methotrexate and anti-TNF therapy, were analysed independently by researchers using inductive thematic analysis.

Results:

Four themes were identified: role of the GP in care delivery to patients under these treatments; their experiences and difficulties with these treatments; their perception of therapy education programmes; improving care delivery practices. The GP's role revolves around repeat prescription of methotrexate and managing for comorbidities, such as vaccination. In regular day-to-day practice, GPs note good tolerance and efficacy with these treatments. However, the increased risk of infection remains a top-of-mind concern and represents a hindrance to the use of these treatments. The most predominant difficulties are drug interactions and how to handle stopping anti-TNF therapy during bacterial infection, especially for GPs in rural area where there is limited access to specialist care. These GPs also report limited access to therapy education programmes. All the GPs voiced the need for a support tool to help them manage these therapies in routine practice.

Conclusion:

Methotrexate and anti-TNF therapies bring specific management issues that warrant tight cooperation between GPs and specialists. This study finds that it seem essential to facilitate dedicated training for GPs and to deploy a support tool.

Disclosure: M. Soubrier, None; **S. Mathieu**, None; **E. Berthet**, None.

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Abstract Number: 123

An Economic Evaluation of Tofacitinib (Xeljanz) Treatment in Rheumatoid Arthritis: Modeling the Cost of Treatment Strategies in the US

Lindsay Claxton[1], Matthew Taylor[1], Michelle Jenks[1], Gene Wallenstein[2], Alan Mendelsohn[3], Jeffrey Bourret[3], Amitabh Singh[3] and Robert Gerber[2], [1]York Health Economics Consortium, University of York, York, United Kingdom, [2]Pfizer Inc, Groton, CT, [3]Pfizer Inc, Collegeville, PA

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Background/Purpose: Tofacitinib is an oral Janus kinase (JAK) inhibitor for the treatment of rheumatoid arthritis (RA). An economic model was developed to evaluate the treatment costs of an RA strategy, including tofacitinib compared with strategies of biologic therapies that are commonly prescribed in the US. The model aimed to address the economic impact of monotherapy and combination therapy in MTX-inadequate responder (IR) patients and combination

therapy in TNFi-IR patients.

Methods: A decision-tree economic model was developed to evaluate costs over a one- or two-year time horizon. The model assessed patients with moderate to severe RA undergoing treatment with tofacitinib 5 mg BID or similarly labeled biologic therapies, either as monotherapy or with methotrexate (MTX), in scenarios where patients had an inadequate response to MTX therapy or after a first TNFi failure (combination therapy only). Response to treatment was modeled as ACR20/50/70 response. ACR response rates at 6 month intervals were sourced from US Prescribing Information, and safety event rates from a meta-analysis. Following an adverse event or a lack of response, it was assumed that 75% of patients switched to the next line of treatment (first to abatacept, and then to rituximab). Cost inputs included drug, monitoring, drug administration, and treatment for minor and serious adverse events. The patient population was based on the total number of all members (i.e. RA and non RA) in an organization; members with RA treated with biologic therapies were estimated using epidemiological data. The economic endpoints were: cost per member per month (PMPM), cost per ACR20 responder, and total costs. Sensitivity analysis adjusted for absolute ACR20 rates (lowering for tofacitinib and increasing for biologics).

Results: Results based on an organization size of 1 million with MTX-IR patients (n=1505) and TNFi-IR patients (n=602) are presented in Table 1. In the MTX-IR population, the monotherapy strategy with tofacitinib alone was associated with the lowest PMPM, cost per ACR20 responder and total costs over 1 and 2 years compared with the TNFi and non-TNFi biologics. Similar results were observed for combination therapy. In the TNFi-IR population, tofacitinib + MTX was associated with a lower PMPM, cost per ACR20 responder and total costs over 1 and 2 years compared with adalimumab + MTX. Tofacitinib strategies with no rebate (0%) were still associated with lower costs compared with adalimumab and etanercept with 20% rebates. Lower costs with tofacitinib were supported by sensitivity analysis.

Table 1: Economic model results (sorted lowest to highest cost based on two-year total costs)						
	Cost PMPM		Cost per ACR20 responder		Total costs	
	One year	Two years	One year	Two years	One year	Two years
MTX-IR patients						
Tofacitinib monotherapy	$4.09	$4.38	$47,830	$96,381	$49,066,725	$105,103,278
Tofacitinib + MTX	$4.21	$4.50	$57,973	$111,334	$50,510,949	$107,966,327
Tocilizumab monotherapy	$4.79	$5.01	$56,536	$111,104	$57,451,755	$120,319,824
Tocilizumab + MTX	$4.85	$5.03	$67,342	$125,179	$58,232,653	$120,752,673
Certolizumab monotherapy	$5.09	$5.22	$73,974	$134,103	$61,079,342	$125,271,312
Certolizumab + MTX	$5.10	$5.27	$65,748	$124,384	$61,230,332	$126,452,249
Etanercept monotherapy	$5.25	$5.41	$66,813	$126,544	$63,056,328	$129,880,666
Adalimumab monotherapy	$5.34	$5.41	$78,393	$140,025	$64,082,494	$129,901,536
Etanercept + MTX	$5.28	$5.48	$60,823	$119,203	$63,332,567	$131,423,554
Adalimumab + MTX	$5.37	$5.50	$67,805	$128,061	$64,428,338	$132,081,552
TNFi-IR patients						
Tofacitinib + MTX	$1.68	$1.80	$57,492	$110,596	$20,180,138	$43,127,524
Adalimumab + MTX	$2.15	$2.18	$77,344	$138,937	$25,753,046	$52,222,968

Conclusion: Tofacitinib 5 mg BID following MTX failure is predicted to be a low cost per patient treatment option when used either as monotherapy or combination therapy compared with biologic regimens. Tofacitinib + MTX in TNFi-IR patients was also predicted to be a low cost treatment option compared with adalimumab + MTX. Tofacitinib was associated with the lowest cost per ACR20 response.

Disclosure: L. Claxton, York Health Economics Consortium, 3,Pfizer Inc, 5; **M. Taylor**, Pfizer Inc, 5,York Health Economics Consortium, 3; **M. Jenks**, York Health Economics Consortium, 3,Pfizer Inc, 5; **G. Wallenstein**, Pfizer Inc, 1,Pfizer Inc, 3; **A. Mendelsohn**, Pfizer Inc, 1,Pfizer Inc, 3; **J. Bourret**, Pfizer Inc, 1,Pfizer Inc, 3; **A. Singh**, Pfizer Inc, 1,Pfizer Inc, 3; **R. Gerber**, Pfizer Inc, 1,Pfizer Inc, 3.

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Abstract Number: 124

Experiences with a Structured Questionnaire for Administrative Personnel

to Discriminate Urgent and Non-Urgent Rheumatic Patients Referred from Primary to Secondary Care

Omar Ghazal and **Michael Schirmer**, Internal Medicine, Clinic VI, Medical University of Innsbruck, Innsbruck, Austria
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Background/Purpose: To gain experiences with a structured questionnaire for discriminating urgent and non-urgent rheumatology appointments by administrative personnel, designed to include all forms of rheumatic diseases. Second, to discuss the results in view of current literature on referral strategies of rheumatic patients from primary to secondary care, including immune-mediated rheumatic diseases.

Methods: In our rheumatology unit a rheumatology urgency score (RUS) has been calculated on the basis of a multi-dimensional questionnaire with five main domains: Administrative information (referral mode, subjective urgency), clinical signs, time of maximal symptom presentation, available laboratory and imaging findings. This questionnaire has been routinely used since july 2013 for assigning appointments at initial consultation, with urgency defined as RUS $\geq$ 4 points. Anonymous score sheets including appointment assignments were provided by the administrative personnel for retrospective analysis. Literature search was last updated in january 2015 to identify evidence for effective strategies reducing waiting times and underlying causes for prolonged waiting times.

Results: Consecutive questionnaires from 153 referrals have been analyzed. Questionnaires with RUS $\geq$ 4 points were calculated and considered as urgent for 75% of the patients (n = 115). Based on the bimodal distribution curve of waiting times, the cut-off between short and long waiting times was defined as 23 days. Mean waiting time for urgent patients was shorter with 14.4 days (±13.1 days) than for non-urgent appointments with 24.6 days (±15.4 days) ($p<0.001$). 27.5% of all appointments were assigned independently from RUS, with 40.5% of questionnaires with RUS <4 resulting in a fast appointment and 16.1% of questionnaires with RUS $\geq$ 4 points resulting in a slow appointment. Without these incorrect assignments, waiting times were shorter for urgent than for non-urgent patients with 8.6 and 38.0 days, respectively ($p<0.001$). Administrative information, clinical signs, time of maximal symptom presentation, laboratory and imaging findings were available in 99.3 %, 94.1%, 77.1%, 33.3%, and 17% of the questionnaires, respectively.

According to the literature, effective strategies resulting in a reduction of referral delay are rapid access services, early arthritis clinics, triage of referrals with use of referral forms and educational programs for primary care physicians. None of the strategies specifically included patients with immune-mediated rheumatic diseases.

Conclusion: The rheumatology urgency score resulted in a bimodal distribution of waiting times, thus distinguishing between urgent- and non-urgent appointments. To achieve better quality in assignment of urgent appointments, administrative personnel has to be further instructed and motivated. RUS has to be further validated in a prospective approach taking into account the subjective and objective physicians' feed-back of urgency and final diagnoses.

Disclosure: O. Ghazal, None; **M. Schirmer**, None.

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Abstract Number: 125

Implementation of a Bone Health Team Markedly Improves Osteoporosis Screening, Diagnosis and Treatment Initiation Rates Compared to Standard Primary Care Practice

Karla L. Miller[1,2], Marissa P. Grotzke[1], Phillip Lawrence[3], Yanina Rosenblum[4], Richard Nelson[5,6], Joanne Lafleur[7,8] and Grant W. Cannon[1], [1]Internal Medicine, Veterans Affairs Salt Lake City Health Care System, Salt Lake City, UT, [2]Internal Medicine-Division of Rheumatology, University of Utah School of Medicine, SLC, UT, [3]Pharmacology, Salt Lake City VA Medical Center and University of Utah, Salt Lake City, UT, [4]Veterans Affairs Salt Lake City Health Care System, Salt Lake City, UT, [5]Epidemiology, Veterans Affairs Salt Lake City Health Care System, Salt Lake City, UT, [6]Division of Epidemiology, University of Utah School of Medicine, Salt Lake City, UT, [7]Pharmacology, Veterans Affairs Salt Lake City Health Care System, Salt Lake City, UT, [8]University of Utah College of Pharmacy, Salt Lake City, UT

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Background/Purpose: Despite the availability of effective therapies for fracture prevention, osteoporosis screening and treatment rates in practice are low. Fracture liaison services are effective at reducing secondary fractures, but primary prevention models are limited. The Salt Lake City VA Health Care System (SLCVAHCS) partnered with primary care providers (PCPs) to develop a bone health team (BHT) to improve the management of patients at risk for osteoporosis. This analysis compared patients enrolled in the BHT to similar patients with standard management.

Methods: Patients enrolled in the community-based outpatient clinics (CBOCs) of the SLCVAHCS from Feb 1, 2012 – Feb 1, 2015 were included if 1) the patient was enrolled in a CBOC PCP panel for 1 year prior to the date of implementation of the BHT, 2) had one PCP visit during this interval and 3) men age ≥70 and women age ≥65. Exclusion criteria were 1) no PCP assignment; or, 2) death in the pre-index period. The primary intervention was placement of a BHT e-consult. Primary outcomes were: completion of dual energy x-ray absorptiometry (DXA) scan; 25(OH) D measurement; diagnosis of osteopenia or osteoporosis; and initiation of osteoporosis medication. All patients started out as unexposed, but some went on to receive the primary intervention; patients were followed until the earliest of: occurrence of a primary outcome; or, the end of the observation period. Between group differences were analyzed using a Cox proportional hazards model with enrollment in BHT as a time-dependent exposure. Multivariable regression models adjusted for age, sex, multiple co-morbidities, baseline pharmacologic agents, site of CBOC, and PCP discipline.

Results: Of the 7,644 patients evaluated, 975 were enrolled in the BHT. This cohort was predominantly male (97.8%) with an average age of 79.8 years. Patients enrolled in BHT were significantly younger, more likely to live in rural areas, and more likely to have a physician as a PCP versus those not enrolled in BHT. More patients in BHT had diabetes, a prior diagnosis of osteoporosis and osteopenia, prior treatment with osteoporosis medications, and a greater likelihood of having been seen by a nurse practitioner. Fewer patients in the BHT had been seen by a physician's assistant, had vitamin D deficiency, or had prior vitamin D testing. In both univariate and multivariable regression analyses, patients in BHT were significantly more likely to undergo DXA, 25(OH) D testing, be diagnosed with osteopenia or osteoporosis, and be treated with osteoporosis therapy (Table).

Table: Univariate and Multivariable Cox Proportional Hazards regression results of BHT Intervention Compared to Standard Management

	Univariate Results				Multivariable Results			
		95% Confidence Interval				95% Confidence Interval		
Outcome	**HR**	**Lower**	**Upper**	**P-value**	**HR**	**Lower**	**Upper**	**P-value**
DXA	111.4	90.9	136.4	<.0001	176.1	125.9	246.3	<.0001
25 OH	1.403	1.258	1.564	<.0001	1.817	1.574	2.098	<.0001
Medication	13.78	10.76	17.64	<.0001	20.24	13.31	30.78	<.0001
Osteopenia	36.34	29.01	45.52	<.0001	51.39	34.62	76.29	<.0001
Osteoporosis	11.22	9.01	13.98	<.0001	18.06	12.50	26.08	<.0001

Conclusion: BHT implementation significantly increases the rate of screening, diagnosis, and treatment of osteoporosis in CBOCs of the SLCVAHCS. The impact on fragility fractures will require longer follow-up. Similar programs could be considered to improve the primary prevention of osteoporosis in other primary care settings.

Disclosure: K. L. Miller, None; **M. P. Grotzke**, None; **P. Lawrence**, None; **Y. Rosenblum**, None; **R. Nelson**, None; **J. Lafleur**, None; **G. W. Cannon**, None.

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Abstract Number: 126

Patients with Osteoarthritis and Rheumatoid Arthritis Seen at 4 Different Routine Rheumatology Care Sites at This Time Have Similar and Patient and Physician Global Estimates of Severity, and Scores for Functional Disability, Pain, and RAPID3

Carlos El-Haddad[1], Isabel Castrejón[2], Kathryn A. Gibson[3], Yusuf Yazici[4], Martin Bergman[5] and Theodore Pincus[2], [1]Rheumatology, Liverpool Hospital, NSW, Australia, [2]Rheumatology, Rush University Medical Center, Chicago, IL, [3]Liverpool Hospital, Liverpool, Australia, [4]NYU Hospital for Joint Diseases, New York, NY, [5]Division of Rheumatology, Taylor Hospital, Ridley Park, PA

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Background/Purpose: RA generally is regarded by physicians and the public as a more severe problem than OA. However, OA has been ranked as the 11th highest contributor to global disability among all diseases (1), and costs of OA and RA each have been found to account for about 1% of the US gross domestic product (2), explained in part by the higher prevalence of OA vs RA. Nonetheless, the standardized mortality ratio (SMR) (which is independent of prevalence) for OA is reported as 1.55 (3), and quite similar to the SMR for RA of 1.5-1.6 (4). Therefore, the severity of OA may be underestimated. We compared patient MDHAQ/RAPID3 (multidimensional health assessment questionnaire/routine assessment of patient data 3) and physician global estimates in patients with a primary diagnosis

of osteoarthritis (OA) or rheumatoid arthritis (RA) at 4 rheumatology clinical settings.

Methods: Patients were seen in routine care at 4 clinical settings: Liverpool Hospital, New South Wales, Australia, Rush University Medical Center, Chicago, IL, NYU Medical Center, New York, NY, and Arthritis and Rheumatology, a solo private practice, Ridley Park, PA. At each site, patients complete an MDHAQ at each visit in the waiting area while waiting to see the rheumatologist. The MDHAQ includes scores for physical function (0-10), pain (0-10), and patient global estimate (0-10), and RAPID3 composite scores of these 3 RA core data set measures (0-30). The physician assigns a global estimate for each patient (DOCGL). Patients with OA were compared to RA patients at each site for mean or median MDHAQ demographic measures, self-report physical function, pain, patient global estimate, RAPID3, and fatigue scores, as well as physician global estimates.

Results: Median scores for patients with OA were higher than for RA in 11 of 16 comparisons of MDHAQ scores (Table). Median DOCGL was higher in OA at 2 sites. Median physical function scores ranged from 1.7 to 2.7 for RA and 1.7 to 3.3 for OA; pain scores from 4 to 5 for RA and 5 to 7 for OA; patient global estimates from 4 to 5 for RA and 5 to 6 for OA; DOCGL from 0 to 4 for RA and 1 to 5 for OA; RAPID3 scores from 9.7 to 11.8 for RA and 11.7 to 16.8 for OA (Table).

Conclusion: Among treated patients, levels of patient physical function, pain, patient and physician global estimates, and RAPID3 in OA patients are in the same range as in RA patients. The findings likely reflect in part better treatments for RA. However, the severity of OA may be underestimated. Better information concerning OA may lead to improved clinical management and resource allocation for OA.

References: **1)** Ann Rheum Dis. 2014;73(7):1323-30. **2)** Arthritis Rheum. 1995;38(10):1351-62. **3)** BMJ. 2011;342:d1165. **4)** Clin Exp Rheumatol. 2008;26(5 Suppl 51):S35-61.

Table: MDHAQ/RAPID3 and RheuMetric scores for patients with RA and OA in 4 clinical settings: Liverpool, Rush, NYU, and Ridley Park

	Liverpool Hospital		**Rush Medical Center**		**NYU Medical Center**		**Ridley Park**	
	RA (n=64)	**OA (n=52)**	**RA (n=173)**	**OA (n=199)**	**RA (n=145)**	**OA (n= 173)**	**RA (n=39)**	**OA (n=41)**
Demographic measures								
Age, mean (SD) years	58.7 (14.0)	66.1 (10.7)	57.9 (15.9)	67.2 (12.1)	49.3 (15.8)	62.6 (12.4)	56.8 (13.9)	67.2 (12.2)
Education level	10 (9-12)	10 (8-12)	14 (12-16)	14 (12-16)	16 (13-18)	16 (13-18)	13.5 (2.2)	13 (1.7)
Female	79.7 %	88.4 %	86.1 %	85.4 %	74 %	78 %	90%	67%
MDHAQ: Patient self-report scores								
MDHAQ-FN	1.7 (0.7-3)	3.3 (2.3-4.7)	2.7 (0.7-3.7)	2.7 (1.3-4)	1.7 (0.3-3.7)	1.7 (0.7-3.3)	1.9 (1.8)	1.8 (1.7)
MDHAQ-PN	4.3 (2.5-8.3)	7.0 (5.5-8.3)	5 (2-7.5)	7 (5-8.5)	4.7 (2-7)	5 (3-7.5)	3.9 (3.2)	3.9 (2.8)
MDHAQ-PATGL	4.3 (1.3-6.8)	6.0 (4.3-8)	4.5 (1.5-7)	5.7 (3.5-8)	5 (1.5-7)	5 (2-6.5)	3.4 (3.0)	4.6 (3.0)
RAPID3	9.7 (5.5-17)	16.8 (11.3-19.7)	11.8 (4.3-18.7)	15.5 (10.2-19.5)	11 (4-16.7)	11.7 (6.7-16.7)	9.2 (7.6)	10.3 (6.9)
RheuMetric: Physician Estimates								
DOCGL	4 (2-5)	5 (3-6)	3.7 (2-5)	4 (3.5-5)	2.5 (1.5-3.5)	2.5 (2-3.5)	3.9 (1.6)	3.6 (1.9)
Values are median and interquartile range unless indicated otherwise								

Disclosure: C. El-Haddad, None; **I. Castrejón**, None; **K. A. Gibson**, None; **Y. Yazici**, None; **M. Bergman**, None; **T. Pincus**, Health Report Services, Inc, 4.

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physician-global-estimates-of-severity-and-scores-f

Abstract Number: 127

Potential Use of Healthcare Databases for Post-Marketing Surveillance Registry: an Example Using Ustekinumab

Huifeng Yun[1], Shuo Yang[2], Fenglong Xie[3], Lang Chen[4], Kevin L. Winthrop[5] and Jeffrey R. Curtis[4], [1]Epidemiology, University of Alabama at Birmingham, Birmingham, AL, [2]Clinical Immunology/Rheumatology, University of Alabama at Birmingham, Birmingham, AL, [3]Rheumatology & Immunology, University of Alabama at Birmingham, Birmingham, AL, [4]University of Alabama at Birmingham, Birmingham, AL, [5]Oregon Health and Science University, Portland, OR
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Background/Purpose:

Underreporting and inherent deficiencies are common using spontaneous reports for post-marketing surveillance. The U.S. Food and Drug Administration (FDA) has recommended sponsors to collect information from multiple sources including creating or working with registries or other observational data for post-marketing surveillance. For new costly drugs, traditional registries are expensive to create, slow to recruit, and are potentially subject to selection biases as to the types of patients enrolled. The current study evaluated the feasibility of utilizing one or more healthcare databases to support safety surveillance of a new biologic medication, with ustekinumab (UST) as an example.

Methods:

Using patients from Medicare 2006-2012, Marketscan 2008-2013, and Optum research database 2008-2013, we identified new users of UST using both non-specific and or specific drug codes. New users were defined as no previous use of UST with all available data. Eligible patients were required to meet the following criteria: 1) ≥ 19 years of age; 2) ≥ 1 one inpatient or dermatologist-given diagnosis code for psoriasis; 3) continuously enrolled with medical and pharmacy coverage during the 6 months prior to UST initiation and throughout follow up. We evaluated the accrual of new UST users by calendar time in each data system.

Results:

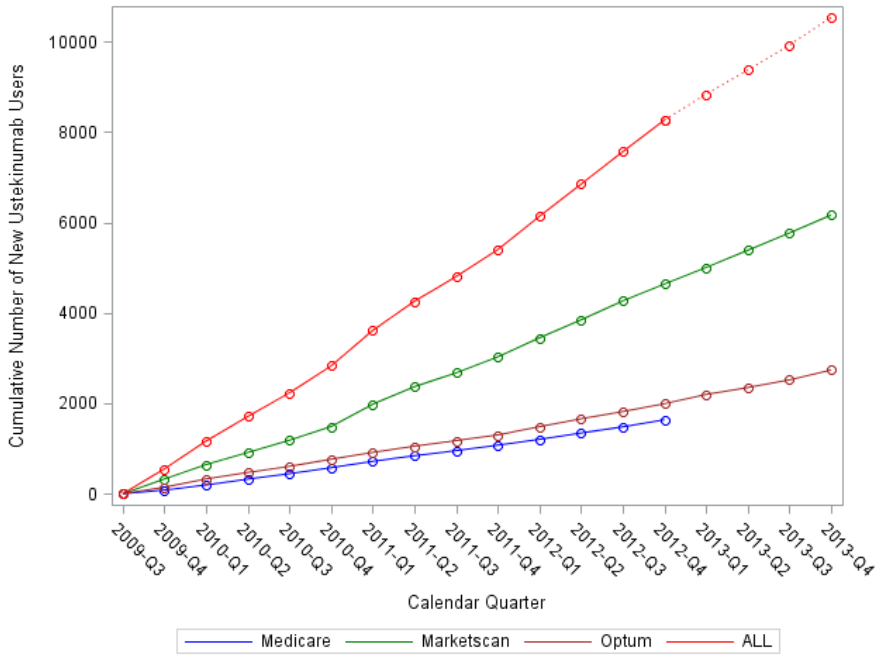
We identified 1636, 6159, and 2735 new UST users in Medicare, Marketscan and Optum databases, respectively (Figure). These patients had median follow-up of 1.5-2.5 years, and they were censored mainly because our study observation period ended, and not because patients dis-enrolled from the health plan. Marketscan provided the largest data source of new UST users, whereas the number of new users was comparable between Medicare and Optum. Within 1 year of FDA licensure, approximately 3,000 new users were identified, and by 2 years, almost 6,000 users were identified. As of the end of 2013, more than 10,000 UST new users were available.

Conclusion:

Utilizing one or more healthcare databases to support post-marketing surveillance for a new biologic shortly after its licensure is feasible, and it yields relatively large sample sizes to study uncommon safety events. This approach can complement more traditional registry-based approaches to detect important safety signals and maximize power for long

term comparative safety analyses.

Figure: Cumulative number of new Ustekinumab users in different data systems by calendar quarter



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Abstract Number: 128

Economic Burden and Treatment Patterns of Cycling Between Non-Biologic Disease Modifying Anti-Rheumatic Drugs (DMARDs) Among Patients with Rheumatoid Arthritis (RA)

Nanxin Li[1], Keith Betts[1], Jenny Griffith[2], Ljubica Ristovska[1], Kevin Douglas[2] and Arijit Ganguli[2], [1]Analysis Group, Inc., Boston, MA, [2]AbbVie Inc., North Chicago, IL

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Background/Purpose:

RA patients with inadequate treatment response often cycle non-biologic DMARDs before initiating a biologic

DMARD. Early and aggressive treatment is a key feature of a treat-to-target approach and a previous study showed that switching to a biologic DMARD compared to cycling another non-biologic DMARD resulted in improved clinical outcomes (Dewitt et al., 2013). This study assessed the economic outcomes and treatment patterns among patients who used 1, 2, or ≥3 non-biologic DMARD(s) before receiving a biologic therapy.

Methods:

Adult patients with ≥2 RA diagnoses (International Classification of Diseases: 714.xx), ≥1 claim for a non-biologic DMARD, and ≥1 claim for a biologic DMARD were identified from a large commercial claims database (2008-2013). The initiation date of the first biologic DMARD was defined as the index date. Based on the number of distinct non-biologic DMARDs initiated between the first RA diagnosis and the index date, patients were classified into three cohorts: those who used 1, 2, or ≥3 non-biologic DMARDs. Baseline characteristics were measured 6 months pre-index date and compared between the three cohorts. All-cause healthcare costs (in 2014 USD) were compared in the follow-up period (12 months post biologic initiation) using multivariable gamma models adjusting for baseline characteristics. Discontinuation of the index biologic DMARD and time to switching to a new DMARD were compared using multivariable Cox proportional hazards models.

Results:

The 1, 2, and ≥3 non-biologic DMARD cohorts included 6,215, 3,227, and 976 patients, respectively. At baseline, patients in the ≥3 non-biologic cohort had the least severe RA, as indicated by the lowest claims-based index for RA severity (CIRAS) score (1 vs 2 vs ≥3: 6.1 vs 5.9 vs 5.8). During the study period, there was a significant association between number of non-biologic DMARDs and higher all-cause total healthcare costs (adjusted mean difference: 1 vs 2: $772, p<0.001; 2 vs ≥3: $2,390, p<0.001); the all-cause medical and pharmacy costs were also significantly higher with the increasing number of non-biologics (Table 1). Patients who cycled more non-biologic DMARDs were also more likely to switch treatment after biologic initiation (1 vs 2: adjusted hazard ratio (HR)=0.89, p=0.005; 2 vs ≥3: adjusted HR=0.89, p=0.087). There were no differences in index biologic discontinuation between the 3 cohorts.

Conclusion:

RA patients who cycled more non-biologic DMARDs had increased economic burden in the 12 months following biologic initiation and were more likely to switch therapy. These results highlight the importance of timely switching to biologic DMARDs for the treatment of RA.

Table 1. Comparison of healthcare costs among patients who used 1, 2, or ≥3 non-biologic DMARDs before the initiation of biologic therapy

	Unadjusted average healthcare costs			Adjusted difference in average healthcare costs			
	Patients who used 1 non-biologic DMARDs (N = 6,215) [A]	Patients who used 2 non-biologic DMARDs (N = 3,227) [B]	Patients who used ≥3 non-biologic DMARDs (N = 976) [C]	1 vs. 2 non-biologic DMARDs Difference [A] - [B]		2 vs. ≥3 non-biologic DMARDs Difference [B] - [C]	
Total all-cause healthcare costs (2014 USD), mean	$32,493	$33,420	$36,422	-$772	**	-$2,390	**
All-cause medical costs	$15,211	$15,459	$17,600	-$107	**	-$1,491	**
Inpatient costs	$3,603	$3,903	$4,831	$14	**	-$631	**
Emergency department costs	$342	$399	$369	-$45	**	$54	**
Outpatient costs	$11,265	$11,157	$12,400	$10	**	-$1,096	**
Rheumatologist visit costs	$2,712	$2,638	$2,388	$215	**	$175	**
All-cause pharmacy costs	$17,282	$17,960	$18,822	-$900	**	-$796	**

**: p < 0.01

Disclosure: N. Li, AbbVie Inc., 5; **K. Betts**, AbbVie Inc., 5; **J. Griffith**, AbbVie Inc., 3,AbbVie Inc., 1; **L. Ristovska**, AbbVie Inc., 5; **K. Douglas**, AbbVie Inc., 3,AbbVie Inc., 1; **A. Ganguli**, AbbVie, Inc., 3,AbbVie, Inc., 1.

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http://acrabstracts.org/abstract/economic-burden-and-treatment-patterns-of-cycling-between-non-biologic-disease-modifying-anti-rheumatic-drugs-dmards-among-patients-with-rheumatoid-arthritis-ra

Abstract Number: 129

Rheumatologists' Approaches to Diagnosis and Treatment of Depression

Erica Heiman, Barton Wise and Richard L. Kravitz, Department of Internal Medicine, UC Davis Medical Center, Sacramento, CA
First publication: September 29, 2015

SESSION INFORMATION

Session Date: Sunday, November 8, 2015
Session Title: Health Services Research Poster I: Diagnosis, Management and Treatment Strategies
Session Type: ACR Poster Session A
Session Time: 9:00AM-11:00AM

Background/Purpose:

Depression in patients with rheumatic disorders contributes to morbidity, mortality, and health care utilization. We set out to examine rheumatologists' approaches to and perceptions of depression in everyday practice.

Methods:

A questionnaire was mailed to 470 practicing rheumatologists in California; 226 (55%of eligible respondents, after removing those returned to sender and who reported they were not in active clinical practice) were included in the final analyses. Respondents provided information on demographics, practice characteristics, attitudes towards mental health, and practices related to depression. Logistic regression models were constructed to assess the relationship of rheumatologists' personal and practice characteristics with their usual depression-related practices (medication management, referral to primary care, and referral to psychiatry).

Results:

Among responding rheumatologists, 51% reported that at least half their patients suffered from depression, many of them untreated. Nearly all providers (99%) reported addressing mental health issues during at least some visits. When these issues were raised, it was usually the physician who initiated the discussion (69%); only 9% reported regular use of a formal screening tool. Rheumatologists were equally likely to prescribe antidepressants, refer to a psychiatrist, or return the patient to the primary care physician; about 60% reported applying each of the 3 strategies to at least half of their patients. In logistic regression models, greater number of visits per week and greater percentage of patients with fibromyalgia were associated with more prescription of antidepressants ($p<.05$).

Conclusion:

Our findings point towards a gap in care provision. Rheumatologists see a great need for mental health services but too often lack the skills and time to address mental health issues.

Disclosure: E. Heiman, None; **B. Wise**, None; **R. L. Kravitz**, Takeda Pharmaceuticals, Lundbeck LLC, 8.

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Abstract Number: 130

Disease Activity Patterns in Incident Onset Rheumatoid Arthritis Patients in the First 3-Years of Follow up

Mark Tatangelo[1], George A. Tomlinson[2], Bindee Kuriya[3] and Claire Bombardier[4], [1]University of Toronto, Toronto, ON, Canada, [2]Medicine, Mount Sinai Hospital, Toronto, ON, Canada, [3]Rheumatology, Mount Sinai Hospital,

University of Toronto, Toronto, ON, Canada, [4]Toronto General Hospital Research Institute, University Health Network, Toronto, ON, Canada

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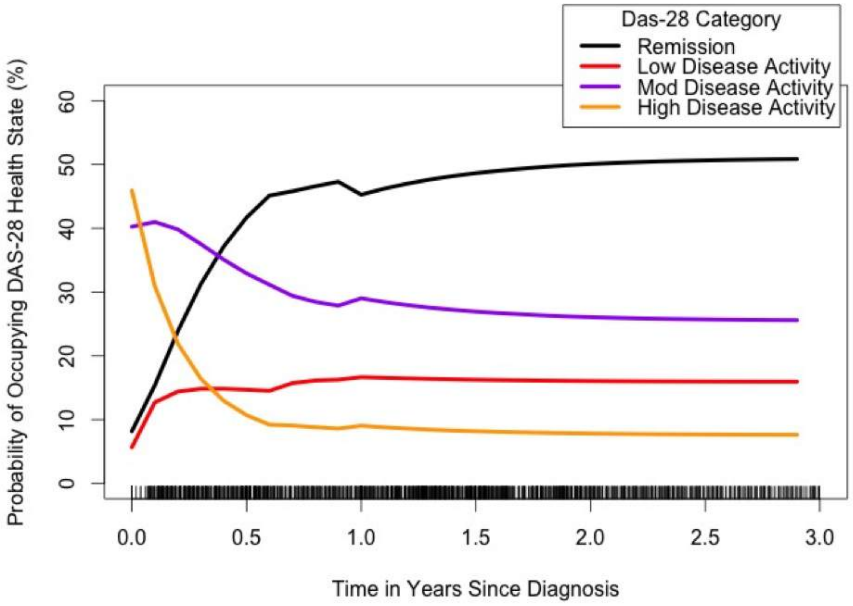
Background/Purpose: Disease progression in longitudinal studies of rheumatoid arthritis (RA) is usually assessed by examining a measure of disease over time fixed time intervals. We sought to use a multi-state model: (1) to provide a descriptive analysis of patients' disease states defined by the DAS-28 disease index throughout the first three years of treatment; (2) to determine the time spent in each disease state; and (3) to estimate the probabilities of changing between disease states.

Methods: Patients were selected from an ongoing prospective study of RA if they had active disease (>= 1 swollen or tender joint) and at least 2 follow-up visits to their rheumatologist. The DAS-28 score was collected at each visit and assigned to one of four category scores, from remission to high disease activity, using the ACR criteria. A multi-state (4-state) Markov model was fitted to describe patient progression through disease states over time to account for the irregular time intervals in our data considering time as a continuous variable allowing us to examine real-world disease course over time. Multiple piecewise transition parameters for the Markov model were fit to determine if patients have differential transitions at different time periods.

Results: There were 3014 visits in 586 patients with visits distributed arbitrarily over the 3-year follow-up window. At baseline, about 50% of patients were in high disease activity, but patients respond rapidly, moving out of this health state spending on average 0.17 years, 95% CI (0.19, 0.23) there. At baseline about 8% of patients were in DAS-28 remission, which rose rapidly at 0.5 years 25% probability and 1 year with about 40% of patients in remission. Once a patient achieved remission, the mean duration before moving to another disease state was 0.81 years, 95% CI (0.67, 0.97). By 1.5 years after initiation of treatment, patients in each disease state remained relatively constant indicating no net movement between health states. The piecewise model indicated that patients at 6-months had a differential movements through disease states then at any other time point. Patients starting in the highest disease state took the longest about 1.1 years to reach their first remission compared to 0.9 and 0.8 years for the moderate and low groups.

Conclusion: Individual patients transition between disease states in the first 3 years of treatment at differential times; the first 6-months are critical with the first year seeing rapid movement between states. Within the first 6-months, dramatic reductions are realized in patients with high disease activity in parallel with an observed increase in the proportion of patients achieving remission. Our analysis indicates the critical first year of treatment before a steady disease state with no net movement will be reached. Major changes in the first year of treatment could be a result of treat-to target strategy.



Abstract Number: 131

Frequency of Lipid Testing and Management Among Rheumatoid Arthritis Patients Compared to the General Population and Patients with Diabetes

Iris Navarro-Millan[1], Shuo Yang[2], Monica Safford[3], Lang Chen[3], Huifeng Yun[4] and Jeffrey R. Curtis[3], [1]Rheumatology, University of Alabama at Birmingham, Birmingham, AL, [2]Clinical Immunology/Rheumatology, University of Alabama at Birmingham, Birmingham, AL, [3]University of Alabama at Birmingham, Birmingham, AL, [4]Epidemiology, University of Alabama at Birmingham, Birmingham, AL

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Background/Purpose: Patients with rheumatoid arthritis (RA) have high coronary heart disease (CHD) burden and accelerated atherosclerotic status. However, limited data suggest that these patients may be screened less frequently than other patients with similar CHD risk. To evaluate the rate of lipid testing and management among RA patients and compare it both to the general population and diabetes (DM) patients.

Methods: We used a mix of private and public health plans claims data from 2006 to 2010 with medical and pharmacy coverage. Eligible participants were required to 1) have at least 12 months of continuous medical and

pharmacy coverage (baseline period), and 2) have 2+ physician diagnosis and relevant medications to categorize them as having 1) RA and DM; 2) RA only; 3) DM only; 4) Neither RA nor DM. Patients with prevalent myocardial infarction (MI)/stroke/CHD during baseline were excluded. Each of these groups had a follow up time of 2 years. We calculated the proportion of patients with low density lipoprotein (LDL) lab test during the 2 year follow-up. In a subgroup analysis, we determined the proportion of patients with lab results available with LDL ≥ 130 mg/dL that initiated treatment with statins. We use chi-square tests to compare differences between the 4 cohorts in the proportion tested for LDL and initiating statins.

Results: There were 428,109 eligible patients distributed between the 4 cohorts (Table). Overall, 60% were women. The overall age distribution was: 12% ≤ 40; 29%, 41-65; and 59% >65 years old. RA patients were less frequently tested for LDL compared to DM patients, with or without RA (p-value <0.001 for all comparisons) (Table). Conditional on having LDL ≥ 130 mg/dL, RA patients were less likely to be started on a statin compared to DM patients (p-value < 0.001), and were marginally more likely to be initiated on statins compared to the general population (p-value = 0.045). There was no difference in the statin prescription trend between DM and RA patients vs. only RA patients (p-value =0.083)

Conclusion: RA patients are less frequently screened and managed for hyperlipidemia compared DM patients. Despite higher CHD risks in RA patients, hyperlipidemia screening and treatment rates in RA patients were no better than the general population. Further studies to investigate the reasons and potential interventions to ameliorate this care gap among RA patients are needed.

Table: Frequency of lipid testing among patients with rheumatoid arthritis, diabetes, both or neither condition

Outcome	RA Only	Diab Only	RA & Diab	Neither
	N =20,148	N = 100,971	N = 3,358	N = 303,632
Screening: LDL checked during 2-year period, %	46	63	62	45
Treatment: statin initiation (among subgroup of patients with lab results available and LDL ≥ 130 mg/dL not already on therapy), %	13	26	28	9

Disclosure: I. Navarro-Millan, None; **S. Yang**, None; **M. Safford**, None; **L. Chen**, None; **H. Yun**, None; **J. R. Curtis**, Roche/Genentech, UCB, Janssen, CORRONA, Amgen, Pfizer, BMS, Crescendo, AbbVie, 2,Roche/Genentech, UCB, Janssen, CORRONA, Amgen, Pfizer, BMS, Crescendo, AbbVie, 5.

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Abstract Number: 132

Delivering a One-Stop, Integrated, Patient-Centred Service for Patients with Rheumatic Diseases. the Finnish Approach

Elena Nikiphorou[1], Paula Väre[1], Kirsi Paalanen[1], Jelena Borodina[1], Arto Kokko[2], Pekka Hannonen[1] and Tuulikki Sokka-Isler[3], [1]Jyvaskyla Central Hospital, Jyvaskyla, Finland, [2]Jyvaskyla Central Hospital, Jyväskylä, Finland, [3]Rheumatology, Jyvaskyla Central Hospital, Jyvaskyla, Finland

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Session Type: ACR Poster Session A

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Background/Purpose:

Rheumatology is mainly an outpatient specialty. Prompt diagnosis & treatment to prevent long-term disability in an integrated, multi-disciplinary approach to care are crucial. In reality though, not many clinics provide this level of service.

Methods:

Descriptive report & patient satisfaction survey of a rheumatology clinic model which was first developed in 1996 to enhance the patient 'journey' through rheumatology services. A patient-satisfaction survey assessed several aspects of care including quality of services, consultations, treatment & patient education. All patients visiting the rheumatology department over a 3-week period were invited to participate.

Results:

All primary care referrals are screened by a rheumatologist to pre-schedule laboratory/radiology tests for the visit. Upon arrival to the clinic, patients check-in at an electronic desk, then are guided by a receptionist to complete the electronic Go-TreatIT monitoring system (assesses patient-reported outcomes e.g. pain, fatigue) at private stations within the clinic. Of all the collected data the program then generates commonly used comparable values e.g. HAQ, DAS28 & BASFI. The patient is reviewed by a doctor in a 30-60 minute consultation depending on whether it is a 1st or follow-up visit, then by a nurse (for diagnosis/treatment education, vaccinations, assessment of psychological status etc). An ultrasound machine & capillaroscopy are available for use in clinic. Patients can be scheduled on the same day to see a nutritionist, physiotherapist, podiatrist or other professionals as needed. An 'early-RA treatment path' is available to ensure early, intensive treatment (with combination triple DMARD therapy, intra articular & oral steroids). Steps in the process will be diagrammatically shown.

Survey: From 141 recipients, 86% completed a questionnaire;67% female;12% were on their first visit. Mean age:54.3 yrs; 37% retired. 51% had a diagnosis of RA; the remaining included ankylosing spondylitis, psoriatic arthritis, fibromyalgia, lupus, vasculitis. Most valued was the information & education provided by doctors/nurses & addressing patients' current issues. 93 % of patient 'agreed' that their medical care was high quality, 77 % 'strongly agreed'. The mean score overall assessment of the service was 90.6/100. Only 6% gave negative feedback. The main complaint was difficulty with using the electronic check-in tool (not GoTreatIT). Some patients expressed disappointment for not finding the cause for their symptoms. None of the patients felt they lacked education on their disease or medication. 92% strongly agreed they were given sufficient education. 6% of patients felt that they were overwhelmed with information, 82% were content with the amount of information given. The multi-disciplinary approach was valued & only 3% would rather see doctor and nurse on separate days.

Conclusion:

The specific clinic model provides an ideal setting for a one-stop service, avoiding unnecessary visits, collecting important patient data & enhancing the patient experience & journey through the system.

Disclosure: E. Nikiphorou, None; **P. Väre**, None; **K. Paalanen**, None; **J. Borodina**, None; **A. Kokko**, None; **P. Hannonen**, None; **T. Sokka-Isler**, None.

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Abstract Number: 133

Advocating for Rheumatoid Arthritis and Cardiovascular Health (ARCH) in a Tertiary Referral Center: A Collaborative and Systems-Based Approach to Improve Access to Care

Barbara Goldstein[1], JoAnn Zell[1], Pearlanne Zelarney[2], Matthew Stern[2], Sarah Meadows[2], Meg Dingae[2], Carmen Egidio[2] and Darlene Kim[2], [1]Medicine, National Jewish Health, Denver, CO, [2]National Jewish Health, Denver, CO
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SESSION INFORMATION
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Background/Purpose: Patients with rheumatoid arthritis (RA) have an increased risk of cardiovascular disease (CVD) as compared to the general population. The European League Against Rheumatism (EULAR) recommends that rheumatologists engage in assessing the CVD risks in RA patients. Multiple barriers such as limited time and lack of familiarity of CVD screening guidelines challenge the feasibility of this practice. Furthermore, recent data suggest that primary care providers fail to assess RA patients consistently or aggressively. At a tertiary referral center, we implemented an innovative system to provide RA patients direct access to cardiology for a CVD risk assessment. In the new RA-CVD clinic workflow, the rheumatologist can screen for CVD risk factors during a clinical visit and refer RA patients using a prescribed order set. Next, the patient is evaluated by cardiology and the 10-year risk for atherosclerotic cardiovascular disease (ASCVD) score is calculated to help guide therapy decisions. In this study, we examined patient access, lipid profiles and medication use before and after the intervention.

Methods: We devised an order set within the electronic medical record (EMR) that was available to all rheumatologists starting January 2015. The order set included a referral to the RA-CVD clinic, electrocardiogram, lipid profile or vertical auto profile (VAP), and hemoglobin A1C. For this study, we reviewed all RA patients presenting to our hospital for new or follow up appointments pre- and post- implementation of the program. Chart review was performed to identify elevated lipid profiles (LDL>130) and statin use. Our cardiology team devised a specific protocol to best risk assess these patients per EULAR guidelines.

Results: Since the launch of our program, 722 RA patients have been seen by the rheumatology practice, 99 (14%) of these patients agreed and were then referred to the RA-CVD clinic. Screening for diabetes and hypercholesterolemia has improved by 60% with the implementation of the program. To date, 13 patients have undergone full risk assessment, however not all patients have been seen partially due to cardiology appointment lag time. Of these patients, 5/13 (38%) patients were started on a statin based on their ASCVD score.

Conclusion: Our study suggests that the creation of a RA-CVD workflow significantly increased the rates of risk factor screening and appeared to provide a forum for necessary interventions. However, lack of cardiology access may limit the strength this program.

Disclosure: B. Goldstein, None; **J. Zell**, None; **P. Zelarney**, None; **M. Stern**, None; **S. Meadows**, None; **M. Dingae**, None; **C. Egidio**, None; **D. Kim**, None.

Abstract Number: 134

Axial Spondyloarthritis: Validation of an Inter-Professional Model of Care

Christopher Hawke[1], Laura Passalent[2,3], Anthony V. Perruccio[4], Kala Sundararajan[5], Nigil Haroon[6], Robert D Inman[7] and Y. Raja Rampersaud[8], [1]Toronto Western Hospital, University of Toronto, Toronto, ON, Canada, [2]Allied Health, Toronto Western Hospital, Toronto, ON, Canada, [3]Physical Therapy, University of Toronto, Toronto, ON, Canada, [4]Orthopaedic Surgery, Brigham & Women's Hospital and Harvard Medical School, Boston, MA, [5]Orthopaedic Research Department, Toronto Western Hospital, Toronto, ON, Canada, [6]Rheumatology, Toronto Western Hospital, University of Toronto, Toronto, ON, Canada, [7]Immunlogy and Institute of Medical Science, Toronto Western Hospital, University of Toronto, Toronto, ON, Canada, [8]Orthopaedic Surgery and Neurosurgery, University Health Network and University of Toronto, Toronto, ON, Canada

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Background/Purpose:

Early detection of axial Spondyloarthritis (axSpA) is challenging given the lack of pathognomonic clinical findings. Clinical overlap with mechanical back pain leaves axSpA a poorly recognized disease entity. Given that effective treatments are now available, early detection of axSpA is critical. To enable primary care detection, the aim of this study was to evaluate an inter-professional model of care (MOC) for detection of axSpA with respect to three essential screening elements: 1) assignment to high vs low risk groups on the basis of clinical characteristics of patients; 2) agreement on mechanical versus inflammatory back pain; 3) interpretation of radiographic sacroiliitis.

Methods:

Patients with >3 months of back pain and age of onset ≤45 years were referred to the program. Exclusion criteria included: leg dominant pain, neurological symptoms, or an established diagnosis of an inflammatory condition. A comprehensive examination was completed by an Advanced Practice Physiotherapist (APP). Investigations included: HLA B27, CRP, ESR, and radiographs of the SI joints. Patients completed an initial assessment with an APP and were subsequently reviewed by a Rheumatologist with experience in axSpA. The APP and Rheumatologist independently categorized each patient's risk of axSpA into 'low', 'medium', or 'high' as well as the risk of mechanical back pain. Each patient's radiographs were interpreted independently by the APP and the Rheumatologist. Final axSpA diagnosis was determined by the Rheumatologist using the Assessment of Spondyloarthritis (ASAS) criteria.

Results:

A total of 123 patients were evaluated using the inter-professional MOC. Fifty-nine percent were female, with a mean age of 35.5 years (±9.6 years). Mean duration of back pain was 7.2 years (+/-8.5, range 3 months to 37 years). Agreement of risk categorization between APP and Rheumatologist was 79.7%, with Kappa coefficient= 0.57 (CI 0.38-0.77). Sensitivity and specificity for the APP (versus final diagnosis) was 71.4% (CI 30.3-94.9%) and 75% (CI 61.9-84.9%) respectively; with a positive predictive value of 25% (CI 9.6-49.4%) and negative predictive value of 95.7% (CI 84.3-99.3%). Radiographic interpretation for the presence of sacroiliitis, as per modified New York Criteria (mNYC), was fair to moderate (Kappa=0.39 left, Kappa=0.42 right) between the APP and Rheumatologist. Patients assigned by the APP and Rheumatologist to the low and high risk groups did not differ with respect to the following:

age, gender, inflammatory back pain, extra articular features, family history, HLA B27 status, ESR, CRP, or radiographic sacroiliitis.

Conclusion:

Using the ASAS criteria and Rheumatologists' final diagnosis as a gold standard, an inter-professional MOC demonstrated high negative predictive value and fair agreement with radiographic interpretation for sacroiliitis consistent with the literature. No significant differences were identified between clinical characteristics when assigning risk scores for axSpA. These preliminary findings suggest that an inter-disciplinary team is an effective MOC when screening for axSpA and represents a possible model for earlier detection within primary care.

Disclosure: C. Hawke, None; **L. Passalent**, None; **A. V. Perruccio**, None; **K. Sundararajan**, None; **N. Haroon**, None; **R. D. Inman**, None; **Y. R. Rampersaud**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/axial-spondyloarthritis-validation-of-an-inter-professional-model-of-care

Abstract Number: 135

Limitations of Treat-to-Target in Rheumatoid Arthritis: Joint Damage Appears As Severe As Inflammation in Contemporary Care at One Site

Theodore Pincus[1], Alex D. Luta[2], Isabel Castrejón[1], Annie Huang[1], Ruchi Jain[1], Sarah L. Everakes[3] and Joel A. Block[4], [1]Rheumatology, Rush University Medical Center, Chicago, IL, [2]Georgetown University, Washington, DC, [3]Internal Medicine, Rush University Medical Center, Chicago, IL, [4]Rush University Medical Center, Chicago, IL

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Background/Purpose: Treatment of rheumatoid arthritis is directed to "treat-to-target," with intensification of therapy in patients with moderate/high disease activity according to a quantitative index toward low disease activity or remission. However, remission or even low disease activity is unusual in even 50% of patients. One study suggests a partial explanation, as about 20% of patients with high index scores whose therapy is not intensified had clinically important joint damage (1). We analyzed physician estimates of inflammation and damage in RA patients in two ways: a) quantitative physician 0-10 visual analog scales (VAS); and b) estimates of the proportion(s) of clinical management decisions attributable to inflammation, damage, and/or distress, totaling 100%.

Methods: All patients seen at a one academic site completed an MDHAQ/RAPID3, and rheumatologists completed a RheuMetric physician checklist which includes 4 0-10 VAS for overall global estimate, inflammation, damage, and distress. A second type of scale asks doctors to estimate the proportion of the decision concerning management that is attributable to inflammation, damage, or distress, totaling 100%. Only the inflammation and damage VAS and proportions are analyzed in this study. Cross tabulations were computed with categories 0-1.9, 2-3.9,4-5.9,6-7.9,and 8-10 for the 0-10 VAS, and 0-19%, 20-39%, 40-59% 60-79%, and 80-100% for the proportion of the decision attributable to inflammation or damage.

Results: Among 72 patients studied, a 0-10 inflammation VAS was estimated as 8-10 in 6% of patients, versus 6-7.9 in 4%, 4-5.9 in 14%, 2-3.9 in 38%, and 0-1.9 in 39% of patients. Overall, only 24% of patients had scores ≥4 for

inflammation. Damage was estimated at 8-10 in 10% of patients, 6-7.9 in 10%, 4-5.9 in 18%, 2-3.9 in 40%, and 0-1.9 in 22%; 37% of patients had damage scores ≥4 . The proportion of clinical management attributable to inflammation was estimated as 80-100% in 10% of patients, 60-79% in 15%, 40-59% in 24%, 20-39% in 18%, and 0-19% in 33%. Damage was estimated as impacting 80-100% of the clinical decision in 36%, 60-79% in 8%, 40-59% in 24%, 20-39% in 18%, and 0-19% in 14% of patients. Overall, inflammation accounted for more than 40% of clinical decisions in 49% of patients, while damage accounted for more than 40% of decisions in 68% of patients.

Conclusion: In one setting, damage appears to impact clinical decisions in contemporary treatment of patients with RA as much as inflammation. This finding may explain in part why clinical trials of established patients indicate only 60% ACR20 responses with all 10 approved biological agents for RA, and may also explain in part why fewer patients than might be expected are in remission. The data suggest that quantitative assessment of physician VASs to assess inflammation and damage (and distress) may be informative in routine care.

Reference: **1)**Tymms K, et al. Arthritis Care Res (Hoboken). 2014;66(2):190-6.

Table: Physician estimates for inflammation and damage in patients with rheumatoid arthritis according to 0-10 visual analog scales and estimates of the proportion of management decisions based on these types of clinical problems

		Physician 0-10 VAS Score for Inflammation (Reversible)					
		8-10	6-7.9	4-5.9	2-3.9	0-1.9	Total
Physician 0-10 VAS Score for Damage (irreversible)	8-10	1	0	2	2	2	7 (10%)
	6-7.9	0	1	0	4	2	7 (10%)
	4-5.9	1	1	1	4	6	13 (18%)
	2-3.9	1	0	3	13	12	29 (40%)
	0-1.9	1	1	4	4	6	16 (22%)
	Total	4 (6%)	3 (4%)	10 (14%)	27 (38%)	28 (39%)	72 (100%)
		% of Clinical Management Based on Inflammation					
		80-100%	60-79%	40-59%	20-39%	0-19%	Total
% of Clinical Management Based on Damage	80-100%	NA	NA	NA	7	19	26 (36%)
	60-79%	NA	NA	3	3	0	6 (8%)
	40-59%	NA	2	12	3	0	17 (24%)
	20-39%	1	7	2	0	3	13 (18%)
	0-19%	6	2	0	0	2	10 (14%)
	Total	7 (10%)	11 (15%)	17 (24%)	13 (18%)	24 (33%)	72 (100%)

Disclosure: T. Pincus, None; **A. D. Luta**, None; **I. Castrejón**, None; **A. Huang**, None; **R. Jain**, None; **S. L. Everakes**, None; **J. A. Block**, None.

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Abstract Number: 136

Physician Patterns of Patient Care in Systemic Lupus Erythematosus: Are We Ordering Unnecessary Tests?

Aman Kugasia[1], Meenakshi Jolly[2], Winston Sequeira[3], Ailda Nika[3], Neha Sehgal[4] and Mary Dollear[5], [1]Internal Medicine, John H Stroger Hospital of Cook County, Chicago, IL, [2]Department of Medicine, Section of Rheumatology, Rush University Medical Center, Chicago, IL, [3]Rheumatology, Rush University Medical Center, Chicago, IL, [4]Indiana University- Bloomington, Valparaiso, IN, [5]Vice President, Lupus Society of Illinois, Chicago, IL

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Background/Purpose: To plan a quality improvement project, we need to understand the practice patterns of physicians. We undertook an online survey of physicians (MDs) (Rheumatologists, Nephrologists and General practitioner) taking care of SLE patients through the Lupus Society of Illinois (LSI) to determine the patterns of medical care provided to SLE patients.

Methods: A 13-item survey was designed to collect data using item development guidelines for surveys. A cover letter explaining the study purpose, improving patient care, was emailed by LSI, and included the link to the survey. This was sent electronically to Rheumatologists and Nephrologists. All data obtained were tabulated; descriptive and stratified data were analyzed using chi square tests and p²0.05 on two-tailed tests.

Results: 86 MD's completed the survey, 97% were Rheumatologists; 46 MDs practiced in academic setting, 27 in private practice, and the remainder in both settings. Mean (SD) age was 55 (12) years. Descriptives for the whole group and stratified by academic or private practice are shown in Table 1. Laboratory tests ordered at each follow up visit were significantly different among academicians as compared to private practice MD's (Table 1). In 8-11% of patients seen in private practice, the laboratory tests ordered routinely at each SLE patient care visit may be unnecessary or avoidable.

Conclusion: There may be avoidable costs associated with laboratory tests ordered at each SLE patient care visit. Physician education about indications for serial routine testing for ANA, ENA and Sjogrens autoantibodies may be indicated to reduce health care costs.

Table 1: Description and Comparison between Groups for Patterns of SLE Care				
Variable	**All MD's**	**Academic**	**Private**	**P value**
N	**86**	**46**	**27**	
Age (mean±SD) years	55±12	56.1 (11.5)	51.7 (11.8)	0.13
Male (%)	56%	24(52%)	15(56%)	0.78
Currently Board Certified (%)	90%	41 (89%)	26 (96%)	0.40
Rheumatologist (%)	97%	45(98%)	27(100%)	1.00
Years out of training in years (%)				
0 to 5	11%	3(7%)	4(15%)	0.56
6 to 10	13%	6(13%)	5(19%)	
11 to 15	12%	5(11%)	3(11%)	
>15	64%	32(70%)	15(56%)	
Practice setting (%)				
Academic	32%			
Private practice	54%			
Both	14%			
Foreign medical graduates (%)	35%	13 (43%)	10(33%)	0.44
Number of hours/week worked				
<10	8%	6(13%)	1(4%)	<0.001
11 to 20	25%	19(41%)	0(0%)	
>20	65%	21(46%)	26(96%)	
Number of SLE patients seen/month				
<10	15%	6(13%)	5(19%)	0.72
11 to 20	29%	12(26%)	8(30%)	
>20	54%	28(61%)	14(50%)	
Average period between SLE visits (%)				
1 to 2 months	12%	7(15%)	2(7%)	0.52
3 to 4 months	81%	36(78%)	24(89%)	
5-6 months	6%	3(7%)	1(4%)	
ANA testing method (%)				
ELISA	28%	8(17%)	12(44%)	0.01
IFA	70%	38(83%)	15(56%)	
Tests ordered at each SLE visit (%)				
ANA	2%	0(0)%	2(8%)	0.13
anti dS-DNA	77%	32(70%)	25(93%)	0.04
anti ENA	5%	0(0)%	3(11%)	0.05
anti SSA/SSB	4%	0(0)%	3(11%)	0.05
C3/C4	82%	40(87%)	21(78%)	0.31
ESR	59%	21(46%)	21(78%)	0.007
C Reactive protein	43%	12(26%)	19(70%)	<0.001
Urinalysis	92%	43(94%)	25(93%)	1
Urine protein/creatinine	36%	20(44%)	8(30%)	0.24
24 hours urine for protein	4%	1(2%)	2(7%)	0.28

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Abstract Number: 137

Willingness to Pay for Highly Effective Drug Treatments in Brazilian Rheumatoid Arthritis Patients

Cleandro Albuquerque[1], Pedro Haddad[2], Vander Fernandes[3], Claudia Marques[4], Sonia Fialho[5], Adriana Kakehasi[6], Fabio Jennings[7], Claiton Brenol[8], Lícia M. H. Mota[9,10], Geraldo Castelar-Pinheiro[2,11], Angela Duarte[12], Iara Giroto[13], Maria Raquel C. Pinto[14], Mariana Toni[15], **Mirhelen Mendes Abreu**[16] and Marcos B. Ferraz[17],

[1]Rheumatology, Hospital Universitário de Brasília - UnB, Brasília, Brazil, [2]Universidade do Estado do Rio de Janeiro - UERJ, Rio de Janeiro, Brazil, [3]Universidade de Cuiabá, Cuiaba MT, Brazil, [4]Disciplina de Reumatologia, Hospital das Clínicas - Universidade Federal de Pernambuco, Recife - PE, Brazil, [5]Rodovia Virgílio Várzea 1510 B, Universidade Federal de Santa Catarina, Florianópolis, Brazil, [6]Rua Astolfo Vieira de Resende, Faculdade de Medicina - UFMG, Belo Horizonte, Brazil, [7]Disciplina de reumatologia, Universidade Federal de São Paulo, Sao Paulo, Brazil, [8]Universidade Federal do Rio Grande do Sul, Porto Alegre RS, Brazil, [9]Rheumatology, University Hospital, Faculty of Medicine, University of Brasília, Brasília/DF, Brazil, [10]Hospital Universitário de Brasília - UnB, Brasília, Brazil, [11]Discipline of Rheumatology, Rio de Janeiro State University, Rio de Janeiro, Brazil, [12]Internal Medicine, Hospital das Clínicas - UFPE, Recife, Brazil, [13]Universidade de Cuiabá, Cuiabá, Brazil, [14]Universidade Federal de Minas Gerais, Belo Horizonte, Brazil, [15]Faculdade de Medicina - UFRGS, Porto Alegre, Brazil, [16]Disciplina de Reumatologia, Universidade Federal do Rio de Janeiro, Rio de Janeiro, Brazil, [17]Universidade Federal de São Paulo, São Paulo, Brazil
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Background/Purpose: Willingness to pay (WTP) is a technique used for valuing health benefits and individual preferences. Brazil's national public health system (Sistema Único de Saúde) grants the population access to costly and effective drugs for the management of rheumatoid arthritis (RA). The aim of this study was to establish WTP valuations for highly effective drug treatments in Brazilian RA patients.

Methods: This cross-sectional multicenter study enrolled adult RA patients (ACR 1987 or ACR/EULAR 2010 criteria) from rheumatology outpatient clinics of the Brazilian public health system. Consecutive patients were asked to reveal the maximum monetary value they would be willing to pay, on a monthly basis, for a hypothetical new intravenous drug offering a 90% improvement in their general health, thus a highly effective drug. Two WTP elicitation tools were used: a payment scale and an open-ended format. Demographic, social and clinical data were gathered from each subject. Disease activity was estimated by DAS28 score and physical function was assessed by HAQ-DI. Descriptive statistics were calculated.

Results: From April 2014 to May 2015, 688 patients (87% female) were assessed in eight Brazilian centers from all over the country. Mean disease duration was 12.7 (8.7) years; mean DAS28 = 3.5 (1.4); mean HAQ-DI = 1.23 (0.8). Subjects had a median of 6 (0 to 21) years of schooling and median household income of US$ 610.3 (0 to 7,909.9) per month. Median WTP values were US$ 22.9 (Q1=11.5; Q3=91.6) on payment scale, and US$ 38.2 (Q1=22.9; Q3=76.3) on open-ended format. On payment scale, 4.2% (28/665) of the respondents assigned zero values for WTP. Overall, 12.4% (83/688) of the subjects added commentaries expressing no willingness to pay at all, regardless of the value (if any) assigned to the elicitation tools. The ratio between median WTP value (open-ended format) and median household income was 6.3%.

Conclusion: This study set WTP valuations of highly effective intravenous drug treatments for chronic, moderately active RA, in outpatient clinics of the Brazilian public health system. The typical population attending to those clinics had low educational and income profile, and had free access to health resources, including medicines, seldom expecting to pay directly for their treatment. The stated WTP values were low, in face of the well known high costs of treating RA patients. Nonetheless, as a proportion of household income, WTP values were in line with the average expenditure of Brazilian families with health resources.

5,AstraZeneca, 5,GlaxoSmithKline, 5,Hospira, 5,Janssen Pharmaceutica Product, L.P., 5,Pfizer Inc, 5,RuiYi, 5,Sanofi-Aventis Pharmaceutical, 5; **A. Duarte**, None; **I. Giroto**, None; **M. R. C. Pinto**, None; **M. Toni**, None; **M. Mendes Abreu**, None; **M. B. Ferraz**, None.

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Abstract Number: 138

Identification and Documentation of Secondary Osteoarthritis in Patients with Primary Inflammatory Arthritides Using a Patient MDHAQ/RAPID3 and a Physician Estimate of Joint Damage to Recognize Patient Complexity and Inform Management Decisions

Kathryn A. Gibson[1], Annie Huang[2], Katherine J. Bryant[3] and Theodore Pincus[2], [1]Liverpool Hospital, Liverpool, Australia, [2]Rheumatology, Rush University Medical Center, Chicago, IL, [3]University of New South Wales, Sydney, Australia

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Background/Purpose: Patients with inflammatory arthritides may have secondary osteoarthritis (OA), which affects decisions concerning clinical management. For example, in one study, about 20% of patients with DAS28 scores >3.2, suggesting that therapy should be intensified according to treat-to-target, did not have intensification because of clinically important joint damage (1). We analyzed patient MDHAQ/RAPID3 scores and physician RheuMetric checklist estimates of damage (as well as overall global estimate, inflammation and distress) to identify and document secondary OA in patients with inflammatory arthritides seen in a busy clinical setting.

Methods: All patients seen at one rheumatology site complete a MDHAQ/RAPID3, and the rheumatologists complete a RheuMetric physician checklist. The MDHAQ includes scores for physical function (0-10), pain (0-10), and patient global estimate (PATGL) (0-10), compiled into a RAPID3 (0-30) score. The 1-page physician RheuMetric checklist includes a standard 0-10 visual analog scale (VAS) for physician global estimate (DOCGL), and 3 further 0-10 VAS for the levels of inflammation or reversible findings (DOCINF), damage or irreversible findings (DOCDAM), and patient distress (e.g. fibromyalgia, depression) (DOCDIS), as well as primary, secondary and tertiary rheumatic diagnoses. Patients with RA, ankylosing spondylitis, psoriatic arthritis, and inflammatory arthritis were classified as "inflammatory arthritides", and were further classified as having or not having comorbid secondary OA. Mean MDHAQ scores and RheuMetric estimates were computed in the two groups; statistical significance was analyzed using 2-tailed t-tests with significance at $p<0.05$.

Results: Overall, 159 patients with inflammatory arthritides were studied, 31 with secondary OA and 128 with no secondary OA. Patients with secondary OA were older ($p=0.043$) and had marginally lower levels of education ($p=0.267$) (Table). All MDHAQ scores were higher in patients with comorbid OA, significantly for physical function ($p=0.004$) and pain ($p=0.043$). RAPID3 scores were 10.8 (moderate severity) in patients with no secondary OA and 14.1 in those with comorbid OA ($p=0.026$). Mean physician damage estimates were 2.9 and 4.2 in patients with no vs comorbid OA ($p=0.013$), and mean physician overall global estimates were 3.6 and 4.5, respectively, in the 2 groups ($p=0.040$). Physician estimates for inflammation and distress did not differ significantly in the 2 groups (Table).

Conclusion: Secondary OA in patients with inflammatory arthritides can be identified and documented on simple MDHAQ and RheuMetric forms in busy clinical settings. This documentation provides evidence of patient clinical complexity and may explain management decisions in certain patients which appear at variance with "treat-to-target" guidelines.

Reference: **1)**Tymms K, et al. Arthritis Care Res (Hoboken). 2014;66:190-6.

Table: Patient MDHAQ scores and physician RheuMetric checklist estimates in patients with inflammatory arthritides who have and do not have secondary osteoarthritis

	All Patients		
	No 2° OA	**Yes 2° OA**	**p value**
N	128	31	
Demographic measures			
Age	56.1	62.5	0.043
Education	11.2	10.4	0.267
Patient MDHAQ/RAPID3 scores			
Physical Function (0-10)	1.9	3.1	0.004
Pain (0-10)	4.8	6.0	0.043
Patient Global Estimate (0-10)	4.1	5.0	0.101
RAPID3 (0-30)	10.8	14.1	0.026
Physician RheuMetric estimates			
Overall Global (0-10)	3.6	4.5	0.040
Inflammation (reversible) (0-10)	2.4	2.1	0.574
Damage (irreversible) (0-10)	2.9	4.2	0.013
Distress (e.g. fibromyalgia) (0-10)	2.7	3.1	0.559

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Abstract Number: 139

One-Year Cost of Etanercept, Adalimumab, and Infliximab per Treated Patient with Chronic Inflammatory Arthritides in US Veterans

Brian Sauer[1], Chia-Chen Teng[2], Tao He[3], Jianwei Leng[4], Chao-Chin Lu[5], Jessica Walsh[6], Neel Shah[7], David J. Harrison[8], Derek Tang[9] and Grant W. Cannon[10], [1]IDEAS Center and Division of Epidemiology, HSR&D SLC VA Medical Center and University of Utah, Salt Lake City, UT, [2]HSR&D SLC VA Medical Center and University of Utah, Salt Lake City, UT, [3]Salt Lake City Veteran Affairs and University of Utah Medical Centers, Salt Lake City, UT, [4]Internal Medicine Division of Epidemiology, HSR&D SLC VA Medical Center and University of Utah, Salt Lake City, UT, [5]Salt Lake City VA and University of Utah, Salt Lake City, UT, [6]Division of Rheumatology, Salt Lake City Veteran Affairs and University of Utah Medical Centers, Salt Lake City, UT, [7]1 Amgen Center Dr, Amgen Inc., Thousand Oaks, CA, [8]Amgen Inc., Thousand Oaks, CA, [9]Amgen, Inc., Thousand Oaks, CA, [10]Division of Rheumatology, Salt Lake City VA Medical Center and University of Utah, Salt Lake City, UT

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Background/Purpose: Understanding the relative cost of tumor necrosis factor inhibitors (TNFi) can improve resource allocation from a payer's perspective. Limited data exists in the VA System on the cost per treated patient across the commonly used TNFi therapies for chronic inflammatory arthritides (CIA). To determine the annual drug and administration cost to the US Department of Veterans Affairs (VA) for etanercept (ETN), adalimumab (ADA), and infliximab (INF) per treated patient targeting rheumatoid arthritis (RA), psoriatic arthritis (PsA), or ankylosing spondylitis (AS).

Methods: The Veterans Health Administration (VHA) databases were used to identify adult patients with ≥1 claim for ETN, ADA, or INF between Jan 1, 2008 and Dec 31, 2011. The patient's first claim for ETN, ADA, or INF ≥1 year following VA enrollment was the index claim and defined the index drug. Patients were required to have a diagnosis of RA (ICD-9-CM 714.0x), PsA (696.0x), or AS (720.0x) and excluded if they had multiple CIAs codes or other conditions (psoriasis, Crohn's disease, ulcerative colitis, juvenile idiopathic arthritis, non-Hodgkin's lymphoma, or chronic lymphocytic leukemia) treated with these agents during the one year prior to and the 30 days following index. Veterans without claims or ≥1 claim(s) for the index drug during the 180 days pre-index period were classified as initiating or continuing patients, respectively. One-year cost of biologics was calculated based on Federal Supply Schedule (ADA) or Big Four (ETN, INF) pricing as of November 2014. Administration costs were based on VA-specific fixed costs per infusion ($169.09) and dispensing costs for subcutaneously administered ($25) biologics.

Results: A total of 10,065 patients with RA (mean age 61.4, ETN: n=5,149; ADA: n=4,155; INF: n=761), 871 patients with PsA (mean age 56.5, ETN: n=490; ADA: n=334; INF: n=47), and 1,511 patients with AS (mean age 51.8, ETN: n=732; ADA: n=675; INF: n=104) were included in the study. The VA incurred greater cost per treated patient for INF users compared with ADA and ETN users across CIAs. Specifically, the one-year cost per treated patient was$15,056, $16,617, and $16,827 for ETN, ADA, and INF in RA; $15,035, $16,016, and $20,465 for ETN, ADA, and INF in PsA; and $14,239, $14,832, and $18,536 for ETN, ADA, and INF in AS. ETN had lower one-year cost per treated patient compared with both ADA and INF across indications in both the cohort of patients initiating and continuing therapy.

Conclusion: Compared with ETN and ADA, INF had higher annual drug and administration cost per treated patient across the investigated CIAs to the US Department of VA.

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Abstract Number: 140

Identifying Psoriatic Arthritis and Ankylosing Spondylitis Patients Responsible for the Highest Costs of Care: Data from a Large US Cohort

Jacqueline B. Palmer, Yunfeng Li, Vivian Herrera and Minlei Liao, Novartis Pharmaceuticals Corporation, East Hanover, NJ

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Background/Purpose: The economic burden of psoriatic arthritis (PsA) and ankylosing spondylitis (AS) in the biologics era is not well understood in the US population. Using a large US medical and pharmacy claims database, we investigated the characteristics, healthcare utilization, costs and treatments of PsA patients with high medical costs.

Methods: Claims data from the MarketScan Commercial and Medicare Supplemental Databases were used to stratify PsA and AS patients into 2 groups based on overall costs: ≥90% quantile (top 10% cost group) and <90% quantile (bottom 90% cost group). Patients included were aged: ≥18 years with ≥2 diagnostic claims for PsA (n=10,832) or AS (n=4,288) between October 1, 2011, and September 30, 2012 (first diagnosis is index date) and were continuously enrolled with medical and pharmacy benefits for 12 months before and after the index date. Baseline demographics, individual comorbidities and an elixhauser comorbidity score were captured. Direct costs included hospitalizations, emergency room and office visits, and pharmacy costs. The Wilcoxon rank sum test was conducted on continuous variables and the chi-square test on categorical variables.

Results: The study included 10,832 PsA patients and 4,388 AS patients. For the PsA top 10% (N=1,083) and bottom 90% groups (N=9,740), mean all-cause medical costs were about 13 times higher $30,591±$51,862 vs. $2,277± $4,138 respectively. Biologics costs were only about 2 times higher $27,254±$18,026 and $12,595±$14,581, respectively. For the AS top 10% (n=428) and bottom 90% groups (n=3,860), mean all-cause medical costs were 20 times higher $42,703±$78,942 vs. $2,491±$4,561, respectively; mean biologics costs were 2 times higher $18,261± $16,048 vs. $10,373±$13,552, respectively. In the PsA cohort, the top 10% cost group was older (mean age 54.7±10.8 y vs 51.6±11.9 y; *P<0.01*), had higher rates of diabetes mellitus (26.5% vs 15.2%, P<0.01), hypertension (43.2% vs 31.4%), hyperlipidemia (29.8% vs 23.8%), and ischemic heart disease (14.4% vs 5.8%) all *P*<0.01. The high cost group also had a higher rate of biologics use (83.4% vs 58.7%; *P<0.01*), compared with the bottom 90% cost group, respectively. The top 10% AS cost group, similarly, was older (mean age 52.1±12.6 y vs 48.7±13.4 y; *P<0.01)* and had higher Elixhauser comorbidities scores (mean, 2.9±2.3 vs 1.8±1.5; *P<0.01*) compared to the bottom 90% cost group, respectively. They also had higher biologics (70.4% vs 50.5%) and oral DMARDS (26.6% vs 21.3%) use all *P*≤0.01, compared with the bottom 90% cost group, respectively.

Conclusion: PsA and AS patients with high costs of care were generally older and more affected by comorbidities than their counterparts with lower costs. Medical costs seem to be the biggest drivers in the high cost subgroup of patients. In AS patients medical costs were almost 20 times higher in the high cost group. PsA high cost patients had 13 times higher medical costs. This study highlights that the majority of patients with AS and PsA have relatively low disease management costs, however there are a subgroup of more costly patients that may require more individual management due to high comorbidity and biologic use.

Disclosure: J. B. Palmer, Novartis Pharmaceutical Corporation, 3; **Y. Li**, Novartis Pharmaceutical Corporation, 3; **V. Herrera**, Novartis Pharmaceutical Corporation, 1,Novartis Pharmaceutical Corporation, 3; **M. Liao**, Novartis Pharmaceutical Corporation, 3.

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Abstract Number: 141

Improved Follow-up of Hypertension in Rheumatology Patients: Results of a Pilot

Christie M. Bartels[1], Edmond Ramly[2], Heather Johnson[3], Yingqi Zhao[1], Zhanhai Li[4], Patrick McBride[3], Kristin Steffen Lewicki[1] and Diane Lauver[5], [1]Department of Medicine, University of Wisconsin (UW) School of Medicine and Public Health (SMPH), Madison, WI, [2]Industrial and Systems Engineering, University of Wisconsin-Madison College of Engineering, Madison, WI, [3]Cardiology/Medicine, University of Wisconsin School of Medicine and Public Health, Madison, WI, [4]University of Wisconsin (UW) School of Medicine and Public Health (SMPH), Madison, WI, [5]University of Wisconsin-Madison School of Nursing, Madison, WI
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Background/Purpose: Hypertension is the most common and most modifiable cardiovascular disease (CVD) risk factor, yet it is uncontrolled in ½ of US adults. Hypertension management protocols are predicted to save more lives than any other systems intervention. However, hypertension protocols are untested in most specialty clinics. Our prior work reported that rheumatologists addressed high blood pressures (BP) in <1/3 of visits, highlighting the need for effective population management strategies given the link between many rheumatologic conditions and CVD. Our objective was to pilot a protocol intervention to facilitate timely primary care follow up for patients with elevated BP readings at rheumatology visits.

Methods: We implemented a pre-post intervention pilot at three academic rheumatology clinics. All adult (≥18 years-old) rheumatology patient visits with BP ≥140/90 during the intervention period (Nov 2014-May 2015) were compared to all pre-intervention visits with BP ≥140/90 (Jan 2012-Sept 2014). Intervention elements included: (1) Defining elevated BP (≥140/90) and rheumatologic CVD risk for the medical assistant/nursing staff (45 min education) and patients (BP brochure), (2) electronic health record (EHR) alerts for staff to re-measure BPs if ≥140/90 (3) EHR prompting brief patient education and timely follow-up order if 2nd BP confirmed ≥140/90, and (4) individualized feedback for patients (BP recorded on brochure) and staff (monthly audit feedback). We assessed the primary outcome of timely (<4 weeks per Medicare metric) blood pressure follow-up in primary care among patients who received regular primary care in this system allowing EHR tracking. We performed a multivariate logistic regression to compare the bivariate timely primary care follow up outcome pre-post intervention controlling for baseline sociodemographics, comorbidities, visit utilization and rheumatology clinic.

Results: We compared the post-intervention cohort of 649 visits with elevated BPs (≥140/90) to 4,818 visits pre-intervention with elevated BPs. Pre-intervention, <2% of visits had BPs re-measured, versus 67% of post-intervention visits, $p<0.001$. Among patients receiving primary care within the system, 42% of post-intervention patients with confirmed high BP completed timely primary care follow-up versus 29% pre-intervention, $p=0.002$. In multivariate logistic regression, the post-cohort had nearly two-fold higher odds of timely follow-up (OR 1.9, 1.4-2.5).

Conclusion: Our intervention supported usual care rheumatology clinic staff to improve timely BP follow up as a population management strategy to reduce CVD risk in rheumatology patients. We plan to examine the impact of the intervention on patients' awareness of CVD risk, subsequent BP management, and hypertension control. Future work will adapt and test this intervention in other specialties and healthcare systems.

Table 1. Pilot intervention visit-level outcomes with Odds Ratios and 95% CI's

	Pre-Intervention n=4,818	Post-Intervention n=649	p
BP Re-measurement	<2% (77/4818)	67% (433/649)	<0.001
Timely Primary Care Follow-up (<4 weeks)	29% (740/2526)	42% (53/125)	<0.002
Unadjusted OR Timely Follow Up	OR=1.8	(1.2-2.6)	<0.001
Adjusted OR Timely Follow Up	OR=1.9	(1.4-2.5)	<0.001

*Adjusted model controls: sociodemographics, comorbidity, utilization & clinic.

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Abstract Number: 142

Exploration of General Practioners' Difficulties with Methotrexate and Anti-TNF Therapies in Routine Practice

Elise Berthet[1], Virginie Moiroud[2], Marion De Rosa[2], **Martin Soubrier**[3] and Sylvain Mathieu[4], [1]Rheumatology, CHU Gabriel Montpied, Clermont-Ferrand, France, [2]Médecine Générale, CHU Gabriel Montpied, Clermont-Ferrand, France, [3]Rheumatology department CHU Clermont-Ferrand, Clermont-Ferrand, France, [4]Rheumatology Department, CHU clermont-Ferrand, Clermont-Ferrand, France

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Background/Purpose:

Chronic inflammatory arthritis affects around 1% of the general population. Disease-modifying drugs like methotrexate (MTX) and in second-line anti tumor necrosis factor (anti-TNF) therapy are increasingly prescribed, which sometimes puts general practitioners (GP) on the frontline of management for these treatments and their adverse effects. The aim of this study was to explore GPs difficulties with MTX and anti-TNF therapies in routine practice.

Methods:

A questionnaire was sent to 1190 GPs across our local region. We collected and compiled their characteristics, their difficulties in routine practice, and their expectations in terms of facilitating management for these treatments.

Results:

Response rate was 24.9%, i.e. 296 responses, including 11 GPs who refused to participate. Our analysis thus focuses on a dataset of 285 respondents: 57% (n=162) are men, 36% (n=103) are urban-community GPs, 55% (n=157) work in

a medical group clinic. Of the 230 GPs following patients on MTX (81%), 113 report difficulties with treatment-related management, chiefly with how to manage infectious episodes (30% of respondents), the onset of side effects (23% of respondents) and drug interactions (31% of respondents). GPs with less than 10 years in practice experience are more difficulties than GPs with more years in practice (66.7% *vs* 46.6% for 10–30 years in practice and 33.9% for 30-plus years in practice; p=0.002). Just 22% (n=41) of GPs surveyed claimed they are ready to initiate MTX therapy. Of the 189 respondent GPs (66%) following patients on anti-TNF, 127 report exactly the same difficulties but with a higher frequency (infectious complications: 53%; side effects: 29%; drug interactions: 39%). 57.2% of GPs (163/285) perceive anti-TNF therapy have a positive risk–benefit ratio, and 36,2% (105/285) expressed no opinion. 80% of the respondents to this survey (228/285) want dedicated further training.

Conclusion:

This study found that over half of GPs following patients on MTX or anti-TNF therapy experience difficulties managing for these treatments. Dedicated further training on these treatments is a key priority for action.

Disclosure: E. Berthet, None; **V. Moiroud**, None; **M. De Rosa**, None; **M. Soubrier**, None; **S. Mathieu**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/exploration-of-general-practioners-difficulties-with-methotrexate-and-anti-tnf-therapies-in-routine-practice

Abstract Number: 143

Fiber Optic Intubation in Patients with Rheumatoid Arthritis Who Had a Surgical Procedure

Gurjot Basra[1], Marylou Cardenas-Turanzas[2], Tayab Andrabi[3], Katy Elizabeth French[3], Bobby Bellard[3], William A Murphy Jr.[4], Maria A. Lopez-Olivo[5] and Maria E. Suarez-Almazor[5], [1]Baylor College of Medicine, Houston, TX, [2]Department of General Internal Medicine, The University of Texas, MD Anderson Cancer Center, Houston, TX, [3]Anesthesiology, The University of Texas, MD Anderson Cancer Center, Houston, TX, [4]Radiology, The University of Texas, MD Anderson Cancer Center, Houston, TX, [5]General Internal Medicine, The University of Texas, MD Anderson Cancer Center, Houston, TX

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Background/Purpose: Fiber optic intubation is the preferred method of airway management during anesthetic procedures for patients with RA. The purpose of our study was to determine the frequency of fiber optic intubation in surgical procedures of patients with RA and cancer.

Methods: All RA patients who attended a preoperative anesthesia consultation at a large cancer center from 2007 to 2014 were eligible for this study. We included adults (> 18 year of age) with diagnosis of RA made by a physician or patients with self-reported history of RA and disease modifying anti-rheumatic drugs (DMARDS) use, including prednisone (past or current). Only first procedure in this time period per patient was included. Cervical spine imaging within 1 year prior to procedure was included. All subluxation reported were reviewed by radiologist for second review and to document to appropriate distances.

Results: In relation to cancer, we found 409 patients (83.4%) had malignancies and 122/409, 29.8% had two or more

cancers diagnosed since admission. A total of 81/490, 16.5% had non-malignant tumors such as thyroid or pancreatic cysts, primary hyperparathyroidism, large lipomas, or benign breast nodules. The patients were followed-up for a mean of 34.5 months (95% CI 32.2 – 36.9). A total of 99 deaths occurred during the period of observation and 3/99 (3%) deaths occurred within 30 days from the date of the procedure. None had spinal cord compression complications. Among those who died, the median age was 67 years (range 36 – 86). Patients who died within 30 days from date of surgery had a median age of 71 years (range 63 – 85) and all three had major surgical procedures: esophagectomy, cystoprostatectomy, or wide neck dissection. Age was not a factor associated with mortality when both groups were compared. Hospital mortality (deaths occurring ≤ 30 days after admission) was 0.6%. None of the patients had spinal cord compression.76% of the patients had imaging done. 12.7% had subluxations C1-C7; 5.3% had RA related C1- C2 subluxation; 8.2% had C2-C7 subluxation. We found different types of RA subluxations: anterior atlanto-axial distance (AAD) in 21 patients was abnormal (3- 13.2 mm); posterior atlanto-axial distance (PAAD) was also abnormal (18-26.8 mm); subaxial distance in 4 patients ranged between 5mm to 16 mm; cranial settling was observed in 3 patients. Other spine abnormalities found were erosions, osteoarthritis, spondylolisthesis, spontaneous fusions, and post-operative fusions. The most common type of intubation was endotracheal in 387 (79.1%). Only 66 out of 492 (13.6%) had fiber optic intubation. There was evidence of neurological post-operative neurological injury in one case (0.2%).

Conclusion: Although fiber optic intubation could reduce the risk of neurological complications in patients with RA and cancer undergoing surgical procedures, few received this airway management. Patients with RA and cancer could be the target of an intervention to educate providers and reduce the risk of neurological complications during surgical procedures. More research is needed to consider this to standardize the airway management in these patients.

Disclosure: G. Basra, None; **M. Cardenas-Turanzas**, None; **T. Andrabi**, None; **K. E. French**, None; **B. Bellard**, None; **W. A. Murphy Jr.**, None; **M. A. Lopez-Olivo**, None; **M. E. Suarez-Almazor**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/fiber-optic-intubation-in-patients-with-rheumatoid-arthritis-who-had-a-surgical-procedure

Abstract Number: 144

One-Year Costs Following Switching Versus Dose-Escalation Among Prevalent Tumor Necrosis Factor Inhibitors Used for Rheumatoid Arthritis

Tao Gu[1], **Derek Tang**[2], Gaurav Deshpande[1], Debra F Eisenberg[1] and David J. Harrison[3], [1]HealthCore, Wilmington, DE, [2]Amgen, Inc., Thousand Oaks, CA, [3]Amgen Inc., Thousand Oaks, CA

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Background/Purpose: Switching a biologic treatment or escalating biologic doses are common approaches used upon biologic treatment failure. The objective of this study was to estimate the one-year costs after switching to another tumor necrosis factor inhibitor (TNFi) versus increasing the dose of the same TNFi among patients with rheumatoid arthritis (RA).

Methods: This was a retrospective cohort study using administrative data for individuals in the HealthCore Integrated Research Databases (HIRD^{SM}). Initially, patients were included if they aged 18-63 with ≥1 claim for INF or ADA

between Jul 1, 2009 and Jan 31, 2013, had ≥1 claim for RA during the 6 months prior to INF/ADA initiation, continuously enrolled between 6 months prior to and 12 months following INF/ADA initiation, and were not exposed to RA-related biologics 6 months prior to INF/ADA initiation or another condition for which RA-related biologics were approved to treat. Subsequently, INF/ADA patients switching to ADA/INF or ETN, or increasing the dose of the current drug in the subsequent year after treatment initiation were identified for further evaluation. Dose-escalation was defined for infliximab as having ≥120% of the expected infusions or an increase of ≥100 mg in dose; and for adalimumab as reaching a 40 mg weekly dose. Patients initiating ETN were not included in this analysis because dose-escalation in ETN has not been allowed per the approved US label. Patients who both dose-escalated and switched to a biologic of interest during the one-year follow-up were classified based on the first event. Costs were obtained from plan and patient paid amounts for biologic drug and administration and adjusted to 2013 dollar value.

Results: Of those who initiated ADA (n=1,437), 103 (7.2%) patients switched to INF/ETN and 103 (7.2%) patients increased their dose. Of those who initiated INF (n=539), 18 (3.3%) patients switched to ADA/ETN and 195 (36.2%) patients increased their dose. The average age was 48.6 (±10.2 [SD]) years and 74.7% were female. ADA initiators who dose-escalated on average incurred $8,843 higher costs compared with those who switched to another TNFi ($30,425 vs. $21,582, p<0.0001). INF initiators who dose-escalated on average incurred $9,022 higher costs compared with those who switched ($27,506 vs. $18,483, p=0.0007).

Conclusion: RA patients on ADA or INF incurred significantly higher costs when they dose escalated compared with switching to a new TNFi. The cost implications of increasing dose should be a consideration when making biologic treatment modifications in RA.

Disclosure: T. Gu, Amgen Inc., 5; **D. Tang**, Amgen Inc., 3,Amgen Inc., 1; **G. Deshpande**, Amgen Inc., 5; **D. F. Eisenberg**, Amgen Inc., 5; **D. J. Harrison**, Amgen Inc., 1,Amgen Inc., 3.

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Abstract Number: 145

Economic Burden of Switching to an Anti-Tumor Necrosis Factor (anti-TNF) Versus a Non-Tumor Necrosis Factor (non-TNF) Biologic Therapy Among Patients with Rheumatoid Arthritis

Zheng-Yi Zhou[1], **Jenny Griffith**[2], Arijit Ganguli[2], Ella Xiaoyan Du[1] and Keith Betts[1], [1]Analysis Group, Inc., Boston, MA, [2]AbbVie Inc., North Chicago, IL

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Background/Purpose: Real world studies comparing the healthcare utilization of anti-TNFs vs. non-TNFs as the next alternative after the failure of the first anti-TNF are scarce. This study aimed to compare healthcare costs, resource utilization, and treatment patterns in RA patients who discontinued an anti-TNF and subsequently switched to an alternative anti-TNF versus those who switched to a non-TNF.

Methods: Adult patients who had ≥2 RA diagnoses and used at least one anti-TNF (adalimumab, etanercept, infliximab, golimumab, or certolizumab) on or after initial RA diagnosis were identified from a large commercial

claims database. Patients who switched to an alternative anti-TNF or a non-TNF (abatacept, rituximab, or tocilizumab) following the initial anti-TNF during 2006-2012 were selected into anti-TNF and non-TNF cohorts. The switching date was defined as the index date. Patient and disease characteristics during the 6-month pre-index (baseline) period were compared. All-cause and RA-related healthcare costs and resource utilization over a 12-month post-index (study) period were compared between the two cohorts using multivariable two-part gamma models and negative binomial models, respectively, adjusted for age, gender, region, insurance plan, index year, comorbidities, co-medications, initial anti-TNF and treatment duration. Treatment patterns (switching and discontinuation) were compared using Cox proportional hazards models.

Results: A total of 2,904 and 934 patients were included in the anti-TNF and the non-TNF cohort, respectively. At baseline, patients in the anti-TNF cohort (vs. non-TNF cohort) were younger (50 vs. 51 years, p<0.01), had less comorbidity burden (Charlson Comorbidity Index 1.3 vs. 1.4, p<0.01), and had a shorter initial anti-TNF duration (1.0 vs. 1.3 years, p<0.01). During the study period, all-cause costs were significantly lower for the anti-TNF cohort compared to the non-TNF cohort with medical ($11,474 vs. $15,846; adjusted diff = $4,590; p<0.01) and pharmacy ($24,433 vs. $29,294; adjusted diff =$5,524; p<0.01) costs contributing to the total cost differences ($35,907 vs. $45,139, adjusted diff = $9,654; p<0.01) (Table 1). RA-related costs were also lower in the anti-TNF cohort compared to the non-TNF cohort (Table 1). Patients in the anti-TNF cohort were likely to have fewer outpatient visits (all-cause: 23.4 vs. 30.2 visits/patient/year, adjusted incident rate ratio = 0.77; p<0.01). Inpatient admissions and emergency department utilization as well as discontinuation and switching rates were not significantly different between the two cohorts.

Conclusion: For patients discontinuing anti-TNF therapy, switching to an alternative anti-TNF was associated with lower medical and pharmacy costs, fewer outpatient visits, and similar treatment patterns, as compared to switching to a non-TNF biologic.

Table 1. Healthcare costs (2014 USD) during the 12-month post-index period

	Average Healthcare Costs (mean ± SD)		Adjusted Difference in Average Healthcare Costs (95% CI)
	Anti-TNF switch N = 2,904	Non-TNF switch N = 934	Anti-TNF switch vs. Non-TNF switch
All-cause costs			
Total costs (medical + pharmacy)	35,907 ± 27,608	45,139 ± 31,342	-9,654 (-11,592 ; -7,645)*
Total medical costs	11,474 ± 24,713	15,846 ± 26,222	-4,590 (-6,485 ; -2,948)*
Inpatient	3,845 ± 20,220	4,570 ± 18,238	-874 (-2,229 ; 512)
Emergency department	377 ± 2,207	343 ± 967	8 (-70 ; 92)
Outpatient	7,252 ± 10,083	10,932 ± 14,333	-3,798 (-4,837 ; -2,923)*
Total pharmacy costs	24,433 ± 12,328	29,294 ± 15,272	-5,524 (-6,758 ; -4,251)*
Index drug	17,412 ± 11,568	22,110 ± 14,159	-5,732 (-6,863 ; -4,607)*
RA-related other drug	4,859 ± 8,623	4,706 ± 8,850	133 (-617 ; 774)
Other drug	2,162 ± 3,185	2,478 ± 4,386	-77 (-376 ; 216)
RA-related costs			
Total costs (medical + pharmacy)	25,678 ± 19,111	32,643 ± 18,804	-7,016 (-8,572 ; -5,579)*
Total medical costs	4,004 ± 15,416	6,707 ± 11,959	-3,205 (-4,480 ; -2,310)*
Inpatient	1,683 ± 14,392	1,739 ± 9,706	-66 (-1,066 ; 778)
Emergency department	62 ± 0,871	53 ± 356	-7 (-55 ; 28)
Outpatient	2,259 ± 4,832	4,915 ± 6,316	-2,894 (-3,497 ; -2,416)*
Total pharmacy costs	21,674 ± 11,551	25,937 ± 14,213	-4,561 (-5,692 ; -3,352)*
Index drug	16,978 ± 11,412	21,327 ± 13,727	-4,845 (-5,914 ; -3,692)*
RA-related other drug	4,696 ± 8,428	4,610 ± 8,770	155 (-598 ; 801)

* P-value < 0.05.

Disclosure: Z. Y. Zhou, Analysis Group, which has received consulting fee from AbbVie to partner on this research, 3; **J. Griffith**, AbbVie, 3,AbbVie, 1; **A. Ganguli**, AbbVie, 3,AbbVie, 1; **E. X. Du**, Analysis Group, Inc., 3; **K. Betts**, AbbVie Inc., 5.

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Abstract Number: 146

Rates of Lipid Testing and Statin Prescription Filling Among U.S. Medicaid Recipients with SLE, 2007-2010

Sarah Chen[1], Michael A. Fischer[2], Hongshu Guan[3], Medha Barbhaiya[4] and Karen H. Costenbader[5], [1]Beth Israel Deaconess Medical Center, Boston, MA, [2]Division of Pharmacoepidemiology and Pharmacoeconomics, Brigham and Women's Hospital, Boston, MA, [3]Rheumatology, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, [4]Internal Medicine, Weill Cornell Medical College, New York, NY, [5]Rheumatology, Immunology and Allergy, Brigham and Women's Hospital, Harvard Medical School, Boston, MA

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Background/Purpose: Given high cardiovascular disease (CVD) risks in SLE patients, lipid testing and statin prescription are widely advocated for those with elevated risks. We examined rates of lipid testing and statin prescription filling among SLE patients within Medicaid in recent years.

Methods: Within Medicaid Analytic eXtract (MAX), containing billing claims from 2007-10 for Medicaid patients from the 29 most populated US states, we identified patients aged 18-65 years with prevalent SLE (>3 ICD-9 codes of 710.0, >30 days apart). We required 6 months of continuous Medicaid enrollment (baseline period) prior to the 3rd code (index date). Baseline data included age, year, sex, race/ethnicity, US region of residence. Subjects were followed from index date until death, Medicaid disenrollment or end of follow-up (12/31/2010). Within claims, CPT codes identified lipid testing and NDC codes identified statin prescription filling. We calculated rates per 1000 person-years for lipid testing and statin prescription filling, and rate ratios (with 95% CIs) to compare rates between sociodemographic groups. We tested for trends in lipid testing and statin prescription rates over time using Cochrane Armitage tests.

Results: Of 37,999 patients with prevalent SLE, 93% were female. Mean age was 41.2 (+ 12.1) years. Race/ethnicity were: 42% Black, 36% White, 16% Hispanic, 2% Native American. Mean follow-up was 19.4 (+ 12.7) months; 746 patients died. In the entire cohort, 11,969 patients (32%) had >1 lipid testing and 6885 (18%) had >1 filled statin prescription. Lipid testing did not differ by sex, but statin prescription was slightly more frequent among men than women. The highest rates of lipid testing were seen among Hispanic and Asian patients (vs. White), older patients (ages 55-65 vs. younger), those living in the West (vs. other regions), and those receiving corticosteroids (vs. not). (**Table**) The highest rates for filled statin prescriptions were observed in older patients (ages 55-65 vs. younger), and those receiving corticosteroids. Black and Native American patients had lower rates of both lipid testing and statin prescription (vs. White patients). No geographic variation in statin prescribing was seen. Rates of both lipid testing (from 235.1 [227.3, 243.2] to 474.6 [450.9, 499.5] per 1000 person-years, p trend <0.0001) and statin prescription (from 81.7 [77.7, 86.0] to 286.4 [268.4, 305.5] per 1000 person-years, p trend <0.0001) increased significantly between 2007-10.

Conclusion: In this large SLE cohort, 32% of patients had >1 lipid testing and 18% filled > 1 statin prescription between 2007-10. Rates of both lipid testing and statin prescription increased significantly during this time. Rates were higher among older patients and those on corticosteroids. Given high CVD and mortality risks among Black and Native American SLE patients, it is noteworthy that these groups had low rates of lipid testing and statin prescriptions.

Table. Rate Ratios for Lipid Testing and Statin Prescription Filling among Medicaid patients with SLE in the U.S., 2007-2010

	Lipid Testing*		Statin Prescriptions**	
Patient Group	**Rate Ratio**	**95% CI**	**Rate Ratio**	**95% CI**
Female	Ref	Ref	Ref	Ref

Sex	**Female**	Ref.	Ref.	Ref.	Ref.
	Male	0.92	0.85-1.01	**1.27**	**1.15-1.41**
Race/Ethnicity	**White**	Ref.	Ref.	Ref.	Ref.
	Black	0.97	0.92-1.02	**0.85**	**0.80-0.91**
	Hispanic	**1.35**	**1.27-1.43**	1.01	0.92-1.10
	Asian	**1.63**	**1.45-1.83**	1.17	0.99-1.38
	Native	**0.78**	**0.61-0.98**	**0.70**	**0.50-0.97**
Age	**18-34**	**0.64**	**0.60-0.68**	**0.22**	**0.20-0.24**
	35-44	**0.81**	**0.76-0.86**	**0.42**	**0.39-0.46**
	45-54	**0.93**	**0.87-0.98**	**0.73**	**0.68-0.79**
	55-65	Ref.	Ref.	Ref.	Ref.
US Region	**West**	Ref.	Ref.	Ref.	Ref.
	Northeast	**0.77**	**0.73-0.82**	0.99	0.90-1.08
	South	**0.77**	**0.73-0.82**	0.96	0.89-1.04
	Midwest	**0.65**	**0.61-0.69**	1.09	0.99-1.19
Receiving Corticosteroids	**Yes**	Ref.	Ref.	Ref.	Ref.
	No	**0.41**	**0.39-0.43**	**0.42**	**0.39-0.45**
Calendar year	**2007**	**0.50**	**0.46-0.53**	**0.29**	**0.26-0.31**
	2010	Ref.	Ref.	Reference	Reference

*CPT codes for lipid screening (80061, 82465, 83700, 83701, 83715, 83716, 83721, 84478, 83718 (Morrato EH, *Arch Pediatr Adolesc Med*, 2010).

**NDC codes used to identify statin use (Bateman BT, *BMJ*, 2015).

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Abstract Number: 147

Fatigue, Coping, Sleeping Disorders and Productivity Were Still Not Frequently Reported in Rheumatoid Arthritis Trials Published in 2014-2015: A Systematic Literature Review

Levent Kilic[1], Abdulsamet Erden[1], Laure Gossec[2] and Umut Kalyoncu[1], [1]Rheumatology, Hacettepe University Faculty of Medicine, Ankara, Turkey, [2]Rheumatology, Pitié Salpetriere Hospital, Paris, France
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Background/Purpose: In a systematic literature review (SLR), frequency of patients reported outcomes (PROs) related with rheumatoid arthritis (RA) was evaluated between 2005 and 2007 (1). Relatively low frequent outcome measures at this SLR were fatigue, utility, psychological status, coping, sleeping disturbance, productivity losses, wellbeing and leisure. Although pain and function are essential domains for patients, priority of patients also include fatigue,

emotional well-being, sleep, coping and physical well-being (2). Objective of this study was to assess frequency and changing trend of PROs related with RA at the last 2 years.

Methods: Literature search was performed in PUBMED MEDLINE database on 01 January 2015. Publications were identified through a search that used the following exploded MeSH term: (''arthritis, rheumatoid'' (MeSH)) with a limitation to ''humans'', ''all adults: 19+ years'', ''English'', ''published in the last 2 years'' and ''clinical trials''. Publications were limited to articles referenced in PUBMED in the last 2 years. Demographic characteristics of patients, study design, treatments assessed and all PROs assessed. **Results** were compared with previous SLR (1).

Results:Of the 479 publications identified by the literature search, 250 were included in the analysis. Of the 250 publications, 113 (45.2%) were randomized controlled trials. One hundred-forty different tools were reported in this SLR. Function (83.4% vs 68.0%), pain (55.9% vs 40.0%), patient global assessment (63.3% vs 49.2%) and quality of life (19.2% vs 18.4%) were still essential PROs. Frequency of fatigue (13.7 vs 14.4), psychological status (7.3 vs 9.6), productivity losses (5.5 vs 6.4) and sleeping disturbance (1.8 vs 2.4) were not changed over time. On the other hand, frequency of morning stiffness (26.6 vs 10.0), coping (6.4% vs 2.0%) and utility (16.5 vs 5.2) were decreased. Although fatigue assessed with valid tools (VAS 7.2%, FACIT 4.8%), other less frequent domains (psychological status, productivity losses, sleeping disturbance, coping) did not have constant and specific tools for RA.

Conclusion: Eight years later, we still did not determine any significant change about PROs in RA trials. Priority of patients, for instance fatigue, psychological status, productivity losses, sleeping disturbance, coping were not sufficiently appear RA trials. One of the major challenge of those PROs was also related with tools. Tools about psychological status, productivity losses, sleeping disturbance and coping had high heterogeneity and low specificity for RA.

Ref:

1. Kalyoncu U, Dougados M, Daurès JP, Gossec L. Reporting of patient-reported outcomes in recent trials in rheumatoid arthritis: a systematic literature. Ann Rheum Dis. 2009;68:183-90.
2. Gossec L, Dougados M, Rincheval N et al. Elaboration of the preliminary Rheumatoid Arthritis Impact of Disease (RAID) score: a EULAR initiative. Ann Rheum Dis. 2009;68:1680-5.

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Abstract Number: 148

An Evaluation of the Virtual Monitoring Clinic, a Novel Nurse-Led Telemonitoring Service for Monitoring Patients with Stable Rheumatoid Arthritis

Li-Ching Chew[1], Julian Thumboo[1], Hui Yang[2] and Xiaohui Xin[3], [1]Department of Rheumatology and Immunology, Singapore General Hospital, Singapore, Singapore, [2]Division of Medicine, Singapore General Hospital, Singapore, Singapore, [3]Academic Clinical Programme, Division of Medicine, Singapore General Hospital, Singapore, Singapore

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Background/Purpose: To study the clinical and patient reported outcomes of the Virtual Monitoring Clinic (VMC), which is novel nurse-led telemonitoring cum pharmacy medication home delivery service for monitoring stable Rheumatoid Arthritis (RA) patients treated with disease-modifying antirheumatic drugs (DMARDs).

Methods: Patients with stable RA enrolled into the VMC programme were followed up prospectively. The primary outcomes evaluated at 1-year were: Disease Activity Score-28 (DAS28), Routine Assessment of Patient Index Data 3 (RAPID3), and patient satisfaction score assessed using an 11-point Likert scale.

Results: Of the 251 patients enrolled, 186 completed 1year of follow-up. 2.3% of the annual workload from the specialist outpatient clinic was freed up as a result of the VMC programme. Statistically significant improvement was seen in the mean satisfaction score (7.70 to 8.16, $p<0.05$), with 63% of the patients opting for VMC as their preferred mode of follow-up. There was a marginal increase in mean DAS28 and RAPID3 scores (2.56 to 2.78 ($p<0.05$) and 5.28 to 6.03 ($p<0.05$) respectively). However, given that at 1-year more than 60% (72.0% based on DAS28 scores and 63.4% based on RAPID3 scores) of the patients' condition remained stable or had improved, and the disease was in remission or low activity for the majority of patients (73.1% measured by DAS28 and 53.2% measured by RAPID3), our assessment was that the VMC preserved or improved RA disease activity for the majority of patients.

Conclusion: The VMC is an effective and well-accepted approach for the management of patients with stable RA.

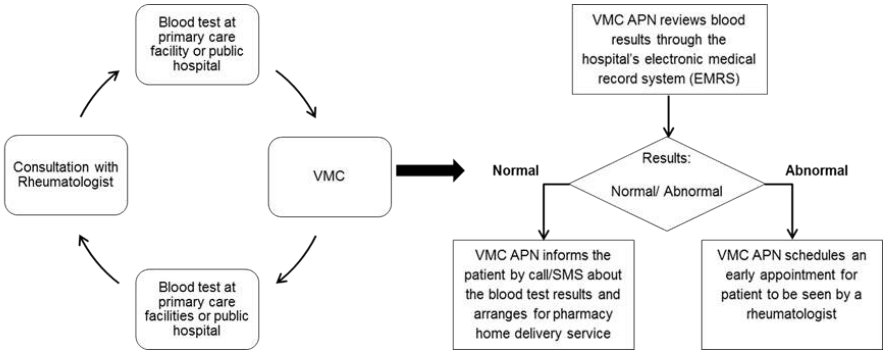

Figure 1. Flowchart illustrating the Virtual Monitoring Clinic (VMC) Workflow

Table 1. Change in the DAS28

	Follow-up DAS28				
Baseline DAS28	Remission	Low Activity	Moderate Activity	High Activity	Total
Remission	66 (65.3)	23 (22.8)	11 (10.9)	1 (1.0)	101 (54.3)
Low Activity	13 (26.5)	19 (38.8)	17 (34.7)	0 (0)	49 (26.3)
Moderate Activity	5 (14.3)	10 (28.6)	20 (57.1)	0 (0)	35 (18.8)
High Activity	0 (0)	0 (0)	1 (100)	0 (0)	1 (0.5)
Total	84 (45.2)	52 (28.0)	49 (26.3)	1 (0.5)	186 (100)

Values are reported as number and percentages.

DAS28, Disease Activity Score 28 joint count.

Table 2. Change in the RAPID3

	Follow-up RAPID3				
Baseline RAPID3	Near Remission	Low Severity	Moderate Severity	High Severity	Total
Near Remission	34 (47.2)	19 (26.4)	19 (26.4)	0 (0)	72 (38.7)
Low Severity	13 (28.3)	11 (23.9)	17 (37.0)	5 (10.9)	46 (24.7)
Moderate Severity	8 (14.3)	11 (20.4)	30 (55.6)	5 (9.3)	54 (29.0)
High Severity	1 (7.1)	2 (14.3)	8 (57.1)	3 (21.4)	14 (7.5)
Total	56 (30.1)	43 (23.1)	74 (39.8)	13 (7.0)	186 (100)

Values are reported as number and percentages.

RAPID3, Routine Assessment of Patient Index Data 3.

Disclosure: L. C. Chew, None; **J. Thumboo**, None; **H. Yang**, None; **X. Xin**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/an-evaluation-of-the-virtual-monitoring-clinic-a-novel-nurse-led-telemonitoring-service-for-monitoring-patients-with-stable-rheumatoid-arthritis

Abstract Number: 149

Characteristics of Patients Diagnosed with Systemic Lupus Erythematosus (SLE) Initiating Treatment with Belimumab in a US Commercially Insured Database: 2010-2014

Deanna Hill[1], Hong Kan[2], Peter Egger[3], David J. Chang[4], Amanda Eudy[1,5], Joe Maskell[3] and Karen H. Costenbader[6], [1]Worldwide Epidemiology, GlaxoSmithKline, Collegeville, PA, [2]Value Evidence and Outcomes, GlaxoSmithKline, Research Triangle Park, NC, [3]Worldwide Epidemiology, GlaxoSmithKline, Stockley Park, United Kingdom, [4]US Medical Affairs, GlaxoSmithKline, Philadelphia, PA, [5]Gillings School of Global Public Health, University of North Carolina, Chapel Hill, NC, [6]Rheumatology, Immunology and Allergy, Brigham and Women's Hospital, Harvard Medical School, Boston, MA

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Session Time: 9:00AM-11:00AM

Background/Purpose: Belimumab, a B-lymphocyte stimulator, was FDA-approved March 2011 for the treatment of adult patients with active, autoantibody-positive SLE receiving standard of care (SOC) medications. Using data from a large, privately-insured US administrative claims database, we sought to identify and characterize a cohort of SLE patients who initiated belimumab treatment.

Methods: A retrospective cohort analysis was conducted in the US Truven Health MarketScan® Commercial Claims and Encounters Database (study ID 204489). Patients were aged 18-64 years at first belimumab infusion (index date) during the study period (2010 - end of available 2014 data). SLE diagnosis was based on ICD-9 code 710.0 documented prior to/on index date. We included patients with complete medical and pharmacy benefits ≥6 months prior to and ≥12 months after the index date. Demographic and clinical characteristics, SOC medication use, healthcare utilization and estimates of SLE disease and flare severity during the 6 month pre-index period were evaluated. Belimumab discontinuation was defined as ≥84 day gap in infusions.

Results: N=762 patients met the inclusion criteria. Mean age at index date was 44 years (SD 11) and 94% were female. Pre-index period diagnosed co-morbidities included musculoskeletal (67%), cardiovascular (41%), central nervous system (39%), mucocutaneous (27%), hematologic (22%) and lupus nephritis (7%) disease. Medications prescribed in the pre-index period included oral corticosteroids (73%), antimalarials (66%), immunosuppressants (60%) and NSAIDs (30%); not mutually exclusive. In the pre-index period, ~80% of patients were prescribed ≥2 SOC medications (excluding NSAIDs), and the mean prednisone-equivalent dosage for the cohort was 7.3 mg/day (SD 13.7); 34% had a mean prednisone-equivalent dose ≥7.5 mg/day. Healthcare utilization in the 6-month pre-index period included ≥1 inpatient visit (12%), emergency department visit (28%) and outpatient procedure (47%) or laboratory test (48%). A disease severity algorithm estimated mild, moderate, and severe disease in the pre-index period for 32%, 55%, and 13% of patients, respectively. Ninety-four percent experienced ≥1 flare in the pre-index period, with the most severe flare classified as mild (17%), moderate (71%) and severe (12%). Mean number of belimumab infusions in the post-index period was 12 (SD 9), with mean 11 months of belimumab use (SD 9). Belimumab was discontinued by

25% of patients during the ≥12-month post-index period, and 60% of patients received belimumab for ≥6 months.

Conclusion: In this large sample of belimumab treatment initiators, there was a high frequency of oral corticosteroid/immunosuppressant use in the 6 months prior to initiating belimumab treatment. Polytherapy was the norm, but ~20% were on either one medication or none. Prior to belimumab treatment, most patients had moderate to severe disease, and nearly all experienced ≥1 flare. More than 50% of patients continued belimumab treatment for ≥6 months. Reasons for discontinuation were not ascertainable in this data source, and future analyses are planned to assess the comparative effectiveness of adding belimumab to SOC treatment.

Disclosure: D. Hill, GlaxoSmithKline, 1,GlaxoSmithKline, 3; **H. Kan**, GlaxoSmithKline, 1,GlaxoSmithKline, 3; **P. Egger**, GlaxoSmithKline, 1,GlaxoSmithKline, 3; **D. J. Chang**, GlaxoSmithKline, 1,GlaxoSmithKline, 3; **A. Eudy**, GlaxoSmithKline, 3; **J. Maskell**, GlaxoSmithKline, 5; **K. H. Costenbader**, GlaxoSmithKline, 5.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/characteristics-of-patients-diagnosed-with-systemic-lupus-erythematosus-sle-initiating-treatment-with-belimumab-in-a-us-commercially-insured-database-2010-2014

Abstract Number: 150

A Preliminary Consensus on Core Outcome Domains for Total Joint Replacement Clinical Trials: An Omeract-Based Study

Jasvinder A. Singh[1] and Michael Dohm[2], [1]University of Alabama at Birmingham, Birmingham, AL, [2]Orthopaedic Surgery, Univ of Arizona, Tucson, AZ, Tucson, AZ

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Background/Purpose:

Outcomes Measures in Rheumatology Trials (OMERACT) has developed a framework based on the WHO's International Classification of Functioning, Disability, and Health (ICF) conceptual model. It proposes four core areas to assess the impact of disease, namely Death, Life Impact, Resource Use/Economic Impact and Pathophysiological Manifestations and within each area to select one or more domains applicable to every condition of interest. The objective of this study was to perform a survey of important stakeholders to develop preliminary recommendations for core domains to be reported in TJR clinical trials.

Methods:

We surveyed two groups of experts, who rated potential core domains (mapped to Outcomes Measures in Rheumatology Trials (OMERACT) filter 2.0 framework) for their relevance to TJR clinical trials during the 2014 American Academy of Orthopaedic surgeons [AAOS] and the 2014 OMERACT meetings. Ratings were on a 1 to 9 scale, 1-3 indicating domain of limited importance, 4-6 being important, but not critical domain, and 7-9 being critical domain.

Results:

17 stakeholders at the AAOS and 19 stakeholders at OMERACT meeting completed the survey. At the two meetings,

86% and 36% were arthroplasty researcher/surgeons, 0% and 10% were patients and 58% and 31% were 55 years and older, respectively. The following domains were rated as candidates for critical core domains by both groups, with a median score of 7 and above (median score from AAOS vs. OMERACT): Joint pain (9 vs. 9), functional ability (8 vs. 9), joint-specific quality of life (8 vs. 7), patient satisfaction (7 vs. 8), revision surgery (8 vs. 7), adverse events (9 vs. 8), death (9 vs. 7.5), serious adverse events (8.5 vs. 8), reoperation (8 vs. 8), and cost (7 vs. 7).

Table 1. Preliminary Core Areas/Domains for TJR Clinical Trials	AAOS Median [IQR]	OMERACT Median [IQR]	Both combined Median [IQR]
Ratings for the Main Domains to be reported in every TJR clinical trial			
Joint Pain	9 [8, 9]	9 [9, 9]	9 [8, 9]
Function or functional ability (ability to function in society, work; work productivity, employability; disability; work disability)	8 [8, 9]	9 [8, 9]	9 [7, 9]
Generic Quality of life (including fatigue, sleep, mood, stress, anxiety, depression)	6 [4, 9]	7 [5.75, 8.25]	7 [5, 8]
Joint-specific Quality of life	8 [7, 9]	7 [5, 7.25]	7 [6, 8]
Patient Satisfaction (satisfaction with the outcome, satisfaction with the procedure)	7 [5, 8]	8 [7, 9]	7.5 [5.75, 9]
Patient expectation of surgical outcome	5 [4, 8]	5 [4, 7]	5 [4, 7]
Revision surgery	8 [6, 9]	7 [7, 9]	8 [6, 9]
Adverse events	9 [8, 9]	8 [7, 9]	8 [7, 9]
Death	9 [8, 9]	7.5 [5, 9]	8 [6, 9]
Ratings for Additional domains for consideration			
Serious Adverse events	8.5 [7, 9]	8 [8, 9]	8 [7, 9]
Cardiac Adverse events (e.g. Myocardial infarction, unstable angina, worsening of congestive heart failure)	7.5 [5.75, 8]	6 [5.5, 7.5]	6 [6, 8]
Pulmonary Adverse events (e.g. Pneumonia, Pulmonary Embolism)	7 [5.75, 8]	6 [5.5, 7]	7 [6, 8]
Reoperation	8 [5.5, 9]	8 [7, 8]	8 [6.25, 8]
Cost	7 [4, 8]	7 [6, 7]	7 [6, 8]
Health care utilization (e.g. length of stay)	5 [3, 7.25]	7 [6, 7]	6 [5, 7]
Readmission (e.g. 90-day readmission)	6.5 [5, 8.75]	7 [6, 7]	7 [6, 9]

Conclusion:

This study lays the foundation for future work by identifying preliminary core domain set for TJR clinical trials. This core domain set will be further vetted with multi-stakeholder input. It will be used for the development of TJR clinical trial core measurement set.

Disclosure: J. A. Singh, Takeda, Savient, 2,Takeda, Savient, merz, Regeneron, Allergan, Crealta, Bioiberica, 5; **M. Dohm**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/a-preliminary-consensus-on-core-outcome-domains-for-total-joint-replacement-clinical-trials-an-omeract-based-study

Abstract Number: 151

Residual Synovitis in Ultrasound (US) Is Associated with an Evolution Towards Rheumatoid Arthritis (RA) in Patients with Inflammatory Polyarthralgia without ANTI-Citrulinated Antibodies (ACPA)

Pascal Zufferey[1,2,3], Claudia Rebell Jr.[4], Alexandre Dumusc[5], Mauro lucini[4], Juerg Hains[6], Alexander K. So Sr.[7] and Charles Benaim[8], [1]Rheumatology, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland, [2]Pierer Decler, Chuv, Lausanne, Switzerland, [3]Rhu /Dal .Chuv, Rheumatology, Lausanne, Switzerland, [4]DAL, RHU/CHUV, lausanne, Switzerland, [5]RHU/CHUV, lausanne, Switzerland, [6]DAL, RHU/CHUV, Lausanne, Syria, [7]Service De Rhumatologie, CHUV, Lausanne, Switzerland, [8]DAL, MPR, Lausanne, Switzerland
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Background/Purpose:

In ACPA positive patients, subclinical synovitis as observed by US has been demonstrated in pre RA patients and seems to be predictive for future development of RA [1]. No such study has yet been conducted in ACPA negative patients.

The primary aim of the study was to assess the value of the US as a screening tool to detect early joint involvement in ACPA- patients complaining of polyarthralgia and to analyse whether such subclinical synovitis is predictive for the future development of an inflammatory disease, in particular RA. The secondary aims were to look for additional clinical and biological predictors of RA development in ACPA- patients

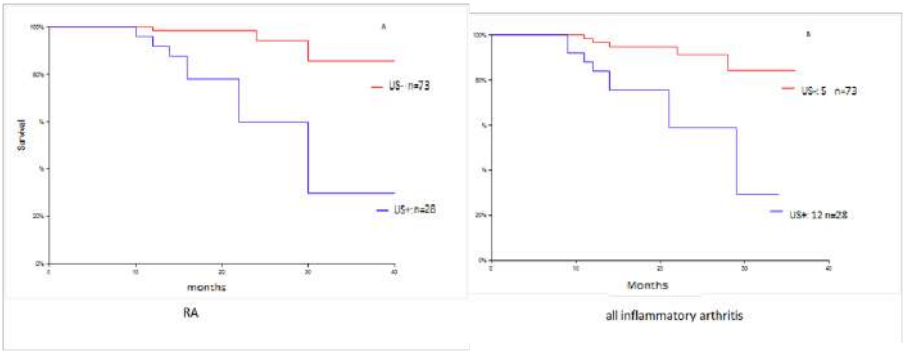
Methods:

This is a retrospective observational study of 101 consecutive ACPA- patients with poly-arthralgia who did not meet the ACR / EULAR 2010 criteria for RA or classification criteria for another inflammatory rheumatology disease before the US examination. These patients were all seen in investigation in our ambulatory unit between 2009 and 2013. To detect significant US synovitis, we applied the criteria of the SONAR score validated among RA patients and controls [2](total B mode score >8, > 2 synovitis: grade 2). For the follow-up, the same diagnostic criteria as baseline were used.

Results:

At baseline (30%) had significant synovitis according to the SONAR criteria. The mean (SD) follow-up time was 18 (7) months in both groups. 17 patients developed a clear inflammatory arthritis (11 RA, 6 another inflammatory arthritis disease). Significant US synovitis at baseline was significantly associated with evolution to RA: 7/28 versus 4/69 (<0.005), sensitivity: 64% specificity: 76%, LR: 2.7. Elevated CRP and clinical synovitis appeared to be additional

predictors of such an evolution. Figure depicts the arthritis free curves (a: before RA, b: before all inflammatory arthritis) according to the presence or not of US synovitis at baseline



Conclusion:

Our study suggests that US can be used as a predictor for the evolution to RA in patients presenting inflammatory polyarthralgia without ACPA.

References: 1: Ann Rheum Dis 2010; 69:417–419, 2: Joint Bone Spine. 2014 Oct;81(5):426-32

Disclosure: P. Zufferey, None; **C. Rebell Jr.**, None; **A. Dumusc**, None; **M. Iucini**, None; **J. Hains**, None; **A. K. So Sr.**, None; **C. Benaim**, None.

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Abstract Number: 152

Anti-CCP Positive Patients without Clinical Synovitis Progress If Ultrasound Positive

Jackie L. Nam[1], Elizabeth M.A. Hensor[1], Laura Hunt[1], Philip G. Conaghan[2], Richard J. Wakefield[1] and Paul Emery[3], [1]NIHR-Leeds Musculoskeletal Biomedical Research Unit and Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds, Leeds, United Kingdom, [2]University of Leeds & NIHR Leeds Musculoskeletal Biomedical Research Unit, Leeds, United Kingdom, [3]NIHR-Leeds Musculoskeletal Biomedical Research Unit, University of Leeds, Leeds, United Kingdom

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SESSION INFORMATION

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Session Title: Imaging of Rheumatic Diseases Poster I: Ultrasound, Optical Imaging and Capillaroscopy

Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose:

To determine whether ultrasound can identify which anti-cyclic citrullinated peptide (anti-CCP) antibody positive

patients with musculoskeletal (MSK) symptoms and without clinical synovitis progress to inflammatory arthritis (IA).

Methods:

In a prospective study, anti-CCP positive patients with new nonspecific MSK symptoms and no clinical synovitis underwent imaging with ultrasound of 32 joints (wrists, MCPs and PIPs of the hands and MTPs of the feet) and were monitored for the development of IA. Grey scale (GS) and power Doppler (PD) findings were scored 0-3 using a standard semi-quantitative method. Cox proportional hazards regression was used to measure associations between (1) the baseline ultrasound findings and subsequent diagnosis of IA using the set of 32 joints and (2) the baseline ultrasound findings within each joint and subsequent development of clinical synovitis within that joint.

Results:

Consecutive patients (n=136; mean age 51 years, 100 females) were followed up for median 18.3 months (range 0.1-79.6). At baseline, 96% had GS and 30% had PD signal in ≥1 joint(s). IA developed in 57(42%) patients after median 8.6 months (range 0.1-52.4). Patients with PD≥2 were at higher risk of progression to IA than those without PD [75% (15/20) vs. 31.9% (29/91), hazard ratio (HR) (95% CI) = 3.7(2.0, 6.9), p<0.001], and progression occurred earlier (median 7.1 vs. 52.4 months). Patients who scored GS ≥2 in the wrists and/or hands at baseline were at higher risk of developing IA than those with no GS in those joints [HR (95% CI) = 2.3(1.0, 4.9), p=0.038]. At the individual joint level, the trend for progression to clinically-detected synovitis was more significant [HR (95% CI) = 31.3(15.6, 62.9), p<0.001 for PD≥2 and HR (95% CI) = 9.4(5.1, 17.5), p<0.001 for GS≥2].

Conclusion:

Ultrasound features of joint inflammation may be detected in anti-CCP positive patients with MSK symptoms without clinical synovitis. Our findings suggest that ultrasound findings predict progression to clinical disease. The risk of clinically-detected synovitis is particularly high in joints showing power Doppler signal.

Disclosure: J. L. Nam, None; **E. M. A. Hensor**, None; **L. Hunt**, None; **P. G. Conaghan**, None; **R. J. Wakefield**, None; **P. Emery**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/anti-ccp-positive-patients-without-clinical-synovitis-progress-if-ultrasound-positive

Abstract Number: 153

Utility of Ultrasound Synovitis Assessment As a Predictor of Flares in Clinically Inactive Joints

Tomas Cazenave[1], Christian A. Waimann[2], Natalia Zamora[1], Gustavo Citera[1] and Marcos G. Rosemffet[1], [1]Rheumatology, Instituto de Rehabilitación Psicofísica, Buenos Aires, Argentina, [2]Rheumatology, Hospital Dr. Hector Cura, Olavarria, Argentina

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Session Time: 9:00AM-11:00AM

Background/Purpose: Several ultrasound (US) studies have shown a high frequency of inflammation in clinically

inactive joints of rheumatoid arthritis (RA)patients. There is controversy in the conduct to be followed in these situations, raising the question of whether a change in the therapeutic approach can prevent the clinical flare of this joints. ***Objective:***To determine the utility of US assessment of clinically inactive joints to predict short-term joint flares in patients with RA.

Methods: :A cohort study including patients with diagnosis of RA (ACR-EULAR 2010 criteria) was designed. Patients were evaluated at baseline and at 3 months, including clinical and ultrasonographic examination of 28 joints. Power Doppler (PD) signal and grayscale (GS) synovitis were graded from 0 to 3, according to standards OMERACT, yielding an overall US score (US-global) resulting from addition of both scores (range 0 -6, 6 being the highest degree of US synovitis). At baseline, the joints were classified as active vs. inactive according to clinical examination (swollen vs. non-swollen). Baseline inactive joints of patients who did not change their treatment were identified. Primary endpoint was defined as the presence of joint clinical flare (development of joint swollening in physical examination in a previously non-swollen joint) at three months follow-up. To evaluate the ability of US to predict joint flare multivariable logistic regression using the US score at baseline as the independent variable adjusted by the presence or absence of joint pain was developed. Based on the multivariate model, the area under the curve (AUC) and the probability of having a joint flare for the different levels of basal US involvement was calculated.

Results: We included a total of 49 patients. The disease duration was 8 ± 5 years, 85% were women, with a mean age of 53 ± 10 years.The mean of DAS28 was 4.8 ± 1.5. A total of 1372 joints were assessed, of which 1079 (79%) were clinically evaluated inactive. These joints showed a mean overall US score of 0.6 ± 0.8 (PD = 0.1 ± 0.3; GS = 0.5 ± 0.6). In patients without treatment variations between visits (n=24; 49%), 518 non-swollen joints at baseline were analyzed separately. Of these joints, 28 (5%) developed a flare at 3 months. In multivariate analysis the presence of pain and the grade of US involvement at baseline were associated with greater likelihood of joint flare (OR: 3.5; 95%CI=1.1-11.4 and OR: 2; 95%CI=1.4-2.9, respectively). **Figure 1**shows the probability of developing joint flare at 3 months according to the US baseline score and the presence of pain.

US Score	Probability of flare	
	Pain present	Pain absent
6	87%	65%
5	77%	48%
4	62%	32%
3	45%	19%
2	29%	10%
1	17%	5%

Conclusion: US evaluation could be helpful for decision-making in non-swollen joints. The likelihood of developing a flare at three months varies from 5% to 87% depending on the US findings and the presence of joint pain.

Disclosure: T. Cazenave, None; **C. A. Waimann**, None; **N. Zamora**, None; **G. Citera**, None; **M. G. Rosemffet**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/utility-of-ultrasound-synovitis-assessment-as-a-predictor-of-flares-in-clinically-inactive-joints

Abstract Number: 154

Clinical Features of Fibromyalgia in Patients with Rheumatoid Arthritis Predict Lower Power Doppler Scores on Ultrasound

Aneela Mian[1], Khaldoun Chaabo[2], Julekha Wajed[3], Bruce W. Kirkham[4] and Toby Garrood[5], [1]Academic Rheumatology, King's College London, London, United Kingdom, [2]Rheumatology, Guy's and St Thomas NHS Trust, London, United Kingdom, [3]Rheumatology, Guys' and St Thomas' NHS Trust, London, United Kingdom, [4]Rheumatology,

Guy's and St. Thomas' Foundation Hospital NHS Trust, London, United Kingdom, [5]Rheumatology, Guy's and St. Thomas' NHS Foundation Trust, London, United Kingdom

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Background/Purpose: Up to 20% of patients with RA have coexisting fibromyalgia(FM). This can make treatment decisions challenging in clinical practice as disease activity scores can be high despite limited clinical evidence of active synovitis. Recent work has suggested that a tender joint count (TJC) minus swollen joint count (SJC)(each out of 28) of ≥7 identifies patients with co-existing FM ('fibromyalgic' RA) with high sensitivity and specificity. Ultrasound (US) of joints particularly power Doppler is predictive of outcomes in RA patients. The aim of this study was to determine whether RA patients with active disease also meeting existing criteria for fibromyalgia had significantly less joint inflammation on ultrasound than those who did not.

Methods: 47 RA patients with DAS28 scores >2.6 were recruited. Patients completed questionnaires including the Widespread Pain Index(WPI), PHQ9(depression), GAD7(anxiety), PHQ15(somatisation), FACIT-fatigue, HAQ and global health assessment VAS. The TJC, SJC, Symptom Severity Score(SSS) and the number of FM soft-tissue tender points were recorded by a physician. Patients underwent a 22-joint US scan by a second blinded physician of the wrists, MCPJs and PIPJs bilaterally. Grey scale(GS) and power Doppler(PD) scores were recorded for each joint on a semiquantitative scale (0-3) for each patient. FM patients were grouped according to the ACR 1990 classification criteria and TJC-SJC >7 individually and in combination. Differences between groups were tested using the Mann-Whitney U test. Significance was set at $p<0.05$

Results: GS scores were significantly lower in patients meeting ACR (GS score 16.7,p=0.025), TJC-SJC (16.7,0.034) or both criteria (15.4, 0.022) than in those who did not (21.8). PD scores were not significantly different for the individual criteria but when combined the scores for patients meeting both criteria were significantly lower compared with patients not meeting these criteria (PD score 2.94 vs 8.33, p=0.028). Significantly higher scores were seen for depression, anxiety, disability and somatization scores in patients meeting either or both FM criteria compared with those who did not.

Conclusion: Our findings show that RA patients who meet the 1990 ACR criteria for FM and who have a TJC minus SJC of ≥7 have significantly lower levels of synovitis on GS and PD US. This suggests that it may be possible to use clinical measures to identify patients not in DAS28 clinical remission into those with higher or lower levels of synovitis on US. Thus there may be a role for composite tools in clinical practice to stratify patients into those who may benefit from continued escalation of immunosupression and those who may benefit from alternative management strategies focussing on improving levels of depression, anxiety and fatigue. We are currently conducting a larger study to explore this further.

	TJ – SJ count ≥7 Pollard et al n=26	≥11 Fibromyagic tender points ACR 1990 classification n=20	Both n=17
Grey scale	16.7 (6.96) p=0.034	16.7 (8.61) p=0.025	15.41 (6.38) p=0.022
Power Doppler	4.44 (5.067) p=0.080	5.11 (10.10) p=0.094	2.94 (3.09) p=0.028

Table 1. Mean score, (SD), p value

Disclosure: A. Mian, None; **K. Chaabo**, None; **J. Wajed**, None; **B. W. Kirkham**, None; **T. Garrood**, None.

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Abstract Number: 155

Absence of Clinical and Ultrasound Activity of Hand and Foot: Is That Possible?: Experience in an Argentinian Rheumatoid Arthritis Cohort

María Victoria Martire[1], Gloria Crespo[2], Diego Puente Trigo[2], Vanesa Duarte[2], Maritza Manzano[2], Leandro Carlevaris Sr.[2], Anastasia Secco[2], Lida Santiago[2], Marta Mamani[2] and Lucila Marino Claverie[2], [1]Hospital Bernardino Rivadavia, Buenos Aires, Argentina, [2]Rheumatology, Hospital Bernardino Rivadavia, Buenos Aires, Argentina

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Session Time: 9:00AM-11:00AM

Background/Purpose: Currently, one of the main goals of rheumatoid arthritis (RA) treatment is to attain remission. Stricter criteria as CDAI, SDAI ACR/ EULAR Boolean have been proposed. Patients with RA, who achieve clinical remission may have residual joint inflammation, which can be detected by ultrasonography (US). However the degree of agreement that stricter criteria present with US findings in patients in remission is not well known, especially on feet assessment. The aim of this study was to assess subclinical synovitis by US and to evaluate the degree of agreement between the remission status as measured by different strict criteria and the absence of activity using US of hands and toes.

Methods: US examination was performed consecutively on 100 patients with RA fullfiling 2010 ACR EULAR criteria

that were in clinical remission (DAS 28-ESR<2.6) for at least 6 months. We evaluated if strict criteria were met (CDAI, SDAI, Boolean, Boolean without VAS general health patient). A rheumatologist specialized in musculoskeletal US, blinded to clinical activity, performed a systematic evaluation on grayscale and power Doppler technique with multifrequency linear transducer (10-18MHz) in longitudinal and transverse sections. The radiocarpal joint, second and third metacarpophalangeal, second and third proximal interphalangeal in both hands and second to fifth metatarsophalangeal joints were assessed bilaterally. Absence of activity was defined as absence of exudative synovitis grade II and III, and power Doppler grade II and III in all the evaluated joints.

Results: 100 US were performed in 1.800 joints of 100 patients. 80% were women (n = 80) and the mean age was 52.7 standar desviation (SD) 12. There were no differences in age, sex, disease duration, treatment, or rheumatois factor andanti-citrullinated protein antibodies positivity between patients with ultrasound activity and without it. The mean DAS28-ESR was 2 SD 0,47, 22% were receiving biologic therapy, the mean disease duration was 8.5 IQR 5-14 years and the mean duration of remission was 11.3 months SD 6. Table 1 shows the remission status in the evaluated patients. Table 2 shows the degree of agreement among different criteria and the absence of activity assessed by ultrasound of hands and feet.

Table 1

	Ultrasound with activity in hands	Ultrasound with activity in foot	Ultrasound without activity in hands	Ultrasound without activity in foot
	n (%)	n (%)	n (%)	n (%)
Remission by B*oolean* n:45	26 (58)	8 (18)	19 (42)	37 (82)
Remission by *Boolean* without VAS n:71	30 (42)	18 (25)	41 (58)	53 (75)
Remission by SDAI n:70	34 (48)	19 (27)	36 (52)	51 (73)
Remission by CDAI n: 62	51 (82)	17 (27)	11 (18)	45 (72)

Table 2

Remission criteria	Agreement	CI 95
Boolean ACR/EULAR	k- 0,1	-0,3-0,09
Boolean without VAS	k 0,4	O,22-0,53
SDAI	k 0,27	0,11-0,42
CDAI	k -0,07	-0,21-0,07

Conclusion: Residual joint inflammation was detected by US in patients in clinical remission on both hands and feet. There was no agreement between the remission status measured by the strict criteria and the absence of activity assessed by US of hands and feet in this study population. Only acceptable agreement was found in hands, with the Boolean criteria that excludes VAS.

Disclosure: M. V. Martire, None; **G. Crespo**, None; **D. Puente Trigo**, None; **V. Duarte**, None; **M. Manzano**, None; **L. Carlevaris Sr.**, None; **A. Secco**, None; **L. Santiago**, None; **M. Mamani**, None; **L. Marino Claverie**, None.

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Abstract Number: 156

Usefulness of the Stricter Remission Criteria for Assessing the Absence of

Subclinical Activity in Rheumatoid Arthritis

María Victoria Martire[1], Maritza Manzano[2], Diego Puente Trigo[2], Vanesa Duarte[2], Gloria Crespo[2], Leandro Carlevaris Sr.[2], Anastasia Secco[2], Marta Mamani[2], Lida Santiago[2] and Lucila Marino Claverie[1], [1]Hospital Bernardino Rivadavia, Buenos Aires, Argentina, [2]Rheumatology, Hospital Bernardino Rivadavia, Buenos Aires, Argentina

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Background/Purpose: It has been seen that patients with rheumatoid arthritis (RA) who achieve remission measured by DAS28 persist with subclinical synovitis in hands and toes when evaluated by ultrasound (US). Unfortunately US is not available in every rheumatology center. Recently, strict criteria like the CDAI, SDAI and ACR EULAR Boolean have been proposed. Therefore it would be interesting to know the accuracy of each set of crteria for assessing the absence of sublinical activity. The aim of this study was to evaluate the accuracy of CDAI, SDAI and ACR EULAR Boolean criteria in RA patients using as gold standard the absence of activity detected by US.

Methods: US examination was performed consecutively on 100 patients with RA fulfilling 2010 ACR EULAR criteria and that were in clinical remission (DAS 28-ESR<2.6) for at least 6 month. Then we evaluated if strict criteria were met (CDAI, SDAI, Boolean). A rheumatologist specialized in musculoskeletal US, blinded to clinical activity, performed a systematic evaluation on grayscale and power Doppler technique with multifrequency linear transducer (10-18MHz) in longitudinal and transverse sections. The radiocarpal joint, second and third metacarpophalangeal, second and third proximal interphalangeal in both hands and second to fifth metatarsophalangeal joints were assessed bilaterally. It was considered as a case if absence of grade II-III exudative synovitis and / or Power Doppler II-III using OMERACT's definitions was found. We defined controls as the ones with at least one of these signs of activity. We evaluated the sensitivity, specificity, positive likelihood ratio, positive predictive value (PPV) and negative predictive value (NPV).

Results: One hundred US were performed in 1.800 joints of 100 patients. 80% were women (n = 80) and the mean age was 52.7 SD 12 and the mean DAS28-ESR was 2 SD 0,47. There were no differences in age, sex, disease duration, treatment, or rheumatoid factor and anti-citrullinated protein antibodies positivity between patients with ultrasound activity and without it. 22% were receiving biologic therapy and the mean disease duration was 8.5 IQR 5-14 years and the mean duration of remission was 11.3 months SD 6. Of the US screening 58 didn't have signs of activity and 42 had synovitis and / or PD grade II-III. Table 1 shows the status of activity and Table 2 shows the results.

Table 1

	Ultrasound without activity in hands and toes
	n (%)
Remission *by Boolean* ACR/EULAR criteria n:45	16 (36)
No Remission by *Boolean* ACR/EULAR criteria n:55	26 (47)
Remission by SDAI n:70	29 (41)
No remission by SDAI n:30	13 (43)
Remission by CDAI n: 62	26 (41)
No remission by CDAI n:38	16 (42)

Table 2

	Sensitivity	Specificity	PPV	NPV	Positive LR
	% (CI 95)	% (CI 95)	% (CI 95)	% (CI 95)	
Boolean	38 (29-48)	50 (40-60)	36 (26-45)	53 (43-63)	0,8 (0,5-1,2)
ACR/EULAR					
CDAI	62 (53-71)	38 (28-47)	42 (32-52)	58 (48-68)	1 (0,8-1,3)
SDAI	69 (60-78)	29 (20-38)	41 (32-51)	57 (47-66)	1 (0,8-1,3)

Conclusion: We found that in this population, which is in remission by DAS28, no one of the three set criteria is of great value for detecting the absence of activity when using US as gold standard.

Disclosure: M. V. Martire, None; **M. Manzano**, None; **D. Puente Trigo**, None; **V. Duarte**, None; **G. Crespo**, None; **L. Carlevaris Sr.**, None; **A. Secco**, None; **M. Mamani**, None; **L. Santiago**, None; **L. Marino Claverie**, None.

Abstract Number: 157

Agreement Between DAS28, ACR/EULAR, SDAI, CDAI and Ultrasound Remission in Patients with Rheumatoid Arthritis Receiving Biological Treatment in Routine Care

Cecilie Heegaard Brahe[1], Lene Terslev[2], Simon Krabbe[3], Mikkel Østergaard[4], Henrik Rogind[5], Hanne Jensen[6], Annette Hansen[7], Jesper Nørregaard[8], Søren Jacobsen[9], Karen Ellegaard[10], Viktoria Fana[1], Lars Juul[7], Tuan K. Huynh[8], Dorte V. Jensen[7], Natalia Manilo[6], Karsten Heller Asmussen[6], Per Brown-Frandsen[9], Søren Tobias Torp-Pedersen[11], Niels Steen Krogh[12] and Merete Lund Hetland[2], [1]Center for Rheumatology and Spine Diseases, Copenhagen Center for Arthritis Research (COPECARE), Center for Rheumatology and Spine Diseases, Rigshospitalet - Glostrup, University of Copenhagen, Denmark, Glostrup, Denmark, [2]Copenhagen Center for Arthritis Research (COPECARE), Center for Rheumatology and Spine Diseases, Rigshospitalet - Glostrup, University of Copenhagen, Denmark, Glostrup, Denmark, [3]Center for Rheumatology and Spine diseases, Copenhagen Center for Arthritis Research (COPECARE), Center for Rheumatology and Spine Diseases, Rigshospitalet - Glostrup, University of Copenhagen, Denmark, Glostrup, Denmark, [4]Center for Rheumatology and Spine Diseases, Glostrup Hospital, Copenhagen Center for Arthritis Research (COPECARE), Center for Rheumatology and Spine Diseases, Rigshospitalet - Glostrup, University of Copenhagen, Denmark, Glostrup, Denmark, [5]Center for Rheumatology and Spine Diseases, Center for Rheumatology and Spine Diseases, Rigshospitalet - Glostrup, University of Copenhagen, Denmark, Glostrup, Denmark, [6]Department of Rheumatology, Copenhagen University Hospital at Frederiksberg-Bispebjerg, Denmark, Frederiksberg, Denmark, [7]Department of Rheumatology, Copenhagen University Hospital at Gentofte - Herlev, Denmark, Gentofte, Denmark, [8]Department of Rheumatology, Copenhagen University Hospital at Nordsjælland, Denmark, Hillerød, Denmark, [9]Center for Rheumatology and Spine Diseases, Rigshospitalet - Glostrup, University of Copenhagen, Denmark, Glostrup, Denmark, [10]Department of rheumatology, Frederiksberg-Bispebjerg Hospital, The Parker Institute, Copenhagen, Denmark, [11]Department of Radiology, Copenhagen University Hospital at Glostrup, Denmark, Glostrup, Denmark, [12]ZiteLab ApS, Copenhagen, Denmark

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Background/Purpose: Different remission criteria are available for patients with rheumatoid arthritis (RA). None of the criteria includes imaging remission, even though studies have shown that many RA patients in sustained clinical remission have synovitis detectable by ultrasound (US), i.e. grey scale synovial hypertrophy and/or Doppler signal in the synovium.

We aim to investigate the agreement between different clinical remission criteria and remission defined by US in patients with RA receiving biological therapy in routine care.

Methods: A total of 117 RA patients in sustained remission (i.e. DAS28 $\leq$2.6 for $\geq$ 1 year and no radiographic progression the last year) on biological therapy were recruited. All patients underwent US of 24 joints for grading of grey scale (GS) synovial hypertrophy (0-3) and synovial Colour Doppler activity (CD) (0-3). Imaging remission was defined in two ways: either GS=0 and CD=0 in all 24 joints, or GS$\leq$1 and CD=0 in all 24 joints.

Results: Baseline characteristics are shown in table 1. At baseline patients received the following disease-modifying antirheumatic drugs (DMARDs): methotrexate (MTX; 72%), sulphasalazine (3%), azathioprine (2%), leflunomide (2%), no DMARDs (21%) and the following treatment with biological therapy: abatacept (2%), adalimumab (28%), certolizumab (3%), etanercept (28%), golimumab (3%), infliximab (27%), tocilizumab (9%).

For patients fulfilling DAS28 remission criteria, US defined remission was present in 9% (GS=0 and CD=0 in all 24 joints, termed “very strict” US remission) or 29% (GS $\leq$ 1 per joint and CD=0 in all 24 joints, termed “strict” US remission) and 24% had CD>1 in at least 1 joint (table 1). For patients fulfilling other criteria for clinical remission (CDAI, SDAI and ACR/EULAR remission), patients were in very strict US remission in 12%, 12% and 10%, respectively and in strict US remission in 28%, 29% and 20%, respectively. CD activity > 1 in at least 1 joint was present in 22%, 25% and 22% of patients, respectively. The anatomical distribution of the GS synovial hypertrophy was 31% in metacarpophalangeal joints, 27% in metatarsophalangeal joints, 19% in wrists, 10% in knees, 7% in elbows and 6 % in ankles. Thus, 33% of the total GS synovial hypertrophy was observed in the feet, which are not included in the DAS28 remission criteria.

There were no significant differences in US findings (GS or CD) between patients in remission vs patients not in remission, no matter which clinical remission criteria were used.

Conclusion:

Subclinical synovitis was frequently detected by US in RA patients treated with biological drugs in routine care showing poor agreement between the clinical remission criteria and US remission. Further studies are needed to evaluate the benefit of US remission as a goal for treat to target strategies on patient-reported outcomes and radiographic progression.

Tabel 1: Baseline characteristics and agreement between clinical remission and ultrasound remission

Characteristics	DAS28 remission Yes (n= 117) 100%	CDAI remission No (n=32) 27%	Yes (n=85) 73%	P-values	SDAI remission No (n=34) 29%	Yes (n=83) 71%	P-values	ACR/EULAR remission No (n=68) 58%	Yes (n=49) 42%	P-values
Age (years)	60 (48-68)	61 (48-67)	60 (48-68)	0.8	61 (50-68)	60 (48-68)	0.6	60 (48-68)	60 (48-67)	0.6
Female gender	68%	72%	67%	0.6	65%	70%	0.6	74%	61%	0.2
IgM-RF positive	66%	66%	66%	0.3	65%	66%	0.3	66%	65%	0.7
X-ray erosions	70%	78%	67%	0.5	82%	65%	0.2	78%	59%	0.06
Disease duration (years)	11 (7-18)	12 (9-26)	11 (6-16)	0.02	12 (8-23)	10 (6-16)	0.05	12 (7-20)	10 (6-15)	0.1
SJC28	0 (0-0)	0 (0-0)	0 (0-0)	0.1	0 (0-0)	0 (0-0)	0.1	0 (0-0)	0 (0-0)	0.8
TJC28	0 (0-0)	0 (0-1)	0 (0-0)	<0.001	0 (0-1)	0 (0-0)	<0.001	0 (0-0)	0 (0-0)	0.008
CRP (mg/mL)	5 (2-6)	5 (2-9)	5 (2-6)	0.6	5 (3-9)	5 (2-5)	0.008	5 (2-6)	5 (1-6)	0.4
Pt. VAS global	13 (4-26)	37 (26-43)	8 (3-17)	<0.001	35 (25-40)	8 (3-15)	<0.001	25 (15-36)	4 (1-7)	<0.001
Total GS score	7 (3-13)	8 (3-14)	7 (3-13)	0.7	8 (4-13)	7 (3-13)	0.5	6 (3-12)	9 (3-15)	0.4
Total CD score	1 (0-2)	0 (0-3)	0 (0-2)	0.8	0 (0-2)	0 (0-2)	0.8	0 (0-2)	0 (0-2)	0.9
CD = 0	54%	59%	53%	0.5	59%	53%	0.6	57%	51%	0.5
CD ≤1	76%	72%	78%	0.5	79%	75%	0.6	75%	78%	0.8
GS = 0	10%	6%	12%	0.4	3%	13%	0.09	10%	10%	0.9
GS ≤ 1	39%	41%	39%	0.9	38%	40%	0.9	44%	33%	0.2
Characteristics		US remission GS=0 and CD=0 No (n=106) 91%	Yes (n=11) 9%	P-values	US remission GS≤1 and CD=0 No (n=83) 71%	Yes (n=34) 29%	P-values			
Age (years)		61 (48-68)	49 (46-63)	0.2	62 (50-69)	51 (45-61)	0.002			
Female gender		67%	82%	0.3	66%	74%	0.4			
IgM-RF positive		67%	55%	0.6	70%	60%	0.2			
X-ray erosions		73%	46%	0.1	75%	59%	0.2			
Disease duration (years)		11 (7-19)	6 (4-12)	0.01	12 (8-20)	11 (5-14)	0.02			
SJC28		0 (0-0)	0 (0-0)	0.2	0 (0-0)	0 (0-0)	0.9			
TJC28		0 (0-0)	0 (0-0)	0.4	0 (0-0)	0 (0-0)	0.9			
CRP (mg/mL)		5 (2-6)	5 (2-5)	0.4	5 (1-8)	5 (3-5)	0.8			
Pt. VAS global		13 (4-26)	10 (6-18)	0.5	11 (4-25)	16 (7-28)	0.3			
Total GS score		8 (4-14)	0 (0-0)	NA	9 (5-15)	2 (0-3)	NA			
Total CD score		1 (0-2)	0 (0-0)	NA	1 (0-2)	0 (0-0)	NA			
CD = 0		50%	100%	NA	37%	100%	NA			
CD ≤1		74%	100%	NA	68%	100%	NA			
GS = 0		1%	100%	NA	1%	32%	NA			
GS ≤ 1		33%	100%	NA	15%	100%	NA			

Values are median (IQR) unless otherwise indicated. Mann-Whitney U test for continuous data. Pearson Chi-square test for binomial data.
US included bilateral scan of the following 24 joints: elbows, wrists, metacarpophalangeal joints 2-5, knees, ankles, metatarsophalangeal joints 2-5.
NA: Non applicable

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Abstract Number: 158

Ultrasound Score of Dominant Hand in Patients with Rheumatoid Arthritis Correlates with DAS28CRP, CDAI and SDAI but Not RAPID-3

Allen P. Anandarajah[1], Bethany Marston[2], Linda Grinnell-Merrick[2] and Ralf G. Thiele[3], [1]Dept of Rheumatology, Univ of Rochester Medical Ctr, Rochester, NY, [2]Rheumatology, University of Rochester Medical Center, Rochester, NY, [3]University of Rochester Medical Center, Rochester, NY

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Background/Purpose: Musculoskeletal ultrasound (MUS) allows for direct visualization of diverse pathologic features such as cortical bone erosions, synovial thickening, and synovial vascularity in the joints affected by rheumatoid arthritis (RA) with high sensitivity, specificity, and accuracy. Therefore, MUS can be a highly sensitive tool for the evaluation of disease activity in RA. However, disease activity in RA is currently measured using traditional clinical measures such as disease activity scores (DAS-28), Clinical Disease Activity Index (CDAI), Simplified Disease Activity Index (SDAI) and Routine Assessment of Patient Index Data (RAPID-3). A limited number of studies have attempted to correlate the measures of clinical disease activity with ultrasound scores.

Purpose: To assess the correlation of different clinical activity scores with a standardized semi-quantitative US score of the dominant hand in RA patients.

Methods: This was a single center study of patients from the RA clinic at the University of Rochester. The DAS-28CRP, CDAI and SDAI are collected as a standard of care in an established RA clinic. Recently, we added RAPID 3 and offered MUS evalaution for all RA patients seen in this clinic. Clinical measures were done by AA and LGM and MUS by RT and BM. MUS was done using a GE Logiq (2014) and the following joints were assessed: dorsal wrist, 2nd, 3rd, 4th and 5th MCPs and the 2nd, 3rd, 4th and 5th PIP. MCP joints 2-5 were scanned from a dorsal aspect, and PIP joints 2-5 were scanned from a volar aspect. The scans were retrospectively scored for presence of synovitis on gray scale and the presence of Power Doppler signal (0=none; 1=mild; 2=moderate and 3=severe) for each joint, with a total score for the hand ranging from 0-54.

Results: To date, a total of 20 patients have completed all the clinical and ultrasound assessments. This cohort is comprised of 11 females and 9 males, of which 17 were sero-positive and 11 had erosive disease. The median age was 62. Scores for all parameters were available for 18 subjects (2 images could not be retrieved). In this cohort, a total of 11 patients were in remission based on DAS-28, 3 had LDA, 3 had moderate disease activity and 1 was with severe disease activity. Using CDAI, we noted that 6 patients were in remission, 7 were with LDA, 4 had moderate and 1 severe disease activity scores. By SDAI criteria, we recorded 7 in remission, 7 with LDA, 3 with moderate and 1 with severe disease activity. Based on RAPID-3, only 4 were in remission, 4 had LDA, 3 moderate and 7 had severe disease activity. The median MUS scores correlated with disease activity scors for remission, LDA, moderate and severe disease activity by DAS-28, CDAI and SDAI as shown in Table 1.

Conclusion: MUS of the dominant hand of patients with RA can provide an easy, inexpensive and accurate measure of disease activity in RA patients. MUS additionally provides the ability to visualize joint damage.

Table 1: median MUS scores for each level of clinical disease activity

	Remission	LDA	Moderate	Severe
DAS-28CRP	1	5	7	24
CDAI	2	4	9	24
SDAI	0.5	4.5	11	24
RAPID-3	0	3	9	6

Disclosure: A. P. Anandarajah, None; **B. Marston**, None; **L. Grinnell-Merrick**, None; **R. G. Thiele**, None.

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Abstract Number: 159

Power Doppler Continuous Quantitative Assessment Techniques Is Faster Than Semiquantitative Assesment in Identification of Therapeutic Response

Florian Berghea[1], Violeta Vlad[2], Mihai Bojinca[3], Luminita Enache[4] and Ruxandra Ionescu[5], [1]Department of Internal Medicine and Rheumatology "Sf. Maria" Hospital, Bucharest, Romania, [2]RCRD Research Center, Bucharest, Romania, [3]Carol Davila University of Medicine and Pharmacy, Internal Medicine and Rheumatology, Cantacuzino Hospital, Bucharest, Romania, [4]Rheumatology, 'Dr. Ion Stoia' Clinical Center of Rheumatic Diseases, Bucharest, Romania, [5]University of Medicine and Pharmacy "Carol Davila", Department of Internal Medicine and Rheumatology "Sf. Maria" Hospital, Bucharest, Romania

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Background/Purpose:

Power Doppler Ultrasound (PD) is widely used to assess the activity of rheumatic diseases (especially in Rheumatoid Arthritis). Up to now a series of qualitative / semiquantitative scales have been proposed in order to facilitate a reliable evaluation of a PD image most of them in two to four steps. A true quantitative assessment of PD image is rarely done; in most of the cases it is performed by manual selection of the worst case scenario frame (i.e. the frame with the highest amount of Doppler signal) from a recorded cine-loop. The feasibility of this technique is questionable: in a previous work we demonstrated the inferiority of manual vs. computerized selection both in terms of quality of the process and the time spent. However the independent software solutions for quantitative analysis of Doppler image (i.e. the analysis of the total number of colorized pixels from a region of interest) are now available; we are able to measure in a timely manner not just the ratio between the colorized and grey pixels (CTR) from a certain region in a single frame but all CTRs of all frames captured in a cine-loop (Continuous Quantitative Assessment – CQA). The objective of our study was to assess the ability of CQA technique to identify changes of PD signal earlier than the classical semiquantitative assessment.

Methods:

24 cases of active RA have been examined according to AIUM guidelines for dorsal aspect of radiocarpal and midcarpal joints. A cine-loop of 4 seconds has been recorded for each case before the administration of an i.v. dose of dexamethasone and after 0.5, 1, 2, 6 and 24 hours. All the recordings have been evaluated independently both in semiquantitative (SQ) and in CQA technique (by using a registred software (RETINA®). For CQA we computed mean and peak CTRs. C-reactive protein was measured before and after 24 hour of therapeutical intervention: a 20% decrease defined the reponders. A one-way repeated measures ANOVA was conducted to determine whether there were statistically significant differences between SQ and CQA scores. Responsiveness of SQ and CQA scores was calculated using Relative Reduction (RR) over time.

Results: 23 cases presented a 20% decrease of CRP level and have been included in the analysis. The therapeutic intervention elicited statistically significant changes in SQ and CQA scores for synovitis (tenosynovitis was not included in this study) as described in the table.

Timepoint	No of responders identified by SQ	No of responders identified by Mean CQA	No of responders identified by Peak CQA	P (SQ vs Mean CQA)
0	NA	NA	NA	NA
0.5	0	2	2	<0.05
1	1	4	5	<0.05
2	1	7	8	<0.05
6	2	9	9	<0.05
24	4	12	15	<0.05

The responsiveness of SQ was inferior to any CQA score ($p<0.05$). However the mean and peak CQA scores correlated well (0.78 for $p<0.001$) – no separate scores seems to be needed.

Conclusion:

To the best of our knowledge, this is the first study to document the difference between semiquantitative and continuous quantitative PD assessment techniques. The CQA seems to offer the opportunity to identify the therapeutic response earlier than the current approach. The method should be tested in different therapeutic scenarios and in larger groups, too.

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When Compared with a Computerized System Both Experienced and in-Training Sonographers Have Difficulties to Select the Best Doppler Image from a Cine-Loop

Florian Berghea[1], Violeta Vlad[2], Lavinia Palanciuc[3], Violeta Bojinca[4], Florentin Vreju[5], Luminita Enache[6], Monica Copotoiu[7], Alexandra Kosevoi[8], Teodora Serban[9], Denisa Stanciu[6], MIHAI ABOBULUI[10], Andreea Borangiu[11], Andra Rodica Balanescu[1] and Ruxandra Ionescu[1], [1]Department of Internal Medicine and Rheumatology “Sf. Maria” Hospital, Bucharest, Romania, [2]RCRD Research Center, Bucharest, Romania, [3]Medical Technology Research Center, Bucharest, Romania, [4]RCRD, Bucuresti, Romania, [5]Rheumatology Department, University of Medicine and Pharmacy Craiova, Craiova, Romania, [6]Rheumatology, 'Dr. Ion Stoia' Clinical Center of Rheumatic Diseases, Bucharest, Romania, [7]18 Nagy Pal Str., Mures County, Tg. Mures Emergency Hospital, Tg. Mures, Romania, [8]Sf. Maria Hospital, Bucharest, Romania, [9]Internal Medicine and Rheumatology, "Dr. I Cantacuzino" Hospital, Bucharest, Romania, [10]RCRD, BUCHAREST, Romania, [11]University of Medicine and Pharmacy “Carol Davila”, Department of Internal Medicine and Rheumatology “Sf. Maria” Hospital, Romania, Bucharest, Romania

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Background/Purpose:

Cine-loop analysis is an ultrasound technology that allows the acquisition of images in a digital form as a sequence of a determined frame number. The images can be reviewed as many time as necessary in order to identify the one with the highest level of information. **Up to now, in musculoskeletal sonography, this was the prefered technique**used to select the best Doppler frame (i.e. the image with the highest level of Doppler signal). The frame is subsequently analyzed in quantitative way (the proportion of total colorized pixels from the total number of existing pixels in a definite region). In order to compare the quantitative Doppler data from different time points a very precise selection of the best Doppler image from a recorded cine-loop is needed. Our study examined the ability of both experienced and in-training sonographers to select the best Doppler image from such a cine-loop using a computerized analytical system as gold standard.

Methods:

The study analised 480 frame selections done in two distinct exercises as following: twenty cine-loops have been recorded using standardized scans; one region of interest (ROI) was marked on each scan and the colorized pixels / total pixels ratio (CTRatio) was computed for each frame of the loop by using an independent software (Retina®). From each loop a number of 4 different frames have been extracted: the one with the highest CTR (named CTR100) and 3 with 5%, 10% and respectively 20% lower level of CTR (named CTR95, CTR90 and CTR80) . All frames emerged from the same loop have been randomly presented to six experienced and six in training sonographers; the request was to select the frame with the highest CTR from each package (twenty packages in total). A similar exercise was performed with CTRs decreasing in steps of 2% (CTR100, CTR98, CTR96, CTR94).

Results:

In the first exercise the CTR100 have been correctly identified in 79.1% cases while in 15.8% of cases CTR95 have been wrongly indicated as CTR100 and in 4.6% of cases theCTR90 was selected. In the 2ndexercise the subjects indicated as CTR100 the following frames: CTR100 in 67% of CTR98 in 18.3%, cases, CTR 96 in 11,6% and CTR94 in 3.1% of cases.

The experienced sonographers performed better than in=training colleagues in both exercises (correct selection in 95 to 75% of cases vs. 90 to 50% of cases in 1st exercise, respectively 90 to 65% of cases vs 75 to 45% of cases in the 2nd exercise).

Conclusion:

Using the computerized analyses as the gold standard, we demonstrated a large heterogeneity across sonographers regarding their ability to identify the best Doppler image (i.e. the one with the highest CTR) even from a small group of frames. The ability is even more questionable when the differences are small. When the quantitative Doppler signal is assessed in the same patient at different timepoints this lack of ability might induce a significant error. When computerized analyses is feasible it should be used in place of the manual selection.

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Abstract Number: 161

Ultrasonographic Evaluation of Rheumatoid Hand: Hand Disability and

Disease Activity Correlation

Dilek Keskin[1], Hatice Bodur[2], Akinci Tan[3] and Levent Oczakar[4], [1]PMR, Numune Training and Research Hospiatl, Ankara, Turkey, [2]PMR, Numune Training and Research Hospital, Ankara, Turkey, [3]Physical Med & Rehab, Hacettepe Univ, Ankara, Turkey, [4]Hacettepe University Medical School, Ankara, Turkey
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Session Time: 9:00AM-11:00AM

Background/Purpose:

To determine hand disability and articular damage in patients with Rheumatoid arthritis (RA) and to define their relation with musculoskeletal ultrasonography (US) findings, clinical and laboratory parameters.

Methods:

The study included 43 RA patients (22 women, 21 men) with a mean age of 55.72±11.76 years. Demographic and clinical parameters including disease duration, duration of morning stiffness, number of tender and swollen joints were recorded. Grip strength, lateral, tip and three-fingered pinch of the dominant hand was measured. The rheumatoid arthritis articular damage (RAAD) score was used to assess the articular damage and deformities of the dominant hand. Hand disability was assessed by special hand disability index (HDI) of Standford Health Assessment Questionnaire (HAQ) and upper extremity Quick Disabilities of Arm, Shoulder, and Hand (QuickDASH) questionnaire was applied to evaluated the disability of upper extremity. C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) were evaluated as laboratory parameters. Musculoskeletal ultrasonography (US) was performed in the selected joints: wrist, metacarpophalengeal (MCP) MCP I, II,III and proximal interphalengeal (PIP) PIF I, II and III; which are most likely to be affected by RA. The presence of synovitis and tenosynovitis and erosions were examined by the grey-scale US (GSUS) and also the presence of synovitis and tenosynovitis in the selected joints were examined by power Doppler US (PDUS).

Results:

GSUS sinovitis sum score was correlated with RAAD, QuickDASH, (respectively r=0.315, p=0.039, r=0.744, p=0.001) GSUS tenosinovits sum score was correlated with RAAD, HDI, DASH, and disease duration (respectively r=0.448, p=0.003, r=0.281, p=0.068, r=0.400, p=0.008, r=0.367, p=0.016). GSUS erosion sum score was correlated with RAAD and disease duration (respectively r=0.403, p=0.007, r=0.455, p=0.002), PDUS tenosinovitis sum score was correlated with lateral pinch and tip pinch (respectively r=0.335, p=0.037, r=0.310, p=0.055).

Conclusion:

Our results suggest that pinch measurements, hand disability, articular damage scores seem to be the most related variables with US findings. Therefore US assessment of the dominant hand should be included in the evaluation and follow-up of the patients with RA.

Abstract Number: 162

Ultrasonography Versus Clinical Examination in Early DMARD-Naïve Rheumatoid Arthritis – a Comparative Study of Synovitis on the Individual Joint Level

Lena B. Nordberg[1], Elisabeth Lie[1], Siri Lillegraven[1], Anna-Birgitte Aga[1], Inge C Olsen[2], Hilde Berner Hammer[3], Till Uhlig[4], Désirée van der Heijde[5], Tore K. Kvien[1], Espen A. Haavardsholm[1] and the ARCTIC Study Group, [1]Dept. of Rheumatology, Diakonhjemmet Hospital, Oslo, Norway, [2]Department of Rheumatology, Diakonhjemmet Hospital, Oslo, Norway, [3]Rheumatology, Diakonhjemmet Hospital, Oslo, Norway, [4]Diakonhjemmet Hospital, Oslo, Norway, [5]Dept. of Rheumatology, Leiden University Medical Center, Leiden, Netherlands

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Background/Purpose: Ultrasonography (US) is increasingly accepted as an important tool in diagnosis and management of rheumatoid arthritis (RA). However, it is not well known to what extent US adds information to clinical examination at the individual joint level. Our objective was to assess concordance between clinical joint examination and US in detecting synovitis at the individual joint level in a cohort of early RA patients.

Methods: 228 patients with early RA who fulfilled the 2010 ACR/EULAR classification criteria were recruited at 11 Rheumatology centers between 2010 and 2013. Patients were required to have symptom duration <2 years (from onset of joint swelling) and to be DMARD na•ve with indication for DMARD treatment. 44 joints were assessed for swelling by a rheumatologist or trained research nurse. US examinations were performed by experienced and well-calibrated sonographers, using a validated gray-scale (GS) and power Doppler (PD) semi-quantitative scoring system with scores 0-3 for GS and PD in each of the following 36 joints: MCP 2-5, radio-carpal (RCJ), distal radio-ulnar (DRUJ), inter-carpal (ICJ), PIP 2-3, elbow, knee, talo-crural and MTP 1-5 bilaterally. We defined US synovitis (US+) as GS ³2 and/or PD ³1. For the wrist the US comparison with clinical joint swelling included one or several of the RCJ, DRUJ and ICJ. Joints were assessed bilaterally and analysed on an aggregated level. Kappa values between clinical joint swelling and US synovitis were calculated for all joints. We specifically assessed the proportion of joints with US synovitis that were not clinically swollen, and vice versa.

Results: The mean age (SD) of the 228 patients was 51.1 (13.8) years, mean (SD) disease duration 7.1 (5.4) months and 62.3% were female. Mean (SD) DAS was 3.47 (1.13) the median (25, 75 percentiles) number of swollen joints was 9 (4, 14), and the median (25, 75 percentiles) number of joints with US synovitis was 7 (3,11). A total of 8208 joints were examined by US. Agreement between US and clinical examination was best in the elbow, wrist and knee (kappa 0.68, 0.53, 0.51, respectively). The proportion of joints with US synovitis that were not clinically swollen ranged from 16% (PIP2) to 76% (MTP1). The six joints with the largest and smallest discrepancies are presented in the table. Similarly, a significant proportion of clinically swollen joints had no US synovitis, ranging from 23% (wrist and elbow) to 70% (ankle).

Table: Comparison of US synovitis and clinical joint swelling in selected joints*						
Joint		Swollen	Not Swollen	Kappa	Proportion of joints with US synovitis and no clinical swelling	Proportion of swollen joints without US synovitis
MTP1	US+	35	112	0.18	76%	43%
	US-	26	282			
MTP5	US+	30	66	0.30	69%	43%
	US-	23	337			
MCP4	US+	28	53	0.33	65%	46%
	US-	24	351			
Wrist	US+	139	62	0.53	31%	23%
	US-	42	213			
PIP3	US+	90	21	0.42	19%	53%
	US-	100	245			
PIP2	US+	100	19	0.45	16%	50%
	US-	100	237			
*Joints are sorted by the proportion of joints with US synovitis and no clinical swelling.						

Conclusion: In this study of patients with early RA we found the level of agreement between US and clinical examination to be somewhat higher in medium to large joints compared to small joints. However, substantial discrepancies between clinical joint swelling and US pathology were found for most joints, and these findings support that US provides additional information compared to clinical examination in most joint areas.

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Abstract Number: 163

Ultrasonographic Assessment Covers Clinical Examination in the Localization of Ankle Pathology in Rheumatoid Arthritis

Yukihiro Toyota[1], Kaoru Minegishi-Takase[1], Maasa Hama[1], Ryusuke Yoshimi[1], Yumiko Sugiyama[1], Naomi Tsuchida[1], Yosuke Kunishita[1], Daiga Kishimoto[1], Reikou Kamiyama[1], Yohei Kirino[1], Mitsuhiro Takeno[1,2], Atsuhisa Ueda[1] and Yoshiaki Ishigatsubo[1,3], [1]Department of Internal Medicine and Clinical Immunology, Yokohama City University Graduate School of Medicine, Yokohama, Japan, [2]Department of Allergy and Rheumatology, Nippon Medical School, Tokyo, Japan, [3]Yokosuka Rheumatic Diseases Center, Yokosuka City Hospital, Yokosuka, Japan
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Background/Purpose: Though rheumatoid arthritis (RA) commonly affects ankle joints, ankle joints are not included in widely used composite measures of disease activity with 28-joint counts. Furthermore, precise clinical examination (CE) is difficult because of its complex anatomical structure. Aim of this study is to clarify the utility of ultrasonographic assessment (US) for evaluating ankle joints by means of comparison to CE in daily clinical practice for RA.

Methods: Sixty RA patients (female 85.0%, age 60.9 ± 15.2 y.o., disease duration 6.92 ± 8.02 years, DAS28-ESR 3.93 ± 1.63) were included. US, CE and patient's visual analog scale for pain (pVAS) of each bilateral ankle were assessed. Bilateral tibiotalar joints and three tendon sites (anterior sites; tibialis anterior, extensor hallucis longi, extensor digitorum longi, medial sites; tibialisposterior, flexor digitorum longi, flexor hallucis longi, lateral sites; peroneus longi and brevis) were assessed by gray scale (GS) and power Doppler (PD) US. Intra-articular synovitis(synovitis) and tenosynovitis were separately assessed using semiquantitative grade (0-3). Positive US findings were defined as GS score ≥2 and/or PD score ≥1, and positive CE findings were defined as joint swelling and/or tenderness.

Results:

A total of 120 ankles were evaluated. Positive US findings were found in 19 (15.8%) tibiotalar joints, 5 (4.2%) anterior sites, 16 (13.3%) medial sites, 13 (10.8%) lateral sites, respectively. When positive US findings were defined as a gold standard, sensitivity and specificity of positive CE findings were 0.68 and 0.81 for synovitis, respectively, and 0.76 and 0.88 for tenosynovitis, respectively. The concordance rate of CE and US were poor ($\kappa = 0.39$) for synovitis, whereas were moderate ($\kappa = 0.58$) for tenosynovitis. When we devided the cases into 4 groups based on the existence of synovitis and tenosynovitis, the group with both US-based synovitis and tenosynovitis showed the highest pVAS (Table). Positive CE findings were highly detected in the joints where US tenosynovitis was positive.

Table. pVAS and clinical examination of ankle among the groups divided according to US-based ankle involvement.

US findings	n	pVAS*	Swollen**	Tender**
Synovitis (-), Tenosynovitis (-)	89	10.8±19.2	9 (10.1%)	6 (6.7%)
Synovitis (+), Tenosynovitis (-)	6	33.3±29.1	2 (33.3%)	1 (16.7%)
Synovitis (-), Tenosynovitis (+)	12	41.2±28.1	9 (75.0%)	7 (58.3%)
Synovitis (+), Tenosynovitis (+)	13	73.2±21.6	8 (61.5%)	6 (46.2%)

＊ P<0.0001 ANOVA test, ＊＊P<0.0001 Kruskal-Wallis test

Conclusion: CE and pVAS often reflect tenosynovitis rather than intra-articular synovitis. US sensitively detects RA involvement in the ankle joints, particularly intra-articular lesions, which are often missed by CE.

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Abstract Number: 164

Subclinical Ankle Involvement in Rheumatoid Arthritis. a Multicentre Ultrasound Study

Diana Ferrusquia-Toriz[1], Tomas Cazenave[2], Marcos Rosenffet[3], Florentin Vreju[4], Bernd Raffeiner[5], Andrea Delle Sedie[6], Fernando Del Pra[7], Carlos Pineda[8] and Marwin Gutierrez[1,9], [1]Research Department, Instituto Nacional de Rehabilitación, Mexico City, Mexico, [2]Rheumatology Section, IREP, Buenos Aires, Argentina, [3]Instituto de Rehabilitación Psicofísica, Buenos Aires, Argentina, [4]Rheumatology Department, University of Medicine and Pharmacy Craiova, Craiova, Romania, [5]Rheumatology Unit, University of Padua, Padua, Italy, [6]Department Rheumatology, University of Pisa, Pisa, Italy, [7]Rheumatology, Instituto de Rehabilitación Psicofísica, Buenos Aires, Argentina, [8]Research Direction, Instituto Nacional de Rehabilitacion, Mexico City, Mexico, [9]Clinica Reumatologica, Università Politecnica delle Marche, Jesi, Italy

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Session Time: 9:00AM-11:00AM

Background/Purpose: Ankle involvement is frequent in rheumatoid arthritis (RA), with at least 90% of patients affected anytime during the disease course though ankle involvement may often be subclinical. *Imaging, especially ultrasound (US), plays a fundamental role in ankle assessment, given that it assesses both joint and peri-articular soft tissue inflammation. Considering that* ankle involvement in RA is underrecognized we decided to investigate the prevalence and characteristics of subclinical ankle involvement in patients with RA by US.

Methods: Sixty-two RA patients without clinical history of ankle involvement and 60 healthy age and sex-matched controls were included. Both RA patients and healthy controls underwent clinical examination including a 28 joint assessment and a comprehensive ankle assessment to exclude tendon or joint involvement. Age, gender, disease duration, visual analogue scale (VAS) for pain and global activity, body mass index (BMI), Disease Activity Score for 28 joints (DAS28), rheumatoid factor (RF), anti-CCP antibodies, erythrocyte sedimentation rate (ESR) and C-Reactive Protein (CRP), were also recorded.

All participants underwent US examination, which was performed by experienced sonographers using both greyscale and power Doppler (PD) technique. Ankles were scanned at the anterior, medial and lateral views, in transverse and longitudinal scans recording the following US pathological findings: exudative or proliferative tenosynovitis/synovitis, presence of peritendinous, intratendinous or intra-articular PD and tendinous ruptures. All US scanning techniques and definitions were used as proposed by the EULAR working group for musculoskeletal ultrasound and OMERACT ultrasound task force.

Results: Sixty-two patients with RA were included (40 female) and 60 healthy sex and age-matched controls. Subclinical ankle involvement was found in 25 of 62 RA patients (40.3%). In 13 ankles (4 intra-articular, 6.45%, and 9 peri-articular, 14.5%) a positive PD was found. In the control group, ankle involvement was seen in 10 (16.6%) patients, with a statistically significant difference (p=0.03) with respect to the study group. No PD was found in this group (p=0.03). Tibio-talar joint proliferative synovitis with positive PD signal, and proliferative tenosynovitis of the tibialis anterior, tibialis posterior and peroneous longus were more frequently seen in the RA group (p=0.002). No correlation between DAS28 and ankle US findings was seen (r=0.13), though DAS28 and the total number of joints with positive PD showed a tendency for positive correlation (r=0.270). No correlation was found between BMI, RF or ACPA with any US finding (r=0.136).

Conclusion: Our results indicate that both grayscale US and PD findings suggestive of subclinical ankle involvement were more frequently found in RA patients. The use of US should be strongly recommended to avoid underestimating ankle involvement in RA patients.

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Abstract Number: 165

Validation of a New Ultrasound Criteria for Subclinical Synovitis in Chronic Inflammatory Polyarthritis

Julio Ramírez[1], Jose Inciarte-Mundo[2], Andrea Cuervo[1], Virginia Ruiz-Esquide[2], M. Victoria Hernández[3], Raimon Sanmarti[2] and Juan D. Cañete[2], [1]Arthritis Unit. Rheumatology, Hospital Clínic of Barcelona, Barcelona, Spain, [2]Rheumatology Department, Hospital Clinic i Provincial, Barcelona, Spain, [3]Arthritis Unit, Rheumatology, Hospital Clinic, Barcelona, Spain

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Background/Purpose:

We have previously reported that patients with subclinical synovitis defined by synovial hypertrophy grade >2 (SH>2) plus power Doppler (PD) signal had higher disease activity, higher levels of serum inflammatory/angiogenic biomarkers [Ramírez J, Arthritis Research and Therapy 2014 Jan 8;16(1):R5] and less were on corticosteroid treatment. The aims of this study were to validate this ultrasound criteria for subclinical synovitis (SH>2+PD) in a different cohort of patients with chronic inflammatory polyarthritis in clinical remission on anti-TNF therapy.

Methods:

Patients diagnosed with RA or polyarticular PsA in clinical remission (DAS28-ESR<2.6) on anti-TNF therapy were included. Ultrasound scans of both hands were performed in all patients, with scoring of Synovial hypertrophy (SH) (grades 0-3) and power Doppler (PD) (grades 0-3). Angiogenic and proinflammatory cytokines were determined by Multiplex ELISA in patients with RA and PsA in remission and compared with the levels of two control cohorts: 22 active RA patients (DAS28>3.2) and 20 healthy controls.

Results:

We included 77 patients [47 PsA and 30 RA, mean age (standard deviation, SD) 57.3 (11.5) years, disease duration 15.7 (8.3) years, DAS28 1.85 (0.41), time of remission 4.2 (3.3) years] of whom 42 were on etanercept, 25 adalimumab and 10 on infliximab. Forty (51.9%) patients were on monotherapy and 38 (49.3%) were receiving tapered doses of TNF antagonists.

Globally, 31 patients had PD signal and 12 had SH>2 plus PD, meeting the criteria of ultrasound-defined subclinical

synovitis. Despite no clinical differences were found, patients with criteria of sonographic subclinical synovitis had significantly higher levels of IL-6, IL-20, PIGF and SDF1.

Interestingly, the serum biomarker profile in PsA in remission was similar to the healthy control, whereas serum biomarker profile in RA in remission was more similar to that of active RA patients.

11 out of 30 RA patients in clinical remission (p=0.0001) versus only 1 PsA patient met criteria for sonographic subclinical synovitis. In line with these findings, significantly more PsA patients were receiving tapered dose of biologics (63.8%), and more frequently as monotherapy (72.3%), compared with RA patients in clinical remission (26.6% and 20%, respectively).

Conclusion:

We have shown that sonographic criteria for subclinical synovitis in patients with chronic inflammatory polyarthritis in remission are useful to identify patients with higher burden of local and systemic inflammation. It remains to be demonstrated if patients meeting that criteria have a higher rate of joint flare and radiographic progression. Finally, our findings suggest that clinical remission under anti-TNF therapy is qualitatively better in PsA than in RA.

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Abstract Number: 166

Validity and Sensitivity to Change of the Semi-Quantitative Omeract Ultrasound Scoring System for Tenosynovitis in Patients with Rheumatoid Arthritis

Mads Ammitzbøll-Danielsen[1], Mikkel Østergaard[2], Esperanza Naredo[3] and Lene Terslev[4], [1]Center for Rheumatology and Spine Diseases, Rigshospitalet - Glostrup, University of Copenhagen, Denmark, Copenhagen Center for Arthritis Research (COPECARE), Center for Rheumatology and Spine Diseases, Rigshospitalet - Glostrup, University of Copenhagen, Denmark, Glostrup, Denmark, [2]Center for Rheumatology and Spine Diseases, Glostrup Hospital, Copenhagen Center for Arthritis Research (COPECARE), Center for Rheumatology and Spine Diseases, Rigshospitalet - Glostrup, University of Copenhagen, Denmark, Glostrup, Denmark, [3]Hospital Severo Ochoa, Madrid, Spain, [4]Copenhagen Center for Arthritis Research (COPECARE), Center for Rheumatology and Spine Diseases, Rigshospitalet - Glostrup, University of Copenhagen, Denmark, Glostrup, Denmark

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Background/Purpose:

Tenosynovitis is frequent in rheumatoid arthritis (RA) patients. One study indicates that tenosynovitis detected by modern imaging has prognostic value with respect to subsequent radiographic progression. The OMERACT ultrasound

(US) study group has in 2012 proposed a new tenosynovitis scoring system. However, the validation of the score is limited, eg. the sensitivity to change during treatment has not been tested.

In a 6-months follow-up study of 51 RA patients with ultrasonographic tenosynovitis, initiating treatment intensification with disease-modifying anti-rheumatic drug (DMARD) and/or biological treatment, to validate the semi-quantitative OMERACT US-scoring system of tenosynovitis by testing its interreader reliability, sensitivity to change, and comparison to clinical evaluation.

Methods:

Fifty-one RA patients, planned for treatment intensification, were included: 43 women (age: mean 55.6; standard deviation (SD) 13.1) and 8 men (mean 49.1; SD 9.34). Thirty-four patients were anti-rheumatoid factor positive and 30 had early RA (duration <1 year). US (by grey-scale (GS) and color Doppler (CD)) and clinical assessment of the flexor and extensor tendon sheaths of the clinically most affected hand and foot was performed at baseline and after 3 and 6 months. Tenosynovitis was assessed using the semi-quantitative scoring system (0-3) proposed by the OMERACT US group for GS and CD calculating a sum score (0-39) for each patient. In 20 patients, US was done independently by 2 physicians at baseline and 6 months, to assess the inter-observer agreement. A GE Logiq E9 with a linear 6-15 ML probe was used. CD frequency was 7.5 MHz, a pulse repetition frequency = 0.4 and gain just below the noise limit. The same Doppler settings were used for all examinations. A binary score for clinical tendon involvement(0-1) was also performed at the same locations as the US score, with reference to published recommendations, calculating a sum score (0-13).

Results:

The interreader agreement, as assessed by the intra-class correlation coefficient (ICC) was very good at baseline (Bas) and for changes (Ch) for GS sum scores (ICC Bas=0.89 ; Ch=0.89) and CD (ICC Bas=0.95 ; Ch=0.90) tenosynovitis. The smallest detectable change (SDC) for change in scores was 0.97 for GS and 0.93 for CD. Tenosynovitis scores had decreased significantly at months 3 and 6 (Table 1). The sensitivity to change, as expressed by the standardized response mean from month 0-6, was high for GS and CD tenosynovitis (0.90 and 0.76, respectively), and moderate (0.59) for the clinical score (Table 1).

Conclusion:

The semi-quantitative OMERACT ultrasound scoring system of tenosynovitis showed high inter-observer agreement and sensitivity to change for both GS and CD.

Table 1

		Baseline	3 months	6 months	Δ 0-3 months		Δ 3-6 months		Δ 0-6 months		SRM 0-3 months	SRM 3-6 months	SRM 0-6 months
Grey scale	Mean (Std. Dev)	3.5 (2.6)	2.1 (1.6)	1.4 (1.4)	-1.4 (2.2)	P < 0001	-0.7 (1.3)	P=0.0001	-2.1 (2.4)	P < 0001	0.6	0.5	0.9
	Median [25;75 pctl]	3.0 [2;4]	2.0 [1;3]	1.0 [0;2]	1.0 [-2;0]		1.0 [-1;0]		-2.0 [-3;-1]				
Colour Doppler	Mean (Std. Dev)	3.4 (3.5)	1.4 (1.9)	0.8 (1.7)	-2.0 (3.3)	P < 0001	-0.6 (1.7)	P=0.0211	-2.6 (3.4)	P < 0001	0.6	0.3	0.8
	Median [25;75 pctl]	3.0 [1;4]	1.0 [0;2]	0.0 [0;1]	-1.0 [-3;0]		0.0 [-1;0]		-2.0 [-3;0]				
Clinical	Mean (Std. Dev)	2.4 (1.9)	1.6 (1.6)	0.9 (1.4)	-0.8 (1.9)	P=0.0043	-0.6 (1.8)	P=0.0181	-1.4 (2.4)	P < 0001	0.4	0.3	0.6
	Median [25;75 pctl]	2.0 [1;3]	1.0 [0;3]	0.0 [0;1]	0.0 [-2;0]		0.0 [-1;0]		-1.0 [-3;0]				

Note: P = Wilcoxon-Pratt tests SRM = Standardized response mean

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Abstract Number: 167

Negative Gaenslen's (Squeeze) Test Has a High Negative Predictive Value

for Significant Ultrasonographic Metatarsophalangeal Involvement in Early Arthritis

Gisela Eugénio[1], Joana F. Ferreira[1], Alexandra Daniel[2], João Pedro Freitas[2], Flávio Costa[2], João Rovisco[2], Margarida Coutinho[2,3], Sara Serra[2], J.A.P. da Silva[2,3] and Cátia Duarte[1,3], [1]Rheumatology, Centro Hospitalar e Universitário de Coimbra - Hospitais da Universidade de Coimbra, EPE, Coimbra, Portugal, [2]Centro Hospitalar e Universitário de Coimbra - Hospitais da Universidade de Coimbra, EPE, Coimbra, Portugal, [3]Faculty of Medicine, Universidade de Coimbra, Coimbra, Portugal

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Background/Purpose: Gaenslen's test positivity is characterized by tenderness upon lateral compression (squeezing) of the metacarpophalangeal (MCP) or metatarsophalangeal (MTP) joints. Joint ultrasonography (US) is a useful clinical tool that has increasingly been applied in routine practice in Rheumatology, given its sensitivity over clinical examination for detection of inflammation. The aim of this work was to evaluate the agreement between Gaenslen's test and MTP US findings.

Methods: Consecutive patients referred to the Early Arthritis Clinic in the Rheumatology Unit, in whom arthritis was identified and feet US performed, were included. The following parameters were assessed at the first consultation: (1) spontaneous pain reported by the patient; (2) squeeze test of the MTPs joints; (3) ultrasound MTP synovitis defined as ≥ grade 2 synovial hyperthrophy and/or ≥ grade 1 power-Doppler, identified by an experienced sonographer. Chi-square and Cohen's kappa tests were used to analyse concordance between both methods.

Results: One hundred patients (200 feet) were included (64% women and a mean age of 53±16 years) with half of the patients referring forefoot symptoms spontaneously. None of them presented Morton's neuroma in US, and significant hallux valgus was identified in 8 feet (4%). The Gaenslen's test was positive in 45.0% cases. Among patients with negative Gaenslen's test, 83.6% were free of US changes. The agreement proportion was lower when Gaenslen's test was positive, with 44.4% having normal US. This difference of proportions was statistically significant ($Chi2=33.882$; $p<0.001$; $Kappa=0.401$), revealing a sensitivity and specificity of 73.5% and 69.7%, respectively. A negative predictive value of 83.6% was obtained for Gaenslen's test.

Conclusion: In this study a negative Gaenslen's test of MTP corresponded to a normal US in 84% of the cases. Thus, Gaenslen's test has a high negative predictive value, and may be used as a screening test to exclude MTP involvement in patients with Early Arthritis, without the need for US examination. Positive Gaenslen's test is not regularly related with US abnormalities and may, therefore, justify US examination. Further studies with larger samples are warranted.

Table 1. Distribution of patient's feet, according to squeeze test and ultrasound of MTPs

		Ultrasound +	Ultrasound -
Squeeze test	+	50	40
	-	18	92

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Abstract Number: 168

Ultrasound Evaluation of the Efficacy of Biologic and Targeted Synthetic Dmards Toward Rheumatoid Arthritis Patients: Kyushu Multicenter Rheumatoid Arthritis Ultrasound Prospective Observational Cohort in Japan

Ayako Nishino[1,2], Shin-ya Kawashiri[1,2], Atsushi Kawakami[1,2], Tamami Yoshitama[2], Nobutaka Eiraku[2], Noki Matsuoka[2], Yukitaka Ueki[2], Akitomo Okada[2], Hiroaki Hamada[2], Toshihiko Hidaka[2], Shuji Nagano[2], Tomomi Tsuru[2], Keita Fujikawa[2] and Yojiro Arinobu[2], [1]Department of Immunology and Rheumatology, Nagasaki University, Nagasaki, Japan, [2]Kyushu multicenter rheumatoid arthritis ultrasound prospective observational cohort study group, Nagasaki, Japan

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Background/Purpose: Few prospective ultrasound (US) cohort studies of rheumatoid arthritis (RA) patients treated by biologic or targeted synthetic DMARDs (b/tsDMARDs) are reported. We have been prospectively investigating the course of active RA patients by US after b/tsDMARDs being introduced in Kyushu region, Japan from June, 2013. This is an interim report to explore the characteristic of RA patients classified as therapeutic responders evaluated by US after b/tsDMARDs being introduced.

Methods: A total 150 RA patients were consecutively recruited from 12 rheumatology centers in Kyushu region in Japan from June 2013 to June 2015. They gave their informed consent to be subjected to the protocol that was approved by the Institutional Review Board of Nagasaki University. Disease activity was consecutively evaluated by both US and clinical composite measures such as DAS28, SDAI every 3 months after introduction of b/tsDMARDs therapies. Twenty-two joints including MCP, PIP and wrist joints of bilateral hands were assessed by US for gray scale (GS) and power Doppler (PD) on semi-quantitative scale from 0 to 3 (each total scores from 0 to 66, respectively). The present

data come from the first 6 months observation. We divided the patients into 2 groups by the mean total US scores at 6 months and the patients, total GS or PD score lower than the mean, were classified as therapeutic responders evaluated by US (US responders). We tried to find the characteristic of US responders at 6 months by multivariate logistic regression analysis.

Results: Eighty-six (30 patients in TNF inhibitors, 30 patients in tocilizumab, 23 patients in abatacept, 3 patients in tofacitinib, respectively) out of 150 patients, who completed the first 6 months observation, were evaluated. In overall, total GS and PD scores improved significantly at 6 months as compared to the baseline ($p < 0.001$, respectively). The mean total GS scores at 6 months were 8 (declined from 13 at baseline) whereas PD scores were 3 (declined from 8 at baseline), respectively. Among the baseline variables including age, gender, disease duration, ACPA (%), RF (%), the use of prednisolone (%), the use of MTX (%), bDMARDs-naïve (%), ESR (mm/hr), CRP (mg/dl), DAS28-ESR, SDAI, total GS score and total PD score, multivariate logistic regression analysis identified that total GS score at baseline (odds ratio 0.84, 95% C.I. 0.76-0.92, $p < 0.001$) is the only predictor of GSUS responder at 6 months. In case of PD, total PD score at baseline (odds ratio 0.86, 95% C.I. 0.77-0.94, $p < 0.001$) and bDMARDs-naïve (odds ratio 3.83, 95% C.I. 1.29-12.32, $p = 0.015$) were the predictors of PDUS responder at 6 months.

Conclusion: The clinical characteristic of patients at baseline involves in US disease activity at 6 months treated by b/tsDMARDs. Physicians are recommended to pay attention to this information to consider the efficacy of DMARDs therapies.

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Abstract Number: 169

Ultrasonographic Signs of Inflammation of Metatarsophalangeal Joints in Rheumatoid Arthritis Patients Who Are Treated to Target

Myrthe van der Ven[1], David F. Ten Cate[2], Andreas Gerards[3], Johannes Jacobs[4], Nanno Swen[5], M.H. de Jager[6], Natalja Basoski[7], Cees Haagsma[8], Mieke Hazes[1] and J.J. Luime[1], [1]Rheumatology, Erasmus University Medical Center, Rotterdam, Netherlands, [2]Department of Rheumatology, Erasmus University Medical Center, Rotterdam, Netherlands, [3]Rheumatology, Vlietland Hospital, Schiedam, Netherlands, [4]Rheumatology & Clinical Immunology, University Medical Center Utrecht, Utrecht, Netherlands, [5]Rheumatology, Medical Center Alkmaar, Alkmaar, Netherlands, [6]Department of Rheumatology, Albert Schweitzer Hospital, Dordrecht, Netherlands, [7]Rheumatology, Maasstadziekenhuis, Rotterdam, Netherlands, [8]Rheumatology, Ziekenhuisgroep Twente, Almelo, Netherlands
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Background/Purpose: The feet are often involved in rheumatoid arthritis (RA), but physical examination of the metatarsophalangeal (MTP) joints to detect arthritis is challenging especially in case of obesity, oedema and

malalignment. Ultrasound has proven to be more sensitive than physical examination to detect (subclinical) synovitis in the MTP joints. Our aim was to determine the frequency of subclinical synovitis in the MTP joints by ultrasound among patients in DAS28 remission or low disease activity, and to assess the evolution of ultrasound synovitis in the feet and DAS28 over time in newly diagnosed RA patients who are treated to target.

Methods: A multicentre cohort of newly diagnosed RA patients (ACR 1987 criteria) was followed prospectively for one year. Patients were treatment naïve for synthetic DMARDs, biological DMARDs and glucocorticoids, and symptom duration was less than one year. All patients were treated to target with regular visits. Demographics, clinical (SJC28, TJC28) and laboratory (ESR, RF, ACCP) parameters were recorded at each visit. Ultrasound examination of the dorsal aspect of MTP2-5 joints was performed at baseline, three months and one year. Images were scored on greyscale (GS;0-3) and power Doppler (PD;0-3). An ultrasound positive MTP joint was defined by GS>1 and/or PD>0. Simple descriptive statistics were used and longitudinal course of DAS28 and number of ultrasound positive MTP joints were plotted for each patient.

Results: At baseline, 174 patients were included of whom 159 completed one year follow-up. At baseline, 109 (73%) patients had at least one ultrasound positive MTP joint. Overall, mean(sd) DAS28 decreased from 4.9(1.3) at baseline to 2.3(1.2) at one year, while the number of ultrasound positive MTP joints decreased from median(interquartile range) 1(0-4) at baseline to 0(0-0) at one year. Discordance in evolution of DAS28 and ultrasound positive MTP joints over one year was seen in 9 patients (6%). After one year of follow-up, 98 (62%) patients were in DAS28 remission (DAS28<2.6) of whom 23 (23%) still had at least one ultrasound positive MTP joint. Twenty-nine patients had low disease activity (DAS28≤3.2) of whom 7 (24%) had at least one ultrasound positive MTP joint.

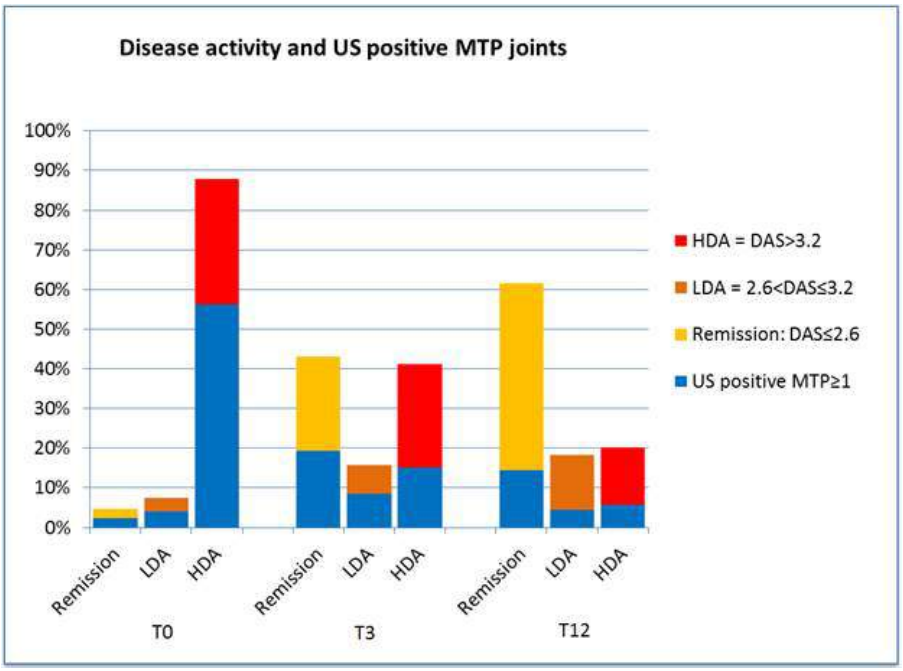
Conclusion: Most patients (94%) improved both in DAS28 score and number of US positive MTP joints during follow-up. However, 23% of the early RA patients in DAS28 remission still had ultrasound synovitis in at least one MTP joint at one year. Monitoring of MTP joints by ultrasound and subsequent steering of treatment might be considered to prevent for example progressive radiological damage.

Table 1. Baseline characteristics and ultrasound findings

	Visit 1 (n = 174)
Age, mean (sd) years	55 (14)
Women, %	64
RF positive, %	66
ACCP positive, %	60

	Visit 1 (n = 174)	*Visit 2 (n = 165)*	*Visit 3 (n = 159)*
DAS28, mean (sd)	4.9 (1.3)	2.9 (1.3)	2.3 (1.2)
SJC, median (IQR)	6 (3-11)	1 (0-4)	0 (0-1)
TJC, median (IQR)	6 (2-10)	1 (0-4)	0 (0-2)
ESR, median (IQR)	27 (12-47)	10 (5-22)	8 (3-17)
DAS28 remission, %	5	43	62
DAS28 LDA, %	7	16	18
US MTP, median (IQR)	1 (0-4)	0 (0-2)	0 (0-0)
US MTP > 0, %	73	43	25

US = ultrasound; LDA = low disease activity; sd = standard deviation; IQR = interquartile range



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Relationship Between Finger Joint Cartilage Evaluated By Ultrasound and Clinical Characteristics in Rheumatoid Arthritis (RA)

Takehisa Ogura[1], Ayako Hirata[1], Hideki Ito[2], Sayaka Takenaka[2], Kennosuke Mizushina[1], Yuki Fujisawa[1], Naoko Yamashita[1], Munetugu Imamura[2], Norihide Hayashi[2] and Hideto Kameda[1], [1]Department of Rheumatology, Toho University Ohashi Medical Center, Tokyo, Japan, [2]Toho University Ohashi Medical Center, Tokyo, Japan
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Background/Purpose: Joint destruction is the primary lesion by bone and cartilage damage in RA. By X-ray examination, cartilage destruction is evaluated as a joint space narrowing, although it is not the direct evaluation of cartilage itself. The aim of the study was to clarify the relationship between the finger joint cartilage evaluated by ultrasound (US) imaging and clinical characteristics in RA.

Methods: We examined 29 RA patients in clinical remission (DAS28-CRP < 2.6). The cartilage layer of metacarpophalangeal (MCP) and proximal interphalangeal (PIP) joints for 2nd to 5th fingers was bilaterally visualized from a dorsal view, with joints in approximately 90 degrees flexion. Cartilage thickness (CT) was measured with

integrated tools on static images, and thickness was compared with other clinical and laboratory parameters.

Results: CT in MCP joints ranged from 0.0 to 0.8 mm (average 0.4 mm), and CT in PIP ranged from 0.0 to 0.5mm (average 0.2mm), respectively. The sum of total CT from 8 fingers ranged from 2.7 to 6.8 mm (average 4.8 mm). CT measured by ultrasound was not correlated with age, DAS28-CRP, functional disability score, positivity of rheumatoid factor and anti-CCP-antibody. However, there was significant relationship between CT and disease duration (r=-0.438, p=0.017). Moreover, CT was reduced in RA patients with elevated serum matrix metalloproteinase-3 (MMP-3) values compared with those with normal MMP-3 values (4.2 versus 5.0, p=0,046).

Conclusion: The US method of direct visualization and quantification of cartilage in MCP and PIP joints can be valid and useful in RA, and our results supported the importance of MMP-3 in the pathophysiology of cartilage destruction.

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Abstract Number: 171

Serum Calprotectin Levels Correlate with Ultrasonographic Synovitis in Rheumatoid Arthritis Patients

Jana Hurnakova[1], Jakub Zavada[1], Petra Hanova[1], Hana Hulejová[1], Martin Klein[1], Herman F Mann[1], Olga Sleglova[1], Marta Olejarova[1], Šárka Forejtová[1], Olga Ruzickova[1], Martin Komarc[2], Jiri Vencovsky[1], Karel Pavelka[1] and Ladislav Senolt[1], [1]Institute of Rheumatology and Department of Rheumatology, 1st Faculty of Medicine, Charles University, Prague, Czech Republic, Prague, Czech Republic, [2]Institute of Biophysics and Informatics of the First Faculty of Medicine, Charles University, Prague, Czech Republic

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Background/Purpose:

Calprotectin (S100A8/9, MRP8/14) has been demonstrated as a promising biomarker of clinical and laboratory disease activity in rheumatoid arthritis (RA). In addition, two small previous studies have shown that calprotectin might by associated with ultrasound-determined synovitis [1,2]. The aim was to evaluate associations between calprotectin and conventional disease markers as well as ultrasound parameters of disease activity in a larger cohort of RA patients.

Methods:

A total of 160 patients with RA (128 females, median disease duration 4.8 years) were recruited in this study. All patients underwent clinical (DAS28, CDAI, SDAI) and ultrasound examination (German US-7 score) [3]. The levels of serum calprotectin and CRP were measured at the time of ultrasound assessment. Clinical and laboratory measures were correlated with ultrasound findings using Spearman´s correlation coefficient. Multiple regression analysis was used to determine the predictive value of calprotectin, CRP and DAS28 to determine GS and PD synovitis scores.

Results:

We found that calprotectin was significantly associated with DAS28 (r=0.332, p<0.001), SDAI (r=0.318, p<0.001), CDAI (r=0.294, p<0.001) and particularly with CRP levels (r=0.551, p<0.001). Moreover, calprotectin significantly correlated with GS (r=0.366, p<0.001) and PD synovitis scores (r=0.350, p<0.001). In multiple regression analysis, DAS28 and calprotectin, but not CRP, were strong predictors of GS (β=0.598, p<0.001; β=0.371, p<0.001, resp.) (adjusted R2=0.680) and PD synovitis scores (β=0.379, p<0.001; β=0.346, p<0.001, resp.) (adjusted R2=0.633).

Conclusion:

Calprotectin is associated with clinical, laboratory and ultrasound parameters of synovial inflammation and may have an additional role in monitoring disease activity in RA.

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Abstract Number: 172

Prospective Assessment of Carotid Intima Media Thickness in Relation to Activity of the Disease in Patients with Rheumatoid Arthritis

Bozena Targonska-Stepniak[1], Mariusz Piotrowski[1], Robert Zwolak[2] and Maria Majdan[3], [1]Rheumatology and Connective Tissue Diseases, Medical University of Lublin, Poland, Lublin, Poland, [2]Rheumatologyand Connective Tissue Diseases, Medical University of Lublin, Lublin, Poland, [3]Department of Rheumatology and Connective Tissue Diseases, Medical University in Lublin, Poland, Lublin, Poland

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Background/Purpose: Rheumatoid arthritis (RA) is a chronic, inflammatory disease that is complicated by accelerated atherosclerosis associated with the risk of adverse cardiovascular (CV) events and death. Traditional risk factors do not fully explain the increased CV risk in RA. RA-related inflammation that is responsible for joint damage may be implicated in the development of accelerated atherosclerosis. Carotid intima-media thickness (cIMT) has been

approved as a surrogate marker of early atherosclerosis. The goal of the study was to assess (1) prospectively cIMT in patients with established RA, (2) the relationship between cIMT and RA activity estimated by clinical examination and ultrasonography of joints.

Methods: The study group consisted of 40 consecutive RA patients, 33 (82,5%) female and 7 male (17,5%) with the mean (SD) age 52.3 (9.8) (range 24-68) and disease duration 18.6 (9.6) years (range 6.5-45). The assessment of cIMT was performed twice, in the space of six years (the initial in 2008 and consecutive in 2014) and was determined by high-resolution B-mode ultrasonography. The activity of RA was estimated by clinical examination [with disease activity score in 28 joints (DAS28)] and ultrasonography of joints (synovial hypertrophy in 24 small joints). At the consecutive visit, high disease activity was observed in 7 (17,5%) patients, and low RA activity or remission in 23 (57,5%). Most patients, 35 (87,5%) were treated with biological disease modifying antirheumatic drugs (DMARDs) during the six years period and only synthetic DMARds were used in 5 (12,5%) patients.

Results: The mean (SD) cIMT value was significantly greater at consecutive than initial assessment [0.86 (0.45) vs 0.75 (0.13) mm, p= 0.02]. The number of RA patients with advanced atherosclerosis (presence of plaques) increased from 6 (15%) at the initial to 9 (22,5%) at the consecutive assessment (NS). The number of patients without atherosclerosis (cIMT < 0.6 mm) deceased from 4 (10%) at the initial to 3 (7,5%) at the consecutive assessment. The value of cIMT correlated positively with the age of patients (p< 0,001) and the two cIMT values correlated with each other (p=0,01). There was no correlation between cIMT value and parameters of RA activity (DAS28 and synovial hypertrophy in ultrasonography). There was a positive correlation between DAS28 value and the number of joints with synovial hypertrophy assessed in ultrasonography.

Conclusion: During the six-years course of established RA, progression of atherosclerosis was observed, estimated by significantly greater mean cIMT value, as well as increased number of patients with atherosclerotic plaques. Progressive atherosclerosis occurred in spite of intensive RA treatment, including biological DMARDs. The process seems to be dependent on the age and was not correlated with the current RA joint activity.

Disclosure: B. Targonska-Stepniak, None; **M. Piotrowski**, None; **R. Zwolak**, None; **M. Majdan**, None.

Abstract Number: 173

The Automated Software-Guided Ultrasound Assessment of Bilateral Common Carotids Intima-Media Thickness for Investigation of Cardiovascular Risk in Psoriasis:Comparison Between Patients with or without Arthritis

Marina Azevedo Dias[1], Laura Maria Silva de Siqueira[2], Bárbara Nascimento de Carvalho[3], Marcelo Pinheiro[4], José Alexandre Mendonça[5] and Karine Luz[6], [1]Univeridade Nove de Julho, Sao Paulo, Brazil, [2]Universidade Nove de Julho, Sao Paulo, Brazil, [3]Universidade Federal de São Paulo, São Paulo, Brazil, [4]Rheumatology Division, Universidade Federal de São Paulo, São Paulo, Brazil, [5]4Rheumatology Unit, Hospital da Pontifícia Universidade Católica (PUC) de Campinas, Campinas, Brazil, Porto Alegre, Brazil, [6]Rheumatology, Universidade Nove de Julho, São Paulo, Brazil

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Background/Purpose: Recent studies have shown the relationship between psoriasis (Ps) and subclinical atherosclerosis (athero). Currently, a new automated ultrasound software, based on radio frequency, called RF-QIMT technology ,proved to be a useful method for assessing subclinical atherosclerosis with the measurement of the intima-media thickness (IMT) in carotid arteries. Aim: To compare the carotid IMT in patients with ordinary Ps and psoriatic arthritis (PsA) through the RF-QIMT. **Methods:** Total of 30 patients with Ps (n = 15), and APs (n = 15) (CASPAR, 2006) were enrolled in this case-control study. Patients with diabetes mellittus, dyslipidemia, previous cardiovascular events and smokers were excluded. We evaluated the measurement of waist circumference, blood pressure, body mass index (BMI) and disease activity, including PASI. Moreover, they were assessed for cardiovascular risk with the Framingham score and the measured the IMT of both common carotids adopting an automatic software (called RF-QIMT) and laboratory tests, including fasting glucose, total cholesterol and fractions and ESR. **Results:** Mean age and disease duration was 50.1 ± 9.8 years and 17.8 ± 11.3 years and 54 ± 13 and 14 ± 9.2 years in patients with Ps and APs, respectively, with a slight predominance of men in those with skin disease (50% vs. 43.8%), but no statistical difference between the groups (p> 0.05). In addition, there was no statistical difference between the groups regarding BMI (28.1 ± 6.1 vs. 26.4 ± 5.6 kg / m2), waist circumference (97.6 ± 13.2 vs. 97.8 ± 14.8 cm and ESR (24.8 ± 17.4 vs. 30.2 ± 29.1 mm). Ps patients had significantly higher PASI than those with APs (9.3 ± 9.7 and 2.5 ± 4.8). On the other hand, APs patients had greater Framingham score (13% vs. moderate risk in Ps 60% the APs, p <0.05). There was no statistical difference in relation to the average values of IMT (0.641 ± 0.744 vs. 0,144mm in Ps ± 0,197mm in APs), the standard deviation (SD) of the six average values indicated by the system, were ranging from 12,6µm to 11,13µm, respectively. Despite, it was found that 60% of the patients with Ps and 80% of those APs had higher IMT measurement than expected (p <0.05). There was no statistically significant correlation between IMT and BMI, CA, PASI and ESR variables. However, there was a statistically significant correlation (r = 0.5; p <0.05) between the IMT measurement and the Framingham score. **Conclusion:** The results show that patients with Ps and APs have high rates of subclinical atherosclerosis, which can be measured by the new adopting an automatic software (called RF-QIMT) of evaluating the IMT, moreover there was correlation and validation with cardiovascular risk score.

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Abstract Number: 174

High Resolution Ultrasound of the Midfoot: Sonography Is Superior to Conventional Radiography in Detection of Osteophytes and Erosions in Inflammatory and Non-Inflammatory Joint Disease

Mathis Camerer[1], Boris P. Ehrenstein[2], Martin Fleck[3], Patrick Hoffstetter[4] and **Wolfgang Hartung**[5], [1]Rheumatology and Clinical Immunology, Asklepios Clinic Bad Abbach, Bad Abbach, Germany, [2]Department of Rheumatology/Clinical Immunology, Asklepios Medical Center, 93077 Bad Abbach, Germany, [3]Department of Internal Medicine I, University of Regensburg, 93042 Regensburg, Germany, [4]Radiology, Asklepios Clinic Bad Abbach, Bad Abbach, Germany, [5]Rheumatology & Clinical Immunology, Asklepios Clinic Bad Abbach, Bad Abbach, Germany
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Background/Purpose:

Ultrasound (US) as well as conventional radiography (CR) are established imaging modalities for the assessment of cortical bone lesions including erosions and osteophytes. Several studies compared both methods in different joint regions, however, midfoot joints have not been addressed so far. Therefore, the diagnostic value of high resolution US was compared to CR in the detection of osteophytes and erosions in the midfoot joints in patients suffering from inflammatory (IJD) and non-inflammatory joint disease (NIJD).

Methods:

Patients with current foot radiographs were included and stratified in two cohorts: IJD and NIJD. The midfoot joints of both feet (talonavicular, calcaneocuboid, medial / intermediate / lateral naviculocuneiform, and 1st to 5th tarsometatarsal joints) were evaluated by US and CR. US was performed with a high end ultrasound device (Logiq E 9, *GE Healthcare, Buckinghamshire, UK)* with a linear hockey stick probe with 8-18 MHz by one author (W.H.) with long standing experience in musculoskeletal US, whereas CR images were evaluated by an expert in musculoskeletalal radiology (P.H.). Both investigators were blinded to diagnoses and results of the complementary imaging modality. US: Presence of osteophytes (cortical protrusions > 1 mm) and erosions (a cortical break > 1 mm according to the OMERACT definition) were analysed for each joint utilizing a dorsal longitudinal scan. Power Doppler (PD) activity was scored on a semi quantitative scale from 0 to 3. CR: X-rays of each foot (posterior–anterior and lateral view) were performed and presence of osteophytes, erosions and joint space narrowing (JSN) were analysed for each joint.

Results:

A total of 2445 joints in 124 patients (90 with IJD, 34 with NIJD) were assessed. US detected significantly more osteophytes (n=344; 14.1%) than CR (n=13; 0.5%), p<.001 by Chi^2. Only 8 osteophytes were observed by both methods. Osteophytes were most frequently detected in the intermediate and lateral naviculocuneiform joints (19.5% and 17.3%) by US, whereas no osteophytes could be identified in these joints by CR. Of the 13 osteophytes dectected by CR, 5 were present in the 1st tarsometatarsal joint and 4 in the talonavicular joint. US identified 60 vs. 3 erosions by CR, only 1 erosion was detected by both methods. There was no significant agreement between US and CR in detecting erosions and osteophytes (κ-statistic .029 - .035). While CR demonstrated a higher prevalence of JSN in IJD (14.8%) compared to NIJD (8.8%), p<.001 by Chi^2, there were more erosions observed by US in IJD (2.9%) than in NIJD (1.3%), p=.026 by Chi^2. Contrary to results from other joint regions, PDUS demonstrated no significant difference of the rate of midfoot joints with hyperperfusion comparing patients with IJD (8.5%) and NIJD (7.8%), p=.839 by Chi^2.

Conclusion:

High resolution US of the midfoot is a valuable tool for the detection of structural bony lesions in the midfoot. Sonography is superior to CR in the identification of osteophytes and erosions in patients suffering from IJD and NIJD.

Disclosure: M. Camerer, None; **B. P. Ehrenstein**, None; **M. Fleck**, None; **P. Hoffstetter**, None; **W. Hartung**, None.

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Abstract Number: 175

Correlating Semiquantitative Ultrasound Scores with Measured Synovial

Thickness

Ralf G. Thiele[1], Darren Tabechian[1], Laura C Coates[2] and Jennifer H. Anolik[1], [1]University of Rochester Medical Center, Rochester, NY, [2]Medicine, University of Rochester, Rochester, NY

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SESSION INFORMATION

Session Date: Sunday, November 8, 2015

Session Title: Imaging of Rheumatic Diseases Poster I: Ultrasound, Optical Imaging and Capillaroscopy

Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose:

In studies of rheumatoid arthritis using ultrasonography (US), findings of synovial thickening are often reported in semiquantitative scores. For synovial biopsies of small joints, selection by US score has been suggested. However, it is not known how consistently US scores translate into a specific measurable synovium thickness in a cohort of RA patients. The aim of this study was to assess consistency of the scoring and the relationship to measurable synovial thickness.

Methods:

Consecutive CCP+ clinic patients fulfilling the 2010 ACR/EULAR RA criteria with ≥1 tender/swollen joint were enrolled. US examinations of dorsal and ulnar wrist and MCPs 2-5 were obtained. All patients were independently scanned by two experienced rheumatologists. A GE Logiq E9 unit was used, with gray scale (GS) frequencies of 15-18 MHz. Measurements were taken using the machine's calipers at maximal joint distension in the dorso-palmar plane. Anatomic landmarks included the hyperechoic bony cortex (or deep hyperechoic duplication of the fibrous joint capsule, if present and visible); intervening hypoechoic synovial tissue; and hyperechoic fibrous joint capsule superficially. Still images were scored for GS synovitis (0-3) by both rheumatologists independently. Tenosynovitis within the extensor carpi ulnaris (ECU) tendon sheath was scored as present (1) or absent (0).

Results:

10 sets of images were scored (7 female and 3 male; biologics, n=3; DMARDs alone, n=4; steroids alone, n=1). 45 joints/regions were measured for maximum depth of synovial thickening (MCP = 35, wrist = 8 and ECU = 2).

Excellent inter operator and inter-reader agreement was achieved for semiquantitative scoring with weighted kappas of 0.98 (95% CI 0.93, 1.00, $p<0.001$, PABAK 0.99)

Average synovial thicknesses for the semi-quantitative scores at each joint region are shown below and were significantly different across the semiquantitative US scores (independent samples Kruskal-Wallis test $p<0.001$). 26 of 28 joints (92.9%) scoring GS ≥2 had a synovial depth of ≥2mm. All wrist joints (6/6) with ≥2 GS synovitis had ≥2mm depth, while 20 of 22 MCP joints with ≥2 GS synovitis had ≥2mm depth.

Joint	Semi-quantitative GS Score	n	Mean synovial thickness in cm	SD	Median	Min	Max	Lower quartile	Upper quartile
MCP	1	13	0.130	0.071	0.1	0.07	0.3	0.09	0.125
	2	14	0.239	0.037	0.235	0.18	0.29	0.21	0.28
	3	8	0.451	0.125	0.475	0.26	0.62	0.343	0.558
Wrist	1	2	0.185	0.078	0.185	0.13	0.24	0.13	n/a
	2	4	0.455	0.149	0.405	0.34	0.67	0.348	0.613
	3	2	0.615	0.078	0.615	0.56	0.67	0.56	n/a
Ulnar	1	2	0.110	0.014	0.110	0.10	0.12	0.1	n/a

Conclusion:

The vast majority of hand and wrist joints graded semiquantitatively at 2 or 3 had at least 2 mm synovial thickening and would be theoretically amenable to biopsy (with a typical 2 mm instrument such as Quick-Core®). Even though experienced rheumatologists can reach excellent inter-reader reliability for semiquantitave US scores, we found significant variation of the actual measured synovial thickness within a given score category. The same score can translate into different mean measured synovial thickness across different joint areas. Greater synovial thickness was measured for wrist joints than MCP joints for a given category. This needs to be taken into account when planning synovial biopsies of small joints.

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Disclosure: R. G. Thiele, None; **D. Tabechian**, None; **L. C. Coates**, AbbVie, Celgene, Janssen, Novartis, Pfizer, MSD, Boehringer-Ingelheim and UCB., 9; **J. H. Anolik**, None.

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Abstract Number: 176

Considerable Discrepancy Between Patient's Assessment and Ultrasonography Assessment on the Most Affected Joint in Rheumatoid Arthritis

Ryusuke Yoshimi[1], Yukihiro Toyota[1], Naomi Tsuchida[1], Yumiko Sugiyama[1], Yosuke Kunishita[1], Daiga Kishimoto[1], Reikou Kamiyama[1], Kaoru Minegishi[1], Maasa Hama[1], Yohei Kirino[1], Mitsuhiro Takeno[1,2], Atsuhisa Ueda[1] and Yoshiaki Ishigatsubo[1,3], [1]Department of Internal Medicine and Clinical Immunology, Yokohama City University Graduate School of Medicine, Yokohama, Japan, [2]Department of Allergy and Rheumatology, Nippon Medical School, Tokyo, Japan, [3]Center for Rheumatic Diseases, Yokosuka City Hospital, Yokosuka, Japan
First publication: September 29, 2015

SESSION INFORMATION

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Session Type: ACR Poster Session A
Session Time: 9:00AM-11:00AM

Background/Purpose: Musculoskeletal ultrasonography (US) is a useful tool for the diagnosis and monitoring of rheumatoid arthritis (RA). It is also helpful for promoting patient-clinician communication by visualizing real-time disease activity. Although patients often request assessment of the most symptomatic joints, there is no evidence for benefits associated with assessment of a selected joint on demand from patients. Here we investigated whether the patient's subjective evaluation for the most affected joint agrees with US assessment.

Methods: Power Doppler (PD) US was performed in 8 joints, including bilateral MCP 2, MCP 3, wrist and knee joints, as a routine examination in a cumulative total of 406 patients with RA. At the examination, patients declared the most symptomatically affected joint. In patients who had the most affected joint except the routine 8 joints, the joint was additionally scanned. PD signals and gray-scale (GS) images were scored semiquantitatively from 0 to 3 in each joint. If PD or GS score of the declared joint was the highest of the scores of scanned joints, the patient's evaluation was regarded as agreeing with US assessment.

Results: Forty-nine patients were asymptomatic. The remaining patients were divided into two groups based on the most symptomatic joints. Group A consisted of 209 patients having the most symptomatic joint among the routine 8 joints, whereas 148 patients having the most symptomatic joint other than the routine 8 joints were included in Group B. In five patients (3.4%) of Group B, PD signals were detected in the most symptomatic joints (shoulder, elbow, MCP 1, and 2 ankles), despite the negative results in the routine 8 joint assessments. In the symptomatic group (Group A and B), the agreement rates of the patient's evaluation with PD and GS scores were 64.4% and 60.2%, respectively. The agreement rate with PD score in Group B was significantly lower than in Group A (51.4% vs 73.7%, $P = 1.9 \times 10^{-5}$). The agreement rate with GS score in Group B was also significantly lower than in Group A (45.3% vs 70.8%, $P = 1.3 \times 10^{-6}$). Among the cases having positive PD score in any joints ($n = 285$), the agreement rate with PD score was 55.4% in the symptomatic group (Figure 1). The agreement rate with PD score in Group B ($n = 109$) was significantly lower than Group A (n = 176) (33.9% vs 68.8%, $P = 1.2 \times 10^{-8}$). Among the cases having positive GS score in any joints ($n = 352$), the agreement rate with GS score was 59.7% in the symptomatic group (Figure 1). The agreement rate with GS score in Group B ($n = 144$) was significantly lower than Group A ($n = 208$) (43.8% vs 70.7%, $P = 5.6 \times 10^{-7}$).

Conclusion: This study suggests that agreement between patient's subjective evaluation and US assessment on the most affected joints was quite poor, especially in case the most symptomatic joint was not included in the routine 8 joints.

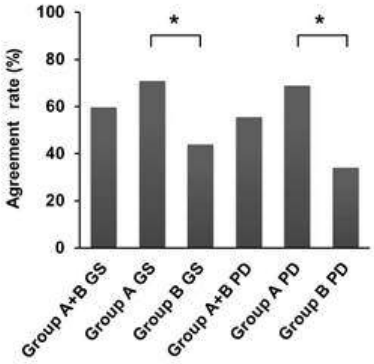

Figure 1 The agreement rates of the patient's evaluation with US assessment on the most affected joints in RA cases with positive US scores.

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Abstract Number: 177

Ultrasonographic Joint Evaluation in Daily Practice: What Is Its Contribution to Clinical Assessment?

Tomas Cazenave[1], Christian A. Waimann[2], Gustavo Citera[1] and Marcos G. Rosemffet[1], [1]Rheumatology, Instituto de Rehabilitación Psicofísica, Buenos Aires, Argentina, [2]Rheumatology, Hospital Dr. Hector Cura, Olavarria, Argentina
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Session Time: 9:00AM-11:00AM

Background/Purpose: Ultrasonography (US) has become a support tool for the daily management of rheumatologic patients. However, when and how to use it remains a subject of discussion. *Objective:*To determine the added value of articular US joint count, compared to clinical joint count for measuring disease activity in patients with rheumatoid arthritis (RA).

Methods: A cross-sectional study including patients with diagnosis of RA (ACR-EULAR 2010) was designed. Patients underwent clinical and US assessment. The clinical examination included 28 joint count visual analog scale (VAS) for global disease activity and erythrocyte sedimentation rate (ESR). Ultrasound evaluation was conducted by two rheumatologists with experience in US who were blind to clinical examination, and included the assessment of 28 joints (according to the DAS28 index). The Power Doppler (PD) signal and gray-scale (GS) were graded from 0-3, according to the OMERACT standards. Swollen joint counts were calculated according to five criteria: One clinical count (Clinical) and four US counts. For the latter, joint swelling was defined according to different standards: a) US Global-OMERACT (PD≥1 presence and / or EG≥1); b) Presence of PD≥1 (US- PD1); c) Presence of PD≥2 (US-PD2); d) Presence of PD = 3 (US-PD3). Additionally DAS28 and the percentage of patients in remission (DAS28≤2.6) were calculated for each joint count criteria.

Results:

We included a total of 49 consecutive RA patients. The mean disease duration was 8 ± 5 years, 85% were women, with a mean age of 53 ± 10 years.

Table 1 shows the different joint counts and their resulting activity rates. The use of the US Global-OMERACT criteria was the method that most frequently detected inflammation. The US swollen joint counts using only the degree of signal PD were not superior to clinical evaluation in the detection of patients with active disease.

Different SJC (28 joints)	SJC (Mean ± SD)	p*	**DAS28** (calculated according to different joint counts)	p&	**Remission** (according to DAS28)
Clinical	5.6 ± 4.8	0.01	4.8 ± 1.5	<0.01	3 (6%)
US-OMERACT	15.6 ±6.1		5.3 ± 1.3		0 (0%)
US-PD1	5.9 ± 4.9		4.8 ± 1.5		3 (6%)
US-PD2	3.2 ± 3.3		4.6 ± 1.4		4 (8%)
US-PD3	0.4 ± 0.8		4.3 ± 1.3		5 (10%)

SJC: swolen joint count

* US-OMERACTwas significantly higher than the other joint counts. & The DAS28 calculated according to US-PD3 count was significantly lower than that calculated by the US-OMERACT.

Conclusion:

In our study US evaluation according to OMERACT criteria was the most sensitive method to detect joint inflammation. However, clinical joint count demonstrated to be a reliable method. Only 6% of patients classified in remission according to clinical examination, were reclassified as active after US assessment. Furthermore, the use of PD signal without GS quantification did not show superiority over clinical examination for the detection of patients with disease activity.

Disclosure: T. Cazenave, None; **C. A. Waimann**, None; **G. Citera**, None; **M. G. Rosemffet**, None.

Abstract Number: 178

3D Ultrasound Doppler Findings in Wrist Tendon Sheaths of Healthy Controls

Mads Ammitzbøll-Danielsen[1], Iustina Janta[2], Søren Torp-Pedersen[3], Esperanza Naredo[2], Mikkel Østergaard[4] and Lene Terslev[5], [1]Center for Rheumatology and Spine Diseases, Rigshospitalet - Glostrup, University of Copenhagen, Denmark, Copenhagen Center for Arthritis Research (COPECARE), Center for Rheumatology and Spine Diseases, Rigshospitalet - Glostrup, University of Copenhagen, Denmark, Glostrup, Denmark, [2]Rheumatology, Hospital General Universitario Gregorio Marañón, Madrid, Spain, [3]Department of Diagnostics, Rigshospitalet and Glostrup Hospital, University of Copenhagen, Glostrup, Denmark, [4]Rigshospitalet-Glostrup, Copenhagen Center for Arthritis Research, Center for Rheumatology and Spine Diseases, Rigshospitalet - Glostrup, Glostrup, Denmark, [5]Copenhagen Center for Arthritis Research (COPECARE), Center for Rheumatology and Spine Diseases, Rigshospitalet - Glostrup, University of Copenhagen, Denmark, Glostrup, Denmark

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Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose:

Even though Doppler ultrasound (US) is used for diagnosing inflammation in arthritides, it is well-known that Doppler signals may be seen in healthy wrist and finger joints (1). Tenosynovitis has been shown to be frequent in rheumatoid arthritis and to predict erosive disease (2). Detailed knowledge of the distribution of feeding vessels in fingers is important to distinguish normal from pathological findings. However, there is no knowledge about Doppler signals in relation to healthy tendon sheaths and the possible pitfalls this may generate.

To investigate presence of feeding vessels in relation to the healthy flexor and extensor tendon sheaths of the wrist by use of 3D Doppler US.

Methods:

Twenty healthy participants were recruited; 10 women in the age 27-54 years and 10 men in the age 27-59 years. None of the participants had finger pain, history of arthritis or any known finger tendon disease, or were smokers.

The participants had US of the palmar and dorsal side of the right wrist. US was carried out using a General Electric Logiq E9 with a 3D ultrasound probe. The Doppler settings were adjusted according to published recommendations (3) with a Doppler frequency of 8.3 MHz and pulse repetition frequency of 0.4. The same Doppler settings were used for all examinations. Specific probe positions on the wrist were selected before study initiation at two different levels (Lister's tubercle and pisiforme). Two scans were made at each position to minimise the risk of missing Doppler findings due to different parts of the cardiac cycle being sampled as the sweep was made. Each tendon sheath was divided into specific areas and the visualized 3D Doppler findings in relation to the tendon sheath were plotted on a schematic drawing (Figure 1A and 1B).

Results:

The overall distribution of feeding vessels was comparable at the level of Lister's tubercle and the level at the pisiforme for the extensor tendons. For the flexor tendons, feeding vessels were more frequent at the level of Lister's tubercle, as shown in figure 1(A and B). Overall feeding vessels were less frequent for compartment V and VI at the level of Lister's tubercle. Feeding vessels were seen less at the superficial location for the extensor tendons, except for compartment I. Radial and dorsal vessels were rare in the tendon sheath of flexor digitorum superficialis and profundus.Intertendineus feeding vessels were mainly seen in the tendon sheath of flexor digitorum superficialis and profundus.

Conclusion:

Feeding vessels in close relation to the extensor and flexor tendon sheaths were common in the wrist of healthy participants and may be a cause of misinterpretation due to artefacts. These vessels should be taken into consideration when diagnosing tenosynovitis in the wrist.

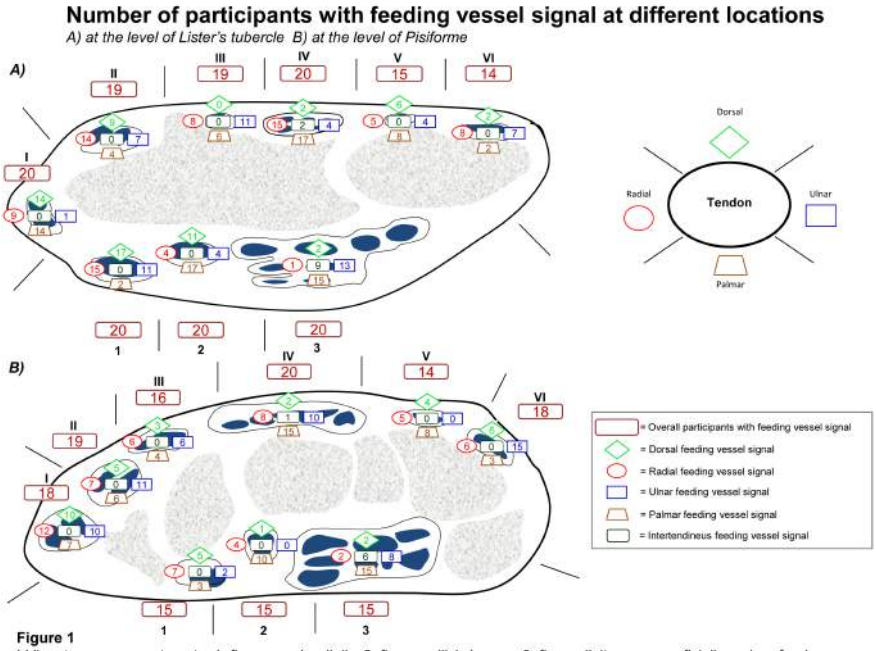

Figure 1
I-VI; extensor compartments 1; flexor carpi radialis 2; flexor pollicis longus 3; flexor digitorum superficialis and profundus

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Disclosure: M. Ammitzbøll-Danielsen, None; **I. Janta**, None; **S. Torp-Pedersen**, None; **E. Naredo**, None; **M. Østergaard**, Abbott Immunology Pharmaceuticals, 9,Pfizer Inc, 9,BMS, 9,UCB, 9,Merck Pharmaceuticals, 9,Janssen Pharmaceutica Product, L.P., 9,Roche Pharmaceuticals, 9; **L. Terslev**, UCB, 8,Abbott Laboratories, 8,MSD, 8,Pfizer Inc, 8,Roche Pharmaceuticals, 8.

Abstract Number: 179

3D Ultrasound Doppler Findings in Finger Tendon Sheaths of Healthy Controls

Mads Ammitzbøll-Danielsen[1], Søren Torp-Pedersen[2], Mikkel Østergaard[3,4], Esperanza Naredo[5] and Lene Terslev[6], [1]Center for Rheumatology and Spine Diseases, Rigshospitalet - Glostrup, University of Copenhagen, Denmark, Copenhagen Center for Arthritis Research (COPECARE), Center for Rheumatology and Spine Diseases, Rigshospitalet - Glostrup, University of Copenhagen, Denmark, Glostrup, Denmark, [2]Department of Diagnostics, Rigshospitalet and Glostrup Hospital, University of Copenhagen, Glostrup, Denmark, [3]Department of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark, [4]Center for Rheumatology and Spine Diseases, Glostrup Hospital, Copenhagen Center for Arthritis Research (COPECARE), Center for Rheumatology and Spine Diseases, Rigshospitalet - Glostrup, University of Copenhagen, Denmark, Glostrup, Denmark, [5]Hospital Severo Ochoa, Madrid, Spain, [6]Copenhagen Center for Arthritis Research (COPECARE), Center for Rheumatology and Spine Diseases, Rigshospitalet - Glostrup, University of Copenhagen, Denmark, Glostrup, Denmark

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Background/Purpose:

Even though Doppler ultrasound(US) is used for diagnosing inflammatory changes it is well-known that Doppler signals are seen in healthy wrist and finger joints. Tenosynovitis has been shown to be frequent in rheumatoid arthritis and to predict erosive disease. Detailed knowledge of the distribution of feeding vessels in fingers is important to distinguish normal from pathological findings. However, there is no knowledge about Doppler signals in relation to healthy tendon sheaths and the possible pitfalls this may generate.

To investigate presence of feeding vessels in relation to the healthy flexor tendon sheaths of the fingers by use of 3D Doppler US.

Methods:

Twenty healthy participants were recruited, 10 women in the age 23-67 years and 10 men in the age 26-54 years. None of the participants had finger pain, history of arthritis or any known finger tendon disease. One participant was a smoker.

The participants had US of the right second and third flexor tendon of the finger (10 men, 10 women). US was carried out using a General Electric Logiq E9 with a 3D ultrasound probe. The Doppler settings were adjusted according to published recommendations with a Doppler frequency of 8.3 MHz and pulse repetition frequency of 0.4. The same Doppler settings were used for all examinations. Specific probe positions on the fingers were selected before study initiation. Two scans were made at each position to minimise the risk of missing Doppler findings, due to different parts of the cardiac cycle being sampled as the sweep was made. Each tendon sheath was divided into specific areas and the visualized 3D Doppler findings in relation to the tendon sheath were plotted on a schematic drawing (Figure 1A).

Results:

The overall distribution of feeding vessels between the 2nd and 3rd flexor tendon were comparable and is shown in

Figure 1A.

The feeding vessels were predominantly seen at ulnar and radial locations, except in the distal part of the metacarpal bones, where the palmar location was common (Figure 1B+C). Palmar vessels were more frequent distally than proximally in the fingers and the dorsal vessels were extremely rare.

Conclusion:

Doppler findings in close relation to the tendon sheaths, due to feeding vessels, were common in flexor tendons of the fingers in healthy participants and may be a cause of misinterpretation. These vessels should be taken into consideration when diagnosing tenosynovitis.

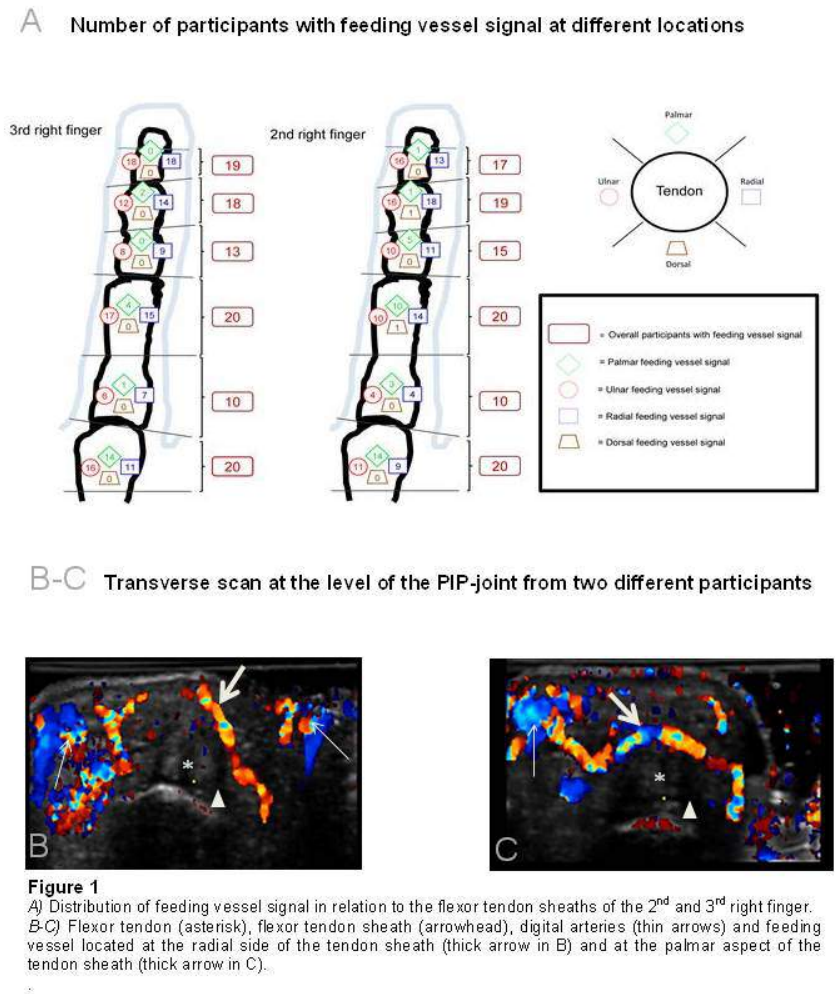

Figure 1
A) Distribution of feeding vessel signal in relation to the flexor tendon sheaths of the 2nd and 3rd right finger. *B-C)* Flexor tendon (asterisk), flexor tendon sheath (arrowhead), digital arteries (thin arrows) and feeding vessel located at the radial side of the tendon sheath (thick arrow in B) and at the palmar aspect of the tendon sheath (thick arrow in C).

Disclosure: M. Ammitzbøll-Danielsen, None; **S. Torp-Pedersen**, None; **M. Østergaard**, Abbott Immunology Pharmaceuticals, 9,Pfizer Inc, 9,BMS, 9,UCB, 9,Merck Pharmaceuticals, 9,Janssen Pharmaceutica Product, L.P., 9,Roche Pharmaceuticals, 9; **E. Naredo**, None; **L. Terslev**, UCB, 8,Abbott Laboratories, 8,MSD, 8,Pfizer Inc, 8,Roche Pharmaceuticals, 8.

finger-tendon-sheaths-of-healthy-controls

Abstract Number: 180

Ultrasound Quantification of Fluid Shifts in the Knees of Arthritis Patients before and after Inflation of a Pneumatic Compressive Device

Richard Meehan[1], **christopher wilson**[2], eric Hoffman[3], Elizabeth Regan[4] and Lynne Altimier[5], [1]Medicine, National Jewish Health, Denver, CO, [2]biomedical enginering, Unviersity of Colorado- Denver, Denver, CO, [3]medicine, national Jewsih Health, westminster, CO, [4]medicine, national Jewish Health.org, denver, CO, [5]radiology, National Jewish Health, denver, CO

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Background/Purpose: Published studies indicate clinicians may miss the intrasynovial knee space during therapeutic injections in excess of 30% of attempts using landmark guided techniques due to small synovial fluid volumes or inexperience of the operator. The purpose of this study was to determine if the fluid volume in the knee available for aspiration or injection could be increased by pneumatic displacement into a target area confirmed using ultrasound imaging.

Methods: 40 knees from 37 consecutive patients from an academic rheumatology practice were studied. All of these patients previously had a medial (27) or lateral (13) knee aspiration or therapeutic injection using a pneumatic compression device. Ultrasound (US) examination was performed during inflation to 100 mmHg and then during deflation. The hook and loop secured device encircled the knee except for a 6 x 9 cm target area available for a US probe or needle placement and was inflated with a hand held manometer. Live images from a GE LOGIQ Book XP ultrasound machine using a 12L-RS probe were recorded onto a Surface Pro laptop computer and analyzed blinded. The fluid compartment (anechoic region) images were analyzed using a histogram based thresholding program which identified the area and linear distance of the anechoic fluid compartment during inflation and deflation.

Results: The study cohort included 28 female and 9 male patients with the following diagnoses: 25 RA, 8 OA, 2 Psoriatic arthritis, and 1 each with SLE and gout. The mean age was 58.6 years (range 23-86) and mean BMI was 26.9 kg/m^2(range 19.1-35.6). The mean increase during inflation vs deflation of the anechoic fluid area was 309% (range 14%-2,048%), $p< 0.001$, and the increase in linear distance during inflation was 182% (range 0%-552%), $p<0.001$ using paired T test analysis. Since none of these patients required a joint aspiration or injection at the time of their study visits, the volume of fluid displaced during a clinically indicated joint aspiration or injection would have likely have been larger than reported in this study.

Conclusion: Quantitative digital image analysis of ultrasound recorded images demonstrate a significant increase in fluid displacement from the synovial space of the knee into a target area available for joint aspiration or injection during inflation to 100 mmHg of a pneumatic compression device. Pneumatic compression may facilitate more successful knee aspirations or injections by increasing the fluid volume in the medial or lateral knee joint space available for needle access and increasing the target area for needle placement.

Disclosure: R. Meehan, State of Colorado Office of Economic Development Grants: Biologic Discovery Evaluation Grant and 2 Advanced Industries Accelerator Grants, 2; **C. wilson**, State of Colorado Industry Accelerator Grant, 2; **E.**

Hoffman, State of Colorado Office of Economic Development Grants: Biologic Discovery Evaluation Grant and 2 Advanced Industries Accelerator Grants, 2; **E. Regan**, None; **L. Altimier**, None.

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Abstract Number: 181

A Vascular Obstacle in Ultrasound Guided Hip Joint Injection

MaryAnn Zhang[1], Monica Pessina[2], Jay B. Higgs[3] and Eugene Y. Kissin[4], [1]Internal Medicine, Boston University School of Medicine, Boston, MA, [2]Anatomy, Boston University School of Medicine, Boston, MA, [3]Rheumatology Service, Brooke Army Medical Center, San Antonio, TX, [4]Boston University School of Medicine, Boston, MA
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Session Time: 9:00AM-11:00AM

Background/Purpose:

Injury of the lateral circumflex femoral artery (LCFA) is a potential cause of bleeding during invasive hip procedures due to its close proximity to the femoral acetabular joint. However, the LCFA is not routinely cited as a structure to avoid during intra-articular hip injections. The purpose of this study was to evaluate the risk of LCFA injury during ultrasound guided hip joint injection.

Methods:

1) We searched the PUBMED database (1967 to Apr 2015) for existing literature on basic techniques for ultrasound guided hip joint injection using the following search string: [“injection” OR “arthrocentesis” OR “aspiration”] AND [“hip” OR “intra-articular” OR “acetabulofemoral” OR “coxofemoral”] AND [“ultrasound” OR “ultrasonography” OR “ultrasound-guided” OR “image-guided”]. 52 non-English studies were excluded. 5 textbooks on musculoskeletal ultrasound were also reviewed. Resulting literature was screened for mention of the LCFA. 2) 18g spinal length needles were inserted under ultrasound guidance into the hip joints of 4 human cadavers. The tissues were dissected with the needles in place to expose the LCFA in relationship to the needle. 3) Rheumatologists trained for 8 months in ultrasound used electronic calipers to mark a planned needle trajectory from skin to hip joint on a live human ultrasound image during a musculoskeletal ultrasound final Observed Structured Clinical Examination (OSCE). Doppler imaging was subsequently used to locate the LCFA, and the closest distance between the planned needle trajectory and arterial signal was recorded.

Results:

1) 709 articles and 5 textbook chapters were reviewed; 11 discussed the technique of ultrasound guidance for hip injection. Of these 11 citations, 7 highlighted the femoral vascular bundle as a structure to avoid but only one specified routine use of Doppler imaging or specifically to avoid the LCFA. 2) In 3 out of the 4 human cadaveric dissections, the needle inserted into the hip under ultrasound guidance also made direct contact with the LFCA. 3) Of 27 OSCE participants, only 2 chose to activate Doppler imaging before marking their simulated hip injection trajectory. The electronic needle trajectory markings were subsequently found to pass through LFCA region Doppler signal in 6 (22%) cases. Among all 27 participants, the mean shortest distance from needle trajectory to arterial signal was 4mm (range 0-11mm).

Conclusion:

The risk of LCFA injury during ultrasound guided hip joint injection is substantial. Although the clinical significance of LCFA injury remains unclear, for high risk individuals (such as those on chronic anticoagulation), we suggest routine use of Doppler imaging as a part of standard hip injection protocols. Further study is required to determine if a more oblique or transverse approach to the hip will reduce the risk of accidental vascular injury.

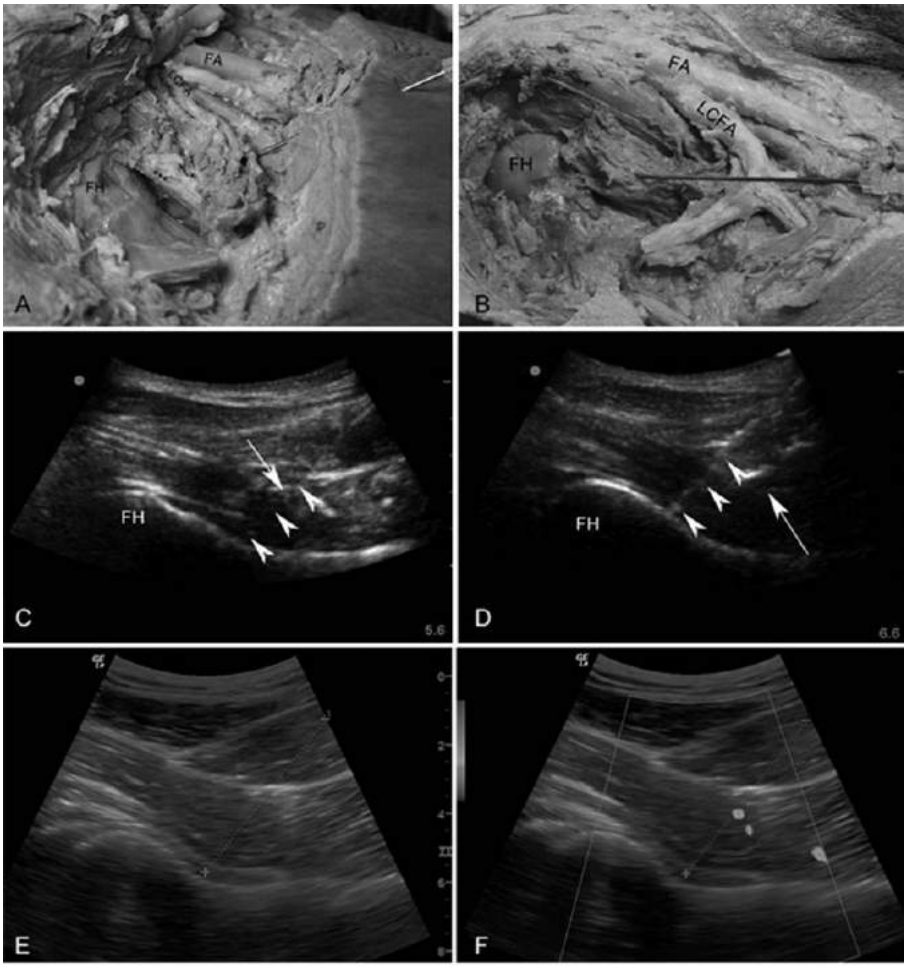

Figure 1. A) Injection of human cadaveric hip joint under ultrasound guidance using anterior longitudinal approach with subsequent dissection. Needle comes in close proximity to lateral circumflex femoral artery (LCFA); surrounding femoral head (FH) and femoral artery (FA) are also exposed. B) Similar dissection as Fig 1 A but with a more oblique approach to needle entry. Injury of the lateral circumflex femoral artery is avoided. C) Ultrasound of image A, showing needle (arrowheads), femoral vessels (arrow), and femoral head (FH). D) Ultrasound of image B. E) Simulated hip injection during OSCE. Electronic calipers mark examinee's planned needle trajectory from skin to hip joint. F) Doppler imaging is subsequently activated and reveals close proximity of LCFA to needle.

Disclosure: M. Zhang, None; **M. Pessina**, None; **J. B. Higgs**, None; **E. Y. Kissin**, None.

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Abstract Number: 182

Agreement Between Ultrasound and Radiography for the Detection of Rhizarthrosis

Maria de los Angeles Gallardo[1], Facundo Vergara[1], Emmanuel Bertiller[2], Javier Rosa[3], Santiago Ruta[1], Ricardo Garcia-Monaco[4] and Enrique R. Soriano[5], [1]Rheumatology Unit, Internal Medicine Service, Hospital Italiano de Buenos Aires, Buenos Aires, Argentina, [2]Rheumatology Unit, Internal Medicine Service, Hospital Italiano de Buenos Aires, Instituto Universitario Hospital Italiano de Buenos Aires, and Fundacion PM Catoggio, Buenos Aires, Argentina, [3]Rheumatology, Hospital Italiano de Buenos Aires, Buenos Aires, Argentina, [4]Radiology and Imagenology Department, Hospital italiano de Buenos Aires, Buenos Aires, Argentina, [5]Internal Medicine, Hospital Italiano de Buenos Aires, Buenos Aires, Argentina
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SESSION INFORMATION

Session Date: Sunday, November 8, 2015

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Session Type: ACR Poster Session A

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Background/Purpose: Trapeziometacarpal (TMC) joint is a common site of osteoarthritis (OA)(rhizarthrosis). Its diagnosis is based on clinical and radiological (X-ray) features. It is not clear the usefulness of ultrasound (US) for the diagnosis of rhizarthrosis. The objective of the present study was to evaluate the utility of US for the diagnosis of rhizarthrosis, compared with X-ray.

Methods: A retrospective analysis of all consecutive patients who had undergone X-ray and US of both hands, no more than 30 days apart, between January 2012 and December 2014 was performed. Demographic and clinical data were recorded. All US examinations were performed by an experienced rheumatologist, blinded to X-ray data, using a MyLab 70 (Esaote) machine provided with 6-18 MHz broad band multifrequency linear transducer. TMC joint was evaluated for the presence of osteophytes, defined as protrusions of cortical bone from the margins of the joint observable in two perpendicular planes. US findings at TMC joint were also graded on a 0 to 3 scale (0= abscence of degenerative changes; 1= mild : presence of osteophytes ≤ 2 mm; 2= moderate: presence of osteophytes > 2 mm; 3= marked: presence of osteophytes > 2 mm associated with loss of normal joint architecture). X-rays were read by another experienced rheumatologist, blinded to US data, to determine the presence of asymmetrical joint space narrowing and/or osteophytes at TMC joint. Using Eaton's criteria, X-ray rhizarthrosis was also graded from 1 to 4 (Stage 1: Normal joint space or slight widening. Subluxation < 1/3; Stage 2: Decreased TMC joint space. Small (< 2 mm) osteophytes or loose bodies. Subluxation < 1/3; Stage 3: More decreased TMC joint space. Subchondral cysts or sclerosis. Osteophytes or loose bodies ≥ 2 mm. At least 1/3 of subluxation; Stage 4: Stage 3 in addition to involvement of the scaphotrapezial joint).

Results: A total of 378 TMC joints from 189 patients were included for the final analysis. One hundred twenty-eight (67.7%) patients were female and mean age (SD) was 64.1 (14) years. X-ray and US diagnosis agreed in 365 out of 378 (96.5%) TMC joints (figure 1). In 71 TMC joints both imaging methods disregarded OA and in 294 both methods confirmed the diagnosis of rhizarthrosis (unweighted kappa value: 0.895 ;95% CI: 0.84-0.95). Intraclass correlation coefficient for rhizarthrosis grades for both imaging modalities was 0.9 (95% CI: 0.88-0.92). Table shows the distribution of Eaton's X-ray stages and US grades of rhizarthrosis.

Conclusion: US and X-ray showed an excellent agreement for the diagnosis of rhizarthrosis and excellent correlation for the severity of the involvement. US might be used for the diagnosis and severity classification of OA of the TMC joint.

Table. Distribution of Eaton's X-ray stages and US grades of rhizarthrosis.

		US				
		Grade 0	**Grade 1**	**Grade 2**	**Grade 3**	
X-ray	**Stage 0**	71	9	2	0	82
	Stage 1	2	60	1	4	67
	Stage 2	1	111	6	5	123
	Stage 3	0	2	45	37	84
	Stage 4	0	0	0	22	22
		74	182	54	68	**378**

Disclosure: M. D. L. A. Gallardo, None; **F. Vergara**, None; **E. Bertiller**, None; **J. Rosa**, None; **S. Ruta**, None; **R. Garcia-Monaco**, None; **E. R. Soriano**, Abbvie; Janssen; UCB; Roche; Bristol Myers Squibb, 2,Abbvie; UCB; Janssen; Roche; Bristol Myers Squibb; Pfizer; Novartis, 8.

Abstract Number: 183

B-Mode and Power Doppler Assessment As Predictors for Short and Long-Term Clinical Outcome in Cts Patients with or without Surgical Treatment

Alexander Marschall[1], Anja Ficjian[1], Martin Stradner[1], Rusmir Husic[1], Dorothea Zauner[2], Werner Seel[3], Nicole E. Simmet[3], Alexander Klammer[1], P Heizer[4], Kerstin Brickmann[1], Judith Gertler[1], Florentine Fürst[1], René Thonhofer[1], Josef Hermann[2], Winfried B. Graninger[5], Stefan Quasthoff[4] and Christian Dejaco[1], [1]Department of Rheumatology and Immunology, Medical University Graz, Graz, Austria, [2]Internal Medicine, Medizinische Universitätsklinik, Graz, Austria, [3]Neurology, Medical University Graz, Graz, Austria, [4]Department of Neurology, Medical University Graz, Graz, Austria, [5]Internal Medicine/Rheumatology, Medical University Graz, Graz, Austria
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Background/Purpose: To investigate the prognostic value of baseline B-mode and Power Doppler (PD) ultrasound assessment of the median nerve in CTS patients with or without surgical treatment, regarding their short and long-term

clinical outcomes.

Methods: Prospective study on 135 patients with suspected CTS, undergoing baseline and two follow-up visits after 3 and 28 months. Clinical, neurophysiological (NCS) and sonographic evaluation was performed at each visit. Cross-sectional Areas (CSA) were sonographically measured at 4 levels at forearm and wrist, and CSA wrist-to-forearm ratios were calculated. PD-signals were subjectively graded from 0-3. Clinical outcomeswere evaluated using the Boston-Questionnaire, DASH-Questionnaire, as well aspatient's assessment of pain and physicians' global assessment according to visual analogue scales (painVAS, physVAS). We conducted multivariate logistic regression models to determine the predictive values of baseline CSA and PD assessments.

Results: Short-term Follow-up visit was completed by 111 Patients and 105 Patients were available for long-term follow-up. At 3 months, 121 wrists (in 80 Patients) have received the final diagnosis of CTS. 13 and 10 CTS Patients showed improvement regarding their BQ at short-term and long-term follow-up, respectively. According to regression analysis, we found that CSA, measured at the level of the Carpal Tunnel inlet, predicted short-term clinical improvement (≥25% according to BQ) in the subgroup of CTS patients undergoing carpal tunnel surgery (OR 1.842, $p < 0.05$), but not in patients treated conservatively ($p=0.804$). CSA or PD assessmentsdid not predict short-term improvement of painVAS, physVAS or DASH, and none of the ultrasound parameters was useful for the prediction of long-term clinical outcomes.

Conclusion: Ultrasound assessment of the median nerve CSA is of limited value to predict short-term clinical outcomes of CTS patients undergoing carpal tunnel release, whereas long-term outcomes are not predicted by sonography results.

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Abstract Number: 184

Rheumatologists and Musculoskeletal Ultrasound: Discrepancy Between Attitudes, Desire and Reality in Routine Practice in South East England

Antigoni Grigoriou[1] and Patrick Kiely[2], [1]Rheumatology, St George's Univeristy Hospitals NHS Foundation Trust, London, United Kingdom, [2]Rheumatology, St George's University Hospitals NHS Foundation Trust, London, United Kingdom

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Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose:

The use of musculoskeletal ultrasound (MSK US) in routine care is expanding. The number of rheumatologists using or seeking to learn the technique is also increasing, though it is unclear how US is being incorporated into routine work practices (RWP). This survey sought to gain an insight into the use of MSK US in a region of Southern England.

Methods:

A questionnaire was designed by the authors to collect information on training, access & service delivery, indications and attitudes towards use of MSK US in RWP. All rheumatology consultants (RC), trainees (RT) and specialist nurses (SN) working in 19 Hospitals (Hs) (4 Medical School Universities, 15 District General) in London South, Kent, Surrey and Sussex regions of England were invited to complete the survey. Data were analysed using simple descriptive and summary statistics.

Results:

A total of 70 questionnaires (51%) were returned (RC 61%, RT 27%, SN 12%) with at least one response from all 19 Hs.

Training: Of the 70 responders (Rs), 42% report having had formal training in the use of US, however only 12% had support for this and 10% have a formal MSK US certificate.

Access & service delivery:MSK US scans are most usually performed by radiologists (64%). In 11 Hs there are also US machines in the rheumatology department, of which 8/11 are currently used for routine care. The routine waiting time for a MSK US is up to 6 weeks.

10 of the 29 Rs who have had training (34%) perform US scans themselves. They report greatest confidence scanning the hands (90%), followed by feet (70%) and 20% are confident to scan all joints. US guided injections are given by 50% and US guided synovial biopsies performed by 20%.

The maximum number of joints scanned in one session varies from 5 – 40 joints, taking an average time of 20 minutes per scan.

Indications:MSK US are requested for diagnostic purposes by 92%, guided injection by 80%, assessment of treatment response by 52%, research purposes by 8% and 75% request a scan at least 1 – 5 times a week. The proportion of Rs requesting MSK US per disease groups is: Inflammatory Arthritis (IA) >85% and soft tissue 63%.

Attitudes: More than 60% of the Rs report that MSK US results often lead to a change in their management plans and that it enhances patients' satisfaction. 82% think it appropriate that RC should perform MSK US scans as part of their RWP. 50% of the RC and 72% of the RT think that proficiency in use of US should be a mandatory part of the rheumatology training curriculum. 51% of the Rs indicated a willingness to learn the technique.

Free text responses revealed concerns about available time and proper training but others commented that MSK US is beneficial in an early IA setting.

Conclusion:

This cross-sectional, observational, multicentre survey demonstrates widespread use of MSK US by rheumatologists in routine care in the South East Coast region of England. 82% of Rs think it appropriate that RC should perform MSK US in RWP and 57% believe training in this should be a mandatory part of the curriculum. In contrast 42% of Rs have had formal training, but only 10% of them have incorporated MSK US into RWP, the majority relying on radiology colleagues to do the scans. This illustrates a discrepancy between attitudes, desire and reality of MSK US use in routine rheumatological practice.

Disclosure: A. Grigoriou, None; **P. Kiely**, None.

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Abstract Number: 185

Success Rate and Utility of Ultrasound Guided Synovial Biopsies in Clinical Practice

Aurélie Najm, Benoît Le Goff and Yves Maugars, Rheumatology, Rheumatology, Nantes, France
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Session Type: ACR Poster Session A
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Background/Purpose: Histological and bacteriological analysis of synovial tissue (ST) can be useful in the diagnosis of arthritis of undetermined origin. Ultrasound can assist this biopsy in directing the needle to relevant sites within the joint as well as allowing an evaluation of synovial inflammation and thickness.

The aims of this study were to describe the indications for US guided synovial biopsies in clinical practice, to determine the rate of success in acquiring ST using this approach and to determine how frequently the synovial biopsy can lead to a definite diagnosis.

Methods: Synovial biopsies of small and large joints were performed under US guidance (Philips HD11 XE) between January 2007 and December 2014 using a semi-automatic core biopsy needle (Tru-cut^{R}).

The patient cohort was characterized clinically. Crystal microscopy, bacteriological (with PCR for Whipple or Lyme disease), mycobacteriological and fungal analysis were performed according to the clinical presentation. Histological features of biopsies were described.

The biopsy procedure was considered as successful if synovial tissue was found at histological examination.

Results: Seventy-two patients underwent 74 synovial biopsies. Fifty-three percent were men and average age was 58,7 years (+/- 16,97).

Biopsies were performed in the following joints: knee (n=42; 56%), ankle (n=7; 10%), wrist (n=7; 10%), shoulder (n=6; 8%), hip (n=4), sterno-clavicular (n=3), elbow (n=3), pubic symphysis (n=1), acromio-clavicular (n=1), first metatarsophalangeal (n=1).

Patients presented with a chronic (> 3 months) monoarthritis in 42 cases (56%), an acute monoarthritis in 17 cases (23%), a chronic polyarthritis in 13 cases (18%), an acute polyarthritis, a chronic tenosynovitis and a chronic bursitis in 1 case respectively.

Biopsies were performed to rule out the diagnosis of septic arthritis in 64 cases (85%) or of villonodular synovitis in 11 cases (15%).

US guided biopsy attempt succeeded in 85% of cases (63 on 74 biopsies performed). Failed biopsies retrieved fibrin deposition or adipose tissue.There was no difference on success rate between small and large joints.

Ten of the 63 biopsies (17,5% of patients) leaded to a definitive diagnosis: 2 septic arthritis (no bacteria found on cultures, but a typical histological aspect), 2 villonodular synovitis, 1 case of amyloid arthritis on a patient having no known myeloma, 1 joint localization of a mantle cell lymphoma, 1 gouty arthritis, 1 osteochondromatosis, 1 Whipple disease (positive PCR on synovial tissue, with negative PCR on synovial fluid) and 1 Lyme arthritis (positive PCR on synovial tissue). The histological analysis of the 54 other biopsies showed a non-specific cell infiltrate with lymphocytes and/or macrophages.

One patient presented a knee hemarthrosis 48 hours after the US guided biopsy.

Conclusion: Ultrasound guided synovial biopsies in clinical practice are performed on patients with heterogeneous features. The rate of success in acquiring synovial tissue is high. The procedure, when successful, leads to a definite diagnosis in more than 1 on 6 patients with an arthritis of undetermined origin.

Disclosure: A. Najm, None; **B. Le Goff**, None; **Y. Maugars**, None.

Abstract Number: 186

B Flow, a Novel Ultrasound Modality in the Assessment of Synovitis in RA

Darren Tabechian[1], Laura C Coates[2], Jennifer H. Anolik[1] and Ralf G. Thiele[1], [1]University of Rochester Medical Center, Rochester, NY, [2]LIMM, Section of Musculoskeletal Disease, University of Leeds, Leeds, United Kingdom
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Background/Purpose:

B flow is a vascular ultrasound (US) technique in which the high resolution aspect of gray scale US is optimized to demonstrate movement of one tissue (particularly of erythrocytes) against the background of stationary structures. Though power Doppler can demonstrate relatively low flow structures such as synovial vessels and the neovascularization characteristic of active synovitis, it is in part a flow-direction dependent technique. B flow has been shown to demonstrate carotid artery stenosis as well as color Doppler techniques while more accurately depicting background non-vascular anatomy [1]. The goal of this study is to evaluate the utility of B flow in the assessment of inflammatory arthritis.

Methods:

In a cohort of 10 patients with CCP positive RA (fulfilling the 2010 EULAR/ACR classification criteria) with at least one swollen joint, 120 joints (wrists and MCP joints) were assessed by gray scale US. 51 of the 120 joints were determined to have grade 1 or greater synovitis and underwent power Doppler and B flow interrogation. Two sonographers independently scanned all patients with a GE logic E9 and a 15Mhz matrix array transducer for PD imaging. B flow was performed with an 18 MHz transducer with settings for venous flow. Image scoring for both PD and b flow was performed by the same 2 rheumatologist sonographers (DT and RT) using a reference scoring atlas [2]

Results:

51 joints were assessed by PD and B flow. There was a good to very good agreement between B flow and PD scores (quadratic weighted kappa 0.62 and prevalence-adjusted and bias-adjusted kappa (PABAK) using quadratic weights k= 0.86, $p<0.0005$). B flow scores were generally lower than PD scores (median B flow score 1, IQ range 0, 2, median PD score 2, IQ range 1, 2). 28 joints showed perfect agreement between modalities giving a percentage exact agreement of 54.9%. 20 of 51 (39.2%) joints had higher PD scores while only 3 of 51(5.88%) had higher B flow scores. Inter-reader reliability was high in both modalities (b flow intraclass correlation coefficient (ICC) 0.978 vs PD ICC 0.964).

Conclusion:

In this pilot study, B flow correlated well with PD in the assessment of rheumatoid synovitis in small and medium sized joints with similarly excellent inter-rater reliability. Both ultrasonographers felt that there were fewer sonographic artifacts with B flow imaging compared to PD and this may explain the lower scores seen on B flow. The ability to clearly demonstrate the background gray scale anatomy while displaying the vascular structures of interest offers advantages over Doppler techniques as artifactual findings can be more clearly recognized and excluded from interpretation.

Funding support provided in part through NIAMS AMP UH2AR067690

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2. Hammer, H.B.,et al., *Examination of intra and interrater reliability with a new ultrasonographic reference atlas for scoring of synovitis in patients with rheumatoid arthritis.* Ann Rheum Dis, 2011.**70**:1995-98

Disclosure: D. Tabechian, None; **L. C. Coates**, AbbVie, Celgene, Janssen, Novartis, Pfizer, MSD, Boehringer-Ingelheim and UCB., 9; **J. H. Anolik**, None; **R. G. Thiele**, None.

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Abstract Number: 187

Detection of Power Doppler Ultrasound Signals in Rheumatic Diseases Using Superb Microvascular Imaging (SMI): Comparison with Conventional Power Doppler Ultrasound

Kazuhiro Yokota[1], Takuma Tsuzuki Wada[2], Yuji Akiyama[2] and Toshihide Mimura[3], [1]Department of Rheumatology & Applied Immunology, Faculty of Medicine, Saitama Medical University, Irama, Japan, [2]Department of Rheumatology & Applied Immunology, Faculty of Medicine, Saitama Medical University, Iruma, Japan, [3]Department of Rheumatology and Applied Immunology, Faculty of Medicine, Saitama Medical University, Saitama, Japan

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Background/Purpose: The detection of power Doppler (PD) ultrasound signals in joints may be considered as the presence of joint inflammation, *i.e.*, synovitis which is a predictor of erosive progression in rheumatoid arthritis (RA). Superb Microvascular Imaging (SMI), a novel ultrasonography, is based on the sensitive Doppler technology with low-motion artifacts than conventional power Doppler ultrasound (cPDUS); furthermore, it can detect low-velocity blood flow signals with high resolution frame rates. Therefore, we evaluated PD ultrasound signals in patients with rheumatic diseases using SMI and cPDUS, and compared the correlations of these signals to clinical and laboratory assessments by these two imaging modalities. Moreover, we also investigated PD ultrasound signals in the difference between

synthetic and biological disease-modifying antirheumatic drugs in patients with RA.

Methods: Twenty-seven patients with RA and 11 non-RA patients with rheumatic diseases were enrolled. We assessed PD signals in the finger, hand, elbow, and knee joints (total 26 joints) by the SMI and cPDUS findings using Aplio 300 (Toshiba Medical Systems). The signals were semiquantified into 4 grades (OMERACT standard, grades 0–3). These individual scores added together to calculate the total SMI score or total cPDUS score (0-114).

Results: The total SMI score was significantly higher than the total cPDUS score in patients with RA (SMI 12.3±11.5 vs. cPDUS 5.2±8.1, $p<0.001$). On the other hand, there was no significant difference between the total SMI and cPDUS scores in patients with non-RA (SMI 0.6±0.7 vs. cPDUS 0.3±0.6, $p=0.1320$). Serum CRP and MMP-3 levels, and HAQ-DI score significantly correlated with the total SMI score in patients with RA (CRP: $r=0.51$, $p=0.006$; MMP-3: $r=0.52$, $p=0.006$; HAQ-DI score: $r=0.41$, $p=0.040$). However, these data did not show up the result of correlation with the total cPDUS score (CRP: $r=0.22$, $p=0.260$; MMP-3: $r=0.26$, $p=0.205$; HAQ-DI score: $r=0.21$, $p=0.295$). In non-methotrexate-treated patients with RA, the total SMI score was significantly higher than the total cPDUS score (n=19, SMI 13.3±11.8 vs. cPDUS 4.1±6.2, $p=0.001$). In contrast, in methotrexate-treated patients with RA, there was no significant difference between the total SMI and cPDUS scores (n=8; SMI 10.0±10.5 vs. cPDUS 7.8±12.1, $p=0.188$).

Conclusion: Our results suggest that SMI can detect PD ultrasound signals more sensitively than cPDUS in patients with RA. Furthermore, it is a requirement for us to pursuit the result of analysis using SMI and cPDUS.

Disclosure: K. Yokota, None; **T. T. Wada**, None; **Y. Akiyama**, None; **T. Mimura**, None.

Abstract Number: 188

Whole-Body Synovial Uptake of a 99mtc-Labelled RGD Peptide Is Highly Correlated with Power Doppler Ultrasound

Toby Garrood[1], Matthew Morrison[2], Dharsha Shivapatham[3], Khaldoun Chaabo[1], Fahim Ul-Hassan[4], Jim Ballinger[4], Gary Cook[5] and Andrew P. Cope[6], [1]Rheumatology, Guy's and St. Thomas' NHS Foundation Trust, London, United Kingdom, [2]GE Healthcare, Amersham, United Kingdom, [3]Department of Rheumatology, Guy's and St. Thomas' NHS Foundation Trust, London, United Kingdom, [4]Nuclear Medicine, Guy's and St. Thomas' NHS Foundation Trust, London, United Kingdom, [5]Imaging Sciences, Kings College London, London, United Kingdom, [6]Academic Department of Rheumatology, King´s College London, London, United Kingdom

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Background/Purpose: Musculoskeletal ultrasound, and specifically power Doppler ultrasound (PDUS), is more sensitive than clinical examination for the assessment of active synovitis in patients with rheumatoid arthritis (RA). In addition, PDUS is predictive of radiographic progression, response to therapy in patients with active disease and of flare in patients in remission. In clinical practice its routine use for assessing large numbers of joints is limited by time constraints. ^{99m}Tc-NC100692 (Maraciclatide) is a tracer consisting of a peptide containing the RGD motif which binds

with high affinity to the integrins $\alpha_v\beta_3$ and $\alpha_v\beta_5$ which are expressed on neoangiogenic blood vessels including those seen in the rheumatoid synovium. This proof-of-concept study aimed to investigate whether uptake of ^{99m}Tc-NC100692 is seen in the joints of patients with active RA and whether this correlates with PDUS.

Methods: 5 patients with active RA (DAS28 >3.2) were recruited. Patients underwent clinical examination including 66/68 swollen/ tender joint counts followed by ultrasound examination of 38 joints with grey scale (GS) and power Doppler (PD) quantification. Each joint was scored on a semi-quantitative scale of 0-3 for GS and PD and a total score for each calculated for each patient. Within 24 hours of the ultrasound patients were injected with 75µg of ^{99m}Tc-NC100692 (740MBq). Whole body planar views and dedicated views of the hands and feet were taken at multiple time points over 3 hours. Images were scored by an observer blinded to the ultrasound findings as positive or negative uptake for each joint (binary score), and in addition a fully quantitative score was obtained for each joint by drawing a region of interest around the joint and correcting for background. The scores were summed to derive a total score for each patient. Ultrasound and ^{99m}Tc-NC100692 scores were tested for correlation with Pearson's correlation coefficient.

Results: Specific uptake of ^{99m}Tc-NC100692 was seen in the joints in all patients with optimal uptake seen at around 2 hours. Specific uptake was also seen in inflamed tendon sheaths at the wrist and ankle. Significant correlation was not seen between DAS28 scores and US scores. Strong correlation was seen between PDUS and whole-body fully quantitative (r^2=0.93, p=0.008) and binary (r^2=0.88, p=0.019) ^{99m}Tc-NC100692 scores . GSUS also correlated strongly with quantitative whole-body ^{99m}Tc-NC100692 scores (r^2=0.79, p=0.042). The imaging procedure was well-tolerated.

Conclusion: We have shown for the first time that a ^{99m}Tc-labelled RGD peptide can specifically image inflamed joints in RA patients. Despite the small numbers, in this pilot study uptake was strongly correlated with PDUS. ^{99m}Tc-NC100692-based planar imaging has the unique advantage of the capacity to image the whole body and hence the total synovial inflammatory load in a single quick acquisition. Furthermore the imaging equipment to perform these scans is widely available in nuclear imaging departments. Hence ^{99m}Tc-NC100692 has potential as an alternative modality for quantifying synovial inflammation in RA patients. Larger studies are planned to investigate ^{99m}Tc-NC100692 imaging in RA patients with a range of disease activities.

Disclosure: T. Garrood, None; **M. Morrison**, Employed by GE Heathcare, 3; **D. Shivapatham**, None; **K. Chaabo**, None; **F. Ul-Hassan**, None; **J. Ballinger**, None; **G. Cook**, None; **A. P. Cope**, None.

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Abstract Number: 189

Indocyanine Green (ICG) -Enhanced Fluorescence Optical Imaging (FOI) in Patients with Active Rheumatoid Arthritis; A Comparative Study with Ultrasound and Association with Biomarkers

Shin-ya Kawashiri[1,2], Ayako Nishino[3], Masataka Umeda[3], Shoichi Fukui[1], Yoshikazu Nakashima[3], Naoki Iwamoto[1], Kunihiro Ichinose[1], Hideki Nakamura[1], Tomoki Origuchi[4], Kiyoshi Aoyagi[2] and Atsushi Kawakami[3], [1]Department of Immunology and Rheumatology, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan, [2]Department of Public Health, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan, [3]Department of Immunology and Rheumatology, Nagasaki University, Nagasaki, Japan, [4]Department of Health Sciences, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan

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Background/Purpose:

Indocyanine green (ICG) -enhanced fluorescence optical imaging (FOI) is a novel diagnostic tool for the assessment of inflammatory arthritis through visualizing vascular beds. Ultrasound (US) can detect joint injury of rheumatoid arthritis (RA) with high sensitivity. We previously reported that US synovitis scores correlate with serum biomarkers such as angiogenesis factors. This study is undertaken to explore the utility of FOI comparing with US and serum biomarkers.

Methods:

Twenty-five active RA patients (mean disease durations 7.5 years and DAS28-ESR 5.90) who fulfilled 2010 RA classification criteria were consecutively enrolled in this study. They gave their informed consent to be subjected to the protocol that was approved by the Institutional Review Board of Nagasaki University. Both FOI and US were performed at the same day. Interpretation of FOI images using Xiralite system was done for an early phase (phase 1, P1), an intermediate phase (phase 2, P2), a late phase (phase 3, P3) and an early electronically generated composite image (CI) from 18 joints including bilateral 2^{nd} -5^{th} metacarpophalangeal (MCP) joints, proximal interphalangeal (PIP) joints and wrist joints (Figure 1). The same joints were scored by gray scale (GS) and power Doppler (PD) by US. FOI assessments of P1, P2, P3, CI as well as GS score and PD score were semi-quantitatively classified from 0 to 3 as described (total scores of each parameter are 0 to 54 from the 18 joints, respectively). Bone erosion was also assessed by US. Forty-five serum biomarkers at the time of FOI/US examinations were measured by multi-suspension cytokine array.

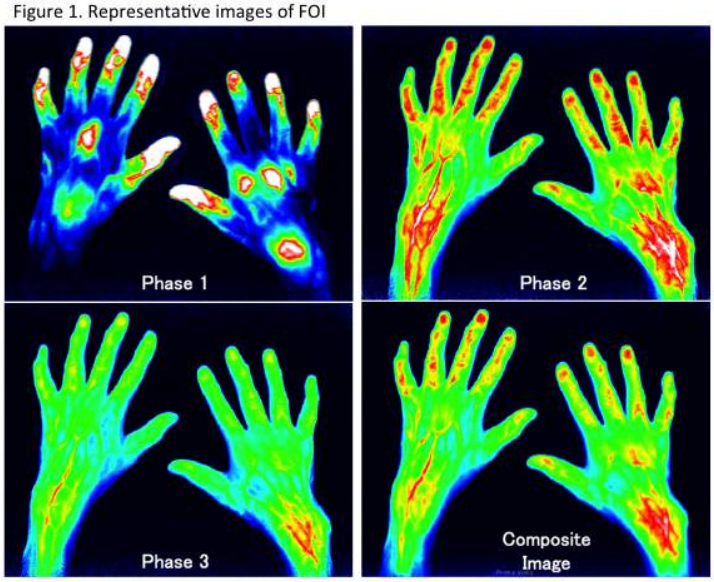
Results:

Positive finding (≥ grade 1) were found in 122, 206, 140, 139 and 148 out of 450 joints in P1, P2, P3, CI and PDUS, respectively. FOI scores were significantly high in the joints where bone erosion was detected by US as compared to those without bone erosion ($p<0.0001$). Among individual patients, each total FOI scores clearly correlated with both GS and PD scores ($r=0.46$-0.71) as well as with DAS28-ESR ($r=0.66$-0.72). In addition, serum IL-6, VEGF and TNF- correlated with FOI scores. Comparing with PDUS ≥ grade 1 or PDUS ≥ grade 2 as the reference, the positive predictive value (PPV) of FOI scores (≥ grade 1) in whole joints were 82.0 (P1), 66.5 (P2), 75.7 (P3) and 76.3 % (CI) toward PDUS ≥ grade 1 or 66.4 (P1), 44.7 (P2), 54.3 (P3) and 56.1 % (CI) toward PDUS ≥ grade 2, respectively.

Conclusion:

Since FOI scores correlate with US scores as well as serum biomarkers, FOI is considered to detect joint inflammation of RA patients with high accuracy. However, the significance of each phase of FOI may be different and need to be further clarified.

Figure 1. Representative images of FOI



Disclosure: S. Y. Kawashiri, None; **A. Nishino**, None; **M. Umeda**, None; **S. Fukui**, None; **Y. Nakashima**, None; **N. Iwamoto**, None; **K. Ichinose**, None; **H. Nakamura**, None; **T. Origuchi**, None; **K. Aoyagi**, None; **A. Kawakami**, None.

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Abstract Number: 190

Ultrasound Imaging with Elastography for the Medical Treatment of Dupuytren's Contracture

Paul John DeMarco[1], Alan K. Matsumoto[1], Nicole Thomas[2], Megan Bishop[1], Andrew Gregory DeMarco[3], Guada Respicio[1], Ashley Beall[1], Robert Rosenberg[1], Theresa Bass-Goldman[1] and Herbert S. B. Baraf[1], [1]The Center for Rheumatology and Bone Research, Wheaton, MD, [2]Rheumatology, Georgetown University Hospital, Washington DC, DC, [3]Duquesne University, Pittsburgh, PA

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Background/Purpose: Dupuytren's contracture is a rheumatic disease characterized by an fibrotic reaction in the palmar aponeurosis, resulting in disability. Medical treatment with up to 3 injections of collagenase clostridium histolyticum (CCH) chemically disrupts the cord to reduce contracture. Transient swelling in the surrounding tissue and, rarely, rupture of the underlying tendon may occur. Ultrasound evaluation, particularly with elastography, may have the possibility to improve clinical decision making, as elastography allows grading of the tensile strength (softness or firmness) of tissues. This pilot study explored Dupuytren's cord changes with a single treatment of CCH; serial

elastography measurements were performed to determine if such follow contributes to clinical decision making.

Methods:

This IRB approved protocol first established the elastographic regional pattern of normal hands as well as untreated Dupuytren's contractures by studying 5 normal subject hands and 5 Dupuytren's contracture hands (MCP or PIP contracture angle > 20^{o} but < 90^{o}). We assessed the response of 10 Dupuytren's cords treated with ultrasound-guided injection of CCH for reduction of contracture. Research staff collected serial physical examinations and Unité Rhumatologique des Affections de la Main (URAM). A separate, blinded, researcher conducted ultrasound imaging. Measurements were taken at baseline, followed by days 1, 2, 3, 15, and 30, to follow the treatment protocol for administration of CCH. The region of the cord was designated the upper segment (UpS) and the region of the underlying tendon was designated the lower segment (LwS). Elastographic regional patterns were graded with a scale used for grading organ based lesions, where grade1 demonstrates mostly red region ("soft tissue") and < 10% blue regions, grade 2 demonstrates > 25% green regions and > 10% but < 25% blue regions, grade 3 demonstrates 25-50% green region and > 25% but <50% blue region and grade 4 demonstrates > 50% blue regions ("hard tissue"); this grading 1-4 was labelled the elastography score (ES). Statistical analysis of response was performed with Shapiro-Wilk test and student t-test.

Results: The normal hand had an average ES of 5.08 in the UpS and an ES of 16 in the LwS. In contrast, the untreated Dupuytren's hand had an average ES of 12.36 in the UpS and an ES of 15.6 in the lower segment. The normal hand ES UpS vs untreated Dupuytren's hand UpS had $p < 0.01$ but the normal hand ES LwS and untreated Dupuytren's hand ES LwS did not. In the treated Dupuytren's hands, the ES UpS at baseline 11.6 decreased to 9.1 in the first 24 hours of treatment and by day 30 was 8.8 and the ES LwS changed from 14.4 to 12.7; the contracture changed from 35.6^{o} to 23^{o} and the URAM scale changed an average of 2 points. The normal hand ES UpS vs treated ES UpS had $p < 0.01$.

Conclusion: This pilot established an elastographic regional scoring system for normal and pathologic tissue affected by a fibrotic disorder and demonstrated that the elastographic regional scoring system could detect response to treatment. This has significant clinical implications for the treatment of Dupuytren's contracture as well as for other rheumatologic fibrotic disorders. Further study with a larger cohort is needed.

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View Abstract and Citation Information Online - http://acrabstracts.org/abstract/ultrasound-imaging-with-elastography-for-the-medical-treatment-of-dupuytrens-contracture

Abstract Number: 191

High Specificity of Spectral Nail Assessment in Psoriatic Arthritis Patients

JOSE ALEXANDRE MENDONÇA, 4Rheumatology Unit, Hospital da Pontificia Universidade Católica (PUC) de Campinas, Campinas, Brazil, Porto Alegre, Brazil; Rheumatology, Instituto de Pesquisa Clínica of Campinas – IPECC, Campinas, Brazil

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Background/Purpose: Ultrasound evaluation of synovitis and enthesitis has changed the management of rheumatic diseases. In the present study we compare Power Doppler (PD) and Spectral Doppler (sD) ultrasonography indices (semiquantitative gray scale and PD scores and resistance index (RI) in the nails of patients with psoriatic arthritis (PsA) and their controls. Potential associations between sD measurements and clinical parameters were also investigated[1,2,3].

Methods: A cross sectional study was done and 44 patients with PsA, if they fulfilled the CASPAR criteria, 10 healthy controls and 6 patients with hands osteoarthritis (OA) were enrolled. Clinical parameters were recorded while US evaluation was performed in patients and controls nails. Nail bed measurements and semiquantitative gray scale (GS) and PD scores were derived for all nails examined, while RI was measured using sD.

Results: Statistically significant lower RI was found in patients with PsA as compared to their controls ***(p<0.001)***. RI measurements in our sample presented high sensibility and specificity for PsA. Area under the **ROC curve** was **0.858** ***(p<0.01)***. Choosing a **cut off point of 0.395** for RI measurements, the test indicates that RI values below **0.4** are associated with **100% sensitivity and 96% specificity** for entheseal inflammatory activity. Lower RI was observed even in PsA patients with no symptom of nail involvement. GS and PD semiquantitative scores were also significantly higher in PsA patients as compared to their controls ***(p<0.05)***. ROC analyzes demonstrated that RI measurements using sD presented high sensibility and specificity for PsA.

Conclusion: Nail sD indices are significantly different in PsA patients independently on the presence of clinically evident nail involvement. These sD parameters might find a place in early diagnosis, monitoring of disease activity and response to therapy in PsA patients.

References:

1. Gutierrez M, Filippucci E, et al. A sonographic spectrum of psoriatic arthritis: “the five targets”. Clin Rheumatol. 2010; 29(2): 133–142.
2. Terslev L, Torp-Pedersen S, Qvistgaard E, von der Recke P, Bliddal H. Doppler ultrasound findings in healthy wrists and finger joints. Ann Rheum Dis 2004; 63:644–648.
3. Mendonça JA, Nogueira JP, Laurido IMM, Vierhout C, et al. Can spectral doppler identify nail enthesitis in psoriatic arthritis? Annals of the Rheumatic Diseases 2014; 73(2):1-1332.

Disclosure: J. A. MENDONÇA, None;

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/high-specificity-of-spectral-nail-assessment-in-psoriatic-arthritis-patients

Abstract Number: 192

Comparison of Bone Scan with Xiralite (FOI) in Patients with Rheumatoid Arthritis and Psoriatic Arthritis

Joerg Polter, Susanne Drynda and **Jörn Kekow**, Clinic for Rheumatology, Vogelsang-Gommern, Germany

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Session Date: Sunday, November 8, 2015

Session Title: Imaging of Rheumatic Diseases Poster I: Ultrasound, Optical Imaging and Capillaroscopy

Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose:

In recent years Xiralite, an ICG-enhanced fluorescence optical imaging (FOI) technology, has gained growing importance as a non-radioactive imaging technique for the detection of inflammatory processes in joints [1]. It was the objective of our study to compare this new technique with conventional bone scans and with clinical findings in rheumatoid arthritis (RA) and psoriatic arthritis (PsA) patients.

Methods:

420 joints of 14 RA patients and 350 joints of 11 PsA patients were analysed by Xiralite, bone scan, and clinical evaluation. Due to the Xiralite system, both hands were the ROI in the study.

Results:

In the RA cohort, 94 out of 420 joints (22%) were identified as inflamed using the bone scan. By means of Xiralite, 97 (23%) inflamed joints were detected. In the clinical examination, 82 joints (19.5%) were found to be swollen.

In PsA patients 48 (14.5%) and 63 (19%) joints were found inflamed using the bone scan and Xiralite, respectively, and 42 out of 330 joints (13%) were swollen.

In 11 out of 14 RA patients (78.5%) and 8 out of 11 PsA patients (75%) the Xiralite and the bone scan produced consistent results in at least 50% of the number of inflamed joints. In 9 RA patients and 4 PsA patients the consistency of both methods was even 75% and higher.

Conclusion:

Our data show comparable numbers of inflamed joints identified by Xiralite and the traditional bone scan with a high degree of consistency. Both techniques have been found equivalent for the identification of affected joints and superior to clinical evaluation. In PsA Xiralite identifies even more inflamed joints than to a bone scan.

References

[1] Werner, SG, Langer HE, Ohrndorf S et al. Inflammation assessment in patients with arthritis using a novel in vivo fluorescence optical imaging technology. Ann Rheum Dis 2011; 71:504-510

Disclosure: J. Polter, None; **S. Drynda**, None; **J. Kekow**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/comparison-of-bone-scan-with-xiralite-foi-in-patients-with-rheumatoid-arthritis-and-psoriatic-arthritis

Abstract Number: 193

Going Back to Basics – Redefining the Normal Pattern in Nailfold Capillaroscopy in a Large Healthy Population: Results of the German “Rheuma-Truck” Cohort

Moritz Schröder, Department of Rheumatology and Hiller Research Institute, Heinrich-Heine University, Duesseldorf, Germany

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SESSION INFORMATION

Session Date: Sunday, November 8, 2015

Session Title: Imaging of Rheumatic Diseases Poster I: Ultrasound, Optical Imaging and Capillaroscopy

Session Type: ACR Poster Session A
Session Time: 9:00AM-11:00AM

Background/Purpose:

Capillaroscopy is as a useful diagnostic tool in various connective tissue diseases characterized by microangiopathy and vasculitis. Different pathological patterns especially for systemic sclerosis are described and validated. However, the morphologic pattern of healthy individuals ("normal") has been disregarded. The normal pattern with its high negative prediction for the development of systemic sclerosis in individuals with Raynauds phenomenon is important for the everyday clinical use and for predictive trials.

Methods:

"Rheuma-Truck" was a mobile rheumatology office located in different city centers of Germany offering a screening for rheumatic diseases including questionnaires, lab-tests and imaging. We performed 200x magnification nailfold capillaroscopy of the 3rd to 5th finger of both hands in visitors without known prediagnosed rheumatic disease. The pictures were evaluated by experts based on the morphological findings. Documented morphologies were hairpin shaped capillaries (HC), tortuous capillaries (TC), ramification, elongation, calibre variations, bulging. Descriptive statistics for mentioned morphologies were obtained as the mean value ± standard deviation (SD), minimum (min), maximum (max), percentiles. Furthermore a possible impact of age, gender, and smoking was evaluated.

Results:

9771 pictures of 748 visitors were evaluated. The mean age of the examined individuals (75% female, 25% male) was 53,6 years. HC was the most documented morphology (mean 76% ± 23%, min 0%, median 80%, max 100%) followed by TC (mean 21% ± 23%, min 0%, median 20%, max 100%). Only 30% of the examined normal fingers showed 100% HC but 97% exclusively HC and TC. Ramification (2,9% ± 8,2%, min 0%, median 0%, max 100%); elongation (1,8% ± 6,4 %, min 0%, median 0%, max 60%); calibre variations (0,8% ± 4,5%, min 0%, median 0%, max 80%) and bulging (0,3% ± 3,0%, min 0%, median 0%, max 60%) are rare. Giant capillaries were seen in 0,07% of the fingers.

Conclusion:

HC dominate the normal pattern but TC are frequently seen in "normal" with significant ($p<0,001$) increasing probability in age and male. There is no significance for the age or gender after adding the results for HC and TC, suggesting a physiologic alteration without prediction for connective tissue diseases. Hence "normal" is defined (2 SD range of the mean) as 80-100% HC and/or TC, <10% calibre variations, <6% bulging, <19% ramifications, <15% elongation and no giant capillaries. This definition should be used as a reference in future trials and clinical use to enlarge the prediction for healthy individuals.

Disclosure: M. Schröder, None;

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/going-back-to-basics-redefining-the-normal-pattern-in-nailfold-capillaroscopy-in-a-large-healthy-population-results-of-the-german-rheuma-truck-cohort

Abstract Number: 194

Events Upstream of Caspase-1 Activation in NLRP3-Mediated Cell Death in NOMID

Jehad H. Edwan, Raphaela Goldbach-Mansky and Robert A. Colbert, National Institute of Arthritis and Musculoskeletal and Skin Diseases, National Institutes of Health, Bethesda, MD

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SESSION INFORMATION

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Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose: Gain-of-function mutations in NLRP3 cause a spectrum of autoinflammatory diseases known as cryopyrin-associated periodic syndromes (CAPS), with neonatal-onset multisystem inflammatory disease (NOMID) being the most severe form of CAPS. These mutations cause excess production of the proinflammatory cytokine IL-β, which is responsible, at least in part, for the phenotype. IL-1β is produced in a pro-form and processed to a mature form by active caspase-1. NLRP3 is a key component of a multiprotein complex known as the inflammasome that mediates the maturation and release of IL-1β, in part through caspase-1 activation, and can induce rapid cell death resulting in the release of other proinflammatory mediators such as apoptosis-associated speck-like protein containing a CARD (ASC). Two pathways to cell death have been implicated. One is caspase-1 dependent 'pyroptosis' and the other is caspase-1-independent 'pyronecrosis'. The precise molecular mechanisms, as well as the role of NLRP3 mutations in cell death, remain to be elucidated. Our recent data (manuscript in revision) provide evidence that caspase-1 inhibition only partially reduces IL-1β release and fails to abrogate cell death in cells from NOMID patients, while cathepsin B inhibition prevents both cell death and IL-1β release. Here we investigated the consequences of caspse-1 and cathepsin B inhibition on the link between released IL-1β and cell death.

Methods: Whole blood cells from NOMID patients and healthy controls were studied. Cells were stimulated with LPS in the presence of inhibitors of caspase-1 or cathepsin B, followed by addition of ATP. Cell supernatants were collected and incubated with IL-1β-capturing beads that bind to both pro- and processed IL-1β. Cells and beads were evaluated by flow cytometry. Supernatants and/or cell lysates from LPS stimulated cells were also evaluated using western blot analysis for IL-1β captured on beads and ASC.

Results: By flow analysis we confirmed that inhibition of cathepsin B in NOMID and healthy control monocytes, results in a significant decrease in IL-1β release and cell death while caspase-1 inhibition fails to inhibit cell death and only partially abrogates IL-1β release. Analysis of IL-1β in supernatants suggests that when caspase-1 is inhibited, only the pro form of IL-1β is found in the supernatant. However, cathepsin B inhibition completely prevents the appearance of IL-1β in supernatants. Furthermore, caspase-1 inhibition has no effect on ASC release, whereas cathepsin B significantly reduced ASC release in both NOMID patients and healthy controls.

Conclusion: These data suggest that cell death in NOMID patients and ATP induced cell death in healthy controls is caspase-1 independent, but requires cathepsin B activation, implicating the pyronecrosis pathway. In addition, our data provide evidence that pro-IL-1β is released from dying/dead cells despite caspase-1 inhibition. These results place caspase-1 activation downstream of cell death events, and disassociate IL-1β processing and cell death in NOMID patients.

Disclosure: J. H. Edwan, None; **R. Goldbach-Mansky**, None; **R. A. Colbert**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/events-upstream-of-caspase-1-activation-in-nlrp3-mediated-cell-death-in-nomid

Abstract Number: 195

Activation of the Pyrin Inflammasome through the RhoA Signaling Pathway in Familial Mediterranean Fever (FMF) and Hyperimmunoglobulinemia D Syndrome (HIDS)

Yong Hwan Park, Geryl Wood, Daniel Kastner and **Jae Jin Chae**, Metabolic, Cardiovascular, and Inflammatory

Disease Genomics Branch, NIH/NHGRI, Bethesda, MD
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SESSION INFORMATION

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Session Type: ACR Poster Session A
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Background/Purpose: Mutations in the genes encoding pyrin and mevalonate kinase (MVK) cause the autoinflammatory diseases familial Mediterranean fever (FMF) and hyperimmunoglobulinemia D syndrome (HIDS), respectively. The inflammation of both diseases is mediated by interleukin-1β (IL-1β). Recently it has been reported that pyrin forms an inflammasome, a multiprotein complex that mediates the maturation of IL-1β by activating caspase-1, in response to bacterial modifications of RhoA. However, the precise molecular mechanism of pyrin inflammasome activation, as well as the mechanism by which FMF-associated mutations activate pyrin, remain to be elucidated. Thus, here we investigated the molecular mechanism of pyrin inflammasome activation and the molecular pathogenesis of FMF and HIDS.

Methods: We studied IL-1β production in immune cells from wild type mice and from several knockout and knockin mouse strains, as well as from FMF and HIDS patients and healthy controls, in response to LPS and/or various other bacterial toxins, and in the presence of pharmacologic agents targeting the Rho GTPase or adenylate cyclase pathways. Protein interactions were studied by immunoprecipitation.

Results: The Clostridial TcdB and C3 toxins, which inactivate RhoA, activate IL-1β maturation by a pathway that is *Mefv*-, *Asc*-, and *Caspase-1*-dependent, but *Nlrp3-, Nlrc4-,* and *Aim2*-independent. IL-1β secretion induced by the Clostridial toxins or from bone marrow-derived macrophages (BMDMs) of FMF knockin (KI) mice is inhibited both by the bacterial CNF toxin, which activates RhoA, and by colchicine. Colchicine also inhibits the constitutive IL-1β secretion from peripheral blood mononuclear cells (PBMCs) of FMF patients. In addition, the constitutive IL-1b secretion from FMF patients' PBMCs or BMDMs of FMF-KI mice is potentiated by cAMP, which has a role in suppressing RhoA through PKA-mediated direct phosphorylation. RhoA inhibition-induced inflammasome activation is mediated by reduced activities of downstream RhoA-effector kinase, serine/threonine protein kinase C-related kinase (PKN/PRK). The kinase domain of PKN binds to pyrin directly and phosphorylates two serine residues (S208 and S242 of human pyrin). The phosphorylated pyrin is recognized by 14-3-3 proteins, which negatively regulate the pyrin inflammasome. The binding affinity of 14-3-3 proteins as well as PKN for FMF-associated mutant pyrin is substantially lower than for wild-type pyrin, and the constitutive IL-1β secretion from FMF or HIDS patients' PBMCs or macrophages of FMF-KI mice is attenuated by activating PKNs. Defects in prenylation, seen in HIDS, lead to RhoA inactivation and consequent pyrin inflammasome activation. Taken together, these data suggest that the inflammations in FMF or HIDS are caused by the constitutive activation of the pyrin inflammasome due to the decreased interaction of pyrin with 14-3-3 proteins.

Conclusion: These data directly implicate Rho GTPase in the regulation of the pyrin inflammasome, and suggest that this pathway is also important in HIDS.

Disclosure: Y. H. Park, None; **G. Wood**, None; **D. Kastner**, None; **J. J. Chae**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/activation-of-the-pyrin-inflammasome-through-the-rhoa-signaling-pathway-in-familial-mediterranean-fever-fmf-and-hyperimmunoglobulinemia-d-syndrome-hids

Abstract Number: 196

The Pyrin Domain-Only Protein POP1 Inhibits NLRP3-Dependent

Inflammatory Disease

Lucia Almeida[1], Sonal Khare[2], Alexander Misharin[3], Rajul Patel[2], Rojo Ratsinmandresy[2], Melissa Wallin[2], Harris R. Perlman[4], David Greaves[5], Hal M. Hoffman[6], Andrea Dorfleutner[1] and Christian Stehlik[2], [1]Medicine/Rheumatology, Northwestern University, Feinberg School of Medicine, Chicago, IL, [2]Northwestern University, Chicago, IL, [3]Medicine/Rheumatology, Northwestern University, Chicago, IL, [4]Feinberg School of Medicine, Northwestern University, Chicago, IL, [5]University of Oxford, oxford, England, [6]University of California at San Diego, San Diego, CA

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Background/Purpose: In response to infections and tissue damage NLRP3 and ASC-containing inflammasome protein complexes are assembled, which promote caspase-1 activation, IL-1b and IL-18 processing and release and pyroptosis. Caspase-1 is also responsible for the release of ASC danger particles, which perpetuate and propagate inflammasome responses to bystander cells. However, excessive or persistent activation causes inflammatory diseases, including Cryopyrin Associated Periodic Syndrome (CAPS). Hence, a well-balanced inflammasome response is crucial to maintain homeostasis. Therefore inflammasome regulatory proteins likely exist to maintain an appropriate level of activity and in particular, to limit its activity during the resolution phase of this response. We propose that PYD-only protein POP1 is one of these proteins.

Methods: Available datasets of CAPS patients in the NCBI Gene Expression Omnibus database were analysed for POP1 expression. Monocyte/macrophage-expressing POP1 transgenic (TG) mice were generated and crossed with conditional NLRP3^{A350V} and Lysozyme M-Cre recombinase (CreL)-expressing mice. Offspring were analysed for CAPS by measuring body weight, survival and histological analysis. ASC-GFP particles were sorted by flow cytometry and used to trigger secondary inflammasome responses, which were analyzed in vitro and in vivo. Cytokines were analyzed by ELISA.

Results: Here we show that the PYD-only protein POP1 inhibits ASC-dependent inflammasome assembly by preventing inflammasome nucleation, and consequently interferes with caspase-1 activation, IL-1b and IL-18 release, pyroptosis and the release of ASC danger particles. Mice lack POP1, but transgenic POP1 expression in monocytes and macrophages protects mice from systemic inflammation triggered by ASC danger particles and CAPS-linked NLRP3mutations. CAPS patients exhibit reduced POP1 expression, suggesting that impaired POP1 expression may contribute to excessive inflammasome-driven inflammation. We further show that POP1 expression itself is regulated by IL-1b and propose that POP1 provides a regulatory feedback loop that shuts down excessive inflammatory responses and thereby prevents systemic inflammation.

Conclusion: POP1 provides a unique mechanism evolved in humans to enable more control for the essential inflammasome-mediated host defense system, thereby guarding against excessive and out of control responses that can cause inflammatory disease.

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Abstract Number: 197

Synergy Between Hematopoietic and Radioresistant Stromal Cells Is Required for Autoimmune Manifestations of Dnase II Deficient Mice

Rebecca Baum[1], Kerstin Nundel[1], Sudesh Pawaria[1,2], Shruti Sharma[1], Patricia Busto[1], Tara Robidoux[1], Katherine A. Fitzgerald[1], Ellen M. Gravallese[3] and Ann Marshak-Rothstein[1], [1]Medicine, University of Massachusetts Medical School, Worcester, MA, [2]Department of Medicine, University of Massachusetts Medical School, Worcester, MA, [3]Lazare Research Bldg Ste 223, University of Massachusetts Medical School, Worcester, MA
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Background/Purpose: Toll-like receptors (TLRs) dependent on Unc93b1 and cytosolic sensors dependent on STING detect microbial and endogenous nucleic acids to initiate inflammatory responses that resolve infection, but also contribute to autoimmune diseases. In the DNase $II^{-/-}$ $IFNaR^{-/-}$ (double knock out, DKO) mouse model, DNA accrual results in STING-dependent inflammatory arthritis as well as Unc93b1-dependent autoimmune manifestations, including ANA production, extramedullary hematopoiesis, and splenomegaly. While the role of hematopoietic cells in driving autoimmunity is well established, the contribution of stromal elements to disease pathogenesis is just beginning to be appreciated. Here we utilized bone marrow chimeras to determine the contribution of hematopoietic vs. radioresistant host cells to autoimmune manifestations in DKO mice.

Methods: Lethally irradiated Het (DNase $II^{+/-}$ $IFNaR^{-/-}$) or DKO mice were reconstituted with Het or DKO stem cells to generate four experimental groups: Het (donor)→Het (recipient), DKO→DKO, Het→DKO and DKO→Het. Additionally, Unc93b1$^{-/-}$ DNase $II^{-/-}$ $IFNaR^{-/-}$triple KO (Unc93b1 TKO) mice were used to generate DKO→Unc93b1 TKO and Unc93b1 TKO→DKO chimeras. Complete hematopoietic repopulation by donor BM cells in all groups was verified by flow cytometry using appropriate markers. Inflammation was assessed by clinical scoring (scale of 1-12), histologic scoring in ankle joints (scale of 1-4), and by measuring matrix metalloproteinase 3 (MMP-3) protein levels in the sera. Splenomegaly, ANA production, and extramedullary hematopoiesis were evaluated as other indicators of disease.

Results: As expected, Het→Het chimeras showed no evidence of arthritis while DKO→DKO mice showed significant inflammation in distal joints. Remarkably, neither the DKO→Het nor Het→DKO mice developed any clinical or histologic signs of arthritis over a 10-month period. Serum MMP3, a surrogate marker for inflammation, reflected the arthritis scores and further confirmed absence of inflammation in the DKO→Het and Het→DKO chimeras. The massive splenomegaly and extramedullary hematopoiesis observed in DKO mice were absent in the Het→Het chimeras and present in DKO→DKO mice. Surprisingly however, the Het→DKO and DKO→Het mice failed to develop splenomegaly or extramedullary hematopoiesis. Furthermore, autoimmune manifestations dependent on Unc93b1 were present in the DKO→Unc93b1 TKO mice but absent in Unc93b1 TKO→DKO chimeras.

Conclusion: These data reveal that both hematopoietic and radioresistant host cells must be DNase II-deficient in order for STING-dependent inflammatory arthritis to develop. Additional features of autoimmunity in these mice known to depend on Unc93b1, and therefore on endosomal TLRs, also require DNase II deficiency in both donor and host compartments, but require functional TLRs only in hematopoietic cells. These findings point to a critical interplay between endosomal and cytosolic nucleic acid receptors in the development of systemic autoimmunity, and suggest that targeting both hematopoietic and non-hematopoietic cells may be advantageous in autoimmune settings.

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Abstract Number: 198

CL-L1 and CL-K1 Complement Associated Pattern Recognition Molecules in Systemic Lupus Erythematosus

Anne Troldborg[1], Steffen Thiel[2], Lisbeth Jensen[3], Magdalena Janina Laska[2], Søren Hansen[4], Bent Deleuran[5,6], Jens Christian Jensenius[2] and Kristian Stengaard-Pedersen[5], [1]clinical medicine, Aarhus University, Aarhus, Denmark, [2]Biomedicine, Aarhus University, Aarhus, Denmark, [3]Biomedicin, Aarhus University, Aarhus, Denmark, [4]Department of cancer and inflammation research, University of Southern Denmark, Odense, Denmark, [5]Rheumatology, Aarhus University Hospital, Aarhus, Denmark, [6]Biomedicin, Aarhus University, 8000, Denmark
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Background/Purpose: The complement system is one of the key players in the pathogenesis of systemic lupus erythematosus (SLE). Collectin liver 1 (CL-L1) and collectin kidney 1 (CL-K1) are recently discovered complement pattern recognition molecules. They form hetero-complexes termed CL-LK that collaborate with associated serine proteases to activate the lectin pathway of complement. The objective of this pilot study was to explore the involvement of CL-LK in a cross-sectional cohort of SLE patients by measuring plasma concentrations and analyze for associations between the plasma concentrations and characteristic SLE manifestations.

Methods: Prospectively, blood samples (citrated plasma), ACR classification criteria and SLE disease activity index score (SLEDAI) were collected from 58 SLE patients. Concentrations in plasma of CL-L1 and CL-K1 were determined in the SLE patients and in age and gender matched healthy controls using time resolved immuno-flourometric assays developed in house.

Results:

RESULTS	SLE Patients (n=58) Median plasma conc. ng/ml (range)	Healthy Controls (n=65) Median plasma conc. ng/ml (range)	Mann-Whitney P value
CL-L1	252(159-365)	306(195-510)	< 0.001
CL-K1	326(221-447)	337(248-495)	0.033

Both the CL-L1 and CL-K1 concentrations were lower in SLE patients than healthy controls ($p < 0.001$ and 0.033). Patients with low complement component 3 (C3) demonstrated a negative correlation between C3 and CL-L1 and CL-K1 ($p=0.022$ and 0.031). The concentrations of CL-L1 and CL-K1 were highly correlated in both SLE patients and in healthy controls ($r=0.576$ and $r=0.592$). We found no significant correlation between disease activity score or organ damage score and plasma concentrations of CL-L1 or CL-K1.

Conclusion : In a cross-sectional cohort of SLE patients, we found differences in the plasma concentrations of CL-L1 and CL-K1 compared to a group of healthy controls. We observed a strong correlation between concentrations of CL-L1 and CL-K1 in both SLE patients and healthy controls substantiating the idea of CL-L1 and CL-K1 being present as heterocomplexes in plasma.

The altered concentrations found in SLE patients and associations to elements of the disease, like hypocomplementemia, support the hypothesis that the lectin pathway plays a role in the pathogenesis of SLE.

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Abstract Number: 199

Human Type 1 and Ncr-Negative Type 3 Innate Lymphoid Cells Accumulate in the Inflamed Synovium in Spondyloarthritis

Nataliya Yeremenko[1,2,3], Silvia Menegatti[4], Troy Noordenbos[1,2,3], Leonieke J.J. van Mens[1,2], Iris C. Blijdorp[1,2,3], Kristine Germar[1,2,3], Jochem Bernink[5], Lars Rogge[4], Hergen Spits[5] and Dominique Baeten[1,2,3], [1]Amsterdam Rheumatology and immunology Center, Amsterdam, Netherlands, [2]Department of Clinical Immunology and Rheumatology, Academic Medical Centre/University of Amsterdam, Amsterdam, Netherlands, [3]Laboratory of Experimental Immunology, Academic Medical Center/University of Amsterdam, Amsterdam, Netherlands, [4]Immunoregulation Unit, Institut Pasteur, Paris, France, [5]Department of Cell Biology and Histology, Academic Medical Centre/University of Amsterdam, Amsterdam, Netherlands

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Background/Purpose: Spondyloarthritis (SpA) is a major form of chronic inflammatory arthritis characterized by inflammation of axial and peripheral joints and by pathologic new bone formation leading to ankylosis. Consistent genetic, experimental, and clinical evidence indicates that IL-23/IL-17 immune axis plays a pivotal role in the pathophysiology SpA. It remains, however, unknown which IL-23 responsive cells are the major cellular source of IL-17 in SpA. Innate lymphoid cells (ILCs) are an emerging family of innate immune cells that produce various cytokines, including IL-17 and IL-22, and play critical roles in regulation of inflammation and tissue remodelling. In this study we investigated the presence and phenotype of ILCs in the peripheral blood and inflamed peripheral joints of patients with SpA.

Methods: Paired peripheral blood (PB), synovial fluid (SF) and synovial tissue (ST) were obtained from SpA patients with actively inflamed knee joints. ILCs (lineage negative, $CD45^{+}CD127^{+}CD161^{+}$) were analysed by flow cytometry.

Results: ILCs were present in all three compartments of patients with SpA. Analysis of ST revealed a significantly increased frequency of total ILCs in the joint compared with PB ((median (IQR) 0.37 (0.12-1.12)% of the lymphocyte population in ST versus 0.06 (0.04-0.09) % of the lymphocyte population in PB, p=0.016). Deep immunophenotyping of ILC subsets showed a statistically significant increase in the frequency of ILC1 ($CRTH2^{-}NKp44^{-}ckit^{-}$) in ST (37.8%; 74.43-20.47%) versus SF (7.27%; 0.6-25.1 %, p=0.008) and PB (3.45%; 1.45-9.25%, p=0.004). The second most prominent ILCs in the joint were NCR-negative ILC3 ($CRTH2^{-}NKp44^{-}ckit^{+}$), composing 33.45% (9.54-50.64%) of the total ILCs. NCR-positive ILC3 ($CRTH2^{-}NKp44^{+}ckit^{+}$) and ILC2 ($CRTH2^{+}$) populations were present in synovium at lower frequencies.

Conclusion: We observed in the inflamed ST of patient with spondyloarthritis an absolute and relative enrichment of both ILC1 and NCR-negative ILC3 as compared to PB and SF. As studies in other tissues such as gut and tonsil revealed that these IL-23 responsive ILC subsets can be an important source of IL-17 and /or IL-22 (1, 2), we will investigate the cytokine production by these synovial ILCs.

References:

1. Geremia et al. J Exp Med. 2011 208(6):1127-1133
2. Bernink et al. Nature Immunology 14(3):221-229

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Abstract Number: 200

Mast Cell Regulation of Aortic IL-6 Expression Involves Histamine-1 Receptor, Suppressor of Cyotkine Signaling-1 and IL-10

Vineesh Raveendran[1], **Jason Springer**[2], Donald Smith[3], Mehrdad Maz[4] and Kottarappat Dileepan[1], [1]Department of Medicine, University of Kansas Medical Center, Kansas City, KS, [2]Division of Allergy, Clinical Immunology and Rheumatology, University of Kansas Medical Center, Kansas City, KS, [3]University of Kansas Medical Center, Kansas City, KS, [4]Division of Rheumatology, University of Kansas Medical Center, Kansas City, KS

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Background/Purpose: IL-6 plays an important role in the pathogenesis of large vessel vasculitis. Lipopolysaccharide (LPS), acting through toll-like receptor 4, enhances both the aortic expression as well as serum levels of IL-6. Previous work by our group has demonstrated that systemic mast cell degranulation will inhibit both the serum and aortic expression of IL-6 in LPS injected mice. Mast cells release many vasoactive substances including histamine, proteases, and IL-10 . Our hypothesis is that the inhibitory effect of mast cells on aortic IL-6 production is mediated through histamine and/or IL-10.

Methods: Two month-old male C57BI6 (WT) and Histamine 1 Receptor (H1R) -/- mice were randomized into four groups, and given intraperitoneal injections with normal saline (control), compound 48/80 (mast cell degranulation agent, 1mg/kg), LPS (1mg/kg) or C48/80+LPS. Mice were sacrificed 24-h later, and levels of the stable metabolites of prostaglandin I_2 (PGI_2) and thromboxane A_2 (TXA_2) in the urine, and IL-6 and IL-10 in sera were quantified.

Results: MC degranulation did not increase PGI_2 in control or in LPS-treated mice of either genotype. LPS injection increased PGI_2 in both genotypes, but the increase was higher in H1R-/- mice. Both C48/80 and LPS increased TXA_2 in WT mice, but only LPS treatment enhanced TXA_2 in H1R-/-mice indicating importance H1R in this pathway. Treatment with C48/80 did not further enhance prostanoid production over LPS. LPS treatment increased serum IL-6 in both genotypes, but the changes were significant only in WT mice. Interestingly, LPS-induced IL-6 production was significantly reduced by MC degranulation in WT mice, but not in H1R-/- mice. In WT mice the inhibition of IL-6 was associated with enhanced aortic expression of SOCS1. In comparison to WT, the basal and induced levels of IL-10 were markedly higher in H1R-/- mice.

Conclusion: Mast cells differentially regulate LPS-induced inflammatory response in WT and H1R -/- mice. These results suggest that MCs regulate LPS-induced systemic and aortic inflammatory response involving H1R, SOCS-1 and IL-10.

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Abstract Number: 201

Innate Lymphoid Cells Are Present at Normal Human Enthesis Providing a Potential Mechanism for Spondyloarthropathy Pathogenesis

Richard Cuthbert[1], Evangelos M. Fragkakis[1], Peter Millner[2], Robert Dunsmuir[2], Yasser El-Sherbiny[1] and Dennis McGonagle[1], [1]Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds, Leeds, United Kingdom, [2]Department of Spinal Surgery, National Health Service, Leeds, United Kingdom

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Background/Purpose: The pathogenesis of murine spondyloarthropathy (SpA) has been intimately linked to the presence of IL-23 responsive, innate like lymphocytes at peripheral and spinal enthesis. Human SpAs are associated with SNPs in genes related to the IL-23 pathway and drugs that block IL-12/23 have shown efficacy. We hypothesised that the normal human enthesis has a population of resident innate lymphoid cells (ILCs) that could be key in governing entheseal immune homeostasis.

Methods: Normal spinal enthesis were harvested from patients undergoing spinal decompression surgery and enzymatically digested prior to sorting or flow cytometry. Cellular immunophenotyping and cell sorting was performed on enthesis samples harvested from 6 patients; ILC3s were identified as lineage (CD3- TCRγδ- TCRαβ- CD19- CD14- CD11c- CD1a- CD303- FcεRI- CD34- CD123-) and CRTH2 negative with positive expression of CD45, CD127, CRTH2, CD117. ILC2 were identified as lineage negative with positive expression of CD45, CD127 and CRTH2. The expression of RORγt transcript was tested in sorted populations by RTqPCR. Anterior cruciate ligament femoral enthesis was obtained from subjects with knee OA and injured enthesis undergoing repair were also collected and analysed by immunohistochemistry (IHC).

Results: All sorted samples contained ILC3s, median proportion 0.09% (range 0.015-0.63). Transcript analysis confirmed the expression of RORγt transcript in sorted ILC3 populations, with ILC3s expressing 51-fold greater relative expression in comparison to unsorted digests. 5 of 6 sorted samples contained ILC2s, median proportion 0.20% (range 0-0.49). RORγt expression was detected in knee OA and there was widespread expression of RORγt in inflammatory infiltrates in injured enthesis as shown by IHC.

Conclusion: Our findings show that ILCs are present in the normal human spinal enthesis and may be greatly increased in frequency following injury. These findings provide strong evidence of ILC presence in normal human enthesis and suggest a potential link between cellular dysregulation of the IL-23/17 axis and SpA pathology at sites of micro damage.

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Abstract Number: 202

Bone Accrual in the Dnase II-Deficient Model of Autoimmunity Requires Sting, As Well As Hematopoietic and Stromal Elements

Rebecca Baum[1], Shruti Sharma[1], Ann Marshak-Rothstein[1], Katherine A. Fitzgerald[1] and Ellen M. Gravallese[2], [1]Medicine, University of Massachusetts Medical School, Worcester, MA, [2]Lazare Research Bldg Ste 223, University of Massachusetts Medical School, Worcester, MA

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Background/Purpose: We have previously identified a role for cytosolic DNA sensors in bone by analyzing mice that develop inflammatory polyarthritis and trabecular bone accrual in the setting of DNA accumulation. In this model, DNA accrues in macrophages due to deletion of DNase II and is detected by cytosolic sensors that signal through stimulator of interferon genes (STING). This results in inflammatory cytokine and Type I IFN production. Type I IFNs in DNase $II^{-/-}$mice lead to anemia-driven embryonic lethality; thus co-deletion of the type I IFNR is essential (DNase II/IFN-IR double deficient (DKO) mouse). Although macrophages are implicated as a critical cell type in this model, new evidence suggests that a stromal component also plays an important role in the observed bone phenotype.

Methods: Histologic analysis of long bones was performed to confirm phenotypes. Macrophages were expanded from bone marrow (BM) of wild type (WT) and STING-deficient mice, transfected with poly(dA:dT) and RNA was analyzed by Nanostring using probe sets for genes in both innate immune and bone-related pathways. RNA was also prepared from whole BM from control and DKO mice, and similar Nanostring analyses were performed. We utilized bone marrow chimeras to determine the contribution of hematopoietic vs. radioresistant host cells to the bone phenotype. Lethally irradiated Het (DNase $II^{+/-}$ $IFNaR^{-/-}$) or DKO mice were reconstituted with Het or DKO stem cells to generate four groups: Het (donor)→Het (recipient), DKO→DKO, Het→DKO and DKO→Het. Complete reconstitution was verified by FACS analysis.

Results: As previously reported (A&R 2014; Vol 66:11S, 788), we found that trabecular bone accumulates in long bone and spleen in DKO mice, two sites of DNA accrual in macrophages. MicroCT, CFU assays for osteoblast precursors, and histomorphometry all supported a predominant role for osteoblasts in this bone phenotype. We showed that STING deficiency abrogated both arthritis and bone accrual in DKO mice. We now show that in total BM from DKO mice, expression of STING itself as well as of Ifi204, a cytosolic DNA sensor in the STING pathway, is up-regulated. BM-derived macrophages were prepared from WT and STING-deficient mice and transfected with poly(dA:dT), resulting in a trend toward up-regulated expression of genes known to promote osteoblast differentiation. STING deficiency abrogates up-regulated expression of these genes. Finally, analysis of bone marrow chimeras demonstrated that only DKO→DKO mice developed trabecular bone accrual, demonstrating that both hematopoeitic and stromal elements are required for expression of the bone phenotype.

Conclusion: Trabecular bone accrual is a feature of the autoimmune DKO mouse model. We have identified candidate factors that may drive osteoblast differentiation and function in this model, the expression of which depend on STING. Furthermore, macrophages contribute to the bone phenotype. However, bone marrow chimeras demonstrate that both hematopoietic and stromal elements are required. Identification of novel pathways linking innate immunity and bone may allow for new targets to treat bone loss in autoimmune disease.

Disclosure: R. Baum, None; **S. Sharma**, None; **A. Marshak-Rothstein**, None; **K. A. Fitzgerald**, None; **E. M. Gravallese**, None.

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Abstract Number: 203

Rescue of Copa Syndrome Cellular Phenotype By Autophagy Modifying Drugs

Levi Watkin[1,2], Briana Burns[1,2], Timothy Vece[3] and Jordan S. Orange[1,2], [1]Baylor College of Medicine, Houston, TX, [2]Center for Human Immunobiology, Texas Children's Hospital, Houston, TX, [3]Pulmonology, Texas Children's

Hospital, Houston, TX
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Background/Purpose: Autoimmunity is a diverse group of complex conditions that can include certain congenital genetic defects leading to loss of self-tolerance with subsequent imbalances of immune homeostasis and pro-inflammatory bias. Recently we reported a monogenic disorder of interstitial lung disease, renal disease, and arthritis with accompanying autoantibodies. This syndrome was found to be mediated by mutations in the coatomer subunit alpha (*COPA*) gene, which belongs to the coatomer-1 (COPI) complex involved primarily in the retrograde transport of proteins from the golgi apparatus to the endoplasmic reticulum (ER). These mutations result in an increase in ER stress, an increase in basal levels of autophagy, and an over activation of mTOR ultimately resulting in a pro-inflammatory environment, particularly increased levels of IL-1β.

Methods: In an effort to provide more rational treatment for COPA syndrome patients we hypothesize that modulation of the autophagy axis will result in a decrease in the pro-inflammatory environment.

Results: Here we show that treatment of COPA mutant expressing cells with autophagy modifying drugs, including rapamycin and chloroquine, result in normalization of autophagosome size, retention of IL-1β and a decrease in caspase-1 activity.

Conclusion: Taken together these data suggest that repairing the underlying cellular defect in ER stress, autophagy, and excessive mTOR activity will alleviate the pro-inflammatory environment, particularly increased IL-1β levels, and lead to a more balanced immune phenotype in COPA syndrome patients.

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Abstract Number: 204

Histone Methylation Profiling in Peripheral White Blood Cells As a Candidate Biomarker for Behcet's Disease

Yoshimi Aizaki[1,2], Yasuto Araki[1,2], Kojiro Sato[1], Yuji Akiyama[1] and Toshihide Mimura[1,2], [1]Department of Rheumatology and Applied Immunology, Faculty of Medicine, Saitama Medical University, Saitama, Japan, [2]Project Research Division, Research Center for Genomic Medicine, Saitama Medical University, Saitama, Japan
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Background/Purpose: Behcet's disease (BD) is a chronic recurrent, multisystem inflammatory disorder. The phenotypic characteristics include oral aphtha, genital ulcers, uveitis and skin lesions. No specific laboratory tests have been known in BD. Reported in BD have been an increased number of γδ T cells in the peripheral blood and hyperactivity of neutrophils. Although a line of evidence has suggested genetic contributions to the disease, etiopathogenesis of BD is still unclear and non-genetic factors, like environment, infection or epigenetics may play pivotal roles in the pathogenesis. Epigenetic mechanisms including posttranslational histone modifications are known to regulate gene expression without altering the genomic sequence. The association of specific histone modifications with gene expression is very well defined, such as tri-methylation of histone 3 lysine 27 (H3K4me27), which may be characteristic of repressed genes, or tri-methylation of histone 3 lysine 4 (H3K4me3), which may present in many active genes. Histone modifications in major rheumatic diseases, such as rheumatoid arthritis, have been investigated, while studies on histone modifications in BD are limited. From the functional point of view, it is important to analyze differences of histone modifications in each functional subclass of the entire peripheral blood nucleated cells. To examine the histone modifications of peripheral blood mononuclear cells (PBMCs) and neutrophils in BD, we have established a novel method analyzing histone methylation in each subset by fluorescence-activated cell sorting (FACS).

Methods: PBMCs and neutrophils were obtained from 13 patients with BD and 12 healthy controls (HC). Diagnosis of BD was made according to the criteria of Behcet's Disease Research Committee of Japan, Ministry of Health, Labour and Welfare of Japan. Four immune cell types were stained surface epitopes: CD4+ T cells, CD8+ T cells, γδ T cells, and CD16+CD66b+ neutrophils. Flow cytometry for H3K4me3 and H3K4me27 were normalized using isotype controls. All samples were analyzed on a FACSCalibur cytometer. As a quantitative measure of H3K4me3 and H3K27me3, mean fluorescence intensity (MFI) was used.

Results: H3K27me3 and H3K4me3 were detected in CD4+ T cells, CD8+ T cells, γδ T cells, and CD16+CD66b+ neutrophils. H3K27me3 MFI levels were not significantly different in those four immune cell types in BD and HC. In contrast, H3K4me3 MFI levels of BD in γδ T cells were significantly increased compared with HC. H3K4me3/H3K27me3 MFI ratio was significantly lower in neutrophils of BD and higher in γδ T cells of BD than that of HC. H3K4me3 MFI and H3K4me3/H3K27me3 MFI ratio of active BD were significantly increased in γδ T cells as compared to inactive BD.

Conclusion: Difference in histone modifications could be detected by FACS in peripheral white blood cells in BD patients. Aberrant histone methylation may be associated with the pathogenesis of BD. It is suggested that histone methylation could be a new candidate-biomarker for BD.

Disclosure: Y. Aizaki, None; **Y. Araki**, None; **K. Sato**, None; **Y. Akiyama**, None; **T. Mimura**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/histone-methylation-profiling-in-peripheral-white-blood-cells-as-a-candidate-biomarker-for-behcets-disease

Abstract Number: 205

Mode of Action of Therapeutic Anti-Citrullinated Protein Antibodies Revealed: Inflammation Reduction Due to Inhibition of Netosis

Renato G.S. Chirivi[1,2], Jos W.G. van Rosmalen[1], Gonny Schmets[1], Helmuth van Es[2] and Jos M.H. Raats[1,2],
[1]ModiQuest BV, Oss, Netherlands, [2]Citryll BV, Nijmegen, Netherlands

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SESSION INFORMATION

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Session Title: Innate Immunity and Rheumatic Disease Poster I

Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose:

Neutrophils together with aberrant Neutrophil Extracellular Trap (NET) formation contribute to the induction and propagation of inflammation. A growing number of studies indicate that Peptidyl Arginine Deiminases (PADs)-mediated conversion of arginine to citrulline residues in proteins are essential for NETosis, generation of auto-antigens, autoimmunity, and the breaking of tolerance in rheumatoid arthritis (RA). In RA patients, enhanced NETosis is observed in circulating and synovial neutrophils, and NET components are observed in blood and joints. We developed a novel first in class NET-inhibiting anti-citrullinated protein antibody (tACPA) treatment for RA.

Methods:

Human neutrophils from blood donors have been used in order to visualize the NETosis-inhibiting properties of tACPA. Furthermore, collagen antibody-induced (CAIA) as well as collagen-induced (CIA) arthritis mouse models have been used in order to test the therapeutic properties of tACPA.

Results:

In the CAIA mouse model, tACPA prevents the onset and/or exacerbation of inflammation, and prevents or strongly reduces joint damage. Therapeutic administration of tACPA resulted in the arrest of inflammation and prevented a further increase of the inflammatory response. Histological analysis of inflamed joints from tACPA-treated mice revealed a significant decrease in neutrophil influx as well as a decrease in joint damage, as compared to control animals. We identified the epitopes recognized by tACPA to be citrullinated domains of histone-2A, 3 and 4. Since neutrophils together with aberrant NET formation contribute to the induction and propagation of inflammation, we investigated whether tACPA's cellular mode of action could be through blocking NET formation or its activity by binding to citrullinated histone-2A, 3 and 4. Other groups have already demonstrated that PAD activity and citrullinated epitopes are essential for NET formation. For this purpose, we isolated neutrophils from blood of healthy human donors and induced NETosis with PMA or calcium ionophore A-23187. Treating neutrophils that undergo NETosis with tACPA led to a 40-60% NET reduction if compared to non-treated cells (n>34 different donors). This observation has been confirmed by Myeloperoxidase activity as well as immunohistochemistry read-outs.

Conclusion:

We have identified antibodies directed against a citrullinated epitope in murine and human histone-2A, 3 and 4. In RA mouse models, we demonstrate that tACPAs exhibit a strong anti-inflammatory activity and prevent the occurrence of swelling and joint damage. We propose that the therapeutic effect of tACPA acts through the inhibition of NET and auto-antigen formation, clearance of formed NETs and toxic histones. In RA patients, extinguishing auto-antigen production offers an orthogonal approach for treating this destructive autoimmune disease, potentially without impacting systemic immunity.

Citryll is developing tACPAs for first in man PoC trials for diseases where dysregulated NETs and NETosis are driving or contributing to disease progression. A particular suited RA patient subpopulation for tACPA therapy are those patients with activated PAD4 enzymes and increased NETosis.

Disclosure: R. G. S. Chirivi, Citryll bv, ModiQuest BV, tA, 1; **J. W. G. van Rosmalen**, ModiQuest BV + tACPA, 3; **G. Schmets**, Modiquest BV + tACPA, 3; **H. van Es**, Citryll BV, tACPA, 1; **J. M. H. Raats**, Citryll BV, ModiQuest BV, tACPA, 1.

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Abstract Number: 206

Activation of Non-Canonical NF-Kappa B Signalling in Dendritic Cells Induces Extrathymic Autoimmune Regulator (AIRE) Expression

Leonie Huitema[1], Boy Helder[1], Ae-Ri Noort[2], Chrissta Maracle[1], Louis Boon[3], Cristina Lebre[4], Frans G.M. Kroese[5] and Sander W. Tas[6], [1]Amsterdam Rheumatology & immunology Center | Department of Experimental Immunology, Academic Medical Center, University of Amsterdam, Amsterdam, Netherlands, [2]Department of Clinical Immunology & Rheumatology and Laboratory for Experimental Immunology, Academic Medical Center, University of Amsterdam, Amsterdam, Netherlands, [3]Bioceros, Utrecht, Netherlands, [4]Div. of Clinical Immunology & Rheumatology, Academic Medical Center/University of Amsterdam, Amsterdam, Netherlands, [5]Rheumatology and Clinical Immunology, University Medical Center Groningen, Groningen, Netherlands, [6]Division of Clinical Immunology and Rheumatology, Academic Medical Center / University of Amsterdam, Amsterdam, Netherlands

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Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose: Immune regulation is necessary for limiting excessive immune responses and for preventing autoimmune diseases. Nuclear factor (NF)-κB signalling plays an important role in the regulation of immune responses. We have previously demonstrated that the activation of the non-canonical NF-κB pathway in dendritic cells (DC) via CD40 stimulation is important for the induction of the immunoregulatory enzyme indoleamine 2,3-dioxygenase (IDO). Non-canonical NF-κB signalling is also important for the expression of Autoimmune Regulator (AIRE) in the thymus, which is essential for establishment of central tolerance. We have recently found extrathymic AIRE-expressing cells (eTACs) in glandular tissue from Sjögren's syndrome patients and in rheumatoid arthritis inflamed synovial tissue. eTACs are mainly antigen presenting cells, including DC, that can induce peripheral tolerance. However, stimuli that induce extrathymic AIRE expression in DC are unknown. Therefore, we studied whether activation of non-canonical NF-κB signalling induces AIRE expression in DC.

Methods: Monocyte-derived DC were generated by culturing healthy donor monocytes for 6 days with GM-CSF and IL-4. Maturation was induced by addition of LPS or CD40 stimulating antibodies and/or RANKL for 48 hours. *AIRE* and *IDO* expression was quantified by qPCR and cleavage of p100 into p52 (indicative of active non-canonical NF-κB signalling) was analyzed by western blot. Presence of AIRE and IDO protein was also analyzed by western blot and immunofluorescence staining. Additionally, *Aire* and *Ido* gene expression was analyzed in anti-CD40 stimulated murine bone marrow-derived (BM)DC generated from wild type and *Nik*$^{-/-}$ mice.

Results: Both anti-CD40 and RANKL stimulation of DC induced cleavage of p100 into p52, accompanied by upregulation of IDO and AIRE expression. Anti-CD40 stimulation also induced *Ido* and *Aire* expression in murine wildtype BMDC, but not in BMDC from *Nik*-/- mice.

Conclusion: Non-canonical NF-κB signaling is involved in AIRE and IDO expression in DC. This may reflect an imunoregulatory program in these cells. Eventually, this knowledge may be exploited to develop new treatment modalities for patients with autoimmune diseases, including DC-based therapies to modulate immune responses.

Disclosure: L. Huitema, None; **B. Helder**, None; **A. R. Noort**, None; **C. Maracle**, None; **L. Boon**, None; **C. Lebre**, None; **F. G. M. Kroese**, None; **S. W. Tas**, None.

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Abstract Number: 208

Neutrophil-Mediated Mechanisms of Drug-Induced Autoimmunity

Jorge Irizarry-Caro[1], Carmelo Carmona-Rivera[1], Elaine Novakovich[1], Venkataraman Subramaniam[2], Paul Thompson[3], Mariana J. Kaplan[4] and Peter C. Grayson[5], [1]National Institutes of Health, National Institute of Arthritis and Musculoskeletal and Skin Diseases, Bethesda, MD, [2]Biochemistry and Molecular Pharmacology, University of Massachusetts, Worcester, MA, [3]University of Massachusetts, Worcester, MA, [4]Systemic Autoimmunity Branch, National Institute of Arthritis and Musculoskeletal and Skin Diseases, National Institutes of Health, Bethesda, MD, [5]National Institute of Arthritis and Musculoskeletal and Skin Diseases, National Institutes of Health, Bethesda, MD
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Background/Purpose:

Certain medications are known to induce autoimmune disease in humans, triggering clinical features and autoantibody profiles that mirror idiopathic systemic lupus erythematosus (SLE) and/or ANCA-associated vasculitis (AAV). Neutrophil extracellular traps (NETs) have been implicated in the pathogenesis of both SLE and AAV, and NETs contain the antigenic targets (double-stranded DNA, MPO and PR3) of autoantibodies typically identified in cases of drug-induced autoimmunity. A subset of patients with SLE have impaired NET degradation likely due to presence of DNase I inhibitors or anti-NET antibodies in serum. These findings suggest that impaired regulation of NETosis triggers an autoimmune response against components of NETs and induces autoimmune diseases, including AAV and SLE. This study explored whether medications commonly implicated in cases of drug-induced autoimmunity (hydralazine and procainamide) and medications less commonly implicated in drug-induced autoimmunity, but more strongly associated with agranulocytosis (minocycline and clozapine), induce NET formation.

Methods: Human and murine neutrophils (PMNs) were incubated with medications of interest for one and four hours, respectively, at varying concentrations to mimic physiologic conditions. To address potential induction of impairments in NET degradation, drug-induced NETs were exposed to 10% serum from healthy control patients for 6 hours. NETs were visualized and quantified using fluorescence microscopy. To investigate whether drugs modulate NETosis through canonical pathways, NET inhibition was quantified when PMNs exposed to medications were incubated with Diphenyleneiodonium chloride (DPI; NADPH-oxidase inhibitor), BB-Cl-amidine (peptidylarginine deiminase (PAD) inhibitor) and specific muscarinic receptors antagonists. Release of hydrogen peroxide was measured by Amplex-Red Hydrogen Peroxide/Peroxidase Assay Kit. Whether these drugs stimulate various toll-like receptors (TLRs) was assessed using a human ligand TLR screening platform.

Results: Hydralazine and procainamide induced NETs in human and murine PMNs, while minocycline and clozapine did not. NET degradation was not impaired by these drugs. Hydralazine, but not procainamide, induced significant release of hydrogen peroxide in PMNs and triggered NET formation through canonical pathways (NADPH and PAD4). In addition, induction of NETs by procainamide was inhibited by addition of the muscarinic antagonists atropine, scopolamine, and specific M1/M3 inhibitors. Neither hydralazine nor procainamide stimulated TLRs in PMNs.

Conclusion: Certain medications implicated in drug-induced autoimmunity trigger formation of NETs via different pathways. Induction of NETs by hydralazine is dependent on PADs and NADPH oxidase. Procainamide induces NETs via stimulation of specific muscarinic receptors on PMNs. NETs may play a causal role in drug-induced autoimmunity.

Disclosure: J. Irizarry-Caro, None; **C. Carmona-Rivera**, None; **E. Novakovich**, None; **V. Subramaniam**, None; **P.**

Thompson, Padlock Therapeutics, 9; **M. J. Kaplan**, None; **P. C. Grayson**, None.

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Abstract Number: 209

Different Autoimmune Rheumatic Diease IgG Have Differential Effects upon Neutrophil Binding, Activation and Neutrophil Extracellular Trap Formation

Akif A. Khawaja[1,2], Charis Pericleous[3], Vera M. Ripoll[2], Joanna C. Porter[4] and Ian Giles[5], [1]Centre for Inflammation and Tissue Repair, Centre for Inflammation and Tissue Repair, University College London, London, United Kingdom, [2]Centre for Rheumatology, Division of Medicine, Centre for Rheumatology, University College London, London, United Kingdom, [3]Rayne Institute, Centre for Rheumatology Research, UCL Division of Medicine, London, United Kingdom, [4]Centre for Inflammation and Tissue Repair, Division of Medicine, Centre for Inflammation and Tissue Repair, University College London, London, United Kingdom, [5]Rayne Intitiute, Centre for Rheumatology Research, UCL Division of Medicine, London, United Kingdom

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Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose:

Dysregulation of neutrophil activation and function is important in the pathogenesis of various inflammatory and autoimmune rheumatic diseases (ARDs). Neutrophil dysfunction is well recognised in rheumatoid arthritis (RA), but has also been described in systemic lupus erythematosus (SLE) and antiphospholipid syndrome (APS). Integrin mediated adhesion modulates several aspects of neutrophil activation and function including: cytokine production; generation of reactive oxygen species (ROS); and the release of neutrophil extracellular traps (NETs), which are associated with disease manifestations in certain ARDs. Autoantibodies from patients with ARDs have been shown to bind to and promote the formation of NETs. Therefore, we investigated the effects of purified IgG from patients with ARDs on ROS generation, integrin mediated neutrophil adhesion and NETosis.

Methods:

Neutrophils and IgG were isolated from patients with APS (n=9), SLE (n=5), RA (n=9) or healthy controls (HC) (n=9). ROS production of phorbol 12-myristate 13-acetate (PMA)-stimulated HC and ARD neutrophils, as well as in HC neutrophils preconditioned with ARD or HC IgG, was measured using an enzymatic assay to assess hydrogen peroxide (H_2O_2) generation. Effects of purified IgG upon neutrophil adhesion to immobilised integrin ligands, including fibrinogen (macrophage-1 antigen; Mac-1/$\alpha_M\beta_2$-dependent) and fibronectin (very late antigen-4; VLA-4/$\alpha_4\beta_1$-dependent) were then determined using a fluorescent adhesion assay. NETosis of IgG-treated HC neutrophils was measured using a novel capture ELISA.

Results:

Stimulation of HC and ARD neutrophils with PMA produced similar rates of H_2O_2 generation (n=4, p=0.2286).

However, exposure of HC neutrophils to SLE (n=5; p<0.001) or RA (n=9; p<0.01) IgG increased H_2O_2 production compared to HC (n=9) IgG. Adhesion of PMA-stimulated HC neutrophils to fibrinogen was increased when incubated with RA (n=9; p<0.05) or SLE (n=5; p<0.001) IgG compared to APS (n=9) and HC (n=9) IgG, which was shown to be mediated by $\alpha_M\beta_2$ through the use of a specific blocking antibody. In contrast, APS IgG increased adhesion of PMA-stimulated HC neutrophils (n=9, p<0.05) to fibronectin compared with RA (n=9), SLE (n=5) and HC (n=9) IgG, that was shown to be dependent on β_1 integrins. We also demonstrated differential effects of IgG on NETosis; with APS (n=3) and SLE (n=4) IgG eliciting greater effects than HC (n=7) and RA (n=14) IgG on spontaneous NETosis of HC neutrophils (p<0.05).

Conclusion:

Neutrophils isolated from patients with ARDs did not display different rates of ROS generation compared to controls. We found however, differential activation of neutrophils using patient IgG on HC neutrophils. In particular, RA and SLE IgG increased ROS generation and neutrophil adhesion to fibrinogen in a $\alpha_M\beta_2$-dependent manner, whilst APS IgG increased neutrophil adhesion to fibronectin in a $\alpha_4\beta_1$-dependent manner. Work is currently underway to further evaluate the intrinsic differences between ARD and HC neutrophils, and to dissect the mechanisms underlying these distinctive patterns of IgG mediated neutrophil activation and their relevance to NETosis and disease pathogenesis.

Disclosure: A. A. Khawaja, None; **C. Pericleous**, None; **V. M. Ripoll**, None; **J. C. Porter**, None; **I. Giles**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/different-autoimmune-rheumatic-diease-igg-have-differential-effects-upon-neutrophil-binding-activation-and-neutrophil-extracellular-trap-formation

Abstract Number: 210

Phenotypically Divergences of Monocyte Subsets and Microparticles in Systemic Lupus Erythematosus Patients

Catalina Burbano[1], **Gloria Vásquez**[2], Mauricio Rojas[3] and Diana Castano[4], [1]Corporación Ciencias Básicas Biomédicas, Grupo de Inmunología celular e Inmunogenética, Universidad de Antioquia. Medellín, Antioquia, Colombia., Medellin, Colombia, [2]Rheumatology, Universidad de Antioquia, Medellin, Colombia, [3]Unidad de Citometría de Flujo, Universidad de Antioquia. Medellín, Antioquia, Colombia., Medellin, Colombia, [4]Grupo Inmunología Celular e Inmunogenética, Universidad de Antioquia, Medellín, Colombia

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Background/Purpose: Mononuclear phagocytes depurate apoptotic cells, microparticles (MPs), and immune complexes (IC), leading to a tolerant or inflammatory microenvironment. The MPs, vesicular structures mainly produced during activation and cell death, have a wide spectrum of biological activities in intercellular communication. We propose circulating MPs must be recognized by monocytes affecting their frequency, maturation, migration, and function. This could have an impact on the clinic and activity of this disease. Then, monocytes and MPs were studied in the peripheral blood from SLE patients and healthy controls.

Methods: Venous blood samples from patients with SLE and healthy controls were collected. Monocytes subsets (classical, intermediate and non classical) were defined based on the expression of CD14 and CD16 in HLA-DR+

cells, and several phenotypic markers were assessed by multiparametric flow cytometry. MPs were isolated from platelet-poor plasma by ultra-centrifugation and characterized by multiparametric flow cytometry.

Results: SLE patients had elevated percentages of MPs that forming IC, IgM+, and IgM+IgG+, and, MP HMGB1+ and C1q+. We did not observed differences in the number of MPs, size, or in the content of DNA, RNA and phosphatidylserine externalization compared to healthy controls. To understand the possible pathways by which mononuclear phagocytes interact with MPs, we evaluated putative receptors in monocytes. Monocyte subsets from SLE patients have decreased expression of the scavenger receptor CD36. Non-classical monocytes had increased expression of FcgR CD64, but not in CD16, CD32, and TOSO (FcmR). The protein subunit that forms the complement receptor 3 (CR3), CD11b, was reduced in classical and intermediate monocytes. These data suggest that circulating MPs of SLE patients are probably less recognized by monocytes through CD36 and CR3, allowing the recognition of them through FcgR and FcmR.

Classical and intermediate monocytes of these patients had reduced expression of CCR2 and CX3CR1; and the CCR5 was reduced in classical monocytes. This suggests that mainly circulating classical and intermediate monocytes from SLE patients have reduced ability to interact with the endothelium and to migrate in response to fractalkine, monocyte chemoattractant protein 1, RANTES, and macrophage inflammatory protein 1α and 1β. On the other hand, we observed a reduced percentage of circulating non-classical monocytes in SLE patients. This result, together with their normal expression of CX3CR1, suggests that this monocyte subset may be recruited into inflamed tissue as the kidney, where they have been observed augmented.

Conclusion: All these evidences, suggest that circulating MPs may interact with phagocytes from patients in a different way than with healthy controls; mediating alterations on their activation patterns, migration, contact with the endothelium, and induction of tissue damage in SLE patients. The identification of the modulatory effect of these MPs in monocytes will provide new potential targets to develop alternative treatments.

Disclosure: C. Burbano, None; **G. Vásquez**, None; **M. Rojas**, None; **D. Castano**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/phenotypically-divergences-of-monocyte-subsets-and-microparticles-in-systemic-lupus-erythematosus-patients

Abstract Number: 211

The Epidemiology of Gout: Marked Increase in Incidence and Comorbidities over 20 Years

Mohanad Elfishawi[1], Nour Zleik[1], Zoran Kvrgic[1], Clement J. Michet Jr.[2], Cynthia S. Crowson[3], Eric L. Matteson[4] and Tim Bongartz[1], [1]Rheumatology, Mayo Clinic, Rochester, MN, [2]Mayo Clinic, Rochester, MN, [3]Health Sciences Research, Mayo Clinic, Rochester, MN, [4]Division of Rheumatology, Department of Internal Medicine and Department of Health Sciences Research, Mayo Clinic, Rochester, MN

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Session Title: Metabolic and Crystal Arthropathies Poster I

Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose: Several studies have suggested that the prevalence of gout has increased over recent years. The majority of this data has been derived from insurance claims databases. However, there are few data available regarding a possible change in the incidence of gout in the United States. We therefore aimed to determine whether

there has been a change in the incidence of gout over the last 20 years, and evaluate possible changes in the clinical presentation of gout.

Methods: The individual medical records of all patients with a potential diagnosis of gout in a defined geographic cohort were reviewed using a resource insuring complete medical record capture. All individuals with a possible diagnosis of incident gout during the time periods January 1st 1989 - December 31st 1992 and January 1st 2009 – December 31st 2010 were identified. Incident cases had to fulfill at least 1 of 3 criteria: the 1977 American College of Rheumatology proposed criteria for gout, the Rome or New York criteria. Demographic and clinical data were abstracted for every incident case. Clinical characteristics were compared between time-periods using chi-square tests. Incidence rates with 95% confidence intervals (CI) were age- and sex-adjusted to the 2010 U.S. white population.

Results: A total of 158 patients with new-onset gout were identified during the 4 year time period between 1989-1992 and 271 patients between the 2 year time period between 2009-2010, translating into age- and sex adjusted incidence rates of 52.1/100 000 (95%CI 43.7-60.5) and 106.9/100 000 (95%CI 94.1-119.8), respectively. The incidence rate ratio for gout of 2.57 (95%CI; 2.11, 3.13) increased significantly over the last 20 years.

Patients diagnosed with gout between 2009-2010 were less likely to present with isolated podagra compared to patients diagnosed 20 years ago (67% versus 80%). Patients with gout incident in the recent period 2009-2010 had higher likelihood of having comorbid conditions compared with 1989-1992, such as hypertension (73% vs. 54%), diabetes (27% vs. 6%), kidney disease (32% vs. 11%), hyperlipidemia (65% vs. 21%), and heart failure (15% vs. 6%), respectively, at the time of their first gout flare. The likelihood of obesity among patient with incident gout increased from 37% to 56% over the last 20 years - with an increase of morbid class III obesity from 3% to 13%.

Conclusion: The incidence of gout has more than doubled in our population-based cohort over the last 20 years. This observation appears to be consistent with the increase in prevalence reported in several studies to date. Patients have become more likely to present with atypical presentations in joint areas other than the 1st MTP joint, which may make the diagnosis more challenging.

The marked increase in various cardiovascular comorbidities and risk factors among patients with incident gout is concerning and emphasizes that gouty arthritis rarely occurs as a stand-alone problem, but rather must be seen as a manifestation of serious systemic metabolic disease.

Disclosure: M. Elfishawi, None; **N. Zleik**, None; **Z. Kvrgic**, None; **C. J. Michet Jr.**, None; **C. S. Crowson**, None; **E. L. Matteson**, Novartis/Sanofi/Centocor-Jansen/Celgene/Amgen/Roche/Genentech/Mesoblast/Pfizer, 2; **T. Bongartz**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/the-epidemiology-of-gout-marked-increase-in-incidence-and-comorbidities-over-20-years

Abstract Number: 212

Rising Incidence and Prevalence of Gout in the Canadian General Population

Sharan K. Rai[1], J Antonio Avina-Zubieta[2], Natalie McCormick[3], Mary De Vera[4], Kamran Shojania[5], Eric C. Sayre[6] and Hyon K. Choi[7], [1]Experimental Medicine, University of British Columbia, Vancouver, BC, Canada, [2]University of British Columbia, Vancouver, BC, Canada, [3]Pharmaceutical Sciences, University of British Columbia, Vancouver, BC, Canada, [4]Faculty of Pharmaceutical Sciences, University of British Columbia, Vancouver, BC, Canada,

[5]Rheumatology, University of British Columbia, Vancouver, BC, Canada, [6]Arthritis Research Canada, Richmond, BC, Canada, [7]Rheumatology, Allergy and Immunology, Massachusetts General Hospital, Harvard Medical School, Boston, MA

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Session Time: 9:00AM-11:00AM

Background/Purpose: Gout is increasingly becoming recognized as the most common form of inflammatory arthritis worldwide; however, no Canadian general population-based data on the disease burden of gout are available. We estimated the incidence and prevalence of gout in an entire Canadian province (British Columbia, BC) from 1997-2012.

Methods: We utilized Population Data BC, an administrative database spanning the province of BC (approximately 4.5 million individuals) that includes all outpatient visits and hospital admissions from 1990-2012. The primary case definition of gout was at least one recorded diagnosis of gout (ICD-9-CM 274 or ICD-10-CA M10) at either a physician or hospital visit. We additionally explored secondary definitions of gout using available detailed medication dispensation information (obtained from BC PharmaNet), including individuals with at least two recorded diagnoses of gout or at least one recorded diagnosis of gout plus at least one dispensation of anti-gout medication (i.e., allopurinol, febuxostat, probenecid, or colchicine). To ensure incident gout cases, we required all newly diagnosed individuals to have at least five years prior without any record of a gout diagnosis. Annual incidence and prevalence estimates were age-sex-standardized using 2012 as the reference. Annual population estimates were obtained from BC Stats.

Results: Of 4,542,508 individuals in BC in 2012, we identified 173,003 prevalent gout cases (68% male, mean age 63 years) for an overall prevalence of 3.81%. The corresponding prevalence in the same calendar year among males and females was 5.22% and 2.41%, respectively. The prevalence additionally increased according to age group, reaching 11.65% among individuals at least 65 years old. We additionally identified 14,892 incident cases in 2012 for an overall incidence rate of 3.28 per 1,000 person-years. The corresponding incidence rates among men and women in 2012 were 4.32 and 2.25, respectively, per 1,000 person-years. Both the prevalence and incidence of gout increased substantially over the study period **(Figures 1a and 1b)**. All secondary case definitions of gout showed similar levels of this increasing trend.

Conclusion: These findings from BC, representative of the Canadian general population, indicate that the incidence and prevalence of gout are substantial and have increased over the past several decades.

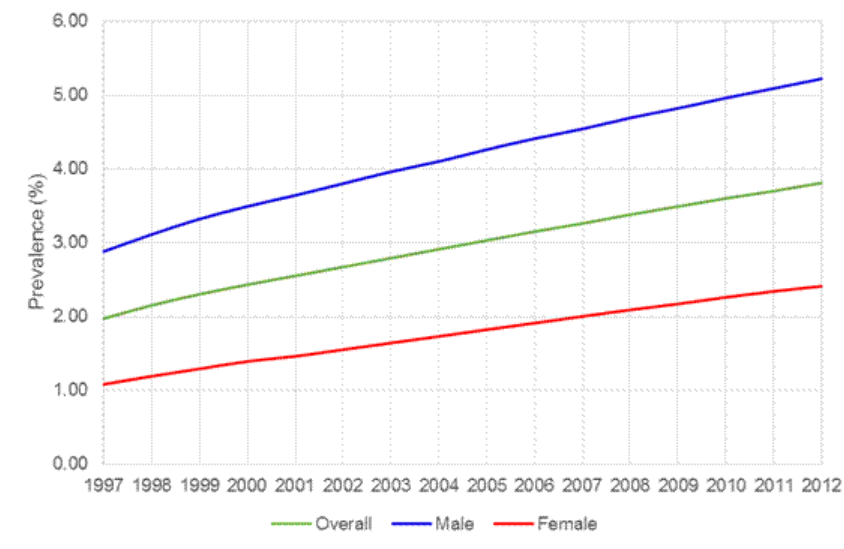

Figure 1a. Annual trends of standardized prevalence (%) in BC, Canada.

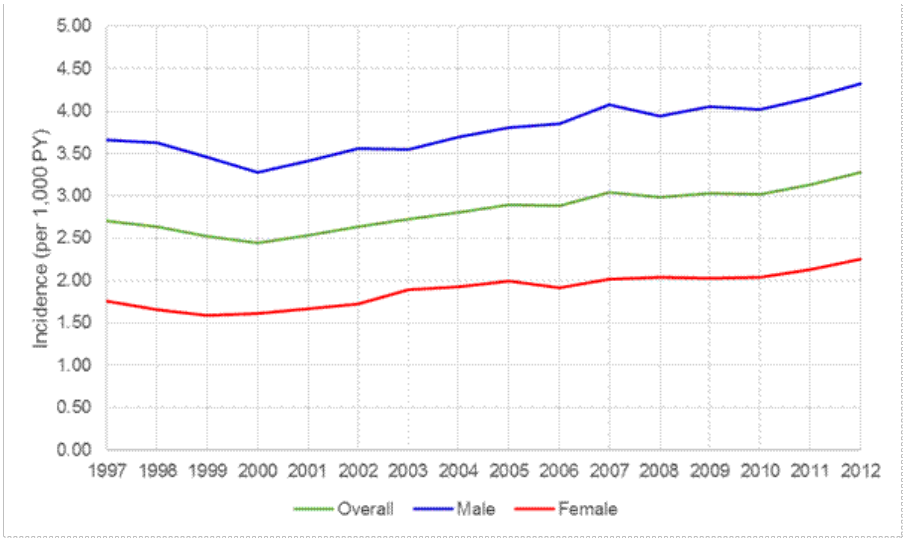

Figure 1b. Annual trends of standardized incidence (per 1,000 person-years) in BC, Canada.

Disclosure: S. K. Rai, None; **J. A. Avina-Zubieta**, None; **N. McCormick**, None; **M. De Vera**, None; **K. Shojania**, None; **E. C. Sayre**, None; **H. K. Choi**, None.

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Abstract Number: 213

A Method for Counting Monosodium Urate Crystals in the Synovial Fluid of Gout Patients

Paola Montagna, Renata Brizzolara, Carmela Ferrone, Stefano Soldano, Maurizio Cutolo and **Marco A. Cimmino**, Research Laboratory and Academic Division of Clinical Rheumatology, Department of Internal Medicine, University of Genova, Genova, Italy

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SESSION INFORMATION

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Session Title: Metabolic and Crystal Arthropathies Poster I

Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose:

Gout is the most common form of arthritis, and its prevalence is increasing. The identification of monosodium urate (MSU) crystals in synovial fluid (SF) or in an aspirate of a tophus is considered to be the gold standard for the definitive diagnosis of gout (1,2). MSU crystal disappearance from SF depends on the reduction of serum uric acid concentrations and is associated with a decrease of joint inflammatory episodes (3). In addition to diagnostic purposes, SF examination, in particular MSU crystals counting, could be used to evaluate the efficacy of therapy.

Aim of the study is to test an objective method for counting MSU crystals in the SF.

Methods: The SFs of 44 consecutive patients affected by gout diagnosed according to the ACR preliminary criteria were studied. Six of the patients underwent multiple SF aspirations for a total of 52 SFs. SF aspirated was divided into two test tubes, for cytological evaluation and crystal detection, respectively. Cytological evaluation included leukocyte and differential count. For crystal detection, 20 µl of fresh SF were placed on a microscope slide and examined by compensated polarized microscopy (400x). For crystal count, the slide was divided into 4 equal parts drawing a cross with a pencil. The method of count was performed by continued viewing and in each quadrant the crystals were counted up to a maximum of 400 (maximum number of crystals/patient was 1600). Two observers evaluated separately 27 SFs and repeated the count in 21 SFs after 24 hours.

Results: Forty of forty-four patients (90.9%) were men; mean age was 65.2±11.8 yrs. Aspirated joints were the knee (48 SFs), elbow (1 SF), 1st metatarsophalangeal joint (2 SFs), and ankle (1 SF). The volume of SF ranged between 0.1 and 45 ml (median 3 ml). Median leukocyte count was 400 cells/µl (range 50-14.000 cells/µl), median percentage of PMN was 9% (range 0%-98%), median crystal count was 179.5 (range 3-1600). Inter-reader agreement was high, with a weighted k of 0.89 (95% CI 0.85-0.94) for the first examination and 0.86 (95% CI 0.80-0.92) for the second one. Intra-reader concordance was also high with a k of 0.89 (95% CI 0.84-0.93) for the first observer, and of 0.85 (95% CI 0.78-0.93) for the second. The intraclass correlation coefficient for the 4 readings was 0.998 (95% CI 0.996-0.999). Maximum time needed for the count was 30 minutes. Number of crystals in the SF did not correlate with the amount of SF (p=0.15), nor with leukocyte count (p=0.52), percentage of PMN (p=0.69), patients' gender (p=0.46), or age (p=0.89). Interestingly, joints with recent (< 1 week) inflammatory reaction had a higher SF crystal count than the asymptomatic ones (460.5 [range 3-1600] vs. 48.5 [range 4-1600], p=0.03).

Conclusion: MSU crystal count in the SF of gout patients is a feasible and highly reliable technique. It could be used to follow the efficacy of urate lowering treatments within the joint, the location where the noxius effect of MSU crystals is more evident.

References: 1. Doherty M. Rheumatology 2009; 48:ii2-ii8. 2. Pascual E et al. Current Opinion in Rheumatology 2011; 23:161-69. 3. Pascual E et al. Ann Rheum Dis 2007; 66: 1056-58.

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Abstract Number: 214

Basic Calcium Phosphate Crystal Interactions with Tenocytes: An in Vitro Model of Calcific Tendinitis

Nicola Dalbeth[1,2], Bregina Pool[1], Ashika Chhana[3], Karen E. Callon[2], Dorit Naot[3], Ryan Gao[2], Brendan Coleman[4], Jillian Cornish[1] and Geraldine M. McCarthy[5], [1]Department of Medicine, University of Auckland, Auckland, New Zealand, [2]University of Auckland, Auckland, New Zealand, [3]Medicine, University of Auckland, Auckland, New Zealand, [4]Orthopedic Surgery, Middlemore Hospital, Auckland, New Zealand, [5]University College Dublin, Dublin, Ireland

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SESSION INFORMATION

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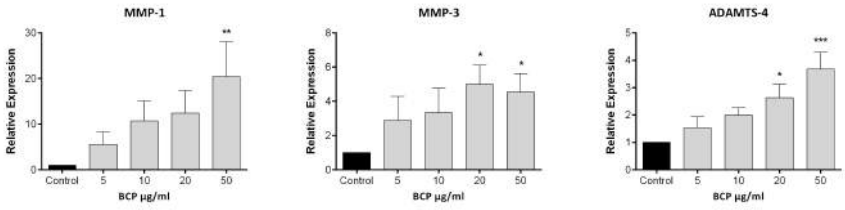
Background/Purpose: Basic calcium phosphate (BCP) crystals frequently deposit in tendons and may cause an acute inflammatory syndrome of calcific tendinitis. Tenocytes are the stromal cells of the tendon and are responsible for maintenance of tendon extracellular matrix. The aim of this study was to determine the effects of BCP crystals on tenocyte function, using an *in vitro* model of calcific tendinitis.

Methods : BCP crystals were synthesized by alkaline hydrolysis of brushite. Primary human tenocytes were prepared by collagenase/dispase digestion from human tendon (biceps, supraspinatus, hamstring) obtained from patients undergoing orthopaedic surgery. BCP crystals (0-50μg/mL) were added to the tenocyte cultures. After 24 hours, cell viability was assessed using the alamarBlue assay and changes in the relative mRNA expression levels of tendon-related genes were analysed using real-time PCR. The effects of cyclo-oxygenase (COX)-1 and COX-2 inhibition on gene expression were analysed by adding 1 μM SC-560 or SC-236 respectively for 45 minutes prior to addition of BCP crystals.

Results: BCP crystals did not alter tenocyte viability or gene expression of tendon extracellular matrix proteins (type 1 collagen, type 10 collagen, and tenomodulin) and inflammatory cytokines (IL-1, IL-6 and TNF-α). In contrast, BCP crystals induced gene expression of matrix metalloprotease (MMP)-1, MMP-3, and a disintegrin and metalloproteinase with thrombospondin motifs (ADAMTS)-4 in a dose dependent manner (Figure). Gene expression of tissue inhibitor of metalloproteinases (TIMP)-1 was also induced (for 50μg/ml BCP, mean (SD) relative expression 2.2 (0.7), ANOVA p for linear trend =0.002), but not TIMP-2 or TIMP-3. COX-1 gene expression was induced (for 50μg/ml BCP, mean (SD) relative expression 2.3 (1.1), ANOVA p for linear trend =0.008), with a similar trend for COX-2 (for 50μg/ml BCP, mean (SD) relative expression 2.6 (1.1), ANOVA p for linear trend =0.08). The COX-2 inhibitor SC-236 suppressed BCP crystal-induced gene expression of MMP-1 (mean change -83%), MMP-3 (-25%), ADAMTS-4 (-51%) and TIMP-1 (-47%). Similar, but generally less pronounced effects were observed with the COX-1 inhibitor SC-560 (mean change MMP-1 -63%, MMP-3 -56%, ADAMTS-4 -31%, TIMP-1 -39%).

Conclusion : BCP crystals induce tenocyte catabolic and anabolic gene expression in a cyclo-oxygenase (1 and 2) dependent manner. These data suggest that BCP crystals interact with tenocytes to influence tendon extracellular matrix integrity.

Figure: Effect of BCP crystals on MMP-1, MMP-3 and ADAMTS-4 gene expression in tenocytes. Data were pooled from four biological repeats and analysed using one-way ANOVA with post hoc Dunnett's tests compared to control (no treatment). *p<0.05, **p<0.01, ***p<0.001.



Disclosure: **N. Dalbeth**, None; **B. Pool**, None; **A. Chhana**, None; **K. E. Callon**, None; **D. Naot**, None; **R. Gao**, None; **B. Coleman**, None; **J. Cornish**, None; **G. M. McCarthy**, None.

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Abstract Number: 215

Calcium Hydroxyapatite Crystals Inhibit Interleukin-6- and Interferon-γ – Induced Anti-Osteoclastogenic Signaling in Human Osteoclast Precursors

Geraldine M. McCarthy[1], Clare C. Cunningham[2], Emma M. Corr[3] and Aisling Dunne[3], [1]University College Dublin, Dublin, Ireland, [2]School of Biochemistry and Immunology, Trinity College Dublin, Dubln, Ireland, [3]School of Biochemistry and Immunology, Trinity College Dublin, Dublin 2, Ireland

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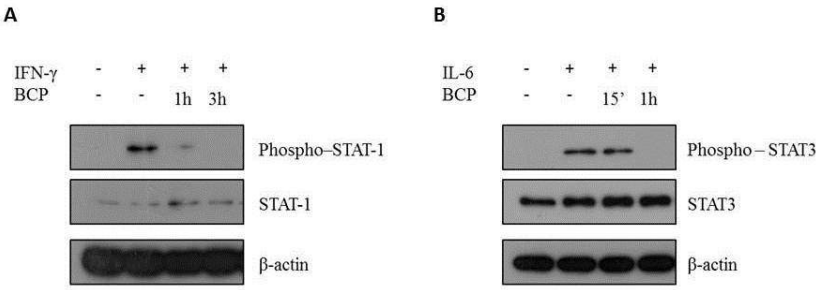
Background/Purpose: Intra-articular calcium hydroxyapatite (HA) crystals are present in the majority of osteoarthritic (OA) joints. They activate macrophages, synovial fibroblasts and articular chondrocytes, resulting in increased cell proliferation and the production of pro-inflammatory cytokines and matrix metalloproteases. This suggests a pathogenic role in OA by causing extracellular matrix degradation and subchondral bone remodeling. Total joint arthroplasty is performed when conservative therapies have proved unsuccessful in OA. However, particles generated from wear of prosthetic implants also induce pro-inflammatory cytokines, which drive osteoclastogenesis through up-regulation of receptor activator of nuclear factor kappa-B (RANK) ligand, an essential cytokine for the differentiation of osteoclasts. These bone-resorbing cells drive periprosthetic osteolysis through secretion of acid and the proteolytic enzyme cathepsin K and contribute to implant loosening. Both interleukin (IL)-6 and interferon (IFN)-γ exhibit anti-osteoclastogenic activity via activation of the JAK/STAT pathway. Titanium and bone cement wear particles can inhibit this effect, via activation of mitogen-activated protein kinases (MAPK) and induction of suppressor of cytokine signaling (SOCS) proteins. As synthetic HA is used as a biomimetic to coat orthopaedic implants, we sought to **1)** determine whether HA crystals promote osteoclastogenesis, **2)** determine whether HA crystals alter anti-osteoclastogenic signaling by IL-6 and IFN-γ and **3)** elucidate the mechanism by which HA crystals may contribute to periprosthetic osteolysis.

Methods: Murine and human macrophages were stimulated with HA crystals for 3, 6 and 24 hours and expression of RANK ligand and cathepsin K was analysed by quantitative PCR. Human osteoclast precursors were stimulated with HA crystals and MAPK activation was detected by Western blot. Osteoclast precursors were treated with HA crystals for 1 hour prior to IL-6 or IFN-γ stimulation, and phosphorylation of signal transducer and activator of transcription (STAT) 1 and 3 was detected by Western blot. Up-regulation of (SOCS) 1 and 3 was analysed by q-PCR

Results: HA crystals (50μg/ml) up-regulate RANK ligand and cathepsin K in murine and human macrophages by 3 to 5-fold. Stimulation of human osteoclast precursors with HA induces the activation of p38, JNK and ERK MAPK. Pre-treatment of human osteoclast precursors with HA crystals inhibits both IFN-γ and IL-6-induced activation of STAT1 and STAT3 respectively (figs A and B). Furthermore, HA crystals up-regulate the expression of SOCS1 and SOCS3, an effect which is reduced by MAPK inhibition.

Conclusion: Based on these studies we propose that HA crystals could contribute 1) to periprosthetic osteolysis and 2) subchondral bone remodelling in OA through up-regulation of RANK ligand, and inhibition of the anti-osteoclastogenic activity of IL-6 and IFN-γ.



Disclosure: G. M. McCarthy, None; **C. C. Cunningham**, None; **E. M. Corr**, None; **A. Dunne**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/calcium-hydroxyapatite-crystals-inhibit-interleukin-6-and-interferon-induced-anti-osteoclastogenic-signaling-in-human-osteoclast-precursors

Abstract Number: 216

Effects of Monosodium Urate Crystals on Mlo-Y4 Cell Viability; Is There a Role for Osteocytes in Erosive Gout?

Ashika Chhana[1], David Musson[2], Karen E. Callon[3], Dorit Naot[1], Gregory Gamble[3], Geraldine M. McCarthy[4,5], Jillian Cornish[3] and **Nicola Dalbeth**[3], [1]Medicine, University of Auckland, Auckland, New Zealand, [2]University of Auckland, Auckland, New Zealand, [3]Department of Medicine, University of Auckland, Auckland, New Zealand, [4]University College Dublin, Dublin, Ireland, [5]Rheumatology, Mater Misericordiae University Hospital, Dublin 7, Ireland
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Background/Purpose: Imaging and histology studies have identified monosodium urate (MSU) crystals present in

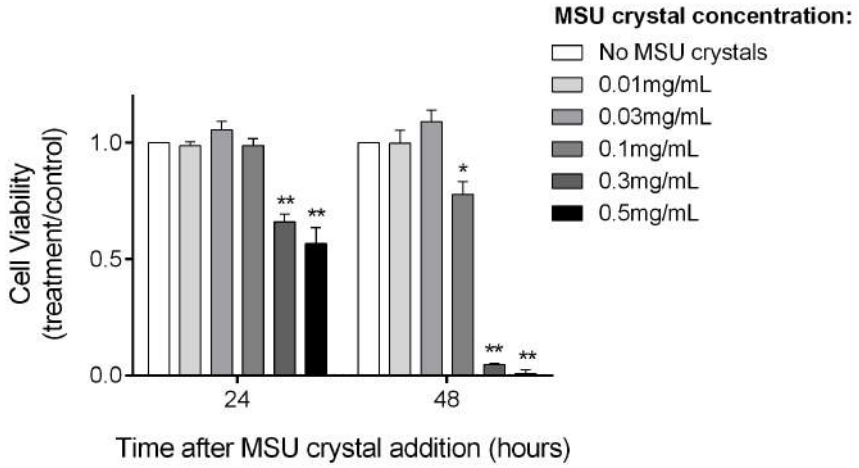
subchondral bone in erosive gout, suggesting that these crystals could interact with osteocytes. Osteocytes are the most abundant cell population within bone (>95% of the cellular component of the adult skeleton) and play a central role in regulating bone remodeling. The aim of this study was to investigate the effects of MSU crystals on osteocyte viability.

Methods: MSU crystals were prepared by recrystallization of uric acid. The murine immortalized osteocyte MLO-Y4 cell line was used in these assays; cells were cultured on plastic (2D) or in 3mg/mL type I collagen gels (3D). MSU crystals or soluble urate (0.01-0.5mg/mL) were added to the cells. After 24 hours, cells were washed and MSU crystals or urate completely removed. Cell viability was assessed using MTT and alamarBlue assays. Viability was assessed in the 2D cultures 24 hours after addition of MSU crystals, and both 24 and 48 hours after addition of MSU crystals in the 3D cultures. Different sizes of MSU crystals were prepared by sonication. Basic calcium phosphate, calcium pyrophosphate and aluminum crystals were tested using the same methods in the 3D cultures.

Results: In the 2D cultures at the 24 hour time point, 0.1-0.5mg/mL MSU crystals reduced MLO-Y4 cell viability by ~70% ($P<0.001$ vs. no MSU). In the 3D collagen gel cultures at the 24 hour time point, 0.3-0.5mg/mL (but not lower concentrations) MSU crystals reduced MLO-Y4 cell viability by ~30-40% ($P<0.001$ vs. no MSU) (Figure). In the 3D collagen gel cultures at the 48 hour time point, 0.1mg/mL MSU crystals reduced MLO-Y4 viability ($P<0.01$ vs. no MSU), and culture with the higher MSU crystal concentrations (0.3-0.5mg/mL) resulted in further reduction of MLO-Y4 cell viability by ~60-70% ($P<0.001$ vs. no MSU) (Figure). Different sizes of MSU crystals (5.6-16.2mm) reduced MLO-Y4 cell viability in a similar manner. The effect on cell viability was specific to MSU crystals, as soluble urate and other types of crystals did not reduce MLO-Y4 cell viability.

Conclusion: MSU crystals inhibit osteocyte viability. Direct crystal-cell contact is not necessarily required to induce this effect. These data suggest that osteocytes may play a role in bone erosion in gout.

Figure: MSU crystals reduce the viability of MLO-Y4 osteocyte-like cells in 3D cultures. Viability was assessed using the alamarBlue assay 24 and 48 hours after the addition of MSU crystals. Data are pooled from three biological repeats and are presented as mean (SEM); two-way ANOVA ($P<0.0001$) with *post hoc* Dunnett's test *$p<0.01$, **$p<0.001$ versus control (no MSU crystals) for the relevant time point.



Disclosure: A. Chhana, None; **D. Musson**, None; **K. E. Callon**, None; **D. Naot**, None; **G. Gamble**, None; **G. M. McCarthy**, None; **J. Cornish**, None; **N. Dalbeth**, None.

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Abstract Number: 217

Circulating Levels of Neo-Epitopes Reflecting Connective Tissue Turnover

As Biomarkers of Gout and Frequent Gout Attacks in Men

Ana Valdes[1], Tina Manon-Jensen[2], Wendy Jenkins[3], Anne Sofie Siebuhr[4], Morten Asser Karsdal[4], Sally Doherty[5], Abhishek Abhishek[3], Helen Richardson[3], Weiya Zhang[6], Michael Doherty[7] and **Anne C. Bay-Jensen**[8], [1]Division of Rheumatology, Orthopaedics and Dermatology, University of Nottingham, Nottingham, United Kingdom, [2]Antibody Research Unit, Nordic Bioscience, 2370, Denmark, [3]Devision of Rheumatology, University of Nottingham, NG5 1PB, England, [4]Biomarkers and Research, Nordic Bioscience, Herlev, Denmark, [5]Division of ROD, University of Nottingham, Nottingham, United Kingdom, [6]Academic Rheumatology, School of Clinical Sciences, University of Nottingham, Nottingham, United Kingdom, [7]Academic Rheumatology, City Hospital, Nottingham, United Kingdom, [8]Biomarkers and Research, Rheumatology, Nordic Bioscience, Herlev, Denmark
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Background/Purpose: Recurrent flares constitute the main clinical burden of gout. The neo-epitope blood-based biomarkers, C1M and C3M, measuring matrix metalloproteinases (MMP)-mediated connective tissue degradation, have previously been shown to be associated with joint inflammation in rheumatoid arthritis and osteoarthritis. The aim of present study was to evaluate the level of C1M and C3M in gout patients compared to matched controls, to investigate the discriminating power of these biomarkers for frequent gout flares.

Methods: Fasting plasma samples from 112 men with gout and 170 age-sex matched controls men without gout (case-control study), and baseline serum samples from 447 community-derived men with gout (RCT) were analysed by ELISA for neo-epitopes from MMP degradation of collagens type I (C1M) and type III (C3M). The log10 of C1M and C3M levels were compared between cases and controls, and between gout patients with three or more gout attacks in the past year (frequent gout flares) and those with two or less attacks, giving the odds ratio (OR[95%-CI) and area under the curve.

Results: The blood levels of the C1M and C3M were significantly associated with gout status in the case-control study: OR=4.1 log10C1M, and OR=82.8 for log10C3M (table). The level of C3M was associated with frequent gout flares; in the case-control participants with an OR=34.4 and in the RCT participants with an OR=5.2 after adjustment for age, BMI and age at first attack (table). C1M was also significantly associated with frequent flares in the RCT participants with OR=2.8. The combination of available clinical variables gives an area under the curve (AUC) of 0.68 and 0.60 for frequent gout attacks in the case-control and RCT groups using a receiver operating characteristic (ROC) analysis. The AUC values increase to 0.74 [0.63-0.84] and 0.66 [0.61-0.71] with the inclusion of log10C1M and log10C3M in the model.

Conclusion: C1M and C3M were strongly associated with gout status in a case-control study in men and with frequent gout flares in two independent groups of men with ongoing gout, suggesting that increased connective tissue turnover predispose to frequent gout flares, and that biomarkers of connective tissue turnover may aid in identifying people at risk of frequent attacks of gout

Table. Association between connective tissue degradation neo-epitopes and gout and frequent gout flares, odds ratios [95% confidence intervals] and p-values are shown for each of the associations tested				
	case-control		**RCT**	
Association with:	**log_{10}C1M**	**log_{10}C3M**	**log_{10}C1M**	**log_{10}C3M**
Gout	OR=4.10 [1.51 - 11.1] p <0.0056	OR=82.8 [9.9-695] p <2.4 x 10^{-5}	---	--
≥3 gout flares unadjusted	OR=5.19 [0.99-27.1] p< 0.051	OR=56.9 [1.26-2564] p<0.037	OR=2.88 [1.22-6.80] p< 0.016	OR=6.51 [2.22-19.1] p< 0.0006
≥3 gout flares adj. age, BMI, age at first attack	OR=4.96 [0.86-28.8] p<0.074	34.3 [0.65-1803] p<0.080	OR=2.83 [1.17-6.81] p< 0.020	OR=5.21 [2.05-18.7] p< 0.0012
≥3 gout flares adj. age, BMI, age at first attack, SUA, tophi, num sites with tophi	--	--	OR=2.70 [1.11-6.51] p< 0.027	OR=5.21 [1.71-15.87] p< 0.0036
		Meta-analysis of both cohorts		
≥3 gout flares adj. age, BMI, age at first attack	OR=3.11 [1.42-6.81] p=0.0056	OR=6.70 [2.33-19.3] p=0.00053		

Disclosure: **A. Valdes**, None; **T. Manon-Jensen**, Nordic Bioscience, 3; **W. Jenkins**, None; **A. S. Siebuhr**, None; **M. A. Karsdal**, Nordic Bioscience Diagnostic, 1,Nordic Bioscience Diagnostic, 3; **S. Doherty**, None; **A. Abhishek**, None; **H. Richardson**, None; **W. Zhang**, None; **M. Doherty**, None; **A. C. Bay-Jensen**, Nordic Bioscience Diagnostic, 1,Nordic Bioscience Diagnostic, 3.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/circulating-levels-of-neo-epitopes-reflecting-connective-tissue-turnover-as-biomarkers-of-gout-and-frequent-gout-attacks-in-men

Abstract Number: 218

Diet-Wide Association Study of Serum Urate Levels in 13,782 Individuals of European Ancestry

Tony R. Merriman[1], Nicola Dalbeth[2], Ruth Topless[3] and Tanya Flynn[3], [1]Biochemistry Dept, PO Box 56, University of Otago, Dunedin, New Zealand, [2]Department of Medicine, University of Auckland, Auckland, New Zealand, [3]University of Otago, Dunedin, New Zealand

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Background/Purpose: Gout is a consequence of an innate immune reaction to monosodium urate crystals deposited in joints. Acute gout attacks are commonly triggered by dietary factors, the most common of which have been associated with raised serum urate levels. However, individuals with gout often identify other foods as their gout triggers. The implementation of a hypothesis free diet-wide association study (DWAS) could reveal foodstuffs that have not previously been associated with urate levels. Our aim was to conduct a DWAS with serum urate as outcome.

Methods: 13,782 individuals of European ancestry from the Atherosclerosis Risk In Communities (n=7228), Coronary Artery Risk Development In (Young) Adults (n=1413), Cardiovascular Health (n=2101) and Framingham Heart (n=3040) studies were used to test for association between serum urate ($\mu molL^{-1}$) and 66 different food items (serves/week). All analyses were adjusted for sex, menopause status, age, BMI, average daily calorie intake and the first four eigenvectors from whole genome principal components analysis. Individuals with gout or kidney disease and those taking urate lowering medications or diuretics were excluded from analyses. Three quality control criteria were applied to the food consumption data to ensure reliable information was used.

Results: Six novel associations with a $P < 0.0008$ (Bonferroni multiple testing threshold) were found. Brown bread, peanut butter, eggs, non-citrus fruit and margarine all had urate lowering effects ($\beta = -0.55; -0.93; -1.09; -0.35$ and -0.36 $\mu molL^{-1}$ per extra serve per week respectively), whilst French-fried potatoes had a urate increasing effect ($\beta = 2.30$ $\mu molL^{-1}$ per extra serve per week). Additionally six known urate modifying foods, beer, cheese, shellfish, tea, skim milk and liquor ($\beta = 1.48; -0.67; 5.11; 0.38; -0.92$ and 1.63 $\mu molL^{-1}$ per extra serve per week) had *P*-values below the multiple testing threshold. Eleven other foods had nominally significant association ($0.0008 < P < 0.05$) – wine, soft drink, fish, poultry, tomato and self-reported added sugar were urate-raising, and cake, apple, peach, banana and cold cereal were urate-lowering.

Conclusion: This research represents the first diet-wide association study in serum urate which considers each food item separately. Several of the novel associations may be confounded by correlations with other foodstuffs, or represent differences in overall diet. However this work represents an unbiased and inclusive understanding of dietary factors influencing urate levels.

Disclosure: T. R. Merriman, None; **N. Dalbeth**, None; **R. Topless**, None; **T. Flynn**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/diet-wide-association-study-of-serum-urate-levels-in-13782-individuals-of-european-ancestry

Abstract Number: 219

Targeted Deep Resequencing Identifies MRP4/ABCC4 as a Gout Risk Locus in the New Zealand Mäori and Pacific Island Populations

Tony R. Merriman[1], James Boocock[2], Callum Tanner[2], Murray Cadzow[2], Amanda Phipps-Green[2], Lisa K. Stamp[3], Nicola Dalbeth[4], Jennie Harre Hindmarsh[5], David B. Mount[6], Hyon Choi[7] and Eli A. Stahl[8], [1]Biochemistry Dept, PO Box 56, University of Otago, Dunedin, New Zealand, [2]University of Otago, Dunedin, New Zealand, [3]Medicine, University of Otago, Christchurch, Christchurch, New Zealand, [4]Department of Medicine, University of Auckland, Auckland, New Zealand, [5]Ngati Porou Hauora Charitable Trust, Te Puia Springs, New Zealand, [6]Renal Division, Brigham and Women's Hospital, Boston, MA, [7]Division of Rheumatology, Allergy and Immunology, Massachusetts General Hospital, Harvard Medical School, Boston, MA, [8]Divisions of Rheumatology and Genetics, Brigham and Women's Hospital, Boston, MA

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Background/Purpose: Genetic variants in uric acid transporters that control serum urate levels in Europeans have been identified by genome-wide association studies. However there is no evidence for association with the organic anion transporters (OAT) 2-4 (encoded by *SLC22A6-A8*) and multi-drug resistance protein 4 (MRP4) encoded by *ABCC4*. The Māori and Pacific (Polynesian) population of New Zealand (NZ) has the highest prevalence of gout worldwide and exhibits lower fractional excretion of uric acid (FEUA) than Europeans. Our aim was to identify genetic variants in the Māori and Pacific *SLC22A6-8* and *ABCC4* genes that influence the risk of gout.

Methods: 218 hyperuricaemic and 205 normouricaemic individuals, the majority (93%) of whom self-reported >=3 Māori and Pacific grandparents, were resequenced over a total of 24.3 kb of promoter, exon and 3' and 5' untranslated region DNA within the four genes. Sequencing was done using Illumina chemistry on a HiSeq 2000 on DNA captured using a custom version of the Roche NimbleGen SeqCap kit. The Genome Analysis Toolkit was used to align reads to the human reference genome and generate variant call files. Replication genotyping for *rs4148500*was done by Taqman over 284 Western Polynesian (Samoa, Tonga, Niue, Tokelau) gout cases and 174 controls, and 471 Eastern Polynesian (EP: NZ and Cook Island Māori) gout cases and 450 controls (that included 187 Māori gout cases and 170 Māori controls from the area of the Ngati Porou tribe). All replication individuals had >=3 self-reported Māori and/or Pacific grandparents. Logistic regression association analysis was done adjusting by age and sex.

Results: A total of 39 variants with frequency greater than 0.05 were detected with the majority (n=26) in *ABCC4*. Of these, six variants in *ABCC4* significantly associated with hyperuricaemia. The most significantly associated (*rs4148500*; $OR_{Hyperuricaemia}$=1.76, *P*=1.6x10^{-3}; monomorphic in Europeans) was also associated with gout in the resequenced sample set (OR=1.86, *P*=9x10^{-4}) and was therefore genotyped over the replication sample set. *Rs4148500* was associated with gout in Western Polynesian (OR=1.47, *P*=0.026) but not in Eastern Polynesian (OR=1.09, *P*=0.52) in this sample set. In the combined (resequence plus replication) sample set the minor allele of *rs4148500* was associated with reduced FEUA in the combined Polynesians (beta=-0.50, *P*=3.8x10^{-3}).

Conclusion: We demonstrate for the first time association of *ABCC4* with hyperuricaemia, gout and FEUA, providing further support for the proposition of MRP4 as a unidirectional urinary uric acid efflux pump for uric acid. The variant was monomorphic (for the protective major allele) in Europeans and can be regarded as the first report of a genetic factor contributing to the increased risk of gout that is specific to people of Western Polynesian ancestry.

Disclosure: T. R. Merriman, None; **J. Boocock**, None; **C. Tanner**, None; **M. Cadzow**, None; **A. Phipps-Green**, None; **L. K. Stamp**, None; **N. Dalbeth**, None; **J. Harre Hindmarsh**, None; **D. B. Mount**, AstraZeneca, 5; **H. Choi**, None; **E. A. Stahl**, None.

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Abstract Number: 220

A Genome-Wide Association Study Reveals Association of the Transferrin Receptor Locus with Gout

Tony R. Merriman[1], Murray Cadzow[2], Callum Tanner[2], Matthew A. Brown[3], Katie Cremin[4], Matthijs Janssen[5], Tim Jansen[6], Leo A. Joosten[7], Timothy Radstake[8], Philip L. Riches[9], Anne-Kathrin Tausche[10], Frederic Lioté[11], Alex So[12,13], Andre M. van Rij[2], Gregory T. Jones[14], Lisa K. Stamp[15], Nicola Dalbeth[16] and Cushla McKinney[2], [1]Biochemistry Dept, PO Box 56, University of Otago, Dunedin, New Zealand, [2]University of Otago, Dunedin, New

Zealand, [3]The University of Queensland Diamantina Institute, Brisbane, Australia, [4]Diamantina Institute, University of Queensland, Brisbane, Australia, [5]Rheumatology Dept, Ziekenhuis Rijnstate, Arnhem, Netherlands, [6]P O Box 581, Haarlem, Netherlands, [7]Department of Medicine, Radboud University Nijmegen Medical Centre, Nijmegen, Netherlands, [8]Radboud University Nijmegen Medical Centre, Nijmegen, Netherlands, [9]Centre for Genomic and Experimental Medicine, Western General Hospital, Edinburgh, United Kingdom, [10]Medizinische Klinik und Poliklinik III, Universitätsklinikum Carl Gustav Carus an der Technischen Universität Dresden, Dresden, Germany, [11]Rheumatology Department; Inserm UMR-S606; Paris-Diderot University, hôpital Lariboisiere, Paris, France, [12]Service De Rhumatologie, CHUV, Lausanne, Switzerland, [13]Department of Rheumatology, CHUV, Lausanne, Switzerland, [14]Surgery, University of Otago, Dunedin, New Zealand, [15]Medicine, University of Otago, Christchurch, Christchurch, New Zealand, [16]Department of Medicine, University of Auckland, Auckland, New Zealand
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SESSION INFORMATION

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Background/Purpose: Acute gouty arthritis results from an innate immune response to monosodium urate (MSU) crystals deposited in the joints and soft tissues of hyperuricaemic individuals. Genome-wide association studies (GWAS) have provided insight into the genetic control of urate homeostasis. However there have been very few genetic insights into the pathogenesis of acute gouty arthritis. Key checkpoints are expected to be in MSU crystal formation and immune response. The aim was to conduct a GWAS in gout using the immune-centric Immunochip.

Methods: 456 European patients with gout fulfilling the 1977 ARA gout classification criteria were genotyped with the Immunochip microarray, which contains single nucleotide variants (SNVs) at loci chosen largely on the basis of association with other immune-mediated phenotypes. SNVs out of Hardy Weinberg equilibrium ($P<1x10^{-7}$) and with minor allele frequency <0.01 were discarded with 139,874 SNVs remaining. The genomic inflation factor was 1.06. Allele frequencies were compared by logistic regression using PLINK software to 1,000 European controls sourced from the 1958 British Birth Cohort. Replication was conducted using Taqman genotyping in 1,190 European cases with gout and 960 NZ controls, with additional data from 11,127 publically-available European controls, and Taqman genotyping of 931 Polynesian cases and 964 controls. For replication, logistic regression analyses were adjusted by age, sex and (for Polynesian) number of self-reported Polynesian grandparents. Replication sample sets were combined by meta-analysis using METAL software. Replication was declared at $P<0.01$.

Results: Five SNVs with P between $1x10^{-5}$ and $6x10^{-5}$ from the discovery GWAS were selected for replication (Table). *Rs1466085*, in the enhancer region 11kb upstream of the transferrin receptor (*TFRC*), was the only variant to replicate (OR=1.30, $P=5x10^{-5}$) in a directionally consistent fashion to the discovery GWAS data (OR=1.77, $P=3x10^{-5}$). Combining the discovery and replication sets yielded $P=6.4x10^{-8}$ at *rs1466085.* There was no evidence for association of *rs1466085* with serum urate levels in European controls (beta=0.003, $P=0.18$).

Conclusion: These data, with $P=10^{-5}$ in both discovery and replication phases, convincingly implicate the region immediately upstream of the transferrin receptor in the etiology of gout in an urate-independent manner. It is important that further genetic fine-mapping and molecular expression experiments are done to confirm *TFRC* as the causal gene in the region.

Table Association of five genetic variants in the genome-wide (discovery) and replication analyses

			Discovery (GWAS)			Replication				Disc and Rep
	Nearest gene	Risk allele	MAF case/cont	OR	*P*		MAF case/cont	OR	*P*	OR, *P*
rs117561283	*IFNG-AS1*	T	0.052/0.024	2.28	$6x10^{-5}$	EUR	0.027/0.021	1.32	0.062	1.57, $1.8x10^{-4}$
						POLY	0.003/0.007	1.06	0.94	
						COMB		1.31	0.067	
rs11761178	*WBSCR28*	A	0.456/0.370	1.43	$1x10^{-5}$	EUR	0.394/0.410	0.90	0.030	-
						POLY	0.775/0.751	1.01	0.91	
						COMB		0.92	0.060	
rs1466085	*TFRC*	A	0.110/0.066	1.77	$3x10^{-5}$	EUR	0.091/0.068	1.29	0.0022	1.37, $6.4x10^{-8}$
						POLY	0.652/0.583	1.32	0.0094	
						COMB		1.30	$5x10^{-5}$	
rs1887406	*ZBTB46*	C	0.249/0.176	1.56	$4x10^{-5}$	EUR	0.200/0.191	1.02	0.69	1.18, $4.9x10^{-4}$
						POLY	0.318/0.279	1.31	0.018	
						COMB		1.08	0.14	
rs6891250	*SORCS2*	C	0.176/0.120	1.57	$5x10^{-5}$	EUR	0.125/0.125	0.98	0.80	1.07, 0.22
						POLY	0.303/0.315	0.90	0.34	
						COMB		0.96	0.45	

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Abstract Number: 221

Clinical and Genetic Characteristics of Diuretic-Associated Gout: A Case-Control Study

Sirisha Mitnala[1], Amanda Phipps-Green[2], Christopher Franklin[1], Anne Horne[3], Lisa K. Stamp[4], Tony R. Merriman[5] and **Nicola Dalbeth**[1,3], [1]University of Auckland, Auckland, New Zealand, [2]University of Otago, Dunedin, New Zealand, [3]Department of Medicine, University of Auckland, Auckland, New Zealand, [4]Medicine, University of Otago, Christchurch, Christchurch, New Zealand, [5]Biochemistry Dept, PO Box 56, University of Otago, Dunedin, New Zealand

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Background/Purpose: Hyperuricaemia and secondary gout are well-recognised complications of diuretic use. Variants in *ABCG2* and *SLC2A9* have been identified as the two major genetic risk factors for gout in genome wide association studies. The aim of this study was to examine the clinical and genetic characteristics of diuretic-associated gout.

Methods: Participants (n=1,365), all fulfilling the 1977 ARA gout classification criteria, were recruited from primary and secondary care. All participants attended a study visit, which included a detailed clinical assessment. Use of diuretic therapy at the time of recruitment was recorded, and was confirmed by electronic dispensing data. The gout-associated *ABCG2 rs2231142* and *SLC2A9 rs11942223* SNPs were genotyped. Clinical and genetic features of diuretic-associated gout were analysed using a case-control study design (diuretics vs. no diuretics). Loop and thiazide diuretics were also analysed separately (participants taking both loop and thiazide diuretics were included in loop diuretic group).

Results: There were 939 participants on no diuretics and 426 participants on at least one diuretic (281 in the loop diuretic group and 145 in the thiazide diuretic group). In the diuretic group, there were more women, later onset of disease, higher rates of cardiac disease, hypertension and type 2 diabetes, higher body mass index, higher serum urate and lower eGFR, compared to those not on diuretics (Table). Gout disease duration, frequency of gout flares and presence of tophi were similar in the two groups (Table). The *ABCG2 rs2231142* minor (risk) allele was present less frequently in the diuretic group (36.1%) than in those not on diuretics (47.6%, p=2.9E-04). *ABCG2 rs2231142* minor (risk) allele positivity was lower in those taking loop diuretics (37.1%) and thiazide diuretics (34.3%). In contrast, there was no significant difference in positivity for the minor (protective) allele for *SLC2A9 rs11942223* between the two groups (p=0.074).

Conclusion: Diuretic-associated gout represents a medically complex condition with frequent comorbid conditions. The observed differences in the *ABCG2* risk allele frequency suggest that some genetic factors play a less dominant role in the etiology of diuretic-associated gout, compared to primary gout.

Table: Clinical and genetic features separated by use of diuretics. Unless specified, data are presented as mean (SD). For genotype analysis, p values were generated by logistic regression adjusting for ancestral group.

	No diuretic (n=939)	**Diuretic (n=426)**	**p**
Male sex, n (%)	829 (88.3%)	299 (70.2%)	2.9E-16
Age, years	53.9 (14.2)	65.3 (11.9)	8.3E-48
Age of onset, years	39.8 (14.8)	51.1 (17.4)	3.5E-28
Duration of gout, years	14.1 (11.8)	14.3 (13.6)	0.82
Māori or Pacific ancestry	553 (58.9%)	220 (51.6%)	0.013
Cardiac disease, n (%)	174 (18.6%)	262 (61.9%)	1.1E-56
Hypertension, n (%)	407 (44.2%)	353 (83.3%)	5.3E-41
Type 2 diabetes, n (%)	120 (13.0%)	146 (34.5%)	2.9E-20
Number of gout flares in previous year	6.6 (10.6)	6.0 (10.7)	0.37
Presence of tophi, n (%)	210 (23.0%)	107 (25.9%)	0.25
Body mass index, kg/m^2	33.1 (6.9)	34.8 (8.7)	7.2E-04
Highest recorded serum urate, mg/dL	8.5 (2.0)	9.0 (2.2)	1.4E-05
eGFR, $mL/min/1.73m^2$	68.5 (18.8)	50.2 (19.5)	1.4E-46
SLC2A9 rs11942223 protective allele (C) present, n (%)	139 (15.5%)	54 (13.3%)	0.074
ABCG2 rs2231142 risk allele (T) present, n (%)	426 (47.6%)	146 (36.1%)	2.9E-04

Disclosure: S. Mitnala, None; **A. Phipps-Green**, None; **C. Franklin**, None; **A. Horne**, None; **L. K. Stamp**, None; **T. R. Merriman**, None; **N. Dalbeth**, None.

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Abstract Number: 222

Serum Delta Neutrophil Index Measurement for Differentiating Acute Gouty Arthritis and Cellulitis in Normouricemic Patients

Jung Yoon Pyo[1], Jason Jungsik Song[2], Yong-Beom Park[1], Soo-Kon Lee[1] and Sang-Won Lee[1], [1]Yonsei University College of Medicine, Division of Rheumatology, Department of Internal Medicine, Seoul, South Korea, [2]Division of Rheumatology, Department of Internal Medicine, Yonsei University College of Medicine, Seoul, South Korea

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Background/Purpose:

Diagnosis of a patient who comes with acute foot pain is often challenging, because both acute gouty arthritis and cellulitis share common clinical manifestations such as redness, warmth, tenderness and soft tissue swelling, and inflammatory markers do not discriminate between those two entities. When it comes to patients with normouricemia, it is even more challenging. Differentiating acute gouty arthritis from cellulitis is critical for deciding treatment strategies, which will prevent the misuse of antibiotics for gout and prevent a delay of antibiotics treatment for cellulitis.

Delta neutrophil index (DNI) is a difference between leukocyte subfractions which corresponds to the fraction of immature granulocyte. DNI was reported to be associated with infection and sepsis, therefore it is considered to be helpful in differentiating acute gouty arthritis and cellulitis.

In this study, we evaluated the utility of DNI as a predictive marker in differentiating acute gouty arthritis and cellulitis in normouricemic patients.

Methods:

We reviewed medical records of total 212 normouricemic patients who were admitted from January 2011 to April 2015. 74 patients had acute gouty arthritis and 138 patients were diagnosed cellulitis of lower limbs, and all the patients had serum uric acid below 7 mg/dL. DNI was automatically determined by the ADVIA 2120 electronic cell analyzer. Multivariate logistic regression was used to find independent variables for predicting cellulitis among variables which had statistical differences in chai-square test or which had clinical implication. Cutoff for categorizing values were determined by receiver operating characteristic (ROC) curve.

Results:

The cellulitis group showed higher levels of white blood cell counts, CRP and lower levels of uric acid. ESR and procalcitonin had no difference between two groups. Patients in acute gouty arthritis group had significant lower

values of DNI than those in cellulitis group (0.7 ± 0.9 % vs 2.6 ± 3.1 %, p<0.0001). In multivariate logistic regression analysis, DNI was the only significant independent factor for discriminating cellulitis from acute gouty arthritis. When we selected DNI value of 1.7% as the cutoff for cellulitis, patients with DNI 1.7% or higher were found to have higher risk for cellulitis than those with DNI less than 1.7% (Odds ratio 4.780).

Conclusion:

The present study seems to be the first to evaluate DNI in gout investigating its usefulness as a novel serologic marker for differentiating acute gouty arthritis from cellulitis. Our findings demonstrate that DNI measurement is useful for predicting cellulitis superior to ESR, CRP or procalcitonin in normouricemic patients and helpful in making decisions about the treatment.

Table 1. Multivariate analysis for the independent variable to predict cellulitis

Variables		Multivariate analysis		
		Odds ratio	95% Confidence interval	P value
WBC count (/?L)	< 10,000 ≥ 10,000	4.124	0.677, 25.136	0.124
DNI (%)	< 1.7% ≥ 1.7%	**4.780**	1.034, 22.093	**0.045**
ESR (mm/hr)	< 40 ≥ 40	0.314	0.037, 2.663	0.288
uric acid (mg/dL)	< 4.5 ≥ 4.5	1.178	0.223, 6.224	0.847
CRP (mg/L)	< 74 ≥ 74	1.967	0.277, 14.093	0.497
procalcitonin (ng/ml)	< 0.9 ≥ 0.9	2.123	0.305, 14.769	0.447

WBC : white blood cell, DNI : delta neutrophil count, ESR : erythrocyte sedimentation rate. CRP : C-reactive protein.

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Abstract Number: 223

Increased Platelet Reactivity in Gout: A Potential Mechanism for Adverse Cardiovascular Events

Richard Conway[1], Claire-Louise Murphy[2], Anne Madigan[2], Patricia Kavanagh[2], Liz Geraghty[2], Laura Helbert[2], Kelly Stephens[3], John J. Carey[4], Eimear Dunne[5], Dermot Kenny[5] and Geraldine M. McCarthy[6], [1]Rheumatology, Mater Misericordiae University Hospital, Dublin 2, Ireland, [2]Rheumatology, Mater Misericordiae University Hospital, Dublin 7, Ireland, [3]Mater Misericordiae University Hospital, Clinical Research Center, Dublin, Ireland, [4]Rheumatology, Galway University Hospitals, Galway, Ireland, [5]Molecular and Cellular Therapeutics, RCSI, Dublin 2, Ireland, [6]University College Dublin, Dublin, Ireland

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Background/Purpose:

Patients with inflammatory arthritis, including gout, have an increased risk of cardiovascular events and mortality. Increased platelet reactivity is a risk marker for cardiovascular events. The glycoprotein VI (GPVI) receptor is found exclusively on platelets and megakaryocytes and is the predominant platelet receptor for collagen. It remains intact on platelets under resting conditions. The proteolytic cleavage of GPVI occurs only upon specific activation of platelets and is detectable in the plasma as soluble GPVI (sGPVI). Therefore elevated plasma sGPVI represents a potential biomarker for platelet hyperreactivity and hence adverse cardiovascular outcomes

Methods:

The aim of this study was to assess platelet reactivity, as measured by plasma sGPVI levels, in acute gout, chronic gout, and acute calcium pyrophosphate (CPP) arthritis, and to compare these to each other and to healthy controls. Following ethics approval and informed consent, blood samples were taken from patients with gout and CPP arthritis. Healthy control samples were obtained from volunteers. Demographic and clinical data were collected for all participants. Blood samples were processed as double spun platelet poor plasma. sGPVI levels were measured using ELISA. Mann-Whitney U test was used to compare groups. Spearman's Rank Correlation Coefficient was used to assess for associations between sGPVI levels and demographic and clinical markers. GraphPad Prism Version 6.05 and IBM SPSS Statistics Version 20 were used for data analysis.

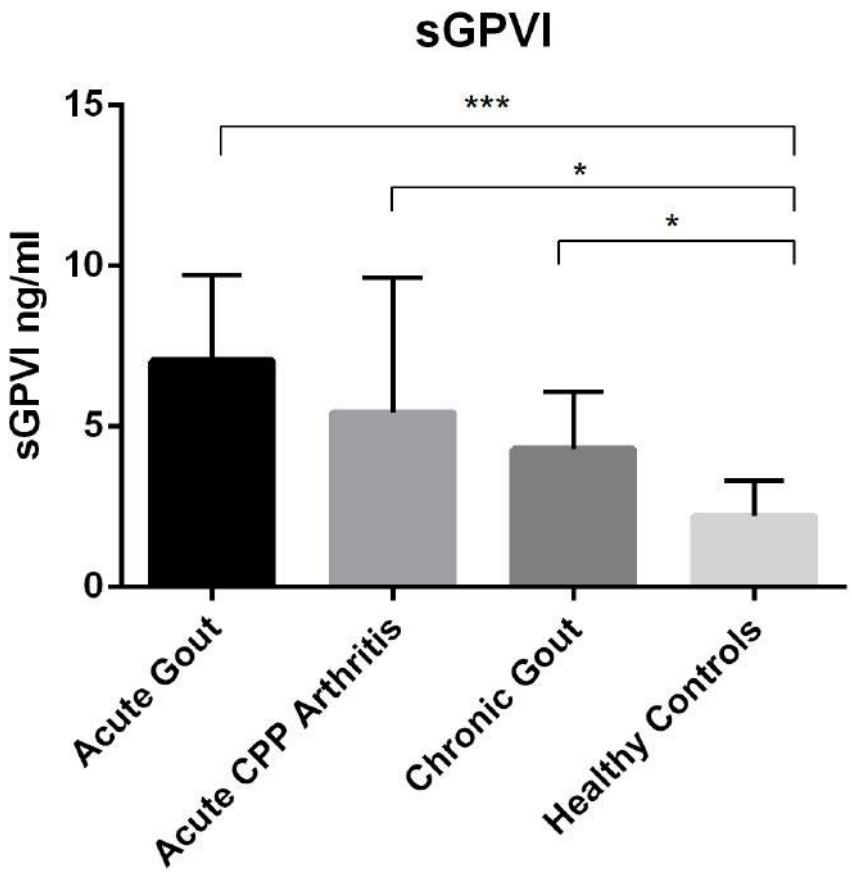
Results:

One hundred and six patients were included in the study, 16 with acute gout, 5 with acute CPP arthritis, 32 with chronic gout, and 53 healthy controls. There were no significant differences in demographic details between the groups. Median (IQR) sGPVI levels were 7.03 ng/ml (3.80, 9.70) in acute gout, 5.42 ng/ml (3.73, 9.63) in acute CPP arthritis, 4.28 ng/ml (2.10, 6.07) in chronic gout, and 2.05 ng/ml (1.69, 3.31) in healthy controls. sGPVI levels in all 3 disease groups were significantly increased compared to healthy controls ($p<0.05$ for each) (Figure 1). GPVI levels in patients with active gout were significantly increased compared to chronic gout ($p=0.02$). There was moderate correlation between sGPVI levels and CRP ($r=0.42$), VASPain ($r=0.42$), and VASQOL ($r=0.51$), and a weak correlation with ESR ($r=0.35$).

Conclusion:

Patients with crystal-induced arthropathies exhibit platelet hyperactivity as demonstrated by elevated plasma sGPVI levels. This was particularly evident during acute gout. Platelet hyperactivity may contribute to the elevated cardiovascular risk in gout patients and GPVI represents an attractive new target as an antiplatelet reagent in this patient population, for whom no anti-thrombotic guidelines exist.

Figure 1: sGPVI levels



Disclosure: R. Conway, None; **C. L. Murphy**, None; **A. Madigan**, None; **P. Kavanagh**, None; **L. Geraghty**, None; **L. Helbert**, None; **K. Stephens**, None; **J. J. Carey**, None; **E. Dunne**, None; **D. Kenny**, None; **G. M. McCarthy**, None.

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Abstract Number: 224

Silent Monosodium Urate Crystals Deposits in Asymptomatic Hyperuricemia Lead to a Higher Need for Coronary Revascularization

Mariano Andrés[1], María Amparo Quintanilla[2], Francisca Sivera[3], José Sánchez-Payá[4], Juan M Ruiz-Nodar[5], Eliseo Pascual[1,6] and Paloma Vela[1,6], [1]Sección de Reumatología, Hospital General Universitario de Alicante, Alicante, Spain, [2]Sección de Cardiología, Hospital General Universitario de Elda, Alicante, Spain, [3]Reumatología, Hospital General Universitario de Elda, Alicante, Spain, [4]Servicio de Medicina Preventiva, Hospital General Universitario de Alicante, Alicante, Spain, [5]Servicio de Cardiología, Hospital General Universitario de Alicante, Alicante, Spain, [6]Departamento de Medicina Clínica, Universidad Miguel Hernández, Alicante, Spain
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Background/Purpose:

Increased cardiovascular (CV) risk in gout relates to crystal-driven inflammation. In a preliminary, cross-sectional study we found that silent deposits of monosodium urate (MSU) crystals in asymptomatic hyperuricemia (AH) associated with a more severe coronary calcification, in comparison to AH alone and normouricemia (NU) [1]. Whether this silent deposit also leads to a poor CV prognosis of AH patients has not been assessed so far. We aimed to compare the incidence of CV events between the study groups in the follow-up period after the admission.

Methods:

Prospective follow up of patients from the previous study [1]; consecutive patients admitted due to an acute coronary event were classified at baseline as NU, AH alone, and AH with crystals after serum uric acid levels, joint ultrasound and polarized microscopy of synovial fluid samples. The date of admission was considered as the index date. Electronic clinical records were reviewed in order to register the occurrence of all-cause death, CV-related death, new ST-elevation (STE) acute coronary event, new non-STE acute coronary event, and need for coronary revascularization during follow-up. Kaplan-Meier curves were plotted for each outcome for between-group comparisons, and a multivariate Cox regression model was built to adjust for CV risk factors.

Results:

140 patients were enrolled, and classified as 66 NU, 61 AH alone, and 13 AH with MSU crystals. Only one patient (from the *AH alone* group) was lost in the follow-up. Median (p25-75) follow-up was 12.0 (8.3-16.0) months. No new STE acute coronary event was registered. No significant differences were found in all-cause or CV-related death. The AH with crystals group showed higher need for new coronary revascularization and higher incidence of new non-STE acute coronary event [Figures A and B, respectively). After adjustment for CV risk factors, a non-sigficant but evident trend towards a higher need for new coronary revascularization was found in the AH with crystals group (aHR 4.5; 95%CI 0.8-24.1, p=0.08); no significant differences in non-STE acute event were found.

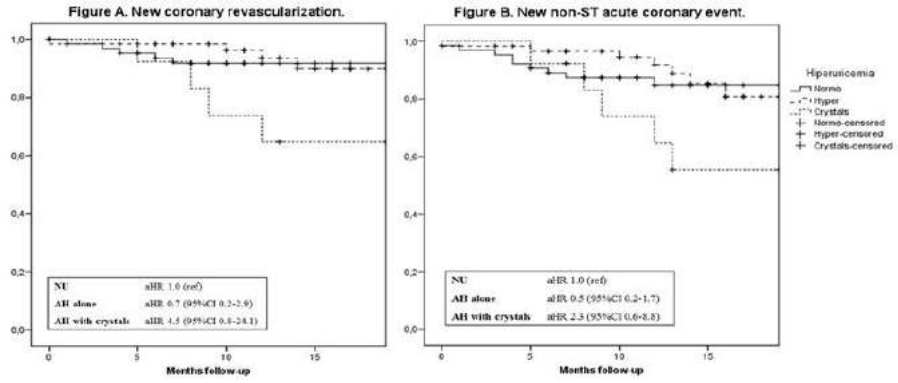
Conclusion:

Silent deposits of MSU crystals in AH appear to lead to a higher need for new coronary revascularization. Low patient numbers likely account for the lack of significance. This finding adds more evidence to the detrimental role of MSU crystals on the arteriosclerotic disease of these subjects.

References:

[1] 2014 ACR Annual Meeting (abstract #829).

Figure:



Disclosure: M. Andrés, None; **M. A. Quintanilla**, None; **F. Sivera**, None; **J. Sánchez-Payá**, None; **J. M. Ruiz-Nodar**,

None; **E. Pascual**, Menarini, 5; **P. Vela**, None.

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Abstract Number: 225

Gout Patients Present Carotid Plaques at Presentation in Spite of Low-Risk Cardiovascular Score

Mariano Andrés[1], Francisca Sivera[2], José Antonio Bernal[1], Neus Quilis[1], Loreto Carmona[3], Paloma Vela[1,4] and Eliseo Pascual[1,4], [1]Sección de Reumatología, Hospital General Universitario de Alicante, Alicante, Spain, [2]Reumatología, Hospital General Universitario de Elda, Alicante, Spain, [3]Instituto de Salud Musculoesquelética, Madrid, Spain, [4]Departamento de Medicina Clínica, Universidad Miguel Hernández, Alicante, Spain
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Gout patients present carotid plaques at presentation in spite of low-risk cardiovascular score.

Background/Purpose:

Gout is associated with an increased cardiovascular (CV) risk related to high prevalence of CV risk factors (CVRF) and to persistent, crystal-led inflammation. Beside proper gout-specific treatment, an accurate CV assessment at first presentation appears essential to initiate strategies to control this increased CV risk. We aimed: 1) to describe the CV profile at presentation of gout patients; 2) to estimate the proportion of patients that may be at very high risk by carotid ultrasound (cUS) despite a low Systematic COronary Evaluation (SCORE); and 3) to evaluate the predictability of the SCORE to identify those patients with carotic plaque.

Methods:

We performed an observational, cross-sectional study of all consecutive crystal-proven gout patients newly seen in our unit. All patients underwent a CV structure consultation that included: presence of CV disease or traditional CVRFs, background of CV disease, blood pressure levels, body mass index, and lab tests (glucose, HbA1C, lipids, creatinine). SCORE was calculated in those without prior CV events. CV risk was stratified as low, moderate, high, or very high, according to current European guidelines [1]. Those patients who were not at a very high CV risk underwent carotid ultrasound (cUS) to assess carotid intima-media thickness (cIMT) and presence of atheroma plaques [2]. The prevalence of carotid plaque in cUS was estimated and its predictability by the SCORE tested by receiver operating curves, estimating the area under the curve (AUC).

Results:

A total of 138 patients were recruited, median aged 65.0 years (p25-75 54.8-74.3), 89.1% males. The prevalence of CVRFs was as follows: 65.9% hypertension, 23.2% diabetes, 51.4% dyslipidemia, and 60.1% smoking background. Glomerular filtration rate was under 60mL/min in 23.9% of patients, and 30.4% had a diagnosis of CV disease. Median SCORE was 3% (p25-75 1-5%). CV risk stratification of patients before cUS is shown in the Figure, prevailing very high risks (38.2%). cUS was performed in 86 patients, finding cIMT>0.9mm in 48 patients (55.8%; 95%CI 45-67) and

atheroma plaques in 39 (45.3%; 95%CI 35-56). A 19.8% of patients showed bilateral carotid plaque. Up to 58.1% of the patients who underwent cUS had their CV risk reclassified, mostly to very high risk (Figure). The AUC for SCORE for predicting unilateral and bilateral plaque were 0.732 (95%CI 0.627-0.837).

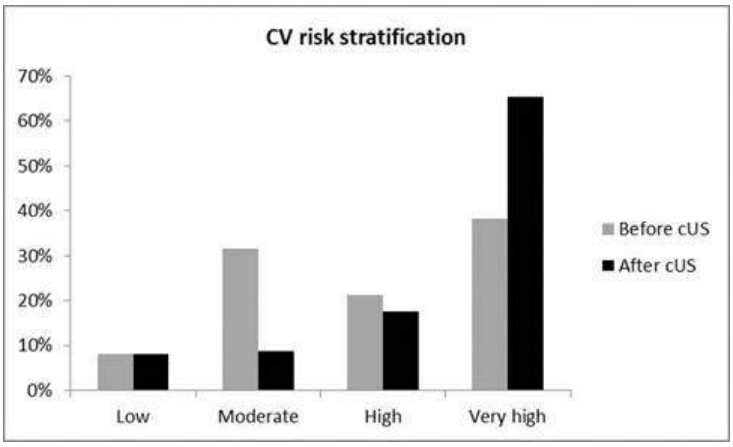
Conclusion:

A majority of newly attended gout patients may be at very high CV risk indicating the need for initiating optimal prevention strategies at this stage. The SCORE tool appears to underestimate the presence of carotid plaque in gout patients.

References:

[1] Eur Heart J. 2012; 33:1635. [2] Cerebrovasc Dis. 2012; 34:290.

Figure:



Disclosure: M. Andrés, None; **F. Sivera**, None; **J. A. Bernal**, None; **N. Quilis**, None; **L. Carmona**, None; **P. Vela**, None; **E. Pascual**, Menarini, 5.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/gout-patients-present-carotid-plaques-at-presentation-in-spite-of-low-risk-cardiovascular-score

Abstract Number: 226

Prevalence of Cardiovascular Disease in Patients with Gout, Osteoarthritis or Both

Daisy Bang[1], Jinfeng Xu[2], Robert T. Keenan[3], Virginia Pike[1], Aaron Lehmann[1], Craig T. Tenner[4], Daria Crittenden[1], Michael H. Pillinger[1] and Svetlana Krasnokutsky[1], [1]Medicine/Rheumatology, NYU School of Medicine/NYU Hospital for Joint Diseases, New York, NY, [2]Biostatistics, New York University School of Medicine, New York, NY, [3]Rheumatology, Duke University, Durham, NC, [4]Medicine, NYU School of Medicine, New York, NY

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Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose: Osteoarthritis (OA) and gout are each associated with increased cardiovascular disease (CVD), but their relative impacts on CV risk are not known. We compared rates of CVD among patients with OA (OA-only), gout (gout-only), or both (gout+OA).

Methods: We used ICD-9 codes to identify male patients from within our VA health care system with OA-only, gout-only, or gout+OA, and an active medical record between August 2007 and August 2008. For each group, we collected baseline demographics and CVD risk factors. The primary outcome was a composite index (CV4) consisting of any diagnosis of myocardial infarction (MI), angina, coronary bypass surgery (CABG), and/or coronary artery disease (CAD). Secondary outcomes included individual diagnoses within the CV4, congestive heart failure (CHF) and death. Logistic regression was used to compare the associations of OA-only, gout-only, and gout+OA with CV outcomes, adjusting for traditional CV risk factors: age, race, hypertension (HTN), diabetes mellitus, hyperlipidemia (HLD), chronic kidney disease (CKD), and smoking.

Results: 1280 gout subjects met inclusion criteria (983 gout-only, 297 gout+OA), along with 1231 OA-only subjects. Gout subjects, with or without OA, had more CVD risk factors at baseline, including HTN, HLD and CKD vs. OA-only. In an unadjusted model, a diagnosis of gout increased the risk for CV4, CAD, angina, CABG, CHF, and death compared to a diagnosis of OA-only. In a fully adjusted model, gout-only subjects continued to have increased risk for all outcomes except MI and death compared to OA-only subjects, while gout+OA subjects exhibited increased risk for angina and CHF (Table 1). Gout+OA did not impart additional risk over gout-only for any outcome except CABG.

Conclusion: Our data suggest that gout is associated with higher risk of CVD compared with OA, that at least some of this increased risk may be independent of traditional risk factors, and that OA does not impart additive CVD risk to patients who also have gout.

Table 1. Relative cardiovascular disease outcomes among OA-only, Gout-only and Gout+OA subjects, adjusted for age, race, HTN, HL, DM, CKD, and smoking. Data are odds ratios with 95% confidence intervals and p-values.

	Gout-only vs OA-only	**Gout+OA vs OA-only**	**Gout+OA vs Gout-only**
CV4 (Primary outcome)	1.271 (1.025,1.574) **p=0.029**	1.263 (0.937,1.692) p=0.121	0.994 (0.739, 1.329) p=0.967
CAD	1.261 (1.010,1.574) **p=0.040**	1.084 (0.796, 1.467) p=0.604	0.860 (0.634, 1.159) p=0.325
Angina	4.367 (2.005,10.609) **p<0.001**	3.374 (1.233, 9.383) **p=0.017**	0.773 (0.337, 1.608) p=0.513
MI	0.972 (0.487, 1.921) p=0.936	1.010 (0.356, 2.481) p=0.984	1.039 (0.371, 2.529) p=0.937
CABG	3.951 (2.249, 7.176) **p<0.001**	1.782 (0.746, 3.961) p=0.170	0.451 (0.202, 0.905) **p=0.036**
CHF	2.379 (1.638, 3.483) **p<0.001**	2.209 (1.378, 3.505) **p<0.001**	0.929 (0.605, 1.399) p=0.729
Death	1.30 (0.826, 2.487) p=0.203	1.870 (0.973, 3.514) p=0.055	1.308 (0.716, 2.317) p=0.367

Disclosure: D. Bang, None; **J. Xu**, None; **R. T. Keenan**, AstraZeneca, 5; **V. Pike**, None; **A. Lehmann**, None; **C. T. Tenner**, None; **D. Crittenden**, Amgen Inc, 1,Amgen, Inc, 3; **M. H. Pillinger**, Takeda Inc, 2,AstraZeneca, 5; **S. Krasnokutsky**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/prevalence-of-cardiovascular-disease-in-patients-with-gout-osteoarthritis-or-both

Abstract Number: 227

Impact of Gout on the Risk of Atrial Fibrillation

Chang-Fu Kuo[1], Matthew J. Grainge[2], Weiya Zhang[3] and Michael Doherty[4], [1]Division of Rheumatoplogy, Allergy and Immunology, Chang Gung Memorial Hospital, Tayuan, Taiwan, [2]Division of Epidemiology and Public Health, School of Community Health Sciences, University of Nottingham, Nottingham, United Kingdom, [3]Academic Rheumatology, School of Clinical Sciences, University of Nottingham, Nottingham, United Kingdom, [4]Academic Rheumatology, City Hospital, Nottingham, United Kingdom
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SESSION INFORMATION
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Session Type: ACR Poster Session A
Session Time: 9:00AM-11:00AM

Background/Purpose:

To examine the risk of atrial fibrillation (AF) at the time of first diagnosis of gout compared to matched controls and to follow incident gout patients and their matched controls after diagnosis to compare their subsequent risk of AF.

Methods:

45,378 incident gout patients and 45,378 age-, sex-, practice-, registration year- and index year-matched controls were identified from the UK Clinical Practice Research Data-link. Index dates were initial diagnosis date for gout patients and their matched controls. The risk of AF at diagnosis (odds ratios [ORs], using conditional logistic regression) and after the diagnosis of gout (hazard ratios [HRs], using Cox proportional models) were estimated, adjusted for body mass index, smoking, alcohol consumption, ischaemic heart disease, heart failure, heart valve disease, hyperthyroidism and other comorbidities and medications.

Results:

The prevalence of AF at index date in gout patients (male, 72.3%; mean age, 62.4 ± 15.1 years) was 7.42% (95% confidence interval [CI], 7.18%–7.66%) and in matched controls 2.83% (95% CI, 2.67%–2.98%). The adjusted OR (95% CI) was 1.45 (1.29–1.62). The cumulative probability of AF at 1, 2, 5 and 10 years after index date was 1.08%, 2.03%, 4.77% and 9.68% in gout patients and 0.43%, 1.08%, 2.95% and 6.33% in controls (log-rank test, $p < 0.001$). The adjusted HRs (95% CIs) was 1.09 (1.03–1.16).

Conclusion:

This population-based study indicates that gout is independently associated with a higher risk of AF at diagnosis and the risk is also higher after the diagnosis.

Disclosure: C. F. Kuo, None; **M. J. Grainge**, None; **W. Zhang**, None; **M. Doherty**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/impact-of-gout-on-the-risk-of-atrial-fibrillation

Abstract Number: 228

Gout and Risk of Non-Vertebral Osteoporotic Fracture

Seoyoung C. Kim[1], Julie M. Paik[2], Jun Liu[3], Gary C. Curhan[2] and Daniel H. Solomon[4], [1]Div. of

Pharmacoepidemiology and Pharmacoeconomics, Div. of Rheumatology, Immunology and Allergy, Brigham and Women's Hospital, Boston, MA, [2]Renal Division, Brigham and Women's Hospital, Boston, MA, [3]Division of Pharmaoepidemiology, Brigham and Women's Hospital, Boston, MA, [4]Division of Rheumatology, Immunology and Allergy, Brigham and Women's Hospital, Boston, MA

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SESSION INFORMATION

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Background/Purpose: Prior studies suggest an association between osteoporosis, systemic inflammation and pro-inflammatory cytokines such as IL-1 and IL-6. Gout is a common inflammatory arthritis characterized by hyperuricemia leading to crystallization of uric acid in joints. Several observational studies, but not all, report a relationship between hyperuricemia and bone mineral density (BMD). Furthermore, it is unknown whether gout has an impact on BMD and the risk of osteoporotic fracture.

Methods: Using data from a US commercial insurance plan (2004-13), we conducted a cohort study to evaluate the incidence rate (IR) of any non-vertebral fracture (i.e. forearm, wrist, hip and pelvis) and hip fracture in patients with and without gout. Gout patients were identified with ≥2 diagnosis codes and ≥1 dispensing for a gout-related drug. Non-gout patients were free of gout diagnosis and received no gout-related drugs; but, the non-gout group had ≥2 physician visits for any diagnosis and ≥1 dispensing for any prescription drugs. Non-vertebral fracture was defined with a combination of diagnosis and procedure codes for invasive/noninvasive treatment for fracture. The index date was the date of the 1st dispensing of a gout-related drug for the gout group or any drug for the non-gout after ≥1-year continuous enrollment. We excluded patients with prior fracture, malignancy, chemotherapy, ESRD, or renal transplantation. The non-gout group was matched to the gout group on age, sex and the index date with a 3:1 ratio. We calculated the incidence rates (IR) of non-vertebral and hip fracture in both groups. Multivariable Cox proportional hazards models compared separately the risk of non-vertebral and hip fractures in patients with and without gout.

Results: We identified 73,202 gout and 219,606 non-gout patients, matched on age, sex, and the index date. The mean age was 60 years and 82% were men. Among patients with baseline uric acid levels available (n=18,176), the mean (SD) uric acid level (mg/dL) was 7.4 (2.0) in gout and 6.0 (1.4) in non-gout. Over the mean 2-year follow-up, the IR of non-vertebral fracture per 1,000 person-years was 2.92 in gout and 2.66 in non-gout. In both groups, the IR of non-vertebral fracture was 3-fold higher in women than men (**Table**), but no significant interaction between sex and effect of gout on fracture was noted (p=0.4). Multivariable HR adjusted for potential risk factors for osteoporotic fracture in gout patients was 0.98 (95%CI 0.85-1.12) for non-vertebral fracture and 0.83 (95%CI 0.65-1.07) for hip fracture. In the subgroup analysis further adjusted for baseline serum uric acid levels, HR of non-vertebral fracture in gout was 1.20 (95%CI 0.54-2.67).

Conclusion: In this large cohort study, gout does not appear to be associated with an increased risk of non-vertebral or hip fracture. Whether serum uric acid is associated with osteoporotic fracture needs to be further studied.

Table. Risk of non-vertebral and hip fracture in gout versus non-gout: age, sex and index date-matched

	Gout (n=73,202)				Non-gout (n=219,606)			
	Cases	Person-years	IR [a] (95% CI)	HR [b] (95% CI)	Cases	Person-years	IR * (95% CI)	HR (95% CI)
Non-vertebral fracture								
All	423	144,678	2.92 (2.65-3.21)	0.98 (0.85-1.12)	1,150	432,841	2.66 (2.51-2.82)	Ref
Women	159	23,651	6.72 (5.75-7.85)	0.89 (0.71-1.12)	493	77,867	6.33 (5.80-6.91)	Ref
Men	264	121,026	2.18 (1.93-2.46)	1.03 (0.86-1.22)	657	354,974	1.85 (1.71-2.00)	Ref
Hip fracture								
All	125	145,115	0.86 (0.72-1.02)	0.83 (0.65-1.07)	392	434,043	0.90 (0.82-0.99)	Ref
Women	44	23,796	1.85 (1.38-2.49)	0.94 (0.61-1.43)	155	78,412	1.98 (1.59-2.32)	Ref
Men	81	121,320	0.67 (0.54-0.83)	0.79 (0.58-1.07)	237	355,630	0.67 (0.59-0.76)	Ref

[a] per 1,000 Person-years, [b] HR is adjusted for over 40 variables including age, sex, prior BMD testing, osteoporosis, other comorbidities, bisphosphonates, steroids, opioids, other medications, and health care utilization factors.

IR: incidence rate, HR: hazard ratio, CI, confidence interval

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View Abstract and Citation Information Online - http://acrabstracts.org/abstract/gout-and-risk-of-non-vertebral-osteoporotic-fracture

Abstract Number: 229

Uric Acid and Incident Dementia over 10 Years

Pascal Richette[1], Aicha Soumare[2], Stéphanie Debette[2], Thomas Bardin[3,4] and Christophe Tzourio[2], [1]Université Paris Diderot, UFR médicale, Paris, France; APHP Hôpital Lariboisière, Fédération de Rhumatologie and Inserm U1132, Hôpital Lariboisière, Paris, France, [2]INSERM Research Center for Epidemiology and Biostatistics (U897) Team

Neuroepidemiology, Bordeaux, France, [3]Service de Rhumatologie, Hôpital Lariboisière, Paris, France, [4]Rhumatology Departement, Hôpital Lariboisière, Paris, France

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Session Title: Metabolic and Crystal Arthropathies Poster I

Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose: In patients with gout, maintaining the serum uric acid (SUA) levels too low with ULT is a matter of concern because UA is thought to be neuroprotective. However, the relation between UA and both dementia and cognitive function, in which both vascular mechanisms and oxidative stress are thought to play a role, has been poorly explored.

Methods: We assessed the longitudinal association between SUA levels and the risk of incident dementia (DSM-IV criteria) over 10 years of follow-up in a large cohort of elderly individuals (3C cohort). Additionally, we investigated the relation between SUA levels and change in cognitive function (minimental state examination, Benton and Isaac tests, Trail making tests) and change in brain MRI patterns (total brain volume, white matter lesions volume and infarct-like brain lesions).

Results: The study sample comprised 1,769 individuals (mean age 72.4, male 39.6 %). During the 10,608 person-years of follow-up (median duration: 9.6 years), 134 participants developed dementia (crude incidence rate: 9.2/1000 person-years) with 94 (70.1%) classified as Alzheimer's disease and 9 (6.7%) as vascular dementia. Dementia was associated with older age, depressive symptoms, and APOE-ε4 genotype. Increasing age and BMI, current smoking, renal impairment, hypertension, history of cardiovascular disease, low HDL cholesterol, hypertriglyceridemia, high CRP and IL-6 levels, as well as the use diuretics, or aspirin were associated with hyperuricemia (all P values <0.001). The multivariate HR of dementia among individuals in the highest tertile of SUA levels as compared with those in the lowest tertile was 1.67 (95% CI 1.04 to 2.71); P for trend=0.05). The association was stronger for vascular dementia (HR 6.37 (95% 0.61 to 66.98)) than for Alzheimer's disease HR 1.71 (95% 0.97-3.03). There was no clear association between SUA levels and change in cognitive performance, nor with change in white matter lesions volume or brain structure as assessed with MRI.

Conclusion: These findings suggest that higher SUA levels are associated with an increase risk of dementia, mainly from vascular cause.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/uric-acid-and-incident-dementia-over-10-years

Abstract Number: 230

Serum Uric Acid As Short Term Mortality Predictor in the Acute Care Setting

Yuval Schwartz[1], Gideon Nesher[2,3] and Gabriel S Breuer[3,4], [1]Medicine, Shaare Zedek Medical Center, Jerusalem, Israel, [2]Internal Medicine, Rheumatology, Shaare Zedek Medical Center, Jerusalem, Israel, [3]Hebrew University School of Medicine, Jerusalem, Israel, [4]Rheumatology, Shaare Zedek Medical Center, Jerusalem, Israel

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Session Time: 9:00AM-11:00AM

Background/Purpose: Many studies have showed that the serum uric acid (SUA) is an independent predictor of adverse cardiovascular events and all-cause mortality, but some studies have yielded conflicting results. Even more contradicted issue is the relationship between SUA and mortality in acutely hospitalized patients. In this context there is scarce data about SUA as an independent predictor of short-come outcome in the hospitalized older patient. The aim of this study is to determine whether SUA obtained within 48 hours after admission can predict short-term outcome.

Methods: The analysis was conducted in an 850-bed medical center. 860 adult patients were admitted to internal medicine departments between March 1st 2014 and June 30th 2014. We evaluated SUA level drawn within 48 hours after admission as predictor of in-hospital mortality. In addition we collected clinical and epidemiological data.

Results: The mean age of patients was 78±14. The mortality rate was 15.1% (130 patients), and the mean SUA was 6.25 ± 2.70 mg/dl. The most common cause for hospitalization was pulmonary infection (16.8%) followed by congestive heart failure exacerbation (9.3%). The mortality rate was 11% (66 patients out of 562) in the group with SUA ≤ 7.5 in comparison to 27% (64 patients out of 171) in the group with SUA above this level [P < .001]. Moreover, SUA was an independent predictor of mortality in multivariate regression analysis, with odds ratio of 2.71 [confidence interval 1.82- 4.04 *P* < .001].

Table 1: Logistic regression analysis

Variables in the Equation	B	S.E.	Wald (df=1)	Exp(B)	95% C.I.for EXP(B)
Gender	0.01	0.2	0.00	1.01	0.69-1.49
Age	0.02	0.01	4.12*	1.02	1-1.03
creatinine	0.13	0.06	4.70*	1.14	1.01-1.29
Uric Acid	0.18	0.04	26.64***	1.2	1.12-1.29
Constant	-4.55	0.72	39.87	0.01	

*p < .05, *** p< .001

Conclusion: SUA level is a strong independent predictor of short-term outcome in elderly patients admitted to internal medicine departments.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/serum-uric-acid-as-short-term-mortality-predictor-in-the-acute-care-setting

Abstract Number: 231

Uric Acid Levels Predict Mortality in Women

Jenni E Kauppi[1], Tuomo Nieminen[2,3], Mika Kähönen[4,5], Anne Kerola[6], Antti Jula[7], Jaana Leiviskä[8] and Markku J.

Kauppi[9,10], [1]School of medicine, University of Tampere, Tampere, Finland, [2]Department of Internal Medicine, South Karelia Central Hospital, Lappeenranta, Finland, [3]Division of Cardiology, Helsinki University Central Hospital, Helsinki, Finland, [4]Department of Clinical physiology, School of Medicine, University of Tampere, Tampere, Finland, [5]Department of Clinical Physiology, Medical Imaging Centre, Pirkanmaa Hospital District, Tampere, Finland, [6]Faculty of Medicine, University of Helsinki, Helsinki, Finland, [7]Department of Health, National Institute for Health and Welfare, Turku, Finland, [8]Department of Health, National Institute for Health and Welfare, Helsinki, Finland, [9]School of Medicine, University of Tampere, Tampere, Finland, [10]Department of Rheumatology, Päijät-Häme Central Hospital, Lahti, Finland
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SESSION INFORMATION

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Background/Purpose:

Hyperuricemia induces chronic inflammation and is associated with many diseases such as metabolic syndrome, high blood pressure, chronic kidney disease and cardiovascular diseases. The best known manifestation is gout. Risk for gout flares begins when serum uric acid exceeds 360mmol/l. That is also internationally used as the limit for hyperuricemia.

Because hyperuricemia is connected with many severe health problems, we investigated whether serum uric acid levels associate with survival in a population-based cohort.

Methods:

The data is based on health study with representative nationwide population sample of adults from a Western society. Information about health and living habits was collected by questionnaires and interviews. Everyone went through a physical examination, and a large range of laboratory tests. The mortality analyses were performed separately for men and women. Unadjusted mortality was calculated for each quintile of uric acid levels. Adjusted prognostic capacity of serum uric acid levels was analyzed with Cox regression with the following covariates: age, body mass index (BMI), diagnoses of coronary artery disease, hypertension and diabetes; fasting serum levels of LDL cholesterol and triglycerides and serum gamma-glutamyl transferase. The end-points were all-cause and cardiovascular mortality, separately.

Results:

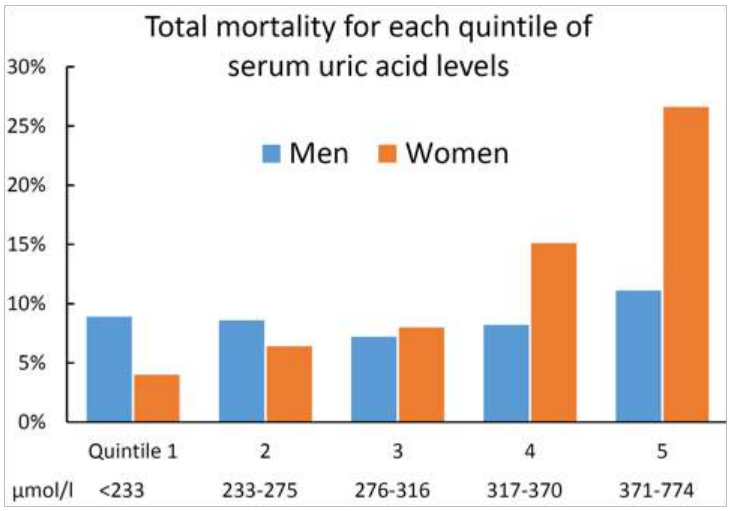
The dataset consisted of 6691 subjects (3703 or 55.3% were women) aged 30 years or more. Mean age was 54 years with interquartile range (IQR) 51–65 years. Mean BMI was 26.9 (IQR 23.6–29.5). At the baseline, mean uric acid level was 303 mmol/l (IQR 243–353mmol/l). The prevalence of hyperuricemia was 1529 (22.9%), being essentially higher than the prevalence of diagnosed gout with 64 participants (1.0%). During the median follow-up of 72 (IQR 70–73) months, the total number of deaths was 607 and number of cardiovascular deaths was 262.

Unadjusted mortality increased systematically along the elevating uric acid level quintile for women but not for men (Figure). Hyperuricemic women had an adjusted hazard ratio (HR) 1.41 (p=0.010) for mortality in comparison to those without hyperuricemia; for men 0.94 (p=0.650). Similarly, HR for cardiovascular mortality was 1.87 (p=0.002) for women and 1.18 (p=0.408) for men

Conclusion:

Our study shows that elevating serum uric acid levels have significant association with the risk of total and

cardiovascular mortality among women. Remarkably, the increase in mortality took place even before the commonly used level of hyperuricemia was reached. This interesting finding confirms results from earlier studies: uric acid level and at least hyperuricemia is a reason for concern even before flares of gout.



Disclosure: J. E. Kauppi, Finnish Cultural Foundation, 2; **T. Nieminen**, None; **M. Kähönen**, None; **A. Kerola**, None; **A. Jula**, None; **J. Leiviskä**, None; **M. J. Kauppi**, Berlin-Chemie/Menarini, 5.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/uric-acid-levels-predict-mortality-in-women

Abstract Number: 232

Hyperuricemia, Urate Lowering Therapy and Kidney Function: A Systemic Review and Meta-Analysis

Gaurav Sharma[1], Abhishek Dubey[1] and Jasvinder A. Singh[2], [1]Internal Medicine, Seth GS Medical College and KEM Hospital, Mumbai, India, [2]University of Alabama at Birmingham, Birmingham, AL

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Background/Purpose: To determine whether hyperuricemia is associated with deterioration of kidney function and to examine whether urate-lowering therapies (ULTs) can improve or maintain kidney function.

Methods: A literature search of various databases was performed. All randomized control trials, controlled clinical trials and observational studies of interest were included. Protocol was registered in PROSPERO database. Duplicate, independent screening of titles and abstracts and data abstraction was done . The primary outcome was renal function (measured by serum creatinine level, changes in GFR, Cystatin C level, progression to chronic kidney disease or end stage renal disease). Meta-analysis for association between increased serum uric acid and renal function (Q1) and for effect of urate lowering therapy on renal function(Q2) was done using RevMan 5.3.

Results: 5817 abstract and titles were screened for uric acid and renal outcomes (Q1) and for urate-lowering therapy and renal outcomes (Q2) questions. 24 studies with 316,391 patients and 5 studies with 522 patients qualified for final analyses, respectively. Mean ages were 20-79 years (Q1) and 35-85 years (Q2). Mean follow-up was 2 to 10 year and 2 months to 2 years, respectively.

We found that individuals with hyperuricemia (defined as serum uric acid ≥ 7 mg/dL in men and ≥ 6 mg/dL in women) had 1.5 times greater odds each of decline of glomerular filtration rate (GFR) by ≥ 3 mL/min/1.73 m^2/year or development of new albuminuria [defined as development of either micro albuminuria :Urine Albumin to Creatinine Ratio(UACR) is 30-300 mg/g or overt proteinuria (UACR > 300 mg/g)] compare to individuals with normal serum uric acid level. Individuals with hyperuricemia developed chronic kidney disease (CKD) about 2 times more frequently than the normourcemic individuals **(Table_1)**.

For Q2, we found 3 studies of Allopurinol (272 patients), 1 for Rasburicase (38 patients) and 1 for Pegloticase (212 patients). Compared to placebo patients treated with standard ULT doses had better glomerular filtration, creatinine clearance and low levels of serum Creatinine and serum Cystatin C **(Table_2);**urine albumin did not differ significantly.

Conclusion: Our systemic review and meta-analysis revealed an important relationship between hyperuricemia and renal function deterioration/renal failure development. Evidence is emerging that ULT use may improve renal function, although more data are needed. These findings indicate that appropriate treatment of hyperuricemia in patients with gout or other hyperuricemic condition may help to preserve kidney function.

Table 1: Comparison of renal functions in Hyperuricemic (serum uric acid ≥ 7 mg/dL in men and ≥ 6 mg/dL in wome) **vs Normouricemic group of individuals.**

Outcome	Odds Ratio [95% CI]	Hazard Ratio [95% CI]	Quality of evidence (Newcastle-Ottawa scale)
Decline in Glomerular Filtration Rate(decline of eGFR ≥ 3mL/min/1.73m2)	**1.48 [1.19, 1.83]**	---- --	Moderate
Albuminuria (defined as both microalbuminuria [Urine Albumin to Creatinine Ratio (UACR) >/= 30 mg/g) and overt is >/= 300 mg/g]	**1.55 [1.16, 2.07]**	---- --	Moderate
Chronic Kidney Disease (GFR </= 60 mL/min/1.73 m2)	**1.12 [1.06, 1.18]**	**1.96 [1.43, 2.70]**	Moderate-high
End Stage Renal Disease (defined as requirement of dialysis or renal transplant)	------	1.12 [0.97, 1.30]	Moderate

Table 2: Comparison of effect Urate-lowering Therapy (ULT) vs Placebo on renal functions.

Number of Studies per outcome	Number of patients per outcome	Outcome	Mean Difference [95 % CI]	Quality of evidence [using Cochrane risk of bias Assessment tool]
2	218	Glomerular Filtration Rate (mL/min/1.73 m2) **Normal value is ≥ 90 mL/min/1.73 m^2	**5.98 [2.09, 9.87]**	High Quality
2	167	Albuminuria (g/day) **Normal is value is excretion of <0.3 g/day	-0.03 [-0.10, 0.03]	Moderate - high
2	92	Serum Creatinine (mg/dL) **Normal range Men: 0.7-1.2 mg/dL Women: 0.6-1.1 mg/dL	**-0.76 [-1.11, -0.40]**	Moderate
1	38	Creatinine Clearance (mL/min) **Normal range Men: 97-137 mL/min Women: 88-128 mL/min	**9.70 [3.18, 16.22]**	Moderate
1	113	Serum Cystatin C (mg/L) **Normal range varies, depending on age and sex.	**-0.50 [-0.78, -0.22]**	High Quality

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Disclosure: G. Sharma, None; **A. Dubey**, None; **J. A. Singh**, Takeda, Savient, 2,Takeda, Savient, merz, Regeneron, Allergan, Crealta, Bioiberica, 5.

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Abstract Number: 233

Gout Does Not Decrease the Risk of Parkinson's Disease: A Systematic Review and Meta-Analysis

Patompong Ungprasert[1], Charat Thongprayoon[2] and Narat Srivali[3], [1]Rheumatology, Mayo Clinic, Rochester, MN,

[2]Internal medicine, Bassett medical center, Cooperstown, NY, [3]Pulmonary and Critical Care Medicine, Mayo Clinic, Rochester, MN

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Gout Does Not Decrease the Risk of Parkinson's Disease: A Systematic Review and Meta-analysis

Background/Purpose: Uric acid is a potent anti-oxidant and hyperuricemia is well-linked to a lower risk of Parkinson's disease (PD), one of the most common neurodegenerative disorders. However, data on gout, the major complication of hyperuricemia, remain unclear.

Methods: Two investigators independently searched published studies indexed in MEDLINE, EMBASE and the Cochrane database from inception to April 2015 using the terms for gout combined with the terms for Parkinson's disease. A manual search of references of selected articles was also performed. The inclusion criteria were as follows: (1) cohort or case-control study evaluating the risk of PD among patients with gout (2) odds ratio (OR), relative risk (RR) or hazard ratio (HR) or standardized incidence ratio (SIR) with 95% confidence interval (CI) were provided (3) subjects without gout and subjects without PD were used as control group in cohort and case-control study, respectively. Study eligibility was independently determined by the two investigators.

RevMan 5.3 software was used to perform the statistical analysis. Point estimates and standard errors were extracted from individual studies and were combined by random-effect model, generic inverse variance method of DerSimonian and Laird. Statistical heterogeneity was assessed using the Cochran's Q test and I^2 statistics.

Results: Out of 351 potentially relevant articles, three case-control studies and two cohort studies were identified and included in the data analysis. The pooled risk ratio of PD in patients with gout was 0.93 (95% CI, 0.79 to 1.09). The statistical heterogeneity of this meta-analysis was high with an I^2 of 87% (Figure 1). The results were not significantly different between males and females (RR 0.85; 95% CI, 0.68 to 1.06 and RR 0.95; 95% CI, 0.76 to 1.19, respectively).

Conclusion: This study did not support the inverse relationship between gout and risk of PD

Disclosure: P. Ungprasert, None; **C. Thongprayoon**, None; **N. Srivali**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/gout-does-not-decrease-the-risk-of-parkinsons-disease-a-systematic-review-and-meta-analysis

Abstract Number: 234

Weight Variables and Their Association with Serum Urate Concentrations and Hyperuricemia in Young Adults

Angelo L. Gaffo[1,2], David R. Jacobs Jr.[3], Huifen Wang[4] and Kenneth G. Saag[5], [1]Rheumatology, Birmingham VA Medical Center, Birmingham, AL, [2]Medicine, University of Alabama at Birmingham, Birmingham, AL, [3]Epidemiology, University of Minnesota, Minneapolis, MN, [4]Nutritional Epidemiology Laboratory, Jean Mayer USDA Human Nutrition Research Center on Aging, Tufts University, Boston, MA, [5]University of Alabama at Birmingham, Birmingham, AL

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Background/Purpose: How body weight, anthropometric parameters, and their changes are associated with serum urate concentrations and hyperuricemia remains unclear. The CARDIA study has been following young adults for 25 years and has detailed anthropometric data along with serum urate levels at multiple follow-up examinations. The present analysis aims to describe the association of weight and anthropometric variables with serum urate and hyperuricemia in young and middle aged-adults.

Methods: We performed multivariable linear regression analyses to determine if weight and anthropometric variables (body mass index [BMI], excess weight, waist circumference, hip circumference, waist to hip ratio) and their changes were associated with serum urate and serum urate changes. In addition, we analyzed associations between changes in BMI and development of incident hyperuricemia using logistic regression during the first and second 10-year periods of CARDIA follow up. We excluded participants with missing serum urate information or missing covariate data (renal function, serum insulin levels, dietary data, alcohol intake, hypertension) from analyses.

Results: Mean age of the study population at enrollment was 24.8 years. At baseline (n=4976) 46% of the included CARDIA populations were women and 51% were African-Americans. Weight and body mass index were associated with serum urate concentrations with comparable strengths at different points in the overall populations, but on later exams (Years 10 and 20 of follow-up) these associations were stronger for men than for women (Figure). Throughout the study, changes in BMI were associated with a small but significant 9-10% of the variance (partial r^2) in serum urate change. In the first 10 years of follow-up, participants who gained more than 25% BMI had a 7.2 fold increased odds (95% confidence interval 4.8-10.8) of incident hyperuricemia after full multivariable adjustment when compared with participants who kept a stable BMI. Losing more than 5% BMI wasn't negatively associated with hyperuricemia during the same study period. Similar results, but of smaller magnitude, were found for BMI changes during starting at year 10 until year 20 (Table).

Conclusion: Weight and body mass index were associated with serum urate concentrations at similar magnitudes. Although BMI changes seem to explain a small proportion of the variance in serum urate change in young adults, gains in BMI during young adulthood are independently associated, in a dose-response fashion, with significantly increased odds of developing hyperuricemia.

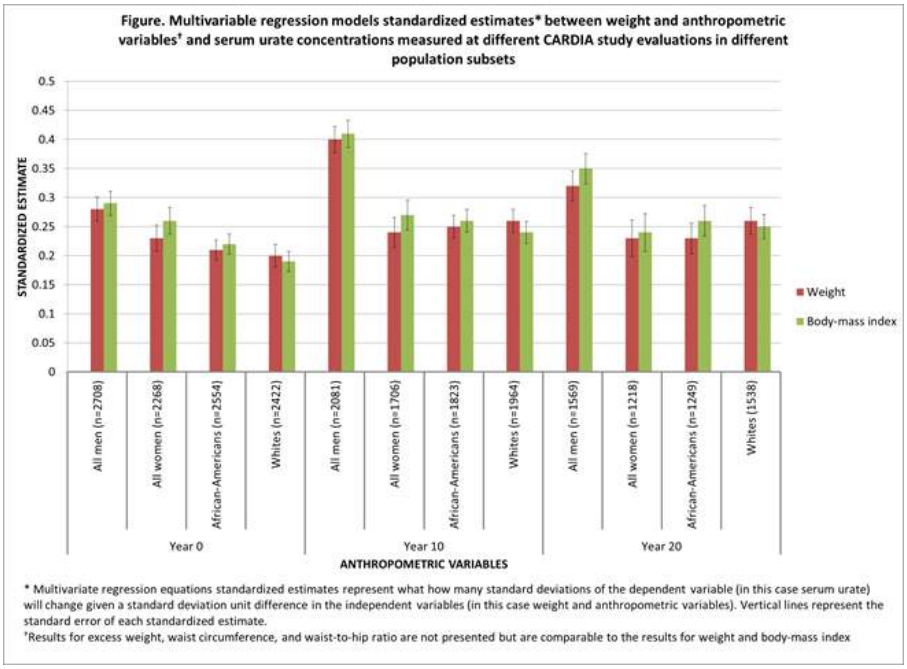

Table. Multivariate odds of incident hyperuricemia associated with changes in body mass index in young adults by the end of 10-year follow-up CARDIA study periods

	BMI change from Year 0 to Year 10 OR (95%CI) N=3272*	BMI change from Year 10 to Year 20 OR (95%CI) N=2168†
No BMI change (-5 to +10 %)	REF (n=1358)	REF (n= 1111)
Greater than 5% reduction in BMI	(n=203)	(n= 192)
Model 1	0.78 (0.39-1.59)	0.88 (0.54-1.44)
Model 2	1.32 (0.63-2.77)	1.14 (0.68-1.92)
Model 3	1.25 (0.59-2.66)	0.78 (0.42-1.45)
Model 4	1.21 (0.56-2.59)	0.69 (0.37-1.30)
10 to 25% increase in BMI	(n=1181)	(n= 704)
Model 1	2.29 (1.71-3.06)	1.60 (1.23-2.08)
Model 2	2.58 (1.90-3.51)	1.94 (1.46-2.57)
Model 3	2.54 (1.87-3.46)	1.58 (1.16-2.14)
Model 4	2.67 (1.94-3.67)	1.92 (1.38-2.67)
Greater than 25% increase in BMI	(n=530)	(n= 161)
Model 1	3.00 (2.15-4.18)	1.87 (1.23-2.84)
Model 2	6.02 (4.11-8.82)	3.27 (2.05-5.20)
Model 3	5.88 (4.00-8.63)	2.84 (1.72-4.69)
Model 4	7.16 (4.76-10.75)	4.48 (2.57-7.81)

*Excludes participants who were hyperuricemic at the year 0 baseline examination

†Excludes participants who became hyperuricemic at or before the year 10 baseline examination

OR= odd ratio, BMI= body mass-index, REF = reference category. Model 1 = unadjusted; model 2 = model 1 further adjusted for race/ethnicity, age, sex; model 3 = model 2 further adjusted for average creatinine, presence of hypertension in first study period and for average creatinine, average insulin levels, seafood intake, use of hypertension medication in second study period; model 4 = model 3 further adjusted for baseline study period serum urate.

Disclosure: A. L. Gaffo, Astra-Zeneca, 5,Cymabay, 5; **D. R. Jacobs Jr.**, None; **H. Wang**, None; **K. G. Saag**, Ardea, AstraZeneca, Creala, Takeda, 2,Ardea, AstraZeneca, Creala, Takeda, 5.

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Abstract Number: 235

Relationship Between Tissue Stress during Gait and Patterns of Urate Deposition and Bone Erosion in Gout: A Biomechanical Computational Modelling Study

Nicola Dalbeth[1], Michelle Deacon[2], Gregory Gamble[1], Kumar Mithraratne[2] and Justin Fernandez[2], [1]Department of Medicine, University of Auckland, Auckland, New Zealand, [2]University of Auckland, Auckland, New Zealand
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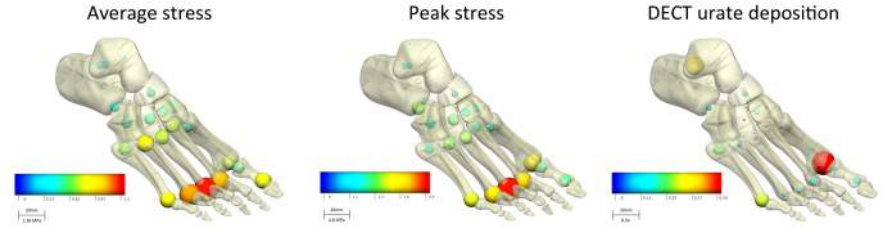
Background/Purpose: Gout typically presents at characteristic sites such as the 1st metatarsophalangeal joint, midfoot or ankle. A potential explanation for this distribution is that tissue stress during biomechanical loading promotes deposition of monosodium urate crystals at certain sites. The aim of this study was to determine whether patterns of high tissue stress during gait are associated with patterns of urate deposition and bone erosion in gout.

Methods: We analysed patterns of foot von Mises stress predicted computationally during gait in 25 volunteers with normal (18-25kg/m^2) body mass index (BMI) and 25 volunteers with high BMI (>25kg/m^2). Von Mises stress is used to evaluate the failure of tissues in bioengineering, and is reported as a single value that accounts for internal stresses in all directions. Von Mises stress patterns within the bones of the feet were compared with patterns of urate deposition and bone erosion in gout using dual energy and conventional computed tomography data.

Results: The highest average and peak von Mises stress during gait was observed at the 3rd metatarsal (MT) head (Figure). In contrast, for both urate deposition (Figure) and bone erosion, the 1st MT head was most frequently affected, with very infrequent involvement of the 3rd MT head. There was no clear relationship between average or peak von Mises stress patterns with patterns of urate deposition or bone erosion ($-0.20 > r < 0.16$ for all comparisons). Although ground reaction forces were higher in those with high BMI ($p<0.0001$), foot contact area was also higher ($p<0.0001$) with similar von Mises stress patterns were observed for the high and low BMI groups ($p>0.29$). Addition of BMI into linear regression models did not alter the findings.

Conclusion: These data do not support the concept that elevated tissue stress during biomechanical loading plays an important role in patterns of monosodium urate crystal deposition or structural damage in gout.

Figure: Foot maps showing the patterns of average tissue stress and peak tissue stress during gait in volunteers and urate deposition in gout. For each map, both the sphere diameter and colour represents the linear range from 0 - maximum value, as shown in the figure keys.



Disclosure: N. Dalbeth, None; **M. Deacon**, None; **G. Gamble**, None; **K. Mithraratne**, None; **J. Fernandez**, None.

Abstract Number: 236

Foot and Ankle Muscle Strength in People with Gout: A Two-Arm Cross-Sectional Study

Sarah Stewart[1], Grant Mawston[2], Lisa Davidtz[3], Nicola Dalbeth[4], Alain Vandal[5], Matthew Carroll[3], Trish Morpeth[6], Simon Otter[7] and Keith Rome[8], [1]School of Podiatry, Auckland University of Technology, Auckland, Niger, [2]Department of Physiotherapy, Auckland University of Technology, Auckland, New Zealand, [3]School of Podiatry, Auckland University of Technology, Auckland, New Zealand, [4]Department of Medicine, University of Auckland, Auckland, New Zealand, [5]Counties Manukau District Health Board, Auckland, New Zealand, [6]Auckland University of Technology, Auckland, New Zealand, [7]School of Health Professions, University of Brighton, Brighton, England, [8]Health & Research Rehabilitation Centre, AUT University, Auckland, AR, New Zealand
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Background/Purpose: Foot and ankle structures are commonly affected in gout. People with gout experience difficulty walking and report high levels of foot pain, disability and impairment. Despite the importance of lower limb and foot muscle strength requirements in walking, the strength of foot and ankle muscles in gout is unknown. The primary aim of this study was to determine differences in foot and ankle muscle strength for ankle plantarflexion, dorsiflexion, inversion and eversion between people with gout and age- and sex-matched controls. The secondary aim was to examine the relationship between foot and ankle muscle strength, and foot pain and disability.

Methods: Peak isokinetic concentric muscle torque was measured for ankle plantarflexion, dorsiflexion, eversion and inversion in 20 participants with gout and 20 matched controls at two testing velocities (30°/s and 120°/s) using a Biodex dynamometer. Peak torque was calculated and normalised to body weight. Foot pain and disability was measured using the Manchester Foot Pain and Disability Index (MFPDI). Differences in peak torque between gout and control participants were analysed using mixed linear models. Pearson's correlation coefficients were used to determine associations between MFPDI scores and peak torque.

Results: Differences in peak torque between gout participants and controls are displayed in the Table below. At both the 30°/s and 120°/s testing velocities, participants with gout had lower ankle peak plantarflexion, inversion, and eversion torque compared with control participants. No differences between gout and control participants were evinced for peak dorsiflexion torque at either 30°/s or 120°/s testing velocities. Mean MFPDI scores were higher in participants with gout compared to controls (p=0.00001). For participants with gout, MFPDI scores were inversely correlated with peak plantarflexion torque at both 30°/s (r=-0.66, p<0.001) and 120°/s (r=-0.44, p=0.008), peak eversion torque at the 120°/s testing velocity (r=-0.36, p=0.045) and peak inversion torque at both 30°/s (r=-0.49, p=0.005) and 120°/s (r=-0.56, p=0.001) testing velocities.

Conclusion: People with gout have reduced foot and ankle muscle strength and experience greater foot pain and disability compared to controls. Foot and ankle strength reductions are strongly associated with increased foot pain and disability in people with gout.

Table. Mean peak torque and difference between gout and controls, N·m/kg

	Mean (SD) peak torque		Difference (95% CI)	*p*
	Control	Gout		
Plantarflexion 30°/s	0.94 (0.10)	0.65 (0.10)	-0.29 (-0.51, -0.07)	**0.010**
Dorsiflexion 30°/s	0.41 (0.08)	0.37 (0.09)	-0.04 (-0.10, 0.03)	0.280
Plantarflexion 120°/s	0.51 (0.19)	0.32 (0.19)	-0.19 (-0.32, -0.05)	**0.008**
Dorsiflexion 120°/s	0.25 (0.14)	0.22 (0.14)	-0.03 (-0.06, 0.01)	0.111
Eversion 30°/s	0.34 (0.07)	0.24 (0.07)	-0.09 (-0.16, -0.03)	**0.005**
Inversion 30°/s	0.37 (0.30)	0.25 (0.30)	-0.12 (-0.21, -0.03)	**0.012**
Eversion 120°/s	0.21 (0.15)	0.17 (0.15)	-0.04 (-0.08, -0.01)	**0.028**
Inversion 120°/s	0.24 (0.48)	0.17 (0.48)	-0.07 (-0.12, -0.02)	**0.005**

Disclosure: S. Stewart, None; **G. Mawston**, None; **L. Davidtz**, None; **N. Dalbeth**, Takeda, AstraZeneca, Pfizer, 5,AstraZeneca, 8,Ardea Biosciences, 2; **A. Vandal**, None; **M. Carroll**, None; **T. Morpeth**, None; **S. Otter**, None; **K. Rome**, None.

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Abstract Number: 237

The Prevalence of Chondrocalcinosis of the Symphysis Pubis on CT Scan and Correlation with Calcium Pyrophosphate Dihydrate Crystal Deposition Disease

Trusha Patel[1], Lawrence Ryan[2], Melissa DuBois[3], Guillermo Carrera[3], Keith Baynes[3], Rajeev Mannem[3] and Jennifer Mulkerin[3], [1]Rheumatology, Medical College of Wisconsin, Milwaukee, WI, [2]Department of Rheumatology, Medical College of Wisconsin, Milwaukee, WI, [3]Radiology, Medical College of Wisconsin, Milwaukee, WI

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Background/Purpose: Calcium pyrophosphate dihydrate (CPP) crystal deposition in articular cartilage can often be seen radiographically as chondrocalcinosis (CC). CPP crystals preferentially deposit in fibrocartilages such as the knee menisci and symphysis pubis (SP). We sought to determine the prevalence of CC in the SP on computed tomography (CT) of the abdomen and pelvis.

Methods: This retrospective study involved readings on 1070 consecutive CTs of the abdomen and pelvis performed over 3 months in patients over 65 years of age. Medical records of 226 patients found to have CC were reviewed to

determine age, gender, documentation of CPPD on problem lists or in medical histories, and whether radiology readings of the CTs mentioned CC.

Results: SP CC was identified in 21.1% (226/1070) of consecutive CT scans with the mean age of CT+ patients being 78.6. Of the 226 patients with SP CC, the observation of CC was documented in only 5.3% (12/226) of the radiology reports. Of the 12 instances in which the radiology reports mentioned CC, this observation was never (0/12) transmitted to the medical history or problem list.

Conclusion: The prevalence of CC in patients older than 65 was 21.1%. Since CTs of the abdomen are not ordered for evaluation of musculoskeletal conditions, this is likely a true prevalence without selection bias. When CC of the SP was present on images, radiologists routinely overlooked or chose not to report CC. Even in the rare instances when it was reported, that information was not added to the medical history or problem list. There are several clinical situations in which recognizing that a patient has CPP deposition (e.g acute monoarthritis) would be useful. Taking the time to review images may yield clinically important findings that are not mentioned anywhere on the patient chart.

Disclosure: T. Patel, None; **L. Ryan**, None; **M. DuBois**, None; **G. Carrera**, None; **K. Baynes**, None; **R. Mannem**, None; **J. Mulkerin**, None.

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Abstract Number: 238

Relationship Between Ultrasonographic Synovial Inflammation and Ultrasonographic Urate Deposition Findings in Patients with Gout

Fernando Perez-Ruiz[1,2], Sandra P. Chinchilla-Gallo[3], Irati Urionagüena[4] and Elena Garmendia[3,5], [1]Rheumatology Division, Hospital Universitario Cruces, Barakaldo, Spain, [2]BioCruces Health Research Institute, Baracaldo, Spain, [3]Rheumatology Division, Hospital Universitario Cruces, Baracaldo, Spain, [4]Rheumatology Division, Hospital Universitario ruces, Baracaldo, Spain, [5]Biocruces Helath Research Institute, Baracaldo, Spain

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Background/Purpose: urate intra-articular deposits are seen in ultrasound as double contour sign (DCS), and hyperechogenic aggregates and tophi, but the extent of contribution of any of these findings to synovial inflammation has yet to be determined. Only tophi have been shown to date sensitivity to change during urate-lowering therapy.

Methods: to evaluate the association between DCS and tophi with the presence of synovial inflammation in ultrasound examination, patients with crystal-proven gout were recruited from two cohorts of prospective follow-up, one on active treatment and the other after withdrawal of urate-lowering therapy, were to be consecutively included. They had to be asymptomatic (no flare, no chronic swelling) for at least 4 years, not on colchicine, NSAID, corticosteroids, or IL-blockers. Ultrasonography of the first metatarsophalangeal joint (1st MTP) and of the non-dominant knee was performed by an skilled explorer who was blinded for clinical data. The DCS was predefined as absent or present and in in less or more than 50% of the synovial surface. In the knee joint, the DCS location was also assessed as present in one or both femoral condyles. The presence of tophi was evaluated as hyperechogenic conglomerates of at least 5mm in

maximum diameter, with a hypoechogenic halo associated. Synovial inflammation was evaluated by the measurement of synovial thickening with a semi-quantitative scale (0-3) and Power-Doppler (PD) with a semiquantitative scale (0-3). Bi-variable and multiple regression analysis were performed.

Results: ultrasonopgraphy was proposed to 100 consecutive patients who fulfilled criteria, of which 88 agreed and attended the appointment. All of them were male, with a median age of 57 ± 9 years, 74% with previous involvement of 1st MTP joint and 59% of the examined knee. Thirteen patients were excluded from analysis due to the presence of ultrasonographic chondrocalcinosis in the knee. The frequency of deposits in both cohorts was not different, a pooled analysis therefore being conducted. The descriptive findings are presented in the table:

%	Any deposit	DCS	Synovitis>0	Synovitis>1	Tophus	PD>0	PD>1
1st MTP	64.7	54.8	29.8	48.8	9.4	48.8	21.2
Knee	52.9	48.2	17.6	53.0	1.2	47.1	25.9

Multiple regression analysis showed that the presence of synovitis >0 was only statistically associated in the 1st MTP to tophi (R^2 0.31), and in the knee to the presence of extense or bilateral DCS and tophi (R^2 0.28). The PD>0 signal was only associated in both 1st MTP and in knee to tophi (R^2 0.25 and 0.18, respectively). The more restrictive analysis of synovitis>1 and PD>1 did not show changes in the results, although numbers were small.

Conclusion: ultrasonographic urate deposits, as tophi or extense double contour) are associated to synovitis or active synovitis (intra-articular synovitis with PD signal) as markers of synovial inflammation. The presence of tophi is the main factor associated, so the resolution of the intra-articular tophi seems to be the principal therapeutic goal for urate-lowering therapy.

Disclosure: F. Perez-Ruiz, AstraZeneca, 5,AstraZeneca, 8,Menarini, 5,Menarini, 8; **S. P. Chinchilla-Gallo**, None; **I. Urionagüena**, None; **E. Garmendia**, None.

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Abstract Number: 239

The Role of Dual Energy Computed Tomography in Diagnosing Acute Gouty Arthritis: Comparison with Ultrasound and Aspiration

Jennifer Lee[1], Ji Yeon Lee[2], Jung Hee Koh[3], Min Kyung Chung[4], Ji Hun Kim[1], Seung-Ki Kwok[5], Ji Hyeon Ju[6] and Sung-Hwan Park[7], [1]Division of Rheumatology, Department of Internal Medicine, College of Medicine, Seoul St. Mary's Hospital, The Catholic University of Korea, Seoul, South Korea, [2]Division of Rheumatology, Department of Internal Medicine, School of Medicine, Catholic University of Korea, Seoul St. Mary's Hospital, Seoul, South Korea, [3]Division of Rheumatology, Department of Internal Medicine, School of Medicine, The Catholic University of Korea, Seoul St. Mary's Hospital, Seoul, South Korea, [4]Division of Rheumatology, Department of Internal Medicine, School of Medicine, The Catholic University of Korea, Seoul St. Mary's Hospital, Seoul, South Korea, [5]Division of Rheumatology, Department of Internal Medicine, Seoul St. Mary's Hospital, The Catholic University of Korea College of Medicine, Seoul, South Korea, [6]Division of Rheumatology, Department of Internal Medicine, College of Medicine, The Catholic University of Korea, Seoul, South Korea, [7]Division of Rheumatology, Department of Internal Medicine, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, South Korea

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Background/Purpose: The gold standard of acute gouty arthritis diagnosis has been to verify the presence of monosodium urate (MSU) crystal in the aspirated fluid of the affected joint. Recently, dual energy computed tomography (DECT) has emerged as a non-invasive MSU detecting tool. This study was undertaken to evaluate the diagnostic accuracy of DECT in acute gouty arthritis and to determine the affecting factors.

Methods: Medical charts of patients who underwent both DECT and ultrasound (US) guided aspiration in suspicion of acute gouty arthritis from August 2013 to March 2015 were retrospectively reviewed. Positive ultrasound findings included effusion with snowstorm appearing microtophi or double contour sign or presence of tophi. For statistical analysis, Mann-Whitney U test was used for continuous variables. Chi-Square test was used for categorical variables.

Results:

A total of 74 patients were analyzed. All patients except one were male and mean age was 45.3 years. Mean disease duration was 46 months, mean serum uric acid level 7.4 mg/dL. Fifty six patients had one or more positive findings of DECT or US or MSU presence in aspirated joint fluid. MSU deposition was observed in 28/61 (46.0%) patients. There were 4 patients who had clinically apparent tophi on physical examination, all of which were detected on DECT. Joint fluid was successfully acquired in 40/61 (65.5%) patients and the presence of MSU crystal was confirmed in 28 patients. Positive US findings were observed in 60/61 (98.4%) patients. 26 patients showed positive findings of both DECT and ultrasound, whereas 34 patients had only positive ultrasound findings. Serum uric acid level, symptom duration was significantly greater in DECT(+) positive group. Of note, DECT could not detect MSU crystal in patientswith high BMI. After adjusting age, multivariate logistic regression revealed that DECT may not be appropriate in patients with high BMI and short symptom duration in acute setting.

Conclusion: DECT can detect MSU deposition in acute gout patients without clinical tophi. However, the probability of false negativity rises in patients with high BMI and short symptom duration.

Disclosure: J. Lee, None; **J. Y. Lee**, None; **J. H. Koh**, None; **M. K. Chung**, None; **J. H. Kim**, None; **S. K. Kwok**, None; **J. H. Ju**, None; **S. H. Park**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/the-role-of-dual-energy-computed-tomography-in-diagnosing-acute-gouty-arthritis-comparison-with-ultrasound-and-aspiration

Abstract Number: 240

Volumetric Assessment of Tophaceous Gout

Ralf G. Thiele[1], Laura Coates[2] and Darren Tabechian[1], [1]University of Rochester Medical Center, Rochester, NY, [2]Medicine, University of Rochester, Rochester, NY

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SESSION INFORMATION

Session Date: Sunday, November 8, 2015

Session Title: Metabolic and Crystal Arthropathies Poster I

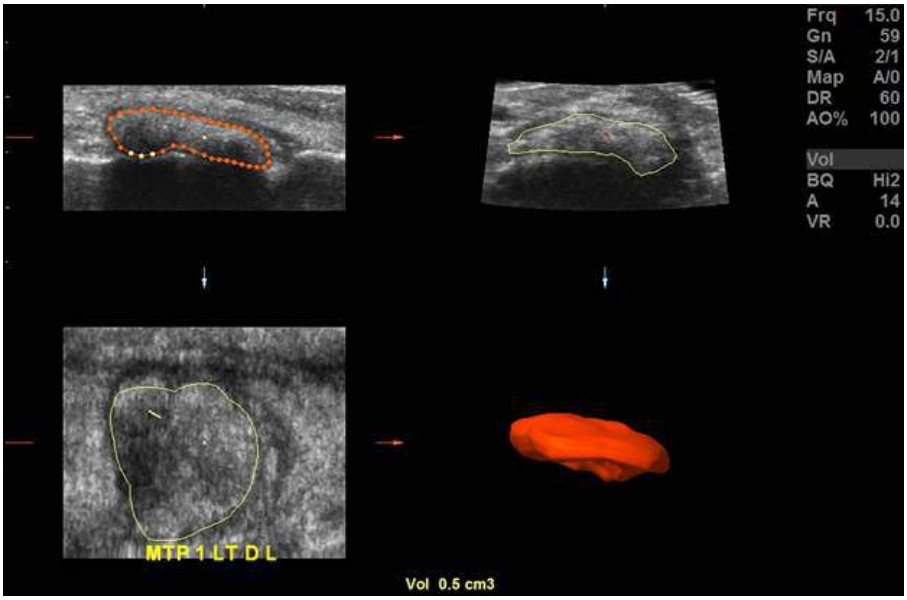
Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose: Ultrasound (US) can identify monosodium urate (MSU) tophi within joints, tendons, bursae and other soft tissues. The ability to readily, quickly and inexpensively assess volumes of tophi would be an attractive goal. Available 3D ultrasound transducers can scan tophi, and volumes can be re-constructed using commercially available software. The aim of this study was to assess the feasibility, repeatability and reproducibility of US volumetric assessment of MSU tophi.

Methods: 14 consecutive patients (9 male, 5 female, 32-84 years) with a history of gout and previously US identified MSU tophi were enrolled. Eleven were on urate lowering drugs (allopurinol, n=7; febuxostat, n=2; pegloticase, n=1). Joint areas included MTP1 n=8, Achilles tendon, n=1; MCP2, n=1, olecranon, n=1; prepatellar, n=1; wrist, n=1. Only 2 had clinically palpable tophi (prepatellar and olecranon bursae). Medial fullness at MTP 1 was palpable in 4, but could not be distinguished by clinical exam from hallux valgus. A GE Logiq E9 built 2014 unit with a RSP6-16-D 4D linear transducer at 15 MHz was used. After placement the probe performed an internal sweep of 3 seconds to obtain the 3D data set. Volumetric analysis was performed using volume calculation software (VOCAL, GE Ultrasound, Wauwatosa, WI.) Tophi were identified as typical hyperechoic material with an anechoic rim, if present. The 3D image was rotated 6 times at 30 degree intervals. The area of the tophus on each orientation was traced manually on the screen. The software provided the volume of the resulting structure in cm3. For each resulting tophus volume, this process was performed twice by the first reader (RT) to test the intra-observer reliability. For 6 tophi, an additional volume calculation was performed by a second rheumatologist-sonographer to test the inter-observer reliability.

Results: The software-aided volume analysis took on average 6 minutes per assessment. Reader 1 (RT) calculated a mean volume of 0.682cm3 (standard deviation (SD) 0.699, range 0.03 to 2.60) in the first reading and 0.705cm3 (SD 0.705, range 0.03 to 2.60) in the second reading. ICC showed excellent intra-reader reliability for reader 1 (0.995, 95% CI 0.985, 0.998). Reader 2 (DT) scored 6 of the 14 scans and calculated a mean volume of 0.607cm3 (SD 0.595, range 0.05 to 1.40). The ICC showed excellent inter-reader reliability between reader 1 and reader 2 (ICC 0.990, 95% CI 0.928, 0.999 using reader 1's first reading and ICC 0.994, 95% CI 0.958, 0.999 – second reading).



Conclusion: Volumetric assessment of MSU tophi by reconstruction of 3D ultrasound is a feasible, fast, inexpensive method to assess the tophus burden with excellent intra- and inter-reader reliability in this study. Future work should evaluate sensitivity to change and with positive results this method could act as an objective outcome measure for clinical trials of urate lowering therapy.

Disclosure: R. G. Thiele, None; **L. Coates**, None; **D. Tabechian**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/volumetric-assessment-of-

Abstract Number: 241

Inflammatory Syndrome in Polyarticular Gout – Description of a Previously Neglected Entity

Valentin S. Schäfer[1], Andreas Krause[2] and Wolfgang A. Schmidt[2], [1]Immanuel Krankenhaus Berlin, Medical Center for Rheumatology Berlin-Buch, Berlin, Germany, [2]Medical Center for Rheumatology and Clinical Immunology Berlin-Buch, Immanuel Krankenhaus Berlin, Berlin, Germany

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Session Type: ACR Poster Session A

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Background/Purpose: Inflammatory polyarticular gout occurs in clinical practice. However, only very few single case reports have been published as yet. This case series aims at describing this previously poorly defined entity.

Methods: This is a retrospective analysis of all consecutive patients of a single rheumatology center between January 2013 and April 2015. Patients were included with polyarticular gout with at least 5 joint regions involved (1st MTP joints, other MTP joints, ankles, knees, wrists, digits, elbows) and highly elevated inflammatory markers (CRP >80 mg/l and/or ESR > 80mm/h). Joint involvement was considered if clinical examination revealed swelling or tophi, or if imaging (ultrasound, dual energy CT or x-ray) showed features consistent with gout. Demographic, laboratory, imaging, clinical parameters and treatment regimens were recorded.

Results: Of the 22 included patients, 18 were male; mean age 67 years (standard deviation (SD), ±11 years); mean BMI 29 (SD ±6). The diagnosis was confirmed in 19 patients by polarization microscopy. All patients fulfilled the new ACR/EULAR classification criteria for gout. Fourteen (64%) patients were newly diagnosed with gout. The other patients had been diagnosed with gout for a mean of 10 years (SD ±10).

All patients except one were admitted to hospital due to the inflammatory syndrome. The median duration of the acute symptoms before presentation to our institution was 13 days (minimal / maximal, 2-90). A mean of 10 joint regions (minimal / maximal, 5-14) were affected. Of note, only 3 patients (14%) had fever (37.8, 38.1, 39°C, respectively). Mean visual analogue scale (VAS) for pain, disease activity and fatigue was 8.3, 8.1, and 6.7.

The mean CRP was 172 mg/l (SD ±83.6 mg/l); mean ESR, 91 mm/h (SD ±24 mm/h). All patients had anemia (mean hemoglobin, 7.2 mmol/l; SD± 0.9mmol/l). Leukocytosis was found in only 6 patients (27%; mean, 14.8 G/l), thrombocytosis in 7 patients (32%; mean 405 G/l) and neutrophilia in 12 patients (54%; mean, 9.9 Gpt/l). In 12 (55%) of patients serum ferritin was elevated (mean 391 µg/l). Procalcitonin was normal in all 11 patients in whom it had been determined. Mean uric acid levels were 531 µmol/l (8.9 mg/dl). In 8 patients (36%) acute renal failure was observed, defined as >1.5 fold increase of creatinine. Ten patients had a glomerular filtration rate (GFR) of 30-60 ml/min; in 2 patients GFR was <30 ml/min.

Seven patients received NSAID, 13 colchicine, and 2 glucocorticoids (GC) as first-line anti-inflammatory drugs. NSAID were replaced by colchicine in all 7 patients because of inefficacy. Colchicine was replaced by GC in 14 of 20 cases, and canakinumab was administered in 2 patients who had not responded well to GC. CRP values of <20 mg/l were reached by 82% of patients after a mean of 26 days (SD ±23 days) after onset of symptoms.

Conclusion: Patients with inflammatory syndrome in polyarticular gout with CRP >80 mg/l and/or ESR >80 mm/h are severely affected but rarely exhibit fever. Anemia is common. Leucocytosis and thrombocytosis are rare. Procalcitonin is usually normal. Renal failure occurs in

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Disclosure: V. S. Schäfer, None; **A. Krause**, Berlin Chemie, 8,Novartis Pharmaceutical Corporation, 5,Novartis Pharmaceutical Corporation, 8; **W. A. Schmidt**, Berlin-Chemie, 8,Berlin-Chemie, 5,Novartis Pharmaceutical Corporation, 8,Novartis Pharmaceutical Corporation, 5.

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Abstract Number: 242

Higher Serum Uric Acid Levels Are Associated with an Increased Risk of Flares: A Systematic Review

Aki Shiozawa[1], Shelagh M Szabo[2], Antoinette Cheung[2], Anna Bolzani[2] and Hyon K. Choi[3], [1]Global Outcomes and Epidemiology Research, Takeda Pharmaceuticals International, Inc, Deerfield, IL, [2]Redwood Outcomes, Vancouver, BC, Canada, [3]Rheumatology, Allergy and Immunology, Massachusetts General Hospital, Harvard Medical School, Boston, MA

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Session Title: Metabolic and Crystal Arthropathies Poster I

Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose: Acutely painful flares represent the typical clinical burden of gout. Effective therapy can reduce serum uric acid (sUA) levels; however, epidemiologic evidence for the relationship between sUA and the risk gout flares is thought to be limited. The objective here was to systematically summarize the evidence of the association between sUA levels and the risk of gout flares.

Methods: A systematic review of the published literature (1946 to present) was conducted in April 2015 in Medline, EMBASE, and Cochrane, using a search strategy including terms for gout, sUA, and flares. Two reviewers screened abstracts and extracted data from eligible articles reporting flares according to sUA level. The number and proportion of patients experiencing flares, or mean (standard deviation [SD] or error [SE]) flares per patient, were tabulated according to sUA category; mean sUA levels were also tabulated by mean gout flares. Studies were classified as retrospective (flares occurred prior to sUA measure) or prospective (flares occurred after sUA measure), and according to the treatment status of the cohort.

Results: Of 866 abstracts, 19 articles presented estimates of flares according to sUA, and 17 presented estimates relevant to these analyses. In the seven studies describing flares according to sUA category, the proportion of the cohort experiencing flares increased in a dose-response fashion with higher sUA levels; as did the mean flares per gout patient (Table 1). The proportion experiencing flares was 1.4- to 2.8-fold higher in the highest sUA categories compared to the lowest. Mean flares also generally increased with higher sUA levels (Table 1). Ten studies also presented data on mean flares according to mean sUA level; these also demonstrated a dose-response relationship. As expected, clinical cohorts tended to show this relationship more clearly than administrative cohorts.

Conclusion: Our systematic review of published articles on the risk of gout flares suggested a dose-response relationship, where higher sUA levels were associated with more flares. The selection, assessment methods, and timing

of outcome measures were variable between studies. As little evidence from prospective studies designed to comprehensively evaluate flares was identified, existing risk measures are likely underestimates. Nevertheless, the existing evidence underscores the need to treat to target as recommended by the recent gout care guidelines.

Table 1: n (%) patients with flares, and mean (SD) flares over time, according to sUA level and the treatment status of the cohort

				Patients with flares		Mean flares				
Study	N	sUA level category	Period of flare measure (yrs)	n	%	Per gout patient	SD (range)	Per gout flare patient	SD	Treatment status
*Retrospective assessment of flares**										
Dalbeth, 2012		89 < 6.0 mg/dL	0.25	--	--	1.2	2.3	--	--	Mixed treated
		184 >= 6.0 mg/dL		--	--	3.2	11.4	--	--	and untreated
Li-Yu, 2001		19 <= 6.0 mg/dL	1	--	--	1.0	(0-3)	--	--	Treated
		38 > 6.0 mg/dL		--	--	6.0	(4-12)	--	--	
*Prospective assessment of flares**										
Halpern, 2009		709 < 6.0 mg/dL	2	350	46.4	0.7	0.8	1.3	0.6	Mixed treated
		1,604 >= 6.0 to < 9.0 mg/dL		981	61.2	0.9	1.0	1.5	0.8	and untreated
		757 >= 9.0 mg/dL		483	63.8	1.1	1.1	1.7	1.0	
Perez-Ruiz, 2011**		27 >= 6.0 to < 7.0 mg/dL	5***	0	0.0	--	--	--	--	Treated
		61 >= 7.0 to < 8.2 mg/dL		13	21.3	--	--	--	--	
		61 >= 8.3 to <9.3 mg/dL		31	50.8	--	--	--	--	
		62 >= 9.3 mg/dL		38	61.3	--	--	--	--	
Sarawate, 2006**		NR < 6.0 mg/dL	5	--	23.0	--	--	--	--	Mixed treated
		NR >= 6.0 to < 8.0 mg/dL		--	33.0	--	--	--	--	and untreated
		NR >= 8.0 mg/dL		--	45.0	--	--	--	--	
Shoji, 2004		NR 5.0 to <6.0 mg/dL		--	12.0	--	--	--	--	Mixed treated
		NR 6.0 to <9.0 mg/dL	2	--	47.7	--	--	--	--	and untreated
		NR >= 9.0 mg/dL		--	89.5	--	--	--	--	
Wu, 2009		633 < 6.0 mg/dL	1	170	26.9	--	--	1.5	0.8	Mixed treated
		1,173 >= 6.0 to < 9.0 mg/dL		509	43.4	--	--	1.6	0.9	and untreated
		432 >= 9.0 mg/dL		235	54.5	--	--	1.7	1.2	

*Retrospective: Flares were assessed prior to sUA measurement; Prospective: Flares were assessed following sUA measurement.
**Perez-Ruiz 2011 also reported mean sUA after urate lowering therapy; but no subsequent flare measures. Sarawate 2006 reported that, among those with flares, mean (SD) sUA was 8.0 (2.0) mg/dL prior to the flare, and 7.7 (2.1) mg/dL after the flare.
***Mean, 56 months follow up
None of the studies with mixed treated and untreated patients stratified both flares and sUA by treatment status

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Disclosure: A. Shiozawa, Takeda Pharmaceuticals International, Inc., 3; **S. M. Szabo**, None; **A. Cheung**, None; **A. Bolzani**, None; **H. K. Choi**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/higher-serum-uric-acid-levels-are-associated-with-an-increased-risk-of-flares-a-systematic-review

Abstract Number: 243

Increase in Risk of Future Attacks in Patients with Incident Gout: A Population-Based Study over 20 Years

Nour Zleik[1], Mohanad Elfishawi[1], Zoran Kvrgic[1], Clement J. Michet Jr.[2], Cynthia S. Crowson[3], Eric L. Matteson[4] and Tim Bongartz[1], [1]Rheumatology, Mayo Clinic, Rochester, MN, [2]Mayo Clinic, Rochester, MN, [3]Health Sciences Research, Mayo Clinic, Rochester, MN, [4]Division of Rheumatology, Department of Internal Medicine and Department of Health Sciences Research, Mayo Clinic, Rochester, MN

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Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose: While there appears to be consensus that non-pharmacological uric acid lowering therapies (diet and lifestyle modifications) should be initiated in every patient presenting with gout, there is much less agreement as to when urate lowering drugs should be considered. Expert opinion ranges from starting uric acid lowering therapy after the first attack of gouty arthritis through a more cautious approach where therapy is only started in patients with more than 3 attacks per year. We aimed to assemble a population-based cohort of patients with newly diagnosed gout

to determine the risk of additional flares after an initial gout attack and explore the role of various demographic, clinical and laboratory predictors that may aid the clinician in quantifying this risk.

Methods: We examined a population-based incidence cohort of patients with gout, diagnosed according to the New York, Rome or ACR preliminary criteria during two time periods: January 1st 1989 - December 31st 1992 and January 1st 2009 – December 31st 2010. All subjects were followed longitudinally through their complete community medical records, until 5 years after their first gout attack, death, migration or July 1st 2012 – whichever came first. Person-year methods were used to estimate and compare flare rates over time. Frailty models (accounting for multiple flares per subject) were used to explore risk factors of subsequent flares.

Results:

429 patients with incident gout (158 patients in the 1989-1992 time period and 271 patients in the 2009-2010 time period) were followed for a mean of 4.2 years. The majority of patients were male (73%) and the mean age (SD) at gout onset was 59.7 (17.3). Isolated podagra was the most common form of joint involvement at disease onset (64.0%) and the mean (SD) serum uric acid level was 8.1 (1.9) mg/dl. 248 patients developed at least 1 subsequent flare (cumulative incidence of first flare was 61.6% by 5 years in 1989-1992 vs 60.3% by 5 years in 2009-2010; p=0.70), with a total of 582 subsequent flares during the entire follow-up period. The rate of subsequent flares increased significantly from 2.82 per 10 person-years (py) in 1989-1992 to 3.49 per 10 py in 2009-2010 (rate ratio [RR]: 1.23; 95% confidence interval [CI]: 1.04, 1.47). Men were at higher risk for subsequent flares than women (HR 1.51, 95% CI 1.14, 2.00). Other predictors were a high serum uric acid level (>6mg/dL in women and >7mg/dL in men) at baseline (HR 2.20, 95% CI 1.49, 3.27), polyarticular involvement (HR 1.46, 95%CI 1.00, 2.13) and diuretic use (HR 1.30, 95%CI 1.03, 1.65). Age and body mass index were not significant predictors of subsequent flare risk.

Conclusion:

The majority of patients in our population-based cohort did develop at least one subsequent flare after an initial diagnosis of gout. The rate of subsequent flare was higher in patients diagnosed in 2009-2010 compared to those diagnosed in 1989-1992. Male sex, use of diuretics, polyarticular involvement and high uric acid levels at first flare were significant predictors of subsequent flares and should be taken into account when deciding on the timing of initiating uric acid lowering therapy.

Disclosure: N. Zleik, None; **M. Elfishawi**, None; **Z. Kvrgic**, None; **C. J. Michet Jr.**, None; **C. S. Crowson**, None; **E. L. Matteson**, None; **T. Bongartz**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/increase-in-risk-of-future-attacks-in-patients-with-incident-gout-a-population-based-study-over-20-years

Abstract Number: 244

Hospitalization and Flare Risk in Patients with Established Gout: A Population-Based Study

Nour Zleik[1], Mohanad Elfishawi[1], Zoran Kvrgic[1], Clement J. Michet Jr.[2], Cynthia S. Crowson[3], Eric L. Matteson[4] and Tim Bongartz[1], [1]Rheumatology, Mayo Clinic, Rochester, MN, [2]Mayo Clinic, Rochester, MN, [3]Health Sciences Research, Mayo Clinic, Rochester, MN, [4]Division of Rheumatology, Department of Internal Medicine and Department of Health Sciences Research, Mayo Clinic, Rochester, MN

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SESSION INFORMATION

Session Date: Sunday, November 8, 2015

Session Title: Metabolic and Crystal Arthropathies Poster I
Session Type: ACR Poster Session A
Session Time: 9:00AM-11:00AM

Background/Purpose: Hospitalization of patients with gout may be associated with an increased risk of arthritic flares, due to administration of IV fluids, discontinuation of established uric acid lowering therapies and other medication changes. While previous studies have suggested an association of gouty arthritis and hospitalization, the absolute flare risk has not been identified. We aimed to determine the risk of flares with future hospitalizations and examine potential predictors of in-hospital gout flares.

Methods: We examined a population-based incidence cohort of patients with gout, diagnosed according to the New York, Rome or ACR preliminary criteria during two time periods: 1989 - 1992 and 2009 – 2010. All subjects were followed longitudinally through their complete medical records, until 5 years after their first gout attack, death or migration, whichever came first. Hospitalizations of each subject were recorded and hospital records were evaluated for a possible flare of gouty arthritis. Person-year methods were used to calculate the rate of flares of gouty arthritis during hospitalizations and out-of-hospital. In addition, mixed logistic regression models with random subject effects (accounting for multiple hospitalizations per subject) were used to explore risk factors of in-hospital gout flares.

Results:

429 patients with incident gout were followed for a mean of 4.2 years. The majority of patients were male (73%) and the mean age (SD) at gout onset was 59.7 (17.3). 169 patients had at least 1 hospitalization (cumulative incidence of first hospitalization was 39.1% for patients diagnosed in 1989-1992 compared to 43.1% for patients diagnosed in 2009-2010; p=0.56), with a total of 454 hospitalizations during the entire follow-up period. The rate of hospitalizations increased marginally from 2.26 per 10 person-years (py) in 1989-1992 to 3.49 per 10 py in 2009-2010 (rate ratio [RR]: 1.19; 95% confidence interval [CI]: 0.98, 1.45).

28 hospitalizations were complicated by a flare of gouty arthritis during a total of 3276 hospital days (9.0 total py) compared to 554 out-of hospital flares during 1784 py of follow-up. The rate of in-hospital flares was 85 per 100 py compared to 8.5 per 100 py out-of-hospital. Hospitalization was associated with a significantly increased risk of gout flares (RR: 10.2; 95% CI: 6.8, 14.5). In addition, the rate of in-hospital flares increased marginally over time (6.3 per 10 py in 1989-1992 vs 11.7 per 10 py in 2009-2010; RR: 1.85; 95% CI: 0.89, 4.00).

Various possible predictors of gout flares during hospitalization were evaluated, including discontinuation of established uric acid lowering therapy, administration of IV fluids, ICU admission, use of diuretics and reason for admission, but none were identified as statistically significant predictors of in-hospital flares.

Conclusion:

Hospitalization represents a significant risk factor for flares of gouty arthritis in patients with a prior diagnosis of gout, although the absolute risk is still low. Future studies are needed to clarify which patient subgroups are at particular risk and if inpatient care related measures can help to prevent arthritic flares during hospitalization.

Disclosure: N. Zleik, None; **M. Elfishawi**, None; **Z. Kvrgic**, None; **C. J. Michet Jr.**, None; **C. S. Crowson**, None; **E. L. Matteson**, None; **T. Bongartz**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/hospitalization-and-flare-risk-in-patients-with-established-gout-a-population-based-study-2

Abstract Number: 245

Seasonal Variation in Acute Gouty Arthritis: Data from Nationwide Inpatient Sample

Paras Karmacharya[1], Ranjan Pathak[2], Madan Aryal[2], Smith Giri[3] and Anthony Donato[4], [1]Internal Medicine, Reading Health System, WEST READING, PA, [2]Internal medicine, Reading Health System, West Reading, PA, [3]Internal medicine, University of Tennessee Health Science Center, Memphis, TN, [4]Internal, Reading Health System, Salt Lake, UT

First publication: September 29, 2015

SESSION INFORMATION

Session Date: Sunday, November 8, 2015

Session Title: Metabolic and Crystal Arthropathies Poster I

Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose: Studies describing seasonal variations in acute gouty arthritis note a seasonal trend, but disagree on timing, with most showing a peak in spring months while others showing peaks later in the year. The peak serum uric acid (SUA) levels however, have been found to be in the summer months. This disparity has led to the hypothesis that the flares might be related to factors other than high SUA levels. Various theories on the effect of weather and immune system changes on the chronobiology of the equilibrium and precipitation of monosodium urate crystals have been proposed. We aimed to shed light on this question by examining the seasonal variation in the incidence of acute gouty arthritis in the US using a large inpatient database.

Methods: We used the Nationwide Inpatient Sample (NIS) database to identify patients aged ≥ 18 years with primary diagnosis of acute gouty arthritis ICD-9-CM code 274.01 from 2009-2011 during hospitalization. We used the Edwards' recognition and estimation of cyclic trend method to study the seasonal variation of the incidence of acute gout and Z-test to compare the seasonal incidences.

Results: A total of 28,172 hospitalizations with primary diagnosis of acute gouty arthritis were reported in during the period. The peak incidence of acute gout was seen in November (peak/low ratio 1.34, 95% CI 1.29-1.38, $p<0.05$) (Figure 1). The highest number of hospitalizations was observed in autumn months while the lowest incidence was observed in spring (28.12% vs. 23.13%, $p<0.001$).

Conclusion: Unlike previous studies, our analysis found the peak incidence of acute gout in the fall with its peak in the month of November. Various environmental (temperature, humidity, diet, physical activity) and biochemical factors (low cortisol levels, high absolute neutrophil counts and plasminogen activator inhibitor-1) have been implicated for the seasonal variation. There have been conflicting data on the correlation of the incidence of acute gouty arthritis with environmental factors such as temperature or humidity. Dehydration during summer months has been postulated to precipitate crystal formation. In contrast, lower temperatures have also been reported to precipitate monosodium urate crystals in vitro, however cooling the joints with ice has been found to improve recovery. Whether our findings are reflective of purine and alcohol intake over the US holidays in November and December is a hypothesis that requires further testing. Further studies are required to verify whether seasonal, hormonal, dietary or immunological changes and acute-phase reactants have a role in the pathogenesis of acute flares. The control of these factors could potentially lead to better management of patients with gout who are at risk of acute attacks and perhaps prevent these attacks.

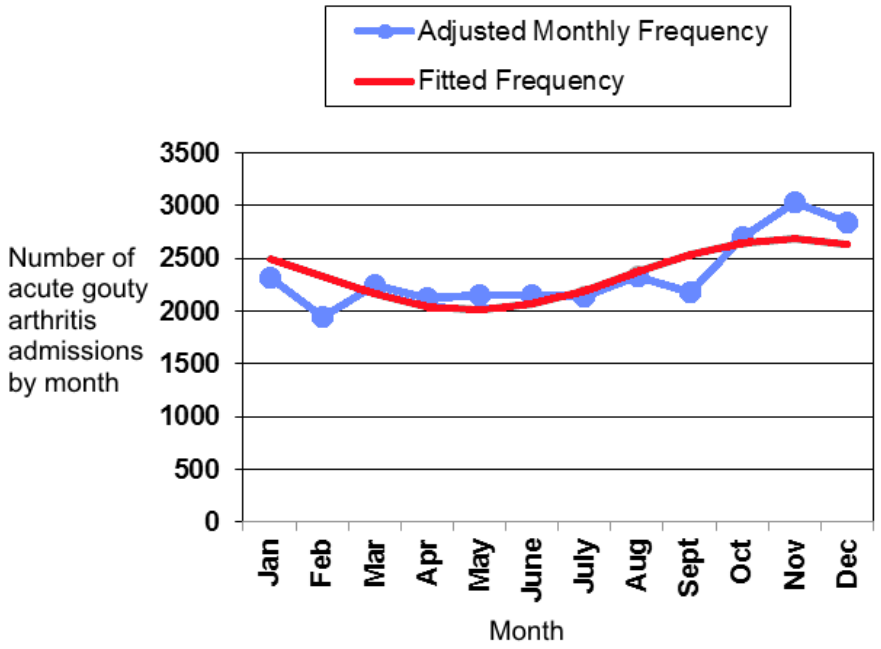

Figure 1. Graph showing seasonal trend for acute gouty arthritis admissions, 2009-2011

Disclosure: P. Karmacharya, None; **R. Pathak**, None; **M. Aryal**, None; **S. Giri**, None; **A. Donato**, None.

Abstract Number: 246

Adult Autoinflammatory Disease Frequency and Our Diagnostic Experience in an Adult Autoinflammatory Clinic

Qingping Yao[1], Felicitas Lacbawan[2] and Jianbo Li[1], [1]Cleveland Clinic, Cleveland, OH, [2]Molecular Genetics Pathology, Cleveland Clinic, Cleveland, OH

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SESSION INFORMATION

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Session Title: Miscellaneous Rheumatic and Inflammatory Diseases Poster I

Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose:

Autoinflammatory diseases (AIDs), aka, periodic fever syndromes include monogenic diseases, such as familial Mediterranean fever (FMF), cryopyrin-associated periodic disease (CAPS), tumor necrosis factor receptor-associated periodic syndrome (TRAPS), and hyper IgD periodic syndrome (HIDS), and polygenic disease like NOD2-associated AID (NAID). A diagnosis of these diseases is clinically challenging in adults, and it often relies on genetic testing. Our aim is to study the disease frequency and report our diagnostic experience.

Methods:

A total of 266 adult patients with clinical phenotypes at presentation were referred due to a concern for AIDs to our Adult AID Clinic at Cleveland Clinic between November 2009 and February 2015. All patients were genotyped for *NOD2*mutations or periodic fever syndrome panel in commercially available genetic testing centers, depending on a clinical suspicion of an individual disease. The case definition included patients of 17 years of age and older and the definite diagnosis of each disease was deemed to be present if both clinical phenotypes and genetic confirmation were met. The patient electronic medical records were examined for demographic, clinical and genetic data. The frequency of positive genetic testing was calculated to estimate the concordance between the clinical diagnosis and genetic confirmation.

Results:

Of 266 patients, 79 (26.4%) were diagnostic of AIDs, including 54 cases of NAID, 13 FMF, 6 TRAPS, 5 CAPS and 1 HIDS. Of the 143 patients at risk for NAID, 37.8% were confirmed to have NAID, with 85% specificity of the *NOD2* genetic testing. Thirteen (44.8%) of 29 patients clinically suspicious for FMF had positive genetic testing. Six (9%) of 66 patients had positive testing for TRAPS. Five (21.7%) of 23 patients had positive testing for CAPS. Only one out of 5 patients was tested positive for HIDS. The demographic and genetic data of these patients with definite AIDs are summarized (Table 1). The frequencies of the genetic tests among these patients were higher (all *P*s <0.001) as compared to the literature controls (Table 2). These data demonstrated that the AIDs diagnosed in our Clinic included NAID, FMF, TRAPS, CAPS and HIDS in a descending order. The concordance between the clinical suspicion and positive genetic testing results was higher for FMF and NAID, but it was extremely low for TRAPS. Since these AIDs share overlapping clinical phenotypes and are indistinguishable frequently, the most commonly encountered diseases, NAID and FMF, should be preferably considered. Given the extreme rarity of TRAPS and HIDS in adults and very low genetic detection rate, we suggest caution be exercised to order the genetic testing for these two disorders.

Conclusion:

Our study demonstrates that NAID and FMF are relatively common in adults. TRAPS and HIDS are extremely rare and the concordance between clinical suspicion and positive genetic testing is very low for both diseases. To be cost-effective, an ordering of genetic testing for AUIDs should highly consider both the disease frequency and stringent phenotypes, and a consultation with experts should be encouraged.

Disclosure: Q. Yao, None; **F. Lacbawan**, None; **J. Li**, None.

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Abstract Number: 247

Severe Inflammation Following Vaccination Against Streptococcus Pneumoniae in Patients with Cryopyrin-Associated Periodic Syndromes

Ulrich A. Walker[1,2], Philip N. Hawkins[3], Rene Williams[4], Hal M. Hoffman[5] and Jasmin B. Kuemmerle-Deschner[6], [1]Rheumatology, Unispital Basel, Basel, Switzerland, [2]Rheumatology, University Hospital, Basel, Basel, Switzerland, [3]University College London Medical School, London, United Kingdom, [4]University College, London, England, [5]University of California at San Diego, San Diego, CA, [6]Universitätsklinikum Tübingen, Klinik fuer Kinder- und Jugendmedizin, Tübingen, Germany

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Background/Purpose: Pneumococcal vaccination is recommended for patients requiring treatment with immunosuppressive drugs. The aim of this report is to describe unusually severe adverse reactions to pneumococcal vaccination in each of seven consecutive patients with cryopyrin associated periodic syndromes (CAPS).

Methods: Seven consecutive patients with CAPS were vaccinated with pneumococcal polysaccharide or conjugate vaccines according to current guidelines. Clinical information was collected retrospectively.

Results: Within a few hours after the vaccination, all seven patients developed severe local reactions at the injection site (Table). Two patients had to be hospitalized for systemic reactions including fever. One patient had developed a severe headache associated with neck stiffness and photophobia. A florid red rash was covering much of the arm where the vaccine had been administered. The patient was admitted to her local hospital that evening with a diagnosis of presumed viral meningitis. Lumbar puncture revealed elevated white cells (96 per cubic millimetre, neutrophils 84%), normal glucose 2.3 mmol/L and elevated protein at 0.79 g/L In all patients, the symptoms resolved in a period of 3 to 17 days. The reaction occurred with pneumococcal vaccines from three different manufacturers and in patients with different CAPS phenotypes. Four vaccination reactions occurred in temporal association with concomitant co-injections of canakinumab, two other vaccination reactions were separated by 15 days from last canakinumab dose. In one case, an event was also observed prior to any canakinumab therapy. Some patients had been vaccinated with a variety of other vaccines without complications.

Table. Clinical characteristics of CAPS patients who developed severe inflammation after pneumococcal vaccination

Case Nr. Age, gender	Clinical presen-tation	NLRP3 Mutation	CAPS duration	CAPS treatment	Vaccine/ manufacturer	Days since last canakinumab	Days until onset	Local symptoms	Systemic reaction	Days until resolution	Previous uneventful vaccines
Case 1 43 years, female	MWS	T348M	43 years	Canakinumab 150 mg every 8 weeks	Pneumovax II / Sanofi Pasteur	New canakinumab dose given on day of vaccination (63 days since previous dose)	0	Swelling, rubor, dolor, calor	Fever, nausea, headache, stiff neck	17	Nil
Case 2 20 years, female	NOMID	L632F	20 years	Canakinumab 300 mg every 8 weeks	Pneumovax II/ Sanofi Pasteur	New canakinumab dose given on day of vaccination (56 days since previous dose)	0	Swelling, rubor, dolor, calor	Fever	12	Influenza
Case 3 26 years, female	NOMID	A352T	26 years	Canakinumab 300 mg every 8 weeks	Pneumovax II/ Sanofi Pasteur	New canakinumab dose given on day of vaccination (49 days since previous dose)	0	Swelling, rubor, dolor, calor	Not known	14	Nil
Case 4 43 years, male	MWS	T348M	43 years	Canakinumab 150 mg every 8 weeks	Pneumovax II/ Sanofi Pasteur	New canakinumab dose given on day of vaccination (63 days since previous dose)	0	dolor	None	4	Influenza
Case 5 24 years, female	MWS	E311K	10 years	Canakinumab 150 mg every 8 weeks	Pneumovax 23/ Merck	Canakinumab was given 15 days prior to vaccination	0	Swelling, rubor, dolor, calor	None	3	Influenza, HiB
Case 6 52 years, female	MWS	E 311K	51 years	Canakinumab 300 mg every 8 weeks	Pneumovax 23/ Merck	Canakinumab was given 15 days prior to vaccination	0	Swelling, rubor, dolor, calor	None	10	Influenza
Case 7		No				No prior or		Swelling,			Diphtheria

7 years, female	FCAS	No known mutation	7 years	None	Prevenar 13/ Wyeth	No prior or concomitant canakinumab	0	rubor, dolor, calor	None	4	Diphtheria Polio Tetanus

Conclusion: Pneumococcal vaccines can trigger a severe local and systemic inflammatory reaction in patients with CAPS and possibly patients with other autoinflammatory diseases. TLR triggering by pneumococcal vaccine components with subsequent inflammasome hyperactivation in CAPS patients with NLRP-3 mutations may explain the high incidence rate of this event, its rapid onset, severity, and systemic nature.

Careful consideration is warranted when implicating current EULAR immunization guidelines in this patient population.

Disclosure: U. A. Walker, Novartis Pharmaceutical Corporation, 5; **P. N. Hawkins**, Novartis Pharmaceutical Corporation, 5; **R. Williams**, None; **H. M. Hoffman**, Novartis Pharmaceutical Corporation, 8,Novartis and Sobi, 5; **J. B. Kuemmerle-Deschner**, Novartis Pharmaceutical Corporation, 8,Novartis and Sobi, 5.

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Abstract Number: 248

Efficacy and Safety of Canakinumab in Patients with CAPS Aged <24 Months: Results from an Open-Label, Multicenter, Phase III Trial

Paul Brogan[1], Michaël Hofer[2], **Jasmin B. Kuemmerle-Deschner**[3], Bernard R. Lauwerys[4], Antonio Speziale[5], K. Abrams[6], Karolynn Leon[7], Xiaoling Wei[8] and Ronald Laxer[9], [1]Department of Paediatric Rheumatology, UCL Institute of Child Health and Great Ormond Street Hospital NHS Foundation Trust, London, United Kingdom, [2]Unité Romande de Rhumatologie Pédiatrique, Hospitalier Universitaire Vaudois, Lausanne, Switzerland, [3]University Hospital Tuebingen, Tuebingen, Germany, [4]Cliniques Universitaires Saint-Luc and Université Catholique de Louvain, Brussels, Belgium, [5]Novartis Pharma AG, Basel, Switzerland, [6]Novartis Pharmaceutical Corporation, East Hanover, NJ, [7]Novartis Pharmaceuticals Corporation, East Hanover, NJ, [8]Novartis Pharma, Beijing, NU, China, [9]University of Toronto, The Hospital for Sick Children, Toronto, ON, Canada

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Background/Purpose: Canakinumab (CAN) is indicated for the treatment of cryopyrin-associated periodic syndrome (CAPS) in patients aged ≥2 years.[1,2] However, the efficacy of CAN has not yet been studied in infants. Here we present the efficacy and safety of CAN in patients with CAPS aged <24 months.

Methods: Patients aged 28 days to 4 years with CAPS received CAN at 2 to 12 mg/kg every 4 or 8 weeks for 56 weeks. Efficacy was evaluated by complete response (clinical response and normal C-reactive protein [CRP] levels) and subsequent relapse. Safety assessments included adverse events (AEs).

Results: Of 17 patients enrolled, 6 were aged <24 months (44 days to 5 months). The phenotypic distribution of patients aged <24 months was: familial cold autoinflammatory syndrome (FCAS, n=1), Muckle–Wells syndrome

(MWS, n=4), and neonatal-onset multisystem inflammatory disease (NOMID, n=1). All 17 patients achieved a clinical response, and 16 achieved a complete response, with 5/6 patients <24 months of age achieving a complete response. One patient aged 1 year with persistently elevated CRP levels did not achieve complete response (Table). Of the patients with a complete response, 4 (2 MWS and 2 NOMID) subsequently relapsed; however, all regained complete response 2 (1 MWS; 1 NOMID) with and 2 (1 MWS; 1 NOMID) without dose escalation. Seven patients required dose escalation to achieve and/or maintain their responses. The proportion of complete responders without a relapse was higher in the <24 months age group (5/5, 88.9%) versus ≥24 months (7/11, 63.6%). The most common AEs were infections, typically involving the upper respiratory tract. Four patients experienced a serious AE (SAE), with no SAE occurring more than once. No patient discontinued due to an AE.

Table. Response assessment

n (%)	**Age <24 months n=6**	**Age ≥24 months n=11**	**Total N=17**
Patients achieving complete response	5 (83.3)	11 (100.0)	16 (94.1)
Patients not achieving complete response	1* (16.7)	0 (0.0)	1 (5.9)
*One-year-old patient with persistently elevated CRP			

Conclusion: Canakinumab is an effective treatment for patients with CAPS aged as young as 44 days. The safety profile of canakinumab was acceptable in younger patients and similar to that observed for older patients.

References:

1. ILARIS (summary of product characteristics). Novartis Europharm Limited; 2014.

2. Chioato A, et al. *Clin Vaccine Immunol*. 2010;17:1952-57.

Disclosure: P. Brogan, Roche Pharmaceuticals and SOBI, 5; **M. Hofer**, Abbvie, 2,Abbvie and Novartis Pharmaceutical Corporation, 5; **J. B. Kuemmerle-Deschner**, Novartis Pharmaceutical Corporation, 8,Novartis and Sobi, 5; **B. R. Lauwerys**, None; **A. Speziale**, Novartis, 3; **K. Abrams**, Novartis Pharmaceutical Corporation, 1,Novartis Pharmaceutical Corporation, 3; **K. Leon**, Novartis Pharmaceutical Corporation, 3; **X. Wei**, Novartis Pharmaceutical Corporation, 3; **R. Laxer**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/efficacy-and-safety-of-canakinumab-in-patients-with-caps-aged

Abstract Number: 250

Postvaccination Antibody Titer Data in CAPS Patients Aged 28 Days to 4 Years Treated with Canakinumab: Results of an Open-Label Phase 3 Trial

Paul Brogan[1], **Michaël Hofer**[2], Jasmin B. Kuemmerle-Deschner[3], Bernard R. Lauwerys[4], Antonio Speziale[5], Ken Abrams[6], Karolynn Leon[6], Xiaoling Wei[7] and Ronald Laxer[8], [1]Department of Paediatric Rheumatology, UCL Institute of Child Health and Great Ormond Street Hospital NHS Foundation Trust, London, United Kingdom, [2]Unité Romande de Rhumatologie Pédiatrique, Hospitalier Universitaire Vaudois, Lausanne, Switzerland, [3]University Hospital Tuebingen, Tuebingen, Germany, [4]Cliniques Universitaires Saint-Luc and Université Catholique de Louvain, Brussels, Belgium, [5]Novartis Pharma AG, Basel, Switzerland, [6]Novartis Pharmaceuticals Corporation, East Hanover, NJ, [7]Novartis Pharma, Beijing, NU, China, [8]University of Toronto, The Hospital for Sick Children, Toronto, ON, Canada

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Background/Purpose: Patients with autoinflammatory diseases treated with immunosuppressive agents reportedly experience an increased risk of serious infections.[1] Therefore, these patients are likely candidates for vaccinations, such as those against the influenza virus and meningococcal infections. A previous report has shown that treatment with canakinumab (CAN) does not affect antibody production after vaccination in healthy volunteers[2]; however, no data are available in patients with cryopyrin-associated periodic syndrome (CAPS) receiving standard childhood vaccines. Here we assess the presence of protective antibody levels following immunization with inactivated vaccines in patients with CAPS.

Methods: Patients aged 28 days to 4 years received CAN at 2 to 12 mg/kg (based on body weight) every 4 or 8 weeks for 56 weeks. Vaccination response was evaluated using postvaccination antibody titers at 0 to 14 (predose assessment), 28, and 57 days after vaccination. Patients were considered assessable for an antibody response to a specific vaccination if they had a predose and at least one postdose antibody titer measurement. However, for patients with adequate predose antibody titers without any difference at subsequent antibody titer measurements, the specific patient vaccination was deemed non-assessable.

Results: Of 17 patients, 7 (aged 5-60 months) received ≥1 vaccinations against *Corynebacterium diphtheria*, *Bordetella pertussis*, *Neisseria meningitidis*, *Clostridium tetani*, influenza type A, influenza type B, *Haemophilus influenza* B, *Streptococcus pneumoniae*, or hepatitis B. The Table summarizes predose antibody titers and the last measured antibody titer during the study for each patient and corresponding vaccination. Of 31 unique patient vaccination cases, only 18 were assessable for a vaccination response, whereas for the remaining 13, patient-vaccination was not deemed assessable. For all 18 (100%) assessable cases, postvaccination antibody titers increased to protective levels compared to the predose measurement. All the 31 vaccination cases showed protective level antibody titers at the last assessment in the study. No CAPS flares were reported with vaccination.

Table. Summary of vaccination assessments

Vaccination		Patient, age (months)						
		31	14	29	5	60	38	27
C. diphtheria [IU/mL]	predose	0.12	0.4	n/a	n/a			
	postdose	>1	>1	>1	>1			
B. pertussis [U/mL]	predose	54.64	15.18*	n/a	n/a			
	postdose	>150	137.9*	>150	16.29			
*N. meningitidis***	predose		7.39		n/a			
	postdose		14.92		9.53			
C. tetani [IU/mL]	predose	0.59	0.12	n/a	n/a			
	postdose	>5	1.06	>5	1.81			
Influenza type A (H1N1) [mm²]	predose					38.49	33.18	56.75
	postdose					56.75	113.10	103.87
Influenza type A (H3N2) [mm²]	predose					56.75	33.18	7.07
	postdose					70.88	78.54	113.10
Influenza type B [mm²]	predose					23.76	33.18	44.18
	postdose					38.49	70.88	95.03
H. influenza B [µg/mL]	predose	0.83	>4.9		n/a			
	postdose	>4.9	>4.9		>4.9			
S. pneumoniae [U/mL]	predose		>10		n/a			5.67
	postdose		>10		>10			8.01
Hepatitis B [mIU/mL]	predose	<10	>250					
	postdose	209.7	>250					

*Patient initially mounted an antibody response, received a booster vaccination, and maintained protective antibody levels

**The ELISA kit used for *Neisseria meningitidis* assessment was qualitative

n/a = predose titer not available; cursive/grey = vaccination response not assessable

Conclusion: Canakinumab appears to have no effect on antibody production against standard childhood nonlive vaccines.

References:

1. Doran, M.F., et al. *Arthritis Rheum.* 2002;46:2287-93.

2. Chioato A., et al. *Clin Vaccine Immunol.* 2010;17:1952-57.

Disclosure: P. Brogan, Roche Pharmaceuticals and SOBI, 5; **M. Hofer**, Abbvie, 2,Abbvie and Novartis Pharmaceutical Corporation, 5; **J. B. Kuemmerle-Deschner**, Novartis Pharmaceutical Corporation, 8,Novartis and Sobi, 5; **B. R. Lauwerys**, None; **A. Speziale**, Novartis, 3; **K. Abrams**, Novartis, 1,Novartis, 3; **K. Leon**, Novartis Pharmaceutical Corporation, 3; **X. Wei**, Novartis Pharmaceutical Corporation, 3; **R. Laxer**, None.

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Abstract Number: 251

A New Genetic Mutation in TNF Receptor Associated Periodic Syndrome (TRAPS)

Mark Leith[1], Auleen Millar[2] and James Burns[3], [1]Rheumatology, Antrim Area Hospital,, Antrim, Northern Ireland, [2]Rhematology, Antrim area hospital, Antrim, Northern Ireland, [3]Antrim area hospital, Antrim, Northern Ireland
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SESSION INFORMATION
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Background/Purpose: ,

We present the case of a family with a new diagnosis of

TRAPs. The father, a 59 year old man with a history of type 2 diabetes mellitus and hypertension had presented to a DGH on numerous occasions since 1990 with recurrent pyrexic episodes associated with rigors, fatigue and arthralgia. This had often been attributed to a lower respiratory tract infection, despite a lack of positive culture results or chest x-ray changes to support this.

He was entirely well between episodes.

He had an extensive travel history over the years but had previously tested negative for malaria and other tropical diseases. His ESR and CRP were elevated with each flare, but had not been checked during asymptomatic periods. He was extensively investigated during each admission, but multiple blood, urine and sputum cultures returned negative.

Methods: ,

He was admitted again in August 2013 with a 4 week history of pyrexia, rigors and elevated inflammatory markers with CRP 150 mg/l and ESR 111 mm/h and a leukocytosis of 11.7x10^9/L. Ferritin was elevated at 1700 ng/ml on this occasion, but he met no other Yamaguchi criteria for Still's disease. Blood and urine cultures were negative as was quantiferon gold testing. HIV and viral serology were negative. His echocardiogram, CT chest, abdomen and pelvis and ultrasound of urinary tracts all found no abnormalities. His ANCA, ANA, ANA to Hep cells, ENA, complement, rheumatoid factor and immunoglobulins were normal. He was also seen by haematology who performed a bone marrow

biopsy which returned morphologically normal with no evidence of malignant cells.

Results: ,

He went on to have a white cell HMPAO whole body scan which showed slight increased uptake in the left side of his manubrium which raised the suspicion of an inflammatory arthropathy, prompting a referral to rheumatology. Bloods were sent to the national amyloid centre on the suspicion of an systemic autoinflammatory syndrome. Results confirmed a new mutation in the region of the TRAPS gene TNFRSF1Aex4-5 C96Wc.375T>G. This is a new mutation not previously reported in the literature.

During this period his son was admitted with pyrexia, abdominal pain and elevated inflammatory markers. CT abdomen revealed no abnormality. Given his father's history of TRAPS, he too was tested and this returned positive for the TRAPS mutation.

Conclusion: ,

Currently he receives prednisolone 0.5-1mg/kg with acute attacks which settle within 5 days. If however he starts to require more than 10 days of treatment or if his annual mean dose of prednisolone is >5mg/day he will require anakinra. His inflammatory markers have remained normal in between attacks to date and he has no evidence of amyloid.

Disclosure: M. Leith, None; **A. Millar**, None; **J. Burns**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/a-new-genetic-mutation-in-tnf-receptor-associated-periodic-syndrome-traps

Abstract Number: 252

Pyrin (MEFV) Mutations in New York: Revisiting the Mount Sinai Experience with Periodic Fever and Serositis

Daniel Bunker and Mark Matza, Medicine, Mount Sinai Medical Center, New York, NY

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Background/Purpose: In 1945, Dr. Sheppard Siegel, a Mount Sinai allergist, described 5 patients with "Benign Paroxysmal Peritonitis," a disorder now recognized as Familial Mediterranean Fever (FMF). By 1964 (Am J Med 36: 893, 1964), he was able to review a cumulative experience with 50 patients affected by this disorder from the New York City area, describing in detail self-limited attacks of intense abdominal pain with accompanying fever, usually found in younger patients of specific ethnicities, including 38 ashkenazi and 4 sephardic jews, and 7 armenians . Possibly affected by the disorder himself, he also identified "progressive nephropathy" as a feared complication, and correctly surmised an underlying genetic cause. Although Dr Siegel was unable to identify an effective treatment, including a search for food allergies, his work overlapped with that of Dr Tsai Fan Yu @ Mount Sinai 1962-86 that established the efficacy of daily colchicine prophylaxis for gout, eventually identified as another autoinflammatory disease. In 1997 FMF was linked to the MEFV gene on chromosome 16 by two groups, and, that year, we established an referral practice for FMF and Amyloidosis at the Mount Sinai Medical center.

Methods: We now report our experience with 51 patients affected by this disease, and /or found to have MEFV mutation over the period 1997-2015.

Results: In our cohort, the most common ethnicity was Sephardic Jewish (17), with varying origins from Morocco (4) to Khazakhstan, and the most common genotype was heterozygous M694V (22%). 9 patients were homozygous, 17 patients were heterozygous, and 10 patients were compound heterozygous. An additional three patients having the typical FMF phenotype (Tel Hashomer criteria) and response to colchicine were wild type, assessed by full DNA sequence analysis. Interestingly, a number of patients with the FMF phenotype and documented MEFV mutations began manifesting symptoms in adulthood; atypical phenotypes seen were periodic fever without serositis, recurrent pleuritis, and recurrent pericarditis. Associated diseases were nonspecific colitis, thalassemia, G6PD deficiency, and one case of primary Sjogren 's syndrome complicated by mesothelioma. Only one patient with typical FMF symptoms eventually developed secondary (AA) amyloidosis. However, one patient homozygous for the M694V mutation had secondary amyloidosis as his initial manifestation of the disease ("phenotype II"), and four additional patients with secondary amyloidosis, and one egyptian man with renal amyloid due to Lect2, were found to have the low penetrance E148Q mutation. Median delay from first attack to diagnosis was 10 years. Treatment modalities included colchicine and anticytokines, notably IL-1 and more recently IL-6 antagonists.

Conclusion:

Availability of genetic testing has allowed analysis of the heterogeneity of genotype-phenotype correlations and distribution frequencies for pyrin mutations in a "melting pot" population from which the initial description of FMF in New York City were made.

Disclosure: D. Bunker, None; **M. Matza**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/pyrin-mefv-mutations-in-new-york-revisiting-the-mount-sinai-experience-with-periodic-fever-and-serositis

Abstract Number: 253

Multiple Serum Cytokine Profiling to Identify Specific Molecular Networks in Attacks of Familial Mediterranean Fever

Tomohiro Koga[1], Kiyoshi Migita[2], Shuntaro Sato[3], Masataka Umeda[4], Shoichi Fukui[5], Ayako Nishino[4], Shinya Kawashiri[6], Naoki Iwamoto[5], Kunihiro Ichinose[5], Mami Tamai[5], Hideki Nakamura[5], Tomoki Origuchi[7], Yukitaka Ueki[8], Kazunaga Agematsu[9], Katsumi Eguchi[10] and Atsushi Kawakami[4], [1]Departments of Immunology and Rheumatology, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan, [2]Department of Rheumatology and Clinical Research Center, Nagasaki Medical Center, Omura, Japan, [3]Clinical Research Center, Nagasaki University Hospital, Nagasaki, Japan, [4]Department of Immunology and Rheumatology, Nagasaki University, Nagasaki, Japan, [5]Department of Immunology and Rheumatology, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan, [6]Department of Public Health, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan, [7]Department of Rehabilitation Sciences, Nagasaki University, Nagasaki, Japan, [8]Rheumatic and Collagen Disease Center, Sasebo Chuo Hospital, Sasebo, Japan, [9]Department of Infectious Immunology, Shinshu University, Graduate School of Medicine, Shinshu, Japan, [10]Department of Rheumatology, Sasebo Chuo Hospital, Sasebo, Japan

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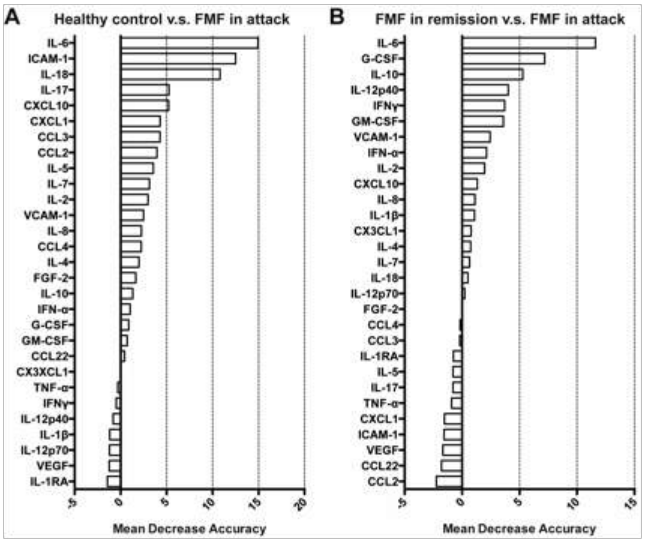
Background/Purpose: Familial mediterranean fever (FMF) is caused by a number of mutations of the *MEFV* gene, coding for a protein named pyrin that acts as a major regulatory component of the inflammasome. It is widely accepted that elevated acute phase proteins such as SAA, CRP and inflammatory cytokines including IL-6, IL-18 are found in active phase of patients with FMF. However serum cytokine profiling of FMF patients still remains to be obscure. The aim of this study was to identify the utility of multiple cytokines measurement for understanding the specific molecular networks in patients with FMF.

Methods: FMF patients in attack or remission were classified by Japan College of Rheumatology-certified rheumatologists through medical records. Serum levels of 45 cytokines were measured by multi-suspension cytokine array from 49 FMF patients, in either attack or remission, and 33 age-matched controls. They gave their informed consent to be subjected to the protocol, which was approved by the Institutional Review Board of Nagasaki University. Multivariate classification algorithms were used to determine discriminating biomarkers.

Results: Twenty-nine out of 45 cytokines were available for further analyses. Serum levels of 8 cytokines (IL-4, IL-6, IL-7, IL-17, IL-18, G-CSF, ICAM-1 and CXCL10) were significantly elevated from FMF in attack than healthy control. Furthermore, eleven cytokines (IL-6, IL-10, IL-12p40, IL-12p70, IFN-alpha, IFN-gamma, GM-CSF, G-CSF, FGF-2, CXCL10 and CX3CL1) were increased from FMF in attack compared to FMF in remission. We performed multivariate classification algorithm and ranked cytokines by their importance (Fig. 1) and found that IL-6, sICAM-1, IL-18 and IL-17 were the best combination to distinguish FMF in attack from healthy control with high accuracy (sensitivity; 92.0%, specificity; 93.9%, accuracy; 93.1%). Among FMF patients, combined measurement of IL-6, G-CSF IL-10 and IL-12p40 discriminated FMF in attack from FMF in remission with high accuracy (sensitivity; 76%, specificity; 90.3%, accuracy; 83.9%).

Conclusion: Our data suggest for the first time that specific molecular interactions are present in patients with FMF based on multiple cytokines measurement. These findings may extend to our further understanding of the activation of inflammasome leading to promote cytokine networks.



Disclosure: T. Koga, None; **K. Migita**, None; **S. Sato**, None; **M. Umeda**, None; **S. Fukui**, None; **A. Nishino**, None; **S. Kawashiri**, None; **N. Iwamoto**, None; **K. Ichinose**, None; **M. Tamai**, None; **H. Nakamura**, None; **T. Origuchi**, None; **Y. Ueki**, None; **K. Agematsu**, None; **K. Eguchi**, None; **A. Kawakami**, None.

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Abstract Number: 254

The Interleukin-1 Inhibitor Canakinumab for Familial Mediterranean Fever: Long-Term Beneficial Effect in a Cohort of 13 Patients

KATERINA LASKARI[1], PANAGIOTA BOURA[2], GEORGE N DALEKOS[3], ALEXANDROS GARYFALLOS[4], DIMITRIOS KAROKIS[5], DIMITRIOS PIKAZIS[6], LOUKAS SETTAS[7], GRIGORIS SKARANTAVOS[8], ELENA TSITSAMI[9] and PETROS P SFIKAKIS[10], [1]Rheumatology Unit, 1st Dept. of Propaedeutic Internal Medicine, Athens University Medical School, Athens, Greece, [2]Clinical Immunology Unit, 2nd Dept. of Internal Medicine, Aristotle University Medical School, Thessaloniki, Greece, [3]Thessaly University Medical School, Larissa, Greece, [4]4th Department of Internal Medicine, Aristotle University Medical School, Thessaloniki, Greece, [5]Private rheumatologist, Patras, Greece, [6]Pathophysiology, Athens University Medical School, Athens, Greece, [7]First Dept. of Internal Medicine, Rheumatology Section, Aristotle University Medical School, Thessaloniki, Greece, [8]Bone Metabolic Unit, 1st Dept. of Orthopedics, Athens University Medical School, Athens, Greece, [9]First Department of Pediatrics, Athens University Medical School, Athens, Greece, [10]1st Dept. of Propaedeutic Internal Medicine, Athens University Medical School, Athens, Greece

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Background/Purpose: Interleukin-1 (IL-1) is a major mediator of the inflammatory cascade in Familial Mediterranean Fever (FMF) and an established therapeutic target (1). To retrospectively assess the efficacy and safety of the IL-1 inhibitor Canakinumab in adult and adolescent FMF patients.

Methods: Thirteen patients (7 men) with genetically confirmed FMF, fulfilling the Tel Hashomer criteria, aged 37 years (median, range 13-70), with median disease duration of 15 years and active disease despite treatment with colchicine (n=9), anakinra (n=1) or both (n=3), received Canakinumab 150mg subcutaneously every 4 (n=7) or 6 (n=2) or 8 weeks (n=4) for a median of 18 months (range 7-53). Canakinumab was given as monotherapy in 9; 4 patients received concomitant treatment with colchicine and/or corticosteroids. The clinical and laboratory parameters during follow up were recorded.

Results: Ten out of 13 patients (77%) achieved complete clinical remission within a median time of 3.5 months, while normalization of all laboratory parameters associated with inflammation occurred in 85% of patients within a median time of 3 months. The remaining patients achieved partial responses, with persisting, albeit milder, arthralgias, exertional leg pain, abdominal pain, anemia, and lower, but abnormal, C-reactive protein levels. Response was maintained until the last visit in all but one patient who relapsed with fever and arthralgias and re-remitted after reducing the Canakimumab administration interval. Overall, in 3 patients, including the patient who relapsed, the interval between Canakinumab injections was reduced in order to achieve complete remission, whereas in another two patients drug administration intervals could be safely increased without disease exacerbation until the last visit. The concomitant corticosteroid dose was significantly reduced during follow up. The recently proposed FMF50 score for assessing outcome in FMF (2) was achieved by 62% and 85% of patients at one month and 12 months, respectively. Canakinumab was well tolerated; one patient experienced an urinary tract infection, which resolved with antibiotics, and another one a viral gastroenteritis, which required short-term hospitalization.

Conclusion: The rapid and sustained response to Canakinumab in the majority of our patients, together with the favorable safety profile, encourages its further use in FMF.

1. Ter Haar N et al. Ann Rheum Dis. 2013;72(5):678-85.

2. Ozen S et al. Ann Rheum Dis. 2014;73(5):897-901.

Disclosure: K. LASKARI, None; **P. BOURA**, None; **G. N. DALEKOS**, None; **A. GARYFALLOS**, None; **D. KAROKIS**, None; **D. PIKAZIS**, None; **L. SETTAS**, None; **G. SKARANTAVOS**, None; **E. TSITSAMI**, None; **P. P. SFIKAKIS**, None.

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Abstract Number: 255

What Acute Phase Reactants Accurately Identify Patients Who Will Develop Amyloidosis in Familial Mediterranean Fever? a Systematic Review

Burak Erer[1], Erkan Demirkaya[2], Seza Ozen[3,4], Tilmann Kallinich[5] and Loreto Carmona[6], [1]Department of Internal Medicine, Division of Rheumatology, Istanbul University, Istanbul Faculty of Medicine, Istanbul, Turkey, [2]Gulhane Military Medical Faculty, Ankara, Turkey, [3]Pediatric Nephrology and Rheumatology, Hacettepe University, Ankara, Turkey, Ankara, Turkey, [4]Deptartment. of Pediatric Rheumatology, Hacettepe University, Ankara, Turkey, [5]Charite, University Medicine Berlin, Berlin, Germany, [6]Instituto de Salud Musculoesqueletica, Madrid, Spain
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Background/Purpose: Familial Mediterranean Fever (FMF) is a prototype of autoinflammatory diseases. Inflammation is expressed by attacks of fever and serositis and elevation of acute phase reactants (AFR). The most dreaded complication of FMF is amyloidosis, being the treatment target to prevent it. There is controversy as to what AFR should be monitored in these patients. The objective was to analyze the performance of the various AFR for the prediction of amyloidosis in FMF.

Methods: We performed a systematic review based on a sensitive search in Medline, Embase, and Cochrane Library, with terms related to FMF, to performance and diagnostic studies, and to longitudinal studies. Selection criteria included: 1) FMF any age; 2) measure of Serum amyloid A (SAA), C-RP, proteinuria, or ESR; 3) amyloidosis should be the outcome measure; 4) sensitivity, specificity, predictive value and other performance parameters could be calculated; and 5) designs should be longitudinal preferably. Two fellows screened the registers captured by the search strategy and collected the data in pre-specified tables. Evidence tables and qualitative synthesis were produced.

Results: The search captured 1516 items of which 26 were selected for detailed review, and 12 were finally included in the review. No study actually analyzed the performance by means of sensitivity and specificity to predict, or even detect, proteinuria or amyloidosis. The studies reviewed combine and stratify variables in a descriptive manner and it is very difficult to interpret the true performance of the tests. Each study was designed *ad hoc*, thus, yielding a high heterogeneity in designs, parameters measured, and results, despite being set from research questions similar to ours. Many are described as longitudinal; however, the measures are actually performed cross-sectionally. We were able to calculate the performance from three studies (See Table), although the performance was not tested in the appropriate population (ill versus healthy controls instead of amyloidosis yes/no). The correlation between measures is low.

Table. Calculated performance of tests

Study	test	Gold standard	Se	Sp	LHR+	LHR-	PPV	NPV
Berkun **Y, et al, 2007**	SAA	Symptomatic vs Asymptomatic	79.3	52.5	1.7	0.4	80.4	52.5
Korkmaz **C, et al, 2002**	CRP	FMF attack/Healthy control	100	94.7	19.0	0.00	98.0	94.7
Korkmaz **C, et al, 2002**	ESR	FMF attack/Healthy control	87.8	100	-	0.12	100.0	100.0
Abbreviations: SAA, Serum amyloid A; C-RP, C-reactive protein; ESR, erythrocyte sedimentation rate; Se, sensitivity; Sp, specificity; LHR, likelihood ratio: PPV, positive predictive value; NPV, negative predictive value.								

Conclusion: The evidence supporting the monitoring of FMF with any AFR over the others is limited and of poor quality in general. Well designed longitudinal studies with a mixture of outcomes should be undertaken. Until them, recommending an AFR over other would be based on expert opinion and indirect evidence.

Disclosure: B. Erer, None; **E. Demirkaya**, None; **S. Ozen**, Novartis Pharmaceutical Corporation, 5,Sobi, 5; **T. Kallinich**, None; **L. Carmona**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/what-acute-phase-reactants-accurately-identify-patients-who-will-develop-amyloidosis-in-familial-mediterranean-fever-a-systematic-review

Abstract Number: 256

The Predominant Attack Type and Associated Clinical-Laboratory Conditions in Patients with Familial Mediterranean Fever

Mustafa Cakar[1], Muharrem Akhan[2], Muhammet Cinar[1] and **Sedat Yılmaz**[1], [1]Rheumatology, Gulhane Medical Faculty, Ankara, Turkey, [2]Internal Medicine, Gulhane Medical Faculty, Ankara, Turkey

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Background/Purpose: Familial Mediterranean Fever (FMF) is an autoinflammatory disease characterized by recurrent attacks of fever and serositis. Abdominal pain is the most frequent symptom of these patients and approximately 95% of the FMF patients experience an abdominal attack sometime during their illness. One of the main concerns in FMF is the impaired oral intake and possible weight loss during abdominal attacks. In this study, we aimed to investigate the association of the clinical conditions with attack type, and weight status in patients with abdominal attacks.

Methods: A group of 118 consecutive patients with a diagnosis of FMF seen in a tertiary rheumatology outpatient clinic were included in the study. The demographical, laboratory, genetic and clinical features of the patients were recorded. Body mass indexes were calculated as kg/m^2. Statistical analysis was made with SPSS 22.0.

Results: 18 % (n=21) of the patients were female. The mean age and BMI's of the study group were 29.05±8.69 (17-53) years and 24.28±3.5 (16.5-33.4) kg/m^2, respectively. The mean disease duration of these patients was 12.32±8.8 (0-39) years. 26% (n=31) of patients were smokers. The levels of the inflammatory markers did not differ significantly with predominant attack types. Patients with arthritis attacks had lower BMI's (23.7±3.4 vs 25.0±3.5 kg/m2, p=0.047) compared to non-arthritis patients (Figure 1). Disease duration from the first symptom or attack was significantly associated with serum uric acid measurements (r=0.280, p=0.041)(Figure 2). BMI was significantly associated with

serum uric acid measurements (r=0.263, p=0.036). Patients with an erysipelas-like erythema had lower serum magnesium levels (1.86±0.11 vs 2.06±0.14 mg/dl, p=0.013). Abdominal peritonitis attacks were associated with lower diastolic arterial pressures (69.8±8.4 vs 73.8±5.4, p=0.024). Myositis attacks and febrile myalgia were associated with higher serum creatinine kinase levels (366.4±317.3 vs 108.5±48.5 U/L, p<0.001). The disease duration, genetic mutation and smoking status lacked any significant association with BMI's (p=0.803, 0.269 and 0.512, respectively).

Conclusion: These preliminary findings are needed to be confirmed in larger cohorts. Especially the correlation between serum uric acid levels and higher disease duration may point to higher cardiovascular risks of FMF patients in time.

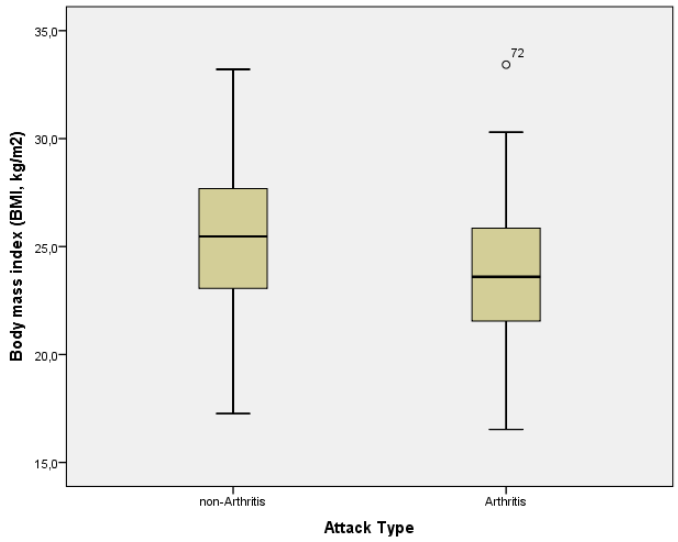

Figure 1. Chart showing the BMI differences of FMF patients in arthritis and non-arthritis attacks (p=0.047).

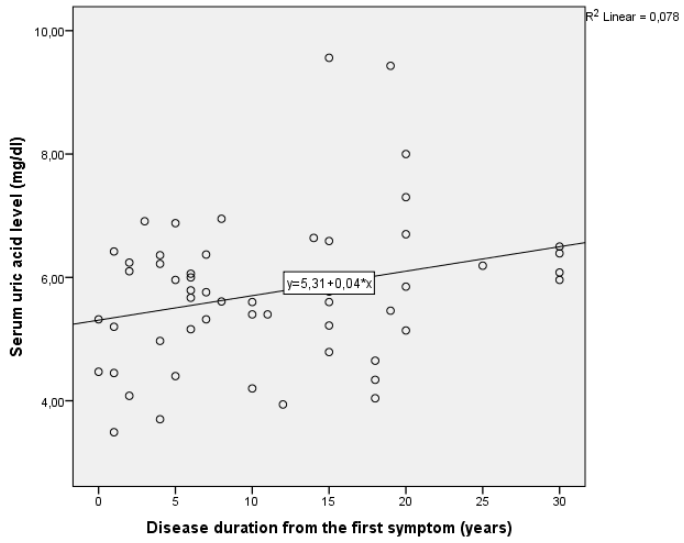

Figure 2. The chart showing the association between serum uric acid levels and disease duration of FMF patients.

Disclosure: M. Cakar, None; **M. Akhan**, None; **M. Cinar**, None; **S. Yılmaz**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/the-predominant-attack-type-and-associated-clinical-laboratory-conditions-in-patients-with-familial-mediterranean-fever

Abstract Number: 257

Investigation of the Arterial Stiffness and Associated Factors in Patients with Familial Mediterranean Fever

Mustafa Cakar[1], Muharrem Akhan[2], Tolga Doğan[2], Gurhan Taskin[3], Kadir Ozturk[4], Muhammet Cinar[1], Erol Arslan[2] and **Sedat Yılmaz**[1], [1]Rheumatology, Gulhane Medical Faculty, Ankara, Turkey, [2]Internal Medicine, Gulhane Medical Faculty, Ankara, Turkey, [3]Internal Medicine Intensive Care, Gulhane Medical Faculty, Ankara, Turkey, [4]Gastroenterology, Gulhane Medical Faculty, Ankara, Turkey

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Background/Purpose: Arterial stiffness represents the viscoelastic properties of the vessel wall. It occurs as a result of known atherosclerotic risk factors such as hypertension, diabetes mellitus, smoking, hypercholesterolemia and aging. It has high cardiovascular risk-predictive value, reproducibility and cost-effectiveness. Familial Mediterranean Fever (FMF) is an autoinflammatory disease characterized by recurrent attacks of fever and serositis. These patients may experience a high risk of cardiovascular events due to the ongoing and recurring inflammatory state. In this study, we aimed to investigate the arterial stiffness and associated factors in patients with FMF.

Methods: A total of 104 subjects were enrolled in the study. 35 of them were healthy controls. 69 patients, of whom 11(16%) were female, were consecutive patients with a diagnosis of FMF examined in a tertiary rheumatology outpatient clinic. The mean ages and BMI's of the patient vs control groups were 27.04±8.0 vs 28.29±4.9 years (p=0.331) and 24.11±3.3 vs 24.48±3.2 kg/m2 (p=0.586). The groups were also matched in terms of gender (p=0.836) and smoking status of the subjects (p=0.058). The demographical, clinical, laboratory and genetic features of the patients were recorded. The predominant attack type was recorded as peritonitis, pleuritis, arthritis, febrile myalgia and erysipelas-like erythema. Tensiomed device (TensoMed Ltd, Budapest, Hungary) was used for arterial stiffness measurements. SPSS 22.0 statistical package was used for statistical analysis.

Results: FMF patients had a significantly higher pulse wave velocity measurements (PWV) (7.73±1.3 vs 7.18±1.1 m/sec; p=0.03), lower brachial and aortic augmentation indexes (-64.6±14.6 vs -54.6±25.9 %, p=0.041 and 4.9±7.4 vs 14.0±11.5 %, p=0.025; respectively) compared to controls. Central aortic pressure and ankle brachial index measurements were statistically similar. 31(45%) of the patients were examined in attack and had significantly higher PWV measurements (8.17±1.6 vs 7.38±0.9 m/sec; p=0.027) compared to symptomless patients. PWV measurements had significant correlations to serum CRP (Figure), WBC, erythrocyte sedimentation rate, fibrinogen, and neutrophil/lymphocyte ratios (r=0.581, 0.251, 0.367, 0.348, 0.337; p<0.001, p=0.049, 0.004, 0.006, 0.007; respectively. The genetic mutation and predominant attack type had no effect on arterial stiffness measurements.

Conclusion: These preliminary results suggest that FMF patients have impaired arterial stiffness measurements, which get worse during attacks, compared to controls. The impaired arterial stiffness measurements seem to be due to the severity of the inflammatory state, rather than attack type and genetic mutations. These data point to higher future cardiovascular risks in FMF patients.

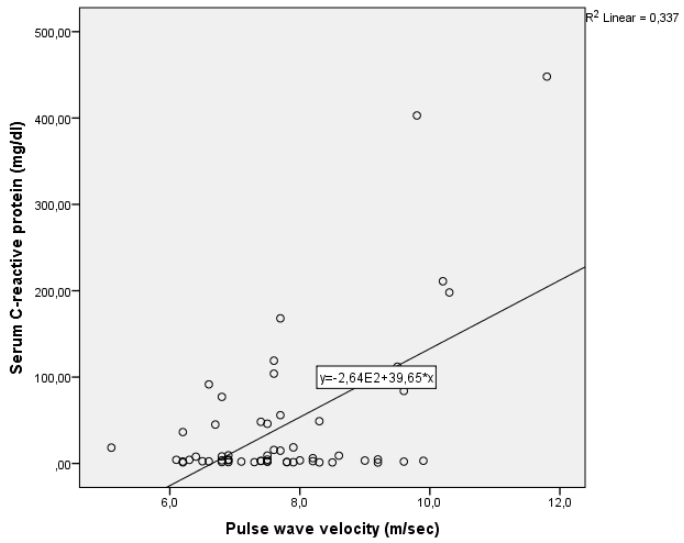

Figure: The association between serum CRP (mg/dl) and PWV (m/sec) in FMF patients.

Disclosure: M. Cakar, None; **M. Akhan**, None; **T. Doğan**, None; **G. Taskin**, None; **K. Ozturk**, None; **M. Cinar**, None; **E. Arslan**, None; **S. Yılmaz**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/investigation-of-the-arterial-stiffness-and-associated-factors-in-patients-with-familial-mediterranean-fever

Abstract Number: 258

Quality of Life Changes with Canakinumab Therapy in Adults with Colchicine Resistant FMF

Ahmet Gul[1], Huri Ozdogan[2], Ozgur Kasapcopur[3], Burak Erer[4], Serdal Ugurlu[5], S. Sevgi[6] and Soner Turgay[7], [1]Department of Internal Medicine, Rheumatology Division, Istanbul University, Istanbul Faculty of Medicine, Istanbul, Turkey, [2]Division of Rheumatology, Department of Internal Medicine, Cerrahpasa Medical Faculty, University of Istanbul, Istanbul, Turkey, [3]Istanbul University, Cerrahpasa Medical School, Department of Pediatric Rheumatology, Professor of Pediatric Rheumatology, Istanbul, Turkey, [4]Istanbul Faculty of Medicine, Istanbul University, Istanbul Faculty of Medicine, Istanbul, Turkey, [5]Rheumatology, Division of Rheumatology, Department of Internal Medicine, Cerrahpasa Medical Faculty, University of Istanbul, Istanbul, Turkey, [6]Novartis Pharma, Istanbul, Turkey, [7]Medical, Novartis Pharma, İstanbul, Turkey

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Session Time: 9:00AM-11:00AM

Background/Purpose:

Introduction: Familial Mediterranean Fever (FMF), the most common form of the hereditary autoinflammatory disorders, is characterized by recurrent attacks of fever along with serosal or synovial inflammation lasting usually 12

to 72 hours. FMF is associated with impaired functional ability, and the persistent disabling features and chronic pain, emotional and physical limitations can have a negative impact on the health-related quality of life (QoL) of the patients.

There is no established treatment available for those resistant or intolerant to standard of care colchicine treatment. Interleukin-1 (IL-1) plays a pivotal role in the pathogenesis of crFMF. Canakinumab, a fully human, selective, anti-IL-1β monoclonal antibody, binds to IL-1β and inactivates its signalling activity. Gul et al. have described the efficacy and safety of canakinumab in adults with colchicine resistant (cr) FMF in a local pivotal phase II trial. Here, we report the effect of canakinumab treatment on QoL measured by SF-36 Questionnaire.

Objectives: This study aimed to show the effects of canakinumab treatment on quality of life by 8 sub-items of SF-36 as well as to see the correlation between the physician global assessments and SF-36 scores.

Methods:

crFMF patients with ≥1 attack/month in the preceding 3-months despite the highest tolerated colchicine dose entered the study. Canakinumab injections were administered at Day 1, Day 29 and Day 57. Changes in the quality of life was recorded in 9 subjects by using SF-36 at Day 1, 8, 29,57, 86,115 and the end of the study.

Results:

In all 8 sub-items (physical functioning, role limitations due to emotional/physical health, energy, emotional-well being, body pain, social functioning and general health) of SF-36 scores improved dramatically with canakinumab treatment, starting from 1st day. However the differences in emotional well-being and role limitations due to emotional problems scores couldn't reach the statistical significance. All scores are showed in tables below. Also there was a strong negative correlation between Physician Global Assessment (PGA) and Physical Component Score(PGS) (R-sq: -0,793). A weaker correlation observed between Mental Component Score(MCS) and Physical Global Assessment (R-sq: -0,540).

Conclusion:

Canakinumab treatment in cr-FMF patients resulted in a rapid improvement in QoL measures. Also these improvements sustained during the withdrawal period. PGA scores seem to be correlating well with SF-36 scores. In addition, Physical Component Score matches with PGA more than Mental Component Score.

Disclosure: A. Gul, None; **H. Ozdogan**, None; **O. Kasapcopur**, None; **B. Erer**, None; **S. Ugurlu**, None; **S. Sevgi**, Novartis Pharmaceutical Corporation, 3; **S. Turgay**, Novartis Pharmaceutical Corporation, 3.

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Abstract Number: 259

How Safe IT Is to TREAT Pregnant FMF Patients with Anakinra ?

Huri Ozdogan[1], Serdal Ugurlu[2] and Bilgesu Ergezen[1], [1]Division of Rheumatology, Department of Internal Medicine, Cerrahpasa Medical Faculty, University of Istanbul, Istanbul, Turkey, [2]Division of Rheumatology, Department of Internal Medicine, Cerrahpasa Medical Faculty, University of Istanbul, Turkey, Istanbul, Turkey

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Background/Purpose: To assess the safety and efficacy of anakinra in pregnant FMF patients.

Methods: Six FMF patients, treated with anakinra during pregnancy were monitored for side effects, fetal and maternal outcomes.

Results: We present six FMF patients who were treated with Anakinra 100 mg/d sc during pregnancy due to severe protracted febrile myalgia in 4, thrombocytopenia in 1 and amyloidosis in 1. One of these patients has been previously reported (1). No anakinra-related adverse event was observed either in the mother-to-be or the fetus during pregnancy and delivery. One patient had an incision-site infection after c-section and one of the babies developed thrombocytopenia as his mother, and improved after treatment with IVIG. Four of these six patients gave birth to healthy babies and two are still pregnant . During the anakinra treatment, all patients recieved anakinra together with cholchicine, except one patient with thrombocytopenia was solely on Anakinra throughout pregnancy. No flare was observed in 3 out of 4 patients in whom Anakinra was was stopped after delivery. Pregnancy-related features are listed in Table 1.

Conclusion:

Anakinra promises to be a safe alternative in pregnant FMF patients who have active disease despite colchicine or intolerant and also can be given transiently during pregnancy and successfully stopped after delivery, as in our patients.

References:.

1) Lachman HJ, et al. Anti IL-1 therapies and pregnancy outcome. Pediatric Rheumatology 2013, 11 (Suppl 1) :A269

Table 1. Pregnancy-related outcomes

Case	Maternal Age	Anakinra Relation to pregnancy	USGs	Weeks at delivery or currrent gestational age	Gender of the baby/fetus	Mode of the delivery	1st minute APGAR	Follow-up duration after birth (months)	Complications after birth
1	33	started at 21st GW and used continiously until birth	normal	Birth at 36th GW	boy	C/S	8	34	No
2	28	started at 12th GW and used until birth	normal	Birth at 40th GW	girl	vaginal	10	22	No
3	31	Conceived on Anakinra (have been on Anakinra since 2012), discontinued at 29th GW, reintroduced at 33th GW due to symptom flare.	normal	Birth at 38th GW	boy	C/S	6	4	Methicillin-Sensitive Staphylococcus Aureus incision-site infection (treated with Tygecycline) in mother
4	24	started at 15th GW and used until birth	normal	Birth at 38th GW	boy	Vaginal	8	4	thrombocyte count of the baby was low (23,000/mm3) (After three courses of IVIG, it was increased to 95,000/mm3

									and a month later to 269,000/mm3)
5	32	started at 16th GW, still using	normal	At 22nd GW	Twin girls				
6	25	Started at 23th GW, still on Anakinra at 29th GW	normal	At 29th GW	girl				

Disclosure: H. Ozdogan, None; **S. Ugurlu**, None; **B. Ergezen**, None.

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Abstract Number: 260

Tocilizumab Is Effective in the Treatment of AA Amyloidosis Secondary to Familial Mediterranean Fever

Huri Ozdogan[1], Serdal Ugurlu[2], Aysa Hacioglu[2], Yasaman Adibnia[2] and Vedat Hamuryudan[2], [1]Division of Rheumatology, Department of Internal Medicine, Cerrahpasa Medical Faculty, University of Istanbul, Istanbul, Turkey, [2]Rheumatology, Division of Rheumatology, Department of Internal Medicine, Cerrahpasa Medical Faculty, University of Istanbul, Istanbul, Turkey

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Background/Purpose:

AA amyloidosis is the long-term complication of various chronic inflammatory diseases avoidable by the treatment of the underlying disease but with no established treatment once diagnosed. Recently there are few reports pointing out that tocilizumab (TCZ) may be effective in controlling AA amyloidosis.

We aim to demonstrate our data on the effect of TCZ in patients with AA amyloidosis secondary to FMF.

Methods:

The follow-up data of FMF patients with histologically proven AA amyloidosis, treated with TCZ (8 mg/kg/mo) is evaluated by assessing the changes in creatinine, creatine clearance, 24-hour urine protein, erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) values measured before and throughout the treatment period. Adverse effects of the treatment were closely monitored.

Results:

TCZ was given to 13 patients with AA amyloidosis secondary to FMF who were also on Colchicine (2.28 ± 0.48 mg/day). Two patients had coexisting ankylosing spondylitis, and one each had systemic lupus erythematosus and Crohn's disease. The mean age was 37.46±9.96 years, the mean disease duration of FMF was 24.15±7.65 and of amyloidosis was 5.52±4.98. The mean follow-up period on TCZ treatment was 12.92 ± 8.44 months. The mean creatinine levels decreased from 1.23±0.89 mg/dl to 1.07 ± 0.59 mg/dl ($p < 0.001$), mean creatine clearance increased from 97.66±54.35 ml/min to 108.46±64.17 ml/min ($p < 0.001$). Renal function was impaired in 4 patients which

improved significantly on TCZ therapy (creatinine from a mean of 2.33±0.76 mg/dl to 1.77±0.47 mg/dl, p=0.005; creatinin clearence from a mean of 37.52±4.51ml/min to 50.82±9.84ml/min, p<0.001). The median of 24-hour urinary protein excretion for the whole group was reduced from 3038.5 mg/dl (IQR 1771-6539) to 1710 mg/d (IQR 634-4953) (p=0.007). The mean level of CRP was reduced from 22.36±20.83 mg/dl to 5.71±5.98 mg/dl (p=0.002) as the mean ESR from 52.42±33.27 mm/h to 38.30±37.50 mm/h (p=0.003).

Twelve of the patients did not experience any FMF attack under TCZ treatment. TCZ was terminated in the patient with concommitant diagnosis of SLE and APLS who had ischemic chest pain after the 12th dose, and in another patient because of an increase in the frequency of attacks associated with erysipelas-like erythema and no decrease in proteinuria. Treatment was also stopped in two other patients; one who was an illicit user of synthetic cannabinoid who developed high blood pressure 5 days after a single infusion and the other who experienced diplopia after the 6th dose. Both of these patients' creatinine increased after termination of the therapy (from1,43mg/dl to 2.85mg/dl;from0.8mg/dlto 3.85mg/dl, respectively) leading them to the end stage renal disease. None of the patients developed infusion reactions.

Conclusion:

TCZ improves the acute phase response and the renal function impaired by amyloidosis secondary to FMF. Among this patient group TCZ treatment is well tolerated and not associated with serious side effects. Further studies are warrented to test the efficacy and safety of TCZ in AA amyloidosis secondary to FMF as well as other inflammatory conditions.

Disclosure: H. Ozdogan, None; **S. Ugurlu**, None; **A. Hacioglu**, None; **Y. Adibnia**, None; **V. Hamuryudan**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/tocilizumab-is-effective-in-the-treatment-of-aa-amyloidosis-secondary-to-familial-mediterranean-fever

Abstract Number: 261

Anakinra Treatment in Patients with Familial Mediterranean Fever: A Single-Center Experience

Serdal Ugurlu[1], Bilgesu Ergezen[2] and Huri Ozdogan[2], [1]Division of Rheumatology, Department of Internal Medicine, Cerrahpasa Medical Faculty, University of Istanbul, Turkey, Istanbul, Turkey, [2]Division of Rheumatology, Department of Internal Medicine, Cerrahpasa Medical Faculty, University of Istanbul, Istanbul, Turkey

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Session Time: 9:00AM-11:00AM

Background/Purpose: To review the patients followed in our center with FMF who received anakinra, an anti IL-1 receptor antagonist, because of insufficient colchicine response.

Methods: FMF patients who were treated with anakinra were retrospectively reviewed with regard to indication, effect on disease activity and acute phase response, adverse events. Patient global assessment was recorded before and after anakinra treatment.

Results:

There were 38FMF patients with FMF who were treated with anakinra for various indications (amyloidosis in 11, colchicine resistant recurrent febrile attacks in 22, colchicine related side effects in 5). Two patients were excluded since they have been on anakinra for less than one month (one with amyloidosis, one pregnant). The mean age of the group was 35.6±11.2 years. The mean duration of the disease was 23.1 ±12,0 years. There were various co-existing pathologies among this study group like multiple sclerosis (1), ankylosing spondylitis (1), SLE (1), Behçet's disease (1), low grade lymphoma (1) and PAN (2). Six patients were pregnant. The mean colchicine dose was 2,09±0,49 mg/d. The mean duration of anakinra treatment was 19.6± 13.2 months. Twenty seven patients reported no attacks after anakinra treatment whereas 5 patients reported at least 50% decrease in the attack frequency. Mean patient global assessment decreased from 8.75±2.1 to 1.72±2.6 under anakinra treatment (p=0.001).

Among the 10 patients with amyloidosis, anakinra was stopped in 2 patients because of increased proteinuria. However, a significant decrease in proteinuria was detected in 5 patients. One patient developed severe injection site reaction and therefore the drug was stopped. Overall, 7 of our patients with amyloidosis are still on Anakinra treatment.

Three patients had a severe allergic reaction (severe disseminated rash in 1 patient and severe injection site reaction in 2 patients) and therefore the drug was stopped. Two patients had infections (one had genital warts and urinary tract infection, the other had sinusitis and folliculitis) and the treatment was terminated. One of our patients reported that her psoriatic lesions got worse on anakinra. Twenty six patients reported no adverse events during the treatment.

Conclusion:

Anakinra was effective in controlling the symptoms in colchicine-resistant FMF cases. It was also effective in FMF related amyloidosis. The major cause of treatment termination was injection site reactions. Anakinra seems to be an effective alternative in patients who have insufficient response to colchicine.

Disclosure: S. Ugurlu, None; **B. Ergezen**, None; **H. Ozdogan**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/anakinra-treatment-in-patients-with-familial-mediterranean-fever-a-single-center-experience

Abstract Number: 262

Canakinumab Therapy in Patients with Familial Mediterranean Fever

Serdal Ugurlu[1], Emire Seyahi[2], Gulen Hatemi[2], Aysa Hacioglu[1], Humeyra Ozcan[1], Fatma Nihan Akkoc[1] and Huri Ozdogan[2], [1]Rheumatology, Division of Rheumatology, Department of Internal Medicine, Cerrahpasa Medical Faculty, University of Istanbul, Istanbul, Turkey, [2]Division of Rheumatology, Department of Internal Medicine, Cerrahpasa Medical Faculty, University of Istanbul, Istanbul, Turkey

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SESSION INFORMATION

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Session Title: Miscellaneous Rheumatic and Inflammatory Diseases Poster I

Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose:

It has been reported that Canakinumab reduced the frequency of attacks in patients with Familial Mediterranean Fever (FMF) resistant to colchicine with no apparent side effects.

We present our experience with Canakinumab in FMF patients resistant or intolerant to colchicine.

Methods:

The charts of the patients with FMF who were on Canacinumab were evaluated retrospectively with regard to response and safety.

Results:

There were 36 patients with FMF (19 F/17 M) receiving canakinumab for various indications. We report 32 (17 F/15 M) who had at least 3 injections. Six patients had concomitant diseases such as psoriasis (1), AS (4), PAN (1), AS and PAN (1) and vasculitis(1). The indications for canakinumab (150mg/mo) were insufficient response to colchicine in 22 (>1 attack/month), amyloidosis in 6, injection site reaction to anakinra in 6 and adverse effects of colchicine (azoospermia in 1, neuropathy in 1, hepatotoxicity in 1, myopathy in 2 patients). The mean age of the patients was 35,71 ± 12,82 years, the mean duration of FMF was 14,87 ± 9,19 years, the mean injection number was 10,53 ± 7,06 and the mean duration of canakinumab therapy was 16,81 ± 10,46 months. Twenty five of the patients had no attacks after canakinumab, 5 patients' attack frequency was reduced more than %50 while two patient's attack frequency remained more than %50. In 6 cases with FMF amyloidosis, proteinuria decreased in 2 (from 15020mg/dl to 364mg/dl and from 6135mg/dl to 280mg/dl), increased in the other 2 (from 1700mg/dl to 4700mg/dl and from 5001mg/dl to 7061mg/dl), and did not change in the remaining 2. Fourteen patients complaining of severe myalgia and calf pain unresponsive to colchicine treatment improved significantly. According to patient global assessment the mean score decreased from 8,18 ± 2,48 to 1,53 ± 2,43 ($p<0.001$). Canacinumab was stopped because of remission (no attacks at least for 3 months) in 5, for pregnancy demand in 1, for unresponsiveness in 2, for increasing proteinuria in 2, and the treatment was also stopped in the patient with oligospermia after being fertile.

Attacks recurred after 4, 7, 12, 12 months from discontinuation of the therapy in 4 patients, and 3 patients are attack-free for 12, 17 and 17 months till now.

Canakinumab was well tolerated in general. None of the patients had injection site reactions. The patient with psoriasis reported a flare in psoriatic plaques, which responded to local treatment. Therapy was discontinued temporarily in one patient who developed mild leucopenia, which did not reccur on a 2-monthly regimen. One other patient with amyloidosis whose proteinuria was stable, developed lichen planus lesions and the treatment had to be stopped. One patient had pneumonia, also he is attack-free for 15 months untill last dose.

Conclusion:

Canacinumab is effective in controlling the attacks in patients with inadequate response to colchicine and may serve as a treatment alternative with a favorable side effect profile. For better understanding the drug's efficacy and safety in the long term there is a need for controlled trials.

Disclosure: S. Ugurlu, None; **E. Seyahi**, None; **G. Hatemi**, None; **A. Hacioglu**, None; **H. Ozcan**, None; **F. N. Akkoc**, None; **H. Ozdogan**, None.

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Abstract Number: 263

Use of Serum Ferritin and Heme Oxygenase 1 for the Diagnosis of Adult-Onset Still's Disease: A Preliminary Report of Multicenter Study

Yohei Kirino[1], Yasushi Kawaguchi[2], Yoshifumi Tada[3], Seiji Minota[4], Toshiyuki Ota[5], Kohei Nagasawa[6], Hiroshi Tsukamoto[7], Syuji Takei[8,9], Takahiko Horiuchi[10], Hiroki Takahashi[11], Hisae Ichida[2], Masahiro Iwamoto[4], Atsuhisa Ueda[1], Akihide Ohta[12], Yoshiaki Ishigatsubo[1,13] and Hypercytokinemia Study Group, [1]Department of Internal

Medicine and Clinical Immunology, Yokohama City University Graduate School of Medicine, Yokohama, Japan, [2]Institute of Rheumatology, Tokyo Women's Medical University, Tokyo, Japan, [3]Department of Internal Medicine, Division of Rheumatology, Saga University, Saga, Japan, [4]Department of Internal Medicine, Division of Rheumatology/Clinical Immunology, Jichi Medical University, Shimotsuke, Japan, [5]Department of Rheumatology, Iizuka Hospital, Iizuka, Japan, [6]Rheumatic Disease Center, Sawara Hospital, Fukuoka, Japan, [7]First Dept of Internal Med, Kyushu University, Fukuoka, Japan, [8]School of Health Sciences, Faculty of Medicine,, Kagoshima University, Kagoshima City, Japan, [9]School of Health Sciences, Faculty of Medicine, Kagoshima University, Kagoshima, Japan, [10]Department of Internal Medicine, Kyushu University Beppu Hospital, Beppu, Japan, [11]epartment of Gastroenterology, Rheumatology and Clinical Immunology, Sapporo Medical University School of Medicine, Sapporo, Japan, [12]Department of Adult and Gerontological Nursing, Saga University School of Medicine, Saga, Japan, [13]Yokosuka Rheumatic Diseases Center, Yokosuka City Hospital, Yokosuka, Japan

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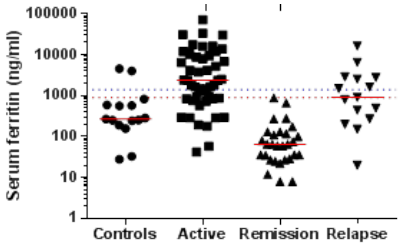
Session Type: ACR Poster Session A
Session Time: 9:00AM-11:00AM

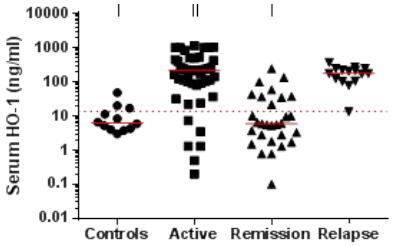
Background/Purpose: Yamaguchi's criteria for classification of adult-onset Still's disease (AOSD) has been widely applied in clinic despite it was established decades ago. However, hyperferritinemia, which is a hallmark of AOSD, is not included in the criteria. Moreover, the criteria require differential diagnosis of malignancy, infection, etc., which has been challenging. Heme oxygenase (HO)-1 is stress-inducible heme degrading enzyme highly expressed in monocyte/macrophage, serum levels of which has been reported as a promising biomarker for AOSD. We here report preliminary data on serum ferritin and HO-1 levels and AOSD disease activity.

Methods: Under the Hypercytokinemia Study Group collaboration, we collected sera from a total of 111 AOSD cases. Those patients were further divided into active, remission, and relapse groups, based on their clinical status. Other rheumatic diseases such as ANCA-associated vasculitis, and culture-positive sepsis were included as disease controls. Serum ferritin and HO-1 levels were measured in all of the collected samples by means of ELISA. An association among clinical symptoms, serum ferritin, and HO-1 was explored.

Results: Serum ferritin and HO-1 levels were significantly higher in active and relapsed AOSD cases compared to disease controls, and were reduced by the treatment. Although significant correlation between serum ferritin and HO-1 levels were observed, there were some discrepancies. After remission-induction therapy, 72.2% of the patients' serum ferritin levels were normalized, but 61.1% of them had high serum HO-1 levels (>13.8 ng/ml). Moreover, 31% of patients in remission exhibited high HO-1 levels, but high ferritin levels were observed only in 6.9% of the patients (figure).

Conclusion: We confirmed that serum ferritin and HO-1 serve as a biomarker for AOSD. Characterization of serum ferritin and HO-1 levels in AOSD disease status merit further investigation. By enrolling more cases and disease controls, we plan to determine use of ferritin and HO-1 for the diagnosis of AOSD (UMIN000012912).





None; **H. Takahashi**, None; **H. Ichida**, None; **M. Iwamoto**, Astellas Pharma, 8,Takeda Phamaceutical, 8; **A. Ueda**, None; **A. Ohta**, None; **Y. Ishigatsubo**, None.

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Abstract Number: 264

Clinical Phenotype and Response to Treatment in Adult-Onset Still's Disease with MEFV Variants

Fumiaki Nonaka[1], Toshimasa Shimizu[2], Katsumi Eguchi[3], Masataka Umeda[4], Yukitaka Ueki[5], Keita Fujikawa[6], Akinari Mizokami[7], Munetoshi Nakashima[8], Michio Yasunami[9], Naoki Iwamoto[4], Atsushi Kawakami[2], Yuka Jiuchi[10] and Kiyoshi Migita[10], [1]Department of Rheumatology and Metabloism, Sasebo City General Hospital, Sasebo, Japan, [2]Department of Immunology and Rheumatology, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan, [3]Department of Rheumatology, Sasebo Chuo Hospital, Sasebo, Japan, [4]Department of Immunology and Rheumatology, Nagasaki University, Nagasaki, Japan, [5]Kyushu multicenter rheumatoid arthritis ultrasound prospective observational cohort study group, Nagasaki, Japan, [6]Arthritis and Connective Tissue Disease, Isahaya Health Insurance General Hospital, Isahaya, Japan, [7]Department of Rheumatology, Isahaya Health Insurance General Hospital, Isahaya, Japan, [8]Department of Rheumatology, Japanese Red Cross Nagasaki Genbaku Hospital, Nagasaki, Japan, [9]Nagasaki University Institute of Tropical Medicine (NEKKEN), Nagasaki, Japan, [10]Department of Rheumatology and Clinical Research Center, Nagasaki Medical Center, Omura, Japan

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Session Time: 9:00AM-11:00AM

Background/Purpose:

Adult-onset Still's disease (AOSD) is a rare inflammatory disorder that has been recently classified as a polygenic autoinflammatory disorder. Patients with Familial Mediterranean Fever (FMF) share clinical features (eg. recurrent fever, skin rash, synovitis and serositis) with the major symptoms of AOSD. FMF is considered to be caused by gain-of-function mutations in the MEFV gene. Although the pathophysiology of AOSD remains unknown, a growing number of studies support the hypothesis that dysregulation of inflammasome activation and subsequent overproduction of interleukin-1β play a pivotal role. The aim of this study was to investigate the allele frequencies of MEFV gene variants and identify clinical phenotypes as well as responses to treatments of AOSD patients with MEFV variants.

Methods:

A retrospective analysis was performed in 50 patients (9 males and 41 females) diagnosed with AOSD based on the diagnostic criteria of Yamaguchi M, et al. and 105 healthy individuals who were enrolled as controls. The study protocol was approved by the institutional review board/ethics committee of Sasebo City General Hospital. Written

informed consent was obtained from each individual for their clinical records to be used in this study. Genetic DNA was extracted from peripheral blood, and exon1, 2, 3 and 10 of the MEFV gene were genotyped by direct sequencing. MEFV mutation frequencies in AOSD patients were compared with controls. Furthermore, clinical features and responses for treatments were examined in patients with or without MEFV variants.

Results:

MEFV variants were identified in 32 AOSD patients (64.0%). No significant difference was found statistically between AOSD patients and healthy subjects in terms of allele frequencies of MEFV exon1 (E84K), exon2 (L110P, E148Q, R202Q, and G304R) and exon3 (P309S and R408Q) variants. However, the carriage rate of exon10 MEFV variants (M694I and G632S) was significantly higher in AOSD patients than that of healthy subjects (6.1% versus 0%, p=0.031). The polycyclic and systemic clinical courses of AOSD disease phenotype were frequently observed in patients with MEFV variants. Biologic agents were administered to 7 patients with MEFV exon2 and/or exon3 variants who were refractory to conventional treatments such as steroid, steroid pulse and immuosuppressants. Six of them were treated with tocilizumab; one was treated with infliximab. All patients except one demonstrated rapid improvement in both clinical and laboratory parameters. The median dosage of prednisolone was reduced. However, one patient treated with tocilizumab developed macrophage activation syndrome.

Conclusion:

Our study provides preliminary evidence that FMF-related MEFV variants may be clinically implicated with the disease phenotype and treatment outcomes of AOSD. Therefore, identification of MEFV variants is beneficial to define clinical phenotypes and predict clinical responses to treatments.

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View Abstract and Citation Information Online - http://acrabstracts.org/abstract/clinical-phenotype-and-response-to-treatment-in-adult-onset-stills-disease-with-mefv-variants

Abstract Number: 265

Tocilizumab Compared with Anakinra in Refractory Adult-Onset Still's Disease. Multicenter Study of 75 Patients

Leyre Riancho-Zarrabeitia[1], Vanesa Calvo-Río[1], Ricardo Blanco[1], Jose L. Hernández[2], Francisco Ortiz-Sanjuán[1], Alejandro Olivé[3], Anne Riveros Frutos[4], Santos Castañeda[5], Javier Narváez[6], Maria Luisa Velloso Feijoo[7], M. Victoria Hernández[8], Alberto Sifuentes Giraldo[9], Olga Maiz-Alonso[10], Esteban Rubio Romero[11], Cristina Mata-Arnaiz[12], Adela Gallego Flores[13], Jordi del Blanco[14], Catalina Gómez-Arango[15], Sara Manrique-Arija[16], Maria Carmen Ordoñez[17], Inmaculada Ros Vilamajo[18], Miguel Angel Caracuel-Ruiz[19], Mercedes Freire[20], Jose Llobet[21], Carlos Marras[22], Concepción Moll Tuduri[23], Chamaida Plasencia[24], Rosa Roselló[25], Ana Urruticoechea[26], Inmaculada Jiménez-Moleón[27], José Antonio Bernal[28], Vera Ortiz-Santamaría[29], Juan Ramón De Dios[30], Mireia Moreno[31], Jordi Fiter[32], Marina de los Riscos[33], Patricia E. Carreira[33], María José Rodríguez Valls Sr.[34], Carmen Gonzalez-Vela[35], Javier Loricera[1], Natalia Palmou[1] and Miguel Angel Gonzalez-Gay[1], [1]Rheumatology, Hospital Universitario Marqués de Valdecilla. IDIVAL, Santander, Spain, [2]Internal Medicine, Hospital Universitario Marqués de Valdecilla. IDIVAL, Santander, Spain, [3]Rheumatology, Hospital U German Trias i Pujol, Badalona, Spain, [4]Rheumatology, Hospital Universitari Germans Trias i Pujol, Barcelona, Spain, [5]Rheumatology, H.U. La Princesa, Madrid, Spain, [6]Rheumatology, Hospital Universitario de Bellvitge, Barcelona, Spain, [7]H Valme, Sevilla, Spain, [8]Arthritis Unit, Rheumatology, Hospital Clinic, Barcelona, Spain, [9]Department of Rheumatology, University Hospital

Ramón y Cajal, Madrid, Spain, [10]Rheumatology, HU Donostia, San Sebastián, Spain, [11]Rheumatology Department,, Hospital Universitario Virgen del Rocío, Sevilla, Spain, [12]Rheumatology, Hospital Laredo, Santander, Spain, [13]Rheumatology, Hospital de Mérida, Mérida, Spain, [14]Rheumatology, H Sant Jaume, Calella, Spain, [15]Rheumatology, Hospital Basurto,, Santander, Spain, [16]Rheumatology, Hospital Universitario Carlos Haya, Malaga, Spain, [17]HRU Carlos Haya, Malaga, Spain, [18]Hospital Son Llàtzer, Palma de Mallorca, Spain, [19]Plaza Cruz Roja, 1, Hospital Reina Sofia, Córdoba, Spain, [20]Hospital Universitario Juan Canalejo, La Coruña, Spain, [21]Hospital San Pau, Barcelona, Spain, [22]Hospital Universitario Virgen de la Arrixaca, Murcia, Spain, [23]H Mateu Orfila, Mahón, Spain, [24]Rheumatology Unit, La Paz University Hospital-Rheumatology, Madrid, Spain, [25]H San Jorge, Huesca, Spain, [26]Hospital Can Misses, Ibiza, Spain, [27]Rheumatology, Hospital San Cecilio, Granada, Spain, [28]Sección de Reumatología, Hospital General Universitario de Alicante, Alicante, Spain, [29]Rheumatology, Hospital General. Granollers., Granollers, Spain, [30]Rheumatology, HU Álava, Vitoria, Spain, [31]Hospital de Sabadell - Institut Universitari Parc Taulí, Sabadell, Spain, [32]Rheumatology, HU Son Espases. Palma de Mallorca., Palma de Mallorca, Spain, [33]Rheumatology, Hospital Universitario 12 de Octubre, Madrid, Spain, [34]Rheumatology, Rheumatolgy Unit. Hospital Jerez, Jerez, Spain, [35]Pathology, Hospital Universitario Marqués de Valdecilla. IDIVAL, Santander, Spain
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Background/Purpose: Interleukin (IL)-1 and IL-6 are pivotal cytokines in the pathogenesis of adult-onset Still's disease (AOSD). Our aim was to compare the efficacy and safety of tocilizumab (TCZ) versus anakinra (ANK) given for at least 1 year to AODS patients refractory to conventional treatment.

Methods: Multicenter study (31 hospitals) of 75 patients (TCZ; n=34 and ANK; n 41) with AODS refractory to conventional immunosuppressive drugs and in many cases also to other biological agents.

Results: Comparisons of the group of patients with TCZ and ANK were: a) Average age: 39±16 vs. 34±14 years (p=0.2) b) Percentage of women: 76.5% vs. 63.4% (p=0.2) c) Median disease duration 4.2 [1-9] vs. 2.2 [0.3 to 4.9] years (p=0.14) d) Average dose of prednisone 15±9.9 mg/day vs. 28.3±22 mg/day (p=0.013) e) Median of conventional

immunosuppressants (2 [1-3] vs 1 [1-2] (p=0.05) f) Median of other biological therapies: 1 [0-2] vs. 0 [0-1] (p=0.04). The initial dose of i.v. TCZ were: 8 mg/kg/4 weeks (n=22), 8 mg/kg/2 weeks (n=10) and 4 mg/kg/4 weeks (n=2). ANK dose was 100 mg/day s.c. Both biologic agents were often combined with a conventional immunosuppressive drug (55.9% vs 70.7%; p=0.2). Both biologi agents yielded a quick and sustained improvement of all clinical and laboratory parameters (Table). The improvement in the clinical parameters was similar in both groups. However an earlier improvement of CRP and ESR was observed following TCZ therapy. After a median follow-up of 19 months [12-31] with TCZ and 15.5 months [4.5 to 50] with ANK (p=0.1), the major adverse effects in the TCZ group were: elevation liver enzymes (n=4), mild to

moderate leucopenia (4), upper respiratory tract infection (3), pneumonia (1), pyelonephritis and severe enterocolitis (1) and spondylodiscitis (1). In the group of ANK: skin lesions (n=8), mild leucopenia (3), myopathy (1), respiratory infection by P. aeruginosa and gluteal abscess (1), herpes zoster (1), osteomyelitis (1) and infection of urinary tract (2). While none of the TCZ-treated required discontinuation of the drug due to inefficacy, ANK had to be discontinued for this reason in 11 patients (p=0.001). Adverse effects leading to discontinuation of the drug were observed in 2 patients with TCZ and 4 patients with ANK (p=0.54).

Conclusion: TCZ and ANK are associated with a rapid and sustained clinical improvement in most patients with

refractory AODS. However, TCZ appears to be more effective than ANK.

TABLE. Clinical manifestations and laboratory parameters (patients with TCZ vs. ANK)

	Basal TCZ (34) / ANK (41)	1 Month TCZ (34) / ANK (41)	3 Months TCZ (34) / ANK (37)	6 Months TCZ (34) / ANK (32)	12 Months TCZ (32) / ANK (27)
Fever, %	58.8 / 78 #	5.9 / 17.1	5.9 / 10.8	5.9 / 0	5.9 / 7.4
Articular, %	97.1 / 87.8	67.6 / 48.7	44.1 / 34.1	26.5 / 28.1	32.4 / 29.6
Rash,%	58.8 / 58.5	5.9 / 9.8	5.9 /10.8	5.9 / 0	5.9 / 3.7
Lymphadenopathy and/or visceromegalies, %	25 / 39	19 / 23	0 / 14	0 / 6	0 / 4
CRP (mg/dl) median [IQR]	8.9 [3.9-23.2] / 8.9 [4.4-14.9]	0.2 [0.1-1.6] / 1.1 [0.13-3.8] *	0.1 [0.01-0,7] / 0.62 [0.1-1.5] *	0.2 [0.01-0.9] / 0.5 [0.2-1.3] *	0.2 [0.03-1.1] / 0.3 [0.06-1.3] *
ESR 1st hr, median [IQR]	52 [45-69] / 60.5 [39-87]	4 [2-12] / 16.5 [10-37] *	4 [2-9] / 16 [6-30] *	4 [2-8] / 8 [4-20] *	2 [2-12] / 6 [2-18]
Leukocytes/mm3, mea± SD	13534±6023 / 15121±7752	8983±4550 / 8101±3655	8044±4360 / 7808±3002	7579±3588 / 7844±2297	8683±3658 / 7843±2703
Anemia, Hb (g/dl), mean ±SD	11.9±1.36 / 10.9±2.07	12.9±1.2 / 12.2±2.03	13.3±1.1 / 12.86±2.13	13.3±1.3 / 13.37±1.6	14±1.3 / 13.7±1.5
Ferritin (ng/ml), median [IQR]	480 [200-808] / 998 [196-4212]	239 [39-358] / 456 [55-1182]	100 [73-132] / 121 [24-353]	107 [53-187] / 179 [52-339]	90 [63-115] / 125 [58-253]

Disclosure: L. Riancho-Zarrabeitia, None; **V. Calvo-Río**, None; **R. Blanco**, None; **J. L. Hernández**, None; **F. Ortiz-Sanjuán**, None; **A. Olivé**, None; **A. Riveros Frutos**, None; **S. Castañeda**, None; **J. Narváez**, None; **M. L. Velloso Feijoo**, None; **M. V. Hernández**, None; **A. Sifuentes Giraldo**, None; **O. Maiz-Alonso**, None; **E. Rubio Romero**, None; **C. Mata-Arnaiz**, None; **A. Gallego Flores**, None; **J. del Blanco**, None; **C. Gómez-Arango**, None; **S. Manrique-Arija**, None; **M. C. Ordoñez**, None; **I. Ros Vilamajo**, None; **M. A. Caracuel-Ruiz**, None; **M. Freire**, None; **J. Llobet**, None; **C. Marras**, None; **C. Moll Tuduri**, None; **C. Plasencia**, None; **R. Roselló**, None; **A. Urruticoechea**, None; **I. Jiménez-Moleón**, None; **J. A. Bernal**, None; **V. Ortiz-Santamaría**, None; **J. R. De Dios**, None; **M. Moreno**, None; **J. Fiter**, None; **M. de los Riscos**, None; **P. E. Carreira**, None; **M. J. Rodríguez Valls Sr.**, None; **C. Gonzalez-Vela**, None; **J. Loricera**, None; **N. Palmou**, None; **M. A. Gonzalez-Gay**, None.

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Abstract Number: 266

Effect of Tocilizumab on Adults Onset Still's Disease in Korean Population: Multicenter Retrospecitve Study of 24 Cases

Seung Taek Song[1], Jin Ju Kim[2], Seung Lee[1], Hye-Jin Jeong[1], Il Woong Sohn[2], Sung Won Lee[2], Joo Hyun Lee[3], Hyoun-Ah Kim[4], Kwang-Hoon Lee[5], Sang Tae Choi[6], Eun Young Lee[7], Kichul Shin[8], Hoon-Suk Cha[9] and Dae-Hyun Yoo[10], [1]Hanyang University Hospital for Rheumatic Diseases, Seoul, South Korea, [2]Department of Rheumatology, Hanyang University Hospital for Rheumatic Diseases, Seoul, South Korea, [3]Department of Rheumatology, Ilsan Paik Hospital, Inje University, Goyang, South Korea, [4]Ajou University Hospital, Suwon, South Korea, [5]Dongguk University Ilsan Hospital, Goyang, South Korea, [6]Internal Medicine, Chung-Ang University College of Medicine, Seoul, South Korea, [7]Internal Medicine, Seoul National University College of Medicine, Seoul, South Korea, [8]Seoul National University College of Medicine, Seoul, South Korea, [9]Division of Rheumatology, Department of Internal Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea, [10]Division of Rheumatology, Department of Internal Medicine, Hanyang University Hospital for Rheumatic Diseases, Seoul, South Korea

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Background/Purpose: Adult onset Still's disease (AOSD) is a rare inflammatory disorder of unknown etiology. Nonsteroidal anti-inflammatory drugs or corticosteroids are first-line drugs for treating AOSD. Immunosuppresants are needed to patients who are refractory to corticosteroids. Recently, it has been reported that biologic agents in AOSD are effective. Although IL-1 targeting therapy is very effective, an anti-interleukin-6 receptor monoclonal antibody may be an effective agent especially in the countries where anti-IL-1 therapy is not easily available. In this study, we reviewed the effect of tocilizumab (TCZ) on AOSD in Korean patients, retrospectively.

Methods: 24 AOSD patients were collected from 7 centers in Korea. The response to TCZ was defined as decreased modified Pouchot's score more than 2 score with decreased acute phase reactants compared to initial treatment of TCZ at least two consecutive months. We used the one-way ANOVA (or Krusal-Wallis test) for continuous variable and chi-square test for trend for categorical variables.

Results:

Patients (18 women/6 men) had a mean age of 44.0 ± 18.4 years and the age of diagnosis was 37.4 ± 20.6 years old. The mean disease duration before TCZ treatment was 48.43 ± 43.7 months. Eleven patients (45.8%) had polycyclic systemic pattern and twelve patients (50.0%) had chronic articular pattern. One patient couldn't be classified due to short disease duration.

Immune modulating agents before TCZ therapy were as follows: methotrexate (n=17), leflunomide (N=6), cyclosporine (n=4) and hydroxychloroquine (n=3). Biologic agents before TCZ therapy were etanercept (N=8), infliximab (n=6), adalimumab (n=4), abatacepts (n=2) and anakinra (n=1). At the time of TCZ treatment, the most frequent clinical manifestation was arthritis (79.2%). Rash (41.7%), fever (41.7%), myalgia (33.3%), and sore throat (20.8%) were accompanied. The baseline laboratory parameters such as leukocytosis, ESR, CRP and serum ferritin showed high level. The mean dosage of TCZ was 6.9 mg/kg (4-8 mg/kg) per 4 weeks and mean duration of TCZ administration was 8.4 ± 6.8 months. The majority of patients showed clinical or laboratory improvement after TCZ therapy. Although the dosage of prednisolone was reduced with clinical improvement at 6th month and 12th month, statistical significance was not showed (Table 1).

In 25.0 % of patients adverse events occurred during TCZ treatment as follows: leukopenia (n=1), gastrointestinal symptoms (n=2), infusion reaction (n=2), and pulmonary tuberculosis (n=1). Four patients (16.7%) relapsed after 5.0±3.6 months of discontinuation of TCZ.

Table 1. Change of clinical manifestations and laboratory parameters before and after TCZ treatment			
	Baseline (N=24)	After 6 months (N=17)	After 12 months (N=11)
Fever*	10(41.7)	1(5.9)	1(9.1)
Sore throat	5(20.8)	1(5.9)	0(0.0)
Rash*	10(41.7)	2(11.8)	1(9.1)
Itching	7(29.2)	2(11.8)	1(9.1)
Myalgia**	8(33.3)	0(0.0)	0(0.0)
Arthralgia/arthritis	19(79.2)	11(64.7)	8(72.7)
Lymphadenopathy	2(8.3)	0(0.0)	0(0.0)
Splenomegaly	2(8.3)	1(5.9)	0(0.0)
Serositis	3(12.5)	0(0.0)	0(0.0)
Modified Pouchot's Score, mean±SD	3.0 ± 1.9	1.3 ± 1.2	1.1 ± 0.7
Leukocytosis, mean±SD	14081.3 ± 6597.3	11810.0 ± 6712.8	12784.6 ± 6741.0
ESR (mm/hour), mean ±SD**	64.7 ± 29.0	14.2 ± 20.0	23.6 ± 29.3
CRP (mg/dL), mean±SD*	5.0 ± 4.2	1.7 ± 2.8	4.6 ± 6.4
Ferritin (ng/mL), mean ±SD	1440.2 ± 2027.3	374.3 ± 857.0	302.6 ± 340.0
Prednisolone dose (mg/day), mean±SD	15.4 ± 10.0	6.8 ± 4.4	7.8 ± 3.0
Values are the number (%), *p < 0.05, **p < 0.005			

Conclusion: TCZ was effective in Korean AOSD patients who were refractory to conventional therapy or other biologic agents. However, larger and prospective study is needed for further investigation.

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Abstract Number: 267

Association of CXCL10 and CXCL13 Levels with Disease Activity and Cutaneous Manifestation in Active Adult-Onset Still's Disease

Hyoun-Ah Kim[1], In Je Kim[2], Jae Ho Han[3], Chang-Hee Suh[1] and Juyang Jung[1], [1]Department of Rheumatology, Ajou University School of Medicine, Suwon, South Korea, [2]Division of Rheumatology, Department of Internal Medicine, Ewha Womans University School of Medicine, Seoul, South Korea, [3]Department of Pathology, Ajou University School of Medicine, Suwon, South Korea

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Background/Purpose: CXCL10 is produced in response to interferon-γ, and tumor necrosis factor-α (TNF-α) triggers the accumulation of activated lymphocytes. CXCL13 is constitutively expressed in secondary lymphoid tissues, and the expression is upregulated by TNF-α, via T cell stimulation. It appears that CXCL10 and CXCL13 could play a potential role in the pathogenesis of adult-onset Still's disease (AOSD), therefore, we investigated the associations between CXCL10 and CXCL13 levels and clinical manifestations in patients with active AOSD.

Methods: Blood samples were collected from 39 active AOSD patients and 40 healthy controls (HC). Of the AOSD patients, follow-up samples were collected from 15 9.6 ± 9.2 months later. CXCL10, CXCL13, and CXCR3 expression levels in biopsy specimens obtained from 26 AOSD patients with skin rashes were investigated via immunohistochemistry.

Results: The CXCL10 level of AOSD patients (1,031.3 ± 2,019.6 pg/mL) was higher than that of HC (104.4 ± 47.9 pg/mL, p=0.006). Also, the CXCL13 level of AOSD patients (158.8 ± 151.2 pg/mL) was higher than that of HC (23.5 ± 18.1 pg/mL, p<0.001). Serum CXCL10 levels correlated with ferritin and systemic scores. Serum CXCL13 levels correlated with those of hemoglobin, C-reactive protein, ferritin, and albumin, and systemic scores. In follow-up AOSD patients, the levels of CXCL10 and CXCL13 fell significantly (153.7 ± 130.1 pg/mL, p=0.002, and 89.1 ± 117.4 pg/mL, p=0.001, respectively). On immunohistochemistry, the percentages of inflammatory cells expressing CXCL10 ranged from 1 to 85%, CXCL13 from 1 to 72%, and CXCR3 from 2 to 65%. The percentage of CXCL10-positive inflammatory cells was higher in skin biopsy samples exhibiting mucin deposition than in those that did not (p=0.01). CXCL13 levels were correlated with those of CD4 and CD68.

Conclusion: Serum CXCL10 and CXCL13 levels may serve as clinical markers for assessment of disease activity in AOSD. CXCL10/CXCR3 and CXCL13 may contribute to the inflammatory response, especially skin manifestations thereof, in AOSD.

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Abstract Number: 268

TLR4 Endogenous Ligand S100A8/A9 Levels in Adult-Onset Still's Disease and Their Association with Disease Activity and Clinical Manifestations

Hyoun-Ah Kim[1], In Je Kim[2], Jae Ho Han[3], Juyang Jung[4], Chang-Hee Suh[4] and You-Sun Kim[5], [1]Department of Rheumatology, Ajou University School of Medicine, Suwan, South Korea, [2]Division of Rheumatology, Department of Internal Medicine, Ewha Womans University School of Medicine, Seoul, South Korea, [3]Department of Pathology, Ajou University School of Medicine, Suwon, South Korea, [4]Department of Rheumatology, Ajou University School of Medicine, Suwon, South Korea, [5]Department of Biochemistry and Molecular biology, Ajou University School of Medicine, Suwon, South Korea

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Background/Purpose: S100A8 and S100A9 are two calcium-binding proteins that belong to the S100 family, and those are expressed by infiltrating monocytes and neutrophils under inflammatory conditions. S100A8/A9 has been suggested as biomarkers of disease activity in patients with systemic juvenile idiopathic arthritis or adult-onset Still's disease (AOSD). We investigated the clinical significance and the pathogenic role of this marker in AOSD.

Methods: Serum samples were prospectively collected from 20 active AOSD patients, 20 rheumatoid arthritis (RA), and 20 healthy controls (HC). S100A8/A9 expression levels in biopsy specimens obtained from 26 AOSD patients with skin rashes and 8 AOSD with lymphadenopathy were investigated via immunohistochemistry. Each marker was recorded as the numbers of positive inflammatory cells divided by the numbers of total inflammatory cells, then expressed as a graded on a scale from 1 to 3: 1,1-33%; 2, 34-66%,; 3, 67-100%. Peripheral blood mononuclear cells (PBMC) from active AOSD and HC were evaluated for interleukin-1β (IL-1β) release, and in vitro study with PBMC and human acute monocytic leukemia (THP-1) cell line was done for cell signal of S100A9 or S100A8/A9.

Results: S100A8/A9 levels of active AOSD (15.43 ± 7.3 μg/mL) were higher than those of RA (4.04 ± 4.18 μg/mL, $p<0.001$) and HC (2.01 ± 1.06 μg/mL, $p<0.001$). The IL-1β and TNF- α levels of AOSD were higher than those of HC. Serum S100A8/A9 levels correlated with IL-1β (r=0.603, p<0.001), TNF- α (r=0.405, p=0.009), ferritin (r=0.698, p<0.001), and CRP (r=0.811, p<0.001). The grade of inflammatory cells expressing S100A8/A9 ranged variably from 1 to 3 in skin and lymph node biopsies of active AOSD. The grading and strength of staining of the positive cells in S100A8/A9 was more intense for karyrrhexis (p=0.028), mucin deposition (p=0.014), and neutrophil infiltration (p=0.006). S100A9 in serum of patients with AOSD was a strong inducer of IL-1β expression in PBMC. S100A9 induced signal transduction pathways, including JNK and p38 in PBMC from AOSD patients and HC.

Conclusion: The data suggest that S100A8/A9 may contribute to the inflammatory response by induction of inflammatory cytokines, and serve as clinicopathologic markers for assessment of disease activity in AOSD.

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Abstract Number: 269

Items of Yamaguchi Criteria Might be Associated with Disease Severity and Prognosis in Adult-Onset Still's Disease

Umut Kalyoncu[1], Dilek Solmaz[2], Hakan Emmungil[3], Ayten Yazici[4], Timucin Kasifoglu[5], Gezmis Kimyon[6], Ayse Balkarli[7], Cemal Bes[8], Mustafa Ozmen[9], Fatma Alibaz-Oner[10], Sukran Erten[11], Yonca Cagatay[12], Gozde Cetin[13], Sedat Yılmaz[14], Fatih Yildiz[15], Omer Nuri Pamuk[16], Orhan Kucuksahin[17], Levent Kilic[1], Abdulsamet Erden[1], Veli Yazisiz[18], Omer Karadag[1], Suleyman Serdar Koca[19], Mutlu Hayran[20], Servet Akar[2], Kenan Aksu[21], Nurullah Akkoc[22], Gokhan Keser[23], Emel Gonullu[24], Bunyamin Kisacik[25], Ahmet Mesut Onat[25], Mehmet Soy[26], Nevsun Inanc[27], Haner Direskeneli[28], Mehmet Sayarlioglu[29], Eren Erken[30], Murat Turgay[31], Ayse Cefle[32], Ihsan Ertenli[1] and Salih Pay[33], [1]Rheumatology, Hacettepe University Faculty of Medicine, Ankara, Turkey, [2]Rheumatology, Dokuz Eylül University Faculty of Medicine, Izmir, Turkey, [3]Rheumatology, Ege University Faculty of Medicine, Izmir, Turkey, [4]Rheumatology, Kocaeli University, Faculty of Medicine, Kocaeli, Turkey, [5]Rheumatology, Eskisehir Osmangazi

University School of Medicine, Eskisehir, Turkey, [6]Department of Rheumatology, Gaziantep University School of Medicine, Gaziantep, Turkey, [7]Department of Rheumatology, Pamukkale University School of Medicine, Denizli, Turkey, [8]Rheumatology, Bolu Izzet Baysal School of Medicine, Bolu, Turkey, [9]Rheumatology, Izmir Ataturk Research and Training Hospital, Izmir, Turkey, [10]Department Rheumatology, Marmara University Faculty of Medicine, Istanbul, Turkey, [11]Rheumatology, Ataturk Training and Research Hospital, Ankara, Turkey, [12]Department of Rheumatology, Bilim University Faculty of Medicine, Istanbul, Turkey, [13]Rheumatology, Sutcu Imam University Faculty of Medicine, Kahramanmaras, Turkey, [14]PsART study group, Ankara, Turkey, [15]Rheumatology, Cukurova University, School of Medicine, Adana, Turkey, [16]Department of Rheumatology, Trakya University Medical Faculty, Edirne, Turkey, [17]Rheumatology, Yildirim Beyazit University School of Medicine, Ankara, Turkey, [18]Rheumatology, Akdeniz University School of Medicine, Antalya, Turkey, [19]İnternal Medicine Division of Rheumatology, Firat University, Faculty of Medicine, Elazig, Turkey, [20]Preventive Oncology, Hacettepe University Faculty of Medicine, Ankara, Turkey, [21]Rheumatology, Ege University School of Medicine, Izmir, Turkey, [22]Department of Rheumatology, Dokuz Eylul University, Faculty of Medicine, Izmir, Turkey, [23]Rheumatology, Ege University Medical Faculty, Izmir, Turkey, [24]Rheumatology, Osmangazi University, Faculty of Medicine, Eskisehir, Turkey, [25]Rheumatology, Gaziantep University School of Medicine, Gaziantep, Turkey, [26]Rheumatology, Abant Izzet Baysal University Faculty of Medicine, Bolu, Turkey, [27]Marmara University Faculty of Medicine, Rheumatology, Istanbul, Turkey, [28]Rheumatology, Marmara University, Faculty of Medicine, Istanbul, Turkey, [29]Department of Internal Medicine Division of Rheumatology, Ondokuz Mayıs University, Faculty of Medicine, Samsun, Turkey, [30]Rheumatology, Cukurova University Faculty of Medicine, Adana, Turkey, [31]Internal Medicine-Rheumatology, Ankara University School of Medicine, Ankara, Turkey, [32]Rheumatology, Kocaeli University Faculty of Medicine, Kocaeli, Turkey, [33]Rheumatology, Gulhane School of Medicine, Ankara, Turkey
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Background/Purpose: Widely accepted outcome measures for disease activity and severity at Adult Onset Still's Disease (AOSD) is not developed until now. Predictive factors for worse prognosis, such as response to initial treatment or life-threatening complications are also not clearly defined Yamaguchi criteria is routinely used for AOSD diagnosis which include 4 major and 4 minor criteria, reflecting almost whole essential AOSD features. These essential features might also be associated with disease severity and the objective of this study was to assess the relationship of arithmetic count of Yamaguchi criteria with clinical, laboratory features and treatment choice.

Methods: At 2012, 19 rheumatology centers collected data on clinical features (demographics, fever, rash, arthralgia, arthritis, myalgia, sore-throat, lymphadenopathy, hepatomegaly, splenomegaly, pleuritis, pericarditis and rare findings including macrophage activation syndrome) laboratory features (complete blood count, neutrophil percentage, ferritin, erythrocyte sedimentation rate, C-reactive protein (CRP), AST, ALT, ALP, GGT, LDH, bilirubin, albumin, triglyceride, total cholesterol, HDL-cholesterol, LDL-cholesterol), treatment choices and disease course, retrospectively. Overall 356 patients were enrolled and 269 of 356 patients were available for further analysis. Yamaguchi items were added arithmetically. Total Yamaguchi scores were between 5 to 8. At the end of statistical analysis, a cut-off of 7 or more score is chosen.

Results: Overall, 269 (56.1% female) patients were assessed. Mean age was 38.5 (14.5) years and mean diagnosis age was 34.9 (14.5) years. Total Yamaguchi score ≥ 7 was present in 83 (30.9%) patients. Hepatomegaly and serositis were found more frequently at Yamaguchi score ≥ 7. Essential laboratory activity parameters, such as ferritin and CRP were also related with high Yamaguchi scores. There was a difference at treatment choices that physicians started

higher dosage of corticosteroids with more frequent methotrexate use (Table).

Conclusion: Higher Yamaguchi scores may be one of the criteria for higher disease activity and severity in AOSD. We suggest that clinical features, level of acute phase reactant/ferritin and treatment choices are affected from disease load.

Table: Clinical, laboratory and treatment differences according toYamaguchi Score in AOSD

	Yamaguchi < 7 n=186	Yamaguchi ≥ 7 n=83	p
Clinical Differences			
Hepatomegaly (%)	20	46	<0.001
Pleuritis (%)	5	17	0.002
Pericarditis (%)	4	13	0.008
Laboratory Differences			
Ferritin mean (SD)	3882 (8608)	7966 (10193)	0.001
Ferritin > 1500 (%)	54.6	88.9	<0.001
Ferritin > 10.000 (%)	10.3	30.9	<0.001
CRP mg/L mean (SD)	117 (78)	158 (90)	<0.001
ALP mean (SD)	154 (147)	203 (160)	0.028
ALP > UL (%)	35	47	0.002
GGT mean (SD)	78 (91)	146 (142)	<0.001
GGT > UL (%)	45	73	<0.001
LDH mean (SD)	576 (698)	953 (1341)	0.008
LDH > UL (%)	43	72	<0.001
Albumin mean (SD)	3.49 (0.56)	3.13 (0.55)	<0.001
Albumin ≤ 3.0 mg/dl (%)	19	37	0.005
Thrombocytosis	41	27	0.023
Treatment Differences			
Initial treatment with methotrexate (%)	53	68	0.021
Baseline corticosteroid dosage (mg) mean (SD)	43.2 (17.9)	51.6 (16.7)	0.001

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Abstract Number: 270

Biologic Agents in Refractory Adult Still's Disease: Better Response Rates and Acceptable Safety with Anakinra and Tocilizumab

Bahtiyar Toz[1], Murat Inanc[1], Burak Erer[2], Nihan Senturk[3], Sevil Kamali[2], Lale Ocal[2] and Ahmet Gul[2], [1]Department

of Internal Medicine, Division of Rheumatology, Istanbul University, Istanbul Faculty of Medicine, Istanbul, Turkey, [2]Department of Internal Medicine, Rheumatology Division, Istanbul University, Istanbul Faculty of Medicine, Istanbul, Turkey, [3]Istanbul Unıversity, Istanbul Faculty of Medicine, Department of Internal Medicine, istanbul, Turkey
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Background/Purpose: There is no randomized controlled trial data to guide us for the management of Adult Still's Disease (AOSD) patients refractory to conventional treatments. We herein aimed to analyze retrospectively the treatment results of a series of refractory AOSD patients, who received different biologics.

Methods: We screened our database for patients diagnosed with AOSD between 1987-2015,and reviewed charts of those patients refractory to corticosteroid and DMARD combination and received biologics including TNF, IL-1 and IL-6 inhibitors. Patients were grouped according to their first biologics as TNF-inhibitors (TNF-i) or others (anakinra (ANK) or tocilizumab (TCZ)).We also analyzed the patient responses according to their disease characteristics as polycyclic or chronic patients. Time to remission were analysed by Kaplan-Meier method, and the association of response with first biological treatment was analysed by regression analysis.

Results: Twenty-four patients with refractory AOSD (chronic:9 and polycyclic:15),who received biologic with a mean duration of 41±27 months. The first biological treatment was TNF-i in 14 and other agents in 10 (ANK in 7 and TCZ in 3).Of the patients,50% were switched from TNF-i to ANK or TCZ. Comparison of the patients according to their first biologic therapy is given in Table 1.The patients who received treatment with other biologics were associated with a better response as the first treatment and tended to achieve remission earlier compared with those who received TNF-i as their first biologicals (median time to remission 4 vs.8 months, log-rank p=0.44).

Joint involvement was more common and skin involvement tended to be more common in the chronic course group (100% vs 50%,78% vs 36%, respectively). While the duration of biologic treatment tended to be longer in the chronic course group (51mo vs 28mo,p=0.04), duration of remission was similar between the groups (26mo vs 20mo, p=0.4). The remission rate tended to be higher in the polycyclic group, whereas CRP and ESH tended to be lower in the chronic group.

Complete remission rates under biologics course were as follows: 70% with TCZ 8mg/kg(n=10), 56% with ANK 100-200mg/d(n=16), 25% with etanercept (n=12), and 18% with infliximab (n=11) treatments. Regression analysis showed that selection of TCZ or ANK biologics as the first biologic was associated with a better response independent of the disease course type(estimate 2.5, 95% CI 0.3-4.7, p=0.026).

No serious infection was observed in patients treated with biologics. In two patients severe skin reactions occurred with ANK and infliximab and, in one patient an immune thrombocytopenia developed under TCZ treatment.

Table 1.Comparison of study variables according to the first biologic agents

	TNF inhibitors n=14	Anakinra (n=7) or Tocilizumab (n=3)
Current age (years)	37±13	35±10
Age at diagnosis (years)	26 (20-59)	26 (5-46)
Follow up (months)	72 (18-252)	54 (26-288)
Gender (%males)	31	46
Sore throat (%)	54	73
Skin involvement (%)	54	46
Joint involvement (%)	85	55
Hepatotoxicity (%)	31	46
CRP (mg/L)	115±88	131±78
ESR (mm/h)	101±30	102±32
Ferritin (ng/ml)	1000 (281-29979)	1280 (424-5181)

Conclusion: This case series of AOSD patients suggest that ANK and TCZ seem to be better treatment choices in terms of remission rate and time to remission in patients refractory to conventional treatments.

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Abstract Number: 271

Investigating an Auto-Inflammatory Component of COPD That Contributes to Progressive Decline in Lung Function Despite Smoking Cessation

Pankti Shah[1], Andrew Osterburg[2], Rebeca Nelson[3], Ben Yaniv[3], Mauricio Orozco-Levi[4] and Michael Borchers[3], [1]Internal Medicine, University of Cincinnati Medical Center, Cincinnati, OH, [2]Internal Medicine Pulmonary Division, University of Cincinnati Medical Center, Cincinnati, OH, [3]University of Cincinnati College of Medicine, Cincinnati, OH, [4]IMIM Hospital del Mar Medical Research Institute, Barcelona, Spain

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Background/Purpose: Most Chronic Obstructive Pulmonary Disease (COPD) cases result from amplification of normal inflammatory responses due to noxious stimuli like cigarette smoke. Yet, the mechanism by which COPD lungs continue to deteriorate despite smoking cessation is not well understood. Here, we explore an auto-inflammatory component of COPD via the study of NKG2D (natural-killer group 2, member D) ligands and a cytokine shown to directly activate natural killer (NK) cells, IL-27. Research in COPD murine models has demonstrated high NKG2D

receptor expression on pulmonary NK cells and NK hyper-responsiveness as a result. NK cell activation then leads to destruction of damaged or stressed pulmonary cells and further deteriorates lung parenchyma. We hypothesize that COPD patient serum will show increased expression of soluble NKG2D ligands and IL-27 correlating to a progressive decline in lung function in active but also former smokers.

Methods: COPD patient serum samples were collected from nine hospitals in Spain (1/2004-3/2006). NKG2D ligand and IL27 expression in COPD patients and healthy subjects was compared via sandwich ELISA method and p-values were determined using independent t-test calculations.

Results: When looking at patient groups defined by smoking status, former and active smokers had increased expression on NKG2D ligands (ULBP2, ULBP3 and MICA) and IL-27 compared to controls. ULBP2 expression comparison showed the following: never smokers = 1.03 pg/mL (N=27, SD ±5.35 pg/mL) compared to active smokers= 18.30 pg/mL (N=22, SD ±71.90 pg/mL, $p<0.05$) and former smokers 25.28 pm/mL (N=29, SD ±119.00, $p<0.05$). ULBP3 expression: never smokers = 25.92 pg/mL (N=27, SD ±72.92 pg/mL) compared to active smokers= 77.50 pg/mL (N=23, SD ±267.55 pg/mL, $p<0.05$) and former smokers 79.12 pg/mL (N=29, SD ±362.06, $p<0.05$). MICA expression: never smokers = 290.28 pg/mL (N= 100, SD ±1737.34 pg/mL) compared to active smokers= 887.06 pg/mL (N=162, SD ±3405.86 pg/mL, $p<0.05$) and former smokers 737.27 pg/mL (N=159, SD ±3767.09, $p<0.05$). IL-27 expression: never smokers = 217.50 pg/mL (N=27, SD ±613.41 pg/mL) compared to active smokers= 432.45 pg/mL (N=23, ±SD 745.27 pg/mL, $p<0.05$) and former smokers 367.26 pg/mL (N=29, SD ±1110.82, $p<0.05$).

Conclusion: Our data shows higher mean quantities of soluble NKG2D ligands and IL-27 in COPD patients compared to healthy controls. Within the COPD patients, the ligand and cytokine expression seen in former smokers was comparable to that of active smokers and significantly elevated compared to healthy controls. These findings give us further insight to diagnosis and management of COPD. Diagnostically, ligand levels could help us differentiate COPD subtypes or ligand expression can correlate with varied disease progression. Future plans involve finding a direct correlation between the expression of NKG2D receptors on lung parenchyma and soluble NKG2D ligands in the serum. We can then utilize this insight of the COPD pathophysiology to evaluate if novel treatments for COPD, like biologic agents, could be used to curtail the process by which COPD lungs continue to deteriorate despite smoking cessation.

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Abstract Number: 272

Are the Autoimmune/Inflammatory Syndrome Induced By Adjuvants (ASIA) and the Undifferentiated Connective Tissue Disease (UCTD) Related to Each Other? a Case-Control Study of Environmental Exposures

Francesco Scanzi[1], Laura Andreoli[1], Maria Martinelli[1], Mara Taraborelli[2], Ilaria Cavazzana[1], Roberta Ottaviani[1], Nice Carabellese[1], Flavio Allegri[1], Franco Franceschini[1], Nancy Agmon-Levin[3], Yehuda Shoenfeld[4] and Angela Tincani[1], [1]Rheumatology and Clinical Immunology, Spedali Civili and University of Brescia, Brescia, Italy, [2]Rheumatology and Clinical Immunology, Spedali Civili of Brescia, Brescia, Italy, [3]Zabludowicz Center for Autoimmune Diseases, Sheba Medical Center, Tel Aviv, Israel, [4]Zabludowicz Center for Autoimmune Diseases, Chaim Sheba Medical Center, Tel Hashomer, Israel Incumbent of the Laura Schwarz-Kipp Chair for Research of Autoimmune Diseases, Sackler Faculty of Medicine, Tel-Aviv University, Tel Aviv, Israel

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Background/Purpose: The Autoimmune/Inflammatory Syndrome induced by adjuvants (ASIA) [1] is an entity that includes different autoimmune conditions observed after exposure to an adjuvant. Patients with Undifferentiated Connective Tissue Disease (UCTD) present many signs and symptoms of "ASIA", alluding to the idea that an exposure to adjuvants can be a trigger also for UCTD. The aim of this control-case study is to investigate prior exposures to adjuvant in 84 patients affected with UCTD and 84 age and sex-matched controls with no family history of autoimmunity.

Methods: An *ad hoc* created questionnaire that lists exposure to the possible triggers of "ASIA", such as vaccinations (HBV vaccine, HAV vaccine, tetanus toxoid vaccine, Haemophilus Influenzae vaccine, Measles-Mumps-Rubella vaccine, Pneumococcal vaccine, HPV vaccine) foreign materials (earrings, piercing, tattoos, silicon breast implants, skin fillers, tooth amalgam, contact lenses, intrauterine device, cardiac valves, artificial joints, metal implants), environmental and occupational exposures (living and/or working near metal or chemical factories, landfills, airports or highways) was administered to both cases and controls. For both groups autoantibodies were analyzed (i.e. antinuclear, anti-ENA, anti-dsDNA, anti-cardiolipin, anti-β2glycoprotein I). Continuous variables were reported as mean and standard deviation, while percentages were reported for categorical variables. T-test was calculated for continuous variables while Chi-square or Fisher's exact tests was used for categorical variables. All statistical tests were two-tailed and only a p value < 0.05 was considered statistically significant.

Results: The Table reports demographic information of the enrolled subjects and those items that were significantly different between cases and controls. As "molecular mimicry" between β2glycoprotein I and tetanus toxoid was described [2], we indeed found that there is a trend toward a higher prevalence of anti-β2glicoprotein I in UCTD who had received a tetanus vaccine in the 10 years before the diagnosis (17/66, 25,7%) in comparison with UCTD patients who did not receive it (3/27, 11,1%) (p=0,10).

Conclusion: As compared with healthy subjects, UCTD patients appeared to have had a greater exposure to adjuvants: HBV and tetanus toxoid vaccinations, metal implants and cigarette smoking. The increased prevalence of allergies proved that UCTD patients have a more reactive immune system, likely on a genetic basis. Thus we can suggest that ASIA and UCTD are two related entities in the "mosaic of autoimmunity": the genetic predisposition and the environmental exposure to adjuvants elicit a common clinical phenotype characterized by signs and symptoms of systemic autoimmunity.

[1] Shoenfeld Y, Agmon-Levin N. J Autoimm 2011;36:4-8.

[2] Stojanović M et al. Immunol Res. 2013;56:20-31.

	UCTD (n=84)	Controls (n=84)	Fisher's exact test
DEMOGRAPHICS			
Female	73 (86,9%)	73 (86,9%)	---
Age at survey (years)	49,2 (±14,7)	48,9 (±14,5)	---
Age at disease onset (years)	43 (±15,7)	---	---
ENVIRONMENTAL EXPOSURES			
HBV vaccination *	10 (11,9%)	2 (2,4%)	p=0,032
Tetanus Toxoid vaccination*	35 (41,7%)	18 (21,4%)	p=0,008
Metal Implants	30 (35,7%)	10 (11,9%)	p=0,001
Ever smoker	35 (41,7%)	22 (26,2%)	p=0,05
Current smoker or past smoker in the ten years before disease onset for cases and before survey for controls	28 (33,3%)	15 (17,9%)	p=0,033
ALLERGIES			
Seasonal or food allergy	21 (25%)	10 (11,9%)	p=0,046
Drug allergy	21 (25%)	7 (8,3%)	p=0,006
AUTOANTIBODIES			
Anti-nuclear antibodies	84 (100%)	3 (3,5%) **	p=<0,0001
Anti-ENA	36 (42,8%)	0	p=<0,0001
Anti-dsDNA	10 (11,9%)	0	p=<0,0001
Anti-CL IgG e/o IgM	14 (16,6%)	1 (1,1%)	p=0,001
Anti-β2GPI IgG e/o IgM	19 (22,6%)	5 (5,9%)	p=0,003

* vaccination in the 10 years before onset for patients and before survey for controls
** low titer positivity, 1:160

Disclosure: F. Scanzi, None; **L. Andreoli**, None; **M. Martinelli**, None; **M. Taraborelli**, None; **I. Cavazzana**, None; **R. Ottaviani**, None; **N. Carabellese**, None; **F. Allegri**, None; **F. Franceschini**, None; **N. Agmon-Levin**, None; **Y. Shoenfeld**, None; **A. Tincani**, None.

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Abstract Number: 273

Progression Predictive Factors in Patients with Undifferentiated Connective Tissue Disease: A Cohort Study

Maria Garcia-Gonzalez, Esmeralda Delgado-Frias, Sagrario Bustabad, Ivan Ferraz-Amaro and Beatriz Rodriguez-Lozano, Rheumatology, Hospital Universitario de Canarias, Santa Cruz de Tenerife, Spain

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SESSION INFORMATION

Session Date: Sunday, November 8, 2015

Session Title: Miscellaneous Rheumatic and Inflammatory Diseases Poster I

Session Type: ACR Poster Session A

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Background/Purpose:

In recent years there has been a growing interest in establishing the concept of Undifferentiated CTD (UCTD) and defining its clinical evolution. Remarkable are the *Marta Mosca et al* studies, who have proposed preliminary definition criteria and reported progression to a Defined CTD (DCTD) in 30% of patients after 5-year follow-up. Some studies have pointed out certain clinical, serological and capillaroscopic features as potential predictive factors, with

contrasting results. In our study we aimed to describe the evolution of a cohort of UCTD patients with at least 5-year follow-up and to establish clinical, serological and capillaroscopic features associated with an increased risk of progression to a DCTD.

Methods:

Patients with first nailfold capillaroscopy (NFC) performed between 1999-2008 who met at least 2 of the following baseline criteria: 1) Raynaud's phenomenon (RP), 2) ANA ≥1/80 and/or positive ENA, 3) pathological NFC pattern, were included. Nailfold capillaroscopies were performed by the same observer with a Leica 10x23 10447123 handheld lighted microscope. The association between outcome and the presence of several baseline features (RP, arthralgias, sicca syndrome, skin and esophageal abnormalities, low complement, Ig and hematologic disorders, ANA titre and pattern, ENA, anti-dsDNA and aPL antibodies, RF, and NFC pattern) was analyzed.

Results:

Among 758 patients with first NFC performed in the cited period, 223 fulfilled inclusion criteria. Ninety seven patients who met classification criteria for a DCTD at disease onset (including Prescleroderma (PSSc)) and 28 with less than 5-year follow-up were excluded. Among 98 analyzed, 97 (99%) were women with a baseline mean age of 42 years (s: ± 15.8). After a mean of 10.6 years follow-up (s: ± 3.1), 61 (62%) remained as UCTD, 23 (24%) evolved into remission and 14 (14%) into DCTD: 8 SLE, 4 PSSc, 1 MCTD, and 1 overlap syndrome. NFC pattern progression was observed in 31% of the patients with a second NFC performed 5 years after disease onset (78/98). Significant differences between clinical outcome and presence of cytopenias (p:0.030), ENA (p:0.008) and aPL antibodies (p:0.032), and a pathological NFC pattern (p:0.026) were observed. Homogeneous (29%) and centromere (36%) patterns were more frequent in DCTD group, while in the remission group was the coarse speckled one (41%) (p:0.117). Positive correlation between ANA titre and outcome was demonstrated (rho:0.21, p:0.025). ANA titre ≥1/640 (OR:17 [1.75-165], p:0.015), a pathological NFC pattern (OR:6.48 [1.48-28.3], p:0.013) and NFC pattern progression after 5-year follow-up (OR:7 [1.35-36.3], p:0.021) were associated with an increased risk of evolving into DCTD.

Conclusion:

1. The rate of progression to DCTD in our cohort was similar to that reported in previous studies.
2. Careful monitoring should be recommended in patients with baseline ANA titre ≥ 1/640 and/or pathological NFC pattern, especially those who present capillaroscopic progression during the follow up.
3. Results concerning potential predictive role of baseline IIF pattern, cytopenias, ENA and aPL antibodies, are coherent with previous studies.

Disclosure: M. Garcia-Gonzalez, None; **E. Delgado-Frias**, None; **S. Bustabad**, None; **I. Ferraz-Amaro**, None; **B. Rodriguez-Lozano**, None.

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Abstract Number: 274

Shrinking Lung Syndrome in Connective Tissue Disease

Helena Borrell Paños[1], Javier Narváez[2], Juan José Alegre[3], Ivan Castellvi[4], Francesca Mitjavila[5], Eulalia Armengol[1], Joan Miquel Nolla[1] and Maria Molina[6], [1]Department of Rheumatology, Hospital Universitario de Bellvitge, Barcelona, Spain, [2]Rheumatology, Hospital Universitario de Bellvitge, Barcelona, Spain, [3]Rheumatology Department, Hospital Universitario Doctor Peset, Valencia, Spain, [4]Rheumatology Unit. Hospital de la Santa Creu i

Sant Pau, Barcelona, Spain, [5]Internal Medicine, Hospital Universitario de Bellvitge, Barcelona, Spain, [6]Department of Pneumology, Hospital Universitario de Bellvitge, Barcelona, Spain

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Background/Purpose:

Shrinking lung syndrome (SLS) is a rare a little known complication associated with systemic lupus erythematosus (SLE) and other connective tissue diseases (CTDs). This study describes the clinical features, investigations, management, and outcome of a series of patients with CTDs and SLS.

Methods:

Ambispective study of 9 patients with SLS and CTDs

Results:

All nine patients were women, with a mean age at SLS diagnosis of 42 years (SD: 11; range 30-64). Eight of these patients had SLE and 1 had mixed connective tissue disease (MTCD). The prevalence of SLS in our cohort of SLE patients was 1,8% *(8/429)*. The median time to onset of SLS after SLE/MCTD diagnosis was 7 years (SD: 6.8; range 1.6-25 yrs). Most patients with SLE had a severe disease with concomitant or previous major organ involvement, especially lupus nephritis (75% of cases). All presented progressive exertional dyspnea of variable severity accompanied by pleuritic chest pain in 89% *(8/9)* of cases. Dry cough or fever was more rarely seen (33%). In 56% *(5/9)* of patients, the syndrome was bilateral. Imaging techniques (chest X-Ray and HRCT) at the evolution showed elevated hemidiaphragms without evidence of interstitial lung disease (ILD) in all cases. Pleural thickening/effusions or basal atelectasis were observed in 56% and 89% of patients, respectively. Pulmonary function tests (PFT) were consistent with a restrictive defect (mean baseline FVC: 59%), while the DLCO was decreased in 89% of cases (mean baseline DLCO: 44.95%). In those to whom diaphragmatic function tests were made, a decrease of the minimum inspiratory pressures (MIP) was observed. Treatment included 0.5 to 1 mg/kg/day of oral prednisone (associated with short-term pulses of intravenous methylprednisolone in 2 cases), associated with beta-agonist. Concomitant immunosuppressive agents (azathioprine, mycophenolate, or methotrexate) were used in 5 patients and rituximab in 4. At the end of the follow-up period (median 31.5 months; range, 3-192), 1 patient cured without functional sequelae. The remaining 8 patients had subjective improvement with stabilization or mild to moderate improvement on PFT. One of these patients finally developed ILD (nonspecific interstitial pneumonitis) several years after SLS onset.

Conclusion:

SLS is a rare complication in CTDs which must be suspected in patients with dyspnea and/or pleuritic chest pain, lung volume reduction with no parenchymal abnormalities and a restrictive ventilatory defect on PTF. The frequent presence of pleuritic chest pain and pleural thickening/effusions at the time of evaluation, suggests that pleuritic inflammation may have an important role in the pathogenesis of this complication.

Disclosure: H. Borrell Paños, None; **J. Narváez**, None; **J. J. Alegre**, None; **I. Castellvi**, None; **F. Mitjavila**, None; **E. Armengol**, None; **J. M. Nolla**, None; **M. Molina**, None.

Abstract Number: 275

A Comparison of the Clinical Features and Natural History of Autoimmune Interstitial Lung Disease Vs. Idiopathic Pulmonary Fibrosis

Sandra Chartrand[1], Lina Peykova[2], Jeffery J. Swigris[3] and Aryeh Fischer[4], [1]Université de Montréal, Montreal, QC, Canada, [2]Rheumatology, National Jewish Health, Denver, CO, [3]National Jewish Health, Denver, CO, [4]University of Colorado School of Medicine, Aurora, CO

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Session Time: 9:00AM-11:00AM

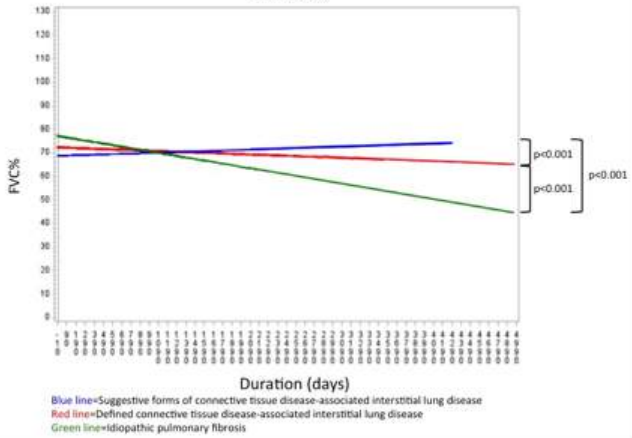
Background/Purpose: We compared clinical features, longitudinal pulmonary physiology, and survival among 3 groups of patients evaluated at our center between February 2008 to August 2014: definite connective tissue disease-associated interstitial lung disease (dCTD-ILD), suggestive CTD-ILD (sCTD-ILD) and idiopathic pulmonary fibrosis (IPF).

Methods : Survival and longitudinal analyses were used to compare survival and changes in percent predicted forced vital capacity (FVC%) over time.

Results : 56 subjects had sCTD-ILD, 191 had dCTD-ILD (99 scleroderma, 42 rheumatoid arthritis, 26 myositis, 14 Sjšgren's syndrome) and 62 had IPF. Compared to IPF (67.9±8.5 years), those with sCTD-ILD (57.5±10.9 years) or dCTD-ILD (54.6±10.3 years) were younger (p<0.001), more likely to be female (16% vs. 67% vs. 71%, respectively), and less likely to be nonsmokers (30.6% vs. 67.9% vs. 52.4%, respectively). Most subjects with sCTD-ILD or dCTD-ILD had a nonspecific interstitial pneumonia pattern on chest HRCT scan (69.2% and 58.1%, respectively). Baseline FVC% was similar between groups (sCTD-ILD: 68.4±16.0% vs. dCTD-ILD: 71.7±15.4% vs. IPF: 73.1±15.9%; p=0.25). Modeled FVC% values are displayed in the Figure.

Figure

Mixed-effects model estimates for percentage of predicted forced vital capacity (FVC%) over time.



During similar follow-up periods (1561±626 vs. 1733±576 vs. 1692±589 days, respectively; p=0.16), there were no deaths in the sCTD-ILD group, 37 (19.4%) in CTD-ILD group and 35 (56.5%) in the IPF group (log-rank p<0.001 for each pairwise comparison).

Conclusion: In this retrospective study, we observed that patients with sCTD-ILD or dCTD-ILD had better FVC% trajectories and survival. The natural history of sCTD-ILD resembled that of dCTD-ILD more than IPF underscoring the importance of differentiating this patient population from idiopathic interstitial pneumonia for purposes of treatment and prognostication.

Disclosure: S. Chartrand, None; **L. Peykova**, None; **J. J. Swigris**, None; **A. Fischer**, Genentech and Biogen IDEC Inc., 2,Actelion Pharmaceuticals US, 5,GlaxoSmithKline, 5,Boehringer Ingelheim, 1,Gilead Sciences, 5,Seattle Genetics, 5,Bristol-Myers Squibb, 5.

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Abstract Number: 276

Long-Term Outcome in Mixed Connective Tissue Disease

Maria Pascual[1], Javier Narváez[2], Gloria Albert Espi[3], Mercè López de Recalde[1], Andrea Zacarias[4] and Juan José Alegre[3], [1]Department of Rheumatology, Hospital Universitario de Bellvitge, Barcelona, Spain, [2]Rheumatology, Hospital Universitario de Bellvitge, Barcelona, Spain, [3]Rheumatology Department, Hospital Universitario Doctor Peset, Valencia, Spain, [4]Hospital Universitari de Bellvitge, Barcelona, Spain

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Session Time: 9:00AM-11:00AM

Background/Purpose: The question of whether mixed connective tissue disease (MCTD) is a distinct entity still remains controversial. For this reason, we have investigated the long-term outcome in a well characterized cohort of patients with MCTD in order to determine the frequency of evolution toward other connective tissue diseases (CTDs).

Methods: Ambispective study of thirty-four MTCD patients, all of them fulfilling the diagnostic criteria proposed by Alarcon-Segovia *(J Rheumatol 1989;16:328-34)*, with a minimal follow-up after the first clinical presentation of at least 2 yr. The endpoint of patient follow-up was the date of the last clinic visit.

Results: At the end of the follow-up period (median ± SD: 90.5 ± 62.1 months; minimum, maximum: 25-228 months), 41.1% of patients *(14/34)* still satisfied MCTD classification criteria of Alarcon-Segovia; 14.7% *(5/34)* evolved into systemic sclerosis [SSc] (fulfilling the 2013 ACR/EULAR classification criteria for SSc), 26.5% *(9/34)* into systemic lupus erythematosus (fulfilling the 2012 SLICC criteria), 8.8% *(3/34)* into seronegative rheumatoid arthritis (fulfilling 2010 ACR-EULAR classification criteria), and 8.8% *(3/34)* developed an overlap syndrome (2 cases of SSc+SLE and 1 case of SSc+RA).

The mean score in patients that meet the 2013 EULAR/ACR criteria for SSc was 11 (minimum, maximum: 9, 16). The mean score in patients satisfying the 2012 SLICC SLE criteria was 6 (minimum, maximum: 5, 9); only 2 of these patients developed major organ involvement.

Using multiple variable regression analysis, the presence of sclerodactyly (OR 1.1; 95% CI 1.1 – 1.7, P =0.04) was associated with evolution into SSc. No clinical predictors of potential evolution toward SLE were identified.

Conclusion: MCTD is a distinct clinical entity but it is evident that the majority of these patients (59% of the cases)

will evolve into another CTD during disease progression.

Disclosure: M. Pascual, None; **J. Narváez**, None; **G. Albert Espi**, None; **M. López de Recalde**, None; **A. Zacarias**, None; **J. J. Alegre**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/long-term-outcome-in-mixed-connective-tissue-disease

Abstract Number: 277

Rituximab in Refractory Mixed Connective Tissue Disease: An Observational Study

Maria Pascual[1], Javier Narváez[2], Gloria Albert Espi[3], Mercè López de Recalde[1], Andrea Zacarias[4] and Juan José Alegre[3], [1]Department of Rheumatology, Hospital Universitario de Bellvitge, Barcelona, Spain, [2]Rheumatology, Hospital Universitario de Bellvitge, Barcelona, Spain, [3]Rheumatology Department, Hospital Universitario Doctor Peset, Valencia, Spain, [4]Hospital Universitari de Bellvitge, Barcelona, Spain

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Session Time: 9:00AM-11:00AM

Background/Purpose: To investigate the safety and preliminary efficacy of rituximab (RTX) in patients with refractory mixed connective tissue disease (MCTD)

Methods: We evaluated 9 patients in this observational cohort study. All received RTX (off label use) in addition to concomitant immunosuppressive agents. RTX treatment consisted of two endovenous infusions of 1 g1 g on days 1 and 15 per treatment cycle separated by a two-week interval. All the patients received premedication to prevent infusion reactions. The endpoint of patient follow-up was the date of the last clinic visit.

Results: All nine patients were women, with a mean age at the time of evaluation of 31 years (SD: 10; range 18-48). The indication for RTX was severe active polyarthritis in 5 cases, progressive nonspecific interstitial pneumonitis (evidence of clinical and functional decline) and inadequate articular response (DAS28 > 3.2) in 2, and autoimmune thrombocytopenia in 1 patient.

The median time to RTX treatment after MCTD diagnosis was 26 months (SD: 34.3; range 5-98 months). Concomitant immunosuppressive agents (azathioprine, mycophenolate, or methotrexate) were used in all patients and hydroxychloroquine in 6. The median follow-up time was 36 months (range, 5 - 80). When data were collected, patients had received a mean of 1.7 cycles (1-5) of RTX, with a dosing interval which ranged from 6 to 15 months.

In general, disease activity declined during therapy. All patients with arthritis achieved clinical remission (DAS28 < 2.6) or low activity (DAS28 ≤ 3.2) by week 16-20, although relapses of disease were frequent with re-treatment being required 6-7 months later. In the 2 patients with NSIP clinical improvement was accompanied by a parallel stabilization or mild improvement in pulmonary function tests (PFT). The autoimmune thrombocytopenia resolved completely after 1 cycle of treatment, without relapses after a follow-up period of 80 months**.**

The concomitant oral steroid dose could be reduced in more than half of the initial dose.

No cases of significant adverse events occurred and none of the patients suffered severe bacterial or opportunistic infections

Conclusion: Our preliminary results suggest that RTX seems to be a safe and useful therapeutic alternative in patients with active MTCD in whom previous treatments have failed, with a steroid-sparing effect.

Disclosure: M. Pascual, None; **J. Narváez**, None; **G. Albert Espi**, None; **M. López de Recalde**, None; **A. Zacarias**, None; **J. J. Alegre**, None.

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Abstract Number: 278

Mitral Valve Prolapse in Patients with Joint Hypermobility Syndrome

Anand Patel[1], Mark Schwartz[1], Liliana Cohen[2], Daniel Shindler[3], Abel Moreyra[1] and Naomi Schlesinger[4,5], [1]Medicine, Rutgers Robert Wood Johnson Medical school, New Brunswick, NJ, [2]Medicine, Rutgers Robert Wood Johnson Medical School, New Brunswick, NJ, [3]Nedicine, Rutgers Robert wood Johnson Medical school, New Brunswick, NJ, [4]Medicine, Rutgers-Robert Wood Johnson Medical School, New Brunswick, NJ, [5]Rutgers-Robert Wood Johnson Medical School, New Brunswick, NJ

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Background/Purpose:

Joint Hypermobility Syndrome (JHS) may predispose to ligamentous rupture, joint dislocations, fibromyalgia, premature osteoarthritis and non-articular complications include Mitral Valve Prolapse (MVP) (Barron J et al Clin Cardiology 1988;11:401).

MVP is a common cardiac abnormality that affects 2 - 5% of the population. It is defined as the systolic billowing of one or both of the mitral leaflets into the left atrium with or without evidence of mitral regurgitation. The current standardized echocardiography (ECHO) diagnostic criteria for MVP is billowing of any portion of the mitral leaflets >2 mm above the annular plane in a parasternal long axis view.

There are limited published studies concerning JHS and MVP however they are thought to be associated. The incidence of MVP in individuals with JHS has been reported to be 8%- 60% (Mishra B et al Br J Rheumatol 1996;35:861)

This study would be the first to examine MVP in patients with JHS using updated diagnostic ECHO criteria.

Methods:

This is a retrospective study of 127 patients ages ≥ 16, diagnosed with JHS (ICD 9: 728.5), based on the revised Beighton criteria (Grahame R et al J Rheumatol 2000;27:1777), seen by a rheumatologist (NS) between 1/1/2011-10/31/2014. The diagnosis of JHS required presence of 2 Major criteria: Beighton score of ≥4 and arthralgia ≥ three months in ≥ four joints, or 1 major and at least 2 minor criteria. ECHOs were performed and read using the new

MVP criteria by ECHO experts (LC, DS). Past medical history that could increase risk to develop MVP including rheumatic fever, endocarditis, polycystic kidney disease, and family history of MVP was reviewed.

Results:

All patients included in the study had a Beighton score of ≥4 (Major Criterion). Most patients were female n=114 (90%). Mean age: 48 (range 16-87 years). Average Beighton score: 6.6 (range: 4-9). Average BMI: 27.5. 73 (57%) were diagnosed with fibromyalgia (ICD 9:729.1)

Echocardiograms were performed in 45 patients (35%) of which 43 (96%) were female with a mean age of 50.5 (range 22-86 years). Average Beighton score: 6.6 (range: 4-9). Average BMI: 28. None of the patients had underlying rheumatic fever, endocarditis or adult polycystic kidney disease.

None of the patients met the updated echocardiographic criteria for MVP.

Conclusion:

This is the first study examining MVP in patients with JHS using the updated MVP ECHO criteria. We did not find ECHO findings consistent with MVP in our JHS patients. This should be studied in other Rheumatology practices since this observation may be cost saving in patients with JHS, who otherwise would have ECHO studies as part of their routine work up.

Disclosure: A. Patel, None; **M. Schwartz**, None; **L. Cohen**, None; **D. Shindler**, None; **A. Moreyra**, None; **N. Schlesinger**, None.

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Abstract Number: 279

Ehlers-Danlos Syndrome Hypermobility Type (Type III) Is Associated with Rheumatological Conditions

Kyla Rodgers[1], Richard Chou[1] and Mary Beth Dinulos[2], [1]Medicine, Geisel School of Medicine at Dartmouth, Lebanon, NH, [2]Pediatrics and Genetics, Geisel School of Medicine at Dartmouth, Lebanon, NH

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Background/Purpose:

Ehlers-Danlos syndrome is a group of inherited conditions caused by genetic mutations in collagen genes, such as COL5A, COL3A, etc, resulting in defects in the structure, production, or processing of collagen or proteins that interact with collagen. The phenotypes of Ehlers-Danlos syndrome vary tremendously among different subtypes or individuals within the same subtype. The present study focuses on retrospective review of subjects who were diagnosed with Ehlers-Danlos syndrome type III, the hypermobility joint syndrome. Individuals of hypermobility joint syndrome often present with hyperextensible joints, chronic back pain, joint pain, among other phenotypic changes. Since hypermobility joint syndrome is also a result of genetic mutations resulting in multiple defects with collagen synthesis

or function, it is conceivable that individuals with this syndrome are more likely to present with rheumatological disorder. The central hypothesis of the present study is that hypermobility joint syndrome increases the prevalence of rheumatological conditions.

Methods: A chart review of electronic medical records at Dartmouth-Hitchcock Medical Center between July 2009 and June 2015 was performed. Once the subjects were identified, detailed chart review was performed to confirm a diagnosis of Ehlers-Danlos syndrome hypermobility type. Pertinent information obtained includes age of diagnosis of hypermobility joint syndrome, gender, any rheumatological conditions such as autoimmune diseases, non-autoimmune conditions (i.e. fibromyalgia), or structural defects, serological workup, and laboratory findings. Subjects were further sorted into the categories of "no rheumatological workup" (ie physical exam only), "limited workup" (ie only ANA and RF), or "complete workup" (all serological markers, HLA B27, ESR, and CRP, etc).

Results: A total of 158 subjects have been identified so far. Of these, 12 subjects were male (age range 8-46) and 146 were female (age range 13-74), with average age at diagnosis of 28.9 years and 36.2 years, respectively. Among the 103 subjects without workup, 5 (4.85%) also had a rheumatological diagnosis (psoriasis or preexisting seronegative RA). Among the 23 subjects with limited workup, 5 (21.74%) presented with a rheumatological disease (psoriasis, RA, PMR). Of the 32 subjects with complete workup, 16 (50%) also had a rheumatological disease (psoriasis, PsA, SS, RP, uveitis, enthesopathy, uSpA, autoimmune thyroiditis, AS, scoliosis, Scheurmann's disease, primary hypogammabulemia, pernicious anemia, fibromyalgia, RA).

Conclusion:

We found that Ehlers-Danlos type III is highly associated with rheumatological conditions, including RA, psoriasis, PsA, fibromyalgia, etc. Based on the finding that these conditions were more prevalent in subjects with complete workup (50%) versus limited (21.74%) or no workup (4.85%), we conclude that rigorous serological studies are necessary to generate a complete clinical understanding and improve symptomatic control in this patient population.

Disclosure: K. Rodgers, None; **R. Chou**, None; **M. B. Dinulos**, None.

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Abstract Number: 280

The Fascia Is a Target Organ of Inflammation in Autoimmune Diseases

Kentaro Noda, Ken Yoshida, Taro Ukichi, Kazuhiro Furuya, Kenichiro Hirai, Isamu Kingetsu and Daitaro Kurosaka, Division of Rheumatology, Department of Internal Medicine, Jikei University School of Medicine, Tokyo, Japan

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SESSION INFORMATION

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Background/Purpose: We previously reported that inflammation occurred early in the fascia of patients with dermatomyositis. We often encounter patients with autoimmune diseases who present with muscle symptoms, such as pain and weakness and biopsies of the affected muscle areas do not show inflammatory cell infiltration among the muscle fibers, thereby leaving the cause of these symptoms unclear. To date, the work-up for autoimmune disease patients presenting with muscle symptoms has focused on the presence or absence of muscle fiber inflammation, and not on the presence or absence of fasciitis. Therefore,we thoroughly investigated the lesions of fasciae and muscles in

patients with muscle symptoms and elevated muscle enzyme levels.

Methods: This study included patients with autoimmune diseases who presented with myalgia, muscle weakness, or elevated serum levels of muscle enzymes (CK and aldolase), and were admitted to the Division of Rheumatology of Jikei University School of Medicine Hospital between April 2007 and December 2013. They underwent magnetic resonance imaging (MRI) and *en bloc* biopsy.

Results: Sixty-three patients presented with myalgia, muscle weakness, and elevated levels of muscle enzymes (CK and aldolase), and consisted of 26 with dermatomyositis (DM), 19 with polymyositis (PM), 9 with clinically amyopathic dermatomyositis (CADM), 7 with systemic lupus erythematosus (SLE), and 2 with adult-onset Still's disease (AOSD). MRI was performed in all sixty-three patients. Fascia involvement was observed in 45 (71.43%) of patients : in 23 (88.46%) out of 26 with DM, 7 (36.84%) out of 19 with PM, 6 (66.67%) out of 9 with CADM, all 7 with SLE, and all 2 with AOSD. Histopathological examination was performed in thirty-five patients. Fasciitis was observed in 23 (65.71%) of patients : in 15 (83.33%) out of 18 with DM, 2 (25%) out of 8 with PM, 3 (50%) out of 6 with CADM, and 3 (100%) out of 3 with SLE. Many patients with fasciitis also had myalgia. However, myositis was not associated with myalgia. Muscle weakness was not associated with fasciitis. A high percentage of patients with normal serum CK levels and elevated serum aldolase levels, developed fasciitis.

Conclusion: Fasciitis occurred in patients with various autoimmune diseases. Patients with myalgia may have fasciitis in autoimmune diseases.

Table. MRI and histopathological findings of fasciae and muscles

	DM	PM	CADM	SLE	AOSD	Total
MRI						
Fascia involvement	23(88.46)	7(36.84)	6(66.67)	7(100)	2(100)	45(71.43)
Muscle involvement	26(100)	16(84.21)	7(77.78)	4(57.14)	0(0)	53(84.13)
Total	26	19	9	7	2	63
Histopathology						
Fasciitis	15(83.33)	2(25)	3(50)	3(100)		23(65.71)
Myositis	18(100)	7(87.5)	2(33.33)	2(66.67)		29(82.86)
Total	18	8	6	3		35

Values are number of patients(%)
DM, dermatomyositis; PM, polymyositis; CADM, clinically amyopathic dermatomyositis;

Disclosure: K. Noda, None; **K. Yoshida**, None; **T. Ukichi**, None; **K. Furuya**, None; **K. Hirai**, None; **I. Kingetsu**, None; **D. Kurosaka**, None.

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Abstract Number: 281

Health Related Quality of Life Is Reduced in Adult Patients with Idiopathic Inflammatory Myopathies

Michal Feldon[1], Payam Noroozi Farhadi[2], Hermine I. Brunner[1], Lukasz Itert[3], Bob Goldberg[4], Abdullah Faiq[2], Jesse Wilkerson[5], Kathryn Rose[5], Frederick W. Miller[2], Lisa G Rider[2] and Edward H. Giannini[6], [1]Pediatric Rheumatology, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, [2]Environmental Autoimmunity Group, NIEHS, NIH, Bethesda, MD, [3]Division of Rheumatology, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, [4]The Myositis Association, Alexandria, VA, [5]Social and Scientific Systems, Inc., Durham, NC, [6]Rheumatology, Cincinnati Children's Hospital Medical Center, Cincinnati, OH

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Background/Purpose: Idiopathic inflammatory myopathies (IIM), such as dermatomyositis (DM), polymyositis (PM) and inclusion body myositis (IBM), are chronic multi-systemic inflammatory conditions. Substantial studies on health related quality of life (HRQOL) in IIM patients are lacking.

The objective of this study was to document the degree of HRQOL impairment in IIM patients.

Methods: Between December 2010 and July 2012, 1,715 patients who met probable Bohan and Peter criteria for myositis residing in the US and Canada registered for the MYOVISION registry study with The Myositis Association. HRQOL was ascertained via the SF-12v2® Health Survey questionnaire. The SF12v2®is a 12-item 4-week recall questionnaire that features two summary measures – the physical component summary [PCS] and the mental component summary [MCS].

This was an exploratory, cross-sectional descriptive study that examined the variation in HRQOL scores in relation to different patient and disease characteristics, and compared the scores of IIM patients to age-and-gender-matched normative U.S. general population and rheumatoid arthritis (RA) patients.

Bivariate analysis was conducted via t-tests to assess the difference in summary scores for each independent variable and a multiple linear regression analysis was performed using a backward elimination model.

Results: There were 702 DM, 481 PM, 465 IBM, as well as 59 adults with juvenile DM (JDM) and eight with juvenile PM (JPM) included in the study (70% females, 87% Caucasian). The median age at diagnosis and duration of disease were 49.9 and 9.2 years, respectively.

The mean summary scores of the SF-12v2®were significantly lower (indicating reduced HRQOL) among the myositis population compared to the age-and-gender-matched normative population and the RA population (Table 1).

In a multiple linear regression (Table 2), older age, effect of disease on work, presence of another autoimmune disease, lung disease, joint involvement and use of multiple medications were all associated with lower PCS scores. Patients treated primarily by rheumatologists had a higher PCS score. The MCS score was lower with joint involvement and a negative effect of myositis on work.

Conclusion: In this largest study of patient reported outcomes in IIM to date, HRQOL was lower among IIM patients compared to the normal population and to RA patients. An association was found between multiple disease parameters and reduced HRQOL, mostly in the physical domain.

Table 1: HRQOL summary scores relative to an age- and gender-matched U.S. normative population and RA patients

	Myositis Patients			U.S Normative Population						RA Patients					
Scale	N	Mean	SE	N	Mean	SE	F	p	ES	N	Mean	SE	F	p	ES
PCS	1715	35.56	0.26	6009	47.84	0.20	1382.7	<.0001	-0.84	463	40.47	0.82	32.5	<.0001	-0.39
MCS	1715	47.26	0.27	6012	52.52	0.21	241.8	<.0001	-0.35	463	48.96	0.79	4.2	0.0415	-0.14

Notes.

SE = Standard Error, F = F statistic for ANOVA with sample as a between-subjects factor p = p-value for F,

ES = Effect Size (Cohen's *d*)

Table 2: Multivariable analysis of the full MYOVISION population for PCS and MCS				
Variable	Physical summary score (PCS)		Mental summary score (MCS)	
	Beta coefficient (Standard Error)	P-value	Beta coefficient (Standard Error)	P-value
Myositis subtype: PM*	-4.28 (0.59)	<.001	-1.00 (0.67)	0.140
Myositis subtype: IBM*	-8.94 (0.80)	<.001	-1.10 (0.83)	0.189
Female	-0.09 (0.58)	0.882	RA	
Caucasian	1.49 (0.80)	0.063	1.08 (0.91)	0.239
Age at Enrollment	-0.08 (0.02)	<.001	0.02 (0.03)	0.551
Effect on Work	-5.43 (0.61)	<.001	-3.52 (0.69)	<.001
Autoimmune Overlap	-1.52 (0.58)	0.009	RA	
Treated by Rheumatologist	1.57 (0.59)	0.008	RA	
Lung Disease	-3.48 (0.58)	<.001	-0.80 (0.66)	0.226
Difficulty Swallowing	-0.56 (0.50)	0.263	-0.96 (0.57)	0.093
Joint Swelling	-2.85 (0.53)	<.001	-2.92 (0.60)	<.001
Received Multiple Immune Modulators	-2.61 (0.55)	<.001	-1.00 (0.62)	0.109
Cancer diagnosis	RA		1.53 (0.74)	0.038
Disease duration	RA		0.08 (0.04)	0.087
Notes: RA = Variables were removed from analysis by backwards elimination at P > 0.1. *The subgroup parameter estimates (PM and IBM) are each relative to the DM subgroup				

Disclosure: M. Feldon, None; **P. Noroozi Farhadi**, None; **H. I. Brunner**, None; **L. Itert**, None; **B. Goldberg**, None; **A. Faiq**, None; **J. Wilkerson**, None; **K. Rose**, None; **F. W. Miller**, None; **L. G. Rider**, None; **E. H. Giannini**, None.

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Abstract Number: 282

Angiogenesis in Fasciitis Associated with Dermatomyositis

Ken Yoshida, Kentaro Noda, Taro Ukichi, Kazuhiro Furuya, Kenichiro Hirai, Isamu Kingetsu and Daitaro Kurosaka, Division of Rheumatology, Department of Internal Medicine, Jikei University School of Medicine, Tokyo, Japan

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Background/Purpose: We have previously demonstrated that fasciitis is a common lesion of dermatomyositis (DM) detectable early after disease onset. Furthermore, *en bloc* biopsy showed that the fascial microvasculature, rather than intramascular microvasculature, is one of the primary sites for inflammatory cell infiltration (Arthritis Rheum. 2010;62:3751-9). We also showed that fasciitis was detectable by Power Doppler ultrasonography in patients with DM. In the current study, we examined whether angiogenesis was observed in fasciitis associated with DM, and which angiogenesis-related factors were expressed.

Methods: We analyzed 12 patients consisting of 6 newly diagnosed with DM and 6 newly diagnosed with polymiositis (PM) in the Division of Rheumatology at Jikei University Hospital. In the current study, all patients underwent *en bloc*

biopsy before treatment. All samples were fixed in 10% neutral-buffered formalin and embedded in paraffin. Total vascular inflammation score (TVIS) was defined as the total number of aggregates of ≥50 perivascular inflammatory cells per 4-mm^2area of the fascia in the 3 fields with the most remarkable perivascular infiltrates in order to evaluate the severity of fasciitis. Immunohistochemical staining was performed on paraffin-embedded sections by using anti-CD31 antibodies to evaluate angiogenesis, and anti-VEGF, anti-IL-6, and anti-TNF-α antibodies to evaluate the expression of angiogenesis-related factors in the fascia. Angiogenesis score (AS) was defined as the total number of CD31-positive blood vessels in the 3 high-power fields (200×) that showed the most remarkable proliferation of the vessels in the fascia. The numbers of VEGF, IL-6, and TNF-α positive cells were counted in the 3 high-power fields (400×) that showed the largest accumulation of these positive cells.

Results: Significant fasciitis, histologically defined as TVIS of ≥3, was detected in all patients with DM. Although mild inflammation of the fascia (TVIS 1) was observed in 1/6 patients with PM, significant fasciitis was not detected in any patients with PM. TVIS and AS in the fascia were significantly higher in patients with DM compared with PM. AS was positively correlated with TVIS in DM-associated fasciitis. The numbers of VEGF and TNF-α positive cells were both significantly higher in the fascia of patients with DM compared with PM. IL-6 positive cells were barely present in the fascia among patients with DM and PM.

Conclusion: Angiogenesis was predominantly observed in the fascia with severe inflammation among patients with DM. Our data suggest that VEGF and TNF-α are involved in DM-associated fasciitis with angiogenesis. Inhibiting VEGF and TNF-α may be a useful therapeutic option to treat inflammatory myopathy, especially DM.

Disclosure: K. Yoshida, None; **K. Noda**, None; **T. Ukichi**, None; **K. Furuya**, None; **K. Hirai**, None; **I. Kingetsu**, None; **D. Kurosaka**, None.

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Abstract Number: 283

Altered Serum Fatty Acid Profiles in Patients with Polymyositis or Dermatomyositis Compared to Healthy Individuals and in Relation to Immunosuppressive Treatment

Joan Raouf[1], Helena Idborg[1], Petter Olsson[2], Per Johan Jakobsson[1], Ingrid E. Lundberg[1] and Marina Korotkova[1], [1]Medicine, Department of Medicine, Rheumatology Unit, Karolinska University Hospital, Karolinska Institutet S-171 76, Stockholm, Sweden, Stockholm, Sweden, [2]Analytical Chemistry, Department of Analytical Chemistry, Stockholm University, Sweden, Stockholm, Sweden

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Session Time: 9:00AM-11:00AM

Background/Purpose:

Polymyositis (PM) and dermatomyositis (DM) are chronic autoimmune diseases, characterized by muscle fatigue. Despite conventional immunosuppressive treatment including high doses of glucocorticoids, only a few patients completely recover muscle function. Our group has recently discovered that immunosuppressive treatment has

significant effects on skeletal muscle gene expression related to lipid and fatty acid (FA) metabolism that may contribute to the persistent muscle weakness in myositis patients. Previous studies have described important effects of FAs on skeletal muscle growth, performance and inflammation. Nevertheless, the involvement of lipids and FA in the pathogenesis of PM and DM has not been elucidated. The aim of the study was to study lipid and FA profiles in sera from patients with PM or DM in comparison to healthy individuals and in relation to immunosuppressive treatment.

Methods:

Serum samples were obtained from 14 patients with established PM or DM with persisting muscle weakness and 12 age and sex matched healthy controls (HC). In a second cohort, serum samples were obtained from 8 new onset PM or DM patients before and after 6 months of conventional immunosuppressive treatment including glucocorticoids. Serum lipids were extracted by using liquid-liquid extraction. FA composition of total lipids was determined by gas chromatography flame ionization detector (GC-FID). FA composition of several lipid classes e.g., triacylglycerols, phospholipids, sphingolipids and lysophospholipids was analyzed by using liquid chromatography tandem mass spectrometry (LC-MS/MS).

Results:

Our preliminary results show that FA composition of total serum lipids was altered in myositis patients compared to HC; the levels of palmitic16:0 acid was significantly higher ($p<0.05$) in myositis patients whereas the levels of arachidonic 20:4(n-6) acid was significantly lower ($p<0.05$). Immunosuppressive treatment affected the FA profiles in total lipids and in lipid classes in the serum from myositis patients. The levels of eicosadienoic acid 20:2(n-6) and eicosapentaenoic 20:5(n-3) acids in myositis patients were significantly higher after treatment compared to before treatment ($p<0.05$). Moreover, the levels of phosphatidylcholine (PC) (32:1), phosphatidylethanolamine (PE) (36:5) and lysophosphatidylcholine (LPC) (16:1) were all significantly higher ($p<0.05$) in myositis patients after treatment compared to before.

Conclusion:

FA composition of total serum lipids was altered in myositis compared to HC. This could be explained by given immunosuppressive treatment as FA composition of serum PC, PE and LPC was altered after 6 months of treatment compared to before treatment. These data suggest that FA metabolism might be deregulated in PM and DM patients and this may contribute to impaired muscle performance and representing a potential therapeutic target in PM and DM.

Disclosure: J. Raouf, None; **H. Idborg**, None; **P. Olsson**, None; **P. J. Jakobsson**, None; **I. E. Lundberg**, None; **M. Korotkova**, None.

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Abstract Number: 284

Validation of the Sporadic Inclusion Body Myositis Physical Functioning Assessment

Valerie Williams[1], Theresa Coles[2], Carla DeMuro[2], Sandra Lewis[2], Nicole Williams[2], Stuart Yarr[2], Victoria Barghout[3], Linda Lowes[4], Lindsay Alfano[4], Bob Goldberg[5], Ari Gnanasakthy[2], **Gorana Capkun-Niggli**[6] and Brian Tseng[7], [1]Psychometrics, RTI Health Solutions, North Carolina, NC, [2]RTI Health Solutions, North Carolina, NC, [3]VEB HealthCare LLC, Morristown, NJ, [4]Nationwide Children's Hospital, Columbus, OH, [5]The Myositis Association, Alexandria, VA, [6]Novartis Pharmaceuticals Corporation, Basel, Switzerland, [7]Novartis Pharmaceuticals Corporation, East Hanover, NJ

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Background/Purpose: Patient-reported outcomes (PROs) assess disease symptoms and impact from the patient's perspective. This research aimed to establish the validity, reliability, and responsiveness of the sporadic Inclusion Body Myositis (sIBM) Physical Functioning Assessment (sIFA) for measuring physical functioning in sIBM patients.

Methods: The development and psychometric evaluation of the sIFA followed the Food and Drug Administration's PRO guidance. Data were collected from three small, non-interventional, observational studies of sIBM patients in the United States, with a subset of 31 patients followed longitudinally for 1 year. Patients completed the sIFA either electronically or using paper forms. The Improved Health Assessment Questionnaire (IHAQ), as well as objective measures of physical functioning, such as the 6 Minute Walk Distance (6MWD) and Short Physical Performance Battery, were included to evaluate construct validity. Measures of reliability (Cronbach's alpha, test-retest intraclass correlations), construct validity (correlations, analyses of variance), and responsiveness (effect size estimates) were computed.

Results: Cronbach's alpha (range: 0.86–0.91) and test-retest reliability (0.91) were highly satisfactory. Correlations with the IHAQ and 6MWD supported convergent validity; for example, the correlations between the sIFA and IHAQ activities scores were strong (range: 0.73–0.85), but the correlations between the sIFA and IHAQ pain scores were weak (range: 0.19–0.29). The sIFA also correlated strongly with the 6MWD (range: -0.59 to -0.60). sIBM patients who were able to walk without assistive devices scored significantly better ($p<0.01$) on the sIFA (range: 36.0–47.1) than those requiring power mobility or wheelchairs (range: 54.9–71.5) and patients who walked >400 meters on the 6MWD scored significantly better ($p<0.01$) on the sIFA (range: 30.0–31.9) than those who walked <300 meters on the 6MWD (range: 56.3–59.5), demonstrating the discriminating ability of the sIFA. Although estimates of responsiveness were small, indicating slow progression of functional impairment, preliminary evidence suggests that the sIFA can be used to detect functional change in sIBM patients.

Conclusion: The psychometric analysis of the sIFA strongly supports its reliability, validity, and responsiveness for assessing the impact of sIBM on patient-reported physical function. The sIFA has the potential to facilitate a more comprehensive evaluation of treatment benefit in sIBM patients.

Disclosure: V. Williams, Novartis Pharmaceutical Corporation, RTI Health Solutions, 9; **T. Coles**, Novartis Pharmaceutical Corporation, RTI Health Solutions, 9; **C. DeMuro**, Novartis Pharmaceutical Corporation, RTI Health Soultions, 9; **S. Lewis**, Novartis Pharmaceutical Corporation, RTI Healthcare Solutions, 9; **N. Williams**, Novartis Pharmaceutical Corporation, RTI Healthcare Solutions, 9; **S. Yarr**, Novartis Pharmaceutical Corporation, RTI Health Solutions, 9; **V. Barghout**, Novartis Pharmaceutical Corporation, 5; **L. Lowes**, Novartis Pharmaceutical Corporation, 5; **L. Alfano**, Nationwide Children's Hospital, Columbus, OH, USA, 5; **B. Goldberg**, None; **A. Gnanasakthy**, Novartis Pharmaceutical Corporation, RTI Healthcare Solutions, 9; **G. Capkun-Niggli**, Novartis Pharmaceutical Corporation, 3; **B. Tseng**, Novartis Pharmaceutical Corporation, 3.

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Abstract Number: 285

Tobacco Smoking in Different Racial Groups Is Differentially Associated with the Development of Myositis Autoantibodies and Interstitial Lung

Disease in the Idiopathic Inflammatory Myopathies

Adam Schiffenbauer[1], Natalie Smith[2], Lisa G Rider[1] and Frederick W. Miller[3], [1]Environmental Autoimmunity Group, NIEHS, NIH, Bethesda, MD, [2]Statistics, Purdue University, Allison Park, PA, [3]Clinical Research Branch / Environmental Autoimmunity Group, NIH, Bethesda, MD

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Background/Purpose: Smoking has been found to be a risk or protective factor in certain autoimmune diseases. Yet, its role in the idiopathic inflammatory myopathies (IIM) has not been fully explored. Thus, we assessed the role of smoking in adult IIM and selected phenotypes among different racial groups.

Methods: Patients with probable or definite dermatomyositis (DM, n=186) and polymyositis (PM, n=250) by Bohan and Peter criteria enrolled in NIH studies for whom smoking history could be obtained from their records were studied. Patients were defined as smokers if they had smoked at least 100 cigarettes in their lifetime. Racial background was self-reported, and included 307 Caucasians, 96 African Americans (AA), and 33 patients of other races. The presence of interstitial lung disease (ILD) was based on physician review of chest-x-ray, chest CT, lung biopsy, and/or pulmonary function tests. Autoantibodies (Abs) were assessed in three composite groups -- anti-synthetase autoantibodies (ASA) (directed against Jo-1, PL-12, PL-7, EJ, KS, OJ antigens), myositis-specific autoantibodies (all ASA and those directed against Mi-2, MJ, TIF-1, SRP antigens), and myositis-associated autoantibodies (directed against Ku, MAS, PM-ScL, tRNA, and U1RNP antigens) -- as well as each autoantibody individually. Categorical comparisons were done using chi-squared analysis or Fisher's exact test. Adjustments for age, race, and gender were done using logistic regression.

Results: There was a significant difference in the frequency of ILD across the 3 racial groups with 60% of AA having ILD compared to 75% of Caucasians and 55% of Other races (p=0.002). In Caucasians and Other races, smoking was positively associated with ILD (OR 1.79, 95% CI 1.07-2.98, p=0.025 and OR 6.53, 95% CI 1.2-35.57, p=0.023 respectively). In AA, no significant association between ILD and smoking was observed (OR 0.82, 95% CI 0.32-2.02).

In Caucasian DM/PM patients, smoking was positively associated with any ASA (OR 2.24, 95% CI 1.28-3.92, p=0.004) and anti-Jo-1 Abs (OR 2.4, 95% CI 1.31-4.4, p=0.004). In Caucasians there was a negative association between smoking and anti-TIF-1 (OR 0.14, 95% CI 0.02-0.93, p=0.018), as well as anti-Mi-2 (p=0.045) and anti-MJ (p=0.025) Abs. In AA, there was no association between smoking status and ASA as a group (Chi-square=0.7, p=0.391), anti-Jo-1 (Chi-square=0.0006, p=0.980), or anti-Mi-2 Abs (Chi-square=0.0265, p=0.871), and there was a negative association between U1RNP Abs and smoking (Chi-square=3.9, p=0.049). Although the number of patients in the Other race category was small, there was a positive association between smoking and ASA (p=0.013), as well as with anti-Jo-1 Abs (p=0.034).

Conclusion: These data suggest that in Caucasians smoking is a risk factor for developing ILD, as well as anti-Jo-1 Abs and ASA, but is protective for anti-TIF-1, -Mi-2, and -MJ Abs. In contrast, in AA, smoking appears to have no impact on the development of ILD, anti-Jo-1 Abs, or ASA. Thus, smoking may differentially modulate the clinical and serologic expression of myositis across racial groups.

Disclosure: A. Schiffenbauer, None; **N. Smith**, None; **L. G. Rider**, Cure JM Foundation, The Myositis Association, 2,aTyr Pharma, Idera Pharamaceuticals, MedImmune, Cure JM, 6,Hope Pharmaceuticals, 9; **F. W. Miller**, None.

racial-groups-is-differentially-associated-with-the-development-of-myositis-autoantibodies-and-interstitial-lung-disease-in-the-idiopathic-inflammatory-myopathies

Abstract Number: 287

Interleukin-35 in Idiopathic Inflammatory Myopathies

Herman F. Mann[1], Hana Hulejova[2,3], Josef Zámecník[4], Jaromir Hacek[5], Mária Filková[6], Olga Kryštufková[7], J Vencovsky[8] and Ladislav Senolt[9], [1]Department of Experimental Rheumatology, Institute of Rheumatology, 1st Faculty of Medicine, Charles University in Prague, Prague 2, Czech Republic, [2]Institute of Rheumatology and Department of Rheumatology, Prague, Czech Republic, [3]1st Faculty of Medicine, Charles University, Prague, Prague, Czech Republic, [4]Department of Pathology and Molecular Medicine, 2nd Medical School and University Hospital Motol, Charles University, Prague, Czech Republic, [5]Department of Pathology and Molecular Medicine, 2nd Medical School and University Hospital Motol, Charles University, Prague, Czech Republic, Prague, Czech Republic, [6]Institute of Rheumatology and Department of Rheumatology, 1st Faculty of Medicine, Charles University in Prague, Prague, Czech Republic, [7]Institute of Rheumatology, Department of Rheumatology of the First Faculty of Medicine, Charles University in Prague, Prague, Czech Republic, [8]Institute of Rheumatology, Charles University, Prague, Czech Republic, [9]Institute of Rheumatology, Prague, Czech Republic

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Session Time: 9:00AM-11:00AM

Background/Purpose: Interleukin-35 (IL-35) is a newly described heterodimeric cytokine that belongs to the IL-12 family and consists of p35 (IL-12a) and EBI3 (IL-27b) subunits. IL-35 exerts immunomodulatory activities in several human autoimmune inflammatory diseases. Our objective was to assess IL-35 expression in muscle tissue and serum levels of IL-35 in myositis patients compared to healthy controls and characterise its potential association with myositis disease activity.

Methods: The expression of IL-35 was studied by primary rabbit anti-human EBI3 polyclonal antibody and mouse anti-human p35 monoclonal antibody in a series of 19 muscle biopsy samples of idiopathic inflammatory myopathies (9 dermatomyositis/DM, 10 polymyositis/PM) and 10 cases of non-inflammatory myopathies and 10 control muscles biopsies. Serum levels of IL-35 were determined in 28 DM, 26 PM and 17 cancer associated myositis patients as well as in 40 healthy controls. Disease activity was evaluated by the score of the Myositis Disease Activity Assessment Tool (MYOACT), including both extramuscular, muscular and the physician's score of overall disease activity.

Results: Both IL-35 subunits were found in immune cells of the inflammatory infiltrates in idiopathic inflammatory myopathies, but not in muscle cells. No immunoreactivity was observed in muscle tissue of healthy controls and in non-inflammatory myopathies. IL-35 serum levels were increased in all myositis patients compared to healthy controls ($p< 0.001$). There were no differences in IL-35 serum levels among myositis subgroups. In patients with PM, but not DM, serum IL-35 levels correlated with MYOACT score ($r=0.548$, $p=0.023$), lactate dehydrogenase ($r=0.621$, $p=0.024$), CRP ($r=0.632$, $p=0.009$) and physician's score ($r=0.514$, $p=0.042$).

Conclusion:

IL-35 subunits are overexpressed in inflamed muscle tissue and elevated circulating IL-35 levels are associated with several disease activity parameters in polymyositis patients. These data suggest potential role of IL-35 in the

pathogenesis of inflammatory myopathies.

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Abstract Number: 288

Myositis Associated Interstitial Lung Disease: Clinical Predictors of Failure to Conventional Treatment and Their Response to Tacrolimus

Niharika Sharma[1], Anisha Dua[1], Michael Putman[2], Rekha Vij[3] and Mary Strek[3], [1]Rheumatology, The University of Chicago, Chicago, IL, [2]Internal Medicine, The University of Chicago, Chicago, IL, [3]Pulmonology, The University of Chicago, Chicago, IL

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SESSION INFORMATION

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Session Title: Muscle Biology, Myositis and Myopathies Poster

Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose:

Interstitial lung disease (ILD) frequently complicates Polymyositis (PM) and Dermatomyositis (DM) and accounts for significant morbidity and mortality in affected patients. Patients with Myositis associated Interstitial Lung Disease (MA-ILD) are often refractory to conventional treatment which commonly includes the use of glucocorticoids with or without azathioprine, methotrexate or mycophenolate. In recent years, tacrolimus has shown favorable outcomes in refractory MA-ILD. Little is known about clinical variables that are associated with a response to treatment. The aim of this study is to evaluate clinical predictors of response to conventional treatment and tacrolimus.

Methods:

This is a retrospective study of 54 patients with MA-ILD seen in Rheumatology and Pulmonology clinics at The University of Chicago. Myositis was diagnosed based on Bohan and Peter criteria and ILD was diagnosed based on abnormalities on CT scan of chest. Chart review was performed and clinical variables were compared between the groups who responded versus failed to conventional treatment. All patients received glucocorticoids with at least one disease modifying agent (DMARDs such as azathioprine, methotrexate, mycophenolate mofetil) as conventional treatment for MA-ILD. In those who failed conventional treatment, and were challenged with tacrolimus, clinical predictors to treatment were again evaluated. We strictly defined improvement in myositis (serial CK and objective muscle weakness) and ILD (serial pulmonary function tests and symptoms including cough and dyspnea). The response to tacrolimus was measured by observing the improvement in myositis, ILD and changes in the doses of glucocorticoids.

Results:

Our study included 30 patients with PM, 20 with DM, and 4 patients with clinically amyopathic dermatomyositis (CADM). The mean age was 44.8 years (14.8 SD), and 48% of patients were African Americans. 23 out of 54 patients failed to respond to conventional treatment. Patients who had PM were more likely to respond to conventional treatment as compared to DM (p=0.017). There were 20 patients who received tacrolimus for treatment of refractory MA-ILD. There was an improvement in ILD in 94% of patients and improvement in myositis in 75% of patients after the addition of tacrolimus.

The mean dose of prednisone at the time of initiation of tacrolimus was 33.6 +/- 4.3 mg. After 3-6 months the mean dose of prednisone was 11.9 +/- 1.8 mg, $p < 0.0001$ (65% decrease) and was 7.32 +/- 1.7 mg, $p < 0.0001$ (78% decrease) by the end of 1 year. The mean dose of azathioprine at the time of initiation of tacrolimus was 88.15 +/- 16.7 mg. By the end of 1 year the mean dose of azathioprine was 48.6 +/- 15.3 mg (p=0.003, 45% decrease).

Conclusion:

PM/DM/CADM is a group of rare, heterogeneous diseases and predicting their response to treatment remains challenging. Patients with PM associated ILD were more likely to respond to conventional treatment than patients with DM associated ILD. Tacrolimus is a favorable option in patients with refractory MA-ILD and was successful in decreasing the dose of baseline glucocorticoids and other DMARDS.

Disclosure: N. Sharma, None; **A. Dua**, None; **M. Putman**, None; **R. Vij**, None; **M. Strek**, None.

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Abstract Number: 289

Evaluation of Usefulness of Krebs Von Den Lungen-6 As a Biomarker of Interstitial Lung Disease with Polymyositis and Dermatomyositis Including in the Short Time Course after Treatment

Masanori Hanaoka, Yasuhiro Katsumata, Yasushi Kawaguchi, Hidenaga Kawasumi, Hisae Terajima-Ichida, Kae Takagi, Akiko Tochimoto, Yuki Ichimura and Hisashi Yamanaka, Institute of Rheumatology, Tokyo Women's Medical University, Tokyo, Japan

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Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose: Because of the extremely variable incidence and outcome of interstitial lung disease (ILD) in polymyositis/dermatomyositis (PM/DM), explorationand validation of biomarkers for diagnosis, prognosis, and response to treatment is mandatory. Lung epithelium-derived proteins such as Krebs von den Lungen-6 (KL-6) and surfactant protein-D (SP-D) are widely used as serum biomarkers for ILD. However, their usefulness in patients with PM/DM is not fully established. We aimed to evaluate the usefulness of KL-6 as a biomarker of ILD with PM/DM, including in the short time course after treatment.

Methods: A total of 42 patients with active PM/DM who were admitted to our hospital from April 2010 through March 2015 were included: 22 with PM, 14 with classical DM, and 6 with clinically amyopathic dermatomyositis (CADM). PM/DM and CADM were diagnosed according to Bohan and Peter's criteria and Sontheimer's criteria, respectively.

Overlap patients with other collagen tissue diseases were excluded to avoid potential confounding. ILD was defined as presence of a diffuse parenchymal lung disease on high-resolution CT such as reticular opacities, ground-glass opacities, and honeycombing. Clinical, radiological, and laboratory data were retrospectively collected from the medical records and statistically analyzed.

Results: Of the 42 study subjects, 30 patients had ILD on high-resolution CT: 24 with PM and classical DM, and 6 with CADM. There was no significant difference in age, sex, or disease duration between patients with and without ILD. Because most of the patients had short disease duration at study entry, % vital capacity (%VC) on admission (pre treatment) was not significantly different between patients with and without ILD ($p = 0.19$). However, serum KL-6 and SP-D levels were significantly higher ($p < 0.01$ and $p = 0.01$, respectively), and % diffusing capacity for carbon monoxide (%DLCO) was significantly lower ($p = 0.049$) in patients with ILD than those without. Levels of serum KL-6 were significantly correlated with %VC, %DLCO, and levels of serum SP-D ($p < 0.01$ in all comparisons) but not with alveolar-arterial oxygen difference ($p = 0.39$). All the patients with ILD were treated with prednisolone. In addition, cyclosporine, tacrolimus, and intravenous cyclophosphamide were administered simultaneously in 19, 6, and 8 patients, respectively. Although most of the patients showed some clinical and/or radiological improvement in 4 weeks, levels of serum KL-6 were not significantly different between those at pre treatment and at 2 or 4 weeks post treatment ($p = 0.59$ and 0.58, respectively).

Conclusion: The present study validated that serum KL-6 is a useful biomarker for the diagnosis of ILD associated with PM/DM. However, the levels of serum KL-6 did not respond immediately by treatment even in the cases with clinical improvement. Serum KL-6 should be used as a biomarker for ILD with PM/DM knowing its strengths and limitations.

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Abstract Number: 290

Cancer and Necrotizing Immune Mopathy: High Incidence in Anti-3-Hydroxy-3-Methylglutaryl-Coenzyme a Reductase Positive and Seronegative Patients but Not in Anti-Single Recognition Particle Positive Patients

Yves Allenbach[1], Jeremy Kaeren[1], Nicolas Champtiaux[1], Yoland Schoindre[1], Kuberaka Mariampillai[1], Aude Rigolet[1], Lucile Musset[2], Jean- Luc Charuel[2], Anthony Behin[3], Bruno Eymard[4], Pascal Laforet[5], Tanya Stojkovic[5], Olivier Boyer[6], Baptiste Hervier[7] and Olivier Benveniste[1], [1]Department de Internal Medicine and Clinical Immunology, Hôpital Pitié-Salpêtrière, AP-PH, UPMC, Paris, France, [2]Laboratoire d'immunochimie, Pitié-Salpêtrière, Paris, France, [3]Institute of Myology, Pitie-Salpetriere Hospital, Paris, France, [4]Department of Neurology, Hôpital Pitié-Salpêtrière, AP-PH, UPMC, Paris, France, [5]Department of Neurology, Myology Institute, Assistance Publique - Hôpitaux de Paris, Pitié-Salpêtrière University, Paris, France, [6]Immunology, Inserm 905 & Institute for Biomedical Research, University of Rouen, Rouen, France, [7]Department de Internal Medicine and Clinical Immunology, Hôpital Pitié-Salpêtrière, AP-PH, UPMC, Paris, Paris, France

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Session Type: ACR Poster Session A
Session Time: 9:00AM-11:00AM

Background/Purpose: Twenty percent of inflammatory myopathy are associated with a synchronous cancer occurring ±3 years around the diagnosis. Malignancy is a major cause of mortality in inflammatory myopathy. The association is mainly reported in dermatomyositis (DM) patients. It has been clarified that DM patients positive for either anti-TIF1γ or anti-NXP2 myositis specific anti-bodies have increased risk of cancer. Some reports showed that malignancy could also occur in patients with necrotizing myopathies (NAM).

We aim to analyse the incidence of cancer in a large cohort of NAM with or without the myositis specific anti-single recognition particle (SRP) or anti-3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR) auto-antibodies.

Methods: One hundred fifteen NAM patients were analysed: 48 SRP patients, 52 HMGCR patients and 15 seronegative NAM. NAM was defined based on pathological criteria.

Results: Malignancy occurred in 28.5% of seronegative NAM patients and in 17.3% of HMGCR patients compared to 6.1% in SRP patients (p=0.04). The median time between the diagnostic of malignancy and the myopathy was 4.9±21 months in seronegative NAM patients, 25.1±58 months in HMGCR patients and 80.1±76.2 months in SRP patients. Synchronous malignancy (±3 years) was diagnosed in 21.4% of seronegative NAM patients, 11.5% of HMGCR patients and 4% of SRP patients (p=0.03). No specific types of cancer was predominant. Compare to the French cancer registry increase incidence of cancer occurs in seronegative NAM and HMGCR NAM with standard incidence ratios of 8.35 [1.7-24.4] and 2.79 [1.02-6.07] respectively. Survival analysis showed that patients suffering from a synchronous cancer had a poor out-come with a median survival of 57.2 years (p<0.0001).

Conclusion: Seronegative NAM and anti-HMGCR patients have an increased risk of malignancy. The presence of cancer is associated with a poor survival. Cancer screening is necessary in seronegative and in anti-HMGCR NAM patients.

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View Abstract and Citation Information Online - http://acrabstracts.org/abstract/cancer-and-necrotizing-immune-mopathy-high-incidence-in-anti-3-hydroxy-3-methylglutaryl-coenzyme-a-reductase-positive-and-seronegative-patients-but-not-in-anti-single-recognition-particle-positive-pa

Abstract Number: 291

Correlations Between Muscle-MRI, Muscle Strength and Creatine Kinase Levels in the Anti-Synthetase Syndrome; A Comparative, Cross-Sectional Study

Helena Andersson[1], Eva Kirkhus[2], Else Merckoll[2], Ragnhild Walle-Hansen[3] and Øyvind Molberg[1], [1]Department of Rheumatology, Institute of Clinical Medicine, Oslo University Hospital, Oslo, Norway, [2]Department of Radiology, Oslo University Hospital, Oslo, Norway, [3]Department of Orthopaedic Surgery, Oslo University Hospital, Oslo, Norway

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Session Type: ACR Poster Session A
Session Time: 9:00AM-11:00AM

Background/Purpose:

Muscle MRI is used to describe the myositis component of the anti-synthetase syndrome (ASS), but the value of the examination is limited by lack of reference data from non-myositis populations. The primary aim of this study was therefore to compare the MRI findings in ASS with healthy age- and gender matched controls.

Methods:

In September 2011, 68/70 ASS patients in the Oslo University Hospital ASS cohort were included in a comparative, cross-sectional study that included muscle MRI, manual muscle testing of 24 muscles (MMT24) and plasma CK. Sex and age-matched healthy controls were randomly collected from the National People Register of Norway in a 1:1 proportion (N=67). MRI was using a 1.5 T scanner with coronal and axial T1-weighted spin echo and short T1 inversion recovery (STIR) sequences of thigh muscles. The images were analyzed by two radiologists blinded for the participant's status. Edema in muscles or fascia was evaluated as present/not present. Fatty infiltration was scored according to the Guttalier grading (0-4) and considered pathological if > 2 [1]. Elevated CK was defined as > 2x upper limit of normal (ULN). The MMT24 score (0-140) was performed by two experienced physiotherapists. Chi-Square and Mann Whitney U-test were used to evaluate statistical significance ($p<0.05$). Pearson's correlation was used to detect correlations.

Results:

Median disease duration for the ASS patients was 71 months and 76% had previously been diagnosed with myositis. Abnormal MRI findings were found in 63% of the patients compared to 18 % in the controls with significant differences in the proportion of muscle and fascia edema, as well as fatty infiltration (Table 1). The MRI findings in the control group were to some extent asymmetric. Median MMT24 scores were lower in ASS than controls, but CK levels did not differ between the groups (Table 1). In ASS patients no correlation was seen between muscle-edema and elevated CK or between MMT24 and elevated CK. MRI abnormalities were detected in 35/52 ASS patients with myositis and in 7/15 cases with no previous myositis signs. There was no difference in MMT24 or CK values between the two ASS subsets. Of the 12 controls with abnormal MRI findings, only one had elevated CK and three had MMT24 score ≤ 137.

Table 1; MRI findings, MMT24 and CK levels in ASS patients and matched controls

	ASS N=68	Controls N=67	p-value
MRI findings n/N (%)			
A Edema in muscles	26/67 (39)	7/66 (11)	<0.001
B Edema in fascia	19/67 (28)	5/66 (8)	<0.003
C Fatty infiltration	25/67 (37)	3/66 (5)	<0.001
A, B and/or C	42/67 (63)	12/66 (18)	<0.001
Other muscle parameters			
Median CK, U/ml (range)	95 (24-1344)	98 (35-839)	<0.676
CK> 2x ULN, n/N (%)	4/67 (6)	1/65 (2)	<0.366
Median MMT24 score (range)	139 (114-140)	140 (130-140)	<0.001

Conclusion:

This comparative study reports significant differences in myositis-related MRI findings between ASS patients and matched controls. Muscle-edema was present in 37% of ASS patients with normal CK but only in 10% of the controls. The study shows that MRI has potential as a complementary tool to assess myositis in ASS, and highlights the need for MRI scoring systems that differentiate patients from controls.

References;

1. Goutallier, D., et al., *Influence of cuff muscle fatty degeneration on anatomic and functional outcomes after simple suture of full-thickness tears.* J Shoulder Elbow Surg, 2003. **12**(6): p. 550-4.

Disclosure: H. Andersson, None; **E. Kirkhus**, None; **E. Merckoll**, None; **R. Walle-Hansen**, None; **Molberg**, None.

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Abstract Number: 292

Neoepitope Biomarkers As Biomarkers of Polymyositis and Dermatomyositis and Functional Status

Anders Nedergaard[1], Kim Henriksen[2], Morten Asser Karsdal[3], Wendy White[4] and Xiang Guo[4], [1]Institute of Sports Medicine Copenhagen, Bispebjerg Hospital, Copenhagen NW, Denmark, [2]Nordic Bioscience, Biomarkers and Research, Herlev, Denmark, [3]Biomarkers and Research, Nordic Bioscience, Herlev, Denmark, [4]Translational Sciences, MedImmune, LLC, Gaithersburg, MD

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Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose:

Polymyositis (PM) and Dermatomyositis (DM) are inflammatory conditions characterized by persistent inflammation of muscle tissue (and for DM also skin). Myositis has been shown to be associated with upregulationof MMP expression and activity in muscle.

Neoepitope biomarkers are peptide biomarkers that are the product of pathology specific post-translational modification, e.g. MMP-mediated proteolytic cleavage. Several such biomarkers have shown to be modulated during inflammatory conditions such as rheumatoid arthritis and synovitis in osteoarthritis, as well as in tissue fibrosis. Thus, we hypothesized that they likewise be differentially modeulatedduring DM or PM, individually or together. **Methods:**

In a previously described clinical trial comprised of 61 myositis patients (28 DM, 23 PM) and 30 age and gender-matched controls, we measured the serum biomarkers MMP-cleaved collagens 1, 3, and 6 (C1M, C3M, C6M), Propeptides of collagens 1 and 3 (P1NP and PRO-C3), MMP-cleaved CPR (CRPM), MMP-cleaved titin (TIM), and caspase-cleaved Myosin light chain 3 (MYL-C3). First we analyzed biomarker levels across PM, DM and controls using one-way ANOVA. Second, we analyzed the ability of the biomarkers to separate PM and DM from healthy controls through logistic regression and Receiver-operator characteristic analysis. Third, we examined the relationship between the biomarkers and the MMT8 score (a manual measurement score of muscle function across 8 muscles),

through multivariate regression analysis. **Results:**

We found that C1M, C3M, CRPM, PINP and PRO-C3 were differentially modulated in PM and DM relative to controls (Figure 1), in the form of downregulation of CRPM and PINP relative to controls and upregulationof PRO-C3 in PM and in C1M and C3M in DM.

Next, we found that biomarkers panels could separate DM, PM and DM+PM from controls with 90%+ sensitivity and specificity (area under the curve for corresponding ROC curves of 0,997, 0.973 and 0,996, Figure 2).

Last, we report that biomarker panels can effectively predict MMT8 scores in PM (best model included C6M, $p<0.0001$), DM (best model included C6M and CRPM, $p<0.0001$) and DM+PM (best model included C6M, CRPM and PRO-C3, $p=0.0001$) **Conclusion:**

First, we can report that neoepitope biomarkers differentially produced in myositis patients relative to healthy controls. Second, we found that neoepitope biomarker panels can discriminate between healthy controls and DM, PM or DM/PM combined with extremely high sensitivity and specificity. Third, we report that biomarker panels, particularly C6M, closely followmuscle function.

Figure 1

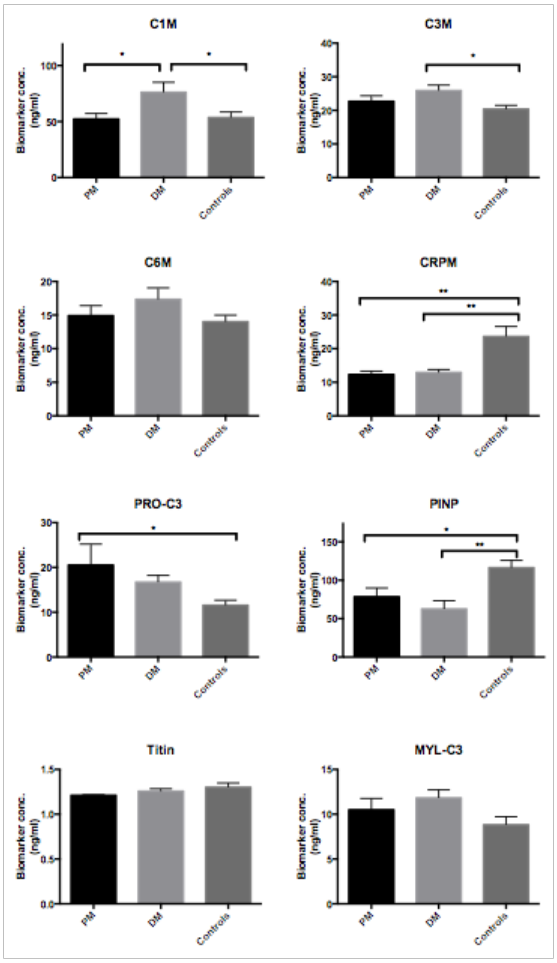
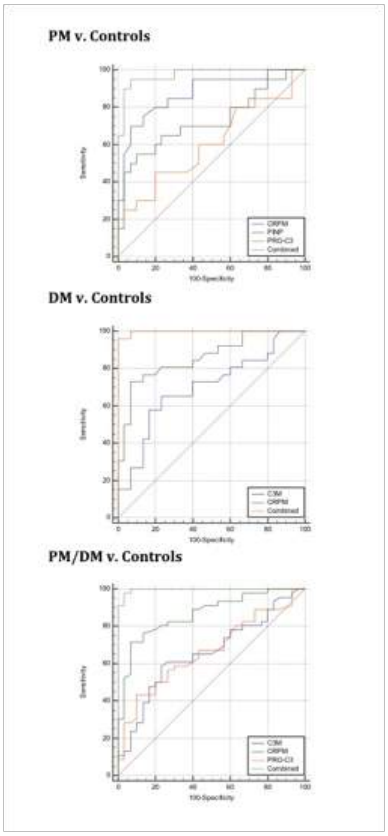


Figure 2



Disclosure: **A. Nedergaard**, None; **K. Henriksen**, Nordic Bioscience Biomarkers and Research, 3; **M. A. Karsdal**, Nordic Bioscience Diagnostic, 1,Nordic Bioscience Diagnostic, 3; **W. White**, AstraZeneca, 1,MedImmune, 3; **X. Guo**, AstraZeneca, 1,MedImmune, 3.

Abstract Number: 293

Measurement of Advanced Glycation Endproducts in the Skin of Patients with Idiopathic Inflammatory Myopathies

Simone Barsotti[1], Chiara Saponaro[2], Rosaria Talarico[3], Alessandra Tripoli[4], Claudia Ferrari[5], Elisabetta Bianchini[6], Nicole Di Lascio[6], Melania Gaggini[2], Amalia Gastaldelli[2], Marta Mosca[7], Maria Aurora Morales[6] and Rossella Neri[5], [1]Division of Rheumatology, Department of Clinical and Experimental Medicine, University of Pisa, Pisa, Italy, [2]National Research Council, Institute of Clinical Physiology, Pisa, Italy, [3]Rheumatology Unit, University of Pisa, Italy, Pisa, Italy, [4]University of Pisa, Rheumatology Unit, Pisa, Italy, [5]Internal Medicine, University of Pisa, Pisa, Italy, [6]Institute of Clinical Physiology, CNR, Pisa, Italy, [7]University of Pisa, Pisa, Italy

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Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose:

Many data suggest that advanced glycation endproducts (AGEs) play an important role the development of atherosclerosis and cardiovascular (CV) disease. AGEs are produced and may accumulate during chronic inflammation, and may impact on patients with idiopathic inflammatory myositis (IIM). The aims of this study was to evaluate whether AGEs are increased in patients with IIM and to explore whether AGE accumulation is related to clinical data, disease activity and measures of subclinical atherosclerosis assessed by ultrasonography sampling of carotid artery.

Methods: Twenty-seven IIM patients (F/M 19/8; mean age 56.7±12.3; mean disease duration 8.8±7 years, 13 polymyositis and 14 dermatomyositis) fulfilling the Bohan and Peter criteria were prospectively enrolled and compared with 29 healthy subjects (HS) matched for age, sex and classical cardiovascular risk factors (smoking habits, diabetes mellitus, hypertension, family history of CV disease, body mass index). AGEs were determined by skin autofluorescence at level of left forearm.

AGEs levels were correlated with demographic data, disease activity parameters (physician and patient's activity using visual analogic scale, manual muscle test 8, muscular enzyme levels, health quality assessment questionnaire), disease duration, cumulative corticosteroids dose. We also collected markers of subclinical atherosclerosis including Intima-Media-Thickness (IMT), mean arterial diameter (mAD) and distensibility coefficient (DC) measured on B-mode ultrasound image sequences of right common carotid artery, 1 cm beneath the bifurcation.

Results:

IIM patients presented higher subcutaneous AGEs than healthy subjects. (mean 2.83 ± 0.6360 DS vs 2.176 ±0.5773 DS) $p<0.001$.

In the IIM group, AGEs are significantly correlated with age ($p=0.011$), and with IMT ($p<0.001$) and mAD ($p=0.035$), while no correlation was found with DC. In healthy subjects, AGEs were significantly correlated with age ($p<0.001$), but no correlations were found between AGEs and IMT, mAD and DC.

In addition, in myositis patients, no correlations were observed between AGEs and gender, classic cardiovascular risk factors, disease duration, cumulative corticosteroid dose, disease activity parameters and laboratory data.

Conclusion:

Our data have shown that IIM patients presented higher AGEs than healthy subjects; a correlation between AGEs and age at the evaluation, and between AGEs and signs of premature atherosclerosis were found. These observations may suggest that, in myositis patients, AGEs may be an early marker of subclinical CV. Further data are necessary to confirm our observation.

Disclosure: S. Barsotti, None; **C. Saponaro**, None; **R. Talarico**, None; **A. Tripoli**, None; **C. Ferrari**, None; **E. Bianchini**, None; **N. Di Lascio**, None; **M. Gaggini**, None; **A. Gastaldelli**, None; **M. Mosca**, None; **M. A. Morales**, None; **R. Neri**, None.

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Abstract Number: 294

A Decline in Pulmonary Function over One Year Predicts Outcome in Myositis-Associated Interstitial Lung Disease

Melissa B. Blom[1], Chester V. Oddis[2], Diane Koontz[3] and **Rohit Aggarwal**[4], [1]Rheumatology, University of Pittsburgh

Medical Center, Pittsburgh, PA, [2]Rheum/Clinical Immunology, University of Pittsburgh, Pittsburgh, PA, [3]Rheumatology, University of Pittsburgh, Pittsburgh, PA, [4]Medicine / Rheumatology, University of Pittsburgh, Pittsburgh, PA

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Session Time: 9:00AM-11:00AM

Background/Purpose: Interstitial lung disease (ILD) is a leading cause of mortality in myositis. Clinical trials in myositis-associated ILD (MA-ILD) are lacking due to the absence of validated outcome measures. Serial pulmonary function tests (PFTs) predict outcome in ILD; however, the degree of change in PFT variables that predict survival has not been studied in MA-ILD. We investigated PFT variable changes over 1 year that predict disease outcome for use in future clinical trials.

Methods: MA-ILD patients were identified from a prospective myositis database (1985-2014). Myositis was defined using the Bohan and Peter classification criteria (probable or definite) *or* anti-synthetase syndrome. The latter was defined by the presence of an anti-synthetase antibody and at least one associated clinical feature. ILD was defined by radiographic fibrosis consistent with ILD. Clinical variables and relative and absolute % change in FVC, FEV-1 and DLCO over 1 year were analyzed for prediction of survival and event-free survival. Relative percent change was defined as [(baseline Ð follow-up)/baseline] x 100, and absolute change was defined as baseline Ð follow-up. Independent variables (relative and absolute % decline in FVC, FEV-1, DLCO by 5/7.5/10/15% over 1 year) were used to predict survival and event-free survival. Event was defined as death or lung transplant. The same independent PFT predictors were evaluated after controlling for baseline PFT values, age, gender and ethnicity. Kaplan Meier and Cox Proportional Hazard model were used for analysis.

Results: 121 MA-ILD patients were identified; 63% (76/121) were female and 87% (101/116) Caucasian with a mean (SD) age at ILD diagnosis of 48 (13.2) years. 104 patients met criteria for anti-synthetase syndrome and 106 (88%) possessed at least one myositis specific antibody. There were 29 events (25 death/9 transplant) with a median (IQR) follow up time of 6.0 (5.2) years from first visit. A relative decline in FVC of 15%, 10% and 7.5%, an absolute decline in FVC of 7.5%, and a relative decline in FEV-1 of 10% predicted survival with HR of 9.2, 8.8, 6.8, 8.9, and 3.5 respectively ($p<0.01$), after controlling for baseline FVC or FEV-1, age at first visit, gender and race (Figure 1). A relative decline in FVC of 15% and 10%, an absolute decline in FVC of 7.5%, and a relative decline in FEV-1 of 10% predicted event-free survival with similar results as above. Relative or absolute declines in %DLCO were not predictive of survival or event- free survival.

Conclusion: Relative declines of 15% and 10% in FVC over 1 year are the best candidates for predicting survival and event-free survival in MA-ILD. Clinical trials for MA-ILD should be done using outcome criteria of 10-15% change in FVC over 1 year.

Figure 1. Kaplan Meier curve for survival outcome in patients with FVC ³10% decline in 1 year of follow up.

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Abstract Number: 295

Reliability of the Cutaneous Dermatomyositis Disease Area and Severity Index Among Dermatologists, Rheumatologists, and Neurologists

Neelam Khan[1,2], Janice Tiao[1,2], Rui Feng[3], Shawn Bird[4], Juliana Choi[1], Michael George[5], Tania Gonzalez-Rivera[5], Jacob L. Kaufman[4], Jin Jun Luo[6], Robert Micheletti[1], Aimee S. Payne[1], Raymond Price[4], Adam I. Rubin[7], Antoine G. Sreih[8], Preethi Thomas[5], Joyce Okawa[7] and Victoria P. Werth[1,9], [1]Department of Dermatology, Hospital of the University of Pennsylvania, Philadelphia, PA, [2]Philadelphia V.A. Medical Center, Philadelphia, PA, [3]Center for Clinical Epidemiology and Biostatistics, University of Pennsylvania, Philadelphia, PA, [4]Department of Neurology, Hospital of the University of Pennsylvania, Philadelphia, PA, [5]Department of Rheumatology, Hospital of the University of Pennsylvania, Philadelphia, PA, [6]Department of Neurology, Temple University School of Medicine, Philadelphia, PA, [7]Department of Dermatology, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA, [8]Department of Rheumatology, University of Pennsylvania, Philadelphia, PA, [9]Philadelphia V.A. Medical Center, Philidelphia, PA

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Background/Purpose: Previous studies have shown that skin lesions in dermatomyositis (DM) are best assessed using the Cutaneous Dermatomyositis Disease Area and Severity Index (CDASI). Although the CDASI has been validated for use by dermatologists, it has not yet been validated for use by other specialists such as rheumatologists and neurologists, who also manage DM patients and evaluate their skin in clinical trials. The purpose of this study is to assess the inter-rater and intra-rater reliability of the CDASI and extend the validation of the CDASI to rheumatologists and neurologists.

Methods: Five dermatologists, five rheumatologists, and five neurologists specializing in neuromuscular medicine individually assessed 15 patients with cutaneous DM using the CDASI and the Physician's Global Assessment (PGA). All physicians received a 30-minute training session on the CDASI and PGA prior to evaluating patients. Each physician also re-rated three patients. Intraclass correlation (ICC) scores <0.5 were considered poor, 0.50 to 0.70 moderate and minimally acceptable, 0.70 to 0.81 good, and >0.81 excellent.

Results: Inter-rater reliability yielded an ICC for CDASI activity that was good for dermatologists and rheumatologists (0.73 and 0.74, respectively) and moderate for neurologists (0.56). The ICC for CDASI damage was excellent for all physicians (dermatologists 0.83, rheumatologists 0.82, neurologists 0.85). For PGA activity, the ICC was moderate for dermatologists (0.61) and rheumatologists (0.69) but poor for neurologists (0.44). The ICC for PGA damage was excellent for neurologists (0.85), good for rheumatologists (0.75), and moderate for dermatologists (0.58) (Table 1).

Intra-rater (test-retest) reliability for CDASI activity was excellent for all physicians (dermatologists 0.94, rheumatologists 0.88, neurologists 0.82). For CDASI damage the scores were excellent for dermatologist and rheumatologists (0.92 and 0.91, respectively) and moderate for neurologists (0.66). For the PGA activity and damage the intra-rater reliability was excellent for dermatologists (0.89 and 0.91, respectively) and good for rheumatologists (0.75 and 0.75, respectively). For neurologists, the PGA activity was good (0.74) but the PGA damage was poor (0.39) (Table 2).

Conclusion: Our data confirm the reliability of the CDASI when used by dermatologists and support the CDASI as a reliable instrument for use by rheumatologists. The data was not as robust for its use by neurologists.

	Within	Within	Within

Table 1. Inter-observer correlation coefficient (95% C.I.)

	dermatologists (n=5)	rheumatologists (n=5)	neurologists (n=5)
CDASI			
Activity	0.73 (0.55-0.90)	0.74 (0.58-0.91)	0.56 (0.33-0.79)
Damage	0.86 (0.76-0.96)	0.82 (0.69-0.94)	0.84 (0.73-0.95)
PGA			
Activity	0.61 (0.40-0.83)	0.69 (0.50-0.88)	0.44 (0.19-0.68)
Damage	0.58 (0.46-0.81)	0.75 (0.60-0.91)	0.85 (0.75-0.96)

	Within dermatologists (n=5)	Within rheumatologists (n=5)	Within neurologists (n=5)
CDASI			
Activity	0.94 (0.88-1.00)	0.88 (0.76-0.99)	0.82 (0.65-0.99)
Damage	0.92 (0.83-1.00)	0.91 (0.82-1.00)	0.66 (0.37-0.95)
PGA			
Activity	0.89 (0.79-1.00)	0.75 (0.53-0.97)	0.74 (0.51-0.97)
Damage	0.91 (0.82-1.00)	0.75 (0.53-0.97)	0.39 (0.00-0.82)

Table 2. Test-retest reliability ICC (95% C.I.)

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Abstract Number: 296

Different Patterns of Involvement of Thigh Muscles in Dermatomyositis and Polymyositis Using Fat-Suppressed Magnetic Resonance Sequences

Nicolo Pipitone[1], Antonella Notarnicola[2], Lucia Spaggiari[3], Gabriele Levrini[4], Arnaldo Scardapane[5], Florenzo Iannone[6], Giovanni Lapadula[6], Giulio Zuccoli[7] and Carlo Salvarani[8], [1]Unità di Reumatologia, Reggio Emilia, Arcispedale Santa Maria Nuova, Bari, Italy, [2]Karolinska Hospital, Rheumatology Unit, Stockholm, Sweden, [3]Radiology, Arcispedale S Maria Nuova, Reggio Emilia, Italy, [4]Arcispedale S Maria Nuova, Reggio Emilia, Italy, [5]Radiology, University of Bari, Bari, Italy, [6]Bari University, Rheumatology, Bari, Italy, [7]Children's Hospital of Pittsburgh, Pittsburgh, PA, [8]Rheumatology, Arcispedale S.Maria Nuova, Reggio Emilia, Italy

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Background/Purpose: MRI is often used to evaluate muscle inflammation in myositis. Muscle edema on fat-suppressed (short tau inversion recovery, STIR) sequences is thought to represent active inflammation. Dermatomyositis (DM) and polymyositis (PM) affect very often thigh muscles. However, it is unclear whether DM and PM differ in the respective

involvement of the various thigh muscle groups. In this study, we aimed to assess which thigh muscle groups are preferentially inflamed in DM and PM, respectively, using MRI fat-suppressed sequences.

Methods: We analysed 72 patients from 2 Rheumatology centers (Reggio Emilia & Bari, Italy), 31 with DM and 41 with PM diagnosed according to Bohan and Peter criteria. MRI edema (1= present, 0= absent) was assessed bilaterally on STIR sequences in 17 thigh/pelvic floor muscles. An MRI composite edema score (0-17) was calculated by adding the separate scores bilaterally and dividing them by two as described in Clin Exp Rheumatol 2012; 30:570. The (single measures) intraclass correlation coefficient (ICC) between the Radiologists involved was 0.78. Fisher's exact test was used for comparison of binomial data.

Results: Age (years, mean±SD) was similar in patients with DM (53 ± 16) and PM (56 ± 16). The F:M ratio was similar in DM (23/8) and PM (32/9). Disease duration (months, mean±SD) was shorter (20±31) in DM than in PM (52±68) (p=0.02). The Table shows the frequency (n° and %) of all thigh muscle groups involved in DM and PM.

TABLE	Compartment	DM (n=31)	PM (n=41)	p value
Gluteus maximus	axial	17 (55%)	13 (32%)	0.06
Quadratus femoris	axial	9 (29%)	1 (2%)	0.002
Vastus lateralis	anterior	15 (48%)	11 (27%)	0.08
Ileopsoas	axial	8 (26%)	3 (7%)	0.046
Vastus medialis	anterior	14 (45%)	10 (24%)	0.08
Tensor fasciae latae	anterior	12 (39%)	4 (10%)	0.005
Rectus femoris	anterior	16 (52%)	10 (24%)	0.03
Sartorius	anterior	13 (42%)	11 (27%)	0.2
Gracilis	medial	15 (48%)	8 (20%)	0.01
Pectineus	medial	8 (26%)	2 (5%)	0.02
Adductor longus	medial	9 (29%)	6 (15%)	0.16
Adductor brevis	medial	12 (39%)	5 (12%)	0.01
Adductor magnus	medial	10 (32%)	10 (24%)	0.6
Short head biceps femoris	posterior	10 (32%)	6 (15%)	0.09
Long head biceps femoris	posterior	12 (39%)	12 (29%)	0.5
Semimembranous	posterior	10 (32%)	8 (20%)	0.3
Semitendineous	posterior	14 (45%)	10 (24%)	0.08

Conclusion: Compared with PM, DM affects more frequently some muscle groups. Posterior muscle groups discriminate poorly between DM and PM. These findings may be useful for differential diagnostic purposes in patients with histological DM without the typical skin rash as well as to target physiotherapy at more frequently affected muscles.

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Abstract Number: 297

How Useful Is Magnetic Resonance Imaging (MRI) in Monitoring Patients with Myositis?

Nicolo Pipitone[1], Antonella Notarnicola[2], Arnaldo Scardapane[3], Gabriele Levrini[4], Lucia Spaggiari[5], Florenzo Iannone[6], Giovanni Lapadula[6], Giulio Zuccoli[7] and Carlo Salvarani[8], [1]Unità di Reumatologia, Reggio Emilia,

Arcispedale Santa Maria Nuova, Bari, Italy, [2]Karolinska Hospital, Rheumatology Unit, Stockholm, Sweden, [3]Radiology, University of Bari, Bari, Italy, [4]Arcispedale S Maria Nuova, Reggio Emilia, Italy, [5]Radiology, Arcispedale S Maria Nuova, Reggio Emilia, Italy, [6]Bari University, Rheumatology, Bari, Italy, [7]Children's Hospital of Pittsburgh, Pittsburgh, PA, [8]Rheumatology, Arcispedale S.Maria Nuova, Reggio Emilia, Italy
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Background/Purpose: MRI is commonly used to assess muscle inflammation in myositis. Muscle edema on fat-suppressed sequences is thought to reflect active inflammation. However, it is unclear how useful MRI is in monitoring patients with myositis, in particular which is its sensitivity to change after treatment onset or intensification. In this study, we aimed to assess changes in the edema of the thigh muscles in a cohort of patients with myositis at their first presentation to our centers (T0) and at follow-up after onset/intensification of immunosuppressive therapy (T1). Ancillary aims were to correlate the extent of muscle edema on MRI with serum creakine kinase (CK) and muscle strength .

Methods: We enrolled in 2 Rheumatology centers 36 patients, 17 with dermatomyositis (DM) and 19 with polymyositis (PM) diagnosed according to Bohan and Peter criteria. The diagnosis of PM was confirmed by histology in all cases. In all patients, CK was measured, manual muscle test (MMT) was performed, and MRI fat-suppressed sequences were acquired within a week. MRI edema (1= present, 0= absent) was assessed bilaterally in 17 thigh and pelvic floor muscles. An MRI composite edema score (0-17) was calculated by adding the separate scores bilaterally and dividing them by two as described in Clin Exp Rheumatol 2012; 30:570-3. The CK upper limit of normal was 190 U/l. The (single measures) intraclass correlation coefficient (ICC) between the Radiologists involved was 0.78. Muscle strength was measured by MMT and graded according to the Medical Research Council extended scale (0-5). The ICC between the 2 physicians performing the MMT was 0.8. Analysis was performed by Wilcoxon sum rank and Spearman's tests, as appropriate

Results: Mean age (years±SD) was 54±15. The ratio F:M was 31:5. MRI was positive (edema score equal to, or greater than 1) in 26 (72%) patients at T0 and in 18 (50%) at T1. Mean MRI edema score was 5±5.2 (mean±SD) at T0 and 2.4±4.5 at T1 (p=0.002). Median and interquartile range (IQR) of MRI edema score were 3.5 (8) at T0 and 0.5 (4.5) at T1. CK was elevated in 22 (61%) patients at T0 and 10 (28%) at T1. CK was 1,816±3,560 at T0 and 531±1,536 at T1 (p=0.002). MMT score was 4.4±0.44 at T0 and 4.6±0.40 at T1 (p=0.02). MRI edema score did not correlate with CK or MMT scores neither at T0 nor T1. Eleven patients had a normal CK but a positive MRI at T0. In 5 of these patients, MRI became negative at T1. In the 11 patients with a normal CK but positive MRI at baseline, MRI edema score decreased from 6.7±5.3 at T0 to 2.4±2.7 at T1 (significance not calculated because of the small sample size).

Conclusion: MRI is a useful tool to monitor patients with myositis, and might particularly have a role in monitoring disease activity in patients with a normal serum CK at baseline. Larger studies are required to confirm our findings.

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Abstract Number: 298

Investigating the Pathogenic Role of ER Stress Pathway Activation in the Idiopathic Inflammatory Myopathies (IIM): Skeletal Muscle Cells As a Source of Cytokines (Myokines)

Adam P. Lightfoot[1], Katarzyna Goljanek-Whysall[2], Kate E. Earl[2], Caroline V. Cotton[2], Anne McArdle[1] and Robert G. Cooper[3], [1]Musculoskeletal Biology, University of Liverpool, Liverpool, United Kingdom, [2]University of Liverpool, Liverpool, United Kingdom, [3]Rheumatic Diseaes Center, Salford Royal Foundation Trust, University of Manchester, Salford, United Kingdom

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Background/Purpose: The idiopathic inflammatory myopathies (IIM) are a collection of autoimmune disorders, characterised by the development of debilitating symmetrical skeletal muscle weakness. IIM Patients also have elevated creatine kinase levels with an array of circulating myositis-specific autoantibodies. Upregulation of major histocompatibility complex (MHC) I molecules *in vitro* and *in vivo*is also a characteristic histological finding, and associated with activation of the Endoplasmic Reticulum (ER) stress response (Nagaraju et al. 2005). Pharmacological activation of the ER stress response is known to cause increased expression of pro-inflammatory muscle-derived cytokines, or myokines (Welc et al. 2013). Based on recent research demonstrating that skeletal muscle acts as a source for many and diverse cytokines, we investigated whether induced MHC I overexpression in myotubes would result in ER stress pathway activation, and release of cytokines.**Methods:** Murine C2C12 myotubes were transfected with a vector to overexpressing MHC I (H2-k^b) using Lipofectamine2000^{TM} transfection reagent with, or without the presence of salubrinal, an ER stress blocking agent. Successful transfection of the MHC I (H2-k^b) vector was confirmed using qPCR. Cellular cytokine gene expression and release was examined using qPCR and Luminex multiplex analysis respectively. ER stress pathway activation was confirmed using qPCR and SDS-PAGE/western blotting. **Results:** The results show that overexpression of MHC I within C2C12 myotubes results in activation of the ER stress pathway, evidenced by upregulation of the ER stress genes, Grp78, ATF6, PERK, IRE1 and XBP-1. ER stress pathway blocking by salubrinal was confirmed by elevated levels of phosphorylated eif2-alpha. Overexpression of MHC I in C2C12 myotubes also resulted in increased gene expression and release of the potentially chemotactic cytokines IL-6, CCL2, CCL4, CCL5 and CXCL-1. This cytokine expression/release was significantly reduced when transfection occurred in the presence of salubrinal. **Conclusion:** Our data builds on previous published findings demonstrating that MHC-1 overexpression in skeletal muscle causes ER stress pathway activation. Our results also demonstrate that muscle is potentially a source of various cytokines, a process mediated here via ER stress pathway activation. These findings suggest that muscle cells may exhibit chemotactic capability, so attracting immune cells. Such myokines release suggests muscle may exert paracrine signals on neighbouring fibres, which could contribute to muscle dysfunction in the absence of immune cells. Skeletal muscle may thus act as a source of cytokines in the IIM. Targeted therapies towards myokine production may thus be worthy of further investigation, to further understand muscle dysfunction in IIM.

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Abstract Number: 299

Subcutaneous Edema, Distal Weakness and Dysphagia Associated with the NXP2 Antibody

Jemima Albayda[1], Iago Pinal-Fernandez[2], Lisa Christopher-Stine[3], Sonye K. Danoff[4], Cheilonda Johnson[5], Christopher Mecoli[6], Julie J. Paik[7], Alim Ramji[8] and Andrew Mammen[9], [1]Rheumatology, Johns Hopkins University School of Medicine, Baltimore, MD, [2]Autoimmune Systemic Diseases Unit, Vall D'Hebron University Hospital, Universitat Autònoma de Barcelona, Barcelona, Spain, [3]Ste 4100 Rm 409, Johns Hopkins University School of Medicine, Baltimore, MD, [4]Medicine/Pulmonary, Johns Hopkins School of Medicine, Baltimore, MD, [5]Medicine/Pulmonology, Johns Hopkins University, Baltimore, MD, [6]Rheumatology, Johns Hopkins University, Baltimore, MD, [7]Division of Rheumatology, Johns Hopkins University School of Medicine, Baltimore, MD, [8]School of Medicine, Johns Hopkins University, Baltimore, MD, [9]Center Tower Ste 5300, Johns Hopkins University School of Medicine, Baltimore, MD

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Background/Purpose:

Myositis specific antibodies are known to be associated with specific phenotypes. The unusual presentation of subcutaneous edema, distal weakness and dysphagia was seen in several successive patients who were found to be positive for the NXP2 antibody. Further analysis was done to determine if this association was more common with this antibody.

Methods:

A retrospective chart review was completed on patients seen in the Johns Hopkins Myositis Center during the period of 2002-2015. Patients were included in our analysis if they met Bohan and Peter criteria for definite or probable dermatomyositis, Sontheimer's criteria for amyopathic dermatomyositis, or dermatomyositis by muscle biopsy using ENMC criteria, with known antibody status and available clinical data. Patients who had confirmed autoantibody testing at a CLIA certified lab were included in this study. One hundred and twenty two patients met the criteria and were included for analysis, with 40 patients being NXP2 positive. Subcutaneous edema was defined as pitting or non-pitting edema of one or more extremity that accompanied the active phase of the disease. Muscle strength was graded for 16 muscle groups using the Medical Research Council (MRC) scale. Dysphagia was determined clinically by patient report. Parametric analysis was used to determine the difference between these variables in patients positive for the NXP2 antibody and those with antibodies other than NXP2.

Results:

The edematous phenotype was seen more commonly in the NXP2 + patients than in the NXP2- patients (45% vs. 10%, $p<0.001$). Overall, NXP2 + patients had statistically significant weakness in distal muscle groups (finger extensors, ankle flexors and ankle extensors) as compared to NXP2- patients. NXP2 is also associated with dysphagia (68% in NXP2+ vs 31% in NXP2-, $p<0.001$). In NXP2+ patients with edema, there was an associated increase in weakness (significant at the deltoids, triceps, wrist extensors and ankle extensors). There was also a trend to have more dysphagia than in those without edema (82% in those with edema vs 57% in those without it, $p=0.1$).

Conclusion:

A specific phenotype of subcutaneous edema associated with more severe muscle weakness, distal involvement and dysphagia is associated with the NXP2 antibody.

Disclosure: J. Albayda, None; **I. Pinal-Fernandez**, None; **L. Christopher-Stine**, None; **S. K. Danoff**, None; **C. Johnson**, None; **C. Mecoli**, None; **J. J. Paik**, None; **A. Ramji**, None; **A. Mammen**, None.

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Abstract Number: 300

Causes of Creatine Kinase Levels Greater Than 1,000 IU/L in Patients Referred to Rheumatology

David Leverenz[1], Oana Zaha[2], Leslie J. Crofford[1] and Cecilia P. Chung[3], [1]Medicine, Vanderbilt University, Nashville, TN, [2]Medicine, Div of Rheumatology and Immunology, Vanderbilt University, Nashville, TN, [3]Medicine, Div of Rheumatology & Immunology, Vanderbilt University, Nashville, TN

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Background/Purpose: Patients with significantly elevated creatine kinase (CK) levels are commonly referred to rheumatologists to evaluate for the presence of an idiopathic inflammatory myopathy (IIM). However, no studies have evaluated the frequency with which IIMs are encountered in this clinical scenario. The purpose of this study was to define the causes of elevated CK levels in patients referred for rheumatology consultation with a CK greater than 1,000 IU/L and to examine the clinical characteristics of these patients to determine if any distinguishing factors could be discerned.

Methods: The Vanderbilt Synthetic Derivative, a de-identified copy of over 2 million patient charts, was searched to identify patients with a CK greater than 1,000 IU/L. Other inclusion criteria were age greater than 18 and containing a document with the word rheumatology. Patients were excluded if rheumatology involvement was unrelated to the elevated CK or if there was inadequate follow-up. These criteria identified 192 patients who were assigned a diagnosis using a pre-defined algorithm. Patients determined to have an IIM were classified using the Bohan and Peter criteria for dermatomyositis (DM) and polymyositis (PM), the Griggs criteria for inclusion body myositis (IBM), or by clinical diagnosis for patients with an overlap syndrome, necrotizing myopathy, or DM/PM not meeting the above criteria. To ensure diagnostic consistency and accuracy, 10% of the charts were examined by an independent reviewer. Each chart was reviewed for pertinent demographic data and clinical characteristics.

Results: A total of 105 (55%) patients were diagnosed with an IIM. The majority of the IIM patients met Bohan and Peter criteria for DM (n=24, 13%), PM (n=41, 21%), or were diagnosed clinically with an overlap syndrome (n=28, 15%). The rest of the IIM patients were diagnosed with a necrotizing myopathy (n=2, 1%), IBM (n=1, <1%), or an IIM not meeting criteria (n=9, 5%). The non-IIM causes were drug or toxin exposure (n=16, 8%), infection (n=12, 6%), trauma (n=10, 5%), myocardial injury (n=5, 3%), hypothyroidism (n=4, 2%), muscular dystrophy (n=4, 2%), neuropsychiatric disorder (n=3, 2%), glycogen storage disorder (n=1, <1%), mitochondrial myopathy (n=1, <1%), idiopathic CK elevation (n=11, 6%), and other diagnoses (n=20, 10%). Several characteristics were found to be significantly different between IIM and non-IIM cases. Patients with an IIM were more likely to be younger (average age 48 vs. 53, p=0.04), female (71% vs. 40%, p<0.001), seen in clinic and not as an inpatient (78% vs. 44%, p<0.001),

have symptoms longer than 6 months (55% vs. 29%, p<0.001), have an ANA greater than or equal to 1:40 (54% vs. 24%, p<0.001), and have a positive Jo-1 antibody (11% vs. 0%, p=0.001). Patients without an IIM had more cardiac and renal comorbidities (61% vs. 31%, p<0.001 and 16% vs. 3%, p=0.002 respectively). There was no significant difference between the CK levels of patients with IIM vs. non-IIM.

Conclusion: More than half of patients referred for rheumatology consultation with a CK greater than 1,000 IU/L were diagnosed with an IIM. Given the importance of prompt diagnosis and treatment, rapid assessment by the consulting rheumatologist for these patients is recommended.

Disclosure: D. Leverenz, None; **O. Zaha**, None; **L. J. Crofford**, None; **C. P. Chung**, NIH, 2.

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Abstract Number: 301

Economic Burden of Sporadic Inclusion Body Myositis in the United States of America: A Retrospective Cohort Study

Haijun Tian[1], Changgeng Zhao[1], Victoria Barghout[2], Zhongyuan Wei[3], Neetu Agashivala[1], Aoife Callan[4] and **Gorana capkun-Niggli**[5], [1]Novartis Pharmaceuticals Corporation, East Hanover, NJ, [2]VEB HealthCare LLC, Morristown, NJ, [3]KMK Consulting Inc, Morristown, NJ, [4]Novartis Pharmaceuticals Corporation, Dublin, Ireland, [5]Novartis Pharmaceuticals Corporation, Basel, Switzerland

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Background/Purpose: Sporadic inclusion body myositis (sIBM) is a rare & debilitating muscle disease characterized by the slow progressive asymmetric weakness, atrophy of proximal & distal muscle, with symptoms generally developing ≥ 50 years of age. This study aimed to describe demographics & clinical profile of sIBM patients, to evaluate their healthcare resource utilization & economic cost compared to a matched general population cohort.

Methods: Using administrative claims data from the Truven MarketScan Commercial & Medicare supplemental database, the sIBM patient cohort included patients (≥50 years) with ≥2 outpatient diagnoses of sIBM ≥7 days apart or with ≥ 1 inpatient sIBM diagnosis identified between January 1, 2010 & December 31, 2012. The date of the first observed diagnosis of sIBM was defined as the index date; patients with ≥1 year continuous enrollment in medical insurance plans pre- & post-index were included. The control cohort was selected from patients without sIBM with ≥ 1 healthcare encounter between January 1, 2010 & December 31, 2012. Patients with diagnoses of congenital hereditary muscular dystrophy/ hereditary progressive muscular dystrophy were excluded. Control patients were matched to sIBM patients by age, gender, region, continuous enrollment of medical benefits in 1: 5 ratio & were assigned the same index date as the paired sIBM patients. Generalized Estimating Equation models with appropriate link functions & two parts models were conducted controlling for matching structure, to assess health care utilization & costs of sIBM patients in the follow up period compared to the control group, adjusting for baseline characteristics and healthcare resource utilization.

Results: 333 sIBM patients & 1,665 matched controls (66% male) with a mean age of 69 years (SD: 9.6) were included in the analysis. Charlson comorbidity index score was significantly higher (P<0.0001) in sIBM patients

(Mean: 2.0 SD: 2.4) compared to controls (Mean: 1.2, SD: 1.9). 11.1% of sIBM patients reported pneumonia compared to 3.2% of the controls, while 22.5% of sIBM patients reported dsyphagia compared to 2.0% of the controls (P<0.0000). Falls requiring medical visit were reported by 8.1% of sIBM patients compared to 1.1% of the controls (P<0.0000). 26% of sIBM patients had an all-cause hospitalizations, 42% had an ER visits & 99% had an office visit compared to the control patients of 12%, 22%, and 95% (P<0.0002), respectively. Number of office visits were significantly higher in sIBM patients compared to control (mean [SD]): 11.4 [7.2] vs. 7.0 [6.3], P<0.0001). Adjusting for baseline characteristics, sIBM patients had higher risk of all-cause hospitalization, (OR: 1.89; 95% CI: 1.34–2.67), all-cause ER visits (OR: 1.94; 95% CI: 1.46–2.58), office visits (OR: 3.03; 95% CI: 0.88–10.49), & had higher healthcare cost (Mean difference: $19,389; 95% CI: 12,855–26,763) compared to the control group.

Conclusion: sIBM imposes a considerable economic burden in terms of increased healthcare resource used & associated costs compared to the matched general population. The major cost driver was outpatient costs.

Disclosure: H. Tian, Novartis Pharmaceutical Corporation, 3; **C. Zhao**, Novartis Pharmaceutical Corporation, 3; **V. Barghout**, Novartis Pharmaceutical Corporation, 5; **Z. Wei**, Novartis Pharmaceutical Corporation, 5; **N. Agashivala**, Novartis Pharmaceuticals Corporation, 3; **A. Callan**, Norartis Ireland Ltd, 3; **G. capkun-Niggli**, Novartis Pharmaceutical Corporation, 3.

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Abstract Number: 302

Resource Utilization in a US Sample of Patients with Sporadic Inclusion Body Myositis

Victoria Barghout[1], Carla DeMuro[2], Bob Goldberg[3], Mark A Price[2], Linda Lowes[4], **Gorana capkun-Niggli**[5], Valerie Williams[6] and Brian Tseng[7], [1]VEB HealthCare LLC, Morristown, NJ, [2]RTI Health Solutions, North Carolina, NC, [3]The Myositis Association, Alexandria, VA, [4]Nationwide Children's Hospital, Columbus, OH, [5]Novartis Pharmaceuticals Corporation, Basel, Switzerland, [6]Psychometrics, RTI Health Solutions, North Carolina, NC, [7]Novartis Pharmaceuticals Corporation, East Hanover, NJ

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Background/Purpose: Sporadic Inclusion Body Myositis (sIBM) is a progressive, idiopathic inflammatory myopathy characterized by dysphagia, weakness of proximal and distal muscles and atrophy. This cross-sectional study aims to characterize the socioeconomic burden of sIBM patients in the United States (US).

Methods: sIBM patients registered for The Myositis Association 2013 and 2014 annual patient conferences completed the Skeletal Muscle Activity and Resource Tool for sIBM (SMART-sIBM). The SMART-sIBM is a measure of self-reported resource utilization developed with extensive sIBM patient input and cognitively tested (sIBM patient interviews) to ensure its relevance to the sIBM patient population. The SMART-sIBM is designed to characterize direct and out-of-pocket expenses including items not reimbursed by US third-party payers. Patients completed the SMART-sIBM either electronically or using paper forms.

Results: Of 102 unique sIBM patients who participated, 31 were assessed both years. For the overall sample, mean age was 67.2 years (range 49–88), and the majority were male (62%), Caucasian (96%). Mean (±SD) number of years since diagnosis was 5.3 (±4.3) and years since first symptoms was 11.3 (±6.4). Approximately 36% of participants were ambulatory without use of an assistive device, 36% used an aid/brace, 17% used power mobility for long distances, 7% used power mobility most of the time, and 4% were not able to walk or stand. The average number of falls in the past month was <1 (range: 0–4) and the average number of healthcare visits due to falls in the past 12 months was 0.71 (±1.8, range: 0–12). In the past 6 months 62% of participants reported visiting specialists for their sIBM and 39% visited a general practitioner. A large majority of sIBM patients (68.4%) reported that they had to make non-reimbursed modifications to their house, apartment, or car because of their sIBM, and 76.5% reported non-reimbursed purchases of special equipment, devices, or aids since diagnosis with sIBM. Paid help for household tasks was required by 37% of participants, 60% relied on unpaid caregivers (87.5% spouse), and 42% reported a change in job status due to sIBM-related functional limitations.

Conclusion:

This study provides resource utilization data for the first time in a US sample of patients with sIBM. sIBM patients experience considerable financial burden, including important out-of-pocket expenses, due to their physical disability and loss of independence.

Disclosure: V. Barghout, Novartis Pharmaceutical Corporation, 5; **C. DeMuro**, Novartis Pharmaceutical Corporation, RTI Health Soultions, 9; **B. Goldberg**, None; **M. A. Price**, Novartis Pharmaceutical Corporation, RTI Health Solutions, 9; **L. Lowes**, Novartis Pharmaceutical Corporation, 5; **G. capkun-Niggli**, Novartis Pharmaceutical Corporation, 3; **V. Williams**, Novartis Pharmaceutical Corporation, RTI Health Solutions, 9; **B. Tseng**, Novartis Pharmaceutical Corporation, 3.

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Abstract Number: 303

Mining RNA-Seq of Peripheral Blood Mononuclear Cells from JDM Alone Compared with JDM Plus Psoriasis for Biomarkers of Disease Activity

Elisha D.O. Roberson[1], Li Cao[2], Gabrielle A. Morgan[3,4,5], Adam Ostrower[3,4,5], Chiang-Ching Huang[6] and Lauren M. Pachman[3,4,5], [1]John T. Milliken Department of Medicine, Division of Rheumatology, Washington University School of Medicine, Saint Louis, MO, [2]John T. Milliken Department of Medicine, Division of Rheumatology, Washington University School of Medicine, St. Louis, MO, [3]Cure JM Program of Excellence in Juvenile Myositis Research, Stanley Manne Children's Research Institute, affiliated with Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, IL, [4]Pediatric Rheumatology, Northwestern University Feinberg School of Medicine, Chicago, IL, [5]Rheumatology/Immunology, Ann & Robert H. Lurie Children's Hosptial of Chicago, Chicago, IL, [6]Zilber School of Public Health, University of Wisconsin, Milwaukee, Milwaukee, WI

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Background/Purpose: Our CureJM JDM Registry/Repository contains sequential samples of peripheral blood mononuclear cells (PBMCs) and sera obtained every 6 months from over 467 children with definite juvenile dermatomyositis (JDM). Recent international genome-wide association studies confirmed that the highest genetic association with JDM is the ancestral HLA locus on chromosome 6, shared with other autoimmune disease, but did not identify novel pathways with genome-wide significance. In our cohort, 7.9% of JDM patients have another autoimmune disease; psoriasis is the most prevalent with 9 cases (2.2%). The purpose of this study was to assay PBMC samples using RNA-Seq to find biomarkers of disease activity for JDM as well as psoriasis.

Methods: After informed consent, PBMCs were obtained from 4 M and 5 F JDM patients (mean age <7), along with 2 M and 2 F controls (mean age 13.5). Of the JDM, 4 had JDM alone, 5 had JDM initially and later in their disease course developed psoriasis; all were tested versus the 4 controls. We utilized 18 total samples from the 9 JDM patients and 4 controls for RNA extraction and stranded RNA-Seq. We aligned the data to GRCh38 with STAR and analyzed differential expression using different strategies, including cuffdiff2, DESeq2, and edgeRun.

Results: Both the JDM-only and JDM pre-psoriasis samples show increased fold-changes (FC) compared to control samples for both *CD69* (FC $\geq$ 3.5) which may be a signal of T cell proliferation and *CD83* (FC $\geq$ 6), a marker enriched on mature dendritic cells. In the pre-psoriatic samples the significant changes included increases in the transcription factors *ATF3* (FC $\geq$ 9) and *NR4A1* (FC $\geq$ 4), as well as *IL1B* (FC $\geq$ 10) and Fos ligand (*FOSL1*; FC $\geq$ 20), in addition to genes associated with TNFα and NFκB signaling as determined by Gene Ontology, Corum, and KEGG annotations. At the time of psoriatic symptoms, the expression of *CD69* had normalized in some patients with previous JDM. The post-psoriatic samples were similar to controls and the majority of the JDM inflammatory signatures had resolved.

Conclusion: 1) Upregulation of *CD69*, *CD83*, along with increased TNFα and NFκB signaling, are components of the pathophysiology of JDM which may resolve as the disease subsides; 2) In the pre-psoriasis state, upregulation of transcription factors *ATF3* and *NR4A1*, as well as *IL1B* and *FOSL1*were documented.

Speculation: These gene expression patterns could represent biomarkers for the evolution of phases of JDM clinical activity, but increased sample size is needed to fully differentiate the JDM and psoriatic signatures.

Disclosure: E. D. O. Roberson, None; **L. Cao**, None; **G. A. Morgan**, None; **A. Ostrower**, None; **C. C. Huang**, None; **L. M. Pachman**, None.

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Abstract Number: 304

Abnormal Pulmonary Function Tests, Interstitial Lung Disease, and Lung Function Decline in Patients with Classic and Clinically Amyopathic Dermatomyositis

Michael George[1], Maryl Kreider[2], Rupal Shah[2], Wallace Miller Jr.[3], Peter A. Merkel[4] and Victoria Werth[5,6], [1]Department of Rheumatology, Hospital of the University of Pennsylvania, Philadelphia, PA, [2]Pulmonary, Allergy & Critical Care, University of Pennsylvania, Philadelphia, PA, [3]Radiology, University of Pennsylvania, Philadelphia, PA, [4]Penn Vasculitis Center, Division of Rheumatology, University of Pennsylvania, Philadelphia, PA, [5]Dermatology, Veterans Affairs Medical Center, Philadelphia, PA, [6]Dermatology, University of Pennsylvania, Philadelphia, PA

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Background/Purpose: Interstitial lung disease (ILD) is common in classic dermatomyositis (DM) and clinically amyopathic dermatomyositis (CADM), in which rash is present without weakness. Previous studies have shown increased mortality from ILD in CADM vs. DM due to increased rates of acute-onset lung disease. This study aimed to 1) identify the frequency of abnormal pulmonary function tests (PFTs) in patients with DM and CADM and 2) assess frequency of ILD and changes in PFTs in patients with abnormal PFTs.

Methods: Medical records of patients in an established single-center outpatient dermatology cohort were screened to identify patients with possible, probable, or definite DM based on Bohan and Peter criteria or CADM based on Sontheimer criteria, excluding overlap connective tissue disease. Charts of patients with any abnormal PFTs (FVC, TLC, or DLCO < 80% predicted) were reviewed in detail. A radiologist blinded to clinical characteristics reviewed chest CTs obtained within 1 year of the first available abnormal PFTs to identify evidence of ILD. Follow-up PFTs were recorded, with significant change defined as a 15% change in DLCO or 10% change in FVC or TLC compared to the first abnormal PFTs.

Results: 128 patients met inclusion criteria, 76 with DM and 52 with CADM. 69 (91%) patients with DM and 47 (90%) with CADM had PFTs available. Abnormal PFTs were present in 34 (46%) patients with DM and 20 (38%) with CADM ($p = 0.48$). Characteristics of these patients are shown (Table 1). A CT was available for review in 39/54 (72%) of patients with abnormal PFTs. Among those with an available CT, ILD was present in 9/23 (39%) patients with DM vs. 6/16 (38%) with CADM ($p = 0.92$). Follow-up PFTs were available for review in 38/39 (97%) patients with median follow-up of 3 years (range 0.5 to 9.5). 32/38 (84%) of patients received immunosuppression during follow-up. At last follow-up, PFTs declined significantly in 4/15 (27%) of patients with ILD and 7/23 (30%) of patients without ILD. Among those with ILD, patients with a history of acute-onset ILD but not CADM were more likely to have a decline in PFTs (Table 2). Anti-Jo-1 antibodies and inflammatory arthritis were more common in patients with PFT decline although differences were not statistically significant.

Conclusion: PFT abnormalities are common and present at similar rates in patients with DM and CADM. In patients with abnormal PFTs, CT evidence of ILD is found at baseline in less than half of patients with either DM or CADM. History of acute-onset ILD is associated with increased frequency of PFT decline. Patients with CADM are not more likely than patients with DM to have a decline in PFTs.

Table 1: Characteristics of patients with classic DM vs CADM with abnormal pulmonary function tests			
	Classic DM (n = 34)	**CADM (n = 20)**	**p-value**
Age, years	52 [45, 62]	59 [50, 68]	0.11
Female	25 (74%)	18 (90%)	0.15
Caucasian	29 (85%)	18 (90%)	0.62
Disease duration, years	1.5 [0.6, 7.2]	1.8 [0.9, 4.0]	0.94
Malignancy within 5 years of diagnosis	6 (18%)	2 (10%)	0.44
Dyspnea at baseline*	13 (38%)	8 (40%)	0.74
Cough at baseline	6 (18%)	6 (30%)	0.35
History of acute onset ILD	2 (6%)	2 (10%)	0.58
Fever associated with DM	3 (9%)	3 (15%)	0.49
Raynaud's phenomenon	5 (15%)	4 (20%)	0.61
Inflammatory arthritis	7 (21%)	5 (25%)	0.71
Mechanic's hands	9 (26%)	10 (50%)	0.08
Echocardiogram with pulmonary hypertension (PASP ³ 35 mmHg)	0/20 (0%)	3/12 (15%)	0.06
Creatine kinase at baseline, units/L	138 [70, 269]	52 [29, 97]	< 0.01
Peak creatine kinase, units/L	395 [221, 2480]	68 [41, 121]	< 0.01
Aldolase at baseline, units/L	4.4 [3.1, 5.9]	4.8 [4.4, 6.3]	0.30
Peak aldolase, units/L	6.2 [4.9, 9.7]	4.8 [4.3, 6.5]	0.06
Hemoglobin at baseline, g/dL	13.6 [12.2, 14.2]	13.5 [12.6, 14.1]	0.71
ANA ³ 1:160	14/29 (41%)	6/18 (30%)	0.53
Anti-Jo-1 antibodies	4/21 (12%)	2/13 (10%)	0.94
Anti-SSA antibodies	3/22 (9%)	1/14 (5%)	0.79
Anti-RNP antibodies	1/10 (3%)	0/9 (0%)	0.53
DLCO % predicted	74 [64, 79]	67 [58, 72]	0.08
FVC % predicted	81 [71, 91]	88 [78, 97]	0.18
TLC % predicted	86 [77, 98]	87 [70, 98]	0.60
Pulmonary function test pattern			

- Isolated low DLCO	14 (41%)	12 (60%)	0.26
- Restriction	8 (24%)	3 (15%)	0.51
- Obstruction	10 (29%)	2 (10%)	0.17
- Mixed or Undetermined**	2 (6%)	2 (10%)	0.62
- Nonspecific FVC reduction	0 (0%)	1 (5%)	0.37

Median [IQR] compared with Wilcoxon rank-sum. Number (%) compared with Chi-squared or Fisher's exact test if expected values ² 5

* Baseline defined as time of the first available abnormal PFTs

** Undetermined if TLC not available and unable to distinguish obstruction from restriction

DM: dermatomyositis, CADM: clinically amyopathic dermatomyositis, ILD: interstitial lung disease, PASP: pulmonary artery systolic pressure, DLCO: diffusion capacity for carbon monoxide, FVC: forced vital capacity, TLC: total lung capacity

Table 2: Characteristics associated with decline in pulmonary function tests* among patients with dermatomyositis with interstitial lung disease on chest CT			
	PFT Decline (n = 4)	**No PFT decline (n = 11)**	**p-value**
Female	3 (75%)	5 (45%)	0.57
Age, years	54 [45, 63]	59 [48, 64]	0.51
Classic Dermatomyositis	2 (50%)	7 (64%)	1.0
Clinically Amyopathic Dermatomyositis	2 (50%)	4 (36%)	1.0
Disease duration at baseline	1.5 [0.5, 3.1]	0.8 [0.3, 1.4]	0.60
Duration of follow-up	4.6 [2.3, 5.7]	3.5 [1.4, 6.8]	0.90
History of acute-onset lung disease	3 (75%)	1 (9%)	0.03
Arthritis	3 (75%)	2 (18%)	0.08
Raynaud's phenomenon	1 (25%)	0 (0%)	0.27
Fever	2 (50%)	2 (18%)	0.52
Never smoker	4 (100%)	6 (55%)	0.23
Non-specific interstitial pneumonia	3 (75%)	9 (82%)	1.0
Cryptogenic organizing pneumonia	1 (25%)	2 (18%)	1.0
Anti-Jo-1 antibodies	3/4 (75%)	1/7 (8%)	0.07
Anti-SSA antibodies	1/3 (25%)	0/7 (0%)	0.09
Immunosuppression during follow-up	4 (100%)	9 (92%)	1.0
Lost to follow-up	0 (0%)	1 (9%)	1.0
Died	1 (25%)	0 (0%)	0.27
Median [IQR] compared with Wilcoxon rank-sum. Number (%) compared with Fisher's exact *PFT decline defined as 15% reduction in DLCO or 10% reduction in FVC or TLC based on American Thoracic Society guidelines			

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Abstract Number: 305

The “Sleeve Sign” in Dermatomyositis

Arash Lahoutiharahdashti[1], Julie J. Paik[2], Jemima Albayda[1], Andrew Mammen[3,4] and Lisa Christopher-Stine[5], [1]Rheumatology, Johns Hopkins University School of Medicine, Baltimore, MD, [2]Division of Rheumatology, Johns Hopkins University School of Medicine, Baltimore, MD, [3]Center Tower Ste 5300, Johns Hopkins University School of Medicine, Baltimore, MD, [4]NIAMS, NIH, Bethesda, MD, [5]Ste 4100 Rm 409, Johns Hopkins University School of Medicine, Baltimore, MD
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Background/Purpose:

Dermatomyositis (DM) is a subset of idiopathic inflammatory myopathies, characterized by proximal skeletal muscle weakness and skin manifestations. Several skin eruptions have been described in DM patients including Gottron's papules, Gottron's sign, heliotrope rash, facial erythema, periungual erythema, shawl sign, V-neck sign, and holster sign. We describe a new skin eruption we have termed the "sleeve sign" observed in 27 patients with DM. To our knowledge, this typical skin finding has not been described before.

Methods:

Two hundred sixty-two patients with a Bohan and Peter diagnosis of definite, probable, or possible DM or a diagnosis of amyopathic DM by Sontheimer's criteria were evaluated in a systematic fashion including a detailed skin examination with distribution and location of cutaneous findings. All patients underwent clinical evaluation between 2004 and 2015. Demographic and clinical information were retrieved by chart review. Patients' sera were tested for myositis-specific antibodies using previously validated immunoprecipitation methods.

Results:

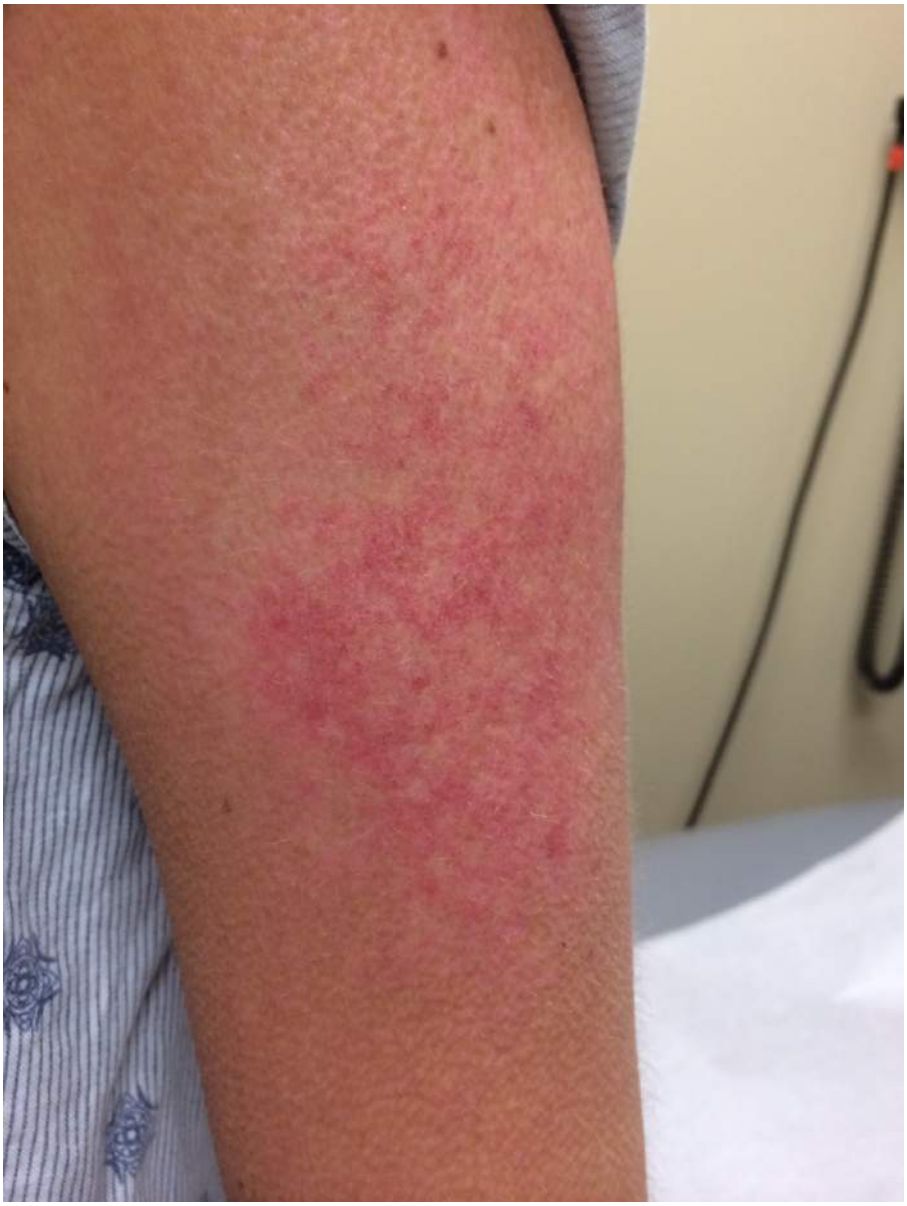
Twenty-seven patients (10.3%) had a history of an erythematous to violaceous macule or patch confined to the lateral aspect of the upper arm detected on physical examination. The location was compatible with the contour of the sleeves. Thus, it was labeled the "sleeve sign" (Figure 1).

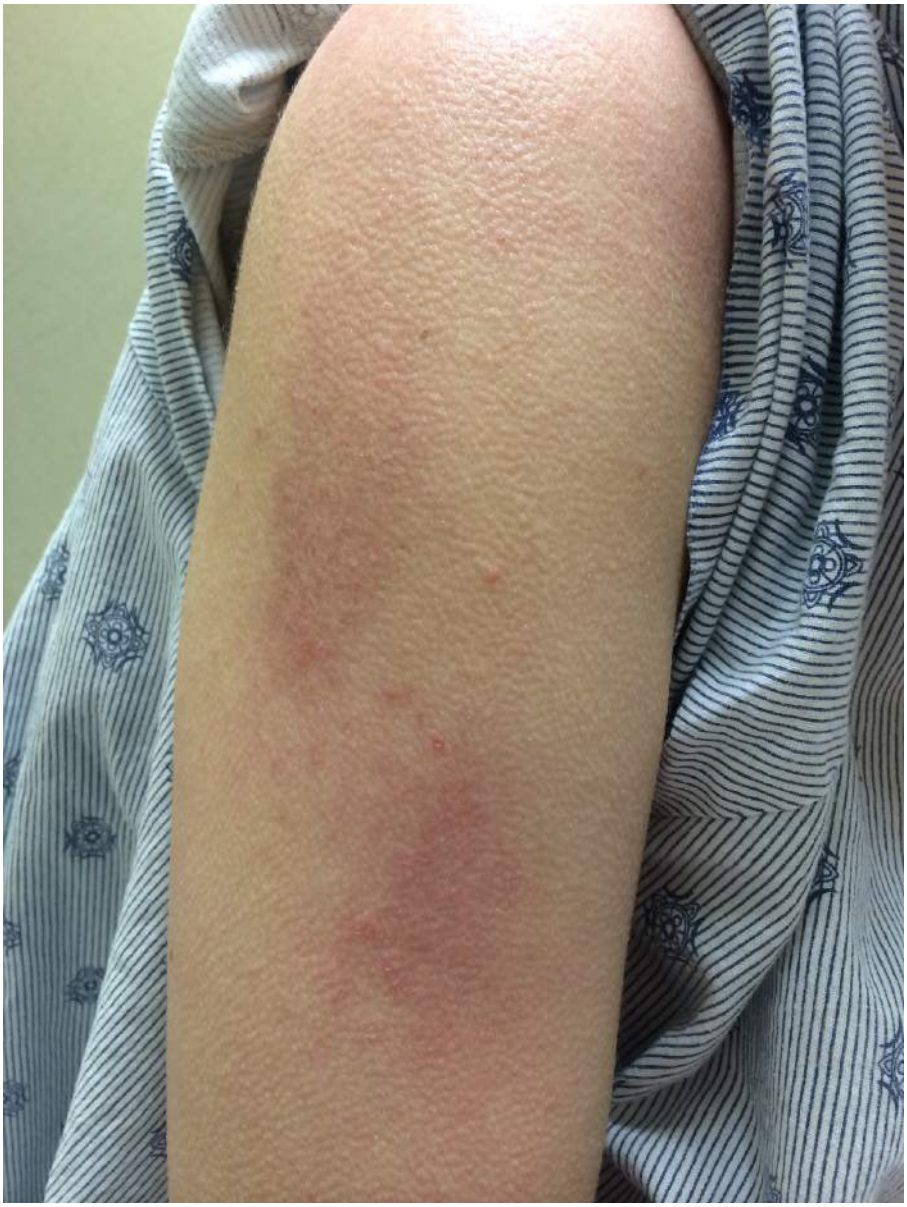
Twenty-five patients (92.6 %) had dermatomyositis (44.4 % definite, 29.6 % probable, and 18.5 % possible) and 2 patients (7.4%) had amyopathic dermatomyositis. The sera from 22 patients (81.5%) were tested for all DM-specific (anti-TIF-1γ, anti-NXP2, and anti-MDA5) and anti-synthetase autoantibodies (anti-Jo1, anti-PL7/PL12, and anti-EJ/OJ). Table 1 summarizes the demographics, clinical manifestations, and myositis-specific autoantibody profile of the study population.

Conclusion:

A macular erythematous to violaceous rash (sleeve sign) may affect the lateral aspect of the upper arms. Although in our study, the sleeve sign was frequently present with other characteristic DM skin findings, the presence of this rash should raise the suspicion of dermatomyositis in the clinically appropriate setting.

Table 1- Demographic, clinical manifestations, and myositis-specific autoantibody profile of patients with sleeve sign	
Age, mean (SD)	44.5 (14.3)
Female, number (frequency)	23 (85.2%)
Race, number (frequency) Caucasian African-American Other	 22 (81.5%) 3 (11.1%) 2 (7.4)
Proximal weakness	21 (77.8%)
The frequency of the skin findings at the same visit the patient presented with sleeve sign	
Heliotrope rash	12 (44.4%)
Malar rash	14 (51.9%)
Gottron's sign	23 (85.2%)
V Sign	16 (59.3%)
Shawl Sign	15 (55.6%)
Nail-bed erythema	17 (63.0%)
Dilated capillary loops	14 (51.9%)
Holster sign	7 (25.9%)
Mechanic's hand	6 (22.2%)
Calcinosis	5 (18.5%)
Raynaud's	3 (11.1%)
Myositis-specific antibodies	
Anti-jo1	2 (10.5%)
Anti-nxp2	4 (22.2%)
Anti-TIF-1γ	13 (65.0%)
DM-specific or anti-synthetase autoantibody negative	4 (18.2%)





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Abstract Number: 306

Investigating the Pathogenic Role of ER Stress Pathways in the Idiopathic Inflammatory Myopathies (IIM): Interrogating the Role of Micro-RNA 133a As an Important Regulator of ER Stress Activation

Adam P. Lightfoot[1], Katarzyna Goljanek-Whysall[2], Anne McArdle[1] and Robert G. Cooper[3,4], [1]Musculoskeletal Biology, University of Liverpool, Liverpool, United Kingdom, [2]University of Liverpool, Liverpool, United Kingdom, [3]Rheumatic Diseaes Center, Salford Royal Foundation Trust, University of Manchester, Salford, United Kingdom, [4]MRC/ARUK Institute of Ageing and Chronic Disease, University of Liverpool, Liverpool, United Kingdom

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Session Time: 9:00AM-11:00AM

Background/Purpose: The Idiopathic Inflammatory Myopathies (IIM) is a heterogeneous group of acquired autoimmune disorders, characterised by symmetrical muscle weakness. Whilst immune cells clearly play a role in muscle weakness induction in IIM, the correlation between inflammatory cell loads and the degree of muscle weakness is poor, while muscle weakness is detectable prior to inflammatory cell infiltrations. It is thus accepted that non-immune mechanisms, such as ER stress induction, are also key contributors to muscle weakness induction in IIM (Lightfoot et al. 2015). However, the mechanisms which regulate ER stress pathway activation here are poorly understood. MicroRNAs are short, non-coding RNAs whose primary role is to post-transcriptionally regulate gene expression. MicroRNAs have been described to regulate a plethora of biological processes, and dysregulation of microRNA expression has been reported in several diseases (Goljanek-Whysall et al. 2012). A study examining various myopathies reported that the expression of multiple microRNAs was dysregulated (Eisenberg et al. 2007). More recently a study examining miRNA expression in the muscle of PM, DM and IBM patients identified that expression of micro-RNA 133a was significantly downregulated in all subtypes of IIM (Georgantas et al. 2007). However, the mechanistic implication of microRNA regulation in the context of IIM remains unelucidated. Micro-RNA 133a is a muscle-specific microRNA, or "myomiR" and is predicted to regulate several genes associated with ER stress pathways. We hypothesise that, given the importance of ER stress pathway activation in IIM and the dysregulation of miR-133a in the muscle of IIM patients, microRNAs may play an important pathogenic role in IIM. Specifically, miR-133a may contribute to chronic ER stress pathway activation here, and thus represent a potential future therapeutic target to minimise non-immune cell mediated muscle weakness. **Methods:** C57Bl6 mice (6-10 months) were treated with a miR-133a mimic, a miR-133a inhibitor or a scrambled miR-133a control. The *anterior tibialis* was excised and RNA isolated and purified using standard TRizol extraction. qPCR and SDS-PAGE was used to examine changes in miR-133a and ER stress pathway gene expressions. C2C12 myotubes overexpressing MHC I was used as an experimental model of ER stress pathway activation to validate our miR-133a findings. **Results:** Our data demonstrate that downregulation of a muscle specific microRNA, i.e miR-133a, resulted in the activation of a specific arm of the ER stress pathway, as demonstrated by upregulation of expression of the ER stress receptor IRE1, and activation of the downstream transcription factor X-box binding protein 1 (XBP-1). Additionally, inhibition of miR-133a resulted in downregulation of the ER stress chaperone Grp78. **Conclusion:** These data suggest that miR-133a may be a key regulator of ER stress pathway activation in skeletal muscle, and which may have implications in the chronic ER stress pathway activation demonstrable in IIM patients.

Disclosure: A. P. Lightfoot, Myositis UK, 2; **K. Goljanek-Whysall**, None; **A. McArdle**, None; **R. G. Cooper**, Myositis UK, 2.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/investigating-the-pathogenic-role-of-er-stress-pathways-in-the-idiopathic-inflammatory-myopathies-iim-interrogating-the-role-of-micro-rna-133a-as-an-important-regulator-of-er-stress-activation

Abstract Number: 307

Screening for Pulmonary Hypertension in the Anti-Synthetase Syndrome; Utility of Four Different Screening Approaches

Helena Andersson[1], Ivar Sjaastad[2], Thomas Schwartz[2], Torhild Garen[3], T. Mogens Aalokken[4] and Øyvind Molberg[1], [1]Department of Rheumatology, Institute of Clinical Medicine, Oslo University Hospital, Oslo, Norway, [2]Institute for

Experimental Medical Research, Oslo University Hospital, Oslo, Norway, [3]Rheumatology, Department of Rheumatology, Oslo University Hospital, Oslo, Norway, [4]Department of Radiology, Oslo University Hospital, Oslo, Norway

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SESSION INFORMATION

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Session Title: Muscle Biology, Myositis and Myopathies Poster

Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose:

Pulmonary hypertension (PH) is a feared complication of the anti-synthetase syndrome (ASS) and has previously been reported to occur in 8% of the patients [1]. Prognosis is currently poor, but may be improved by earlier referral to diagnostic right heart catheterization (RHC) and therapeutic interventions. Data on non-invasive screening approaches for PH in ASS are limited. Here, the aim was to test the utility of four different and complementary PH screening approaches.

Methods:

In September 2011, 68/70 living ASS patients from the Oslo University Hospital ASS cohort were included in a cross-sectional study where pulmonary function tests (PFT), Echocardiography (Echo) and HRCT of the lungs were performed. In addition, medical reports from six dead patients with confirmed PH by RHC were analyzed. Arbitrary cut-off values for PH suspicion were defined as follows; (1) DLCO < 50 % of expected value, (2) a ratio between FVC% and DLCO% >1.6, (3) Arteria pulmonalis (A Pulm) diameter ≥ 30 mm on lung CT, (4) estimated mean pulmonary arterial pressure (mPAP) ≥ 45 mmHg by Echo. HRCT and Echo analysts were blinded to the participant's clinical status. Chi-Square test was used to evaluate statistical significance, $p<0.05$.

Results:

Median disease duration for the 68 patients was 71 months (6-362) and 97 % of the patients had been diagnosed with interstitial lung disease. Median DLCO% was 62% (range12-87), median FVC /DLCO ratio was 1.33 (0.53-3.03) and the median estimated mPAP and pulmonary artery diameters were 23 mmHg (0-98) and 29 mm (20-45), respectively. Altogether, 16/74 patients had performed RHC, confirming PH in 11/16 patients.

Values below the arbitrary PH suspicion cut-offs were frequent, most frequent was increased diameter of A Pulm, seen in 30/72 (42%) patients. Values suspicious of PH in DLCO, FVC/DLCO ratio, and estimated mPAP were seen in 34%, 28% and 17%, respectively. The correlations between the four variables and confirmed/not confirmed PH are seen in Table 1; Significant correlations were seen between all four variables and confirmed PH, most with the diameter of A Pulm.

Table 1;Correlations between different parameters and Pulmonary Artery Pressure

Parameters	Not confirmed PH	Confirmed PH	p-value
A Pulm < 30 mm, n/N(%)	42/62 (68)	0/10 (0)	<0.001
A Pulm > 30 mm, n/N(%)	20/62 (32)	10/10 (100)	
mPAP <45mmHg,n/N(%)	58/62 (94)	2/10 (20)	<0.001
mPAP >45mmHg,n/N(%)	4/62 (6)	8/10 (80)	
DLCO ≥ 50%, n/N (%)	45/60 (75)	1/10 (10)	<0.001
DLCO ≤ 50%, n/N (%)	15/60 (25)	9/10 (90)	
FVC/DLCO <1.6 n/N (%)	46/60 (77)	4/10 (40)	<0.027
FVC/DLCO >1.6 n/N(%)	14/60 (23)	6/10 (60)	

Conclusion:

Although a small number of patients with confirmed PH, this study shows significant correlation between all tested screening-tools for PH and confirmed PH. All patients (N=10) with confirmed PH had a diameter of A Pulm > 30 mm, and 8/10 had a mPAP of > 45mmHg, indicating these two methods as possible screeningtest for PH. Further studies on PH and it's predictors are most warranted.

Disclosure: H. Andersson, None; **I. Sjaastad**, None; **T. Schwartz**, None; **T. Garen**, None; **T. M. Aalokken**, None; **Molberg**, None.

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Abstract Number: 308

Nailfold Capillaroscopy in Patients with Early Onset-Dermatomyositis

Renata Miossi, Fernando Henrique Carlos de Souza and Samuel Katsuyuki Shinjo, Rheumatology Division, Rheumatology Division, Faculdade de Medicina da USP, São Paulo, Brazil

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Session Date: Sunday, November 8, 2015

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Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose: Nailfold capillaroscopy (NC) has been demonstrated to be an important tool in the treatment of patients with juvenile dermatomyositis (JDM) and systemic sclerosis. However, NC has been scarcely studied in adult patients with DM. Therefore we analyzed NC specifically in adult patients with early onset-DM and also evaluated the possible correlation between NC abnormalities and clinical and activity parameters of DM.

Methods: The present cross-sectional single-center study included 39 consecutive adult patients with early onset-DM (Bohan & Peter, 1975) followed in our Rheumatology outpatient clinic. The early onset was defined as DM diagnosis up to 24 months. We excluded patients with diabetes mellitus, malignancy associated-DM, amyopathic DM or other autoimmune diseases. The NC was performed using Olympus®stereomicroscope. A semiquantitative rating scale was used to score capillaroscopy changes. Myositis disease activity assessment tools were used to assess disease activity [Manual Muscle Testing (MMT), Myositis Disease Activity Assessment Visual Analogue Scales (MYOACT), Health Assessment Questionnaire (HAQ), physician's VAS, patient's VAS, serum muscle enzymes levels].

Results: The median age of patients was 42.0 (interquartile range: 36.0-55.0) years, with 69.2% Caucasian and 71.8% female gender. The median time of DM diagnosis was 1.0 (0.0-1.0) year, whereas the time duration between symptoms onset and DM diagnosis was 4.0 (3.0-12.0) months. The results presented median value of 75 (62-80) for MMT, 1.00 (0.13-2.41) for HAQ, 4.5 (3.0-5.8) cm for physician's VAS, 5.0 (2.0-6.0) cm for patient's VAS, 11 (6-21) for MYOACT, 174 (95-598) U/L for creatine kinase and 6.0 (3.8-12.0) U/L for aldolase. Concerning treatment, 92.3% were using prednisone 40 (10-60) mg/day and 76.2% at least one immunosuppressive drug. Thirty-two (82.1%) patients had scleroderma capillary (SD)-like pattern in the NC [density of 6.2 (4.0-7.6) capillaries/mm; 43.6% with severe avascular areas; 15.4% with high degree of micro-hemorrhages; 87.2% with bushy capillaries; 87.2% with dilated capillaries; 61.5% with giant capillaries, 89.7% with neoangiogenesis). The SD-like pattern correlated positively with HAQ, patient's and physician's VAS. The capillary density correlated positively with "shawl" sign, patient's and physician's VAS, whereas the neoangiogenesis correlated positively with patient's VAS, MMT, HAQ and serum creatine kinase levels (P<0.05). The micro-hemorrhages correlated negatively with pulmonary involvement, while dose of prednisone correlated negatively with SD-like pattern (P<0.05). No significant correlations between NC and other demographic, clinical and laboratory parameters were observed.

Conclusion: Similarly to JDM, the NC may provide helpful information about patients with early onset-DM by: (a) contributing to an early diagnosis and (b) correlating with disease activity parameters. Additional investigations with larger series of patients and prospective studies may be useful to reinforce our data.

Disclosure: R. Miossi, None; **F. H. C. de Souza**, None; **S. K. Shinjo**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/nailfold-capillaroscopy-in-patients-with-early-onset-dermatomyositis

Abstract Number: 309

Plasma Levels of Heat Shock Protein 90 Are Increased in Idiopathic Inflammatory Myopathies and Correlate with Disease Activity, Skeletal Muscle, Heart and Lung Involvement

Hana Storkanova[1], Olga Krystufkova[2], Martin Klein[3], Herman F Mann[1], Lucia Vernerova[2], Maja Spiritovic[4], Josef Zámecník[5], Karel Pavelka[6], Ladislav Senolt[3], Jiri Vencovsky[1] and Michal Tomcík[1], [1]Institute of Rheumatology, Department of Rheumatology, 1st Faculty of Medicine, Charles University, Prague, Czech Republic, [2]Institute of Rheumatology and Department of Rheumatology, 1st Faculty of Medicine, Charles University, Prague, Czech Republic, [3]Institute of Rheumatology and Department of Rheumatology, 1st Faculty of Medicine, Charles University, Prague, Czech Republic, Prague, Czech Republic, [4]Faculty of Physical Education and Sport, Charles University, Prague, Czech Republic, [5]Department of Pathology and Molecular Medicine, 2nd Medical School and University Hospital Motol, Charles University, Prague, Czech Republic, [6]Charles University, Prague, Czech Republic

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Background/Purpose: Heat shock proteins (Hsps) are chaperones playing important roles in skeletal muscle physiology, adaptation to exercise or stress, and in activation of inflammatory cells. Hsp90 expression was shown to be increased in regenerating and atrophic muscle fibers, and in macrophages and cytotoxic T-cells actively invading nonnecrotic muscle fibers in polymyositis. The aim of our study was to assess plasma Hsp90 in patients with idiopathic inflammatory myopathies (IIM) and to characterize its association with IIM-related features.

Methods: A total of 277 patients with IIM (198 females, 79 males; mean age 54.8; disease duration 4.1 years; dermatomyositis (DM, 104)/polymyositis (PM, 104)/cancer associated myositis (CAM, 42)/ necrotizing myopathy (IMNM, 27)) and 100 age-/sex-matched healthy individuals were included. Patients with PM/DM fulfilled Bohan and Peter diagnostic criteria and CAM was defined as cancer occurring within 3 years of the diagnosis of myositis. Plasma Hsp90 levels were measured by ELISA (eBioscience, Vienna, Austria). Clinical disease circumstances were evaluated by Myositis Disease Activity Assessment (MYOACT), Myositis Intention to Treat Index (MITAX), Myositis Damage Index (MDI), physician and patient global activity using visual analogue scales (VAS) and manual muscle testing (MMT8). Levels of CK, LD, ALT, *AST*and CRP were analyzed by routine laboratory techniques and IIM-associated autoantibodies by immunoprecipitation. Data are presented as median (IQR).

Results: Plasma Hsp90 levels were increased in IIM patients compared to healthy controls (20.2 (14.3-40.1) vs. 9.2 (7.2-12.6) ng/ml, $p < 0.0001$), and between individual subgroups of IIM and healthy controls (PM: 19.4 (14.5-40.4), DM: 22.4 (14.3-43.5), CAM: 19.1 (12.3-29.8), IMNM: 19.6 (15.7-50.0) ng/ml, $p < 0.0001$ for all). Hsp90 levels in all patients positively correlated with LD and AST ($r=0.551$, $p < 0.0001$; $r=0.372$, $p < 0.0001$, respectively), and there was a trend towards correlation with CK ($r=0.111$, $p=0.068$). Increased Hsp90 was associated with decreased MMT8 values ($r=-0.136$, $p=0.029$), in particular with proximal muscles. Hsp90 positively correlated with patient and doctor disease activity ($r=0.222$, $p=0.0004$; $r=0.217$, $p=0.0005$, respectively), pulmonary and muscle disease activity ($r=0.201$, $p=0.001$; $r=0.146$, $p=0.018$, respectively), MITAX and MYOACT ($r=0.175$, $p=0.005$; $r=0.159$, $p=0.012$, respectively), and with MDI extent/severity ($r=0.215$, $p=0.003$; $r=0.120$, $p=0.041$, respectively). Higher Hsp90 was found in patients with IIM-associated interstitial lung disease, cardiac involvement and dysphagia (25.4 vs. 18.9, $p=0.004$; 27.5 vs. 19.3, $p=0.004$; 25.0 vs. 18.2, $p=0.018$, respectively). Increased Hsp90 was associated with higher prednisone equivalent dose ($r=0.180$, $p=0.007$) and treatment with DMARDs (22.0 vs. 18.9, $p=0.013$).

Conclusion: We demonstrate increased Hsp90 plasma levels in IIM patients that are associated with disease activity and damage, and with the involvement of proximal skeletal muscles, the heart and lungs. Hsp90 might become a useful biomarker of disease activity and muscle involvement in IIM.

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Abstract Number: 310

Hyaluronic Acid Injections in Knee Osteoarthritis Patients Are Associated with Delay to Knee Arthroplasty

Kevin Ong[1], Allen Anderson[2], Edmund Lau[3], Faizan Niazi[4], Anke Fierlinger[4], Steven Kurtz[1] and **Roy Altman**[5], [1]Exponent, Inc., Philadelphia, PA, [2]Tennessee Orthopaedic Alliance, Powderly, KY, [3]Exponent, Inc., Menlo Park, CA, [4]Ferring Pharmaceuticals, Inc., Parsippany, NJ, [5]David Geffen School of Medicine, UCLA, Los Angeles, CA
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SESSION INFORMATION

Session Date: Sunday, November 8, 2015
Session Title: Osteoarthritis - Clinical Aspects Poster I: Treatments and Metabolic Risk Factors
Session Type: ACR Poster Session A
Session Time: 9:00AM-11:00AM

Background/Purpose: Although only few nonoperative treatment options for knee osteoarthritis (OA) are available, there continues to be debate about the effectiveness of hyaluronic acid (HA) injections, particularly in light of recent clinical practice guidelines by AAOS and recommendations by OARSI, ACR, and recent systematic reviews. Thus, we investigated whether the formulation of HA may be contributing to some of the reported variation in clinical outcomes. This study evaluated whether the use of HA injections is associated with a delay to knee arthroplasty (KA) and whether there was a difference in effect size by formulation of HA injections. **Methods:** A retrospective, observational study design based on the 5% sample of Part B Medicare data from 2007 to 2012 was used to identify knee OA patients who underwent KA. The time to KA was compared between patients who were coded with HA injection use ("HA") and those who were not ("no HA"), using quantile regression with propensity score adjustment. These were further stratified by HA formulation between bioengineered HA (high molecular weight (HMW) and medium MW (MMW) Bio-HA) and non-bioengineered HA (high MW (HMW) and low MW (LMW) non-Bio-HA).

Results: A total of 23,008 knee OA patients (n=17,007 "no HA"; n=6,001 "HA") subsequently underwent KA and were included in the study. After adjusting for potential confounding patient factors and propensity scores, the "HA" cohort was found to be associated with a delay to KA of 7.1 months (95% CI: 6.6 to 7.5 months; $p<0.001$) compared to the "no HA" cohort. When compared to the "no HA" cohort, patients who were treated with HMW Bio-HA were found to have the longest time to KA over patients treated with other HA formulations (Figure 1 and Table 1). However, when comparing between HA formulations, LMW non-Bio-HA was found to have the shortest time to KA, while the remaining three formulations had similarly longer time to KA (Table 1).

Conclusion: Our analysis of elderly knee OA patients showed a significantly longer delay to KA for those who were treated with HA. The delay may provide additional time for patients to better control pre-existing conditions prior to KA, which could aid in reducing postoperative morbidity. Furthermore, there appears to be some differences in the effect of HA formulation, in particular molecular weight, on the delay to KA.

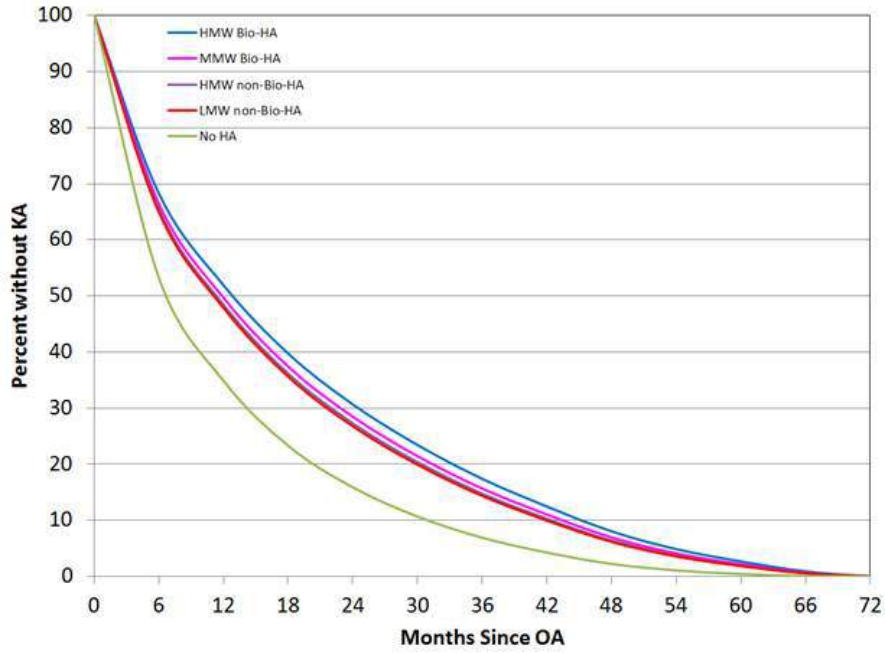

Figure 1: Survivorship curves (KA as the endpoint) for "no HA" and "HA" cohorts. **Table 1.** Difference in time to KA (in months) between patient cohorts with propensity score adjustment (*positive means more delay, negative means less delay)

Vs. no HA	**Difference in time to KA***
HMW non-Bio-HA	+6.8 mos. (p<0.001)
LMW non-Bio-HA	+7.6 mos. (p<0.001)
MMW Bio-HA	+7.5 mos. (p<0.001)
HMW Bio-HA	+8.6 mos. (p<0.001)
Vs. HMW Bio-HA	**Difference in time to KA***
HMW non-Bio-HA	+0.5 mos. (p=0.387)
LMW non-Bio-HA	-2.9 mos. (p<0.001)
MMW Bio-HA	-0.8 mos. (p=0.175)

Disclosure: K. Ong, Ferring Pharmaceuticals, Stryker Orthopaedics, Biomet, Paradigm Spine, Pacira Pharmaceuticals, Medtronic, Stryker Mako Surgical,, 9,Zimmer, Ethicon, 9; **A. Anderson**, DePuy Mitek, 5,Acquire B2B, Web instruction, 9,AOSSM, Herodicus Society, Rock Group, 6,Am J Orthop, 8,OrthoPediatrics, Reconstruction system, ACL tears, 9; **E. Lau**, Ferring Pharmaceuticals, 9; **F. Niazi**, Ferring Pharmaceuticals, 3; **A. Fierlinger**, Ferring Pharmaceuticals, 3; **S. Kurtz**, Smith & Nephew; Stryker; Zimmer; Biomet; Depuy Synthes; Medtronic; Invibio; Stelkast; Formae; Kyocera Medical; Wright Medical Technology; Ceramtec; DJO; Celanese; Aesculap; Spinal Motion; Active Implants, Ferring Pharmaceuticals, 2,Exponent, Inc., 9; **R. Altman**, Cytori, Ferring, Iroko, Johnson & Johnson, Novartis, Oletec, Strategic sciences and Technologies, Teva, 5,Pfizer, Ferring, Oletec, Q Med, 9,Iroko, 8,Ferring, 9.

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Abstract Number: 311

Comparison Between Intra Articular Ozone and Placebo in the Treatment of Knee Osteoarthritis: A Multicentric, Comparative, Randomized and Double-Blinded Clinical Trial

Carlos Jesus[1], Virginia Trevisani[2,3] and Fânia Santos[4], [1]Health Evidence Based, Escola Paulista de Medicina - Universidade Federal de São Paulo, São Paulo, Brazil, [2]Health Evidence Based, Universidade Federal de São Paulo, Sâo Paulo, Brazil, [3]Health Evidence Based, Universidade Federal de São Paulo, São Paulo, Brazil, [4]Geriatrics and Gerontology Departament, Escola Paulista de Medicina - Universidade Federal de São Paulo, São Paulo, Brazil
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SESSION INFORMATION

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Session Title: Osteoarthritis - Clinical Aspects Poster I: Treatments and Metabolic Risk Factors
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Session Time: 9:00AM-11:00AM

Background/Purpose: Osteoarthritis (OA) is a common, progressive condition, which is associated with severe pain, functional disability and impairment of health related quality of life, causing a significant social and economic burden. There are no currently approved OA treatments capable of slowing OA-related structural progression or delaying the need for total knee replacement. Ozone (O3) is a triatomic variety of oxygen, applied to the human organism with therapeutic aims, mainly in chronic diseases that have little benefit with allopathic medicine, like the rheumatic disease osteoarthritis. However, there are only a few articles about the use of intra articular ozone in the treatment of knee osteoarthritis and they are just case reports. ***Objective:*** To determine if knee osteoarthritis treatment with intra articular ozone is more effective than knee osteoarthritis treatment with intra articular placebo in relation to pain reduction, joint functional improvement and quality of life. ***Methods:*** Randomized, double-blinded, placebo controlled clinical trial. Ozone was generated by using an Ozone & Life O&L 3.0RM generator. Patients from treatment group received an injection of ozone 20µg/ml 10ml. Patients from placebo group received an injection of air 10 ml. Both groups were treated once a week during 8 consecutive weeks. We evaluated Visual Analogic Scale (VAS), Lequesne's Index, Timed Up and Go Test (TUG Test), SF-36 questionnaire, Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) and Geriatric Pain Measure (GPM) after allocation, after 4^{th} and 8^{th} injections and 8 weeks after the last injection. Normally distributed variables were analyzed using parametric methods and those with asymmetric distribution with nonparametric statics. It was performed an intention-to-treat analysis. ***Results:*** 98 subjects, 63 from ozone group and 35 from placebo group completed the study. Groups were similar in relation to sociodemographic data. TUG presented no significant difference between the groups. In relation to Lequesne's Index, there was a significantly statistical difference from 4^{th} week on ($p<0.001$) and that was maintained until 16^{th} week ($p<0.001$), favorable to ozone group. Similar results were observed in relation to VAS ($p<0.000$) and to GPM ($p<0.001$), showing a pain reduction and improvement in daily activities in ozone group soon after the beginning of the intervention and during the treatment. From the second evaluation on, according to SF36, there was sensible improvement in all levels of quality of life, showing that ozone had a remarkable effect on the treatment group patients' lives. ***Conclusion:*** Our study showed the efficacy of intra articular treatment of knee osteoarthritis with ozone in relation to pain reduction and improvement of joint function and life quality.

Disclosure: C. Jesus, None; **V. Trevisani**, None; **F. Santos**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/comparison-between-intra-articular-ozone-and-placebo-in-the-treatment-of-knee-osteoarthritis-a-multicentric-comparative-randomized-and-double-blinded-clinical-trial

Abstract Number: 312

Safety, Efficacy and Biomarker Outcomes of a Novel, Intra-Articular, Injectable, Wnt Inhibitor (SM04690) in the Treatment of Osteoarthritis of the Knee: Interim, Exploratory Analysis of Results from a Randomized, Double-Blind, Placebo-Controlled Phase 1 Study

Yusuf Yazici[1], Timothy E. McAlindon[2], Roy Fleischmann[3], Allan Gibofsky[4], Nancy E. Lane[5], Alan J. Kivitz[6], Nebojsa Skrepnik[7], Eddie Armas[8], Christopher J. Swearingen[1], Anita DiFrancesco[1], Jeyanesh R. S. Tambiah[1], John Hood[1] and Marc C. Hochberg[9], [1]Samumed, San Diego, CA, [2]Tufts Medical Center, Boston, MA, [3]University of Texas Southwestern Medical Center, Dallas, TX, [4]Weill Cornell Medical College and Hospital for Special Surgery, New York, NY, [5]UC Davis Medical Center, Sacramento, CA, [6]Altoona Center for Clinical Research, Duncansville, PA, [7]Tucson Orthopaedic Institute, Tucson, AZ, [8]Well Pharma Medical Research, Miami, FL, [9]University of Maryland School of Medicine, Baltimore, MD, USA, Baltimore, MD

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SESSION INFORMATION

Session Date: Sunday, November 8, 2015

Session Title: Osteoarthritis - Clinical Aspects Poster I: Treatments and Metabolic Risk Factors

Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose: Knee osteoarthritis (OA) is characterized by the destruction of articular cartilage, subchrondral bone alterations and varying degrees of synovitis. Current OA treatments are limited to relieving pain as there are no drug therapies approved which treat the underlying cause of the disease. The Wnt signaling pathway is known to play a central role in the formation of joint tissues and altered Wnt signaling has been associated with cartilage loss in preclinical and clinical studies.[1] SM04690 is a small molecule inhibitor of the Wnt pathway which is administered via intra-articular (IA) injection. This report provides interim safety, efficacy and biomarker data from an ongoing phase I randomized, double-blind, placebo-controlled, dose-escalation clinical trial of SM04690 in knee OA subjects.

Methods: Subjects with symptomatic, radiographic knee OA were randomized to receive a single IA injection in the target knee with either 0.03, 0.07, 0.23 mg SM04690 or placebo (volume 2mLs) in a 4:1 SM04690 (N=16):placebo (N=4) ratio. Safety, pharmacokinetics (PK), efficacy (WOMAC Total, Function, Pain subscales), and biomarker data (P1NP, β-CTXI and COMP) were collected at baseline prior to injection and during the 24-week follow-up period. Exploratory analyses of efficacy outcomes were conducted using a baseline-adjusted repeated measures analysis of covariance (ANCOVA).

Results: 61 subjects (average age 62.6 [±5.7] years, female N=41 [67%], average BMI 30.4 [±4.7] kg/m^2) were enrolled. At time of abstract submission, 41 subjects had completed the 24-week trial: Cohort 1: 0.03 mg (N=17), Cohort 2: 0.07 mg (N=16) and placebo (N=8). Cohort 3 (subjects treated with 0.23 mg [N=16] and placebo [N=4]) are ongoing and data not reported. Serum levels of SM04690 in both 0.03 and 0.07 mg groups were below limits of detection at all time points. No DLTs or SAEs were reported in the 0.03 mg cohort. 2 DLTs, paroxysmal tachycardia, (also an SAE), and increased pain were reported in 0.07 mg cohort: Both were deemed unrelated to SM04690 by safety review adjudication. 35 AEs were reported; 5 (14%) considered possibly or probably related to study drug (4 increased knee pain, 1 acne). At Week 24, improvements were seen in both 0.03 mg and 0.07 mg cohorts (respective change from baseline: WOMAC Total, -23.1 and -22.8; WOMAC Function, -16.7 and -16.2; WOMAC Pain, -4.9 and -4.5; all P<0.001) (Table). Biomarker data showed significant reduction in COMP in the 0.07 mg group at Weeks 12 (-130.13 ng/mL, P=0.001) and 24 (-127.93 ng/mL, P=0.002) (Table). There were no significant changes in COMP in the 0.03 mg group, or in β-CTX or P1NP in either 0.03 mg or 0.07 mg groups.

Conclusion: These interim data from an ongoing phase 1 trial suggest that one intra-articular injection with a novel Wnt inhibitor SM04690 into the knee in OA subjects appears safe and may be effective in reducing pain and improving

function.

Reference: 1. Gelse K. *Osteoarthr Cartil* 2012; 20(2):162-71

Table. Change in WOMAC and Biomarker Outcomes over 24 Weeks in SM04690 0.03 mg and 0.07 mg Cohorts

			SM04690 0.03 mg		SM04690 0.07mg	
			Mean (SD)	**Median [Min, Max]**	**Mean (SD)**	**Median [Min, Max]**
WOMAC Total [0-96]	Baseline		54.5 (9.1)	56 [33, 69]	52.7 (11.6)	53 [26, 70]
	Week 12	*Actual*	29.1 (14.2)	27 [0, 64]	26.1 (22.0)	24.5 [0, 96]
		*Change**	-22.0	95% CI: (-29.7, -14.2)	-26.0	95% CI: (-35.2, -16.8)
			P*<0.001		**P*<0.001**	
	Week 24	*Actual*	27.9 (16.2)	29 [0, 61]	25.9 (15.8)	28 [0, 55]
		*Change**	-23.1	95% CI: (-30.9, -15.3)	-22.8	95% CI: (-32.0, -13.5)
			P*<0.001		**P*<0.001**	
WOMAC Function [0-68]	Baseline		39.1 (7.2)	40 [21, 48]	37.6 (7.8)	38 [21, 49]
	Week 12	*Actual*	20.3 (10.5)	19 [0, 45]	18.4 (15.9)	17.5 [0, 68]
		*Change**	-16.1	95% CI: (-21.7, -10.5)	-18.6	95% CI: (-25.3, -12.0)
			P*<0.001		**P*<0.001**	
	Week 24	*Actual*	19.9 (11.7)	21 [0, 43]	18.4 (11.3)	20 [0, 40]
		*Change**	-16.7	95% CI: (-22.3, -11.0)	-16.2	95% CI: (-22.9, -9.6)
			P*<0.001		**P*<0.001**	
WOMAC Pain [0-20]	Baseline		10.8 (2.0)	11 [8, 14]	10.8 (2.9)	11 [4, 16]
	Week 12	*Actual*	6.3 (2.7)	6 [0, 13]	5.3 (4.4)	5 [0, 20]
		*Change**	-3.9	95% CI: (-5.5, -2.2)	-5.4	95% CI: (-7.3, -3.5)
			P*<0.001		**P*<0.001**	
	Week 24	*Actual*	5.2 (3.2)	5 [0, 11]	5.4 (3.1)	5 [0, 11]
		*Change**	-4.9	95% CI: (-6.5, -3.2)	-4.5	95% CI: (-6.5, -2.6)
			P*<0.001		**P*<0.001**	
COMP [ng/mL]	Baseline		475.3 (167.63)	461.7 [228, 952]	486.5 (490.01)	360.0 [213, 2292]
	Week 12	*Actual*	473.8 (142.09)	422.0 [294, 732]	314.3 (266.05)	252.5 [124, 1272]
		*Change**	41.02	95% CI: (-32.04, 114.09)	-130.13	95% CI: (-205.76, -54.50)
			P*=0.26		**P*=0.001**	
	Week 24	*Actual*	369.6 (191.93)	335.8 [208, 985]	318.6 (91.94)	297.9 [155, 551]
		*Change**	-51.89	95% CI: (-125.78, 22.00)	-127.93	95% CI: (-206.07, -49.78)
			P*=0.16		**P*=0.002**	

*Estimated within Cohort from Repeated Measures ANCOVA Modeling Change from Baseline adjusting for Baseline over all time points.

Disclosure: Y. Yazici, Samumed, 3; **T. E. McAlindon**, Sanofi Aventis, Samumed, Flexion, Novartis, Federal Trade Commission, Abbvie, McNeil Consumer HC, 5,Tufts MCPO, 3; **R. Fleischmann**, Abbvie, 2,Amgen, 2,Ardea, 2,AstraZeneca, 2,Bristol-Myers Squibb, 2,Celgene, 2,GlaxoSmithKline, 2,Janssen Pharmaceutica Product, L.P., 2,Eli Lilly and Company, 2,Merck Pharmaceuticals, 2,Pfizer Inc, 2,Resolve, 2,Roche Pharmaceuticals, 2,Sanofi-Aventis Pharmaceutical, 2,UCB, 2,AbbVie, 5,Akros, 5,Amgen, 5,AstraZeneca, 5,Bristol-Myers Squibb, 5,Celgene, 5,Janssen Pharmaceutica Product, L.P., 5,Eli Lilly and Company, 5,Pfizer Inc, 5,Roche Pharmaceuticals, 5,UCB, 5; **A. Gibofsky**, Abbvie, Drais, Celgene, Horizon, Iroko, Medac, Pfizer Inc, Relburn, Samumed, and Takeda, 5,AbbVie, Amgen, Celgene, Iroko, Pfizer Inc, 8,AbbVie, Amgen, Bristol-Myers Squibb, GlaxoSmithKlyne, Johnson & Johnson, and Pfizer Inc, 1; **N. E. Lane**, Samumed, 5; **A. J. Kivitz**, Samumed, 5,Samumed, 2; **N. Skrepnik**, Ortofix, Sanofi-Genzyme, Ampio, QMed, VM Pharma, Theorem, Samumed, 5; **E. Armas**, None; **C. J. Swearingen**, Samumed, 3; **A. DiFrancesco**, Samumed, 3; **J. R. S. Tambiah**, Samumed, 3; **J. Hood**, Samumed, 3; **M. C. Hochberg**, Samumed, 5.

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Abstract Number: 313

Magnetic Resonance Imaging Outcomes Using an Intra-Articular Injection (SM04690) in the Treatment of Osteoarthritis of the Knee: Interim, Exploratory Analysis of Results from a Randomized, Double-Blind, Placebo-Controlled, Phase 1 Study

Yusuf Yazici[1], Sharmila Majumdar[2], Timothy E. McAlindon[3], Roy Fleischmann[4], Allan Gibofsky[5], Marc C. Hochberg[6], Christopher J. Swearingen[1], Anita DiFrancesco[1], Jeyanesh R. S. Tambiah[1], John Hood[1] and Nancy E. Lane[7], [1]Samumed, San Diego, CA, [2]Radiology, UCSF School of Medicine, San Francisco, CA, [3]Rheumatology, Tufts Medical Center, Boston, MA, [4]University of Texas Southwestern Medical Center, Dallas, TX, [5]Weill Cornell Medical College and Hospital for Special Surgery, New York, NY, [6]Department of Medicine, University of Maryland, Baltimore, MD, [7]Center for Musculoskeletal Health, Univ of California at Davis, Sacramento, CA
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SESSION INFORMATION
Session Date: Sunday, November 8, 2015
Session Title: Osteoarthritis - Clinical Aspects Poster I: Treatments and Metabolic Risk Factors
Session Type: ACR Poster Session A
Session Time: 9:00AM-11:00AM

Background/Purpose: Knee osteoarthritis (OA) is characterized by the destruction of articular cartilage, subchrondral bone alterations and varying degrees of synovitis. Current OA treatments are limited to relieving pain as there are no drug therapies approved which treat the underlying cause of the disease. The Wnt signaling pathway is known to play a central role in the formation of joint tissues and altered Wnt signaling has been associated with cartilage loss in preclinical and clinical studies.[1] SM04690 is a small molecule inhibitor of the Wnt pathway which is administered via intra-articular (IA) injection. This report provides interim magnetic resonance imaging (MRI) data from an ongoing phase I randomized, double-blind, placebo-controlled, dose-escalation clinical trial of SM04690 in knee OA subjects.

Methods: Subjects with symptomatic, radiographic knee OA were randomized to receive a single IA injection in the target knee with either 0.03, 0.07, 0.23 mg SM04690 or placebo (volume 2mLs) in a 4:1 SM04690 (N=16):placebo (N=4) ratio. Knee MRIs were obtained with a 16 channel knee coil on a 3.0T MRI machine using a standard diagnostic protocol, and were collected at baseline visit (which could occur ≤28 days prior to study injection), Week 12 and 24. Average cartilage thickness over covered subchondral bone was reported for medial and lateral femoral condyles as well as medial and lateral tibial plateaus. Also, the average of the lowest 1% of cartilage thickness was reported for all 4 compartments. The total for both average thickness and lowest thickness were derived by summing each of the 4 compartments' observations. An exploratory analysis of change in imaging outcomes was conducted using repeated measures analysis of covariance (ANCOVA) adjusting for baseline.

Results: 61 subjects (average age 62.6 [±5.7] years, female N=41 [67%], average BMI 30.4 [±4.7] kg/m^2) were enrolled. At time of abstract submission, 41 subjects had completed the 24-week trial: Cohort 1: 0.03 mg (N=17), Cohort 2: 0.07 mg (N=16) and placebo (N=8). Cohort 2 24-week imaging data are under review and Cohort 3 (subjects treated with 0.23 mg [N=16] and placebo [N=4]) is ongoing; these data are not reported at this time. At Week 12, total average cartilage thickness decreased 0.07 mm and 0.02 mm for 0.03 mg and 0.07 mg, respectively, adjusting for the baseline value (Table). However, total average thickness of the lowest 1% increased 0.10 mm and 0.08 mm for 0.03 mg and 0.07 mg, respectively, adjusting for baseline value. Moreover, total average cartilage thickness increased 0.02 mm and total average thickness of the lowest 1% increased 0.12 mm in the 0.03 mg group at Week 24.

Conclusion: Preliminary data from this interim, exploratory analysis of MRI outcomes from an ongoing Phase 1 trial suggest that SM04690 may maintain or increase cartilage thickness, both at the site of maximal cartilage degradation as well as overall.

Reference: 1. Gelse K. *Osteoarthr Cartil* 2012; 20(2):162-71

Table. Summary of MRI Measurements at Weeks 12 and 24 for SM04690 0.03mg and 0.07 mg Cohorts

			SM04690 0.03 mg		SM04690 0.07 mg	
			Mean (SD)	Median [Min, Max]	Mean (SD)	Median [Min, Max]
MRI Cartilage Thickness						
Total Average Thickness (mm)	Baseline		5.4 (1.1)	5.6 [3.6, 7.4]	5.4 (0.7)	5.2 [4.3, 6.7]
	Week 12	*Actual*	5.4 (1.2)	5.5 [3.7, 7.6]	5.4 (0.7)	5.1 [4.3, 6.8]
		*Change**	-0.07	95% CI: (-0.24, 0.10)	-0.02	95% CI: (-0.21, 0.16)
			P*=	0.398	P*=	0.704
	Week 24	*Actual*	5.6 (1.0)	5.7 [4.0, 7.1]		
		*Change**	0.02	95% CI: (-0.16, 0.19)		*Under Review*
			P*=	0.837		
Total Average Thickness of Lowest 1% (mm)	Baseline		3.8 (1.4)	3.7 [1.6, 6.8]	3.8 (1.4)	3.8 [1.0, 6.0]
	Week 12	*Actual*	3.8 (1.6)	3.9 [1.1, 7.2]	3.9 (1.4)	4.0 [1.7, 6.4]
		*Change**	0.10	95% CI: (-0.12, 0.32)	0.08	95% CI: (-0.33, 0.49)
			P*=	0.344	P*=	0.581
	Week 24	*Actual*	4.0 (1.4)	4.2 [1.4, 6.4]		
		*Change**	0.12	95% CI: (-0.10, 0.34)		*Under Review*
			P*=	0.273		

*Estimated within Cohort from Repeated Measures ANCOVA Modeling Change from Baseline adjusting for Baseline over all time points.

Disclosure: Y. Yazici, Samumed, 3; **S. Majumdar**, GE Healthcare, 2,Samumed, 5; **T. E. McAlindon**, Sanofi Aventis, Samumed, Flexion, Novartis, Federal Trade Commission, Abbvie, McNeil Consumer HC, 5,Tufts MCPO, 3; **R. Fleischmann**, Abbvie, 2,Amgen, 2,Ardea, 2,AstraZeneca, 2,Bristol-Myers Squibb, 2,Celgene, 2,GlaxoSmithKline, 2,Janssen Pharmaceutica Product, L.P., 2,Eli Lilly and Company, 2,Merck Pharmaceuticals, 2,Pfizer Inc, 2,Resolve, 2,Roche Pharmaceuticals, 2,Sanofi-Aventis Pharmaceutical, 2,UCB, 2,AbbVie, 5,Akros, 5,Amgen, 5,AstraZeneca, 5,Bristol-Myers Squibb, 5,Celgene, 5,Janssen Pharmaceutica Product, L.P., 5,Eli Lilly and Company, 5,Pfizer Inc, 5,Roche Pharmaceuticals, 5,UCB, 5; **A. Gibofsky**, Abbvie, Drais, Celgene, Horizon, Iroko, Medac, Pfizer Inc, Relburn, Samumed, and Takeda, 5,AbbVie, Amgen, Celgene, Iroko, Pfizer Inc, 8,AbbVie, Amgen, Bristol-Myers Squibb, GlaxoSmithKlyne, Johnson & Johnson, and Pfizer Inc, 1; **M. C. Hochberg**, Samumed, 5; **C. J. Swearingen**, Samumed, 3; **A. DiFrancesco**, Samumed, 3; **J. R. S. Tambiah**, Samumed, 3; **J. Hood**, Samumed, 3; **N. E. Lane**, Samumed, 5.

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Abstract Number: 314

A Double-Blind, Randomized, Controlled, Four Parallel Arm, Dose-Finding Study to Evaluate the Efficacy, Safety, Tolerability, and Pharmacokinetics of Single Intra-Articular (IA) Injections of Fasitibant in Patients with Symptomatic OA of the Knee

Claudia Gabriele Werner[1], Karel Pavelka[2], Andrea Nizzardo[3], Cristina Rossi[3], Simona Scartoni[3], Maria Paola Contini[3], Serena di Molfetta[3], Monica Bertolotti[3], Angela Capriati[3] and Carlo Alberto Maggi[4], [1]Clinical Research, A. Menarini Research & Business Service GmbH, Berlin, Germany, [2]Institute of Rheumatology and Department of Rheumatology, First Faculty of Medicine, Charles University, Prague, Czech Republic, [3]Clinical Research Department, Menarini Ricerche S.p.A., Florence, Italy, [4]Menarini Ricerche S.p.A., Florence, Italy

First publication: September 29, 2015

SESSION INFORMATION

Session Date: Sunday, November 8, 2015

Session Title: Osteoarthritis - Clinical Aspects Poster I: Treatments and Metabolic Risk Factors

Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose:

Fasitibant (FAS) is a competitive, potent and selective antagonist of the bradykinin B2 receptor administered IA for SOAK. In response to positive outcomes in a previous exploratory RCT, a phase 2 double blind RCT to evaluate FAS, given as single IA injection at three different doses *versus* placebo, was conducted at 25 clinical sites in Europe and US.

Methods:

Patients with moderate to severe symptomatic knee OA were randomized (1:1:1:1) to single IA injections of either FAS (1 mg, 2.5 mg or 5 mg) or Placebo (saline) given as 1 ml solution. IA administration was performed by clinical investigators experienced with the use of the IA injection route.

The efficacy variable of primary interest was the change in pain intensity evaluated as change of WOMAC VA 3.1 A (total pain) subscore (A1-5, VAS 0-500 mm) from baseline over 2 weeks post treatment. Secondary measures included WOMAC Index, WOMAC stiffness (B) and functional impairment (C) subscores, pain at rest, pain after 15 meters walk (100 mm VAS) and patient global assessment (PGA) scores.

Safety was assessed by monitoring of lab tests, vital signs, ECG, physical examinations including the target knee, adverse events and concomitant medications.

Results:

All randomized patients (Intention-to-Treat-ITT, n=431) were allocated to the study treatment; with FAS 1mg (n=108), FAS 2.5 mg (n=108), FAS 5mg (n=107) and Placebo (n=108), with balanced demographic and baseline characteristics across treatment arms. Single IA injections of fasitibant did not significantly discriminate for WOMAC A pain over Placebo, with all treatments showing a decrease at week 1 and at week 2 post administration (Table 1). The time to first use of rescue medication (secondary endpoint) discriminated significant from placebo in the fasitibant 5 mg dose group (Kaplan-Meyer analysis; $p< 0.0154$). Fasitibant was well tolerated. There were no related SAEs. The majority of TESSs were mild or moderate. Severe TESSs occurred only in 12 patients (2.8%). Only 29 TESSs were considered related, most of them in placebo group (n=13). Lab tests, ECGs and vital signs were in general unremarkable and similar between treatments.

Conclusion:

The primary efficacy analysis has not shown any statistical significant evidence of superiority of fasitibant at any dose *over*Placebo on pain reduction from baseline over 2 weeks after randomisation; however fasitibant 5 mg treated patients used statistically significant less rescue medication, which might be considered as an indirect evidence of its efficacy. The very high placebo response as well as the long duration of OA-symptoms (8.5±7.06 years) in all treatment groups may have contributed to the lack of efficacy as reported for other RCT in patients with symptomatic knee OA. Fasitibant was in general safe and local tolerability at the target knee was good.

Table 1: Change versus baseline for WOMAC pain over two weeks (ITT Population)

WOMAC A **(0-500 mm VAS)**		Placebo **(N=108)**	Fasitibant 1 mg **(N=108)**	Fasitibant 2.5 mg **(N=108)**	Fasitibant 5 mg **(N=107)**	Overall **(N=431)**
Baseline	Mean/% (SD)	275.5/100% (39.81)	286.5/100 % (40.04)	282.7/100% (40.08)	278.3/100% (38.11)	280.8/100% (39.61)
1 week post treatment	Mean/% (SD)	-93.7/-34.5% (94.15)	-91.8/-32.7% (101.85)	-110.0/-39.5% (99.48)	-109.8/-39.7% (94.65)	-101.3/-36.6% (97.63)
2 weeks post treatment	Mean/% (SD)	-117.2/-42.9% (90.15)	-106.1/-37.5% (101.88)	-131.5/-47.4% (96.41)	-115.9/-42.2% (104.61)	-117.7/-42.5% (98.48)
Inferential analysis over two weeks: Fasitibant 1 mg vs. placebo p=0.5156, Fasitibant 2.5 mg vs. Placebo p=0.2505, Fasitibant 5 mg vs. Placebo p=0.5739						

Disclosure: C. G. Werner, Menarini Ricerche S.p.A., 3; **K. Pavelka**, None; **A. Nizzardo**, Menarini Ricerche S.p.A., 3; **C. Rossi**, Menarini Ricerche S.p.A, 3; **S. Scartoni**, Menarini Ricerche S.p.A., 3; **M. P. Contini**, Menarini Ricerche S.p.A., 3; **S. di Molfetta**, Menarini Ricerche S.p.A., 3; **M. Bertolotti**, Menarini Ricerche S.p.A., 3; **A. Capriati**, Menarini Ricerche S.p.A., 3; **C. A. Maggi**, Menarini Ricerche S.p.A., 3.

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Abstract Number: 315

Structural Effects of Sprifermin in Knee Osteoarthritis: A Post-Hoc Analysis on Cartilage and Non-Cartilaginous Tissue Alterations

Frank Roemer[1], Aida Aydemir[2], Stefan Lohmander[3], Michel Crema[4], Monica D. Marra[5], Norma Muurahainen[2], Felix Eckstein[6] and Ali Guermazi[7], [1]Radiology, Boston University School of Medicine, Boston, MA, [2]EMD Serono, Billerica, MA, [3]Lund University, Lund, Sweden, [4]Department of Radiology, Boston University School of Medicine, Boston, MA, [5]Department of Radiology, BUSM, Boston, MA, [6]Paracelsus Med Univ, Chondrometrics GmbH, Salzburg, Austria, [7]Boston University School of Medicine, Boston, MA

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SESSION INFORMATION

Session Date: Sunday, November 8, 2015

Session Title: Osteoarthritis - Clinical Aspects Poster I: Treatments and Metabolic Risk Factors

Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose:

A randomized, double-blind, placebo-controlled phase 1b clinical trial of sprifermin (rhFGF18) in knee OA assessed central medial tibio-femoral compartment cartilage thickness on quantitative MRI (qMRI) as structural primary endpoint and reported no statistically significant response (Lohmander et al. Arthritis Rheumatol 2014;66:1820-31). However, the drug was associated with dose-dependent effects in the lateral tibio-femoral compartment.

Methods:

Sprifermin was administered in 2 cycles of 3 weekly intra-articular injections at 10, 30, and 100 µg. MRIs were assessed semi-quantitatively (sq) by expert radiologists. The post-hoc analysis focused on structural changes in the 100 µg subgroup (n=57) and matching placebo subgroup (n=18) evaluating changes from baseline (BL) up to 12 months. Assessed were cartilage morphology (lesions), bone marrow lesions (BMLs), meniscal damage and extrusion, Hoffa- and effusion-synovitis using the semiquantitative WORMS scoring system. Analyses included multi-dimensional assessment: Delta subregional [DSR] approach (including number of subregions [SRs] showing worsening (>0), no change (0) and improvement (<0), negative values indicating improvement and positive values indicating worsening) and Delta-sum [DSM] approach (including total sum of grades for SRs showing worsening, no change and improvement). Analyses were performed on a whole knee level and separately for medial and lateral tibio-femoral joints (MTFJ, LTFJ), and patello-femoral joint (PFJ). Mann−Whitney−Wilcoxon tests assessed differences between treatment groups. P-values were not adjusted for multiple testing.

Results:

At BL, no significant differences were observed between placebo and treatment groups for all sqMRI parameters, except for whole knee cartilage morphology (29.97 ± [standard deviation] 16.00 for treatment vs 21.11 ± 14.76 vs placebo, p=0.040). For change in cartilage morphology, statistically significant differences were seen from BL to 12 months using DSR approach, with lower values on sprifermin (corresponding to less worsening) vs placebo for the PFJ (0.22 ± 0.55 vs treatment 0.02 ± 0.23, p=0.046), with similar results observed using the DSM approach. Although not statistically significant, less worsening vs placebo was observed in the LTFJ (DSR, 0.11 ± 0.32 vs treatment 0.05 ± 0.48). For change in BMLs, statistically significant changes from 6 to 12 months were observed for the whole knee, with negative values indicating improvement and positive values worsening (placebo 0.44 ± 1.20 vs treatment −0.14 ± 1.24, p=0.042), and borderline for LTFJ (0.22 ± 0.65 vs treatment -0.05 ± 0.80 p=0.064) using the DSR approach. No notable changes from BL were observed for remaining analyzed parameters.

Conclusion:

Cartilage morphology showed less worsening from BL to 12 months and BMLs showed improvement after 100 ug Sprifermin treatment from 6 to 12 months compared to placebo. The potential effect of Sprifermin on subchondral bone (BMLs) is a novel finding that warrants further exploration. This finding may be explained by altered loading as a result of cartilage surface restoration or by direct effects on bone.

Disclosure: F. Roemer, Boston Imaging Core Lab, 4; **A. Aydemir**, EMD Serono, 3; **S. Lohmander**, None; **M. Crema**, Boston Imaging Core Lab, 1; **M. D. Marra**, Boston Imaging Core Lab, 1; **N. Muurahainen**, EMD Serono, 3; **F. Eckstein**, Chondrometrics GmbH, 1,Merck Serono, 5; **A. Guermazi**, Boston Imaging Core Lab, LLC, 1,TissueGene, 5,OrthoTrophix, 5,MerckSerono, 5,Genzyme Corporation, 5.

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Abstract Number: 316

Effect of Vitamin D on Effusion-Synovitis in Knee Osteoarthritis: a Randomized Controlled Trial

Xia Wang[1], Flavia Cicutinni[2], Xingzhong Jin[1], Benny Samuel Eathakkattu Antony[3], Anita Wluka[2,4,5], Weiyu Han[1],

Leigh Blizzard[6], Tania Winzenberg[7], Graeme Jones[8] and Changhai Ding[8], [1]Menzies institute for medical research, University of Tasmania, Hobart, Australia, [2]Department of Epidemiology and Preventive Medicine, School of Public Health and Preventive Medicine, Monash University, Melbourne, Australia, [3]Musculoskeletal, Menzies Research Institute Tasmania, University of Tasmania, Hobart, Australia, [4]Epidemiology & Preventive Med, Monash University, Melbourne, Australia, [5]Department of Epidemiology and Preventive Medicine, Monash University, Armadale, Australia, [6]Statistics, Menzies Research Institute Tasmania, University of Tasmania, Hobart, Tasmania, Australia, [7]Menzies Institute for Medical Research, University of Tasmania, Hobart,7000, Australia, [8]Musculoskeletal Unit, Menzies Institute for Medical Research, University of Tasmania, Hobart, Australia
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SESSION INFORMATION

Session Date: Sunday, November 8, 2015
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Session Time: 9:00AM-11:00AM

Background/Purpose: To examine the effect of vitamin D supplementation on synovial inflammation in patients with knee osteoarthritis (OA) and low vitamin D levels over 24 months.

Methods: In a multi-center, parallel, randomized, placebo-controlled and double-blind trial, symptomatic knee OA patients with a low 25-(OH)D level (12.5 to 60 nmol/l) were recruited. 413 patients (age 63.2±7.0 years, 208 females) were allocated monthly to a 50,000IU vitamin D_3 capsule (n=209) or placebo (n=204) for 24 months. In this post-hoc analysis, the primary outcome was change in total knee effusion-synovitis volume assessed using magnetic resonance imaging (MRI). Secondary outcomes included change in regional effusion-synovitis volume, change in semi-quantitative effusion-synovitis score and dichotomized minimal clinical important improvement in effusion-synovitis volume. Generalized linear regression models were used to compare differences between groups in both intention-to-treat and per protocol analyzes.

Results: Serum 25-(OH)D level increased markedly in the vitamin D group (40.6 nmol/l) compared with placebo (6.7 nmol/l) over 24 months. Overall total effusion-synovitis volume significantly increased in all patients (baseline: 8.0 ± 8.5 ml, follow-up: 9.0 ± 10.5 ml), but the increase was less in the vitamin D group than controls (0.26 ml (16% p.a.) versus 2.20 ml (60% p.a.), $p = 0.02$). This effect was evident in suprapatellar pouch (0.04 ml (19% p.a.) versus 2.53 ml (148% p.a.), $p = 0.03$), but not in central region (0.12 ml (10% p.a.) versus 0.40 ml (39% p.a.), $p = 0.12$). The likelihood of achieving a minimal clinical important improvement in total (relative risk: 1.22 p.a.; $p = 0.05$) and suprapatellar (relative risk: 1.27 p.a.; $p = 0.03$) effusion-synovitis were significantly higher in vitamin D group compared to placebo. Additionally, change in 25-(OH)D levels was negatively associated with change in total effusion-synovitis volume in whole sample ($p = 0.09$). Adverse events were similar.

Conclusion: Supplementation of vitamin D in knee OA patients over 24 months can reduce the worsening of knee joint effusion-synovitis, especially in suprapatellar pouch.

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Abstract Number: 317

Relation of Incident Bisphosphonate Use to Trajectory of Joint-Space

Width

Tuhina Neogi[1], Na Lu[2], Jingbo Niu[1], Jeffrey Duryea[3] and Yuqing Zhang[1], [1]Clinical Epidemiology Research and Training Unit, Boston University School of Medicine, Boston, MA, [2]Boston University School of Medicine, Boston, MA, [3]Radiology, Brigham and Women's Hospital, Boston, MA
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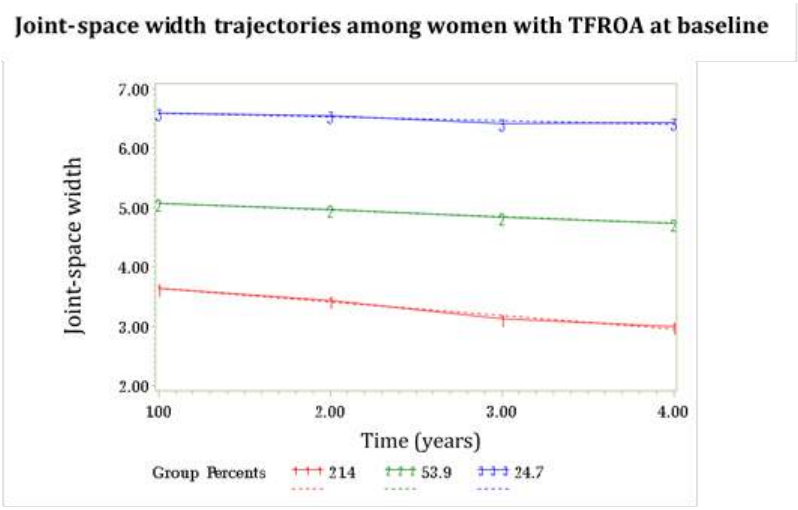
Background/Purpose: Trials regarding bisphosphonate (Bisph) effects in knee osteoarthritis (OA) have been conflicting, and are unable to provide insights into long-term effects. While Bisph may have beneficial articular cartilage effects, there are theoretical concerns about their long-term effects on bone due to decreased bone turnover, which could have consequences for bone's biomechanical properties. We therefore sought to evaluate the effects of incident Bisph use (to avoid prevalent user bias) on joint-space width (JSW) among knees with OA over a 4-year period.

Methods: OAI participants had bilateral fixed-flexion knee x-rays and clinical factors assessed at 0, 12, 24, 36, and 48 mo. We limited our sample to females with tibiofemoral radiographic OA (TFROA) at baseline, and defined incident Bisph users as those that did not report using a Bisph at baseline, but subsequently did so. Quantitative radiographic JSW was assessed with software that delineated the margins of the femoral condyle and tibial plateau and measured JSW at fixed locations with respect to an anatomical coordinate system. We focused on medial JSW at x=0.250 (ICC >0.99) among all knees, and stratified by baseline radiographic OA (ROA) status. To be included, JSW measurements had to occur in ≥2 visits, with appropriate film quality, beam angle, and tibial plateau-rim distance. We agnostically categorized knees into distinct groups of JSW loss using a group-based semiparametric mixture model to identify these trajectories (SAS macro proc traj). This method does not force data to fit a particular model, and improves precision by using several measurements. Follow-up time for the trajectory determination started at the visit at which incident Bisph use was identified, or at the 12-mo visit for non-users. The number of distinct trajectories was determined by optimal model fit statistics (BIC), and we required trajectory differences of ≥10%. We then examined the relation of incident Bisph use to JSW trajectory groups using logistic regression, adjusting for age, BMI, knee injury, education, prior fracture, and baseline KL grade.

Results: There were a total of 1303 female subjects who had TFROA at baseline and the necessary JSW readings, with 65 incident users. Three distinct trajectory groups were identified (**Figure**), with rates of JSW loss being 0.23 mm/yr for group 1 (21.4% of the sample), 0.11 mm/yr for group 2 (53.9%), and 0.06 mm/yr for group 3 (24.7%). Incident Bisph users were less likely to be in group 1 (worst group) than group 3 (best group) compared with non-users, though this was not statistically significant (adj. OR 0.60, 95% CI 0.26-1.04). Similar results were found for incident Bisph users in group 2 vs. group 3 (adj. OR 0.65, 95% CI 0.34-1.24).

Conclusion: Incident Bisph use may be associated with a lower rate of JSW loss, but we lack sufficient precision to definitively assess this relation.



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Dual Variable Domain-Immunoglobulin (Dvd-Igâ„¢) Abt-981 Simultaneously and Dose-Dependently Inhibits Interleukin-1 Î‘lpha and -1 Î’eta in Subjects with Knee Osteoarthritis

Susanne X. Wang[1], Ralf Loebbert[2], Erik Sampson[3], Mary Saltarelli[1], Jeroen Medema[1] and Feng Hong[3], [1]AbbVie Inc., North Chicago, IL, [2]AbbVie Deutschland GmbH & Co. KG, Ludwigshafen, Germany, [3]AbbVie Inc., Worcester, MA

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Background/Purpose: ABT-981 is a novel human Dual-Variable Domain Immunoglobulin (DVD-Ig™) that inhibits interleukin (IL)-1α and IL-1β. The purpose of this study is to evaluate IL-1α and IL-1β protein levels in serum, and IL-1α, IL-1β, and IL-1Ra (IL-1 receptor antagonist) mRNA levels in peripheral blood leukocytes (PBLs) in patients with knee osteoarthritis (OA).

Methods: In a randomized, double-blind, placebo (PBO)-controlled, multiple dose study (NCT01668511), 27 knee OA patients received ABT-981 (0.3, 1, or 3 mg/kg; n=7 each group) or PBO (n=6) subcutaneously every 2 wks (4 doses total). Serum samples were collected on days 1 (predose), 5, 15, 19, 29, 33, 43, 47, 57, and 113. Peripheral blood was collected on days 1, 5, 57, and 113. Imperacer® Immuno-PCR assays (Chimera Biotec) were used to detect free protein concentration of IL-1α/IL-1β in serum. Total RNA isolated from PBLs was converted to cDNA for quantitative PCR detection of IL-1a, IL-1b, and IL-1Ra mRNAs. Changes in biomarkers in ABT-981 groups were compared with baseline (BL) and PBO. Repeated measures analysis was performed using SAS 9.2. Adjusted *P* values were calculated using Bonferroni method.

Results: Mean BL serum IL-1α level was 7.1 pg/mL. In all ABT-981 groups serum IL-1α levels significantly (P<.001) decreased from day 5 to 57 (2 wks after last dose), a decrease of 75-95% from BL. Decreases were maintained until day 113 in 1 (-69.8%, P<.001) and 3 mg/kg groups (-58.3%, P=.005). IL-1α level in 0.3 mg/kg group recovered to near BL level on day 113. Compared with PBO, serum IL-1α levels in all ABT-981 groups were significantly decreased from day 5 to 113 (P<.001). Mean BL serum IL-1β level was 0.46 pg/mL. In the 1 and 3 mg/kg groups serum IL-1β levels significantly decreased 48.7-87.1% from BL (P≤.01) throughout the study. Compared with PBO, serum IL-1β levels were significantly decreased in the 1 and 3 mg/kg groups (P<.001), and a downward trend was observed in 0.3 mg/kg group (P=.034). PBL IL-1a mRNA was undetectable in all dose groups and at all time points. At day 5, IL-1b mRNA expression significantly decreased in 3 mg/kg group (P<.001) and a downward trend in 1 mg/kg group (P=.092). IL-1Ra mRNA expression levels in PBLs did not show dose dependent changes in the treatment groups.

Conclusion: Simultaneous robust inhibition serum of IL-1α and IL-1β with ABT-981 was observed in this study in a dose-dependent manner. The prolonged inhibition of IL-1α and IL-1β in the 1 and 3 mg/kg groups indicates a long lasting biological effect of ABT-981 even after the drug has been ~97% cleared from the system (day 113). The dose-dependent decrease of IL-1b mRNA expression in PBLs on day 5 coincides with decrease in serum IL-1β protein. However, transient decrease in PBL IL-1b mRNA, despite persistent decreases in serum IL-1a and IL-1b levels, suggest that other cytokines also play a role in regulating IL-1b transcription in these cells. In conclusion, serum levels of IL-1a and IL-1b proteins and PBL IL-1b mRNA are dose-dependently inhibited in knee OA subjects dosed with ABT-981 and represent candidate measurements of target engagement.

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Abstract Number: 319

Phase 1 Studies of Anti-Interleukin-1 Dual-Variable Domain Immunoglobulin in Healthy Subjects and Patients with Osteoarthritis

Susanne X. Wang[1], Wei Liu[1], Ping Jiang[1], Martin Okun[1], Richard Preston[2], Carlos J. Lozada[2], David Carter[1] and Jeroen Medema[1], [1]AbbVie Inc., North Chicago, IL, [2]University of Miami Miller School of Medicine, Miami, FL

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Background/Purpose: Interleukin (IL)-1 is a catabolic cytokine that plays an important role in pathogenesis and progression of osteoarthritis (OA). Two phase 1 clinical trials investigated the use of a novel human dual-variable domain–immunoglobulin (DVD-Ig™) simultaneously targeting IL-1α and IL-1β (ABT-981).

Methods: ABT-981 was evaluated in a randomized, double-blind, placebo (PBO)-controlled single ascending dose (SAD) trial and a multiple ascending dose (MAD) trial (NCT01668511). In the SAD trial, 56 healthy subjects were divided into 7 cohorts. Each cohort received single intravenous (IV) or subcutaneous (SC) dose of ABT-981 (0.3, 1, 3, 10 mg/kg IV or 0.3, 1, 3 mg/kg SC) or PBO in a 6:2 ratio. In the MAD trial, 36 patients with mild/moderate knee OA

were divided into 4 cohorts. Cohorts 1–3 received ABT-981 (0.3, 1, 3 mg/kg) or PBO in a 7:2 ratio every 2 weeks (EOW) for total of 4 SC injections; cohort 4 received ABT-981 (3 mg/kg) or PBO in 7:2 ratio every 4 weeks for total of 3 SC injections. Safety, tolerability, pharmacokinetics (PK), and anti-drug antibodies (ADAs)were assessed in both trials. In addition, a panel of serum/urine biomarkers of target engagement, inflammation and joint degradation were evaluated in the MAD trial.

Results: The incidence of adverse events (AEs) was similar with single-dose ABT-981 vs PBO via IV (66.7% vs 50.0%) or SC (55.6% vs 66.7%) routes and multiple SC doses of ABT-981 vs PBO (53.6% vs 62.5%). The most common AEs with ABT-981 vs PBO was diarrhea (IV: 20.8% vs 12.5%) and headache (SC: 22.2% vs 0%) in the first trial, and injection-site reaction (17.9% vs 0%) in the second trial. In MAD trial, absolute neutrophil count (ANC) decreased dose-dependently, starting at 48 hours and reaching nadir by 14 days; lowest ANC values observed with 3 mg/kg. One patient had a transient grade 2 neutropenia after 1 dose in 3 mg/kg EOW group, along with serious AE of grade 3 bronchitis/viral syndrome both considered possibly study-drug related.

In MAD trial, ABT-981 at all 3 doses significantly reduced serum levels of high-sensitivity C-reactive protein (hsCRP; $P<0.05$), matrix metalloproteinase (MMP)-degraded type 1 collagen (C1M; $P<0.05$ at 1 and 3 mg/kg), IL-1α ($P<0.001$), and IL-1β ($P<0.001$). Serum concentrations of MMP-degraded type 3 collagen (C3M; 1 and 3 mg/kg) and MMP-degraded CRP (CRPM; 3 mg/kg) demonstrated decreasing trends ($0.05<P<0.1$) with ABT-981 treatment but did not reach statistical significance.

Conclusion: The results of these phase 1 trials demonstrate that ABT-981 was well tolerated and had dose-proportional PK in healthy subjects and patients with knee OA. The similar safety profiles between ABT-981 and PBO support phase 2 investigation of ABT-981 in patients with OA. Through simultaneous inhibition of IL-1α and IL-1β in patients with OA, ABT-981 significantly reduced serum hsCRP levels, indicating a reduction in systemic inflammation, and C1M levels, indicating a dampening of inflammation-mediated joint destruction. Additionally, the observed serum C1M, C3M and CRPM decreases suggest that ABT-981 may ameliorate inflammation-mediated tissue destruction and chronic tissue inflammation in patients with inflammation-driven OA.

Disclosure: S. X. Wang, AbbVie, 1,AbbVie, 3; **W. Liu**, AbbVie, 1,AbbVie, 3; **P. Jiang**, AbbVie, 1,AbbVie, 3; **M. Okun**, AbbVie, 1,AbbVie, 3; **R. Preston**, AbbVie, 2; **C. J. Lozada**, AbbVie, 2,AbbVie, 5; **D. Carter**, AbbVie, 1,AbbVie, 3; **J. Medema**, AbbVie, 1,AbbVie, 3.

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Abstract Number: 320

Effectiveness of Bracing in Elderly with Knee Osteoartritis: A Randomized Controlled Trial

Christine Brumini Sr.[1], Jamil Natour[2], Lais Yumi Miura[1] and Anamaria Martinez[2], [1]Rheumatology, University Federal of Sao Paulo, São Paulo, Brazil, [2]Rheumatology Division, Federal University of Sao Paulo, Sao Paulo, Brazil
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Background/Purpose: Osteoarthritis (OA) is highly prevalent in the elderly, with the knee being the most commonly

affected joint in this population. Knee braces are often used to prevent common problems in knees during daily activities. The purpose of these devices is to decrease pain and improve functionality. In the literature some studies have tested the effectiveness of unloader brace for valgus or varus. However, the braces most used in our clinical setting and the less costly ones have not been evaluated in quality studies in the literature. There are no studies that compared the effectiveness between the knee brace with metal hinges (no alignment) and knee brace without metal hinges (neoprene sleeve). The purpose is to evaluate the effectiveness of knee braces on pain, function and quality of life in the elderly with knee OA.

Methods: Elderly with knee OA, both genders, with pain scale between 3-7cm on a 10cm pain numeric scale were included. Of the 222 patients screened, 120 met the eligibility criteria and were randomized to the groups: neoprene sleeve (without metal hinges); brace (with metal hinges - no alignment) or control group (CG). The groups neoprene sleeve (NSG) and brace (BG) received knee brace and were instructed to use it in daily activities, every day, during three months. Assessment for pain (NPS), function (WOMAC and Knee Lequesne), quality of life (SF-36) and performance tests (6MWT, TUGT and FTSS) were done at baseline and after 45, 90 and 180 days by a blinded assessor.

Results: Forty patients were randomly assigned to the each group. At baseline the groups were homogeneous for all measures, except for gender where the CG had more women and the pain domain of SF-36 where pain was higher in the CG. The analysis between the groups using ANOVA for repeated measures for pain (NPS), show statistically significant difference between groups over time (p=0,049), with the BG showing better results. Statistically significant differences were found between groups over time for: function - WOMAC questionnaire (global, p=0,005; pain, p=0,004 and function, p<0,001) and Knee Lequesne (p= 0,009) and quality of life - functional capacity domain the SF-36 (0,046) with better results to BG.

Conclusion: The knee brace was effective in improving pain, function and some aspects of quality of life in elderly with knee OA.

Table 1 – Between-groups comparison

		T0			T45			T90			T180		p
	GC	**GSH**	**GCH**	**GC**	**GSH**	**GCH**	**GC**	**GSH**	**GCH**	**GC**	**GSH**	**GCH**	ANOVA
NPS	6.0 ± 1.1	6.0 ± 1.4	6.1 ± 1.1	5.9 ± 2.1	5.2 ± 2.1	5.0 ± 2.3	5.4 ± 1.8	4.8 ± 1.8	4.6 ± 2.0	5.9±1.6	5.4±1.8	4.3±2.3	0.049*
WOMAC													
Global	42.6 ± 17.5	42.1 ± 16.7	40.5 ± 17.4	48.2 ± 16.7	36.1 ± 16.2	34.0 ± 17.6	44.3 ± 17.8	36.5 ± 19.1	29.1 ± 17.2	45.1±18.4	34.9±19.3	29.9±18.7	0.005*
Pain	8.0 ± 4.2	8.5 ± 4.0	7.4 ± 3.6	9.4 ± 3.7	6.4 ± 3.7	5.5 ± 3.7	8.0 ± 3.8	6.7 ± 4.2	4.8 ± 3.9	8.1±4.2	5.8±3.6	5.2±4.0	0.004*
Stiffness	2.6 ± 2.5	2.8 ± 2.0	2.4 ± 2.2	2.8 ± 2.4	2.3 ± 1.9	1.8 ± 2.2	2.9 ± 2.0	2.7 ± 2.4	1.8 ± 1.9	2.7±2.4	2.2±2.1	1.8±2.1	0.408
Function	32.0 ± 12.4	30.8 ± 12.0	31.0 ± 13.1	35.4 ± 12.2	27.4 ± 12.0	26.8 ± 12.9	33.5 ± 14.4	27.3 ± 14.3	22.5 ± 12.3	33.4±12.7	26.7±14.6	23.0±13.9	<0.001*
Lequesne	13.4 ± 3.3	13.0 ± 3.2	12.4 ± 3.0	14.3 ± 3.0	12.2 ± 3.4	11.8 ± 3.4	14.0 ± 3.3	12.1 ± 3.3	11.5 ± 3.8	14.3±3.2	12.4±3.4	10.7±4.2	0.009*
SF-36													
Physical functioning	21.6 ± 15.6	22.5 ± 14.3	27.0 ± 19.5	19.4 ± 17.3	29.6 ± 21.1	29.9 ± 20.8	22.3 ± 20.0	29.4 ± 19.1	37.1 ± 22.1	25.3±19.1	32.8±20.0	37.1±25.2	0.049*
Role physical	43.1 ± 45.6	39.4 ± 42.7	43.1 ± 47.0	38.1 ± 47.0	55.0 ± 47.4	41.9 ± 46.1	30.6 ± 41.8	47.5 ± 44.9	49.4 ± 49.2	30.8±45.1	39.4±46.3	53.5±48.3	0.104
Bodily pain	34.7± 13.6	45.7 ± 22.7	49.5 ± 18.6	38.3 ± 16.1	44.3 ± 17.4	51.5 ± 23.6	37.7 ± 15.1	47.6 ± 19.0	55.8 ± 22.1	40.1±14.7	49.8±22.7	53.9±19.7	0.760
General health	58.8 ± 19.4	59.0 ± 23.3	63.4 ± 17.7	56.1 ± 21.6	59.9 ± 24.6	65.0 ± 17.3	52.6 ± 21.8	62.2 ± 23.9	69.3 ± 19.0	56.8±20.9	61.7±25.0	66.4±18.7	0.185
Vitality	50.4 ± 19.3	57.4 ± 18.3	51.4 ± 20.3	48.3 ± 21.3	58.2 ± 19.4	54.8 ± 19.4	44.3 ± 21.7	54.4 ± 15.9	58.1 ± 21.7	44.8±20.8	58.6±19.0	55.6±23.7	0.071
Social functioning	68.1 ± 22.8	72.8 ± 30.5	73.1 ± 26.6	65.9 ± 23.0	77.8 ± 23.9	80.0 ± 23.3	64.7 ± 25.3	75.9 ± 26.3	80.6 ± 20.8	65.3±27.2	79.0±23.7	80.9±25.0	0.269
Role emotional	48.3 ± 50.0	36.7 ± 47.0	59.2 ± 49.2	40.8 ± 47.4	57.5 ± 48.3	59.2 ± 47.4	43.3 ± 49.6	55.0 ± 48.7	55.0 ± 50.4	48.8±47.7	63.3±47.0	62.4±47.3	0.094
Mental health	59.5 ± 20.4	65.1 ± 22.2	68.2 ± 18.3	58.3 ± 19.4	69.0 ± 17.7	67.5 ± 22.4	54.6 ± 22.7	66.2 ± 21.5	69.2 ± 22.6	55.1±25.1	68.5±18.4	67.1±22.4	0.137
TUGT	14.3 ± 3.5	14.1 ± 4.2	13.5 ± 3.2	15.0 ± 6.2	13.4 ± 4.9	12.6 ± 2.8	13.9 ± 3.9	13.1 ± 4.5	12.4 ± 2.9	14.1±4.8	12.6±4.0	12.4±3.6	0.515
6MWT	311.2 ± 87.6	324.1 ± 97.2	343.6 ± 72.8	305.4 ± 78.9	338.9 ± 77.3	356.5 ± 72.9	298.1 ± 80.4	327.4 ± 68.0	362.8 ± 88.0	291.8±79.7	335.1 ±72.6	361.1±8.5	0.155
FTSS	22.7 ± 6.9	22.7 ± 7.0	21.7 ± 8.3	25.2 ± 12.4	21.3 ± 7.1	20.1 ± 8.2	24.4 ± 9.5	21.8 ± 7.7	20.1 ± 7.5	24.1±9.0	20.7±7.3	20.2±6.2	0.086

ANOVA= analysis of variance for repeated measures; CG= control group; NSG= neoprene sleeve group; BG= brace group; T0= baseline; T45= evaluation after 45 days; T90= evaluation after 90 days; T180= evaluation after

180 days; NPS= numerical pain scale; WOMAC= Western Ontario and McMaster Universities Osteoarthritis Index; Lequesne= Lequesne´s algofuncional questionnaire; SF-36= Short-form-36; TUGT= timed up and go test;

6MWT= 6-minutes walk test; FTSS= five times sit to stand.*Statistically significant p value (<0,05).

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Effects of Bariatric Surgery on Long-Term Quality of Life Outcomes for Obese Patients with Osteoarthritis

Ankita Satpute[1], Deepak L. Bhatt[2], Sangeeta Kashyap[3], Philip Schauer[4], Colin O'Rourke[5], James Bena[5] and **M. Elaine Husni**[6], [1]Case Western Reserve University School of Medicine, Cleveland, OH, [2]Brigham and Women's Hospital Heart & Vascular Center, Boston, MA, [3]Endocrinology, Diabetes and Metabolism, Cleveland Clinic Foundation, Cleveland, OH, [4]General Surgery, Cleveland Clinic Foundation, Cleveland, OH, [5]Department of Quantitative Health Sciences, Cleveland Clinic Foundation, Cleveland, OH, [6]Rheumatology Dept A50, Cleveland Clinic Foundation, Cleveland, OH

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Background/Purpose:

Osteoarthritis (OA) remains a debilitating burden for patients and a challenge to their physicians, as there is no known cure. Obesity has been linked to OA progression and is a possible modifiable risk factor. Consequently patients undergoing bariatric surgery may help elucidate the complex relationship of massive weight loss in patients with OA. This is the first randomized, controlled study that will evaluate the effects of massive weight loss through bariatric surgery on long-term quality of life for obese patients with OA.

Methods:

Medical records of the 150 subjects in the STAMPEDE trial were individually reviewed for documented evidence of OA. STAMPEDE is a randomized, controlled trial that evaluated the efficacy of medical therapy alone (n=50) versus medical therapy in combination with bariatric surgery (n=100) in 150 obese patients with uncontrolled Type II diabetes. The criteria used for OA diagnosis for each patient included one or more of the following: American College of Rheumatology criteria for knee or hip OA (26.9%); radiographic evidence of degenerative change in the hip, knee, ankle, foot or spine (37.3%); or physician documented OA (35.8%). A total of 67 OA patients were included: 18 in the medical group and 49 in the surgical. Demographics at baseline were similar between both groups with no significant differences in patient characteristics (mean age 51, female 44/67, mean BMI 36.6). Linear mixed effect models were used to compare changes in SF-36 scale scores at 1 and 3 years between surgical and medical groups and were adjusted for baseline scores. Analyses were performed using SAS software (version 9.3; Cary, NC).

Results:

At 1 year following intervention, patients who received bariatric surgery when compared to those treated with medical management alone demonstrated statistically significant improvements in the following SF-36 domains: physical functioning, general health, and energy/fatigue. Improvement in the overall physical component score was also statistically significant. At 3 years post-intervention, although improvements were preserved in these domains, only the general health category sustained statistical significance. (See Table 1)

Conclusion:

These results demonstrate that massive weight loss following bariatric surgery has the potential to greatly improve the quality of life for patients suffering from osteoarthritis. Although statistical significance was not preserved for all SF 36

domains at 3 year follow-up, statistical trends in these domains at 3 years reflect similar improvements from 1 year. Further study elucidating factors such as activity level, maintenance of weight loss, and metabolic cytokines, may need to be performed to understand how we can preserve the impacts of bariatric surgery.

Table 1.

SF-36 Factor	Diff: Yr1 Change	Yr 1 P-value	Diff: Yr3 Change	Yr 3 P-value
Physical Functioning	11.76 (0.84,22.68)	**0.036**	9.23 (-2.33,20.78)	0.11
Physical Role	8.13 (-10.50,26.75)	0.39	6.58 (-13.80,26.97)	0.52
Pain	10.09 (-1.45,21.63)	0.086	4.74 (-7.88,17.35)	0.46
General Health	19.37 (9.99,28.75)	**< 0.001**	11.10 (0.89,21.31)	**0.034**
*Overall Physical	11.94 (2.54,21.34)	**0.014**	7.86 (-2.35,18.06)	0.13
Emotional Problems Role	2.72 (-13.60,19.05)	0.74	-3.44 (-21.23,14.35)	0.70
Energy/Fatigue	20.83 (9.21,32.45)	**< 0.001**	6.64 (-5.60,18.89)	0.28
Emotional Well-Being	-0.36 (-8.04,7.32)	0.92	-0.95 (-9.24,7.34)	0.82
Social Functioning	1.68 (-7.99,11.35)	0.73	-0.48 (-11.08,10.12)	0.93
*Overall Mental	6.36 (-2.39,15.11)	0.15	0.66 (-8.80,10.12)	0.89

*overall physical and mental scores represent a mean of the physical and mental components of the SF-36 respectively

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Reduction of Treatment Needed for Knee Osteoarthritis after Bariatric Surgery

Evan Wilder[1], Janice Lin[1], Fernando Bomfim[1], Thayer Mukherjee[1], Lucy O'Shaughnessy[1], Lauren Browne[1], Myriam Weill[1], Kevin Gernavage[1], Farah Taufiq[1], Renata La Rocca Vieira[2], Christine Ren-Fielding[3], Manish Parikh[4], Steven B. Abramson[5] and **Jonathan Samuels**[6], [1]NYU Langone Medical Center, New York, NY, [2]Department of Radiology, NYU Langone Medical Center, New York, NY, [3]Department of Surgery, New York University School of Medicine, New York, NY, [4]Department of Surgery, NYU Langone Medical Center, New York, NY, [5]Dept of Rheumatology/Medicine, Hosp for Joint Diseases/NYU, New York, NY, [6]Rheumatology, NYU - Hospital for Joint Diseases, New York, NY

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Background/Purpose: Medical treatment for knee osteoarthritis (KOA) can be limited and risk morbidity. Weight loss

reduces the arthritis burden and may preclude aggressive treatment. Bariatric surgery trumps diet/exercise for sustainable weight loss; studies suggest improvement in KOA pain long after surgery. We prospectively evaluate the prevalence of painful KOA in obesity and track the effect of bariatrics on knee pain and function. Our hypothesis is that successful weight loss surgery decreases the need for KOA management.

Methods: We screened patients prior to bariatric surgery, targeting knee pain for ≥1 month and a visual analog scale pain ≥30mm. We excluded those with lupus, inflammatory arthritis, psoriasis, or bilateral total knee replacements. Pre-op assessments included BMI, Radiographic severity by Kellgren-Lawrence (KL) grade, questionnaires for knee pain/function (i.e. Knee Injury and Osteoarthritis Outcome Score), and an inventory of KOA treatment – including visits to musculoskeletal subspecialists, medication (oral/topical/intraarticular) and physical therapy. We reassessed patients at 1, 3, 6 and 12 months post surgery, also calculating percent excess weight loss (%EWL).

Results: Of 536 patients considering bariatric surgery, we found 308 with knee pain and enrolled 176 (91.5% female; mean BMI 43.6 kg/m^2±7, range 32-61; mean age 42 ±11, range 18-73). Radiographic severity was well distributed (KL0-KL4). Higher KL grade and BMI correlated with worse pre-op symptoms (data not shown). Patients with worse baseline KL scores visited specialists more often (KL0=33% vs KL3-4=72%, p=0.001) and were more likely to use at least one prescribed treatment (KL0=19% vs KL3-4=57%, p=0.001).

For the 150 patients who completed bariatric surgery, average knee pain and function improved at each post-operative interval, correlating with %EWL sustained over time (data not shown). We found a marked decrease in treatment used at the intervals, including the 6 month followup. The percent of patients using over the counter analgesics dropped from 87.5% to 47.2% (p<0.0001), visits to specialists fell from 55.7% to 24.7% (p<0.0001), and patients needing the various prescribed treatments decreased from 40.3% to 12.4% (p<0.0001).

While the attenuated need for KOA treatment trended with %EWL, those with post-op BMI >40 had an increased need for knee specialists - up from 33.3% to 71.4% (post-op month 1 to 12) with a pre-op baseline 53.8%. Conversely, specialist visits for patients with a BMI <40 only rose from 26.8% to 28.6% with a pre-op baseline of 58.6%. Prescription KOA treatment in the post-op BMI>40 group also rose from 11.1% to 43% (post-op month 1 to 12) from pre-op baseline 38.7%, while those patients remaining under a BMI of 40 saw their use of prescription KOA treatment fall from 17.1% to 14.3% with pre-op baseline 42.9%.

Conclusion: The improvement in KOA symptoms from bariatric weight loss is reflected by a significantly decreased need for treatment. This reduction is sustained over time except in the patients whose BMI remains above 40. While radiographic severity correlates with patients' treatment patterns at baseline, it does not appear to limit their ability to decrease knee treatment with successful weight loss surgery.

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Perioperative Interventions for Smoking Cessation in Hip and Knee Arthroplasty for Osteoarthritis and Other Non-Traumatic Diseases

Aseem Bharat[1] and **Jasvinder A. Singh**[2], [1]Medicine/Rheumatology, University of Alabama at Birmingham, Birmingham, AL, [2]University of Alabama at Birmingham, Birmingham, AL

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Background/Purpose: Total knee and hip arthroplasty (TKA and THA) are very common surgeries performed in patients who suffer from pain and functional limitation due to symptomatic arthritis, when medical management has failed. These surgeries are usually elective, and are associated with excellent outcomes including significant improvement in function, quality of life and reduction in pain severity. Smoking is a modifiable risk factor for patients failing to improve dramatically after a Total Hip Arthroplasty or Total Knee Arthroplasty surgeries. Our objective was to assess the benefits and harms of perioperative smoking cessation interventions on outcomes and complications after knee or hip replacement.

Methods: An expert librarian searched six databases for any clinical trials of relevance, including the Cochrane Central Register of Controlled Trials (CENTRAL), OVID MEDLINE, CINAHL, EMBASE, Science Citation Index and Current Controlled Trials databases. Studies were included if they used perioperative smoking cessation as an intervention in patients undergoing TKA/THA, were randomized or quasi-randomized and provided clinical outcomes. Two review authors independently reviewed all titles and abstracts, selected appropriate studies for full review and reviewed the full-text articles for the final selection of included studies. For each study, they independently abstracted study characteristics, safety and efficacy data and performed risk of bias assessment. Disagreements were resolved by consensus. The primary outcomes of interest were wound complications, revision or reoperation rate, any postoperative complication within 30-days of the surgery, venous thromboembolism, death, function: as assessed by validated outcome and pain.

Results: Three RCTs with 311 participants were included that had the data for the outcomes comparing Counselling/Nicotine replacement versus No counselling/Smoking cessation program. The outcomes of interest found to be statistically significantly associated with Smoking cessation interventions were postoperative complications within 30 days of arthroplasty(OR= 0.23) and smoking cessation after surgery (4 weeks,OR= 9.06; 1 year,OR= 6.5; after 1 year, OR= 0.15). Detailed data results are shown in Table. 1

Conclusion: With an overall high grade of evidence, Perioperative smoking cessation therapy is significantly more efficacious than placebo in preventing incidence of complications after knee or hip replacement. Long-term surveillance studies are needed for safety assessment.

Table. 1 **Counselling/Nicotine replacement versus No counselling/Smoking cessation program in hip and knee arthroplasty for osteoarthritis and other non-traumatic diseases**

Outcomes	**Illustrative comparative risks (per 1000)**		**Odds Ratio (95% CI)**
	No counselling or Smoking cessation program	**Counselling/Nicotine replacement versus No counselling/Smoking cessation program**	
Any complication within 30 days	**594**	**252**	**OR 0.23** (0.12 to 0.41)
Cardiovascular complication within 30 days	**57**	**18**	**OR 0.3** (0.02 to 4.57)
Delirium	**77**	**18**	**OR 0.22** (0.02 to 2.02)
Fever of unknown origin within 30 days	**19**	**7**	**OR 0.37** (0.01 to 9.24)
Gastrointentinal complication within 30 days	**9**	**16**	**OR 1.69** (0.06 to 44.08)
Hematoma 30 days post op	**104**	**40**	**OR 0.36** (0.11 to 1.2)
Other wound complication within 30 days	**74**	**41**	**OR 0.54** (0.1 to 3.11)
Pulmonary complication within 30 days	**19**	**12**	**OR 0.62** (0.08 to 5.16)
Renal insufficiency	**19**	**6**	**OR 0.3** (0.01 to 7.63)
Secondary Surgery	**154**	**35**	**OR 0.2** (0.04 to 1.01)
Subfascial involvement	**77**	**18**	**OR 0.22** (0.02 to 2.02)
Urinary tract complication within 30 days	**167**	**83**	**OR 0.45** (0.13 to 1.58)
UTI	**115**	**89**	**OR 0.75** (0.21 to 2.63)
Vascular	**19**	**18**	**OR 0.93** (0.06 to 15.22)
Wound infection within 30 days	**74**	**41**	**OR 0.54** (0.1 to

days			3.11)
Other Wound related complications	**442**	**73**	**OR 0.1** (0.03 to 0.31)
Stopped smoking before surgery	**67**	**661**	**OR 27.26** (7.46 to 99.57)
Stopped smoking 4 weeks after surgery	**67**	**393**	**OR 9.06** (2.5 to 32.85)
Stopped smoking 1 year after surgery	**44**	**232**	**OR 6.5** (1.38 to 30.55)
Stopped smoking 1 year follow up	**956**	**763**	**OR 0.15** (0.03 to 0.72)

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Activity Limitations in Persons with Low, Medium, and High Levels of Pain Prior to Total Knee Replacement: Implications for Appropriateness and Efficacy

Ilana M. Usiskin[1], Heidi Y. Yang[1], Bhushan R. Deshpande[1], Jamie E. Collins[2], Griffin L. Michl[1], Savannah R. Smith[3], Kristina M. Klara[1], Jeffrey N. Katz[2] and Elena Losina[4], [1]Orthopaedic and Arthritis Center for Outcomes Research, Brigham and Women's Hospital, Boston, MA, [2]Orthopaedic and Arthritis Center for Outcomes Research, Department of Orthopedic Surgery, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, [3]Orthopedic and Arthritis Center for Outcomes Research, Brigham and Women's Hospital, Boston, MA, [4]Orthopaedic and Arthritis Center for Outcomes Research, Department of Orthopaedic Surgery, Brigham and Women's Hospital and Harvard Medical School, Boston, MA

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Background/Purpose: Historically, persons with knee OA considered for total knee replacement (TKR) have had severe pain, as reflected in high WOMAC scores, in addition to extensive structural changes and limited mobility. The WOMAC Pain scale captures basic mobility domains, including pain at rest (sitting or lying down), standing, walking, and using stairs. More recently, patients undergoing TKR have had lower WOMAC Pain scores, raising questions about

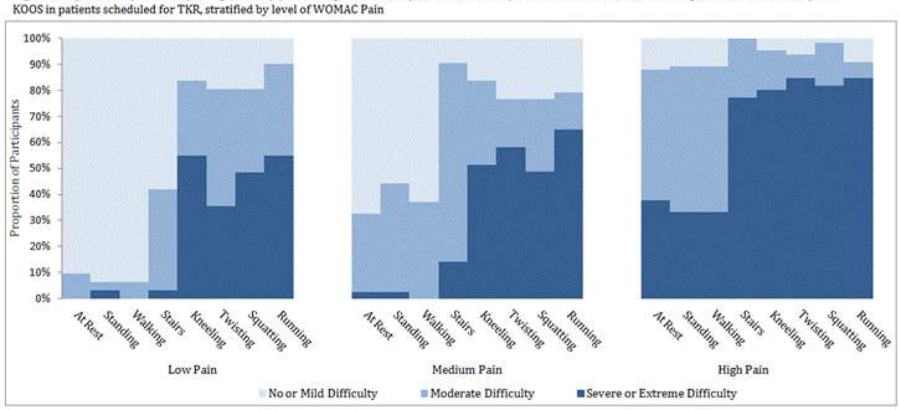
the appropriateness of TKR in these patients. We hypothesized that pain in TKR patients with low WOMAC pain scores is provoked by more demanding activities such as kneeling, twisting, and squatting. Difficulty with these activities may compromise their quality of life and lead to TKR. We sought to evaluate the degree of difficulty with more rigorous recreational activities in persons undergoing TKR with low, medium, and high levels of WOMAC Pain.

Methods: We used baseline data from the Study of Physical Activity Rewards after Knee Surgery (SPARKS). Participants completed baseline questionnaires within 8 weeks prior to TKR, which included the WOMAC Pain and Knee Injury and Osteoarthritis Outcomes Score (KOOS) Sports and Recreational Activity scales. We stratified subjects into three groups according to WOMAC Pain scores (0–100, 100 worst): Low (<25), Medium (26–40), and High (>40). Within each pain group we assessed the difficulty subjects reported with going up and down stairs, twisting or pivoting, kneeling, squatting, and running.

Results: The sample consisted of 140 persons scheduled to undergo TKR, with an average age of 66 (SD 8) years. The mean WOMAC Pain score was 42 (SD 20). 22% of study participants were in the Low Pain group, 31% in the Medium Pain group, and 47% in the High Pain group. Those with lower WOMAC Pain scores tended to be older: mean age 68 years for those in Low Pain compared to 63 years for those in High Pain. 42% of patients in the Low Pain group reported at least moderate pain using stairs, compared to 91% and 100% of those in the Medium and High Pain groups (Figure). About half of patients in the Low Pain group reported severe or extreme difficulty with squatting, kneeling, or running, while an additional 30% reported moderate difficulty with those same tasks.

Conclusion: Persons with low or medium WOMAC Pain undergoing TKR seldom report pain with basic mobility yet frequently report substantial difficulty with more demanding daily activities, such as using stairs, kneeling, and squatting. TKR is likely to allow these patients to regain the ability to perform these activities that are fundamental to their quality of life. Determining the effectiveness of TKR based on improvements in WOMAC Pain may be limited in patients with low preoperative WOMAC pain scores. Assessment of TKR effectiveness should consider improvement in the ability to perform more demanding but important daily activities such as kneeling, squatting and using stairs.

Figure. Proportion of patients reporting difficulty performing basic mobility tasks measured by the WOMAC and more demanding activities measured by the KOOS in patients scheduled for TKR, stratified by level of WOMAC Pain



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Abstract Number: 325

Best Performing Definition of Accelerated Knee Osteoarthritis

Jeffrey Driban[1], Grace H. Lo[2], Charles B. Eaton[3], Lori Lyn Price[4], Bing Lu[5] and Timothy E. McAlindon[1], [1]Tufts Medical Center, Boston, MA, [2]VA HSR&D Center for Innovations in Quality, Effectiveness and Safety; Medical Care

Line and Research Care Line; Department of Medicine, Michael E. DeBakey VA Medical Center, Baylor College of Medicine, Houston, TX, [3]Family Medicine and Community Health(Epidemiology), Alpert Medical School of Brown University, Pawtucket, RI, [4]Clinical Care Research, Tufts Medical Center, Boston, MA, [5]Brigham & Women's Hospital and Harvard Medical School, Boston, MA

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Background/Purpose: Accelerated knee osteoarthritis (AKOA) may be a unique subset of knee osteoarthritis (KOA) that is associated with a knee injury and greater age, body mass index (BMI), and knee pain. There are several definitions of AKOA, making it challenging to understand this phenotype. It is important to compare the performance of these AKOA definitions. Therefore, we evaluated agreement among several definitions of AKOA and construct validity by comparing their individual associations with injury, age, obesity, and knee pain.

Methods: We selected knees from the Osteoarthritis Initiative (OAI) that had no radiographic KOA (Kellgren-Lawrence [KL]=0 or 1) at baseline and had quantitative medial joint space width (JSW) measures on high-quality radiographs at >2 consecutive visits (n=1,061 knees, 738 participants). Quantitative medial JSW was based on a semi-automated method and location specific (x=0.25). We compared a KL-based definition of AKOA, which accounts for changes throughout a knee, to 4 JSW-based definitions that are derived from previous latent class analyses: 1) stringent JSW (averaged): average JSW loss >1.05 mm/year over 4 years, 2) stringent JSW (consistent): JSW loss >1.05 mm/year for >2 years, 3) lenient JSW (averaged): average JSW loss >0.25 mm/year over 4 years, and 4) lenient JSW (consistent): JSW loss >0.25 mm/year for >2 years. We also defined AKOA as progression from no radiographic KOA to end-stage KOA (KL=3 or 4) within 4 years. We calculated kappa statistics between the JSW-based definitions and KL-based definition of AKOA. We then examined how the different definitions influenced the effect size of group differences (AKOA or no AKOA) of an injury during the first four years of the OAI, baseline age, baseline BMI, and average WOMAC pain score from baseline and the first four annual visits as a form of construct validity.

Results: Over 4 years the incidence rate of AKOA was 0.7%, 1.2%, 18.1%, 24.7%, and 11.2% based on the stringent JSW (averaged and consistent), lenient JSW (averaged and consistent), and KL-based definitions. Everyone meeting the stringent JSW definition also met the KL-based definition. There was fair-moderate agreement between the lenient JSW (averaged) and KL-based definitions. KL-based definition led to larger effect sizes for injury, age, BMI, and average pain.

Conclusion: A KL-based definition of AKOA may be ideal because it offers greater effect estimates for known risk factors for the condition. The performance of the KL-based definition may be related to the broader definition of joint deterioration compared with those focused on just joint space alone.

Table 1. Low level of agreement between the JSW-based definition of accelerated knee osteoarthritis (KOA) and KL-based definition of accelerated KOA.

	Average JSW Loss >1.05 mm/year		2+ Years with JSW Loss > 1.05 mm		Average JSW Loss >0.25 mm/year		2+ Years with JSW Loss > 0.25 mm	
KL-Based Definition of Accelerated KOA	No (n = 992) n (%)	Yes (n = 7) n (%)	No (n = 987) n (%)	Yes (n = 12) n (%)	No (n=818) n (%)	Yes (n = 181) n (%)	No (n = 752) n (%)	Yes (n = 247) n (%)
Accelerated KOA (n = 112)	105 (94%)	7 (6%)	100 (89%)	12 (11%)	36 (32%)	76 (68%)	49 (44%)	63 (56%)
No Accelerated KOA (n = 887)	887 (100%)	0 (0%)	887 (100%)	0 (0%)	782 (88%)	105 (12%)	703 (79%)	184 (21%)
Kappa Statistic	0.11		0.18		0.44		0.23	

Percentages are by row. KL = Kellgren-Lawrence; KOA = knee osteoarthritis; JSW = joint space width

Table 2. Differences between those with and without accelerated knee osteoarthritis (KOA) based on definitions of accelerated KOA that had moderate agreement

	KL-based Definition			Average JSW Loss > 0.25 mm/year			Average JSW Loss > 0.25 mm/year (Among those w/o KL-based AKOA)		
	No (n = 887)	Yes (n = 112)	Effect Size[1]	No (n=818)	Yes (n = 181)	Effect Size[1]	No (n=818)	Yes (n = 105)	Effect Size[1]
Baseline Age (years)	59 (9)	60 (8)	d=0.41 (0.25, 0.54)	59 (9)	61 (9)	d=0.24 (0.12, 0.37)	59 (9)	60 (9)	d=0.16 (0.03, 0.29)
Baseline BMI (kg/m^2)	27.5 (4.5)	29.8 (4.6)*	d=0.50 (0.37, 0.62)	27.5 (4.6)	29.2 (4.5)*	d=0.37 (0.24, 0.49)	27.5 (4.6)	28.5 (4.4)*	d=0.36 (0.10, 0.36)
Average WOMAC Pain	1.4 (2.0)	2.7 (2.3)*	d=0.61 (0.48, 0.74)	1.4 (2.0)	2.4 (2.5)*	d=0.47 (0.35, 0.60)	1.4 (2.0)	1.8 (2.4)	d=0.21 (0.08, 0.34)
Recent knee injury n (%)	110 (13%)	40 (36%)	OR=3.9 (2.5, 6.0)	100 (12%)	50 (33%)	OR=2.9 (2.0, 4.3)	100 (12%)	20 (21%)	OR=1.8 (1.1, 3.1)

Average WOMAC pain across the first five visits. Mean (SD) unless noted otherwise.
1. Effect size: d = mean difference/standard deviation for continuous measurements and OR = odds ratio for recent knee injury.
KL = Kellgren-Lawrence; KOA = knee osteoarthritis; JSW = joint space width

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Older Adults without Extreme Obesity Are at Highest Risk for Accelerated Knee Osteoarthritis

Jeffrey Driban[1], Grace H. Lo[2], Charles B. Eaton[3], Lori Lyn Price[4], Bing Lu[5], Mary Barbe[6] and Timothy E. McAlindon[7], [1]Tufts Medical Center, Boston, MA, [2]VA HSR&D Center for Innovations in Quality, Effectiveness and Safety; Medical Care Line and Research Care Line; Department of Medicine, Michael E. DeBakey VA Medical Center, Baylor College of Medicine, Houston, TX, [3]Family Medicine and Community Health(Epidemiology), Alpert Medical School of Brown University, Pawtucket, RI, [4]Clinical Care Research, Tufts Medical Center, Boston, MA, [5]Brigham & Women's Hospital and Harvard Medical School, Boston, MA, [6]Temple University School of Medicine, Philadelphia, PA, [7]Division of Rheumatology, Tufts Medical Center, Boston, MA

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Background/Purpose: Accelerated knee osteoarthritis (AKOA) may be a unique subset of knee osteoarthritis (KOA). AKOA is more common among those who are older, overweight, or had a recent knee injury. These three risk factors interact to exacerbate an individual's risk for AKOA. Identifying which subset of individuals are at most risk for AKOA will help clinicians recognize patients that need more frequent follow-up visits to ensure early detection of AKOA. Therefore, we explored age and body mass index (BMI) to identify a subset of individuals who are at high risk for AKOA compared with common KOA.

Methods: In the Osteoarthritis Initiative we studied participants without KOA on their baseline radiographs (Kellgren-Lawrence [KL] < 2). We compared 2 groups: 1) AKOA: > 1 knee progressed to end-stage KOA (KL Grade 3 or 4) within 48 months and 2) common KOA: > 1 knee increased in radiographic scoring within 48 months (excluding those with AKOA). Age and BMI were collected at the baseline visit. A recent knee injury was a self-reported injury within a year prior to a knee meeting the definition of AKOA or common KOA. We reviewed 3-dimensional surface and contour graphs with age, BMI, and probability of AKOA versus KOA on the axes to identify groups that have the highest probability of AKOA compared with common KOA (see Figure). After we identified two possible subsets as high risk we conducted a logistic regression with AKOA as the outcome and age-BMI groups as the predictor

(adjusting for sex and recent knee injury). We also explored stratified analyses among those with and without a recent knee injury.

Results: Among 1,637 participants, 52 (3.2%) individuals had AKOA and 184 (11.2%) had common KOA. We identified two high-risk sets of individuals (Figure 1B): 1) individuals > 65 years of age with BMI < 35kg/m^2 (n = 64, 27%) and 2) individuals < 65 years of age with BMI > 32.5 kg/m^2 (n = 43, 18%). We defined all other participants as low risk. Overall, older individuals with a BMI < 35kg/m^2 were 3.5 times more likely to develop AKOA instead of common KOA than individuals at low risk (see Table). In contrast, younger individuals with a BMI > 32.5 kg/m^{2}were not statistically more likely to develop AKOA instead of common KOA. These findings were consistent among those with and without a recent knee injury (see Table).

Conclusion: While older age and greater BMI are associated with AKOA we found that older individuals with a BMI < 35kg/m^{2}were more likely to develop AKOA than common KOA. Individuals with these characteristics who also report knee pain should be carefully monitored to detect early signs of AKOA.

Figure 1. Probability of Accelerated Knee Osteoarthritis (AKOA) Compared with Common Knee Osteoarthritis (KOA) by Age and Body Mass Index.
A. Surface plot of the probability of AKOA (vertical axis) by age and body mass index as continuous variables.
B. Surface plot of the probability of AKOA (vertical axis) by age and body mass index categorized by World Health Organization criteria. Red boxes highlight high-risk subsets of interest (> 65 years with BMI < 35 kg/m^2, <65 years with BMI ≥32.5 kg/m^2)

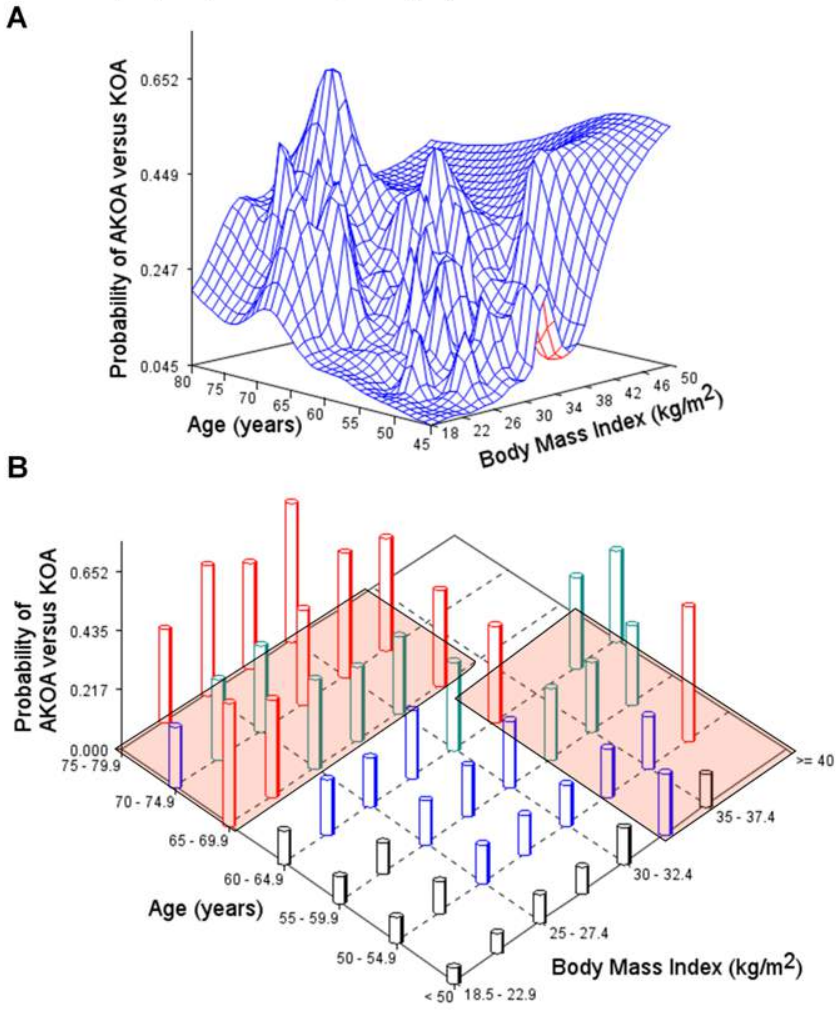

Table. Interaction Between Age, Body Mass Index Influences the Risk of Accelerated Knee Osteoarthritis (KOA)

	Common KOA	Accelerated KOA	Adjusted Odds Ratio (95% Confidence Interval)
	(REF)		Accelerated KOA
All Participants	*(n = 184)*	*(n = 52)*	
Low Risk Group (n = 129)	110 (60%)	19 (37%)	REFERENCE
Older with BMI < 35 kg/m^2 (n = 64)	40 (22%)	24 (46%)	**3.47 (1.70, 7.10)**
Younger with BMI ≥ 32.5 kg/m^2 (n = 43)	34 (18%)	9 (17%)	1.43 (0.58, 3.53)
Injured	(n = 18)	(n = 13)	
Low Risk Group (n = 14)	11 (61%)	3 (23%)	REFERENCE
Older with BMI < 35 kg/m2 (n = 9)	2 (11%)	7 (54%)	**10.27 (1.25, 84.25)**
Younger with BMI ≥ 32.5 kg/m2 (n = 8)	5 (28%)	3 (23%)	1.74 (0.23, 13.23)
Un-injured	(n = 166)	(n = 39)	
Low Risk Group (n = 115)	99 (60%)	16 (41%)	REFERENCE
Older with BMI < 35 kg/m2 (n = 55)	38 (23%)	17 (44%)	**2.68 (1.23, 5.86)**
Younger with BMI ≥ 32.5 kg/m2 (n = 35)	29 (17%)	6 (15%)	1.32 (0.47, 3.70)

Note: The model with all participants was adjusted for sex and injury. The models among those with and without an injury were adjusted for sex. The cut-off for age was 65 years. **Bold font** = significant odds ratios.

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Abstract Number: 327

The Relation of Plasma Vitamin K Status to Meniscal Pathology in Knee Osteoarthritis: The Multicenter Osteoarthritis Study

Jia Liu[1], Martin Englund[2], Sarah Booth[3], David T. Felson[4], Michael C. Nevitt[5], Cora E. Lewis[6], James Torner[7], Anyu Hu[8] and Tuhina Neogi[4], [1]Boston Medical Center, Boston, MA, [2]Clinical Epidemiology Unit, Orthopedics, Dept of Clinical Sciences Lund, Lund University, Lund, Sweden, [3]HRNCA, Tufts Medical Center, Boston, MA, [4]Clinical Epidemiology Research and Training Unit, Boston University School of Medicine, Boston, MA, [5]Epidemiology and Biostatistics, UCSF, San Francisco, CA, [6]Preventive Medicine, University of Alabama at Birmingham, Birmingham, AL, [7]University of Iowa, UIowa, Iowa City, IA, [8]Clinical Epidemiology Research Unit, Boston University School of Medicine, Boston, MA

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Background/Purpose: Vitamin K is an essential cofactor in bone and cartilage mineralization. Low serum vitamin K has been associated with increased prevalence of hand and knee osteoarthritis (OA), higher risk of developing knee OA and cartilage lesions, and, in one study, worsening of meniscal lesions; however, incidence of meniscal damage was not assessed. Meniscal damage is a potent risk factor for knee OA, and severe knee OA is associated with meniscal

damage. We therefore sought to identify whether vitamin K status was associated with the prevalence and incidence of meniscal pathology on MRI.

Methods: The Multicenter Osteoarthritis (MOST) Study is a NIH-funded longitudinal cohort study of adults with or at high risk for developing knee OA. Participants had knee x-rays and 1.0T MRIs at 0 and 30 months. MRI evidence of meniscal pathology was evaluated using WORMS. Meniscal integrity was graded on a 0-4 scale in 3 subregions of the medial and lateral menisci, respectively, and medial and lateral meniscal extrusion were graded on a 0-2 scale. We defined meniscal pathology as any abnormality of meniscal integrity (score ≥1 in any subregion) or meniscal extrusion (medial or lateral score ≥1). Vitamin K status was determined by plasma phylloquinone levels at baseline, and categorized as insufficient (<1.0nM) or sufficient (≥1.0nM); there were too few to analyze true deficiency (<0.5nM). We excluded baseline coumadin users. We examined the relation of vitamin K status to knee-specific baseline presence of meniscal pathology in the whole sample, and to development of meniscal pathology at 30 months among subjects without meniscal pathology at baseline using binary regression with robust variance estimation to obtain prevalence ratios (PR) and risk ratios (RR), respectively. We used GEE to account for correlations between two knees within a person. All analyses were adjusted for age, sex, BMI, vitamin D, smoking status, race, and prior knee injury. Analyses were also stratified by radiographic OA status.

Results: 1457 knees from 1048 subjects (mean age 62.0±7.9 years, BMI 29.9±4.9 kg/m^2, 62.4% female, 34.0% with insufficient vitamin K levels) were included in the cross-sectional analysis. Of these, 535 knees did not have meniscal pathology at baseline and were used in the longitudinal analysis. The prevalence of meniscal pathology was high. Vitamin K status was not significantly associated with either the prevalence or incidence of meniscal pathology (**Table**). Effects were similar when stratified by radiographic OA status.

Conclusion: Plasma vitamin K insufficiency was not associated with prevalence or incidence of meniscal pathology over 30 months. Given the high prevalence of meniscal pathology at baseline, we may need to examine the effects of vitamin K on meniscal pathology at an earlier age, or in a cohort not specifically selected for OA risk to avoid the possibility of depletion of susceptibles.

Table: Relation of vitamin K to meniscal pathology

Cross-sectional analysis (N= 1457 knees, 1048 subjects)		
Baseline Vitamin K status (Prevalence)	Prevalence of meniscal pathology (knee-based) (%)	Adjusted* Prevalence Ratio (95% CI), p-value
Insufficient (<1nM) (n=494 (34%) knees)	293 (59.3)	0.98 (0.90-1.08), p=0.7
Sufficient (≥1nM) (n=963 (66%) knees)	586 (60.9)	1.00 (reference)
Longitudinal analysis (N=535 knees, 448 subjects)		
	Incidence of meniscal pathology over 30 months (knee-based) (%)	Adjusted* Risk Ratio (95% CI), p-value
Insufficient (<1nM) (n= 191 (36%) knees)	21 (11.0)	0.96 (0.79-1.16), p=0.7
Sufficient (≥1nM) (n= 344 (64%) knees)	44 (12.8)	1.0 (reference)
*Adjusted for: age, sex, BMI, vitamin D level, smoking status, race, prior knee injury		

Disclosure: J. Liu, None; **M. Englund**, None; **S. Booth**, None; **D. T. Felson**, None; **M. C. Nevitt**, None; **C. E. Lewis**, None; **J. Torner**, None; **A. Hu**, None; **T. Neogi**, None.

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Abstract Number: 328

Associations Between Body Composition Measures of Obesity and Radiographic Osteoarthritis in Older Adults: Data from the Dong-Gu Study

Kyung-Eun Lee[1], Lihui Wen[1], Yi-Rang Yim[1], Ji-Eun Kim[1], Jeong-Won Lee[1], Dong-Jin Park[2] and Shin-Seok Lee[1], [1]Chonnam National University Medical School and Hospital, Gwangju, South Korea, [2]Rheumatology, Chonnam National University Medical School and Hospital, Gwangju, South Korea

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Background/Purpose: We examined the effects of fat deposition on radiographic osteoarthritis (OA) to determine the role of obesity in the pathology of radiographic OA.

Methods: Data were taken from the Dong-gu cohort, a cross-sectional study of 2,367 subjects. Baseline characteristics, waist circumference (WC), fat mass, and fat percentage were collected, along with X-rays of the knees and hands. Waist-to-hip ratio (WHR) was defined as the ratio of waist and hip circumferences. Diabetes mellitus was defined as fasting glucose > 126 mg/dL or the use of hypoglycemic medication. Hypertension was defined as systolic blood pressure ≥ 140 mmHg, diastolic blood pressure ≥ 90 mmHg, or use of antihypertensive medication. Total knee and hand radiographic OA scores were summed using a semi-quantitative grading system, and then stratified by gender using a multiple linear regression model.

Results: After adjusting for confounders, weight was the only factor significantly associated with knee radiographic OA, regardless of gender ($p = 0.027$ and $p < 0.001$, for males and females, respectively). Regarding the hand, fat percentage had the largest effect on radiographic OA in males (Eta = 0.007, $p = 0.008$), while WHR was the most significant factor in females (Eta = 0.009, $p = 0.001$). For the knee, fat mass was the most important factor for radiographic OA in males (Eta = 0.012, $p = 0.001$), while in females, body mass index (BMI) was the most important factor (Eta = 0.059, $p < 0.001$). Among the variables, only fat percentage was significantly related to both hand and knee radiographic OA in both genders (all $p < 0.01$).

Conclusion: Regardless of gender, mechanical stress was significantly associated with knee radiographic OA. Otherwise, fat deposition correlated with hand and knee radiographic OA in both genders, while the distribution of fat tissue was significantly associated with hand and knee radiographic OA only in females, with the largest effect on hand and knee radiographic OA.

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Abstract Number: 329

Serum Leptin and Risk of Knee Pain and Osteoarthritis: Multicenter Osteoarthritis Study

Devyani Misra[1], Jingbo Niu[2], David T. Felson[2], Michael C. Nevitt[3], James Torner[4], Cora E. Lewis[5], Anyu Hu[6], Sadao Jinno[7] and Tuhina Neogi[8], [1]Medicine, Section of, BUSM, Boston, MA, [2]Clinical Epidemiology Research and Training Unit, Boston University School of Medicine, Boston, MA, [3]Epidemiology and Biostatistics, UCSF, San Francisco, CA, [4]University of Iowa, UIowa, Iowa City, IA, [5]Preventive Medicine, University of Alabama at Birmingham, Birmingham, AL, [6]Clinical Epidemiology Research Unit, Boston University School of Medicine, Boston, MA, [7]BUSM, Boston, MA, [8]Clinical Epidemiology, BUSM, Boston, MA

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Serum Leptin and Risk of Knee Pain and Osteoarthritis: Multicenter Osteoarthritis Study

D. Misra, J. Niu, D.T. Felson, M. Nevitt, J. Torner, C.E. Lewis, A. Hu, S. Jinno, T. Neogi

Background/Purpose: Obesity is a major risk factor for knee osteoarthritis (OA). Leptin, a proinflammatory adipose tissue product that is highly correlated with adiposity, has been associated with risk of knee OA. Given that leptin is proinflammatory, it could contribute to synovial inflammation. Since synovial inflammation leads to pain in knee OA, it is particularly relevant to study the association of leptin with pain and symptomatic knee OA. Thus, we evaluated the longitudinal association of serum leptin with risk of incident knee pain, incident radiographic and symptomatic knee OA in community-dwelling older men and women.

Methods: We included participants from Multicenter Osteoarthritis (MOST) study, a NIH-funded, longitudinal, observational study of individuals with or at high risk for knee OA, who had serum leptin measured at baseline and knee radiographs at baseline and follow up visits (30-, 60- and 84-month visits). We limited our study sample to those without radiographic OA (KL grade < 2 and no patellofemoral OA) in either knee at baseline. Serum leptin was not normally distributed and highly correlated with body mass index (BMI); thus, we first created BMI residuals of the log of serum leptin and then created tertiles. Incident radiographic knee OA was defined by development of Kellgren-Lawrence grade≥2 or patellofemoral OA by the 84-month visit. Incident symptomatic knee OA was defined by presence of knee pain (both at the telephone screen and clinic visit) in addition to incident radiographic OA changes in the knee by the 84-months. The association of leptin tertiles with incident knee pain, incident radiographic and incident symptomatic OA was assessed using logistic regression with GEE to calculate Odds Ratios (OR), adjusting for age, BMI, race, site, knee injury, knee surgery and CES-D score. All analyses were sex-specific since leptin levels and potentially its effects may be sex-specific.

Results: Among 690 subjects (mean age 60.6 yrs, mean BMI 29.1 kg/m^2 and 62.5% women), mean serum leptin level at baseline was 37022.5 pg/ml in women and 15099.1 pg/ml in men. At the 84 month visit, there were 80, 226 and 64 knees with incident pain, incident radiographic and incident symptomatic OA, respectively. We found a significant increase in the risk of incident knee pain in women (p for trend =0.003) but not in men (**Table 1**). Although the results

did not reach statistical significance, there was a slight increase in the risk of symptomatic OA but not in radiographic OA, in women and men (**Table 1**).

Conclusion: Serum leptin is associated with incident knee pain in women and may be associated with symptomatic OA in men and women but not with radiographic OA. Larger studies are needed to confirm the findings and evaluate leptin as a target for treatment of pain in knee OA.

Table 1: Association of baseline serum leptin tertiles with risk of incident knee pain and osteoarthritis

	Women			Men		
Log Leptin BMI residual tertiles	**N (%)**	**Crude OR**	**Adjusted* OR (95% CI)**	**N (%)**	**Crude OR**	**Adjusted* OR (95% CI)**
	Incident knee pain					
Lowest tertile	8 (6)	1.0 (reference)	1.0 (reference)	13 (13)	1.0 (reference)	1.0 (reference)
Middle tertile	18 (13)	2.41	3.21 (1.18-8.68)	8 (10)	0.74	0.82 (0.29-2.27)
Highest tertile	23 (15)	2.93	4.70 (1.64-13.48) P for trend=0.003	10 (11)	0.88	1.14 (0.41-3.20)
	Incident radiographic OA					
Lowest tertile	50 (23)	1.0 (reference)	1.0 (reference)	22 (18)	1.0 (reference)	1.0 (reference)
Middle tertile	47 (21)	0.91	0.96 (0.56-1.63)	32 (26)	1.62	1.90 (0.93-3.87)
Highest tertile	55 (25)	1.16	1.26 (0.75-2.14)	33 (26)	0.79	1.03 (0.49-2.20)
	Incident symptomatic OA					
Lowest tertile	13 (6)	1.0 (reference)	1.0 (reference)	7 (6)	1.0 (reference)	1.0 (reference)
Middle tertile	15 (7)	1.15	1.31 (0.52-3.34)	11 (9)	1.63	1.81 (0.60-5.68)
Highest tertile	13 (6)	1.01	1.28 (0.50-3.28)	7 (6)	1.01	1.41 (0.48-4.15)

*Adjusted for age, BMI, race, site, knee injury, knee surgery and CES-D score

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Disclosure: D. Misra, None; **J. Niu**, None; **D. T. Felson**, None; **M. C. Nevitt**, None; **J. Torner**, None; **C. E. Lewis**, None; **A. Hu**, None; **S. Jinno**, None; **T. Neogi**, None.

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Abstract Number: 330

Calf Muscle Adiposity Is Associated with Impaired Physical Performance in Knee OA

Michael Davison[1], Monica R. Maly[2], Jonathan D. Adachi[3] and Karen A. Beattie[4], [1]School of Medicine, McMaster University, Hamilton, ON, Canada, [2]School of Rehabilitation Science, McMaster University, Hamilton, ON, Canada, [3]Division of Rheumatology, McMaster University, Hamilton, ON, Canada, [4]Medicine, McMaster University, Hamilton, ON, Canada

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Session Time: 9:00AM-11:00AM

Background/Purpose: Knee osteoarthritis (OA) is a degenerative disease associated with significant muscle weakness and disability. Ectopic fat in the thigh, including intramuscular fat (intraMF; fat within a muscle belly) and intermuscular fat (IMF; fat within the deep fascia and between muscles bellies), is associated with impaired strength and physical performance in knee OA. Despite the role of calf muscles in creating power for gait and mobility, there has been little investigation of calf muscle composition in knee OA. We investigated the relationships between calf muscle adiposity, IMF and intraMF volume with physical performance in women with knee OA.

Methods: Women (n=20) with radiographic knee OA had the calf of their most symptomatic knee imaged using 3.0T magnetic resonance imaging (MRI). The iterative decomposition of water and fat with echo asymmetry and least-squares estimation (IDEAL) sequence obtained 10 fat-separated axial images (3 mm slice thickness). Images were analyzed using SliceOmatic® software with region-growing to quantify IMF, intraMF and lean muscle volumes (cm^3) (Figure 1). Muscle adiposity was calculated as the percent of total muscle volume consisting of intramuscular fat; this was calculated for the whole calf and individually for the medial gastrocnemius (MG), lateral gastrocnemius (LG), soleus (SOL), and tibialis anterior (TA). Participants performed five physical performance tests, and rated their knee pain using a numeric pain rating scale. Linear regression analyses were performed.

Results: Mean sample characteristics (±SD): age 65±5 y; BMI 30±5 kg/m^2. After adjusting for knee pain, whole calf muscle adiposity, but not IMF or intraMF volume, was associated with poor performance on the timed up-and-go (TUG), stair ascent/descent test (SADT), and 6 minute walk test (6WT) (Table 1). Furthermore, MG adiposity, but not LG, SOL or TA adiposity, was associated with poor performance on the TUG, SADT, 6WT, and 40 meter fast-paced walk test (40FPWT) (Table 2).

Conclusion: Whole calf, and particularly medial gastrocnemius adiposity, are associated with poor physical performance in women with knee OA. The medial gastrocnemius may be important in mobility disability in OA. Further investigation of longitudinal changes in calf muscle composition in knee OA are required.

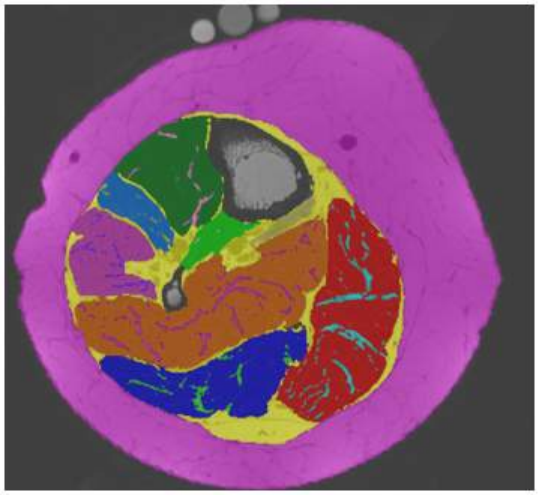

Figure 1. Axial 3.0T MRI of the calf after tissue segmentation.

Table 1. After adjusting for knee pain, the regression (B) coefficient (alpha value) demonstrating relationships between total calf muscle adiposity or intermuscular fat volume and several physical performance measures in women with knee OA.

Physical Performance Tests	Whole Calf Muscle Adiposity (%)	Calf IntraMF Volume (cm^3)	Calf IMF Volume (cm^3)
30-s Chair Stand Test (reps)	-0.942 (0.128)	-0.312 (0.368)	-0.142 (0.454)
Timed Up-and-Go (s)	0.471 (0.012)*	0.189 (0.079)	0.099 (0.094)
Stair Ascent/Descent Test (s)	1.718 (0.013)*	-8.878 (0.118)	0.297 (0.179)
40-m Fast-Paced Walk (m/s)	-0.064 (0.140)	0.735 (0.063)	-0.019 (0.144)
6-min Walk Test (m)	-21.343 (0.034)*	-0.018 (0.450)	-4.951 (0.110)

Intramuscular fat (IntraMF); Intermuscular Fat (IMF).

*Significant at $p<0.05$.

Table 2. After adjusting for knee pain, the regression (B) coefficients (alpha value) demonstrating relationships between muscle adiposity of the medial and lateral gastrocnemius, soleus or tibialis anterior with several physical performance measures in women with knee OA.

Physical Performance Tests	MG Muscle Adiposity (%)	LG Muscle Adiposity (%)	SOL Muscle Adiposity (%)	TA Muscle Adiposity (%)
30-s Chair Stand Test (reps)	-0.392 (0.268)	-0.691 (0.261)	-0.454 (0.315)	-1.062 (0.129)
Timed Up-and-Go (s)	0.286 (0.006)*	0.261 (0.180)	0.240 (0.089)	0.075 (0.745)
Stair Ascent/Descent Test (s)	1.208 (0.001)*	0.142 (0.848)	0.763 (0.147)	0.529 (0.535)
40-m Fast-Paced Walk (m/s)	-0.065 (0.004)*	0.001 (0.975)	-0.025 (0.441)	-0.033 (0.512)
6-min Walk Test (m)	-18.137 (0.001)*	0.114 (0.991)	-10.748 (0.150)	-2.277 (0.851)

Medial Gastrocnemius (MG); Lateral Gastrocnemius (LG); Soleus (SOL); Tibialis Anterior (TA).

*Significant at $p<0.05$.

Disclosure: M. Davison, None; **M. R. Maly**, None; **J. D. Adachi**, None; **K. A. Beattie**, None.

Abstract Number: 331

Are Metabolic Factors Associated with Shoulder Osteoarthritis? a Multicentric Study.

Pierre-Antoine Juge[1], Laure Bérard[2], Salma Kotti[3], Tabassome Simon[4], Francis Berenbaum[5], Geoffroy Nourissat[6] and Jérémie Sellam[7], [1]Rheumatology Department, Saint-Antoine Hospital, Paris, France, [2]Rheumatology Department, Le Havre Hospital, Le Havre, France, [3]Unité de Recherche Clinique de l'Est Parisien, Saint-Antoine Hospital, Paris, France, [4]Unité de Recherche Clinique de l'Est Parisien URCEST, Saint-Antoine Hospital, AP-HP, Univ Paris 06, Paris, France, [5]Rheumatology, Inserm UMRS_938, AP-HP, St Antoine Hospital, Univ Paris 06, DHU i2B, Paris, France, [6]Orthopedic surgery, Clinique des Maussins & St-Antoine Hospital AP-HP, Paris, France, [7]Rheumatology and Inserm UMRS_938, AP-HP, St Antoine Hospital, Univ Paris 06, DHU i2B, Paris, France

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Background/Purpose: Aging, trauma and obesity are the 3 main risk factors for knee, hip and hand osteoarthritis (OA).

It is noteworthy that risk factors for shoulder OA (SOA) have been much less studied. SOA is divided into 2 anatomical subtypes: i) primary SOA (i.e., centered SOA) and ii) rotator cuff-related OA (i.e., non-centered SOA). We hypothesized that metabolic factors are preferentially associated with the primary SOA than the mechanical-induced rotator cuff-related SOA.

Methods: This 2004-2012 retrospective multicentric study included patients with SOA at the time of joint surgery from 1 rheumatology and 2 orthopedic departments specialized in upper limb surgery. Clinical characteristics, especially hypertension, dyslipidemia, obesity (defined as body mass index >30), type 2 diabetes mellitus, current/past smoking, cardiovascular diseases and dysthyroidism were collected using medical files and phone calls to the patients for missing data. Primary SOA and rotator cuff-related SOA were defined by rheumatologists or surgeons using the standard radiographs. Exclusion criteria were history of a high-energy trauma on the shoulder, chronic inflammatory arthritis, avascular necrosis of the humeral head and age below 30 years-old. We first compared primary SOA and rotator cuff-related SOA using the chi-2 or Student t-test for all characteristics. Then a multivariate analysis using logistic regression was performed to determine specific factors associated with primary SOA.

Results: We included 147 patients (mean ± SD age 75.8 ±10 years-old) including 101 women (68.7%). Primary SOA involved 99 patients and the other 48 had rotator cuff-related SOA. The comparison between the 2 groups indicated that primary SOA patients were older (primary SOA *versus* rotator cuff arthropathy: 77.5 ±9 *vs* 72.4 ±11 years-old; p=0.004) and had more dysthyroidism (15% *vs* 4%; p=0.05) without difference in each cardio-metabolic disturbance (body mass index: 27.2 ±5.1 *vs* 27.3 ±4.5; type 2 diabetes: 13% *vs* 15%; hypertension: 64% *vs* 66%; dyslipidemia: 36% *vs* 31% p=non-significant) or in their accumulation between the 2 groups.

Multivariate analysis indicated that older age was independently associated with primary SOA (odds ratio 95% confidence interval): 1.06 (1.02-1.1) p=0.004), while cardiovascular event diseases was more less associated with this subtype (OR (95%IC): 0.27 (0.089-0.824); p=0.02). Dysthyroidism tended to be also associated with primary SOA (OR (95%IC): 3.47 (0.67-18.9); p=0.14).

Conclusion: Conversely to what expected, metabolic disturbances were not more prevalent in the primary SOA compared to the rotator cuff-related SOA. Surprisingly, whereas the primary OA population was older, CV diseases were more frequent in the rotator cuff-related SOA.

Disclosure: P. A. Juge, None; **L. Bérard**, None; **S. Kotti**, None; **T. Simon**, None; **F. Berenbaum**, None; **G. Nourissat**, None; **J. Sellam**, None.

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Abstract Number: 332

Adipokine SERUM Levels in Patients with EARLY Knee Osteoarthritis with and without Metabolic Syndrome

Istar Guzman[1], Rolando Espinosa-Morales[2], Ignacio-Alfredo Valerio-Morales[3], Austreberto Sanchez[1], Paulina P[4] and Carlos Lozada[1], [1]Rheumatology, National Institute of Rehabilitation, Mexico, Mexico, [2]Mexican Board of Rheumatology, Mexico City, Mexico, [3]Rheumatology, National Institute of Rehablitation, Mexico, Mexico, [4]Rheumatology, National institute of Rehabilitation, Mexico, Mexico

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Session Type: ACR Poster Session A
Session Time: 9:00AM-11:00AM

Background/Purpose:

Osteoarthritis is a chronic, inflammatory, multifactorial disease. The metabolic syndrome (MS) has been linked to this disease; adipokines levels have been associated in the pathogenesis of OA, several studies have described this association in patients with late OA, however few studies had described the behavior in patients with early OA.

Objectives:

To assess the levels of adipokines and inflammatory cytokines in three groups: 1. Healthy people, 2. Early OA with MS and 3. Early OA without MS.

Methods:

A cross-sectional study was realized, which included patients with early knee OA who met the inclusion criteria: patients with osteoarthritis according ACR criteria, early knee OA (Kellgren and Lawrence classification ≤ 2), overweight or obesity. Patients included were divided divided into two groups, with and without metabolic syndrome (MS) and were compared with a group of control patients. Demographic data were collected and serum adipokines and inflammatory cytokines were evaluated by ELISA (R & D Systems®). Descriptive statistics and bivariate applied using nonparametric tests, with 13® STATA software.

Results:

164 patients with OA and 42 healthy controls were studied. The mean age was 49.6 ± 6.0 in the osteoarthritis group with metabolic syndrome (OAMS), 46.55 ± 6.98 and 46.92 ± 6.7 for groups of osteoarthritis without metabolic syndrome (OAnMS) and healthy controls respectively. There were 83.3% women in the group of OA with metabolic syndrome, 89.1% OA without metabolic syndrome group and 95.2 % in the control. The mean BMI was 31.32 ± 4.04 OAMS group, 27.60 ±12.62 OAnMS and 26.48 ± 4.83 for the control group.

We evaluted the serum levels of cytokines: NGF, IL-6, IL-8, HGF, MPC-1, TNF-α, IL-β and PAI-1 and we found stadistical differences between groups. Most of the cytokines were higher in patients with OAMS group "NGF (nerve growth factor), HGF (hepatocyte growth factor), MCP-1 (macrophage chemoattractant protein-1), TNF-α (tumor necrosis factor-α) and PAI-1 (plasminogen activator inhibitor-1)" and the levels of IL-β were the same in all groups and other cytokines like IL-6 and IL-8 were increased in the healthy control group. Regarding the adipokines, as it shows in table 1, adiponectin was found higher in patients with OAnMS, and like the resistin and leptin were significantly in the OAMS group.

Conclusion:

We found a significant difference between the levels of cytokines and adipokines, this supports that in the early stages of OA, adipokines levels are elevated, it is likely that in the future, we can be study patients with OA phenotypes according to the serum levels of adipokines. It is noteworthy that our entire population was overweight, including the control group. A possible confounding factor is that the three groups studied were overweight, which can influence the levels of adipokines.

Table 1. Serum adipokines found in the different study groups and the statistical significance

Adipokines Mediana (Range)	OAMS group	OAnMS group	Healthy control group	p value
Leptin	866 (126.7- 5173)	308.06 (15.48- 7034)	401 (21.1-1436)	<0.003
Adiponectin	43387.25 (2532.5-311188)	47098.25 (4170-334473)	28113.5 (6478-152486)	0.046
Resistin	23923.75(1079.3 - 105250.5)	29492 (3085-101692)	8652.5 (3212-33977)	<0.001

Disclosure: I. Guzman, None; **R. Espinosa-Morales**, None; **I. A. Valerio-Morales**, None; **A. Sanchez**, None; **P. P**, None; **C. Lozada**, None.

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Abstract Number: 333

Smoking and Knee and Hip Osteoarthritis Evolution. Results from the Knee and Hip Osteoarthritis Long-Terme Assessment Cohort

christian roux[1], joel Coste[2], Bernard Mazieres[3], Coralie Roger[4], eric Fontas[5], Bruno fautrel[6], Jacques Pouchot[7,8], Patrice Fardellone[9,10], Anne-Christine Rat[11,12], alain Saraux[13], Francis Guillemin[14] and Liana Euller Ziegler[15], [1]Rheumatology, LAMHESS laboratory, sofia antipolis university, CHU Pasteur 2, Nice, France, nice, France, [2]Biostatistique, Unité INSERM 875, Hotel Dieu, Paris, france, Paris, France, [3]Rheumatology department, Hospital Toulouse, france, toulouse, France, [4]Direction recherche clinique, Hopital universitaire de Nice, nice, France, [5]Direction recherche clinique, CHU de Nice, france, Nice, France, [6]rheumatology department, Hospital Pitié Salpétrière, Paris, france, Paris, France, [7]internal medicine, Hôpital Européen Georges Pompidou, AP-HP, Paris, France, [8]Paris University, Internal medicine, Paris, France, [9]Rheumatology, Hopital Nord Amiens, Amiens, France, [10]Department of Rheumatology, Amiens University hospital, Amiens, France, [11]CHU Nancy, Clinical Epidemiology and Evaluation, Université de Lorraine, Paris Descartes University, APEMAC, EA 4360, Nancy, France, [12]Service de Rhumatologie, Nancy-University, Paris Descartes, Metz P Verlaine, EA 4003; Department of clinical epidemiology and evaluation, Nancy University Hospital; Department of rheumatology, Nancy University Hospital, Vandoeuvre les Nancy, France, [13]Rheumatology Department, CHU la cavale Blanche, brest, france, Brest, France, [14]Department of Clinical Epidemiology and Evaluation, Nancy University Hospital, Nancy-University, EA 4003, Nancy, France, [15]151 rte de St Antoine de Gines, CHU de Nice -Université Nice Sophia Antipolis, Nice, France

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Session Time: 9:00AM-11:00AM

Background/Purpose:

Relations between smoking and osteoarthritis remains discussed. The protective effect found in previous epidemiological studies has not been confirmed by recent studies and meta analyses. This study aims to investigate the effect of smoking on pain, function and structural evolution in hip and knee symptomatic osteoarthritis.

Methods:

The subjects studied were enrolled in the KHOALA cohort (Knee and Hip OsteoArthritis Long-term Assessment) which has been described in detail elsewhere. Briefly, it is a population-based cohort of 878 subjects aged from 40 to 75 years with symptomatic lower limb OA (knee and/or hip). Data were collected at baseline and after three years during an outpatient visit, and each year with self-administered questionnaires. The data collected included demographic characteristics, and annual data for pain (0-100), function (Harris Hip Score and Womac), smoking information (duration, amount and ongoing). Standard radiographs of both hips were obtained at baseline and at three years. The progression of hip and or knee osteoarthritis was evaluated according to the radiological Kellgren-Lawrence score (KL), osteophytes scores (0-3) per location and swelling. Univariate and multivariate statistical analysis were performed adjusted on age, BMI, sex and diabetes. the subjects were divided into smokers, non-smokers and former smokers.

Results:

873 subjects have been included, 119 smokers, 215 former smokers et 539 non-smokers, 64% of smokers and 31 % of former smokers have smoked during over 20 years. 40% of smokers have smoked 20 pack years. 20 subjects were not taken into account due to lack of data. Baseline characteristics are presented in table with comparisons between baseline and 3 years

At 3 years, no difference has been shown between different groups about function, pain and structural evolution for the hip (0.16) and knee (p=0.9) as for the laying prosthesis (p=0.4 and p=0.5). But smokers (OR=0.33 [0.11-1.09]) and former smokers (OR=0.30[0.1-0.85]) developed fewer osteophytes only in the knee either in medial and lateral condyles (p=0.037 and 0.07). The dose of intoxication (p = 0.026 (OR = 0.98 [0.97-1]) and the duration of intoxication (p = 0.0005 (OR = 0.98 [0.97-0.99]) were significantly associated with the development of these osteophytes. No difference is found for other structural parameters.

Conclusion:

Our results shows that smoking does not influence function and pain but smokers and ancient smokers seems to develop less osteophytesat femoral level. As a possible explanation, recent experimental studies have shown that nicotine upregulated collagen synthesis, chondrocytes proliferation and influences TGFβ synthesis which is involved in the formation of osteophytes.these results needs to be confirmed.

		Smokers Baseline	former smokers Baseline	Non mokers Baseline	P*	P**	P***
Age mean (SD)		57 (9)	62 (8)	63 (8)	0.0001		
BMI mean (SD)		28.2 (6)	29.1 (6)	29.8 (6)	0.009		
Knee Pain (0-100) median		30	25	35	0.01	NS	NS
Knee Function (womac) median		28.1	25	31.3	0.03	NS	NS
Smoking dose (pack-year) mean (SD)		21 (16)	16 (15)				
Smoking duration (years) mean (SD)		29 (13)	19 (12)				
Knee OA KL≥2 (%)	n	79 (94)	148 (92.5)	376 (82.2)	NS	NS	NS
Knee Osteophytes MC n(%)		**45 (53.6)**	**87 (54.4)**	**239 (58.6)**	**NS**	**0.03**	**0.04**
Knee osteophytes LC (%)	**n**	**17 (20.2)**	**42 (26.3)**	**129 (31.6)**	**0.04**	**0.05**	**0.06**
Knee osteophytes MP (%)	n	29 (35)	64 (40)	169 (41)	0.4	NS	NS
Knee osteophytes LP (%)	n	52 (62)	95 (59)	245 (60)	0.9	NS	NS
Hip OA KL≥2 (%)	n	(38.5)	(27.9)	(29)	0.01	NS	NS
Hip function (Harris) median		84	78.9	80	NS	NS	NS

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Abstract Number: 334

Lifetime Risk of Symptomatic Hand Osteoarthritis: The Johnston County Osteoarthritis Project

Jin Qin[1], Kamil E. Barbour[1], Louise Murphy[1], Charles G. Helmick[1], Nancy A. Baker[2], Kristina Theis[1], Todd Schwartz[3,4], Jordan B. Renner[5], Amanda Nelson[6], Kelli Allen[7] and Joanne M. Jordan[8], [1]Arthritis Program, Centers for Disease Control and Prevention, Atlanta, GA, [2]University of Pittsburgh, Pittsburgh, PA, [3]Biostatistics, University of North Carolina at Chapel Hill, Chapel Hill, NC, [4]Thurston Arthritis Research Center, University of North Carolina at Chapel Hill, Chapel Hill, NC, [5]UNC School of Medicine, University of North Carolina, Chapel Hill, NC, [6]Division of Rheumatology, Allergy, and Immunology and Thurston Arthritis Research Center, University of North Carolina, Chapel Hill, NC, [7]University of North Carolina, Chapel Hill, NC, [8]Thurston Arthritis Research Center, University of North Carolina, Chapel Hill, NC

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SESSION INFORMATION

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Session Title: Osteoarthritis - Clinical Aspects Poster I: Treatments and Metabolic Risk Factors

Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose:

Osteoarthritis (OA) affects 27 million adults in the United States. Symptomatic hand osteoarthritis (SHOA) is a common condition that affects hand strength and function. Lifetime risk, defined as the probability of developing a condition over the course of a lifetime, has been used to convey person-level risk of other chronic conditions including breast cancer, and more recently estimates of symptomatic knee and hip OA have been published. To better understand the overall burden of SHOA, as well as to guide targeted interventions, we estimated the lifetime risk of SHOA and whether the risk is different by potential risk factors.

Methods:

We analyzed data from the Johnston County Osteoarthritis Project, an on-going population-based prospective cohort study in residents of Johnston County, North Carolina. Data were collected among 2,218 adults ≥ 45 years at the first (1999-2004) and second (2005-2010) time period. The presence of SHOA at each time period was defined by self-reported symptoms (pain, aching, and stiffness) and radiographic OA (ROA) in the same hand. ROA was defined as a Kellgren-Lawrence grade ≥2 in at least 3 total joints out of the 15 joints in each hand, and at least one of them being the distal interphalangeal joint (361 participants met this criteria in at least one time period). Lifetime risk, defined as the proportion of the population who will develop SHOA in at least one hand by age 85, was estimated using the predicted marginal probability from generalized estimating equations logistic regression, accounting for clustered variance from the stratified random sampling design and multiple measurements within participant. Additionally, sampling weights were applied in analyses to make appropriate population-based statistical inferences. The overall and stratified lifetime risk by sex, race and obesity (BMI≥30 kg/m²) are presented.

Results:

The lifetime risk of SHOA was 39% (95% confidence intervals [CIs] 34-45%) overall. Nearly one of two women (48%; CIs 41-55%) developed SHOA by age 85 compared with one of four men (25%; CIs 19-31%). Lifetime risk of SHOA was 47% (CIs 38-57%) among the obese participants, higher than that among those who were not obese (36%; CIs 29-42%). Race-specific estimates were 40% (CIs 34-47%) among whites and 32% (CIs 21-44%) among African-American adults.

Conclusion:

Almost 40% of people will develop SHOA by age 85. The risk is particularly high among women and obese adults. SHOA has substantial public health implications considering its high lifetime risk, and its impact on functional impairment of the hands and quality of life.

These findings underscore the need for increased use of public health and clinical interventions to address the impact of SHOA on individuals and society. Earlier diagnosis can allow earlier use of the same standard interventions used for other types of OA. These include self-management education, losing weight if overweight/obese, physical/occupational therapy, thermal modalities, joint protection techniques, provision of assistive devices, and acetaminophen/NSAID use, which may contribute to maintaining better function and fewer symptoms.

Disclosure: J. Qin, None; **K. E. Barbour**, None; **L. Murphy**, None; **C. G. Helmick**, None; **N. A. Baker**, None; **K. Theis**, None; **T. Schwartz**, None; **J. B. Renner**, None; **Nelson**, None; **K. Allen**, None; **J. M. Jordan**, None.

osteoarthritis-the-johnston-county-osteoarthritis-project

Abstract Number: 335

Prevalence of Hand Osteoarthritis and Factors Associated with Pain in Korean Farmers

Young Sun Suh[1], Yun-Hong Cheon[1], Hyun-Ok Kim[1], Ki-Soo Park[2], Hye Song Lim[1], Min-Gyu Jeon[1], Young-Sool Hah[3] and Sang-Il Lee[1], [1]Division of Rheumatology, Department of Internal Medicine, Gyeongsang National University School of Medicine, Jinju, South Korea, [2]Department of Preventive Medicine, Gyeongsang National University School of Medicine, Jinju, South Korea, [3]Clinical Research Institute, Gyeongsang National University School of Medicine, Jinju, South Korea

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Session Time: 9:00AM-11:00AM

Background/Purpose: Farming activity is burdened work with excessive use of hands. Thus, farmers are expected to have high prevalence of hand osteoarthritis (HOA). However, there is a lack of studies investigating prevalence and characteristics of HOA in Korean farmers. Therefore, we conducted this study to investigate the prevalence of HOA and to identify factors that influence hand pain among farmers in rural areas of Korea.

Methods: The study was conducted from June 2013 to Dec 2014 with 700 farmers in Gyeong-nam Province of Korea. Clinical evaluation for hand joints was performed and the plain radiographs of both hands were taken. The Australian/Canadian Osteoarthritis Hand Index (AUSCAN) was used to assess pain severity of hand joints. Radiographic HOA was defined as Kellgren–Lawrence (KL) grade≥2 on plain radiographs and symptomatic HOA as KL grade≥2 with pain/aching/stiffness at the same joints. Severe HOA was defined KL grade≥3. Presence of HOA at individual level was defined as ≥1 affected joint. Depressive symptoms were assessed using the Patient Health Questionnaire (PHQ-2).

Results: Participants comprised of 53% women and 47% men with mean age of 59.7±8.6 years. The mean farming duration was 30.0±14.3 years. The overall prevalence of radiographic and symptomatic HOA was 59.1%, and 13.9%, respectively. The prevalence of radiographic and symptomatic HOA was higher in women (62.3%, 14.8%) than in men (55.6%, 12.8%). Among participants with radiographic HOA, AUSCAN pain scores were also higher in women (99.9±106.8) than men (68.0±99.9, p=0.002). Linear regression analysis showed that women and depressive symptoms were associated with AUSCAN pain score after adjustment for radiographic severity of HOA, total numbers of affected joints, and frequently repetitive hand use or and pinch grip working during harvest.

Conclusion: The prevalence of HOA and AUSCAN pain scores were higher in women compared to men. And AUSCAN pain scores were associated with female gender and depressive symptoms. Therefore, our results show the need for depression care management in female farmers to reduce hand pain.

Abstract Number: 336

Lack of Uniform Diagnostic Criteria for Erosive OA: A Systematic Review

Supraja Yeturi[1], Payal Patel[2], Gazeley David[2] and Ann K. Rosenthal[3], [1]Rheuamtology, Medical college of Wisconsin, Milwaukee, WI, [2]Medical College of Wisconsin, Milwaukee, WI, [3]Div of Rheumatology, Medical College of WI, Milwaukee, WI

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Background/Purpose:

Erosive osteoarthritis (EOA) is a potentially important subtype of osteoarthritis initially described in the 1960s. Since that time, EOA has been the focus of substantial literature describing its clinical presentation, epidemiology, genetics, and response to therapy. We set out to review clinical studies of EOA in order to determine if there was general agreement about diagnostic criteria.

Methods:

Ovid, Pubmed, and Google Scholar were searched using the phrase "erosive osteoarthritis" from the years 1962-2015. References that were not pertaining to EOA, were exclusively animal studies, or were not in English were eliminated from review.

Results:

After reviewing all 180 papers, we identified 50 papers which described the inclusion and exclusion criteria utilized in the study and included more than 3 patients. The numbers of patients varied between 9 and 355. A synopsis of the inclusion/exclusion criteria is shown in Table 1. Six of the 50 studies used no clinical inclusion criteria, which we defined as features obtained by history or physical examination. In the remaining 44 studies, ACR criteria for hand OA were the most commonly used clinical inclusion criteria (33/44). Radiographic inclusion criteria were cited in all 50 studies but varied widely. Eighteen studies required only a single involved joint. The Verbruggen-Veys scale was designed to stage hand osteoarthritis and was used in 7/50 papers. In the majority of studies (35/50) the authors designed their own radiographic definitions. Sixteen of the 50 studies described no exclusion criteria. The most frequently employed exclusion criteria were an alternative diagnosis (31/50), a positive rheumatoid factor or anti- CCP antibody (8/50), or a family history of psoriasis (7/50). There were no clear trends with time in the choice of diagnostic criteria.

Table 1. The number of published studies of EOA utilizing various types of diagnostic criteria out of a total of 50 studies. *

Clinical Inclusion Criteria			Radiographic Inclusion Criteria				Exclusion Criteria		
ACR hand OA	Misc	None	Joints involved	V-V scale	Kelgren - Lawrence scale	Kalman scale	Alternative Diagnosis	Labs	Family history
33	11	6	≥1 18 ≥2 10 ≥3 2	7	5	3	31	8	7

V-V is Verbruggen-Veys

Conclusion:

The considerable heterogeneity in the definition of EOA renders this literature difficult to interpret. Despite a heavy reliance on radiographic findings, there is little agreement about even a radiographic definition of this disease. Progress in understanding and treating patients with EOA will require the development of clear classification criteria.

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Abstract Number: 337

Construct Validity of the Doyle Index in the Outcome Domain of Joint Activity in Hand Osteoarthritis Patients

W. Damman[1], R. Liu[1], M.C. Kortekaas[1,2], F.R. Rosendaal[3], D. van der Heijde[4] and M. Kloppenburg[1], [1]Rheumatology, Leiden University Medical Center, Leiden, Netherlands, [2]Department of Rheumatology, Flevoziekenhuis, Almere-Stad, Netherlands, [3]Clinical Epidemiology, Leiden University Medical Center, Leiden, Netherlands, [4]Department of Rheumatology, Leiden University Medical Center, Leiden, Netherlands

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Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose:

The Outcome Measures in Rheumatology (OMERACT) working group on hand osteoarthritis (OA) has endorsed a preliminary set of core domains for outcome measures in clinical trials. One domain is joint activity, reflecting the underlying osteoarthritic process, such as inflammation and/or subchondral bone activity, leading to pain and destruction.

The Doyle Index (DI), a measurement of joint tenderness, is proposed as an instrument to assess joint activity, however validity and its added value over other domains like self-reported pain is unknown. Therefore, construct validity of the DI is investigated.

Methods:

Data were used of two cohorts with primary hand OA patients: HOSTAS (n=507, mean (SD) age 61 (9) years, 86% women) and ECHO (n=56, age 62 (9) years, 86% women). Self-reported pain was assessed by Australian/Canadian Hand OA Index (AUSCAN, Likert scale, 0-20) and Visual Analogue Scale (VAS) 1-100. Tenderness on palpation (0-3) was assessed in24 joint units: all DIP, PIP, 1^{st} IP, 1^{st} MCP and 1^{st} CMC joints individually and 2^{nd}-5^{th} MCP joints as one joint group. In each patient the DI was the summated score of the 24 joint units (max. 72).

Contrast-enhanced MRI of the right DIP and PIP joints (8 joint units) were performed in a subgroup of HOSTAS (n=93) and images were scored for synovitis and bone marrow lesions (BMLs), both 0-3, following standardized methods. Ultrasound (US) was performed in the ECHO study and all hand joints (the same 24 joint units as in DI) were scored for grey scale (GS) synovitis and power Doppler signal (PDS), both 0-3, following standardized methods.

MRI or US scores were summated scores of synovitis and BMLs or GS synovitis and PDS, respectively, of all imaged joint units.

To assess construct validity, first, non-parametric correlation coefficients between DI and self-reported pain or US or MRI scores were calculated. Subsequently, quartiles of DI (lowest vs highest) of MRI and US scores were compared with Mann-Whitney U test.

Results:

Baseline data and non-parametric correlations are depicted in table 1. DI varied from 0 to 48 and correlated moderately to self-reported pain in both studies.

Correlations for DI and US and MRI scores were low. Median DI differed between lowest quartile and highest quartile scores (figure 1) for the US score (p=0.050) and MRI score (p=0.066).

Conclusion:

Doyle Index seems a promising instrument to assess joint activity in clinical trials in hand OA. Further work on metric properties, including sensitivity-to-change, is needed in hand OA and its subgroups.

Table 1: Baseline data and non -parametric correlations in the ECHO and HOSTAS studies, cohorts with primary hand osteoarthritis patients.

Variable, median (range)	ECHO study	HOSTAS study	
	all joint units	Total, all joint units	MRI-subgroup, right DIP and PIP joints
Doyle Index	9.5 (0 to 32)	4 (0 to 48)	1 (0 to 10)
AUSCAN pain	10 (0 to 19)	10 (0 to 20)^	na
VAS pain	49 (0 to 99)	35.5 (0 to 93.5) *	na
MRI score	na	na	6 (0 to 27)
US score	11.5 (0 to 38)	na	na
Non-parametric correlations , Spearman's rho			
DI-AUSCAN	0.46 ($p < 0.01$)	0.38 ($p < 0.01$)	na
DI-VAS	0.38 ($p < 0.01$)	0.41($p < 0.01$)	na
DI-US score	0.29 ($p < 0.05$)	na	na
DI-MRI score	na	na	0.25 ($p < 0.05$)

*n=364, ^n=503.

Abbreviations: na = not applicable, DI = Doyle Index, VAS = Visual Analogue Scale, US = ultrasound

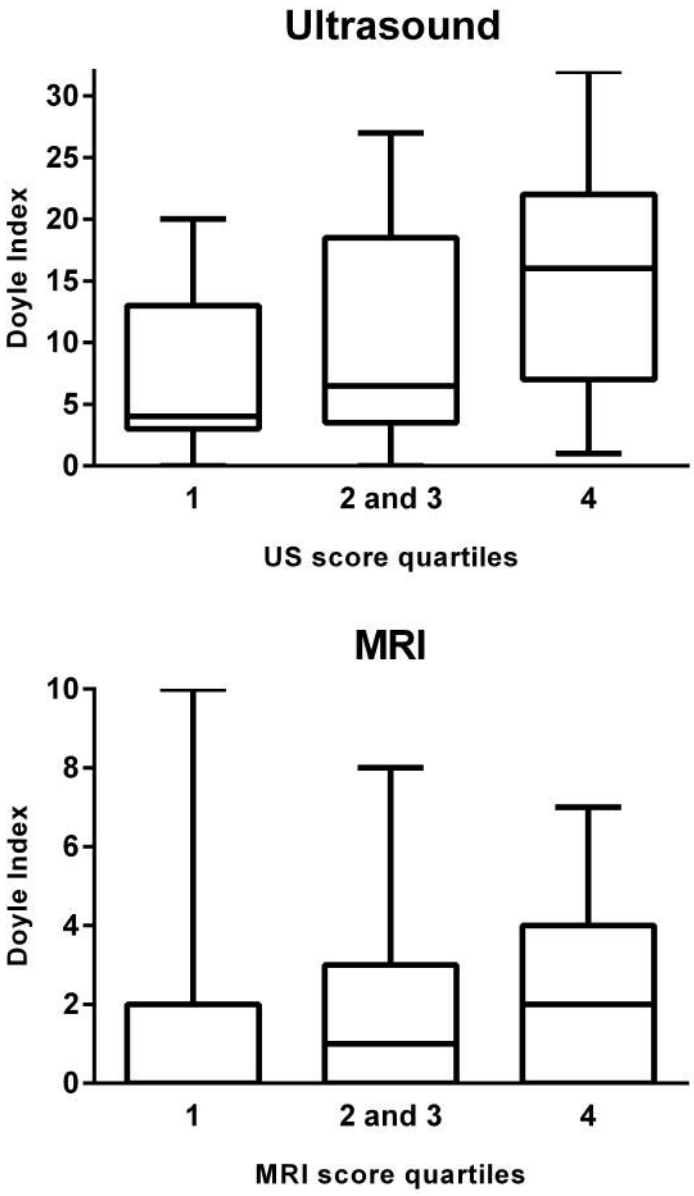

Figure 1: boxplots of median Doyle Index in percentile groups of US or MRI score with 25th and 75th percentile, minimum and maximum.
Doyle was calculated for US score in 24 joint units: all DIP, PIP, IP, 1st MCP and 1st CMC joints individually and 2nd-5th MCP joints as one joint group. For MRI it was calculated in the right DIP and PIP joints (8 joint units).

Disclosure: W. Damman, None; **R. Liu**, None; **M. C. Kortekaas**, None; **F. R. Rosendaal**, None; **D. van der Heijde**, None; **M. Kloppenburg**, Dutch Athritis Association, 2.

Abstract Number: 338

Smoking and Alcohol Use Are Associated with Structural and Inflammatory Hand Osteoarthritis Features in a Population Based Study

Karin Magnusson[1], Alexander Mathiessen[2], Hilde Berner Hammer[2], Bård Natvig[3], Kåre Birger Hagen[1], Nina Østerås[1] and Ida K. Haugen[4], [1]Department of Rheumatology, National Advisory Unit on Rehabilitation in Rheumatology, Diakonhjemmet Hospital, Oslo, Norway, [2]Department of Rheumatology, Diakonhjemmet Hospital, Oslo, Norway, [3]General Practice, Oslo University, Oslo, Norway, [4]Rheumatology, Diakonhjemmet Hospital, Oslo, Norway

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Background/Purpose: Smoking has been shown to have a potential protective effect on radiographic knee osteoarthritis (OA), possibly mediated through lower body weight in smokers. A recent animal study showed an association between chronic alcohol consumption and OA-like pathological changes, whereas no studies have explored this potential association in humans. By studying the relationship between harmful health behavior and OA in the hands, we avoid mediation by body weight. Hence, our aim was to explore whether smoking and alcohol use are associated with hand OA features.

Methods: We included 530 persons from the Musculoskeletal pain in Ullensaker study (MUST), Norway (mean (SD) age 65 (8.0) years and 71% females) with radiographic hand OA in 1 or more joints and no inflammatory joint diseases. The participants were grouped into three categories based on their self-reported smoking status; Current (daily), former (quit > 6 months ago) and never smokers. Persons reporting to consume alcohol daily, weekly or monthly were categorized as drinkers. Conventional hand radiographs were obtained, and the number of finger joints with radiographic OA (Kellgren-Lawrence grade 2 or more) was calculated (0-30 scale). Participants having one or more joint(s) with ultrasound-detected grey-scale synovitis were classified as having inflammatory OA. We studied the associations between smoking and alcohol (as the independent variables) and the severity of radiographic OA, AUSCAN pain and presence of inflammatory OA (as the dependent variables), using linear and logistic regression analyses. Separate models were performed for smoking and alcohol. Analyses were adjusted for age, sex and education status.

Results: Current smoking was significantly associated with fewer joints with radiographic OA independent of age, sex and education status (Table 1). There was also a trend that former smoking was related to less radiographic hand OA, but the association was not statistically significant in the adjusted analyses. Being a drinker was significantly associated with inflammatory OA in the adjusted analyses (Table 1). Neither smoking nor alcohol use were associated with increased hand pain (data not shown). Additional adjustment for alcohol use and smoking in respective sensitivity analyses did not attenuate the results.

Table 1. The associations between smoking and alcohol exposure and structural and inflammatory hand OA features.					
	N (%) persons	**Number of joints with radiographic hand OA**		**Presence of inflammatory hand OA**	
		Crude B (95% CI)	Adjusted B (95% CI) *	Crude OR (95% CI)	Adjusted OR (95% CI) *
Smoking					
Never smoker	256 (48.3%)	0.00 (ref.)	0.00 (ref.)	1.00 (ref.)	1.00 (ref.)
Former smoker	203 (38.3%)	**-1.10 (-2.18 to -0.01)**	-0.77 (-1.81 to 0.27)	0.94 (0.64 to 1.40)	1.02 (0.67 to 1.53)
Current smoker	71 (13.3%)	**-3.07 (-4.38 to -1.76)**	**-1.77 (-3.07 to -0.48)**	**0.53 (0.28 to 0.99)**	0.57 (0.30 to 1.12)
Alcohol					
Abstinence	82 (15.5%)	0.00 (ref.)	0.00 (ref.)	1.00 (ref.)	1.00 (ref.)
Drinker	448 (84.5%)	-0.11 (-1.51 to 1.29)	0.57 (-0.68 to 1.81)	1.41 (0.83 to 2.37)	**2.06 (1.16 to 3.66)**
* Adjusted for age, sex and education status.					

Conclusion: Our results suggest a protective effect of smoking on radiographic hand OA whereas alcohol consumption may increase the risk of joint inflammation in hand OA. Future longitudinal studies are needed to explore the causal associations.

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Abstract Number: 339

More Inflammatory Signs on Ultrasound, Severe Pain and Stiffness Are Associated with Erosive Than Non-Erosive Hand Osteoarthritis

Olga Sleglova[1], Olga Ruzickova[2], Karel Pavelka[1] and Ladislav Senolt[2], [1]Institute of Rheumatology, Department of Rheumatology, 1st Faculty of Medicine, Charles University, Prague, Czech Republic, [2]Institute of Rheumatology and Department of Rheumatology, 1st Faculty of Medicine, Charles University, Prague, Czech Republic, Prague, Czech Republic

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Background/Purpose: Hand osteoarthritis (HOA) causes considerable pain and disability. Radiographic HOA features show only a modest association with symptoms in HOA. Ultrasound is an easy non-invasive procedure, which is able to visualize synovial inflammation and joint effusion. HOA is a heterogeneous group of disorders with two main subsets including non-erosive disease and erosive, sometimes referred to as inflammatory, HOA. Few studies demonstrated inflammatory ultrasound changes and more severe clinical symptoms in patients with erosive compared with non-erosive disease, however the results are inconclusive.

Methods: The aim of the study was to compare pain, stiffness, physical impairment and ultrasound features between patients with erosive and non-erosive HOA in a cross-sectional study. Consecutive patients with symptomatic HOA fulfilling the American College of Rheumatology (ACR) criteria were included in this study. Joint pain and swelling were assessed. Patients reported joint pain on 100 mm visual analogue scale (VAS). Pain, joint stiffness and disability were assessed by the Australian/Canadian OA hand index (AUSCAN). Radiographs of both hands were examined and erosive disease was defined by at least one erosive interphalangeal joint. Synovial hypertrophy and power Doppler signal (PDS) were scored with ultrasound. Synovitis was graded on a scale of 0–3 and osteophytes were defined as cortical protrusions seen in two planes.

Results: Altogether, 134 patients (13 male) with symptomatic nodal HOA were included in this study between April 2012 and January 2015. Out of these patients, 72 had erosive disease. Patient's characteristics are given in table 1. The disease duration ($p<0.01$), duration of morning stiffness ($p<0.01$) and number of clinically swollen joints ($p<0.05$) were significantly higher in patients with erosive compared with non-erosive disease. According to the AUSCAN, patients with erosive compared with non-erosive disease had more pain ($p<0.05$) and stiffness ($p<0.01$). US-detected pathologies such as gray-scale synovitis total score ($p<0.001$), intensity of PDS ($p<0.01$) and number of osteophytes ($p<0.01$) were significantly higher in patients with erosive compared with non-erosive disease (table 1). There were no significant differences in consumption of non-steroidal anti-inflammatory drugs (NSAIDs), analgesics and symptomatic slow-acting drugs (SYSADOA) for OA between both groups.

Table 1.

	All patients	Non-erosive HOA	Erosive HOA	P
Age, years (mean ± SD)	65.98 ± 8.16	64.25 ± 7.61	67.48 ± 8.33	NS
Female, no. (%)	121 (90.29%)	55 (88.70%)	66 (91.66%)	NS
Disease duration (years)	8.54 ± 7.14	7.52 ± 7.02	9.42 ± 7.13	<0.01 *
BMI, kg/m2	27.53 ± 4.33	27.50 ± 4.12	27.55 ± 4.49	NS
AUSCAN, total	21.60 ± 10.44	20.05 ± 9.98	22.93 ± 10.65	<0.05 *
AUSCAN A, pain	8.16 ± 4.26	7.73 ± 4.18	8.53 ± 4.29	<0.05 *
AUSCAN B, function	1.96 ± 0.87	2.02 ± 0.98	1.90 ± 0.77	NS
AUSCAN C, stiffness	11.34 ± 6.27	10.16 ± 5.78	12.36 ± 6.48	<0.01 *
VAS, pain (mm)	43.91 ± 21.42	41.85 ± 21.49	45.69 ± 21.19	NS
Morning stiffness (min)	21.12± 37.84	18.55± 29.06	23.34± 43.89	<0.01 *
Tender joints, no.	7.66 ± 3.34	7.32 ± 3.41	7.96 ± 3.25	NS
Swollen joints, no.	3.69 ± 4.42	3.45 ± 3.86	3.89 ± 4.78	<0.05 *
Ultrasound				
Synovial hypertrophy	6.72 ± 8.06	4.47 ± 6.09	8.67 ± 8.99	<0.001*
Power Doppler signal	1.99 ± 2.72	1.61 ± 2.07	2.31 ± 3.14	<0.01*
Osteophytes, no.	11.95 ± 5.31	10.6 ± 5.59	13.11 ± 4.76	<0.01*

* Significantly higher in patients with erosive HOA

Conclusion: In general, this study shows that patients with erosive HOA have more severe pain and stiffness associated with US-detected synovial hypertrophy, inflammatory signs and osteophyte formation than patients with non-erosive disease.

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Abstract Number: 340

Radiographic Assessment of Hand Osteoarthritis – the Role of Oblique View Images

Kevin Staats[1], Ilse-Gerlinde Sunk[1], Claudia Schueller-Weidekamm[2], Gabriela Supp[3], Birgit Niederreiter[4], Tanja A. Stamm[5], Josef S. Smolen[6] and **Klaus Bobacz**[1], [1]Medical University of Vienna, Vienna, Austria, [2]Department of Radiology, Medical University of Vienna, Vienna, Austria, [3]Rheumatology, Medical University of Vienna, Vienna, Austria, [4]Rheumatology, Internal Medicine III, Medical University of Vienna, Vienna, Austria, [5]Internal Medicine III, Vienna Medical University, Vienna, Austria, [6]Dept of Medicine 3, Division of Rheumatology, Medical Univ Vienna, Vienna, Austria

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SESSION INFORMATION

Session Date: Sunday, November 8, 2015

Session Title: Osteoarthritis - Clinical Aspects Poster I: Treatments and Metabolic Risk Factors

Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose: To evaluate the role of oblique view images in the radiographic assessment of hand osteoarthritis (HOA).

Methods: 159 patients of our HOA cohort were included. X-ray images were analyzed according to the interphalangeal osteoarthritis radiographic simplified (iOARS) score (pa views) or examined with regard to radiographic alterations that could not be detected in pa images (oblique views). Spearman's correlation was applied to examine the relationship of dorsal osteophytes (dOP) and radiographic features/severity of joint damage. Differences between groups were determined by Student's t test.

Results: A total of 4770 joints were examined. Oblique views showed additional information in 12.98% oft the analyzed joints. dOPs seem to be the most important radiographic changes found in oblique view images and occured with a prevalence of 12.4% (n=158) in DIP, 8.2% (n=26) in CMC-I and 7.2% (n=92) in PIP joints. Further calcualtions revealed a subgroup of patients displaying dOP in the oblique views without any radiographic changes in the plain images (DIP: 10.1%, CMC-I: 8.2% and PIP: 7.2%).

Conclusion: Prevalence data on dOP in HOA are provided. Oblique view images allow us to detect a subgroup of patients with HOA displaying dOP without any radiographic alterations in plain view images.

Disclosure: K. Staats, None; **I. G. Sunk**, None; **C. Schueller-Weidekamm**, None; **G. Supp**, None; **B. Niederreiter**, None; **T. A. Stamm**, None; **J. S. Smolen**, None; **K. Bobacz**, None.

Abstract Number: 341

Construct Validity of Four Hand Mobility Measures in Hand Osteoarthritis (HOA)

Féline Kroon[1], Jessica Bijsterbosch[1], Ingrid Meulenbelt[2], Frits R. Rosendaal[3], Désirée van der Heijde[1] and Margreet Kloppenburg[1,3], [1]Rheumatology, Leiden University Medical Center, Leiden, Netherlands, [2]Molecular Epidemiology, Leiden University Medical Center, Leiden, Netherlands, [3]Clinical Epidemiology, Leiden University Medical Center, Leiden, Netherlands

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SESSION INFORMATION

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Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose: The OMERACT HOA working group recently proposed ‘hand mobility' as an outcome measure in HOA trials, although no disease specific instruments are available yet. We aimed to investigate the construct validity of four hand mobility tests, validated in other rheumatic diseases, in HOA and its subsets.

Methods: 207 participants from the Genetics ARthrosis and Progression study with symptomatic HOA following ACR criteria completed standardized questionnaires. Hand mobility was examined by trained assessors with the Hand Mobility in Scleroderma test (HAMIS, scale 0-27, higher worse), fingertip to palm distance (FPD, millimetres, higher worse), modified Kapandji index (MKI, 0-50, higher better), and number of hand joints with limited mobility (0-30, higher worse). Subscores for thumb base and finger HOA subsets were calculated for HAMIS (thumb abduction and pincer grip (0-6), versus finger flexion, extension and abduction (0-9)) and MKI (thumb opposition (0-10), versus finger flexion and extension (0-40)). Radiographs were scored using OARSI atlas. With multivariable linear regression the capability to measure unique concepts was investigated. Complete and (thumb/finger) subscores were compared in cumulative probability plots, exploring whether scores differed between participants with complaints at different sites (carpometacarpal joint (CMCJ) only, interphalangeal joint (IPJ) only and both sites). Data were analysed in SPSS V20.0.

Results: Participants displayed large variation in mobility scores (table, figure). Strongest correlations were with OARSI osteophyte score (r_s 0.43-0.52), number of joints with bony swellings (r_s 0.46-0.58) AUSCAN function (r_s 0.27-0.36), grip strength (r_s 0.08-0.33) and AUSCAN pain (r_s 0.25-0.34). All tests showed similar correlations with these outcomes, and in multivariable models 35-46% of the scores were explained by a combination of structural damage, disability and strength; pain and joint activity did not contribute substantially. Probability plots demonstrated that FPD and MKI measure finger more than thumb mobility (figure). Additional plots showed that subscores differ per HOA subset. Only HAMIS-derived thumb subscores distinguished the CMC subset.

Conclusion: The tests show similar and acceptable levels of construct validity. Despite a large variation in scores, they appear to measure in part a unique domain. HAMIS, FPD and MKI perform similarly for finger mobility, although only HAMIS can measure thumb mobility specifically. Other metric properties and the potential of separate thumb- and finger-tests need to be studied.

Table 1. Characteristics of included participants (n=207)*	
Age, mean (SD)	64.7 (6.9)

Women, N (%)	178 (86.0%)
Symptomatic HOA subsets	
CMCJ OA only , N (%)	7 (3.4%)
IPJ OA only, N (%)	74 (35.7%)
Symptoms at both sites, N (%)	126 (60.9%)
Number of self-reported painful joints (0-30)	8 (0-30)
AUSCAN pain subscale (0-20)	8 (0-20)
AUSCAN function subscale (0-36)	16 (0-36)
Grip strength, kg	19.5 (3.5-49)
Number of joints with bony swelling (0-30)	14 (2-26)
Total OARSI osteophyte score (0-88)	10 (0-51)
Total OARSI JSN score (0-88)	18 (0-49)
Hand mobility tests	
HAMIS (0-27)	3.5 (0-20.5)
Finger palm distance, mm	7 (0-191)
Modified Kapandji Index (0-50)	48 (27-50)
Number of joints with limited mobility (0-30)	2 (0-30)

*median (range) unless otherwise stated

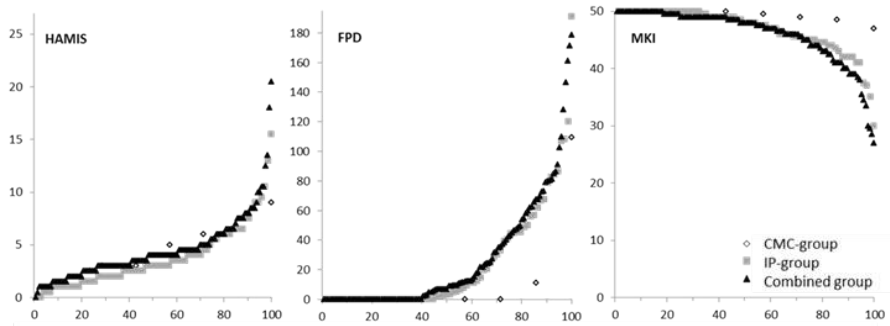

Figure 1. Cumulative probability plots of HAMIS, FPD and MKI in subgroups of participants with CMCJ complaints (n=7), IPJ complaints (n=74) and complaints at both sites (n=126).

Disclosure: F. Kroon, None; **J. Bijsterbosch**, None; **I. Meulenbelt**, None; **F. R. Rosendaal**, None; **D. van der Heijde**, None; **M. Kloppenburg**, Dutch Arthritis Association, Pfizer, 2.

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Abstract Number: 342

The Effect of Erosive Status on Systemic Inflammatory Biomarkers in Hand Osteoarthritis

Alexander Mathiessen[1], Nina Østerås[2], Tore K. Kvien[3], Hilde Berner Hammer[4] and Ida K. Haugen[5], [1]Department of Rheumatology, Diakonhjemmet Hospital, Oslo, Norway, [2]National Advisory Unit on Rehabilitation in Rheumatology, Department of Rheumatology,, Diakonhjemmet Hospital, Oslo, Norway, [3]Dept. of Rheumatology, Diakonhjemmet Hospital, Oslo, Norway, [4]Rheumatology, Diakonhjemmet Hospital, Oslo, Norway, [5]P.O. Box 23, Diakonhjemmet Hospital, Vinderen, Norway

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SESSION INFORMATION

Session Date: Sunday, November 8, 2015

Session Title: Osteoarthritis - Clinical Aspects Poster I: Treatments and Metabolic Risk Factors

Session Type: ACR Poster Session A
Session Time: 9:00AM-11:00AM

Background/Purpose : It is debated whether erosive hand osteoarthritis (OA) is a separate inflammatory subset of hand OA, or just a severe form of the same disease. Cross-sectional studies on ESR and CRP are limited in numbers, performed on small cohorts, and have show conflicting results, with higher as well as lower serum levels in erosive OA compared to non-erosive OA.[1-4] With a large OA cohort, we have the opportunity to explore this further, and hereby compare the serum levels of inflammatory biomarkers in erosive and non-erosive hand OA.

Methods: We included subjects with radiographic hand OA (i.e. Kellgren-Lawrence grade ≥ 2 in one or more finger joint(s)) from a community-based OA cohort, and measured their plasma levels of erythrocyte sedimentation rate (ESR) and C-reactive protein (using a high-sensitivity assay; hsCRP). Erosive status was defined as having one or more interphalangeal joint(s) with radiographic central erosions, and rheumatic inflammatory comorbidities were excluded. In crude linear regression analyses, we explored whether erosive hand status was associated with higher levels of ESR and hsCRP (log-transformed) as compared to non-erosive hand OA. In adjusted analyses, age, sex and body mass index (BMI) were added to the model. To explore the association between OA-related joint inflammation and systemic inflammatory markers, we performed additional analyses, in which the sum scores of ultrasound-detected synovitis in the hands (range 0-90) and the knees (range 0-6) were included in the model. Significance level was set at $p<0.05$.

Results: Non-erosive and erosive hand OA were present in 373 (76%) and 119 (24%) subjects, respectively (Table).

In crude analyses, there were significant associations between erosive hand OA status and higher log-transformed ESR (ß = 0.23, 95% CI 0.05,0.41) as well as hsCRP (ß = 0.22, 95% CI –0.1,0.45). After adjusting for age, sex and BMI, the associations were not longer significant for neither ESR (ß =, 95% CI) nor hsCRP (ß = 0.11, 95% CI –0.12,0.35). Ultrasound-detected synovitis sum scores for the hands and knees were not related to higher systemic inflammatory markers with ß = 0.02 (95% CI –0.01,0.04) and ß = –0.02 (95% CI –0.10,0.05) for ESR and ß = 0.02 (95% CI –0.01,0.04) and ß = –0.01 (95% CI –0.11,0.09) for hsCRP, respectively.

Conclusion: Persons with erosive hand OA have higher ESR and hsCRP as compared to non-erosive hand OA. However, the higher levels of systemic inflammatory markers are explained by age, sex and BMI, rather than local joint inflammation. Both erosive and non-erosive hand OA is associated with local joint inflammation with no effect on systemic inflammatory markers.

Table:

	Non-erosive hand OA (n=373)	Erosive hand OA (n=119)	p-value
Age, mean (SD)	64.5 (8.3)	68.1 (6.6)	0.38
Sex, n(%) women	67%	76%	0.09
Body mass index, mean (SD)	28.3 (5.0)	28.5 (4.2)	0.44
hsCRP, median (IQR)	1.39 (0.61–3.23)	1.57 (0.90–2.80)	0.14
ESR, median (IQR)	11.0 (6.0–17.0)	14.0 (8.0–22.0)	0.006
Grey scale synovitis sum score in hands, median (IQR)	1 (0–4)	5 (1–9)	<0.001
Grey-scale synovitis sum scores in knees, median (IQR)	0 (0–1)	0 (0–1)	0.14

References: 1) Vannini A, et al. Acta reumatologica portuguesa; 2013. 2) Punzi L, et al. Ann Rheum Dis; 2005. 3)

Olejarova M, et al. Joint, bone, spine: revue du rhumatisme; 2000. 4) Bijsterbosch J, et al. Ann Rheum Dis; 2011.

Disclosure: A. Mathiessen, None; **N. Østerås**, None; **T. K. Kvien**, None; **H. B. Hammer**, None; **I. K. Haugen**, None.

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Abstract Number: 343

Efficacy of Odanacatib in Postmenopausal Women with Osteoporosis: Subgroup Analyses of Data from the Phase 3 Long-Term Odanacatib Fracture Trial

Kenneth G. Saag[1], Peter Alexandersen[2], Claude-Laurent Benhamou[3], Nigel Gilchrist[4], Johan Halse[5], E. Michael Lewiecki[6], Kurt Lippuner[7], Michael McClung[8], Masataka Shiraki[9], Carolyn A. DaSilva[10], Nadia Verbruggen[11], Boyd B. Scott[10] and Antonio Lombardi[10], [1]University of Alabama at Birmingham, Birmingham, AL, [2]Center for Clinical and Basic Research, Vejle, Denmark, Ballerup, Denmark, [3]Hôpital d'Orléans-la-Source, Orléans, France, Orleans, France, [4]The Princess Margaret Hospital, Christchurch, New Zealand, Christchurch, New Zealand, [5]Osteoporoseklinikken, Oslo, Norway, Oslo, Norway, [6]New Mexico Clinical Research & Osteoporosis Center, Albuquerque, New Mexico, USA, Albuquerque, NM, [7]Bern University Hospital, Bern, Switzerland, Bern, Switzerland, [8]Oregon Osteoporosis Center, Portland, Oregon, USA, Portland, OR, [9]Research Institute and Practice for Involutional Diseases, Nagano, Japan, Nagano, Japan, [10]Merck & Co., Inc, Kenilworth, NJ, USA, Kenilworth, NJ, [11]MSD Europe Inc., Brussels, Belgium, Brussels, Belgium

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SESSION INFORMATION

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Session Title: Osteoporosis and Metabolic Bone Disease - Clinical Aspects and Pathogenesis Poster

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Session Time: 9:00AM-11:00AM

Background/Purpose: Odanacatib (ODN), a selective oral inhibitor of cathepsin K, is in development for the treatment of osteoporosis. In the Phase 3, Long-Term Odanacatib Fracture Trial (LOFT; NCT00529373) of postmenopausal women with osteoporosis, ODN significantly reduced fracture risk and led to progressive increases in BMD at the lumbar spine (LS) and total hip (TH) vs. placebo. The incidence of AEs and serious AEs has been previously presented. Major cardiovascular events overall were generally balanced but there were numerically more adjudicated strokes in the ODN group. Final blinded, independent adjudication of all major cardiovascular events is ongoing. Pre-specified analyses evaluated the efficacy of ODN in different patient subgroups.

Methods: Women aged ≥65 years without a baseline radiographic vertebral fracture (VFx) and a TH or femoral neck (FN) BMD T-score between -2.5 and -4.0 or with a prior VFx and a TH or FN T-score between -1.5 and -4.0 were randomized (1:1) to ODN 50 mg/week or placebo. All patients received vitamin D3 (5600 IU/week) and calcium as required to achieve ~1200 mg/day. Treatment effects on primary endpoints (new and worsening morphometric vertebral, incident hip, non-VFx) were investigated in patient subgroups, including baseline age, race, bisphosphonate intolerance, prior radiographic VFx, and baseline BMD.

Results: 16,713 women were randomized (16,071 included in analyses) at 387 centers in 40 countries. Baseline mean age was 72.8 years, 57% Caucasian, 46.5% with prior VFx. Mean BMD T-scores were: LS -2.7, TH -2.4, and FN -2.7. The risk reduction of ODN vs. placebo for primary fracture endpoints was generally consistent across all subgroups.

For morphometric VFx, the relative risk reductions (RRR) for participants with or without prior VFx were 51% and 60%, respectively; for age groups <70 and ≥70 years, the RRRs were 57% and 53%, respectively (Table). RRR for morphometric VFx based on baseline LS BMD T-score tertiles (≥-2.22; -3.25< to <-2.22; ≤-3.25) were 54%, 47% and 58%, respectively. In bisphosphonate-intolerant patients, the RRR for morphometric VFx, hip and non-VFx were 52%, 48% and 17% respectively consistent with the overall study population.

Conclusion: In postmenopausal women with osteoporosis, the effect of ODN vs. placebo was generally consistent among various predefined subgroups in reducing the risk of new and worsening morphometric vertebral, hip and non-VFx.

Table. Interval-censored analysis of time to first morphometric vertebral fracture and time to first adjudicated osteoporotic fracture (hip and non-vertebral): subgroup analyses (Full-Analysis-Set population; base study)

	ODN 50 mg OW versus Placebo OW					
	Morphometric vertebral[a]		Hip[b]		Non-vertebral[b]	
	N	HR (95% CI)	N	HR (95% CI)	N	HR (95% CI)
Overall	13,680	0.46 (0.40, 0.53)	16,071	0.53 (0.39,0.71)	16,071	0.77 (0.68,0.87)
No prior vertebral fracture	7367	0.40 (0.31, 0.52)	8601	0.48 (0.31, 0.74)	8601	0.77 (0.63, 0.93)
Prior vertebral fracture	6313	0.49 (0.41, 0.59)	7470	0.58 (0.38, 0.87)	7470	0.77 (0.65, 0.92)
Age, years						
<70	4501	0.43 (0.32, 0.58)	5067	0.53 (0.27, 1.05)	5067	0.80 (0.63, 1.02)
≥70	9179	0.47 (0.40, 0.56)	11,004	0.53 (0.38, 0.74)	11,004	0.76 (0.65, 0.88)
Race						
Caucasian	7561	0.42 (0.35, 0.52)	9085	0.46 (0.31, 0.69)	9085	0.77 (0.66, 0.90)
Asian	2442	0.57 (0.41, 0.79)	2832	0.56 (0.25, 1.26)	2832	0.87 (0.60, 1.25)
Other	3677	0.47 (0.34, 0.64)	4154	0.67 (0.38, 1.18)	4154	0.71 (0.54, 0.93)
Baseline BMD						
Lumbar spine BMD T-score						
≥ Top tertile (-2.22)	4168	0.42 (0.30, 0.58)	4961	0.50 (0.29, 0.85)	4961	0.85 (0.68, 1.06)
Bottom tertile (-3.25) to < top tertile (-2.22)	4283	0.53 (0.39, 0.70)	4948	0.35 (0.19, 0.66)	4948	0.67 (0.53, 0.85)
< Bottom tertile (-3.25)	4232	0.46 (0.36, 0.59)	4923	0.65 (0.38, 1.08)	4923	0.75 (0.60, 0.95)
Total hip BMD T-score						
≥ Top tertile (-2.08)	4456	0.50 (0.38, 0.67)	5171	0.48 (0.24, 0.95)	5171	0.77 (0.62, 0.97)
Bottom tertile (-2.65) to < top tertile (-2.08)	4429	0.38 (0.29, 0.50)	5158	0.40 (0.21, 0.77)	5158	0.81 (0.64, 1.02)
< Bottom tertile (-2.65)	4208	0.46 (0.37, 0.59)	5012	0.63 (0.42, 0.95)	5012	0.74 (0.59, 0.92)

[a]Analyses based on generalized linear model for binary data with cloglog link and terms for time interval, treatment, stratum, geographic region, subgroup and treatment by subgroup interaction.

[b]Analyses were based on Cox proportional hazards model with terms for treatment, stratum and geographic region.

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fracture-trial

Abstract Number: 344

Results of a Phase 2 Clinical Trial to Evaluate the Effects of Romosozumab in Japanese Women with Postmenopausal Osteoporosis

H Ishibashi[1], DB Crittenden[2], **A Miyauchi**[3], C Libanati[4], J Maddox[2], L Chen[2] and A Grauer[2], [1]Ina Hospital, Saitama, Japan, [2]Amgen Inc., Thousand Oaks, CA, [3]Miyauchi Medical Center, Osaka, Japan, [4]UCB Pharma, Brussels, Belgium
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SESSION INFORMATION
Session Date: Sunday, November 8, 2015
Session Title: Osteoporosis and Metabolic Bone Disease - Clinical Aspects and Pathogenesis Poster
Session Type: ACR Poster Session A
Session Time: 9:00AM-11:00AM

Background/Purpose: Romosozumab is a sclerostin inhibitor that rapidly increases bone mineral density (BMD) through a dual effect on bone, causing increased bone formation and decreased bone resorption, as shown in a global phase 2 study in postmenopausal women with low bone mass (McClung et al *NEJM* 2014). Here we report the key results of a phase 2 dose-ranging study to assess the efficacy and safety of romosozumab in a Japanese population (NCT01992159).

Methods: This randomized, double-blind, placebo-controlled study enrolled Japanese postmenopausal women aged 55–85 years with a lumbar spine (LS), total hip (TH), or femoral neck (FN) DXA T score ≤ –2.5. Women were randomized to receive placebo or 1 of 3 doses of subcutaneous romosozumab (70 mg, 140 mg, or 210 mg) once monthly (QM) for 12 months. The primary endpoint was percentage change from baseline in LS BMD at month 12. Secondary endpoints included percentage change from baseline in LS BMD at month 6, TH and FN BMD at months 6 and 12, and percentage change from baseline in serum bone turnover markers.

Results: Women enrolled in the study (N = 252) had a mean (standard deviation) age of 68 (6.4) years and mean LS, TH, and FN T-scores of –2.7, –1.9, and –2.3, respectively. All romosozumab doses significantly increased BMD compared with placebo at each of the three skeletal sites at month 12 ($P < 0.01$). The largest improvements were observed with romosozumab 210 mg QM, which resulted in BMD gains from baseline of 16.9% and 4.7% at the LS and TH, respectively (Fig.), and 3.8% at the FN, at month 12. All doses of romosozumab increased P1NP and reduced CTX vs placebo by week 1 ($P < 0.0001$). In the 210 mg QM group, P1NP levels peaked at month 1 (median increase 101.1%) and fell below placebo levels by month 12; CTX levels were lowest at week 1 (median decline 45.6%) and were still below placebo at month 12. Subject incidences of adverse events and serious adverse events were generally comparable between treatment groups. Numerical differences were observed between the total romosozumab vs placebo groups for subject incidence of mild to moderate osteoarthritis adverse events (6.9% vs 0%) and mild injection-site reactions (3.7% vs 1.6%).

Conclusion: In this study of Japanese women with postmenopausal osteoporosis, romosozumab treatment resulted in rapid, large, and significant gains in BMD compared with placebo and baseline, and the 210 mg QM dose showed the

greatest efficacy. Romosozumab was generally well tolerated in this population. Global phase 3 studies evaluating the 210 mg QM dose for the treatment of osteoporosis are underway.

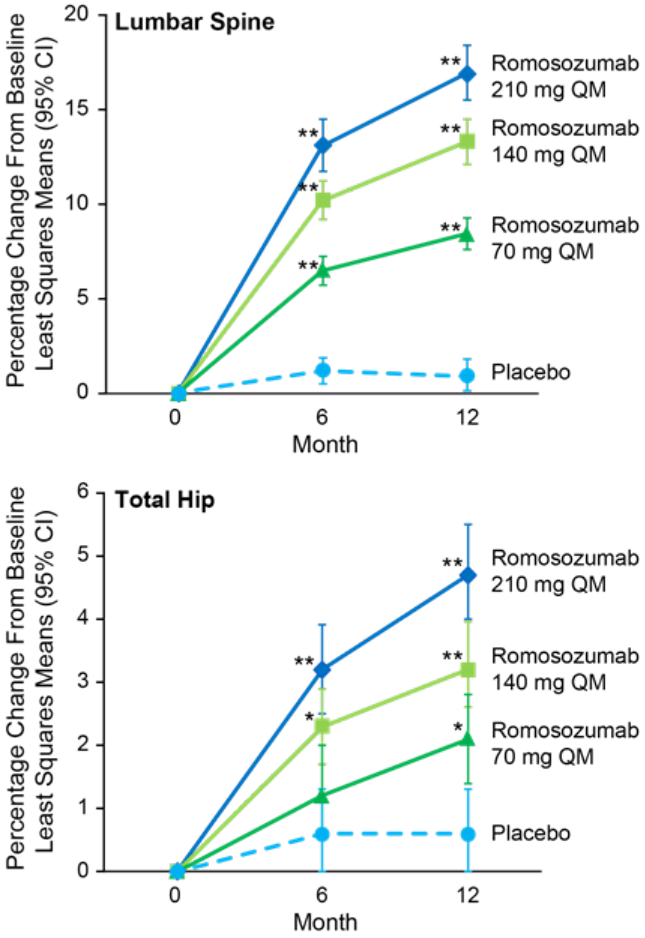

Fig. Percentage change in BMD from baseline in women receiving placebo or romosozumab (70 mg, 140 mg, or 210 mg) QM for 12 months. Estimated least squares means for the changes by linear models are presented. *BMD*, bone mineral density; *QM*, every month.
*$P < 0.01$ vs placebo; **$P < 0.0001$ vs placebo.

Disclosure: H. Ishibashi, None; **D. Crittenden**, Amgen, 1,Amgen, 3; **A. Miyauchi**, Amgen Astellas BioPharma K.K, 5; **C. Libanati**, Amgen, 1,UCB Pharma, Ex-employee Amgen, 3; **J. Maddox**, Amgen, 1,Amgen, 3; **L. Chen**, Amgen, 1,Amgen, 3; **A. Grauer**, Amgen, 1,Amgen, 3.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/results-of-a-phase-2-clinical-trial-to-evaluate-the-effects-of-romosozumab-in-japanese-women-with-postmenopausal-osteoporosis

Abstract Number: 345

Relationship Between Total Hip BMD T-Score and Incidence of Nonvertebral Fracture with up to 8 Years of Denosumab Treatment

S Ferrari[1], C Libanati[2], CJF Lin[2], S Adami[3], **JP Brown**[4], F Cosman[5], E Czerwinski[6], LH de Gregório[7], J Malouf[8], J-Y Reginster[9], NS Daizadeh[2], A Wang[2], RB Wagman[2] and EM Lewiecki[10], [1]Geneva University Hospital, Geneva, Switzerland, [2]Amgen Inc., Thousand Oaks, CA, [3]University of Verona, Verona, Italy, [4]Laval University and CHU de Québec (CHUL) Research Centre, Québec City, QC, Canada, [5]Helen Hayes Hospital, West Haverstraw, NY, [6]Krakow

Medical Center, Krakow, Poland, [7]CCBR, Rio de Janeiro, Brazil, [8]Universitat Autònoma de Barcelona, Barcelona, Spain, [9]University of Liège, Liège, Belgium, [10]New Mexico Clinical Research & Osteoporosis Center, Albuquerque, NM

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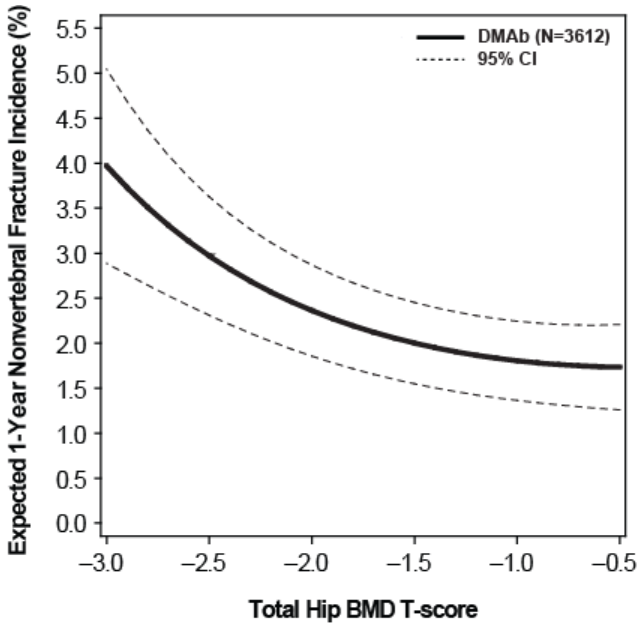
Session Time: 9:00AM-11:00AM

Background/Purpose: The relationship between BMD T-score and fracture risk has not been established in patients on therapy. We previously reported that denosumab (DMAb) treatment over 8 years enabled a substantial proportion of women with osteoporosis to achieve non-osteoporotic BMD T-scores (Ferrari, ASBMR 2014). Further improvement in T-score would only be meaningful if it were associated with fracture reductions; thus, we investigated the relationship between total hip BMD T-score and the incidence of nonvertebral fracture through 8 years of DMAb therapy.

Methods: For these analyses, women received DMAb for 3 years during the FREEDOM trial (N=3902). A large subset of these women enrolled in the Extension and received DMAb for up to an additional 5 years, for a total of up to 8 years of continued treatment (N=2343). A repeated-measures model was first used to estimate each subject's BMD T-scores during the entire follow-up, specifically at each unique nonvertebral fracture time among all subjects at risk at the time of each fracture. Cox's proportional-hazards model was then fitted with time to nonvertebral fracture as the response and total hip BMD T-score time course as a time-dependent covariate.

Results: The incidence of nonvertebral fracture was lower with higher total hip BMD T-score throughout a wide and clinically relevant T-score interval (Figure). For example, total hip BMD T-scores of –2.5 and –1.5 were associated with 1-year nonvertebral fracture incidences of about 3.0% and 2.0%, respectively. The relationship flattened at a T-score somewhere between –2.0 and –1.0, similar to what is known to occur in untreated subjects. This inverse relationship between total hip BMD T-score and nonvertebral fracture incidence was maintained regardless of age or prior fracture (data not shown).

Conclusion: Higher total hip BMD T-scores during DMAb treatment were associated with a lower incidence of nonvertebral fracture, which is similar to the relationship previously established in treatment-naïve patients. Improvements of similar magnitude in BMD would result in different reductions in fracture risk depending on the baseline BMD value. Our findings highlight the importance of BMD measurement in patients on osteoporosis treatment as a predictor of fracture risk and support the concept that a specific T-score should be further evaluated as a practical goal for therapy.



N=number of subjects randomized to DMAb in FREEDOM who had an observed total hip BMD T-score at FREEDOM baseline and ≥ 1 observed total hip BMD T-score during FREEDOM or the Extension.

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Abstract Number: 346

Autoantibodies to Osteoprotegerin Are Independently Associated with Low Hip Bone Mineral Density and Increased Fractures in Axial Spondyloarthritis

Sizheng Zhao[1,2], Barbara Hauser[3], Micaela Visconti[3], Philip L. Riches[3], Stuart H. Ralston[3] and Nicola Goodson[1,2], [1]Musculoskeletal Biology I, Institute of Ageing and Chronic Disease, University of Liverpool, Liverpool, United Kingdom, [2]Department of Rheumatology, Aintree University Hospital, Liverpool, United Kingdom, [3]Centre for Genomic and Experimental Medicine, Western General Hospital, Edinburgh, United Kingdom

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SESSION INFORMATION

Session Date: Sunday, November 8, 2015
Session Title: Osteoporosis and Metabolic Bone Disease - Clinical Aspects and Pathogenesis Poster
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Background/Purpose: Axial spondyloarthritis (axSpA) is associated with osteoporosis. However the underlying causes are incompletely understood. Osteoprotegerin (OPG) is a bone protective protein that acts as a decoy receptor for RANK-L and inhibits osteoclastogenesis. Previous work has suggested that antibodies to OPG (OPG-Ab) occur more commonly in patients with autoimmune disease and may be associated with increased bone turnover. The aim of this study was to determine whether OPG-Ab are associated with bone health in axSpA.

Methods: Patients with a clinical diagnosis of axSpA were recruited from routine outpatient clinics at two centres in the United Kingdom between 2011-2015. Patient demographics and disease characteristics and fracture history were recorded. All had BMD assessment using anteroposterior dual-energy X-ray absorptiometry (AP-DEXA). Serum levels of OPG-Ab were measured from each patient in triplicate using an in-house ELISA (intra-assay coefficient of variation 10.4%). Patients were considered to be positive for OPG-Ab if values were ≥13units (3 standard deviations above the mean in 100 healthy controls). Associations between OPG-Ab and disease characteristics were assessed by univariate logistic regression. Association with BMD and fractures were assessed by linear and logistic regression, respectively (adjusted for age, gender, duration since diagnosis, BMI and study centre).

Results: We studied 134 patients of whom 75% were male. The mean age was 47 (SD±15) years, and 71% were HLA-B27 positive. 16 patients tested positive for OPG-Ab (11.9%). Presence of OPG-Ab was not associated with patient demographics, axSpA disease characteristics/activity, but was associated with increasing years of disease duration (OR 1.04; 95%CI 1.00, 1.07; P=0.045). OPG-Ab positive patients had reduced hip (but not spinal) BMD and increased history of fracture (Table 1). OPG-Ab positivity was associated with reduced t-score at the hip (ß=-0.83; 95%CI -1.47,-0.18; P=0.012) and increased odds of any fracture (OR_{adj}4.63; 95%CI 1.36, 15.8; P=0.014).

Conclusion: This cross-sectional study demonstrates that the prevalence of OPG-Ab is much higher in axSpA than the healthy population (population prevalence 1%, P<0.001). In axSpA presence of OPG-Ab was strongly and independently associated with hip BMD and history of fractures. This raises the possibility that OPG-Ab may contribute to the bone loss and increased fracture risk observed in axSpA. Spinal BMD is not accurately assessed by AP-DEXA due to presence of syndesmophytes, and it is likely that vertebral BMD will be reduced to a similar extent at the spine. Future studies should utilize lateral spinal DEXAs. OPG-Ab positive axSpA patients may warrant more rigorous bone protection and BMD monitoring.

Table 1 Difference in bone mineral density (BMD) between OPGa positive and negative patients.

	Total	Positive (n=16)	Negative (n=118)	P-value
Height (cm)	171 ± 9.8	166 ± 8	171 ± 10.0	0.064
Weight (kg)	81.8 ± 17.3	82.6 ± 15.2	81.7 ± 17.6	0.860
BMI (kg/m^2)	28.0 ± 5.4	29.9 ± 5.4	27.7 ± 5.3	0.130
Spine BMD (g/cm^2) n=114	1.161 ± 0.224	1.244 ± 0.230	1.149 ± 0.221	0.125
Spine T-score n=113	0.027 ± 1.684	0.600 ± 1.650	-0.060 ± 1.681	0.158
Hip BMD (g/cm^2) n=106	0.988 ± 0.173	0.890 ± 0.144	1.004 ± 0.173	0.018
Hip T-score n=105	-0.449 ± 1.174	-1.167 ± 1.095	-0.329 ± 1.149	0.010
Hip osteopenia	36 (34%)	10 (67%)	26 (29%)	0.007
Hip osteoporosis	4 (4%)	2 (13%)	2 (2%)	0.097
Any fractures	31 (23%)	8 (50%)	23 (19%)	0.007

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Safety Observations with 3 Years of Denosumab Exposure: Comparison Between Subjects Who Received Denosumab during the Pivotal 3-Year Trial and Subjects Who Crossed over to Denosumab during the Extension

NB Watts[1], JP Brown[2], S Papapoulos[3], EM Lewiecki[4], DL Kendler[5], P Dakin[6], RB Wagman[6], A Wang[6], NS Daizadeh[6], S Smith[6] and HG Bone[7], [1]Mercy Health, Cincinnati, OH, [2]Laval University and CHU de Québec (CHUL) Research Centre, Québec City, QC, Canada, [3]Leiden University Medical Center, Leiden, Netherlands, [4]New Mexico Clinical Research & Osteoporosis Center, Albuquerque, NM, [5]University of British Columbia, Vancouver, BC, Canada, [6]Amgen Inc., Thousand Oaks, CA, [7]Michigan Bone and Mineral Clinic, Detroit, MI

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Background/Purpose: Denosumab (DMAb) is approved for the treatment of postmenopausal women with osteoporosis at increased risk for fracture. In the pivotal 3-year FREEDOM trial comparing placebo (Pbo) and DMAb, questions arose regarding imbalances of low-frequency adverse events and some common adverse reactions. Here, we examined the incidences of these events in women who originally received Pbo during FREEDOM and then received DMAb for 3 years during the FREEDOM Extension (cross-over group). This provided a unique opportunity for comparison with the original 3-year Pbo and DMAb FREEDOM observations.

Methods: In FREEDOM, postmenopausal women with osteoporosis received Pbo or DMAb for 3 years. Women were eligible for the Extension if they completed the 3-year FREEDOM visit, missed no more than 1 dose of investigational product (IP) during FREEDOM, and agreed to enroll. During the Extension, all women received DMAb. Three-year cumulative incidences of selected adverse events of interest observed during FREEDOM for the Pbo and DMAb groups were also determined for the first 3 years of DMAb exposure during the Extension for the cross-over group. For each of these 3 groups, the safety analyses included women who received ≥ 1 dose of IP during the respective 3-year periods (FREEDOM Pbo, N=3883; FREEDOM DMAb, N=3879; Extension cross-over DMAb, N=2206). Selected safety events of interest included malignancy, pancreatitis, endocarditis, delayed fracture healing, serious infections, serious opportunistic infections, and serious cellulitis or erysipelas, in addition to the top 5 most frequent adverse events in the US prescribing information (USPI; back pain, pain in extremity, musculoskeletal pain, hypercholesterolemia, and cystitis).

Results: The incidences of these adverse events in the cross-over DMAb group during the first 3 years of the Extension were similar to or lower than the incidences reported in FREEDOM and did not show a trend for increasing risk of any of these events (Table). For example, the incidence of serious adverse events of cellulitis or erysipelas observed in FREEDOM DMAb subjects (0.31%) was not observed in the FREEDOM Pbo subjects who crossed over to DMAb (0.05%) in the Extension.

Conclusion: Analyses of 3-year safety data from FREEDOM (Pbo and DMAb groups) and 3-year safety data from the Extension (cross-over DMAb group) did not show an increasing trend regarding the imbalances of low-frequency events and some common adverse reactions observed in FREEDOM.

Table. Incidences of Events of Interest

	FREEDOM (3 years)		Extension (3 years)
Event of Interest, n (%)	Placebo N = 3883	Denosumab N = 3879	Cross-over Denosumab N = 2206
Adverse Events			
Malignancy[a]	167 (4.30)	187 (4.82)	108 (4.90)
Pancreatitis[b]	3 (0.08)	7 (0.18)	2 (0.09)
Endocarditis	0 (0.00)	3[f] (0.08)	0 (0.00)
Delayed fracture healing[c]	5 (0.13)	2 (0.05)	NA
Delayed fracture healing[d]	1 (0.03)	0 (0.00)	1 (0.05)
Serious Adverse Events			
Infections	134 (3.45)	160 (4.12)	81 (3.67)
Opportunistic infections[e]	3 (0.08)	4 (0.10)	2 (0.09)
Cellulitis or erysipelas	1 (0.03)	12 (0.31)	1 (0.05)
Top 5 Most Frequent Events in USPI			
Back pain	1343 (34.59)	1344 (34.65)	318 (14.42)
Pain in extremity	432 (11.13)	451 (11.63)	171 (7.75)
Musculoskeletal pain	291 (7.49)	297 (7.66)	118 (5.35)
Hypercholesterolemia	236 (6.08)	280 (7.22)	145 (6.57)
Cystitis	225 (5.79)	228 (5.88)	125 (5.67)

Treatment groups are the original randomized assignments in FREEDOM. Seven placebo subjects who received 1 dose of denosumab in FREEDOM were analyzed in the denosumab column in US PI.
N = Number of subjects who received ≥ 1 dose of investigational product.
Includes only treatment-emergent adverse events; based on MedDRA version 13.0.
[a] Based on neoplasms benign, malignant and unspecified (including cysts and polyps) system organ class excluding benign events used in the FREEDOM Extension
[b] Based on acute pancreatitis event of interest search strategy
[c] Based on delayed fracture healing response collected on Clinical Fracture Summary CRF II in FREEDOM
[d] Based on AE reporting of delayed fracture-healing events and subsequently selected by search strategy
[e] Includes aspergillosis, herpes zoster, pulmonary tuberculosis, and tuberculosis
[f] No causative pathogen was identified in any of the 3 cases reported as endocarditis. One subject was hospitalized for treatment with antibiotics. One had endocarditis listed as a consideration in a fatal event of multi-organ failure due to sepsis; however, no treatment details from the case were available. The third case was listed as "non-serious," and the patient did well without long-term antibiotic therapy. Further information is not available.

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Abstract Number: 348

Incidence Rate of Potential Osteonecrosis of the Jaw Among Women with Postmenopausal Osteoporosis Treated with Prolia or Bisphosphonates

Fei Xue[1], Rachel B Wagman[1], Susan Yue[1], Shawna Smith[1], Tarun Arora[2], Jeffrey R. Curtis[2], Vera Ehrenstein[3], Henrik T Sørensen[3], Grethe Tell[4], Helle Kieler[5], Florence T Wang[6], David D Dore[6] and J Michael Sprafka[1], [1]Amgen

Inc., Thousand Oaks, CA, [2]University of Alabama at Birmingham, Birmingham, AL, [3]Aarhus University Hospital, Aarhus, Denmark, [4]University of Bergen, Bergen, Norway, [5]Karolinska Institutet, Stockholm, Sweden, [6]Optum, Waltham, MA

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Background/Purpose: Although a higher risk of osteonecrosis of the jaw (ONJ) has been associated with antiresportive treatment based on spontaneous reports and observational studies, no study has systematically assessed the ONJ risk associated with Prolia (denosumab 60 mg). This study estimates the incidence rate (IR) of ONJ in users of Prolia or BP for postmenopausal osteoporosis (PMO) in administrative databases.

Methods: Using administrative data from US Medicare, Optum and Scandinavian national medical registries (Denmark, Norway and Sweden), postmenopausal women with a diagnosis of osteoporosis or osteoporotic fracture, or osteoporosis medications were identified from May 2010 to Dec 2011 (Medicare and Scandinavian national registries) or Mar 2013 (Optum). Women were followed for incident event of potential ONJ defined by ICD codes. Prolia and BP (oral and IV) exposure was updated in a time-varying manner and characterized “as treated”, with and without a 1-year extension following the on-treatment period defined as the days supplied + 60 days. The age-standardized IR of ONJ was computed for each exposure cohort.

Results: A total of 2,561,119 women with PMO were identified from Medicare (1,995,915), Optum (193,003), Denmark (106,691), Norway (95,628) and Sweden (169,882). The IR (95% CI) per 100,000 person-years of ONJ in women with PMO was 40 (38–42) in Medicare, 27 (20–34) in Optum, 37 (27–50) in Denmark, 17 (11–26) in Norway and 25 (17–38) in Sweden. In Medicare, when exposure cohorts were classified only by the on-treatment period, the IR (95% CI) was 70 (28–145) in the Prolia only cohort and 90 (11–328) in the Prolia + BP cohort, and ranged from 45 (41–49) to 77 (7–310) in cohorts exposed to BP only (Table 1). When exposure cohorts were classified by on-treatment plus 1-year post-treatment period, the IR (95% CI) was numerically lower in the Prolia only cohort [59 (11–180)] and the Prolia + BP cohort [76 (30–160)], and remained similar in cohorts exposed to BP only [ranging from 45 (42–48) to 84 (53–125)] relative to the corresponding on-treatment only cohorts (Table 2). The number of ONJ cases in the other data systems was too low (0–2) in Prolia users to allow a robust estimation of the IR.

Conclusion: The descriptive analysis based on Medicare suggested the IR of potential ONJ was low in the PMO population and did not differ substantially by treatment. The number of cases in other data systems was low and precluded meaningful interpretation of the ONJ IR, especially in Prolia recipients. To confirm these results, further analysis based on medically confirmed cases and adjustment for confounders is warranted.

Table 1. Distribution of cases and age-standardized incidence rates (95% CI) of potential osteonecrosis of the jaw (ONJ) identified by ICD codes in women with postmenopausal osteoporosis during time on-treatment with Prolia or bisphosphonates.

Exposure Cohorts	US Medicare	United Healthcare	Scandinavian National Medical Registries		
			Denmark	Norway	Sweden
	Number of Cases				
BP only*	659	32	30	18	30
Oral BP only†	553	30	29	17	30
IV BP only‡	<11£	2	1	1	0
IV BP + oral BP§	<11£	0	0	0	0
Prolia only#	<11£	2	1	0	0
Prolia + BP¶	<11£	0	0	0	0
	Age-standardized Incidence Rate (95% CI)/100,000 person-years				
BP only*	48 (44, 52)	30 (19, 45)	40 (26, 68)	31 (17, 75)	23 (15, 36)
Oral BP only†	45 (41, 49)	29 (19, 44)	39 (25, 67)	32 (16, 80)	24 (16, 37)
IV BP only‡	66 (53, 81)	44 (4 , 183)	87 (0, 528)	32 (0, 195)	NA
IV BP + oral BP§	77 (7, 310)	NA	NA	NA	NA
Prolia only#	70 (28, 145)	434 (27, 1935)	72 (0, 437)	NA	NA
Prolia + BP¶	90 (11, 328)	NA	NA	NA	NA

* Exposed to any BP (oral and/or IV) without concomitant Prolia treatment
† Exposed to any oral BP without concomitant treatment with Prolia or IV BP
‡ Exposed to any IV BP without concomitant treatment with Prolia or oral BP
§ Exposed to both IV BP and oral BP without concomitant treatment with Prolia
# Exposed to Prolia without concomitant BP treatment (oral or IV)
¶ Exposed to both Prolia and BP (oral and/or IV)
£ Data Use Agreement with CMS prohibits cell size of 10 or less to be displayed

Table 2. Distribution of cases and age-standardized incidence rates (95% CI) of potential osteonecrosis of the jaw (ONJ) identified by ICD codes in women with postmenopausal osteoporosis during time on-treatment plus 1-year post-treatment with Prolia or bisphosphonates.

Exposure Cohorts	US Medicare	United Healthcare	Scandinavian National Medical Registries		
			Denmark	Norway	Sweden
	Number of Cases				
BP only*	912	45	36	27	36
Oral BP only†	778	43	34	26	36
IV BP only‡	108	1	2	0	0
IV BP + oral BP§	26	1	0	1	0
Prolia only#	<11£	1	0	0	0
Prolia + BP¶	<11£	1	1	0	0
	Age-standardized Incidence Rate (95% CI)/100,000 person-years				
BP only*	47 (44, 50)	27 (19, 38)	41 (28, 65)	44 (27, 80)	22 (15, 32)
Oral BP only†	45 (42, 48)	27 (18, 38)	40 (27, 64)	45 (27, 83)	22 (15, 33)
IV BP only‡	65 (52, 79)	10 (0, 53)	163 (20, 583)	NA	NA
IV BP + oral BP§	84 (53, 125)	189 (5, 1,054)	NA	87 (0, 530)	NA
Prolia only#	59 (11, 180)	81 (2, 453)	NA	NA	NA
Prolia + BP¶	76 (30, 160)	906 (23, 5,050)	169 (0, 1,032)	NA	NA

* Exposed to any BP (oral and/or IV) without concomitant Prolia treatment
† Exposed to any oral BP without concomitant treatment with Prolia or IV BP
‡ Exposed to any IV BP without concomitant treatment with Prolia or oral BP
§ Exposed to both IV BP and oral BP without concomitant treatment with Prolia
# Exposed to Prolia without concomitant BP treatment (oral or IV)
¶ Exposed to both Prolia and BP (oral and/or IV)
£ Data Use Agreement with CMS prohibits cell size of 10 or less to be displayed

Disclosure: F. Xue, Amgen, 3,Amgen, 1; **R. B. Wagman**, Amgen, 1,Amgen, 3; **S. Yue**, Amgen, 1,Amgen, 3; **S. Smith**, Amgen, 1,Amgen, 3; **T. Arora**, Amgen, 2; **J. R. Curtis**, Roche/Genentech, UCB, Janssen, Corrona, Amgen, Pfizer, BMS, Crescendo, AbbVie, 2,Roche/Genentech, UCB, Janssen, Corrona, Amgen, Pfizer, BMS, Crescendo, AbbVie, 5; **V. Ehrenstein**, Amgen, 2; **H. T. Sørensen**, Amgen, 2; **G. Tell**, Amgen, 2; **H. Kieler**, Amgen, 2; **F. T. Wang**, Amgen, 2; **D. D. Dore**, Amgen, 2; **J. M. Sprafka**, Amgen, 1,Amgen, 3.

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Abstract Number: 349

Comparison Between the American Recommendations and the Japanese Guidelines for Glucocorticoid-Induced Osteoporosis in Japanese Patients with Rheumatoid Arthritis

Takefumi Furuya, Shigeki Momohara, Atsuo Taniguchi and Hisashi Yamanaka, Institute of Rheumatology, Tokyo Women's Medical University, Tokyo, Japan

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Background/Purpose: In 2014, the Japanese Society for Bone and Mineral Research (JSBMR) updated their guidelines for the management and treatment of glucocorticoid-induced osteoporosis (GIO) and incorporated a new scoring method that does not use the Fracture Risk Assessment Tool (FRAX®). In this study, using the JSBMR guidelines [1] and the American College of Rheumatology (ACR) 2010 recommendations for the prevention and treatment of GIO, we compared our evaluations of Japanese patients with rheumatoid arthritis (RA) who were treated with glucocorticoids.

Methods: The Institute of Rheumatology Rheumatoid Arthritis (IORRA) study, which began in 2000, was a prospective cohort study of RA patients conducted at the Institute of Rheumatology, Tokyo Women's Medical University (Tokyo, Japan). Applying ACR recommendations and JSBMR guidelines, we evaluated 1,752 of these Japanese patients who were over the age of 50 years (mean age 63 years) and had been treated with glucocorticoids. The ACR recommendation is to prescribe osteoporosis treatments for patients treated with ≥ 7.5 mg/day prednisolone or whose 10-year risk of major osteoporotic fractures is > 10%. The Japanese GIO guidelines identify age, glucocorticoid dose, lumbar bone mineral density, and prior fragility fractures as factors predictive of bone fracture, and the fracture risk for an individual can be calculated as the sum of the scores for each risk factor with a score of 3 representing the optimal cut-off score for pharmacological intervention.

Results: Among the female RA patients older than 50 years who were treated with glucocorticoids (n = 1,438), in accordance with the ACR recommendations and the Japanese guidelines, 1,183 (82%) and 1,119 (78%) patients, respectively, should have received osteoporosis treatments (Table). Among the male RA patients older than 50 years who were treated with glucocorticoids (n = 314), the ACR recommendations and the Japanese guidelines propose that 217 (69%) and 267 (85%) patients, respectively, should have received osteoporosis treatments (Table). Among the male patients, the Japanese guidelines would recommend significantly more patients receive osteoporosis treatments compared with the ACR recommendations ($P < 0.0001$).

Table: Japanese patients older than 50 years and treated with glucocorticoids for RA for whom osteoporosis treatments were recommended*

Recommendations/guidelines	Female (n = 1,438)	Male (n = 314)
ACR	182 (12.7%)	3 (1.0%)
JSBMR	118 (8.2%)	53 (16.9%)
ACR and JSBMR	1001 (69.6%)	214 (68.2%)
None	137 (9.5%)	44 (14.0%)

* Data are n (%).

Conclusion: The updated Japanese GIO guideline appears to be a simple and useful tool to use when treating Japanese RA patients with glucocorticoids. The ACR recommendations may have underestimated the need for osteoporosis treatment in male patients with RA compared with the Japanese guideline, although prospective studies are necessary to conclude.

Reference

[1] Suzuki Y, et al. Guidelines on the management and treatment of glucocorticoid-induced osteoporosis of the Japanese Society for Bone and Mineral Research: 2014 update. J Bone Miner Metab. 2014;32:337-50.

Disclosure: T. Furuya, None; **S. Momohara**, AbbVie, 2,Asahi Kasei, 2,Bristol Myers Squibb, 2,Chugai, 2,Daiichi Sankyo, 2,Eisai, 2,Mitsubishi Tanabe, 2,Nakashima Medical Co., Ltd., 2,Santen Pharmaceutical Co., Ltd., 2,Taisho Toyama Pharmaceutical Co. Ltd, 2,Takeda, 2; **A. Taniguchi**, None; **H. Yamanaka**, Abbott Immunology Pharmaceuticals, 2,AbbVie, 2,Asahikasei, 2,Astellas, 2,AstraZeneca, 2,Bristol-Myers Squibb, 2,Chugai, 2,Daiichi Sankyo, 2,Eisai, 2,GlaxoSmithKline, 2,Janssen Pharmaceutica Product, L.P., 2,Mitsubishi Tanabe, 2,MSD, 2,Nippon Kayaku, 2,Pfizer Inc, 2,Santen, 2,Taishotoyama, 2,Takeda, 2,Teijin, 2,Abbott Immunology Pharmaceuticals, 5,AbbVie, 5,Astellas, 5,AstraZeneca, 5,Bristol-Myers Squibb, 5,Chugai, 5,Daiichi Sankyo, 5,Eisai, 5,Mitsubishi Tanabe, 5,Nippon Kayaku, 5,Pfizer Inc, 5,Takeda, 5,Teijin, 5,Abbott Immunology Pharmaceuticals, 8,AbbVie, 8,Astellas, 8,Bristol-Myers Squibb, 8,Chugai, 8,Eisai, 8,Mitsubishi Tanabe, 8,Pfizer Inc, 8,Takeda, 8,Teijin, 8.

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Abstract Number: 350

Atypical Femur Fracture in Rheumatoid Arthritis Patients Treated with Bisphosphonates: A Nested Case-Control Study

JungHee Koh[1], Ji Hyeon Ju[2], Min Kyung Chung[3], Ji Hun Kim[3], Seung Min Jung[4], Ji Yeon Lee[2], Jennifer Lee[3], Seung-Ki Kwok[5] and Sung-Hwan Park[3], [1]Seochogu, Banpodaero, 222, Division of Rheumatology, Department of Internal Medicine, College of Medicine, Seoul St. Mary's Hospital, The Catholic University of Korea, Seoul, South Korea, [2]Division of Rheumatology, Department of Internal Medicine, College of Medicine, The Catholic University of Korea, Seoul, South Korea, [3]Division of Rheumatology, Department of Internal Medicine, College of Medicine, Seoul St. Mary's Hospital, The Catholic University of Korea, Seoul, South Korea, [4]Division of Rheumatology, Department of Internal Medicine, school of medicine, The catholic university of Korea, Seoul, South Korea, [5]seungki73@catholic.ac.kr, Division of Rheumatology, Department of Internal Medicine, College of Medicine, The Catholic University of Korea, Seoul, South Korea

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SESSION INFORMATION

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Session Title: Osteoporosis and Metabolic Bone Disease - Clinical Aspects and Pathogenesis Poster
Session Type: ACR Poster Session A
Session Time: 9:00AM-11:00AM

Background/Purpose: Patients with rheumatoid arthritis (RA) are diagnosed with osteoporosis earlier than and those without RA, and are therefore exposed to Bisphosphonates (BPs) for longer. The long-term BPs treatment is one of the suggested predisposing factors for atypical femur fracture (AFF). Thus the aims of the present study were to examine the incidence and clinical characteristics of BPs-associated AFF and to identify predictors of AFF in patients with RA.

Methods: An age- and sex- matched nested case-control study was conducted based on 7 years of data collected at Seoul St. Mary's Hospital, a tertiary rheumatology center. All patients treated with BPs met the 2010 RA classification criteria. AFFs were defined as atraumatic or low-trauma fractures of the subtrochanteric or femoral shaft (Figure 1A). Ten cases of AFF were identified by reviewing surgical procedures and radiographs of the low extremities. The study included 40 age- and sex-matched controls with RA but without AFF. The femorotibial angle (FTA) was measured on radiographs taken with the patient standing to examine alignment of the lower limb under weight-bearing conditions (Figure 1B).

Results: All patients with AFF were female (age, 66.3±8.7 years) and 90% of cases involved fracture of the proximal femur. The mean length of BPs exposure for patients with AFF was 7.4±3.2 years. Patients with AFF had longer exposure to BPs and a smaller FTA ($P < 0.001$ and 0.010, respectively, Table 1). There were no differences in RA duration, medications taken during the previous 6 months, and bone mineral density in the femur and lumbar spine between patients with and without AFF. Multivariate logistic analyses identified BPs exposure (odds ratio [OR], 2.145; 95% confidence interval [CI], 1.175–4.283) and interestingly a FTA < 175°Æ (OR, 114.796; 95% CI, 2.263–5821.991) as being associated with an increased risk of AFF.

Conclusion: RA patients with a valgus deformity and receiving long-term BPs are at higher risk of AFF than matched RA control subjects. These patients should be carefully followed up with X-rays or dual energy bone densiometry.

Figure 1(A) Anteroposterior radiopraph shows right atypical subtrochanteric fracture and a cortical thickness at the left lateral cortex (arrow) (B) Measurement of femorotibial angle (FTA) on a radiograph. The FTA is the lateral angle between the axis of the femoral shaft and that of the tibial shaft

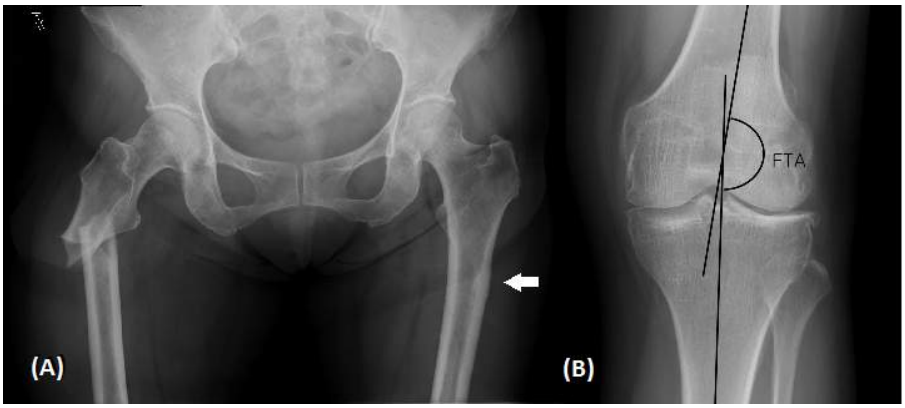

Table 1. Clinical characteristics of rheumatoid arthritis patients ever exposed bisphosphonates according to experience atypical femur fracture

	Non-fracture	Atypical fracture	P-value
BMI, kg/m^2	22.2±2.7	23.7±1.9	0.090
RA duration, yrs	12.7±10.1	10.2±5.0	0.454
Total bisphosphonates exposure*, yrs	3.8±2.3	7.4±3.2	<0.001
Drug holiday, n (%)	18 (45)	0	0.009
Cumulative oral prednisolone dose, g	5.2±4.3	8.7±12.7	0.417

* In case of AFFs, total BPs exposure was computed just before fracture.

Disclosure: J. Koh, None; **J. H. Ju**, None; **M. K. Chung**, None; **J. H. Kim**, None; **S. M. Jung**, None; **J. Y. Lee**, None; **J. Lee**, None; **S. K. Kwok**, None; **S. H. Park**, None.

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Abstract Number: 351

Trabecular Bone Score Is Severely Affected in Male Patients with Chronic Obstructive Pulmonary Disease

Marta Arévalo Salaet[1], Enrique Casado Burgos[1], M Gallego[1], Luis Del Rio[2], Marta Larrosa[3] and Jordi Gratacos[4], [1]Hospital Universitari Parc Taulí, Sabadell, Spain, [2]CETIR Medical Centre, Terrassa, Spain, [3]Rheumatology, Hospital Parc Taulí, Sabadell, Spain, [4]Rheumatology, Hospital de Sabadell, Sabadell, Spain

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Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose:

Patients with chronic obstructive pulmonary disease (COPD) have a high risk of osteoporosis and fractures. In a cohort of male patients with COPD we reported 33% of vertebral fractures, with 27% of fractures in patients with normal bone mineral density (BMD)[1]. Trabecular Bone Score (TBS) has been described as an index of bone microarquitecture, and could be a new assessment tool to detect bone quality impairment in these patients.

Analysis of TBS in a sub-cohort of male patients with COPD and its possible association with BMD, corticoid use, COPD severity or vertebral fractures.

[1]Casado E, et al. JBMR 2007; 22 (S1): S202.

Methods:

Male patients, older than 50 years, with COPD defined according to ATS/ERS classification (FEV_1/FVC<70%) were included. Exclusion criteria: Other concomitant pulmonary disease, rheumatologic and/or vertebral disease that may lead to missinterpretation of BMD by DXA. BMD was determined by dual-energy X-ray absorptiometry (DXA) at lumbar spine and proximal femur. Vertebral fractures were assessed by thoracic and lumbar X-ray. Corticosteroid use in the previous five years and number of hospitalizations were recorded in all patients.

Results:

We included 98 patients. Mean age 67.8±7.5 years. 38% patients had a mild pulmonar disease, 39% moderate and 23% had a severe disease ((FEV_1/FVC<30%). 29 patients (30%) had morphometric vertebral fractures. Mean BMD T-score at lumbar spine -1.67±1.55, at femoral neck -1.81±1.04, and al total hip -1.31±1.14. Mean TBS was 1.035±0,135 (T-score -2.85±1.18). TBS was lower in fractured patients (T -2.59±1.16 vs -2.34±1.22; p=NS). According to COPD severity TBS was lower in patients with modereate disease (T-2.57±1.34) and severe disease (T -2.54±1.34) than in patients with mild disease (T -2.19±1.32), although without reaching significant differences. We didn't find any significant assotiation between TBS and corticosteroid use.

Conclusion:

TBS is severely affected in male patients with chronic obstructive pulmonary disease, especially in patients with moderate and severe pulmonar disease. Low TBS seems to be associated with vertebral fractures in this population.

Disclosure: M. Arévalo Salaet, None; **E. Casado Burgos**, None; **M. Gallego**, None; **L. Del Rio**, None; **M. Larrosa**, None; **J. Gratacos**, None.

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Abstract Number: 352

Low Bone Density Is Associated with Atherosclerotic Disease in Patients with Psoriatic Arthritis

Eirik Ikdahl[1,2], Hege Kilander Høiberg[3], Silvia Rollefstad[2], Andreas P Diamantopoulos[4,5], Grunde Wibetoe[2], Arthur Kavanaugh[6], Inge C Olsen[7], Tore K. Kvien[7], Anne Grete Semb[8] and Glenn Haugeberg[9], [1]Rheumatology, Diakonhjemmet Hospital, Oslo, Norway, [2]Preventive Cardio-Rheuma Clinic, Department of Rheumatology, Diakonhjemmet Hospital, Oslo, Norway, [3]Department of Rheumatology, Hospital of Southern Norway, Kristiansand, Norway, [4]Rheumatology, Haugesund Hospital for Rheumatic Diseases, Haugesund, Norway, [5]Rheumatology, Hospital of Southern Norway Trust, Kristiansand, Norway, [6]University of California San Diego, La Jolla, CA, [7]Dept. of Rheumatology, Diakonhjemmet Hospital, Oslo, Norway, [8]Diakonhjemmet Hospital, Oslo, Norway, [9]Rheumatology, The Norwegian University of Science and Technology, Trondheim, Norway

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Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose:

There is an evidence vacuum concerning the mechanisms underlying the high atherosclerotic cardiovascular disease (ASCVD) burden in patients with psoriatic arthritis (PsA). In the general population, osteoporosis and low bone mineral density (BMD) are risk factors for ASCVD. However, this has not been established for patients with PsA. The T-score represents a patient's BMD compared to the BMD of a healthy 30-year old and is the most commonly used measure when screening for osteoporosis. The aim of the present study was to evaluate if low BMD, measured by T-score, is correlated with ASCVD in patients with PsA.

Methods:

In this cross-sectional study, patients with PsA, recruited from an outpatient clinic, underwent a thorough clinical rheumatology examination, carotid ultrasound, laboratory tests and BMD measurements by dual-energy X-ray absorptiometry (DXA) scans. Established ASCVD was defined as a previous ASCVD event (acute myocardial infarction, coronary interventions, transient ischemic attack [TIA] and ischemic stroke), established peripheral artery disease or atherosclerotic carotid artery plaque(s). Unadjusted and adjusted analyses of variance (ANOVA) were applied to compare the T-score between patients with and without ASCVD. In addition, we performed logistic regression analyses with ASCVD as the dependent variable, both unadjusted and adjusted (age, gender and BMI) and evaluated the Nagelkerke R^2 as a proxy for the degree of correlation between ASCVD and T-score, traditional CVD risk factors, inflammatory biomarkers and PsA disease activity variables.

Results:

In the cohort of 137 PsA patients, 51 (37%) had ACSVD, 70 (51%) were male and the median (IQR) age and disease duration was 53.0 (44.5, 59.5) and 7.8 (3.2, 12.5) years, respectively. The T-score was significantly lower in patients with ACVD compared to those without (p=0.001) (Table). This finding was largely robust to adjustments for demographic data (p=0.04), traditional CVD risk factors (p=0.03-0.06), inflammatory biomarkers (p<0.05), PsA disease activity (p=0.03-0.10) and common rheumatology drugs (p=0.02-0.04). In logistic regression analyses with ASCVD as the dependent variable, the Nagelkerke R^2 value for T-score (unadjusted: 0.11, adjusted: 0.27) was higher than for ACVD risk factors (unadjusted: 0.003-0.04, adjusted: 0.23-0.25), inflammatory biomarkers (unadjusted: 0.005-0.05, adjusted: 0.24) and PsA disease activity variables (unadjusted: <0.001-0.04, adjusted: 0.23-0.26).

Conclusion:

Our study provides the first evidence of an association between ACVD and low BMD in PsA patients, which was robust to adjustments. In addition, ACVD was more strongly correlated with the T-score than with traditional CVD risk factors, inflammatory biomarkers or PsA disease activity. Our results suggest that there may be indication for CVD risk evaluation including carotid ultrasound in PsA patients with low BMD.

T-score in patients with and without established atherosclerosis.

	PsA patients without ASCVD (n=86) Mean±SE	PsA patients with ASCVD (n=51) Mean±SE	p-value
Unadjusted	0.81±0.14	0.03±0.18	0.001
Demographic data*	0.71±0.13	0.24±0.17	0.04
Adjusted for demographic data and the following traditional CVD risk factors*			
Smoke (daily)	0.72±0.13	0.26±0.17	0.04
LDL-c mmol/L	0.72±0.13	0.23±0.17	0.03
HDL-c mmol/L	0.72±0.13	0.24±0.17	0.04
Triglycerides mmol/L	0.72±0.13	0.23±0.17	0.03
Total Cholesterol mmol/L	0.72±0.13	0.23±0.17	0.03
Systolic blood pressure mmHg	0.68±0.13	0.26±0.17	0.06
All traditional ASCVD risk factors	0.70±0.14	0.25±0.17	<0.05
Adjusted for demographic data and the following inflammation biomarkers*			
ESR mm/hr	0.70±0.13	0.25±0.17	<0.05
CRP mg/L	0.70±0.13	0.25±0.17	<0.05

Disclosure: E. Ikdahl, None; **H. Kilander Høiberg**, None; **S. Rollefstad**, None; **A. P. Diamantopoulos**, None; **G. Wibetoe**, None; **A. Kavanaugh**, None; **I. C. Olsen**, None; **T. K. Kvien**, None; **A. G. Semb**, None; **G. Haugeberg**, Pfizer Norway, 2.

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Adjusted for demographic data and the following PsA disease activity parameters***			
DAS28 (ESR)	0.71±0.13	0.23±0.17	0.03
DAS28 (CRP)	0.72±0.13	0.22±0.17	0.03
PASI	0.70±0.13	0.22±0.17	0.04
Tender joint count (68 joints)	0.69±0.13	0.22±0.17	0.04
Swollen joint count (66 joints)	0.66±0.13	0.29±0.17	0.10
Pain (VAS100)	0.70±0.13	0.24±0.17	0.04
Patient global assesment (VAS100)	0.72±0.13	0.22±0.17	0.03
Physical function	0.71±0.13	0.24±0.17	0.04
MHAQ	0.70±0.13	0.24±0.17	0.04
Adjusted for demographic data and following medications*			
Prednisolone	0.71 ±0.13	0.24±0.17	0.04
b-DMARDs	0.72±0.13	0.21±0.17	0.03
s-DMARDs	0.70±0.13	0.25±0.17	0.04
NSAIDs	0.72±0.13	0.17±0.17	0.02

*Age, gender, BMI

**Disease activity variables according to the GRAPPA-OMERACT

PsA: Psoriatic arthritis, ASCVD: Atherosclerotic cardiovascular disease, LDL-c: Low-density lipoprotein cholesterol, HDL-c: High-density lipoprotein cholesterol, ESR: Erythrocyte sedimentation rate, CRP: C-reactive protein, DAS28: Disease activity score with 28 joints, PASI: Psoriasis Area Severity Index, MHAQ: modified health assessment questionnaire, b-DMARDs: biologic disease-modifying anti-rheumatic drugs, s-DMARDs: synthetic disease-modifying anti-rheumatic drugs.

Abstract Number: 353

A Longitudinal Cohort Study of Weekly Teriparatide, Denosmab, and Bisphosphonates for Prevention of Vertebral Fractures in Glucocorticoid-Induced Osteoporosis

Hisaji Oshima[1], Mari Ushikubo[1], Kumiko Akiya[1], **Ikuko Tanaka**[2], Shigenori Tamaki[2] and Keisuke Izumi[3],

[1]Department of Connective Tissue Diseases, National Tokyo Medical Center, Tokyo, Japan, [2]NAGOYA Rheumatology Clinic, Nagoya, Japan, [3]National Tokyo Medical Center, Tokyo, Japan

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Background/Purpose: Although weekly teriparatide (56.5ug, wTPTD) and denosmab (DMAB) have been developed as potent anti-osteoporotic agents, effects of these agents on prevention of osteoporotic fractures in glucocorticoid-induced osteoporosis (GIO) have not yet well demonstrated. We conducted a cohort study to clarify effects of wTPTD and DMAB when compared with bisphosphonates (BIS) on osteoporotic vertebral fractures in GIO.

Methods: A one-year cohort study recruiting 223 patients (196 women) with connective tissue diseases was conducted in Tokyo, Japan. Means of age, disease duration, total prednisolone (PSL) dosages, and daily PSL dosages (dPSL) of subjects were 65+/-15 (yo, +/-SD), 11+/-11 (y), 25+/-29 (g) and 6.4+/-5.7 (mg/day), respectively. Vertebral fractures were defined from X-ray films with the semi-quantitated method (SQ; Genant, 1993). Lumbar bone mineral densities (BMD) were measured with Lunar 3030 (GE). Prevalent vertebral fractures were seen in 103 (46%) patients. Bisphosphonates, wTPTD, and DMAB were used in 149, 53, and 21 patients, respectively.

Results: 1) The BMD at the base line was 0.916 +/- 0.181, and showed no difference between treatment groups. The daily PSL was significantly increased ($p<0.03$) in the group of wTPTD than in BIS and DMAB (10.5, 6.0, and 6.0, respectively). 2) Incident vertebral fractures were observed in 24 (16%), 2 (4%), and 2 (10%) in BIS, DMAB, and wTPTD, respectively. 3) A multivariate logistic regression analysis revealed that statistically significant factors for incident fractures were BMD (per 0.1 decrease, OR; 1.40, 95%CI; 1.02–1.91), dPSL (per 5mg increase, 1.95, 1.29–2.95), prevalent fractures (5.16, 1.85–14.4), DMAB (vs BIS, 0.01, 0.001-0.05), wTPTD (vs BIS, 0.12, 0.03-0.88). 4) There were no significant differences in severe adverse effects between the treatment groups.

Conclusion: These results suggested that wTPTD and DMAB might be more effective than bisphosphonates for prevention of osteoporotic vertebral fractures in patients treated with glucocorticoids.

Disclosure: H. Oshima, None; **M. Ushikubo**, None; **K. Akiya**, None; **I. Tanaka**, None; **S. Tamaki**, None; **K. Izumi**,

None.

Abstract Number: 354

Association Between Bone and Clinical Parameters in Ankylosing Spondylitis

Vladimira Boyadzhieva[1], Mariana Ivanova[2], Nikolay Stoilov[1], Rumen Stoilov[3], Rasho Rashkov[4], Didier Hans[5] and Rozier Berengere[5], [1]Rheumatology, University Hospital (MHAT) St Ivan Rilski, Sofia, Bulgaria, [2]University Hospital "St. Iv. Rilski", Clinic of Rheumatology, Sofia, Bulgaria, [3]University Hospital (MHAT) St Ivan Rilski, Sofia, Bulgaria, [4]Department of Rheumatology, MHAT Sveti Ivan Rilski, Sofia, Bulgaria, [5]Center of Bone Diseases, Lausanne University Hospital, Lausanne, Switzerland

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Session Time: 9:00AM-11:00AM

Background/Purpose: Ankylosing spondylitis (AS) is a chronic inflammatory rheumatological disease of unknown origin that primarily affects the axial skeleton, including the sacroiliac joints and spine, but also the peripheral joints and entheses.

This study aimed to evaluate the relationship between physical function, disease activity, spinal mobility and bone parameters in ankylosing spondylitis (AS)

Methods:). Fifty patients were examined: 27 men and 23 women. None of the patients exhibited evidence of a fracture in any of the visualized vertebrae. The clinical assessment included Bath AS Disease Activity Index (BASDAI), AS Disease Activity Score (ASDAS-CRP), Bath AS Functional Index (BASFI), Bath AS Metrology Index (BASMI). Lumbar spine and femoral neck bone mineral density (BMD), spinal trabecular bone score (TBS) and the TBS T-score were calculated by dual-energy X-ray absorptiometry (DXA).

Results: Using the WHO categorization scheme, 50% of the patients were deemed to have normal lumbar BMD, 36% were osteopaenic, and 14% were osteoporotic. This compares with normal TBS in 50% of the patients, with partially-degraded and fully-degraded micro-architecture seen in 34% and 16%, respectively. We found moderately strong inverse correlations between TBS and BASMI (r=-0.34; p=0.02), between the TBS T-score and BASMI (r=-0.35; p=0.01) and between femoral BMD and BASMI (r= -0.395; p=0.004). The correlation coefficient for the relationship between the TBS T-score and age was -0.29 (p=0.045), suggesting a weak inverse association, while TBS only exhibited a borderline inverse correlation with age (r=-0.27; p=0.06). Femoral BMD was moderately inversely correlated with age (r=-0.44; p=0.001). In addition, the lumbar spine TBS and TBS T-score were moderately to strongly correlated with BMI (both r=-0.65; p<0.001). No significant correlations were observed between bone parameters and other markers of disease activity, physical function, or applied therapy administered for AS. Subject`s age was independently associated with a femoral neck BMD < -1.00 (OR = 1.08, 95% CI 1.01 to 1.15, p=0.03).

Conclusion:

In summary, spine BMD can be erroneously influenced by osteoproliferation, unlike the TBS and TBS T-score. The limitations in spinal mobility predicted abnormal results for these two TBS parameters. The TBS may be a better indicator of bone health than BMD in AS.

Disclosure: V. Boyadzhieva, None; **M. Ivanova**, None; **N. Stoilov**, None; **R. Stoilov**, None; **R. Rashkov**, None; **D. Hans**, None; **R. Berengere**, None.

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Abstract Number: 355

The Clinical and Genetic Spectrum of Low Alkaline Phosphatase in Adults

Leyre Riancho-Zarrabeitia[1], Maria T. García-Unzueta[2], Jair A. Tenorio[3], Juan Gómez-Gerique[4], Víctor L Ruiz Pérez[3], Karen E. Heath[3], Pablo Lapunzina[3] and José A. Riancho[5], [1]Rheumatology, Hospital Universitario Marqués de Valdecilla. IDIVAL, Santander, Spain, [2]Biochemistry, Hospital Universitario Marqués de Valdecilla. IDIVAL, Santander, Spain, [3]Institute of Medical and Molecular Genetics. Hospital U. La Paz. IdiPAZ. Autonomous University of Madrid. CIBERER., Madrid, Spain, [4]Biochemistry, Hospital Universitario Marqués de Valdecilla. IDIVAL. Santander. Spain, Santander, Spain, [5]Internal Medicine, Hospital Universitario Marqués de Valdecilla. IDIVAL. University of Cantabria, Santander, Spain

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Session Time: 9:00AM-11:00AM

Background/Purpose:

Different from infantile forms, adult forms of hypophosphatasia have less severe manifestations and may go unrecognized. Low serum levels of alkaline phosphatase (ALP), the enzyme encoded by the ALPL gene, are a hallmark of hypophosphatasia. However, the clinical significance and the underlying genetics of low ALP in unselected populations are unclear.

Methods:

In order to clarify this issue, we performed a clinical and biochemical study of subjects with reduced serum ALP activity. The screening of the coding sequences and intron/exon boundaries of ALPL gene was performed by direct sequencing using the BrightDye Terminator cycle kit.

Results:

Forty two adult individuals with unexplained persistently low serum ALP were studied. There was a 3:1 female:male ratio. Age range was 20-77 yr. Although many subjects experienced minor complains, such as mild musculoskeletal pain (60%), none had major health problems. ALPL mutations were found in 21 out of 42 subjects (50%). Twenty patients carried heterozygous mutations; whereas 1 had a homozygous mutation. Eight mutations were novel and had not been previously described. Eighteen of the 21 patients with mutations (86%) had a missense mutation; in 1 case the mutation caused a splice change and there were 2 frameshift mutations. Most mutations were located in exons 5 and 6 (12 aminoacid positions were mutated in 17 patients) and were predicted to have a damaging effect on the protein

activity, both according to the structure-based Polyphen webtool (13 mutations) and the evolutionary criteria proposed by Silvent (14 mutations). The presence of a mutated allele was associated with premature tooth loss (48% versus 12%; p=0.04), slightly lower levels of serum AP (30±6 vs 25±6 u/l; p=0.002) and higher levels of enzyme substrates, such as serum pyridoxal phosphate (p<0.0001) and urine phosphoetanolamine (p<0.0001), as well as mildly increased serum phosphate (p=0.03). Ten patients had pyridoxal phosphate levels above the normal range, a test frequently used when hypophosphatasia is suspected. All carried a gene mutation; predicted to be deleterious in 9 cases and of doubtful significance in one.

Conclusion: One half of adults with persistently low levels of total alkaline phosphatase had a mutated allele of the ALPL gene. Although clinical manifestations are usually mild, in about 50% of them enzyme activity is low enough to cause substrate accumulation and may predispose to disorders of the teeth and other calcified tissues.

Disclosure: L. Riancho-Zarrabeitia, None; **M. T. García-Unzueta**, None; **J. A. Tenorio**, None; **J. Gómez-Gerique**, None; **V. L. Ruiz Pérez**, None; **K. E. Heath**, None; **P. Lapunzina**, None; **J. A. Riancho**, None.

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Abstract Number: 356

Assessment of the Effect of 12 Months Administration of Denosumab in Patients with Rheumatic Diseases

Kosuke Ebina[1], Makoto Hirao[2], Jun Hashimoto[3], Keisuke Hagihara[4], Hideki Yoshikawa[5] and Takaaki Noguchi[6], [1]Orthopaedic Surgery, Osaka University Graduate School of Medicine, Osaka, Japan, [2]Orthopaedic Surgery, Osaka University, Graduate School of Medicine, Suita, Japan, [3]Dept of Rheumatology, Osaka-Minami Medical Center, Kawachinagano City, Japan, [4]Kampo Medicine, Osaka University, Graduate School of Medicine, Suita, Japan, [5]Department of Orthopedics, Osaka University Graduate School of Medicine, Suita Osaka, Japan, [6]Orthopaedic Surgery, Osaka University, Graduate School of Medicine, Osaka, Japan

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SESSION INFORMATION

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Session Title: Osteoporosis and Metabolic Bone Disease - Clinical Aspects and Pathogenesis Poster

Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose:

In patients with rheumatic diseases (RD), pro-inflammatory cytokines induce receptor activator of nuclear factor kappa-B ligand (RANKL), which plays a crucial role in inducing osteoclasts differentiation and consequent osteoporosis and bone erosion. Glucocorticoid (GC) is often used to treat RD, while strongly inhibits bone formation and increases fracture risk. Denosumab (DMAb) is an anti-RANKL antibody which strongly inhibits bone resorption, while its effect in RD (especially in GC-induced osteoporosis) remains unknown.

Methods:

DMAb was introduced in 181 RD patients (160 female, 61.6 years old, 127 RA, 31 SLE, 5 dermatomyositis, 4 sarcoidosis, 14 other diseases, 77.2% taking prednisolone (PSL) with average dose 4.3mg/day, 21.4% taking biologics, lumbar spine (LS) T-score -1.7, femoral neck (FN) T-score -2.2, total hip (TH) T-score -1.9, prior treatment; bisphosphonate (BP) 63.4%, teriparatide (TPTD) 18.6%, naïve 16.6%) and followed up for 12 months by

monitoring bone mineral density (BMD) and bone turnover markers.

Results:

Baseline FN T-score showed negative correlation with baseline serum CRP levels (r=-0.24, P<0.01) and bone resorption marker Isoform 5b of tartrate-resistant acid phosphatase (TRACP-5b; r=-0.44, P<0.001）, suggesting high inflammation levels and increased bone resorption is associated with low bone mass in RD patients. BMD increase from baseline→6→12 months was as follows. LS; 0→2.8→4.7%, TH; 0→1.5→2.9%, FN; 0→1.7→2.7%. There was no significant difference in BMD increase between the difference of prior osteoporosis treatment (BP, TPTD, and naïve) or the presence or absence of combined oral GC [without PSL (n=41); LS 0→3.2→4.4%; FN 0→2.2→2.5%, with PSL (5.6mg/day; n=140); LS 0→2.9→4.8%; FN 0→1.7→2.9%] or the dose of combined PSL [PSL<5mg/day (n=108); LS 0→3.4→4.9%; FN 0→2.3→2.9%, with PSL≧5mg/day (n=73); LS 0→2.3→4.6%; FN 0→1.2→2.4%]. In addition, there was no significant difference in baseline levels of bone turnover markers, which converged to constant levels regardless of the presence or absence of combined oral GC [TRACP-5b; without PSL; 267→238→126 mU/dl, with PSL; 298→151→113 mU/dl] . On the other hand, patients with high dose of combined oral GC (PSL≧5mg/day; n=73), compared to low dose users (PSL<5mg/day; n=108), was associated with lower TRACP-5b (94 vs 133 mU/dl; P<0.01) and undercarboxylated osteocalcin (ucOC; 0.9 vs 1.5 ng/ml; P<0.05) levels, but not with bone formation marker Type I collagen N-terminal propeptide (P1NP; 18.2 vs 18.2 ug/l) at 12 months. BMD increase (%) of LS at 12 months was positively correlated with baseline value of bone turnover markers〔TRACP-5b（r=0.34, P<0.001）, ucOC（r=0.29, P<0.01）〕and their decreasing rate at 6 months [TRACP-5b（r=0.31, P<0.01）, ucOC（r=0.30, P<0.01）].

Conclusion:

Our findings indicate that DMAb increased BMD regardless of prior osteoporosis treatment and combined oral GC dose. High dose of combined oral GC (PSL≧5mg/day) significantly decreased serum TRACP-5b and ucOC levels, while sustained serum P1NP levels compared to that of low dose GC users (PSL<5mg/day). Sustained bone formation and greater bone resorption inhibition induced by DMAb in high dose GC users may contribute to sustained BMD increase.

Disclosure: K. Ebina, None; **M. Hirao**, None; **J. Hashimoto**, None; **K. Hagihara**, None; **H. Yoshikawa**, None; **T. Noguchi**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/assessment-of-the-effect-of-12-months-administration-of-denosumab-in-patients-with-rheumatic-diseases

Abstract Number: 357

Human Parathyroid Hormone for Preventing and Treating Glucocorticoid-Induced Osteoporosis: Cochrane Systematic Review and Meta-Analysis

Akira Onishi[1], Akira Sato[2], Masahiro Iwasaku[2] and Toshi Furukawa[2], [1]Department for Rheumatology, Kobe University Hospital, Kobe, Japan, [2]Kyoto University Graduate School of Medicine / School of Public Health, Kyoto, Japan

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Background/Purpose: Although glucocorticoid-induced osteoporosis is the most common cause of secondary osteoporosis, providing effective treatment remains a challenge. Bisphosphonates are currently recommended for treatment and prevention of glucocorticoid-induced osteoporosis in several international guidelines. However, some people cannot tolerate any of the available bisphosphonate therapy because of their adverse effects. Moreover, bone resorption is inhibited with bisphosphonates, while the primary action of glucocorticoids is to decrease bone formation. On the other hand, human parathyroid hormone (hPTH) stimulates bone formation. As a result, hPTH may have significant advantages for treatment and prevention of glucocorticoid-induced osteoporosis. To the best of our knowledge, this topic has not yet been systematically reviewed. We therefore examine the benefit and harm of hPTH in the prevention and treatment of glucocorticoid-induced osteoporosis.

Methods: We searched three different databases (Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE and EMBASE) as well as reference lists of retrieved studies and review articles published between January 1966 and October 2014. All relevant randomized controlled trials that assess the efficacy of hPTH for the prevention or treatment of glucocorticoid-induced osteoporosis were included. All papers meeting strict inclusion criteria were scrutinized for data on population size, participants characteristics, vertebral fracture, non-vertebral fractures, bone mineral density (BMD) at the lumber spine, withdrawals due to adverse events, serious adverse events.

Results: A total of 1,784 articles were initially identified and 414 of these articles were duplicates and therefore excluded. After the initial screening, 20 full-length articles were selected for detailed analysis on the basis of title or abstract. Eventually, four studies (17 articles) met all the inclusion criteria. Two studies compared hPTH with bisphosphonate while the other studies assessed the efficacy of hPTH comparing with placebo or no treatment. A total of 595 patients were covered by these studies, with women accounting for a median of 52.7 percent and the median of the mean age was 56.7 years. We could not pool data on the vertebral fracture or non-vertebral fracture because there were no fractures in one study that compared hPTH with bisphosphonate, while the other showed fewer vertebral fractures in hPTH than in bisphosphonate (P =0.004) whereas the incidence of non-vertebral fractures was similar (P = 0.36). Patients in hPTH had an greater increase in change from baseline in BMD at lumber spine than patients in bisphosphonate (pooled percentage change: 3.77: 95% confidence interval: 1.99-5.56).The pooled analysis showed fewer withdrawals due to adverse events in hPTH than bisphosphonate (odds ratio (OR): 0.45, 95% confidence interval: 0.24-0.86) while that for serious adverse events was similar (OR: 0.80, 95% confidence interval: 0.32-2.00).

Conclusion: hPTH seems to be more effective than bisphosphonate.

Disclosure: A. Onishi, None; **A. Sato**, None; **M. Iwasaku**, None; **T. Furukawa**, None.

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Abstract Number: 358

Bone Microstructure Assessed By Hrpqct in Subjects with Hyperuricemia without Arthritis

Roland Kocijan[1], Arastoo Nia[1], Christian Muschitz[2], David Simon[3], Corinna Geiger[1], Judith Haschka[4], Arnd Kleyer[3], Sara Bayat[5], Juergen Rech[5], Annemarie Kocijan[6], Larissa Dzirlo[7], Monika Graninger[7] and Heinrich Resch[1], [1]Medical Department II, Karl Landsteiner Society for Gastroenterology and Rheumatology, St. Vincent Hospital, Vienna, Austria, [2]Medical Department II, St. Vincent Hospital, Vienna, Austria, [3]Department of Internal Medicine 3, University of Erlangen-Nuremberg, Erlangen, Germany, [4]Internal Medicine 3, Rheumatology and Immunology, University of Erlangen-Nuremberg, Erlangen, Germany, [5]Department of Internal Medicine 3, Rheumatology & Immunology, University of Erlangen-Nuremberg, Erlangen, Germany, [6]Optimal Essen e.U., Vienna, Austria, [7]Medical Department III, St. Vincent Hospital, Vienna, Austria

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Background/Purpose:

Gouty arthritis is a common inflammatory joint disorder and hyperuricemia (HU) is known to be the main risk factor. Beside clinical signs of inflammation such as pain and swelling, gout is associated with local bone loss. Higher serum uric acid concentrations correspond with higher bone mineral density (BMD), a lower prevalence of non-vertebral fractures and a lower bone turnover. Other inflammatory joint disorders such as rheumatoid arthritis (RA) and psoriatic arthritis (PsA) are associated with low BMD, altered bone microstructure and consequently secondary osteoporosis. To date there is no information about the influence of HU on bone microstructure. The objectives were to investigate trabecular and cortical bone microstructure, volumetric BMD (vBMD), bone turnover markers in female and male subjects with HU without signs and symptoms of arthritis and respective controls with low serum uric acid.

Methods:

Otherwise healthy male and female subjects with HU (uric acid>7.5 mg/dl) and respective controls with low serum uric acid (CO, uric acid<6.0 mg/dl) were included. Patients with known gouty arthritis, inflammatory disorders, osteoporosis, liver or kidney diseases were excluded.

Microstructure and vBMD were assessed by HR-pQCT (XtremeCT, SCANCO Medical, Brüttisellen, Switzerland) at the ultra-distal radius (standard non weight bearing bone site) in all subjects.

Total vBMD (Tot.BMD, mgHA/cm^3), trabecular vBMD (Trab.BMD, mgHA/cm^3) and cortical vBMD (Ct.BMD, mgHA/cm^3) were evaluated. Microstructure analyses included the trabecular bone volume fraction (BV/TV), trabecular number (Tb.N, 1/mm), inhomogeneity of the trabecular network (Tb.1/N.SD, mm), trabecular thickness (Tb.Th, mm) and cortical thickness (Ct.Th, mm). Bone turnover markers including Cross Laps (CTX), reflecting osteoclast activity, Procollagen type 1 Amino-terminal Propeptide (P1NP), reflecting osteoblast activity, intact parathyroid hormone (iPTH), 25-hydroxyvitaminD(25-OH vitamin D), calcium and phosphate were measured.

Results:

29 subjects with HU (57.4±10.1 years) and 15 CO (57.7±11.3) were analyzed. Serum uric acid was 8.9±1.4 mg/dl in HU and 4.4±1.0 mg/dl in CO. Body Mass Index (BMI, 30.0±6.4 vs. 26.9±6.1) was non-significantly different between HU and CO.

Similar results were found for Tot.BMD (p=0.590) and Ct.BMD (p=0.566). Trab.BMD differed by trend in HU (p=0.068) but not BV/TV (p=0.201), Tb.N, (p=0.071), inhomogeneity of trabecular network (p=0.227), Tb.Th (p=0.614) as well as Ct.Th (p=0.271).

Vitamin D levels, CTX, P1NP, calcium or phosphate were similar and within normal range in the two groups. iPTH levels were higher by trend in HU when compared to CO (p=0.053).

Conclusion:

Our results suggest similar volumetric bone mineral density and bone microstructure in subjects with HU and subjects with low serum uric acid levels. Despite the well-known negative effects of uric acid on local bone loss, HU does not seem to be a predictive factor for systemic bone loss. This is in contrast to other inflammatory joint diseases such as RA and PsA where systemic bone loss and changes in microarchitecture start before the onset of clinical disease.

Disclosure: R. Kocijan, None; **A. Nia**, None; **C. Muschitz**, None; **D. Simon**, None; **C. Geiger**, None; **J. Haschka**,

None; **A. Kleyer**, None; **S. Bayat**, None; **J. Rech**, None; **A. Kocijan**, None; **L. Dzirlo**, None; **M. Graninger**, None; **H. Resch**, None.

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Abstract Number: 359

Diminished Health-Related Quality of Life As Measured By the Short Form-10 in Children with Hypophosphatasia

Thomas J. Weber[1], Eileen K. Sawyer[2], Scott Moseley[2] and Priya S. Kishnani[1], [1]Duke University Medical Center, Durham, NC, [2]Alexion Pharmaceuticals, Cheshire, CT

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Background/Purpose: Hypophosphatasia is a rare metabolic disease caused by loss-of-function mutation(s) in the gene encoding the tissue non-specific alkaline phosphatase (ALP). In children, low tissue non-specific ALP activity leads to deficient skeletal mineralization and complications that may include poor growth, proximal muscle weakness, pain, and compromised physical function. The impact of these symptoms on health-related quality of life is not known.

Methods: The Short Form-10 (a short version of the Child Health Questionnaire) was administered as part of the internet-based Hypophosphatasia Impact Patient Survey (HIPS) developed to characterize the burden of disease in patients with hypophosphatasia. Outreach from 2009-2011 by patient advocacy groups provided awareness of the survey to patients or caregivers and invited participation. Summary statistics were calculated for the norm-based Physical Health and Psychosocial Summary scores (healthy population mean=50, standard deviation [SD]=10) and for each individual question.

Results: Forty-four children (50% male, 80% via caregiver respondents) participated in the Hypophosphatasia Impact Patient Survey, of which 39 completed the Short Form-10. Mean (SD) age at the time of the survey was 6.8 (4.8) years; age at onset of hypophosphatasia symptoms was 0.9 (1.0) years. The majority of children reported pain (82%, 38/44), including in the joints (61%, 27/44) and bones (52%, 23/44), and muscle weakness (66%, 29/44). Thirty-six percent (16/44) reported fractures. The mean Physical Health score (23.7, 95% confidence interval [CI]: 17.2-30.3, n=39) was >2 SD below normal. The mean Psychosocial Summary score (45.6, 95% CI: 41.9-49.3, n=39) revealed a small decrease relative to population norms. The majority of children reported limitations in high energy activities such as riding a bike or skating (79%, 31/39); basic activities such as bending, lifting, and stooping (64%, 25/39); and school work or activities with friends (62%, 24/39) due to physical health problems. Eighty-two percent (32/39) reported experiencing pain in the past 4 weeks. Behavioral and emotional problems limited school or social activities in 33% (13/39) of children, and behavior was rated by the respondent as “Good” or higher for 90% (35/39) of the children.

Conclusion: As reported by caregivers/patients and consistent with the reported burden of symptoms, hypophosphatasia has a high physical impact on children which reduces their ability to keep up with peers and participate in normal childhood activities, including both high energy and daily living activities, substantially diminishing health-related quality of life. The lower impact of hypophosphatasia on psychosocial health reported herein may reflect higher resilience to disease in children compared with adults, or the influence of parental report. An understanding of the impact of hypophosphatasia on health-related quality of life is important for evaluating future treatment options. Further

studies are needed to characterize health-related quality of life longitudinally in these patients.

Disclosure: T. J. Weber, Alexion Pharmaceuticals, Inc., 5; **E. K. Sawyer**, Alexion Pharmaceuticals, Inc., 3; **S. Moseley**, Alexion Pharmaceuticals, Inc., 3; **P. S. Kishnani**, Alexion Pharmaceuticals, Inc., 5,Alexion Pharmaceuticals, Inc., 6.

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Abstract Number: 360

Massive Elimination of Multinucleated Osteoclasts By Eupatilin Is Due to Dual Inhibition of Transcription and Cytoskeletal Rearrangement

Myeung Su Lee[1], Ju-Young Kim[2], Chang-Hoon Lee[3], Wan-Hee Yoo[4], Won Seok Lee[4], Myong-Joo Hong[5] and Jaemin Oh[2], [1]Internal Medicine, School of Medicine, Wonkwang University, Iksan, Chonbuk, South Korea, [2]Anatomy, Wonkwang University, Iksan, South Korea, [3]Rheumatology, Department of Internal Medicine, School of medicine, Wonkwang university, Iksan, Chonbuk, South Korea, [4]Rheumatology, Department of Internal Medicine, Chonbuk National University Medical School and Research Institute of Clinical Medicine, Jeonju, South Korea, [5]Internal Medicine, Presbyterian Medical center, Jeonju, South Korea

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Background/Purpose: Osteoporosis is an ageing-associated diseases requiring better therapeutic modality. Eupatilin is a major flavonoid from Artemisia. We aimed to evaluate the effects of eupatilin on RANKL-induced osteoclast differentiation and its mechanism of action.

Methods: ICR mice were divided into 4 groups: saline-treated (Control), only LPS-treated, only eupatilin-treated, and LPS and eupatilin-treated groups. Eupatilin or PBS was administered orally 1 day before LPS injection. Eupatilin or PBS was administered orally every other day for 8 days. LPS was injected intraperitoneally on days 1 and 4. The mice were sacrificed after 8 days, and the left femurs were analyzed by high-resolution micro-computed tomography. To confirm the therapeutic effect of eupatilin on LPS-induced bone loss in vivo, ICR mice were divided into 6 groups : PBS-treated, LPS-treated, and LPS plus eupatilin-treated groups. Eupatilin or PBS was administered orally every day from 4, 6, or 8 days. LPS was injected intraperitoneally on days 1 and 4. Mice were sacrificed after 10 days, and the left femurs were analyzed by high-resolution micro-CT. We further assessed the effect of eupatilin on OVX-induced bone loss. Eight-week-old female C57BL/6 mice were either 6 sham-operated mice or 12 OVX mice. OVX mice were divided into two groups: OVX controland eupatilin groups. After, eupatilin was administrated orally for 4 weeks. Femur metaphysic regions were scanned using a high-resolution micro-CT.

Results: Upon stimulation prior to RANKL treatment or poststimulation of BMCs in the presence of RANKL with eupatilin complete blockade of RANK-dependent osteoclastogenesis was accomplished. This blockade was accompanied by inhibition of rapid phosphorylation of *Akt, GSK3b*, *ERK* and *IkB* as well as downregulation of c-Fos and NFATc1 at protein levels, suggesting that transcriptional suppression is a key acting mechanism on the anti-osteoclastogenesis. Transient reporter assays or gain of function assays confirmed that eupatilin was, indeed, a potent transcriptional inhibitor in osteoclasts (OC). Surprisingly, when multinucleated osteoclasts (MNCs) were cultured on

bone scaffolds in the presence of eupatilin bone resorption activity was also completely blocked by dismantling actin ring, suggesting that another major acting site of eupatilin is cytoskeletal rearrangement. The eupatilin-treated MNCs revealed a shrunk cytoplasm and accumulation of multi-nuclei, eventually becoming fibroblast-like cells. No apoptosis occurred. Inhibition of phosphorylation of *cofilin* by eupatilin suggests that actin may play an important role in the catastrophic morphological change of MNCs. Human OC were similarly responded to eupatilin. When eupatilin was administered to LPS-induced osteoporotic mice after manifestation of osteoporosis, it was capable of preventing bone loss. The ovariectomized (OVX) mice remarkably exhibited bone protection effects.

Conclusion: Taken together, eupatilin is an effective versatile therapeutic intervention for osteoporosis as dual blockaders; 1) transcriptional suppression of c-Fos and NFATc1 of differentiating OC and 2) inhibition of actin rearrangement of pathogenic MNCs.

Disclosure: M. S. Lee, None; **J. Y. Kim**, None; **C. H. Lee**, None; **W. H. Yoo**, None; **W. S. Lee**, None; **M. J. Hong**, None; **J. Oh**, None.

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Abstract Number: 361

Sodium Intake and Osteoporosis. Findings from the Women's Health Initiative

Laura Carbone[1], Karen Johnson[2], Ying Huang[3], Mary Pettinger[4], Thomas Fridtjof[5], Jane A. Cauley[6], Carolyn Crandall[7], Lesley Tinker[8], Meryl LeBoff[9], Jean Wactawksi-Wende[10], **Monique Bethel**[11], Wenjun Li[12] and Ross Prentice[3], [1]Rheumatology, Georgia Regents University, Augusta, GA, [2]Preventive Medicine, University of Tennessee Health Science Center, Memphis, TN, [3]Biostatistics, University of Washington, Seattle, WA, [4]Fred Hutcinson Cancer Research Center, Seattle, WA, [5]University of Tennessee Health Science Center, Memphis, TN, [6]Department of Epidemiology, Univ of Pittsburgh, Pittsburgh, PA, [7]Medicine, University of California Los Angeles, Los Angeles, CA, [8]Fred Hutchinson Cancer Research Center, Seattle, WA, [9]Brigham and Women's Hospital, Boston, MA, [10]University of Buffalo, Buffalo, NY, [11]Internal Medicine, Georgia Regents University, Augusta, GA, [12]Medicine, Division of Preventive Medicine, University of Massachusetts Medical School, Worcester, MA

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Background/Purpose: The relationship of sodium intake to bone mineral density (BMD) in postmenopausal women has not been established, and no study to date has examined its relationship with fracture risk. The purpose of this study was to examine whether sodium intake is associated with changes in BMD at the lumbar spine, total hip, femoral neck and total body and with incident fractures and whether this relationship is modified by potassium and/or calcium intake among women in the Women's Health Initiative (WHI).

Methods: Data from 69,735 postmenopausal women in the WHI were included in this report. Linear regression models and Cox proportional hazard models were used to estimate the relationships between calibrated sodium intake, changes in BMD, and incident fractures that occurred during WHI follow-up, and to ascertain whether calibrated potassium or calcium intake modified these relationships. Models were adjusted for demographics, clinical factors and

medication use.

Results: The median calibrated sodium intake was 2891.6 mg/day (range: 1234.5-7574.9mg/day). There was no association between whether or not sodium intake was above the median and changes in BMD at the total hip, femoral neck or lumbar spine from baseline to three ($p>0.24$) or six years ($p>0.16$) or with all fractures, osteoporotic fracture sites other than the spine and hip (other fractures) and spine fractures ($p> 0.13$). Sodium intakes above the median were associated with significant increases in BMD at the total body from baseline to three years ($p=0.02$), though changes from baseline to six years were not significant ($p=0.36$). Sodium intake above the median was also associated with fewer hip fractures ($p=0.03$). Levels of sodium intake above or below currently recommended guidelines for cardiovascular disease (2300 mg /day) were not associated with changes in BMD at any skeletal site from baseline to three ($p> 0.66$) or six years ($p> 0.74$) or with incident fractures ($p\geq0.70$). There was no association of sodium intake with incident fractures after adjusting for potassium intake ($p\geq0.30$). Calcium intake did not modify the association between sodium intake and changes in BMD or risk of incident fracture ($p\geq0.20$).

Conclusion: Adherence to current population-based recommended intakes for sodium intake is unlikely to significantly impact osteoporosis. The surprising association of higher sodium intakes with fewer hip fractures merits further study.

Disclosure: L. Carbone, None; **K. Johnson**, None; **Y. Huang**, None; **M. Pettinger**, None; **T. Fridtjof**, None; **J. A. Cauley**, None; **C. Crandall**, None; **L. Tinker**, None; **M. LeBoff**, None; **J. Wactawksi-Wende**, None; **M. Bethel**, None; **W. Li**, None; **R. Prentice**, None.

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Abstract Number: 362

Reference Curves of Bone Parameters Obtained By High Resolution Peripheral Quantitative Computed Tomography (HR-pQCT) in Healthy Women from 20 to 85 Years Old

Jackeline Couto Alvarenga[1], Henrique Fuller[2], Sandra G. Pasoto[2], Stephanie Boutroy[3] and Rosa M R Pereira[4], [1]Division of Rheumatology, Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil, [2]Rheumatology Division, Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil, [3]INSERM U831 and Université de Lyon, Lyon, France, [4]Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil

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Background/Purpose: Bone is a dynamic tissue, and its formation and resorption are continuous processes that promote changes throughout the life of the organism, and changes in bone microstructure contribute to fracture risk. High-Resolution peripheral Quantitative Computed Tomography (HR-pQCT) can assess microstructural and biomechanical properties of human distal end. Faced with so multitude of applications and perspectives of HR-pQCT, it is necessary to establish normal standard curves. The aim of this cross-sectional study is to establish normal values related to age, weight and height using HR-pQCT regarding volumetric bone mineral density (vBMD), microstructure, cortical porosity and estimated bone strength at the distal radius and tibia from a women population aged 20 to 85 years.

Methods: References curves were calculated in 450 healthy women (> 50 women per decade). The HR-pQCT acquisitions (XtremeCT, Scanco Medical) were performed using the standard scanning protocol. Statistical analysis including linear regression models were developed to predict the values of the twenty normal curves measured according to age, weight and height. The outcome variables used in our analyses included the following: **Volumetric bone density parameters** (mg HA/ccm): trabecular bone density (Tb.vBMD), cortical bone density (Ct.vBMD); **Bone structure parameters:** number of trabeculae (Tb.N, 1/mm), trabecular thickness (Tb.Th, mm), trabecular separation (Tb.Sp, mm), cortical thickness (Ct.Th, mm); **Cortical porosity parameters:** cortical porosity (Ct.Po, 1), mean cortical pore diameter (Ct.Po.Dm, mm); **Finite element analysis (FEA):** stiffness (S, kN/mm), estimated failure load (F.Load, N).

Results: Evaluation of the distal radius by HR-pQCT: All parameters showed linear curves with age, except for Ct.Po, S and F.Load. Positive correlations were observed between stiffnewomenss and Tb.vBMD (r: 0.644, $p < 0.001$), Ct.vBMD (r: 0.521, $p < 0.001$), Tb.N (r: 0.245, $p < 0.001$), Tb.Th (r: 0.616, $p < 0.001$), Ct.Th (r: 0.619, $p < 0.001$), Ct.Po.Dm (r: 0.140, $p < 0.001$) and F.Load (r: 0.995, $p < 0.001$). In contrast, weak negative correlations were detected between S and Tb.Sp (r: -0.312, $p < 0.001$) and Ct.Po (r: -0.162, $p= 0.015$). **Evaluation of the tibia by HR-pQCT:** All obtained curves were linear, except for Ct.vBMD, Ct.Th and Ct.Po. The cortical density and thickness showed a plateau until about 50 years of age, following by a decreasing curve. Positive correlations were observed between stiffness and Tb.vBMD (r: 0.571, $p < 0.001$), Ct.vBMD (r: 0.316, $p < 0.001$), Tb.N (r: 0.298, $p < 0.001$), Tb.Th (0.355, $p < 0.001$), Ct.Th (r: 0.392, $p < 0.001$) and F.Load (r: 0.955, $p < 0.001$). Moreover, negative correlations were found between S and Tb.Sp (r: -0.354, $p < 0.001$) and Ct.Po (r: -0.273, $p < 0.001$).

Conclusion: This study established a set of reference data for HR-pQCT parameters in a heathy women population, which will be useful for interpreting clinical data from patients in clinical practice and in future studies.

Disclosure: J. C. Alvarenga, None; **H. Fuller**, None; **S. G. Pasoto**, None; **S. Boutroy**, None; **R. M. R. Pereira**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/reference-curves-of-bone-parameters-obtained-by-high-resolution-peripheral-quantitative-computed-tomography-hr-pqct-in-healthy-women-from-20-to-85-years-old

Abstract Number: 363

Determination of the Osteoporotic Vertebral Fractures By a New Quantitative Approach: Intervertebral Volume Index

Omer Kuru[1], Yasemin Ulus[2], Halil Sen[2], Bunyamin Sahin[3] and Ayhan Bilgici[2], [1]Physical Medicine And Rehabilitation Division of Rheumatology, Ondokuz Mayis University School of Medicine, Samsun, Turkey, [2]Physical Medicine and Rehabilitation Division of Rheumatology, Ondokuz Mayis University School of Medicine, Samsun, Turkey, [3]Anatomy, Ondokuz Mayis University School of Medicine, Samsun, Turkey

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Session Date: Sunday, November 8, 2015

Session Title: Osteoporosis and Metabolic Bone Disease - Clinical Aspects and Pathogenesis Poster

Session Type: ACR Poster Session A

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Background/Purpose: Vertebral fractures caused by osteoporosis are quite common and have a negative effect on quality of the life. But they may not be clinically detectable. Computed tomography (CT) is an appropriate method in examining and evaluating the vertebral fractures because it shows bone details accurately, clearly and quickly.

Stereology is a science which is used to obtain quantitative data about the structure using two-dimensional section from the three dimensional structures. In this study, we aimed to describe a new method that demonstrates objectively the decrease percentage of the volume of the fractured vertebral body according to the average volume of the neighboring vertebrae using the volume intervertebral volume index (IVF).

Methods: Forty women, who admitted to the Ondokuz Mayis University, Department of Physical Medicine and Rehabilitation and who were diagnosed with osteoporosis by bone mineral density (BMD) and osteoporotic vertebral compression fracture by routine thoracolumbar radiographs, were included in the study. CT images of the patients were taken with 3 mm thickness in axial plane were converted to the sagittal orientation. Vertebrae volumes were calculated using the Cavalieri principle, which is one of the stereological methods in ImageJ software. Reduction in the volume of the fractured vertebra was calculated as percentages based on above and below vertebral volumes.

Results: It was determined that the measured volume of the fractured vertebra at each fracture level decreased by 67.70% compared to the expected vertebral volume that was calculated according to volumes of the above and below vertebrae of the fractured vertebra. In all patients, significant differences were determined between the average detected volume and the expected volume of the fractured vertebrae ($p < 0.001$).

Conclusion: In this study, the method that we used may be cheap, safe and quick way for determining osteoporotic vertebral fracture volume as unbiased and the most accurate. This method, which allows obtaining objective data in the detection of vertebral fracture, does not require an additional procedure or equipment because of it is obtained from CT images which is routinely used in all radiology centers. Therefore, it can be suggested that this method may be used routinely.

Disclosure: O. Kuru, None; **Y. Ulus**, None; **H. Sen**, None; **B. Sahin**, None; **A. Bilgici**, None.

Abstract Number: 364

Very High Frequency of Fragility Fractures Associated with High-Dose Glucocorticoids in Postmenopausal Women: A Retrospective Study

Goichi Kageyama[1], Takaichi Okano[1], Yuzuru Yamamoto[1], Keisuke Nishimura[1], Daisuke Sugiyama[2], Jun Saegusa[1], Goh Tsuji[3], Shunichi Kumagai[4] and Akio Morinobu[1], [1]Department of Rheumatology, Kobe University Hospital, Kobe, Japan, [2]Department of Preventive Medicine and Public Health, Keio University, Tokyo, Japan, [3]The Center for Rheumatic Diseases, Shinko Hospital, Kobe, Japan, [4]The Center of Rheumatic Diseases, Shinko Hospital, Kobe, Japan
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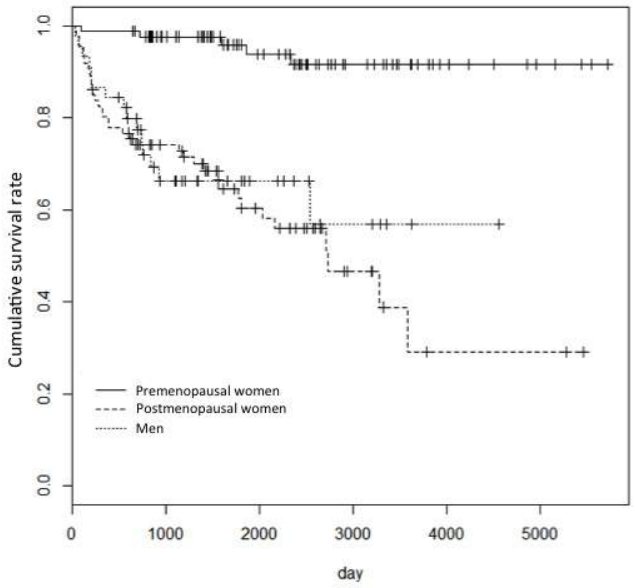
Background/Purpose: To evaluate the incidence of fragility fractures associated with high-dose glucocorticoid therapy in patients with systemic rheumatic disease.

Methods: A retrospective study of patients who were treated with high-dose prednisolone (more than 0.8 mg/kg) for systemic rheumatic disease at Kobe University Hospital from April 1988 to March 2012. The primary outcome was a major osteoporotic fracture (defined as a clinical vertebral, hip, forearm, or proximal humerus fracture) after high-dose

glucocorticoid therapy. For postmenopausal women and men over 40 of age, the patient's fracture risk at the beginning of high-dose glucocorticoid therapy was assessed by the World Health Organization's Fracture Risk Assessment Tool (FRAX).

Results: Of 229 patients (median age: 49 years), 57 suffered a fragility fracture during the observation period (median observation period: 1558 days). Of 84 premenopausal patients, 5 suffered a fracture. In contrast, of 86 postmenopausal female, 36 suffered a fracture. Fragility fractures were far more frequent than predicted by the FRAX score. Bisphosphonate use did not reduce the risk of fragility fractures. Patients with FRAX scores over 8.3% had a particularly high risk of fracture.

Conclusion: Fragility fractures associated with high-dose glucocorticoid therapy are common among postmenopausal women. Bisphosphonate does not prevent fragility fractures in patients undergoing high-dose glucocorticoid therapy. Alternative drugs should be considered as a first-line prophylactic measure.



	FRAX 10-year probability of osteoporotic fractures	Mean FRAX (%)	Number of patients	Fractures	Fracture rate (%)	Median observation period (year)
Total (n=131)	0%- <5.3%	3.6	33	6	18.2	1.4
	5.3%-<9%	7.0	32	12	37.5	2.0
	9%-<15%	11.7	30	13	43.3	2.1
	>=15%	26.7	36	20	55.6	0.8
Postmenopausal women (n=86)	0%- <6.3%	4.1	22	5	22.7	3.2
	6.3%-<12%	8.7	19	8	42.1	3.9
	12%-<22%	15.2	23	12	52.2	0.7
	>=22%	32.9	22	11	50.0	0.7
Men over 40 years of age (n=45)	0%- <4.5%	3.2	12	2	16.7	1.4
	4.5%-<6.6%	5.5	10	3	30.0	0.3
	6.6%-<9.2%	7.7	11	4	36.4	1.5
	>=9.2%	12.3	12	6	50.0	1.6

	Total (n=131)		Postmenopausal Women (n=86)		Men over 40 years of age (n=45)	
	Adjusted hazard ratio	95% CI	Adjusted hazard ratio	95% CI	Adjusted hazard ratio	95% CI
FRAX (continuous, log-transformed)	2.26	1.52-3.38	2.41	1.45-3.99	3.21	1.03-9.98
Bisphosphonate comparison subjects	1	(reference)	1	(reference)	1	(reference)
Bisphosphonate treatment group	0.84	0.45-1.54	0.67	0.31-1.44	1.21	0.41- 3.54
Active Vitamin D comparison subjects	1	(reference)	1	(reference)	1	(reference)
Active Vitamin D treatment group	0.82	0.47-1.43	0.72	0.36-1.44	1.27	0.40-3.87
No mPSL Pulse treatment	1	(reference)	1	(reference)	1	(reference)
mPSL Pulse treatment group	1.14	0.61-2.13	1.68	0.79-3.61	0.4604	0.13-1.69
No prior high-dose GC treatment	1	(reference)	1	(reference)	1	(reference)
Prior high-dose GC treatment	2.49	1.18-5.28	1.24	0.43-3.60	3.46	1.12 -10.73

Disclosure: G. Kageyama, None; **T. Okano**, None; **Y. Yamamoto**, None; **K. Nishimura**, None; **D. Sugiyama**, None; **J. Saegusa**, None; **G. Tsuji**, None; **S. Kumagai**, None; **A. Morinobu**, None.

Abstract Number: 365

Can We Use Bone Turnover Markers As Targets for Antiresorptive Treatment in Postmenopausal Osteoporosis? an Analysis from Two Phase 3 Clinical Trials

JP Brown[1], P Dakin[2], P Hadji[3], MR McClung[4], PD Miller[5], J-Y Reginster[6], RB Wagman[2], A Wang[2] and E McCloskey[7], [1]Laval University and CHU de Québec (CHUL) Research Centre, Quebec City, QC, Canada, [2]Amgen Inc., Thousand Oaks, CA, [3]Philipps-University of Marburg, Marburg, Germany, [4]Oregon Osteoporosis Center, Portland, OR, [5]Colorado Center for Bone Research, Lakewood, CO, [6]University of Liège, Liège, Belgium, [7]University of Sheffield, Sheffield, United Kingdom

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Background/Purpose: Bone turnover markers (BTMs) respond faster than bone mineral density as an indicator of response to therapy in osteoporotic patients; however, it remains unclear when and how best to evaluate treatment

response using BTMs. Denosumab (DMAb) has a dynamic BTM profile over the 6-month dosing period (ie, reduction in turnover with release of inhibition at the end of the dosing interval). This analysis assessed the use of potential target values for serum C-telopeptide of type 1 collagen (CTX) and serum procollagen type 1 N-terminal propeptide (P1NP) to explore guidance to clinicians for monitoring postmenopausal women with osteoporosis (PMO) during treatment.

Methods: BTMs measured at baseline in treatment-naïve PMO entering FREEDOM, a large randomized, placebo-controlled study of DMAb (Cummings et al *NEJM* 2009), were used to derive threshold values at the 5th percentiles of the observed distributions. The relevant values for serum CTX (N = 7594) and P1NP (N = 1023) were 0.2 ng/mL and 25.8 ng/mL, respectively. These BTM target values were applied to the study populations of DECIDE (Brown et al *JBMR* 2009) and STAND (Kendler et al *JBMR* 2010) enabling evaluation of a population-based assessment of BTM target values. DECIDE (N = 1189) and STAND (N = 504) were phase 3, randomized, double-blind, double-dummy studies to compare the efficacy and safety of DMAb (60 mg subcutaneously every 6 months) with alendronate (ALN; 70 mg weekly oral tablet) in treatment-naïve PMO or PMO already receiving ALN, respectively. The percentage of subjects in each treatment group with BTMs below the predefined target values was evaluated midcycle at month 3 after the 1st dose of DMAb, which also enabled trough values for ALN, and then re-evaluated at month 9. Subjects with BTM values below the predefined targets at baseline were excluded from the analysis.

Results: A total of 1112 (93.5%) women in DECIDE and 155 (30.8%) women in STAND had CTX values ≥ 0.2 ng/mL and P1NP values ≥ 25.8 ng/mL at baseline. Table 1 reports the percentage of subjects with CTX and P1NP values below the respective targets at months 3 and 9. The predefined target values were almost universally achieved at 3 and 9 months on DMAb, whereas the target for CTX, for example, on ALN was only achieved in 49.1% and 19.0% of treatment-naïve and ALN-pretreated PMO, respectively, at month 3.

Conclusion: In this population-based analysis, in both treatment-naïve and pretreated PMO, BTMs have utility in determining response, and awareness of failure to reach a treatment target may help improve clinical management.

Table 1 Percentage of Subjects With CTX < 0.2 ng/mL or P1NP < 25.8 ng/mL at Follow-up

		CTX < 0.2 ng/mL		P1NP < 25.8 ng/mL	
		Alendronate (N = 544)	Denosumab (N = 568)	Alendronate (N = 544)	Denosumab (N = 568)
DECIDE	Month 3	49.1	95.1*	65.6	98.0*
	Month 9	66.5	96.4*	80.7	97.0*
		CTX < 0.2 ng/mL		P1NP < 25.8 ng/mL	
		Alendronate (N = 83)	Denosumab (N = 72)	Alendronate (N = 83)	Denosumab (N = 72)
STAND	Month 3	19.0	97.1*	41.0	98.5*
	Month 9	15.6	100.0*	52.0	100.0*

N = total number of subjects with baseline CTX ≥ 0.2 ng/mL and P1NP ≥ 25.8 ng/mL.
CTX, serum C-telopeptide of type 1 collagen; *P1NP*, serum procollagen type 1 N-terminal propeptide. *$P < 0.0001$; Pearson's chi-square test for between-group comparisons.

Disclosure: J. Brown, Abbvie, Amgen, Eli Lilly, Novartis, Takeda, 2,Amgen, Eli Lilly, Radius, 5,Amgen, Eli Lilly, 8; **P. Dakin**, Amgen, 1,Amgen, 3; **P. Hadji**, Amgen, 2,Amgen, 5,Amgen, 8; **M. McClung**, Amgen, Lilly, Merck, 5,Alexion Pharmaceuticals, Inc., 8; **P. Miller**, Alexion, Amgen, Merck, Merck Serono, Boehringer Ingelheim, Regeneron, National Bone Health Alliance, Lilly, Pfizer, Radius, 2,Owner & Medical Director of Colorado Center for Bone Research, 4,Alexion, Radius, Amgen, Lilly, 5,Alexion, Radius, Amgen, Lilly, 8; **J. Y. Reginster**, Servier, Novartis, Negma, Lilly, Wyeth, Amgen, GlaxoSmithKiine, Roche, Merckle, Nycomed, NPS, Theramex, UCB, 5,Merck Sharp and Dohme, Lilly, Rottapharm, IBSA, Genevrier, Novartis, Servier, Roche, GlaxoSmithKiine, Teijin, Teva, Ebewee Pharma, Zodiac, Analis, Theramex, Nycomed, Novo-Nordisk, Nolver, 9,Bristol Myers Squibb, Merck Sharp & Dohme, Rottapharm, Teva, Lilly, Novartis, Roche, GlaxoSmithKiine, Amgen, Servier, 2; **R. Wagman**, Amgen, 1,Amgen, 3; **A. Wang**, Amgen, 1,Amgen, 3; **E. McCloskey**, ActiveSignal, Amgen, ARUK, I3 Innovus, MRC, IOF, Unilever, 2,ActiveSignal,

Amgen, Consilient Healthcare, GSK, Internis, Lilly, Merck, Synexus, UCB, 5,Amgen, Consilient Healthcare, GSK, Internis, Lilly, UCB, 9.

Abstract Number: 366

Cost-Effective Osteoporosis Treatment Intervention Thresholds Based on FRAX in Portugal

Andréa Marques[1], Oscar Lourenço[2], Ortsäter Gustaf[3], Fredrik Borgström[3] and Jose Da Silva[4], [1]Rheumatology, Centro Hospitalar Universitário de Coimbra, Coimbra, Portugal, [2]Centro de Estudos e Investigação em Saúde da Universidade de Coimbra, Faculty of Economics. University of Coimbra, Coimbra, Portugal, [3]Quantify Research, Stockholm, Sweden, [4]Faculty of Medicine. University of Coimbra, Coimbra, Portugal

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Background/Purpose:

The aim of the present study was to identify the FRAX®Port (FRAX® validated for Portugal) ten-year major and hip osteoporotic fracture probabilities, above which pharmacologic interventions become cost effective in the Portuguese context.

Methods:

A previously developed and validated state transition Markov cohort model was populated with epidemiologic, economic and quality-of-life fracture data from Portugal. Cost-effective FRAX-based intervention thresholds for generic alendronate, zoledronic acid, denosumab and teriparatide when compared to “no intervention” were calculated assuming a willingness to pay of €32,000 (2 times national Gross Domestic Product per capita) per QALY (Quality-Adjusted Life Years).

Results:

In the Portuguese epidemiological and economic context, treatment with generic alendronate is cost-effective for people aged 50+, presenting 10-year probabilities (FRAX®Port) at or above 8.8% for major osteoporotic fractures and 2.5% for hip fractures. These values increase to 20.4% and 10.1% for zoledronic acid, 34.9% and 10.1% for denosumab and to 77.8% and 62.6% to teriparatide for major osteoporotic and hip fractures respectively. A tool is provided to perform the calculation of cost-effective intervention thresholds for different medications, according to age group and diverse levels of willingness to pay (WTP).

Conclusion:

Cost-effective intervention thresholds, for different medications, age-groups and WTP, based on 10-year probabilities of major and hip fracture probabilities calculated with FRAX®Port are provided.

Disclosure: A. Marques, None; **O. Lourenço**, None; **O. Gustaf**, None; **F. Borgström**, None; **J. Da Silva**, None.

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Abstract Number: 367

Prevention and Treatment of Bone Loss Following Hematopoietic Stem Cell Transplantation: A Systematic Review and Meta-Analysis

Xerxes Pundole[1], **Maria A. Lopez-Olivo**[2], Hira Cheema[3], Gabriela Sanchez Petitto[4], Maria E. Suarez-Almazor[5] and Huifang Lu[6], [1]General Internal Medicine, The University of Texas, MD Anderson Cancer Center, Houston, TX, [2]Department of General Internal Medicine, The University of Texas, MD Anderson Cancer Center, Houston, TX, [3]Texas Tech Odessa, Odessa, TX, [4]The University of Texas, Health Science Center, Houston, TX, [5]The Department of General Internal Medicine, The University of Texas, MD Anderson Cancer Center, Houston, TX, [6]General Internal Medicine, AT &EC, The University of Texas, MD Anderson Cancer Center, Houston, TX

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Background/Purpose: The main goal of our study was to evaluate the efficacy and safety of bisphosphonates and/or general preventive strategies in the prevention and treatment of post-transplant bone loss.

Methods: We conducted a comprehensive search in electronic databases until September 2014. We retrieved articles describing patients with bone loss or fractures who received hematopoietic stem cell transplantation (HSCT). Study selection, data collection and quality assessment were independently performed by two pairs of investigators. Studies were included if they were controlled trials, with a follow-up period of at least 12 months. Our primary outcome was change in BMD. Secondary outcomes included fracture, and bone turnover markers levels. Meta-analyses were performed when there were two or more studies with similar outcomes.

Results: Eleven publications were included (8 studies randomized trials (12 publications) and 3 studies non-randomized trials with a control group (4 publications)). 565 participants underwent HSCT for hematological diseases or malignancies: 85.7% underwent allogeneic HSCT, 1.4% underwent autologous HSCT, and 12.9% did not report the type of HSCT. Participant's age varied from 15 to 70 years. Seven comparisons were evaluated: (i) Zolendronic acid + Calcium + Vitamin D versus Calcium + Vitamin D; (ii) Pamidronate + Calcium +Vitamin D + hormone replacement therapy (HRT) versus Calcium + Vitamin D + HRT; (iii) Risedronate + Calcium +Vitamin D versus Calcium + Vitamin D; (iv) Zolendronic acid + Calcium versus Calcium alone; (v) Calcium +Vitamin D +HRT versus Calcium + Vitamin D; (vi) Calcium + Calcitonin versus no intervention; (vii) Calcium alone versus no intervention. Percent change in BMD in lumbar spine was higher when comparing any bisphosphonate groups compared with non-bisphosphonate groups at 12-24 months (see Table). The risk of fractures or x-ray findings of subclinical vertebral fractures was not increased in any of the comparison groups during the study period. A greater reduction in various bone turnover and resorption marker levels was observed in the bisphosphonate groups compared to patients in the control groups at 1-12 months, including: bone alkaline phosphatase, urinary hydroxyproline excretion, serum type 1 procollagen amino-terminal propeptide, urinary- type 1 collagen amino-terminal telopeptide, serum type 1 collagen cross-linked carboxy-terminal telopeptide beta, serum type 1 collagen carboxy-terminal telopeptide, and tartrate resistant acid phosphatase 5b. Flu-like symptoms were higher in Zolendronic acid treated patients.

Conclusion: Bisphosphonates are promising in the prevention and treatment of bone loss following HSCT. However bisphosphonates should be used with caution since they are not free of adverse effects.

	Follow-up (months)	# studies	Sample size	Measure	Effect size [95% CI]
Zolendronic acid +Calcium + Vitamin D versus Calcium + Vitamin D					
Bone Mineral Density mean change at Lumbar Spine	12	2	90	MD	**0.09 [0.05, 0.14]**
Bone Mineral Density mean change at Femoral Neck	12	2	90	MD	**0.06 [0.02, 0.11]**
Pamidronate + Calcium +Vitamin D +HRT versus Calcium + Vitamin D +HRT					
Bone mineral density percentage change at Lumbar Spine	12	2	145	MD	**3.88 [1.41, 6.35]**
Bone mineral density percentage change at Total Hip	12	2	145	MD (R)	**9.12 [0.89, 17.36]**
Bone mineral density percentage change at Trochanter	12	1	66	MD	**4.90 [1.01, 8.79]**
Risedronate + Calcium +Vitamin D versus Calcium + Vitamin D					
Bone mineral density percentage change at lumbar spine	12	3	97	MD (R)	**8.24 [5.64, 10.85]**
Bone mineral density percentage change at femoral neck	12	2	61	MD	**5.50 [4.74, 6.26]**
Zolendronic acid + Calcium versus Calcium alone					
Bone mineral density percentage change at lumbar spine	12	1	53	MD	**-1.50 [-1.71, -1.29]**
	24	1	53	MD	**-1.70 [-2.32, -1.08]**
Bone mineral density percentage change at femoral neck	12	1	53	MD	**0.36 [0.21, 0.51]**
	24	1	53	MD	**0.72 [0.04, 1.40]**

(R), random-effects model; MD, mean difference; HRT, hormone replacement therapy

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Disclosure: X. Pundole, None; **M. A. Lopez-Olivo**, None; **H. Cheema**, None; **G. Sanchez Petitto**, None; **M. E. Suarez-Almazor**, None; **H. Lu**, None.

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Abstract Number: 368

The Effects of Monitoring on a Quality Indicator for Glucocorticoid–Induced Osteoporosis and Trends of the Drug Variation in a Japanese Hospital

Masei Suda[1], Masato Okada[1], Yasuhiro Suyama[2], Mitsumasa Kishimoto[1] and Tokutaro Tsuda[1], [1]Immuno-Rheumatology Center, St. Luke's International Hospital, Tokyo, Japan, [2]Rheumatology, JR Tokyo General Hospital, Tokyo, Japan

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Background/Purpose: Glucocorticoid-induced osteoporosis (GIOP) is one of the most clinically significant side effects of glucocorticoid use, and the prevention of GIOP has become more important in these days. The American College of Rheumatology (ACR) published the recommendations for the prevention and treatment of GIOP in 2010, and it recommended patients on prednisolone as low as 7.5 mg daily or its equivalent for more than 3 months to take anti-osteoporosis drugs. Quality indicators (QI) has been received an increasing attention in rheumatology field. However, few studies have reported the clinical use of QI in the GIOP care. Herein, we repot the efficacy of monitoring for the QI for GIOP. Besides, It is well known that the adherence to bisphosphonate relate with the risk reduction of fracture, and monthly bisphosphonate greatly improves patient's adherence. Therefore, we analyzed the prescription trend of monthly bisphosphonate as well.

Methods: We studied all patients who were prescribed prednisolone as low as 7.5 mg daily or its equivalent for more than 3 months in our institution. We divided patients into 3 groups based on gender and age; male as group A, female younger than 50 year-old as group B, and female older than 50 year-old as group C. Group A and B were recommended to take vitamin D analogue, and group C was recommended to take bisphosphonates with vitamin D analogue following the ACR 2010 guideline for GIOP. Since 2011, we started monitoring of QI for GIOP and shared the result with other department in the seasonal QI meeting. Moreover, we informed the need of GIOP treatment to each attending physician if his/her patient was a candidate for the GIOP prophylaxis, by writing the recommended regimen to patients' chart. Clinical data from 2010 to 2013 were collected to compare the adherence rate in each group (A-C) before and after the investigation. We also measured an adherence rate of each department as a subanalysis. Furthermore, we searched for the trend of drug variation other than vitamin D, especially prescription rate of daily, weekly, monthly bisphosphonates.

Results: After implementation of monitoring, the adherence to the QI standards had elevated year by year until 2013 (69.0% in maximum). In the subanalysis, there were substantial gap in the adherence rate between each department.There was increasing trend in prescription rate of monthly bisphosphonates from 2011. The trend was most prominently seen in rheumatology department. In other departments, the mainstay of osteoporosis treatment was daily or weekly bisphosphonates.

Conclusion: Implementation of monitoring on a QI for GIOP significantly improved adherence to the QI standards, which followed the 2010 ACR GIOP guidelines.Despite institution-wide announcements of QI goals, a substantial information gap may exist between the various clinical subspecialties involved in GIOP patient care.

Disclosure: M. Suda, None; **M. Okada**, None; **Y. Suyama**, None; **M. Kishimoto**, None; **T. Tsuda**, None.

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Abstract Number: 369

Incidence of Fragility Hip Fractures over 10 Years (2004-13) in Three UK Centres with Reference to Local Fracture Prevention ('fracture liaison') Service Activity

Gavin Clunie[1] and Jonathan Belsey[2], [1]Rheumatology, Cambridge University Hospital NHS Foundation Trust, Cambridge, United Kingdom, [2]JB Medical, Sudbury, United Kingdom
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Background/Purpose: Fracture Liaison Services systematically identify patients with fragility fracture and screen patients for osteoporosis and associated conditions and instigate evidence-based 'secondary' fracture prevention management. The success of such a service is thus demonstrated by its effect on reducing secondary fractures, particularly hip fractures, which are most important in terms of causing morbidity and their cost. There is a need for Fracture Liaison Services to demonstrate a direct and specific effect on fracture prevention.

Methods: A Fracture Liaison Service was implemented at The Ipswich Hospital in 2003. Expected hip fracture incidence 2004-13 for the hospital was estimated by applying age and sex specific hip fracture rates, derived from UK Hospital Episode Statistics (2007-8) to changes in the demographic profile of the local population (2001 and 2011 population census) and applied to the 2009 estimates of the Hospital catchment population (Public Health England). Hip fracture (codes ICD10 S72.0-3) rate ratios were then calculated comparing observed (local derived) versus expected hip fractures. SDs and CIs for the rate ratios were estimated using the Poisson function. **Results** were compared with data derived similarly from Norwich, an area with no Fracture Liaison Service and Cambridge, where a Hospital-based service has been in place since 2006.

Results: Over a 10y period 2004-13: annual hip fracture incidence varied 355-511 (Ipswich), 684-798 (Norwich) and 448-706 (Cambridge). There was no change in hip fracture incidence 2004-13 (versus expected) in Norwich, where there had been no service activity (rate ratio mean 0.97 [CIs 0.9-1.04]). For the hospitals where a service had been active, non-parametric trend analysis showed a significant reduction in hip fractures 2004-13 (all ages >55y) in Cambridge ($p<0.05$) and at Ipswich (service from 2003) mean hip fracture rate ratio decreased 15% (1.1[CI ±0.26] to 0.93[CI ±0.22]; NS) for subsequent 5y periods (2004-8 and 2009-13) at ages <75y (though no significant trend for hip fracture reduction for all ages >55y).

Conclusion: Overall, these analyses, based on low event numbers, fairly wide fracture rate ratio CIs (±0.1) and the need to derive accurate population demographic and expected hip fracture data, illustrate the challenges in linking changes in hip fracture incidence to local Fracture Liaison Service activity. There is, however, some evidence to suggest hip fracture reduction in areas where a Fracture Liaison Service had been active, but no evidence of a change in hip fractures (versus expected) even in the non-elderly, in an area with no historic service activity.

Disclosure: G. Clunie, None; **J. Belsey**, None.

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Abstract Number: 370

Impact of Didactic Lecture on Osteoporosis Screening and Fracture Risk Assessment Among House Staff

Meghan Greenfield[1], Jordan Brodsky[2] and Erin Patton[3], [1]Rheumatology, University Of Washington, Seattle, WA, [2]Medicine, Albert Einstein College of Medicine, Bronx, NY, [3]Medicine/Rheumatology, Mount Sinai Beth Israel, New York, NY

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Background/Purpose: It has been estimated that 12 million Americans over the age of 50 have osteoporosis. Of those, only 30% of eligible women age 65 and older have had a bone density test. Previous studies of academic hospitals with resident outpatient primary care providers have concluded that residents are following the current guidelines for screening for osteoporosis with DEXA scans. However, the use of The Fracture Risk Assessment Tool (FRAX) score for the identification of patients at high-risk for fracture is highly underutilized. Further education of residents in the form of a didactic lecture may improve the osteoporosis screening practices among house staff.

Methods: Resident outpatient primary care providers in the Internal Medicine Department at one academic medical center were given a didactic lecture on the principles of osteoporosis screening, including current guidelines and utilization of the FRAX score. The electronic medical record system at two outpatient care centers was reviewed for one week prior to and one week after the didactic lecture. Patients with the following screening criteria were identified: women over age 65 or men over age 70, and postmenopausal women with at least one documented risk factor, including previous fracture, parent with a fractured hip, current smoking, glucocorticoid use, rheumatoid arthritis, secondary osteoporosis, and alcohol use (three or more drinks/day). Each chart was evaluated for osteoporosis risk assessment by house staff.

Results: Eleven Internal Medicine residents were present for the didactic lecture. Five residents were PGY1 level, three residents were PGY2 level, and three residents were PGY3 level. 73% were male and 27% were female. A total of 59 patients met the criteria for chart review during the one week prior to the didactic lecture. Of those 59 patients, 13 (22.0%) had osteoporosis risk addressed during that visit. A total of 79 patients met the criteria for chart review during the one week after the didactic lecture. Of those 79 patients, 32 (40.5%) had osteoporosis risk addressed during that visit.

Conclusion: A didactic lecture improved osteoporosis screening from 22.0% to 40.5%. This results in a relative increase in screening by 54.3%. After the lecture, residents achieved a higher screening rate than is nationally achieved at this time1. It is imperative that house staff be further educated on current osteoporosis screening tools, such as the FRAX score, to better prevent future fracture among those at risk. An expanded study should include a longer time period of chart review, in order to further evaluate the impact of didactic lecture on current practices in the resident-led outpatient setting.

References:

1. U.S Preventive Services Task Force. Screening for Osteoporosis: U.S Preventive Services Task Force Recommendation Statement. Annals of Internal Medicine. 1 March 2011. Vol 154, no 5.

2. J. Brodsky, M.D.; M. Greenfield, M.D., E. Patton, M.D. Osteoporosis Screening and Fracture Risk Assessment Tool Usage Among House Staff. Poster presentation: Interdisciplinary Osteoporosis Symposium 2013, Chicago, IL.

Disclosure: M. Greenfield, None; **J. Brodsky**, None; **E. Patton**, None.

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New Vertebral Fractures after Vertebroplasty: Two Year Results from a Randomised Placebo-Controlled Trial

Margaret P. Staples[1], B Matthew Howe[2], Michael Ringler[2], Peter Mitchell[3], Chris Wriedt[4], John Wark[5], Peter Ebeling[6], Richard Osborne[7], David Kallmes[2] and **Rachelle Buchbinder**[8], [1]Monash Department of Clinical Epidemiology, Cabrini Institute and Monash University, Malvern, Australia, [2]Department of Radiology, Mayo Clinic College of Medicine, Rochester, MN, [3]Department of Radiology, The University of Melbourne, Royal Melbourne Hospital, Melbourne, Australia, [4]MIA Radiology, Melbourne, Australia, [5]Department of Medicine, The University of Melbourne, Royal Melbourne Hospital, Melbourne, Australia, [6]Department of Medicine, Monash University, Monash Medical Centre, Melbourne, Australia, [7]Public Health Innovation, Deakin University, Melbourne, Australia, [8]Monash Department of Clinical Epidemiology, Cabrini Institute and Monash University, Melbourne, Australia
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Background/Purpose: We previously reported the results of a randomized participant and outcome assessor blinded controlled trial that found no beneficial effect of vertebroplasty (VP) over placebo for people with acute osteoporotic fractures up to 24 months and no between-group differences in incident clinical vertebral fractures. A secondary aim was to determine the effect of VP on the risk of further radiologically apparent vertebral fracture at 12 and 24 months.

Methods: The trial was registered (ACTRN012605000079640), and conducted between April 2004 and October 2010. Eligible participants had one or two acute osteoporotic vertebral compression fractures of at least grade 1, confirmed by history, radiograph and the presence of bone oedema. They were randomly assigned to VP (n=38) or placebo (n=40). Cement volume and leakage were recorded for the VP group during the cement injection and on imaging post-procedure.

Plain thoracolumbar radiographs were taken at baseline, 12 and 24 months. Two independent radiologists assessed these for new and progressed fractures at the same, adjacent and non-adjacent levels. Discrepancies were resolved by consensus at the completion of the review process.

A total sample of 164 participants (82/group) was needed to show a three-fold increase in the risk of further vertebral fractures at 24 months assuming a 10% event rate in the placebo group. Recruitment difficulties led to trial enrolment being terminated early after reaching sufficient numbers to address the primary efficacy outcomes but insufficient to assess the safety outcomes.

Results: Baseline characteristics were similar between the two groups (31 females in each group, mean (SD) age, median (interquartile range) duration of symptoms and one or more prior vertebral fractures was 74.2 (14.0), 9.0 (3.8 to 13.0) and 18 (47%) in the VP group, and 78.9 (9.5), 9.5 (3.0 to 17.0) and 21 (52%) in the placebo group).

At 12 and 24 months, radiographs were available for 45 (58%) and 47 (60%) participants respectively. There were no between-group differences for new or progressed fractures: 32 and 40 in the VP group after 12 and 24 months compared with 21 and 33 in the placebo group (hazard ratio (HR) 1.80, 95% confidence interval (CI) 0.08 to 3.94). Similar results were seen when considering only adjacent (HR (95% CI): 2.30 (0.57 to 9.29)), and non-adjacent (HR (95% CI): 1.45 (0.55 to 3.81) levels. In all comparisons there was a consistent trend towards higher risk of any type of fracture in the group undergoing VP.

Within the VP group, fracture risk was unrelated to total cement volume (HR (95% CI): 0.91 (0.71 to 1.17)), relative cement volume (HR (95% CI): 1.31 (0.15 to 11.48)), cement leakage (HR (95% CI): 1.20 (0.63 to 2.31)), age, sex, site of treated level, use of bisphosphonates at baseline or current bisphosphonate use, glucocorticoid use or duration of use, previous vertebral fracture or bone mineral density.

Conclusion: While our results indicate a possible increase in risk of radiologically apparent vertebral fractures

following VP, we did not have sufficient power to draw definitive conclusions. Further adequately powered studies are needed to address this question.

Disclosure: M. P. Staples, None; **B. M. Howe**, None; **M. Ringler**, None; **P. Mitchell**, None; **C. Wriedt**, None; **J. Wark**, None; **P. Ebeling**, None; **R. Osborne**, None; **D. Kallmes**, None; **R. Buchbinder**, None.

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Abstract Number: 372

Prevalence of Atypical Fractures in a Tertiary Hospital

Miren Uriarte Ecenarro, Nerea Errazquin Aguirre, César Antonio Egües Dubuc, Carlos Francisco Meneses Villalba, Vicente Aldasoro Caceres, Joaquin Belzunegui Otano and Gaspar De la Herran, Donostia University Hospital, San Sebastian, Spain

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Background/Purpose:

Actually, Biphosphonates are considered the first line treatment for osteoporosis. One of the side effects of the continuous treatment with these drugs is the development of atypical fractures. These are generally subtrochanteric, although they can appear anywhere in the femoral diaphysis, with a low prevalence (1.1% of all the femur fractures). Their incidence grows with the time to exposure to bisphosphonates.

To determine the prevalence of atypical fractures according to the American Society of Mineral and Bone Research (ASMBR) criteria between 2011 and 2014 in the Universitary Hosptial of Donostia (Guipúzcoa, Spain) and describe the demographic and sanitary features in these patients.

Methods:

Retrospective research of clinical data of patients operated of hip fracture and/or femur fractures between November 2011 and December 2014 Variables included were: age, sex, race, clinical features, treatment received, and presence or absence of diseases and pharmacological treatments that participate in the bone remodeling.

Results:

921 patients operated of hip fracture and 76 of diaphyseal fracture. 6 patients met the clinical and radiologic criteria of the ASMBR for an atypical fracture, 100% of these had received a long term treatment with biphosphonates and ment the 6,57% of the diaphyseal fractures, the 0,12% of the hip fractures and the 0,6% of the total of the fractures studied. The most used biphosphonate was Alendronate, being in the 66,6% of the patients the first treatment used for osteoporosis. The median time of exposure to biphosphonates was 8,5 years (IQR=3).

In the 83,3% of the patients the fracture was situated in the medial third of the femoral diaphisis.

	DEMOGRAPHIC		TREATMENT FOR OSTEOPOROSIS		FRACTURE	COMORBIDITIES	
ID	SEX	AGE	MEDICATION	TIME	LOCATION	DISEASES	OTHER DRUGS (Heparin, Steroids, Anticonvulsants, others)
1	Female	42	1.- Alendronate	1.- 10 years	Diaphyseal femur (1/3 medium)	No	No
			2.- Teriparatide	2.- 2 years			
			3.- Ibandronate	3.- 2 years			
			4.- Denosumab + Strontium ranelate	4.- 1 year			
2	Female	63	1.- Alendronate	1.- 10 years	Diaphyseal femur (1/3 medium)	Hipothyroidism	No
3	Female	73	1.- Alendronate	1.- 6 years	Subtrochanteric	Diabetes mellitus	No
			2.- Denosumab	2.- 6 months			
4	Female	77	1.- Alendronate	1.- 8 years	Diaphyseal femur (1/3 medium)	Hipothyroidism	No
5	Female	83	1.- Risedronate	1.- 6 years	Diaphyseal femur (1/3 medium)	No	No
			2.- Alendronate	2.- 3 years			
6	Female	88	1.- Risedronate	1.- 5 years	Diaphyseal femur (1/3 medium,)	Hipothyroidism	No
			2.- Alendronate	2.- 2 years			

Conclusion:

- In our study the prevalence of atypical fractures with biphosphonates was low, a 0,6% of all of the fractures studied.

- No alternative cause was found, nor clinical nor pharmacological, to the take of biphosphonates that explained the atypical fractures.

Disclosure: M. Uriarte Ecenarro, None; **N. Errazquin Aguirre**, None; **C. A. Egües Dubuc**, None; **C. F. Meneses Villalba**, None; **V. Aldasoro Caceres**, None; **J. Belzunegui Otano**, None; **G. De la Herran**, None.

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Abstract Number: 373

Compared to Non-Users, Current Glucocorticoids Users Have Less Prevalent Fractures at the Same Bone Mass: Results of a Large Cross-Sectional Study

Marwan Bukhari[1], Nicola Goodson[2,3] and Maarten Boers[4], [1]Rheumatology, Royal Lancaster Infirmary, Consultant and Honorary Senior Lecturer, Lancaster, United Kingdom, [2]Rheumatology, University of Liverpool, Liverpool, United Kingdom, [3]Rheumatology, University Hospital Aintree, Liverpool, United Kingdom, [4]Amsterdam Rheumatology and Immunology Center, VU University Medical center, Amsterdam, Netherlands

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Background/Purpose: It is widely believed that use of glucocorticoids (GC) increase risk of fracture through reduction in bone quality as well as reduction in bone mineral density (BMD). Data supporting the 'bone quality hypothesis' come from a post-hoc analysis of two trials with limited numbers of fractures (van Staa). In a preliminary unadjusted analysis from a large cross-sectional study we surprisingly found that patients on GC had a lower prevalence of fractures.(Bukhari et al) We now report the effect of GC on fracture in the same population, adjusting for BMD and

other risk factors including treatments at presentation.

Methods: We used data from patients referred by their general practitioner or secondary care doctor for first BMD estimation by Dual X-Ray absorptiometry (DEXA) in the North West of England. Patients details recorded at time of scan included age, Body Mass Index (BMI), and the presence of risk factors: smoking, alcohol, family history of osteoporosis, history of clinical fragility fracture, rheumatoid arthritis and drug treatment, specifically GC and antiresorptive agents (mostly bisphosphonates). DEXA assessed BMD in the spine (mean of L1-L4 vertebrae) and femoral neck. Two subpopulations were identified at the extremes: patients on current GC and those with no prior exposure to GC. The prevalence of BMD fractures in each group was compared by chi-square test. A logistic model was fitted to adjust for possible confounding by imbalances in risk factors and BMD.

Results: 20210 subjects were included in the analysis, mean age was 63.2 years (SD 13.0 years), 82% were female. 32% had as history of fracture and 3772 (19%) were on GC at referral. Patients on GC vs unexposed were of similar age: 63.1 vs 62.8 years (p=0.21); As previously reported GC patients had higher bone mass at both sites 1.09 vs 1.04 g/cm2 at lumbar spine (p<0.001) and 0.9 vs 0.90 g/cm2 in the femoral neck (p<0.01). Less GC patients had a history of fracture: (13% vs 22%; OR 0.53 95%CI 0.49,0.58 p<0.001). 19.5% of GC patients were on antiresorptive agents vs 7.2 % of controls (P<0.01) . Modelling steroids as a dependent variable adjusting first for BMD at hip and then BMD at spine and for all the risk factors, gave an odds ratio of fracture 0.56(95%CI 0.52; 0.61) and 0.55(95%CI 0.51,061) repsectively. Restricting the analysis to patients who were not on antiresorptive treatment at the time of scanning (n=18,226 in the spine and 17,490 in the hip) yielded similar results: spine OR of fracture 0.54 (95%CI 0.49; 0.60); hip OR of fracture 0.54 (95%CI 0.49; 0.60).

Conclusion: The surprising, apparently protective effects of GC on bone quality from this large cross-sectional study cannot be explained by known confounding factors. These results are likely subject to unmeasured confounding and need to be interpreted with caution. The finding could be due to confounding by indication for DEXA .However, they suggest that current GC use is associated with less prevalent fractures at the same bone mass level, directly contradicting commonly held views about the detrimental effect of GC on bone. It will be worth exploring in a large longitudinal cohort.

References: Van Staa TP et al, Arthritis and Rheumatism 2003:48;3224-9. Bukhari et al, Ann Rheum Dis 2015;74(Suppl2): 527.

Disclosure: M. Bukhari, None; **N. Goodson**, None; **M. Boers**, None.

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Abstract Number: 374

High Prevalence of Osteoporosis and Fractures Is Associated with Abdominal Adiposity and Decreased Muscular Strength in Primary Necrotizing Vasculitides

Karine Briot[1], Bertrand Dunogué[2], Alexis Regent[3], Pascal Cohen[2], Alice Berezne[2], Sami Kolta[1], Xavier Puéchal[2], Claire Le Jeunne[4], Luc Mouthon[5], Christian Roux[1], Loïc Guillevin[6] and Benjamin Terrier[2], [1]Rheumatology B Department, Hôpital Cochin, Paris, France, [2]Internal Medicine, National Referral Center for Rare Systemic Autoimmune Diseases, Hôpital Cochin, Paris, France, [3]Service de médecine interne, Hôpital Cochin, Paris, France, [4]Department of Internal Medicine, Hotel-Dieu Hospital, AP-HP, Paris, Paris, France, [5]Department of Internal Medicine, Department of Internal Medicine, Cochin Hospital, Referent Center for Necrotizing Vasculitis and Systemic Sclerosis, Paris-Descartes University, AP-HP, Paris, France, [6]Internal Medicine, Hopital Cochin, Paris, France

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Background/Purpose:

Overall survival of primary necrotizing vasculitides, including ANCA-associated vasculitis (AAV) and polyarteritis nodosa (PAN), has greatly improved over the last 50 years. Because of a longer survival and prolonged treatment, long-term sequelae and comorbidities have now become a major concern. Studies assessing the prevalence of osteoporosis, fractures and their determinants, in these patients are lacking. The aim of this study is to assess the prevalence of osteoporosis and fractures in patients with vasculitides and to identify variables associated with their presence.

Methods:

Patients with AAV and PAN seen in our department were prospectively included in an ongoing cross-sectional study assessing bone complications and other sequelae (OSTEOVAS cohort). Lumbar spine and hip bone mineral density (BMD), body composition (lean and fat masses) and abdominal fat masses (visceral and subcutaneous) were measured by Dual X-ray Absorptiometry (DXA). Vertebral fractures were assessed using the Vertebral Fracture Assessment (VFA) measured by DXA.

Results:

One hundred and twenty consecutive patients were analyzed (66 females and 54 males, mean age 53±18 years, with a median disease duration of 54 months). Diagnoses were granulomatosis with polyangiitis in 61 patients, eosinophilic granulomatosis with polyangiitis in 30, PAN in 14, microscopic polyangiitis in 13, and cryoglobulinemia vasculitis in 2 cases. The median daily dose of glucocorticoids was 8.5 mg/day (0-80), with an estimated total cumulative dose of 15000±10000 mg of glucocorticoids. Osteoporosis was observed in 36 patients (30%) and low trauma fractures in 33 patients (27.5%). Overall, osteoporosis and/or previous fractures were observed in 54 patients (45%). Among them, only 18 (33%) received an antiosteoporotic treatments, and 20 (37%) and 34 (63%) had calcium and vitamin D supplementation.

Variables significantly associated with bone disease in multivariate analysis were an increased visceral adipose tissue (VAT) and subcutaneous adipose tissue (SAT) ratio [OR 1.03 (1.01-1.05); P=0.005], decreased calcium intakes [OR 0.998 (0.997-1.00); P=0.02] and decreased grip strength [OR 0.22 (0.08-0,60), P=0.003]. Variables significantly associated with fractures in multivariate analysis were an increased age [OR 1.05 (1.01-1.08); P=0.006], decreased calcium intakes [OR 0.998 (0.996-1.00); P=0.046] and increased Vascular Damage Index (VDI) evaluating sequelae related to vasculitis and/or treatments [OR 1.28 (1.02-1,60), P=0.03]. Finally, using multiple linear regression analysis, femoral neck BMD was independently associated with age (P=0.0003), skeletal muscle mass (P<0.0001), VDI (P=0.008), and grip strength (P=0.03).

Conclusion: Osteoporosis and fractures are observed in nearly half of patients with primary necrotizing vasculitides and only 33% received an antiosteoporotic treatment. Increase in abdominal adiposity and decrease in muscular function are strongly associated with bone complications. Bone complications assessment, cardiovascular risk and muscular function should be assessed and managed in clinical practice in patients with primary necrotizing vasculitides.

Disclosure: K. Briot, None; **B. Dunogué**, None; **A. Regent**, None; **P. Cohen**, None; **A. Berezne**, None; **S. Kolta**, None; **X. Puéchal**, None; **C. Le Jeunne**, None; **L. Mouthon**, None; **C. Roux**, None; **L. Guillevin**, None; **B. Terrier**, None.

Abstract Number: 375

RA May Not Confer Addition Risk of Osteoporosis in Male Patients – Results of Cohort Analysis and Literature Review

Khush Aujla[1], Javeria Bhawal[1], Katie Langley[2] and Vikas Majithia[1], [1]Division of Rheumatology, University of Mississippi Medical Center, Jackson, MS, [2]University of Mississippi Medical Center, Jackson, MS

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Background/Purpose:

Osteoporosis (OP) is a common disease and is increasingly being recognized in males. A number of underlying diseases including rheumatoid arthritis (RA) have been associated with it and this relationship has been well proven in females but remains unclear in males with RA. This study was done to evaluate the association between RA and OP in male population. We analyzed male cohort at UMMC, followed by a PubMed literature review.

Methods:

585 men who underwent DEXA scan performed at UMC from 2005-2012 were included in the analysis of retrospective cohort with documented RA. A PubMed literature search was performed using keywords- Male, OP and RA yielding 775 articles (limiting data to English and publication year > 1960), 663 articles were excluded with abstract review, 112 underwent full text review with 7 having relevant data. Only 4 studies had sufficient data to be included in the pooled analysis, while other 3 studies had to be analyzed individually. Data looking at mean male bone mineral density (from the National Health and Nutritional and Examination Survey (NHANES) compiled by the CDC) was matched by age and used for control. Z-scores were calculated using age adjusted Standard Deviation values from the NHANES database.

Results:

UMC Retrospective Cohort. RA patients	Normal DEXA	Osteoporosis	P-value
RA N=38/291	10.81% (16/148)	15.38% (22/143)	NS

Study	Age	#patients	Study Mean Lumbar BMD	Control Mean Lumbar BMD	Z-score
Haugeberg et al, 2000	59.9±11.3	91	0.907 gm/cm2	0.803 gm/cm2	0.811
Oelzner, 2008	57.9±11.8	108	0.623 gm/cm2	0.821 gm/cm2	-1.589
Nolla et al, 2006	60.34±13.0	187	0.739 gm/cm2	0.823 gm/cm2	-0.656
Loddler et al, 2004	53.8±11.9	87	0.803 gm/cm2	0.858 gm/cm2	-0.433

Total patients	Overall Mean Lumbar BMD	Overall Mean Z-score	Association
473	0.768 gm/cm2	-0.467	Unclear

Conclusion:

This analysis suggests that relationship of RA and OP in male patients remains unclear and confusing. Although no firm conclusions can be drawn, the results of our cohort analysis and review of literature suggest that RA diagnosis and disease activity may not add any increase in the risk of developing OP in men. The association of RA and risk fracture was also not clear in this analysis. Sub-analysis done in the studies suggested; “age” as a factor conferring the risk of OP in RA. Furthermore, the literature search revealed that limited data is available looking at this association, and more studies are needed to clarify the association between RA and male OP.

Disclosure: K. Aujla, None; **J. Bhawal**, None; **K. Langley**, None; **V. Majithia**, None.

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Abstract Number: 376

The Relationships Between Bone Mineral Density and Radiographic Features of Hand or Knee Osteoarthritis in Older Adults: Data from the Dong-Gu Study

Kyung-Eun Lee[1], Lihui Wen[1], Yi-Rang Yim[1], Ji-Eun Kim[1], Jeong-Won Lee[1], Dong-Jin Park[2], Shin-Seok Lee[1] and Shin-Seok Lee's group, [1]Chonnam National University Medical School and Hospital, Gwangju, South Korea, [2]Rheumatology, Chonnam National University Medical School and Hospital, Gwangju, South Korea

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Background/Purpose: The relationship between osteoarthritis (OA) and osteoporosis has exhibited contradictory features over the past four decades. We evaluated this relationship using separate analysis of the radiographic features of OA whether various radiographic features of OA were associated differently with bone mineral density (BMD) in the Korean elderly.

Methods: Data were derived from the Dong-gu cohort; 2,377 subjects were enrolled in the present cross-sectional study. Baseline characteristics, the BMDs of the lumbar spine and femoral neck, and X-rays of knees and hands, were collected. A semi-quantitative grading system was used to estimate the severities of individual radiographic features. We adjusted for confounders using multiple linear regression modeling to analyze the relationships.

Results: After adjustment for confounders, knee and hand OA total scores were negatively associated with the BMDs of the lumbar spine and femoral neck ($p < 0.001$, both), except for the total knee OA score and lumbar spine BMD. In detail, hand osteophytes and sclerosis exhibited positive relationships with the BMDs of the lumbar spine and femoral neck ($p < 0.001$ for all). On the contrary, however, knee joint space narrowing (JSN), hand JSN, and hand subchondral cysts were negatively associated with the BMD of the lumbar spine and femoral neck ($p< 0.001$ for all). Knee JSN and hand subchondral cysts exerted the greatest effects on BMD.

Conclusion: Separate analysis of the radiographic features of OA better reveals associations of OA with the BMD of the lumbar spine and femoral neck.

Disclosure: K. E. Lee, None; **L. Wen**, None; **Y. R. Yim**, None; **J. E. Kim**, None; **J. W. Lee**, None; **D. J. Park**, None; **S. S. Lee**, None.

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Abstract Number: 377

Hand Bone Impairment By High-Resolution Peripheral Quantitative Computed Tomography in Patients with Diffuse Systemic Sclerosis: Correlation with Clinical Parameters, Quality of Life and Capillaroscopic Findings

Marilia Sampaio-Barros[1], Liliam Takayama[2], Jackeline Couto Alvarenga[3], Ana Paula Luppino-Assad[2], Percival D Sampaio-Barros[4] and Rosa M R Pereira[5], [1]Rheumatology, Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil, [2]Division of Rheumatology, University of São Paulo, sao paulo, Brazil, [3]Division of Rheumatology, Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil, [4]Faculdade de Medicina da Universidade de São Paulo, Rheumatology Division, Brazil, Sao Paulo, Brazil, [5]Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil

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Background/Purpose: Skin thickening and hand joint involvement induce bone loss and contribute to functional disability in patients with dcSSc. The high-resolution peripheral quantitative CT (HR-pQCT) can analyze the microarchitecture and bone mass at distal radius and allow the better understanding of bone impairment in dcSSc. The objetive is to analyze the volumetric BMD (vBMD) and bone microarchiteture by HR-pQCT in dcSSc patients, and correlates with the disease clinical variables.**Methods:** 38 dcSSc patients and 76 healthy controls (HC) were selected. HR-pQCT were performed in distal radius using X-Treme CT (Scanco). The SSc clinical and HR-pQCT parameters were correlated. **Results:** The density, structure and mechanical characteristics were significantly impaired in dcSSc compared to HC, with decrease of trabecular BMD [Tb.BMD], cortical BMD [Ct.BMD], trabecular number [TbN], trabecular thickness [TbTh], cortical thickness [CtTh], stiffness [S] ($p<0.05$). Clinical and HR-pQCT parameters were correlated: **BMI** with Tb.BMD ($r=+0.67$, $p<0.001$), Tb.N ($r=+0.55$, $p<0.0001$), Tb.Th ($r=+0.47$, 0.003); Tb.Sp ($r=-0.45$, $p=0.004$); Ct.Th ($r=+0.45$, $p=0.04$). Right/left **Range of motion** with Tb.BMD ($r=+0.41$, $p=0.01$; $r=+0.39$, $p=0.02$), Ct.BMD ($r=+0.46$, $p=0.03$; $r=+0.49$, $p=0.001$), Tb.N ($r=+0.05$, $p=0.005$; $r=+0.44$, $p=0.006$), Tb.Sp ($r=-0.43$, $p=0.008$; $r=-0.4$, $p=0.01$), Ct.Th ($r=+0.39$, $p=0.01$; $r=+0.420$, $p=008$). **Grip Strength (HAQ)** with Tb.N ($r=-0.33$; $p=0.04$), Tb.Sp ($r=+0.37$, $p=0.02$). The following clinical manifestations were associated with worse HR-pQCT parameters: **Esophageal dismotility** with Tb.BMD (109.23±45.53 vs 147.17±35.71, $p=0.01$), Tb.N (1.5±0.44 vs 1.88±0.27, $p=0.006$), Tb.Sp (0.69±0.34 vs 0.47±0.1, $p=0.02$); **Intersticial lung Disease** with Tb.BMD (113.81±40.89 vs 158.46±47.66, $p=0.01$), Tb.N (1.49±0.44 vs 1.87±0.31, $p=0.006$), Tb.Sp (0.7 ±0.35 vs 0.48±0.12, $p=0.02$), Tb.Th (0.06±0.01 vs 0.07±0.01, $p=0.02$), Ct.Th (0.52±0.15 vs 0.7±025, $p=0.007$); **Acroosteolysis** with Tb.BMD (103.61±36.6 vs 153.27±42.37, $p<0.001$), Tb.N (1.5±0.44 vs 1.88±0.27, $p=0.006$), Tb.Sp (0.69±0.34 vs 0.47±0.1, $p=0.02$), **Scl-70** with Tb.Th (0.06±0.008 vs 0.07±0.01, p=0,03), Ct.Th (0.52±0.18 vs 0.66±0.22, $p=0.03$); **Late capillaroscopy pattern** with Ct.BMD (803.79±112.91 vs 873.07±69.75, $p=0.03$) Tb.Th (0.07±0.01 vs 0.06±0.008, p=0,03), Ct.Th (0.66±0.22 vs 0.52±0.18, $p=0.03$). No correlation was observed with age, menopausal age, digital ulcers, Modified Rodnan skin score, Medsger Disease Severity Index. **Conclusion:** dcSSc patients had lower bone quality and bone mass at distal radius compared to HC. Quality of life and clinical parameters showed a significant correlation suggesting that the SSc clinical profile should indicate patients at increased risk of bone disease.

Disclosure: M. Sampaio-Barros, None; **L. Takayama**, None; **J. C. Alvarenga**, None; **A. P. Luppino-Assad**, None; **P. D. Sampaio-Barros**, None; **R. M. R. Pereira**, None, 2.

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Abstract Number: 378

Osteoporotic Fragility Tibia/Fibula Fractures Are Not Asociated with a Low Body Mass Index: An Observational Study

Vishnu Kammath[1] and Marwan Bukhari[2], [1]Faculty of Health and Medicine, Lancaster University, Lancaster, United Kingdom, [2]Rheumatology, Royal Lancaster Infirmary, Consultant and Honorary Senior Lecturer, Lancaster, United Kingdom

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SESSION INFORMATION
Session Date: Sunday, November 8, 2015
Session Title: Osteoporosis and Metabolic Bone Disease - Clinical Aspects and Pathogenesis Poster
Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose: Tibia/Fibula (Tib/Fib) fractures are one of osteoporotic fragility fractures. They have been suggested to be more likely to occur secondary to osteoporosis (OP) than any other fracture (1). Furthermore, as they are more likely to be open fractures, are more prone to infections and other co-morbidities. It is known that body mass index (BMI) is a protective factor in fragility fractures whilst low Bone Mineral Density (BMD) is known to be predictor of fragility fractures. However the specific predisposing factors for Tib/Fib fragility fractures are not known. Furthermore risk of factues is determined using the femoral neck in the FRAX (tm) tool. Use of lumbar spine BMD has not been examined as a specific predictor. We aimed to use a Case-Control approach to examine these predictors for Tib/Fib fractures.

Methods: A cohort of patients referred after a Tib/Fib fragillity fracture for a DEXA scan in the North West of England between 2004 and 2011 were identified, and were age and sex matched with scanned controls that had no indications for a scan. Students T-Test and Chi 2 test were used to test for any differences between the groups in terms of continuous and categorical variables respectively. Logistic models were fitted examining the contribution of risk factors to tib/fib using BMD in the femoral neck and the lumbar spine.

Results: 797 patients were matched to 797 controls, 679 (85%) were female. Mean age in both cases and controls was 64.3years (SD11.3). Surprisingly, mean BMI was higher in the fracture group 28.3 kg/m2 vs 26.7 kg/m2 ($p<0.01$). This was mostly due to the fracture group being heavier (74.6kg vs 69.7 kg $p<0.01$) Univariate analysis showed an unadjusted odds ratio of 1.06 (95%CI 1.04,1.08) , after adjustment for the lumbar spine BMD , the difference persisted (OR 1.06 95%CI 1.04,1.08) and after adjusting for femoral neck BMD this also persisted (OR 1.05 95%CI 1.02,1.09). This would suggest that that BMI does not influence the risk of developing Tib/Fib fragility fractures. This is contrary to what is stated in literature in relation to fragility fractures.

Conclusion: This study would seem to indicate that people with higher BMI values tend to get Tib/Fib fragility fractures compared to a control population. this persisted after adjusting for BMD, an obvious confounder. This suggests that other factors are involved in increasing the risk of Tib/Fib fractures. Further work is therefore needed to assess other predictors for Tib/Fib fractures.

Disclosure: V. Kammath, None; **M. Bukhari**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/osteoporotic-fragility-tibiafibula-fractures-are-not-asociated-with-a-low-body-mass-index-an-observational-study

Abstract Number: 379

Validation of a Short Calcium Intake List to Estimate Daily Dietary Calcium Intake of Patients with Osteoporosis

Linda Rasch[1], Marian de van der Schueren[2], Lilian van Tuyl[1], Irene Bultink[1] and **Willem Lems**[1], [1]Amsterdam Rheumatology and immunology Center, location VU University Medical Center, Department of Rheumatology, Amsterdam, Netherlands, [2]Department of Nutrition and Dietetics, VU University Medical Center, Amsterdam, Netherlands

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SESSION INFORMATION

Session Date: Sunday, November 8, 2015

Session Title: Osteoporosis and Metabolic Bone Disease - Clinical Aspects and Pathogenesis Poster

Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose: Calcium supplements are prescribed for prevention of osteoporotic fractures, but excess intake has been associated with cardiovascular events. The most adequate tools for estimating dietary calcium intake are time-consuming, while an accurate estimation is a prerequisite to be able to prescribe the adequate amount of supplementation. The aim of this study is to validate a Short Calcium Intake List (SCaIL) that is feasible in daily clinical practice, with an extensive dietary history (DH) as reference method.

Methods: Based on the Dutch food groups which contribute most to daily dietary calcium intake and on portion sizes determined in our earlier validation study, a new three-item, one minute SCaIL was designed. As a reference method, an extensive DH with specific focus on calcium products and extra attention for portion sizes was performed. Beforehand, a difference of ≥250 mg calcium between both methods was considered clinically relevant.

Results: Sixty-six patients with either primary (n=40) or secondary (n=26) osteoporosis were included. The SCaIL showed a very small and clinically non-relevant difference with the DH: mean 24 ± 350 mg calcium per day (1146 ± 440 vs 1170 ± 485, respectively; p=0.568). Sensitivity and specificity of the SCaIL, compared to the DH, were 73% and 80%, respectively. However, in 50% of the individuals, a clinically relevant difference was observed between both methods, while in 17% a difference of ≥500 mg was observed.

Conclusion: The SCaIL is a quick and easy questionnaire to estimate dietary calcium intake at a group level, but is not sufficiently reliable for use in individual patients. Remarkably, mean dietary calcium intake via the DH is 1170 mg per day, which indicates that a large proportion of osteoporosis patients might not even need calcium supplementation.

Disclosure: L. Rasch, None; **M. de van der Schueren**, None; **L. van Tuyl**, None; **I. Bultink**, None; **W. Lems**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/validation-of-a-short-calcium-intake-list-to-estimate-daily-dietary-calcium-intake-of-patients-with-osteoporosis

Abstract Number: 380

Osteoporosis Screening and Treatment of Rheumatoid Arthritis Patients at a Teaching Institution

Sheena Ogando[1], Calie Santana[2], Irene Blanco[3] and Barbara Mendez[1], [1]Rheumatology, Montefiore Medical Center, Bronx, NY, [2]Medicine, Montefiore Medical Center, Bronx, NY, [3]Rheumatology, Albert Einstein College of Medicine, Bronx, NY

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SESSION INFORMATION

Session Date: Sunday, November 8, 2015

Session Title: Osteoporosis and Metabolic Bone Disease - Clinical Aspects and Pathogenesis Poster

Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose: Glucocorticoids are effective at treating rheumatologic diseases but are known to increase fracture risk. In 2010, the ACR developed recommendations for the prevention and treatment of glucocorticoid induced osteoporosis (GIOP) based on risk factors, FRAX score, and prednisone dose. The purpose of this study is to evaluate compliance with the ACR GIOP recommendations in a large teaching institution.

Methods: Men and women seen at the fellows' general rheumatology clinic at Montefiore Medical Center (Bronx, NY) who were ≥50y with history of rheumatoid arthritis between 1/2015 and 2/2015 were included. Charts were reviewed for DEXA Screening within 2 years of visit and appropriate bisphosphonate usage based on the risk stratification proposed by the ACR.

Results: 52 patients were evaluated. 92.3% were women with a mean age of 66.5 years. In this cohort, 13.5% were Black. Only 67% of the patients were appropriately screened with an up to date DEXA (Figure 1). Patients that were not screened tended to be younger (62.6 v 67.2, p=0.08). Also male patients were less likely to be screened (6.6% v 14.3%). There was no statistically significant difference in screening in women or by race. Out of the 35 patients that were appropriately screened, 32% were not appropriately treated (figure 2). 6 of these 11 patients were candidates for treatment due to being medium risk and on prednisone. 3 of 11 were candidates for treatment due to their osteoporotic T-score. One patient was low risk but was on prednisone 7.5mg and warranted treatment. Another patient was low risk on prednisone 5mg daily but was inappropriately on a bisphosphonate.

Conclusion: Overall, 53% of the patients in our academic institution were not appropriately screened or treated for GIOP. Although not statistically significant, RA patients that were not effectively screened tended to be patients of younger age and male. This study concludes that rheumatologists underutilize osteoporosis screening and preventative treatment, which is prudent toward preventing debilitating fractures and its subsequent impact on diminished quality of life. Provider education on screening and treatment of GIOP may be an area for quality improvement for both primary care and rheumatology.

Figure 1

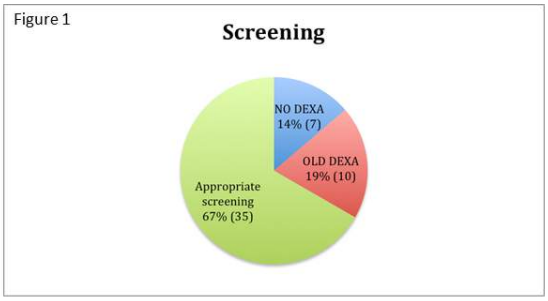
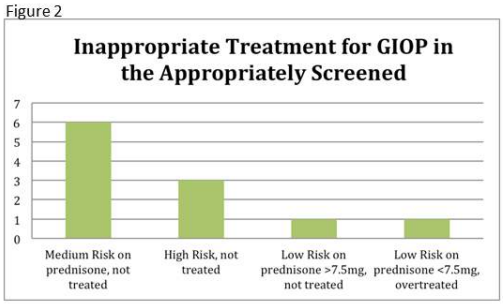


Figure 2



Disclosure: S. Ogando, None; **C. Santana**, None; **I. Blanco**, None; **B. Mendez**, None.

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http://acrabstracts.org/abstract/osteoporosis-screening-and-treatment-of-rheumatoid-arthritis-patients-at-a-teaching-institution

Abstract Number: 381

Associations Between Vitamin D Insufficiency, Osteoporotic Fractures and Comorbidites

Eugenio Chamizo Carmona[1], Juan Jose Aznar Sánchez[1,2], Raul Veroz Gonzalez[2], Tamara Libertad Rodriguez Araya[1], Piter José Cossio Jimenez[2] and Sara María Rojas Herrera[3], [1]Rheumatology, Hospital de Mérida, Mérida, Spain, [2]Hospital de Mérida, Mérida, Spain, [3]Rheumatolotgy, Hospital de Mérida, Mérida, Spain
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SESSION INFORMATION
Session Date: Sunday, November 8, 2015

Session Title: Osteoporosis and Metabolic Bone Disease - Clinical Aspects and Pathogenesis Poster
Session Type: ACR Poster Session A
Session Time: 9:00AM-11:00AM

Background/Purpose:

Vitamin D deficiency is highly prevalence, especially in adults and elderly population. There is controversy about its relationship with increased cardiovascular risk, osteoporosis and bone fractures.

To describe the vitamin D levels in a population evaluated with suspected osteoporosis in a Bone Metabolism Unit and its relationship to other diseases.

Methods:

We selected the patients attended in the Bone Metabolism Unit of the Hospital of Mérida between June 2013 and June 2014 that have at least one determination of 25-OH-cholecalciferol, bone densitometry and complete clinical history.

Results:

We included 171 patients between 34 and 75 years (mean 64.5, SD 11.75), 11 men and 160 postmenopausal women. The detected levels of 25-OH-cholecalciferol were normal (>30ng/ml) in 75 and deficient in 96 patients (56.14%). Deficiency was severe (<10ng/ml) in 11, moderate (10 to 20ng/ml) in 48 and mild (between 20 and 30ng/ml) in 37 patients. We didn´t find any correlation (Pearson coefficient) between the levels of 25-OH-cholecalciferol and age (-0.17), lumbar spine T-score (0.1) and hip T-score (-0.004), major and hip fracture risk using FRAX without BMD (0.13 for both) and with BMD (-0.017 and -0.063, respectively). Neither we didn´t find any association between levels of 25-OH-cholecalciferol and the existence of comorbidities and cardiovascular risk. Patients with severe deficiency (<10ng/ml) of 25-OH-cholecalciferol had higher rates of presence of cardiovascular risk factors (RR 5.87, 95%CI 1.16, 1.87) and bone fractures (OR 3.76 95%CI 1.75, 13.18).

Conclusion:

Severe deficiency of 25-OH-cholecalciferol was significantly associated with the presence of bone fractures, irrespective of BMD values and FRAX risk. Levels below 10ng/ml of 25-OH-cholecalciferol were more frequent in patients who had at least one cardiovascular risk factor. No association between vitamin D deficiency and the presence of comorbidities was found.

Disclosure: E. Chamizo Carmona, None; **J. J. Aznar Sánchez**, None; **R. Veroz Gonzalez**, None; **T. L. Rodriguez Araya**, None; **P. J. Cossio Jimenez**, None; **S. M. Rojas Herrera**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/associations-between-vitamin-d-insufficiency-osteoporotic-fractures-and-comorbidites

Abstract Number: 382

Twelve Months after Osteoporosis Associated Fracture – Has Adequate Therapy Been Initiated?

Christoph Hemmeler[1], Sabrina Morell[2], Paul Hasler[1] and Thomas Gross[2], [1]Rheumatology, Kantonsspital Aarau, Aarau, Switzerland, [2]Traumatology, Kantonsspital Aarau, Aarau, Switzerland
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SESSION INFORMATION

Session Date: Sunday, November 8, 2015
Session Title: Osteoporosis and Metabolic Bone Disease - Clinical Aspects and Pathogenesis Poster
Session Type: ACR Poster Session A
Session Time: 9:00AM-11:00AM

Background/Purpose: Evidence shows that of ten patients taking medication against osteoporosis one will avoid subsequent fractures, decreasing the risk by > 50 %. On the other hand, epidemiologic studies indicate that merely 15 – 30 % of the affected cases are initiated on adequate therapy.

Methods: All cases over fifty years of age admitted to the traumatology department with a fracture were investigated with osteodensitometry and standard of care laboratory parameters. A questionnaire was provided to gather data in a quality assurance program. Therapy was recommended according to the FRAX validated for Switzerland. One year after the fracture, the patients and their family physicians were invited to answer a questionnaire targeted at evaluating compliance with the recommendation provided after discharge from the hospital.

Results: 101 of 127 patients that we were able to contact answered the query (79%; median 72 years, 80% females; 83% low-energy trauma). 54% stated that they regularly took a specific medication against osteoporosis. 66 % were supplemented with vitamin D and 67 % with calcium. 30 % were on all three medications. Reasons given by 41 % of the patients for not taking medication were lack of prescription by the treating physician, 17 % considered the treatment unnecessary, 4 % indicated a lack of interest. Financial reasons, drug intolerance, old age and illness were each given as reasons by 2 %. Other reasons were given in 22 %.

Family physicians stated that in 87 % and 75 % prescriptions were given for vitamin D and calcium supplementation, respectively, for specific therapy in 58 % and a combination of all three in 42 %. Reasons for failure to prescribe medications were lack of interest in 18 %, insufficient confidence in the therapeutic recommendation therapy in 10 %, insufficient information about the therapy in 12 % and other reasons including intolerance or morbidity (20 % of other reasons). There was significant divergence between the reasons given by patients and treating physicians ($p<0.001$).

Conclusion: One year after an osteoporotic fracture at most half of the patients were taking adequate medication against osteoporosis. Though this result is higher than those reported in the literature, the indicated lack of information and the discrepancy between the reasons given by the patients and their family physicians provide the scope for optimization with improvements in communication and information.

Disclosure: C. Hemmeler, None; **S. Morell**, None; **P. Hasler**, None; **T. Gross**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/twelve-months-after-osteoporosis-associated-fracture-has-adequate-therapy-been-initiated

Abstract Number: 383

Stiffness Index Study in Ehler Danlos Syndrome

Chandralekha Ashangari, Henykumar Patel, Neelesh Gupta and Amer Suleman, DEPARTMENT OF CARDIOLOGY, THE HEARTBEATCLINIC, DALLAS, TX
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SESSION INFORMATION
Session Date: Sunday, November 8, 2015
Session Title: Osteoporosis and Metabolic Bone Disease - Clinical Aspects and Pathogenesis Poster
Session Type: ACR Poster Session A
Session Time: 9:00AM-11:00AM

Background/Purpose: Ehlers-Danlos syndrome is a group of inherited disorders that affects connective tissues primarily skin, joints and blood vessel walls. Ehlers-Danlos syndromes usually have overly flexible joints and stretchy, fragile skin. The purpose of this research is to measure the Stiffness index(T Score and Z score) by Achilles express. Achilles express Ultrasonometry provides a measurement of physical properties of bone. Two of the most commonly used ultrasound measures are Speed Of Sound (SOS, in m/sec) and Frequency Attenuation (Broadband Ultrasound Attenuation; BUA in dB/MH2) of a sound wave as it travels through bone.

Methods: 38 EDS patients and 23 non EDS controls are randomly selected from our clinic and Stiffness index is calculated by Achilles express. To express the ultrasound results, the Achilles combines the SOS and BUA values to calculate a clinical measure called the Stiffness Index (SI).Measurement of SOS in the heel involves accurate determination of the transit time of a sound wave as it passes through the heel. This is compared to the time required for a signal to pass through the water bath alone. Stiffness Index combines BUA and SOS into single clinical measure that has a lower precision error than either variable alone. SI= [0.67*BUA + 0.28*SOS] – 420.T score higher than -1.0 indicates low risk,score between -1.0 and -2.5 indicates intermediate risk,score lower than -2.5 indicates high risk.ANOVA analysis is performed

Results: Out of 61 subjects, 98% are females (n=60, age 31.49±11.53) , 2% are males (n=2, age 17),Mean age of 38 EDS patients (31.31±11.10) ,Mean age of 23 non EDS controls (30.79±11.02) , ANOVA:Stiffness index (Mean ± Standard deviation) in 38 EDS patients 92.73±16.65, In 23 non EDS controls 103.43±15.50 (Stiffness index EDS vs non EDS, P=0.01), T Score EDS vs Non EDS controls (-0.5±1.09 Vs 0.23±0.96 ,P =0.01), Z score EDS vs Non EDS controls (-0.3±1.12 Vs 0.33±0.86 ,P =0.02).

Conclusion: Patients with EDS appear to have low stiffness index at a young age. They may be predisposed to osteopenia or osteoporosis. Further research is needed to develop a proper strategy to avoid future complications.

Disclosure: C. Ashangari, None; **H. Patel**, None; **N. Gupta**, None; **A. Suleman**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/stiffness-index-study-in-ehler-danlos-syndrome

Abstract Number: 384

Dental Treatments, Tooth Extraction, and Osteonecrosis at Jaw in Japanese Patients with Rheumatoid Arthritis; Results from the IORRA Cohort Study

Takefumi Furuya, Shigeki Momohara, Atsuo Taniguchi and Hisashi Yamanaka, Institute of Rheumatology, Tokyo Women's Medical University, Tokyo, Japan

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SESSION INFORMATION

Session Date: Sunday, November 8, 2015

Session Title: Osteoporosis and Metabolic Bone Disease - Clinical Aspects and Pathogenesis Poster

Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose: Oral health is an important issue for the patients with rheumatoid arthritis (RA) because many RA patients were treated with bisphosphonates and bisphosphate use appears to be associated with osteonecrosis at Jaw (ONJ), and periodontitis is a potential risk factor for RA. Limited data exist in the literature concerning the dental treatment, tooth extraction, and ONJ in Japanese patients with RA. This study aimed to evaluate the dental treatments, tooth extraction, and ONJ in our Institute of Rheumatology Rheumatoid Arthritis (IORRA) cohort.

Methods: The IORRA cohort was established in 2000 as a single institute-based large cohort of Japanese RA patients conducted at the Institute of Rheumatology, Tokyo Women's Medical University (Tokyo, Japan). More than 100 publications have described various characteristics of Japanese RA patients using this cohort. Patients with RA enrolled in IORRA cohort completed self-administered questionnaires as part of the April IORRA surveys of 2014, which included their dental treatment, tooth extraction at dentists during the past 6 months from October 2013 to March 2014, and past history of ONJ. The past histories of ONJ were validated with the patients' medical records. Logistic regression was used to determine the association variables and tooth extraction.

Results: Among 5,779 Japanese patients with RA (median age 65 years old, female 85%), 2,323 patients (40.2%) and 378 (6.5%) reported to have dental treatment and extracted tooth at dentist during the past 6 months, respectively. Among 1,257 patients with RA treated with oral bisphosphonate and denosmab, 533 patients (42.4%) and 83 (6.6%) reported to have dental treatment and extracted tooth during the 6 months, respectively. Among the patients who had tooth extraction and took bisphosphonate during the 6 months (n = 34), 22 (64.7%) were advised to stop bisphosphonates before the tooth extraction by physicians and dentists. In multivariate model, advanced age (P = 0.0060) and current smoking (P = 0.0072) were associated with tooth extraction. Among the patients, 25 patients reported to have a history of ONJ. Among them, we confirmed ONJ with their medical records in 6 patients during the past 36 months (Table). Among the 6 patients with ONJ, they were all female aged over 65 years old, 5 and 4 were treated with oral bisphosphonates and prednisolone, respectively, at the diagnosis of ONJ, 1 had a history of oral bisphosphonate treatment, and 2 were complicated with diabetes. The incidence rate of ONJ was 0.35/1,000 person-years in all RA patents, 0.93/1,000 person-years in female RA patients over 65 years.

Table. Clinical characteristics of 6 Japanese RA patients with ONJ

Age at the diagnosis of ONJ	Gender	Oral bisphosphonate use	Prednisolone use
80	Female	7 years	5 mg/day
66	Female	10 years	6 mg/day
77	Female	5 years	5 mg/day
79	Female	Until 1 year ago	none
77	Female	5 years	1 mg/day
66	Female	10 years	none

Conclusion: In Japanese patients with RA, many patients have dental treatment and tooth extraction at dentists. Japanese physicians should consult dentists before and after prescribing bisphosphonates and denosmab especially for elderly female RA patients taking prednisolone.

Disclosure: T. Furuya, None; **S. Momohara**, AbbVie, 2,Asahi Kasei, 2,Bristol Myers Squibb, 2,Chugai, 2,Daiichi Sankyo, 2,Eisai, 2,Mitsubishi Tanabe, 2,Nakashima Medical Co., Ltd., 2,Santen Pharmaceutical Co., Ltd., 2,Taisho Toyama Pharmaceutical Co. Ltd, 2,Takeda, 2; **A. Taniguchi**, None; **H. Yamanaka**, Abbott Immunology Pharmaceuticals, 2,AbbVie, 2,Asahikasei, 2,Astellas, 2,AstraZeneca, 2,Bristol-Myers Squibb, 2,Chugai, 2,Daiichi Sankyo, 2,Eisai, 2,GlaxoSmithKline, 2,Janssen Pharmaceutica Product, L.P., 2,Mitsubishi Tanabe, 2,MSD, 2,Nippon Kayaku, 2,Pfizer Inc, 2,Santen, 2,Taishotoyama, 2,Takeda, 2,Teijin, 2,Abbott Immunology Pharmaceuticals, 5,AbbVie, 5,Astellas, 5,AstraZeneca, 5,Bristol-Myers Squibb, 5,Chugai, 5,Daiichi Sankyo, 5,Eisai, 5,Mitsubishi Tanabe, 5,Nippon Kayaku, 5,Pfizer Inc, 5,Takeda, 5,Teijin, 5,Abbott Immunology Pharmaceuticals, 8,AbbVie, 8,Astellas, 8,Bristol-Myers Squibb, 8,Chugai, 8,Eisai, 8,Mitsubishi Tanabe, 8,Pfizer Inc, 8,Takeda, 8,Teijin, 8.

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Abstract Number: 385

Urinary Cell-Free Microrna's As Biomarkers of Lupus Nephritis in

Children

Khalid Abulaban[1], Ndate Fall[2], Jun Ying[3], Kasha Wiley[4], Ravi Nunna[3], Prasad Devarajan[5], Alexei A. Grom[4], Michael Bennett[6], Stacy P. Ardoin[7] and Hermine I. Brunner[8], [1]Pediatric Rheumatology, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, [2]Division of Rheumatology, Cincinnati Children's Hospital, Cincinnati, OH, [3]University of Cincinnati, Cincinnati, OH, [4]Division of Rheumatology, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, [5]Dept of Nephrology, Cincinnati Children`s Hospital Medical Center, Cincinnati, OH, [6]Division of Nephrology, Cincinnati Children`s Hospital Medical Center, Cincinnati, OH, [7]Pediatric & Adult Rheumatology, Ohio State University, Columbus, OH, [8]Pediatric Rheumatology Collaborative Study Group, Cincinnati Children's Hospital Medical Center, Cincinnati, OH

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SESSION INFORMATION

Session Date: Sunday, November 8, 2015

Session Title: Pediatric Rheumatology – Clinical and Therapeutic Aspects Poster I: Lupus, Scleroderma, JDMS

Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose:

MicroRNAs (miRNAs) are single-stranded RNAs involved in the regulation of host genome expression at the post-transcriptional level. The objective of this study was to investigate whether select urinary cell-free microRNA's may serve as biomarkers in children with active lupus nephritis (LN) and to assess their relationship to the recently identified combinatorial urine biomarkers, a.k.a. the LN-Panel (neutrophil gelatinase associated lipocalin, monocyte chemotactic protein 1, transferrin, and beta-trace protein).

Methods:

In this prospective longitudinal cohort study, miRNAs (125a, 127, 146a, 150 and 155) were measured using real-time polymerase chain reaction in the urine pellet (PEL) and supernatant (SUP) in 14 patients with active LN, 10 patients with active extra-renal SLE, and 10 controls (five juvenile idiopathic arthritis and five fibromyalgia patients). The concentrations of the LN-Panel biomarkers were also assayed. Traditional LN-measures (complement levels of C3 and C4, anti-dsDNA antibodies, protein to creatinine ratio) and the renal and extra-renal disease activity were measured using renal and extra-renal domain scores of the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI), respectively.

Results:

SUP levels of miR-125a, miR-150, and miR-155 were at least weak to strongly associated with most of the LN-Panel biomarkers (Pearson correlation coefficients; $0.3 < r < 0.9$; $p<0.05$), but generally no more than weakly with the renal domain of the SLEDAI or traditional LN-measures (r-<0.5)(table). In the PEL, miRNA levels did not correlate with any of the LN-measure (LN-Panel, traditional LN-measures, renal-SLEDAI).

Conclusion:

Levels of cell-free miR-125a, miR-150, and miR-155 in the urine supernatant but not the sediment are differentially excreted with active LN and may complement, but are unlikely superior to the LN-Panel for estimating concurrent LN activity.

Table:Associations of MiRNA levels in the urine supernatant vs. traditional measures **Values are Pearson correlation coefficients of log-transformed urine concentrations the miRNAs listed with miR, micro RNA ; BTP, beta trace protein ; NGAL, neutrophil gelatinase associated lipocalin ; MCP, monocyte chemotactic protein 1; WBC, white blood count ; DSDNA, anti-double stranded DNA titer ;

* SLEDAI, Systemic Lupus Erythematosus Disease Activity Index, range 0 - 105; 0 inactive LN

[1]Renal-SLEDAI, renal domain of the Systemic Lupus Erythematosus Disease Activity Index.

[2]Extrarenal SLEDAI, Sum of the Systemic Lupus Erythematosus Disease Activity Index except the renal domain score

Variables **	*miR125a*	*miR127*	*miR146a*	*miR150*	*miR155*
LN-Panel					
Transferrin	**0.44**	-0.24	-	**0.65**	**0.54**
BTP	**0.73**	-0.24	**-0.37**	**0.68**	**0.35**
NGAL	**0.48**	-	-0.27	**0.39**	-
MCP-1	**0.44**	**0.34**	-	**0.45**	**0.68**
WBC (k/mcL)	0.23	-	-	**0.40**	-
Hemoglobin (mg/dL)	-	-	-	-	-
Platelets count (k/mcL)	**-0.39**	-0.24	-	-	-
ESR (mm/hr)	-	0.24	-	-	-
Anti-dsDNA titer	-	**-0.33**	**-0.30**	-	-0.29
C3 level (mg/dL)	**-0.32**	-	0.24	--	**-0.36**
C4 level (mg/dL)	-	-	-	-	-0.29
Total SLEDAI*	**0.31**	-	-0.28	-	-
Renal - SLEDAI[1]	-	-	**-0.32**	-	-
Extrarenal SLEDAI[2]	0.27	-	-	-	-

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Chronic Arthritis in Systemic Lupus Erythematosus: Distinct Features in 336 Pediatric and 1,830 Adult Patients

Natali W. Gormezano[1], Clovis A Silva[2], **Nadia E Aikawa**[3], Diego L. Barros[4], Mariana A. da Silva[4], Carini I. Otsuzi[4], Katia T. Kozu[5], Luciana Seguro[4], Rosa M R Pereira[6] and Eloisa Bonfá[4], [1]Pediatric Rheumatology Unit, Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil, [2]Pediatric Rheumatology, Faculdade de Medicina da Universidade de São Paulo, Sao Paulo, Brazil, [3]Rheumatology, Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil, [4]Rheumatology Division, Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil, [5]Pediatrics, Faculdade de Medicina da Universidade de São Paulo, Sao Paulo, Brazil, [6]Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil

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Session Time: 9:00AM-11:00AM

Background/Purpose: Acute articular involvement is an important feature of childhood systemic lupus erythematosus (cSLE) and adult-onset (aSLE) patients, and it has been described in up to 70% of children and 90% of adults. In

contrast, evaluation of chronic arthritis (CA) has been restricted to case reports or small series in cSLE and aSLE patients. Moreover, comparison of clinical and laboratorial parameters in both SLE groups with CA is lacking in the literature. Therefore, the objective of the present study was to determine the overall prevalence of CA, and to compare clinical/laboratorial features and treatment in a large population of children and adult lupus patients.

Methods: This retrospective study evaluated medical charts of 336 cSLE and 1,830 aSLE patients (ACR criteria) followed in the same tertiary hospital. Demographic data, arthritis characteristics, clinical features, disease activity (SLEDAI-2K) and treatment were recorded. CA was defined as synovitis with least 6 weeks duration. Rhupus syndrome was characterized as the association of SLE and juvenile idiopathic arthritis/rheumatoid arthritis with erosion. Jaccoud's arthropathy was defined as a non-erosive subluxation leading to severe deformity of the hands and feet, mild aching and little or no evidence of synovitis.

Results: Frequencies of CA were similar in cSLE and aSLE patients (2.3% vs. 3.7%,p=0.261). Hands (62% vs. 58%,p=1.000), wrists (62% vs. 48%,p=0.480) and knees (50% vs. 17%,p=0.053) were the most frequently involved joints in both groups. Ankles were significantly more involved in cSLE (100% vs. 16%,p<0.001). The median of disease duration until CA diagnosis was shorter in cSLE (0 vs. 10 years,p<0.001). Children presented more polyarthritis than adults (75% vs. 32%,p=0.024), as well as median number of joints with arthritis [8.5(1-18) vs. 3(1-9),p=0.017] and number of joints with limitation on motion [1.5(0- 24) vs. 0(0-4),p=0.004]. Further analysis of cSLE and aSLE patients at CA diagnosis revealed higher frequencies of hepatomegaly (25% vs. 0,p=0.009), splenomegaly (25% vs. 0,p=0.009), alopecia (37% vs. 1.4%,p=0.002), pericarditis (25% vs. 0, p=0.009), nephritis (37% vs. 3%,p=0.006), hematuria (37% vs. 1.4%,p=0.002), lupus anticoagulant (40% vs. 1.6%, p=0.012) and anticardiolipin IgM (40% vs. 1.5%,p=0.012) and higher median of SLEDAI-2K [10.5(1-20) vs. 6(4-16),p=0.029] in the former group. Frequencies of rhupus syndrome (12% vs. 17%,p=1.0) and concomitant Jaccoud's arthropathy (0 vs. 17%,p=0.343) were similar in cSLE and aSLE patients at CA diagnosis. The frequencies of glucocorticoid, antimalarials and methotrexate use were similar in both groups (p>0.05).

Conclusion: We identified that chronic arthritis in SLE has distinct features in children with very early onset, polyarticular involvement and often associated with active disease. We further demonstrated that rhupus is not a relevant cause of CA in cSLE and aSLE patients, suggesting that CA represents a distinct manifestation of lupus.

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Abstract Number: 387

Features of 847 Childhood-Onset Systemic Lupus Erythematousus Patients in Three Age-Related Groups at Diagnosis: A Brazilian Multicenter Study

Clovis A Silva[1], **Roberta C. Gomes Sr.**[2], Marco F. Silva[3], Katia T. Kozu[4], Eloisa Bonfá[5], Rosa M R Pereira[6], Maria Teresa Terreri[7], Claudia S. Magalhães Sr.[8], Silvana B. Sacchetti Sr.[9], Roberto Marini Sr.[10], Melissa Fraga[11], Luciana M. Carvalho Sr.[12], Cássia M. Barbosa[13] and Magda Carneiro-Sampaio Sr.[14], [1]Pediatric Rheumatology, Faculdade de Medicina da Universidade de São Paulo, Sao Paulo, Brazil, [2]Pediatric Rheumatology Unit, Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil, [3]Pediatric Rheumatology Unit-Children's Institute,, Faculdade de Medicina da Universidade de São Paulo, Sao Paulo, Brazil, [4]Pediatrics, Faculdade de Medicina da Universidade de São Paulo, Sao Paulo, Brazil, [5]Division of Rheumatology, Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil, [6]Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil, [7]Pediatrics, Universidade Federal de Sao Paulo, São Paulo, Brazil, [8]Pediatric Rheumatology Unit, São Paulo State University – Faculdade de

Medicina de Botucatu, São Paulo, Brazil, [9]Pediatric Rheumatology Unit, Irmandade da Santa Casa de Misericórdia de São Paulo, São Paulo, Brazil, [10]Pediatric Rheumatology Unit, State University of Campinas, São Paulo, Brazil, [11]Pediatrics, Universidade Federal de São Paulo / UNIFESP, São Paulo, Brazil, [12]Pediatric Rheumatology Unit, Ribeirão Preto Medical School – University of São Paulo, São Paulo, Brazil, [13]Pediatric Rheumatology Unit, Hospital Infantil Darcy Vargas, São Paulo, Brazil, [14]Pediatric Allergology and Immunology Unit, Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil
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Background/Purpose: Previous retrospective evaluations suggested that age at diagnosis may influence disease expression in terms of initial clinical presentation, pattern of organ involvement and serological findings in childhood systemic lupus erythematosus (cSLE) patients. However, the small sample size of previous studies, particularly regarding the early-onset cSLE patients (<6 years), precludes a definitive conclusion about their findings. In addition, no data is available regarding the relevance of age in Latin-American c-SLE population. Therefore, the main objective of the present large multicenter study was to compare demographic data, clinical and laboratory findings at disease diagnosis in three different age-related cSLE groups.

Methods: A retrospective multicenter study was performed in 847 cSLE patients from 10 Pediatric Rheumatology services of São Paulo state, Brazil. Patients were divided in three age-related cSLE groups: A - early-onset (<6 years), B - school age (≥6 and <12 years) and C - adolescent (≥12 and < 18 years). An investigator meeting was held to define the protocol, to harmonize clinical parameters definition and disease activity tool scoring. Demographic data, clinical and laboratorial features, and disease activity (SLEDAI-2K) were evaluated.

Results:

Groups of cSLE patients were divided: A 39 (4%), B 395 (47%) and C 413 (49%). Of 39 cSLE patients of group A, 3 (8%) were infants, 4 (10%) toddlers and 32 (82%) preschool. Complete C1q deficiency was observed in 3/74 (4%) cSLE patients, all of them of group A. Groups were similar regarding frequencies of nephritis (47% vs. 51% vs. 49%, p=0.742), neuropsychiatric involvement (37% vs. 25% vs. 24%, p=0.348), autoimmune hemolytic anemia (19% vs. 23% vs. 19%, p=0.237), thrombocytopenia (11% vs. 18% vs. 14%, p=0.264) and median of SLEDAI-2K at disease diagnosis [15(5-41) vs. 15(0-58) vs. 14(0-49) p=0.831). Frequencies of female gender, autoantibodies profile, acute phase proteins and low complement levels were also comparable in these three groups (p>0.05). Of note, frequencies of fever (78% vs. 61% vs. 47%, p<0.0001), hepatomegaly (42% vs. 29% vs. 14%, p<0.0001), splenomegaly (28% vs. 12% vs. 4%, p<0.0001) and discoid lupus (13% vs. 4% vs. 4%, p<0.020) were significantly higher in the group A compared to groups B and C. In contrast, the frequencies of weight loss >2kg (19% vs. 28% vs. 36%, p<0.017), photosensitivity (34% vs. 41% vs. 51%, p<0.006), leukopenia<4,000/mm^3 (14% vs. 25% vs. 30%, p<0.048) and lymphopenia<1,500/mm^3 (22% vs. 41% vs. 47%, p=0.011) were significantly lower in the group A.

Conclusion:

Our large multicenter study identified that the initial presentation of cSLE is characterized by comparable high frequencies of internal organ involvements and some distinct clinical and laboratorial features in early-onset and adolescent groups.

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Pain, Fatigue and the Psychological Impact on Health-Related Quality of Life in Childhood-Onset Lupus

Jordan T. Jones[1], Natoshia Cunningham[2], Catherine Donnelly[3], Susmita Kashikar-Zuck[4] and Hermine I. Brunner[5], [1]Division of Rheumatology, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, [2]Behavioral Medicine & Clinical Psychology, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, [3]Internal Medicine, University of Cincinnati, Cincinnati, OH, [4]Behavioral Medicine and Clinical Psychology, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, [5]Pediatric Rheumatology Collaborative Study Group, Cincinnati Children's Hospital Medical Center, Cincinnati, OH

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Background/Purpose: Childhood-onset lupus (cSLE) is a chronic autoimmune disease that has negative impact on health-related quality of life (HRQoL), especially when increased disease activity and damage exist, however, even with well controlled disease, HRQoL with cSLE remains lower compared to healthy populations. Chronic disease and related symptoms (pain, fatigue and poor sleep) as well as psychological factors (depression, anxiety and difficulty coping) can impair participation in developmentally appropriate activities. However, the impact of these potentially modifiable factors in relation to HRQoL in youth with cSLE is unknown. O*bjectives* of this study were to evaluate pain, fatigue and psychological functioning of cSLE patients and examine how these factors impact HRQoL.

Methods: As part of an ongoing study, cSLE patients (n= 65; 8 – 20 years) followed at Cincinnati Children's Hospital, were asked to complete measures of *pain* (Pain visual analog scale), *fatigue* (PedsQL Multidimensional Fatigue Scale), *depression* (Children's Depression Inventory I), *anxiety* (Screen for Child Anxiety Related Disorders), *pain coping* (Pain Coping questionnaire, Pain Catastrophizing scale), *sleep* (Adolescent Sleep Wake Scale), and *HRQoL* (PedsQL Generic Core scale and Rheumatology Module, Functional Disability Inventory). Measures of disease activity (Systemic Lupus Erythematosus Disease Activity Index, and physician completed visual analog scale of cSLE disease activity [0-10; 0=inactive]) were also obtained.

Results: Subjects were 83% female with mean age of 16.1 years (SD 2.6) and mean SLEDAI score of 5.6 (SD 5.6). Fatigue was present in 63% of the patients; clinically relevant pain (Pain-VAS > 3), anxiety (SCARED ≥ 25) and depressive symptoms (CDI-I > 12) were observed in 38%, 38% and 31% of the patients, respectively; 60% had moderate catastrophizing (PCS ≥ 15). On average, the PedsQL-GC/RM for cSLE were lower than those observed in healthy populations (Table 1). Reduced PedsQL-GC/RM scores were highly correlated with greater levels of fatigue, anxiety, and depressive symptoms (Pearson r > 0.65), but had weak correlation with disease activity (Pearson r < 0.25). Regression analysis demonstrated HRQoL was most impacted by fatigue, and pain when evaluating all factors concurrently ($p < 0.001$; Table 2).

Conclusion: cSLE is associated with decreased HRQoL, psychological aspects of health are prevalent and markedly contribute to low HRQoL. Fatigue, pain, and anxiety symptoms are present in a large subgroup of patients and need to be addressed to achieve optimal health outcomes.

Table 1. Health-related quality of life (HRQoL) and modifiable factors

Measures	Normative population mean (SD)	cSLE mean (SD)	Frequency, n (%) above cutoff value†	p-value
HRQoL Variables				
PedsQL Generic Core Scale	83.9 (12.5)	71.3 (18.4)		0.001
PedsQL Rheumatology Module	84.4 (18.0)	73.8 (18.5)		0.001
Functional Disability Index (FDI)		6.9 (7.7)		
FDI > 12			11 (17%)	
Modifiable Factors				
Fatigue	80.5 (13.3)	57.5 (21.4)		0.001
Anxiety (SCARED)		22.3 (17.4)		
SCARED ≥ 25			25 (38%)	
Mood (CDI-I)		9.8 (8.4)		
CDI-I > 12			20 (31%)	
Pain (Pain-VAS)		2.8 (2.6)		
Pain-VAS > 3			25 (38%)	
Pain Catastrophizing (PCS)		18.5 (11.6)		
PCS ≥ 15			39 (60%)	
Pain Coping		2.6 (0.6)	*	
Sleep		4.2 (0.5)	**	

† Denotes cutoff values for clinically important symptoms for each variable where applicable

* Denotes no established normative or cutoff value; range 1-5, higher values = worse coping

** Denotes no established normative or cutoff value; range 1-6, higher values = better sleep

Table 2. Hierarchical regression analyses predicting HRQoL (PedsQL-GC & PedsQL-RM)

Predictor	Predicting PedsQL-GC				Predicting PedsQL-RM			
Variable	β*	p-value	R^{2**}	R^2 change	β*	p-value	R^{2**}	R^2 change
Step 1			0.30	0.30			0.33	0.33
Pain	-0.55	<0.001			-0.57	<0.001		
Step 2			0.71	0.41			0.55	0.22
Fatigue	0.70	<0.001			0.52	<0.001		
Step 3			0.76	0.05			0.67	0.12
Anxiety	-0.14	0.13			-0.36	0.002		
Mood	-0.21	0.06			-0.14	0.28		
Coping	0.06	0.42			-0.06	0.50		
Catastrophizing	-0.00	0.97			-0.04	0.72		

* Represents the standardized coefficients

** Coefficient of multiple determination (how much model variance is predicted by each step, and the change with each additional step added to the model)

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Abstract Number: 389

Clinical and Serological Differences Between Juvenile-Onset and Adult-Onset Systemic LUPUS Erythematosus Patients from a National Registry of Patients

TC Salman-Monte[1], V Torrente-Segarra[2], I Rúa-Figueroa[3], J Calvo-Alen[4,5], FJ Lopez Longo[6,7], M Galindo[8,9] and JM Pego-Reigosa[10], [1]Rheumatology, Hospital del Mar/Parc de Salut Mar, Barcelona, Spain, [2]Rheumatology, Hospital General Hospitalet-Moisès Broggi, Hospitalet Llobregat, Spain, [3]Rheumatology, Hospital de GC Dr Negrin, Las Palmas GC, Spain, [4]Rheumatology Division, Sierrallana Hospital, Torrelavega, Spain, [5]Rheumatology, Hospital Sierrallana. Torrelavega, Torrelavega, Spain, [6]Department of Rheumatology, Hospital General Universitario Gregorio Marañón, Madrid, Spain, [7]Rheumatology, Gregorio Marañón Hospital, Madrid, Spain, [8]Servicio de Reumatología, Instituto de Investigación Hospital 12 de Octubre (I+12), Madrid, Spain, [9]Servicio de Reumatología, Hospital 12 de Octubre, Madrid, Spain, [10]Rheumatology, EOXI Vigo, Vigo, Spain

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Background/Purpose: To assess clinical and serological differences between patients with juvenile-onset systemic lupus erythematosus (jSLE) and adult-onset (aSLE) from a National database.**Methods:** Data included in the transverse phase of the National Register of lupus of the Spanish Society of Rheumatology (RELESSER –T) were analysed, which includes retrospective data from SLE patients. Inclusion criteria: patients with SLE with > or = 4 ACR criteria for SLE who were divided into 2 groups: disease date onset < 18 years and > 18. Sociodemographic, clinical, serological, activity, treatment and cumulative damage and chronicity data were collected. Associative descriptive statistical analysis was performed.**Results:** we reviewed 3.428 aSLE (89.6 % women) and 484 jSLE (89.8 % girls), 93.1 % Caucasian in both groups; age at diagnosis: 38.1±14 and 16.6 ± 6.3 years, respectively; average delay in diagnosis 24.7±47.4 and 39.9±5 months, respectively; mean age at followup: 48.8 ± 14.3, 31.5 ± 30 years, respectively. Table 1 shows all significant differences ($p < 0.05$). In aSLE 68.7 % had positive anti-DNA Ab vs. 82.9 % of jSLE ($p < 0.001$). Table 1

VARIABLE	aSLE (N=3.428)	jSLE (N=484)	p-value
Nephritis	2491 (74.1%)	256 (54.2%)	0.000
No	867 (25.9%)	216 (45.8%)	
Yes			
HTA (with nephritis)	2966 (90.0%)	385 (84.6%)	0.000
No	328 (10%)	70 (15.4%)	
Yes			
Creat clearance <5	3184 (95.2%)	430 (97.2%)	0.007
No	160 (4.8%)	36 (7.8%)	
Yes			
Proteinuria >3.5 g/24hs	3226 (96.8%)	437 (94.5%)	0.007
No	106 (3.2%)	26 (5.5%)	
Yes			
Chronic renal failure	3241 (97.8%)	437 (94.1%)	0.000
No	72 (2.2%)	27 (5.9%)	
Yes			
Recurrent nephritis	1641 (87.3%)	227 (74.9%)	0.000
No	237 (12.7%)	76 (25.1%)	
Yes			
AntiDNAds Ab	1048 (31.3%)	80 (17.0%)	<0.001
No	2300 (68.7%)	391 (83.0%)	
Yes			
Organic brain syndrome	3282 (97.5%)	448 (94.7%)	0.001
No	83 (2.5%)	25 (5.3%)	
Yes			
TTP	3286 (97.8%)	452 (96.3%)	0.046
No	72 (2.2%)	17 (3.7%)	
Yes			
SLE family background	2128 (84.8%)	286 (78.7%)	0.003
No	381 (15.2%)	77 (21.3%)	
Yes			
SLEDAI	2.4 ± 3.5	3.3 ± [4.1]	0.000
	2 [0-4]	2 [0-4]	
KATZ	2.4 ± 1.5	3.1 ± 1.9	0.000

	2 [1-3]	3 [2-4]	
CHARLSON	2.4 ± 1.9 2 [1-3]	1.6 ± 1.2 1 [1-2]	0.000
Steroid treatment (ever) No Yes	450 (13.7%) 2813 (86.3%)	33 (7.0%) 433 (93%)	0.000
Azathioprine No Yes	2295 (70.9%) 939 (29.1%)	33 (26.8%) 90 (73.2%)	0.000
Ciclophosphamide No Yes	2633 (81.3%) 604 (18.7%)	296 (63.9%) 167 (36.1%)	0.000
Micophenolate Mofetil No Yes	2824 (87.6%) 399 (12.4%)	345 (75.3%) 113 (24.7%)	0.034
Mycophenolic acid No Yes	3112 (97.9%) 66 (2.1%)	425 (95.4%) 18 (4.6%)	0.000
IV immunoglobuline No Yes	3093 (96.4%) 120 (3.6%)	414 (90.9%) 41 (9.1%)	0.000
Rituximab No Yes	3061 (94.4%) 179 (5.6%)	413 (89.7%) 47 (10.3%)	0.000
Splenectomia No Yes	3194 (98.6%) 45 (1.4%)	445 (96.9%) 14 (3.1%)	0.008
Dyalisis No Yes	3135 (97.3%) 84 (2.7%)	440 (95.0%) 23 (5%)	0.002
Kidney transplantation No Yes	3172 (98.6%) 42 (1.4%)	444 (96.7%) 15 (3.3%)	0.001
Osteoporosis No	3085 (92.4%) 252 (7.6%)	455 (96.8%) 15(3.2%)	0.001

Yes			
Fibromyalgia No Yes	3135 (93.3%) 224 (6.7%)	461 (97.6%) 11 (2.4%)	0.000
Anti-Ro Ab No Yes	2015 (60.5%) 1315 (39.5%)	310 (66.6%) 155 (33.4%)	0.011
Secondary Sjögren No Yes	2850 (84.7%) 508 (15.3%)	447 (93.5%) 31 (6.5%)	0.000

Conclusion: jSLE have higher percentage of nephritis, hypertension (associated with nephritis), anti-DNA, Creat clearance < 5, proteinuria > 3.5, recurrent nephritis, chronic renal failure, organic brain syndrome and thrombotic thrombocytopenic purpura and more SLE family background. jSLE also have higher SLEDAI, Katz, but lower Charlson scores. Secondary Sjögren (anti-RO), fibromyalgia and osteoporosis are more common in aSLE. jSLE receive more steroid treatment, synthetic immunosuppressants, IV immunoglobuline, rituximab, splenectomy, dialysis and kidney transplantation.

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Abstract Number: 390

Treatment and Outcomes in Pediatric SLE Patients in South Africa

Laura Lewandowski[1], Christiaan Scott[2], Laura Schanberg[3] and Nathan Thielman[4], [1]Pediatric Rheumatology, Duke University Medical Center, Durham, NC, [2]Rheumatology, Red Cross War Memorial Children's Hospital, Cape Town, South Africa, [3]Duke University, Durham, NC, [4]Duke Hubert Yeargan Center for Global Health, Durham, NC
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Background/Purpose:

Although African children with SLE may be at high risk for poor outcomes based on race, socioeconomic status, and

age, little research has investigated this population. We have initiated the first registry of this high risk pediatric SLE (pSLE) population in South Africa (SA). Here, we present the first comparison of treatment and outcomes between a South African pSLE cohort (PULSE) and a North American pSLE cohort (Childhood Arthritis and Rheumatology Research Alliance (CARRA) Registry).

Methods:

We conducted a cross sectional analysis (retrospective chart review) of pSLE patients in Cape Town, SA from 1988-2014 meeting ACR criteria for pSLE. Patient age, gender, race, presenting features, clinical and serologic disease markers, and treatment were recorded and compared to an established North American pSLE cohort.

Results:

The SA cohort includes 72 patients; mean age 11.5 years, 83% female. The SA cohort had increased rates and severity of lupus nephritis and high disease activity at enrollment (**Table 1**) SA patients had increased use of cyclophosphamide (942% vs 29%), methotrexate (30% vs 19%), and azathioprine (61% vs 16%). PSLE patients in the CARRA cohort had increased use of antimalarials and mycophenolate mofetil (**Table 2**). The PULSE cohort had high rates of end organ damage with 63% having a SLICC-DI score >0. Within the SA cohort, 13% went on to develop ESRD, of which 9% required transplant, strikingly higher than North American peers. (**Table 3**)

Conclusion:

The PULSE cohort is the largest registry of pSLE patients in Africa to date. Children in SA receive different therapy and demonstrate a striking increase in poor renal outcomes, end stage renal disease, and irreversible organ damage compared to North American peers. These differences may be due to treatment, health care access, racial predisposition, or a combination of factors. Further prospective research is required to determine the burden of pSLE in South Africa, and identify risk factors for poorer outcome in this high risk population.

Table 1. Features at Enrollment

	PULSE N=72	**CARRA N=982**	**P value**
Mean age of SLE diagnosis (mean, SD)	11.5 (3.5)	12.4 (3.2)	0.027
Average disease duration, yrs (mean, SD)	2.4 (3.2)	3.5 (3.0)	0.001
% Female (n)	82.3 (56)	82.5 (810)	0.873
% White (n)	6 (4)	45 (426)	
% Other (n)	3 (2)	20 (190)	
% Age ≤13 at diagnosis (n)	75 (53)	51 (475)	<0.001
% ANA positive (n)	96 (69)	91 (888)	0.065
% Anti-dsDNA positive (n)	82 (60)	60 (576)	<0.001
% Lupus Nephritis (n)	61 (44)	41 (409)	<0.001
Average SLEDAI Score [range 0-105] (SD)	20.6 (9.9)	4.8 (1.9)	<0.001**
% renal biopsy (n)	58 (41)	44 (428)	0.049
% of biopsied patients with ISN classification	100 (41)	65 (280)	<0.001

Table 2. Treatment History at Enrollment

	PULSE N=72	**CARRA N=982**	**P value**
% steroids (n)	93 (66)	94 (917)	0.725
% antimalarial (n)	78 (54)	92 (853)	0.001
% cyclophosphamide (n)	42 (30)	29 (267)	0.022
% MMF (n)	42 (28)	60 (556)	0.004
% azathioprine (n)	61 (41)	16 (146)	0.001
% methotrexate (n)	30 (19)	19 (184)	0.019
% rituximab (n)	6 (4)	10 (99)	__
% IVIg (n)	12 (8)	2 (17)	__

Table 3. Disease Damage at Enrollment

classification			
% biopsied with lupus nephritis (n)	100 (41)	100 (428)	1.000
% biopsied class I (n)	0 (0)	1 (6)	0.998
% biopsied class II (n)	7 (3)	9 (39)	0.999
% biopsied class III (n)	4 (2)	22 (95)	0.020
% biopsied class IV (n)	57 (24)	26 (112)	0.001
% biopsied class V (n)	23 (9)	15 (66)	0.250
% biopsied class VI (n)	7 (3)	0	0.001

	PULSE N=72	CARRA N=982	P value
% ESRD (n)	13	NR*	--
% Dialysis (n)	16 (11)	1 (11)	<0.001
% Transplant (n)	9 (6)	0.7 (7)	<0.001
%Mortality (n)	7 (5)	NR*	--

*NR indicates not reported in this cohort.

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Current Provider Practices and Perceived Barriers for Mental Health Care of Adolescents with SLE

Andrea Knight[1,2,3], Michelle Vickery[2], Eyal Muscal[4], Alaina Davis[5], Julia Harris[6], Arzu Soybilgic[7], Karen Onel[8], Laura E. Schanberg[9], Tamar Rubinstein[10], Beth S. Gottlieb[11], Tracey Wright[12], Emily von Scheven[13] and for the CARRA Investigators, [1]Rheumatology, Children's Hospital of Philadelphia, Philadelphia, PA, [2]PolicyLab, Children's Hospital of Philadelphia, Philadelphia, PA, [3]Center for Pediatric Clinical Effectiveness, Children's Hospital of Philadelphia, Philadelphia, PA, [4]Pediatric Rheumatology, Baylor College of Medicine, Texas Children's Hospital, Houston, TX, [5]Pediatric Rheumatology, Vanderbilt University School of Medicine, Monroe Carell Junior Children's Hospital, Nashville, TN, [6]Pediatric Rheumatology, Children's Mercy Kansas City, Kansas City, MO, [7]Pediatric Rheumatology, University of Illinois College of Medicine, Chicago, IL, [8]Pediatric Rheumatology, Univ of Chicago, Chicago, IL, [9]Dept of Pediatrics, Duke University Medical Center, Durham, NC, [10]Division of Pediatric Rheumatology, Albert Einstein College of Medicine, Children's Hospital at Montefiore, Bronx, NY, [11]Pediatric Rheumatology, The Steven and Alexandra Cohen Children's Medical Center of New York, The Hofstra North Shore-LIJ School of Medicine, New Hyde Park, NY, [12]Pediatrics/Rheumatology, UT Southwestern Medical Center, Dallas, TX, [13]Dept of Pediatric Rheumatology, Univ of California San Francisco, San Francisco, CA

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Background/Purpose: Depression and anxiety are common in adolescents with SLE. Barriers to mental health intervention in pediatric rheumatology care are unclear. We aimed to determine current provider practices and

perceived barriers to mental health care for adolescents with SLE.

Methods: We conducted a web-based survey from May-June 2015 among members of the Childhood Arthritis and Rheumatology Research Alliance (CARRA). Inclusion criteria were providers caring for adolescents with SLE, with an available email address. The survey assessed provider demographics, current practices and barriers for mental health care of adolescents with SLE. Participants rated potential barriers on a 4-point Likert scale as: "never=0", "sometimes=1", "often=2" or "very often=3". We defined significant barriers as those rated "often" or "very often", and ranked them by frequency. We used multivariable negative binomial regression to examine associations of demographics with the number of significant barriers to mental health care. Provider covariates included: type (attending or trainee MD/DO, NP, PA); sex; years in practice; mental health training. Practice covariates included: setting; location; size; upper age limit of patients treated; SLE population size and insurance composition; presence of a specialized SLE clinic; involvement in SLE research.

Results: Of 375 eligible CARRA members, 120 (32%) responded. After exclusions (13 incomplete, 6 not in clinical care), 101 were analyzed. Eighty percent of respondents were attending physicians, 43% had >10 years in practice, 95% were university-affiliated and 72% were female. Fifty-four percent said identification of depression/anxiety in adolescents with SLE was currently inadequate and 47% said treatment was inadequate. Routine screening for depression and anxiety was supported by 84% and 71%, respectively, and 89% thought screening should occur in outpatient rheumatology. Although 54% reported practicing routine informal mental health screening, only 9% used a standardized screening tool. The most frequent barriers to routine screening in rheumatology were limited time and staff resources (Table 1). The most frequent barriers to treatment were limited availability and long waiting lists for mental health providers. Mental health training beyond medical school (IRR=0.34, 95% CI 0.16-0.73, $p<0.01$) and experience treating adults with SLE (IRR=0.36, 95% CI 0.20-0.64, $p<0.01$) were associated with fewer barriers. Interest in receiving training for mental health evaluation was endorsed by 90% and prescribing mental health medications by 60% of respondents.

Conclusion: Significant barriers exist to addressing the need perceived by rheumatologists for improved mental health care of adolescents with SLE. On-site resources and enhanced mental health training for pediatric rheumatologists may help overcome these barriers.

Table 1: Significant Barriers to Mental Health Care for Adolescents with SLE as Perceived by Respondents (N=101)		
Perceived Barriers to Routine Mental Health Screening*	**Rank**	**N (%) of Respondents**
Limited time during the encounter	1	77 (76)
Lack of staff resources to screen	2	74 (73)
Limited availability of mental health providers	3	66 (65)
Lack of staff resources to follow up results	4	65 (64)
Lack of institutional support	5	55 (54)
Limited space	6	45 (44)
Provider lack of mental health knowledge	7	29 (28)
Patient willingness to be screened	8	28 (27)
Parent willingness to have child screened	9	24 (23)
Language barriers	10	13 (12)
Provider discomfort with results	11	15 (14)
Confidentiality concerns	12	10 (9)
Perceived Barriers to Mental Health Treatment*	**Rank**	**N (%) of Respondents**
Limited availability of locations of mental health providers	1	76 (75)
Long waiting lists for mental health providers	2	76 (75)
Parent/patient uncertainty about where to obtain services	3	63 (62)
Time burden for patients/families	4	61 (60)
Insurance concerns	5	59 (58)
Cost to patients/families	6	53 (52)
Patient perceived lack of usefulness of mental health services	7	49 (48)
Transportation problems	8	49 (48)
Provider lack of knowledge of available mental health providers	9	41 (40)
Patient/parent concerns about what others will think	10	41 (40)
Parent perceived lack of usefulness of mental health services	11	39 (38)
Patient/parent distrust of mental health providers	12	34 (33)
Communication barriers between medical & mental health providers	13	29 (28)
Language barriers	14	21 (20)
Confidentiality concerns	15	13 (12)
* Potential barriers in survey were based on known correlates of unmet need for mental health services from the Methods for the Epidemiology of Child and Adolescent Mental Disorders Study (Flisher et al. *Psychol Med* 1997, 27(5):1145-1154), and known factors affecting integrated mental health care in primary care settings (Gunn et al. *Journal of clinical psychology* 2009, 65(3):235-252).		

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From Childhood to Adulthood: Longitudinal Trajectory of Damage in Patients with Childhood-Onset Systemic Lupus Erythematosus (cSLE)

Lily Siok Hoon Lim[1,2,3,4], Eleanor Pullenayegum[5], Lillian Lim[6], Dafna Gladman[7], Brian Feldman[8] and Earl Silverman[9], [1]Institute of Health Policy Management and Evaluation, University of Toronto, Toronto, ON, Canada, [2]Rheumatology, SickKids, Toronto, ON, Canada, [3]Rheumatology, Hospital for Sick Children, Toronto, ON, Canada, [4]Children's Hospital Research Institute of Manitoba, University of Manitoba, Winnipeg, MB, Canada, [5]Child Health Evaluative Sciences, The Hospital for Sick Children, Toronto, ON, Canada, [6]Pediatrics, The Hospital for Sick Children, Toronto, ON, Canada, [7]Rheumatology, University of Toronto, Toronto Western Hospital, Toronto, ON, Canada, [8]Division of Rheumatology, The Hospital for Sick Children and University of Toronto, Toronto, ON, Canada, [9]Division of Rheumatology, Hospital for Sick Children and University of Toronto, Toronto, ON, Canada
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Background/Purpose: Outcomes of patients with cSLE over time and into adulthood are poorly understood. There has been no information about the longitudinal trajectory of organ damage in cSLE patients. We undertook this study to: 1) determine the longitudinal damage trajectory– as measured by the American College of Rheumatology (ACR)/ SLE International Collaborating Clinics (SLICC) SLE damage index (SDI)– in patients with cSLE. 2) identify both baseline and disease course (time-varying) predictors of damage trajectory.

Methods: Single centre, retrospective, inception cohort. We included 473 patients who were diagnosed and followed, from 1st January 1985 to 30th September 2011. To be included, patients had to be <18 years at diagnosis, have satisfied the ACR classification criteria for SLE, were treated for <3 months with steroids or an immunosuppressant for any other disease, and have had at least 3 visits. Longitudinal pediatric-age data was obtained from our research database while adult-age data was obtained from either a research database or patients' charts. Clinical information at every visit was collected: for SLE disease activity index 2000 (SLEDAI2K), the SDI, laboratory results, and medications. Longitudinal trajectory of damage fit best with a 2nd order fractional polynomial (0.5,1). Predictors were identified using a weighted generalized estimating equation (WGEE). Time-varying predictors: disease activity, individual items of SLEDAI2K, corticosteroid, immunosuppressant and antimalarial exposures, were lagged by 6, 12, 18 and 24 months in different models.

Results: 67/473 (14%) patients were lost to follow-up. There were 14097 visits, totaling 3290 patient-years. The median follow-up duration was 5.5 years. The median age at diagnosis was 14.1 years and median age at last visit was19.5 years (range 6.0–41.9 years). 65% of patients were >18 years old at last follow-up. The predicted average population damage was 0.7 at 5 years, 1.3 at 10 years, 1.9 at 15 years, 2.3 at 20 years and 2.7 at 25 years. Cataract (14%) was the most common item of damage, followed by avascular necrosis (10%) and osteoporosis (5%). Only 2 patients had myocardial infarctions. Life-threatening major organ manifestations predicted higher initial damage but the accrual of damage slowed down over time. Higher prednisone dose (12, 24 months before) and the use of

cyclophosphamide (6, 12,18, 24 months before) predicted an increased damage trajectory at current visit. Antimalarial exposure (6 months before), mucosal ulcers (6,12,18,24 months before) and pericarditis (6 months before) were protective against an increase in damage trajectory.

Conclusion: Patients with cSLE accrue damage steadily throughout their disease course into adulthood. We identified the baseline factors that predict higher initial damage and influence damage trajectory. Over time, SLE clinical features and therapeutic exposures during the course of disease, predicted a change in damage trajectory.

Disclosure: L. S. H. Lim, None; **E. Pullenayegum**, None; **L. Lim**, None; **D. Gladman**, None; **B. Feldman**, None; **E. Silverman**, None.

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Abstract Number: 393

From Childhood to Adulthood: Identifying Latent Classes of Disease Activity Trajectories in Childhood-Onset Systemic Lupus Erythematosus Patients

Lily Siok Hoon Lim[1], Eleanor Pullenayegum[2], Lillian Lim[3], Dafna Gladman[4], Brian Feldman[5] and Earl Silverman[6], [1]Rheumatology, Hospital for Sick Children, Toronto, ON, Canada, [2]Department of Clinical Epidemiology & Biostatistics, McMaster University, Hamilton, ON, Canada, [3]Pediatrics, The Hospital for Sick Children, Toronto, ON, Canada, [4]Rheumatology, University of Toronto, Toronto Western Hospital, Toronto, ON, Canada, [5]Division of Rheumatology, The Hospital for Sick Children and University of Toronto, Toronto, ON, Canada, [6]Division of Rheumatology, Hospital for Sick Children and University of Toronto, Toronto, ON, Canada

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Background/Purpose: Although SLE patients are thought to follow different patterns of disease courses, no information is available about the longitudinal disease activity or the number of possible different disease courses. This study sought to: 1) determine the longitudinal disease activity trajectory in childhood-onset SLE (cSLE) patients; 2) determine the number of latent classes of disease activity trajectories and 3) identify factors predictive of membership in different disease trajectories.

Methods: Single centre longitudinal inception cohort of cSLE patients (onset <18 years) diagnosed and followed from Jan 1985 to Sep 2011. Clinical data from childhood to adulthood was obtained: pediatric data from our institutional cSLE database, adult data from the Toronto Lupus database or extracted from clinical charts from rheumatologists' offices. Longitudinal disease trajectory was constructed using data from every clinic visit in the 1st 10 years after diagnosis. Longitudinal SLE activity is a latent construct that is imperfectly measured with SLE disease activity index 2000 (SLEDAI2K) and prednisone exposure. Longitudinal mean population trajectories of SLEDAI2K and prednisone use were first fitted with the mixed effects model. SLEDAI2K and prednisone use were then jointly modeled in a Bayesian growth mixture model (GMM).

Results: 473 patients were included. 82% were females, median age of diagnosis was 14.1 years. There were 11992

visits, 2666 patient years. By the end of 10 years, 67% of the population had transferred to adult care. Mean population SLEDAI2K and prednisone trajectories of cSLE patients showed rapid decline to low activity levels within 2 years after diagnosis. However, joint GMM showed 5 latent classes were present in this cohort of cSLE patients in the following distributions: 30(6%), 57 (12%), 79 (17%), 92(19%), 215 (45%). Class1 patients have chronic moderate-high disease activity, class 2 had moderate initial disease activity and continued moderate long-term prednisone use, class 3 had initial high disease activity but achieved long-term remission, class 4 had high initial disease activity but relapsed later, class 5 had chronic low-grade disease activity. Across all classes, there was chronic use of prednisone (at least 5-10 mg/day) among cSLE patients in the first 10 years after diagnosis. Baseline major organ involvement, ethnicity, age at diagnosis and the number of baseline ACR criteria predicted membership in different classes.

Conclusion: cSLE patients could be subclassified into 5 distinct classes of disease activity trajectories. Baseline organ involvement and personal demographic factors could predict membership in the distinct disease activity trajectory classes.

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Abstract Number: 394

Clinical Features of Children with Silent Lupus Nephritis

Hiroyuki Wakiguchi[1], Syuji Takei[2,3], Tomohiro Kubota[1], Yuichi Yamasaki[1], Tsuyoshi Yamatou[1], Yasuhito Nerome[1], Harumi Akaike[1], Yukiko Nonaka[1], Tomoko Takezaki[1], Hiroyuki Imanaka[1] and Yoshifumi Kawano[1], [1]Department of Pediatrics, Kagoshima University Graduate School of Medical and Dental Sciences, Kagoshima, Japan, [2]School of Health Sciences, Faculty of Medicine, Kagoshima University, Kagoshima, Japan, [3]Department of Pediatrics, Kagoshima University Graduate School of Medical and Dental Sciences, Kagoshma, Japan
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Background/Purpose: Lupus nephritis (LN) is the major findings in systemic lupus erythematosus (SLE). LN with some pathologic findings in the kidney but had normal urine were called as silent LN (sLN); renal biopsy revealed that 70% of sLN patients were in Class I/II and 20% in Class III/IV in adult survey. However, there were few studies to examine sLN in juvenile SLE (JSLE). Therefore, clinical and renal pathologic findings in children with sLN were examined.

Methods: JSLE patients whose onset was before 16 years old, referred to our hospital from 2000 to 2011, were recruited in the study. Patients were divided into two groups according to urinary findings at the first examination; sLN and overt LN (oLN). Clinical findings such as gender, age at onset, ISN/RPS pathologic classification, general analysis of whole blood, and urinary findings after 3 years of therapy were retrospectively examined and compared between the two groups by using the Mann-Whitney *U*-test or the Fisher exact test.

Results: A total of 31 JSLE patients were involved in the study. Of the 31 patients, 18 (58%) were sLN and 13 (42%) were oLN. As to gender, the incidence of male was significantly higher in sLN group (33%) than oLN group (0%) (P =

0.028). Pathologic findings of ISN/RPS classification in sLN patients were Class I in 3, Class II in 12, and Class III in 3. In oLN patients, those were Class II in 3, Class III in 6, Class IV in 2, Class V in 1, and Class III + V in 1. Complement C3 level showed no statistical difference between the two groups. However, in sLN group, complement C3 levels in Class II (56 ± 23 mg/dL) and Class III (37 ± 19 mg/dL) were significantly lower than that observed in Class I (96 ± 26 mg/dL) (P = 0.02 and 0.04, respectively). Anti-dsDNA antibody titer showed no statistical difference between the two groups. On the other hand, anti-Sm antibody titer was significantly higher in sLN group (67 ± 54 U/mL) compared to oLN group (30 ± 49 U/mL) (P = 0.015). Urinary findings were still normal in 17/18 (94%) of sLN patients after 3 years of therapy.

Conclusion: In conclusion, these results suggest that complement C3 level and anti-Sm antibody may be a useful tool for predicting the severity and associated with the pathogenesis of sLN in JSLE, respectively. Though the all of the male patients were in sLN group, more than 90% of sLN patients maintained normal urinary findings at 3 years after initiating therapy. Considering the general concept that the prognosis of JSLE in male is more severe than that of female's, the present study may indicate that the early therapeutic intervention from sLN stage is essential to prevent the progression of renal damage.

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Depression Risk Among Adults with Childhood- and Adult-Onset Systemic Lupus Erythematosus: 11 Years of Follow-up

Erica F. Lawson[1], Andrea Knight[2], Laura Trupin[3], Patricia P. Katz[3] and Edward H. Yelin[4],
[1]Pediatrics/Rheumatology, UC San Francisco, San Francisco, CA, [2]Pediatrics/Rheumatology, Children's Hospital of Philadelphia, Philadelphia, PA, [3]Medicine/Rheumatology, University of California San Francisco, San Francisco, CA, [4]Medicine/Rheumatology, UC San Francisco, San Francisco, CA

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Background/Purpose:

Neuropsychiatric syndromes are prevalent in childhood-onset systemic lupus erythematosus (cSLE), but the long-term risk of depression in adults with cSLE is unknown. We compared the prevalence of depression among adults with cSLE to those with adult-onset SLE (aSLE) using the UCSF Lupus Outcomes Study (LOS).

Methods:

Data derive from the 2002-2012 cycles of the LOS, an annual longitudinal telephone survey of diverse English-speaking individuals with confirmed SLE. Participants aged 18-45 years (N=520) were included. Respondents were classified as childhood-onset if age at diagnosis was <18 years (N=112). Mental health was assessed with the Center for Epidemiological Studies Depression Scale (CESD), the ACR Committee on Neuropsychiatric Lupus' suggested

measure of depression in SLE, using validated cutoff values. Outcome variables included CESD≥24 (indicative of major depression) and CESD≥20 (indicative of a mood disorder). We performed repeated measures analysis using generalized estimating equations to compare cSLE and aSLE with and without adjustment for other characteristics that could affect depression risk. Age, gender, non-white ethnicity, marital status, poverty, education attained, obesity, self-reported disease activity according to the Systemic Lupus Activity Questionnaire (SLAQ) score, and physical disability according to the SF-36 Scale of Physical Function (SF36-PF) were included as covariates.

Results:

Respondents with cSLE were younger at baseline (26±7 v. 35±6), more likely to be male (13% v. 5%), and more likely to be ethnic minorities (60% v. 46%), all $p<0.01$. Mean age at diagnosis was 14±3 for respondents with cSLE as compared to 27±6 for those with aSLE. Mean disease duration at baseline was 13±7 years in the cSLE group and 8±6 years in the aSLE group. Mean baseline SLAQ score was 12±8 for all respondents. Prevalence of depressed mood at baseline was slightly higher among respondents with aSLE, though not statistically significant (23% vs. 29% for major depression and 31% vs. 35% for all mood disorders). Respondents with aSLE were more likely to have ever taken medication to treat depression (59% vs. 43%, $p=0.01$). In multivariate analysis, the odds of major depression among participants with cSLE was increased as compared to those with aSLE (OR=1.7, 95% CI 1.1-2.6) after adjustment for covariates (Table 1).

Conclusion:

Onset of SLE in childhood may be an independent risk factor for the development of major depression in early adulthood, with other important predictors including older age, lower educational attainment, increased disease activity and decreased physical function. Appropriate screening and treatment for depression is important to maximize long-term quality of life and functional outcomes in patients with cSLE.

Table 1. Adjusted and unadjusted odds ratios for the presence of major depression among individuals age 18-45 with SLE*

Variable	Unadjusted OR for major depression (95% CI)	Adjusted OR for major depression (95% CI)†
Childhood-onset SLE	0.8 (0.5-1.1)	**1.7 (1.1-2.6)**
Age	**1.02 (1.00-1.03)**	**1.04 (1.01-1.06)**
Female	1.8 (0.9-3.8)	1.1 (0.5-2.1)
Non-white ethnicity	1.2 (0.9-1.7)	1.2 (0.9-1.7)
Unmarried	**1.1 (1.0-1.4)**	1.2 (0.9-1.5)
Poverty¶	**1.8 (1.4-2.3)**	1.1 (0.8-1.6)
Education#	**3.3 (2.5-4.2)**	**2.1 (1.5-2.9)**
Obesity%	**1.3 (1.0-1.7)**	1.0 (0.7-1.3)
Increasing disease activity (SLAQ)	**1.14 (1.12-1.16)**	**1.11 (1.08-1.14)**
Decreasing physical function (SF36-PF)	**1.06 (1.05-1.07)**	**1.02 (1.01-1.04)**

*OR = odds ratio; 95% CI = 95% confidence interval; SLAQ = Systemic Lupus Activity Questionnaire (0-47); SF36-PF = SF-36 Scale of Physical Functioning (0-100)

† OR adjusted for variables shown

¶ Income below 125% of the Federal poverty level

Less than a bachelor's degree attained

% BMI ≥ 30

Disclosure: E. F. Lawson, None; **A. Knight**, None; **L. Trupin**, None; **P. P. Katz**, None; **E. H. Yelin**, None.

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Abstract Number: 396

A Comparison of the Illness Experience Reported Via the Patient Reported Outcomes Measurement Information System Between Patients with Childhood-Onset Systemic Lupus Erythematosus, Juvenile Idiopathic Arthritis, and Widespread Chronic Musculoskeletal Pain

Michael J. Holland[1], Jordan Jones[1], Esi M. Morgan DeWitt[2], Susmita Kashikar-Zuck[3], David D. Sherry[4], Adam C. Carle[5], Bin Huang[6], Constance Mara[7] and Hermine I. Brunner[1], [1]Pediatric Rheumatology, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, [2]Rheumatology, Cincinnati Children's Hospital Medical Center, Cincinnati,

OH, [3]Behavioral Medicine & Clinical Psychology, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, [4]Pediatric Rheumatology, Children's Hospital of Philadelphia, Philadelphia, PA, [5]University of Cincinnati Department of Pediatrics, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, [6]Biostatistics and Epidemiology, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, [7]James M. Anderson Center for Health Systems Excellence, Cincinnati Children's Hospital Medical Center, Cincinnati, OH
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SESSION INFORMATION

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Session Title: Pediatric Rheumatology – Clinical and Therapeutic Aspects Poster I: Lupus, Scleroderma, JDMS
Session Type: ACR Poster Session A
Session Time: 9:00AM-11:00AM

Background/Purpose:

The Patient Reported Outcomes Measurement Information System (PROMIS®), developed by the National Institutes of Health, seeks to create standardized instruments to measure patient reported health-related quality of life (HRQoL) across diverse domains, both within and *between* disease processes. Our objective was to use PROMIS pediatric short form responses to conduct a comparison of HRQoL between childhood-onset systemic lupus erythematosus (cSLE), juvenile idiopathic arthritis (JIA), and widespread chronic musculoskeletal pain (CMP)

Methods:

We compared cross-sectional data from a cohort of 100 children diagnosed with cSLE to a cohort of 121 patients diagnosed with JIA, and 66 patients diagnosed with widespread chronic musculoskeletal pain (CMP). Specifically we compared mean PROMIS pediatric short form T scores across conditions using ANOVA and post-hoc Tukey honest significant difference testing. We also compared mean pediatric quality of life inventory (Peds QL) general core (GC) total scores for cSLE and JIA via T-test.

Results:

Compared both to patients with cSLE and JIA, CMP had significantly worse PROMIS T-scores in every category aside from Peer Relationships (see table 2). cSLE and JIA patients' PROMIS T-scores did not differ significantly, except for lower mobility reported by patients with JIA ($p = 0.026$). Comparison of cSLE and JIA via mean Peds QL GC total scores showed cSLE fared significantly worse. The level of difference in PROMIS scores observed between CMP patients and cSLE/JIA was marked, with large F scores (17 or greater, in context of a critical difference of 2).

Conclusion:

We showed significantly poorer HRQoL in children with widespread chronic musculoskeletal pain compared to JIA and SLE patients (who did not differ significantly from each other). This result emphasizes the importance of HRQoL to children with rheumatologic and pain conditions, in addition to more objectively demonstrable physical pathology. Assessment of patient reported outcomes helps to identify areas for intervention to improve HRQoL. Further, given the significant difference between cSLE and JIA seen on the PEDS QL GC measures (but not PROMIS) additional validation of the PROMIS short forms is required to ensure that they address all quality of life domains relevant for SLE

Table 1. Demographics and Mean Scores

Values are mean (SD) unless stated otherwise	cSLE	JIA	CMP	
Total N	100	121	66	
Female N (%)	80 (80%)	86 (71.1%)	*121 (83.5%)*	
Age (yrs)	15.8 (2.2)	13 (2.7)	15.35 (2.2)	p-value:
Peds QL GC Summary Score	70.63 (17.8)	75.7 (15.3)		**0.025**
PROMIS Short Forms				
Anxiety	48.02 (11)	45 (9.6)	56.49 (9.39)	
Depressive	47.84 (11.9)	47.2 (9.3)	58.38 (8.7)	
Fatigue	50.73 (14.1)	48.1 (11.4)	66.32 (8.69)	
Mobility	46.85 (10.1)	44.8 (9.6)	32.51 (6.42)	
Upper Extremity	46.4 (7.9)	46.4 (9.9)	38.05 (9.62)	
Pain	50.25 (11.7)	51.3 (8.8)	63.34 (5.62)	
Peer Relations	49.67 (13)	51.4 (8.8)	47.88 (11.47)	

*Data for larger studied group of patients with chronic musculoskeletal pain, data for subgroup with widespread chronic musculoskeletal pain not available.

**Compares cSLE to JIA only, similar data not available for widespread chronic musculoskeletal pain.

Table 2: Comparison of cSLE with JIA and Generalized Pain

p-value *(Diff)* *95% Confidence interval*	SLE vs JIA (A)	SLE vs CMP (B)	JIA vs CMP (C)	p-value (A- C)	F-value
PROMIS Short Forms					
Anxiety	0.20 (-2.3) -5.54 - 0.90	<0.0001 (8.47) 4.69-12.25	<0.0001 (10.79) 7.15-14.43	<0.0001	25.05
Depressive Symptoms	0.8563 (0.74) -4.03 - 2.55	<0.0001 (10.54) 6.69- 14.39	<0.0001 (11.28) 7.56-15.0	<0.0001	28.74
Fatigue	0.3775 (-2.13) -5.89-1.63	<0.0001 (15.59) 11.18-20.0	<0.0001 (17.7) 13.46-21.98	<0.0001	52.002
Mobility	0.026 (-3.25) -6.20--0.31	<0.0001 (-14.34) -17.8- -10.88	<0.0001 (-11.09) -14.42-7.76	<0.0001	50.229
Upper Extremity	0.6193 (-1.2) -4.23- 1.83	<0.0001 (-8.35) -11.9- -4.80	<0.0001 (-7.15) -10.58-3.73	<0.0001	17.07
Pain Interference	0.3941 (1.65) -1.33- 4.63	<0.0001 (13.09) 9.59- 16.59	<0.0001 (11.44) 8.07-14.82	<0.0001	43.897
Peer Relationships	0.485 (1.73) -1.82- 5.23	0.5693 (-1.79) -5.95-2.37	0.099 (-3.52) -7.54-0.50	0.1134	2.193

Disclosure: M. J. Holland, None; **J. Jones**, None; **E. M. Morgan DeWitt**, None; **S. Kashikar-Zuck**, None; **D. D. Sherry**, None; **A. C. Carle**, None; **B. Huang**, None; **C. Mara**, None; **H. I. Brunner**, None.

Abstract Number: 397

Longitudinal Observation of Psychological Factors and Health-Related Quality of Life in Childhood-Onset Lupus

Catherine Donnelly[1], Jordan T. Jones[2], Ji Li[3], Natoshia Cunningham[4], Susmita Kashikar-Zuck[5] and Hermine I. Brunner[2], [1]Internal Medicine, University of Cincinnati, Cincinnati, OH, [2]Division of Rheumatology, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, [3]Department of Pediatrics, Peking Union Medical College Hospital, Beijing, China, [4]Behavioral Medicine & Clinical Psychology, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, [5]Behavioral Medicine and Clinical Psychology, Cincinnati Children's Hospital Medical Center, Cincinnati, OH

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Session Time: 9:00AM-11:00AM

Background/Purpose: Childhood-onset Lupus (cSLE) is associated with decreased Health-related Quality of Life (HRQoL), and disease activity measures are often unrelated to overall perception of health. The patient's perspective is necessary to further understand disease effect as cSLE is a chronic, episodic health condition impacting critical points in a child's psychosocial development. The objective of this study is to assess disease experience trends in patients with cSLE by evaluating patients' reports of psychological factors (fatigue, depression, anxiety, sleep), and their potential effect on HRQoL.

Methods: As part of an ongoing, longitudinal study, twenty cSLE patients (age 8-20 years) were assessed at two separate clinic visits approximately 6 months apart. Patients completed validated measures of fatigue (PedsQL Multidimensional Fatigue Scale), depressive symptoms (Children's Depression Inventory; CDI-1), anxiety (Screen for Child Anxiety Related Disorders; SCARED), sleep (Adolescent Sleep Wake Scale; ASWS), and HRQoL (PedsQL Generic Core scale and Rheumatology module). Physician assessments were completed for disease activity (Systemic Lupus Erythematosus Disease Activity Index-2K), damage (SLICC/ACR Damage Index), and visual analog scales of disease activity.

Results: Patients were 90% female, mean age 16.5 years (SD 2.8), 40% African American, and 55% Caucasian. cSLE was well controlled at visit 1 and 2 with mean SLEDAI ≤ 5 in 70% and damage was absent in 75%. Fatigue was reported by 65% of patients at both visits. Clinically relevant anxiety (SCARED$\geq$25) was reported in 40% and 35% at visit 1 and 2, respectively, which is higher than prior reported prevalence rates in cSLE patients. Clinically significant depressive symptoms (CDI-1>12) were reported in 25% and 30% at visit 1 and 2, respectively, which is similar to previous reported prevalence rates in cSLE patients. Of the five sleep quality ASWS subscales, cSLE patients have most difficulty 'going to bed' and 'returning to wakefulness', however reported similar overall mean scores to normative US teens surveyed. HRQoL measures remained lower compared to healthy populations over time (Table 1).

Conclusion: Lower HRQoL was observed over the 6 month study period, concomitant with ongoing difficulties with fatigue, anxiety and depression in many patients, despite stable disease activity and no increased damage. These findings suggest a persistent disease burden that is not being addressed by current management practices which focus on preventing tissue damage. A routine assessment of fatigue and psychological factors as part of standard of care is necessary in order to determine the need for potential behavioral interventions that could improve HRQoL for patients with cSLE. Further investigation into sleep behaviors and potential effect on sleep quality is needed.

Table 1. Paired T-tests for Comparison of Visit 1 and 2 Measures

Measures	Normative Population mean (SD)	cSLE mean (SD) VISIT 1	cSLE mean (SD) VISIT 2	t	p
HRQoL Measures					
PedsQL Generic Core Scale	83.9 (12.5)	74.7 (20.7)	76.7 (20.6)	-0.767	0.453
PedsQL Rheumatology Module	84.4 (18.0)	74.7 (18.6)	79.9 (19.7)	-2.081	0.051
Psychological Factors					
Fatigue (PedsQL-FS)	80.5 (13.3)	58.5 (22.3)	61.8 (25.7)	-1.354	0.192
Depression (CDI-1)	9.09 (7.0)	8.4 (8.3)	8.5 (9.4)	-0.101	0.921
Anxiety (SCARED)	17.4 (12.1)	22.0 (16.4)	18.8 (17.4)	1.775	0.092
Sleep (ASWS)* Total		4.09 (0.79)	4.21 (0.74)	-1.177	0.253
Go to Bed		4.05 (1.29)	3.8 (1.27)	0.954	0.352
Fall Asleep		4.05 (1.14)	4.23 (0.94)	-1.190	0.248
Maintain Sleep		4.26 (1.05)	4.50 (0.99)	-1.609	0.123
Reinitiate Sleep		4.62 (0.62)	4.94 (0.72)	-2.188	0.041
Return to Wake		3.47 (1.25)	3.54 (1.21)	-0.428	0.673
Disease Measures					
SLEDAI-2K		4.8 (4.9)	4.5 (3.6)	0.304	0.764
Physician Global		1.5 (1.4)	1.4 (1.3)	0.438	0.666
SLICC/ACR Damage Index		0.4 (0.82)	0.4 (0.82)		

PedsQL Generic Core and Peds QL Rheumatology module higher scores represent better quality of life.

PedsQL-FS higher scores represent less fatigue.

CDI-1 higher scores indicate higher level of depressive symptoms; score >12 reflects clinically significant depressive symptoms.

SCARED higher scores represent more anxiety; score ≥25 reflects clinically relevant anxiety.

*ASWS higher scores represent better sleep quality. No established normative or cutoff value; range 1-6 with higher values representing better sleep.

SLEDAI-2K higher scores represent increased disease activity.

Physician Global higher scores represent higher disease activity.

SLICC/ACR Damage Index higher scores represent increased disease damage.

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Abstract Number: 398

Clinical and Serological Profile of Children with Positive SSA-Ro/SSB-La Antibodies

Juan G. Ovalles-Bonilla[1], Juan C. Nieto[1], Francisco Javier López Longo[1], Julia Martínez-Barrio[2], Iustina Janta[1], Esperanza Naredo[1], Carlos M. Gonzalez[1], Michelle Hinojosa[1], Natalia Bello[1], Belen Serrano[1], Carmen Mata[1], Claudia Sáenz Tenorio[1], Diana C. Hernández[1], Lara Valor[1], Indalecio Monteagudo[1] and Luis Carreño[1], [1]Rheumatology, Hospital General Universitario Gregorio Marañón, Madrid, Spain, [2]Servicio de Reumatologia, Hospital General Universitario Gregorio Marañón, Madrid, Spain

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Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose: Several studies have shown the relationship between anti-SSA-Ro/SSB-La antibodies and Systemic Lupus Erythematosus (SLE), Sjögren Syndrome (SS) and other autoimmune diseases in adult population. However, the expression of these autoantibodies and clinical correlation in juvenile patients is poorly described. To characterize the clinical and serological profile and primary rheumatic diseases in pediatric patients with positive anti-SSA-Ro and/or anti-SSB-La antibodies.

Methods: The data was obtained from a long term prospective cohort of patients under age 18 diagnosed with rheumatic diseases in a tertiary hospital in Spain. Demographic, clinical, and laboratory data were collected from 1986 to 2010. Patients were divided into 2 groups: anti-SSA-Ro/SSB-La positive and anti-SSA-Ro/SSB-La negative.

Results: A total of 187 patients were tested for anti Extractable Nuclear Antigens (ENA), with a following mean time of 11 years. Mean age at disease onset was 12.6 years and 77% were female. Fifty-four (28.9%) anti-SSA-Ro/SSB-La positive subjects were compared against 133 (71.1%) anti-SSA-Ro/SSB-La negative subjects. Among positive cases, 13 (24.1%) patients were double-positive for anti-SSA-Ro and anti-SSB-La, 51 (94.4%) were positive for anti-SSA-Ro and 3 (5.5%) were single-positive for anti-SSB-La. The anti-SSA-Ro/SSB-La antibodies were found less frequently ($p=0.003$) in the overlapping syndromes, and more frequently in SLE ($p=0.007$). In addition rheumatoid factor ($p<0.001$), anti-Sm ($p<0.001$) and anti-RNP ($p<0.001$) were frequently co-expressed with anti-SSA-Ro/SSB-La antibodies. Finally the anti-SSA-Ro/SSB-La positive group presented more hematological and skin manifestations than the negative group ($p<0.05$).

CLINICAL AND SEROLOGICAL PROFILE OF CHILDREN WITH POSITIVE SSA-RO/SSB-LA ANTIBODIES			
FEATURES	Anti-SSA-Ro/SSB-La (+) N=54 (%)	Anti-SSA-Ro/SSB-La (-) N=133 (%)	p
Age at Disease Onset (Sd, Range)	12.6 (4.4, 1-17)	12.4 (4.4, 1-17)	0.76
Sex	47 (87)	98 (73.7)	0.05
Systemic Lupus Erythematosus	41 (75.6)	71 (53.4)	0.007
Overlapping Syndromes	16 (14.8)	58 (38.3)	0.003
Polymyositis	2 (3.7)	8 (6)	N/A
Primary Sjögren Syndrome	2 (3.7)	2 (1.5)	N/A
Mixed Connective Tissue Disease	1 (1.9)	1 (0.8)	N/A
ANTIBODIES			
Rheumatoid Factor	20 (39.2)	19 (14.5)	<0.001
Anti-DNA	35 (71.4)	58 (51.8)	0.02
Anti-Sm	15 (30)	12 (9.6)	<0.001
Anti-RNP	20 (48.8)	20 (25.0)	<0.001
CLINICAL FEATURES			
Inflammatory Fever	18 (33)	34 (25.6)	0.28
Arthralgias	39 (72.2)	98 (73.7)	0.84
Arthritis	33 (61.1)	71 (53.4)	0.33
Malar Rash	25 (46.3)	39 (29.3)	0.02
Photosensibility	23 (42.6)	36 (27.1)	0.03
Pleurisy	9 (16.7)	19 (14.3)	0.68
Pericarditis	8 (14.8)	15 (11.3)	0.50
Cardiac Arrhythmias	3 (5.6)	3 (2.3)	0.25
Renal Manifestations	23 (42.6)	44 (33.1)	0.22
Hematologic Manifestations	40 (74.1)	73 (54.9)	0.01

Conclusion: Similarly to adults, we observed a relationship between anti-SSA-Ro/SSB-La antibodies and SLE in pediatric patients. However a low proportion of childhood primary SS exists in our anti-SSA-Ro/SSB-La positive cases. This could be explained by underdiagnoses related to the atypical clinical presentation of SS in pediatric population. Single-positive anti-SSB-La patients are uncommon, the clinical significance of this serological result remains uncertain in children.

References: Rheumatol Int (2014) 34:1123–1127.

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Abstract Number: 399

Management of Lupus Anticoagulant Hypoprothrombinemia Syndrome in Juvenile Systemic Lupus Erythematosus – Single Center Experience

J. Brian Shirley[1], Patricia Rosillo[1], Andrea Ramirez[1] and Anna Carmela Sagcal-Gironella[2], [1]Allergy, Immunology and Rheumatology, Baylor College of Medicine/Texas Children's Hospital, Houston, TX, [2]Pediatrics, Baylor College of Medicine, Texas Children's Hospital, Houston, TX

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SESSION INFORMATION

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Session Type: ACR Poster Session A

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Background/Purpose: Lupus anticoagulant hypoprothrombinemia syndrome (LAHS) is a rare phenomenon that leads to concomitant thrombosis and hemorrhage thus presenting a therapeutic dilemma. In children, this acquired prothrombin deficiency may be associated with infection or autoimmunity, specifically systemic lupus erythematosus (SLE). LAHS in juvenile SLE (jSLE) has a protracted course requiring long-term immunosuppressive therapy. Due to the rarity of this syndrome and paucity of reported cases, there is lack of standardized management. We describe a case series of jSLE patients with LAHS managed with an aggressive combination therapy.

Methods: We retrospectively reviewed the medical records of 3 jSLE patients at our institution from 2007 to 2015. All patients fulfilled at least 4 of the ACR classification criteria for SLE. Literature review was also performed to compare our cohort with reported cases of LAHS in jSLE.

Results:

Patient 1 is an 8 y.o. Caucasian female who presented with ascites, pleural and pericardial effusions, hepatosplenomegaly and pancytopenia. She had epistaxis and pulmonary hemorrhage. Labs notable for positive lupus anticoagulant (LAC) and strongly positive IgG and IgM prothrombin antibodies (PTabs). Initial therapy included plasmapheresis, IV rituximab, IV cyclophosphamide, pulse IV methylprednisolone, and prothrombin complex; subsequent therapy with IVIG, tapering course of oral prednisone and mycophenolate mofetil (MMF).

Patient 2 is a 17 y.o. Hispanic female who presented with hemorrhagic shock from severe coagulopathy and excessive menorrhagia, epistaxis, pulmonary hemorrhage, pancytopenia and fever. Labs notable for almost undetectable Factor 2 (2%; ref range 50-100%), strongly positive IgG and IgM PTabs, and positive LAC. Initial therapy included IV rituximab, IV cyclophosphamide, pulse IV methylprednisolone and prothrombin complex; subsequent therapy with IVIG, tapering course of oral prednisone and azathioprine.

Patient 3 is an 18 y.o. Hispanic male with prolonged history of recurrent epistaxis and bruising. Earlier therapy for presumed infection associated LAHS included prolonged IV and oral steroid and oral methotrexate. He then presented acutely with fever, abdominal pain, thrombocytopenia, serositis, adrenal hemorrhage and microthrombic skin lesions. Labs strongly positive for IgG PTabs and LAC. Initial therapy included IV rituximab and pulse IV methylprednisolone; subsequent therapy with IVIG, repeat rituximab, tapering course of oral prednisone and azathioprine. Patients 1 & 2's PTabs normalized within 4 months from disease onset. Presently, all patients are on minimal oral prednisone (1, 2.5, and 5mg daily). At 1 year from initial aggressive immunotherapy, all patients have achieved clinical remission.

Conclusion: LAHS presents a challenge in management considering the dichotomous manifestation of thrombosis and hemorrhage. While no consensus exists for optimal therapy, we report 2 patients achieving normalization of PTabs and all patient with clinical remission within a year of presentation while currently on minimal therapy. Perhaps early aggressive combination immunosuppressive therapy may have more favorable outcomes.

Disclosure: J. B. Shirley, None; **P. Rosillo**, None; **A. Ramirez**, None; **A. C. Sagcal-Gironella**, None.

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Abstract Number: 400

Disease Activity and Health Care Utilization Among Young Adults with Childhood-Onset Lupus Transitioning to Adult Care: Data from the Pediatric Lupus Outcomes Study

Erica F. Lawson[1] and Aimee O. Hersh[2], [1]Pediatrics/Rheumatology, UC San Francisco, San Francisco, CA, [2]Pediatrics/Rheumatology, University of Utah, Salt Lake City, UT

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SESSION INFORMATION

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Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose:

Individuals with childhood-onset systemic lupus erythematosus (cSLE) must transfer from pediatric- to adult-oriented health care as they enter adulthood. However, few studies have assessed outcomes of the transition from pediatric to adult care in cSLE. The goal of this study is to examine disease activity and health care utilization among young adults with cSLE who are undergoing or have recently completed the transition to adult care.

Methods:

Data derive from the baseline interview of the Pediatric Lupus Outcomes Study, an annual longitudinal telephone survey of 91 diverse English- and Spanish-speaking participants age 18-30 with confirmed cSLE (age of onset <18 years). Subjects were recruited from pediatric and adult rheumatology clinics; diagnosis of cSLE was confirmed by chart review. To define a cohort undergoing transition from pediatric to adult care, we included respondents who received care from a pediatric rheumatologist currently or in the past (N=85). We assessed disease activity according to the Systemic Lupus Activity Questionnaire (SLAQ), self-reported SLE flare in the past 3 months, current immunosuppressive medication use (any steroid, DMARD or biologic medication), current health insurance coverage, and health care utilization over the past year. Bivariate analyses were used to compare individuals cared for by adult rheumatologists to those who continue in pediatric care.

Results:

Mean baseline age was 21±3 years, and mean age at diagnosis was 13±3 years. Ethnicities included White (48%), Black (5%), Asian (20%), Latino (24%), multi-ethnic (5%) and other (6%). 38 respondents (45%) had transferred care out of pediatric rheumatology (Table 1). Most respondents were currently insured (93%), however those who had transferred were more likely to report difficulty obtaining insurance (34% v. 11%, p=0.008). 32% had visited an emergency department and 27% had received inpatient care in the past year, with similar rates in adult and pediatric care groups. There was no difference in disease activity (SLAQ score 9 v. 11) or likelihood of self-reported flare over the last 3 months (31% vs. 26%) among those who had transferred to adult rheumatology vs. those who had not. Those who remained in pediatric care were significantly more likely to have seen a rheumatologist in the past year (94% v. 68%, p=0.002) and more likely to be taking immunosuppressive medications (89% v. 34%, p<0.001).

Conclusion:

Many individuals in this cohort of young adults with cSLE continue with active lupus. In spite of similar disease activity among those who had left pediatric care and those who had not, young adults who had transferred to adult care were significantly less likely to access routine rheumatology care or take immunosuppressive medication, and more likely to encounter difficulty obtaining health insurance coverage. Improving access to adult rheumatology care may be important to prevent poor health outcomes in cSLE.

Table 1. Demographics, disease characteristics and healthcare utilization among young adults with cSLE in pediatric rheumatology care vs. young adults with cSLE who have transferred to adult care.

	Pediatric rheumatology care (n=47)	**Adult rheumatology care (n=38)**	
	N (%) or Mean (SD)	***N (%) or Mean (SD)***	***P***
Demographics			
Age (years)	19 (1)	24 (3)	<0.001
Female	41 (87)	36 (95)	NS
Non-white ethnicity	35 (74)	29 (11)	<0.001
Age at diagnosis (years)	13 (3)	13 (2)	NS
Disease Characteristics			
Renal biopsy ever	25 (54)	18 (47)	NS
Cyclophosphamide use ever	7 (15)	19 (50)	<0.001
Disease activity (SLAQ)*	11 (11)	9 (10)	NS
Self-reported flare in the past 3 months	14 (31)	10 (26)	NS
Health Care Utilization			
Current medications			
Plaquenil	41 (89)	24 (63)	0.005
Steroid	36 (76)	7 (18)	<0.001
DMARD	33 (70)	12 (32)	<0.001
Biologic	0 (0)	0 (0)	NS
Insurance coverage	45 (96)	34 (89)	NS
Difficulty obtaining insurance	5 (11)	13 (34)	0.008
Rheumatology visit in the past year	44 (94)	26 (68)	0.002
General MD visit in the past year	23 (51)	15 (41)	NS
ED visit in the past year	18 (38)	9 (24)	NS
Hospitalization in the past year	14 (30)	9 (24)	NS

*SLAQ = Systemic Lupus Activity Questionnaire (0-47)

Disclosure: E. F. Lawson, None; **A. O. Hersh**, None.

outcomes-study

Abstract Number: 401

Racial and Ethnic Disparities in Depression Diagnosis and Treatment for Adolescents with SLE: Analysis of a National Medicaid Sample

Andrea Knight[1], Ming Xie[2] and David Mandell[3], [1]Pediatrics/Rheumatology, Children's Hospital of Philadelphia, Philadelphia, PA, [2]University of Pennsylvania, Center for Mental Health Policy and Services Research, Philadelphia, PA, [3]Psychiatry and Pediatrics, University of Pennsylvania, Center for Mental Health Policy and Services Research, Philadelphia, PA

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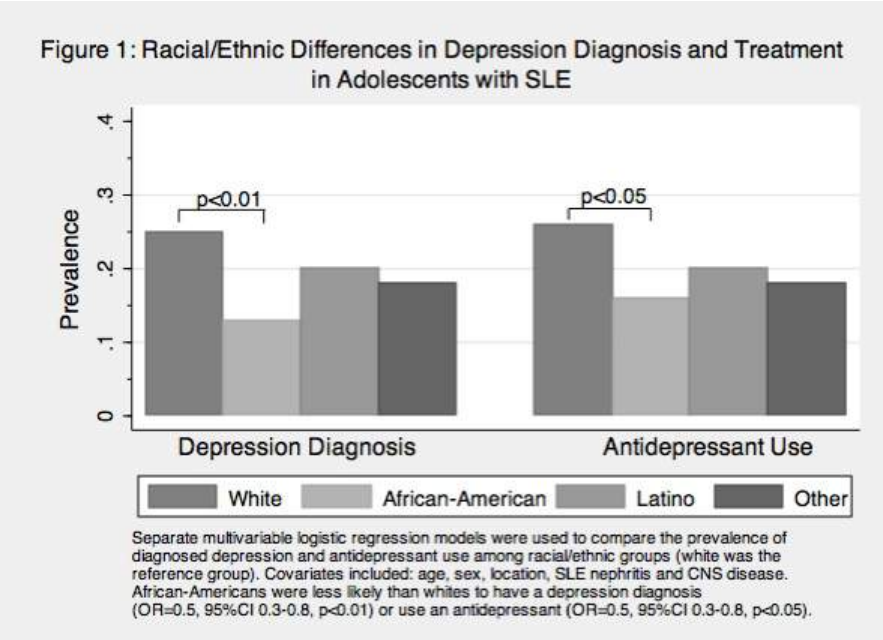
Session Time: 9:00AM-11:00AM

Background/Purpose: Adolescents with systemic lupus erythematosus (SLE) are at high risk for depression. Racial/ethnic minorities are disproportionately affected by SLE, and previous studies suggest a higher risk of untreated depression in these groups. We aimed to compare the prevalence of diagnosed depression and treatment between racial/ethnic groups of adolescents with SLE.

Methods: We conducted a cross-sectional study using claims data from the Centers for Medicare and Medicaid Services Medicaid Analytic Extract data files from 49 states and the District of Columbia. We included adolescents aged 10 to 18 years, with continuous enrollment from January 1, 2006 to December 31, 2007, and a diagnosis of SLE, defined as having >=3 outpatient visit claims with an ICD-9 primary diagnosis code for SLE of 710.0, each recorded at least 30 days apart. We categorized race/ethnicity as: white, African-American, Latino and other. We conducted unadjusted and adjusted logistic regression analyses to compare the following between racial/ethnic groups: 1) depression diagnoses and 2) antidepressant use. Covariates included: age, sex, urban vs. rural location, presence of SLE nephritis and central nervous system (CNS) disease, defined as seizures or stroke.

Results: We identified 970 adolescents with SLE; 15% were white, 42% African American, 27% Latino and 16% of other races/ethnicities. The mean age was 14.7 (SD=2.0), 83% were female and 85% were of urban location. Nephritis was present in 36% and CNS disease in 16%. Seventeen percent of the sample had depression diagnosis and 21% used an antidepressant. In adjusted analyses, African-Americans were less likely than whites to have a depression diagnosis (OR=0.5, 95%CI 0.3-0.8, $p<0.01$) or use an antidepressant (OR=0.5, 95%CI 0.3-0.8, $p<0.05$) (Figure 1). Older adolescents were more likely to be diagnosed with depression (OR=1.1, 95% CI 1.0-1.2, $p<0.01$) and use an antidepressant (OR=1.2, 95% CI 1.1-1.3, $p<0.001$), as were those with CNS disease (OR=2.9, 95% CI 2.0-4.3, $p<0.001$).

Conclusion: In the context of other studies showing under-treatment of depression in African-American adolescents, our results suggest that African-Americans with SLE may be at higher risk for under-diagnosis and under-treatment than adolescents with SLE of other race/ethnicity. Interventional strategies for depression in adolescents with SLE should address disparities in mental health care.



Disclosure: A. Knight, None; **M. Xie**, None; **D. Mandell**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/racial-and-ethnic-disparities-in-depression-diagnosis-and-treatment-for-adolescents-with-sle-analysis-of-a-national-medicaid-sample

Abstract Number: 402

Predicting Area Under the Curve of Mycophenolate Mofetil in Childhood-Onset Systemic Lupus Erythematosus

Roberto Ezequiel Borgia[1], Masanobu Takeuchi[2], Deborah M. Levy[3], Shinya Ito[4] and Earl Silverman[5], [1]Division of Rheumatology, The Hospital for Sick Children, Toronto, ON, Canada, [2]Program of Physiology & Experimental Medicine, Peter Gilgan Centre For Research and Learning (PGCRL), The Hospital for Sick Children, Toronto ON, Toronto, ON, Canada, [3]Rheumatology, The Hospital for Sick Children, Toronto, ON, Canada, [4]3Division of Clinical Pharmacology and Toxicology, The Hospital for Sick Children Toronto ON, Toronto, ON, Canada, [5]Division of Rheumatology, Hospital for Sick Children and University of Toronto, Toronto, ON, Canada

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SESSION INFORMATION

Session Date: Sunday, November 8, 2015

Session Title: Pediatric Rheumatology – Clinical and Therapeutic Aspects Poster I: Lupus, Scleroderma, JDMS

Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose: Mycophenolate mofetil (MMF) is an immunosuppressive drug used off-label for the treatment of childhood-onset systemic lupus erythematosus (cSLE). Therapeutic drug monitoring (TDM) of MMF's active metabolite, Mycophenolic acid (MPA), has been increasingly used in order to achieve a target area under the curve (AUC) and improve cSLE patient outcomes. However, multiple timed blood samples are required to estimate AUC. We applied a population pharmacokinetics (PK) approach to derive a prediction model of MMF AUC in cSLE patients, so that we could test validity of limited sampling strategies

Methods: Our retrospective analysis included cSLE patients (≥ 4/11 ACR classification criteria) followed at the Hospital for Sick Children, Toronto. Patients were on stable dose of MMF for at least 6 weeks with no concomitant calcineurin inhibitors. Blood samples at baseline (trough levels), 1 h, 2h and 6 h were used for AUC estimation. A population pharmacokinetics (popPK) model describing MPA plasma concentration was developed using nonlinear mixed effects modeling (NONMEM) software. A Bayesian estimator based on the population pharmacokinetic model was used to predict the MPA AUC_{0-12}. The final model was examined using goodness of fit, bootstrap method and visual predictive check. The individual MPA AUC_{0-12} predicted by a Bayesian estimator was compared to the individual MPA AUC_{0-12}calculated by a limited sampling strategy formula (1) to evaluate validity of the model.

Results: We included 648 samples from 90 cSLE patients to build the popPK model. 128 samples with time window +/- 10 minutes from 32 patients were included to compare the AUC predicted by popPK model with the AUC calculated by the formula. All patients had normal liver/kidney function. The median age was 16 years (range: 6-19). Mean MMF dose was 626 mg/m^2 (SD: 19) and the mean formula-derived AUC was 67.2mg- h/L (SD:4.5). The MPA PK was best described by a 2-compartment model with lag time and first order absorption. The popPK model-derived MPA AUC_{0-12} was closely correlated to the observed AUC calculated by the formula (r^2=0.93, P<0.01) (Fig. 1). However, correlation between Ctrough and the model-predicted AUC was poor (r^2=0.47). Also, none of the other MPA concentrations at single time point (1h, 2h and 6h post-dose) showed significant correlation with the model-derived AUC. The covariate analysis identified body weight as individual factor influencing the apparent oral clearance and volume distribution. Different steroid dosage, concomitant use of proton-pump inhibitors or ethnicity did not influence in observed and predicted AUC.

Conclusion: MPA trough levels, or levels based on a single post-dose time point (such as 1h, 2h or 6h) are not a reliable predictor for MPA AUC_{0-12}.

1. Filler G, Mai I. Limited sampling strategy for mycophenolic acid area under the curve. Ther Drug Monit. 2000;22(2):169-73.

Disclosure: R. E. Borgia, None; **M. Takeuchi**, None; **D. M. Levy**, None; **S. Ito**, None; **E. Silverman**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/predicting-area-under-the-curve-of-mycophenolate-mofetil-in-childhood-onset-systemic-lupus-erythematosus

Abstract Number: 403

Proteinuria in Childhood Onset Lupus Nephritis: When Does It Go Away ?

Justin Hung Tiong Tan[1], Sook Fun Hoh[2], Manasita Tanya[1], Lena Das[1], Ma Thin Mar Win[3], Yiong Huak Chan[3] and Thaschawee Arkachaisri[1,4], [1]Rheumatology and Immunology, KK Women's and Children's Hospital, Singapore, Singapore, [2]Nursing, KK Women's and Children's Hospital, Singapore, Singapore, [3]Biostatistics Unit, Yong Loo Lin School of Medicine, Singapore, Singapore, [4]Paediatrics, Duke-NUS Graduate Medical School, Singapore, Singapore
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SESSION INFORMATION
Session Date: Sunday, November 8, 2015
Session Title: Pediatric Rheumatology – Clinical and Therapeutic Aspects Poster I: Lupus, Scleroderma, JDMS
Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose:

The time to recovery from proteinuria in patients with lupus nephritis (LN) receiving standard treatment has been described in adult, but not in children. In adult, 52% recovered from proteinuria within 2 years and 3/4 within 5 years. We aim to determine the time to recovery from proteinuria and to identify factors predicting time to improvement.

Methods:

Twenty-four childhood-onset lupus nephritis (cLN) patients receiving standard treatment, were identified from our lupus registry followed from Jan 1, 2009 to May 31, 2015. Indication for biopsy includes persistent proteinuria ≥ 0.5 gm/day or spot protein/creatinine ratio > 0.2. Demographic, clinical, laboratory, disease activity indices and histological data were collected. Time to recovery from proteinuria was assessed by Kaplan-Meier analysis. Risk factors associated with proteinuria resolution were evaluated using cox-regression models.

Results:

Twenty-four cLN patients (66.7% females) were recruited. Majority were Chinese (54.2%), followed by Malays (29.2%). No Indian patients had LN. 83.3% cLN patients presented at diagnosis. Median time to protein clearance was 5.8 months (Fig 1). About 90% recovered from proteinuria within 18 months. Higher SLEDAI-2K scores at diagnosis was associated with shorter time to protein clearance. (HR 1.155, 95% CI 1.046-1.275, p=0.004). Older age, higher chronicity index and nephrotic at baseline were associated with longer time to protein clearance while gender, race, activity index and low complement were not significant risk factors. (Table 2)

Table 1 Characteristics of cLN patients.

Variables	Results
SLE patients with lupus nephritis	24 (30.0)
Age at onset, year	11.9 (10.2-13.9)
Age at diagnosis, year	12.3 (10.2-14.3)
Age at lupus nephritis onset, year	13.08 (11.4-15.2)
Lag period, month	1.4 (0.5-2.1)
Length of follow-up, month	43.5 (26.6-72.1)
ESR* (reference : 0-10 mm/50 min)	72.5 (51.7-135.7)
CRP* (reference : 0-9.9 mg/L)	5.0 (1.9 – 10.0)
C3 § (G/L)	0.31 (0.26-0.37)
C4 § (G/L)	0.03 (0.02-0.05)
Albumin* (g/L)	25.0 (21.2-30.7)
Creatinine* (umol/L)	62.0 (53.0-79.5)
Proteinuria* (g/day)	1.6 (0.9-4.6)
Activity Index (reference : 0-24)	8 (5-10)
Chronicity Index (reference : 0-12)	1 (0-2)
Patients who had no proteinuria at last clinic visit	22 (91.6)
Patients who had renal biopsy	23 (95.8)
Histology (WHO Classification): *Class III* *Class III/V* *Class IV* *Class IV/V*	 4 (17.4) 3 (13.0) 12 (52.2) 4 (17.4)
Hypertension Renal Impairment Nephrotic Oliguria Hematuria Pyuria	10 (41.7) 8(33.3) 12 (50.0) 4 (16.7) 24 (100.0) 19 (79.2)
ICU admissions	2 (8.3)
SLEDAI-2K* Modified SLEDAI-2K* BILAG* SLAM*	24.0(20.0-28.7) 20.0 (16.0-24.7) 21.0 (13.0-24.7) 12.5 (9.2-17.7)
Azathioprine Mycophenolate Mofetil Cyclophosphamide Hydroxychloroquine	8 (33.3) 22 (91.7) 21 (87.5) 24 (100.0)

Results for nominal data are n (%) and for continuous data are median (IQR)

*at baseline

§ C3 and C4 at baseline, reference range is based on normal set of testing laboratory at the time of clinic visit.

ESR = Erythrocyte Sedimentation Rate, CRP = C-Reactive Protein, C3 = Complement 3, C4 = Complement 4, SLEDAI-2K = SLE Disease Activity Index 2000, SLAM = Systemic Lupus Activity Measures, BILAG = British Isle Lupus Assessment Group

Hypertension is defined as SBP and/or DBP ≥ 95th percentile for gender, height and age; Renal impairment is defined as those with raised urea and creatinine; Nephrotic is defined as those with proteinuria > 40 mil m^2 day; Oliguria is defined as urine output less than 1 ml/kg/hr; hematuria is defined as presence of RBC > 5 hpf; pyuria is defined as WBC > 5 hpf

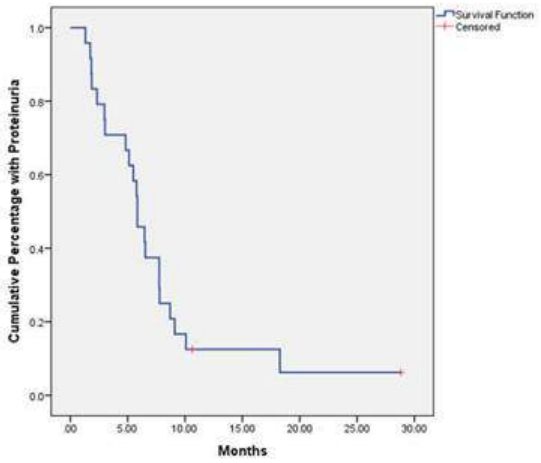

Figure 1 Kaplan-Meier for Time To Proteinuria Clearance

Table 2 Risk factors predicting shorter time to protein clearance

Risk Factors	Hazard Ratio	p value	95% CI
Male	0.995	0.993	0.317-3.122
Malays versus Chinese	0.842	0.805	0.216-3.290
Age ‡	0.714	0.029	0.528-0.967
SLEDAI-2K ‡	1.155	0.004	1.046-1.275
Nephrotic†	5.713	0.012	1.458-22.389
Activity Index††	1.222	0.103	0.960-1.554
Chronicity Index††	0.503	0.008	0.303-0.836
Low C3	9.189	0.068	0.847-99.704

‡ at baseline
† nephrotic syndrome is defined as proteinuria exceeding 40 $ml/m^2/hr$
†† based on National Institute of Health (NIH) Activity and Chronicity Index

Conclusion:

Faster urinary protein clearance was demonstrated in our cLN cohort receiving standard treatment compared to that of adults (5.8 months vs 2 years) and 90% achieved in 18 months. Patients with higher disease activity at baseline seem to respond better to treatment with shorter time to protein clearance. Consistent with adult findings, patients with higher level of proteinuria at baseline needed longer time to achieve protein clearance.

Disclosure: J. H. T. Tan, None; **S. F. Hoh**, None; **M. Tanya**, None; **L. Das**, None; **M. T. M. Win**, None; **Y. H. Chan**, None; **T. Arkachaisri**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/proteinuria-in-childhood-onset-lupus-nephritis-when-does-it-go-away

Abstract Number: 404

Long-Term Outcomes of Macrophage Activation Syndrome in Childhood-Onset Systemic Lupus Erythematosus

Roberto Ezequiel Borgia[1], Maya Gerstein[1], Deborah M. Levy[2], Earl Silverman[2] and Linda T Hiraki[2], [1]Division of Rheumatology, The Hospital for Sick Children, Toronto, ON, Canada, [2]The Hospital for Sick Children, Toronto, ON, Canada

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SESSION INFORMATION

Session Date: Sunday, November 8, 2015

Session Title: Pediatric Rheumatology – Clinical and Therapeutic Aspects Poster I: Lupus, Scleroderma, JDMS

Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose: Macrophage activation syndrome (MAS) is a life-threatening inflammatory complication of childhood-onset systemic lupus erythematosus (cSLE). There are few reports of long-term outcomes of MAS complicating cSLE. Our aim is to compare long-term outcomes between MAS and non-MAS patients with cSLE seen at a single tertiary centre.

Methods: Our retrospective review included all patients followed at the Hospital for Sick Children, Toronto, diagnosed with cSLE (≥ 4/11 ACR classification criteria and/or ≥ 4/11 SLICC classification criteria) between January 2002 and December 2012. Within this cohort we identified cSLE patients also diagnosed with MAS (as per Pediatric Rheumatologist's expert opinion). We analyzed prospectively collected data including: 1) demographics: gender, age of diagnoses; 2) SLE major organ involvement (proliferative and membranous lupus nephritis and CNS involvement); 3) immunosuppressive drugs; 4) average daily dose of corticosteroids and 5) SLICC damage index at last visit. Continuous variables were compared using Student's t test and categorical variables were compared using Fisher's test as appropriate.

Results: 402 patients with cSLE were identified. Of those, 34 (8.4 %) patients were also diagnosed with MAS. The majority (76%) of patients with MAS developed it concomitantly with their SLE diagnosis. There was no statistically significant difference in the proportion of patients with major organ involvement between MAS and non-MAS patients (Table). A larger proportion of MAS patients received calcineurin inhibitors and IVIG as compared with non-MAS patients ($p < 0.01$). Azathioprine was used more frequently in non-MAS patients than in patients with MAS ($p = 0.01$). There was no difference in the average daily dose of steroids, frequency of cyclophosphamide or biologic therapy use throughout follow-up. The proportion of patients who sustained damage (SLICC ≥ 1) at last visit was similar between the groups.

Conclusion: We observed that MAS was most likely to be diagnosed concomitantly with cSLE diagnosis. Despite the life-threatening nature of MAS complicating cSLE, we observed comparable rates of major organ involvement, average dose of steroids, use of cytotoxic drugs and disease associated damage between those cSLE patients with MAS and those non-MAS patients throughout their follow-up. As expected, calcineurin inhibitors and IVIG were more commonly used among those with MAS.

Table. Characteristics of MAS and non-MAS cSLE patients.

Demographics	MAS n=34	non-MAS n=368	p-value
Female, n (%)	26 (76)	305 (82)	0.34
Age at diagnosis, mean (SD)	13 (2.8)	13 (3.2)	0.58
Follow-up in years, mean (SD)	3.5 (1.6)	4 (2.4)	0.19
Major organ involvement, n (%)			
Lupus Nephritis	14 (41)	111 (30)	0.24
CNS involvement	9 (26)	87 (23)	0.67
Medications[1], n (%)			
MMF[2] or Mycophenolate sodium	17 (58)	119 (49)	0.43
Azathioprine	11 (38)	149 (62)	0.01
Cyclophosphamide IV	10 (34)	66 (27)	0.51
Methotrexate	3 (10)	49 (20)	0.31
Calcineurin inhibitors[3]	12 (41)	21 (9)	<0.01
IVIG[4]	9 (31)	26 (10)	< 0.01
Rituximab	0	28 (12)	0.05
Average daily dose of steroids[5], mean (SD)	18 (7.4)	18 (18.6)	1.0
Damage (SLICC ≥ 1) at last visit[6], n (%)	6 (18)	57 (19)	1.0

1. Nonsteroidal medication validated in 29 MAS and 240 non-MAS patients; 2. Mycophenolate mofetil; 3. Tacrolimus or Cyclosporine; 4. Intravenous immunoglobulin; 5. Steroids reported as mg/day of prednisone equivalents; 6. SLICC scores at final visit validated in 32 MAS and 297 non-MAS patients.

Disclosure: R. E. Borgia, None; **M. Gerstein**, None; **D. M. Levy**, None; **E. Silverman**, None; **L. T. Hiraki**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/long-term-outcomes-of-macrophage-activation-syndrome-in-childhood-onset-systemic-lupus-erythematosus

Abstract Number: 405

Anti-C1q Antibodies As Potential Diagnostic and Prognostic Biomarkers in Juvenile Systemic Lupus Erythematosus

Thaschawee Arkachaisri[1,2], Justin Hung Tiong Tan[1], Manasita Tanya[1], Sook Fun Hoh[3], Lena Das[4] and Jing Yao Leong[5,6], [1]Rheumatology and Immunology, KK Women's and Children's Hospital, Singapore, Singapore, [2]Paediatrics, Duke-NUS Graduate Medical School, Singapore, Singapore, [3]Nursing, KK Women's and Children's Hospital, Singapore, Singapore, [4]Dept of Rheumatology, Cincinnati Children`s Hospital Medical Center, Cincinnati, OH, [5]Duke-National University of Singapore Graduate Medical School, Singapore, Singapore, [6]SingHealth Translational Immunology and Inflammation Centre, Singapore Health Services Pte Ltd, Singapore, Singapore

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SESSION INFORMATION

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Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose:

Anti-C1q antibodies (AC1q) were shown to strongly correlate with the occurrence and activity of lupus nephritis in adult SLE. Data of the antibodies in jSLE are rare. We aim to explore AC1q role as a diagnostic biomarker and to assess their validity in monitoring jSLE global disease activity in our Southeast Asian jSLE cohort.

Methods:

Eighty two jSLE patients were recruited and 72 patients with 517 patient-visits with complete clinical data/blood samples were studied. Disease activity indices including mS-2K (SLEDAI without lab), SLAM and BILAG were recorded. Anti-dsDNA, antinucleosome Abs (ANu, H1-stripped) and aC1q were measured by ELISA. Patients were evaluated at 1-3 mo intervals depending on their disease severity. Patients were grouped into 3 disease activity groups: no activity (ID), minimal activity (MD) = mild activity with no therapeutic intervention or activity with improvement from previous visit and active disease activity (AD) = new case or flare or persistent activity/refractory to treatment. 94 JIA, 10 JDM, 12 MCTD/UCTD, 13 vasculitides, 13 ANA-positive and 30 other inflammatory conditions made up 172 controls (median age (IQR) 14.6 (11.4-17.6) years). Descriptive statistics were used to describe data. Mann-Whitney/Kruskal-Wallis tests were used to compare data, Spearman's rho for correlation and Kaplan-Meier test for time-to-flare studies.

Results:

72 cSLE (81% female) with median age of 16.5 (14.6-19.0) yrs and median disease duration of 53.1 (26.2-82.4) mo were included. Chinese (48%) and Malay (28%) were majority. Hematologic disease (96%), arthritis (56%), malar rash (45%) and renal disease (39%) were among most common manifestations. All patients had ANA positivity at onset. Fig 1 shows significant differences in AC1q levels between controls vs. jSLE and among disease activity groups ($p < 0.001$). Table 1 reveals strong diagnostic properties of AC1q. The presence of nephritis associated with AC1q ($p=0.036$). Correlation analysis showed fair to moderate correlations with ESR, C3, C4, anti-dsDNA and ANu but weak against clinical indices. AC1q levels increase at median of 4.8 mo (0-12.83) prior to global disease flare in 64% of visits.

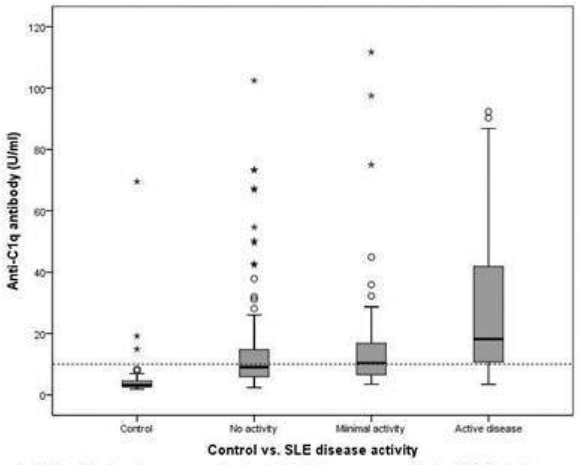

Figure 1 **Anti-C1q Abs levels among control and SLE disease group,** Median (IQR, U/ml)
Control (n=172) 3.16 (2.61-4.54)
No activity (n=125) 9.03 (5.85-14.92); Minimal activity (n=58) 10.41 (6.52-17.15); Active disease (n=54) 18.21 (10.63-42.08)
All pairs antibody level comparison are significantly different (p<0.001), Minimal vs. active disease (p=0.002) except no activity vs. minimal disease (p=0.21)

Table 1 Diagnostic properties of Anti-C1q vs. anti-dsDNA antibodies*				
	Anti-C1q antibody		anti-dsDNA antibody	
Sensitivity:	0.52 (0.38-0.66)		0.88 (0.98-0.93)	
Specificity:	0.98 (0.95-0.99)		0.99 (0.96-0.99)	
Positive likelihood ratio:	29.86 (9.42-94.69)		114.63 (16.24-809.23)	
Negative likelihood ratio:	0.49 (0.36-0.66)		0.13 (0.07-0.23)	
Positive predictive value	0.89 (0.72-0.98)		0.98 (0.93-0.99)	
Negative predictive value	0.88 (0.83-0.92)		0.94 (0.88-0.97)	
Diagnostic odds ratio:	61.23 (17.12-218.98)		910.00 (112.81-7340.94)	
*value (95% Confidence Interval)				
Correlation studies comparing anti-C1q and anti-dsDNA antibodies				
Correlation coefficients (rho)	Anti-C1q antibodies n = 237$^{\delta}$		Anti-dsDNA antibody n = 457$^{\delta}$	
	rho	p-value	*rho*	p-value
ESR	0.36	<0.001	0.33	<0.001
C3	-0.34	<0.001	-0.57	<0.001
C4	-0.46	<0.001	-0.51	<0.001
Anti-dsDNA	0.33	<0.001		
Anti-nucleosome Ab	0.42	<0.001	0.84	<0.001
Anti C1q Ab			0.59	<0.001
mS-2K	0.18	0.005	0.19	<0.001
SLAM	0.28	<0.001	0.29	<0.001
BILAG	0.20	0.002	0.20	<0.001
*Controls n=172, cSLE n=72 (35 active disease + 13 newly diagnosed) $^{\delta}$patient-visits				

Conclusion:

Our initial findings showed strong diagnostic properties of AC1q in our cSLE cohort. The presence of AC1q was associated with lupus nephritis and its levels seem to fluctuate with global, if not only renal disease activity. The rise in the levels may signal a flare in two-third of the jSLE pts. A longer, prospective study is needed to validate these initial findings in our region.

Disclosure: T. Arkachaisri, None; **J. H. T. Tan**, None; **M. Tanya**, None; **S. F. Hoh**, None; **L. Das**, None; **J. Y. Leong**, None.

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Abstract Number: 406

Long Term Follow up of Inner City Pediatric Patients with Lupus Nephritis

Janice Desir[1], Beatrice Goilav[2], Ellen Silver[3] and Irene Blanco[4], [1]Pediatric Nephrology, Children's Hospital at Montefiore/Albert Einstein College of Medicine, Bronx, NY, [2]Division of Nephrology, Children's Hospital at Montefiore, Bronx, NY, [3]Pediatrics, Albert Einstein College of Medicine, Bronx, NY, [4]Medicine, Albert Einstein College of Medicine, Bronx, NY

First publication: September 29, 2015

SESSION INFORMATION

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Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose:

In children with SLE, 80% have renal involvement, which is a major prognostic factor for both morbidity and mortality. Few studies have focused on long-term outcomes of this underserved population, who are at increased risk for high disease severity. This project evaluates high risk children with biopsy confirmed lupus nephritis (LN) to assess clinical and demographic factors that may be related to ESRD and/or death.

Methods:

We conducted a retrospective chart review of patients with LN from 1997-2011 at the Children's Hospital at Montefiore. Patients were less than 20 years old at time of biopsy and followed up to 5 years post biopsy or onset of renal failure/death. We compared nonESRD patients (NonE) to those with ESRD and/or death (ESRD) at baseline and looked at: creatinine, pyuria, hematuria, renal histology, protein to creatinine ratio (uP/C), albumin, hemoglobin, age, gender, race, insurance and medications.

Results:

A total of 36 patients were evaluated. 86% lived in the Bronx and more than 60% were from low-income/high poverty areas. The mean age was 14.4 + 2.5 years and 69.4% were female. 92.0% were African American, Hispanic or multiracial. Histology revealed 14% Mesangial LN (Class II,5/36), 56% Proliferative LN (Class III or Class IV, 20/36) 31% Membranous LN (Class V, 11/36). 61% were Medicaid insured (n=22) vs 39% privately insured (n=14). In the ESRD group 100% (n=9) were Medicaid vs 48% (n=13/27) in the NonE.

Development of ESRD was not associated with creatinine, pyuria, hematuria, histology, uP/C, albumin, hemoglobin, age, gender, race and medications at the time of biopsy. However, having private insurance was significantly protective where 100% of those with Medicaid developed ESRD ($P = 0.006$).

Conclusion:

In our cohort, 25% of children went on to develop ESRD. The only factor that was significant for this was being Medicaid insured. This suggests the type of access to healthcare and associated non-genetic factors may play a role in progressive disease among this group.

Disclosure: J. Desir, None; **B. Goilav**, None; **E. Silver**, None; **I. Blanco**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/long-term-follow-up-of-inner-city-pediatric-patients-with-lupus-nephritis

Abstract Number: 407

Inter-Observer Variability of the Histological Classification of Lupus Glomerulonephritis in Children

Louise Oni[1], Michael Beresford[2], David Witte[3], Anastasios Chatzitolios[4], Neil Sebire[5], Rajeev Shukla[6], Jun Ying[7]

and **Hermine I. Brunner**[8], [1]Department of Paediatric Nephrology, Alder Hey Children's Hospital, Liverpool UK, Liverpool, England, [2]University of Liverpool, Institute of Translational Medicine (Child Health), Alder Hey Children's Foundation NHS Trust, Liverpool, United Kingdom, [3]Rheumatology, Cincinnati Children's Hospital, Cincinnati, OH, [4]Department of Histopathology, Southmead Hospital, Bristol, UK, Bristol, England, [5]Department of Paediatric Histopathology, Great Ormond Street Hospital for Children NHS Trust, London, England, [6]Department of Paediatric Histopathology, Alder Hey Children's Hospital, Liverpool UK, Liverpool, England, [7]Center for Biostatistical Services, University of Cincinnati College of Medicine, Cincinnati, OH, [8]Pediatric Rheumatology Collaborative Study Group, Cincinnati Children's Hospital Medical Center, Cincinnati, OH
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Background/Purpose:

The gold standard for diagnosis and classification of lupus nephritis (LN) is according to the renal histology. The inter-observer reliability between histologists is variable. The aim of this study was to assess the inter-observer reliability of the 2003 International Society of Nephrology/Royal Pathology Society (ISN/RPS) histological classification criteria in children with LN.

Methods:

Four expert nephropathologists independently reviewed the renal histology slides from children with using electronic software. Diagnostic consistency was quantified using the kappa statistic for nominal categories (Class 1 – 6) and intra-class correlation (ICC) for numeric scores of histological activity (max 24), chronicity (max 12) or tubulointerstitial markers of disease (max 21). The level of agreement (strength of the kappa coefficient or ICC) was interpreted as: 0.01-0.20 slight; 0.21-0.40 fair; 0.41-0.60 moderate; 0.61-0.80 good; 0.81-1.00 excellent. As Class III or IV LN typically result in change of treatment, sub-analysis assessed whether there was agreement between these classes (Class I/II termed ‘no treatment change’, and Class III/IV termed as ‘treatment change’).

Results:

The majority of the biopsies (n=55) were graded as Class IV LN (42%) and the median activity score was 4 (0-7), chronicity score 2 (1-3) and tubulointerstitial score 4 (3-6). Nephropathologists showed moderate agreement in assigning LN Classes (kappa score 0.33+0.10; good is >0.6). There was significant variation in the level of agreement between the centres (0.07-0.60). Histological activity had excellent agreement (all ICC >0.75, $p<0.001$), whereas raters had variable agreement in assigning chronicity and tubulointerstitial scoring (ICC range 0.20-0.82 and -0.13-0.66 respectively). With regards to treatment changes, 14 biopsies would not have resulted in treatment change and 29 may have altered treatment and the level of agreement remained poor (kappa 0.24+0.11).

Conclusion:

Internationally agreed classification criteria for LN histology, guide the management of LN. Clinicians and researchers should be aware of the variable level of agreement in their interpretation of LN findings and that is similar in children as it is reported in adults. Histological features of activity have the most consistent agreement. Additional consensus criteria may be necessary to improve the inter-rater variability in the other features.

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Characterization of Pediatric Systemic Lupus Erythematosus with Acquired Angioedema

Marietta De Guzman[1], Diana Bayer[2], Roshni Sambasivan[3], Debra Canter[4], Martha Curry[5] and Anna Carmela Sagcal-Gironella[6], [1]Pediatric Immunology, Allergy, and Rheumatology, Baylor College of Medicine, Texas Children's Hospital, Houston, TX, [2]Division of Allergy, Immunology andPulmonology, University of Iowa Carver College of Medicine, Iowa, IA, [3]Pediatric Immunology, Allergy and Rheumatology, Baylor College of Medicine, Texas Children's Hospital, Houston, TX, [4]Pediatric Immuology, Allergy and Rheumatology, Baylor College of Medicine, Texas Children's Hospital, Houston, TX, [5]Pediatric Immunology, Allergy and Rheumatology, Baylor College of Medicine, Texas Children's Hospital, Houston, TX, [6]Pediatrics, Baylor College of Medicine, Texas Children's Hospital, Houston, TX

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Background/Purpose: Acquired angioedema, defined as non-hereditary angioedema without associated urticaria, is an uncommon but potentially life-threatening feature among adults with systemic lupus erythematosus (SLE). Although autoantibodies to C1 esterase inhibitor have been identified as a potential mechanism for non-histaminergic acquired angioedema in SLE, the exact pathophysiologic mechanisms remain unclear. The incidence and prevalence of angioedema in pediatric SLE (pSLE) is unknown. In this study, we sought to define and characterize acquired angioedema in pediatric systemic lupus erythematosus in a single pediatric rheumatology center.

Methods: We conducted a chart review pSLE patients seen in a single center between 2000 and 2014. Data included family history and clinical presentation of angioedema.

Results: A total of 160 pSLE patients were included. Nine (6%) had history of acquired angioedema, 8 were females, 7 were African American, 2 were Hispanics. Median age at diagnosis was 14 years, and with a mean follow up of 47 mos. No patient had family history of angioedema. Most common ACR SLE criteria met were hematologic (89%), arthritis (67%), renal (5 or 56%). All 5 patients with renal disease had proliferative lupus nephritis, 2 of whom with Class IV lupus nephritis. Two patients has neurologic involvement. Immunoserologic features include antibodies to DAT (100%), dsDNA (89%), Sm (55%), RNP (6/9%), SSA (5/9%) and phospholipid (44%); significantly low C3 and C4 (100%) were noted in all patients. C1 esterase function and nonfunction assays were normal or elevated. Antibodies to C1 esterase were not noted in 4 patients in which the test was done. Angioedema was present within 6 weeks of SLE diagnosis for 6 (67%) patients; head and neck were the most common sites (8/9), with torso and extremity involvement in 4/9 patients. No patient developed respiratory symptomatology. Resolution of the angioedema was noted in all patients following initiation of corticosteroids treatment. Angioedema was recurrent and feature of clinical disease flare in 2 patients (22%).

Conclusion: Acquired angioedema in a single center cohort of pSLE was described as disease manifestation. Future research needs to address its underlying pathophysiologic mechanisms and its clinical significance in treatment and course of pSLE.

Table 1 Clinical Presentation of Acquired Angioedema in 9 pSLE patients

Patient	Age(yr)/Gender	Ethnicity	Time of angioedema to SLE Diagnosis	Angioedema Site
Pt 1	14 F	Hispanic	28 wks	Face (eyes, lips)
Pt 2	12 F	African American	4 wks	Face (eyes, lips), tongue, UEs, torso
Pt 3	15 F	African American	4-12 wks	Face (eyes, lips) UEs
Pt 4	15 F	African American	28 wks	Face, neck, UEs
Pt 5	17 F	African American	4 weeks	UEs, LEs
Pt 6	12 F	African American	28 wks	Face (eyes, lips)
Pt 7	6 F	African American	2-4 wks	Face (lips) tongue
Pt 8	12 M	African American	3-4 wks	Face (lips)
Pt 9	14 F	Hispanic	12-24 wks	Face (lips and eyes)

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Disease Activity, Disease Damage and Predictive Factors in Juvenile Onset Mixed Connective Tissue Disease – a Norwegian Nationwide Study

Siri Opsahl Hetlevik[1], Berit Flatø[1,2], Marite Rygg[3,4], Ellen Berit Nordal[5] and Vibke Lilleby[6], [1]Department of Rheumatology, Oslo University Hospital, Rikshospitalet, Oslo, Norway, [2]Department of Rheumatology, Oslo University Hospital, Institute for Clinical Medicine, University of Oslo, Oslo, Norway, [3]Department of Pediatrics, St Olav University Hospital, Trondheim, Norway, [4]Department of Laboratory Medicine, Children's and Women's health, Norwegian University of Science and Technology, Trondheim, Norway, [5]Department of Pediatrics, University Hospital of North Norway, Tromsø, Norway, [6]Rheumatology, Oslo University Hospital, Oslo, Norway
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Background/Purpose:

Mixed Connective Tissue Disease (MCTD) is a rare rheumatic disease with overlapping features from Systemic Lupus Erythematosus (SLE), Systemic Sclerosis (SSc) and Polymyositis. Juvenile onset MCTD (JMCTD) accounts for approximately 25% of all cases, but knowledge about disease activity and possible organ damage after long-term disease is limited. The purpose of this study is to describe disease activity- and damage in JMCTD after long-term follow-up, and identify possible predictive factors for unfavourable outcome.

Methods:

A cohort of 48 patients with JMCTD from all regions of Norway was examined in a cross-sectional study. Inclusion criteria were fulfilment of the Kasukawa- or Alarcon-Segovia criteria and symptom-onset before 18 years. All patients were clinically examined after mean disease duration of 16.4 (SD 9.9) years. Data from the time of diagnosis were obtained by chart reviews in 45 patients.

As there are no validated criteria for disease activity and damage in MCTD, the following disease activity- and damage scores attributable to SLE, SSc and Juvenile Idiopathic Arthritis (JIA) were used: Systemic Lupus Erythematosus Disease Activity Index (SLEDAI), Rodnan skin score, Systemic Lupus International Collaborating Clinics/ACR Damage Index (SLICC/ACR DI) and Juvenile Arthritis Damage Index (JADI). Remission was defined as fulfilment of the Wallace criteria for remission in JIA, plus the absence of leucopoenia, myositis, progressive lung- or esophageal manifestations and progressive sclerodactyly. Active disease was defined as absence of remission.

Results:

At 16 year follow-up, 31 patients (65%) were considered to have active disease, and 17 (35%) were in remission on or off medication (table 1).

Table 1

Variables at examination after mean 16 year disease duration	Total N = 48	Inactive disease (n = 17)	Active disease (n = 31)	*p* value
RF positive, n (%)	18 (38)	2 (13)	15 (50)	0.01
Anti-RNP titer (median, range)	158 (0-240)	99 (0-240)	222 (0-240)	0.09
Anti-RNP ≥ 240	18 (38)	3 (18)	15 (48)	0.04
ESR (median, range)	9.0 (2-54)	7.0 (3-16)	11,0 (2-54)	0.32
CRP (median, range)	0.7 (<0.6-15)	0.7 (<0.6-3.3)	0.7 (<0,6-15)	0.73
Physicians Global Assessment VAS (Median, range)	15.5 (1-58)	4.0 (1-29)	22.0 (4-58)	0.0
Fatigue VAS (median, range)	47.0 (1-98)	18.0 (1-98)	51.5 (1-96)	0.11
Raynaud VAS (median, range)	32.0 (1-87)	19.0 (1-77)	49 (1-87)	0.02
SLEDAI (mean, SD)	0.5 (1.2)	0.12 (0.3)	0.71 (1.5)	0.03
Rodnan skin score n = 40 (mean, SD)	0.9 (2.2)	0.2 (0.8)	1.2 (2.5)	0.08
SLICC/ACR DI (mean, SD)	0.7 (0.7)	0.71 (0.85)	0.74 (0.68)	0.88
SLICC/ACR DI ≥ 1 (n, %)	21 (44)	12 (39)	9 (53)	0.58
Active joints (mean, SD)	1.1 (2.3)	0	1.1 (2.7)	0.04
Joints with limited range of motion (mean, SD)	5.2 (8.5)	3.5 (8.1)	6.1 (8.6)	0.31
JADI (mean, SD)	1.9 (5.1)	0.94 (1.8)	2.5 (6.2)	0.22

The patients with active disease had more frequently high levels of anti-RNP and positive Rheumatoid Factor (RF) than

those in remission. Twenty one patients (44%) had a SLICC score of 1 or more. The main reason for the high score was the large proportion with signs of pulmonary fibrosis (21 patients, 44%), where 21 (44%) had reduced diffusion capacity or vital capacity, and 12 patients (25%) had CT-verified pulmonal fibrosis.

Disease duration, positive RF at diagnosis and number of months treated with prednisolone were associated with persistently active disease after 16 years, but only the presence of positive RF at diagnosis was identified as a predictor in the multivariate analysis at follow-up (OR 6.84, 95% CI 1.6-29.8).

Conclusion:

In this Norwegian cohort of juvenile onset MCTD, we found that after 16 years of disease duration, 65% had ongoing active disease, and these patients had more frequently high levels of anti-RNP and positive RF. A large proportion of the patients had signs of disease damage with a score of ≥1 assessed with SLICC/ACR DI.

Presence of positive RF at time of diagnosis predicted ongoing active disease.

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Characteristics of the Juvenile Systemic Sclerosis Cohort within the Childhood Arthritis and Rheumatology Research Alliance (CARRA) Registry

Brandi E. Stevens[1], Kathryn S. Torok[2], Suzanne C. Li[3], Nicole Hershey[1], Megan Curran[4], Gloria C. Higgins[5], Katharine Moore[6], C. Egla Rabinovich[7], Anne M. Stevens[8] and Childhood Arthritis and Rheumatology Research Alliance, Stanford, CA, [1]Division of Rheumatology, Children's Hospital of Pittsburgh of UPMC, Pittsburgh, PA, [2]Pediatric Rheumatology, Scleroderma Center of Pittsburgh, Children's Hospital of Pittsburgh of UPMC, Pittsburgh, PA, [3]Pediatrics, Joseph M Sanzari Children's Hospital, Hackensack University Medical Center, Hackensack, NJ, [4]Pediatric Rheumatology, Ann and Robert H. Lurie Children's Hospital of Chicago, Chicago, IL, [5]Pediatric Rheumatology Ohio State University, Nationwide Childrens Hospital, Columbus, OH, [6]Pediatric Rheumatology, Seattle Children's Hospital, Seattle, WA, [7]Pediatric Rheumatology, Duke University Medical Center, Durham, NC, [8]Seattle Children's Res Inst, Seattle Children's Hospital, University of Washington, Seattle, WA

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Background/Purpose: Systemic sclerosis (SSc) is a rare multisystem autoimmune disease characterized by vasculopathy and organ fibrosis. We present baseline data on the North American observational juvenile systemic sclerosis (jSSc) cohort from the CARRA registry.

Methods: Descriptive statistics were used for demographic, clinical, and laboratory features.

Results: For the 64 children with SSc in the database, baseline CARRA visit occurred a median of 3.6 yrs after disease onset. The median age of onset was 10.3 yr. Median age at first pediatric rheumatology (PRH) evaluation was 11.8 yr, with 23% having a $\geq$ 2 yr delay to PRH. Demographics and clinical manifestations are detailed in Table 1. Overlap with juvenile dermatomyositis was identified in 3 individuals, with mixed connective tissue disease in 1. Of those with documented testing for specific antibodies, 80% were ANA positive, 46% anti-Scl70 and 15% ACA. Three of 15 patients tested for anti-PM-Scl antibodies were positive.

The most prevalent organ manifestations were dermatologic (93%) and vascular (92%), with Raynaud phenomenon as the most common feature. Multiple organ systems were affected in 93%. Reported prior or current medications included use of DMARDs in 87%, steroids in 53%, and biologics in 10%.

While the median Physician Global Disease Activity (PGA) score was 2, patient reported measures reflected the presence of functional impairment and perceived deficiencies in overall well-being (Table 2). ACR functional class was > class I for 36% of individuals at baseline and for 74% individuals at worst function.

Conclusion: Within the CARRA registry, most jSSc patients were female and Caucasian with a median age of onset of 10.3 years. From limited comparison, baseline clinical data from this cohort are similar to the jSSc cohort described by Martini et al in 2006 except the inclusion of overlap patients. While ANA positivity is similar or lower than other cohorts, ACA positivity is higher which may reflect factors aside from disease, such as changes in commercially available ANA testing. Overlap syndrome, present in 29-37% of patients in 2 other cohorts, may be under recognized. This identifies a potential gap in serologic testing, such as anti-PM-Scl, and identification of jSSc subtypes.

Significant morbidity is seen in this cohort, with the majority of individuals having multisystem involvement. Even with low disease activity scores, patients and providers reported impacts on function, pain, and quality of life. This identifies the need for development of accurate serologic identification and clinical measurement indices of damage, activity, and severity for jSSc.

Table 1. Patient Characteristics

Demographics	**n (%)**
Gender	
Female	54 (84%)
Race, Ethnicity	
Caucasian	50 (78%)
African American	12 (19%)
Asian	2 (3%)
Non-Hispanic	55 (86%)

	Median yrs (IQR)
Age at Disease Onset	10.3 (6.3-13.1)
Time from Onset to PRH	0.8 (0.14-1.9)
Time from Onset to CARRA Baseline	3.6 (1.8-6.3)

Clinical Manifestations

Percentages are given for those with no missing data for the characteristic

Manifestation	**Affected (%)**
Dermatologic	54 (93%)
Skin Thickening/Induration	37 (64%)
Face	27 (47%)
Proximal to MCPs	28 (48%)
Proximal to Elbow	9 (16%)
Trunk	4 (7%)
Sclerodactyly	36 (62%)
Telangiectasia	21 (36%)
Calcinosis	6 (10%)
Other Dermatologic	5 (9%)
Vascular	54 (92%)
Raynaud's	43 (73%)
Nailbed Capillary Abnormalities	41 (70%)
Digital Ulceration/Gangrene	27 (46%)
Musculoskeletal	27 (46%)
Contractures	20 (34%)
Arthritis	11 (19%)
Myositis	7 (12%)
Tendinopathy	3 (5%)
GI	25 (42%)
GI Dysmotility	12 (20%)
Documented GERD	11 (19%)
Dysphagia	10 (17%)
Esophagitis	2 (3%)
Malabsorption	1 (2%)
Other	4 (7%)

Manifestation	**Affected (%)**
Pulmonary	20 (34%)
Restrictive Lung Disease	13 (22%)
Decreased DLCO/Hypoxemia	11 (19%)
Radiologic or Pathologic Fibrosis	6 (10%)
Parenchymal Pulmonary Disease	4 (7%)
Dyspnea	4 (7%)
Pulmonary Hypertension	1 (2%)
Other	2 (3%)
Renal	2 (3%)
Renovascular Hypertension	1 (2%)
Other	1 (2%)
Cardiac	1 (2%)
Pericardial effusion	1 (2%)
Multiple Organ Involvement	54 (93%)
Number of organs affected	
None	1 (2%)
One	3 (5%)
Two	14 (24%)
Three	18 (31%)
Four or More	22 (38%)
Total organs affected, median(IQR)	3 (2-4)

Table 2. Physician and Patient Based Assessments. Percentages are given for those with no missing data for the characteristic.

Physician Assessments	
	Median (IQR)
Physician Global Disease Activity*, n=56	2 (1-3)
ACR Functional Class	**n (%)**
Current at Baseline, n=61	
Class I	39 (64%)
Class II	15 (25%)
Class III	4 (7%)
Class IV	3 (5%)
Worst Ever, n=53	
Class I	14 (26%)
Class II	26 (49%)
Class III	8 (15%)
Class IV	5 (9%)

Patient/Parent Reported Global Function and Quality of Life Metrics, n=64	
	Median (IQR)
Childhood Health Assessment Questionnaire	0.13 (0.0-0.63)
Pain Scale*	1 (0-4)
Global Well Being Scale*	3 (1-5)
Health Related Quality of Life	**n (%)**
Excellent	9 (14%)
Very good	22 (35%)
Good	28 (44%)
Poor	4 (6%)
Very Poor	0 (0%)

*Physician global assessment of disease activity, patient reported global wellbeing, and patient reported pain were measured on a 0-10 numeric rating scale, 10 indicating worst disease, poorest wellbeing, or worst pain, respectively.

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Patient Reported Outcomes in Juvenile Dermatomyositis: Assessing the Importance of Different Measures to Patients and Families

Heather Tory[1], Ruy Carrasco[2], Thomas Griffin[3], Melissa M. Hazen[4], Adam M. Huber[5], Philip Kahn[6], Angela Byun

Robinson[7], Susan Kim[8] and The Childhood Arthritis and Rheumatology Research Alliance Juvenile Dermatomyositis Quality Measures Workgroup, [1]Rheumatology, Connecticut Children's Medical Center, Hartford, CT, [2]Pediatric Rheumatology, Specially For Children, Austin, TX, [3]Rheumatology, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, [4]Rheumatology, Children's Hospital Boston, Boston, MA, [5]Pediatric rheumatology, IWK Health Centre, Halifax, NS, Canada, [6]Pediatric Rheumatology, New York University, New York, NY, [7]Pediatrics, Rainbow Babies & Children's Hospital / Case Medical Center, Cleveland, OH, [8]Division of Immunology, Boston Children's Hospital, Boston, MA

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Background/Purpose: Patient reported outcomes (PROs) are becoming increasingly important in the care of patients with chronic disease. Involving patients in their own care significantly improves health care outcomes, health care utilization and patient satisfaction. Robust PROs have not been well defined for patients with juvenile dermatomyositis (JDM). We sought to assess the importance of different PROs to patients with JDM and their families to help guide development of these measures and care discussions.

Methods: A survey was developed by members of the Childhood Arthritis and Rheumatology Research Alliance JDM Quality Measures Workgroup through a consensus process and was distributed to approximately 2100 email addresses of families of patients with JDM through the Cure JM foundation. Data were abstracted in a standardized database for analysis, including demographics, myositis characteristics, functional disability, and rating of importance of a variety of common PROs.

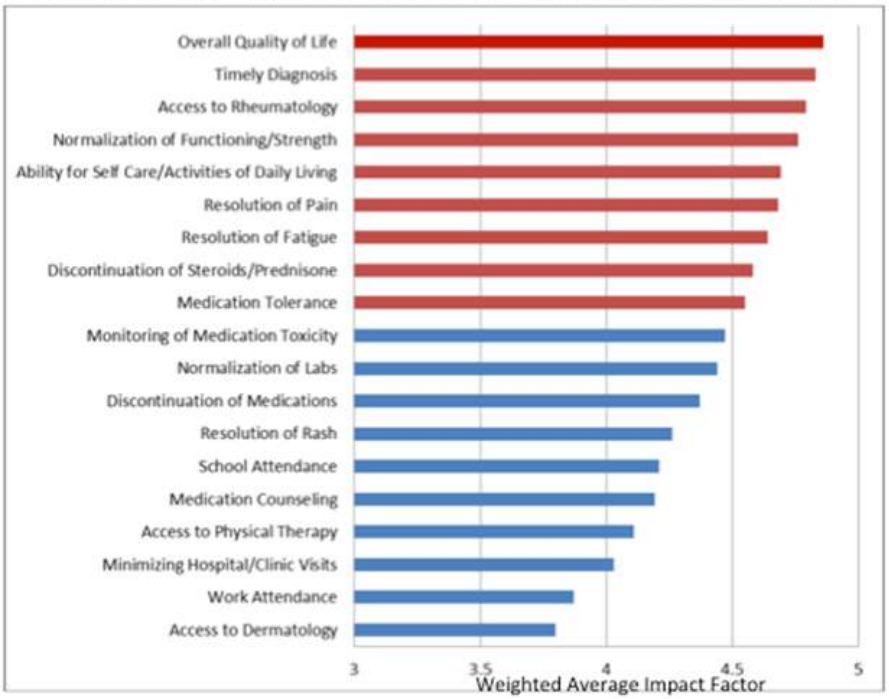
Results: Overall, 194 relatives of patients with inflammatory myositis responded to the survey. Nearly all patients (187, or 97.4%) were diagnosed with JDM, while 5 (2.6%) were diagnosed with juvenile polymyositis. Of the respondents, 168 (93%) were parents and the remainder were grandparents and other relatives. The majority of patients were female (140, or 73%). There was a wide range of age at diagnosis (1 to 16 years), with average time to diagnosis 6.7 months (range 1 to over 40). Most patients (166, or 86%) were Caucasian/white, 21 (11%) were Hispanic and 15 (8%) were African American.

The PROs that families of patients with JDM rated as having the highest importance (weighted average over 4.5 out of 5) included overall quality of life (173, or 89% reporting this among the most important factors), timely diagnosis (171, or 89%), access to a rheumatologist (166, or 86%), normal function and strength (155, or 80.3%), ability to perform self-care (146, or 75%), resolution of pain (145, or 75%), discontinuation of steroids (143, or 74%), resolution of fatigue (135, or 70%), and medication tolerance (135, or 70%). Conversely, access to a dermatologist and physical therapy, work attendance, minimizing hospital visits, medication counseling and monitoring of medication toxicity, discontinuation of medications, normalization of labs, resolution of rash, and school attendance were not rated as highly (**Figure 1**).

Families of patients diagnosed within the past 2 years tended to rate all of the PROs as more important compared to those with diagnoses over 2 years ago, as did families of patients with high current functional impact from the disease, compared to those with low current functional impact.

Conclusion: Patients and their families with JDM find certain PROs more meaningful and relevant than others, which should be taken into account when establishing quality metrics and caring for patients with JDM.

Figure 1: The relative importance of a variety of PROs to patients with JDM, reported from highest to lowest weighted average impact factor.



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Update on the Juvenile Systemic Sclerosis Inception Cohort Project. Characteristics of the First 50 Patients at First Assessment. Www.Juvenile-Scleroderma.Com

Ivan Foeldvari[1], Jens Klotsche[2], Valda Staņeviča[3], Ekaterina Alexeeva[4], Maria M. Katsicas[5], Maria Teresa Terreri[6], Ana Paula Sakamoto[7], Rolando Cimaz[8], Mikhail Kostik[9], Tadey Avcin[10], Maria Jose Santos[11], Monika Moll[12], Dana Nemkova[13], Flavio Sztajnbok[14], Cristina Battagliotti[15], Juergen Brunner[16], Despina Eleftheriou[17], Alberto Sifuentes Giraldo[18], Liora Harel[19], Mahesh Janarthanan[20], Tilmann Kallinich[21], Kirsten Minden[22], Susan Mary Nielsen[23], Kathryn S. Torok[24], Yosef Uziel[25] and Nicola Helmus[26], [1]Hamburger Zentrum für Kinder-und Jugendrheumatologie, Hamburg, Germany, [2]Epidemiology unit, German Rheumatism Research Center, Berlin, Germany, [3]Pediatric cathedra, Riga Stradiņš University, Riga, Latvia, [4]Rheumatology, Scientific Center of Children's Health, Moscow, Russia, [5]Immunology & Rheumatology., Hospital de Pediatrìa Garrahan, Buenos Aires, Argentina, [6]Pediatrics, Universidade Federal de Sao Paulo, São Paulo, Brazil, [7]Assistant doctor, Pediatric Rheumatology Unit, Universidade Federal de São Paulo, São Paulo, Brazil, [8]Department of Paediatrics, University of Florence and Anna Meyer Children's Hospital, Florence, Italy, Florence, Italy, [9]State Pediatric Medical University, Saint-Petersburg, Russia, [10]University Children's Hospital, Ljubljana, Slovenia, [11]Rheumatology, Hospital Garcia de Orta, Almada, Portugal, [12]Pediatric Rheumatology, University Childrenhospital, Tübingen, Germany, [13]Pediatric Rheumatology Unit, Department of Pediatrics and

Adolescent Medicine, General University Hospital in Prague, Prague, Czech Republic, [14]Universidade Federal do Rio de Janeiro, Rio de Janeiro, Brazil, [15]Hospital de Niños Dr Orlando Alasia, Santa Fé, Argentina, [16]Universitätsklinik für Kinder- u. Jugendheilkunde, Innsbruck, Austria, [17]Paediatric Rheumatology Department, Great Ormond Street Hospital for Children NHS Trust, London, United Kingdom, [18]Department of Rheumatology, University Hospital Ramón y Cajal, Madrid, Spain, [19]Pediatric Rheumatology Unit, Schneider Children's Medical Center,Tel Aviv University, Petach Tikvah, Israel, [20]Pediatric Rheumatology, Chennai, India, [21]Charite, University Medicine Berlin, Berlin, Germany, [22]Chidlrens´ hospital, Charité University Medicine, Berlin, Germany, [23]Rigshospitalet, Copenhagen, Denmark, [24]Pediatric Rheumatology, Children's Hospital of Pittsburgh of UPMC, Pittsburgh, PA, [25]Meir Medical Center, Kfar Saba, Israel, [26]Hamburg Centre for Pediatric and Adolescent Rheumatology, Hamburg, Germany
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SESSION INFORMATION

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Background/Purpose: Juvenile systemic sclerosis (jSSc) is an orphan autoimmune disease. Currently just retrospective data exist regarding evolvement of organ involvement. In the previous retrospective studies assessment of the organ involvement was not standardized. Our project is the first one, where data of jSSc patientes were collected prospectively and with a standardized assessment.

Methods: Patients with jSSc were recruited worldwide and were prospectively assessed, using the proposed standardized patient assessment protocol. Data of the juvenile systemic sclerosis inception cohort have been contributed to the DeSScipher project which was funded by a grant of the European Community's Framework Programme 7 under grant agreement N° 305495."

Results:

24 centers from 16 countries agreed to participate on the project. The assent and consent forms were translated into the local native languages. Until now 50 patients have been enrolled with a mean disease duration of 6.1 years. Thirtyseven (74%) of the 50 patients were females. The mean age of the onset of Raynaud´s phenomenon was 9.2 years (2-16 years), the youngest 2 years old. The mean age at the onset of the non-Raynaud presentation of jSSc was 9.7 years (2.3-16.00 years). 34 (68%) of the 50 have diffuse subtype. 5 in the diffuse (14.7%) and 3 in the limited subtype (19%) had an overlap feature.

At the time of the inclusion the mean modified Rodnan Skin Score was 16.7. 32/48 (67%) had already capillary changes and 25/48 (52%) already had history of ulcerations, 12/48 (25%) had active ulcerations at the time of the inclusion. 35/50 (70%) had cardiopulmonary involvement, 18/50 (36%) had signs of interstitial lung disease. 5 (10%) patients had pulmonary hypertension. Four (8%) had renal involvement, but no renal crisis. 20/50 (40%) had gastrointestinal involvement and 15 (30%) of them esophageal involvement. 38/49 (77.5%) had musculoskeletal involvement. ANA positivity occurred in 36/47 (77%) and 15/40 (37.5%) of them were anti-Scl 70 positive. 2/29 (7%) had anticentromere positivity.

Conclusion: We present the data on the first 50 patients with jSSc included in our cohort. The current recruitment data confirms that pediatric patients are different from the adult patients, with a higher proportion of diffuse subset patients with 68% and 16% of patients with overlap features. Anti-centromere antibodies occuring only in 7% of patients.

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Is There a Difference in the Presentation of Diffuse and Limited Subtype of Juvenile Systemic Sclerosis in Childhood? Results from the Juvenile Scleroderma Inception Cohort Www.Juvenile-Scleroderma.Com

Ivan Foeldvari[1], Jens Klotsche[2], Valda Stanevicha[3], Maria M. Katsicas[4], Maria Teresa Terreri[5], Ana Paula Sakamoto[6], Rolando Cimaz[7], Mikhail Kostik[8], Tadey Avcin[9], Maria Jose Santos[10], Monika Moll[11], Dana Nemkova[12], Flavio Sztajnbok[13], Cristina Battagliotti[14], Juergen Brunner[15], Despina Eleftheriou[16], Alberto Sifuentes Giraldo[17], Liora Harel[18], Mahesh Janarthanan[19], Tilmann Kallinich[20], Kirsten Minden[21], Susan Mary Nielsen[22], Kathryn S. Torok[23], Yosef Uziel[24] and Nicola Helmus[25], [1]Hamburger Zentrum für Kinder-und Jugendrheumatologie, Hamburg, Germany, [2]Epidemiology unit, German Rheumatism Research Center, Berlin, Germany, [3]Pediatric cathedra, University Childrens Hospital, Riga, Latvia, [4]Service of Immunology & Rheumatology. Hospital de Pediatrìa Prof Dr.Juan.P. Garrahan, MD, Buenos Aires, Argentina, [5]Pediatrics, Universidade Federal de Sao Paulo, São Paulo, Brazil, [6]Assistant doctor, Pediatric Rheumatology Unit, Universidade Federal de São Paulo, São Paulo, Brazil, [7]Department of Paediatrics, University of Florence and Anna Meyer Children's Hospital, Florence, Italy, Florence, Italy, [8]State Pediatric Medical University, Saint-Petersburg, Russia, [9]University Children's Hospital, Ljubljana, Slovenia, [10]Rheumatology, Hospital Garcia de Orta, Almada, Portugal, [11]Pediatric Rheumatology, University Childrenhospital, Tübingen, Germany, [12]Pediatric Rheumatology Unit, Department of Pediatrics and Adolescent Medicine, General University Hospital in Prague, Prague, Czech Republic, [13]Universidade Federal do Rio de Janeiro, Rio de Janeiro, Brazil, [14]Hospital de Niños Dr Orlando Alasia, Santa Fé, Argentina, [15]Universitätsklinik für Kinder- u. Jugendheilkunde, Innsbruck, Austria, [16]Paediatric Rheumatology Department, Great Ormond Street Hospital for Children NHS Trust, London, United Kingdom, [17]Department of Rheumatology, University Hospital Ramón y Cajal, Madrid, Spain, [18]Pediatric Rheumatology Unit, Schneider Children's Medical Center,Tel Aviv University, Petach Tikvah, Israel, [19]Pediatric Rheumatology, Chennai, India, [20]Charite, University Medicine Berlin, Berlin, Germany, [21]Chidlrens´ hospital, Charité University Medicine, Berlin, Germany, [22]Rigshospitalet, Copenhagen, Denmark, [23]Pediatric Rheumatology, Scleroderma Center of Pittsburgh, Children's Hospital of Pittsburgh of UPMC, Pittsburgh, PA, [24]Meir Medical Center, Kfar Saba, Israel, [25]Hamburg Centre for Pediatric and Adolescent Rheumatology, Hamburg, Germany

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Background/Purpose:

Juvenile systemic sclerosis (jSSc) is an orphan autoimmune disease. Several publications in adults looked at the differences between limited and diffuse subtypes. There is rarity of data regarding this topic in pediatric jSSc. The juvenile scleroderma inception cohort (www.juvenile-scleroderma.com) is a prospective standardized register for patients with jSSc.

Methods:

Patients with jSSc were included worldwide into the juvenile scleroderma inception cohort. We compared the demographics and clinical features of the ljSSc and djSSc. Data of the juvenile systemic sclerosis inception cohort have been contributed to the DeSScipher project which was funded by a grant of theEuropean Community's Framework Programme 7 under grant agreement N° 305495.

Results:

Up till now 50 patients were enrolled, 34 (68%) with djSSc and 16 (32%) with ljSSc. 5 in the diffuse (15%) and 3 in the limited subtype (19%) had an overlap feature. The mean follow up of the patients in the cohort was 6.4 years in the djSSc and 5.5 years in ljSSc. 74% in the djSSc and 75% in the ljSSc group were female. The mean age at the onset of Raynaud´s Phenomenon was 8.4 years in the jdSSc and 10.8 years in ljSSc group (p=0.061) while the mean age at the onset of the first non-Raynaud presentation was 8.8 years in djSSc and 11.6 years ljSSc (p=0.010). At the time of the inclusion the mean modified Rodnan Skin Score was 20.4 in the djSSc and 8.9 in ljSSc (p=0.002). 72% in jdSSc and 56% in the ljSSc of patients (p=0.35) had already capillary changes, but 64% in djSSc and only 26% in ljSSc (p=0.015) had already history of ulcerations and 33% presented with active ulceration in the djSSc and 6% in the ljSSc (p=0.074). 71% of djSSc and 68 % of ljSSc had cardiopulmonary involvement. Four patients had pulmonary hypertension. 3 of them had djSSc. 44% in djSSc and 19% in ljSSc group (p=0.117) showed signs of interstitial lung disease on imaging. Four patients had renal involvement, 3 of them had djSSc, no renal crisis was reported. 47% in the djSSc and 25% in the ljSSc (p=0.216) had gastrointestinal involvement. Around 76% in djSSc and 81% in ljSSc had musculoskeletal involvement. Anti-Scl 70 positivity was found in 10/27 (37%) of djSSc and 5/13 (38%) in ljSSc. Only 2 patients and only in the djSSc group had anticentromere antibody.

Conclusion:

We present the data on the first 50 patients with jSSc included in our cohort. Patients with djSSc and ljSSc differ in several characteristics. Patients with djSSc were younger at onset, had more often capillary changes and active ulcerations, pulmonary hypertension and renal involvement. The characteristics of the pediatric subtypes differs from adults with SSc.

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Abstract Number: 414

Performance of the Adult Systemic Sclerosis Classification in Juvenile Systemic Sclerosis Patients. Results from the Juvenile Systemic Sclerosis Inception Cohorte Www.Juvenile-Scleroderma.Com

Ivan Foeldvari[1], Jens Klotsche[2], Valda Stanevicha[3], Ekaterina Alexeeva[4], Maria M. Katsicas[5], Maria Teresa

Terreri[6], Ana Paula Sakamoto[7], Rolando Cimaz[8], Mikhail Kostik[9], Tadey Avcin[10], Maria Jose Santos[11], Monika Moll[12], Dana Nemkova[13], Flavio Sztajnbok[14], Cristina Battagliotti[15], Juergen Brunner[16], Despina Eleftheriou[17], Alberto Sifuentes Giraldo[18], Liora Harel[19], Mahesh Janarthanan[20], Tilmann Kallinich[21], Kirsten Minden[22], Susan Mary Nielsen[23], Kathryn S. Torok[24], Yosef Uziel[25] and Nicola Helmus[26], [1]Hamburger Zentrum für Kinder-und Jugendrheumatologie, Hamburg, Germany, [2]Epidemiology unit, German Rheumatism Research Center, Berlin, Germany, [3]University Childrens Hospital, Riga, Latvia, [4]Rheumatology, Scientific Center of Children's Health, Moscow, Russia, [5]Hospital de Pediatria, Buenos Aires, Argentina, [6]Pediatrics, Universidade Federal de Sao Paulo, São Paulo, Brazil, [7]Assistant doctor, Pediatric Rheumatology Unit, Universidade Federal de São Paulo, São Paulo, Brazil, [8]Pediatric Rheumatology, Anna Meyer Children's Hospital, Florence, Italy, [9]State Pediatric Medical University, Saint-Petersburg, Russia, [10]University Children's Hospital, Ljubljana, Slovenia, [11]Rheumatology, Hospital Garcia de Orta, Almada, Portugal, [12]Pediatric Rheumatology, University Childrenhospital, Tübingen, Germany, [13]Pediatric Rheumatology Unit, Department of Pediatrics and Adolescent Medicine, General University Hospital in Prague, Prague, Czech Republic, [14]Pediatric Rheumatology Division, Adolescent Health Care Unit, Universida de do Estado do Rio de Janeiro., Rio de Janeiro, Brazil, [15]Hospital de Niños Dr Orlando Alasia, Santa Fé, Argentina, [16]Universitätsklinik für Kinder- u. Jugendheilkunde, Innsbruck, Austria, [17]Paediatric Rheumatology Department, Great Ormond Street Hospital for Children NHS Trust, London, United Kingdom, [18]Department of Rheumatology, University Hospital Ramón y Cajal, Madrid, Spain, [19]Pediatric Rheumatology Unit, Schneider Children's Medical Center,Tel Aviv University, Petach Tikvah, Israel, [20]Pediatric Rheumatology, Chennai, India, [21]Charite, University Medicine Berlin, Berlin, Germany, [22]Epidemiology, Charite, DRFZ, Berlin, Germany, [23]Rigshospitalet, Copenhagen, Denmark, [24]Pediatric Rheumatology, Scleroderma Center of Pittsburgh, Children's Hospital of Pittsburgh of UPMC, Pittsburgh, PA, [25]Meir Medical Center, Kfar Saba, Israel, [26]Hamburg Centre for Pediatric and Adolescent Rheumatology, Hamburg, Germany
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Background/Purpose:

The new adult classifiction criteria (1) for Systemic Sclerosis (SSc) were recently published and the pediatric criteria were published in 2007 (2). None of these criteria were validated in a pediatric cohort of patients.

Methods:

We validated the adult SSc criteria in the juvenile SSc inception cohort stratified by the disease duration of the patients. We performed a latent class analysis on the adult SSc criteria for investigating the pattern of presentation of juvenile patients adjusted for disease duration.

Results:

All pediatric patients in the cohort fulfilled the adult classification criteria of proximal skin sclerosis from MCP joint. It is the main criteria of the pediatric classification system and it already gives sufficient points to be classified as SSc. Raynauds' phenomena (73%) and nail fold changes (57%) were the most common items fulfilled by the juveniles. The pediatric patients had a mean score of 15.3 at <6 months (n=16), 15.5 at <12 months (n=31), 16.5 at < 24 months (n=62) and 17.1 at <48 months (n=86). The latent class analysis on the adult SSc criteria resulted in 3 groups of juvenile SSc patients (table 1). All patients in the first severely affected group had proximal skin sclerosis, fingertip pitting scars, nail fold changes and raynauds' phenomena. In the mild third group (n=33), the item skin sclerosis was

most important, the other criteria played a minor role in that group.

Table 1. Results of the latent class analysis on the adult SSc criteria in the inception cohort of juvenile systemic sclerosis.

	Class I n=16 %	Class II n=37 %	Class III n=33 %
Proximal skin sclerosis	100.0	100.0	100.0
Puffy Fingers	0.0	0.0	0.0
Sclerodactyly	100.0	100.0	100.0
Digital tip ulcers	81.3	0.0	0.0
Fingertip pitting scars	100.0	44.4	36.4
Telangiectasia	0.0	0.0	0.0
Nailfold changes	100.0	78.4	12.1
PH	12.5	13.5	0.0
ISL	81.3	29.7	39.4
Raynauds	100.0	94.6	36.4
SSc AB	18.8	74.3	3.2

Conclusion:

All pediatric patients fulfilled the adult classification criteria. The cumulative score increased continuously with an increasing disease duration. The latent class analysis revealed 3 groups of jSSc patients regarding the performance of adult SSc criteria. An adaption of jSSc criteria, that patients without skin involvement can be included, would be important, to increase the number of patients with early diagnosis.

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Abstract Number: 415

Development of a Juvenile Systemic Sclerosis Response Index (JSSRI)

Ivan Foeldvari[1], Gyorgyi Zoltan[2], Eileen Baildam[3], Ezgi Deniz Batu[4], Michael Blakley[5], Mustafa Cakan[6], Megan Curran[7], Antonia Kienast[8], Kim Fligelstone[9], Dana Nemkova[10], Clarissa Pilkington[11], Nicolino Ruperto[12], Maria

Tsinti[13], Elena Tsitsami[14], Kristina Urbanvica[15] and Tamas Constantin[16], [1]Hamburger Zentrum für Kinder-und Jugendrheumatologie, Hamburg, Germany, [2]Semmelweiss University Budapest, Budapest, Hungary, [3]Paediatric Rheumatology, Alder Hey Children's NHS Foundation Trust, Liverpool, United Kingdom, [4]Hacettepe University Vasculitis Center (HUVAC), Ankara, Turkey, [5]Internal Medicine and Pediatrics, Indiana University School of Medicine and Riley Hospital for Children at IU Health, Indianapolis, IN, [6]Pediatric Rheumatology University Childrens Hospital Istanbul, Istanbul, Turkey, [7]Pediatric Immunology/Rheum, UCSF, San Francisco, CA, [8]Hamburg Centre for Pediatric and Adolescent Rheumatology, Hamburg, Germany, [9]FESCA - Scleroderma parents organisation, UK, United Kingdom, [10]Pediatric Rheumatology Unit, Department of Pediatrics and Adolescent Medicine, General University Hospital in Prague, Prague, Czech Republic, [11]Paediatric Rheumatology Department, Great Ormond Street Hospital for Children NHS Trust, London, United Kingdom, [12]Pediatrica II, Instituto Giannina Gaslini, PRINTO, Genoa, Italy, [13]Ped rheum univ child hosp athen, Athena, Greece, [14]First Department of Pediatrics, Athens University Medical School, Athens, Greece, [15]Pediatric Rheumatology, Riga, Latvia, [16]Semmelweis University, Budapest, Hungary
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Background/Purpose:

Juvenile systemic sclerosis (jSSc) is an orphan disease. We have currently new promising effective medication to treat systemic sclerosis, but no valid outcome measures to assess the activity of the disease. In the frame of the juvenile scleroderma working group of Paediatric Rheumatology European Society (PRES JSWG), we developed a provisional response index for jSSc.

Methods:

The facilitating committee designed a 3-round Delphi-exercise to obtain a core set of disease activity measures in jSSc. The members of the international paediatric rheumatology email board, the PRES juvenile scleroderma working group and the active participants of the juvenile scleroderma inception cohort project were invited to participate in our online surveys. In Round 1, they were asked to add unique items in 21 preleminary domains. Round 2 judged the items' applicability and importance using a 1-10 scale. Previous respondents were asked to re-rate uncertain (score 4-7) items in Round 3. The aforementioned were followed by a face-to-face Nominal Group discussion to decide final items and domain structure.

Results:

52 participants of Round 1 suggested a total of 131 items for the 21 domains. In round 2, 56 responders rated the significance of the items. Most of the participating experts took part in the 3rd Round by assessing the uncertain items. The Nominal Group accepted 11 main domains for further validation (global disease activity, biomarkers, Rayneud phenomenon, digital ulcers, skin, pulmonary, cardiac, gastrointestinal and renal involvement, 'health related qualaity of life and function') containing 41 items (see table 1). We have also felt essential to collect data regarding the development of the children.

table 1:

Global disease activity
- Global disease activity according to physician by visual analogue scale (VAS)
- Global disease activity according to patient / parent by VAS
- Scleroderma-related condition rating by physician as in the last 3 months
- Scleroderma-related condition rating by patient / parent as in the last 3 months

Biomarkers
- ESR
- CRP
- Hemoglobin

Raynaud phenomenon
- Raynaud activity score
- Raynaud severity due to patient by VAS

Digital ulcers
- Number of digital ulcers
- Newly occured digital ulcers
- Digital ulcer severity due to patient by VAS

Skin
- Modified Rodnan skin score (mRSS)
- Newly occured calcinosis
- Newly occured teleangiectasia
- Presence of scleroderma-related edema

Pulmonary
- Forced vital capacity (FVC)
- Diffusion capacity (DLCO)
- 6 minute walk test
- Borg index

Cardiac
- Left Ventricular ejection fraction (EF) by echocardiography
- Right Ventricular ejection fraction (EF) by echocardiography
- Newly occured carditis
- Newly occured arrythmia
- Pro-BNP level
- New onset or worsening of pulmory arterial hypertension (PAH)

Gastrointestinal
- New onset of swallowing difficulties
- Change in stool frequency
- New sign of reflux

Renal
- Newly occured hypertension
- Newly occured renal crisis
- Proteinuria (by spot urine)
- Creatinine clearence (in severe muscle loss, EDTA claerance should be measured)
- Change in glomerular filtration rate (GFR)

Health related quality of life and function
- PEDSQL between 8-16 years or SF-36 over 16 years of age

Childhood health assessment questionnaire (CHAQ)
Pain assessment by VAS as in CHAQ
Fatigue assessment by VAS

(Essential paediatric data to collect)
Weight
Height
Growth velocity
Tanner stage

Conclusion:

We reached consensus and developed a Response Index, which should help to conduct clinical trials in jSSc. The validation of the JSSRI is planned on the patients of the Juvenile Scleroderma Inception Cohort.

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Prospective, Standardized, Longitudinal Assessment Reveals Higher Prevalence of Extracutaneous Manifestations in a Pediatric Localized Scleroderma Cohort

Kaveh Ardalan, Christina Kelsey and Kathryn S. Torok, Pediatric Rheumatology, Children's Hospital of Pittsburgh of UPMC, Pittsburgh, PA

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Background/Purpose: Localized scleroderma (LS) is an autoimmune condition whose hallmarks are progressive skin fibrosis and atrophy. However, LS is unique among skin diseases for its wide range of reported extracutaneous manifestations (ECMs), including joint contractures, limb-length discrepancies, hemifacial atrophy, uveitis, neurologic sequelae, reflux, and dysphagia. Prior studies reported ECMs in 15-22% of LS patients, but were limited by retrospective, cross-sectional designs. This study aims to describe a standardized, comprehensive list of ECMs, captured prospectively, in a large pediatric LS cohort.

Methods: We extracted demographic and clinical data from the National Registry for Childhood Onset Scleroderma (NRCOS) database as part of an ongoing study on quality of life in LS. Patients included were between 4-16 years old, enrolled in NRCOS from 2002-2013, and had at least one completed Children's Dermatology Life Quality Index (i.e. CDLQI, a dermatologic quality of life measure). Patients in NRCOS were assessed for a comprehensive, standardized list of ECMs, prospectively at all clinic visits.

Data was examined to determine if patients had ECMs attributable to LS (per physician judgment), the type of ECM and organ/system involved, the total number of ECMs ever experienced by patients (throughout follow-up in clinic), and proportion of patients with ECMs by organ system.

Results: Eighty subjects were included in analysis. The majority were female (73%) and Caucasian (92%). At initial visit, subjects were a median 10.4 years old (IQR = 8.0-13.2 years old). LS subtypes were representative of pediatric onset disease (e.g. 33.8% linear limb/trunk, 17.5% linear head/face, 13.8% generalized morphea, 15% circumscribed morphea, 20% mixed subtype). Subjects had a median of 29.5 months of follow-up (IQR: 14.0 to 50.3 months).

Sixty-six percent (n=53) of patients experienced at least one ECM over a median follow-up period of 29.5 months per patient. The mean number of ECMs experienced by patients was 2 (median 1.5, IQR = 0-3). Forty-nine percent of patients had at least one musculoskeletal ECM (n=39), 23% orofacial (n=18; all also having hemifacial atrophy), 19% neurologic (n=15), 8% ocular (n=6), 4% gastroenterologic (n=3), and 5% vascular (i.e. Raynaud's phenomenon; n=4). Table 1 shows specific ECMs by organ system.

Table 1: Prevalence of Extracutaneous Manifestations by Organ System

	n	%
Musculoskeletal		
Arthralgia	27	39
Joint Contracture	21	26
Limb Circumference Discrepancy	18	23
Limb Length Discrepancy	6	8
Myalgia	5	6
Arthritis	4	5
Gait Abnormality	4	5
Myositis	2	3
Muscle Weakness	2	3
Cramping	1	1
Orofacial		
Hemifacial Atrophy	18	23
Dental Problems (e.g. malocclusion, abnormal eruption, gum recession)	10	13
Tongue Atrophy	3	4
TMJ	1	1
Tongue Spasm	1	1
Ocular		
Dry Eye	4	5
Episcleritis/Scleritis	2	3
Pseudopapilledema with Optic Nerve Thickening	1	1
Gastroenterologic		
Dysphagia or Esophageal Dysmotility	3	4
Constipation	1	1
Abdominal Pain	1	1
Neurological		
Headache	12	15
Peripheral Neuropathy	3	4
MRI Brain Abnormalities	3	4
Bell's Palsy	1	1
Ataxia	1	1
Dysarthria	1	1
Cognitive Dysfunction	1	1
Intention Tremor	1	1
Vascular		
Raynaud's Phenomenon	4	5
Other		
Dry Mouth	2	3
Fatigue	2	3
Nephritis	1	1
Pressure Sores Due to Contracture	1	1

Erythema Nodosum	1	1

Conclusion: The present study suggests that rates of ECMs in pediatric LS patients may be significantly higher than previously reported. Musculoskeletal ECMs were most prevalent, followed by orofacial, neurologic and ophthalmologic ECMs, with lower but still notable rates of gastroenterologic ECMs and Raynaud's phenomenon. These findings suggest that LS should not be primarily construed as a skin disease, but rather a systemic illness with potentially wide ranging and serious sequelae unfolding over many years.

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Abstract Number: 417

Gender Differences in Pediatric Localized Scleroderma: Clinical and Patient-Reported Outcomes

Kaveh Ardalan[1], Nicole Hershey[1], Jonathan Yabes[2], Eveline Wu[3], Suzanne C. Li[4], Robert C. Fuhlbrigge[5], C. Egla Rabinovich[6], Kathryn S. Torok[1] and The CARRA Registry Investigators, [1]Pediatric Rheumatology, Children's Hospital of Pittsburgh of UPMC, Pittsburgh, PA, [2]Department of Medicine, University of Pittsburgh, Pittsburgh, PA, [3]Pediatrics, University of North Carolina - Chapel Hill, Chapel Hill, NC, [4]Pediatrics, Joseph M Sanzari Children's Hospital, Hackensack University Medical Center, Hackensack, NJ, [5]Program in Rheumatology, Division of Immunology, Boston Children's Hospital, Boston, MA, [6]Pediatric Rheumatology, Duke University Medical Center, Durham, NC
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Background/Purpose: Localized scleroderma (LS) is an autoimmune disease of the skin and underlying tissue that leads to progressive fibrosis and disability in growing children. Pediatric LS is known to affect females more frequently than males, but differences by gender are not well characterized. We examined the LS cohort enrolled in the Childhood Arthritis and Rheumatology Research Alliance (CARRA) registry for gender differences.

Methods: Descriptive statistics for demographic, clinical, and patient-reported data were performed. Statistical differences between genders were assessed using t-test or Wilcoxon rank sum test and Chi-square or Fisher exact test depending on the variable type and distribution.

Results: A total of 369 participants were included in the analysis. The majority of participants were white (n = 333; 90%) and female (n = 279; 76%). Median age at onset was 7.7 years old (IQR: 4.5-11.2), median age at first rheumatologist visit was 10.0 years old (IQR: 6.8-12.9), and median time to rheumatologist was 0.9 years (IQR: 0.4-2.4). The majority of the population had linear subtype of either trunk/limb or head (n = 195; 52%). A total of 53 (14%) patients were diagnosed with circumscribed subtype, 33 (9%) with generalized morphea, with other subtypes present in smaller proportions. Patients with mixed subtype comprised 21% of the cohort.

Females were older at disease onset than males (median: 8.3 years old vs. 6.3 years old, p = 0.01). Females also were

older at time of first rheumatologist visit than males (median: 10.4 years vs. 8.8 years, p = 0.01), but time from onset to first rheumatologist visit was not significantly different by gender. Males were more likely than females to have muscle atrophy (35% vs. 20%, p = 0.009) and abnormal CK levels (16% vs. 7%, p = 0.035). Males were also more likely to experience hemifacial atrophy than females, with this trend approaching significance (15% vs. 7.5%, p = 0.056). Median global well-being score for the overall group was 1 (IQR: 0-3) on a 0-10 scale with lower scores indicating better well-being. However, a higher proportion of females than males reported worse global well-being than the median (48.5% vs. 30.3%, p = 0.003). When pain scale was dichotomized (0 = no pain vs. > 0 = pain reported), a trend was noted towards a higher proportion of females reporting the presence of pain (44% vs. 33%, p = 0.091). No other gender differences for demographic, clinical, or patient-reported outcomes were demonstrated.

Conclusion: In this analysis of a large multicenter sample of LS patients, males more frequently showed evidence of muscle involvement and hemifacial atrophy despite comparable frequency of LS subtypes. Although these clinical differences suggest males might have more severe disease features, female patients reported worse overall well-being and more frequently reported pain. Further study is warranted to better characterize gender differences in LS clinical features and patient-reported outcomes and to examine underlying reasons for such differences.

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Relationship of Race, Ethnicity, and Outcomes in Pediatric Localized Scleroderma: Possible Differences in Disease Activity

Kaveh Ardalan[1], Nicole Hershey[1], Jonathan Yabes[2], Kathryn S. Torok[1] and The CARRA Registry Investigators, [1]Pediatric Rheumatology, Children's Hospital of Pittsburgh of UPMC, Pittsburgh, PA, [2]Department of Medicine, University of Pittsburgh, Pittsburgh, PA

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Background/Purpose: Pediatric localized scleroderma (LS) is an autoimmune skin and soft tissue disease that causes morbidity via progressive skin fibrosis and extracutaneous manifestations (ECMs), such as arthritis or uveitis. Studies in other pediatric rheumatic disease populations have shown racial/ethnic differences in outcomes, but such differences have not received significant attention in LS. We examined racial/ethnic differences in the LS cohort enrolled in the Childhood Arthritis and Rheumatology Research Alliance (CARRA) registry.

Methods: Participants with a sole diagnosis of LS (i.e. no other rheumatic diseases) and complete data for gender and race/ethnicity were included for analysis. Participants who were both white (race) and non-Hispanic (ethnicity) were included in the non-Hispanic white (NHW) group. All other participants (i.e. nonwhite race, multiracial, and/or Hispanic ethnicity) were in the racial/ethnic minority (REM) group.

Depending on the variable type and distribution, t-test or Wilcoxon rank sum test and Chi-square or Fisher exact test

were used to assess differences in outcomes and baseline visit variables between NHW and REM group.

Results: A total of 369 participants were included, with 301 (82%) in the NHW group and 68 (18%) in the REM group. Most participants were white (n = 333; 90%) and 42 (11%) were Hispanic. The majority of participants were female (n = 279; 76%). Median age at onset was 7.7 years old (IQR: 4.5-11.2) and at first rheumatologist visit was 10.0 years old (IQR: 6.8-12.9). The study sample was representative of the major LS subtypes, with linear trunk/limb subtype most common (n = 126; 34.1%). The REM group showed trends toward lower rates of linear trunk/limb subtype (23.5% vs. 36.5%; $p = 0.057$) and higher rates of linear face/scalp subtype (26.5% vs. 16.9%; $p = 0.099$). REM participants were significantly more likely to report under $50,000 in annual household income (45.8% vs. 28.2%; $p = 0.025$).

Participants in the REM group were significantly more likely to have active disease (i.e. PGA > 0 in 80% vs. 58%; $p = 0.002$). Median PGA was also significantly higher in the REM group than in the NHW group (2 [IQR: 1-3] vs. 1 [IQR: 0-3]; $p = 0.015$). No differences were noted for patient-reported outcomes (pain scale, global well-being scale, quality of life, Childhood Health Assessment Questionnaire). No differences were noted in other potential confounders of PGA, including: age at onset and first rheumatologist visit; time from onset to first rheumatology visit; lesion location; ECMs; laboratory tests (i.e. ANA, creatine kinase, aldolase); present/past systemic immunosuppressive treatment; or hemifacial atrophy.

Conclusion: REM group LS patients enrolled in this large, multicenter cohort were more likely than NHW to have active disease. Differences in rates of disease subtypes (linear trunk/limb vs. face/scalp) and socioeconomic status (e.g. annual household income) were also noted and their possible contribution to the relationship of race/ethnicity and disease activity warrants further investigation. Future studies should collect detailed sociodemographic data, examining both clinical and social determinants of outcomes in LS.

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Abstract Number: 419

Development and Preliminary Validation of a New Composite Disease Activity Measure for Juvenile Dermatomyositis

Alessandro Consolaro[1], Giulia Camilla Varnier[1], Cristina Ferrari[1], Jaime De Inocencio[2], Adele Civino[3], Marija Jelusic-Drazic[4], Elena Tsitsami[5], Jelena Vojinovic[6], Balahan Makay[7], Graciela Espada[8], Clara Malattia[1], Susan Maillard[9], Alberto Martini[1], Clarissa Pilkington[10], Angelo Ravelli[1,11] and Kiran Nistala[12], [1]Pediatria II, Istituto Giannina Gaslini, Genova, Italy, [2]Hospital 12 de Octubre, Madrid, Spain, [3]Ospedale Cardinale G. Panico, Tricase, Italy, [4]University Hospital Center, Zagreb, Croatia, [5]First Department of Pediatrics, Athens University Medical School, Athens, Greece, [6]Faculty of Medicine, University of Nis, Nis, Serbia, [7]Pediatric Rheumatology, Eylul University, Izmir, Turkey, [8]Rheumatology Section, Childrens Hosp Ricardo Gutierrez, Buenos Aires, Argentina, [9]Paediatric Rheumatology, Great Ormond Street Hospital NHS Foundation Trust for Children, London, United Kingdom, [10]Rheumatology, Great Ormond Street Hospital for Children NHS Trust, London, United Kingdom, [11]University of Genova, Genova, Italy, [12]Centre for Rheumatology, University College London, London, United Kingdom

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Background/Purpose: Evaluation of the level of disease activity is a fundamental component of the clinical assessment of children with JDM. The global tools that are currently available for the assessment of the overall disease activity in JDM are centered on physician's evaluation, neglecting parent's or child's perception. Furthermore, these instruments are lengthy and complex. There remains the need for a concise and easily administered tool that provides an absolute measure of disease activity for use in future trials in JDM. Aim of the study was to develop and test a new composite disease activity score for JDM, named the Juvenile Dermatomyositis Activity Index (JDMAI)

Methods: The JDMAI includes 4 measures: 1) physician global assessment of disease activity on a 0-10 VAS, 2) parent/patient global assessment of well-being on a 0-10 VAS, 3) muscle strength assessment, and 4) cutaneous disease activity. Validation analyses were conducted on 140 patients included in a multinational study and were based on evaluation of construct validity, responsiveness to change, and discriminant validity. Four versions of the JDMAI were tested, which differed items 3) and 4). Three versions included the hybrid MMT/CMAS (hMC), reversed and divided by 10, as measure of muscle strength (range 0-10), and the cutaneous domain of the DAS (range 0-9) (JDMAI-1), a cutaneous VAS (range 0-10) (JDMAI-2), or the skin involvement type and distribution items of the DAS (range 0-7) (JDMAI-3) as measures of skin activity. A fourth version of the score (JDMAI-4) included the 3 CMAS items of the hMC (head lift; sits up, floor rise) (range 0-20) for muscle strength and the skin involvement and distribution items of the DAS for skin activity.

Results:

Construct validity: Spearman's correlations of all JDMAI versions were: strong ($r > 0.7$) with total DAS (0.80 0.90), parents' disease activity VAS (0.73 to 0.80), and CHAQ (0.72 to 0.80); moderate (r 0.4-0.7) with CMAS (-0.63 to 0.65, -0.80 for JDMAI-4), pain VAS (0.55 to 0.60), fatigue VAS (0.62 to 0.70); poor ($r < 0.4$) with LDH (0.27 to 0.32), and ESR (0.35 to 0.38). Correlation of all JDMAI versions with the Myositis Damage Index and CPK was not significant.

Responsiveness to change between 2 consecutive visits : SRM ranged from 0.72 (JDMAI-1) to 0.78 (JDMAI-4).

Discriminant validity: all JDMAI versions discriminated between patients rated in remission, continued active disease, and flare by the physician ($p < 0.001$) and by the parent ($p < 0.001$), and between patients with high, moderate, or low disease activity according to the physician ($p < 0.001$).

Conclusion: All JDMAI versions showed good construct validity and responsiveness to change, and excellent discriminant validity. We have shown that the JDMAI is a valid instrument for the assessment of disease activity in JDM and is, therefore, potentially applicable in standard clinical care, observational studies, and clinical trials.

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Description of the Juvenile Localized Scleroderma Subgroup of the Childhood Arthritis and Rheumatology Research Alliance (CARRA) Registry

Eveline Y. Wu[1], Suzanne C. Li[2], Kathryn S. Torok[3], Yamini Virkud[4], Robert C. Fuhlbrigge[5], C. Egla Rabinovich[6] and CARRA Registry Investigators, [1]Pediatrics, University of North Carolina at Chapel Hill, Chapel Hill, NC, [2]Pediatrics, Hackensack University Medical Center, Hackensack, NJ, [3]Pediatric Rheumatology, Children's Hospital of Pittsburgh of UPMC, Pittsburgh, PA, [4]Pediatrics, Massachusetts General Hospital for Children, Boston, MA, [5]Pediatric Rheumatology, Boston Children's Hospital, Boston, MA, [6]Pediatric Rheumatology, Duke University Medical Center, Durham, NC

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Background/Purpose: Localized scleroderma (LS) is a chronic inflammatory and fibrosing skin disease. We present baseline data on the juvenile LS (jLS) cohort from the Childhood Arthritis and Rheumatology Research Alliance (CARRA) registry, a multicenter observational pediatric rheumatic disease registry.

Methods: Descriptive statistics were used for demographic, clinical and laboratory features. Data analysis included the two-sample t-test, chi-square test, Fisher's exact test, logistic regression, and analysis of variance as appropriate.

Results: Of 386 children in the database, 76% were female and 80% were Caucasian. Mean age at onset was 8.2 yr (± 4.2). Mean age at first pediatric rheumatology (PRH) evaluation was 9.6 yr (± 4.1), yet 18% had ≥ 2 yr delay from onset to first PRH visit. Linear scleroderma (LiS) was the most common subtype (54%), followed by circumscribed morphea (CM) (16%), generalized morphea (GM) (9%), eosinophilic fasciitis (1%), and pansclerotic morphea (1%). 19% of children had mixed subtype, and LiS-CM was the most frequent combination (61%). Among LiS patients with face-scalp localization (34%), neurologic and ocular diseases were reported in 11% and 4%, respectively.

ANA positivity was found in 48% tested and was not associated with disease subtype or age at onset. ANA positivity, however, was associated with features of non-cutaneous disease damage, specifically joint contracture ($p=0.04$), muscle atrophy ($p=0.01$), and extremity shortening ($p<0.01$). Other laboratory findings included elevated aldolase was associated with joint contracture ($p=0.01$), and elevated CK was associated with muscle atrophy ($p=0.04$) and extremity shortening ($p=0.02$).

Children with any functional limitation (baseline worst ever ACR functional class II, III, and IV) (30%) had earlier first PRH visit (mean 0.98 yr ± 1.52) compared to those without limitation (class I) (mean 1.6yr ± 2.2, $p=0.01$). Poorer function also correlated with presence of arthritis, muscle atrophy, joint contracture, and extremity shortening (all $p<0.001$). Medications were similar to the 259 subjects prior analyzed (CARRA 2014 abstract) with subcutaneous or oral methotrexate (97%) and pulse or long term daily corticosteroids (68%) being the most commonly used, followed by mycophenolate mofetil (16%). The only significant difference in treatment according to subtype was the use of topical therapy instead of systemic in superficial morphea.

Conclusion: In the CARRA registry, jLS occurred more frequently in females and Caucasians. LiS was the most common subtype. Almost 1/5 of children had a ≥ 2 yr delay from symptom onset to PRH referral. Children without limitations are referred later, highlighting the insidious onset and need for educating referring providers. There is significant morbidity, with 30% of children reporting functional limitations. Poorer function correlated with presence of arthritis, muscle atrophy, joint contracture, and limb shortening. An elevated CK or aldolase was associated with presence of muscle atrophy, joint contracture, and/or limb shortening, suggesting they may be possible predictors of muscle involvement.

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Abstract Number: 421

Clinical Analysis and Outcome of Interstitial Lung Disease with Juvenile Dermatomyositis

Satoshi Sato, Yoji Uejima, Eisuke Suganuma, Tadamasa Takano and Yutaka Kawano, Division of Infectious Diseases and Immunology, Saitama Children's Medical Center, Saitama, Japan

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Background/Purpose: Juvenile dermatomyositis (JDM) is the most common idiopathic inflammatory myositis in children. It is a heterogeneous disease and clinical manifestations range from a relatively mild disease, to that causing significant morbidity and mortality. Especially, JDM that associated interstitial lung disease (ILD) may vary from asymptomatic to severe, rapidly leading causes of fatal outcome. The aim of this study is to determine the clinical and laboratory features of JDM complicated with ILD.

Methods: During March 1984 and May 2015, we retrospectively reviewed the clinical and laboratory features of twenty nine patients who were diagnosed as definite and probable JDM.

Results: Eight cases (27.6%) were complicated with ILD. The mean age was 6.3 years (2-13 years), and 75% of the patients were female. Cutaneous manifestations including Gottron's rash in 6, malar rash in 3, heliotrope rash in 1, skin ulcers in 2 each. The common systemic manifestations were myalgias in 5, arthralgia in 7, fever 6. Five cases had proximal muscle weakness. Anti-Jo-1 antibodies was positive in 2, anti-MDA-5 in 2. The testing for serum KL-6 was elevated in all cases. Respiratory symptoms were initially noticed in three cases. These two of three cases that were found to contain anti-MDA5 antibodies had rapid-progressive ILD (RPILD). One patient with anti-Jo-1 antibodies had ILD and polyarthritis was diagnosed as antisynthetase syndrome. All 8 patients were treated with glucocorticoids; 4 required pulse steroids therapy, 6 required immunosuppressive agents (methotrexate, Cyclosporin A, intravenous cyclophosphamide, mycophenolate mofetil (MMF),

intravenous immunoglobulin, Adalimumab. 3 patients with RPILD died of respiratory failure. Five (62.5%) patients showed no featured of myositis after a follow up of 3 years to 12 years. 5 patients had a normal CK levels.

Conclusion:

ILD is one of the most serious complications with JDM, especially positive for anti-MDA5 antibodies.

Table

	Case1	Case2	Case3	Case4	Case5	Case6	Case7	Case8
Sex	Female	Male	Female	Female	Female	Female	Female	Male
Age at onset of JDM (yr)	3	8	10	5	2	2	13	7
CK(IU/l)	916	148	1374	32	90	90	257	194
Aldolase (IU/l)	50.4	18.1	82.6	9.9	16.4	15.7	17.6	16.1
Antinuclear antibody	1:2560	negative	1:1280	1:2560	1:40	1:40	negative	1:80
Other Ab	dsDNA	Jo-1, RF	non	Jo-1	MDA5, RF	MDA5, RF	TPO	non
KL-6	1720	454	975	686	1290	904	376	2950
Treatment	PSL, CyA, MMF	PSL, CyA, MMF, anti-TNF	PSL	mPSL, PSL,CyA, MMF	mPSL, PSL,CyA IVCY, IVIG	mPSL, PSL,CyA IVCY,	PSL,CyA MTX	mPSL, PSL

Disclosure: **S. Sato**, None; **Y. Uejima**, None; **E. Suganuma**, None; **T. Takano**, None; **Y. Kawano**, None.

Abstract Number: 422

Mood Disorder Is Highly Prevalent in a Multi-Ethnic Urban Pediatric Lupus Cohort

Tamar Rubinstein[1,2], Dawn Wahezi[1,2], Jay Mehta[3,4], Norman Ilowite[3,5], Debbie Rybak[6], Jordan Brodsky[6], Nicole Jordan[6], Ruth Stein[5,7] and Chaim Putterman[6], [1]Pediatric Rheumatology, Albert Einstein College of Medicine, Bronx, NY, [2]Pediatric Rheumatology, Children's Hospital at Montefiore, Bronx, NY, [3]Division of Pediatric Rheumatology, Children's Hospital at Montefiore, Bronx, NY, [4]Division of Pediatric Rheumatology, Albert Einstein College of Medicine, Bronx, NY, [5]Pediatrics, Albert Einstein College of Medicine, Bronx, NY, [6]Division of Rheumatology, Albert Einstein College of Medicine, Bronx, NY, [7]Pediatrics, Children's Hospital at Montefiore, Bronx, NY
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Background/Purpose: While mood disorder, most commonly manifesting as depression and anxiety symptoms, is often reported in pediatric lupus patients, prevalence rates vary widely. Many published studies did not use validated tools to systematically screen cohorts. Furthermore, although mood disorders occur more frequently in urban, minority, low-income individuals, little is known about the prevalence of mood disorder in pediatric SLE patients from these populations.

Methods: We screened patients for mood disorder who were between the ages of 10-21 and enrolled in the Einstein

Lupus Cohort. Patients met the ACR 1997 revised SLE criteria or SLICC 2012 SLE criteria, and were recruited from pediatric rheumatology clinics in Bronx, NY. To screen for mood disorder we used the Patient Health Qustionaire-9 (PHQ-9) and the Generalized Anxiety Disorder 7-item scale (GAD-7), validated screening tools for depressive symptoms and anxiety symptoms, respectively, in patients ≥10 years of age.

Results: Forty-two patients were screened over a 9 month period with follow up screens on 24 patients (57%) at subsequent visits. The cohort was 83% female, 52% Hispanic, and 40% black. The median age of patients at their baseline screens was 18.4 (IQR 15.3, 19.7). Medicaid-covered patients comprised 79% of the cohort. The median SLEDAI score at baseline was 4 (IQR 2, 8) and 17% of patients had a previous history of neuropsychiatric SLE (NPSLE). The median baseline PHQ-9 score was 5 (IQR 3, 8) and the median baseline GAD-7 score was 3 (IQR 1, 7). Twenty-one percent of patients screened positive for depression at baseline, including 7% who had suicidal ideation or thoughts of self-harm, while 19% screened positive for anxiety. The most commonly endorsed depressive symptoms on baseline and follow-up screens were fatigue (79% of screens), difficulty sleeping (69%), anhedonia (63%), and changes in appetite (55%). The most commonly endorsed anxiety symptoms were irritability (70%) and excessive worrying (67%). Neither PHQ-9 nor GAD-7 scores correlated with SLEDAI or age of patient. From baseline to first follow-up visit, 54% of patients had worsening PHQ-9 scores; whereas 65% of patients had improved or stable GAD-7 scores from baseline to the next screens (Table 1). No significant differences were seen between scores based on sex, race/ethnicity, or history of NPSLE.

Conclusion: Depressive and anxiety symptoms are prevalent in a pediatric SLE cohort with high disease activity from an urban, primarily minority, and low-income cohort. Suicidal ideation and thoughts of self-harm were also not uncommon. Mood disorder symptoms did not correlate with disease activity, and were not associated with a NPSLE history. The high prevalence of mood disorder in this pediatric SLE cohort, if corroborated in other cohorts, may indicate that systematic screening for mood disorder in pediatric lupus patients should become standard of care.

Table 1: Mood disorder screening in pediatric patients of the Einstein Lupus Cohort	
Patient characteristics	**N (patients) = 42**
Sex	
Female	35 (83%)
Male	7 (17%)
Race/ethnicity	
Black	16 (40%)
Hispanic	22 (52%)
Other	4 (10%)
Age (median, IQR)	18.4 (15.3, 19.7)
Medicaid	33 (79%)
SLEDAI (baseline, median, IQR)	4 (2, 10)
PHQ-9 (baseline, median, IQR)	5 (3, 8)
Positive screens (PHQ-9 ≥10 or suicidal ideation)	9 (21%)
PHQ-9 ≥10	8 (19%)
Suicidal ideation	3 (7%)
GAD-7 (baseline, median, IQR)	3 (0, 7)
Positive screens (GAD-7 ≥10)	7/37 (19%)
Patients with follow-up screens	24 (57%)
Patients with 2 visits	15 (36%)
Patients with 3 visits	3 (7%)
Patients with 4 visits	3 (7%)
	N (screens) = 84
PHQ-9 (median, IQR)	5 (2, 8)
Positive screens (PHQ-9 ≥10 or suicidal ideation)	20/84 (24%)
PHQ-9 ≥10	16/84 (19%)
Suicidal ideation	9/84 (11%)
Increase from baseline to first follow-up	13/24 (54%)
GAD-7 (median, IQR)	3 (1, 7)
Positive screens (GAD-7 ≥10)	14/79 (18%)
Increase from baseline to first follow-up	7/20 (35%)

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Abstract Number: 423

Institutional and Regional Variation in Childhood SLE 30-Day Hospital Readmission Rates: A Comparative Effectiveness Research Using the Pediatric Health Information System Database

Breanna Beltz[1], Mohammad Shah[2], Mary Toth[3] and **Moussa El-Hallak**[4], [1]Hiram College, Akron, OH, [2]Patient Safety and Quality Services, Akron Children's Hospital, Akron, OH, [3]Rheumatology, Akron Children's Hospital, Akron, OH, [4]Dept of Pediatric Rheumatology, Akron Children's Hospital, Akron, OH

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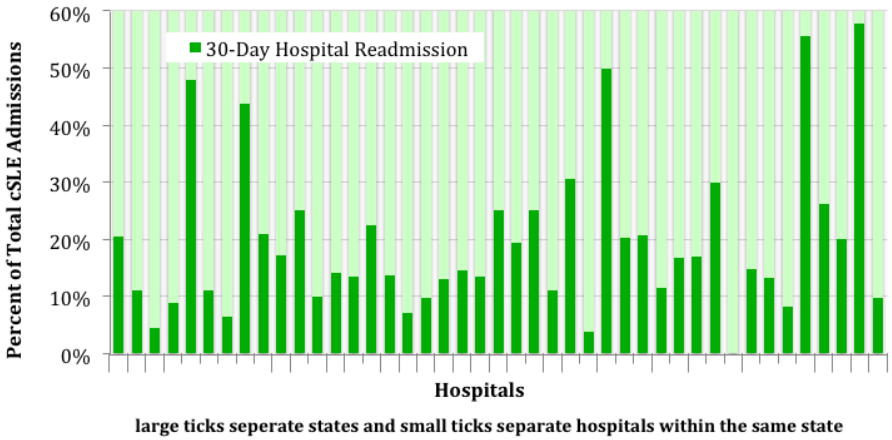
Session Time: 9:00AM-11:00AM

Background/Purpose: Early hospital readmission is emerging as an indicator of care quality. The reported 30-day hospital readmission (30-DHR) rate for pediatric patients is 6.5%. However, Childhood SLE (cSLE) has a wide spectrum of health care complexity and disease course. There is limited data describing cSLE rehospitalizations patterns and its impact on the health care system. In this study we sought to describe patient- and hospital-level characteristics for cSLE 30-DHR.

Methods: The Pediatric Health Information System (PHIS) database was used to query cSLE for 5 years (2009-2013). Data collection included patient characteristics, hospital characteristics (also collected from American Hospital Association), length of stay (LOS), day of discharge, payer type and hospital charges. Primary outcome measures analyzed was 30-DHR after prior discharge. Multilevel models were used to accommodate dependence between observations. Patient characteristics (such as gender & race) were nested in patients and hospital characteristics (such as total beds & total 30-DHR) were nested in hospitals. Independent observations were analyzed within the encounter.

Results: There were 1,755 unique cSLE patients and 3,751 admissions with total hospital charges of $191M USD. Among that sample, there were more female (81%) than male (19%) patients. The overall cSLE 30-DHR rate was 28 per 100 admissions (ranged from 0-58); 79 (5%), 35 (2%), and 95 (5%) patients experienced 2, 3, and ≥4 30-DHR respectively. Thirty-day all-cause hospital readmissions for cSLE patients in PHIS hospitals cost the health care system $7M USD annually. There was a 3-fold variation in hospital service costs (between upper and lower quartile) with median admission's adjusted hospital charges of $13,904**. Patients with 30-DHR had lower median LOS (2 vs 4 days) and were more likely discharge on weekend (Sat & Sun)**. Weekend discharges also seemed to have lower LOS of 2 days**. Patients with more diagnosis count and chronic conditions during index admission were less likely to be readmitted**. Total 30-DHR per hospital was associated with total admissions but not hospital size (represented as total beds) or service area (represented as outpatient visits). There was institutional and regional variation in 30-DHR**. Age and race/ethnicity were not statistically significant for 30-DHR. **($P < 0.01$).

Conclusion: 30-DHR is high among admitted cSLE patients. Most hospitalizations in cSLE are for the treatment of disease manifestations, infections or associated medical co-morbidities. There is a variation between hospitals that may be due to patient population or practice differences. Our study highlights the need for additional research to understand these differences and to identify the most cost-effective strategies for managing cSLE across the continuum of care.



Disclosure: B. Beltz, None; **M. Shah**, None; **M. Toth**, None; **M. El-Hallak**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/institutional-and-regional-variation-

in-childhood-sle-30-day-hospital-readmission-rates-a-comparative-effectiveness-research-using-the-pediatric-health-information-system-database

Abstract Number: 424

Magnetic Resonance and Echocardiographic Strain Rate Imaging for the Early Detection of Cardiac Involvement in Juvenile Systemic Sclerosis

Francesco Zulian[1], Marta Balzarin[1] and Elena Reffo, Biagio Castaldi, Giorgia Martini, Alessandra Meneghel, Ornella Milanesi, [1]Department of Pediatrics, University of Padua, Padua, Italy

First publication: September 29, 2015

SESSION INFORMATION

Session Date: Sunday, November 8, 2015

Session Title: Pediatric Rheumatology – Clinical and Therapeutic Aspects Poster I: Lupus, Scleroderma, JDMS

Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose: Cardiac involvement is one of the worst prognostic factors in JSSc. The diagnosis is usually based on clinical symptoms, EKG and conventional echocardiography, but histological studies proved that the prevalence of cardiac involvement is higher than expected. Some studies on adults demonstrated that cardiac Magnetic Resonance Imaging and Strain Rate imaging (SR) identify early cardiac involvement in SSc but little is known about their use in juvenile SSc. In this study, we investigated whether subclinical cardiac involvement can be detected by using cardiac MRI and echocardiographic SR imaging in a cohort of JSSc patients.

Methods: Consecutive patients with JSSc, according to the PRES/EULAR/ACR criteria (1), evaluated from January to May 2015, were enrolled in this observational cross sectional study. Demographic and clinical features were collected from the clinical reports. Disease severity was evaluated by the J4S score (2). Each patient underwent EKG, conventional echocardiography, speckle tracking SR and cardiac contrast enhanced MRI. Normal standard for age and body surface area-matched values validated for pediatric age were used as reference (3,4).

Results: Twelve patients, 8 females, mean age 12.8 years, mean disease duration 5.0 years entered the study. Ten had a diffuse form of disease, 2 limited. Three patients (25%) had previously had symptomatic cardiac involvement: 1 cardiac arrest during sustained ventricular tachycardia, 1 not sustained ventricular tachycardia, 1 pericarditis. Conventional echocardiography showed normal left ventricular ejection fraction and diastolic function in all patients, except for the one with previous episode of ventricular fibrillation. Also EKG was abnormal only in this patient. SR imaging (mean -17,9%) was abnormal in 4 patients (33,3%), all with the diffuse SSc; two of them never had cardiac symptoms and their EKG and echocardiography were normal. Cardiac MRI was altered in 2 (16,6%) patients: fibrosis and dyskynesias were found in a symptomatic patient with abnormal EKG, conventional echocardiography and SR; another asymptomatic patient showed dilated ventricles but no fibrosis. No correlation with J4S score was found.

Conclusion: Cardiac MRI and SR imaging allowed to detect early cardiac abnormalities in 3 patients (25%) with neither cardiac symptoms nor abnormal EKG and echocardiography, so they could be considered as valid, non invasive tools for the assessment of early cardiac involvement in JSsc. Prospective multicentric studies are needed to confirm these data.

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Disclosure: F. Zulian, None; **M. Balzarin**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/magnetic-resonance-and-echocardiographic-strain-rate-imaging-for-the-early-detection-of-cardiac-involvement-in-juvenile-systemic-sclerosis

Abstract Number: 425

Impact of in Utero Hydroxychloroquine Exposure on Age of Onset of Cutaneous Neonatal Lupus

Julie Barsalou[1], Nathalie Costedoat-Chalumeau[2], Cesar Fors-Nieves[3], Ummara Shah[4], Patrick Brown[5], Carl Laskin[6], Nathalie Morel[2], Kateri Levesque[7], Jill P. Buyon[8], Earl Silverman[9] and Peter M. Izmirly[10], [1]Pediatric Rheumatology, CHU Sainte-Justine, Université de Montréal, Montréal, QC, Canada, [2]Internal Medicine Department, Cochin Hospital, "René-Descartes Paris V" University, Paris, France, [3]Division of Rheumatology, NYU School of Medicine, New York, NY, [4]Medicine, Strong Memorial Hospital, University of Rochester, Rochester, NY, [5]University of Toronto, Toronto, ON, Canada, [6]Medicine, Rheumatology and Obstetrics and Gynecology, University of Toronto and LifeQuest Centre for Reproductive Medicine, Toronto, ON, Canada, [7]Internal Medicine, CHU Ste-Justine, Montréal, QC, Canada, [8]NYU School of Medicine, New York, NY, [9]Division of Rheumatology, Hospital for Sick Children and University of Toronto, Toronto, ON, Canada, [10]Rheumatology, NYU School of Medicine, New York, NY
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SESSION INFORMATION
Session Date: Sunday, November 8, 2015
Session Title: Pediatric Rheumatology – Clinical and Therapeutic Aspects Poster I: Lupus, Scleroderma, JDMS
Session Type: ACR Poster Session A
Session Time: 9:00AM-11:00AM

Background/Purpose: Biopsy specimens of cutaneous neonatal lupus (cNL) lesions usually show interface dermatitis. Hydroxychloroquine (HCQ) is an effective treatment for interface dermatitis seen in connective tissue diseases. It may also be of benefit for cNL. Due to the transplacental passage of HCQ, fetuses of treated mothers are exposed to HCQ. Neonates are not continued on HCQ after delivery, therefore HCQ levels are expected to decline after birth. The aim of this study was to asses if in utero exposure to HCQ delayed the onset of cNL.

Methods: A multicenter retrospective cohort was assembled that included all cases of cNL found in 3 data sources. Inclusion criteria were: infant born to a woman positive for anti-Ro ± anti-La antibodies, infant diagnosed with cNL, known age of onset of cNL and documentation of maternal medications during pregnancy. Kaplan-Meier survival analysis was used to assess if HCQ delayed the onset of cNL. Proportions of infants developing cNL within distinct time frames were compared between those HCQ exposed and non exposed.

Results: A total of 327 cases of cNL were included: N=190 from the Research Registry for Neonatal Lupus, N=107 from the SickKids Neonatal Lupus cohort and N=30 from the French Registry of Neonatal Lupus. Twenty-eight (8.6%) infants were exposed to HCQ. Infants exposed to HCQ had overall similar baseline characteristics to those not exposed (Table 1). Survival analysis showed no statistically significant difference in the median number of weeks to cNL onset: HCQ exposed 6.0 (95% CI: 5.7-6.3) vs non exposed 4.4 (95% CI: 3.8-5.0) weeks; p=0.452 (Figure 1). Although no statistically significant difference was seen, the survival curves showed a delayed onset of rash during the first postnatal month in infants exposed to HCQ in utero. The frequency of infants developing cNL within specific time

frames did not significantly segregate by HCQ exposure (Table 2).

Conclusion: Although in utero HCQ exposure did not significantly delay the time of onset of cNL, survival curves suggest later onset of cNL in those exposed to HCQ perhaps due to protection conferred by HCQ when neonatal HCQ blood levels still remain within a detectable range.

Table 1. Baseline characteristics of the 327 patients

	Patients (N)	Exposed to HCQ (N=28)	Non exposed to HCQ (N=299)	p value
Maternal characteristics				
Diagnosis, N (%)	326			<0.001
Asymptomatic/Undifferentiated autoimmune syndrome		3 (10.7)	151 (50.5)	
SLE		13 (46.4)	65 (21.8)	
Cutaneous lupus		2 (7.2)	3 (1.0)	
Sjogren's syndrome		4 (14.3)	47 (15.8)	
Sjogren's syndrome and SLE		6 (21.4)	25 (8.4)	
Sjogren's syndrome and RA		0	1 (0.4)	
Dermatomyositis		0	1 (0.4)	
Overlap connective tissue disease		0	1 (0.4)	
RA or juvenile idiopathic arthritis		0	4 (1.3)	
Antibody status, N (%)				
Anti-Ro positive	325	28 (100)	297 (100)	-
Anti-La positive	317	23 (85.2)	222 (76.6)	0.306
Medication intake, N (%)				
Fluorinated steroids	326	3 (10.7)	38 (12.8)	0.999
Non-fluorinated steroids	327	12 (42.9)	32 (10.7)	<0.001
Azathioprine	327	1 (3.6)	2 (0.7)	0.236
IVIG	326	0	6 (2.0)	0.999
Children characteristics				
Sex, female:male, N	326	15:13	172:126	0.671
Age of onset of cNL, weeks (median (IQR))	327	6.0 (4.0-8.0)	4.4 (2.0-8.9)	0.435

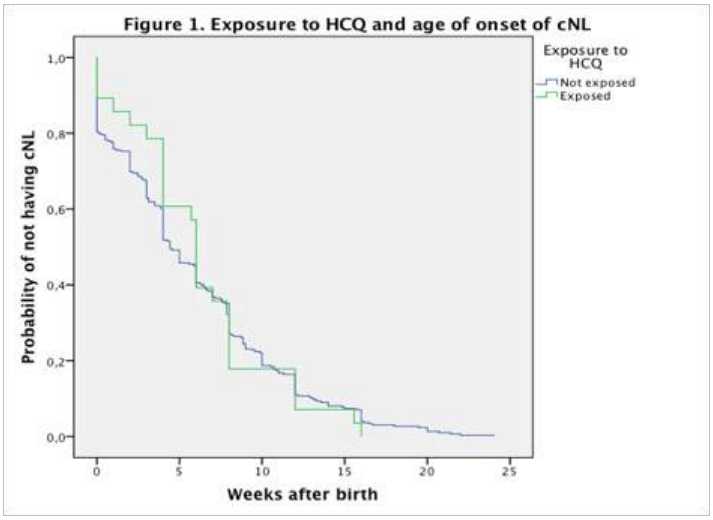

Table 2. Proportion of infants developing cNL within specific time frames as per exposure status to HCQ				
Cutoffs of age of onset of cNL		Exposed to HCQ N (%)	Non exposed to HCQ N (%)	p value
A.	Rash present at birth	3 (10.7)	59 (19.7)	0.244
B.	Rash onset <2 weeks	5 (17.9)	90 (30.1)	0.172
C.	Rash onset <4 weeks	11 (39.3)	144 (48.2)	0.368

Disclosure: J. Barsalou, None; **N. Costedoat-Chalumeau**, None; **C. Fors-Nieves**, None; **U. Shah**, None; **P. Brown**, None; **C. Laskin**, None; **N. Morel**, None; **K. Levesque**, None; **J. P. Buyon**, None; **E. Silverman**, None; **P. M. Izmirly**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/impact-of-in-utero-hydroxychloroquine-exposure-on-age-of-onset-of-cutaneous-neonatal-lupus

Abstract Number: 426

The Risk of Hospitalized Infection Following Initiation of Biologic Agents Versus Methotrexate in the Treatment of Juvenile Idiopathic Arthritis

Timothy Beukelman[1], Fenglong Xie[2], John Baddley[3], Lang Chen[4], Melissa L. Mannion[5], Kenneth G. Saag[4], Jie Zhang[6] and Jeffrey R. Curtis[4], [1]Rheumatology, University of Alabama at Birmingham, Birmingham, AL, [2]Rheumatology & Immunology, University of Alabama at Birmingham, Birmingham, AL, [3]Medicine, University of Alabama at Birmingham, Birmingham, AL, [4]University of Alabama at Birmingham, Birmingham, AL, [5]Pediatrics, University of Alabama at Birmingham, Birmingham, AL, [6]Epidemilogy, University of Alabama at Birmingham, Birmingham, AL
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SESSION INFORMATION
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Session Title: Pediatric Rheumatology – Clinical and Therapeutic Aspects Poster I: Lupus, Scleroderma, JDMS
Session Type: ACR Poster Session A
Session Time: 9:00AM-11:00AM

Background/Purpose:

Biologic agents are highly effective for the treatment of juvenile idiopathic arthritis (JIA) but have the potential risk of increased serious infections. Using observational administrative claims data, we compared the rate of hospitalized infections among patients with JIA newly starting biologic agents versus newly starting methotrexate (MTX) without concurrent biologic use.

Methods:

We used national U.S. Medicaid analytic eXtract (MAX) administrative claims files from 2000 – 2010 inclusive. New users of the 5 available tumor necrosis factor inhibitors (TNFi), the interleukin 1 inhibitor anakinra (ANA), and MTX (without concurrent biologic use) were defined by a 6 month clean period of non-use ("baseline"). Patients with a physician diagnosis code for JIA before age 16 years and prior to new use were included. Follow-up began on the day of the first prescription fill and medication exposures were extended for 90 days beyond the days supplied by each fill. The outcome was hospitalization with any infection as the primary discharge diagnosis. Cox proportional hazards models were used to generate hazard ratios adjusted (aHR) for age, sex, race, comorbidities, baseline mean daily oral systemic glucocorticoid (GC) dose, and infections during baseline. Among biologic users, concurrent MTX use during follow-up was treated as a time-varying covariate. Sensitivity analyses included shortening the medication exposure risk window and including all hospital discharge diagnoses in the outcome assessment.

Because nearly all patients who were new users of ANA were expected to have systemic JIA (sJIA) and there is no reliable physician diagnosis code to identify sJIA patients in the MTX comparator cohort, we attempted to identify patients with a high likelihood of having sJIA based upon any physician diagnoses for macrophage activation syndrome or any use of relatively sJIA-specific medications (cyclosporine or tacrolimus in the absence of uveitis, anakinra, canakinumab, rilonacept, thalidomide, lenalidomide) at any time.

Results:

We identified 3075 new MTX users (204 with sJIA), 3471 new TNFi users (60% etanercept, 28% adalimumab, 11% infliximab), and 247 new ANA users. Crude infection rates per 100 person-years were: MTX 1.46 (39/2668); TNFi 1.70 (66/3887); ANA 8.41 (19/226); MTX with sJIA 2.64 (3/114). The aHR for TNFi vs MTX was 1.11 [0.69-1.79]. Among TNFi users, concurrent MTX use suggested an increased risk of infection that was not statistically significant (aHR 1.44 [0.89-2.34]). The aHR for ANA vs MTX was 2.92 [1.77-7.71] and was 2.91 [0.62-13.5] vs MTX users with sJIA. Among all patients in the study, baseline high dose oral GC (>10mg/day) was associated with increased infection risk compared to no GC use (aHR 1.86 [1.16-2.97]). The results were robust to sensitivity analyses.

Conclusion:

There was no significant increased risk of hospitalized infection among new TNFi users compared to new MTX users. New ANA users had an increased risk of infection compared to MTX, even when restricted to MTX users who likely had sJIA. High dose oral GC was associated with a significantly increased risk of infection among all children with JIA. Further investigation about the risk of infection in children with sJIA is needed.

Disclosure: T. Beukelman, UCB, 5,Genentech/Roche, 5,Novartis Pharmaceutical Corporation, 5; **F. Xie**, None; **J. Baddley**, Pfizer, Astellas, Merck, 5,BMS, 2; **L. Chen**, None; **M. L. Mannion**, None; **K. G. Saag**, Amgen, Ardea/AstraZenaca, Crealta, Lilly, Merck, Takeda, 2,Abott, Amgen, Ardea/AstraZeneca, BMS, Crealta,Lilly, Merck, Pfizer, Roche/Genetech, 5; **J. Zhang**, None; **J. R. Curtis**, Roche/Genentech, UCB, Janssen, CORRONA, Amgen, Pfizer, BMS, Crescendo, AbbVie, 2,Roche/Genentech, UCB, Janssen, CORRONA, Amgen, Pfizer, BMS, Crescendo, AbbVie, 5.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/the-risk-of-hospitalized-infection-following-initiation-of-biologic-agents-versus-methotrexate-in-the-treatment-of-juvenile-idiopathic-arthritis

Abstract Number: 427

The Impact of Biologic Agent Initiation after 1 Versus 2 Prior Csdmards in Patients with Rheumatoid Arthritis

Dimitrios A. Pappas[1,2], Jenny Griffith[3], Chitra Karki[2], Mei Liu[4], Joel M. Kremer[5], Arijit Ganguli[3] and Jeffrey D. Greenberg[2,6], [1]Columbia University, New York, NY, [2]Corrona, LLC, Southborough, MA, [3]AbbVie Inc., North Chicago, IL, [4]352 Turnpike Rd, Corrona, LLC, Southborough, MA, [5]Albany Medical College and The Center for Rheumatology, Albany, NY, [6]NYU School of Medicine, New York, NY
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SESSION INFORMATION
Session Date: Sunday, November 8, 2015
Session Title: Rheumatoid Arthritis - Clinical Aspects Poster I
Session Type: ACR Poster Session A
Session Time: 9:00AM-11:00AM

Background/Purpose: Patients with Rheumatoid Arthritis (RA) who don't respond to conventional synthetic disease modifying anti-rheumatic drugs (csDMARDs) should be treated with biologic agents(1). The objective of this analysis was to evaluate the impact of initiating a biologic agent early (after failure to 1 csDMARD) versus later (after failure to 2 csDMARDs).

Methods: RA patients starting their first biologic agent after enrollment in Corrona between May 2002 and July 2014 and with at least 1 year of follow-up in the registry were included in the analysis. Baseline characteristics of patients initiating a biologic agent after therapy with 1 vs 2 csDMARDs were compared. The second csDMARD could be added to the first csDMARD or substitute therapy with the first csDMARD. The two cohorts were matched using propensity score (PS). Disease activity and functionality outcomes were assessed at 1 year post biologic initiation among the matched groups. The rate of biologic drug changes in the first year after biologic initiation were evaluated among the matched groups. Time to initiation of biologic and time spent in moderate/high disease activity prior to biologic initiation were evaluated. Mixed logistics and mixed linear regression models were used to evaluate binary and continuous outcomes.

Results: A total of 1612 patients initiated their first biologic after therapy with 1 csDMARD (group 1) and 288 patients after therapy with 2 csDMARDs (group 2). Baseline characteristics at the time of the biologic initiation for group 1 (vs group 2) were: 75.4% females (vs 78.5%), age (mean ±SD) of 57.4±13.2 years (vs 57.5±12.3), Caucasian race 89.1% (vs 93.8%), disease duration 6.3± 8.4 (vs 6.9±7.3), baseline CDAI 19.9±14.0 (vs 19.4±13.2) seropositivity 81.8% (vs 78%). After PS matching 288 patients remained in each group. Similar improvements in disease activity occurred in both groups after 1 year of follow up: 53.4% in group 1 vs. 49.3% in group 2 achieved LDA (p=0.4), mean (SD) CDAI change was 8.4 (13.2) in group 1 vs 7.1 (13.5) in group 2 (p=0.2) and mean (SD) HAQ change was 0.08 (0.36) in group 1 vs 0.06 (0.41) in group 2 (p=0.5). Switching to an alternate biologic occurred in 7.6% and 15.3% of patients in group 1 and 2, respectively, while 14.2% and 15.3% discontinued biologic therapy at 1 year (p=0.01). The time since initiation of the first csDMARD to initiation of the first biologic was 13.3 ±15.9 months for biologic initiators in group 1 vs 20.7±19.7 in group 2 (p<0.01). Time spent in moderate or high disease prior to initiation of the biologic agent was 8.1±10.8 months in group 1 vs 13.7±14.9 months in group 2.

Conclusion: Earlier initiation of a biologic agent was associated with a shorter period of time spent in moderate/high RA disease activity and a higher likelihood of remaining on the same biologic at 1 year after initiation.

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Disclosure: D. A. Pappas, Corrona, LLC, 3,Novartis, 9; **J. Griffith**, AbbVie, Inc., 1,AbbVie, Inc., 3; **C. Karki**, Corrona, LLC, 3; **M. Liu**, Corrona, LLC, 3; **J. M. Kremer**, Corrona, LLC., 3,Corrona, LLC., 1,AbbVie, Amgen, BMS, Genentech, Lilly, Pfizer, 5; **A. Ganguli**, AbbVie, Inc, 1,AbbVie, Inc., 3; **J. D. Greenberg**, Corrona, LLC., 3,Corrona, LLC., 1,AstraZeneca, Celgene, Genentech, Janssen, Novartis, Pfizer, 5.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/the-impact-of-biologic-agent-initiation-after-1-versus-2-prior-csdmards-in-patients-with-rheumatoid-arthritis

Abstract Number: 428

Use of Rituximab Compared to Anti-TNF Agents As Second and Third Line Therapy in Patients with Rheumatoid Arthritis: 6-Year Follow-up Report from the Rhumadata® Clinical Database and Registry

Denis Choquette[1], Louis Bessette[2], Boulos Haraoui[1], Frédéric Massicotte[1], Jean-Pierre Pelletier[1], Jean-Pierre Raynauld[1], Marie-Anaïs Rémillard[3], Diane Sauvageau[1], Édith Villeneuve[1], Louis Coupal[1], Jacques Brown[4] and Angèle Turcotte[4], [1]Rheumatology, Institut de recherche en rhumatologie de Montréal (IRRM), Montréal, QC, Canada, [2]Centre d'Ostéoporose et de Rhumatologie de Québec (CORQ), Québec, QC, Canada, [3]Rhumatology, Institut de recherche en rhumatologie de Montréal (IRRM), Montréal, QC, Canada, [4]Rheumatology, Centre d'ostéoporose et de rhumatologie de Québec (CORQ), Québec, QC, Canada

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Session Title: Rheumatoid Arthritis - Clinical Aspects Poster I

Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose: The order of use of biologic agents after failing a TNF inhibitor is still a question for debate. Phase III trial data in TNF-IR patients show comparable efficacy results across biologic agents and limited head-to-head studies have been published. Prospective registries offer a unique opportunity to observe the effectiveness (combined evaluation of efficacy and safety profile over time) of these agents in a real world clinical setting where all patients with a specific diagnosis and treated in the center are included. We report here a sixth year follow-up analysis. Our aim is to evaluate if patients with rheumatoid arthritis (RA) treated with rituximab (RIT) after failing a first or a second anti-TNF agents (TNF-IR) have different six-year retention rate than patients similarly prescribed anti-TNF agents (pooled adalimumab, etanercept or infliximab) and compare the treatment strategies of using RIT as second or third biologic treatment .

Methods: Data from TNF-IR RA patients prescribed adalimumab (ADA), etanercept (ETA), infliximab (INF) or rituximab (RIT) as second or third biologic agents on or after January 1st2007 was extracted and subjects taking either ADA, ETA or INF were pooled to form the anti-TNF cohort. Baseline demographics included age, disease duration, HAQ-DI, fatigue and pain visual analog scale evaluations (VAS), TJC, SJC, DAS 28 ESR and SDAI. Six-year drug retention rates were estimated and compared using Kaplan-Meier survival estimates. Statistical analysis was performed using SAS version 9.3. RHUMADATA® is a clinical database and registry used in daily clinical practice at the IRRM and CORQ. All patients with RA are followed over time irrespective of their treatment.

Results: The data from 231 RA patients were extracted, 155 and 76 having respectively failed a first and a second anti-TNF agent. No clinically significant differences in baseline variables were observed between treatment groups in second and third intention. The 6 year retention rates of second line RIT and anti-TNF use were 80.1% and 19.1% respectively (Log-rank p< 0.0001). In patients having failed two anti-TNF, subsequent use of RIT and anti-TNF agents respectively demonstrated 6 year retention rates of 53.6% and 37.2% (Log-rank p=0.0473). Second versus third line use was numerically (80.1% vs 53.6%) and statistically superior (Log-rank p=0.0029).

Conclusion:

As second and third line agent, in TNF-IR RA patients, RIT demonstrates a better 6 year retention rate than anti-TNF agents. Second line use demonstrated a statistically better retention rate than third line use. This suggest that using rituximab as a second agent after failing a first anti-TNF agent is a better strategy than waiting to use it after two different anti-TNF failure.

Disclosure: D. Choquette, None; **L. Bessette**, None; **B. Haraoui**, None; **F. Massicotte**, None; **J. P. Pelletier**, None; **J. P. Raynauld**, None; **M. A. Rémillard**, None; **D. Sauvageau**, None; **Villeneuve**, None; **L. Coupal**, None; **J. Brown**, None; **A. Turcotte**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/use-of-rituximab-compared-to-anti-tnf-agents-as-second-and-third-line-therapy-in-patients-with-rheumatoid-arthritis-6-year-follow-up-report-from-the-rhumadata-clinical-database-and-registry

Abstract Number: 429

Treatment Preferences of Patients with Early Rheumatoid Arthritis: A Discrete-Choice Experiment

Glen S. Hazlewood[1,2], Claire Bombardier[3], George A. Tomlinson[4], Carter Thorne[5], VP Bykerk[6], Andrew Thompson[7], Diane Tin[8] and Deborah Marshall[9], [1]Medicine, University of Calgary, Calgary, AB, Canada, [2]Institute of Health, Policy, Management and Evaluation, University of Toronto, Toronto, ON, Canada, [3]Division of Rheumatology and Institute of Health Policy, Management, and Evaluation, University of Toronto, Toronto, ON, Canada, [4]Institute for Health Policy, Management and Evaluation, University of Toronto, Toronto, ON, Canada, [5]Southlake Regional Health Centre, Newmarket, ON, Canada, [6]Rheumatology, Hospital for Special Surgery, New York, NY, [7]Rheumatology, St Joseph's Hlth Ctr, London, ON, Canada, [8]The Arthritis Program, Southlake Regional Health Centre, Newmarket, ON, Canada, [9]University of Calgary, Calgary, AB, Canada

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SESSION INFORMATION

Session Date: Sunday, November 8, 2015

Session Title: Rheumatoid Arthritis - Clinical Aspects Poster I

Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose: Treatment choices in early rheumatoid arthritis need to balance benefits, risks, and other considerations such as dosing and monitoring. The objective of this study was to determine the preferences of patients with early rheumatoid arthritis (RA) for these competing issues.

Methods: We assessed patients' preferences using a discrete-choice experiment. Consecutive adult patients with early RA (<2 years since diagnosis) in 2 Canadian centres were presented 13 different sets of three treatment options described by 8 attributes (clinical trial outcomes, risks, monitoring and dosing regimens) and asked to choose one. We

estimated the value that patients placed on each attribute level using a main-effects multinomial logit model, and explored preference heterogeneity through latent-class analysis.

Results: 152 patients completed the survey (86% response rate): mean age 52, 63% female, disease duration 7.8 months. Fourteen (9%) were DMARD naïve, and 44% had changed DMARD treatment within 3 months. Treatment benefits (increasing the chance of a major symptom improvement (ACR50 response) and reducing the chance of serious joint damage) were most important. Of potential adverse events, a 'small risk of serious infections/possible increased risk of cancer' was the most important. Patients were willing to accept this risk for an increase of 15% in the chance of a major symptom improvement (Table 1). Patients had an aversion to intravenous therapy, but were relatively indifferent to other dosing regimens. Alcohol restriction and the need to have regular eye exams to screen for eye toxicity were unimportant. Through latent-class analysis, we identified two patient groups – 46% who were highly benefit-driven, and others who were more risk averse, particularly to the possible risk of cancer/infection (Table 1).

Conclusion: Patients with early RA were generally risk-tolerant and preferred oral and subcutaneous based treatments that provided the greatest chance of benefit, but clinicians need to be aware of important preference differences and tailor treatment approaches appropriately.

Table 1: Relative importance of undesirable treatment characteristics

Treatment characteristic	Absolute increase in probability of major symptom improvement (ACR50 response) required to accept characteristic		
	Overall analysis (all patients)	Latent class analysis	
		Benefit-driven subgroup (46% of patients)	Risk-averse subgroup (54% of patients)
Trial outcomes			
Chance of serious joint damage increased from 2% to 30%	31% (26 to 35)	27% (23 to 32)	47% (34 to 65)
Chance of stopping due to a side effect increased from 2% to 20%	9.5% (6.3 to 13)	6.8% (4.1 to 9.6)	18% (8.7 to 30)
Rare risks and monitoring			
Possible increased risk of cancer and small risk of serious infection	15% (13 to 18)	3.6% (2.1 to 5.2)	48% (38 to 64)
Rare risk of lung/liver reaction (need regular bloodwork)	7.6% (5.6 to 9.7)	2.2% (0.60 to 3.8)	25% (18 to 35)
Need to restrict alcohol	3.1% (1.2 to 5.0)	0.95% (-0.58 to 2.5)	9.9% (4.3 to 17)
Need regular eye exams (to watch for build up in back of eye)	1.3% (-0.59 to 3.2)	0.68% (-0.88 to 2.2)	3.8% (-1.6 to 9.7)
Dosing regime			
Weekly injections instead of weekly pills	0.39% (-4.5 to 5.4)	-1.6% (-5.5 to 2.4)	9.6% (-4.2 to 25)
3 meds (weekly + 6 daily pills) instead of weekly pills	2.8% (-2.3 to 8.0)	-1.2% (-5.4 to 2.9)	17% (2.6 to 34)
IV infusions every 8 weeks instead of injections every 2 weeks	14% (9.2 to 20)	8.4% (4.3 to 13)	26% (11 to 45)

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Abstract Number: 430

Adoption of Treat to Target Management in the Context of Achievable Goals and Satisfaction in RA

Peter C. Taylor[1], Juan J Gomez-Reino[2], Rieke Alten[3], Philippe Bertin[4], Roberto Caporali[5], Emma Sullivan[6], Robert Wood[7], James Piercy[7], Radu Vasilescu[8], Dean Spurden[9] and Jose Alvir[10], [1]Kennedy Institute of Rheumatology, Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences, University of Oxford Botnar Research Centre, Oxford, United Kingdom, [2]Desarmen of Rheumatology, Unit Hospital Clinico Universitario, Santiago, Spain, [3]Internal Medicine, Rheumatology & Clinical Immunology, Schlosspark-Klinik, University Medicine Berlin, Berlin, Germany, [4]Rheumatology, CHU Dupuytren, Limoges, France, [5]University of Pavia and IRCCS Policlinico S. Matteo Foundation, Pavia, Italy, [6]Adelphi Real World, Manchester, United Kingdom, [7]Adelphi Real World, Macclesfield, United Kingdom, [8]Medical Affairs, Pfizer Inc, Brussels, Belgium, [9]Pfizer Inc, Tadworth, United Kingdom, [10]Global Health and Value, Pfizer Inc, New York, NY
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Background/Purpose: The approach of setting disease activity targets and adjusting therapy appropriately to achieve the target has been proven to optimize outcomes in Rheumatoid Arthritis (RA). Target setting is not yet universal and targets may evolve with rheumatologists' increasing understanding of the patient's RA and their response to treatment over time.

Methods: Data were drawn from the Adelphi 2014 Rheumatology Disease Specific Programme, a survey of rheumatologists and their RA patients in France, Germany, Italy, Spain and the UK. Rheumatologists provided patient demographics, details of treat to target (T2T) approach (if any), satisfaction with RA control and time since RA diagnosis. Patients were allocated to one of two cohorts based on time since RA diagnosis: <2 years, ≥2 years. The cohorts were compared on the T2T approach the treating rheumatologist had reported: aspirational (T2T goal stated as remission), pragmatic (T2T goal stated as something other than remission), T2T approach not adopted for the patient. The level of physician satisfaction with RA control was compared across the T2T approaches within each cohort. Appropriate univariate tests were performed to assess for statistically significant associations, nominal p values were reported.

Results: 307 rheumatologists provided data for 2,536 patients, of whom 2,381 had a time since diagnosis reported (mean age: 52.5; 71% female). 24.3% (579 patients) of patients had been diagnosed with RA <2 years ago and the remaining 75.7% (1,802 patients) diagnosed ≥ 2 years ago. Physicians had a T2T approach with no target, pragmatic target and aspirational target in 48.0%, 16.6% and 35.4% respectively.

Patients with a shorter time since diagnosis (<2 years) were more likely than patients with a longer time since diagnosis to have no target (57.9% vs. 44.9% respectively; p<0.0001) and less likely to have a pragmatic target (7.8% vs. 19.4%; p<0.0001). Levels of aspirational targets were similar regardless of the duration since diagnosis (34.4% vs. 35.7%).

Physician satisfaction with RA control was lower in patients with a shorter time since diagnosis (65.1% vs. 77.0%; p<0.0001). In these patients with a shorter time since diagnosis, satisfaction by T2T approach was 56.3%, 64.4%, 70.4%, for aspirational, pragmatic and no target respectively. In patients with a longer diagnosis, satisfaction by T2T approach was 82.4%, 62.9%, 78.7%, for aspirational, pragmatic and no target respectively (p<0.0001).

Conclusion: This research shows that a T2T approach is not used for almost half RA patients, although use of T2T is more common among those who have been diagnosed ≥2 years ago. The satisfaction level with disease control is also higher in these patients. However, the higher use of pragmatic T2T approaches in patients with longer disease duration suggests that current treatment options may not comprehensively succeed in meeting the early aspirations of remission for RA patients.

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Abstract Number: 431

Treatment Target in a Disease Activity Score Steered Treatment Protocol in Early Arthritis Patients: Low Disease Activity or Remission

Gülsah Akdemir[1], Iris M. Markusse[2], Johannes H.L.M. van Groenendael[3], André J. Peeters[4], Esmeralda T. Molenaar[5], Pit J.S.M. Kerstens[6], Willem F. Lems[7], T. W. J. Huizinga[1] and Cornelia F. Allaart[1], [1]Rheumatology, LUMC, Leiden, Netherlands, [2]LUMC, Leiden, Netherlands, [3]Rheumatology, Franciscus Hospital, Roosendaal, Netherlands, [4]Rheumatology, RDGG, Delft, Netherlands, [5]Rheumatology, Groene Hart Hospital, Gouda, Netherlands, [6]Rheumatology, Reade, Amsterdam, Netherlands, [7]Rheumatology, VU Medical Center, Amsterdam, Netherlands
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Background/Purpose: To compare physicians' opinion on and adherence to treatment study protocols targeted at either Disease Activity Score (DAS) ≤2.4 or <1.6.

Methods: The BeSt study compared 4 treatment strategies in 508 early rheumatoid arthritis (RA, 1987 criteria) patients, targeted at DAS ≤2.4, at 3 monthly evaluations. Seven years later, in roughly the same rheumatology clinics, the IMPROVED study started with methotrexate and prednisone in 479 early RA (2010 criteria) and 122 undifferentiated arthritis (UA) patients, followed by 2 randomization arms targeted at DAS remission (<1.6), at 4 monthly evaluations. We evaluated physicians' adherence to the protocols and assessed associated opinions and conditions during 4 year follow up by Generalized Linear Mixed Models (GLMM).

Results: Protocol adherence (PA) over 4 years was higher in BeSt than in IMPROVED (mean over time 88% and 69%, respectively). PA decreased during follow up in both studies from 100% to 77% (BeSt) and to 55% (IMPROVED). Protocol violations (PV) occurred in IMPROVED in (mean over time) 23% and in BeSt in 12%. In IMPROVED, more PV were against required treatment intensification/restart (64%), compared to 33% against required drug tapering/discontinuation, whereas in BeSt this was almost similar (47% and 42%, respectively). Where the physician incorrectly didn't taper/stop, the measured DAS was (median 0.6 (IQR -0.9;-0.3)) lower than the target DAS <1.6 (IMPROVED) and (0.7 (-1.2;-0.3)) lower than target DAS≤2.4 (BeSt). Where they incorrectly didn't intensify/restart, the measured DAS was (0.5 (0.2;0.8)) above the DAS target <1.6 (IMPROVED), and (0.7 (0.3;1.3)) above target DAS≤2.4 (BeSt). In BeSt the odds for PV were higher if physicians were not satisfied with the current treatment effect, disagreed with the DAS, or with the next treatment step (table 1). In IMPROVED the odds for PV were higher if physicians disagreed with the DAS or with the next treatment step, but disagreement with the current treatment effect

was associated with fewer PV. We formulated conditions where objective and subjective measures of disease activity differed, and might therefore induce a higher risk for PV. In table 1 the odds for PV associated with these conditions in the BeSt and IMPROVED are shown.

Conclusion: Physicians mostly followed both DAS steered treatment study protocols but over 4 years follow up PA decreased in both studies and more in the IMPROVED. Where the protocol was not followed, the difference between measured and target DAS appeared smaller in the IMPROVED than in the BeSt. A DAS slightly over target (>1.6) requiring drug intensification resulted in more PV than a DAS under the target requiring drug tapering in the IMPROVED. These results may indicate that physicians intend to follow a DAS <1.6 steered protocol but especially reluctant to increase therapy when elements of a DAS >1.6 may not represent true disease activity.

Table 1 GLMM analysis with protocol violation as outcome variable.

	BeSt			IMPROVED		
Opinions	**OR**	**95% CI**	**p-value**	**OR**	**95% CI**	**p-value**
Not satisfied treatment effect	1.39	1.04;1.87	0.028	0.60	0.48;0.75	<0.001
Disagreement with DAS	2.45	2.01;2.99	<0.001	3.87	3.15;4.80	<0.001
Not satisfied next treatment step	2.79	2.31;3.37	<0.001	3.27	2.58;4.13	<0.001
Conditions						
SJC≤1 and TJC≥2	0.96	0.80;1.16	0.698	2.87	2.47;3.33	<0.001
SJC≤1 and ESR≥28	1.04	0.77;1.41	0.787	1.59	1.23;2.05	<0.001
SJC≤1 and VASpt≥20mm	1.06	0.88;1.27	0.540	2.02	1.74;2.33	<0.001
VASpt≥20mm higher than VASph	1.38	1.15;1.66	<0.001	2.11	1.76;2.53	<0.001
VASph≥20mm higher than VASpt	1.35	0.96;1.88	0.085	0.89	0.62;1.29	0.549

GLMM: Generalized Linear Mixed Models; DAS: disease activity score; SJC: swollen joint count; TJC: tender joint count; ESR: erythrocyte sedimentation rate; VASpt: visual analogue scale general health of the patient; VASph: visual analogue scale general health of the physician; OR: odds ratio; CI: confidence interval.

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Additional Intensive Treatment for Rheumatoid Arthritis Patients with Positive Power Doppler Signals Reduce the Radiological Joint Damage Even after Achieving Clinical Remission -SCRUM Study-

Tadashi Okano[1], Kentaro Inui[2], Masahiro Tada[3], Yuko Sugioka[4], Kenji Mamoto[1], Tatsuya Koike[4] and Hiroaki Nakamura[1], [1]Orthopedic Surgery, Osaka City University Graduate School of Medicine, Osaka, Japan, [2]Orhtopedic Surgery, Osaka City University Graduate School of Medicine, Osaka, Japan, [3]Orthopedic surgery, Osaka City General Hospital, Osaka, Japan, [4]Center for Senile Degenerative Disorders (CSDD), Osaka City University Graduate School of Medicine, Osaka, Japan

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Background/Purpose: The latest recommendations for the treatment of rheumatoid arthritis (RA) focus on the achievement of clinical remission. However, joints with subclinical positive power Doppler (PD) signals in ultrasonography (US) might be exposed to the risk of joint damage progression even after the achievement of clinical remission. The aim of this study was to assess subclinical synovitis by US and evaluate the effects of additional intensive treatment for preventing joint damage among RA patients in clinical remission.

Methods:

This study was based on the SCRUM (suppress the joint destruction in clinical remission patients who have active synovitis of ultrasonographic assessment by increasing the dose of methotrexate) study, an open-label, randomized trial. US examination was performed consecutively for 134 patients with RA in clinical remission defined as DAS (Disease activity score) 28<2.6. US assessment was performed at 34 synovial sites in 30 joints. The gray scale (GS) and PD signals were scored in each joint using a semi-quantitative scale from 0 to 3. According to the results of US assessment, the patients with PD positive synovitis (PD³1 in at least one joint) were randomly assigned to two groups; the patients increased the dose of MTX (intensive treatment group) or the patients continue their current treatment (coutinuous treatment group). The patients without active synovitis continued their current treatment (PD negative group). Standard radiographs of hands and forefeet were obtained at baseline, week 24 and 52. Radiological joint damage was assessed according to the modified total Sharp score (mTSS). The primary endpoint of the study was a change of mTSS after 52 weeks compared to the baseline.

Results:

Of 134 patients with clinical remission, PD positive synovitis was found in 101 patients (75.4%) at baseline. After the randomization, 51 patients were assigned to intensive treatment group and 50 patients to coutinuous treatment group. Thirty-seven patients in intensive treatment group (72.5%), 42 patients in coutinuous treatment group (84%) and 20 patients in PD negative group (60.6%) completed this study until week 52. Total PD score was significantly decreased inintensive treatment group comparing to coutinuous treatment group (-3.9 vs -2.0, p=0.019). The progression of mTSS was significantly suppressed in intensive treatment group compared to coutinuous treatment group at both week 24 (0.27 and 1.02, p=0.007) and week 52 (1.03 and 2.02, p=0.038). Especially, the progression of mTSS in patients treated with biologics in intensive treatment group (n=16) was suppressed as same as PD negative group (0.75 and 0.80, respectively) at week 52.

Conclusion:

In conclusion, clinical remission according to composite indexes allowed the presence of subclinical active synovitis that might induce structural joint damages. Subclinical active synovitis should be controlled by additional treatment and this results in the prevention of the joint damage progression. Evaluation of subclinical active synovitis by using high resolution US should be important even in patients achieving clinical remission and it should be treated more intensively.

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Abstract Number: 433

Rheumatoid Arthritis (RA) Biologic Switching and Cycling in a Large US Managed Care Population

Machaon Bonafede[1], Jeffrey R. Curtis[2], Donna McMorrow[1], Chieh-I Chen[3] and **George J. Joseph**[4], [1]Truven Health Analytics, Cambridge, MA, [2]Immunology & Rheumatology, University of Alabama at Birmingham, Birmingham, AL, [3]Regeneron Pharmaceuticals, Inc., Tarrytown, NY, [4]Global Health Economics & Outcomes Research (HEOR), Sanofi, Bridgewater, NJ

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Background/Purpose: A majority of RA patients who switch from a tumor necrosis factor inhibitor (TNFi) to another biologic disease-modifying anti-rheumatic drug (DMARD) are TNFi cyclers (Bonafede M et al. Adv Ther 2012;29:664-74). The objective of this study was to examine subsequent biologic switching among RA patients in a large US managed care population after they switched between two TNFi ("TNFi cyclers"), between a TNFi and a non-TNFi, or between two non-TNFi.

Methods: Index claims from January 2010 to June 2014 were analyzed from the Truven Health MarketScan® Commercial database. The "index claim" was the first claim for a biologic DMARD or tofacitinib. Patients were required to be ages 18-64 years at index with ≥12 months of continuous medical and pharmacy enrollment pre- and post-index, ≥1 claim for RA (ICD-9-CM 714.0x) at baseline (pre-index) or within 30 days post-index, ≥1 claim for a different biologic at baseline, no claim for the index agent at baseline, and no claim for any other autoimmune condition. Patients who switched therapy again within 6 months or within 12 months after the index date were categorized based on baseline and index therapy.

Results: Of the 7304 patients who met the selection criteria, 82.1% were female. Mean age was 50.1 years (SD=9.5) and mean Deyo Charlson Comorbidity Index Score was 1.4 (SD=0.9). A total of 4764 (65.2%) patients were TNFi cyclers, 1826 (25.0%) switched from a baseline TNFi to an index non-TNFi, 418 (5.7%) switched from a baseline non-TNFi to an index TNFi, and 296 (4.1%) switched from a baseline non-TNFi to an index non-TNFi. Mean age at index was similar across cohorts (49.5 to 51.9 years); 80.9% to 84.5% of patients in each cohort were female. The table summarizes the proportion of patients who switched therapy again in the first 6 or 12 months post-index. For patients who switched from a baseline TNFi to an index non-TNFi, compared with TNFi cyclers, the odds ratio for switching therapy again was 0.619 (95% CI: 0.53, 0.72; $p<0.01$) within 6 months and 0.824 (95% CI: 0.73, 0.93; $p<0.01$) within 12 months.

Conclusion: RA patients who switch biologic therapy frequently switch again within 12 months. Compared with patients who switch between two TNFi (TNFi cyclers), patients who switch from a TNFi to a non-TNFi are less likely to switch therapy again within 6 or 12 months.

Table. Proportion of Patients Who Switched Therapy Again After the Index Date.

Baseline and Index Therapy	Switched Again Within 6 Months, n (%)	Switched Again Within 12 Months, n (%)
TNFi to TNFi ("TNFi cyclers") (N=4764)	910 (19.1)	1,616 (33.9)
TNFi to non-TNFi (N=1826)	233 (12.8)*	543 (29.7)*
Non-TNFi to TNFi (N=418)	75 (17.9)	134 (32.1)
Non-TNFi to non-TNFi (N=296)	34 (11.5)*	73 (24.7)*

*$p < 0.01$ compared with TNFi cyclers.

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Abstract Number: 434

Duration of Remission By Currently Available Criteria Can Predict Physical Functioning, but Not Radiological Progression in Early Rheumatoid Arthritis Patients

Nicole P.C. Konijn[1], Lilian H.D. van Tuyl[1], Maarten Boers[1,2], D den Uyl[1], M.M. ter Wee[1], P.J.S.M. Kerstens[3,4], Alexandre E. Voskuyl[5], Michael T. Nurmohamed[1,3], Dirkjan van Schaardenburg[3,6] and Willem F. Lems[1,3],
[1]Rheumatology, Amsterdam Rheumatology and immunology Center, VU University medical center, Amsterdam, Netherlands, [2]Epidemiology & Biostatistics, VU University medical center, Amsterdam, Netherlands, [3]Rheumatology, Amsterdam Rheumatology and immunology Center, Reade, Amsterdam, Netherlands, [4]Rheumatology, Westfriesgasthuis, Hoorn, Netherlands, [5]Rheumatology, Amsterdam Rheumatology and immunology Center, location VU University medical center, Amsterdam, Netherlands, [6]Rheumatology, Amsterdam Rheumatology and immunology Center, Academic Medical Center, Amsterdam, Netherlands
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Background/Purpose: Several sets of remission criteria have been developed. The ACR/EULAR criteria were validated against their potential to predict prognosis of rheumatoid arthritis (RA) [1]. Duration of remission was not studied, but is likely to be an even better predictor of RA prognosis. We investigated whether remission at one point in time and sustained remission during 26, 52 and 78 weeks of treatment are predictive of RA prognosis in early RA patients after 104 weeks of treatment.

Methods: In the COBRA-light trial [2,3], patients were assessed for remission according to Boolean, SDAI, CDAI, RAPID, DAS44 and DAS28 criteria at 26, 52, 78 and 104 weeks of treatment. ‘Sustained' was defined as remission present at 1) 26 and 52 weeks, and 2) at 26, 52 and 78 weeks. Following the methodology of the ACR/EULAR remission committee [1] good outcome was defined as 1) DHAQ≤0 and HAQ consistently ≤0.5 and 2) DSHS≤0, between 52 and 104 weeks. Logistic regression analyses studied the potential of the above remission criteria to predict good outcome: both at one point in time and according to the two defined periods of sustained remission. Patients with missing data of remission criteria at ≥1 visits (n=64) were excluded from these preliminary analyses.

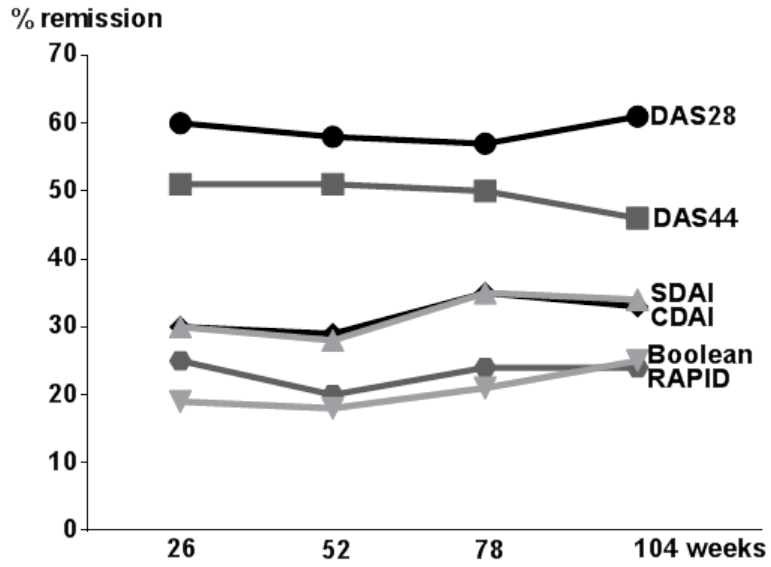
Results: Hundred early RA patients (66% women, mean age 53 years) were included. Remission percentages at 26, 52, 78 and 104 weeks after treatment are shown in Figure 1. The proportion of patients in sustained remission during

26-52 and 26-52-78 weeks respectively were: Boolean: 10%, 8%; RAPID: 13%, 12%; SDAI:19%, 16%; CDAI: 19%, 17%; DAS44: 36%, 30%; and DAS28: 44%, 38%. Low, stable HAQ scores were seen in 40% of the patients, and lack of radiological progression in 81%. All remission criteria were predictive of low, stable HAQ scores between 52 and 104 weeks of follow-up, both at single points in time, as well as during periods of sustained remission, except for sustained Boolean remission. Sustained remission periods resulted in higher odds ratio's for a low, stable HAQ compared to remission at one point in time, except for DAS28 remission at 52 weeks. None of the criteria were predictive of lack of radiological progression, neither at one point in time nor during periods of sustained remission, except for RAPID remission at 52 weeks.

Conclusion: Early RA patients that reach remission according to any of the available criteria during short or sustained periods are likely to retain a good physical function in the subsequent months, in which sustained periods of remission might be a stronger predictor than remission at one point in time. In contrast, radiological damage progression does not seem to be associated as strongly with (sustained) remission, probably as a consequence of the low radiological damage progression overall.

Ref.: 1. Felson, Arthritis Rheum 2011; 2. Den Uyl, Ann Rheum Dis 2014; 3. Ter Wee, Ann Rheum Dis 2015.

Figure 1: Remission percentages after 26, 52, 78 and 104 weeks of treatment in the COBRA-light trial (n=100)



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Abstract Number: 435

Impact of Sarilumab on Fatigue, Pain, Morning Stiffness, Productivity, and Health Related Quality of Life (HRQoL) in Patients with Active Rheumatoid Arthritis Who Were Inadequate Responders or Intolerant of Anti-TNF-Î± Therapy: Results from a Phase 3 Study (RCT)

Vibeke Strand[1], Mark Kosinski[2], Neil Graham[3], Chieh-I Chen[3], George J. Joseph[4], Deborah Bauer[5], Yong Lin[5], Cesar Pacheco-Tena[6] and Roy Fleischmann[7], [1]Biopharmaceutical Consultant, Portola Valley, CA, [2]QualityMetric Inc, Lincoln, RI, [3]Regeneron Pharmaceuticals, Inc., Tarrytown, NY, [4]Global Health Economics & Outcomes Research (HEOR), Sanofi, Bridgewater, NJ, [5]Sanofi, Bridgewater, NJ, [6]Universidad Autónoma de Chihuahua, Chihuahua, Mexico, [7]University of Texas Southwestern Medical Center, Dallas, TX
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Background/Purpose : Sarilumab, a human monoclonal antibody directed against the IL-6 receptor, in combination with non-biologic DMARDs, demonstrated efficacy in the TARGET RCT (NCT01709578). TEAEs and SAEs were more frequent in the sarilumab-treated groups. Laboratory findings were consistent with IL-6 blockade and observations from the MOBILITY study. From an RA patient perspective, fatigue, morning stiffness, pain, ability to participate in family/leisure activities, and work are important outcomes to assess treatment effectiveness. These analyses present the effects of sarilumab+DMARD on the pre-defined secondary endpoints of fatigue, AM stiffness, pain, work within and outside the home and participation in family/leisure activities, and HRQoL at Week 24, as well as change in patient global assessment of disease activity (PtGA) and physical function by Health Assessment Questionnaire (HAQ).

Methods : The intent-to-treat population included 546 patients randomized 1:1:1 to placebo, sarilumab 150 mg every 2 weeks (q2w) or 200 mg q2w + background DMARDs. Patient-reported outcomes (PRO) included Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F), AM stiffness, Pain VAS, Work Productivity Survey (WPS),Rheumatoid Arthritis Impact of Disease (RAID), and Short Form-36 (SF-36) assessed at baseline, Weeks 2 (FACIT, RAID, Pain and AM stiffness only), 4, 12, and 24. PRO changes from baseline to week 24 were analyzed using mixed-model repeated measures using region, number of prior TNFis, visit, treatment, and treatment by visit interaction as fixed effects and baseline PRO scores as covariates.

Results: Baseline SF-36 Physical (PCS) and Mental Component Summary (MCS) scores were >2 and >1 standard deviation below normative values, respectively, indicating significant disease burden. Statistically significant ($p<0.025$, simple Bonferroni adjustment) improvements versus placebo+DMARD in FACIT-F, AM stiffness, pain, WPS and RAID were reported by patients receiving sarilumab 150 mg+DMARD and similarly for sarilumab 200 mg+DMARD. SF-36 PCS significantly improved for both doses with no worsening of SF-36 MCS. Significant improvements were seen for 5/8 SF-36 domain scores for sarilumab 150mg + DMARD and 7/8 domain scores for sarilumab 200mg + DMARD. PtGA and HAQ, included in the primary analysis, were statistically significantly improved with both doses of sarilumab. With few exceptions, statistically significant improvements between sarilumab treatment groups and placebo exceeded the minimum clinically important difference (MCID) for those PROs with established MCIDs.

Conclusion: In this Phase 3 RCT, TNF-IR RA patients receiving either dose of sarilumab+DMARD reported statistically significant and clinically meaningful changes from baseline in fatigue, AM stiffness, pain, productivity and participation, RA impact scores and HRQoL at Week 24.

Table 1. HRQoL, Fatigue, WPS, and RAID at Baseline and Week 24

PRO	Placebo (N=181)	Sarilumab 150 mg + DMARD (N=181)	Sarilumab 200 mg + DMARD (N=184)
SF-36 PCS			
Baseline mean	29.73	30.28	29.36
Mean change from baseline	**6.51**	**8.54**	**9.87**
LSM difference, P-value		3.250 (p=0.0004)	4.075 (p<0.0001)
SF-36 MCS			
Baseline mean	38.52	38.60	39.08
Mean change from baseline	**6.04**	**7.52**	**7.55**
LSM difference, P-value		1.515 (p=0.2026)	2.013 (p=0.0854)
SF-36 PF			
Baseline mean	26.29	31.24	32.29
Mean change from baseline	**14.99**	**18.72**	**18.32**
LSM difference, P-value		7.680 (p=0.0039)	8.303 (p=0.0016)
SF-36 RP			
Baseline mean	36.78	33.96	34.77
Mean change from baseline	**13.78**	**20.24**	**21.81**
LSM difference, P-value		7.059 (p=0.0075)	9.046 (p=0.0005)
SF-36 BP			
Baseline mean	27.71	28.76	23.89
Mean change from baseline	**21.56**	**26.52**	**32.61**
LSM difference, P-value		7.563 (p=0.0029)	10.927 (p<0.0001)
SF-36 GH			
Baseline mean	36.46	37.21	33.86
Mean change from baseline	**11.35**	**13.74**	**18.03**
LSM difference, P-value		3.525 (p=0.0776)	6.473 (p=0.0011)
SF-36 VT			
Baseline mean	36.32	38.42	36.25
Mean change from baseline	**13.93**	**16.22**	**19.29**
LSM difference, P-value		5.317 (p=0.0167)	7.373 (p=0.0008)
SF-36 SF			
Baseline mean	45.58	45.47	48.52
Mean change from baseline	**17.42**	**21.95**	**20.65**
LSM difference, P-value		6.452 (p=0.0203)	6.770 (p=0.0138)
SF-36 RE			
Baseline mean	47.90	46.03	48.95
Mean change from baseline	**12.46**	**16.94**	**16.30**
LSM difference, P-		3.837 (p=0.1847)	4.46 (p=0.1168)

value			
SF-36 MH			
Baseline mean	52.58	54.83	53.81
Mean change from baseline	**10.71**	**12.60**	**14.27**
LSM difference, P-value		2.823 (p=0.1715)	4.717 (p=0.0211)
FACIT-F			
Baseline mean	24.00	24.76	23.71
Mean change from baseline	**9.18**	**11.02**	**11.62**
LSM difference, P-value		3.045 (p=0.0078)	3.246 (p=0.0040)
Morning Stiffness (VAS)			
Baseline mean	64.75	66.75	70.18
Mean change from baseline	**-25.13**	**-34.7**	**-37.9**
LSM difference, P-value		-10.646 (p=0.0008)	-12.137 (p<0.0001)
WPS			
P-value**		0.0004	0.0003
RAID			
Baseline mean	6.68	6.25	6.83
Mean change from baseline	-2.40	-2.79	**-3.24**
LSM difference, P-Value		-0.750 (p=0.0057)	-1.006 (p=0.0002)
Pain VAS			
Baseline mean	68.96	69.32	74.76
Mean Change from Baseline	-27.65	-36.28	-30.60
LSM difference, P-value		-10.632 (p=0.0004)	-12.379 (p<0.0001)

LSM Least Square Means;

PCS = Physical Component Summary Measure

MCS = Mental Component Summary Measure

PF = Physical Functioning Scale

RP = Role Physical Scale

BP = Bodily Pain Scale

GH = General Health Scale

VT = Vitality Scale

SF = Social Functioning Scale

RE = Role Emotional Scale

MH = Mental Health Scale

FACIT-F = Functional Assessment of Chronic Illness Therapy Fatigue Scale

WPS = Work Productivity Survey – Rheumatoid Arthritis

RAID = Rheumatoid Arthritis Impact of Disease

*Mean change from baseline_ Bolded score changes are greater than MCID.

** Global test for the change from baseline in the eight WPS-RA scores

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Abstract Number: 436

Ultrasonographic Disease Activity in Rheumatoid Arthritis Patients Who Are in Clinical Remission According to Different Remission Criteria: Should We Insist on Achieving Boolean Remission?

Gulsen Ozen[1], Ali Ugur Unal[1], Atakan Topcu[2], Pamir Atagunduz[1], Haner Direskeneli[1] and Nevsun Inanc[1], [1]Department of Rheumatology, Marmara University Faculty of Medicine, Istanbul, Turkey, [2]Department of Internal Medicine, Marmara University Faculty of Medicine, Istanbul, Turkey

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Background/Purpose: At the present time remission is the target for treatment of rheumatoid arthritis (RA). Various composite indices are available that can be used to define remission. Although the new ACR/EULAR Boolean criteria is more stringent than others, it is difficult to achieve and even more difficult to sustain this Boolean remission. In this study we aimed to determine the difference of the ultrasonographically (US) assessed actual disease activity of the patients with Boolean remission compared to patients in remission according to other remission criteria.

Methods: RA patients in clinical remission (DAS28-ESR<2.6) for at least 3 months were included to this cross-sectional study. All patients' remission status according to DAS28-ESR-3, DAS28-CRP, SDAI, CDAI and Boolean based definitions were assessed. A standard gray scale (GS) and power Doppler (PD) US examination of 28 joints (included in DAS28) for the presence of synovitis was performed by an experienced sonographer (NI) blinded to clinical data. US synovitis GS and PD signals were semiquantitatively graded from 0 to 3. Total PD and GS synovitis scores of all sites are recorded as sum scores of PD and GS, respectively.

Results: A total of 55 out of 302 RA patients (18.2%) in DAS28 remission were enrolled (F/M=35/20, mean age 52.2±12.0, disease duration 11.0±6.5 years, biologic treatment 43.6%, RF or Anti-CCP positivity 76.4%). Of those 55 patients, 41 (74.5%), 36 (65.5%), 31 (56.4%) and 25 (45.5%) fulfilled the DAS28-ESR-3, SDAI, CDAI and Boolean remission criteria, respectively. SDAI and Boolean remission had the highest percentage of patients with PD signals ≤1, which has shown to be associated with erosion development and worse functional outcome. However despite that, those differences in US disease activity parameters (both PD and GS synovitis sum scores and percentages of patients without PD and GS signals [with both omitting and including grade 1 signals]) in remission patients according to different criteria were not statistically significant. US disease activity parameters of clinical remission group according to different criteria were similar as well, compared to their counterpart nonremission group.

Conclusion: US verified joint inflammation is the lowest in RA patients who are in remission according to Boolean and SDAI criteria. The clinical significance of this statistically nonsignificant inflammatory activity compared to other clinical remission criteria should be assessed in prospective studies. Till then, in clinical practice if Boolean remission could not be achieved, SDAI and also other clinical remission criteria could also be preferred as the remission target.

Table 1. Differences in US disease activity findings and acute phase reactants depending on remission status defined by different criteria

	DAS28-ESR REM (n=55)	DAS28-CRP REM (n=53)	DAS28-ESR-3 REM (n=41)	SDAI REM (n=36)	CDAI REM (n=31)	Boolean REM (n=25)
PD sum score (0-84)	2 (0-5)	2 (0-5)	1 (0-4.5)	1 (0-4.7)	1 (0-4)	1 (0-4.5)
GS sum score (0-84)	4 (1-8)	3 (1-8)	3 (1-7.5)	4 (1-8)	4 (0-8)	3 (0-6.5)
PDGS sum score (0-168)	5 (1-13)	5 (1-14)	5 (1-11.5)	4.5 (1.2-12.5)	4 (1-11)	4 (0.5-11)
US joint count with PD signal (0-28)	1 (0-3)	1 (0-3)	1 (0-3)	1 (0-3)	1 (0-3)	1 (0-3)
US joint count with GS signal (0-28)	3 (1-4)	3 (1-4)	2 (1-4)	2.5 (1-4)	2 (0-4)	2 (0-4.5)
PD =0 ⌊	17 (30.9)	17 (32.1)	13 (31.7)	10 (27.8)	10 (32.3)	9 (36)
PD≤1 ⌊	31 (56.4)	31 (58.5)	26 (63.4)	22 (71)	19 (61.3)	16 (64)
GS=0 ⌊	10 (18.2)	10 (18.9)	9 (22)	7 (19.4)	8 (25.8)	7 (28)
GS≤1 ⌊	25 (45.5)	25 (47.2)	21 (51)	16 (44.4)	15 (48.4)	12 (48)
PD=0 and GS=0 ⌊	9 (16.4)	9 (17)	8 (19.5)	6 (16.7)	7 (22.6)	6 (24)
PD≤1 and GS≤1 ⌊	23 (41.8)	23 (43.3)	19 (46.3)	15 (41.7)	15 (48.4)	12 (48)
USJC with PD=0 ⌊	17 (30.9)	17 (32.1)	13 (31.7)	10 (27.8)	10 (32.3)	9 (36)
USJC with PD≤1 ⌊	31 (56.4)	31 (58.5)	26 (63.4)	22 (61.1)	19 (61.3)	16 (64)
USJC with GS=0 ⌊	10 (18.2)	10 (18.9)	9 (22)	7 (19.4)	8 (25.8)	7 (28)
USJC with GS≤1 ⌊	25 (45.5)	25 (47.2)	21 (51.2)	16 (44.4)	15 (48.4)	12 (48)

**The values were presented as median (25-75p) unless indicated otherwise.* ⌊ *The values were presented as n (%)*

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Abstract Number: 437

Is Mode of Action Important When Switching Biologic Monotherapy in Rheumatoid Arthritis? Drug Adherence Results from the Swedish Ssatg Registry

Tanja Schjødt Jørgensen[1], Carl Turesson[2], Meliha C. Kapetanovic[3], Martin Englund[4,5], Aleksandra Turkiewicz[4], Robin Christensen[1], Henning Bliddal[1], Pierre Geborek[3] and Lars Erik Kristensen[1], [1]The Parker Institute, Department of Rheumatology, Copenhagen University Hospital, Bispebjerg and Frederiksberg, Copenhagen, Denmark, [2]Lund University, Rheumatology, Dept. of Clinical Sciences,, Malmö, Sweden, [3]Department of Clinical Sciences Lund, Section of Rheumatology Lund University and Skåne University Hospital, Lund, Sweden, [4]Orthopedics, Department of Clinical Sciences Lund, Lund University, Lund, Sweden, [5]Clinical Epidemiology Unit, Orthopedics, Dept of Clinical Sciences Lund, Lund University, Lund, Sweden

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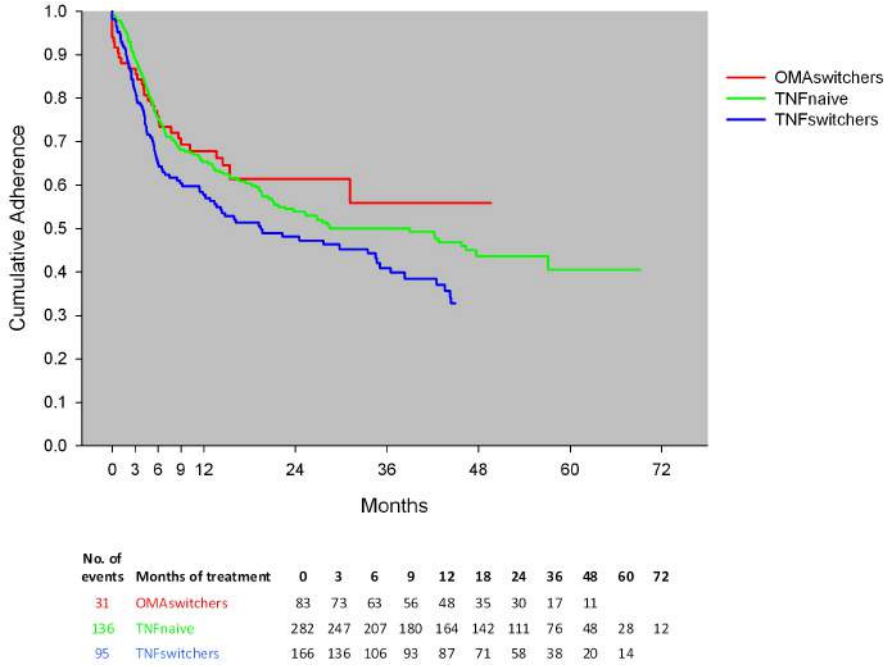
Background/Purpose: About 30% of patients receiving biologic therapy do not have concomitant conventional synthetic DMARDs (csDMARDs). Little is known about the role of different mode of actions when switching biologic therapy. The objective of the present study was to evaluate the impact of anti-TNF and other modes of action on drug adherence in RA patients switching monotherapy.

Methods: All RA patients registered in a regional biologic DMARD (bDMARD) database as initiating bDMARD as monotherapy, i.e. without concomitant csDMARDs, from 1st of January 2006 through 31st of December 2012, were eligible for inclusion. After initiation of the first dose of biologic monotherapy, drug adherence for biologic naïve patients receiving anti-TNF and for patients switching to 2nd course of anti-TNF or a different bDMARD was estimated using life-table technique.

Results: A total of 531 patients with RA were included (80% women, disease duration: mean 12.6 [SD 11.5]), age: mean 56.7 years [SD 14.1], no. of previous DMARDs: median 3.0 [IQR 2.0 to 5.0], EQ-5D: median 0.52 [IQR 0.16 to 0.66], and DAS28: mean 5.0 [SD 1.3]). There was a statistically significant difference in drug adherence when comparing anti-TNF switchers (n=166) to those switching to other modes of action (OMA switchers) (n=83) (p=0.02) (see Figure). There was no statistically significant difference between anti-TNF naïve patients (n=282) and OMA switchers (p=0.30) (see Figure).

Conclusion: When switching to other modes of action biologics after anti-TNF failure, drug adherence was as good as when treated with an anti-TNF as 1st course. However, switching to a 2nd anti-TNF showed significantly inferior drug adherence rates compared to bDMARDs with other modes of action. This suggest that bDMARDs with other modes of action should be considered as the first choice for patients not tolerating csDMARDs and who have had an inadequate response to their first anti-TNF agent.

Figure: Drug adherence of anti-TNF and other modes of action on drug adherence in RA patients switching monotherapy.



No. of events	Months of treatment	0	3	6	9	12	18	24	36	48	60	72
31	OMAswitchers	83	73	63	56	48	35	30	17	11		
136	TNFnaive	282	247	207	180	164	142	111	76	48	28	12
95	TNFswitchers	166	136	106	93	87	71	58	38	20	14	

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Abstract Number: 438

Comparison of the Stanford and Indian Health Assessment Questionnaires for Disability Outcomes in a Phase 3, Randomized, Double-Blind, Active Comparator Study of Infliximab and Biosimilar Infliximab BOW15 in Rheumatoid Arthritis

Arvind Chopra[1], Manjit Saluja[2], Alastair Knight[3], Lucy Shneyer[4], Cheryl Lassen[5], Michael Wyand[6] and Jonathan Kay[7], [1]Rheumatology, Centre for Rheumatic Diseases, Pune 411001, India, [2]Centre for Rheumatic Diseases, Pune 411001, India, [3]Data Management, Evicom Ltd, Twickenham, United Kingdom, [4]Shneyer Statistics, Denville, NJ, [5]Epirus Biopharmaceuticals, Zug, Switzerland, [6]Epirus Biopharmaceuticals, Boston, MA, [7]University of Massachussets Medical School, Worcester, MA

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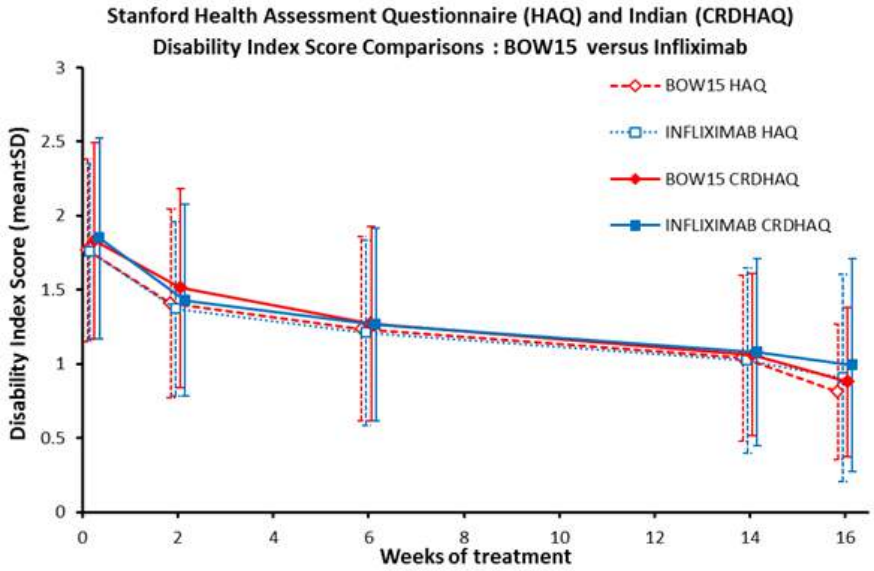
Background/Purpose: The Stanford Health Assessment Questionnaire (HAQ) includes several questions that are more relevant to rheumatoid arthritis (RA) patients in Western countries than to those in India. The Center for Rheumatic Diseases (CRD) Pune developed a modified version of the HAQ (CRDHAQ) to reflect daily activities unique to India and other Asian countries, such as arising from sitting cross-legged on the floor, which may be more difficult to perform than corresponding activities in Western countries. We compared the performance of both questionnaires in a clinical trial conducted in India.

Methods: Indian patients with RA for ≥2 years were randomized in a 54-week clinical trial comparing biosimilar infliximab (IFX) BOW15 to reference IFX (rIFX), which included an initial 16-week double-blind phase followed by an open-label extension in which responders received BOW015. All subjects completed both HAQ and CRDHAQ at weeks 0 (baseline), 2, 6, 14 and 16. Disability index (DI) scores from baseline for both instruments were compared in the ITT population by analysis of covariance within and between treatments.

Results: 189 subjects were, randomized to receive BOW015 (n=127) or rIFX (n=62), of whom 181 subjects (120 receiving BOW015 and 61 receiving rIFX) completed the blinded phase of the study. Baseline HAQ-DI scores were 1.77±0.61 and 1.76±0.60 and baseline CRDHAQ-DI scores were 1.83±0.66 and 1.85±0.67, respectively (mean±SD). The baseline CRDHAQ-DI scores were significantly higher than HAQ-DI scores for each treatment (P<0.05). Data for all time points are shown in Figure 1.

Figure 1.



There were no statistically significant differences between HAQ-DI and CRDHAQ-DI scores from baseline between treatments across each assessment period. Improvements from baseline in each score were statistically significant from week 2 through week 16 for both treatments and both HAQ and CRDHAQ (P<0.001). These decreases in DI by treatment corresponded to comparable increases in %ACR20 responders observed at the time points.

Conclusion: CRDHAQ and HAQ, yielded comparable results when administered to Indian RA patients, and reflected significant functional improvement at week 2. Thus, either the Stanford HAQ or CRDHAQ can be used to assess functional improvement in clinical trials conducted in this patient population with daily activities different from those of Western RA patients.

Disclosure: A. Chopra, Epirus Biopharmceuticals, 2,Epirus Biopharmceuticals, 5; **M. Saluja**, Epirus

Biopharmceuticals, 2; **A. Knight**, Alastair Knight, 5; **L. Shneyer**, Epirus Biopharmceuticals, 5,Merck Pharmaceuticals, 1; **C. Lassen**, Epirus Biopharmaceurticals, 3; **M. Wyand**, Epirus Biopharmaceuticals, 3; **J. Kay**, Amgen, 5,AbbVie Inc., 5,Boehringer Ingelheim GmbH, 5,Bristol-Myers Squibb, 5,Eli Lilly and Company, 5,Epirus Biopharmaceuticals, Inc., 5,Genentech Inc., 5,Hospira, Inc., 5,Janssen Biotech, Inc., 5,Merck Sharp & Dohme Corp., 5,Nippon Kayaku Co., 5,Novartis Pharmaceutical Corporation, 5,Pfizer Inc., 5,Samsung Bioepis, 5,Roche Pharmaceuticals, 5,UCB, Inc., 5,AbbVie, Inc., 2,Eli Lilly and Company, 2,Pfizer Inc, 2,Roche Pharmaceuticals, 2.

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Abstract Number: 439

Progression of Radiographic Joint Destruction in Patients with Rheumatoid Arthritis Treated with a Biologic Agent in Combination with Methotrexate Versus a Biologic Alone: A Systematic Review and Meta-Analysis of Randomized Trials

Tanja Schjødt Jørgensen[1], Simon Tarp[1], Daniel E. Furst[2], Anna Døssing[1], Peter C. Taylor[3], Henning Bliddal[1] and Robin Christensen[1], [1]Musculoskeletal Statistics Unit, The Parker Institute, Department of Rheumatology, Copenhagen University Hospital, Bispebjerg and Frederiksberg, Copenhagen, Denmark, [2]Medicine, University of California, Los Angeles, David Geffen School of Medicine, Los Angeles, CA, [3]Nuffield Dept. of Orthopaedics, Rheumatology and Musculoskeletal, Sciences, Kennedy Institute of Rheumatology, University of Oxford,, Oxford, United Kingdom
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Session Time: 9:00AM-11:00AM

Background/Purpose : One of the frequently claimed advantages of biologic agents is their potential to arrest radiographic progression. The ability of disease-modifying antirheumatic drugs (DMARDs; typically methotrexate, MTX) is less well defined because the effect of DMARDs when added to biologic agents (bDMARDs) on radiographic progression has only sporadically been investigated in randomized trials. The objective of the present study was to review the evidence on radiographic joint destruction in patients with RA between therapies combining MTX with a bDMARD and bDMARD in monotherapy.

Methods: A systematic review and meta-analysis of randomized trials was performed to identify trials relating treatment of RA with MTX in combination with bDMARD, compared to a bDMARD in monotherapy. According to the protocol a major outcome was radiographic joint progression assessed by total sharp score (TSS). A random-effects model was applied for meta-analysis with standardized mean difference and 95% confidence intervals (SMD, 95%CI) and inconsistency (I^2, %) estimated using Review Manager. The protocol is available from PROSPERO: CRD42014014633.

Results: From the 14 trials that were eligible for inclusion (1), only 7 trials assessed radiographic joint progression (Trial duration ranging from 24 to 104 weeks). The use of the Intention to treat population was frequently ‘unclear/inadequate', reducing our confidence in the estimates. The overall analysis of changes in radiographic joint progression showed an SMD of 0.16 [0.09 to 0.23, P<.0001] – apparently with no heterogeneity (P= .58) and inconsistency (0%). Using an SD of 20 TSS unit, this effect size corresponds to a difference between the groups of 3.2

TSS units in favor of concomitant use of MTX when treating with a biologic (after approximately 52 weeks; see Figure). We found no reason to suspect that the added value of MTX varied with the choice of bDMARD (Test for subgroup differences P= .66).

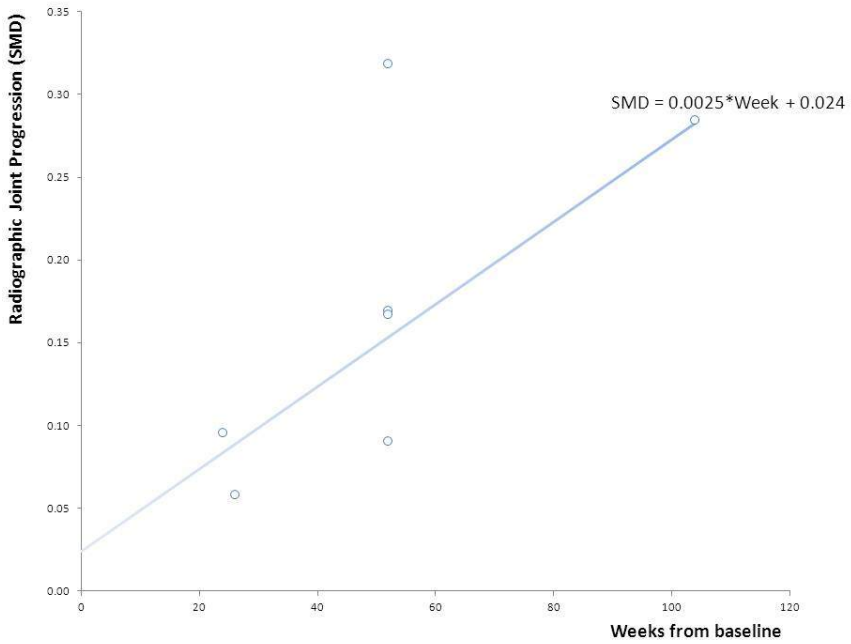
Conclusion: This study provides moderate quality evidence that combining the prescribed bDMARD with concomitant use of MTX is significantly more efficacious in preventing structural joint destruction compared to patients taking biologics as monotherapy.

Reference:

1) Jørgensen TS, et al. Ann Rheum Dis2015;74(Suppl2): 239

Acknowledgement: This study was supported by unrestricted grants from The Oak foundation, and AbbVie (Denmark).

Figure



Disclosure: T. S. Jørgensen, AbbVie and Roche, 2; **S. Tarp**, AbbVie and Roche, 2; **D. E. Furst**, Gilead, 2,GlaxoSmithKline, 2,NIH, 2,Novartis Pharmaceutical Corporation, 2,Pfizer Inc, 2,Roche Pharmaceuticals, 2,Genentech and Biogen IDEC Inc., 2,UCB, 2,Abbvie, 5,Actelion Pharmaceuticals US, 5,Amgen, 5,Bristol-Myers Squibb, 5,Cytori, 5,Janssen Pharmaceutica Product, L.P., 5,Gilead, 5,GlaxoSmithKline, 5,NIH, 5,Novartis Pharmaceutical Corporation, 5,Pfizer Inc, 5,Roche Pharmaceuticals, 5,Genentech and Biogen IDEC Inc., 5,UCB, 5,Abbvie, 8,Actelion Pharmaceuticals US, 8,Bristol-Myers Squibb, 2,Amgen, 2,Actelion Pharmaceuticals US, 2,Abbvie, 2,UCB, 8; **A. Døssing**, None; **P. C. Taylor**, None; **H. Bliddal**, AbbVie and Roche, 2; **R. Christensen**, AbbVie, MSD, and Roche, 2.

Abstract Number: 440

Clinical Characteristics of Rheumatoid Arthritis Patients Achieving HAQ Remission with 6 Months of Biologic Treatment

Yusuke Miwa[1], Ryo Takahashi[1], Airi Maeoka[1], Shinichiro Nishimi[1], Nao Oguro[1], Sho Ishii[1], Mika Kobuna[1], Takahiro Tokunaga[1], Masayu Umemura[1], Tsuyoshi Kasama[1], Katsunori Inagaki[2] and Yoichi Toyoshima[3], [1]Div of Rheumatology, Showa University School of Med, Shinagawa-ku Tokyo, Japan, [2]Department of Orthopedics, Showa University School of Med, Tokyo, Japan, [3]Showa University School of Med, Shinagawa-ku Tokyo, Japan
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SESSION INFORMATION
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Session Title: Rheumatoid Arthritis - Clinical Aspects Poster I
Session Type: ACR Poster Session A
Session Time: 9:00AM-11:00AM

Background/Purpose: Biologic agents are highly effective for rheumatoid arthritis (RA); however, not all cases achieve health assessment questionnaire (HAQ) remission. Although previous studies have reported the prognostic factors, there is no report on predictive factors for HAQ remission. To study predictive factors for HAQ remission, which is one of the treatment goals in RA, after using biologic agents for 6 months.

Methods:

The subjects were 333 RA patients treated with biologic agents for 6 months. The following patient's characteristics were investigated: age, gender, the number of previous drugs, disease duration, the type of biologic agents, baseline steroid dosage, MTX dosage, serum RF, MMP-3, ACPA, TNF-α, and IL-6. For evaluation we used SDAI for RA disease activity, HAQ for ADL, Short Form (SF)-36 for QOL, and Hamilton Depression Rating Scale (HAM-D) or Self-rating depression scale (SDS) for depression status. HAQ remission was defined by HAQ≦0.5 after 6 months of treatment. The subjects were divided into two groups: patients with HAQ≦0.5 and patients with HAQ>0.5 at 6 months, and a retrospective study was conducted. 101 patients were excluded from the study due to loss to 6-month follow-up, and a total of 232 patients were analyzed.

Results: Compared with a group of RA patients without HAQ remission (n=68), a group of patients with HAQ remission (n=164) had younger age (54.8 ± 15.2 vs. 61.8 ± 13.3, p=0.0011), lower baseline steroid dosage (3.4 ± 3.7mg vs. 4.5 ± 3.5mg, p=0.037), lower serum MMP-3 (196 ± 234 ng/ml vs. 321 ± 551, p=0.047), lower SDAI (22.5 ± 13.4 vs. 32.1 ± 12.9, p<0.001), lower HAQ (0.39 ± 0.51 vs. 1.08 ± 0.54, p<0.001), higher SF-36 (p<0.05 in all categories), lower SDS (40.4 ± 9.9 vs. 43.5 ± 9.2, p=0.033), and lower HAM-D (5.0 ± 4.3 vs. 8.4 ± 5.0≦Ap<0.001)

were detected based on univariate analysis. On the other hand, only in lower HAQ score (p=0.0001) and “mental health” item of the SF-36 (p=0.0189) were detected based on logistic regression analysis.

Conclusion:

It was suggested that RA patients with lower HAQ and lower depression scores at baseline are more likely to achieve HAQ remission with biologic treatment.

Disclosure: Y. Miwa, None; **R. Takahashi**, None; **A. Maeoka**, None; **S. Nishimi**, None; **N. Oguro**, None; **S. Ishii**, None; **M. Kobuna**, None; **T. Tokunaga**, None; **M. Umemura**, None; **T. Kasama**, None; **K. Inagaki**, None; **Y. Toyoshima**, None.

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Abstract Number: 441

Ultrasound Assessment of Early Response to Certolizumab Pegol Can Predict Future Response in Patients with Rheumatoid Arthritis

Takanori Fujimura, Takashi Fujimoto, Ryota Hara, Naoki Shimmyo, Yasunori Kobata, Akira Kido, Yasuhiro Akai and Yasuhito Tanaka, The Center for Rheumatic Diseases, Nara Medical University, Kashihara, Japan

First publication: September 29, 2015

SESSION INFORMATION

Session Date: Sunday, November 8, 2015

Session Title: Rheumatoid Arthritis - Clinical Aspects Poster I

Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose: Certolizumab pegol (CZP) is a PEGylated Fab’ fragment of a humanized anti-TNF antibody with high affinity to TNF. It brings rapid improvement of the signs and symptoms of RA and it has been shown that attainment of clinical response at first 12 week predict better longterm outcomes. Musculoskeletal ultrasound (US) has been proved to be useful at assessing synovitis precisely in patients with RA. There are few reports, however, that verify the early response to CZP in RA patients by US and whether early US assessment of synovitis can predict future clinical response is unclear. In the present study we describe the early response to CZP in RA patients by US examination and ascertain whether US is useful for predicting future clinical response.

Methods: Seventeen patients with RA were treated with CZP. Patients were treated with subcutaneous CZP 400 mg at weeks 0, 2, 4 followed by 400mg every 4 weeks or 200mg every 2 weeks. The mean age of patients was 52.2 years old and the mean disease duration was 6.0 years. The mean disease activity at baseline (week 0) was 4.67 and 23.2 for 28-joint disease activity score (DAS28) and simplified disease activity index (SDAI), respectively. The mean modified health assessment questionnaire (mHAQ) was 0.49. Twelve patients (71%) were naïve to biologic agents. Fifteen (88%) and 7 (41%) patients were treated with methotrexate and glucocorticoids concurrently. At baseline and weeks 2, 4 and 12, US examination was performed at bilateral MCP, PIP, IP, and wrist joints. Gray-scale (GS) and pulse Doppler (PD) signal was recorded in each joint using semi-quantitative score (0 to 3). The sum of these scores obtained from each joint was used as GSUS and PDUS score.

Results: At weeks 0, 2, 4, and 12, mean GSUS score was 23.5, 20.1, 16.4 and 15.5, respectively. Mean PDUS score at weeks 0, 2, 4, and 12 was 14.4, 10.5, 10.7 and 9.8, respectively. Both GSUS and PDUS score were improved significantly as early as 2 weeks after treatment (p=0.0428 and 0.0119) and gradually reduced during study period. At week 12, both of DAS28 and SDAI were significantly improved than those at baseline (3.42 and 11.6, p=0.0029 and

0.0007, respectively). Clinical response was evaluated as achievement of DAS remission (DAS<2.6), and we classified 4 patients (24%) in whom DAS remission was achieved at week 12 as "responders". The US assessment at week 2 was compared between CZP-treated patients (responders vs non-responders at week 12). At week 2, three patients out of responders (75%) showed marked reduction of PDUS score to less than 50% of baseline (PDUS 50 response). By contrast, in the 13 patients of non-responders at week 12, only one patient (7.7%) attained PDUS 50 response. Thus, in responders at week 12, the proportion of early US responders (PDUS 50 response at week 2) was significantly higher than that in non-responders (75% vs 7.7%, p=0.0223).

Conclusion: Early response to CZP in patients with RA were confirmed by US examination. Early US assessment of synovitis can predict future clinical response in CZP treatment.

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Abstract Number: 442

Use of Adjunctive Neuroregulatory Medication to Improve Etanercept Treatment Response for Patients with Inflammatory Arthritis: A Pilot Study

Andrew Holman[1] and Edmund Ng[2], [1]Inmedix, Normandy Park, WA, [2]Statistical Thinking, Seattle, WA
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SESSION INFORMATION
Session Date: Sunday, November 8, 2015
Session Title: Rheumatoid Arthritis - Clinical Aspects Poster I
Session Type: ACR Poster Session A
Session Time: 9:00AM-11:00AM

Background/Purpose: As a proposed inflammatory biomarker for autoimmune disease[1,2], the autonomic nervous system (ANS) has been assessed as a predictor of anti-TNF treatment outcome[3] and as an adjunctive therapeutic target[4-6] to elevate a stagnant remission rate in rheumatoid arthritis which has languished at 27% by ACR70 response[7] for many years.

Methods: This retrospective, community-based study assessed consecutive patients initiating biologic treatment of inflammatory arthritis. In an effort to improve outcome by 28-joint count (swollen and tender), neuroregulatory medications, many of which reduce ANS sympathetic tone, were added to etanercept for patients exhibiting an incomplete therapeutic response to traditional immunosuppression (etanercept combined with DMARDs, prednisone and/or NSAID). Statistical analysis included t-test and logistic regression.

Results: Sixty-six patients (70% female, mean age of 50.8±13.0 years, mean duration of disease 9.7±6.4 years, mean prior DMARD use 2.3±1.4, mean ESR 26.6±27.8) initiated etanercept at 25mg BIW for treatment of their inflammatory joint disease (39 seropositive rheumatoid, 13 seronegative rheumatoid, 14 psoriatic arthritis by ACR criteria). All but five continued etanercept for a mean 20.7±7.7 months for an etanercept retention rate of 92%. Three subjects discontinued for personal reasons, one died of unrelated issues and one was lost to follow-up. Overall, initial joint count decreased after addition of etanercept from 11.6 to 1.3 with 79% achieving >=70% reduction in joint count by LOCF (74% by BOCF).

Baseline doses of prednisone and methotrexate were 6.7 mg/d (n=42) and 19.14 mg/wk (n=32), respectively. Ultimately, prednisone was discontinued in 62% (26 of 42); methotrexate was discontinued in 75% (24 of 32); other DMARDs were discontinued in 79% (22 of 28); and NSAIDs were discontinued in 48% (14 of 29). Neuroregulatory medications were used by 36 subjects (55%), including lorazepam 1-2 mg po qhs (18%), clonazepam 1-2 mg po qhs (15%), pramipexole 0.5-4.5 mg po qhs (29%), trazodone 50-100 mg po qhs (21%), other antidepressants (14%), and anti-epileptics (1%). Regression analysis was unable to identify any factor beyond the frequent use of neuroregulatory medications able to reconcile the clinical treatment response to etanercept seen in this cohort relative to historical etanercept treatment outcomes.

Conclusion: Pure ANS therapies, such as vagal nerve stimulation, are already in human RA trials. Although uncontrolled, this data continues to suggest the relevance of further inquiry into the potential benefit of employing an adjunctive neuroregulatory ANS strategy to improve outcomes with immunosuppressive therapies.

1. Elenkov IJ et al Pharmacological Reviews 2000;52:595-638. 2. Koopman FA et al Mol Med 2011;17(9-10):937-948. 3. Holman AJ et al *Autonomic Neurosci Basic Clinical* 2008 Dec 5;143(1-2):58-67. 4. Koopman FA et al ACR 2012 abstract #451. 5. Shimizu M et al ACR 2003 abstract #114 6. Bencherif M et al Mol Life Sci. 2011;68(6):931-949. 7. Moreland LW et al J Rheum 2006 May;33(5):854-61.

Disclosure: A. Holman, Inmedix, 4; **E. Ng**, Inmedix, 5.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/use-of-adjunctive-neuroregulatory-medication-to-improve-etanercept-treatment-response-for-patients-with-inflammatory-arthritis-a-pilot-study

Abstract Number: 443

Drug Survival and Reasons for Discontinuation of Biological Disease Modifying Antirheumatic Drug in Thai Patients with Rheumatoid Arthritis: Analysis from the Thai Rheumatic Disease Prior Authorization (RDPA) Register

Pongthorn Narongroeknawin[1], Wanruchada Katchamart[2], Parawee Suwannalai[3], Nuntana Kasitanon[4], Tasanee Kitumnuaypong[5], Ajanee Mahakkanukrauh[6] and Boonjing Siripaitoon[7], [1]Rheumatic Disease Unit, Department of Internal Medicine, Phramongkutklao Hospital and Phramongkutklao College of Medicine, Bangkok, Thailand, [2]Division of Rheumatology, Department of Medicine, Faculty of Medicine Siriraj hospital, Mahidol University, Bangkok, Thailand, [3]Division of Allergy, Immunology and Rheumatology, Department of Medicine, Faculty of Medicine Ramathibodi Hospital, Mahidol University, Bangkok, Thailand, [4]Division of Rheumatology, Department of Internal Medicine, Faculty of Medicine, Chiang Mai University, Chiang Mai, Thailand, [5]Rheumatology Unit, Department of Internal Medicine, Rajavithi Hospital, Bangkok, Thailand, [6]Division of Allergy, Immunology and Rheumatology, Department of Medicine, Faculty of Medicine, Khon Kaen University, Khon Kaen, Thailand, [7]Division of Rheumatology, Department of Medicine, Faculty of Medicine, Prince of Songkla University, Songkla, Thailand
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SESSION INFORMATION

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Session Title: Rheumatoid Arthritis - Clinical Aspects Poster I

Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose:

To evaluate long-term efficacy and safety of biological disease modifying antirheumatic drug (bDMARD) in real-life practice and identify risk factors related to remission and drug discontinuation in rheumatoid arthritis (RA) patients.

Methods:

Two hundred and fifty-six patients fulfilling 1987 ACR or 2010 ACR/EULAR classification criteria for RA and starting bDMARD between December 2009 and October 2014 were selected from the RDPA register. Baseline demographic and clinical data were retrieved. The cumulative probability of bDMARDs discontinuation over 5 years of follow-up and factors associated with remission and bDMARDs withdrawals was analyzed.

Results:

Almost half (46%) of patients were initially treated with rituximab (RTX), followed by etanercept (ETN) 33% and infliximab (IFX) 21%. Less than 10% of patients were subsequently switched to a second bDMARD (ETN to RTX 62.5%, IFX to RTX 33.3% and RTX to IFX 4.2%). In patients who continued using the first bDMARDs, remission had been achieved in 7.2% and 21.5% at 1 year and 5 years, respectively. In multivariate analysis, the factor predicting remission from first bDMARD was male gender with hazard ratio (HR) 1.9 (95%CI 1.05-3.45). At 3 years follow-up, the drug survival rates were 67%, 44%, and 37% for RTX, ETN, and IFX, respectively. The probability of bDMARD continuation during 5 year of follow-up is shown in figure. In multivariate analysis, RTX was significantly associated with highest drug survival. Hazard ratio for drug discontinuation were 2.60 (95%CI 1.53-4.42) for IFX and 2.15 (95%CI 1.36-3.42) for ETN compared to RTX.

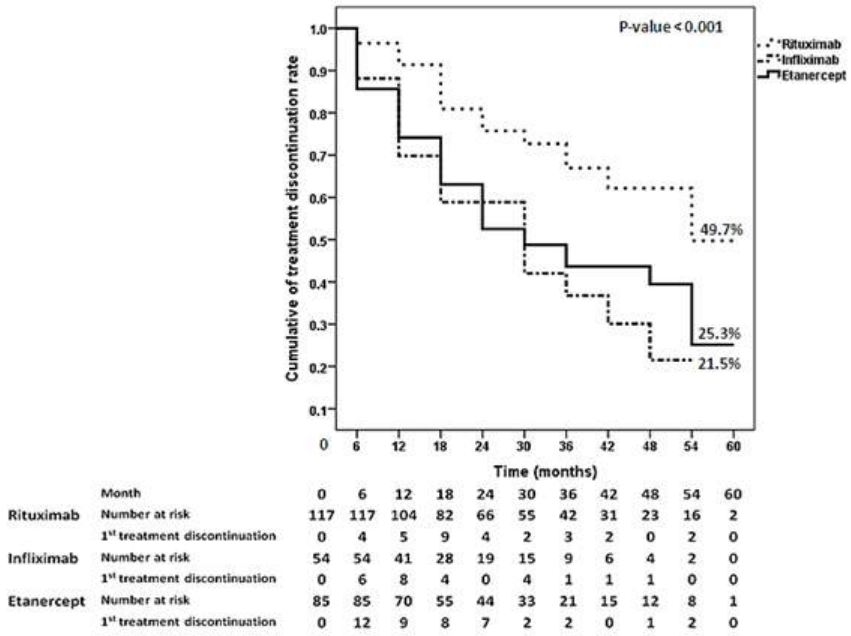
Thirty-nine percent of patients stopped treatments, due to inadequate response (42%), serious adverse event (SAE) (22%), non-adherence (14%), and remission/low disease activity (13%). SAE comprised of non-mycobacterium infection (32%), mycobacterium infection (24%) and malignancy (12%). There were 5 deaths (4/5 in RTX group) because of lung cancer, community-acquired pneumonia, aspiration pneumonia, hepatitis B virus infection, and sudden cardiac arrest.

Conclusion:

During 5 years of follow-up, 61% of patients continued using the first bDMARD. The leading cause of drug discontinuation was inadequate response. Non-mycobacterium infection was the most common SAE.

Financial support:

This study was supported by the Thai Rheumatism Association.



	Month	0	6	12	18	24	30	36	42	48	54	60
Rituximab	Number at risk	117	117	104	82	66	55	42	31	23	16	2
	1st treatment discontinuation	0	4	5	9	4	2	3	2	0	2	0
Infliximab	Number at risk	54	54	41	28	19	15	9	6	4	2	0
	1st treatment discontinuation	0	6	8	4	0	4	1	1	1	0	0
Etanercept	Number at risk	85	85	70	55	44	33	21	15	12	8	1
	1st treatment discontinuation	0	12	9	8	7	2	2	0	1	2	0

Figure. Drug survival rate for biological disease modifying antirheumatic drugs

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Disclosure: P. Narongroeknawin, None; **W. Katchamart**, None; **P. Suwannalai**, None; **N. Kasitanon**, None; **T. Kitumnuaypong**, None; **A. Mahakkanukrauh**, None; **B. Siripaitoon**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/drug-survival-and-reasons-for-discontinuation-of-biological-disease-modifying-antirheumatic-drug-in-thai-patients-with-rheumatoid-arthritis-analysis-from-the-thai-rheumatic-disease-prior-authorizatio

Abstract Number: 444

TNF Inhibitor Use Across Countries in Two Time Periods Using the Meteor Database

Karen Salomon-Escoto[1], Nisha Kini[1], Sharina D. Person[1], J.A.P. da Silva[2], Gianfranco Ferraccioli[3], T. W. J. Huizinga[4], Robert B.M. Landewé[5], RJ Moots[6], D. van der Heijde[7], Douglas J. Veale[8], Ellen M. Gravallese[1] and Jonathan Kay[1], [1]University of Massachussets Medical School, Worcester, MA, [2]Centro Hospitalar e Universitário de Coimbra - Hospitais da Universidade de Coimbra, EPE, Coimbra, Portugal, [3]Rheumatology and Internal Medicine, Catholic University of the Sacred Heart, Rome, Italy, [4]Rheumatology, Department of Rheumatology, Leiden University Medical Center, Leiden, Netherlands, [5]Department of Rheumatology, Amsterdam Rheumatology Center, Amsterdam, Netherlands, [6]Department of Musculoskeletal Biology, University of Liverpool, Liverpool, United Kingdom, [7]Department of Rheumatology, Leiden University Medical Center, Leiden, Netherlands, [8]Dublin Academic Medical Centre, Translational Rheumatology Research Group, Dublin, Ireland

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SESSION INFORMATION

Session Date: Sunday, November 8, 2015

Session Title: Rheumatoid Arthritis - Clinical Aspects Poster I

Session Type: ACR Poster Session A

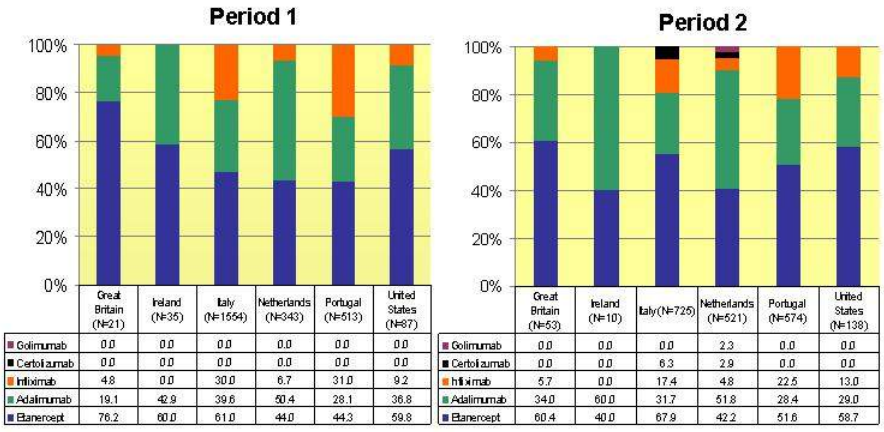
Session Time: 9:00AM-11:00AM

Background/Purpose: Biologic agents are effective treatment for rheumatoid arthritis (RA), but factors exist that may influence the prescription of these drugs in different countries. We compared the prescription of TNF inhibitors (TNFi) among RA patients during two time periods by rheumatologists in Great Britain, Ireland, Italy, the Netherlands, Portugal, and the US who used the METEOR database. We hypothesized that the relative distribution of TNFi prescriptions for RA may vary among countries with different healthcare systems.

Methods: The international online Measurement of Efficacy of Treatment in the Era of Outcome in Rheumatology (METEOR) database is used at 124 hospitals in 38 countries and contains demographic and clinical data about >32,000 RA patients. This database was queried to compare use of TNFi (infliximab, etanercept, adalimumab, certolizumab pegol, and golimumab) during two one-year periods: July 2009-June 2010 (Period 1) and July 2011-June 2012 (Period 2). Data were extracted for 2553 patients in Period 1 and 2021 patients in Period 2. We compared TNFi use across the five countries separately for each time period. For each country, we also compared TNFi use during Period 1 to that during Period 2. A chi-square test was used to calculate significance, Fisher's exact test was used to analyze cell size <5 and SAS 9.3 was used for all analyses.

Results: Relative use of each TNFi differed significantly across all countries within each time period ($p<0.0001$). Comparing TNFi use at US sites to sites in EU countries combined, infliximab was prescribed significantly less at US sites (9.2% vs. 25.7%, $p<0.0001$) for Period 1. Use of other TNFi did not differ significantly for either time period between US sites and all EU sites combined. When TNFi use was compared across the two time periods, use of infliximab and adalimumab was significantly lower (17.3% vs. 29.9%, $p<0.0001$, and 31.7% vs. 39.5%, $p=0.0003$, respectively) and use of etanercept was significantly higher (67.8% vs.61.0%, $p=0.0015$) in Italy during Period 2, compared to Period 1. In Portugal, infliximab use was significantly lower (22.4% vs. 30.9%, $p=0.0015$) and etanercept use was significantly higher (51.5% vs. 44.2%, $p = 0.0159$) during Period 2, compared to Period 1. Otherwise, relative prescription of individual TNFi did not differ significantly across the two time periods in any other countries.

<>Image/graph:



Conclusion: The relative prescription of various TNFi, as recorded in the METEOR database, differed significantly across several EU countries and the US during two distinct time periods. Infliximab was prescribed significantly more often than other TNFi at sites in those EU countries examined compared to the US sites in period 1. In Italy and Portugal, etanercept was prescribed significantly more than other TNFi in period 2, compared to period 1. Further study is warranted to identify factors that drive the different TNFi prescribing patterns in these countries.

Disclosure: K. Salomon-Escoto, None; **N. Kini**, None; **S. D. Person**, None; **J. A. P. da Silva**, None; **G. Ferraccioli**, None; **T. W. J. Huizinga**, None; **R. B. M. Landewé**, None; **R. Moots**, AbbVie, 5,BMS, 5,Celgene, 5,Chugai,

5,Hospira, 5,MSD, 5,Napp, 5,Pfizer Inc, 5,Roche Pharmaceuticals, 5,USB Pharma, 5; **D. van der Heijde**, None; **D. J. Veale**, None; **E. M. Gravallese**, None; **J. Kay**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/tnf-inhibitor-use-across-countries-in-two-time-periods-using-the-meteor-database

Abstract Number: 445

Persistence with Biologic Monotherapy in Comparison with Combination Therapy with Disease-Modifying Antirheumatic Drugs in Patients with Rheumatoid Arthritis; Results from a Rheumatoid Arthritis Cohort

Arthur Lau[1], Mohammad Movahedi[2,3], Mark Tatangelo[4], Claire Bombardier[3,5,6] and OBRI investigators, [1]Division of Rheumatology, McMaster University, Hamilton, ON, Canada, [2]JSS Medical Research, St-Laurent, QC, Canada, [3]Toronto General Hospital Research Institute, University Health Network, Toronto, ON, Canada, [4]Clinical Decision Making and Health Care, Toronto General Hospital Research Institute, University Health Network, Toronto, ON, Canada, [5]University of Toronto, Department of Medicine (DOM) and Institute of Health Policy Management, and Evaluation (IHPME), Toronto, ON, Canada, [6]Division of Rheumatology, Mount Sinai Hospital, Toronto, ON, Canada
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SESSION INFORMATION
Session Date: Sunday, November 8, 2015
Session Title: Rheumatoid Arthritis - Clinical Aspects Poster I
Session Type: ACR Poster Session A
Session Time: 9:00AM-11:00AM

Background/Purpose:

Clinical evidence suggests concomitant treatment with a biologic Disease-Modifying Antirheumatic Drug (bDMARD) and a conventional synthetic DMARD (csDMARD), especially with methotrexate (MTX) has greater efficacy than treatment with a bDMARD as monotheapy in patients with rheumatoid arthritis (RA). However, not all patients are able to tolerate a csDMARD. Our objective was to compare the persistence of a bDMARD used as monotherapy, versus combination therapy in patients with active RA.

Methods:

Physician data were collected from the Ontario Best Practices Research Initiative Rheumatoid Arthritis Registry (OBRI- RA), a clinical registry of RA patients followed in routine care. Inclusion criteria comprised of patients over age 18 years, active RA (defined as ³1 swollen joint) and started on their 1st bDMARD within 30 days before registry enrolment, or started after enrolment. Combination therapy was defined as treatment with a bDMARD plus at least one csDMARD, while monotherapy was defined as treatment with only a bDMARD.

The primary outcome was persistence with 1st bDMARD therapy, which was defined as the length of time the patients continued to receive their first bDMARD therapy. Persistence treatment was examined using Kaplan-Meier survival analysis. Patients were censored at date of 1st bDMARD stop, switch to another bDMARD or at date of last follow-up, whichever came first.

Results:

Among 2591 RA patients, 701 patients started their 1st bDMARD within 30 days before cohort enrolment or after

enrolment with the mean (standard deviation) of follow-up 1.9 (1.6) person-years. A total of 598 (85.3%) patients were on combination therapy, and 103 (14.7%) patients were on monotherapy. At baseline, there was a similar mean age, proportion of females between the two groups. A TNFα inhibitor was the biologic used in 22.6% and 14.5% of the monotherapy and combination group respectively.

The mean time to failure of 1st bDMARD was 4.3 years (95%CI: 3.7-4.9) and 4.6 years (95%CI: 4.3-4.8) in the monotherapy and combination group respectively. At 12 months follow-up, 74% (95%CI: 64-81) in the monotherapy group and 81% (95%CI: 77 -84) in the combination group remained on their first bDMARD (table 1).

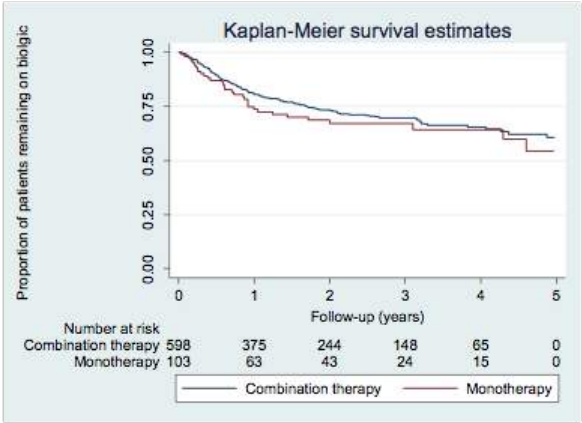
Conclusion:

Our study demonstrates that a higher proportion of patients on monotherapy failed therapy at 12 months, and the mean time to treatment failure was shorter with monotherapy, but these results were not statistically significant. Although combination therapy is recommended, these real-world results suggest that patients who are unable/unwilling to continue on a csDMARD, bDMARD monotherapy can still provide an efficacious option.

Table 1: Survival function (95% CI) for patients stopping their initial bDMARD therapy by year of follow-up for the monotherapy versus combination group in patients with active rheumatoid arthritis

Time (year)	Whole cohort N=701	Monotherapy N=103	Combination therapy N=598
1	0.80 (0.76-0.83)	0.74 (0.64-0.81)	0.81 (0.77-0.84)
2	0.72 (0.69-0.76)	0.67 (0.56-0.76)	0.73 (0.69-0.77)
3	0.69 (0.65-0.73)	0.67 (0.56-0.76)	0.70 (0.65-0.74)
4	0.65 (0.61-0.70)	0.64 (0.52-0.74)	0.66 (0.60-0.70)
5	0.60 (0.53-0.65)	0.55 (0.38-0.69)	0.61 (0.54-0.67)

Figure 1: Time to failure of 1st bDMARD therapy in monotherapy group versus combination group in patients with active rheumatoid arthritis.



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Abstract Number: 446

Low Disease Activity at 12 Weeks and 24 Weeks Is Predictive of Normalized Health-Related Quality of Life in Methotrexate-Experienced Patients with Active Rheumatoid Arthritis Treated with Intravenous

Golimumab Plus Methotrexate

Clifton O. Bingham III[1], Michael Weinblatt[2], Rene Westhovens[3], Lilianne Kim[4], Chenglong Han[5], Stephen Xu[4], Kim Hung Lo[4], Kezhen L. Tang[4], Elizabeth C. Hsia[4,6], Dennis Parenti[7] and Shelly Kafka[7], [1]Rheumatology, Johns Hopkins University, Baltimore, MD, [2]Brigham and Women's Hospital, Boston, MA, [3]UZ Gasthuisberg, Leuven, Belgium, [4]Janssen Research & Development, LLC, Spring House, PA, [5]Janssen Global Services, LLC, Malvern, PA, [6]University of Pennsylvania, Philadelphia, PA, [7]Janssen Scientific Affairs, LLC, Horsham, PA
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Session Title: Rheumatoid Arthritis - Clinical Aspects Poster I
Session Type: ACR Poster Session A
Session Time: 9:00AM-11:00AM

Background/Purpose: Previous analyses in patients (pts) with rheumatoid arthritis (RA) have evaluated the relationship between controlling disease activity and achieving long-term improvements in health-related quality of life (HRQoL) using the DAS28 or ACR20 to assess clinical response. However, the clinical disease activity index (CDAI) is more commonly used among community practicing rheumatologists. This analysis examined the predictive value of achieving low disease activity (CDAI≤10) and normalization of long-term HRQoL.

Methods: In the phase 3 GO-FURTHER trial, 592 pts with active RA despite MTX therapy were randomized (2:1) to IV golimumab (GLM) 2mg/kg+MTX or placebo (PBO)+MTX at wks 0 and 4, then q8w; PBO pts crossed over to GLM at wk16 (early escape) or wk24 (crossover). In this post-hoc analysis, disease activity was measured using the CDAI, and HRQoL was assessed using patient-reported outcomes: FACIT-Fatigue, HAQ-DI, and SF-36 physical/mental component summary (PCS/MCS) scores and individual domain scores. Normalization of HRQoL (based on the means for the general population) was defined as follows: FACIT-Fatigue ≥43.6, HAQ-DI ≤0.5, and SF-36 PCS/MCS and domain scores ≥50. Logistic regression analyses (adjusted for gender, age, current smoking status, and baseline CDAI score and PRO assessments) were performed to evaluate the relationship between achieving low disease activity (CDAI ≤10) and normalization of HRQoL at each time point through 2 years. Additionally, the predictive value of achieving CDAI≤10 at wk12 and wk24 and normalization of HRQoL at 1 year and 2 years was also assessed.

Results: Greater proportions of pts in the IV GLM 2mg/kg+MTX group achieved CDAI ≤10 compared with the PBO+MTX group at wk12 (19.6% vs 9.8%; p=0.0026) and wk24 (38.2% vs 18.5%; p<0.0001) (PBO-controlled period). Achieving a CDAI ≤ 10 was strongly associated with normalized HAQ-DI, FACIT-Fatigue, SF-36 PCS/MCS scores and SF-36 domain scores at each time point through 2 years (p<0.0001 for most variables). Pts who achieved CDAI ≤10 at wk12 or wk24 were more likely to achieve normalized HAQ-DI, FACIT-Fatigue, SF-36 PCS/MCS scores, and SF-36 domain scores at 1 year than were pts with CDAI >10 (Odds ratio [OR] range: 1.8-5.9 and 1.7-6.6, respectively). Similar results were observed for pts with CDAI ≤10 at wk12 or wk24 and normalized HRQoL at 2 years (OR range: 2.2-4.6 and 2.0-3.7, respectively).

Conclusion: Greater proportions of GLM+MTX pts achieved CDAI ≤10 at wks 12 and 24 compared with PBO+MTX. Achieving low disease activity (CDAI ≤10) at either wk12 or wk24 was predictive of achieving normalized HAQ-DI, FACIT-Fatigue, SF-36 PCS/MCS scores, and SF-36 component scores at 1 year and 2 years in pts with active RA.

Disclosure: C. O. Bingham III, Janssen Research & Development, LLC., 2,Janssen Research & Development, LLC., 5; **M. Weinblatt**, Janssen Research & Development, LLC., 5; **R. Westhovens**, Janssen Research & Development, LLC., 5; **L. Kim**, Janssen Research & Development, LLC, 3; **C. Han**, Janssen Global Services, LLC, 3; **S. Xu**, Janssen Research & Development, LLC, 3; **K. H. Lo**, Janssen Research & Development, LLC, 3; **K. L. Tang**, Janssen Research & Development, LLC, 3; **E. C. Hsia**, Janssen Research & Development, LLC, 3; **D. Parenti**, Janssen Scientific Affairs, LLC, 3; **S. Kafka**, Janssen Scientific Affairs, LLC, 3.

Abstract Number: 447

Components of Treatment Delay in Rheumatoid Arthritis Differ According to Autoantibody Status

Arthur G Pratt[1], Ben Hargreaves[2], Dennis W Lendrem[2], Osman Aslam[2] and John D Isaacs[2], [1]Institute of Cellular Medicine (Musculoskeletal Research Group), National Institute for Health Research Newcastle Biomedical Research Centre based at Newcastle Hospitals Foundation Trust and Newcastle University, Newcastle upon Tyne, United Kingdom, [2]Institute of Cellular Medicine (Musculoskeletal Research Group), NIHR Newcastle Biomedical Research Centre, Newcastle Hospitals Foundation Trust and Newcastle University, Newcastle upon Tyne, United Kingdom

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Session Time: 9:00AM-11:00AM

Background/Purpose:

Despite a proliferation of early arthritis (EA) clinics intended to expedite the diagnosis of rheumatoid arthritis (RA), patients continue to experience substantial and multifactorial delays between symptom onset and treatment initiation. In this study we determined whether time to treatment following symptom onset differs between rheumatoid arthritis (RA) patients according to autoantibody status.

Methods:

A single-centre retrospective analysis of a UK early RA inception cohort was undertaken to identify those components of the “patient journey” that differed by serological sub-type. Where available, the components studied included (i) symptom onset to assessment in primary care, (ii) primary care assessment to secondary care rheumatology referral, (iii) rheumatology referral to rheumatology assessment, and (iv) rheumatology assessment to disease modifying anti-rheumatic drug (DMARD) initiation. Non-parametric ANOVA were used to compare groups, and time-to-event data were analysed using Kaplan-Meier survival plots.

Results:

173 RA patients were diagnosed over a 31 month period, of whom 80 (46%) were anti-citrullinated peptide antibody / rheumatoid factor “double-seropositive” (ACPA+/RF+), 53 (31%) ACPA-/RF-, 17 (10%) ACPA+/RF- and 23 (13%) RF+/ACPA-. Overall, ACPA+/RF+ patients experienced significantly longer symptom duration before disease modifying anti-rheumatic drug (DMARD) initiation (p=0.006). This was accounted for by delays in their presentation to primary care following symptom onset (Figure 1A). By contrast, ACPA-/RF- patients were significantly more likely to experience delays in DMARD initiation after presenting to secondary care (Figure 1B).

Conclusion:

Causes of treatment delays in early RA differ according to patients' autoantibody status. More insidious symptom onset and/or distinct health-seeking behaviours amongst ACPA+/RF+ patients may contribute to late presentations in primary care, whereas ACPA-/RF- patients experience delayed diagnosis and treatment in secondary care. These observations

could inform future design of service delivery for early arthritis patients.

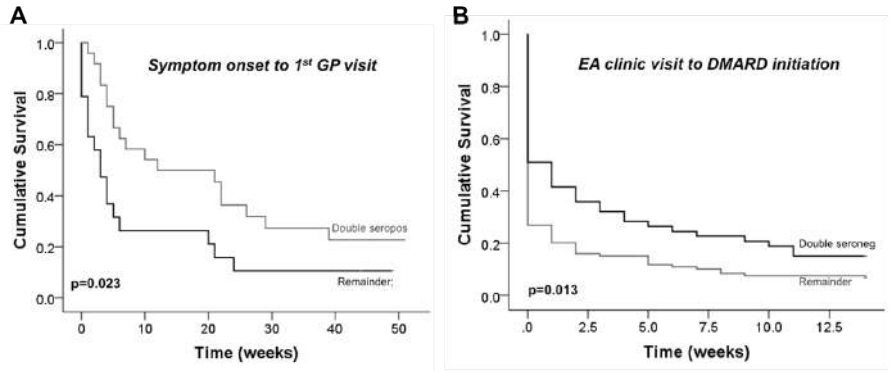

Figure 1. "Survival" from (A) symptom onset to 1st primary care visit and (B) 1st EA clinic consultation to DMARD initiation, stratified by autoantibody status as indicated.

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Abstract Number: 448

A Majority of Early Rheumatoid Arthritis (ERA) Patients Reach Remission By 6 Months in Usual Rheumatology Care

Tuomas Rannio[1], Juha Asikainen[2], Pekka Hannonen[3], Timo Yli-Kerttula[4], Päivi Ekman[5], Laura Pirilä[6], Markku Mali[7], Laura Kuusela[7], Maija Puurtinen-Vilkki[7], Saara Kortelainen[8], Johanna Paltta[7], Kirsi Taimen[7], Heidi Mäkinen[9], Pia Isomäki[9], Terhi Uotila[9], Markku J. Kauppi[10], Kari Laiho[11], Satu Nyrhinen[11], Tuulikki Sokka-Isler[1] and FIN-ERA study group, [1]Rheumatology, Jyvaskyla Central Hospital, Jyvaskyla, Finland, [2]Jyväskylä Central Hospital, Jyväskylä, Finland, [3]Jyvaskyla Central Hospital, Jyvaskyla, Finland, [4]Sairaalantie 3, Central Hospital of Satakunta, Pori, Finland, [5]Central Hospital of Satakunta, Pori, Finland, [6]Tyks, P.O. Box 52, Turku University Central Hospital, Turku, Finland, [7]Turku University Central Hospital, Turku, Finland, [8]Alvar Aallontie 275, Turku University Central Hospital, Turku, Finland, [9]Tampere University Hospital, Tampere, Finland, [10]Department of Rheumatology, Päijät-Häme Central Hospital, Lahti, Finland, [11]Päijät-Häme Central Hospital, Lahti, Finland
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Background/Purpose: Finnish national combination treatment trials have demonstrated excellent outcomes in patients with ERA including 90% of patients reaching DAS28 remission at 6 months. Whether similar results are reached in

clinical praxis are not known. We herein report characteristics, disease activity and DAS28 remission rates at 6 months in ERA patients treated in 5 Finnish outpatient clinics.

Methods: FIN-ERA is the first national multicenter observational cohort of adult patients with early inflammatory arthritis, clinically diagnosed as RA between Oct 2011 and Sep 2014. Data comprising demographic, clinical and treatment characteristics were collected as a part of routine care. Treatment decisions were made by treating rheumatologists with cooperation with the patient. Finnish treatment recommendations emphasize early and active therapy with combination of csDMARDs and prednisolone starting at the diagnosis, and unlimited glucocorticoid injections to all swollen joints.

Results: Out of 605 recruited patients, 566 completed baseline, 3 and 6 months visit and had full data for disease activity score (DAS28-3) with ESR. In the entire cohort, the mean age was 56±16 yrs, the median (IQR) duration of symptoms was 6(3,11) mo, rheumatoid factor (RF) and anti cyclic-citrullinated peptide antibodies (anti-CCP) were evident in 68% and 69%, respectively. At baseline, a total of 23% of patients had radiographic erosions. A total of 484 (86%) fulfilled the ACR/EULAR 2010 classification criteria for RA at baseline. Figure 1 represents the mean DAS28-3 for RA patients at baseline, 3 mo and at 6 mo at FIN-ERA clinics A-E. The respective mean HAQ and DAS28 (with ESR, 4 variables,DAS28-4) at baseline were 1.0±0.7 (data for 83%) and 4.3±1.4 (data for 88%). The corresponding values for HAQ and DAS28-4 at 6 mo were 0.4±0.5 (data for 86%) and 2.1±1.1 (data for 93%). A total of 73% met DAS28-4 remission at 6 mo. Remission rates were similar in patients classified as undifferentiated arthritis (14% of the cohort), and did not differ significantly according to serology. A total of 57% of ERA patients were in sustained DAS28-4 remission at 3 and 6 mo. Figure 2 represents DAS28-4 remission rates at 3 and 6 mo at 5 FIN-ERA clinics. In a multivariate model, lower disease activity at baseline and male gender predicted remission (DAS28-3<2.6) at 6 mo, while age, RF/anti-CCP, erosiveness, or clinic remained statistically unsignificant. A total of 75% received MTX based combination csDMARD therapy at baseline, and 1.4% bDMARDs within 6 mo.

Conclusion: A majority of ERA patients reach early and sustained DAS28 remission in Finland.

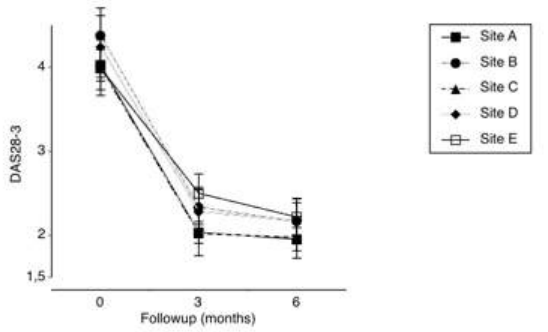

Figure 1. DAS28-3 (mean, 95% CI) in patients with early RA in 5 FIN-ERA clinics

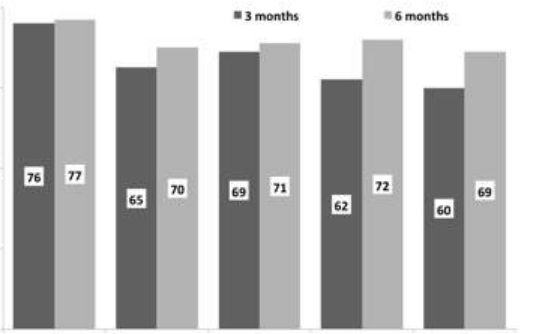

Figure 2. DAS28-4 remission rates at 5 FIN-ERA sites (P = n.s. between sites, χ2-test)

Disclosure: T. Rannio, None; **J. Asikainen**, None; **P. Hannonen**, None; **T. Yli-Kerttula**, None; **P. Ekman**, None; **L. Pirilä**, None; **M. Mali**, None; **L. Kuusela**, None; **M. Puurtinen-Vilkki**, None; **S. Kortelainen**, None; **J. Paltta**, None; **K. Taimen**, None; **H. Mäkinen**, None; **P. Isomäki**, None; **T. Uotila**, None; **M. J. Kauppi**, None; **K. Laiho**, None; **S. Nyrhinen**, None; **T. Sokka-Isler**, None.

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Abstract Number: 449

Change from SC to IV Abatacept and Back in Patients with Rheumatoid Arthritis As Simulation of a Vacation: A Prospective Phase IV, Open Label Trial (A-BREAK)

Ruediger Mueller[1], Michael Gengenbacher[2], Symi richter[3], Jean Dudler[4], Burkhard Moeller[5] and Johannes von Kempis[6], [1]Rheumatology, MD, St. Gallen, Switzerland, [2]Bethesdaspital, Basel, Switzerland, [3]Bethsdaspital, Basel, Switzerland, [4]Kantonsspital Fribourg, Fribourg, Switzerland, [5]Rheumatology, Inselspital-University Hospital, Bern, Switzerland, [6]Rheumatology, Kantonsspital St. Gallen, St. Gallen, Switzerland

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Session Title: Rheumatoid Arthritis - Clinical Aspects Poster I

Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose:

Holiday seasons can present a major problem to RA patients treated with weekly subcutaneous biologics, including subcutaneous (SC) abatacept. Therefore an evaluation of the use of IV-abatacept treatment to cover a 4-week break may present an acceptable alternative.

Objective:

To study the efficacy and safety of a single intravenous (IV) course with abatacept in Patients with rheumatoid arthritis currently receiving weekly injections of SC abatacept to simulate a patient “vacation” followed by a switch back to SC abatacept.

Methods:

This open label, prospective, single arm 24-weeks trial recruited patients with established RA and in low disease activity (LDA) under treatment with SC abatacept for at least 3 months to receive a single dose of IV abatacept (day 0) and to be continued on SC abatacept from day 28 on (NCT01147341). DMARD- and/or biologic-inadequate responders were included and previous exposure to IV abatacept was allowed in a maximum of 50% of the patients.

Results:

Baseline characteristics of the 49 patients (per protocol) were typical for a cohort of RA patients with established disease (mean disease duration 8.31 years) in LDA under treatment. Two patients dropped out of the study (1 flare, 1 patient decision). The proportion of patients with DAS 28 $\leq$3.2 at day 28 was 93.9% (95%CI 83.5-97.9) at day 28, 91.7% (95%CI 80.4-96.7) at day 84 and 93.6 (95%CI 82.8-97.8) at the end of the study, day 168. This proportion

remained stable throughout the entire follow up. The average DAS 28 at baseline was 1.74 (SD ±0.72) at baseline, 2.03 (SD ±1.03) at day 28, 1.86 (SD ±0.91) at day 84 and 1.96 (SD ±0.92) at the end of the study, day 168. Pre-exposure to IV abatacept and having failed MTX or anti TNF did not influence the average DAS 28 or the proportion of patients maintaining LDA. The average HAQ-DI was stable throughout the study. Adverse events occurred in 75% of subjects. Four serious adverse events (SAE) were described during the study. None of them was related to the investigational product and all SAE could be resolved during hospitalization. Discontinuation of abatacept was not necessary in these patients. There were no deaths, neoplasms, and opportunistic or other serious infections (intention to treat).

Conclusion:

This prospective, open label study of abatacept shows for the first time that switching from weekly SC to IV abatacept and back after 4 weeks is an effective and safe way to bridge holidays in RA patients in LDA.

Disclosure: R. Mueller, Bristol-Myers-Squibb, Princeton, NJ, USA, 2; **M. Gengenbacher**, None; **S. richter**, None; **J. Dudler**, None; **B. Moeller**, None; **J. von Kempis**, Bristol-Myers-Squibb, Princeton, NJ, USA, 2.

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Abstract Number: 450

Use of Tofacitinib in a Real World Setting: Clinical Features in a Cohort of Patients Using the Database Jointman Compared to a Published Clinical Trial

Sergio Schwartzman[1], Keith Knapp[2], Gary Craig[3], Karen Ferguson[4] and Howard Kenney[5], [1]Rheumatology, Hospital for Special Surgery, New York, NY, [2]Arthritis Northwest, Spokane, WA, [3]Discus Analytics, Inc., Spokane, WA, [4]Arthritis Northwest PLLC., Spokane, WA, [5]Rheumatology, Arthritis Northwest, Spokane, WA

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Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose:

It is well accepted that patients studied in pharmaceutically sponsored clinical trials do not always represent the types of patients seen in clinical practice. Therefore, a description of clinical and laboratory data of patients in community practice may provide important and perhaps unique information.

The purpose of this analysis is to characterize the type of patients in a real world (RW) setting receiving tofacitinib (TFA) using the rheumatoid arthritis (RA) registry, JointMan® (JM). This database was launched in 2009 with a mission to provide a practical outcome tool to manage patients with RA in a traditional office based clinical setting.

Methods:

This is a descriptive, observational study comparing the patient characteristics of a clinical office based population of

patients enrolled in JM to the ORAL Step study (OS), a pharmaceutically sponsored study of TNF-IR patients receiving TFA.

JM captures RA diagnostic criteria and selected disease features, formal joint counts, outcome measures, serology, medication efficacy and safety and reason for discontinuation of medications. OS was chosen as a comparator as this patient cohort was the most comparable to the JM TFA treated group. Data was collected from Nov 2012 to March 31, 2015. Continuous covariates were compared using a T- test; categorical covariates were compared using a chi-square test. Due to the retrospective methodology, complete data was not always available.

Results:

A total of 5700 unique RA patients and 133,000 encounters have been recorded.

Over the study period, there were 156 RA patients newly prescribed TFA. All patients in JM had received at least one anti-TNF agent prior to TFA initiation and the mean number of TNF inhibitor agents used was 1.8. Only 21% of patients in JM were treated with concomitant MTX. The population treated with TFA in the JM was 81% female and in OS 85% (p=0.383). The mean age at start of TFA was 60 in JM whereas in OS it was 54.2 (p=0.004). Patients had a mean duration of disease of 3.8 years in the JM whereas in the OS cohort disease duration was 13.0 years ($P < 0.001$). If a patient lacked a definitive diagnosis date, their first JM assessment date was used. Joint count scoring differed in the two cohorts: 66/68 in OS, 28 in JM. Irrespectively, both groups had a high disease activity as measured by mean CDAI score in JM of 26.7 and DAS 28-4 (ESR) of 6.5 in the OS.

Conclusion:

In this RW setting some patient characteristics were comparable to those seen in published trials. Similar to OS, in JM there was a predominance of females with a similar mean age and patients had high disease activity at initiation of therapy. However, differences were also noted. TFA was used much earlier in the disease course than in OS. Interestingly, TFA was used more commonly as monotherapy in JM than in combination with methotrexate.

Although randomized clinical trials differ markedly from observational studies and there are limitations of both types of studies, important information can be gleaned from such a comparison. The differences in trial designs, selection bias, information bias, confounding by indication, must be considered when interpreting these results.

Disclosure: S. Schwartzman, Discus Analytics, 9,Dascus Analytics, 1,Pfizer Inc, 1,Pfizer Inc, 5,Pfizer Inc, 8; **K. Knapp**, Discus Analytics, 1,Dascus Analytics, 3; **G. Craig**, Discus Analytics, 1,Discus Analytics, 9,Pfizer Inc, 2; **K. Ferguson**, Discus Analytics, 1; **H. Kenney**, Discus Analytics, 1,Discus Analytics, 9,Pfizer Inc, 2.

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Abstract Number: 451

Efficacy of Tofacitinib in a Real World Setting Using the Database Jointman

Sergio Schwartzman[1], Keith Knapp[2], Gary Craig[3], Karen Ferguson[4] and Howard Kenney[5], [1]Rheumatology, Hospital for Special Surgery, New York, NY, [2]Arthritis Northwest, Spokane, WA, [3]Discus Analytics, Inc., Spokane, WA, [4]Arthritis Northwest PLLC., Spokane, WA, [5]Rheumatology, Arthritis Northwest, Spokane, WA

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Background/Purpose:

Tofacitinib (TFA) was approved for the treatment of rheumatoid arthritis (RA) in November of 2012. It is well accepted that patients studied in pharmaceutically sponsored clinical trials do not always represent the types of patients seen in clinical practice. There is limited efficacy data published on real world (RW) patients receiving TFA.

The purpose of this analysis was to assess the efficacy of TFA on patients in a RW setting receiving TFA using the RA registry, JointMan (JM). This database was launched in 2009 with a mission to provide a practical outcome tool to manage patients with RA in a traditional office based clinical setting.

Methods:

This is a descriptive observational efficacy study comparing the outcomes of RA patients on TFA. JM captures RA diagnostic criteria and selected disease features, formal joint counts, DAS 28, CDAI, SDAI, RAPID3, VECTRA, CRP and ESR, Rheumatoid Factor, CCP, medication use, toxicities and reason for discontinuation. Both patient and physician data is collected electronically.

CDAI score was used as the outcome measure to define treatment response. Efficacy was compared from the time of initiation of TFA used to the date to their last active encounter date. The mean average of all patients' CDAI scores at initiation and their last active encounter date were compared using a paired T-Test.

Results:

A total of 5700 unique RA patients and 133,000 encounters have been recorded since 2009. There were 156 RA patients prescribed tofacitinib, of those 91 had multiple JM encounters.

All patients in JM had received at least one anti-TNF agent and the mean number of TNF inhibitor agents used was 1.8. The mean CDAI score at initiation was 25.8 (high disease activity) and at last observation the mean was 19.8 (moderate disease activity). Comparing the means with a paired T-Test resulted in t=3.89 (p=0.002, CI 2.79 to 8.62). The percentage of patients in high disease activity decreased by 21.4 points. The distribution of patients by disease activity are displayed in Table 1. 61% of patients were still on TFA at time of analysis. Mean duration was 212 days. There were 12 missing stop reasons (13%), 32 (35%) had a non-serious adverse event some of whom discontinued therapy and the remainder of patients continued on therapy.

Initial TFA Encounter				
	N	**%**	**SD**	**CI**
High	50	56.2%	9.51	2.64
Moderate	28	31.5%	2.80	1.04
Low	11	12.4%	1.44	0.85
Remission	0	0	N/A	N/A

Last TFA Encounter				
	N	**%**	**SD**	**CI**
High	31	34.8%	9.84	3.46
Moderate	36	40.4%	2.95	0.97
Low	17	19.1%	1.97	0.93
Remission	5	5.6%	0.08	0.07

Conclusion:

The results from this study indicate that patients in a real world setting are prescribed TFA after receiving at least one anti-TNF agent and that TFA reduces disease activity from a CDAI mean of high disease activity to moderate disease

activity over a period of approximately 7 months. Most patients prescribed this agent continue therapy. Additional work is needed to identify which characteristics are critical to define variables predictive of low disease activity and remission.

Disclosure: S. Schwartzman, Discus Analytics, 9,Dascus Analytics, 1,Pfizer Inc, 1,Pfizer Inc, 5,Pfizer Inc, 8; **K. Knapp**, Discus Analytics, 1,Dascus Analytics, 3; **G. Craig**, Discus Analytics, 1,Discus Analytics, 9,Pfizer Inc, 2; **K. Ferguson**, Discus Analytics, 1; **H. Kenney**, Discus Analytics, 1,Discus Analytics, 9,Pfizer Inc, 2.

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Abstract Number: 452

Associations Between Arthritis Patient, Disease-Specific and Provider Characteristics and Medication Information Source Use

Lorie Geryk[1], Susan J. Blalock[2], Robert DeVellis[3], Joanne M. Jordan[3] and Delesha Carpenter[4], [1]Division of Pharmaceutical Outcomes and Policy, University of North Carolina Eshelman School of Pharmacy, Chapel Hill, NC, [2]Eshelman School of Pharmacy, University of North Carolina at Chapel Hill, Chapel Hill, NC, [3]Thurston Arthritis Research Center, University of North Carolina, Chapel Hill, NC, [4]Division of Pharmaceutical Outcomes and Policy, University of North Carolina Eshelman School of Pharmacy, Asheville, NC

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Background/Purpose: Few studies have described how patient, disease-specific, and provider factors are associated with medication information source use among arthritis patients. We address this research gap by describing characteristics associated with arthritis patients' use of 15 medication information sources.

Methods: Adult osteoarthritis or rheumatoid arthritis patients completed an online cross-sectional survey. Patients (n=328) self-reported sociodemographic (i.e., age, gender, race/ethnicity, education level, marital status), clinical (i.e., year of diagnosis, age at diagnosis, arthritis type, current number of arthritis medicines taken, medication adherence, arthritis severity, comorbidities), and sociobehavioral (satisfaction with doctor-provided medication support, medication self-efficacy, and arthritis medication-taking concerns) characteristics. Patients were asked how much medicine information they sought and/or were given from fifteen different information sources (e.g., doctor, Internet, spouse/partner, medicine package inserts) when they are prescribed a new arthritis medicine. Patients' responses (range: 1= "none" to 4= "a lot") were averaged and higher mean scores corresponded to greater medication information source use. Correlations were inspected and covariates significant at the $p \leq 0.05$ level were subsequently examined using multivariable linear regression analyses to investigate whether sociodemographic, clinical, and sociobehavioral factors were associated with medication source use.

Results: On average, patients were 56 years old (±13; range 19–85) and were taking 2.5 arthritis medications. Most patients were female (79%) and white (80%); the median arthritis duration was 11 years. In multivariate analysis, the following independent variables remained significantly positively associated with arthritis medication information source use: always adherent (b = .13, p =.024), more medications taken ((b = .09, p <.0001), more medicine-taking concerns (b = .11, p =.001), more satisfaction with doctor medication support (b = .21, <.007), and Black race (b= .25, =.002).

Conclusion: Information source use varied with patient, clinical, and sociobehavioral factors. These findings have implications for public health efforts related to medication education for arthritis patients.

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Abstract Number: 453

Highly Elevated Rheumatoid Factor Is a Risk Factor for Abatacept Treatment Failure in Japanese Patients with Rheumatoid Arthritis

Shunya Kaneshita[1], Chisun Min[1], Omata Fumio[2], Masei Suda[1], Ryo Rokutanda[1], Hisanori Shimizu[3], Tokutaro Tsuda[1], MItsumasa kishimoto[4], Ken-ichi Yamaguchi[3] and Masato Okada[3], [1]Immuno-Rheumatology Center, St. Luke's International Hospital, Tokyo, Japan, [2]Center for Clinical Epidemiology, St.Luke' International Hospital and St. Luke's Life Science Institute, Tokyo, Japan, [3]Allergy and Rheumatology, St. Luke's International Hospital, Tokyo, Japan, [4]St. Luke's International Hospital, Tokyo, Japan

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Background/Purpose: It is valuable to predict the effectiveness of biologics in the patients with rheumatoid arthritis (RA) to avoid unnecessary side effects and to save medical resource. Few studies have addressed which patients' baseline characteristics can predict clinical response in Japanese population. The aim of this study was to determine risk factors for abatacept treatment failure in Japanese population.

Methods: Retrospective cohort study was conducted in tertiary referral hospital in Tokyo, Japan. Consecutive 32 patients who had been treated with abatacept between October 2010 and May 2015 were included. We excluded the patients with abatacept treatment for less than 24 weeks. 32 patients were divided into two groups in terms of clinical responsiveness at 24 weeks using disease activity score 28 C-reactive protein (DAS28-CRP). DAS28-CRP more than 2.1 was defined as treatment failure. Candidate variables were age, gender, disease duration, DAS28-CRP, bone erosion, concomitant use of methotrexate (MTX), previous biologics, comorbidities such as other connective tissue diseases (CTDs) and/or interstitial pneumonia (IP), smoking, alcohol consumption, family history of CTDs, laboratory values including rheumatoid factor (RF), anti-cyclic citrullinated peptide (anti-CCP) antibodies, and antinuclear antibodies (ANA). RF > 45 IU/ml was defined as highly elevated RF. We performed bivariate analyses and logistic regression analysis.

Results:

Mean age (SD) of 32 patients was 64.8 years-old (12.5). 27 (84%) were female. 18 (56%) patients had treatment failure. The median (range) of disease duration was 1783 days (127 to 14379). In bivariate analyses, non-responder were more likely to be female (71.4% vs 94.4%, P value=0.14), have more tender joints (TJ) (median (range) 4 (1 to 13) vs 6.5 (1 to 13), P=value 0.17), and high titer RF (35.7% vs 83.3% P=value 0.01). For clinical response by abatacept, crude odds ratio of age, female gender, number of TJ, highly elevated RF, DAS28-CRP and CCP positivity was 1.05 (95% CI 0.99 to 1.12, P value=0.14), 6.8 (95% CI 0.86 to 143.31, P value=0.07), 1.19 (95% CI 0.96 to 1.53,

P value=0.12), 10.5 (95% CI 1.85 to 88.66, P value=0.007), 1.5(95% CI 0.73 to 3.40, P value=0.28), 0.78(95% CI 0.13 to 3.99, P value=0.77) respectively.

In multivariate analysis, adjusted odds ratio of age, female gender, number of TJ, highly elevated RF, DAS28-CRP and CCP positivity was 1.13 (95% CI 1.00 to 1.36, P value=0.05), 18.63 (95% CI 0.45 to 4042.6, P value=0.13), 1.71 (95% CI 0.97 to 4.09, P value=0.06), 14.49 (95% CI 0.98 to 622.01, P value=0.05), 3.09 (95% CI 0.32 to 59.00 P value=0.34), respectively.

Conclusion: In contrast to previous studies, highly elevated RF is a marginally significant risk factor for abatacept treatment failure in Japanese RA patients.

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Abstract Number: 454

No Sex Bias in the Escalation of Therapy in the Treatment of Early Inflammatory Arthritis

Stephanie Garner[1], Cheryl Barnabe[2], Gilles Boire[3], Carol Hitchon[4], Edward C. Keystone[5], Boulos Haraoui[6], J Carter Thorne[7], Diane Tin[8], Janet E. Pope[9], VP Bykerk[10] and CATCH Investigators, [1]University of Calgary, Calgary, AB, Canada, [2]Cumming School of Medicine, University of Calgary, Calgary, AB, Canada, [3]Department of Medicine/Division of Rheumatology, Université de Sherbrooke, Sherbrooke, QC, Canada, [4]Department of Rheumatology, University of Manitoba, Winnipeg, MB, Canada, [5]Mount Sinai Hospital, University of Toronto, Toronto, ON, Canada, [6]Institut de Rhumatologie, Montreal, QC, Canada, [7]University of Toronto, Toronto, ON, Canada, [8]The Arthritis Program, Southlake Regional Health Centre, Newmarket, ON, Canada, [9]University of Western Ontario, London, ON, Canada, [10]Rheumatology, Mount Sinai Hospital, University of Toronto, Toronto, ON, Canada
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Background/Purpose: Several studies have shown that females with early inflammatory arthritis have higher disease activity, worse functional impairment and worse patient-reported outcomes but do not acquire more radiographic damage. It is hypothesized that the current measurement tools for disease activity are biased against females. The Hospital Universitario La Princesa Index (HUPI) is a validated tool in early RA and has been proposed to correct sex bias by adjusting for both the tender joint count (TJC 28) and ESR for males and females. The purpose of this study was to assess for sex differences in disease activity states between males and females as measured by the DAS28 and the HUPI, and whether there are differences in escalation of therapy between the sexes.

Methods: Data from the Canadian Early Arthritis Cohort (CATCH) were used for a sex-stratified analysis of disease activity and treatment escalation at 3, 6, 12, 24 and 60- month follow-up. Patients were included if they met the ACR 1987 or 2010 classification criteria for RA and their sex was documented. For the analysis, patients were classified into remission, low disease activity and moderate/high disease activity using the DAS28 and the HUPI cutpoints.

Treatment escalation was defined as any of: 1) increased dose of methotrexate; 2) addition of a new DMARD; 3) addition of a biologic agent; or 4) switching a biologic agent.

Results: 2228 patients (1619 females, 609 males) met the inclusion criteria. Females were younger (52 vs 58 years, $p<0.001$) and more frequently seropositive (72% vs 64%, $p<0.001$). Males had more erosions at baseline (14% vs 9%, $p<0.004$) and higher swollen joint count (9 vs 7, $p<0.001$). The DAS28 was similar in both groups at baseline (5.1 vs 5.0, $p=0.6$) but HUPI score were higher in males (8.9 vs 8.3, $p<0.0001$). More females were taking NSAIDs (60% vs 52%, $p<0.001$) and steroids (81% vs 59%, $p<0.002$) at inception to the cohort but these differences resolved by twelve months. The proportion of patients on DMARDs and biologic agents did not differ by sex at any time point. There were no sex differences in the escalation of therapy when patients were stratified by DAS28 or HUPI disease activity level (Table 1). More males were in DAS28 remission at 60 months (67% vs 52%,$p=0.01$) but the same proportion were in HUPI remission (53% vs 50%). There were no sex differences in the proportion of patients with erosions at 24 and 60 months.

Conclusion: There were no sex differences in treatment or escalation of therapy by disease activity state. Increased effort to treat to target for all patients is warranted.

Table 1. Escalation of Therapy in DAS28 or HUPI Moderate or High Disease Activity States, Stratified by Sex

	DAS28 Moderate/High		HUPI Moderate/High	
	Male	Female	Male	Female
Month 3	45%	46%	45%	50%
Month 6	33%	36%	33%	39%
Month 12	20%	26%	20%	27%
Month 24	33%	26%	34%	31%
Month 60	27%	14%	27%	15%

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Abstract Number: 455

Predictors of Real-World Treatment Sustainability in RA Patients Treated with Abatacept in Canada: Implications for Routine Care

Janet E. Pope[1], Emmanouil Rampakakis[2] and John S. Sampalis[3], [1]University of Western Ontario, London, ON, Canada, [2]JSS Medical Research, St-Laurent, QC, Canada, [3]Clinical Research, JSS Medical Research, Westmount, QC, Canada

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Background/Purpose: Treatment sustainability can measure drug effectiveness and encompasses drug effectiveness, safety, and compliance. Recent data suggest that differences in retention may exist between biologic agents even among the same class[1-3]. However, the majority of data for real-world sustainability of biologics pertains to TNF-inhibitors. This analysis assessed the durability of treatment with the T cell co-stimulatory inhibitor abatacept in RA patients in Canadian routine practice and evaluated the determinants of treatment sustainability.

Methods: Data on RA patients administered abatacept in routine practice via the Orencia Response Program network, between August 2006 and February 2011 who had at least one follow-up evaluation, were included. Treatment sustainability was assessed with the Kaplan Meier (KM) estimator of the survival function. Parameters associated with treatment sustainability were assessed with multivariate Cox regression using a backwards selection method. Potential predictors considered were: number of previous biologics, monotherapy vs. combination therapy, home vs. clinic infusions, age, sex, severity of disease, presence of comorbidity, and years since diagnosis. The impact of these parameters on HAQ was assessed with mixed models with repeated measures.

Results: A total of 1,771 patients were included with mean (SD) age of 57.6 (13.2) years and duration since diagnosis of 16.5 (11.0). The majority (77.2%) were females. Overall, 672 (37.9%) patients discontinued after a mean (SE) KM-based time to discontinuation of 26.8 (0.5) months. In multivariate survival analysis, increased number of previous biologics [$HR_{1 \text{ vs. } 0}$ (95% CI): 1.48 (1.14-1.19, P=0.004; $HR_{\geq 2 \text{ vs. } 0}$ (95% CI): 1.71 (1.34-2.18), P<0.001] and abatacept monotherapy [$HR_{\text{Mono vs. Combination}}$ (95% CI): 1.23 (1.05-1.45), P=0.011] were associated with shorter duration of treatment while home infusions [$HR_{\text{Home vs. Clinic}}$ (95% CI): 0.78 (0.67-0.93), P=0.004] and the presence of a comorbidity [$HR_{\text{Yes vs. No}}$ (95% CI): 0.68 (0.58-0.80), P<0.001] were associated with increased treatment sustainability. When assessing the impact of these parameters on HAQ, only the number of previous biologics was identified as a significant predictor of lower response (P=0.009) after adjusting for potential confounders, with lower number of biologics being associated with improved response [$B_{0 \text{ vs. } \geq 2}$ (SE): -0.12 (0.04), P=0.002; $B_{1 \text{ vs. } \geq 2}$ (SE): -0.05 (0.03), P=0.167].

Conclusion: This real-world analysis identified the number of previous biologics, concomitant DMARD use, infusion location, and presence of comorbidity as independent predictors of abatacept treatment sustainability. The number of previous biologics may be associated with differences in effectiveness as measured by the HAQ whereas the other predictors may be associated with other reasons for discontinuation.

1. Neovius M et al. Ann Rheum Dis. 2013 Nov 27. Epub ahead of print.
2. Du Pan SM et al. Arthritis Rheum. 2009 May 15;61(5):560-8.
3. Frazier-Mironer A et al. Joint Bone Spine. 2014 Jul;81(4):352-9.

Disclosure: J. E. Pope, Bristol-Myers Squibb, 2; **E. Rampakakis**, Bristol-Myers Squibb, 2; **J. S. Sampalis**, Bristol-Myers Squibb, 2.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/predictors-of-real-world-treatment-sustainability-in-ra-patients-treated-with-abatacept-in-canada-implications-for-routine-care

Abstract Number: 456

Disease and Treatment Characteristics That Might Influence Long-Term Retention with Biologics in the Real-World Clinical Setting: Experience from the Rhumadata Clinical Database and Registry

Denis Choquette[1], Louis Bessette[2], Boulos Haraoui[3], Jean-Pierre Raynauld[1], Diane Sauvageau[1], Angèle Turcotte[4], Édith Villeneuve[1] and Louis Coupal[1], [1]Rheumatology, Institut de recherche en rhumatologie de Montréal (IRRM), Montréal, QC, Canada, [2]Centre d'Ostéoporose et de Rhumatologie de Québec (CORQ), Québec, QC, Canada, [3]Institut de Rhumatologie, Montreal, QC, Canada, [4]Rheumatology, Centre d'ostéoporose et de rhumatologie de Québec (CORQ), Québec, QC, Canada
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Disease and Treatment Characteristics that Might Influence Long-term Retention with Biologics in the Real-world Clinical Setting: Experience from the Rhumadata Clinical Database and Registry

Background/Purpose: Patient adherence and sustainability of the regimen plays an important role in the long term outcomes. Biologic disease-modifying antirheumatic drugs (bDMARDs) have revolutionized the treatment of rheumatoid arthritis (RA), yet drug discontinuation is common. We aim to investigate factors that might influence long-term retention with biologics in a population-based of real-life unselected RA cohort.

Methods: RA patients (pts) treated with abatacept (ABA) or an anti-TNF inhibitor, adalimumab (ADA), etanercept (ETA), or infliximab (INF) were grouped according to their experience with biologics. Patient characteristics were compared using ANOVA with Bonferroni correction. Kaplan-Meier methods were used to compute the cumulative incidence of drug discontinuation.

Results: The first cohort included 403 pts receiving 1st line biologic (62 ABA, 111 ADA, 195 ETA, 35 INF) and the second cohort included 189 pts on their 2nd biologic (76 ABA, 47 ADA, 47 ETA, 19 INF). 11.9% of pts in the first (14.5% ABA, 8.1% ADA, 14.4% ETA, 5.7% INF) and 25.9% of pts (26.3% ABA, 27.7% ADA, 29.8% ETA, 10.5% INF) in the second cohort were on biologic monotherapy. Approximately 66% (66.7% first; 66.1% second cohort) of pts were rheumatoid factor (RF) positive. Anti-cyclic citrullinated peptide antibodies (anti-CCP) were detected in 62.0% and 55.4% of pts in the first and second cohort, respectively. Neither the RF status nor the use of biologics as monotherapy vs in combination with non-bDMARDs had a significant impact on long term retention. However, retention probability was significantly higher in the first cohort in anti-CCP positive vs negative patients, Figure 1. The anti-CCP positivity did not affect retention in the second cohort. In the second cohort treatment with ABA was associated with significantly higher retention compared to anti-TNFs, Figure 2.

Conclusion: The anti-CCP positivity was associated with significantly higher retention when biologics were used first line. This is important as anti-CCP antibodies are predictors of an aggressive disease. These results are compatible with other registries that indicate that anti-CCP might have an impact on retention rates. There were no significant differences in the retention rates in the first cohort. In the second cohort treatment with ABA was associated with significantly higher retention compared to anti-TNFs.

Figure 1.

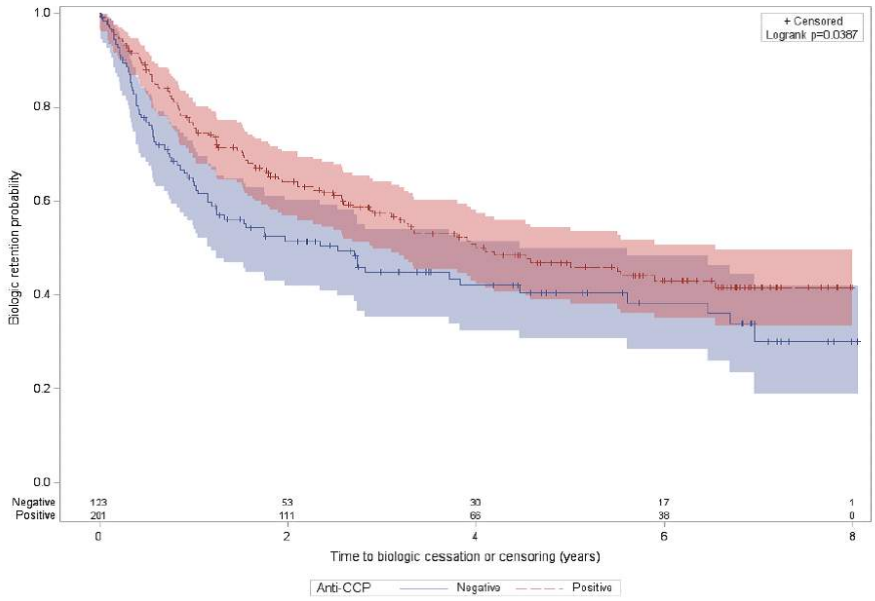
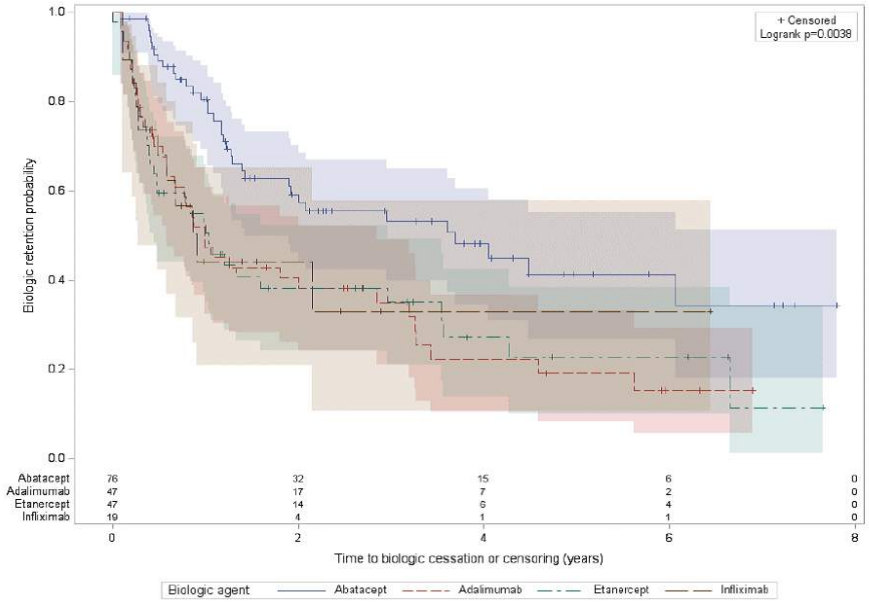


Figure 2.



Disclosure: D. Choquette, AbbVie, Amgen, Celgene, Bristol-Myers Squibb, Janssen Pharmaceutical Product, L.P., Pfizer Inc, Roche, Novartis, UCB, Hospira, Sanofi, Merck, 5; **L. Bessette**, AbbVie, Amgen, Celgene, Bristol-Myers Squibb, Janssen Pharmaceutical Product, L.P., Pfizer Inc, Roche, UCB, 5,AbbVie, Amgen, Celgene, Bristol-Myers Squibb, Janssen Pharmaceutical Product, L.P., Pfizer Inc, Roche, UCB, 2; **B. Haraoui**, Abbvie, Celgene, Amgen, BMS, Janssen, Pfizer, Roche and UCB Pharma, 2,Abbvie, Celgene, Amgen, BMS, Janssen, Pfizer, Roche and UCB Pharma, 5; **J. P. Raynauld**, None; **D. Sauvageau**, None; **A. Turcotte**, AbbVie, Amgen, Celgene, Bristol-Myers Squibb, Janssen Pharmaceutical Product, L.P., Pfizer Inc, Roche, UCB, Eli Lilly, 5; **Villeneuve**, AbbVie, Amgen, Bristol-Myers Squibb, 5; **L. Coupal**, None.

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Abstract Number: 457

RA Patients with Medicare Only Insurance Have Similar Clinical Outcomes As Patients with Private Insurance Despite Having Less Access to Biologics

Marcia S. Genta[1], Amnon Sonnenberg[2] and Robert M. Genta[3], [1]Dallas Arthritis Center, Dallas, TX, [2]Medicine - Gastroenterology, Portland VAMC - Oregon Health & Science University, Portland, OR, [3]Laboratory, Dallas Arthritis Center, Dallas, TX

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Background/Purpose: We have previously shown that patients with Medicare only coverage without financial assistance from foundations were significantly less likely to receive Biologics than patients with other types of coverage (Genta MS, *Arthr Rheumatol*, 2014;66:10:S39). In that study we did not evaluate disease activity. The purpose of the present study was to determine whether Medicare only patients were less likely to have low disease activity scores than patients covered by other insurance.

Methods: Patients with established RA and DAS28 CRP (DAS) activity score followed in a solo practice were stratified into the following categories, based on their insurance coverage: 1) Medicare only: Medicare, no supplemental insurance, no medication-specific financial support; 2) Medicare Integrated: Medicare with a supplemental insurance (private or public insurances or Medicare part D); and 3) Private only: by a private insurance only with no public coverage. Three treatment groups were considered: DMARDs only; DMARDs and Biologics; and Biologics only. Demographics, median DAS Scores, and disease activity clinical categories were compared by unadjusted Odds Ratios (OR) and by the t test.

Results: Insurance data and DAS were available for 163 patients. The Medicare only group included 52 patients (median age 70 years, range 49-88; 77% women; 9 White, 21 African American and 22 Hispanic). There were 20 patients with Medicare Integrated (age 68, range 46-80; 85% women; 9 White, 8 African American, and 3 Hispanic). Of the 91 patients with private insurance only (age 59 years, range19-89; 79% women) 29 were White, 32 African American, and 30 Hispanic. Thus, Medicare only patients were more likely to be non-White than both other groups (OR 2.49 95% CI 1.10 – 5.64; $p<0.05$). Median DAS scores were similar in the three groups (17, 14, and 20, respectively). Treatment groups and DAS-based clinical categories are summarized in Table 1. Although patients with Medicare only were more likely to be on DMARDs only than patients in the other two groups (OR 2.29 95% CI 1.14 – 4.60; $p<0.02$) they were in a DAS Remission or Low clinical category as frequently as those with other insurance plans who were more likely to receive Biologics with or without DMARDs.

Insurance	DMARD Only (%)	Biologics Only (%)	DMARDs and Biologics (%)	No Therapy (%)	Remission or Low (%)	Moderate or High (%)
Medicare (n = 52)	36 (69)	4 (8)	11 (21)	1 (2)	45 (87)	7 (13)
Medicare+ (n = 20)	7 (35)	5 (25)	8 (40)	0	18 (90)	2 (10)
Private (n = 91)	48 (53)	7 (8)	30 (33)	6 (7)	79 (87)	12 (13)

Conclusion: This study confirms our previous finding that patients with Medicare only are less likely to receive Biologics than those who have other insurances. Nevertheless, in this small sample, it appeared that these patients were not adversely affected by this limitation, as shown by low disease activity and remission rates similar to those with other types of coverage.

Disclosure: M. S. Genta, None; **A. Sonnenberg**, None; **R. M. Genta**, None.

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Abstract Number: 458

First Year Canadian Experience with Subcutaneous Abatacept in Routine Practice for the Treatment of Patients with Rheumatoid Arthritis: Data from the Orencia Response Program (ORP) Network

Boulos Haraoui[1], Louis Coupal[2], Radmila Day[3], Lionel Budry[4] and Youb Chalabi[5], [1]Institut de Rhumatologie de Montréal and University of Montreal, Montreal, QC, Canada, [2]Rheumatology, Institut de recherche en rhumatologie de Montréal (IRRM), Montréal, QC, Canada, [3]None, Montreal, QC, Canada, [4]Bristol Myers Squibb Canada, St-Laurent, QC, Canada, [5]Bristol Myers Squibb, Montreal, QC, Canada

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Background/Purpose: The subcutaneous (SC) formulation of abatacept (ABA) has been available in Canada since January 2014. Here we report first year experience with SC ABA in Canadian RA patients (pts). Canadian guidelines recommend the use of anti-TNFs or other mode of action biologics, including abatacept, after inadequate response to DMARD.[1] Furthermore, the availability of an SC formulation of a biologic increases the treatment options available to pts, particularly those wishing to self-administer their therapy.

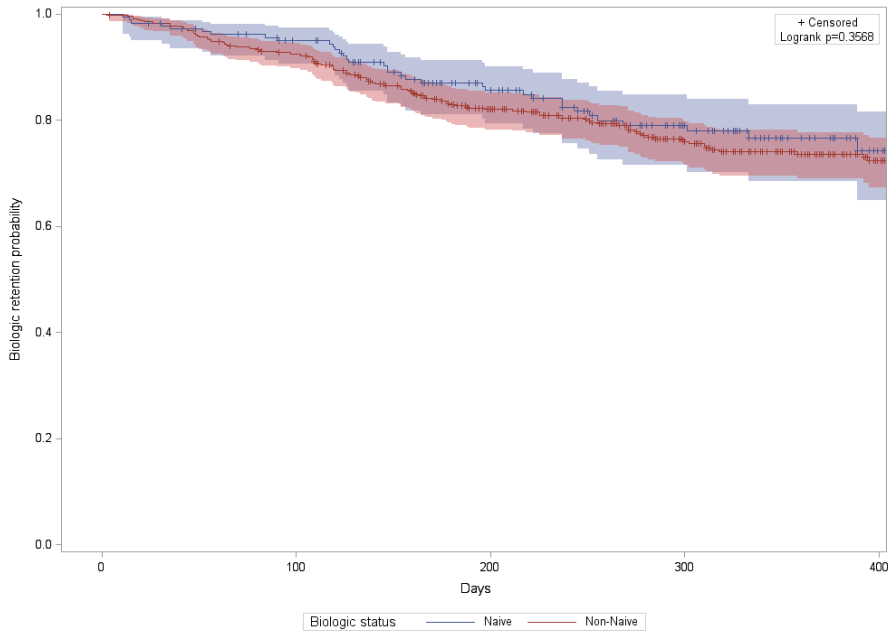
Methods: Canadian RA patients who accepted treatment with abatacept (Orencia®) were enrolled in the Orencia® Response Program (ORP) registry. RA pts treated with SC ABA in routine practice between Jan – Dec 2014, were included in this analysis. Durability of treatment with SC ABA was assessed using Kaplan-Meier survival analysis.

Results: As of December 2014, a total of 1152 pts received SC ABA. Out of these, 698 (61%) received SC ABA as the first or second line biologic therapy and 454 (39%) as third or fourth line. The median age of pts prescribed SC ABA was 60 years (range 16-89); 79.3% were females; and the median time since diagnosis for the entire cohort was 11 years. 72% of pts had severe and 23% had moderate disease. The majority of pts received their treatment at home (68%), followed by rheumatology (12%) or ORP clinic (7%). Only 12 (1%) of pts received the treatment at a doctor's office. 12-month persistence rates were similar in biologic naïve and non-naïve patients: 76.7% (SD=3.7%) for pts receiving SC ABA first line (biologic naïve) and 73.6% (SD=2.2%) for biologic experienced (non-naïve pts), Figure 1.

Conclusion: This data demonstrate that SC ABA can be used early in the course of the disease (first or second line biologic therapy) as well as in patients who fail several previous lines of biologics. Treatment with abatacept resulted in high 1-year persistency rates in both biologic naïve pts as well as those who failed one or more previous lines of biologic therapy.

[1]Bykerk VP, et al. J Rheumatol. 2012;39(8):1559-1582.

Figure 1. First year persistency rates in patients receiving SC abatacept



Disclosure: B. Haraoui, Abbvie, Celgene, Amgen, BMS, Janssen, Pfizer, Roche and UCB Pharma, 2,Abbvie, Celgene, Amgen, BMS, Janssen, Pfizer, Roche and UCB Pharma, 5; **L. Coupal**, None; **R. Day**, Bristol-Myers Squibb, 5; **L. Budry**, Bristol-Myers Squibb, 3; **Y. Chalabi**, Bristol-Myers Squibb, 3.

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Abstract Number: 459

The Effect of Rheumatoid Factor and Anti-Cyclic Citrullinated Peptide Positivity on Drug Survival of Abatacept in Patients with Rheumatoid Arthritis in Routine Care: The Results from Turkbio Registry

Ihsan Ertenli[1], Omer Karadag[1], Yavuz Pehlivan[2], Ediz Dalkilic[3], Ahmet Mesut Onat[4], Bunyamin Kisacik[5], Gercek Can[6], Servet Akar[7], Sedat Capar[8], Umut Kalyoncu[1], Mustafa Ferhat Oksuz[9], Emine Figen Tarhan[7] and Nurullah Akkoc[6], [1]Rheumatology, Hacettepe University Faculty of Medicine, Ankara, Turkey, [2]Department of Rheumatology, Uludag University Faculty of Medicine, Bursa, Turkey, [3]Department of Rhematology, Uludag University Faculty of Medicine, Bursa, Turkey, [4]Rheumatology, Gaziantep University School of Medicine, Gaziantep, Turkey, [5]Rheumatology Department, Gaziantep University School of Medicine, Gaziantep, Turkey, [6]Department of Rheumatology, Dokuz Eylul University, Faculty of Medicine, Izmir, Turkey, [7]Department of Internal Medicine, Division of Rheumatology, Izmir Katip Celebi University School of Medicine, Izmir, Turkey, [8]Dokuz Eylül University Faculty of Statistics, Izmir, Turkey, [9]Rheumatology, Uludag University Faculty of Medicine, Bursa, Turkey
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SESSION INFORMATION

Session Date: Sunday, November 8, 2015
Session Title: Rheumatoid Arthritis - Clinical Aspects Poster I
Session Type: ACR Poster Session A
Session Time: 9:00AM-11:00AM

Background/Purpose: Abatacept (ABA) is a biological anti-rheumatic drug used in Rheumatoid Arthritis (RA). In TURKBIO, Turkish Biologic Registry, data on patient characteristics, diagnosis, previous treatment and outcomes of ABA have been collected since 2011. Drug retention is a useful measure of effectiveness since it combines both clinical response and tolerability. The objective of this study was to investigate the effect of rheumatoid factor (RF) and Anti-Cyclic Citrullinated Peptide (Anti-CCP) positivity on drug survival of ABA in clinical practice for patients with RA.

Methods: By the end of May 2015, 266 patients received intravenous and subcutaneous ABA from 5 participating centers of the TURKBIO registry were included in the analysis. Demographic and clinical data including age, sex, disease duration, drug retention rate and reasons for discontinuation of drug were collected. Kaplan-Meier survival analysis was performed to estimate the drug survival. Subgroups were compared by log-rank.

Results: Of the 266 patients receiving ABA, 83.8% were female and median age was 55.0 years (range: 19.0-81.0). The median disease duration was 9.0 years (range: 1.0 year-53.0 years). 72.6% of were treated with ABA as first line biotherapy (n=193), 21.8% as second line (n=58) and 3.4% as third line (n=9). The rate of RF positive patients was 54.1% and anti-CCP positive was 68.1% among the patients treated with ABA in the registry. Estimated drug survival rates for ABA in 6^{th} month, 1^{st} year and 2^{nd} year were 76.1 %, 65.5% and 52.2% . Median drug survival was 26 months. One-year drug survival of first line and $>1^{st}$ line ABA treatment were 68.7% and 57.9%, respectively (p=0.084). There was a trend for a higher one year drug survival rate among anti-CCP (+) patients as compared to those who were anti-CCP (-) (73.1% versus 56.4%; p=0.087), whereas one-year drug survival rates were very similar for RF (+) and RF (-) patients at 63.4% and 64.8%, respectively (p=0.462) Drug survival curves for RF (+)/(-) and Anti-CCP (+)/(-) groups are given in Figure 1 and 2, respectively.

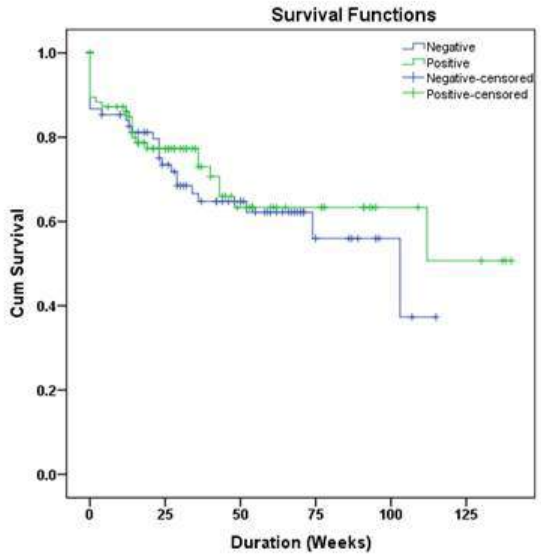

Figure 1. Drug survival curve in RF (+) and (-) patients.

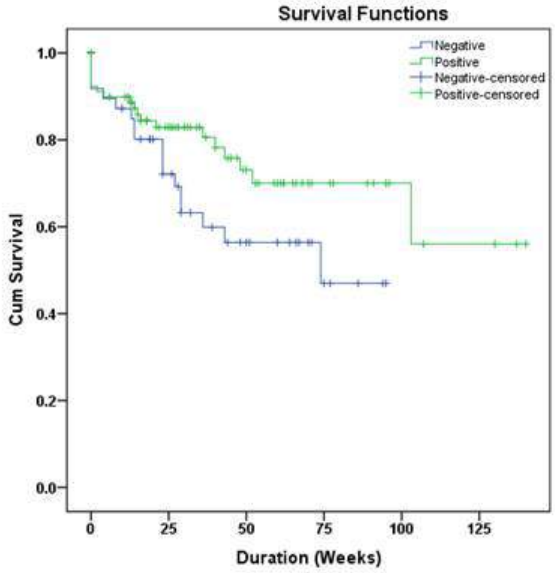

Figure 2. Drug survival curve in anti-CCP (+) and (-) patients

Conclusion: One year drug survival rate of ABA among patients enrolled in the TURKBIO registry is similar to those which has been reported in some other European countries. One year drug survival rates appear to be better among patients who are positive for anti-CCP, but not for RF as compared to those who are negative for the corresponding antibodies, which needs to be explored in future studies.

Disclosure: I. Ertenli, None; **O. Karadag**, None; **Y. Pehlivan**, None; **E. Dalkilic**, None; **A. M. Onat**, None; **B. Kisacik**, None; **G. Can**, None; **S. Akar**, None; **S. Capar**, None; **U. Kalyoncu**, None; **M. F. Oksuz**, None; **E. F. Tarhan**, None; **N. Akkoc**, None.

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Abstract Number: 460

Changes in Body Composition and Metabolic Profile during Treatment with Tocilizumab in Patients with Rheumatoid Arthritis

Anne Tournadre[1], Bruno Pereira[2], Frederic Dutheil[3], Vincent Sapin[4], Charlotte Giraud[5], Sandrine Malochet-Guinamand[6], Thomas Frayssac[7], Sylvain Mathieu[5], Jean-Jacques Dubost[8] and Martin Soubrier[8], [1]Rheumatology, UNH-UMR 1019 INRA University of Auvergne and Rheumatology department CHU Clermont-Ferrand, Clermont-Ferrand, France, [2]Biostatistics unit (DRCI), CHU Clermont-Ferrand, Clermont-Ferrand, France, [3]Preventive and Occupational Medicine, CHU G. Montpied Laboratory of Metabolic Adaptations to Exercise in Physiological and Pathological conditions EA3533, Clermont-Ferrand, France, [4]Biochemistry and Molecular Biology Department CHU Clermont-Ferrand, Clermont Université, Université d'Auvergne, EA7281, Clermont-Ferrand, France, [5]Rheumatology, Rheumatology department CHU Clermont-Ferrand, Clermont-Ferrand, France, [6]Rheumatology Department,, Rheumatology department CHU Clermont-Ferrand, Clermont-Ferrand, France, [7]Rheumatology, Rheumatology department CHU Clermont-Ferrand, Clermont-ferrand, France, [8]Rheumatology department CHU Clermont-Ferrand, Clermont-Ferrand, France

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Background/Purpose:

Rheumatoid arthritis (RA) is characterized by increased cardiovascular risk and metabolic changes including cachectic obesity, insulin resistance, dyslipidemia. DMARDs decrease inflammation and could thus improve cardiovascular risk but their effects on body composition and metabolic profile remain unclear. We investigated the effects of tocilizumab, an inhibitor of the IL6 pathway on body composition and metabolic profile in active RA.

Methods: We conducted an open 1-year follow-up study of 21 patients with active RA treated with tocilizumab. Waist circumference (WC), body mass index (BMI), body composition (dual-energy x-ray absorptiometry), lipid profile, fasting glucose, blood pressure, and arterial stiffness were measured at baseline when started tocilizumab, 6 months and 1 year of treatment. At baseline, RA patients were compared with 21 controls matched for age, sex, BMI and metabolic syndrome. The longitudinal data were explored using a random-effect models. To assess the issue of missing data, the estimation methods developed by Verbeke and Molenberghs were considered in this study.

Results: 21 RA patients, including 16 women with a mean age of 57.8 ± 10.5 years were included. RA duration was 8.5 years [IQR 1.7 – 21.5]. At baseline, 19 patients received a DMARD, 14 steroids, 11 cholesterol-lowering drug, 1 anti-diabetic drug, 6 antihypertensive medication. 18 patients have previously received at least one biologic. The mean DAS 28 at baseline was 4.7 ±1 and decreased significantly at 6 and 12 months (2.92±0.8 and 2.8±1.5 respectively, $p<0.001$). Compared to controls, RA patients had significantly lower total (42.1±11.1 vs 47.5±8.7, $p=0.02$) and appendicular lean mass (17.7±5.4 vs 20.1±3.9, $p=0.03$). During treatment with tocilizumab, no changes for WC, blood pressure, fasting glucose, lipid profile or arterial stiffness were observed. Significant weight gain (61.8±19.3 vs 63.7±16.1 kg $p=0.005$) and BMI (23.6±6.7 vs 24.8±6, $p<0.001$) were observed at 1 year without changes for fat composition. In contrast, lean mass (42.1±11.1 vs 43.2±11.3 Kg, $p=0.01$) and fat free mass index (16.7±3 vs 17.4±3.02, $p=0.01$) increased at 1 year. There was a significant gain in appendicular lean mass (17.7±5.4 vs 18±5.3 and 18.7±5.6 Kg, $p=0.04$ and $p<0.001$ respectively) and skeletal muscle mass index (6.7±1.4 vs 6.9±1.4 and 7.2±1.5, $p=0.03$ and $p<0.001$ respectively) at 6 and 12 months with a significant change between 6 and 12 months ($p=0.017$). Moreover, distribution of the fat was modified during the follow-up. A decrease in trunk/peripheral fat ratio (0.77±0.2 vs 0.7±0.17 $p<0.001$) and an increase in subcutaneous adipose tissue (SAT) (241.3±173.3 vs 264±154.3 $p=0.009$) were observed at 1 year whereas visceral adipose tissue (VAT) and VAT/SAT ratio did not change.

Conclusion:

Despite weight gain during treatment with IL6 inhibitor, no increase in fat but a modification in fat distribution has been observed. In contrast, muscle gain with increase in lean mass at 1 year suggested that blocking IL6 might be efficient in rheumatoid cachexia and sarcopenia.

Disclosure: A. Tournadre, None; **B. Pereira**, None; **F. Dutheil**, None; **V. Sapin**, None; **C. Giraud**, None; **S. Malochet-Guinamand**, None; **T. Frayssac**, None; **S. Mathieu**, None; **J. J. Dubost**, None; **M. Soubrier**, None.

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Abstract Number: 461

Etanercept Has a Better Retention Rate at 10 Years Than Adalimumab in Patients with Rheumatoid Arthritis. Results from Rhumadata®: A Real-

Life Clinical Database and Registry

Denis Choquette[1], Louis Bessette[2], Jacques Brown[3], Boulos Haraoui[1], Frédéric Massicotte[1], Jean-Pierre Pelletier[1], Jean-Pierre Raynauld[1], Marie-Anaïs Rémillard[4], Diane Sauvageau[1], Angèle Turcotte[3], Édith Villeneuve[1] and Louis Coupal[1], [1]Rheumatology, Institut de recherche en rhumatologie de Montréal (IRRM), Montréal, QC, Canada, [2]Centre d'Ostéoporose et de Rhumatologie de Québec (CORQ), Québec, QC, Canada, [3]Rheumatology, Centre d'ostéoporose et de rhumatologie de Québec (CORQ), Québec, QC, Canada, [4]Rhumatology, Institut de recherche en rhumatologie de Montréal (IRRM), Montréal, QC, Canada

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Background/Purpose: Very few studies have compare different agents used in the treatment of rheumatoid arthritis (RA) over the very long term. The majority of them have a short duration, are open-label, have selection criteria, and compare outcome measures such as DAS score, DAS improvement, HAQ improvement and so on. Rhumadata, a real-life database and registry, enrols all patients for whom a specific diagnosis such as RA has been made thus enabling comparisons of retention rates in a large population and the analysis of potential predictors of retention. Our objectives are to compare the retention rate of adalimumab and etanercept after DMARDs failure in a population of RA patients and identify potential predictors of retention rate.

Methods: Data of RA patients prescribed either etanercept (ETA) or adalimumab (ADA) as first biologic agent on or after January 1st, 2002 was extracted. The data included age and gender, disease characteristics, clinical variables, patient and physician specific assessments, laboratory measures and composite assessment of disease activity (DAS28-ESR, SDAI and CDAI). All patients were followed until they discontinued their treatment or June 2, 2015, the date at which the data was extracted from Rhumadata®. Secondary diagnoses and comorbidities established at or before the administration of the biologic agents were coded using the ICD-9-CM codes. Infections occurring during treatment, biologic status (ongoing or stopped) and the reasons for biologic cessation were also extracted. The 10-year drug retention rates were estimated and compared using Kaplan-Meier survival estimates and potential predictors were identified using univariate proportional hazard regression models. Statistical analysis was performed using SAS version 9.4.

Results: The data from 548 RA patients (184 prescribed ADA and 364 etanercept) as first biologic agent were extracted from the RHUMADATA® clinical registry and database. The patients were mostly women (74.5%) and had an average age of 53.3(SD=12.8). The patients had an average disease duration of 7.1 years (SD=8.0) and provided 2327.3 person-years of observation. The 10-year retention rates of ADA and ETA were estimated at 27.2% (SD=3.9%) and 35.0% (SD=3.1%) respectively and an overall significant difference in retention rate was observed (log-rank p -value = 0.0031). Inefficacy of biologic was the principal reason for drug cessation (46% in both ADA and ETA) followed by adverse events (14.8% ADA and 11.7% ETA). Univariate proportional hazard models identified the biologic used (HR (ADA vs ETA) = 1.402, 95% CI: 1.120 to 1.755) and fatigue-VAS (HR (per unit increase in fatigue-VAS) = 1.402, 95% CI: 1.120 to 1.755) as significant predictors of retention (alpha=0.05). Concurrent use of nbDMARDs did not however reach statistical significance (HR (combination vs monotherapy) = 1.157, 95% CI: 0.842 to 1.591).

Conclusion: After 10 years of continuous exposure to a first biologic agent, etanercept offers a clinically small but statistically significant advantage over adalimumab in a population of RA patients.

Inefficacy of biologic was the principal reason for drug cessation (46% in both ADA and ETA) followed by adverse events (14.8% ADA and 11.7% ETA).

Disclosure: D. Choquette, None; **L. Bessette**, None; **J. Brown**, None; **B. Haraoui**, Abbott, Amgen, BMS, Janssen, Pfizer, Roche and UCB Pharma, 2,Abbott, Amgen, BMS, Janssen, Pfizer, Roche and UCB Pharma, 5,Abbott, Amgen, BMS, Janssen, Pfizer, Roche and UCB Pharma, 8; **F. Massicotte**, None; **J. P. Pelletier**, None; **J. P. Raynauld**, None; **M. A. Rémillard**, None; **D. Sauvageau**, None; **A. Turcotte**, None; **Villeneuve**, None; **L. Coupal**, None.

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Abstract Number: 462

Radiographic Progression in Patients with Early Rheumatoid Arthritis Has Not Become Milder over the Past Decades

Carola Wassenberg[1], Rolf Rau[2], **Siegfried Wassenberg**[3], Dietmar Krause[4] and Christoph Fiehn[5], [1]Radiology, Friedrich Ebert Krankenhaus, Neumünster, Germany, [2]Expert in Rheumatology, Düsseldorf, Germany, [3]Rheumaklinik, Themistocles Gluck hospital - Rheumazentrum Ratingen, Ratingen, Germany, [4]Dept. for Medical Informatics, Biometry and Epidemiology, Ruhr University, Bochum, Germany, [5]ACURA Centre for Rheumatic Diseases, Baden-Baden, Germany

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Session Time: 9:00AM-11:00AM

Background/Purpose:

Retrospective studies have promoted the idea that RA has become a milder disease over the past decades[i], [ii]. These findings are questionable because of the impact of changing treatment strategies and DMARD use in these studies.

In one rheumatologic center in Germany the strategy to treat all newly diagnosed RA patients (pts) with either MTX or parenteral gold (gold) was established already in the 1970ies and kept constant for more than 20 years. In case of inefficacy or intolerability one treatment was usually replaced by the other. MTX and gold have been shown to be almost equally effective on disease activity and radiographic progression (RP) in early RA[iii]. This provided the unique opportunity to test the hypothesis of a secular trend to milder disease course in almost uniformly treated cohorts from three different decades.

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[i] Welsing PMJ et al. Arthritis Rheum 2005;52:2616–24

[ii] Sokka T et al. J Rheumatol 2004;31:1073–82

[iii] Rau R et al. Br J Rheumatol 1998;37:1220-6

Methods:

All pts first presenting in the center in the years 1978-1980, 1990 and 2000 with early (< 3 yr) physician confirmed RA were followed radiographically in regular intervals. ESR and RF status were available. Hand and feet radiographs from baseline and 1 and 3 years follow up were read with the Ratingen Score (RS) (range 0-190). Multiple regression

analysis (MRA) was performed with age, gender, belonging to one of the three cohorts, disease duration, RF status, baseline radiographic score and the first DMARD as possible influencing factors on RP.

Results:

Baseline demographics, disease characteristics, mean RS and mean annual RP in 1styear of the three cohorts are given in Table 1.

Table 1

Cohort (year)	n	Age (StD)	Gender, % female	Dis. Duration months (StD)	ESR mm/h (StD)	% RF-positive	Baseline RS (StD)	RS – Annual Progression 1st yr (StD)
1978-80	84	54.2 (± 9.2)	82.1	13.5 (±10.7)	31 (±22)	54,8	4.68 (±3.97)	1.75 (±2.15)
1990	47	58.2 (±10.7)	72.3	10.0 (± 7.0)	33 (±18)	80.9	5.00 (±3.74)	1.53 (±1.56)
2000	75	60.1 (±10.4)	72.0	8.8 (± 8.0)	37 (±19)	86.7	3.30 (±2.80)	1.52 (±1.47)

The results of the MRA are displayed in Table 2

Table 2

Variable	Parameter Estimate	Standard Error	t-Value	Pr> |t|
Intercept	-0.09621	0.12189	-0.79	0.4309
Age	0.00102	0.00170	0.60	0.5496
Cohort	-0.01948	0.02662	-0.73	0.4651
Gender	0.07271	0.04790	1.52	0.1306
Disease Duration	0.00106	0.00171	0.62	0.5366
RF Status	0.11064	0.04709	2.35	0.0198
RS at Baseline	0.02737	0.00449	6.09	<.0001
Gold as 1st Treatment	0.01697	0.05035	0.34	0.7365
MTX as 1st Treatment	0.03296	0.06115	0.54	0.5905

After MRA the increase of the RS did not differ between the cohorts (p=0.5496) with the RS at baseline (p <0.0001) and RF status (p = 0.0198) being the only parameters that showed a significant impact on radiographic progression.

Conclusion:

As almost all pts were treated with either one of two equally effective agents irrespective from the date of their first presentation, one may assume that RP was equally influenced by DMARD therapy in all three cohorts. A shift towards milder disease course over two decades would have led to less progression in the later cohorts compared to the early 1978-80 cohort. In contrast we found RP to be almost constant over time. The much better performance of many pts with early RA in recent years compared to the past is therefore most probably explained by more and better treatment options now available to most pts and that the concept of treat to target in early RA that has become widely accepted by rheumatologist.

Disclosure: C. Wassenberg, None; **R. Rau**, None; **S. Wassenberg**, None; **D. Krause**, None; **C. Fiehn**, None.

patients-with-early-rheumatoid-arthritis-has-not-become-milder-over-the-past-decades

Abstract Number: 463

Treatment with Biologic Agents for RA in Patients with MTX-Associated Lymphoproliferative Disorders

Takayuki Katsuyama[1], Ken-ei Sada[1], Noriko Toyota-Tatebe[2], Katsue S. Watanabe[1], Toru Kiguchi[3] and Jun Wada[2], [1]Department of Medicine and Clinical Science, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Science, Okayama, Japan, [2]Department of Medicine and Clinical Science,, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Science, Okayama, Japan, [3]Department of Internal Medicine, Chugoku Central Hospital, Fukuyama, Japan

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Session Type: ACR Poster Session A

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Background/Purpose:

Methotrexate (MTX) is known as an anchor drug for the treatment of rheumatoid arthritis (RA), and MTX-associated lymphoproliferative disorders (MTX-LPD) is of current interest. However, clinical course and optimum therapies in the patients with MTX-LPD remain uncharacterized.

Methods:

We enrolled RA patients who had been diagnosed as LPD during MTX therapy from January 2009 to December 2014. Baseline data including age, sex and duration of RA and MTX treatment were collected. Histopathological diagnosis, Epstein–Barr encoding region (EBER) *in situ* and serum EB virus (EBV) DNA were assessed. We evaluated the relationship between the characteristics and clinical outcome of LPD. We also described the clinical course and the treatment for RA after the diagnosis of MTX-LPD.

Results:

Twenty-two patients (17 female and 5 male) were enrolled in this study. The age at the diagnosis of LPD was 68.4 ± 9.0 years and they were treated for 15.5 ± 14.7 years and under the treatment of MTX for 80.6 ± 80.2 months. Biopsy was performed in 18 patients, and 10 of them (55.6 %) were diagnosed as diffuse large B cell lymphoma and 2 as marginal zone B cell lymphoma. EBER *in situ* was positive in 10 of 17 patients (58.8%), and the serum EBVDNA was detected in 8 of 11 (72.7%). MTX was withdrawn immediately after the diagnosis of LPD in all cases. The withdrawal resulted in the remission of LPD in 18 cases (81.8%, non-chemotherapy group), whereas 4 cases required chemotherapy (chemotherapy group). Serum EBVDNA was positive in all patients of non-chemotherapy group, while negative in all of chemotherapy group (p= 0.0003). The positive rate of EBER *in situ* was not significantly different between two groups (61.5 % vs. 50.0%, p=0.682). Age and the duration of MTX treatment were comparable whereas the history of RA was significantly longer in chemotherapy group than in non-chemotherapy group (29 years vs. 13 years, p= 0.0035). After the diagnosis of LPD, they were treated for 37.3 ± 22 months, and the relapse or exacerbation of RA was observed in 13 patients (61.9 %) after 9.2 ± 10 months. Nine patients were treated with various biologic agents, excluding rituximab, for RA relapse. The eight of nine patient sustained LPD remission after treatment with biologic agents; however one case was diagnosed as angioimmunoblastic T cell lymphoma and experienced recurrence of LPD during tocilizumab (TCZ) therapy. She was treated with chemotherapy. TCZ was switched to other biologic

agents, and no recurrence of LPD was observed. There was no difference of the duration of RA and the positive rate of EBER and EBVDNA between patients with and without RA relapse after LPD diagnosis.

Conclusion:

The present study revealed that the positivity of serum EBVDNA was useful to predict the better clinical outcome of MTX-LPD. There was no established evidence of biologic therapies in RA patients with MTX-LPD but they seem to be effective and rather safe for most of RA patients after MTX-LPD diagnosis.

Disclosure: T. Katsuyama, None; **K. E. Sada**, None; **N. Toyota-Tatebe**, None; **K. S. Watanabe**, None; **T. Kiguchi**, None; **J. Wada**, None.

Abstract Number: 464

Biologic Therapy Treatment Complications in the Alberta Aboriginal Population with Rheumatoid Arthritis

Cheryl Barnabe[1], Yufei Zheng[2], Arto Ohinmaa[2], Brenda Hemmelgarn[3], Gilaad Kaplan[4], Liam Martin[5] and Walter Maksymowych[6], [1]Cumming School of Medicine, University of Calgary, Calgary, AB, Canada, [2]Institute of Health Economics, Edmonton, AB, Canada, [3]Division of Nephrology, University of Calgary, Calgary, AB, Canada, [4]Division of Gastroenterology, University of Calgary, Calgary, AB, Canada, [5]Medicine, University of Calgary, Calgary, AB, Canada, [6]Medicine, Medicine, University of Alberta, Edmonton, AB, Canada
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Biologic Therapy Treatment Complications in the Alberta Aboriginal Population with Rheumatoid Arthritis

Background/Purpose: Aboriginal people with rheumatoid arthritis (RA) have more severe disease and an increased number of comorbid conditions, which may result in higher rates of adverse events when using biologic therapy.

Methods: The Alberta Biologics Pharmacosurveillance Program (ABioPharm) is a longitudinal RA cohort study, linked to population-based administrative databases (physician claims and hospitalizations). We calculated incidence rate ratios (IRR) for adverse events comparing Aboriginal to non-Aboriginal groups, including all-cause hospitalization, serious infections, malignancy (lung, breast, colorectal, lymphoproliferative), cardiovascular events (myocardial infarction, congestive heart failure, cerebrovascular disease), thromboembolic events and death, using Poisson regression to adjust for age at biologic start, low socioeconomic status, urban vs rural residence, comorbidities (Deyo-Charlson), number of rheumatologist visits, history of joint replacement surgery, extra-articular features, baseline DAS28, baseline HAQ, number of previous DMARDs, steroids at baseline visit, and standardized for age and sex.

Results: The cohort includes 1,545 patients (n=83 Aboriginal) with a total of 8,145 person-years of follow-up. Aboriginals were younger at initiation of the first biologic (50 vs 55 years), with more comorbidities, higher baseline DAS28ESR scores (mean 6.11 vs 5.19) and slower rates of improvement for tender and swollen joint counts in the first

year of treatment. Aboriginals had a higher risk of all-cause hospitalization (IRR 1.4, 95%CI 1.1 to 1.8, p=0.01), malignancy (IRR 2.6, 95%CI 1.1 to 5.7, p=0.02) and thromboembolic events (IRR 2.7, 95%CI 1.7 to 4.2, p<0.001). They also had higher risk of serious infections (IRR 3.2, 95%CI 2.5 to 4.0, p<0.001), with significantly more episodes of skin and soft tissue infections (IRR 3.8, 95%CI 1.5 to 9.6), osteomyelitis (IRR 6.6, 95%CI 1.8 to 25.1) and pyelonephritis (IRR 8.4, 95%CI 2.0 to 35.3). Aboriginal patients were similar to non-Aboriginal patients in the risk for cardiovascular events (IRR 0.7, 95%CI 0.5 to 1.1, p=0.03). The mortality rate was 0.7 per 100 person-years in the non-Aboriginal group, with no deaths in the Aboriginal group.

Conclusion: Aboriginal patients experience higher rates of all-cause hospitalization, serious infections, malignancy and thromboembolic events, but not cardiovascular events, during treatment with biologic therapy. These findings are important to inform treatment decisions to initiate biologic therapy in Aboriginal patients, and the need for frequent monitoring during therapy.

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Abstract Number: 465

MRI Bone Erosion at Baseline Predicts the Subsequent Radiographic Progression in Early-Stage RA Patients Who Achieved in Sustained Clinical Good Response: Sub-Analysis from Nagasaki University Early Arthritis Cohort

Mami Tamai[1], Yoshikazu Nakashima[1], Kazuhiko Arima[2], Junko Kita[1], Masataka Umeda[1], Shoichi Fukui[1], Ayako Nishino[1], Takahisa Suzuki[1], Yoshiro Horai[1], Akitomo Okada[3], Tomohiro Koga[1], Shin-ya Kawashiri[1,2], Naoki Iwamoto[1], Kunihiro Ichinose[1], Satoshi Yamasaki[4], Hideki Nakamura[1], Tomoki Origuchi[5], Kiyoshi Aoyagi[2], Masataka Uetani[6], Katsumi Eguchi[7] and Atsushi Kawakami[1], [1]Department of Immunology and Rheumatology, Nagasaki University, Nagasaki, Japan, [2]Department of Public Health, Nagasaki University, Nagasaki, Japan, [3]Japanese Red Cross Nagasaki Genbaku Hospital, Nagasaki, Japan, [4]Hiroshima University, Hiroshima, Japan, [5]Department of Rehabilitation Sciences, Nagasaki University, Nagasaki, Japan, [6]Department of Radiology and Radiation Research, Nagasaki University, Nagasaki, Japan, [7]Department of Rheumatology, Sasebo Chuo Hospital, Sasebo, Japan
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Background/Purpose: Given the improved detection of joint injury by MRI than by clinical examination, EULAR recommendations for the use of imaging of the joints in the clinical management of RA states that MRI is useful in monitoring disease activity. However, there are few clinical investigations searching whether MRI findings are even helpful to consider radiographic progression in RA patients who achieved in sustained clinical good response. The present study is to examine whether MRI findings at baseline are useful to predict subsequent radiographic progression in early-stage RA patients who achieves in sustained clinical good response.

Methods: This is a sub-analysis from the 1-year observational study from 76 early-stage RA patients recruited consecutively from Nagasaki University Early Arthritis Cohort in which the subjects received Gd-enhanced MRI of both wrists and finger joints. They gave their informed consent to be subjected to the protocol that was approved by the Institutional Review Board of Nagasaki University. All patients had been received DMARDs during 1 year after entry. The sustained clinical good response was defined by decrement of DAS28 ≥1.2 at 3 months as well as achievement of DAS28 remission through 6 months to 1 year. Synovitis, bone oedema and bone erosion determined by Gd-enhanced MRI were scored by OMERACT-RAMRIS. Plain radiographic damage was studied by Genant-modified Sharp score and the radiographic progression was defined as Δ progression > 0 at 1 year (Δ score > 0). We have investigated whether MRI findings are helpful to predict subsequent radiographic progression in the sustained clinical good responders.

Results: Twenty-four patients were classified as sustained clinical good responders and examined in the present study. Median age, disease duration were 56 y.o, 2.0 months and median DAS28-CRP, CRP (mg/dl), MMP-3 (ng/ml) were 4.40, 0.52 and 87.2, respectively. Rate of ACPA-positive and RF-positive were 91.7 and 83.3%. Median RAMRIS synovitis, bone edema, bone erosion score and Genant-modified Sharp score at baseline were 6, 0.5, 0 and 0, respectively. Among the 24 sustained clinical good responders, five patients developed radiographic progression at 1 year. Multivariate logistic regression analysis has identified that baseline RAMRIS bone erosion score (1 increase, Odds ratio 3.00, 95% C.I. 1.10-8.20, *p*-value 0.032) is the only independent predictor toward the development of radiographic progression at 1 year. In addition, cut-off point 0.5 of baseline MRI bone erosion score showed the best discriminative value toward radiographic progression (sensitivity 100.0%, specificity 73.7%).

Conclusion: Our present data suggest that MRI bone erosion involves in subsequent radiographic progression of early-stage RA even successfully treated by treating RA to target (T2T) strategy. Physicians are recommended to pay attention to the presence of MRI bone erosion in these patients.

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Abstract Number: 466

Clinical Factors, Anti-Citrullinated Peptide Antibodies and MRI-Detected Subclinical Inflammation in Relation to Progression from Clinically Suspect Arthralgia to Arthritis

H.W. van Steenbergen[1], L. Mangnus[2], M. Reijnierse[3], T. W. J. Huizinga[1] and A.H.M. van der Helm- van Mil[2], [1]Leiden University Medical Center, Leiden, Netherlands, [2]Rheumatology, Leiden University Medical Center, Leiden, Netherlands, [3]Radiology, Leiden University Medical Center, Leiden, Netherlands

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Background/Purpose: Patients with Clinically Suspect Arthralgia (CSA) have, according to their rheumatologists, an increased risk on rheumatoid arthritis (RA), but their actual outcome is unexplored. This longitudinal study investigated (1) progression from CSA to clinically detectable arthritis and (2) associations of clinical factors, serological factors (among which anti-citrullinated peptide antibodies (ACPA)) and MRI-detected subclinical inflammation with arthritis development.

Methods: 150 CSA-patients were followed ≥6 months. At baseline, clinical and serological data were collected and unilateral 1.5T-MRI of MCP, wrist and MTP-joints was made. MRI-scoring was done according to the RA MRI scoring system. Subclinical MRI-inflammation was defined based on MRI-results of 193 symptom-free persons.

Results: During follow-up (median=75 weeks, interquartile range=40-106 weeks), 30 patients developed clinical arthritis; 87% did so <20 weeks after inclusion. In multivariable analyses, age, localisation of initial symptoms in small and large joints (compared to small joints only), CRP-level, ACPA-positivity and subclinical MRI-inflammation significantly associated with arthritis development; ACPA and MRI-inflammation were most strongly associated (hazard ratio (95% confidence interval) respectively, 6.43 (2.57-16.05) and 5.07 (1.77-14.50)). After 1-year follow-up, 31% of the patients with MRI-inflammation and 71% of the ACPA-positive patients with MRI-inflammation had progressed to arthritis. Forty-three percent of the patients that developed arthritis within 1-year were ACPA-negative; 78% of them had subclinical MRI-inflammation at baseline. When MRI-inflammation was absent arthritis development was infrequent (6% in all CSA-patients and 3% in ACPA-negative CSA-patients).

Conclusion: Subclinical MRI-inflammation precedes clinical arthritis with a few months. Subclinical MRI-inflammation is, independent of other factors such as ACPA, associated with arthritis development.

Disclosure: H. W. van Steenbergen, None; **L. Mangnus**, None; **M. Reijnierse**, None; **T. W. J. Huizinga**, None; **A. H. M. van der Helm- van Mil**, None.

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Abstract Number: 467

Clinical Outcomes of Patients with Active Rheumatoid Arthritis with Normal Acute-Phase Reactant Values

In Je Kim[1], Hyesook Park[2], Sang-Cheol Bae[3] and Jisoo Lee[4], [1]Division of Rheumatology, Department of Internal Medicine, Ewha Womans University School of Medicine, Seoul, South Korea, [2]Dep of Preventive medicine, Ewha Womans University School of medicine, Seoul, South Korea, [3]Hanyang University Hospital for Rheumatic Diseases, Seoul, South Korea, [4]Internal Medicine, Ewha Womans Univeristy School of Medicine, Seoul, South Korea
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Background/Purpose:

Despite high clinical disease activity measured by joint counts and global assessments, some patients with active

rheumatoid arthritis (RA) have normal acute-phase reactant (APR) values. This group of patients may have less aggressive disease or may represent earlier phase of the disease, but clinical outcomes of these patients were not previously explored.

We aimed to determine the clinical outcomes of patients with clinically active RA but has normal APR values.

Methods:

Of 2,583 patients with RA enrolled in the KORean Observational study Network for Arthritis (KORONA) registry, 400 patients who had Clinical Disease Activity Index (CDAI) score of >2.8 at baseline, biologic-naïve, and ESR and CRP drawn at both baseline and two-year follow-up visits were identified. Patients were grouped according to baseline APR levels; neither elevated ESR nor CRP (normal APRs), either ESR or CRP elevated (one APR-positive), and both elevated ESR and CRP (both APRs-positive).

Results:

Of patients with active RA, 39% had normal APR; 27% were one APR-positive; only 34% had both APRs-positive. Baseline tender and swollen joint counts, CDAI and HAQ-DI scores were significantly lower in normal APRs group compared with APRs-positive groups ($p<0.0001$). However, mean disease duration was not significantly different between 3 groups. At two-year follow-up, mean DAS28 scores were lower in normal APRs group ($p<0.0001$), and CDAI scores showed trend toward lower values ($p=0.062$). Patients with normal APRs were less likely to use glucocorticoids and biologics. Although remission rate was comparable in 3 groups when measured by CDAI, DAS28 remission rate was significantly in higher normal APRs group.

Conclusion:

Active RA patients with normal APRs have milder disease, better clinical outcomes and require less aggressive treatment compared with APRs-positive patients. Composite disease activity measures which do not include APRs should be considered for monitoring disease activity in patients with normal APRs because disease activity indexes including APRs in its scoring result in underestimation of their disease activity.

Disclosure: I. J. Kim, None; **H. Park**, None; **S. C. Bae**, None; **J. Lee**, None.

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Abstract Number: 468

Clinical and Ultrasonographic Inflammation in DMARD-Naïve Early Rheumatoid Arthritis (RA) – Impact of the 2010 ACR/EULAR Classification Criteria Versus the 1987 ACR Classification Criteria

Maria K. Jonsson[1,2,3], Siri Lillegraven[2], Lena B. Nordberg[2], Anna-Birgitte Aga[2], Hilde B. Hammer[4], Inge C Olsen[2], Bjørg-Tilde Fevang[1,5], Tore K. Kvien[2], Espen A. Haavardsholm[2] and the ARCTIC Study Group, [1]Dept. of Rheumatology, Haukeland University Hospital, Bergen, Norway, [2]Dept. of Rheumatology, Diakonhjemmet Hospital, Oslo, Norway, [3]Dept. of Clinical Science, University of Bergen, Bergen, Norway, [4]Department of Rheumatology, Diakonhjemmet Hospital, Oslo, Norway, [5]Department of Clinical Science, University of Bergen, Bergen, Norway

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Background/Purpose: ACR and EULAR published new classification criteria for RA in 2010, aiming for early identification of patients at risk of developing persistent and erosive arthritis. Ultrasonographic examination (US) yields information on inflammation in joints and tendons in RA. Our aim was to investigate whether US inflammation, as well as clinical measures of inflammation, were different in disease modifying anti-rheumatic drug (DMARD) naïve patients fulfilling only the 2010 ACR/EULAR criteria compared to patients fulfilling both the 2010 ACR/EULAR and the 1987 ACR classification criteria for RA.

Methods: RA patients (n=235) who fulfilled the 2010 ACR/EULAR classification criteria were recruited between 2010 and 2013. All patients had symptom duration from first swollen joint < 2 years and were DMARD-naïve with indication for DMARD treatment. US inflammation was evaluated as grey-scale (GS) synovitis and vascularization assessed by power Doppler (PD) in 32 joints by a standardized protocol, with range 0-3 for each joint (1). Clinical inflammation was assessed by 44 swollen joint count, Ritchie Articular Index (RAI), erythrocyte sedimentation rate (ESR) and the Disease Activity Score (DAS). Disease characteristics were compared between the groups using chi-square test, t-test and Mann-Whitney U-test as appropriate.

Results: The 235 patients included had mean (SD) age 51.4 (13.7) years, median disease duration [25, 75 percentiles] 5.7 [2.8, 10.2] months, 62.1% were female, and 81.3% were positive for anti-citrullinated protein antibodies (ACPA). Inflammation assessed by DAS, ESR and US was significantly higher in patients fulfilling both the 1987 and 2010 criteria, compared to patients only fulfilling the 2010 criteria (Table). There was no significant discrepancy in gender distribution, age, disease duration or the proportion of ACPA-positive individuals when comparing the two groups.

Conclusion: Patients with early RA fulfilling only the new 2010 ACR/EULAR criteria had less severe disease, both clinically, biochemically and assessed by ultrasonography, compared to patients fulfilling both the 1987 ACR criteria and the 2010 ACR/EULAR criteria. This may reflect the change in treatment strategies that has occurred over time, with earlier initiation of DMARD treatment. Long-term outcomes of function and morbidity are needed to understand the potential shift in the RA construct caused by the implementation of the new classification criteria.

Table: Disease characteristics in patients fulfilling only the 2010 ACR/EULAR classification criteria versus both the 1987 ACR and the 2010 ACR/EULAR classification criteria.

	Patients fulfilling only the 2010 ACR/EULAR criteria n=77	**Patients fulfilling both the 2010 ACR/EULAR criteria and the 1987 ACR criteria n=158**	***p*-value**
Female % (n)	62.3 (48)	62.0 (98)	0.96
Age, years[1]	51.5 (12.8)	51.4 (14.2)	0.99
ACPA-positive % (n)	79.2 (61)	82.3 (130)	0.57
Disease duration[3], months[2]	6.1 [2.9, 9.9]	5.5 [2.8, 10.2]	0.82
DAS-score[1]	2.9 (1.1)	3.7 (1.0)	**<0.001**
Swollen joint count[2]	5 [3, 10]	11 [7, 15]	**<0.001**
ESR, mm/hr[2]	16 [10, 26]	22 [13, 36]	**0.002**
Ritchie Articular index[2]	5 [3, 8]	8 [4, 13]	**<0.001**

Total US score GS[2]	12 [7, 22]	21 [13, 30]	**<0.001**
Total US score PD[2]	4 [2, 9]	8 [4, 15]	**<0.001**
[1]Mean (SD). [2]Median [25, 75 percentiles]. [3]Disease duration from first swollen joint.			

http://acrabstracts.org/abstract/clinical-and-ultrasonographic-inflammation-in-dmard-naive-early-rheumatoid-arthritis-ra-impact-of-the-2010-acreular-classification-criteria-versus-the-1987-acr-classification-criteria

Abstract Number: 469

Window of Opportunity to Achieve Major Outcomes in Early Rheumatoid Arthritis Patients: How Persistence with Therapy Matters

Virginia Pascual-Ramos[1] and Irazú Contreras-Yáñez[2], [1]Immunology and Rheumatology, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico, [2]Inmunología y Reumatología, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico

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Background/Purpose: The window of opportunity concept states that there are superior clinical responses and the potential for remission, when patients with rheumatoid arthritis (RA) are managed earlier and aggressively with disease modifying anti-rheumatic drugs (DMARD). Benefits will be achieved if patients follow prescribed treatment reasonably close. **Objectives** of the study were to investigate whether timing of first non-persistence period and/or duration of persistence with DMARD during the first 4 years of follow-up predicted disease outcomes at the 5th year, in a cohort of early RA patients initiated in 2004 and to identify additional outcome´s predictors.

Methods: Up to February 2015, charts from 107 patients with at least 5 years of follow-up and prospective 6 month-apart assessments of disease activity, of disability and of persistence were reviewed. Non-persistence was defined as omission of at least one DMARD and/or corticosteroids for at least seven consecutive days; regarding methotrexate, one weekly missing dose was considered non-persistence. Persistence was recorded through an interview (up to 2008) and thereafter through a questionnaire; persistence duration was recorded in months. Treatment modifications because adverse events and/or indicated by a physician for any reason were not considered under non-persistent construct. At the 5th year, disease activity was defined according to disease activity score on 28 joints (DAS28) and disability according to health assessment questionnaire (HAQ); both were derived as the mean of corresponding individual scores from all the visits performed during the 5th year. Descriptive statistics and linear and Cox regression analyses were used. All the patients signed informed consent.

Results:

At study entry, patients were more frequently middle-aged (39.1±13.3 years) female (88.8%), with high disease activity and disability; more than 80% had autoantibodies. Over the first 4 year´s follow-up, 54.2% of the patients were indicated oral corticosteroids and all traditional DMARDs. Almost 70% had at least 1 period of non-persistence and their follow-up (median, 25-75 quartiles [25Q-75Q]) to 1st non-persistence period was 13 months (1-31).

Gender, baseline DAS28 and persistence duration predicted DAS28 at the 5th year, and the strongest impact was due to months of persistence. Also, age and persistence duration predicted HAQ at the 5th year. When model were applied in female subpopulation, persistence duration still a predictor of subsequent outcomes.

During the 5th year, 68 patients (56 women) achieved sustained remission (DAS28 below 2.6); in females (N=56, 83%), baseline DAS28 (OR: 0.65, 95% CI: 0.50-0.83, p=0.001) and persistence duration (OR: 1.04, 95% CI: 1-1.08, p=0.05) were its predictors. Also, 84 patients achieved sustained function (HAQ below 0.21) and baseline DAS28 and age were the only predictors. Timing of first non-persistence period did not impact outcomes.

Conclusion: Persistence duration with DMARDs within the first 4 years of the disease predicted subsequent favorable outcomes in early RA patients; additional predictors were younger age, male gender and lower disease activity at diagnosis.

Disclosure: V. Pascual-Ramos, None; **I. Contreras-Yáñez**, None.

Abstract Number: 470

Disease Outcome in Patients Fulfilling the 2010 Classification Criteria for Rheumatoid Arthritis: The Impact of the Different Criteria Components

Ellen Sauar Norli[1,2], Gina Hetland Brinkmann[2,3], Tore K. Kvien[2], Olav Bjørneboe[1], Anne Julsrud Haugen[3], Halvor Nygaard[4], Cathrine Thunem[5], Elisabeth Lie[2] and Maria Dahl Mjaavatten[2], [1]Dept. of Rheumatology, Martina Hansens Hospital, Sandvika, Norway, [2]Dept. of Rheumatology, Diakonhjemmet Hospital, Oslo, Norway, [3]Dept. of Rheumatology, Østfold Hospital Trust, Fredrikstad, Norway, [4]Dept. of Rheumatology, Lillehammer Hospital of Rheumatic Diseases, Lillehammer, Norway, [5]Dept. of Rheumatology, Betanien Hospital, Skien, Norway
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Background/Purpose:

The 2010 ACR/EULAR classification criteria for rheumatoid arthritis (2010 RA criteria) facilitate early classification of rheumatoid arthritis (RA). The criteria yield a score ranging 0-10, with the cut-off for definite RA set at 6 or more points. In general, diagnostic certainty increases with an increasing number of criteria points. Our objective was to study the 2-year outcome in a cohort of patients (pts) with very early arthritis fulfilling the 2010 RA criteria at baseline, according to the contribution from the 4 different criteria components (joint involvement, serology, acute phase reactants, duration).

Methods:

1118 pts (age 18-75 years) with arthritis of maximum 16 weeks' duration were included in the NOR-VEAC (Norwegian Very Early Arthritis Clinic) study from 2004 to 2010. All pts who fulfilled the 2010 RA criteria at baseline and had follow-up data were included in the current analyses. Two clinical outcome groups were defined: "Persistent disease" (pts prescribed with DMARDs, with a final clinical diagnosis of RA and/or one or more swollen joints at last visit) and "self-limiting arthritis" (no DMARD use ever, final clinical diagnosis not RA and no swollen joints at last visit). The association between the components of the 2010 RA criteria and outcome was examined by univariable and multivariable logistic regression. Additionally, we performed subgroup analyses in the pts with only 6 criteria points.

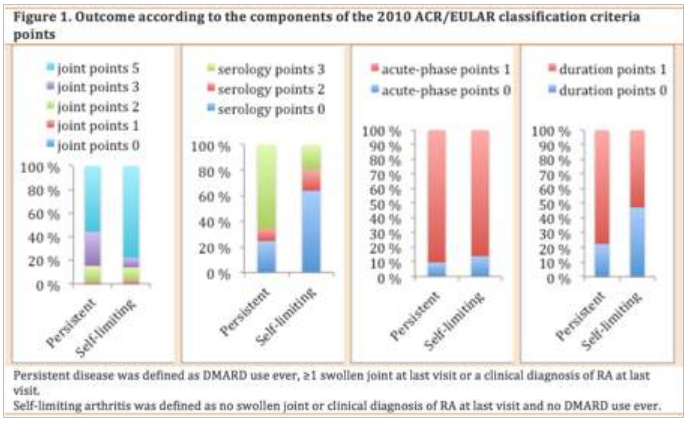
Results:

Of the 256 pts fulfilling the 2010 RA criteria (age 52.8±13.9 years, 63.3% females, median (25-75 perc.) duration of joint swelling 63.5 (40.0-83.0) days, 57.4% anti-CCP positive, DAS28 5.2±1.3), 36 had self-limiting arthritis. The pts with self-limiting vs persistent disease more often had 5 joint involvement points (77.8 vs 55.9%, p=0.013), 0 serology points (63.9 vs 24.5%, p<0.0005) and 0 duration points (47.2 vs 22.3%, p=0.002). Multivariable logistic regression showed that absence of serology points (OR 4.7, [2.2-10.1]) and duration points (OR 2.4, [1.1-5.1]) were independent predictors of self-limiting arthritis.

A total of 66 pts had only 6 criteria points, and 52.8% (19/36) of the pts with self-limiting arthritis belonged to this group. When the 6 points consisted of 5 joint involvement points and 1 acute phase point, 43.3% had self-limiting arthritis, as opposed to 16.7% for other 6-point combos (p=0.017). Pts with an additional duration point (5 joint involvement points, 1 acute phase point and 1 duration point) less frequently had self-limiting arthritis (19.5 vs 43.3%, p=0.03).

Conclusion:

In this study of 256 pts fulfilling the 2010 RA criteria at baseline, we found that not having a duration point or any serology points were associated with self-limiting arthritis. Pts with 6 criteria points made up by 5 joint involvement points and 1 acute phase point had a high likelihood of having self-limiting arthritis during the 2-year follow-up.



Disclosure: E. S. Norli, None; **G. H. Brinkmann**, None; **T. K. Kvien**, None; **O. Bjørneboe**, None; **A. J. Haugen**, None; **H. Nygaard**, None; **C. Thunem**, None; **E. Lie**, None; **M. D. Mjaavatten**, None.

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Abstract Number: 471

Impact of Baseline Anti-Cyclic Citrullinated Peptide 2 Antibody Titer on Efficacy Outcomes Following Treatment with Subcutaneous Abatacept or Adalimumab

Jeremy Sokolove[1], M Schiff[2], Roy Fleischmann[3], Michael Weinblatt[4], SE Connolly[5], A Johnsen[5], J Zhu[5], MA Maldonado[5], S Patel[5] and WH Robinson[6], [1]Stanford University School of Medicine, Palo Alto, CA, [2]University of Colorado, Denver, CO, [3]University of Texas Southwestern Medical Center, Dallas, TX, [4]Brigham and Women's Hospital, Boston, MA, [5]Bristol-Myers Squibb, Princeton, NJ, [6]Medicine, Division of Immunology and Rheumatology, Stanford University School of Medicine, Stanford, CA

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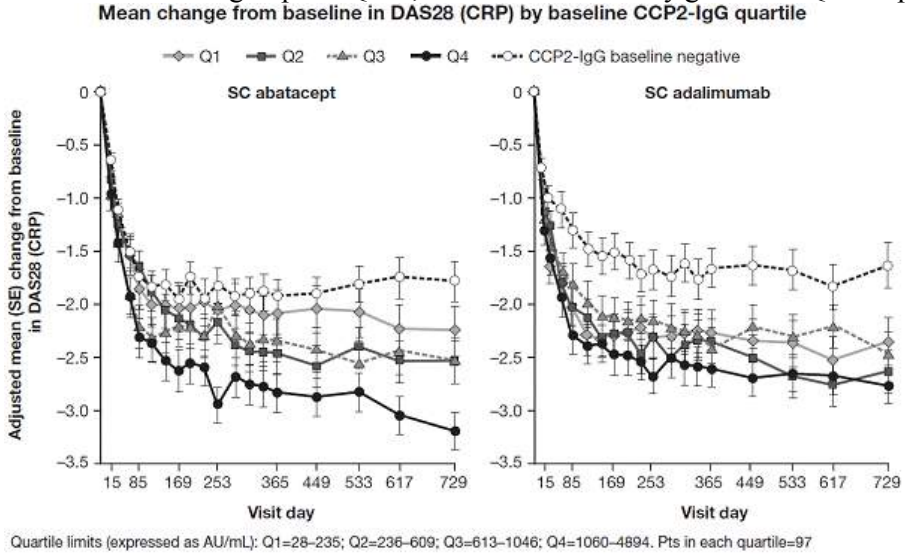
Background/Purpose: In patients (pts) with RA, the predictive value of baseline (BL) titers of anti-citrullinated protein antibodies (ACPA), a known biomarker for RA and disease progression,[1,2] on treatment outcomes is not well understood. In this *post hoc* analysis of the AMPLE study,[3] we assessed the efficacy of SC abatacept (ABA) and adalimumab (ADA) in pts with different BL levels of anti-cyclic citrullinated peptide 2 (CCP2) antibodies (a surrogate for ACPA).

Methods: Pt samples were analyzed by anti-CCP2 immunoglobulin (IgG) ELISA[4] and efficacy outcomes were assessed in positive pts divided into equal quartiles (Q) based on BL titer. Q1–Q4 represent increasing titers of anti-CCP2 antibody. Efficacy outcomes analyzed by Q were: mean change from BL in DAS28 (CRP) and HAQ-DI over time, and remission rates in terms of CDAI, SDAI, and DAS28 [CRP] <2.6-defined remission. Mean change from BL was determined by analysis of covariance, with treatment and DAS28 (CRP) stratification as factors, and BL values as a covariate. Data are also presented for change from BL in DAS28 (CRP) over time in pts who were anti-CCP2 antibody negative at BL. **Results:** There were 97 pts per Q. The numbers of pts per treatment group in each Q were (ABA, ADA): Q1=42, 55; Q2=51, 46; Q3=46, 51; Q4=46, 51. Overall BL characteristics were generally comparable, with no discernible pattern across Qs and treatment groups. For example, pts in ABA Q4 and ADA Q2 had numerically higher DAS28 (CRP) but lower HAQ-DI scores than pts in other Qs. For ABA, mean improvements from BL in DAS28 (CRP) and HAQ-DI were greater in the highest titer anti-CCP2 Q compared with the other Qs. The 95% CI of these measures for the highest and lowest titer Q did not overlap. There was no apparent association between these efficacy measures and BL anti-CCP2 titer in the ADA group. Adjusted mean change from BL in DAS28 (CRP) over time by BL anti-CCP2 Q, including pts anti-CCP2 negative at BL, is shown in the Figure. Reductions in DAS28 (CRP) and HAQ-DI by Year 2 were generally comparable in Q1–3 in both ABA and ADA groups. Remission rates across all indices were broadly similar in ABA and ADA groups in Q1–3, but were numerically greater in Q4 compared with Q1–3 in the ABA group only.



Conclusion: Higher titer anti-CCP2 antibody at BL is correlated with better efficacy in pts from the AMPLE study treated with abatacept, but not with adalimumab.[5]

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2. van der Woude D, et al. *Ann Rheum Dis* 2010;**69**:1554–61.

3. Schiff M, et al. *Ann Rheum Dis* 2014;**73**:86–9.

4. Anti-CCP2 ELISA, Euro Diagnostica. http://www.eurodiagnostica.com/upload/files/fileLibrary/ProductSheet_CCPlus_Screen120504.pdf. Accessed 15 Jan 2015.

5. This abstract was first presented at the EULAR Congress, 10–13 June 2015, Rome, Italy (AB0274) and published in the corresponding supplement of *Ann Rheum Dis*.

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Abstract Number: 472

Quality Assessment in Clinical Management of Patients with Rheumatoid Arthritis. Are We Using the “Treat to Target” Strategy?

Jose Luis Andreu[1,2], Maria Auxiliadora Martin[3], H Corominas[4], Jose Javier Perez Venegas[5], Jose Andres Roman Ivorra[6,7], Angel Gil[8], Fernando Sánchez-Alonso[9], Tamara Jiménez[10] and Miguel Angel Sánchez-Ruiz[10], [1]Rheumatology, Hospital Universitario Puerta de Hierro Majadahonda, Majadahonda, Spain, [2]Rheumatology, HU Puerta de Hierro Majadahonda, Madrid, Spain, [3]Research Unit of Spanish Society of Rheumatology,, Madrid, Spain, [4]CapiCAT group (Nailfold Capillaroscopy group from the Catalan Society for Rheumatology)., Catalonia, Spain, [5]Rheumatology, Hospital de Jerez de la Frontera, Jerez de la Frontera, Spain, [6]Rheumatology, H.U. P. La Fe, Valencia, Spain, [7]Servicio de Reumatología, Servicio de Reumatología Hospital Universitario La Fe, Valencia, Spain, [8]Cátedra de Resultados en Salud, Universidad Rey Juan Carlos, Madrid, Spain, [9]Unidad de Investigación. Sociedad Española de Reumatología, Madrid, Spain, [10]Universidad Rey Juan Carlos, Madrid, Spain

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SESSION INFORMATION
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Background/Purpose:

The current paradigm of optimal clinical management of patients with rheumatoid arthritis (RA) recommends reaching a

state of remission or low activity of the disease, assessed by composite indexes of activity, by means of a tight control and a dynamic adjustment of available therapeutic options, using a "treat to target" strategy. The aim of this work is to assess the level of implementation of the "treat to target" strategy and other parameters of medical quality in clinical records (CRs) of RA patients in Spanish rheumatology departments.

Methods:

Adult RA patients fulfilling 2010 ACR-EULAR criteria for RA and diagnosed between January 1st, 2010 and December 31st, 2013 in Spanish rheumatology departments were included. From every centre, 19 patients were randomly chosen from a computerized anonymized list provided by every department. Independent auditors assessed the CRs, verifying the fulfilling of the quality criteria included in an assessment tool specifically developed for this project. The study was approved by the ethic committees of every participant hospital. Descriptive statistics were used for the presentation of the results.

Results:

A total of 254 CRs from 14 rheumatology departments were included. An explicit assessment of the disease activity as a determinant element considered to choose the therapy was recorded in 32% of the CRs. An optimal escalation of methotrexate dose was registered in 77% of the cases. Use of a composite disease activity score (DAS28, SDAI, CDAI) was reported in 88% of the cases. Disease activity monitoring every 6-8 months after reaching the therapeutic target was recorded in 57% of the cases. In 96 % of the cases, the clinicians had registered patient´s comorbidities and these associated conditions had been considered in planning the therapeutic approach and objective. In only 3.8 % of the CRs, visits every 4 weeks using a composite activity score had been reported during the early stage while trying to reach remission after diagnosis. Starting a DMARD in the first two weeks after diagnosis was recorded in only 30 % of the cases.

Conclusion:

Currently, the implementation of the “treat to target” strategy is scarcely registered in clinical records of patients diagnosed with RA in Spanish rheumatology departments.

Disclosure: J. L. Andreu, None; **M. A. Martin**, None; **H. Corominas**, None; **J. J. Perez Venegas**, None; **J. A. Roman Ivorra**, None; **A. Gil**, None; **F. Sánchez-Alonso**, None; **T. Jiménez**, None; **M. A. Sánchez-Ruiz**, None.

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Abstract Number: 473

Methotrexate, Blood Pressure and Arterial Wave Reflection in Rheumatoid Arthritis

Leena R Baghdadi[1,2,3], Richard J Woodman[2], **E Michael Shanahan**[4] and Arduino A Mangoni[3], [1]Department of Family and Community Medicine, King Saud University, Riyadh, Saudi Arabia, [2]Flinders Centre for Epidemiology and Biostatistics, Flinders University, Adelaide, Australia, [3]Department of Clinical Pharmacology, Flinders University, Adelaide, Australia, [4]Department of Rheumatology, Flinders University, Adelaide, Australia
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Session Time: 9:00AM-11:00AM

Background/Purpose: Methotrexate (MTX) use has been associated with reduced cardiovascular morbidity and mortality in patients with rheumatoid arthritis (RA). Although MTX has anti-inflammatory effects, there is little evidence to support additional salutary effects on markers of cardiovascular risk such as blood pressure (BP) and arterial wave reflection (augmentation index, AIx), an indirect marker of arterial stiffness. Observational studies have suggested a lower systolic BP (SBP) in MTX users, approximately 3 mmHg, but it is unknown whether this is independent of anti-inflammatory effects. Thus, the purpose is to investigate associations between MTX, SBP and AIx in RA patients.

Methods: Using a cross-sectional study design, a total of 86 patients with RA (diagnosed using the 2010 American College of Rheumatology criteria) were recruited from rheumatology outpatient clinics at Flinders Medical Centre and Repatriation General Hospital, Adelaide, Australia. Participants were classified according to MTX exposure: MTX and non-MTX (defined as off MTX for >1 year or MTX naïve).

Results: There were 56 MTX (70% female; mean age 61 years) and 30 non-MTX patients (76% female; mean age 63 years). After adjusting for age, mean ±SD clinical SBP was significantly lower in MTX patients (124±1.9 mmHg, $p<0.001$) compared to non-MTX patients (131±2.9 mmHg, $p<0.001$). There were similar differences for central SBP 115 ±1.9 vs. 122 ±3 mmHg, $p<0.001$). MTX use was also associated with lower AIx (28%, 95% CI= 25.7, 29.9 vs. 31%, 95% CI= 27.5, 34.5, $p< 0.001$). Changes in the global inflammatory marker (ESR) and disease activity score (DAS28) and anti-CCP were not significantly associated with clinical SBP ($p=0.80$, 0.79 and 0.65) or AIx ($p=0.86$, 0.76 and 0.051), respectively. Changes in the short-term inflammatory marker CRP were associated with SBP ($\beta=0.42\pm0.17$, $p=0.02$), but not AIx ($\beta=0.86\pm0.1$, $p=0.37$).

Conclusion: Our findings show that the use of MTX is associated with lower systolic blood pressure, which is associated with reduced inflammation. The lower arterial wave reflection in MTX patients was independent of changes in inflammation.

Disclosure: L. R. Baghdadi, None; **R. J. Woodman**, None; **E. M. Shanahan**, None; **A. A. Mangoni**, None.

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Abstract Number: 474

Trends in the Use of Opiates in Rheumatoid Arthritis (RA) Compared to Non-RA: A Population Based Study in 2003-2012

J.A. Zamora-Legoff[1], Sara J. Achenbach[2], Cynthia S. Crowson[3], John M. Davis III[1] and Eric L. Matteson[4], [1]Division of Rheumatology, Mayo Clinic, Rochester, MN, [2]Department of Health Sciences Research, Mayo Clinic, Rochester, MN, [3]Health Sciences Research, Mayo Clinic, Rochester, MN, [4]Division of Rheumatology, Department of Internal Medicine and Department of Health Sciences Research, Mayo Clinic, Rochester, MN

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Background/Purpose: Opiates are often used to treat difficult to manage pain, however, little is known about the trends of use for opiates in a modern cohort of patients with rheumatoid arthritis (RA). We aimed to evaluate the use of opiates in patients with RA compared to non-RA subjects.

Methods: Retrospective prescription data was examined from 2003-2012 in well-defined population-based incidence cohort of patients with RA by 1987 ACR criteria in 2003-2007 and age/sex matched to non-RA subjects. Any opiate use was defined as one or more prescriptions in the study period and chronic use was defined as 60 days or more of prescribed opiates (at usual dose and usual schedule) in a 6 month period; or those subjects using fentanyl, methadone and controlled/sustained release oxycodone. Disease severity indicators used were RF/ACPA positivity, rheumatoid nodules and erosions in the first year, male sex, and ESR values. Poisson models and age and sex adjusted Cox models were used to examine differences in opiate use between the cohorts.

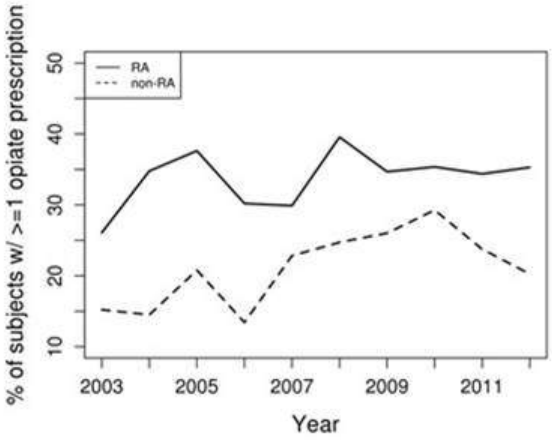
Results: A total of 404 subjects (202 pairs; 69%female) were included in the study with a mean age of 55 ± 15.7 and a mean follow-up date of 6.5 ± 2.4 years. The most frequently prescribed opiate in our study was oxycodone (40%) followed by hydrocodone (20%).

Opiate use (any) was high in both cohorts (35% RA vs 20% non-RA in 2012). Patients with RA had a 54% higher rate of opiate use compared to non-RA subjects (rate ratio {RR}: 1.54; 95% confidence interval {CI}: 1.36, 1.74; Fig. 1a). Chronic opiate use was also common in both cohorts (11% RA vs 7% non-RA in 2012). Patients with RA had a 70% higher rate of chronic opiate use (RR: 1.70; 95% CI: 1.15, 2.53) compared to non-RA subjects (Fig. 1b).

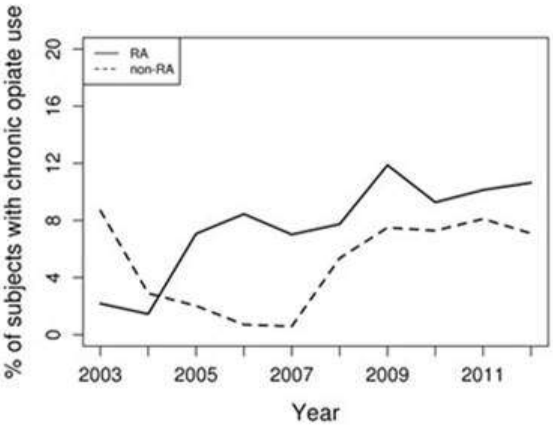
The rate of chronic opiate use increased in both cohorts by 11% per year with no apparent difference in time trends between the cohorts (interaction p=0.46). Women in both cohorts were more likely to be chronic opiate users than men (Hazard ratio [HR]: 1.82; 95% CI: 1.01-3.29). Compared to non-RA subjects, chronic opiate use was higher in younger patients with RA (age 18-49; 3.4% RA vs. 0.5% non-RA), we saw no difference in those over 65 years of age (interaction p=0.007), and a numerically intermediate risk in those 50 to 64. The only marker of disease severity and chronic opiate use was presence of rheumatoid nodules (HR: 1.95; 95% CI: 1.00-3.81).

Conclusion: Opiate use is common. Throughout the study period, rates of any opiate use remained stable but were always significantly higher in patients with RA than those without RA. However, rates of chronic opiate use increased in both cohorts over time and were consistently higher in patients with RA, especially among younger patients and women. In RA, opiate use was generally not related to disease severity indicators suggesting an alternate pain generating pathway.

A. Percentage of rheumatoid arthritis (RA) and non-RA subjects with any opioid prescription according to calendar year



B. Percentage of rheumatoid arthritis (RA) and non-RA subjects with chronic opiate use according to calendar year



Disclosure: J. A. Zamora-Legoff, None; **S. J. Achenbach**, None; **C. S. Crowson**, None; **J. M. Davis III**, None; **E. L. Matteson**, Novartis/Sanofi/Centocor-Jansen/Celgene/Amgen/Roche/Genentech/Mesoblast/Pfizer, 2.

Abstract Number: 475

Benefits of Achieving Comprehensive Disease Control (CDC) in Patients with Rheumatoid Arthritis: Evidence from the Corrona Registry

Arthur Kavanaugh[1], Carol J. Etzel[2,3], Wendi Malley[3], Chitra Karki[3], Jeffrey D. Greenberg[3,4], Yanjun Bao[5], Naijun Chen[5] and Vishvas Garg[6], [1]University of California, San Diego School of Medicine, LaJolla, CA, [2]The University of Texas MD Anderson Cancer Center, Houston, TX, [3]Corrona, LLC, Southborough, MA, [4]NYU School of Medicine, New York, NY, [5]AbbVie Inc., North Chicago, IL, [6]AbbVie, North Chicago, IL

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SESSION INFORMATION

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Session Title: Rheumatoid Arthritis - Clinical Aspects Poster I
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Session Time: 9:00AM-11:00AM

Background/Purpose: Based on international task force recommendations, the primary goal of rheumatoid arthritis (RA) treatment is to: achieve control of symptoms to greatest extent possible, prevent progression of structural damage, and normalize functional status and social participation (1). A Current definition of comprehensive disease control (CDC) defined as DAS28 (CRP) <2.6, HAQ DI <0.5, D mTSS (modified Sharp score) ≤0.5 has been assessed using data from three clinical trials (DE019, PREMIER and OPTIMA) (2). The objective of this study was to examine the potential incremental benefit of achieving CDC using real world data from Corrona, a large observational RA registry in the USA. Because there were not enough patients who achieved remission but not CDC, data were assessed for patients who achieved CDC compared to those achieving LDA but not CDC, using various measures of LDA.

Methods: RA patients ≥18 years of age in moderate/high disease activity (CDAI>10) with available CDAI, mHAQ and data on new radiographic progression at index visit and at 6m were included, regardless of disease modifying anti-rheumatic drug (DMARD) therapy status. Corrona patients were classified as achieving CDC vs not achieving CDC based on a previously constructed model including age, gender, disease activity index (CDAI), modified health assessment questionnaire (mHAQ) and presence of any new radiographic progression. Patient characteristics at index visit and 6m were compared between predicted CDC achievers and non-achievers but in LDA as defined by other measures like CDAI, DAS28-CRP, mDAS and RAPID3.

Results: There were 1627 patients who met the inclusion criteria of which 20% were CDC achievers (n=331) and 80% non-achievers (n=1296). CDC achievers had significantly lower patient reported pain, fatigue, presence of morning stiffness at baseline, 6m and greater change from baseline. In addition, fewer CDC achievers reported quality of life problems at 6m from baseline compared to cohorts who achieved LDA (defined by CDAI, DAS28-CRP, and mDAS) (**Table**). However same degree of differences in work status, patient pain and fatigue and quality of life measures were not seen in the cohort achieving LDA defined by RAPID3. Patients who achieved LDA (RAPID3) reported lower patient reported pain and fewer patients were disabled at 6m when compared to the CDC achievers. (**Table**).

Conclusion: In this real world analyses, patients who achieved CDC had significant improvement in clinical, structural and functional efficacy outcomes at 6 months compared to the patients who did not achieve CDC but were in LDA defined by CDAI, DAS28-CRP, or mDAS with the exception of RAPID3, where we observed better outcomes for certain patient reported measures. Further studies to assess incremental value of CDC over remission will be valuable.

References: 1. Smolen JS et al. 2010 doi: 10.1136/ard.2009.123919. 2. Emery P et al. 2014 Aug 19. pii: annrheumdis-2014-205302.

Table: Change in patient outcomes at 6 months from baseline among CDC achievers and CDC non-achievers

	CDC achievers, change from baseline				CDC non-achievers but in LDA, change from baseline			
Outcomes	cohort 1 CDAI	cohort 2 DAS28-CRP	cohort 3 mDAS	cohort 4 RAPID3	cohort 1 CDAI	cohort 2 DAS28-CRP	cohort 3 mDAS	cohort 4 RAPID3
Pain, mean (SD)	14.5 (24.1)	12.7 (23.5)	14.5 (24.1)	14.3 (24)	10.6 (25.8)	11.37 (23)	10.4 (27.3)	17.1 (25.7)
Fatigue, mean (SD)	10.04 (29)	6.6 (30.1)	10.04 (29)	9.9 (29.1)	6.5 (26.3)	9.2 (27.4)	5.8 (26.3)	9.6 (26.1)
Morning stiffness in hours, mean (SD)	0.59 (2.3)	0.5 (2.1)	0.59 (2.3)	0.6 (2.3)	0.37 (3.8)	0.4 (3)	0.19 (2.9)	0.2 (2.9)
Morning stiffness*	11.1%	10.8%	11.1%	11.3%	3.1%	4.1%	3.9%	5.3%
Percent not disabled**	1%	1%	1%	0.9%	5%	7%	4%	3%

*percent of patients (out of total) who had ≥ 1hour of morning stiffness at baseline and no morning stiffness at 6m **percent of patients (out of total) that were disabled at baseline and not disabled at 6 months

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Disclosure: A. Kavanaugh, Amgen Abbvie Jannsen Pfizer Novartis, 2; **C. J. Etzel**, Corrona, LLC., 3; **W. Malley**,

Corrona, LLC., 3; **C. Karki**, Corrona, LLC, 3; **J. D. Greenberg**, Corrona, LLC., 3,Corrona, LLC., 1,AstraZeneca, Celgene, Genentech, Janssen, Novartis and Pfizer, 5; **Y. Bao**, AbbVie, Inc., 1,AbbVie, Inc., 3; **N. Chen**, AbbVie, Inc., 1,AbbVie, Inc., 3; **V. Garg**, AbbVie, Inc., 1,AbbVie, Inc., 3.

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Abstract Number: 476

Clinical Disease Activity Measures Change Substantially and Irregularly over Time in Individual Rheumatoid Arthritis Patients Considered to be in Steady State

Ole Rintek Madsen[1,2] and Emilie Lund Egsmose[3], [1]Department of Reumatology/C, Copenhagen University Hospital Gentofte, Hellerup, Denmark, [2]The DANBIO registry, Copenhagen University Hospital Glostrup Rigshospitalet, Glostrup, Denmark, [3]Department of Rheumatology/C, Copenhagen University Hospital Gentofte, Hellerup, Denmark
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Background/Purpose:

Assessment of clinical markers of disease activity is routine in monitoring patients with rheumatoid arthritis (RA) in daily practice. Changes in clinical measures may reflect natural variation (measurement error) or “real change”. Natural variation is assessed in individuals who are considered to be in “steady state”. We examined natural variation of traditional clinical disease markers in biologically treated patients with stable RA according to EULAR response criteria.

Methods:

233 RA patients treated with a biological agent and with stable disease were identified in the Danish rheumatology registry (DANBIO). According to EULAR response criteria, stable disease was defined as a change in DAS28-CRP ≤ 0.6 between two consecutive visits. Paired data from a single set of such two consecutive visits were extracted for each patient. Data comprised DAS28-CRP and its components, patient global assessment (PaGl), pain, HAQ-DI and physician global assessment (PhGl). Variation of the disease markers on the individual level was expressed as lower and upper 95% limits of agreement (LLoA;ULoA) between two consecutive assessments and changes on the group level as the bias (mean of individual differences) according to the Bland-Altman method. Associations were assessed by Pearson's correlation analyses.

Results:

Male/female ratio was 56/177, mean age 60±15 years, mean inter-visit time duration 22±21weeks, mean DAS28-CRP 3.1±1.2, and mean change in DAS28-CRP 0.0±0.3 (range -0.6 to 0.6) (NS). Results of the variation analyses are shown in the Table. No changes between the repeated tests were found on the group level but limits of agreement in individual patients were wide for all measures. Intra-individual changes was not explained by inter-visit time duration (r = 0.0 to -0.1, NS). Moreover, intra-individual changes of the different measures were not or only weakly inter-correlated (r = -0.3 to 0.1, NS or $p < 0.05$). Changes between the repeated tests were similar for males and females (NS).

Conclusion:

Traditional markers of disease activity varied substantially and irregularly over time in individual RA patients considered to be in steady state. These variations reflect, by definition, measurement errors, and should be taken into consideration when monitoring patients in the daily clinic.

Table. Agreement between two consecutive assessments of clinical measures in RA patients with stable disease activity (change in DAS28-CRP ≤ 0.6).

	Visit 1	Visit 2	bias	p	**LLoA**	**ULoA**
Clinical measure	mean±SD					
Swollen joints (0-28)	1.6±2.3	1.6±2.3	0.0±1.7	1.0	-3.3	3.3
Tender joints (0-28)	3.0±5.0	3.0±4.8	0.0±2.0	1.0	-3.9	3.9
PaGl (0-100)	37.4±26.5	38.0±27.0	0.7±14.8	0.5	-28.3	29.7
CRP (mg/l)	8.4±13.2	8.8±17.2	0.5±16.6	0.6	-32.0	33.0
HAQ-DI	1.0±1.2	1.0±1.1	0.0±1.3	0.9	-2.5	2.5
Pain (0-100)	32.4±25.2	31.9±25.8	-0.5±18.0	0.7	-35.8	34.8
PhGl (0-100)	15.1±14.8	14.9±15.7	0.2±11.3	0.8	-22.3	21.9

LLoA: Lower limit of agreement; ULoA: Upper limit of agreement.

Disclosure: O. Rintek Madsen, None; **E. L. Egsmose**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/clinical-disease-activity-measures-change-substantially-and-irregularly-over-time-in-individual-rheumatoid-arthritis-patients-considered-to-be-in-steady-state

Abstract Number: 477

On-Demand Use of Etanercept Only for Disease Flares Reduced the Disease Activity Score and Structural Damage Equivalent to Fully-Use of Etanercept in RA Patients

Kentaro Inui[1], Tatsuya Koike[2], Masahiro Tada[3], Yuko Sugioka[2], Kenji Mamoto[4], Tadashi Okano[4], Akira Sakawa[5], Kenzo Fukushima[6] and Hiroaki Nakamura[4], [1]Orthopaedic Surgery, Osaka City University Graduate School of Medicine, Osaka, Japan, [2]Center for Senile Degenerative Disorders (CSDD), Osaka City University Graduate School of Medicine, Osaka, Japan, [3]Orthopaedic Surgery, Osaka City General Hospital, OSAKA, Japan, [4]Orthopedic Surgery, Osaka City University Graduate School of Medicine, Osaka, Japan, [5]Orthopaedic Surgery, Osaka City Juso Hospital, Osaka, Japan, [6]Orthopaedic Surgery, Fujiidera Municipal Hospital, Fujiidera, Japan
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Background/Purpose: Biological disease-modifying antirheumatic drugs (bDMARDs) are essential in the treatment of rheumatoid arthritis (RA). Biological DMARDs are particularly recommended for patients with active RA who may

incur further joint damage. However, in daily clinical practice, some patients with RA do not accept or discontinue bDMARDs because of their high cost. Similar to use of glucocorticoids, the use of bDMARDs may be limited to periods of high disease activity to help reduce patient costs. For this option to work well, the efficacy of a bDMARD should be maintained when restarting the same bDMARDs after several periods of discontinuation, bDMARDs holiday. We conducted a prospective, nonrandomized, non-blinded study (RESUME study: UMIN000008164) to examine the sustained efficacy of etanercept (ETN) after starting and stopping ETN several times in the patients with rheumatoid arthritis.

Methods: Thirty-one bDMARD-naive patients with RA with moderate to severe disease activity (Disease Activity Score 28 [DAS28] of ≥3.2) were enrolled in this study with written consent from 1 January 2011 to 31 December 2012. Their average age was 60 years and average disease duration was 5 years. ETN was administered at 50 mg/week and discontinued when low disease activity (LDA) (DAS28 of <3.2) was achieved. Upon recurrence, the same dose of ETN was administered with observation every 2 months. This strategy was maintained for 2 years. If patients did not achieve LDA within 3 months of ETN administration, other synthetic DMARDs other than glucocorticoids and tacrolimus were administered. If LDA was not achieved within 6 months, the patients were withdrawn from the trial. Clinical measure by DAS28, blood test, radiography (mTSS) was analyzed at baseline, 1 year, and 2year visit. In order to compare the structural damage of this study population, another series of 31 patients with RA treated with fully-use of ETN were evaluated by mTSS.

Results: Thirteen of the 31 patients had an inadequate response to ETN and were withdrawn from the study. Five patients had no flare-up of disease activity after discontinuation of ETN during the observation period. In the remaining 13 patients (8 women), on-demand use of ETN was carried out to maintain LDA. The mean dose of methotrexate in these 13 patients was 10 mg/week, rheumatoid factor was positive in 11 patients, and the mean follow-up period was 20.5 months. All 13 patients achieved LDA at the final follow-up after starting and stopping the ETN several times. The cost-saving calculation was approximately 28% among the five patients who maintained LDA with no need to restart ETN. Structural remission (DmTSS =<0.5) was achieved in 82% of the 13 patients as evaluated by the total Sharp score in 1 year, and 50% in 2 years. Structural remission rate in this study population in 1 year was equivalent to that of full dose use (p=0.464, Fisher's exact probability test).

Conclusion: On-demand use of ETN for disease flares reduced disease activity score and structural damage at low cost.

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Abstract Number: 478

Impact of Comorbidities on the Multi-Biomarker Disease Activity Test in Rheumatoid Arthritis Patients

Jeffrey R. Curtis[1], Jeffrey D. Greenberg[2], Leslie Harrold[3] and J. Lynn Palmer[4], [1]University of Alabama at Birmingham, Birmingham, AL, [2]Corrona, LLC, Southborough, MA, [3]Department of Medicine, UMass Memorial Medical Center, Worcester, MA, [4]Corrona Research Foundation, Albany, NY

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Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose:

The multi-biomarker disease activity (MBDA) score [Vectra] has been evaluated in a number of settings, yet has only limited data evaluating whether it is influenced by comorbidities common to rheumatoid arthritis (RA) patients.

Methods:

Using data from the CORRONA registry through (December, 2014), we conducted a cross-sectional analysis of RA patients who had received at least one MBDA test performed as part of standard of care, concurrent with C reactive protein (CRP) ordered on the same day. Patients were characterized descriptively by MBDA category (low, <=29; moderate 30-44; and high, >= 45) and by CRP, ESR, swollen joint count and CDAI category. LOESS plots of MBDA score by SJC were stratified by common comorbidities (smoking, fibromyalgia, COPD, diabetes, body mass index [BMI]) to visually evaluate the influence of the comorbidity on the MBDA score. Ordinary least squares regression was used to evaluate the association between MBDA score and age, sex, comorbidities and RA-related factors. The comorbidities were considered confounders if adjusting for them changed the MBDA-SJC association by more than 10% (change-in-estimate criterion).

Results:

A total of 585 patients had at least 1 MBDA test concurrent with a CRP performed for standard of care reasons. Patient characteristics were mean (IQR) 65 (54,73) years, 78% female, 66% white, 27% Hispanic. Mean (IQR) BMI was 28.0 (24.5, 32.1); comorbidity prevalence was 10% (diabetes), 3% (COPD), 5% (fibromyalgia); 12% current, 39% former, and 49% never smokers. A total of 72% (n=423) of patients had normal CRP (<10 mg/L); of these, 31% had high, 44% had moderate, and 25% had low disease activity as classified by MBDA (Figure 1).

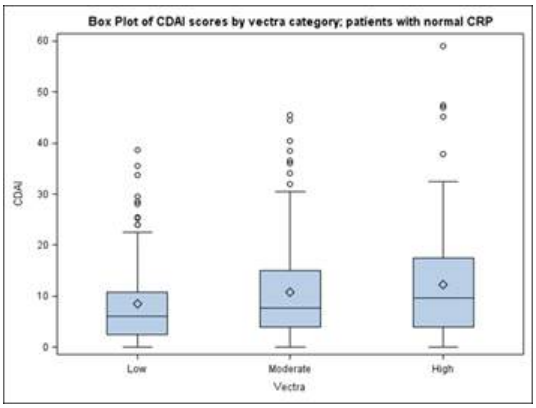
The MBDA score was significantly associated with SJC (correlation coefficient 0.20, $p < 0.0001$), and was minimally different between patients who did and did not have each of the comorbidities . In bivariate models, there was no significant association between MBDA score and fibromyalgia, diabetes, or COPD, and these factors did not yield confounding between either MBDA score and SJC, nor MBDA and CDAI. CRP alone explained 33% of the variance (R^2) in MBDA score. In the multivariable model, MBDA remained significantly associated with both SJC and CDAI even after adjusting for age, sex, comorbidities, BMI, current steroid use, and other factors.

Conclusion:

In this real-world RA registry, the MBDA score was associated with RA disease activity and was negligibly affected by comorbidities common to RA patients. Approximately one-third of patients with normal CRP levels had high MBDA scores, suggesting the potential that MBDA may provide an opportunity to use an objective lab measure to identify RA patients with active disease even when CRP is normal.

Figures 1: Distribution of CDAI according to MBDA score category for RA patients

with normal CRP (< 10mg/L) [n=423]



Disclosure: J. R. Curtis, Roche/Genentech, UCB, Janssen, CORRONA, Amgen, Pfizer, BMS, Crescendo, AbbVie, 2,Roche/Genentech, UCB, Janssen, CORRONA, Amgen, Pfizer, BMS, Crescendo, AbbVie, 5; **J. D. Greenberg**, Corrona, LLC., 3,Corrona, LLC., 1,AstraZeneca, Pfizer, Celgene, Novartis, 5; **L. Harrold**, Astra Zeneca, Pfizer, 2,Pfizer, Roche/Genentech, 5,Corrona, 3; **J. L. Palmer**, None.

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Abstract Number: 479

How to Recruit Anti-CCP Positive Patients from Primary Care

Jackie L. Nam[1], Laura Hunt[1], Elizabeth M.A. Hensor[1] and Paul Emery[1,2], [1]NIHR-Leeds Musculoskeletal Biomedical Research Unit and Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds, Leeds, United Kingdom, [2]Division of Rheumatic and Musculoskeletal Disease, University of Leeds, Leeds Institute of Molecular Medicine and LMBRU, Leeds, United Kingdom

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Background/Purpose:

Around 1% of the population test positive for anti-cyclic citrullinated peptide (anti-CCP) antibodies. This biomarker predicts progression to rheumatoid arthritis (RA) but over a variable time-frame. To increase its clinical relevance, this study sought to determine (1) if the proportion of anti-CCP positive individuals could be enriched by case selection of people attending primary care with new nonspecific musculoskeletal (MSK) symptoms but without clinical synovitis (CS) and (2) whether these individuals progress rapidly to inflammatory arthritis (IA), in particular RA.

Methods:

In this prospective cohort study, individuals aged ≥18 years with new nonspecific MSK symptoms, without CS, were recruited from primary care in the U.K. Anti-CCP positive individuals were invited for follow-up in the rheumatology department, Leeds. Those who tested negative were sent questionnaires 12 months later.

Results:

2028 individuals were recruited. Of the 2.8% (57/2028) who were anti-CCP positive, 47% (27/57) developed IA [24 RA; 1 undifferentiated IA (UIA); 2 polymyositis]; 92.6% (25/27) within 12 months, [median (IQR) 1.8 (1.0-4.3) months, range 0.3 to 16.1]. Of the anti-CCP negative individuals, 1.3% (20/1559) developed IA (13 RA; 1 UIA; 6 psoriatic arthritis); 75% (15/20) within 12 months. The RR for developing RA within 12 months in the anti-CCP positive group was 66.8 (32.2-138.4, p<0.001); for IA it was 45.5 (95%CI 25.4-81.6, p<0.001).

Conclusion:

Selecting individuals with new nonspecific MSK symptoms without CS enriched the prevalence of anti-CCP positivity to 2.8%. Those who tested positive had a high risk of rapidly developing RA. The cost effectiveness of this approach will need to be determined.

Disclosure: J. L. Nam, None; **L. Hunt**, None; **E. M. A. Hensor**, None; **P. Emery**, Pfizer, MSD, AbbVie, UCB, Roche, Bristol-Myers Squibb, 5.

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Abstract Number: 480

Comparative 10-Year Retention Rates of Adalimumab Used in Mono and Combination Therapy in Rheumatoid Arthritis (RA) Patients from the Rhumadata Clinical Database and Registry

Denis Choquette[1], Louis Bessette[2], Jacques Brown[3], Boulos Haraoui[1], Frédéric Massicotte[1], Jean-Pierre Pelletier[1], Jean-Pierre Raynauld[1], Marie-Anaïs Rémillard[4], Diane Sauvageau[1], Angèle Turcotte[3], Édith Villeneuve[1] and Louis Coupal[1], [1]Rheumatology, Institut de recherche en rhumatologie de Montréal (IRRM), Montréal, QC, Canada, [2]Centre d'Ostéoporose et de Rhumatologie de Québec (CORQ), Québec, QC, Canada, [3]Rheumatology, Centre d'ostéoporose et de rhumatologie de Québec (CORQ), Québec, QC, Canada, [4]Rhumatology, Institut de recherche en rhumatologie de Montréal (IRRM), Montréal, QC, Canada

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Session Time: 9:00AM-11:00AM

Background/Purpose: The recent publication of the concerto trial comparing the use of adalimumab in monotherapy versus in association with methotrexate (MTX) at dose varying from 2.5 to 20 mg weekly increased the awareness of the importance of anti-drug antibody in lowering the efficacy of adalimumab in patients with RA. Rhumadata®, a real life clinical database and registry, gives a unique opportunity to compare the two strategies over the very long term. Our objective is to evaluate the impact the combination of MTX over monotherapy on long term retention rate of adalimumab in a population of patients with RA followed at the *institut de recherche en rhumatologie de Montréal* (IRRM) ant the *Centre d'ostéoporose et de rhumatologie de Québec*(CORQ) and entered in the RHUMADATA® Clinical database and registry.

Methods: Data of RA patients who had been prescribed adalimumab (ADA) in any intention on or after January 1st

2002 was extracted. The data included age and gender, disease characteristics, clinical variables, patient and physician specific assessments, and laboratory measures. Composite assessment of disease activity including the DAS28-ESR and the simplified and clinical disease activity indices (SDAI and CDAI) were calculated using readily available formulas. All patients were followed until they discontinued their treatment or June 2, 2015, the date at which the data was extracted from Rhumadata®. Secondary diagnoses and comorbidities established at or before the administration of the biologic agents were coded using the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes. Infections occurring while on treatment, biologic status (ongoing or stopped) and the reasons for biologic cessation were also extracted. The 10-year drug retention rates were estimated and compared using Kaplan-Meier survival estimates. Statistical analysis was performed using SAS version 9.4.

Results: The data from 290 patients prescribed ADA (219 in combination therapy and 71 in mono therapy) in any intention were extracted from the RHUMADATA® clinical registry and database. The patients were mostly women (73.1%) and had an average age of 52.6(SD=12.8). The patients had an average disease duration of 7.4 years (SD=7.6) and were exposed to ADA for an average of 3.0 years (SD=3.1) providing 883.3 person-years of treatment. Patients prescribed MTX received an average daily dose of 15.4 mg (SD=6.1). The 10-year retention rates of ADA used in MONO and COMBO therapy were estimated at 13.6% (SD=5.4%) and 22.4% (SD=3.4%) respectively and an overall significant difference in retention rate was observed (log-rank p -value = 0.0107).

Conclusion: Using adalimumab in combination with methotrexate improve significantly the retention rate in patients suffering of RA

Disclosure: D. Choquette, None; **L. Bessette**, None; **J. Brown**, None; **B. Haraoui**, None; **F. Massicotte**, None; **J. P. Pelletier**, None; **J. P. Raynauld**, None; **M. A. Rémillard**, None; **D. Sauvageau**, None; **A. Turcotte**, None; **Villeneuve**, None; **L. Coupal**, None.

Abstract Number: 481

Time to Disease-Modifying Anti-Rheumatic Drug Treatment for New Patients with Rheumatoid Arthritis – Single Center Experience

Rok Ješe[1], Aleš Ambrožič[1], Natasa Gaspersic[2], Alojzija Hocevar[1], Boris Lestan[1], Martina Plešivčnik Novljan[2], Sonja Praprotnik[1], Ziga Rotar[1], Alenka Šipek Dolničar[1] and Matija Tomšič[1], [1]Department of Rheumatology, University Medical Centre Ljubljana, Ljubljana, Slovenia, [2]Department of Rheumatology, University Medical Centre Ljubljana, 1000 Ljubljana, Slovenia

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Background/Purpose:

In early rheumatoid arthritis (RA), initiation of disease-modifying anti-rheumatic drugs (DMARD) within 12 weeks of symptom onset is associated with a significant benefit in long-term disease outcome. Our objective was to determine the proportion of patients with RA in whom DMARD therapy was initiated within the desired time frame.

Methods:

A retrospective chart review of adult patients diagnosed with RA during year 2014 was performed at the rheumatology department of an integrated secondary/tertiary teaching hospital, which provides rheumatology services for a population of more than 500.000 residents. Potential cases were identified by searching the electronic medical records for ICD-10 codes M05.* and M06.* Electronic and paper records of patients were then thoroughly reviewed. Cases fulfilling the 2010 ACR/EULAR classification criteria for RA were included in the analysis. Dates were recorded for onset of inflammatory joint symptoms, initial assessment by a rheumatologist and initiation of DMARD therapy. The percentage of patients treated with DMARD within 12 weeks of symptom onset and the median times for delay were then calculated.

Results:

Between January 1st 2014 and December 31st 2014, 87 new cases of RA were identified at our Department of Rheumatology. Within 12 weeks of symptom onset, 52% of new RA patients were examined by a rheumatologist and 38% of patients were started on DMARD therapy, median time to consultation was 9.9 weeks [IQR 4.4-25.2 weeks], median time to establishment of diagnosis was 12.7 weeks [IQR 5.9-25.9 weeks] and median DMARD treatment delay was 14.4 weeks [IQR 7.6-27.7 weeks]. The preferred DMARD agent was methotrexate (77%), followed by sulfasalazine (9%) and leflunomide (2%). 12% of patients were not prescribed DMARD treatment for various reasons (mainly non-compliance and advanced age).

Table: Demographic data and clinical history	
Gender (female/male) (%)	78/22
Age, years (mean ± SD)	61.5 ± 15.2
Tender joint count (mean ± SD)	9.1 ± 7.6
Swollen joint count (mean ± SD)	8.7 ± 5.8
Erythrocyte sedimentation rate (ESR), mm/h (mean ± SD)	46 ± 23.3
C-reactive protein (CRP), mg/l (mean ± SD)	38 ± 44.0
Positive rheumatoid factor, %	62.1
Positive anti-CCP, %	67.8
DAS28 3v (mean ± SD)	5.4 ± 1.2
Time from symptom onset to first rheumatologist assessment, weeks (median)	9.9 (IQR, 4.4–25.2)
Time from symptom onset to DMARD initiation, weeks (median)	14.4 (IQR, 7.6–27.7)

Conclusion:

38% of new patients with RA were treated with a DMARD within the recommended time frame of 12 weeks. Most of the treatment delay was due to the time elapsed between symptom onset and consultation with a rheumatologist, suggesting the potential additional benefit of improved education of patients and primary care physicians.

Disclosure: R. Ješe, None; **A. Ambrožič**, None; **N. Gaspersic**, None; **A. Hocevar**, None; **B. Lestan**, None; **M. Plešivčnik Novljan**, None; **S. Praprotnik**, None; **Z. Rotar**, None; **A. Šipek Dolničar**, None; **M. Tomšič**, None.

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Abstract Number: 482

Erosions in the Foot at Baseline Are Predictive of Orthopedic Shoe Use

after 10 Years of Treat to Target Therapy

Sytske Anne Bergstra[1], Rosaline van den Berg[2], Naghmeh Riyazi[3], Gerda M. Steup-Beekman[4], Peter A.H.M. van der Lubbe[5], Pit J.S.M. Kerstens[6], Willem F. Lems[7], T. W. J. Huizinga[8], Robert B.M. Landewé[9,10] and Cornelia F. Allaart[1], [1]Department of Rheumatology, Leiden Universitary Medical Center, Leiden, Netherlands, [2]Leiden University Medical Center, Leiden, Netherlands, [3]Rheumatology, Haga Hospital, The Hague, Netherlands, [4]Rheumatology, Department of Rheumatology, Leiden University Medical Center, Leiden, Netherlands, [5]Vlietland Hospital, Schiedam, Netherlands, [6]Department of Rheumatology, Reade, Amsterdam, Netherlands, [7]Department of Rheumatology, VU Universitary Medical Center, Amsterdam, Netherlands, [8]Department of Rheumatology, Leiden University Medical Center, Leiden, Netherlands, [9]Amsterdam Rheumatology & Immunology Center, Academic Medical Center, Amsterdam, Netherlands, [10]Atrium Medical Center, Heerlen, Netherlands
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Background/Purpose: Orthopaedic shoes (OS) may help to reduce pain and increase activity participation in rheumatoid arthritis (RA) patients, but should ideally not be needed. We investigated the prevalence and potential risk factors of OS use in RA patients after 10 years of targeted treatment.

Methods: In the 4 treatment arms of the BeSt study, 508 patients with recent onset RA were treated aiming at disease activity score (DAS) ≤2.4. After 10 years, patients were asked if they used OS. Baseline characteristics of users and non-users were compared. Univariable binary logistic regression was performed with OS use as outcome, and baseline total Sharp/van der Heijde score (SHS), foot erosions and foot joint space narrowing (JSN) as continuous and dichotomous variables (cut-off ≥1) as potential predictors. Next, statistically significant predictors ($p<0.1$) were tested in a multivariable model simultaneously with rheumatoid factor (RF), smoking status, anti-citrullinated protein antibodies (ACPA) and DAS. Timing of OS use being unavailable, non-baseline factors were not considered. For highly correlated variables both associated with OS use, only the strongest contributing variable was added to the model. Predictors with statistically significant contribution were kept in the final model. Interaction of each predictor with treatment arm was tested and ruled out.

Results: Of 285/508 patients (56%) information was available regarding OS use at year 10. Responders to the question were younger than non-responders [age mean (SD) 51.3 (12.0) vs 58.4 (14.8) years, $p<0.001$], but were similar regarding gender, smoking status, ACPA, DAS, SHS, JSN and erosions (all baseline). Twenty-one percent (57/273) of the patients reported OS use after 10 years [68.4% female, mean (SD) age 50.3 (11.0) years, DAS 4.6 (0.9), SHS 4.7 (5.3), erosions 1.0 (2.3), JSN 1.0 (1.9), ACPA+ 83.3%, RF+ 77.2%, all baseline]. OS users were more often ACPA+ (77.2% vs 65.8%) and had more erosions [mean (SD) 1.25 (2.4) vs 0.48 (2.5), all $p<0.05$]. Univariable logistic regression showed that only foot erosions contributed significantly to the model as binary (OR 1.95, CI95: 1.1-4.8) but not as continuous variable (OR 1.06, CI95: 0.9-1.2). Neither total SHS nor foot-JSN (binary or continuous) contributed significantly to the model. Multivariable logistic regression showed that baseline foot erosions (binary; OR 1.85, CI95: 1.1-5.3), ACPA+ (OR 4.88, CI95: 2.0-10.6) and DAS (OR 1.72, CI95: 1.2-2.6) were independent predictors of OS use after 10 years. Combining baseline foot erosions, ACPA+ and baseline DAS created the best model.

Conclusion: Despite 10 years of DAS≤2.4 targeted treatment, 21% of recent onset RA patients with available data after 10 years used OS. Presence of foot erosions at treatment start predicts OS use after 10 years; the risk increases for ACPA+ patients and to a lesser extent for patients with higher baseline DAS.

Table 1: Logistic regression models to predict which patients will use orthopaedic shoes within 10 years of treatment start.

	Variable	N patients	Odds Ratio	95% confidence interval	P	Maximum Likelihood R^2
	Univariate predictors					
	SHS yes/no	268	1.99	0.99; 4.00	0.054	0.015
	Erosions foot yes/no	271	2.32	1.12; 4.80	0.045	0.018
	JSN foot yes/no	273	1.50	0.79; 2.86	0.152	0.006
	SHS	268	1.03	0.98; 1.09	0.206	0.006
	Erosions foot	271	1.06	0.95; 1.19	0.316	0.003
	JSN foot	273	1.08	0.94; 1.26	0.208	0.004
	Multivariable models					
1	Erosions foot yes/no	264	2.39	1.09; 5.25	0.029	0.090
	ACPA		5.06	1.95; 13.15	0.001	
	Rheumatoid Factor		0.84	0.35; 2.00	0.694	
	DAS		1.76	1.19; 2.61	0.005	
	Smoking status		1.09	0.55; 2.16	0.815	
2	Erosions foot yes/no	264	2.42	1.11; 5.27	0.026	0.090
	ACPA		4.64	2.03; 10.62	<0.001	
	DAS		1.77	1.20; 2.62	0.004	

SHS =Sharp/van der Heijde score, JSN = joint space narrowing, ACPA = anti-citrullinated protein antibodies, DAS = disease activity score. For all binary variables "no" was used as the reference category.

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Abstract Number: 483

Antibody to Malondialdehyde-Acetaldehyde (MAA) Adducts Serve As Biomarkers of Treatment Response in Rheumatoid Arthritis

Ted R. Mikuls[1], Brian Coburn[1], Harlan Sayles[2], Fang Yu[3], Mary Brophy[4], James R. O'Dell[1], Lynell W. Klassen[5] and Geoffrey M. Thiele[1], [1]Omaha VA Medical Center and University of Nebraska Medical Center, Omaha, NE, [2]University of Nebraska Medical Center, Omaha, NE, [3]Public Health, University of Nebraska Medical Center, Omaha, NE, [4]VA Boston Heathcare System, Boston, MA, [5]Dept of Internal Medicine, Omaha VA Medical Center and University of Nebraska Medical Center, Omaha, NE

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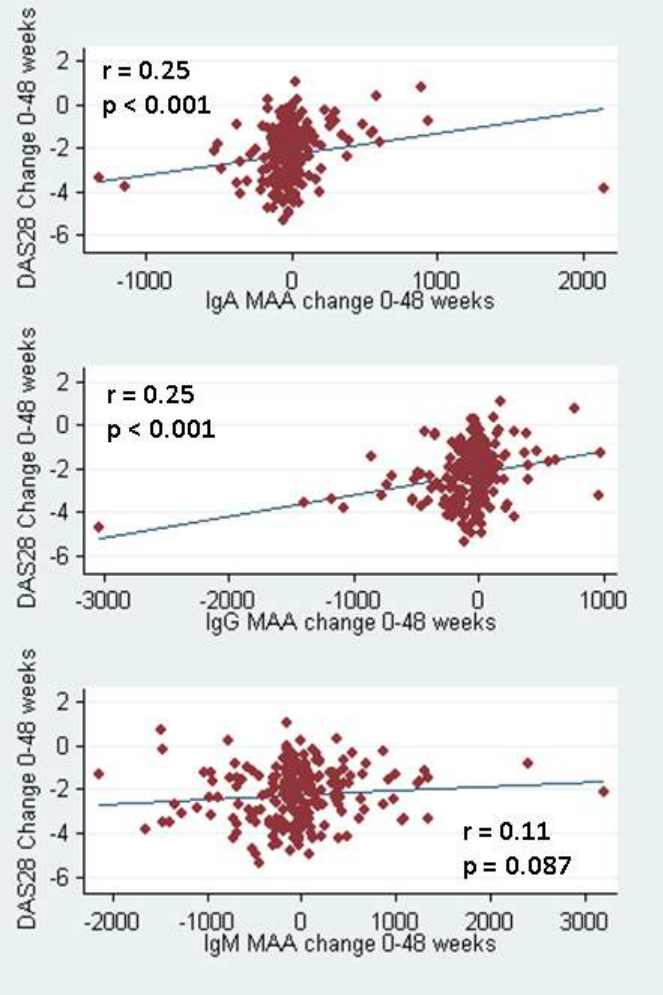
Background/Purpose: Previous reports have demonstrated that malondialdehyde-acetaldehyde (MAA) adducts are produced as a byproduct of oxidative stress and lipid peroxidation and are expressed in RA joint tissues (Thiele GM, Arthritis Rheumatol 2015). Moreover, MAA adducts co-localize with citrullinated proteins and promote robust T cell and antibody responses, the latter being associated with RA disease severity. Whether anti-MAA antibody concentrations predict treatment response in RA is unknown. The objective of this study was to examine the role of anti-MAA antibody isotypes in predicting RA treatment responses in a group of well-characterized patients participating in a randomized controlled trial.

Methods: As part of a secondary analysis of the Rheumatoid Arthritis Comparison of Active Therapies (RACAT) trial, banked serum from baseline, 24, and 48 weeks (n=255) were tested for anti-MAA antibody isotypes (IgA, IgG, IgM) using ELISA. In the 48-week trial, patients with active disease despite methotrexate (MTX) were randomized to receive triple therapy (MTX/sulfasalazine/hydroxychloroquine) or MTX/etanercept. Associations of treatment response with baseline antibody isotype concentrations and changes in antibody concentrations at 24 and 48 weeks were examined using non-parametric Spearman correlations. The primary treatment outcome in this analysis was the change in DAS28-ESR at 48 weeks.

Results: As previously reported (O'Dell JR, N Engl J Med, 2013), patients in the RACAT study had a mean age of ~57 years, 46% were women, and patients had a mean (SD) DAS28 at enrollment of 5.8 (1.9). There were no associations of baseline anti-MAA antibody concentration with treatment response at 24 or 48 weeks. Likewise, there were no associations of change in antibody concentrations with treatment response at 24 weeks. In contrast, changes in IgA and IgG anti-MAA antibody isotype concentrations from baseline to 48 weeks were significantly associated with treatment responses ($r=0.25$; $p<0.001$ for both isotypes) (Figure).

Conclusion: Treatment response in RA over one year of follow-up is strongly associated with declines in both IgA and IgG anti-MAA antibody isotypes, associations that are not apparent after just 6 months. These results and prior studies showing the importance of lipid peroxidation in both MAA adduct formation and RA suggest that anti-MAA antibodies may mediate or act as a marker of RA disease activity promoted through oxidative stress. Further studies will be needed to assess whether this relationship is dependent on specific therapies and to elucidate mechanisms through which reduced anti-MAA antibodies are associated with improved treatment responses in RA.



Disclosure: T. R. Mikuls, None; **B. Coburn**, None; **H. Sayles**, None; **F. Yu**, None; **M. Brophy**, None; **J. R. O'Dell**,

None; **L. W. Klassen**, None; **G. M. Thiele**, None.

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Abstract Number: 484

Race Plays a Role in Influencing the Modest Lipid Lowering Effects of Hydroxychloroquine in Patients with Rheumatoid Arthritis, Independent of Statin Use

Myriam Guevara[1], Bernard NG[1] and Nancy Gove[2], [1]Rheumatology, University of Washington, Seattle, WA, [2]Biostatistics, Seattle Children's, Seattle, WA

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SESSION INFORMATION

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Session Title: Rheumatoid Arthritis - Clinical Aspects Poster I

Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose: Despite remarkable improvements in RA treatment, there is evidence indicating that the mortality gap between RA patients and the general population is not closing. The increase in mortality in RA is predominantly due to cardiovascular (CV) disease. Literature suggests that important links exist between RA inflammation and atherosclerosis in CV diseases.Dyslipidemia is a well-known risk factor of atherosclerosis. Previous studies have suggested that anti-malarials, chloroquine diphosphate and hydroxychloroquine(HCQ), used in the treatment of autoimmune diseases, have a beneficial effect on the lipid levels. However the studies had small sample sizes. We have analyzed a Veterans Affair (VA) RA cohort of 2925 patients to characterize the effect of 4 months use of HCQ in lipid levels.

Methods: Data for this cohort was obtained from the department of VA administrative data base. All adult (age>=18 years) individuals with a diagnosis of RA (ICD 9 code) at 2 or more outpatient visits from 1999 to 2009 ,were identified. Only patients with at least one lipid level measured at 120-180 days prior to staring HCQ were included. Lipids levels at pre start date of HCQ and post start date of HCQ (120-180 days) were compared using students t-test and then adjusted for age, sex, race, CRP and statin use with multivariable regression (ANOVA/ANCOVA) for the change in different lipid levels. To give equal weight to covariables we conducted an analysis of marginal means for race in each lipid level. All analyses were performed with STATA 11.

Results:

	Yes on Statin	No on Statin	All	Demographics
Gender	402 (15.61%)	2174 (84.39%)	2576	Lipid changes in HCQ users

Male (N/%)			
Age (mean/SD)	69 (9.6)	64(12.20)	
Race White (N/%)	369 (15.50%)	1868 (83.50%)	2237
AA (N/%)	28 (8.26%)	312 (91.74%)	340
Others (N/%)	13 (3.06%)	123 (4.92%)	136
Unknown (N/%)	15 (3.53%)	197 (7.88%)	212
Pre-CRP mg/dl (mean/SD)	16.13 (13.53)	5.16 (12.14)	
Post-CRP mg/dl (mean/SD)	11.22 (37.9)	5.90(17.94)	

	Pre-mean (SE)	Post-mean (SE)	Total Difference	P value
Cholesterol	176.17 (.87)	171.65 (.90)	4.52	0.00
LDL	103.77 (.76)	98.86 (.76)	4.91	0.00
HDL	45.80 (.32)	46.18 (.32)	-0.38	0.06
Non-HDL	130.37 (.85)	125.46 (.86)	4.91	0.00
AI	4.17 (.38)	4.0 (.03)	0.17	0.00

Lipid changes in HCQ users by statin use groups.

	Yes Statins Mean (SD)	No Statins Mean (SD)
Change in Cholesterol	2.32 (37.72)	2.41 (33.18)
Change in LDL	4.76 (30.52)	5.09 (31.78)
Change in HDL	-0.35 (9.78)	- 0.41 (1.09)
Change in non HDL	2.92 (37.069)	5.52 (32.17)
Change in AI	.068 (1.29)	.164 (1.29)

After adjusting for sex, age, race, statin use and post crp values > 10mg/dl using a linear regression, the factor driving the change in the different lipid levels was race (p values for total cholesterol (TC) 0.006,LDL 0.09, non-HDL 0.03, TC/HDL 0.08 and HDL 0.17). When looking at race individually using marginal means analysis the race in the subgroup others was the more influential.

Conclusion: Our results suggest gender and race play a role in the effects of HCQ on lipid profiles in RA patients.Use of HCQ in males is found to be associated with positive changes in the lipid profiles independent from the use of statins. There is a suggestion that whites and African Americans might be less susceptivle to HCQ effect on lipid profiles.

Disclosure: M. Guevara, None; **B. NG**, None; **N. Gove**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/race-plays-a-role-in-influencing-the-modest-lipid-lowering-effects-of-hydroxychloroquine-in-patients-with-rheumatoid-arthritis-independent-of-statin-use

Abstract Number: 485

Evaluate the Dose Efficacy Response Relationship of Baricitinib in Patients with Rheumatoid Arthritis

Xin Zhang, Laiyi Chua, C. Steven Ernest II, William Macias, Terence Rooney and Lai San Tham, Eli Lilly and Company, Indianapolis, IN

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Background/Purpose: Baricitinib (Bari) is an oral inhibitor of Janus kinases (JAK) selective for JAK 1 and 2. It has demonstrated dose-dependent efficacy in patients with moderate-to-severe rheumatoid arthritis (RA) who have an inadequate response to methotrexate in multiple phase 2 studies. The objective of this analysis was to characterize the dose/exposure-response (D/E-R) relationship of Bari to optimize selection of doses and dose regimens for the phase 3 program.

Methods: Pharmacokinetics (PK) and efficacy data are available in patients with RA from two Phase 2 studies, Study JADA (n=278, Keystone E, et al.) and Study JADN (n=143, Tanaka Y, et al.), respectively. Study JADA used doses of 1, 2, 4, and 8 mg QD for up to 24 weeks and 2 mg BID for 12 weeks, and Study JADN used doses of 1, 2, 4, and 8 mg QD for up to 12 weeks. A Population PK (PopPK) model was developed to characterize plasma concentration-time profiles and identify potential covariates using NONMEM (version 7.2). A semi-mechanistic population PK/pharmacodynamic (PK/PD) model was developed to describe the time course and D/E-R relationship for the key efficacy endpoints, ACR20/50/70 and DAS28-CRP response rates. A placebo effect was accounted for in both PD models. A sequential PK and PK/PD analysis approach was used. The developed PK/PD model was subsequently applied to simulate ACR20/50/70 and DAS28-CRP response rates following various doses and dosing regimens (QD vs BID) to help optimizing dose selection for phase 3 studies.

Results: The models adequately described the PK and the longitudinal dose/exposure-response relationships for ACR20/50/70 and DAS28-CRP for all regimens tested in the phase 2 studies. The mean terminal half-life of BARI was estimated to be approximately 14 hours. Renal function was identified as a significant covariate on the clearance of BARI. No patient factors had a significant impact on the PK/PD relationship. PD steady state was attained approximately 12 weeks after treatment for all endpoints. Based on the dose/response curve, 4 mg approached the maximum effect and offered additional efficacy benefits over 2 mg. Simulations suggested that at the same total daily doses, QD and BID dosing regimens achieved similar average plasma concentrations at steady state. In addition, the efficacy responses were comparable between the QD and BID dosing regimens for all efficacy endpoints at the same total daily doses based on the simulations.

Conclusion: Based on modeling and simulations with phase 2 data over a dose range of 1-8 mg (QD and BID), 4 mg and 2 mg QD were selected for further investigation for the BARI phase 3 studies, with 4 mg QD identified as the preferred phase 3 dose. At the same total daily dose, splitting the dose into a BID regimen does not provide any advantage over QD dosing for any of the efficacy endpoints.

References:

Keystone E, et al. Safety and efficacy of baricitinib at 24 weeks in patients with rheumatoid arthritis who have had an inadequate response to methotrexate. Ann Rheum Dis. 2015;74(2):333-340.

Tanaka Y, et al. Efficacy and safety of baricitinib in Japanese RA patients during a 52 week extension phase. Art Rheum. 2014;66(11):S652.

Disclosure: X. Zhang, Eli Lilly and Company, 1,Eli Lilly and Company, 3; **L. Chua**, Eli Lilly and Company, 1,Eli Lilly and Company, 3; **C. S. Ernest II**, Eli Lilly and Company, 1,Eli Lilly and Company, 3; **W. Macias**, Eli Lilly and Company, 1,Eli Lilly and Company, 3; **T. Rooney**, Eli Lilly and Company, 1,Eli Lilly and Company, 3; **L. S. Tham**, Eli Lilly and Company, 1,Eli Lilly and Company, 3.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/evaluate-the-dose-efficacy-response-relationship-of-baricitinib-in-patients-with-rheumatoid-arthritis

Abstract Number: 486

Persistence Among Rheumatoid Arthritis Patients Initiating Intravenous

or Subcutaneous Anti-Tumor Necrosis Factor Therapy in a Large US Registry Cohort

Dennis Parenti[1], Shelly Kafka[1], George W. Reed[2], Jeffrey D. Greenberg[2,3] and Raphael DeHoratius[1,4], [1]Janssen Scientific Affairs, LLC, Horsham, PA, [2]Corrona, LLC, Southborough, MA, [3]NYU School of Medicine, New York, NY, [4]Kimmel School of Medicine, Thomas Jefferson University, Philadelphia, PA

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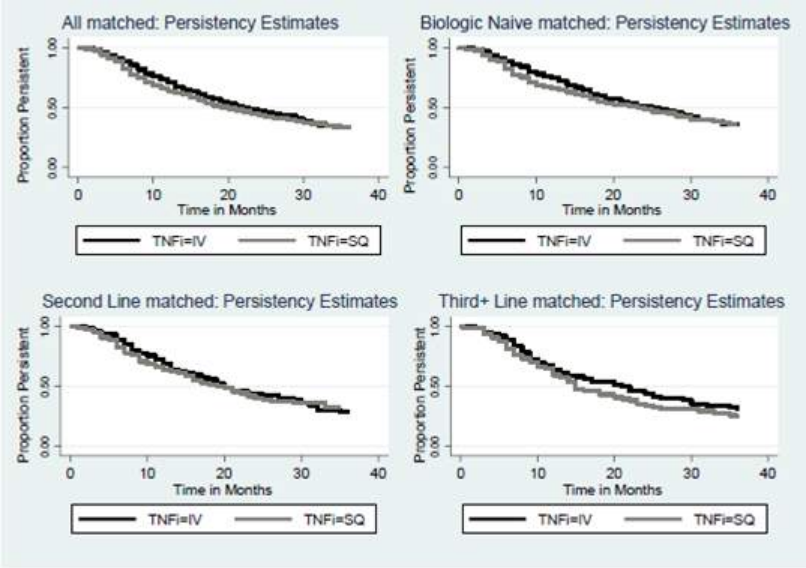
Background/Purpose: The objective of this analysis was to examine persistence with intravenous (IV) and subcutaneous (SC) anti-TNF therapies among rheumatoid arthritis (RA) patients (pts) within the US CORRONA RA registry.

Methods: A retrospective analysis from the CORRONA RA registry was used for analyses. Adult RA pts (biologic-naïve and biologic-experienced) with moderate-to-severe RA (CDAI>10) who initiated anti-TNF biologics within the CORRONA registry after June 1, 2009 and had ≥6 months of follow up were eligible. Pts receiving IV anti-TNF therapy were compared with those receiving SC anti-TNF therapy. Propensity scores (PS) were generated to match IV anti-TNF initiators to SC anti-TNF initiators, stratified by line of therapy. Variables used for PS matching were based on characteristics with standardized differences of ≥0.1 including age, gender, duration of RA, work status, smoking status, insurance, prednisone use, monotherapy, prior serious infections, patient global, morning stiffness, year of initiation, time from initiation to 6 month visit, and prior number of biologics to control for population imbalances. Time-varying hazard ratios (HR) comparing persistence in matched IV vs SC through 48 months were estimated and stratified by line of therapy.

Results: A total of 1544 pts were included (772 each for IV and SC therapy). In each treatment group, 387 pts were bio-naïve, 220 had received 1 prior biologic, and 165 had received ≥2 prior biologics. Among all pts, significantly greater proportions of patients receiving IV therapy remained on that agent compared with pts receiving SC therapy (p=0.002) during the first 12 months (HR=0.76 [0.63-0.90]). No significant differences in persistence were observed from 24 – 48 months (HR=1.09 [0.88-1.35], p=0.45) (Figure 1). Similar results were observed for pts who were biologic-naïve (0-12 mons: HR=0.69 [0.52-0.90], p=0.007) and who had received 1 prior biologic (0-12mons: HR=0.80 [0.59-1.10], p=0.17). For pts who had received ≥2 biologics, there was no significant difference in persistence between patients receiving IV or SC anti-TNF therapy.

Conclusion: Within the first 12 months of initiating anti-TNF therapy, pts receiving IV therapy who were biologic-naïve or had received only one prior biologic were more likely to remain on treatment compared with those receiving SC anti-TNF agents. These results may have implications on cost savings, in the first year of treatment, that need to be investigated in further studies.

Figure1. Persistence estimates for matched populations.



Disclosure: D. Parenti, Janssen Scientific Affairs, LLC, 3; **S. Kafka**, Janssen Scientific Affairs, LLC, 3; **G. W. Reed**, Corrona, LLC, 3; **J. D. Greenberg**, Corrona, LLC., 3,Corrona, LLC., 1,AstraZeneca, Pfizer, Celgene, Novartis, Genentech, Janssen, 5; **R. DeHoratius**, Janssen Scientific Affairs, LLC, 3.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/persistence-among-rheumatoid-arthritis-patients-initiating-intravenous-or-subcutaneous-anti-tumor-necrosis-factor-therapy-in-a-large-us-registry-cohort

Abstract Number: 487

Early Rheumatoid Arthritis Patients in the Worse Disease Trajectory Group Fail to Achieve Improvement in Physical Function

Cheryl Barnabe[1], Ye Sun[2], Susan J. Bartlett[3,4], Gilles Boire[5], Carol Hitchon[6], Edward C. Keystone[7], Boulos Haraoui[8], J Carter Thorne[2], Diane Tin[9], Janet E. Pope[10], VP Bykerk[11] and CATCH Investigators, [1]Cumming School of Medicine, University of Calgary, Calgary, AB, Canada, [2]University of Toronto, Toronto, ON, Canada, [3]Division of Rheumatology, Johns Hopkins School of Medicine, Baltimore, MD, [4]Medicine , Divisions of Clinical Epidemiology, Rheumatology, Respirology, McGill University, Montreal, QC, Canada, [5]Department of Medicine/Division of Rheumatology, Université de Sherbrooke, Sherbrooke, QC, Canada, [6]Department of Rheumatology, University of Manitoba, Winnipeg, MB, Canada, [7]Mount Sinai Hospital, University of Toronto, Toronto, ON, Canada, [8]Institut de Rhumatologie, Montreal, QC, Canada, [9]The Arthritis Program, Southlake Regional Health Centre, Newmarket, ON, Canada, [10]University of Western Ontario, London, ON, Canada, [11]Rheumatology, Mount Sinai Hospital, University of Toronto, Toronto, ON, Canada

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Background/Purpose: Disease trajectories in early rheumatoid arthritis (ERA) are characterized by differences in absolute levels of disease activity and rates of improvement, with patients in the worse disease trajectories experiencing worse quality of life outcomes and persistent fatigue. Our objective was to determine if the magnitude of improvements in physical function, as measured by the Health Assessment Questionnaire (HAQ), also vary in the heterogeneous disease trajectories.

Methods: Cluster-based trajectory modeling identified 5 mutually exclusive ERA disease activity trajectories by posterior membership probability using DAS28 over 24 months (described in Table 1). Baseline values and mean changes in the HAQ scores were examined for differences by trajectory group using ANCOVA, with adjustment for covariates (age, sex, number of comorbidities, low income, smoking, race).

Results: The cohort includes 1586 patients (mean 54 years, 181 days of symptoms, 73% female, 82% Caucasian, 18% smokers, 70% seropositive). Half (50%) begin in high disease activity state (DAS), of which only 20% rapidly reach remission (Group 1). Group 5 only achieves moderate disease activity by 24 months, despite higher frequency of use of steroids and biologic therapy. HAQ scores were similar between Groups 1, 4 and 5 at baseline (Table 1). In Group 1 scores improve by 1.08 (SD 0.68) by 12 months but in Group 5 the HAQ fails to reach the minimal clinically important difference for improvement (0.22) and worsens from month 12 to 24 (Figure 1).

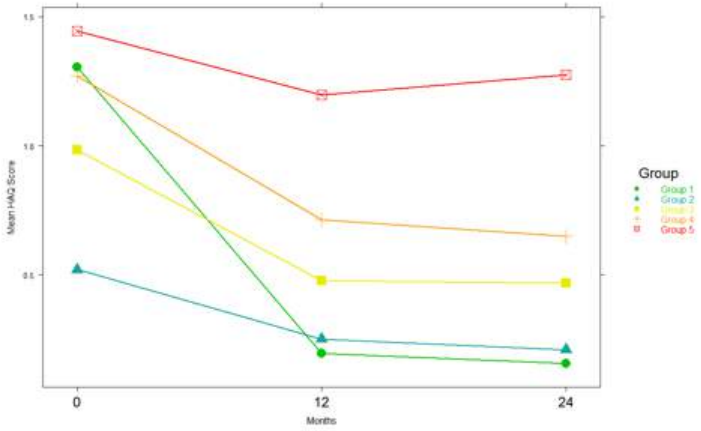
Conclusion: Novel strategies are needed to identify which patients are at risk for disparate outcomes so that effective care plans can be enacted to preserve function.

Table 1. Mean (SD) HAQ Scores at Baseline and Change Over 24 Months, by Trajectory Group

	Baseline	Change
Group 1 (HDAS to REM)	1.21 (0.70)	-1.08 (0.68)
Group 2 (MDAS to REM)	0.54 (0.53)	-0.34 (0.51)
Group 3 (MDAS to LDAS)	0.83 (0.62)	-0.34 (0.61)
Group 4 (HDAS to LDAS)	1.39 (0.65)	-0.71 (0.78)
Group 5 (HDAS to MDAS)	1.34 (0.64)	-0.13 (0.66)

Legend: HDAS high disease activity state; REM remission; MDAS moderate disease activity state; LDAS low disease activity state

Figure 1. HAQ Scores by Trajectory Group, months 0-24



Disclosure: C. Barnabe, None; **Y. Sun**, None; **S. J. Bartlett**, PCORI, 2,NIH, 9; **G. Boire**, None; **C. Hitchon**, Health Sciences Centre Foundation, 2; **E. C. Keystone**, Janssen Inc., 2,Abbott/AbbVie, 5,Amgen, 2,Bristol-Myers Squibb, 5,Janssen Inc., 5,Hoffmann-La Roche, Inc., 5,Janssen Inc., 2,Janssen Inc., 5,Merck Pharmaceuticals, 5,Merck Pharmaceuticals, 5,Pfizer Pharmaceuticals, 5,Pfizer Pharmaceuticals, 5; **B. Haraoui**, Abbott, Amgen, BMS, Janssen, Pfizer, Roche and UCB Pharma, 2,Abbott, Amgen, BMS, Janssen, Pfizer, Roche and UCB Pharma, 5,Abbott, Amgen, BMS, Janssen, Pfizer, Roche and UCB Pharma, 8; **J. C. Thorne**, Amgen, Canada, 5; **D. Tin**, None; **J. E. Pope**, None; **V. Bykerk**, None.

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Abstract Number: 488

Six-Year Retention Rates with Abatacept Vs TNF Inhibitors in the Treatment of Rheumatoid Arthritis: Experience from the Real-World Rhumadata Clinical Database and Registry

Denis Choquette[1], Louis Bessette[2], Boulos Haraoui[3], Jean-Pierre Raynauld[1], Diane Sauvageau[1], Angèle Turcotte[4], Édith Villeneuve[1] and Louis Coupal[1], [1]Rheumatology, Institut de recherche en rhumatologie de Montréal (IRRM), Montréal, QC, Canada, [2]Centre d'Ostéoporose et de Rhumatologie de Québec (CORQ), Québec, QC, Canada, [3]Université de Montréal, Montreal, QC, Canada, [4]Rheumatology, Centre d'ostéoporose et de rhumatologie de Québec (CORQ), Québec, QC, Canada

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Background/Purpose: The sustainability of any regimen is an important factor to consider when selecting therapy for chronic conditions, such as rheumatoid arthritis (RA). Recent reports suggest that patients (pts) treated with abatacept (ABA) might have better retention rates than those treated with anti-TNFs. We aim to further assess long term retention rates of ABA in comparison with anti-TNFs in the first and second lines of treatment in a real life setting using the Rhumadata database and clinical registry.

Methods: RA patients treated at the *Institut de recherche en Rhumatologie de Montréal* (IRRM) and the *Centre d'Ostéoporose et de Rhumatologie de Québec* (CORQ) with either ABA or an anti-TNF inhibitor, adalimumab (ADA), etanercept (ETA), or infliximab (INF) as first biologic (first cohort) or second biologic (second cohort) after January 1st 2007. Descriptive statistics were used to describe patient characteristics. Characteristics were compared using ANOVA with Bonferroni correction. Kaplan-Meier methods were used to compute the cumulative incidence of treatment discontinuation.

Results: The first cohort included 403 pts (62 ABA, 111 ADA, 195 ETA, and 35 INF) and the second cohort included 189 pts (76 ABA, 47 ADA, 47 ETA, and 19 INF). No clinically significant differences in baseline characteristics were noted between treatment groups. There were no significant differences in retention rates between ABA and anti-TNFs in the first cohort, Figure 1. The estimated 6-years drug retention rates were 52.3% (SD=8.4%) for ABA, 37.8% (SD=4.9%) for ADA, 43.6% (SD=4.3%) for ETA and 45.6% (SD=8.8%) for INF. In the second cohort, in patient with RA having failed a first anti-TNF agent, retention rates with ABA were significantly higher compared to anti-TNFs, Figure 2. For this cohort, the estimated 6-years drug retention rates were 41.2% (SD=7.4%) for ABA, 15.2%

(SD=6.3%) for ADA, 22.7% (SD=7.5%) for ETA and 33.1% (SD=13.1%) for INF. The significantly higher retention rates with ABA in the second cohort were maintained regardless of RF or anti-CCP status or whether the biologics were used as monotherapy or in combination with DMARDs. Lack of efficacy (40.1% and 57.3% in the first and second cohort, respectively) and adverse effects (13.9% and 12.2% in the first and second cohort, respectively) were the most commonly cited reasons for discontinuation.

Conclusion: As a first line biologic, in patient with RA, ABA has similar 6-year retention rates as anti-TNFs. As a second line biologic, in patient with RA, ABA has significantly higher 6-years retention rates compared to anti-TNFs.

Figure 1.

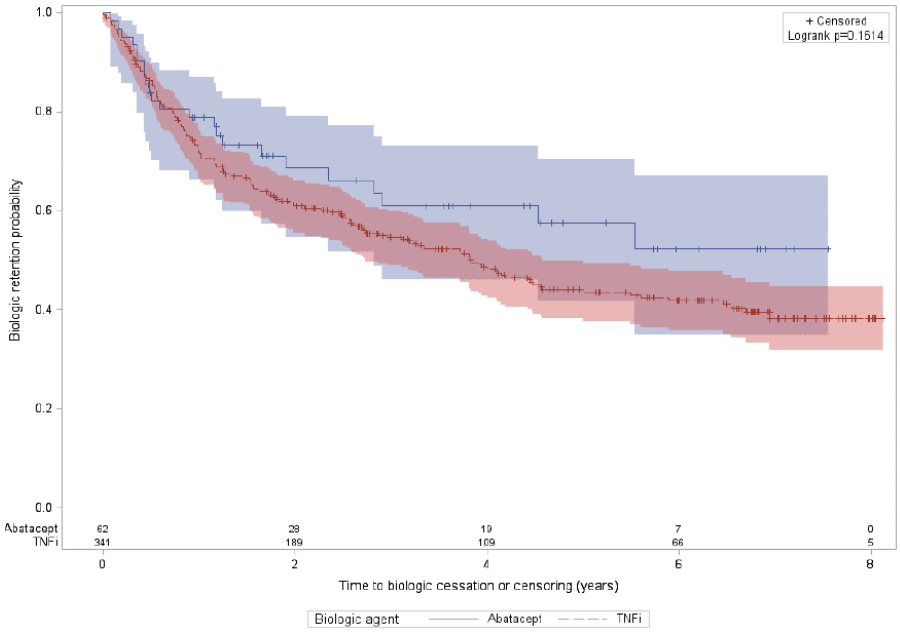
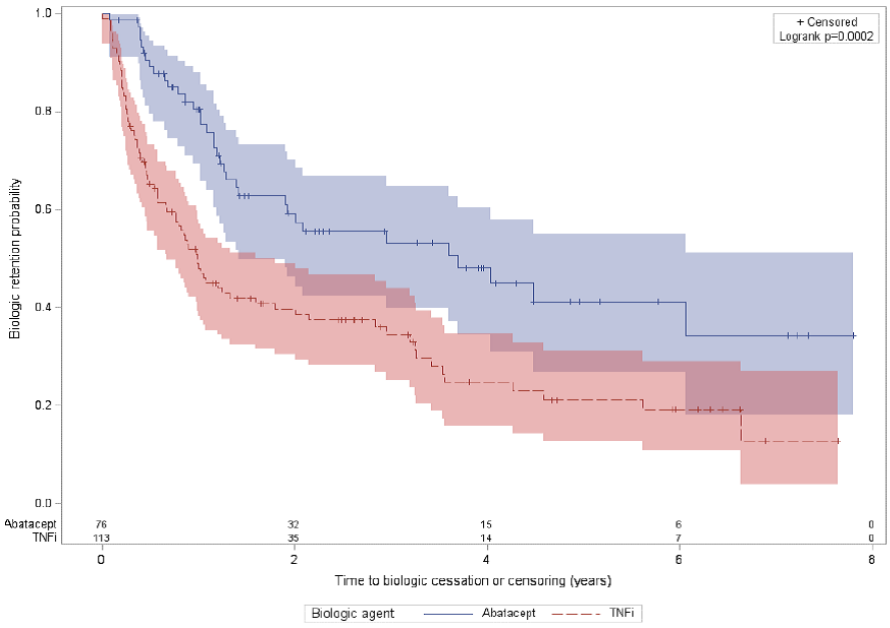


Figure 2.



Disclosure: D. Choquette, AbbVie, Amgen, Celgene, Bristol-Myers Squibb, Janssen Pharmaceutical Product, L.P., Pfizer Inc, Roche, Novartis, UCB, Hospira, Sanofi, Merck, 5; **L. Bessette**, AbbVie, Amgen, Celgene, Bristol-Myers

Squibb, Janssen Pharmaceutical Product, L.P., Pfizer Inc, Roche, UCB, 5,AbbVie, Amgen, Celgene, Bristol-Myers Squibb, Janssen Pharmaceutical Product, L.P., Pfizer Inc, Roche, UCB, 2; **B. Haraoui**, Abbvie, Celgene, Amgen, BMS, Janssen, Pfizer, Roche and UCB Pharma, 2,Abbvie, Celgene, Amgen, BMS, Janssen, Pfizer, Roche and UCB Pharma, 5; **J. P. Raynauld**, None; **D. Sauvageau**, None; **A. Turcotte**, AbbVie, Amgen, Celgene, Bristol-Myers Squibb, Janssen Pharmaceutical Product, L.P., Pfizer Inc, Roche, UCB, Eli Lilly, 5; **Villeneuve**, AbbVie, Amgen, Bristol-Myers Squibb, 5; **L. Coupal**, None.

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Abstract Number: 489

Drug Survival and Toxicity of Methotrexate Monotherapy in Daily Clinical Practice. Results from an Early Arthritis Clinic

Christian A. Waimann[1,2], Margarita Landi[3], Fernando Dal Pra[3], Gustavo Citera[4], Maria Celeste Orozco[4], Osvaldo Luis Cerda[3], Federico Ceccatto[5], Sergio Paira[5], Francisco Colombres[6], Alberto Berman[7], Horacio Berman[7], Anastasia Secco[8], Marta Mamani[8], Maritza Manzano[8], Maria Victoria Martire[8], Francisco Caeiro[9], Maria Haye Salinas[10], Alejandro J. Alvarellos[10], Ana C. Alvarez[10], Javier Rosa[11], Valeria Scaglioni[12], Enrique R. Soriano[11], Josefina Marcos[13], Mercedes Argentina García[14], AC Costi[15], Alejandro Martinez[16], Oscar Luis Rillo[16], Edson Veloso[17], Ricardo V. Juárez[18], Maria Elena Crespo[19], Ana Quinteros[20], Doralia Vasquez[20], C Ledesma[21], Gabriela Salvatierra[21], R Quintana[22], Monica Sacnun[23] and Marcelo Abdala[24], [1]Rheumatology, Hospital Dr. Hector Cura, Olavarria, Argentina, [2]Rheumatology section, Instituto de Rehabilitación Psicofísica, Buenos Aires, Argentina, [3]Instituto de Rehabilitación Psicofísica, Buenos Aires, Argentina, [4]Rheumatology, Instituto de Rehabilitación Psicofísica, Buenos Aires, Argentina, [5]Hospital Jose Maria Cullen, Santa Fe, Argentina, [6]Tucuman, Centro Médico Privado de Reumatología, Tucumán, Argentina, [7]Centro Médico Privado de Reumatología, Tucumán, Argentina, [8]Rheumatology, Hospital Bernardino Rivadavia, Buenos Aires, Argentina, [9]Reumatología, Hospital Privado de Córdoba, Córdoba, Argentina, [10]Rheumatology, Hospital Privado de Córdoba, Córdoba, Argentina, [11]Hospital Italiano, Buenos Aires, Argentina, [12]Rheumatology, Hospital Italiano, Buenos Aires, Argentina, [13]HIGA San Martín, La Plata, Argentina, [14]Rheumatology Unit, HIGA San Martín, La Plata, Argentina, [15]Rheumatology, HIGA San Martín, La Plata, Argentina, [16]Rheumatology, Hospital General de Agudos “Dr. Ignacio Pirovano”, Buenos Aires, Argentina, [17]Sanatorio y Universidad Adventista Del Plata, Entre Rios, Argentina, [18]Rheumatology Section, Hospital Señor del Milagro, Salta, Argentina, [19]Hospital Señor del Milagro, Salta, Argentina, [20]Centro Integral De Reumatologia, Tucumán, Argentina, [21]Instituto Provincial De Rehabilitación Integral, Santiago del Estero, Argentina, [22]Rheumatology, Hosp. Provincial, Rosario, Argentina, [23]Hosp. Provincial, Rosario, Argentina, [24]Hospital Provincial del Centenario, Santa Fe, Argentina

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Session Type: ACR Poster Session A

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Background/Purpose: Several trials had reported the efficacy and toxicity of methotrexate monotherapy in patients with early rheumatoid arthritis. However, patients outside clinical trials could be more complex and heterogeneous,

with a wide range of comorbidities and clinical characteristics. The aim of our study was to estimate the drug survival and toxicity of methotrexate monotherapy in real life setting.

Methods: We included a cohort of DMARDs naïve patients with diagnosis of early rheumatoid arthritis (RA) of less than 2 years of disease duration. Data was collected every 3 months, including sociodemographic characteristics, functional status, disease activity and medication (dose, treatment strategy and toxicity). The primary outcome was methotrexate monotherapy survival. Time to outcome was assessed from treatment initiation to the end of methotrexate monotherapy (drug suspension or addition of DMARDs/biologics) or last follow-up. Kaplan-Meier product limit method was used to estimate outcome probability. Cox proportional hazards models were fit to determine possible predictors of methotrexate monotherapy survival. A p-value of 0.05 was considered statistically significant.

Results: We included 563 DMARDs (disease-modifying antirheumatic drugs) naive patients with early rheumatoid arthritis. Mean follow-up was 24 ± 16 months. Mean age was 51 ± 14 years, 82% were female and disease duration was 7 ± 6 months. Baseline DAS28 and HAQ were 4.0 ± 1.2 and 0.9 ± 0.6, respectively. Methotrexate (MTX) was the most frequently DMARD used [505 (90%)], followed by Leflunomide [LFN, 193 (34%)], Hydroxychloroquine [HCQ, 105 (19%)] and Sulfazalazine [SFZ, 22 (4%)]. When analyzing treatment strategy, first choice was Methotrexate monotherapy in 384 (68%) of the cases. MTX mean dose was 16 ± 4 mg/week and 44% used MTX doses higher or equal than 20 mg/week. One hundred and fifty patients (40%) had to stop methotrexate monotherapy, with a median survival of 26 months (failure rate = 0.027/patient-months of follow-up). Main reasons for suspension were as follow: addition or substitution of DMARs/biologics due to inefficacy (79%), adverse event (7%) and others (14%). On multivariate analysis, being younger, having a higher disease activity and initial concomitant treatment with prednisone ≥10mg/day, were associated with a higher methotrexate monotherapy survival (Table 1)

Conclusion: In daily clinical practice, 4 out of 10 patients with early rheumatoid arthritis fail to methotrexate monotherapy, being inefficacy the main reason for discontinuation. Only 7% of patients had to stop treatment due to adverse events. Younger age, higher disease activity and initial combination with prednisone ≥10mg/day were associated with a higher methotrexate monotherapy survival.

Table 1. Cox proportional hazard model

	HR	p-value	95%CI%	
Male sex	0.958	0.856	0.605	1.518
Age (years)	0.985	0.018	0.972	0.997
Disease duration (months)	1.008	0.631	0.976	1.041
Baseline DAS28	1.155	0.033	1.012	1.319
Time to first DMAR (months)	0.999	0.724	0.997	1.002
Methotrexate initial dose (mg/week)	1.016	0.585	0.960	1.075
Mean initial dose of prednisone				
<10 mg/day	----	----	----	----
≥10 and <20 mg/day	1.780	0.001	1.254	2.527
≥20 mg/day	3.338	0.008	1.365	8.163

Disclosure: **C. A. Waimann**, None; **M. Landi**, None; **F. Dal Pra**, None; **G. Citera**, None; **M. C. Orozco**, None; **O. L. Cerda**, None; **F. Ceccatto**, None; **S. Paira**, None; **F. Colombres**, None; **A. Berman**, None; **H. Berman**, None; **A. Secco**, None; **M. Mamani**, None; **M. Manzano**, None; **M. V. Martire**, None; **F. Caeiro**, None; **M. Haye Salinas**, None; **A. J. Alvarellos**, None; **A. C. Alvarez**, None; **J. Rosa**, None; **V. Scaglioni**, None; **E. R. Soriano**, Abbvie; Janssen; UCB; Roche; Bristol Myers Squibb, 2,Abbvie; UCB; Janssen; Roche; Bristol Myers Squibb; Pfizer; Novartis, 8; **J. Marcos**, None; **M. A. García**, None; **A. Costi**, None; **A. Martinez**, None; **O. L. Rillo**, None; **E. Veloso**, None; **R. V. Juárez**, None; **M. E. Crespo**, None; **A. Quinteros**, None; **D. Vasquez**, None; **C. Ledesma**, None; **G. Salvatierra**, None; **R. Quintana**, None; **M. Sacnun**, None; **M. Abdala**, None.

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methotrexate-monotherapy-in-daily-clinical-practice-results-from-an-early-arthritis-clinic

Abstract Number: 490

Personalizing the Treat to Target Approach in Rheumatoid Arthritis

Eric M. Ruderman[1], Jennifer Beaumont[2], Azra Muftic[2], Arthur M. Mandelin II[1], Amy Eisenstein[2], George J. Greene[2] and David Cella[2], [1]Medicine, Division of Rheumatology, Northwestern University Feinberg School of Medicine, Chicago, IL, [2]Medical Social Sciences, Northwestern University Feinberg School of Medicine, Chicago, IL
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SESSION INFORMATION
Session Date: Sunday, November 8, 2015
Session Title: Rheumatoid Arthritis - Clinical Aspects Poster I
Session Type: ACR Poster Session A
Session Time: 9:00AM-11:00AM

Background/Purpose:

The treat to target (T2T) approach has become part of the standard of care in RA management. Implicit in this approach is patient involvement in shared decision making, to ensure that treatment decisions meet the needs of the patient as well as the goals of the provider. The Patient Reported Outcomes Measurement Information System (PROMIS) is a validated set of assessment tools to measure patient reported health status across a variety of medical conditions. We sought to learn whether the use of elements from PROMIS could inform the T2T approach, and to understand whether patient reports of disease impact correlate with objective clinical measures. We report here the baseline status of the patients enrolled in the study.

Methods:

Patients with a diagnosis of RA by 2010 criteria were recruited from our academic clinical practice. Patients were stratified at baseline by disease activity (remission or low disease activity, CDAI $\leq$ 10 vs. moderate or high disease activity, CDAI > 10), and we made an effort to balance the 2 groups. Patients will be treated for 1 year, using a T2T approach that recommends consideration of therapeutic escalation when CDAI > 10, with data collected at routine clinic visits. At each visit, we collect standard RA assessments, including joint counts, RAPID3, and CDAI scores. Patients complete a PROMIS assessment quantifying their health status in 5 domains: pain, fatigue, depression, physical function, and social function. Patients are also asked to select priority targets, consisting of 5 items from the domain they deem most important; answers to these questions are also collected at each visit. Table 1 shows the demographics, clinical status and PROMIS measures for the first 94 patients enrolled.

Results:

Compared to the US general population reference values for PROMIS (m=50; SD=10), patients had worse fatigue (m=56.7), pain (m=57.7), and physical function (m=42.3). Baseline scores on depression and social functioning were close to the average of the general US population. Patients with CDAI > 10 scored worse across all domains than those with CDAI $\leq$ 10. When selecting prioritization areas for treatment targets, 38% of patients selected physical function, followed by 35% of participants selecting pain, 16% selecting fatigue, 6% selecting depression, and 4% selecting social function; those with active disease were much more likely to select pain (45% vs. 18%).

Conclusion:

Pain, physical function, and fatigue, the 3 domains in which patients reported worse health status than the general population, were also the areas most frequently selected by patients as priority targets for treatment. Physicians are

informed of the PROMIS scores at each visit, and we will track their impressions of the impact of these data on their treatment decisions. We will also explore, at a patient level, the correlation between PROMIS scores and standard disease activity measures

Table 1

	CDAI ≤ 10 (n=45)*	CDAI > 10 (n=42)*	All (n=94)
Mean Age			53.2
Female (n, %)	42 (93%)	40 (95%)	89 (95%)
College or Professional Degree (n, %)	35 (78%)	30 (71%)	69 (73%)
Employed (n, %)	31 (69%)	25 (60%)	58 (62%)
Smoker (n, %)	4 (9%)	2 (5%)	6 (6%)
PROMIS Pain (mean)	53.6	62.1	57.7
PROMIS Fatigue (mean)	53.1	59.8	56.7
PROMIS Depression (mean)	49.2	53.8	51.4
PROMIS Physical Function (mean)	45.2	39.4	42.3
PROMIS Social Function (mean)	50.0	44.7	47.4

*Baseline CDAI not recorded in 7 patients

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Abstract Number: 491

A Paradigm Shift in the Disease Assessment of Rheumatoid Arthritis : From Blood to Urine Testing

Wan-Uk Kim[1], Yune-Jung Park[2], Seung-Ah Yoo[3], Bong Ki Hong[3], Gi myo Kim[4], Susanna Choi[5], Saseong Lee[3] and Chul-Soo Cho[6], [1]Internal Medicine, Seoul St. Mary's Hospital, The Catholic University of Korea, Seoul, South Korea, [2]Internal Medicine, St. Vincent's Hospital, The Catholic University of Korea, Suwon, South Korea, [3]Institute of Bone and Joint Diseases, The Catholic University of Korea, Seoul, South Korea, [4]Institute of bone and joint diseases, Catholic university, seoul, South Korea, [5]Institute of Bone and Joint diseases, The Catholic University of Korea, seoul, South Korea, [6]Internal Medicine, Yeouido St. Mary's Hospital, The Catholic University of Korea, Seoul, South Korea
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Background/Purpose: To optimize treatment for rheumatoid arthritis (RA), it is ideal to monitor disease activity on a daily basis such as glucose measurement since RA activity fluctuates over time. Urine can be collected routinely at

home by patients themselves and tested for systemic inflammation. Recently, we had identified 4 urinary biomarker candidates-- gelsolin (GSN), orosomucoid (ORM)1, ORM2, and soluble CD14 (sCD14)-- in RA patients through transcriptomics and proteomics studies.

Methods: Here, we investigated the clinical significance of the aforementioned urinary biomarker candidates in a prospective manner, focusing on their role in predicting RA activity and providing prognosis. Urinary concentrations of the four proteins were determined by enzyme-linked immune-sorbent assay. RA activity and severity were determined by assessing disease activity score 28 and X-rays of hands and feet of patients, respectively.

Results: Urinary ORM1, ORM2, and sCD14 levels were elevated in RA patients. They were positively correlated with the status of the disease activity. In particular, urine determinations of one or two biomarkers (e.g. ORM1+ORM2 or sCD14+ORM2) efficiently represented the presence of high RA activity without the need for blood markers. In parallel, a more rapid radiographic progression in three years was observed in patients with higher ORM2 levels. In multivariate analysis, urinary ORM2 level was an independent risk factor for RA progression. Combination of urinary ORM2 and serum C-reactive protein synergistically increased the predictability for radiographic progression (the adjusted odds ratio: 46·5). *In vitro* functional studies revealed that ORM2 was mainly produced by RA synoviocytes in the joints, directly contributing to proinflammatory responses.

Conclusion: Our urinary biomarkers provide novel candidates for patient-driven measurements of RA activity at home and can shift the paradigm from blood to urine testing in the assessment of RA activity and prognosis in hospitals.

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Abstract Number: 492

Correlations Between Clinical, Laboratory and Ultrasound Joint Examination in RA Patients Treated with Rituximab

Andreea Borangiu[1], Diana Mazilu[1], Ioana Saulescu[1], Evelina Iachim[2], Laura Grosanu[1], Cosmin Constantinescu[1], Andra Balanescu[1], Denisa Predeteanu[1], Ruxandra Ionescu[1] and Daniela Opris[1], [1]University of Medicine and Pharmacy "Carol Davila", Department of Internal Medicine and Rheumatology "Sf. Maria" Hospital, Bucharest, Romania, [2]Carol Davila Medicine and Pharmacy University, Bucharest, Romania

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Background/Purpose: Correct assessment to biologics in rheumatoid arthritis (RA) patients is extremely important regarding future patient management. There is still an open debate about the utility of joint ultrasound (US) parameters and the monitoring of the activity.

Methods:

52 consecutive RA patients on stable RTX treatment administered each 6 months were evaluated. Clinical and US evaluation were performed by two independent assessors, the same day as all laboratory tests. The scanning technique and the settings of the machine (ESAOTE MY LAB70, 15MHz linear probe) were the same for all patients. Examinations were performed by a trained ultrasonographer blinded to all clinical evaluations. US of both hands (dorsal wrist, 2nd to 5th volar metacarpophalangeal and 2nd to 4th volar proximal interphalangeal) was done. All patients were separated in 2 groups according to calculated SDAI, patients having SDAI <3.3 being included in remission group and those with higher SDAI in active disease group.

Results:

86.5% were females, mean age 57.21(11.35) years, mean disease duration 14.12(7.68) years, 82.7% had a csDMARD associated to RTX . Mean DAS28 ESR was 3.12(1.27) and mean SDAI was 7.83(7.75). No significant correlations were found between active synovitis score and VAS (r=0.189, P=0.179), PGA (r=0.251, P=0.073), ESR (r=0.154, P=0.275), nor CRP (r=0.173, P=0.220). Active synovitis score correlated to tender joint count (r=0.368, P=0.007), swollen joint count (r=0.413, P=0.002), SDAI score (r=0.339, P=0.014) and DAS28 score (r=0.348, P=0.011). Boolean remission correlated inversely to number of PD joints (r=-0.416, P=0.002), active sinovitis (r=-0.492, P<0.001). There were significant differences between patients with active disease and RA remission based on SDAI score regarding tender joint count, swollen joint count, ESR, PD joint count, total PD score and active synovitis (see table). SDAI remission correlated inversely to PD joint number (r=-0.383, P=0.005), active synovitis (r=-0.385, P=0.005) and total PD score (r=-0.456, P=0.001). SDAI remission did not correlate to GS joint number (r=-0.039, P=0.785) nor to total GS score (r=-0.140, P=0.324).

	SDAI Remission (SD)	**SDAI Active Disease (SD)**	**P**
DMARD use	0.85(0.37)	0.82(0.38)	
Tender joint count	0.08(0.277)	2.67(3.79)	**0.018**
Swollen joint count	0.00(0.00)	1.95(2.74)	**0.014**
CRP	4.43(5.59)	11.55(17.81)	0.165
ESR	9.15(4.70)	23.41(17.93)	**0.007**
RF	21.57(30.69)	34.01(48.62)	0.409
ACPA	249.41(611.87)	407.92(672.44)	0.471
GS joint number	6.23(3.94)	5.95(2.72)	0.776
PD joint number	1.08(1.75)	2.33(1.51)	**0.016**
Total GS score	8.62(5.37)	10.00(5.29)	0.420
Total PD score	1.08(1.75)	3.23(2.28)	**0.003**
Active synovitis	0.46(0.51)	0.85(0.36)	**0.005**

Conclusion: Total PD score and PR joint numebr, but not GS score or GS joint number, correlates with SDAI remission in RA patients treated with RTX.

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Abstract Number: 493

Diagnostic Delay in Early Arthritis: Ten Years-Experience of a Single Center

Francesca Benaglio, Silvia Balduzzi, Serena Bugatti, Garifallia Sakellariou, Carlomaurizio Montecucco and Roberto Caporali, Division of Rheumatology, University of Pavia, IRCCS S. Matteo Foundation, Pavia, Italy, Pavia, Italy

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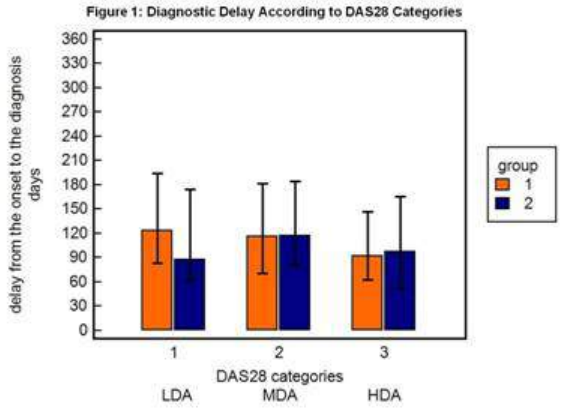
Session Time: 9:00AM-11:00AM

Background/Purpose: In the last 10 years a big effort has been made to reduce the diagnostic delay in patients with early arthritis, in order to start treatment as early as possible and to improve outcomes. The aim of this study is to assess whether diagnostic delay in patients evaluated at our Early Arthritis Clinic (EAC) changed between 2005 and 2014.

Methods: among patients referred to our EAC (disease duration <12 months) between 01/01/2005 to 31/12/2014, those with a diagnosis of rheumatoid arthritis (RA) (according to 1987 and/or 2010 classification criteria) or undifferentiated arthritis (UA) with a complete data-set were recruited. Patients were divided into 2 groups according to the time of diagnosis (group 1: 2005-2009; group 2: 2010-2014). A comparison among demographic and clinical features was performed.

Results: a total of 513 patients were evaluated: 305 patients into the group 1 (74.8% women, mean age 58 ys) vs. 208 patients into the group 2 (73.1% women, mean age 56.5 ys). The time from the onset of symptoms to the diagnosis showed no differences between groups (105 days IQR 66-171 vs. 107 IQR 67-177; p= ns). A total of 42% of the group 1 and 39% of the group 2 had the diagnosis established within 90 days (p= ns); 35.5% vs. 37% between 3 and 6 months (p= ns); 15% vs. 17% between 6 and 9 (p= ns); 7.5 % vs. 7% between 9 and 12 (p= ns). The delay from the referral at our EAC to the visit showed no differences between the groups (20 days IQR 11-31 vs. 20 IQR 13-28; p= ns). At baseline patients in the group 2 showed lower disease activity as for DAS28 (4.97 ± 1.19 vs. 4.57 ± 1.21; p= 0.0003), number of tender joints (7 IQR 3-13 vs. 5 IQR 2-9; p= 0.0009), swollen joints (7 IQR 4-12 vs. 5 IQR 3-8; p <0.0001), ESR (24 IQR 13-42 vs. 21 IQR 10-38; p= 0.0051), VAS-GH (44 IQR 25-50 vs. 50 IQR 30-60; p= 0.0056). In terms of serologic positivity and diagnosis there were no differences (64.6% of RA patients into the group 1 vs. 67.3% of RA patients into the group 2; p= ns).

Comparing DAS28 categories at baseline there were no differences in the diagnostic delay: patients with baseline DAS28 <3.2 had a delay of 124 days (IQR 88-194) in the group 1 vs. 88 (IQR 62-175) in the group 2 (p= ns); patients with baseline DAS28 between 3.2 and 5.1 had a delay of 116 days (IQR 71-182) vs. 117 (IQR 80-184) (p= ns), patients with baseline DAS28 >5.1 had a delay of 92 days (IQR 63-147) vs. 98 (IQR 52-166) (p= ns) (figure 1).



Conclusion: the reduction of disease activity observed during 10 years doesn't depend on a reduced diagnostic delay. Currently, up to the 60% of the diagnosis is still not made within the first 90 days from the onset of symptoms, period conventionally considered a window of opportunity. There is therefore a substantial room for improvement only partially linked to the delay between the referral at EAC and the diagnosis: education programs for patients and primary care physicians in order to reduce the diagnostic delay are still necessary.

Disclosure: F. Benaglio, None; **S. Balduzzi**, None; **S. Bugatti**, None; **G. Sakellariou**, None; **C. Montecucco**, None; **R. Caporali**, UCB Pharma, Roche, 8,AbbVie, Pfizer Inc, MSD, 5.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/diagnostic-delay-in-early-arthritis-ten-years-experience-of-a-single-center

Abstract Number: 494

High C-Reactive Protein at Baseline Is Associated with Long-Term Treatment Persistence in Patients with Rheumatoid Arthritis Treated with Rituximab

Maria Joao Gonçalves[1,2], Geraldine Cambridge[3] and Maria J. Leandro[3], [1]Rheumatology Department, Centre for Rheumatology and Bloomsbury Rheumatology Unit, University College London, London, United Kingdom, [2]Rheumatology Department, Lisbon Academic Medical Centre, Lisbon, Portugal, [3]Centre for Rheumatology and Bloomsbury Rheumatology Unit, University College London, London, United Kingdom

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Session Time: 9:00AM-11:00AM

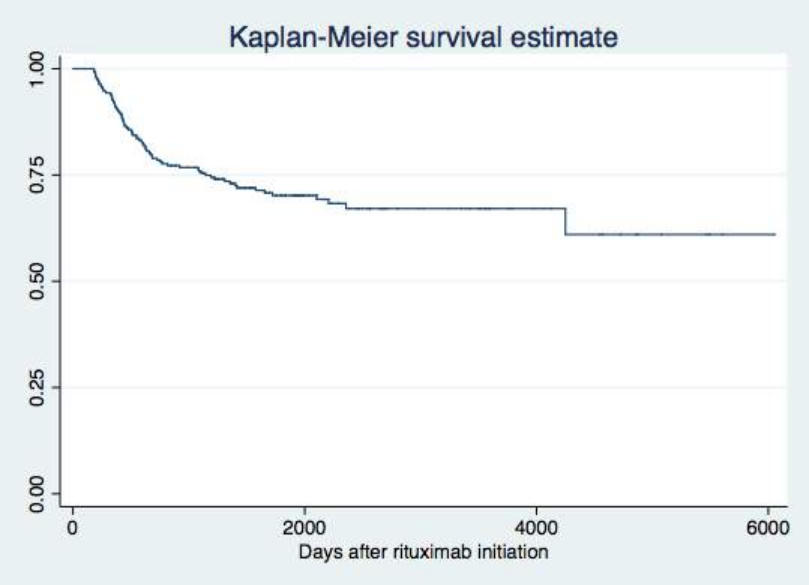
Background/Purpose: B cell depletion with rituximab (RTX) is an established treatment for RA. It was first introduced at UCL in 1998 and at this centre patients are followed up in a dedicated weekly clinic. Initial treatment protocols included combination with cyclophosphamide, but since 2001 patients are treated with cycles of 2x1g RTX. Initial retreatment strategies based on retreatment at flare evolved in the last 6 years patients to retreatment to avoid flare, based on the duration of response to initial cycles. We aim to characterize RTX drug survival in our cohort and determine 5 years drug retention predictors.

Methods: We conducted a retrospective cohort study of RA patients treated with RTX at UCL between 1998 and 2015. Medical records of 248 RA patients were reviewed; demographic and clinical data was collected. All patients fulfilled 1987 ACR classification criteria. Drug survival data was analysed using Kaplan-Meier estimates. Predictors for 5-years drug retention were determined by a multivariate logistic regression model.

Results: Of the 248 patients included, 81% were female, 80.9% Caucasians. Mean age (SD) was 60.75±15.4yrs and mean age at diagnosis was 39.25±16.2yrs. RF and ACPA were positive in 89% and 84.6% of patients, respectively. History of smoking was present in 59.43%. The most frequent comorbidities were hypertension (30.8%), osteoporosis (20.1%) and thyroid disease (15.43%). Mean follow up duration after RTX initiation was 1737±1206 days (maximum 6055 days). At 2 and 5 years, 78% and 61% patients remained on rituximab (figure 1). Baseline DAS28 was on average 5.93±1.25, CRP 2.2±2.9mg/L. Majority of patients received concomitant therapy with other DMARDs/steroids, MTX 46%, SSZ 21.4%, leflunomide 6.85%, hydroxichloroquine 14.1% and low-dose prednisolone 28.6%. Main reasons for RTX discontinuation were: inefficacy 49 patients (44 primary failures, 6 secondary failures), adverse events 18 patients, pregnancy 1 patient and death 5 patients.

In univariate analysis, current age, disease duration, RF seropositivity, CRP at baseline, number of previous biologics and concomitant use of prednisolone were associated with long-term RTX retention (>5 years). In multivariate analysis, only CRP at baseline kept statistical significance (p=0.014).

Conclusion: Overall, high drug retention rates were observed, independent of concomitant use of conventional DMARDs. In multivariate analysis, higher baseline CRP was associated with long-term drug survival. We found that secondary failures were rare (8% of drop outs) with the current retreatment strategy based on the prevention of flare.



Disclosure: M. J. Gonçalves, None; **G. Cambridge**, None; **M. J. Leandro**, None.

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Abstract Number: 495

Prognostic Significance of Residual Inflammation and Autoantibodies for Disease Relapse upon DMARD Suspension in Patients with Rheumatoid Arthritis in Sustained Remission after DAS-Driven Therapy

Antonio Manzo[1], Serena Bugatti[1], Francesca Benaglio[1], Garifallia Sakellariou[1], Barbara Vitolo[1], Carlomaurizio Montecucco[1] and Roberto Caporali[2], [1]Rheumatology and Translational Immunology Research Laboratories (LaRIT), Division of Rheumatology, IRCCS Policlinico S.Matteo Foundation/University of Pavia, Pavia, Italy, [2]Division of Rheumatology, Rheumatology and Translational Immunology Research Laboratories (LaRIT), Division of Rheumatology, IRCCS Policlinico S.Matteo Foundation/University of Pavia, Pavia, Italy

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Background/Purpose:

Early diagnosis and treat-to-target strategies with conventional DMARDs in rheumatoid arthritis (RA) have allowed the achievement of remission in a significant percentage of the cases in daily practice. Whether and in which patients

treatments can be suspended with maintenance of health is currently unclear. In this study, we investigated the outcomes of methotrexate (MTX) suspension and predictors of disease recurrence in a real life single centre cohort of early RA patients followed prospectively under DMARD- and glucocorticoid-free conditions.

Methods:

All RA patients included in this current prospective observational study derived from the Pavia's Early Arthritis Clinic and were treated according to a DAS-driven step-up protocol with MTX in monotherapy. Patients achieving stable DAS28 remission and fulfilling the following criteria were eligible for drug suspension: 1) fulfillment of the 2010 ACR/EULAR classification criteria for RA within 12 months from baseline visit; 2) MTX introduced within 12 months from symptoms' onset; 3) ≥24 months of continuative MTX; 4) DAS28 <2.6 for ≥6 months in the absence of glucocorticoids. Patients were followed-up at three-months intervals through complete clinical and ultrasonographic (hands-feet) assessments. Radiographs were repeated annually. Treatment was reintroduced in case of DAS28≥3.2 in a single occasion or 3.2<DAS28≥2.6 for >6 months.

Results:

Seventy RA patients with at least 6 months of follow-up following DMARDs discontinuation were considered. Baseline stratification according to remission stringency showed SDAI remission in 57/70 (81.4%), ACR/EULAR Boolean remission in 52/70 (74.3%) and absence of clinical and ultrasonographic synovitis (SJC44=0 and power Doppler signal in hands-feet=0) in 23/70 (32.9%). Treatment restart due to disease recurrence was observed in 28/70 patients (40%) over 2 years of follow-up, with a median (IQR) time until retreatment of 6 (6-10.5) months. None of the clinical characteristics at the time of diagnosis showed predictive significance. Worsening of disease activity was more likely to occur in patients not in remission according to the SDAI (HR [95% CI] 2.56 [1.15-5.70], p=0.02). Below this threshold, remission stringency failed to show any protective role, with 10/23 (43.5%) patients showing disease recurrence despite absence of clinical and subclinical synovitis at the time of drug suspension. Among patients in SDAI remission, IgG ACPA were the only predictor of relapse, independent of remission duration and the residual inflammatory degree at baseline (HR [95% CI] 4.38 [1.50-12.89], p=0.008). IgG ACPA-IgM rheumatoid factor (RF) double positivity showed increased predictive ability (HR [95% CI] 7.11 [2.38-21.25], p<0.001).

Conclusion:

Despite deep and sustained remission following early treatment and treat-to-target approaches in routine clinical care, DMARD suspension appears a feasible option only in a proportion of RA patients. The autoimmune status is the strongest predictor of disease reactivation in patients achieving stringent clinical and ultrasonographic control of the inflammatory process.

Disclosure: A. Manzo, None; **S. Bugatti**, None; **F. Benaglio**, None; **G. Sakellariou**, None; **B. Vitolo**, None; **C. Montecucco**, None; **R. Caporali**, UCB Pharma, Roche, 8,AbbVie, Pfizer Inc, MSD, 5.

Abstract Number: 496

Increased Serum Lipids Under Tocilizumab Is Not Influenced By Methotrexate

Manfred Herold[1], Peter Fasching[2], Winfried Graninger[3], Raimund Lunzer[4], Omid Zamani[5] and Burkhard Leeb[6], [1]Internal Medicine VI, Medical University of Innsbruck, Austria, Innsbruck, Austria, [2]Department of Internal Medicine V, Wilhelminen Hospital Vienna, Vienna, Austria, [3]Division of Rheumatology and Immunology, Medical University of Graz, Graz, Austria, [4]Department of Internal Medicine, Hospital Barmherzige Brüder Graz-Eggenberg, Graz, Austria,

[5]Rheumazentrum Favoriten Vienna, Wien, Austria, [6]2nd Dept. of Medicine, State Hospital Stockerau, Center for Rheumatology Lower Austria, Stockerau, Austria

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SESSION INFORMATION

Session Date: Sunday, November 8, 2015

Session Title: Rheumatoid Arthritis - Clinical Aspects Poster I

Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose:

Increased serum lipid levels in patients being treated with tocilizumab (TCZ) is known from several clinical trials[1,2]. It is not known whether additional methotrexate (MTX) alters TCZ's influence on serum lipid levels.

Methods:

Statistical analyses were performed with data from the OPTIMISE trial (EUDRACT No. 2011-001863-39) running in Austria from January 2012 to August 2013. Seventy-seven patients with mild to moderate rheumatoid arthritis (RA) and inadequate response (DAS28 >2.6 and ≤4.5) to a stable dose of MTX (15 - 25 mg/week) were enrolled and received three infusions of TCZ (8 mg/kg) iv every 4 weeks plus MTX. Patients (n = 65) achieving good or moderate EULAR response at week 12 were randomized into Group A (TCZ 8 mg/kg plus MTX) or Group B (TCZ 8 mg/kg plus MTX placebo). Blood was drawn every four weeks and, among other blood parameters, also cholesterol (total, HDL, LDL) and triglycerides were measured. Statistical comparisons were done between the three time points: week 0 (baseline), week 12 (end of therapy TCZ plus MTX) and week 24 (end of TCZ plus MTX or TCZ plus MTX placebo).

Results:

A moderate increase was found in total cholesterol (median of both groups together; 201 mg/dl at baseline, 223 in week 12, 221 in week 24), HDL (63 mg/dl at baseline, 69 in week 12, 66 in week 24) and LDL (118 mg/dl at baseline, 132 in week 12, 130 in week 24). The two groups differed significantly between baseline and week 12. Triglyceride levels did not change significantly. Comparison of the amount of lipid level change from week 12 to week 24 (TCZ plus MTX versus TCZ plus MTX placebo) between the groups was not significant. Only one difference (increase baseline to week 24) revealed a borderline (p = 043; t test) statistical significance between groups.

Conclusion:

RA patients with mild to moderate disease activity show a distinct change in cholesterol levels under successful TCZ and MTX therapy. These lipid levels remained unchanged between week 12 and 24 under continuous therapy with TCZ alone or in combination with MTX. It is unclear as to whether the increase in cholesterol (total, HDL, LDL) is a sign of disease control or a direct effect of TCZ on lipid syntheses.

Literature:

1. Souto A et al. Lipid profile changes in patients with chronic inflammatory arthritis treated with biologic agents and tofacitinib in randomized clinical trials: a systematic review and meta-analysis Arthritis Rheumatol 2015;67:117-27

2. Kawashiri SY et al. Effects of the anti-interleukin-6 receptor antibody, tocilizumab, on serum lipid levels in patients with rheumatoid arthritis. Rheumatol Int. 2011;31:451-6

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tocilizumab-is-not-influenced-by-methotrexate

Abstract Number: 497

Treatment Outcomes in Elderly Patients with Rheumatoid Arthritis: Results from a Nationwide Korean Biologics Registry

Seung Min Jung[1], Ji Yeon Lee[1], Jung Hee Koh[1], Seung-Ki Kwok[2], Ji Hyeon Ju[1], Chong-Hyeon Yoon[1] and Sung-Hwan Park[1], [1]Division of Rheumatology, Department of Internal Medicine, College of Medicine, The Catholic University of Korea, Seoul, South Korea, [2]seungki73@catholic.ac.kr, Division of Rheumatology, Department of Internal Medicine, College of Medicine, The Catholic University of Korea, Seoul, South Korea
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SESSION INFORMATION
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Session Time: 9:00AM-11:00AM

Background/Purpose: Rheumatoid arthritis (RA) is a chronic inflammatory disease, predominantly affecting women in their fifth and sixth decades of life. Although population aging increases the mean age of patients with RA, the data in elderly patients are still limited. We aimed to investigate the treatment outcome and the risk factors for poor outcome in elderly patients with RA.

Methods: This cross-sectional study analyzed the data of 1,227 patients with RA who were recruited for KOrean college of rheumatology BIOlogics (KOBIO) registry between 2013 and 2014. The demographic data, drugs, and disease activity were collected for all available participants. We compared the disease status between elderly patients (age ≥ 65) and younger patients (age < 65), and investigated the clinical factors affecting disease activity.

Results: Of 1,227 patients in KOBIO registry, 244 patients with RA were aged 65 or over. The proportion of men was higher ($p = 0.012$), and the duration of disease was longer ($p < 0.001$) in elderly patients compared to younger patients. The prevalence of comorbid condition determined by Charlson Comorbidity Index and Elixhauser's Comorbidity Measures was higher in elderly group ($p = 0.001$). Treatment of methotrexate was more frequent in younger group ($p = 0.004$), while use of other medications was comparable. More patients in elderly group had a high disease activity (disease activity score in 28 joints > 5.1, simple disease activity index > 40, and clinical disease activity index > 22), which was independently associated with longer duration of disease, presence of comorbidity, and non-use of methotrexate ($p = 0.002$, $p < 0.001$, and $p = 0.029$, respectively). Especially, diabetes was closely related with poor treatment outcome.

Conclusion: This study suggests that disease activity might be insufficiently controlled in elderly patients with RA. The meticulous efforts would be required to reach therapeutic target of RA, regardless of age.

Disclosure: S. M. Jung, None; **J. Y. Lee**, None; **J. H. Koh**, None; **S. K. Kwok**, None; **J. H. Ju**, None; **C. H. Yoon**, None; **S. H. Park**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/treatment-outcomes-in-elderly-patients-with-rheumatoid-arthritis-results-from-a-nationwide-korean-biologics-registry

Abstract Number: 498

Non-Adherence to Disease-Modifying Anti-Rheumatic Drugs in Patients with Rheumatoid Arthritis: An Italian Survey

Gerolamo Bianchi[1], Antonio Carletto[2], Oscar M. Epis[3], Crescenzio Scioscia[4], Angelo Semeraro[5], Chiara Donati[6], Laura Bazzichi[7], Giovanni Lapadula[8], Luigi Sinigaglia[9] and Andrea Lo Monaco[10], [1]Div Reumatologia, Ospedale La Colletta, Genoa, Italy, [2]Rheumatology Unit, University of Verona, Verona, Italy, [3]Rheumatology Unit, A.O. Ospedale Niguarda Ca' Granda, Milan, Italy, [4]DIM - Sezione di Reuamtologia Università degli Studi di Bari "Aldo Moro", Bari, Italy, [5]Unità Operativa di Reumatologia ASL Taranto, Taranto, Italy, [6]Roche S.p.A., Monza, Italy, [7]Division of Reumatology, Univeristy of Pisa, Pisa, Italy, [8]D.I.M.I.M.P, Rheumatology Unit - University of Bari, Bari, Italy, [9]Rheumatology Dep, I.O.G. Pini, Milan, Italy, [10]Ospedale S. Anna, Ferrara, Italy
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SESSION INFORMATION
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Session Time: 9:00AM-11:00AM

Background/Purpose: In patients (pts) with rheumatoid arthritis (RA), the non-adherence to therapy may impair the clinical outcomes, being often associated with the disease flare and increased disability. The objectives of this survey were to confirm previous data about the extent of non-adherence to treatment with conventional disease-modifying anti-rheumatic drugs (cDMARDs) alone or with biological DMARDs (bDMARDs) in a larger sample of RA pts in Italy and to identify the profile of cDMARDs non-adherent pts

Methods: This was the second part of a self-reported survey started in 2014 in RA pts treated with cDMARDs in Italy. In the hospital waiting room, pts were asked to fill out an anonymous paper based questionnaire. Fieldwork: December 3rd 2014 – March 6th 2015

Results:

A total of 1,568 RA pts treated with cDMARDs were recruited from 29 Italian centers (females: 72.6%; mean age: 55 years; mean time since RA diagnosis: 9 years; pts already on treatment for other concomitant diseases: 58%): 685 pts (43.7%) were treated with cDMARDs alone and 883 pts (56.3%) were treated in combination with a biologic drug.

Overall, the proportion of pts reporting non-adherence to cDMARDs was 39.2% (n=615): 37.5% (n=257) of pts treated with cDMARDs alone and 40.5% (n=358) of pts treated in combination cDMARD + biologic drug. Among cDMARDs non-adherent pts, 86.3% reported to take “almost always” the cDMARDs treatment, 12% “seldom” and 1.6% “never”, with similar rates for pts treated with cDMARDs alone and in combination with a biologic drug. The main reason given for cDMARDs pts non-adherence was forgetfulness (49.9%); other reasons reported were: side effects fear (25.2%), the feeling they were taking too many drugs (16.6%) and the thought of feeling better (13.5%). Interestingly, 34.5% of the total 615 cDMARDs non-adherent pts did not mention cDMARDs non-adherence to their physician, particularly younger pts (aged ≤ 40 years).

Compared to the overall rate of cDMARDs non-adherence (39.2%), frequency of cDMARDs non-adherence was significantly higher (66.7%) in pts reporting a heavy impact of cDMARDs treatment on their life or an impairment of some aspects of their life, such as social life (55.9%), due to cDMARDs treatment.

Considering pts lifestyle, the rate of cDMARDs non-adherence was higher in pts taking care of family members (non-adherence rate: 43.9%), having an occasional rather than full-time job (49%), rarely practicing sports or hobbies (43.3%), receiving help by family members or caregivers (47.9%), taking also corticosteroids in combination (46.8%)

Conclusion: Results of this second part of the survey confirm that among RA pts cDMARDs non-adherence is quite

widespread (39.2%). Moreover, it is an unrecognised phenomenon in a considerable proportion of non-adherent pts (34.5%), who find difficult to talk to their physician about this issue. cDMARDs non-adherence appears strictly related to the impact of cDMARDs treatment on pts quality of life and is higher in pts treated with cDMARDs in combination with a biologic drug (40.5%), in more severely affected pts and in pts treated with more drugs. Lifestyle appears to be less related to treatment adherence, being more adherent pts with a regular way of life

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Abstract Number: 499

Efficacy of Tocilizumab Monotherapy in Patients with RA Is Not Influenced By ACPA Positivity

Manfred Herold[1], Peter Fasching[2], Winfried Graninger[3], Raimund Lunzer[4], Omid Zamani[5] and Burkhard Leeb[6], [1]Internal Medicine VI, Medical University of Innsbruck, Austria, Innsbruck, Austria, [2]Department of Internal Medicine V, Wilhelminen Hospital Vienna, Vienna, Austria, [3]Division of Rheumatology and Immunology, Medical University of Graz, Graz, Austria, [4]Department of Internal Medicine, Hospital Barmherzige Brüder Graz-Eggenberg, Graz, Austria, [5]Rheumazentrum Favoriten Vienna, Wien, Austria, [6]2nd Dept. of Medicine, State Hospital Stockerau, Center for Rheumatology Lower Austria, Stockerau, Austria
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SESSION INFORMATION
Session Date: Sunday, November 8, 2015
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Session Time: 9:00AM-11:00AM

Background/Purpose:

Rheumatoid arthritis (RA) patients with anti-citrullinated peptide antibodies (ACPA) need a more aggressive therapy (1). Tocilizumab (TCZ) seems to be the biologic with best response rates when used in monotherapy. It is unclear whether therapeutic response to TCZ monotherapy or TCZ plus methotrexate (MTX) is influenced by ACPA status.

Methods:

Statistical analyses were performed with data from the OPTIMISE trial (EUDRACT No. 2011-001863-39) running in Austria from January 2012 to August 2013. Seventy-six patients with mild to moderate RA and inadequate response (DAS28 >2.6 and ≤4.5) to a stable MTX dose (15 - 25 mg/wk) were enrolled and received three infusions of TCZ (8 mg/kg) iv every 4 weeks + MTX. Patients achieving good or moderate EULAR response at week 12 (n = 65) were randomized into Group A (TCZ 8 mg/kg plus MTX) or Group B (TCZ 8 mg/kg plus MTX placebo). Every four weeks disease activity was estimated with DAS28 (Disease Activity Score with 28 joint counts), SDAI (Simplified Disease Activity Index), CDAI (Clinical Disease Activity Index) and RADAI-5 (Rheumatoid Arthritis Disease Activity Index 5). In both groups patients were assigned to the anti-CCP-positive or -negative group. Group A included 17 patients anti-CCP-positive and 13 patients anti-CCP-negative; Group B 19 patients anti-CCP-positive and 14 patients anti-CCP-negative. Statistical comparisons analyzed three time points (week 0, baseline; week 12, end of therapy TCZ plus

MTX and week 24, end of TCZ plus MTX or TCZ plus MTX placebo).

Results:

In the anti-CCP-positive and the anti-CCP-negative group DAS28, CDAI, SDAI and RADAI-5 changed significantly ($p<0.001$) from baseline to week 12, but did not change from week 12 to week 24. Between-group comparison revealed no significant difference in any disease activity marker at any time point.

Conclusion:

In the anti-CCP-positive and the anti-CCP-negative group DAS28, CDAI, SDAI and RADAI-5 changed significantly ($p<0.001$) from baseline to week 12, but did not change from week 12 to week 24. Between-group comparison revealed no significant difference in any disease activity marker at any time point.

Literature

1. In the anti-CCP-positive and the anti-CCP-negative group DAS28, CDAI, SDAI and RADAI-5 changed significantly ($p<0.001$) from baseline to week 12, but did not change from week 12 to week 24. Between-group comparison revealed no significant difference in any disease activity marker at any time point.

Disclosure: M. Herold, None; **P. Fasching**, None; **W. Graninger**, None; **R. Lunzer**, None; **O. Zamani**, None; **B. Leeb**, None.

Abstract Number: 500

Ofatumumab for Rheumatoid Arthritis: A Cochrane Systematic Review and Meta-Analysis

Vidhu Anand[1], Sachit Anand[2], Sushil Garg[3], Maria A. Lopez-Olivo[4] and **Jasvinder A. Singh**[5], [1]University of Minnesota, Minneapolis, MN, [2]All India Institute of Medical Sciences, New Delhi, India, [3]The University of Minnesota, Minneapolis, MN, [4]General Internal Medicine, The University of Texas, MD Anderson Cancer Center, Houston, TX, [5]University of Alabama at Birmingham, Birmingham, AL

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Session Title: Rheumatoid Arthritis - Clinical Aspects Poster I

Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose: Ofatumumab is a unique anti-CD20 monoclonal antibody with its epitope more proximal and distinct from the epitope recognized by rituximab or by other anti-CD20 monoclonal antibodies. The proximity of this epitope probably accounts for the high efficiency of B-cell killing. The significant role of B-cells in RA and the uniqueness of ofatumumab's epitope resulting in more efficient killing than other B-cell deleting antibodies makes it ideal for use in RA. Our objective was to assess the benefits and harms of ofatumumab in reducing disease activity, pain, and improving function in people with RA.

Methods: We searched multiple databases for eligible studies as well as the websites of the regulatory agencies for

reported adverse events using the search strategy developed by a Cochrane librarian. We included randomized controlled trials comparing ofatumumab alone, or in combination with disease-modifying anti-rheumatic drugs (DMARDs) or biologics, to placebo or DMARDs or biologics alone or in combination with DMARDs, with no restrictions with regard to the dosage.Two authors independently assessed search results, trial quality and risk of bias, and extracted data.

Results: Our search identified three trials with low risk of bias, including 654 patients (383 in ofatumumab group and 271 in control group), for analysis. A stable methotrexate dose was allowed in all patients. Compared with placebo, patients in the ofatumumab group were 3.1 times more likely to achieve an ACR50 (RR 3.12, 95% CI 1.98 to 4.91). The efficacy was noted in patients with (RR, 95% CI: 3.76 (1.47 to 9.59) and without prior TNF-failure (RR, 95% CI: 2.78 (1.6 to 4.84), when given a dose of 700 mg, but not for the 300mg or the 1000 mg dose. The number needed to treat to achieve an ACR 50 response was 6 (95% CI 4 to 7). Patients in the ofatumumab group were 2.3 times more likely to achieve an ACR20 response (RR 2.3, 95% confidence interval (CI) 1.76 to 3.01). Only one trial found improvement in ACR70 response. A significant reduction in disease activity was found in ofatumumab-treated patients compared to placebo. The quality of life was also significantly improved with the ofatumumab treatment , as measured by SF-36 summary score (Mean Difference, 2.48, 95% CI 2.23, 2.73). Total withdrawals and withdrawals due to adverse effects were not statistically different between ofatumumab and placebo. However, withdrawal due to lack of efficacy were significantly lower in the ofatumumab treated patients compared to the placebo group (RR 0.24, 95% CI 0.10 to 0.60). The risk of adverse events was higher in ofatumumab group compared to placebo (RR 1.5, 95% CI 1.37 to 1.72). The incidence of serious adverse events was however not significantly different between ofatumumab and placebo (RR 1.72, 95% CI 0.91 to 3.26). The heterogeneity of the included trials was low (I^2=0%), for all the outcomes.

Conclusion: This systematic review and meta-analysis suggests that ofatumumab is efficacious and safe for the treatment of rheumatoid arthritis compared to placebo. The adverse events profile appears to be acceptable at the present but long-term trials and post-marketing surveillance are required to further assess efficacy and harms.

Disclosure: V. Anand, None; **S. Anand**, None; **S. Garg**, None; **M. A. Lopez-Olivo**, None; **J. A. Singh**, Takeda, Savient, 2,Takeda, Savient, merz, Regeneron, Allergan, Crealta, Bioiberica, 5.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/ofatumumab-for-rheumatoid-arthritis-a-cochrane-systematic-review-and-meta-analysis

Abstract Number: 501

Change in RF Titers Reflects RA Disease Activity and Predicts Therapeutic Response during TNF Inhibitor Therapy; Patients with a Continuous Reduction of Serum RF Levels Show Good Response

Takayoshi Owada, Kazuhiro Kurasawa, Yuta Takamura, Yumeko Namiki, Ayae Tanaka, Ryutaro Yamazaki, Harutsugu Okada, Satoko Arai, Reika Maezawa, Keiko Hatanaka and Yoshiki Ishii, Clinical Immunology, Dokkyo Medical University, Mibu, Tochigi, Japan

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Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose: Serum RF was detected in 26-90% of RA patients, and high-titer RF has been shown a poor prognosis factor in RA and predictor of resistance to RA therapy. Several reports have shown that tumor necrosis

factor (TNF) inhibitors decrease serum RF levels. However, it remains unclear whether changes in serum RF level during TNF inhibitors therapy reflects RA disease activity and predicts therapeutic response.

Methods: Subjects were 61 RA patients who filled ACR RA criteria 1987, were biologics-naïve, were treated with TNF inhibitors, and had moderate to high disease activity (DAS28-CRP≧2.7) and high titer of serum RF (≧100IU/ml). Their medical records were reviewed retrospectively. Serum RF titers were measured every visit t during TNF inhibitors treatment by using immunonephelometry, and more than 10% of changes in RF levels was judged as significantly. RA disease activity was measured by DAS28-CRP. Treatment responsiveness was assessed by EULAR response criteria.

Results: Subjects were 61 patients with 13 male and 48 female, 55.5 years (average) of age and 5.9 years (median) of disease duration. TNF inhibitors were 23 of infliximab, 32 of etenercept, 5 of adalmumab and 1 of golimumab. MTX were given to 40 patients with 7.7 mg (average) /week. At baseline serum RF levels were 386+415 U/ml (average +SD) and 221U/ml (median), and DAS28-CRP were 4.54 (average). Three months after TNF inhibitor therapy, RF titers were decreased in 87% of cases (347 at baseline and 135 U/ml at 3month, reduction rate; 61%), while 13% failed to reduce RF levels (751 at baseline and 830 U/ml Reduction rate; -10.5%). DAS28-CRP of patients without RF reduction (n=6) were 4.05 at baseline, 3.06 at 3 month at 3month and 2.83 at 12 month. Only 1 (17%) and 1 cases (17%) achieved clinical remission and low disease activity by DAS28-CRP at 12 month, and 2 cases (33%) satisfied good response by EULAR response criteria at 12 month. Among patients with RF reduction at 3month, 48% of cases showed re-elevation of RF titers (379 at baseline, 156 at 3month and 226 U/ml at 12 month) and others revealed continuous reduction of the titers (318 at base line, 117 at 3month and 63 U/ml at 12 month). DAS28-CRP of patients with RF re-elevation after 3month (n=26) were 4.58 at baseline, 2.80 at 3 month, 2.92 at 12 month. Among them clinical remission and low disease activity by DAS28-CRP were achieved in39% and 12%, respectively, and 46% of patients showed good response. DAS28-CRP of patients with RF continuous reduction (n=29) were 4.62 at baseline, 2.37 at 3 month, 2.08 at 12 month. Among them clinical remission and low disease activity by DAS28-CRP were achieved in 58% and 21%, respectively, and 79.3 % of patients showed good response, which was significantly high compared to those without RF reduction and those with re-elevation.

Conclusion: Three month after TNF inhibitors RF titers were reduced in 90% of patients. Those who failed decrease RF titers showed poor response to the therapy. Among patients with RF reduction at 3 month, 50% of them showed re-elevation of RF titers and others revealed continuous reduction of RF. Approximately 80% of patients with a continuous reduction of RF levels shows good response. Therefore, change in RF titers predicts therapeutic response of RA.

Disclosure: T. Owada, None; **K. Kurasawa**, None; **Y. Takamura**, None; **Y. Namiki**, None; **A. Tanaka**, None; **R. Yamazaki**, None; **H. Okada**, None; **S. Arai**, None; **R. Maezawa**, None; **K. Hatanaka**, None; **Y. Ishii**, None.

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Abstract Number: 502

Decreased Vaccine Responses in Rheumatoid Arthritis Patients Receiving Anti-TNF Treatment and Relationship to B Cell Subsets

Jennifer Barnard[1], Nida Meednu[2], Kelly Callahan[1], Karen Boyle[3], Lynette Keyes-Elstein[3], Beverly Welch[4], Ellen Goldmuntz[5] and **Jennifer H. Anolik**[1], [1]University of Rochester Medical Center, Rochester, NY, [2]Medicine- Allergy, Immunology and Rheumatology, University of Rochester Medical Center, Rochester, NY, [3]Rho Federal Systems, Inc., Chapel Hill, NC, [4]6610 Rockledge Dr., NIAID/NIH, Bethesda, MD, [5]DAIT, NIAID/NIH, Bethesda, MD

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Session Time: 9:00AM-11:00AM

Background/Purpose: TNF is a key pro-inflammatory cytokine in normal immune responses and pathologically in the rheumatoid arthritis (RA) synovium, thus representing a key treatment target but one where potential negative effects on responses to natural infection and vaccination must be balanced. We hypothesized that some of the clinical efficacy of TNF blockade in RA may be mediated by effects on the B cell compartment and have previously reported that RA patients on anti-TNF (etanercept) have a disruption of germinal center (GC) reactions in peripheral lymphoid tissue (Anolik, J Immunol., 2008, 180: 688). Here, we characterized vaccine responses in RA patients recently started on TNF blockade.

Methods: We randomized subjects in a 2:1 ratio to receive standard dosing regimens of etanercept or adalimumab for 24 WK. The subjects met the 1987 ACR criteria for RA, clinically active (DAS28>4.4), and were on MTX. Disease activity and response was assessed based on DAS28-CRP. Twenty eight of 63 randomized subjects participated in a vaccine sub-study receiving vaccination with Hepatitis A (accelerated 12 and 16 WK), Hepatitis B (accelerated 20 mg at 12, 16, 20 WK), diphtheria/tetanus (dT) booster (12 WK) or combination. Response to Hep B was defined as an antibody titer ≥12 up to 36 WK after randomization. Response to Hep A was defined as a detectable antibody at any point after immunization (to 20 WK). dT booster responder was defined as a titer > 1.0 IU/mL and a ratio to pre-boost of > 3.0. Flow cytometry of B cells was performed at baseline and at 12 and 24 WK. Expression of CD19, IgD, CD27, CD38 and CD24 were used to identify B cell subsets.

Results: A surprisingly high fraction of patients receiving Hep B vaccination were non-responders (NR) (78%, n=18/23). All 5 patients who responded to Hep B were receiving etanercept. Responses to Hep A were higher (48%, n=10/21). Two out of 5 patients who received dT vaccine were responders. For patients who received both Hep A and Hep B vaccinations (n=14), 21% responded to both (n=3), 14% responded to Hep A vaccine alone (n=2), and 64% of patients did not respond to either vaccines (n=9). In the group receiving both vaccines, we analyzed the B cell compartment by flow cytometry. There were no significant differences in the % of core B cell subsets: switched memory, double negative memory, un-switched memory, and naïve B cells at baseline and 12 and 24 WK after anti-TNF treatment between those responding to at least 1 vaccine (R) and those not responding (NR). The mean % (SE) of germinal center-like B cells in the R group was significantly higher than the NR group over all visits (GC like: CD19+IgD-CD27-CD38++CD24-) (R: baseline 2.3±0.66, WK12 1.9±0.50, WK24 2.2±0.44 vs. NR: baseline 0.9±0.49, WK12 0.8±0.39, WK24 0.6±0.33; p=0.04 overall mean, 0.01 WK24).

Conclusion: These data suggest that the *in vivo* generation of B cell memory in response to the T dependent neoantigens hepatitis B and hepatitis A is impaired in RA patients treated with anti-TNF. The % GC B cells in the periphery may correlate with responses to vaccination.

Disclosure: J. Barnard, None; **N. Meednu**, None; **K. Callahan**, None; **K. Boyle**, None; **L. Keyes-Elstein**, None; **B. Welch**, None; **E. Goldmuntz**, None; **J. H. Anolik**, None.

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Abstract Number: 503

Predictors for Attaining Remission at Two Consecutive Visits in Newly Diagnosed Early RA Patients

T. Martijn Kuijper[1], J.J. Luime[2], P.H.P. de Jong[3], A. H. Gerards[4], Derkjen van Zeben[5], I. Tchetverikov[6], P.B.J. de

Sonnaville[7], M. van Krugten[8], B. Grillet[9], Mieke Hazes[10] and A.E.A.M. Weel[11,12], [1]Rheumatology, Erasmus MC, Rotterdam, Netherlands, [2]Department of Rheumatology, Erasmus Medical Centre, Rotterdam, Netherlands, [3]Department of Rheumatology, Erasmus Medical Center, Rotterdam, Netherlands, [4]Rheumatology, Vlietland Hospital, Schiedam, Netherlands, [5]Rheumatology, Sint Franciscus Gasthuis, Rotterdam, Netherlands, [6]Albert Schweitzer Ziekenhuis, Dordrecht, Netherlands, [7]Oosterschelde Hospital, Goes, Netherlands, [8]Rheumatology, Admiraal de Ruyter Hospital, Vlissingen, Netherlands, [9]Rheumatology, ZorgSaam Hospital, Terneuzen, Netherlands, [10]Rheumatology, Erasmus MC, University Medical Center Rotterdam, Rotterdam, Netherlands, [11]Rheumatology, Erasmus University Medical Center, Rotterdam, Netherlands, [12]Department of Rheumatology, Maasstad Hospital, Rotterdam, Netherlands
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Background/Purpose:

Early and intensive treatment with DMARDs are essential for remission induction in newly diagnosed RA patients. However, demographic, psychosocial and disease related factors may play a role as well.

Objectives:

To investigate which demographic, psychosocial and disease related factors are associated with attaining remission at two consecutive visits in early RA patients treated in a treat-to-target manner

Methods:

We used 2 years follow-up data from patients participating in the tREACH trial[1,2] in which induction therapy strategies were compared: (A) combination high dose conventional therapy ((MTX + sulfasalazine + hydroxychloroquine or (B) MTX. Both groups had glucocorticoid (GCs) bridging. Disease activity (DAS) was assessed every 3 months. Remission was defined as DAS<1.6 at 2 consecutive visits (3 months). Univariate and multivariate logistic regression analyses were performed including demographic, disease related and psychosocial factors evaluated at baseline as predictors for attaining remission during 24 months of follow-up.

Results:

281 patients (68% female; mean DAS 3.4, median HAQ 1.00) were included. During 2 years of follow-up, 139 of 281 (49%) patients (group A: 93 (51%), group B: 46 (47%)) attained remission at 2 consecutive visits. Univariate analysis revealed that older age and female sex were associated with a lower chance of attaining remission (demographic factors). Similar relations were observed for higher DAS, HAQ and worse physical functioning (disease factors) and higher levels of anxiety, depression, fatigue and passive coping with pain (psychosocial factors). In multivariate analysis within blocks of covariates, age and sex maintained significance in the block of demographic factors, DAS and ACPA positivity in the block of disease factors and fatigue in the block of psychosocial factors. In the final model combining the independent block predictors, age, sex and fatigue remained significant.

Conclusion:

In the tREACH trial, 50% of early RA patients attained remission within 2 years of follow-up. Older age, female sex, higher baseline DAS, ACPA positivity and fatigue were important predictors for not attaining remission, but in the final model only age, sex and fatigue remained. Results suggest that high levels of fatigue may prevent patients from attaining remission despite treatment according to a tight control and treat-to-target strategy.

References

1. Claessen *et al*. BMC Musculoskelet Disord 2009:71.

2. De Jong *et al*. Ann Rheum Dis. 2013 Jan;72

Table 1 Predictors for attaining remission

	Univariate		Multivariate, within block of covariates*		Multivariate, all**	
	OR	p	OR	P	OR	P
Demographics						
Age	**0.983**	**0.047**	**0.979**	**0.033**	**0.976**	**0.036**
Sex (female)	**0.343**	**<0.001**	**0.279**	**<0.001**	**0.326**	**0.001**
Dutch ethnicity	1.229	0.549				
Paid work	0.789	0.079				
Disease						
MTX monotherapy	0.883	0.619				
DAS (baseline)	**0.662**	**0.002**	**0.651**	**0.002**		
HAQ (baseline)	**0.578**	**0.005**				
SvH (baseline)	0.964	0.305				
RF positive	1.230	0.499				
ACPA positive	0.589	0.083	**0.498**	**0.035**		
Duration of complaints	1.000	0.716				
Physical functioning (SF36 PCS)	**1.047**	**0.021**				
Psychosocial						
Mental functioning (SF36 MCS)	1.026	0.173				
Internal locus of control (MHLC)	1.062	0.066				
External locus of control (MHLC)	0.982	0.488				
Chance locus of control (MHLC)	1.010	0.698				
Anxiety (HADS)	**0.929**	**0.035**				
Depression (HADS)	**0.893**	**0.004**				
Fatigue (VAS)	**0.940**	**0.008**	**0.936**	**0.006**	**0.947**	**0.024**
Coping with pain (CORS)	**0.951**	**0.048**				

* After backward selection, variables with p<0.20 in univariate analysis were entered

** After backward selection, variables with p<0.05 in multivariate within block of covariates were entered

Abbreviations:

ACPA Anti-Citrullinated Protein Antibody	MTX Methotrexate
CORS Coping with Rheumatic Stressors	PCS Physical Component Scale
DAS Disease Activity Score	RF Rheumatoid Factor
HADS Hospital Anxiety and Depression Scale	SF36 Short-Form 36
	SvH Sharp-van der

HAQ Health Assessment Questionnaire MCS Mental Component Scale MHLC Multidimensional Health Locus of Control	Heijde Score VAS Visual Analogue Scale

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Abstract Number: 504

Influence of CDAI Measurement on the Decision of Community Rheumatologists to Initiate or Change Biologic Treatment

Alan K. Matsumoto[1], Herbert S. B. Baraf[2], Janna Radtchenko[3], Jason Drenning[4] and Bruce Feinberg[5], [1]Rheumatology, Arthritis & Rheumatism Assoc, Wheaton, MD, [2]The Center for Rheumatology and Bone Research, Wheaton, MD, [3]Health Care Analytics, Cardinal Health, Dallas, TX, [4]Healthcare Analytics, Cardinal health, Dallas, TX, [5]Cardinal Health, Dublin, OH

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Background/Purpose: Periodic measurement of disease activity using validated tools such as the Clinical Disease Activity Index (CDAI) is considered an important aspect of care for patients with rheumatoid arthritis. Treat to target strategies mandating changes in therapy to achieve low disease activity measures have been well studied. However, much less is known about the use of these measures and the influence on physician behavior in routine clinical practice.

Methods: Seventy nine rheumatologists from 35 practices in the mid-Atlantic participated in a payer sponsored rheumatologist developed RA treatment clinical pathway which required CDAI measurement at each visit. To be considered compliant with the pathway, practices were required to enter all RA patients insured by the payer into Pathway Compliance Software, utilize oral DMARDs for at least 3 months prior to use of a biologic agent, prescribe the biologic agent at the lowest approved dose and increase dose according to the package guidelines. Patients were not required to change biologics for ongoing disease activity, but biologics could not be initiated, switched or increased if the patient was in CDAI remission. Practices achieving 80% compliance with the program were offered increased reimbursement to offset the cost of data collection and program compliance.

Results: From 1/1/12 to 12/31/2013, 3,200 patients were enrolled in the pathway and had at least 2 physician encounters. Of these patients, 586 patients started a new biologic(s) in the study period: 137 started their first biologic and 449 switched to another biologic(s), 301 patients were evaluated based on availability of follow up CDAI scores. Mean CDAI scores at the visits during which biologic therapy was initiated or changed was 13.1 and 12.2 respectively. Mean CDAI scores for each of the groups in 3 months since biologic initiation or switch were 10.4 and 11.3 respectively and improved by 27% in biologic naïve group and 7% in biologic switch group. Of the total 4,048 visits with CDAI scores, 587 visits were associated with high CDAI scores, 333 of them (57%) resulted in therapy modification. In patient visits with CDAI scores showing high disease activity (CDAI>22), but without change in therapy to a first time biologic or a second biologic, mean CDAI, PGA (Patient's Global Disease Activity), EGA (Evaluator's Global Disease Activity), SJC (swollen joint count) and TJC (tender joint count) scores were 34.7, 6.0, 5.2, 7.5, and 15.3 compared to patients who switched at high disease activity with the mean CDAI, PGA, PhGA, SJC, and TJC of 36.8, 5.5, 5.4, 9.3, 15.8 respectively (p>.05).

Conclusion: Starting biologic therapy positively impacts clinical outcomes as measured by CDAI score; however CDAI scores do not seem to always impact the decision to start or switch the biologic. More research is needed to fully elucidate the decision drivers having the highest impact on the decision to switch therapy.

Disclosure: A. K. Matsumoto, Abbvie, Amgen, Pfizer, Takeda, 2; **H. S. B. Baraf**, Abbvie, 5,UCB, 5,Cardinal Health, 5; **J. Radtchenko**, None; **J. Drenning**, None; **B. Feinberg**, None.

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Comparative Effectiveness and Time to Response Among Abatacept, Adalimumab, Certolizumab, Etanercept, Infliximab, Rituximab and Tocilizumab in a Real World Routine Care Registry

Yusuf Yazici[1], Hannah Bernstein[1] and Christopher Swearingen[2], [1]Department of Medicine, Division of Rheumatology, New York University School of Medicine, New York, NY, [2]Pediatrics & Biostatistics, University of Arkansas, Little Rock, AR

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Background/Purpose: With the availability of multiple biologic agents, each with different modes of action, use of real world registries provide the manner in which to examine comparative effectiveness in the absence of head-to-head clinical trials inform physicians how they might be used for the treatment of rheumatoid arthritis

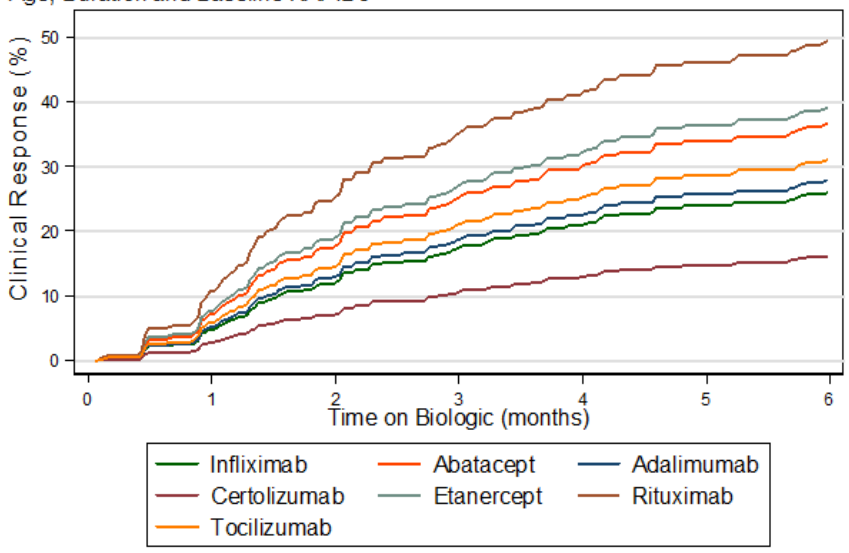
Methods: Arthritis Registry Monitoring Database (ARMD) has been collecting prospective patient data since 2005 in all patients seen in routine care. Each patient in this setting (with any diagnosis) completes a 2-sided, 1-page MDHAQ (multidimensional health assessment questionnaire) at every visit while waiting to see the physician in the infrastructure of clinical care. The MDHAQ includes scales for physical function, pain, patient global estimate (PATGL), fatigue, and a self-report RADAI painful joint count. Usage of the biologic medications abatacept, adalimumab, certolizumab, etanercept, infliximab, rituximab and tocilizumab along with self-reported disease activity and clinic measures were

abstracted. Treatments were considered to be independent of each other as no individual received biologic medications in combination. Time to first response defined as an improvement in RAPID3 of at least 3.6 was calculated; change from biologic medication initiation to first response for self-reported disease activity and clinic measures was estimated. For those individuals with no response, time to last follow-up was calculated and this was defined as lack of efficacy. Differences in time to first response between biologic medications versus lack of efficacy were estimated using competing risks proportional hazards model, adjusting for age, duration of disease, baseline RAPID3.

Results: 4217 encounters were reviewed for this analysis. A total of 1789 treatment observations were abstracted in 316 subjects. For those subjects with a baseline RAPID3 ≥ 3.6, average age of the cohort was 51.5 years (±14.5), average duration 9.3 years (±9.3), 213 (85%) were female, and average baseline RAPID3 was 14.8 (±6.3). Using infliximab as a reference, improved efficacy was estimated with abatacept (SHR = 1.5), etanercept (SHR = 1.6) and rituximab (SHR=2.3) adjusting for age, duration and baseline RAPID3. Increased age led to a decreased likelihood of response (SHR=0.99, P=0.045). As expected, the higher the baseline RAPID3, the likelihood of a positive treatment response also increased (SHR=1.09, P<0.001). Adalimumab and tocilizumab had some improved efficacy, while certolizumab had decreased efficacy compared to infliximab.

Conclusion: Our data suggest that there are no major differences in efficacy of adalimumab, abatacept, etanercept and infliximab and time to response when treating RA patients. With no difference in clinical outcomes, most treatment decisions may be based on ease of use and safety data of respective biologics agents when they are being considered for RA treatment.

Figure. Cumulative Incidence of Achieving Clincal Response Adjusted for Age, Duration and Baseline RAPID3



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Abstract Number: 506

Evaluation of Persistence and Outcomes in Patients Treated with TNF and Non-TNF Biologics Following Treatment Clinical Pathway in Rheumatoid Arthritis

Alan K. Matsumoto[1], Herbert S. B. Baraf[2], Janna Radtchenko[3], Jason Drenning[4] and Bruce Feinberg[5], [1]Rheumatology, Arthritis & Rheumatism Assoc, Wheaton, MD, [2]The Center for Rheumatology and Bone Research, Wheaton, MD, [3]Health Care Analytics, Cardinal Health, Dallas, TX, [4]Healthcare Analytics, Cardinal health, Dallas, TX, [5]Cardinal Health, Dublin, OH
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Background/Purpose: Use of biologic agents for the treatment of rheumatoid arthritis continues to grow rapidly, with the cost of these agents putting a significant strain on health care budgets. Although rheumatologists and third party payers share the goal of ensuring quality of care for RA patients, rheumatologists fear potential limitation of access to biologics due to cost while third party payers are concerned about the rising expenses associated with the use of these agents. Treatment pathways have been suggested as a tool to address these issues.

Methods: Seventy nine rheumatologists from 35 practices in the mid-Atlantic region participated in a payer-sponsored, rheumatologist-developed RA treatment clinical pathway. To be considered compliant with the pathway, practices were required to enter all RA patients insured by the payer, utilize oral DMARDs for at least 3 months prior to use of a biologic agent, prescribe the biologic agent at the lowest approved dose, and increase dose according to package guidelines. Initial biologic therapy could include any of the TNF, abatacept (SC or IV) or tocilizumab (SC or IV). Rituximab or tofacitinib were reserved for previous biologic failures. Patients were not required to change biologics for ongoing disease activity, but biologics could not be initiated, switched or increased in dose if the patient was in Clinical Disease Activity Index (CDAI) remission. Persistence and mean CDAI were calculated and evaluated at 6 and 12 months for patients on TNF and non-TNF agents.

Results: From 1/1/12 to 12/31/2013, Of 3200 patients on the pathway, 586 patients started a new biologic(s) in the study period, 137 started their first biologic and 449 switched to another biologic. 301 patients were analyzed at treatment initiation based on their CDAI score availability of which 159 initiated TNF agents and 142 initiated non TNF- agents. Of these patients, 65% were persistent on therapy at 6 months on TNF agents and 84% on non-TNF agents; at 12 months, 52% were persistent on TNF agents and 65% on non-TNF agents. The mean CDAI scores at 6 months were 7.7 for TNF group versus 10.2 for non-TNF group (p=.010); while at 12 months the mean CDAI scores were 8.6 in TNF and 10.7 in non-TNF group respectively although the difference was not statistically significant as assessed by t-test (p=.23). Overall the mean CDAI score for patients who initiated a biologic was 12.6, while the mean CDAI score for patients who persisted on their biologic for a year was 9.7.

Conclusion: Persistence decreased over time in both TNF and non-TNF patients with higher rate of drop off occurring in patients on TNF. Patients exhibit improvement in CDAI scores, while participating in the Pathway program. Guideline-driven care is taking into consideration both efficacy and costs and has no negative impact on patient reported outcomes.

Disclosure: A. K. Matsumoto, Abbvie, Amgen, Pfizer, Takeda, 2; **H. S. B. Baraf**, Abbvie, 5,UCB, 5,Cardinal Health, 5; **J. Radtchenko**, None; **J. Drenning**, None; **B. Feinberg**, None.

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Abstract Number: 507

Meta-Analysis of the Time Course of the Response to Adalimumab Plus Methotrexate or Methotrexate Monotherapy in Clinical Trials of Patients with Rheumatoid Arthritis

Xin Wang[1], **Arthur Kavanaugh**[2], Désirée van der Heijde[3], Maxime Dougados[4], Stefan Florentinus[1], Yihan Li[1], Iain Sainsbury[1] and Josef S. Smolen[5], [1]AbbVie Inc., North Chicago, IL, [2]University of California San Diego, La Jolla, CA, [3]Leiden University Medical Center, Leiden, Netherlands, [4]René Descartes University and Hôpital Cochin, Paris, France, [5]Medical University of Vienna and Hietzing Hospital, Vienna, Austria
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Background/Purpose: Adalimumab (ADA) plus methotrexate (MTX) and MTX treatments for rheumatoid arthritis (RA) have been assessed in phase 2–4 clinical trials. This meta-analysis used 5 such studies to create a maximum efficacy (Emax) model describing the time course of the change from baseline in the 28-joint Disease Activity Score (DAS28) based on C-reactive protein (CRP).

Methods: DAS28(CRP) is a validated, continuous clinical efficacy endpoint for assessing signs and symptoms in RA patients (pts); change from baseline was modeled using a 3-parameter, nonlinear Emax model of ADA+MTX or MTX efficacy over time (up to 52 wks). Emax models for the DAS28(CRP) time course for each treatment and each study were built using data from pts with early (n=3 studies) and established (n=2) RA. Contributions of baseline covariates were assessed using the least absolute shrinkage and selection operator (LASSO) penalized linear regression model.

Results: Emax model estimates for DAS28(CRP) responses to ADA+MTX and MTX treatments are in **Table 1**. Visual inspection confirmed that modeled time courses for DAS28(CRP) responses to ADA+MTX and MTX treatments were consistent with observed mean and median values of the combined studies; residual variability for DAS28(CRP) change was 1.1 in both groups. The modeled DAS28(CRP) response to MTX appeared to develop more slowly vs response to ADA+MTX (9.4 vs 3.1 wks for 50% effect). The effects of RA duration on DAS28(CRP) responses were estimated by modeled time courses for ADA+MTX and MTX in pts with early (duration=0.4 y, no prior DMARD use) and established (duration=5 y, prior DMARD use) RA; all other covariates were fixed. The DAS28(CRP) responses to MTX and ADA+MTX were greater in pts with early vs established RA **(Figure 1)**. When the covariate for baseline disease activity was set to DAS28(CRP)=5.5 (less active RA) vs 6.5 (more active RA), the model predicted greater responses to either treatment in pts with more active RA **(Figure 2)**.

Conclusion: Time courses of DAS28(CRP) responses to ADA+MTX and MTX treatments over 52 wks were well characterized by Emax models incorporating baseline covariates. The models predicted the greatest treatment differences between ADA+MTX and MTX during the first 24 wks and greater DAS28(CRP) responses to either treatment in pts with early RA and more active RA at baseline.

Table 1. 52-Week Emax Model Estimates for DAS28(CRP) Responses			
		Parameter Estimates	
Covariate at Baseline		**MTX**	**ADA+MTX**
Body mass index, kg/m^2		0.005	0.023**
RA duration, y		0.059**	0.001
DAS28		–0.682**	–0.632**
Prior DMARD use		0.343**	0.661**
CRP		–0.013	–0.034**
Subject Global Assessment of disease activity		–0.008**	–0.005**
Physician Global Assessment of disease activity		0.007**	0.003**
Subject Global Assessment of pain		0.004*	0.004**
Health Assessment Questionnaire		0.276**	0.232**
Model Parameters			
b_0		0.304	–0.470**
ED_{50}		9.381**	3.085**
*P<0.01; **P<0.001.			

Figure 1. Effect of RA Duration and Prior DMARD use for ADA+MTX and MTX Treatment

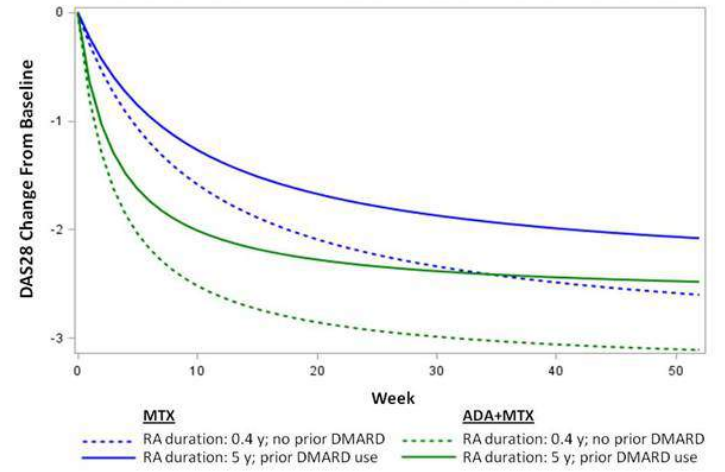
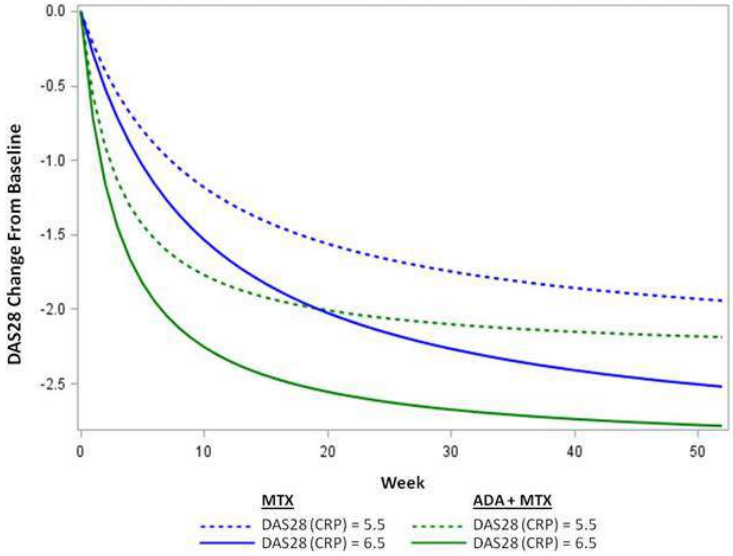


Figure 2. Effect of Baseline DAS28(CRP) for ADA+MTX and MTX Treatment



Disclosure: X. Wang, AbbVie, 3,AbbVie, 1; **A. Kavanaugh**, AbbVie, 2,AbbVie, 5; **D. van der Heijde**, AbbVie, Amgen, AstraZeneca, BMS, Centocor, Chugai, Daiichi, Eli Lilly, GSK, Janssen Biologics, Merck, Novartis, Novo-Nordisk, Otsuka, Pfizer, Roche, Sanofi-Aventis, Schering-Plough, UCB, Vertex, 2,AbbVie, Amgen, AstraZeneca, BMS, Centocor, Chugai, Daiichi, Eli Lilly, GSK, Janssen Biologics, Merck, Novartis, Novo-Nordisk, Otsuka, Pfizer, Roche, Sanofi-Aventis, Schering-Plough, UCB, Vertex, 5; **M. Dougados**, AbbVie, Pfizer, UCB, Merck, Lilly, Roche, BMS, 2,AbbVie, Pfizer, UCB, Merck, Lilly, Roche, BMS, 5; **S. Florentinus**, AbbVie, 3,AbbVie, 1; **Y. Li**, AbbVie, 3,AbbVie, 1; **I. Sainsbury**, AbbVie, 3,AbbVie, 1; **J. S. Smolen**, AbbVie, 2,AbbVie, 5.

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Abstract Number: 508

Impact of Race on Patient Global Scores and the Misclassification of Disease Activity

Shriyanka Jain[1], Uzma Khan[1], Amy Lundholm[2] and Martin Bergman[3], [1]Internal Medicine, Mercy Catholic Medical Center, Darby, PA,

[2]Rheumatology, Roger Williams Medical Center, Providence, RI, [3]Medicine, Drexel University College of Medicine, Philadelphia, PA
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Background/Purpose: Disease activity measurement is a cornerstone of the Treat to Target strategy. However, all currently used measures include a Patient Global Score (PtGLB) as one of the components. We assessed disparities in Patient Global Scores in White vs. Black patients in a community based practice and its impact CDAI.

Methods: Data from random visits of 236 RA patients was obtained. Data regarding patient demographics, as well as other measures of clinical status were evaluated. Regression analysis was used to determine impact of race on PtGLB, controlling for age, sex, disease duration, education level, swollen joint count, and Fibromyalgia co-diagnosis. CDAI was calculated by using standard measures and, also, corrected for ethnicity.

Results: 236 patients with RA, 198 Caucasian and 38 of African descent were analyzed. Two sample t-test to compare the two racial groups revealed no significant differences in age, duration of disease, education level, Fibromyalgia co-diagnosis, and swollen joint count (all p-values >0.05). Statistically significant differences were found in gender and PtGLB, with a higher proportion of female patients and higher PtGLB in the black population (mean of 5.09, 95% CI 4.15 – 6.04 vs. 3.62, 95% CI 3.23 – 4.02) (p=0.004). Higher Provider Global Scores were seen in the black population vs. the white population (1.92, 95% CI 1.09 – 2.75 vs. 1.27, 95% CI 1.04-1.50) (p=0.04).

After controlling for age, sex, duration of disease, education level, Fibromyalgia co-diagnosis, and swollen joint count, it was found that the average patient-reported global assessment score was 3.83 in the white population vs. 5.17 in the black population (D= 1.34).

When CDAI scores were calculated without correcting for influence of race on PtGLB, the mean CDAI score in whites were lower than in the blacks (10.97, 95% CI 9.59 – 12.36 vs. 14.35, 95% CI 10.05 – 18.64). 57% (112 of 198 patients) of whites were in low disease activity or remission state vs. 37% (14 of 38 patients) of the black population. (p=0.033)

After correcting for the influence of race, the percentage of patients in remission/low disease state in the black population increased to 47% (18 of 38 patients). After correction thee was no statistically significant differences between the two groups. (p=0.374)

Conclusion: African-American patients on average have higher self-reported global disease activity levels. This may lead to misclassification of patients as being outside of the remission/low disease activity range, which may lead to over-treatment of patients who would otherwise have no changes made to their management plan.

Further studies with larger numbers of patients and inclusion of additional racial/ethnic groups to substantiate the results of this study are required.

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Abstract Number: 509

In Early Undifferentiated Polyarthritis, 14-3-3η Seroreversion or Sustained Negativity Is Associated with Better Radiographic Outcomes, Even in DAS-28 Remitters

Gilles Boire[1,2], Nathalie Carrier[3], Artur de Brum-Fernandes[1,4], Patrick Liang[1,4], Ariel Masetto[2,5], Yuan Gui[6], Jane Savill[6], Sara Michienzi[6], Henri Ménard[7], Walter Maksymowych[8] and Anthony Marotta[6], [1]Rheumatology Division, Centre Hospitalier Universitaire de Sherbrooke, Sherbrooke, QC, Canada, [2]Department of Medicine/Division of Rheumatology, University of Sherbrooke, Sherbrooke, QC, Canada, [3]Division of Rheumatology, Université de Sherbrooke, Sherbrooke, QC, Canada, [4]Department of Medicine/Division of Rheumatology, Université de Sherbrooke, Sherbrooke, QC, Canada, [5]Department of Medicine/Division of Rheumatology, Université de Sherbrooke, Centre Hospitalier Universitaire de Sherbrooke, Sherbrooke, QC, Canada, [6]Augurex Life Sciences Corp., Vancouver, BC, Canada, [7]MSK Research Axis, McGill University Health Center Research Institute, Montreal, QC, Canada, [8]Department of Medicine, University of Alberta, Edmonton, AB, Canada
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SESSION INFORMATION
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Session Title: Rheumatoid Arthritis - Clinical Aspects Poster I
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Background/Purpose: Advancements in RA treatment approaches with DMARDs and biological agents have enabled disease remission goals that were previously considered unattainable. The concept of "tight control" strategies tailored to individual patients defines specific clinical targets for DAS remission, reduction of CRP and ESR to normal measures and the halting of joint damage within a reasonable time frame. 14-3-3η is normally a ubiquitous intracellular protein that in RA, is released into the extracellular space where it acts as a ligand that potently induces MMPs, RANKL as well as TNFα and IL-6. 14-3-3η is available as a highly specific diagnostic blood test for RA and is modifiable over the disease course, lending itself well to serial testing for disease monitoring to healthy, negative levels. The aim of this study was to examine whether seroreversion of 14-3-3η to negative levels at 18 months is associated with a better radiographic outcomes at 30 and 42 months in RA patients.

Methods: Serum 14-3-3η levels were measured at baseline (BL) in 331 patients with recent onset polyarthritis (Sherbrooke EUPA), in which tight control was applied and 60 months follow-up completed. 14-3-3η positivity was defined as ≥0.19 ng/ml. Mean age was 60 years, 62% were female, and median (IQR) duration of symptoms was 4 (1.7-5.7) months. At 18 and 30 months, radiographic follow-up data was available for 320 and 310 patients, respectively. ANOVA analysis was performed to assess the significance of differences in radiographic outcomes from BL to 18 months based on 14-3-3η positive status at BL and 18 months. DAS remission at 18 months was defined as <2.6. Differences in mean ΔSHS from 18 to 30 and 42 months based on 18 month 14-3-3η positivity was assessed using the Student t-test.

Results: Out of 320 patients, 147 (46%) patients were 14-3-3η positive at BL. At 18 months, 126 (86%) remained positive (RP) and 21 (14%) became negative (BN). Of the 173 (54%) that were negative at BL, 154 (89%) remained negative (RN) and 19 (11%) became positive (BP). In evaluating radiographic progression from BL to 18 months, ANOVA analysis revealed that the mean (SD) ΔSHS was lowest in those patients that BN for 14-3-3η [2.7 (3.9)] or RN [2.5 (4.8)] versus patient groups that RP [4.3 (5.7)] or BP [6.0 (10.5)], p=0.009. Sub-grouping of patients according to DAS28 remission revealed despite achieving a DAS28 <2.6, patients that were 14-3-3η positive at 18 months had significantly higher ΔSHS from 18 to 30. Similar observations were apparent in non-remitters (table).

		14-3-3η at 18 mo	N	Mean	Std. Dev	p-value
Not in remission at 18 mo	ΔSHS from 18-30	positive	67	4.9403	8.37724	0.002
		negative	73	1.5616	4.00689	
	ΔSHS from 18-42	positive	67	8.9254	14.70963	0.006
		negative	76	3.6447	6.98895	
Remission at 18 mo	ΔSHS from 18-30	positive	70	3.1714	4.66865	0.002
		negative	95	1.4211	2.4779	
	ΔSHS from 18-42	positive	68	3.7941	8.39609	0.136
		negative	92	2.3261	3.65883	

Conclusion: Patients with early polyarthritis who are 14-3-3η seronegative and remain negative or revert from positive to negative levels at 18 months, have less radiographic progression at 30 and 42 months. Aiming for negative 14-3-3η levels as part of treat-to-target strategies may assist clinical efforts to halt joint damage progression.

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Abstract Number: 510

Histologic Scoring of Arthroplasty Synovial Samples May Predict RA Flare

Susan M. Goodman[1], Rivka Friedlander[2], Caroline Figgie[2], Alessandra B. Pernis[3], Cristina T. Rozo[4], Ellen M. Gravallese[5], Edward F. DiCarlo[6], Laura T. Donlin[7], Mark P. Figgie[8], Reena Khianey[9], Anh Hoang[1], Kathleen Andersen[10], Luvana Chowdhury[11] and VP Bykerk[12], [1]Rheumatology, Hospital for Special Surgery, New York, NY, [2]Research, Hospital for Special Surgery, New York, NY, [3]Autoimmunity & Inflammation, Hospital for Special Surgery, New York, NY, [4]535 East 70th Street, Hospital for Special Surgery, New York, NY, [5]Lazare Research Bldg Ste 223, University of Massachusetts Medical School, Worcester, MA, [6]Laboratory Medicine, Hospital for Special Surgery, New York, NY, [7]Arthritis and Tissue Degeneration Program and the David Z. Rosensweig Genomics Research Center, Hospital for Special Surgery, New York, NY, [8]Orthopaedics, Hospital for Special Surgery, New York, NY, [9]Medicine, Hospital for Special Surgery, New York, NY, [10]Hospital for Special Surgery, New York, NY, [11]Autoimmunity and Inflammation Program/Research, Hospital for Special Surgery, New York, NY, [12]Rheumatology, Mount Sinai Hospital, University of Toronto, Toronto, ON, Canada
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Background/Purpose: Patients with established RA undergoing total joint arthroplasty (TJA) frequently experience a disease flare within 6 weeks of surgery. This study aims to determine which histopathologicfeatures indicating active synovial inflammation in tissue obtained during TJA was associated with patients who experience post-op flare.

Methods: Synovial tissue obtained at the time of TJA from a cohort of well-characterized RA patients was examined by 2 experienced musculoskeletal pathologists for features known to be associated with rheumatoid arthritis. Significant previously described synovial pathologic features selected by unadjusted logistic regression included synovial lymphocytic and plasma cell infiltration, sclerosis/fibrosis, synovial lining hyperplasia, vascularity, and mucoid change were combined as a limited pathology score. Patient's summary scores were compared to clinical status, including flare yes/no whether in the 6 week postoperative course. Inter-pathologist reliability, along with disease characteristics and flare status correlations, were assessed using Spearman's correlation coefficient. Flare was classified using patient self-report and MD agreement based on chart review. Immunohistochemicalstaining for Rho Kinase pathway markers was performed.

Results: Baseline and disease characteristics from 37 RA patients showed no differences in those who reported flare (n=23) vs. those who did not (n=14) (**Table 1**). Pathologist scoring of summed synovial inflammatory features were highly correlated between (Spearman's rho=.55, p-value=0.01) and within (Spearman's rho=0.7, p<0.01) readers. While there was no correlation between the summary pathology score and baseline disease characteristics (DAS28CRP/flare: rho=0.2, CRP/ flare: rho=0.2) **,** flare was associated with synovial lymphocytic infiltration (OR 4.2, 95% CI 1.2-14.9, p=0.03), and plasma cell infiltration (OR 6.3, 95%CI 1.7- ∞, p<0.01). Sclerosis/fibrosis was not significantly associated with flare (OR 0.9, 95%CI 0.4-2.2, p=0.78) (**Table 2)**. The pERM staining (surrogate marker for ROCK activation) could be observed in different cellular components but the staining pattern did not differentiate flarers.

Conclusion: Inflammatory histological features in synovial tissue at the time of surgery are associated with a higher risk for post-operative flare. The notion that RA at the time of arthroplastyrepresents "burnt-out disease" should be re-evaluated.

This study was supported by the Clinical Translational Science Center (CTSC) (UL1-TR000457-06)

Table 1: Cohort Characteristics	All (n=37)	Flare (n=23)	Non-Flare (n=14)	p-value
Age, mean (SD)	58 (12)	56 (12)	60 (11.5)	0.50
Female (%)	29 (78%)	19 (83%)	10 (71%)	0.44
Race: White	28 (76%)	16 (70%)	12 (86%)	0.22
ACPA+ and/or RF+	16 (43%)	13 (57%)	3 (21%)	0.12
Total Hip Arthroplasty	22 (59%)	15 (65%)	7 (50%)	0.49
Total Knee Arthroplasty	15 (41%)	8 (35%)	7 (50%)	
Meets 1987 or 2010 RA criteria	27 (73%)	17 (74%)	10 (71%)	1.00
Education: college/university	32 (86%)	19 (83%)	13 (93%)	0.63
BMI	28.9 (6.6)	29.1 (7.8)	28.6 (4.2)	0.89
Ex-smokers	17 (46%)	8 (35%)	9 (64%)	0.22
Baseline Biologics use	22 (59%)	16 (70%)	6 (43%)	0.17
DAS-28 CRP	4.0 (1.2)	4.2 (1.1)	3.6 (1.2)	0.32
CRP, mg/dL	2.0 (3.6)	2.7 (4.4)	0.9 (0.5)	0.55
Limited Pathology Score	7.0 (3.2)	7.6 (3.5)	5.9 (2.3)	0.11
Flare and Non-Flare patient and disease characteristics tested by Wilcoxon Two-Sample statistical test				

Table 2: Odds ratio estimates of histologic features seen in tissue sample & likelihood of flare				
	Odds ratio	Lower Limit (95%)	Upper Limit (95%)	P-value
Synovial lymphocytic infiltration	**4.2**	**1.2**	**14.9**	**0.03**
Synovial lining hyperplasia	1.3	0.5	3.7	0.59
Plasma cell infiltration	**6.3**	**1.7**	**infinity**	**<0.01**
Mast cells	3.0	0.6	14.7	0.18
Synovial mucoid change	0.8	0.4	1.5	0.46
Vascularity	1.6	0.5	5.5	0.47
Binucleate plasma cells	0.8	<0.1	infinity	1.00
Germinal centers	1.8	0.2	infinity	0.67
Sclerosis/fibrosis	0.9	0.4	2.2	0.78
Fibrin	4.8	1.0	23.9	0.06
Giant cells	0.3	0.1	1.8	0.21
Synovial giant cells	5.3	0.4	75.8	0.22

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Pretreatment Prediction of Response to Anti-Cytokine Therapy Using Serum Cytokine/Chemokine/Soluble Receptors in Individual Rheumatoid Arthritis Patient

KAZUYUKI YOSHIZAKI, Organic Fine Chemicals, The Institute of Scientific and Industrial Research, Osaka University, Suita, Japan
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Background/Purpose: In clinical practice in rheumatoid arthritis (RA), it has been noted that each anti-rheumatic therapy delivers a different outcome for individual RA patients and this makes it difficult to prescribe the most efficacious treatment for them. Being able to predict a patient's response/outcome before they are treated would allow doctors to prescribe the cytokine therapy that is the most efficacious for each RA patient. It is critical to identify molecular biomarkers that can predict patient response to anti-TNF-a or anti-IL-6 based therapies before patients are treated so that non-effective therapies are eliminated and more effective ones can be prescribed for patients at an earlier stage. We believe that identifying reliable predictive biomarkers will make it easier to follow EULAR's treat-to-target recommendation by allowing clinicians to know in advance if a treatment strategy will achieve the treatment goal (target) that has been pre-determined for each RA patient.

Methods: We enrolled 138 RA patients (naïve and non-naïve to anti-cytokine therapy) and measured 31 cytokines/chemokines/soluble receptors in their serum before administering tocilizumab or etanercept for 16 weeks. We selected parameters that correlated with patient's week 16 DAS28-CRP score by multiple linear analyses and identified biomarkers that could predict if patients would experience complete remission or non-remission by multiple logistic analyses.

Results: Multiple linear regression analysis based on patients' week 16 DAS28 revealed that sgp130, logIL-6, logIL-8, logEotaxin, logIP-10, logVEGF, logsTNFR-I and logsTNFR-II serum levels before therapy were potential biomarkers to predict biologic naïve patients' week 16 DAS28. Sgp130, logIP-10, logsTNFR-II and logIL-6 were predictive of complete remission or non-remission to tocilizumab therapy by multiple logistic analyses. A high sgp130 level was the most reliable predictor of patients' outcome. Additionally, we found logIL-9, logVEGF and logTNF-a to be less reliable at predicting the week 16 DAS28 score in naïve etanercept patients. Most of these biomarkers, especially sgp130, are involved in RA pathogenesis and IL-6 signal transduction, which further suggests that they are highly reliable.

Conclusion: We discovered reliable biomarkers that can predict clinical disease activity and outcome before RA patients undergo anti-IL-6 and anti TNF-a therapy. Most of the predictive biomarkers are involved in RA pathogenesis. Predicting treatment disease activity and outcome for anti-IL-6 reagent can assist doctors to more effectively pursue EULAR's treat-to-target approach by identifying in advance if IL-6 blockades will allow individual RA patients to reach their treatment target.

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Abstract Number: 512

Physical Function and Inflammatory Activity in Rheumatoid Arthritis Patients. Is Disease Duration Important?

Emmanuel Bertiller[1], Facundo Vergara[1], Maria de los Angeles Gallardo[1], Javier Rosa[2], Erika Catay[3], Marina Scolnik[1], Maria Victoria Garcia[4], Mirtha Sabelli[5] and Enrique R. Soriano[6], [1]Rheumatology Unit, Internal Medicine Service, Hospital Italiano de Buenos Aires, Instituto Universitario Hospital Italiano de Buenos Aires, and Fundacion PM Catoggio, Buenos Aires, Argentina, [2]Rheumatology, Hospital Italiano de Buenos Aires, Buenos Aires, Argentina, [3]Rheumatology Unit, Internal Medicine Service, Hospital Italiano de Buenos Aires, Instituto Universitario Hospital Italiano de Buenos Aires, and Fundacion PM Catoggio,, Buenos Aires, Argentina, [4]Internal Services, Rheumatology Unit, Internal Medicine Service, Hospital Italiano de Buenos Aires, Instituto Universitario Hospital Italiano de Buenos Aires, and Fundacion PM Catoggio, Buenos Aires, Argentina, [5]Cabrera 2964 Piso 6, Rheumatology Unit, Internal Medicine Service, Hospital Italiano de Buenos Aires, Instituto Universitario Hospital Italiano de Buenos Aires, and Fundacion PM Catoggio, Buenos Aires, Argentina, [6]Internal Medicine, Hospital Italiano de Buenos Aires, Buenos Aires, Argentina
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Background/Purpose: HAQ (Health Assessment Questionnaire) assesses functional disability in rheumatoid arthritis (RA) patients. Correlation between HAQ and disease activity might change according to the length of the disease. The purpose of our study was to assess this correlation in RA patients according to disease duration

Methods: RA patients ≥18 years (ACR/EULAR 2010 criteria) seen between March and May 2014 were included. At the inclusion visit: age, gender, disease duration, tender and swollen joint count (28 joints), disease activity by CDAI (Clinical Disease Activity Index) and physical function (HAQ-A, argentine Spanish validated version) were recorded. Patients were divided in two groups according to disease duration (≤ or >5 years). Variables were compared between both groups. Spearman correlation between CDAI and HAQ was calculated in each subgroup. Receiver Operating Characteristic (ROC) curve was used to assess the discriminating power of HAQ in patients in clinical remission (by CDAI), for the whole group and in the different age subgroups

Results: 104 patients, 91 females (88%), mean age of 60 years were included. Table 1 shows patients demographics and clinical features, by age group. While there were no significant differences in disease activity measurements, patients with longer disease duration had significantly worse HAQ-A. There was a significant correlation between HAQ-A and CDAI ($r=0.50$ $p<0.001$) for the total group. In patients with<5 years of disease duration (n=38) the correlation was $r=0.69$ ($p<0.0001$), whereas a lower correlation was found ($r= 0.48$ $p<0.001$) in patients with >5 years of disease duration (n=66). Patients on CDAI remission had significantly lower HAQ-A values than patients not in remission in both disease duration groups. However independently of remission status, patients with longer disease duration had significantly higher HAQ-A values than patients with short disease duration (table 2). The best cutoff value for HAQ–A to discriminate patients in remission (CDAI) using the ROC curve, in patients with shorter disease (≤5 years) was 0.125(AUC:0.85; 95% CI:0.74-0.96; Sensitivity (Se):76%; Specificity (Sp):92% and 0.875(AUC:0.81; 95% CI: 0.69-0.92 Se:59% Sp:90%) in patients with longer disease duration(>5 years)

Table 1

Characteristics	**Total group (N= 104)**	**Disease duration < 5 years (n=38)**	**Disease duration > 5 years (n=66)**	**P value**
Mean age (DS)	60 (14)	58.7 (16.7)	60.2 (11.7)	0.608
Females, n (%)	91 (88)	33 (87)	58 (88)	0.878
Mean years of Disease duration (SD)	10.1 (10.6)	1.3 (0.98)	15 (10.2)	<0.0001
Rheumatoid Factor positive, (n=96), n (%)	62 (65)	24/37 (65)	38/59 (64)	0.964
Anti-CCP positive, (n=87), n (%)	71 (82)	26/34 (76.5)	45/53 (85)	0.322
Mean CDAI (DS)	8,9 (10)	9.7 (12.2)	8.4 (8.4)	0.5320
Mean HAQ (DS)	0,64 (0,73)	0.37 (0.6)	0.8 (0.8)	0.0040
Mean pain VAS (DS)	29 (26,3)	27.3 (25.3)	29.7 (27.1)	0.6573
Mean VAS PGA (DS)	27 (27)	27.1 (27.2)	26.9 (27.3)	0.9644
Mean VAS PhGA (DS)	22 (20)	21.7 (20.6)	22.9 (20.2)	0.7862
On Methotrexate, n (%)	83 (80)	33 (87)	50 (76)	0.175
On Biologics, n(%)	33(32)	1 (2.6)	32 (49)	<0.0001
On Steroids, n(%)	25(24)	12 (32)	13 (20)	0.175

Table 2

	CDAI remision (n=33)	CDAI no remision (n=71)	P value
Mean HAQ-A, (SD), Patients < 5 years disease duration	(n=13) 0,03 (0,1)	(n= 25) 0,55 (0,7)	0,0105
Mean HAQ-A, (SD), Patients > 5 years disease duration	(n=20) 0,3 (0,5)	(n= 46) 1 (0,8)	0,0002
P value	0.0264	0.0078	

Conclusion: Correlation between disability measured by HAQ-A and disease activity measured by CDAI was better in patients with shorter disease duration.Patients with longer disease duration had higher functional disability independently of disease activity. Different HAQ-A values might need to be chosen as treatment targets for patients with different duration of disease

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Abstract Number: 513

Cumulative Association of Genetic Variants with Rheumatoid Joint Damage Progression in Mexican Americans and European Americans

Rector Arya[1], Inmaculada del Rincon[2], Jose Felix Restrepo[3], Vidya S Farook[4], Christopher P Jenkinson[5], Ravindranath Duggirala[6] and **Agustin Escalante**[7], [1]Pediatrics, University of Texas Health Science Center at San Antonio, San Antonio, TX, [2]Medicine, University of Texas Health Science Center at San Antonio, San Antonio, TX, [3]Rheumatology, University of Texas Health Science Center at San Antonio, San Antonio, TX, [4]Genetics, Texas Biomedical Research Institute, San Antonio, TX, [5]University of Texas Health Science Center at San Antonio, San Antonio, TX, [6]Regional Academic Health Center, Harlingen, TX, [7]Dept. of Medicine-Rheumatology, University of Texas Health Science Center at San Antonio, San Antonio, TX

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Background/Purpose:

Genealogical and genetic association studies have suggested that joint damage in rheumatoid arthritis (RA) may be heritable. We and others have found a number of specific genetic variants associated the extent of rheumatoid joint damage. Here, we estimate the cumulative association of single nucleotide polymorphisms (SNPs) associated with joint damage in a cohort of Mexican Americans (MA) and European Americans (EA) with RA.

Methods:

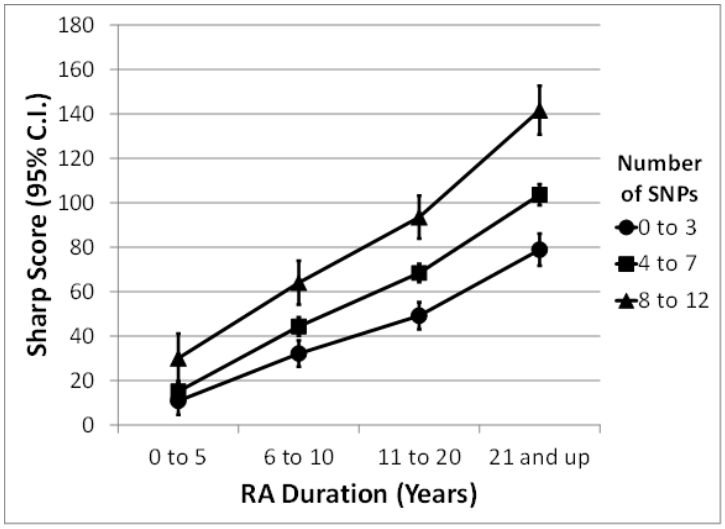
We recruited MA and EA patients with RA from rheumatology practices, and followed them over time. We used the Immunochip array to identify single nucleotide polymorphisms associated with the extent of radiographic joint damage on the latest available radiograph, quantified by inverse normal Sharp scores. Association analyses were conducted using PLINK, adjusting for age at RA onset, sex, RA duration and the first two ethnic principal components to adjust for population stratification. Association analyses were stratified by ethnic group. We excluded SNPs with call rates below 95% or minor allele frequencies below 1%, and patients with admixture or cryptic kinship relationships. We used the six SNPs with the strongest association with joint damage in each ethnic group as defined by a P-value $\leq 10\text{-}5$, to construct a cumulative scale by summing the number of damage-associated alleles in each patient. We examined the association of the cumulative SNP scale with joint damage progression over the duration of the study using scale x RA duration product terms in generalized estimating equations adjusted for age at RA onset, sex and ethnic group.

Results:

Genotypic and joint damage data were available for 675 MAs and 410 EAs. These patients had 3,186 Sharp scores available, covering a period of 4,149 patient-years (mean 3.8 years per patient, range 0 to 19). The Sharp score increased by 4.1 per year of disease (95% C.I. 3.98, 4.35), without difference between ethnic groups. The mean number of damage-associated SNPs in each patient was 4.4 (range 0 to 12), each additional SNP associated with an increase Sharp progression rate of 0.2 per year (95% CI 0.1, 0.3; $P \leq 0.001$). Among patients with 3 or less risk alleles, Sharp increased by 3.6 per year (3.4, 3.9); among patients with 4 to 6 alleles, Sharp increased by 4.1 per year (3.9, 4.3), and among patients with 7 or more alleles, Sharp increased by 4.9 per year (4.5, 5.3). The figure plots Sharp score over disease duration, according to the number of damage associated SNPs.

Conclusion:

Genetic variants associated with joint damage display a cumulative association, patients with a greater number of SNPs displaying greater joint damage. These findings may provide insights into the biology of joint damage in RA and if validated in other populations, could be of use for the early identification of RA patients at risk for joint damage.



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Abstract Number: 514

MRI Bone Oedema at Enrollment Predicts the Development of Rapid Radiographic Progression at 1 Year Toward Patients with Early-Stage Rheumatoid Arthritis: Results from Nagasaki University Early Arthritis Cohort

Yoshikazu Nakashima[1], Mami Tamai[2], Toru Michitsuji[3], Toshimasa Shimizu[2], Shoichi Fukui[4], Masataka Umeda[1], Ayako Nishino[1], Tomohiro Koga[3], Shin-ya Kawashiri[5], Naoki Iwamoto[2], Kunihiro Ichinose[2], Yasuko Hirai[4], Hideki Nakamura[4], Tomoki Origuchi[6] and Atsushi Kawakami[4], [1]Department of Immunology and Rheumatology, Nagasaki University, Nagasaki, Japan, [2]Department of Immunology and Rheumatology, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan, [3]Department of Rheumatology, Unit of Translational Medicine, Graduate School of Biomedical Sciences, Nagasaki University, Nagasaki, Japan, [4]Nagasaki University, Nagasaki, Japan, [5]Kyushu multicenter rheumatoid arthritis ultrasound prospective observational cohort study group, Nagasaki, Japan, [6]Department of Rehabilitation Sciences, Nagasaki University, Nagasaki, Japan

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Background/Purpose: To clarify whether MRI bone oedema predicts the development of rapid radiographic progression (RRP) in Nagasaki University Early Arthritis Cohort patients with early-stage rheumatoid arthritis (RA).

Methods: Early-stage RA patients (n=76) were enrolled and underwent Gd-enhanced MRI of both wrists and finger joints. Synovitis, bone oedema and bone erosion were evaluated using the Rheumatoid Arthritis Magnetic Resonance Imaging score (RAMRIS). RRP was defined as an annual increment > 3 at 1 year by plain radiographs and the Genant-modified Sharp score. A multivariate logistic regression analysis was performed to establish the risk factors for RRP, using patients' characteristics, serum variables, MRI findings, therapeutic responses and regime.

Results: The patients' median age was 54.5 yrs, and their median disease duration at enrollment was 3 months. RRP was found in 12 of the 76 patients at 1 year. A univariate analysis revealed that matrix metalloproteinase-3, RAMRIS bone oedema score and RAMRIS bone erosion score were associated with RRP. Multivariate logistic regression analyses demonstrated that the RAMRIS bone oedema score at enrollment (5-point increase, OR 2.18, 95%CI 1.32–3.59, p=0.002) is the only independent predictor of the development of RRP at 1 year. An ROC analysis identified the best cut-off value for RAMRIS bone oedema score as 5.

Conclusion: Our findings suggest that MRI bone oedema is closely associated with the development of RRP in early-stage RA patients. Physicians should carefully control the disease activity when MRI bone oedema is observed in early RA patients.

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Abstract Number: 515

Are Changes in Autoantibody Levels Reflecting Change in Prognosis of Rheumatoid Arthritis?

Manuel Unger[1], Farideh Alasti[1], Paul Studenic[1], Josef S. Smolen[2,3] and Daniel Aletaha[1], [1]Department of Internal Medicine 3, Division of Rheumatology, Medical University Vienna, Vienna, Austria, [2]2nd Department of Medicine, Hietzing Hospital, Vienna, Austria, [3]Department of Medicine 3, Division of Rheumatology, Medical University Vienna, Vienna, Austria

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Background/Purpose: The presence of rheumatoid factor (RF) and antibodies against citrullinated peptides (ACPA) is associated with progression of joint damage in patients with rheumatoid arthritis (RA). RF and ACPA levels may change during the course of therapy, but it not clear, if such changes in autoantibody levels also reflect a change in prognosis of RA. Here, we aimed to investigate whether changes of RF and ACPA reflect a true change in prognosis of RA.

Methods: A cohort of 450 RA outpatients was identified based on classifiable RA by the 2010 ACR/EULAR classification criteria, the presence of at least 2 available radiographs of hands and feet 3 years (30 to 42 months) apart, as well as availability of serological tests for RF and ACPA taken within 3 months prior or after each radiograph. Radiographic images were scored using the modified Sharp/van der Heijde (SvH) method.

Logistic regression analysis was used to examine the effect of RF and ACPA at baseline and after 3 years on significant damage progression (defined as increase of >=5 on the SvH score); results were adjusted for disease activity, expressed as Simplified Disease Activity Index (SDAI).

Results: At baseline, RF and ACPA were positive in 60.2% and 61.6%, respectively, of patients. Mean (SD) RF levels were 183.6 (517.2) IU/ml at baseline and 111.2 (247.2) IU/ml after 3 years; ACPA levels were 187.2 (232.6) IU/ml and 145.3 (169.5) IU/ml, respectively. Over the 3-year course, RF levels changed by a mean (SD) of 72.4 (409.7) IU/ml ($p<0.001$) and ACPA levels by 41,9 (120.8) IU/ml ($p<0.001$). SDAI levels at baseline and after 3 years were 13.8 (11.3) and 8.7 (8.8), respectively.

Univariate logistic regression showed a clear association of radiographic progression with higher levels of RF at baseline (p=0.039), but not

after 3 years (p=0.515). When adjusting these effects for time-integrated levels of disease activity, they essentially remained unchanged (p=0.052 and p=0.513, respectively; table), despite the expected highly significant association of disease activity and progression. Similarly to RF, the effect of ACPA on radiographic progression was significant at baseline before and after adjusting for disease activity, but in contrast to RF, remained so also after three years (table).

Conclusion: RF levels seem to comprise reversible and irreversible components. RF is associated with progression of RA, although removal of the reversible component also eliminated this association. This association was independent of disease activity during the observed period. ACPA is poorly reversible and the association with progression remained unchanged from baseline to year 3.

RF		Wald	Sig.	**ACPA**		Wald	Sig.
Crude	RF at X-ray (BL)	4.250	0.039	Crude	ACPA at X-ray (BL)	11.333	0.001
	RF at X-ray (Yr3)	0.424	0.515		ACPA at X-ray (Yr3)	12.979	0.000
Adjusted for disease activity	RF at X-ray (BL)	3.760	0.052	Adjusted for disease activity	ACPA at X-ray (BL)	10.604	0.001
	SDAI (AUC)	10.868	0.001		SDAI (AUC)	11.200	0.001
	RF at X-ray (Yr3)	0.427	0.513		ACPA at X-ray (Yr3)	12.010	0.001
	SDAI (AUC)	11.662	0.001		SDAI (AUC)	11.117	0.001

Disclosure: M. Unger, None; **F. Alasti**, None; **P. Studenic**, None; **J. S. Smolen**, None; **D. Aletaha**, None.

Abstract Number: 516

Immunological and Ultrasound Characteristics of Patients with Rheumatoid Arthritis in Clinical Remission – Can We Use These to Predict Outcomes?

Hanna Gul[1], Maria Jesus Isorna Porto[2], Elizabeth M.A. Hensor[3], Frederique Ponchel[4], Richard J. Wakefield[5] and Paul Emery[6], [1]Rheumatology, Leeds Institute of Rheumatology and Musculoskeletal Medicine, Leeds, United Kingdom, [2]Internal Medicine, Complejo Hospitalario Universitario A Coruña, A Coruña, Spain, [3]NIHR Leeds Musculoskeletal Biomedical Research Unit, Leeds Teaching Hospitals NHS Trust, Leeds, United Kingdom, [4]Musculoskeletal Disease, University of Leeds, Leeds, United Kingdom, [5]University of Leeds, Leeds, United Kingdom, [6]Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds, Leeds, United Kingdom

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Background/Purpose: Remission is the key treatment goal in rheumatoid arthritis (RA). Although clinical remission is increasingly achieved, many patients progress both structurally and functionally. We currently do not routinely assess immunological markers or perform ultrasound imaging to define remission.

We aimed to document the variability of clinical, patient-reported, imaging and immunological characteristics of RA patients in clinical remission and to correlate these with outcomes.

Methods: In a retrospective, observational study patients with an RA diagnosis (1987 or 2010 ACR/EULAR criteria) were selected from our early inflammatory arthritis database; the lowest observation of 3-variable DAS28CRP≤3.2 after diagnosis was chosen as the index visit. We defined flare as loss of index visit state [remission (<2.6) or low disease activity (LDA; 2.6-3.2)]. We collected clinical data, patient-reported outcomes and ultrasound Power Doppler (PD) and Grey Scale (GS) findings. Frequencies of naïve $CD4^+$T-cells, Inflammation related cells (IRC), regulatory T-cells (Treg) measured and analysed by advanced 8-colour flow-cytometry were compared with reference range values obtained from 120 healthy controls.

Results: We included 633 patients (69% female; mean age 57.6 years) with a minimum DAS28CRP≤3.2 (mean 1.87/SD 0.68). Of these, 513 were in DAS-defined clinical remission. The majority (75%) were taking conventional synthetic DMARD therapy only, 45% as monotherapy. Inflammatory markers, joint counts and levels of disability/function and life impairment were generally low, as expected.

Positive PD signal was present in 43% (141/326) of patients in remission; 76% (248/326) had evidence of GS changes >1 in ≥1 joint. In LDA, PD and GS changes were 64% (46/72) and 85% (61/72) respectively.

In remission, abnormal T-cell numbers were seen in 9% (4/46), 26% (12/46) and 50% (23/46) for naïve, IRC and Treg's respectively. For LDA, the figures were 40% (2/5), 60% (3/5) and 100% (5/5).

15% (85/559) of patients flared within 6 months of the index visit. Odds of flare were higher in females, those with higher DAS28, longer disease and/or remission duration and evidence of PD synovitis (Table 1).

Conclusion: Despite being in DAS-defined clinical remission, a substantial proportion of patients exhibit PD synovitis on ultrasound and have evidence of T-cell abnormalities. Current remission criteria are composite scores and do not measure inflammation directly. Validation of imaging techniques and identification of remission biomarkers could lead to a better understanding of what constitutes true remission, with relevance for disease stability. Further work is required to assess the predictive value of T-cell abnormalities for flare.

		% (n) flared within 6 months	Odds ratio (95% CI), *P* value
Age, per year		n/a	1.00 (0.99, 1.02), p=0.608
Sex	Male	8.8% (15/171)	reference
	Female	18.0% (70/388)	2.29 (1.27, 4.13), p=0.006
Disease duration, per month		n/a	0.97 (0.96, 0.99), p<0.001
Remission duration, per month		n/a	0.94 (0.91, 0.96), p<0.001
DMARD	None	12.7% (9/71)	reference
	Synthetic	16.6% (70/422)	1.37 (0.65, 2.89)
	Biologic	7.7% (5/65)	0.57 (0.18, 1.81)
DAS28 (<2.6)	Remission	12.9% (58/449)	reference
	LDAS (2.6-3.2)	24.5% (27/110)	2.19 (1.31, 3.67), p=0.003
PD	0	12.0% (22/183)	reference
	>0 in any joint	17.8% (31/174)	1.59 (0.88, 2.87), p=0.126
GS	0-1	10.1% (8/79)	reference
	>1 in any joint	16.2% (45/278)	1.71 (0.77, 3.81), p=0.185

Table 1: Associations between clinical and imaging findings at the index visit and the unadjusted odds of flare within 6 months.

Disclosure: H. Gul, None; **M. J. Isorna Porto**, None; **E. M. A. Hensor**, None; **F. Ponchel**, None; **R. J. Wakefield**, None; **P. Emery**, None.

Abstract Number: 517

Investigating Psychological Predictors of Biologic Treatment Response in Patients with Severe Active Rheumatoid Arthritis

Bethan England[1], Lis Cordingley[2], Darren Plant[3], Ann Morgan[4], Anthony Wilson[5], Kimme L. Hyrich[6], Anne Barton[7] and BRAGGSS Syndicate, [1]University of Manchester, Manchester, United Kingdom, [2]School of Community Based Medicine, University of Manchester, Manchester, United Kingdom, [3]arc Epidemiology Unit, Manchester, United Kingdom, [4]Leeds Institute of Rheumatic and Musculoskeletal Medicine and NIHR-Leeds Musculoskeletal Biomedical Research Unit, University of Leeds, Leeds, United Kingdom, [5]Genomic Medicine, The University of Sheffield, Sheffield, United Kingdom, [6]Arthritis Research UK Centre for Epidemiology, The University of Manchester, Manchester, United Kingdom, [7]NIHR Manchester Musculoskeletal Biomedical Research Unit, Manchester Academic Health Science Centre, Manchester, United Kingdom
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Background/Purpose:

Biologic therapy is now a cornerstone of RA management, but treatment response is variable, failing in up to 40% of patients. To direct appropriate treatments towards those patients most likely to benefit, reliable predictors of treatment response must be identified. Response is usually measured using DAS28, using clinical, biochemical, and patient-reported data. It has recently been shown that psychological factors influence individual DAS28 components, notably tender joint count and patient visual analogue scale (VAS) (*Arthritis Care Res 2014,* 66:861-868).

We hypothesised that psychological factors also influence change in DAS28 after biologic therapy, and that individual components of DAS28 would be affected disproportionately.

Methods:

Data from the BRAGGSS cohort was used: a multicentre, observational study of RA patients with severe active disease according to NICE criteria and undergoing biologic therapy.

Clinical and demographic data were collected from patients about to commence a biologic drug, then at three and six months. Illness beliefs, treatment beliefs, and mood were assessed at the same timepoints using validated measures: the Brief Illness Perceptions Questionnaire (B-IPQ), the Beliefs about Medications Questionnaire (BMQ), and the Hospital Anxiety and Depression Scale (HADS), respectively.

The relationships between psychological factors at baseline and 3- and 6-month change in DAS28 components were analysed using linear regression.

Results:

At baseline, 75.5% of 1847 patients were female, with a mean age of 58.4, DAS28 of 5.74 and HAQ of 1.74. 73.1% patients received anti-TNF drugs. There were significant associations ($p<0.05$) between nine of the 12 psychological factors with patient VAS, and six psychological factors with tender joint count. Three B-IPQ items and HADS depression were associated with CRP ($p<0.05$). At six months, no associations between baseline B-IPQ scores and changes in composite DAS28 were observed but BMQ and HADS anxiety scores showed a significant association ($p<0.05$). Interestingly, an association was found between baseline illness beliefs and changes in CRP, indicating that with lower baseline psychological scores inflammation was more reduced; for example, personal control ($\beta=-0.786$, $p=0.05$), treatment control ($\beta=-1.48$, $p=0.005$) and coherence ($\beta=-1.623$, $p=<0.001$). This was true at both three and six months follow-up.

Conclusion:

This study confirms earlier findings suggesting that baseline psychological factors affect baseline DAS28, especially patient-reported measures. Interestingly, psychological factors were significantly correlated with change in CRP at both 3 and 6 months, suggesting psychological state may be a driver of inflammation in RA and that the most appropriate approach for some patients may include addressing psychological wellbeing.

Overall, psychological factors were associated disproportionately with individual components of DAS28, but not with change in composite DAS28 score. This illustrates that reporting of individual DAS28 components may highlight individual patients' differing needs despite superficially similar composite scores.

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Abstract Number: 518

Antibody Responses to Citrullinated Porphyromonas Gingivalis Peptidylarginine Deiminase: Associations with Disease Risk Factors and Severity in Rheumatoid Arthritis

Priyanka Vashisht[1], Jeffrey Payne[2], Geoffrey M. Thiele[3], Harlan Sayles[4], Fang Yu[5], Michael J. Duryee[6], Carlos D. Hunter[6], Benjamin Wiese[1], Anne-Marie Quirke[7], Patrick Venables[7] and Ted R. Mikuls[8], [1]Internal Medicine - Rheumatology, University of Nebraska Medical Center, Omaha, NE, [2]College of Dentistry, University of Nebraska Medical Center, Lincoln, NE, [3]Research Services 151, Omaha VA Medical Center, Omaha, NE, [4]University of Nebraska Medical Center, Omaha, NE, [5]Public Health, University of Nebraska Medical Center, Omaha, NE, [6]Internal Medicine Division of Rheumatology, University of Nebraska Medical Center, Omaha, NE, [7]Kennedy Institute of Rheumatology, University of Oxford, Oxford, United Kingdom, [8]Medicine, University of Nebraska Medical Center, Omaha, NE

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Background/Purpose:

Rheumatoid arthritis (RA) is characterized by autoimmunity to citrullinated proteins. *Porphyromonas gingivalis* (*Pg*) has been proposed as an epidemiologic link between RA and periodontitis (PD) and expresses peptidylarginine deiminase (PPAD). In addition to catalyzing citrullination, PPAD itself can be citrullinated. Reports have demonstrated a heightened immune response to cit-PPAD that is specific to RA and that might serve as a potential mechanism for breaching immunologic tolerance. There have been no studies examining the association of anti-cit-PPAD antibody with RA risk factors or measures of disease severity. The objective of the present study was to examine the association of anti-cit-PPAD antibody with known RA risk factors and disease severity.

Methods:

Patients with RA (n=285) were studied in a post-hoc analysis of a case-control study that included standardized full-mouth examination to assess PD status. ACPA specific to CCP, cit-enolase, and cit-H2A (histone) and antibody to the immunodominant peptide of cit-PPAD (CPP3) were measured using ELISA. Anti-CPP3 was defined as concentrations ≥2.5 SD above the mean in 330 osteoarthritis controls, while anti-cit-enolase and anti-cit-H2A were defined as concentrations ≥2 SD above the control mean. Associations of RA risk factors (smoking, PD, and HLA-DRB1 shared epitope [SE]) with anti-CPP3 positivity were examined using the chi-square test; associations with disease activity and radiographic severity (hand films and oral panoramic films) were examined using Wilcoxon rank-sum tests. Associations of anti-CPP3 with ACPA concentrations were examined using Spearman rank correlations.

Results:

Anti-CPP3 positivity was observed in 100 RA cases (35%) with positivity nearly exclusive to anti-CCP antibody positive RA; only 3 of 43 anti-CCP negative RA cases were positive for anti-CPP3. Associations of anti-CPP3 antibody with patient factors and RA disease severity measures are shown in Table 1, with significant associations between anti-CPP3 antibody and HLA-DRB1 SE status, erosion score on hand films, alveolar bone loss, and RF. There were significant correlations of anti-CPP3 antibody concentrations with ACPA concentrations including anti-CCP (r 0.54; $p < 0.001$), anti-cit-enolase (r 0.63; $p < 0.001$), and anti-cH2A (r 0.41; $p < 0.001$).

Conclusion:

As previously observed with ACPA, antibody to citrullinated PPAD is increased in RA and is associated with worse oral and joint radiographic damage in RA in addition to HLA-DRB1 SE and higher titers of RF. Moreover, anti-CPP3 antibody is strongly correlated with circulating ACPA, supporting a potential pathogenic role for *Pg* expressed PPAD in RA disease pathogenesis and progression.

Table 1: Associations of anti-CPP3 antibody with patient factors and measures of disease activity / severity

Characteristic	Anti CPP3 positive (N=100)	Anti CPP3 negative (N=185)	p-value
Demographics			
Age , years(SD)	61 (11)	58 (12)	0.060
Male gender (%)	66	62	0.465
Race			0.890
Caucasian	77	78	
African-American	18	16	
Other	5	6	
RA Risk factors			
Smoking status			0.422
Never	35	39	
Format	42	44	
Current	23	17	
HLA-DRB1 SE status	86	70	**0.004**
PD(Eke criteria)			0.066
None/mild (%)	11	22	
Moderate (%)	54	47	
Severe (%)	35	31	
Disease activity/severity			
DAS-28-CRP	4.1 (1.4)	3.9 (1.4)	0.278
Hand / wrist radiographs			
Sharp score	21 (21)	18 (24)	0.067
Joint space narrowing	16 (16)	14 (17)	0.097
Erosion score	5 (8)	4 (9)	**0.009**
Oral panoramic radiography			
Mean alveolar bone loss	9.9 (8.5)	7.5 (6.5)	**0.020**
Sites>20% bone loss (mean %)	13.6 (22.2)	9.0 (17.3)	**0.035**
RF, IU/ml	321 (497)	221 (488)	**0.001**

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Abstract Number: 519

In Indigenous North Americans at High Risk for RA Complement C5 Level Is Associated with ACPA Positivity and C5a with Transition to Synovitis Even after Correcting for in Vitro Complement Activation Found with Prolonged Sample Storage

Ceri Richards[1], Carol Hitchon[2], Xiaobo Meng[3], Irene Smolik[4], David Robinson[4] and Hani S. El-Gabalawy[4], [1]Internal Medicine, University of Manitoba, Winnipeg, MB, Canada, [2]Department of Rheumatology, University of Manitoba, Winnipeg, MB, Canada, [3]University of Manitoba, Winnipeg, MB, Canada, [4]Arthritis Center, University of Manitoba, Winnipeg, MB, Canada

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Background/Purpose: Complement activation, a key component of innate immunity and activator of adaptive immunity has been linked to RA pathogenesis. Anti-citrullinated peptide antibody (ACPA) and rheumatoid factor (RF) may cause complement activation. We examined the association of the terminal complement component C5 and its breakdown product C5a with ACPA in a preclinical Indigenous North American (INA) population at high risk for severe RA.

Methods: C5, C5a, and ACPA were examined by enzyme-linked immunosorbent assay ELISA, RF by nephlometry, in 267 sera from INA with RA (n=43), first degree relatives (FDR) (ACPA positive n=16; ACPA negative n=64) and FDR who later developed synovitis (FDR-S; n=10). Samples were spun and stored at -20C. ACPA positive FDRs samples were matched to one or two ACPA negative FDR samples based on date of sample collection. Levels were correlated with sample storage duration to assess for *in vitro* complement activation. Associations between C5, C5a, ACPA, and subject group were determined using Chi squared, Mann Whitney U tests and Wilcoxon signed ranks tests for paired samples. Correlations were tested by Spearman correlation. Multivariable models controlling for time stored, ACPA, RF, visit sequence and sex were generated to determine the independent influence of ACPA on C5 and C5a serum levels. Data are reported as median (interquartile range (IQR)) and B with 95% confidence limits (CL).

Results: C5a levels increased with increasing time stored (rho=0.69; p<0.0001); C5 levels decreased (rho= -0.33;p=0.002); median (IQR) time stored 6.3(5.5) years). This presumed *in vitro* activation was most important for samples stored over 5 years. In FDR samples matched for time stored, C5a and C5 levels were similar between FDR persistently ACPA positive vs ACPA negative (C5a 17.8 (6.3) vs 17.0 (6.7) ng/ml; p=ns; C5 135.2 (81.7) vs 130.8 (87.5) µg/ml; p=ns). Comparing all samples from FDRs, C5 levels were higher in ACPA positive vs ACPA negative samples (135.2 (46.6) vs 71.2 (75) µg/ml; p<0.001). Using linear regression to determine predictors of C5 levels in 153 samples from 80 FDR, the presence of ACPA independently predicted higher C5 level (B (CL) 42 (17-71)) after correcting for duration of time sample stored, visit sequence, sex and RF (titre > 40 U/ml being positive). This association with ACPA was not seen for C5a. In FDR-S (n=10), ACPA titers increased prior to synovitis. FDR-S had higher C5a levels than FDR (238 (225) vs 133 (362) ng/ml; p<0.0001) an association that was significant after correcting for duration of storage, visit sequence, ACPA, RF and sex (B=95(16-174); p=0.02).

Conclusion: In vitro complement activation may occur with prolonged sample storage and must be considered in any analysis of stored samples. C5 level is independently predicted by ACPA in FDR in an INA prospective cohort suggesting decreased activity of the terminal complement cascade in the presence of ACPA. Those who transitioned to synovitis showed evidence of increased complement activity and prior to onset of synovitis showed expansion of ACPA. ACPA related complement cascade activation in imminent synovitis cannot be confirmed based on this data.

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Abstract Number: 520

Antibody to Porphyromonas Gingivalis in Pre-Clinical Rheumatoid Arthritis

Brian Coburn[1], Kevin D. Deane[2], Jess D. Edison[3], Geoffrey M. Thiele[1], Michael J. Duryee[4], Carlos D. Hunter[4], Jeffrey Payne[5], Fang Yu[6], Harlan Sayles[6], V. Michael Holers[2], Jill M. Norris[7], William R Gilliland[8], Jeremy Sokolove[9], WH Robinson[9] and Ted R. Mikuls[1], [1]Omaha VA Medical Center and University of Nebraska Medical Center, Omaha, NE, [2]Division of Rheumatology, University of Colorado School of Medicine, Aurora, CO, [3]Walter Reed National Military Medical Center, Bethesda, MD, [4]Internal Medicine Division of Rheumatology, University of Nebraska Medical Center, Omaha, NE, [5]College of Dentistry, University of Nebraska Medical Center, Lincoln, NE, [6]University of Nebraska Medical Center, Omaha, NE, [7]Epidemiology, University of Colorado Denver, Aurora, CO, [8]Rheumatology Service, Walter Reed National Military Medical Center, Bethesda, MD, [9]VA Palo Alto Healthcare System and Stanford University, Palo Alto, CA
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Background/Purpose:

Periodontitis (PD) has been implicated as an etiologic risk factor in rheumatoid arthritis (RA), an association that is speculated to be related to the oral pathogen *Porphyromonas gingivalis* (Pg). Among prokaryotes, Pg has the unique ability to citrullinate antigens, and anti-Pg immunity in established RA has been linked to the expression of anti-citrullinated protein antibody (ACPA). To date, no studies have investigated whether an association exists between anti-Pg antibody and pre-clinical ACPA expression or the future development of RA. The objective of this study was to evaluate the association between anti-Pg antibodies and development of RA as well as RF and anti-CCP2 antibodies in preclinical RA.

Methods:

A longitudinal case-control design was used to study 73 U.S. military personnel who eventually developed seropositive RA and 73 controls, matched on age at diagnosis, sex, race, number of samples available, duration of sample storage and enlistment region. Stored serum samples taken prior to RA diagnosis were tested for RF (isotypes and nephelometry), anti-CCP2 antibody, and antibody to Pg outer membrane antigen. Generalized estimating equations (GEE) were used to determine the association of anti-Pg antibody with RA case status. In secondary analysis, mixed effects linear regression was used to determine the association between anti-Pg antibody and autoantibody concentrations in preclinical RA. All antibody levels were log-transformed for analysis.

Results:

At the time of diagnosis, RA cases had a mean (±SD) age of 40 (10) years, 59% were men, and a majority were Caucasian (67%). Cases and controls had a mean of 3.5 (1.3) samples available for analysis (2.9 ± 1.3 pre-diagnosis among cases) with a median of 1.4 (IQR 0.8-2.7) years from the last sample prior to diagnosis to diagnosis. As shown in the Table, there was no association of pre-clinical anti-Pg antibody and RA case status (p=0.32). Among cases, there was no association between anti-Pg and anti-CCP2 antibody concentrations (p=0.63). However, anti-Pg antibody levels were significantly associated with RF measured by nephelometry (p=0.009). Although not reaching statistical significance, isotype analysis demonstrated the strongest association between anti-Pg antibody and RF IgM concentration.

Conclusion:

There was no evidence in this study to support an association of anti-Pg antibody with the risk of developing seropositive RA nor was anti-Pg antibody associated with circulating ACPA during the pre-clinical period. The association of anti-Pg antibody with RF warrants further investigation, particularly in light of recent work demonstrating that RF acts synergistically with ACPA in promoting inflammation in RA.

Table Associations of anti-*P. gingivalis* (Pg) antibody levels) with RF and anti-CCP2 in preclinical samples from RA cases

	Coefficient	p-value
RF nephelometry, IU/ml	0.34	0.009
RF isotypes, IU/ml		
IgM	0.33	0.13
IgA	0.18	0.29
IgG	-0.04	0.89
Anti-CCP2, U/ml	0.16	0.63

* Linear mixed effects models include fixed effects for differing slopes over time before and after 1250 days prior to diagnosis. The models included random intercepts to take into account individual variation in RF or anti-CCP levels; all antibody concentrations log-transformed

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Disclosure: B. Coburn, None; **K. D. Deane**, None; **J. D. Edison**, None; **G. M. Thiele**, None; **M. J. Duryee**, None; **C. D. Hunter**, None; **J. Payne**, None; **F. Yu**, None; **H. Sayles**, None; **V. M. Holers**, Shared patent with Stanford University for use of biomarkers to predict clinical phenotypes in rheumatoid arthritis., 7; **J. M. Norris**, None; **W. R. Gilliland**, None; **J. Sokolove**, Bristol-Myers Squibb, 2; **W. Robinson**, None; **T. R. Mikuls**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/antibody-to-porphyromonas-gingivalis-in-pre-clinical-rheumatoid-arthritis

Abstract Number: 521

Targeted Quantitative Analysis to Identify Citrullinated Peptides in the Synovial Fluid of Patients with Rheumatoid Arthritis

Min Jueng Kang[1], Ji Soo Kim[2], Eugene C. Yi[1] and Eun Young Lee[2], [1]Molecular Medicine and Biopharmaceutical Sciences, Department of Molecular Medicine and Biopharmaceutical Sciences, Graduate School of Convergence Science and Technology, and College of Medicine or College of Pharmacy, Seoul National University, Seoul, South Korea, [2]Division of Rheumatology, Department of Internal Medicine, Seoul National University College of Medicine, Seoul, South Korea

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SESSION INFORMATION

Session Date: Sunday, November 8, 2015

Session Title: Rheumatoid Arthritis - Human Etiology and Pathogenesis Poster I

Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose: The protein/peptide citrullination is a post-translational modification and the citrullinated peptide epitopes are recognized by anti-citrullinated protein/peptide antibody (ACPA), which is a major diagnostic or prognostic marker for rheumatoid arthritis (RA). Together with ACPA, specific citrullinated endogenous protein/peptide autoantigens in the major inflammatory lesions of RA (e.g, synovial fluid) may provide valuable information for the development of early diagnosis and therapeutic intervention.

Methods: Synovial fluids obtained from RA (n=4) and osteoarthritis (OA) (n=4) patients were pooled, separately. Peptides in each pooled synovial fluid were extracted using centrifugal filtration and solid phase extraction, and then analyzed by a Q-Exactive mass spectrometer. ScaffoldPTM (v.2.1.3) was used to validate peptide identification and citrullination site mapping. Elevated levels of RA-specific citrullinated peptides are validated by targeted MS/MS analysis with synovial fluids from RA (n=30), OA (n=15), and ankylosing spondylitis (AS) (n=5).

Results: We have identified total 1094 endogenous peptides originated from 120 proteins using LC-MS peptide profiling experiment with pooled RA and osteoarthritis (OA) synovial fluids, separately. Among them 121 peptides derived from 9 proteins (FGA, FGB, SAA1, HMGN2, PTMA, SRGN, COL5A3, PRG4, and APOBR) were found to be citrullinated. The majority of citrullinated peptides were detected only in RA synovial fluid where some identified FGA citrullinated peptides are previously known citrullination sites of FGA, which validate our experiment. We also identified an RA unique citullinated peptide, which has not been reported in the past. To verify RA specific citrullinated peptides, targeted MS/MS analysis of selected citullinated peptides with synovial fluids from RA (n=30), OA (n=15), and ankylosing spondylitis (n=5) patients is being conducted.

Conclusion: We have identified unique citrullinated peptides present in RA synovial fluid. To validate representing citrullinated peptides in RA, we have undertaken targeted MS/MS analysis of selected citrullinated peptides using RA, OA, and AS synovial fluids. The eventual results from the independent cohort studies will confirm unique citullinated peptide markers present in RA synovial fluid, which may provide their diagnostic or therapeutic values for RA.

Disclosure: M. J. Kang, None; **J. S. Kim**, None; **E. C. Yi**, None; **E. Y. Lee**, None.

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Abstract Number: 522

The Expression of mRNA for Peptidylarginine Deiminase Type 2 and Type 4 in CD34+ Cells of the Bone Marrow in Rheumatoid Arthritis

Tatsuo Nagai[1], Tetsuya Tomita[2], Hideki Yoshikawa[2] and Shunsei Hirohata[1], [1]Rheumatology and Infectious Diseases, Kitasato University School of Medicine, Kanagawa, Japan, [2]Department of Orthopedics, Osaka University Graduate School of Medicine, Suita Osaka, Japan

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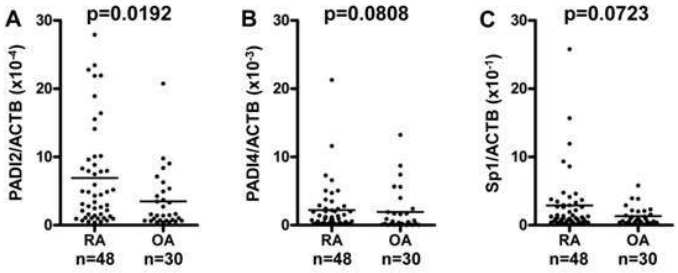
Background/Purpose: We previously showed that bone marrow (BM) CD34+ cells from rheumatoid arthritis (RA) patients have abnormal capacities to respond to tumor necrosis factor alpha and to differentiate into fibroblast-like cells producing MMP-1, resembling type B synoviocyte. In addition, we have recently demonstrated that the mRNA expression of nuclear factor kappa B1, Krüppel-like factor 5 and FK506-binding protein 5 in BM CD34+ cells is significantly higher in RA patients than osteoarthritis (OA) patients. Antibodies directed to citrullinated proteins are extremely specific for RA. Citrullination is catalyzed by a group of peptidylarginine deiminase (PAD) enzymes. PAD family members are categorized into five isoforms (PAD1, 2, 3, 4 and 6). Several studies have disclosed that PAD2 and PAD4 are expressed in rheumatoid synovial tissue or in mononuclear cells of rheumatoid synovial fluid. Moreover, Sp1 has been shown to regulate transcription of these PADI genes. The current study therefore examined the mRNA expression of PADI2, PADI4 and Sp1 transcription factor in BM CD34+ cells from RA patients.

Methods: BM samples were obtained from 48 patients with RA (6 males and 42 females: mean age 58.8 years) and 30 patients with OA (3 males and 27 females: mean age 71.1 years), who gave informed consent, during joint operations via aspiration from iliac crest. CD34+ cells were

purified from the BM mononuclear cells by positive selection with magnetic beads. The expression of mRNA for PADI2, PADI4 and Sp1 was examined by quantitative reverse transcription PCR and is shown as the ratio of the copy numbers to those of b-actin mRNA.

Results: The expression of mRNA for PADI2 was significantly higher in RA BM CD34+ cells than OA BM CD34+ cells (Fig. A). Compared to OA BM CD34+ cells, PADI4 and Sp1 gene expression levels of RA BM CD34+ cells manifested no statistically significant increase (Fig. B and C). The mRNA expression levels of PADI2, PADI4 and Sp1 were not correlated with serum C-reactive protein or with the administration of methotrexate or oral steroid. PADI2 gene expression was significantly correlated with PADI4 ($p<0.0001$, $r=0.7143$) and Sp1 ($p<0.0001$, $r=0.7954$) gene expression in RA BM CD34+ cells.

Conclusion: These results indicate that the enhanced expression of PADI2 mRNA in BM CD34+ cells plays a pivotal role in the pathogenesis of RA, and might be closely associated with mRNA expression of PADI4 or Sp1.



Disclosure: T. Nagai, None; **T. Tomita**, None; **H. Yoshikawa**, None; **S. Hirohata**, None.

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Abstract Number: 523

Elevated Antibody Response to Porphyromonas Gingivalis Detected in Sera Years before the Clinical Onset of Rheumatoid Arthritis

Nastya Kharlamova[1], Ulf Bergström[2], Natalia Sherina[3], Lennart T.H. Jacobsson[2,4], Lennart Truedsson[5], Karin Lundberg[1] and **Carl Turesson**[2], [1]Rheumatology Unit, Department of Medicine, Solna, Karolinska Institute, Stockholm, Sweden, [2]Rheumatology, Department of Clinical Sciences, Malmö, Lund University, Malmö, Sweden, [3]Rheumatology Unit, Department of Medicine, Solna, Karolinska Institutet, Stockholm, Sweden, [4]Department of Rheumatology and Inflammation Research, Sahlgrenska Academy at Gothenburg University, Gothenburg, Sweden, [5]Section of Microbiology, Immunology and Glycobiology, Department of Laboratory Medicine, Lund University, Lund, Sweden
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Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose: Chronic periodontitis has been associated with rheumatoid arthritis (RA), and *Porphyromonas gingivalis* has been proposed as the mechanistic link, due to its unique property among pathogens to express a citrullinating enzyme (denoted *P.* PAD). We have recently demonstrated elevated anti-*P. gingivalis* antibody levels in patients with anti-citrullinated protein antibody (ACPA) positive RA compared to controls. To investigate this aetiological hypothesis further, we have analysed the anti-*P. gingivalis* antibody response in pre-RA individuals in relation to the development of the ACPA response.

Methods: Incident cases of RA were identified among participants (n=30447) in a community based health survey linked to local and national registers, followed by a structured review of the medical records. One control from the health survey, matched for age, sex and year of inclusion, was selected for each validated case. Anti-CCP2 antibody status was determined by the standard commercial ELISA method (Euro-Diagnostica AB). Anti-*P. gingivalis* IgG were detected by in-house ELISAs, using a citrullinated peptide derived from *P.* PAD (CPP3) and the arginine-containing equivalent (RPP3), or purified arginine gingipainB (RgpB) protein, as coating antigens. Cut off values for these antibodies were set at the 98th percentile among the controls. Analyses were stratified by time from inclusion in the health survey to RA diagnosis (1-5 and 6-13 years, respectively).

Results:

Serum was available from 166 cases (78% women), diagnosed with RA at a median of 5 years (IQR 3-8; range 1-13) after inclusion in the health survey. Anti-CPP3 and anti-RPP3 antibodies were detected in 6.0% and 5.4% of the pre-RA cases, respectively, whereas anti-CCP2 was positive in 22.3% of pre-RA cases. Positive anti-CPP3 antibodies were more frequent among anti-CCP2 antibody positive pre-RA cases (13.5 % *vs.* 3.9 %; p=0.04), whereas there was no such difference for anti-RPP3 IgG. Anti-CCP3 and anti-RPP3 antibodies occurred 1-5 years before RA diagnosis (7.2 % for both antibodies) as well as among those investigated 6-13 years before RA diagnosis (4.8% and 3.6%, respectively). Among anti-CPP3 positive pre-RA cases, levels of anti-CPP3 IgG were higher in those sampled ≤5 years before diagnosis (median 22.6 AU/ml (interquartile range (IQR) 17.0-29.2) *vs.* median 13.7 AU/ml (IQR 12.7-14.7; p=0.001), whereas there was no such difference for anti-RPP3 IgG (median 5.7 AU/ml; IQR 3.5-8.7 *vs.* median 4.2 AU/ml; IQR 3.9-14.6; p=0.71). Anti-RgpB IgG levels were not significantly different in pre-RA cases compared to controls (median 110.4 AU/ml;IQR 53.0-233.5 *vs.* median 94.4 AU/ml IQR 45.5-194.1; p=0.15).

Conclusion: Antibodies to *P.gingivalis* antigens occur years before RA diagnosis in a subset of pre-RA individuals. Presence of anti-CPP3 antibodies is associated with anti-CCP2 antibody positivity in the pre-clinical phase of RA, suggesting that the antibody response to citrullinated *P.*PAD in the context of chronic periodontitis could be one mechanism through which the early RA-specific immune phenotype can develop.

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Abstract Number: 524

Plasma Concentrations of Antibodies to Porphyromonas Gingivalis Are Increased before Onset of Symptom of Rheumatoid Arthritis

Linda Johansson[1], Natalia Sherina[2], Nastya Kharlamova[3], Barbro Larsson[2], Lena Israelsson[4], **Solbritt Rantapaa-Dahlqvist**[5] and Karin Lundberg[3], [1]1Public Health and Clinical Medicine/Rheumatology, Umeå University, Umeå, Sweden, [2]2Rheumatology Unit, Department of Medicine, Karolinska Institute, Stockholm, Sweden, [3]Rheumatology Unit, Department of Medicine, Solna, Karolinska Institute, Stockholm, Sweden, [4]Rheumatology Unit, Department of Medicine, Karolinska Institutet, Stockholm, Sweden, [5]Department of Public Health and Clinical Medicine/ Rheumatology, Umeå University, Umeå, Sweden

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Background/Purpose: Chronic periodontitis has been considered as an important determinant in both occurrence and severity of rheumatoid arthritis (RA). It has been hypothesized that citrullination by the periodontal pathogen *Porphyromonas gingivalis* may play an important role in the development of RA-specific autoimmunity, by breaking immune tolerance to citrullinated proteins and trigger the production of anti-citrullinated protein antibodies (ACPA). In support of this hypothesis, we have recently demonstrated elevated anti-*P. gingivalis* antibody levels in RA compared to controls, specifically in ACPA+ RA. The aim of the present study was to further investigate the role of *P. gingivalis* in RA aetiology, by analysing the anti-*P. gingivalis* antibody response in plasma samples collected before the onset of RA.

Methods: A case-control study was preformed within the Medical Biobank of Northern Sweden. The study included 251 individuals who donated in total 422 plasma samples predating the onset of clinical symptoms of RA, and 198 population-based controls from the same cohort. The median (IQR) predating time until onset of RA was 5.2 (6.2) years. For 192 individuals diagnosed with RA, plasma was available from the time point of RA diagnosis, and 152 of these patients had also donated plasma before the onset of symptoms. All samples were analysed by in-house ELISAs for the presence of antibodies to virulence factor arginine gingipainB (RgpB) purified from *P. gingivalis*, and a citrullinated peptide (denoted CPP3) derived from the *P. gingivalis* PAD enzyme. Based on ROC curve analysis on RA patients and controls, a cut-off for anti-CPP3 IgG positivity was set at the 96th percentile. The anti-*P. gingivalis* antibody data was evaluated in relation to the development of the classical ACPA response.

Results: The concentration of anti-RgpB IgG levels was significantly increased in RA patients (mean±SEM; 114.4±16.9 AU/ml), and importantly also in the pre-symptomatic individuals (152.7±14.8 AU/ml), when compared to controls (82.2±12.1 AU/ml, $p < 0.001$ for both). Antibodies against CPP3 were detected in 8% of the RA population, and in 5% of pre-symptomatic individuals, with elevated levels in both RA patients (9.29±1.81 AU/ml) and in pre-symptomatic individuals (4.33±0.59 AU/ml), compared to controls (2.36±0.58 AU/ml, $p < 0.001$ for both). The anti-CPP3 antibody response followed the classical ACPA response, with increasing antibody levels over time, whilst the anti-RgpB IgG response was stable in pre-symptomatic individuals during the pre-dating time and (if anything) showed a trend towards lower levels after RA diagnosis, potentially as a result of anti-inflammatory treatment.

Conclusion: Antibody levels against *P. gingivalis* were significantly increased in RA patients compared to controls, and more importantly, these

antibodies were detected years before onset of symptoms of RA, supporting an aetiological role for *P. gingivalis* in the development of autoimmunity and autoimmune disease in a subset of RA patients.

Disclosure: L. Johansson, None; **N. Sherina**, None; **N. Kharlamova**, None; **B. Larsson**, None; **L. Israelsson**, None; **S. Rantapaa-Dahlqvist**, None; **K. Lundberg**, None.

Abstract Number: 525

Association Between Fine Specificity of Anti-Citrullinated Peptide Antibodies and High Resolution Computed Tomography Parenchymal Lung Changes in Patients with Early RA

Vijay Joshua[1], Katerina Chatzidionysiou[1], Gudrun Reynisdottir[1], Aase Haj Hensvold[1], Linda Mathsson-Alm[2], Monika Hansson[3], Leonor Nogueira[4], Anders Eklund[5], Guy Serre[4], Johan Grunewald[5] and Anca I Catrina[6], [1]Rheumatology Unit, Department of Medicine, Solna, Karolinska Institute, Stockholm, Sweden, Stockholm, Sweden, [2]ThermoFisher Scientific, Uppsala, Sweden, Uppsala, Sweden, [3]Rheumatology Unit, Department of Medicine, Karolinska Institutet, Stockholm, Sweden, [4]Unité Différenciation Épidermique et Autoimmunité Rhumatoïde, Unité Mixte de Recherche, INSERM,Toulouse, France, Toulouse, France, [5]Division of Respiratory Medicine, Department of Medicine, Solna, Karolinska Institutet, Stockholm, Sweden, Stockholm, Sweden, [6]Unit of Rheumatology, Department of Medicine Solna, Karolinska University Hospital, Karolinska Institutet, Stockholm, Sweden

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Background/Purpose:

We previously showed that anti-CCP2 antibodies are associated with parenchymal lung abnormalities in patients with early RA[1]. This study aims to examine the association between ACPA fine specificities and parenchymal lung changes in an early RA cohort.

Methods:

Patients with newly diagnosed RA according to the ACR 1987 classification criteria and naïve to treatment with oral glucocorticoids or DMARDs were eligible for the study. High-resolution computed tomography (HRCT) was performed in order to assess the presence of parenchymal lung changes (ground glass changes, nodules, infiltrates or fibrosis). ImmunoCAP was used to detect RF IgA, RF IgM, anti-CCP2 IgA, anti-CCP2 IgG and ISAC microarray system[2]was used to detect antibodies against 10 citrullinated (Cit) peptidic antigens: CCP-1 (Filaggrin), CEP-1 (α-enolase), Vim 2-17, Vim 60-75 (Vimentin), Fib β 36-52, Fib α 573, Fib α 591, Fib α 36-50, Fib β 60-74, Fib α 621-635 (Fibrinogen).

Logistic regression analysis was performed to examine possible associations between parenchymal lung changes at the time of RA diagnosis and autoantibodies, adjusted for age and sex. Due to the potential risk for effect modification of smoking and the strong association between smoking and Cit peptides, we stratified the cohort according to ever vs. never smokers.

Results:

A total of 106 patients with available HRCT were included in the analysis. The mean (SD) age was 57 (14) years. The majority were females (69%); 73% were ever smokers while 29% were current smokers; 70% were positive for RF and 69% were positive for anti-CCP2. Parenchymal lung changes were found in 58 patients (54.7%). Higher age, RF IgA, CCP2 IgG, ever smoking and pack-years above 24 were significant predictors of parenchymal lung changes (table 1). Some ACPA fine specificities, especially against Cit Fib and Cit Vim peptides, were associated to parenchymal lung changes in ever smokers (table 2). The risk of having parenchymal changes increased parallel to the increase of the number of ACPA specificities (table 2). Having five or more ACPA specificities at the time of diagnosis increased the risk of having lung abnormalities in ever smokers by 6.6 times (OR=5.8, 95% CI=1.6-27.3).

Conclusion:

The presence of RF IgA, anti-CCP2 IgG, antibodies to Cit Fib and Cit Vim peptides were strongly associated to parenchymal lung changes in ever smokers with early RA. The more ACPA fine specificities, the higher the risk of having parenchymal lung changes at the time of RA diagnosis.

1. Reynisdottir G, et al., Arthritis Rheumatol 2014
2. Hansson M, et al., Arthritis Res Ther 2012

Disclosure: V. Joshua, None; **K. Chatzidionysiou**, None; **G. Reynisdottir**, None; **A. H. Hensvold**, None; **L. Mathsson-Alm**, None; **M. Hansson**, None; **L. Nogueira**, None; **A. Eklund**, None; **G. Serre**, None; **J. Grunewald**, None; **A. I. Catrina**, None.

Variable	OR (95% CI)	P-value
Age	**1.0 (1.0-1.1)**	**0.006**
Age (≥65 vs. < 65)	**2.5 (1.1-5.9)**	**0.03**
Sex (Male vs. Female)	1.7 (0.7-4.0)	0.22
RF		
Any	2.0 (0.8-4.5)	0.12
IgM	2.0 (0.8-4.5)	0.12
IgA	**2.7 (1.2-5.9)**	**0.02**
Anti-CCP2		
Any	**2.6 (1.1-6.0)**	**0.03**
IgG	**2.3 (1.0-5.4)**	**0.05**
IgA	1.5 (0.7-3.6)	0.32
Bone erosions	1.1 (0.4-2.8)	0.84
Smoking (% ever)	**2.6 (1.1-6.2)**	**0.04**
Smoking (% current)	1.8 (0.7-4.2)	0.20
Pack-years (median (IQR))	**1.1 (1.0-1.1)**	**0.001**
Pack-years 1-11 vs. 0	1.3 (0.4-3.8)	0.69
	2.2 (0.8-6.6)	0.15
12-23 vs. 0	**6.9 (2.0-23.5)**	**0.002**
≥ 24 vs, 0		

Table 1. Predictors of parenchymal lung abnormalities at the time of RA diagnosis in patients with early RA (symptoms duration < 1 year).

	Non-smokers [N=29]		Ever smokers [N=77]	
	OR (95% CI)	P-value	OR (95% CI)	P-value
Any CCP2	7.4 (0.6-86.6)	0.11	5.0 (1.5-16.2)	0.007
CCP2 IgG	7.4 (0.6-86.6)	0.11	4.2 (1.3-13.2)	0.01
CCP2 IgA	1.1 (0.1-9.7)	0.91	1.6 (0.6-4.5)	0.38
Any RF	2.6 (0.4-17.7)	0.32	2.6 (0.9-7.6)	0.09
RF IgA	1.4 (0.2-7.6)	0.73	4.7 (1.6-13.7)	0.004
RF IgM	2.6 (0.4-17.7)	0.32	2.6 (0.9-7.6)	0.09
Cit Fibrinogen peptides	2.3 (0.4-13.1)		3.0 (1.0-8.8)	
Fib β 36-	1.1 (0.2-5.9)		2.7 (0.9-	

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http://acrabstracts.org/abstract/association-between-fine-specificity-of-anti-citrullinated-peptide-antibodies-and-high-resolution-computed-tomography-parenchymal-lung-changes-in-patients-with-early-ra

Abstract Number: 526

Citrullinated Fibrinogen Promotes Bone Marrow Mesenchymal Stem Cells to Assume a Proinflammatory Phenotype

Yue Sun, Wei Deng, Weiwei Chen, Genhong Yao, Xuebing Feng and **Lingyun Sun**, Department of Rheumatology and Immunology, The Affiliated Drum Tower Hospital of Nanjing University Medical School, Nanjing, China

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Background/Purpose: Mesenchymal stem cells (MSC) are not only immune-inhibitory cells, and may act as pro-inflammatory cells due to lack of a proper “licensing”. The role of MSC in autoimmune settings of rheumatoid arthritis (RA) has remained to be elucidated. Citrullinated fibrinogen (cfb) has been considered as one of the important autoantigens in RA and contributes to perpetuate the disease. Our study aimed to analyze the responses of bone marrow derived MSC (BMSC) to cfb.

Methods: BMSC were isolated from RA and osteoarthritis (OA) patients and exposed to cfb or native fibrinogen (fb). Proinflammatory cytokines stimulated by cfb were determined by quantitative PCR and ELISA. To evaluate the role of the toll like receptor 4 (TLR4)-NFκB pathway in the induction of cytokines by cfb, parallel experiments were performed using inhibitors of TLR4 or NFκB pathway. To investigate whether BMSC retain their immunosuppressive properties after exposure to cfb, we detected the effects of cfb primed BMSC on proliferation of peripheral blood mononuclear cells (PBMC).

Results: The autoantigen cfb increased the gene expression and protein production of IL-6, IL-8 and CCL2 in BMSC from both RA and OA patients. However, the production of IL-1β and TNFα were unaffected by cfb. Compared with fb, cfb induced significantly higher expression of the pro-inflammatory cytokines (IL-6, IL-8 and CCL2) in these cells. Blocking experiments showed the participation of TLR4-NFκB pathway in the induction of these cytokines. The autoantigen cfb also compromised the ability of BMSC to inhibit PBMC proliferation, as well as, impaired the potency of BMSC to produce the key immunomodulatory molecule indoleamine dioxygenase (IDO).

Conclusion: Our results suggest that cfb promotes pro-inflammatory responses in BMSC and negatively affects their immunomodulatory functions. Citrullinated fibrinogen may act as a dangerous “licensing” for BMSC and thereby contributing to the propagation of inflammation in RA.

Disclosure: Y. Sun, None; **W. Deng**, None; **W. Chen**, None; **G. Yao**, None; **X. Feng**, None; **L. Sun**, None.

View Abstract and Citation Information Online -
http://acrabstracts.org/abstract/citrullinated-fibrinogen-promotes-bone-marrow-mesenchymal-stem-cells-to-assume-a-proinflammatory-phenotype

Abstract Number: 527

52 cit	3.9)	0.35	7.6)	0.05
Fib α 573 cit	2.3 (0.4-13.0)	0.87	3.9 (1.3-12.5)	0.07
Fib α 612-635 cit	2.0 (0.2-14.3)	0.35 0.47	2.2 (0.8-6.4)	0.02 0.16
Fib β 60-74 cit	4.6 (0.7-28.3)	0.10	2.2 (0.8-6.5)	0.14
Fib α 36-50 cit	2.7 (0.4-15.8)	0.29 0.67	1.2 (0.4-3.6)	0.80 0.60
Fib α 591 cit	0.6 (0.04-8.4)		1.4 (0.4-4.7)	
Cit Vimentin Peptides	3.5 (0.5-24.9)	0.22	2.9 (1.0-8.5)	0.06
Vim 2-17 cit	1.2 (0.2-6.5)	0.80	2.9 (1.0-8.6)	0.05
Vim 60-75 cit	4.9 (0.7-32.7)	0.10	2.2 (0.8-6.3)	0.15
CEP-1 (α-enolase)	0.4 (0.06-2.4)	0.30	2.0 (0.7-6.0)	0.20
N. ACPAs 0 (ref)	2.6 (1.9-35.9)	0.47	5.2 (1.3-21.2)	0.02
1-4	3.6 (0.3-44.7)	0.32	6.6 (1.6-27.3)	0.009
> 4				

Table 2. Association between rheumatoid factor (RF), anti-CCP and ACPA fine specificities according to smoking status (never smokers and ever smokers), as assessed by logistic regression adjusted for age and sex. (All ACPA fine specificities were analyzed but not shown in the table).

Characterisation of the Antibody Response to a Citrullinated Peptide – Derived from the Porphyromonas Gingivalis Peptidyl Arginine Deiminase Enzyme – in Patients with Rheumatoid Arthritis

Nastya Kharlamova[1], Xia Jiang[2], Natalia Sherina[3], Monika Hansson[4], K. Lundberg[5] and Lars Alfredsson[6], [1]Rheumatology Unit, Department of Medicine, Solna, Karolinska Institute, Stockholm, Sweden, [2]Rheumatology, karolinska institutet, skärholmen, Sweden, [3]Rheumatology, karolinska institutet, Stockholm, Sweden, [4]Rheumatology Unit, Department of Medicine, Karolinska Institutet, Stockholm, Sweden, [5]Karolinska Institute, Stockholm, Sweden, [6]The Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden

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Background/Purpose: It has been hypothesized that *Porphyromonas gingivalis* - the only known pathogen to express a citrullinating enzyme (called *P.*PAD) - is etiologically linked to the development of anti-citrullinated protein antibody (ACPA) positive RA, via citrullination of its own as well as human proteins, generating autoantigens and the subsequent production of ACPA. In support of this hypothesis, it was recently shown that *P.*PAD can auto-citrullinate and that a subset of RA patients has elevated antibody levels towards citrullinated *P.*PAD. In the present study, we have characterized this antibody response in more details.

Methods: The antibody response to a citrullinated *P.*PAD-derived peptide denoted CPP3 (and the arginine-containing equivalent RPP3) was analysed in the Swedish population-based case-control cohort EIRA (n=2,859 RA cases; n=373 controls) using the ImmunoCAP ISAC microarray system (PhaDia Multiplexing Diagnostics). ACPA status, smoking habits, genetics, CRP levels and DAS28 data were retrieved from the EIRA database. Unconditional logistic regression analysis was used to calculate odds ratios (OR) with 95% confidence intervals (CI) for the association of different risk factors with different RA subsets.

Results:

With 98% specificity, using the EIRA control population to set cut-off, 10.4% of EIRA RA cases had antibodies to CPP3, and interestingly, 5.4% had antibodies to RPP3. In the same cohort, 65% were anti-CCP2 antibody positive. The majority of anti-CPP3 antibody positive patients were confined to the CCP2 positive population, and anti-CPP3 antibody levels correlated strongly with other ACPA fine-specificity levels (r = 0,99; p < 0,0001). When comparing CCP2+ / CPP3+ patients with CCP2+ / CPP3- patients, a significantly stronger association was found between smoking and the double positive subset (OR=2.88; 95% CI: 2.11-3.92) than between smoking and the CCP2 single positive subset (OR=1.75; 95% CI: 1.54-1.99) (p<0.0012), while we could not detect any significant difference with respect to the association of *HLA-DRB1* shared epitope and the two different subsets of RA (OR=7.27; 95% CI: 4.82-10.97 and OR=5.52; 95% CI: 4.58-6.64, for CCP2+ / CPP3+ and CCP2+ / CPP3- RA, respectively, p=0.32). As with the ACPA response in general, there was only a weak correlation between anti-CPP3 antibody positivity and baseline DAS28 and CRP levels.

Conclusion:

Conclusions: A small subset of RA (10.4%), mainly anti-CCP2+ RA, had an antibody response to CPP3. This antibody response associated with the ACPA response and showed similar characteristics as other ACPA fine-specificities, in relation to RA risk factors and disease activity scores. However, a subset of RA patients also had an antibody response to the arginine-containing RPP3 peptide (5.4%), which is not the case for most arginine-containing epitopes. Contrary to the other ACPA targets, CPP3 is a bacterial peptide sequence, and in a subset of patients, this antibody response could represent an aetiological link between *P. gingivalis* infection and ACPA+ RA development.

Disclosure: N. Kharlamova, None; **X. Jiang**, None; **N. Sherina**, None; **M. Hansson**, None; **K. Lundberg**, None; **L. Alfredsson**, None.

Abstract Number: 528

RA33 Challenges the Paradigm of Autoantigen Selection in Rheumatoid Arthritis

Maximilian F. Konig[1], Jon Giles[2], Peter A. Nigrovic[3] and Felipe Andrade[1], [1]Division of Rheumatology, The Johns Hopkins University School of Medicine, Baltimore, MD, [2]Rheumatology, Columbia University Medical Center, NY, NY, [3]Department of Medicine, Division of Rheumatology, Immunology and Allergy, Brigham and Women's Hospital, Harvard Medical School, Boston, MA

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SESSION INFORMATION

Session Date: Sunday, November 8, 2015

Session Title: Rheumatoid Arthritis - Human Etiology and Pathogenesis Poster I

Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose:

Antibodies against citrullinated proteins (ACPAs) are the autoimmune hallmark of rheumatoid arthritis (RA), and can precede the onset of symptomatic disease by years. By introducing neo-epitopes into self-proteins, posttranslational protein citrullination is thought to break immune tolerance and drive autoimmunity in RA. While many RA autoantigens are recognized in a citrulline-dependent context, some antigens are targeted as native (unmodified) proteins in RA, including Fc-gamma (targeted by rheumatoid factor), hnRNP A2/B1 (RA33), peptidylarginine deiminase type 4 (PAD4) and calpastatin among others. How these antibody systems fit into the current paradigm of autoantigen citrullination in RA is not known.

Methods:

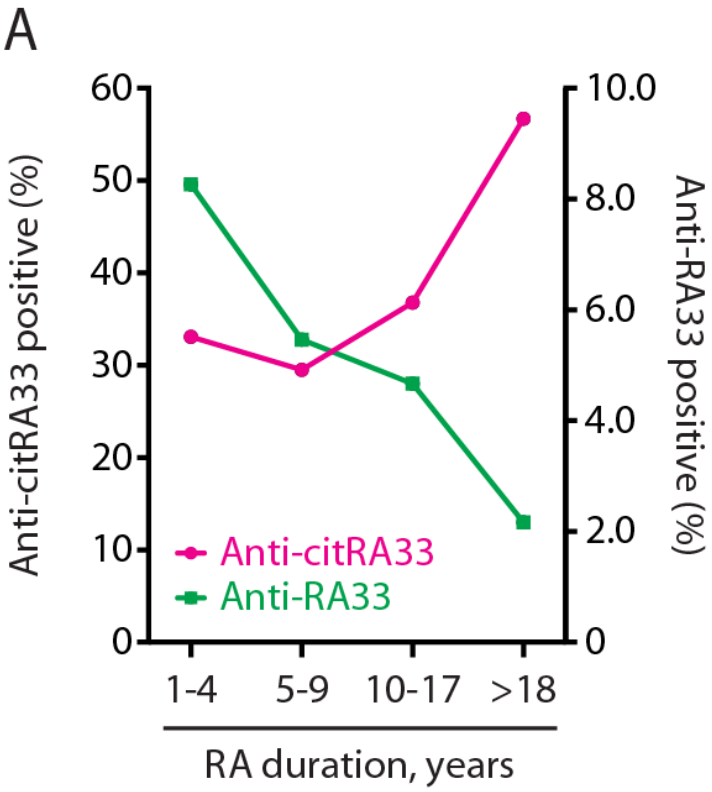
Synovial fluid (SF) cell samples from patients with RA were analyzed by mass spectrometry (MS) and immunoblotting. HnRNP A2/B1/A2b/B1b (RA33) was cloned from RA SF cell cDNA, and expressed as recombinant proteins in an *E coli* system. Purified RA33 splicing variants were citrullinated in vitro using human rPAD4. Patients with RA (n=196 from the baseline visit of a prospective cohort study) and healthy controls (n=56) were assayed in parallel for antibodies against native and citrullinated hnRNP B1b by quantitative ELISA. Patients fulfilled the American College of Rheumatology 1987 revised criteria for the classification of RA. Antibody specificity against native and citrullinated RA33 was further analyzed by immunoblotting and immunoprecipitation (IP) using in vitro transcribed-translated, radiolabeled RA33.

Results:

We found that RA33, a classic native autoantigen in RA, is citrullinated in the rheumatoid joint. MS analysis of RA SF cells and in-vitro citrullinated RA33 confirmed citrullination in 16/25 arginine residues of the full-length protein. Using native and citrullinated antigen, we demonstrated that RA33 is targeted by patient sera in three ways: only as a native protein; both as a native and as a citrullinated protein (double-reactive sera); and only as a citrullinated protein. These distinct patterns of reactivity were confirmed by IP, immunoblotting and competition assays. Anti-(native) RA33 antibodies were almost exclusively detected in early RA (Figure A). In contrast, anti-citRA33 antibodies were positively associated with disease duration, and most commonly detected in patients with long established disease (>18 years post diagnosis). The unique subset of double-reactive patients appeared to identify a transitional disease phase in the evolution of an exclusively anti-native to a mature anti-citrullinated protein antibody response in RA.

Conclusion:

The study of RA33 suggests that native and citrullinated proteins targeted by autoantibodies in RA are part of a single antibody system, which appears to evolve with disease duration. This challenges the paradigm of citrullination as the inciting principle underlying loss of tolerance in RA.



Disclosure: M. F. Konig, None; **J. Giles**, None; **P. A. Nigrovic**, None; **F. Andrade**, None.

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Abstract Number: 529

Immunoglobulin-a and Immunoglobulin-G Isotypes of Anti-CCP Antibodies Are Present in the Sputum of Subjects at Risk for Future Development of RA

Kristen Demoruelle[1], Linh Ho[2], Michael H. Weisman[3], Ryan W. Gan[4], Mark C. Parish[1], Marie L. Feser[1], Chelsie Fleischer[1], Michael Mahler[5], Andrea Seaman[5], Jill M. Norris[4], V. Michael Holers[1] and Kevin D. Deane[1], [1]Division of Rheumatology, University of Colorado School of Medicine, Aurora, CO, [2]University of Colorado School of Medicine, Aurora, CO, [3]Rheumatology, Cedars-Sinai Medical Center, Los Angeles, CA, [4]Epidemiology, Colorado School of Public Health, Aurora, CO, [5]Inova Diagnostics, San Diego, CA
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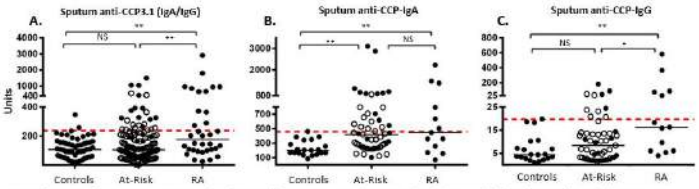
Background/Purpose: Serum elevations of anti-CCP prior to inflammatory arthritis (IA) in RA suggest that anti-CCP is generated at a site outside of the joints. Data suggest this site is likely a mucosal surface. To test the hypothesis that anti-CCP is generated in the lung mucosa, we examine levels of specific anti-CCP isotypes in the sputum of subjects at risk for future development of RA.

Methods: From the Studies of the Etiology of RA (SERA) we studied 34 serum anti-CCP3.1(+) patients with RA (2010 criteria), 142 subjects without IA but At-Risk for future RA based on serum CCP3.1 positivity (N=43) or family history of RA (N=99) and 56 serum CCP3.1(-) healthy controls. Simultaneously collected serum and induced sputum were tested by ELISA for anti-CCP3.1 (IgG/IgA Inova Diagnostics). Sputum from a subset of subjects was also tested for isotype-specific anti-CCP-IgA and CCP-IgG (Inova Diagnostics, research use only). For each CCP, sputum positivity was set based on levels present in <5% of controls.

Results: Sputum anti-CCP3.1 levels were elevated in RA and At-Risk subjects and highest in RA (Figure Panel A, $p<0.01$). In At-Risk subjects, 25/142 (18%) were sputum anti-CCP3.1(+) of whom 13 were serum CCP3.1(-) (Figure A). Furthermore, anti-CCP3.1/total IgG+IgA ratios were

higher in sputum than serum ($p<0.01$) supporting local lung generation and not serum translocation. For CCP isotypes, sputum anti-CCP-IgA levels were elevated and similar between RA and At-Risk subjects (Figure B, p=0.66). In contrast, sputum anti-CCP-IgG levels were higher in RA than At-Risk subjects (Figure C, p=0.02). Also, At-Risk subjects had higher rates of sputum anti-CCP-IgA positivity compared to IgG (42 *vs.* 19%, p=0.02), while in RA sputum anti-CCP-IgA and IgG positivity was similar (46 *vs.* 38%, p=1.0). Finally, in At-Risk subjects, sputum anti-CCP3.1 positivity was not affected by age or sex, but subjects with serum CCP3.1(+) and >10 pack-years of smoking had higher rates of sputum CCP3.1 positivity (Table).

Conclusion: Sputum testing identifies anti-CCP generation in the lung in a portion of individuals At-Risk for RA. Furthermore, sputum anti-CCP-IgA are more prevalent than IgG in At-Risk subjects which is in contrast to anti-CCP-IgA and IgG positivity rates in established RA which are similar. These findings suggest that in some subjects, anti-CCP-IgA generation in the lung may be an important factor in early loss of tolerance. Moreover, the development of sputum anti-CCP-IgG may be an important aspect of transition to articular RA. Longitudinal studies are needed to explore factors (including smoking) that may directly influence the development of mucosal autoimmunity in RA.



Distribution of Sputum anti-CCP levels. Median sputum anti-CCP3.1 levels were highest in RA (Panel A). Sputum anti-CCP-IgA levels were not significantly different between At-Risk and RA subjects (Panel B), but sputum anti-CCP-IgG was significantly higher in RA compared to At-Risk subjects (Panel C). — Median level; - - - Cut-off for positivity; ○ Serum CCP3.1 (-); ● Serum CCP3.1 (+); ** p<0.01; * p<0.05; NS – non-significant

Table. Subject demographics and prevalence of positivity for sputum anti-CCP

	Controls (N=56)	At-Risk (N=142)	RA (N=34)	P-Value[1]
Age, Mean ± SD	36 ± 13	52 ± 15	53 ± 10	<0.01
Female (%)	88%	67%	59%	<0.01
Non-Hispanic white (%)	70%	75%	59%	0.36
Ever smoker (%)	21%	32%	47%	0.09
>10 pack-years smoking (%)	0%	11%[2]	41%	<0.01
Self-reported history of lung disease (%)	13%	25%	29%	0.26
Serum CCP3.1 (+), N (%)	-	43/142 (30%)[3]	34/34 (100%)	<0.01
Sputum CCP3.1 (+), N (%)	-	25/142 (18%)	12/34 (35%)	0.02
Sputum CCP-IgA (+), N (%)	-	22/53 (42%)[4]	6/13 (46%)[5]	0.76
Sputum CCP-IgG (+), N (%)	-	10/53 (19%)[4]	5/13 (38%)[5]	0.14

1. For demographics, P-value is comparing all 3 groups using ANOVA and chi-square testing. Controls were younger and more often female. RA subjects were more often smokers. For serum/sputum CCP positivity, P-value is comparing At-Risk and RA subjects using chi-square testing.
2. At-Risk subjects with a >10 pack-year smoking had higher sputum anti-CCP3.1 positivity rates compared to subjects without a >10 pack-year smoking history [6/15 (40%) vs. 19/127 (15%), p=0.02]
3. At-Risk subjects with serum anti-CCP3.1 positivity had higher sputum CCP3.1 positivity rates compared to serum anti-CCP3.1(-) At-Risk subjects [12/43 (28%) vs. 13/99 (13%) p=0.04]
4. In At-Risk subjects, sputum anti-CCP-IgA positivity rates were higher compared to anti-CCP-IgG positivity [22/53 (42%) vs 10/53 (19%), p=0.02].
5. In RA subjects, sputum anti-CCP-IgA and IgG positivity rates were similar [6/13 (46%) vs. 5/13 (38%), p=1.0]

Disclosure: K. Demoruelle, None; **L. Ho**, None; **M. H. Weisman**, None; **R. W. Gan**, None; **M. C. Parish**, None; **M. L. Feser**, None; **C. Fleischer**, None; **M. Mahler**, Employee of Inova Diagnostics, 3; **A. Seaman**, Employee of Inova Diagnostics, 3; **J. M. Norris**, None; **V. M. Holers**, Shared patent with Stanford University for use of biomarkers to predict clinical phenotypes in rheumatoid arthritis., 7; **K. D. Deane**, None.

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Abstract Number: 530

Immunomodulation of Naïve RA Patients PBMCs with a Multi-Epitope Peptide Derived from Citrullinated Autoantigens

Smadar Gertel[1], Yehuda Shoenfeld[2] and **Howard Amital**[3], [1]Sheba Medical Center, Zabludowicz Center for Autoimmune Diseases, affiliated to Sackler Faculty of Medicine, Tel-Aviv University, Ramat Gan, Israel, [2]Head Dept of Medicine B, Sheba Medical Center, Ramat-Gan, Israel, [3]Sheba Medical Center, Tel-Hashomer, Israel
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Background/Purpose:

Citrullinated peptides are major targets of disease-specific autoantibodies in rheumatoid arthritis (RA).

We generated a multi-epitope citrullinated peptide (Cit-ME), derived from major prevalent citrullinated autoantigens (citrullinated filaggrin, β-fibrinogen, vimentin and collagen type II).

Our aim was to test the ability of the Cit-ME peptide to immunomodulate cytokines gene expression and to alter the Treg subset in culture when incubated with peripheral blood mononuclear cells (PBMC) derived from newly diagnosed RA patients

Methods:

Naïve RA-patient's derived PBMC were incubated in the presence of either the Cit-ME or citrullinated-β-fibrinogen peptide derived from a single prevalent citrullinated autoantigen (1.25µg/ml). Immunomodulation by the peptides was compared to matched non-citrullinated peptides and to traditional biological therapies as Infliximab and Tocalizumab. Following incubation of 24-72 hours with the experimental components we analyzed immune-modulation of cytokines by real-time PCR and analysis of T regulatory population by flow cytometry.

Results:

We found that PBMC from RA patients, incubated in the presence of either Cit-ME or citrullinated-β-fibrinogen, elicited up-regulation of the TGF-β gene expression (16% and 8%, respectively) as compared to the medium control. The Cit-ME elevated the frequencies $CD4^{+}FoxP3^{+}$ T cells (18%) as compared to the medium. In addition, both citrullinated peptides were shown to down-regulate the mRNA expression of the pathogenic cytokines TNF-α and IL-1β. Furthermore we found that the citrullinated peptides were more effective in downregulating the inflammatory state of the PMMC as compared to the effect of the biological agents.

Conclusion:

Citrullinated autoantigens can immunomodulate the inflammatory response in PBMC of patients with RA in culture.

Disclosure: S. Gertel, None; **Y. Shoenfeld**, None; **H. Amital**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/immunomodulation-of-naive-ra-patients-pbmcs-with-a-multi-epitope-peptide-derived-from-citrullinated-autoantigens

Abstract Number: 531

Immune Responses to Mycobacterium Heat Shock Protein 70 Accompany Self-Reactivity to Human Bip in Rheumatoid Arthritis

Hirofumi Shoda[1], Shuji Sumitomo[1], Keishi Fujio[2] and Kazuhiko Yamamoto[1], [1]Department of Allergy and Rheumatology, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan, [2]Department of Allergy and Rheumatology,Graduate School of Medicine, The University of Tokyo, Tokyo, Japan
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SESSION INFORMATION
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Background/Purpose: Molecular mimicry is believed to be an important mechanism of autoimmunity development. We previously demonstrated that imbalance between effector and regulatory T cells specific for BiP, a member of heat shock protein 70 family, induced autoimmne responses in rheumtaoid arthritis (RA). However, the reason why BiP-specific effector T cells developed in RA remains unclear. Here, we examined the immunological linkages between human heat shock proteins (HSPs) and Mycobacterium (Myc) HSPs in RA because the sequences of HSPs are preserved through the species.

Methods: Serum antibodies to bacteria (Mycobacterium and E.Coli) and human HSPs (HSP10, HSP40, HSP60, HSP70) in RA were measured by ELISA. Proliferation of peripheral blood mononuclear cells (PBMCs) from HLA-DR4-positive RA patients in response to MycHSP70-derived and BiP-derived peptides was examined using ^{3}H-thymidine uptake. The effect of immunity on MycHSP70, was evaluated by immunizing HLA-DR4-trangenic mice with MycHSP70 and CFA, and measuring serum antibodies by ELISA. $CD4^{+}$ T cell proliferation in response to MycHSP70 and BiP epitopes was measured by ^{3}H-thymidine uptake. MycHSP70-derived peptide was orally administered to collagen-induced arthritis (CIA) and scores were observed.

Results: Serum titers of antibodies against MycHSP70 were significantly elevated in RA patients and correlated with serum anti-BiP and anti-ciurullinated BiP antibody titers. A MycHSP70-derived HLA-DR4 major epitope was identified using proliferative capasity of RA PBMCs as an indicator. The major T-cell epitope, $MycHSP70^{287-306}$, was located at the corresponding position in the major epitope for human $BiP^{336-355}$, and PBMC proliferations in response to $MycHSP70^{287-306}$ and $BiP^{336-355}$ were highly correlated. These two peptides shared the common amino acid sequences which were important for HLA-DR4 binding. Immunization with MycHSP70 induced BiP-specific T cell proliferation, and development of anti-BiP antibodies. Moreover, oral administration of $MycHSP70^{287-306}$resulted in amelioration of CIA and inhibition of BiP and collagen-specific T cell proliferations .

Conclusion: Immune responses to MycHSP70 were associated with adaptive immunity against BiP in RA. Mycobacterium exposure in the daily environment could trigger the immune responses. Further examination of the immune response against BiP could reveal a mechanism for the development of related autoantibodies including ACPA upon exposure to a certain spectrum of microbes.

Disclosure: H. Shoda, None; **S. Sumitomo**, None; **K. Fujio**, Astellas, BMS, Daiichi-Sankyo, MitsubishiTanabe, Pfizer, Santen, Takeda, Chugai, Eisai, Taisho Toyama, UCB, and Janssen., 2; **K. Yamamoto**, Boehringer Ingelheim, UCB, Eisai, Toyoma-chemical, Pfizer, Taisho Toyama, 5,Boehringer Ingelheim, Astellas, AbbVie, Eisai, Pfizer, Bristol-Myers, Janssen, UCB, Asahikasei, Santen, Ono, Taisho Toyama, Daiichisankyo, Chugai, Mitsubishi Tanabe, Eli Lilly Japan, Nipponkayaku, Takeda, 8,Immunofuture, 1,Immunofuture, 6,Astellas, TEIJIN, Bristol-Myers, Pfizer, AbbVie, Daiichisankyo, Nipponkayaku, Chugai, Mitsubishi Tanabe, Janssen, Eisai, Santen, 2.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/immune-responses-to-mycobacterium-heat-shock-protein-70-accompany-self-reactivity-to-human-bip-in-rheumatoid-arthritis

Abstract Number: 532

Plasma Levels of Bone Morphogenetic Protein (BMP) Subgroups and Their Inhibitors (noggin, sclerostin) in Rheumatoid Arthritis Patients and Correlation with Disease Activity, Clinical and Radiographic Progression: Preliminary Results

Ozge Kockara[1], Sebnem Ataman[2], Merve Sibel Gungoren[3], Filiz Akbiyik[3] and Erdem Karabulut[4], [1]Physical Medicine and Rehabilitation, Ankara University Faculty of Medicine, Ankara, Turkey, [2]Rheumatology Department, Ankara University Faculty of Medicine, Ankara, Turkey, [3]Medical Biochemistry, Hacettepe University Faculty of Medicine, Ankara, Turkey, [4]Biostatistics, Hacettepe University Faculty of Medicine, Ankara, Turkey

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Session Time: 9:00AM-11:00AM

Background/Purpose: Rheumatoid arthritis (RA) is an inflammatory disease that leads to bone erosion. Bone morphogenetic proteins (BMPs) have favourable effects in the recovery of bone damage by stimulating the differentiation of osteoblasts. The effect of BMPs and their inhibitors in the mechanism of bone destruction has not been identified yet. The plasma levels of BMP 2, 3, 4, 5, 6, 7, 9, 14, noggin, sclerostin in RA patients and healthy volunteers were compared and correlated with the disease activity, clinical and radiographic progression.

Methods: In this prospective cohort study, 138 RA patients fulfilling the 1987 ACR criteria and 80 healthy volunteers aged 18-65 years were recruited. Group 1 consists of 85 patients using non-biologic disease-modifying antirheumatic drugs (DMARD) and group 2 consists of 53 patients using anti-TNFa. Control group was identified as Group 3. All groups were matched on age and sex. Tender/swollen joint, erythrocyte sedimentation rate (ESR), c-reactive protein (CRP), DAS28-ESR, DAS28-CRP, pain and health assessment questionnaire (HAQ) were evaluated

clinically. Structural damage was measured by using van der Heijde modified total Sharp scoring method (mTSS). Blood samples were collected. The plasma levels of BMPs, noggin and sclerostin were measured by ELISA method. In all groups, the plasma levels of BMPs and their inhibitors were analyzed by Kruskal-Wallis one-way analysis of variance. Differences between group 1 and group 2 were compared by chi square test and Mann-Whitney U test. P value of 0.05 was considered statistically significant.

Results: Baseline characteristics of group 1 and 2 were shown in table 1 and the comparison of the plasma levels of BMPs in all groups was shown in table 2. The correlation between HAQ and BMP 2, 5,7,14, sclerostin (r=-0,290 p=0,008, r=-0,219 p=0,046, r=0,229 p=0,037, r=-0,273 p=0,013, r=-0,388 p<0.001); between DAS28-ESR and BMP 2, 5,14, sclerostin (r=-0,236 p=0,03, r=-0,259 p=0,017, r=-0,216 p=0,047, r=-0,358 p=0,001); between DAS28-CRP and BMP 2, 5, sclerostin (r=-0,257 p=0,018, r=-0,236 p=0,03, r=-0,330 p=0,002) were statistically significant in DMARD group. There was no correlation in anti-TNF group.

Conclusion: The plasma levels of BMP 2, 4, 5, 6, 7, 9, 14 are increased, whereas BMP subgroup inhibitors which are BMP 3, noggin and sclerostin are decreased and the differences between the results of RA patients using anti-TNFa and healthy volunteers were statistically significant. In this 1-year follow-up study, the plasma levels of BMPs and their inhibitors, HAQ, mTSS and clinical evaluation will be repeated one year later.

Table:1 Baseline Characteristics of RA Patients Groups

		Group 1 (DMARD) (n=85)	Group 2 (anti-TNFα) (n=53)	P-Values
Disease Duration	Mean (month) (Std Dev)	109,1 (103,6)	153,9 (105,5)	**0,005**
	Median (month) (Min;Max)	72 (1 – 408)	132 (6 – 360)	
RF	Positivity % (n)	52,9 (45)	54,7 (29)	0,862
	Negativity % (n)	41,2 (35)	45,3 (24)	
Anti-CCP ab	Positivity % (n)	42,4 (36)	26,4 (14)	0,159
	Negativity % (n)	38,8 (33)	43,4 (23)	
Sero	Positivity % (n)	65,9 (56)	60,4 (32)	0,513
	Negativity % (n)	34,1 (29)	39,6 (21)	
Tender Joint	Mean (Std Dev)	6,03 (6,98)	5,01 (5,41)	0,609
	Median (Min;Max)	3,00 (0 – 28)	3,00 (0 – 21)	
Swollen Joint	Mean (Std Dev)	0,64 (1,00)	0,66 (1,31)	0,428
	Median (Min;Max)	0,00 (0 – 4)	0,00 (0 – 6)	
ESH	Mean (Std Dev) (mm/hr)	20,4 (15,7)	26,1 (19,6)	0,158
	Median (Min;Max)	16 (1 – 87)	23 (1 – 66)	
CRP	Mean (Std Dev) (mg/L)	11,7 (26,8)	12,7 (16,5)	0,586
	Median (Min;Max)	4,5 (1 - 221,9)	5,2 (1 - 62)	
DAS28-ESH	Mean (Std Dev)	3,50 (1,35)	3,54 (1,48)	0,869
	Median (Min;Max)	3,47 (0,56 – 6,53)	3,49 (0,21 – 6,68)	
Disease Activity (DAS28-ESH)	- Remission % (n)	27,1 (23)	26,4 (14)	0,801
	- Low Disease Activity % (n)	15,3 (13)	18,9 (10)	
	- Moderate Disease Activity % (n)	44,7 (38)	37,7 (20)	
	- High Disease Activity % (n)	12,9 (11)	17 (9)	
DAS28-CRP	Mean (Std Dev)	3,18 (1,23)	3,18 (1,34)	0,987
	Median (Min;Max)	3,01 (1,21 – 5,91)	3,04 (1,21 – 6,70)	
Disease Activity (DAS28-CRP)	- Remission % (n)	32,9 (28)	41,5 (22)	0,542
	- Low Disease Activity % (n)	20 (17)	11,3 (6)	
	- Moderate Disease Activity % (n)	40 (34)	39,6 (21)	
	- High Disease Activity % (n)	7,1 (6)	7,5 (4)	
Pain for VAS (1-100)	Mean (Std Dev)	24,94 (20,33)	28,68 (24,04)	0,46
	Median (Min;Max)	20 (0 – 80)	25 (0 – 100)	
HAQ (0 – 3)	Mean (Std Dev)	0,34 (0,39)	0,47 (0,54)	0,728
	Median (Min;Max)	0,20 (0 – 1,90)	0,25 (0 – 1,85)	

Table 2: The comparison of the plasma levels of BMP subgroups and their inhibitors

	Dunn's test results (Adjusted p values)		
	Control-DMARD	Control-anti TNF	DMARD-anti TNF
BMP-2	<0,001	<0,001	0,686
BMP-3	<0,001	<0,001	0,006
BMP-4	0,012	<0,001	0,020
BMP-5	0,687	<0,001	<0,001
BMP-6	1,000	<0,001	<0,001
BMP-7	0,933	0,001	<0,001
BMP-9	0,203	<0,001	<0,001
BMP-14	1,000	<0,001	<0,001
NOG	<0,001	<0,001	<0,001
SOST	<0,001	<0,001	0,005

Disclosure: O. Kockara, None; **S. Ataman**, Roche Pharmaceuticals, 5,Pfizer Inc, 5,UCB, 5,Mustafa Nevzat, 5,BMS, 5,MSD, 5; **M. S. Gungoren**, None; **F. Akbiyik**, None; **E. Karabulut**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/plasma-levels-of-bone-morphogenetic-protein-bmp-subgroups-and-their-inhibitors-noggin-sclerostin-in-rheumatoid-arthritis-patients-and-correlation-with-disease-activity-clinical-and-radiographic

Abstract Number: 533

The Interferon Gene Signature in Early Rheumatoid Arthritis Demonstrates No Significant Association with Disease Activity

Faye A H Cooles[1], Amy E. Anderson[2], Catharien Hilkens[3] and John D Isaacs[4], [1]Musculoskeletal Research Group, Newcastle University,

Newcastle upon Tyne, United Kingdom, [2]Musculoskeletal Research Group, Institute of Cellular Medicine, Newcastle University, Newcastle upon Tyne, United Kingdom, [3]Musculoskeletal Research Group, Newcastle University, Newcastle Upon Tyne, United Kingdom, [4]Newcastle University and the Freeman Hospital, Newcastle-upon-Tyne, United Kingdom
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Session Type: ACR Poster Session A

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Background/Purpose: An interferon-α gene signature (IGS) has been demonstrated in a number of rheumatological conditions, including rheumatoid arthritis (RA) where it is present in about 20-30% of patients. In established RA the IGS does not correlate with any disease activity parameters however ongoing immunomodulatory treatment may mask any underlying associations. We therefore wished to investigate any association between the IGS and disease activity in early RA patients prior to administration of any disease modifying therapy.

Methods: Disease modifying drug naïve patients fulfilling the ACR/EULAR criteria for a new diagnosis of RA were recruited from the Early Arthritis Clinic at the Freeman Hospital, Newcastle-upon-Tyne, UK. Clinical parameters included sex, age, swollen joint count (SJC), tender joint count (TJC), patient reported visual analogue scale of disease severity (VAS), disease activity score (DAS-28), inflammatory markers (CRP, ESR), autoantibody status (seropositive defined as either rheumatoid factor and/or anti CCP antibody positive) and symptom duration. In addition whole blood RNA was collected in Tempus Blood RNA tubes at diagnosis and following RNA extraction the expression of 5 interferon-α response genes (MXA, IFI6, OAS-1, ISG-15 and IFI-44L) was quantified using TAQMAN real-time PCR. Using the whole blood expression of these genes in an independent healthy control population an interferon gene score was calculated as previously published (Feng et al., Arthritis and rheumatism. 2006; 54(9):2951-62). Statistical tests were performed using GraphPad prism v5 (GraphPad Software, Inc) and included linear regression and Mann-Whitney U tests. Significance was taken when $p<0.05$.

Results:

We recruited 36 early RA patients. Median age was 59 years [range 30-91] and male:female ratio was 1:2. The healthy control population (n=17) had a median age 33 [range 23-57] and a male:female ratio 1:1. Notably age and sex had no significant association with the IGS within our early RA cohort ($p=0.549$ and $p=0.513$ respectively, linear regression). We found no significant difference in IGS score between our early seropositive RA and seronegative RA ($p=0.925$, Mann=Whitney U). Furthermore there was no association between any of the disease activity parameters measured (SJC, TJC, VAS, DAS-28, symptom duration, ESR and CRP) and the interferon gene score or individual gene expression ($p>0.05$ for all, linear regression).

Conclusion:

We demonstrate the novel finding that in early, drug naïve RA the IGS does not associate with markers of disease activity. This is similar to what has been shown in established RA. We know however that a high IGS score may predict poor response to certain therapies therefore, rather than reflecting inflammation/disease activity, interferon-α exposure may represent a distinct pathological process within a subset of RA patients. We propose that understanding this heterogeneity further is likely to assist in the development of novel therapeutic pathways for a subset of RA patients.

Disclosure: F. A. H. Cooles, None; **A. E. Anderson**, None; **C. Hilkens**, None; **J. D. Isaacs**, None.

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Abstract Number: 534

Antibodies to Malondialdehyde-Acetaldehyde Adducts Are Highly Expressed in Rheumatoid Arthritis Synovial Fluid

Rafid Rahman[1], Geoffrey M. Thiele[2], Andy Hollins[3], Michael J. Duryee[1], Daniel Anderson[3], Bartlett Hamilton[4], Kaleb Michaud[5], Lynell W. Klassen[6] and Ted R. Mikuls[3], [1]Internal Medicine Division of Rheumatology, University of Nebraska Medical Center, Omaha, NE, [2]Omaha VA Medical Center and University of Nebraska Medical Center, Omaha, NE, [3]University of Nebraska Medical Center, Omaha, NE, [4]University of Nebraska Medical Center and Omaha VA Medical Center, Omaha, NE, [5]Rheumatology & Immunology, University of Nebraska Medical Center and National Data Base for Rheumatic Diseases, Omaha, NE, [6]Dept of Internal Medicine, Omaha VA Medical Center and University of Nebraska Medical Center, Omaha, NE
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Background/Purpose: Malondialdehyde-acetaldehyde (MAA) adducts are expressed in synovial tissues in rheumatoid arthritis (RA). Post-translational MAA modifications are pro-inflammatory, promoting robust anti-MAA antibody responses that are correlated with markers of RA disease severity. Whether anti-MAA antibodies are produced locally in affected joint tissues is not known. If present in higher concentrations in synovial fluid (SF) than in sera, this would support a potential pathogenic role of these antibodies in RA. The objective of this study was to evaluate the expression of anti-MAA antibody isotypes in paired SF/serum samples of patients with RA and OA to better understand the relationship of circulating antibody with antibody expressed locally in joints.

Methods: Paired serum/SF samples were examined, drawn from 29 RA patients and 13 OA patients on the same day, banked, and frozen at -70^{0}C until analysis. Anti-MAA antibody isotypes (IgA, IgG, and IgM) were measured in arbitrary units (AU) using ELISA and examined as means ± SEMs. Paired t-tests were used to compare anti-MAA antibody concentrations in SF vs. serum, while RA/OA comparisons were made separately for SF and serum using a Student's t-test.

Results: Anti-MAA antibody concentrations were numerically higher in RA-SF vs. OA-SF for IgA and IgM, a difference that reached statistical significance for the IgG isotype (p=0.008) (Figure 1). There were no significant RA-OA differences for any of the circulating anti-MAA antibody isotypes. In analyses of paired RA samples, IgG (663±121 vs. 219±76 AU, p<0.001) and IgM (1148±328 vs. 464±115 AU, p=0.033) anti-MAA antibody isotypes were significantly higher in the SF vs. serum. IgA anti-MAA antibody concentrations in RA SF did not differ significantly from paired sera (Figure 2). There were no differences in anti-MAA antibody concentrations in paired SF/serum samples from OA patients.

Conclusion: These results complement a previous report demonstrating that MAA adducts are expressed in inflammatory joint tissues in patients with RA. For the first time, these results show that anti-MAA antibodies, particularly the IgM and IgG isotypes, are also present in significantly higher concentrations in the joint compared to the circulation. It is possible that anti-MAA antibody may be produced locally or alternatively that these antibodies accumulate in joint tissues. Taken together, these results suggest that anti-MAA antibody could play an important pathogenic role and that its detection in SF could serve as an informative RA biomarker.

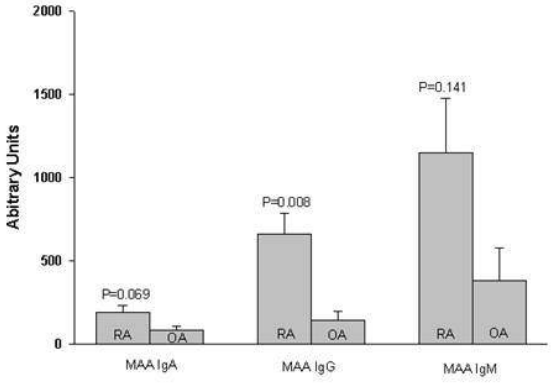

Figure 1:

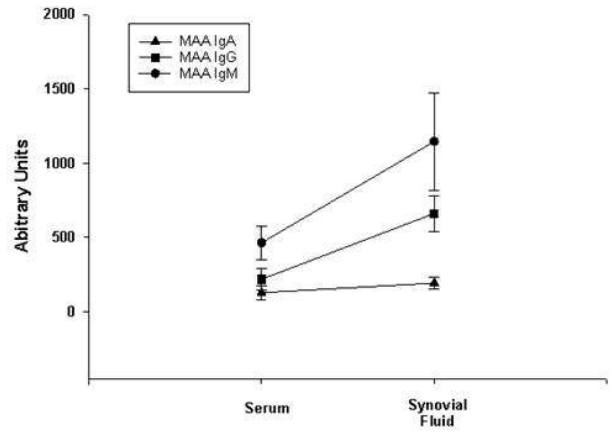

Figure 2:

Disclosure: R. Rahman, None; **G. M. Thiele**, None; **A. Hollins**, None; **M. J. Duryee**, None; **D. Anderson**, None; **B. Hamilton**, None; **K. Michaud**, None; **L. W. Klassen**, None; **T. R. Mikuls**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/antibodies-to-malondialdehyde-acetaldehyde-adducts-are-highly-expressed-in-rheumatoid-arthritis-synovial-fluid

Abstract Number: 535

Taurine As a Biomarker for Prediction of Response to Biologic Therapy in Rheumatoid Arthritis

Soshi Takahashi[1], Jun Saegusa[2], Ikuko Naka[1], Kosaku Tsuda[1], Takaichi Okano[1], Kengo Akashi[1], Miwa Nishida[1], Keisuke Nishimura[2], Sho Sendo[2], Yo Ueda[1], Akira Onishi[3], Yoshinori Kogata[2], Goichi Kageyama[2] and Akio Morinobu[2], [1]Department of Rheumatology, Kobe University Hospital, Kobe, Japan, [2]Rheumatology and Clinical Immunology, Kobe University Graduate School of Medicine, Kobe, Japan, [3]Rheumaology and Clinical Immunology, Kobe University Graduate School of Medicine, Kobe, Japan

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Session Time: 9:00AM-11:00AM

Background/Purpose: To identify a serum biomarker for prediction of the response to biologics (Bio) in patients with rheumatoid arthritis (RA), we performed serum metabolomics analysis in RA patients before and after Bio treatment.

Methods: We collected the fasting serum samples of RA patients prior to starting or switching Bio treatment due to increased disease activity despite prior treatment with DMARDs or Bio. Twenty-seven patients were included (TNF-α inhibitors (TNFi) 13, tocilizumab (TCZ) 6, abatacept (ABT) 8). The average age was 60.1 (42-74) years old. There were 3 non-responders in TNFi group, and 1 in ABT. We also collected fasting serum samples from 12 healthy volunteers, and used as healthy controls (HC). We performed metabolome analysis using a Gas Chromatograph Mass Spectrometer (GCMS-QP2010 ultra). Multivariate statistics was carried out by using Simca P+ software.

Results: We detected 99 metabolites from the serum samples. The level of 44 of them was significantly different in RA patients (before Bio treatment) compared to HC. The 2D-plots of the principal component analysis (PCA) scores for all 99 metabolites showed distinct clustering for the two subject group. We have identified several metabolites which greatly contributed to the observed separation of the metabolomics profiles of the RA patients and HC by the corresponding 2D-PCA. Regarding prediction of response to biologics treatment, we revealed that patients with low serum levels of taurine at baseline showed good response to Bio treatment. The ROC analysis of taurine revealed an area under the curve of 0.900, with a specificity of 83.3% and sensitivity of 93.3% at the cutoff level of 0.00056 (P<0.001). In addition, we demonstrated that the serum levels of asparagine was significantly correlated with the DAS28-CRP (P<0.01, r^2=0.269), and significantly increased after Bio treatment (P<0.05).

Conclusion: Our present findings indicate that the pathogenesis of RA is accompanied by variations in the serum levels of low molecular weight metabolites, which supports the potential for using GCMS-based metabolomics as a diagnostic and monitoring tool for RA, and taurine may be a novel biomarker to predict the therapeutic response to Bio in RA.

Disclosure: S. Takahashi, None; **J. Saegusa**, None; **I. Naka**, None; **K. Tsuda**, None; **T. Okano**, None; **K. Akashi**, None; **M. Nishida**, None; **K. Nishimura**, None; **S. Sendo**, None; **Y. Ueda**, None; **A. Onishi**, None; **Y. Kogata**, None; **G. Kageyama**, None; **A. Morinobu**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/taurine-as-a-biomarker-for-prediction-of-response-to-biologic-therapy-in-rheumatoid-arthritis

Abstract Number: 536

Increased Circulating CD14brightCD16+ Intermediate Monocytes Are Regulated By TNF-Alpha and IL-6 Axis in Accompany with Disease Activity in Rheumatoid Arthritis Patients

Masako Tsukamoto[1], Katsuya Suzuki[2], Noriyuki Seta[3], Keiko Yoshimoto[2], Kunihiro Yamaoka[2] and Tsutomu Takeuchi[2], [1]Division of Rheumatology, Department of Internal medicine, Keio University School of Medicine, Tokyo, Japan, [2]Division of Rheumatology, Department of Internal Medicine, Keio University School of Medicine, Tokyo, Japan, [3]Department of Internal Medicine, Tokyo Dental College, Ichikawa

General Hospital, Chiba, Japan
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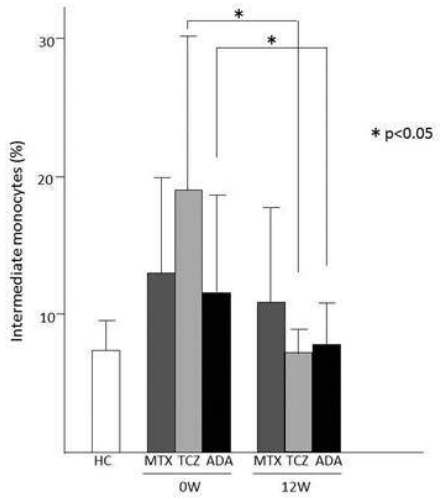
Background/Purpose: Recently, three different subsets of circulating monocytes: $CD14^{bright}CD16-$ (classical), $CD14^{bright}CD16+$ (intermediate) and $CD14^{dim}CD16+$ (nonclassical) monocytes have been defined. It has been reported that circulating intermediate subset increased in coronary artery disease and inflammatory disease such as infection and auto-inflammatory disease. However, the pathogenesis of increase of intermediate monocytes in inflammatory condition is still unclear and the relationship between cytokines and intermediate monocytes is unknown particularly in rheumatoid arthritis (RA). The purpose of this study is to investigate influence on intermediate monocytes by anti-cytokine treatment in patients with RA.

Methods: 32 RA patients and 14 healthy control subjects (HC) were enrolled in this study. All patients had never received a treatment with methotrexate (MTX) or biological agents. Peripheral blood samples and clinical records of the patients were obtained at the time of 0, 12 and 24 weeks after treatment. Peripheral blood samples were also obtained from HC. The expression levels of CD14 and CD16 on monocytes were measured by flow cytometry (FCM).

Results: 8 patients received anti-IL-6 receptor antibody, tocilizmab (TCZ) treatment alone, 12 patients received anti-TNF-a antibody, adalimumab (ADA) with MTX treatment and others received only MTX treatment. FCM analysis revealed that the proportion of intermediate monocytes significantly increased in patients at baseline compared with HC. The proportion of intermediate monocytes significantly decreased after TCZ and ADA treatment ($p=0.029$ and $p=0.012$, Fig 1). The proportion of intermediate monocytes were significantly and positively correlated with DAS28-ESR score ($r=0.47$, $p<0.01$) and DAS28-ESR score decreased in accompany with the proportion of intermediate monocytes after inhibition of inflammatory cytokine signal.

Conclusion: We showed that $CD14^{bright}CD16+$ intermediate monocytes significantly decreased with the change of disease activity by key cytokines, IL-6 or TNF-a signal blockade in RA. This result indicates that the proportion of circulating monocytes is controlled by IL-6 and TNF-a axis and is important for reflecting disease activity in RA.

Fig 1) The proportion of intermediate monocytes significantly decreased after TCZ and ADA treatment.



Disclosure: M. Tsukamoto, None; **K. Suzuki**, None; **N. Seta**, None; **K. Yoshimoto**, None; **K. Yamaoka**, Pfizer, Chugai Pharma, Mitsubishi-Tanabe Pharma, Takeda Industrial Pharma, GlaxoSmithKline, Nippon Shinyaku, Eli Lilly, Janssen Pharma, Eisai Pharma, Astellas Pharma and Actelion Pharmaceuticals., 8; **T. Takeuchi**, Astellas Pharma Inc, Bristol-Myers KK, Chugai Pharmaceutical Co, Ltd, Daiichi Sankyo Co, Ltd, Eisai Co, Ltd, Mitsubishi Tanabe Pharma Corp, Pfizer Japan, Santen Pharmaceutical Co, Ltd, Takeda Pharmaceutical Co, Ltd, Teijin Pharma Ltd, AbbVie GK, Asahi Kas, 2,AbbVie GK, Bristol-Myers KK, Chugai Pharmaceutical Co, Ltd, Eisai Co, Ltd, Janssen Pharmaceutical KK, Mitsubishi Tanabe Pharma Corp, Pfizer Japan Inc, Takeda Pharmaceutical Co, Ltd, Astellas Pharma Inc, and Daiichi Sankyo Co, Ltd; and consultant fees from, 8.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/increased-circulating-cd14brightcd16-intermediate-monocytes-are-regulated-by-tnf-alpha-and-il-6-axis-in-accompany-with-disease-activity-in-rheumatoid-arthritis-patients

Abstract Number: 537

The Course of Bone Marrow Edema in Early Undifferentiated and Rheumatoid Arthritis; A Longitudinal MRI Study on Bone Level

W.P. Nieuwenhuis[1], H.W. van Steenbergen[2], W. Stomp[3], T. Stijnen[4], T. W. J. Huizinga[1], J.L Bloem[3], D. van der Heijde[1], M. Reijnierse[3] and A.H.M. van der Helm- van Mil[2], [1]Rheumatology, Leiden University Medical Center, Leiden, Netherlands, [2]Leiden University Medical Center, Leiden, Netherlands, [3]Radiology, Leiden University Medical Center, Leiden, Netherlands, [4]Medical Statistics, Leiden University Medical Center, Leiden, Netherlands
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Background/Purpose:

In rheumatoid arthritis (RA) patients, bone marrow edema (BME)-scores are associated with development of erosions. However, little is known on the course and outcome of BME at bone level. Therefore this study determined the association of BME and MRI-synovitis in the same bone longitudinally.

Methods:

1,947 bones of MCP, wrist and MTP-joints of 59 patients presenting with rheumatoid or undifferentiated arthritis were studied using 1.5T MRI at baseline, after four and twelve months. Scanning and scoring of BME, synovitis and erosions were performed according to RAMRIS. The relation of the course of BME and synovitis to erosive progression at bone level during 1-year was evaluated.

Results:

Of the bones showing BME at baseline (n=203), BME persisted in 56%, disappeared in 39%, and disappeared-reappeared seldom (5%). Stratified analyses at baseline revealed that BME was associated with erosive progression, in presence and in absence of local synovitis (ORs 7.5 95%CI 3.8-14.9 and 6.9 95%CI 1.9-25.6). Local synovitis, however, was not associated with erosive progression (OR 2.0 95%CI 0.6-7.0 in presence of BME and 1.9 95%CI 0.8-4.1 in the absence of BME). In multivariable GEE-analyses, persistent BME was strongly associated with erosive progression (OR 60 95%CI 17-318), in contrast to persistent synovitis (OR 1.4 95%CI 0.4-5.3).

Conclusion:

BME frequently persists during the first year. Persistent BME was strongly associated with erosive progression in the same bone, independent of local synovitis. No independent association was observed for persistent synovitis. These findings are relevant for the comprehension on the development of erosions in RA.

Disclosure: W. P. Nieuwenhuis, None; **H. W. van Steenbergen**, None; **W. Stomp**, None; **T. Stijnen**, None; **T. W. J. Huizinga**, None; **J. L. Bloem**, None; **D. van der Heijde**, None; **M. Reijnierse**, None; **A. H. M. van der Helm- van Mil**, None.

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Abstract Number: 538

Multidrug Resistant Lymphocytes of Patients with Rheumatoid Arthritis Are Predictive for DMARD and Glucocorticoid Treatment Response

Jan Piet van Hamburg[1], Sandra M.J. Paulissen[2], Nadine Davelaar[1], Mieke Hazes[3] and Erik Lubberts[1], [1]Rheumatology and Immunology, Erasmus MC, University Medical Center Rotterdam, Rotterdam, Netherlands, [2]Room Nb-84, Erasmus MC, University Medical Center Rotterdam, Rotterdam, Netherlands, [3]Rheumatology, Erasmus MC, University Medical Center Rotterdam, Rotterdam, Netherlands
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Background/Purpose: A large fraction of patients with RA does not respond to treatment with glucocorticoids (GCs) and disease-modifying anti-rheumatic drugs (DMARDs), or becomes resistant in time. Multidrug resistance may underlie the lack of response, but markers to predict or monitor drug resistance in RA are lacking. In this study, drug efflux capacity and multidrug transporter expression were investigated on various lymphocyte populations in relation to combined DMARD/GC therapy response.

Methods: Peripheral and/or synovial lymphocytes were obtained from: healthy individuals, established inflammatory arthritis patients and DMARD/GC therapy responders and non-responders at baseline and after 6 months of therapy. Drug efflux capacity, indicated by rhodamine-123 (Rh123) and calcein transport, and MDR1, MRP1 and ABCG2 expression were analysed for total lymphocytes, as well as for B, CD4+ T, CD8+ T and natural killer (NK) cells.

Results: Compared to healthy individuals, lymphocytes from patients with inflammatory arthritis showed a higher drug efflux capacity and expressed higher MDR1 and MRP1 levels. DMARD/GC non-response was associated with lower MDR1 expression and Rh123 efflux by naïve CD8+ T cells at baseline and increased MRP1 expression and calcein efflux after 6 months of treatment. Blocking MRP1 activity partially inhibited calcein efflux by peripheral and synovial lymphocytes, indicating additional MRP1-independent drug resistance.

Conclusion: Multidrug resistant lymphocytes are present in RA. In addition, MDR1 expression and activity in naïve CD8+ T cells was identified as a marker to distinguish DMARD/GC therapy responders from non-responders at baseline. Moreover, increased calcein efflux capacity by lymphocytes during DMARD/GC treatment is associated with the lack of response on this treatment. Implementation of these findings in current diagnostic and treatment protocols might lead to improved personalized RA treatment strategies.

Disclosure: J. P. van Hamburg, None; **S. M. J. Paulissen**, None; **N. Davelaar**, None; **M. Hazes**, None; **E. Lubberts**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/multidrug-resistant-lymphocytes-of-patients-with-rheumatoid-arthritis-are-predictive-for-dmard-and-glucocorticoid-treatment-response

Abstract Number: 539

Quantification of T-Cell Receptor Excision Circles (TREC) from Peripheral Blood in Patients with Inflammatory Polyarthritis of Recent Onset (EPA): Association with Radiographic Joint Damage

Alexandre Osborne[1], Nathalie Carrier[2], Artur J de Brum-Fernandes[3], Patrick Liang[3], Ariel Masetto[4] and **Gilles Boire**[3], [1]Clinical Sciences Program, Université de Sherbrooke, Sherbrooke, QC, Canada, [2]Division of Rheumatology, Université de Sherbrooke, Sherbrooke, QC, Canada, [3]Department of Medicine/Division of Rheumatology, Université de Sherbrooke, Sherbrooke, QC, Canada, [4]Department of Medicine/Division of Rheumatology, Université de Sherbrooke, Centre Hospitalier Universitaire de Sherbrooke, Sherbrooke, QC, Canada
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Session Time: 9:00AM-11:00AM

Background/Purpose: Patients with established Rheumatoid arthritis (RA) present evidence for an exhausted immune system. It is not known whether patients seen at the Early inflammatory PolyArthritis (EPA; 1-12 month symptom duration) stage already present with immune exhaustion. Quantification of T-cell receptor excision circles (TREC) in peripheral blood is a readily available measure of T cell thymic output.

Objective. To explore if low TREC numbers in EPA patients are associated with poorer disease outcomes.

Methods: Variables allowing calculation of disease activity indices (DAS-28 and SDAI), hand and feet X-rays scored using the modified Sharp method (SHS) and DNA from peripheral blood were serially collected at inclusion and at pre-specified times during follow up from consecutive EPA patients from the Early Undifferentiated PolyArthritis (EUPA) cohort and from healthy controls with similar sex and age distribution. TREC numbers per 10^5 nucleated cells in peripheral blood were estimated by quantitative polymerase chain reaction (qPCR) using the method described by Cheynier et al **(***Methods Mol Biol* 2007;**380:**197-213**)**. The effect of sex and increasing age on log-transformed TREC numbers were analyzed using Pearson correlations and repeated measures ANOVA. Receiver Operating Characteristics (ROC) curves using baseline TREC numbers were drawn to determine the best cut-off to predict significant joint damage (SHS ≥5) at 30 months. Levels of TREC at baseline and outcomes over time were correlated using linear regression, repeated measures ANOVA or generalized estimating equations for binary outcomes (GEE).

Results: We report on 73 EPA patients (93% RA; median duration 4.7 months; 48 women; mean 54.8 years) and on 98 healthy controls with similar age and sex. The median (IQR) number (per 10^5 nucleated cells) of TREC at inclusion was 88.6 (25.1-269.1) for EPA patients and 129.3 (45.4-289.4) for controls (p=0.112). In both patients and controls, TREC numbers decreased with increasing age, and women as a group had higher numbers. TREC numbers at baseline inversely correlated with disease activity but this correlation was lost during follow up. At baseline, ROC curves revealed that a value of < 128 TREC per 10^5 nucleated cells best identified patients with SHS ≥5 at 30 months (AUC = 0.613; sensitivity = 0.600; specificity = 0.731; RR (95% CI) = 1.91 (1.01-3.31), p=0.024). TREC < 128 also associated with SHS ≥ 5 at baseline (AUC = 0.716; sensitivity = 0.786; specificity = 0.678; RR (95% CI) = 3.77 (1.64-8.66), p<0.001). There was a trend between TREC levels < 128 at baseline and radiographic progression (ΔSHS ≥ 5) from baseline to follow up: RR (95%CI) = 2.24 (0.92-5.50); p=0.077.

Conclusion: Our age and sex results in healthy controls parallel published results. In EPA patients, baseline TREC numbers were correlated with initial but not subsequent disease activity. Low baseline TREC levels were associated with more joint damage at baseline and trended to predict more progression during follow up. Measurement of TREC numbers represents a novel promising biomarker in EPA patients, potentially identifying patients who already have developed the exhausted RA phenotype, those most likely to develop severe joint damage.

Disclosure: A. Osborne, None; **N. Carrier**, None; **A. J. de Brum-Fernandes**, None; **P. Liang**, None; **A. Masetto**, None; **G. Boire**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/quantification-of-t-cell-receptor-excision-circles-trec-from-peripheral-blood-in-patients-with-inflammatory-polyarthritis-of-recent-onset-epa-association-with-radiographic-joint-damage

Abstract Number: 540

Clinical Relevance of Etanercept Levels and Anti-Etanercept Antibodies in Long-Term Treatment of Rheumatoid Arthritis Patients

Susanne Drynda and **Jörn Kekow**, Univ of Magdeburg, Clinic of Rheumatology, Vogelsang-Gommern, Germany
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Background/Purpose:

Biological compounds have belonged to the therapeutic options for the treatment of rheumatoid arthritis for about 15 years. The application of biological substances is subject to a risk of developing antibodies against these structures, causing adverse events or loss of efficacy. It was the aim of the study to analyse the clinical relevance of anti-drug antibodies and drug levels in the course of a long term treatment of patients with rheumatoid arthritis with etanercept (ETN).

Methods:

In this retrospective analysis, 508 serum samples from 102 RA patients (84 female/18 male, mean age 50.8±1.5 years, mean disease duration 10.8±0.8 years) were obtained after 6, 12, 24, 36 and 48 months of treatment with ETN, and selected for determination of anti-ETN antibodies and drug levels. If available, serum samples obtained at least 2 weeks after discontinuation of ETN treatment (due to side effects, non-response, remission or surgery) were used for analysis to exclude any interference of high drug levels with the anti-drug antibody assay. For the determination of anti-ETN and ETN levels, Promonitor® - assays (Proteomika, Spain) were used according to the manufacturer's instructions.

Results:

Mean baseline disease activity (DAS28) of 5.77±0.11 decreased to 3.72±0.14, 3.46±0.12, 3.43±0.15 and 3.16±0.15 after 6, 12, 24 and 48 months of ETN treatment. No anti-ETN antibodies were found at any time point, neither in the course of treatment nor in samples from 72 of these patients obtained at least two weeks after discontinuation of ETN treatment (mean 51±3.9 months, range 18-120 months).

Mean ETN serum levels were 3.58±0.17µg/ml, 4.33±0.24µg/ml, 4.22±0.29µg/ml, 4.21±0.27 and 4.66±0.42µg/ml after 6, 12, 24, 36 and 48 months respectively. ETN levels remained stable in most patients, mean levels between individual patients ranged between 0.9 and 9.91µg/ml. In the lower quartile of patients with mean ETN level <2.5µg/ml, the DAS28 decreased from 5.46±0.26 to 3.79±0.19 (-1.67), 4.06±0.45 (-1.40), and 3.74±0.40 (-1.72) after 6, 24 and 48 months. A stronger DAS28 improvement was found in the upper quartile >5.07µg/ml from 6.10±0.21 to 3.74±0.33 (-2.36), 3.19±0.23 (-2.91), and 3.03±0.19 (-3.07) respectively.

Conclusion:

Our study confirms the lack of anti-drug antibodies in a large cohort of RA patients in the course of a long-term treatment with ETN. The absence

of anti-ETN antibodies in serum samples after discontinuation of therapy confirms this result by exclusion of false negative results resulting from interference with high ETN levels in the course of treatment.

ETN serum levels are subject to strong variations between individual patients. A significant reduction of disease activity was found in each quartile, the greatest mean reduction was observed in the group with the highest ETN serum levels.

Disclosure: S. Drynda, Pfizer Pharma GmbH, Germany, 2; **J. Kekow**, Pfizer Pharma GmbH, Germany, 2.

Abstract Number: 541

Microrna-125b Expression in PBMCs Is Associated with Disease Activity in Patients with Early Rheumatoid Arthritis

Veronika Hruskova[1,2], Romana Jandová[3], Lucia Vernerova[4], Herman F Mann[5], Klára Prajzlerová[4], Maria Filkova[4], Karel Pavelka[5], Jiri Vencovsky[5] and Ladislav Senolt[5], [1]Institute of Rheumatology and Department of Rheumatology; Faculty of Science Charles University, Prague, Czech Republic, [2]Faculty of Science, Charles University, Prague, Czech Republic, [3]Institute of Rheumatology and Department of Rheumatology, Prague, Czech Republic, [4]Institute of Rheumatology and Department of Rheumatology, 1st Faculty of Medicine, Charles University, Prague, Czech Republic, [5]Institute of Rheumatology and Department of Rheumatology, 1st Faculty of Medicine, Charles University, Prague, Czech Republic, Prague, Czech Republic

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Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose: MicroRNAs (miRNAs) are small non-coding RNAs that function as negative regulators of gene expression at posttranscription level and play a significant role in rheumatoid arthritis (RA) (1). The expression of TNF-α, a key pro-inflammatory cytokine of RA pathogenesis, is negatively regulated by miR-125b (2). Therefore, the aim of this study was to evaluate the expression of miRNA-125b in peripheral blood mononuclear cells (PBMCs) and its association with disease activity and achievement of remission in early RA patients.

Methods: A total of 60 patients (44 females; mean age 54.1 years) with early rheumatoid arthritis were studied. Total RNA was isolated from PBMCs collected from patients before and three months after the start of glucocorticoids and disease modifying antirheumatic drugs. The expression of miRNA-125b was determined by quantitative PCR. Small nucleolar RNA RNU44 was used for normalization. Relative expression was calculated as 2^{DCt}. Disease activity of RA patients was assessed according to the 28-Joint Count Disease Activity Score (DAS28), the Simplified Disease Activity Index (SDAI) and Clinical Disease Activity Index (CDAI).

Results: We found an inverse association between miRNA-125b expression and disease activity as assessed by DAS28 (r= -0.404; p= 0.001), SDAI (r= -0.334; p= 0.009) and CDAI (r= -0.263; p= 0.043) at baseline. The expression of miRNA-125b was significantly up-regulated three months after the start of treatment in all RA patients (p=0.005). The up-regulation of miRNA-125b after the three months of treatment was particularly observed in patients who achieved DAS28 defined remission compared to those who did not achieve the treatment target after 12 months. Age, sex, autoantibodies (RF-IgM, anti-CCP) and smoking did not affect miRNA-125b expression in PBMC.

Conclusion: The up-regulation of miRNA-125b in PMBCs following treatment initiation may represent potential biomarker predicting achievement of remission in early RA patients.

Acknowledgement: IGA project No NT 14498

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Disclosure: V. Hruskova, None; **R. Jandová**, None; **L. Vernerova**, None; **H. F. Mann**, None; **K. Prajzlerová**, None; **M. Filkova**, None; **K. Pavelka**, None; **J. Vencovsky**, None; **L. Senolt**, None.

Abstract Number: 542

Reduced Expression of Mir-204 in Early RA Promotes Inflammatory Pathways in Synovial Fibroblasts

Clare E Tange[1], Anna Engler[1], Christoph Kolling[2], Andrew Filer[3], Christopher Buckley[4], Beat A. Michel[1], Renate E. Gay[1], Steffen Gay[1] and Caroline Ospelt[1], [1]Center of Experimental Rheumatology, University Hospital Zurich, Zurich, Switzerland, [2]Upper Extremity Dept., Schulthess Clinic Zurich, Zurich, Switzerland, [3]University of Birmingham, Birmingham, United Kingdom, [4]University of Birmingham, Rheumatology Research Group, Birmingham, United Kingdom

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Background/Purpose: Synovial fibroblasts (SF) from the joints of RA patients display an activated and invasive phenotype. They produce a number of pro-inflammatory cytokines and proteolytic enzymes and in consequence play a crucial role in perpetuating inflammation and mediating local damage in RA. Several microRNA are known to be involved in the aggressive phenotype of RASF, therefore, we set out to identify microRNA which were differentially expressed in these cells at a very early stage of disease.

Methods: SF were obtained from patients with undifferentiated arthritis (symptom duration <3 months). Patients were classified as resolving arthritis or very early RA depending on whether they fulfilled the ACR criteria for classification within the subsequent 18 months. microRNA expression was measured by TaqMan low density array (TLDA). For functional experiments SF were isolated from RA patients undergoing joint replacement surgery. SF were stimulated with IL-1β (1 ng/ml), TNFα (10 ng/ml), TGFβ (10 ng/ml), BLP (300 ng/ml), poly I:C (10 µg/ml) or LPS (100 ng/ml) for 24h. For long term stimulations cells were cultured with TGFβ (10 ng/ml) for 72h, or TNFα (10 ng/ml) for 7 days. Endogenous miR-204 was down regulated using Lipofectamine transfection with specific miRNA inhibitors. Total RNA was isolated, and miR-204 expression quantified by Taqman qPCR. The concentrations of IL-6, IL-8, MMP1 and MMP3 were measured in cell culture supernatants by ELISA. Adhesion and proliferation of cells were all quantified using the xCELLigence system.

Results: TLDA analysis identified miR-204 as an interesting candidate which was down regulated in SF from very early RA patients. PCR in additional samples confirmed that miR-204 was significantly lower in SF derived from very early RA patients compared to those from patients with resolving arthritis ($p<0.05$) or healthy controls ($p<0.001$). miR-204 expression was also reduced in SF following stimulation with poly I:C (x-fold: 0.63 ± 0.04, $p<0.05$), and after prolonged exposure to TGFβ (x-fold: 0.58 ± 0.06, $p < 0.001$) or TNFα (x-fold: 0.64 ± 0.11, $p<0.05$). Compared to transfection with a control inhibitor, inhibition of miR-204 in SF resulted in a significant increase in the production of IL-6 (1332 ± 173.6 vs 2087 ± 274.5 pg/ml), IL-8 (78.26 ± 22.76 vs 212.4 ± 38.33 pg/ml), MMP1 (127.8 ± 21.47 vs 360.6 ± 92.94 pg/ml) and MMP3 (129.4 ± 62.29 vs 518.4 ± 78.6 pg/ml). We were also able to show that miR-204 inhibition results in decreased attachment and proliferation of SF.

Conclusion: The reduced miR-204 expression observed in SF from very early RA patients suggests that this microRNA is not altered as a consequence of chronic inflammation, but instead represents an early change in the development of RA. This novel finding, together with the increase in basal cytokine and MMP production observed following miR-204 inhibition, suggest an important functional role of this microRNA in regulating SF activation. We therefore hypothesize that miR-204 targets a master regulator of inflammatory pathways in SF and its down regulation in early RA contributes to the activated and aggressive phenotype observed in RASF.

Disclosure: C. E. Tange, EMDO foundation, Herzog-Egli foundation, 2; **A. Engler**, None; **C. Kolling**, None; **A. Filer**, None; **C. Buckley**, None; **B. A. Michel**, None; **R. E. Gay**, None; **S. Gay**, None; **C. Ospelt**, None.

Abstract Number: 543

The IL-20 Receptor Axis in Early Rheumatoid Arthritis: Novel Inflammation-Independent Links Between Autoantibody Positivity and Radiographic Progression

Tue Wenzel Kragstrup[1,2,3], Stinne Greisen[1], Morten Aagaard Nielsen[1], Chris Rhodes[2], Kristian Stengaard-Pedersen[3], Merete Lund Hetland[4],

Kim Hørslev-Petersen[5], Peter Junker[6], Mikkel Østergaard[7], Malene Hvid[1,8], Thomas Vorup-Jensen[1], William H. Robinson[2,9], Jeremy Sokolove[2,10] and Bent Deleuran[1,3,8], [1]Department of Biomedicine, Aarhus University, Aarhus, Denmark, [2]VA Palo Alto Healthcare System and Stanford University, Palo Alto, CA, [3]Department of Rheumatology, Aarhus University Hospital, Aarhus, Denmark, [4]DANBIO, Copenhagen Center for Arthritis Research, Center for Rheumatology and Spine Diseases, Rigshospitalet, Glostrup, Denmark, [5]Rheumatology, Rheumatology King Christian X's Hospital, Graasten, Denmark, [6]University of Southern Denmark, Odense, Denmark, [7]Copenhagen University Hospital Glostrup, Copenhagen, Denmark, [8]Department of Clinical Medicine, Aarhus University, Aarhus, Denmark, [9]Division of Immunology and Rheumatology, Stanford University School of Medicine, Stanford, CA, [10]Stanford University School of Medicine, Stanford, CA
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SESSION INFORMATION

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Session Type: ACR Poster Session A
Session Time: 9:00AM-11:00AM

Background/Purpose:

Rheumatoid arthritis (RA) is often characterized by the presence of rheumatoid factor (RF), anti-citrullinated protein antibodies (ACPAs) and bone erosions. Successful treatment can compromise the normal immune response, increasing the risk of infections. The interleukin 20 receptor (IL-20R) axis comprising IL-19, IL-20, and IL-24 ("the IL-20R cytokines") and their shared receptors activates tissue homeostasis processes but not the immune system (Figure 1A). Consequently, modulation of the IL-20R axis may not lead to immunosuppression, making it an interesting drug target. The objective of this study was to determine the role of the IL-20R axis in early RA with focus on associations of the three cytokines with clinical disease activity and prognosis.

Methods:

The IL-20R cytokines were measured in plasma samples from treatment naive early RA patients during 24 months treatment with methotrexate, adalimumab/placebo and intra-articular glucocorticoid injections (the OPERA trial) (n=152) and healthy controls (n=88). IL-20R1 and IL-22R expression was studied in paired peripheral blood and synovial fluid cells from RA patients (n=15) with at least one swollen joint (for obtaining synovial fluid) with flow cytometry and confocal microscopy. Heat aggregated human gamma globulins (HAGGs) and immune complexes containing citrullinated fibrinogen (cFb-ICs) were used to stimulate macrophages. Osteoclasts (OCs) derived from synovial fluid cells were used to assess the effect of the IL-20R cytokines.

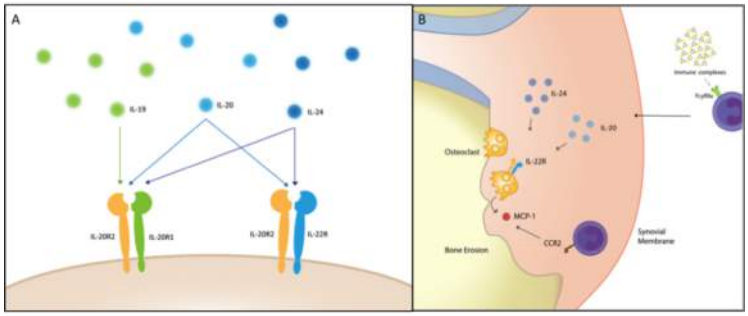
Results:

The plasma concentrations of IL-20 and IL-24 (but not IL-19) were increased in early RA patients compared with healthy controls (both $P<0.002$) and decreased after 6 months of treatment (both $P<0.0001$). The expression of IL-22R (but not IL-20R1) was increased on monocytes from RA synovial fluid compared with monocytes from both RA and healthy control peripheral blood. The plasma concentrations of IL-20 and IL-24 were increased in RF and ACPA positive compared with negative early RA patients (all $P<0.0001$). HAGGs and cFb-ICs stimulated the production of the IL-20R cytokines by myeloid cells. Increased baseline plasma concentrations of IL-20 and IL-24 were associated with Sharp-van der Heijde score progression after 24 months (SpearmanÕs rho=0.19 and 0.26, both $P<0.05$) in the early RA patients. The IL-22R was expressed by OC precursors and in multinucleated OCs and these cells were activated by IL-20 and IL-24.

Conclusion:

This study suggests that IL-20 and IL-24 link RA-associated autoantibodies with activation of OCs and radiographic progression via the IL-22R1 (Figure 1B). Modulation of this axis holds promise as feasible anti-erosive treatment modalities in seropositive RA.

Figure 1.



Abstract Number: 544

IL-6 May Have an Important Role in the Resistance to Anti-TNF Therapies of Human T-Lymphotropic Virus Type 1 (HTLV-1) Positive Rheumatoid Arthritis (RA) Patients; HTLV-1 Infected Cells Activate the Inflammatory Responses of RA Synovial Fibroblasts

Kunihiko Umekita[1], Shunichi Miyauchi[1], Kazuyoshi Kubo[1], Kazumi Umeki[1], Hajime Nomura[1], Mao Komura[1], Koushou Iwao[1], Ichiro Takajo[1], Yasuhiro Nagatomo[1], Toshihiko Hidaka[2] and Akihiko Okayama[1], [1]Department of Rheumatology, Infectious Diseases and Laboratory Medicine, University of Miyazaki, Miyazaki, Japan, [2]Kyushu multicenter rheumatoid arthritis ultrasound prospective observational cohort study group, Nagasaki, Japan

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Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose: We reported that human T-lymphotropic virus type 1 (HTLV-1) positive patients with rheumatoid arthritis (RA) had higher inflammation and greater resistance to anti-TNF treatment than HTLV-1 negative patients. The levels of plasma IL-6 and CCL20 in HTLV-1 positive RA patients was significantly higher than in HTLV-1 negative patients. The objectives of this present study are to investigate the efficacy and safety of anti-IL-6 receptor antibody, tocilizumab (TCZ) treatment to HTLV-1 positive RA who were who were not responsive to anti-TNF therapies. In addition, we investigated whether HTLV-I infected cells modulates the expression of cytokine, chemokine, and matrix metalloproteinase in RA synovial fibroblast (RASF) in vitro.

Methods: We identified 5 of 6 HTLV-1 positive RA patients, who were not responsive to anti-TNF therapies, were administered TCZ treatment as their secondary biologics in our biologics cohort study. Therapeutic response at 3 months after beginning of treatment with TCZ was evaluated using EULAR response criteria. We also analyzed the changing of C-reactive protein (CRP), erythrosedimentation rate (ESR), disease activity score in 28 joints (DAS28) and clinical disease activity score (CDAI). As secondary endpoints, discontinuation rate of TCZ treatment and safety, especially the development of adult T-cell leukemia (ATL), were evaluated over a one-year period. HTLV-1 infected (MT2 or Hut102) or non-infected (Jurkat) cell-lines were co-cultured with RASF for 48h. To avoid direct-interaction between these cells, we setup transwell co-culture system using inserts with 0.4um pore membrane. The levels of 25 cytokines in cell culture medium were measured using multiplex cytokine assay (Luminex, Millipore). The level of soluble IL-6 receptor (sIL-6R) in culture medium was measured using ELISA. The phosphorylation of NF-kB p65 in RASF co-cultured with HTLV-1 infected or non-infected cells were determined by immune blotting. The expression of IL-6, CCL20,

VEGF, and MMP1 mRNA in RASF was measured using real-time quantitative PCR.

Results: According to EULAR response criteria, the rate of good, moderate and no response after treatment with TCZ in HTLV-1 positive RA patients was 60, 40, and 0%, respectively. The rate of low disease activity was 60 %. The levels of CRP, ESR, DAS28, and CDAI were significantly decreased after treatment with TCZ. The efficacy of TCZ treatment sustained for at least one-year period. During the one-year observation period, no patients developed ATL. The protein levels of IL-6, CCL20, IFN-γ and sIL-6R in mono-culture medium of HTLV-1 infected cell lines was higher than in that of Jurkat cell. The phosphorylation of NF-kB p65 was increased in RASF co-cultured with HTLV-1 positive cells. The expression of IL-6, CCL20, VEGF and MMP1 mRNA increased in RASF co-cultured with HTLV-1 infected cells, but not with Jurkat cell.

Conclusion: TCZ improved response to therapy in HTLV-1 positive RA who were who were refractory to anti-TNF therapies. In vitro study showed that HTLV-1 infected cells induced the expression of IL-6, CCL20, VEGF and MMP in RASF. Taken together, these results suggested that IL-6 may play an important role in the pathogenesis of HTLV-1 positive RA patients.

Disclosure: K. Umekita, None; **S. Miyauchi**, None; **K. Kubo**, None; **K. Umeki**, None; **H. Nomura**, None; **M. Komura**, None; **K. Iwao**, None; **I. Takajo**, None; **Y. Nagatomo**, None; **T. Hidaka**, None; **A. Okayama**, None.

Abstract Number: 545

Baseline Serum Soluble Interleukin–2 Receptor Alpha (sIL–2Rα) Levels Increased as Intervals Decreased from Cohort Entry to Onset of Incident Rheumatoid Arthritis (pre–RA), not Observed in Matched Control (CN) Subjects

Alfonse T. Masi[1], Azeem A. Rehman[1], Jean C. Aldag[1] and Huaping Wang[2], [1]Medicine, University of Illinois College of Medicine at Peoria, Peoria, IL, [2]Pediatrics, University of Illinois College of Medicine at Peoria, Peoria, IL

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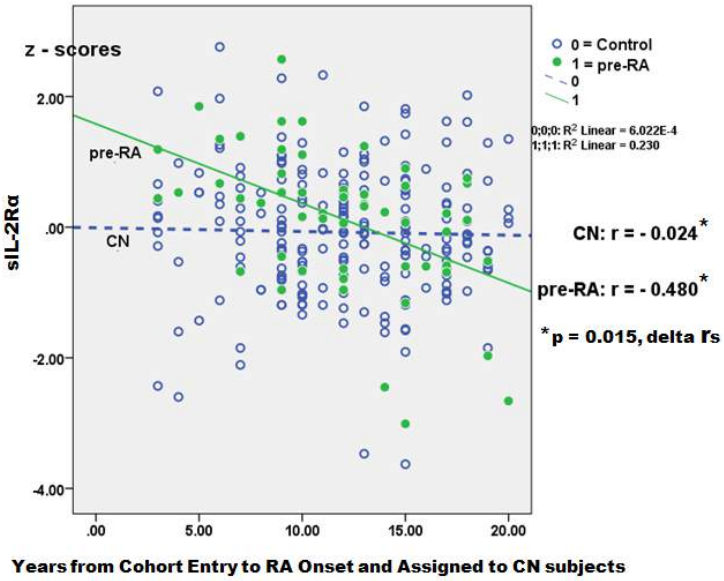
Session Time: 9:00AM-11:00AM

Background/Purpose: Baseline sIL-2Rα levels predicted total mortality in both pre-RA and matched CN subjects, in a preceding prospective cohort study (A&R 2010; 62:S19). Now, the trend of serum sIL-2Rα levels is analyzed over a 20-year interval between cohort entry to incident RA onset, in pre-RA and matched CN subjects.

Methods: The community-based cohort (N = 21,061 adults) was enrolled in 1974, yielding 54 new onset RA cases, 3 to 20 (mean 12) years after entry (1977 – 1994). Cohort CN subjects (n = 216) were matched on 1974 entry criteria (4 CN**:** 1 pre-RA). Stored (-70ºC) sera were assayed (ELISA) "blindly", using R & D Systems high sensitivity kits for: sIL-2Rα; sTNF-R1; 3 inflammatory cytokines; and 2 acute phase protein levels. Natural log and z-score transformations were performed on all continuous baseline assay variables. Matched CN subjects were assigned the intervals to RA onset, within 54 separate sets. Partial (age-adjusted) correlations of intervals (X-axis) and baseline serum biomarker levels (Y-axis) were compared in study groups. Independent predictors of baseline sIL-2Rα levels (interval from cohort entry to RA onset and other variables of interest) were identified by multiple regression (MR) models.

Results: Baseline sIL-2Rα and sTNF-R1 levels correlated strongly in total 270 subjects ($r = 0.464$, $p < 0.001$) and in each study group (54 pre-RA, $r = 0.473$, $p < 0.001$; 216 CN, $r = 0.470$, $p < 0.001$). In pre-RA, sIL-2Rα levels increased significantly with decreased interval from 1974 cohort entry to RA onset ($r = -0.480$, $p < 0.001$), not found in CN ($r = -0.025$, $p = 0.744$), the difference being significant ($p = 0.001$) (Fig). In a MR model of pre-RA, baseline sIL-2Rα levels were significantly predicted by (1) interval (yrs) from cohort entry to RA onset (beta = -0.372, $p = 0.002$) and (2) sTNF-R1 levels (beta = 0.376, $p = 0.002$), but not by: entry age; sex; cigarette smoking; or 2013 survival status. In 216 CN, sIL-2Rα level was predicted only by sTNF-R1 (beta = 0.434, $p < 0.001$), not by the pre-RA interval (beta = -0.011, $p = 0.862$) or other variables in the model (Table).



Predictors of Baseline sIL-2Rα Levels in pre-RA vs CN

Independent Variables in Multiple Regression	pre-RA (n = 54)		Control (n = 216)	
	beta	p	beta	p
Cohort Entry to RA Onset (yrs) *	- 0.372	0.002	- 0.011	0.862
Baseline sTNF-R1 Level	0.376	0.002	0.434	< 0.001
Age at Cohort Entry	- 0.121	0.345	- 0.031	0.667
Sex	- 0.215	0.072	0.091	0.153
Cigarette Smoking (7-scale)	0.082	0.486	0.116	0.077
Surival Outcome in 2013	- 0.004	0.977	0.073	0.322

*p = 0.015, difference in beta correlations of pre-RA (-0.372) vs CN (-0.011)

Conclusion: The novel temporal trend of sIL-2Rα levels may reflect multi-year immunological up-regulation before clinical onset of RA and deserves further study for confirmation.

Disclosure: A. T. Masi, None; **A. A. Rehman**, None; **J. C. Aldag**, None; **H. Wang**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/baseline-serum-soluble-interleukin2-receptor-alpha-sil2r-levels-increased-as-intervals-decreased-from-cohort-entry-to-onset-of-incident-rheumatoid-arthritis-prera-not

Abstract Number: 546

Adipokines and Insulin-like Growth Factor 1 As Predictors of Clinical and Radiographic Outcomes in Early Rheumatoid Arthritis

Adrian Levitsky[1], Kerstin Brismar[2], Saedis Saevarsdottir[3], Karen Hambardzumyan[1], Anna Andersson[1] and Ronald F. van Vollenhoven[1], [1]Department of Medicine, Unit for Clinical Therapy Research, Inflammatory Diseases (ClinTRID), The Karolinska Institute, Stockholm, Sweden, [2]Department of Molecular Medicine and Surgery, Unit of Growth and Metabolism, The Karolinska Institute, Stockholm, Sweden, [3]Department of Medicine, Rheumatology Unit, The Karolinska Institute and Karolinska University Hospital, Stockholm, Sweden

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Session Time: 9:00AM-11:00AM

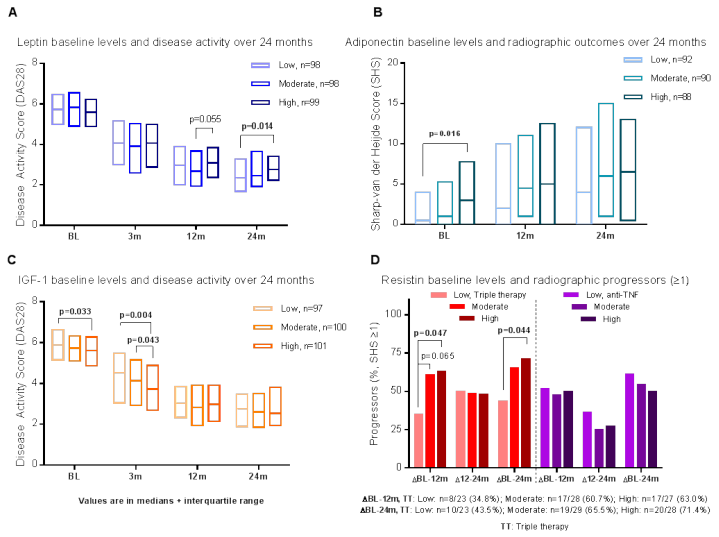
Background/Purpose: Adipokines are cytokines/hormones primarily synthesized in white adipose tissue. In rheumatoid arthritis (RA), some

adipokines have been associated with worse outcomes (1-3). The aim of this study was to determine whether adipokine or insulin-like growth factor 1 (IGF-1) serum measurement at baseline (BL) could predict future disease activity and radiographic outcomes in patients with early RA.

Methods: Serum levels of adiponectin, leptin, IGF-1, and resistin at RA diagnosis were analyzed in 330 patients enrolled in the Swedish pharmacotherapy (SWEFOT) trial (207 with Body Mass Index (BMI)). All patients received methotrexate (MTX) for 3 months. Thereafter, responders (DAS28≤3.2) remained on MTX, while non-responders were randomized to triple therapy (MTX+sulfasalazine+hydroxychloroquine) or anti-TNF add-on (MTX+infliximab). The biomarker levels were divided into tertiles for further analyses, after adjustment for known level differences to due sex (adiponectin and leptin) and age (IGF-1 SD score). Disease activity (DAS28) and radiographic damage (Sharp-van der Heijde Score, SHS) were evaluated over 24 months.

Results: Adiponectin and leptin levels – but not IGF-1 or resistin – were inversely and directly proportional, respectively, to BMI, which was associated with worse DAS28 over 24 months. Disease activity did not differ between tertile groups of leptin at BL (diagnosis), but patients with high BL leptin had significantly higher DAS28 at 24 months (Figure A). On the other hand, among initial MTX responders, high/moderate (n=54) vs. low BL leptin (n=27) was associated with less rapid radiographic progression from BL-12 months (ΔSHS≥5, 7.4% vs. 29.6%, p=0.036). Disease activity did not differ significantly between adiponectin groups, however, they were directly proportional to BL SHS with a numerical trend over time (Figure B).

Patients with low BL IGF-1 had higher DAS28 up until 3 months, but it was not significant thereafter (Figure C). In addition, more radiographic progressors were observed between those with low vs. high IGF-1 among initial MTX responders (BL-12 months, n=19 vs. 31, respectively: ΔSHS≥1, 68.4% vs. 32.3%, p=0.013; BL-24 months, n=21 vs. 32: 81.0% vs. 50.0%, p=0.023). For resistin, there were more progressors among those with high BL levels among triple therapy-treated patients (Figure D), which was not observed among the anti-TNF or MTX responder groups.



Conclusion: Differences in certain adipokines and IGF-1 were associated with clinical and radiographic outcomes within specific treatment groups. Thus, they may be useful predictors and may give insight into pathogenic mechanisms influencing RA outcomes such as high BMI and disease activity.

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Disclosure: A. Levitsky, None; **K. Brismar**, None; **S. Saevarsdottir**, None; **K. Hambardzumyan**, None; **A. Andersson**, None; **R. F. van Vollenhoven**, AbbVie, BMS, GSK, Pfizer, Roche, UCB, 2,AbbVie, Biotest, BMS, Crescendo, GSK, Janssen, Lilly, Merck, Pfizer, Roche, UCB, Vertex, 5.

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Abstract Number: 547

Abatacept Does Not Improve Subclinical Atherosclerosis Despite Good Response in Rheumatoid Arthritis: A Cohort Study

Kensuke Kume[1], Kanzo Amano[1,2], Susumu Yamada[1], Toshikatsu Kanazawa[3], Kazuhiko Hatta[4], Kuniki Amano[5] and Noriko Kuwaba[6], [1]Rheumatology, Hiroshima Clinic, Hiroshima, Japan, [2]rheumatology., hiroshima clinic, Hiroshima, Japan, [3]rheumatology, hiroshima clinic, hiroshima, Japan, [4]Rheumatology, Hatta Clinic, Kure, Japan, [5]Rheumatology, Sky Clinic, Hiroshima, Japan, [6]Medical Research, Sanki Clinical Link, Hiroshima, Japan

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SESSION INFORMATION

Session Date: Sunday, November 8, 2015

Session Title: Rheumatoid Arthritis - Small Molecules, Biologics and Gene Therapy Poster I

Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose: Abatacept (ABT) is very effective in treating rheumatoid arthritis(RA)[1]. Patients with RA have an increased risk of cardiovascular disease (CVD), and rheumatologists need to develop primary prevention strategies for CVD in RA patients[2, 3]. For example, some biologics used to treat RA also reduce subclinical atherosclerosis and may improve morbidity in CVD[4, 5]. There is no evidence that ABT effect subclinical atherosclerosis. To examine the effect on subclinical atherosclerosis in disease modified anti-rheumatic-drugs (DMARDs) resistant RA patients in a cohort study design.

Methods: 75 RA patients with moderate to severe active disease despite DMARDs treatment (disease activity score: DAS28>3.2) were received ABT (125mg every week subcutaneously). Subclinical atherosclerosis was assessed with cardio-ankle vascular index (CAVI) and augmentation index corrected for a heart rate of 75 beats per minute (AIx@75) at baseline and 24 weeks follow-up. Clinical data were collected at regular visits. CAVI is combined pulse wave velocity (PWV) and **flow mediated dilation**, and CAVI measures arterial wall stiffness independent of blood pressure and it is superior to brachial ankle PWV as an index of atherosclerosis. No new all treatments (stating, low lipids drug, and etc.) were allowed.

Results: 65 patients completed this study. There were no changes in CAVI(12.68 ± 1.76 and 12.71± 2.11; p = 0.96) and AIx@75(32.45 ± 9.8, 33.21 ± 12.6; p = 0.87) from baseline to 24 weeks follow up.DAS 28-ESR score improved significantly from baseline to 24 weeks(5.87±2.15, 2.57±1.32: p=0.01). There were no There was no change in systolic and diastolic blood pressure Total cholesterol/LDL cholesterol ratio, atherogenic index and triglycerides. Changes of CAVI and AIx@75 were not correlated with changes of disease activity from baseline to 24 weeks follow up. (CAVI: p=0.75, AIx@75: p=0.81).No patients suffered from new CV disease.

Conclusion: These findings suggest that ABT did not improve subclinical atherosclerosis after 24 weeks follow up despite good control of disease activity in rheumatoid arthritis.

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2.van Halm VP, et al. Rheumatoid arthritis versus diabetes as a risk factor for cardiovascular disease: a cross-sectional study, the CARRE Investigation. Ann Rheum Dis 2009; 68:1395–400.

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Abstract Number: 548

Comparison of Dose Escalation and Co-Therapy Intensification Between Patients with Rheumatoid Arthritis Initiating Biologic Treatment with Etanercept, Adalimumab and Infliximab

J Carter Thorne[1], Gilles Boire[2], Andrew Chow[3], Kirsten Garces[4], Fang Liu[5], Melanie Poulin-Costello[6], Valery Walker[5] and Boulos Haraoui[7], [1]Southlake Regional Health Centre, Newmarket, ON, Canada, [2]Department of Medicine/Division of Rheumatology, Université de Sherbrooke, Sherbrooke, QC, Canada, [3]Credit Valley Rheumatology, Mississauga, ON, Canada, [4]Amgen Canada Inc, Mississauga, ON, Canada, [5]Optum, Burlington, ON, Canada, [6]Amgen Canada Inc., Mississauga, ON, Canada, [7]Institut de rhumatologie de Montréal, Montreal, QC, Canada
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Session Time: 9:00AM-11:00AM

Background/Purpose: The individual response to anti-TNFs etanercept (ETA), infliximab (INF) and adalimumab (ADA) in rheumatoid arthritis (RA) may vary. Options for managing inadequate response include dose escalation of the anti-TNF agent and/or intensification of co-therapy, which can lead to higher drug costs, patient inconvenience and greater risk of adverse events. The Canadian Drug Utilization in Rheumatoid Arthritis (CADURA) study compared dose escalation, intensification of DMARDS and steroids, and switches to another biologic between patients with RA initiating ETA, ADA or INF.

Methods: This was a retrospective chart review of RA patients treated in 11 clinical practices across Canada. Patients were 18 years or older who initiated an anti-TNF between January 1, 2006 and December 31, 2012, with no prior use of biologic DMARD. Outcomes were assessed over 12 and 18 months. For the 12- month analysis, patients were required to have ≥3 physician visits following initiation and ≥1 visit during months 9-15; the 18 month analysis also required ≥ 1 visit during months 15-21. Dose-escalation of anti-TNF was defined as the first occurrence of any upward adjustment in dose or dosing frequency of the anti-TNF from the label indication: ETA, 25 mg twice weekly or 50 mg once weekly; ADA, 40 mg once every other week; INF, 3mg/kg every 8 weeks after the 3rd infusion. Additional outcomes were: 1) anti-TNF dose-escalation and/or DMARD intensification and 2) anti-TNF dose-escalation and/or DMARD and/or steroid intensification. Intensification included any increase in dose or dosing frequency, any addition, any switch from oral to subcutaneous injection (DMARD), or any intramuscular or intra-articular injections (steroid) 3 months after initiation of the anti-TNF.

Results: The 12-month analysis included 314 patients (mean age 56.3 years [range: 21-90 yrs]; 77% female; mean RA duration 9.0 yrs [range: 2-26 yrs]). Among patients initiating ADA, 83% had concomitant DMARD vs 72% of patients initiating ETA and 75% initiating INF. There were 217 patients in the 18-month analysis. No dose escalation occurred with ETN over 12 and 18 months, vs 38% and 32% for INF (p<0.001) and 2% and 2% for ADA (p=0.199, p=0.218). Over 18 months, dose escalation and/or DMARD and/or steroid intensification was less frequent among ETA (16%) vs INF (44%, p=0.005) and ADA (34%, p=0.004). By 18 months, 22% of patients initiating ADA had switched to another biologic compared with 6% of ETN patients (p=0.001).

Conclusion: Physicians more frequently used dose escalation when treating with INF, and DMARD and/or steroid intensification when treating with ADA. Patients treated with ETN had no dose escalation, were less likely to have DMARD and/or steroid intensification than patients initiating INF or ADA over 12 and 18 month, and were less likely to switch to another biologic over 18 months than patients initiating ADA.

Table. Anti-TNF Dose Escalation, DMARD or Steroid Intensification, Switches and Discontinuations over 12 Months and 18 Months

	12 months after anti-TNF initiation					18 months after anti-TNF initiation				
	ETN N=156	INF N=32	ADA N=126	*P* ETN vs INF	*P* ETN vs ADA	ETN N=102	INF N=25	ADA N=90	*P* ETN vs INF	*P* ETN vs ADA
	n (%)	n (%)	n (%)			n (%)	n (%)	n (%)		
Anti-TNF dose escalation	0 (0%)	12 (38%)	2 (2%)	**<0.001**	0.199	0 (0%)	8 (32%)	2 (2%)	**<0.001**	0.218
Anti-TNF dose escalation and/or DMARD intensification	17 (11%)	13 (41%)	18 (14%)	**<0.001**	0.468	11 (11%)	10 (40%)	17 (19%)	**0.001**	0.151
Anti-TNF dose escalation and/or DMARD and/or steroid intensification	25 (16%)	15 (47%)	35 (28%)	**<0.001**	**0.019**	16 (16%)	11 (44%)	31 (34%)	**0.005**	**0.004**
Discontinue anti-TNF and switch to another biologic	7 (4%)	1 (3%)	12 (10%)	1.000	0.101	6 (6%)	1 (4%)	20 (22%)	1.000	**0.001**
Discontinue anti-TNF but no switch to another biologic	6 (4%)	0 (0%)	6 (5%)	0.592	0.772	2 (2%)	0 (0%)	6 (7%)	1.000	0.150

Disclosure: J. C. Thorne, Amgen, Canada, 5; **G. Boire**, None; **A. Chow**, None; **K. Garces**, Amgen, 3; **F. Liu**, Amgen, 5; **M. Poulin-Costello**, Amgen, 3; **V. Walker**, Amgen, 5; **B. Haraoui**, Amgen, 2,Amgen, 9.

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Abstract Number: 549

Calprotectin (MRP8/MRP14), a Major Leukocyte Protein, Is Highly Associated to Ultrasound Detected Synovitis and Is Responsive to Biologic Treatment

Hilde Berner Hammer[1], Hilde Haugedal Nordal[2,3] and Tore K. Kvien[4], [1]Rheumatology, Diakonhjemmet Hospital, Oslo, Norway, [2]Dept of Rheumatology, Haukeland Univerity Hospital, Bergen, Norway, [3]Department of Clinical Science, University of Bergen, Broegelmann Research Laboratory, Bergen, Norway, [4]Dept. of Rheumatology, Diakonhjemmet Hospital, Oslo, Norway

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Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose:

Calprotectin (MRP8/MRP14, S100A8/A9) is a protein abundant in cytosol of granulocytes and monocytes/macrophages and released during cell activation. It reflects clinical disease activity in patients with rheumatoid arthritis (RA). Ultrasonography (US) is sensitive for detecting synovitis (grey scale, GS) and vascularization (power Doppler, PD). There is only published one small study showing associations between calprotectin and US in RA patients.

To study the associations between calprotectin and a comprehensive US examination as well as clinical/laboratory variables and to explore the responsiveness of calprotectin to biologics in a large cohort of RA patients.

Methods:

A total of 141 patients with RA (mean (SD) age of 50.3 (13.3) years and disease duration 9.9 (8.6) years, 81% women, 77% anti-CCP positive) starting different biologic medication (including 66,7% anti-TNF) were examined at baseline and after 1, 2, 3, 6 and 12 months for calprotectin, CRP, ESR, clinical variables as well as US of 36 joints and 4 tendons (wrist (incl. RU, IC, RU), MCP 1-5, PIP 2-3, elbow, knee, ankle, MTP 1-5, ECU and tib.post. tendons bilaterally). Both GS and PD pathology were scored semi-quantitatively 0-3 by one sonographer (HBH) (Siemens Antares Excellence version, 5-13MHz probe, PRF 391Hz, no updates during the study). At each examination EDTA-plasma was frozen at -80 degrees, and all calprotectin concentrations were analyzed at the same time (normal levels ≤ 900 µg/L). Changes from baseline were assessed by Wilcoxon T-test, differences between groups by Mann-Whitney and correlations by Spearman's rank.

Results:

All variables decreased significantly from baseline (table 1) ($p<0.001$). Calprotectin had higher correlations with CRP during the study (range r=0.46-0.76), than with ESR (range r= 0.31-0.56), while the correlations between ESR and CRP was 0.47-0.69 (all correlations $p<0.001$). Prednisolone users at baseline (55%, median 7.5 mg) had higher levels of calprotectin ($p=0.006$), sum score GS ($p=0.02$) and number of swollen joints ($p=0.02$), while no differences were found between the groups for ESR, CRP or the other variables. Calprotectin was highly associated with US scores during the study, with higher correlations than ESR or CRP (table 2).

	Baseline	1 month	2 months	3 months	6 months	12 months
Calprotectin µg/L	1149 (698-1949)	739 (501-1223)	659 (436-1105)	673 (443-1122)	653 (409-982)	637 (453-954)
ESR mm/h	22 (11-35)	14 (7-26)	14 (8-28)	16 (7-24)	14 (7-21)	14 (7-21)
CRP mg/L	6 (2-12)	2 (1-7)	2 (1-5)	2 (1-5)	1 (1-5)	2 (1-4)
GSUS sum score	27 (17-43)	24 (15-37)	23 (14-37)	21 (13-32)	18 (12-27)	17 (11-25)
PDUS sum score	11 (4-24)	9 (3-17)	6 (3-17)	7 (2-14)	5 (1-11)	4 (1-8)
Assessor's global VAS (study nurse)	27 (18-38)	20 (10-30)	17 (11-26)	15 (10-25)	13 (8-20)	13 (8-20)
DAS28	4.4 (3.1-5.4)	3.6 (2.7-4.7)	3.2 (2.6-4.4)	3.2 (2.3-4.2)	2.9 (2.3-3.7)	2.8 (2.1-3.9)
Number of swollen joints (of 32)	6 (3-11)	4 (2-9)	4 (2-7)	3 (1-7)	2 (0-5)	1 (0-4)
Number of tender joints (of32)	4 (2-11)	4 (1-9)	3 (0-7)	3 (0-7)	1 (0-4)	1 (0-5)
Patient's global VAS	46 (20-67)	25 (10-46)	22 (8-36)	19 (5-37)	16 (5-33)	19 (6-33)

	Sum score Grey scale 36 joints and 4 tendons						**Sum score power Doppler 36 joints and 4 tendons**					
	Baseline	1 month	2 months	3 months	6 months	12 months	Baseline	1 month	2 months	3 months	6 months	12 months
Calprotectin	0.59**	0.51**	0.50**	0.37**	0.48**	0.25*	0.62**	0.53**	0.53**	0.46**	0.47**	0.31**
ESR	0.19*	0.04	0.06	0.01	0.19*	0.01	0.30**	0.14	0.15	0.12	0.21*	0.15
CRP	0.41**	0.21*	0.30**	0.18*	0.33**	0.20*	0.47**	0.23*	0.33**	0.26*	0.35**	0.30**

Conclusion:

In this first large study exploring calprotectin and US, calprotectin was found to be highly associated with both sum GS and PD scores. In addition, calprotectin was not suppressed by use of prednisolone like CRP/ESR and it was highly responsive to biologic medication. These findings support the use of calprotectin as an inflammatory marker in RA patients.

Disclosure: H. B. Hammer, None; **H. H. Nordal**, None; **T. K. Kvien**, None.

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Abstract Number: 550

Can Anti-TNF-Induced Autoantibody Conversion be Reversed By Switching to Abatacept Therapy in Patients with RA on Background MTX?

Maya H. Buch[1], A Johnsen[2], DA Wong[2] and M Schiff[3], [1]University of Leeds and Leeds Teaching Hospitals NHS Trust, Leeds, United Kingdom, [2]Bristol-Myers Squibb, Princeton, NJ, [3]University of Colorado, Denver, CO

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Background/Purpose: Anti-TNF therapy for RA is associated with antinuclear (ANAs) and anti-double-stranded DNA (anti-dsDNA) autoantibodies.[1,2] The effect of biologics on autoantibody-positive patients is unknown. We explored ANA and anti-dsDNA antibody development during abatacept (ABA) and anti-TNF treatment (ATTEST/AMPLE trials) and effects of switching to ABA in patients with ANA/anti-dsDNA (ATTEST). **Methods:** All patients had active RA, were biologic naïve and MTX inadequate responders. ATTEST: patients were randomized to IV ABA (～10mg/kg q4w), infliximab (IFX; 3mg/kg q8w) or placebo, on background MTX. At Month 6, placebo-treated patients started ABA (blinding maintained); ABA- and IFX-treated patients continued treatment. Patients completing the 1-year DB period were eligible to receive ABA (open-label long-term extension [OLE]). AMPLE (2-year head-to-head trial): patients were randomized to SC ABA (125mg weekly) or SC adalimumab (ADA; 40mg biweekly), on background MTX. Serum ANA and anti-dsDNA were measured at baseline, Month 6, Year 1 and 2 in ATTEST, and at baseline, Year 1 and 2 in AMPLE.

Results: In the ATTEST DB period, 156 patients received IV ABA and 165 received IFX; 132 and 136 patients received IV ABA in the OLE, respectively. In AMPLE, 318 patients received SC ABA and 328 received ADA. At baseline in ATTEST, 69 patients (32 IV ABA/37 IFX) were ANA+ and 26 (11 IV ABA/15 IFX) were anti-dsDNA+; AMPLE: 166 were ANA+ (72 SC ABA/94 ADA) and 6 anti-dsDNA+ (1 SC ABA/5 ADA). In both studies, a higher percentage of patients seroconverted (negative–positive, baseline–Year 1) with anti-TNFs versus ABA (Table); this difference continued during AMPLE Year 2. In ATTEST, 48.5% (ANA) and 48.3% (anti-dsDNA) of IFX-treated patients who entered the OLE seroconverted (negative–positive, baseline–Year 1), falling to 22.4% and 13.3%, respectively, at Year 2 after switching to ABA. The percentage of patients who seroreverted (baseline positive–negative) increased from 12.1% to 20.6% on switching from IFX to ABA (Table).

			Seropositive (baseline negative to post-baseline positive)		Seronegative (baseline positive to post-baseline negative)	
ATTEST			**IV ABA + MTX**	**IFX + MTX**	**IV ABA + MTX**	**IFX + MTX**
ANA	DB period*	Month 6	1.7 (2/115)	32.2 (38/118)	37.5 (12/32)	22.2 (8/36)
		Year 1	6.5 (7/107)	47.7 (51/107)	46.7 (14/30)	11.4 (4/35)
	OLE†		**ABA-to-ABA**	**IFX-to-ABA**	**ABA-to-ABA**	**IFX-to-ABA**
		Year 1 (baseline)	6.1 (6/98)	**48.5 (48/99)‡**	48.0 (12/25)	**12.1 (4/33)‡**
		Year 2	14.6 (14/96)	**22.4 (22/98)‡**	40.7 (11/27)	**20.6 (7/34)‡**
Anti-dsDNA	DB period*	Month 6	0.8 (1/128)	38.6 (51/132)	20.0 (2/10)	21.4 (3/14)
		Year 1	2.4 (3/127)	47.7 (61/128)	25.0 (2/8)	7.1 (1/14)
	OLE†		**ABA-to-ABA**	**IFX-to-ABA**	**ABA-to-ABA**	**IFX-to-ABA**
		Year 1 (baseline)	2.5 (3/118)	**48.3 (57/118)‡**	16.7 (1/6)	**7.1 (1/14)‡**
		Year 2	2.6 (3/114)	**13.3 (15/113)‡**	37.5 (3/8)	**33.3 (5/15)‡**
AMPLE			**SC ABA + MTX**	**ADA + MTX**	**SC ABA + MTX**	**ADA + MTX**
ANA		Year 1	5.2 (12/229)	13.3 (28/210)	31.9 (23/72)	18.1 (17/94)
		Year 2	6.3 (12/190)	14.7 (24/163)	45.0 (27/60)	18.5 (15/81)
Anti-dsDNA		Year 1	0.3 (1/299)	9.9 (29/293)	100.0 (1/1)	60.0 (3/5)
		Year 2	0 (0/248)	12.2 (29/237)	100.0 (1/1)	75.0 (3/4)

Data are % (n/N). *ITT population; †only pts who entered the OLE; ‡pts switched to IV ABA + MTX; ANA=antinuclear antibodies; Anti-dsDNA= anti-double-stranded DNA; DB=double blind; OLE=open-label long-term extension

Conclusion: In ATTEST, switching from infliximab to abatacept seemed to reverse autoantibody induction observed with anti-TNF treatment. In both trials, anti-TNF therapy was associated with greater autoantibody induction than abatacept. These data imply an effect of T-cell co-stimulation blockade on B-cell function and autoantibody production.[3]

1. Charles PJ, et al. *Arthritis Rheum* 2000;**43**:2383–90.

2. Eriksson C, et al. *Ann Rheum Dis* 2005;**64**:403–7.

3. This abstract was first presented at the EULAR Congress, 10–13 June 2015, Rome, Italy (AB0469) and published in the corresponding supplement of *Ann Rheum Dis*.

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Abstract Number: 551

Baseline Autoantibodies Preferentially Impact Abatacept Efficacy in Patients with RA Who Are Biologic Naïve: 6-Month Results from a Real-World, International, Prospective Study

R Alten[1], HG Nüßlein[2], M Galeazzi[3], H-M Lorenz[4], X Mariette[5], A Cantagrel[6], M Chartier[7], G Desachy[8], C Poncet[9], C Rauch[10] and M Le Bars[11], [1]Schlosspark-Klinik University Medicine, Berlin, Germany, [2]University Erlangen, Nürnberg, Germany, [3]University of Siena, Siena, Italy, [4]University Hospital, Heidelberg, Germany, [5]Université Paris-Sud, Paris, France, [6]Purpan Hospital, Toulouse, France, [7]Chiltern International, Neuilly, France, [8]Excelya, Boulogne-Billancourt, France, [9]Docs International, Nanterre, France, [10]Bristol-Myers Squibb, Munich, Germany, [11]Bristol-Myers Squibb, Rueil-Malmaison, France

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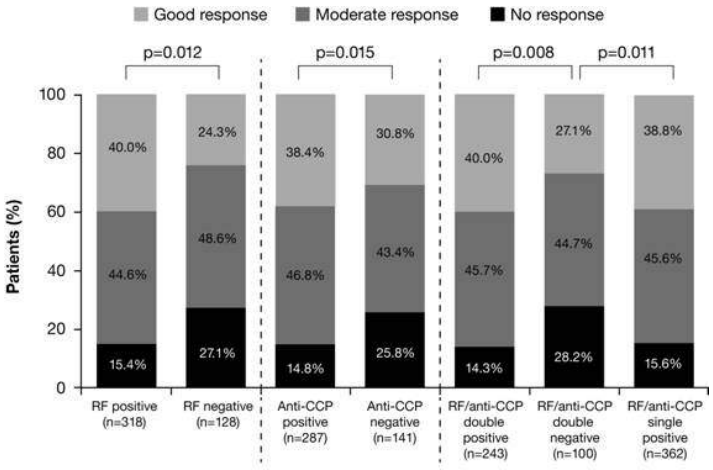
Background/Purpose: In a recent meta-analysis, neither rheumatoid factor (RF) nor anti-cyclic citrullinated peptide (anti-CCP) antibody status were associated with clinical response to treatment with anti-TNF agents.[1] In contrast, anti-CCP positivity may be associated with increased abatacept efficacy in patients (pts) with prior biologic failure[2,3] and in biologic-naïve pts.[4] In this analysis, the efficacy of abatacept after 6 months' follow-up in biologic-naïve pts enrolled in the ACTION study was compared in RF/anti-CCP-positive versus -negative pts. **Methods:** ACTION is a 2-year, international, multicenter, prospective, observational study evaluating retention and effectiveness of IV abatacept in pts with RA. Baseline characteristics and clinical outcomes were evaluated at 6 months and compared for anti-CCP/RF-positive and -negative pts who were biologic naïve using analysis of variance on ranks for quantitative variables and Fisher exact tests for qualitative variables. EULAR response was based on DAS28 (ESR or CRP) and derived from individual core components, as were mean CDAI and Boolean remission. **Results:** In 672 biologic-naïve pts, RF status was reported in 577 (86%) pts (412 [71%] positive) and anti-CCP antibody status in 552 (82%) pts (364 [66%] positive); 308/511 (60%) pts were double positive and 127/511 (25%) pts were double negative. Clinical outcomes at 6 months were more beneficial for pts who were RF or anti-CCP positive versus negative, including EULAR good or moderate response versus no response (Figure); mean (95% CI) CDAI (calculated) (RF: 10.8 [9.8, 11.8] vs 15.3 [13.4, 17.2]; p<0.001; anti-CCP: 10.9 [9.8, 12.0] vs 14.3 [12.4, 16.2]; p=0.002) and Boolean remission (RF: 13.3% vs 4.0%; p=0.008; anti-CCP: 12.5% vs 6.3%; p=0.096). Similarly, significant differences in clinical outcomes were observed for pts who were RF/anti-CCP single positive or double positive versus double negative, respectively, including EULAR good or moderate response versus no response (Figure); mean (95% CI) CDAI (calculated) (11.1 [10.2, 12.1] and 10.5 [9.3, 11.6] vs 14.5 [12.3, 16.7]; p=0.003 and p=0.001, respectively) and Boolean remission (12.3% and 13.8% vs 3.8%; p=0.025 and



P value for likelihood of a good/moderate EULAR response versus no response based on DAS28 (ESR or CRP)

p=0.013, respectively). **Conclusion:** These are the first prospective real-world data showing superior efficacy of abatacept in biologic-naïve pts who are RF and/or anti-CCP positive versus negative, even when using stringent remission criteria. The association between autoantibody status and clinical outcomes with abatacept may be linked to the mechanism of action. 1. Lv Q, et al. *PLoS One* 2014;**9**:e89442. 2. Gottenberg JE, et al. *Ann Rheum Dis* 2012;**71**:1815–9. 3. Fujii T, et al. *Arthritis Rheum* 2013;**65**(Suppl.10):465.

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Abstract Number: 552

The Relationship Between Efficacy and Toxicity in Patients with Rheumatoid Arthritis Receiving Methotrexate in Combination with Adalimumab

Gerd Burmester[1], Gurjit S. Kaeley[2], Arthur Kavanaugh[3], Cem Gabay[4], Daryl MacCarter[5], Peter Nash[6], Tsutomu Takeuchi[7], Anabela Cardoso[8], Shufang Liu[9], Hartmut Kupper[10] and Jasmina Kalabic[11], [1]Department of Rheumatology and Clinical Immunology, Charité - Universitätsmedizin Berlin, Berlin, Germany, [2]University of Florida, Jacksonville, FL, [3]University of California, San Diego School of Medicine, LaJolla, CA, [4]Rheumatology, Geneva University Hospital, Geneva, Switzerland, [5]Coeur d'Alene Arthritis Clinic, Coeur d'Alene, ID, [6]Department of Medicine, University of Queensland, Brisbane, Australia, [7]Keio University School of Medicine, Tokyo, Japan, [8]Torre Oriente, AbbVie, Lisboa, Portugal, [9]Immunology Development, AbbVie, North Chicago, IL, [10]AbbVie Deutschland GmbH & Co. KG, Ludwigshafen, Germany, [11]AbbVie, North Chicago, IL

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Background/Purpose: Combination treatment of rheumatoid arthritis (RA) with methotrexate (MTX)+adalimumab (ADA) has been shown to be more effective than ADA monotherapy. However, MTX is associated with known toxicity. Here we assessed the relationship between MTX-related toxicity and achieved efficacy of ADA+MTX treatment.

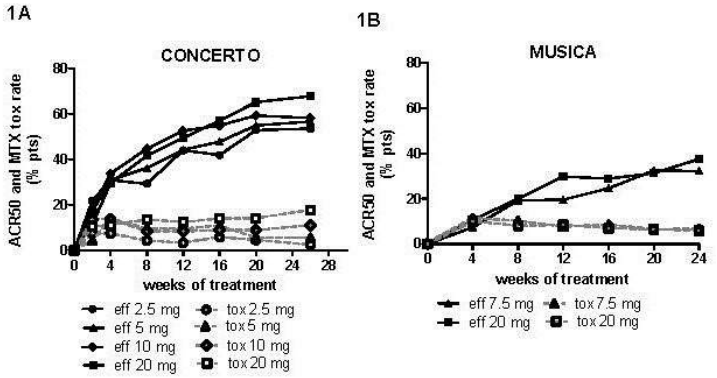
Methods: Data were from 2 randomized controlled trials. In CONCERTO[1], early RA patients (pts) initiated ADA + 2.5, 5, 10 or 20 mg/week (wk) MTX for 26 wks. In MUSICA[2], pts with moderate-severe RA and an inadequate response to MTX initiated ADA + 7.5 or 20 mg/wk MTX for 24 wks. Efficacy was assessed by ACR50. MTX toxicity was assessed by collecting information from pts at each visit on 18 pre-specified MTX- related adverse events (AE) reported in the MTX product label: abnormal hair loss or sweating, chronic dry cough, conjunctivitis,

dizziness, excessive fatigue/malaise, fever and/or chills, infection, nausea and/or vomiting, oral ulcers, skin pigment changes, rash/hives, stomach discomfort, tinnitus, unexplained visual changes/diarrhea or weight loss. The observed efficacy of initiated ADA+concomitant MTX, and MTX-related AE are reported.

Results: In CONCERTO, pts were MTX–naïve. During the study, the mean duration of MTX exposure was 174.6 days. Overall, 113/395 pts (28.6%) reported 345 MTX-related AEs, including 1 serious AE (SAE, excessive fatigue and/or malaise); 10 events (in 2 pts) led to discontinuation. Pts in the 10/20 mg MTX groups reported the most AE. Pts in the 20 mg MTX group had both, the highest ACR response rate, and MTX-related AE. For each MTX dosage group, AE rates remained steady, whereas ACR50 response rates to ADA + MTX increased over time (Fig 1A). At Wk 26, the ACR50 response rates ranged from 54- 68%; MTX-related AE rates ranged from 2.4-17.8%. In MUSICA, the mean duration of prior MTX exposure was 1.5 yrs; mean prior MTX dosage was 17.3 mg/wk. During the study, the mean duration of MTX exposure was 157.5 days. Overall, 71/309 pts (23%) reported 185 MTX-related AEs; including 5 SAEs (4 infections and 1 fever and/or chills); 6 events (in 4 pts) led to discontinuation. MTX-related AE were reported at similar rates for both MTX dosage groups and peaked at Wk 4, whereas ACR50 response rates increased with time for both groups (Fig 1B). At Wk 24, the ACR50 response rates were 32.3% and 37.5% while the MTX-related AE rate was 6.5%.

Conclusion: In pts with early and established RA initiating ADA in combination with MTX, treatment efficacy was achieved despite reported MTX-related toxicity. Most MTX-related AE were mild and led to study discontinuation in 0.5% and 1.3% pts in CONCERTO and MUSICA respectively. While rates of MTX -related AE remained steady, efficacy of ADA+MTX increased during both trials.

Ref: 1) Burmester GR et al. *ARD* 2014; 0:1-8. 2) Kaeley GS et al. *ACR 2013 Ann Meeting, Boston, MA, USA*: S1147



Disclosure: G. Burmester, Abbvie, Pfizer, UCB, Roche, 2,Abbvie, Bristol-Myers Squibb, Pfizer, Merck, MedImmune, UCB, Roche, 5,Abbvie, Bristol-Myers Squibb, Pfizer, Merck, UCB, Roche, 8; **G. S. Kaeley**, AbbVie, 5; **A. Kavanaugh**, AbbVie Inc., Amgen, Astra-Zeneca, BMS, Celgene, Centocor-Janssen, Pfizer, Roche, and UCB, 9; **C. Gabay**, AbbVie, Amgen, BMS, MSD, Pfizer, Roche, Celgene, Sanofi, Regeneron, 9; **D. MacCarter**, AbbVie, 9; **P. Nash**, Abbvie, BMS, Roche, Pfizer, Janssen, Amgen, Sanofi-Aventis, UCB, Eli-Lilly, Novartis, Celgene, 9; **T. Takeuchi**, Chugai Pharmaceutical Co,. Ltd., 2; **A. Cardoso**, AbbVie, 9; **S. Liu**, AbbVie, 9; **H. Kupper**, AbbVie, 9; **J. Kalabic**, AbbVie, 9.

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Abstract Number: 553

Body Mass Index Does Not Influence the Efficacy of Abatacept in Patients with RA Who Are Biologic Naïve: 6-Month Results from a Real-World, International, Prospective Study

R Alten[1], HG Nüßlein[2], M Galeazzi[3], H-M Lorenz[4], X Mariette[5], A Cantagrel[6], M Chartier[7], G Desachy[8], C Poncet[9], C Rauch[10] and M Le Bars[11], [1]Schlosspark-Klinik University Medicine, Berlin, Germany, [2]University Erlangen, Nürnberg, Germany, [3]University of Siena, Siena, Italy, [4]University Hospital, Heidelberg, Germany, [5]Université Paris-Sud, Paris, France, [6]Purpan Hospital, Toulouse, France, [7]Chiltern International, Neuilly, France, [8]Excelya, Boulogne-Billancourt, France, [9]Docs International, Nanterre, France, [10]Bristol-Myers Squibb, Munich, Germany, [11]Bristol-Myers Squibb, Rueil-Malmaison, France

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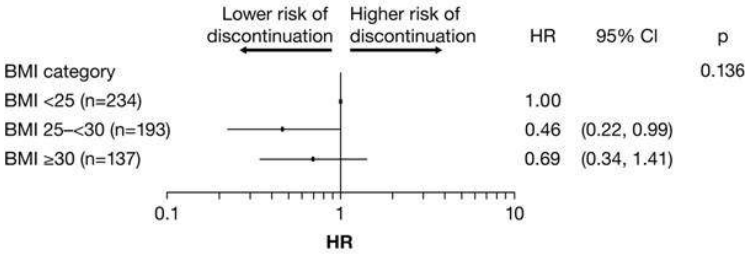
Background/Purpose: In RA, obesity may negatively affect clinical response to anti-TNF agents.[1] In contrast, real-world data show abatacept efficacy and retention are unaffected by BMI in patients (pts) with prior biologic failure.[2,3] Here, response to abatacept was assessed after 6 months, according to BMI, in biologic-naïve pts enrolled in the ACTION study. **Methods:** ACTION is a 2-year, international, multicenter, prospective, observational study evaluating retention and effectiveness of IV abatacept in pts with RA. In this 6-month analysis of biologic-naïve pts enrolled in ACTION, baseline characteristics and clinical response were compared by BMI subgroup: underweight/normal (<25 kg/m^2), overweight (25–<30 kg/m^2) and obese (≥30 kg/m^2). Time to abatacept discontinuation (overall and due to efficacy and safety) was estimated using Kaplan–Meier survival analysis and compared using log-rank tests. **Results:** BMI was reported in 643/672 (96%) pts: 264/643 (41%) were underweight/normal, 224/643 (35%) overweight and 155/643 (24%) obese. Higher baseline BMI was associated with more active disease (mean [95% CI] DAS28 [CRP] [derived] 4.6 [4.5, 4.7], 4.8 [4.7, 5.0] and 5.1 [4.9, 5.2] for BMI <25, 25–<30 and ≥30 kg/m^2, respectively), possibly due to a relation between fat tissue and chronic inflammation[4], and numerically more women (74, 66 and 81%), more metabolic disorders (22, 29 and 46%) and fewer RF positive (77, 68 and 67%) and anti-cyclic citrullinated peptide positive (71, 63 and 63%) pts (for BMI <25, 25–30 and ≥30 kg/m^2, respectively). Overall retention rates at 6 months (Kaplan–Meier analysis) did not differ across groups (84, 89 and 87%, for BMI <25, 25–<30 and ≥30 kg/m^2, respectively; log-rank p=0.290); no significant differences between groups were observed in discontinuation rates due to safety (log-rank p=0.683) or efficacy (log-rank p=0.516). After adjustment for baseline characteristics, BMI was still not significantly associated with risk of discontinuation (reference BMI <25 kg/m^2; HR [95% CI] 0.46 [0.22, 0.99] and 0.69 [0.34, 1.41] for BMI 25–<30 and ≥30 kg/m^2, respectively; figure). No significant differences in the percentage of pts in EULAR moderate or good response and no response were observed by BMI (80.7, 86.1 and 77.0% and 19.3, 13.9 and 23.0% of pts with BMI <25, 25–<30 and ≥30 kg/m^2, respectively; p=0.178).

Figure. Adjusted risk of discontinuation by BMI group (adjusted for baseline characteristics)



HR=Hazard ratio

Conclusion: BMI does not impact abatacept retention or clinical response in biologic-naïve pts with RA. Unlike anti-TNFs, obesity is not a risk factor for reduced efficacy of abatacept. These results are similar to those observed in real-world studies in pts with prior biologic failure.[2,3]

1. Gremese E, et al. *Arthritis Care Res* 2013;**65**:94–100.
2. Iannone F, et al. *Ann Rheum Dis* 2014;**73**(Suppl 2):498.
3. Nüßlein H, et al. Arthritis Rheum 2014;66(Suppl.11):S1088.
4. Ferraccioli G, et al. *Swiss Med Wkly* 2011;**141**:w13211.

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Abstract Number: 554

On Drug and Drug-Free Remission By Baseline Disease Duration: Abatacept Versus Methotrexate Comparison in Patients with Early Rheumatoid Arthritis

VP Bykerk[1], Gerd Burmester[2], BG Combe[3], Daniel E. Furst[4], T. W. J. Huizinga[5], DA Wong[6] and Paul Emery[7], [1]Weill Cornell Medical College, New York, NY, [2]Department of Rheumatology and Clinical Immunology, Charité - Universitätsmedizin Berlin, Berlin, Germany,

[3]Montpellier University, Montpellier, France, [4]Medicine, University of California, Los Angeles, David Geffen School of Medicine, Los Angeles, CA, [5]Leiden University Medical Center, Leiden, Netherlands, [6]Bristol-Myers Squibb, Princeton, NJ, [7]University of Leeds, Leeds, United Kingdom

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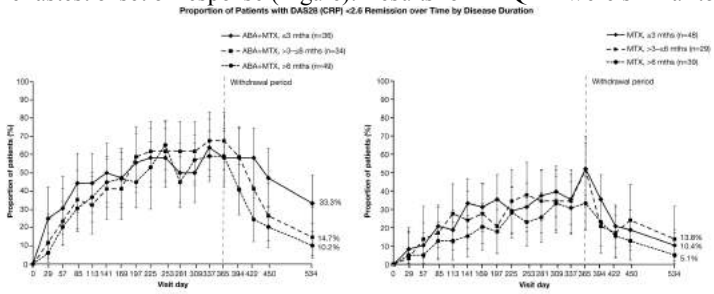
Background/Purpose: Patients with RA and longer disease duration generally do not respond as well to treatment with DMARDs as patients with a shorter duration of disease. Earlier use of biologic DMARDs can improve disease control.[1,2] The AVERT trial provides the opportunity to examine outcomes in patients with varying degrees of early disease duration in which the definition for disease duration is well defined across groups. **Methods:** Patients with early active RA (clinical synovitis in ≥2 joints for ≥8 weeks, persistent symptoms for ≤2 years and DAS28 [CRP] ≥3.2), and who were anti-cyclic citrullinated peptide-2 positive, were randomized to SC abatacept (ABA) 125 mg/week + MTX, SC ABA 125 mg/week alone or MTX alone for 12 months. All RA treatment was removed after 12 months in patients with DAS28 (CRP) <3.2.[3] In this *post hoc* analysis, proportions of patients achieving protocol-defined remission (DAS28 [CRP] <2.6) or improvement in HAQ-DI (≥0.3 units from baseline) were assessed by ≤3 months', >3 to ≤6 months' or >6 months' disease duration (defined as the duration of persistent symptoms at baseline) and treatment group. Adjusted mean changes from baseline in HAQ-DI were also evaluated by disease duration. **Results:** Patients were randomized and treated with ABA+MTX (n=119) or MTX (n=116): 36 and 48 with ≤3 months'; 34 and 29 with >3 to ≤6 months'; 49 and 39 with >6 months' disease duration, respectively. No systematic differences were seen in baseline demographics and clinical characteristics for patients grouped by disease duration. Irrespective of baseline disease duration, a higher proportion of ABA+MTX-treated patients achieved Month 12 and sustained (Month 18) remission, compared with MTX alone. A higher proportion of ABA+MTX-treated patients with disease duration ≤3 months maintained remission following all treatment withdrawal compared with longer disease durations and MTX alone (Figure). ABA+MTX-treated patients with ≤3 months' disease duration also had the fastest onset of response (Figure). Results for HAQ-DI were similar to the overall population, regardless of baseline disease duration.



Conclusion: Disease duration of ≤3 months was associated with faster onset of clinical response and the ability to achieve higher rates of drug-free remission following treatment with abatacept+MTX in AVERT.[4]

1. Westhovens R, et al. *Ann Rheum Dis* 2009;68:1870–7.

2. Emery P, et al. *Ann Rheum Dis* 2010;69:510–6.

3. Emery P, et al. *Ann Rheum Dis* 2014;73(Suppl 2):69.

4. This abstract was first presented at the EULAR Congress, 10–13 June 2015, Rome, Italy (FRI0152) and published in the corresponding supplement of *Ann Rheum Dis*.

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duration-abatacept-versus-methotrexate-comparison-in-patients-with-early-rheumatoid-arthritis

Abstract Number: 555

Outcomes Associated with Non-Medical Switching/Discontinuation of Anti-TNF Inhibitors Among Patients with Rheumatoid Arthritis

Douglas C. Wolf[1], Martha Skup[2], Hongbo Yang[3], Elizabeth Faust[3], **Jenny Griffith**[2], Jingdong Chao[2] and Mark Lebwohl[4], [1]Atlanta Gastroenterology Associates, Atlanta, GA, [2]AbbVie Inc., North Chicago, IL, [3]Analysis Group, Inc., Boston, MA, [4]Mount Sinai Medical Center, New York, NY

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Background/Purpose: Patients with RA are often treated with anti-tumor necrosis factor (TNF) agents. However, patients with a stable response to anti-TNF therapy may discontinue or switch treatments for non-medical reasons such as cost reduction. We evaluated real-world clinical outcomes associated with non-medical switching of anti-TNF therapies among patients with RA in the USA.

Methods: A rheumatologist-administered chart review collected online data (from 1/2011 through 4/2014) on patients with a diagnosis of RA who had a physician-reported stable response to an anti-TNF therapy for ≥6 months (baseline period). Patients who maintained response and either discontinued or switched for non-medical reasons from the anti-TNF (discontinuers) were matched to a patient visiting the same rheumatologist within a 60 day period who did not switch/discontinue therapy for non-medical reasons (continuers). Non-medical reasons for switching/discontinuing therapy included increased copay, change of insurance, job loss, or other economic factors that limited affordability of medication. Switchers/discontinuers were followed for 12 months from the date of discontinuation; continuers were followed for 12 months from the date of an office visit within 2 months of a matched switcher/discontinuer's discontinuation date. Differences between cohorts in baseline sociodemographic characteristics, disease severity (categorized as mild, moderate, or severe), comorbidities, medication use (anti-TNF and other RA-related drugs), and resource utilization were assessed with descriptive statistics. Generalized linear models were used to compare disease flares, disease control, and use of medical services between groups during the follow-up period, after adjustment for baseline characteristics.

Results: 83 matched pairs of switchers/discontinuers (69.9% switchers/30.1% discontinuers) and continuers were analyzed (N=166). Switchers/discontinuers were more likely than continuers to be Hispanic (27.7% vs 15.7%, *P*=.041); otherwise, there were no significant differences between cohorts in baseline sociodemographic and disease characteristics, comorbidities, medication use, or resource utilization. In the follow-up period approximately 48% of switchers/discontinuers had well-controlled disease symptoms as assessed by the rheumatologist, a significantly lower rate (adjusted odds ratio=0.15, *P*<.001) than continuers (84%). Compared with continuers, switchers/discontinuers had a significantly greater risk of flares and more frequent flares across all disease severity levels; they also had an increased risk of emergency department visits and more repeat emergency department visits (both *P*<.05; **Table**).

Conclusion: In this real-world study of patients with RA, discontinuation of an anti-TNF therapy for non-medical reasons was associated with significantly worse clinical outcomes and increased health care resource use.

Table. Treatment Response and Health Care Resource Utilization Among Patients with RA				
	Odds Ratio/Incidence Rate Ratio (Anti-TNF Switchers/Discontinuers vs Continuers[a])			
	Unadjusted	*P*-value	Adjusted	*P*-value
Likelihood of ≥1 Flare	3.29	<.001*	3.63	<.001*
Mild RA[b]	1.90	.018*	2.26	.005*
Moderate RA[b]	5.78	<.001*	5.76	<.001*
Severe RA[b]	2.83	.013*	2.88	.018*
Number of Flares	1.63	.041*	3.73	<.001*
Mild RA[b]	1.53	.016*	2.51	<.001*
Moderate RA[b]	1.68	.110	5.83	<.001*
Severe RA[b]	1.88	.128	10.10	<.001*
Likelihood of ≥1 urgent care visit[c]	3.02	.039*	6.05	.024*
Likelihood of ≥1 inpatient stay	2.05	.325	3.87	.185
Likelihood of ≥1 ED visit	4.32	.046*	6.94	.022*
Number of ED visits	8.00	.015*	9.85	.008*
Number of outpatient visits[d]	1.13	.119	1.09	.199

*_P_-value <.05.

[a]Non-medical reasons for switching/discontinuing anti-TNF therapy included increased copay, switching of insurance, job loss, or other economic factors that limited affordability of medication.

[b]Mild, moderate, and severe disease, based on physician opinion.

[c]Urgent care was defined as inpatient stays or ED visits.

[d]Patients were required to have ≥1 outpatient visit in the study period.

ED, emergency department.

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Abstract Number: 556

Induction-Maintenance in Early RA: A Meta-Analysis of Trials Using MTX Plus Adalimumab As Induction Therapy

Sharzad Emamikia[1], Elizabeth V. Arkema[2], Noémi Györi[1], Jacqueline Detert[3], Katerina Chatzidionysiou[1], Maxime Dougados[4], Gerd Burmester[5] and Ronald F. van Vollenhoven[1], [1]Department of Medicine, Unit for Clinical Therapy Research, Inflammatory Diseases (ClinTRID), The Karolinska Institute, Stockholm, Sweden, [2]Karolinska Institutet, Stockholm, Sweden, [3]Department of Rheumatology and Clinical Immunology, Germany, Charité - Universitätsmedizin Berlin, Berlin, Germany, [4]Paris-Descartes University, Paris, France, [5]Department of Rheumatology and Clinical Immunology, Charité - Universitätsmedizin Berlin, Berlin, Germany

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Background/Purpose: The goal of rheumatoid arthritis (RA) treatment is remission or, when not achievable, low-disease-activity (LDA). Initial combined therapy with MTX + anti-TNF achieves these goals more often but at a high cost. Some trials have therefore used the combined treatment for a limited time only ("induction-maintenance"). However, it has remained unclear if the benefits from the induction phase are sustained during maintenance, and individual trials may not have been sufficiently powered to resolve this issue. Therefore, we performed a meta-analysis of trials using the initial combination of MTX+Adalimumab in DMARD-naïve early RA-patients.

Methods: A systematic literature search was performed for induction-maintenance randomized controlled trials where initial combination therapy was compared with MTX-monotherapy in patients with clinically active early RA. Our primary outcome was the proportion of patients who achieved LDA (DAS28≤3.2) and/or remission (DAS28<2.6), at 12-52 weeks of follow-up comparing patients who started with MTX+ADA to those who started with MTX alone. A random effects model was used to pool the risk ratio (RR) for clinical remission and LDA.

Results: The literature search identified 2810 studies that matched the predefined search terms. We identified four published randomized trials (Table 1), where MTX+ADA was given as initial therapy and where ADA was withdrawn in a subset of patients after LDA/remission had been achieved. For two of these trials (Guépard and Hit-Hard) original data were re-examined, for the other two (Optima and Opera) only published data were available. As expected, the RR of achieving clinical remission or LDA with combination therapy was significantly greater than with MTX monotherapy; 1.76 (95%CI 1.51-2.06) and 1.45 (95%CI 1.03-2.08), respectively. Most importantly, the pooled RRs for achieving clinical remission and LDA at follow-up after discontinuation of ADA were 1.30 (95%CI 0.90-1.87) and 1.22 (95%CI 0.95-1.58), respectively, with significant heterogeneity between trials. Opera featured consistent use of intra-articular glucocorticoid-injections as a treat-to target strategy and therefore a sensitivity analysis excluding Opera was performed where the pooled RR for achieving clinical remission and LDA, at follow-up after discontinuation of ADA, were 1.56 (95%CI 1.21-2.00) and 1.37 (95%CI 1.09-1.72), respectively, without significant heterogeneity (Figure 1).

Conclusion: This meta-analysis supports the hypothesis that in early RA, initial therapy with MTX+ADA is associated with a higher chance of retaining LDA and/or remission even after discontinuation of ADA.

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Abstract Number: 557

Early Intensification of Treatment Induces Superior Outcomes in Two Randomized Trials According to Predicted Vs. Observed Radiographic Progression in Rheumatoid Arthritis

Adrian Levitsky[1], Marius C. Wick[2], Timo Möttönen[3], Marjatta Leirisalo-Repo[4], Leena Laasonen[5], Hannu Kautiainen[6,7], Markku Korpela[8], Ronald F. van Vollenhoven[1] and Vappu Rantalaiho[8], [1]Department of Medicine, Unit for Clinical Therapy Research, Inflammatory Diseases (ClinTRID), The Karolinska Institute, Stockholm, Sweden, [2]Radiology, Karolinska University Hospital, Stockholm, Sweden, [3]Internal Medicine, Division of Rheumatology, Turku University Central Hospital, Turku, Finland, [4]Rheumatology, University of Helsinki and Helsinki University Hospital, Helsinki, Finland, [5]Helsinki Medical Imaging Center, University of Helsinki and Helsinki University Hospital, Helsinki, Finland, [6]Unit of Primary Health Care, University of Helsinki and Helsinki University Hospital, Helsinki, Finland, [7]Unit of Primary Health Care, Kuopio University Hospital, Kuopio, Finland, [8]Department of Internal Medicine, Center for Rheumatic Diseases, Tampere University Hospital, Tampere, Finland
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Background/Purpose:

Predicted vs. Observed Radiographic Progression in early Rheumatoid Arthritis (POPeRA) is a method that has previously confirmed the relative radiographic efficacy of synthetic disease-modifying antirheumatic drugs (DMARDs) and anti-TNF treatment (1, 2). Here, we applied the POPeRA technique to the randomized Finnish Rheumatoid Arthritis Combination trial (3) (FIN-RACo, combination vs. single) as well as the NEO-RACo trial (4) (combination+anti-TNF vs. combination+placebo) in order to demonstrate how various treatment modalities affect radiographic progression.

Methods:

POPeRA utilizes the baseline radiographic score divided by the patient-reported symptom duration in months before baseline to predict radiographic outcomes over time, and simulates how patients would progress as if not on treatment. It was applied to 144 and 90 patients with eRA from the FIN-RACo and NEO-RACo trials, respectively. The Larsen score (FIN-RACo) and Sharp-van der Heijde score (SHS) (NEO-RACo) was available at baseline, 2, and 5 years. For FIN-RACo, patients were randomized either to a single DMARD (all starting with sulfasalazine; 60% had prednisolone in accordance to the physician's judgment) or to more intensive DMARD combination therapy (all starting with triple therapy: methotrexate+sulfasalazine+hydroxychloroquine with prednisolone). In NEO-RACo, all patients were assigned to FIN-RACo combination protocol plus a randomized 6-month induction of either placebo or anti-TNF treatment (infliximab). For both trials, treatment became unrestricted after 2 years.

Results:

In FIN-RACo, combination vs. single therapy resulted in superior outcomes in the change from predicted progression over 2 and 5 years (mean 35.7% reduction vs. -32.9%, a worsening from predicted, p=0.001; 34.2% vs. -17.8%, p=0.003, n=72, respectively). Patients positive for rheumatoid factor (RF) (n=102) had significantly worse changes from predicted at 2 and 5 years than RF-negative patients (n=42) (-13.6 vs. 38.1, p=0.035; -6.7 vs. 44.3, p=0.002, respectively). Superiority for combination vs. single therapy was observed in both RF-positive and RF-negative patients.

In NEO-RACo, combination+6-month anti-TNF therapy (n=44) led to significantly greater reductions from predicted progression than combination+placebo (n=46) both at 2 and 5 years of follow-up (98.5% vs. 83.4%, p=0.005; 92.4% vs. 82.5%, p=0.027, respectively). However, anti-TNF add-on treatment was superior only among RF-positive patients (n=67).

Conclusion:

These results confirm that conventional combination therapy in eRA has a

long-term radiographic benefit versus monotherapy. Using the POPeRA method, the addition of anti-TNF induction therapy for 6 months was shown to further increase the long-term radiographic benefit in RF-positive patients.

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Disclosure: A. Levitsky, None; **M. C. Wick**, None; **T. Möttönen**, Abbvie, Amgen, BMS, Eli Lilly, MSD, Pfizer, Roche, 5; **M. Leirisalo-Repo**, Abbvie, Boehringer Ingelheim, BMS, MSD, Pfizer, Regeneron, Roche, 5; **L. Laasonen**, Abbvie, Pfizer, MSD, VTT (Technical Research Centre of Finland Ltd.), 5; **H. Kautiainen**, None; **M. Korpela**, None; **R. F. van Vollenhoven**, AbbVie, BMS, GSK, Pfizer, Roche, UCB, 2,AbbVie, Biotest, BMS, Crescendo, GSK, Janssen, Lilly, Merck, Pfizer, Roche, UCB, Vertex, 5; **V. Rantalaiho**, Orion-Farmos Research Foundation, 2,Abbvie, BMS, GSK, Pfizer, MSD, Roche, UCB Pharma, 5.

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Abstract Number: 558

Tuberculosis Risk Among Patients with Rheumatoid Arthritis in a United States Claims Database Initiating Abatacept and Other Biologic Disease-Modifying Antirheumatic Drugs: Analyses Using International Classification of Diseases Codes and a Published Claims Algorithm

N Baker[1], S Suissa[2], H Kawabata[1], M Skovron[3], V Moorthy[4] and TA Simon[1], [1]Bristol-Myers Squibb, Hopewell, NJ, [2]McGill University, Montreal, QC, Canada, [3]Epidemiologist, Lawrenceville, NJ, [4]Mu Sigma, Northbrook, IL

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Background/Purpose: Tuberculosis (TB), a reportable disease world-wide, is rare in the US (2013 incidence rate [IR]: 3 cases per 100,000 persons)[1] and is an event of interest in patients (pts) receiving biologic (b)DMARDs. Large healthcare claims databases are useful in assessing rare events, but confirmation of TB in the absence of information on culture results can be challenging. Typically, an International Classification of Diseases, Ninth Revision (ICD-9) code is used to identify an event, although these codes may be limited by varying sensitivity and poor positive predictive value.[2] In a published study by Calderwood et al., combinations of diagnostic codes, dispensed anti-TB medications and procedure codes (e.g. chest radiographs or sputum staining for acid-fast bacteria) detected TB cases with high sensitivity. Dispensing of two or more anti-TB medications was the most sensitive criterion, with a sensitivity of 89%.[3] The present analysis compares TB risk in pts using abatacept or other bDMARDs via these two methods. **Methods:** Adults diagnosed with RA in the MarketScan® Commercial and Supplemental Medicare databases who initiated treatment with abatacept or another bDMARD between July 1, 2006 and July 31, 2012 were included in the analysis. Included pts had at least 180 days of continuous health plan enrollment prior to and ≥1 day following initiation of the qualifying RA treatment. TB cases were defined using two methods: 1) at least 1 claim for an ICD-9 code indicating TB after initiation of a bDMARD and 2) applying the algorithm described by Calderwood et al.[3] IRs (per 1000 person-years) were calculated using both methods. A Cox regression analysis, adjusted for propensity score and prior bDMARD use, was conducted to compare the 2 cohorts. **Results:** Using the first method, there were 22 cases of TB among 10,898 abatacept initiators vs 63 cases among 37,441 initiators of other bDMARDs, corresponding to an IR (95% CI) of 2.65 (1.66, 4.01) vs 1.99 (1.53, 2.55), respectively. Using the second method, there were 3 cases of TB among abatacept initiators vs 5 cases among initiators of other bDMARDs, corresponding to an IR (95% CI) of 0.36 (0.07, 1.05) vs 0.16 (0.05, 0.37), respectively. The adjusted hazard ratio (95% CI) comparing abatacept initiators with initiators of other bDMARDs was 2.38 (0.95, 5.98) using method 1 and 1.00 (0.06, 15.99) using method 2.

Conclusion: Although we are unable to determine true positive or negative cases of TB in the claims-based data, applying the Calderwood algorithm provided estimates consistent with published rates of TB among pts with RA.[4] These results are also consistent with previous research demonstrating that TB diagnostic codes alone have poor positive predictive value. Validated algorithms are important when using claims-based data to evaluate TB events among pts with RA and in studies assessing the relationship between TB and treatment for RA.

1. Centers for Disease Control and Prevention. http://www.cdc.gov/tb/statistics/tbcases.htm. Accessed January 2015. 2. Winthrop KL, et al. *Pharmacoepidemiol Drug Saf* 2011;**20**:229–35. 3. Calderwood MS, et al. *Public Health Rep* 2010;**125**:843–50. 4. Arkema EV, et al. *Ann Rheum Dis* 2014; Published Online First: doi:10.1136/ annrheumdis-2013-204960.

Disclosure: N. Baker, Bristol-Myers Squibb, 1,Bristol-Myers Squibb, 3; **S. Suissa**, Bristol-Myers Squibb, Genentech, Roche, 5; **H. Kawabata**, Bristol-Myers Squibb, 1,Bristol-Myers Squibb, 3; **M. Skovron**, Bristol-Myers Squibb, 1,Bristol-Myers Squibb, New York University, 5; **V. Moorthy**, None; **T. Simon**, Bristol-Myers Squibb, 3.

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Abstract Number: 559

Herpes Zoster and Tofacitinib: The Risk of Concomitant Nonbiologic Therapy

Kevin L. Winthrop[1], Jeffrey R. Curtis[2], Stephen Lindsey[3], Hernan Valdez[4], Haiyun Fan[5], Lisy Wang[6], Alan M. Mendelsohn[5] and Eustratios Bananis[5], [1]Oregon Health & Science University, Portland, OR, [2]The University of Alabama at Birmingham, Birmingham, AL, [3]Ochsner Medical Center, Baton Rouge, LA, [4]Pfizer Inc, New York, NY, [5]Pfizer Inc, Collegeville, PA, [6]Pfizer Inc, Groton, CT

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Background/Purpose: Patients with RA are at increased risk for herpes zoster (HZ). Tofacitinib is an oral Janus kinase inhibitor for the treatment of RA. Treatment with tofacitinib appears to increase the risk of HZ.[1] However, it is unclear whether the use of concomitant nonbiologic DMARDs or glucocorticoids (GCs) further increases HZ risk in patients with RA using tofacitinib.

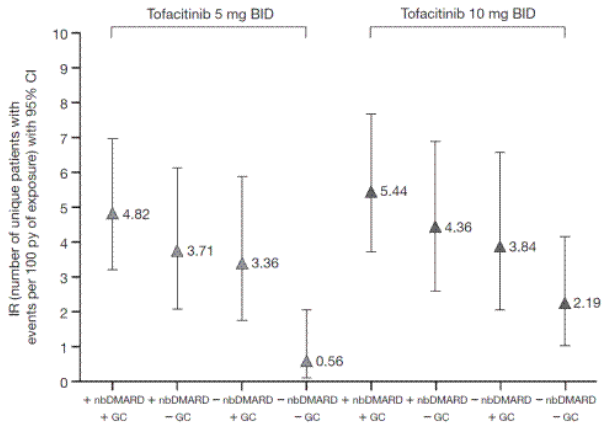
Methods: We identified reports of serious and non-serious HZ from Phase (P)1/P2/P3 and long-term extension (LTE) studies of tofacitinib in RA patients (data cut April 3, 2014; one LTE study still ongoing; database unlocked), and calculated crude incidence rates (IRs) for all HZ (serious and non-serious; unique patients with events per 100 patient-years [py]) with 95% confidence intervals (CIs). Patients were censored at study withdrawal, first HZ event, or death. Within P3 studies we described HZ rates in stratified fashion according to concomitant nonbiologic DMARDs and baseline GC use. To evaluate risk factors for HZ, we used pooled P1/P2/P3/LTE data and performed univariate and multivariable analyses using logistic regression. Stepwise selection with an entry and stay criterion of α=0.1 was used to form the final multivariable model.

Results: In 19 pooled P1/P2/P3 and LTE studies (total: 6192 patients; 16,839 py of exposure) HZ was reported in 636 tofacitinib-treated patients: IR 4.0 (3.7, 4.4). IRs for HZ varied widely across regions of enrollment, being lowest in Eastern and Western Europe (2.4 [2.0, 2.9] and 3.3 [2.4, 4.4], respectively) and highest in Japan/Korea: IR 8.1 (7.0, 9.4). The IR for United States/Canada/Australia was 4.3 (3.7, 5.1). Within P3 studies, IRs varied according to tofacitinib dose, background nonbiologic DMARDs (92% of patients using DMARDs were using MTX), and baseline GCs: IRs per 100 py were lowest for tofacitinib 5 mg twice daily (BID) monotherapy without GCs (IR 0.6 [0.1, 2.0]) and highest for tofacitinib 10 mg BID with DMARDs and GCs (IR 5.4 [3.7,7.7]) (Figure). Multivariable analysis showed that age, baseline GC use, concomitant DMARD use, tofacitinib dose (10 mg BID vs 5 mg BID), smoking history and region were likely predictors of HZ (Table).

Conclusion: Among patients with RA using tofacitinib, concomitant use of nonbiologic DMARDs or GCs appears to increase the risk and overall IR per 100 py of HZ from 0.56 to 4.82 with 5 mg BID. Limiting the use of GCs or MTX could potentially mitigate HZ risk.

References: 1. Winthrop KL, et al. Arthritis Rheumatol 2014; 66: 2675-84.

Figure. IRs for HZ within pooled Phase 3 studies of tofacitinib, with and without nonbiologic DMARDS and/or GCs



Total pts, N	579	394	320	296	550	419	313	329
Total tofacitinib exposure, py	603	412	367	361	606	429	346	419
Unique pts with events, n	28	15	12	2	32	18	13	9

Includes patients from all regions
BID, twice daily; CI, confidence interval; GC, glucocorticoids; IR, crude incidence rate; nbDMARD, nonbiologic disease-modifying antirheumatic drug; pts, patients; py, patient years

Table. Multivariable analysis of HZ risk factors with tofacitinib				
Factors	**Comparisons**	**Odds Ratio**	**95% CI**	**P-value**
Age*				<0.001
	Units = 23.724*	2.101	1.750, 2.523	
Average tofacitinib dose group**				0.019
	Tofacitinib 10 mg vs 5 mg BID	1.237	1.035, 1.479	
Background therapy				0.052
	DMARDs vs monotherapy	1.189	0.998, 1.417	
Baseline GC dose group				<0.001
	>0 mg - ≤5 mg vs 0 mg (no use)	1.677	1.352, 2.081	
	>5 mg vs 0 mg (no use)	1.533	1.203, 1.954	
Region				<0.001
	Asia vs Western Europe	2.788	1.951, 3.986	
	Eastern Europe vs Western Europe	1.078	0.739, 1.574	
	Latin America vs Western Europe	1.632	1.107, 2.406	
	US/Canada/Australia vs Western Europe	1.411	0.983, 2.025	
Smoking status				0.023
	Ex/non-smoker vs current smoker	1.379	1.070, 1.778	

For the multivariable analysis, a stepwise procedure was used to screen the factors: age, gender, disease duration, average tofacitinib dose, baseline DAS28-4(CRP), baseline ALC, diabetes, BMI, baseline COPD, smoking status, baseline glucocorticoid use, and region to analyze the occurrence of HZ events.

*Odds Ratios calculated for continuous variables are the factor by which the odds of HZ being present increased in response to an increase of 2 standard deviations in a given variable.

**Tofacitinib dose was grouped based on the averaged TDD: if 0<TDD<15 mg, then the dose group of tofacitinib is 5 mg; if TDD ≥15 mg, the dose group of tofacitinib is 10 mg.

ALC, absolute lymphocyte count; BID, twice daily; BMI, body mass index; CI, confidence interval; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; DAS28-4, disease activity score in 28 joints (4-variable); DMARD, disease-modifying antirheumatic drug; GC, glucocorticoid; HZ, herpes zoster; TDD, total daily dose; US, United States

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Disclosure: K. L. Winthrop, Pfizer Inc, 2; **J. R. Curtis**, Pfizer Inc, 2,Pfizer Inc, 5; **S. Lindsey**, Pfizer Inc, 8; **H. Valdez**, Pfizer Inc, 1,Pfizer Inc, 3; **H. Fan**, Pfizer Inc, 1,Pfizer Inc, 3; **L. Wang**, Pfizer Inc, 3,Pfizer Inc, 1; **A. M. Mendelsohn**, Pfizer Inc, 1,Pfizer Inc, 3; **E. Bananis**, Pfizer Inc, 1,Pfizer Inc, 3.

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Abstract Number: 560

Impact of Anti-Citrullinated Protein Antibody Status and Response to Abatacept

Leslie Harrold[1,2], KK Gandhi[3], H Litman[4], S Kelly[3], YF Li[5], E Alemao[3], S Deveikis[4] and J Greenberg[1,6], [1]Corrona, LLC, Southborough, MA, [2]Dept of Medicine, University of Massachusetts Medical School, Worcester, MA, [3]Bristol-Myers Squibb, Princeton, NJ, [4]Corrona, LLC., Southborough, MA, [5]University of Massachusetts Medical School, Worcester, MA, [6]NYU School of Medicine, New York, NY

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Background/Purpose: Response to therapies may vary based on anti-citrullinated protein antibodies (ACPA) status. We compared treatment response to abatacept in ACPA-positive versus -negative RA patients (pts) in a US national observational cohort. **Methods:** Using the Corrona RA registry, we identified new initiators of abatacept between February 2006 and January 2014. ACPA testing (ELISA assay for cyclic citrullinated peptide 2 seropositivity) was performed within 6 months of initiation. Disease activity was assessed using CDAI at both initiation and at a follow-up visit at 1 year (±3 months). The primary outcome was change in CDAI from baseline, with a secondary outcome examining achievement of low disease activity (LDA; CDAI ≤10) among those who initiated abatacept when in moderate or high disease activity, and

achievement of remission (CDAI ≤2.8) when initiated with low, moderate or high disease activity. Multivariable linear and logistic models were performed. Additionally, at 1 year we evaluated the proportion of ACPA-positive and -negative pts who remained on abatacept, switched to another biologic, or discontinued abatacept without initiating another biologic. **Results:** We identified 149 abatacept initiators who met inclusion criteria (64 with ACPA <20 units/mL [considered negative] and 85 with ACPA ≥20 units/mL [considered positive]). Most pts were female, Caucasian, aged 55.9–57.5 years, with moderate disease activity and a median disease duration of 4–6 yrs (Table 1). The majority (77.9%) of pts had prior exposure to at least 1 biologic or small molecule. Treatment with abatacept was associated with a mean change (95% CI) in CDAI of –5.24 (–8.42, –2.06) in the ACPA-negative group compared with –7.99 (–10.71, –5.27) in the ACPA-positive group (Table 2). Achievement of LDA occurred in 24.5% (95% CI 12.9, 36.1) of ACPA-negative patients vs 35.2% (24.1, 46.3) in the ACPA-positive group. Similarly, achievement of CDAI-defined remission occurred in 3.2% (95% CI 0, 7.5) of ACPA-negative patients vs 17.1% (8.9, 25.2) in the ACPA-positive group. Among the respective ACPA-negative and ACPA-positive pts, at 1 year 54.5% vs 72.9% remained on abatacept, 28.1% vs 16.5% switched to another biologic and 17.2% vs 10.6% discontinued the drug without initiating another biologic.

Conclusion: There was a suggestion of a greater response in ACPA-positive abatacept users compared with ACPA-negative users although not significant. The analyses were limited by sample size, warranting further evaluation.

Table 1. Baseline characteristics

	Population comparisons		
Baseline characteristics	**ACPA negative n=64**	**ACPA positive n=85**	**p-value**
Mean age (SD), yrs	57.5 (13.1)	55.9 (12.6)	0.40
Female, n (%)	56 (87.5)	69 (81.2)	0.30
Caucasian, n (%)	56 (87.5)	61 (71.8)	0.10
Median disease duration (IQR), yrs	4 (10)	6 (11)	0.24
Mean CDAI score (SD)	22.9 (12.6)	22.2 (12.1)	0.84
Mean number of prior cDMARDs (SD)	1.8 (1.0)	1.9 (1.2)	0.90
Number of prior biologics/small molecules, n (%)			
0	12 (18.8)	21 (24.7)	0.80
1	25 (39.1)	30 (35.3)	
2	20 (31.3)	27 (31.8)	
3+	7 (10.9)	7 (8.2)	

ACPA=anti-citrullinated protein antibodies; cDMARD=conventional DMARD; IQR=interquartile range

Table 2. Outcomes

	ACPA negative n=64	**ACPA positive n=85**	**Unadjusted estimate**	**Multivariable Adjusted estimate***	
Primary outcome	**Mean (SE)**	**Mean (SE)**	**p-value**	**Beta coefficient (SE)**	**p-value**
Change in CDAI	–5.24 (1.62)	–7.99 (1.39)	0.20	–2.03 (1.87)	0.28
Secondary outcome	**%**	**%**	**p-value**	**OR (95% CI)**	**p-value**
Overall achievement of LDA	24.5	35.2	0.20	2.00 (0.73, 5.5)	0.18
Overall achievement of remission	3.2	17.1	0.008	N/A†	N/A†

*Adjusted for age, sex, BMI, co-morbidities, disease duration, morning stiffness, baseline disease activity, and prior biologic/targeted synthetic DMARD use

†Owing to the small number of patients who achieved remission, the ability to adjust for more than one covariate in the model at one time was limited

ACPA=anti-citrullinated protein antibodies; LDA=low disease activity (CDAI ≤10); OR=odds ratio; remission (CDAI ≤2.8)

Disclosure: L. Harrold, Pfizer, AstraZeneca, 2,Pfizer, Genentech, 5,Corrona LLC, 3; **K. Gandhi**, Bristol-Myers Squibb, 1,Bristol-Myers Squibb, 3; **H. Litman**, Corrona LLC, 3; **S. Kelly**, Bristol-Myers Squibb, 1,Bristol-Myers Squibb, 3; **Y. Li**, None; **E. Alemao**, Bristol-Myers Squibb, 3,Bristol-Myers Squibb, 1; **S. Deveikis**, Corrona LLC, 3; **J. Greenberg**, Corrona LLC, 3,Corrona LLC, 1,AstraZeneca, Celgene, Genentech, Janssen, Novartis and Pfizer, 5.

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Abstract Number: 561

Improvement in Disease Activity and the Long-Term Risk of Serious Infectious Events in Rheumatoid Arthritis Patients Treated with Certolizumab Pegol

Jeffrey R. Curtis[1], Marc de Longueville[2], Cathy O'Brien[2] and Boulos Haraoui[3], [1]University of Alabama at Birmingham, Birmingham, AL, [2]UCB Pharma, Brussels, Belgium, [3]Department of Medicine, Centre Hospitalier de l'Université de Montréal, Montréal, QC, Canada
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Background/Purpose:

Anti-TNF drugs are an effective treatment option for rheumatoid arthritis (RA) patients (pts) but have been associated with an increased incidence of serious infectious events (SIEs). High disease activity has been suggested to be a predictor of SIEs in RA. Here we examine whether improvement in disease activity over time is associated with a reduced risk of SIEs in certolizumab pegol (CZP)-treated RA patients.

Methods:

CZP safety data from bio-naïve patients were pooled from the RAPID1 and RAPID2 randomized clinical trials (RCTs; NCT00152386/NCT00160602) and their open-label extensions (OLEs; NCT00175877/NCT00160641). Post-hoc analyses included all SIEs with onset after the first CZP dose and up to 84 days after the last CZP dose or withdrawal. A multivariate Cox proportional hazards model (selection criteria: entry $p \leq 0.2$, stay $p \leq 0.25$) was used to estimate the relative risk (hazard ratio [HR]) of baseline (BL) and time-dependent pt covariates to SIEs. BL covariates selected by the final Cox model were age (<65; ≥65 yrs) and medically-treated comorbidity (diabetes, COPD, cardiac disorder hypertension, hyperlipidemia, transient ischemic attack or cerebrovascular disorder). Time-dependent covariates were measured at each pt visit (≤12 week intervals) and included DAS28(CRP), HAQ-DI and flare (increase >1.2 in DAS28[CRP] between visits). Pts were categorized by decrease in DAS28(CRP) between specific time points and the assessment performed before the first CZP dose (absolute decrease: <0.6; 0.6–1.2; 1.2–2.6; ≥2.6); pts with >1 DAS28(CRP) assessment in a time interval were categorized using the largest decrease in that interval. Incidence rates (IRs) of SIEs were calculated per 100 patient-years (PY), with 95% confidence intervals (CIs).

Results:

1506 bio-naïve CZP pts were included, with a total exposure of 5778.6 PY (max pt exposure: 6.40 PY; median exposure per pt: 4.79 PY). In total, 201 pts reported ≥1 SIE (IR 3.66/100 PY [3.17–4.21]) over ~6 yrs of CZP treatment. According to the Cox model, pts experiencing a flare had more than double the risk of SIEs (HR 2.21 [1.41–3.47]); also, an increment of 0.125 in HAQ-DI was associated with a 27% increase in the risk of SIEs (HR 1.27 [1.03–1.56]). By contrast, a one unit decrease in DAS28(CRP) was associated with a 17% reduction in the risk of SIEs (HR 0.83 [0.75–0.92]). Furthermore, the observed incidence of SIEs over time was generally lower among pts with an absolute decrease ≥2.6 in DAS28(CRP) (Table).

Conclusion:

Over time, lower disease activity was associated with a reduced risk of SIEs in CZP-treated RA pts and, conversely, flare was associated with increased risk. This study suggests that, in line with current treat-to-target guidelines, reducing disease activity may help to decrease the long-term risk of SIEs associated with anti-TNF drugs.

Table: Observed incidence of SIEs over time in patients categorized by absolute decrease in DAS28(CRP) since the first CZP dose

		Absolute decrease in DAS28(CRP) [a]			
		<0.6	0.6–1.2	1.2–2.6	≥2.6
Overall	Patients at risk (n) [b]	210	323	920	1157
	Exposure (100 PY)	1.596	2.626	14.954	38.086
	IR/100 PY (95% CI) [c]	6.32 (3.03, 11.63) [d]	5.77 (3.23, 9.51) [d]	3.97 (3.02, 5.13)	3.25 (2.70, 3,88)
Time interval since first CZP dose (days)					
>0–360 (~1 year)	Patients at risk (n) [b]	[e]	[e]	716	848
	Exposure (100 PY)			4.835	6.951
	IR/100 PY (95% CI) [c]			6.27 (4.23, 8.95)	4.80 (3.30, 6.74)
>360–720 (~2 years)	Patients at risk (n) [b]			468	942
	Exposure (100 PY)			3.098	7.961
	IR/100 PY (95% CI) [c]			3.25 (1.56, 5.97)	4.69 (3.30, 6.47)
>720–1080 (~3 years)	Patients at risk (n) [b]			348	843
	Exposure (100 PY)			2.521	7.324
	IR/100 PY (95% CI) [c]			4.42 (2.21, 7.91)	3.02 (1.90, 4.58)
>1080–1440 (~4 years)	Patients at risk (n) [b]			323	799
	Exposure (100 PY)			2.229	6.879
	IR/100 PY (95% CI) [c]			3.60 (1.55, 7.09)	3.51 (2.25, 5.23)
>1440–1800 (~5 years)	Patients at risk (n) [b]			255	744
	Exposure (100 PY)			1.655	6.355
	IR/100 PY (95% CI) [c]			1.21 (0.15, 4.37)	2.85 (1.69, 4.50)
>1800–2160 (~6 years)	Patients at risk (n) [b]			159	548
	Exposure (100 PY)			0.616	2.617
	IR/100 PY (95% CI) [c]			N/A (0 events)	1.92 (0.62, 4.48)

[a] Absolute decrease in DAS28(CRP) was calculated from the last assessment prior to the first CZP dose; [b] Number of patients with at least one recorded change in DAS28(CRP) in the indicated time interval; [c] IR of SIEs observed during the indicated time interval since the first CZP dose; [d] The majority of SIEs occurred during the first year of CZP treatment; [e] The low number of events reported in each time interval did not allow a reliable assessment of the respective IRs. A single SIE was reported in patients with missing DAS28(CRP) scores (data not shown). N/A: not applicable.

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Abstract Number: 562

Evaluation of T Helper Cell 1(Th1) – and T Helper Cell 17(Th17) – Associated Chemokines As Prognostic Biomarkers for Tumor Necrosis Factor (TNF) Inhibitor Therapy in Rheumatoid Arthritis (RA)

Bobby Kwanghoon Han[1], Andrea Bottaro[2], Igor Kuzin[2] and Nancy J. Olsen[3], [1]Division of Rheumatology, Cooper Medical School of Rowan University, Voorhees, NJ, [2]Department of Biomedical Sciences, Cooper Medical School of Rowan University, Camden, NJ, [3]Divsion of Rheumatology, Department of Medicine, Penn State MS Hershey Medical Center, Hershey, PA

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Session Type: ACR Poster Session A

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Background/Purpose: TNF inhibitors have been used as a treatment for moderate to severe RA patients. However, reliable biomarkers that

predict therapeutic response to TNF inhibitors are lacking. In RA, Th1 cells stimulate macrophage activation via IFNγ and lead to secretion of TNF. Th17 cells are another pro-inflammatory Th subset which secrete IL17 and have also been involved in the pathogenesis of RA. In this study, we investigated whether Th1- and Th17- associated chemokines may represent useful prognostic biomarkers for TNF inhibitor treatment in RA.

Methods: We recruited RA patients from the Cooper University Hospital Rheumatology Clinic. The inclusion criteria for this study were: 1. diagnosis of RA by ACR criteria, 2. active RA defined by DAS >4.4, 3. clinical indication for initiating adalimumab or etanercept treatment. The exclusion criteria were: 1. diagnosis of other connective tissue diseases, 2. diagnosis of chronic infection. We obtained complete medical history and physical exam, demographic information, medications and laboratory data. At baseline and 14 weeks after TNF inhibitor therapy, we assessed DAS28 ESR and measured serum levels of Th1-associated chemokines (CXCL9, 10, 11) and Th17-associated chemokine (CCL20) using commercial ELISA kits. Responders and non-responders were defined as patients who had good/moderate response and no response at week 14 by EULAR response criteria. Wilcoxon two sample test was performed to compare chemokine levels.

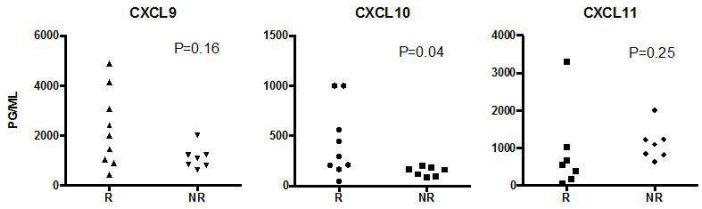
Results: We assessed 16 RA patients who started either adalimumab or etanercept. Their baseline characteristics, summarized in Table 1, show no significant differences between responders (n=9) and non-responders (n=7). Responders showed a trend toward higher levels of baseline Th1 chemokines compared to non- responders (Fig 1). CXCL10 levels were significantly higher in responders (437 ± 354 vs 144 ± 45 pg/ml, p=0.04) while CXCL9 (2266 ± 1517 vs 1126 ± 452 pg/ml, p=0.16),and CXCL11 (887 ± 1114 vs 515 ± 853 pg/ml, p=0.25) differences did not reach statistical significance. There were significant correlations between CXCL9 and CXCL10 (r =0.61, p=0.01) and between CXCL9 and CXCL11 (r=0.66, p=0.01). CCL20 levels were lower in responders but were not significantly different (15.6 ± 12.0 vs 33.8 ± 41.8 pg/ml, p=0.63).

Conclusion: Elevated baseline levels of Th1 cytokines including CXCL9, 10 and 11 appear to be associated with favorable responses to TNF inhibitors whereas Th17 chemokine, CCL20, may be associated with unfavorable responses.

Table 1. Baseline characteristics of RA patients

	Responders (n=9)	Non-responders (n=7)	p value
Age (years)	45.6	50.6	0.43
Gender (female %)	89	86	1.00
Duration (years)	5.3	5.8	0.87
RF or CCP positivity (%)	56	43	1.00
DAS28 ESR	6.1	6.8	0.23
ESR (mm)	31	31	1.00
Concomitant MTX (%)	78	100	0.57

Figure 1. Baseline Th1 chemokine level in responders (R) and non-responders (NR)



Disclosure: B. K. Han, None; **A. Bottaro**, None; **I. Kuzin**, None; **N. J. Olsen**, None.

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Abstract Number: 563

Abatacept Plus Methotrexate Can Effectively and Safely Regain the Target of Remission Following Re-Treatment for Flares after Drug-Free Withdrawal in Patients with Early Rheumatoid Arthritis

Paul Emery[1], G Burmester[2], VP Bykerk[3], B Combe[4], Daniel E. Furst[5], M Maldonado[6] and T. W. J. Huizinga[7], [1]University of Leeds, Leeds,

United Kingdom, [2]Charité – University Medicine Berlin, Berlin, Germany, [3]Hospital for Special Surgery, New York, NY, [4]Service d'Immuno-Rheumatologie, Montpellier, France, [5]Medicine, University of California, Los Angeles, David Geffen School of Medicine, Los Angeles, CA, [6]Bristol-Myers Squibb, Princeton, NJ, [7]Leiden University Medical Center, Leiden, Netherlands
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Background/Purpose: Assessing Very Early Rheumatoid arthritis Treatment (AVERT) was a Phase IIIb, randomized, active-controlled study to evaluate the efficacy and safety of abatacept (ABA) treatment in three phased periods: during treatment, following withdrawal of all therapies and during re-exposure. Here, we present data from the withdrawal and re-exposure periods.

Methods: MTX-naïve, anti-cyclic citrullinated peptide 2-positive patients (pts) with early RA (active synovitis in ≥2 joints for ≥8 wks, DAS28 [CRP] ≥3.2 and onset of symptoms within ≤2 yrs) were initially randomized to 12 months of weekly SC ABA 125 mg + MTX, ABA 125 mg monotherapy or MTX alone (treatment period). Pts with DAS28 (CRP) <3.2 at Month 12 then entered a 12-month withdrawal period with no treatment. All pts with protocol-defined flare after Month 15 could receive open-label ABA + MTX (re-exposure period) for 6 months.

Results: Most pts could not remain treatment-free after complete treatment withdrawal, due to worsening disease activity (172/225; 76.4%) during the 12-month withdrawal period. Of those who entered the withdrawal period, rates of pts maintaining DAS28 (CRP) <2.6 free of all drugs at 24 months were 14.0, 12.3 and 11.3% for ABA + MTX, ABA mono and MTX alone, respectively. Rates of pts ever achieving a major clinical response (MCR) at 24 months were 40.3, 25.9 and 15.5% for ABA + MTX, ABA mono and MTX alone, respectively. A total of 146 pts entered the re-exposure period and 140 completed. Their baseline demographics and disease characteristics were similar to those of pts at study entry (mean RA duration ~0.5 yrs). The mean (SD) DAS28 at re-exposure period entry was 5.47 (1.27) and, at the end of the re-exposure period, was 2.43 (0.95). A total of 62% (78/126) of evaluable pts were in DAS28 (CRP) remission on re-exposure period Day 169. The mean (SD) HAQ at re-exposure period entry was 1.45 (0.64) and, at the end of the re-exposure period, was 0.63 (0.57). Over 12 months of the withdrawal period, the numbers (%) of serious AEs were 2 (2.4), 0 (0) and 5 (6.7), respectively, and only 1 serious infection was reported in the MTX alone arm (pyelonephritis; 337.4 pt-yrs). In the re-exposure period, no pts discontinued due to AEs and no serious infections were reported (292.2 pt-yrs). The overall rates of infections were 8.9 and 16 (incidence rate/100 pt-yrs) in the withdrawal and re-exposure periods, respectively (overall rates were 110.7 and 72.8 in the first and second 6 months of the initial treatment period). Multivariate analysis to identify predictors of time to flare and achieving DAS28 (CRP) <2.6 in the re-exposure period will be presented.

Conclusion: Re-treatment with abatacept + MTX can effectively recapture prior remission following flare after complete withdrawal of therapy. The likelihood of ever achieving a MCR was more likely in pts in the abatacept + MTX arm (> abatacept > MTX). There were far fewer infection events in the combined withdrawal period and re-exposure period than in the initial treatment period and only 1 serious infection was reported in the combined withdrawal period and treatment period suggesting re-treatment is well tolerated.

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Abstract Number: 564

Value of Antinuclear Antibodies As a Predictor of Therapeutic Efficacy of Biologics in Rheumatoid Arthritis

Corina Mogosan[1], Luminita Enache[1], Denisa Stanciu[1], Daniela Opris[2], Simona Rednic[3], Magda Parvu[4], Horatiu Popoviciu[5], Ruxandra Ionescu[2] and Catalin Codreanu[1], [1]Rheumatology, 'Dr. Ion Stoia' Clinical Center of Rheumatic Diseases, Bucharest, Romania, [2]University of Medicine and Pharmacy "Carol Davila", Department of Internal Medicine and Rheumatology "Sf. Maria" Hospital, Bucharest, Romania, [3]Rheumatology,

Emergency County Clinical Hospital Cluj Napoca, Cluj-Napoca, Romania, [4]Internal Medicine, “N.Gh. Lupu” Clinical Hospital, Bucharest, Romania, [5]Rheumatology, Emergency County Hospital, Targu Mures, Romania
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Background/Purpose: Therapeutic target in rheumatoid arthritis (RA) aims at achieving remission or low disease activity. Among the known poor prognostic factors are anti–citrullinated protein antibody (ACPA) and rheumatoid factor (RF). Clinical significance and therapeutic implications of the positivity of antinuclear antibodies (ANA) in serum of RA patients before starting the biological treatment is still under debate.

Purpose: The implications of ANA positivity, as a prognostic factor, in the therapeutic response to biologic therapy in RA, as measured by DAS28 score.

Methods: observational study; all data were gathered from the electronic database of Romanian Registry of Rheumatic Diseases (RRBR) which comprises all RA patients following biological treatment in the country. There were included only RA patients who were evaluated for the presence of ANA, before initiating any biologic therapy.

Results: 740 RA patients were included in the study, mean age 56.50 years (± 12.59), 84.5% women, mean disease duration 12.54 years (± 7.67). At baseline (prior to any biologic start), 26.9% patients were positive for ANA, 89.8% for RF, 37% for ACPA, 35.1% were double seropositive (for RF and ACPA) while 13.1% were triple seropositive (RF, ACPA, and ANA) and the mean DAS28 was 5.09 ± 2.35. 72.4% patients were treated with TNF-alpha blockers, while 27.6% with anti-CD20 drugs. During evolution, 22% of subjects required switch of therapy. Biologics persistency (the duration of therapy under one drug) was 31.70 (± 29.95) months and the latest DAS 28 score was 2.90 ± 1.41. There were statistically significant differences between DAS28 values at all assessments, depending on the presence of ANA. At biological start, DAS28 score in ANA positive group was 5.70 ± 2.06, while in ANA negative group was 4.86 ± 2.41 ($p < 0.001$). Concerning efficacy, assessed by the latest DAS28, ANA positive group had a score of 3.32 ± 1.61, compared to 2.74 ± 1.30 in ANA negative patients ($p < 0.001$). The drug persistence in ANA positive patients was 22.65 ± 25.68 months, versus 34.86 ± 30.71 months in ANA negative group ($p < 0.001$). For patients who required switch of therapy, DAS28 score at switch time was 5.42 ± 1.52 in ANA positive group, versus 4.79 ± 1.80 in ANA negative group ($p = 0.05$). There is a poor positive association between ANA positivity and DAS28 at all assessments ($r = 0.2$, $p < 0.01$) and ACPA positivity ($r = 0.2$, $p < 0.01$) and a negative correlation between ANA positivity and drug persistence ($r = -0.2$, $p < 0.01$). Linear regression showed that the best predictor of the current value of DAS28 is ANA positivity, independent of the presence of RF, ACPA, double or triple seropositivity ($t=2$, $p<0.05$).

Conclusion: ANA positivity in patients with RA, before starting any biological therapy, may be a poor prognostic factor for the therapeutic efficacy, as well as for the drug persistence. More studies are needed to confirm these observations.

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Abstract Number: 565

Factors Associated with Sustained Response in Patients with Rheumatoid Arthritis Who Received Rituximab within the US Corrona Registry

Leslie Harrold[1,2], Ani John[3], George W. Reed[1], Chitra Karki[2], Robert Magner[1], Joel M. Kremer[4], Ashwini Shewede[3] and Jeffrey Greenberg[2,5], [1]University of Massachusetts Medical School, Worcester, MA, [2]Corrona, LLC, Southborough, MA, [3]Genentech, Inc., South San Francisco, CA, [4]Albany Medical College and The Center for Rheumatology, Albany, NY, [5]NYU School of Medicine, New York, NY
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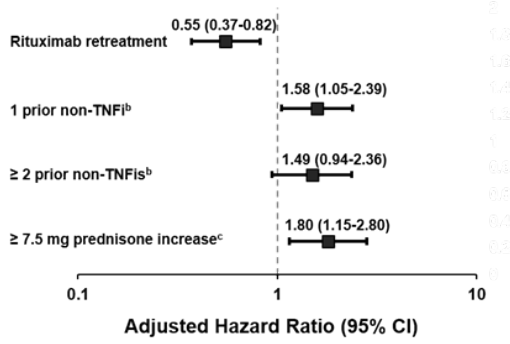
Background/Purpose: The goal of treatment for patients with rheumatoid arthritis (RA) is to achieve and maintain low disease activity (LDA) or remission. Little information is available on the likelihood and predictors of sustained response following LDA/remission among patients receiving rituximab. The objective of this analysis was to examine factors associated with sustained response in patients with RA treated with rituximab in the Corrona registry.

Methods: Corrona is a US-based, prospective, observational cohort of nearly 40,000 patients with RA. Patients with moderate or high disease activity (Clinical Disease Activity Index [CDAI] > 10) who initiated rituximab and who achieved LDA/remission (CDAI ≤ 10) within 12 months of their last rituximab infusion were included. Patients were followed until loss of response (CDAI > 10), initiation of another biologic or small molecule or exit from the registry. Covariates ascertained at the time of rituximab initiation included functional status, CDAI and patient-reported pain. Covariates examined at LDA/remission were demographic and clinical characteristics, prior medications and concomitant steroid and conventional synthetic disease-modifying antirheumatic drug (csDMARD) use. Time from rituximab initiation to LDA/remission was estimated. Time-varying covariates included rate of rituximab retreatment, number of prednisone dose increases and csDMARD initiations over time. Survival analyses and Cox proportional hazard regression models estimated the likelihood of sustained response following rituximab treatment and associations between covariates of interest and sustained response.

Results: Of the 1184 patients who initiated rituximab and had ≥ 1 follow-up appointment, 306 patients achieved LDA/remission within 12 months of their last rituximab infusion (median [IQR] time to LDA/remission, 5 [3-10] months). Most patients were female (76%) with a median (IQR) age of 60 (52-68) years; over 84% of patients had received ≥ 2 prior biologics. Of these patients, 34% received rituximab retreatments at a median (IQR) rate of 1.01 (0.71-1.36) retreatments per year. Twelve months after achievement of LDA/remission, 49% of patients maintained their response. In adjusted models (**Figure**), rituximab retreatment was associated with a significantly increased likelihood of sustained response, while prednisone dose increases ≥ 7.5 mg and use of 1 prior non–tumor necrosis factor inhibitor (TNFi) biologic were associated with increased likelihood of loss of response.

Conclusion: In this cohort of patients with refractory disease and use of several prior biologics who achieved LDA/remission following rituximab treatment, rituximab retreatment was associated with significantly greater sustained response. Increased prednisone doses and prior non-TNFi biologic use, factors that are likely surrogate markers of more severe disease, were associated with shorter sustained response.

Figure. Adjusted Analysis of Key Factors Associated With Loss of Sustained LDA/Remission in Patients Treated With Rituximab[a]



CDAI, Clinical Disease Activity Index; LDA, low disease activity; mHAQ, modified Health Assessment Questionnaire; RA, rheumatoid arthritis; TNFi, tumor necrosis factor inhibitor.
[a] Adjusted analysis includes all significant covariates from the unadjusted analysis (rituximab retreatment, BMI, mHAQ, classification of global functional status in RA and prednisone dose) as well as covariates defined a priori as those factors previously shown to influence likelihood of sustained LDA/remission (age, sex, disease duration, no. of prior TNFis and disease activity at the time of rituximab initiation).
[b] Zero prior TNFis is referent.
[c] No prednisone dose increase is referent.
[d] Other factors assessed that were not significant (not shown) included age, sex, BMI, duration of RA, baseline CDAI, mHAQ, functional status, no. of prior TNFis and prednisone dose increases < 7.5 mg.

Disclosure: L. Harrold, Corrona, LLC, 2; **A. John**, Genentech, Inc, 3; **G. W. Reed**, Corrona, LLC, 3; **C. Karki**, Corrona, LLC, 3; **R. Magner**, None; **J. M. Kremer**, Corrona LLC, 1,Corrona, LLC, 3,Genentech, Inc., 5,Genentech, Inc., 2; **A. Shewede**, Genentech, Inc., 3; **J. Greenberg**, Corrona, LLC, 1,Corrona, LLC, 3,AstraZeneca, 5,Celgene, 5,Novartis Pharmaceutical Corporation, 5,Pfizer Inc, 5.

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Abstract Number: 566

Genome-Wide Trans-Ancestry Meta-Analysis of Herpes Zoster in RA and Pso Patients Treated with Tofacitinib

Nan Bing[1], HuanYu Zhou[1], BaoHong Zhang[1], John D Bradley[2], Makoto Nagaoka[3], Hernan Valdez[4], Michael Vincent[1] and James D. Clark[1], [1]Pfizer Inc, Cambridge, MA, [2]Pfizer Inc, Groton, CT, [3]Pfizer Inc, Tokyo, Japan, [4]Pfizer Inc, New York, NY

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Background/Purpose: Tofacitinib is an oral Janus kinase inhibitor for the treatment of rheumatoid arthritis (RA). Rates of herpes zoster (HZ) were higher than observed with other agents used to treat RA in tofacitinib RA development program, especially in Japan and Korea.[1] Higher than expected HZ rates were also recognized in the tofacitinib psoriasis (PsO) studies in Japan. It is important to identify mechanisms of increased risk of HZ infection for patients receiving tofacitinib. The objectives of this study were to determine if the increased risk of HZ seen with tofacitinib are associated with genetic risk factors, and whether the genetic risk factor can inform the mechanisms of increased HZ rate under tofacitinib that varied across ethnicities.

Methods: We performed a trans-ethnic and trans-indication meta-analysis of genome-wide association study in a total of 5,246 tofacitinib-treated subjects in RA, PsO Phase 2, 3 and long-term extension (LTE) studies (data cut-off April 2014; LTE ongoing, database not locked), by evaluating ~8 million genetic variants on HZ event (case vs control) and time to HZ event via logistic and Cox regression, respectively.

Results: After adjusting for age, baseline absolute lymphocyte count, genetically defined ethnicity and concomitant methotrexate use (RA only), we identified five loci associated with either increased HZ event rate and/or shorter time to HZ event at genome wide significance ($P < 5 \times 10^{-8}$). Two associations were noteworthy based on biological plausibility. A SNP near *CD83* (and *LINC01108*) was associated with increased risk of HZ events (meta-analysis OR = 3.7, $P = 2.1 \times 10^{-8}$). The frequency of the risk allele was low in Caucasians (<3%) and rare in Japanese (<0.1%). CD83 is expressed on multiple immune subsets, is a marker of dendritic cell maturation and B cell activation and is down-regulated in dendritic cells by VZV infection suggesting a plausible mechanism. The second association was near *IL-17RB*, and this SNP was associated with faster rate of HZ onset (meta-analysis HR = 3.6, $P = 7.6 \times 10^{-10}$). This association was driven by a risk allele common in Japan (~17% in the general Japanese population) but <0.2% in Caucasians. *IL-17RB* is highly expressed on iNKT2 and iNKT17 cells, whereas iNKT1 cells are *IL-17RB* negative and dependent on JAK-dependent IL-15. iNKT cell deficiency with low production of interferon gamma by iNKT cells is linked to disseminated varicella in response to vaccination in two case reports, despite a generally intact immune system. Overexpression of IL-25, the ligand for *IL-17RB*, also leads to recurrence of varicella, suggesting that the ratio of iNKT1 to iNKT2 and 17 cells is important.

Conclusion: Genetic analysis of ~5,300 individuals treated with tofacitinib has identified multiple loci that are associated with increased risk of HZ. The risk allele of one of these polymorphisms is significantly more prevalent in the Japanese population. A possible iNKT cell skewing mechanism is suggested that will be evaluated in future studies.

REFERENCE: 1. Winthrop KL et al. Arthritis Rheumatol 2014; 66: 2675-84.

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Disclosure: N. Bing, Pfizer Inc, 1,Pfizer Inc, 3; **H. Zhou**, Pfizer Inc, 1,Pfizer Inc, 3; **B. Zhang**, Pfizer Inc, 1,Pfizer Inc, 3; **J. D. Bradley**, Pfizer Inc, 1,Pfizer Inc, 3; **M. Nagaoka**, Pfizer Inc, 1,Pfizer Inc, 3; **H. Valdez**, Pfizer Inc, 1,Pfizer Inc, 3; **M. Vincent**, Pfizer Inc, 1,Pfizer Inc, 3; **J. D. Clark**, Pfizer Inc, 1,Pfizer Inc, 3.

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Abstract Number: 567

Rituximab Associated Late Onset Neutropenia – a Rheumatology Case Series and Review of the Literature

William Monaco[1], William F.C. Rigby[2] and Jonathan Jones[3], [1]Internal Medicine, Dartmouth-Hitchcock Medical Center, Lebanon, NH, [2]Geisel School of Medicine at Dartmouth, Lebanon, NH, [3]Rheumatology, Dartmouth-Hitchcock Medical Center, Lebanon, NH

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Background/Purpose: Rituximab (RTX) has been associated with late onset neutropenia (LON), defined as an absolute neutrophil count (ANC) < 1.5 x 10^9/L at least 4 weeks after the last infusion. Reports of LON are primarily found in the hematology literature. We determined the incidence of LON in patients with rheumatic disease at a single tertiary medical center, ascertained patient characteristics, and performed a literature review.

Methods: We performed a retrospective study of patients at Dartmouth-Hitchcock Medical Center that received RTX for a rheumatologic disease between 2006-2014 and developed LON. In addition, we reviewed 4 case series of LON after RTX was given for rheumatologic disorders.

Results: We found 11 patients who developed LON (6 male and 5 female, average age 63), which was 6.5% of 168 patients receiving RTX. The most common diagnosis was RA (9 LON patients and 73% of all patients who got RTX). The average time to LON after RTX therapy was 90 days (range of 40 to 198 days). The average ANC nadir was 0.5 x 10^9/L, and while 3 patients received granulocyte colony-stimulating factor (G-CSF), all patients' neutrophil counts normalized. The median total dose of RTX prior to LON was 5 gms. 4 patients presented with an infection (biliary sepsis, pneumonia, cellulitis, and perirectal abscess), 2 presented with fever without an infectious etiology, 1 patient complained of abdominal pain, and 4 cases were found with routine blood work (1 of these patients was hospitalized with a large bowel obstruction). 8 of the 11 patients were given a repeat infusion of RTX after recovery of their neutrophil count; none went on to re-develop LON. Bone marrow biopsies from 4 patients had the predominant cell line as lymphocytes, comprising an average of 41% (range 24-50%) of the cellular aspirate followed by monocytes (16%), promyelocytes (12%), and neutrophils/bands (8%).

From the literature, we identified 36 patients (8 male and 28 female, average age 55) who developed LON after RTX therapy. Again, the most common diagnosis was RA (58% of patients). Compared to our cohort, these patients had similar times to LON, ANC nadir, and average RTX dose prior to LON. Most patients presented asymptomatically and all survived. Neutrophil counts recovered in all patients spontaneously or with G-CSF. If patients received G-CSF, the only difference was time to recovery of neutrophil counts: 6.4 ± 3.2 days with G-CSF vs 11.2 ± 6.3 days without G-CSF (p=0.04). There were no reported cases of LON recurrence when patients were given RTX after recovery of neutrophil counts.

Conclusion: LON is a rare complication of RTX affecting approximately 5% of patients. While these patients can present with infection, they typically recover without serious sequelae. Among reported cases, RTX rechallenge does not lead to recurrence of neutropenia. Though the etiology of LON is unknown, there is some evidence that LON is caused by an imbalance of lymphopoiesis and granulopoiesis and/or maturation arrest at the promyelocyte stage.

Disclosure: W. Monaco, None; **W. F. C. Rigby**, None; **J. Jones**, None.

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Abstract Number: 568

Superiority of Initial Combination- over Step up Therapy in Treatment to the Target of Remission in Daily Clinical Practice in Early Rheumatoid Arthritis Patients: Results from the DREAM Registry

Laura M.M. Steunebrink[1], G.A. Versteeg[1], Harald E. Vonkeman[2], Peter M. ten Klooster[3], Ina H. Kuper[1], Arie E. van der Bijl[4], Piet L.C.M. van Riel[5] and Mart A.F.J. van de Laar[1], [1]Rheumatology, Medisch Spectrum Twente - Arthritis Center Twente, Enschede, Netherlands, [2]Ariensplein 1, Medisch Spectrum Twente - Arthritis Center Twente, Enschede, Netherlands, [3]Pcgr, University of Twente, Enschede, Netherlands, [4]Isala Klinieken, Zwolle, Netherlands, [5]Rheumatology, Bernhoven, Uden, Netherlands
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Background/Purpose: Treat-to-target (T2T) of remission strategies has been widely accepted as the standard of care for patients with Rheumatoid Arthritis (RA). In early RA, implementation of T2T in daily clinical practice has been shown to provide earlier clinical improvement. However, the optimal treatment protocol is still not clear.

The objective of this study is to compare the effectiveness of two T2T strategies: a step up approach starting with methotrexate (MTX) monotherapy (cohort I) versus an initial combination approach (cohort II) starting with high dose of MTX, hydroxychloroquine (HCQ) and an optional intramuscular triamcinolone acetonide (TCA) injection in early RA patients.

Methods: Baseline demographics, clinical and patient-reported outcome measures and one-year follow-up data were used. A total number of 128 patients from cohort II were case-control matched with 128 patients from cohort I on gender, age and baseline disease activity. Twelve month follow-up data were available for 121 patients in both cohorts. The primary outcome was the proportion of patients having reached at least one DAS28 <2.6 (DAS28 remission) after 1 year. Secondary outcomes were time to achieve remission and mean-changes in DAS28 scores at 6 months and 1 year. **Results** were analyzed using chi-square tests for proportional differences, t-tests for mean differences and Kaplan-Meier survival analysis for between-group differences in time to achieve remission. The course over time was compared between groups by specifying a linear mixed model with strategy and time as fixed factors. An ante-dependence structure was used as a model for the covariance matrix, since it gave the best fit to the data. Post-hoc ANCOVA analyses were performed with baseline DAS28 score as a covariate.

Results: After one year of follow-up, remission was reached at least once in 77.3% of the patients in cohort II versus 71.9% in cohort I (p=0.391). Median time to first remission was 17 weeks in cohort II versus 27 weeks in cohort I (p=0.044). A significant time by strategy interaction was found. Post-hoc analysis revealed a significant difference between strategies at 6 months (p=0.04, mean difference = 0.295, 95% CI= 0.01 - 0.58) but not at 12 months (p=0.36, mean difference = 0.128, 95% CI= -0.14 - 0.4).

Conclusion: In patients with early RA treated according to the T2T principles, the initial combination therapy with MTX and HCQ and optional TCA resulted in significantly quicker remission and lower disease activity at 6 months than the step up strategy starting with MTX monotherapy. At 12 months, no significant differences remained in mean DAS28 scores or the proportion of patients in remission.

Disclosure: L. M. M. Steunebrink, None; **G. A. Versteeg**, None; **H. E. Vonkeman**, None; **P. M. ten Klooster**, None; **I. H. Kuper**, None; **A. E. van der Bijl**, None; **P. L. C. M. van Riel**, None; **M. A. F. J. van de Laar**, None.

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Abstract Number: 569

Neurophil to Lymphocyte Ratio Is a Reliable Marker of Treatment Response in Rheumatoid Arthritis Patients during Tocilizumab Therapy

Byeongzu Ghang[1], Doo-Ho Lim[2], Soo Min Ahn[3], Wook Jang Seo[4], Seokchan Hong[3], Yong-Gil Kim[2], Chang-Keun Lee[2] and Bin Yoo[2], [1]Division of Rheumatology, Department of Internal Medicine, Univerisy of Ulsan College of Medicine, Asan Medical Center, Seoul, South Korea, [2]Division of Rheumatology, Department of Internal Medicine, Department of Rheumatology, University of Ulsan College of Medicine, Asan Medical Center, Seoul, South Korea, [3]Division of Rheumatology, Department of Internal Medicine, University of Ulsan College of Medicine, Asan Medical Center, Seoul, South Korea, [4]Internal Medicine, Seoul Veterans Hospital, Seoul, South Korea
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Background/Purpose: Tocilizumab, an interleukin-6 (IL-6) receptor antagonist, is an effective drug for the treatment of rheumatoid arthritis (RA). During administration of tocilizumab, previous studies have shown that the levels of erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), classic acute phase reactants, might not be elevated even in RA patients with high inflammatory activity due to infection. Therefore, we evaluated whether neutrophil–lymphocyte ratio (NLR), which has been recently introduced as a useful parameter for monitoring the disease activity in systemic inflammatory diseases, reflect treatment response to tocilizumab therapy better than ESR and CRP in patients with RA.

Methods: A total of 72 RA patients treated with tocilizumab in a single tertiary referral hospital from Jan 2013 to Dec 2014 were initially included in our study. We excluded 30 patients due to infection (n=9), administration less than six months (n=8), adverse event (n=6), violation of interval (n=5), pregnancy (n=1), and combined malignancy (n=1). Out of the remaining 42 patients, 14 experienced flare-up during tocilizumab therapy. Flare-up was defined as events that needed either dose escalation of steroid, intra-articular steroid injection or switch tocilizumab to another biologic agent. The data were retrospectively reviewed with the electronic medical records. We compared levels of inflammatory markers including leukocyte count, ESR, CRP and NLR at flare-up and stable state before flare-up. Moreover, 28 patients with stable RA after tocilizumab administration were also evaluated. The levels of inflammatory markers were compared at three and six months after initiation of tocilizumab.

Results: In the group of patients who experienced flare-up during tocilizumab treatment, the levels of CRP were not significantly different between those measured at stable state and flare-up (0.32 ± 0.45 vs 0.73 ± 1.03 mg/dL, p=0.110). The levels of ESR and the values of NLR were

significantly different between those measured at stable state and flare-up (14.9 ± 15.8 vs 24.3 ± 23.3 mm/hr, p=0.041 and 1.98 ±1.01 vs 4.05 ± 3.42, p=0.002). The levels of ESR and CRP measured at flare-up ranged within the normal limit in eight and nine patients each, and four and three patients each had decreased levels of ESR and CRP at flare-up compared with those at stable state. However, the values of NLR in all patients except one patient increased significantly at flare-up compared to stable state, and the percentage of increment ranged from -13 to 437%(105 ± 42). In the group of patients who were stable during tocilizumab treatment, the levels of NLR did not change between those measured at three and six months after initiation of tocilizumab (1.47 ± 0.70 vs 1.30 ± 0.69, p=0.233).

Conclusion: The levels of CRP did not reflect treatment response to tocilizumab administration in RA patients, whereas the values of NLR were significantly increased in the flare group. The values of NLR were more associated with treatment response to tocilizumab than the levels of ESR. Thus, our present findings suggest that NLR is more valuable for evaluating the disease activity in patients with RA during tocilizumab therapy.

Disclosure: B. Ghang, None; **D. H. Lim**, None; **S. M. Ahn**, None; **W. J. Seo**, None; **S. Hong**, None; **Y. G. Kim**, None; **C. K. Lee**, None; **B. Yoo**, None.

Abstract Number: 570

Dose Selection of Namilumab, an Anti-GM-CSF Monoclonal Antibody: An Integrated Pharmacokinetic and Pharmacodynamic Approach for Phase II Studies in Patients with Rheumatoid Arthritis

Thomas Wagner[1], Ulrich Thienel[2], Eva-Maria Vieser[3], Bernard Souberbielle[4] and Gezim Lahu[1], [1]Takeda Pharmaceuticals, Zurich, Switzerland, [2]Takeda Pharmaceuticals, Deerfield, IL, [3]AMGEN Research (Munich) GmbH, Munich, Germany, [4]Takeda Pharmaceuticals, London, United Kingdom

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Background/Purpose: Granulocyte macrophage-colony stimulating factor (GM-CSF) mediates a range of immunological and inflammatory processes, and plays a role in a variety of inflammatory diseases. Namilumab (AMG203), a human immunoglobulin G1 (IgG1) monoclonal antibody with high affinity for the GM-CSF ligand, is under investigation in rheumatoid arthritis (RA) and psoriasis. Selection of an appropriate dosing schedule using modelling and simulation for proof-of-concept (PoC) studies is a key step in drug development. The objective of this analysis was to integrate clinical and non-clinical pharmacokinetic (PK) and pharmacodynamic (PD) data to identify an appropriate subcutaneous dosage for namilumab PoC and traditional Phase II studies.

Methods: A range of data was used to build the fundamentals of the analysis. Initially, the effective concentration of 22E9, a surrogate mouse antibody of namilumab, in a collagen-induced arthritis (CIA) mouse model was combined with the outcome of an ex-vivo cellular inhibition assay for namilumab in order to suggest an efficacious concentration range (22E9 and namilumab have similar neutralising potencies against murine and human GM-CSF, respectively). In addition, PK and PD similarities and differences between namilumab and anti-TNF-α antibodies, as well as known cytokine levels in joints of patients with RA, were used to support the predicted efficacy range of namilumab. These concentrations were translated into human doses using a population PK model developed based on data from two Phase I studies of namilumab in healthy volunteers (single ascending intravenous doses up to 8 mg/kg) and patients with mild-to-moderate RA (repeated subcutaneous doses of 150 or 300 mg; PRIORA, NCT01317797).

Results: The EC_{50} for namilumab was calculated as 11 µg/mL in the CIA mouse model, which was supported by results of the ex-vivo blood assay. In addition, the observation of similar affinities of anti-TNF-α antibodies (12–90 pM) and namilumab (46 pM), in conjunction with target expression in the synovium in similar ranges of magnitude, indicated that targeting clinical concentration ranges seen with anti-TNF-α antibodies should translate into clinical efficacy. Next, a population PK model was applied to translate clinical concentration ranges into dosing schedules. Doses from 20 to 150 mg were selected with the intent to cover low, medium and high efficacious exposures in RA and psoriasis. In addition, a loading dose was suggested for a selected Phase II trial.

Conclusion: Integration of preclinical and clinical PK and PD data for namilumab and combination of these with data from anti-TNF-α antibodies was essential to determine the appropriate namilumab dose schedule for evaluation in Phase II studies.

Disclosure: T. Wagner, Takeda Pharmaceuticals Inc., 3; **U. Thienel**, Takeda Pharmaceuticals Inc., 3; **E. M. Vieser**, Amgen Research (Munich) GmbH, 3; **B. Souberbielle**, Takeda Pharmaceuticals International, 1,Takeda Pharmaceuticals Inc., 3; **G. Lahu**, Takeda Pharmaceuticals Inc., 3.

Abstract Number: 571

Malignancy Data in Tofacitinib-Treated Japanese Patients with Rheumatoid Arthritis

Yoshiya Tanaka[1], Tsutomu Takeuchi[2], Hisashi Yamanaka[3], Naonobu Sugiyama M.D., Ph.D[4], Takunari Yoshinaga[4], Kanae Togo[4], Jamie Geier[5], Mary Boy[5] and Carol Connell[5], [1]The First Department of Internal Medicine, University of Occupational and Environmental Health, Kitakyushu, Japan, [2]Keio University School of Medicine, Tokyo, Japan, [3]Tokyo Women's Medical University, Tokyo, Japan, [4]Pfizer Japan Inc, Tokyo, Japan, [5]Pfizer Inc, Groton, CT

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Background/Purpose: Tofacitinib is an oral Janus kinase inhibitor for the treatment of rheumatoid arthritis (RA). In the global tofacitinib RA clinical program, rates and types of malignancies remained stable over time with increasing tofacitinib exposure; the overall malignancy incidence rate (IR) (excluding non-melanoma skin cancer [NMSC]) was 0.85 (95% CI, 0.70-1.02) events per 100 patient-years (pt-yrs); age- and sex-adjusted standardized incidence ratio (SIR) vs. US SEER database was 1.17 (95% CI, 0.96-1.41).[1] This analysis evaluated malignancy (excluding NMSC) in Japanese RA (JRA) pts in the tofacitinib clinical program, compared with JRA and Japanese general populations (JGP).

Methods: Malignancy data were pooled from 2 Phase (P) 2, 1 P3 and 1 open-label long-term extension (LTE) RA studies conducted in Japan (April 2014 data cut). Pts received tofacitinib 5 or 10 mg twice daily (BID) in P3 and LTE; also 1, 3, and 15 mg BID in P2.

Malignancy data were also obtained for: JGP aged 16-<75 yrs (2010 data from the Cancer Information Service, National Cancer Center, Japan)[2]; Japan Medical Data Center (JMDC) RA population aged 16-<75 yrs (Jan 2005 to Oct 2013).

Results: 556 JRA pts (1705 pt-yrs of exposure) received tofacitinib in P2/P3/LTE studies; 22 pts had malignancies. From JMDC (23,481 pts in total), 14,728 pts received any treatment for RA; 2,317 pts received nonbiologic or biologic DMARDs.

Cumulative IRs for malignancy (excluding NMSC) in tofacitinib-treated JRA pts in clinical trials are shown in the Figure; SIRs (95% CI) for malignancy (excluding NMSC) were 2.13 (1.33-3.22) vs. JGP, 1.21 (0.76-1.83) vs. JMDC population receiving any treatment for RA, and 0.87 (0.55-1.32) vs. JMDC population receiving nonbiologic or biologic DMARDs (Table).

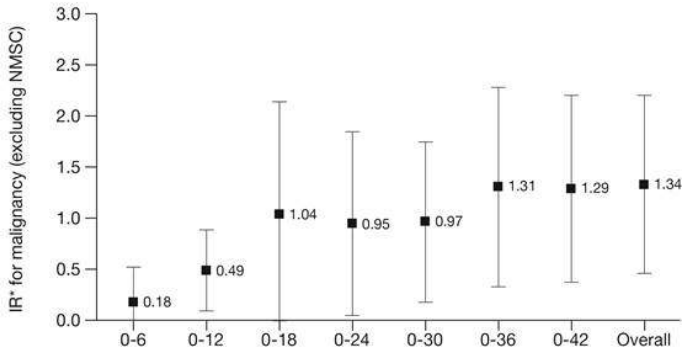
Conclusion: Following numerically lower incidence rates over months 0-12 with possible effect of pre-randomization screening, the risk of all malignancies (excluding NMSC) among JRA pts exposed to tofacitinib appears stable with increasing exposure to tofacitinib. The overall malignancy rate in the tofacitinib-treated JRA population was similar to the JMDC RA populations, and was increased compared with the JGP. Given the limited pt-yrs accrued to date in Japan, ongoing post-marketing surveillance will further evaluate malignancy among JRA pts exposed to tofacitinib.

References:

1. Curtis et al. Ann Rheum Dis doi:10.1136/annrheumdis-2014-205847.

2. Cancer Information Service, National Cancer Center, Japan http://ganjoho.jp/en/professional/statistics/table_download.html (accessed Feb 24, 2015)

Figure. Cumulative incidence rate* for malignancy (excluding NMSC) for tofacitinib-treated RA patients in Japanese clinical trials



N	556	556	556	556	556	556	556	556
Total exposure (pt-yr)	254.2	489.3	709.6	917.1	1114.6	1301.0	1473.8	1703.8
Pts with events (n)	1	6	10	13	16	18	19	22
IR* per 100 pt-yr	0.18	0.49	1.04	0.95	0.97	1.31	1.29	1.34
95% CI	0.00–0.52	0.09–0.89	0.00–2.14	0.05–1.85	0.18–1.75	0.33–2.29	0.37–2.21	0.46–2.21

*Age- and sex-adjusted to the Japanese general population, 2010
CI, confidence intervals; IR, incidence rate; NMSC, non-melanoma skin cancer; pt-yr, patient-years

Table. Crude IR and SIR for malignancy (excluding NMSC) for tofacitinib-treated RA patients in Japanese clinical trials compared with reference populations

		Crude IR (95% CI), events/100 pt-yrs	SIR (95% CI)
Comparator population	**Tofacitinib-treated RA patients in Japanese clinical trials**	1.29 (0.81, 1.96)	-
Reference populations	**JGP**	0.55 (0.55, 0.55)	2.13 (1.33, 3.22)
	JMDC population receiving any treatment for RA	0.77 (0.68, 0.88)	1.21 (0.76, 1.83)
	JMDC population receiving nonbiologic or biologic DMARDs	1.09 (0.81, 1.42)	0.87 (0.55, 1.32)

CI, confidence intervals; IR, incidence rates; JGP, Japanese general population – 2010; JMDC, Japan Medical Data Center RA population – Jan 2005 to Oct 2013; NMSC, non-melanoma skin cancer; pt-yrs, patient-years; SEER, US National Cancer Institute Surveillance and Epidemiology and End Results database, 1992–2011; SIR, standardized incidence ratios.

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Abstract Number: 572

Predictors of Long-Term Retention of Infliximab and Golimumab in Rheumatoid Arthritis: An Analysis from a Prospective, Observational Registry

Edward C. Keystone[1], Philip Baer[2], Mary J. Bell[3], Andrew Chow[4], Louis Bessette[5], Boulos Haraoui[6], Wojciech Olszynski[7], John Kelsall[8],

Emmanouil Rampakakis[9], John S. Sampalis[9], Allen J Lehman[10], Francois Nantel[11], Brendan Osborne[12], Cathy Tkaczyk[12] and Karina Maslova[10], [1]University of Toronto/Rebecca MacDonald Centre for Arthritis and Autoimmune Disease, Toronto, ON, Canada, [2]Section on Rheumatology, Ontario Medical Association/Journal of the Canadian Rheumatology Association, Toronto, ON, Canada, [3]Rheum Div, Sunnybrook Health Sciences Centre/University of Toronto, Toronto, ON, Canada, [4]University of Toronto/McMaster University, Mississauga, ON, Canada, [5]Centre d'Ostéoporose et de Rhumatologie de Québec (CORQ), Québec, QC, Canada, [6]Institut de Rhumatologie de Montréal and University of Montreal, Montreal, QC, Canada, [7]University of Saskatchewan, Saskatoon, SK, Canada, [8]Mary Pack Arthritis Centre, Vancouver, Vancouver, BC, Canada, [9]JSS Medical Research, St-Laurent, QC, Canada, [10]Janssen Inc., Toronto, ON, Canada, [11]19 Green belt Dr, Janssen Inc., Toronto, ON, Canada, [12]Medical Affairs, Janssen Inc., Toronto, ON, Canada
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Background/Purpose:

Previous studies have shown differences in treatment retention between anti-TNF agents. Furthermore, although inconsistent, data from the literature suggest that some factors (e.g. concomitant methotrexate use) may be associated with improved retention of certain anti-TNF agents. The aim of this analysis was to compare the long-term retention of infliximab (IFX) and golimumab (GLM) and to identify independent predictors of retention in patients with rheumatoid arthritis (RA) followed in Canadian routine practice

Methods:

BioTRAC is an ongoing, prospective registry of patients initiating treatment for RA, ankylosing spondylitis, or psoriatic arthritis with IFX or GLM. Eligible people for this analysis included RA patients treated with IFX who were enrolled since 2002 or with GLM enrolled since 2010; patients not discontinued who had a follow-up of <18 months were excluded. Independent predictors of long-term retention, defined as ≥18 months, were assessed with multivariate logistic regression using backwards variable selection. Receiver operator curve (ROC) analysis was used to determine the optimal cut-off points of CDAI for long-term retention

Results:

A total of 972 patients (76.3% female) were included with mean (SD) age of 55.9 (13.8) years and disease duration of 8.6 (9.1) years at baseline. The majority were biologic naïve (94.5%), treated with IFX (84.8%), and received a concomitant DMARD (88.5%) at baseline; 35.9% were treated with a corticosteroid (CS). Mean (SD) disease parameters at baseline were: CDAI: 35.3 (17.5); HAQ: 1.6 (0.7); swollen joint count (0-28): 10.3 (6.8); tender joint count (0-28): 12.0 (7.9); patient global (VAS cm): 6.0 (2.5); physician global (0-10 NRS): 6.4 (2.1).

Six hundred (61.7%) patients received treatment for ≥18 months. In univariate analysis, age [OR (95% CI): 0.99 (0.98-1.00)], disease duration [0.97 (0.95-0.99)], enrolment year [1.10 (1.06-1.15)], male gender [0.68 (0.50-0.94)], GLM vs. IFX use [2.24 (1.58-3.19)], biologic naiveté [0.58 (0.33-1.01)], and baseline DMARD use [0.54 (0.36-0.80)] were identified as potential predictors of retention (P<0.100). Baseline CS use [0.86 (0.66-1.13)], CDAI [1.00 (0.99-1.00)], and HAQ [0.98 (0.81-1.17)] did not have an impact. Upon multivariate adjustment, older age [0.98 (0.97-1.00)] and male gender [0.50 (0.29-0.85)], were associated with significantly lower odds of discontinuation, while more recent enrolment year was associated with higher odds [1.36 (1.20-1.54)].

Lower disease activity (CDAI remission vs. low vs. moderate vs. high) at 6 or 12 months was associated with significantly (P<0.001) higher probability of long-term retention. ROC curve analysis identified a CDAI score at 6 months ≤15.7 (AUC=0.652; P<0.001) and a score at 12 months ≤14.6 (AUC=0.679; P<0.001) as most accurately predicting long-term retention

Conclusion:

The results of this analysis have shown that treatment retention of IFX and GLM in real-world are comparable. Age, gender, and enrolment year, possibly signifying differences in patient preferences or changes over time in clinical practice, as well as CDAI score of 15 or less at 6 or 12 months were identified as significant independent predictors of long-term retention

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Disclosure: E. C. Keystone, Abbott/AbbVie, 5,Amgen, 2,Bristol-Myers Squibb, 5,Hoffmann-La Roche, Inc., 5,Janssen Inc., 2,Janssen Inc., 5,Merck Pharmaceuticals, 5,Pfizer Pharmaceuticals, 5; **P. Baer**, Janssen Inc., 5,AbbVie, 5,Amgen, 5,BMS, 5,Pfizer Inc, 5,Roche Pharmaceuticals, 5; **M. J. Bell**, Janssen Inc., 5; **A. Chow**, Janssen Inc., 5; **L. Bessette**, Janssen Inc., 5; **B. Haraoui**, Janssen Inc.,, 5; **W. Olszynski**, Janssen Inc., 5; **J. Kelsall**, Janssen Inc., 5; **E. Rampakakis**, Bristol-Myers Squibb, 2; **J. S. Sampalis**, JSS Medical Research, 3; **A. J. Lehman**, Janssen Inc., 3; **F. Nantel**, Janssen Inc., 3; **B. Osborne**, Janssen Inc., 3; **C. Tkaczyk**, Janssen Inc., 3; **K. Maslova**, Janssen Inc., 3.

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Abstract Number: 573

Association Between Three Measures of Oral Glucocorticoid Exposure and Potential Adverse Events Among Patients with Rheumatoid Arthritis

Jennie Best[1], Amanda Farr[2], Gregory Lenhart[2], Khaled Sarsour[1], Marni Stott-Miller[2] and Yong Gil Hwang[3], [1]Genentech, South San Francisco, CA, [2]Truven Health Analytics, Cambridge, MA, [3]Department of Medicine, University of Pittsburgh, Pittsburgh, PA
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Session Type: ACR Poster Session A
Session Time: 9:00AM-11:00AM

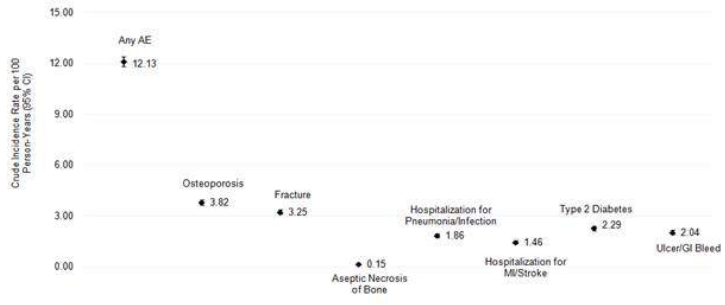
Background/Purpose: Oral glucocorticoids are commonly used to treat rheumatoid arthritis (RA). However, their use may be associated with potential adverse events. Therefore, the objective was to evaluate the association between exposure to oral glucocorticoids and incident adverse events, using three different measures of oral glucocorticoid exposure.

Methods: This retrospective cohort study utilized two large administrative claims databases. Patients with RA aged 18 years and older with at least one prescription claim for an oral glucocorticoid between 1/1/2010-12/31/2013 (index date) were identified. Patients were required to be continuously enrolled for 12 months prior to index date with no claims for oral glucocorticoids, to be continuously enrolled for 1 month after index date and have no diagnoses for other autoimmune conditions. Oral glucocorticoid use was measured in monthly panel periods after the index date. The following measures were captured: cumulative dose in prednisone-equivalent milligrams, months on therapy, and months since last use. Presence and time from index date to any potential adverse event assessed (osteoporosis, fracture, aseptic necrosis of bone, hospitalization for pneumonia or infection, hospitalization for myocardial infarction or stroke, type 2 diabetes, ulcer/gastrointestinal bleed) were measured. Cox proportional hazards models with time-fixed and time-varying covariates were fit to the data.

Results: There were 36,502 RA patients identified; average age 58.2 years and 78.3% female. Patients were followed for a total of 60,663 years. During follow-up, 17,512 patients (48.0%) had at least 3 months with oral glucocorticoid exposure. Mean cumulative dose/month was 59 mg. 7,358 (20.2%) patients had evidence of a potential adverse event. Unadjusted incidence rates are presented in Figure 1. Results from time-varying models are presented in Table 1. Higher cumulative dose and more months of treatment were associated with a significantly increased risk of adverse event, while an increase in the time since last glucocorticoid use was associated with a significantly decreased risk of adverse event. These trends were noted in individual models and in models including all three exposure measures.

Conclusion: Among patients with RA, greater exposure to oral glucocorticoids, operationalized as higher cumulative dose and more months of treatment, was associated with increased risk of experiencing an adverse event. Greater time since last exposure was associated with a decreased risk. It is important for clinicians to consider steroid-sparing treatments for RA patients.

Figure 1.



AE, adverse event; CI, confidence interval; GI, gastrointestinal; MI, myocardial infarction.

Table 1.

	Hazard Ratio (95% Confidence Interval)	p-value
Model 1a: Unadjusted		
Additional 100 mg in cumulative dose	1.0067 (1.0054-1.0080)	<0.0001
Model 1b: Adjusted*		
Additional 100 mg in cumulative dose	1.0055 (1.0042-1.0068)	<0.0001
Model 2a: Unadjusted		
Additional month with use	1.0311 (1.0253-1.0369)	<0.0001
Model 2b: Adjusted*		
Additional month with use	1.0233 (1.0176-1.0292)	<0.0001
Model 3a: Unadjusted		
Additional month since last use	0.9837 (0.9798-0.9877)	<0.0001
Model 3b: Adjusted*		
Additional month since last use	0.9847 (0.9807-0.9887)	<0.0001
Model 4a: Unadjusted		
Additional 100 mg in cumulative dose	1.0030 (1.0010-1.0049)	0.0034
Additional month with use	1.0184 (1.0104-1.0264)	<0.0001
Additional month since last use	0.9914 (0.9869-0.9959)	0.0002
Model 4b: Adjusted*		
Additional 100 mg in cumulative dose	1.0029 (1.0011-1.0048)	0.0021
Additional month with use	1.0099 (1.0021-1.0178)	0.0128
Additional month since last use	0.9901 (0.9856-0.9946)	<0.0001
*Adjusted for time-varying biologic and non-biologic DMARD use and time-fixed age, gender, region, health plan type, urbanicity, payer, Charlson Comorbidity Index, number of unique 3-digit diagnosis codes, number of unique National Drug Codes, asthma diagnosis, cancer diagnosis, hypothyroidism diagnosis, ischemic heart disease diagnosis, and Paget's disease/osteomalacia diagnosis.		

Disclosure: J. Best, Genentech Inc, 1,Genentech Inc, 3; **A. Farr**, Truven Health Analytics, 9; **G. Lenhart**, Truven Health Analytics, 9; **K. Sarsour**, Roche, 1,Roche, 3; **M. Stott-Miller**, Truven Health Analytics, 9; **Y. G. Hwang**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/association-between-three-measures-of-oral-glucocorticoid-exposure-and-potential-adverse-events-among-patients-with-rheumatoid-arthritis

Abstract Number: 574

Metabolomic Profiling Predicts Outcome of Rituximab Therapy in Rheumatoid Arthritis

Shannon Sweeney[1], Arthur Kavanaugh[2], Alessia Lodi[3], Bo Wang[1], David L. Boyle[4], Stefano Tiziani[5] and **Monica Guma**[6], [1]University of Texas at Austin, Austin, TX, [2]University of California San Diego, La Jolla, CA, [3]nutritional Sciences, University of Texas at Austin, Austin, TX, [4]Division of Rheumatology, Allergy and Immunology, University of California, San Diego, La Jolla, CA, [5]Nutritional Sciences, University of Texas at Austin, Austin, TX, [6]Pharmacology, University of California, San Diego, La Jolla, CA

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SESSION INFORMATION

Session Date: Sunday, November 8, 2015

Session Title: Rheumatoid Arthritis - Small Molecules, Biologics and Gene Therapy Poster I

Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose: We hypothesized that characterization of patients' metabolic profiles, utilizing both high-resolution ^{1}H-nuclear magnetic resonance (NMR) and mass spectrometry (MS), might help predict response to rituximab therapy in rheumatoid arthritis (RA).

Methods: 23 active seropositive RA patients on concomitant methotrexate were treated with rituximab (1g intravenously; days 0 and 14; without peri-infusional steroids). Clinical outcome was determined 6 months after treatment. Patients were classified as responders or non-responders according to the ACR20 responses. Blood was collected before (baseline) and at 6 months after rituximab therapy. A Bruker Avance 700 MHz spectrometer and a Thermo Scientific Q Exactive Hybrid Quadrupole-Orbitrap Mass Spectrometer were used on ultrafiltered peripheral blood samples at baseline and 6 months after rituximab therapy. Data processing and statistical analysis were performed in the MATLAB programming environment. Pathway analysis was performed using VANTED software. Significantly different metabolites were identified and the relationship between metabolites and clinical outcome was studied.

Results: Multivariate statistical analysis of the ^{1}H-NMR baseline spectra successfully discriminated between RA patients classified as rituximab responders (n = 14) and non-responders (n = 9), at baseline and 6 months after rituximab treatment. A two sample t-test produced p-values of less than 0.05 for seven metabolites which were decreased in responders: phenylalanine, 2-hydroxyvalerate, succinate, choline, glycine, acetoacetate, and tyrosine. Lipids analysis by MS also discriminated between RA patients. Prior to treatment, most observed classes of glycerophospholipids were downregulated in rituximab responders, including phosphatidylethanolamines, phosphatidylserines, and phosphatidylglycerol. Opposite trend was observed in phosphatidylinositols. Following treatment with rituximab, several of these trends were reversed in responders, suggesting that response to rituximab is related to shifts in phospholipid composition in responders.

Conclusion: The relationship between blood profiles and patient response to rituximab therapy suggests that the application of ^{1}H-NMR and MS profiling may be a promising clinical tool for RA therapy optimization. Additional metabolic profile studies are needed to determine if metabolic profiling can predict response to this and other biological therapies in RA patients**.**

Disclosure: S. Sweeney, None; **A. Kavanaugh**, None; **A. Lodi**, None; **B. Wang**, None; **D. L. Boyle**, None; **S. Tiziani**, None; **M. Guma**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/metabolomic-profiling-predicts-outcome-of-rituximab-therapy-in-rheumatoid-arthritis

Abstract Number: 575

Predictive Factors for Achieving Low Disease Activity at 52 Weeks after Switching from Tumor Necrosis Factor Inhibitors to Abatacept: Results from a Multicenter Observational Cohort Study of Japanese Patients

Toshihisa Kojima[1], Nobunori Takahashi[1], Koji Funahashi[1], Shuji Asai[2], Toki Takemoto[2], Nobuyuki Asai[3], Tatsuo Watanabe[2], Naoki Ishiguro[4] and TBCR Study Group, [1]Department of Orthopedic Surgery, Nagoya University Hospital, Nagoya, Japan, [2]Nagoya University Hospital, Nagoya, Japan, [3]Orthopedic Surgery, Nagoya University Hospital, Nagoya, Japan, [4]Department of Orthopedic Suregery, Nagoya University Hospital, Nagoya, Japan

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Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose: : Currently, there is no clarity regarding which biologic to switch to when patients fail to respond to TNF inhibitors (TNFis). Detailed information for predicting long-term outcomes when switching from TNFis to ABT would be helpful in clinical practice. This study aimed to identify predictive factors for achieving low disease activity (LDA) in rheumatoid arthritis (RA) patients switching from tumor necrosis factor inhibitors to abatacept (ABT).

Methods: Patients who were registered in the multicenter observational cohort study in Japan were enrolled in this study. Predictive factors for LDA achievement at each time point were determined by univariate and multivariate logistic regression analyses. The cut-off of DAS28-CRP and DDAS28-CRP from baseline up to 24 weeks for LDA achievement at 52 weeks were explored using receiver operating characteristic (ROC) curves.

Results: Of 2,771 RA patients registered until 2013, 76 with moderate or high disease activity were selected. Fifty-three percent of patients received ABT with MTX (mean dose; 7.8 mg/week), and 26% achieved LDA. In total, the drug retention rate at 52 weeks was 76.3%. Multivariate analysis confirmed that DAS28-CRP at 12 weeks and DDAS28-CRP from baseline to 12 weeks were independent factors for LDA achievement at 52 weeks [OR: 0.26, 95% confident interval (CI): (0.12-0.56), OR: 0.25, 95% CI: (0.11-0.57), respectively]. DAS28-CRP at

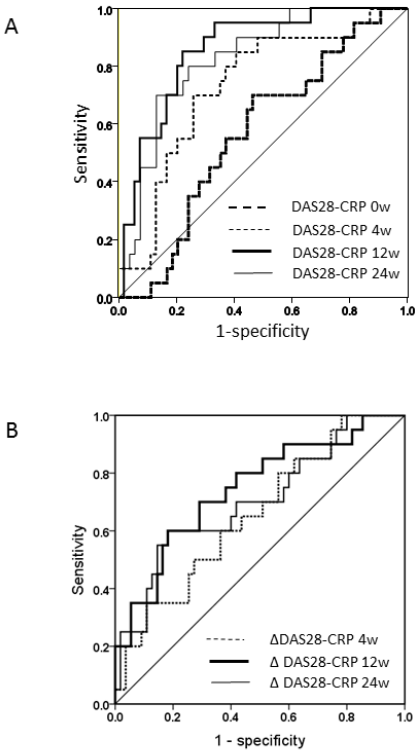
baseline was not the factor.

We confirmed the association between DAS28-CRP at each time point and LDA achievement at 52 weeks based on ROC curves. DAS28-CRP at 4, 12, and 24 weeks was associated with LDA achievement (AUC at 4 weeks, 0.74; 12 weeks, 0.86; 24 weeks, 0.83) (Fig. A), and that between DDAS28-CRP from baseline to each time point (AUC from baseline to 4 weeks, 0.66; to 12 weeks, 0.75; to 24 weeks, 0.70) (Fig. B).

The best cut-off values of DAS28-CRP at 12 weeks and DDAS28-CRP from baseline to 12 weeks for LDA at 52 weeks were 3.9 (sensitivity: 0.85, specificity: 0.78) and -0.97 (sensitivity: 0.70, specificity: 0.70), respectively. Seventy-one percent of patients who achieved both of these cut-off values at 12 weeks achieved LDA at 52 weeks.

Conclusion: We examined the effectiveness of switching from TNFis to ABT in clinical practice. Our findings suggest the need to consider the clinical course up to 12 weeks in order to predict long-term outcomes. These findings should be useful and applicable to the "treat to target" strategy in real-world clinical settings.

Fig.



Disclosure: T. Kojima, Speaker's fee, 8; **N. Takahashi**, None; **K. Funahashi**, None; **S. Asai**, None; **T. Takemoto**, None; **N. Asai**, None; **T. Watanabe**, None; **N. Ishiguro**, AbbVie, Chugai, Daiichi-Sankyo, Eisai, Mitsubishi Tanabe, Pfizer and Takeda, 5,AbbVie, Chugai, Daiichi-Sankyo, Eisai, Mitsubishi Tanabe, Pfizer and Takeda, 8.

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Abstract Number: 576

Possibility of Extension of the Administration Interval of Tocilizumab in the Treatment of Rheumatoid Arthritis

Masao Sato[1] and Masao Takemura[2], [1]Rheumatology, Matsunami General Hospital, Gifu, Japan, [2]Matsunami Reserch Park, Gifu, Japan
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Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose:

Biologics constitute an important drug category in the pharmacological treatment of rheumatoid arthritis (RA). Drug-free remission (REM) may also be achievable if the condition is responsive to treatment. In RA patients who had been treated with tocilizumab (TCZ) and whose disease activity was well-controlled, the administration interval of TCZ was extended, and a follow-up observation was carried out.

Methods:

The study was conducted on 101 RA patients treated with TCZ, who could be followed up for 52 weeks or longer. The cases were analyzed by dividing into two groups: a group of 41 patients whose administration interval was extended after achievement of a state of low disease activity (LDA) (extended-interval administration group, E-group), and a group of 61 patients for whom the doses continued to be administered at 4-week intervals in accordance with the package insert (standard-administration group, S-group). Evaluation of disease activity was conducted by using DAS28-ESR.

Results:

Comparison between S-group and E-group showed significant differences ($p<0.05$) in the following background items at the time of introduction of TCZ therapy: swollen joint count (SJC): 18.7±7.6 and 15.6±8.4, CRP (mg/dl): 2.77±3.01 and 1.81±2.56, DAS28-CRP: 6.1±1.5 and 5.6±1.4, CDAI: 51.7±16.6 and 43.6±17.5, and SDAI: 50.0±18.4 and 49.8±18.5. In E-group, extension of the interval was attempted at an average of 31.6 weeks (11 weeks to 101 weeks) after initiation of the introduction of TCZ therapy. In average, the duration of persistence of LDA until initiation of the extension of administration intervals was 23.1 weeks (4 weeks to 78 weeks). The changes in DAS28-ESR scores were examined after initiation of the extension of the administration interval; and the findings showed that the scores were 2.00±0.93 at the time of the initiation of the extension, 2.02±0.92 at 12 weeks, 2.11±1.13 at 24 weeks, 2.16±1.00 at 36 weeks, and 2.06±1.00 at 52 weeks. The REM rate was 70.7% at the time of the initiation of the extension, 65.9% at 24 weeks, and 61.0% at 52 weeks. In 7 patients (17.1%), relapse developed within 52 weeks following the extension of the administration interval of TCZ, and in all cases, resetting the administration interval back to 4 weeks led to an improvement of the patients' condition and an achievement of LDA within 24 weeks. The patients who relapsed showed significant differences in terms of the duration of the persistence of LDA until initiation of the extension, as well as in terms of ESR and DAS28-ESR scores at the time of the initiation of the extension ($p<0.05$). Based on the ROC curve, the DAS28-ESR at the time of initiation of the extension of the administration interval showed an AUC of 0.732 with a cut-off value of 1.81 weeks; and the duration of the persistence of LDA until initiation of the extension of the administration interval showed an AUC of 0.735 with a cut-off value of 14.0 weeks.

Conclusion:

Extension of administration intervals was carried out in 40% of RA patients treated with TCZ. For 82.9% of the cases, disease activity was maintained at a good level for a period of 52 weeks or longer.

Disclosure: M. Sato, None; **M. Takemura**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/possibility-of-extension-of-the-administration-interval-of-tocilizumab-in-the-treatment-of-rheumatoid-arthritis

Abstract Number: 577

Use of Subcutaneous MTX Does Not Prolong the Use of Traditional DMARD in Multi-DMARD Regimens and Has Insignificant Differences in Liver Enzymes Abnormalities When Compared with Oral MTX in Patients with Rheumatoid Arthritis: A Veteran Affairs Administrative Database Study

Bernard Ng, Rheumatology, U.S. Department of Veterans' Affairs- Puget Sound Healthsystem, Seattle, WA; Division of Rheumatology, University of Washington, Seattle, WA

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Session Type: ACR Poster Session A

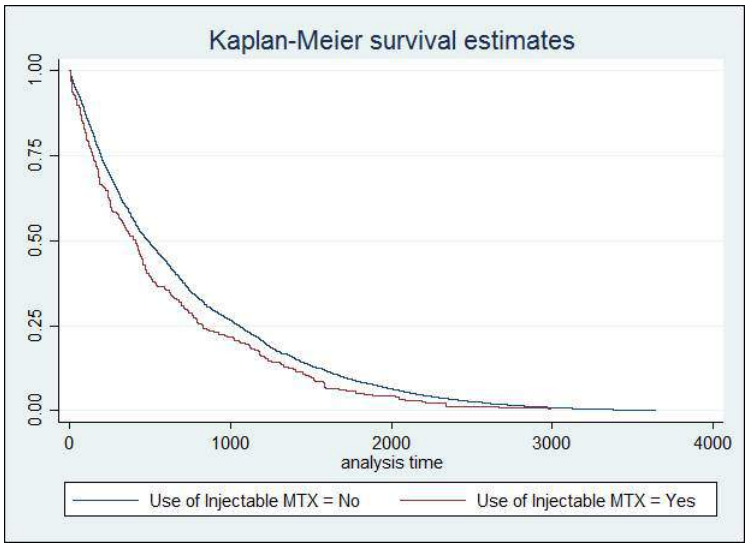
Session Time: 9:00AM-11:00AM

Background/Purpose: Our previous analyses using the national administrative database from Veteran Health Administration showed that RA patient who were switched from oral to subcutaneous MTX due to intolerance or lack of response were more likely to stay on methotrexate monotherapy longer. We seek to determine if RA patients who were on multiple traditional DMARD stay longer on traditional DMARD when subcutaneous MTX was used. We also compare the occurrences of liver enzymes abnormalities between those on subcutaneous MTX with those on oral therapy.

Methods: The duration of multiple traditional DMARD therapy, defined as the time between starting the use of a multiple traditional DMARD regimen that includes methotrexate and the switch to or addition of biologics, is compared between those on oral methotrexate and those on subcutaneous methotrexate for at least 30 days using a Wilcoxon-Matt-Whitney test. Factors that could potentially influence the duration of multiple traditional DMARD use include: gender, age, race, and maximum MTX dose. These factors were assessed using a log-rank test and Kaplan-Meier curves; Cox regression models were run to correct for patient variables. Liver enzyme abnormalities were compared between patients on subcutaneous and oral MTX who received MTX monotherapy for >30 days; abnormal alanine aminotransferase (ALT) levels and aspartate aminotransferase (AST) levels were defined as exceeding twice the upper limit of normal.

Results: Of the 13,254 patients who were treated with a DMARD for at least 90 days, 6541 were on more than one DMARD at any point in time, and in 3586, MTX was included in the multiple DMARD regimens. There were 1837 biologic starts among these 3586 patients (1604 were treated with oral MTX, 197 with subcutaneous MTX). Patient treated with oral MTX remained on multiple traditional DMARD for a mean (SD) of 683 (650) days compared with 580 (595) days for patients treated with subcutaneous MTX (P=0.014). Based on log-rank tests (see figure), the use of subcutaneous MTX was associated with significantly shorter duration of traditional multiple DMARD therapy use (P=0.025). After adjustment for patient variables using Cox regression models, the association of subcutaneous MTX use with the duration on multiple traditional DMARD therapy was no longer significant (P=0.107). Age and race remained significantly associated after corrections. Of the patients treated with MTX who had ALT and/or AST levels assessed, the rates of abnormal ALT and AST levels were not significantly different between those receiving oral and subcutaneous MTX (P=0.090 and P=0.924, respectively).

Conclusion: Unlike the duration of MTX monotherapy, the duration of multiple traditional DMARD use was not significantly associated with use of subcutaneous MTX. Among those using MTX for >30 days, there was no significant differences in liver enzyme abnormalities between patients treated with subcutaneous MTX and oral MTX.



Disclosure: B. Ng, Antares Pharma, 2;

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/use-of-subcutaneous-mtx-does-not-prolong-the-use-of-traditional-dmard-in-multi-dmard-regimens-and-has-insignificant-differences-in-liver-enzymes-abnormalities-when-compared-with-oral-mtx-in-patients-w

Abstract Number: 578

Study of the Production of Antinuclear Antibodies and Anti-Ds DNA Antibodies in Rheumatoid Arthritis Patients Treated with TNF Inhibitors

Ran Matsudaira[1,2], Naoto Tamura[3], Yoshichika Sugisaki[2], Tomoko Ito[4], Kentaro Minowa[2], Michihiro Ogasawara[2], Ken Yamaji[2], Yoshinori Kanai[1], Kenjiro Yamanaka[1] and Yoshinari Takasaki[2], [1]Division of Internal Medicine and Rheumatology, Sasaki institute Kyoundo Hospital, Tokyo, Japan, [2]Department of Internal Medicine and Rheumatology, Juntendo University, School of Medicine, Tokyo, Japan, [3]Department of

Internal Medicien and Rheumatology, Juntendo University, School of Medicine, Tokyo, Japan, [4]Department of Internal Medicine and Rheumatology, Juntendo University School of Medicine, Tokyo, Japan
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Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose:

The production of autoantibodies, such as anti-nuclear antibodies (ANA) and anti-ds DNA antibodies (anti-DNA), is commonly observed in patients who have been treated with tumor necrosis factor (TNF) inhibitors. We had reported that accelerated anti-DNA production was predominantly observed in patients treated with infliximab (IFX), and this occurred more frequently in anti-Ro/SS-A antibodies (anti-Ro) positive rheumatoid arthritis (RA) patients. The purposes of this study were to examine whether the positive rate of ANA and anti-DNA before and after commencement of treatment is different among TNF inhibitors and to compare the positive rates between anti-Ro-positive and -negative patients. Moreover, we investigated the relationship between the production of such autoantibodies and clinical response.

Methods:

We examined 246 patients with RA treated with TNF inhibitors as the first biologics DMARDs: IFX; 116, etanercept (ETN); 64, adalimumab (ADA); 36, and golimumab (GLM); 30 and studied positive rate of ANA and anti-DNA before and after commencement of each TNF inhibitors. ANA was tested using an indirect immunofluorescent assay on fixed HEp-2 cell substrate. Anti-DNA was measured using a radioimmunoassay (RIA). A part of anti-DNA positive patients were tested anti-DNA isotype of IgG, IgM, and IgA by enzyme-linked immunosorbent assay. We compared the positive rate of ANA and anti-DNA between anti-Ro-positive and -negative patients. Clinical response was evaluated by EULAR response using disease activity score (DAS) 28/CRP.

Results:

The positive rate of ANA before and after commencement of IFX, ETN, ADA, and GLM were 63.8% to 89.7%, 56.3% to 68.8%, 72.2% to 75.0%, and 66.7% to 63.3%, respectively. Sixty-five patients (26.4%) were anti-DNA positive after TNF inhibitors, and anti-DNA titers increased from baseline after IFX, ETN, ADA, and GLM were 4.3% to 41.4%, 1.6% to 10.9%, 8.3% to 25.0%, and 0.0% to 3.3%, respectively. Both ANA and anti-DNA were significantly elevated after treated with IFX than other TNF inhibitors ($p<0.001$ and $p<0.001$, respectively). Moreover, the positive rate of anti-DNA in patients treated with IFX and ADA was notably increased in anti-Ro-positive patients compared to anti-Ro-negative patients (68.2% vs 35.1%; $p=0.009$, 66.7% vs 16.7%; $p=0.039$, respectively). On the other hand, only one patient was anti-DNA positive after treated with GLM and there was no anti-Ro-positive patient who anti-DNA was detected after treated with GLM. In 38 patients with positive anti-DNA by RIA, isotype of IgM was found in 34 cases (89.5%) after treatment, while IgG and IgA was positive in few patients. Furthermore, 35 of 65 patients increased anti-DNA after treated with TNF inhibitors were stopped or switched biologics because of inefficacy and this observation was found in most of the patients with anti-Ro (71.4%).

Conclusion:

The production of anti-DNA after treated with TNF inhibitors was frequently increased in anti-Ro-positive patients and it was suggested to relate to the lesser clinical response and to decrease the continuation rate. In addition, the production of autoantibodies was different among TNF inhibitors and it might be considered to select the treatment of TNF inhibitors.

Disclosure: R. Matsudaira, None; **N. Tamura**, None; **Y. Sugisaki**, None; **T. Ito**, None; **K. Minowa**, None; **M. Ogasawara**, None; **K. Yamaji**, None; **Y. Kanai**, None; **K. Yamanaka**, None; **Y. Takasaki**, None.

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Abstract Number: 579

Methotrexate Does Not Influence 1-Year Bone Mineral Density in Rheumatoid Arthritis: A Systematic Review and Meta-Analysis

Richard Koch[1], Thomas Barnetche[2], Adeline Ruyssen-Witrand[1], Alain Cantagrel[1], Arnaud Constantin[3] and Yannick Degboé[4], [1]Rheumatology Center, Purpan University Hospital, Toulouse, France, [2]Rheumatology Department, Pellegrin University Hospital, BORDEAUX, France, [3]Inserm U558, Rheumatology Center, Purpan University Hospital, Toulouse, France, [4]Rheumatology, Rheumatology Center, Purpan University Hospital, Toulouse, France
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Session Time: 9:00AM-11:00AM

Background/Purpose: Rheumatoid arthritis (RA) is associated with reduction of bone mineral density (BMD) and increased risk of peripheral and axial fractures. Methotrexate is the first-line treatment in this disease. MTX has been suspected to play a noxious role on bone of patients treated for leukemia or RA. We aimed to assess the effect of MTX on BMD after 1 year of treatment, in patients with RA.

Methods: We performed a systematic review and a meta-analysis of the literature. Two authors (RK and YD) independently screened PubMed-Medline, the Cochrane library and Ovid journals databases. Key words were: "rheumatoid arthritis" AND "methotrexate" AND ("mineral densityÓ or "remodeling markers" or "formation" or "resorptionÓ or "boneÓ). Data, including BMD variation, were extracted using a predetermined form. We selected all prospective studies, with assessment of baseline and 1-year lumbar spine, femoral neck or hip BMD, in patients treated by methotrexate monotherapy. This screening was supplemented by hand searching of relevant references in selected papers. Studies were limited to those concerning human species, published in English, before March 2015. Pooled BMD variation was computed by meta-analysis.

Results: We identified 433 articles in PubMed database and 7 in Cochrane or Ovid databases. We selected 5 eligible references for the systematic review and 4 relevant for meta-analysis. We analyzed 144 patients. 106 were women, 94 displayed early arthritis (<1 year), they had active RA. Two studies included in the meta-analysis contained possibility of bisphosphonates treatment and steroids therapy (Table 1). Meta-analysis concerning 1-year lumbar BMD variation did not show a significant variation: 0.00 g/cm^2, 95% confidence interval (95%CI) [-0.02, 0.02] (Figure 1a). Meta-analysis concerning 1-year femoral neck BMD variation showed a non-significant variation: -0.01 g/cm^2, 95%CI [-0.04, +0.01] (Figure 1b). Meta-analysis was not possible for 1-year total hip BMD variation. Estimated heterogeneity of studies was high.

Table 1. Main characteristics of the studies included in the meta-analysis

Reference	Study type	MTX Population	Age, mean +/- SD	Disease duration (year)	Percentage female	Corticotherapy (Prednisone ³10_mg/day)	Bisphosphonates	DAS 28 +/- SD
Van Der Goes, 2013	Randomized, placebo-controlled, double-blind	84	52 +/- 13	< 1	65	Yes	Yes	3.2 +/- 1.1
Haugeberg, 2009	Randomized, placebo-controlled, double-blind	10	53.1 +/- 13.7	< 1	70	Yes	Yes	7 +/- 0.9
Marotte, 2007	Case-control	99	53.9 +/- 15.9	10.9 +/-8.9	79	No	Yes	5 +/- 1.15
Minaur, 2002	Non- randomized, longitudinal	28	62.6 +/- 8.9	6.6	79	No	No	5.27 +/- 1
Mazzantini, 2000	Non-randomized, longitudinal	22	59 +/- 9	9 +/- 9	100	No	No	-

Figure 1a. Lumbar BMD meta-analysis

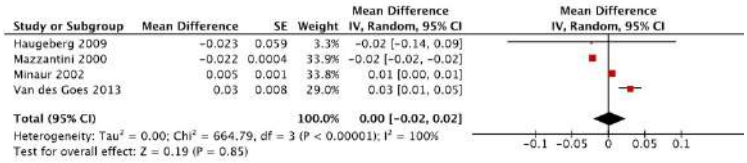
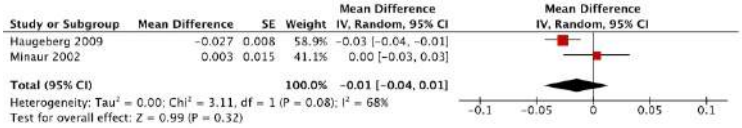


Figure 1b. Femoral BMD meta-analysis



Conclusion: We did not observed a significant variation of 1-year lumbar and femoral neck BMD in patients treated by MTX, thus suggesting a neutral effect of MTX on BMD in RA.

Disclosure: R. Koch, None; **T. Barnetche**, None; **A. Ruyssen-Witrand**, None; **A. Cantagrel**, None; **A. Constantin**, None; **Y. Degboé**, None.

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in-rheumatoid-arthritis-a-systematic-review-and-meta-analysis

Abstract Number: 580

Treatment with Biologic Agents in Rheumatoid Arthritis and Mortality Risk in Clinical Practice

Leticia Leon[1], Luis Rodriguez-Rodriguez[1], Alejandro Gomez-Gomez[2], Pilar Macarrón[2], Margarita Blanco[2], Juan A Jover[2] and Lydia Abasolo[1], [1]Instituto de Investigación Sanitaria San Carlos (IdISSC), Madrid, Spain, [2]Rheumatology, Hospital Clínico San Carlos, Madrid, Spain
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Background/Purpose: It is a well-known fact the decline of life expectancy in Rheumatoid Arthritis (RA) being the increased mortality in these patients a constant concern in Rheumatology. This increment in mortality has been linked to multiple factors such as disease activity and treatment. The purpose of our study was to assess the mortality rate and to evaluate the mortality risk in a cohort of RA patients with and without Biologic Agents (BA). Other factors associated to mortality risk were also investigated.

Methods: An inception cohort of RA patients diagnosed between January 2000 and December 2004, were recruited from a Rheumatology outpatient clinic of a tertiary Hospital in Madrid, Spain, and followed for up to 13.5 years after diagnosis. Dependent variable was death (obtained from the National Death Index) and independent variable was use of BA. Covariables: sociodemographic (age, sex, level of studies), clinical (DAS-28, HAQ, hospital admissions, comorbidity, rheumatoid factor [RF]) and therapy (concomitant corticoids, Disease Modifying Antirheumatic Drugs [DMARDs] and BA). Survival techniques were used to estimate the mortality rate (MR) in our cohort, expressed per 1,000 patient-years with their respective confidence interval [95 % CI]. They were follow-up until lost of follow-up, death or end of the study. The influence BA on mortality rate was analyzed using multivariable Cox proportional hazards models adjusting by age, sex, disability, comorbidity, calendar year, disease severity and other variables. BA were used in a time-dependent manner. **Results** were expressed by hazard ratio (HR) and 95% CI.

Results: We included 576 patients and 711 courses of therapy. 75% were women with a mean age at diagnosis of 59±years. The mean DAS and HAQ at diagnosis were 3.8±1.2 and 0.7±0.6 respectively. 68% patients were taking corticoids, 113 (19.6%) BA and 86% DMARDs (median [p25-75]: 2 [1-3]), being MTX the most prevalent (70%). There were 133 deaths per 5,441 person-years at risk in the total cohort. MR was estimated in 27 [22.5-31.6]. MR for BA was 12.6 [6-26] and for the rest 28.4 [23.8-33.8]. The unadjusted HR of mortality in BA was 0.37 [0.17-0.8] (p=0.011). Controlling by confounders (age, gender, calendar time, comorbidity, disease activity, quality of life), the HR for death in those treated with BA was 0.72 [0.3-1.6], p=0.4) versus those not treated. Other variables independently associated with death were: age at diagnosis (HR: 1.09 [1.07-1.11]), positive RF (HR: 1.94 [1.3-2.8]), hospital admissions (HR: 1.19 [1.12-1.25]), HAQ > 1.5 (HR: 1.98 [1.07-3.6]) and MTX use (HR: 0.4 [0.29-0.66]).

Conclusion: This study describes mortality rate in real-life conditions in an inception cohort of RA patients. After controlling by factors that influence mortality, we found that survival in patients receiving BA is not different than those receiving other classic DMARDs. We have assessed the role of other variables in the risk of mortality.

Abstract Number: 581

Optimization of Treatment Intervals of Tocilizumab and Golimumab By Measuring Serum Trough Levels in Rheumatoid Arthritis Patients

Yoshinobu Matsuura[1], Masashi Narazaki[2], Masayuki Nishide[2], Yasuhiro Kato[2], Hideki Yorifuji[2], Toru Hirano[3], Yoshihito Shima[3], Toshio Tanaka[2], Atsushi Ogata[4] and Atsushi Kumanogoh[3], [1]Internal Medicine, Allergy and Rheumatic diseases, Osaka University Graduate School of Medicine, Suita, Japan, [2]Osaka University Graduate School of Medicine, Suita, Japan, [3]Respiratory Medicine, Allergy and Rheumatic Diseases, Osaka University Graduate School of Medicine, Suita, Japan, [4]Osaka University Graduate School of Medicine and NTT West Osaka Hospital,

Osaka, Japan
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Background/Purpose:

Biologic agents have dramatically improved the outcome of rheumatoid arthritis (RA) patients. However, the administration dose and treatment intervals of these agents are usually fixed for individual patients. Hence, patients displaying disease remission receive an unnecessary high dose of medication. The immunosuppressive action of biologics in this medication strategy exposes patients to a high risk to gain infectious diseases and causes increased medical costs. In this study, we optimized the treatment intervals of the biologics tocilizumab and golimumab by monitoring their serum trough levels in individual patients.

Methods:

Japanese RA patients were treated either with intravenous tocilizumab (TCZ) 8mg/kg or subcutaneous golimumab (GLM) 50mg every 4 weeks (n=49 or n=20, respectively) and enrolled to analyze their serum trough levels of the respective biologics. Recombinant human soluble IL-6 receptor or human TNFα was coated on ELISA plates and bound TCZ or GLM in patient sera was detected with anti-human IgG1 antibody. The disease activity was evaluated with DAS-CRP. Treatment intervals were prolonged for patients with low disease activity displaying tocilizumab or golimumab serum trough levels>1μg/ml.

Results:

We monitored significant differences of the serum trough levels of the respective agent among individual patients. TCZ ranged from 0.25μg/ml to 52μg/ml (17.4 ± 10.4μg/ml), while GLM ranged from 0.25μg/ml to 10.9μg/ml (3.34 ± 3.13μg/ml). A positive correlation between age and serum trough levels was found in the TCZ group (P=0.0101, r^2=0.3863). However, we did not find any correlation between the disease activity and serum trough levels of the biologics in both TCZ and GLM groups. In the TCZ group, the mean trough level was 16.8μg/ml ± 8.1μg/ml at 4-weeks and was reduced to 11.1μg/ml ±9.0μg/ml after 5-weeks and 3.09μg/ml ±3.29μg/ml after 6-weeks. 24 patients with low disease activity displaying serum trough level >1μg/ml of TCZ agreed to prolong treatment intervals. 13 of the 24 patients showed a TCZ serum level >1μg/ml even after prolongation of medication without any disease exacerbation. However, 11 of 24 patients displayed a decreased TCZ serum trough level <1μg/ml. In this group 3 patients had a increased DAS-CRP score whereas in 8 patients the disease activity was not affected. In the GLM group, the mean trough serum level was 3.34μg/ml ± 3.13μg/ml after 4-weeks and was reduced to 2.85 μg/ml ± 2.51μg/ml after 5-weeks and 1.41μg/ml after 6-weeks. The disease activity didn't change after modification of the medication interval.

Conclusion:

Significant difference of serum trough levels of biologics was observed among RA patients treated with TCZ or GLM. Maintenance of a certain serum trough levels by monitoring concentration of biologics may allow optimization of treatment intervals without increasing the disease activity and may lead to decrease medical costs.

Disclosure: Y. Matsuura, Chugai, 2,Mitsubishi Tanabe Pharma corporation, 2; **M. Narazaki**, Chugai, 2,Mitsubishi Tnabe pharma corporation, 2; **M. Nishide**, Chugai, 2,Tanabe Mitsubishi pharma corporation, 2; **Y. Kato**, Chugai, 2,Tanabe Mitsubishi pharma corporation, 2; **H. Yorifuji**, Chugai, 2,Tanabe Mitsubishi pharma corporation, 2; **T. Hirano**, Chugai, 2,Tanabe Mitsubishi pharma corporation, 2; **Y. Shima**, Chugai, 2,Tanabe Mitsubishi Pharma corporation, 2; **T. Tanaka**, Chugai, 2,Tanabe Mitsubishi Pharma corporation, 2; **A. Ogata**, Chugai, 2,Tanabe Mitsubishi pharma corporation, 2; **A. Kumanogoh**, Chugai, 2,Tanabe Mitsubishi pharma corporation, 2.

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Abstract Number: 582

Biological Drugs Dose Tapering in Inflammatory Rheumatic Diseases: 2 Year Results at Basurto University Hospital

Juan María Blanco-Madrigal[1], Maria Luz Garcia Vivar[1], Catalina Gomez Arango[1], Olaia Fernández Berrizbeitia[1], Clara Perez Velasquez[1], Ignacio Torre Salaberri[2], Jose Francisco Garcia Llorente[3], Eva Galindez-Agirregoikoa[4], Esther Ruiz Lucea[1] and Iñigo Gorostiza[5], [1]Rheumatology, Basurto University Hospital, Bilbao, Spain, [2]Rheumaytology, Basurto University Hospital, Bilbao, Spain, [3]Rheumatology, Basurto University Hospital., Bilbao, Spain, [4]Rheumatology, Hospital Universitario de Basurto, Bilbao, Spain, [5]Research Department, BASURTO UNIVERSITY HOSPITAL, BILBAO, Spain

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Background/Purpose:

Last years, biological dose tapering in patients with inflammatory diseases has become a routine clinical practice. Since 2011 we are applying a dose reduction protocol in our biological monographic consultation and our day hospital : etanercept dosage from 50 mgrs to 25 mgrs subcutaneous weekly injection, adalimumab 40 mgrs subcutaneous injection administration spacing of 2 to 3 weeks, tocilizumab, dose reduction from 8 mgrs/kg to 6 mgrs/kg. Thus we have achieved optimization rates in our patients close to 40% at the end of 2013.

The aim of this study is to analyze baseline characteristics and course of the disease in these optimized patients, in order to improve our treatment protocols if possible.

Methods: : Retrospective analysis of data from clinical records and database of 115 patients under therapy with etanercept, adalimumab and tocilizumab, with at least two year evolution of dose reduction or withdrawal. We consider baseline features, drug, time of dose tapering, including frecuency, time and course of flares if happened. We used SPSS 21.0 for statistical analysis

Results:

115 patients (59 female and 56 male), 34% with rheumatoid arthritis (RA), 62.6% with axial or peripheral spondylitis (SPa), including psoriatic arthritis, and 3.5% juvenile idiopatic arthritis (JIA), most of them with longstanding disease (148.47 months, range 18-638), and long time disease remission at optimization (33.46 months, range 6-134). 26 patients stopped biological treatment, but most of them (22) for other clinical conditions (surgery, infection, poor adherence, adverse events, malignancy). Optimized patients kept in remission for 34,24 months (range 10-77).

32.2% of patients flared, 46,2% suffering from RA and 26.4% with SPa, which means statistically significant difference (chi square 4.45, p=0.035). There was no significant difference among biological drugs analized in terms of flare at any indication, or when you considered SPa, but the differences reached significance when you compare flared RA patients under adalimumab (18.8%) and etanercept (46.3%), Chi square: 16.5; p<0,001.

RA patients flared earlier than SPa patients, with statistical significance (Log Rank test p: 0,027), and this was not influenced by concomitant therapy or the use of metotrexate, but by the biological drug used: RA patients under etanercept flared earlier than SPa (difference in survival curve). This did not occur among patients under adalimumab.

Extraarticular disease (psoriasis, uveitis, diarrhea) was the main manifestation of flare in 42% of our SPa patients.

Conclusion: In our experience dose reduction of biological therapies is safe and cost effective, even withdrawall is possible in selected cases. Concerning therapy with etanercept, we must consider a most conservative dose reduction protocol, at least in our RA patients. In SPa patients we must pay close attention extraarticular manifestations specially when dose tapering.

Disclosure: J. María Blanco-Madrigal, None; **M. L. Garcia Vivar**, None; **C. Gomez Arango**, None; **O. Fernández Berrizbeitia**, None; **C. Perez Velasquez**, None; **I. Torre Salaberri**, None; **J. F. Garcia Llorente**, None; **E. Galindez-Agirregoikoa**, None; **E. Ruiz Lucea**, None; **I. Gorostiza**, None.

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Abstract Number: 583

A Serological Biomarker of Active MMP3, but Total MMP3, Can Early Assess Treatment Efficacy and Differentiate Doses of Tocilizumab and an Early Change in Active MMP3, but Not Total MMP3, Is Associated with Radiographic Change at 1 Year

Anne Sofie Siebuhr[1], Stephanie Nina Kehlet[2], Kishwar Musa[2], Inger Byrjalsen[3], Morten Asser Karsdal[4] and Anne C. Bay-Jensen[5], [1]Rheumatology, Nordic Bioscience, Biomarkers and Research, Herlev, Denmark, [2]Laboratory, Nordic Bioscience, Herlev, Denmark, [3]Research & Development, Nordic Bioscience, Herlev, Denmark, [4]Biomarkers and Research, Nordic Bioscience, Herlev, Denmark, [5]Biomarkers and Research, Rheumatology, Nordic Bioscience, Herlev, Denmark

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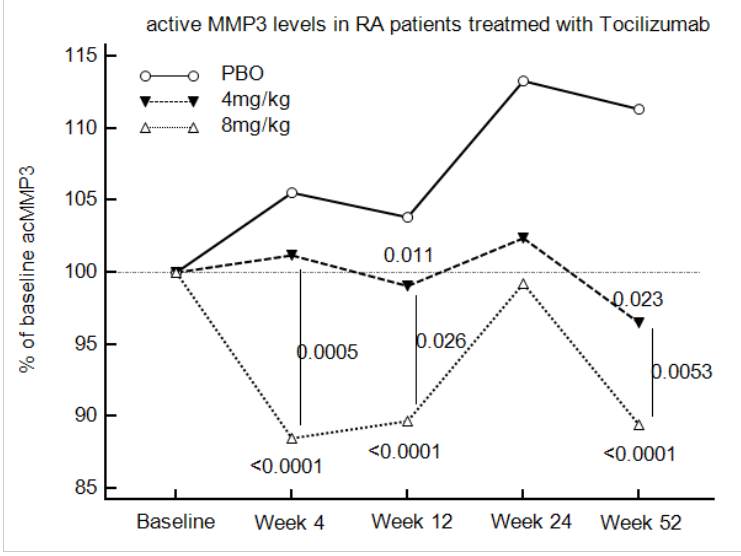
Background/Purpose: Protease activity, especially MMP3, is known to be increased with arthritis, such as rheumatoid arthritis. MMP3 is mainly expressed by fibroblasts; a key cell in arthritis. In RA, Serum levels of MMP3 isassociated with structural progression and elevated compared to OA. The present methods for assessing MMP3 is ELISA of total MMP3 (tMMP3) or the activity by using a substrate. However, neither of these approaches provide serological information about the level of the active form of MMP3 (acMMP3). In this study we used a serological biomarker detecting acMMP3, to investigate if this biomarker was a biomarker of treatment efficacy (Tocilizumab; TCZ), aid in dose-finding and if it was related to radiographic progression.

Methods: LITHE biomarker study (n=585) was a 1-year phase III, double-blind, placebo (PBO)-controlled, parallel group study of 4 or 8 mg/kg every 4 weeks, in RA patients on stable doses of methotrexate (MTX). acMMP3 was tested in serum from baseline (BL) and week 4, 16, 24 and 52 and tMMP3 in serum from BL and week 4 and 16. Patients not reaching ACR20 remission at week 16 or 24 received rescue treatment (escape); 4mg/kg patients received 8mg/kg for the rest of the study. Spearman's correlation was analysed between BL level of acMMP3 (log transformed) and clinical measures. Associations between BL acMMP3 and change in JSN and mTSS were investigated in the PBO group was assessed by Spearman's correlations. Change in acMMP3 levels were studied as a function of time and treatment. Relation to radiographic progression was assessed t-test when segregating the treated population into 2 group; more or less than 35% change in acMMP3 at week 16 .

Results: At BL tMMP3, but not acMMP3, was correlated with radiographic change (erosion rho 0.22 and modified total sharp score rho: 0.21) at 1 year and HAQ (rho -0.19) at 24 weeks and acMMP3, and tMMP3 were correlated to each other (rho 0.15). Percentage change in acMMP3 at week 16 in the TCZ groups was negatively correlated to change in radiographic change at 1 year (erosion rho -0.20 and modified total sharp score rho -0.20), but for joint space narrowing only in the 4mg/kg group (rho -0.27). Percentage change in tMMP3 at week 16 in the 4mg/kg group was correlated to disease activity measures (DAS rho 0.21, HAQ rho 0.20, VAS pain rho 0.21). acMMP3 was dose-dependently decreased by TCZ (p=0.026) already at week 4, whereas tMMP3 was decreased by treatment (p=0.0001) without dose-differentiation. Furthermore, acMMP3 was decreased in escapers compared to non-escapers at 1 year.

Conclusion: Serum acMMP3 and tMMP3 were efficacy biomarkers of TCZ at week 4 and acMMP3, but not tMMP3, differentiated doses. The change in acMMP3 at week 16 was inversely associated with radiographic change at 1 year, whereas the change in tMMP3 was associated with disease activity. This study illustrates that the activity of a protease can assess early, who will benefit from TCZ.



Disclosure: A. S. Siebuhr, None; **S. N. Kehlet**, Nordic Bioscience, Laboratory, 3; **K. Musa**, Nordic Bioscience Diagnostic, 3; **I. Byrjalsen**, Nordic Bioscience Diagnostic, 3; **M. A. Karsdal**, Nordic Bioscience Diagnostic, 1,Nordic Bioscience Diagnostic, 3; **A. C. Bay-Jensen**, Nordic Bioscience Diagnostic, 1,Nordic Bioscience Diagnostic, 3.

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Abstract Number: 584

Positivity for Rheumatoid Factor Is Associated with a Better Short-Term Response and Long-Term Drug Retention of Abatacept: Results from Consecutive 508 Patients with Rheumatoid Arthritis in a Japanese Multicenter Registry

Nobunori Takahashi[1], Toshihisa Kojima[1], Koji Funahashi[2] and Naoki Ishiguro[3], [1]Department of Orthopedic Surgery, Nagoya University Hospital, Nagoya, Japan, [2]Nagoya University Hospital, Nagoya, Japan, [3]Department of Orthopedic Suregery, Nagoya University Hospital, Nagoya, Japan

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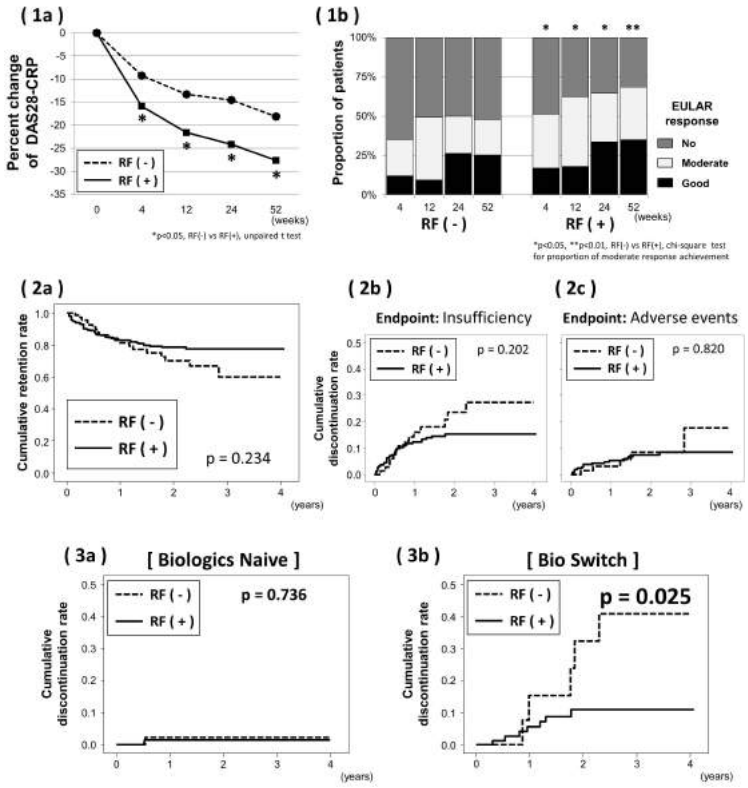
Background/Purpose: Abatacept (ABT) is a biologic drug and has been available for rheumatoid arthritis (RA) patients since 2010 in Japan. There have still been few reports describing the association of rheumatoid factor (RF) with the short- and long-term clinical results of ABT. The aim of this study is to demonstrate whether the positivity for RF is associated with the short-term (52 weeks) clinical response to ABT and the long-term (4 years) drug retention rate of ABT using data from a Japanese multicenter registry system for RA patients treated with biological DMARDs.

Methods: Participants were consecutive 508 patients with RA who were prospectively registered in the Tsurumai Biologics Communication Registry and treated with ABT. Demographic data and the following parameters of disease activity were collected; TJC, SJC, patient global assessment, ESR, and serum CRP at baseline, 4, 12, 24, and 52 weeks. The last observation carried forward (LOCF) method was used in each analysis. Survival analysis was performed with the Kaplan-Meier method and log-rank test. We compared these clinical indices between the patients with and those without RF positivity.

Results: At baseline, mean age was 65.1 years, disease duration was 13.1 years, and DAS28-CRP was 4.36. Of the 508 patients, 78.8% was female, 77.5% was RF positive (>20 mg/dl), and 42.7% had prior biologics history (Bio-switch). Percent change of DAS28-CRP was significantly greater in the RF positive group from 4 weeks throughout 52 weeks ($p < 0.05$) (Fig. 1a). The proportion of patients that achieved EULAR moderate response was also greater in the RF positive group from 4 to 52 weeks ($p < 0.01$) (Fig. 1b). Overall drug retention rate was 60.0% in the RF negative and 77.5% in the RF positive group at 4 years (Fig. 2a). Discontinuation rate due to insufficient efficacy (Insufficiency) was 27.2% in the RF negative and 15.3% in the RF positive group (Fig. 2b). Discontinuation rate due to adverse events was similar between the groups (Fig. 2c). Within the bioswitch patients, the RF negative group demonstrated significantly higher discontinuation rate due to secondary failure (40.8 vs 11.0%) (Fig. 3b). The hazard ratio (HR) for secondary failure, adjusted for sex, age, disease duration, concomitant MTX and PSL, and baseline DAS28-CRP, was 4.17 (95%CI 1.20-14.45) for RF negative versus RF positive. On the other hand, RF positivity did not affect the discontinuation rate in the Bio-naïve patients (Fig. 3a).

Conclusion: We found that RF positivity was associated with better short-term response to ABT. We also found that RF positivity significantly improve the long-term incidence rate of discontinuation due to secondary failure in the bio-switch patients. It is necessary to establish the strategy for additional therapeutic intervention, such as concomitant drugs, in this patients group to improve the short- and long-term clinical results of ABT.



Disclosure: N. Takahashi, Takeda Pharma Co., 8,Janssen Pharmaceutical, 8,Astellas Pharma Co., 8,Takeda Pharma Co., 8,Eisai, 8,Bristol-Myers Squibb, 8; **T. Kojima**, Takeda Pharma Corporation, 2,Janssen Pharmaceutical, 2,Astellas Pharma Corporation, 2,Mitsubishi Tanabe Pharma Corporation, 8,Takeda Pharma Corporation, 8,Eisai Pharma Corporation, 8; **K. Funahashi**, Abbvie Japan Co. Ltd, 8,Eisai Co. Ltd, 8,UCB Japan Co. Ltd, 8,Mitsubishi Tanabe Pharma Co., 8,Takeda pharmaceutical Co. Ltd, 8,Pfizer Co. Ltd, 8,Chugai Pharma Co. Ltd, 8,Janssen Pharma KK, 8,Bristol-Myers Squibb, 8; **N. Ishiguro**, Takeda Pharma Co., 8,Janssen Pharma, 8,Astellas Pharma Co., 8,Mitsubishi Tanabe Pharma Co., 8,Eisai, 8,Pfizer Inc, 8,Chugai, 8,Bristol-Myers Squibb, 8,UCB Japan Co. Ltd, 8.

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Abstract Number: 585

Outcomes after Discontinuing Tumor Necrosis Factor Inhibitor in Rheumatoid Arthritis: 2 Years of 'post-Golimumab' after Completion of the 5-Year Extension Study in Korea

Kichul Shin[1], Hyun Mi Kwon[2], Seong-Wook Kang[3], Won Park[4], Sung-Hwan Park[5,6], Chang-Hee Suh[7,8], Hyun Ah Kim[9,10], Seung-Geun Lee[11], Choong Ki Lee[12], Sang-Cheol Bae[13], Soo-Kon Lee[14] and Yeong Wook Song[15], [1]Division of Rheumatology, SMG-SNU Boramae Medical Center, Seoul, South Korea, [2]Division of Rheumatology, Department of Internal Medicine, Seoul National University Hospital, Seoul, South Korea, [3]Division of Rheumatology, Chungnam National University Hospital, Gwangju, South Korea, [4]Division of Rheumatology, Inha University Hospital, Incheon, South Korea, [5]Division of Rheumatology, Department of Internal Medicine, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, South Korea, [6]Division of Rheumatology, Department of Internal Medicine, College of Medicine, Seoul St. Mary's Hospital, The Catholic University of Korea, Seoul, South Korea, [7]Allergy-Rheumatology, Ajou University School of Medicine, Suwon, South Korea, [8]Division of Rheumatology, Ajou University Hospital, Suwon, South Korea, [9]Internal Medicine, Hallym Univ Sacred Heart Hosp, Anyang, South Korea, [10]Division of Rheumatology, Hanlim University Hospital, Anyang, South Korea, [11]Division of Rheumatology, Busan University Hospital, Busan, South Korea, [12]Division of Rheumatology, Youngnam National University Hospital, Daegu, South Korea, [13]Hanyang University Hospital for Rheumatic Diseases, Seoul, South Korea, [14]Division of Rheumatology, Yonsei University College of Medicine, Seoul, South Korea, [15]Division of Rheumatology, Department of internal medicine, Seoul National University Hospital, Seoul, South Korea
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Background/Purpose: Tumor necrosis factor inhibitors (TNFi) have helped patients achieve remarkable outcomes as in improving synovitis and halting structural damages in severe cases of rheumatoid arthritis (RA). Nowadays academic interests lie towards strategies of 'tapering' or 'discontinuing' biological therapy, especially in cases where patients are being maintained in clinical remission for an adequate period. However, not many studies have traced the outcomes after discontinuing TNFi.

Methods: The 'Investigation of outcomes after Golimumab discontinuation' or GOLD study, is an observational study participated by 10 centers nationwide, following up clinical data of Korean RA patients who were enrolled in the 5-year extension study of GO-BEFORE and GO-FORWARD. Medical records of the 2-year post-golimumab period were reviewed and pertinent clinical data including DAS scores, prescriptions, comorbidities, laboratory findings, as well as radiographic images were analyzed.

Results: The 60 RA patients (male 5, female 55) had the following mean values at discontinuation (baseline); age of 51.0 years, disease duration of 16.5 years, and a DAS28-CRP score of 2.71. At the 2-year time point, 9/60 (15%) patients had restarted biologics. The mean period restarting biologics was 18.7 months (range 4~28) after discontinuation. Baseline characteristics of the 'biologic restarters' and 'non-biologic users' are depicted in the table. New joint damage was discovered only in non-biologic users (4/51 patients) at 2 years.

Conclusion: The GOLD study based on 'deliberate' discontinuation of TNFi in RA patients with low disease activity shows that patients with higher swollen joint counts, physician's global assessment score at the time point of discontinuation tend to restart biologics in the near future. New joint damage ensued only in those off biologics.

Table. Baseline characteristics between the 2 groups at discontinuation*

	Biologic Restarters (n= 9)	Non-biologic Users (n= 51)	*P* value
Age, years	49.9	51.2	0.73
ACR20, %	66	82	0.27
ACR50, %	44	55	0.56
ACR70, %	44	31	0.44
DAS remission, %	33	53	0.27
Rheumatoid factor, %	89 (8/9)	47 (24/51)	0.16
Anti-CCP, %	100	100	-
Swollen joint count, n	10.1	1.7	**< 0.01**
Tender joint count, n	10.7	3.8	0.28
Patient's global assessment (0-10)	4.25	3.27	0.29
Physician's global assessment (0-10)	3.21	1.69	**0.05**
HAQ	1.291	0.666	0.15
C-reactive protein, mg/dL	0.34	0.52	0.07
Erythrocyte sedimentation rate, mm/hr	41.5	32.2	0.42
DAS28-CRP	3.18	2.65	0.29
DAS28-ESR	4.18	3.27	0.17
Patient's with bone erosion, %	88 (7/8)	49 (25/51)	0.12
Patient's with joint space narrowing, %	75 (6/8)	47 (24/51)	0.44

Mean values are presented.

*Based on whether biologic had been restarted within 2 years after golimumab discontinuation

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View Abstract and Citation Information Online - http://acrabstracts.org/abstract/outcomes-after-discontinuing-tumor-necrosis-factor-inhibitor-in-rheumatoid-arthritis-2-years-of-post-golimumab-after-completion-of-the-5-year-extension-study-in-korea

Abstract Number: 586

Titer of Anti-Citrullinated Peptide Antibody Affects the Efficacy of First Biological Treatment in Rheumatoid Arthritis

Yoshikazu Ogawa[1], Nobunori Takahashi[2], Koji Funahashi[2], Shuji Asai[3], Toki Takemoto[3], Tatsuo Watanabe[3], Nobuyuki Asai[2], Naoki Ishiguro[4] and Toshihisa Kojima[2], [1]orthopedic surgery, Nagoya University Hospital, Nagoya, Japan, [2]Department of Orthopedic Surgery, Nagoya University Hospital, Nagoya, Japan, [3]Nagoya University Hospital, Nagoya, Japan, [4]Department of Orthopedic Suregery, Nagoya University Hospital, Nagoya, Japan

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SESSION INFORMATION

Session Date: Sunday, November 8, 2015

Session Title: Rheumatoid Arthritis - Small Molecules, Biologics and Gene Therapy Poster I

Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose:

Anti-citrullinated protein antibody (ACPA) has been an important marker in diagnosing rheumatoid arthritis (RA). Its predictive value remains unclear; therefore, here we investigated whether the pre-treatment ACPA titer is able to predict the treatment efficacy of first biological treatments in RA.

Methods:

Records of relevant patients with RA were collected from the Tsurumai Biologic Communication Registry, wherein the department of Nagoya University and 20 affiliated hospitals in Japan are enrolled. The relevant data of a total of 388 patients with RA who met the 2010 ACR–EULAR classification criteria for RA were completely recorded in regard to DAS28ESR before and after biological treatment. The ACPA status was divided into three categories: negative (0–4.4 U/ml), low-positive (4.5–13.5 U/ml), and high-positive (>13.5 U/ml). The 154 ACPA low-positive patients and 172 ACPA high-positive patients were compared with regard to the effect of ACPA titer on biological treatment. Only bio-naïve patients were included in this study, whereas patients who received second or latter biological treatment were excluded. We analyzed the relevant data using analysis of covariance (ANCOVA) with pre-treatment DAS28ESR as covariant.

Results:

The demographic characteristics of each group at baseline are presented in Table 1. Pre-treatment DAS28ESR was significantly associated with DAS28ESR improvement, where the higher pre-DAS28ESR, the larger DAS28ESR improvement ($p < 0.01$; Figure 1). Pre-treatment DAS28ESR was 5.11 in ACPA low-positive patients and 5.25 in ACPA high-positive patients, and DAS28ESR improvement in the two groups was 2.49 and 2.22, respectively. Compensating each DAS28ESR according to the pre-biological treatment value using ANCOVA as the whole mean value, which is 5.19, DAS28ESR improvement was 2.54 in ACPA low-positive patients and 2.17 in ACPA high-positive patients, respectively, and the difference was significant ($p < 0.05$; Table 2).

Conclusion:

The ACPA titer significantly affected DAS28ESR improvement after first biological treatment. In addition, the efficacy of first biological treatment was inferior in ACPA high-positive patients compared with that in ACPA low-positive patients with RA.

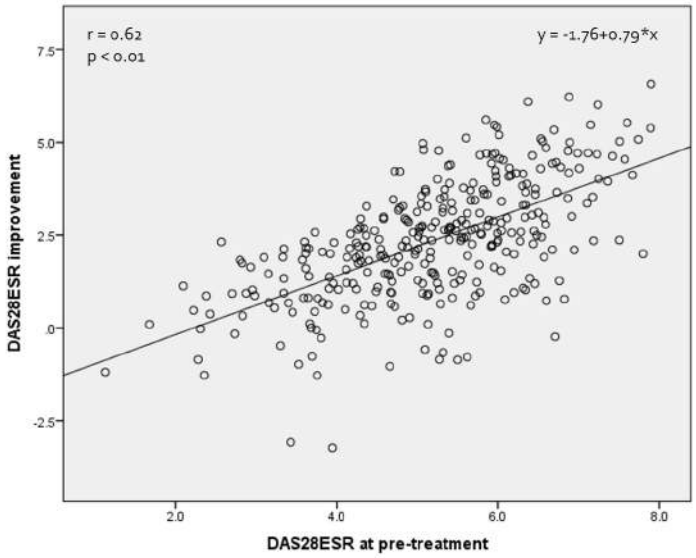

Figure 1. Relationship between DAS28ESR at pre-treatment and DAS28ESR improvement

Table 1. Characteristics of ACPA low-positive and high-positive, as measured at baseline.

	ACPA low-positive (n = 154)	ACPA high-positive (n = 172)	p
Age, Mean ± SD years	57.2 ± 14.3	56.7 ± 14.2	0.73
Sex, % female	79.2	79.7	1
Disease duration, Mean ± SD years	9.6 ± 9.8	7.7 ± 9.6	0.1
Stage, I / II / III / IV, %	16.2/25.3/22.1/36.4	26.2/25.0/26.2/22.6	<0.05
Class, I / II / III / IV, %	13.6/50.6/35.1/0.6	36.9/47.0/14.3/1.8	<0.05
Methotrexate, %	81.8	75.6	0.18
Methotrexate dose (mg/week), Mean ± SD mg	8.7 ± 2.5	8.4 ± 3.0	0.4
Oral steroids, %	54.4	52.7	0.82
Oral steroids dose (prednisone equivalent mg/day), Mean ± SD mg	4.8 ± 2.1	4.8 ± 2.4	0.83
Biologic agents, %			<0.05
Abatacept	8.4	14.5	
Adalimumab	18.2	13.4	
Certolizumab Pegol	1.3	5.2	
Etanercept	43.5	18.6	
Golimumab	5.8	7.6	
Infliximab	17.5	22.1	
Tocilizumab	5.2	18.6	

Table 2. DAS28ESR improvement in each group and pairwise comparisons

Dependent Variable: DAS28ESR improvement

	Estimates				Pairwise Comparisons				
ACPA status	Mean	Std. Error	95% Confidence Interval		Mean Difference	Std. Error	Sig.b	95% Confidence Interval for Difference b	
			Lower Bound	Upper Bound				Lower Bound	Upper Bound
low-positive	2.546 a	0.102	2.346	2.747	.381*	0.14	0.01	0.105	0.656
high-positive	2.166 a	0.096	1.976	2.355	-.381*	0.14	0.01	-0.656	-0.105

a Covariates appearing in the model are evaluated at the following values: DAS28ESR at pre-treatment = 5.186207505330619.
b Adjustment for multiple comparisons: Least Significant Difference (equivalent to no adjustments).
* The mean difference is significant at the .05 level.

Disclosure: Y. Ogawa, None; **N. Takahashi**, None; **K. Funahashi**, None; **S. Asai**, None; **T. Takemoto**, None; **T. Watanabe**, None; **N. Asai**, None; **N. Ishiguro**, None; **T. Kojima**, None.

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Abstract Number: 587

Defining the Conditions Under Which Long-Term Glucocorticoid Treatment Has a Good Benefit-Risk Ratio

Cindy Strehl[1], Johannes W J Bijlsma[2], Maarten de Wit[3], Maurizio Cutolo[4], Raphaele Seror[5], Kevin L. Winthrop[6], Frank Buttgereit[1] and EULAR Task Force on Glucocorticoids, [1]Department of Rheumatology and Clinical Immunology, Charité University Medicine, Berlin, Germany, [2]Rheumatology and Clinical Immunology, University Medical Center Utrecht, Utrecht, Netherlands, [3]Medical Humanities, VU Medical Centre, Amsterdam, Netherlands, [4]Research Laboratory and Academic Division of Clinical Rheumatology, Department of Internal Medicine, University of Genova, Genova, Italy, [5]Department of Rheumatology, Assistance Publique–Hopitaux de Paris, Hôpitaux Universitaires Paris-Sud, Le Kremlin

Bicêtre, France, [6]Division of Infectious Diseases, Oregon Health and Science University, Portland, OR
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Background/Purpose: Glucocorticoids (GC) are used to treat a wide range of inflammatory diseases including rheumatic and musculoskeletal diseases. EULAR recommendations on GC therapy are up to date but uncertainty about the benefit-risk ratio of GC persists. To address this issue, a multidisciplinary EULAR task force was assembled. Bearing in mind the known beneficial effects of GC, the primary aim was to achieve consensus when formulating conditions under which these drugs have an acceptable low level of harm, based on systematic evaluation of available evidence on adverse effects (AE).

Methods: Focussing on the four most worrisome AE of GC (cardiovascular disease (CVD), effects on bone, GC-induced hyperglycaemia & diabetes mellitus and infections), a systematic literature review was performed and discussed in the expert group. One breakout group per AE discussed the relevant evidence in detail and presented their results to the other group members following a structured questionnaire for final discussion. The questions addressed dose-harm relationships, relevant patient characteristics, co-morbidities, co-medications and both preventive and therapeutic measures with regard to the AE mentioned above.

Results:

The common basis for the group´s work was (i) an initial agreement with current guidelines stating there is convincing evidence for the beneficial effects of GC also at low dosages and (ii) the view that data on AE are limited (e.g. in terms of duration of GC use), sometimes both contradictory and biased. As a result of the critical appraisal of available evidence, the task force members agreed that for the majority of patients:

- at **dosages of ≤5mg/d**prednisone equivalent the benefits are greater than the risks with the exception of patients at high risk for CVD who may require preventive measures

- **at dosages of >10mg/d**the risks are greater than the benefits, with the exception of patients with (partial) GC resistance

At **dosages between >5 and ≤10mg/d**, the level of harm depends on patient-specific characteristics such as disease activity, presence of additional risk factors, and preventive measures. In general, an early diagnosis, low disease activity, low cumulative GC dosage, healthy life style (including appropriate exercise) and both, monitoring and treatment of risk factors and co-morbidities, respectively, represent factors which reduce the risk of harm. For each AE of GC, specific factors can affect the risk and, therefore, the level of harm in both directions. Moreover, for some GC induced AE (i) specific patient groups are at higher risk, (ii) certain co-morbidities increase the risk and (iii) the genetic background and (iv) specific disease characteristics may have impact on the risk of harm. Thus, the level of harm varies between individuals, and consequently our consensus is valid for the majority of patients rather than every individual patient.

Conclusion: There is no absolute condition or conditions under which GC always have an acceptable low level of harm. However, based on currently available evidence, our consensus provides the rationale to accomplish a relatively safe use of GC in the majority of patients.

Disclosure: C. Strehl, None; **J. W. J. Bijlsma**, None; **M. de Wit**, None; **M. Cutolo**, None; **R. Seror**, None; **K. L. Winthrop**, None; **F. Buttgereit**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/defining-the-conditions-under-which-long-term-glucocorticoid-treatment-has-a-good-benefit-risk-ratio

Abstract Number: 588

Prospective Study about Extension of Dosing Interval with Tocilizumab Therapy in Rheumatoid Arthritis Patients in Remission Maintenance

Jun Kikuchi, Akiko Shibata, Ryota Sakai, Kentaro Chino, Tsuneo Kondo, Ayumi Okuyama, Hirofumi Takei and Koichi Amano, Department of Rheumatology and Clinical Immunology, Saitama Medical Center, Saitama Medical University, Saitama, Japan
First publication: September 29, 2015

SESSION INFORMATION
Session Date: Sunday, November 8, 2015
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Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose: Tocilizumab (TCZ) is clinically effective against rheumatoid arthritis (RA) and over 50% of RA patients who had completed 5 years of TCZ treatment maintained remission[1)]. However, long-term treatment of biologics is often the cause of economic burden and restriction of treatment options. Although there are some trials to stopping biologics for patients in remission[2)], efficacy and tolerability of extended dosing interval with TCZ is not known. Objective of this study is to evaluate the efficacy and tolerability of 6-week extended dosing interval with TCZ in RA patients in remission.

Methods: Eligible patients were those who met the 2010 ACR/EULAR classification criteria. Consecutive patients at our institute who had received over 6 times of TCZ injection in remission maintained over 3 months with their informed consent between December 2013 and December 2014. The cut-off value of remission was DAS28-ESR <2.6. Last observation carried forward method was used for consecutive analysis.

Results: Fifteen patients were enrolled. At baseline, mean age was 52.0 ± 13.9 year-old, and the percentage of female was 78.6%. Mean disease duration was 11.0 ± 10.8 years. 21.4% and 7.1% of patients used concomitant methotrexate and glucocorticoids, respectively. 35.7% of patients previously used biologics. Mean duration until beginning the extension of dosing interval from starting TCZ was 38.6 ± 22.1 months. Mean duration until achieving remission from starting TCZ was 1.96 ± 2.56 months. Mean DAS28-ESR was 0.98 ± 0.74 at baseline. 77.8% of patients were seropositive. Thirteen (86.7%) patients have completed TCZ with 6-week extended dosing interval until Week 24, and all of them maintained in remission, though DAS28-ESR mildly increased to 1.55 ± 0.21 at Week 24 (p=0.026, baseline *vs* Week 24). CRP and ESR also tended to increase until Week 6 (p=0.071 and p=0.220, respectively), but did not change between Week 6 and Week 24 (p=0.842 and p=0.661, respectively). The change in DAS28-ESR at Week 24 did not correlate with the baseline parameters including age, sex, disease duration, CRP, ESR, MMP-3 and the seropositivity. The patients whose durations until achieving remission from starting TCZ were shorter tended to maintain lower disease activities (Spearman's rho=0.49, p=0.072). One patient dropped from the study because of the RA flare and returned to 4-week interval at Week 18. Five adverse events were noted in 5 patients. TCZ was discontinued due to the recurrence of lymphoproliferative disorder in one patient at Week 12. The other 4 events (2 mild upper respiratory infections, the fracture of humerus by falling accident and ureterolithiasis) did not lead to cessation of TCZ.

Conclusion: This trial suggested that 6-week extended dosing interval with TCZ therapy is effective and tolerable in RA patients as remission maintenance in daily clinical practice.

Reference:

1) Nishimoto N, et al. Ann Rheum Dis. 2009; 68: 1580-4.

2) Nishimoto N, et al. Mod Rheumatol 2014; 24: 17-25.

Disclosure: J. Kikuchi, None; **A. Shibata**, None; **R. Sakai**, None; **K. Chino**, None; **T. Kondo**, None; **A. Okuyama**, None; **H. Takei**, None; **K. Amano**, Chugai pharmaceutical Co. Ltd., 2.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/prospective-study-about-extension-of-dosing-interval-with-tocilizumab-therapy-in-rheumatoid-arthritis-patients-in-remission-maintenance

Abstract Number: 589

Adalimumab Concentration at 16 Weeks of Treatment Is Associated with Treatment Discontinuation within One Year

Mieke F. Pouw[1,2], Denis Mulleman[3], Mike T. Nurmohamed[1,4], Theo Rispens[5], Gilles Paintaud[3], Gertjan Wolbink[1,2] and David Ternant[3], [1]Rheumatology, Jan van Breemen Research Institute | Reade, Amsterdam, Netherlands, [2]Immunopathology, Sanquin Research, Amsterdam, Netherlands, [3]Université François-Rabelais de Tours, CNRS 7292, Tours, France, Tours, France, [4]Rheumatology, VU University Medical Center, Amsterdam, Netherlands, [5]Sanquin Research, Amsterdam, Netherlands

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Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose:

Anti-drug antibodies (ADAb) in patients treated with adalimumab have been associated with decreased adalimumab concentrations and loss of clinical response, and therefore treatment discontinuation. A large proportion of patients is immunized against adalimumab, but not in every

patient ADAb are detectable due to drug interference. Formation of ADAb at initiation is possibly triggered by low drug levels in the patient and vice versa higher drug levels could possibly leed to tolerance in the patient. Since the presence of ADAb is associated with decreased adalimumab concentrations and treatment discontinuation, these concentrations may give an estimation of the presence of ADAb, however, no cutoff concentration has been investigated yet. This study aimed at determining a cutoff value for adalimumab trough concentration for treatment discontinuation due to the presence of ADAb.

Methods:

This study was conducted in a prospective observational cohort study of 272 consecutive rheumatoid arthritis (RA) patients treated with adalimumab at the Department of Rheumatology, Jan van Breemen Research Institute | Reade, Amsterdam, the Netherlands. Patients were treated with adalimumab 40 mg every other week. The dosing schedule was increased to 40 mg every week in patients with an inadequate response, (22 patients before 16 weeks). Blood samples were collected before next injection after 4, 16, 28, 40 and 52 weeks of treatment to measure adalimumab concentrations and to detect the presence of ADAb using an ELISA and RIA (radioimmunoassay, Sanquin, Amsterdam). Patients were followed during one year.

Data were analyzed using ROC curve analysis. Youden index was used to estimate the cutoff value for adalimumab concentration which predicts discontinuation within one year due to ADAb presence *versus*patients not discontinuing treatment (ADAb+ and ADAb-) and patients discontinuing treatment for which no ADAb were detected (ADAb-).

Results:

The area under the ROC curve (AUC) is 0.8968 (95% CI 0.8391 to 0.9546, $p<0.0001$). The cutoff concentration which maximizes Youden index is 5.0 mg/L with sensitivity of 77,5%, specificity of 90,9%, a positive predictive value of 30.3% and negative predictive value of 98.8%.

Conclusion:

Patients who have adalimumab concentrations lower than 5 mg/L at 16 weeks after start of treatment, have a higher risk of treatment discontinuation within one year due to ADAb formation than patients who have higher concentrations at that time point. A patient whose adalimumab concentration is below 5 mg/L at week 16 has a 30% chance to form detectable antibodies against adalimumab, whereas for a patient above this cutoff value, this chance is only 1.2%.

Disclosure: M. F. Pouw, None; **D. Mulleman**, None; **M. T. Nurmohamed**, None; **T. Rispens**, None; **G. Paintaud**, None; **G. Wolbink**, Pfizer Inc, 2,Pfizer Inc, 5,Amgen, 5,AbbVie, 5,UCB, 5,BMS, 5; **D. Ternant**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/adalimumab-concentration-at-16-weeks-of-treatment-is-associated-with-treatment-discontinuation-within-one-year

Abstract Number: 590

Expression Levels of Selected Genes May Predict Response to TNF Alpha Blockers or Rituximab in the Individual Rheumatoid Arthritis Patient

Daphna Paran[1], Shlomo Pundak[2], Yaniv Kotler[2], Yoav Smith[3], Uri Arad[4], David Levartovsky[5], Ilana Kaufman[4], Victoria Furer[4], Ofir Elalouf[4], Adi Broyde[1], Sara Pel[4], Dan Caspi[4] and Ori Elkayam[4], [1]Rheumatology, Tel Aviv Sourasky Medical Center and the Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel, [2]Genefron Ltd. Jerusalem Israel, Jerusalem, Israel, [3]Genomic Data analysis Hadassah Medical School Hebrew University, Jerusalem Israel, Jerusalem, Israel, [4]Rheumatology, Tel-Aviv Sourasky Medical Center and the Sackler Faculty of Medicine, Tel-Aviv University, Tel-Aviv, Israel, [5]Rheumatology, Tel-Aviv Sourasky Medical Center, Sackler Faculty of Medicine, Tel-Aviv University, Tel-Aviv, Israel

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SESSION INFORMATION

Session Date: Sunday, November 8, 2015

Session Title: Rheumatoid Arthritis - Small Molecules, Biologics and Gene Therapy Poster I

Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose: Patients with Rheumatoid arthritis (RA) have a variety of therapeutic options however tools to predict individual patients' response are limited. The purpose of this study is to evaluate the ability of a Genefron diagnostic kit to predict RA patient response to TNF α blockers or rituximab

Methods:

Sixteen RA patients were assessed before starting a biologic agent: TNFα blockers (n=10) or rituximab (n= 6). Patients were re-evaluated 3

months after starting treatment. Assessment included swollen joint count (SJC), tender joint count (TJC), patient assessment of disease activity and pain by VAS, physician assessment of disease activity by VAS and health assessment questionnaire (HAQ). Genefron personal diagnostic kits measure the expression level of selected genes (IFN related genes, ubiquitin, genes activating the innate system) by quantitative real time PCR (qRT PCR) aiming to predict treatment outcome for each patient. Blood samples were obtained from each patient before administration of the biologic agent (T_0) and 20-24 hours later (T_{24}). RNA was extracted from PBMC samples and cDNA was transcribed from the RNA samples by high capacity cDNA reverse transcription. qRT PCR results were obtained using selected gene probes.

Results:

The TNFα blocker group included 9 females/1 male with a median age of 62±10 years and a disease duration of 9.5±16.2 years. A significant decrease in disease activity was observed after 3 months of treatment. Five patients achieved an ACR 20 response. Mean DAS 28 decreased from 5.6±0.9 to 4.3±1.4. The Genefron diagnostic kit predicted the response in 9 of 10 patients, resulting in a prediction accuracy of 90%, sensitivity of 75% and specificity of 100%. The rituximab group included 5 females/1male with a median age of 68±9.3 years and a disease duration of 9±8.5 years. Three patients achieved an ACR 20 response. The Genefron diagnostic kit predicted the response correctly in all 6 patients.

Conclusion:

In this small group of patients, the Genefron diagnostic kit predicted the response to TNFα blockers and rituximab in a high percentage of patients. These preliminary results require further confirmation in large scale studies to assess whether this kit may possibly aid in the selection of a suitable biological drug for the individual RA patient.

Disclosure: D. Paran, Genefron, 2; **S. Pundak**, Genefron, 1; **Y. Kotler**, Genefron, 1; **Y. Smith**, Genefron, 1; **U. Arad**, None; **D. Levartovsky**, None; **I. Kaufman**, None; **V. Furer**, None; **O. Elalouf**, None; **A. Broyde**, None; **S. Pel**, None; **D. Caspi**, None; **O. Elkayam**, Genefron, 2.

Abstract Number: 591

Rosuvastatin Improves Endothelial Function in Patients with Inflammatory Joint Diseases, Longitudinal Associations with Atherosclerosis and Arteriosclerosis

Eirik Ikdahl[1], Jonny Hisdal[2], Silvia Rollefstad[1], Inge C Olsen[3], Tore K. Kvien[4], Terje R. Pedersen[5] and Anne Grete Semb[6], [1]Preventive Cardio-Rheuma Clinic, Department of Rheumatology, Diakonhjemmet Hospital, Oslo, Norway, [2]Section of Vascular Investigations, Oslo University Hospital Aker, Oslo, Norway, [3]Department of Rheumatology, Diakonhjemmet Hospital, Oslo, Norway, [4]Dept. of Rheumatology, Diakonhjemmet Hospital, Oslo, Norway, [5]Department of Preventive Cardiology, Ullevaal University Hospital, Oslo, Norway, [6]Preventive Cardio-Rheuma clinic, Department of Rheumatology, Diakonhjemmet Hospital, Oslo, Norway

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SESSION INFORMATION

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Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

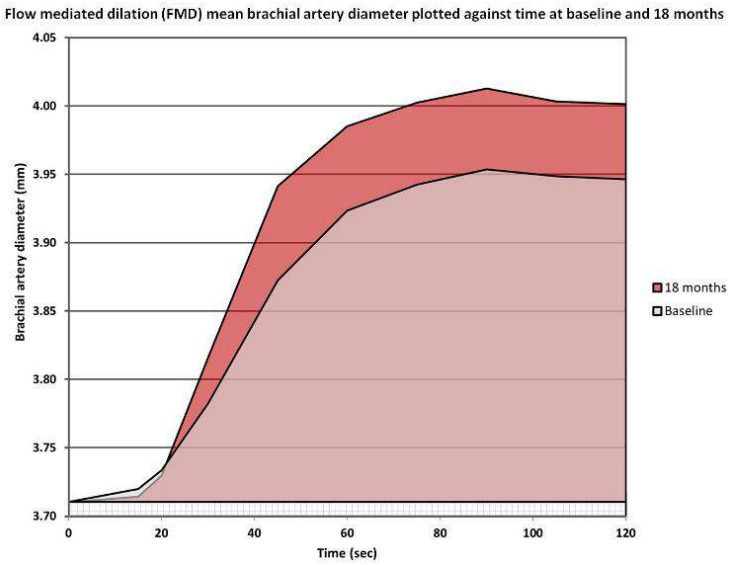
Background/Purpose: Endothelial dysfunction is an early step in the formation of atherosclerotic lesions and can be quantified by the degree of flow mediated vasodilation (FMD) of the brachial artery. FMD is a predictor of cardiovascular (CV) events in the general population and is lower in patients with inflammatory joint diseases (IJD) compared to the general population. Restoration of endothelial function to normal levels has been proposed as an important factor in the process of atherosclerotic plaque regression. Our aim was to investigate the effect of long-term rosuvastatin therapy on FMD in patients with IJD and carotid artery plaque(s) (CP). Furthermore, we evaluated associations between change in FMD (ΔFMD) and change in CP height, arterial stiffness [aortic pulse wave velocity (aPWV) and augmentation index (AIx)], lipids, rheumatic disease activity and inflammatory variables.

Methods: Eighty-five statin naïve patients with IJD and ultrasound verified CP (rheumatoid arthritis: 53, ankylosing spondylitis: 24, psoriatic arthritis: 8) received rosuvastatin treatment for 18 months to obtain low density lipoprotein cholesterol goal <1.8 mmol/L. All patients underwent assessment of FMD, aPWV, AIx and carotid ultrasound at baseline and at study end. Change in FMD from baseline to study end was analyzed using paired-samples t-test. Furthermore, multiple linear regression analyses, adjusted for age, gender and use of biologic disease-modifying anti-rheumatic drugs, were applied to evaluate associations between DFMD and change in CP height, aPWV, AIx, lipids, disease activity/inflammatory variables and medication. In addition, the mean diameter of the brachial artery as a result of FMD was plotted against time at baseline and 18 months.

Results: The patient cohort had 60% females and the median (IQR) age and disease duration was 61.0 (56.0-67.0) and 18.0 (8.3-26.0) years,

respectively. The mean ±SD FMD was significantly improved from 7.10 ±3.14 % at baseline to 8.70 ±2.98 % at study end (p<0.001). Multiple linear regression analyses revealed that the FMD improvement was linearly associated with the improvement in arterial stiffness as measured by AIx: β (CI): -0.09 (-0.18, 0.00) (p=0.05) and CP height regression: β (CI): -3.10 (-4.95, -1.25) (p=0.001). DFMD was not associated with changes in lipid levels, disease activity, inflammatory variables or medication. The mean diameter of the brachial artery as a result of FMD was plotted against time at baseline and 18 months is shown in figure.

Conclusion: Long-term lipid lowering with rosuvastatin improved endothelial function measured by FMD in IJD patients with atherosclerotic disease. The statin-induced improvement in endothelial function was linearly associated with reduced arterial stiffness and CP regression. Our results support the hypothesis that restoration of endothelial function plays an important role in the process of atherosclerotic regression.



Disclosure: E. Ikdahl, None; **J. Hisdal**, None; **S. Rollefstad**, None; **I. C. Olsen**, None; **T. K. Kvien**, None; **T. R. Pedersen**, None; **A. G. Semb**, None.

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Abstract Number: 592

The Impact of Tobacco Smoking on the Effectiveness of Abatacept in Rheumatoid Arthritis: Data from a Paneuropean Analysis of RA Registries

Axel Finckh[1,2], Jacques Gottenberg[3], M. Victoria Hernández[4], Florenzo Iannone[5], Elisabeth Lie[6], Helena Canhao[7], Karel Pavelka[8], Carl Turesson[9], Merete Lund Hetland[10] and Xavier Mariette[11], [1]Rheumatology Division, University Hospital of Geneva, Geneva, Switzerland, [2]Div of Rheumatology, University of Geneva, Geneva, Switzerland, [3]Hautepierre, Strasbourg, France, [4]Arthritis Unit, Rheumatology, Hospital Clinic, Barcelona, Spain, [5]Interdisciplinary Department of Medicine (DIM), Rheumatology Unit, University of Bari, Bari, Italy, [6]Dept. of Rheumatology, Diakonhjemmet Hospital, Oslo, Norway, [7]Rheumatology Research Unit, Instituto de Medicina Molecular, Lisbon, Portugal, [8]Institute of Rheumatology, Department of Rheumatology, 1st Faculty of Medicine, Charles University, Prague, Czech Republic, [9]Lund University, Rheumatology, Dept. of Clinical Sciences,, Malmö, Sweden, [10]Copenhagen Center for Arthritis Research (COPECARE), Center for Rheumatology and Spine Diseases, Rigshospitalet - Glostrup, University of Copenhagen, Denmark, Glostrup, Denmark, [11]Université Paris-Sud, AP-HP, Hôpitaux Universitaires Paris-Sud, Paris, France

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Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose:

It has previously been shown that current smoking is a predictor of poor response to methotrexate or anti-TNF treatment in rheumatoid arthritis (RA). The impact of smoking for response to biologic DMARDs (bDMARDs) with different modes of action is not known. The objective of this

study was to investigate the effect of smoking on the effectiveness of abatacept (ABA) in patients (pts) with RA.

Methods:

This is a pooled observational database analysis of 9 European RA registries (ARTIS-SE, ATTRA-CZ, BIOBADASER-ES, DANBIO-DK, GISEA-IT, NOR-DMARD-NO, ORA-FR, SCQM-CH, Reuma.PT). Inclusion criteria for this analysis were a diagnosis of RA, initiation of ABA and available information on current smoking status. The primary endpoint was ABA drug retention. A secondary endpoint was EULAR good or moderate response rate at one year, estimated by longitudinal interpolation (mixed linear model) and corrected for drug retention (Lundex[1]).Time to discontinuation was defined as the time between drug initiation and last administration plus one dispensation interval. Drug retention was analyzed using a Cox proportional hazards model, adjusting for potential confounders, including calendar year of treatment initiation, patient demographics, country of origin and disease characteristics.

Results:

We identified 4476 pts initiating ABA with 7881 pt-years (PY) of follow-up, of whom 721 (16%) were current smokers, and 3755 were non-smokers. Smokers were significantly younger (mean age 55.2 versus 58.4 yrs, $p<0.001$), with shorter disease durations (10 vs 13 yrs, $p<0.001$), more often RF-positive (78% vs 73%, $p=0.03$), more commonly males (27.5% vs 17.8%, $p<0.001$), with lower disease activity at baseline (DAS28 4.6 vs 4.8, , $p<0.01$) and less prior bDMARD exposure (median number of past bDMARDs 1 vs 2, $p<0.001$). Smoking was associated with an increased risk of ABA discontinuation for any reason (crude median survival time of 1.67 yrs vs 1.99 yrs for non smokers, $p=0.04$, hazard ratio (HR) (95% CI): 1.12, (1.01-1.32)), even after adjusting for potential confounding factors (HR (95% CI): 1.17 (1.01-1.35), $p=0.03$). When examining the role of current smoking on specific causes of drug discontinuation, only discontinuations due to ineffectiveness were associated with smoking (crude HR: 1.17, $p=0.03$; adjusted HR 1.17, $p=0.10$), but not discontinuations due to adverse events (crude HR: 1.03, $p=0.80$; adjusted HR 1.17, $p=0.38$). The EULAR good or moderate response rates at one year were lower in smokers than in non-smokers (73% versus 84%) ($p<0.001$). The Lundex based on EULAR good or moderate response rates were also lower in smokers then in non-smokers (48% versus 56%). The effect of smoking on ABA effectiveness was not modified by country of origin.

Conclusion:

Data from this Pan-European registry analysis suggest that smoking is associated with a decreased effectiveness of ABA, with higher discontinuation rates and lower response rates, as has previously been reported for methotrexate and anti-TNF agents. The difference in drug retention was modest and mainly due to discontinuations related to ineffectiveness. The mechanisms underlying this association remain to be elucidated and unmeasured confounding cannot be ruled out.

[1] A&R 2006;54:600-6

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Abstract Number: 593

Predicting the Need for Additional Treatment in Early Rheumatoid Arthritis Patients Treated to Target on Methotrexate Monotherapy

Xavier Teitsma[1], Johannes Jacobs[2], Paco Welsing[3], Thasia Woodworth[4], Attila Pethö-Schramm[5], Michelle Borm[6], Corrado Bernasconi[5], Floris Lafeber[1] and Johannes W J Bijlsma[7], [1]Department of Rheumatology and Clinical Immunology, University Medical Center Utrecht, Utrecht, Netherlands, [2]Rheumatology & Clinical Immunology, University Medical Center Utrecht, Utrecht, Netherlands, [3]Department Rheumatology and clinical immunology, University Medical Center Utrecht, Utrecht, Netherlands, [4]Medicine, Division of Rheumatology, David Geffen School of Medicine, Los Angeles, CA, [5]F. Hoffmann-La Roche, Basel, Switzerland, [6]Beneluxlaan 2a, Roche Nederland BV, Woerden, Netherlands, [7]Rheumatology and Clinical Immunology, University Medical Center Utrecht, Utrecht, Netherlands

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Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose:

Joint damage and functional disability can be reduced by intensive treatment of newly diagnosed rheumatoid arthritis (RA) patients during the "window of opportunity". Although methotrexate (MTX) is considered the anchor disease-modifying anti-rheumatic drug (DMARD) for initial RA treatment, the majority of patients need additional treatment due to inefficacy or MTX-associated adverse events. Predictors of the need to add another treatment to MTX may identify patients who can benefit from intensive treatment. Starting combination treatment in such patients earlier can improve the likelihood of timely RA control.

Methods:

In U-ACT-EARLY, a double blind, placebo-controlled treatment strategy trial, 108 patients with newly diagnosed RA (1987 or 2010 criteria) were randomized to initiate MTX monotherapy according to treat-to-target principles. MTX was increased to 30 mg/week (or maximum tolerable dose) until remission (DAS28-ESR <2.6 with SJC < 4) was achieved. In the absence of remission at maximum MTX dose (~20 weeks), hydroxychloroquine (HCQ) 200 mg bid was added. If after 12 weeks, remission still was not reached, tocilizumab (TCZ) was added to MTX-HCQ. Baseline demographic, clinical, laboratory, and functional assessment data were evaluated; missing data were imputed using multiple imputation. Multivariate logistic regression with univariate preselection was used to identify factors predictive for patients requiring additional treatment.

Results:

Patients had mean disease duration ~4 weeks and high DAS28-ESR (Table 1). Fifty-six of 108 patients (51.9%) added TCZ to MTX-HCQ due to inefficacy (n=52) or adverse events (n=4) (fig.1). Multivariate logistic regression analysis identified higher DAS28-ESR (p<.001) and smoking (p=.067) as main baseline predictors for addition of TCZ. Model discrimination was reasonable with an area under the receiver operating characteristic (ROC) curve of 0.72 (95% CI: 0.63-0.82). Table 2 shows the observed probability of adding therapy for the 2 predictor categories.

Conclusion:

The majority of very early RA patients initiating MTX monotherapy in a treat-to-target strategy required addition of TCZ to achieve remission. Patients actively smoking with higher baseline DAS28-ESR scores were more likely to require additional treatment.

Disclosure: X. Teitsma, None; **J. Jacobs**, None; **P. Welsing**, None; **T. Woodworth**, F. Hoffmann-La Roche, 3; **A. Pethö-Schramm**, F. Hoffmann-La Roche, 3; **M. Borm**, Roche Nederland B.V., 3; **C. Bernasconi**, F. Hoffmann-La Roche, 5; **F. Lafeber**, None; **J. W. J. Bijlsma**, F. Hoffmann-La Roche, 5.

Abstract Number: 595

Discovery of Serum Protein Biomarkers of Response to Adalimumab in Rheumatoid Arthritis and Their Relationship to Biomarkers of Response to Infliximab

Ignacio Ortea[1], Bernd Roschitzki[2], Eva Tomero[3], Juan G. Ovalles-Bonilla[4], Javier Lopez-Longo[5], Inmaculada de la Torre[5], Isidoro Gonzalez-Alvaro[6], Juan J Gomez-Reino[7] and **Antonio Gonzalez**[8], [1]Maimónides Health Research Institute (IMIBIC), Cordoba, Spain, [2]Functional Genomics Center Zurich, University and ETH Zurich, Zurich, Switzerland, [3]Rheumatology, Hospital Universitario de La Princesa. IIS La Princesa, Madrid, Spain, [4]Rheumatology, Hospital General Universitario Gregorio Marañón, Madrid, Spain, [5]Gregorio Marañon Hospital, Madrid, Spain, [6]Hospital Univ. de La Princesa, IIS Princesa, Madrid, Spain, [7]Instituto Investigacion Sanitaria- Hospital Clinico Universitario de Santiago, Santiago de Compostela, Spain, [8]Laboratorio Investigacion 10 and Rheumatology Unit, Instituto Investigacion Sanitaria- Hospital Clinico Universitario de Santiago, Santiago de Compostela, Spain

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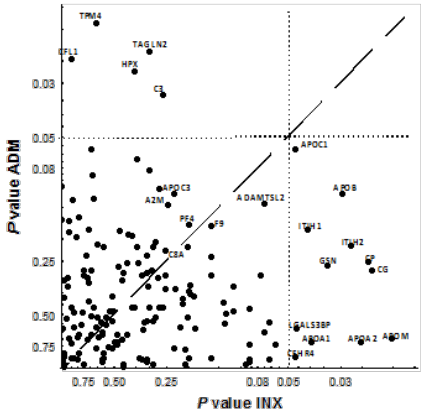
Background/Purpose:

Biomarkers of response to treatment in rheumatoid arthritis (RA) are sorely needed given the large inter-individual variability in efficacy of the available drugs. However, some authors think it will be difficult to distinguish between response to the different drugs. The doubts on biomarkers

are based in the broadly similar efficacy of all bDMARDs and the lack of validated biomarkers to date, although the best-established, as seropotivity, show clear drug-specific association. **Methods:**

Discovery of biomarkers of response to adalimumab (ADM) was based in combined depletion of the most abundant serum proteins, 8-plex iTRAQ labeling, two-dimensional LC fractionation, protein identification and relative quantification with a hybrid Orbitrap mass spectrometer. The results were compared and combined with an identical study of response to infliximab (INX) (1). **Results:**

262 proteins were identified in all the samples with at least 2 peptides and 95% confidence. Nine proteins presented differences between non-responders (NR) and responders (R) ($P < 0.05$), representing candidate biomarkers of response to ADM. None of them was coincident with the previously identified 14 candidate biomarkers of response to INX. In addition, the NR/R differences in response to ADM and to INX were not correlated ($r_{spearman}$= 0.07; P= 0.40), and were inversely correlated when only the significant proteins were considered ($r_{spearman}$= -0.69; P= 0.0023) as shown in Fig. 1.



The combined analysis of response to ADM and to INX, however, identified eight proteins (ADAMTSL2, A2M, APOB, APOC3, F9, C3, C8A and PF4), showing that discordance was not universal. **Conclusion:**

Potential biomarkers of response to ADM were identified. This panel was independent of the previously obtained in response to INX. The pathways highlighted in the two studies were also different. These results suggest that mechanisms of inter-individual variability are partly drug-specific, and that it will be possible to obtain biomarkers orienting the election of drugs.

1. Ortea I, *et al. J Proteomics*. 2012;77:372-82.

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Disclosure: I. Ortea, None; **B. Roschitzki**, None; **E. Tomero**, None; **J. G. Ovalles-Bonilla**, None; **J. Lopez-Longo**, None; **I. de la Torre**, Eli Lilly and Company, 3; **I. Gonzalez-Alvaro**, None; **J. J. Gomez-Reino**, None; **A. Gonzalez**, None.

Abstract Number: 596

Long-Term High Remission Rates and Distinct Trajectories of Disease Activity Following the Implementation of Treat-to-Target in Early Rheumatoid Arthritis

Letty G.A. Versteeg[1], Laura M.M. Steunebrink[1], Ina H. Kuper[1], Peter M. ten Klooster[2], Arie E. van der Bijl[3], Harald E. Vonkeman[4] and Mart A.F.J. van de Laar[1], [1]Rheumatology, Medisch Spectrum Twente - Arthritis Center Twente, Enschede, Netherlands, [2]Pcgr, University of Twente, Enschede, Netherlands, [3]Isala Klinieken, Zwolle, Netherlands, [4]Ariensplein 1, Medisch Spectrum Twente - Arthritis Center Twente, Enschede, Netherlands

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Session Time: 9:00AM-11:00AM

Background/Purpose: Treat-to-target (T2T) in early Rheumatoid Arthritis (RA) has been successfully implemented in daily clinical practice. Patients achieve remission very early and during a follow-up of three years T2T leads to persistent low disease activity in most patients and high remission rates. Unfortunately, some patients do not respond to this approach and remain in - or return to - moderate or high disease activity. These patients should be recognized early, as they might benefit from alternative therapeutic approaches. The aim of this study is to describe the five year clinical outcome of implementation of a T2T strategy in early RA. We aim to identify subgroups of patients with distinct long-term trajectories of disease activity.

Methods: In DREAM remission induction cohort I, patients with newly diagnosed RA were treated according to a T2T step-up strategy aiming at remission. Treatment consisted of methotrexate, followed by the addition of sulfasalazine and subsequently exchange of sulfasalazine with a tumor necrosis factor inhibitor in case of persistent disease activity. The mean change in the disease activity score in 28 joints (DAS28) was analysed with a linear mixed model. Subgroups of patients with distinct trajectories of disease activity were described and predictors will be identified.

Results: Data of 229 patients were used (63% female, mean age 57 years, 78% fulfilling the ACR 1987 criteria). Remission rates at 12 weeks, 24 weeks, 1 year, 3 years and 5 years were 31.1%, 48.8%, 60.6%, 63.6% and 63.2%, respectively. Mean DAS28 improved from 4.93 (95% CI 4.79 – 5.07) at baseline to 2.44 (95% CI 2.28 – 2.60) after five years (p<0,0001). Four subgroups with distinct trajectories of disease activity could be identified. A very small group (2.2%) could be classified as non-responders: they did not achieve remission at any moment during the first five year of follow-up. The second group (21.4%), the poor-responders, reached remission only after the first year. The third and largest group (68.1%), the responders, achieved remission within the first year and then had a varied course of disease activity. Finally, the fourth group with the best outcome (8.3%) achieved remission in the first year and remained in remission during the whole follow-up. Analysis of predictors will follow.

Conclusion: Implementation of a treat-to-target per-protocol treatment strategy leads to high long-term remission rates in daily clinical practice. Four groups with distinct trajectories of disease activity could be described. Predictors will be identified and presented during the 2015 ACR annual meeting.

Disclosure: L. G. A. Versteeg, None; **L. M. M. Steunebrink**, None; **I. H. Kuper**, None; **P. M. ten Klooster**, None; **A. E. van der Bijl**, None; **H. E. Vonkeman**, None; **M. A. F. J. van de Laar**, None.

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Abstract Number: 597

JAK Inhibition Significantly Reduced Fibrogenesis in Rheumatoid Arthritis Patients

Shintaro Hirata[1], Natasja Stæhr Gudman[2], Kentaro Hanami[1], Satoshi Kubo[1], Anne C. Bay-Jensen[2], Morten Asser Karsdal[3] and Yoshiya Tanaka[1], [1]The First Department of Internal Medicine, University of Occupational and Environmental Health, Japan, Kitakyushu, Japan, [2]Nordic Bioscience, Biomarkers and Research, Herlev, Denmark, [3]Biomarkers and Research, Nordic Bioscience, Herlev, Denmark

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Session Time: 9:00AM-11:00AM

Background/Purpose: Connective tissue degradation and formation is markedly increased in rheumatoid arthritis (RA). Increased tissue formation may result in fibrosis, whereas increased degradation may result in joint and tissue destruction. Different interventions such as anti-TNF-Î±, Anti-IL6R and JAK may provide both similar and different responses on key tissues.

Quantification of circulating levels of specific neo-epitopes of the extracellular matrix may act as biomarkers of connective tissue turnover and thereby may be used as objective tools for monitoring treatments effects in RA. Type II collagen formation (PRO-C3) has been demonstrated to be both a diagnostic marker for the presence of liver fibrosis and in addition to provide prognostic information on progression.

The aim of the study was to investigate the effect of fibrogenesis biomarkers in RA patients as an effect of methotrexate (MTX) combined with either tocilizumab (TCZ, anti-IL-6R), tofacitinib (TOFA, JAK inhibitor), adalimumab (ADA, anti-TNF-Î±) or given as a monotherapy.

Methods: 149 RA patients were included at the time of initiating one of the following treatments: 1) MTX; 23, 2) ADA+MTX; 49, 3) TOFA+MTX; 27, and 4) TCZ+MTX; 50. Serum samples were drawn along with Sharp-vdH score (SHS) and other clinical data at baseline and again 1 year after initiation of treatment (follow-up). Type III collagen formation, PRO-C3, ASAT, and ALAT were measured in the serum samples. Wilcoxon matched-paired rank test was performed. Error bars are shown as SEM.

Results: Anti-TNF-Î±, and anti-IL6-R resulted both in statistical increase in the liver enzymes ASAT and ALAT, whereas JAK intervention did

not. Interestingly, the PRO-C3 marker was significantly (P<0.05) inhibited by JAK inhibition in the TOFA group from 19.9ng/ml on average at baseline to 16.4ng/ml at follow-up, whereas the other treatments did not affect PRO-C3 significantly. Also, although serum EGF levels were decreased by anti-TNF and anti-IL-6, they are increased by TOFA.

Conclusion: Increased tissue remodeling is a characteristic of rheumatoid arthritis, in which both formation and degradation is affected. JAK inhibition resulted in a significant attenuation of a marker of fibrogenesis and could be involved in mesenchymal-epithelial transition, which warrant further investigation of the effect if JAK inhibition compared to that of anti-TNF-Î± and anti-IL6R.

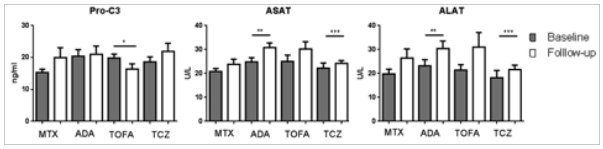

*Figure 1, Evaluations of ASAT, ALAT and Pro-C3 at baseline and follow-up. Difference between baseline and Follow-up was evaluated by mean of Wilcoxon match pairs signed rank test. *p<0.05, ** p<0.01, ***p<0.001. Error bars are illustrated as SEM.*

Disclosure: S. Hirata, None; **N. S. Gudman**, Nordic Bioscience Diagnostic, 3; **K. Hanami**, None; **S. Kubo**, None; **A. C. Bay-Jensen**, Nordic Bioscience Diagnostic, 1,Nordic Bioscience Diagnostic, 3; **M. A. Karsdal**, Nordic Bioscience Diagnostic, 1,Nordic Bioscience Diagnostic, 3; **Y. Tanaka**, None.

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Abstract Number: 598

Economic Impact of Decreasing Adalimumab and Etanercept Doses and Drug Monitoring in Patients with Rheumatoid Arthritis in Clinical Remission: Preliminary Study from a Local Biologics Unit

José Rosas[1], Francisca Llinares-Tello[2], José Miguel Senabre[1], Gregorio Santos-Soler[1], Esteban Salas-Heredia[1], Xabier Barber[3], Ana Pons[4], Catalina Cano[4], Marisa Lorente[5] and Juan Molina[6], [1]Rheumatology, Hospital Marina Baixa, Villajoyosa, Spain, [2]Clinical Analysis, Hospital Marina Baixa, Clinical Analysis, Villajoyosa, Spain, [3]Centro de Investigación Operativa, Miguel Hernández University, Elche, Spain, [4]Hospital Marina Baixa, Nursing, Villajoyosa, Spain, [5]Marina Baixa Hospital, Nursing, Villajoyosa, Spain, [6]Hospital Marina Baixa, Clinical Analysis, Villajoyosa, Spain

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Background/Purpose: To evaluate the economic impact of adalimumab (ADL) and etanercept (ETN) dose reduction (by decreasing treatment frequency) and drug monitoring in patients with rheumatoid arthritis (RA) in clinical remission.

Methods: ADL, ETN and anti-drug antibody levels were measured using Promonitor-ADL, Promonitor-ETN, Promonitor-Anti-ADL and Promonitor-Anti-ETN ELISA kits (Progenika, Grifols, Spain), respectively, during 2013-2014. Cut-points for ADL and ETN levels were 0.024 and 0.035 mg/L, respectively, and for Anti-ADL and Anti-ETN antibodies 3.5 and 132 AU/mL, respectively. Sera were drawn immediately before each injection. Clinical remission was defined as sustained DAS28-ESR≤2.6 during 6 consecutive months. The following was collected: RA progress, time on biologic treatment, reason for drug withdrawal or for resuming the conventional frequency, ultrasound activity index (Doppler) in 12 joints, and basal (ADL every 14 days; ETN every 7 days) and decreased (ADL every 18-21-28 days; ETN every 10-14 days) frequencies. Annual doses avoided were calculated for the modified frequency of ADL (every 18 days: 5.8 doses; every 21 days: 8.7 doses and every 28 days: 13 doses) and ETN (every 10 days: 15.5 doses and every 14 days: 26 doses). Savings during the two years, and the theoretical number of patients that could have been treated with costs saved were calculated (ADL and ETN dose prices were 500€ and 250€, respectively).

Results: Drug and anti-drug antibody levels were measured in 45 RA patients accounting for a total of 94 tests. 87% of patients were women, average age of 60.5±18 years. Average disease duration was 15±9.8 years and average ADL and ETN treatment durations were 5.2±1.3 and 5.1±1.8 years, respectively. Average time of decreased treatment frequency for both drugs was 1.2±0.7 years. ADL and ETN was the first line biological drug in 73% and 37% of patients, respectively. Synthetic DMARDS were given in 100% and 78% of patients on ADL and ETN, respectively. 87% of patients with a modified dosing frequency maintained clinical remission. Two ADL patients (7%, those treated every 18 days) resumed the conventional frequency and 4 ETN patients (22%, 3/75% treated every 10 days and 1/25% treated every 14 days: average of 6

months on modified frequency). Anti-drug antibodies were not detected in any patient after 1 year follow up. Table 1 summarizes clinical, drug monitoring and impact of savings data. During 2013 and 2014 22 RA patients started biologic therapy. Cost savings consequence of optimization allowed treatment of 22 new patients during 1 year.

Conclusion: Decreasing ADL and ETN dosing frequency with sustained clinical activity is possible in RA patients in remission by monitoring disease activity and serum drug levels. Dose optimization enables significant savings. Antibodies are not detected in patients with a decreased treatment frequency. It is likely that patients with a long term remission require less drug level.

	Adalimumab				**Etanercept**			
Frequency (days)	18	21	28	Total	10	14	Total	ADL+ETN
Patients/tests	12/21	11/26	4/7	27/51	10/23	8/18	18/41	45/94
Mean Anti-TNF level (mg/L)	6.58	8.34	2.9	-	2.32	1.45	-	-
Anti-drug antibodies (%)	0	0	0	0	0	0	0	0
Mean DAS28-VSG	1.82	1.9	2.8	-	1.73	1.86	-	-
Mean years on reduced frequency (SD)	1.5 (0.9)	1.2 (0.5)	1.2 (0.9)	1.3 (0.8)	1.0 (0.4)	1.2 (0.7)	1.1 (0.6)	1.2 (0.7)
Doses avoided, n	91.6	106	62.4	260	210	338	548	-
Savings (€)	45,800	53,070	31,200	130,070	52,500	84,500	137,000	267,070
Patients treated with savings, n	3.8	4.4	2.6	10.8	4.4	7	11.4	22.2

Disclosure: J. Rosas, None; **F. Llinares-Tello**, None; **J. M. Senabre**, None; **G. Santos-Soler**, None; **E. Salas-Heredia**, None; **X. Barber**, None; **A. Pons**, None; **C. Cano**, None; **M. Lorente**, None; **J. Molina**, None.

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Abstract Number: 599

An Examination of Dose Escalation Among Remicade (infliximab) Users in a US RA Registry

Jeffrey R. Curtis[1], Ying Shan[2], Joel M. Kremer[3], Katherine Saunders[4], Dennis Parenti[5] and Shelly Kafka[5], [1]University of Alabama at Birmingham, Birmingham, AL, [2]UMass Memorial Medical Center, Worcester, MA, [3]Albany Medical College, Albany, NY, [4]Corrona LLC, Atlanta, GA, [5]Janssen Scientific Affairs, LLC, Horsham, PA

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Background/Purpose: Limited data are available about infliximab(IFX) dose escalation. This analysis examines the frequency of dose escalation among IFX patients using data from the US CORRONA RA registry and describes the characteristics of patients who dose escalate vs those who do not.

Methods: RA patients initiating IFX at a dose of ≤5 mg/kg on or after 6/1/2009 with at least 1 follow-up visit with dose information were eligible for analysis. Subgroup analysis was performed among patients with follow-up at 1yr to compare characteristics between those who dose escalated vs those who did not. Dose escalation was defined as an increase of >1mg/kg in dose and/or a decrease in the frequency of dosing by at least 1 wk (e.g. q 8 wks to q7 wks). Censoring occurred if patients switched to another biologic or left the registry. Descriptive statistics were used to compare baseline characteristics of infliximab patients stratified by number of biologics, and also comparing those who dose escalated vs

those who did not within the 1st yr after initiating therapy.

Results: A total of 716 patients initiated IFX after June 2009. Common characteristics included mean age (61yrs), women (78%), mean weight (83kg), RF + (70%) and CCP+ (67%), baseline CDAI (22.5), and insurance status (Medicare 46%, Medicaid 6%). Differences between those who initiated IFX as their 1st, 2nd, or 3rd biologic included RA duration (7.0, 9.6, 11.0 yrs, respectively, $p < 0.001$), college education (50, 61, 66%, respectively, $p = 0.002$), number of prior DMARDs (1.6, 1.8, 2.0; $p < 0.001$), proportion receiving monotherapy (12, 15, 26%), and prednisone use (31, 29, 35%).

Over 3yrs follow-up, the proportions of patients escalating IFX significantly differed, ranging from a low of 21% at 1 yr for patients using IFX as 1st line to a high of 81% at 3yrs for patients using it as 3rd line (Table, $p = 0.0024$ for between-group differences). In patients with follow-up data at 12mo (n=608), there were some baseline characteristics associated with dose escalating vs not in the 1st yr of therapy including shorter RA duration($p = 0.03$), greater number of prior biologics ($p=0.04$), monotherapy ($p = 0.03$), greater prednisone use ($p=0.01$), and higher CDAI ($p=0.04$) and related disease activity measures.

Conclusion: Dose escalation of IFX is relatively frequent over time. Patients with more severe RA undergo dose escalation more commonly than those with less severe disease. Understanding long term benefits and persistence and related factors following dose escalation may help optimize dose escalation as a treatment strategy compared to switching.

Follow-up time	First line N=373	Second Line N=210	Third line N=133
12 months, %	21	31	30
24 months, %	35	46	58
36 months, %	49	62	81

Table: proportion of patients increasing infliximab dose over time according to its use as a first, second, or third line biologic agent

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Abstract Number: 600

Tocilizumab Serum Trough Levels and Disease Activity in Rheumatoid Arthritis

Virginia Ruiz-Esquide[1], Pascal Zufferey[2], Jose Inciarte-Mundo[1], Jordi Yagüe[3], M. Victoria Hernández[4], Julio Ramirez[1], Jeanne Berner[2], Mariona Pascal[3], Andrea Cuervo[1], Juan D. Cañete[5] and Raimon Sanmarti[1,6], [1]Arthritis Unit. Rheumatology, Hospital Clínic of Barcelona, Barcelona, Spain, [2]Rheumatology, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland, [3]Immunology, Hospital Clínic of Barcelona, Barcelona, Spain, [4]Hospital Clínic i Provincial, Barcelona, Spain, [5]Arthritis Unit, Rheumatology, Hospital Clínic of Barcelona, Barcelona, Spain, [6]Arthritis Unit. Rheumatology Department, Hospital Clínic of Barcelona, Barcelona, Spain
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Background/Purpose:

Tocilizumab (TCZ) is a humanized anti-IL-6R monoclonal antibody approved for the treatment of active rheumatoid arthritis (RA) (EMA: 8mg/kg q4w). Response to treatment may depend on the dose as well as on the achieved seric levels.

Purpose

To analyze the serum levels of TCZ in two cohorts of RA patients on chronic treatment with IV TCZ and its relationship with disease activity and disease remission. To establish a cut-off point of TCZ serum levels with high discriminative capacity for disease remission.

Methods:

Cross-sectional study of 2 cohorts (Barcelona, Spain and Lausanne, Switzerland) that included all RA patients on chronic treatment with **IV**TCZ. Demographic, disease activity, serum markers, TCZ trough levels (detectable levels > 1 µg/ml) (LISA TRACKER Tocilizumab Theradiaag, France) and IL6 levels (ELISA) were analyzed. Samples were collected just before treatment infusion. TCZ levels were correlated with different clinical and serological parameters. Multivariate logistic regression was calculated to determine variables associated with remission (DAS28 ≤2.6). ROC curve analysis was performed to study the discriminatory capacity of the area under the curve (AUC) of TCZ levels associated with remission.

Results:

77 RA patients were included (40 Barcelona Cohort, 37 Lausanne Cohort). 89.6% were women, with a mean age of 55.17 ± 13.4 years and a disease duration of 13.8 ± 8.4 years; 70.1% were FR and/or anti-CCP positive. 42.9% of patients were on monotherapy, 40.3% were receiving low dose glucocorticoids and 22.1% were on reduced dose of TCZ (6 or 4 mg/kg q4w). 43 patients (56.6%) were on remission. Swiss patients had lower disease activity and were more frequently on remission, and used corticosteroids and DMARD combination therapy less frequently. 20 patients (26%) had undetectable levels of TCZ (<1 µg/ml). This situation was associated with significantly higher levels of CRP, lower levels of IL-6 and higher DAS28; but there were no differences in tender and swollen joint count (Table). Patients in remission had higher levels of TCZ and had more frequently detectable levels of TCZ in comparison with those patients that were not in remission. The cut-off point of 3.48 µg/ml had the greatest discriminative capacity for clinical remission (AUC 0.724; 95% CI: 0.607-0.840; p=0.001) with a sensitivity of 79.5% and a specificity of 67%. In the multivariate analysis the presence of levels ≥ 3.48 µg/ml of TCZ and the use of corticosteroids were independently associated with clinical remission.

Conclusion: Detectable levels of TCZ (≥1 µg/ml) in RA patients in chronic treatment with TCZ were associated with a lower CRP values. The cut-off point of serum TCZ with best discriminative capacity for clinical remission was 3.48 µg/ml. Serum levels of TCZ ≥ 3.48 µg/ml may be more adequate to achieve clinical remission or low disease activity.

Table. Patients with detectable and undetectable serum levels of TCZ.

	Undetectable Serum trough levels <1µg/ml (n=20)	**Detectable Serum trough levels ≥1µg/ml (n=57)**	***p***
Reduced dose, n (%)	9 (45)	8 (14)	***0.010***
FR and/or anti-CCP+, n (%)	18 (85)	37 (64.9)	0.154
IL-6 serum levels, mean ±SD (*pg/ml*)	2.8 ± 2.3	7.4 ± 0.9	***<0.001***
CRP, mean ± SD (*mg/dl*)	1.02 ± 1.3	0.1 ± 0.2	***0.007***
ESR, mean ± SD (mm/h)	17.1 ± 26.6	7 ± 6.1	0.107
TJC, mean ± SD	2.45 ± 2.8	1.86 ± 3.1	0.452
SJC, mean ± SD	2.15 ± 3.3	2.09 ± 2.4	0.930
DAS 28-ESR, mean ± SD	3.04 ± 1.2	2.24 ± 1	***0.005***
Remission DAS 28-ESR ≤ 2.6, n (%)	6 (30)	37 (64.9)	***0.008***
Low Disease Activity DAS28-ESR ≤ 3.2, n (%)	13 (65)	48 884.2)	0.057
CDAI mean ± SD	11.69 ± 7.7	10.58 ± 5.9	0.611
Corticosteroids, n (%)	8 (40)	23 (40.4)	1.000
Monotherapy, n (%)	8 (40)	25 (43.8)	0.799

Disclosure: V. Ruiz-Esquide, None; **P. Zufferey**, None; **J. Inciarte-Mundo**, None; **J. Yagüe**, Novartis Pharmaceutical Corporation, 2; **M. V. Hernández**, None; **J. Ramirez**, None; **J. Berner**, None; **M. Pascal**, None; **A. Cuervo**, None; **J. D. Cañete**, None; **R. Sanmarti**, None.

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Abstract Number: 601

Step-Down Strategy of Spacing TNF-Blockers Injections for Established Rheumatoid Arthritis in Remission: A within Randomized Control Trial Based Cost-Utility Analysis

Antoine Vanier[1], Florence Tubach[2], Toni Alfaiate[3], Xavier Mariette[4] and Bruno Fautrel[5], [1]Biostatistics, Public Health and Medical Informatics, AP-HP Pitié-Salpêtrière Hospital / Pierre and Marie Curie University Paris 6, Paris, France, [2]Epidemiology and Clinical Research, AP-HP Bichat Hospital / University of Paris-Diderot / INSERM CIC-EC 1425, Paris, France, [3]Epidemiology and Clinical Research, AP-HP Bichat Hospital / INSERM CIC-EC 1425, Paris, France, [4]Université Paris-Sud, AP-HP, Hôpitaux Universitaires Paris-Sud, Paris, France, [5]Rheumatology, AP-HP Pitié-Salpêtrière Hospital / Pierre and Marie Curie University Paris 6 GRC-08 (EEMOIS), Paris, France

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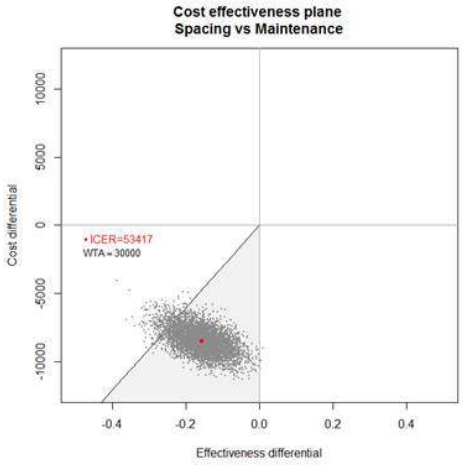
Background/Purpose: Once remission is achieved for patients with rheumatoid arthritis (RA), treatment down-titration should be attempted, for safety issues or economic reasons. One of the proposed strategies, recently tested in the STRASS trial*, is to progressively space injections of TNF-blockers. The objective was to assess the Incremental Cost-Effectiveness Ratio (ICER) of a strategy of progressive spacing of TNF-blocker injections (S-arm) over another maintaining them at full-dose (M-arm) in RA patients in stable remission.

Methods: The study was a French multi-centre 18-month equivalence randomized open-label controlled trial. It included patients receiving etanercept (ETA) or adalimumab (ADA) at stable dose for ≥ 1 year; in remission on 28-joint Disease Activity Score (DAS28) for ≥ 6 months; and with stable joint damage. In the S-arm, the interval between 2 subcutaneous injections was increased every 3 months by 50% in 4 steps, to a complete stop at step 4. If remission was not maintained, spacing was suspended or reversed to the previous interval. Costs engaged within the study-period (medical costs (drugs, consultations and medical tests, use of emergency room and hospitalizations) and costs relative to sick leave) measured in euros were assessed. Utilities values used to compute Quality Adjusted Life Years (QALYs) were derived from the French EQ-5D, assessed at baseline and every 6 months. The ICER was estimated. A probabilistic sensitivity analysis was performed by computing 5000 ICERs (bootstrap). The probability of cost-effectiveness (p of CE) of the spacing strategy was computed for different Willingness to Accept (WTA) compensation for QALY loss thresholds. The impact of missing data was investigated.



Results: Analyses were performed on 44 patients in the S-arm and 54 in the M-arm with complete data. In the S-arm, TNF-blockers were stopped for 34.1% of the patients, tapered for 43.2%, maintained at full-dose for 18.2%. After 18 months of follow-up, patients in the S-arm gained 1.106 QALYs while it was 1.264 in the M-arm (mean differences in QALYs of -0.158). After 18 months, total mean cost was 12 452 euros in the S-arm and 20 892 euros in the M-arm (mean cost difference of -8440 euros). The estimated ICER was 53 417 euros saved per QALY lost. The p of CE of the spacing strategy was 0.94 and 0.59 for WTA thresholds at 30 000 and 50 000 euros respectively.

Conclusion: The spacing strategy was found to be less efficient in terms of QALY gains. Nonetheless, the spacing strategy is associated to substantial cost reduction. The acceptability of such a QALY loss reported to the cost avoided remains to be determined, since no consensual threshold has been determined for WTA compared to willingness-to-pay.

*Fautrel et al, ARD 2015

Disclosure: A. Vanier, None; **F. Tubach**, None; **T. Alfaiate**, None; **X. Mariette**, Biogen Idec, 2,Pfizer Inc, 2,Bristol-Myers Squibb, 5,Pfizer Inc, 5,AstraZeneca, 5,GlaxoSmithKline, 5; **B. Fautrel**, AbbVie, 5,BMS, 5,MSD, 5,Nordic Pharma, 5,Pfizer Inc, 5,Roche Pharmaceuticals, 5,SOBI, 5,UCB, 5.

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Abstract Number: 602

Efficacy of Very Low Dose (100mg) Rituximab in Active Rheumatoid Arthritis Despite Combination DMARD-Single Center, Prospective, Observational Study

Padmanabha Shenoy[1] and **Manish Bavaliya**[2], [1]Dept. of rheumatology and clinical immunology, Amrita Institute of medical science and research institute, Kochi, India, [2]Department of rheumatology and clinical immunology, Amrita institute of medical sciences and research institute, Kochi, India

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Background/Purpose: Rituximab is an anti-CD20 antibody that represents a therapeutic alternative for the patients with rheumatoid arthritis. It has been proven that rituximab at a dose of 2 gm is very effective in patients with DMARD and antiTNF failures. But the cost of this therapy is high and increases the economic burden. Limited data has shown that B cell is possible even with lower dosage to what is recommended.

Methods: In this open label, prospective, observational study at tertiary care center sero positive RA patients who responded inadequately to combination of DMARD, were given single dose of 100 mg of rituximab. B cell numbers in the peripheral blood was assessed by Flow cytometry and B cell depletion was defined as B cell numbers < 0.01 %.Efficacy was evaluated using B cell depletion after 2 weeks and disease activity score in 28 joints (DAS28) on monthly bases. Those patients who did not achieve EULAR moderate response were given second dose of rituximab 500mg.

Results: : 14 patients(12 females and 2 males; mean age 47 ± 7.1years) were included in the study. Mean duration of the disease was 8 ± 6.8 years .RF was positive in 13 out of 14 and Anti CCP antibody was positive in all patients. At baseline mean DAS score was 6.2 ± 0.79 and mean CD 19 % was 11.03 ± 4.53%. After 2 weeks of rituximab, B cell depletion was achieved in 11 patients (79%) and mean DAS28 was 2.86 ± 0.84 at the end of 24 weeks. Two patients were given second dose of 500mg rituximab after 8 weeks of first dose. Out of 14 patients, 8 achieved good EULAR response and 6 achieved moderate EULAR response. At 24 weeks ,7 (50%) patients were in remission.

Conclusion: : Early results from this study are very promising and show that low dose rituximab is effective in treating RA patients with inadequate response to DMARD.

Disclosure: P. Shenoy, None; **M. Bavaliya**, None.

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Abstract Number: 603

Which Seronegative RA Patients Respond to Rituximab? – Preliminary Analysis of a Merged Clinical Trials Dataset

Elizabeth M.A. Hensor[1,2], **Edward M. Vital**[1,2] and Paul Emery[1,2], [1]Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds, Leeds, United Kingdom, [2]NIHR Leeds Musculoskeletal Biomedical Research Unit, Leeds Teaching Hospitals NHS Trust, Leeds, United Kingdom
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Background/Purpose:

Seronegative RA patients have inferior clinical response to rituximab [1]. However, there is significant heterogeneity in this group of patients for baseline clinical features (e.g. radiographic erosion, or alternative markers of B cell dysfunction such as ANA or hypergammaglobulinaemia), as well as for clinical response to rituximab. These features may help to predict response [2]. Objective: To identify clinical predictors of response to rituximab in seronegative RA as a means to select patients suitable for B cell targeted biologics

Methods:

Baseline demographic and clinical characteristics will be extracted from RF and CCP2 negative patients in the following clinical trials: REFLEX, DANCER, IMAGE, SERENE and SUNRISE (which recruited 376 RF-CCP- patients). This preliminary analysis includes data on 88 patients from rituximab-treated arms of SERENE and IMAGE with complete data, but does not include analysis of erosions or ANA. We used 6 month DAS28, adjusted for baseline DAS28 as our primary response outcome, and tested each variable using univariate linear regression.

Results:

Table 1 shows the result of univariate analysis of each potential predictor. Positive coefficients indicate increase in adjusted 6-month DAS28 for presence (categorical variables) or unit increase (continuous variables) in the characteristic. Negative coefficients indicate characteristics

associated with a reduction in in 6-month adjusted DAS28.

Characteristic	Coefficient (95% CI)	*P* value
Age, per year	0.01 (-0.01, 0.04)	0.233
Female	0.47 (-0.27, 1.21)	0.208
BMI, per unit	0.04 (0.00, 0.08)	0.046
Total IG (ln-trans)*, per unit	-0.67 (-1.65, 0.31)	0.176
IGA (ln-trans)*, per unit	-0.34 (-0.91, 0.23)	0.237
IGG (ln-trans)*, per unit	-0.62 (-1.55, 0.30)	0.185
IGM (ln-trans)*, per unit	-0.03 (-0.64, 0.58)	0.922
Smoker Ex	0.67 (-0.09, 1.41)	0.082
Current	0.11 (-0.72, 0.94)	0.795
Disease duration (ln-trans)	-0.01 (-0.29, 0.28)	0.959
N previous DMARDs 1-2	0.13 (-0.49, 0.76)	0.671
>2	0.26 (-1.23, 1.75)	0.729
Oral glucocorticoid at baseline	-0.68 (-1.28, -0.08)	0.028
DAS28, per unit	0.49 (0.20, 0.77)	0.001
HAQ-DI, per unit	0.19 (-0.32, 0.71)	0.459

Conclusion: Response to rituximab in seronegative RA is associated with lower BMI and use of oral glucocorticoids, with a trend to association with never smoking in univariate analyses. Our data were consistent with a previously-reported association of response with hypergammaglobulinaemia but we cannot confirm clinical utility of IgG as predictor in this analysis. Final analysis will include data from 376 patients using comprehensive multivariable modelling, including erosion and ANA data.

Disclosure: E. M. A. Hensor, None; **E. M. Vital**, Roche Pharmaceuticals, 2,Roche Pharmaceuticals, GSK, UCB, Chugai, 5; **P. Emery**, Janssen R & D, LLC, 2.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/which-seronegative-ra-patients-respond-to-rituximab-preliminary-analysis-of-a-merged-clinical-trials-dataset

Abstract Number: 604

Calprotectin and TNF Antagonist Serum Trough Levels Identify Active Ultrasound Synovitis in Rheumatoid Arhritis and Psoriatic Arthritis Patients in Remission or Low Disease Activity

Jose Inciarte-Mundo[1], Julio Ramírez[1], Virginia Ruiz-Esquide[1], M. Victoria Hernández[1], Oscar Camacho[1], Sonia Cabrera-Villalba[1], Andrea Cuervo[1], Mariona Pascal[2], Jordi Yagüe[2], Juan D. Cañete[1] and Raimon Sanmarti[1], [1]Rheumatology Department, Hospital Clinic i Provincial, Barcelona, Spain, [2]Immunology Department, Hospital Clinic i Provincial, Barcelona, Spain
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Background/Purpose:

An accurate assessment of disease activity is needed in Rheumatoid arthritis (**RA**) and Psoriatic Arthritis (**PsA**) patients in remission or low disease activity for clinical decision-making. Calprotectin a major S100 leukocyte protein and TNF antagonist (**TNFa**) serum trough levels are associated with disease activity. Residual power Doppler ultrasound synovitis (**PDUS**) is *predictive* of clinical *flare* in this group of patients.

Objectives:

To analyze the relationship between PDUS with calprotectin and TNFa serum trough levels in RA and PsA patients in clinical remission or low disease activity. To correlate calprotectin levels with serum trough levels of TNFa.

Methods :

Cross-sectional analysis from a prospective cohort study of RA (ACR 1987) and PsA patients (CASPAR) treated with TNFa [etanercept (**ETN**), adalimumab (**ADA**), and infliximab (**IFX**)] for ≥ 3 months in clinical remission (DAS28-ESR<2.6) or low disease activity (DAS28-ESR<3.2) in ≥2 consecutive visits. The patients underwent clinical, laboratory, and PDUS assessment at visit 4 (12 months of follow-up). Calprotectin serum levels (using kits from Calpro AS) and TNFa serum trough levels (using kits from Promonitor®, Progenika) were determined. A rheumatologist experienced in musculoskeletal ultrasound and blinded to clinical and laboratory data performed US assessment with a high sensitivity equipment (MyLabTwice®, Esaote, Italy. 8-14 MHz linear probe). 22-joint B-mode synovial hypertrophy (**SH**) and PDUS signal were scored from 0-3 at each joint. Global indices for SH and PDUS signal were calculated. Ultrasound active synovitis (**UAS**) was defined as intraarticular synovitis detected with power Doppler signal.[1]

Results :

Ninety-two patients (42 RA, 50 PsA) out of 100 patients included at study entry completed the follow-up at 12 months (visit 4). 43 patients had UAS (27 RA and 16 PsA). UAS patients showed higher disease activity, higher calprotectin levels and lower drug serum trough levels, even when analyzed by diagnostic (RA or PSA) (**table 1**). When a more stringent UAS criteria were apply (SH grade 2+PDUS)[2], only calprotectin can distinguish between them [active (*n*=15) 3.48(0.2-5.5) *vs*. inactive (*n*=77) 1.47(0.06-4.8), *p*=<0.001]. Calprotectin and serum trough levels inversely correlated with PDUS score in ADA (rho=-.591, p=<0.001 and rho=-.842,p=<0.001,respectively) and ETN (rho=-.313,p=0.039 and rho=-.649,p=<0.001,respectively). Calprotectin serum levels inversely correlated with ADA serum trough levels (rho=-.461, *p*=0.008), non-significant correlations were observed with ETN and IFX.

Conclusion :

Calprotectin and TNFa serum trough levels may help to identify ultrasound active synovitis in RA and PsA patients in clinical remission/low disease activity.

	GLOBAL (*n*=92)		**RA (*n*=42)**		**PsA (*n*=50)**	
	PDUS negative (*n*=49)	**PDUS positive (*n*=43)**	**PDUS negative (*n*=15)**	**PDUS positive (*n*=27)**	**PDUS negative (*n*=34)**	**PDUS positive (n=16)**
Female, n (%)	26 (53.1)	33 (76.7)	11 (73.3)	23 (85.2)	15 (44.1)	10 (62.5)†
Age, median (range), *years*	56 (33-78)	60 (30-81)	62 (49-78)	64 (30-81)	53 (33-77)	55 (40-72)
Disease duration, median (range) *years*	13 (1-28)	17 (2-44)	13 (8-28)	17 (2-44)	13.5 (1-28)	16 (3-36)
Concomitant sDMARD, *n* (%)	22 (44.9)	25 (58.1)	11 (73.3)	21 (77.8)	11 (32.4)	4 (25)
Reduced dose, *n* (%)	25 (51)	17 (39.5)	4 (26.7)	8 (29.6)	21 (61.8)	9 (56.3)
Calprotectin, median (range), *µg/mL*	1.0 (0.6-3.7)	2.68 (0.225.54)*	1.44 (0.2-2.4)	2.95 (0.2-5.5)†	0.70 (0.06-3.7)	2.36 (0.9-4.6)*
CRP, median (range), *mg/dl*	0.07 (0.1-0.6)	0.20 (0.01-1.4)†	0.07 (0.02-0.1)	0.30 (0.01-1.4)†	0.08 (0.01-0.6)	0.09 (0.01-0.3)
ESR, median (range), *mm/h*	8 (2.-29)	13 (2-43)*	10 (2-24)	13 (2-43)	8 (2-29)	13 (4-32)†
DAS28-ESR, median (range)	1.78 (1-2.7)	2.36 (1.1-3.2)*	2.08 (1.5-2.6)	2.62 (1.3-3.2)†	1.67 (1-2.7)	2.15 (1.1-3.1)†
SDAI, median (range)	6 (2-8)	6 (2-11)†	6.02 (2-8)	6.26 (2-11)†	5.10 (2-8)	6.04 (2-8.3)
CDAI, median (range)	6 (2-8)	6 (2-11)	6 (2-8)	6 (2-11)	5 (2-8)	6 (2-8)
ADA serum trough levels, median (range), *µg/mL*	7.08 (4.1-12)	1.06 (0.2-12)*	8.39 (4.2-12)	1.68 (0.6-12)†	6.95 (4.1-12)	0.88 (0.2-9.8)†
ETN serum trough levels, median (range), *µg/mL*	1.69 (0.1-4.7)	0.91 (0.06-2.3)†	2.54 (0.2-4.7)	0.98 (0.7-2.3)†	1.38 (01-3.5)	0.91 (0.6-1.6)
IFX serum trough levels, median (range), *µg/mL*	3.21 (0.7-7.7)	1.92 (0.1-6.5)†	8.39 (4.2-12)	1.68 (0.6-12)†	3.21 (0.7-7.7)	2.86 (0.1-6.5)

*$p<0.001$

†$p<0.05$

References:

1. Naredo E. Arthritis Rheum.2007;57(1):116-2.

2. Ramírez J. Arthritis Res Ther.2014;16(1):R5.

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Abstract Number: 605

Monitoring of Epstein Barr Virus, Cytomegalovirus and Varicella Zooster Virus Load in Patients Receiving Tocilizumab for Rheumatoid Arthritis

cindy mourgues[1], cecile henquell[2], Zuzana Tatar[3], Bruno Pereira[4], cynthia nourisson[5], Anne Tournadre[6], Martin Soubrier[7] and Marion Couderc[7], [1]puy de dome, CHU gabriel montpied clermont ferrand, clermont ferrand, France, [2]virology, CHU gabriel montpied virology, clermont ferrand, France, [3]Rheumatology, CHU G.-Montpied, Clermont-Ferrand, France, [4]Biostatistics unit (DRCI), CHU Clermont-Ferrand, Clermont-Ferrand, France, [5]rheumatology, chu gabriel montpied, clermont ferrand, France, [6]Rheumatology, UNH-UMR 1019 INRA University of Auvergne and Rheumatology department CHU Clermont-Ferrand, Clermont-Ferrand, France, [7]Rheumatology department CHU Clermont-Ferrand, Clermont-Ferrand, France

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Background/Purpose:

Tocilizumab (TCZ) is an interleukin 6 (IL-6) inhibitor that is used in Rheumatoid Arthritis (RA) treatment (1). Due to the role played by IL-6 in viral immunosurveillance, we studied the effect of TCZ on the viral load for the Epstein Barr Virus (EBV), Cytomegalovirus (CMV) and Varicella Zoster Virus (VZV) in patients with RA.

Methods:

This was a prospective monocenter study of RA patients taking TCZ. All patients satisfy the 2010 ACR-EULAR classification criteria for RA. Demographic, clinical and laboratory data were collected on each patient. Viral loads (VL) were determined in whole blood (using the Biomerieux EBV and VZV R-gene quantification kit, Abbott Real Time CMV kit) at TCZ initiation and during treatment follow-up. A difference between two viral loads of 0.5log10 copies/ml of whole blood was considered significant.

Results:

22 patients were evaluated. There were 20 (91%) women of a mean age of 57.8 + 11.2 with seropositive and erosive (74%). RA that had been progressing for a mean of 11.3 + 9.7 years. TCZ was administered alone (36.7%) or in combination with methotrexate (MTX) (50%).

When TCZ was introduced, the EBV VL was positive in eight patients with a mean VL value of 1777.2 + 3518.3 (3.5 + 0.4 log10) copies/ml. Only one patient had a positive CMV VL. The VZV VL was negative in all patients. After 9.2 + 4.8 months had lapsed, EBV VL and CMV VL became negative in six of eight patients (p=0.02) and did not significantly vary in the remaining two patients. No VL (EBV, CMV, VZV) became positive. A positive EBV VL did not correlate with RA activity (DAS28ESR, DAS28CRP) or with inflammatory biomarkers (ESR and CRP). RA activity significantly declined after six months of TCZ treatment (DAS28ESR after six months 2.8 + 1.1 vs. 5.14 + 0.9 [p<0.001]).

The treatments of positive EBV patient were collected among 6 patients with EBV VL become negative after TCZ perfusions and 50% of patients did not take any DMARDS.

Conclusion:

In our study, TCZ did not increase the VL of EBV, CMV or VZV. This is the first report on the influence of TCZ on the VL of EBV, CMV and VZV in RA patients. Our EBV results are identical to those that we reported on anti-TNF, which were found by other teams as well (2, 3). Nevertheless, although we did not demonstrate any changes in CMV or VZV VL in patients taking TCZ, but there were reported several cases of severe infection (4;5;6;7). Most of RA patient have still glucocorticoid which can also influence the immunosurveillance for virus (8). Studies involving larger patient populations are necessary.

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Abstract Number: 606

Impaired Kidney Function Improves Treatment Response after 6 Months of Methotrexat Treatment in Rheumatoid Arthritis Patients

Paul Studenic[1], Farideh Alasti[1], Josef S. Smolen[2,3], Helmuth Haslacher[4] and Daniel Aletaha[5], [1]Department of Internal Medicine 3, Division of Rheumatology, Medical University Vienna, Vienna, Austria, [2]Department of Medicine 3, Division of Rheumatology, Medical University Vienna, Vienna, Austria, [3]2nd Department of Medicine, Hietzing Hospital, Vienna, Austria, [4]Laboratory Medicine, Medical University Vienna, Vienna, Austria, [5]Department of Internal Medicine III; Division of Rheumatology, Medical University Vienna, Vienna, Austria

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SESSION INFORMATION

Session Date: Sunday, November 8, 2015

Session Title: Rheumatoid Arthritis - Small Molecules, Biologics and Gene Therapy Poster I

Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose:

Methotrexate (MTX) and leflunomide are categorized as DMARDs of first choice in treating rheumatoid arthritis patients. MTX should be used cautiously in patients with impaired kidney function, but treatment with MTX may also show an increased effectiveness in these patients, because of accumulation. If MTX is contraindicated, for instance because of more severely impaired kidney function, leflunomide can be used without dose adjustment. We aimed to explore the role of the kidney function for the 6 month treatment response to either methotrexate or leflunomide in RA patients.

Methods:

We selected patients from a longitudinal RA database, who started MTX monotherapy or leflunomide treatment and had clinical follow ups over at least 6 months. In a multivariable regression analyses, we used change in the simplified disease activity index (SDAI) after 6 months as dependent variable, and baseline SDAI, creatinine (or glomerular filtration rate), and MTX dose as independent variables.

Results:

We identified 256 patients starting MTX (80% female, 59% rheumatoid factor, RF, positive; mean±SD: SDAI: 17.2±12, creatinine: 0.83±0.14 mg/dl, glomerular filtration rate (GFR): 83±22 ml/min, end MTX dose: 20.6±6.1) and as comparator group 80 patients starting a treatment of at least 6 months with leflunomide (86% female, 57% RF positive, mean±SD SDAI: 13.6±8.8, creatinine:0.85±0.23, GFR: 88±53).

Regression analyses in the MTX cohort showed that that, after adjusting for MTX dose, higher creatinine was associated with higher SDAI response after 6 months of treatment (p=0.029). Analogously, in a separate analysis lower GFR was also significantly associated with larger clinical improvement (p=0.04) (**Figure).** SDAI response in patients with impaired kidney function and lower MTX dose (GFR <75ml/min and <20mg of MTX, respectively) was similar to patients with normal kidney function and higher MTX dose (GFR >75ml/min and ≥25mg of MTX). In patients treated with leflunomide, creatinine as well as GFR were not associated with SDAI change after 6 months of treatment (p=0.585, p=0.962, respectively).

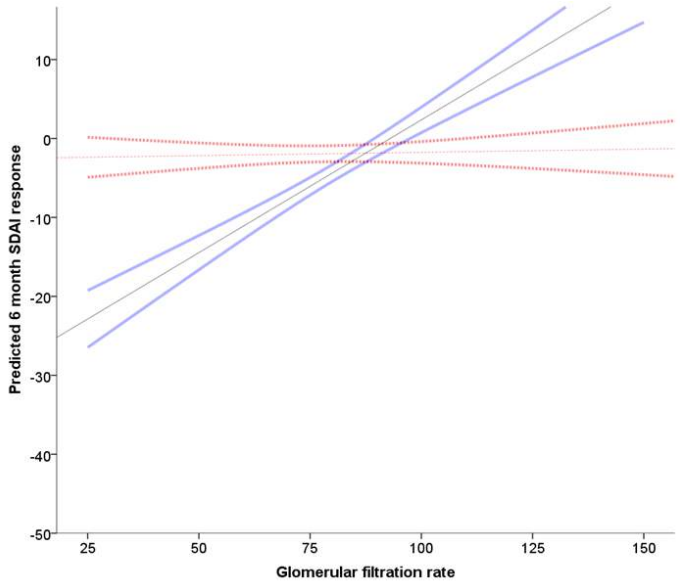

Figure: Regression splines for SDAI response at 6 months of MTX treatment (blue with confidence intervals) and leflunomide (red dotted with CI) predicted by glomerular filtration rate

Conclusion:

We demonstrated here that patients with impaired renal function seem to benefit in terms of SDAI response during treatment with methotrexate. This was not found in patients treated with leflunomide. Higher treatment responses in patients with impaired kidney function indicate increased clinical benefit. This could also indicate room for higher MTX doses, which are historically limited to 25mg/week, in patients with normal kidney function and accompanied folate substitution.

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Abstract Number: 607

Serum Progranulin (PRGN) Level Is Not a Biomarker for Responsiveness to Tumor Necrosis Factor (TNF)-Antagonist Therapy in Rheumatoid Arthritis (RA) Patients

Rosy Rajbhandary[1], Rebekah Neal[2], **Jennifer Johnson**[3], Qingyun Tian[4], Jinlong Jian[5], Chuanju Liu[6] and William Stohl[2],
[1]Medicine/Rheumatology, LAC+ USC Medical Center, Los Angeles, CA, [2]Div of Rheumatology, USC, Los Angeles, CA, [3]Medicine, Keck School of Medicine of USC, Los Angeles,, CA, [4]Nyu,Hid,301 E 17th St, New York University Medical Center, New York, NY, [5]301 E. 17th St., Rm 1600, New York, NY, [6]NYU Hospital for joint Diseases, New York, NY
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Background/Purpose: PRGN is a growth factor that binds TNF receptors without triggering TNF-like activity, thereby serving as a naturally-occurring antagonist of TNF -mediated inflammatory signaling. In multiple mouse arthritis models, PRGN inhibits TNF-activated intracellular signaling and development of joint inflammation. We hypothesized that endogenous PRGN levels may affect responsiveness to TNF-antagonist therapy in RA patients. Accordingly, we conducted a pilot observational study in RA patients to assess whether serum PRGN levels would either predict and/or reflect responsiveness to TNF-antagonist therapy. TNF may play a greater role in driving disease in RA patients who bear low PRGN levels (PRGN-low) than in RA patients who bear high PRGN levels (PRGN-high). If correct, then PRGN-low would be more responsive to TNF-antagonist therapy than PRGN-high.

Methods: We enrolled 40 Hispanic RA patients who had never received TNF-antagonist therapy and who, in the judgment of their respective

physicians, were candidates for TNF-antagonist therapy. Prior to initiation of TNF-antagonist therapy and at regularly scheduled visits for 12 months following initiation of such therapy, disease activity was assessed by DAS28-CRP, and blood samples were collected for serum PRGN levels (measured by ELISA). Assignment of level of disease activity (high, moderate, low) and degree of clinical response (no, moderate, good, remission) was based on EULAR criteria.

Results: Of the 40 RA patients enrolled. 34 were female and 6 were male: median (range) age, 53 (22-75) years; median (range) years of symptoms, 4 (1-29); median (range) tender joints, 16 (0-28); median (range) swollen joints , 7 (0-25); median (range) ESR, 43 (7-105); median (range) CRP, 12 (1-195); median (range) DAS28-CRP, 5.59 (3.28-8.04). 31 patients had high disease activity, and 9 had moderate disease activity. 20 patients had radiographic erosive disease; 23 were taking methotrexate; 3 were taking corticosteroids; 29 were taking hydroxychloroquine; 2 were taking leflunamide; and 19 were taking sulfasalazine. Based on the distribution of baseline serum PRGN levels, 9 RA patients were classified as PRGN-high, and 31 patients were classified as PRGN-low. No statistical differences were noted in baseline parameters between PRGN-high and PRGN-low.

Of the 40 patients, 35 initiated TNF-antagonist therapy (8 PRGN-high, 27 PRGN-low). At the last follow-up visit, 19 achieved clinical remission, 4 achieved a good response, 8 achieved a moderate response, and 4 had no response. As determined by log-rank analysis, there were no differences in achievement of moderate/good responses, good responses, or clinical remission between PRGN-high and PRGN-low. Post-initiation visits were divided into 4 intervals (1-91 days; 92-182 days; 183-273 days: ≥274 days); there were no differences in DAS28-CRP between PRGN-high and PRGN-low at any interval. Serum PRGN levels declined following initiation of TNF-antagonist therapy, but changes in serum PRGN levels did not correlate with changes in DAS28-CRP.

Conclusion: Serum PRGN levels neither predict nor reflect clinical responsiveness to TNF-antagonist therapy in RA patients.

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Abstract Number: 608

Safety of Surgery in Patients with Rheumatoid Arthritis Treated By Abatacept: Data from the French Orencia in Rheumatoid Arthritis (ORA) Registry

Augustin Latourte[1], Jacques Gottenberg[2], Cécile Luxembourger[3], Isabelle Pane[4], Pascal Claudepierre[5], Pascal Richette[1], Pierre Lafforgue[6], Philippe Ravaud[4], BG Combe[7], Alain G. Cantagrel[3], Jean Sibilia[8], Rene-Marc Flipo[9], Philippe Gaudin[10], Olivier Vittecoq[11], Thierry Schaeverbeke[12], Maxime Dougados[13], Francis Berenbaum[14], Jérémie Sellam[15], Xavier Mariette[16] and Raphaèle Seror[17], [1]Fédération de Rhumatologie, Hôpital Lariboisière, Assistance Publique-Hôpitaux de Paris, Paris, France, [2]Rheumatology, Department of Rheumatology, Strasbourg University Hospital, Strasbourg, France, [3]Rheumatology, Centre Hospitalier Universitaire, Toulouse Purpan, Toulouse, France, [4]Centre de Recherche en Epidémiologie et Statistiques, INSERM U1153, Centre d'Épidémiologie Clinique, Hôpital Hôtel-Dieu, Assistance Publique-Hôpitaux de Paris (AP-HP), Descartes University, Paris, France, [5]Rheumatology, Université Paris Est Créteil, Créteil, France, [6]Rheumatology, APHM, Aix Marseille University, Marseille, France, [7]Rhumatologie, Immuno-Rhumatologie, Hopital Lapeyronie, Montpellier, France, [8]Department of Rheumatology, Strasbourg University Hospital, Strasbourg, France, [9]Rheumatology, Hopital R Salengro CHRU, Lille, France, [10]Department of Rheumatology, University Hospital Grenoble, Grenoble, France, [11]University Hospital, Rouen, France, [12]Rheumatology Department, Bordeaux Hospital, Bordeaux, France, [13]Medicine Faculty, Paris-Descartes University, Paris, UPRES-EA 4058, Cochin Hospital, Rheumatology B, Paris, France, [14]Rheumatology, Inserm UMRS_938, AP-HP, St Antoine Hospital, Univ Paris 06, DHU i2B, Paris, France, [15]Rheumatology and Inserm UMRS_938, AP-HP, St Antoine Hospital, Univ Paris 06, DHU i2B, Paris, France, [16]Université Paris-Sud, AP-HP, Hôpitaux Universitaires Paris-Sud, Paris, France, [17]Rheumatology, AP-HP Bicêtre Hospital / Paris-Sud University, Le Kremlin-Bicêtre, France
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Background/Purpose: The aim of this study was to investigate the frequency and risk factors of postoperative complications in rheumatoid arthritis (RA) patients treated with abatacept in routine care.

Methods: The ORA registry is a French nationwide prospective cohort which recruited 1032 patients receiving abatacept for RA according to ACR criteria in routine care. Data for patients who underwent surgery while treated with abatacept (including the 4 months following last infusion) were reviewed to describe the frequency of postoperative complications. Characteristics of patients and surgeries were compared

between patients with and without complications to identify factors associated with complications. Quantitative variables were compared by the Mann-Whitney test, and qualitative variables were compared by the Fisher's exact test.

Results: We identified 215 (20.8 %) patients who underwent 284 surgeries between June 2008 and December 2012, including 189 (66.5%) orthopedic surgeries and 35 (12.3%) abdominal surgeries. Twenty (7.0%) surgeries, in 20 patients (9.3%), entailed complications, of which 11 infections (3.9% of surgeries) and 6 delayed healing (2.1% of surgeries). Abatacept was discontinued after 3 (15.0%) surgeries in the complicated group versus 28 (10.6%) in the group without complications, and this difference was not significant (p=0.467). No death was reported. Characteristics of patients and surgeries with and without complications are shown in table 1. Co-morbidities and associated treatments were not different between both groups. The median time between the last infusion of abatacept and surgery was 5.9 weeks (interquartile range [IQR] 3.8-8.8 weeks), with no difference between patients with and without complications (5.1 vs 6.0 weeks, p=0.14). The median time between the initiation of abatacept and surgery was significantly shorter in the complicated group (9 [IQR 2-19] vs. 16 months [IQR 8-26], p=0.0065), while DAS28 score at the time of surgery was similar between both groups (3.86 vs 3.43, p=0,25). Orthopedic surgeries were associated with a higher rate of postoperative complications (9,5% vs. 2,1%, p=0,025), but no difference was found in each subgroup of orthopedic procedures (i.e. hand/wrist, foot/ankle, spine surgeries or arthroplasty).

Conclusion: In real life RA patients treated with abatacept and undergoing surgery, there is no specific predictive factor of complications except an orthopedic vs non-orthopedic procedure (like in every RA patient) and a shorter time after initiation of abatacept. The latter factor, also found in our rituximab AIR registry (Godot et al, Arthritis Care Research 2013), is probably a bias due to the healthy drug survival effect. Interestingly, the median time between the last infusion of abatacept and the surgery was short: 5 to 6 weeks and did not influence the rate of post-operative complications.

Table 1. Characteristics of patients and surgeries and univariate analysis of predictive factors of postoperative complications after surgery for RA patients treated with abatacept. IQR = interquartile range ; ABA = abatacept ; DAS28 = Disease Activity Score in 28 joints using the erythrocyte sedimentation rate.

Patients' characteristics			
	Patients without complications (n=195)	Patients with complications (n=20)	p
Age, median (IQR), years	61,0 (52,5-70,0)	60,5 (52,8-68,8)	0,80
Women (%)	80,9	85	1
Disease duration at baseline, median (IQR), years	13,0 (7,0-20,8)	12,5 (6,5-24,3)	0,37
DAS28 at baseline, median (IQR)	5,32 (4,38-6,22)	5,52 (4,78-6,43)	0,68
RF positivity (%)	57,9	60,0	1
Anti-CCP positivity (%)	48,7	50,0	1
RA-related extraarticular involvement (%)	12,8	0	0,14
Ever smoking (%)	18,5	30,0	0,24
Diabetes mellitus (%)	4,1	5,0	0,59
High blood pressure (%)	25,1	30,0	0,59
Previous severe, chronic, or recurrent infections (%)	36,9	30,0	0,21
Chronic lung disease (%)	22,6	15,0	0,37
Cardiac insuffisiency (%)	21,0	15,0	0,77
Previous DMARDs before ABA (%)	94,4	90,0	0,34
Previous anti-TNF agent before ABA (%)	79,5	85,0	0,77
Surgeries characteristics			
	Surgeries without complications (n=264)	Surgeries with complications (n=20)	p
Duration of ABA treatment before surgery, median (IQR), months	16,0 (8,0-26,0)	9,0 (2,0-19,0)	0,0065
Delay between last ABA infusion and surgery, median (IQR), weeks	6,0 (3,9-8,9)	5,1 (3,1-7,1)	0,14
Concomitant DMARDs at the time of surgery (%)	65,5	80,0	0,23
MTX dosage, median (IQR), mg	15,0 (10,0-20,0)	15,0 (12,5-17,5)	0,76
Concomitant oral corticosteroids at the time of surgery (%)	61,7	60,0	1
Oral corticosteroids dosage, median (IQR), mg	7,0 (5,0-10,0)	10,0 (6,8-15,0)	0,07
Preoperative DAS28, median (IQR)	3,43 (2,72-4,26)	3,86 (3,23-4,50)	0,25
Orthopedic surgery (%)	64,8	90,0	0,025
Hand/wrist surgery (%)	15,2	5,0	0,33
Foot/ankle surgery (%)	16,3	53,8	0,06
Arthroplasty (%)	21,2	25,0	0,78
Spine surgery (%)	5,3	10,0	0,31
Abdominal surgery (%)	15,3	0	0,15
Nonorthopedic and nonabdominal surgery (%)	20,8	10,0	0,38

Disclosure: A. Latourte, None; **J. Gottenberg**, None; **C. Luxembourger**, None; **I. Pane**, None; **P. Claudepierre**, None; **P. Richette**, None; **P. Lafforgue**, None; **P. Ravaud**, None; **B. Combe**, None; **A. G. Cantagrel**, None; **J. Sibilia**, None; **R. M. Flipo**, None; **P. Gaudin**, None; **O. Vittecoq**, None; **T. Schaeverbeke**, None; **M. Dougados**, None; **F. Berenbaum**, None; **J. Sellam**, None; **X. Mariette**, None; **R. Seror**, None.

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Abstract Number: 609

A Reduction in Serum Uric Acid Levels May be Related to Methotrexate Efficacy in Early Rheumatoid Arthritis: Data from a Canadian Arthritis Cohort

Jason Lee[1], VP Bykerk[2], George Dresser[3], Gilles Boire[4], Boulos Haraoui[5], Carol Hitchon[6], J Carter Thorne[2], Diane Tin[7], Shahin Jamal[8], Edward C. Keystone[9], Janet E. Pope[10] and CATCH Investigators, [1]Rheumatology, Western University, St. Joseph's Hospital, London, ON, Canada, [2]University of Toronto, Toronto, ON, Canada, [3]Clinical Pharmacology and Toxicology, Western University, London, ON, Canada, [4]Department of Medicine/Division of Rheumatology, Université de Sherbrooke, Sherbrooke, QC, Canada, [5]Institut de Rhumatologie, Montreal, QC, Canada, [6]University of Manitoba, Winnipeg, MB, Canada, [7]The Arthritis Program, Southlake Regional Health Centre, Newmarket, ON, Canada, [8]Vancouver Coastal Health, Vancouver, BC, Canada, [9]Mount Sinai Hospital, University of Toronto, Toronto, ON, Canada, [10]Monsignor Roney Bldg/Rheum, University of Western Ontario, St Joseph Health Care, London, ON, Canada

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Session Type: ACR Poster Session A

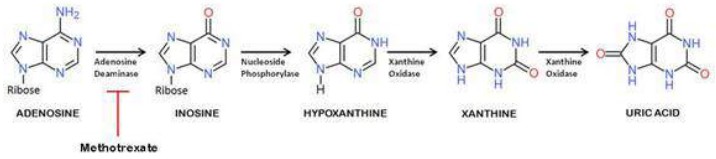
Session Time: 9:00AM-11:00AM

Background/Purpose: The mechanism of methotrexate in rheumatoid arthritis (RA) is complex. It may increase adenosine levels by blocking conversion to of xanthine to uric acid (UA). This study was done to determine if methotrexate lowers UA in early RA (ERA).

Methods: Data were obtained from CATCH (Canadian Early Arthritis Cohort), an incident ERA cohort. All ERA patients with serial UA measurements were included comparing those with methotrexate use vs. no methotrexate (controls). Analyses were exploratory. Patients with concomitant gout or taking uric acid lowering therapies were excluded.

Results: Forty-nine of 2524 ERA patients were identified with data available for both pre-methotrexate UA levels vs. post-methotrexate UA levels (300 µmol/L vs. 273 µmol/L respectively (p=0.035)). The control group not taking methotrexate had a mean baseline uric acid level of 280 µmol/L and a follow-up level of 282 µmol/L (p=0.448); mean change in UA with methotrexate was -26.8 µmol/L, vs. 2.3 µmol/L in no methotrexate group (p=0.042). Methotrexate users with a decrease in UA had a mean lower DAS28 score of 2.37 vs. controls (3.26) at 18 months (p=0.042). Methotrexate users who decreased UA had a lower SJC of 0.9 at 18 months vs. methotrexate users without lowering of UA who had a SJC of 4.5 (p=0.035). Other analyses were not significant.

Conclusion: Methotrexate response is associated with lowering of uric acid in ERA compared to non-users, and may be due to changes in adenosine levels. Methotrexate response is associated with lower UA and fewer swollen joints compared to non-responders.



	Included Methotrexate Users with UA Decrease	Included Methotrexate Users with UA Increase	Methotrexate Non-Users (Controls)	p-value
Number of Patients (%)	32 (1.3)	17 (0.7)	40 (1.6)	(N/A)
Meeting 2010 ACR/EULAR Classification Criteria for Rheumatoid Arthritis, no. (%)	29 (91)	17 (100)	29 (72)	0.316
Positive Rheumatoid Factor (RF) serology at baseline, no. (%)	22 (69)	12 (71)	26 (65)	0.270
Positive Anti-CCP at baseline, no. (%)	27 (84)	14 (82)	21 (53)	**0.006**
Symptom duration at baseline, mean ± SD (Days)	181.44 ± 86.67	227.71 ± 149.10	144.25 ± 71.25	**0.011**
Number of DMARDs, mean ± SD	2.9 ± 0.9	3.2 ± 0.9	1.2 ± 0.7	**< 0.001**
Swollen joint count (28), mean ± SEM				
Baseline	8.00 ± 6.61	8.53 ± 5.69	5.95 ± 4.99	0.192
12 months	3.45 ± 4.59	3.87 ± 4.09	2.03 ± 3.24	0.199
18 Months	0.89 ± 2.02	4.47 ± 6.30	2.30 ± 3.63	**0.017**
24 Months	0.82 ± 1.61	2.36 ± 2.65	1.18 ± 1.81	0.054
DAS28, mean ± SD				
Baseline	4.93 ± 1.37	4.96 ± 1.53	4.61 ± 1.49	0.572
12 months	2.93 ± 1.52	3.43 ±1.60	2.86 ± 1.36	0.445
18 Months	2.37 ± 1.37	3.19 ± 1.66	3.26 ± 1.70	0.096
24 Months	2.43 ± 1.29	3.26 ± 1.75	2.97 ± 1.35	0.174

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Abstract Number: 610

Risk of Herpes Zoster in Patients with Rheumatoid Arthritis Treated with Biologic Disease-Modifying Therapy Compared with Conventional Therapy

Hyun Mi Kwon, Sang Jin Lee, Ji Ae Yang, Jin Young Moon, Eun Young Ahn, Jin Kyun Park, Eun Young Lee, Yeong Wook Song and Eun Bong Lee, Division of Rheumatology, Department of Internal Medicine, Seoul National University Hospital, Seoul, South Korea

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Background/Purpose: Patients with rheumatoid arthritis (RA) are at increased risk for herpes zoster (HZ) infection. RA treatment including

immunosuppressant medications could further exacerbate the risk. The aim of this study was to investigate the effects of conventional (cDMARDs) and biologic disease-modifying antirheumatic drugs (bDMARDs) on the risks of HZ infection in RA patients.

Methods: In this retrospective cohort study, a total of 277 RA patients were enrolled, who ever received bDMARDs at Seoul National University Hospital between August 2003 to February 2015. Among the enrolled patients, 718 treatment episodes of cDMARDs and bDMARDs were identified, which included infliximab, etanercept, adalimumab, golimumab, rituximab, abatacept, and tocilizumab. Baseline information included demographics, disease duration, comorbidity, smoking history, rheumatoid factor, anti-CCP antibodies, erythrocyte sedimentation rate, C-reactive protein, and concomitant cDMARDs at initiation of treatment. After identifying all episodes of HZ infection, crude incidence rates of HZ per 100 patient-years (95% confidence intervals [CI]) were calculated.

Results: Among 718 treatment courses, 277 (38.6%) used cDMARDs, 66 (9.2%) infliximab, 175 (24.4%) etanercept, 95 (13.2%) adalimumab, 9 (1.3%) golimumab, 41 (5.7%) rituximab, 31 (4.3%) abatacept, and 24 (3.3%) tocilizumab. A total of thirty-one episode of HZ occurred, sixteen occurred in cDMARDs treatment courses and twenty-one occurred in bDMARDs, 2 infliximab, 8 etanercept, 5 adalimumab, 3 rituximab, and 3 abatacept. The crude incidence rate per 100 patient-years was 2.4 (95% CI, 1.4-3.9) for cDMARDs, 2.2 (0.3-7.9) for infliximab, 1.8 (0.8-3.6) for etanercept, 3.7 (1.2-8.4) for adalimumab, 3.9 (0.8-11.0) for rituximab, and 8.5 (1.8-23.1) for abatacept (Table 1).

Conclusion: bDMARDs do not always increase the risk of HZ infection in RA patients, although HZ infection rates vary between different bDMARDs.

Table 1. Crude incidence Rates of Herpes Zoster Events per 100 patient-years

	Observed patient-years	Herpes zoster Events number	100 patient-years	95% CI
Total (n=718)	1470.2	37	2.5	1.8-3.5
cDMARDs (n=277)	662.1	16	2.4	1.4-3.9
Infliximab (n=66)	89.8	2	2.2	0.3-7.9
Etanercept (n=175)	440.3	8	1.8	0.8-3.6
Adalimumab (n=95)	135.9	5	3.7	1.2-8.4
Golimumab (n=9)	11.2	0	0.0	0-28.5
Rituximab (n=41)	77.1	3	3.9	0.8-11.0
Abatacept (n=31)	35.5	3	8.5	1.8-23.1
Tocilizumab (n=24)	18.3	0	0.0	0-18.5

Abbreviations: cDMARDs, conventional disease-modifying antirheumatic drugs; CI, confidence interval

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Abstract Number: 611

The Rapid Kinetics of Optimal Treatment with Subcutaneous Methotrexate in Early Inflammatory Arthritis

Anna O'Connor[1], J Carter Thorne[2], Diane Tin[3] and Janet E. Pope[4], [1]Schulich School of Medicine and Dentistry, University of Western Ontario, London, ON, Canada, [2]University of Toronto, Toronto, ON, Canada, [3]The Arthritis Program, Southlake Regional Health Centre, Newmarket, ON, Canada, [4]Monsignor Roney Bldg/Rheum, University of Western Ontario, St Joseph Health Care, London, ON, Canada

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Session Title: Rheumatoid Arthritis - Small Molecules, Biologics and Gene Therapy Poster I

Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose: Methotrexate (MTX) is standard treatment in RA. Absorption is better in subcutaneous MTX (scMTX), which may impact speed of onset. In RA, earlier time to remission improves long-term results. Objectives were to determine the speed of onset of scMTX with optimal care in early rheumatoid arthritis (ERA).

Methods: Patients with ERA were studied for outcomes at baseline, 6 weeks and 12 weeks comparing the interval change in DAS28 from 0 to 6 weeks (early period) and 6 to 12 weeks (late period) to see if more benefit was observed in very early treatment with scMTX. Repeated measures ANOVA analyses were performed. The proportion of patients achieving CDAI, SDAI, DAS28 remission and/or low disease activity across time was compared.

Results: 103 patients were included from a single site inception cohort between 2008 to 2014: age 56.2+16.0; 64% female; 57.3% ever-smokers; 59% RF+; mean disease duration 5.3+3.5 months; 83% met ACR 2010 criteria for RA. All included patients received MTX (98.0% scMTX, 98% 25mg/week). Few patients reported headache (3%), nausea (4%), and gastrointestinal symptoms (1.0%), with no dropouts secondary to MTX intolerance in the first 3 months. The mean change in outcomes between the early and late time periods are demonstrated in Table 1, with significantly greater change seen in the early period for several outcome measures. There were a larger proportion of patients achieving SDAI, CDAI and DAS28 remission and/or low disease activity state in the early versus late period, as shown in Table 2. There was a significant improvement when using combination DMARD therapy with sc MTX compared to MTX alone at each time point for many disease measures (TJC, CRP, DAS28, CDAI, SDAI and HAQ), however combination DMARD cohort size was small (n=9). Co-medication with steroids included 33% intra-articular, 14% oral, 14% intra-muscular, and 20% combination steroids. The use of intra-articular steroids with MTX yielded the most disease measures that improved significantly in the early group (0-6wks) vs. later (6-12wks).

Conclusion: ScMTX is rapid, as the change in many disease activity scores was significantly greater between 0-6wks compared to 6-12wks. The use of combination therapy with DMARDs gave added value over methotrexate monotherapy, although generalizability is limited by sample size in the combination cohort. Intra-articular steroid injections may contribute to the early effect of treatment in the first six weeks, supporting early effective combination therapy with scMTX including joint injections as best practice for rapid improvement.

Disease Measure	N	Mean Difference in Disease Activity Score		Mean Difference Early vs. Late	Significantly greater change in early period?	p
		Early Period (0–6 wks)	Late Period (6-12 wks)			
TJC	86	- 4.01	- 3.74	- 0.27	No	0.86
SJC	86	- 6.59	- 1.35	- 5.24	Yes	0.00**
TJC28	86	- 2.57	- 2.99	+ 0.42	No	0.71
SJC28	86	- 5.94	- 1.36	- 4.51	Yes	0.00**
Pain	86	- 3.36	- 0.01	- 3.44	Yes	0.00**
Fatigue	86	- 1.98	- 0.18	- 1.80	Yes	0.00**
Sleep	82	- 2.65	- 0.003	- 2.60	Yes	0.00**
PTGA	86	- 3.79	+ 0.15	- 3.93	Yes	0.00**
HAQ	73	- 0.43	- 0.26	- 0.16	No	0.13
MDGA	82	- 3.09	- 0.55	- 2.54	Yes	0.00**
ESR	76	- 8.96	- 3.75	- 5.21	No	0.50
CRP	33	- 13.76	- 4.37	- 9.38	Yes	0.04*
DAS28ESR	72	- 1.89	- 0.23	- 1.66	Yes	0.00**
DAS28CRP	32	- 2.33	- 0.16	- 2.17	Yes	0.00**
CDAI	82	- 15.33	- 4.65	- 10.87	Yes	0.00**
SDAI	31	- 33.62	- 6.85	- 26.77	Yes	0.00**

Table 1: Comparison of mean change in disease scores between early period (0 – 6 weeks) and late period (6 – 12 weeks). Several disease activity measures demonstrated a statistically significant improvement in the early period compared to the late period (SJC, SJC28, pain, fatigue, sleep, PTGA, MDGA, CRP, DAS28ESR, DAS28CRP, CDAI, SDAI).

Remission Score		Baseline No. (%)	6 weeks No. (%)	12 weeks No. (%)
CDAI	N	102	96	89
	Remission (≤ 2.8)	0 (0.0)	16 (16.7)	17 (19.1)
	Low Activity (2.9-10.0)	9 (8.8)	25 (26.0)	48 (53.9)
	Moderate Activity (10.1-22.0)	26 (25.5)	37 (38.5)	21 (23.6)
	High Activity (> 22)	67 (65.7)	18 (18.8)	3 (3.4)
SDAI	N	97	58	37
	Remission (≤ 3.3)	0 (0.0)	4 (6.9)	3 (8.1)
	Low Activity (3.4-11.0)	3 (3.1)	13 (22.4)	16 (43.2)
	Moderate Activity (11.1-26)	15 (15.5)	19 (32.8)	13 (35.1)
	High Activity (≥ 26)	79 (81.4)	22 (37.9)	5 (13.5)
DAS28	N	94	85	76
	Remission (≤ 2.4)	2 (2.1)	22 (25.9)	23 (30.3)
	Low Activity (2.5-3.6)	9 (9.6)	28 (32.9)	33 (43.4)
	Moderate Activity (3.7-5.5)	40 (42.6)	29 (34.1)	19 (25.0)
	High Activity (≥ 5.5)	43 (45.7)	6 (7.1)	1 (1.3)

Table 2: Proportion of patients achieving CDAI, SDAI, and DAS28 remission at 0, 6 weeks and 12 weeks. There was a larger proportion of patients achieving CDAI, SDAI, DAS28 remission between 0 – 6 weeks (16.7%, 6.9%, 25.9%, respectively) compared to 6 – 12 weeks (2.4%, 1.2%, 4.4%).

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Abstract Number: 612

Thromboembolic Events Are Not Associated with Anti-Adalimumab Antibodies

Gerd Burmester[1], Cem Gabay[2], Dilek Arikan[3], Anabela Cardoso[4], Jasmina Kalabic[3], Nathan Pfeifer[3], Nupun A. Varothai[3], Stefan Florentinus[5] and Josef S. Smolen[6], [1]Department of Rheumatology and Clinical Immunology, Charité - Universitätsmedizin Berlin, Berlin, Germany, [2]Rheumatology, Geneva University Hospital, Geneva, Switzerland, [3]AbbVie, North Chicago, IL, [4]Torre Oriente, AbbVie, Lisboa, Portugal, [5]AbbVie Inc., North Chicago, IL, [6]Department of Medicine 3, Division of Rheumatology, Medical University Vienna, Vienna, Austria
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Session Title: Rheumatoid Arthritis - Small Molecules, Biologics and Gene Therapy Poster I

Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose: Treatment of rheumatoid arthritis (RA) with anti-Tumor Necrosis Factor (TNF) such as adalimumab may result in some patients (pts) developing anti-adalimumab antibodies (AAA). Findings from a case control study suggest that occurrence of thromboembolic events is higher in pts treated with adalimumab, who developed AAA, compared to those who did not[1]. The objective was to determine if thromboembolic events occur at a higher frequency in pts positive for AAA (AAA+) compared to pts who did not have AAA (AAA-) across several RA clinical trials.

Methods: This was a post hoc analysis of data from the following clinical trials of adalimumab in pts with RA: DE001, DE004, DE005, DE007, DE009 (ARMADA), DE010, DE011, DE013 (PREMIER), DE019, DE035, DE037, M02-575 (CHANGE), M06-859, M10-261, M12-071 (MUSICA), M12-073 (CONCERTO), and M13-390. Pts with RA who received any adalimumab dose were included in the analysis. The incidence rate of treatment-emergent thromboembolic events which occurred up to the last measurement of AAA, were summarized for AAA+ and AAA- pts as events/ 100 patient years (E/100PY). Preferred terms of the Medical Dictionary for Regulatory Activities (MedDRA) system organ class (17.1) were used to code the events. Arterial events such as transient ischemic attack (TIA), cardiovascular accident (CVA), myocardial infarction (MI), and venous events, such as deep vein thrombosis (DVT) with or without pulmonary embolism, superficial vein thrombosis, and thrombosis at unusual sites were included.

Results: A total of 3995 pts were included; 367 were AAA+ with 276.6 patient years (PY) of adalimumab exposure and 3628 were AAA-, with 2255.7 PY of adalimumab exposure. One out of 367 (0.3%) pts who was AAA+ and 29/3628 (0.8%) pts who were AAA- reported a thromboembolic treatment- emergent adverse event (AE) **(Table)**. In the AAA+ pts, the incidence of AE was 0.4 E/100PY (1 event, a cardiac disorder which did not lead to adalimumab discontinuation). In the AAA- pts, 1.4 E/100PY were reported; <0.1 E/100PY (1 cerebrovascular accident and 1 DVT) led to adalimumab discontinuation. Incidence of serious AEs was 0.4 E/100PY in the AAA+ pts and 0.7 E/PY in the AAA- pts.

Conclusion: Across multiple clinical trials of adalimumab in pts with RA, the incidence rate of embolic and thromboembolic events including DVT was not found to be greater in pts with AAA compared to pts who did not develop these antibodies.

Treatment – emergent thromboembolic events occurring up to last AAA measurement date

	All treatment-emergent thromboembolic events E (E/100 PY)		Treatment-emergent thromboembolic events leading to discontinuation E (E/100 PY)	
System Organ Class	AAA+ N=367, PY=276.6	AAA- N=3628, PY=2255.7	AAA+ N=367, PY=276.6	AAA- N=3628,PY=2255.7
Any adverse event	1 (0.4)	32 (1.4)	0	2 (<0.1)
Cardiac disorders	1 (0.4)	9 (0.4)	-	-
- Acute MI	0	2 (<0.1)	-	-
- MI	1 (0.4)	6 (0.3)	-	-
- Acute coronary syndrome	0	1 (<0.1)	-	
Nervous system disorders	0	8 (0.4)	-	1 (<0.1)
Vascular disorders	0	15 (0.7)	-	1 (<0.1)

AAA+, pts positive for anti-adalimumab antibody; AAA-, pts negative for anti-adalimumab antibody; E, events; PY, patient years; E/100PY, events per 100 patient years

Reference:

1. Korswagen et al. Arthritis Rheum, 2011, 63(4):877-83

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Abstract Number: 613

Correlation Between Efficacy of Tocilizumab and Levels of Oxidative Stress Markers in Patients with Rheumatoid Arthritis: the 52-Week Analysis

Hiroaki Niiro[1], Hiroshi Tsukamoto[2], Yojiro Arinobu[2], Mitsuteru Akahoshi[2], Hiroki Mitoma[2], Kensuke Oryoji[3], Yasushi Inoue[4], Takuya Sawabe[5], Shuji Nagano[6], Hiroaki Nishizaka[7], Seiji Yoshizawa[8], Yoshifumi Tada[9], Shigeru Yoshizawa[10], Takeshi Otsuka[11], Akira Ueda[12], Hitoshi Nakashima[13], Takahiko Horiuchi[14] and Koichi Akashi[2], [1]Clinical Education Center, Kyushu University Hospital, Fukuoka, Japan, [2]Department of Medicine and Biosystemic Science, Kyushu University Graduate School of Medical Sciences, Fukuoka, Japan, [3]The Center for Rheumatic Diseases, Matsuyama Red Cross Hospital, Matsuyama, Japan, [4]Department of Rheumatology, Japanese Red Cross Fukuoka Hospital, Fukuoka, Japan, [5]Hiroshima Red Cross Hospital and Atomic-bomb Survivors Hospital, Hiroshima, Japan, [6]Kyushu multicenter rheumatoid arthritis ultrasound prospective observational cohort study group, Nagasaki, Japan, [7]Kitakyushu Municipal Medical Center, Kitakyushu, Japan, [8]Hamanomachi Hospital, Fukuoka, Japan, [9]Department of Internal Medicine, Division of Rheumatology, Saga University, Saga, Japan, [10]Department of Rheumatology, Fukuoka Hospital, National Hospital Organization, Fukuoka, Japan, [11]Munakata Medical Association Hospital, Munakata, Japan, [12]Department of Internal Medicine, Miyazaki Prefectural Hospital, Miyazaki, Japan, [13]Div of Nephrol & Rheumatol, Dept of Int Med, Faculty of Medicine, Fukuoka University, Fukuoka, Japan, [14]Department of Internal Medicine, Kyushu University Beppu Hospital, Beppu, Japan

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Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose: Despite their profound inhibitory effects on inflammation and bone destruction, it remains unclear whether biological therapies can improve the long-term prognosis of patients with rheumatoid arthritis (RA). Enhanced risk of atherosclerotic cardiovascular (CV) disease is a key feature of RA. Oxidative stress is closely associated with the process of atherosclerosis. In the present study we have investigated the correlation between efficacy of 52-week treatment with tocilizumab (TCZ) and levels of oxidative stress markers in patients with RA.

Methods: Patients treated with TCZ were prospectively studied with informed consent. Efficacy of TCZ and levels of 8-OHdG and 8-iso-PGF2a in urine were evaluated by enzyme immunoassay and enzyme-linked immunosorbent assay, respectively, at baseline and 52 weeks.

Results: Thirty out of 82 patients with RA (mean age 61.0 years old; mean disease duration 7.5 years; concomitant MTX 60%) were studied at the 52-week analysis. The rate of DAS28 (ESR) and CDAI remission at 52 weeks was 76.7% and 33.3%, respectively. In all patients levels of 8-OHdG in urine were decreased (at baseline, 12.5 ng/mg Cr; at 6 months, 9.5 ng/mg Cr), while levels of 8-iso-PGF2a in urine were not altered (at baseline, 355.4 pg/mg Cr; at 6 months, 387.4 pg/mg Cr). Intriguingly, however, levels of 8-OHdG and 8-iso-PGF2a were both decreased in a subgroup of patients with RA who took concomitant MTX, at an early stage of disease, or achieved CDAI remission.

Conclusion: Efficacy of 52-week treatment with TCZ correlated with reduced levels of oxidative stress markers in RA patients. This trend was noted in a subpopulation of patients with RA who took concomitant MTX, at an early stage of disease, or achieved CDAI remission. Together, these findings suggest that treatment with TCZ improves the long-term prognosis of patients with RA by lowering the risk of CV events.

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Abstract Number: 614

Time to First Signs of Loss of Response in Rheumatoid Arthritis Patients Treated with

Anti TNF Agents: Correlations with Serum Drug Level, Immunogenicity and Csdmard Association

Diana Mazilu[1], Daniela Opris[1,2], Evelina Iachim[3], Claudia Deaconu[4], Ioana Saulescu[1], Andreea Borangiu[1], Laura Grosanu[1], Cosmin Constantinescu[1], Andra Balanescu[1], Denisa Predeteanu[1] and Ruxandra Ionescu[1], [1]University of Medicine and Pharmacy "Carol Davila", Department of Internal Medicine and Rheumatology "Sf. Maria" Hospital, Bucharest, Romania, [2]Rheumatology and Internal Medicine, Carol Davila Medicine and Pharmacy University, Sfanta Maria Clinical Hospital, Bucharest, Romania, [3]Carol Davila Medicine and Pharmacy University, Bucharest, Romania, [4]Department of Internal Medicine and Rheumatology "Sf. Maria" Hospital, Bucharest, Romania
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Session Type: ACR Poster Session A
Session Time: 9:00AM-11:00AM

Background/Purpose: Drug immunogenicity is one of the main mechanisms behind therapeutic failure in rheumatoid arthritis (RA) patients. Our aim was to follow for 2 years RA patients treated with anti TNF agents and to analyze whether the duration of efficacious anti TNF treatment is correlated to their serum drug level at the moment of disease flare, immunogenicity and csDMARD association.

Methods: Ninety two RA patients already treated with anti TNF agents (infliximab, adalimumab, etanercept) were included in a prospective study for 2 years. The clinical activity was measured by DAS28-ESR and SDAI scores. Patient's follow-ups were done every 2 months for infliximab (IFX) and every 3 months for etanercept (ETN) and adalimumab (ADL). At the moment of first sign of treatment failure, serum samples were obtained before anti TNF drug administration. Serum drug and anti-drug antibodies levels were measured by ELISA.

Results: Sixty five patients experienced signs of treatment failure and consequently they were tested for serum drug and anti-drug levels. Eighteen patients were excluded from final analysis due to changes in therapy that could affect serum drug level and immunogenicity, as increase in anti TNF agent dose and a new csDMARD association. Twenty patients treated with IFX experienced loss of response. Eleven patients had undetectable IFX serum level and 9 patients - detectable IFX serum level. The mean IFX treatment duration until the disease flare was not different in these 2 groups: 29.36±17.56 months vs. 40.66±36.96 months (P=0.379). Efficacious treatment duration did not correlate to IFX drug level (r=0.176, P=0.458) at the moment of disease flare, nor with combination therapy with csDMARD (r=-0.045, P=0.852). Nine patients had anti IFX antibodies, but their presence did not correlate to IFX efficacious time (r=0.302, P=196). Serum ETN drug and anti ETN antibodies levels were measured in 18 patients. Only 3 patients had undetectable ETN level. The mean ETN efficacious treatment duration was not significantly different between patients with detectable vs. undetectable ETN serum level (47.8±38.5 months vs. 57.67±23.75 months, P=0.679). Treatment duration did not correlate to ETN serum level(r=-0.244, P=0.328), nor to csDMARD association(r=-0.012, P=0.962). Nine patients treated with ADL for mean 45.56±23.88 months experienced first signs of loss of response. Only one patient had undetectable drug level being on efficacious treatment with ADL for 36 months. The mean efficacious treatment duration in patients with detectable ADL serum level was 46.7±25.2 months. Treatment duration did not correlate to ADL serum level (r=0.377, P=0.318), nor with csDMARD association (r=0.413, P=0.270).

Conclusion: The efficacious treatment duration of anti TNF agents in RA patients seems not to correlate to serum drug level at the moment of first signs of loss of response and may not be influenced by csDMARD association.

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Abstract Number: 615

Rituximab Non Responders Fail to Down Regulated CD19 on Naive B Cells

Hans-Peter Brezinschek[1], Florentine Fürst-Moazedi[1], Sonja Kielhauser[2], Martin Stradner[3] and Winfried Graninger[4], [1]Internal Medicine/Division of Rheumatology, Medical University Graz, Graz, Austria, [2]Internal Medicine/Division of Rheumatology and Immunology, Medical University Graz, Graz, Austria, [3]Department of Rheumatology and Immunology, Medical University Graz, Graz, Austria, [4]Rheumatology and Immunology, Medical University of Graz, Graz, Austria
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Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose:

CD19 is a membrane glycoprotein of the immunoglobulin superfamily and part of the hetero-oligomeric complex comprising the complement receptor type 2, which positively regulates BCR activation. In the tight skin (TSK/+) mouse model for human SSc it has been demonstrated that down regulation of CD19 significantly decreased skin fibrosis, B cell hyper proliferation and IL-6 production.

The purpose of this study was to analyze the effect of rituximab treatment (RTX) in rheumatoid arthritis (RA) and systemic sclerosis (SSc) patients on the CD19-expression on peripheral blood B cells.

Methods: B cells from 21 RA patients and 8 SSC patients were analyzed before and 24 or 48 weeks after initiation of the B cell depleting therapy with RTX. RA patients received 2x 1000mg RTX and the DAS28 was determined before and 24 months thereafter to calculate the EULAR response. SSc patients received 2x 500mg RTX every 3 month and the Rodnan skin score (RSS) and the diffusing capacity of the lung for carbon monoxide (DLCO) were measured before and 48weeks later. CD19 surface expression was determined by mean fluorescence intensity (MFI) and compared with the MFI of CD45 on the cells of interest. B cells were divided into naïve (IgD+/CD27-) and post switch memory cells ((IgD-/CD27+).

Results: Fifteen RA patients had after 6 month a good EULAR response, whereas 6 RA patients were EULAR non responders. In contrast, all SSc patient had a significant improvement in their RSS and DLCO after 1 year. The MFI of CD45 on B cells was not significantly different from the MFI on non B cells and was similar between the patients group. Thus, the MFI±SEM on B cells of RA and SSC patients before RTX was 40,890 ± 2,240 and 32,129 ± 6,718, respectively. The respective CD45 MFI on non-B cells was 41,123 ± 2,896 and 35,710 ± 7,989. Even after RTX no significant alteration was found. In contrast, the MFI of CD19 was significantly reduced on B cells after RTX with the greatest reduction in SSC B cells (9,016 ± 845 and 3,804 ± 281, $p \leq 0.0001$), followed by B cells from RTX-responders (9,156 ± 719 and 5,975 ± 585, $p \leq 0.008$) and RTX-non responders (9,492 ± 603 and 6,712 ± 818, $p \leq 0.031$). Interestingly, analyzing CD19 expression on the B cell subsets demonstrated that naïve B cells in RTX-non responders had no significant reduction in MFI (9,596 ± 677 and 6,890 ± 1,302, $p=0.1663$) compared to RTX responders in RA (9,214 ± 745 and 6,466 ± 635, $p \leq 0.018$) or SSc (8,672 ± 977 and 3,673 ± 607, $p \leq 0.016$). RTX induced the down regulation of CD19 on all post switch B cells irrespective of the treatment response.

Conclusion: These data suggest, that RTX affects disease activity not only by eliminating B cells but also by reduceing the expression of the costimulatory surface molecule CD19. Interestingly, in RTX-non responders newly produced naïve B cells do not significantly down regulate CD19. Thus, they might still be able to activate T cells or produce pro inflammatory cytokines.

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Abstract Number: 616

Risk Factors for the Exacerbation of Interstitial Lung Disease (ILD) after Administration of Biologic Dmards in RA Patients with Pre-Existing ILD

Tamao Nakashita[1], Akira Dibatake[2], Kotaro Matsumoto[3], Yoto Hamada[4] and Shinji Motojima[5], [1]Department of Rheumatology and Allergy, Kameda Medical Center, Kamogawa-city, Japan, [2]Department of Rheumatology and Allergy, Kameda Medical Center, Kamogawa, Japan, [3]Department of Rheumatology and Allergy, Kameda Medical Center, kamogawa, Japan, [4]Department of Rheumatology and Allergy, Kameda Medical Center, Kamogwa, Japan, [5]Department of Rheumatology and Allergy, Kameda Medical Center, Kamogawa city, Japan

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Session Time: 9:00AM-11:00AM

Background/Purpose: Interstitial lung disease (ILD) associated with RA is a big concern particularly in Japanese patients evidenced by the reports that the cause of death in approximately 10 % of patients with RA is ILD. We have reported that ILD exacerbated in 24 % (14/58) of RA patients associated with ILD when TNF-inhibitors were administrated and 2 of 14 died of ILD, although the degree of exacerbation was minimal

in half of the patients (Nakashita T, et al. BMJ open 2014). We extended this study, namely, we added the number of patients, elongated the observation periods and tried to extract the risk factors for the exacerbation of ILD after administration of bDMARDS.

Methods:

Subjects were 93 patients with RA (male/female = 40/53, mean age 63) associated with ILD who were administrated with various bDMARDS. Chest X-ray film (CXR) was taken at least every 3 months. Chest CT scan was done before and every yearly, and when newly developed shadows were found on CXR or when patients complained of respiratory symptoms for more than 2 weeks, chest CT scan was done. The severity of ILD was graded into 4, grade 0 to grade 3, according to the extent of ILD on chest CT by the method of Gochuico et al. (Arch Intern Med 2008). Chest CT images were graded by 2 independent respirologists. The patterns of ILD were also evaluated by 2 respirologists. Risk factors for the exacerbation of ILD were extracted by discriminant analysis.

Results:

The mean observation period was 23.9 months (range 2 – 90 months). MTX and prednisolone (PSL) were under use at the introduction of bDMARD in 61 % (mean 7.6 mg/week) and in 85 % (mean 7.2 mg/day), respectively. The administrated bDMARDS were as follows; abatacept (ABT) in 23, adalumumab (ADA)in 2, certolizumab (CZP) in 3, etanercept (ETN) in 43, infliximab (IFX) in 10, and tocilizumab (TCZ) in 12, respectively. The ILD grades were 1 in 54 patients, 2 in 29, and 3 in 10, respectively. The ILD patterns evaluated by HRCT were NSIP in 72 patients, UIP in 8, and OP in 13, respectively. Exacerbation of ILD was recognized in 15 patients (16 %), with the mean administration period of 6.5 months (2 – 14 months). The bDMARDS at the time of ILD exacerbation ware ABT in 1, ADA in 1, ETN in 8, and IFX in 5, respectively. Discriminant analysis was done incorporating 19 variables such as kind of bDMARDS, age, gender, duration of bDMADS administration , ILD pattern, ILD grade, dose of MTX and PSL, KL-6 value, DAS28ESR, RF titer, and others, and only 1 significant risk factor (TNF-inhibitors) was extracted. Odds ratio of ILD exacerbation for TNF-inhibitors was 10.

Conclusion: We should be cautious for the exacerbation of ILD when TNF-inhibitors were administrated.

Disclosure: T. Nakashita, None; **A. Dibatake**, None; **K. Matsumoto**, None; **Y. Hamada**, None; **S. Motojima**, None.

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Abstract Number: 617

Biological Down-Titration in RA: Patient Profile and Response to Retreatment in Flaring Patients

Juan P. Vinicki[1], Miguel Arredondo[1], Esther Ramirez[2], Ana M. Ortiz Garcia[3], Santos Castañeda[4], Alberto Morell[1], Rosario Garcia-Vicuña[3] and **Jose María Alvaro-Gracia**[4], [1]Unidad de Terapias Biológicas, Hospital Universitario de La Princesa. IIS La Princesa, Madrid, Spain, [2]Farmacia, Hospital Universitario de La Princesa. IIS La Princesa, Madrid, Spain, [3]Rheumatology, Hospital Universitario de La Princesa. IIS La Princesa, Madrid, Spain, [4]Hospital Universitario de La Princesa. IIS La Princesa, Madrid, Spain

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SESSION INFORMATION

Session Date: Sunday, November 8, 2015
Session Title: Rheumatoid Arthritis - Small Molecules, Biologics and Gene Therapy Poster I
Session Type: ACR Poster Session A
Session Time: 9:00AM-11:00AM

Background/Purpose: Down-titration of biological therapy (BT) in rheumatoid arthritis (RA) patients with a good clinical response is frequently applied in daily clinical practice. An important factor in order to know if this can be safely applied is the response to retreatment in flaring patients. We have analyzed the risk of relapse and the effectiveness of retreatment in RA patients receiving BT (in daily clinical practice) who had been previously down-titrated.

Methods: Retrospective observational study from a single center. RA patients receiving BT (infliximab, adalimumab, etanercept, certolizumab pegol, abatacept and tocilizumab) previously down-titrated (quarterly dose of BT less than or equal to 83% of the approved dose) were included. Retreatment consisted of increasing the dose to previous or standard (European Medicines Agency approved) dose, at the discretion of the attending physician. Relapse was defined as an increase greater than or equal to 0.6 points from baseline DAS28 or according to the attending physician criteria. Response to retreatment was considered if patients achieved the same level of DAS28 (remission, low or moderate disease activity) as prior to down-titration. Numerical data are expressed as mean and standard deviation for continuous variables and percentages for qualitative variables. Univariate and multivariate analysis was used in order to identify potential predictors of greater risk of relapse after BT down-titration.

Results: Two hundred and fifty-six RA patients were under BT and 91 patients were down-titrated of whom 52% were in remission, 24% with

low disease activity and 24% with moderate disease activity according to DAS28. Most patients (68.1%) were receiving first line BT. Twenty eight patients relapsed and received retreatment at full dose (61%) or previous dose (39%). The average time between down-titration and retreatment was 17.2 ± 13.7 months. Mean DAS28 at the time of retreatment was 4.01 ± 0.99. Most patients (75%) achieved a clinical response before 6 months of retreatment, regardless the use of standard or previous dose. No statistically significant predictors of flare were identified although a trend to greater risk of flaring was observed in patients not in remission at down-titration.

Conclusion: Although down-titration carries a risk of relapse in RA, most patients achieve a good response after retreatment.

Disclosure: J. P. Vinicki, None; **M. Arredondo**, None; **E. Ramirez**, None; **A. M. Ortiz Garcia**, Spanish Society of Rheumatology, 2; **S. Castañeda**, None; **A. Morell**, None; **R. Garcia-Vicuña**, None; **J. M. Alvaro-Gracia**, BMS, Janssen-Cilag, MSD, Pfizer, Roche, UCB, 5,BMS, Janssen-Cilag, MSD, Pfizer, Tigenix, Roche, UCB, 8.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/biological-down-titration-in-ra-patient-profile-and-response-to-retreatment-in-flaring-patients

Abstract Number: 618

The Multi-Biomarker Disease Activity Score in Methotrexate Incomplete Responders Predicts Clinical Responses to Non-Biological Versus Biological Therapy in Early RA

Karen Hambardzumyan[1], Rebecca J. Bolce[2], Saedis Saevarsdottir[3], Kristina Forslind[4,5], Johan A Karlsson[6] and Ronald F. van Vollenhoven[1], [1]Department of Medicine, Unit for Clinical Therapy Research, Inflammatory Diseases (ClinTRID), The Karolinska Institute, Stockholm, Sweden, [2]Crescendo Bioscience Inc., South San Francisco, CA, [3]Department of Medicine, Rheumatology Unit, The Karolinska Institute and Karolinska University Hospital, Stockholm, Sweden, [4]Department of Medicine, Helsingborgs Lasarett, Section of Rheumatology, Helsingborg, Sweden, [5]Departments of Rheumatology, Helsingborgs Hospital and University of Lund, Helsingborg and Lund, Sweden, [6]Section of Rheumatology, Department of Clinical Sciences Lund, Lund University, Lund, Sweden

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SESSION INFORMATION

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Session Title: Rheumatoid Arthritis - Small Molecules, Biologics and Gene Therapy Poster I

Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose: The Swedish Farmacotherapy (SWEFOT) trial and other trials in rheumatoid arthritis (RA) demonstrated that in MTX incomplete responder patients (MTX-IR) the addition of anti-TNF was only marginally better than stepping up to triple therapy (TT) at the group level. However, it is likely that each treatment choice is better for some subsets of patients. We here evaluate whether the multi-biomarker disease activity (MBDA) score could be used to predict optimal choice of second-line treatment.

Methods: 157 MTX-IR patients from the SWEFOT trial were analyzed. Last observation carried forward was applied in case of incomplete data. Proportions of clinical responders at year 1 among patients with low (<30) moderate (30-44) and high (>44) MBDA scores at randomization (Month 3) were compared by Fisher's exact test. Overall difference of the responses in the two therapy arms was analyzed by Breslow-Day test (for homogeneity of odds ratio).

Results: For patients with a low MBDA (<30) score at randomization, the likelihood of response to TT was significantly greater than to anti-TNF (88% vs. 18%, p=0.006), whereas for patients with high MBDA (>44) the reverse was true (35% vs. 58%, p=0.04, Figure 1A). Comparison of ROC curves with MBDA as a predictor for each treatment identified a threshold of 38 as optimal, corresponding to the lowest quartile of MBDA values in this population. The overall difference of the responses to the treatments based on this cut-off (≤ vs. >38) was highly significant (p=0.001, Figure 1B).

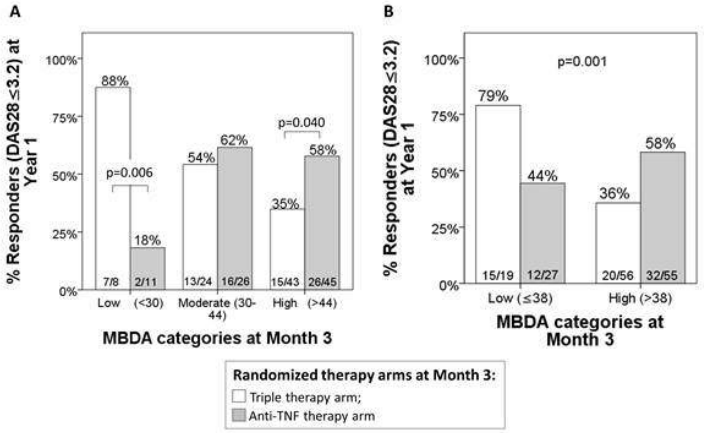

Figure 1. Proportion of responders (DAS28≤3.2) at Year 1 among different categories according to the MBDA score at Month 3. Patients grouped into 3 categories: low (<30), moderate (30-44) and high (>44) **(A)**. Patients grouped into 2 categries: low (≤38) and high (>38) **(B)**.

Conclusion: In patients with early RA and incomplete response to MTX, MBDA score predicts the relative efficacy of subsequent treatment with triple therapy versus anti-TNF. Perhaps most importantly, low MBDA score identifies a subset of patients who are significantly more likely to respond to conventional triple therapy than to anti-TNF. These findings may have major implications for the development of more individualized and cost-effective therapeutic algorithms in RA.

Disclosure: K. Hambardzumyan, None; **R. J. Bolce**, Myriad Genetics Inc., 1,Crescendo Bioscience, 3,Myriad Genetics Inc., 4; **S. Saevarsdottir**, None; **K. Forslind**, None; **J. A. Karlsson**, None; **R. F. van Vollenhoven**, Abb Vie, BMS, GSK, Pfizer, Roch, UCB, 2,Abb Vie, Biotest, BMS, Crescendo Bioscience, GSK, Janssen, Lilly, Merck, Pfizer, Roch, UCB, Vertex, 5.

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Abstract Number: 619

Long-Term Adverse Events after Daily Concomitant Treatment with 10mg Prednisone in the 2-Year Computer Assisted Management in Early Rheumatoid Arthritis Trial-II

Maria de Hair, Nicole IJff, Johannes Jacobs and Jacob van Laar, Rheumatology & Clinical Immunology, University Medical Center Utrecht, Utrecht, Netherlands

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SESSION INFORMATION

Session Date: Sunday, November 8, 2015

Session Title: Rheumatoid Arthritis - Small Molecules, Biologics and Gene Therapy Poster I

Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

On behalf of the Society for Rheumatology Research Utrecht (SRU)

Background/Purpose: To investigate the frequency of long-term adverse events (AEs) in early rheumatoid arthritis (RA) patients treated additionally with prednisone 10 mg/day.

Methods: In the Computer Assisted Management in Early Rheumatoid Arthritis (CAMERA) II trial patients initiated treatment with methotrexate (MTX) with 10 mg/d prednisone or placebo for 2 years; the trial was tight-controlled aiming for remission. Thereafter, patients were followed according to a protocol in clinical care. The occurrence of adverse events (AEs) with onset after the 2 year trial period as well as the use of prednisone after the end of the 2 year trial period, when it was the strategy to taper and stop the prednisone, was collected retrospectively from the patient medical charts. For the patients in the former prednisone strategy (pred), the proportion of patients who discontinued prednisone and time until discontinuation of prednisone was described. The frequency of long-term AEs in the pred group versus the former placebo strategy (plac) was analyzed using Fisher's Exact tests.

Results:

Of the 236 patients included in the CAMERA-II trial, follow-up data was available of 118 patients (4 of 7 participating centers; data of the other

patients are being collected): pred N=57, plac N=61; no longer followed according to protocol N=17. The median (IQR) follow-up time after the end of the 2-year trial period was 83 (61-100) and 79 (65-95) months, respectively. 49 (86%) patients treated with prednisone discontinued prednisone after median (IQR) 12 (3-88) months after the trial period. The other patients could not discontinue prednisone due to an increase in RA disease activity when tapering prednisone. The number (%) of AEs are described in Table 1. No statistically significant difference between the two groups was found for any of the AEs, except for cardiovascular diseases; there was a trend toward increased mortality.

Table 1. Frequency of adverse events in the pred vs plac groups

Adverse event (AE)	pred N=57	plac N=61	p-value
≥ 1 AE, n (%)	23 (40.4)	22 (36.1)	0.71
Hypertension, n (%)	2 (3.5)	7 (11.5)	0.17
Diabetes mellitus II, n (%)	1 (1.8)	1 (1.6)	1.00
Gastrointestinal, n (%)	1 (1.8)	0 (0.0)	0.48
Cataract, n (%)	5 (8.8)	7 (11.5)	0.76
Glaucoma, n (%)	0 (0.0)	0 (0.0)	-
Fracture, n (%)	7 (12.3)	8 (13.1)	1.00
Cardiovascular, n (%)	10 (17.5)	3 (4.9)	0.04
Mortality, n (%)	6 (10.5)	1 (1.6)	0.06

Conclusion: Overall, a low occurrence of AEs was found in this preliminary study, but we found an increased cardiovascular risk for the early RA patients treated at least during 2 years with 10mg/d prednisone.

Disclosure: M. de Hair, None; **N. IJff**, None; **J. Jacobs**, None; **J. van Laar**, None.

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Abstract Number: 620

Evaluation of Patients from the Non-Biologic Arms of Inflammatory Arthritis Clinical Trials Identifies Several Predictors of Remission, As Well As, Distinct Responder Subgroups

Brian Tom[1] and Deborah P.M. Symmons[2], [1]Biostatistics Unit, Medical Research Council, Cambridge, United Kingdom, [2]NIHR Manchester Musculoskeletal Biomedical Research Unit, Central Manchester University Hospitals NHS Foundation Trust, Manchester, United Kingdom

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SESSION INFORMATION

Session Date: Sunday, November 8, 2015

Session Title: Rheumatoid Arthritis - Small Molecules, Biologics and Gene Therapy Poster I

Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose: The RA-MAP consortium is a UK flagship industry-academic partnership investigating clinical and biological predictors of disease outcome in patients with rheumatoid arthritis (RA).

Methods: One RA-MAP workstream investigated clinical predictors of remission by collation of patient-level data from non-biologic arms of academic- and industry-sponsored clinical trials, completed since 2002, evaluating therapies in early inflammatory arthritis and RA. Anonymised data on key baseline and follow-up variables were requested and amalgamated. Logistic regression was used to identify predictors of remission at 6 months, as defined by DAS28-ESR. Initial models considered separate effects of potential predictors after adjusting for age, gender, disease duration, race and treatment arm. Multivariate models were built with variables important at initial screen and with low percentage of missing values. Latent class mixed models were used to characterise disease activity over time, adjust for potential predictors and introduce random effects, and to cluster trajectories that may identify clinically important sub-populations. Both Akaike and Bayesian information criteria were used to decide on number of clusters.

Results: 19 trials were received, comprising 3555 patients with over 30,000 baseline and follow-up records. The non-biologic arms included treatment with placebo, intramuscular steroids, methotrexate or other DMARDs, or methotrexate in combination with other drugs. 78% of patients were female, 86% white and 72% rheumatoid factor positive. Mean age at onset (SD) was 46.7 (13.9) years. Mean age (SD) and median disease duration (IQR) at entry were 52.8 (12.8) years and 3 (1-9) years respectively. Mean baseline DAS28-ESR, 28-swollen and tender joint counts (SDs) were 6.4 (1.1), 12 (6) and 14.7 (7.2). Remission rate, 6 months from entry, was 11% (95%CI 9.8%-12.3%). In the final multivariate

logistic model, remission at 6 months was predicted by being white, male, younger, never smoked, RF negative, methotrexate naïve at entry, randomised to methotrexate singly or in combination, better functional health and lower levels of baseline disease activity (Table 1). Latent class mixed modelling suggested patients could be clustered into sub-populations that included fast improver and non-responder groups and one or two intermediate classes - a slower improver group and a possible sub-population that improved in the first 6 months then showed no further improvement.

Conclusion: Through this novel partnership, the RA-MAP project has confirmed several known factors related to non-biologic induced remission. The remission rate of 11% provides a benchmark for non-biologic arms of future RA trials. The potential to stratify RA patients into distinct disease activity trajectories was demonstrated and may become the basis of personalising treatment choices.

Table 1: Logistic regression for remission

Predictors	log(Odds Ratio)	Standard Error	p-value
Age at Entry, years	-0.0177	0.006	0.0037
Gender	0.7661	0.1668	<0.0001
Male v Female			
Disease Duration, years	-0.0157	0.0193	0.4142
Race	1.1430	0.3585	0.0014
White v Rest			
Treatment Arm	0.4770	0.4958	0.3360
DMARDs v Placebo	0.6842	0.3468	0.0485
Methotrexate v Placebo	0.9306	0.4110	0.0236
Methotrexate + Other Drugs v Placebo	-0.1648	0.4340	0.7042
Intramuscular Steroids v Placebo			
Smoking Status	-0.7288	0.3226	0.0239
Current Smoker v Never Smoker	-0.4899	0.2636	0.0631
Ex/Not Current Smoker v Never Smoker	-1.0718	0.2974	0.0003
Not Collected v Never Smoker			
DAS28-ESR at Baseline	-0.2803	0.0866	0.0012
Erythrocyte Sedimentation Rate (ESR), mm/hr	-0.0082	0.0038	0.0302
Rheumatoid Factor Positivity	-0.3600	0.1661	0.0302
Yes v No	-0.1175	0.7292	0.8719
Unknown v No			
Health Assessment Questionnaire (HAQ)	-0.5049	0.1337	0.0002
Methotrexate History Status	-1.9309	0.3150	<0.0001
On Currently v Naïve	-0.4215	0.3229	0.1918
Previously On v Naïve			

Disclosure: B. Tom, None; **D. P. M. Symmons**, None.

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Abstract Number: 621

Previous Diagnosis of Sjögren's Syndrome As Rheumatoid Arthritis or Systemic Lupus Erythematosus

Astrid Rasmussen[1], Lida Radfar[2], Kiely Grundahl[3], David M. Lewis[4], Donald U Stone[5,6], C. Erick Kaufman[7], Daniel J Wallace[8], Michael H. Weisman[9], Swamy Venuturupalli[10], Christopher J Lessard[11], Biji Kurien[12], Juan-Manuel Anaya[13], Michael D. Rohrer[14], Raj Gopalakrishnan[15], Glen D Houston[16], James Chodosh[17], Pamela J Hughes[18], Nelson L. Rhodus[19], John Ice[1], Kimberly Hefner[20], Jennifer A. Kelly[21], Kathy L. Sivils[1] and R. Hal Scofield[1,22,23], [1]Arthritis and Clinical Immunology Research Program, Oklahoma Medical Research Foundation, Oklahoma

City, OK, [2]Oral Diagnosis and Radiology Department, University of Oklahoma Health Sciences Center College of Dentistry, Oklahoma City, OK, [3]Arthritis and Clinical Immunology Research Program, Oklahoma Medical Research Foundation, Oklahoma CIty, OK, [4]College of Dentistry, Department of Oral and Maxillofacial Pathology, University of Oklahoma Health Sciences Center, Oklahoma City, OK, [5]Department of Ophthalmology, Johns Hopkins University, Riyadh, Saudi Arabia, [6]Research Department, King Khaled Eye Specialist Hospital, Riyadh, Saudi Arabia, [7]College of Medicine, University of Oklahoma Health Sciences Center, Oklahoma City, OK, [8]Division of Rheumatology, Cedars-Sinai Medical Center, Los Angeles, CA, [9]Rheumatology, Cedars-Sinai Medical Center, Los Angeles, CA, [10]Cedars-Sinai Medical Center, West Hollywood, CA, [11]Arthritis and Clinical Immunology, Oklahoma Medical Research Foundation, Oklahoma City, OK, [12]Arthritis and Immunology, Oklahoma Medical Research Foundation, Oklahoma City, OK, [13]Center for Autoimmune Diseases Research (CREA), Universidad del Rosario., Bogota, Colombia, [14]Hard Tissue Research Laboratory, University of Minnesota School of Dentistry, Minneapolis, MN, [15]Diagnostic and Biological Sciences, Division of Oral Pathology, University of Minnesota, Minneapolis, MN, [16]Heartland Pathology, Oklahoma City, OK, [17]Ophthalmology, Massachusetts Eye and Ear Infirmary, Harvard Medical School, Boston, MA, [18]Division of Oral and Maxillofacial Surgery, University of Minnesota, Minneapolis, MN, [19]Department of Oral Surgery, University of Minnesota School of Dentistry, Minneapolis, MN, [20]Hefner Eye Care and Optical Center, Oklahoma City, OK, [21]Arthritis & Clinical Immunology Research Program, Oklahoma Medical Research Foundation, Oklahoma City, OK, [22]Department of Medicine, University of Oklahoma Health Sciences Center, Oklahoma City, OK, [23]US Department of Veterans Affairs Medical Center, Oklahoma City, OK
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SESSION INFORMATION
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Session Time: 9:00AM-11:00AM

Background/Purpose: The diagnosis of Sjögren′s Syndrome (SS) is often difficult and many patients are symptomatic for years with other diagnoses before confirmation of SS. Overlapping clinical and serologic features of SS with other connective tissue disorders, in particular rheumatoid arthritis (RA) and systemic lupus erythematous (SLE), may in part drive the misdiagnoses.

Methods: 1191 subjects with sicca were evaluated in a multi-disciplinary clinic and classified for SS based on the American-European Consensus Criteria. They were interrogated for a past history of suspicion or diagnosis of RA, SLE or SSc and these diseases were confirmed or ruled out by applying the corresponding classification criteria if the patients responded affirmatively.

Results: 531 (44.6%) subjects reported previous diagnosis or suspicion of RA, SLE or SSc; we confirmed the suspected diagnosis in 130, but the remaining 401 (75.5%) did not meet criteria for these diseases. Of those previously diagnosed with another illness, 183 (45.6%) met criteria for primary Sjögren′s syndrome. Rheumatoid factor was present in 31/71 patients with a previous diagnosis of RA compared to 185/830 without a history of RA diagnosis ($p<0.0001$), while 118/147 with a diagnosis of SLE had positive ANA compared to 621 of 926 without the diagnosis ($p=0.012$). Age also influenced prior diagnoses: people with suspected RA were older than those without the diagnosis ($p<0.0001$), while patients with SLE suspicion were younger ($p=0.009$). Presence of anti-Ro/SSA showed a gradient that was progressively less common in subjects who were pure SS, RA and/or SLE overlap with SS, misdiagnosed RA or SLE, and lowest in non-SS sicca. History of a diagnosis of RA or SLE did not distinguish Sjögren′s syndrome from non-Sjögren's sicca.

Conclusion: Among subjects classified as Sjögren′s syndrome, the presence of a positive ANA or rheumatoid factor was associated with a previous, apparently erroneous diagnosis of SLE or RA, respectively.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/previous-diagnosis-of-sjogrens-syndrome-as-rheumatoid-arthritis-or-systemic-lupus-erythematosus

Abstract Number: 622

Sjögren's Syndrome Foundation Clinical Practice Guidelines for Management of Dry Eyes

Frederick B Vivino[1], **Gary Foulks**[2], S. Lance Forstot[3], Peter Donshik[4], Joseph Forstot[5], Michael Goldstein[6], Michael Lemp[7], J. Daniel Nelson[8,9], Kelly K. Nichols[10,11], Stephen C. Pflugfelder[12], Jason Tanzer[13], Penny Asbell[14], Deborah S. Jacobs[15,16], Katherine M Hammitt[17] and Sjogren's Syndrome Foundation Clinical Practice Guidelines Committee, [1]University of Pennsylvania, Philadelphia, PA, [2]Department of Ophthalmology and Visual Sciences, University of Louisville, Louisville, KY, [3]Corneal Consultants of Colorado, Littleton, CO, [4]Department of Ophthalmology, University of Connecticut Health Center, Farmington, CT, [5]Rheumatology Associates of South Florida, Boca Raton, FL, [6]New

England Eye Center, Tufts Medical Center, Boston, MA, [7]Department of Ophthalmology, Georgetown University, Washington, DC, [8]Ophthalmology, HealthPartners Specialty Center, St. Paul, MN, [9]Dept. of Ophthalmology, University of Minnesota, St. Paul, MN, [10]School of Optometry, The University of Alabama at Birmingham, Birmingham, AL, [11]College of Optometry, (formerly) University of Houston, Houston, TX, [12]Ocular Surface Center, Baylor College of Medicine, Cullen Eye Institute, Houston, TX, [13]Department of Oral Health and Diagnostic Sciences, University of Connecticut School of Dental Medicine, Farmington, CT, [14]Dept of Ophthalmology, Icahn School of Medicine at Mount Sinai, New York, NY, [15]Boston Foundation for Sight, Needham, MA, [16]Cornea and External Diseases, Massachusetts Eye and Ear, Boston, MA, [17]Vice President of Medical and Scientific Affairs, Sjögren's Syndrome Foundation, Bethesda, MD
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Session Type: ACR Poster Session A
Session Time: 9:00AM-11:00AM

Background/Purpose: Dry eyes can compromise quality of life in Sjogren's Syndrome (SS) and is often one of the most troublesome symptoms. Clinical practice guidelines were developed to provide evidence based consensus recommendations for SS dry eyes management.

Methods: Following the principles of AGREE, a national panel of eye care providers and consultants with representation from rheumatology and oral medicine was convened to evaluate peer-reviewed publications and develop guidelines for the evaluation and management of SS dry eye disease. Definitions from the 2007 Report of the International Workshop on Dry Eye (DEWS) were used to identify patient subsets and clinical issues. Studies on non-SS dry eye disease guided management when considered essential or helpful. Bias was reduced as much as possible by pre-defining parameters for literature searches. Publications were graded for level of evidence according to the American Academy of Ophthalmology Preferred Practice Pattern guidelines and, for strength of the recommendation according to GRADE (Grading of Recommendations, Assessment, Development and Evaluation). Recommendations were formulated and revised using a Delphi consensus process with 75% agreement required for consensus. Revision of guidelines that failed to achieve consensus was permitted up to 3 rounds before the recommendation was discarded.

Results: Key recommendations for all SS dry eye patients included: 1) evaluation of symptoms of discomfort and visual disturbance 2) determination of the relative contribution of aqueous tear deficiency vs. evaporative tear loss to the patient's dry eyes 3) use of objective parameters (tear film stability, tear osmolality, degree of lid margin disease, ocular surface damage) to stage the severity of dry eye disease and 4) a stepwise treatment algorithm based on disease severity that includes patient education as to the nature of the problem, aggravating factors, and goals of treatment; tear supplementation and stabilization, control of inflammation of the lacrimal glands and ocular surface, systemic therapy with secretogogies, and tear preservation measures.

Conclusion: Management of dry eyes in SS necessitates a comprehensive evaluation to identify the cause or causes of dry eyes as well as the gradation of severity based upon symptoms and objective parameters. A stepwise algorithm based on overall dry eye disease severity and response to prior therapy is recommended.

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Abstract Number: 623

Seronegative Sjögren's Syndrome Is Characterized By a Lower Prevalence of B-Cell Related Clinical Manifestations and a Lower Biologic Systemic Activity

Luca Quartuccio[1], Chiara Baldini[2,3,4], Elena Bartoloni Bocci[5], Roberta Priori[6], Francesco Carubbi[7], Laura Corazza[1], Alessia Alunno[8], Serena Colafrancesco[6], Nicoletta Luciano[2], Roberto Gerli[9], Roberto Giacomelli[10], Guido Valesini[11], Stefano Bombardieri[12] and Salvatore De

Vita[13,14], [1]S. Maria della Misericordia, University of Udine, Italy, Udine, Italy, [2]Internal Medicine, University of Pisa, Pisa, Italy, [3]University of Pisa, Rheumatology Unit, Pisa, Italy, [4]Department of Internal Medicine, Rheumatology Unit, University of Pisa, Pisa, Italy, [5]Rheumatology Unit, Department of Medicine, University of Perugia, Pila, Italy, [6]Rheumatology Unit, Sapienza University of Rome, Rome, Italy, [7]Rheumatology Clinic, University of L'Aquila, L'Aquila, Italy, [8]Clinical and Experimental Medicine, Rheumatology Unit, University of Perugia, Perugia, Italy, [9]Rheumatology Clinic, University of Perugia, Perugia, Italy, [10]University of L'Aquila, L'Aquila, Italy, [11]Internal Medicine and Medical Specialties Department, Policlinico Umberto I, La Sapienza University of Rome, Roma, Italy, [12]Rheumatology Unit, University of Pisa, Italy, Pisa, Italy, [13]Santa Maria della Misericordia Hospital, University of Udine, Udine, Italy, [14]Rheumatology, DSMB, University Hospital Santa Maria della Misericordia, Udine, Italy
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Background/Purpose: The American-European Consensus Group (AECG) Criteria (1) for Sjögren's syndrome (SS) require the presence of at least one of the following two conditions: the histopathology (focus score > / = 1) or the presence of anti- SSA and / or SSB antibodies. The study aims to compare patients who, while satisfying the AECG criteria, do not present the positivity for anti-SSA/SSB antibodies, with patients that meet the AECG criteria and are positive for anti-SSA/SSB antibodies.

Methods: 598 patients were selected from the database of the Italian study group on SS (2) based on the following criteria: 1. Fulfillment of the AECG criteria for SS, 2. Execution of the biopsy of the minor salivary glands, 3. Search for anti-SSA/SSB antibodies, 4. Absence of hepatitis C virus infection. Univariate and multivariate analyses were performed. Differences were considered significant for P value <0.05. Variables with P <0.1, were then selected for the multivariate analysis.

Results: 206 patients were positive for histopathology, but negative for autoantibodies (group 1), 342 were positive for both the histopathology and for anti-SSA/SSB antibodies (group 2), and finally 50 patients were negative for the histopathology and positive for anti-SSA/SSB antibodies (group 3). This group has been excluded from the comparisons for the small size.

We found the following statistically significant differences between the two groups of patients (group 1 vs. group 2): age at diagnosis [mean ± standard error (SE)] (55 ± 0.8 vs. 48 ± 0.8, p <0.0001), glandular swelling (52/206 vs. 121/342, p = 0.013), skin involvement (14/206 vs. 47/342, p = 0.01), hematologic involvement (47/206 vs. 124/342, p = 0.001), leukopenia (36/170 vs. 110/230, p = 0.0001), lymphoma (22/342 vs. 2/206, p = 0.002), low C3 (24/187 vs. 63/316, p = 0.04), low C4 (12/187 vs. 43/316, p = 0.013), hypergammaglobulinemia (37/200 vs. 214/336, p <0.0001), ANA (323 vs. 133/202 / 337, p <0.0001), rheumatoid factor (59/198 vs. 224/331, p <0.0001), serum cryoglobulins (24/278 vs. 5/149, p = 0.039). The duration of follow-up (mean ± SE) was higher in the group 2 (4.0 ± 0.4 vs. 5.6 ± 0.3, p = 0.001).

By contrast, there were no statistically significant differences for the following variables: sex, dry eye, dry mouth, joint involvement, Raynaud's phenomenon, purpura, kidney, lung, central and peripheral nervous system involvements, stomach, heart or muscle involvements, fibromyalgia, and the presence of serum monoclonal component, or prevalence of thyroiditis.

By multivariate analysis the following variables were selected as associated with the group 2: antinuclear antibodies (OR 6.9 95% CI 3.2 to 15.1), hypergammaglobulinemia (OR 5.1 95% CI 2.9 to 9.0), rheumatoid factor (OR 2.3 95% CI 1.4 to 3.9), age at diagnosis (OR 0.9 95% CI from 0.96 to 0.99).

Conclusion: B-cell related clinical manifestations and biologic activity appears less relevant in seronegative SS. Personalized treatment in SS as well as trial design of new therapies for SS should take into account these differences for patients' recruitment beyond the fulfillment of the classification criteria.

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Sjögren's Syndrome Foundation Clinical Practice Guidelines for Oral Disease Management: Caries Prevention

Frederick B Vivino[1], Domenick Zero[2], Michael Brennan[3], **Troy Daniels**[4], Carol Stewart[5], Athena Papas[6], Andres Pinto[7], James Sciubba[8],

Ibtisam Al-Hashimi[9], Mahvash Navazesh[10], Nelson L. Rhodus[11], Mabi Singh[12], Ava Wu[13], Philip Fox[14], Stephen Cohen[15], Theresa Lawrence Ford[16], Sharon Tracy[17], Julie Frantsve-Hawley[17], Katherine M. Hammitt[14] and Sjogren's Syndrome Foundation Clinical Practice Guidelines Committee, [1]Rheumatology, University of Pennsylvania, Philadelphia, PA, [2]Indiana University School of Dentistry, Indianapolis, IN, [3]Carolinas Medical Center, Charlotte, NC, [4]Orofacial Sciences, UCSF School of Medicine & Dentistry, San Francisco, CA, [5]University of Florida College of Dentistry, Gainesville, FL, [6]Oral Medicine, Tufts University, Boston, MA, [7]Case Western Reserve University, Cleveland, OH, [8]The John Hopkins School of Medicine, Baltimore, MD, [9]Baylor College of Dentistry, Dallas, TX, [10]University of Southern California, Los Angeles, CA, [11]Department of Oral Surgery, University of Minnesota School of Dentistry, Minneapolis, MN, [12]Tufts University School of Dental Medicine, Boston, MA, [13]University of California School of Dentistry, San Francisco, CA, [14]Sjögren's Syndrome Foundation, Bethesda, MD, [15]Dr. Stephen Cohen-Doctor My Eyes, Scottsdale, AZ, [16]North Georgia Rheumatology Group, PC, Lawrenceville, GA, [17]American Dental Association, Chicago, IL
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Background/Purpose: Salivary dysfunction in Sjögren's (SS) can lead to serious and costly oral complications including accelerated caries and, in some cases, loss of dentition. Clinical Practice Guidelines for oral disease management were developed to improve the quality and consistency of care.

Methods: Following the principles of AGREE as well as ACR and ADA recommendations for guidelines development, a national panel of oral medicine experts with representation from other specialties convened to define clinically significant oral care issues for guidelines recommendations. Clinical questions were developed in a PICO (Population, Intervention, Comparison and Outcomes) format for the first overarching topic in oral management of Caries Prevention and included use of fluoride, antimicrobials, salivary stimulants, and non-fluoride remineralizing agents. A systematic literature search was conducted on articles from January 1991 to April, 2015 selected according to pre-established parameters. Data were extracted by at least two members and evidence rated by the full group. Evidence grading and strength of the recommendations were based on a variation of GRADE (Grading of Recommendations, Assessment, Development and Evaluation). Recommendations were finalized following a Delphi consensus panel process involving at least 40 dentists and dental hygienists from academia and community-based practice and other healthcare professionals with a minimum of 75% agreement required for consensus. Revision of guidelines that failed to achieve consensus was permitted up to 3 rounds before the recommendation was discarded.

Results: Final recommendations include: 1) Topical fluoride SHOULD BE USED in all Sjögren's patients with dry mouth (Strong); 2) Chlorhexidine administered by varnish, gel or rinse MAY BE CONSIDERED in SS patients with dry mouth and high root caries rate (Weak); 3) While no studies link improved salivary flow to caries prevention, it is generally accepted by the oral health community that increasing saliva may contribute to decreased caries incidence. Therefore, in SS patients with dry mouth, increasing saliva through gustatory, masticatory or pharmaceutical stimulation (*e.g.* sugar-free lozenges or chewing gum, pilocarpine or cevimeline) MAY BE CONSIDERED (Weak); and 4) Non-fluoride remineralizing agents MAY BE CONSIDERED as an adjunct therapy in Sjögren's patients with dry mouth and a high root caries rate. (Moderate).

Conclusion: The incidence of caries in SS patients can be lessened with the use of topical fluoride and other preventative strategies. Development of guidelines for caries management, restoration and oral mucosal management are currently in progress.

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Sjögren's Syndrome Foundation Clinical Practice Guidelines for Management of Systemic

Disease

Frederick B Vivino[1], Steven E. Carsons[2], Ann Parke[3], Nancy Carteron[4], Vidya Sankar[5], Richard Brasington[6], Robert Fox[7], William Ehlers[3], Michael Brennan[8], Robert Hal Scofield[9], Katherine M Hammitt[10] and Sjogren's Syndrome Foundation Clinical Practice Guidelines Committee, [1]Rheumatology, University of Pennsylvania, Philadelphia, PA, [2]Rheumatology, Allergy and Immunology, Winthrop University Hospital, Mineola, NY, [3]University of Connecticut, Farmington, CT, [4]University of California, San Francisco, CA, [5]Univeristy of Texas, San Antonio, TX, [6]Washington University, St Louis, MO, [7]Rheumatology Clinic, La Jolla, CA, [8]Carolinas Medical Center, Charlotte, NC, [9]Arthritis & Clinical Immunology Program, Oklahoma Medical Research Foundation; Department of Medicine, University of Oklahoma Health Sciences Center; US Department of Veterans Affairs Medical Center, Oklahoma City, OK, [10]Vice President of Medical and Scientific Affairs, Sjögren's Syndrome Foundation, Bethesda, MD

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Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose: There are currently no FDA approved immunomodulating agents available for treatment of the extraglandular manifestations of Sjogren's (SS). Clinical practice guidelines were developed for the rheumatologic/systemic manifestations of SS in order to improve quality and consistency of care.

Methods: Following the principles of AGREE and ACR recommendations for guidelines development, key stakeholders were surveyed to define clinically important management issues. Of 97 initial questions, 16 were selected for rheumatology guidelines development, redefined using the PICO (Patient, Intervention, Comparison, Outcome) format and prioritized. Guidelines development was completed for the first 3 topics: use of DMARDS for treatment of inflammatory musculoskeletal pain (MSK), management of fatigue and use of biological therapy. Each PICO question was assigned to a 3 member topic review group (TRG) for systematic literature review, data extraction and drafting of one or more guidelines. All articles were reviewed by at least 2 TRG members. Quality of evidence and strength of recommendation were rated using a modification of GRADE. Guidelines were drafted based on the available medical evidence and/or expert opinion. The clinical rationale, evidence summaries, data extraction tables, and drafted recommendations were submitted to a consensus expert panel for consideration and approval. Each panel was comprised of 30-40 participants including clinicians (rheumatologists, other specialists), nurses and patients. A modified Delphi process was used with 75% agreement required for consensus. Revision of guidelines that failed to achieve consensus was permitted up to 3 rounds before the recommendation was discarded.

Results: Consensus was achieved for 20 guideline recommendations. Eighteen recommendations required 1 Delphi round, 1 required 2 and 1 required 3. Key recommendations included: 1) a decision tree for the use of oral DMARDs for MSK with hydroxychloroquine (HCQ) as first line therapy; 2) use of self-care measures and exercise to reduce fatigue and the use of HCQ in selected patients with fatigue. The committee also recommended that 3) the use of rituximab may be considered in certain clinical situations including, vasculitis with or without cryoglobulinemia, severe parotid swelling, inflammatory arthritis, pulmonary disease and mononeuritis multiplex; The committee 4) strongly discouraged the use of TNFα inhibitors for sicca symptoms and for the majority of clinical contexts in primary SS.

Conclusion: Development of clinical practice guidelines for systemic manifestations should improve the standard and uniformity of care for SS and help define areas for future study. The guidelines committee updates its systematic reviews regularly and will revise recommendations as needed.

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Abstract Number: 626

Efficacy of Belimumab and Targeting of Rheumatoid Factor Positive B-Cells in Sjögren's Syndrome: Follow-up of the Open-Label Phase II Study

Luca Quartuccio[1], Sara Salvin[2], Laura Corazza[1], Saviana Gandolfo[2], Martina Fabris[3] and Salvatore De Vita[4], [1]S. Maria della Misericordia,

University of Udine, Italy, Udine, Italy, [2]Rheumatology Clinic, University of Udine, Udine, Italy, [3]Clinic of Rheumatology, University of Udine, Udine, Italy, [4]Santa Maria della Misericordia Hospital, University of Udine, Udine, Italy
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Background/Purpose: Belimumab, a monoclonal anti-B lymphocyte Stimulator (BLyS) antibody is preliminary found to be effective in Sjögren's syndrome (SS) patients with moderate to high systemic activity in the phase II open-label BELISS study (1). Belimumab was administered for 12 months in 30 SS patients coming from two Centres (Udine, Italy and Paris, France) (1, 2). The ESSDAI score and the serum levels of rheumatoid factor (RF) and IgM immunoglobulins were significantly affected by this treatment in the long term (2). The aim of this study is to report the one year follow-up after the end of the BELISS study in the Italian cohort of patients in order to further support the clinical and biological benefits of belimumab in SS.

Methods: Clinical and laboratory data of 13 SS patients were collected at one year after the end of the belimumab treatment in the BELISS study. No other immunosuppressors were employed in these patients after the end of the trial. Clinical evaluation was also available up to three years for all the patients. Patients (all female, age 54±15) were all anti-SSA and/or anti-SSB positive. Statistical comparisons by t-test were performed between baseline data and month +12 after the end of the trial, and between the last evaluation in the trial (i.e., week 52) and month +12 after the end of the trial. **Results** are reported as mean±standard deviation (SD).

Results: The ESSDAI score was 8,8±6,9 at baseline, 3,5±3,7 at week 52 (end of the trial) and 7,0±5,7 at month 12 after the end of the trial (baseline vs. month +12, p=0,2; week 52 vs. month +12, p=0,003). Thus, a significant increase in the ESSDAI score was observed between week 52 (end of the trial) and month +12 after the end of the trial, with the mean score coming back in the range of moderate disease activity from the low level. Clinical worsening started between month +6 and month +12. Interestingly, after the end of the trial, the development of B-cell lymphoma from non neoplastic parotid sialadenitis was observed in two patients, and in a third patient a stage progression of local MALT lymphoma was recorded. In an additional patient new onset of hypergammaglobulinemic purpura was documented. RF level was 79,2±86,1 IU/ml at baseline, 59,0±65,7 IU/ml at week 52 (end of the trial), 174,1±220,3 IU/ml at month 12 after the end of the trial (baseline vs. month +12, p=0,5; week 52 vs. month +12, p=0,008). IgM level was 177,6±92,8 mg/dl at baseline, 131,9±73,6 mg/dl at week 52 (end of the trial), 165±84,6 mg/dl at month 12 after the end of the trial (baseline vs. month +12, p=0,3; week 52 vs. month +12, p=0,04).

Conclusion: targeting BLyS by belimumab seems to be effective in SS. A possible control of RF-positive B cell clones in SS by belimumab may be suggested. However, this effect may require a continuous and prolonged suppression of BLyS.

References: (1) Mariette X, et al. Ann Rheum Dis. 2015;74(3):526-31. (2) De Vita S, et al. Ann Rheum Dis 2015;74(Suppl 2):338.

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Abstract Number: 627

Clinical Subsets and Presenting Features in Primary Sjögren's Syndrome: Results from a Single Center Inception Cohort Study

Chiara Baldini[1], Francesco Ferro[1], Nicoletta Luciano[1], Rosaria Talarico[1], Leonardo Lorenzini[1], Daniela Martini[1], Marta Mosca[2] and Stefano Bombardieri[1], [1]Rheumatology Unit, University of Pisa, Italy, Pisa, Italy, [2]University of Pisa, Pisa, Italy
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Background/Purpose: Aim of the study was to characterize the spectrum of presenting clinical features in a single-centre inception cohort of patients with primary Sjögren's syndrome (SS) focusing in particular on the leading symptoms for the diagnosis, on the mean latency between the onset and the diagnosis and, on how the clinical presentation may impact on the long term follow-up of the disease.

Methods: Data were obtained from an inception cohort of patients with SS (AECG 2002) recruited from 2000. The following data were recorded: demographics, presenting symptoms leading to the diagnosis, mean latency from the onset of the disease to the diagnosis, patients' laboratory assessment, histological data at the diagnosis and clinical features at last follow-up. Descriptive statistics were used to assess clinic-serological correlations.

Results: Among 378 patients enrolled (368 F) 99.2% were Caucasians. Mean age (SD) of patients at diagnosis was 51(15) years, and mean latency between the onset of the disease and the diagnosis was 78 (71) months. At disease onset, four clinical subsets were recognizable. The vast majority of the patients presented either isolated sicca symptoms (127/378, 33.7%) or sicca symptoms associated with Raynaud's phenomenon, artralgias/arthritis, and mild cytopenias (188/378, 49.7%). A third subset (23/378, 6%) was characterized by the presence of more severe systemic manifestations, including: interstitial lung disease (8/23), serositis (5/23), polineuropathy (3/23), central nervous system involvement (3/23), myositis (1/23) skin rashes (1/23) and renal involvement (2/23). Finally, a fourth subset (40/378, 10.6%) was represented by patients presenting recurrent salivary gland enlargement, purpura , peripheral nervous involvement and/or other features traditionally associated with a higher risk for non-Hodking's lymphoma (NHL) occurrence. Patients with isolated sicca symptoms were significantly older, presented less likely a positivity for anti-Ro/SSA, anti-La/SSB autoantibodies and Rheumatoid Factor and showed a lower mean focus score (FS) in the minor salivary gland biopsies. Patients presenting risk factors for lymphoma had a higher mean FS, and were more likely to present low C4 levels, cryoglobulins and monoclonal gammopathy. At last follow-up severe systemic manifestations requiring immunosuppressants were observed in additional 35 patients who had presented at the onset only mild signs of autoimmunity and in 9 patients who had also developed a NHL over the time. Overall, 24 patients developed a NHL; out of them, 21/24 had presented either salivary gland enlargement, purpura and/or peripheral nervous involvement since the diagnosis.

Conclusion: In this study we described different clinical subsets in patients with SS at the diagnosis. The impact of the disease clinical presentation on the subsequent disease course seems to be not negligible thus highlighting the importance of a comprehensive disease assessment since the early phases of the disease.

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Abstract Number: 628

Poor Prognosis of Patients with Primary Sjögren Syndrome Who Fulfilled at Diagnosis the Classification Criteria for Concomitant Cryoglobulinemic Vasculitis

Soledad Retamozo[1,2], Hoda Gheitasi[3], Luca Quartuccio[4], Belchin Kostov[5], Laura Corazza[4], Albert Bové[3], Antoni Sisó-Almirall[5], Myriam Gandía[3], Manuel Ramos-Casals[1], Salvatore De Vita[6] and Pilar Brito-Zerón[1], [1]Department of Autoimmune Diseases, CELLEX-IDIBAPS, Hospital Clínic, Barcelona, Barcelona, Spain, [2]Rheumatology Unit, Hospital Privado Centro Médico de Córdoba, Córdoba, Argentina, [3]Department of Autoimmune Diseases, IDIBAPS, Hospital Clínic, Barcelona, Spain, [4]S. Maria della Misericordia, University of Udine, Italy, Udine, Italy, [5]Primary Care Research Group, Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Primary Care Centre Les Corts, CAPSBE, Barcelona, Spain, [6]Santa Maria della Misericordia Hospital, University of Udine, Udine, Italy
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Background/Purpose:

To evaluate the fulfilment of classification criteria for cryoglobulinemic vasculitis (CV) at diagnosis in a large cohort of patients with primary Sjögren syndrome (SS) and their correlation with poor outcomes.

Methods:

We included 515 consecutive patients tested for serum cryoglobulins who fulfilled the 2002 classification criteria for primary SS. CV classification criteria and serum cryoglobulins at diagnosis were assessed as predictors of death and lymphoma using Cox proportional-hazards regression analysis adjusted for age and gender.

Results:

Positive serum cryoglobulins were detected in 65 (12%) patients, of whom 21 (32%) fulfilled CV classification criteria. Patients with CV had a higher frequency of type II cryoglobulinemia (86% vs. 43%, p=0.04), a higher mean cryocrit level (6.58% vs. 1.25%, p<0.001), and a higher cumulated mean ESSDAI score (35.3 vs. 16.2, p<0.001) in comparison with patients carrying serum cryoglobulins who did not fulfill CV criteria. After a mean follow-up of 110 months, 45 (9%) patients developed B-cell lymphoma and 33 (6%) died. In comparison with patients without cryoglobulinemia, patients with cryoglobulins showed a high risk of development of B-cell lymphoma; the risk was higher for those who fulfilled the CV criteria (HR 7.47, CI95% 3.38-16.53) than for those who did not fulfill the CV criteria (HR 2.56, CI95% 1.03-6.35); statistical differences were found in the univariate analysis, but were not confirmed by the multivariate models. With respect to mortality, patients with CV had a higher risk of death in both the univariate (HR 11.68, CI95% 4.44-30.74) and multivariate (HR 4.36, CI95% 1.32-14.47) adjusted models in comparison with those without cryoglobulins.

Conclusion:

Patients with primary SS who fulfilled the classification criteria for cryoglobulinemic vasculitis at diagnosis are at higher risk of death.

Disclosure: S. Retamozo, None; **H. Gheitasi**, None; **L. Quartuccio**, None; **B. Kostov**, None; **L. Corazza**, None; **A. Bové**, None; **A. Sisó-Almirall**, None; **M. Gandía**, None; **M. Ramos-Casals**, Bristol-Myers Squibb, 2; **S. De Vita**, None; **P. Brito-Zerón**, None.

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Abstract Number: 629

Salivary Gland Ultrasonography As an Useful Tool to Distinguish Patients with Sjögren's Syndrome at Risk for Non-Hodgkin's Lymphoma Development

Chiara Baldini[1], Nicoletta Luciano[1], Francesco Ferro[1], Chiara Stagnaro[1], Daniela Martini[1], Marta Mosca[2] and Stefano Bombardieri[1], [1]Rheumatology Unit, University of Pisa, Italy, Pisa, Italy, [2]University of Pisa, Pisa, Italy

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SESSION INFORMATION

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Session Title: Sjögren's Syndrome Poster I: Clinical Insights into Sjögren's Syndrome

Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose: Salivary gland ultrasonography has been proposed as a promising novel tool for the diagnosis of primary Sjögren's syndrome (SS). An increasing number of studies have shown strong correlations between parenchymal inhomogeneity and disease histological and serological features. However, the correlation between abnormal findings at the salivary gland ultrasonography and traditional risk factors for lymphoma development has not been explored, yet. Aim of this study was to evaluate whether potential abnormalities at the salivary gland ultrasonography might be correlated to any of the traditional histological and serological risk factors for lymphoma development in order to assess the role of salivary gland ultrasonography in the prognostic stratification of primary SS patients.

Methods: Patients with SS (AECG 2002) and different disease duration were consecutively enrolled in this study and systematically evaluated for traditional risk factors for lymphoma (current or past history). Salivary gland ultrasonography was performed by using a Logic 9 system. A simplified scoring system based on parenchymal inhomogeneity (ranging from grade 0 to grade 4) was adopted to assess major salivary gland involvement on the ultrasound. A grade ≥2 was considered as pathological.

Results: We included in the study 127 patients with SS (mean age = 57±5 yrs; disease duration= 14±7 yrs). The mean ultrasonographic score of the overall population was 2.5±2.3 (range 0-8). Seventy-nine patients (62.2%) presented a moderate to severe parenchymal inhomogeneity (i.e ultrasonographic score ≥2). A significantly higher mean ultrasonographic score was detected in patients with history of purpura (4.5±2.7 vs 2.4±2.3, p=0.01), salivary gland enlargement (4.3±1.9 vs 1.8±2.0, p<0.001), positivity for cryoglobulins (5.52±1.8 vs 2.4±2.3, p=0.008), and presence of germinal center in the minor salivary gland biopsy (3.9±2.3 vs 1.6±2.1, p<0.001).The overall ultrasonographic score directly correlated with the IgG levels (r=0.384, p=0.000) and inversely with both C4 levels (r= -0.207, p=0.000) and lymphocytes count (r=-232, p=0.01).

Conclusion: This study suggested that salivary gland ultrasonography may represent a non invasive additional tool to be used in clinical practice for the prognostic stratification of patients with SS and, specifically to distinguish those patients at higher risk for lymphoma development.

Disclosure: C. Baldini, None; **N. Luciano**, None; **F. Ferro**, None; **C. Stagnaro**, None; **D. Martini**, None; **M. Mosca**, None; **S. Bombardieri**, None.

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Abstract Number: 630

Can Extraglandular Manifestations Differentiate Primary Sjögren's Syndrome from Sjögren's-Systemic Lupus Erythematosus Overlap Syndrome?

Steven E. Carsons[1], Suneel Movva[2], Sabatino Ienopoli[3], Steven Aziz[4], Maryam Gul[5], Rose Calixte[6] and Tracy Brodsky[7], [1]Rheumatology, Allergy and Immunology, Winthrop University Hospital, Mineola, NY, [2]Rheumatology, Winthrop University Hospital, Mineola, NY, [3]Medicine, Winthrop University Hospital, Mineola, NY, [4]Winthrop, Mineola, NY, [5]Internal Medicine, Winthrop University Hospital, Mineola, NY, [6]Winthrop University Hospital, Mineola, NY, [7]NYIT, Old Westbuyr, NY
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Background/Purpose:

Differentiating between primary Sjögren's syndrome (PSS) with systemic manifestations (SM), and Sjögren's -SLE overlap syndrome (OL) can be a clinical challenge. Approximately 30 % of PSS patients have systemic manifestations, while 30 % of SLE patients display sicca symptoms and are SS-A/B positive. This study was undertaken to determine if the prevalence and pattern of SM can differentiate PSS with SM from OL.

Methods:

Charts of 118 patients were retrospectively evaluated to compare the prevalence of SM, and association of diagnosis with twelve categories of SM. Of 118 patients, 91 were classified as PSS and 27 were classified as OL. All PSS patients met AECG criteria for PSS, and had two or fewer ACR SLE criteria. OL patients were defined as having greater than two AECG criteria, and greater than two SLE criteria. The cohorts were also compared with respect to serological features. Two-sample test and Wilcoxon rank sum test were used to test for association between SM and diagnostic category. All associations with $p<0.3$ were further tested using an adjusted logistic regression model.

Results:

There were no significant differences in demographics between PSS and OL patients. However, in the adjusted model white race was more common 4.09 times more common in PSS. There were no significant differences in frequency of xerostomia and xeropthalmia between PSS and OL. Neurologic disease was the most prevalent SM in PSS (43 %), whereas arthritis was most common in OL (52%). There were significant differences in association between PSS and OL with regards to arthritis ($p<0.001$), leukopenia ($p=0.009$), thrombocytopenia ($p=0.001$), and serositis ($p=0.037$) . There was no significant difference in prevalence of renal manifestations. There also were similar rates of Raynaud's. Positivity for SS-A, and SS-B was similar. Overall, patients with OL had a higher median number of EGM than patients with PSS ($p=0.009$).

Conclusion:

Conclusion

PSS and OL patients are similar with regards to age of presentation and gender, but the two groups differ significantly in ethnicity with non-Caucasian race more likely to develop overlap features with SLE. Xerostomia and xeropthalmia cannot differentiate between these groups. Inflammatory arthritis, leukopenia, thrombocytopenia, and serositis may assist in differentiating between PSS and OL. Lower than expected rates of renal disease in the OL group suggest a possible modifying effect of the Sjögren's phenotype. SS-A, and SS-B as well as Raynaud's do not appear to discriminate between these two disease states.

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Abstract Number: 631

Usefulness of the Minimally-Invasive Minor Salivary Gland Biopsy in Patients Presenting with Sicca Syndrome: Prospective Evaluation of 200 Patients

Soledad Retamozo[1], Pilar Brito-Zerón[1], Albert Bové[2], Hoda Gheitasi[2], Courtney Grant[3], Daphne Superville[4], Belchin Kostov[5], Antoni Sisó-Almirall[5], Llucia Alós[6] and Manuel Ramos-Casals[1], [1]Department of Autoimmune Diseases, CELLEX-IDIBAPS, Hospital Clínic, Barcelona, Barcelona, Spain, [2]Department of Autoimmune Diseases, IDIBAPS, Hospital Clínic, Barcelona, Spain, [3]University of Glasgow, Glasgow, United Kingdom, [4]Massachusetts Institute of Technology (MIT), Cambridge, MA, [5]Primary Care Research Group, Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Primary Care Centre Les Corts, CAPSBE, Barcelona, Spain, [6]Department of Pathology, Hospital Clínic, Barcelona, Spain
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Session Type: ACR Poster Session A
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Background/Purpose:

Sicca syndrome is a clinical presentation that is common for several systemic diseases that may infiltrate the exocrine glands. The most frequent disease is Sjögren's syndrome (SS), but other systemic diseases such as sarcoidosis, amyloidosis of IgG4-related disease may also infiltrate salivary glands. We analyzed the safety and usefulness of a new diagnostic tool for investigating minor salivary glands (minimally-invasive biopsy technique) in patients presenting with sicca syndrome.

Methods:

We present a prospective analysis of 200 patients presenting with sicca syndrome (defined by the presence of xerostomia and xerophthalmia, with positive results for ocular tests and/or parotid scintigraphy) in whom a minimally-invasive biopsy of minor salivary glands was carried out at a single center. For all biopsy samples, a cumulative focus score of lymphoplasmacytic infiltration was evaluated (Chisholm Mason score, CMs), together with investigation of other infiltrative processes caused by granuloma, amyloid, lipids or IgG4-positive cells.

Results:

All biopsies but two disclosed salivary gland tissue. Only 28 patients (14%) reported transient adverse events recovered completely during the first 24h. Histopathological diagnosis was available in 189 cases (158 women, 31 men, mean age 59 years): 44% of patients showed a non-specific chronic sialoadenitis (NSCS) (CMs=1-2), 21% focal lymphocytic sialoadenitis (FLS) suggestive of primary Sjögren syndrome (CMs=3-4), 12% chronic atrophic sialadenitis (CAS) (CMs unclassifiable), 18% normal glandular tissue (CMs=0) and other diagnosis in the remaining 4% (1 case of amyloidosis, 1 of sarcoidosis, 6 of lipoid infiltration and 1 salivary oncocytic cystadenoma); no patient had IgG4-related disease. The higher mean age was found in patients with CAS (69 years), followed by those with NSCS (59 years), those with FLS (57 years) and those with a normal result (54 years) ($p<0.001$). A higher frequency of FLS was found in patients with positive immunological markers including RF, anti-Ro, anti-La, hypocomplementemia and cryoglobulins ($p<0.05$). The percentage of patients diagnosed with Sjögren syndrome varied according to the concomitant systemic features: 13% of patients presenting with an isolated sicca syndrome had FLS in comparison with 32% of those who present with extraglandular involvement ($p<0.05$).

Conclusion:

We found sialoadenitis in nearly 80% of patients presenting with sicca syndrome. One quarter of these patients were diagnosed with Sjögren syndrome (focal lymphocytic sialadenitis). An older age was associated with a higher frequency of atrophic and chronic histopathological findings, while the presence of systemic features was associated with a higher frequency of focal lymphocytic sialadenitis. Only 1% of patients showed other systemic infiltrative diseases (one case of sarcoidosis, one of amyloidosis); no patient showed infiltration by IgG4+ cells.

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Abstract Number: 632

Isolated Atrioventricular Block of Unknown Origin in the Adult and Autoimmunity: Diagnostic and Therapeutic Considerations Exemplified By Three Anti-Ro/SSA-Associated Cases

Antonio Brucato[1], Pietro Enea Lazzerini[2], Pier Leopoldo Capecchi[3], Anna Valenti[4], Lucia Baldi[5], Maria Romana Bacarelli[3], Claudia Nucci[5], Valentina Moscadelli[3], Gabriella Morozzi[3], Mohamed Butjdir[6,7,8] and Franco Laghi Pasini[3], [1]Internal Medicine, Ospedale Papa Giovanni XXIII

Bergamo, Bergamo, Italy, [2]Department of Medical Sciences, Surgery and Neurosciences, University of Siena, Siena, Italy, [3]Medical Sciences, Surgery and Neurosciences, University of Siena, Siena, Italy, [4]Internal Medicine, Hospital Papa Giovanni XXIII, Bergamo, Italy, [5]Cardiology, University of Siena, Siena, Italy, [6]Medicine, Cell Biology and Pharmacology, State University of New York at Downstate Medical Center, New York, NY, [7]NYU School of Medicine, New York, NY, [8]Research Department, VA New York Harbor Healthcare System, New York, NY
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Session Time: 9:00AM-11:00AM

Background/Purpose: Circulating anti-Ro/SSA antibodies may rarely affect the adult conduction-system. A direct autoantibody-mediated electrophysiological inhibition of cardiomyocyte calcium-channels (*acquired form*) or an ante-natal subclinical injury induced by maternally-acquired anti-Ro/SSA with an autoantibody-independent worsening with age until a late diagnosis in the adulthood (*late progressive congenital form)* are the putative mechanisms involved.

Methods: We collected three clinical cases that provide further evidences of this view.

Results:

Case 1. A 29-years-old woman presented with chest pain and faintness. The ECG demonstrated the presence of III° atrioventricular block (AVB). The clinical history was negative except for autoimmune thyroiditis and subclinical positivity for anti-Ro/SSA A pacemaker was implanted but after methylprednisolone 40 mg/daily normal AV conduction was restored.

Case 2. A I°AVB with episodes of II°AVB and high-grade AVB was discovered in an asymptomatic 23-year-old woman who underwent routine screening. Her clinical history was negative. A previous ECG demonstrated that I°AVB was already present at 9 years of age. Anti-Ro/SSA were negative, but these antibodies were positive in the mother. A backup permanent pacemaker was implanted.

Case 3. A 21-year-old woman with autoimmune thyroiditis presented with III°AVB. The laboratory evaluation demonstrated a positive test for anti-Ro/SSA-52kD (immuno-Western blot), although FEIA testing was negative. Her mother was totally asymptomatic for connective tissue diseases (CTDs), but was found to be positive for anti-Ro/SSA-52kD (immuno-Western blot). Methylprednisolone 1 mg/Kg/day was initiated resulting in a rapid disappearance of III°AVB. At the interruption of the therapy 3 months after there was the reoccurrence of complete AVB, and again methylprednisolone rapidly restored normal AV conduction. The opportunity of implanting a pace-maker is under consideration.

Conclusion: these 3 cases provide an exemplification of the different forms of anti-Ro/SSA-associated AVB in adults. The patient 1 and patient 2 represent respectively a case of *acquired form* and a case as a *late progressive congenital form*. Finally, the patient 3 may represent a *mixed form*, in which both the above mechanisms have been involved. In conclusion a specific anti-Ro/SSA testing (ELISA + immuno-Western blot) in the patient and patient's mother may be diagnostic in rare adults with unexplained AVB, also in the absence of signs of CTDs; if anti-Ro/SSA are present, a prompt immunomodulating therapy may induce a rapid reversion of this life-threatening rhythm disturbance, thus avoiding or delaying pacemaker implantation.

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Abstract Number: 633

Anti-Centromere Antibodies Are Associated with More Severe Exocrine Glandular Dysfunction in Primary Sjögren's Syndrome: An Analysis of the Sjögren's International Collaborative Clinical Alliance Cohort

Alan N. Baer[1], Leah Medrano[2] and Mara McAdams-Demarco[3], [1]Division of Rheumatology, Johns Hopkins University School of Medicine, Baltimore, MD, [2]Medicine (Rheumatology), Johns Hopkins University School of Medicine, Baltimore, MD, [3]Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD
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Session Title: Sjögren's Syndrome Poster I: Clinical Insights into Sjögren's Syndrome
Session Type: ACR Poster Session A
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Background/Purpose: Anti-centromere antibodies (ACA) define a subgroup of Sjögren's syndrome (SS) patients who are often older, have more frequent Raynaud's phenomenon, and a lower frequency of anti-SSA and anti-SSB antibodies, hyperglobulinemia, rheumatoid factor, and leucopenia. We sought to determine whether the presence of ACA is associated with more severe impairment of exocrine glandular function in SS.

Methods: We obtained data on 3297 participants of the Sjögren's International Collaborative Clinical Alliance (SICCA) registry with suspected or established SS for whom there were complete data on the three objective criteria for SS (as defined by the ACR classification criteria). We identified 1361 who could be classified with SS by these criteria and who did not have a definite diagnosis of an underlying connective tissue disease by criteria extant at the time of SICCA registration. The presence of anti-centromere antibodies was determined by immunofluorescence on HEp-2 cells and was performed as part of the routine serologic evaluation of SICCA participants (Quest Diagnostics, Madison, NJ).

Results: ACA were present in 82 (6%) of the 1361 primary SS participants and were associated with an older median age (59 vs 52; p<0.0001), female gender (99 vs 93%; p=0.0379), and lower frequencies of anti-SSA and/or anti-SSB antibodies (29 vs 82%, p<0.0001), rheumatoid factor (39 vs 60%, p=0.0003), and IgG>1445 mg/dl (30 vs 58%). Median focus score was higher in the ACA (+) patients: 2.8 vs 2.5, p=0.0433). There was an increased frequency of Raynaud's phenomenon (62 vs 28%, p<0.0001), sclerodactyly (16 vs 1%, p<0.0001) and dilated nailfold capillary loops (20 vs 5%, p<0.0001) in the ACA (+) vs ACA (-) subjects. The 2013 Systemic Sclerosis classification criteria were fulfilled by 14/82 (17%) of the ACA (+) subjects. Exocrine gland function was worse in the ACA (+) compared to the ACA (-) subjects: Schirmer's test value (mean of both eyes): median 4.5 vs 6.5 mm/5 min, p=0.0002; unstimulated whole saliva flow rate: median 0.077 vs 0.367 ml/5 min, p<0.0001. In univariate analyses, duration of dry eye and dry mouth symptoms was not associated with ACA status. Individuals with ACA had an increased risk of UWSF<0.1 ml/min [OR=12.1 (95% CI, 4.9-40.7)] and Schirmer value <5 mm/5 min [OR=2.5 (95% CI, 1.5-4.4) after correcting for age, gender, presence of anti-SSA/SSB, and focus score.

Conclusion: ACA are uncommon in primary SS but define a subset characterized by more severe impairment of exocrine glandular function, in addition to older age and a lower frequency of anti-SSA/SSB antibodies, rheumatoid factor and hyperglobulinemia. This impairment of glandular function is independent of age, gender, focus score, and SSA/SSB serology. Although the majority have Raynaud's phenomenon, only a minority have sufficient other clinical features to satisfy the 2013 classification criteria for systemic sclerosis.

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Abstract Number: 634

Big Data International Primary Sjögren Syndrome Registry: Baseline Characterization and Diagnostic Approach in 6047 Patients Fulfilling the 2002 AE Criteria

Pilar Brito-Zerón[1], **Soledad Retamozo**[1,2], Margit Zeher[3], Astrid Rasmussen[4], Elke Theander[5], Jacques Gottenberg[6], Chiara Baldini[7], Luca Quartuccio[8], Roberta Priori[9], Valeria Valim[10], Marika Kvarnström[11], Aike Kruize[12], Gabriela Hernandez-Molina[13], Elena Bartoloni-Bocci[14], Sonja Praprotnik[15], David A. Isenberg[16], Gunnel Nordmark[17], Michele Bombardieri[18], Yasunori Suzuki[19], Roser Solans[20], Roberto Giacomelli[21], Daniel S. Hammenfors[22], Steven E. Carsons[23], Hendrika Boostma[24], Cristina F. Vollenweider[25], Fabiola Atzeni[26], Kathy Sivils[27], Thomas Mandl[28], Salvatore De Vita[29], Marie Wahren-Herlenius[11], Mitsuhiro Kawano[30], Roberto Gerli[31], Arjan Vissink[32], Johan G. Brun[33], Virginia Trevisani[34], Jorge Sánchez-Guerrero[35], Xavier Mariette[36], Manuel Ramos-Casals[1] and on behalf of the EULAR-SS Task Force, [1]Department of Autoimmune Diseases, CELLEX-IDIBAPS, Hospital Clínic, Barcelona, Barcelona, Spain, [2]Rheumatology Unit, Hospital Privado Centro Médico de Córdoba, Córdoba, Argentina, [3]University of Debrecen, Debrecen, Hungary, [4]Arthritis and Clinical Immunology Research Program, Oklahoma Medical Research Foundation, Oklahoma City, OK, [5]Skåne University Hospital Malmö, Lund University, Malmo, Sweden, [6]Hôpitaux Universitaires de Strasbourg, Strasbourg, France, [7]Rheumatology Unit, University of Pisa, Italy, Pisa, Italy, [8]Clinic of Rheumatology, Department of Medical and Biological Sciences (DSMB), Santa Maria della Misericordia Hospital, University of Udine, Udine, Italy, [9]Rheumatology Unit, Sapienza University of Rome, Rome, Italy, [10]Rheumatology, Universidade Federal do Espírito Santo, Vitória, Brazil, [11]Department of medicine, Rheumatology unit, Karolinska Institutet, Stockholm, Sweden, [12]Rheumatology and Clinical Immunology, University Medical Center Utrecht, Utrecht, Netherlands, [13]Immunology and Rheumatology, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico city, Mexico, [14]Department of Medicine, Rheumatology Unit, University of Perugia, Perugia, Italy, [15]Department of Rheumatology, University Medical Centre Ljubljana, Ljubljana, Slovenia, [16]Rayne Institute, Centre for Rheumatology Research, UCL Division of Medicine, London, United Kingdom, [17]Medical Sciences, Uppsala University, Uppsala, Sweden, [18]Experimental Medicine and Rheumatology, Queen Mary University of London, London, United Kingdom, [19]Kanazawa University Graduate School of Medicine, Kanazawa, Japan,

[20]Department of Internal Medicine, Hospital Vall d'Hebron, Barcelona, Spain, [21]University of L'Aquila, L'Aquila, Italy, [22]Department of Rheumatology, Haukeland University Hospital, Bergen, Norway, [23]Rheumatology, Allergy and Immunology, Winthrop University Hospital, Mineola, NY, [24]University of Groningen, University Medical Center Groningen, Groningen, Netherlands, [25]Rheumatology, German Hospital, Buenos Aires, Argentina, [26]Rheumatology Unit, L. Sacco University Hospital of Milan, Milan, Italy, [27]Oklahoma Medical Research Foundation, Oklahoma City, OK, [28]Dept of Rheumatology, Skåne University Hospital Malmö, Lund University, Malmo, Sweden, [29]Santa Maria della Misericordia Hospital, University of Udine, Udine, Italy, [30]Division of Rheumatology, Kanazawa University Graduate School of Medicine, Kanazawa, Japan, [31]University of Perugia, Perugia, Italy, [32]Department of Oral and Maxillofacial Surgery, University of Groningen, University Medical Center Groningen, Groningen, Netherlands, [33]Haukeland University Hospital, Bergen, Norway, [34]Health Evidence Based, Universidade Federal de São Paulo, São Paulo, Brazil, [35]Rheumatology, Mount Sinai Hospital and University Health Network, Toronto Canada, Toronto, ON, Canada, [36]Université Paris-Sud, AP-HP, Hôpitaux Universitaires Paris-Sud, Paris, France
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Background/Purpose:

To analyse the epidemiological, clinical and immunological characteristics at diagnosis of the largest international cohort of patients diagnosed with primary Sjögren syndrome (SS) according to the 2002 AE classification criteria.

Methods:

The Big Data Sjögren Project is an international, multicentre registry formed in 2014 to take a “high-definition” picture of the main features of primary SS at diagnosis by merging international SS databases. International experts participating in the EULAR-SS Task Force were invited to participate. By June 2015, the database included 6120 consecutive patients recruited from 14 countries (Europe, America and Japan), of whom 6047 fulfilled the 2002 classification criteria for primary SS (some diagnostic tests are pending in the remaining patients). The main features at diagnosis (time of criteria fulfilment) or at recruitment were collected and analysed.

Results:

Of the 6047 patients, 5648 (93.4%) were women and 399 (6.6%) were men (female:male ratio, 14:1), with a mean age at diagnosis of primary SS of 49.96 years (range, 5-97), of which 79% were Caucasian and 81% from European countries. The frequency of fulfilment of the 2002 criteria was: 94.1% for dry eye, 93.6% for dry mouth, 88.3% for positive salivary gland biopsy, 86% for positive ocular tests, 79.1% for positive oral tests and 72.2% for positive Ro/La autoantibodies. With respect to the criteria fulfilled, 10.6% fulfilled 3 criteria, 30.6% 4 criteria, 40.7% 5 criteria and 18% all 6 criteria. The percentage of diagnostic tests performed varied from 70% to nearly 100%: Ro/La autoantibodies were tested in 99.5% of patients, ocular diagnostic tests (Schirmer’s test and/or corneal stainings) in 89.7%, oral tests in 81.3% and salivary gland biopsy in 71.8% of patients. The four diagnostic tests included in the 2002 AE criteria were made (complete diagnostic approach) in 3459 (57%) patients, while in the remaining 2588 (43%), only two or three tests were made (incomplete diagnostic approach). A complete diagnostic approach was more frequent in patients from non-European countries (73% vs 55%, $p<0.001$), Ro/La negative patients (79% vs 50%, $p<0.001$), ANA-negative patients (75% vs 57%, $p<0.001$), RF-negative patients (66% vs 55%, $p<0.001$) and patients with normal C3/C4 values (74% vs 59%, $p<0.001$).

Conclusion:

In the largest cohort of primary SS patients diagnosed homogeneously according to the 2002 AE criteria, a full diagnostic evaluation was made in less than 60% of patients. In addition, the diagnostic approach was heterogeneous and varied according to the geographical area and the baseline immunological profile; in contrast, gender and age did not influence the number of diagnostic tests made to achieve fulfilment of the criteria.

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Abstract Number: 635

Seronegative Sjögren's Syndrome Is Associated with a Higher Frequency of Patient-Reported Neuropathic Pain: An Analysis of the Sjögren's International Collaborative Clinical Alliance Cohort

Alan N. Baer[1] and Julius Birnbaum[2], [1]Division of Rheumatology, Johns Hopkins University School of Medicine, Baltimore, MD, [2]Medicine (Rheumatology), Johns Hopkins University School of Medicine, Baltimore, MD

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Session Date: Sunday, November 8, 2015

Session Title: Sjögren's Syndrome Poster I: Clinical Insights into Sjögren's Syndrome

Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose: Patients with Sjögren's syndrome (SS) and negative SSA/SSB serology (ie. seronegative SS) have phenotypic characteristics different than seropositive ones, and thus may constitute a disease subset with a unique pathogenesis. Since these patients are older and have a lower frequency of hypergammaglobulinemia, rheumatoid factor, hypocomplementemia, they might be expected to have a more benign phenotype. However, recent reports highlight that these patients have more severe pain and a higher frequency of small fiber sensory neuropathy. We sought to determine if self-reported neuropathic pain was more prevalent among primary SS participants of the Sjögren's International Collaborative Clinical Alliance (SICCA).

Methods: We obtained data on 3297 participants (pts) of the SICCA registry with suspected or established SS for whom there were complete data on the three objective criteria for SS (as defined by the ACR classification criteria). We identified 1361 who could be classified with SS by these criteria and who did not have a definite diagnosis of an underlying connective tissue disease. Responses of each pt to written questions regarding the presence and frequency of neuropathic pain symptoms were analyzed; these questions were adapted from validated tools for this purpose.

Results: SSA/SSB serology was positive in 1071 and negative in 290 of the primary SS participants. Reports of painful dysesthesia were higher in the seronegative SS pts: "persistent or frequent burning discomfort" (27 vs 18%, p=0.0006; χ^2); "sharp 'jabbing' needle-like pain" (37 vs 28%, p=0.0038), and "more or less continuous 'prickling' or 'tingling' feeling" (40 vs 35%, p=0.0846). In contrast, there were no differences in reports of decreased ability to feel surface features, pain/cuts/injuries, and hot from cold. Depression, assessed by responses to the PHQ-9 questionnaire, was more frequent in the seronegative SS pts (scores≥10, 32 vs 22%, p=0.0004). In a multivariate analysis, we found that pts who reported dysesthetic neuropathic pain were 1.6 times more likely to have negative SSA/SSB serology (95% CI 1.1-2.2; p=0.013) than those with positive serology, after controlling for age, gender, ethnicity, duration of dry eye and dry mouth, and depression.

Conclusion: Self-report of neuropathic pain is more prevalent in seronegative primary SS, a finding which is independent of age, gender, ethnicity, duration of sicca symptoms, and concomitant depression. Although our findings need to be verified with validated neuropathic pain scales, they suggest that seronegative SS has a pathogenesis unique from that of seropositive SS.

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Abstract Number: 636

Utility of IgA Anti-Alpha-Fodrin Antibodies in Combination with Rheumatoid Factor and/or Antinuclear Antibodies As Substitute Immunological Criterion for Sjögren's Syndrome

Gabriela Hernandez-Molina[1], Carlos Núñez-Álvarez[2], Juanita Romero-Diaz[1], Carmen Ávila-Casado[3], Carlos Hernández-Hernández[4], Maria Luisa Calderillo[4], Martha Marroquín[4], Claudia Recillas-Gispert[5] and Jorge Sánchez-Guerrero[6], [1]Immunology and Rheumatology, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico city, Mexico, [2]Immunology and Rheumatology, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico, [3]Pathology, University Health Network, Toronto Canada., Toronto, ON, Canada, [4]Dental Service, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico city, Mexico, [5]Ophtalmology, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico city, Mexico, [6]Rheumatology, Mount Sinai Hospital and University Health Network, Toronto Canada, Toronto, ON, Canada

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Background/Purpose: Anti-SSA/SSB antibodies represent the most specific serologic marker of Sjögren's syndrome; however, in up to 30% of SS patients the test is negative. Anti-alpha-fodrin (AFA) antibodies have been associated with SS; thus, we aimed to evaluate the utility of AFA antibodies in combination with RF and/or ANA as alternative immunological criterion in SS.

Methods: 350 patients (100 each diagnosed with RA, SLE, and scleroderma, each, according to current classification criteria, and 50 with clinical diagnosis of primary SS) were selected from our patient registry and assessed for SS using a structured approach. All patients were tested for ANA, RF, anti-SSA/SSB, and AFA antibodies. *Diagnosis of SS* was made on clinical basis by two rheumatologists with expertise in SS who independently evaluated every patient considering the results of the 6-item screening questionnaire, history of parotid enlargement, Schirmer-I test, Wafer test, NSWSF rate, fluorescein staining test, autoantibodies, lip biopsy, medical notes from Ophthalmology and Oral Medicine, and medical chart review. *Non-SS diagnosis* was defined as lack of clinical diagnosis and not fulfilling either AECG and/or ACR criteria. *Statistical analysis.* We focused on patients testing negative for anti-SSA and/or anti-SSB antibodies. The 2012 ACR SS criteria were applied to each study participant substituting the immunological criterion as follows: 1) RF plus ANA >1:320, 2) RF plus AFA, 3) ANA plus AFA, 4) RF alone, and 5) Two positive tests out of RF, ANA >1:320, or AFA. We estimated the sensitivity (SN), specificity (SP), positive predictive value (PPV), negative predictive value (NPV), and positive likelihood-ratio with 95% CI, for each criterion item.

Results: 236 (67%) patients tested negative for anti-SSA/SSB antibodies, of whom 65 (27.5%) were clinically diagnosed as SS, and 149 (63%) with non-SS. The performance of ACR criteria using diverse substitute immunological criterion is shown in the table. RF + AFA, and ANA + AFA performed similarly as RF + ANA >1:320 as substitute immunological criterion. Although RF + ANA >1:320 performed well, incorporating AFA improved the number of SS patients classified by the ACR criteria. Particularly, the model 2 out of RF, ANA, or AFA, improved the sensitivity of 2012 ACR SS Criteria to capture SS patients with negative anti-SSA and/or anti-SSB serology from 37 to 46 out of 65 patients studied.

Conclusion: RF plus AFA, and ANA plus AFA antibodies performed similarly as RF plus ANA >1:320, as a substitute immunological criterion in patients with SS with negative anti-SSA/SSB serology. However incorporating AFA to RF and ANA >1:320 in a 2 out of 3 model improves the sensitivity to capture SS patients with negative anti-SSA/SSB serology. This improvement will benefit clinical studies and clinical trials in SS.

Immunological Criterion	SN 95% CI	SP 95% CI	PPV 95% CI	NPV 95% CI	LR+ 95% CI	LR- 95% CI
FR + ANA >1:320	56.9 44-69.1	93.9 88.8-97.2	80.4 66.2-90.6	83.3 76.8-88.6	9.4 4.8-18.3	0.46 0.35-0.61
FR + AFA	61.5 48.6-73.3	88.5 82.3-93.2	70.1 56.6-81.5	84.0 77.4-89.4	5.3 3.3-8.7	0.43 0.32-0.59
AFA+ANA >1:320	64.6 51.7-76.8	85.9 79.2-91.0	66.6 53.6-78.1	84.7 78.2-90.3	4.5 2.9-7.1	0.41 0.29-0.56
RF alone	33.8 22.5-46.5	87.2 80.8-92.1	53.6 37.4-69.3	53.6 37.4-69.3	2.6 1.55-4.5	0.76 0.63-0.91
Two out of three FR,ANA>1:320 or AFA	70.7 58.1-81.4	78.5 71.0-84.8	58.9 47.2-69.9	86.0 78.3-91.3	3.3 2.33-4.6	0.37 0.25-0.55

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Abstract Number: 637

Repeated B Lymphocyte Depletion Therapy with Rituximab in Sjögren's Syndrome: A Single Center Experience

Francesco Ferro[1], Chiara Baldini[1], Nicoletta Luciano[1], Maurizio Mazzantini[1], Daniela Martini[1], Sara Galimberti[2], Valentina Donati[3], Marta Mosca[4] and Stefano Bombardieri[1], [1]Rheumatology Unit, University of Pisa, Italy, Pisa, Italy, [2]Hematology Unit, University of Pisa, Italy, Pisa, Italy, [3]Department of Pathology, AOUP, Pisa, Italy, Pisa, Italy, [4]University of Pisa, Pisa, Italy

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Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose: Recent insights from open studies and randomized clinical trials have shown the effectiveness of Rituximab (RTX) in controlling disease activity, patients' subjective symptoms and patient-reported outcomes in primary Sjögren's syndrome (SS). To date, only few cases of patients with SS undergoing repeated B lymphocyte depletion courses with RTX have been described. Aim of this study was to assess safety and efficacy of repeated B-cell depletion with RTX in patients with primary SS.

Methods: Out of an inception cohort of 378 patients (AECG 2002) we selected those subjects who had been treated with multiple courses of RTX on the basis of disease activity and/or lymphoproliferative complications. In addition to patients' demographics, clinical and serological features, we retrieved the following information: indication for RTX therapy, previous and concomitant treatments, number of RTX courses, regimens, time to re-treatment, changes in the ESSDAI, in lab and serology tests and adverse events.

Results: Out of 17 SS patients who had been treated with RTX, we identified 5 female who had received repeated B lymphocyte depletion therapy. Patients had median age of 60 years (range31-65) and median disease duration of 36 months (range 12-120). All the patients were positive for antinuclear antibodies, anti-Ro/SSA and Rheumatoid Factor (RF); 2/5 (40%) had also a positivity for anti-La/SSB and cryoglobulins. HCV antibody test resulted negative in all patients. Initial indications for RTX included: MALT non-Hodgkin's lymphoma (NHL) (3/5), central and peripheral nervous involvement (pns)(1/5) and diffuse skin vasculitis (1/5). Three patients received 2 cycles of RTX, 1 received 3 cycles and 1 received 4 cycles. Indications for re-treatment included: MALT lymphoma recurrence (1/5) and/or increased disease activity in the other cases. Median ESSDAI before RTX re-treatment was 11 (range 6-13) with patients presenting mainly enlargement of major salivary glands, reactive lymphoadenopathy, skin vasculitis, neuropathy and glomerulonephritis. Moreover, all patients presented low C3/C4 levels, and/or hypergammaglobulinemia and/or cryoglobulins. Three patients presented a high titer of RF and 2/5 had a moderate lymphopenia. Each course consisted of 1 g RTX intravenous (IV) on days 1 and 15 or 375 mg/m2 IV once weekly for 4 doses. Median interval between courses was 9 months (range 8-48). Multiple courses of RTX resulted in significant improvement of the ESSDAI and IgG levels compared with baseline ($p<0.05$). Despite not statistically significant, we also observed beneficial effects on C3, C4, RF and ESR. Retreatment with RTX was well-tolerated. None of the patients developed mild serum-sickness-like disease. Infectious events included: recurrent urinary tract infection (2/5), skin infection (1/5) and Herpes Zoster reactivation (1/5). Falls in total Ig levels occurred in one patient requiring Ig replacement therapy.

Conclusion: Repeated B-lymphocyte depletion over a median 36-months period appears to be an acceptable and relatively well-tolerated therapy in SS. Further studies are needed to investigate optimal indications and timing of retreatment of RTX in SS patients.

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Abstract Number: 638

Assessment of Myocardial Abnormalities in Primary Sjögren Syndrome Using a Comprehensive Cardiac Magnetic Resonance Approach

Natsumi Ikumi[1], Hitomi Kobayashi[2], Yasuyuki Kobayashi[3], Hirotake Inomata[4], Yosuke Nagasawa[4], Kaita Sugiyama[4], Hiromi Karasawa[1], Takamasa Nozaki[4], Hidetaka Shiraiwa[4], Mitsuhiro Iwata[2], Noboru Kitamura[5], Yoshihiro Matsukawa[1] and Masami Takei[2], [1]Division of Heamatology and Rheumatology, Nihon University School of Medicine, Tokyo, Japan, [2]Division of Hematology and Rheumatology, Nihon University School of Medicine, Tokyo, Japan, [3]Advanced Biomedical Imaging Informatics, St.Marianna University School of Medicine, Kawasaki, Japan, [4]Nihon University School of Medicine, Tokyo, Japan, [5]NIhon University School of Medicine, Tokyo, Japan

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Background/Purpose: Primary Sjögren syndrome (pSS) shares many clinical, inflammatory, and immunological features with rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE). SLE and RA are characterized by a high risk of cardiac involvement. However, there are limited data on the risk of overt cardiac involvement in pSS. We sought to use a cardiac magnetic resonance imaging (CMR) approach to assess cardiac involvement and determine its association with disease characteristics in pSS patients without cardiac symptoms.

Methods: Consecutive pSS patients, according to ACR classification criteria (2012), without a history or clinical findings of hypertension, cardiovascular disease, diabetes, or dyslipidemia underwent contrast CMR. Late gadolinium enhancement (LGE) was obtained for the assessment of myocardial fibrosis. Using a black-blood T2-weighted image (T2-WI), myocardial inflammation could be assessed. Sjögren syndrome disease activity index (ESSDAI) was determined. Eighty percent patients had documentation of a minor salivary gland biopsy. Salivary gland biopsy data were classified by focus score (FS). We investigated the patients in terms of prevalence of CMR abnormalities and explored possible associations between CMR abnormalities and pSS disease characteristics.

Results: Thirty-six female pSS patients were enrolled (mean age: 55.9 ± 7.1 years). On average, cardiovascular risk was low for the group, with patients demonstrating no ECG abnormalities, and the patients had generally low traditional cardiovascular risk factors, with a mean Framingham 10-year hard cardiovascular risk score of 4% ± 2%. The mean ESSDAI was 3.5 ± 2.1. Twelve pSS patients (33%) demonstrated myocardial abnormalities. T2-WI was seen in 4 pSS patients (11%). LGE was found in 11 pSS patients (30%), 3 of whom also demonstrated T2-WI. The main finding observed in 7 of these 11 patients (63%) was a linear pattern without coronary distribution. A patchy nodular enhancement pattern was observed in 4 patients (36%). Compared with LGE- and T2-WI-negative patients, LGE- and T2-WI-positive patients showed no significant difference related to ESSDAI. Anti-SSB antibodies were significantly higher in LGE-positive than LGE-negative patients ($p = 0.002$). Raynaud phenomenon was significantly associated with LGE- and T2-WI-positive patients ($p = 0.006$ and $p = 0.04$, respectively). Other pSS characteristics such as disease duration, commodities, and cardiovascular risk factors were not significantly associated with myocardial abnormalities. The greatest relative difference between LGE-positive and -negative patients was observed in focus score ≥ 3, with an adjusted odds ratio of 3.0. After adjusting for confounding by age, pSS duration, and anti-SSB antibodies, the association of LGE with Raynaud phenomenon remained significant ($p = 0.023$).

Conclusion: Subclinical myocardial involvement, as detected by cardiac MRI, was frequent in pSS patients without cardiac symptoms. Our results suggest that Raynaud phenomenon has a role in promoting cardiac involvements in patients with pSS.

Disclosure: N. Ikumi, None; **H. Kobayashi**, None; **Y. Kobayashi**, None; **H. Inomata**, None; **Y. Nagasawa**, None; **K. Sugiyama**, None; **H. Karasawa**, None; **T. Nozaki**, None; **H. Shiraiwa**, None; **M. Iwata**, None; **N. Kitamura**, None; **Y. Matsukawa**, None; **M. Takei**, None.

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Abstract Number: 639

Association Between Insomnia and EULAR Sjögren's Syndrome Patient-Reported Index in Korean Patients with Primary Sjögren's Syndrome

Jaehyung Hur[1], Sang Wan Chung[1], You Jung Ha[2], Eun Ha Kang[3], Yeong Wook Song[4] and Yun Jong Lee[5], [1]Division of Rheumatology, Department of Internal Medicine, Seoul National University Bundang Hospital, Seongnam-si, South Korea, [2]Division of Rheumatology, Department of Internal Medicine,Seoul National University Bundang Hospital, Seongnam, South Korea, [3]Department of Internal Medicine, Seoul National University Bundang Hospital, Seongnam-si, South Korea, [4]Division of Rheumatology, Department of Internal Medicine, Seoul National University Hospital, Seoul, South Korea, [5]Internal Medicine, Seoul National University Bundang Hospital, Seongnam-si, South Korea

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Background/Purpose: EULAR Sjögren's syndrome Patient-Reported Index (ESSPRI) is an index to evaluate symptom severity and recommended

as an efficacy measure for clinical trials in primary Sjögren's syndrome (pSS) patients. The prevalence of sleep disturbance has reportedly increased in pSS and sleep disturbance could affect pSS symptom severity. However, the association between insomnia and ESSPRI in pSS has not been reported.

Methods: Forty-three pSS patients, who fulfilled the American-European Consensus Group (AECG) criteria, consecutively were enrolled. The patients completed questionnaires on quality of life (EQ5D), ESSPRI, insomnia (Insomnia Severity Index, ISI), sleep quality (Pittsburgh Sleep Quality index, PSQI), fatigue (Fatigue Severity Score, FSS), and depression (Korean Beck Depression Inventory, KBDI). Additionally, they were evaluated by 100 mm-VAS scale for patient global assessment (PGA), oral or eye dryness, eyeball pain, and anxiety. Data were also collected on demographic, clinical, and laboratory variables.

Results: Among 43 pSS patients, 10 (23.3%) had clinical insomnia (ISI>14) and 24 (55.8%) had no sleep disturbance (ISI<8). Patients with clinical insomnia had significantly higher ESSPRI (p=0.005), scores for FSS and KBDI (both p<0.01), and VAS levels for dry eye, eyeball pain, anxiety, and PGA (all p<0.05) than those without clinical insomnia. Furthermore, they had significantly lower EQ5D score (p=0.005). ISI was significantly correlated with ESSPRI, scores of EQ5D, FSS, and KBDI, and VAS levels of oral or eye dryness, nocturnal xerostomia, eyeball pain, anxiety, and PGA (all p<0.05). The distribution of ISI was significantly different according to tertiles of ESSPRI (p<0.05, Figure 1). When high levels were defined by the upper tertile of each continuous variables or according to the cuff off points for ISI, KBDI, and FSS, a logistic regression analysis showed that high ESSPRI was significantly associated with high PGA (p<0.01, OR 10.3) and clinical insomnia (p<0.05, OR 12.5, Table 1).

Conclusion: Our results suggest that clinical insomnia is able to independently affect ESSPRI levels and insomnia symptom might be a target to improve ESSPRI levels in pSS patients.

Table 1. Logistic regression analysis of the association of between high ESSPRI (defined as the highest tertile) and clinical insomnia

	Beta	Odds ratio	95% CI	P value
High PGA* for pSS	2.330	10.28	1.88 – 56.16	0.007
Clinical insomnia	2.522	12.45	1.72 – 89.94	0.012

*, high PGA was defined as the highest tertile.

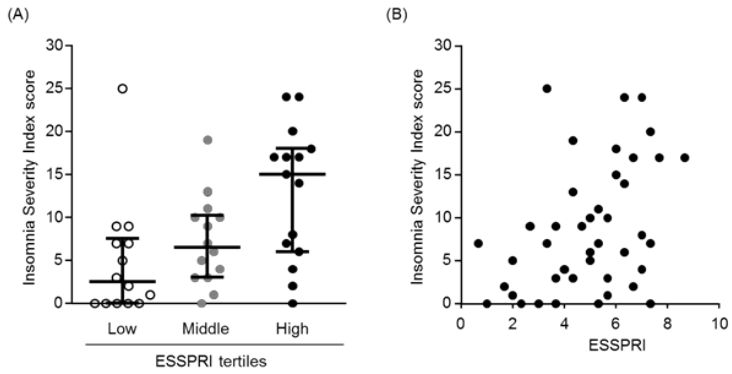

Figure 1. The association between Insomnia Severity Index (ISI) and ESSPRI. (A) ISI scores increased according to tertiles of ESSPRI in pSS patients. P value was calculated by Kruskal-Wallis test. (B) Scatter plot showed a positive correlation between ESSPRI and ISI in pSS patients. P value was calculated by Spearman's correlation.

Disclosure: J. Hur, None; **S. W. Chung**, None; **Y. J. Ha**, None; **E. H. Kang**, None; **Y. W. Song**, None; **Y. J. Lee**, None.

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Abstract Number: 640

Sjögren's Syndrome in Male Patients Presents with Higher Autoantibody Levels and More Extraglandular Manifestations

Jorge Ramírez[1,2], Marika Kvarnstrom[2,3] and Marie Wahren-Herlenius[1,2], [1]Department of Medicine, Karolinska Institutet, Solna, Sweden, [2]Department of Medicine, Experimental Rheumatology Unit, Solna, Sweden, [3]Department of Medicine, Unit of Rheumatology, Karolinska Institutet, Karolinska University Hospital, Stockholm, Sweden

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Background/Purpose:

Primary Sjögren's syndrome (pSS) and SLE are chronic autoimmune diseases that predominantly affect women, with a female:male ratio of approximately 9:1. SLE in men is more severe than in women, but studies of sex-related clinical features in pSS have given ambiguous results. In this study, we therefore investigated the clinical presentation of pSS in men and women in a cohort of pSS at time of diagnosis, all treatment naïve cases collected in a population-based manner during a 5-year period.

Methods:

Patients represent incident cases of pSS in Stockholm County from January 1, 2007 to December 31, 2011, and were diagnosed at the Department of Rheumatology at the Karolinska University Hospital, Stockholm, Sweden (women n=136, men n=10). Patients were examined according to an established protocol including clinical and laboratory investigations and all fulfilled the 2002 revised American–European Consensus Criteria (AECC). Extraglandular manifestations (EGM) were defined as those included in the EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI). Serum was sampled at the time of diagnosis, anti-Ro52 levels were measured by ELISA and a cut off at 80 AU was used for categorization into high and low levels. The Chi-square test was used for analyzing frequencies of patient subgroups and prevalence of EGM, and the Mann-Whitney U-test was used when comparing autoantibody levels and age at diagnosis between female and male patients with pSS.

Results:

Male patients were younger at the time of pSS diagnosis than female patients (48.0 ±12.2 versus 57.0 ±14.1, p=0.04). No difference was observed for frequencies of Ro and La autoantibodies, but male patients with pSS displayed a tendency towards higher Ro52-autoantibody levels (p=0.06), and more male patients had high levels (p=0.03). Notably, cutaneous vasculitis was more common in male patients with pSS (p<0.001), and pulmonary disease in terms of interstitial lung disease and alveolitis occurred more often in male patients with pSS (p<0.001 and p<0.001). No EGM was more common in female pSS patients. Further, concomitant presentation of EGM was more common in male than in female patients (p=0.02).

Conclusion:

There are differences in the clinical presentation of pSS between the sexes. Our study, based on a cohort of incident, treatment naïve cases collected in a population-based manner during a 5-year period, indicates that disease onset is earlier in men, and that the immune-activity is higher. Importantly, half of the male patients presented one or more EGM at diagnosis, supporting the conclusion that pSS in men represents a more severe form of disease, regardless of the lower risk for males to develop the disease.

Disclosure: J. Ramírez, None; **M. Kvarnstrom**, None; **M. Wahren-Herlenius**, None.

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Abstract Number: 641

Pain, Xerostomia and Younger Age Are Major Determinants of Fatigue in Korean Primary Sjögren's Syndrome Patients: A Comprehensive Analysis of a Cohort Study

JungHee Koh[1], Seung-Ki Kwok[2], Min Kyung Chung[3], Jennifer Lee[3], Ji Yeon Lee[4] and Sung-Hwan Park[3], [1]Seochogu, Banpodaero, 222, Division of Rheumatology, Department of Internal Medicine, College of Medicine, Seoul St. Mary's Hospital, The Catholic University of Korea, Seoul, South Korea, [2]seungki73@catholic.ac.kr, Division of Rheumatology, Department of Internal Medicine, College of Medicine, The Catholic University of Korea, Seoul, South Korea, [3]Division of Rheumatology, Department of Internal Medicine, College of Medicine, Seoul St. Mary's Hospital, The Catholic University of Korea, Seoul, South Korea, [4]Division of Rheumatology, Department of Internal Medicine, College of Medicine, The Catholic University of Korea, Seoul, South Korea

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Background/Purpose: Fatigue is a common clinical manifestation in patients with primary Sjögren¡¯s syndrome (PSS). The aims of this study were to investigate the association between fatigue severity and other clinical characteristics in PSS patients and to determine the factors contributing to fatigue.

Methods: We analyzed 219 participants from the Korean Initiative of PSS (KISS) prospectively. The KISS was formed in 2013 with the aim of establishing a nationwide prospective cohort to obtain overall clinical data and samples from PSS patients and to develop diagnostic and treatment tools for PSS. All participants fulfilled the 2002 American-European Consensus group and/or the 2012 American College of Rheumatology classification criteria. Fatigue was assessed according to the fatigue domain of the European League Against Rheumatism Sjögren¡¯s Syndrome Patient-Reported Index (ESSPRI). Health related quality of life (HRQOL) was evaluated using the EuroQol-5 dimension (EQ-5D). Multiple linear regression analysis was used to estimate the effect of each variable on fatigue severity.

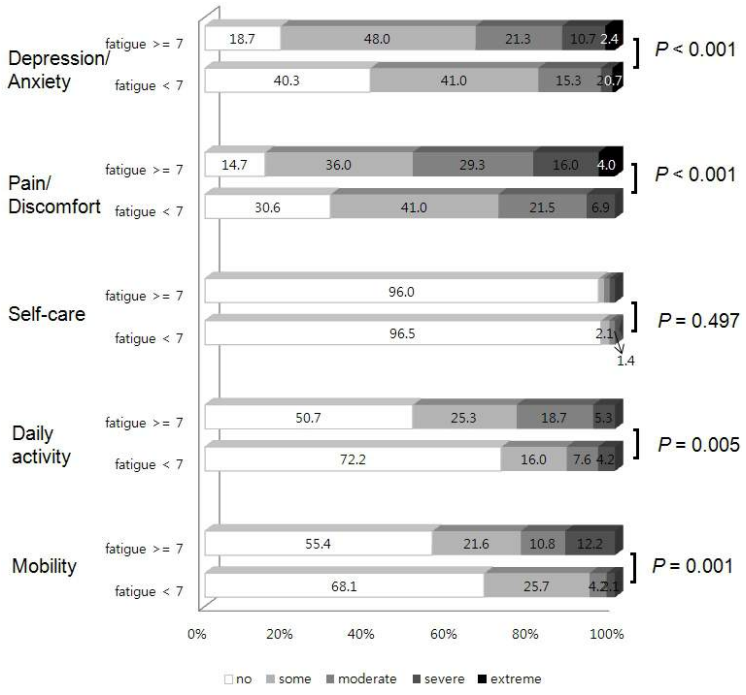
Results: The median age of all participants was 54 (IQR, 46–60) years and a median PSS duration was 2.3 (IQR, 0.5–5.4) years were included in the study. The median total ESSPRI score was 5 (interquartile range, 4–6). Thirty-four percent of patients reported a fatigue score >= 7. Younger and premenopausal patients presented with more fatigue (P = 0.028 and < 0.001, respectively). A higher xerostomia inventory score (*P* < 0.001) and Ocular Surface Dryness Index (*P* < 0.001) were observed in patients with a fatigue score >= 7. Pain, xerostomia inventory and age were determined to be significantly associated with fatigue severity after adjusting for depression/anxiety by multivariate linear regression analysis (Table 1). The median EQ-5D TTO value was 0.85 (IQR, 0.78–0.91), and the median EQ-5D VAS score was 70 (IQR, 50–80). PSS patients with a fatigue score >= 7 were associated with worse mobility, daily activity, pain/discomfort, and depression/anxiety EQ-5D scores (*P* < 0.001) (Figure 1). Moderate correlations were detected between fatigue and EQ-5D TTO values (*rho* = -0.397, *P* < 0.001) and the EQ-5D VAS score (*rho*= -0.311, *P* < 0.001).

Conclusion: In Korean patients with PSS, younger age, xerostomia, and pain were all found to increase the risk of fatigue, and fatigue was significantly associated with HRQOL.

Table 1. Stepwise multiple regression models of ESSPRI fatigue score and its predictors

Variables	Estimate (SE)	Standardized estimate (¥â)	p-value	R^2
ESSPRI pain	0.377 (0.053)	0.435	<0.001	0.205
Xerostomia Inventory	0.045 (0.018)	0.164	0.003	0.238
Age	-0.039 (0.013)	-0.177	0.002	0.272
Ocular Surface Dryness Index	0.013 (0.007)	0.123	0.053	0.305
Intercept	6.730 (1.412)	0	<0.001	

Figure 1. Health status according to the EQ5D of the KISS cohort and its comparison between patients with an ESSPRI fatigue score ¡Ã 7 versus < 7.



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Abstract Number: 642

Assignable Causes for Fatigue in Primary Sjögren's Syndrome: Data from the UK Primary Sjögren's Syndrome Registry

Rebecca L Lambson[1], Ben Hargreaves[2], Dennis W Lendrem[2], Victoria Hindmarsh[3], Claire Humphrey[3], Sheryl Mitchell[3], Bridget Griffiths[4], Simon Bowman[5], UKPSS Registry[6] and **Wan-Fai Ng**[7], [1]Newcastle University, Medical School, Newcastle upon Tyne, United Kingdom, [2]Institute of Cellular Medicine (Musculoskeletal Research Group), NIHR Newcastle Biomedical Research Centre, Newcastle Hospitals Foundation Trust and Newcastle University, Newcastle upon Tyne, United Kingdom, [3]Freeman Hospital, Newcastle upon Tyne, United Kingdom, [4]Rheumatology, Freeman Hospital, Newcastle Upon Tyne, United Kingdom, [5]Rheumatology Dept, University Hospital Birmingham, Birmingham, United Kingdom, [6]Newcastle University, Newcastle upon Tyne, United Kingdom, [7]NIHR Newcastle Biomedical Research Centre, Newcastle University, Newcastle upon Tyne, United Kingdom

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Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose:

Fatigue is frequently reported as an important symptom in need of management by patients with Primary Sjögren's Syndrome (SS) [1-3]. It can be severe, having a major effect on quality of life, but many patients report that their fatigue is not always well managed [3, 4]. Furthermore, PSS patients often present with complex multiple co-morbidities, but, until now no analysis of assignable causes of fatigue has been attempted in this patient group. This study attempts to identify the aetiology of fatigue in a large cohort of PSS patients.

Methods:

We studied fatigue in 795 PSS patients from the UK Primary Sjögren's Syndrome Registry. All patients met the American-European Consensus Group criteria [5] for PSS. The objective of the study was to identify assignable causes of fatigue in PSS patients. The following conditions were considered potentially treatable conditions that can cause fatigue independent of PSS: thyroid disease, diabetes mellitus, celiac disease, significant anaemia (Hb<10), and depression. Medications that can cause drowsiness (e.g. antipsychotics) were also included in the analysis.

Results:

43% (n=340) of patients had assignable cause(s) other than PSS for their fatigue. Of these, 50% (n=172) had hypothyroidism or abnormal TSH, 8% (n=28) had depression, 6% (n=20) had celiac disease, 6% (n=20) had non-insulin-dependent-diabetes, 2% (n=7) had insulin-dependent-diabetes, and 2% (n=7) had significant anaemia. Concurrent medications ranged from 0-26 with 50% (n=169) of the cohort with an assignable cause for their fatigue taking medications that can cause drowsiness. 78% (n=266) of these patients had 1 assignable cause for their fatigue apart from SS, 19% (n=64) had 2 assignable causes and 3% (n=10) had 3.

Having said this, the fatigue in the majority of patients in this study cohort was unassignable (57%, n=455). There were few other tangible differences between those with an assignable cause for their fatigue to those without. The number of pSS medications prescribed ranged from 0-8, with 56% (n=444) of the total cohort taking at least 1 medication. 601 patients from the entire cohort (n=795) were classed as having "abnormal fatigue" (score of >2 on the profile of fatigue score), of those with an assignable cause for their fatigue 82% (n=279) had "abnormal fatigue" compared to 71% (n=322) patients whose cause of fatigue is unknown. Physical fatigue was ranked as the first or second most important symptom in need of improvement by 71% (n=243) patients with an assignable cause for their fatigue and 69% (n=316) in those without an assignable cause for their fatigue.

Conclusion:

Overall, 70% of PSS patients rate their fatigue as one of the most important symptoms needing improvement demonstrating the need for fatigue management. A significant proportion (43%) of PSS patients have assignable causes for fatigue other than PSS. Fatigue management is critical to patients with PSS, therefore, screening for and appropriate management of any other assignable causes of patients' fatigue is important. However, the majority of PSS patients with fatigue have no obvious assignable causes, further investigation into the biological basis of fatigue in PSS is necessary.

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Abstract Number: 643

Ethnicity of Sjögren's Syndrome

Rohan Sharma[1], Astrid Rasmussen[2], Lida Radfar[3], David M. Lewis[4], Kiely Grundahl[5], C. Erick Kaufman[6], Donald U. Stone[7], Joan T. Merrill[8], Christopher Lessard[9], Kathy L. Sivils[9] and Robert Hal Scofield[10], [1]Medical Service, US Department of Veterans Affaris Medical Center, Oklahoma City, OK, [2]Arthritis and Clinical Immunology Research Program, Oklahoma Medical Research Foundation, Oklahoma City, OK, [3]Oral Diagnosis and Radiology Department, University of Oklahoma Health Sciences Center College of Dentistry, Oklahoma City, OK, [4]College of Dentistry, Department of Oral and Maxillofacial Pathology, University of Oklahoma Health Sciences Center, Oklahoma City, OK, [5]Arthritis and Clinical Immunology Research Program, Oklahoma Medical Research Foundation, Oklahoma CIty, OK, [6]Medicine, University of Oklahoam Health Sciences Center, Oklahoma City, OK, [7]Ophthalmology, University of Oklahoam Health Sciences Center; Dean McGee Eye Center, Oklahoma City, OK, [8]Clinical Pharmacology, Oklahoma Medical Research Foundation, Oklahoma City, OK, [9]Oklahoma Medical Research Foundation, Oklahoma City, OK, [10]Arthritis & Clinical Immunology Program, Oklahoma Medical Research Foundation; Department of Medicine, University of Oklahoma Health Sciences Center; US Department of Veterans Affairs Medical Center, Oklahoma City, OK
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Background/Purpose:

We undertook this study to describe the racial and ethnic diversity of SS compared to that found among patients with SLE. SLE is known to be more common and severe in Black Americans than White Americans, and related to SS in regard to clinical manifestations and serological findings.

Methods:

Individuals with sicca were evaluated by a rheumatologist, ophthalmologist and a dentist in our Sjögren's syndrome research clinic. Detailed history and physical examination with stimulated and timed whole unstimulated salivary flow (WUSF) and a lip biopsy along with collection and storage of saliva, ocular surface staining with Lissamine green and fluorescein, an unanaesthetised Schirmer's test, collection and storage of tears as well as general laboratory tests were performed. Subjects were classified using ACEG and ACR criteria for primary SS (pSS). We compared the non-Hispanic Black pSS subjects to the non-Hispanic White pSS subjects with one to four age and sex match in terms of clinical manifestations, focus score, WUSF, Schirmer's, Lissamine green, anti-Ro (or SSA) and anti-La (or SSB) antibody positivity. We also compared the study group with subjects with non-Sjogren's Sicca (nSS) and those in a SLE cohort followed in the same facility. P values were corrected for multiple comparisons. Due to low representation of other ethnic groups in our study population we only considered non-Hispanic Blacks and non-Hispanic Whites in the study.

Results:

We classified 327 subjects in the clinic as pSS of which 201 were considered for the study. Among these 187 (92.1%) were self-identified as White, while only 14 (6.9%) were self-identified as Black. There were 7 (3.05%) Blacks and 223 (96.95%) whites in nSS group. Among the SLE subjects, there were 106 (29.5%) Black and 253(61.5%) as White. Thus, we found that black Americans were 5 times more likely to have SLE compared to pSS (χ^2=36.17, p <0.00001, OR=5.45), while there was no such difference when compared to subjects with nSS (control group)(χ^2=2.76,p=0.0966,OR=0.41). We next compared the clinical manifestations found in Black and White subjects with pSS. Concerning the classification criteria, we found no statistical difference for positive versus negative results. We also evaluated pSS subjects for systemic manifestations. Black subjects with pSS were found to have higher incidence of hypergamaglobulinemia-IgG type ($p=4.98\times10^{-7}$ by Fisher's Exact test) than corresponding Whites. There were no statistically significant differences in other extra-glandular clinical or laboratory findings.

Conclusion: In contrast to SLE, where the disease risk and severity are known to be greater in Black Americans as compared to Whites, pSS shows no such predilection.

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Abstract Number: 644

Predicting the Risk for Lymphoma Development in Sjögren's Syndrome: An Easy to Use Clinical Tool

Sofia Fragkioudaki[1], **Clio Mavragani**[2] and Haralampos M. Moutsopoulos[3], [1]Physiology, Medical School of Athens, Department of Physiology, Athens, Greece, [2]Physiology, Department of Physiology, School of Medicine, National Kapodistrian University of Athens, Athens, Greece, [3]Department of Pathophysiology, Medical School of Athens, Department of Pathophysiology, Athens, Greece

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Background/Purpose: Studies from our and other laboratories have shown that clinical, laboratory and serological features at the first evaluation of a patient with primary Sjogren's syndrome (pSS), can predict non-Hodgkin lymphoma (NHL) development in the future. In this study, we aimed to create a predictive model for NHL development, based on risk factors found at a routine clinical, serological and histopathological evaluation.

Methods: In the present retrospective case control study, clinical, serological and histopathological variables at the time of SS diagnosis (based on revised European/American classification criteria) were recorded in 381 pSS patients and 92 pSS patients complicated by NHL, after thorough chart review. For the identification of predictors for NHL development multivariate logistic regression models were constructed. The probability for NHL development was estimated, by adding the observed risk factors consecutively, one to the other.

Results: Clinical, serological and histopathological manifestations at the time of SS diagnosis, including salivary gland enlargement (SGE), palpable purpura, peripheral neuropathy, Raynaud's phenomenon, lymphadenopathy, the presence of autoantibodies against Ro/SSA and/or La/SSB antigens, rheumatoid factor (RF) positivity, low C4 complement levels, cryoglobulinemia, monoclonal gammopathy and Tarpley score ≥ 3 in minor salivary gland biopsy, were shown as independent predictors for lymphoma development (Table 1). The probability for NHL development in pSS patients, depending on the presence of the above mentioned risk factors, was 25.5% [OR (95%CI): 4.44 (2.07-7.50), p<0.0001] for patients carrying anti-Ro/anti-La antibodies, 39.4% [OR (95%CI): 3.61 (2.10-6.25), p<0.0001] for those having in addition to autoantibodies a Tarpley score ≥ 3, 54.7% [OR (95%CI): 5.93 (3.15-11.16), p<0.0001], for those having in addition to the above risk factors SGE, 72.7% [OR (95%CI): 9.16 (2.36-35.58), p=0.001] for those having also a monoclonal gammopathy and 80% [OR (95%CI): 13.03 (1.43-118.61), p=0.01] for those having additionally lymphadenopathy. This probability reached 100%, if in the latter subset of risk factors any of the remaining found risk factors was added. When ROC curves for the predictive model were fitted, the area under the curve (AUC) was 0.86, 95%CI: 0.81-0.90, p<0.0001.

Conclusion: This work showed that if more than five (anti-Ro/La antibodies positivity, Tarpley score ≥ 3, SGE, monoclonal gammopathy and lymphadenopathy) of the observed adverse predictors are present at the first evaluation of a pSS patient, the probability for lymphoma development is 100%.

Table 1. Independent adverse predictors for SS related NHL development, identified by multivariate analysis.

	Independent risk factors	OR [95%CI]	p-value
Clinical	SGE	5.27 [3.07-9.04]	<0.0001
	Lymphadenopathy	4.45 [2.45-8.11]	<0.0001
	Raynaud's phenomenon	1.64 [0.92-2.92]	0.09
	Palpable purpura	3.31 [1.79-6.08]	<0.0001
	PNS involvement	3.02 [0.87-10.49]	0.08
Serological	Monoclonal gammopathy	4.76 [1.63-13.92]	0.004
	RF positivity (>20IU/ml)	3.36 [1.54-7.34]	0.002
	Anti-Ro/SSA or/and anti-La/SSB positivity	7.50 [2.21-25.52]	0.001
	Low C4 levels (< 20 mg/dl)	2.94 [1.46-5.91]	0.002
	Cryoglobulinemia	2.71 [1.16-6.32]	0.02
Histopathological	Tarpley score ≥ 3 in MSG biopsy	5.84 [2.73-12.47]	<0.0001

SS: Sjogren's syndrome, SGE: salivary gland enlargement, NHL: non-Hodgkin's lymphoma, PNS: peripheral nervous system, RF: rheumatoid factor, MSG: minor salivary gland

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Disclosure: S. Fragkioudaki, None; **C. Mavragani**, None; **H. M. Moutsopoulos**, None.

Abstract Number: 645

Subclinical Cardiovascular Involvement in Patients with Primary Sjögren Syndrome

Alberto Batticciotto[1], Federica Rigamonti[1], Fabiola Atzeni[1], Marco Antivalle[1], Rossella Talotta[1], Laura Boccassini[1], Luigi Gianturco[2], Maurizio Turiel[2], Andrea Doria[3] and Piercarlo Sarzi-Puttini[1], [1]Rheumatology Unit, L. Sacco University Hospital, Milano, Italy, [2]Cardiology Unit, IRCCS-Galeazzi Orthopedic Institute, Milan, Italy, [3]Department of Medicine-DIMED, University of Padova, Padova, Italy
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Background/Purpose:

Different studies showed that systemic inflammation, elevated levels of inflammatory cytokines and immune dysregulation, typical of the inflammatory autoimmune disease, play a role in accelerated atherosclerosis. However, only few studies focused on sub-clinical cardiovascular (CV) involvement in patients with primary Sjögren's syndrome (pSS) are available (1). Aim of our study was to investigate sub-clinical CV involvement in pSS patients by means of carotid stiffness, asymmetric dimethyl arginine (ADMA) plasma levels, intima-media thickness (cIMT) and coronary flow reserve (CFR).

Methods:

Fifty-three consecutive outpatients with pSS (7 M, 46 F; mean age 59.8 yrs, range 43-80 yrs; mean disease duration of 59.5 months, range 6-156 months) without classical CV risk factors and/or known CV diseases, and 22 matched healthy controls were enrolled. MyLab 60 machine (Esaote,Italy) with radio frequency technology for evaluating quality intima media thickness (RF-QIMT) and quality arterial stiffness (RF-QAS) was used to assess cIMT and pulse wave velocity (PWV), respectively. Dipyridamole transthoracic stress echocardiography was performed by IE33 (Philips Medical Systems, USA) in order to obtain CFR values. Plasma ADMA levels, inflammatory markers and autoantibodies were also evaluated.

Results:

pSS group was matched with control in terms of age (59.8±8.5 vs 59.25±2.08 yrs, p=0.14), sex (46F, 7M vs 16F, 6M, p=0.8), BMI (25.5±3.3 vs 23.69±1.12. p=0.17) and blood pressure values (126.66±13.4 vs 125.61±12.48, p=0.59 and 79.4±4.6 vs 80.45±8.25. p=0.32). Serum levels of CRP (3.72±2.89 Vs 0.41±0.09 mg/L, p<0.0001), ESR (30.25±20.2 Vs 4.8±0.24, p<0.0001) and, although within the normal range, total cholesterol (182.77±7.12 Vs 163.33±5.59, p<0.001) were significantly lower in the control group. PWV and ADMA plasma levels, as markers of subclinical atherosclerosis and endothelial dysfunction respectively, were significantly higher (9.2±1.8m/s vs 6.8±0.9m/s. p<0.0001 and 0.76±0.07 vs 0.54±0.05 μM, p<0.0001) in pSS group. QIMT values were similar in the two groups; however, the percentage of pSS patients with abnormal value was higher compared with controls (47/53 vs 12/22, p=0.001). Although within the normal range, CFR values in pSS patients were lower than in controls (2.6±0.23 vs 3.2±0.32 p<0.0001).

Conclusion:

Higher ADMA levels, higher PWV values, higher percentage of patients with pathological Q-IMT and normal CFR values, suggested that pSS patients compared to healthy controls suffer from early endothelial dysfunction and sub-clinical atherosclerosis.

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Abstract Number: 646

Sicca Syndrome in Rheumatoid Arthritis: Is It a Real Sjögren's?

George Fragoulis[1], James Reilly[1], Shauna Kerr[1], Iain. B. McInnes[1] and Haralampos M. Moutsopoulos[2], [1]Institute of Infection, Immunity and Inflammation, College of Medicine, Veterinary Medicine and Life Sciences, University of Glasgow, Glasgow, United Kingdom, [2]Department of Pathophysiology, Medical School of Athens, Department of Pathophysiology, Athens, Greece

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Background/Purpose: The histopathological hallmark and a major diagnostic criterion of Sjögren's syndrome (SS) is the presence of periductal lymphocytic infiltrates in the labial minor salivary glands (LMSG). SS can occur either as an entity alone (primary SS-pSS) or with rheumatoid arthritis (RA) and other autoimmune diseases. Sicca symptoms (primarily ocular) are observed in around 20-25% of RA patients. The present study examines the LMSG infiltrates in sicca-RA patients and compares their composition with this described in pSS.

Methods: 100 consecutive RA patients (2010 ACR criteria) answer a validated sicca symptoms questionnaire. Positive responders were evaluated for ocular and oral dryness including a LMSG biopsy. All samples in addition to haematoxylin and eosin were stained for the immunocyte populations in serial sections [CD3: total T cells, CD4 and CD8: T cell subpopulations, CD20: B cells, CD68: macrophages (MΦ), S100 and fascin: interdigitating and follicular dendritic cells (DC)]. Stained cells and total mononuclear cells (MNC) were counted in the entire section. Counts were expressed as cell incidence (percentage of cell type number/total infiltrating MNC number).

Results:

44/100 RA patients responded positively for sicca symptoms. Their anthropometric and clinicoserologic characteristics are shown in Table 1. In total, 30 out of 100 RA patients had LMSG with a focus score ≥ 1. The immune cell composition in LMSG was found to differ from that of pSS [1] (Table 2): The incidence of DC and MΦ was higher, T cells were increased in severe lesions (ANOVA test, $p=0.03$) and DCs were inverse correlated with lesion severity (S100: $p= 0.0004$, $r=-0.56$; fascin: $p=0.08$, $r=-0.29$). In sicca-RA patients, MΦ and DC incidence correlated positively with the patients' RA score (ACR criteria) (CD68: $p<0.0001$, $r=0.65$; S100: $p=0.01$, $r=0.41$; fascin: $p=0.07$, $r=0.31$) and was higher in those who had biopsy focus score<1 and were anti-Ro negative [MΦ ($p=0.02$) and DC (S100: $p=0.002$; fascin: $p=0.001$)].

Conclusion:

The cell composition of the LMSG infiltrates of sicca-RA patients is different compared to that seen in biopsies of pSS patients. These differences, coupled with the known genetic and serologic dissimilarities may further attest for diverse pathophysiologic process operating in the genesis of these two entities.

References

1. Characteristics of the minor salivary gland infiltrates in Sjögren's syndrome. Christodoulou MI, Kapsogeorgou EK, Moutsopoulos HM. J Autoimmun. 2010 34(4):400-7

Patients characteristics	N=44
Epidemiological	
Age, median (range)	57.2 (32-71)
Sex (m/f)	2/42

Table 1. a. ACR 2010 RA criteria, at the time of diagnosis.

Table 2. MSG biopsy lesion composition in RA patients with sicca compared to primary SS patients [1]

Total follow up (months); median (range)	80 (6-264)
RA precedes/coincide/SS precedes No (%)	20/20/4 (45.5/45.5/9)
Evolution time RA to SS (months); (mean ± SD)	89.8 ± 79.1
Criteria	
Ocular dryness (subjective), No (%)	38 (86.4)
Oral dryness (subjective), No (%)	24 (54.5)
Rose Bengal (positive), No (%)	27 (61.4)
Schirmer's test (positive), No (%)	28 (63.6)
Unstimulated salivary flow, No (%)	23 (52.3)
Biopsy Tarpley score, median (range)	1 (0-4)
Biopsy Focus score, median (range)	0.96 (0-12)
RA criteria score[a] median (range)	7 (6-10)
Laboratory	
Anemia, No (%)	14 (31.8)
Thrombopenia, No (%)	3 (6.8)
Leukopenia, No (%)	1 (2.3)
ANA positive, No (%)	34 (77.3)
RF positive, No (%)	34 (77.3)
Anti-CCP positive, No (%)	23 (52.3)
Anti-Ro/SSA positive, No (%)	15 (34.1)
Anti-La/SSB positive, No (%)	2 (4.5)
C3 (mg/dl), mean ± SD	112.7 ± 24.5
C4 (mg/dl), mean ± SD	22.6 ± 7.0
Clinical	
Fatigue, No (%)	10 (22.7)
Fever, No (%)	11 (25.0)
Raynaud's phenomenon, No (%)	14 (31.8)
Morning stiffness, No (%)	33 (75.0)
Renal/Lung/Liver involvement, No (%)	8 (18.2)
Serositis, No (%)	3 (6.8)
Myositis, No (%)	1 (2.3)
Peripheral nerve involvement, No (%)	5 (11.4)
Purpura, No (%)	8 (18.2)
Salivary Gland Enlargement, No (%)	5 (11.4)
Lymphoma, No (%)	2 (4.5)

	Percentage or ratio		Correlation with MSG lesion severity (No Infiltrates/4mm2)	
	Primary SS [1]	RA with sicca	Primary SS [1]	RA with sicca
%CD20	44.19 ± 1.8	42.9 ± 1.92	r = 0.50 p= 0.001	r= 0.131 p= 0.452
%CD3	48.07 ± 1.8	44.4 ± 1.57	r= - 0.65, p < 0.0001	r= 0.191 p= 0.281
%CD4	32.94 ± 1.9	26.4 ± 1.7	r= - 0.58 p = 0.0003	r= 0.231 p= 0.181
%CD8	15.42 ± 1.0	17.4 ± 1.16	r= - 0.41 p <0.0001	r= - 0.256 p= 0.133
%CD68 MΦ	4.48 ± 0.67	5.69 ± 0.48	r= 0.46 p= 0.005	r= - 0.278 p= 0.105
%S100 DC	0.70 ± 0.10	1.89 ± 0.24	r= - 0.40 p = 0.015	r= - 0.565 p= 0.0004
%Fascin DC	1.89 ± 0.22	3.96 ± 0.36	NS	r= - 0.294 p= 0.08
%CD3/%CD20	1.26 ± 0.12	1.15 ± 0.08	r= - 0.59 p <0.001	r= - 0.046 p= 0.794
%CD4/%CD8	2.56 ± 0.29	2.02 ± 0.31	r= - 0.41 p= 0.015	r= 0.285 p= 0.09

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Abstract Number: 647

Involvement of Peripheral Nervous System in Primary Sjögren Syndrome, a Gessar Analysis

M. Mayer[1], S. Velez[2], F. Zazzetti[2], J. C. Barreira[2], L. Galvan[1], G. Bennasar[3], L. R. Carlevaris[3], A. Secco[3], C. Asnal[4], P. Pucci[4], C. Amitrano[4], A. Nitsche[4], M. C. Khoury[5], F. Caeiro[6], N. Benzaquén[6], J.P. Pirola[6], M. Colazo[6], O.L. Rillo[7], S. Papasidero[7], J. Demarchi[7], L. Raitti[8], M. N. Tamborenea[9], M. L. Santiago[9], P. Alba[10], B. Busamia[10], G. Salvatierra[11] and A. Catalán Pellet[3], [1]Rheumatology, Buenos Aires British Hospital, CABA, Argentina, [2]Rheumatology, Buenos Aires British Hospital, Buenos Aires, Argentina, [3]Rivadavia Hospital, CABA, Argentina, [4]German Hospital, CABA, Argentina, [5]Statistics, Buenos Aires British Hospital, CABA, Argentina, [6]Private Hospital of Cordoba, Cordoba, Argentina, [7]Tornú Hospital, CABA, Argentina, [8]Bessone Clinic, CABA, Argentina, [9]OMI, Buenos Aires, CABA, Argentina, [10]Córdoba Hospital, Cordoba, Argentina, [11]IPRI, Santiago del Estero, Santiago del Estero, Argentina

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Background/Purpose: Primary Sjögren's syndrome (pSS) is an autoimmune disease characterized by dysfunction of the exocrine glands. The frequency of neurological manifestations in pSS ranges from 0-70% depending on the inclusion criteria and diagnostic methods. Peripheral neuropathy (PN) is usually is a late onset event in primary Sjögren Syndrome associated with purpura, cryoglobulinemia, hypocomplementemia and increased risk of lymphoma. Objectives: To describe the frequency of PN in patients with pSS and identify related factors.

Methods: Adult patients in the GESSAR (Sjogren study group Argentina Society of Rheumatology) database who met 2002 criteria for pSS. Demographic, clinical, laboratory and electromyogram (EMG) findings were recorded. PN was defined with clinic manifestations and EMG. Other causes of PN were excluded. To compare groups, all patients with PN were included (cases) and a random sample of patients without PN (controls) with a 1:4 ratio was used. Mann-Whitney was used for numeric variables and X2 or Fisher's for categorical. An α of 0.05 was considered significant.

Results:

Of 368 patients, 95% were female. Mean age at analysis was 55 y/o (21-87) and 50 y/o (20-89) at diagnosis. The frequency of PN was 11.68% (43/368). Sensory PN was found in 63% (28/43), predominantly small fibers involvement in 41.8% (18/43), axonal PN in 20.9% (9/43) and ataxic in 2.3% (1 / 43). Somatosensory manifestations were found in 37% (16/43) with axonal involvement in 30.2% (13/43) and mononeuritis multiplex in 6.9% (3/43), none had autonomic PN. When comparing groups (43 vs 172 controls) patients with PN had a higher frequency of vasculitis (11.7% vs 1.7%;p=0.002), purpura (23.8% vs 4.7%,p=0.0001), renal tubular acidosis (7.6% vs 1.2%,p=0.020), leucopenia (30.7% vs. 12.1%,p=0.005), low C3 (48.5% vs. 10.3%, p=0.0001) and C4 (66.6% vs. 18.2%,p=0.0001), (+) Anti-Ro/SSA (85.3% vs. 66.6%,p=0.019), (+) RF (72.5% vs. 52.1%,p=0.022), cryoglobulinemia (42.1% vs. 10.9%,p=0.0001) and higher frequency of hypergammaglobulinemia (60.5% vs 44.6%,p=0.09), Raynaud's (27.5% vs 11.6%,p=0.051) and glomerulonephritis (4.6% vs 0.5%,p=0.018), although without statistical significance.

Conclusion:

The frequency of PN was 12%, similar to other cohorts. Small fibers and axonal somatosensory PN were the most common. PN was significantly associated with vasculitis, purpura, renal tubular acidosis, cryoglobulinemia, leucopenia, hypocomplementemia and anti-Ro and RF positivity.

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Abstract Number: 648

Klinefelter's Syndrome (47,XXY) Among Men with Sjögren's Syndrome

Valerie M Harris[1], Joshua Cavett[2], Biji Kurien[3], Ke Liu[4], Kristi A. Koelsch[5], Lida Radfar[6], David M. Lewis[7], Donald U. Stone[8], Shibo Li[9], Barbara Segal[10], Daniel J Wallace[11], Michael H. Weisman[12], Jennifer A. Kelly[13], Marta Alarcon-Riquelme[14], Bernado Pons-Estel[15], Roland Jonsson[16], Xianglan Lu[9], Jacques Gottenberg[17], Juan-Manuel Anaya[18], Deborah S. Cunninghame-Graham[19], Edward C. Keystone[20], Andrew J.W. Huang[21], Michael T. Brennan[22], Pamela Hughes[23], G Illei[24], Corinne Miceli[25], VP Bykerk[26], Gideon Hirschfield[27], Gang Xie[28], Wan-Fai Ng[29], Gunnel Nordmark[30], Per Eriksson[31], Roald Omdal[32], Nelson L. Rhodus[33], Maureen Rischmueller[34], Michael D. Rohrer[35], Marie Wahren-Herlenius[36], Torsten Witte[37], Xavier Mariette[38], Christopher Lessard[39], John B. Harley[40], Kathy L. Sivils[39] and Robert Hal Scofield[41], [1]Pathology, University of Oklahoma Health Sciences Center, Oklahoma City, OK, [2]Medicine, University of Oklahoma Health Sciences Center, Oklahoma City, OK, [3]Arthritis and Immunology, Oklahoma Medical Research Foundation, Oklahoma City, OK, [4]3333 Burnet Ave., University of Cincinnati & Cincinnati Childre, Cincinnati, OH, [5]Arthritis and Clinical Immunology, Oklahoma Medical Research Foundation, Okalahoma City, OK, [6]Oral Diagnosis and Radiology Department, University of Oklahoma Health Sciences Center College of Dentistry, Oklahoma City, OK, [7]College of Dentistry, Department of Oral and Maxillofacial Pathology, University of Oklahoma Health Sciences Center, Oklahoma City, OK, [8]King Khaled Eye Specialist Hospital, Riyadh, Saudi Arabia, [9]Pediatrics, University of Oklahoma Health Sciences Center, Oklahoma City, OK, [10]Rheumatology, Univ of Minnesota, Minneapolis, MN, [11]Cedars-Sinai Medical Center, West Hollywood, CA, [12]Rheumatology, Cedars-Sinai Medical Center, Los Angeles, CA, [13]Arthritis & Clinical Immunology Research Program, Oklahoma Medical Research Foundation, Oklahoma City, OK, [14]Arthritis & Clinical Immunology, Oklahoma Medical REsearch Foundtion, Oklahoma City, OK, [15]Hospital Provincial de Rosario, Rosario, Argentina, [16]Broegelmann research laboratory, Bergen, Norway, [17]Hautepierre, Strasbourg, France, [18]Cell Biol and Immunogenetics, CIB-Rosario University, Medellin, Colombia, [19]Department of Medical and Molecular Genetics, King's College London, London, United Kingdom, [20]Mount Sinai Hospital, University of Toronto, Toronto, ON, Canada, [21]Department of Ophthalmology and Visual Sciences, Washington University, St Louis, MO, [22]Department of Oral Medicine, Carolinas Medical Center, Charlotte, NC, [23]Division of Oral and Maxillofacial Surgery, Department of Developmental and Surgical Science, University of Minnesota School of Dentistry, Minneapolis, MN, [24]Sjögren's Clinic, NIDCR/NIH, Bethesda, MD, [25]Rheumatology, PARIS, France, [26]University of Toronto, Toronto, ON, Canada, [27]Centre for Liver Research, Institute of Biomedical Research, School of Immunity and Infection, College of

Medical and Dental Sciences, University of Birmingham, Birmingham, United Kingdom, [28]Mount Sinai Hospital, Toronto, ON, Canada, [29]Institute of Cellular Medicine, Newcastle University, Newcastle upon Tyne, United Kingdom, [30]Medical Sciences, Uppsala University, Uppsala, Sweden, [31]University Hospital, Rheumatology clinic, Linköping, Sweden, [32]Department of internal medicine, Clinical Immunology unit, Stavanger, Norway, [33]Department of Oral Surgery, University of Minnesota School of Dentistry, Minneapolis, MN, [34]Rheumatology, Queen Elizabeth Hospital, Adelaide, Australia, [35]Hard Tissue Research Laboratory, University of Minnesota School of Dentistry, Minneapolis, MN, [36]Department of Medicine, Experimental Rheumatology Unit, Solna, Sweden, [37]Department of Immunology and Rheumatology, Hannover Medical School, Hannover, Germany, [38]Université Paris-Sud, AP-HP, Hôpitaux Universitaires Paris-Sud, Paris, France, [39]Oklahoma Medical Research Foundation, Oklahoma City, OK, [40]Center for Autoimmune Genomics and Etiology (CAGE), Cincinnati Children's Hospital Medical Center, Cincinnati, OH, [41]Arthritis & Clinical Immunology Program, Oklahoma Medical Research Foundation; Department of Medicine, University of Oklahoma Health Sciences Center; US Department of Veterans Affairs Medical Center, Oklahoma City, OK
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SESSION INFORMATION

Session Date: Sunday, November 8, 2015
Session Title: Sjögren's Syndrome Poster I: Clinical Insights into Sjögren's Syndrome
Session Type: ACR Poster Session A
Session Time: 9:00AM-11:00AM

Background/Purpose:

Primary Sjögren's syndrome (pSS) has a strong female bias of greater than 10 to 1. This difference in risk of disease between the sexes has not been explained. We hypothesize that the number of X chromosomes is important for this bias, and that examination of patients for rare X chromosome aneuploides will inform the sex bias for those with a normal chromosome complement.

Methods:

We evaluated the hypothesis of an X chromosome dose effect by analyzing the presence of 47,XXY (Klinefelter's syndrome, 1 in 500 live male births) among a large cohort of subjects with pSS. All subjects with pSS met the American-European Consensus Classification Criteria for Sjögren's syndrome. The presence of extranumerary X chromosomes was determined by examination of fluorescence intensity of single nucleotide polymorphisms from the X and Y chromosomes from either Illumina genome-wide association study platform or the ImmunoChip. Karyotype or fluorescent *in situ* hybridization confirmed some of these results.

Results: Among 126 pSS men, there were 4 with 47,XXY. This was significantly different from healthy controls (1 of 1254 had 47,XXY, p=0.0012 by Fisher's exact test) as well as when compared to men with rheumatoid arthritis and the expected population frequency, but not different from published results in men with systemic lupus erythematosus (SLE). Using Bayes' theorem along with the population prevalence of Sjögren's and Klinefelter's syndromes as well as the finding of ~1 in 30 Sjögren's men with 47,XXY, we calculate that men with Klinefelter's syndrome have a risk of pSS about equal to that of women.

Conclusion: Combined with our previous data that 3 of 1,033 SS women, but only in two of the 7,074 female controls, have 47,XXX, which is found in 1 in 1000 live female births (p=0.02, OR=10.29, 95% CI: 1.18-123.47), these results are consistent with the hypothesis that the number of X chromosomes is important for the sex bias of pSS.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/klinefelters-syndrome-47xxy-among-men-with-sjogrens-syndrome

Abstract Number: 649

Measures of Health-Related Quality of Life in Psoriatic Arthritis: Are They Sensitive to Both Joint and Skin Aspects?

Mwidimi Ndosi[1], Ming-Anne Hsu[2], J. Cappelleri[3], Amit Chhabra[4], Heather Jones[5] and Philip S. Helliwell[6], [1]School of Healthcare, University

of Leeds, Leeds, United Kingdom, [2]445 Eastern Point Road, Pfizer Inc, Groton, CT, [3]Statistics, Pfizer Inc, New London, CT, [4]Pfizer Inc, Collegeville, PA, [5]Inflammation Global Medical Affairs, Pfizer, Collegeville, PA, [6]Section of Musculoskeletal Disease, University of Leeds, Leeds, United Kingdom

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SESSION INFORMATION

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Session Title: Spondylarthropathies and Psoriatic Arthritis - Clinical Aspects and Treatment Poster I: Clinical Aspects and Assessments

Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose:

Psoriatic Arthritis Quality of Life (PsAQol), Ankylosing Spondylitis Quality of Life (ASQoL), and Dermatology Life Quality Index (DLQI) are tools that assess different aspects of health-related quality of life (HRQoL) in psoriatic arthritis (PsA). We aimed to determine if each of the three tools capture HRQL domains relevant to both skin and joints.

Methods:

Patients with PsA (physician diagnosed) completed PsAQoL, ASQoL, and DLQI in a 15-country longitudinal study [1] designed to develop new composite measure for PsA. We used Rasch analysis to determine the reliability and validity, including how well the tools targeted the skin and joint aspects of HRQoL.

We assessed the following: (i) fit to the Rasch model to determine different aspects of validity in PsA, (ii) person- separation index to determine internal consistency, (iii) differential item functioning (DIF) across five regions (Asia, Europe, N. America, S. America and the UK) to determine cross-cultural validity, and (iv) person-item threshold location maps to determine targeting of the tools to skin and joint aspects of HRQoL.

Results:

The sample comprised 503 patients (male/female = 286/217) with mean (SD) age, 50.8 (13.1), and PSA duration, 9.8 (9.9) years.

Expectations of the Rasch model were satisfied only in N America PsAQoL, UK ASQoL and both UK & N America DLQI datasets. Reliability was adequate and the measures were invariant to age and gender. There were not enough data in each country to reliably determine cross-cultural invariance, therefore targeting and discrimination properties of the tools were based on N. American dataset (Figure 1).

DLQI targeted better (than PsAQoL) articular and skin aspects of HRQoL. DLQI discriminated better HRQoL related to skin involvement (fig 1B and 1F) but not spinal involvement (fig 1D), where ASQoL was better at discriminating this aspect ($F(1,66) = 13.76$, $p<0.001$).

Figure 1. Targeting and discriminating properties of the tools

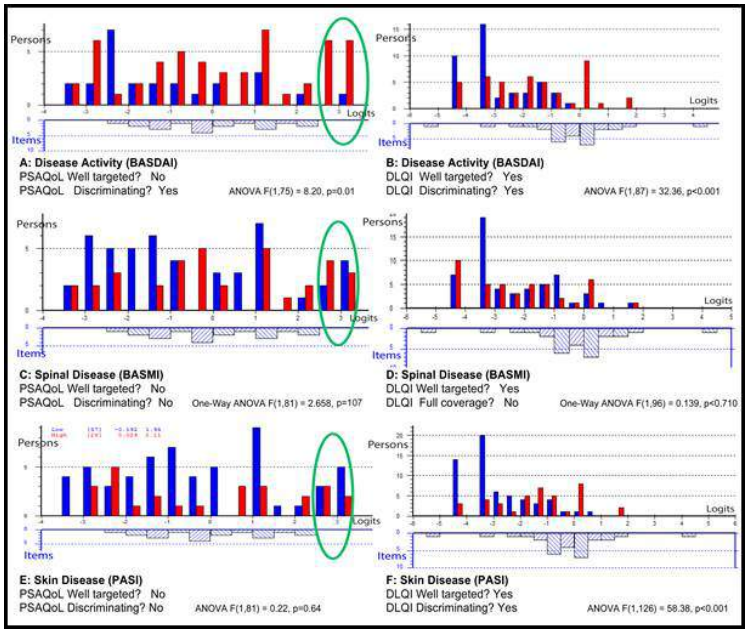

Figure legends: The left side of the plots represents low PSAQoL or QLQI scores (good HRQoL). The right side represents high scores (impaired HRQoL). The blue plots represent people with low/mild disease while the red plots those with severe disease. Significant ANOVA p-values suggest ability of the tool to discriminate between persons with low/high disease. Green circles mark persons with severe HRQoL not targeted by PsAQoL items.

Conclusion:

The data suggest that PsAQoL does not cover the full spectrum of HRQoL in psoriasis. Conversely, DLQI does not cover the full spectrum of HRQoL of articular disease in PsA. PsAQoL, (or ASQoL) and DLQI complement each other in capturing both joint and skin aspects of HRQoL. Confirmation of these findings is needed using larger datasets.

References:

1. Helliwell PS, et al. The development of candidate composite disease activity and responder indices for psoriatic arthritis (GRACE project). Ann Rheum Dis 2013;**72**(6)986-91

Disclosure: M. Ndosi, None; **M. A. Hsu**, Pfizer Inc, 3,Pfizer Inc, 1; **J. Cappelleri**, Pfizer Inc, 1; **A. Chhabra**, Pfizer Inc, 3; **H. Jones**, Pfizer, Inc, 3,Pfizer, Inc, 1; **P. S. Helliwell**, None.

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Abstract Number: 650

ASDAS-Based Remission Was Less Frequent Than Basdai-Based Remission, and Both Were Related to CRP and Smoking in Early Axial Spondyloarthritis

Daniel Wendling[1], Xavier Guillot[2], Laure Gossec[3], Clément Prati[4], Alain Saraux[5] and Maxime Dougados[6], [1]Université de Franche-Comté, Besançon, France, [2]Service de Rhumatologie, CHRU J Minjoz, Besançon, France, [3]Rheumatology, Pitié Salpetriere Hospital, Paris, France, [4]Service de Rhumatologie, CHU J Minjoz, Besancon, France, [5]Rheumatology Department, CHU de la Cavale Blanche, Brest Cedex, France, [6]Cochin University Hospital, Paris, France

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Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose:

Remission is the final goal for treat to target strategy in axial spondyloarthritis (axSpA). No clear definition is currently recognized, but ASDAS-CRP inactive state or BASDAI threshold (1) have been proposed. The frequency of remission using these definitions and factors associated with remission are unknown in early axSpA.

Aim.

To evaluate the percentage of patients in remission in early AxSpA, comparing different definitions of remission, and to evaluate factors associated with remission at inclusion in the DESIR cohort and after 24 months.

Methods:

DESIR is a prospective observational cohort of patients with recent onset (less than 3 years) inflammatory back pain, beginning before 45 years, suggestive of axial SpA. For each of three definitionsof remission (ASAS partial remission (PR), ASDAS-CRP less than 1.3(ASDAS-R), BASDAI less than 3.6 (1)(BASDAI-R)), the ability to detect patients in remission according to the two other definitions was assessed using ROC curves and Areas Under the Curve (AUC). Data at baseline (M0) and M24 were analyzed, to look for factors (clinical, biological and imaging) associated with remission in uni and multivariate analysis by logistic regression.

Results:

706 patients were evaluated at M0 and 577 at M24. At M0, the percentage of patients in remission was 4% (PR), 8% (ASDAS) 34 % (BASDAI), and at M24 : 15%, 24% and 54% respectively, in the whole population and in Amor, ESSG and ASAS classified patients, but lower in mNY patients (data not shown). BASDAI less than 3.6 detected best patients in PR and ASDAS-R, with AUC of 0.84 and 0.86 respectively. In univariate analysis at M0, lower ESR and CRP, DKK-1, low BMI, male gender, absence of psoriasis, less smoking, HLA-B27 positivity, ASAS criteria fulfillment, positive sacro iliac imaging, less analgesics use and less subsequent use of anti TNF at M24 were associated with remission (ASDAS-R, BASDAI-R). No association was found with age, disease duration, enthesitis, uveitis, IBD, NSAID use, mSASSS. In multivariate analysis, remission was associated with lower ESR, less smoking, use of analgesics. At M24, low ESR and CRP, female gender, less smoking, less NSAID use , lower NSAID score, ASAS criteria fulfillment, lower biologics use and lower systemic steroid use were associated with

remission in univariate analysis. In multivariate analysis, remission was associated with less smoking, less analgesics, ASAS clinical arm fulfillment, less NSAIDs (ASDAS-R), low CRP(ASDAS-R), low BMI(BASDAI-R).

Remission	ASDAS-R ASDAS < 1.3	r,p	BASDAI-R BASDAI<3.6	r,p
M0 N=706	CRP Smoking Analgesics	-0.59 *** -1.5 ** 1.55 ***	ESR Smoking Analgesics	-0.04 * -0.93 * 1.39 **
M24 N=577	CRP Smoking ASDAS clinical NSAIDs Analgesics	-0.6 *** -1.08 * 1.76 * -1.4 ** -2.02 ***	BMI Smoking ASAS clinical Analgesics	-0.14 ** -1.16 ** 1.28 * -1.74 ***

Results of multivariate analysis; r : regression coefficient , *p<0.05 ; **p<0.001; ***p<0.0001

Conclusion:

In this population suggestive of early SpA, BASDAI less than 3.6 seems a fair assessment of remission. As expected, acute phase reactants and analgesics were associated with remission at baseline and M24, but smoking appears as a major marker of disease activity and remission in early AxSpA.

(1) Godfrin-Valnet M, J Rheumatol. 2014;41(3):617-8.

Disclosure: D. Wendling, None; **X. Guillot**, None; **L. Gossec**, None; **C. Prati**, None; **A. Saraux**, None; **M. Dougados**, None.

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Abstract Number: 651

The Prediction of Long-Term Minimal Disease Activity and Its Benefits in Patients with Psoriatic Arthritis

Philip J. Mease[1], Arthur Kavanaugh[2], Laura C Coates[3], Iain McInnes[4], Maja Hojnik[5], Ying Zhang[6], Jaclyn K. Anderson[6], Alex Dorr[6] and Dafna Gladman[7], [1]Rheumatology Research, Swedish Medical Center, Seattle, WA, [2]University of California San Diego, La Jolla, CA, [3]Leeds Teaching Hospitals Trust, Leeds, United Kingdom, [4]University of Glasgow, Institute of Infection Immunity and Inflammation, Glasgow, United Kingdom, [5]AbbVie, Ljubljana, Slovenia, [6]AbbVie, North Chicago, IL, [7]Rheumatology, University of Toronto, Toronto Western Hospital, Toronto, ON, Canada

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Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose:

Minimal disease activity (MDA)[1] is a clinically meaningful and comprehensive treatment target for psoriatic arthritis (PsA). The purpose was to determine if baseline (BL) disease activity and/or patient (pt) demographics predict the ability to achieve MDA at weeks (wks) 12 through 144 in pts with PsA, and to evaluate patient-reported outcomes (PROs) at wk 24 and 144 associated with achieving MDA.

Methods: Data was from the ADEPT trial, where PsA pts were randomized to adalimumab or placebo for 24 wks, followed by an open-label (OL) period out to 144 wks. In this post-hoc analysis, BL characteristics which predicted achievement of MDA at wk 12, 24, 48, 96 and 144

were identified by univariate (UV) and multivariate (MV) analyses (LASSO). A more stringent assessment was made for correlation with sustained MDA (defined as MDA achievement at 2 time points, 12 wks apart). Continuous variables were age, weight, modified total Sharp score (mTSS), tender/swollen joint count (T/SJC), Pt Global Assessment of disease activity (PtGA) or pain (PtGA-pain), Physician's Global assessment of disease activity (PhGA), HAQ, enthesitis (2 sites), Psoriasis Area Severity Index (PASI) and Physician's Global Assessment of Psoriasis (PhGA-Psoriasis). Categorical variables were gender, smoking, alcohol use, methotrexate use, investigator-reported spondylitis, CRP (<2.87 vs ≥2.87), duration of psoriasis/ PsA (< 5 or ≥5 years). Pts achieving MDA were termed achievers and those who did not, non-achievers (NA). Quality of life (QoL) - related PROs assessed at wks 24 (and for completers at wk144), were Dermatology Life Quality Index (DLQI), SF-36, and Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) score.

Results:

The numbers of MDA achievers vs NA were as follows: 18.9% vs 81.1% (wk 12, N=127); 21.6% vs 78.4 (wk 24, N=125); 40.5% vs 59.5% (wk 48, N=116); 38.5% vs 61.5% (wk 96, N=104); 43.2% vs 56.8% (wk 144, N=88). In the UV analysis, lower PtGA-pain, TJC, SJC, enthesitis and HAQ at BL were associated with MDA at later time points. Sustained MDA at all/most time points was associated with lower TJC, SJC, HAQ and enthesitis at BL. MV analysis confirmed BL HAQ as a significant limiting factor for achieving MDA at later time points. A one unit increase in BL HAQ reduced the odds of achieving MDA at later time points by 64-77%. Lower age, TJC and HAQ at BL were associated with sustained MDA at wk 48; lower BL enthesitis with sustained MDA at wk 144. At week 24, MDA achievers demonstrated significantly better scores for QoL-related PROs compared to NA[2]; for pts completing 144 weeks, no significant differences in PRO scores were observed.

Conclusion: Lower scores at BL for HAQ increased the likelihood of MDA at later time points. Lower age and impairment at BL, as measured by TJC, HAQ and enthesitis increased the likelihood of reaching sustained MDA, suggesting the importance of early intervention. MDA achievers had significantly improved QoL compared to NA at wk 24; however, among pts completing 144 weeks, these differences were not evident.

Ref:

1. Coates LC, et al. ARD 2010;69:48
2. Mease P et al. ACR 2014 Ann meeting, Boston MA, USA. S697

Disclosure: P. J. Mease, AbbVie, Amgen, Biogen Idec, Bristol Myers, Celgene, Genentech, Janssen, Lilly, Merck, Novartis, Pfizer and UCB., 9; **A. Kavanaugh**, AbbVie Inc., Amgen, Astra-Zeneca, BMS, Celgene, Centocor-Janssen, Pfizer, Roche, and UCB, 9; **L. C. Coates**, AbbVie, Celgene, Janssen, Novartis, Pfizer, MSD, Boehringer-Ingelheim and UCB., 9; **I. McInnes**, AbbVie, Amgen, Janssen, Novartis, Pfizer, and UCB., 9; **M. Hojnik**, AbbVie, Amgen, BMS, Celgene, Eli Lilly, Janssen, Novartis, Pfizer, UCB., 9; **Y. Zhang**, AbbVie, 1,AbbVie, 3; **J. K. Anderson**, AbbVie, 1,AbbVie, 3; **A. Dorr**, AbbVie, 1,AbbVie, 3; **D. Gladman**, AbbVie, Amgen, BMS, Celgene, Eli Lilly, Janssen, Novartis, Pfizer, UCB., 9.

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Abstract Number: 652

The Performance of Different Classification Criteria Sets for Spondyloarthritis in the Worldwide ASAS-Comospa Study

Pauline Bakker[1], Anna Moltó[2], Adrien Etcheto[3], Rosaline van den Berg[4], Floris van Gaalen[1], Robert B. M. Landewé[5], Filip van Den Bosch[6,7], Maxime Dougados[8] and Désirée van der Heijde[9], [1]Rheumatology, Leiden University Medical Center, Leiden, Netherlands, [2]Rheumatology, Hospital Germans Trias i Pujol, Badalona, Spain, [3]Université Paris René Descartes and Hôpital Cochin, Paris, France, [4]Leiden University Medical Center, Leiden, Netherlands, [5]Rheumatology, University Hospital Maastricht, Maastricht, Netherlands, [6]Department of Rheumatology, Ghent University Hospital, Ghent, Belgium, [7]Rheumatology, Ghent University Hospital, Ghent, Belgium, [8]Cochin University Hospital, Paris, France, [9]University Hospital, Maastricht, Netherlands

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Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

The performance of different classification criteria sets for spondyloarthritis in the ASAS-COMOSPA study

Background/Purpose: Spondyloarthritis (SpA) includes patients with (predominantly) axial spondyloarthritis (axSpA) and patients with (predominantly) peripheral spondyloarthritis (pSpA) including psoriatic arthritis (PsA). Over time, several classification criteria sets have been developed to cover the whole spectrum of SpA. However, the performance of the different classification criteria sets has been insufficiently

evaluated. By this study we aim to compare the performance of different SpA classification criteria sets in the worldwide ASAS-COMOSPA study.

Methods: The ASAS-COMOSPA study is an international, cross-sectional study. Patients clinically diagnosed with SpA by the rheumatologist were included consecutively via routine care. For this analysis, patients were classified according to the ESSG, AMOR, mESSG (addition of MRI), mAMOR (addition of MRI), CASPAR and ASAS criteria for axSpA and pSpA.

Results: From 5 continents, 22 participating countries included 3984 patients: age 44 ± 14 years, 65% male gender, 56.2% HLA-B27+, psoriasis: 21.4%, uveitis: 19.6%, peripheral arthritis: 61.5%, mNY+ 64.4%, sacroiliitis on MRI (ASAS definition): 33.6%, negative rheumatoid factor (RF): 80.6%. Patients with up to 6 missing values were included (missing values set as absent); patients with ≥7 variables missing were left out of the analysis. Most common missing variables: MRI of the sacroiliac joints (ASAS definition; MRI-SI) (n=1951), juxta-articular bone formation (n=999), HLA-B27 (n=907), good response to NSAIDs (n=803), RF (n=613), radiographic sacroiliitis (n=341). Patients were classified according to the different classification criteria sets (table): data shown for all patients (left) and for patients with complete data regarding presence/absence of (radiographic/MRI) sacroiliitis and HLA-B27 (right). In addition, the overlap between the different classification criteria sets was assessed for patients with back pain and patients without back pain. The majority (of the patients) was classified by AMOR & ESSG & ASAS axSpA-criteria (n=1068). Most of the patients that were picked up by 1 criteria set only were classified by the ASAS axSpA-criteria (n=141; n=27 by AMOR and n=25 by ESSG). Similar trends were seen with regard to the mESSG and mAMOR-criteria. Regarding the patients with no back pain (peripheral complaints): again substantial overlap between the criteria was seen (ASAS pSpA, AMOR, ESSG, CASPAR).

Conclusion: In this worldwide ASAS-COMOSPA study including established patients with SpA according to the rheumatologist, most patients fulfil several classification criteria sets; the biggest overlap between AMOR, ESSG and ASAS SpA. If patients fulfil only 1 criteria set this is most frequently the ASAS axSpA-criteria.

Classification criteria	**Number of patients fulfilling the criteria n (%)** All patients Total n = 3942	**Number of patients fulfilling** **the criteria n (%)** Patients with complete data regarding imaging and HLA-B27 Total n = 1693
AMOR	3282 (83.3%)	1338 (79.0%)
mAMOR	3454 (87.6%)	1480 (87.4%)
ESSG	3485 (88.4%)	1437 (84.9%)
mESSG	3652 (92.6%)	1578 (93.2%)
ASAS SpA	3558 (90.3%)	-
Axial SpA	2955 (75.0%)	1414 (83.5%)
Both arms	1737 (58.8%)	935 (66.1%)
mNY+	976 (56.2%)	193 (20.6%)
MRI+	169 (9.7%)	150 (16.0%)
Both	592 (34.1%)	592 (63.3%)
Imaging arm only	984 (33.3%)	381 (26.9%)
mNY+	539 (54.8%)	80 (21.0%)
MRI+	245 (24.9%)	182 (47.8%)
Both	200 (20.3%)	119 (31.2%)
Clinical arm only	234 (7.9%)	98 (6.9%)
Peripheral SpA	603 (15.3%)	-
CASPAR	852 (21.6%)	-

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Abstract Number: 653

Clinical Responses and Improvements in Patient-Reported Outcomes Are Associated with Increased Productivity in the Workplace and at Home in Axial Spondyloarthritis Patients

Treated with Certolizumab Pegol

Désirée van der Heijde[1], Juergen Braun[2], Martin Rudwaleit[3], Oana Purcaru[4] and Arthur Kavanaugh[5], [1]Leiden University Medical Center, Leiden, Netherlands, [2]Rheumazentrum Ruhrgebiet, Herne, Germany, [3]Klinikum Bielefeld, Bielefeld, Germany, [4]UCB Pharma, Brussels, Belgium, [5]University of California San Diego, La Jolla, CA

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SESSION INFORMATION

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Session Title: Spondylarthropathies and Psoriatic Arthritis - Clinical Aspects and Treatment Poster I: Clinical Aspects and Assessments
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Session Time: 9:00AM-11:00AM

Background/Purpose:

Axial spondyloarthritis (axSpA) includes ankylosing spondylitis (AS) and non-radiographic axSpA (nr-axSpA).[1] AS significantly affects patient (pt) workplace productivity in both performance and disease-related absenteeism.[2] The impact of nr-axSpA on productivity is less well characterized. Few studies investigate associations between improvements in workplace and household productivity and symptom relief with available therapies in axSpA. Here we evaluate the association between improvements in clinical and pt-reported outcomes (PROs) and improvements in productivity in the workplace and at home in axSpA pts treated with certolizumab pegol (CZP), including AS and nr-axSpA pts.

Methods:

Associations between clinical outcomes or PROs and work and household productivity were made using Week (Wk) 24 data from the double-blind and placebo-controlled period of RAPID-axSpA (NCT01087762),[3] for pts originally randomized to CZP. Clinical outcomes included achievement of ASAS40 and ASDAS Major Improvement (MI). PROs included achievement of MCID for BASFI (≥1 decrease from baseline [BL]), total back pain (≥1 decrease from BL) and ASQoL (≥2 decrease from BL). Responders and non-responders at Wk24 were compared in terms of change from BL (CFB) in workplace and household productivity, as assessed using the validated arthritis-specific Work Productivity Survey.[4] Groups were compared using a non-parametric bootstrap-t method. Missing data were imputed using LOCF for WPS outcomes and NRI for clinical outcomes and PROs.

Results:

218 CZP pts entering RAPID-axSpA were included in Wk24 analyses (121 AS; 97 nr-axSpA). Pts employed at Wk24: 73.9% axSpA; 73.6% AS; 74.2% nr-axSpA. Overall, pts achieving a clinical or PRO response at Wk24 reported greater improvements in workplace and household productivity than non-responders (Table). Improvements in ASQoL and clinically meaningful reductions in functional limitation and pain were associated with improved workplace absenteeism and presenteeism. Similar results were seen in both AS and nr-axSpA pts. Numerically greater CFB was seen in nr-axSpA pts, potentially due to a slightly higher BL productivity burden in nr-axSpA vs AS.[5] Responders also reported greater improvements in participation in family, social and leisure activities (not shown). Results should be interpreted with caution, due to differences in pt number between groups and because analyses were not adjusted for differences in BL productivity.

Conclusion:

Clinical responses and clinically meaningful improvements in PROs are associated with improved workplace and household productivity in axSpA pts treated with CZP, including both AS and nr-axSpA pts.

References:

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2. van der Heijde D. Ann Rheum Dis 2013;72:87
3. Landewé R. Ann Rheum Dis 2014;73:39–47
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Table: Change from baseline in workplace and household productivity at Week 24 of RAPID-axSpA in CZP-treated patients (full analysis set) by responder status for clinical outcomes and PROs

			Workplace productivity [a], mean CFB (SD)				Household productivity [b], mean CFB (SD)			
			n	Days missed [c]	Days with productivity reduced by ≥50% [d]	Level of arthritis interference on productivity [e]	n	Days missed [c]	Days with productivity reduced by ≥50% [d]	Level of arthritis interference on productivity [e]
ASAS40	Responders	axSpA	88	-1.2 (3.2)	-3.9 (6.2)*	-3.1 (2.5)***	113	-3.2 (5.9)	-4.8 (7.5)	-3.1 (2.6)***
		AS	49	-1.0 (2.4)	-3.4 (6.1)	-3.0 (2.4)*	64	-2.5 (4.8)	-3.8 (6.6)	-3.0 (2.4)*
		nr-axSpA	39	-1.4 (3.9)	-4.5 (6.4)	-3.2 (2.7)**	49	-4.1 (7.0)	-6.0 (8.4)	-3.3 (2.8)**
	Non-responders	axSpA	66	-0.6 (4.4)	-1.0 (8.8)	-1.5 (2.8)	105	-2.8 (9.2)	-3.6 (9.5)	-1.8 (2.9)
		AS	38	-1.0 (4.6)	-0.8 (8.9)	-1.7 (2.8)	57	-3.1 (8.0)	-4.1 (8.6)	-1.9 (2.6)
		nr-axSpA	28	0.0 (4.0)	-1.3 (8.7)	-1.1 (2.8)	48	-2.4 (10.5)	-2.9 (10.6)	-1.6 (3.2)
ASDAS MI	Responders	axSpA	83	-1.4 (3.5)	-4.3 (6.9)**	-3.0 (2.6)***	108	-3.4 (5.7)	-4.3 (7.6)	-3.0 (2.6)**
		AS	47	-1.0 (3.0)	-3.4 (6.5)	-2.7 (2.6)	62	-2.9 (4.9)	-3.7 (6.9)	-2.9 (2.5)
		nr-axSpA	36	-1.9 (4.0)**	-5.5 (7.2)**	-3.4 (2.7)***	46	-4.1 (6.7)	-5.0 (8.5)	-3.2 (2.7)*
	Non-responders	axSpA	71	-0.4 (4.0)	-0.7 (7.9)	-1.6 (2.7)	110	-2.6 (9.1)	-4.2 (9.4)	-1.9 (2.9)
		AS	40	-1.0 (4.1)	-0.9 (8.4)	-2.0 (2.7)	59	-2.7 (7.9)	-4.2 (8.2)	-2.0 (2.5)
		nr-axSpA	31	0.4 (3.7)	-0.5 (7.1)	-1.1 (2.7)	51	-2.5 (10.5)	-4.1 (10.7)	-1.8 (3.4)
BASFI MCID	Responders	axSpA	111	-1.3 (3.6)	-3.9 (7.0)**	-2.9 (2.6)***	150	-3.8 (7.3)*	-5.1 (8.0)*	-3.0 (2.7)***
		AS	63	-1.0 (3.4)	-3.6 (7.1)***	-2.9 (2.4)**	85	-3.0 (5.6)	-4.0 (7.0)	-3.0 (2.4)***
		nr-axSpA	48	-1.7 (3.8)	-4.3 (6.8)	-2.9 (2.8)	65	-4.8 (8.9)**	-6.6 (8.9)***	-3.0 (3.2)*
	Non-responders	axSpA	43	0.0 (3.9)	0.7 (8.0)	-1.0 (2.7)	68	-1.3 (8.2)	-2.2 (9.4)	-1.4 (2.6)
		AS	24	-1.0 (3.8)	1.5 (7.5)	-1.1 (2.7)	36	-2.3 (8.3)	-4.0 (8.7)	-1.3 (2.4)
		nr-axSpA	19	1.3 (3.7)	-0.4 (8.8)	-0.9 (2.8)	32	-0.3 (8.2)	-0.2 (9.8)	-1.5 (2.9)
Total back pain MCID	Responders	axSpA	126	-1.4 (3.5)***	-3.5 (7.2)***	-2.7 (2.6)***	177	-3.4 (7.5)	-4.7 (8.5)	-2.7 (2.8)*
		AS	71	-1.4 (3.4)	-2.8 (7.0)	-2.8 (2.5)	96	-3.0 (6.3)	-4.2 (7.6)	-2.8 (2.5)**
		nr-axSpA	55	-1.5 (3.7)	-4.4 (7.4)	-2.7 (2.8)	81	-4.0 (8.8)	-5.4 (9.5)	-2.5 (3.1)
	Non-responders	axSpA	28	1.4 (3.9)	1.3 (8.0)	-0.8 (2.9)	41	-1.2 (8.0)	-2.0 (8.4)	-1.7 (2.8)
		AS	16	0.9 (3.6)	0.3 (9.5)	-0.8 (2.8)	25	-2.0 (7.4)	-3.2 (7.6)	-1.2 (2.4)
		nr-axSpA	12	2.0 (4.4)	2.5 (5.7)	-0.8 (3.3)	16	0.2 (8.8)	-0.1 (9.4)	-2.4 (3.2)
ASQoL MCID	Responders	axSpA	116	-1.2 (4.1)**	-3.5 (7.0)*	-3.0 (2.5)***	158	-4.0 (7.3)***	-5.6 (8.6)***	-3.1 (2.7)***
		AS	64	-1.3 (3.9)*	-3.4 (7.3)**	-2.9 (2.5)**	88	-3.4 (6.4)	-5.3 (7.9)***	-3.0 (2.4)***
		nr-axSpA	52	-1.1 (4.4)	-3.7 (6.8)	-3.0 (2.6)	70	-4.8 (8.4)**	-5.9 (9.4)*	-3.1 (3.1)***
	Non-responders	axSpA	38	0.0 (1.9)	0.1 (8.4)	-0.6 (2.8)	60	-0.3 (7.8)	-0.6 (7.4)	-0.9 (2.4)
		AS	23	0.0 (1.6)	1.0 (7.4)	-1.0 (2.6)	33	-1.2 (6.6)	-0.3 (5.2)	-1.0 (2.2)
		nr-axSpA	15	0.1 (2.3)	-1.5 (10.0)	-0.1 (3.0)	27	0.7 (9.1)	-0.9 (9.5)	-0.8 (2.6)

Nominal p values for the difference in mean CFB between responders and non-responders: *p<0.05, **p<0.01 and ***p<0.001. [a] Workplace productivity results shown for Week 24 employed patients; [b] Household productivity results shown for Week 24 patients overall; [c] CFB in the number of days missed due to arthritis in the last month; [d] CFB in the number of days with productivity reduced by ≥50% due to arthritis in the last month; [e] CFB in the level of arthritis interference on productivity in the last month, as measured on a 0–10 point scale (0=no interference, 10=complete interference).

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Abstract Number: 654

Associations Between Skin Outcomes By Body Area Affected and Health-Related Quality of Life in Patients with Psoriatic Arthritis Treated with Certolizumab Pegol

Alice B. Gottlieb[1], Bengt Hoepken[2], Luke Peterson[3] and Peter C. Taylor[4], [1]Dermatology, Tufts Medical Center, Boston, MA, [2]UCB Pharma, Monheim, Germany, [3]UCB Pharma, Raleigh, NC, [4]Nuffield Dept. of Orthopaedics, Rheumatology and Musculoskeletal, Sciences, Kennedy Institute of Rheumatology, University of Oxford,, Oxford, United Kingdom

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Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose:

Patients (pts) with psoriatic arthritis (PsA) report poorer health-related quality of life (HRQoL) compared to the general population. As with psoriasis (PSO), it is expected that HRQoL may be worse in PsA pts with skin manifestations affecting visible body areas. Previous reports of RAPID-PsA (NCT01087788) demonstrated improvements in clinical outcomes and HRQoL in PsA pts treated with certolizumab pegol (CZP) over 96 weeks (wks).[1] Here we report improvements in skin outcomes by body area affected and investigate associations with HRQoL.

Methods:

RAPID-PsA was double-blind and placebo (PBO)-controlled to Wk24, dose-blind to Wk48 and open-label to Wk216. Pts had active PsA and failed ≥1 DMARD. Pts were randomized at baseline (BL) to PBO or CZP. Primary clinical endpoint (Wk12 ACR20 response) was reported previously.[2] Skin outcomes are presented for Wk0 CZP-randomized pts with ≥3% PSO body surface area (BSA) at BL. PASI scores are presented by body region. Spearman correlations are calculated to assess BL associations between Dermatology Life Quality Index (DLQI) and PASI in all pts with ≥3% PSO BSA at BL. Absence of PSO was defined as PASI=0 by body region and summarized separately by PsA subgroups with/without respective body region PSO at BL. Observed data are shown.

Results:

Of 409 pts randomized, 273 received CZP from Wk0 (166 [60.8%] had ≥3% BSA at BL; mean BL PASI 12.0). RAPID-PsA primary endpoint was met (ACR20 [NRI]: 58.0%, 51.9% vs 24.3%; for CZP 200 mg Q2W, 400 mg Q4W vs PBO). HRQoL improvements to Wk24, assessed by HAQ-DI, were maintained to Wk96 (mean change from BL HAQ-DI [SD]: -0.5 [0.6] at Wk24; -0.6 [0.6] at Wk96).

Improvements in mean PASI body region scores were observed to Wk96 of CZP treatment (mean PASI body region scores at BL vs Wk96 were: Head: 12.0 vs 1.7; Upper extremities: 12.2 vs 1.9; Trunk: 10.8 vs 1.4; Lower extremities: 12.9 vs 2.4).

A moderate, positive correlation was observed at BL between DLQI and total PASI score (r=0.50) and in the PASI body regions of upper extremities, trunk and lower extremities (range, r=0.43–0.50), and a weak, positive correlation was shown between DLQI and PASI head (r=0.28). Correlations between changes in PASI and DLQI to Wk24 were similar to BL correlations.

Over 40% of pts with body region PSO at BL achieved absence of PSO at Wk24; by Wk96, this increased in all regions and was as high as 79% (Table). Overall, only 9 pts without body region PSO at BL developed PSO in that region.

Conclusion:

Improvements in all PASI body region scores were observed in PsA pts following 96 wks of CZP treatment. DLQI had moderate positive correlations with all PASI body regions apart from the head (weakly correlated). At Wk96, absence of body region PSO was attained in at least half of pts with PSO of the respective body region at BL.

References:

1. Mease P. Ann Rheum Dis 2014;73(S2):90
2. Mease P. Ann Rheum Dis 2014;73(1):48–55

Table: Proportion of PsA patients achieving absence of body region psoriasis to Week 96 of RAPID-PsA (CZP dose-combined)

	Body region psoriasis at baseline							
	Head		Upper extremities		Trunk		Lower extremities	
	Affected (N=145)	Absent (N=20)	Affected (N=137)	Absent (N=28)	Affected (N=115)	Absent (N=50)	Affected (N=131)	Absent (N=34)
Week 24, n/N (%)	69/128 (53.9)	14/16 (87.5)	59/121 (48.8)	23/23 (100.0)	61/98 (62.2)	45/46 (97.8)	49/117 (41.9)	27/27 (100.0)
Week 96, n/N (%)	85/108 (78.7)	11/13 (84.6)	62/99 (62.6)	19/22 (86.4)	60/80 (75.0)	39/41 (95.1)	53/99 (53.5)	20/22 (90.9)

One patient with baseline ≥3% psoriasis body surface area had missing PASI assessment at baseline and was excluded from these analyses.

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Abstract Number: 655

Rasch Analysis of the Hospital Anxiety and Depression Scale in Psoriatic Arthritis: Results from the Presta Study.

Mwidimi Ndosi[1], Ming-Anne Hsu[2], J. Cappelleri[3], Heather Jones[4], Amit Chhabra[5] and Philip S. Helliwell[6], [1]School of Healthcare, University of Leeds, Leeds, United Kingdom, [2]445 Eastern Point Road, Pfizer Inc, Groton, CT, [3]Statistics, Pfizer Inc, New London, CT, [4]Inflammation Global Medical Affairs, Pfizer, Collegeville, PA, [5]Pfizer Inc, Collegeville, PA, [6]Section of Musculoskeletal Disease, University of Leeds, Leeds, United Kingdom

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Background/Purpose:

The Hospital Anxiety and Depression Scale (HADs) is a generic measure of psychological status comprising anxiety and depression subscales. The aim of this study was to assess the psychometric properties of HADs in psoriatic arthritis (PsA), to calibrate the scale, and to provide interval-level scale for use in parametric analyses when required.

Methods:

We used HADS data from patients with PsA recruited in PRESTA trial. [1] The data was subjected to Rasch analysis to determine fit to the Rasch model (implying construct validity and unidimensionality), reliability and targeting in subjects with PsA.

Results:

The number of evaluable subjects was 740 at baseline, 701 at week 12, and 653 at week 24. Both the anxiety subscale and the depression subscale satisfied the expectation of the Rasch model (table 1). The overall scale was shown to fit the Rasch model (item-by-severity interaction Chi-Square = 15.878, p = 0.601) and had excellent reliability (person separation index = 0.888). Validity and reliability of HADS were confirmed at baseline and both follow-up visits.

Figure 1 presents person location relative to all items (logarithmically transformed scores) along the same scale (logits). The top plot representing 'persons severity'; those with higher scores (impaired psychological status) on the right of the scale and those with lower scores (better psychological status) on the left. The bottom plot presents relative 'difficulty' of the items. HADS appears to be well targeted across all 'severity' levels, providing for calibration of the scale by transforming raw scores into interval-level (Rasch-transformed) scores.

Conclusion:

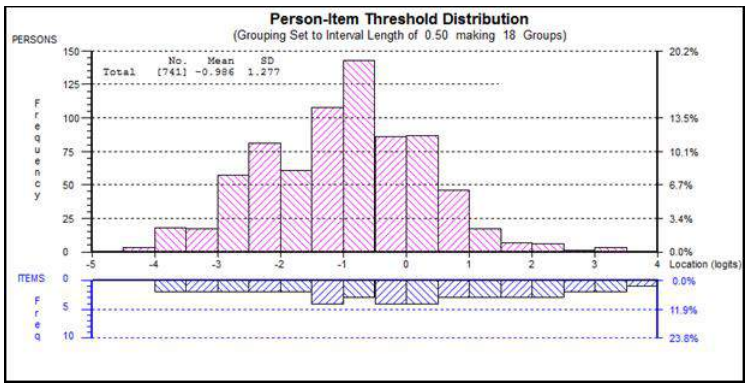
The validity and reliability of the HADS are confirmed in PsA and continues to be a useful psychological status instrument to use in PsA clinical studies. Raw scores can be Rasch-transformed into interval scores for use alongside other outcomes in parametric analyses.

Table 1. Fit Statistics for the Anxiety and Depression Subscales in PsA (Baseline).

Subscale	Location	SE	Item Fit Residuals	Chi-Square	DF	p-value
Anxiety	-0.120	0.021	-0.074	6.494	9	0.690
Depression	0.120	0.022	0.356	9.384	9	0.403

SE, Standard error; DF, Degrees of freedom, Non-significant p-value for Chi-Square suggests fit to Rasch model

Figure 1. Person-item Threshold Distribution Showing Targeting of the HADS (Baseline Data)



References:

1. Sterry W, et al. Comparison of two etanercept regimens for treatment of psoriasis and psoriatic arthritis: PRESTA randomised double blind multicentre trial. BMJ 2010;340(c147)

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Abstract Number: 656

Convergent Construct Validity of PsAID12 in a Psoriatic Arthritis Cohort at Baseline

Umut Kalyoncu[1,2], Levent Kilic[1], Abdulsamet Erden[1], Omer Karadag[1], Sule Apras Bilgen[1], Sedat Kiraz[1], Ihsan Ertenli[1], Clifton Bingham[3] and Ana-Maria Orbai[2], [1]Rheumatology, Hacettepe University Faculty of Medicine, Ankara, Turkey, [2]Rheumatology, Johns Hopkins University, Baltimore, MD, [3]Johns Hopkins University, Baltimore, MD

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Session Time: 9:00AM-11:00AM

Background/Purpose: The Psoriatic Arthritis Impact of Disease (PsAID) PRO measure was developed for clinical trials (9 item) and routine care (12 item) in Psoriatic arthritis (PsA) in multiple languages including Turkish. PsAID12 items (pain, fatigue, skin, work/leisure, function, discomfort, sleep, coping, anxiety, embarrassment, social life, depression) are 11 point numerical rating scales from 0 none/very well to 10 extreme/very poorly. PSAID12≤4 is considered patient acceptable symptom state. The performance of PsAID12 has not been reported to date in an independent PsA cohort.

Methods: Hacettepe University Rheumatology Biological database is a single center registry of 2700 patients with inflammatory arthritis (including PsA) on biologicals followed longitudinally. We collect demographics, clinical characteristics, 28 tender/swollen joint counts, CRP, health assessment questionnaire (HAQ), dermatology life quality index (DLQI), Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Bath Ankylosing Spondylitis Functional Index (BASFI), 100mm visual analog scales (VAS) for patient global assessment (PtGA), fatigue and pain. At the baseline visit we calculated: Spearman correlation coefficient of PSAID12 with measures of disease activity, function, quality of life and symptoms; and kappa statistic for agreement of PSAID12>4 with DAS28>2.6 and BASDAI>4.

Results: There were 163 PsA patients 66.3% female, 27.6% axial disease, mean(SD) (yrs) age 44.8(11.8), duration of PsA 10.3(7.3) and psoriasis 16.8(8.7). Mean(SD) scores were PsAID12 4.1(2.5), DAS28 3.04(1.41) and BASDAI 3.9(2.2). A PsAID12 score >4 (52.8% patients) was associated with female (59% vs 40%, p=0.020), BMI>30 (66.6% vs 43.5%, p=0.005), diabetes (80.0% vs 50.0%, p=0.027), hypertension (70.0% vs 48.8%, p=0.036), no axial disease (57.6% vs 40.0%, p=0.044). Correlations between measures are presented in Table. PsAID12>4 agreement with DAS28>2.6 was kappa=0.53 (95%CI 0.38-0.67) and with BASDAI>4 was kappa=0.60 (95%CI 0.48-0.73).

Conclusion: In this group of PsA patients, PSAID12 had moderate-high correlation with PROs reflecting PsA symptoms, functional impairment and quality of life, but not with CRP. PSAID12had moderate-high agreement with PsA disease activity as measured by DAS28 and BASDAI. Our data support convergent construct validity of PsAID12 in an independent PsA cohort. Additional evaluations of longitudinal construct validity and responsiveness are needed.

Table : Correlation coefficients of PsAID12 with disease activity and PsA outcome measures

	PSAID12	DAS28*	BASDAI	Pain	Fatigue	BASFI	HAQ-DI	DLQI	PtGA	CRP (mg/dL)
PSAID12	1.00	0.55	0.72	0.54	0.54	0.67	0.69	0.59	0.64	0.22
DAS28	0.55	1.00	0.59	0.57	0.57	0.47	0.47	0.28	0.67	0.51
BASDAI	0.72	0.59	1.00	0.73	0.68	0.76	0.64	0.33	0.75	0.22
Pain	0.54	0.57	0.73	1.00	0.67	0.53	0.52	0.36	0.83	0.24
Fatigue	0.53	0.57	0.68	0.67	1.00	0.51	0.49	0.29	0.75	0.19
BASFI	0.67	0.47	0.76	0.53	0.51	1.00	0.75	0.39	0.55	0.25
HAQ-DI	0.69	0.47	0.64	0.52	0.49	0.75	1.00	0.45	0.49	0.22
DLQI	0.59	0.28	0.33	0.36	0.29	0.39	0.45	1.00	0.38	0.02
PtGA	0.64	0.67	0.75	0.83	0.75	0.55	0.49	0.38	1.00	0.23
CRP (mg/dL)	0.22	0.51	0.22	0.24	0.19	0.25	0.22	0.02	0.23	1.00

*DAS-28 data was available for 130 patients.

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Abstract Number: 657

Routine Assessment of Patient Index Data 3 Score (RAPID3) and Psoriasis Quality of Life (PQoL-12) Assess Different Domains in Psoriasis (PsO) and Psoriatic Arthritis (PsA) Patients

Kiana Vakil-Gilani[1], Alexis Dinno[2], Neha Garg[3] and Atul A. Deodhar[4], [1]Arthritis and Rheumatic diseases, Oregon Health and Science University, Portland, OR, [2]School of Community Health, Portland State University, Portland, OR, [3]Rheumatology, Oregon Health and Science University, Portland, OR, [4]Division of Arthritis & Rheumatic Diseases, Oregon Health & Science University, Portland, OR

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Session Title: Spondylarthropathies and Psoriatic Arthritis - Clinical Aspects and Treatment Poster I: Clinical Aspects and Assessments

Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose:

PQoL-12 is a validated composite tool (range: 0–120) assessing patients' quality of life in PsO and PsA. RAPID3 is another validated composite index (range: 0–10) measuring physical function, pain and patient global assessment in rheumatoid arthritis and ankylosing spondylitis, but not in PsO/PsA. If RAPID3 could be used to assess PsO/PsA patients' quality of life, it may save time in busy practices. This study investigates the correlation between PQoL-12 and RAPID3 in PsO and PsA patients, and also the cut-off values for RAPID3 that correlate best with PQoL-12 of 48 (mild) and 96 (moderate QoL impairment).

Methods:

Data from PsO and PsA patients seen from 2008 onwards in the Center of Excellence in Psoriasis and Psoriatic Arthritis clinic at Oregon Health & Science University were used (N= 555, 390 with PsO, 165 with PsA). Nonlinear least squares regressions modeled PQoL-12 with functions of RAPID3 while controlling for time since first visit. Nonparametric ROC analysis determined RAPID3 scores best correlating with PQoL-12 cut-

offs.

Results:

Baseline mean age was 46.7(12.8) and 45.9(12.8) years for PsO and PsA. The M:F ratio was 3:2 and 1:1 for PsO and PsA. Mean disease duration was 0.93(1.08) and 1.11(1.20) years for PsO and PsA. Baseline mean PQoL-12 was 65.8 (29.5) and 75.2 (29.2), and RAPID3 was 2.4 (2.01) and 3.7 (2.4) for PsO and PsA. For PsO, PQoL-12 was explained by RAPID3 (b = 16.6; s.e.= 1.63), RAPID3^2(b = -1.22 ; s.e. = 0.0701), time since first visit (b = -0.00211 ; s.e.= 0.00467), and a saturation (q = 281; s.e. = 116) of time since first visit^2 (b = 0.000211; s.e.= 0.000174) with adjusted R^2=0.414 (figure 1). For PsA, PQoL-12 was explained by RAPID3 (b =12.9; s.e.= 2.99), change (q = 2.28; s.e. = 81.5) in slope of RAPID3 (b =-7.39 ; s.e.=3.38), time since first visit (b = -0.00172 ; s.e.= 0.00685), and a saturation (q = 223; s.e. = 116) of time since first visit^2 (b =0.000417; s.e.= 0.000388=4) with adjusted R^2=0.340 (figure2). RAPID3 cut-offs for PQoL–12 scores of 48 and 96 in PsO were 1.38 and 7.22 (71.2% and 88.4% correctly classified) and in PsA were 2.06 and 6.61 (70.4% and 89.0% correctly classified).

Conclusion:

RAPID3 correlates poorly with PQoL-12. These indices assess different aspects of PsO and PsA, and provide distinct and important information regarding the patients' diseases.

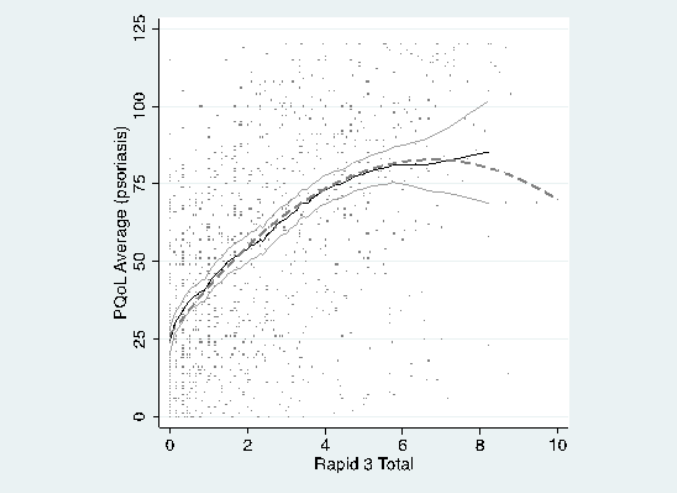

Figure 1- Nonparametric regression of PQoL-12 on RAPID3 in PsO

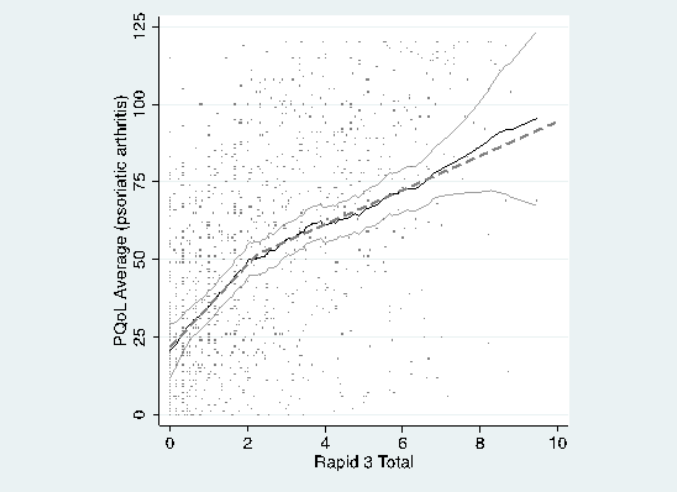

Figure 2- Nonparametric regression of PQoL-12 on RAPID3 in PsA

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Abstract Number: 658

Health Related Quality of Life in Psoriatic Arthritis from the Perspective of People Living with the Condition

Ana-Maria Orbai[1,2], Suzanne Grieb[3], Clifton Bingham[4], Michelle Jones[4], Grazyna Purwin[5] and Katherine Clegg-Smith[6], [1]Rheumatology, Johns Hopkins University School of Medicine, Baltimore, MD, [2]Rheumatology, Johns Hopkins University, Baltimore, MD, [3]Johns Hopkins Bayview Medical Center, Center for Child and Community Health Research, Baltimore, MD, [4]Johns Hopkins University, Baltimore, MD, [5]Johns Hopkins Arthritis Center, Baltimore, MD, [6]Health, Behavior and Society, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD
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Session Time: 9:00AM-11:00AM

Background/Purpose: Psoriatic arthritis (PsA) is a complex inflammatory disease with variable phenotype affecting skin, joints, ligaments/tendons, nails, and the spine. Heterogeneity of clinical manifestations complicates PsA assessment and broadens its impact (1). PsA activity is a difficult concept to measure since outcome measures in use do not systematically cover health areas prioritized by patients (2). The experience of PsA from the perspective of patients, while essential for choosing outcome measures, is not known.

Methods: Patients with PsA meeting CASPAR criteria followed longitudinally in an academic clinic were recruited after informed consent. Focus groups (FG) and individual interviews were conducted using a semi-structured guide on the following topics: 1) presence of PsA in daily life; 2) life changes since diagnosis; 3) PsA activity. Qualitative data were analyzed by 3 researchers (1 physician, 1 medical anthropologist, 1 sociologist) using inductive thematic analysis and discussions to achieve consensus.

Results: Data were analyzed from 8 participants in 2FGs and 25 participants in individual interviews. Demographics and clinical characteristics are described in Table and represent the range of PsA manifestations.

Table. Participant demographics and clinical characteristics			
Participant demographics and characteristics	**FG1 (n=5)**	**FG2 (n=3)**	**Individual interviews (n=25)**
Age (years), mean(SD)	60 (8.5)	54.3 (4.7)	52.9 (10.6)
Sex, n(%)			
Female	4 (80)	3	16 (64)
Male	1 (20)	0	9 (36)
Race, n(%)			
African American	0	0	0
Asian	0	0	1 (4)
Caucasian	5	3	23 (92)
Other	0	0	1 (4)
Ethnicity, n(%)			
Hispanic	0	0	0
Non-Hispanic/Latino	1	1	15(60)
Not reported	4	2	10(40)
Psoriatic arthritis symptom duration (yrs), mean(SD)	15.2 (13.7)	6.7 (6.4)	15.8 (10.2)
Psoriatic arthritis disease diagnosis duration (yrs), mean(SD)	14.0 (13.7)	6.7 (6.4)	11.5 (10.8)
CASPAR criteria			
Psoriasis, n(%)			
Ever	5	3	24(96)
None	0	0	1 (4)
Nail Psoriasis, n(%)			
Ever	2(40)	2(67)	8(32)
None	3(60)	1(33)	17(68)
Dactylitis, n(%)			
Ever	2(40)	1(33)	10(40)
None	3(60)	2 (67)	15(60)
Rheumatoid factor, n(%)			
Positive	0	0	2 (8)
Negative	3(60)	3	18(72)
Unknown	2(40)	0	5(20)
Juxta-articular new bone formation, n(%)			
Yes	1(20)	1(33)	2 (8)
None	1(20)	2(67)	12(48)
Unknown	3(60)	0	11(44)
Patient Reported Outcomes			
mHAQ* (range 0-3), mean(SD)	0.55 (0.69)	0.17 (0.29)	0.31 (0.38)
Pain VAS** (0-100), mean(SD)	41.2 (29.6)	36.7 (53.3)	37.8 (27.6)
Patient Global Disease Activity VAS, mean(SD)	41.8 (30.5)	38.3 (52.0)	34.3 (30.3)
Fatigue VAS, mean(SD)	44.2 (35.7)	35 (52.0)	38.0 (31.8)
Stiffness VAS, mean(SD)	53.3 (37.9)	37.7 (50.0)	41.4 (29.0)
Patient Joints VAS, mean(SD)	45.6 (40.7)	29.7 (39.6)	39.5 (29.2)
Patient Skin VAS, mean(SD)	46.3 (25.6)	21.3 (25.2)	30.5 (34.1)
Medications			
Biologic, n(%)			

Yes	5	3	16(64)
DMARD only	0	0	9(36)
*mHAQ modified Health Assessment Questionnaire, score range 0-3 **VAS visual analog scale 0-100mm			

Several overarching themes and corresponding codes were identified: 1) Psoriatic disease state/symptoms; 2) Life impact; 3) Strategies to minimize life impact. A draft conceptual framework based upon the coding structure for the PsA experience is illustrated in Figure 1.

Conclusion: Participants described the PsA experience not only through symptoms but also through life impact and individual strategies to prevent/minimize impact on their life. Comprehensive PsA assessment may need to include measures for life impact and also for effectiveness of individual compensating strategies.

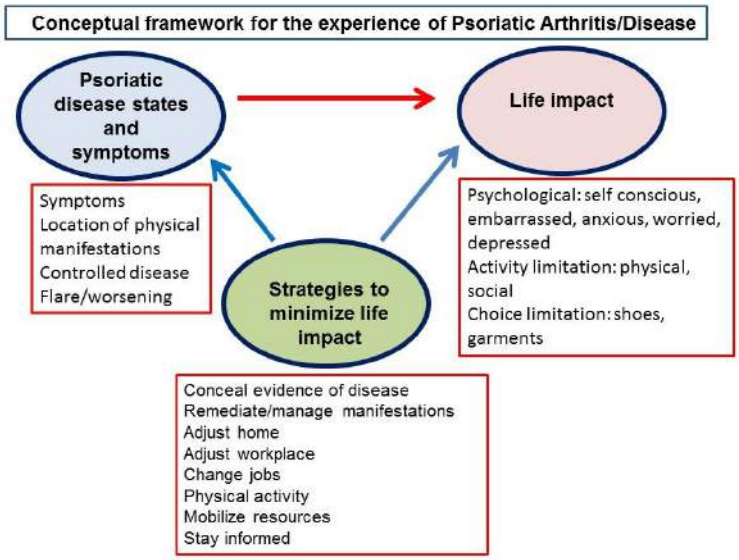

Figure 1. Conceptual framework for PsA experience elicited from qualitative research with participants with PsA.

1. Taylor WJ, et al. Effect of psoriatic arthritis according to the affected categories of the international classification of functioning, disability and health. J Rheum. 2010;37:1885-91.
2. Stamm TA, et al. Concepts important to patients with psoriatic arthritis are not adequately covered by standard measures of functioning. Arthritis Rheum. 2007;57:487-94.

Disclosure: A. M. Orbai, None; **S. Grieb**, None; **C. Bingham**, UCB Pharma, 5; **M. Jones**, None; **G. Purwin**, None; **K. Clegg-Smith**, None.

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Abstract Number: 659

Does the Inclusion of Extra-Articular Manifestations Improve Validity of the Self-Administered Comorbidity Questionnaire Modified for Spondyloarthritis (SpA-SCQ)? Results from ASAS-Comospa

Ivette Essers[1,2], Carmen Stolwijk[1,2], Adrien Etcheto[3], Anna Molto[4], Filip van Den Bosch[5], Désirée van der Heijde[6], Robert B.M. Landewé[7,8], Astrid van Tubergen[1,2], Maxime Dougados[4,9] and Annelies Boonen[1,10], [1]School for Public Health and Primary Care (CAPHRI), Maastricht University, Maastricht, Netherlands, [2]Rheumatology, Maastricht University Medical Center, Maastricht, Netherlands, [3]Cochin Hospital, Paris Descartes University, Paris, France, [4]Hopital Cochin, Paris Descartes University, Paris, France, [5]Department of Rheumatology, Ghent University Hospital, Ghent, Belgium, [6]Department of Rheumatology, Leiden University Medical Center, Leiden, the Netherlands, Leiden, Netherlands, [7]Rheumatology, Atrium Medical Center, Heerlen, Netherlands, [8]Department of Rheumatology, Amsterdam Rheumatology Center, Amsterdam, Netherlands, [9]Rheumatology Department, Hôpital Cochin, Paris, France, [10]Maastricht University Medical Center, Maastricht, Netherlands

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Session Time: 9:00AM-11:00AM

Background/Purpose: The self-administered comorbidity questionnaire (SCQ) was developed to understand the impact of 13 common comorbidities on functioning and resource utilisation. In patients with ankylosing spondylitis, we recently showed that criterion- and construct validity of the SCQ was good, and improved after removing rheumatic items from the questionnaire (SpA-SCQ) (1). However, this modification (SpA-SCQ) does not address uveitis, psoriasis and inflammatory bowel disease, which are frequently occurring extra-articular manifestations (EAMs) in spondyloarthritis (SpA), and might have a relevant impact on disease specific and generic outcomes. The aim of the present study was to assess and compare criterion and construct validity of the SpA-SCQ and the SpA-SCQ with 3 items representing the EAMs ("SpA-SCQ-EAM").

Methods: Data from the CO-MOrbidities in SPA (COMOSPA) study, conducted in 22 countries, were used. We hypothesised that the criterion validity of the added EAM, assessed by agreement (kappa) between patients' self-reported and physicians' confirmed diagnoses of each of the three EAM, was good. For construct validity, we hypothesised that the SpA-SCQ-EAM would correlate moderate (r>0.30) and somewhat better (r-difference >0.05) than SpA-SCQ with demographics, physical function (BASFI), work-ability (WPAI) and health utility (EQ-5D),and that both would have low correlation with disease activity (ASDAS-CRP). We further hypothesized that the SpA-SCQ(-EAM) correlated better with these outcomes (but not disease activity) than the rheumatic disease comorbidity index (RDCI).

Results: 3,984 patients (age 43.6 (SD 13.9) years, 2,588 (65.0%) male, disease duration 8.2 (SD 9.3) years, of which 2,217/3,067 (72.4%) HLA-B27 positive) contributed to the analyses. The mean SpA-SCQ was 2.0 (SD 2.8) and the SpA-SCQ-EAM 2.8 (SD 3.3). The agreement between patient and physician diagnosed EAMs was substantial to almost perfect (uveitis κ=0.81, IBD κ=0.74, psoriasis κ=0.78), and was not systematically different across countries. Table 1 shows the correlations between the SpA-SCQ-(EAM) and outcomes, and makes clear that the hypothesis of a better correlation of the SpA-SCQ-EAM than SpA-SCQ with outcomes could not be confirmed. On the other hand, both the SpA-SCQ and the SpA-SCQ-EAM performed better with respect to the correlations with outcomes than the RDCI (Table 1). Similar results were found for patients with axial and 'pure' peripheral SpA.

Conclusion: EAMs can be reliably assessed through self-report by patients with SpA. Notwithstanding, adding the EAMs to the SpA-SCQ can improve the face validity of this questionnaire. Both the SpA-SCQ and SpA-SCQ-EAM correlated better with health outcomes than the RDCI in patients with (axial and peripheral) SpA.

Table 1: Construct Validity of the SpA-SCQ and the SpA-SCQ-EAM

	SpA-SCQ	SpA-SCQ-EAM	RDCI
SpA-SCQ	-	**0.95**	**0.59**
SpA-SCQ-EAM	-	-	**0.56**
RDCI	-	-	-
Male gender	**0.10**	**0.11**	-0.01
Age (years)	**0.38**	**0.40**	**0.44**
Disease duration (years)	**0.20**	**0.22**	**0.25**
BMI	**0.27**	**0.29**	**0.28**
ASDAS-CRP	**0.09**	**0.07**	**0.06**
CRP	-0.01	-0.03	-0.01
BASFI	**0.35**	**0.35**	**0.26**
Global well-being	**0.21**	**0.20**	**0.12**
Influence work productivity	**0.21**	**0.20**	**0.11**
Influence on daily activities	**0.30**	**0.30**	**0.17**
EQ-5D (French tariff)	**-0.33**	**-0.34**	**-0.20**

Bold: correlation coefficient significant

The SpA-SCQ was based on the following items: heart disease, hypertension, lung disease, diabetes, ulcer or other stomach disease, kidney disease, anaemia or other haematological disease, cancer, depression and fractures. For the SpA-SCQ-EAM we also included uveitis, inflammatory bowel disease and psoriasis. The RDCI was based on the information collected by the physician, only depression was based on the information from the patients.

SpA-SCQ, spondyloarthritis self-administered comorbidity questionnaire; EAM: extra-articular manifestations; RDCI, Rheumatic Disease Comorbidity Questionnaire; BMI, body mass index; ASDAS, Ankylosing Spondylitis Disease Activity Score; CRP, C-reactive protein; BASFI, Bath Ankylosing Spondylitis Functional Index; EQ-5D, EuroQoL index

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Abstract Number: 660

Comparison of the Four Validated Psoriatic Arthritis Screening Tools in Diagnosing Psoriatic Arthritis in Patients with Psoriasis [Compaq Study]

Aman Sharma[1], Sushant Mishra[2], Sunil Dogra[3] and Harish Kancharla[2], [1]Internal Medicine (Rheumatology Unit), Postgraduate Institute of Medical Education and Research, Chandigarh, India, [2]Department of Internal Medicine,, PGIMER,, Chandigarh, India, [3]Department of Dermatology, PGIMER,, Chandigarh, India

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Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose: Although there are various Psoriatic arthritis (PsA) screening questionnaires, the most optimal screening instrument is not known. The objective of the present study was to evaluate the sensitivity and specificity the four psoriatic arthritis screening tools (TOPAS II, PASE, PEST and EARP) in diagnosing Psoriatic Arthritis in patients with Psoriasis with CASPAR as gold standard.

Methods:

This was a non-interventional, cross sectional study in which 302 patients diagnosed with PsO completed the Toronto Psoriatic Arthritis Screening Questionnaire (TOPAS II), Psoriatic Arthritis Screening And Evaluation (PASE), Psoriasis Epidemiology Screening Project (PEST) and Early Arthritis For Psoriasis Patients (EARP) prior to rheumatologic evaluation. The cutoff scores used in the original validation studies of these questionnaires were used to designate positive and negative cases. Sensitivities and specificities of these questionnaires were determined by comparing the score with the diagnosis made by the CASPAR criteria.

Results:

Out of 302 patients with PsO, 45 had PsA according to CASPAR criteria (14.9%). 27 patients had a TOPAS II score of ≥8 suggestive of PsA. The mean TOPAS II score of the PsO patients was 2.93±2.6 and that of PsA patients was 6.84±1.9. 36 patients had a PEST questionnaire score of ≥3 suggestive of PsA. The mean PEST score of the PsO patients was 0.86±1.24, that of PsA patients was 2.73±1.45. For calculation of PASE score, 2 cutoffs were used separately. 50 patients had a PASE questionnaire score of ≥44 (recommended in a validation study of PASE) suggestive of PsA. 47 patients a PASE score 47(used in development of PASE questionnaire). 72 patients had EARP questionnaire score of ≥3 suggestive of PsA. The mean EARP score of the PsO patients was 1.44±2.33 and that of PsA patients was 5.47±2.25.The sensitivities and specificities of EARP, $PASE_{44}$, $PASE_{47}$ PEST, and ToPAS II were 91.1%, 80%, 75.6%, 53.3%, 44.4% and 87.9%, 94.6%, 94.9%, 95.3% 97.3% respectively.

Conclusion: Out of the four screening questionnaires, EARP was most sensitivity while TOPAS II had least sensitivity. TOPASII had highest specificity while EARP had least specificity.

Disclosure: A. Sharma, None; **S. Mishra**, None; **S. Dogra**, None; **H. Kancharla**, None.

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Abstract Number: 661

ASDAS Can be Reliably Calculated When Only the Patient's Overall Basdai Score Is Available, but Not the Score(S) of Its Individual Component(S)

Pinar Cetin[1], **Gokce Kenar**[1], Sedat Capar[2], Handan Yarkan[1], Berrin Zengin[1], Ismail Sari[1], Merih Birlik[1], Fatos Onen[1] and Nurullah Akkoc[3], [1]Rheumatology, Dokuz Eylul University Faculty of Medicine, Izmir, Turkey, [2]Dokuz Eylül University Faculty of Statistics, Izmir, Turkey, [3]Department of Rheumatology, Dokuz Eylul University, Faculty of Medicine, Izmir, Turkey

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Background/Purpose: ASDAS is a composite measure of disease activity for ankylosing spondylitis (AS). Its calculation includes three BASDAI questions, BASDAI Q2 (back pain), Q3 (peripheral pain/swelling), and Q6 (morning stiffness), plus ESR or CRP, depending on the version. In many patients' clinical records, BASDAI total score is included but the scores of its individual components are missing. Our aim was to assess the validity of imputing missing BASDAI items from the overall BASDAI score in order to calculate the patient's ASDAS in such a clinical situation.

Methods: Patients with complete baseline data for ASDAS and BASDAI components were identified from our local AS database. Original ASDAS calculations were repeated by replacing each or all of the BASDAI items included in the formula with the overall BASDAI score. Kappa statistics was used to assess the agreement between the original and the imputed ASDAS scores, in classifying patients into different disease activity states (inactive, moderate, high and very high). The mean difference between scores was calculated. The analysis was completed with the *Bland–Altman* method.

Results: 403 patients with AS (age 44.4±11.8 years; 73.7% males) with a mean disease duration of 9.7±8.1 years were included in this analysis. Their mean (SD) BASDAI, ASDAS-CRP and ASDAS-ESR scores were 3.6 (2.3), 3.1 (1.1), and 3.1 (1.1), respectively. Kappa values ranged from 0.80 to 0.89 (weighted kappa values from 0.84 to 0.96), with lower limits of the 95%CI all over 0.75 in the different imputation schemes (Table 1). The largest mean difference between the original and the imputed scores was 0.17.

Conclusion: The close agreement between the original and the imputed ASDAS scores observed in this analysis support the validity of imputing missing BASDAI items from the overall BASDAI, when the score(s) of its individual component(s) are lacking.

Table 1. Agreement between the original ASDAS and imputed scores after replacing individual BASDAI item values with overall BASDAI scores

	Agreement level between the methods		**Limits of agreement between the methods***		
	Kappa value	**95% CI**	**Mean difference**	**Lower limit**	**Upper limit**
ASDAS CRP vs ASDAS CRP imputed for three BASDAI items	0.8	0.74 to 0.85	0.07	−0.4	0.53
ASDAS CRP vs ASDAS CRP imputed for BASDAI item 2	0.8	0.75 to 0.85	0.17	−0.25	0.59
ASDAS CRP vs ASDAS CRP imputed for BASDAI item 3	0.88	0.84 to 0.92	−0.09	−0.38	0.2
ASDAS CRP vs ASDAS CRP imputed for BASDAI item 6	0.83	0.78 to 0.88	−0.02	−0.02	0.26
ASDAS ESR vs ASDAS ESR imputed for three BASDAI items	0.88	0.84 to 0.92	−0.02	−0.47	0.43
ASDAS ESR vs ASDAS ESR imputed for BASDAI item 2	0.89	0.85 to 0.93	0.12	−0.16	0.4
ASDAS ESR vs ASDAS ESR imputed for BASDAI item 3	0.82	0.78 to 0.88	−0.12	−0.49	0.26
ASDAS ESR vs ASDAS ESR imputed for BASDAI item 6	0.88	0.84 to 0.93	−0.02	−0.34	0.31

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Abstract Number: 662

Can the New Contest Questionnaire Identify Psoriatic Arthritis in a Primary Care Population?

Laura C Coates, Laura J Savage, Anna R. Moverley and Philip S. Helliwell, Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds, Leeds, United Kingdom
First publication: September 29, 2015

SESSION INFORMATION
Session Date: Sunday, November 8, 2015
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Background/Purpose: There is a need for screening questionnaires to identify patients with psoriasis who have undiagnosed psoriatic arthritis but the optimal method is unknown. We developed the CONTEST questionnaires using the most discriminative items from 3 existing tools:

CONTEST consists of 8 yes/no items and CONTESTji the same items with the addition of a joint manikin. Our aim was to test the new proposed CONTEST questionnaires alongside the validated PEST questionnaire in a primary care setting.

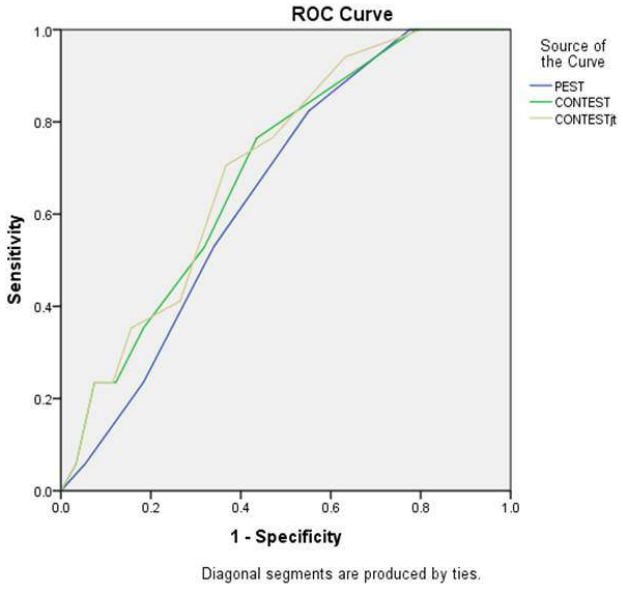
Methods: Patients with psoriasis were identified from 5 GP surgeries in Yorkshire and a random sample were invited to participate in the study. Patients had to be over 18 years old, have a diagnosis of psoriasis and no diagnosis of PsA, RA or AS. Consenting patients were asked to complete the PEST and CONTEST questions and were then assessed by a dermatologist and rheumatologist. Diagnosis of PsA was made by the assessing rheumatologist as lab and radiographic data were unavailable to assess the CASPAR criteria. Receiver operator characteristic (ROC) curve analysis was used to assess the PEST and CONTEST questionnaires using physician diagnosis as the gold standard. Sensitivity and specificity of potential cut points were examined.

Results: A total of 932 packs were sent out to recruit 191 (20.5%) participants attending for assessment. Of these, 169 (88.5%) had current or previous psoriasis. Using physician diagnosis 17 (10.1%) were found to have previously undiagnosed PsA, 90 (53.3%) were found to have another musculoskeletal complaint and 62 (36.7%) had no musculoskeletal problems.

Using ROC curve analysis, all of the questionnaires showed a significant ability to identify PsA. The area under the curve (AUC) for the CONTEST and CONTESTjt questionnaires was slightly higher than that of PEST (see table 1) but there was no significant difference between any of the questionnaires. Examining the sensitivities and specifities for the different cut points, suggested that a PEST score of ≥2 would perform better in this dataset, and optimal scores for CONTEST and CONTESTjt seemed to be 3 and 4 respectively.

Conclusion: The accuracy of the PEST and CONTEST questionnaires to identify PsA appeared similar with slightly higher AUC for the CONTEST questionnaires. Optimal cut points in this study appeared lower than in previous studies (PEST≥2, CONTEST≥3, CONTESTjt≥4).

Test	Score	AUC	Sensitivity	Specificity
PEST	2	0.652	0.824	0.449
	3	0.652	0.529	0.660
	4	0.652	0.235	0.816
CONTEST	2	0.694	0.882	0.388
	3	0.694	0.765	0.565
	4	0.694	0.529	0.680
	5	0.694	0.353	0.816
CONTESTjt	2	0.704	0.941	0.337
	3	0.704	0.765	0.531
	4	0.704	0.706	0.633
	5	0.704	0.412	0.735
	6	0.704	0.353	0.844



Disclosure: L. C. Coates, Janssen Pharmaceutica Product, L.P., 2,Janssen Pharmaceutica Product, L.P., 8; **L. J. Savage**, Janssen Pharmaceutica Product, L.P., 8; **A. R. Moverley**, None; **P. S. Helliwell**, Janssen Pharmaceutica Product, L.P., 8,Pfizer Inc, 5.

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Abstract Number: 663

Mases Correlates Linearly with Disease Activity and Patient Related Outcomes in Patients with Axial Spondyloarthritis within the Scqm Cohort

Ruediger Mueller[1], Toni Kaegi[2], Nicole Graf[3], Johannes von Kempis[4] and J.J. Luime[5], [1]Rheumatology, MD, St. Gallen, Switzerland, [2]Kantonsspital St. Gallen, St. Gallen, Switzerland, [3]graf biostatistics, Winterthur, Switzerland, [4]Rheumatology, Kantonsspital St. Gallen, St. Gallen, Switzerland, [5]Department of Rheumatology, Erasmus Medical Centre, Rotterdam, Netherlands
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Background/Purpose:

Enthesitis is one of the potential extra-axial manifestations found in patients with spondyloarthritis (SpA). Enthesitis can be quantified using the MASES (Maastrich Ankylosing Spondylitis Enthesitis *Score*), consisting 13 pre-defined entheses assessed for tenderness. There are few data on the MASES outside of RCTs. To better understand enthesitis real live data could be helpful.

Objective:

To analyse cross-sectionally the correlation of enthesitis with clinical and personal outcome parameters in patients with axial spondyloarthritis.

Methods:

We included all patients from the Swiss national registry SCQM with axial spondyloarthritis and valid MASES at baseline. Patients were analysed for demographics at baseline, medical history, physical assessments (BASMI, BASFI, BASDAI) and patient centred outcomes (SF36). Data was analysed using descriptive statistics and linear regression.

Results:

3241 patients were included into the study with MASES data available at baseline. 45.9% of the patient had no documented entheseal affection at baseline (MASES = 0). Patients had an average age of 41.6 years, symptom duration of 11.8 years and disease duration of 6.3 years since diagnosis on average. There was a predominance (57.5%) for the male gender. 59.7% of the patients were HLA B27 pos. and 60.5% of the patients were suffering from radiographic axial disease as defined by positivity for the New York criteria.

The percentage of patients with a higher MASES (0-13) decreased linearly (slope -63.5, $R^2 = 0.48$). In parallel, average clinical scores BASDAI, BASFI, BASMI, ASDAS, patient´s global assessment of disease activity increased linearly with increasing MASES (BASDAI: slope 0.23, $R^2 = 0.89$; BASFI: slope 0.27, $R^2 = 0.87$; BASMI: slope 0.09, $R^2 = 0.82$; ASDAS: slope 0.09, $R^2 = 0.90$, patient´s global: slope 0.23; $R^2 = 0.85$) whereas the SF 36 decreased (physical component score: slope -0.73, $R^2 = 0.76$; mental component score: slope -0.72, $R^2 = 0.67$).

Conclusion:

Entheseal involvement is a frequently occurring contributor to disease activity and function in patients with axial SpA. MASE scores correlate well with disease activity and patient centred outcomes.

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Abstract Number: 664

Patient Reported Outcomes and Assessment of the Quality of Life in a Cohort of Patients Affected By Enteropathic Spondyloarthritis: Definitive Results of a Monocentric Prospective Observational Study at One Year

Chiara Avellini[1], Laura Bolognini[2], Alessia Farinelli[1], Monia Ciferri[3], Greta Gambacorta[3], Devis Benfaremo[3], Serena Cedraro[3], Matteo

Rossini[3], William Capeci[3], Lucia Manfredi[3], Laura Postacchini[3], Giammarco Fava[2], Piergiorgio Mosca[2], Giovanni Pomponio[3], Michele Maria Luchetti[3] and Armando Gabrielli[3], [1]Scienze Cliniche e Molecolari, Clinica Medica, Università Politecnica delle Marche, Ancona, Italy, [2]Gastroenterologia, Azienda "Umberto I-G.M.Lancisi-G.Salesi", Ancona, Italy, [3]Clinica Medica, Università Politecnica delle Marche, Ancona, Italy
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Session Time: 9:00AM-11:00AM

Background/Purpose:

Enteropathic spondyloarthritis (ES) are included in the group of the spondyloarthritis (SpA). Because articular involvement is the most frequent extra-intestinal manifestation in patients with inflammatory bowel diseases (IBD), the coexistence of gut and articular inflammation advocates an integrated approach for the clinical management of these patients in clinical practice (Olivieri I. et al. *Autoimmun Rev* 2014, 8:822-30).

We carried out a clinical study, henceforth defined **SPIB** (**SP**ondyloarthritis in **I**nflammatory **B**owel disease), in the outpatient clinics and in the clinical ward of the gastroenterology and internal medicine departments, having the following end-points; a) the early diagnosis of ES; b) the evaluation of the quality of life before and after therapeutic integrated approach.

Methods:

From January, 2014 to January 2015, 198 consecutive IBD pts were screened; 48 refused to participate to the study and 154 were evaluated at baseline and after 6 and 12 months for gastrointestinal symptoms and activity, patient-reported outcomes of the quality of life and rheumatologic symptoms (Fig.1, table I). Upon a gastroenterologist and rheumatologist evaluation, the therapeutic strategy was chosen in concert based on gastrointestinal and joint disease activity, and the presence of peripheral and/or axial involvement of the joints.

Results:

65 (33,6%) of the 154 pts complained of articular symptoms and in 51 of 65 (25,8% of all IBD pts) an active enteropathic SpA (ES) was diagnosed. Peripheral arthritis was present in 23 pts (45%) and axial involvement in 28 pts (55%). Articular symptoms had been present for 5±4,9 yrs in 51% of the ES pts. The quality of life in the cohort of ES pts, compared to that of IBD pts, was significantly worsened by articular symptoms (Fig.1A). At baseline, 20 ES pts were treated with methotrexate, 2 with salazopyrine, 5 with infliximab, and 23 with adalimumab.

After 12 months of treatment, 90% of the ES pts reported a significant improvement in their quality of life (Fig.1B). A significant improvement of both gastrointestinal (Fig.1B) and articular disease (Fig.1C) was achieved in 88% of the patients, mostly in pts receiving anti-TNF-alfa drugs.

Conclusion:

The early diagnosis of enteropathic spondyloarthritis and the choice of the optimal therapeutic strategy constitute a novel major topic in clinical practice (Olivieri I. et al. *Autoimmun Rev* 2014, 8:822-30).

Our study reinforces the importance of an integrated clinical evaluation of ES pts carried out by the gastroenterologist and rheumatologist, for a correct diagnosis and the choice of the optimal therapeutic strategy.

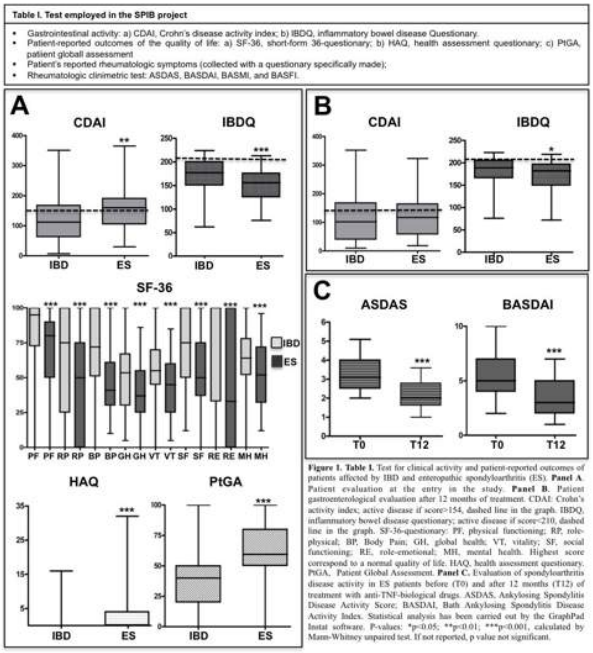

Figure 1. Table I. Test for clinical activity and patient-reported outcomes of patients affected by IBD and enteropathic spondyloarthritis (ES). **Panel A**. Patient evaluation at the entry in the study. **Panel B**. Patient gastroenterological evaluation after 12 months of treatment. CDAI: Crohn's activity index; active disease if score>154, dashed line in the graph. IBDQ, inflammatory bowel disease questionary; active disease if score<210, dashed line in the graph. SF-36-questionary: PF, physical functioning; RP, role-physical; BP, Body Pain; GH, global health; VT, vitality; SF, social functioning; RE, role-emotional; MH, mental health. Highest score correspond to a normal quality of life. HAQ, health assessment questionary. PtGA, Patient Global Assessment. **Panel C**. Evaluation of spondyloarthritis disease activity in ES patients before (T0) and after 12 months (T12) of treatment with anti-TNF-biological drugs. ASDAS, Ankylosing Spondylitis Disease Activity Score; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index. Statistical analysis has been carried out by the GraphPad Instat software. P-values: *p<0.05; **p<0.01; ***p<0.001, calculated by Mann-Whitney unpaired test. If not reported, p value not significant.

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Abstract Number: 665

Construct Validity of Disease Activity for Psoriatic Arthritis Composite Index and Tentative Cut-Off Values in a Cohort of Patients with Psoriatic Arthritis

Josefina Gallino Yanzi[1], Emilce Schneeberger[1], Osvaldo Luis Cerda[1], Cecilia Zaffarana[1], Margarita Landi[1], Marcos G. Rosemffet[2], Natalia Zamora[3], Tomas Cazenave[2], Fernando Dal Pra[1], Paula Kohan[4], Emilio Buschiazzo[5] and Gustavo Citera[2], [1]Instituto de Rehabilitación Psicofísica, Buenos Aires, Argentina, [2]Rheumatology, Instituto de Rehabilitación Psicofísica, Buenos Aires, Argentina, [3]Reumatologia, Instituto de Rehabilitación Psicofisica, Buenos Aires, Argentina, [4]Hospital Dr. E. Tornu, Buenos Aires, Argentina, [5]Rheumatology, Hospital Sr Del Milagro, Salta, Argentina

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Session Time: 9:00AM-11:00AM

Background/Purpose: Disease Activity for Psoriatic Arthritis (DAPSA) is a composite index that assesses disease activity in patients with Psoriatic Arthritis (PsA) taking into account peripheral arthritis. The aim of our study was to validate DAPSA and to evaluate its performance using minimal disease activity (MDA) and different cut-off points.

Methods: Patients ≥18 years with PsA according to CASPAR criteria, belonging to RAPSODIA cohort were included. We recorded demographic data, clinical presentation, comorbidities and treatment. Morning stiffness, pain and global activity by patient and physician were assessed using visual analogue scale (VAS). We evaluated tender (68) and swollen joints (66), dactylitis and enthesitis by MASES (Maastricht Ankylosing Spondylitis Enthesitis Score). CRP and ESR were measured. ASQoL (Ankylosing Spondylitis Quality of Life), PsAQoL (Psoriatic Arthritis Quality of Life), HAQ (Health Assessment Questionnaire,) BASFI and BASDI were completed. DAS28 (Disease Activity Score), DAPSA, SDAI (Simplified Disease Activity Index), CDAI (Clinical Disease Activity Index), and CPDAI (Composite Psoriatic Disease Activity Index) were calculated. Hypothetical cases of patients with PsA with data necessary to calculate DAPSA were assessed by 10 rheumatologists trained in the evaluation of patients with PsA. They had to consign if the patient was in remission, low, moderate or high disease activity. *Statistical analysis*: Student T test and ANOVA for continuous variables and Chi2 test and Fisher's exact test for categorical variables.

Spearman Rho, and ROC curves for cut-off points.

Results: We included 112 patients, 57 males (50.9%), with a median age of 54 years (IQR 42-63) and median disease duration of 9 years (IQR 5-15). DAPSA had excellent correlation with DAS28 (Rho:0.85), CDAI (Rho:0.95), SDAI (Rho:0.94) and tender joint count (Rho:0.84), and good with BASDI (Rho:0.68), CPDAI (Rho:0.58), ASQoL (Rho:0.63), PsAQoL (Rho:0.51), BASFI (Rho:0.58), HAQ (Rho:0.59), swollen joint count (Rho:0.69), pain (Rho:0.79) and patient´s global activity (Rho:0.72). Patients who achieved MDA were significantly discriminated by DAPSA (mean 4.9±4.21 vs 20.6±12.5) as well as by the other composite indexes. Using established cut-off values of SDAI for Rheumatoid Arthritis (RA) and experts opinion we performed ROC curves for different cut-off values for DAPSA. Based on these values, a DAPSA score ≤ 5.3 was considered remission, 5.4 to 14.8 low disease activity, 14.9 to 37.7 moderate disease activity and ≥ 37.8 high disease activity. These cut-off values had a sensitivity and specificity ≥ 90%, with an area under the curve of 98%.

Conclusion: DAPSA is a valid and easy to calculate index for peripheral joint activity in PsA patients. It can perfectly discriminate patients in MDA and we proposed possible cut-off values for different disease activity states.

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View Abstract and Citation Information Online - http://acrabstracts.org/abstract/construct-validity-of-disease-activity-for-psoriatic-arthritis-composite-index-and-tentative-cut-off-values-in-a-cohort-of-patients-with-psoriatic-arthritis

Abstract Number: 666

Disease Activity Indices and Body Mass Index: Cross-Sectional Analysis of a Large Psoriatic Arthritis Cohort

Umut Kalyoncu[1], Ozun BayndÄ±r[1], Barış Yılmazer[1], Ediz Dalkilic[2], Kenan Aksu[1], Mustafa Ferhat Oksuz[1], E.Figen Tarhan[1], Meryem Can[1], Orhan Kucuksahin[1], Gezmis Kimyon[1], Lutfi Akyol[1], Ahmet Mesut Onat[1], Bunyamin Kisacik[1], Abdulsamet Erden[1], Ahmet Omma[1], Duygu Ersozlu Bakirli[1], Cem Ozisler[1], Emel Gonullu[1], Seval Pehlevan[1], Dilek Solmaz[1], Muhammet Cinar[1], Gozde Cetin[1], Abdurrahman Tufan[1], Muge Aydin Tufan[1], Levent Kilic[1], Sukran Erten[1], Timucin Kasifoglu[1], Senol Kobak[1], Soner Senel[1], Servet Akar[1], Metin Ozgen[1], Esen Kasapoglu-Gunal[1], Veli Yazisiz[1], Sedat Yılmaz[1], Salim Donmez[1], Ä°smail Dogan[1], Hamide Kart Koseoglu[1], Funda Erbasan[1], Fatih Yildiz[1], Cemal Bes[1], Ayse Balkarli[1], Ali Sahin[1], Rıdvan Mercan[1], Fatoş Arslan[1], Atalay Dogru[1], Salih Pay[1], Sule Yavuz[1], Necati Cakir[1], Yasemin Kabasakal[1] and Sibel Z. Aydin[1], [1]PsART study group, Ankara, Turkey, [2]Department of Rhematology, Uludag University Faculty of Medicine, Bursa, Turkey
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Background/Purpose: Well known comorbidities of Psoriatic arthritis (PsA) such as cardiovascular disease, metabolic syndrome and diabetes mellitus are closely related with body mass index (BMI). Obesity is a risk factor for development of arthritis in patients with psoriasis but at the same time can be a marker of disease severity. Our objective was to assess association of disease activity indicies with obesity in a multicenter large PsA cohort.

Methods: PsART (**Ps**oriatic **A**rthritis **R**egistry of **T**urkey) is a prospective, multicentre, web-based, nationwide study in Turkey on patients with PsA. Patients are consecutively recruited to this registry, if they are diagnosed as PsA. Until May 2015, 1060 PsA patients from 37 centers enrolled to PsART. BMI≥30 was defined as obesity. The demographics were recorded including tender/swollen joint counts, body surface area (BSA), ESR, health assessment questionnaire (HAQ), Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Bath Ankylosing Spondylitis Functional Index (BASFI), 100mm visual analog scale (VAS) for patient global assessment (PtGA), physician global assessment (PGA), fatigue, pain. Minimal disease activity (MDA) items (SJC≤1, TJC≤1, HAQ≤0.5, PtGA≤20, BSA≤3, pain≤15) and PGA, BASDAI, BASFI, fatigue, ESR used the following cut-offs to dichotomize groups: PGA≤20, BASDAI<20, BASFI<20, fatigue<20, ESR < ULN.

Results: Within PsA patients whose BMI data were available (n=1054), 64.5% was female. Mean (SD) age was 46.8 (12.9) years with a disease duration of 188 (135) months for psoriasis and 77 (89) months for psoriatic arthritis. Mean (SD) BMI was 27.9 (5.2) and 30.9% of patients had a BMI>30. Obese patients were older (50.5 (11.8) vs 45.1 (12.9), p<0.001), had a lower education level (7.0 (4.2) vs 9.2 (4.5) years, p<0.001) and more frequent comorbidities such as DM (25.2% vs 11,4%, p<0.001) and HT (36.2% vs 19.6%, p<0.001). These patients had more fatigue, higher BASDAI and BASFI scores, and moderate PGA, pain and ESR (Table). Minimal disease activity items (except PtGA) were similar according to BMI. Disease activity groups by BMI categories are shown in Table.

Conclusion: Obesity was foud to be associated with a lower probability of achieving sustained MDA state in a longitudinal PsA cohort (1). On the other hand, our results did not support to association of obesity and achieving low disease activity. . Interstingly, other than MDA items

especially fatigue was significantly higher at obese patients. Fatigue has multidimensional affect on impact of patients' health, and may be linked to body weight in inflammatory diseases.

Table. Disease activity and patient reported measures by BMI categories

	BMI > 30	**BMI<30**	**p-value**
SJC ≤ 1 n (%)	204/304 (67.1)	466/693 (67.3)	0.96
TJC ≤ 1 n (%)	134/311 (43.1)	318/688 (46.2)	0.36
BSA ≤ 3 n (%)	67/123 (54.5)	150/243 (61.7)	0.18
PtGA ≤ 20 n (%)	33/240 (13.7)	103/486 (21.2)	**0.016**
PGA ≤ 20 n (%)	42/218 (19.3)	129/454 (28.4)	**0.011**
PGA mean (SD)	35.3 (20.5)	31.5 (22.9)	**0.037**
Pain ≤ 15 n (%)	47/250 (18.8)	116/497 (23.3)	0.16
Pain mean (SD)	45.3 (27.3)	40.0 (27.9)	**0.015**
HAQ ≤ 0.5 n (%)	98/247 (39.7)	273/580 (47.1)	0.050
Fatigue ≤ 20 n (%)	36/248 (14.5)	117/492 (23.8)	**0.003**
Fatigue mean (SD)	48.2 (26.2)	40.4 (27.6)	**<0.001**
BASDAI ≤ 20 n (%)	45/196 (22.9)	135/404 (33.4)	**0.009**
BASDAI mean (SD)	40.6 (25.1)	33.8 (25.8)	**0.003**
BASFI ≤ 20 n (%)	68/200 (34.0)	202/397 (50.9)	**<0.001**
BASFI mean (SD)	32.1 (24.3)	24.5 (23.6)	**<0.001**
ESR < UL n (%)	128/306 (41.8)	324/638 (50.9)	**0.010**
ESR mean (SD)	26.2 (18.6)	23.0 (20.3)	**0.019**
Available data includes; SJC 997, TJC 999, BSA 366, PtGA 726, PGA 672, Pain 747, HAQ 827, Fatigue 740, BASDAI 600, BASFI 597 and ESR 944.			

1. Eder L, et al. Ann Rheum Dis 2015;74:813–817

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Abstract Number: 667

Comparison of Patient and Provider Assessments of Response to Therapy for Psoriatic Arthritis

Tobee Gunter[1] and Jessica Walsh[2], [1]Rheumatology, School of Medicine, University of Utah Internal Medicine, Salt Lake City, UT, [2]Division of Rheumatology, Salt Lake City Veteran Affairs and University of Utah Medical Centers, Salt Lake City, UT

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Session Time: 9:00AM-11:00AM

Background/Purpose:

Little is known about how psoriatic arthritis patients and their providers perceive response to therapy. Discrepancies in perceptions of therapy response may indicate that providers are not adequately measuring the aspects of disease that are meaningful to patients. Insufficient assessments of disease states may lead to non-ideal therapies and may contribute to patient non-compliance.

Methods:

Comparisons of patient and provider assessments of response to therapy formulate possible discrepancies. Of the 109 patients enrolled in the Psoriatic Arthritis Research Consortium (PARC) during August 2014 to June 2015, 64 patients rated their response(s) to therapy. Participants and their providers rated response to therapy on a 4-point scale (Very well, Moderately well, A little, Not at All). Participant response ratings were categorized as concordant if their rating was the same as the provider. Discordant participant responses were categorized as either less favorable or more favorable than the provider's rating. Participant and disease characteristics were compared between participants with discordant and concordant ratings. These characteristics included age, gender, alcohol use, current smoker(s), Body Mass Index, education, disability, IBP, radiographic changes, and psoriatic fingernails.

Table 1. Baseline demographics, PsA characteristics, and therapies

n=64	No. (%) or Mean (SD)
Age	53.0 (14.1)
Female gender	35 (54.7%)
White race	60 (93.8%)
Ethnicity (hispanic/latino)	2 (3.1%)
Body Mass Index	29.3 (7.5)
Psoriatic arthritis duration from onset (years)	13.7 (13.5)
Psoriatic arthritis duration from diagnosis (years)	6.6 (8.8)
Synovitis documented by physician	57 (89.1%)
Dactylitis documented by physician	12 (18.8%)
Enthesitis documented by physician	35 (54.7%)
Inflammatory back pain	20 (31.3%)
Tender joint count (0-68)	4.7 (8.2)
Swollen joint count (0-66)	1.6 (3.1)
Classification Criteria for PsA diagnosis	49 (76.6%)
PGAxBSA	1.8 (4.7)
Peripheral radiographic changes consistent with PsA	28 (43.8%)
Axial radiographic changes consistent with PsA	10 (15.6%)
Biologic and non-biologic DMARDs, current	52 (81.3%)
Biologic and non-biologic DMARDs, past	10 (15.6%)

PGAxBSA = psoriasis Physician Global Assessment x Body Surface Area

Results: Forty percent of response ratings were concordant between participants and providers, while 29. 3% of participant ratings were less favorable than the provider ratings and 30.5% were more favorable.

Table 2. Comparisons of patient and provider ratings

	Concordant ratings (reference)	Discordant ratings Less Favorable ratings		More Favorable ratings	
	n=18	n=13	p value or % change	n=17	p value or % change
Education (yrs)	16.2 (2.9)	14.8 (2.9)	0.19	14.4 (2.5)	0.06
Age	55.9 (15.5)	49.1 (15.6)	0.24	49.7 (11.0)	0.19
Body Mass Index	30 (6.8)	29.7 (8.2)	0.93	28.5 (7.2)	0.53
Psoriatic fingernails	4 (22.2%)	7 (53.9%)	31.7%	10 (58.8%)	36.6%
Inflammatory Back Pain	6 (33.3%)	3 (23.1%)	10.2%	4 (23.5%)	9.8%
Peripheral radiographic changes	7 (38.9%)	6 (46.2%)	7.3%	8 (47.1)%	8.2%
Axial radiographic changes	1 (5.6%)	2 (15.4%)	9.8%	4 (23.5%)	17.9%
Female	9 (50.0%)	9 (69.2%)	19.2%	9 (53%)	3.0%
Alcohol Use	9 (50.0%)	4 (30.8%)	19.2%	4 (23.5%)	26.5%
Current Smokers	0 (0.0%)	1 (7.7%)	7.7%	1 (5.9%)	5.9%
Disabled	1 (5.6%)	2 (15.4%)	9.8%	2 (11.8%)	6.2%
Not working because of PsA	0 (0.0%)	0 (0.0%)	0%	3 (17.7%)	17.7%

n=number of patients evaluated with rating

Conclusion:

Participants and providers rated response to therapy identically 40.2% of the time. Discordant response ratings were similarly distributed in the less favorable and more favorable categories. No differences in participant or disease characteristic were identified when discordant ratings were compared to concordant ratings.

Disclosure: T. Gunter, None; **J. Walsh**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/comparison-of-patient-and-provider-assessments-of-response-to-therapy-for-psoriatic-arthritis

Abstract Number: 668

Pasdas, Cpdai and MDA Evolution in the First 6 Months after Diagnosis of Early Psoriatic Arthritis Patients: Results of the Depar Study

Jolanda Luime[1], Ilja Tchetverikov[2], Marijn Vis[3], Cathelyne Appels[4], Wiebo van der Graaff[5], Josien Veris[6], Andreas Gerards[7], Hans van Groenendaal[8], Mark Kok[9], Lindy-Anne Korswagen[10], Cor Stolk[11] and Cicero, [1]Department of Rheumatology, Erasmus Medical Centre, Rotterdam, Netherlands, [2]Albert Schweitzer Ziekenhuis, Dordrecht, Netherlands, [3]Rheumatology, ErasmusMC, Rotterdam, Netherlands, [4]Rheumatology, Amphia Hospital, Breda, Netherlands, [5]Rheumatology, Rivas hospital, Gorinchem, Netherlands, [6]Rheumatology, Reumazorg Zuid West Nederland, Goes, Netherlands, [7]Rheumatology, Vlietland Hospital, Schiedam, Netherlands, [8]Rheumatology, Reumazorg Zuid West Nederland, Roosendaal, Netherlands, [9]Maasstadweg 21, Maasstad Ziekenhuis, Rotterdam, Netherlands, [10]Rheumatology, Sint Fransicus Gasthuis, Rotterdam, Netherlands, [11]-, Patient Partner, Bunnink, Netherlands

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SESSION INFORMATION

Session Date: Sunday, November 8, 2015
Session Title: Spondylarthropathies and Psoriatic Arthritis - Clinical Aspects and Treatment Poster I: Clinical Aspects and Assessments
Session Type: ACR Poster Session A
Session Time: 9:00AM-11:00AM

Background/Purpose:

Several disease activity measures were developed for use in psoriatic arthritis (PsA) . Little data is available on their performance in usual care. This study aims to describe longitudinal evolution of the PASDAS, CPDAI and MDA in the first 6 months after treatment start and in addition treatment initiation and disease characteristics at baseline.

Methods:

Data was used from PsA patients participating in the ongoing DEPAR cohort in 11 Dutch hospitals in the period August 2013 to May 2015. Data was analyzed using a linear mixed model to evaluate PASDAS (0-10) and CPDAI (0-15) over time and descriptives were used to summarize patient characteristics and treatment and % of patients achieving MDA (5 out of 7 domains).

Results:

Untill May 2015 213 patients had had a baseline assessment, 177 had a 3 months and 139 a 6 months assessment. 52% were male; the mean age was 50.3 years (sd 21.7). Mono-, oligo-, and polyarthritis were present in 21% (48.9 sd 12.9; 51% male), 38% (48.8 sd 13.6; 61% male) and 33% (53.7 sd 14.3; 48% male), respectively. 6.5% was diagnosed with enthesitis and 1.5% with axial disease only. Methotrexate was started in 110 patients (51.6%), while 11 patients (6.1%) received prednisone monotherapy (IA or IM), Sulfasalazine was given to 5 patients (2.3%) and 9 patients used other DMARDS (4.6%; 4 used a biological at baseline due to skin disease). Further baseline details are presented in table 1. At baseline PASDAS scored 2.6 (sd 0.70; n=115), CPDAI 5.9 (sd2.9; n=113) and MDA was present in 13 patients (9%; n=145). Over time all measures decreased, see figure 1. At 3 months low PASDAS(<=3.2) was achieved by 95% of the patients, low CPDAI(<=4) by 51% and MDA by 23% and at 6 months this was 97%, 54% and 24%, respectively.

Conclusion:

Methotrexate was the most common DMARD initiated after diagnosis of Psoriatic Arthritis. MDA evolution over time seems the most stringent criterion to guide treatment on compared to the PASDAS and CPDAI in a real world early Psoriatic Arthritis Cohort. Further evaluation of these measures is needed to assess the impact on patient's quality of life and radiological progression.

Table 1 Baseline disease characteristics of DEPAR patients (n=213)

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Disease characteristic	*Patients (n=)*	Mean / %	sd
Tender Joint Count	*212*	5.41	7.15
Swollen Joint Count	*212*	3.44	5.76
Dactylitis (%)	*212*	24%	
Enthesitis (LEI and MASES)	*213*	0.56	1.12
Lei	*213*	0.65	1.06
PASI	*211*	5.71	8.54
CRP (median; IQR)	*168*	5	2-9
DLQI	*181*	3.43	4.43
HAQ	*184*	0.65	0.52
Bodily Pain (SF36)	*176*	50	18.21
Physical functioning (SF36)	*175*	40.87	8.65
Mental functioning (SF36)	*175*	47.52	10.66
VAS global	*172*	42.86	26.34
VAS joints	*172*	43.21	27.32
VAS psoriasis	*172*	30.64	28.07
VAS pain	*146*	45.12	27.02
PASDAS	*115*	2.09	0.86
CPDAI	*175*	5.9	2.31
MDA (%)	*145*	9%	

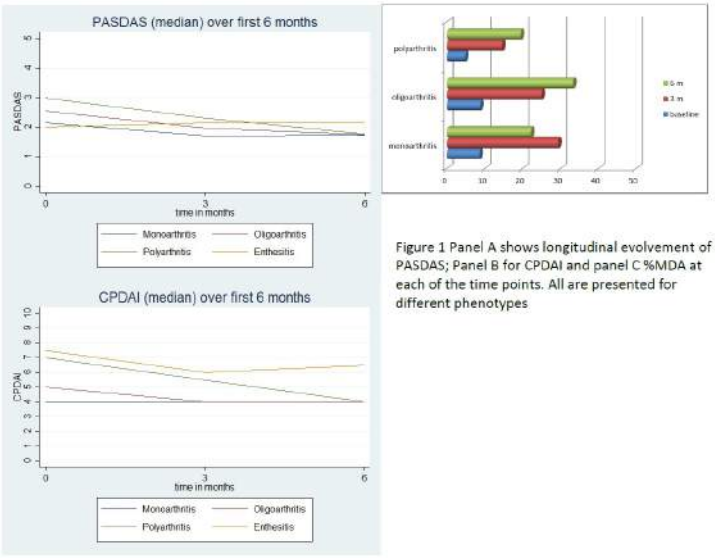

Figure 1 Panel A shows longitudinal evolvement of PASDAS; Panel B for CPDAI and panel C %MDA at each of the time points. All are presented for different phenotypes

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Disclosure: J. Luime, None; **I. Tchetverikov**, None; **M. Vis**, None; **C. Appels**, None; **W. van der Graaff**, None; **J. Veris**, None; **A. Gerards**, None; **H. van Groenendaal**, None; **M. Kok**, None; **L. A. Korswagen**, None; **C. Stolk**, None.

Abstract Number: 669

Assessment of Spinal Mobility in Axial Spondyloarthritis: First Validation Steps of a New Electronic Quantification Tool

Xenofon Baraliakos, David Kiefer, Susanne Herbold and Jürgen Braun, Rheumazentrum Ruhrgebiet, Herne, Germany
First publication: September 29, 2015

SESSION INFORMATION

Session Date: Sunday, November 8, 2015

Session Title: Spondylarthropathies and Psoriatic Arthritis - Clinical Aspects and Treatment Poster I: Clinical Aspects and Assessments

Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose: Spinal mobility is a major health issue of patients with axial spondyloarthritis (axSpA), especially in ankylosing spondylitis (AS) while non-radiographic axSpA (nr-axSpA) has been less well studied in this regard. The available tools such as the BASMI and, indirectly, also the BASFI have limitations in exactly quantifying spinal mobility. In this study, we evaluate the performance of a newly developed electronic tool to measure spinal mobility.

Methods: Consecutive patients with axSpA, mechanical back pain and healthy controls were examined by the Epionics spine device (ESp), a novel electronic system, which measures the range of motion (ROM) for spinal mobility using non-invasive angle sensor strips in 12 evenly spaced locations along the spine. ESp has been shown to reliably measure the ROM for all domains of spinal mobility (flexion, extension, rotation and combinations). Physical examinations (BASMI), questionnaires (BASFI) and a recently proposed tool to assess function (ASPI, 1) were performed in parallel. The assessors were unaware of the results of the other tests. The time to use the device was measured. Statistical comparisons between groups were performed with the Mann-Whitney-U-test.

Results: A total of 65 patients with axSpA (38 (58%) with AS and 27 (42%) with nr-axSpa), 48 patients with mechanical back pain (mBP) and 20 healthy controls (HC) were included in this prospective study. The BASFI and BASMI values were generally higher in patients with AS (4.1±2.3 and 2.7±2.3) vs. nr-axSpA (3.8±1.9 and 1.2±1.0), mBP (4.0±2.4 and 1.3±1.1) and HC (0.5±0.7 and 0.6±0.8). Using ESp, the measured range of ROM AS patients performed worse in all aspects (Table). The mean duration of performance of ESp was 12±3 minutes.

		Spinal flexion	Spinal extension	Rotation to left	Rotation to right	Lateral flexion to left	Lateral flexion to right	Flexion and rotation from left to right	Extension and rotation from left to right	Flexion and rotation from right to left	Extension and rotation from right to left
AS	Mean	39,2	16,4	20,2	21,4	16,1	17,0	31,7	5,6	33,3	5,7
	SD	17,2	12,9	9,7	9,0	8,8	9,5	16,8	5,4	16,6	5,2
nr-axSpA	Mean	46,5	21,6	26,2	24,8	21,6	23,0	39,3	7,2	39,8	6,9
	SD	14,2	9,6	9,2	8,7	7,1	7,1	14,6	4,6	13,0	5,9
p-value nr-axSpA vs. AS		***0,124***	***0,018***	***0,011***	***0,159***	***0,006***	***0,008***	***0,043***	***0,134***	***0,122***	***0,410***
mBP	Mean	48,4	23,9	22,7	24,6	23,6	25,5	43,8	9,8	44,2	8,7
	SD	13,0	12,0	10,0	9,7	7,9	7,1	13,2	7,7	12,5	7,6
p-value mBP vs. AS		***0,033***	***0,001***	***0,266***	***0,214***	***0,001***	***0,001***	***0,001***	***0,010***	***0,315***	***0,784***
HC	Mean	51,6	28,2	26,8	27,9	30,4	30,9	45,9	10,1	47,7	10,4
	SD	11,4	11,5	10,6	9,1	7,6	8,8	12,3	10,7	10,9	9,3
p-value HC vs. AS		***0,007***	***0,001***	***0,033***	***0,022***	***0,001***	***0,000***	***0,004***	***0,245***	***0,318***	***0,722***

Table: ROM (in angles) for the different patient subgroups

Conclusion: The Epionics spine device had good construct, content and face validity in this first study, which prospectively compared patients with axSpA, mechanical back pain and healthy volunteers. It will be interesting to study its correlation to single BASMI and BASFI items and to learn whether it provides higher sensitivity to change as compared to conventional assessments of spinal mobility and function.

Disclosure: X. Baraliakos, None; **D. Kiefer**, None; **S. Herbold**, None; **J. Braun**, None.

Abstract Number: 670

Evaluation of the Predictive Value of Non-Specific Musculoskeletal Symptoms in Preclinical Phases of Psoriatic Arthritis

Lihi Eder[1], Ari Polachek[1], Cheryl Rosen[2], Vinod Chandran[1], Richard J. Cook[3] and Dafna D. Gladman[1], [1]Rheumatology, University of Toronto, Toronto Western Hospital, Toronto, ON, Canada, [2]Dermatology, University of Toronto, Toronto Western Hospital, Toronto, ON, Canada, [3]Statistics and Actuarial Science, University of Waterloo, Waterloo, ON, Canada

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Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose: Limited information exists about the characteristics of pre-clinical phases of psoriatic arthritis (PsA). We aimed to assess whether the presence and trends in non-specific musculoskeletal symptoms predict the development of PsA in a prospective cohort of patients with psoriasis.

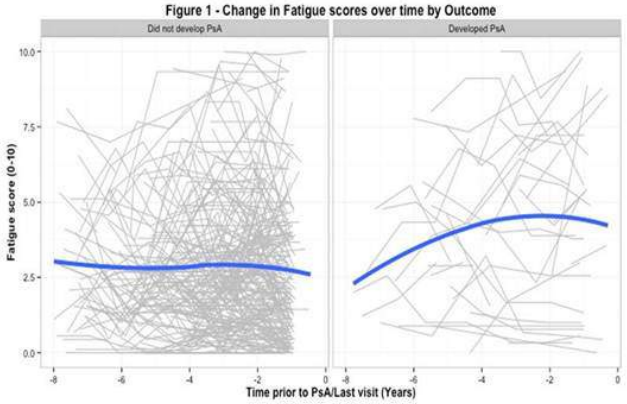
Methods: This prospective cohort study involved patients with psoriasis who were assessed at baseline by a rheumatologist to exclude the presence of clinical inflammatory arthritis. The study participants were assessed annually according to a standard protocol. The presence of musculoskeletal symptoms and patients' scores of pain (visual analogue scale (VAS) 0-10), fatigue (Fatigue Severity Scale), stiffness (VAS 0-10) and physical functioning (SF-36 physical component score) were recorded at each visit. These variables served as predictors for the development of PsA. Patients who developed inflammatory arthritis or spondylitis were classified as PsA if they fulfilled the CASPAR criteria. Cox proportional hazard models, involving fixed and time-dependent explanatory variables were fitted to obtain estimates of relative risk (RR) for the onset of PsA in multivariate models controlling for age, sex, body mass index, nail pitting and psoriasis area and severity index (PASI).

Results: The results of 410 patients with psoriasis who were followed for an average duration of 45.1±25.3 months were analyzed. A total of 57 patients developed PsA since enrollment (mean duration to diagnosis of PsA 46±27.8 months). At baseline, the presence of arthralgia in women (RR 2.6, 95% Confidence Interval (CI) 1.2, 5.9), heel pain (RR 4.2, 95% CI 1.3, 13.8), fatigue score (RR 1.2, 95% CI 1.04, 1.3) and stiffness score (RR 1.2, 95% CI 1.1, 1.3) predicted subsequent development of PsA. In addition, an increase from baseline in fatigue score (RR 1.3, 95% CI 1.1, 1.5), pain score (RR 1.3, 95% CI 1.1, 1.6) and stiffness score (RR 1.2, 95% CI 1.0, 1.4) and a worsening in physical function score (RR

0.96, 95% CI 0.92, 0.99) predicted the development of PsA. The changes in fatigue and stiffness scores over time are shown in Figures 1-3.

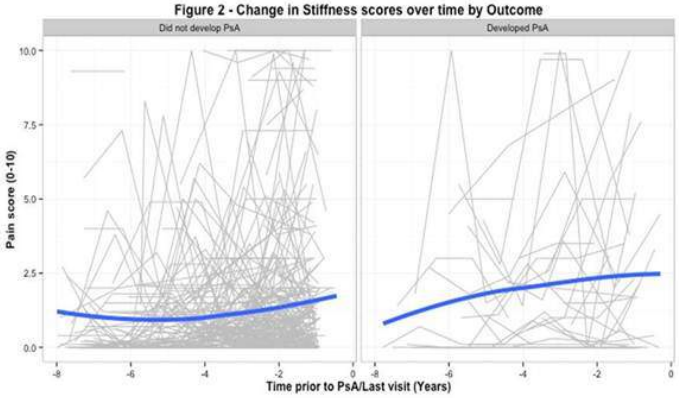
Conclusion: A preclinical phase exists in patients with PsA prior to the diagnosis of the disease. This phase is characterized by non-specific musculoskeletal symptoms including joint pain, fatigue and stiffness.

Figure 1 - Change in Fatigue scores over time by Outcome



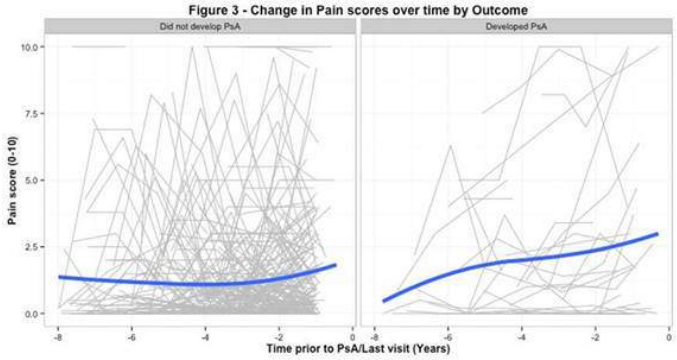
Changes in fatigue scores (by FSS) over time prior to development of PsA or last assessment (years). **Gray lines-** sequences of measurements for individual patients. **Blue line:** lowess curve of mean fatigue score

Figure 2 - Change in Stiffness scores over time by Outcome



Changes in stiffness score (by VAS) over time prior to development of PsA or last assessment (years). **Gray lines-** sequences of measurements for individual patients. **Blue line:** lowess curve of mean stiffness score

Figure 3 - Change in Pain scores over time by Outcome



Changes in pain score (by VAS) over time prior to development of PsA or last assessment (years). **Gray lines-** sequences of measurements for individual patients. **Blue line:** lowess curve of mean pain score

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Disclosure: L. Eder, None; **A. Polachek**, None; **C. Rosen**, None; **V. Chandran**, None; **R. J. Cook**, None; **D. D. Gladman**, None.

Abstract Number: 671

Discrepancy Between Patients and Physicians Acceptable Symptomatic States in Axial Spondyloarthritis: Findings from the RAPID-AxSpA Study

Maxime Dougados[1], **Owen Davies**[2], Tommi Nurminen[3], Geoffroy Coteur[4] and Laure Gossec[5], [1]Medicine Faculty, Paris-Descartes University, Paris, UPRES-EA 4058, Cochin Hospital, Rheumatology B, Paris, France, [2]UCB Pharma, Slough, United Kingdom, [3]UCB Pharma, Monheim, Germany, [4]UCB Pharma, Brussels, Belgium, [5]Sorbonne Universités, UPMC Univ Paris 06 GRC-UPMC 08 (EEMOIS); AP-HP, Hôpital Pitié Salpêtrière Rheumatology Department, Paris, France

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Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose:

Discordance between patient (pt) and physician (phy) assessment of disease activity (DA) in spondyloarthritis (SpA) is recognized, with phys tending to score DA less severely than pts.[1]Perceptual differences need to be understood to improve pt-phy dialogue, set shared treatment goals and ultimately improve outcomes. The objectives were to: 1. Investigate the proportion of axial SpA (axSpA) pts with acceptable symptomatic states as scored by the pt or their phy before and after initiation of anti-TNF treatment and 2. Explore discrepancies between pt and phy assessments.

Methods:

RAPID-axSpA (NCT01087762) was double-blind and placebo (PBO) controlled to Week (Wk) 24.[2]Pts fulfilled ASAS criteria and had active axSpA. At baseline (BL) 325 pts were randomized 1:1:1 to PBO, or certolizumab pegol (CZP) 200 mg Q2W / 400 mg Q4W. In addition to conventional axSpA outcomes (eg ASDAS / BASDAI) information on pt acceptable symptomatic state was collected from the pt (Pt Acceptable Symptomatic State [PASS]) and their phy (Phy Acceptable Symptomatic State [PhSS]) (see Box for questions).

Analyses also investigated underlying DA thresholds considered ‘acceptable’ by pts or phys. Based on pt’s global assessment of DA (PtGADA) and PASS, interval-censored observations estimated each pt’s ‘acceptability threshold’. Assuming normal distribution, the mean was estimated using LIFEREG in SAS (v 9.3). Similar procedure was used for phys.

Results:

Of 324 pts assessed, 218 received CZP from Wk0 and 106 PBO. At BL 29 (9%) pts were in PASS and 120 (37%) in PhSS, despite high DA in pts with PhSS (mean ASDAS 3.8; BASDAI 6.4). Similar proportions of pts and phys agreed regarding pt symptomatic state at BL (62%) and Wk24 (68%; Fig A); this was similar for CZP and PBO (BL CZP 62%, PBO 63%; Wk24 CZP 67%, PBO 70%).

Improvements following CZP treatment (dose combined) were seen from Wk1 (Fig B). Differences in proportions of pts in PASS vs PhSS at BL were maintained to Wk24, with 104 (48%) CZP treated pts in PASS and 158 (73%) in PhSS (Fig B). At Wk24 mean underlying DA level considered ‘acceptable’ was similar for pts and phys and was not dependent on treatment (PtGADA CZP 3.9 vs PBO 3.7; PhGADA CZP 3.9 vs PBO 4.0).

Preliminary analyses investigating BL characteristics indicate that pts with Wk24 PASS had lower BL DA scores than pts without; no differences were seen for pts in / not-in PhSS at BL or Wk24.

Conclusion:

CZP treatment was associated with improvements in PASS and PhSS to Wk24. Despite high DA at BL over a third of phy scored pts as having acceptable symptomatic states, which represented a notable discrepancy compared to pt scoring. This discrepancy was maintained to Wk24 and was independent of treatment. These findings confirm previous reports of discordance in phy and pt assessment of DA and highlight a need for closer partnership between phys and pts to set shared treatment goals.

References:

1. Desthieux C. Ann Rheum Dis 2015;74(S2):498

2. Landewé R. Ann Rheum Dis 2014;73:39–47

Box: Questions asked to assess patient or physician acceptable symptomatic state

PASS	*"Considering all the different ways your disease is affecting you, if you were to stay in this state for the next few months, do you consider that your current state is satisfactory?"*
PhSS	*"Considering the current level of symptoms your subject is experiencing due to his/her spondyloarthritis, if he/she was to maintain the same level of symptoms for the next few months, is this clinical state acceptable to you as the treating physician?"*

Figure A: Proportion of patients and physicians in agreement or discordance regarding patient symptomatic state at baseline and Week 24 for all axSpA pts (CZP and PBO combined) in the RAPID-axSpA trial

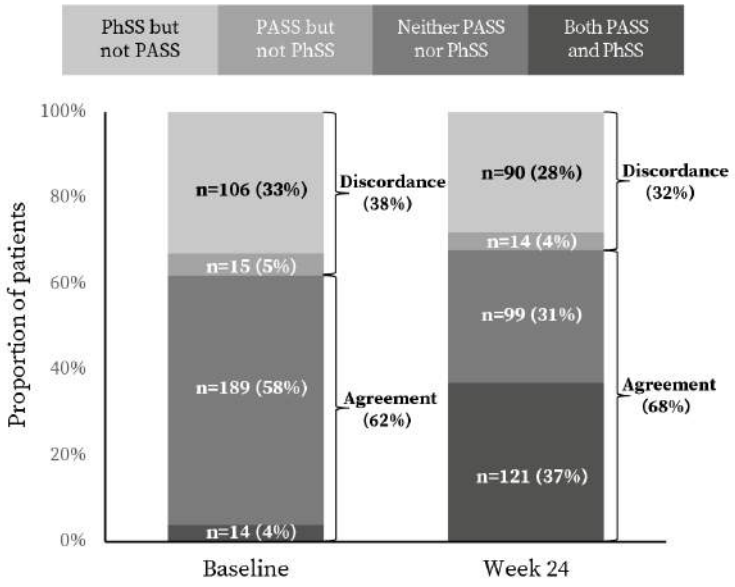
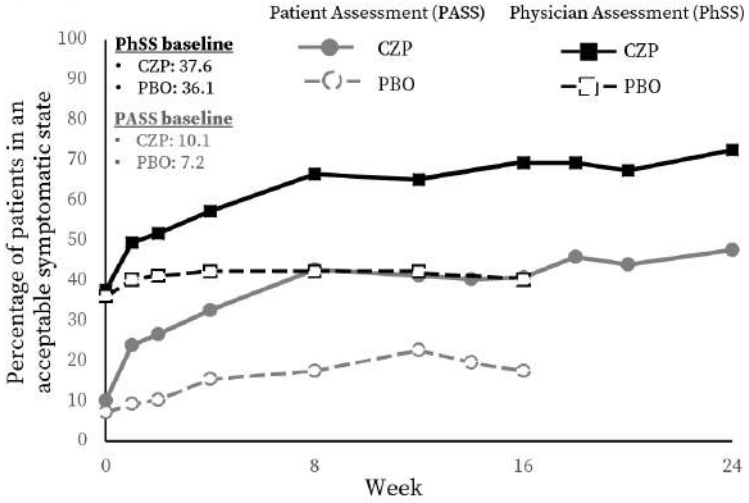


Figure B: Proportion of Wk0 CZP (dose-combined) and PBO patients in PASS and PhSS to Week 24 of the RAPID-axSpA trial [NRI]



Disclosure: M. Dougados, UCB Pharma, Abbvie, Pfizer, Lilly, Novartis, 2,UCB Pharma, Abbvie, Pfizer, Lilly, Novartis, 5; **O. Davies**, UCB Pharma, 1,UCB Pharma, 3; **T. Nurminen**, UCB Pharma, 3; **G. Coteur**, UBC Pharma, 1,UCB Pharma, 3; **L. Gossec**, UCB Pharma, 2,AbbVie, 5,Bristol-Myers Squibb, 5,Celgene, 5,Chugai, 5,Janssen, 5,Novartis, 5,Pfizer, 5,Roche, 5,UCB Pharma, 5,OMERACT Executive Commitee, 6.

Abstract Number: 672

Validity of Ankylosing Spondylitis Diagnoses in the Health Improvement Network

Maureen Dubreuil[1,2], Christine Peloquin[3], Yuqing Zhang[4], Hyon Choi[5], Robert D Inman[6] and Tuhina Neogi[7], [1]Rheumatology, VA Boston Healthcare System, Boston, MA, [2]Rheumatology, Boston University School of Medicine, Boston, MA, [3]Clinical Epidemiology Unit, Boston University School of Medicine, Boston, MA, [4]BUSM, Boston, MA, [5]Division of Rheumatology, Allergy and Immunology, Massachusetts General Hospital, Harvard Medical School, Boston, MA, [6]Immunlogy and Institute of Medical Science, Toronto Western Hospital, University of Toronto, Toronto, ON, Canada, [7]Clinical Epidemiology, BUSM, Boston, MA

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Session Type: ACR Poster Session A
Session Time: 9:00AM-11:00AM

Background/Purpose: Because ankylosing spondylitis (AS) is relatively uncommon, large electronic medical record (EMR) databases with longitudinal follow up offer an important opportunity for epidemiologic research in AS. However, the validity of AS diagnoses recorded by a general practitioner in such databases is unknown. We sought to assess the validity of several algorithms for identifying AS patients in The Health Improvement Network (THIN).

Methods: THIN is an EMR database of over 10 million persons in the UK, with data entered by general practitioners (GPs). In 2014, we administered a questionnaire to the GPs of 100 patients aged 18-59 years for whom at least one AS diagnostic code was recorded during years 2000-2013. As high positive predictive value (PPV) is of critical importance in epidemiologic studies of AS (i.e.- accurate identification of subjects who truly have AS), our questionnaire was designed to determine the PPV of an AS diagnostic code, using the GP's clinical impression as the "gold standard". We also determined characteristics for other AS case identification algorithms including: more than one AS diagnostic code, absence of osteoarthritis (OA) or rheumatoid arthritis (RA) codes, prescription of a nonsteroidal anti-inflammatory drug (NSAID), or presence of a disease modifying anti-rheumatic drug (DMARD) or biologic.

Results: Questionnaires were returned for 85 out of 100 patients with an AS code, and in 61 of those patients the GP's clinical impression confirmed the AS diagnosis, resulting in an overall positive predictive value (PPV) of 72% (**Table**). The highest PPV (89%) was with an algorithm requiring two AS codes at least 7 days apart, however PPV was also high for an algorithm requiring at least one AS diagnostic code plus a DMARD or biologic drug prescription (86%). Sensitivity was reduced with algorithms requiring 2 AS codes (64%) and a DMARD/biologic prescription (30%). Algorithms also requiring prescription of an NSAID, or the absence of an OA or RA code had lower PPV (71-75%) and higher sensitivity (95-98%).

Conclusion: AS case identification algorithms of: (A) two AS diagnostic codes separated by at least 7 days or (B) one AS diagnosis plus a DMARD or biologic prescription provided the highest PPV in THIN. One or both of these algorithms should be used for AS case identification in epidemiologic studies in THIN.

Table. Ankylosing spondylitis case identification algorithms and characteristics in The Health Improvement Network

Algorithm	Total (N)	Confirmed AS (N)	PPV (95% CI)	Sensitivity* (95% CI)
One or more AS codes	85	61	71.8 % (60.5-83.1)	N/A
Two AS codes, > 7 days apart	44	39	88.6 % (78.7-98.6)	63.9 % (48.9-79.0)
AS + absence of OA code	77	58	75.3 % (76.0-97.3)	95.1 % (89.5-100)
AS + absence of RA code	80	58	72.5 % (61.0-84.0)	95.1 % (89.5-100)
AS + DMARD or Biologic	21	18	85.7 % (69.5-100)	29.5 % (8.4-50.6)
AS + NSAID	84	60	71.4 % (60.0-82.9)	98.4 % (95.1-100)

AS = ankylosing spondylitis, DMARD = disease modifying anti-rheumatic drug, NSAID =nonsteroidal anti-inflammatory drug, OA = osteoarthritis, RA = rheumatoid arthritis, N/A= not assessable.

*Sensitivity with the additional feature (e.g. absence of an OA code) for a verified diagnosis of AS by GP report among patients with at least one code for AS, not the overall sensitivity and specificity of the algorithm as false negatives were unavailable.

Disclosure: M. Dubreuil, None; **C. Peloquin**, None; **Y. Zhang**, None; **H. Choi**, None; **R. D. Inman**, None; **T. Neogi**, None.

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Abstract Number: 673

Characterization of Psoriatic Arthritis [Psa] in a Large, Integrated Health Plan: Demographics, Referral Patterns and Care Management

Vibeke Strand[1], Melody Chin[2], Arijit Ganguli[3], Ridhima Nerlekar[4], Victoria Kelly[5], Daniel Chin[6] and Alice Pressman[4], [1]Biopharmaceutical Consultant, Portola Valley, CA, [2]University of California, San Francisco, San Francisco, CA, [3]AbbVie Inc., North Chicago, IL, [4]Research, Development, and Dissemination, Sutter Health, Walnut Creek, CA, [5]Rheumatology, Palo Alto Medical Foundation, Palo Alto, CA, [6]Clinical Evidence and Outcomes, AbbVie, North Chicago, IL

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Background/Purpose:

Despite guidelines and evidence indicating that early diagnosis and treatment of PsA is critical, few studies have described referral and care-management patterns in a real-world setting. This study estimated the prevalence and incidence of PsA in the Sutter Health system, a large integrated U.S. health delivery network, and explored referral patterns and associated care-management practices within this population.

Methods: This was a retrospective review of electronic medical records and medical claims data of patients (age ≥18yrs) diagnosed with PsA

(ICD-9-code 696.x) from 2011-2013. Medical chart review by a rheumatologist and/or registered nurse of a sample of prevalent and incident PsA patients was utilized to confirm the diagnosis. Prevalence and incidence rates (defined as no PsA report 2 years before the index PsA record) were estimated annually/100,000 patients. Care management included ascertainment of the physician type recording the first PsA diagnosis and/or treating the patient (specialist vs. non-specialist). Referral patterns ascertained the physician type making the first referral to a specialist.

Results:

Among 1,362,288 adults (≥18 yrs, 59% female) in the health plan, 2,029 were identified as diagnosed with PsA. The average 1-year period prevalence was 161/100,000; incidence: 43/100,000. Mean age at incident diagnosis was 53 years (s=14.3) for women and 51 years (s=13.6) for men. Chart review revealed low rates for misclassification (5%) of PsA diagnosis. Approximately 54% of all PsA-related encounters were with rheumatologists. The majority of care was provided by rheumatology, primary care, and dermatology, accounting for 54%, 21%, and 19% encounters, respectively. Rheumatologists were first to diagnose PsA in 61% patients followed by primary care physicians (PCP): 24%, dermatologists: 10%, and others: 5%. Of those referred to a rheumatologist, 65% were referred by a PCP, followed by dermatologists: 6%, other rheumatologists: 4%, orthopedists: 3%, podiatrists: 2%, others: 3% and self/ no record: 18%. Overall, in sampled patients, non-rheumatologist providers were less likely to perform a joint exam or document joint abnormalities, and no providers documented a disease activity score. Of 1665 prevalent cases with a documented encounter with a rheumatologist within the system, 557 (33%) were prescribed biologic agents, 851 (51%) DMARDs, and 359 (22%) steroids. Among 2029 prevalent cases, 346 (17%) had no documented encounter with a Sutter Health rheumatologist; 30% were prescribed biologics and 26% DMARDs. Chart review revealed that most of these patients had had contact with specialists outside the network.

Conclusion:

Estimated prevalence of PsA in the Sutter Health System was similar to U.S. estimates: between 0.02 and 0.25%. Although rheumatologists provided the majority of care, many patients did not have a record of a rheumatology encounter. Further research is needed to better understand gaps in PsA health care in real world settings.

Disclosure: V. Strand, AbbVie, Alder, Amgen, BMS, Celgene, Genentech, Janssen, Novartis, Pfizer, and UCB, 5,Abbvie, Amgen, BMS, Celgene, Genentech, Janssen, Novartis, Pfizer, and UCB, 9; **M. Chin**, None; **A. Ganguli**, AbbVie, Inc., 3; **R. Nerlekar**, None; **V. Kelly**, None; **D. Chin**, AbbVie, 3; **A. Pressman**, None.

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Abstract Number: 674

Clinical Characteristics of Japanese Patients with Reactive Arthritis Induced By Intravesical BCG Therapy for Bladder Cancer: A 19 Years Two-Center Retrospective Study

Hirofumi Nishikawa[1], Yoshinori Taniguchi[1], Takashi Karashima[2], Tetsushi Aita[3], Susumu Nishiyama[3], Yasuhiko Yoshinaga[3], Yoshitaka Kumon[4], Yoshiko Shimamura[1], Kosuke Inoue[1], Taro Horino[1], Taro Shuin[2] and Yoshio Terada[1], [1]Kochi University, Nankoku, Japan, [2]Urology, Kochi University, Nankoku, Japan, [3]Kurashiki Medical Center, Kurashiki, Japan, [4]Chikamori Hospital, Kochi, Japan

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Background/Purpose:

Intravesical instillation of BCG is used as an effective immunotherapy of bladder cancer. However it may have, as adverse event, a reactive arthritis (ReA) and the incidence are known as about 0.5 to 1 %. To evaluate clinical characteristics and incidence of Japanese patients with ReA induced by intravesical BCG therapy (iBCG) for bladder cancer.

Methods: The clinical symptoms, laboratory, and imaging findings of Japanese patients who received iBCG (n=453 (182 and 271 in Kochi University Hospital (KUH) and Kurashiki Medical Center (KMC), respectively)) for bladder cancer from March 1997 to April 2015 (for 19 years) were retrospectively assessed. Especially, the patients with ReA and conjunctivitis/uveitis were examined. All data are presented as mean ± SD.

Results: Of the patients received iBCG (age 71±10 and 69±11; male/female 134/48 and 215/56 in KUH and KMC, respectively), 50/182 (27%) and 35/271 (13%), 51/182 (28%) and 48/271 (18%), and 78/182 (43%) and 73/271 (27%) in KUH and KMC presented fever, hematuria and painful urination, respectively. ReA was revealed in 4/182 (2.2%) and 3/271 (1.1%), uveitis in 3/182 (1.6%) and 1/271 (0.4%), and conjunctivitis in 15/182 (8.2%) and 14/271 (5.2%) in KUH and KMC, respectively. As the total evaluation, ReA was revealed in 7/453 (1.5%). Moreover, most patients with ReA also had hepatic dysfuntion. All ReA were developed after 3-times of iBCG. Clinical, ultrasound and FDG-PET/CT findings of ReA induced by iBCG showed asymmetric polyarthritis/polyenthesitis pattern in shoulder, sternoclavicular joints, spinous process, sacroiliac joints, ischial tuberosity, hip, knee and ankle. Laboratory examinations showed high CRP (>10mg/dl), 25% HLA-B27 positivity (in 1 of 4 cases), 50% HLA-B51 positivity (in 2 of 4 cases). All ReA patients were improved by treatments with prednisolone and isoniazid.

Conclusion: The incidence of ReA induced by iBCG in Japanese population was 1.5 % and it might be almost equal or more than the incidence, 0.5 to 1 %, in the Western countries from previous reports. Positive HLA-B27 was revealed in 25% of ReA patients as background in our study, suggesting lower frequency than 51 to 55% in the Western countries. Therefore, besides HLA phenotype, a cross reaction between a mycobacterium epitope and an antigen of joint cartilage might be suggested in the pathogenesis of ReA induced by iBCG in Japan.

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Abstract Number: 675

Vitamin D Deficiency in Rheumatoid Arthritis, Ankylosing Spondylitis and Psoriatic Arthritis. Results of the CARMA Study

Ana Urruticoechea[1], Maria Auxiliadora Martin[2], Santos Castañeda[3], Carlos Alberto Sánchez-Piedra[2], Carlos González-Juanatey[4], Javier Llorca[5], Federico Díaz-González[6] and Miguel Angel Gonzalez-Gay[7], [1]Hospital Can Misses, Ibiza, Spain, [2]Research Unit of Spanish Society of Rheumatology,, Madrid, Spain, [3]Rheumatology, H.U. La Princesa, Madrid, Spain, [4]Division or Cardiology, Hospital Lusus Augusti, Lugo, Spain, [5]Department of Epidemiology and Computational Biology, School of Medicine, University of Cantabria, and CIBER Epidemiología y Salud Pública (CIBERESP), IDIVAL, Santander, Spain, [6]Investigation Unit, Sociedad Española de Reumatológía, Madrid, Spain, [7]Rheumatology, Hospital Universitario Marqués de Valdecilla. IDIVAL, Santander, Spain

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Session Time: 9:00AM-11:00AM

Background/Purpose:

To study the association between 25-hydroxyvitamin D (25(OH)D) levels and the clinical characteristics of patients with chronic inflammatory rheumatic diseases (CIRD).

Methods:

Cross section from the baseline visit of the CARMA project (CARdiovascular in rheuMAtology), a 10-year prospective study evaluating the risk of cardiovascular events in rheumatoid arthritis (RA), ankylosing spondylitis (AS) and psoriatic arthritis (PsA) patients, and non-CIRD patients who attended rheumatology outpatient clinics from 67 hospitals in Spain. Non-CIRD group was frequency matched by age with the joint distribution of the three CIRD groups included in the study. 25(OH)D deficiency was defined if 25(OH)D vitamin levels were < 20 ng/ml.

Results:

2.234 patients (775 RA, 738 AS and 721 PsA) and 677 non-CIRD subjects were assessed. The median [p25-p75] 25(OH)D levels were: 20.4 [14.4-29.2] ng/ml in RA, 20.9 [13.1-29.0] in AS, 20.0 [14.0-28.8] in PsA, and 24.8 [18.4-32.6] ng/ml in non-CIRD patients. 25(OH)D deficiency was detected in 40.5% RA, 39.7% AS, 40.9% PsA and 26.7% non-CIRD controls ($p<0.001$). A statistically significant positive association between RA and 25(OH)D deficiency was found (adjusted (adj.) OR=1.46; 95% CI=1.09-1.96); p= 0.012. This positive association did not reach statistical significance for AS (adj. OR 1.23; 95%CI=0.85-1.80) and PsA (adj. OR 1.32; 95%CI=0.94-1.84). When the parameters of disease activity, severity or functional impairment were assessed, a marginally significant association between 25(OH)D deficiency and ACPA positive in RA patients (adj. OR=1.45; 95%CI=0.99-2.12; p=0.056), and between 25(OH)D deficiency and BASFI in AS patients (adj. OR=1.08; 95%CI=0.99-1.17); p=0.07) was also found.

Conclusion:

Patients with CIRD, in particular those with RA, show an increased risk of having 25(OH)D deficiency compared to non-CIRD controls.

Disclosure: A. Urruticoechea, None; **M. A. Martin**, None; **S. Castañeda**, None; **C. A. Sánchez-Piedra**, None; **C. González-Juanatey**, None; **J. Llorca**, None; **F. Díaz-González**, None; **M. A. Gonzalez-Gay**, None.

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Abstract Number: 676

What Proportion of Patients with Psa Fail to Achieve MDA Based on Patient Reported Outcomes? an Analysis from a Prospective, Observational Registry

Proton Rahman[1], J Antonio Avina-Zubieta[2], Regan Arendse[3], William G Bensen[4], Philip Baer[5], John Kelsall[6], Michael Starr[7], Jacqueline Stewart[8], Dalton Sholter[9], Michel Zummer[10], Leo Picard[11], Emmanouil Rampakakis[12], Eliofotisti Psaradellis[13], Karina Maslova[14], Allen J Lehman[14], Francois Nantel[15,16], Cathy Tkaczyk[17] and Brendan Osborne[17], [1]Medicine, Memorial University, St John's, NF, Canada, [2]Arthritis Research Canada / University of British Columbia, Vancouver, BC, Canada, [3]University of Saskatchewan, Saskatoon, ON, Canada, [4]St Joseph's Healthcare Hamilton, Hamilton, ON, Canada, [5]Section on Rheumatology, Ontario Medical Association/Journal of the Canadian Rheumatology Association, Toronto, ON, Canada, [6]Mary Pack Arthritis Centre, Vancouver, Vancouver, BC, Canada, [7]Rheumatology, McGill University, Montreal, QC, Canada, [8]Penticton Regional Hospital, Penticton, BC, Canada, [9]Rheumatology Associates, Edmonton, AB, Canada, [10]Rheumatology, Hôpital Maisonneuve-Rosemont and University of Montreal, Montreal, QC, Canada, [11]Rhumatologie Moncton, Moncton, NB, Canada, [12]JSS Medical Research, St-Laurent, QC, Canada, [13]JSS Medical Research, Montreal, QC, Canada, [14]Janssen Inc., Toronto, ON, Canada, [15]Schering Plough Canada Inc., Janssen Inc., Kirkland, QC, QC, Canada, [16]19 Green belt Dr, Janssen Inc., Toronto, ON, Canada, [17]Medical Affairs, Janssen Inc., Toronto, ON, Canada

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Session Time: 9:00AM-11:00AM

Background/Purpose: Recent treat-to-target guidelines in PsA recommend that minimal disease activity (MDA) is achieved as early as possible. Patient reported outcomes (PROs) have been criticized for not accurately assessing PsA disease activity as they may reflect aspects not directly related to PsA such as fibromyalgia, depression or other comorbidities. The aim of this analysis was to assess the proportion of patients failing to achieve MDA based on PROs in a real-world, routine clinical care setting in Canada.

Methods: BioTRAC is an ongoing, prospective registry of patients initiating treatment for rheumatoid arthritis, ankylosing spondylitis, or PsA with infliximab (IFX) or golimumab (GLM). Eligible participants for this analysis included those with PsA treated with IFX who were enrolled since 2005 or with GLM enrolled since 2010 and with available MDA information at baseline, 6 months, and/or 12 months. MDA was defined as the fulfillment of ≥5 of the following criteria: TJC28≤1, SJC28≤1, PASI≤1 or BSA≤3, pain (VAS)≤15 mm, PtGA (VAS)≤20 mm, HAQ≤0.5, tender entheseal points ≤1. Near MDA was defined as fulfillment of 4/7 criteria.

Results: A total of 196 PsA patients (51.4% male) were included with a mean (SD) age of 49.8 (11.1) years and disease duration since diagnosis of 5.4 (6.3) years. The majority (62.2%) received concomitant DMARD therapy. The proportion of patients with MDA at baseline, 6 months and 12 months was 11.7%, 43.5%, and 44.8%, respectively. Overall, achievement of each individual MDA criterion was: TJC28: 43.0% of cases; SJC28: 51.3%; PASI 68.7%; pain: 27.7%; PtGA: 34.9%; HAQ: 36.8%; entheseal points: 79.4%. Among the 309 instances of non-MDA, 51 (16.5%) were near MDA cases. The most common reason for non-MDA in near MDA cases was patient-reported pain (82.4%) followed by PtGA (68.6%), and HAQ-DI (60.8%). Assuming that these criteria were met (i.e., not included in the MDA formula), the total number of MDA instances would increase from 29.6% to 36.7% (HAQ), 37.6% (PtGA), and to 39.2% (pain).

Conclusion:

The results of the current analysis have shown that, similar to prior analyses in RA, the most common limiting factors in achieving MDA in PsA are PROs, including PtGA, pain, and HAQ-DI, accounting for as many as 82.4% of near MDA cases. Further analyses are required to identify the determinants of the differences in PROs and clinical outcomes.

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Inc, 5; **L. Picard**, Janssen Inc., 5; **E. Rampakakis**, JSS Medical Research, a Contract Research Organization, 3; **E. Psaradellis**, employee of JSS Medical Research, 3; **K. Maslova**, Employee of Janssen Inc., 3; **A. J. Lehman**, employee of Janssen Inc., 3; **F. Nantel**, Janssen Inc., 3; **C. Tkaczyk**, Janssen Inc., 3; **B. Osborne**, Janssen Inc., 3.

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Abstract Number: 677

Satisfaction in Psoriatic Arthritis Patients Despite Active Joint Disease

Daniel E. Furst[1], Emma Sullivan[2], James Pike[3], James Piercy[4], Jacqueline Palmer[5] and Vivian Herrera[5], [1]Medicine, University of California, Los Angeles, David Geffen School of Medicine, Los Angeles, CA, [2]Adelphi Real World, Manchester, United Kingdom, [3]Statistics, Adelphi Real World, Macclesfield, United Kingdom, [4]Adelphi Real World, Macclesfield, United Kingdom, [5]Novartis Pharmaceuticals Corporation, East Hanover, NJ

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Background/Purpose:

Psoriatic Arthritis (PsA) is a chronic immune-mediated condition with multiple manifestations; joint inflammation with subsequent joint damage is a key component. Across a number of immunological conditions a high level of patient satisfaction is reported, despite patients having ongoing disease activity.

The objective is to describe and compare the characteristics of PsA patients with active joint disease who are satisfied with their current PsA treatment against those who are unsatisfied.

Methods:

Data were extracted from the Adelphi 2011 / 2014 Rheumatology Disease Specific Programmes, two 'Real World' surveys of US rheumatologists and their PsA patients. Selected rheumatologists who make treatment decisions for PsA patients were recruited. Rheumatologists provided patient demographics, PsA disease characteristics and comorbidities. Patients reported their satisfaction with current control of their PsA, and impairment via the Work Productivity Activity Impairment (WPAI) and alternative HAQ-DI (excluding aids and devices) questionnaires.

Descriptive statistics including means and frequencies were derived for the population with active joint disease (defined as more than 3 tender joints) and stratified by patient satisfaction with PsA treatment (satisfied or dissatisfied).

Results:

From the database, 78 patients were identified with active joint disease and patient satisfaction reported. 54 (69.2%) patients were satisfied with the treatment of their PsA and the remaining 24 (30.8%) dissatisfied. Compared with dissatisfied patients with active joint disease, satisfied patients tended to be older (53.5 vs. 44.3 years), of male gender (59.3% vs. 50.0%), had a longer duration since PsA diagnosis (6.5 years vs. 3.6) and more likely receiving a biologic DMARD (bDMARD) therapy (64.8% vs. 56.5%). The level of disease activity in the joints was similar in satisfied and dissatisfied patients (mean tender joints: 7.9 vs 7.8; swollen joints: 5.1 vs. 5.0) but the extent of skin involvement was lower in satisfied patients (BSA >3%: 71.4% vs. 82.6%). Overall among patients with active joint disease the most common concomitant conditions were hypertension (30.8%), obesity (25.6%), depression (23.1%), elevated cholesterol (21.8%), diabetes (20.5%), and anxiety (19.2%). Dissatisfied patients had more comorbidities overall (2.2 vs. 1.6) and in particular a greater proportion of dissatisfied patients had depression (33.3% vs. 18.5%) and anxiety (33.3% vs. 13.0%) and were less impaired by their PsA (mean % WPAI activity impairment: 38.5% vs. 47.9%; mean alternative HAQ-DI: 0.657 vs. 0.761).

Conclusion:

These findings add further evidence that even when patients have active joint disease they may still report being satisfied, and suggests that with longer disease duration or prescription of bDMARD therapy, physicians and patients may settle for sub-optimal control of the joint aspects of PsA particularly in relation to joint involvement. These findings serve as a signal that there are challenges to managing PsA appropriately as patients progress in their disease, although further investigation and validation in a larger sample is needed.

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2,Genentech and Biogen IDEC Inc., 2,UCB, 2,Abbvie, 5,Actelion Pharmaceuticals US, 5,Amgen, 5,Bristol-Myers Squibb, 5,Cytori, 5,Janssen Pharmaceutica Product, L.P., 5,Gilead, 5,GlaxoSmithKline, 5,NIH, 5,Novartis Pharmaceutical Corporation, 5,Pfizer Inc, 5,Roche Pharmaceuticals, 5,Genentech and Biogen IDEC Inc., 5,UCB, 5,Abbvie, 8,Actelion Pharmaceuticals US, 8,Bristol-Myers Squibb, 2,Amgen, 2,Actelion Pharmaceuticals US, 2,Abbvie, 2,UCB, 8; **E. Sullivan**, Adelphi Real World, 3,Novartis Pharmaceutical Corporation, 9; **J. Pike**, Adelphi Real World, 3,Novartis Pharmaceutical Corporation, 9; **J. Piercy**, Adelphi Real World, 3,Novartis Pharmaceutical Corporation, 9; **J. Palmer**, Novartis Pharmaceutical Corporation, 3; **V. Herrera**, Novartis Pharmaceutical Corporation, 3,Novartis Pharmaceutical Corporation, 1.

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Abstract Number: 678

Clinical Characteristics and Disease Activity in Psoriatic Arthritis Patients with Dactylitis or Enthesitis: Results from Corrona Registry

Philip J. Mease[1], Chitra Karki[2], Carol J. Etzel[2,3], Arthur Kavanaugh[4], Christopher T. Ritchlin[5], Wendi Malley[2], Vivian Herrera[6], Jacqueline B. Palmer[6] and Jeffrey D. Greenberg[2,7], [1]Swedish Medical Center and University of Washington School of Medicine, Seattle, WA, [2]Corrona, LLC, Southborough, MA, [3]The University of Texas MD Anderson Cancer Center, Houston, TX, [4]University of California San Diego, La Jolla, CA, [5]Allergy, Immunology and Rheumatololgy Division, University of Rochester Medical Center, Rochester, NY, [6]Novartis Pharmaceuticals Corporation, East Hanover, NJ, [7]New York University School of Medicine, Millburn, NJ

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Background/Purpose: Psoriatic arthritis (PsA) exhibits considerable heterogeneity in its presentation and course, which contributes to the complexity of diagnosis and assessment. Enthesitis, inflammation at the insertion sites of tendons and ligaments, and dactylitis, the diffuse swelling of digits, are important extra-articular manifestations of PsA and are present in many patients. The objective of this analyses was to characterize the demographic and clinical characteristics of PsA patients with dactylitis or enthesitis and evaluate the association with outcomes such as minimal disease activity (MDA) and functional status, measured by health assessment questionnaire (HAQ) in a large national observational cohort of PsA and spondyloarthritis patients (Corrona).

Methods: All PsA patients ≥18 years enrolled in the Corrona registry were included in the study. Descriptive analyses of patient characteristics, disease activity, and functionality measures at registry enrollment were assessed for patients with and without enthesitis and dactylitis. Regression models were used to evaluate the associations of enthesitis and dactylitis status, separately, with the clinical outcome measures MDA and HAQ (0-3); adjusted for age, gender, race, BMI, disease duration, history of biologic use, history of conventional synthetic DMARD use, and history of prednisone use.

Results: Of the 1567 PsA patients included in the analysis, 228 (14.6%) had dactylitis and 420 (26.8%) had enthesitis at enrollment. Patients with enthesitis or dactylitis had greater disease activity, as reflected in swollen and tender joint count, DAS28-CRP,and CDAI; a lower percentage were in minimal disease activity (MDA) and higher pain and fatigue compared to those who did not have dactylitis or enthesitis (Table). Multivariable analysis showed patients with dactylitis were almost 3 times (OR=2.53, 95% CI=1.55, 4.15) more likely to not be in MDA compared to patients with no dactylitis and patients with enthesitis were over 4 times (OR=4.38, 95% CI=2.77, 6.95) more likely to not be in MDA compared to patients with no enthesitis. Sensitivity analysis evaluating the associations between enthesitis and a modified MDA (5/6 criteria excluding enthesitis) showed consistent results (OR=1.88, 95% CI=1.23, 2.86). Adjusted models showed a mean difference of 0.08 (95% CI= -0.02, 0.17) in HAQ in patients with dactylitis compared to patients with no dactylitis, although not statistically significant. A significant difference of 0.16 (95% CI=0.09, 0.24) in HAQ was seen in patients with enthesitis compared to those who did not have enthesitis.

Conclusion: PsA patients with enthesitis or dactylitis are more likely to have elevated disease activity than patients without these manifestations and have less likelihood of being in MDA and to have worse functional status as assessed by the HAQ.

Table: Baseline characteristics of PsA patients by dactylitis/enthesitis status				
Patient characteristics	**Dactylitis (n = 228)**	**No Dactylitis (n = 1339)**	**Enthesitis (n = 420)**	**No Enthesitis (n = 1147)**
Demographics				
Age (years, mean [SD])	51.8 (13.3)	54.2 (13.3)†	52.5 (13.5)	54.3 (13.2) †
Sex (% female)	48.2%	53.2%	59.2	50†
BMI (kg/m^2, mean [SD])	32 (7.2)	31.5 (7.2)	31.7 (6.9)	31.5 (7.3)
Disease characteristics				
BSA >3% (%)	41.6%	35.5%	37.2%	36.1%
Disease duration (years, mean [SD])	7.7 (8.9)	8.7 (8.9)	7.5 (8.9)	9 (8.9) †
68 Tender joint count (n, median [IQR])	2 (0 – 8)	1 (0 – 5)*	6 (1 – 14)	0 (0 – 3)*
66 Swollen joint count (n, median [IQR])	2 (0 – 6)	0 (0 – 2)*	1 (0 – 4)	0 (0 – 2)*
DAS28-CRP (mean [SD])	3.1 (1.2)	2.7 (1)*	3.2 (1.1)	2.6 (1)*
CDAI (mean [SD])	14.7 (10.9)	11.4 (8.2)*	14.8 (10.8)	10.9 (7.6)*
CRP (mg/L, mean [SD])	4.4 (10.7)	6.9 (16.1) †	3.5 (7.7)	6.3 (13.4)
MDA (%)	13.5%	34.2%*	11.1%	37.1%*
History of comorbidities				
Cardiovascular disease (%)	53.5%	60.6%†	58.1%	60.2%
Any cancer (%)	6.1%	7.5%	6.7%	7.6%
Serious infections (%)	6.6%	4.6%	5.2%	4.8%
Patient reported outcome measures				
HAQ (0-3) (mean [SD])	0.7 (0.7)	0.6 (0.6)	0.8 (0.7)	0.6 (0.6)*
Pain VAS (0-100) (mean [SD])	42 (29.2)	36.8 (29.1) †	44.3 (28.8)	35.1 (28.9)*
Fatigue (0-100) (mean [SD])	43.5 (28.6)	40 (29.4)	46.7 (28.7)	38.2 (29.2)*
*p-value <0.0001; †p-value<0.05. BMI: Body mass index; BSA: Body Surface Area; SD: Standard deviation; IQR: Interquartile range; CDAI: clinical disease activity index; CRP: C - reactive protein; MDA: minimal disease activity; HAQ: Health assessment questionnaire; VAS: Visual Analogue Scale. History of any cancer excludes non-melanoma skin cancer; serious infections: those infections that led to hospitalization to IV antibiotics.				

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Abstract Number: 679

Patients with Psoriatic Arthritis and Oligoarthritic Subtype Report Higher Disease Burden Than Patients with a Polyarthritic Pattern – Data from the German Collaborative Arthritis Centres

Dörte Huscher[1], Katinka Albrecht[2], Sascha Bischoff[2], Katja Thiele[2], Frank Behrens[3], Kathrin Fischer[4], Ulrich von Hinüber[5], Susanna Späthling-Mestekemper[6], Siegfried Wassenberg[7] and Angela Zink[1], [1]German Rheumatism Research Centre and Charité University Medicine, Berlin, Germany, [2]German Rheumatism Research Centre, Berlin, Germany, [3]CIRI/Rheumatology & Fraunhofer TMP, Goethe University, Frankfurt, Germany, [4]Praxis fuer Innere Medizin, Aerztehaus Schoenwalde, Greifswald, Germany, [5]Practice-based rheumatologist, Hildesheim, Germany, [6]Practice-based rheumatologist, München, Germany, [7]Rheumaklinik, Themistocles Gluck hospital - Rheumazentrum Ratingen, Ratingen, Germany

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Background/Purpose: Psoriatic arthritis (PsA) divides into different subtypes, of which polyarthritis and spondylitis would be expected with the highest disease severity. We compared disease burden in PsA patients with oligo- and polyarthritic subtype in the national database of the German Collaborative Arthritis Centres.

Methods: We added a specific PsA module to the standard documentation of the national database of the German arthritis centres, containing data on the predominant PsA subtype (according to physicians' decision), associated skin, joint and other musculoskeletal manifestations. In addition to the Dermatology Life Quality Index (DLQI 0-30), patients reported specific questions concerning PsA-related disease burden. Between 2007 and 2013, in total 707 patients were documented.

Results: PsA patterns comprised 41% oligoarthritis (OA), 46% polyarthritis (PA), 6.4% arthritis of the distal interphalangeal joints (ADIP) or exclusively axial PsA (aPsA) each, and 0.8% patients with dominant arthritis mutilans. Age was comparable between all groups; female proportion was highest in OA. Disease severity was assessed by the physician as highest in aPsA, disease activity as highest in PA and ADIP. Focussing on OA and PA, joint and axial involvement, dactylitis, osteoproliferations and comorbid conditions were more frequent in OA, while psoriasis severity was higher in PA. OA was less often treated with biologics, while use of NSAIDs and opioids was higher than in PA. Patient reported outcomes (PRO) were worse in OA with regard to joint and skin conditions, pain and fatigue. When matching OA and PA by disease duration and gender (n=222 pairs with similar age, data not shown), disparities in physician's disease assessment and PROs as well as treatment differences persisted. In addition to the higher comorbid burden, current regular smoking was more frequently seen in OA patients (23% vs. 16%).

Table 1: Patient characteristics of different PsA subtypes

	predominant oligoarthritis	predominant polyarthritis	predominant arthritis of the DIP joints	exclusively axial PsA
n	287	324	45	45
Age (mean)	56.3	55.1	57.4	54.4
female sex	63.4%	58.6%	53.3%	53.3%
disease duration (median)	11.1	7.2	7.6	11.2
high disease severity	7.4%	10.1%	2.3%	20.9%
disease activity*, 4-10	12.1%	15.5%	16.7%	11.9%
any tender joints (76 joint count)	64.9%	48.4%	54.5%	52.5%
any swollen joints (74 joint count)	42.9%	32.4%	45.5%	10.0%
axial involvement	35.3%	22.0%	-	100.0%
dactylitis	14.1%	9.0%	20.5%	7.0%
enthesitis	16.2%	14.7%	18.2%	18.2%
psoriasis, moderate to severe	12.1%	20.2%	22.7%	18.6%
body surface area (0-100%)	4.1%	5.4%	5.1%	6.8%
nail involvement	34.3%	38.6%	60.0%	37.5%
radiologic alterations	51.7%	48.8%	73.5%	32.3%
osteoproliferations	63.6%	43.2%	77.3%	43.8%
comorbid conditions	82.8%	68.3%	69.8%	81.0%
synthetic DMARDs	80.4%	78.7%	66.7%	74.4%
biologic DMARDs	11.1%	16.8%	9.5%	4.7%
systemic glucocorticoids	23.4%	25.2%	16.7%	18.6%
NSAIDs	57.9%	46.2%	42.9%	65.1%
opiods	14.2%	7.0%	9.5%	37.2%
PRO: joint condition*, 7-10	26.3%	15.5%	32.4%	38.9%
PRO: skin condition*, 7-10	15.3%	9.5%	12.1%	29.4%
PRO: pain*, 7-10	29.5%	17.6%	26.8%	47.5%
PRO: fatigue*, 7-10	28.0%	19.4%	29.3%	48.8%
DLQI, very to extremely large (11-30)	10.9%	6.5%	12.1%	16.1%

* Numerical rating scale with range 0-10, 10 indicating worst status; PRO = patient reported outcome

Conclusion: Despite comparable disease activity and severity measured by clinical examination PsA patients with oligoarthritic compared to polyarthritic subtype show a higher patient reported disease burden, which has to be further examined. Optimising therapy, incorporating comorbidities and councelling the patient against smoking may bear potential to further improve quality of life in PsA-OA.

Abstract Number: 680

Variability over Time in Patient-Reported Outcome Measures in Patients with Ankylosing Spondylitis

Ivette Essers[1,2], Matthias Busch[2], Annelies Boonen[1,3], Sofia Ramiro[4], Désirée van der Heijde[5], Robert B.M. Landewé[6,7] and Astrid van Tubergen[1,2], [1]School for Public Health and Primary Care (CAPHRI), Maastricht University, Maastricht, Netherlands, [2]Rheumatology, Maastricht University Medical Center, Maastricht, Netherlands, [3]Maastricht University Medical Center, Maastricht, Netherlands, [4]Rheumatology, Leiden University Medical Center, Leiden, Netherlands, [5]Department of Rheumatology, Leiden University Medical Center, Leiden, the Netherlands, Leiden, Netherlands, [6]Rheumatology, Atrium Medical Center, Heerlen, Netherlands, [7]Department of Rheumatology, Amsterdam Rheumatology Center, Amsterdam, Netherlands

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Background/Purpose: The BASDAI, BAS-G, and a VAS for spinal pain (VAS-pain) are used to assess disease outcomes in AS. The intervals with which these patient-reported outcome measures (PROMs) are assessed vary widely, depending on the purpose of the assessment, and as such variability in outcome may occur. However, it is currently unknown what the extent and relevance of this variability is, and what the consequences of applying increasing intervals are on follow-up of individual patients. The aim of the study was to evaluate in AS 1) the variability of self-reported disease activity, patient global and spinal pain during 2 years of follow up, 2) the clinical relevance of this variability on a patient level, and 3) the effect of increasing intervals between two measurements on this variability on a measurement level.

Methods: Dutch patients from the Outcome in AS International Study (OASIS) completed the BASDAI, BAS-G, and VAS-pain every 2 months during 2 years. Mixed linear models were used to analyze time trends in the average scores over time. The minimal clinically important difference (MCID) was used to detect relevant changes (worsening or improvement) between two measurements. On a patient level, the frequency of exceeding the MCID, using intervals of 2 months, was calculated. Next, the intervals between two measurements (from 2- to 24-months) were increased to investigate the variability using all available measurements from individual patients.

Results: 90 patients (mean age 47.3 (SD 11.4) years, 68% male, mean symptom duration 25.2 (SD 11.3) years) completed the PROMs. The mean of each measure was stable over time. On the patient level, however, large variability was found. Using 2-months intervals, the average frequency of exceeding the MCID (in either direction) was 4.7 (SD 2.5) times for the BASDAI, 3.3 (SD 2.3) for the BAS-G, and 2.8 (SD 2.0) for the VAS-pain in the 2-year period (from a maximum of 12). On an observational level, exceeding of the MCID was frequently seen in all intervals. This markedly increased with prolongation of the interval in observations showing worsening over time (Table 1).

Conclusion: Substantial variability in the BASDAI, BAS-G, and VAS-pain was found in individuals over time. Clinically relevant changes were frequently observed, especially in observations with worsening more frequently relevant changes occurred with prolongation of the intervals. This intermediate information between two measurements, which may be clinically important, might be missed when intervals are prolonged.

Table 1. Observations exceeding the MCID with different time intervals in a 2-year follow up period

Measurement instrument	Interval (months)	Number of measurements	Number (%) of measurements exceeding MCID			
			Improvement	p-value	Worsening	p-value
BASDAI	2	1044	213 (20.4%)	0.91	199 (19.1%)	**<0.01**
	4	957	205 (21.4%)		186 (19.4%)	
	6	870	169 (19.4%)		181 (20.8%)	
	12	609	131 (21.5%)		146 (24.0%)	
	18	348	72 (20.7%)		85 (24.4%)	
	24	87	17 (19.5%)		31 (35.6%)	
BAS-G	2	1008	136 (13.5%)	0.12	145 (14.4%)	**<0.01**
	4	924	150 (16.2%)		162 (17.5%)	
	6	840	136 (16.2%)		138 (16.4%)	
	12	588	96 (16.3%)		124 (21.1%)	
	18	336	66 (19.6%)		82 (24.4%)	
	24	84	17 (20.2%)		23 (27.4%)	
VAS-pain	2	984	109 (11.1%)	0.23	122 (12.4%)	**<0.01**
	4	902	106 (11.8%)		138 (15.3%)	
	6	820	97 (11.8%)		124 (15.1%)	
	12	574	84 (14.6%)		111 (19.3%)	
	18	328	37 (11.3%)		66 (20.1%)	
	24	82	9 (11.0%)		25 (30.5%)	

BASDAI, MCID=1.0; BAS-G, MCID=1.5: VAS-pain; MCID=2.0.

These analyses were performed by using all available measurements per patient with intervals of 2-, 4-, 6-, 12- and 24-months. A Chi Square test was performed to evaluate if the number of observations exceeding the MCID was different between the intervals.

MCID; minimal clinically important difference. BASDAI; Bath Ankylosing Spondylitis Disease Activity Index. BAS-G; Bath Ankylosing Spondylitis Patient Global Score. VAS-pain; Visual Analogue Pain spinal pain.

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Abstract Number: 681

Impact of Disease Duration on Patient Reported and Clinical Outcomes in Patients with Ankylosing Spondylitis Treated with Anti-TNF: An Analysis from a Prospective, Observational Registry

Michael Starr[1], Michel Zummer[2], Denis Choquette[3], Boulos Haraoui[4], Dalton Sholter[5], Regan Arendse[6], Isabelle Fortin[7], Louis Bessette[8], Proton Rahman[9], Emmanouil Rampakakis[10], Eliofotisti Psaradellis[11], Allen J Lehman[12], Karina Maslova[12], Brendan Osborne[13], Francois Nantel[14,15] and Cathy Tkaczyk[13], [1]Rheumatology, McGill University, Montreal, QC, Canada, [2]Rheumatology, Hôpital Maisonneuve-Rosemont and University of Montreal, Montreal, QC, Canada, [3]Rheumatology Department, Institut de Rhumatologie de Montréal and University of Montreal, Montreal, QC, Canada, [4]Institut de Rhumatologie de Montréal and University of Montreal, Montreal, QC, Canada, [5]Rheumatology Associates, Edmonton, AB, Canada, [6]University of Saskatchewan, Saskatoon, SK, Canada, [7]Centre de Rhumatologie de l'Est du Québec, Rimouski, QC, Canada, [8]Centre d'Ostéoporose et de Rhumatologie de Québec (CORQ), Québec, QC, Canada, [9]Medicine, Memorial University, St John's, NF, Canada, [10]JSS Medical Research, St-Laurent, QC, Canada, [11]JSS Medical Research, Montreal, QC, Canada, [12]Janssen Inc., Toronto, ON, Canada, [13]Medical Affairs, Janssen Inc., Toronto, ON, Canada, [14]Schering Plough Canada Inc., Janssen Inc., Kirkland, QC, QC, Canada, [15]19 Green belt Dr, Janssen Inc., Toronto, ON, Canada

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Background/Purpose: Previous studies have shown that treatment outcomes are affected by disease-related aspects (e.g., disease severity and chronicity, treatment type and intensity) and patient-related factors (e.g., stress and mood). The aim of this analysis was to compare ankylosing spondylitis (AS) patient profiles in terms of patient characteristics and disease parameters based on disease duration and to investigate the impact of disease duration on patient reported and clinical outcomes in patients treated with anti-TNF in a Canadian routine clinical practice setting.

Methods:

Biologic Treatment Registry Across Canada (BioTRAC) is an ongoing, prospective registry of patients initiating treatment for rheumatoid arthritis, ankylosing spondylitis, or psoriatic arthritis with infliximab (IFX) or golimumab (GLM). Eligible people for this analysis included AS pts treated with IFX and enrolled since 2005 or with GLM and enrolled since 2010. Pts were classified in three subgroups (≤1 yr, 2-10 yrs, >10 yrs) based on the tertile distribution of the time elapsed since their diagnosis. The impact of disease duration on outcomes upon adjusting for potential confounders was assessed with generalized linear models and logistic regression.

Results: A total of 580 AS pts were included in this analysis with a mean (SD) age of 45.8 (12.2) yrs and disease duration since diagnosis of 8.3 (10.2) yrs. The majority were male (61.8%) and 92.6% were biologic naïve. At baseline, mean (SD) BASFI was 5.6 (2.6), BASDAI was 6.2 (2.2), and ASDAS was 3.6 (1.0). With the exception of age which was significantly higher among pts with longer disease duration (43.7 vs. 43.5 vs. 50.0, respectively; P<0.001) no significant between-group differences were observed in baseline demographics and disease parameters.

Upon 6 months of treatment, clinically meaningful and statistically significant improvements were observed in BASFI, BASDAI and ASDAS which were further enhanced at 12 months. Upon adjusting for baseline age and respective parameter levels, pts diagnosed within ≤1 yr experienced significantly lower improvements in BASFI (-1.5 vs. -2.3; P=0.030), BASDAI (-1.6 vs. -2.9; P<0.001), and ASDAS (-1.5 vs. -2.3; P=0.030) at 12 months as compared to pts with disease duration >10 ys. For ASDAS, concomitant DMARD use was also identified as a significant predictor of improved outcome (P=0.042). Gender and prior biologic experience did not have a significant impact on outcomes. Inactive disease or moderate disease activity, based on ASDAS, was achieved by 47.2% of pts while clinically important and major improvements were observed for 54.9% and 32.7% of pts, respectively. Similarly to the absolute improvements, pts diagnosed within ≤1 yr were significantly less likely to achieve these endpoints.

Conclusion: The results of this real-world analysis have identified prior disease duration at anti-TNF initiation as a significant independent predictor of treatment outcome. In addition, concomitant use of a DMARD was associated with significantly higher improvement in ASDAS. These results suggest that pts with early disease may be harder to treat and highlight the need for more aggressive treat-to-target approaches in this patient subgroup.

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Abstract Number: 682

Misalignment Between Physician and Patient Satisfaction with Current Psoriatic Arthritis Treatment

Daniel E. Furst[1], Emma Sullivan[2], James Pike[3], James Piercy[4], Jacqueline Palmer[5] and Vivian Herrera[5], [1]Medicine, University of California, Los Angeles, David Geffen School of Medicine, Los Angeles, CA, [2]Adelphi Real World, Manchester, United Kingdom, [3]Statistics, Adelphi Real World, Macclesfield, United Kingdom, [4]Adelphi Real World, Macclesfield, United Kingdom, [5]Novartis Pharmaceuticals Corporation, East Hanover, NJ

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Background/Purpose:

Psoriatic Arthritis (PsA) is a chronic immune related condition affecting the joints and commonly occurs alongside psoriasis. Well-established

physician patient relationships are instrumental to obtaining the best patient outcomes.

The objective of this analysis was to assess the extent of misalignment between physicians and their PsA patients in terms of satisfaction with current control of their PsA. We then compared aligned and misaligned patients in terms of demographic factors, drug treatments, symptoms, comorbid conditions and patient reported outcomes.

Methods:

Data were drawn from the Adelphi 2011 and 2014 Rheumatology Disease Specific Programmes surveys of rheumatologists and their PsA patients in the USA. Rheumatologists with responsibility for managing PsA patients were recruited and provided patient demographics, clinical details, comorbidities and satisfaction with PsA treatment. Patients reported their satisfaction, and completed the Work Productivity Activity Impairment (WPAI) questionnaire, and alternative HAQ-DI (excluding aids and devices) questionnaire.

Levels of satisfaction agreement between physician and patient responses were constructed and compared: aligned (physician and patient both satisfied, or physician and patient both dissatisfied with PsA treatment) and misaligned (physician and patient reported satisfaction with PsA treatment was different). Descriptive statistics including means and frequencies were derived.

Results:

From 305 paired rheumatologists and PsA patient records, 233 (76.4%) were ‘aligned’, consisting of 65.3% with both physician and patient satisfied, and 11.1% with both dissatisfied.72 (23.6%) cases were ‘misaligned’. The aligned and misaligned groups were similar in terms of age (mean 50.0, 49.8) and sex (% female: 44.6, 45.8). However, the aligned group had longer time since diagnosis compared with misaligned (mean years: 6.4, 5.2) and were more likely to receive biologic DMARD (bDMARD) therapy (% receiving bDMARD: 62.9, 49.3).

The misaligned group tended to be more symptomatic, having higher TJC (mean 5.6 vs. 2.9), SJC (mean: 3.7, 1.9), higher BSA (>3% BSA affected: 64.2% vs. 55.1%), higher number of PsA symptoms (mean: 6.8, 4.9). The most common concomitant conditions were hypertension (28.9%), elevated cholesterol (20.0%), depression (14.1%), obesity (13.8%) and anxiety (10.8%). A greater proportion of misaligned patients had depression (20.8% vs. 12.0%) and anxiety (15.3% vs. 9.4%). As reported in the WPAI, the misaligned were also more impaired in their overall work (mean 38.7% vs. 21.4%), while at work i.e. presenteeism (mean 36.2% vs. 16.5%) and in their daily activities (mean 38.7% vs. 22.3%). Additionally they had higher disability (mean alternative HAQ-DI score: 0.563 vs. 0.369).

Conclusion:

Misalignment between rheumatologists and their PsA patients in satisfaction with PsA treatment exists in almost a quarter of cases. In cases of misalignment, disease severity and patient reported outcomes were worse. The findings suggest that a greater degree of alignment might result in improved outcomes, although further research would be required to verify this hypothesis.

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Abstract Number: 683

Referral Strategies for the Early Diagnosis of Axial Spondyloarthritis- a Systematic Review

Abhijeet Danve[1] and Atul A. Deodhar[2], [1]Internal Medicine - Rheumatology, University of Nebraska Medical Center, Omaha, NE, [2]Division of Arthritis & Rheumatic Diseases, Oregon Health & Science University, Portland, OR

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Background/Purpose:

Axial Spondyloarthritis (axSpA) is often misdiagnosed or diagnosed late (average delay 8 to 11 years) since low back pain (LBP) is very

common in general population and only 5% of those have axSpA. Effective screening and selective referral of high-risk patients (Pt) can help avoid this delay. There are no recommendations for a referral strategy for axSpA in the United States (US). We performed a systematic review to assess the effectiveness of various referral strategies on the final diagnosis of axSpA, and feasibility of their use in US health system.

Methods:

Pubmed and EMBASE search was performed to identify relevant articles using MeSH terms. After screening abstracts and titles of 135 retrieved articles, 9 full length articles were included for initial review. Three articles were excluded; 2 had different outcome and one was poor quality study. We included a single abstract since it describes the only available study in the US assessing a referral strategy. Final review included 6 full articles and 1 abstract. Data about referral source, referral strategy, Pt characteristics and outcomes were collected. Feasibility was determined by ease of the application of a strategy.

Results:

Most studies used "age at symptom onset <45 years and duration >3 months" as entry criterion (EC) for referral. Pt fulfilling EC only or EC plus combinations of spondyloarthritis (SpA) features (inflammatory back pain (IBP), HLA-B27 (B27), imaging sacroiliitis (iSI), good response to NSAIDS, family history of SpA, uveitis) were referred to rheumatologists. Commonest sources of referral were primary physicians, physical therapists and orthopedists. (See table) Application of simple (EC + 1 of 3 features) and complex strategies (EC + 2 of 5 or 2 of 6 features) produced similar results with 35-45% Pt finally diagnosed as axSpA. Even among studies that used only EC, 33 % to 41% of Pt were diagnosed to have axSpA. Simple strategy of fulfilling EC + 1 of 3 of IBP, B27 and iSI was found to be convenient, feasible and widely acceptable in multicenter studies. Presence of >1 SpA features was associated with higher likelihood of axSpA (24.6%, 44.9%, and 75.5 % for 1, 2 and 3 features respectively). As a single SpA feature in addition to EC, iSI, B27 and IBP were associated with final diagnosis of axSpA in 50%, 55% and 24% respectively, thus confirming low specificity of IBP.

Conclusion:

Referral strategies are effective tools for screening Pt with chronic back pain for presence of axSpA. Simple strategies work equally well compared to complex strategies. With appropriate application of any strategy, rheumatologist will need to see 2-3 Pt with chronic LBP to identify one Pt with axSpA. We believe that in the US, referring Pt with chronic LBP for >3 months, age of onset <45 years AND one of IBP, B27, iSI to rheumatologist for assessment of possible axSpA would be practical, with an acceptable efficacy.

Table

Author /Year	Referring physicians	Strategy	N	Male (%)	Mean symptom duration ∞	Age# (years)	AxSpA (%)	AS (%)	Nr axSpA (%)
Brandt 2007 (F)	Ortho Primary care	LBP>3mth, Onset at<45 years ≥1 of IBP, + HLA-B27, Sacroiliitis on available imaging	350	48.6	7.7 yr	37 *	**45.4**	50.3	49.7
Hermann 2009 (F)	GP	Calin criteria (4/5)	92	41	3.3 yr	32**	**33**	53.3	46.7
Braun 2011 (F)	Ortho	LBP >2m <10year , onset<45 ≥1 of AM stiffness,, Improvement with exercise, not rest, waking at night, improvement with NSAID	322	50	N/A	36*	**35**	41.6	58.4
Poddubnyy 2011 MASTER Study (F)	GP and Ortho	LBP >3m, Onset<45 years AND Strategy 1- ≥1 of of IBP, + HLA-B27, Sacroiliitis on available imaging Strategy 2- 2 of 5- IBP, + HLA-B27, Sacroiliitis on available imaging, positive family history for AS, good response to NSAID	318 242	53 55	9.2 yr 8.8 yr	38.4 37.5	**41.8** **36.8**	61.6 61.8	38.4 38.2
Sieper 2012 RADAR Study (F)	Primary care Other- (GP, neuro, ortho)	LBP >3m, Onset<45 years AND Strategy 1- ≥1 of of IBP, + HLA-B27, Sacroiliitis on available imaging Strategy 2- 2 of 6- IBP, + HLA-B27, Sacroiliitis on available imaging, positive family history for AS, good response to NSAID, EAM	504 568	47 55	N/A N/A	N/A N/A	**35.6** **39.8**	77 78	23 22
van den Berg 2013 (F)	GP Eye Gastroente rology	LBP >3 mth but <2 years Onset<45 years	157	33	13.4 months	N/A	**41.4**	18	82
Deodhar 2014 PreSpA study (A	Self Rheumatol ogy Other physicians	LBP >3 mth, Onset<45 yr ≥1 of IBP, + HLA-B27, Sacroiliitis on available imaging	751	50	14 yr	N/A	**46**	31	69

F- Full length article A–Abstract N -number of referred patients * Mean **Median ∞ -For patients diagnosed with axSpA # For patients diagnosed as AxSpA LBP-Low back pain
Nr- axSpA- Non radiographic axial spondyloarthritis EAM- Extra articular manifestations

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Abstract Number: 684

Evaluation of Patient Acceptable Symptom State in Patients with Axial Spondylarthritis;

Similar Thresholds for Radiographic and Non-Radiographic Subgroups

Pinar Cetin[1], Gercek Can[1], Gokce Kenar[1], Handan Yarkan[1], Berrin Zengin[1], Ismail Sari[1], Merih Birlik[1], Fatos Onen[1] and Nurullah Akkoc[2], [1]Rheumatology, Dokuz Eylul University Faculty of Medicine, Izmir, Turkey, [2]Department of Rheumatology, Dokuz Eylul University, Faculty of Medicine, Izmir, Turkey

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Background/Purpose: The Patient Acceptable Symptom State (PASS), a single-question outcome, has been defined as an absolute level of patient well-being. A few studies have assessed PASS in patients with ankylosing spondylitis (AS), but it is not known whether the results of those studies apply also to the group of non-radiographic (nr) axial spondylarthritis (axSpA). The objective of this study is to estimate the PASS values for disease activity and several patient reported outcomes both in the whole group of axSpA and in the two subgroups of AxSpA.

Methods: This single-center cross-sectional analysis included patients fulfilling the ASAS criteria for axSpA, who have been registered in our local database. All patients responded to the global yes/no question for PASS. A variety of other outcome measures in regard with global scales, disease activity, functional status, health status and quality of life were collected at the same time. The thresholds at which patients rated themselves in PASS for disease activity (BASDAI and ASDAS) and for each of the assessed patient self-reported outcome measures were estimated using the 75th centile (25th centile for SF 36)estimation and receiver operating characteristic (ROC) analyses in the whole group, as well as in each subgroup of axSpA. Contributors which can affect PASS were evaluated with logistic regression analysis.

Results: The analysis was based on 356 axSpA patients (261 AS, 95 nr-axSpA) with a mean age of 42.2±12.0 years and mean disease duration of 14.7±10.8 years. Of the patients with axSpA, 271 (%76.1) considered themselves in PASS (76.6% in AS, 74.7% in nr-axSpA). PASS thresholds for disease activity and all other assessed outcome measures were shown in table and there were not significant difference between AS and nr-axSpA group. PASS cut-off points for BASDAI, BASFI and HAQ identified by the 75th percentile method were slightly higher than those determined by the ROC analysis, but similar for the rest of the outcome measures. The patients with an acceptable status had significantly lower mean disease activity scores and good results with the all outcome measures. PASS had no relationship with age, sex, disease duration and education (years) in logistic regression analysis. Of the axSpA patients with BASDAI (≥4), 61.4% and those with ASDAS (>3.5), 50% rated themselves in PASS, whereas 5.5% of the patients with a BASDAI score <2, and 4.5% of those with ASDAS <1.2 were not in PASS.

Conclusion: PASS thresholds for disease activity and outcome measures were similar to the figures previously reported in some studies with no apparent difference between patients with AS and nr-axSpA. However, more than half the Turkish axSpA patients considered themselves in PASS, which needs to be evaluated in further studies.

Table. Patient Acceptable Symptom State (PASS) cut-off points for disease activity and health status measures in all patients.

Parameter	PASS + 75th Percentile threshold*	ROC cut off	Area under the curve	Sensitivity/ Specificity
Disease activity BASDAI (0-100mm)	46.0	39.5	0.74	68/65
ASDAS	3.1	3.0	0.74	72/68
Functional measures BASFI (0-100mm)	40.0	35.5	0.72	69/64
HAQ-S	0.9	0.79	0.72	67/64
Global scales Pain VAS (0-100mm)	51.0	49.5	0.75	69/69
Global VAS (0-100mm)	56.8	47.5	0.77	65/73
SF 36 PCS	36.0	38.5	0.73	67/69
MCS	41.0	43.5	0.71	67/63
Quality of life ASqol	8.0	6.5	0.71	68/63
EQ 5D	0.84	0.71	0.72	66/64

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Sacroiliitis Misdiagnosed As Spondyloarthritis: Clinical Analysis of 581 Cases

Feng Huang, **Yanyan Wang**, Zheng Zhao and Jianglin Zhang, Rheumatology, Chinese PLA General Hospital, Beijing, China
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Background/Purpose: To study other disease conditions which can present with bone marrow edema of the sacroiliac joints mimicking spondyloarthritis(SpA).

Methods: In a retrospective study of 581 patients from January 2007 to January 2014 for inflammatory back pain datas, including clinical manifestations, laboratory examinations, imaging manifestations and sacroiliac joint biopsy pathological features of these patients were reviewed. All of these patients from Chinese PLA General Hospital. The Images were read independently by at least 2 experienced rheumatologists.

Results: Of the 581 patients, 455 (78.3%) were male, and 436 (75%) cases were diagnosed Ankylosing Spondylititis(AS)/SpA. HLA-B27 positivity rate was 87% among those diagnosed with AS/SpA, Among the 145 patients whose diagnosis was not AS/SpA, HLA-B27 positivity rate was only 8% in 145 patients. 46, 40 and 30 patients had an infectious etiology (pyogenic sacroiliitis/tuberculous infectious sacroiliitis/Brucellar infectious sacroiliitis), sclerosing osteitis or hypophosphatemia osteomalacia (HO) respectively. Other less common diagnoses included diffuse idiopathic bone hypertrophy, palmoplantar pustulosis arthritis and sacroiliac joint gout. The causes of HO included 15 cases of tumor-induced osteomalacia, 4 cases of long-term oral adefovir dipivoxil, 3 cases of Fanconi syndrome, 2 cases of hyperparathyroidism, 2 cases of Sjogren's syndrome complicated with renal tubular acidosis. Patients with infectious sacroiliitis presented with MRI abnormalities

which included bone marrow edema, erosion of bone and joint, 44 of the 46 patients who had an infectious sacroiliitis show adjacent muscle involvement in MRI.

Conclusion: Sacroiliitis not due to AS is quite common in daily practice. Rheumatologists should suspect a different diagnosis when patients respond poorly to NSAIDs, have unexplained low grade fever or other clinical manifestations which cannot be fully explained by AS/SpA. This is even more important when making the decision of using anti-TNF therapy or other immunosuppressive agents.

Disclosure: F. Huang, None; **Y. Wang**, None; **Z. Zhao**, None; **J. Zhang**, None.

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Abstract Number: 686

Does an Educational Leaflet Improve Attendance for Screening for Psoriatic Arthritis?

Laura C Coates, Laura J Savage, Anna R. Moverley and Philip S. Helliwell, Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds, Leeds, United Kingdom

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Background/Purpose: There is a need for screening to identify patients with psoriasis who have PsA. We developed an educational leaflet about the risk of PsA to improve screening attendance. Our aim was to investigate the prevalence of PsA in primary care and whether an educational leaflet can improve attendance.

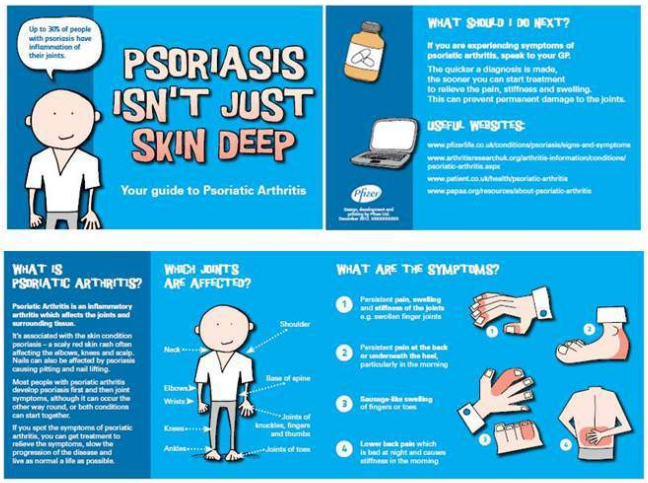
Methods: Patients with psoriasis were identified from 5 GP surgeries in Yorkshire and a random sample were invited to participate. Patients had to be ≥18 years old, have a coded diagnosis of psoriasis and no diagnosis of PsA, RA or AS. At each site, patients were randomised 1:1 to receive study information alone or with the educational leaflet. Consenting patients were then assessed by a dermatologist and rheumatologist. Diagnosis of PsA was made by the assessing rheumatologist. To compare the response rate, we assumed a difference of 20% (50% without leaflet, 70% with leaflet). With an alpha=0.05 and beta 0.9, using a two sided test a minimum sample size of 248 was required. 191 attendees were required for assessment of screening questionnaires.

Results: A total of 932 packs were sent out to recruit 191 (20.5%) participants attending. Of these, 169 (88.5%) had current or previous psoriasis. Using physician diagnosis 17 (10.1%) were found to have previously undiagnosed PsA, 90 (53.3%) were found to have another musculoskeletal complaint and 62 (36.7%) had no musculoskeletal problems. Using data from the practices and correcting for misdiagnosis of psoriasis, the estimated prevalence of PsA was 18.1%.

Overall the response rate was lower than predicted and was not significantly higher when patients received the educational leaflet (22.8% vs 18.3%, p=0.08). Response rates varied by practice (14.7 to 30.6%). Socioeconomic data of the registered patients at each practice provided national statistics on deprivation with each practice given a decile score. In our study, one practice had a deprivation score of 3 (third most deprived), one had a score of 7 and the rest had a score of 10 (least deprived decile). Analysing the impact of the leaflet on response rates by deprivation showed that there was a significant increase in response with the leaflet for deprivation decile of 3 (see table, p<0.001) but no significant differences in the other practices.

Conclusion: The total prevalence of PsA within patients with psoriasis in primary care is estimated at 18.1%, and from a sample of 191, 10.1% are diagnosed with new PsA at screening. An educational leaflet about PsA did not improve attendance for screening overall, but did significantly improve attendance in practices with higher levels of socioeconomic deprivation.

Deprivation Index	Information given	No of packs sent	Response rate (%)	Pearson Chi Squared	P value
3	Leaflet	46	30.4	13.21	<0.001
	No leaflet	54	3.7		
7	Leaflet	75	18.7	1.92	0.166
	No leaflet	75	10.7		
10	Leaflet	340	22.6	0.18	0.894
	No leaflet	342	22.2		



Disclosure: L. C. Coates, Janssen Pharmaceutica Product, L.P., 2,Janssen Pharmaceutica Product, L.P., 8; **L. J. Savage**, Janssen Pharmaceutica Product, L.P., 8; **A. R. Moverley**, None; **P. S. Helliwell**, Janssen Pharmaceutica Product, L.P., 8,Pfizer Inc, 5.

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Abstract Number: 687

Mucosal Dysregulation in First-Degree Relatives of Ankylosing Spondylitis Patients

Amy Sargious Kehl[1], Carol Landers[2], Tina Wu[2], Dermot McGovern[3] and Michael H. Weisman[1], [1]Rheumatology, Cedars-Sinai Medical Center, Los Angeles, CA, [2]Cedars-Sinai Medical Center, Los Angeles, CA, [3]Department of Inflammatory Bowel & Immunobiology Research Institute, Cedars-Sinai Medical Center, Los Angeles, CA

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Background/Purpose:

It has been observed that ankylosing spondylitis (AS) patients have a high frequency of asymptomatic chronic gut inflammation, with as many as 60% of AS patients with evidence of microscopic gut inflammation without gastrointestinal symptoms. While much is known about the clinical relationship between AS and IBD, little is understood about the directionality of these relationships or the role of the gut in the pathogenesis of AS. This study aimed to investigate if healthy asymptomatic first-degree relatives (FDRs) of ankylosing spondylitis patients have evidence of subclinical gut inflammation that precedes development of musculoskeletal signs and symptoms of AS.

Methods:

30 healthy FDRs of AS patients between the ages of 18 and 50 years old were recruited for the purpose of this study, of which 18 are included in the current cross-sectional analysis. We collected serum biomarkers of gut inflammation including anti-*Saccharomyces cerevesiae* antibodies (ASCA), antineutrophil cytoplasmic antibodies (ANCA), anti-I2 (associated with anti-*Pseudomonas* activity), anti-*Eschericia coli*outer membrane porin C (anti-OmpC) and anti-flagellin antibodies (anti-CBir1), as well as stool samples to measure fecal calprotectin. Clinical data about symptoms and signs of ankylosing spondylitis was obtained using the Toronto Axial Spondyloarthritis Questionnaire in Inflammatory Bowel Disease (IBD.) Finally, we obtained a pelvic MRI on all subjects using STIR (Short TI Inversion Recovery) sequences to rule in or out the presence of asymptomatic axial spondyloarthritis. FDRs with no MRI evidence of disease will be followed and assessed yearly for the development of AS.

Results:

Of 18 FDRs included in the current analysis, six were found to be HLA B27 positive. Six FDRs (33%) reported back pain, and four FDRs (22%) reported heel pain. No participants reported other extra-articular manifestations and no participants reported gastrointestinal symptoms. On MRI, two FDRs (11%) were found to have evidence of definite sacroiliitis. Four FDRs (11%) were found to have a fecal calprotectin level which was in the upper range of normal. Six FDRs (33%) were found to have at least one positive IBD antibody, five of which have CBir positivity (27%). Two FDRs (11%) had a positive ASCA antibody. Of the six FDRs with a positive IBD antibody, 50% were HLA B27 positive and none reported back pain, gastrointestinal symptoms, or had MRI evidence of sacroiliitis.

Conclusion:

A substantial proportion of healthy FDRs of AS patients have an elevated serum IBD antibody profile, specifically with respect to anti-CBir1, without evidence of clinical IBD, suggestive of mucosal dysregulation. This study will contribute to our understanding of the directionality of the AS-gut inflammation relationship as well as the role of the gut in the etiology of AS. With increasing understanding of whether gut inflammation precedes AS, we can develop a prediction tool for determining who is at risk of developing the disease and begin to intervene at the earliest possible stage in order to delay the onset of debilitating symptoms.

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Abstract Number: 688

Clinical Improvements in Psoriasis and Psoriatic Arthritis with Surgical Weight Loss

Monica Sethi[1], Christine Ren-Fielding[2], Ana Clara Caminer[3,4], Jose U. Scher[5] and **Soumya M. Reddy**[6], [1]Department of Surgery, Division of Bariatric Surgery, New York University School of Medicine, New York, NY, [2]Department of Surgery, New York University School of Medicine, New York, NY, [3]Rheumatology, Facultad de Ciencias Médicas, Universidad Nacional de Rosario, Rosario, Argentina, [4]Rheumatology, Sanatorio Parque, Rosario, Argentina, [5]Department of Medicine, Division of Rheumatology, New York University School of Medicine, New York, NY, [6]Division of Rheumatology, New York University School of Medicine, New York, NY
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Background/Purpose: Obesity is more prevalent among patients with psoriasis and psoriatic arthritis (PsA). This correlation appears to be related to fat tissue-driven systemic inflammation. Although bariatric surgery has been shown to improve several obesity-related comorbidities, the effects of surgical weight loss on psoriasis and PsA are unknown. Our objective was to investigate the effects of weight loss from bariatric surgery on psoriasis and PsA.

Methods: A retrospective database of 9,073 bariatric surgeries performed at a single center between 2002-2013 was queried. Patients with a diagnosis of psoriasis prior to surgery were identified. Patients were contacted about their history of psoriasis, PsA, change in symptoms, and treatment modalities pre- and postoperatively. The primary outcome was the percentage of patients who reported improvement (reduction of >5 on rating scale 0-10) in psoriasis and PsA after surgery. Secondary analyses were performed to define factors associated with improvement in psoriasis and PsA.

Results: We identified 128 patients with a preoperative diagnosis of psoriasis. Eighty-six (67%) patients completed the study. Baseline patient characteristics are listed in Table 1. The mean time from surgery was 6.1 years, with a mean excess weight loss (EWL) of 46.2%. Twenty-one (24%) patients with psoriasis also had a preoperative diagnosis of PsA

At the time of contact, 55% of psoriasis and 62% of PsA patients reported subjective improvement of their disease. Disease severity rating (0-10 scale) significantly decreased from prior to surgery compared to 1 year post surgery for psoriasis (5.6 vs 4.4, $p<0.01$) and PsA (6.4 vs 4.5, $p=0.01$), and was more pronounced among severe (rating >5) psoriasis (7.7 vs 5.7, $p<0.01$) and PsA (8.2 vs 4.8, $p<0.01$).

In secondary analyses of patients with severe psoriasis and PsA, higher EWL at recent follow-up was significantly associated with improvement in psoriasis (59.5 vs 43.5%, $p=0.046$) and higher EWL at 1 year was associated with a trend in PsA improvement (55.4 vs 43.8%, $p=0.47$). Improvement in disease among severe psoriasis patients was associated with higher rating of disease at the time of surgery (8.9 vs 7.4, $p<0.01$) and older age at diagnosis (37 vs 26yr, $p=0.02$).

Conclusion: Although the natural history of psoriasis and PsA is typically chronic, a majority of patients experience improvement after bariatric

surgery. Our results indicate an association between EWL and symptomatic improvement in severe cases of psoriasis. Factors such as older age at diagnosis of psoriasis and severity of psoriasis may be used to identify patients with a greater likelihood of improvement. Despite study limitations, we show for the first time an improvement in PsA after bariatric surgery and a possible association with surgical EWL. Larger prospective studies are needed to further define the true effect of surgical weight loss on psoriasis and PsA.

Table 1: Baseline Characteristics of Study Population (n=86)	
Male Gender, n (%)	33 (38%)
Age (years), mean (SD)	46.5 (12.6)
Preoperative Weight (lb), mean (SD)	288 (55)
Preoperative Body Mass Index (kg/m^2), mean (SD)	45.8 (6.8)
Type of Surgery, n (%) Laparoscopic Adjustable Gastric Band (LAGB) Roux-en-Y Gastric Bypass (RYGB) Laparoscopic Sleeve Gastrectomy (LSG) Biliopancreatic Diversion (BPD)	78 (91%) 6 (7%) 1 (1%) 1 (1%)
Duration of psoriasis at surgery (years), mean (SD)	18.7 (13.4)
Age at diagnosis of psoriasis (years), mean (SD)	28.2 (13.8)
Family history of psoriasis, n (%)	38 (44%)
Treatment with biologics prior to surgery, n (%)	19 (22%)
Diagnosis of psoriatic arthritis, n (%)	21 (24%)
Duration of psoriatic arthritis at surgery (years), mean (SD)	16.9 (12.4)
Age at diagnosis of psoriatic arthritis (years), mean (SD)	38.3 (14.7)
Family history of psoriatic arthritis, n (%)	2 (10%)
Treatment with biologics prior to surgery, n (%)	13 (62%)

SD Standard Deviation; *n*= number of psoriasis patients

Disclosure: M. Sethi, None; **C. Ren-Fielding**, Apollo Endosurgery, 5; **A. C. Caminer**, None; **J. U. Scher**, None; **S. M. Reddy**, Novartis, 5,Janssen, 5.

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Abstract Number: 689

Are Individual or Country Level Socio-Economic Determinants Related to Disease Activity and Self-Reported Physical Function in Patients with Spondyloarthritis – Results from Multi-National Cross-Sectional Study Comospa

Polina Putrik[1], Sofia Ramiro[2], Andras Keszei[3], Maxime Dougados[4], Anna Moltó[5], Désirée van der Heijde[2], Robert B.M. Landewé[6] and Annelies Boonen[7], [1]Department of Internal Medicine, Division of Rheumatology, Maastricht University Medical Center, Maastricht, Netherlands, [2]Rheumatology, Leiden University Medical Center, Leiden, Netherlands, [3]Epidemiology, Maastricht University, Maastricht, Netherlands, [4]Université Paris René Descartes and Hôpital Cochin, Paris, France, [5]Paris Descartes University, Rheumatology Department, Cochin Hospital, AP-HP. INSERM (U1153): Clinical Epidemiology and Biostatistics, PRES Sorbonne Paris-Cité,, Paris, France, [6]Department of Rheumatology, Amsterdam Rheumatology Center, Amsterdam, Netherlands, [7]Maastricht University Medical Center, Maastricht, Netherlands
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Background/Purpose:

In RA, previous studies observed inequalities across countries as well as individual level socio-economic factors, and unequal uptake of biologic DMARDs (bDMARDs) played an important role in these inequalities. It is not known whether the same pattern is present for patients with spondyloarthritis (SpA). Our objectives were to assess (1) independent associations of country level and individual socio-economic determinants of health in patients with SpA and (2) if confirmed, whether this relation is mediated by uptake of bDMARDs.

Methods:

Data from the cross-sectional multinational (22 countries) study Comorbidities in Spondyloarthritis (COMOSPA) was used. ASDAS-CRP and BASFI were the outcomes. First, the contribution of individual socio-economic factors (age, gender, and education) was explored, adjusting for BMI, comorbidities, presence of extra-articular manifestations and axial SpA. Next, country of residence (separate variable for each country) or country's welfare was added to the model. Country's welfare was defined as Gross Domestic product (GDP) per capita (low, medium or high). Multivariable linear regression models were used. Interactions between (1)education (2)age and (3)gender with GDP were tested. The mediating role of uptake of bDMARDs in the relationship between education and ASDAS or GDP and ASDAS was explored by testing indirect effects.

Results:

3984 patients from 22 countries worldwide (41 to 337 subjects/country) were included. Mean age was 44 yrs. (SD14), 65% males, 13% had primary and 45% secondary education, 83% axial SpA. Mean ASDAS and BASFI were 2.4 (SD1.1) and 3.0 (SD2.7), respectively. Five to 68% of patients were currently treated with bDMARDs. Females (vs. males) had higher BASFI (β=0.70 [95%CI 0.54;0.86]) while gender was not relevant for ASDAS and effect of age was negligible for both outcomes. Lower educated individuals had higher ASDAS and BASFI (β=0.21 [0.09;0.33] and β=0.60 [0.37;0.85], respectively) (Table). Large country differences were observed after adjusting for individual confounders. Low GDP (vs. high GDP) was associated with higher ASDAS (β=0.70 [0.60;0.79]) but lower BASFI (β=-0.21 [-0.42;-0.01] (Table). No interactions were detected. Current uptake of bDMARDs did not mediate relationship between education or GDP with ASDAS.

Table. Association between individual and country level (GDP) factors with ASDAS and BASFI. Results of multivariable linear regression model (β [95%CI]).

	ASDAS	**BASFI**
Age, years	*-0.01* [-0.01;-0.00]	*0.02* [0.01;0.02]
Gender (female vs male)	0.04 [-0.04;0.12]	*0.70* [0.54;0.86]
Education		
Low education vs. University diploma	*0.21* [0.09;0.33]	*0.60* [0.37;0.85]
Secondary education vs. University diploma	*0.11* [0.04;0.19]	*0.60* [0.44;0.75]
Rheumatic diseases comorbidity index (RDCI, 0-9)	*0.13* [0.09;0.17]	*0.50* [0.42;0.57]
Disease duration, years	Not included	0.01 [0.00;0.02]
Body-mass index (BMI)		
Underweight vs normal	0.23 [0.00;0.46]	-0.09 [-0.54;0.37]
Overweight vs normal	*0.11* [0.02;0.19]	*0.23* [0.06;0.40]
Obesity vs normal	*0.28* [0.18;0.39]	*0.59* [0.38;0.80]
Presence of axial SpA (yes vs no)	*0.16* [0.06;0.26]	*1.12* [1.05;1.19]
GDP		
Middle vs High GDP	*0.10* [0.01;0.20]	*-0.27* [-0.47;-0.08]
Low vs High GDP	*0.70* [0.60;0.79]	*-0.21* [-0.42;-0.01]

GDP – Gross Domestic Product in int.$ ASDAS - Ankylosing Spondylitis Disease Activity Score; BASFI - Bath Ankylosing Spondylitis Function Indices

Conclusion:

Lower education was associated with worse disease activity and function in SpA. In addition, even after adjusting for individual factors, substantial differences in these outcomes remained between countries. Interestingly, low GDP societies had higher objectively measured disease activity (ASDAS), but appeared to score slightly better on the more subjective assessment of physical function (BASFI). Relationship between low socio-economic status (individual or country level) and higher disease activity could not be attributed to lower uptake of biologic DMARDs.

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Abstract Number: 690

The Impact of Ankylosing Spondylitis in Turkey on Productivity at Work Outside Home and within the Household

Dilek Solmaz[1], Pinar Cetin[2], Omer Nuri Pamuk[3], Ayse Cefle[4], Gokhan Keser[5], Mehmet Akif Ozturk[6], Mehmet Sayarlioglu[7], Murat Turgay[8], Nevsun İnanc[9], Refik Ali Sari[10], Servet Akar[11], Soner Sener[12], Suleyman Serdar Koca[13], Senol Kobak[14], Taskin Senturk[15], Umut Kalyoncu[16], Veli Cobankara[17], Yasar Karaaslan[18], Yavuz Pehlivan[19] and **Nurullah Akkoc**[20], [1]Rheumatology, Namik Kemal University Faculty of Medicine, Tekirdag, Turkey, [2]Rheumatology, Dokuz Eylul University Faculty of Medicine, Izmir, Turkey, [3]Rheumatology, Trakya University Faculty of Medicine, Edirne, Turkey, [4]Ä°nternal Medicine Division of Rheumatology, Kocaeli University, Faculty of Medicine, Kocaeli, Turkey, [5]Rheumatology, Ege University Medical Faculty, Izmir, Turkey, [6]Internal Medicine-Rheumatology, Gazi University School of Medicine, Ankara, Turkey, [7]Department of Internal Medicine Division of Rheumatology, Ondokuz Mayıs University, Faculty of Medicine, Samsun, Turkey, [8]Internal Medicine-Rheumatology, Ankara University School of Medicine, Ankara, Turkey, [9]Rheumatology, Marmara University Faculty of Medicine, İstanbul, Turkey, [10]Karadeniz Technical University Faculty of Medicine, Trabzon, Turkey, [11]Department of Internal Medicine, Division of Rheumatology, Izmir Katip Celebi University School of Medicine, Izmir, Turkey, [12]Rheumatology, Erciyes University Faculty of Medicine, Kayseri, Turkey, [13]İnternal Medicine Division of Rheumatology, Firat University, Faculty of Medicine, Elazig, Turkey, [14]Rheumatology, Sifa University Faculty of Medicine, 35100, Turkey, [15]Rheumatology, Adnan Menderes University School of Medicine, Aydin, Turkey, [16]Rheumatology, Hacettepe University School of Medicine, Ankara, Turkey, [17]Division of Rheumatology, Pamukkale University, Denizli, Turkey, [18]Rheumatology, Numune Research and Teaching Hospital, Ankara, Turkey, [19]Department of Rheumatology, Uludag University Faculty of Medicine, Bursa, Turkey, [20]Department of Rheumatology, Dokuz Eylul University, Faculty of Medicine, Izmir, Turkey
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Background/Purpose: Ankylosing Spondylitis (AS) is associated with a high disease burden. The greatest contributor to the burden is loss of productivity. The data on productivity loss in Turkish patients with AS is scarce. Work Productivity Survey (WPS) is a validated tool in AS to assess productivity during the preceding month, both at work and at home. The aim of this study is to assess work productivity in Turkish AS patients using the WPS.

Methods: A total of 397 patients with AS (males:71.4%, mean age: 40.5, mean disease duration 6.8 years) from 19 rheumatology centers across Turkey were included in the study. Patients, with the help of a health professional, completed questionnaires for BASDAI, BASFI, HAQ-S, ASQoL and EQ-5D, total and nocturnal pain and WPS. Student's t test was used to compare continuous variables and chi square analysis was used to compare categorical variables. The association between the responses to WPS questions and scores of disease activity, functional and quality of life scores was assessed using Kendall correlation coefficients.

Results: Of all the patients, 62.4% of were employed, 16.1% were homemakers, 9.6% were retired, 3.0% were student and 5.3% were unable to work due to AS. Non-working patients, as compared to the working patients, were older (44 vs 38, p: <0.001), more likely to be female (54% vs 14%, p: <0.001) and had less favorable scores for BASDAI (3.8 vs 3.0, p: <0.015), BASFI (2.9 vs 2.3, p: 0.001), HAQ (0.8 vs 0.5, p: <0.001), EQ-5D (0.6 vs 0.7, p: 0.005) and productivity. Working AS patients reported missing 1.2 days of work and had 2.8 days productivity reduced by at least half. As compared to the working patients, the non-working patients missed more days of housework (5.4 vs 2.9), more days of family, social or leisure activities, more and had more days with outside help, more days with reduced productivity in house work in the past month (for all comparisons, p: <0.001). However, no difference was observed between the working and not working female patients. WPS questions were shown to have moderate correlation with other clinical and health related quality scores either at workplace or at home (range from r: 0.268 to r: 0.481) (Figure).

Conclusion: AS has a considerable impact on productivity for working and non-working patients, particularly in females. WPS is a useful tool to appreciate the burden of disease in patients with AS not only at workplace, but at also at home, which may be even more important in populations with a low women's workforce participation rates.

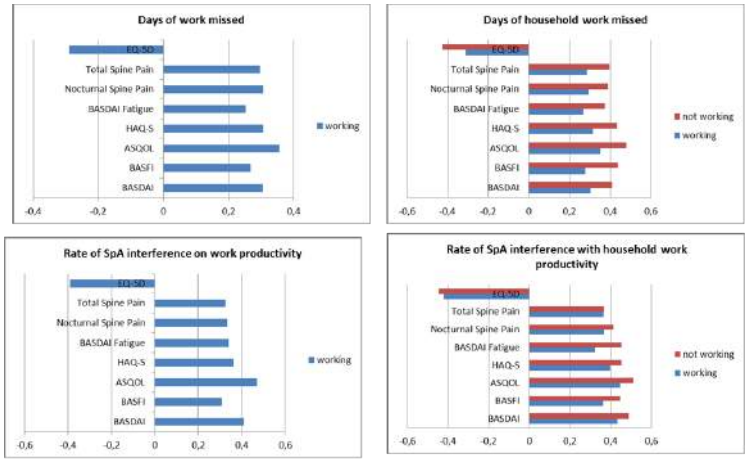

Figure: Kendall correlation coefficient between WPS and clinical and health related quality of life assessments

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Abstract Number: 691

Standards for the Classification of Non-Radiographic Axial Spondyloarthritis: A European Real World Study

Tim Holbrook[1], Robert Wood[1], **Christopher Black**[2], Xiaohan Hu[2] and Sumesh Kachroo[2], [1]Adelphi Real World, Macclesfield, United Kingdom, [2]CORE, Merck & Co., Inc., Rahway, NJ

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Background/Purpose: Classification of non-radiographic axial spondyloarthritis (nr-axSpA) requires the presence of Assessment of Spondyloarthritis international Society (ASAS) criteria for AxSpA, without radiologic evidence of sacroiliitis according to the modified New York Criteria. Existing evidence is limited relating to diagnostics in a real-world setting. The aim of this analysis was to investigate how patients are being classified as nr-axSpA in a real-world consulting sample.

Methods: Data were taken from the 2014 nr-axSpA Disease Specific Programme a cross-sectional, multi-national survey of nr-axSpA patients and their rheumatologists conducted in France, Germany, Italy, Spain and the UK. Physicians were asked to recruit their next 2 consecutive, consulting nr-axSpA patients. Inclusion in the survey was based on diagnosis of nr-axSpA by the rheumatologist, regardless of how the patient was actually diagnosed. No specific classification criteria were required. Physicians completed patient record forms containing patient demographics, clinical measurements and symptomology at diagnosis and criteria used to classify the patient with nr-axSpA. Observations were weighted to ensure findings were more representative of the patient population. The weight was applied when calculating all percentages, means and SDs.

Results: A total of 631 patients were included in the analysis (mean age 41.8±12.0 [SD], 70.4% male). Physicians reported that in over half (52.5%) of their patients, the nr-axSpA diagnosis was made using the ASAS criteria, however, 29.5% were diagnosed without any form of classification criteria. The majority (93.7%) of patients had inflammatory back pain (IBP) at diagnosis, while 21.7% had enthesitis, 3.4% had uveitis, 9.4% had dactylitis and 2.9% had psoriatic skin lesions. A family history of Ankylosing Spondylitis (AS) was reported in 18.5% of patients. Mean time since diagnosis was 51.6±59.9 months, while 17.4% of patients were 45 or older at onset of disease. Evidence of sacroiliitis was identified at diagnosis via X-ray or magnetic resonance imaging in 69.1% of patients. Only 149 patients had further information reported regarding sacroiliitis at diagnosis; 56.7% had IBP at diagnosis and sacroiliitis either grade ≥2 bilaterally or grade ≥3 unilaterally, fulfilling the classification for an AS diagnosis.

Conclusion: While there are guidelines in place to aid the classification of nr-axSpA, in real-world practice it appears that there remains some inconsistency in how physicians classify the condition. Under-use of the recommended guidelines suggests an unmet need in accurate classification of nr-axSpA and therefore optimal treatment decisions for patients.

Disclosure: T. Holbrook, Merck Pharmaceuticals, 5; **R. Wood**, Merck Pharmaceuticals, 5; **C. Black**, Merck Pharmaceuticals, 3; **X. Hu**, Merck Pharmaceuticals, 3; **S. Kachroo**, Merck Pharmaceuticals, 3.

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Abstract Number: 692

Association Between Improvement in Enthesopathy and Quality of Life: Results from a Phase 3 T in Psoriatic Arthritis Patients

Arthur Kavanaugh[1], Luis Puig[2], Alice B. Gottlieb[3], Christopher T. Ritchlin[4], Yin You[5], Shu Li[5], Michael Song[5], Proton Rahman[6] and Iain. B. McInnes[7,8], [1]University of California San Diego, La Jolla, CA, [2]Universitat Autònoma de Barcelona, Barcelona, Spain, [3]Tufts Medical Center, Boston, MA, [4]Allergy, Immunology and Rheumatololgy Division, University of Rochester Medical Center, Rochester, NY, [5]Janssen Research & Development, LLC, Spring House, PA, [6]Rheumatology, Memorial University of Newfoundland, St Johns, NF, Canada, [7]Institute of Biomedical and Environmental Health Research, University of the West of Scotland, Glasgow, United Kingdom, [8]Institute of Infection, Immunity and Inflammation, College of Medicine, Veterinary Medicine and Life Sciences, University of Glasgow, Glasgow, United Kingdom

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Background/Purpose: To assess the relationship between improvement or worsening in enthesopathy and changes in functioning and quality of life (QOL) in patients with psoriatic arthritis (PsA).

Methods: Adult PsA patients (n=615) with active disease (≥5 SJC and ≥5 TJC;CRP≥0.3mg/dL) despite DMARD and/or NSAIDs were randomized to UST45mg, 90mg, or PBO at weeks 0, 4, and q12weeks. Patients treated with prior anti-TNF agents were excluded. Stable concomitant MTX was permitted but not mandated. At week16, pts with <5% improvement in TJC & SJC entered blinded early escape (PBO→UST45mg; UST45mg→90mg; 90mg→90mg). Presence or absence of enthesopathy, HAQ and SF-36 were assessed at baseline and week 24. In this post-hoc analysis, the enthesopathy was focused on the Achilles tendon and plantar fascia and was assessed as present or absent. Patients were categorized for enthesopathy into three categories: improved (enthesopathy present at baseline, but not at week 24), worsened (enthesopathy present at week 24, but not at baseline), and unchanged. Patients with an enthesopathy assessment missing at either time point were included in the unchanged category. Improvements in quality of life (assessed by the Short Form-36 mental and physical component scores [SF-36 PCS and SF-36 MCS] and physical function (assessed by the Health Assessment Questionnaire-Disability Index [HAQ-DI]) were assessed by enthesopathy status.

Results: 80% of patients (n=491) reported enthesitis at baseline, and the proportion of patients with enthesopathy was similar in the combined ustekinumab (47.2%) and placebo (52.1%) groups. At week 24, the proportions of patients with enthesopathy were 23.2% and 38.2% for the combined ustekinumab and placebo groups, respectively. Across all patients, those who had an improvement in enthesopathy had a greater improvement in functioning and QOL, compared with those who did not (Table). The results were consistent when the analysis was done separately for each treatment group. Even when the analysis was restricted to those who achieved an ACR 20 response, patients with an improvement in enthesopathy still showed a greater improvement in functioning and QOL compared to those who did not (Table).

Table Enthesopathy status and mean (SD) changes from baseline at week 24

	Enthesopathy Status		
	Worsened	Unchanged	Improved
Overall			
% improvement in HAQ-DI	n=21 17.7(35.9)	n=339 22.6(66.0)	n=113 37.5(47.0)
Change in SF-36 PCS	n=22 4.1(7.1)	n=333 4.9(8.7)	n=116 6.7(9.1)
Change in SF-36 MCS	n=22 -1.5(8.8)	n=333 3.5(10.1)	n=116 6.7(9.6)
ACR 20 responders			
% improvement in HAQ-DI	n=8 33.7(32.8)	n=145 52.8(37.0)	n=72 53.4(39.1)
Change in SF-36 PCS	n=8 8.7(7.4)	n=150 8.7 (8.8)	n=72 9.5(8.8)
Change in SF-36 MCS	n=8 3.5(8.0)	n=150 5.2(10.2)	n=72 7.7(9.4)

Conclusion: Ustekinumab treatment can significantly improve enthesopathy associated with psoriatic arthritis.There is an association between improvement in enthesopathy of the Achilles tendon and plantar fascia and improvement in physical function and quality of life in patients with PsA.

Disclosure: A. Kavanaugh, Janssen R & D, LLC, 2; **L. Puig**, Janssen R & D, LLC, 2; **A. B. Gottlieb**, Janssen R & D, LLC, 2; **C. T. Ritchlin**, Janssen Scientific Affairs, LLC, 2; **Y. You**, Janssen R & D, LLC, 3; **S. Li**, Janssen R & D, LLC, 3; **M. Song**, Janssen R & D, LLC, 3; **P. Rahman**, Janssen R & D, LLC, 2; **I. B. McInnes**, Janssen R & D, LLC, 2.

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Abstract Number: 693

Clinical and Imaging Features of Reactive Arthritis in Guatemala City

Helga Raquel Garcia Ferrer[1], A Garcia Kutzbach[2], Isa Iraheta[3], Jose U. Scher[4], Joan Von Feldt[5,6] and Alexis Ogdie-Beatty[7], [1]Society for Worldwide Med Exchange, North Bay Village, FL, [2]Internal Medicine, Rheumatology Unit (AGAR), Francisco Marroquin University, School of Medicine, Guatemala City, Guatemala, [3]Rheumatology, Guatemalan Association against Rheumatic Diseases (AGAR), Guatemala City, Guatemala, [4]Department of Medicine, Division of Rheumatology, New York University School of Medicine, New York, NY, [5]Philadelphia VA Medical Center, Philadelphia, PA, [6]University of Pennsylvania, Philadelphia, PA, [7]Medicine/Rheumatology, University of Pennsylvania, Philadelphia, PA

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Session Time: 9:00AM-11:00AM

Background/Purpose: Reactive arthritis (ReA) is an inflammatory arthritis that typically follows infection. The objectives of this study were to describe the joint and enthesial involvement among patients with ReA in Guatemala City and to examine the prevalence of SI joint disease on Xrays and Achilles enthesopathy on ultrasound in patients with ReA and controls.

Methods: We performed a prospective cross-sectional study between January and October 2014 in Guatemala City. ReA was defined as inflammatory arthritis following a gastrointestinal (GI) or genitourinary infection (GU) and meeting the ASAS peripheral spondyloarthropathy criteria. Cases were identified in AGAR Rheumatology clinic and controls with a GI or GU infection in the preceding 3-6 months were recruited from primary care clinics in the same institution. A standardized questionnaire ascertained infection details, family history, medication and herbal

supplement use, medical comorbidities, employment, place of residence (urban vs rural), smoking status, and literacy. Subjects completed the mini-nutritional assessment, a pain assessment, a standardized joint and enthesis examination by same observer, radiographs of the sacroiliac (SI) joints interpreted by a trained radiologist and 2 blinded rheumatologists, and ultrasound of the bilateral Achilles Tendons.

Results: 33 patients with ReA and 31 controls were enrolled. Mean age was 39 (SD 11.3) and 36 (SD 10.1) respectively. None of the controls had swollen or tender joints or entheses. We found that 32 cases (97%) had a recent history of peripheral arthritis. History of uveitis was present in 20 cases (60%). The most frequently tender joint was the right sacroiliac joint (N=27, 81%) followed by left sacroiliac joint (N=25, 75%). The most frequently swollen joint was the left ankle (N=4, 12%) followed by right ankle (N=3, 9%). The most frequently tender enthesis was the Achilles tendon, right and left (N=22 each, 67%) followed by right medial femoral condyle (N=17, 52%). The most common finding on sacroiliac joint Xray was bilateral sacroiliitis (N=15, 45%). Bilateral SI joint abnormalities were also found in 10 controls (32%). Inflammation was noted on Achilles tendon ultrasound in 13 (39%) cases and in one (3 %) of the controls.

Conclusion: Reactive Arthritis is the most common form of the Spondyloarthropathies in Guatemala City. To our knowledge, this is the first study in the Central American region to examine clinical and imaging features of ReA. A strength of the study was inclusion of a control group exposed to infection. We found a high prevalence of peripheral arthritis, tender SI joints, and uveitis. Additionally, Achilles tendon ultrasound was positive in nearly 40% of patients (compared to 3% of controls). Interestingly, SI joint xrays were frequently abnormal in both cases and controls (45% vs 32%).

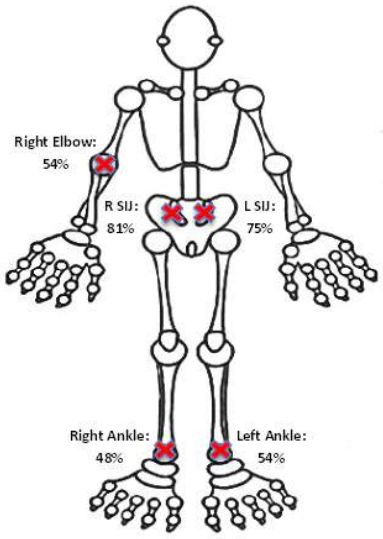

Figure. Tender joints among patients with reactive arthritis in Guatemala City. Abbreviation: SIJ = Sacroiliac joint.

Disclosure: H. R. Garcia Ferrer, None; **A. Garcia Kutzbach**, None; **I. Iraheta**, None; **J. U. Scher**, None; **J. Von Feldt**, None; **A. Ogdie-Beatty**, None.

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Abstract Number: 694

Quality of Life in Patients with Active Peripheral Spa Is Similarly Impaired As in Other Rheumatic Diseases and Influenced By Disease Activity but Not Disease Duration

Philip J. Mease[1], Désirée van der Heijde[2], Manish Mittal[3], Avani D. Joshi[3], Yaoyao Xu[3], Aileen L. Pangan[3] and In-Ho Song[3], [1]Swedish Medical Center and University of Washington School of Medicine, Seattle, WA, [2]Dept. of Rheumatology, Leiden University Medical Center, Leiden, Netherlands, [3]AbbVie Inc., North Chicago, IL

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Background/Purpose: There is a lack of data on the quality of life (QoL) in patients (pts) with active peripheral spondyloarthritis (pSpA). The purpose of this study was to assess the QoL in pts with pSpA, and compare it to the QoL across other rheumatic diseases.

Methods: Data for this analysis originated from the following five trials of adalimumab versus placebo for various rheumatic diseases: ABILITY-2 for pSpA; ABILITY-1 for non-radiographic axial SpA (nr-axSpA); ATLAS for ankylosing spondylitis (AS); DE019 for rheumatoid arthritis (RA), and ADEPT for psoriatic arthritis (PsA). In each dataset, the QoL at baseline was measured by the Short Form 36 (SF-36) mental component summary (MCS) and physical component summary (PCS). Differences from the norms for an age-and gender- matched healthy control population at baseline were calculated for each rheumatic disease. In order to assess the influence of disease activity and disease duration on MCS and PCS, patients were stratified into tertiles by disease activity or disease duration. The difference in MCS and PCS and the 95% CI for the extreme tertiles (lower vs higher) was compared to that for an age- and gender-matched normal population. Lower vs. higher disease activity was defined as: Bath Ankylosing Spondylitis Disease Activity Score (BASDAI) ≤4.8 or >6.5 for pSpA; ≤6.0 and >7.1 for nr-axSpA; ≤5.6 and >7.1 for AS; 28-joint count disease activity score based on C-reactive protein [DAS28(CRP)] ≤5.3 and >6.1, for RA; Patient's global assessment (PtGA) ≤39 and >60 for PsA. Shorter vs. longer disease duration was defined as: ≤2.6 or >3.4 years (yrs) for pSpA; ≤0.5 or >2.3 yrs for nr-axSpA; ≤5.2 or >13.4 yrs for AS; ≤5 or >12.9 yrs for RA; ≤4.2 or >11.2 yrs for PsA.

Results: Across the five rheumatic diseases, the differences in SF-36 MCS and PCS compared to the norms for an age- and gender-matched population were similar (table). However, the observed difference from the norm was greater for the PCS than for the MCS indicating a greater impact on physical function. For each disease, higher disease activity, but not longer disease duration was associated with a significantly greater difference in PCS and MCS compared to the norms.

Conclusion: Patients with pSpA suffer from a poor quality of life, to a similar extent compared with the other rheumatic diseases included here. Results indicate that current disease activity and not disease duration contributes to this impairment of physical and mental health.

Table: Mean Difference compared to age- and gender matched population norms for SF-36 PCS and MCS at baseline, mean (95% CI)

	nr-axSpA (ABILITY-1), N=185	pSpA (ABILITY-2), N=165	AS (ATLAS), N=311	PsA (ADEPT), N=310	RA- (DE019), N=605
PCS	-18.3 (-19.5, -17.2)	-16.7 (-18.0, -15.5)	-18.8 (-19.6, -17.9)	16.4 (-17.5, -15.3)	-15.9 (-16.6, -15.2)
MCS	-6.6 (-8.4, -4.9)	-5.9 (-7.7, -4.1)	-6.4 (-7.7, -5.1)	-3.2 (-4.5, -2.0)	-2.8 (-3.8, -1.9)
SF-36 PCS/MCS in patients with lower vs. higher disease activity					
PCS-lower	-15.2 (-17.0, -13.3)*	-13.13 (-15.5,-10.7)*	-15.4 (-16.9, -13.8)*	-10.0 (-11.7, -8.2)*	-12.0 (-13.3, -10.8)*
PCS-higher	-21.4 (-23.5, -19.4)*	-18.9 (-21.0, -16.9)*	-21.8 (-23.3, -20.4)*	-23.0 (-24.6, -21.3)*	-18.9 (-19.9, -17.8)*
MCS-lower	-3.1 (-6.1,-0.2)*	-0.03 (-2.7, 2.6)*	-3.7 (-5.7, -1.6)*	0.6 (-1.4, 2.6)*	0.5 (-1.0, 2.1)*
MCS-higher	-11.2 (-14.1, -8.2)*	-9.6 (-12.2, -7.1)*	-10.5 (-13.0, -7.9)*	-7.1 (-9.4, -4.7)*	-6.7 (-8.3, -5.0)*
SF-36 PCS/MCS in patients with shorter vs. longer disease duration					
PCS-shorter	-19.6 (-21.6, -17.5)	-18.2 (-20.6, -15.9)	-19.5 (-21.1, -17.9)	-14.3 (-16.1, -12.5)	-16.0 (-17.2 -14.8)
PCS- longer	-17.9(-20.0, -15.9)	-15.5 (-18.0, -13.1)	-18.0 (-19.6, -16.5)	-16.8 (-18.9, -14.6)	-15.8 (-16.9, -14.6)
MCS-shorter	-7.4 (-10.6, -4.3)	-5.9 (-9.3, -2.4)	-7.6 (-9.8, -5.3)	-1.6 (-3.7,0.5)	-3.3 (-4.8, -1.8)
MCS-longer	-4.8 (-8.0, -1.7)	-5.1 (-8.3, -1.9)	-7.2 (-9.5, -5.0)	-3.5 (-5.9, -1.2)	-2.6 (-4.3, -0.9)
*p<0.001 for difference between groups with lower vs. higher disease activity.					

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Abstract Number: 695

Is a Geriatric Rheumatology Sub-Group Worth Distinguishing? Disease Characteristics of a Geriatric Psoriatic Arthritis (Gero PsA) Subgroup Compared with Those of below 45 Years of Age

Euthalia Roussou, Rheumatology, Dr, London, United Kingdom
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Background/Purpose: Adult rheumatologist assess conditions in patients aged 18 and above. There is no distinction to those of the frail age of 65 and above who could belong to a geriatric rheumatology group. **Aims:**To assess whether there are differences between psoriatic arthritis (PsA) patients aged above 65 years (y). To compare demographic, (gender ratio, ethnicity, social habits) disease characteristics, activity and function(disease duration, delay in diagnosis, ESR, CRP, Night pain, sleep disturbance, BASDAI, BASFI) and treatment (Tx)options as wells as treatment effect, and well being over past week (wbpw) and over past 6 months (wb6m) of those above 65y with those aged below 45y.

Methods: From total 719 patients (pts) with Spondyloarthritis (SpA) registered in the London Registry of SpA (LoRoS) which has been developed aiming to assess differences in SpAs between ethnic groups over time, (ethics approval REC 07/H0701/74) 247 pts had confirmed PsA by CASPAR. From the total of 247 pts, 45 pts had their baseline characteristics recorded at age 65y (or above) and formed the Gero PsA group (gPsA) which has been analysed and compared with those patients who entered in the registry at age below45y (b45) (n=73). The remaining patients belonging in the intermediate age group of between 45 to 64 (intag)(n=124) has been analysed where there were discrepancies.

Results: Table shows the disease characteristics of the geroPsA group compared with those of below 45, ssd and CI. The statistically significant difference(ssd) between the ethnic groups studied in our cohort compatible with national ethnic migration reports. Smoking reported by more b45 but did not reach ssd. There was no difference in the Tx between the gPsA and the b45 except a borderline difference in the Tx with Sulphasalazine (SSZ)in that more pts b45 were on SSZ [P=0.08 (CI= -0.21 to 0.18)] while more gPsA patients had joint surgery (p=0.01; CI=0.065 to 0.45).

Conclusion: PsA patients above the age of 65y have differences compared with the younger age group and can form a distinct geriatric PsA group. Differences identified in our cohort were related to ethnicity, social habits, inflammatory markers, function and treatment options and effect.

Items	Gero PsA(n=45) mean (sd)	Below45y (n=73) mean (sd)	Pvalues	CI (lower to upper
Gender	16:29(1:2)	24:49(1:2)	n/a	
Ethnic group	Caucasian=38/45 (84.4%)	caucasian=38/73 (52%)	p=0.03	
	Asian =3/45 (6.6%)	Asian=29/73 (42.4%)	p=0.04	
	African =4/45 (8.8)	African=3/73 (4%) mixed race 1/73	p=0.7	
Alcohol intake	57.7%	46.5%	p=0.02	0.0028 to 0.44
Delay in diagnosis (years)	9.4 (15.3)	3.3 (3.9)	p=0.05	0.002 to 12.2
Disease duration	11.9 (15.5)	4.6 (4.2)	p=0.02	1.1 to 13.4
ESR	23.7 (19)	19.1(22)	p=0.2	=3.1 to 12.3
CRP	7.6 (6.8)	7.6(6.6)	p=0.9	-3.3 to 3.2
Night Pain	3.9(3.3)	5.4(3)	p=0.06	-3.2 to 0.09
Sleep disturbance	3.9 (3.3)	5.3(3.2)	p=0.1	-3.4 to 0.48
BASDAI score	5.2(2.3)	6.06(2.2)	p=9.1	-2.07 to 0.3
BASFI score	5.63 (2.7)	4.09(2.6)	p=0.02	0.23 to 2.85
Treatment effect (VAS) perceived	5.1(2.7)	4.04(2.04)	p=0.08	-0.17 to 2.3
Well being past week	4.58(2.8)	5.46(2.7)	p=0.1	-2.17 to 0.41

Disclosure: E. Roussou, None;

disease-characteristics-of-a-geriatric-psoriatic-arthritis-gero-psa-subgroup-compared-with-those-of-below-45-years-of-age

Abstract Number: 696

Current and Past Smoking Are Associated with Functional Impairement and Increased Disease Activity in Axial Spondyloarthritis: Systematic Review and Meta-Analysis

Kristina SCHREIBER[1], Thomas Barnetche[2], BG Combe[3], Jacques Morel[1] and Claire I. Daien[1], [1]Department of rheumatology, Lapeyronie Hospital and Montpellier University, Montpellier, France, [2]Rheumatology Department, Pellegrin University Hospital, BORDEAUX, France, [3]Lapeyronie, Montpellier, France

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Background/Purpose: The influence of smoking on the development of rheumatoid arthritis, the severity of the disease and the response to treatment is well established. The impact of tobacco use in patients with axial spondyloarthritis (axSpA) is only beginning to emerge. The aim of our study was to review the literature to evaluate the impact of tobacco on the development of axSpA, the activity and the severity of the disease and the therapeutic response.

Methods: Using PUBMED database, COCHRANE and a manual search, we review the literature with the keywords: "Spondylarthropathies"[Mesh] OR "spondylitis"[Mesh] OR "spondylitis, ankylosing "[Mesh] OR "spondylarthropathy" OR spondylitis OR spondylarthropathies) AND (tobacco OR "tobacco"[Mesh] OR smoking OR "smoking"[Mesh] OR "cigarette" OR "environmental" OR "environmental factors". The articles on psoriatic arthritis were excluded. Smoking status was divided into current smoker (CS), past smoker (PS), never smokers (NS), ever smoker (ES) with ES=CS + PS, and non-smokers= PS + NS.

Results: Among 511 articles (493 from PUBMED, 17 from COCHRANE and one from the manual search), we include 15 articles (2 abstracts from congress). No significant difference was found between ES and NS in terms of age at symptoms onset (-0.67 [-3.18 to 1.83]; I^2 = 47%; p=0,60, n=2), on erythrocyte sedimentation rate (ESR) (+2,87 [-7.73 to13.46]; I^2 = 85%; p=0.60; n=2), on C-reactive protein (CRP) (+3.12 [-2.3 to 8.55]; I^2 = 89%; p=0.26; n=3), on BASDAI (+0.16 [-0.05 to 0.37]; I^2 = 12%; p=0.14; n=3), and on HAQ (0.0 [-0.2- 0.2]; I^2 = 83%; p=1.0; n=2). Conversely, BASFI (+0.69 [0.44 to 0.93]; I^2 = 0%; p<0.001; n=3) and ASDAS-CRP was higher in ES versus NS (+0.14 [0.03to 0.25]; I^2 = 0%; p=0.01; n=2). Comparing CS to non-smokers, we found a trend to increased CRP (+2.74 [-0. 44 to 5.93]; I^2 = 0%; p=0.09; n=3) and BASDAI (+ 0.48 [-0.07to1.03]; I^2 = 84%; p=0.08; n=5) and a significant increase of BASFI in (+1 [0.35 to 1,66]; I^2 = 74%; p=0.003; n=5).The systematic review of literature showed that ES had higher inflammation on MRI and axial structural damage on MRI and radiographs than NS. Response to tumour necrosis factor-alpha inhibitor treatment evaluated by BASDAI 50% at 6 and 12 months was decreased in ES compared to NS.

Conclusion: Current and past smocking is associated with an increased disease activity (BASDAI and ASDAS-CRP respectively) and functional impairment. Pathogenesis remains to be determined. Smoking cessation should be encouraged in axSpA although these results suggest that it may not impact disease prognosis.

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Abstract Number: 697

Identification Methods for Axial Spondyloarthritis in American Veterans

Jessica Walsh[1], Jianwei Leng[2], Brian Breviu[3], Daniel Clegg[4], Tao He[2] and Brian Sauer[5], [1]Division of Rheumatology, Salt Lake City Veteran Affairs and University of Utah Medical Centers, Salt Lake City, UT, [2]Salt Lake City Veteran Affairs and University of Utah Medical Centers, Salt Lake City, UT, [3]Department of Internal Medicine, Salt Lake City Veteran Affairs and University of Utah Medical Centers, Salt Lake City, UT, [4]Rheumatology, Salt Lake City Veteran Affairs and University of Utah Medical Centers, Salt Lake City, UT, [5]Salt Lake City VA Medical Center and University of Utah, Salt Lake City, UT

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Background/Purpose: Current methods for identifying people with axial spondyloarthritis (AxSpA) in large datasets are inadequate because billing codes for most types of spondyloarthrtis (SpA) do not indicate the presence or absence of axial involvement and nomenclature for AxSpA is varied and evolving. This has substantially limited observational research of AxSpA and AxSpA subtypes. The objective of this study was to develop methods for identifying AxSpA in national Veteran Health Administration (VHA) datasets

Methods: Algorithms for identifying veterans with AxSpA were designed to include combinations of SpA features and billing codes (Figure 1). Terms that represent SpA features were identified in clinical documents with natural language processing (NLP). Methods were developed to test and refine the algorithms. Data and computing resources included the Corporate Data Warehouse, Decision Support System, and the Veteran Affairs Informatics and Computing Infrastructure (VINCI).

Results: Terms representing SpA features were explored, identified, selected, extracted, and annotated for the development of NLP modules, using methods and technologies shown in Table 1, Step 1. Methods and software were also designed to build reference populations, identify veterans fulfilling the algorithms, and test the algorithms (Table 1, Steps 2-4). The accuracy of NLP modules exceeded the target accuracy of 90% (Table 2).

Conclusion: The methods for identifying terms representing SpA features in clinical documents are feasible, and SpA feature terms have been identified with high accuracy. Further work is required to apply, test, and refine the algorithms in reference populations with and without AxSpA.

Figure 1. Algorithms for identifying axial spondyloarthritis

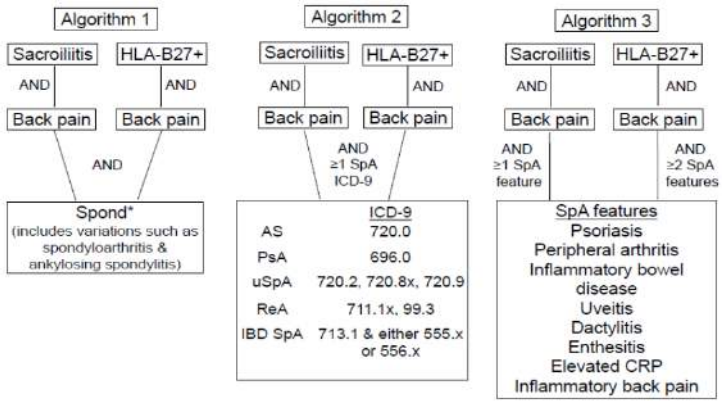

Table 1. Methods for identifying axial spondyloarthritis		
Steps		Software
1	**Identify terms in clinical documents that represent SpA features. For each term:**	
1a	Explore term variations (alternative wording, misspellings, descriptions, etc.) in randomly sampled clinical documents - Identify root words for each variation (includes word fragments with wild cards[*]) - Select root words that represent the intended term in ≥40% of reviewed documents	Voogo
1b	Identify term variations in VA documents - Query root words in VA datasets to identify all term variations mentioned in all documents - Determine the number of times each variation was mentioned in all documents in the database	SQL
1c	Select common and meaningful term variations - Exclude rarely used variations - Exclude variations that don't represent the intended term (not meaningful)	Excel
1d	Extract sections of text containing the selected term variation (snippets) from all documents	Snapshot
1e	Annotate randomly selected snippets - Identify the parts of text necessary to determine if the extracted term represents the intended SpA term - Classify the snippet text according to whether or not it represents the intended term (yes/no/possible) - Develop & revise annotations guidelines - Train annotators until inter-rater agreement is >90% - Annotate 1500 snippets for NLP	Visual Tagging Tool (VTT), eHOST
1f	Develop NLP module - Develop sets of rules (machine learning) that train NLP software how to classify terms in the context of the surrounding text - Test and revise NLP modules with additional annotated snippets until accuracy is >90% for each term	Support Vector Machines (SVM), RED
1g	Classify patients with discordant snippet classifications - Develop and apply rules for classifying patients with snippets assigned to different categories (yes & no)	SQL
2	Develop reference population of veterans with and without AxSpA	
2a	Develop cohort of 2500 randomly selected veterans - Enrich cohort by selecting veterans with at least 2 rheumatology clinic encounters - Create tables with data relevant for determining AxSpA status for each veteran (rheumatology clinic notes, reports from articular radiographs, DMARD exposure, anti-CCP, RF, HLA-B27, etc.) - Import tables into Chart Reviewer software and set software parameters	SQL ChartReview eHOST
2b	Classify veteran in rheumatology reference population - Develop classification guidelines - Determine inter-rater agreement between classifiers - Classify veterans in reference population as AxSpA or no AxSpA	SQL ChartReview eHOST
3	Identify veterans fulfilling algorithms	
	Sequentially apply NLP modules and coded ICD-9 data to: - Rheumatology reference population - General veteran population	SQL
4	Test & refine algorithm(s)	
4a	Test & refine algorithm(s) in the rheumatology reference population - Calculate sensitivity, specificity, and accuracy of each algorithm - If algorithm accuracy is <85%, revise processes ± algorithms	SQL
	Test and refine algorithm(s) in the general veteran population	

4b	- Review charts of randomly selected veterans fulfilling algorithms & manually classify as AxSpA or no AxSpA - Calculate specificity of each algorithm using manual classification as reference - If algorithm specificity is <85%, revise processes ± algorithms	SQL
5	Alternative plan (if necessary)	
	If performance of all algorithms is suboptimal, develop a model that will statistically identify the most predictive combination(s) of terms	SQL

Table 2. Identification of terms in clinical documents that represent SpA features

Term	# Root words with true positive rate >40%	# Term variations found in VA documents	# Meaningful variations in ≥100 documents	# Extracted snippets	Annotator IRR [Kappa (%)]	NLP Accuracy (%)
	(Step 1a)	(Step 1b)	(Step 1c)	(Step 1d)	(Step 1e)	(Step 1f)
Sacroiliitis	16	905	506	326,436	98.1	91.1
Spond*	6	9593	134	802,757	94.8	93.5
HLA-B27+	1	299	3	774,140	93.3	97.2
Back pain	34	4359	416	1,547,520	100	NA*
*NLP unnecessary since extraction methods yielded 97% true positive classification of randomly sampled snippet						

Disclosure: J. Walsh, None; **J. Leng**, None; **B. Breviu**, None; **D. Clegg**, None; **T. He**, None; **B. Sauer**, None.

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Abstract Number: 698

Is It Possible to Identify Psoriasis Patients Who Will Develop Axial Disease? Real Life Data from Psart (Psoriatic Arthritis Registry of Turkey)

Sibel Z. Aydin[1], Ozun BayndÄ±r[1], Barış Yılmazer[1], Kenan Aksu[1], Ediz Dalkilic[2], Mustafa Ferhat Oksuz[1], E.Figen Tarhan[1], Meryem Can[1], Orhan Kucuksahin[1], Gezmis Kimyon[1], Lutfi Akyol[1], Ahmet Mesut Onat[1], Bunyamin Kisacik[1], Abdulsamet Erden[1], Ahmet Omma[1], Duygu Ersozlu Bakirli[1], Cem Ozisler[1], Emel Gonullu[1], Seval Pehlevan[1], Dilek Solmaz[1], Muhammet Cinar[1], Gozde Cetin[1], Abdurrahman Tufan[1], Muge Aydin Tufan[1], Levent Kilic[1], Sukran Erten[1], Timucin Kasifoglu[1], Senol Kobak[1], Soner Senel[1], Servet Akar[1], Metin Ozgen[1], Esen Kasapoglu-Gunal[1], Veli Yazisiz[1], Sedat Yılmaz[1], Salim Donmez[1], Ä°smail Dogan[1], Hamide Kart Koseoglu[1], Funda Erbasan[1], Fatih Yildiz[1], Cemal Bes[1], Ayse Balkarli[1], Ali Sahin[1], Rıdvan Mercan[1], Fatoş Arslan[1], Atalay Dogru[1], Salih Pay[1], Sule Yavuz[1], Necati Cakir[1], Yasemin Kabasakal[1] and Umut Kalyoncu[1], [1]PsART study group, Ankara, Turkey, [2]Department of Rhematology, Uludag University Faculty of Medicine, Bursa, Turkey
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Is it possible to identify psoriasis patients who will develop axial disease? Real life data from PsART (**Ps**oriatic **A**rthritis **R**egistry of **T**urkey)

S. Z. Aydýn, Ö. Bayýndýr [1] , B. Yýlmazer [1],K. Aksu [1], E. Dalkýlýç [1], M. F. Öksüz [1], E. F. Tarhan [1], M. Can [1], O. Küçükþahin [1] , G. Kimyon [1], L. Akyol [1], A. M. Onat [1], B. Kýsacýk [1], A. Erden [1], A. Omma [1], E. D. Ersözlü Bozkýrlý [1], C. Özipler [1], E. Gönüllü [1] , S. Masatlýoglu Pehlevan [1], D. Solmaz [1], M. Çýnar [1], G. Yýldýrým Çetin [1], A. Tufan [1], M. Aydýn Tufan [1], L. Kýlýç [1], S. Erten [1], T. Kaþifoglu [1], S. Kobak [1], S. Þenel [1], S. Akar [1], M. Özgen [1], E. Kasapoglu Günal [1], V. Yazýsýz [1], S. Yýlmaz [1], S. Dönmez [1], I. Dogan [1], H. Kart Köseoglu [1], F. Erbasan [1], F. Yýldýz [1], C. Bes [1], A. Balkarlý [1], A. Þahin [1], R. Mercan [1], F. Arslan [1], A. Dogru [1], S. Pay [1], S. Yavuz [1], N. Çakýr [1], Y. Kabasakal [1], U. Kalyoncu

[1]PsART study group, Ankara, Turkey

Background/Purpose: Psoriatic arthritis (PsA) is a complex disease with various patterns of joint involvement. PsART (**Ps**oriatic **A**rthritis **R**egistry of **T**urkey) is a prospective, multicentre, nationwide study in Turkey which was built with the objective of understanding the nature of the

disease, clarify differences among different presentation types of PsA and identifying poor prognostic factors. Here we present the cross sectional characteristics of a large group of PsA patients from the registry, with an emphasis on factors associated with axial disease.

Methods: PsART was built in May 2014. Patients are consecutively recruited to this registry, if they are diagnosed as PsA, regardless of any disease characteristics. Data collection was performed through a website. Disease characteristics, treatments and comorbidities were collected in addition to disease activity and function assessment.

Results: Until June 2015, 1060 patients were recruited. Within these 64.5 % (684/1060) were female.. The mean (SD) duration of PsA was 77.7 (89) months. Arthritis was the initial finding in 4.4% and psoriasis preceded in 85.8% (Table). Patients with axial involvement were significantly younger than the other forms of arthritis ($p<0.0001$). Other factors that were associated with axial disease were type of psoriasis (pustular type 31.4% in axial disease vs 21.4 in non-axial forms; $p=0.008$), smoking (43.7% vs 33.3%; $p=0.008$) and having nail disease (53.3% vs 44.6%; 0.013).

Patients who had pustular type of psoriasis, nail disease and smoked had a 1.86 relative risk for having axial disease compared to patients who doesn't have at least one them.

Conclusion: The patient characteristics of the PsART are comparable to the previously reported registries, supporting its external validity. The pattern of arthritis may be foreseen in patients with pustular type of psoriasis and nail disease especially if they have a history of smoking.

Age (mean(SD))	47 (12.9)
BMI (mean (SD))	28 (5.2)
Polyarthritis n (%)	373 (35.2%)
Axial involvement n (%)	270 (25.9%)
Oligoarthritis n (%)	296 (28.4%)
Monoarthritis (%)	30 (2.8%)
DIP joint involvement n (%)	67 (6.3%)
Arthritis mutilans n (%)	6 (0.6%)
Nail disease	504 (47.5%)

Table: Characteristics of PsA patients from PsART. *: data given as mean (SD).

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Abstract Number: 699

Improving Ankylosing Spondylitis Specific Outcomes at 6 Months Utilising a Novel Self-Management Education Program

Charles Inderjeeth[1,2,3,4], Jean McQuade[5], Warren Raymond[6], Clara Connor[7], Jack Edelman[8], Nicola Cook[9] and Kathy Briffa[10],
[1]Rehabiltation and Aged care and Rheumatology, Sir Charles Gairdner Hospital and University of Western Australia, Nedlands, Australia, [2]North Metropolitan Health Service, University of Western Australia, Perth, WA, Australia, [3]Subiaco Rheumatology Clinic, Subiaco, Australia, [4]Linear Clinical Research Ltd, Perth, Australia, [5]Arthritis WA, Wembley, Australia, [6]Rheumatology and Geriatric Medicine, Sir Charles Gairdner Hospital and University of Western Australia, Nedlands, Australia, [7]Arthritis and Osteoporosis WA, Perth, Australia, [8]Rheumatology, Sir Charles Gairdner Hospital, Perth, Australia, [9]Royal Perth Hospital, Perth, Australia, [10]School of Physiotherapy and Exercise Science, Curtin University, Perth, Australia
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Background/Purpose : Disease specific self-management interventions are rare. After a needs assessment, focus group discussions, and *Plan, Do, Study, Act* (PDSA) model we developed and tested the *Self Management for Ankylosing Spondylitis* (SMAS) program, for people with Ankylosing Spondylitis (AS). We examined the benefits of an SMSA program for people with AS regarding change in health status, quality of life, and disease activity.

Methods: 134 people were recruited in this case cohort intervention. Exclusion criteria: <18yo; non-English speaking; co-morbid inflammatory musculoskeletal disease; and/or visual, auditory, or cognitive impairment. Participants attended a weekly 2.5 hour self-management education session facilitated by same two health professionals over 6 weeks. The scripted content included multidimensional strategies including stretches; and optional 7th week supervised exercise class.

Demographic, AS disease management characteristics, medication patterns, and outcomes were measured at baseline, 6 weeks, 3 and 6 months using repeated measures ANOVA for: back pain (VAS), fatigue (MAF), anxiety and depression (HAD), health distress (HDq), fatigue severity scale (FSS), pain self-efficacy (PSEQ), quality of life (SF-36) and Evaluating Ankylosing Spondylitis Qol (EASIQol), global perceived health (GPH), patients disease global assessment (PDGA). AS outcomes were analysed using repeated measures ANOVA for: Bath Ankylosing Spondylitis – Global, Disease Activity Index, and Functional Index (BAS-G, BASDAI, & BASFI), and Ankylosing Spondylitis QoL (ASQol).

Results: At baseline, 43.3% were male, and the mean age was 47.2 ± 15.1 years. The median time to AS diagnosis from the index symptom experience was 3 years with an IQR (1-6). The BAS-G improved between baseline and 3 months (p=0.011) and were sustained at 6 months (p=0.039). The BASDAI improved between baseline and 3 months (p=0.01) and were sustained at 6 months (p=0.009). The ASQol improved between baseline and 6 months (p=0.051). A positive trend were seen for the MAFs GFI, back pain (i.e. nocturnal and total), and the PDGA over the 6 months although these trends were not statistically significant. The composite SF-36 (physical and mental), HADs, HDq, FSS, composite Easiqol (physical, disease activity, wellbeing, and social), PSEQ demonstrated no improvement over the study. There was no significant change in medication usage over the 6 months.

Conclusion: SMAS for AS is independently effective in improving AS specific Disease activity, but global QOL scores did not change.

Table 1: Repeated Measures ANOVA for Quality of Life and Disease Activity tools over time.

Repeated Measures ANOVA	Baseline	WK6	WK6-BL	3MO	3M-BL	6MO	6MO-BL	Within-Subjects Contrasts
	Mean (SE)	Mean (SE)	p-value	Mean (SE)	p-value	Mean (SE)	p-value	p-value
AS Specific Tools								
BAS-G Score	6.09 (0.40)	5.83 (0.36)	0.548	4.89 (0.37)	0.011	5.03 (0.40)	0.039	0.004
BASDAI	5.30 (0.36)	4.83 (0.37)	0.107	4.36 (0.35)	0.01	4.30 (0.37)	0.009	0.005
AS Qol	8.83 (1.08)	8.17 (1.00)	0.409	7.50 (0.88)	0.104	7.03 (1.01)	0.051	0.059
BASFI	4.06 (0.40)	4.03 (0.34)	0.94	3.62 (0.31)	0.118	3.80 (0.40)	0.446	0.266
General Intervention Assessments								
MAFs - GFI	26.14(2.33)	26.50 (2.43)	0.853	23.91 (2.67)	0.333	21.79 (2.67)	0.081	0.06
Back Pain Nocturnal	4.72 (0.41)	4.10 (0.41)	0.142	4.28 (0.42)	0.317	3.97 (0.43)	0.092	0.151
Back Pain Total	5.59 (0.45)	5.21 (0.38)	0.383	4.90 (0.36)	0.091	4.59 (0.46)	0.076	0.143
PDGA	5.24 (0.38)	5.07 (0.42)	0.634	4.66 (0.39)	0.176	4.55 (0.42)	0.081	0.246
SF 36 (Composite)	102.24 (2.07)	103.52 (1.74)	0.429	103.59 (1.59)	0.446	104.31 (1.76)	0.265	0.552
HADS	14.90 (1.62)	14.83 (1.64)	0.962	14.52 (1.43)	0.799	13.69 (1.54)	0.417	0.741
HDq	2.35 (0.25)	2.30 (0.27)	0.858	2.15 (0.26)	0.443	2.00 (0.26)	0.172	0.396
FSS	40.88 (1.87)	41.86 (1.69)	0.517	No Data	No Data	41.29 (1.93)	0.79	0.79
EasiQol (Composite)	35.78 (6.04)	36.11 (3.19)	0.950	30.44 (3.86)	0.228	30.33 (6.18)	0.492	0.544
PSEQ	36.62 (2.51)	36.31 (2.20)	0.861	36.66 (1.97)	.987	37.17 (2.59)	0.832	0.978

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Abstract Number: 700

Problems of Untranslatability: Example of Turkish Version of Basdai

Pamir Atagunduz[1], Elmar Mammadov[2], Ina Dervishi[2], Metin Beyatlı[2], Kubra Nur Salcı[3], Nafisa Auwal Abdulhamid[4], Gulsen Ozen[5], Ali Ugur Unal[1], Zeynep Erturk[1], Nevsun Inanc[5] and Haner Direskeneli[5], [1]Rheumatology, Marmara University School of Medicine, Istanbul, Turkey, [2]None, Marmara University School of Medicine, Istanbul, Turkey, [3]Marmara University School of Medicine, istanbul, Turkey, [4]Marmara University School of Medicine, Istanbul, Turkey, [5]Department of Rheumatology, Marmara University Faculty of Medicine, Istanbul, Turkey

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Background/Purpose: Translators of self-report forms commonly encounter problems related to untranslatability, a term used to describe words that cannot be meaningfully translated from one language to another.We give an example of Turkish translation of Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), a self-report questionnaire, to illustrate the problems mentioned above.

Methods:

It was noted by the physicians in outpatient rheumathology clinic that the translation of "tender points" in the Turkish version of BASDAI was not correctly understood by the patients. For this purpose, we designed a study that would assess patients' subjective understanding of the item comprising this term to detect enthesitis (4^{th} question, Q4). Initially, BASDAI self-report form was administered to 106 patients, followed by a semistructured interview lead by trained investigators.

Immediately after the interview, participants were asked to rate (on a scale from 0 to 10 on a visual analogue scale) the 4^{th} item one more time (after receiving explanation of what was intended to be asked, BASDAI-E). Afterwards, an entheses examination was performed by a blinded investigator using both "Leeds Enthesitis Index" and "Maastricht Ankylosing Spondylitis Enthesitis Score", and the patients were asked to evaluate the degree of pain they felt during the exam on a scale from 0 to 10. The physical examination was used as the objective measure for detecting the presence and severity of enthesitis, and the level of patients' understanding of the 4^{th}item was elicited by the difference between the scores given in standart BASDAI and those given with the Q4 replaced with the entheses examination scoring of enthesis (BASDAI-Q4).

Results:

Of the 106 patients who participated in this study, 41 (38.7%) were male, and 65 (61.3%) were female. Mean age of the participants was 43.8 (SD=10.91). On average, patients have been diagnosed with Ankylosing Spondylitis for 9.25 years (SD=7.03) and recall having symptoms for 13.57 (SD=9.13) years. Thirteen patients reported the Q4 as "not understood". Twenty eight patients reported not to have an enthesitis area in BASDAI where as 39 patiens were found to have no enthesitis on physical examination. Twenty patients reported enthesitis in BASDAI had no enthesitis on physical examination. And 15 reported no enthesitis in BASDAI had on physical examination. Mean BASDAI score (3.94±2.39) was significantly higher when compared to the BASDAI-Q4 (2.95±2.56) ($p<0.0001$, 95% CI 0.54 to 1.44). Explanation of the domains (BASDAI-E) did not affect the mean BASDAI (3.60±2.62 vs. 3.94± 2.39, $p=0.079$, 95% CI 0.04 to 0.07).

Conclusion: Discrepancies arising between the real and the comprehended meaning of untranslatable terms in self reports, lead to statistically meaningful changes in the total BASDAI score, therefore affecting the whole treatment approach of these patients. We argue that this type of terms should not be tried to be translated into single-sentence questions in self reports. Instead, other methods, including visual or verbal explanations should be attempted for a better understanding by the patients.

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Abstract Number: 701

Is Skin Disease More Important to Women or Men in the Assessment of Disease Activity in Psoriatic Arthritis?

Maqbool Sheriff[1], Michel Zummer[2], J Antonio Avina-Zubieta[3], Proton Rahman[4], Wojciech Olszynski[5], Michael Starr[6], Philip Baer[7], Emmanouil Rampakakis[8], Eliofotisti Psaradellis[9], Cathy Tkaczyk[10], Brendan Osborne[10], Karina Maslova[11], Francois Nantel[12] and Allen J Lehman[11], [1]Nanaimo Regional General Hospital, Nanaimo, BC, Canada, [2]Rheumatology, Hôpital Maisonneuve-Rosemont and University of Montreal, Montreal, QC, Canada, [3]Medicine, University of British Columbia, Department of Medicine, Division of Rheumatology, Vancouver, BC, Canada, [4]Rheumatology, St. Clare's Mercy Hospital, St. John's, NF, Canada, [5]University of Saskatchewan, Saskatoon, SK, Canada, [6]Rheumatology, McGill University, Montreal, QC, Canada, [7]Section on Rheumatology, Ontario Medical Association/Journal of the Canadian Rheumatology Association, Toronto, ON, Canada, [8]JSS Medical Research, St-Laurent, QC, Canada, [9]JSS Medical Research, Montreal, QC, Canada, [10]Medical Affairs, Janssen Inc., Toronto, ON, Canada, [11]Janssen Inc., Toronto, ON, Canada, [12]19 Green belt Dr, Janssen Inc., Toronto, ON, Canada

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Background/Purpose:

Patient global assessment of disease activity (PtGA) is a standard outcome measure used both in randomized controlled trials and in clinical practice to ascertain patient subjective perception of disease activity in psoriatic arthritis (PsA). Given that previous studies have shown gender-specific differences with respect to disease parameters and patient reported outcomes, the aim of this analysis was to compare the patient profile at initiation of the first anti-TNF agent and to assess whether skin disease has a bigger impact on PtGA in women vs. men with PsA treated with infliximab (IFX) or golimumab (GLM) in a Canadian real-world, routine clinical practice setting.

Methods:

BioTRAC is an ongoing, prospective registry of patients initiating treatment for rheumatoid arthritis, ankylosing spondylitis, or PsA with IFX or GLM. Eligible people for this analysis included PsA patients treated with IFX who were enrolled since 2005 or with GLM enrolled since 2010. The correlation between disease parameters was assessed with the Pearson's correlation coefficient (r), while generalized linear models were used to assess the independent predictors of PtGA.

Results:

A total of 238 patients (51.7% male) were included. At baseline, no significant differences in age (49.9 vs. 50.1; P=0.907), disease duration (4.8 vs. 6.2; P=0.214), or concomitant DMARD use (60.2% vs. 58.3%; P=0.765) were observed between genders. Mean (SD) disease parameters (men vs. women) were: PASI: 2.7 vs. 2.7, P=0.985; swollen joint count (SJC28): 4.3 vs. 5.2, P=0.121; tender joint count (TJC28): 5.6 vs. 7.7, P=0.016; HAQ: 1.18 vs. 1.51, P<0.001; pain (VAS mm): 44.2 vs. 50.0, P=0.101; PtGA: 45.4 vs. 51.2, P=0.114; MDGA (0-10 NRS) = 4.9 vs. 5.4, P=0.111.

Overall, a weak linear correlation was observed between PASI and PtGA in both men (r=0.272; P<0.001) and women (r=0.203; P<0.001). A moderate to strong correlation was observed between SJC28 and PtGA (mean: r=0.421, P<0.001; women: r=0.398; P<0.001). Univariate analysis independent of time of assessment showed that female gender (ΔPtGA=3.6; P=0.050), higher PASI [ΔPtGA (for each increase in PASI by 1)=2.2; P<0.001], and higher SJC28 (ΔPtGA=3.2; P<0.001), but not baseline age or disease duration, were associated with increased PtGA. However, upon adjusting for PASI (ΔPtGA=1.6; P<0.001) and SJC28 (ΔPtGA=2.7; P<0.001), no significant differences in PtGA were observed between genders.

Conclusion:

The results of this analysis show that, upon adjusting for PASI and SJC28, no significant differences exist in PtGA between genders. Furthermore, the association of PtGA was stronger with SJC28 than with PASI in both men and women, suggesting that both genders place more emphasis on articular disease severity than on skin symptoms when evaluating the global status of PsA.

Disclosure: M. Sheriff, Janssen Inc., 5; **M. Zummer**, Janssen Inc, 5; **J. A. Avina-Zubieta**, Janssen Inc., 5; **P. Rahman**, Janssen Inc, 5; **W. Olszynski**, Janssen Inc., 5; **M. Starr**, Janssen Inc, 5; **P. Baer**, Janssen Inc., 5,AbbVie, 5,Amgen, 5,BMS, 5,Pfizer Inc, 5,Roche Pharmaceuticals, 5; **E. Rampakakis**, Bristol-Myers Squibb, 2; **E. Psaradellis**, JSS Medical Research, 3; **C. Tkaczyk**, Janssen Inc., 3; **B. Osborne**, Janssen Inc., 3; **K. Maslova**, Janssen Inc., 3; **F. Nantel**, Janssen Inc., 3; **A. J. Lehman**, Janssen Inc., 3.

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Abstract Number: 702

Is Skin Disease More Important to Patients or Physicians in the Assessment of Disease Activity in Psoriatic Arthritis?

Dalton Sholter[1], Proton Rahman[2], J Antonio Avina-Zubieta[3], John Kelsall[4], Regan Arendse[5], Majed M. Khraishi[6], S Shaikh[7], William G. Bensen[8], Emmanouil Rampakakis[9], John S. Sampalis[10], Francois Nantel[11], May Shawi[12], Susan Otawa[13], Cathy Tkaczyk[13] and Allen J Lehman[12], [1]Rheumatology Associates, Edmonton, AB, Canada, [2]Rheumatology, St. Clare's Mercy Hospital, St. John's, NF, Canada, [3]Medicine, University of British Columbia, Department of Medicine, Division of Rheumatology, Vancouver, BC, Canada, [4]Mary Pack Arthritis Centre, Vancouver, Vancouver, BC, Canada, [5]University of Saskatchewan, Saskatoon, SK, Canada, [6]Nexus Clinical Research, St Johns, NF, Canada, [7]Niagara Peninsula Arthritis Centre, Hamilton, ON, Canada, [8]St Joseph's Healthcare Hamilton, Hamilton, ON, Canada, [9]JSS Medical Research, St-Laurent, QC, Canada, [10]McGill University, Montreal, QC, Canada, [11]19 Green belt Dr, Janssen Inc., Toronto, ON, Canada, [12]Janssen Inc., Toronto, ON, Canada, [13]Medical Affairs, Janssen Inc., Toronto, ON, Canada

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Background/Purpose:

Patient (PtGA) and physician (MDGA) global assessment of disease activity are standard outcome measures used in clinical practice and research to ascertain patient and physician subjective perception of disease activity in psoriatic arthritis (PsA). Given that the PtGA and MDGA measure the same construct from two different perspectives, assessing their concordance may provide valuable insight on patient and physician differences with respect to the relative importance placed on specific disease parameters. The aim of this analysis was to assess the agreement between PtGA and MDGA, and to compare the correlation of PtGA or MDGA with the Psoriasis Area and Severity Index (PASI) in PsA patients treated with infliximab (IFX) in a Canadian real-world, routine clinical practice setting.

Methods:

BioTRAC is an ongoing, prospective registry of patients initiating treatment for rheumatoid arthritis, ankylosing spondylitis, or PsA with IFX or golimumab as first biologics or after having been treated with a biologic for <6 months. Eligible people for this analysis included PsA patients treated with IFX who were enrolled between 2005 and 2012. The correlation between disease parameters was assessed with the Spearman's rho coefficient (r), while the intraclass correlation coefficient (ICC) and Cronbach's alpha (CA) was used to assess internal consistency.

Results:

A total of 92 patients (52.2% male) were included with a mean (SD) age of 48.7 (9.9) years and disease duration of 6.8 (9.1) years. At baseline, mean (SD) disease parameters were: PASI = 3.3 (5.6); swollen joint count (SJC28) = 4.0 (3.8); tender joint count (TJC28) = 5.9 (5.3); PtGA = 5.0 (2.8); MDGA = 5.8 (2.2) cm. Prior to IFX initiation, 78 (84.8%) patients had been treated with a traditional DMARD (71.7% with methotrexate).Overall, a strong agreement was observed between PtGA and MDGA (r=0.632). The correlation of PASI with PtGA was low (r=0.213), whereas it was moderate with MDGA (r=0.343) (Figure 1). Overall, internal consistency was poor between PASI and both PtGA (CA = 0.373, ICC = 0.229) and MDGA (CA = 0.445, ICC = 0.286) although it was higher with the latter. Multivariate linear regression resulted in the exclusion of PtGA from the model, also supporting the stronger association of MDGA with PASI. When considering other disease parameters, PtGA showed a very strong correlation with pain (r=0.885) and strong with HAQ-DI (r=0.596),whereas a strong correlation was observed between MDGA and both pain and HAQ-DI (r=0.652 and r=0.520, respectively).

Conclusion:

The results of this analysis show that the association of PASI is stronger with MDGA when compared to PtGA. However, patient-reported pain and HAQ-DI were better correlated with PtGA and MDGA when compared to PASI, suggesting that both patients and rheumatologists place more emphasis on pain and functional activity than on skin symptoms when evaluating the global status of PsA.

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Abstract Number: 703

Isotretinoin-Induced Spondilartropathy-Related Symptoms: A Prospective Study

Bunyamin Kisacik[1], Nuriye Kayiran[2], Orhan Zengin[1], Ali Kalem[3], Gezmis Kimyon[4], Emine Ozkul Kilinc[3], Yavuz Pehlivan[5], Necmettin Kirtak[6] and Ahmet Mesut Onat[4], [1]Ä°nternal Medicine Division of Rheumatology, Gaziantep University, Faculty of Medicine, Gaziantep, Turkey, [2]physician, Gaziantep, Turkey, [3]Physician, Gaziantep, Turkey, [4]PsART study group, Ankara, Turkey, [5]Department of Rheumatology, Uludag University Faculty of Medicine, Bursa, Turkey, [6]Prof., Gaziantep, Turkey

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Background/Purpose: Acne vulgaris is a chronic inflammatory disease of accumulation of the pilosebaceous unit in the skin and has a multifactorial aetiology. Isotretinoin is a one of the systemic retinoids and is an effective treatment option for severe and treatment-resistant acne. However, isotretinoin can cause rheumatologic. We aimed to present follow-up results in terms of rheumatologic symptoms of the patients who received systemic therapy for the treatment of acne (isotretinoin and tetracycline) in this prospective, observational study.

Methods: Forty-five patients were started on isotretinoin and 32 patients were started on tetracycline for acne treatment in 2011. Patients were evaluated by rheumatologic symptoms, rheumatological examination, erythrocyte sedimentation rate, C-reactive protein and the Bath Ankylosing Spondylitis Disease Activity (BASDAI) scoring before the treatment, at the time of acute symptoms and after the treatment on 3rd and 6thmonths.

Results: Unilateral Achilles enthesopathy had developed in 3 patients, both Achilles enthesopathy and unilateral sacroiliitis had developed in 1 patient, and inflammatory low back pain had developed in 6 patients in the isotretinoin group; on the other hand, no rheumatologic symptoms were observed in the tetracycline group.

Conclusion: As a result, spondialartropathy (SPA) findings were determined in up to 23.1% of the patients who received isotretinoin treatment.

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Abstract Number: 704

Is Axial Involvement Underestimated in Patients with Psoriatic Arthritis? Data from the Bepas Cohort

Kurt de Vlam[1], Rik Lories[2], Serge Steinfeld[3], Filip van Den Bosch[4], Adrien Nzeusseu Toukap[5], Michel G. Malaise[6], Veerle Taelman[7], Filip van Bruwaene[8], Marc Vanden Bergh[9], Rik Joos[10], Jan Lenaerts[11], Piet Geusens[12], Silvano Dalli'Armelina[13], Isabelle Peene[14], Griet De Brabanter[15], Marthe van den Berghe[16], Jiangang Qu[17], Martin Maertens[18] and Hermine Leroi[19], [1]Katholieke Universiteit Leuven, Leuven, Belgium, [2]university hospitals leuven, Leuven, Belgium, [3]clinique saint jean, bruxelles, Belgium, [4]Rheumatology, Ghent University Hospital, VIB, Ghent, Belgium, [5]Department of Rheumatology, Cliniques Universitaires St Luc, Brussels, Belgium, [6]Department of Rheumatology- GIGA Research - Arthropôle - University of Liège - CHU Liège, Liège, Belgium, [7]Heilig Hart ziekenhuis, Leuven, Belgium, [8]H.H. Ziekenhuis, Roeselare, Belgium, [9]Grand Hôpital de Charleroi Saint Joseph, Charleroi, Belgium, [10]ZNA Jan Palfijn, Antwerpen, Belgium, [11]Reuma Instituut, Hasselt, Belgium, [12]reumaclinic, Genk, Belgium, [13]Notre Dame de Grace, Gosselies, Belgium, [14]Rheumatology, AZ sint Jan Brugge, 8000 Brugge, Belgium, [15]AZ St Lucas, Assebroek, Belgium, [16]ASZ, Aalst, Belgium, [17]Iris Sud, Bruxelles, Belgium, [18]AZ Damiaan, Oostende, Belgium, [19]MSD Belgium, Bruxelles, Belgium
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Session Title: Spondylarthropathies and Psoriatic Arthritis - Clinical Aspects and Treatment Poster I: Clinical Aspects and Assessments
Session Type: ACR Poster Session A
Session Time: 9:00AM-11:00AM

Background/Purpose:

Psoriatic arthritis (PsA) is a common form of chronic arthritis strongly associated with the skin disease psoriasis. Although PsA has been included in the spondyloarthritis concept, PsA is often considered to be predominantly peripheral and may be characterized by arthritis, dactylitis and enthesitis. Consequently randomized controlled trials, screening procedures for early detection and treatment strategies largely focus on peripheral disease. Axial involvement is considered less common and is often treated as a variant of ankylosing spondylitis. The BEPAScohort (Belgian Epidemiological Psoriatic Arthritis Study) is a large prospective multicenter real life cohort set up in 17 Belgian large academic and non academic rheumatology practices that offers a unique opportunity to study the axial involvement in this patient group. Purpose:(1) To estimate the prevalence of axial involvement in patients with PsA in general and in the different subtypes; (2) to estimate the prevalence of inflammatory back pain in patients with PsA; (3) to estimate gender differences in spinal involvement in patients with PsA; (4) to estimate the influence of disease duration on spinal manifestations.

Methods:

Patients included in the BEPAS cohort were evaluated for the presence of a clinical phenotype indicating axial involvement, the specific presence of spinal complaints(reported by patients) and the presence of inflammatory back pain according the Rudwaleit criteria. Demographics and clinical features were recorded. BASDAI and BASMI were calculated. Spinal radiographs are collected at entry and after 2 years.

Results:

461 patients (mean age: 52.79 years (+/-12.29), male 57%) were recruited in the 17 centers from December 2012 to July 2014. A spinal phenotype was identified in 342 patients: 0.7% has pure axial disease whereas 73.7% of the the total patient population has combined peripheral and axial involvement. At entry, 159 patients reported spinal pain with no gender difference. Inflammatory back pain (fulfilling at least 2 out of 4 criteria) was present in 243 patients. BASMI in the overall population cohort (n=440) was 3.76 and BASDAI overall population (n=456) was 1.86 with slightly higher values in female than in male patients. 90% of the patients reported a BASDAI lower than 3.5. A family history of ankylosing spondylitis is reported in 3.3% of the patients. Clinical characteristics and demographics are listed in table 1.

Conclusion:

This large cohort reports a higher frequency of spinal complaints than that reported in other cohorts. A considerable number of patients have inflammatory back pain suggesting that inflammatory axial involvement in PsA should not be underestimated. Surprisingly BASDAI are rather low. This may indicate a lower severity as compared to other forms of spondyloarthritis.

Table1	**N**	**global**	**male**	**female**
Age		52.79 (+/- 12.29)	53.05 (+/- 12.23)	52.43 (+/- 12.41)
Gender		461	263	198
Symptoms duration	450	11.91 +/- 10.83	11.37 +/- 9.79	12.64 +/- 12.08
Disease duration	459	8.60 +/- 9.30	8.46 +/- 8.74	8.79 +/- 10.00
Family history PsA/Spa	456	227 (49.8%)	127 (48.5%)	135 (51.5%)
Ankylosing Spondylitis		15 (3.3%)	5 (1.9%)	10 (5.2%)
HLA B27	158	26 (16.5%)	12 (13%)	14 (21.2%)
Joint involvement currently				
reported spinal pain currently	457	34.8%		
hiparthritis	351	4%		
IBP (Rudwaleit =>2/4 criteria)	423	57.4%	132/243(54.3%)	111/180(61,6%)
Cutaneous involvement currently				
BSA (%)	279	5,25 (+/- 10,50)	6,10(+/-12,11)	3,99(+/-7,35)
PASI	302	2,38(+/-4,31)	2,94(+/-4,98)	1,66(+/-3,12)
Nail	459	122 (26,6%)	85 (32,3%)	37 (18,9%)
Clinical involvement at entry		**N of total**	**N of male(263)**	**N of female(198)**
BASMI	440	3,76 (+/-1,21)	3,65 (+/-1,24)	3,90 (+/-1,16)
tender/swollen joints	461	275(59,65%)	149(56,65%)	126(63,63%)
dactylitis	461	64(13,9%)	41(15,58%)	23(11,61%)
enthesitis	461	111(24,1%)	51(19,39%)	60(30,30%)
Disease activity				
abnormal CRP (=>5mg/l)	430	125(29,1%)	64 (25,3%)	61(34,5%)
abnormal ESR (>10mm/h)	391	102(26,1%)	50(22,5%)	52(30,8%)
BASDAI	456	1,86(+/-1,18)	1,70(+/-1,17)	2,07(+/-1,17)

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Abstract Number: 705

Sex Differences in Psoriatic Arthritis: Evaluation of a Real-Life Cohort of 2,118 Italian Patients Treated with Methotrexate

Carlo Selmi[1,2], Elena Generali[3], Greta Carrara[4], Carlo Alberto Scirè[4] and RECORD Study Group of the Italian Society for Rheumatology, [1]BIOMETRA Department, University of Milan, Milan, Italy, [2]Internal Medicine- Unit of Rheumatology and Clinical Immunology, Humanitas Clinical and Research Center, Rozzano, Italy, [3]Internal Medicine- Unit of Rheumatology and Clinical Immunology, Humanitas Clinical and Research Center, Rozzano (MI), Italy, [4]Epidemiology Unit – Italian Society for Rheumatology (SIR), Milano, Italy
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Background/Purpose: The influence of sex in psoriatic arthritis (PsA) features and treatment outcomes has not been fully elucidated. We investigated the differences between sexes in biologic initiation and methotrexate (MTX) retention rate in a large real-life cohort of patients with PsA .

Methods: This is a retrospective cohort study based on administrative health databases of the Northern Italian Lombardia region (with a 10 million population). Data were extracted from the RECORD database of the Italian Society for Rheumatology. Patients with PsA were defined by the presence of disease specific copayment exemptions, and MTX treatment included as its first prescription. Demographic data, comorbidities (measured using the Charlson Index) and concomitant treatments were recorded. Baseline demographic and disease variables were compared using the chi squared test, two-sample *t* test or Mann-Whitney U test, as appropriate. Cox regression analysis was used for comparing initiation of biologic treatment and MTX retention rate. All statistical tests were two-sided with a level of significance set at 0.05.

Results: A total of 2,118 PsA cases treated with MTX were included and their demographic, clinical and therapeutic features are reported in **Table 1**. We observed significant differences between sexes in the age at the first MTX prescription (55.1±12 in women vs. 51.9±12.5 in men) and concomitant treatment with antidepressants (7.2% in women vs. 2.2% in men). Men and women with PsA were comparable for disease duration, Charlson Index and concomitant arthritis medications (NSAIDs and glucocorticoids). MTX was discontinued in 984 subjects (person-year 8,807.53, incidence rate 0.11, 95% CI 0.10-0.12). The Cox regression analysis for MTX retention rate reported a crude HR of 1.00 (95% CI 0.88-1.14), while the adjusted HR was 1.09 (95% CI 0.96-1.24). A total of 616 subjects (person-year 10,823.3, incidence rate 0.05, 95%CI 0.047-0.055) started a biologic treatment (283 etanercept, 45.9%; 185 adalimumab, 30%; 121 infliximab, 20%, 27 golimumab, 4.4%). No differences were observed between sexes (etanercept 56% vs. 43.8%, adalimumab 50% vs. 49.7%, infliximab 54.5% vs. 45.4%, golimumab 59% vs 40%). The Cox regression analysis for biologic initiation reported a crude HR for sex of 0.81 (95%CI 0.69-0.96, *p*=0.018) and an adjusted HR of 0.80 (95%CI 0.68-0.95; *p*=0.012).

Conclusion: Our data from a real-life cohort of patients with PsA treated with MTX suggest that women are younger at first MTX prescription and are more frequently precribed antidepressants despite similar use of NSAIDs and glucocorticoids or comorbidities. MTX retention rate does not differ between sexes. Female sex is negatively associated with biologic initiation, possibly reflecting different prescription patterns between sexes.

Table 1.

	Total (n = 2,118)	Women (n=1,077)	Men (n=1,041)	*p value*
Age at 1^ MTX prescription, years, mean (SD)	53.5 (12.4)	55.1 (12)	51.9 (12.5)	0.000
Disease duration, years, mean (SD)	6.05 (3.75)	6.05 (3.75)	6.06 (3.74)	NS
Charlson Index = 0, n (%)	1,674 (79%)	842 (78.2%)	832 (80%)	NS
Charlson Index > 1, n (%)	444 (21%)	53 (21.8%)	832 (20%)	NS
Concomitant NSAIDs	933 (44%)	486 (45.1%)	447 (42.9%)	NS
Concomitant glucocorticoids	571 (27%)	301 (27.9%)	270 (25.9%)	NS
Concomitant antidepressants	101 (4.8%)	78 (7.2%)	23 (2.2%)	0.000

life-cohort-of-2118-italian-patients-treated-with-methotrexate

Abstract Number: 706

Undifferentiated Spondylarthritis May More Frequent in Japanese

Hitoshi Goto[1], Noriyuki Hayashi[1], Shinsuke Yamada[2] and Masaaki Inaba[3], [1]Rheumatology, Osaka City University Graduate School of Medicine, Osaka, Japan, [2]Rheumatology, Osaka City University Graduate School of Midicine, Osaka, Japan, [3]Osaka City University Graduate School of Medicine, Osaka, Japan

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Background/Purpose: Because of low frequency of HLA-B27 (lower than 1%), the prevalence of the spondarthritis (SpA) is thought to be much lower than rheumatoid arthritis (RA) in Japanese. Therefore an evaluation of the inflammatory back pain and enthesitis is not routinely performed, and early diagnosis of the spondarthritis (SpA) is not substantially performed. We examined the presence of clinical findings to suggest SpA in each of the positive cases of the anti-cyclic citrullinated peptide antibody(ACPA) and the negative cases of ACPA in Japanese.

Methods: We randomly selected 300 cases from the patients who had musculoskeletal symptoms as chief complaint in outpatient clinic of Rheumatology, Osaka City University Hospital.We retrospectively examined frequency of clinical findings of SpA including enthesitis, dactylitis, the arthritis of axis joints and the inflammatory back pain according to clinical records in cases of ACPA positive, and ACPA negative.

Results: Among 300 cases, 95 cases showed positive of ACPA and 205 cases showed negative. In the ACPA positive cases, only two cases showed more than one enthesitis, but 88 cases showed either enthesitis (80 cases) or ductilitis (10 cases), the arthritis of axis joints (62 cases), inflammatory lumbago (2 cases) in the ACPA negative cases. The cases with findings to suggest potential of SpA are more frequently in ACPA-negative cases in Japanese. However, the patients themselves actually rarely reported these symptoms, therefore findings suggesting SpA were possibly missed unless we took physical examination adequately.

Conclusion: The Japanese SpA patients may have relatively mild symptoms and may be diagnosed seronegative RA rather than undifferentiated SpA. It is necessary to take physical examination appropriately in ACPA-negative Japanese patients even if they meet classification criteria of RA to prevent passing over SpA, moreover it is necessary to find genetic marker in Japanese such as HLA-B27 in Caucasian.

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Abstract Number: 707

Change of Enthesial Involvement Under Treatment Was Independent from the Therapeutic Strategy in Patients with Axial Spondyloarthritis within the Scqm Cohort

Ruediger Mueller[1], Toni Kaegi[2], Nicole Graf[3], Johannes von Kempis[4] and J.J. Luime[5], [1]Rheumatology, MD, St. Gallen, Switzerland, [2]Kantonsspital St. Gallen, St. Gallen, Switzerland, [3]graf biostatistics, Winterthur, Switzerland, [4]Rheumatology, Kantonsspital St. Gallen, St. Gallen, Switzerland, [5]Department of Rheumatology, Erasmus Medical Centre, Rotterdam, Netherlands

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Background/Purpose:

Enthesitis is one of the potential extra-axial manifestations found in patients with spondyloarthritis (SpA). Enthesitis can be quantified using the MASES (Maastrich Ankylosing Spondylitis Enthesitis *Score*), consisting 13 pre-defined entheses assessed for tenderness. Evidence regarding treatment of enthesitis is limited. There are no specific recommendations for treatment of enthesitis in SpA. To better understand the impact of enthesitis real live data are needed.

Objective:

To analyse the development of enthesitis under treatment.

Methods:

We included all patients from the Swiss national registry SCQM with axial spondyloarthritis and valid MASES at baseline. Patients were analysed for changes in MASES subsequent to treatment in separate for: (A) MASES 0-13; (B) grouped MASES = 0 vs. MASES 1-5 vs. MASES 6-13; (C) time point in treatment strategy (1^{st}, 2^{nd} vs 3^{rd} therapeutic strategy for treatment of axial SpA); (D) response to synthetical DMARDs vs. biologic agents; (E) response to Etanercept vs. antibody-based TNF antagonists (Adalimumab, Infliximab, Golimumab, and Certolizumab). The results of the correlation analyses were calculated using linear regression. Differences between two groups were compared with the Mann-Whitney *U* test and between more than two groups with the Kruskal-Wallis test.

Results:

3241 patients were included into the study. 45.9% of the patient had no enthesial affection at baseline (MASES = 0). The average response of MASES after 1 year increase linearly with increasing average MASES scores (slope -0.41, $R^2 = 0.78$). For detailed responses per group please refer to the table.

	Response at 12 (±3) months, number of patients assessed (n)*	**p-value**
MASES 0	+0.48 (n=667)	p<0.001
MASES 1-5	-1.02 (n=628)	
MASES 6-13	-3.59 (n=176)	
1^{st} therapeutic decision	-1.22 (n=360)	p=0.163
2^{nd} therapeutic decision	-0.62 (n=93)	
3^{rd} and later therapeutic decision	-1.35 (n=74)	
Treatment with TNF antagonists	-1.15 (n=454)	p=0.967
Treatment with synthetical DMARDs	-1.03 (n=59)	
Treatment with Etanercept	-0.97 (n=132)	p=0.540
Treatment with antibody-based TNF antagonists	-1.23 (n=323)	

* Calculated on Patients with available data

Summary:

Patients with a higher MASES developed a significantly better reduction in MASES as compared to patients with lower MASES. Almost one out of two patients with a MASES of 0 at baseline developed an entheseal affection during follow up under treatment. Changes of MASES under TNF antagonist or DMARD treatment did not differ in our cohort. No differences in the therapeutic response to different TNF antagonists were detected.

Conclusion:

Entheseal involvement is a neglected problem in axial SpA patients affecting minimum half of the patients. A focussed therapeutic strategy for entheseal involvement is needed.

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Abstract Number: 708

Development of an Activity Disease Score in Patients with Uveitis

Esperanza Pato Cour[1], Maria Auxiliadora Martin[2], Santiago MuÑoz Fernandez[3], Adela Castello[4], Fernando Sanchez-Alonso[5], David Diaz-Valle[6], Rosalía Mendez[7] and Uveitis MeVa Group, [1]Rheumatology, Hospital Clínico San Carlos, Madrid, Spain, [2]Research Unit of Spanish Society of Rheumatology,, Madrid, Spain, [3]Rheumatology, Hospital Infanta Sofía, Madrid, Spain, [4]Cancer Epidemiology Unit, National Center for Epidemiology, Instituto de Salud Carlos III, Madrid, Spain, Madrid, Spain, [5]Unidad de Investigación, Spanish Society of Rheumatology, Madrid, Spain, [6]Hospital Clínico San Carlos de Madrid, Madrid, Spain, [7]Ophthalmology, Hospital Clínico San Carlos, Madrid, Spain
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Background/Purpose: Uveitis is commonly defined as inflammation of the uvea, the vascular middle layer of the eye. Standardized and validated outcome measures are lacking in uveitis management, which makes it difficult to compare the efficacy and responses to treatment.

To develop a disease activity score for patients with uveitis and determine its discriminating ability to classify patients based on the level of activity.

Methods: Multicenter cross-sectional observational study. The construct "uveal inflammation activity" was defined as intraocular inflammation. 7 dimensions and 14 items were identified and were agreed among experts through a two-round Delphi technique. The dimensions were: visual acuity, anterior chamber, vitreous cavity and posterior segment inflammation, uveitic macular edema, patient and physician global assessment. 8 Spanish hospitals with uveitis units participated in the study. Patients diagnosed with uveitis, older than 5 years and inflammatory activity at the time of the visit, were selected. Primary endpoint: uveitis inflammatory activity, defined as any intraocular inflammation and categorized as mild, moderate and severe. An ordinal logistic regression model was built whose dependent variable was the inflammatory activity (mild, moderate, severe). The modelling accuracy to classify the patient in the right category was assessed with the Area Under the Curve (AUC). Two AUC measures were calculated: one for the discrimination of mild versus moderate and severe activity level of uveitis and another for the discrimination of mild and moderate versus severe activity.

Results: 195 patients were included, 54% were women and the mean age was 45.8±16.1 years. The results of the regression model revealed that the uveitis was more severe in patients with an elevated number of anterior chamber cells ($OR_{4\ cells\ vs\ 0cells}$=27.85;95%CI=3.42;226.75), high degree of vitreous haze ($OR_{severe\ vs\ null}$=3.95;95%CI=1.40;11.16), macular edema over 315 micras ($OR_{>315\ vs\ \leq 315}$=3.58;95%CI=1.56;8.21), presence of vessel sheathing ($OR_{yes\ vs\ no}$=4.43;95%CI=1.71;11.53), higher patient's evaluation ($OR_{1\text{-}unit\ increase}$=1.23;95%CI=1.09;1.39), presence of papilitis ($OR_{yes\ vs\ no}$=4.05;95%CI=1.18;13.92) and elevated number of choridal or retinal lesions ($OR_{\geq 6\ vs\ 0}$=4.99;95%CI=1.08;23.01). The discriminant capacity of disease activity index is 87% (95%CI:82%-92%) for discriminating patients with mild uveitis from patients with moderate or severe uveitis and 88%(95%CI:84%-95%) for discriminating patients with mild or moderate uveitis from patients with severe uveitis.

Conclusion: This composite disease activity index in uveitis integrates all ocular inflammatory activity and takes into account the assessment of the patient and the doctor. The index has a high capacity to classify the inflammatory activity of the patients with uveitis.

Abstract Number: 709

Progression of Patients with Non-Radiographic Axial Spondyloarthritis to Ankylosing Spondylitis: A Population-Based Cohort Study

Runsheng Wang[1], Sherine Gabriel[2] and Michael M. Ward[1], [1]NIH/NIAMS, Bethesda, MD, [2]Division of Rheumatology; Department of Health Sciences Research, Mayo Clinic, Rochester, MN
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Background/Purpose: The long-term outcome of patients with non-radiographic axial spondyloarthritis (nr-axSpA) is unclear, particularly whether few or most progress to ankylosing spondylitis (AS). Our objective was to examine the progression to AS in a population-based inception cohort of patients with nr-axSpA.

Methods: The Rochester Epidemiology Project (REP) is a longstanding population-based study of health in residents of Olmsted County, Minnesota. Using a combination of diagnostic and procedural codes for back pain, HLA-B27 and pelvis MRI, we searched the REP from 1985 to 2010 for subjects who potentially fulfilled ASAS criteria for nr-axSpA. We performed detailed review of medical records to identify subjects who satisfied either the ASAS clinical arm or imaging arm criteria, and followed them until March 15th, 2015. We collected demographic, clinical, laboratory and radiology information. We used survival analysis to measure time to progression to AS.

Results: After screening 2151 potential candidates, we identified 83 subjects who met ASAS criteria for nr-axSpA (18 in the imaging arm and 65 in the clinical arm). Fifty-three percent of the subjects were men. The average age at inclusion was 33.3 ± 8.3 years. The age of back pain onset was 30.3 ± 7.9 years. The mean follow up was 10.6 ± 5.6 years.

Sixteen (19%) subjects developed radiographic sacroiliitis that met modified New York criteria for AS. The probabilities of remaining as nr-axSpA at 5, 10, and 15 years were 93.6% (95% confidence interval (CI) 88.3% to 99.2%), 82.7% (74.1% to 92.3%), and 73.6% (62.7% to 86.3%), respectively (fig 1). In a sensitivity analysis using the date of last negative pelvis film as the time for censoring, the probabilities were 89.6% (81.4% to 98.7%), 70.4% (57.0% to 86.8%), and 53.9% (38.3% to 75.8%) at 5, 10, and 15 years, respectively. Subjects in imaging arm progressed more frequently (28%) and rapidly than those in clinical arm (17%), with a hazard ratio of 3.50 (95% CI 1.15 to 10.6), p=0.02 (fig 2). Men tended to progress more often than women, but the difference was not statistically significant.

Conclusion: In this population-based study, a minority of patients with nr-axSpA progressed to AS after 15 years of follow up. This suggests that the classification criteria of nr-axSpA identifies many patients unlikely to progress to AS, or that nr-axSpA is a prolonged prodromal state, requiring longer follow up to evolve to AS.

Figure 1. Kaplan Meier curve of progression from nr-axSpA to AS, with 95% CI (dashed line). X axis: year of follow up; Y axis: proportion remained to be nr-axSpA.

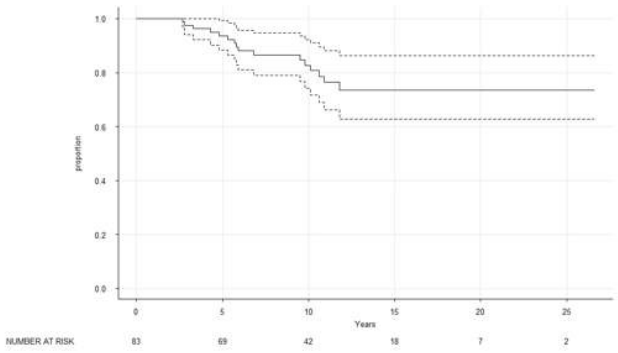
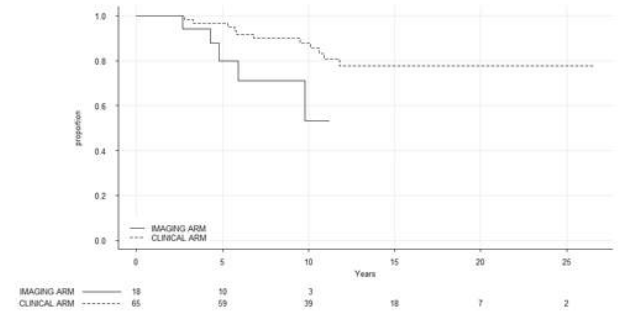


Figure 2. KM curve of progression to AS stratified by inclusion criteria.



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Abstract Number: 710

Baseline Characteristics of Early, Delayed, and Non-Responders in a Non-Radiographic Axial Spondyloarthritis Study

Walter Maksymowych[1], Jack F Bukowski[2], Lisa Marshall[3], Annette Szumski[4] and Heather Jones[3], [1]Department of Medicine, University of Alberta, Edmonton, AB, Canada, [2]Clinical Affairs, Pfizer, Collegeville, PA, [3]Inflammation Global Medical Affairs, Pfizer, Collegeville, PA, [4]Department of Biostatistics, Pfizer, Collegeville, PA

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Background/Purpose: Most clinical trials evaluating anti-TNF agents for treating non-radiographic axial SpA (nr-axSpA) place the primary endpoint at 12 wks, and most formularies require assessment of response 12-16 wks after starting anti-TNF therapy. However, data from the EMBARK study (ClinicalTrials.gov identifier: NCT01258738) suggest the 24-wk time point may be more appropriate for evaluating response to etanercept (ETN). This analysis aimed to compare the baseline (BL) characteristics of patients with early, delayed, and no treatment response.

Methods: Patients had axial SpA per Assessment of SpondyloArthritis international Society (ASAS) criteria without meeting modified NY radiographic criteria; Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score ≥4, disease symptoms for >3 months and <5 yrs, and had failed ≥2 NSAIDs. Patients were randomized to double-blind ETN 50 mg/wk or placebo for 12 wks, then received open-label ETN 50 mg/wk. This analysis includes the open-label modified intent-to-treat (mITT) population that was randomized to ETN. For ASAS20 and ASAS40 response, patients were split into 3 groups: early (12-wk) responders, delayed (24-wk) responders, and non-responders. Observed case (OC) and non-responder imputation (NRI) analyses were performed. Patients with missing data were excluded (OC analysis) or considered non-responders (NRI analysis). Comparison of BL characteristics used one-way analysis of variance with treatment as a factor for continuous variables and Fisher's exact test or chi-square test for yes/no variables.

Results: 99 patients were in the mITT population, OC analysis. Mean (SD) age was 31.8 (7.8) yrs, 64.7% were male, and duration of disease symptoms was 2.4 (2.0) yrs; 66.7% of patients were human leukocyte antigen B27 (HLA-B27)+ and 83.8% had sacroiliitis on MRI (*P*=non-significant across response groups for all). For ASAS20 and ASAS40 responses, the OC analysis demonstrated significant BL differences among response groups for the following: CRP, BASDAI, ankylosing spondylitis disease activity score, patient global assessment, total back pain, inflammation, and Spondyloarthritis Research Consortium of Canada (SPARCC) SI joint score (table). Overall, values for BL disease characteristics were higher (more severe) for responders than non-responders, and highest for early responders. No significant BL differences existed in tender/swollen joint count, enthesitis, Maastricht Ankylosing Spondylitis Enthesitis Score, physician global assessment, or prior response to NSAIDs, per ASAS20 or ASAS40 response. NRI analysis results were similar.

Conclusion: Evaluating ASAS20 and ASAS40 results according to early, delayed, and no response demonstrated significant differences in several BL clinical characteristics and SPARCC MRI scores. These results may aid clinicians in treating patients with nr-axSpA.

Table: Baseline Disease Characteristics of Early and Late Responders and Non-responders								
Baseline Characteristic	Week 12 Responders		Week 24 Responders		Non-Responders		*P*-value*	
	ASAS20 N=55	ASAS40 N=35	ASAS20 N=16	ASAS40 N=15	ASAS20 N=28	ASAS40 N=49	ASAS20	ASAS40
CRP, mg/L	8.9 (12.7)	11.6 (14.7)	9.3 (10.8)	3.1 (3.0)	2.6 (2.6)	5.3 (7.9)	0.0182†	0.0106†
CRP, mg/L, median	4.3	5.5	3.9	2.6	1.5	2.0		
Elevated CRP (>3 mg/L), n (%)	32 (58.2)	23 (65.7)	8 (50.0)	6 (40.0)	8 (28.6)	19 (38.8)	0.0366	0.0427
BASDAI, 0-10 cm VAS	6.2 (1.7)	6.3 (1.6)	6.3 (1.4)	6.3 (1.5)	5.3 (2.0)	5.5 (1.9)	0.0382	0.0344
BASFI, 0-10 cm VAS	4.6 (2.3)	4.9 (2.4)	3.9 (2.5)	4.5 (1.7)	3.7 (2.6)	3.6 (2.5)	ns	0.0152
ASDAS-CRP	3.2 (0.9)	3.5 (0.9)	3.3 (0.9)	2.9 (0.7)	2.4 (0.7)	2.7 (0.9)	0.0003	0.0001
PtGA, 0-10 cm VAS	6.4 (1.7)	6.6 (1.8)	5.8 (1.8)	6.1 (1.6)	4.4 (2.8)	5.0 (2.5)	0.0001	0.0009
Total back pain, 0-10 cm VAS	6.0 (2.1)	6.5 (2.1)	5.8 (2.2)	5.8 (1.6)	4.3 (2.7)	4.6 (2.6)	0.0022	0.0003
Inflammation,‡ 0-10 cm VAS	6.5 (2.1)	6.8 (2.0)	6.1 (1.8)	6.5 (2.1)	4.8 (2.2)	5.2 (2.1)	0.0014	0.0003
SPARCC MRI SIJ score (0-72)	10.3 (10.7)	12.7 (11.4)	6.1 (5.1)	7.0 (7.9)	5.0 (8.8)	5.2 (7.8)		
SPARCC MRI SIJ score (0-72), median	6.2	8.0	4.8	4.0	2.8	3.1	0.0168†	0.0007†
SPARCC MRI 6-DVU spinal score (0-108)	6.0 (8.8)	6.7 (9.9)	2.3 (2.9)	5.5 (7.2)	3.5 (3.8)	3.2 (3.8)	ns	0.0258†
SPARCC MRI 6-DVU spinal score (0-108), median	2.0	3.0	1.5	2.0	2.3	1.5		

Values are mean (SD) unless otherwise noted. Observed case analysis, ETN/ETN group.

**P*-value across early, late, and non-responders; one-way analysis of variance with treatment as factor.

†*P*-value shows significant differences in mean value among the 3 response groups.

‡Inflammation is mean of the 2 morning stiffness-related BASDAI scores.

ASDAS-CRP, Ankylosing Spondylitis Disease Activity Score based on C-reactive protein; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; CRP, C-reactive protein; DVU, discovertebral units; MRI, magnetic resonance imaging; ns, non-significant; PtGA, patient global assessment; SIJ, sacroiliac joint; SPARCC, Spondyloarthritis Research Consortium of Canada; VAS, visual analog scale.

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Abstract Number: 711

Gender Specific Differences in Ankylosing Spondylitis at Treatment Initiation in Patients Treated with Infliximab or Golimumab

Michael Starr[1], Michel Zummer[2], Denis Choquette[3], Boulos Haraoui[4], Proton Rahman[5], Maqbool Sheriff[6], Niall Jones[7], Emmanouil Rampakakis[8], Eliofotisti Psaradellis[9], Brendan Osborne[10], Allen J Lehman[10,11], Karina Maslova[11], Francois Nantel[12,13] and Cathy Tkaczyk[10], [1]Rheumatology, McGill University, Montreal, QC, Canada, [2]Rheumatology, Hôpital Maisonneuve-Rosemont and University of Montreal, Montreal, QC, Canada, [3]Rheumatology Department, Institut de Rhumatologie de Montréal and University of Montreal, Montreal, QC, Canada, [4]Institut de Rhumatologie de Montréal and University of Montreal, Montreal, QC, Canada, [5]Medicine, Memorial University, St John's, NF, Canada, [6]Nanaimo Regional General Hospital, Nanaimo, BC, Canada, [7]Division of Rheumatology, University of Alberta, Edmonton, AB, Canada, [8]JSS Medical Research, St-Laurent, QC, Canada, [9]JSS Medical Research, Montreal, QC, Canada, [10]Medical Affairs, Janssen Inc., Toronto, ON, Canada, [11]Janssen Inc., Toronto, ON, Canada, [12]Schering Plough Canada Inc., Janssen Inc., Kirkland, QC, QC, Canada, [13]19

Green belt Dr, Janssen Inc., Toronto, ON, Canada
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Background/Purpose:

The prevalence of ankylosing spondylitis (AS) is 2-3 times higher in men compared to women. Recent studies have suggested that clinical differences exist between both genders with women experiencing a higher burden of disease. This analysis examined gender-specific differences with respect to patient and disease parameters at initiation of infliximab (IFX) or golimumab (GLM) for the treatment of AS in a Canadian routine clinical practice setting.

Methods: Biologic Treatment Registry Across Canada (BioTRAC) is an ongoing, prospective registry of patients (pts) initiating treatment for rheumatoid arthritis, ankylosing spondylitis, or psoriatic arthritis with IFX or GLM. Pts with AS treated with IFX who were enrolled since 2002 or with GLM enrolled since 2010 were included in this analysis. Between group differences were assessed with the Fisher's Exact test or the independent samples t-test, while linear regression was used to assess the independent association of gender with HAQ-DI, ASDAS, BASDAI, and BASFI improvements at 12 months.

Results:

A total of 539 AS pts were included in this analysis; 188 (34.9%) pts were treated with GLM and 351 (65.1%) with IFX. The majority of pts were male (61.8%). Mean age and disease duration were comparable between genders for both GLM and IFX (Table 1). Overall, disease parameters were similar for GLM with the exception of BASDAI where higher disease severity was observed among females. Among pts treated with IFX, between gender differences were observed for CRP with significantly lower levels in female pts; however BASDAI and HAQ-DI where significantly higher in females compared to males.

Table 1: Patient Characteristics at Baseline by Gender			
Parameter **Mean (SD) / %**	**Male**	**Female**	**P-Value**
AS-GLM	**n=115**	**n=73**	
Age: years	46.3 (15.2)	44.4 (11.8)	0.498
Disease duration: years	5.2 (10.0)	6.0 (10.6)	0.704
C-Reactive Protein (CRP): mg/L	12.6 (15.2)	17.5 (50.5)	0.389
ESR: mm/hr	18.0 (16.6)	22.0 (16.2)	0.152
Patient Global (PtGA): VAS mm	52.7 (28.5)	60.7 (21.2)	0.058
Physician Global (MDGA): NRS 0-10	5.2 (2.4)	5.6 (1.9)	0.172
Morning stiffness: min	56.4 (45.2)	60.1 (47.1)	0.603
HAQ-DI	1.02 (0.62)	1.08 (0.58)	0.489
ASDAS	3.3 (1.0)	3.5 (0.8)	0.126
BASDAI	5.6 (2.3)	6.5 (1.7)	***0.007***
BASFI	5.2 (2.6)	5.3 (2.2)	0.587
Prior biologic (<6 months)	6.1%	2.7%	0.486
Concomitant DMARD	7.0%	5.5%	0.769
Concomitant NSAID	23.5%	31.5%	0.240
AS-IFX	**n=218**	**n=133**	
Age: years	45.1 (12.0)	47.0 (10.8)	0.163
Disease duration: years	9.6 (10.3)	8.8 (9.6)	0.505
C-Reactive Protein (CRP): mg/L	19.2 (26.9)	12.5 (17.6)	***0.012***
ESR: mm/hr	23.5 (21.3)	24.5 (20.6)	0.672
Patient Global (PtGA): VAS mm	58.1 (27.0)	59.2 (28.3)	0.864
Physician Global (MDGA): NRS 0-10	6.3 (2.1)	6.3 (2.1)	0.881
Morning stiffness: min	84.5 (115.9)	87.5 (131.8)	0.824
HAQ-DI	1.11 (0.58)	1.27 (0.63)	***0.019***
ASDAS	3.7 (1.0)	3.6 (1.0)	0.482
BASDAI	6.0 (2.1)	6.6 (2.1)	***0.013***
BASFI	5.9 (2.5)	6.1 (2.5)	0.458
Prior biologic (<6 months)	6.4%	8.3%	0.527
Concomitant DMARD	26.1%	24.8%	0.802
Concomitant NSAID	56.4%	51.9%	0.440

Regression analysis showed that, upon adjusting for baseline levels, female gender (ΔBASDAI=0.603; P=0.035) was associated with increased BASDAI at 12 months of treatment as compare to males. HAQ-DI, ASDAS, and BASFI, on the other hand, at 12 months were comparable between genders.

Conclusion:

Overall, at anti-TNF initiation, female AS pts experience greater disease activity relative to men at initiation of biologic therapy. Whether this represents a gender bias in prescribing, concomitant fibromyalgia, a gender based difference in the acceptance of biologic treatment or disease assessment, requires additional research.

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Factors Associated with Anti-TNF Treatment in a Longitudinally Followed Ankylosing Spondylitis (AS) Cohort

Mary Gibson[1], MinJae Lee[2], Michael M. Ward[3], Lianne S. Gensler[4], Matthew A. Brown[5], Shervin Assassi[6], Colton Pence[1], Laura A.

Diekman[7], Mohammad H. Rahbar[8], Michael H. Weisman[9] and John D. Reveille[1], [1]Rheumatology, University of Texas Health Science Center at Houston, Houston, TX, [2]Biostatistics/Epidemiology/Research Design (BERD) Core | Center for Clinical and Translational Sciences, University of Texas Health Science Center at Houston, Houston, TX, [3]NIH/NIAMS, Bethesda, MD, [4]Medicine/Rheumatology, University of California, San Francisco, San Francisco, CA, [5]The University of Queensland Diamantina Institute, Brisbane, Australia, [6]Rheumatology, University of Texas Medical School at Houston, Houston, TX, [7]Rheumatology, University of Texas Medical School, Houston, TX, [8]The University of Texas Health Science Center at Houston, Houston, TX, [9]Rheumatology, Cedars-Sinai Medical Center, Los Angeles, CA
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Background/Purpose: TNF-α inhibitor therapy is recommended by ASAS/EULAR guidelines for ankylosing spondylitis (AS) patients with moderate-to-high disease activity despite inadequate response to NSAIDs in addition to education and exercise. The purpose of this study is to evaluate factors associated with anti-TNF-α use over a 13 year period in a longitudinal cohort of AS patients enrolled between 2003 and 2013.

Methods: A prospective cohort study of 607 AS patients meeting modified New York criteria were followed for at least 2 years from 5 sites. Patients underwent a comprehensive standardize clinical evaluation and completed questionnaires assessing their disease activity and functional impairment by the BASDAI and BASFI respectively. Demographic, social, and psychological variables were collected. Current medication lists as well as ESR and CRP levels were determined at each visit. Multivariable longitudinal analyses using mixed effect logistic regression models were conducted to assess the clinical, demographic, and lab features associated with anti TNF-α usage accounting for correlation of repeated measures over time.

Results: The patients were 73% male and 82% of white race, with a mean age of 42.7 years (SD = 13.8), mean disease duration of 18 years (SD = 13.2) and average length of follow up of 4.96 years. TNF-α inhibitor therapy was used in 45% of patients at baseline visit, with increased rate of usage over the 13 year study period (p=0.0001). Multivariable longitudinal associations between independent variables and anti TNF-α usage for the 607 AS patients (Table 1) demonstrated significant associations with greater disease activity in the previous week (by patient global assessment) and higher baseline BASRI scores. On the other hand, patients with disease duration of more than 20 years, those with elevated CRP, or those using NSAIDs or prednisone were less likely to be using anti-TNFα therapy. Male gender, BASFI score, BASDAI score, Center for Epidemiologic Studies Depression (CES-D) scale score, greater pain severity (on a visual analog scale), acetaminophen and tramadol use were not significantly associated with usage of TNF-α inhibitors.

Conclusion: This large, prospective, longitudinal cohort study shows multiple subjective and objective factors associated with anti TNF-α therapy. Patients with longstanding disease, laboratory evidence of inflammation and using anti-inflammatory medications were less likely to be using anti-TNF therapy. Those with more severe radiographic changes at baseline and higher patient global assessment of disease activity were more likely to be using TNF-α inhibitors.

Table 1 Multivariable Associations of Selected Variables on Longitudinal anti TNF-α use (N = 607)

Variable	Odds Ratio (95% CI)	p value
Male	1.22 (0.65, 2.3)	0.54
Disease Duration at baseline ≥ 20yrs	0.44 (0.25, 0.8)	0.007
BASFI ≥ 40	1.11 (0.69, 1.79)	0.67
BASDAI ≥ 40	0.85 (0.55, 1.31)	0.46
CES-D >16	0.93 (0.61, 1.42)	0.75
Elevated CRP	0.3 (0.22, 0.42)	<0.0001
Pain severity score ≥ 50	0.68 (0.43, 1.05)	0.085
Patient Global Assessment ≥ 23	2.22 (1.26, 3.93)	0.006
BASRI baseline≥ 6	2.08 (1.12, 3.85)	0.02
NSAID use	0.32 (0.23, 0.44)	<0.0001
Prednisone use	0.53 (0.27, 1.03)	0.059
Tramadol use	1.5 (0.6, 3.74)	0.38
Acetaminophen use	1.17 (0.79, 1.75)	0.43
Diabetic medication use	0.68 (0.24, 1.94)	0.47
Osteoporosis medication use	1.34 (0.59, 3.03)	0.49

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Abstract Number: 713

Clinical and Imaging Efficacy of Etanercept in Early Non-Radiographic Axial Spondyloarthritis: 104-Week Treatment Results

Maxime Dougados[1], Désirée van der Heijde[2], Joachim Sieper[3], Juergen Braun[4], Gustavo Citera[5], Filip van Den Bosch[6,7], Ronald Pedersen[8], Randi Bonin[9], Heather Jones[10], Lisa Marshall[10], Sameer Kotak[11], Isabelle Logeart[12], Bonnie Vlahos[13], Jack F Bukowski[9] and Walter Maksymowych[14], [1]Rheumatology Department, Hôpital Cochin, Paris, France, [2]Department of Rheumatology, Leiden University Medical Center, Leiden, Netherlands, [3]Medical Department I, Rheumatology, Charité Universitätesmedizin Berlin, Berlin, Germany, [4]Rheumazentrum Ruhrgebiet, Herne, Germany, [5]Rheumatology, Consultorios Reumatológicos Pampa, Buenos Aires, Argentina, [6]Department of Rheumatology, Ghent University Hospital, Ghent, Belgium, [7]Rheumatology, Ghent University Hospital, Ghent, Belgium, [8]Department of Biostatistics, Pfizer, Collegeville, PA, [9]Clinical Affairs, Pfizer, Collegeville, PA, [10]Inflammation Global Medical Affairs, Pfizer, Collegeville, PA, [11]Global Health and Value, Pfizer, New York, NY, [12]Medical Affairs, Pfizer, France, Paris, France, [13]GIPB - Clinical Sciences, Pfizer, Collegeville, PA, [14]Department of Medicine, University of Alberta, Edmonton, AB, Canada

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Background/Purpose: In the multiphase, randomized, placebo (PBO)-controlled EMBARK study (ClinicalTrials.gov identifier: NCT01258738), clinical signs/symptoms and MRI-measured inflammation were evaluated in patients with early, active non-radiographic axial spondyloarthritis (nr-axSpA) after 12 wks of double-blind (DB) treatment with etanercept (ETN)[1]and 92 wks of open-label (OL) ETN.

Methods: Patients who satisfied Assessment of SpondyloArthritis international Society (ASAS) classification criteria for axSpA, but not modified New York radiographic criteria, and who were unresponsive to ≥2 NSAIDs received DB ETN 50 mg/wk or PBO for 12 wks, followed by OL ETN 50 mg/wk (ETN/ETN or PBO/ETN) to wk 104. All patients continued background NSAIDs. Pre-specified analyses of conventional clinical assessments included ASAS, ASDAS (high sensitivity CRP [hs CRP]), BASDAI, and BASFI; the Spondyloarthritis Research Consortium of Canada (SPARCC) scoring method was used for MRI assessment of SI joint and spine inflammation. Post hoc analysis of sustained ASDAS remission (ASDAS <1.3 for ≥24 continuous wks over 104 wks; no missing data) was also conducted. Binary and continuous endpoints were analyzed in all patients with wk-12 efficacy data who continued into the OL period, received ≥1 ETN dose in OL period, and were included in the modified intent-to-treat (mITT) population in the DB period using non-responder imputation (NRI) and last observation carried forward (LOCF) approaches, respectively. A Cochran-Mantel-Haenszel chi-square test and ANCOVA were used for between-group comparisons of binary and continuous endpoints, respectively, at wk 12.

Results: Of 215 randomized patients (DB-phase mITT population), 205 entered and 169 completed the OL phase (ETN/ETN, n=100/n=83; PBO/ETN, n=105/n=86). At the end of the DB phase (wk 12), 33% and 15% of patients in the ETN and PBO groups achieved ASAS40 (P<0.01, between groups); at the end of the OL phase (wk 104), 49% and 51% of patients in the ETN/ETN and PBO/ETN groups achieved this endpoint (table). By wk 104, 51% (51/100) and 58% (61/105) of ETN/ETN- and PBO/ETN-treated patients achieved sustained ASDAS remission. Significantly greater mean reductions from wk 0 to wk 12 in SPARCC SI joint and spinal scores were seen in patients receiving ETN vs PBO (-3.8 vs -0.8, P<0.001; -2.1 vs -1.2, P<0.05); between wk 0 and wk 104, these scores decreased by -5.4 and -3.5 (SI joint) and -1.9 and -0.8(spinal) in patients receiving ETN/ETN and PBO/ETN. From wk 0 to wk 104, 8% and 7% of patients in the ETN/ETN and PBO/ETN groups had serious adverse events; no new safety signals were seen.

Table. Effects of ETN in patients with nr-axSpA in the EMBARK study*				
	DB phase (wk 12)		OL phase (wk 104)	
	ETN	PBO	ETN/ETN	PBO/ETN
Endpoint	% Patients Achieving Endpoints (n/N)			
ASAS40	33.3† (35/105)	14.8 (16/108)	49.0 (49/100)	51.4 (54/105)
ASAS20	52.4‡ (55/105)	36.1 (39/108)	61.0 (61/100)	65.7 (69/105)
ASDAS inactive disease (<1.3)	40.0# (42/105)	17.4 (19/109)	48.0 (48/100)	59.1 (62/105)
BASDAI50	43.8† (46/105)	23.9 (26/109)	57.0 (57/100)	62.9 (66/105)
	Mean (SD) at wk 0/ Mean (SE) D from wk 0 to wk 12		Mean (SE) D from wk 0 to wk 104	
ASDAS-hsCRP	3.0 (0.9) / -1.1# (0.1)	3.0 (1.0) / -0.5 (0.1)	-1.6 (0.1)	-1.7 (0.1)
BASDAI	6.0 (1.8) / -2.0‡ (0.3)	6.0 (1.9) / -1.3 (0.3)	-3.4 (0.2)	-3.9 (0.2)
BASFI	4.2 (2.5) / -1.4‡ (0.2)	3.9 (2.5) / -0.8 (0.2)	-2.4 (0.2)	-2.4 (0.2)
SPARCC SI joint score	8.0 (9.7) / -3.8# (0.7)	7.7 (10.1)/ -0.8 (0.6)	-5.4 (1.0)	-3.5 (0.8)
SPARCC spinal score	4.7 (7.1) / -2.1‡ (0.5)	3.5 (5.6) / -1.2 (0.5)	-1.9 (0.8)	-0.8 (0.4)

*In all patients with wk-12 efficacy data who continued into the OL period, received ≥1 ETN dose in OL period, and were included in the DB mITT population. Binary endpoints at wk 12, LOCF; at wk 104, NRI. Continuous endpoints at wks 12 and 104, LOCF.

†$P<0.01$; ‡$P<0.05$; #$P<0.001$, between-group comparisons.

Conclusion: Patients with early, active nr-axSpA and an inadequate response to NSAIDs demonstrated improvement in clinical and imaging outcomes that was sustained through 104 wks of etanercept treatment.

Reference: 1. Dougados M, et al. *Arthritis Rheum.* 2014:66:2091-102.

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Abstract Number: 714

Baseline MRI and CRP As Predictors of Response to Etanercept in the Management of Patients with Non-Radiographic Axial Spondyloarthritis (nr-axSpA)

Matthew A. Brown[1], Paul A. Bird[2], Philip C. Robinson[3], Philip J. Mease[4], Filip van Den Bosch[5], Christine Surian[6], Zirke Wiid[6], Heather Jones[7], Annette Szumski[8] and Lisa Marshall[7], [1]Translational Research Institute, University of Queensland Diamantina Institute, Brisbane, Australia, [2]University of New South Wales, Sydney, Australia, [3]University of Queensland & Royal Brisbane and Women's Hospital, Brisbane, Australia, [4]Rheumatology Research, Swedish Medical Center, Seattle, WA, [5]Department of Rheumatology, Ghent University Hospital, Ghent,

Belgium, [6]Pfizer Australia, Sydney, Australia, [7]Inflammation Global Medical Affairs, Pfizer, Collegeville, PA, [8]Department of Biostatistics, Pfizer, Collegeville, PA

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Background/Purpose: Treatment with tumor necrosis factor α (TNFα) inhibitors has been shown to be effective in improving disease activity and functional capacity in patients with non-radiographic axial spondyloarthritis (nr-axSpA). Evidence suggests that clinical response to anti-TNFα agents tends to be enhanced in nr-axSpA patients with magnetic resonance imaging (MRI)-documented sacroiliac (SI) joint inflammation and elevated C-reactive protein (CRP). The objective of this study was to determine if MRI sacroiliitis positivity and/or elevated CRP at baseline are predictive of changes in measures of disease activity following etanercept (ETN) treatment in patients with nr-axSpA.

Methods: Patients with symptom duration >3 mths–<5 yrs, meeting ASAS axSpA classification criteria but not radiographic criteria for AS, having BASDAI ≥4, and failure of ≥2 NSAIDs were randomized to 12 weeks of double-blind treatment with ETN 50 mg QW or PBO. Both groups continued stable NSAID therapy. Standard clinical outcomes were assessed in 4 patient subgroups based on MRI sacroiliitis (positive/negative [+/-]) and hsCRP (elevated/normal [+/-]) status at baseline. MRI sacroiliitis positivity was defined according to the ASAS definition of a positive MRI result; elevated hsCRP was based on the ULN and defined as >3 mg/L.

Results: A total of 215 subjects (ETN, n=106; PBO, n=109) were included in these analyses. At baseline, breakdown according to MRI sacroiliitis and CRP status was: MRI-/CRP-, n=26; MRI+/CRP-, n=97; MRI-/CRP+, n=15; MRI+/CRP+, n=77. At Week 12, the primary endpoint of ASAS40 was achieved by more patients receiving ETN than those receiving PBO irrespective of MRI/CRP status at baseline (Table). The greatest ASAS40 response was observed in those patients with MRI+/CRP+ at baseline and the lowest response was seen in the MRI-/CRP- subgroup. Similar observations were made for other clinical endpoints with a markedly higher proportion of MRI+/CRP+ patients achieving BASDAI 50 and clinically important improvement (Δ≥1.1) in ASDAS-CRP/ESR than those in the other MRI/CRP subgroups.

Endpoint		MRI-/CRP-	MRI+/CRP-	MRI-/CRP+	MRI+/CRP+
ASAS40	**ETN**	2/11 (18.2)	10/46 (21.7)	4/7 (57.1)	19/41 (46.3)*
	PBO	0/14 (0)	8/50 (16.0)	0/7 (0)	8/36 (22.2)
ASAS20	**ETN**	6/11 (54.5)	17/46 (37.0)	5/7 (71.4)	27/41 (65.9)
	PBO	2/14 (14.3)	20/50 (40.0)	1/7 (14.3)	16/36 (44.4)
ASDAS-CRP	**ETN**	2/11 (18.2)	17/45 (37.8)*	3/7 (42.9)	32/41 (78.0)†
	PBO	0/14 (0)	9/50 (18.0)	3/8 (37.5)	14/36 (38.9)
ASDAS-ESR	**ETN**	4/11 (36.4)	16/42 (38.1)	3/6 (50.0)	28/40 (70.0)‡
	PBO	1/14 (7.1)	11/50 (22.0)	1/6 (16.7)	10/35 (28.6)
BASDAI50	**ETN**	2/11 (18.2)	14/46 (30.4)	4/7 (57.1)*	26/41 (63.4)†
	PBO	2/14 (14.3)	13/50 (26.0)	0/8 (0)	11/36 (30.6)

*p<0.05, †p<0.01, ‡p<0.001 vs PBO

Values are patients achieving endpoint n/N (%). Values for ASDAS-CRP/ESR are patients achieving clinically important improvement Δ≥1.1

Conclusion: Our analyses suggest that in patients with early, active nr-axSpA and an inadequate response to ≥2 NSAIDs, a combination of MRI positivity and elevated hsCRP at baseline had a positive predictive value on joint inflammation score and clinical response of ETN subjects. A larger sample size is required to definitively test these findings. Further exploratory analyses are being undertaken to determine the predictive value of HLA-B27 status, gender and age on treatment response in each group.

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Abstract Number: 715

Investigating the Role of Vitamin D in Patients with SLE

Briana K. Ply[1] and Diane L. Kamen[2], [1]Medical University of South Carolina, Charleston, SC, [2]Medicine, Medical University of South Carolina, Charleston, SC

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SESSION INFORMATION

Session Date: Sunday, November 8, 2015

Session Title: Systemic Lupus Erythematosus - Clinical Aspects and Treatment Poster Session I

Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose:

Vitamin D is a steroid hormone that not only functions in maintaining calcium and bone metabolism, but also displays immunoregulatory and anti-inflammatory properties. Recent studies demonstrate a correlation between vitamin D insufficiency / deficiency and increased disease activity in SLE, but less is known about the role of vitamin D in specific complications of SLE. In the current case-control study, we aimed to evaluate the relationship between low levels of vitamin D and disease activity in SLE compared to controls.

Methods:

We compared serum 25-hydroxyvitamin D (25(OH)D) levels between diagnosed SLE cases with controls, and examined disease characteristics in relationship to 25(OH)D status among cases. The majority of SLE patients and all controls are Gullah African Americans recruited prospectively into the SLE in Gullah Health (SLEIGH) study, currently ongoing since 2003. SLE disease characteristics were assessed by the SLEDAI scores to measure disease activity and damage, respectively. Patients met at least 4 of the 11 ACR Classification Criteria for SLE and active disease was defined as SLEDAI ≥ 6. Data was utilized from a RedCap database of baseline and follow-up visits and included the following: demographics, medical history, SLEDAI, and 25(OH)D serum levels. Our longitudinal population cohort consisted of 392 diagnosed SLE patients (90.7% women, 74% African American; mean age (visit age) 40.9 +/- 15.4 years, mean age at diagnosis 30.9 +/- 14.5 years) and 127 healthy controls (91.7% women; 100% African American, mean age 43.1 +/- 12.8 years) were used.

Results: Out of the 352 patients, 65.2 patients had vitamin D insufficiency [25(OH)D < 30 ng/ml], 40.3 patients had vitamin D deficiency [25(OH)D < 20 ng/ml], and 10.8 patients had severe vitamin D deficiency [25(OH)D < 10 ng/ml]. In the control group, 92.1 subjects had vitamin D insufficiency, 74.8 subjects had vitamin D deficiency, and 40.9 subjects had severe vitamin D deficiency. 25(OH)D deficiency was significantly associated with African Americans (OR 3.74, 95% CI 1.06-2.83), obese SLE patients (OR 1.56, 95% CI 0.95-2.58), current smokers (OR 9.50, 95% CI 1.96-46.15), age at visit (OR 0.97, 95% CI 0.95-0.99), active disease SLE patients (OR 2.2, 95% CI 18.4-22.2), and SLEDAI score (p=0.03, OR 1.09).

		SLE patients (N = 392)	**Controls (N = 127)**
Mean 25(OH) D		26.0 +/- 14.7	15.9 +/- 13.0
25(OH)D < 30 ng/mL	**P-value**	65.2%	92.1%
African American	<0.01	86.2%	100%
Obese	0.01	39.8%	85.7%
Active SLE	<0.01	25.4%	N/a
25(OH)D < 20 ng/mL	**P-value**	40.3%	74.8%
African American	<0.01	92.3%	100%
Obese	0.004	45.5%	75.0%
Active SLE	<0.01	28.8%	N/a
25(OH)D < 10 ng/mL	**P-value**	10.8%	40.9%
African American	<0.01	94.9%	100%
Obese	0.78	**N/s**	**N/s**
Active SLE	<0.01	36.7%	N/a

Conclusion:

Vitamin D deficiency was prevalent in SLE patients (65.2%) and controls (92.1%). African Americans were significantly more likely to be 25(OH)D deficient (86.2%, $p<0.01$), adjusting for visit age, BMI, gender, smoking status, and disease duration. 25(OH)D concentration is significantly associated with obese SLE patients, current smokers, visit age, and having high disease activity by SLEDAI. Our study suggests that vitamin D deficiency, especially in African American patients, is significantly associated with disease activity in SLE.

Disclosure: B. K. Ply, None; **D. L. Kamen**, None.

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Abstract Number: 716

Urinary Proteomics Identifies Three Novel Biomarkers for Lupus Nephritis Activity: Retinol Binding Protein, Alpha-1-Antichymotrysin and Haptoglobin

Amita Aggarwal[1], Sudhir sinha[2], Ranjan Gupta[3], Liza Rajasekhar[4], Akhilesh Yadav[3], Ramnath Misra[1] and Virsingh Negi[5], [1]Clinical Immunology, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, India, [2]Department of Biochemistry, CSIR-central drug research institute, Lucknow, India, [3]Department of Clinical Immunology, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, India, [4]Department of Rheumatology, Nizam Institute of Medical Sciences, Hyderabad, India, [5]Department of Clinical Immunology, JIPMER, Puducherry, India

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Background/Purpose: Urinary biomarkers have a potential for identification, follow-up and assessment of response to treatment in patients with lupus nephritis. Urinary proteomics can help in identification of new biomarkers. Thus we have used urinary proteomics in order to identify proteins that are seen uniquely in patients with active lupus nephritis.

Methods: Urine samples from patients with active and inactive lupus (SLEDAI<4) were collected, spun and immediately frozen at -80°C. After protein extraction, 2D gels were run followed by MALDI-TOF-TOF of the differentially expressed spots in urine from patients with active nephritis to identify the proteins. Biomarkers identified were measured by ELISA in a large group of patients as well as in urine samples from healthy control, RA and diabetes with proteinuria. In addition patients with active nephritis were followed up and samples collected at 6 and 12 months. Disease assessment was done using SLEDAI. All urinary values were normalized to creatinine excretion. Non-parametric tests were used for analysis

Results: There were 88 patients with SLE (Table) and 20 each of healthy controls, RA and diabetes. In addition samples from 33 patients with active nephritis at 0 and 6 months from 2 different centers were also used for validation.

Among the many spots that were differentially expressed in active lupus nephritis as compared to inactive lupus and healthy control, three were selected and identified as retinol binding protein (RBP), alpha-1-antichymotrypsin (AAC) and haptoglobin (HAP).

Table. Clinical and laboratory parameters of SLE patients (cross sectional analysis)

	Active Nephritis	Active Non-Renal	Inactive Disease
Number	45	24	19
F:M	56:2	19:5	38:1
Median age in years	27 (12 - 50)	28.5 (15 - 50)	28 (14 - 48)
rSLEDAI	8 (4-16)	0(0)	0 (0)
SLEDAI	18 (6-28)	10 (5-20)	0 (0-4)
C3 (mg/dl)	48.5 (16.9 - 125)	66.7 (17.3 - 163)	117 (34.2 - 194)
C4 (mg/dl)	7.8 (5.3 – 55.7)	11.05 (5.3 – 32.2)	24.15 (5.6 – 44.7)
Anti-ds DNA (IU)	200 (13 - >300)	185(<6.25 - >300)	44 (<6.25 - 200)
Urinary protein/creatinine ratio	3.22 (0.12 – 8)	0 (0 – 1.45)	0 (0 – 0.87)
Serum Creatinine (mg/dl)	0.9 (0.4 – 3.87)	0.82 (0.4 – 1.4)	0.8 (0.4 – 1.3)
Normalized RBP	0 (0 – 0.75)	0 (0 – 0.21)**	0 (0 – 0.29)*
Normalized AAC	8.67 (1.4-33.7)	1.65 (.06 – 13.2)**	0.4 (0.08 – 52.7)**
Normalized HAP	2.79 (0.02 – 3.8)	0 (0 – 5.4)**	0 (0 – 2.06)**

p-value *= <0.05 ,**= <0.001 as compared to active nephritis group.

On validation, RBP levels were higher in patients with active lupus nephritis as compared to other groups (Table 1; p<0.05) except patient with diabetes. The urinary levels had good correlation with renal SLEDAI (r=0.284; p<0.008) and SLEDAI(r=0.316; p<0.003).On longitudinal study the levels normalized in majority at 6 and 12 months (p<0.01).

AAC levels were much higher in patients with active nephritis as compared to all other groups (Table ; p<0.001) including diabetics. The urinary levels had moderate correlation with renal SLEDAI(r=0.577; p<0.001) and SLEDAI (r=0.461; p<0.001). On follow up the levels reduced at 6 and 12 months (p<0.01).

Haptoglobin levels were more than 10 fold higher than other groups (Table 1; p<0.001). HAP levels also correlated well with renal SLEDAI (r=0.594; p<0.001) and SLEDAI (r=0.371; p<0.001). In majority the levels fell at 6 and 12 months (p<0.001).

A patient who developed ESRD at 6 months had persistently high levels of all three biomarkers. In the second set of samples of active nephritis all the three biomarkers had a significant fall at 6 months (n=33) (p<0.001) as compared to baseline.

Conclusion: Haptoglobin, retinol binding protein and alpha-1 anti-chymotrypsin are potential biomarkers for lupus nephritis activity.

Disclosure: A. Aggarwal, None; **S. sinha**, None; **R. Gupta**, None; **L. Rajasekhar**, None; **A. Yadav**, None; **R. Misra**, None; **V. Negi**, None.

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Abstract Number: 717

Systemic Lupus Erythematosus and the Evaluation of Poor Sleep: The Sleeps Pilot Study

Alicia Hinze[1], Philip Chu[1], Dany Thekkemuriyil[1], Yo-El Ju[2], Deepali Sen[3], Seth Eisen[1] and Alfred Kim[1], [1]Rheumatology, Washington University School of Medicine, Saint Louis, MO, [2]Neurology, Washington University School of Medicine, Saint Louis, MO, [3]Division of Rheumatology, Washington University School of Medicine, Saint Louis, MO

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Background/Purpose: Sleep disturbances occur in many autoimmune diseases and are ranked highly as an unmet need in patients with SLE. We hypothesized that poor sleep increased SLE disease activity and decreased quality of life (QoL). The aims of this pilot study was to describe in

SLE patients: 1) the prevalence of sleep problems, 2) evaluate the impact of sleep problems on quality of life (QoL), and 3) compare sleep problems with disease activity.

Methods: 27 patients with a confirmed diagnosis of SLE according to the 1997 ACR classification criteria for SLE or the SLICC classification criteria for SLE were enrolled in this cross-sectional study. Comorbid conditions were identified by patient's clinic intake assessment and review of electronic medical records. Patients completed three sleep surveys at the enrollment visit: Pittsburgh Sleep Quality Index (PSQI), Patient Reported Outcomes Measurement Instrument System (PROMIS) short form for Sleep Disturbance, and PROMIS short form for Sleep Related Impairment. Disease activity assessed using SLEDAI2K Responder Index-50 (S2K RI-50). Lupus Impact Tracker (LIT) evaluated patient reported QoL. Student's t-test compared means from independent samples, ANOVA compared categorical variables with normally distributed continuous variables, and Kruskal Wallis compared categorical variables with non-normally distributed continuous variables.

Results: 1) Prevalence of sleep problems in patients with SLE was 85% as defined by PQSI score > 5 (Table 1). SLE patients experience greater sleep disturbance and sleep impairment as measured by the PROMIS surveys when compared to the general population. 2) SLE QoL was significantly higher in patients with good sleep. 3) Increased S2K RI-50 scores were observed in patients with poor sleep, though results did not reach statistical significance.

Conclusion: There is a higher prevalence of poor sleep quality among patients with SLE and this was shown to strongly associated with patient reported QoL. Higher SLE disease activity was seen in patients with poor sleep, though directionality of this association is unable to be determined in this small, cross-sectional study. Longitudinal studies with actigraphy are currently underway to further examine this relationship.

	SLE cohort	Non-SLE controls	p value	
PQSI score (average)	9.96	N/A	N/A	
PROMIS Sleep Disturbance Score (average)	56	50	0.007	
PROMIS Sleep Related Impairment Score (average)	59	50	0.001	
	% SLE pts	S2K RI-50 score (mean)	χ^2	p value
PQSI ≤ 5	15	1.2	1.36	0.24
PQSI > 5	85	3.0		
PROMIS Sleep Disturbance score < 40 (group 1)	7.4	2.0		
PROMIS Sleep Disturbance score ≥ 40 to 60 (group 2)	55.6	2.9	Group 3 vs group 1=1.74	Group 3 vs group 1=0.19
PROMIS Sleep Disturbance score ≥ 60 (group 3)	37.0	5.0	Group 3 vs group 2=2.58	Group 3 vs group 2=0.11

Table 1

Disclosure: A. Hinze, None; **P. Chu**, None; **D. Thekkemuriyil**, None; **Y. E. Ju**, None; **D. Sen**, None; **S. Eisen**, None; **A. Kim**, Kypha, Inc., 2,Amgen, Janssen, Pfizer, 5.

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Abstract Number: 718

Urinary MBL : A Promising Biomarker for Predicting Flare in Lupus Nephritis

Sarit sekhar Pattanaik[1], Madhukara HM[1], Aditya kumar Panda[2], Rashmi ranjan Sahoo[1], Rina Tripathy[3] and Bidyut kumar Das[1], [1]Medicine, SCB Medical College, Cuttack, India, [2]Centre for Life science, Central University of Jharkand, Ranchi, India, [3]Biochemistry, SCB Medical College, Cuttack, India

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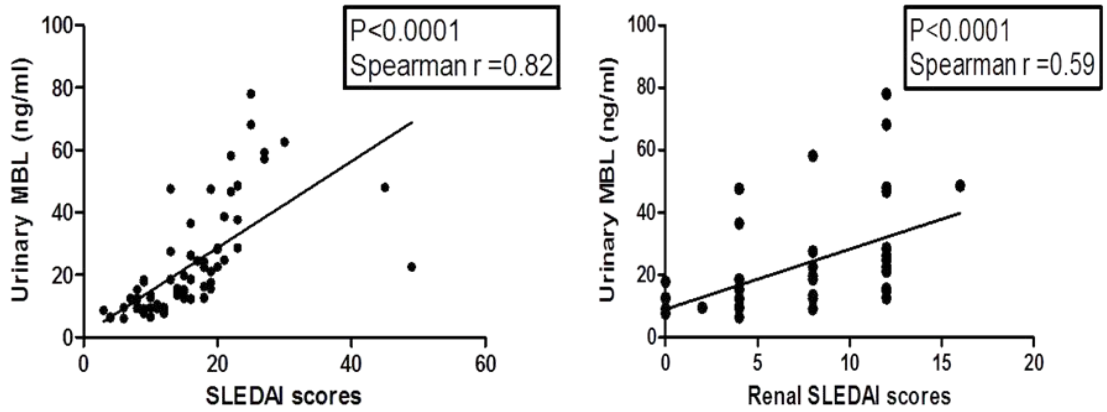
Session Time: 9:00AM-11:00AM

Background/Purpose: Nephritis is the most common cause of mortality and morbidity in SLE, develops in 40 to 70% of cases in 5-10 years with 60% mortality. It is important to detect early involvement and flare for proper management. Renal biopsy, though gold standard for diagnosis, is invasive and cannot be serially repeated for monitoring. Mannose binding lectin (MBL) , member of the collectin type of proteins of PRR family activates complement cascade or acts as opsonin. Studies have shown that plasma MBL levels are elevated in SLE patients and significantly correlate with disease activity of SLE. We hypothesized that urinary MBL would correlate with disease activity in SLE Nephritis.

Methods: In a cross sectional hospital based observational study 65 consecutive cases of SLE nephritis fulfilling the ACR criteria were enrolled. Plasma & urinary MBL levels are measured by ELISA, according to the manufacturer's instructions (R&D systems, Minneapolis, MN, USA). Clinical, serological and other markers of disease activity (C3, C4 and anti-dsDNA) were measured by standard laboratory procedures. Disease activity scores like SLEDAI 2K and renal SLEDAI were calculated. Renal biopsy was done to correlate urinary MBL levels with histopathological staging. Statistical analysis was done using Graphpad prism v5.01.

Results: Urinary MBL was high in patients of SLE Nephritis compared to healthy controls(p=0.01), furthermore patients with nephritis flare (renal SLEDAI >4) had significantly higher levels of plasma & urinary MBL compared to non flare patients(p=0.0008,p=0.004).Urinary MBL showed a strong positive correlation with proteinuria (p<0.0001,r=0.47), SLEDAI (p<0.0001,r=0.82) and renal SLEDAI (p<0.0001,r=0.59), and an inverse correlation was observed between urinary MBL and C3(p=0.03,r=-0.21),C4(p=0.04,r=-0.19). Urinary MBL levels progressively increased with higher histological staging(ISN/RPS)

Conclusion: This is the first study demonstrating a role for urinary MBL in predicting SLE nephritis flare.



Significant positive correlation of Urinary MBL with SLEDAI and renal SLEDAI scores

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Disclosure: S. S. Pattanaik, None; **M. HM**, None; **A. K. Panda**, None; **R. R. Sahoo**, None; **R. Tripathy**, None; **B. K. Das**, None.

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Abstract Number: 719

Cell of Origin of Diffuse Large B-Cell Lymphoma (DLBCL) in Patients with Systemic Lupus Erythematosus (SLE)

Basile Tessier Cloutier[1], Pedro Farinha[2], **Sasha Bernatsky**[3], Eva Baecklund[4], Ann E. Clarke[5], Rosalind Ramsey-Goldman[6], Randy Gascoyne[7] and SLICC Investigators, [1]Clinical Epidemiology, McGill University, Montreal, QC, Canada, [2]Pathology, BC Cancer Agency, Vancouver, BC, Canada, [3]Rheum/Clin. Epid., McGill MUHC/RVH, Montreal, QC, Canada, [4]Rheumatology, Department of Medical Sciences, University Hospital, Uppsala, Sweden, [5]Immunology/Epidemiology, Montreal General Hospital, Montreal, QC, Canada, [6]Fsm # M300, SLICC, Chicago, IL, [7]Pathology, University of British Columbia, BC Cancer Agency, Vancouver, BC, Canada

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Background/Purpose:

SLE has been consistently associated with an increased incidence of malignant lymphoma, especially the DLBCL subtype. Since the last WHO classification of 2008 DLBCL are now further divided, based on the cell-of-origin (COO) subtypes. The two major subtypes were defined by gene expression profiling of fresh frozen (FF) samples as germinal centre B-cell-like (GCB) and activated B-cell-like (ABC). Using tissue

microarray (TMA) and immunohistochemistry (IHC) in diagnostic formalin fixed paraffin embedded (FFPE) in biopsies, COO is routinely defined as GCB or non-GCB. The ABC/non-GCB subtype presents the worse prognosis and has previously been associated with rheumatoid arthritis. Our objective was to compare the frequency of non-GCB and GCB subtypes in DLBCL within a cohort of patients diagnosed with lupus.

Methods:

From a multi-centre cohort, 13 cases of DLBCL in lupus patient were identified, for which tissue and pathologic diagnosis were available. Tissue microarrays (TMA) were then built and submitted to Vancouver where IHC and scoring was performed. Immunostains were performed including lineage markers (CD20, CD3) and COO markers CD10, BCL6, MUM1, GCET1 and FOXP1. The COO was determined using both the Hans and Choi algorithms.

Results:

Eleven cases of DLBCL in patients with established SLE could be included for analysis. The diagnosis of DLBCL was confirmed by a reference hematopathologist. In the SLE DLBCL cases, BCL6 was positive in 5/11 (45%), CD10 in 2/11 (18%), FOXP1 7/11 (64%), in GCET1 0/11 (0%) and MUM1 4/11 (36%). Of the SLE DLBCL cases, 7/11 (64%) were classified as non-GCB and 4/11 (36%) were classified as GCB. This contrasts with a recent analysis of COO based on a population-based registry study of DLBCL in British Columbia (n = 348) using the Hans algorithm, with 59% GCB and 41% non-GCB.

Conclusion:

In conclusion, DLBCL arising in patients with a prior history of SLE show an enrichment of non-GCB cell-of-origin subtype, mimicking data seen in rheumatoid arthritis. Although a small sample size, these findings suggest that like lymphoma development in the face of chronic inflammation, DLBCL arising in SLE patients and related autoimmune disorders tends to be enriched in the ABC/non-GCB subtype. These findings have implications as we enter an era of COO-specific treatments based on improved biological understanding. Further studies are planned to increase the size of the cohort.

Disclosure: B. Tessier Cloutier, None; **P. Farinha**, None; **S. Bernatsky**, None; **E. Baecklund**, None; **A. E. Clarke**, None; **R. Ramsey-Goldman**, None; **R. Gascoyne**, None.

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Abstract Number: 720

Biomarkers in Lupus Nephritis: The Possible Role of Serum Cystatin C, Serum β2-Microglobulin, Urinary Î±1-Microglobulin and Albuminâ„Creatinine Ratio

Luca Petricca[1], Elisa Gremese[1], Laura Messuti[1], Franca Forni[2], Clara Di Mario[1], Marcin Nowik[1], Maria Rita Gigante[1], Gerardo Marino[3] and Gianfranco Ferraccioli[1], [1]Division of Rheumatology, Institute of Rheumatology, Catholic University of the Sacred Heart, Rome, Italy, [2]Department of Laboratory Medicine, Catholic University of the Sacred Heart, Rome, Italy, [3]Division of Rheumatology, Institute of Rheumatology and Affine Sciences, Catholic University of the Sacred Heart, Rome, Italy

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Background/Purpose: Lupus nephritis (LN) may severely affect SLE prognosis and an effective treatment of LN requires correct diagnosis, timely intervention and early treatment of any disease relapse. Biomarkers able to early identify disease relapse are still lacking. The aim of the study was to evaluate if some serum (cystatin C, β2-microglobulin) and urinary (α1-microglobulin and ACR- albumin/creatinine ratio) parameters can be more useful than the conventional parameters in monitoring lupus nephritis and in predicting exacerbations of renal involvement in SLE.

Methods: 73 consecutive SLE patients with renal involvement (active or inactive at baseline) were enrolled. Serum cystatin C and β2-microglobulin, and urinary α1-microglobulin and ACR values were evaluated at baseline (T0) and after 3 (T3) and 6 (T6) months of follow-up, along with routine clinical and laboratory examination. Renal relapse was defined as an arising of 24 hours proteinuria up to 500 mg and/or appearance of active urinary sediment and/or microematuria (>5 red blood cells/hpf).

Results:

Of the 73 LN patients (86.3% female, mean age 38.5±12.0 years, disease duration 13.0±8.8 years), 49 had inactive and 24 active renal disease at baseline. Patients with active nephritis had higher SLEDAI ($p<0.01$) and 24 hours proteinuria ($p<0.01$) values, as expected, as well as higher

levels of cystatin (1.3±0.8 vs 1.0±0.6 mg/l, p=0.01), α1-microglobulin (22.3±82.2 vs 1.2±4.3 mg/l, p=0.005) and ACR (299.5±432.2 vs 76.7±241.2 mg/g, p<0.01) with respect to patients with inactive LN.

During the follow-up, 11 out of the 49 patients with inactive LN at T0 presented some renal relapse. The 11 patients relapsed during the six-month of follow-up showed at baseline higher values of cystatin C (1.6±0.9 vs 0.9±0.2 mg/l, p=0.001), serum β2-microglobulin (4.0±2.6 vs 2.0±0.8 mg/dl, p=0.001), urinary α1-microglobulin (5.2±8.2 vs 0.0±0.2 mg/l, p<0.01) and ACR (279.9±440.1 vs 6.9±12.0 mg/g, p<0.01), than patients with stable inactive nephritis, while no differences were found in traditional parameters (C3 levels, anti-DNA title and/or positivity, 24 hours proteinuria, SLEDAI, serum creatinine).

Conclusion: This study seems to show that these biomarkers can be integrated to the conventional parameters for predicting lupus nephritis exacerbations.

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Abstract Number: 721

Geographic Differences in Demographics, Clinical Characteristics, and Standard of Care in Multinational Studies of Patients with Moderate to Severe Systemic Lupus Erythematosus

Richard Furie[1], M Khamashta[2], L Wang[3], J Drappa[3], W Greth[3] and G Illei[3], [1]Division of Rheumatology, North Shore - LIJ Health System, New York, NY, [2]Graham Hughes Lupus Research Laboratory, The Rayne Institute, St Thomas' Hospital, London, United Kingdom, [3]MedImmune, Gaithersburg, MD

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Background/Purpose: Most randomized controlled trials (RCTs) in systemic lupus erythematosus (SLE) include stratification factors to ensure a balanced allocation of subgroups that might respond differently to therapeutic interventions. Strata could include baseline disease activity, baseline corticosteroid dosage, or race. Despite such stratification, geographic differences have influenced responses in some studies. Sifalimumab and anifrolumab, fully human, IgG1 κ monoclonal antibodies, have each been investigated in Phase II studies in SLE (NCT01283139 and NCT01438489). Sifalimumab binds to and neutralizes the majority of IFN-α subtypes, while anifrolumab binds to the type I IFN receptor and thus prevents signaling by any of the type I IFNs. This study analyzed potentially impactful differences in baseline characteristics between geographic regions.

Methods: This *post-hoc* analysis first combined data from the two studies and then compared the baseline characteristics of the region with an expected high placebo plus standard of care response rate (Region 1 [R1]: Central America, South America, Eastern Europe, Asia) to those of the region with an expected low placebo plus standard of care response rate (Region 2 [R2]: North America, Western Europe, South Africa). Eligibility criteria, similar for the two studies, resulted in the enrollment of patients with moderate to severe SLE with inadequate responses to standard of care. Patients with severely active lupus nephritis or severe neuropsychiatric SLE were excluded.

Results: Of the 736 randomized and dosed patients, 68.9% were from R1, and 31.1% were from R2. There were no significant baseline differences between regions in mean SLEDAI-2K, BILAG 2004 composite, or Physician's Global Assessment scores. However, differences were seen in other clinical characteristics as well as demographic and background medication use (table).

Conclusion: SLE patients enrolled in RCTs from different geographic regions had notable differences in some demographic and baseline clinical characteristics as well as in standard of care medications. These differences may impact the analysis of the treatment response to standard of care and/or investigational drug. Therefore, the possibility of an imbalance in patients recruited from regions with expected high or low standard of care response should be considered in the design of SLE RCTs.

Demographics, Clinical Characteristics, and Standard of Care Medications

	Region 1 (N=507)	Region 2 (N=229)	*P*-value
Age, years, mean (SD)	38.0 (11.8)	43.0 (11.4)	<0.001
Body mass index, kg/m^2, mean (SD)	25.2 (5.0)	28.1 (7.3)	<0.001
Disease duration, months, mean (SD)	81.8 (75.8)	131.2 (92.4)	<0.001
SLICC/ACR Damage Index, mean (SD)	0.5 (0.9)	1.1 (1.5)	<0.001
Double-stranded DNA antibodies, %	85.0	67.3	<0.001
Hypocomplementemia, %			
C3	44.8	33.6	0.005
C4	29.0	18.3	0.002
Background medications, %			
Azathioprine	28.8	12.2	<0.001
Mycophenolate	5.1	21.0	<0.001
Corticosteroids	94.1	65.1	<0.001
Prednisone (or equivalent) ≥10 mg/d	66.9	36.7	<0.001

ACR, American College of Rheumatology; DNA, deoxyribonucleic acid; SD, standard deviation; SLICC, Systemic Lupus International Collaborative Clinics

P-values calculated using 2 sample t-test for comparison of means and chi-square test for comparison of percentages.

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Biomarkers/Pathways Discovery of Lupus Nephritis By Urine Proteomics

Michelle Petri[1], Wei Fu[2], Adnan Kiani[1], Lauren DeVine[1], Conover Talbot Jr.[1] and Robert Cole[1], [1]Johns Hopkins University School of Medicine, Baltimore, MD, [2]Rheumatology, Johns Hopkins University School of Medicine, Baltimore, MD

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Background/Purpose: We have previously validated several urine proteomic biomarkers for Lupus Nephritis (osteoprotegerin, MCP-1, VCAM-1 and urine TWEAK). In this discovery effort we looked for urine biomarkers for Class IV and V Lupus Nephritis.

Methods: This analysis is based on specimens from six different SLE patients, three with Class IV Lupus Nephritis, two with Class V and one SLE control. Protein differences in urine samples were determined by quantitative proteomics using TMT 6-plex isobaric mass tags after immunoaffinity depletion of albumin on an Agilent MAR6 column. Raw spectrum-level values were extracted and filtered to less than 1% FDR and 30% isolation interference using Thermo Scientific Proteome Discoverer software. These data were imported into the Partek Genomics Suite for normalization and further analyses.

Results: Some urine biomarkers such as **afamin and orosomucoid 1(alpha-1-acid glycoprotein)** were consistently higher in Class IV/V,

compared to control**.** Some other biomarkers such as **apolipoprotein A-I and transthyretin** were only higher in Class V, which might allow them to serve as a biomarker to distinguish Class V from IV. Some of the biomarkers discovered might not be surprising. For example, several hemoglobin urine biomarkers (**HBG2, HBB, etc.**) were found to be higher in Class V, but are common in any patient with poor renal function.

Based on these lower/higher levels of urine proteins, possible pathways potentially important in Lupus Nephritis were identified using Ingenuity Pathway Analysis software. Table 2 presents the most likely pathways. The second column shows the protein modules associated in the pathway. The third column shows the comparisons from which the pathway was identified.

Table 1 Biomarkers identified in different comparisons

	Gene Name (NCBI)	*IV vs. Cont*	*V vs. Cont*	*IV vs. V*	*IV and V vs. Cont*
	Fc fragment of IgG, low affinity IIIa, receptor (CD16a)	Lower in IV			
CADM2	**cell adhesion molecule 2**	Lower in IV			
APOC1	**apolipoprotein C-I**		Higher in V		
LCP1	**lymphocyte cytosolic protein 1 (L-plastin)**	Higher in IV		IV higher than V	
ADIPOQ	**adiponectin, C1Q and collagen domain containing**			IV higher than V	
CFHR1	**complement factor H-related 1**	Higher in IV	Higher in V		Higher in Cases
AZGP1	**alpha-2-glycoprotein 1, zinc-binding**	Higher in IV	Higher in V		Higher in Cases
HMGN2	**high mobility group nucleosomal binding domain 2**			IV higher than V	
PGLYRP2	**peptidoglycan recognition protein 2**			IV higher than V	
HYAL1	**hyaluronoglucosaminidase 1**		Lower in V		Lower in Cases
PZP	**pregnancy-zone protein**	Higher in IV	Higher in V		Higher in Cases
AFM	**afamin**	Higher in IV	Higher in V		Higher in Cases
TTC26	**tetratricopeptide repeat domain 26**			IV higher than V	
ORM1	**orosomucoid 1**	Higher in IV	Higher in V		Higher in Cases
FCGRT	**Fc fragment of IgG, receptor, transporter, alpha**	Lower in IV			Lower in Cases
MPO	**myeloperoxidase**	Higher in IV			
SERPINA6	**serpin peptidase inhibitor, clade A (alpha-1 antiproteinase, antitrypsin), member 6**		Higher in V		Higher in Cases
CARD18	**caspase recruitment domain family, member 18**		Lower in V		
BCHE	**butyrylcholinesterase**	Higher in IV			Higher in Cases
ORM2	**orosomucoid 2**	Higher in IV	Higher in V		Higher in Cases
APOA1	**apolipoprotein A-I**		Higher in V	IV lower than V	
MB	**myoglobin**		Higher in V		
KRT85	**keratin 85, type II**			IV lower than V	
SELL	**selectin L**	Higher in IV			Higher in Cases
S100A12	**S100 calcium binding protein A12**			IV higher than IV	
MUC5B	**mucin 5B, oligomeric mucus/gel-forming**		Higher in V	IV lower than V	
APOA2	**apolipoprotein A-II**			IV lower than V	
FUCA2	**fucosidase, alpha-L- 2, plasma**		Higher in V		

TTR	**transthyretin**		Higher in V		Higher in Cases
CA1	**carbonic anhydrase I**		Higher in V	IV lower than V	Higher in Cases
UBE2V2	**ubiquitin-conjugating enzyme E2 variant 2**			IV lower than V	
CD300LF	**CD300 molecule-like family member f**		Higher in V		
AHSP	**alpha hemoglobin stabilizing protein**		Higher in V		
HBG2	**hemoglobin, gamma G**		Higher in V	IV lower than V	
ZNF648	**zinc finger protein 648**		Higher in V	IV lower than V	
HBB	**hemoglobin, beta**		Higher in V	IV lower than V	
KRT33B	**keratin 33B, type I**		Higher in V	IV lower than V	
SERPINA1	**serpin peptidase inhibitor, clade A (alpha-1 antiproteinase, antitrypsin), member 1**			IV higher than IV	
HBD	**hemoglobin, delta**		Higher in V		
RBP2	**retinol binding protein 2, cellular**	Higher in IV			
KRT86	**keratin 86, type II**			IV lower than V	
HBA1	**hemoglobin, alpha 1**			IV lower than V	
KRT36	**keratin 36, type I**			IV lower than V	
POMC	**proopiomelanocortin**		Lower in V		
FABP4	**fatty acid binding protein 4, adipocyte**			IV higher than IV	

Table 2 Pathways identified by comparing Class IV and V with control

Name	*Modules*	*Associated Comparisons*
Acute Phase Response Signaling	CP,ORM2,ITIH3,CRP,A2M, C4A/C4B, ORM1,RBP2, SERPINA1,IL1RAP,FTL,TTR,ALB	IV, V
Production of Nitric Oxide and Reactive Oxygen Species in Macrophages	LYZ,APOB,ORM1,MPO,ORM2, SERPINA1,APOC1,ALB	IV,V
LXR/RXR Activation	LYZ,C4A/C4B,APOB,ORM1,ORM2, SERPINA1,IL1RAP,APOC1,A1BG,ALB,TTR	IV, V
IL-12 Signaling and Production in Macrophages	LYZ,APOB,ORM1,ORM2,SERPINA1, APOC1,ALB	IV,V
FXR/RXR Activation	C4A/C4B,APOB,ORM1,ORM2, SERPINA1,APOC1,A1BG,ALB,TTR	IV,V
Atherosclerosis Signaling	LYZ,APOB,ORM1,ORM2,SERPINA1, APOC1,VCAM1,ALB	IV,V
LPS/IL-1 Mediated Inhibition of RXR Function	GSTM1,FABP4,IL1RAP,GSTA2, APOC1,ALDH1A3,FABP2	IV,V
Clathrin-mediated Endocytosis Signaling	LYZ,APOB,ORM1,ORM2, SERPINA1,APOC1,TFRC,ALB	IV,V
Melatonin Degradation III	MPO	IV,V
Glutathione-mediated Detoxification	GSTM1,GSTA2	IV,V
Retinoate Biosynthesis I	RBP2,ALDH1A3	IV
Pyrimidine Ribonucleotides De Novo Biosynthesis	NUDT5,CMPK1	IV
Pyrimidine Ribonucleotides Interconversion	NUDT5,CMPK1	IV
RAR Activation	RBP2,RPL7A,ALDH1A3	IV
PXR/RXR Activation	GSTM1,GSTA2	IV
Xenobiotic Metabolism Signaling	GSTM1,GSTA2,FTL,ALDH1A3	IV
Extrinsic Prothrombin Activation Pathway	FGB,SERPINC1,FGG	V
Lymphotoxin β Receptor Signaling	VCAM1,DIABLO	V
Coagulation System	A2M,FGB,SERPINC1,FGG	V
IL-17 Signaling	CRP,MUC5B	V

Conclusion: In this discovery effort several interesting pathways were identified that might be important in Lupus Nephritis overall or differentially in Class IV versus Class V. In particular, reactive oxygen species, IL-12, LPS/IL-1, IL-17, atherosclerosis and coagulation pathways might be novel targets. Validation of this discovery effort is underway.

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Oral Ulcers in Systemic Lupus Erythematosus: Characterization and Clarification of an Important Clinical Manifestation

Robert Durcan[1], Wei Fu[2] and Michelle Petri[3], [1]Beaumont Hospital, Dublin, Ireland, [2]Rheumatology, Johns Hopkins University School of Medicine, Baltimore, MD, [3]Johns Hopkins University School of Medicine, Baltimore, MD

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Background/Purpose: Oral ulcers (OU) are a common manifestation of systemic lupus erythematosus (SLE). They are included in both classification criteria and disease activity indices. Despite this, there has been little done to further characterize them. This work was undertaken to evaluate the disease specific features associated with OU in SLE. We then sought to specifically evaluate a subgroup of individuals regarding the patient reported features of OU in SLE.

Methods: The prevalence of OU in a large SLE cohort was examined and their relationship to the other SLICC criteria explored using logistic regression. Phase 2 involved the administration of a questionnaire outlining the characteristics, location, duration and number of OU.

Results: There were 2417 SLE patients in the initial analysis. The frequency of OU in the cohort was 51.6%. Male gender (OR=0.48, 95% CI =0.35, 0.66) and African-American race (OR=0.52, 95% CI = 0.33, 0.80) were negatively associated with oral ulcers. The relationship between OU and the other SLICC clinical and laboratory criteria, after adjusting for ethnicity, are as outlined in Table1.

Oral ulcers were positively associated with cutaneous lupus, alopecia and arthritis. They were associated with pleurisy but not pericarditis. Oral ulcers were negatively associated with “seropositivity” (low complement, high anti-dsDNA) and renal lupus. 123 patients were surveyed (3 could give no details). 68 (56.6%) had as history of OU. Mean duration of OU was 7.43 days (range: 1 to 90). Regarding location, 22 (32.4%) described them on their tongue, 23 (33.8%) on the palate and 50 (73.5%) on their buccal mucosa. 34 (50%) described crops of OU. Addressing pain, 54 of the 68 patients provided information. 34 (63%) said that they only had painful episodes, 12 (22%) had only painless episodes, and 8 (15%) have both.

Table 1 Relationship between OU and the other SLE manifestations.

SLICC Criteria		History of OU (%)	No OU (%)	Odds ratio	95% CI	P value (unadjusted)	P value (adjusted for ethnicity)
Acute cutaneous lupus	Malar Rash	55.6	42.4	1.58	(1.34,1.86)	<.0001	<.0001
	Bullous Lupus	1.1	0.4	2.61	(0.91,7.43)	0.0883	0.0731
	Photosensitivity	60.7	43.3	1.84	(1.56,2.17)	<.0001	<.0001
Chronic cutaneous lupus	Discoid Lupus	20.4	18.4	1.38	(1.12,1.71)	0.2124	0.0027
Alopecia		60.9	49.2	2.11	(1.77,2.52)	<.0001	<.0001
Arthritis		74.2	69.3	1.32	(1.1,1.59)	0.0078	0.0024
Serositis	Pleurisy	46.9	39.6	1.39	(1.18,1.64)	0.0003	0.0001
	Pericarditis	22.1	21.8	1.12	(0.92,1.36)	0.8705	0.2655
Renal	Proteinuria	37.8	50.7	0.68	(0.57,0.8)	<.0001	<.0001
Neurologic	Seizures	9.5	9.5	1.01	(0.77,1.34)	0.9906	0.9255
	Acute Confusional State	5.0	3.2	1.60	(1.05,2.43)	0.0259	0.0297
Hemolytic Anemia		8.5	11.7	0.75	(0.57,0.99)	0.0120	0.0393
Leukopenia		46.5	45.4	1.16	(0.99,1.37)	0.6081	0.0718
Thrombocytopenia		19.2	21.6	0.89	(0.73,1.09)	0.1493	0.2493
ANA		96.2	96.9	0.88	(0.56,1.38)	0.3328	0.5775
Anti-dsDNA		58.2	65.2	0.77	(0.65,0.91)	0.0004	0.0022
Anti-Sm		19.0	22.0	1.01	(0.82,1.25)	0.0753	0.9244
Anti-phospholipid	LAC	25.7	27.1	0.88	(0.73,1.07)	0.4738	0.1977
	Anticardiolipin	48.6	48.5	0.99	(0.84,1.16)	0.9683	0.8645
	Anti-beta 2 gly	27.8	30.3	0.85	(0.67,1.07)	0.2859	0.1682
Low complement	C3	51.1	58.7	0.78	(0.66,0.92)	0.0002	0.0034
	C4	45.7	49.4	0.88	(0.75,1.04)	0.0683	0.1274
Coombs		17.3	23.4	0.75	(0.60,0.94)	0.0008	0.0133

Conclusion: Mouth ulcers occur in 51% of SLE patients. They are negatively associated with “seropositivity” (meaning anti-dsDNA and low complement) and with renal lupus. Surprisingly, they are associated with pleurisy but not pericarditis. The majority occur on the buccal mucosa. In contradistinction to the ACR criteria, 63% of patients have painful episodes.

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Abstract Number: 724

Mycophenolate Mofetil in Non-Renal Manifestations of Systemic Lupus Erythematosus. an Observational Cohort Study

Konstantinos Tselios[1], Dafna Gladman[2], Jiandong Su[2] and Murray Urowitz[2,3], [1]Medicine, University of Toronto, Toronto Western Hospital, Toronto, ON, Canada, [2]Rheumatology, University of Toronto, Toronto Western Hospital, Toronto, ON, Canada, [3]Rheumatology, U of Toronto, Toronto Western Hospital, Toronto, ON, Canada

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Background/Purpose: Mycophenolate mofetil (MMF), along with corticosteroids, is considered as the standard of care in lupus nephritis (LN); however, its efficacy in extra-renal manifestations of systemic lupus erythematosus (SLE) is less well known. This study aimed to determine its effectiveness in non-renal lupus.

Methods: One hundred seventy seven SLE patients (diagnosis according to the 1997 ACR criteria or 3 criteria and a compatible renal biopsy) were enrolled; 105 for whom MMF was introduced for active LN (age 35.6±10.7 years, disease duration 8.9±7.8 years) and 72 for extra-renal manifestations (age 38.6±11.7 years, disease duration 11.7±9.2 years). The main indication for MMF initiation was based on the respective SLE Disease Activity Index (SLEDAI-2K) element that was present at that time. Patients were subdivided according to the major non-renal manifestation (central nervous system involvement, vasculitis, musculoskeletal features, skin disease, serositis, immunological and hematological abnormalities). Improvement was defined as the absence of the initial clinical or laboratory manifestation after 6 and 12 months. The statistical software SAS 9.3 was used for analysis; $p<0.05$ was considered significant.

Results: Cumulatively, the initial clinical manifestation or hematological abnormality was resolved in 42/72 non-renal patients (58.3%) after 6 months and in 45/72 (62.5%) after 12 months. Corticosteroid dose was reduced in 44/72 (61.1%, $p<0.001$) patients (mean dose 18.4±12.6mg/day at baseline to 12.1±9.0mg/day after 12 months, $p<0.05$). In renal patients, 40 (38.1%) had complete resolution of the extra-renal manifestation after 6 months, while 53 (50.5%) achieved complete response after 12 months. Prednisone dose was reduced in 73/105 patients (69.5%) after 12 months (mean dose 29.2±16.6mg/day at baseline to 15.3±9.7mg/day, $p<0.001$). Details on the improvement rates of the different clinical features are shown in the table.

		CNS	VASC	MSK	Renal	Skin	SERO	IMMUNO	HEMA
Non-renal patients (n=72)	Baseline	11	2	19	0	27	8	45	10
	6 months	8 (72.7%)	2 (100%)	11 (57.9%)	0 (0%)	7 (25.9%)	6 (75%)	11 (24.4%)	8 (80%)
	12 months	8 (72.7%)	1 (50%)	14 (73.7%)	0 (0%)	11 (40.7%)	5 (62.5%)	12 (26.7%)	6 (60%)
Renal patients (n=105)	Baseline	7	6	11	105	30	7	85	3
	6 months	3 (42.9%)	6 (100%)	10 (90.9%)	20 (19%)	10 (33.3%)	4 (57.1%)	15 (17.6%)	2 (66.7%)
	12 months	6 (85.7%)	6 (100%)	11 (100%)	29 (27.6%)	16 (53.3%)	7 (100%)	15 (17.6%)	2 (66.7%)

CNS: central nervous system, VASC: vasculitis, MSK: musculoskeletal (arthritis, myositis), SERO: serositis, IMMUNO: immunological abnormalities (low C3/C4 and/or increased anti-DNA titers, HEMA: hematological abnormalities.

Conclusion: MMF is an efficacious therapeutic approach for the management of refractory non-renal manifestations of SLE in 6 and 12 months, leading to complete resolution of the initial clinical manifestation in more than half of the patients and significant reduction in corticosteroid dose.

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Abstract Number: 726

Associates of Pleurisy of Pericarditis in Systemic Lupus Erythematosus (SLE)

Seungwon Ryu[1] and Michelle Petri[2], [1]Konkuk University School of Medicine, Seoul, South Korea, [2]Johns Hopkins University School of Medicine, Baltimore, MD

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Background/Purpose: Serositis is one of the classification criteria for systemic lupus erythematosus and a common type of extra renal flare. Comparison of associates of pleurisy and pericarditis separately has not been previously done in Caucasians and African Americans.

Methods: 2,390 SLE patients in the Hopkins Lupus Cohort were analyzed for demographic, clinical and serologic associates of pleurisy or pericarditis, defined using the SELENA revision of the SLE Disease Activity Index (SLEDAI). We reported associates with a p-value of less than 0.05 for both and for pleurisy or pericarditis separately.

Results: 43% had pleurisy and 22% had pericarditis. African-American ethnicity was associated with pericarditis. Renal lupus and seizure were associated only with pericarditis, whereas arthritis was associated only with pleurisy. Only pericarditis was associated with anti-RNP and anti-Sm. Both pleurisy and pericarditis are associated with anti-dsDNA and low complement.

Table 1. Demographic Characteristics Associated with Serositis in SLE (p<0.0001)

Characteristics	Subgroup	Negative	Positive	OR	95% CI	P-value
Factors significantly associated with only Pericarditis						
African-American ethnicity	Pericarditis	38.54%	53.64%	1.85	1.51-2.26	<0.0001
Factors significantly associated with only Pleurisy						
Age at SLE Diagnosis	Pleurisy	33.44±13.54	31.03±12.01			<0.0001
Factors significantly associated with both Pericarditis and Pleurisy						
None						

Table 2. Clinical and Laboratory Features Associated with Serositis in SLE (p<0.0001)

Characteristics	Subgroup	Negative	Positive	OR	95% CI	P-value
Factors significantly associated with only Pericarditis						
Proteinuria	Pericarditis	40.37%	57.36%	1.99	1.63-2.42	<0.0001
Nephrotic Syndrome	Pericarditis	15.33%	26.78%	2.02	1.60-2.55	<0.0001
Seizure	Pericarditis	8.23%	14.31%	1.86	1.39-2.50	<0.0001
Factors significantly associated with only Pleurisy						
Arthritis	Pleurisy	66.32%	79.48%	1.97	1.63-2.37	<0.0001
Arthralgia	Pleurisy	87.66%	95.85%	3.25	2.30-4.60	<0.0001
Malar Rash	Pleurisy	45.75%	54.26%	1.41	1.20-1.65	<0.0001
Factors significantly associated with both Pericarditis and Pleurisy						
Fever	Pericarditis	32.60%	50.76%	2.13	1.75-2.60	<0.0001
	Pleurisy	29.39%	45.95%	2.04	1.72-2.42	<0.0001
Lymphadenopathy	Pericarditis	28.35%	41.79%	1.81	1.48-2.22	<0.0001
	Pleurisy	26.34%	37.78%	1.7	1.43-2.02	<0.0001
Raynaud's Syndrome	Pericarditis	48.90%	63.34%	1.81	1.48-2.21	<0.0001
	Pleurisy	47.08%	58.37%	1.58	1.34-1.86	<0.0001
Hemolytic Anemia	Pericarditis	8.34%	16.37%	2.15	1.61-2.87	<0.0001
	Pleurisy	7.91%	12.87%	1.72	1.31-2.26	<0.0001

Table 3. Serologic Features Associated with Serositis in SLE (p<0.0001)

Characteristics	Subgroup	Negative	Positive	OR	95% CI	P-value
Factors significantly associated with only Pericarditis						
Anti-RNP	Pericarditis	25.89%	37.82%	1.74	1.41-2.14	<0.0001
Anti-Sm	Pericarditis	17.97%	28.80%	1.85	1.47-2.32	<0.0001
Factors significantly associated with only Pleurisy						
None						
Factors significantly associated with both Pericarditis and Pleurisy						
Anti-DNA	Pericarditis	58.74%	73.09%	1.91	1.54-2.36	<0.0001
	Pleurisy	58.01%	66.99%	1.47	1.24-1.74	<0.0001
Low C3	Pericarditis	51.86%	65.46%	1.76	1.44-2.15	<0.0001
	Pleurisy	50.81%	60.10%	1.46	1.24-1.72	<0.0001
Low C4	Pericarditis	44.85%	57.63%	1.67	1.38-2.04	<0.0001
	Pleurisy	43.77%	52.75%	1.43	1.22-1.69	<0.0001
ESR	Pericarditis	71.71%	83.85%	2.05	1.59-2.64	<0.0001
	Pleurisy	70.40%	79.51%	1.63	1.35-1.98	<0.0001

Conclusion: Pleurisy is more common than pericarditis. There are specific associates of pericarditis (African-American ethnicity, renal lupus, seizure, anti-RNP and anti-Sm) and pleurisy (arthritis). This challenges the dogma that serositis has one mechanism in SLE.

Disclosure: S. Ryu, None; **M. Petri**, None.

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Abstract Number: 727

Repository Corticotropin Injection (H.P. Acthar® Gel) Attenuates Disease Activity in Patients with Persistently Active Systemic Lupus Erythematosus (SLE) Requiring Corticosteroids

Richard Furie[1], Maya Das[2], Daner Li[2], Shanique Smythe[2], Ericka Mathura[2] and Patrice Becker[2], [1]Division of Rheumatology, North Shore LIJ Health System, Lake Success, NY, [2]Research & Development, Mallinckrodt Pharmaceuticals, Ellicott City, MD

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Session Date: Sunday, November 8, 2015

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Session Type: ACR Poster Session A

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Background/Purpose:

Melanocortins such as corticotropin and alpha-MSH may modulate steroid-independent immune responses relevant to SLE pathophysiology. We previously reported that repository corticotropin injection (RCI), an FDA approved melanocortin therapeutic, attenuated B cell development, circulating autoantibody titers, and disease activity in a murine SLE model, supporting the efficacy of RCI as a treatment alternative for patients with SLE.

Methods:

This 8 wk double-blind randomized placebo-controlled study assessed clinical efficacy of RCI in patients with persistently active SLE despite moderate dose corticosteroids. The primary objective was to explore the effects of RCI on the Hybrid SLE Disease Activity Index (hSLEDAI), with key secondary objectives to evaluate effects on British Isles Lupus Assessment Group-2004 (BILAG), Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI), and 28-joint count score. Patients were eligible if they had persistently active SLE (hSLEDAI >2) with arthritis and/or skin involvement and BILAG A or B in mucocutaneous and/ or musculoskeletal systems despite 7.5-30 mg prednisone daily for ≥ 4 wk prior to screening. 38 subjects were randomized to receive SC RCI 80 U every other day (RCI80; n=13) or 40 U daily (RCI40; n=13), or SC Placebo gel (n=12). Study medication was maintained at the assigned regimen for 4 wk, then tapered over 4 wk to 2x/wk administration of the assigned dose. Clinical response was assessed by change from baseline for hSLEDAI (wk 2, 4, 6 & 8), BILAG, CLASI, and Tender & Swollen Joint Count (wk 4 & 8).

Results:

Mean hSLEDAI scores at baseline were 9.8±2.1, 8.7±2.9, 11.3±3.3, and 10.0±3.3 in the Placebo, RCI40, RCI80, and combined RCI groups, respectively (mean ±SD). Baseline BILAG and CLASI scores were similar between groups, though tender swollen joint count was higher in subjects randomized to RCI80 vs RCI40 or Placebo (p≤ 0.05). RCI led to significant improvement in key efficacy endpoints compared with Placebo, including total hSLEDAI and BILAG scores, CLASI Activity, and Tender & Swollen Joint Count. There were no significant differences in the incidence of treatment-emergent adverse events between groups.

Activity index *change from baseline*	**Time**	**Placebo** *LS mean (SE)*	**RCI 40U QD** *LS mean (SE)*	**RCI 80U QOD** *LS mean (SE)*	**RCI (combined)** *LS mean (SE)*
hSLEDAI	**4 wk**	-1.2 (0.6)	-1.2 (0.6)	-2.1 (0.6)	-1.6 (0.4)
	6 wk	-1.4 (0.7)	-2.9 (0.7)	-3.5 (0.7)* **p=0.045*	-3.2 (0.5)* **p=0.040*
	8 wk	-0.8 (0.9)	-3.7 (0.9)* **p=0.026*	-3.9 (0.9)* **p=0.020*	-3.8 (0.6)* **p= 0.008*
BILAG	**4 wk**	-4.7 (1.6)	-5.2 (1.5)	-7.2 (1.6)	-6.1 (1.1)
	8 wk	-1.8 (1.5)	-8.1 (1.4)* **p=0.005*	-9.3 (1.6)* **p=0.002*	-8.6 (1.0)* **p=0.001*
CLASI Activity	**4 wk**	-0.2 (0.7)	-2.2 (0.7)* **p=0.051*	-1.7 (0.7)	-2.0 (0.5)* **p=0.050*
	8 wk	-0.6 (1.0)	-3.7 (1.0)* **p=0.030*	-2.3 (1.1)	-3.1 (0.7)* **p=0.047*
Tender & Swollen Joint Ct	**4 wk**	-2.5 (0.8)	-2.3 (0.7)	-3.5 (0.8)	-2.8 (0.5)
	8 wk	-2.5 (0.5)	-2.8 (0.5)	-4.4 (0.6)* **p=0.019*	-3.5 (0.4)

Conclusion:

These data demonstrate that RCI reduces disease activity in patients requiring corticosteroids for persistently active SLE, and that improvements occur within 8 wk of treatment initiation. The tolerability, steroid-sparing effects, and impact of RCI on long-term disease control are being further evaluated in an ongoing open-label extension of this study.

Disclosure: R. Furie, Mallinckrodt Pharmaceticals, 9; **M. Das**, Mallinckrodt Pharmaceuticals, 9,Mallinckrodt Pharmaceuticals, 1; **D. Li**, Mallinckrodt Pharmaceuticals, 3,Mallinckrodt Pharmaceuticals, 1; **S. Smythe**, Mallinckrodt Pharmaceuticals, 3,Mallinckrodt Pharmaceuticals, 1; **E. Mathura**, Mallinckrodt Pharmaceuticals, 3,Mallinckrodt Pharmaceuticals, 1; **P. Becker**, Mallinckrodt Pharmaceuticals, 3,Mallinckrodt Pharmaceuticals, 1.

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Abstract Number: 728

Autoimmune Hemolytic Anemia and Thrombocytopenia in a Single Centre Cohort of Patients with Systemic Lupus Erythematosus from Turkey : Clinical Associations and Effect on Disease Damage and Survival

Bahar Artim-Esen[1], Sevil Kamali[1], Ahmet Gul[1], Lale Ocal[2] and Murat Inanc[1], [1]Department of Internal Medicine, Division of Rheumatology, Istanbul University, Istanbul Faculty of Medicine, Istanbul, Turkey, [2]Department of Internal Medicine, Rheumatology Division, Istanbul University, Istanbul Faculty of Medicine, Istanbul, Turkey

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Background/Purpose:

Hematologic involvement is common in patients with SLE. Thrombocytopenia and autoimmune hemolytic anemia (AIHA), prevalences of which have been reported as 10-40 % and 5-10 % respectively, have considerable impact on prognosis. Herein, we aimed to investigate the frequencies of these hemocytopenias, their clinical and serological associations and effect on disease outcome in a large single centre cohort of patients.

Methods:

We analysed our cohort of 852 patients who fulfilled at least 4 of the ACR criteria for SLE. The data presented was the cumulative clinical and serological manifestations throughout the follow-up period. Hemolytic anemia was defined as a drop in hemoglobin accompanied by increased reticulocyte count, high serum lactate dehydrogenase and reduced haptoglobin levels in the presence of a positive Coombs' test. Thrombocytopenia was defined as a platelet count of $<100x10^9/mm^3$. Demographic characteristics, clinical features, autoantibody profiles, damage and mortality data retrieved from the database were compared between patients with and without each hematological abnormality. The X^2 test, logistic regression and Kaplan-Meier survival analyses were used.

Results:

There were 93 (10.9%) patients with AIHA and 215 (25.3%) with thrombocytopenia. Patients with AIHA was significantly younger at diagnosis (27±13 vs 31±12, $p<0.05$) and significantly had a shorter disease duration (95±84 vs 118±85 mo, $p<0.05$). AIHA and thrombocytopenia were both associated with neuropsychiatric (NP) involvement ($p<0.05$) and associated with each other ($p<0.05$) and leukopenia ($p<0.05$). Comparison of patients with AIHA or thrombocytopenia to the rest of the cohort displayed significant associations with antiphospholipid syndrome (APS), anticardiolipin (aCL) antibodies and lupus anticoagulant (LA). In patients with thrombocytopenia the relationship with APS features, namely both thrombosis and pregnancy morbidity, was stronger ($p<0.001$). Compared to the rest of the cohort, more patients in both groups had organ damage and their mean SLICC damage score was significantly higher. Association to NP damage was discernible in both groups ($p<0.05$). In addition, damage in renal and cardiovascular domains and diabetes were more pronounced in patients with thrombocytopenia ($p<0.001$). Kaplan Meier survival analysis showed that patients with AIHA had significantly reduced survival rates at 10 (94 vs 77%) and 20 (88 vs 77%) years ($p<0.001$). In the thrombocytopenia group, despite the lack of significant differences, there was a tendency for lower survival rates.

Conclusion:

We demonstrated that both AIHA and thrombocytopenia were associated with aCL antibodies, coexisting APS and NP involvement and damage in our cohort. There was a strong link between AIHA and thrombocytopenia. Patients with AIHA had a younger age at disease onset with reduced survival. No significant reduction in survival rates was observed in patients with thrombocytopenia. However, besides NP involvement, thrombocytopenia delineated a subgroup of patients with a higher renal and cardiovascular damage which perceivably can affect prognosis. Overall, AIHA and thrombocytopenia may predict a poorer outcome in patients with SLE.

Disclosure: B. Artim-Esen, None; **S. Kamali**, None; **A. Gul**, None; **L. Ocal**, None; **M. Inanc**, None.

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Abstract Number: 729

The Effect of Belimumab on Peripheral Blood Cells in Patients with Systemic Lupus Erythematosus

Cosmin Dascalu[1], Anne Davidson[2], Meggan C. Mackay[3], Richard Furie[4], Weiqing Huang[5] and Cynthia Aranow[6], [1]Medicine/Rheumatology, North Shore- Long Island Jewish, Manhasset, NY, [2]Autoimmunity and Musculoskeletal Diseases, Feinstein Inst for Med Rsch, Manhasset, NY, [3]Autoimmune & Musculoskeletal Disorders, The Feinstein Institute for Medical Research, Manhasset, NY, [4]Division of Rheumatology, North Shore LIJ Health System, Lake Success, NY, [5]Autoimmunity and Musculoskeletal Diseases, Feinstein Institute for Medical Research, Manhasset,

NY, [6]Feinstein Institute for Medical Research, Mahasset, NY
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Background/Purpose: The anti-BAFF antibody belimumab is the first biologic drug approved for treatment of mild-moderate SLE. While the efficacy of belimumab for this indication is not questioned, the mechanism for drug efficacy in humans remains to be established. Mouse studies have shown that BAFF regulates the selection of naïve autoreactive B cells, particularly between the transitional T1 and transitional T2 stage, but that not all autoreactive specificities are subject to regulation by BAFF. Whether belimumab regulates the autoreactive B cell repertoire in humans is not yet known. In addition, an acute increase in CD27+ memory B cells has been noted in patients treated with belimumab. Whether this reflects memory B cell expansion or mobilization, or expansion of the CD27+ B1 subset is not known.

Methods: Peripheral cells from 15 SLE patients treated with Belimumab for >3 years were compared to cells from 17 matched SLE patients and 12 healthy donors. Blood was also collected from 7 patients before and 4-8 weeks after initiation of belimumab treatment. Dendritic cell, monocyte, T cell and B cell subsets were analyzed by multi-parameter flow cytometry. Immunoglobulin heavy chain gene libraries were generated from sorted naive B cells using primers from iRepertoire.

Results: As expected, B cell numbers were 85% lower in chronically treated belimumab subjects than in SLE or healthy controls. Although all B cell subsets were depleted by belimumab, there was relative sparing of the class switched memory subset. In 60% of the patients B cell deletion occurred before the transitional stage, presumably in the bone marrow and in the other 40% it occurred between the T1 and T3 stage. Naïve B cell populations were sorted for immunoglobulin repertoire analyses and good quality libraries were obtained from 14/15 subjects; deep sequencing and analysis are in progress. A modest increase in CD27+ B cells that occurred in patients newly starting belimumab was accounted for by an increase in class switched memory cells but not non-class switched memory or B1 cells. There were no significant differences in dendritic cell, monocyte or T cell subsets between the three groups.

Conclusion: The effects of belimumab on human B cells are more variable than those in mice and deletion often occurs at an earlier stage of B cell development than the peripheral T1 stage. The increase in CD27+ B cells previously observed early after belimumab therapy is due to an increase in class switched memory cells. Pending repertoire analyses will inform us as to whether there is preferential depletion of autoreactive B cells in belimumab treated patients.

Disclosure: C. Dascalu, None; **A. Davidson**, None; **M. C. Mackay**, None; **R. Furie**, GSK, 5,GSK, 2; **W. Huang**, None; **C. Aranow**, None.

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Abstract Number: 730

Early Symptoms of Systemic Lupus Erythematosus As Reported By Members of the German Lupus Erythematosus Patient Association

Nicolai Leuchten[1], Barbara Milke[1], Borgi Winker-Rohlfing[2], David I. Daikh[3], Thomas Dorner[4], Sindhu R. Johnson[5], Martin Aringer[1] and on behalf of the SLE Classification Criteria Steering Committee, [1]Medicine III, University Medical Center and Faculty of Medicine at the TU Dresden, Dresden, Germany, [2]Lupus Erythematodes Selbsthilfegemeinschaft e.V., Wuppertal, Germany, [3]Rheumatology, UCSF/VA Medical Center, San Francisco, CA, [4]Charité University Medicine Berlin, Berlin, Germany, [5]Dept of Rheumatology, Toronto Western and Mt. Sinai Hospitals, University of Toronto, Toronto, ON, Canada
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Background/Purpose: EULAR and ACR have jointly funded a project to develop systemic lupus erythematosus (SLE) classification criteria, aiming at earlier and more accurate classification of the disease. This abstract reports on an early phase of that project, aimed at collecting potential candidate criteria. The objective of this study was to identify early symptoms of SLE from the patient perspective. Since SLE patients usually experience the onset and diagnosis as a critical life event, memories of this time appear remarkably accurate.

Methods: As approved by the local ethics committee, we conducted a cross-sectional survey of German SLE patients. An anonymous self-report questionnaire was published in the "Schmetterling" the quarterly journal of the "Lupus erythematodes Selbsthilfegemeinschaft", the German SLE patient association. Patients were asked for year of and age at their initial diagnosis. The questionnaire included typical organ manifestations, symptoms and autoantibodies. In addition, patients were asked to add additional symptoms in free text. For each symptom, boxes were provided to indicate the presence of the symptom before diagnosis, in the first year of diagnosis and at the time of completion of the questionnaire.

Results: 300 patient questionnaires were completed and mailed. Of the respondents, 93% were female, their mean age at diagnosis was 36 years, their mean disease duration was 17 years, 82% reported to definitely be ANA-positive. Joint, skin and kidney involvement were reported at 82%, 65% and 34%, respectively. 22% of patients reported fibromyalgia. For the time before and shortly after diagnosis, more than 50% of the patients reported fatigue (90%), joint pain (87%), hypersensitivity to sunlight (79%), myalgias (77%), skin rashes (71%), fever (53%), hair loss (51%) and Raynaud's (50%). Approximately one third (35%) affirmed shortness of breath. Free text symptoms reported frequently before or early in diagnosis are listed in Table 1.

Table 1: Symptoms added in free text by at least 10 patients for the time before or shortly after the SLE diagnosis

	n (%)
Diarrheas/abdominal pain	32 (11%)
Headache/migraine	31 (10%)
Sicca symptoms	30 (10%)
Depression/mood disorder	25 (8%)
Cognitive impairment	23 (8%)
Dizziness/vertigo	18 (6%)
Polyneuropathy/paresthesias	15 (5%)
Sleep disturbance	12 (4%)

Conclusion: For a Caucasian European SLE patient population, the overall characteristics suggested meaningful representation. While many symptoms were reported as expected, a significant number of patients volunteered gastrointestinal complaints and symptoms of the central and peripheral nervous system. These data add to the information on early SLE symptoms that may be relevant for distinguishing early SLE from other diseases.

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Abstract Number: 731

Damage and Mortality in SLE: Cluster Analysis of Patients from SLE Registry from the Spanish Society for Rheumatology (RELESSER)

JM Pego-Reigosa[1,2], Ana Lois-Iglesias[3,4], Francisco Javier Lopez Longo[5], María Galindo[6], J Calvo-Alen[7], Jacobo de Uña[8], Vanessa Balboa[9], Alejandro Olivé[10], Coral Mouriño-Rodríguez[1], Maria Teresa Oton Sanchez[11], Jesus Ibañez[12], Maria Loreto Horcada[13], Ana Sánchez Atrio[14], Carlos Alberto Montilla Morales[15], Rafael-Benito Melero González[1], Ricardo Blanco[16], Elvira Diez Alvarez[17], Monica Fernandez Castro[18], Esther Ruiz Lucea[19], José Hernández Beiraín[20], Marian Gantes[21], Blanca Hernández-Cruz[22], Angela Pecondon-Español[23], Nuria Lozano-Rivas[24], Gema Bonilla[25], Vicente Torrente-Segarra[26], Iñigo Rúa-Figueroa[27] and RELESSER EASSER Group, [1]Rheumatology, EOXI Vigo, Vigo, Spain, [2]Rheumatology, Instituto de Investigación Biomédica de Vigo(IBIV), Vigo, Spain, [3]Rheumatology, Hospital Ntra Señora de La Esperanza, Santiago de Compostela, Spain, [4]Rheumatology, University A Coruña, A Coruña, Spain, [5]Servicio de Reumatologia, Hospital General Universitario Gregorio Marañón, Madrid, Spain, [6]Servicio de Reumatología, Instituto de Investigación Hospital 12 de Octubre (i+12), Madrid, Spain, [7]Rheumatology, Hospital de Sierrallana, Torrelavega, Spain, [8]Statistics and OR, Vigo University, Vigo, Spain, [9]Statistics and OR, Viho University, Vigo, Spain, [10]Rheumatology, Hospital Germans Trias i Pujol, Badalona, Spain, [11]Rheumatology, Hospital of Torrejón, Madrid, Spain, [12]Rheumatology, Hospital Povisa, Vigo, Spain, [13]Rheumatology, Complejo Hospitalario de Navarra, Pamplona, Spain, [14]University Hospital Príncipe de Asturias, Immune System Diseases, Rheumatology department, Alcalá de Henares, Madrid, Spain, [15]Rheumatology, Hospital Universitario de Salamanca, Salamanca, Spain, [16]Rheumatology, Hospital Universitario Marqués de Valdecilla. IDIVAL, Santander, Spain, [17]Rheumatology, Hospital de León, León, Spain, [18]Rheumatology, Hospital Puerta de Hierro, Madrid, Spain, [19]Rheumatology, Hospital de Basurto, Bilbao, Spain, [20]Rheumatology, Hospital Insular de Gran Canaria, Las palmas Gran Canarias, Spain, [21]Rheumatology, Hospital Universitario de Canarias, La Laguna; Tenerife, Spain, [22]Rheumatology, Hospital Universitario Virgen Macarena, Sevilla, Spain, [23]Rheumatology, Hospital Miguel Servet, Zaragoza, Spain, [24]Rheumatology, Hospital Virgen de la Arrixaca, Murcia, Spain, [25]Rheumatology, Hospital La Paz - IdiPaz, Madrid, Spain, [26]Hospital General Hospitalet-Sant Joan Despí Moisès Broggi, Hospitalet Llobregat, Barcelona, Spain, [27]Rheumatology, Hospital Universitario Dr Negrín. Las Palmas, Las Palmas de Gran Canaria, Spain

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Background/Purpose:

Damage in SLE is associated with mortality. Not every damage manifestation is associated in the same way. Some studies were made assessing this relation but in small and heterogeneous samples making difficult to obtain meaningful conclusions. Purpose:To evaluate patterns of damage accrual and mortality in a large sample of SLE patients.

Methods:

SLE patients from RELESSER were studied. After K-means cluster analysis, different clusters of patients with similar characteristics in terms of damage accrual were identified. Kaplan-Meier log-rank test and Cox regression were used to analyse mortality in each group.

Results:

3,656 SLE patients from 45 Rheumatology Units across Spain were studied. 90.33% were women. 93.15% were Caucasian, 5.21% Latinamerican and 1.64% other races. Mean age (±SD) at SLE diagnosis was 35.16±14.67 years. Mean follow-up time (±SD) was 120.19±87.67 months. Mean SLICC/ACR damage index (SDI) score was 1.15±1.67. Average number of organ systems affected in terms of damage was 0.65±1.06. 207 (5.66%) patients died.

The SDI organ systems most frequently damaged were: musculoskeletal(MS) (13.78%), ocular (8.51%), cardiovascular(CV)(7.99%) and renal (6.15%). The least frequently present were: gastrointestinal (1.96%), diabetes mellitus (2.41%) and premature gonadal failure (2.52%).

Three clusters (C) were formed. C1 had mild or no damage. All patients in C2 had MS damage but no CV. In C3 all patients had CV damage.

Among the 3 clusters, there were statistically significant differences ($p<0.001$) in the prevalence of damage in each organ system assessed by the SDI, in the average SDI score, in the number of SDI organ systems damaged and mortality rate. Comparative detailed data are shown in the table below.

In C3 patients were older at SLE diagnosis and had higher % of males, differences statistically significant between the 3 clusters for both variables ($p<0.001$).

Comparing survival curves of the 3 clusters, the log-rank test showed significant differences ($p <0.001$ for the triple and double comparisons). Analysing the survival rate at 10, 20 and 30 years from diagnosis of SLE, it was found lower survival in patients of C2 and C3 compared to C1 ($p =0.068$ when C2 is compared to C1 at 10 years, $p<0.01$ for all the other cases). Between C2 and C3, there were no significant differences in survival at 10 years and it was significantly lower in C3 at 20 and 30 years ($p=0.025$ for both).

Cox regression analysis showed that, compared with C1, the mortality hazard ratio of C2 and C3 was 1.9 and 3.5 higher respectively, being statistically significant, $p<0.001$ in both.

Conclusion:

SLE patients can be divided into different homogeneous groups (clusters) based on damage accrual. These clusters have different mortality rates.

Factors:	CLUSTER 1 n=2949 (80.66%)	CLUSTER 2 n=415 (11.35 %)	CLUSTER 3 N=292 (7.99%)	p-value
Damage:				
Ocular	171 (5.8)	76 (18.3)	64 (21.9)	<0.001
Neuropsychiatric	123 (4.2)	47 (11.3)	51 (17.5)	<0.001
Renal	132 (4.5)	36 (8.7)	57 (19.5)	<0.001
Pulmonary	58 (2.0)	33 (8.0)	41 (14.0)	<0.001
Cardiovascular	0	0	292 (100)	<0.001
Peripheral Vascular	88 (3.0)	37 (8.9)	38 (13.0)	<0.001
Gastrointestinal	44 (1.5)	15 (3.6)	12 (4.1)	<0.001
Musculoskeletal	0	415 (100)	89 (30.5)	<0.001
Skin	56 (1.9)	35 (8.4)	33 (11.3)	<0.001
Diabetes	56 (1.9)	12 (2.9)	20 (6.8)	<0.001
Malignancy	114 (3.9)	38 (9.2)	18 (6.2)	<0.001
Premature gonadal failure	48 (1.6)	28 (6.7)	16 (5.5)	<0.001
Deads	102 (3.7)	45 (10.8)	60 (20.5)	<0.001
Damage	684 (23.2)	415 (100)	292 (100)	<0.001
Mean number of domains damaged	0.30 (± 0.62)	1.86 (±1.05)	2.50 (± 1.38)	<0.001
SLICC	0.68 (± 1.11)	2.60 (± 1.78)	3.82 (± 2.40)	<0.001
Age at SLE diagnosis				
Gender	34.43 (± 14.07)	36.68 (± 15.75)	40.26 (± 15.60)	
Male	257 (8.7)	40 (9.7)	56 (19.2)	
Female	2686 (91.3)	374 (90.3)	236 (80.8)	<0.001
Race	2644 (92.4)	384 (95.8)	279 (96.9)	<0.001
Caucasian	8 (0.3)	0	0	0.0746
Afroamerican	163 (5.7)	14 (3.5)	8 (2.8)	0.6420
Latinoamerican	20 (0.7)	1 (0.2)	0	
Asian/Oriental	26 (0.9)	2 (.05)	1 (0.3)	
Other	30.23 (± 51.30)	35.27 (± 62.80)	32.76 (± 59.64)	
SLE duration				
Follow-up time	109.93 (± 81.29)	167.12 (± 98.95)	154.9 (± 100.17)	<0.001

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Abstract Number: 732

Decreased Disease Activity and Corticosteroid Usage and Improved Quality of Life during Belimumab Treatment in Patients with Systemic Lupus Erythematosus – a Prospective Real-Life Observational Study

Ioannis Parodis[1], Christopher Sjöwall[2], Andreas Jönsen[3], Agneta Zickert[1], Martina Frodlund[2], Daniel Ramsköld[1], Anders A. Bengtsson[3] and Iva Gunnarsson[1], [1]Department of Medicine, Rheumatology Unit, Karolinska Institutet, Stockholm, Sweden, [2]Rheumatology/AIR, Department of Clinical and Experimental Medicine, Linköping University, Linköping, Sweden, [3]Department of Clinical Sciences, Section of Rheumatology, Lund University, Lund, Sweden
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SESSION INFORMATION

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Session Title: Systemic Lupus Erythematosus - Clinical Aspects and Treatment Poster Session I
Session Type: ACR Poster Session A
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Background/Purpose: Belimumab is the first biologic drug approved to treat Systemic Lupus Erythematosus (SLE). The efficacy of belimumab has been demonstrated through 2 phase III clinical trials. Real-life experiences are anticipated in order to form an opinion of how belimumab is used in clinical praxis and provide guidance for improvements in its future use. We investigated the clinical effects of belimumab in patients with active SLE despite standard of care therapy.

Methods: Fifty-two patients from Karolinska (n=25), Skåne (n=19), and Linköping (n=8) University Hospitals treated with belimumab were enrolled in this study and followed longitudinally. Global disease activity was assessed using the SLE Disease Activity Index 2000 (SLEDAI-2K), Systemic Lupus Activity Measure-Revised (SLAM-R), and a 100 mm Visual Analogue Scale (VAS) for Physician's Global Assessment (PGA). Organ damage was evaluated according to the Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index (SDI). Quality of Life (QoL) was evaluated by patients' reports for pain, fatigue and well-being levels using 100 mm Visual Analogue Scales. Global health outcome was determined by the EuroQol Research Foundation 5 Dimension (EQ-5D) health questionnaire, scored according to the UK tariff. Functional status was assessed using the Stanford Health Assessment Questionnaire (HAQ) functional disability index.

Results: Belimumab was mainly given for musculoskeletal (n=24), mucocutaneous (n=24), hematological (n=10), renal (n=5), respiratory (n=4), and neurological (n=3) manifestations.

Significant decreases over time were observed for SLEDAI-2K (median baseline score: 7; range: 2–24; $p<0.001$), corresponding to a decrease of 3.42 over a year, SLAM-R (median baseline score: 13; range: 5–26; $p<0.001$) and PGA ($p<0.001$). We also observed decreases of prednisone equivalent dosages (mean baseline dose: 12.3 mg/day; range: 0–60 mg/day; $p<0.001$), corresponding to a decrease of 4.93 mg/day over a year. C4 levels increased significantly ($p=0.006$), but C3 levels remained unchanged. We observed significant improvements in well-being ($p<0.001$), pain ($p<0.001$) and fatigue ($p=0.018$), but no significant changes in HAQ and no significant improvements in EQ-5D. SDI scores remained stable.

Reasons for discontinuation included inadequate or uncertain effect (n=7), flare (n=5: increased proteinuria; arthritis, headache; rash, alopecia; biopsy-proven lupus nephritis WHO class III; CNS-lupus), adverse events (n=3: acute myeloid leukemia; ground glass opacity in computed tomography scan of the lungs, pulmonary arterial hypertension; insomnia, arrhythmia), allergic reactions (n=2) and pregnancy plans (n=2).

Conclusion: In this real-life observational study, belimumab treatment decreased disease activity, reduced corticosteroid usage and improved the patients' quality of life in terms of pain, fatigue and well-being over time, but had no significant effects on their functional status. There was no progression of organ damage during the follow-up. The tolerability and safety profiles of belimumab in this study were comparable with those in previous reports from the phase III trials.

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Abstract Number: 733

Late Onset Systemic Lupus Erythematosus: A Different Disease Subset?

Anne Riveros Frutos[1], Melania Martínez-Morillo[1], Irma Casas[2,3], Iñigo Rúa-Figueroa[4], JM Pego-Reigosa[5], M. Jesús García de Yebenes[6], Alejandro Olivé[1], José Rosas[7], Paloma Vela Casasempere[8], Monica Ibanez Barcelo[9], Vicente Torrente[10], Ivan Castellvi[11], Javier Narváez[12], Mireia Moreno[13], Ricardo Blanco[14], Víctor Martínez Taboada[15], Jaime Calvo[16], Ángeles Aguirre Zamorano[17], Mercedes Freire[18], Enrique

Raya[19], Celia Erausquin[20], Esther Uriarte[21], Elvira Diez Alvarez[22], Tomás Vázquez Rodríguez[23], Antonio Fernandez-Nebro[24], Eva Tomero[25], Paloma García de la Peña[26], Ana Sánchez Atrio[27], Monica Fernandez Castro[28], Antonio Zea[29], Patricia Richi[30], Francisco Javier López Longo[31], María Galindo[32], Patricia E. Carreira[33], Gema Bonilla[34], Carlos Marras Fernandez-Cid[35], Maria Loreto Horcada[36], Carlos Alberto Montilla Morales[37], Blanca Hernández-Cruz[38], José Luis Marenco de la Fuente[39], Marian Gantes[40], Olaia Fernández Berrizbeitia[41], Juan José Alegre[42], Ángela Pecondón Español[43], Manuel Rodríguez-Gómez[44], Victor Quevedo[45], José Hernández Beiraín[46] and Lucía Silva Fernández[47], [1]Rheumatology, Hospital Universitari Germans Trias i Pujol, Barcelona, Spain, [2]Preventive Medicine, Hospital Universitari Germans Trias i Pujol, Barcelona, Spain, [3]preventive medicine, Hospital Universitari Germans Trias i Pujol, barcelona, Spain, [4]Rheumatology, Hospital Universitario Dr. Negrin, Las Palmas de Gran Canarias, Spain, [5]Rheumatology, Hospital Meixoeiro, Vigo, Spain, [6]Research Unit of the SER, Madrid, Spain, [7]Rheumatology, Hospital Marina Baixa, Villajoyosa, Spain, [8]Rheumatology, Hospital General de Alicante, Alicante, Spain, [9]H. Son Llatzer, Palma de Mallorca, Spain, [10]Hospital Sant Joan de Déu, Esplugues de Llobregat, Spain, [11]Unitat de Reumatologia., Hospital de la Santa Creu i Sant Pau, Barcelona, Spain, [12]Rheumatology Department, Hospital Universitari de Bellvitge, L'Hospitalet de Llobregat, Spain, [13]Rheumatology, Hospital Parc Taulí, Sabadell, Spain, [14]Reumatologia, Hospital Universitario Marques de Valdecilla, Santander, Spain, [15]Rheumatology, Hospital Marqués de Valdecilla, Santander, Spain, [16]Rheumatology, Hospital de Sierrallana, Torrelavega, Spain, [17]Rheumatology, IMIBIC-Reina Sofia Hospital, Cordoba, Spain, [18]Rheumatology, Hospital Universitario Juan Canalejo, La Coruña, Spain, [19]Rheumatology, Hospital Clínico San Cecilio, Granada, Spain, [20]Rheumatology, Hospital de Gran Canaria Dr Negrin, Las Palmas GC, Spain, [21]Reumatología, Hospital de Donosti, Donosti, Spain, [22]Rheumatology, Hospital de León, León, Spain, [23]Rheumatology, Hospital Lucus Augusti, Lugo, Spain, [24]Rheumatology, Hospital Universitario Carlos Haya, Malaga, Spain, [25]Hospital La Princesa. Madrid., Madrid, Spain, [26]Rheumatology, Hospital Universitario Madrid Norte Sanchinarro, Madrid, Spain, [27]Hospital Principe de Asturias. Madrid, Madrid, Spain, [28]Rheumatology, Hospital Puerta de Hierro, Madrid, Spain, [29]Hospital Ramón y Cajal, Madrid, Spain, [30]Hospital Infanta Sofía, Madrid, Spain, [31]Hospital Gregorio Marañón, Madrid, Spain, [32]Rheumatology, Hospital 12 de octubre, Madrid, Spain, [33]Hospital 12 de Octubre, Madrid, Spain, [34]Rheumatology, Hospital La Paz, Madrid, Spain, [35]Hospital Virgen de la Arrixaca, Murcia, Spain, [36]Rheumatology, Complejo Hospitalario de Navarra, Pamplona, Spain, [37]Hospital Clínico Universitario de Salamanca, Salamanca, Spain, [38]Rheumatology, Hospital Universitario Virgen Macarena, Sevilla, Spain, [39]Rheumatology, Hospital de Valme, Seville, Spain, [40]Hospital Universitario de Canarias, Tenerife, Spain, [41]Rheumatology, Basurto University Hospital, Bilbao, Spain, [42]Rheumatology Department, Hospital Universitario Doctor Peset, Valencia, Spain, [43]Rheumatology, Hospital Miguel Servet, Zaragoza, Spain, [44]Complejo Hospitalario Universitario de Ourense, Ourense, Spain, [45]Rheumatology, Hospital de Monforte, Lugo, Spain, [46]Rheumatology, Hospital Insular de Gran Canaria, Las palmas Gran Canarias, Spain, [47]Hospital Universitario de Guadalajara, Guadalajara, Spain
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Background/Purpose: To describe the demographic, clinical and immunological manifestations in patients with late onset systemic lupus erythematosus (SLE)

Methods: Patients diagnosed of SLE in the RELESSER data base (National Registry of Patients with Systemic Lupus Erythematosus of the Spanish Society of Rheumatology) were included**.** Late-onset was defined as >50 years of age at time of first SLE-related symptom. Design: multicenter retrospective cross-sectional study. Socio-demographic variables, comorbidities, classification, clinical and immunological manifestations were evaluated. Pearson´s chi-square test, t-Student

Results: Of the 3628 patients included: 566 (15.6%) patients had late-onset SLE, 3062 (84.4%) patients were younger than 50 years. The mean age at diagnosis was 60.7(Sd 8.5) years in the late-onset SLE and 30.5 (Sd 9.96) years in the younger onset group. In the late onset group: 91 (16.1%) were male and 475 (83.9%) women. The male/female ratio was 5/1. Diagnosis in the younger onset group was sooner than in late-onset group (28.2 Sd 48.9 days compared with 45.3 Sd 70.3 days with P <0.0001).

Comparing comorbidities by age group, it was found that SLE patients over 50 years of age had more comorbidities with p<0.0001. Secondary Sjogren's syndrome was more frequent in the older age group (p<0.001). Table 1: Clinical manifestations. During follow-up 205 patients died: 74 (14.3%) with late-onset SLE and 131 (4.7%) younger than 50 years (P <0.0001). Evaluating the cause of death, the group of younger patients had higher mortality due to SLE with statistical significance. The cause of death from severe infections and cancer was higher in patients over 50 years, but without statistical significance

Clinical manifestation		Older than 50 years. N (%)	Younger than 50 years. N (%)	Missing N (%)	VALUE OF P
Systemic Manifestations	Lymphadenopathy	36(6,5%)	332(11%)	95 (2,6%)	0,002
Cutáneous Manifestations	Inflamatory rash	286(51,9%)	2076(87,9%)	84 (2,3%)	<0,0001
	Alopecia	115(21%)	1161(38,7%)	108 (3,0%)	<0,0001
Osteoarticular Manifestations	Avascular bone necrosis	9(1,6%)	140(4,7%)	89 (2,4%)	0,001
	Arthritis	74(13,2%)	285(9,4%)	81 (2,2%)	0,007
	Osteoporosis	94(17,3%)	164(5,5%)	141 (3,9%)	<0,0001
Pulmonary Manifestations	Pleural fibrosis	19(3,4%)	52(1,7%)	64 (1,7%)	0,009
	Pulmonary thromboembolism	24(4,3%)	79(2,6%)	55 (1,5%)	0,030
Cardiovascular Manifestations	Valvular disease	68(12,3%)	150(5%)	113 (3,1%)	<0,0001
	Valvular dysfunction	31(5,9%)	90(3,1%)	245 (6,7%)	0,001
	Angina	31(5,5%)	37(1,2%)	75 (2,1%)	<0,0001
	Acute myocardial infarction	26(4,7%)	45(1,5%)	83 (2,3%)	<0,0001
	Cardiomyopathy	41(7,4%)	63(2,1%)	100 (2,7%)	<0,0001
Peripheral vascular Manifestations	Raynaud	131(24,1%)	1055(35,7%)	160 (4,4%)	<0,0001
Renal Manifestations	Lupus nephritis	78(14,3%)	1003(33,4%)	110 (3,0%)	<0,0001
	HTA in the first outbreak	39(7,1%)	360(12,4%)	201 (5,5%)	<0,0001
	Hematuria	94(17,7%)	940(32,8%)	264 (7,2%)	<0,0001
	Pyuria	47(9%)	687(24,6%)	337 (9,2%)	<0,0001
	Creatinine clearance = 50 irreversible	41 (7,4%)	150 (5%)	131 (3,6%)	0,025
	Proteinuria = 3,5g/24hs	6(1,1%)	127(4,3%)	145 (4,0%)	<0,0001
	End stage renal disease	8(1,5%)	89(3%)	164 (4,5%)	0,039
Neuro psychiatric Manifestations	Lupus headache	13(2,4%)	199(6,6%)	110 (3,0%)	<0,0001
	Depression	122(22,2%)	481(16%)	111 (3,0%)	<0,0001
Ocular Manifestations	Cataract	111(20,3%)	201(6,7%)	123 (3,4%)	<0,0001
Immunology	Complement	327(59,2%)	2433(81,2%)	108 (3,0%)	<0,0001
	Ac anti RNP positive	84(15,2%)	792(26,9%)	162 (4,4%)	<0,0001

Conclusion: Patients with late-onset SLE have a higher risk of mortality than the younger-onset SLE. The diagnostic delay is higher in patients over 50 years. This group of patients have more comorbidities and higher risk of joint, pulmonary and cardiovascular involvement, on the contrary renal involvement is less common

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Abstract Number: 734

Disease Patterns, Flare Incidence and Organ Damage Among Filipino Patients with Systemic Lupus Erythematosus: a One-Year Observational Study

Mary Flor Joy Edar, Leonid Zamora, Catherine Macapagal and Sandra V. Navarra, Rheumatology, University of Santo Tomas Hospital, Manila, Philippines

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Session Title: Systemic Lupus Erythematosus - Clinical Aspects and Treatment Poster Session I

Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose: This study describes the disease patterns, flare incidence, hospitalizations and causes of mortality in a cohort of Filipino patients with systemic lupus erythematosus (SLE), observed over a period of 1 year at a single tertiary care center.

Methods: Included were SLE patients consecutively seen at the Rheumatology Lupus Clinics of the University of Santo Tomas Hospital in Manila, Philippines from 2012 to 2014 who were assessed over a period of at least 1 year up to May 2015. Data were obtained at minimum 3 time-points: baseline, 12 + 1 month from baseline, and at least 1 clinic visit or hospitalization within the 12-month period. Demographics, SLE disease characteristics, SLICC/ACR Damage Index (SDI), and medications history were obtained at baseline. SLE Disease Activity Index (SLEDAI), SLE flare index (SFI) and flare characteristics, reasons for hospitalizations and causes of mortality when applicable, were obtained at each clinic or hospital visit.

Results: 162 SLE patients (148, 91% females) participated in this study, with mean 27.96 years + 10.09 SD (range 5-59) age at diagnosis and mean 8.51 + 6.24 SD (range 1-32) years disease duration. Mucocutaneous (151, 93%), musculoskeletal (142, 88%) and renal (107, 66%) were the most common organ system involvement. Cataracts were the most common SDI involvement (23, 19%), followed by cerebrovascular accident (CVA) (18, 15%) and avascular necrosis (15, 13%). Mean cumulative prednisone / equivalent dose was 29.07 g+ 24.58 SD. Other medications included hydroxychloroquine (86%), mycophenolate mofetil (57%), cyclophosphamide (44%), azathioprine (22.6%), tacrolimus (4.8%), belimumab (3.6%) and rituximab (2.4%). Over the 1 year observation period, there were total 89 flares in 74 (46%) patients, 27 of which were characterized as severe; 35 (44%) of flares involved the kidneys. Sixty-five (40%) were identified to have relapsing/remitting course, 57 (35%) had chronic active disease and 16 (10%) had long quiescent disease; 24 (15%) were in remission ie without corticosteroids and immunosuppressants. Of 11 patients who were hospitalized, 5 were due to infection, 4 for disease flare, and 2 for infection with concommitant disease activity. In addition, 6 patients died during the 1 year study period, 5 of whom had active disease and/ or systemic infection at the time of death.

Conclusion: This prospective observational study describes disease patterns, morbidity and mortality in a cohort of Filipino SLE patients, reflecting the high costs of health resource utilization and burden of illness among these patients.

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Abstract Number: 735

Belimumab Reduces the Frequency of Flares and Prevents Damage Progression in SLE Patients: Experience in a Clinical Practice Setting

Luca Iaccarino[1], Silvano Bettio[1], Rossella Reggia[2], Margherita Zen[3], Micol Frassi[2], Laura Andreoli[2], Linda Nalotto[1], Mariele Gatto[1], Lara Pea[2], Nicola Bassi[1], Maddalena Larosa[1], Alessandra Zanola[2], Leonardo Punzi[4], Angela Tincani[2] and Andrea Doria[1], [1]Department of Medicine-DIMED, University of Padova, Padova, Italy, [2]Rheumatology and Clinical Immunology, Spedali Civili and University of Brescia, Brescia, Italy, [3]Division of Rheumatology, University of Padova, Padova, Italy, [4]Unit of Rheumatology, University of Padova, Padova, Italy

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Background/Purpose: To investigate the efficacy and safety of belimumab in patients affected with active systemic lupus erythematosus (SLE) refractory to standard therapy.

Methods: Fifty-eight patients, 54 female and 4 male, mean age 39.9±10.7 years, mean disease duration 13.1±8.3 years, affected with SLE (ACR criteria), with active disease manifestations and active serology (low C3/C4 and high dsDNA) unresponsive to standard therapy were treated with belimumab (10 mg/kg at day 0, 14 and 28 and then every 28 days). SLEDAI-2K, SLICC/ACR damage index (SDI), anti-dsDNA, C3 and C4 serum levels, and prednisone daily dose were recorded at baseline, at month 3, 6, 9, 12, and every 6 months thereafter. SDI calculated 5 years before the initiation of belimumab was also considered. DAS-28, 24-hour proteinuria, CLASI (Cutaneus LE Disease Area and Severity Index), blood cell count were recorded to evaluate organ response to belimumab. SLE flares were defined by SLEDAI flare index and flare rate was reported as number of flare/100 patients/year. SLE flare rate was evaluated in the 12 months before and after belimumab initiation.

Adverse events (AEs) were recorded at every clinical evaluation and were defined as follow: infectious AEs, non-infectious AEs, infusion or hypersensitivity reactions. AE were considered severe (SAEs) in case of hospitalization and/or death and/or life-threatening manifestations.

Results: Mean follow-up period was 14.1±7.7 months. Refractory manifestations requiring the use of belimumab as add on therapy were musculoskeletal (35.9%), mucocutaneous (27.2%), renal (22.1%), hematologic (11.7%), and constitutional (3.1%). At 3, 6, 9, 12, and 18 months of follow-up SLEDAI-2K, prednisone daily dose and DAS-28 significantly declined compared with baseline (Table 1). Moreover, a reduction of 24-hour proteinuria and CLASI (Table 1) and an increase in C3 and C4 values, although not significant, was also found. We observed 82 flares/100 patients/year before and 37 flares/100 patients/year (p=0.0001) after belimumab initiation. SDI was 0.62±0.65 five years before belimumab initiation, 0.86±1.03 at baseline and 0.86±1.03 after 18 months of follow-up.

One hundred fifty-one AEs were observed. Thirty five patients (60.3%) experienced ≥1AEs. Infectious AEs, non-infectious AEs, infusion and hypersensitivity reactions were 50.4%, 17.2%, 1.3% and 31.1% of total AEs, respectively. Two SAEs were observed, one non-infectious (deep vein thrombosis) and one infectious AEs (pneumonia). No severe infusion reactions and no discontinuation due to AEs were observed.

Conclusion: Belimumab was effective and safe in a clinical practice setting. Notably, belimumab reduced the number of flares and prevented the progression of damage in our patients with active SLE.

Table 1. Reduction of disease activity parametrs in 58 SLE patients treated with belimumab

	N° Patients	Baseline	3 months	6 months	9 months	12 months	18 months
SLEDAI-2K	58	9.1±3.7	6.2±4,1**	5.6±3.4**	5.7±3.4**	5.2±3.1**	5,43±3.1*
Prednisone daily dose (mg/day)	58	11.4±6.5	9.2±4.8	7.6±3.9*	7.4±4.3*	5.9±2.2**	4.8±2.3**
DAS-28	23	4.1±1.1	2.54±0.8**	2.56±1.2**	2.30±1.1**	1.92±0.9**	1.7±0.2**
24-h proteinuria (mg/die)	14	1.3±0.7	1.1±1.0	0.96±0.6	0.8±0.6	0.6±0.5	0.7±0.7
CLASI	15	5.9±3.8	4.0±3.4	3.4±3.5	3.2±3.5	2.00±1.8	2.56±2.8

* p<0.01, ** p<0.001

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Abstract Number: 736

Complement Activation As a Marker for Increased Thrombosis Risk in SLE Patients with Antiphospholipid Antibodies

H. Michael Belmont[1], Janet Nwaukoni[2] and Jill P. Buyon[2], [1]Hosp for Joint Disease, New York, NY, [2]Medicine, Division of Rheumatology, New York University School of Medicine, New York, NY
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Session Time: 9:00AM-11:00AM

Background/Purpose: We and others have suggested that complement activation can serve as an initiating signal that increases the thrombosis risk in SLE patients with antiphospholipid antibodies. Generation of complement activation products can result in proinflammatory and/or prothrombotic responses providing a permissive environment for the pathological effects of antibodies to negatively charged phospholipid protein complexes.

Methods: We analyzed the NYU SLE SAMPLE Biorepository initiated in September 2013 which consists of 539 patients fulfilling ACR and/or SLICC criteria for systemic lupus erythematosus. We identified 91 patients whose criteria included the presence of one or more for the following APLS antibodies: lupus anticoagulant, IgG or IgM anti-β_2-glycoprotein-I, or IgG or IgM anticardiolipin antibodies and determined if these patients received SLEDAI points for hypocomplementemia during any encounter. We then reviewed each patient's medical record to identify the prevalence of thrombosis defined as DVT, PE, CVA, arterial occlusion with gangrene or amputation, and obstetric events as well as noncriteria manifestation of thrombocytopenia or valvulitis. We then compared the prevalence of these APLS manifestations in the SLE patients with and without evidence of complement activation.

Results: The NYU SLE SAMPLE biorepository includes 539 patients (90% female, mean age 43.0 ± .9, and 10 % men, mean age 41.0 ± .3). 54% Caucasian, 31% African American, 15% Asian, 30% Hispanic White, and 5% Hispanic Black. 91 of the 539 SLE patients had APLS antibodies, 79 female and 12 male (mean age 43.0 ± .2, 56% Caucasian, 33% African American, and 11% Asian). 24 % Hispanic white and 4% Hispanic Black. The total number of patients with adverse events is 48 of 91 (53%) with 29/48 (60%) in the SLE patients with APLS and evidence of hypocomplementemia and 19/43 (44%) in the patients without evidence of hypocomplementemia. The most common thrombotic event was DVT followed by CVA.

Conclusion: The prevalence of APLS as a criteria in the NYU SLE registry is 91 of 539 and adverse events were more common in the patients with evidence of hypocomplementemia (29/48, 60%) as compared to the patients without complement activation (19/43, 44%).These findings can inform decisions regarding which patient subsets may benefit from the prophylactic use of low-dose aspirin for primary prevention in asymptomatic lupus patients. Moreover, future clinical trials should be stratified on the basis of complement consumption to be sure that equal numbers of these patients appear in both the experimental and comparator treatment arms. Finally, future prospective studies should explore the interaction between complement activation products, platelets, neutrophils, mononuclear cells, endothelial cells, coagulation cascade, etc. in the adverse events that constitute antiphospholipid syndrome.

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Abstract Number: 737

A Paper Patient-Based Flare Study in SLE

Joanna Sturgess[1], Elizabeth Allan[1], **David A. Isenberg**[2], Cynthia Aranow[3], Martin Aringer[4], Anca Askanase[5], Sang-Cheol Bae[6], Sasha R Bernatsky[7], Ian N. Bruce[8], Jill P. Buyon[9], Ricard Cervera[10], Ann Clarke[11], Mary Anne Dooley[12], Paul R. Fortin[13], Ian Giles[2], Ellen M. Ginzler[14], Dafna Gladman[15], Caroline Gordon[16], Bridget Griffiths[17], John G. Hanly[18], Murat Inanc[19], Søren Jacobsen[20], Diane L. Kamen[21], Munther Khamashta[22], Peter Lanyon[23], S. Sam Lim[24], Susan Manzi[25], Marta Mosca[26], Ola Nived[27], Christine A. Peschken[28], Michelle Petri[29], Kenneth C. Kalunian[30], Anisur Rahman[31], Rosalind Ramsey-Goldman[32], Guillermo Ruiz-Irastorza[33], Jorge Sánchez-Guerrero[34], Matteus Schneider[35], Kristján Steinsson[36], Gunnar K. Sturfelt[37], Murray Urowitz[38,39], Ronald F. van Vollenhoven[40], Carlos Vasconcelos[41], Daniel J Wallace[42], Asad Zoma[43], Joan T. Merrill[44], Eric Morand[45], Sharon Chambers[46], Nathalie Costedoat-Chalumeau[47] and Sara Croca[2], [1]Statistics, London School of Hygiene and Tropical Medicine, London, United Kingdom, [2]Rayne Institute, Centre for Rheumatology Research, UCL Division of Medicine, London, United Kingdom, [3]Feinstein Institute for Medical Research, Mahasset, NY, [4]Rheumatology, Universitatsklinikum, Dresden, Germany, [5]Columbia University College of Physicians & Surgeons, New York, NY, [6]Hanyang University Hospital for Rheumatic Diseases, Seoul, South Korea, [7]Division of Rheumatolog, McGill Unversity Health Cener, Montreal, QC, Canada, [8]Central Manchester University Hospital NHS Foundation Trust and Manchester Academic Health Science Centre, NIHR Manchester Musculoskeletal Biomedical Research Unit, Manchester, United Kingdom, [9]Medicine, Division of Rheumatology, New York University School of Medicine, New York, NY, [10]Department of Autoimmune Diseases, Hospital Clínic, Barcelona, Spain, [11]Division of Rheumatology, Department of Medicine, University of Calgary,

Calgary, AB, Canada, [12]UNC Kidney Centre, Chapel Hill, NC, [13]Université Laval, CHU de Québec, Québec, QC, Canada, [14]Medicine/Box 42, SUNY-Downstate, Brooklyn, NY, [15]Rheumatology, University of Toronto, Toronto Western Hospital, Toronto, ON, Canada, [16]Rheumatology (East Wing), Medical School, Birmingham, United Kingdom, [17]Rheumatology, Freeman Hospital, Newcastle Upon Tyne, United Kingdom, [18]Rheumatology, Division of Rheumatology, Capital Health and Dalhousie University, Halifax, NS, Canada, [19]Department of Internal Medicine, Division of Rheumatology, Istanbul University, Istanbul Faculty of Medicine, Istanbul, Turkey, [20]Rheumatology, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark, [21]Medicine, Medical University of South Carolina, Charleston, SC, [22]Graham Hughes Lupus Research Laboratory, The Rayne Institute, St Thomas' Hospital, London, United Kingdom, [23]Rheumatology, Queens Medical Centre Nottingham, Nottingham, United Kingdom, [24]Emory University School of Medicine, Atlanta, GA, [25]Rheumatology, Allegheny Health Network, Pittsburgh, PA, [26]University of Pisa, Pisa, Italy, [27]Rheumatology, Inst of Clinical sciences, Lund, Sweden, [28]Rheumatology, Univ of Manitoba, Winnipeg, MB, Canada, [29]Rheumatology, Johns Hopkins University Hospital, Baltimore, MD, [30]Division of Rheumatology, Allergy & Immunology, UCSD School of Medicine Center for Innovative Therapy, La Jolla, CA, [31]Academic Centre for Rheumatology, University College London, London, United Kingdom, [32]Northwestern University Feinberg School of Medicine, Chicago, IL, [33]Universidad del Pais Vasco, Servicio de Medicina Interna, Hospital de Cruces, Bizkaia, Spain, [34]Rheumatology, Mount Sinai Hospital and University Health Network, Toronto Canada, Toronto, ON, Canada, [35]MNR-Klinik, Heinrich-Heine-Univ Dusseldorf, Dusseldorf, Germany, [36]Rheumatology, Univ. Hospital, Reykjavik, Iceland, [37]Department of Rheumatology, Univ Hospital Lund, Lund, Sweden, [38]University of Toronto, Toronto, ON, Canada, [39]Rheumatology, U of Toronto, Toronto Western Hospital, Toronto, ON, Canada, [40]Department of Medicine, Unit for Clinical Therapy Research, Inflammatory Diseases (ClinTRID), The Karolinska Institute, Stockholm, Sweden, [41]Medicina Interna, Unidade de Imunologia Clínica - Hospital Santo António, Oporto, Portugal, [42]Cedars-Sinai Medical Center, West Hollywood, CA, [43]Rheumatology, Hairmyres Hospital, East Kilbride, United Kingdom, [44]Clinical Pharmacology, Oklahoma Medical Research Foundation, Oklahoma City, OK, [45]Medicine, Monash University, Clayton, Australia, [46]TrinCay Medical Services, Camana Bay, Cayman Islands, [47]Internal Medicine Department, Cochin Hospital, "René-Descartes Paris V" University, Paris, France
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Session Type: ACR Poster Session A
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ACR Abstract – A Paper Patient-Based Flare Study in Systemic Lupus Erythematosus (SLE)

Isenberg D, Sturgess J, Allan E, Aranow C, Aringer M, Askanase A, Sang-Cheol B, Bernatsky S, Bruce I, Buyon J, Cervera R, Chambers S, Cortedoat-Chalumeau N, Croca S, Clarke A, Dooley Mary Anne, Fortin P, Giles I, Ginzler E, Gladman D, Gordon C, Griffiths B, Hanly J, Inanc M, Jacobsen S, Kamen D, Khamashta M, Lanyon P, Lim, Manzi S, Moreland E, Mosca M, Nived O, Peschken C, Petri M, Kalunian K, Rahman A, Ramsey-Goldman R, Ruiz-Irastorza G, Sanchez-Guerrero J, Schneider M, Steinsson K, Sturfet G, Urowitz M, van Vollenhoven R, Vasconcelos C, Wallace D, Zoma A, Merrill J

Background/Purpose:

Data are restricted with regard to the usefulness of activity indices when assessing flares in patients with SLE. One study of 16 flaring SLE patients provided modest encouragement (1) but a recent cohort review (2) indicated that medication changes may not be appropriate in defining the degrees of flare. We now report assessments of flares from 989 SLE case histories provided by rheumatologists from over 30 centres in 10 different countries.

Methods:

Each case history was abstracted from medical records of real patients and provided together with an opinion as to whether each patient was experiencing a severe, moderate or mild flare or 'ongoing/grumbling' disease. Two further opinions were sought on each case history from the panel of rheumatologists and ultimately 451 patient histories, for which there was complete agreement about their flare status were selected for further study. Six different pairs of rheumatologists, were each asked to agree the assessments of approximately 30 cases using BILAG 2004 or SELENA-SLEDAI flare indices or the revised SELENA flare index.

Results:

For all three tools, the Flare classification generated by each, matched the consensus view of the cases in a similar proportion of times [BILAG-2004 – 66%; SELENA Flare – 65%; SELENA-SLEDAI – 75%; the slightly higher rate in the SELENA-SLEDAI being due to the single mild/moderate category].The corresponding weighted kappas for each tool were BILAG 0:82; SELENA flare 0.64; SELENA-SLEDAI 0.59).

Of particular note was a consistent pattern across all three tools of over-scoring moderate flares as severe. Closer examination of the data suggests that this over-scoring is driven by treatment. Removal of treatment decisions from the assessment of flare using the SELENA-Flare and SELENA-SLEDAI tools led to an increase in the proportion of correctly assessed cases to 72% and 80% respectively (weighted kappa; 0.68 and 0.74).

Conclusion:

Distinguishing different types of flare in patients with SLE remains a challenge. Given the difficulty caused by the inadequate provision of data in some of the case histories (making accurate BILAG assessment in particular problematic on occasion) the results are nevertheless very encouraging.

The overall performance characteristics of these flare instruments suggest that they can be useful in clinical trials where results are studied at the group level, whereas in clinical flare assessment must still be based on clinical judgement.

1. Isenberg D et a. Am Rheum Dis 2011; 70; 54

2. Thanou et al. Rheumatology 2014; 53; 2175

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Abstract Number: 738

Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of the BCL-2 Inhibitor Venetoclax (ABT-199) in a Phase 1 Single and Multiple Ascending Dose Study in Female Patients with Systemic Lupus Erythematosus

Peng Lu[1], Roy Fleischmann[2], Craig Curtis[3], Stanislav Ignatenko[4], Monali Desai[5], Shekman L. Wong[5], Kristie M. Grebe[1], Jiewei Zeng[5], Jeroen Medema[5] and James Stolzenbach[5], [1]AbbVie Inc., Worcester, MA, [2]University of Texas Southwestern Medical Center, Dallas, TX, [3]Compass Research Center, Orlando, FL, [4]Charité Research Organization, Berlin, Germany, [5]AbbVie Inc., North Chicago, IL

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Background/Purpose: Apoptosis is needed to eliminate auto-reactive T and B cells during immune responses; failure of elimination is important in development of systemic lupus erythematosus (SLE). The BCL-2 family helps regulate immune cell homeostasis; elevated Bcl-2 expression may contribute to cell death abnormalities for auto-reactive cells. Venetoclax (ABT-199), a selective, small-molecule BCL-2 inhibitor, was examined in a phase 1 study of safety, tolerability, pharmacokinetics, and pharmacodynamics (PD) in female patients (pts) with SLE.

Methods: This was a single and multiple ascending dose, double-blind, randomized, placebo-controlled study (NCT01686555) in women aged 18–65 y with SLE for >6 mo, receiving stable SLE therapy. Twelve cohorts were planned (N=96); in each cohort, 6 pts received venetoclax and 2 received placebo. Pts in cohorts 1–6 received single doses of venetoclax 10, 30, 90, 180, 300, and 500 mg, respectively. Pts in the multiple ascending dose arms (cohorts 7–12) received 2 cycles (once daily for 1 wk, then 3 wk off in each cycle) of venetoclax 30, 60, 120, 240, 400, and 600 mg, beginning after safety evaluation of the single-dose venetoclax 90-mg cohort.

Results: In 98 enrolled pts, common adverse events (AEs) were headache and gastrointestinal disorders (diarrhea, nausea, vomiting; **Table**). Most drug-related AEs were mild to moderate; no serious AE was reported with venetoclax. There were no deaths and no clinically relevant abnormalities of vital signs or electrocardiograms. Exposure to venetoclax was dose proportional, with a half-life of ~7–17 h after single doses. PD effects of Bcl-2 inhibition included dose-dependent reductions of total lymphocytes and subsets **(Figure)** after single and multiple venetoclax doses up to 600 mg. B cells were most sensitive to Bcl-2 inhibition, with >80% reduction from baseline in high-dose groups. For lymphocytes and T cells, changes were less marked with multiple dosing, and recovery of total lymphocytes occurred during the dosing interval of cyclic

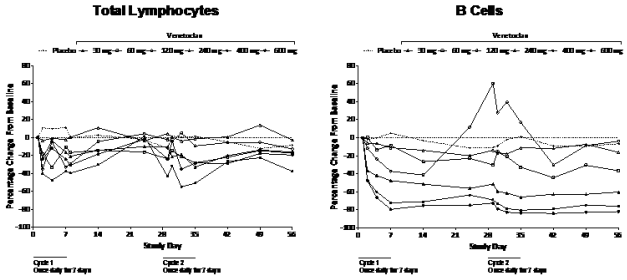
multiple dose regimens **(Figure)**. Compared with lymphocytes and subsets, levels of neutrophils, platelets, reticulocytes, hemoglobin, and safety laboratory values showed no consistent patterns or marked changes across single- and multiple-dosing groups.

Conclusion: In female SLE pts, venetoclax was well tolerated in single (10–500 mg) and multiple (30–600 mg) doses; exposure appeared consistent with findings in cancer pts. PD assessments demonstrated specific reductions of lymphocytes and subsets by inhibition of BCL-2, as expected from preclinical and ex vivo findings.

Table. Adverse Events (AEs) in Patients Who Received Venetoclax

	Single Doses, mg							Multiple Doses, mg						
AE, n (%)	**10 (n=6)**	**30 (n=6)**	**90 (n=6)**	**180 (n=6)**	**300 (n=6)**	**500 (n=6)**	**Placebo (n=12)**	**30 (n=6)**	**60 (n=6)**	**120 (n=6)**	**240 (n=6)**	**400 (n=6)**	**600 (n=7)**	**Placebo (n=13)**
Any	5 (83.3)	6 (100)	4 (66.7)	3 (50.0)	2 (33.3)	2 (33.3)	6 (50.0)	5 (83.3)	4 (66.7)	2 (33.3)	3 (50.0)	5 (83.3)	4 (57.1)	6 (46.2)
Study drug-related	2 (33.3)	4 (66.7)	3 (50.0)	0	0	2 (33.3)	4 (33.3)	2 (33.3)	3 (50.0)	2 (33.3)	1 (16.7)	2 (33.3)	3 (42.9)	4 (30.8)
Severe	0	0	1 (16.7)	0	0	0	0	0	1 (16.7)	0	0	0	0	0
Serious	0	0	0	0	0	0	0	0	0	0	0	0	0	1 (7.7)
Headache	1 (16.7)	2 (33.3)	1 (16.7)	2 (33.3)	0	2 (33.3)	3 (25.0)	2 (33.3)	3 (50.0)	1 (16.7)	0	2 (33.3)	1 (14.3)	3 (23.1)
Diarrhea	0	2 (33.3)	0	1 (16.7)	0	0	1 (8.3)	0	1 (16.7)	0	0	0	2 (28.6)	0
Nausea	0	3 (50.0)	1 (16.7)	0	0	0	0	1 (16.7)	2 (33.3)	1 (16.7)	1 (16.7)	1 (16.7)	2 (28.6)	3 (23.1)
Vomiting	0	1 (16.7)	0	0	1 (16.7)	0	1 (8.3)	1 (16.7)	2 (33.3)	0	0	0	1 (14.3)	0

Figure. Percentage changes from baseline in total lymphocytes and B cells during multiple dosing of venetoclax.



Disclosure: P. Lu, AbbVie, 3; **R. Fleischmann**, AbbVie, 5,AbbVie, 2; **C. Curtis**, AbbVie, 2; **S. Ignatenko**, AbbVie, 2; **M. Desai**, AbbVie, 3; **S. L. Wong**, AbbVie, 3; **K. M. Grebe**, AbbVie, 3; **J. Zeng**, AbbVie, 3; **J. Medema**, AbbVie, 3; **J. Stolzenbach**, AbbVie, 3.

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Abstract Number: 739

Prednisone Increases Both Arterial and Venous Thrombosis in SLE

Katharine Hickman[1], Laurence S Magder[2] and Michelle Petri[3], [1]University College London, London, United Kingdom, [2]University of Maryland School of Medicine, Baltimore, MD, [3]Rheumatology, Johns Hopkins University Hospital, Baltimore, MD

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Background/Purpose: An increasing number of studies have investigated factors that are associated with thrombosis in SLE. However, few have examined risk factors specific for venous thrombosis in patients with SLE and no study to date has compared the relative influence of risk factors on venous versus arterial thrombosis prospectively. We examined the effect of traditional and disease specific risk factors on both venous and arterial thrombosis.

Methods: The analysis is based on 1951 patients who were enrolled in a prospective cohort from April 1987 through September 2014. In 12,638 person years of follow up, 189 thrombotic events were observed. We fit separate multivariable models for venous and arterial thrombosis that included variables that were most important based on the age-adjusted and preliminary regression models.

Results: Table 1 includes variables that were independently associated with thrombosis. Even after controlling for all the other variables in the model, there was a strong association between recent systolic blood pressure, diabetes and current prednisone dose on both venous and arterial thrombosis. Recent cholesterol was an independent risk factor only for venous thrombosis but not arterial thrombosis. Current Plaquenil use was protective only against venous thrombosis. A history of lupus anticoagulant was associated with an increased risk of venous thrombosis, but was not significant for arterial thrombosis (p=0.17.) A history of low C3 was associated with an increased risk of venous thrombosis whilst recent low C3 was more important than a history of low C3 when considering arterial thrombosis.

Table 1: Independent Risk Factors for Venous and Arterial Thrombosis Based on a Multivariable Model

	Venous Thrombosis		Arterial Thrombosis	
Variable	Risk Ratio (95% CI)	P – value	Risk Ratio (95% CI)	P- Value
Recent SBP 140 mmHg +	1.9 (1.2, 3.1)	0.010	1.6 (1.1, 2.4)	0.028
Recent Cholesterol 200-249 (vs. < 200) 250+ (vs. < 200)	1.2 (0.7, 2.0) 1.8 (1.0, 3.3)	0.54 0.071	Not a significant independent risk factor	
Diabetes	2.5 (1.5, 4.0)	0.002	1.9 (1.2, 2.9)	0.0034
History of low C3	2.0 (1.1, 3.4)	0.020		
Recent low C3	Not a significant independent risk factor		1.7 (1.1, 2.5)	0.021
History of Lupus Anticoagulant	1.6 (1.0, 2.6)	0.036	1.3 (0.9, 2.0)	0.17
Current Prednisone Treatment (mg/day) 1-9 10-19 20+	1.3 (0.7, 2.4) 1.9 (1.0, 3.6) 3.3 (1.6, 6.5)	0.35 0.04 0.0008	1.8 (1.1, 3.0) 3.1 (1.9, 5.2) 6.4 (3.7, 11.3)	0.019 <0.0001 <0.0001
Current Plaquenil Treatment	0.7 (0.4, 1.0)	0.070	0.8 (0.5, 1.1)	0.21

Conclusion: Venous or arterial thromboses are equally associated with modifiable risk factors such as blood pressure and diabetes (however only venous thrombosis was associated with cholesterol in the multivariate model). Current use of prednisone at a dose greater than 20mg increased the risk of both arterial and venous thrombosis more than any other risk factor.

Disclosure: K. Hickman, None; **L. S. Magder**, None; **M. Petri**, None.

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Abstract Number: 740

The Prevalence of Anti-DFS70 Antibodies in an International Inception Cohort of Systemic Lupus Erythematosus

May Choi[1], John G. Hanly[2], Murray Urowitz[3,4], Juanita Romero-Diaz[5], Caroline Gordon[6], Sang-Cheol Bae[7], Sasha Bernatsky[8], Daniel J Wallace[9], Joan T. Merrill[10], David A. Isenberg[11], Anisur Rahman[12], Ellen M. Ginzler[13], Paul R. Fortin[14], Dafna Gladman[15], Jorge Sanchez-Guerrero[16], Michelle Petri[17], Ian N. Bruce[18], Mary Anne Dooley[19], Rosalind Ramsey-Goldman[20], Cynthia Aranow[21], Graciela S. Alarcon[22], Kristján Steinsson[23], Ola Nived[24], Gunnar K. Sturfelt[25], Susan Manzi[26], Munther Khamashta[27], Ronald F. van Vollenhoven[28], Asad Zoma[29], Guillermo Ruiz-Irastorza[30], S. Sam Lim[31], Thomas Stoll[32], Murat Inanc[33], Kenneth C. Kalunian[34], Diane L. Kamen[35], Peter Maddison[36], Christine A. Peschken[37], Søren Jacobsen[38], Anca Askanase[39], Jill P. Buyon[40], W. Winn Chatham[41], Manuel Ramos-Casals[42], Yvan St. Pierre[43], Ann E. Clarke[44] and Marvin J. Fritzler[1], [1]Medicine, University of Calgary, Calgary, AB, Canada, [2]Rheumatology, Division of Rheumatology, Capital Health and Dalhousie University, Halifax, NS, Canada, [3]Rheumatology, TWH, Toronto, ON, Canada, [4]Rheumatology, U of Toronto, Toronto Western Hospital, Toronto, ON, Canada, [5]Immunology and Rheumatology, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico city, Mexico, [6]Rheumatology (East Wing), Medical School, Birmingham, United Kingdom, [7]Rheumatology, Hanyang University Hospital for Rheumatic Diseases, Seoul, South Korea, [8]Rheum/Clin. Epid., McGill MUHC/RVH, Montreal, QC, Canada, [9]Cedars-Sinai Medical Center, West Hollywood, CA, [10]Clinical Pharmacology, Oklahoma Medical Research Foundation, Oklahoma City, OK, [11]Rayne Institute, Centre for Rheumatology Research, UCL Division of Medicine, London, United Kingdom, [12]Centre for Rheumatology Research, U College of London, London, United Kingdom, [13]Medicine/Box 42, SUNY-Downstate, Brooklyn, NY, [14]Rheumatology, University of Laval, Quebec, QC, Canada, [15]Rheumatology, University of Toronto, Toronto Western Hospital, Toronto, ON, Canada, [16]Rheumatology, Toronto Western Hospital, Toronto, ON, Canada, [17]Rheumatology, Johns Hopkins University Hospital, Baltimore, MD, [18]Central Manchester University Hospital NHS Foundation Trust and Manchester Academic Health Science Centre, NIHR Manchester Musculoskeletal Biomedical Research Unit, Manchester, United Kingdom, [19]UNC Kidney Centre, Chapel Hill, NC, [20]Northwestern University Feinberg School of Medicine, Chicago, IL, [21]Feinstein Institute for Medical Research, Mahasset, NY, [22]Medicine, University of Alabama at Birmingham, Birmingham, AL, [23]Rheumatology, Univ. Hospital, Reykjavik, Iceland, [24]Rheumatology, Inst of Clinical sciences, Lund, Sweden, [25]Department of Rheumatology, Univ Hospital Lund, Lund, Sweden, [26]Rheumatology, Allegheny Health Network, Pittsburgh, PA, [27]Graham Hughes Lupus Research Laboratory, The Rayne Institute, St Thomas' Hospital, London, United Kingdom, [28]Department of Medicine, Rheumatology Unit, Karolinska Institutet, Stockholm, Sweden, [29]Rheumatology, Hairmyres Hospital, East Kilbride, United Kingdom, [30]Universidad del Pais Vasco, Servicio de Medicina Interna, Hospital de Cruces, Bizkaia, Spain, [31]Emory University School of Medicine, Atlanta, GA, [32]Abteilung Rheumatologie/Rehab, Kantonsspital Schaffhausen, Schaffhausen, Switzerland, [33]Department of Internal Medicine, Division of Rheumatology, Istanbul University, Istanbul Faculty of Medicine, Istanbul, Turkey, [34]Division of Rheumatology, Allergy & Immunology, UCSD School of Medicine Center for Innovative Therapy, La Jolla, CA, [35]Medicine, Medical University of South Carolina, Charleston, SC, [36]School of Sport, Health and Exercise Sciences, Bangor University, George Building, Bangor, Gwynedd, LL57 2PZ, UK., Bangor, United Kingdom, [37]Rheumatology, Univ of Manitoba, Winnipeg, MB, Canada, [38]Rheumatology, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark, [39]Columbia University College of Physicians & Surgeons, New York, NY, [40]Medicine, Division of Rheumatology, New York University School of Medicine, New York, NY, [41]Medicine/Clinical Immunology and Rheumatology, University of Alabama at Birmingham, Birmingham, AL, [42]Department of Autoimmune Diseases, CELLEX-IDIBAPS, Hospital Clínic, Barcelona, Barcelona, Spain, [43]Clinical Epidemiology, Research Institute of the McGill University Health Centre, Montreal, QC, Canada, [44]Immunology/Epidemiology, Montreal General Hospital, Montreal, QC, Canada
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SESSION INFORMATION

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Background/Purpose: Autoantibodies to the nuclear autoantigen dense fine speckles 70 (DFS70) are associated with a new paradigm whereby when they are found in isolation (monospecific – no other detectable autoantibodies), they are purported to rule out the diagnosis of systemic lupus erythematosus (SLE) and other anti-nuclear antibody (ANA)-related conditions. Anti-DFS70 can be screened by indirect immunofluorescence (IIF) and quantified and confirmed by chemiluminescence immunoassay (CIA). The reported frequency of anti-DFS70 by CIA in SLE is low compared to healthy individuals (0-6% vs. 7-20%). Furthermore, anti-DFS70 monospecificity is reported to be low in SLE patients (<1%). To date, there have been no studies examining the frequency of anti-DFS70 in early inception SLE cohorts. The purpose of this study was to determine the prevalence of anti-DFS70 in newly diagnosed SLE patients and to identify any univariate associations with demographic and clinical features.

Methods: Patients fulfilling the American College of Rheumatology (ACR) Classification Criteria for SLE were enrolled in the Systemic Lupus Erythematosus International Collaborating Clinics (SLICC) inception cohort within 15 months of diagnosis. Demographic and clinical data, including disease activity (SLEDAI-2K), were collected at enrollment. ANAs were detected by IIF on HEp-2 cells (ImmunoConcepts, Sacramento, CA), and extractable nuclear antigens (ENAs) and double-stranded DNA (ds-DNA) by an addressable laser bead immunoassay (FIDIS Connective 13, TheraDiag, Paris). Anti-DFS70 antibodies were measured by CIA using cutoffs suggested by the manufacturer (Inova Diagnostics Inc., San Diego, CA).

Results: 1137 patients were included; 89.4% were female and 94.4% were ANA IIF positive (Table 1). The frequency of anti-DFS70 by CIA

was 7.1% [95%CI: 5.7-8.8%] (81/1137 patients). 11/1137 (0.97%) [95%CI: 0.5-1.7%] of the entire cohort were positive for anti-DFS70 only with no detectable ENA or anti-dsDNA and were therefore considered ÔmonospecificÕ for anti-DFS70. Patients with a negative anti-DFS70 by CIA were more likely than those with a positive anti-DFS70 to have other SLE-related autoantibodies including anti-U1-RNP (31.5% vs. 21.0%), anti-Ro60 (46.3% vs. 34.6%), and anti-SSB (16.0% vs. 4.9%). Age, gender, ethnicity, disease features included in the ACR classification criteria, SLEDAI-2K score, or concomitant therapies did not differ between the anti-DFS70 negative and positive patients.

Conclusion: The prevalence of anti-DFS70 measured by CIA in newly diagnosed SLE patients was at the high end of the range as compared to that in previously published SLE cohorts (7.1% vs. 0-6%). However, "monospecific" anti-DFS70 was rare (0.97%) in this SLE inception cohort and, therefore, the presence of monospecific anti-DFS70 is a potentially useful test to discriminate between ANA positive healthy individuals and those newly diagnosed with definite SLE.

Table 1. Baseline demographic, clinical, and autoantibody profile anti-DFS negative and positive patients newly diagnosed with SLE

	DFS-negative N = 1056	DFS-positive N = 81	Difference (95%CI)
Mean age at diagnosis, yrs (±SD)	34.6 (13.8)	32.4 (14.6)	2.3 (-0.8, 5.5)
Female (%)	943 (89.9)	73 (90.1)	0.8 (-7.7, 6.0)
Ethnicity (%)			
Asian	232 (22.1)	15 (18.5)	3.5 (-6.7, 10.9)
Black	168 (16.0)	7 (8.6)	7.3 (-1.1, 12.2)
Hispanic	32 (3.1)	5 (6.2)	3.1 (-0.6, 10.7)
White	568 (54.1)	51 (63.0)	9.2 (-2.1, 19.3)
Other[1]	49 (4.7)	3 (3.7)	0.9 (-5.8, 3.8)
ANA (%)	997 (94.4)	76 (93.8)	0.6 (-3.3, 8.2)
DFS ANA IIF (%)	7 (0.7)	10 (12.3)	11.7 (6.1, 20.6)
Anti-dsDNA (%)	654 (61.9)	45 (55.6)	6.4 (-4.4, 17.6)
Other autoantibodies (%)			
Ribosomal-P	166 (15.7)	9 (11.1)	4.6 (4.3, 10.3)
Sm	252 (23.9)	13 (16.0)	7.8 (-2.0, 14.8)
U1-RNP	333 (31.5)	17 (21.0)	10.6 (1.1, 18.5)
PCNA	73 (6.9)	7 (8.6)	1.7 (-3.0, 10.0)
Ro52	374 (35.4)	22 (27.2)	8.3 (-2.7, 17.2)
Ro60	489 (46.3)	28 (34.6)	11.7 (0.5, 21.7)
SSB	169 (16.0)	4 (4.9)	11.1 (3.7, 14.9)
None[2]	142 (13.4)	11 (13.6)	0.1 (-6.1, 9.5)
Nephritis[3] at enrollment (%)	294 (29.5)	16 (21.3)	8.1 (-2.8, 16.4)
Mean # ACR criteria (±SD)	4.8 (1.1)	4.6 (1.0)	0.1 (-0.1, 0.4)
Mean SLEDAI-2K score (±SD)	5.3 (5.2)	6.2 (5.3)	-0.8 (-2.0, 0.4)
Medications (% using)			
Steroids	690 (68.7)	49 (65.3)	3.4 (-6.8, 15.0)
Immunosuppressant	400 (39.8)	23 (30.7)	9.2 (-2.4, 19.0)
Anti-Malarial	668 (66.5)	56 (74.7)	8.1 (-3.1, 17.1)
Biologic	8 (0.8)	0 (0.0)	0.8 (-3.8, 1.5)

[1]Native North American, Native Hawaiian or other Pacific Islanders, others
[2]No other autoantibodies
[3]Lupus nephritis was diagnosed by renal biopsy or fulfilling the ACR criteria for lupus nephritis

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Abstract Number: 741

Satisfaction and Impact Associated with the Addition of Belimumab to Systemic Lupus Erythematosus (SLE) Treatment: A Cross-Sectional Survey of US Rheumatologists and Their Patients

Katie Pascoe[1], Steve Lobosco[2], David Bell[3], Ben Hoskin[3], Sulabha Ramachandran[4], Bonnie Pobiner[5] and David Chang[6], [1]Value Evidence and Outcomes, GlaxoSmithKline, Uxbridge, United Kingdom, [2]Adelphi Real World Ltd., Macclesfield, United Kingdom, [3]Autoimmune, Adelphi Real World Ltd., Manchester, United Kingdom, [4]Value Evidence and Outcomes, GlaxoSmithKline, Renaissance Centre, PA, [5]Immuno-Inflammation Therapy Area, GlaxoSmithKline, Triangle Park, NC, [6]US Medical Affairs, GlaxoSmithKline, Philadelphia, PA
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Background/Purpose: Patient and physician treatment satisfaction influences long-term adherence with a treatment regimen. The primary objective was to identify factors linked to satisfaction with the use of belimumab in clinical practice, in the United States (US). Understanding the impact of belimumab on clinical and patient outcomes was a secondary objective.

Methods: The Adelphi Lupus Plus Project (GSK study 202146) involved US rheumatologists (n=70) who completed paper-based data collection forms for five consecutive, eligible patients. Patients were ≥18 years old, diagnosed with SLE for ≥6 months, and receiving intravenous belimumab plus standard SLE care for ≥3months. Each rheumatologist only included one patient who had received belimumab for 3-6 months. The Western Institutional Review Board granted an IRB exemption for this study.

Results: The belimumab cohort (n=376) was 95% female, mean age 42, and Caucasian (56.1%) or African American (27.1%). Mean time since SLE diagnosis was 7 years and mean time treated with belimumab was 13 months, 65% were employed or were students. The majority of patients had disease involving both skin and joints (64%); 19.8% had only joint involvement. Prior to adding belimumab, most had 'moderate' (60%) or 'severe' (24%) disease and disease that was "deteriorating" (85%).

The patient self-completion form was completed by 72% of patients (n=270). The majority of patients (86%) reported a level of satisfaction with belimumab; 28% were 'very satisfied', 32% 'satisfied' and 26% were 'somewhat satisfied'. Most physicians were satisfied with belimumab (83%). Concordance between physician and patient satisfaction was moderate (Kappa Score = 0.4541). Predefined, multivariate analysis identified factors strongly associated with satisfaction (Table 1).

Table SEQ Table * ARABIC 1. Multivariate analyses identified factors associated with patient and physician satisfaction with beliumumab. Factors reported by the patient are denoted by (Pt) and by the Rheumatologist (Rh)	
	OR (95% CI)
PATIENT SATISFACTION	
Patient satisfaction is associated with:	
Improved ability to engage in leisure activities (Pt)	4.66 (2.12 - 10.25)
Reduction in fatigue severity (Rh)	3.72 (1.77 - 7.79)
General symptom improvement (Pt)	3.02 (1.15 - 7.94)
Improvement in pain/achiness (Pt)	2.71 (1.12 - 6.52)
Satisfaction with time taken to receive belimumab (Pt)	2.69 (1.40 - 5.15)
Satisfaction with frequency of belimumab (Pt)	1.94 (1.04 - 3.62)
Patient dissatisfaction is associated with:	
More severe disease prior to belimumab (Rh)	0.36 (0.14 - 0.92)
Current use of immunosuppressants (Rh)	0.40 (0.19 - 0.84)
RHEUMATOLOGIST SATISFACTION	
Physician satisfaction is associated with:	
Improvement in pain/achiness (Pt)	6.16 (2.20 - 17.24)
Satisfaction with frequency of belimumab (Pt)	3.91 (2.02 - 7.56)
Reduction in fatigue severity (Rh)	3.76 (1.93 - 7.35)
Physician dissatisfaction is associated with:	
Disease classed as currently ‘deteriorating or unstable ' (Rh)	0.13 (0.06 - 0.26)
Disease not classed as currently ‘mild' (Rh)	0.29 (0.13 - 0.63)
Improved ability to remember things (Pt)	0.43 (0.22 - 0.87)
Current use of immunosuppressants (Rh)	0.46 (0.26 - 0.83)
Higher numbers of flares in last 12 months (Rh)	0.75 (0.63 - 0.91)

Patient satisfaction was higher for those treated with belimumab for > 6 months, versus 3-6 months. For the majority of patients, physicians reported an improvement in overall symptoms (89%), reduction in flare severity (75%) and flare frequency (75%) since starting belimumab. Patients themselves stated an improvement in overall symptoms (89%), fatigue (83%), and pain (83%). Patients also reported improvements in feeling rested upon waking (91%), improved concentration (59%), and work (52%), as well as an improved ability to engage in leisure activities, daily activities and caring for children.

Conclusion: Adding belimumab improved symptoms of fatigue and pain and both factors were positively associated with patient and physician satisfaction. Improvement in the ability to engage in leisure activities and general symptom improvement were strongly associated with higher patient satisfaction. This insight into satisfaction should enhance the dialog between physicians and their patients about the outcomes expected during belimumab initiation; in turn, this may improve adherence.

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Abstract Number: 742

IgM Antibodies Against Malondialdehyde and Phosphorylcholine Are T Cell Dependent and Strong Protection Markers for Atherosclerosis in SLE

Md Mizanur Rahman[1], Ingiäld Hafström[2], Anquan Liu[1] and Johan Frostegård[1], [1]Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden, [2]Department of Medicine, Rheumatology unit, Karolinska Institutet, Stockholm, Sweden
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Background/Purpose:

Atherosclerosis is characterized by activated immune competent cells and lipid oxidation, where two major epitopes forming adducts are phosphorylcholine (PC) and malondialdehyde (MDA). We here study the regulation and properties of IgM antibodies against these (anti-PC and anti-MDA) and their role in SLE where atherosclerosis and CVD are much increased.

Methods:

Peripheral blood mononuclear cells (PBMC), B, CD3 T, CD4 T and CD8 T cell were isolated from buffy coat. PBMC derived monocyte were differentiated into dendritic cells (DCs) and treated with or without PC-KLH or MDA-HSA. For activation naïve autologous T cells were co-cultured with pre-treated DCs. B cell alone, or with CD3 T, CD4 T or with CD8 T cells were cultured to examine anti-PC IgM production. In addition to mixed B cell with CD3 T cell culture, B cells with CD3 T cells were also cultured in transwell co-culture plate. Further, B cells alone and mixed B cell with CD3 T cell cultures with or without anti HLA II or CD40 blocking antibody were cultured 6 days. Also, CD40 was silenced and cultured similar days.

Antibody level in serum of SLE patients from the SLEVIC cohort (n=114) were compared with age- and sex-matched population-based controls (n=108). Common carotid intima-media thickness (IMT) and plaque occurrence were determined by B-mode ultrasound. Plaques were graded according to echogenicity (a measure of vulnerability).

Results:

Flow cytometry analysis showed PC-KLH and MDA-HSA stimulated DC mediated T cell activation. In addition, pro-inflammatory effects of inflammatory lipids were inhibited by anti-PC and anti-MDA.

More than 8 fold higher levels of anti-PC IgM were detected by ELISA in mixed B cell with CD3 T cell cultures in comparison to B cells alone. After the co-culture of B and CD3 T cells in transwell plate there were no increased antibody levels indicating that B and T cells need to interact to augment anti-PC IgM production. Furthermore, anti-PC IgM was abolished by anti HLA II blocking antibody in mixed B and CD3 T cells culture, also inhibited by CD40 blocking antibody. In addition, CD40 role was ensured by CD40 gene silencing. Further, the lack of increased anti-PC IgM in mixed B with CD8 T cells culture and the increased levels of anti-PC in mixed B with CD4 T cells culture support the role of helper T cell for the anti-PC IgM production.

In serum having high levels, above 66rdpercentile, of both anti-PC and anti-MDA was a striking protection marker for plaque prevalence and vulnerability (OR 0.08, CI (0.01-0.46) and OR 0.10 and CI (0.01-0.82) respectively)

Conclusion:

Anti-MDA and anti-PC are T-cell dependent, anti-inflammatory and strong protection markers for atherosclerosis and plaque vulnerability in SLE and in general. This finding could indicate an underlying mechanism in autoimmune disease, namely low levels of natural antibodies and opens up therapeutic possibilities with these antibodies in autoimmune diseases.

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Abstract Number: 743

Behavior of Complement Levels and Risk of Organ Involvement in SLE Patients

Ignacio Javier Gandino[1], Marina Scolnik[1], Emmanuel Bertiller[1], Valeria Scaglioni[2] and Enrique R. Soriano[3], [1]Rheumatology Unit, Internal

Medicine Service, Hospital Italiano de Buenos Aires, Instituto Universitario Hospital Italiano de Buenos Aires, and Fundacion PM Catoggio, Buenos Aires, Argentina, [2]Rheumatology, Hospital Italiano, Buenos Aires, Argentina, [3]Internal Medicine, Hospital Italiano de Buenos Aires, Buenos Aires, Argentina

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Background/Purpose: the complement system plays a major role in autoimmune diseases, and in particular in systemic lupus erythematosus (SLE). Complement deficiencies are a genetic risk factor for SLE. Also a reduction in complement levels has been associated with an increase in SLE activity, with certain organ involvement (ie glomerulonephritis) and as a predictor of a SLE flare. Our objective was to analyze clinical course of SLE patients with permanent low complement levels, and compare them with those with fluctuant levels or persistently normal levels.

Methods: complement determinations (C3 and C4 levels) were analyzed in patients with SLE (fulfilling ACR or SLICC criteria) seen at a University hospital between 2000 and 2013. Patients were grouped in those with permanent C3 and/or C4 low values (low complement group) those with C3 and C4 constant normal values (normal complement group), and those with fluctuant values (periods of normal and periods of low values, during follow up: fluctuant group). Mortality, clinical characteristics, organ involvement and antibodies were analyzed and compared between groups.

Results: Two hundred and seventy SLE patients were included (242 females, 89.6%), mean age at diagnosis was 34.2 years (SD 15.8). Patients were divided according to complement levels during follow up in 3 groups: persistent low complement levels (n=79), normal complement levels (n=116), and fluctuant levels (n=75). Demographics, clinical and serological characteristics are shown in table 1. Mortality was similar between the three groups (5%, 4% and 7%, respectively). Lupus glomerulonephritis was more frequent in patients with fluctuant levels of complement (both proliferative and membranous glomerulonephritis). Patients with normal complement had less frequency of hematological involvement and antiDNA antibodies. On multivariable analysis persistent low complement levels were neither associated with mortality nor with organ damage as measured by SLICC (SLICC>0). Only increased age was associated with mortality, and increased age and neurologic involvement with SLICC >0.

Conclusion: Different behavior of complement levels in SLE patients was not associated with differences in outcomes (mortality and organ damage). Although there were some differences in organ involvement (higher prevalence of glomerulonephritis in fluctuant levels group, and hematological involvement and anti DNA antibodies in low and fluctuant levels groups), do not appear to represent clear different sub-groups of patients.

Table 1. SLE patients grouped by behavior of complement levels during follow up.

	Normal complement (n=116)	Persistent Low complement (n=79)	Fluctuant complement (n=75)	P value
Females, n (%)	107 (92.2)	70 (88.6)	65 (86.7)	0.439
Age at diagnosis, average, years (SD)	36.4 (16.5)	32.4 (14.7)	32.7 (15.8)	0.1397
Follow-up, median, years (IQR)	6.4 (8.2)	6.1 (7.6)	9.2 (5.6)	0.345
Fulfilling ACR criteria, n (%)	76 (65.5)#	64 (81)*	66 (88)&	0.001 * and & vs #
Fulfilling SLICC criteria, n (%)	96 (82.7)#	73 (92.4)	74 (98.7)&	0.001 & vs #
Cutaneous Lupus, n (%)	76 (65.5)	50 (63.3)	44 (58.7)	0.773
Oral ulcers, n (%)	24 (20.7)	19 (24.1)	20 (26.7)	0.624
Serositis, n (%)	37 (31.9)	15 (18.9)	17 (22.7)	0.102
Artritis, n (%)	59 (50.9)	47 (59.5)	35 (46.7)	0.261
Neurologic, n (%)	15 (12.9)	7 (8.9)	7 (9.3)	0.598
Renal, n (%)	57 (49)#	44 (56)*	56 (75)&	0.002 & vs # and *
Leukopenia or lymphopenia, n (%)	35 **(30.2)#**	39 (49.4)*	34 (45.3)&	0.007 * vs # and 0.033 & vs #

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Abstract Number: 744

Longitudinal Assessment of Th1 and Th2 Cytokines: A Comparison Between Adult-Onset and Childhood-Onset Systemic Lupus Erythematous

Karina Pelicari[1], Mariana Postal[1], Nailu A. Sinicato[2], Fernando A. Peres[1], Roberto Marini

Thrombocytopenia	20 **(17.2)#**	28 (35.4)*	25 (33.3)&	0.026 * and & vs #
ANA positive, n (%)	109 (94)	77 (97.5)	68 (90.7)	0.202
DNA positive, n (%)	52 (44.8)#	54**(68.3)***	57 **(76)&**	<0.001 * and & vs #
Sm positive, n (%)	12 (10.3)	10 (12.7)	8 (10.7)	0.882
Lupus anticoagulant positive, n (%)	14 (12.1)	16 (20.2)	11 (14.7)	0.254
Anticardiolipins positive, n (%)	17 (14.7)	20 (25.3)	13 (17.3)	0.405
SLICC at the end of follow up, mean (SD)	0.98 (1.4)	1 (1.4)	1.33 (1.7)	0.2345

Sr.[3], Lilian Tereza Costallat[4] and **Simone Appenzeller**[5], [1]Medicine, State University of Campinas, Campinas, Brazil, [2]Pediatrics, State University of Campinas, Campinas, Brazil, [3]Pediatric Rheumatology Unit, State University of Campinas, São Paulo, Brazil, [4]RUA EZEQUIEL MAGALHAES,26, Unicamp, Campinas, Brazil, [5]Division of Rheumatology, Faculty of Medical Science, State University of Campinas, São Paulo, Brazil

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Session Time: 9:00AM-11:00AM

Background/Purpose:

The clinical presentation may be different between adult-onset SLE (aSLE) and childhood-onset SLE (cSLE). The profile of cytokine may the clarify of SLE pathophysiology. The aim of this study was to determine the serum levels of Th1 (IL-12), Th2 (IL-6 e IL-10) longitudinally as well as its possible associations in aSLE and cSLE.

Methods:

The included SLE patients were recruited from outpatient Rheumatology and Pediatric Rheumatology –State University of Campinas, matched for disease duration. Sera samples were obtained quarterly from all participants, in each routine visit we made a blood collection, totaling four different periods in all patients, in the absence of infections. We further assessed disease activity through of the SLE Disease Activity Index (SLEDAI) and damage through Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index (SDI), mood and anxiety through Becks Depression (BDI) and Anxiety Inventory (BAI) and current drug exposures. Th1 (IL-12), Th2 (IL-6 and IL-10) cytokines levels were measured by ELISA using commercial kits. Data were compared by non-parametric tests.

Results:

We included 63 cSLE patients (mean age 19.7±4.3 and disease duration 7.35±4.22), 67 aSLE patients (mean age 39.9±11.8 and disease duration 7.73±3.18) and 40 healthy controls (mean age 29.6±10). In aSLE patients compared with healthy controls during the four periods evaluated, IL-6 levels were significantly increased in patients (p=0.03, p=0.003, p=0.002, p=0.002), IL-12 fluctuated during the period evaluated (p=0.75, p=0.50, p=0.01, p=0.001) and IL-10 It had no significant difference (p=0.32, p=0.13, p=0.99, p=0.08). In cSLE patients compared with healthy controls, we observed a significantly increase of IL-12 (p=0.04, p=0.001, p=0.01, p=0.02), we did not observe significant difference in IL-10 (p=0.94, p=0.85, p=0.81, p=0.95) and IL-6 (p=0.66, p=0.14, p=0.25, p=0.21). Comparing the levels of cytokines between aSLE and cSLE, we observed that IL-12 fluctuated during the period evaluated (p=0.07, p=0.001, p=0.99, p=0.14) and had no significant difference in IL-6 (p=0.97, p=0.11, p=0.15, p=0.53) and IL-10 (p=0.09, p=0.29, p=0.59, p=0.25). We did not observe an association between disease activity and cytokines in any period (p>0.05). The aSLE patients had a significant decrease of disease activity indices during periods evaluated (p=0.021), There was no significant difference in disease activity among cSLE and aSLE patients (p>0.05). No significant difference in SDI scores between aSLE and cSLE (p=0.10). Regarding medication, we observed that aSLE (p=0.001) and cSLE (p=0.001) patients had a significant decrease of use of prednisone during the four periods. In disorders of mood and anxiety, during the four evaluated periods, no significant variation in BAI, cSLE (p=0.52) and aSLE (p=0.13), and BDI, cSLE (p=0.29) and aSLE (p=0.65) was observed. When comparing the patients we observed that aSLE have significantly higher scores of BDI (p≤0.002) and BAI (p≤0.006) than cSLE.

Conclusion:

Cytokines behave differently in aSLE and cSLE patients. The analyzed cytokines fluctuated throughout the study period, however were not associated with disease activity markers.

Disclosure: K. Pelicari, None; **M. Postal**, None; **N. A. Sinicato**, None; **F. A. Peres**, None; **R. Marini Sr.**, None; **L. T. Costallat**, None; **S. Appenzeller**, None.

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Abstract Number: 745

Changes in Serum Albumin Levels Correlate Highly with Severity and Activity of SLE

Bao Nguyen[1], Dawn Piarulli[2], Jennifer Johnson[3] and David Horwitz[1,4], [1]Medicine, Keck School of Medicine of USC, Los Angeles, CA, [2]Internal Medicine, Division of Rheumatology, Keck School of Medicine of USC, Los Angeles, CA, [3]Medicine, Keck School of Medicine of USC, Los Angeles,, CA, [4]Medicine-Rheumatology-Immun, Keck School of Medicine of USC, Los Angeles, CA

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SESSION INFORMATION

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Session Title: Systemic Lupus Erythematosus - Clinical Aspects and Treatment Poster Session I

Session Type: ACR Poster Session A

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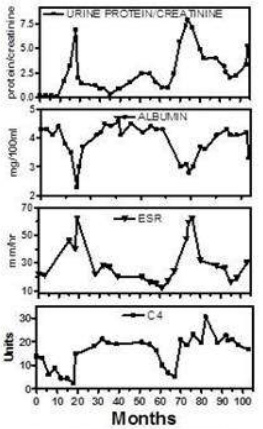

Fig. 1 Relationship between changes in the urine protein/creatinine ratio with serum albumin, ESR and C4. In this patient the relationship with C3 and HCT was similar.

Background/Purpose: When a complex patient with long term lupus is seen for the first time, there is a need for a readily and commonly available serum marker to graphically indicate the severity and course of their disease. Serum albumin levels are known to reflect SLE activity, especially lupus nephritis, but the utility of this marker to assess longitudinal activity has not been studied. Here we have compared serum albumin levels with other measures of lupus activity

Methods: We selected 10 patients with lupus nephritis followed at the USC+LAC Medical Center for 1 to 10 years. Other patients without nephritis were also studied. Using the urine protein/creatinine (UPC) ratio as a reference standard for nephritis, we looked for the correlation with serum albumin levels, ESR, CRP, hematocrit, anti-dsDNA levels, serum C3, and C4. Both Pearson and Spearman r values were calculated and p values determined. The UPC of patients studied was >2.

Results: The Table shows that changes in serum albumin levels correlated highly with UPC in all patients studied ($p < 0.01$). C3 levels were the only other marker to correlate significantly with UPC in more than one half of the half the subjects. However, as an example of how lab markers can relate to UPC, Fig.1 shows a significant correlation of all markers examined in a patient we treated for more than 8 years. In cases without lupus nephritis, similar decreases in serum albumin levels were observed in patients with severe organ system disease, but not in lupus patients with only moderate skin involvement or serositis. There was no relationship with serum albumin levels disease activity in most cases of rheumatoid arthritis.

Conclusion: With the increased use of the computerized medical record, we believe that in the first encounter of a lupus patient with longstanding disease, graphing serum albumin levels will reveal useful information regarding the severity of systemic activity, and the dates of this involvement. Inspection of the medical record on these dates will reveal the response or lack of response to the agents used, and the rheumatologist can then rapidly formulate the appropriate treatment regimen for that patient in a timely manner.

Table Correlation of lab tests with Urine Protein Creatinine Ratio

	Albumin	α-DNA	CRP	ESR	C3	C4	HCT
Mean correlation coefficient (r value)	-0.87	0.54	0.44	0.49	-0.64	-0.47	-0.46
P <0.05 n=10	100%	30%	10%	30%	60%	40%	30%

Abstract Number: 746

Multi-Center Delphi Exercise Reveals Important Key Items in Classifying SLE

Bimba F. Hoyer[1], Gabriela Schmajuk[2], Martin Aringer[3], Sindhu R. Johnson[4,5], David I. Daikh[6], Thomas Dorner[7] and on behalf of the SLE criteria steering committee, [1]Charité University Medicine, Department of Medicine/Rheumatology and Clinical Immunology and German Rheumatism Research Centre Berlin (DRFZ), Berlin, Germany, [2]San Francisco VA Medical Center, University of California, San Francisco, San Francisco, CA, [3]Rheumatology, Medicine III, University Clinical Center, Technical University Dresden, Dresden, Germany, [4]Medicine, Toronto Scleroderma Program, Toronto Western Hospital, Toronto General Hospital, Mount Sinai Hospital, and University of Toronto, Toronto, ON, Canada, [5]Dept of Rheumatology, Toronto Western and Mt. Sinai Hospitals, University of Toronto, Toronto, ON, Canada, [6]Rheumatology, UCSF/VA Medical Center, San Francisco, CA, [7]Department of Medicine/Rheumatology and Clinical Immunology and German Rheumatism Research Centre Berlin (DRFZ), Charité University Medicine, Berlin, Germany

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SESSION INFORMATION

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Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose:

EULAR and ACR have jointly funded a project to improve existing classification criteria for SLE; this abstract reports on the early phase of this project. Classification criteria are being developed using multicriteria decision analysis methods. The goal of the initial phase of this project was to generate a broad set of items potentially useful for the classification of SLE and select a list of candidate items for use in forced-choice decision analysis. The aims were to include items that encompass a broad spectrum of SLE, including patients whose disease is in the early stage as well as those in the late stage, and that are in accordance with criteria used for diagnosis of SLE in clinical practice.

Methods:

135 expert lupus clinicians were asked to independently rate items derived from the ACR and SLICC classification criteria for their importance in diagnosing early and established SLE, respectively, in an online survey. Answers were retrieved from 120 experts (N= 54 from EULAR centres, n=66 from North American). In addition, open commentary fields were provided for the suggestion of novel items.

Results:

Interestingly, while 58% of those would not diagnose SLE without a positive ANA by immunofluorescence on at least one occasion, 23% said they would make a diagnosis and 19% were unsure. The experts were in agreement that characteristic autoantibodies as well as specific renal features and skin manifestations are key for diagnosing SLE, regardless of whether early or established SLE. When asked about organ system involvement, 51,1% stated that one organ system would been sufficient for making the diagnosis of SLE, but that additional typical laboratory features (ANA, dsDNA) would be required.

Notably, 85% of the expert group would make the diagnosis of SLE if renal pathology shows lupus nephritis, but skin histology was not rated nearly as specific.

Conclusion:

A survey of international SLE experts indicates that they consider a broad range of items for the diagnosis of SLE. Nevertheless, it is interesting that a majority would diagnose SLE based only on renal pathology, as suggested by the SLICC group, as well as upon single organ system involvement in the presence of additional laboratory findings such as ANA and dsDNA. These ideas will be explored in more detail in the next phases of the project.

Table 1:

Would you make the diagnosis of SLE in absence of ANA (immunofluorescence)?	Yes 23%	No 58%	Unsure 19%
How many organ systems would be enough for you to make the diagnosis of SLE?	52% one organ system	38% two organ systems	6% three organ systems
Would one pathological finding be enough to make the diagnosis?	Yes 85%	No 15%	

Disclosure: B. F. Hoyer, None; **G. Schmajuk**, None; **M. Aringer**, None; **S. R. Johnson**, None; **D. I. Daikh**, None; **T. Dorner**, None.

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Abstract Number: 747

Depletion of Serum Soluble CD40L Characterizes the Association Between Systemic Lupus Erythematosus and Thrombotic Thrombocytopenic Purpura: Longitudinal, Single-Center Study

Javier Merayo-Chalico[1], Ana Barrera-Vargas[2], Jorge Alcocer-Varela[2] and Diana Gómez-Martín[2], [1]Immunology and Rheumatology, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico, [2]Department of Immunology and Rheumatology, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico

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Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose: Patients with systemic lupus erythematosus (SLE) have a higher incidence of thrombotic thrombocytopenic purpura (TTP). Differentiating TTP from SLE activity may represent a challenge to clinicians, and there is no adequate biomarker to help distinguish between both entities. The aim of this study was to correlate different molecules associated with vascular and platelet regulation in patients with SLE-associated TTP at diagnosis (dx), after plasmapheresis (ap) and at remission (rem).

Methods: We included 73 subjects (13 SLE/TTP patients, 14 SLE-remission, 13 active hematological SLE, 14 non-hematological active SLE and 19 healthy controls). Patients were diagnosed with TTP in the presence of the following parameters: microangiopathic hemolytic anemia, thrombocytopenia ≤100,000 cel/µl, high LDH levels and negative Coombs test. Patients with SLE were diagnosed with at least ≥ 4 ACR classification criteria. We obtained serum samples for each subject, including serial samples for SLE/TTP patients (dx, ap and rem). Serum sCD40L and VEGF were measured by ELISA, and different cytokine levels were measured by luminometry.

Results: The main characteristics of each group are depicted in table 1. We found increased sCD40L levels in active hematological and non-hematological SLE in comparison to SLE/TTP^{dx} (p=0.039 and 0.001 respectively), but there were no differences between SLE/TTP^{rem} and active hematological SLE (3044±403 vs 3397±708 pg/ml, p=0.77). Interestingly, mean sCD40L levels progressively increased in treated SLE/TTP patients (see table) an also a positive correlation between sCD40L and VEGF levels was found (r=0.62, p=0.004), regardless of the improvement in platelet count. There were no significant differences in SLEDAI score among TTP and active SLE groups (p=0.54). Furthermore, CXCL1 levels were lower in SLE/TTP^{dx} *vs* active hematological SLE (22.5±5.7 vs 136.7±33.5 pg/ml, p=0.040). Other analyzed cytokines (IL2, 6, 8, 10, TNFα e IFNγ) were not different among groups.

Conclusion: Our findings suggest that SLE/TTP patients have sCD40L depletion at baseline, which represents a differential serologic profile from active SLE. After the proper treatment is initiated, sCD40L levels increase progressively. It is possible that the depletion of this costimulatory molecule could be associated with recruitment at the vascular wall, denoting its potential pathogenic role in microangiopathy-associated endothelial dysfunction. Prospective studies, which ideally should include TTP patients without any autoimmune disease, are needed to confirm those findings.

Table 1. Clinical and serologic characteristics of the different groups

Groups (n)	Age, years (mean ±SEM)	SLEDAI, points (mean ±SEM)	Hemoglobin g/dl (mean ±SEM)	Platelets cells/ µl x10^3 (mean±SEM)	Leukocytes cells/mm^3x10^3 (mean±SEM)	VEGF pg/ml (mean ±SEM)	CD40L pg/ml (mean ±SEM)
Healthy controls (19)	31±2	N/A	N/D	N/D	N/D	558±163	5709±840
SLE remission (14)	39±4	0	14.4±0.19	248±13	5.56±0.42	26 1±93	3754±650
Active SLE	-	-	-	-	-	-	-
Hematological(13)	31±3	14.7±1.7	8.80±0.45	106±13	7.31±1	119±69	3397±708
Non hematological (14)	28±2	16.9±1.4	10.1±0.23	296±37	8.33±1.27	268±131	4138±667
SLE/TTP (13)	32±5	-	-	-	-	-	-
At diagnosis	-	16±0.6	7.00±0.37	66±8	5.83±1.24	54±41	1131±410
Postplasmapheresis	-	N/A	8.00±0.57	102±25	7.25±0.70	89±30	1515±440
Remission	-	N/A	9.17±0.53	223±34	7.68±0.80	187±76	3044±403

N/A= Not Applicable; N/D= Not Determined

Abstract Number: 748

Comparison of Systemic Lupus Erythematosus in 3 Different Asian Ethnic Groups: Results from the 1000 Faces of Lupus Cohort

Mai Nguyen[1], Earl Silverman[2], Janet E. Pope[3], Paul R. Fortin[4], Ann E. Clarke[5], Christian Pineau[6], Sasha R Bernatsky[7], C Douglas Smith[8], Gaëlle Chédeville[9], Lori B. Tucker[10], Michel Zummer[11], Marie Hudson[6], Adam M. Huber[12], Deborah M. Levy[13], Hector Arbillaga[14], Carol Hitchon[15], Christine A. Peschken[16] and CaNIOS 1000 Faces Investigators, [1]Medicine, University of Manitoba, Winnipeg, MB, Canada, [2]Division of Rheumatology, Hospital for Sick Children and University of Toronto, Toronto, ON, Canada, [3]University of Western Ontario, London, ON, Canada, [4]Medicine, CHU de Québec - Université Laval, Québec, QC, Canada, [5]Immunology/Epidemiology, Montreal General Hospital, Montreal, QC, Canada, [6]Medicine, McGill University, Montreal, QC, Canada, [7]Division of Rheumatolog, McGill Unversity Health Cener, Montreal, QC, Canada, [8]The Arthritis Centre, TOH Riverside Campus, Ottawa, ON, Canada, [9]Rheumatology, McGill University, Montreal, QC, Canada, [10]Rheumatology, BC Children's Hospital, Vancouver, BC, Canada, [11]Rheumatology, Hôpital Maisonneuve-Rosemont and University of Montreal, Montreal, QC, Canada, [12]Pediatric rheumatology, IWK Health Centre, Halifax, NS, Canada, [13]Rheumatology, The Hospital for Sick Children, Toronto, ON, Canada, [14]Calgary Rheumatology, Calgary, AB, Canada, [15]University of Manitoba, Winnipeg, MB, Canada, [16]Rheumatology, Univ of Manitoba, Winnipeg, MB, Canada

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Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose: Ethnic variations in systemic lupus erythematosus (SLE) are well described, with more prevalent and severe disease in

non-Caucasians including North American Asians. However, Asian ethnicity includes broad cultural, geographic and genetic diversity, and there is limited data examining SLE among Asian ethnicity subsets. We describe SLE in 3 Asian subgroups from a large SLE cohort.

Methods: The 1000 Faces of Lupus is a multicentre Canadian cohort of over 2000 SLE patients. Sociodemographics, ACR classification criteria (ACRc), autoantibodies, disease activity scores (SLEDAI), Systemic Lupus International Collaborating Clinics damage index (SDI) scores, and treatments are collected using standardized tools. Ethnicity was self-reported and Asian subgroups were divided by geographic country of origin into East Asian (EA), Southeast Asian (SEA), South Asian (SA) and Central Asian (CA). Data at cohort entry for Asians and Caucasians were abstracted and cross-sectional univariate analyses including T tests, one-way ANOVA, and chi-square tests were performed.

Results: There were 334 Asians (176 EA, 78 SEA, and 78 SA, and 2 CA), and 1275 Caucasians. CA were excluded. Onset age for Asians was similarly young (EA=23±13 years; SEA=21±10 years; SA=20±11 years) compared to Caucasians (33±15 years, p<0.001). Childhood onset was frequent in Asians (EA=49%; SEA=51%; SA=61%) compared to Caucasians (17%, p<0.001). Over 40% of all Asians were immigrants. The proportion of males was higher in Asians (EA=15%; SEA=16%; SA=19%) compared to Caucasians (10%, p=0.008). ACRc or SLEDAI scores were not different, while all Asians had a higher frequency of nephritis (EA=57%; SEA=63%; SA=51%), compared to Caucasians (33%, p<0.001). More Asians were dsDNA+ (ever) (EA=62%; SEA=63%; SA=78%) compared to Caucasians (52%, p<0.001). SEA were most frequently antiSm+ and antiRNP+ (ever) (EA=31%; SEA=50%; SA=30%; p=0.01, and EA=20%; SEA=32%; SA=22%; p=0.03), but all Asians were higher than Caucasians (19%, p<0.001; 16%, p<0.001). More SA were antiphospholipid antibody positive (ever) (EA=26%; SEA=18%; SA=37%, p=0.04) but overall not different from Caucasians (24%). Over 90% of Asians graduated high school compared to Caucasians (83%, p=0.007). Most Asians were in the highest income tier (EA=55%; SEA=42%; SA=58%), similar to Caucasians (51%). Treatment with prednisone (EA=55%; SEA=67%; SA=65%), cyclophosphamide (EA=13%; SEA=21%; SA=20%), and mycophenolate (EA=15%; SEA=19%; SA=9%) was relatively frequent in Asians, likely reflecting the high frequency of nephritis. The mean disease duration in Asians was 8 years but most had not accumulated damage (SDI=0 in 66% EA; 64% SEA; 79% SA) compared to Caucasians (47%, p<0.001).

Conclusion: This is the first study to compare SLE in North American Asian subgroups. Childhood onset SLE is more common in Asians than Caucasians. Disease appears severe but not different between the Asian groups. People of Asian subcontinental ethnic origin are the fastest growing ethnic group in North America. Young onset age and a high proportion of 1st generation immigrants suggest the potential for a growing burden of SLE in this population. Future studies of outcomes and optimal treatments are indicated.

Disclosure: M. Nguyen, None; **E. Silverman**, None; **J. E. Pope**, Amgen, 2; **P. R. Fortin**, GlaxoSmithKline, 5,Lilly, 5,AbbVie, 5; **A. E. Clarke**, None; **C. Pineau**, None; **S. R Bernatsky**, None; **C. D. Smith**, None; **G. Chédeville**, None; **L. B. Tucker**, None; **M. Zummer**, Janssen Inc, 5; **M. Hudson**, None; **A. M. Huber**, None; **D. M. Levy**, None; **H. Arbillaga**, None; **C. Hitchon**, None; **C. A. Peschken**, None.

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Abstract Number: 749

Microvesicles Containing Nucleic Acids and Expressing Immunoglobulins and HMGB1 Are Abundant in Patients with Systemic Lupus Erythematosus

Fariborz Mobarrez[1], Håkan Wallén[2], Iva Gunnarsson[3], Johanna Gustafsson[4], Agneta Zickert[3], David Pisetsky[5,6] and Elisabet Svenungsson[4], [1]Department of Medicine, Karolinska Institutet, Rheumatology Unit, Karolinska University Hospital, Stockholm, Sweden, [2]Division of Cardiovascular Medicine, Karolinska Institutet, Department of Clinical Sciences, Stockholm, Sweden, [3]Department of Medicine, Rheumatology Unit, Karolinska Institutet, Stockholm, Sweden, [4]Department of Medicine, Karolinska Insitutet, Rheumatology Unit, Karolinska University Hospital, Stockholm, Sweden, [5]Medical Research Service, Durham VA Hospital, Durham, NC, [6]Department of Medicine, Duke University Medical Center,, Durham, NC

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Session Title: Systemic Lupus Erythematosus - Clinical Aspects and Treatment Poster Session I

Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose:

Systemic lupus erythematosus (SLE) is a prototypic autoimmune disease characterized by immune complexes of antinuclear antibodies. As a source of these antigens, increased levels of apoptosis and defective clearance of dead cells have been proposed. As now recognized, during apoptosis and cell activation, microvesicles (MVs) are released extra-cellularly. MVs are small membrane bound vesicles that enclose intracellular contents. To determine whether MVs contain nuclear molecules and can form immune complexes, we quantified by flow cytometry the content of nucleic acids; High Mobility Group Box-1 (HMGB1), a non-histone protein with alarmin activity; and bound immunoglobulin on MVs from SLE patients and controls.

Methods:

Fasting plasma samples from 294 patients with SLE (4≥ of 1982 ACR criteria) and 309 age- and sex-matched population controls were investigated. MVs were analyzed by flow cytometry as vesicles less than 1.0 μm in size and positive for SYTO 13, a cell permeable dye binding to DNA or RNA. We also measured expression of HMGB1, IgG and IgM on MVs.

To determine whether factors in SLE blood can bind MVs, MVs from healthy volunteers were incubated for 60 min at room temperature with plasma from SLE patients (n=5). After incubation, the MVs were isolated and the amounts of IgG and IgM were measured.

Results:

Blood of SLE patients had significantly higher numbers of MVs containing nucleic acids and these MVs expressed more HMGB1, IgG and IgM as compared to controls (Figure 1A-D).

In-vitro experiments revealed that incubation of MVs obtained from healthy volunteers with MV-free plasma obtained from SLE patients, significantly increased the levels of IgG and IgM on MVs (IgG: 0.3±0.03 vs 0.64±0.07 mean fluorescence intensity (MFI); IgM: 0.29±0.02 vs 0.41±0.08 MFI; $p<0.0001$ and $p<0.05$ respectively).

Conclusion:

MVs containing nucleic acids are significantly more abundant in the blood of SLE patients than in controls. Many of these MVs expose the alarmin HMGB1, IgG and in particular, IgM on their surface. Furthermore, plasma from SLE patients increased immunoglobulin binding on MVs from controls. Together, these studies indicate that release of MVs into the blood is a feature of SLE and that immunoglobulins can bind to antigenic sites on MVs. Since MVs are plentiful, form immune complexes, and display an alarmin, these vesicles could drive SLE pathogenesis as a source of immune complexes and immunostimulatory molecules such as HMGB1.

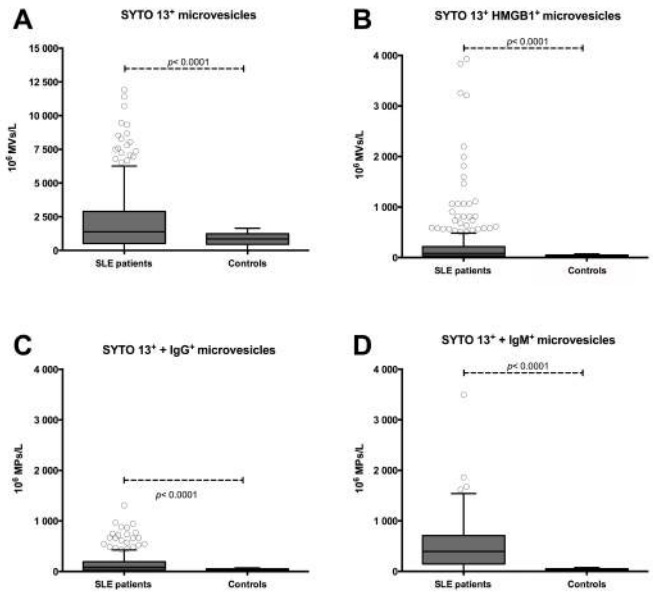

Figure 1. Microvesicles were analyzed by flow cytometry and defined as vesicles less then 1.0 μm in size and positive for SYTO 13 (A) and co-expression of HMGB1 (B), IgG (C) and IgM (D), in SLE patients and matching controls.

Disclosure: F. Mobarrez, None; **H. Wallén**, None; **I. Gunnarsson**, None; **J. Gustafsson**, None; **A. Zickert**, None; **D. Pisetsky**, None; **E. Svenungsson**, None.

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Abstract Number: 750

Belimumab for Systemic Lupus Erythematosus: A Cochrane Systematic Review and Meta-Analysis

Jasvinder A. Singh[1] and Nipam Shah[2], [1]University of Alabama at Birmingham, Birmingham, AL, [2]University fo Alabama at Birmingham, Birmingham, AL

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Session Title: Systemic Lupus Erythematosus - Clinical Aspects and Treatment Poster Session I
Session Type: ACR Poster Session A
Session Time: 9:00AM-11:00AM

Background/Purpose:

Belimumab is a new approved treatment option for patients with lupus. Our objective was to perform a systematic review of benefits and harms of belimumab for systemic lupus erythematosus (SLE).

Methods:

We searched multiple databases for eligible studies using a search strategy developed by a Cochrane librarian. We included randomized controlled trials (RCTs) or controlled clinical trials (CCTs) of belimumab (alone or in combination) compared to placebo/control treatment, in adults with lupus. Two authors independently assessed search results, trial quality and risk of bias, and extracted data. Review manager was used for data analyses.

Results:

Four studies (N=2205) qualified for qualitative and/or quantitative analyses. 5 studies pooled data from up to three of these original studies. Compared to placebo, belimumab 10mg/kg (approved dose) was associated with significantly higher likelihood of achieving improvement/reduction in SELENA-SLEDAI score (a validated SLE disease activity score) by >=4-points and SLE responder index (SRI) at 52-weeks (level of evidence, high for both outcomes; I^2 =0% for both) with risk ratios of 1.29 (95% CI 1.10 to 1.51, I^2= 0%) and 1.31 (95% CI 1.11 to 1.55, I^2= 0%) , respectively. Change in HRQOL, assessed by SF-36 PCS score improvements, with belimumab 10mg/kg was a mean 1.35 units (95% CI 0.68 to 3.38) greater change than placebo, which did not meet statistical or clinical significance of 2.5-5 unit greater improvement (level of evidence, moderate; I^2 =0%). The proportion of patients with >=1 serious AE, >=1 serious infection and withdrawals due to adverse events did not differ significantly between belimumab 10mg/kg and placebo;1.09 (95% CI 0.76 to 1.56), 0.97(95% CI 0.53 to 1.78); 1.40 (95% CI 0.32 to 6.22) (level of evidence, moderate; I^2 =0% for all three). Mortality was rare, and didn't differ significantly between belimumab 10 mg/kg and placebo (level of evidence, low; I^2=0%). Belimumab-treated patients were also more likely than placebo-treated patients to experience improvement (decrease of >=0.3) in patient global assessment (PGA) and were able to reduce corticosteroid dose by >=50% and less likely to have any SLE flare and severe SLE flare. Similar findings were noted for efficacy of belimumab 1 mg/kg compared to placebo.

The number needed to treat (NNT) for SRI at 52 weeks was 8 (95% CI: 5 to 23) and the number needed to treat (NNT) for SELENA-SLEDAI at 52 weeks was 8 (95% CI: 5 to 25). We found overall quality of evidence to be high. Belimumab at 10mg/kg dose was found to be associated with higher improvements in disease signs and symptoms and disease activity (greater effects on SRI, SELENA-SLEDAI, BILAG, PGA) than belimumab at 1mg/kg dose.

Conclusion:

At the FDA-approved dose of 10mg/kg, belimumab was associated with significantly more benefits compared to placebo in patients with lupus based on well-designed high-quality RCTs that used validated outcomes. Evidence related to harms is inconclusive and of low quality.

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Rituximab Induced Serum Sickness: A Systematic Review

Paras Karmacharya[1], **Dilli Poudel**[1], Ranjan Pathak[1], Anthony Donato[2], Sushil Ghimire[1], Smith Giri[3], Madan Aryal[1] and Clifton O. Bingham III[4], [1]Internal Medicine, Reading Health System, WEST READING, PA, [2]Internal medicine, Reading Health System, WEST READING, PA, [3]Internal medicine, University of Tennessee Health Science Center, Memphis, TN, [4]Rheumatology, Johns Hopkins University, Baltimore, MD

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Background/Purpose: Rituximab (anti-CD20 monoclonal antibody) has been frequently used to treat various autoimmune diseases in which B-cells are participants, and for hematological malignancies in which CD20-bearing cells are increased. Infusion reactions including fever, chills and rigors, as well as allergic (Type IV) anaphylactoidspectrum reactions and less commonly serum sickness (or Type III) hypersensitivity reaction have been reported with its administration. It is important to recognize this as re-exposure can result in recurrent and more severe manifestations. We perform a systematic review and meta-analysis to characterize RISS in autoimmune diseases and hematological malignancies.

Methods: A comprehensive search of MEDLINE, EMBASE, ACR and EULAR databases was performed for relevant articles of patients with RISS from inception to September 2014 (Figure 1). Statistical analysis of demographic and clinical features was performed using Microsoft EXCEL 2007 and SPSS version 20.0.

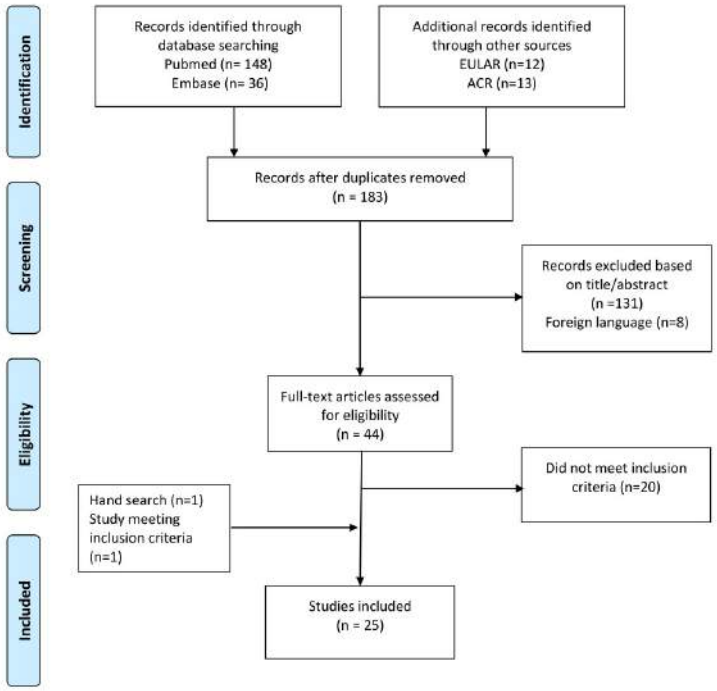
Results: In the 33 patients (from 25 reports) with RISS, the mean age of presentation was 39.1±17.5 years with a female preponderance (n=23, 76.67%). The majority of cases were associated with an underlying autoimmune condition (n=28, 84.85%), most commonly immune thrombocytopenic purpura (n=10) and Sjögren'ssyndrome (n=7 and lymphomas in 5/33 cases (15.15%) (Table 1). Symptoms of RISS began 6.63±3.83 days following infusion with most episodes occurring during the first cycle. Classic triad of serum sickness (fever, rash and arthralgia) was reported in 16 (48.5%) cases. Time from drug exposure to symptom onset was significantly greater with the first doses of rituximab compared to the second dose (mean time 10.00 vs. 4.05 days, P=0.002), and time to resolution was significantly greater for rheumatologic vs. hematological indications (mean time 2.50 vs 1.00 days, P=0.035). Corticosteroids were the most commonly used treatment (n=21), with all cases reporting a complete resolution of symptoms in 2.15±1.34 days.

Conclusion: It is important to recognize and diagnose RISS clinically as it may mimic exacerbation of various rheumatologic conditions such as RA. Although elevated RF, immunoglobulins and HACA levels may play a role in the pathogenesis, these are not predictable markers, as the serologic and Ig levels are features of the underlying disease. RISS is often a benign condition with prompt and complete resolution with corticosteroids. That some patients have experienced recurrent RISS with re-exposure indicates that providers should carefully weigh risks and benefits of continuing or reintroducing rituximab.

SN	Author, Year	Study Design	Condition	Age/Sex	Dosing Protocol (amount x doses)	Dose Causing SS (cycle number, dosing number in the cycle)	Onset of SS from Last Dose	H/O Immediate Transfusion Reaction	Antibody Profile	Treatment for SS	Remarks
Autoimmune Diseases											
1	D'Arcy et al.,2001	Case Study	Autoimmune Polyneuropathy	45/M	NA	1,NA	10	No	NA	IV MP pulse	-
2	Herishanu et al.,2002	Case Study	Refractory ITP	48/F	Mentioned as weekly dose	2,NA	6	No	ANA negative	IV MP 500mg x 2d	-
3	Hellerstedt et al.,2003	Case Study	SLE	23/F	NA	1,2	1	No	NA	IV Steroid bolus	-
4	Catuogno et al.,2005	Case Study	Cryoglobulinemia	60/F	375 mg/m2 x 4	1,1	7	No	RF positive (RA test, Fii latex, Waaler-Rose)	IV Betamethasone 4mg	-
5	Pijpe et al.,2005	Open-Label Phase II study	Sjögren's Syndrome	41/F	375 mg/m2 x 4	1,2	5-7	No	RF (125 KIU/L); anti-SSA positive; anti-SSB positive; HACA positive	IV MP 1000mg	-
6	Pijpe et al.,2005	Open-Label Phase II study	Sjögren's Syndrome	39/F	375 mg/m2 x 4	1,2	5-7	No	RF (16 KIU/L); anti-SSA positive; anti-SSB positive; HACA positive with 1.32% activity	IV MP 1000mg	-
7	Pijpe et al.,2005	Open-Label Phase II study	Sjögren's Syndrome	27/F	375 mg/m2 x 4	1,2	5-7	No	RF (569 KIU/L); anti-SSA positive; HACA positive with <1% activity	NA	-
8	Wang et al.,2005	Prospective	Chronic ITP	14/F	375 mg/m2 x 4	1,2	7-14	No	NA	NA	-
9	Wang et al.,2005	Prospective	Chronic ITP	12/F	375 mg/m2 x 4	1,3	7-14	No	NA	NA	-
10	Wang et al.,2005	Prospective	Chronic ITP	12/F	375 mg/m2 x 4	1,1	NA	Yes	NA	NA	-
11	Bennett et al.,2006	Prospective	Chronic ITP	12/M	375 mg/m2 x 4	1,2	After second dose	No	NA	NA	-
12	Bennett et al.,2006	Prospective	Chronic ITP	11/F	375 mg/m2 x 4	1,2	After second dose	No	NA	NA	-
13	Schutgens et al.,2006	Case Study	Sjögren's Syndrome	46/F	375 mg/m2 x 4	1,NA	2	No	NA	oral Prednisone 20 mg/d	MALT of right parotid gland

14	Devauchelle et al.,2007	Prospective	Sjögren's Syndrome	NA	375 mg/m2 x 4	1,2	NA	No	NA	NA	-
15	Finger et al.,2007	Case Study	Polyclonal Hypergammaglobulinemia	45/F	NA	1,1	7	No	NA	IV HCT 125 QID x 3 days	Associated Sjögren's Syndrome
16	Finger et al.,2007	Case Study	Polyclonal Hypergammaglobulinemia	38/F	1000 mg x 2	2,2	1	No	NA	IV HCT 125 QID x 3 days	-
17	Seror et al.,2007	Retrospective	Sjögren's Syndrome	43/F	375 mg/m2 x 4	1,2	3	No	RF (499 IU/L); anti-SSA positive; anti-SSB positive; HACA (significant level)	None	Salivary Lymphoma (MALT)
18	Dass et al.,2008	Randomised, double-blind, placebo-controlled pilot study	Sjögren's Syndrome	NA	1000 mg x 2	1,1	7	No	anti-SSA positive; anti-SSB (78% positive in treatment group)	IV steroid	-
19	Godeau et al.,2008	Prospective multicenter phase 2 study	Chronic ITP	NA	375 mg/m2 x 4	1,NA	NA	No	NA	NA	-
20	Medeot et al.,2008	Prospective Study	Relapsed or refractory ITP	NA	375 mg/m2 x 4	1,2	Soon after	No	NA	Steroid	-
21	Mehsen et al.,2008		MCTD	30/F	NA	1,1	13	No	NA	oral anti-Histaminics	-
22	Goto et al.,2009	Case Study	Chronic ITP	8/M	375 mg/m2 x 4	2,2	10	No	ANA (<40x); RF (0.30); anti-DNA (1 IU/ml); HACA (244 ng/ml)	Oral PDS 1.8 mg/kg/day x 1 mo;	-
23	Sène et al.,2009	Case Series	Cryoglobulinemia	47/M	1000 mg x 2	2,1	7	No	NA	NA	Hep C positive
24	Sène et al.,2009	Case Series	Cryoglobulinemia	53/F	1000 mg x 2	2,1	9	No	NA	NA	Hep C positive
25	Guenno et al.,2011	Case Study	Chronic ITP	31/F	375 mg/m2 x 4	1,1	13	No	RF negative	IV MP 120 mg x 1d then oral Steroid x 7d	-
26	Kumar et al.,2012	Case Study	RA	60/F	1000 mg x 2	2,1	6	Yes	RF (44.4 U/ml); anti-CCP (114 U/ml); ANA (negative)	IV MP 80mg x once; Levocetrizine	-
27	Sandhu et al.,2012	Case Study	Post kidney transplant rejection	52/M	NA	1,NA	14	No	ANA negative; RF negative; anti-CCP (0.5 Units/ml); anti-SSA (8 U/ml); anti-SSB (9 U/ml); anti-DNA (4 U/ml)	IV MP 500mg/d x 3d	Acute cellular and humoral rejection
	Ungprasert		Sjögren's Syndrome and							IV MP x 2d then	

28	et al.,2013	Case Study	SLE	50/F	NA	2,1	7	No	NA	oral Prednisone x 7d	-
Hematologic Diseases											
29	Portlock et al., 2005	Prospective Phase 2 study	Lymphoma	51/F	375 mg/m2 x 4	2,1	7	No	HACA positive	Prednisone	Follicular lymphoma, previously treated
30	Portlock et al., 2005	Prospective Phase 2 study	Lymphoma	70/M	376 mg/m2 x 4	1,2	5	No	HACA negative	Prednisone	Follicular lymphoma, previously untreated
31	Todd et al., 2006	Case Study	Lymphoma	68/M	375 mg/m2 x 4	1,1	13	No	ANA normal; RF normal: anti-CCP normal; HACA negative	IA MP 80mg then oral Prednisone 20 mg/d tapered over 4 wks	Mantle cell, stage 2a
32	Disperati et al., 2007	Case Study	Lymphoma	52/F	180mg/m^2 x 4	5,1	2	Yes; during prior two cycles	RF negative; ANA negative	IV MP, IV Diphenhydramine and IV Mepiridine	Stage IV follicular
33	DeMonaco et al., 2007	Case Study	Lymphoma	47/F	375 mg/m2 x 4	4,2	7	No	HAMA negative	Steroid x 10d	Follicular, grade 3 of 3



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A Strong Association Between Gout and Diuretic Use Among Lupus Patients

Eric Wise[1], Emily Lewis[2], Puja Khanna[2,3], Lili Zhao[4] and W Joseph McCune[5], [1]Rheumatology, University of Michigan, Ann Arbor, MI, [2]Rheumatology, University of Michigan, Ann Arbor, MI, [3]Division of Rheumatology/Dept. of Internal Medicine, University of Michigan Medical Center, Ann Arbor, MI, [4]Department of Statistic, University of Michigan, Ann Arbor, MI, [5]Int Med/ Rheum, University of Michigan, Ann Arbor,

MI

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Background/Purpose: Although gout has historically been thought to be a rare in patients with SLE, recent case series suggest that the incidence of gout in SLE may be greater than previously thought. Here we report a retrospective analysis of a large lupus cohort to determine the prevalence and risk factors for gout in an outpatient population.

Methods: Patients from the University of Michigan lupus cohort who met criteria for acute gout were identified by either the 1977 ACR or the 1968 New York gout criteria. All patients met 4 ACR criteria for a diagnosis of lupus and were seen in the outpatient rheumatology clinic between 1997 and 2014. Characteristics of the patients identified as having gout, including age, race sex, uric acid levels, medication use, and lupus activity were recorded and compared to the 827 remaining patients in the cohort without a diagnosis of gout..

Results: 27 of 856 lupus cohort patients were identified as having gout, including six with crystal-proven gout. Of these 27, 8 were male, 10 were black, 15 white and 2 were of Asian ancestry and the average age at the time of presentation with gout symptoms was 55 years. The average BMI was 33.5 +/- 6.8. All patients were hyperuicemic with an average uric acid level of10.8 +/- 2.3. Compared to the cohort as a whole, a significant number (12/27 patients) were treated with a loop diuretic (p=0.001) and a significant number (6/27) were treated with a thiazide diuretic (p=0.01). Reduced renal function, defined as CKD stage IIIa or worse was found in 17/27 (p=0.0001) patients. 25/27 were taking some dose of prednisone with an average of 6 mg, a minimum of 1 mg and a maximum of 13 mg. A total of 6/27 patients had a history of kidney transplant and were being treated with cyclosporine. C3 and C4 Complement levels were within the normal range for all 27 patients.

Conclusion: Gout was documented according to standard criteria in 27/854 (3.2%) of patients in the lupus cohort. Most risk factors including age, male sex, and kidney transplant history were non modifiable. However there was a striking association between gout and the administration of a diuretic, either for edema (12/27 patients) or for other indications (6/27 patients), especially in the setting of impaired renal function. Lupus patients with a history of compromised renal function who are being treated with diuretics should be monitored closely for hyperuricemia and symptoms of gout.

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Abstract Number: 753

Serum Levels of Tenascin-C Discriminate Patients with Active SLE from Inactive Patients and Healthy Controls, and Predict the Need to Escalate Immunosuppressive Therapy

Jakub Zavada[1], Michal Uher[2], Radka Svobodova[3], Marta Olejarova[1], Marketa Husakova[3], Hana Ciferska[3], Hana Hulejova[4], Ladislav Senolt[3] and Jiri Vencovsky[3], [1]Institute of Rheumatology and Department of Rheumatology, 1st Faculty of Medicine, Charles University, Prague, Czech Republic, Prague, Czech Republic, [2]Institute of Biostatistics and Analyses, Masaryk University, Brno, Czech Republic, [3]Institute of Rheumatology, Prague, Czech Republic, [4]Institute of Rheumatology and Department of Rheumatology, Prague, Czech Republic

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Session Type: ACR Poster Session A

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Background/Purpose: The aim of this study was to examine whether circulating levels of the pro-inflammatory glycoprotein tenascin-C (TSC) are useful as an activity-specific or predictive biomarker in SLE.

Methods: Serum TSC levels were determined by ELISA at inception visit in a prospective cohort of 59 SLE patients, and in 65 healthy controls (HC). SLE patients were followed for a median of one year, and disease activity (assessed by SLEDAI-2K), and changes in glucocorticoids (GC) and immunosuppressants (IS) were serially recorded every 3-6 months. We examined cross-sectional relationship between serum concentrations of TSC and SLE status, SLEDAI-2K scores, strata of disease activity, and levels of anti-dsDNA, anti-nucleosomal antibodies and

C3, C4. We also explored the utility of TSC levels to predict disease flare defined as (i) increase in SLEDAI ≥3, (ii) new/increased GC, and (iii) new/increased GC or IS.

Results: Baseline characteristics are shown in table 1. There was no statistical difference in the mean levels of TSC between all SLE patients and HC. However, in SLE patients with active disease (SLEDAI≥ 6) the levels of TSC were significantly higher than in HC (p=0.004) or patients with no/low disease activity (p=0.004). In SLE patients, TSC levels were significantly associated with the positivity of anti-dsDNA (p=0.03) and anti-nucleosomal antibodies (p=0.008), and there was a trend to a positive correlation with SLEDAI (R=0.25, p=0.06) and clinical SLEDAI scores (R=0.25, p=0.06) – see table 2. Higher baseline levels of serum TSC showed significantly greater risk of disease flare defined as the need to escalate glucocorticoids (HR 1.39; 95% CI: 1.11- 1.73, p = 0.004) or any immunosuppressive therapy (HR 1.25, 95% CI: 1.02-1.52, p=0.028). We also conducted a separate analysis in which serum TSC level was treated as a categorical variable. In accordance with the result above, the risk of reaching the flare (ii) or (iii) was significantly higher in the group of patients wither higher TSC levels (see table 3).

Conclusion: TSC is not disease-specific, but it seems to indicate the activity of SLE and may predict the need to escalate immunosuppressive therapy. TSC levels may thus serve as a useful activity-specific and predictive biomarker in SLE. **Acknowledgements:** This study was supported by grant IgA NT 13707.

Table 1 Baseline characteristics

		SLE (n=59)	**Healthy controls (n=65)**
Female	n (%)	55 (93 %)	45 (69%)
Age (years)	mean (SD)	44 (16)	48 (14)
Caucasian	n (%)	59 (100%)	65 (100%)
TSC (ng/ml)	mean (SD)	533 (193)	487 (164)
Disease duration (years)	mean (SD)	7 (7)	
SLEDAI 2K	mean (SD)	3.7 (3.5)	
cSLEDAI-2K (only clinical SLEDAI items)	mean (SD)	2.2 (3.0)	
SLEDAI 2K ≥ 4	n(%)	30 (53 %)	
TSC (ng/ml) in pts. with SLEDAI 2K ≥ 4	mean (SD)	578 (229)	
SLEDAI 2K ≥ 6	n(%)	19 (33 %)	
TSC (ng/ml) in pts. with SLEDAI 2K ≥ 6	mean (SD)	634 (255)	
ANA+	n(%)	54 (95 %)	
Anti dsDNA +	n(%)	22 (38 %)	
Low complement	n(%)	28 (48 %)	
Anti-nucleosomal +	n(%)	25 (46 %)	
Oral glucocorticoids	n(%)	35 (59 %)	
Immunosuppressants	n(%)	15 (25%)	

Table 2 Cross-sectional associations between serum TSC levels and clinical and laboratory parameters of SLE patients at inception visit (univariate regression analysis)

	Univariate analyses		Univariate analyses (age and sex adjusted)	
Variable	**β* (95% CI)**	**p value**	**β* (95% CI)**	**p value**
SLE patients vs. HC	46 (-17; 110)	0.151	44 (-24; 112)	0.205
SLE pts. with SLEDAI ≥ 4 vs. HC	91 (9; 173)	**0.029**	87 (-5; 179)	0.063
SLE pts. with SLEDAI ≥ 6 vs. HC	147 (50; 245)	**0.004**	139 (34; 245)	**0.010**
SLE pts. with SLEDAI ≥ 4 vs. SLEDAI < 4	98 (-3; 199)	0.058	104 (-9; 217)	0.070
SLE pts. with SLEDAI ≥ 6 vs. SLEDAI < 6	153 (50; 256)	**0.004**	161 (54; 267)	0.004
SLE patients (categorical variables)				
Anti-dsDNA IF (positive vs. negative)	115 (12; 218)	**0.029**	112 (3; 221)	**0.044**
Anti-nucleosomal (positive vs. negative)	138 (38; 238)	**0.008**	131 (30; 234)	**0.013**
Complement C3/C4 (low vs. normal)	-4 (-107; 99)	0.938	-14 (-123; 94)	0.793
SLE patients (continuous variables)				
SLEDAI-2K	14 (-1; 29)	0.061	14 (-1.5; 30)	0.074
cSLEDAI-2K (only clinical SLEDAI items)	16 (-1; 33)	0.060	16 (-1.0; 34)	0.065
C3 (g/l)	-9 (-209; 192)	0.931	5 (-205; 216)	0.958
C4 (g/l)	-232 (-695; 230)	0.319	-210 (-694; 273)	0.386
Anti-nucleosomal (units)	-0.2 (-0.7; 0.3)	0.403	-0.2 (-0.7; 0.3)	0.460
Anti-dsDNA (titre)	27 (-22; 75)	0.266	30 (-21; 81)	0.230

The regression coefficient β corresponds to the difference in TSC levels between groups (when assessing categorical variables) or to the change in TSC associated with a 1 unit increase in the assessed variable (when assessing continuous variables). HC = Healthy control.

Table 3 Performance of baseline TSC levels to predict disease flares (cox proportional hazard analysis)				
Flare definition	**Univariate analyses**		**Univariate analyses (age and sex adjusted)**	
	Tenascin as continuous variable			
	HR* (95% CI)	**p value**	HR* (95% CI)	**p value**
Increase in SLEDAI ≥3	1.19 (0.87; 1.63)	0.277	1.21 (0.86; 1.68)	0.270
New/increased GC	1.39 (1.11; 1.73)	**0.004**	1.37 (1.11; 1.70)	**0.004**
New/increased GC or IS	1.25 (1.02; 1.52)	**0.028**	1.23 (1.01; 1.49)	**0.035**
	Tenascin as categorical variable (> 659 ng/ml) *			
Increase in SLEDAI ≥3	1.42 (0.28; 7.21)	0.672	1.52 (0.27; 8.64)	0.636
New/increased GC	3.77 (1.60; 8.88)	**0.002**	3.57 (1.48; 8.59)	**0.005**
New/increased GC or IS	2.45 (1.10; 5.46)	**0.028**	2.23 (0.98; 5.08)	0.056
* The threshold value of 659 ng/ml for TSC was generated using ROC analysis of relationship between active SLE (SLEDAI≥ 6) and baseline TSC. GC = glucocorticoid. IS = immunosuppressant.				

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Abstract Number: 754

Glutathione S Transferases (GST) Polymorphisms Are Independents Predictors of Efficacy and Toxicity in Lupus Nephritis Treated with Cyclophosphamide

Alexandra Audemard-Verger[1], Nicolas Martin Silva[2], Céline Verstuyft[3], Nathalie Costedoat-Chalumeau[4], Aurélie Hummel[5], Véronique Le Guern[4], Karim Sacre[6], Olivier Meyer[7], Eric Daugas[8], Cecile Goujard[9], Audrey Sultan[2], Thierry Lobbedez[2], Lionel Galicier[10], Jacques Pourrat[11], Claire Le Hello[2], Michel Godin[12], Remy Morello[2], Marc Lambert[13], Eric Hachulla[13], Philippe Vanhille[14], Guillaume Queffeulou[15], Jacques Potier[15], Jean Jacques Dion[16], P Bataille[17], Dominique Chauveau[18], Guillaume Moulis[19], Dominique Farge[20], Pierre Duhaut[21], Bernadette Saint Marcoux[22], Alban Deroux[23], Jennifer Manuzak[24], Camille Francès[25], Olivier Aumaître[26], Holy Bezanahary[27], Laurent Becquemont[28] and Boris Bienvenu[29], [1]Internal Medicine, CHU Caen, caen, France, [2]CHU Caen, caen, France, [3]Pharmacology, Hopital Bicêtre, Le Kremlin Bicêtre, France, [4]Internal Medicine Department, Cochin Hospital, "René-Descartes Paris V" University, Paris, France, [5]Necker, paris, France, [6]Internal Medicine, Hospital Bichat, Paris, France, [7]Rheumatology, Hopital Bichat, Paris, France, [8]Internal Medicine, AP-HP Hôpital Bîchat, Paris, France, [9]Bichat, Paris, France, [10]Clinical Immunology, St Louis Hospital, Paris, France, [11]Nephrology, Rangeuil Hospital, Paris, France, [12]CHU Rouen, Rouen, France, [13]CHU Lille, Lille, France, [14]Department of Nephrology and Internal Medicine, Hospital of Valenciennes, Valenciennes, France, Valenciennes, Valenciennes, France, [15]Ch Cherbourg, Cherbourg, France, [16]Ch Charleville Mezeiere, Charleville Mezeiere, France, [17]Ch Boulogne sur Mer, Boulogne sur Mer, France, [18]CH Toulouse, Toulouse, France, [19]CHU Purpan, Toulouse, France, [20]Internal Medicine, Hopital St Louis, Paris, France, [21]Department of Internal Medicine and RECIF, CHU Amiens, Amiens, France, [22]CH Aulnay sous Bois, Aulnay sous Bois, France, [23]Internal Medicine, CHU Grenoble, Grenoble, France, [24]Institut Cochin, Paris, France, [25]Dermatology Service, Tenon Hospital, Paris, France, [26]Department of Internal Medicine 2. Referal center for SLE/APS, CHU Pitié-Salpêtrière, Paris, France, [27]Internal Medicine, University Hospital of Limoges, Limoges, France, [28]KB, Paris, France, [29]Internal Medicine, Hospital Caen, Caen, France

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SESSION INFORMATION

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Session Title: Systemic Lupus Erythematosus - Clinical Aspects and Treatment Poster Session I
Session Type: ACR Poster Session A
Session Time: 9:00AM-11:00AM

Background/Purpose: Cyclophosphamide (CYC) is effective in inducing remission of lupus nephritis (LN). CYC, as a pro-drug, requires bioactivation through multiple hepatic cytochrome P450s and glutathione S transferases (GST). Methods: We conducted a retrospective study that included 70 patients with proliferative LN treated with CYC. Patients were genotyped for polymorphisms of the *CYP2B6, CYP2C19, GSTP1, GSTM1* and *GSTT1* genes. We examined the association between these genotypes and achievement of renal response and occurrence of side effects. **Results:** In univariate analysis, patients expressing the *GSTP1* null genotype showed a trend toward a lower probability of achieving renal response (73.3% versus 91.2%, p=0.059). Expression of the *GSTM1* null genotype was associated with a higher occurrence of side effects (43.9% versus 21.4%, p<0.05). In multivariate analysis, the *GSTP1* null genotype was an independent factor of treatment lower response (p<0.05). The only factor that influenced the occurrence of side effects was the polymorphism of *GSTM1* (p<0.05). No association between polymorphisms of the cytochrome P450 gene and efficacy or side effects was observed. **Conclusion:** Despite small sample size, this study suggests that determination of *GST* genotypes may be valuable for predicting the renal response and occurrence of side effects in lupus nephritis patients treated with CYC.

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Abstract Number: 755

Validating the RAIL Algorithm in Adult Lupus Nephritis Patients

Gaurav Gulati[1], Khalid Abulaban[2], Jun Ying[3], Xiaolan Zhang[4], Huijuan Song[5], Qing Ma[6], Christopher Haffner[6], Kasha Wiley[7], Michael Bennett[8], Brad H. Rovin[5] and Hermine I. Brunner[9], [1]Division of Immunology, Allergy and Rheumatology, University of Cincinnati College of Medicine, Cincinnati, OH, [2]Pediatric Rheumatology, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, [3]University of Cincinnati, Cincinnati, OH, [4]Ohio State University, Columbus, OH, [5]Ohio State University Medical Center, Columbus, OH, [6]Cincinnati Children's Hospital and Medical Center, Cincinnati, OH, [7]Division of Rheumatology, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, [8]Division of Nephrology, Cincinnati Children`s Hospital Medical Center, Cincinnati, OH, [9]Pediatric Rheumatology Collaborative Study Group, Cincinnati Children's Hospital Medical Center, Cincinnati, OH
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Background/Purpose:

Lupus Nephritis (LN) significantly contributes to morbidity and mortality among Systemic Lupus Erythematosus (SLE) patients. We have established the Renal Activity Index for Lupus (RAIL) in pediatric LN with an accuracy of > 92% in predicting activity. The goal of this study was to validate the RAIL algorithm for adults with LN.

Methods:

Adult SLE patients who required a kidney biopsy as part of their standard care were enrolled. A urine sample was collected at the time of biopsy. Demographic information, SLE status (diagnostic criteria, laboratory and clinical data, renal disease activity (R-SLEDAI) and chronicity (SDI-R)), medications were collected. Kidney biopsies were read in a blinded fashion and the National Institute of Health Activity and Chronicity indices (NIH-AI, NIH-CI) were reported. Patients were dichotomized as high activity or not based on their NIH-AI scores. Fifteen urinary biomarkers (UBMs) were collected and the **SIX UBMs**used in pediatric RAIL data were used for the analysis (neutrophil gelatinase associated lipocalin, monocyte chemotactic protein 1, ceruloplasmin, adiponectin, hemopexin, kidney injury molecule 1). Urinary microalbumin and creatinine concentrations were measured to normalize for proteinuria in the analysis. Adult RAIL predictors were firstly assessed of associations to AI using univariate analyses, followed by prediction analyses to develop the RAIL algorithms using stepwise multiple logistical regression

models. Predictive accuracy of the RAIL algorithm was calculated using the area under the Receiver Operating Characteristic (ROC) curve (AUC).

Results:

We studied 75 adults (mean age 32.4±10.1 years) and the majority were females (78.7%) with equal representation for Caucasian and African American ethnicities (46.7%). Their mean NIH-AI and NIH-CI scores were 4.57± 4.11 and 3.23 ± 2.59, respectively. 11 (15%) patients had high activity with NIH AI scores >10. Age, gender, ethnicity and LN stage were not significantly different between the two activity groups. Using the 6 UBMs used in the pediatric RAIL algorithm, an excellent prediction was obtained (AUC 0.87 (0.77, 0.97)). Using adult population based UBMs with total 10 UBMs there was notable improvement in diagnostic accuracy of the model (AUC 0.92 (0.84, 1.00)). The RAIL algorithms showed little noticeable improvement with adjustment for creatinine and microalbumin [Table 1].

Conclusion:

We have successfully validated the pediatric RAIL algorithm among adults to accurately and reliably measure LN disease activity. Further, in adults we found that adjustment for microalbumin or creatinine levels dose not cause a great change in diagnostic accuracy of RAIL. Using an adult model based RAIL with 10 UBMs does increase the accuracy of the algorithm. Further studies to independently validate and further study the relationship of these UBMs with specific biopsy findings are needed.

TABLE 1: Diagnostic Accuracy of RAILs using Pediatric Model and Adult Model

		CREATININE adjusted		CREATININE adjusted	MICROALBUMIN
	Raw Score	Score	Raw Score	Score	adjusted Score
Statistics	(UBMs = 6)	(UBMs =6)	(UBMs=10)	(UBMs=10)	(UBMs=10)
AUC	0.87 (0.77, 0.97)	0.90 (0.83, 0.98)	0.92 (0.84, 1.00)	0.94 (0.88, 0.99)	0.90 (0.83, 0.98)
Sensitivity	90.9%	90.9%	90.9%	90.9%	90.9%
Specificity	71.0%	77.4%	83.6%	83.6%	78.7%
Positive Likelihood Ratio	3.13	4.02	5.54	5.54	4.27
Negative Likelihood Ratio	0.13	0.12	0.11	0.11	0.12
Logit cut	-1.68	-1.41	-1.86	-1.72	-1.83

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Abstract Number: 756

Axl, Ferritin, IGFBP2 and TNFR2 As Biomarkers in Systemic Lupus Erythematosus

Chi Chiu Mok[1], Huihua Ding[2], Marwa Kharboutli[3] and Chandra Mohan[2], [1]Medicine, Tuen Mun Hospital, Hong Kong, Hong Kong, [2]Biomedical Engineering, University of Houston, Houston, TX, [3]Department of Biomedical Engineering, University of Houston, Houston, TX

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Background/Purpose:

To evaluate the performance of 4 novel serum protein markers for detecting concurrent disease activity in systemic lupus erythematosus (SLE).

Methods:

Consecutive patients who fulfilled >=4 ACR criteria for SLE and healthy controls were recruited for serological testing of 4 serum protein markers identified by a proteomic screening study using a commercially available antibody-coated microarray, namely Axl, Ferritin, insulin growth factor binding protein-2 (IGFBP2) and tumor necrosis factor receptor-2 (TNFR2) (assayed by ELISA kits from the R&D Systems [Minneapolis, Minnesota, USA] - Axl (Cat#: DY154), TNFR2 (Cat#: DY726), IGFBP2 (Cat#: DY674); Ferritin was assayed using an ELISA kit from Raybiotech, Inc [Norcross, Georgia, USA]). Elevated levels of these markers were defined as values ≥ mean + 2SD of the controls. SLE disease activity was assessed by the SELENA-SLEDAI, physician's global assessment (PGA) and the SELENA flare instrument. Levels of these markers were correlated with disease activity scores and conventional markers of SLE activity. The specificity and sensitivity of these markers in detecting clinical SLE activity was determined.

Results:

94 SLE patients (98% women; age 28.7±9.4 years, disease duration 5.4±5.0 years) and 49 healthy controls were studied. Fifty-two (55%) patients had clinically active SLE (SLEDAI score ³6 or having a flare by the SELENA flare instrument). The SLEDAI and PGA score of the patients was 8.3±1.1 and 1.11±0.92, respectively. Organ damage, defined as a SDI damage score of ≥1, was present in 37 (39%) of patients. Among the 52 patients with clinically active SLE, the involved organ systems were as follows: renal (60%), mucocutaneous (50%), musculoskeletal (40%) and hematological (25%). Elevated anti-dsDNA titer (>25% of the upper normal range) was present in 44 (85%) patients and depressed complement C3 level was present in 45 (87%) patients. The serum concentrations of Axl, ferritin, IGFBP2 and TNFR2 were significantly higher in patients with active SLE than inactive SLE or controls. The levels of these markers correlated strongly and significantly with the levels of anti-dsDNA, C3, clinical SLEDAI (total SLEDAI minus points contributed by low C3 and elevated anti-dsDNA) (Axl ρ=0.39; TNFR2 ρ=0.59; Ferritin ρ=0.52; IGFBP2 ρ=0.61; P <0.001 in all) and PGA scores (P<0.001 in all). The sensitivity of these markers in detecting SLE activity (Axl 0.67; TNFR2 0.77; Ferritin 0.71; IGFBP2 0.69) was lower than that of elevated anti-dsDNA (0.85) or depressed C3 (0.87), but their specificity for ascertaining clinical SLE activity were generally higher (Axl 0.79; TNFR2 0.71; Ferritin 0.76; IGFBP2 0.76; anti-dsDNA 0.45; C3 0.33). Levels of Axl, TNFR2 and IGFBP2, but not ferritin, could differentiate active renal from active non-renal or inactive SLE. The specificity of Axl (0.68) and IGFBP2 (0.71) for active lupus renal disease was higher than that of elevated anti-dsDNA (0.40) or depressed C3 (0.32).

Conclusion:

Serum proteomic markers are potentially useful for diagnosing SLE and monitoring disease activity. The performance of Axl and IGFBP2 in monitoring lupus nephritis should be further studied in a larger longitudinal cohort of SLE patients.

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Abstract Number: 757

The Ratio Between TNF-a and P-Albumin – a Suggested Measure of Disease Activity in SLE

Susanna Eketjäll[1], Helena Idborg[2], Johanna Gustafsson[3], Agneta Zickert[2], Marika Kvarnstrom[4], Vilija Oke[5], Susanne Pettersson[4], Per Johan Jakobsson[4], Iva Gunnarsson[4] and **Elisabet Svenungsson**[4], [1]Department of Clinical Neuroscience, Karolinska Institutet, Solna, AstraZeneca Translational Sciences Centre, Science for Life Laboratory, Personal Healthcare and Biomarkers, Stockholm, Sweden, [2]Department of Medicine, Rheumatology Unit, Karolinska Institutet, Stockholm, Sweden, [3]Department of Medicine, Rheumatology Unit, Karolinska Institutet, Karolinska University Hospital, Stockholm, Sweden, [4]Department of Medicine, Unit of Rheumatology, Karolinska Institutet, Karolinska University Hospital, Stockholm, Sweden, [5]Department of medicine, Unit of Rheumatology, Karolinska Institutet, Karolinska University Hospital, Stockholm, Sweden
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Background/Purpose:

There is presently no consensus on how to best measure disease activity in systemic lupus erythematosus (SLE). Available validated measures, such as SLE Disease Activity Index (SLEDAI) and SLE Activity Measure (SLAM), are composite scores that in addition to laboratory tests require investigation by a physician. These scores are insensitive to change and have failed to differentiate treatment responses in clinical trials. It would be an important step forward, for clinical practice and for clinical trials, if one or several biomarkers could be used as proxies for disease activity in SLE.

Methods:

In a cross-sectional setting we examined 433 patients with SLE (fulfilling four or more of the 1982 revised ACR criteria) and 322 age and gender matched population controls. Disease activity was assessed according to both SLEDAI and SLAM by a rheumatologist. Basic laboratory tests and analyses on MSD 30-plex cytokine assay (Mesoscale Discovery, K15054D) were performed on fasting blood samples (total >50 biomarkers). The discriminatory power for investigated biomarkers was tested between patients and controls. Correlations with SLAM/SLEDAI scores were calculated among patients.

Results:

Many biomarkers discriminated between patients and controls. Best discriminatory power ($p<1x10^{-35}$) was observed for: TNF-α, IL-6, orosomucoid, plasma (P)-albumin and sedimentation rate (SR), see table.

Variables with the strongest correlation with SLAM/SLEDAI (Spearman correlation $\rho>0.20$ or $\rho<-0.20$) are presented in the table. Strong positive correlations were observed for TNF-α, and negative for P-albumin. The ratio between TNF- α and P-albumin improved the correlations, see figure. As SR is part of SLAM, and Complement factor 4 (C4) an item in SLEDAI, expected positive correlations were observed, see table.

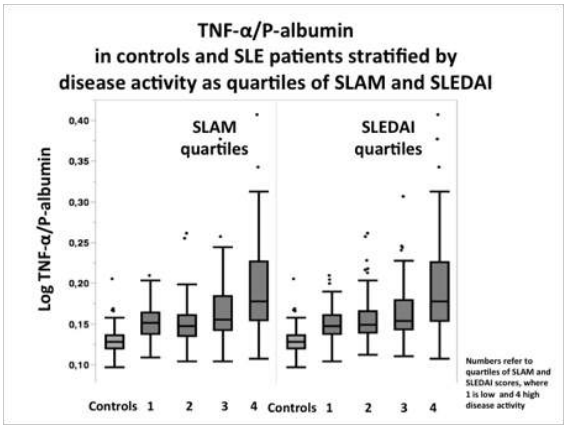
Conclusion:

Of more than 50 investigated biomarkers TNF-α was the best discriminator between SLE patients and controls. Furthermore TNF-α was the biomarker, which correlated best with disease activity. These correlations were further improved by the ratio between TNF-α and P-albumin. We propose that the TNF-α/P-albumin ratio merits further investigations as a clinically useful biomarker for diagnostic and surveillance purposes in SLE.

Biomarkers with the best Discriminatory Power between SLE patients and controls and/or strongest Correlations with SLE Disease Activity, as measured by SLEDAI and SLAM

Biomarker	Patients (95 % CI)	Controls (95 % CI)	p-value Patients vs. Controls	SLEDAI Spearman's ρ	SLAM Spearman's ρ
TNF-α pg/ml	5.6 (5.2 - 6.0)	2.6 (2.2 - 3.0)	7.0×10^{-63}	0.32 $p= 6.0 \times 10^{-12}$	0.34 $p=5.0 \times 10^{-13}$
IL-6 pg/ml	2.1 (1.9 - 2.4)	0.7 (0.4 - 1.0)	2.5×10^{-60}	0.24 $p=9.6 \times 10^{-7}$	0.23 $p=1.3 \times 10^{-6}$
IL-15 pg/ml	3.6 (3.4 – 3.7)	2.2 (2.0 - 2.3)	3.4×10^{-29}	0.26 $p=8.6 \times 10^{-9}$	0.28 $p= 4.0 \times 10^{-9}$
MIP-1β pg/ml	91.3 (86.5 -96.2)	48.7 (43.0 – 54.3)	3.8×10^{-27}	0.20 $p=4.2 \times 10^{-5}$	0.16 p= 0.0009
IL-8 pg/ml	8.6 (7.6 - 9.7)	3.6 (2.4 - 4.7)	3.8×10^{-28}	0.16 p= 0.0009	0.18 p= 0.0002
MCP-1 pg/ml	148 (137–160)	74 (61 – 87)	3.0×10^{-16}	0.23 $p=1.0 \times 10^{-6}$	0.23 $p= 1.5 \times 10^{-6}$
IL-10 pg/ml	1.7 (1.4 -1.9)	0.46 (0.10- 0.82)	8.1×10^{-8}	0.26 $p=8.6 \times 10^{-8}$	0.20 $p= 2.8 \times 10^{-5}$
IP-10 ng/ml	1.6 (1.4 – 1.8)	0.5 (0.2 - 0.6)	1.2×10^{-16}	0.23 $p=1.4 \times 10^{-6}$	0.19 p= 0.0001
C4 g/L	0.15 (0.15–0.16)	0.21 (0.20 -0.22)	3.2×10^{-27}	-0.35 $p= 8.0 \times 10^{-14}$	-0.12 p=0.02
Orosomucoid g/L	0.98 (0.95 -1.0)	0.72 (0.69 -0.75)	7.1×10^{-38}	0.21 1.0×1^{-5}	0.28 $p= 3.1 \times 10^{-9}$
Sedimentation rate mm/hr	25.8 (24.2 - 27.3)	10.2 (8.5 - 12.1)	5.6×10^{-34}	0.27 $p=7.7 \times 10^{-9}$	0.48 $p= 4.0 \times 10^{-25}$
P-Albumin g/L	38.2 (37.7 - 38.6)	42.7 (42.2 - 43.2)	1.6×10^{-36}	-0.33 $p= 9.0 \times 10^{-13}$	-0.31 $p= 5.0 \times 10^{-11}$
Ratio TNF-α/ P-albumin	0.16 (0.15 - 0.17)	0.06 (0.05 - 0.07)	**2.8×10^{-49}**	**0.37 $p= 1.0 \times 10^{-15}$**	**0.38 $p=2.0 \times 10^{-16}$**

Discriminatory power was calculated with student's T-test or Mann Whitney U test as appropriate, depending on biomarker distribution. Correlations between biomarkers and disease activity scores were calculated using Spearman's correlation coefficients. SLEDAI = SLE Disease Activity Index, SLAM = SLE Activity Measure TNF = tumor necrosis factor, IL= interleukin, MIP= Macrophage inflammatory protein, MCP= monocyte chemotactic protein, IP= Interferon gamma-induced protein , C4 = complement factor 4, P=plasma



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Abstract Number: 758

Dominican Patients with Systemic Lupus Erythematosus Residing in New York City Have a Higher SLICC/ACR Damage Index Than Those in the Dominican Republic

Laura Geraldino-Pardilla[1], Ivonne Canto[2], Thania Perez[3], Jossiell Then[2], Esthela Loyo[4] and Anca D. Askanase[5], [1]Division of Rheumatology, Columbia University College of Physicians & Surgeons, New York, NY, [2]Rheumatology, Hospital Regional Universitario Jose Maria Cabral y Baez, Santiago, Dominican Republic, [3]Columbia University, College of Physicians & Surgeons, New York, NY, [4]Rheumatology, Hospital Regional Universitario, Santiago, Dominican Republic, [5]Department of Medicine Rhemuatology, Colombia University, New York, NY

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Background/Purpose: Higher accrual of damage has been reported in Hispanics with systemic lupus erythematosus (SLE) in the United States. This study was initiated to evaluate the clinical characteristics including the accumulated damage of Dominican patients with SLE residing in

New York City (NYC) compared to Dominicans with SLE living in the Dominican Republic (DR).

Methods: One-hundred and fifty-one Dominican SLE patients fulfilling ACR SLE criteria were cross-sectionally studied: 76 from NYC and 75 from the Dominican Republic. Socio-demographic and clinical characteristics, disease activity (SLEDAI-2K), SLICC/ACR- damage index (SDI), and comorbidities were compared between the two patient groups and linear regression models were constructed to test the association with the SDI, adjusting for pertinent covariates.

Results: The mean age was 40 (±14), and 36 (±11) years for the NYC and DR patients, respectively. Both groups had a median disease duration of 8 years and mild disease activity based on their last SLEDAI-2K. The NYC patients were more likely to have discoid lesions (20% vs. 3%), positive anti-ds-DNA (79% vs. 64%), and anti-SSB antibodies (41% vs. 7%). Prevalence of hypertension, diabetes, antiphospholipid antibody syndrome, and use of medications other than corticosteroids did not differ among the groups. Those in the DR had more lupus nephritis (LN) (64% vs. 47%), were more likely to be on corticosteroids (83% vs. 38%), and less likely to have medical insurance (25% vs. 100%) (Table 1). However, a higher SDI was seen in NYC patients (0.96 vs. 0.24, p=<0.0001), driven by a higher prevalence of damage in the neuropsychiatric (16% vs. 3%, p=0.009)), renal (22% vs. 4%, p=0.0009), pulmonary (22% vs. 1%, p=<0.0001), and musculoskeletal (32% v s. 16%, p=0.02) domains. This association remained statistically significant after adjusting for pertinent covariates (1.26 vs. 0.57, p=<0.0001) (Figure 1).

Conclusion: SLE Dominican patients residing in NYC have a higher SDI than those in the DR. Longitudinal studies are needed to ascertain whether this difference is due to biological, environmental factors, or immigration patterns, or may reflect a survival bias.

Table 1. Patient characteristics.

	DR (n=76)	NYC (n=75)	P value
Socio-Demographics			
Age (years)	36 ± 11	40 ± 14	0.09
Female	70 (93%)	68 (89%)	0.40
Health insurance	19 (25%)	76 (100%)	<0.0001
SLE Characteristics			
Disease duration (years)	8.8 ± 3	8.4 ± 6	0.14
SLEDAI-2K	4 (0-8)	3 (1-8)	0.25
Lupus nephritis	46 (61%)	36 (47%)	0.08
Raynaud's	2 (3%)	23 (30%)	<0.0001
Antimalarials	70 (96%)	72 (95%)	0.74
Prednisone current	62 (83%)	29 (38%)	<0.0001
Mycophenolate mofetil ever	50 (67%)	41 (54%)	0.14
Cyclophosphamide ever	26 (35%)	19 (25%)	0.02
Azathioprine ever	30 (40%)	20 (26%)	0.10
Antiphospholipid Antibody	10 (13%)	5 (7%)	0.16
Auto-Antibodies			
dsDNA	48 (64%)	60 (79%)	0.04
SSA	36 (48%)	48 (63%)	0.06
SSB	5 (7%)	31 (41%)	<0.0001
Smith	26 (35%)	34 (45%)	0.21
RNP	31 (41%)	41 (54%)	0.16
Cardiovascular risk factors			
Hypertension	17 (23%)	10 (13%)	0.13
Diabetes	1 (1%)	5 (7%)	0.21
Current smoking	0	12 (26%)	0.0009

Table 1. Characteristics are expressed as n (%), as the mean ± SD, or as the median (interquartile range).

Figure 1. SDI in SLE Dominican Patients in NYC vs DR.

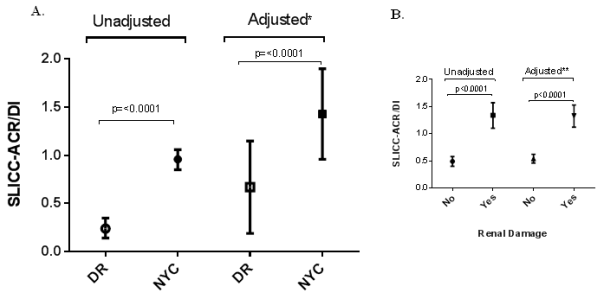

Figure 1. **A.** Mean and 95% C.I. values of the log transformed SLICC/ACR-DI +1 per group of SLE Dominican patients living in the Dominican Republic versus in New York City. *Adjusted for health insurance status, anti-SSB antibody positivity, current use of tacrolimus and prednisone, diabetes, and smoking. **B.** Mean and 95% C.I. values of the log transformed SLICC/ACR-DI +1 per presence or absence of renal damage. **Adjusted for SLEDAI-2K, history of lupus nephritis, and antimalarial use.

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Abstract Number: 759

Prolactin Level Is Independently Associated with Circulating CD4+CD28null in Systemic Lupus Erythematosus Patients

Manuel Ugarte-Gil[1,2], César Sánchez-Zúñiga[3], Rocio V. Gamboa-Cardenas[1], Madeley Aliaga-Zamudio[3], Francisco Zevallos[1], Giannina Tineo-Pozo[3], Jorge M. Cucho-Venegas[1], Ana Mosqueira-Riveros[3], Risto Perich-Campos[1,4], Jose Alfaro-Lozano[1], Mariela Medina[1], Zoila Rodriguez-Bellido[1,4], Graciela S. Alarcon[5] and Cesar A. Pastor-Asurza[1,4], [1]Rheumatology, Hospital Guillermo Almenara Irigoyen. EsSalud, Lima, Peru, [2]Universidad Cientifica del Sur, Lima, Peru, [3]Molecular Biology, Hospital Guillermo Almenara Irigoyen. EsSalud, Lima, Peru, [4]Universidad Nacional Mayor de San Marcos, Lima, Peru, [5]Medicine, University of Alabama at Birmingham, Birmingham, AL

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Background/Purpose: Peripheral CD4+CD28null T-cells are a subset of long-lived cytotoxic CD4+ T-cells with pro-inflammatory functions, and they are increased in autoimmune and cardiovascular diseases. Prolactin has several pro-inflammatory functions, and in patients with SLE has been associated with disease activity, pro-inflammatory body mass distribution and disease damage. The aim of this study was to determine whether prolactin levels are independently associated with this T-cell subset in SLE patients.

Methods: This cross-sectional study was conducted in consecutive SLE patients seen in our Rheumatology Department from September 2013 to April 2014. An interview, medical records review, physical examination and laboratory tests were performed. SLE was defined using the 1997 revised and updated ACR criteria. Prolactin levels were recorded in ng/ml. Disease activity was ascertained using the SLEDAI, disease damage with the SLICC/ACR damage index (SDI) and comorbidities with the Charlson Comorbidity Index (CCI). Use of prednisone was recorded as current dose and total time of exposure. Use of antimalarials and immunosuppressives was recorded as current, past or never. CD4+CD28null frequency was analyzed by flow-cytometry. The association of prolactin levels and CD4+CD28null T-cells was examined by univariable and multivariable linear regression models, adjusting for age at diagnosis, gender, disease duration, CCI, SLEDAI, SDI and use of prednisone, antimalarials and immunosuppressive drugs. All analyses were performed using SPSS 21.0.

Results: One hundred and four patients were evaluated; they were representative of the entire cohort (n=268); their mean (SD) age at diagnosis was 36.5 (13.6) years, 96 (92.3%) were female; all patients were mestizo (mixed Caucasian and Amerindian ancestry). Disease duration was 7.2 (6.5) years. The SLEDAI was 5.3 (3.9), the SDI 0.9 (1.3) and the CCI 1.4 (0.8). The current dose of prednisone was 7.0 (5.2) mg/d and the total time of exposure to prednisone was 6.8 (7.0) years; 82 (78.8%) and 12 (11.5%) were current and former users of antimalarials. Forty-seven (45.2%) and 26 (25.0%) were current and former users of immunosuppressive drugs. Prolactin levels were 20.6 (19.7) ng/ml. The percentage of CD4+CD28null was 17.7 (15.1) In the univariable analysis, prolactin levels were positively associated with a higher percentage of CD4+CD28null (B= 0.26, 95% IC= 0.12-0.40; p<0.001) and remained associated in the multivariable analysis (B=0.20, 95%CI= 0.04-0.37, p=0.018).

Conclusion: In SLE patients, prolactin levels are independently associated with a higher percentage of CD4+CD28null. These data support the role of prolactin as a proinflammatory hormone among autoimmune diseases and could explain its association with damage accrual.

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Abstract Number: 760

Impact of Baseline Concomitant Medication Use on Belimumab Efficacy and Safety in Patients with Systemic Lupus Erythematosus (SLE)

Andreas Schwarting[1], Mary Anne Dooley[2], David Roth[3], Lisa Edwards[4], April Thompson[4] and Barbara Wilson[4], [1]ACURA Kliniken, Bad Kreuznach, Germany, [2]University of North Carolina, Chapel Hill, NC, [3]GlaxoSmithKline, King of Prussia, PA, [4]GlaxoSmithKline, Chapel Hill,

NC

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Session Title: Systemic Lupus Erythematosus - Clinical Aspects and Treatment Poster Session I

Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose: Belimumab is licensed as add-on therapy to standard lupus care (SoC) in patients with active SLE. Physicians have inquired about the efficacy and safety of belimumab 10 mg/kg used in combination with various concomitant SLE medications.

Methods: We conducted a post hoc analysis (Study 201224) of the efficacy and safety of intravenous belimumab 10 mg/kg plus SoC versus placebo (SoC) in four baseline concomitant medication groups, from the BLISS-52 and BLISS-76 combined database: steroids only, anti-malarials (AM) only, steroids + anti-malarials (steroids + AM), and steroids + anti-malarials + immunosuppressants (steroids + AM + IS). The primary endpoint was the SLE Responder Index (SRI) at Week 52. Safety was examined using adverse events (AEs).

Results: The size of the baseline concomitant medication groups varied (below). Steroid + AM was the largest concomitant medication group and had the shortest disease duration. Patients receiving multiple concomitant medications were younger; disease activity appeared similar across groups. Steroid doses over 7.5 mg/day were common.

	Steroids only	AM only	Steroids + AM	Steroids + AM + IS
Baseline	n=139	n=77	n=346	n=272
Mean age, years	39.4	43.1	36.5	34.9
Disease duration, years	7.1	7.1	5.7	6.4
Mean (SD) steroid dose	15.3 (8.41)	NA	11.5 (7.58)	12.7 (8.95)
% steroid use >7.5 mg	86%	NA	62%	64%
SELENA-SLEDAI	10.4	9.5	9.5	9.9
Mean PGA score	1.5	1.4	1.4	1.4
Primary endpoint, Week 52				
SRI (PBO, BEL)	49%, 59%	38%, 40%	44%, 59%	32%, 42%

AM, anti-malarials; BEL, belimumab; IS, immunosuppressants; PBO, placebo; PGA; Physician Global Assessment; SD, standard deviation; SELENA-SLEDAI, Safety of Estrogens in Lupus Erythematosus: National Assessment-Systemic Lupus Erythematosus Disease Activity Index; SRI, SLE Responder Index

At Week 52, SRI improvement was highest for belimumab 10 mg/kg (59%) compared with placebo in the steroids only (49%) and steroids + AM (44%) groups. Overall, the incidence of AEs was comparable between concomitant medication groups; the steroids + AM group had a numerically higher percentage of serious AEs reported for belimumab (8% placebo, 16% belimumab) compared with SoC.

Patients were not randomized by concomitant medications group at baseline, therefore, subgroup size differed; the study was not powered to examine differences in these concomitant medication subgroups.

Conclusion: These data may be helpful in understanding practice trends and the associated effects when belimumab is added to a treatment regimen. Data interpretation is limited by the use of baseline concomitant medication use, as over 52 weeks, treatment regimens may have changed.

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Disclosure: A. Schwarting, GlaxoSmithKline; Actelion, 5; **M. A. Dooley**, Lilly, 9,Aurinia, 9,GSK, 5,Genentech and Biogen IDEC Inc., 5,EMD Serono, 5,Medimmune, 5,UCB, 5; **D. Roth**, GlaxoSmithKline, 1,GlaxoSmithKline, 3; **L. Edwards**, GlaxoSmithKline, 1,Parexel, 3; **A. Thompson**, GlaxoSmithKline, 1,GlaxoSmithKline, 3; **B. Wilson**, GlaxoSmithKline, 1,GlaxoSmithKline, 3.

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Abstract Number: 761

Neurometabolic Alterations in Korean Lupus Patients with Chronic Daily Headache

Ji-Min Kim[1], Tae-Han Lee[1], Chang-Nam Son[1], Sung Soo Kim[2], Hyuk Won Chang[3] and Sang-Hyon Kim[1], [1]Division of Rheumatology, Department of Internal Medicine, Dongsan Medical Center, Keimyung University School of Medicine, Daegu, South Korea, [2]Division of Rheumatology, Department of Internal Medicine, Ulsan University School of Medicine, GangNeung Asan Hospital, Gangneung, South Korea, [3]Department of Radiology, Keimyung University School of Medicine, Daegu, South Korea

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Background/Purpose:

Neuropsychiatric systemic lupus erythematosus (SLE) includes a broad spectrum of neurologic and psychiatric manifestations. One of the most commonly observed neuopsychiatric symptoms is headache. However, the lack of specific clinical distinctions for headache in SLE has made it difficult to elucidate its pathophysiology. Proton magnetic resonance spectroscopy (^{1}H-MRS) permits the detection of neuronal metabolic alterations noninvasively. Most studies used ^{1}H-MRS to compare patients with minor NPSLE vs patients with major NPSLE or they compared the SLE patients according to the existence of NPSLE. However, no study has been conducted using ^{1}H-MRS with a focus on specific symptoms, such as headache. The aim of this study is to evaluate the neurometabolic changes in patients with SLE who suffer from chronic daily headache (CDH).

Methods:

SLE patients with CDH (primary headache occurring at least 15 days per month for longer than 3 months), fibromyalgia patients with CDH, and healthy controls were recruited. Subjects were all Korean. ^{1}H-MRS metabolite ratios were evaluated in bilateral basal ganglia (BG) and bilateral peritrigonal white matter (PWM).

Results:

^{1}H-MRS showed a significantly decreased *N*-acetylaspartate (NAA)/creatine (Cr) ratios in right BG in SLE patients with CDH compared to fibromyalgia patients with CDH and healthy controls (p=0.029 and p=0.020, respectively). Left PWM NAA/Cr and Choline (Cho)/Cr ratios of SLE patients with CDH were lower than those of fibromyalgia patients with CDH (p=0.019 and p=0.029, respectively). NAA/Cr and Cho/Cr ratios were similar between fibromyalgia patients with CDH and healthy controls.

Conclusion:

This study suggests the clues that CDH in patients with SLE might be associated with neuronal dysfunction and neurometabolic changes. The distinctive neurometabolic features found in patients with SLE suggest the possible existence of different mechanisms in the development of CDH.

Disclosure: J. M. Kim, None; **T. H. Lee**, None; **C. N. Son**, None; **S. S. Kim**, None; **H. W. Chang**, None; **S. H. Kim**, None.

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Abstract Number: 762

The Interferon Signature Correlates with Longitudinal Disease Severity in Systemic Lupus Erythematosus, but Adds Little to Conventional Prognostic Indicators

Arundip Asaduzzaman[1], Babak Noamani[2], Denisse Bonilla[3], Dafna Gladman[4], Murray Urowitz[5,6], Paul R. Fortin[7], Carolina Landolt-Marticorena[8] and Joan E. Wither[9], [1]Rheumatology, Toronto Western Hospital, University of Toronto, Toronto, ON, Canada, [2]Genetics and developmental biology, University Health Network, Toronto, ON, Canada, [3]University Health Network, Toronto, ON, Canada, [4]Rheumatology, University of Toronto, Toronto Western Hospital, Toronto, ON, Canada, [5]University of Toronto, Toronto, ON, Canada, [6]Rheumatology, U of Toronto, Toronto Western Hospital, Toronto, ON, Canada, [7]Université Laval, CHU de Québec, Québec, QC, Canada, [8]1E420/Div of

Rheumatology, University Health Network, Toronto, ON, Canada, [9]Rheumatology, University Health Network, Toronto, ON, Canada
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Session Time: 9:00AM-11:00AM

Background/Purpose:

Type I interferon (IFN) is thought to play an important part in the pathophysiology of systemic lupus erythematosus (SLE), and cross-sectional data suggests an association between IFN-induced gene expression and SLE disease activity. However, interest in the IFN signature as a clinical biomarker has been tempered by a lack of fluctuation with disease activity over relatively brief durations (1-2 years) of follow up. In previous work we observed a significant reduction in the IFN signature in patients who had achieved prolonged clinical remissions off prednisone and immunosuppressives, as compared to relapsing and remitting SLE patients. This led us to question whether the IFN signature could act as a prognostic marker of disease severity.

Methods:

IFN induced gene expression was measured in the whole peripheral blood at baseline in 73 SLE patients, using nCounter (NanoString) multiplexed profiling. The expression levels of five representative interferon responsive genes were summed to yield a composite IFN-5 score. Adjusted mean SLEDAI-2K, number of flares, mean steroid dose, immunosuppressive use, and change in SLICC/ACR damage index (SDI) were obtained for all patients over the subsequent five year period. Clinical outcomes were compared to the baseline IFN-5 score by linear regression.

Results:

Of the 73 patients, 65 patients completed five years of follow-up, with 3 patients dying over the study period. As observed in previous studies, the IFN-5 score was positively associated with baseline disease activity ($p=0.0007$) and negatively associated with baseline age ($p=0.004$) and disease duration ($p=0.003$). Upon analysis of clinical outcomes over the subsequent 5 years, the baseline IFN-5 score demonstrated a significant positive association with the adjusted mean SLEDAI at the end of the study period ($p=0.003$), number of flares ($p=0.03$), and number of immunosuppressives used ($p=0.03$). There was also a positive trend between the IFN-5 score and mean steroid dose ($p=0.23$) and progression of damage ($p=0.46$). However, in a multivariate analysis incorporating conventional prognostic indicators including age, baseline disease activity, disease duration, immunosuppressive use, and the IFN-5 score, only age and baseline disease activity were independently associated with the outcome as measured by the adjusted mean SLEDAI-2K.

Conclusion:

Although higher interferon scores correlate with several clinical markers of increased disease severity over the subsequent 5 years, they do not appear to be independently associated with disease severity. This suggests that measurement of the interferon signature may be of limited utility as a prognostic biomarker.

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Abstract Number: 763

Lupus-Related SNPs and Risk of Diffuse Large B-Cell Non-Hodgkin Lymphoma

Sasha Bernatsky[1,2], John Spinelli[3], Patrick M. Gaffney[4], Karin E Smedby[5], Rosalind Ramsey-Goldman[6], Sophia Wang[7] and Ann E. Clarke[8], [1]Rheum/Clin. Epid., McGill MUHC/RVH, Montreal, QC, Canada, [2]Clinical Epidemiology, Research Institute of the McGill University Health Centre, McGill University, Montreal, QC, Canada, [3]School of Population and Public Health, University of British Columbia, Vancouver, QC, Canada, [4]Arthritis and Clinical Immunology, Oklahoma Medical Research Foundation, Oklahoma City, OK, [5]Clinical Epidemiology Unit, Department of Medicine Solna, Karolinska Institutet and Karolinska University Hospital, Stockholm, Sweden, [6]Fsm # M300, Northwestern University, Chicago, IL, [7]Division of Cancer Etiology, Department of Population Sciences, Beckman Research Institute, Duarte, CA, [8]Immunology/Epidemiology, Montreal General Hospital, Montreal, QC, Canada
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Session Time: 9:00AM-11:00AM

Background/Purpose: The determinants behind the increased risk of non-Hodgkin Lymphoma (NHL) in systemic lupus (SLE) are unclear. The most common type of NHL in SLE (as in the general population) is the Diffuse Large B-Cell lymphoma (DLBCL) subtype. Using data from a recent NHL genome-wide association study (GWAS), our objective was to determine if certain lupus-related single nucleotide polymorphisms (SNPs) were also associated with the risk of DLBCL.

Methods: We focused on 28 SNPs associated with SLE in European Caucasians; all of these SNPs of which have been strongly associated with lupus risk, with a p value of 10-7 or stronger. Our hypothesis was that these SNPs would also be associated with DLBCL. GWAS data on European Caucasians from International Lymphoma Epidemiology Consortium (InterLymph) studies and participating cohort studies were based on a total of 3,857 DLBCL cases and 7,666 controls. For each SLE-related SNP, the odds ratios and 95% confidence intervals (CIs) were computed using a log-additive logistic regression model. **Results** from three previously conducted DLBCL GWAS studies were pooled in a fixed-effect meta-analysis. With 28 multiple comparisons, an alpha of 0.05 would correspond to a Bonferroni-corrected p value of 0.0018.

Results: Among the 28 SLE-related SNPs investigated, two were clearly associated with risk of DLBCL when correcting for multiple comparisons. These two included the rs3024505 SNP on chromosome 1, a variant allele of IL10 (OR per risk allele =1.14, 95% CI 1.05-1.23, p value 0.0013), and the HLA SLE risk allele rs1270942 on chromosome 6 (OR per risk allele 1.20, 95% CI 1.08-1.33, p value 0.0007). Of additional possible interest were the rs4810485 and rs2205960 SNPs. The OR for the rs4810485 (CD40 gene) risk allele was 1.09 (5% CI 1.02, 1.16, p value 0.013). The rs2205960 SNP, encoding a cytokine of the tumor necrosis factor superfamily, TNFSF4 was associated with an OR per risk allele of 1.08, 95% CI 1.02-1.15, p value 0.044.

Discussion: In terms of a link between the SLE-related rs3024505 SNP and DLBCL, serum IL-10 levels have previously been suggested as a prognostic factor in NHL and IL-10 prevents spontaneous death of germinal center B cells by induction of the bcl-2 protein. Existing data also suggest that some HLA polymorphisms influence risk of DLBCL, CD40 is a member of the tumour necrosis superfamily and it has a central role in regulating B-cell proliferation; CD40 is expressed on several B-cell neoplasms including DLBCL. Finally, tumor necrosis factor ligand superfamily involvement has been suggested in the pathology of malignant lymphomas.

Conclusion: These data suggest several plausible pathways linking DLBCL and SLE.

Disclosure: S. Bernatsky, None; **J. Spinelli**, None; **P. M. Gaffney**, None; **K. E Smedby**, None; **R. Ramsey-Goldman**, None; **S. Wang**, None; **A. E. Clarke**, None.

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Abstract Number: 764

Gastrointestinal Adverse Events of Azathioprine in Daily Clinical Practice: Independent of Thiopurine Methyltransferase Activity

Eun Young Ahn[1], Hyun Mi Kwon[1], Sung-Hwan Park[2], Yeong Wook Song[1] and Kichul Shin[3], [1]Division of Rheumatology, Department of Internal Medicine, Seoul National University Hospital, Seoul, South Korea, [2]Division of Rheumatology, Department of Internal Medicine, Seoul St. Mary's Hospital, Seoul, South Korea, [3]Division of Rheumatology, Department of Internal Medicine, Seoul Metropolitan Government-Seoul National University Boramae Medical Center, Seoul, South Korea

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Session Time: 9:00AM-11:00AM

Background/Purpose: Azathioprine (AZA) is a commonly used immunosuppressive agent for a number of systemic rheumatic diseases. Although it is regarded to be relatively safe to prescribe in daily clinical practice, untoward rare side effects, especially gastrointestinal adverse events (GIAE) are sporadic, severe and troublesome. There is currently no test or guideline to help predict or prevent this event.

Methods: We reviewed medical records of patients followed at a rheumatology outpatient clinic in a single center (2012.3.1-2015.2.28, SMG-SNU BRMH). Clinical parameters including demographic data, underlying conditions, AZA dose and duration of use, concomitant medications,

and laboratory exams were analyzed. Patients with AZA GIAE were defined as those having severe nausea, vomiting or diarrhea, and malaise during AZA ingestion unexplained otherwise. In total, 12 patients with GIAE and 37 control patients (with no side effects after 6 months of AZA) were identified, and among those, whole blood was drawn from 10 GIAE patients and 23 age/gender-matched controls for thiopurine methyltransferase (TPMT) testing (Green Cross Labs).

Results: The baseline data of AZA GIAE patients showed mean age of 58.4 years, and 58% were females. Mean disease duration of the underlying condition was 29.9 months. The initial dose of AZA was 56.3 mg/d, and GIAE was detected after 57.9 days, when on 85.4 mg/d (all mean values). Around that same period, the control group was on 66.7 mg/d of AZA (p= 0.057). Other clinical parameters between the two groups were comparable. TPMT genotype all GIAE patients were that of wild type, and mean TPMT enzymatic activity of GIAE patients and controls were 34.42 U, 34.23 U, respectively (p= 0.97). Notable laboratory results are described below (table).

Conclusion: These results suggest that early prediction of AZA GIAE is still challenging; physician's awareness, gradual AZA dose increment, early follow-up of liver function tests are conventional, yet important principles to follow.

Table. Selected notable laboratory findings at the period of the adverse event of azathioprine

Laboratory test	GIAE (n=12)	Controls* (n=35)	*p*-value
White blood cells, mm^3	8055 ± 856.0	7120 ± 523.7	*p*= 0.367
Aspartate aminotransferase, IU/L	115.2 ± 28.7	24.9 ± 2.3	*p*< 0.001
Alanine aminotransferase, IU/L	171.7 ± 46.3	20.5 ± 2.3	*p* < 0.001
Alkaline phosphatase, IU/L	260.3 ± 83.5	83.7 ± 11.5	*p*= 0.0014
Erythrocyte sedimentation rate, mm/hr	32.2 ± 7.3	19.4 ± 3.5	*p*= 0.0854
C-reactive protein, mg/dL	1.0 ± 0.3	0.4 ± 0.1	*p*= 0.0505

*Laboratory value at 57.9 ± 14 days after starting azathioprine

GIAE, gastrointestinal adverse event

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Abstract Number: 765

Clinical Improvements in Systemic Lupus Erthematosus Are Correlated to Cellular and Soluble Biomarkers in Classical Complement Pathway

Chaim Putterman[1], Jill P. Buyon[2], Richard Furie[3], Rosalind Ramsey-Goldman[4], Kenneth Kalunian[5], John Conklin[6], Tyler O'Malley[7], Derren Barken[8] and Thierry Dervieux[7], [1]Division of Rheumatology, Albert Einstein College of Medicine, Bronx, NY, [2]NYU School of Medicine, New York, NY, [3]NSLIJHS, Lake Success, NM, [4]Northwestern University Feinberg School of Medicine, Chicago, IL, [5]UCSD School of Medicine, La Jolla, CA, [6]1261 Liberty Way Suite C, Exagen Diagnostics, Vista, CA, [7]Research and Development, Exagen Diagnostics, Vista, CA, [8]Exagen Diagnostics, Vista, CA

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Background/Purpose : There is a need to identify biomarkers that track disease response in systemic lupus erythematosus (SLE). The value of various biomarkers in monitoring of SLE subjects with active disease was assessed. This consisted of cell bound complement activation products (CB-CAPS, erythrocytes EC4d, EC3d), complement (C3 and C4) levels anti-dsDNA, anti-chromatin, anti-C1q and Complement Receptor 1 (ECR1).

Methods : SLE patients enrolled in this prospective biomarker study all presented with active disease. At baseline, all subjects were screened

for abnormal CBCAPS (e.g. erythrocytes C4d [EC4d]> 14 MFI). Those with disease activity accompanied by elevated CBCAPS were followed monthly for 12 consecutive visits at 4 week intervals. At each visit, the non-serological (ns) SELENA-SLEDAI (without anti-dsDNA and low complement components) and the BILAG score index were determined as was a random protein to creatinine (P/C) ratio. Short form 36 questionnaires (SF-36) were also collected. All soluble markers were determined using immunoassays, while cellular markers (EC4d, EC3d and ECR1) were determined using flow cytometry. Statistical analysis consisted of generalized linear mixed models with random intercept and fixed slopes. All investigators were blinded to CBCAPS, anti-C1q and anti-chromatin throughout the study. Anti-dsDNA titers and serum C3/C4 levels were available to investigators throughout the study.

Results : A total of 36 CB-CAPS positive SLE patients (mean age 34 years; 94% female) were enrolled and evaluated monthly for a total of 385 consecutive study visits (average 11 visits per patient). The majority of these subjects presented with anti-dsDNA positivity (64%) and low complement (72%). Clinical improvements were observed during the study, with significant decrease in ns-SELENA SLEDAI scores, BILAG index score, P/C ratio, and increase in all domains of the SF-36 ($p<0.01$). By univariate analysis, the longitudinal changes in the ns-SELENA-SLEDAI were significantly associated with all biomarkers measured ($p<0.05$). The change in BILAG index score correlated with 6/8 biomarkers ($p>0.05$ for anti-dsDNA and anti-chromatin) while the changes in proteinuria correlated with EC4d, ECR1, C3, C4 and anti-C1q. EC4d and EC3d levels were each associated with improving quality of life in 6/8 domains of the SF-36. In contrast, the other markers were each associated with 2 or fewer SF-36 domains. By multivariate analysis both complement C4 and EC3d were associated with the ns-SELENA-SLEDAI and BILAG index scores ($p<0.06$)(Table). Similarly, both complement C4 and EC4d were associated with proteinuria ($p<0.01$).

Conclusion : CBCAPS are helpful in monitoring SLE disease in combination with complement C3 and C4.

Table: Multivariate analysis of the clinical improvements

Outcome variables	Predictor 1 Complement C4 (mg/dl)	Predictor 2: EC3d or EC4d (log net MFI)
ns-SELENA-SLEDAI*	-0.11±0.004; p<0.01	0.65±0.35 p=0.06
BILAG Index	-0.25±0.07; p<0.01	2.03±0.61; p<0.01
Proteinuria (g/g)	-0.04±0.02; p=0.04	0.86±0.22; p<0.01

*For 10 mg/dl increase in C4 (predictor 1) and one log Net MFI decrease in CBCAPS (predictor 2), the ns-SELENA-SLEDAI change was -0.11x[10] + 0.65x[-1]=-1.75

Disclosure: C. Putterman, Exagen, 2; **J. P. Buyon**, Exagen, 2; **R. Furie**, Exagen, 2; **R. Ramsey-Goldman**, Exagen, 2; **K. Kalunian**, Exagen, 5; **J. Conklin**, Exagen, 3; **T. O'Malley**, Exagen, 3; **D. Barken**, Exagen, 3; **T. Dervieux**, Exagen, 3.

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Abstract Number: 766

Clinical and Immunological Characteristics of 150 Systemic Lupus Erythematosus Patients in Urban Jamaica

Keisha Maloney[1], Trevor Ferguson[2] and Karel De Ceulaer[3], [1]Department of Medicine,, University of the West Indies, Kingston 7, Jamaica, [2]Epidemiology Research Unit, Tropical Medicine Research Institute, University of the West Indies, Kingston 7, Jamaica, [3]Internal Medicine, University of the West Indies, Kgn 7, Jamaica

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Background/Purpose:

Epidemiological studies in systemic lupus erythematosus (SLE) have been reported in the literature in many countries and ethnic groups. Although SLE in Jamaica has been described in the past, there has not been a detailed evaluation of SLE patients in urban Jamaica a largely Afro-Caribbean population. The goal of this study was to describe the clinical features particularly disease activity, damage index and immunological features of 150 SLE subjects.

Methods:

150 adult patients (≥ 18 years) followed in rheumatology clinic at a tertiary rheumatology hospital center (1 of 2 of the major public referral centers in Jamaica) and the private rheumatology offices in urban Jamaica who fulfilled four or more SLICC criteria were included. Data was collected by retrospective chart review, detailed clinical interview and examination and laboratory investigations. Hence demographics, SLICC criteria, immunological profile, SLEDAI-2K and SLICC/American College of Rheumatology (ACR) damage index (SDI) were documented.

Results:

: Of the 150 patients 145 were female and 5 were male (F: M=29:1); the mean age at SLE onset was 33.2 ± 10.9. Mean disease duration was 11.3 ±8.6 years. The most prevalent clinical SLICC criteria was musculoskeletal with 94% of subjects experiencing arthralgia/arthritis followed by mucocutaneous manifestations of alopecia (68.7%) and malar rash (46%). The most common laboratory SLICC criteria were positive ANA (90.6%) followed by anti-dsDNA (63.3%) and low complement (C3) levels (25.3%). 27% of patients met SLICC diagnostic criteria with only a positive ANA/ds-DNA and lupus nephritis on renal biopsy. The lowest SLICC score of 3 occurred in 2 patients in whom there was a positive ANA and biopsy proven lupus nephritis. 42 patients (28%) presented with lupus nephritis and 37 patients (24.7%) had neuropsychiatric manifestations. Mean SLEDAI score was 6.9 ± 5.1 with a range of 0-32. The most frequent manifestations of active SLE was found in the immunological laboratory variables of the disease namely increased ds-DNA binding (81.3%) and low complement levels (26.7%) and the clinical variable of arthritis in 27.3%. Organ damage occurred in 129 patients (86%); Mean SDI was 2.4 ± 1.8, range of 0-9. Every single organ system was affected by damage. The most frequent organ system involved in damage was the peripheral vascular system (75 patients, 50%), neurological (47 patients, 31.3%), skin (38 patients, 25.3%), ocular (29 patients, 19.3%), diabetes (28 patients, 18.67%), cardiovascular (18 patients, 12%) and renal (15 patients, 10%).

Conclusion: These results are similar to the clinical manifestations reported in other Afro-Caribbean populations; however distinct differences exist with respect to organ involvement and damage particularly with respect to renal involvement which appears to be reduced in this cohort. These differences support the need that further studies are required among similar groups of African descent to determine the spectrum of SLE that exists within this group.

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Abstract Number: 767

Estimating the Pre-Test Probability of Systemic Lupus Erythematosus By Utilizing Anti-Double Stranded DNA and Cell Bound Complement Activation Products Testing from Rheumatology Based Practices in the United States

Stuart L. Silverman[1], Derren Barken[2], John Conklin[3], Claudia Ibarra[4] and Thierry Dervieux[5], [1]OMC Clinical Research Center, Beverly Hills, CA, [2]Exagen Diagnostics, Vista, CA, [3]1261 Liberty Way Suite C, Exagen Diagnostics, Vista, CA, [4]Clinical Laboratory, Exagen Diagnostics, Vista, CA, [5]Research and Development, Exagen Diagnostics, Vista, CA

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Background/Purpose : Clinicians are aware that the interpretation of any clinical diagnostic test and post-test probability of disease is highly influenced by pre-test probability or prevalence of the condition in which the test result is used. We have recently established that a group of primary fibromyalgia and systemic lupus erythematosus (SLE) patients can be distinguished by anti-dsDNA and cell bound complement activation products (CB-CAPS) in multi-analyte assay (MAAA) panel. The purpose of this study was to translate these findings in the context of patients evaluated for SLE or another mimicking disease by community based rheumatologists in the United States.

Methods : From February 2014 to May 2015, a total of 35,792 CB-CAPS in MAAA panels were requested by 902 physicians during the course of clinical diagnostic care of 35,792 patients (mean ± SD 51±15 years, 84% females). Venous blood was collected from all patients and shipped to our NY/CAP accredited centralized laboratory conducting routine testing for CB-CAPS (erythrocyte and B-lymphocyte C4d) plus a panel of diagnostic immunology markers including anti-nuclear antibodies (ANA) and anti-double stranded DNA antibodies. Abnormal CB-CAPs are defined by EC4d or BC4d levels above the upper 95th percentile of a group of normal healthy individuals. CB-CAPS are combined with anti-dsDNA and other anti-cellular antibodies in two consecutive tiers of analysis that produces a positive or negative assessment reported to ordering clinicians. For the purpose of this study, de-identified laboratory result assessments were extracted from our clinical laboratory information

system and analyzed in our population health data warehouse system. Pre-test probability of SLE was estimated using the method developed by Rogan and Gladen (*Am J Epidemiol. 1978 107:71)* that uses sensitivity (Se), specificity (Sp), and positivity rate (R) for the diagnostic: prevalence= [R – (1-Sp)]/(Se – (1-Sp)]. Predictive values of positive test assessments (PPV) were derived from pre-test probability using standard statistics.

Results : In this cohort of 35,792 patients, positivity rate of ANA was 49%, anti-dsDNA 5.0%, CB-CAPS 10% and CB-CAPS in MAAA panel 14% (Table). Applying the formula for estimation of SLE prevalence (pre-test probability) yielded very similar rates from 16-20%. The predictive value of a positive test (PPV) ranged from 59% to 86%. Furthermore CB-CAPS in MAAA positive test results identified of a higher number of SLE patients (n=4259) than anti-dsDNA alone (n=1047), with fewer false positive results.

Conclusion : These tests are being used by rheumatologists appropriately in patient populations where the possibility of SLE is being considered. In this context high CB-CAPs in MAA identified more true SLE patients with fewer false positive results.

Table: Derivation of pre-test and post probability of SLE in US rheumatology based practice

	Positivity Rate	Sens.	Spec.	Pre-test probability	PPV	True positive	False positive
Anti-dsDNA	5.0%	17.3%	>97.5%	16.9%	58.5%	1047	743
High CB-CAPS	10.1%	44.4%	96%	15.6%	66.6%	2408	1207
CB-CAPS in MAAA	13.9%	60.0%	>97.5%	19.8%	85.6%	4259	716

Disclosure: S. L. Silverman, Exagen, 8,Exagen, 2; **D. Barken**, Exagen, 3; **J. Conklin**, Exagen, 3; **C. Ibarra**, Exagen, 3; **T. Dervieux**, Exagen, 3.

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Abstract Number: 768

The Lupus Foundation of America Rapid Evaluation of Activity in Lupus (LFA-REAL) Instrument Correlates Between Trained Clinical Investigators and Clinicians

Anca Askanase[1], Teja Kapoor[2], Cynthia Aranow[3], Karen H. Costenbader[4], Jennifer Grossman[5], Diane L. Kamen[6], S. Sam Lim[7], Mimi Kim[8], Paola Daly[9,10], Leslie M. Hanrahan[11] and Joan T. Merrill[12], [1]NYU School of Medicine, New York, NY, [2]Columbia University, New York, NY, [3]Feinstein Institute for Medical Research, Mahasset, NY, [4]Rheumatology, Immunology & Allergy, Brigham & Women's Hospital, Boston, MA, [5]Rheumatology, UCLA, LA, CA, [6]Medicine, Medical University of South Carolina, Charleston, SC, [7]Emory University School of Medicine, Atlanta, GA, [8]Biostatistics and Research Design Resource, Albert Einstein Coll Med, Bronx, NY, [9]Lupus Foundation of America, Washington DC, DC, [10]Lupus Foundation of America, Washington, DC, [11]Lupus Fnd of America, Washington, DC, [12]Oklahoma Medical Research Foundation, Oklahoma City, OK

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Background/Purpose: Current SLE disease activity measures, such as SLEDAI and BILAG, can be challenging to score and interpret, making them impractical for use in a busy clinic and difficult to evaluate when used as outcomes in clinical trials. The LFA- REAL is composed of individual visual analog scales (0-100mm each) representing different manifestations of SLE. A clinician can quickly rate only the active features in a given patient, immediately generating organ-specific as well as total disease activity scores. The objective of this study was to compare LFA-REAL scores between clinical investigators (investigators) trained in scoring SLE disease activity instruments and clinicians without specialized SLE instrument training (clinicians), and to correlate REAL scores with other disease activity measures.

Methods: 99 SLE patients in four rheumatology clinics were evaluated, of whom 70 returned for an additional follow-up assessment. At each visit, an investigator scored SLEDAI, BILAG, PGA, and LFA-REAL and a clinician scored only the LFA-REAL. Level of agreement was determined by Spearman rank correlations.

Results : The study included 93% women, 31% Caucasian, mean age 43.4 years, mean disease duration 10 years. Mean (SD) of the disease activity scores for the first and second visits are shown below. There was excellent correlation between the clinician and investigator REAL scores at both visits (ρ=0.80 for visit 1; 0.86 for visit 2).

		SLEDAI	BILAG	PGA	REAL
Visit 1	Investigator	5.5 (4.5)	6.7 (7.8)	33.6 (24.5)	46.2 (42.9)
	Clinician	---	---	---	56.1 (53.6)
Visit 2	Investigator	5.2 (5.2)	6.0 (9.1)	31.9 (21.2)	41. 3 (36.7)
	Clinician	---	---	---	48.3 (42.6)

Global REAL scores also correlated well with the PGA, SLEDAI, and BILAG.

	SLEDAI (ρ)	BILAG (ρ)	PGA (ρ)
Visit 1 Investigator REAL Clinician REAL	0.70 0.58	0.86 0.70	0.79 0.63
Visit 2 Investigator REAL Clinician REAL	0.72 0.58	0.88 0.81	0.81 0.63
Change (V2-V1) Investigator REAL Clinician REAL	0.63 0.56	0.61 0.42	0.80 0.50

Organ specific correlations between the REAL and individual BILAG organs were > 0.7 for musculoskeletal, mucocutaneous and renal domains, for both investigators and clinicians.

Conclusion: The LFA-REAL shows promise as an efficient tool for clinical trials and for accurate monitoring of patient progress by busy clinicians without special instrument training. Community input, refinement and formal validation is planned to optimize the format, consistency and applicability of the instrument.

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Abstract Number: 769

Evaluation of Soluble Alpha-Klotho in Neuropsychiatric Systemic Lupus Erythematosus

Kunihiro Ichinose[1], Takeshi Ushigusa[2], Masataka Umeda[1], Tomohiro Koga[2], Atsushi Kawakami[2] and Shuntaro Sato[3], [1]Department of Immunology and Rheumatology, Nagasaki University, Nagasaki, Japan, [2]Department of Immunology and Rheumatology, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan, [3]Clinical Research Center, Nagasaki University Hospital, Nagasaki, Japan

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Evaluation of Soluble alpha-Klotho in Neuropsychiatric Systemic Lupus Erythematosus

ABSTRACT

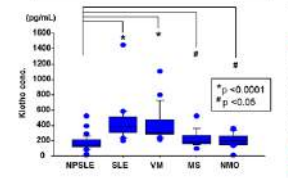
Background/Purpose: Neuropsychiatric systemic lupus erythematosus (NPSLE) is a serious complication in SLE that presents a variety of symptoms. No reliable diagnostic markers for NPSLE have been identified, because of the variability of NPSLE manifestations and the absence of appropriate diagnostic criteria. Alpha-Klotho is a single-pass transmembrane protein expressed in multiple tissues, especially brain and kidneys. A reduction of Klotho protein is known to be associated with endothelial dysfunction and neuronal damage.

Methods: We sought to determine whether soluble alpha-Klotho (s-Klotho) in cerebrospinal fluid (CSF) could be a candidate marker for the diagnosis of NPSLE. We retrospectively analyzed the laboratory data, symptoms and radiological image findings of patients with NPSLE (n=34) admitted to our hospital during a 10-year period from 2006 through 2015. Patients with SLE (n=17), viral meningitis (VM) (n=19), multiple sclerosis (MS) (n=15) or neuromyelitis optica (NMO) (n=16) were included as controls. The s-Klotho level in the CSF of each subject was measured by enzyme-linked immunosorbent assay. We conducted univariate and multivariable competing-risks regression analyses to determine the predictive factors for diagnosing NPSLE. We also evaluated a cutoff value of s-Klotho for the diagnosis of NPSLE by determining the receiver operating characteristic (ROC) curve.

Results: There was no significant difference in the clinical background between the NPSLE and SLE patients. The median CSF s-Klotho level in the NPSLE, SLE, VM, MS and NMO groups (in pg/mL) were 136.7, 380.2, 302.1, 186.4 and 203.1, respectively. We found that the CSF s-Klotho levels of the NPSLE patients were significantly lower than those of the other groups. The multivariable analyses revealed that lower CSF s-Klotho level (odds ratio [OR], 0.98; 95% confidential interval [CI], 0.96–0.99), lower anti-Smith antibodies (U/mL) (OR, 0.93; 95%CI, 0.82–0.99) and higher C3 (mg/dL) (OR, 1.08; 95%CI, 1.02–1.18) were significant factors for predicting NPSLE. The sensitivity and specificity of the CSF s-Klotho level for the diagnosis of NPSLE were 94.1% and 76.5%, respectively at the cut-off value of 294.8 pg/mL.

Conclusion: Our data suggested that lower CSF s-Klotho levels may be associated with the endothelial dysfunction and neuronal damage in NPSLE patients. The determination of CSF s-Klotho levels may contribute to the diagnosis of NPSLE and may help elucidate the mechanisms underlying this disease.

Figure:CSF α-Klotho in NPSLE was significantly lower than SLE



	CSF α-Klotho(pg/mL)	vs. NPSLE
NPSLE, median (IQR)	136.7 (113.3 - 205.4)	-
SLE, median (IQR)	380.2 (306.8 - 527.6)	<0.0001*
VM, median (IQR)	302.1 (282.8 - 479.2)	<0.0001*
MS, median (IQR)	186.4 (158.7 - 288.5)	0.0186*
NMO, median (IQR)	203.1 (148.3 - 257.6)	0.0447*

Table:Variables identified by multivariable regression analysis as predicting diagnostic value in NPSLE

	Univariate			Multivariable			Final model		
	OR	CI	P-value	OR	CI	P-value	OR	CI	P-value
α-Klotho(CSF)	0.98	0.96 – 0.99	0.0004*	0.98	0.96 – 0.99	<0.0001*	0.98	0.96 – 0.99	<0.0001*
α-Klotho(serum)	0.99	0.98 – 1.00	0.4004						
Age at sampling	0.99	0.95 – 1.05	0.8435						
Sex (female)	0.47	0.02 – 3.51	0.4664						
Disease duration	1.01	0.95 – 1.09	0.709						
SLEDAI score	1.09	0.99 – 1.23	0.0936	1.15	0.99 – 1.52	0.2109			
Anti-ds DNA antibodies(IU/mL)	1	0.99 – 1.03	0.3037						
Anti-Smith antibodies(U/mL)	0.95	0.90 – 0.99	0.0047*	0.93	0.83 – 0.99	0.0432*	0.93	0.82 – 0.99	0.0322*
C3(mg/dL)	1.02	1.00 – 1.05	0.1048	1.08	1.02 – 1.18	0.0137*	1.08	1.02 – 1.18	0.0052*
C4(mg/dL)	1.04	0.98 – 1.19	0.2148						
APS (positive)	1.08	0.26 – 4.63	0.9117						
CSF IL-6(pg/mL)	1	0.99 – 1.02	0.5698						

Disclosure: K. Ichinose, None; **T. Ushigusa**, None; **M. Umeda**, None; **T. Koga**, None; **A. Kawakami**, None; **S. Sato**, None.

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Abstract Number: 770

Circulating Levels of iC3b and C3 Correlate with Sledai-2K Responder Index-50 (S2K RI-50) Disease Activity Scores: The Castle (Complement Activation Signatures in Systemic Lupus Erythematosus) Study

Alfred Kim[1], Vibeke Strand[2], Nancy Mathis[1], Deepali Sen[3], Jonathan Miner[3], Elizabeth Schramm[1], Robin Bruchas[4], Nick Staten[4], Paul Olson[4],

Chad Stiening[4] and John Atkinson[1], [1]Rheumatology, Washington University School of Medicine, Saint Louis, MO, [2]Adjunct, Division of Immunology / Rheumatology, Stanford University, Palo Alto, CA, [3]Division of Rheumatology, Washington University School of Medicine, Saint Louis, MO, [4]Kypha, Inc., Saint Louis, MO
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Background/Purpose: A major unmet need in SLE is the identification of a biomarker that consistently tracks with disease activity. One current approach is measuring complement activation by evaluating consumption of serum C3 and C4. However, since they are acute phase reactants (Gabay & Kushner, *NEJM*, **340**:448, 1999), interpretation of these levels is challenging as serum levels may not decrease until late in a disease flare (Sturfelt & Sjoholm, *Int Arch Allergy Appl Immunol*, **75**:75, 1984). iC3b is a proteolytically derived molecule of C3b, and increases with complement activation. iC3b/C3 ratio measures complement consumption relative to production, which may provide for a more accurate assessment of complement activation. We hypothesize that blood iC3b and iC3b/C3 levels will provide as a more specific and reliable marker of complement activation and disease activity in SLE.

Methods: 90 adult SLE patients were enrolled in this observational study, encompassing 188 longitudinal visits. C3 and C4 were measured by nephelometry; iC3b using the Kypha lateral flow assay test. Linear models analysis was used to generate predictive models of S2K RI-50 scores using iC3b, C3, iC3b/C3 ratio, C4, anti-dsDNA Abs, ESR, and CRP from single visit data. Mixed model repeated measures analysis was used to evaluate longitudinal data.

Results: Using single visit data, blood levels of iC3b, C3, iC3b/C3 ratio, C4, and ESR each correlated with SLE disease activity (Table 1). Linear models analysis yielded a predictive model using iC3b/C3 ratio, C4, and ESR. In the longitudinal dataset, after modeling for variance structure, S2K RI-50 scores increased by 0.52 for every 1 unit increase in iC3b/C3 ratios (Table 2). C4 was also found to mildly influence S2K RI-50 scores.

Conclusion: iC3b/C3 ratios correlated with S2K RI-50 scores and linear model analysis confirmed the predictive value of iC3b to S2K RI-50 scores. After adjusting for both correlation and other covariates, the longitudinal data further established a significant relationship between iC3b/C3 ratios and SLE disease activity. These data warrant further investigation of iC3b as a potential biomarker for disease activity in SLE.

Table 1. Univariate and linear model analysis from single visit data

	R^2	p value
iC3b	0.138	0.0004
C3	0.172	<0.0001
C4	0.173	<0.0001
dsDNA	0.013	0.2963
ESR	0.126	<0.0001
CRP	0.026	0.1451
iC3b/C3	0.273	<0.0001
iC3b/C3, C4, ESR (linear model)	0.333	<0.0001

Table 2. Mixed model repeated measures analysis from longitudinal data

Predictor	Estimate ± standard error	p value
iC3b/C3 ratio	0.52 ± 0.15	0.0010
ESR	0.23 ± 0.12	0.0515
CRP	0.07 ± 0.07	0.2788
C4	-0.03 ± 0.01	0.0027
dsDNA	-0.06 ± 0.12	0.6313

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Abstract Number: 771

Convergent Validity of New Disease Assessment Instruments in Systemic Lupus Erythematosus in Relation to Sledai-2K

Christopher Collins[1], W. Winn Chatham[2], Howard Busch[3], Norman B. Gaylis[4], Emily Hautamaki[5] and Siva Narayanan[6], [1]MedStar Washington Hospital Center, Washington, DC, [2]Medicine/Clinical Immunology and Rheumatology, University of Alabama at Birmingham, Birmingham, AL, [3]Science & Research Institute, Jupiter, FL, [4]Arthritis & Rheumatic Disease Specialties, Aventura, FL, [5]Ipsos Healthcare, Washington, DC, [6]Global Evidence, Value and Access, Ipsos Healthcare, Washington, DC
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Background/Purpose: Current validated disease assessment instruments (DAIs) in systemic lupus erythematosus (SLE) such as SLEDAI-2K and BILAG, require disease expertise and/or involve complex scoring systems, and are often impractical for use in daily clinical practice and hence are seldom used routinely in clinical practice. In an attempt to address this issue, several new simplified DAIs in SLE are in different stages of development, including SLE Activity Tracking Evaluation Tool (LAST; 14 items; includes medications, Physician Global Assessment (PhGA) 0-10 scale, Patient Global Assessment (0-10 scale), C3, C4 & anti-dsDNA lab measures), Clinical LAST (C-LAST; 11 items; similar to LAST, without lab measures), Total Lupus Activity Score (TLAS; 30 items; includes 15 physician clinical assessments and 15 patient self-assessment of lupus symptoms), and Simple Disease Assessment for People with Lupus Erythematosus (SIMPLE; 17 items; includes patient self-assessment of lupus symptoms, Lupus Impact Tracker, steroid medication, C3, C4 & proteinuria). The primary objective of this analysis is to assess the convergent validity of these various tools as well as PhGA indices in relation to SLEDAI-2K at baseline in a diverse sample of SLE patients in the US.

Methods: This is a prospective real-world observational cohort study of SLE patients receiving standard care at two academic and two private practice settings in the US. Consecutive patients meeting study criteria were screened within the study recruitment window. Physicians and patients are asked to complete their respective portions of the studied instruments at four different time points: baseline, 3 months, 6 months, and 12 months; PhGA:0-3 scale and SLEDAI-2K was completed for all patients; BILAG was assessed for patients at the academic sites; TLAS and SIMPLE for approx. 152 patients each; LAST & C-LAST algorithm for 169 patients each. Baseline data (presented here) was analyzed and Pearson correlation coefficients were calculated comparing mean SLEDAI-2K score to the individual DAI scores. Correlations with BILAG will be assessed in the longitudinal analysis in the future.

Results: A total of 201 SLE patients consented and enrolled in the study (mean age: 45 yrs; female: 91%; Black/African American (AA): 56%; Hispanic: 10%). At study entry (baseline), mean SLEDAI-2K score was 3.4 (range: 0-16); each of the DAIs (PhGA:0-10 scale, PhGA:0-3 scale, LAST, C-LAST, SIMPLE & TLAS) had a statistically significant positive correlation with the SLEDAI-2K, as shown in table-1. Analysis stratified by AA and non-AA status revealed similarly significant correlations between SLEDAI-2K and the other DAIs.

Conclusion: In the baseline cross-sectional analysis, each of the studied DAIs appeared to have convergent validity with the SLEDAI-2K. Further analyses with longitudinal data will assess additional metric properties of these instruments.

Table 1. DAI Scores and Correlations with SLEDAI-2K

Assessments	n	Median Score (IQR)	Mean Score (SD; range)	Pearson correlation with SLEDAI-2K r; p-value
LAST (0=No activity - 100=High activity)	169	23.0 (15.0-32.0)	23.9 (13.0; 0-70.0)	0.566; <0.0001
PhGA:0-10 scale (0=No activity - 10=High activity)	168	2 (1-3)	2.3 (1.9; 0–8)	0.563; <0.0001
SIMPLE (0=No activity - 100=High activity)	152	21.5 (15.1-27.8)	23.2 (11.2; 6.2-68.5)	0.560; <0.0001
PhGA:0-3 scale (0=No activity - 3=High activity)	201	1 (N/A)	0.9 (0.7; 0-3)	0.553; <0.0001
C-LAST (0=No activity - 70=High activity)	169	20.0 (12.5-27.5)	20.3 (11.1; 0-50.0)	0.450; <0.0001
TLAS (0=No activity - 120=High activity)	153	56 (50-64)	56.9 (10.8; 31.0-86.0)	0.348; <0.0001
SLEDAI-2K (0=No activity - 105=High activity)	199	2 (0-6)	3.4 (3.2; 0-16)	N/A

Disclosure: C. Collins, GlaxoSmithKline, 2; **W. W. Chatham**, GlaxoSmithKline, 2; **H. Busch**, GlaxoSmithKline, 2; **N. B. Gaylis**, GlaxoSmithKline, 2; **E. Hautamaki**, GlaxoSmithKline, 2; **S. Narayanan**, GlaxoSmithKline, 2,GlaxoSmithKline, 1.

Abstract Number: 772

Post-Phlebotomy Stability of Soluble and Cellular Forms of Complement Activation: Implications in SLE Diagnostic Assays

John Conklin[1], Basil Jones[2], Tyler O'Malley[3], Duncan Poling[4], JoAnne Ligayon[5], Leilani Wolover[6], Ying Qu[7], Claudia Ibarra[8], Puja Chitkara[9] and Thierry Dervieux[3], [1]1261 Liberty Way Suite C, Exagen Diagnostics, Vista, CA, [2]Exagen Diagnostics, Vista, CA, [3]Research and Development, Exagen Diagnostics, Vista, CA, [4]Research and Development, Exagen Diagnostics Inc., Vista, CA, [5]Flow Cytometry, Exagen Diagnostics Inc., Vista, CA, [6]Research and Development, Exagen Diagnostics, Inc., Vista, CA, [7]Exagen Diagnostic Inc, Vista, CA, [8]Clinical Laboratory, Exagen Diagnostics, Vista, CA, [9]Rheumatology, Center For Arthritis and Rheumatologic Excellence, Chula Vista, CA
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Background/Purpose: Deregulation and activation of the classical complement system is known to be associated with systemic lupus erythematosus (SLE). As such, several investigators have proposed that the determination of C4d fragment, the activation product of C4 in its soluble or cell-bound form to erythrocytes (EC4d), or B-lymphocytes (BC4d) could help diagnose SLE. However, one of the challenges in

determining complement activation is the stability of these products post-phlebotomy. Our objective was to quantify the effects of time and temperature on soluble and cell bound C4d.

Methods: Venous blood was collected in EDTA-containing tubes from 12 subjects with SLE (67% females, mean age 39 years) and 15 normal healthy volunteers (NHV) (48% females, mean age 38 years). All subjects enrolled provided informed consent. Following venipuncture, the blood was equally distributed into polypropylene tubes and stored at either 4°C or ambient room temperature (22°C) for up to two days post phlebotomy. These conditions mimic the transportation condition of a typical specimen. Starting on the day of collection (day 0), and the following two days, plasma was isolated from the stored whole blood. Soluble plasma C4d concentration was determined using immunoassays (MicroVue C4d EIA, Quidel). EC4d and BC4d were determined from stored whole blood using flow cytometry and reported as net mean fluorescence intensity (MFI). The relationship between the change in the markers from baseline as a function of time and temperature was estimated with linear mixed-effect models.

Results: Soluble C4d (baseline levels 0.8±0.3 µg/ml) was significantly affected by both time (increase of 1.1 ± 0.1 µg/ml per day) and storage conditions (increase of 0.7 ± 0.1 µg/ml at ambient temperature versus 4°C) (Table 1). After two days storage at ambient temperature, soluble C4d levels increased by more than 2 fold compared to baseline plasma concentrations. By comparison, EC4d and BC4d levels were not significantly impacted by time and storage at ambient temperature. EC4d and BC4d levels were 15.9 and 62.5 net MFI after two days storage at room temperature, respectively, by comparison to 15.8 and 65.5 net MFI at day 0. In this small population of subjects, elevated CBCAPS (EC4d>14 net MFI or BC4d>60 net MFI) were 73% sensitive for SLE and 100% specific (vs. NHV).

Conclusion: Our data suggest soluble C4d is unstable during transportation and delivery of specimen to the clinical laboratory. However, cell-bound C4d is a stable measure of complement activation and could be used as complement activation biomarker in multi-centered studies.

Table 1: Estimates for biomarker change as a function of storage days and temperature. Days represent the per-day change of each marker at 4°C. Ambient temperature represents the overall increase for each marker at that temperature.

*The predicted soluble C4d concentration at 2 days storage at ambient temperature is 0.8 + 1.1×[2] + 0.7×[1] = 3.1 µg/mL

Marker (Units)	Day0 Levels (CI95%)	Days	Ambient Temperature (22°C)
Soluble C4d (µg/mL)	0.8 ± 0.3	1.1 ± 0.1	0.7 ± 0.1
EC4d (Net MFI)	15.8 ± 2.8	-0.2 ± 0.2	0.1 ± 0.3
BC4d (Net MFI)	65.5 ± 12.8	-2.0 ± 1.3	1.1 ± 2.1

Disclosure: J. Conklin, Exagen, 3; **B. Jones**, Exagen Diagnostics Inc., 3; **T. O'Malley**, Exagen, 3; **D. Poling**, Exagen Diagnostics Inc., 3; **J. Ligayon**, Exagen Diagnostics Inc., 3; **L. Wolover**, Exagen Diagnostics Inc., 3; **Y. Qu**, Exagen Diagnostics Inc., 3; **C. Ibarra**, Exagen, 3; **P. Chitkara**, Exagen Diagnostics, 6; **T. Dervieux**, Exagen, 3.

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Abstract Number: 773

Clinical Evaluation of Patients with Positive Antibodies to Extractable Nuclear Antigens but Negative ANA

Megan L. Krause[1], Michael Ettore[2], Melissa R. Snyder[3], Cynthia S. Crowson[4] and Kevin G. Moder[1], [1]Rheumatology, Mayo Clinic, Rochester, MN, [2]Laboratory Medicine and Pathology, Mayo Clinic, Rochester, MN, [3]Laboratory Medicine, Mayo Clinic, Rochester, MN, [4]Health Sciences Research, Mayo Clinic, Rochester, MN

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Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose: In the setting of a negative ANA, antibodies to extractable nuclear antigens (ENA) should be correspondingly negative, but alternative clinical scenarios occasionally arise. This study evaluated the frequency of ANA negative/ENA positive results and associated clinical information, including diagnoses.

Methods: All patients from a single institution who underwent ANA and ENA testing on a single blood draw in 2014 were evaluated for occurrence of a negative ANA with positive ENA. ANA testing was performed via enzyme-linked immunosorbent assay, and ENA via multiplex flow immunoassay, including SS-A, SS-B, Smith, RNP, Scl70, and Jo-1. This testing was part of routine clinical practice and performed at the

discretion of the clinical provider. The first 100 individuals in chronologic order of testing were further evaluated for clinical diagnoses by review of the complete medical record.

Results: A total of 4123 patients had ANA and ENA testing performed on the same draw. The majority were ANA negative (3267, 79%). Two hundred-eighty (6.8%) had at least one positive ENA result paired with a negative ANA. Of these, the vast majority (270, 96%) had only a single positive ENA result. The most common positive result was RNP (54%) followed by SS-A (19%), SS-B (16%), and Scl70 (14%). Smith (1%) and Jo-1 (0%) were exceedingly rare. Ten patients had double positive results, with the most common combination of RNP/Scl70 in 4.

Among the first 100 patients, 61 were female. The mean (standard deviation) age at testing was 56.5 (16.0) years. Ninety-nine had a single positive result; 1 patient had a double positive of RNP and Scl70. The most common positive antibody was RNP (56%) followed by SS-A (18%), Scl70 (15%), and SS-B (12%). No patients had positive Smith or Jo-1 antibodies. Neurology was the most common specialty to order the test (28%) followed by Rheumatology (27%), Pulmonary (15%), and Primary Care (13%) with Dermatology and Internal Medicine subspecialities accounting for the remaining.

Only 1 patient had a history of lupus with diagnosis occurring 20 years earlier and no current evidence of active disease. One patient was diagnosed with drug induced lupus in the setting of TNF inhibitor use for inflammatory bowel disease. One additional patient had lupus panniculitis. Six patients were felt to have Sjögren's syndrome while another 7 were diagnosed with undifferentiated connective tissue disease. An additional 6 patients had what was felt to represent "possible" connective tissue disease. Five patients had a diagnosis of rheumatoid arthritis or seronegative inflammatory arthritis. Another patient was diagnosed with large/medium vessel vasculitis. Ten patients had thyroid disease. Four patients had diagnosis of new malignancy or recurrence. Twenty individuals had peripheral neuropathy or dysesthesias. An additional 11 patients had interstitial lung disease as a part of their presentation.

Conclusion: ANA negative/ENA positive results, while rare, do occur. It is quite uncommon to have a diagnosis of lupus but does not exclude the possibility of connective tissue disease. This emphasizes the importance of a corresponding clinical history and exam to interpret serologies.

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Abstract Number: 774

Anti-Nuclear Antibodies Have High Sensitivity for Systemic Lupus Erythematosus: Results of a Systematic Literature Review and Meta-Regression of Diagnostic Data

Nicolai Leuchten[1], Ralph Brinks[2], Annika Hoyer[3], Monika Schoels[4], Martin Aringer[1], Sindhu R. Johnson[5], David I. Daikh[6], Thomas Dorner[7], George Bertsias[8] and on behalf of the SLE Classification Criteria Steering Committee, [1]Medicine III, University Medical Center and Faculty of Medicine at the TU Dresden, Dresden, Germany, [2]Hiller Center for Research in Rheumatology, Duesseldorf, Germany, [3]Institute for Biometry and Epidemiology, German Diabetes Center, Duesseldorf, Germany, [4]2nd Department of Medicine, Hietzing Hospital, Vienna, Austria, [5]Dept of Rheumatology, Toronto Western and Mt. Sinai Hospitals, University of Toronto, Toronto, ON, Canada, [6]Rheumatology, UCSF/VA Medical Center, San Francisco, CA, [7]Charité University Medicine Berlin, Berlin, Germany, [8]Rheumatology, Clinical Immunology, and Allergy, University of Crete, Heraklion, Greece

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Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose: EULAR and ACR have jointly funded a project to improve existing SLE classification criteria, aiming at earlier and more accurate classification of the disease. This abstract reports on an early phase of that project.

ANA constitute the immunological hallmark of SLE, and ANA testing is widely used for SLE diagnosis based on its reportedly high sensitivity. Although indirect immunofluorescence on Hep-2 cells (IIF-Hep2) is considered the gold standard of ANA testing (1), the performance of different ANA titers and the possibility of including positive ANA as an entry criterion for the classification of SLE have not been systematically evaluated. We therefore reviewed the literature on the performance of IIF-Hep2 ANA testing for the classification/diagnosis of SLE.

Methods: A systematic literature search was conducted in MEDLINE, EMBASE and Cochrane trial database for articles published between January 1990 and March 2014. The research question was structured according to PICO (Population, Intervention, Comparator, Outcome) format rules, and PRISMA recommendations were followed where appropriate. Meta-regression analysis for diagnostic tests was performed using the ANA titer as independent variable and sensitivity and specificity as dependent variables.

Results: A total of 3919 publications were screened in abstract and title and 623 articles were evaluated in full-text. Of these, 61 matched the eligibility criteria and were included in the analysis. The included studies comprised 10,309 SLE patients in total, of whom 9,797 (95.0%) were reported to be ANA positive at various titers. For ANA at titers of 1:40, 1:80 and 1:160, meta-regression gave sensitivity values of 98.6% (95% confidence interval [CI] 97.7-99.1%), 97.9% (CI 96.9-98.6%) and 95.9% (CI 93.9–97.3%), respectively. The corresponding specificities were 72.5% (CI 63.8-79.7%), 79.6% (CI 72.4-85.3%) and 89.6% (CI 84.8-93.0%), respectively.

Conclusion: The results of this systematic literature search and meta-regression confirm the high sensitivity of a positive ANA test for SLE. However, a small subgroup of true ANA negative SLE patients suggests that positive ANA should not be an absolute entry criterion for classifying SLE, but that it might function well in a combined entry criterion, such as positive ANA and/or low complements.

Reference: (1)Agmon-Levin et al, Ann Rheum Dis 2014; 73: 17ff

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Disclosure: N. Leuchten, None; **R. Brinks**, None; **A. Hoyer**, None; **M. Schoels**, None; **M. Aringer**, None; **S. R. Johnson**, None; **D. I. Daikh**, None; **T. Dorner**, None; **G. Bertsias**, None.

Abstract Number: 775

Identification of Candidate Items for Revised Classification Criteria for Systemic Lupus Erythematosus

Gabriela Schmajuk[1], Bimba F. Hoyer[2], Martin Aringer[3], Sindhu R. Johnson[4], Thomas Dorner[5], **David I. Daikh**[6] and SLE Classification Criteria Steering Committee, [1]San Francisco VA Medical Center, University of California, San Francisco, San Francisco, CA, [2]Charité University Medicine, Department of Medicine/Rheumatology and Clinical Immunology and German Rheumatism Research Centre Berlin (DRFZ), Berlin, Germany, [3]Rheumatology, Medicine III, University Clinical Center, Technical University Dresden, Dresden, Germany, [4]Dept of Rheumatology, Toronto Western and Mt. Sinai Hospitals, University of Toronto, Toronto, ON, Canada, [5]Charité – Universitätsmedizin, Berlin, Germany, [6]Rheumatology, UCSF/VA Medical Center, San Francisco, CA

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Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose:

EULAR and ACR have jointly funded a project to improve existing classification criteria for SLE; this abstract reports on the early phase of this project. Classification criteria are being developed using multicriteria decision analysis methods. The goal of the initial phase of this project was to generate a broad set of items potentially useful for the classification of SLE and select a list of candidate items for use in forced-choice decision analysis. The aims were to include items that encompass a broad spectrum of SLE, including patients whose disease is in the early stage as well as those in the late stage, and that are in accordance with criteria used for diagnosis of SLE in clinical practice.

Methods:

Items of potential utility for SLE classification criteria were identified by a large international group of lupus clinicians in independent exercises via response to online surveys. In the first survey, respondents were asked to evaluate existing ACR and SLICC classification items and invited to propose additional, nontraditional clinical items. Submitted novel candidate items were summarized, de-duplicated, and the number of total items reduced via a Delphi process.

Results:

135 individuals were invited to participate in each survey. In the first survey, 120 (89% response rate) proposed a total of 196 unique novel items for consideration. Combining items with significant overlap resulted in 159 items, including six that each contained one or more closely related modifiers. Nine items that are difficult to routinely assess in current clinical practice (eg, “elevated MCP1”) were removed from consideration. The resulting 150 items were evaluated in a second online survey. Items achieving a threshold significance score were retained for inclusion in SLE case scenarios to be evaluated by lupus clinicians in the next phase of the project.

Conclusion:

This approach to the development of SLE classification criteria represents application of state-of-the-art methods for criteria development. The

resulting core item list will be assessed for discriminative characteristics in specific clinical scenarios to create a weighted item list. The performance (sensitivity, specificity) of the weighted item list will then be compared to existing classification criteria using data collected from SLE patients and controls.

Table. Sample submitted, novel items for evaluation in new SLE classification criteria

General manifestations	Laboratory findings	Other organ manifestations
Constitutional symptoms (fevers, fatigue, weight loss)	Anti C1q antibody	Chillblain lupus
Family history of Autoimmune disease (first and second degree relatives)	Anti chromatin antibody	Cytoid bodies (retinal)
History of miscarriages	Anti thyroid antibodies	Diffuse alveolar hemorrhage
Persistent adenopathy	Complement fragments	Early cardiovascular disease
	von Willebrand factor antigen	Interstitial lung disease
		Libman-Sacks endocarditis
		Lupus band test
		Acute confusional state
		Nasal ulcers
		Pre-eclampsia
		Persistent proteinuria (>0.5g/day)
		Pulmonary arterial hypertension

Disclosure: G. Schmajuk, None; **B. F. Hoyer**, None; **M. Aringer**, None; **S. R. Johnson**, None; **T. Dorner**, None; **D. I. Daikh**, None.

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Abstract Number: 776

Sensitivity of Antinuclear Antibody By Immunofluorescence Testing for Detection of Anti-Ro/SSA Antibodies

Ivan Alcantara-Arreola[1], Nina Tello-Winniczuk[2] and **Alejandro Diaz-Borjon**[3], [1]Hospital Angeles Lomas, Huixquilucan, Mexico, [2]Division of Internal Medicine / Rheumatology, Hospital Angeles Lomas, Huixquilucan, Mexico, [3]Med/Div of Rheumatology, Hospital Angeles Lomas, Huixquilucan, Mexico

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Session Title: Systemic Lupus Erythematosus - Clinical Aspects and Treatment Poster Session I

Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose:

A positive ANA test is a diagnostic criterion for several rheumatic diseases, although it may appear in other autoimmune disorders and healthy individuals. An ideal diagnostic test should be both specific and sensitive. Current recommendations from ACR suggest ANA done by IIF in Hep-2 cells as an initial test to investigate autoimmunity and anti-ENA are only recommended for patients who test positive for ANA. However, there is scarce evidence of the advantages of this practice versus focalized auto-antibody evaluation according to clinical suspicion. ANA negative lupus has been reported at 5%, these patients test positive for anti-Ro/SSA and/or anti-La/SSB.

We aimed to establish the sensitivity of ANA to detect anti-Ro/SSA antibodies since we consider this stepwise approach might lead to sub diagnosing patients.

Methods: We reviewed immunological studies sent to Quest Diagnostics between January 2010 up to December 2014. Inclusion criteria were patients who had both ANA and anti-Ro/SSA done simultaneously; we excluded patients in which any one of those were missing. We obtained the sensitivity of ANA for detection of anti-Ro/SSA.

Results:

In total 900 tests were reviewed. Both ANA by IIF and anti-Ro/SSA by ELISA were done in 499 patients of whom 71 patients (14.22%) had positive anti-SSA. Of these, 33 patients (46.47%) had positive ANA and 38 patients (53.53%) had negative ANA. Considering presence of ANA at any titer as positive, sensitivity of the test was 77.5%; considering ANA positive with a titer of at least 1:320 sensitivity decreased to 46.5%.

Conclusion: The ACR recommendations of evaluating for rheumatic disease with ANA exclusively are based on cost-efectiveness more than evidence. We found a sensitivity of 77.5% at best considering any titer as positive. According to our findings 22.5% to 53.5% of individuals with positive anti-Ro/SSA could go undetected. We find the ANA test to be a poor initial test to investigate for the presence of anti-Ro/SSA antibodies. Our most important limitation is our sample size, another one is that actual autoimmune disease could not be confirmed since we did not have access to clinical data; however our findings warrant further investigation. The ANA test done by Hep-2 has a lower sensitivity in detecting anti-Ro/SSA than that reported in the literature, making it a poor screening test in patients suspected to have rheumatic disease associated with anti-Ro/SSA antibodies. Changes in the proposed diagnostic algorithm may be at hand.

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Disclosure: I. Alcantara-Arreola, None; **N. Tello-Winniczuk**, None; **A. Diaz-Borjon**, UCB, 8,Sanofi-Aventis Pharmaceutical, 6,Janssen Pharmaceutica Product, L.P., 6.

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Abstract Number: 777

SLE-KeyTM Rule-out Test to Assess Lupus in Anti-Nuclear Antibody Positive Subjects Using the Immunarray iCHIP®

D. Scott Batty[1], I.R. Cohen[2], Chaim Putterman[3], Nicole Jordan[4], Keren Jakobi[5], Rachel Sorek[5], Yakov Blumenstein[5], Pennina Safer[5] and David Pisetsky[6], [1]ImmunArray Inc., Richmond, VA, [2]Weizmann Institute of Science, Rehovot, Israel, [3]Division of Rheumatology, Albert Einstein College of Medicine, Bronx, NY, [4]Montefiore Medical Center, New York, NY, [5]ImmunArray LTD, Rehovot, Israel, [6]Duke University Medical Center and Durham VAMC, Durham, NC

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Background/Purpose:

SLE is associated with a broad spectrum of autoantibodies, but currently there is no single serologic test to diagnose SLE definitively. Diagnosis is thus based on multiple ACR or SLICC criteria, including autoantibodies taken together in routine clinical settings. Anti-nuclear antibody (ANA) testing is a standard procedure in evaluating suspected lupus patients. While the test is highly sensitive [97 percent of patients with lupus will have a positive ANA test(1) (ANA+)], the test has poor specificity since approximately 13.8 % of healthy individuals test positive at a 1:80 dilution(2). As a result, ANA+ results can be misleading, leading to patient concern, unnecessary testing and even inappropriate therapy (3). A test to rule out the diagnosis of lupus in ANA+ patients without disease would be a valuable adjunct to current serological testing and important application of the SLE-*Key*TM Rule Out technology.

Methods:

We previously developed the SLE-*key*TM Rule Out test to exclude the diagnosis of SLE based on the iCHIP®(4) by profiling 250 SLE patients compared to 250 healthy controls and developing classifier algorithms. In the current study, serum samples from 136 self-declared healthy

controls were available for comparative ANA testing and were sent to an external lab for fluorescence ANA (fANA) analysis.

Results:

Four different classification methods (support vector machine, Logistic regression, linear discriminant analysis and Quadratic discriminant analysis) were used to develop and validate classifier algorithms to differentiate SLE patients from the ANA positive and negative healthy subjects. Of the 136 healthy samples, 24 samples (17.6%) were found to be ANA+ at the dilution of 1:80 by fANA testing. The SLE-Key™ classification models excluded SLE in up to 80% of these ANA+ subjects, depending on the particular statistical model.

Conclusion:

SLE-*Key*™ classifiers can successfully rule out the diagnosis of SLE in up to 80% of ANA+ subjects depending on the analytic approach. These initial findings suggest that the iCHIP™ technology can be applied to develop more refined classifications to rule out SLE in the ANA+ population.

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Abstract Number: 778

Associations Between Autoantibodies and Clinical Manifestations in Systemic Lupus Erythematosus: Data from a Multiethnic Latin American Cohort

Manuel Ugarte-Gil[1,2], Daniel Wojdyla[3], Ignacio Garcia-Valladares[4], Rocio V. Gamboa-Cardenas[1], Yelitza Gonzalez-Bello[5,6], Guillermo J. Pons-Estel[7], Cesar A. Pastor-Asurza[1,8], Ignacio Garcia-De La Torre[9,10], Graciela S. Alarcon[11], Bernado Pons-Estel[12] and GLADEL (Grupo Latinoamericano de Estudio de Lupus), [1]Rheumatology, Hospital Guillermo Almenara Irigoyen. EsSalud, Lima, Peru, [2]Universidad Cientifica del Sur, Lima, Peru, [3]Universidad Nacional de Rosario, Argentina, Rosario, Argentina, [4]Centro de Estudios de Investigación Básica y Clínica, SC., Guadalajara, Jalisco, Mexico, [5]Immunology and Rheumatology, Hospital General de Occidente, Secretaria de Salud Jalisco, Guadalajara, Jalisco, Mexico, [6]Immunology and Rheumatlogy, Universidad de Guadalajara, Zapopan, Jalisco, Mexico, [7]Department of Autoimmune Diseases, Hospital Clinic, Barcelona, Spain, [8]Universidad Nacional Mayor de San Marcos, Lima, Peru, [9]Immunology and Rheumatology, Hospital General de Occidente, Secretaria de Salud Jalisco, Zapopan, Jalisco, Mexico, [10]Universidad de Guadalajara, Guadalajara, Jalisco, Mexico, [11]Medicine, University of Alabama at Birmingham, Birmingham, AL, [12]Hospital Provincial de Rosario, Rosario, Argentina

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Background/Purpose: Analyses of the association between autoantibodies and SLE clinical manifestations using cluster analyses assume that centroid and within-cluster residuals are similar inside the cluster and different between clusters. However, these antibodies and their combinations within a cluster may have different clinical impact; moreover, the residuals of two clusters may not be different enough leading to incorrect conclusions. We have therefore evaluated these associations individually and in combinations overcoming the problems noted above.

Methods: Patients with available data for anti-dsDNA, anti-histone, anti-Sm, anti-RNP, anti-Ro and anti-La from a multinational SLE cohort were included. Autoantibodies were evaluated individually and in pre-specified combinations (anti-dsDNA + anti-histone; anti-Sm + anti-RNP; anti-Ro + anti-La). About 100 clinical manifestations were systematically recorded using a common protocol. Logistic regressions were used to examine the association between autoantibodies and clinical manifestations and components of the last SLICC/ACR Damage Index (SDI) and a Poisson regression with the last total SDI.

Results: Three hundred and thirty-eight patients representative of the entire cohort (n=1480) other than for their ethnic distribution (50.6% vs. 38.1%, Caucasians; 37.9% vs. 45.3%, Mestizo and 11.5% vs. 16.6%, others p=0.001) were studied. Of them, 329 (97.3%) fulfilled ≥4ACR criteria. Mean age at diagnosis was 28.5 (SD: 11.5) years, 308 (91.1%) were female; follow-up was 4.6 (1.7) years. Baseline SLEDAI was 10.5 (7.6) and baseline SDI was 1.0 (1.3). The associations between clinical manifestations and autoantibodies are depicted in Tables 1 and 2. The associations between autoantibodies and the last SDI and its components are depicted in Table 3.

Table 1: Associations between autoantibodies and clinical manifestations in SLE patients. (Individual associations)

	OR (CI95%)	P
Anti-dsDNA		
Proteinuria	2.10 (1.32-3.34)	0.002
Anti-histone		
Photosensitivity	0.57 (0.36-0.92)	0.020
Discoid lupus	0.40 (0.18-0.90)	0.027
Renal failure	4.15 (1.21-14.23)	0.024
Anti-Sm		
Motor or sensitive disorders	0.34 (0.13-0.90)	0.030
Cerebrovascular disorders	0.12 (0.02-0.67)	0.016
Hemolytic anemia	0.41 (0.19-0.91)	0.028
Leukopenia	2.22 (1.30-3.81)	0.004
Anti-RNP		
Raynaud phenomenon	1.98 (1.17-3.35)	0.011
Lung serositis	0.48 (0.27-0.84)	0.010
Anti-Ro		
Motor or sensitive disorders	2.43 (1.08-5.48)	0.032
Xerophthalmia	2.91 (1.06-7.97)	0.038
Anti-La		
Discoid lupus	3.65 (1.32-10.05)	0.012
Valve involvement	8.09 (1.82-35.90)	0.006

OR: Odds ratio. 95%CI: 95% confidence interval. Only significant interactions are shown.

Table 2: Associations between autoantibodies and clinical manifestations in SLE patients (Interactions).

	Anti-dsDNA+		Anti-histone+		p value for the interaction
	Anti-histone- OR (95%CI); p value	Anti-histone+ OR (95%CI); p value	Anti-dsDNA- OR (95%CI); p value	Anti-dsDNA+ OR (95%CI); p value	
Lymphopenia	0.83 (0.42-1.67); 0.599	**3.05 (1.42-6.87); 0.005**	0.97 (0.52-1.82); 0.914	**3.55 (1.55-8.36); 0.003**	0.015
Any hematologic involvement	0.66 (0.31-1.46); 0.292	**2.70 (1.10-7.10); 0.035**	0.86 (0.42-1.80); 0.677	**(3.51-1.36-9.54); 0.011**	0.022

OR: Odds ratio. 95%CI: 95% confidence interval.

Table 3: Associations between autoantibodies and last SDI in SLE patients.

		Total SDI	Neuropsychiatric component	Cardiovascular component	Peripheral vascular component
		RoM (95%CI); p value	OR (95%CI); p value	OR(95%CI); p value	OR(95%CI); p value
Interaction					
Anti-dsDNA+	Anti-histone -	**0.65 (0.48-0.88); 0.005**			
	Anti-histone +	1.09 (0.87-1.37); 0.449			
Anti-histone+	Anti-dsDNA-	1.12 (0.90-1.40); 0.316			
	Anti-dsDNA+	**1.87 (1.38-2.55); <0.001**			
p-value for the interaction		0.006			
Anti-Sm+	Anti-RNP-	**0.73 (0.56-0.96); 0.021**	**0.28 (0.09-0.85); 0.025**		
	Anti-RNP+	1.22 (0.86-1.73); 0.263	1.87 (0.53-6.64); 0.332		
Anti-RNP+	Anti-Sm-	0.71 (0.50-1.01); 0.057	0.41 (0.12-1.50); 0.179		
	Anti-Sm+	1.19 (0.92-1.53); 0.184	2.81 (0.94-8.42); 0.066		
p-value for the interaction		0.017	0.027		
Individual autoantibodies					
Anti-Sm				**0.43 (0.19-0.96); 0.040**	
Anti-La		**1.52 (1.23-1.88); <0.001**			**3.18 (1.01-9.97); 0.047**

SDI: SLICC/ACR damage index. RoM: Rate of Means. OR: Odds ratio. 95%CI: 95% confidence interval.

Conclusion: Autoantibodies profiles are associated with different manifestations and damage among SLE patients. Anti-histone positivity, among anti-dsDNA positive patients and anti-La positivity were associated with damage accrual, but anti-Sm positivity among anti-RNP negative patients was negatively associated with damage accrual. The interaction between autoantibodies should be evaluated in larger populations in order to evaluate less frequent manifestations.

Disclosure: M. Ugarte-Gil, None; **D. Wojdyla**, None; **I. Garcia-Valladares**, None; **R. V. Gamboa-Cardenas**, None; **Y. Gonzalez-Bello**, None; **G. J. Pons-Estel**, None; **C. A. Pastor-Asurza**, None; **I. Garcia-De La Torre**, None; **G. S. Alarcon**, None; **B. Pons-Estel**, None.

Abstract Number: 779

Mapping Perceptions of Medication Decision Making Facilitators: The Importance of Patient Context

Haiyan Qu[1], Jinoos Yazdany[2], W. Winn Chatham[3], Ricahrd Shewchuk[4] and **Jasvinder A. Singh**[1], [1]University of Alabama at Birmingham, Birmingham, AL, [2]University of California, San Francisco, San Francisco, CA, [3]Medicine/Clinical Immunology and Rheumatology, University of Alabama at Birmingham, Birmingham, AL, [4]University fo Alabama at Birmingham, Birmingham, AL

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Background/Purpose: Our objective was to derive a cognitive map of how stakeholders perceive patient-identified facilitators to establish a theoretical framework for the purpose of developing future interventions to improve medication decision-making process for lupus patients.

Methods:

We first conducted 8 Nominal group technique (NGT) meetings and a card-sort task were used to obtain formative data from 52 lupus nephritis patients at two teaching hospitals. Patients prioritized 98 facilitators as having relatively more influence in their own decision-making processes. Next, 24 stakeholders independently grouped those 98 facilitators based on similarities. The data were analyzed using multidimensional scaling and hierarchical cluster analysis. The stakeholders also used a 5-point Likert scale to indicate their level of agreement or disagreement, with the ability of each facilitator that can be used to improve patient decision-making processes.

Results: The stakeholders included 11 physicians, 3 patients, 2 patient representatives, and 8 medical professionals. A 2-dimensional 10-cluster cognitive map provided an organizational

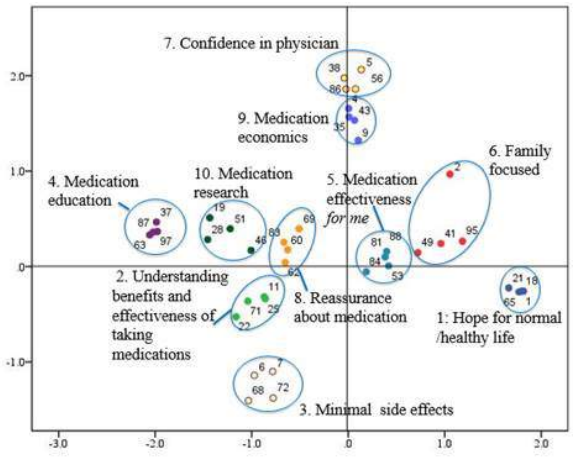
framework for understanding those facilitators: 1) Hope for normal/healthy life, 2) Understanding benefits and effectiveness of taking medications, 3) Minimal side effects, 4) Medication education, 5) Medication effectiveness for me, 6) Family focused, 7) Confidence in physician, 8) Reassurance about medication, 9) Medication economics, and 10) Medication research. We mapped the facilitators along 2 dimensions: the x-axis represented patients' internal needs about lupus treatment with medication education on the left and family focused on the right. The y-axis represented external issues with confidence in physician at the top, and minimal side effects at the bottom. The top 4 facilitators from each cluster are depicted in the Figure 1 and mean ratings are listed in the Table 1. Based on their ratings, stakeholders highly agreed that the hope for normal/healthy life cluster (mean ± SD, 4.67±0.12) is most important. They indicated that the Medication research cluster (3.41 ± 0.56) is least important.

Conclusion: The identified clusters generated by stakeholder agreement using cognitive mapping provide a basis for a theoretical framework, such as the theory of reasoned action, from which to develop future tailored interventions to improve patient decision-making processes.

Table 1. Clusters of Facilitators and Attributes in Each Cluster

Card#	Cards	Mean	SD
	Cluster 1: Hope for normal/healthy life	**4.67**	**.12**
1	Wanting to live as normal life as possible	4.78	.42
18	To be able to live a normal life without so many complications	4.70	.47
65	Wanting to be healthier to work/to live	4.68	.48
21	Desire to stay active/healthy	4.50	.67
	Cluster 2: Understanding benefits and effectiveness of taking medications	**4.46**	**.12**
11	Knowing how effective the medication is	4.57	.51
25	Knowing what the benefits are for me if I take the medication	4.52	.51
71	Understanding how important the medication is for me	4.30	.56
22	Getting an explanation of side effects and the benefits the medicine has for my kidney	4.43	.59
	Cluster 3: Minimal side effects	**4.26**	**.20**
68	If the medicine had the least amount of side effects	4.00	.82
72	If it does not have extreme side effects	4.35	.57
7	Knowing that it won't aggrevate other conditions (e.g., having side effects on lung)	4.22	.67
6	Knowing about the side effects	4.48	.51
	Cluster 4: Medication education	**3.65**	**.37**
87	Hearing about studies that have been done and if they were successful	3.96	.98
97	Seeing how much research is available about the medication	3.87	.97
63	Would like more research on the failure of medication	3.14	.94
37	Having proof of concept (evidence/statistics--that the medication works)	3.65	.83
	Cluster 5: Medication effectiveness *for me*	**3.65**	**.39**
81	You've tried everything else and nothing has worked	4.00	.74
88	Knowing that the drug won't affect my ability to have children	3.43	1.38
53	Having a positive outlook on my diagnosis and treatment	3.96	1.07
84	The fewer the medicine, the better	3.22	1.20
	Cluster 6: Family focused	**3.64**	**.46**
41	To be able to have a healthy pregnancy in the future	3.27	1.35
95	Being able to do the stuff that my spouse expects me to do	3.57	1.34
49	Not having to have as many doctor visits	3.41	1.05
2	My kids are the reason and I want be there for them (if I don't take the medication, I am a mess)	4.30	.70
	Cluster 7: Confidence in physician	**3.59**	**.39**
56	If the doctor tell you what he wants and expects to see happen with you if you take the medication	3.57	.73
86	It would be nice to know if the doctors are not being paid/sponsored for prescribing the medication	3.65	1.23
38	Doctor's knowledge of the drugs prescribed	4.04	.93
5	Because the doctors know more than I do	3.09	1.12
	Cluster 8: Reassurance about medication	**3.48**	**.12**
60	Hearing about people who have been treated with this medication and that it worked	3.65	1.15
83	Getting education about how the medicine would affect my pregnancy	3.43	1.38
62	If I will be able to stop taking medicine after a period of time	3.36	.90
69	Understanding how the medicine will affect my ability to have children in the future	3.45	1.44
	Cluster 9: Medication economics	**3.47**	**.12**
35	Having resources to pay for the drugs	3.57	1.08
43	Being able to afford it	3.50	1.19
4	Low cost	3.52	1.31
9	If it is affordable	3.30	1.33
	Cluster 10: Medication research	**3.41**	**.56**
19	Knowing if it is approved by FDA or is it just an experimental drug	3.04	1.11
28	Having proof that the medication works	4.22	.80
51	Researching on my own	3.39	.58
46	Knowing how long the medicine has to be taken--the shorter the better	3.00	.93
Total		**3.83**	**.56**

Figure 1. Clusters of Facilitators and Attributes in Each Cluster



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Abstract Number: 780

Long-Term Prognosis and Factors Associated with Damage Accrual in Japanese Patients with Systemic Lupus Erythematosus

Yoko Wada[1], Hisashi Hasegawa[2], Takeshi Kuroda[3], Masaaki Nakano[4] and Ichiei Narita[1], [1]Department of Clinical Nephrology and Rheumatology, Niigata University Graduate School of Medical and Dental Sciences, Niigata, Japan, [2]Division of Clinical Nephrology and Rheumatology, Niigata City General Hospital, Niigata, Japan, [3]Health Administration Center, Niigata University, Niigata, Japan, [4]Department of Medical Technology, School of Health Sciences, Faculty of Medicine, Niigata University, Niigata, Japan

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Background/Purpose: Systemic lupus erythematosus (SLE) is a multisystemic autoimmune disease characterized by fluctuating disease activity over periods of years. The estimated 5-year survival rate of patients with SLE has improved greatly from 50% to over 90% over the last several decades, and the 10-year survival rate has also increased to nearly 90%. In patients who survive longer than 10 years, the major cause of death has become not simply active SLE itself, and recently the management of SLE has been aimed at not only remission induction and control of disease activity, but also long-term prevention of organ damage resulting from treatment and complications. In SLE patients, organ damage has been principally assessed using the Systemic Lupus International Collaborating Clinics (SLICC)/American College of Rheumatology (ACR) Damage Index (SDI), which has been extensively validated. In this study, we examined the long-term outcome, causes of death, and factors associated with damage accrual using the SDI in a single-center cohort of SLE patients.

Methods: We examined a cohort of 557 patients who had been referred to Niigata University Hospital and diagnosed as having SLE between 1961 and 2013. The patients' data at the latest visit were collected from their clinical records on April 2014, and causes of death were also defined on the basis of those data. Survival from the time of diagnosis was calculated by the Kaplan-Meier method. The SDI was calculated, and analyzed using Spearman's correlation coefficient and stepwise multiple regression analysis to reveal the factors associated with any organ damage.

Results: Data from 458 of the patients were successfully obtained. The overall 5-year survival rate was 89.9%, the 10-year survival rate was 86.0%, the 20-year survival rate was 78.6%, and the 30-year survival rate was 76.4%. The patients diagnosed after 2000 had a significantly high 5-year survival rate of 97.1%. Among 115 patients who died during the observation period, the main causes of death were infections (22.6%),

vascular disease (22.6%), and SLE-related complications (21.7%). Of the 343 patients who were alive at the time of this study, common complications were hypertension (40.8%), dyslipidemia (26.8%), diabetes mellitus (15.7%), and osteonecrosis (11.1%). The mean SDI was 0.80±1.07 and was positively correlated with age (r=0.2963, p<0.001), disease duration (r=0.1459, p<0.001), and hypertension (r=0.2299, p<0.001), whereas it was negatively correlated with administration of bisphosphonate (r=-0.115, p=0.049). Stepwise multiple regression analysis selected age (standardized beta=0.2762, p<0.001), hypertension (standardized beta=0.2267, p<0.001), and antiphospholipid antibody syndrome (standardized beta=0.1533, p=0.005) as positive independent variables, whereas administration of bisphosphonate (standardized beta=-0.1295, p=0.016) was selected as a negative independent variable.

Conclusion: These results suggest the significance of disease control as well as management of chronic complications such as hypertension and osteoporosis to prevent organ damage in SLE patients receiving long-term treatment.

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Anti-Nucleosome Antibodies Versus Anti-DNA Antibodies in the Diagnosis and Monitoring of Activity of Systemic Lupus Erytematosus

Helena Borrell Paños[1], Javier Narváez[2], Jordi Bas[3], Eulàlia Armengol[1], Maria Aparicio[1], Maria Pascual[1], Mercè López de Recalde[1] and Joan Miquel Nolla[1], [1]Department of Rheumatology, Hospital Universitario de Bellvitge, Barcelona, Spain, [2]Rheumatology, Hospital Universitario de Bellvitge, Barcelona, Spain, [3]Immunology Department. Hospital Universitari de Bellvitge, Barcelona, Spain
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Background/Purpose:

Recently, the study of anti-nucleosome antibodies (ANUCs) has been suggested that they may be useful in the diagnosis of systemic lupus erythematosus (SLE) and in the monitoring of disease activity.

Our objective was to compare the diagnostic performance of ANUCs versus anti-nDNA in the diagnosis of SLE and analyze their correlation with markers of disease activity.

Methods:

ANUCs and anti-nDNA were prospectively determined in 122 patients with SLE (SLICC 2012 criteria) and 136 patients without the disease (control population). ANUC determination was determined using a dot-blot + ELISA and anti-nDNA using FEIA + IFI. For each of the antibodies, sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio (LR+), negative likelihood ratio (LR-) and diagnostic accuracy were calculated for the SLE diagnosis. Diagnostic accuracy was calculated according to the following formula: (true positives + true negatives) / (true positives + true negatives + false positives + false negatives).

The correlation of the ANUC titer with different markers of SLE activity (SLEDAI 2K, anti-nDNA antibody titer, lymphocyte count, C3 and C4 complement fractions, ESR and C reactive protein) was analyzed using a Pearson product-moment correlation coefficient.

Results:

In the 122 patients with SLE, 80 (66%) were ANUC positive and 83 (68%) were anti-nDNA positive: 62 (51%) patients were ANUC and anti-nDNA positive, 18 (15%) were ANUC positive/anti-nDNA negative, 21 (17%) were ANUC negative/anti-nDNA positive, and 21 (17%) were ANUC and anti-nDNA negative.

Eleven (8%) patients in the control population were anti-nDNA positive, and 39 (29%) control patients were ANUC positive. Patients from the control population with positive ANUC had psoriasis (many of them were treated with anti-TNF therapy), infections (pneumonia, HCV, or HIV infection), or an autoimmune disease (pemphigus, Crohn's disease, glomerulonephritis associated with ANCA, primary anti-phospholipid syndrome, rheumatoid arthritis, or autoimmune hepatitis).

The following table shows the diagnostic value of both antibodies:

	ANUC	Anti-DNAn
Sensitivity	66%	68%
Specificity	71%	91%
PPV	67%	88%
NPV	70%	76%
LH +	2.30	8.4
LH -	0.47	0.34
Accuracy	0.686	0.806

The ANUC titer was significantly correlated with the SLEDAI-2K score (r = 0.425, p = 0.031), anti-nDNA titer (r = 0.603, p = 0.001), the number of lymphocytes (r = -0.410; p = 0.038), and ESR (r = 0.414, p = 0.036). No statistically significant correlation was observed with levels of complement or CRP.

Conclusion:

ANUCs exhibit similar sensitivity as anti-nDNA for SLE diagnosis but a lower specificity. Therefore, the presence of ANUCs does not appear to increase diagnostic accuracy.

A simultaneous determination of ANUCs and nDNA increases the diagnostic yield, whereas ANUCs are useful in diagnosing disease in anti-nDNA negative patients.

The ANUC titer was positively correlated with disease activity and can therefore be considered a complementary marker in monitoring these patients

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Disclosure: H. Borrell Paños, None; **J. Narváez**, None; **J. Bas**, None; **E. Armengol**, None; **M. Aparicio**, None; **M. Pascual**, None; **M. López de Recalde**, None; **J. M. Nolla**, None.

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Abstract Number: 782

A Proposal for Assessing Systemic Lupus Erythematosus Activity By a Multimodal Instrument That Includes Clinical Variables, Physician Assessment and Modification of Treatment

Francisco Espinoza Sr.[1] and K Kalunian[2], [1]Rheumatology Department, Division of Internal Medicine, School of Medicine, University of Los Andes, Santiago, Chile, [2]UCSD School of Medicine, La Jolla, CA
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Background/Purpose:

Assessment of systemic lupus erythematosus (SLE) is complex due to its heterogeneous manifestations and its fluctuant clinical course. Current instruments stressed one specific aspect of disease activity such as improvement, flares or ongoing activity, but clinicians should evaluate all these aspects with one-single instrument. We designed a new instrument based on classic lupus descriptors but we added parameters such as treatment modifications and changes in physician global assessment (PGA). Here we present our preliminary results.

Methods:

A cross-sectional study was performed. All the patients satisfied the 2012 SLICC classification criteria for SLE. The instrument was based on thirty descriptors grouped in one of the following categories: clinical activity (CA) (visceral, mucocutaneous and articular involvement and constitutional symptoms), physician global assessment (PGA) (0 to 3), biologic activity (BA) (SLE autoantibodies and erythrocyte sedimentation rate (ESR)) and treatment (T) (corticosteroids, DMARDs and biologic treatment). A positive score (+1 to +4) was assigned according to descriptor severity. A negative score (-1 to -3) was assigned whether both a reduction in PGA or in treatment was verified in the last month. A comparison with both SLEDAI score and SELENA-SLEDAI flare index (SFI) was performed by T test and linear regression analyses.

Results:

Fifty-two SLE patients were included, 94.5% were females. Mean age was 45.1 (± 13.9) years. Lupus nephritis was recorded in 13.4% of patients. Mean SLEDAI was 4.85 (± 2.4) and the mean value of the new instrument was 5.12 (± 3.42). A good correlation with SLEDAI was noted (r= 0.8, CI95% 0.63-0.89, p< 0.001). Thirteen patients (25%) experienced at least 1 episode of severe flare according to SFI. In those patients where a severe flare was retained by an increase of SLEDAI of more of 12 points, an increase of 15.4 (± 3.6) points was noted in the new instrument. Remarkably, in the group of patients where a severe flare was retained by steroid / immunossuppresor introduction or hospitalization, SLEDAI increased only by 5.4 (± 2.2). By contrast the new instrument showed a mean increase of 16 (±1.4) points.

Conclusion:

These preliminary data show that this new instrument has a good correlation with SLEDAI score and it is sensitive to recognize flare episodes that are not retained by an increase in SLEDAI. The performance of this instrument must be tested in a longitudinal cohort. Our future goal is to assess SLE recognizing persistent activity, flares and improvements through a one-single instrument.

Disclosure: F. Espinoza Sr., None; **K. Kalunian**, MedImmune, 2.

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Abstract Number: 783

Osteonecrosis in Systemic Lupus Erythematosus: Predictive Factors

Nimrit Dhillon[1], Dafna Gladman[1], Jiandong Su[1] and Murray Urowitz[1,2], [1]Rheumatology, University of Toronto, Toronto Western Hospital, Toronto, ON, Canada, [2]Rheumatology, U of Toronto, Toronto Western Hospital, Toronto, ON, Canada

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Background/Purpose: We recently reported the frequency of symptomatic osteonecrosis (ON) among systemic lupus erythematosus (SLE) patients of the lupus cohort to be 13.6%

The aim of this study is to identify predictive factors for the development of osteonecrosis in patients with SLE.

Methods:

Patients who developed ON after clinic entry were identified from the Lupus Clinic Database. ON was defined as patients with clinical symptoms and osteonecrosis confirmed by imaging (radiographs, bone scan, CT, MRI). Cases were matched to controls (SLE patients without ON) by gender, year of entry to clinic, year of birth, and disease duration.

Univariate conditional logistic regressions were carried out on each potential predictor, and variables meeting the p-value < 0.2 or clinically regarded as important risk factors were selected for multivariate regression analysis.

Results: 1781 patients with SLE were in the Lupus Clinic Database. Of these, 171 cases of symptomatic ON were identified and 162 cases were successfully matched to controls (Table 1).

Age at ON, black race, steroid-related SLICC damage, mean total cholesterol 3 years prior to ON or last visit, mean steroid dose, cumulative steroid dose, and mean duration of immunosuppressant and bisphosphonate use were included in the multivariate analysis. Mean steroid and cumulative months on bisphosphonate were independent predictors for ON adjusting for other covariates in the model, with odds ratio and 95% confidence intervals of 1.036 (1.012, 1.061) and 1.018 (1.000, 1.035) correspondingly. However, only small numbers of patients were on bisphosphonate therapy (cases = 28, controls = 16).

Table 1

	Cases (n=162)	Controls (n-162)
Female gender	148 (91.4%)	148 (91.4%)
Age at ON or last visit (years)*	36.98 ± 12.45	37.48 ± 12.34
Age at SLE diagnosis (years)*	27.77 ± 10.56	27.94 ± 9.74
Black Race	30 (18.5%)	16 (9.9%)
Disease duration at ON/last visit (years)*	9.35 ± 8.75	9.54 ± 9.05
AMS 3 years before ON/last visit*	6.17 ± 4.73	6.10 ± 5.94
AMS without dsDNA or complement 3 years before ON/last visit*	5.43 ± 4.47	5.36 ± 5.77
SLICC at ON/last visit*	1.29 ± 1.56	1.04 ± 1.63
SLICC steroid-related damage at ON/last visit*	1.07 ± 1.36	0.79 ± 1.31
Raynaud's ever before ON/last visit	83 (51.2%)	94 (58.0%)
Smoking ever at ON/last visit	49 (30.2%)	54 (33.3%)
CNS ever at ON/last visit	69 (42.6%)	61 (37.7%)
Vasculitis ever at ON/last visit	51 (31.5%)	45 (27.8%)
Arthritis ever at ON/last visit	46 (28.4%)	51 (31.5%)
Renal ever at ON/last visit	94 (58.0%)	100 (61.7%)
Total cholesterol 3 yrs before ON or last visit*	5.39 ± 1.22	5.08 ± 1.49
APLA positivity ever at ON/last visit	37 (22.8%)	41 (25.3%)
Cumulative steroids dose to ON/last visit (g)*	31.00 ± 30.11	23.74 ± 40.98
Average steroids dose to ON/last visit (mg)*	17.14 ± 11.15	11.81 ± 12.87
Antimalarial treatment before ON/last visit	103 (63.6%)	106 (65.4%)
Duration of immunosuppressive treatment before ON/last visit (months)*	22.88 ± 35.05	16.98 ± 39.06
Duration of bisphosphonate treatment before ON/ last visit (months)*	5.23 ± 20.98	2.85 ± 13.01

*Mean ± standard deviation

Conclusion: Osteonecrosis remains an important comorbidity among patients with SLE, and corticosteroid use remains a significant risk factor. Continued judicious use of corticosteroid therapy is needed in mitigating this event, and ongoing studies are needed to identify additional predictive factors.

Disclosure: N. Dhillon, None; **D. Gladman**, None; **J. Su**, None; **M. Urowitz**, None.

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Abstract Number: 784

Electronic Health Record (EHR) As a Powerful Tool to Establish Clinical Research Lupus Cohorts

Srilatha Kothandaraman[1], Frederick Ramsey[2], David Fleece[3], Aaron Sorenson[2], Lai Ping[4], Srikanth Mukkera[1], King Goh[1] and Roberto Caricchio[5], [1]Rheumatology, Temple University, Philadelphia, PA, [2]Clinical Sciences, Temple University, Philadelphia, PA, [3]Pediatrics, Temple University, Philadelphia, PA, [4]Temple University, Philadelphia, PA, [5]Medicine, Rheumatology, Temple University, Philadelphia, PA

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Background/Purpose:

Enhancing a typical EHR through implementation and utilization of research-validated instruments is termed Electronic Data Capture (EDC). EDC is found to be more efficient than standard paper-based data collection systems for accuracy, timeliness, speed and quality. We report our experience in establishing a validated lupus cohort via EDC for clinical, quality improvement and translational research and to determine predictors of damage index as the initial validation step

Methods:

Since January 2014 customized, lupus-specific documentation flow sheets such as the Systemic Lupus Erythematosus (SLE) disease activity index (SLEDAI) and Systemic Lupus International Collaborating Clinics (SLICC) damage index (SDI) were built and deployed within our Epic Care EHR for all patients with a 710.0, ICD-9 diagnosis of SLE when seen in the rheumatology clinic. Diagnosis was retrospectively validated by the SLICC classification criteria and patients met at least four. A retrospective-prospective cohort study design was implemented in which the SLE indices were linked to longitudinal EHR data collected every visit. The EHR data include demographics, vitals, comprehensive past history, medications, and labs. An example of data linking included the aligning of lab results, which shortly preceded or immediately followed clinic visits during which SLE indices scores were recorded. All statistical analyses were performed using SAS 9.4.

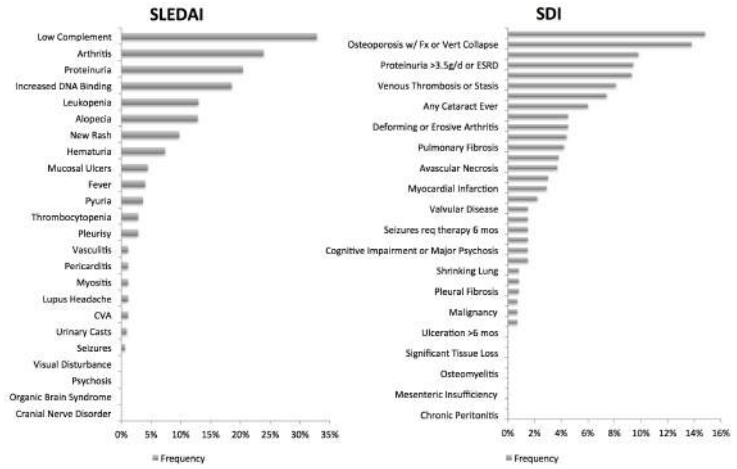
Results:

180 patients were enrolled in the cohort. 61.1% were African American and a significant number were hypertensive (60%). Mean SLEDAI was 3.6. Mean SDI (n=137) was 1.4. 62% had an SDI score of ³ 1. The frequency of SLEDAI and SDI components is shown in figure 1. Factors associated with worse SDI were older age (p=0.001), female gender (p=0.09), presence of hypertension (p=0.002), positive Smith/RNP (p=0.10) antibody, elevated ESR (p=0.006) and CRP (p=0.07), use of antiplatelet/anticoagulant agents (p=0.01). Hydroxychloroquine use (79.4%) (p=0.0005), positive SS-A/B (p=0.03/0.07) and pleuritis (p=0.03) were associated with lower damage. The association of worse damage with age, hypertension and protective effect of hydroxychloroquine were analogous to the SLICC and Hopkins lupus cohort.

Conclusion:

EHR-EDC is a powerful tool for clinical and translational research. The careful design, validation and integration within the EHR along with lupus indices allow regular automatic data extraction. Therefore with the increasing availability of EHR, the generation of cohorts for lupus and other diseases should also be achievable by centers with limited clinical research resources. Finally EHR-EDC also enables routine performance assessment for continuous improvement of care for lupus patients. Our lupus cohort had significant cardiovascular burden and was associated with worse damage, therefore requiring aggressive preventive measures.

Figure 1



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View Abstract and Citation Information Online - http://acrabstracts.org/abstract/electronic-health-record-ehr-as-a-powerful-tool-to-establish-clinical-research-lupus-cohorts

Abstract Number: 785

Further Validation of Simple Index As a Simple Disease Activity Assessment Tool for SLE

Nisarg Gandhi[1], Meenakshi Jolly[2], Alana Nevares[3] and Winston Sequeira[1], [1]Rheumatology, Rush University Medical Center, Chicago, IL, [2]Department of Medicine, Section of Rheumatology, Rush University Medical Center, Chicago, IL, [3]Internal Medicine, Cook County Hospital, Chicago, IL

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SESSION INFORMATION

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Background/Purpose:

An easy, quick tool, requiring minimal training or physician input for disease activity (DA) assessment in SLE, would have potentially greater uptake for routine use among rheumatologists and primary care physicians. Furthermore, integration into busy work flow processes would be easier for the same reason. Most DA tools for SLE are complex, require training and physician time; and are not performed during routine care visits for most SLE patients. SIMPLE (Simple Disease Assessment for People with Lupus Erythematosus) [1] is a numeric composite index based on patient reported questions and two laboratory values, and requires minimal input from health care provider which can be provided by nurse or a physician extender. Here, we prospectively evaluate the correlation of SIMPLE index with physician based DA measure.

Methods:

Fifty consenting patients meeting ACR classification criteria for SLE were recruited from two academic center clinics. Primary outcome of interest was correlation between Simple Index (SI) and SELENA-SLEDAI (SS). Secondary outcome of interest was correlation between SI and Physician Global Assessment (PGA). Patients filled the self-reported components of SI in the waiting room prior to their visit. PGA, SS and total numeric BILAG were assessed at the same visit by the physician. Descriptive and spearman correlational analyses were obtained. Stratified analysis by fibromyalgia status (FMS) was also conducted. P value of ≤ 0.05 was considered significant on two tailed tests. We considered correlation coefficient of <0.30, 0.30 to 0.49 and >0.50 as weak, moderate and strong correlation, respectively.

Results:

Mean (SD) age was 41.4+13 yrs, and 90% participants were women. Ethnic background of the participants was as follows: 56% Blacks, 24% Whites, 10% Asians and 10% others. Median (IQR) SI was 27.8 (18.3). Range for SI was 58.4. Median (IQR) values of PGA, total SS, total numeric BILAG and SDI were 0.5 (0.8), 4.0(6.0), 10.5(9.0) and 1.0(1.0), respectively. Spearman correlation coefficient between SI and PGA and SS were 0.547 (p 0.001), 0.545(p 0.001), respectively. In a sub analysis excluding fibromyalgia patients, these correlations were 0.718(p 0.001, n=34), 0.622(p 0.001, n=36) respectively.

Conclusion:

SIMPLE index is strongly correlated with PGA and SS in SLE, and the correlation is even stronger is SLE patients without FMS. It is quick, easy and requires minimal physician input. Larger and longitudinal studies that include patients with greater DA and test responsiveness are currently ongoing.

Reference:

[1] Simple Disease Assessment for People with Lupus Erythematosus. A&R. 2014; 66 (11):s312

Disclosure: N. Gandhi, None; **M. Jolly**, Pfizer Inc, 7; **A. Nevares**, None; **W. Sequeira**, None.

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Abstract Number: 786

Anti-Carbamylated Protein Antibodies Identify Systemic Lupus Erythematosus Patients with Erosive Arthritis: Analysis of a Regional Swedish Register

Alf Kastbom[1], Philip Wallin[2], Michael Ziegelasch[1], Thomas Skogh[1], Leendert Trouw[3] and **Christopher Sjöwall**[1], [1]Department of Clinical and Experimental Medicine, Rheumatology/AIR, Linköping, Sweden, [2]Linköping University, Clinical and Experimental Medicine, Sweden, Rheumatology/AIR, Linköping, Sweden, [3]Rheumatology, Leiden University Medical Center, Leiden, Netherlands
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Background/Purpose:

Articular manifestations affect a majority of patients with systemic lupus erythematosus (SLE), at least at some time during the disease course. Several investigators have estimated the frequency of erosive arthritis in SLE to about 5%. Detection of antibodies to 'cyclic citrullinated peptide' (anti-CCP) is an important diagnostic and prognostic tool in arthritis, since it is highly specific for rheumatoid arthritis (RA) and predictive of erosive disease. While anti-CCP reactivity in RA is citrulline-dependent, it has been suggested that anti-CCP in SLE is generally not, and thus also reacts with the corresponding 'cyclic arginine peptide' (CAP). Recently, it has been shown that antibodies targeting carbamylated proteins (anti-CarP) may occur in anti-CCP/rheumatoid factor negative cases even before the onset of RA. We analyzed anti-CCP, anti-CAP and anti-CarP in sera from patients in our well-characterized regional SLE register and related the findings to X-ray data, physical function and smoking habits.

Methods:

We included 236 patients (88% women) in the 'Clinical Lupus Register in Northeastern Gothia'. 212 had established disease, whereas the remaining 24 had recent-onset SLE at the timepoint of blood sampling. 75% met the ACR criterion for arthritis. Cases were classified as SLE according to any of the following criteria sets: the 1982 American College of Rheumatology criteria (84%) or the 2012 Systemic Lupus International Collaborating Clinics (SLICC-12) criteria (99%). IgG anti-CCP and anti-CAP ELISA kits (Euro-Diagnostica) were used. IgG anti-CarP was quantified with ELISA as previously described. X-ray data (hands, wrists and/or feet) were available in medical records of 91 cases (39%).

Results:

16 patients (6.8%), all meeting SLICC-12, were anti-CCP positive, 9 of whom were also anti-CAP positive. 4 of the 7 patients with citrulline-dependent anti-CCP had a history of biopsy-proven nephritis. 23 patients (9.7%), all meeting SLICC-12, were anti-CarP positive. Only 6 of the anti-CarP positive cases were identified as anti-CCP positive. Neither anti-CCP nor anti-CarP were associated with arthritis judged by physical examination, nor to any other SLE phenotype. The presence of anti-CarP was associated with a positive lupus anticoagulant test (Fisher's exact test, p=0.019). Smoking habits and HAQ did not associate with any of the antibodies. X-ray-proven erosions were found in 10 patients (4.2%) and were significantly associated with anti-CarP (Fisher's exact test, p=0.025), whereas the association with anti-CCP did not reach statistical significance (Fisher's exact test, p=0.07).

Conclusion:

Erosive arthritis is uncommon in SLE and our findings are in line with previous observations reporting a prevalence of 4-5%. Anti-CarP antibodies have previously not been studied in SLE. Herein, we demonstrate that anti-CarP in SLE: (1) is more frequently found than anti-CCP; (2) mainly identifies a different subgroup of cases compared with anti-CCP; and (3) associates significantly with erosive disease.

Disclosure: A. Kastbom, None; **P. Wallin**, None; **M. Ziegelasch**, None; **T. Skogh**, None; **L. Trouw**, None; **C. Sjöwall**, None.

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Abstract Number: 787

Validation of Lupuspro V1.8, Disease Targeted Patient Reported Outcome for Systemic Lupus Erythematosus

Meenakshi Jolly[1], Nisarg Gandhi[2], Alana Nevares[3] and Winston Sequeira[2], [1]Department of Medicine, Section of Rheumatology, Rush University Medical Center, Chicago, IL, [2]Rheumatology, Rush University Medical Center, Chicago, IL, [3]Internal Medicine, Cook County Hospital, Chicago, IL

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Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose:

Disease Specific Patient reported outcome measure tools capture unique domains relevant to patients with a specific disease. LupusPRO is targeted towards measuring health (HRQOL) and non-health related quality of life (Non HRQOL) among patients with systemic lupus erythematosus (SLE). LupusPRO V 1.7 and its translated versions in various languages have measurement equivalence and are responsive to changes in changes in patient reported changes in health and physician based disease activity assessments. However, items pertaining to sleep, or impact of vitality and pain on quality of life were placed together in the same domain (Vitality-Pain) based on factor loadings in initial studies and in interest of parsimony. For purposes of charting changes in individual components of this combined domain (Pain-Vitality), we separated the sleep, pain and vitality items into separate domains, keeping intact the concepts, content and language of the items, in version 1.8. We present

the psychometric properties of LupusPRO v1.8, with special attention to LupusPRO domains of sleep, vitality and pain.

Methods:

Fifty consenting SLE patients fulfilling ACR classification criteria were given self-administered surveys (MOS SF36 FACIT-Fatigue, Pain, Insomnia Severity Index for sleep, Perceived Stress Scale (PSS)-4, Patient Health Questionnaire-9 (PHQ-9) for depression, LupusPRO V 1.8) to complete at routine care visit. Disease activity and damage were assessed at visit using SELENA-SLEDAI (SS), numeric BILAG and SLICC-SDI/ACR (SDI). Internal consistency reliability (ICR) for each domain was obtained using cronbach alpha. Convergent construct validity (CV) with corresponding domains of SF36 was tested using spearman correlation coefficient.

Results:

Mean (SD) age was 41.4±13 yrs., 90% participants were women. Ethnic background was as follows: 56% Blacks, 24% Whites, 10% Asians and 10% others. Median (IQR) values of PGA, total SS, and SDI were 0.5 (0.8), 4.0(6.0) and 1.0(1.0), respectively. Results for LupusPRO V1.8 domains descriptives, ICR and CV are shown in Table 1. ICR for LupusPRO sleep, vitality and pain domains exceeded 0.80. LupusPRO Sleep domain scores inversely and strongly correlated with the Insomnia severity index scores, while LupusPRO Vitality (4 items) correlated strongly with FACIT-Fatigue (13 items) and SF36 Vitality scores. LupusPRO Pain domain correlated strongly with the Pain score and SF36 Bodily pain domain. Lupus symptom domain (3 items) showed significant correlation with PGA, SS and BILAG. LupusPRO domains of Physical and Emotional Health had good ICR and significant correlation with corresponding SF36 domains (Table 1).

Conclusion:

LupusPRO V1.8 (including its sleep, vitality and pain domains) has acceptable reliability and validity. It offers significant advantages over LupusPRO V1.7 and its 36 items comprehensively cover HRQOL in SLE.

Table 1: Validity and Reliability of LupusPRO V1.8

HRQOL	Items	Median (IQR)	ICR	Conv. Validity rho (p value)
Lupus Syptoms	1-3	66.7 (41.7)	0.80	PGA -0.40 (0.02), SELENA-SLEDAI -0.36 (0.03), Numeric BILAG -0.31 (0.05)
Cognition	4-5	75.0 (43.8)	0.86	
Lupus Medications	6-7	75.0 (37.5)	0.63	
Procreation	8-9	100 (3.13)	0.74	
Physical Health	10-14	85.0 (32.5)	0.93	PF 0.43 (0.002); RP 0.39 (0.006)
Sleep	15-17	66.7 (41.7)	0.83	INSOMNIA SCORE -0.66 (<0.001)
Vitality	18-21	62.5 (43.8)	0.92	VT 0.53 (<0.001); FACIT-FT -0.78 (<0.001)
Pain	22-25	68.8 (43.8)	0.96	BP 0.78 (<0.001); PAIN INDEX -0.61 (<0.001)
Emotional Health	26-31	56.3 (41.7)	0.88	PHQ-9 0.55 (<0.001); MH 0.34 (0.0.02); PSS -0.36 (0.01)
Body Image	32-36	75.0 (45.0)	0.95	
Total HRQOL	1-36	72.3 (25.6)		Numeric BILAG -0.38 (0.03)
Non HRQOL				
Desires-Goals	37-40	62.5 (39.1)	0.87	
Social-Support	41-42	75.0 (50.0)	0.78	
Coping	43-45	75.0 (41.7)	0.76	
Satisfaction with Care	46-49	100.0 (28.1)	0.96	
Total NonHRQOL	37-49	70.8 (29.7)		

PGA: Physician Global Assessment, SF-36 Domains: PF-Physical Function, RP-Role Physical, VT-Vitality, BP-Bodily Pain, MH-Mental Health. PHQ: Patient Health Questionnaire for Depression, FACIT-FT: FACIT-Fatigue.

Disclosure: M. Jolly, Pfizer Inc, 7; **N. Gandhi**, None; **A. Nevares**, None; **W. Sequeira**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/validation-of-lupuspro-v1-8-disease-targeted-patient-reported-outcome-for-systemic-lupus-erythematosus

Abstract Number: 788

Identification of Molecular Biomarkers to Distinguish Systemic Lupus Erythematosus with Skin Involvement from Discoid Lupus Erythematosus and Subacute Cutaneous Erythematosus: Provisional Results from Cross-Sectional Studies

Matteo Cesaroni[1], Jarrat Jordan[1], Jessica Schreiter[1], Marc Chevrier[1], Grace Wang[2], Cesar Calderon[3], Alexa Piantone[2], Ian Gourley[4], Stanley Cohen[5], Scott Fretzin[6], Anna Wozniacka[7], Victoria P. Werth[8] and Jacqueline Benson[1], [1]Estrela Lupus Venture, Janssen Research and Development, LLC., Spring House, PA, [2]Janssen Research and Development, Spring House, PA, [3]37 Derwen Dr., Janssen Research and Development, Havertown, PA, [4]1329 Anthony Wayne drive, Janssen Research and Development, Wayne, PA, [5]Metroplex Clinical Research

Center, LLC, Dallas, TX, [6]Dawes Fretzin Clinical Research Group, LLCC, Indianapolis, IN, [7]Medical University of Lodz, Lodz, Poland, [8]Philadelphia VA Medical Center, Philadelphia, PA
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Background/Purpose:

Sub-classification of Lupus Erythematosus (LE) patients is largely based on defined clinical criteria while biological factors associating with or contributing to these clinical features are less defined. Further elucidation of molecular events present in distinct clinical subsets of LE patients may aid in the identification of subjects more responsive to existing therapeutics, disease-classifying biomarkers and new therapeutic targets. To that end, cross-sectional studies were undertaken with SLE subjects having active skin involvement and subjects with Discoid Lupus Erythematosus (DLE) or Subacute Cutaneous LE (SCLE) to determine if LE patient subsets with skin manifestations can be molecularly distinguished.

Methods:

A prospective multicenter cross-sectional biomarker study (NOCOMPOUNDLUN0001) was undertaken with LE patients having SLE, SCLE or DLE, all with active cutaneous involvement at time of sample collection. A second single center independent study also occurred to procure SLE, SCLE, DLE and healthy volunteer (HV) samples. In total, samples from 6 SLE, 21 SCLE, 19 DLE and 10 HV were collected under informed consent. Serum collected from these donors was extensively profiled for autoantibody specificities and cytokines using ProtoArray® and DiscoveryMAP® v 3.3 systems, respectively. In addition, RNA was extracted from skin biopsy collections at lesional and/or non-lesional sites from individual subjects or from HV donors and gene expression quantified using Affymetrix arrays. All data was further analyzed using "R" software. Topological networks were created using Ayasdi.

Results:

Serum samples from DLE, SCLE, SLE and HV subjects were extensively profiled for autoantibody specificities and soluble cytokines. Protein array chips containing more than 9,000 protein features were utilized to determine if unique autoantibody specificity profiles associate with LE patient sub classifications. Antibodies against 84 distinct proteins were significantly elevated in the sera of LE versus HV subjects. 55, 10, and 16 of these were uniquely enriched in DLE, SCLE and SLE subsets, respectively. Cytokine profiling was also performed using a bead-based panel containing over 300 analytes. 75 cytokines were significantly elevated in the sera of LE versus HV subjects. Of these, 5, 33, and 5 were uniquely enriched in DLE, SCLE and SLE patient subsets, respectively. 15 cytokines were elevated across DLE, SCLE and SLE subjects versus HV. Gene expression data from skin also demonstrated unique gene signatures for each LE subset. Topological networks from this data set corroborated these findings and indicate that unique proteomic and gene expression profiles associate with specific LE patient subsets.

Conclusion:

In the LE cohorts examined, serum autoantibody and cytokine profiles were identified that distinguished subsets of cutaneous patients or were commonly elevated across SLE, DLE and SCLE subjects. These findings correlated with the identification of SLE, DLE and SCLE specific molecular pathways in skin found by gene expression array. Further studies with more subjects are required to further validate these findings.

Disclosure: M. Cesaroni, Johnson & Johnson, 3,Johnson & Johnson, 1; **J. Jordan**, Johnson & Johnson, 1,Johnson & Johnson, 3; **J. Schreiter**, Johnson & Johnson, 1,Johnson & Johnson, 3; **M. Chevrier**, Johnson & Johnson, 1,Johnson & Johnson, 3; **G. Wang**, Johnson & Johnson, 1,Johnson & Johnson, 3; **C. Calderon**, Johnson & Johnson, 1,Johnson & Johnson, 3; **A. Piantone**, Johnson & Johnson, 1,Johnson & Johnson, 3; **I. Gourley**, Johnson & Johnson, 1,Johnson & Johnson, 3; **S. Cohen**, Johnson & Johnson, 5,Amgen, 5,BMS, 5,Medac, 5,Pfizer Inc, 5,Amgen, 2,BMS, 2,Abbvie, 2,UCB, 2,Janssen Pharmaceutica Product, L.P., 2,Roche Pharmaceuticals, 2,Pfizer Inc, 2; **S. Fretzin**, Johnson & Johnson, 5,Johnson & Johnson, 2; **A. Wozniacka**, Johnson & Johnson, 2; **V. P. Werth**, Johnson & Johnson, 2; **J. Benson**, Johnson & Johnson, 1,Johnson & Johnson, 3.

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Abstract Number: 789

Direct Coombs Positivity in SLE

Nour Abou Assalie[1], Wei Fu[2] and Michelle Petri[3], [1]Saint Agnes Hospital, Baltimore, MD, [2]Rheumatology, Johns Hopkins University School of Medicine, Baltimore, MD, [3]Johns Hopkins University School of Medicine, Baltimore, MD

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Background/Purpose: The Coombs test is now one of the SLICC classification criteria for SLE classification. We investigated the association of the Coombs test with other clinical manifestations, in particular with autoimmune hemolytic anemia.

Methods: 2417 patients with SLE (age 50.8 +/- 14.3, 92.4% females) in a longitudinal cohort were included. The direct Coombs test was determined at cohort entry. Patients were then followed quarterly.

Results: 20% had a positive coombs test. The association of the direct Coombs test with other clinical and laboratory manifestations is shown in Table 1.

Table 1:

	Odds Ratio (95% CI)	**p-value**
Fever	1.45 (1.16,1.82)	0.0011
Lymphadenophathy	1.68 (1.34,2.11)	<.0001
Mouth Ulcers	0.69 (0.55,0.85)	<.0001
Vasculitis	2.01 (1.51,2.67)	<.0001
Leg Ulcers	2.44 (1.34,4.42)	0.0034
Panniculitis	0.97 (0.48,1.94)	0.9217
Pleuritis	1.46 (1.17,1.82)	<.0001
Pericarditis	1.46 (1.13,1.87)	0.0032
Proteinuria	2.59 (2.06,3.25)	<.0001
Nephrotic Syndrome	1.91 (1.48,2.48)	<.0001
Hematuria	2.08 (1.65,2.62)	<.0001
Renal Insufficiency	1.97 (1.53,2.53)	<.0001
Seizure	1.57 (1.11,2.21)	0.0099
Psychosis	1.94 (1.14,3.3)	0.0149
Hemolytic Anemia	12.76 (9.34,17.44)	<.0001
Leukopenia <4	1.78 (1.42,2.22)	<.0001
Platelet<100	2.19 (1.72,2.8)	<.0001
LAC (RVVT)	2.14 (1.7,2.71)	<.0001
Anticardiolipin	1.63 (1.3,2.04)	<.0001
Anti B2 glycoprotein	1.9 (1.43,2.52)	<.0001
Sjogren's Syndrome	0.52 (0.38,0.72)	<.0001
Hepatomegaly	2.86 (1.7,4.82)	<.0001
Splenomegaly	2.75 (1.75,4.33)	<.0001
Anti-dsDNA	3.19 (2.43,4.18)	<.0001
Anti-Sm	1.81 (1.41,2.32)	<.0001
Anti-Ro	1.66 (1.32,2.09)	<.0001
Anti-La	1.63 (1.21,2.19)	0.0013
Anti-RNP	1.71 (1.35,2.16)	<.0001
Low CH50	2.34 (1.73,3.15)	<.0001
Low C3	3.17 (2.47,4.08)	<.0001
Low C4	3.32 (2.61,4.22)	<.0001
ESR	4.68 (3.23,6.8)	<.0001

Only 38% of those with the direct Coombs test ever developed an autoimmune hemolytic anemia. Those who did develop hemolytic anemia were significantly more likely to have renal and CNS-SLE (Table 2).

Table 2:

	OR (95% CI)	P-value
High School Education	0.26 (0.13,0.53)	0.0001
Fever	1.94 (1.28,2.93)	0.0017
Pericarditis	1.75 (1.12,2.74)	0.0137
Nephrotic Syndrome	1.72 (1.09,2.71)	0.0192
Renal Insufficiency	1.94 (1.25,3.02)	0.0031
Renal Failure	3.02 (1.61,5.66)	0.0006
Seizure	2.41 (1.33,4.37)	0.0039
Meningitis	3.92 (1,15.38)	0.0505
Stroke	3.28 (1.35,7.93)	0.0085
Thrombocytopenia	1.95 (1.27,3)	0.0023
Anticardiolipin	0.59 (0.39,0.89)	0.0132
Heart Murmur	2.14 (1.41,3.23)	0.0003
Hepatomegaly	5.75 (2.24,14.76)	0.0003
Splenomegaly	2.73 (1.32,5.68)	0.0070

Conclusion: The direct Coombs test is strongly associated with hemolytic anemia but only 38% develop hemolytic anemia. Those who do develop hemolytic anemia are more likely to have had renal or CNS-SLE. Direct Coombs positivity that leads to hemolytic anemia portends a particularly poor prognosis.

Disclosure: N. Abou Assalie, None; **W. Fu**, None; **M. Petri**, None.

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Abstract Number: 790

An Intervention to Improve Quality of Life for African-American Lupus Patients

Edith M. Williams[1], Johnese Bostic[2], Alyssa Adkins[3], Larisa Bruner[2], Jiajia Zhang[2], Diane L. Kamen[4] and Jim Oates[4], [1]Institute for Partnerships to Eliminate Health Disparities, University of South Carolina, Columbia, SC, [2]University of South Carolina, Columbia, SC, [3]University of South Carolina, Greenville, SC, [4]Medicine, Medical University of South Carolina, Charleston, SC

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Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose: The Intervention to **I**mprove **Q**uality of life for **A**frican-America**N** lupus patients (IQAN) Project is designed to examine whether a uniquely tailored intervention program can improve quality of life, decrease indicators of depression, and reduce perceived and biological indicators of stress in African American lupus patients. This study builds on three decades of work conducted in the field of arthritis self-management but differs in that the intervention mode, the disease (lupus), and the study population (African-Americans) are unstudied or understudied.

Methods: A unique 'a-la-carte' self-management program was offered to 50 African-American lupus patients participating in a longitudinal observational web-based SLE Database at the Medical University of South Carolina (MUSC). Each individualized intervention plan (IIP) included 1-4 options, including a mail-delivered arthritis kit, addition and access to a message board, participation in a support group, and enrollment in a local self-management program. A 'set menu' control group of 50 lupus patients was offered a standardized chronic disease self-management program only, and a control group of 50 lupus patients received usual care (UC), void of intervention components. Validated measures of stress, depression, and quality of life were collected in all patients in each condition before and after intervention activities. All participants met at least four components of the 1997 ACR revised criteria for SLE. In order to evaluate changes between baseline and 6 months post-intervention and 12 months post-intervention, compact scores were calculated after merging similar variables within the same topic area. Compact scores were then compared for each group, using two-sample t-tests.

Results: Between baseline and 6 months post-intervention, marginally significant improvements were observed in areas of stress management and pain management. The mean number of times participants applied stress management techniques increased from 0.69 to 1.68 in the intervention group ($p=0.05$). Improvements in the other two groups were not significant. The mean score of the intervention group increased from 8.83 to 11.29 ($p=0.08$) in the frequency of managing pain by applying positive techniques, but the other two groups did not display such improvements. Between baseline and 12 months post-intervention, an increasing trend persisted in the intervention group in the frequency of applying stress management techniques ($p=0.02$). Additionally, decreasing trends in activity limitation were observed in both the intervention and set-menu control groups.

Conclusion: Self-selection of program components has not been explored as an approach to improve disparate trends in quality of life, disease activity and depression, and stress among African-American lupus patients, but better self-management outcomes have been documented when participants are able to choose/dictate the content and/or pace of the respective treatment/intervention program. As there is currently no "gold standard" self-management program specifically for SLE, the IQAN project may have a considerable impact on future research and policy decisions.

Disclosure: E. M. Williams, None; **J. Bostic**, None; **A. Adkins**, None; **L. Bruner**, None; **J. Zhang**, None; **D. L. Kamen**, None; **J. Oates**, None.

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Abstract Number: 791

Impact of Online Education and Social Media Intervetion for Self-Management in Adolescents with SLE

Lisabeth Scalzi[1] and Nancy J. Olsen[2], [1]Internal Medicine andPediatrics, Hershey Medical Center, Hershey, PA, [2]Divsion of Rheumatology, Department of Medicine, Penn State MS Hershey Medical Center, Hershey, PA

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Session Time: 9:00AM-11:00AM

Background/Purpose: Self-management (SM) skills are vital to the physical and emotional health adolescents with systemic lupus erythematosus (SLE). These self-management skills may also affect successful transition to independent self-care. We developed an online educational course for young adults with SLE as well as a social media site where participants could discuss the content of the educational site, or other spontaneous issues, during the 8 week intervention.

Methods: SLE patients were recruited to participate in an 8-week, 8 module online SLE educational course. Participants were randomized to answer questions at the end of each week either in a written journal (control) or on a social media site (SM). Outcome measures were examined in the entire group and between the two groups before and after the intervention. These measures included medication adherence (as measured by the Medication Adherence Self-report Inventory (MASRI) and the Mediation Possession Ratio (MPR)), empowerment processes and outcomes, sense of agency (SOC) and sense of community (SOC), quality of life (as measured by the Simple Measure of Impact of Lupus Erythematosus in Youngsters (SMILEY), and self-efficacy (using the Children's Arthritis Self-Efficacy Scale (CASE) questionnaire.

Results: 33 SLE patients, ages 13-24, participated in the study. The control (N=15) and SM (N=18) groups were similar in age, race, gender, and disease duration. The overall mean MPR and MASRI were quite high for this group of subjects. The mean MPR and MASRI for all subjects improved throughout the study. All of the secondary measures described, including SOC, SOA, empowerment outcomes, and quality of life, improved over the course of the study as well. Some measures showed a more robust improvement in the SM group, including SOA, SOC, and CASE. In particular, those participants who participated in the SM group had significantly better empowerment outcomes as compared to the control subjects.

Conclusion: We have developed an online education intervention for young adults with SLE, which improves self-management skills. Additional involvement in social media with other young adults with SLE appears to improve empowerment. This intervention would be ideal for a multi-site trial.

Disclosure: L. Scalzi, None; **N. J. Olsen**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/impact-of-online-education-and-social-media-intervetion-for-self-management-in-adolescents-with-sle

Abstract Number: 792

Incidence and Persistence of Cervical Human Papillomavirus Infection in Mexican Systemic Lupus Erythematosus Women

Claudia Mendoza Pinto[1], Mario García-Carrasco[2,3], Verónica Vallejo-Ruiz[4], Socorro Méndez-Martínez[5], Alejandro Taboada-Cole[6], José Luis

Totolhua Ramírez[7], Julio Reyes-Leyva[4] and Aurelio López-Colombo[8], [1]Systemic Autoimmune Diseases Research Unit, HGR 36-CIBIOR, Instituto Mexicano del Seguro Social, Puebla, Mexico, [2]Systemic Autoimmune Diseases Research Unit, HGR 36-CIBIOR Instituto Mexicano del Seguro Social, Puebla, Mexico, [3]Inmunología y Reumatología, Universidad Autónoma de Puebla, Puebla, Mexico, [4]Molecular Biology and Virology Laboratory, CIBIOR, Instituto Mexicano del Seguro Social, Puebla, Mexico, [5]Research Coordination Delegation, Instituto Mexicano del Seguro Social, Puebla, Mexico, [6]Systemic Autoimmune Disease Research Unit, HGR 36, Instituto Mexicano del Seguro Social, Puebla, Mexico, [7]Department of Pathology, HGR 36, Instituto Mexicano del Seguro Social, Puebla, Mexico, [8]State Research and Education Department, UMAE,Hospital de Especialidades, Instituto Mexicano del Seguro Social, Puebla, Mexico
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SESSION INFORMATION

Session Date: Sunday, November 8, 2015
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Session Type: ACR Poster Session A
Session Time: 9:00AM-11:00AM

Background/Purpose:

The risk of high-grade squamous intraepithelial lesions is significantly increased in SLE patients compared with healthy female controls. High-risk human papillomavirus infection (HR-HPV) is associated with the risk of cervical dysplasia and carcinoma. However, longitudinal studies analyzing HPV persistence in SLE women are limited. Our objective was to study the incidence, persistence, cumulative prevalence, and clearance of HPV infection in patients with SLE and to assess risk factors for the acquisition and persistence of HPV infection.

Methods:

Prospective, observational cohort study of 127 SLE women. Patients were evaluated at baseline and at 3 years. Traditional and SLE-related disease risk factors were collected. A gynaecological evaluation and cervical cytology screening were made. HPV detection and genotyping were made by PCR and linear array.

Results:

The cumulative prevalence of HPV infection increased significantly (22.8% at baseline vs. 33.8% at 3 years; p = < 0.001). With respect to type-specific HPV infection, 20.1% of patients experienced 42 incident infections. The risk of acquiring any HPV infection was 10.1 per 1000 patient-months. The cumulative prevalence of HR-HPV infection (19.6% at baseline vs. 29.1% at 3 years; p = 0.007) and multiple HPV infection (11.0% at baseline vs. 15.7% at 3 years; p = 0.03) also increased significantly. The most frequent newly-acquired HR types were HPV-16 (2.4 per 1000 patient-months) and 53 (1.4 per 1000 patient-months). Detection of the same type of HPV at two examinations occurred in only 6 (12.8%) of incident infections. At 3 years, 41 (87.2%) prevalent infections were cleared. Independent risk factors associated with incident HPV infection included higher number of lifetime sexual partners (OR= 1.8, 95% CI= 1.11-3.0) and cumulative cyclophosphamide dose (OR= 3.9, 95% CI= 1.2-12.8). Potential risk factors associated with persistent HPV infection included lupus activity at baseline (p = 0.03) pre-existing HVP infection (p = 0.008), and multiple HVP infection at baseline (p < 0.001). However, those possible associations were not confirmed when logistic multivariate analysis was performed.

Conclusion: In women with SLE, the cumulative prevalence of HPV infection, including HR-HPV and multiple HPV infections, increased significantly over time. Most persistent infections were LR-HPV. Number of lifetime sexual partners and cumulative cyclophosphamide dose were independently associated with incident HPV infection.

Disclosure: C. Mendoza Pinto, None; **M. García-Carrasco**, None; **V. Vallejo-Ruiz**, None; **S. Méndez-Martínez**, None; **A. Taboada-Cole**, None; **J. L. Totolhua Ramírez**, None; **J. Reyes-Leyva**, None; **A. López-Colombo**, None.

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Abstract Number: 793

Mesenchymal Stem Cells Promote the Generation of CD206+ Macrophage and Increase Its Phagocytic Activity in Systemic Lupus Erythematosus

Wei Deng, Weiwei Chen, Zhuoya Zhang, Saisai Huang, Wei Kong, Yue Sun, Xuebing Feng, Xiaojun Tang, Genhong Yao and **Lingyun Sun**, Department of Rheumatology and Immunology, The Affiliated Drum Tower Hospital of Nanjing University Medical School, Nanjing, China
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Session Time: 9:00AM-11:00AM

Background/Purpose: Umbilical cord (UC)-derived mesenchymal stem cells (MSCs) have been confirmed to exert therapeutic effects on systemic lupus erythematosus (SLE). Deficiency in SLE macrophages exhibits excessive activation and inefficient clearance of self nuclear antigens. However, whether the benefit effect of UCMSCs on SLE was mediated by regulatory effects on macrophages remains to be elucidated. We aim to explore whether UCMSCs could educate SLE macrophage to become a kind of alternatively activated macrophage and increase its phagocytic activity.

Methods: UCMSCs were injected into B6.MRL-*Fas*^{lpr} mice. The therapeutic effects of MSCs transplantation were evaluated by the renal pathology, proteinuria, spleen index, T lymphocyte subpopulation and plasma cells. Murine peritoneal/renal macrophages were isolated to detect the proportion of alternatively activated macrophage (F4/80^{+}CD206^{+}). To determine the phagocytic activity of murine peritoneal/renal macrophages, FITC-labeled flurospheres were added into the cultures. The uptake of FITC-labeled flurospheres was determined by flow cytometry. CD14^{+} monocytes were isolated from peripheral blood of healthy donors (HC) and SLE patients. We cultured human monocytes for 7 days with macrophage colony-stimulating factor (M-CSF) to generate macrophages, and then cocultured them for 2 more days with UCMSCs in a transwell culture system. The levels of CD206 and phagocytic activity of macrophages were detected by flow cytometry.

Results: Compared with C57BL/6 mice, B6.MRL-*Fas*^{lpr} mice macrophages exhibited lower level of CD206, the marker of alternatively activated macrophages. In addition, the phagocytic activity of B6.MRL-*Fas*^{lpr} mice macrophages was also decreased. UCMSCs transplantation could rescue both the proportion of CD206^{+} macrophages and the phagocytic activity. Interestingly, the proportion of CD206^{+} macrophages was positively correlated with the phagocytic activity. Similar to the lupus mice, macrophages from SLE patients showed lower expression of CD206 and phagocytic activity. SLE macrophages cocultured with UCMSCs consistently increased the expression of CD206 and phagocytic activity. In addition, the up-regulation of phagocytic activity by UCMSCs was only appeared in CD206^{+} macrophages. This phenomenon was also observed in UCMSCs transplanted SLE patients. Furthermore, the addition of specific neutralizing antibodies/inhibitor/siRNA of HGF, TGFβ1, PGE2 and HO-1 could not reverse the effects of UCMSCs on SLE macrophages.

Conclusion: UCMSCs could alleviate SLE through promoting the generation of CD206^{+} macrophage and increasing its phagocytic activity, and these effects was independent of HGF, TGFβ1, PGE2 and HO-1.

Disclosure: W. Deng, None; **W. Chen**, None; **Z. Zhang**, None; **S. Huang**, None; **W. Kong**, None; **Y. Sun**, None; **X. Feng**, None; **X. Tang**, None; **G. Yao**, None; **L. Sun**, None.

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Abstract Number: 794

CD163+ Macrophages Display Mixed Polarizations in Discoid Lupus Skin

Benjamin Chong[1], Lin-chiang Tseng[1], Gregory Hosler[2], Noelle Teske[1], Song Zhang[3], David R. Karp[4], Nancy J. Olsen[5] and Chandra Mohan[6], [1]Dermatology, University of Texas Southwestern Medical Center, Dallas, TX, [2]Propath, Dallas, TX, [3]Clinical Sciences, University of Texas Southwestern Medical Center, Dallas, TX, [4]UT Southwestern Medical Center, Dallas, TX, [5]Divsion of Rheumatology, Department of Medicine, Penn State MS Hershey Medical Center, Hershey, PA, [6]Biomedical Engineering, University of Houston, Houston, TX
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Background/Purpose: Discoid lupus erythematosus (DLE) is the most common form of chronic cutaneous lupus. Lesional skin of DLE patients contains macrophages that may transition from a pro-inflammatory M1 subtype to an anti-inflammatory M2 subtype, and vice versa. To test our hypothesis that M1 macrophages would be increased in DLE skin, we examined macrophage features in DLE and normal skin using histochemical and gene expression approaches.

Methods: DLE lesional and normal control skin samples were analyzed for CD163 expression by immunohistochemistry. Gene expression of RNA from both skin groups was compared by microarrays and quantitative RT-PCR. Double immunofluorescence studies were performed to characterize protein expression of CD163^{+} macrophages.

Results: CD163^{+} macrophages were increased near the epidermal-dermal junction and perivascular areas in DLE lesional skin compared with normal skin. Gene set enrichment analysis comparing differentially expressed genes in DLE and normal skin with previously published gene sets associated with M1 and M2 macrophages [1] showed strong overlap between up-regulated genes in DLE skin and M1 macrophages ($p=0.02$) (Table 1). Quantitative RT-PCR showed that several M1 macrophage-associated genes (e.g. CXCL10 (47.2 fold change (FC), CCL5 (25.9 FC), STAT1 (11.96 FC), TNF-α (1.92 FC), CD127 (8.01 FC), $p<0.05$) had amplified mRNA levels in DLE skin (Figure 1a-e). However, double immunofluorescence studies of CD163^{+} macrophages revealed co-expression of M1 (CXCL10, TNF-α, CD127), and M2 (CD209, TGF-β) macrophage-related proteins in DLE skin.

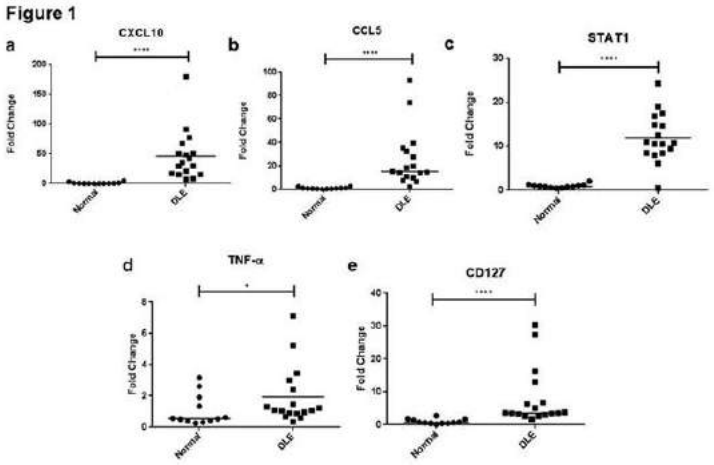
Conclusion: The variation of macrophage subtypes in DLE skin may reflect their propensity to switch polarization and possible transition from a M1-dominant acute phase to an M2-dominant chronic phase, though this requires verification. Macrophage plasticity makes these cells ideal targets for future therapies.

References: 1. Fuentes-Duculan J, Suarez-Farinas M, Zaba LC, Nograles KE, Pierson KC, Mitsui H *et al.* A subpopulation of CD163-positive macrophages is classically activated in psoriasis. J Invest Dermatol 130 (2010) 2412-22.

Table 1. Gene set enrichment analysis of differentially expressed genes in DLE lesional and normal skin.

Name	Size	ES	NES	p-value	FDR q-value
IFN-γ-stimulated (M1) macrophages up-regulated	113	0.92	1.25	0.02	0.02
IFN-γ stimulated (M1) macrophages down-regulated	16	-0.55	-1.24	0.25	0.25
IL-4 stimulated (M2) macrophages up-regulated	26	0.39	0.97	0.49	0.49
IL-4 stimulated (M2) macrophages down-regulated	1	0.95	1.11	0.27	0.27

Abbreviations: DLE – discoid lupus erythematosus, ES – enrichment score, FDR – false discovery rate, IFN – interferon, IL – interleukin, NES – normalized enrichment score



Disclosure: B. Chong, Daavlin Corporation, 2; **L. C. Tseng**, None; **G. Hosler**, None; **N. Teske**, None; **S. Zhang**, None; **D. R. Karp**, None; **N. J. Olsen**, None; **C. Mohan**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/cd163-macrophages-display-mixed-polarizations-in-discoid-lupus-skin

Abstract Number: 795

High Mobility Group Box-1 (HMGB1) Affects Macrophage Polarization and Phagocytosis in Systemic Lupus Erythematosus Patients

Fleur Schaper[1], Gerda Horst[1], Karina de Leeuw[1], Hendrika Bootsma[1], Pieter C Limburg[2], Peter Heeringa[3], Marc Bijl[4] and Johanna Westra[5], [1]Rheumatology and Clinical Immunology, University Medical Center Groningen, University of Groningen, Groningen, Netherlands, [2]Laboratory Medicine, University Medical Center Groningen, University of Groningen, Groningen, Netherlands, [3]Pathology and Medical Biology, University Medical Center Groningen, University of Groningen, Groningen, Netherlands, [4]Internal Medicine and Rheumatology, Martini Hospital, Groningen, Netherlands, [5]Rheumatology and Clinical Immunology, University of Groningen, University Medical Center Groningen, Groningen, Netherlands

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Session Title: Systemic Lupus Erythematosus - Human Etiology and Pathogenesis Poster I

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Session Time: 9:00AM-11:00AM

High mobility group box-1 (HMGB1) affects macrophage polarization and phagocytosis in systemic lupus erythematosus patients.

F Schaper, G Horst, K de Leeuw, H Bootsma, PC Limburg, P Heeringa, M Bijl, J Westra

Background/Purpose: Decreased phagocytosis of apoptotic cells, leading to necrosis and exposure of nuclear autoantigens, plays an important role in the pathogenesis of Systemic Lupus Erythematosus (SLE). One of these nuclear autoantigens is High Mobility Group Box 1 (HMGB1), which acts as an alarmin when secreted. Increased serum levels have been found in SLE patients. We hypothesized that increased HMGB1 levels might lead to skewing in the differentiation of monocytes into M1 macrophages, instead of M2 macrophages. As M1 macrophages are less efficient phagocytes this might fuel SLE. We studied expression of M1 and M2 markers of peripheral blood monocytes and *in vitro* differentiated macrophages of SLE patients were compared to healthy controls (HC). Phagocytic capacity of macrophages and the effect of HMGB1 on differentiation of macrophages and phagocytosis was also investigated.

Methods: For this study SLE patients with quiescent or mild disease (SLEDAI 0-5) and age- and sex-matched HC were included. Monocytes and differentiated M1 and M2 macrophages were phenotyped by flow cytometry for expression of CD86 (M1 marker) and CD163 (M2 marker). Monocytes of 19 patients and HC were isolated by negative sorting and analyzed by RT-qPCR to determine mRNA levels of CD86, TLR2, TLR4, TNF-α, IL-6 (M1) and CD163, Mannose Receptor, and IL-10 (M2). HMGB1 was added (4 or 24 hours) during M2 differentiation to investigate the effect on macrophage phenotype and effect on phagocytosis of apoptotic Jurkat cells.

Results: Expression of CD86 on monocytes was similar between patients and HC, but expression of CD163 was significantly lower on monocytes from SLE patients ($p=0.022$). Moreover, IL-6 mRNA levels were significantly increased in monocytes of patients ($P<0.0001$). After cytokine induced differentiation no differences were observed between M1 and M2 macrophages from SLE patients and HC regarding surface receptor expression and phagocytic capacity. Addition of HMGB1 during differentiation of M2 macrophages resulted in high IL-6 and TNF-α mRNA expression in macrophages. Preincubation of HMGB1 with apoptotic Jurkat cells resulted in reduced phagocytosis by M2 macrophages.

Conclusion: Monocytes from SLE patients display an M1-like phenotype, shown by decreased expression of CD163 and increased IL-6 mRNA expression. *In vitro* differentiation abolishes these differences between SLE and HC. HMGB1 induces differentiation into M1-like phenotype and reduces phagocytosis of apoptotic cells. So, this study shows that the phenotype of monocytes or macrophages is determined by their environment, such as presence of cytokines and HMGB1, and thereby contributes to the pathogenesis of SLE.

Disclosure: F. Schaper, None; **G. Horst**, None; **K. de Leeuw**, None; **H. Bootsma**, None; **P. C. Limburg**, None; **P. Heeringa**, None; **M. Bijl**, None; **J. Westra**, None.

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Abstract Number: 796

Single Cell Gene Expression Studies in Lupus Patient Monocytes Reveal a Unique Anti-Inflammatory Population of Non-Classical Monocytes Associated with Clinical Quiescence

Zhongbo Jin[1], Wei Fan[2,3], Mark A. Jensen[4], Jessica M. Dorschner[1], Danielle Vsetecka[1], Shreyasee Amin[5], Ashima Makol[6], Floranne C. Ernste[7], Thomas Osborn[7], Kevin G. Moder[5], Vaidehi Chowdhary[5] and Timothy B. Niewold[1], [1]Division of Rheumatology and Department of Immunology, Mayo Clinic, Rochester, MN, [2]Department of Rheumatology, Ren Ji Hospital, School of Medicine, Shanghai Jiao Tong University, China, Shanghai, China, [3]Mayo Clinic, Rochester, MN, [4]Divsion of Rheumatology and Department of Immunology, Mayo Clinic, Rochester, MN, [5]Rheumatology, Mayo Clinic, Rochester, MN, [6]Division of Rheumatology, Department of Internal Medicine, Mayo Clinic, Rochester, MN,

[7]Division of Rheumatology, Mayo Clinic, Rochester, MN
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Background/Purpose:

Our previous gene expression studies in sorted immune cell populations in SLE has shown that different cell types from the same blood sample demonstrate diverse gene expression parameters. These studies also suggested that heterogeneity in gene expression runs deeper than major immune cell subsets. In this study, we examine IFN signatures in single monocytes isolated from SLE patients.

Methods:

$CD14^{++}CD16^{-}$ classical monocytes (CLs) and $CD14^{dim}CD16^{+}$ non-classical monocytes (NCLs) from 14 SLE patients were purified by magnetic separation. The Fluidigm single cell capture and pre-amplification System was used for single cell capture and target gene pre-amplification. Fluidigm Biomark system (Rt-PCR system) was used to quantify expression of 87 monocyte-related genes. IFN-induced genes in monocytes were identified by culturing monocytes isolated from whole blood of healthy controls with or without IFN-α. Genes significant up-regulated by IFN were identified as IFN-induced genes in current study. Limit of Detection (LOD) of Rt-PCR was set at 28 cycles. An individual cell IFN score was given based upon the sum of expression of IFN-induced genes. Hierarchical clustering was generated by using Cluster 3.0 and Java Treeview.

Results: Both CLs and NCLs demonstrated a wide range of expression of IFN-induced genes, and NCL monocytes had higher IFN scores than CL monocytes. Hierarchical clustering of all cells displayed clustering of cells in subsets within the CL and NCL lineages, as well as expression patterns that were shared by both lineages. We found four gene sets that clustered monocytes functionally. These included an IFN-induced gene set, two inflammatory gene sets, and one immunosuppressive gene set. Interestingly, we could define a large subset of NCL monocytes with upregulation of suppressive transcripts (including TGF-β and PDL1) and IFN-induced transcripts were also upregulated, while the two inflammatory gene sets were down-regulated. These cells were highly over-represented in a patient with inactive disease who was on immunosuppressants at the time of blood draw. The proportion of anti-inflammatory gene set expressing NCLs was inversely correlated with anti-dsDNA titers (rho = -0.77, p=0.0051) and positively correlated with C3 complement (rho = 0.68, p=0.030) in the SLE patient group, suggesting that these cells are also associated with serological quiescence.

Conclusion: Using single cell gene expression, we have identified a unique population of NCL monocytes in SLE patients with upregulation of a combination of anti-inflammatory and IFN-induced transcripts. These cells correspond with clinical and serological quiescence.

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Abstract Number: 797

Divergent Phenotypic Patterns Between Systemic Lupus Erythematosus and Healthy Anti-Nuclear Antibody Positive Individuals Reveal Distinct Differences in B Cell and Myeloid Populations Among Ethnicities

Samantha Slight-Webb[1], Rufei Lu[2], Holden T. Maecker[3], Paul J. Utz[4], Joel M. Guthridge[1] and Judith A. James[5], [1]Arthritis and Clinical Immunology, Oklahoma Medical Research Foundation, Oklahoma City, OK, [2]Clinical Immunology, Oklahoma Medical Research Foundation, Oklahoma City, OK, [3]Division of Immunology and Rheumatology, Stanford University School of Medicine, Stanford, CA, [4]Medicine, Stanford University School of Medicine, Stanford, CA, [5]Arthritis & Clinical Immunology Research Program, Oklahoma Medical Research Foundation, Oklahoma City, OK
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Background/Purpose: Systemic lupus erythematosus (SLE) is an autoimmune disorder that arises from genetic and environmental factors. Thus, patients with different ancestral backgrounds display differences in clinical presentation and severity that are likely a result of variation in cell physiology. Prior to SLE diagnosis, most SLE patients transition from anti-nuclear antibody negative (ANA-) to anti-nuclear antibody positive (ANA+), however, ANA positivity does not obligate autoimmune disease. Understanding differences in immune cell physiology between ANA+ healthy individuals and individuals that go on to clinical SLE remains a critical goal in the understanding of SLE etiology and is likely to vary by ethnicity.

Methods: Blood specimens and information on disease activity were collected from 56 European American (EA) and 38 African American (AA) individuals classified as either ANA- healthy controls, ANA+ healthy individuals or SLE patients. SLE patients were matched by age (±5 years), race, and gender to an ANA+ and ANA- healthy control. Single-cell analysis of cell surface markers was completed by mass cytometry on PBMCs and cellular heterogeneity was visualized using viSNE. Further, phospho-specific flow cytometry was used to measure basal levels of pERK, pPLCγ2 and p38 and expression following CD3/CD28 (TCR) and anti-IgG and IgM (BCR) stimulation.

Results: Compared to ANA- controls, EA ANA+ individuals had a higher frequency of myeloid cells ($p=0.048$), specifically myeloid derived suppressor-like cells ($CD33^{+}CD11b^{+}HLA\text{-}DR^{-}CD14^{\pm}$) were higher in ANA+ individuals ($p=0.037$) compared to SLE patients. Further, EA SLE patients had an increased frequency of $CD14^{+}CD33^{-}$ activated monocytes compared to healthy controls ($p<.05$), which positively correlated with SLEDAI disease activity ($p=0.040$). EA effector T cells had elevated basal levels of p38 and pERK ($p<0.005$) in ANA+ individuals compared to ANA- controls. However, following TCR stimulation, the fold change of pERK and p38 in effector CD4+ T cells was significantly decreased in ANA+ individuals and remained the same in SLE patients compared to ANA- controls ($p<0.05$). Interestingly, AA SLE patients and ANA+ individuals had no myeloid cell differences, but did have variations in B cell and CD4+ T cell subsets. Decreased frequencies of transitional B cells ($CD27^{-}CD38^{+}CD24^{+}$) were observed in AA SLE patients compared to both healthy controls ($p=.007$). In addition, $CD4^{+}CD27^{+}$ T cells were elevated in AA SLE patients compared to controls ($p<0.05$). AA SLE patients had higher basal expression of p38 and pERK in myeloid cell subsets. Following BCR stimulation, ANA+ AA individuals had increased fold change in myeloid cell pERK compared to ANA- controls ($p=0.026$), however, B cell pERK expression following BCR stimulation was decreased in SLE patients compared to ANA+ individuals ($p=.0225$).

Conclusion: Our results indicate that early differences in myeloid cell subsets of European Americans and lymphocyte subsets of African Americans may contribute to loss of tolerance and systemic inflammation in autoimmunity. Further, differences in cell signaling in SLE patients and ANA+ individuals may enhance these defects.

Disclosure: S. Slight-Webb, None; **R. Lu**, None; **H. T. Maecker**, None; **P. J. Utz**, None; **J. M. Guthridge**, None; **J. A. James**, None.

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Abstract Number: 798

Keratinocyte-Associated IL-6 Is Elevated in Cutaneous Lupus Rashes and Production of IL-6 By Keratinocytes Is Enhanced in Non-Involved Lupus Skin

Jasmine Stannard[1], Emily Myers[2], Tamra J. Reed[3], Lori Lowe[4] and J. Michelle Kahlenberg[5], [1]Int. Medicine/Rheumatology, University of Michigan, Ann Arbor, MI, [2]Georgetown University, Washington, DC, [3]Internal Medicine, Rheumatology, University of Michigan, Ann Arbor, MI, [4]Dermatology, University of Michigan, Ann Arbor, MI, [5]Internal Medicine, Division of Rheumatology, Division of Rheumatology, University of Michigan Medical Center, Ann Arbor, MI

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Session Time: 9:00AM-11:00AM

Background/Purpose: Systemic lupus erythematosus (SLE) is a devastating autoimmune disease with severe complications such as immune-complex mediated nephritis and scarring skin lesions. Treatment modalities for cutaneous lesions are often ineffective and pathogenic mechanisms driving rash development remain poorly understood. Interleukin-6 (IL-6) is a pro-inflammatory cytokine which has gotten recent attention in SLE as IL-6 is increased in the serum of active patients and blockade of IL-6 is therapeutic in several murine lupus models. Further, several phase I human trials have suggested IL-6 blockade may be promising for treatment of SLE. However, the role that IL-6 plays in cutaneous lupus erythematosus (CLE) rashes remains unclear.

Methods: All studies were approved by the University of Michigan Internal Review Board (IRB# 72843 and 66116). RNA was isolated from formalin fixed, paraffin-embedded biopsies of CLE rashes, which were obtained from the University of Michigan Pathology database. Real-time PCR was used to determine the expression level of the myxovirus (influenza virus) resistance 1 (MX-1) and interleukin-6 (IL6) genes. Biopsies were stained for IL-6 using immunohistochemistry. Skin biopsies were obtained from uninvolved skin of SLE patients with a history of cutaneous involvement or healthy controls followed by isolation and culture of keratinocytes. At confluence, cultures were treated with various concentrations of TLR ligands or UVB and IL-6 release was measured via ELISA.

Results: Real-time PCR analysis of subacute cutaneous lupus erythematosus (sCLE) (n=21) and discoid (DLE) (n=22) rashes demonstrated a significant upregulation of both the IFN-regulated gene, MX1, and the pro-inflammatory cytokine IL-6 when compared with control samples (n=9). Immunohistochemical analysis of skin biopsies confirmed upregulation of IL-6 in the epidermis when compared to control. Keratinocytes from healthy skin of lupus patients produced significantly more IL-6 when stimulated by TLR2, 3 or 4 agonists or exposed to UVB radiation when compared to identical passage keratinocytes from healthy controls.

Conclusion: IL-6 is increased at the RNA and protein level within cutaneous lupus biopsies when compared to healthy control skin. Keratinocytes are a major producer of IL-6 in the skin and lupus keratinocytes have enhanced production of IL-6 in response to TLR ligands and UV radiation. These data suggest that the epidermis, which is an important barrier for environmental insults, is primed for IL-6 production and that this may be one mechanism by which factors such as UV exposure may trigger rash development. Further investigations should focus on the pathogenic significance of IL-6 upregulation in the skin and whether targeting this pathway will have an impact on cutaneous disease activity.

Disclosure: J. Stannard, None; **E. Myers**, None; **T. J. Reed**, None; **L. Lowe**, None; **J. M. Kahlenberg**, None.

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Abstract Number: 799

Transcriptional Profiling of Cutaneous Lupus Reveals Pronounced Changes in Keratinocyte and Myeloid Lineage Expressed Genes and Demonstrates Uniquely Regulated Interferon Pathways Between Rash Subtypes

Celine C. Berthier[1], Jasmine Stannard[2], Emily Myers[3], William Swindell[4], Lori Lowe[4], Tamra J. Reed[5], Johann Gudjonsson[4] and **J. Michelle Kahlenberg**[6], [1]Nephrology, Division of Nephrology, University of Michigan Medical Center, Ann Arbor, MI, [2]Int. Medicine/Rheumatology, University of Michigan, Ann Arbor, MI, [3]Internal Medicine, Rheumatology, Georgetown University, Washington, DC, [4]Dermatology, University of Michigan, Ann Arbor, MI, [5]Internal Medicine, Rheumatology, University of Michigan, Ann Arbor, MI, [6]Internal Medicine, Division of Rheumatology, Division of Rheumatology, University of Michigan Medical Center, Ann Arbor, MI

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SESSION INFORMATION

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Session Title: Systemic Lupus Erythematosus - Human Etiology and Pathogenesis Poster I

Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose: Cutaneous lupus rashes can be substantial, disfiguring, and often refractory to usual lupus therapies. Phenotypic presentation and risk of systemic lupus manifestations differs by rash subtype and pathogenic factors contributing to rash remain poorly understood. For this study, we evaluated the transcriptional profiles of discoid lupus (DLE) and subacute cutaneous lupus (sCLE) rashes and characterized them in the context of contributing cellular populations and the unique profiles which may contribute to individual rash phenotype.

Methods: Formalin-fixed paraffin-embedded (FFPE) tissue blocks of 26 DLE and 27 sCLE rash biopsies were acquired from the University of Michigan Anatomic Pathology repository. RNA was isolated from five 10 micron sections and analyzed via Affymetrix ST 2.1 array. Gene expression changes were compared to 7 similarly treated and isolated healthy control biopsies. Genomatix, Ingenuity and *in silico* immunophenotyping were used for data analysis.

Results: Using q-value of <0.01 and|log Fold Change|>1 as filters, we identified 394 genes commonly upregulated and 175 genes commonly downregulated in sCLE and DLE compared to control. Genomatix analysis confirmed enhancement of known lupus-associated pathways (especially type I interferon (IFN) regulated genes), and transcription factor analysis revealed important gene regulation by STAT1, STAT4 and IRF1. Upregulation of TLR2 and inflammasome-associated genes were also noted. Immunophenotypic analysis demonstrated a significant proportion of upregulated genes were likely to be derived from myeloid cells within the skin. Alternatively, many of the downregulated genes were associated with keratinocytes. 173 genes were uniquely regulated in DLE and 116 genes were uniquely regulated in sCLE. Unique to DLE, a strong upregulation of IFN gamma associated pathways was noted and Ingenuity pathway analysis identified IL-4 as a likely prominent regulator of DLE-specific gene expression. In sCLE, type I IFN signaling predominated and unique expression of CD14 and the chemokines CCL20 and CCL2 were seen.

Conclusion: These data suggest that DLE and sCLE have overlapping and unique changes which may guide pathologic phenotype. Importantly, the role of myeloid populations in cutaneous lupus pathogenesis should be considered. Confirmation and further study of these identified dysregulated genes may identify targets for novel therapy of cutaneous lupus lesions.

Disclosure: C. C. Berthier, None; **J. Stannard**, None; **E. Myers**, None; **W. Swindell**, None; **L. Lowe**, None; **T. J. Reed**, None; **J. Gudjonsson**, None; **J. M. Kahlenberg**, None.

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Abstract Number: 800

A High-Throughput System for Quantification of in Vitro Neutrophil Extracellular Trap Formation with Fluorescence Immunocytochemistry

Tineke Kraaij[1], Sylvia Kamerling[1], Ton Rabelink[1], René E. M. Toes[2], Cees van Kooten[1] and Onno Teng[1], [1]Nephrology, LUMC, Leiden, Netherlands, [2]Rheumatology, Leiden University Medical Center, Leiden, Netherlands

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Background/Purpose:

Neutrophil extracellular traps (NETs) consist of decondensed chromatin and antimicrobial peptides and are able to trap and kill pathogens. Several studies suggest a pathogenic role for NETosis in autoimmune disease (AID), such as systemic lupus erythematosus (SLE), ANCA-associated vasculitis (AAV) and rheumatoid arthritis (RA). For investigation of NET triggers in relation to AID, NET release should be quantified with a standard and reliable method. Thus far, methods for NET quantification are heterogeneous, e.g. based on fluorescence microscopy, measuring DNA release or measuring other NET components. The aim was to develop an assay for inducing and quantifying NETs, preferably applicable to use in a high-throughput system.

Methods:

Neutrophils were isolated from healthy volunteers and were labelled with a membrane staining, PKH26, for visualization in immunocytochemistry (ICC). Neutrophils were seeded in a 96-well plate and incubated with different stimuli. IgG aggregates were used as a positive control. Extracellular DNA was stained with Sytox green. Further stainings used were Hoechst, anti-myeloperoxidase (MPO), anti-neutrophil elastase (NE) and anti-citrullinated histon3 (acitH3). Images were obtained with a BD Pathway 855 that was programmed to automatically and randomly obtain pictures from different locations within the well. Titration experiments with IgG aggregates were performed to induce NET release and image NETs with a 10x, 20x and 40x magnification lens. Subsequently NETs were quantified and the results obtained with different lenses were compared to find the optimal magnification for NET visualization and quantification.

Results:

We found that IgG aggregates were able to induce NET release in a dose-dependent manner. NET release in this assay was confirmed with acitH3, NE and MPO stainings. We quantified the amount of NETs with ImageJ software, by determining the ratio between positive Sytox green area and the positive PKH26 area, of which we found that it accurately represents the amount of cells present. NET quantification using different magnification lenses showed that the 20x magnification was able to capture the same amount of information compared to the 40x magnification and was able to increase the area for analysis up to 11% of the total area compared to the standard 2%.

Conclusion:

We developed a semi-automatic and reproducible system that reliably quantifies the NET-inducing capacity of many samples simultaneously and that is applicable as a high throughput system.

Disclosure: T. Kraaij, None; **S. Kamerling**, None; **T. Rabelink**, None; **R. E. M. Toes**, None; **C. van Kooten**, None; **O. Teng**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/a-high-throughput-system-for-quantification-of-in-vitro-neutrophil-extracellular-trap-formation-with-fluorescence-immunocytochemistry

Abstract Number: 801

Artesunate Modulates Atherosclerosis Related Factors through the Inhibition of STAT1

Xuebing Feng[1], Weiwei Chen[2], Lihui Xiao[1] and Lingyun Sun[2], [1]Department of Rheumatology, The Affiliated Drum Tower Hospital of Nanjing University Medical School, Nanjing, China, [2]Department of Rheumatology and Immunology, The Affiliated Drum Tower Hospital of Nanjing University Medical School, Nanjing, China

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Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose: While type I interferon (IFN) has been linked to atherosclerosis progression in systemic lupus erythematosus (SLE), little is known about its regulation and intervention. In this study, we assessed the effect of IFN-alpha on several classic atherosclerosis related factors, including macrophage migration inhibitory factor (MIF), vascular endothelial growth factor (VEGF) and numbers of peripheral endothelial progenitor cells (EPC), and explored the role of artesunate (ART), an anti-malarial agent extracted from Chinese herbs, on this process.

Methods: Levels of MIF and VEGF in serum or cultured supernatants were measured by ELISA, and numbers of peripheral EPC were detected by flow cytometry. Their relationships with IFN scores that calculated by 5 type I IFN gene (LY6E, OAS1, OASL, ISG15 and MX1) expression levels were assessed by Spearman correlation analysis. ART at different concentrations was added to human umbilical vein endothelial cells (HUVEC) cultures with or without prior IFN- alpha 1b stimulation and to SLE peripheral blood mononuclear cells (PBMC) cultures. To find out how ART regulated IFN signaling, the levels of total and phosphorylated (p) STAT1, 3, 5 in cultured HUVECs were tested by Western blot.

Results: Compared to age- and gender- matched normal controls, SLE patients had lower EPC numbers, lower VEGF levels, but higher MIF levels (all $p < 0.0001$). The reduction of EPC numbers and the increase of MIF levels were tightly correlated with the elevation of IFN score in SLE patients (both $p < 0.001$). *In vitro* cultures showed that HUVEC produced significantly higher amount of MIF after IFN-alpha stimulation, while VEGF levels varied at different time periods by showing a decline after 12 hours stimulation but an increase at 24 hours. ART at 20 μmol/L significantly suppressed IFN-alpha promoted VEGF and MIF production at 24 hours, along with the dramatic decline of IFN inducible gene expressions. Similar to that in HUVEC, ART treatment also inhibited VEGF and MIF production in SLE PBMC cultures. As shown in Figure 1, over-expression of p-STAT1, but not p-STAT3 or 5, was detected after IFN-alpha stimulation, which was completely reversed at the presence of ART.

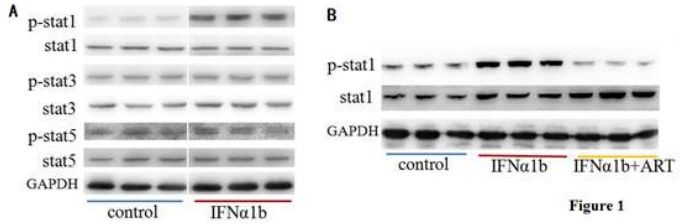

Figure 1

Conclusion: Our data supports a potential role for type I IFN signaling in atherosclerosis. ART may down-regulate IFN-alpha modulated pro-atherosclerotic factors through the inhibition of STAT1 phosphorylation, thus could have therapeutic effect on SLE-associated atherosclerosis.

Abstract Number: 802

Identification of Cyclin-Dependent Kinase 1 As a Novel Regulator for Controlling Type I Interferon Signaling in Systemic Lupus Erythematosus

Lingling Wu[1], Bo Qu[1], Yuting Qin[1] and Nan Shen[1,2], [1]Shanghai Institute of Rheumatology,Renji Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China, [2]The Center for Autoimmune Genomics and Etiology (CAGE),Cincinnati Children's Hospital Medical

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Session Time: 9:00AM-11:00AM

Background/Purpose:

Type I interferon (IFN) signaling has been a central pathogenic pathway in systemic lupus erythematosus (SLE). The application of specific inhibitors of IFN pathway has emerged as a promising treatment for SLE and it would be interesting to pharmacologically modulate the sensitivity to IFNa receptor stimulation .In this study, we screened 463 genes to identify novel regulators and tried to find a novel therapeutic target for the over-activated IFN signaling in SLE.

Methods:

High throughput ISRE-luciferase assay was used to screen candidate genes regulating IFN signaling pathway. Western blot was used to investigate IFN signal transduction. qRT-PCR was used to detect the expression of individual ISGs. Differential expression of CDK1 and ISGs between SLE patients and healthy controls was analyzed using data from RNA-seq and microarray experiments.

Results:

We developed a high-throughput ISRE-luciferase assay by co-transfection of ISRE-luciferase plasmids with a siRNA library of 463 genes in HELA cells. 60 genes which significantly enhanced ISRE activity (greater than 2 folds) and 14 genes which inhibited ISRE activity (approximately 50% reduction) were identified. And then we analysed expression of candidate genes in whole blood from SLE patients and healthy donors by using microarray data. As CDK1 could effected ISRE activity obviously and had a differiential expression between SLE patients and healthy control.What's more , CDK inhibitors also functioned in many clinnical trials for malignancy disease,we wonder whether CDK1 inhibitor could be a repositioning drug for SLE. Since we have seen that CDK1 enhanced IFN induced ISRE mediated reporter gene expression, we further tested the expression of ISGs and IFN induced phosphorylation of STAT1 could also be altered by knocking down CDK1 . After identifying the vital effect of CDK1 on IFN signaling, we wondered whether CDK1 was responsible for the amplified IFN signaling in SLE patients. We found CDK1 was over-expressed in peripheral blood mononuclear cells (PBMCs) and renal biopsies of SLE patients and was positively correlated with the "IFN scores". Meanwhile, CDK1 expressed higher in the patients with severe disease than those with mild or moderate disease. Since we have proposed that CDK1 might be the reason for excessive IFN signaling in SLE, we further tested if CDK1 inhibitor, RO-3306, could alleviate the over-activated IFN signaling in SLE patients. PBMCs obtained from 5 SLE patients who had high IFN scores were treated with RO-3306 and the expression of ISGs were significantly reduced.Meanwhile, RO-3306 could also function in kidney cells from lupus mice expressed high level of ISGs . These indicated a potential role of RO-3306 as a candidate for modulating IFN signaling sensitivity in SLE patients.

Conclusion:

Our data suggest that CDK1 is a positive regulator of IFN signaling pathway. Over-expression of CDK1 in SLE might contribute to the abnormally amplified type I IFN signaling and inhibition of CDK1 could be used to interfere with the type I IFN signaling in SLE. Our data extend the knowledge of specific mechanism of abnormal IFN signaling pathway in SLE, and indicate a novel therapeutic target for SLE treatment.

Disclosure: L. Wu, None; **B. Qu**, None; **Y. Qin**, None; **N. Shen**, None.

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Abstract Number: 803

Interferon-Alpha Mediated Lowering of Pentraxin-3 Levels in Systemic Lupus Erythematosus?

Lina Wirestam[1], Helena Enocsson[2], Christopher Sjöwall[2], Thomas Skogh[2], Maija-Leena Eloranta[3], Lars Rönnblom[3] and **Jonas Wetterö**[2], [1]Department of Clinical & Experimental Medicine, Rheumatology/AIR, Linkoping, Sweden, [2]Department of Clinical and Experimental Medicine, Rheumatology/AIR, Linköping, Sweden, [3]Medical Sciences, Rheumatology clinic, Uppsala, Sweden
First publication: September 29, 2015

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Session Date: Sunday, November 8, 2015
Session Title: Systemic Lupus Erythematosus - Human Etiology and Pathogenesis Poster I
Session Type: ACR Poster Session A
Session Time: 9:00AM-11:00AM

Background/Purpose:

The type I interferon (IFN) system is important in the pathogenesis of systemic lupus erythematosus (SLE). We have previously shown an inhibitory effect of IFN-α on interleukin (IL)-6/IL-1 mediated hepatocyte production of C-reactive protein (CRP) *in vitro* as well as *in vivo*, partly explaining the poor correlation between disease activity and circulating CRP in SLE. The non-hepatic long pentraxin 3 (PTX3) belongs to the same protein family, and shares some key properties with CRP regarding the handling of cellular debris. This study aimed to evaluate PTX3 as a potential biomarker in SLE, as well as to assess its possible interference with IFN-α by targeting levels in patients and in mechanistic studies on isolated leukocytes.

Methods:

Sera from 243 SLE patients meeting the 1982 ACR and/or the 2012 SLICC classification criteria, and 100 healthy controls were analysed for PTX3 (ELISA) and IFN-α (dissociation-enhanced lanthanide fluoroimmunassay). Disease activity (SLEDAI-2K) varied considerably among the SLE patients at the time point of blood sampling. The majority had established SLE, whereas 9% had recent onset disease.

Neutrophils and peripheral blood mononuclear cells (PBMC) were isolated by density gradient centrifugation of heparinised blood from healthy donors. Leukocyte PTX3 production was stimulated by IL-1β, tumour necrosis factor (TNF), lipopolysaccharide (LPS), and IFN-α. Cell supernatants were analysed for PTX3 by ELISA.

Results:

PTX3 levels were significantly lower in SLE patients (median 2.5 ng/ml) compared to healthy controls (median 4.5 ng/ml); ($p < 0.0001$). PTX3 levels were not correlated with SLEDAI-2K, but with leukocyte-associated variables. Cross-sectional analysis revealed a slight negative correlation between PTX3 and IFN-α ($r=-0.154$, $p=0.017$). Patients with no detectable IFN-α (<1 U/ml) had however significantly higher levels of PTX3 (median 2.7 ng/ml) compared to patients with IFN-α >1 U/ml (median 2.1 ng/ml; $p=0.01$).

In vitro experiments showed IFN-α dependent inhibition of stimulated PTX3 production in healthy blood donor PMBC. No such effect was observed in neutrophils.

Conclusion:

Average PTX3 levels are lower in SLE patients compared to controls. IFN-α partly inhibits leukocyte PTX3 production *in vitro*, and its inverse correlation with PTX3 in SLE implies that IFN-α mediated suppression of PTX3 synthesis also occurs *in vivo*. Since pentraxins have a suggested protective role in SLE, these findings are of interest regarding the handling of apoptotic material and the pathogenesis of SLE.

Disclosure: L. Wirestam, None; **H. Enocsson**, None; **C. Sjöwall**, None; **T. Skogh**, None; **M. L. Eloranta**, None; **L. Rönnblom**, None; **J. Wetterö**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/interferon-alpha-mediated-lowering-of-pentraxin-3-levels-in-systemic-lupus-erythematosus

Abstract Number: 804

Prolactin Induces Interferon Regulatory Factor 1 Activation and Histone H4 Hyperacetylation in Primary Monocytes Comparable to Changes Seen in Monocytes from Systemic Lupus Erythematosus Patients

Yiu Tak Leung[1], Kathleen E. Sullivan[2], Kelly Maurer[3], Li Song[4] and Lihua Shi[3], [1]Medicine/Rheumatology, University of Pennsylvania, Philadelphia, PA, [2]Allergy Immunology, The Children's Hospital of Philadelphia, Philadelphia, PA, [3]Immunology ARC 1216, The Children's Hospital of Philadelphia, Philadelphia, PA, [4]Allergy Immunology, Children's Hospital of Philadelphia, Philadelphia, PA
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Session Type: ACR Poster Session A
Session Time: 9:00AM-11:00AM

Background/Purpose:

: Epigenetic changes have been described in systemic lupus erythematosus (SLE) and offer a potential explanation for the chronicity of disease. We previously found a global increase in histone H4 acetylation (H4ac) in SLE monocytes and transcription factor motif analysis found 63% of genes with increased H4ac had potential interferon regulatory factor (IRF) 1 binding sites within the 5kb upstream region. We identified specific H4 lysine acetyl groups with significant hyperacetylation in SLE monocytes, as well as an imbalance in specific histone acetyltransferases (HATs) and histone deacetylases (HDACs) in favor of hyperacetylation. We then demonstrated that IRF1-overexpression can drive H4 hyperacetylation and showed IRF1 recruitment of HAT p300 to target genes with increased IRF1 binding and pathological expression in SLE monocytes.

IRF1 is highly inducible by prolactin, a hormone implicated in the pathogenesis of SLE: hyperprolactinemia has been reported in 15-33% of SLE patients as compared to 0.4-3% of controls. Prolactin upregulation of IRF1 can lead to H4ac in Nb2 T cells, representing a potential pathological pathway in SLE. Prolactin-induced IRF1 activation in primary monocytes and THP1 cells was examined, with the aim to identify IRF1 interactions with histone acetyltransferases (HATs) and histone deacetylases (HDAC) leading to pathological H4ac in SLE.

Methods:

Flow cytometry for acetylated H4 lysines: K5, K8, K12, K16 were run on the Accuri C6 with isotype controls. H4ac was defined in primary monocytes from 12 normal males under both unstimulated and prolactin-stimulated conditions. Real-time quantitative reverse transcription polymerase chain reaction (qRT-PCR) evaluated HAT/HDAC expression in monocytes. IRF1 activation by prolactin in primary monocytes was studied by immunofluorescence confocal microscopy. Further interactions of IRF1 and HATs/HDACs were studied in THP1 cells by ChIP analysis.

Results:

Flow cytometry found significantly increased total H4ac, H4K5, H4K8, H4K12, and H4K16 acetylation (p = 0.01, 0.01, 0.01, 0.002, 0.04) in monocytes stimulated at prolactinoma levels (2000 ng/mL); acetylation at total H4ac, H4K5, H4K8, H4K12, and H4K16 was also increased at pregnancy levels (200 ng/mL).

Immunofluorescence showed translocation of IRF1 from the cytoplasm to the nucleus in prolactin-stimulated primary monocytes at both 200 ng/mL and 2000 ng/mL cells by 1 hr, demonstrating IRF1 activation.

qRT-PCR studies of HAT/HDAC expression patterns found increases in PCAF and ATF2 expression monocytes stimulated by prolactin that was dose dependent (p = 0.12 and 0.05). This is comparable to the increase in PCAF expression that was seen in SLE. Additionally, ChIP assays in THP1 cells suggested that prolactin-stimulation can recruit p300 to IRF1 and prolactin target genes.

Conclusion:

These data demonstrate that prolactin stimulation of monocytes induces IRF1 activation and a pattern of acetylated H4 that corresponds to the changes seen in SLE. This helps to explain the known association of prolactinomas with SLE. The identification of candidate HATs that associate with IRF1 in the context of prolactin stimulation may provide for potential therapeutic targets in SLE.

Disclosure: Y. T. Leung, None; **K. E. Sullivan**, Baxter, 2,Immune Deficiency Foundation, 5,Janssen Pharmaceutica Product, L.P., 5; **K. Maurer**, None; **L. Song**, None; **L. Shi**, None.

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Abstract Number: 805

Interferon Activity in Early and Established SLE: Interferon Score Is Lower in Early Disease and Not Seen without Antibodies to Extractable Nuclear Antigens

Alaa A A Mohamed[1,2,3], Md Yuzaiful Md Yusof[1,4], Yasser El-Sherbiny[5], Paul Emery[5,6] and Edward M. Vital[2,5], [1]Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds, Leeds, United Kingdom, [2]NIHR Leeds Musculoskeletal Biomedical Research Unit, Leeds Teaching Hospitals NHS Trust, Leeds, United Kingdom, [3]Rheumatology and Rhabilitation, Assiut University, Assiut, Egypt, [4]NIHR Leeds Musculoskeletal Biomedical Research Unit,Leeds Teaching Hospital NHS Trust, Leeds University, Leeds, United Kingdom, [5]Leeds Institute of Rheumatic and Musculoskeletal Medicine, Leeds University, Leeds, United Kingdom, [6]3. NIHR Leeds Musculoskeletal Biomedical Research Unit, Leeds Teaching Hospital NHS Trust, Leeds University, Leeds, United Kingdom

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Background/Purpose:

SLE patients have increased expression of interferon-stimulated genes (ISG) and multiple autoantibodies. Some patients initially present with early incomplete SLE (E-ILE) with ANA but not full SLE criteria. These patients may or may not progress to established SLE. To understand progression of autoimmunity, we compared autoantibodies and ISG expression between E-ILE and established SLE.

Methods:

We studied patients with SLE (≥4 ACR/SLICC criteria (n=86)), E-ILE (1-3 ACR/SLICC criteria including ANA <1 year (n=23)), RA (n=19), and age and sex matched healthy controls (n=20). 33 Type 1 ISGs were analysed in PBMCs using TaqMan®. Relative expression was ln-transformed and normalised to HC (value - HC mean / HC SD) and summed to give a 33-gene-IFN score. Antibodies to dsDNA, Ro52, Ro60, La, Sm, RNP and Chromatin were analysed using Bioplex-2000. Two-way ANOVA was used to compare IFN score vs. presence of extractable nuclear antigens (ENA) between groups.

Results:

Descriptively there was a strong relationship between interferon score and diagnosis of SLE. Mean (95% CI) IFN score was 3.0 (-12.2, 18.2) in RA, which was not substantively different from the HC mean (0). IFN score was considerably higher than HC in SLE [45.6 (34.8, 56.3)]. In E-ILE, IFN score was intermediate [22.3 (0.9, 43.7)]. Formal statistical comparisons were not attempted due to the variation in sample sizes between the groups.

There was a strong relationship between autoantibody status and interferon score. Interferon score was significantly higher in those with positive ENA antibodies (all $p<0.05$) but did not differ according to anti-dsDNA status (Fig 1).

This relationship between ENA status and interferon score was stronger in E-ILE (mean score ENA negative -25.6 vs. positive 47.8) than in established SLE (negative 22.9 vs positive 59.7; interaction=0.099; Fig 2). Indeed, in ENA-negative E-ILE, mean interferon score was significantly lower than HC ($p=0.027$).

Conclusion:

ISG expression is increased in E-ILE in patients with antibodies to ENA, but is low in their absence. In established SLE, ISG expression is higher, and interferon activity is increased even in the absence of ENA antibodies. This suggests that during progression to established SLE there is increasing dysregulation of interferon activity. This may be due to: diversification of the antibody repertoire during progression (not measured by this assay), or because in established SLE IFN becomes stimulated by other immune mediators or tissue damage. Longitudinal follow up will help resolve this question.

Disclosure: A. A. A. Mohamed, None; **M. Y. Md Yusof**, None; **Y. El-Sherbiny**, None; **P. Emery**, Janssen R & D, LLC, 2; **E. M. Vital**, Roche Pharmaceuticals, 2,Roche Pharmaceuticals, GSK, UCB, Chugai, 5.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/interferon-activity-in-early-and-established-sle-interferon-score-is-lower-in-early-disease-and-not-seen-without-antibodies-to-extractable-nuclear-antigens

Abstract Number: 806

STAT1 Activation Promotes TLR8 Overexpression and Facilitates Mirokine Signaling Via Exosomes Containing a Mir-21 Endogenous Ligand: A Novel Innate Inflammatory Pathway in Systemic Lupus Erythematosus

Giancarlo R. Valiente[1,2], Nicholas A. Young[2], Lai-Chu Wu[3,4], Jeffrey Hampton[5], Mary Severin[6], Amy Lovett-Racke[6] and Wael N. Jarjour[7], [1]Medical Scientist Training Program, The Ohio State University College of Medicine, Columbus, OH, [2]Rheumatology & Immunology, The Ohio State University Wexner Medical Center, Columbus, OH, [3]Immunology and Rheumatology, The Ohio State University Wexner Medical Center, Columbus, OH, [4]Biological Chemistry and Pharmacology, The Ohio State University College of Medicine, Columbus, OH, [5]Immunology and Rheumatoloty, The Ohio State University Wexner Medical Center, Columbus, OH, [6]Microbial Infection and Immunity, The Ohio State University College of Medicine, Columbus, OH, [7]Dept of Rheumatology/Medicine, The Ohio State University Wexner Medical Center, Columbus, OH
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Session Type: ACR Poster Session A
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Background/Purpose:

The adaptive arm of the immune system plays a significant role in the pathophysiology of Systemic Lupus Erythematosus (SLE). However, recent studies suggest that innate immunity may also serve an important pathological role. Toll-like Receptor-8 (TLR8) is an innate immunity receptor that binds to single-stranded viral RNA sequences that is regulated by the transcription factor STAT1 and is also upregulated by estrogen. Intriguingly, recent work has uncovered that miR-21 can act as an endogenous TLR8 ligand in cancer cells via an exosomal delivery approach.

Methods:

Microarray data was acquired from a publicly available database. Peripheral Blood Mononuclear Cells (PBMCs) from patients meeting the ACR 1997 criteria for SLE or healthy controls were treated with estrogen, miR-21, and a known TLR8 agonist. To examine the functional significance of STAT1 and Estrogen Receptor-a (ERa), siRNA targeted against these proteins was utilized. Samples were collected at various time points for qPCR or Western blot analysis. Liposomal complexes containing fluorescently-labeled miR-21-Cy3 (red) were incubated with THP-1 cells; cells were imaged in real time using fluorescent microscopy and TLR8 expression was measured by qPCR.

Results:

Microarray data indicated an over 4-fold increase in myeloid cell STAT1 expression in patients with SLE as compared to healthy subjects. Estrogen stimulated STAT1 expression and phosphorylation of STAT1 were enhanced at the protein level in primary human cells and cell lines. Using siRNA to target either STAT1 or ERa, estrogen-mediated TLR8 induction was inhibited. Stimulation with miR-21 not only greatly induced expression of STAT1 but TLR8 expression was also significantly upregulated.

Conclusion:

Analogous to a cytokine or chemokine, exosome-encapsulated miR-21 can function as an inflammatory signaling molecule, or miRokine, by virtue of being an endogenous ligand for TLR8. Collectively, our data elucidates a novel innate inflammatory pathway in SLE by showing that estrogen-mediated expression of STAT1 promotes TLR8 expression, which can subsequently be activated and further stimulated by miR-21. Our data suggest that endogenous TLR ligands functioning through miRokine signaling may significantly influence autoimmune inflammation. Future focus of this work will be to identify additional agonists and to block exosomal miRNA signaling using antagomiR-based silencing.

References:

1. Fabbri, M., et al., *MicroRNAs bind to Toll-like receptors to induce prometastatic inflammatory response.* Proc Natl Acad Sci USA, 2012. **109**(31): p. E2110-6.

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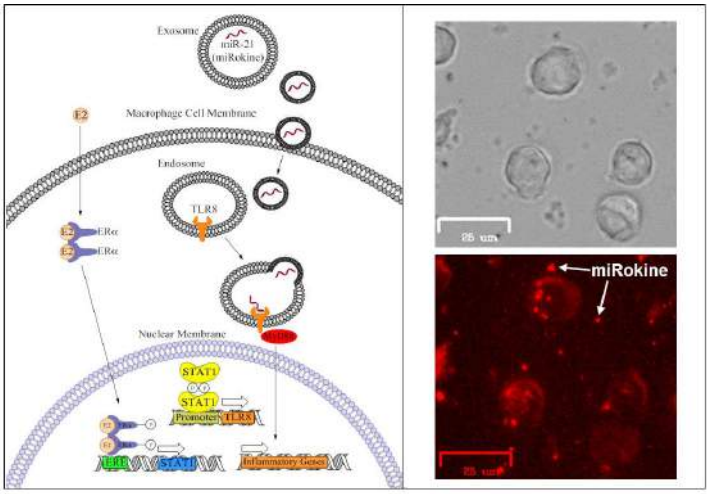

Disclosure: G. R. Valiente, None; **N. A. Young**, None; **L. C. Wu**, None; **J. Hampton**, None; **M. Severin**, None; **A. Lovett-Racke**, None; **W. N. Jarjour**, None.

Abstract Number: 807

High Levels of Serum IFN-Alpha Mark a Subgroup of SLE Patients with Distinct Immunophenotypic Features and Hyperresponsiveness to Toll-like Receptor Stimulation

Uma Thanarajasingam[1], Mark A. Jensen[2], Jessica M. Dorschner[3] and Timothy B. Niewold[3], [1]Division of Rheumatology, Mayo Clinic, Rochester, MN, [2]Divsion of Rheumatology and Department of Immunology, Mayo Clinic, Rochester, MN, [3]Division of Rheumatology and Department of Immunology, Mayo Clinic, Rochester, MN

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SESSION INFORMATION

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Session Title: Systemic Lupus Erythematosus - Human Etiology and Pathogenesis Poster I

Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose:

IFN-alpha is a pathogenic factor in SLE. High serum interferon activity (IFN-high) marks a subgroup of SLE patients strongly associated with increased disease severity and autoantibody formation. Genetic variations associated with risk for SLE are enriched within this subgroup, however differences in the cellular immune system between IFN-high and IFN-low patients remain largely unknown. In this study, we sought to better characterize the IFN-high and IFN-low subgroups in human SLE by studying relevant immune cell subsets, and stimulated cytokine responses post whole blood stimulation by Toll-like receptor (TLR) agonists.

Methods:

SLE patients (n= 25) meeting ACR criteria for SLE and healthy controls (n=10) were recruited. Serum IFN-activity scores were calculated using the WISH assay, and used to bin patients as IFN-high and IFN-low. Demographic and serologic data were analyzed. Immune cell subsets including plasmacytoid dendritic cells (pDCs) and $CD19^{+}CD24^{hi}CD38^{hi}$ regulatory B cells (Bregs) were quantitated by flow cytometry of whole blood. Microspheres allowed for the quantitation of absolute numbers of CD24 and CD38 receptors on Bregs. Whole blood was dispensed into tubes coated with the TLR agonists LPS, CpG and R848 (Tru-Culture.) The stimulated IFN-alpha production was measured by WISH. Flow and Tru-Culture stimulation were performed within 6 hours of less of phlebotomy.

Results:

Of the 25 patients studied, 9 were IFN-high and 16 were IFN-low. Compared to IFN-low, IFN-high patients were younger (39.0 versus 46.5 years) and had more autoantibodies such as anti-Sm and anti-dsDNA, similar to previous studies. Medication usage was not significantly different between groups. The frequency of circulating pDCs was significantly lower in IFN-high SLE patients as compared to controls ($p=0.0159$). The frequency of Bregs and their surface expression of CD38 was also lower in IFN-high compared IFN low and controls. With respect to TLR signaling, both IFN-high and IFN-low SLE patients responded more robustly to R848 stimulation than controls. Interestingly, IFN-high patients responded more dramatically to LPS than IFN-low SLE patients ($p<0.05$), and controls ($p=0.05$).

Conclusion:

We have observed clinical and novel biologic differences between IFN-high and low SLE subgroups. The fact that pDC counts were only reduced in the high IFN patients would suggest trafficking out of the circulation and into inflamed tissue prior to IFN production. We find decreased Breg numbers and decreased CD38 expression in the IFN-high patients, which could indicate decreased regulatory potential from this cell type in high IFN SLE. Finally, our study demonstrates that IFN-high patients are significantly more responsive to TLR4 stimulation– a novel finding that may shed light on differential responses to SLE therapies. Further studies of Breg function in SLE and the stimulated inflammatory cytokine response are ongoing.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/high-levels-of-serum-ifn-alpha-mark-a-subgroup-of-sle-patients-with-distinct-immunophenotypic-features-and-hyperresponsiveness-to-toll-like-receptor-stimulation

Abstract Number: 808

Heritable Endotheliopathy and ApolipoproteinL1 Risk Traits in SLE

Ashira Blazer[1], Andrew Markham[2], Sara Rasmussen[3], Jill P. Buyon[4], H. Michael Belmont[5], Shilpi Mehta-Lee[6], Janet Nwaukoni[4], Peter M. Izmirly[7] and Robert Clancy[4], [1]Division of Rheumatology, NYU School of Medicine, New York, NY, [2]Medicine, New York University School of

Medicine, New York, NY, [3]Department of Medicine, Division of Rheumatology, New York University School of Medicine, New York, NY, [4]Medicine, Division of Rheumatology, New York University School of Medicine, New York, NY, [5]Hosp for Joint Disease, New York, NY, [6]Obstetrics and Gynecology, New York University School of Medicine, New York, NY, [7]Rheumatology, NYU School of Medicine, New York, NY

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Background/Purpose:

With higher prevalence of renal and cardiovascular diseases (CVD), as well as HTN, African American (AA) SLE patients experience accelerated damage accrual and excess morbidity and mortality. Genome wide association studies have identified two Apolipoprotein L1 (APOL1) risk variants (RV) in individuals of African Ancestry which confer an evolutionary advantage in resisting African Trypanosomiasis, but an increased risk of renal failure and CVD in homozygous carriers across many disease states. As an innate immune factor, APOL1 expression is regulated by inflammatory conditions. This study focused on RV dependent clinical correlates in SLE, and the interaction between the SLE inflammatory milieu and APOL1 expression.

Methods:

Genotyping was done by conventional PCR/sequencing in 93 AA SLE subjects. Chart review furnished clinical data including demographics, comorbidities, medications, and laboratory values. Serum sE-selectin (as a marker CVD risk) was measured by ELISA and mean concentrations stratified by carrier status (ancestral, RV heterozygous, RV homozygous). APOL1-genotyped primary human endothelial cells (ECs) isolated from healthy AA fetal cord tissue were used to address inflammation-dependent APOL1 expression. Inflammatory conditions present in SLE were simulated using IFNα and supernatants from TLR stimulated macrophages. PCR products were genotyped to establish concordance with chromosomal DNA.

Results:

The ancestral (WT/WT), RV heterozygous, and RV homozygous groups comprised 37.6%, 49.4%, and 13% of the cohort respectively. Subjects were AA (100%) and predominantly female (90.3%). There were no significant differences in age, SLE duration or disease activity (SLEDAI scores), current proteinuria, or history of nephritis among the groups. However, a significantly increased risk of hypertension in heterozygous (OR: 3.6 p: 0.01) and homozygous (OR: 5.6 p: 0.04) RV subjects vs ancestral controls, supported an incomplete dominance model. In the RV heterozygous and homozygous groups, increased sE-selectin concentration was associated with SLEDAI >8, increased dsDNA, and decreased C4 (p= 0.009, 0.003, 0.03 respectively). In contrast, there were no associations between the above parameters and sE-selectin in the ancestral group (p= 0.93, 0.53, 0.57 respectively). Primary EC cultures from 5 healthy subjects (WT/WT= 1, RV/WT= 2, RV/RV= 2) were plated in serum free media, IFN-α, or supernatant from macrophages previously activated with ssRNA, hY3 (SLE-relevant TLR 7/8 agonist). Cells were > 95% CD31 positive by FACS analysis. At 4 hours IFN-α alone, and macrophage supernatants increased APOL1 expression 9.21 fold (+/-1.8; p= 0.001) and 3.99 fold (+/-0.61; p= 0.0004) vs no treatment, respectively. RV heterozygous cells showed biallelic expression on genotyping of the qPCR product. Fold increase of sE-selectin was 2.24 (+/-0.2) (p=0.009) in response to IFNα.

Conclusion:

Chronic inflammation in SLE may lead to RV over-expression in EC and resultant systemic endothelial dysfunction. In AA SLE patients, tighter inflammatory control may be a step forward in preventing APOL1 RV-related damage in vascular beds.

Disclosure: A. Blazer, None; **A. Markham**, None; **S. Rasmussen**, None; **J. P. Buyon**, None; **H. M. Belmont**, None; **S. Mehta-Lee**, None; **J. Nwaukoni**, None; **P. M. Izmirly**, None; **R. Clancy**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/heritable-endotheliopathy-and-apolipoproteinl1-risk-traits-in-sle

Abstract Number: 809

Patients with SLE Who Are Anti-Factor Xa IgG Positive Are Less Likely to Have Atherosclerotic Plaque

Claire-Louise Murphy[1], Sara Croca[1], Bahar Artim-Esen[2], Laura Hanns[3], Charis Pericleous[1], Thomas McDonnell[1], Yiannis Ioannou[4], David A. Isenberg[1], Anisur Rahman[1] and Ian Giles[5], [1]Rayne Institute, Centre for Rheumatology Research, UCL Division of Medicine, London, United Kingdom, [2]Department of Internal Medicine, Division of Rheumatology, Istanbul University, Istanbul Faculty of Medicine, Istanbul, Turkey,

[3]Rheumatology, Arthritis Research UK Centre for Adolescent Rheumatology, UCL Division of Medicine, London, United Kingdom, [4]Rayne Institute, Arthritis Research UK Centre for Adolescent Rheumatology, UCL Division of Medicine, London, United Kingdom, [5]Rayne Intitiute, Centre for Rheumatology Research, UCL Division of Medicine, London, United Kingdom

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Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose:

Patients with SLE have an increased risk of cardiovascular disease (CVD), which is not fully explained by traditional risk factors and may be mediated by systemic inflammation and autoantibodies. Increasing interest has focussed upon the involvement of pro-coagulant serine proteases (SP), thrombin (Thr) and Factor (F)Xa, in atherosclerotic plaque formation. These SP have extended cellular/inflammatory effects beyond coagulation through their activation of protease activated receptors (PARs). Direct inhibitors of FXa and Thr have been shown to reduce pro-inflammatory effects and stabilise atherosclerotic plaque in ApoE mice. Levels of anti-FXa and anti-Thr IgG are raised in patients with SLE compared with healthy controls, but the effects of these IgG on atherosclerosis are unknown. Here we explore associations between presence and number of sub-clinical atherosclerotic plaques detected by a vascular ultrasound study in 100 patients with SLE and the presence of anti-FXa and/or anti-Thr in the same patients.

Methods:

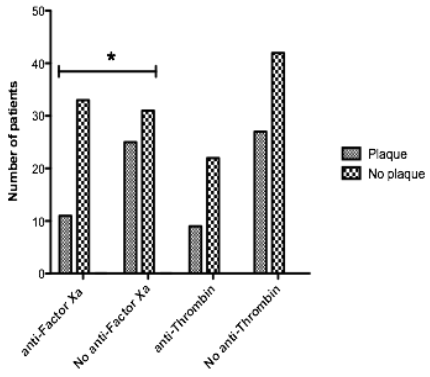
Carotid and femoral arteries of 100 patients fulfilling ACR criteria for SLE but with no history of previous CVD were scanned by ultrasound. We recorded presence of plaque, number of plaque sites, total plaque area and intima media thickness. Serum samples from these patients, taken at or near the time of scanning, were tested for anti-FXa and anti-Thr IgG by ELISA. Statistical analysis of the association of antibody positivity/negativity and presence/absence of plaque was determined by chi^2 test.

Results:

Of the 100 patients, 95% were female with mean age of 45.2 (range 20-66, SD 12.4) years. Overall, 36% had plaque and 64% had no plaque. Anti-FXa IgG were found in 44% and anti-Thr IgG in 31% of all patients. Anti-FXa IgG positivity was seen in 33/64 (52%) of patients without plaque and 11/36 (31%) of patients with plaque ($p<0.04$). Among the 36 patients with plaque, the number of plaque sites per patient was lower in anti-FXa positive than in anti-FXa IgG negative patients ($p<0.02$). Although anti-Thr IgG positivity was also higher in patients without plaque (22/64 = 39%) compared to patients with plaque (9/36 = 25%), this difference did not reach statistical significance ($p=0.3$). There was no association between anti-Thr positivity and number of plaque sites.

Conclusion:

Patients with SLE who were positive for anti-FXa IgG had reduced atherosclerotic plaque burden (presence and total number of sites) compared with patients who were anti-FXa IgG negative. A similar relationship however, was not found between anti-Thr IgG and plaque. Further research is now required to determine whether anti-FXa IgG may be protective against the pro-atherogenic effects of FXa in patients with SLE.



Patients with SLE and atherosclerotic plaque are less likely to have Factor Xa antibodies than patients with SLE without atherosclerotic plaque (* p value<0.0422). There was no association between anti-thrombin positivity and atherosclerotic plaque.

Disclosure: C. L. Murphy, None; **S. Croca**, None; **B. Artim-Esen**, None; **L. Hanns**, None; **C. Pericleous**, None; **T. McDonnell**, None; **Y. Ioannou**, None; **D. A. Isenberg**, None; **A. Rahman**, None; **I. Giles**, None.

less-likely-to-have-atherosclerotic-plaque

Abstract Number: 810

Human Parvovirus B19 Nonstructural Protein 1 (NS1) Helicase Breaks Tolerance to Self dsDNA: A Model for Viral Induction of Autoimmunity

Heidi Pirttinen[1], Kanoktip Puttaraksa[1], Robert J. Lagier[2], Stanley J. Naides[3] and **Leona Gilbert**[1], [1]Department of Biological and Environmental Science, University of Jyväskylä, Jyväskylä, Finland, [2]Research Support, Alameda, Quest Diagnostics Alameda, Alameda, CA, [3]Immunology, Quest Diagnostics Nichols Institute, San Juan Capistrano, CA

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Background/Purpose: B19 virus (B19V) is common, infects all ages, and is associated with various clinical syndromes including SLE-like autoimmunity. We previously demonstrated that B19 NS1, a superfamily 3 (SF3) viral helicase, is expressed in human cells non-permissive for virion production, damages host cell DNA by single strand nicking and bulky adduct formation, induces apoptosis, and produces apoptotic bodies (ApoBods) that are internalized by phagocytic cells. We hypothesized that ApoBods containing B19 NS1-modified DNA could break tolerance to self DNA. We developed an *in vivo* mouse model in which mice were inoculated with B19 NS1-induced ApoBods; we then examined serum dsDNA antibody production and tissue damage.

Methods: A baculovirus expression vector was used to tranduce B19 NS1 in HEp-G2 cells. ApoBods were harvested from culture supernatants at 72 hours post transduction. ApoBods generated by an inducer of apoptosis, staurosporine, were used as a positive control for ApoBods. BALB/c mice were untreated or injected subcutaneously with PBS, or 25 µg, 50 µg or 100 µg, respectively, of B19 NS1-induced ApoBods or staurosporine-induced ApoBods. Pristane, known to induce a lupus-like murine disease, was used as a positive control for autoimmunity induction. Serum dsDNA antibodies were examined with a *Crithidia luciliae* indirect immunofluorescence assay (IFA) using an anti-mouse IgG conjugate and quantitated with an in-house dsDNA ELISA. Paraffin-embedded tissue sections were examined for immune cell infiltration and damage.

Results: The *Crithidia* assay demonstrated positive kinetoplast and nuclear fluorescence staining with sera from mice treated with pristane, staurosporine ApoBods, or B19 NS1 ApoBods. dsDNA antibody by ELISA from 100 µg B19 NS1 ApoBod treated mice was significantly higher than untreated ($p<0.0001$), PBS-treated ($p<0.0001$), 100 µg Staurosporine ApoBod-treated ($p<0.0006$), and pristane-treated mice ($p<0.02$). Tissue histology revealed immune cell infiltration in kidney, brain, liver, and heart in treated groups, but not in untreated or PBS control groups.

Conclusion: B19 NS1 ApoBod inoculation induces dsDNA autoantibodies and tissue damage. While B19 NS1 ApoBod-, staurosporine ApoBod-, and pristane-treated mice all had tissue damage and dsDNA antibody by *Crithidia* testing, the B19 NS1 ApoBod-treated group had significantly elevated dsDNA antibody by ELISA compared to the other groups. This study supports the hypothesis that B19V and possibly other SF3 helicase-expressing viruses, such as Epstein-Barr virus, can induce tissue damage and dsDNA antibody production above that seen with ApoBods alone; dsDNA antibody production may be induced through helicase modification of self DNA.

Disclosure: H. Pirttinen, None; **K. Puttaraksa**, None; **R. J. Lagier**, None; **S. J. Naides**, None; **L. Gilbert**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/human-parvovirus-b19-nonstructural-protein-1-ns1-helicase-breaks-tolerance-to-self-dsdna-a-model-for-viral-induction-of-autoimmunity

Abstract Number: 811

Antibody Response to Periodontogenic Bacterium Aggregatibacter Actinomycetemcomitans and Lupus

Harini Bagavant[1], Nina Wolska[2], Stan Kamp[3], Joel M. Guthridge[1], Judith A. James[4], Joan T. Merrill[3] and Umesh S Deshmukh[1], [1]Arthritis and Clinical Immunology, Oklahoma Medical Research Foundation, Oklahoma City, OK, [2]Arthritis and Clinical Immunology Program, Oklahoma Medical Research Foundation, Oklahoma City, OK, [3]Clinical Pharmacology, Oklahoma Medical Research Foundation, Oklahoma City, OK, [4]Oklahoma Medical Research Foundation, Oklahoma City, OK

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Background/Purpose: Periodontitis is an inflammation of the soft and hard tissues supporting the tooth. *Aggregatibacter actinomycetemcomitans (Aa)*, a gram negative bacterium, is strongly associated with the aggressive form of periodontitis, particularly in young females. *Aa* and its toxins induce apoptotic cell death in immune cells and hence can modulate the mucosal immune responses. In this study, we tested the hypothesis that an infection with *Aa* is associated with increased autoimmunity in lupus patients.

Methods: Circulating antibodies to *Aa* are indicative of an ongoing or prior infection with the organism. Thus, serum antibodies to *Aa* in lupus patients and controls from the Oklahoma cohort of rheumatic disease were measured by ELISA. The lupus patients with anti-*Aa* antibody units higher than mean+2SD of controls were classified as positive for anti-*Aa*. To determine the association between anti-*Aa* and autoantibodies to lupus-associated antigens (dsDNA, Ro/SSA, La/SSB, Sm, RNP, Ribosomal P, and Jo-1), contingency tables were constructed and statistical significance calculated using Fisher's exact test. Neutrophil extracellular traps (NETs) are suspected to be the source of autoantigens in lupus. Thus, the ability of *Aa* to induce NETosis was tested by using bone marrow derived neutrophils from lupus-prone mice. NET formation was evaluated by staining for DNA and citrullinated histones.

Results: A significant number of lupus patients (128/534, 23.97%) were positive for anti-*Aa* antibodies, compared to controls (1/21; 4.76%; p=0.037). Stratification of lupus patients by race showed that African American patients had significantly higher anti-*Aa* antibody titers as compared to patients of Caucasian origin. However, regardless of the race, anti-*Aa* antibody positivity was significantly associated with higher anti-dsDNA (p=0.002). No association was observed with other autoantibody specificities. Incubation of neutrophils with *Aa* readily induced NETosis.

Conclusion: This study shows that an ongoing or prior infection with the periodontogenic bacterium *Aa* is associated with increased anti-dsDNA in lupus patients. Our data suggests the possibility that *Aa* induced NETosis might be involved in the amplification of anti-dsDNA response in lupus patients. Considering that the incidence of periodontitis is higher in African Americans, our study provides a strong rationale to investigate the possible link between periodontal disease and lupus in African American patients

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Disclosure: H. Bagavant, None; **N. Wolska**, None; **S. Kamp**, None; **J. M. Guthridge**, None; **J. A. James**, None; **J. T. Merrill**, None; **U. S. Deshmukh**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/antibody-response-to-periodontogenic-bacterium-aggregatibacter-actinomycetemcomitans-and-lupus

Abstract Number: 812

SLAMF3 Mediated Co-Stimulation Promotes Activation of the IL-2/IL-2R/STAT5 Pathway and Regulatory T Cells Differentiation in Human Naïve CD4+ T Cells – Implications for SLE

Denis Comte[1,2], Maria P. Karampetsou[1], Katalin Kis-Toth[1], Nobuya Yoshida[1], Julie Solomon[1], Vasileios C. Kyttaris[1] and George C. Tsokos[1], [1]Division of Rheumatology, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, [2]Division of Immunology and Allergy, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland

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Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose: SLE is a multisystem autoimmune disease that displays quantitative and qualitative deficiencies of regulatory T cells (Treg), notably because of a compromised IL-2 production. Signaling lymphocyte activator molecule receptor family 3 (SLAMF3) is a type I transmembrane receptor implicated in co-regulatory mechanism of T cell activation. We examined the effects of SLAMF3 mediated co-stimulation on the IL-2 response of peripheral $CD4^+$ T cells from SLE patients.

Methods: T cells or naive CD4+ T cells isolated from SLE patients and matched controls were stimulated with plate bound anti-CD3, anti-SLAMF3 and/or anti-CD28 antibodies. Cells were then stained for surface markers (CD4, CD8, CCR7, CD45RA, CD25, CD122, CD127, SLAMF3), for intracellular cytokines (IL-2) and/or transcription factors (pSTAT5, FoxP3) and analyzed by flow cytometry. CD25 mRNA levels

were evaluated by qPCR, and pSTAT5/STAT5 ratio by western immunoblots. Cells proliferation was determined by CFSE dilution. Treg differentiation was performed on naive $CD4^+$ T cells cultured under Treg polarizing conditions (in the presence of IL-2 and TGFb) for 6 days. Suppression capacity was determined by assessing the proliferation of autologous CFSE-labeled T cells in the presence of induced Treg.

Results: Stimulation of naive $CD4^+$ T cells with anti-CD3/anti-SLAMF3 upregulated surface CD25 (IL-2Ra) and CD122 (IL-2Rb), at higher level compared to anti-CD3/anti-CD28 activation. Anti-CD3/anti-SLAMF3 co-stimulation of naive $CD4^+$ T cells led to increased phospho-STAT5 (pSTAT5) levels compared to anti-CD3/anti-CD28 activation. Although naive $CD4^+$ T cells from SLE patients displayed decreased pSTAT5 levels compared to control subjects upon anti-CD3 or anti-CD3/anti-CD28 stimulation, co-stimulation of SLE T cells with anti-SLAMF3 restored pSTAT5 to a normal level. The effect of SLAMF3 on the IL-2/IL-2R/STAT5 signaling pathway does not occur through increased IL-2 production, as the percentage of IL-2 producing cells remained comparable between anti-CD3 and anti-CD3/anti-SLAMF3 mediated co-stimulation. Exogenous IL-2 increased proliferation of anti-CD3/anti-SLAMF3-activated $CD4^+$ T cells compared to anti-CD3/anti-CD28 stimulation. Naive $CD4^+$ T cells activated with anti-CD3/anti-SLAMF3 under Treg polarizing condition expressed high levels of FoxP3 and CD25, low level of CD127, and, more importantly, exhibit a potent suppressive effect.

Conclusion: SLAMF3-mediated co-stimulation enhances naive $CD4^+$ T cell response to IL-2 in SLE patients and promotes Treg generation. These results suggest that using a monoclonal antibody directed against SLAMF3 may increase the response to IL-2 in conditions where its availability is compromised, like SLE.

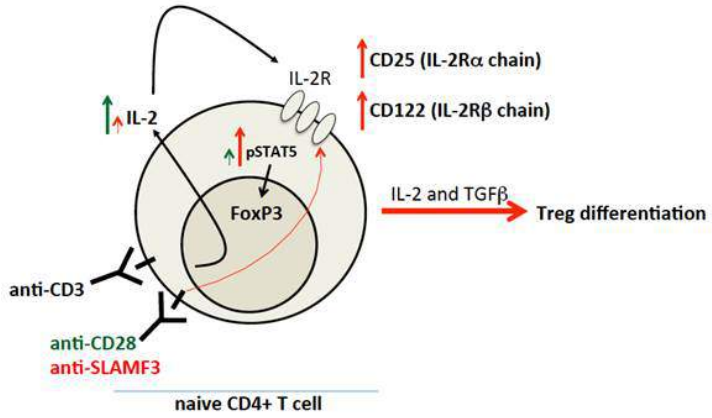

Figure 1. SLAMF3 mediated co-stimulation promotes the IL-2 response of naive CD4+ T cells

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Disclosure: D. Comte, None; **M. P. Karampetsou**, None; **K. Kis-Toth**, None; **N. Yoshida**, None; **J. Solomon**, None; **V. C. Kyttaris**, None; **G. C. Tsokos**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/slamf3-mediated-co-stimulation-promotes-activation-of-the-il-2il-2rstat5-pathway-and-regulatory-t-cells-differentiation-in-human-naive-cd4-t-cells-implications-for-sle

Abstract Number: 813

Expression of Inducible Costimulator Ligand (ICOSL) on CD4+ T Cells in Patients with Systemic Lupus Erythematosus

Minyoung Her[1], Dongyook Kim[1], JeongHa Park[2] and Donghoon Han[3], [1]Department of Internal medicine, Division of Rheumatology, Inje university, Busan Paik hospital, Busan, South Korea, [2]Wallas Memorial Baptist Hospital, Busan, South Korea, [3]Inje university, Busan Paik hospital, Busan, South Korea

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Session Time: 9:00AM-11:00AM

Background/Purpose: Inducible costimulator (ICOS) is an immunostimulatory receptor that belongs to the CD28/CTLA4 family. ICOSL (ICOS ligand), which belongs to the B7 family, is the ligand for ICOS and is crucial for T helper cell and B cell differentiation. The costimulatory signal of ICOS/ICOSL in T cell/antigen presenting cell interactions might be involved the pathogenesis of systemic lupus erythematosus (SLE). Clinical trial of monoclonal antibody targeting ICOSL in SLE is underway. However, the expression of ICOSL and the role of ICOS/ICOSL signaling in

the interactions between T cells in the pathogenesis of SLE are not well characterized. We investigate the expression and function of the ICOSL on T cells in patients with SLE

Methods: To investigate the expression of the ICOSL on CD 4+ T cells, we evaluated surface ICOSL expression on CD4+ T cells in peripheral blood (PB) from 24 patients with SLE, PB from 15 healthy controls using flow cytometry. We also evaluated soluble ICOSL expression in the plasma of 24 patients with SLE and 14 healthy controls. To explore the role of ICOS/ICOSL signaling in CD4+ T cells in SLE, we examined CD4+ T cell proliferation from seven patients with SLE. After blockade of the ICOS/ICOSL signal using anti-ICOSL antibody or ICOS immunoglobulin, CD4+ T cell proliferation in response to treatment with anti-CD3 antibody was evaluated. During the proliferation assay, cytokine levels (ILF-gamma, TNF-alpha and IL-17) in the CD4+ T cell culture supernatants were assessed.

Results: The proportion of ICOSL+ CD 4+ T cells was significantly increased in the PB of patients with SLE (13.6 ± 7.6%, range 3~29%) as compared with the level observed in the PB of healthy controls (1.3 ± 1.2 %, range 0~4%, $P < 0.01$). The soluble ICOSL protein level in patients with SLE was significantly higher than that of healthy controls (43.0 ± 39.2 pg/mL vs 2.0± 2.9 pg/mL,$P < 0.01$). The level of soluble ICOSL protein correlated with surface ICOSL expression on the CD4+ T cells (γ =0.69, $P<0.01$). After blocking of the ICOS/ICOSL pathway, the suppression of CD4+ T cell proliferation was not significantly different between the two treatment groups (ICOS immunoglobulin and anti-ICOSL antibody) and the control groups. The expression level of TNF-alpha and IL-17 were also significantly depressed in the treatment groups (ICOS immunoglobulin) compared to the control groups.

Conclusion: In this study, we found that ICOSL, a ligand of ICOS, was significantly up-regulated on CD4+ T cells in the PB in patients with SLE. In addition, blockade of ICOS/ICOSL signaling suppressed the expression of TNF–alpha and IL-17 but it did not affect CD4+ T cell proliferation. Our results support a contribution of the ICOS/ ICOSL pathway to the pathogenesis of SLE.

Disclosure: M. Her, None; **D. Kim**, None; **J. Park**, None; **D. Han**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/expression-of-inducible-costimulator-ligand-icosl-on-cd4-t-cells-in-patients-with-systemic-lupus-erythematosus

Abstract Number: 814

Lupus Drives Atherosclerosis through CD4+CXCR3+ T Cells and Plasmacytoid Dendritic Cells

Tiphaine Goulenok[1], Marc Clement[2], Nicolas Charles[3], Brigitte Escoubet[4], Marie-Paule Chauveheid[5], Thomas Papo[6] and Karim Sacre[7], [1]University Paris Diderot - APHP - Bichat Hospital, aris, France, [2]University Paris Diderot - INSERM U1148, Paris, France, [3]INSERM U699, Paris, France, [4]University Paris- Diderot - APHP - Hôpital Bichat, Paris, France, [5]Internal Medicine, Bichat-Claude Bernard Hospital, University Paris-7, Paris, France, [6]CHU Bichat, Paris, France, [7]Internal Medicine, University Paris-7, INSERM U1149, APHP, Bichat Hospital, Paris, France

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SESSION INFORMATION

Session Date: Sunday, November 8, 2015

Session Title: Systemic Lupus Erythematosus - Human Etiology and Pathogenesis Poster I

Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose:

Accelerated atherosclerosis is the leading cause of death in systemic lupus erythematosus (SLE). How SLE promotes accelerated atherosclerosis remains elusive. The purpose of this study was to show that actors of SLE pathogenesis – such as CD4+ T cells and plasmacytoid dendritic cells (pDCs) - contribute to atherosclerosis.

Methods: Internal carotid wall thickness was prospectively assessed, as a measure of atherosclerosis, in 51 SLE patients asymptomatic for cardiovascular disease and 18 controls. The expression of CXCR3, a chemokine receptor involved in tissue migration of T cells, on peripheral blood mononuclear cells was measured. We analyzed in vitro the effect of pDCs-derived IFN-α production on CD4+ T cells and on CXCR3 ligands production by endothelial cells. Eventually, the impact of TLR-9 stimulated pDCs on atherosclerosis development was studied in a mouse model

Results:

SLE patients displayed an increased frequency of pro-inflammatory CD4+ T cells expressing CXCR3 that correlates with subclinical atherosclerosis. Furthermore, IFN-α produced by pDCs upon TLR-9 stimulation enhances both CD4+CXCR3+ T cells expansion and CXCR3 ligands production by endothelial cells in vitro. Eventually, TLR-9 stimulation of pDCs was shown to accelerate atherosclerosis development in ApoE-/- mice by enhancing the CD4+CXCR3+ T cells recruitment in arterial wall.

Conclusion: In SLE, IFN-α produced by pDCs both expands CD4+T cells expressing CXCR3 and induces endothelial cells to secrete CXCR3 ligands, which drive CD4+T cell migration into the arterial wall and atherosclerosis. Our findings support a multi-step model in which SLE-immune dysfunction is associated with the development of atherosclerosis

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Disclosure: T. Goulenok, None; **M. Clement**, None; **N. Charles**, None; **B. Escoubet**, None; **M. P. Chauveheid**, None; **T. Papo**, None; **K. Sacre**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/lupus-drives-atherosclerosis-through-cd4cxcr3-t-cells-and-plasmacytoid-dendritic-cells

Abstract Number: 815

Lys63-Polyubiquitination By the E3 Ligase Casitas B-Lineage Lymphoma-b Modulates Peripheral Regulatory T Cell Tolerance in Patients with Systemic Lupus Erythematosus

Diana Gómez-Martín[1], Jorge Alcocer-Varela[1], Jorge Romo-Tena[1], Ana Barrera-Vargas[1] and Javier Merayo-Chalico[2], [1]Department of Immunology and Rheumatology, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico, [2]Immunology and Rheumatology, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico

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SESSION INFORMATION

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Session Time: 9:00AM-11:00AM

Background/Purpose:

The interplay between effector and regulatory T cells (Tregs) is a key element among peripheral tolerance mechanisms in Systemic Lupus Erythematosus (SLE). Resistance to suppression has been acknowledged as part of the defects shown by lupus T cells. The E3 ligase Cbl-b has been shown to modulate T cell unresponsiveness in SLE. However its role in peripheral Tregs tolerance has not been addressed. The aim of this study was to assess Cbl-b expression and its relationship to the resistance to suppression phenotype, as well as the ubiquitination profile in SLE.

Methods:

We included 30 SLE patients (20 with active disease and 10 with clinical remission) and 30 age and gender matched healthy controls. Peripheral blood mononuclear cells were isolated by density-gradient sedimentation. Effector ($CD4^+CD25^-$) and Tregs ($CD4^+CD25^+CD127^-$) were purified by magnetic selection. The expression of Cbl-b and the ubiquitination profile were analyzed by western blot. Proliferative responses were assessed in allogeneic and autologous cocultures by CFSE method. Differences were assessed by t Student test. $p<0.05$ was considered as statistically significant.

Results:

We found decreased Cbl-b expression in Tregs from SLE patients in comparison to healthy controls (1.1±0.9 vs 2.5±1.8+6, p=0.003), which was associated with resistance to suppression in proliferation assays (r=0.633, p=0.039). This phenomenon was related to a differential polyubiquitination profile characterized by deficient expression of Lys63 (K63) substrates in regulatory T cells from SLE patients when compared to healthy controls. We analyzed different signaling molecules that are prone to K63 regulation and found increased expression of phosphorylated STAT3 (pSTAT3) in T cells from SLE patients in comparison to healthy controls.

Conclusion: Our data suggest that Cbl-b is able to regulate the interplay between effector and Tregs, particularly, the resistance to suppression by regulating the K63 polyubiquitination profile in T cells from SLE patients. Moreover, deficient K63 polyubiquitination mainly of STAT3 is associated to the enhanced pSTAT3 expression and might play a role in the maintenance of resistance to suppression in SLE, as has been previously reported for other autoimmune diseases.

Disclosure: D. Gómez-Martín, None; **J. Alcocer-Varela**, None; **J. Romo-Tena**, None; **A. Barrera-Vargas**, None; **J. Merayo-Chalico**, None.

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Abstract Number: 816

Incomplete Tolerance in Anergic B Cells in SLE: T Helper Signals Restore B Cell Receptor Signaling in Autoreactive Anergic B Cells By Upregulating CD45 Phosphatase Activity

Peter Szodoray[1], Stephanie M. Stanford[2], Oyvind Molberg[3], Nunzio Bottini[2] and Britt Nakken[1], [1]Institute of immunology, Rikshospitalet, Oslo University Hospital, Oslo, Norway, [2]Cellular Biology, La Jolla Institute for Allergy and Immunology, La Jolla, CA, [3]Department of Rheumatology, Rikshospitalet, Oslo University Hospital, Oslo, Norway

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SESSION INFORMATION

Session Date: Sunday, November 8, 2015

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Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose: We recently identified a human B cell population, which is naturally autoreactive and tolerized by functional anergy. This population was naïve, fully mature, negative for surface IgM and expressing only IgD BCR (BND cells: naïve, D-only). The BND cells have antibody variable region genes in germline configuration and a significant proportion of anergic cells exhibit natural reactivity to antinuclear antigens and dsDNA. Break of B cell tolerance leading to presence of autoantibodies in systemic autoimmune rheumatic diseases may cause the initiation and perpetuation of autoimmune processes. The aim of this study was therefore to investigate if anergy in BND cells could be overcome by T cell mediated signals, as has been reported in murine systems. Furthermore, investigate the molecular mechanisms underlying this process, and determine whether autoreactive BND cells are tolerized in Systemic Lupus Erythematosus (SLE) patients.

Methods: Untouched naive and BND human B cells from healthy blood donors or SLE patients were purified and cultured in the presence of T cell help (e.g. IL-4 and CD40L) followed by functional assays such as Ca2+-flux, phospho-flow (pSyk, pLyn) and standard flow cytometry measurements of intracellular and surface B cell markers. Finally, CD45 phosphatase activity was measured utilizing a novel fluorescent peptide-based assay.

Results: Here we report that T helper signals reverse the state of anergy allowing BND cells to fully respond to antigenic stimulation by restoring signaling through the B cell receptor. The mechanism was dependent on increased activity of the tyrosine phosphatase CD45, and CD45-dependent activation of Lyn and Syk kinases. CD45 phosphatase activity was upregulated by T cell help both in BND and naïve B cells, suggesting that CD45 is a key regulator of B cell receptor signaling thresholds mediated by T cell help. Furthermore, we found that BND cells obtained from SLE patients exhibited increased CD45 activity and B cell receptor signaling capacity, thus being less tolerized,than BND cells from healthy controls.

Conclusion: We discovered that T helper signals regulate CD45 phosphatase activity in B cells, and that this lead to increased B cell receptor signaling and recovered ability of tolerized BND cells to respond to antigen. Strikingly, we found that BND cells obtained from SLE patients were less tolerized than BND cells from healthy controls. This raises the possibility that BND cells could represent precursors of autoantibody-secreting plasma cells and suggests a role for these autorective B cells in contributing to autoimmunity if not properly controlled. Our data provide new insight in the break of humoral immune tolerance with possible diagnostic and therapeutic implications in patients with SLE and other systemic autoimmune and rheumatic diseases.

Disclosure: P. Szodoray, None; **S. M. Stanford**, None; **O. Molberg**, None; **N. Bottini**, None; **B. Nakken**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/incomplete-tolerance-in-anergic-b-cells-in-sle-t-helper-signals-restore-b-cell-receptor-signaling-in-autoreactive-anergic-b-cells-by-upregulating-cd45-phosphatase-activity

Abstract Number: 817

Circulating Endothelial Cell (CEC) and CEC-Bound C4d Levels As Biomarkers of Systemic Lupus Erythematosus

Chau-Ching Liu[1], Susan Manzi[2] and Joseph Ahearn[3], [1]Allegheny Singer Research Institute, Pittsburgh, PA, [2]Rheumatology, Allegheny Health Network, Pittsburgh, PA, [3]Allegheny Singer Research Institute, Allegheny Health Network, Pittsburgh, PA

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Session Title: Systemic Lupus Erythematosus - Human Etiology and Pathogenesis Poster I

Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose:

Accelerated atherosclerotic disease has been widely recognized in patients with SLE. Circulating endothelial cells (CECs) are a rare cell population believed to detach from the vessel wall as a result of vascular injury. Increased numbers of CECs have been reported previously in patients with SLE. However, the interaction between complement and CECs with regard to inflammatory vascular injury in SLE has not been explored. Previous studies have shown that complement activation product C4d is present specifically on platelets of SLE patients and correlates with cerebrovascular disease. These observations led us to hypothesize that increased numbers of CECs bearing C4d may serve as a sensitive and specific biomarker of SLE-associated vascular diseases.

Methods:

To verify this hypothesis, a pilot study investigating CEC numbers and CEC-bound C4d levels was conducted using the blood samples taken from 129 patients with SLE, 125 patients with other immune-inflammatory diseases, and 30 healthy individuals. Peripheral blood mononuclear cells were isolated, and CECs therein were detected and analyzed for surface-bound C4d by flow cytometry.

Results:

Preliminary results showed that CEC numbers per se were not significantly elevated in patients with SLE. Notably, however, the levels of CEC bearing C4d (CEC-C4d) were significantly elevated in patients with SLE (specific median fluorescence intensity (SMFI) = 16.7), compared to patients with other diseases (SMFI = 5.7; p <0.001) and healthy controls (SMFI = 3.5; p <0.001). In a preliminary cross-sectional analysis, CEC-C4d measure was 45% sensitive and 100% specific for SLE versus healthy controls, and 86% specific for SLE versus other diseases. Furthermore, there was a correlation between CEC-C4d and platelet-bound C4d levels (Spearman r = 0.40, p <0.001). Because platelets play important roles in hemostasis and thrombosis and have increasingly been recognized as being important mediators of inflammation, this finding suggests an interactive participation of platelets and CECs in SLE-associated inflammatory vascular disease.

Conclusion:

The results obtained indicate that CEC-C4d is a potential diagnostic marker of SLE and possibly a stratification biomarker for vasculature-specific SLE disease activity.

Disclosure: C. C. Liu, Exagen Dgnostics, 7; **S. Manzi**, Exagen Dagnostics, 7; **J. Ahearn**, Exagen Diagnostics, 7.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/circulating-endothelial-cell-cec-and-cec-bound-c4d-levels-as-biomarkers-of-systemic-lupus-erythematosus

Abstract Number: 818

Cell-Bound Complement Activation Products (CB-CAP) Profiles in Patients with Pre-Systemic Lupus Erythematosus

Chau-Ching Liu[1], Xizoqin Tang[2], Susan Manzi[3] and Joseph Ahearn[4], [1]Allegheny Singer Research Institute, Pittsburgh, PA, [2]Allegheny Health Network, Pittsburgh, PA, [3]Rheumatology, Allegheny Health Network, Pittsburgh, PA, [4]Allegheny Singer Research Institute, Allegheny Health Network, Pittsburgh, PA

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Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose:

The onset of SLE, a prototypical autoimmune disease characterized by immune dysregulation and consequential inflammatory tissue injury, may be insidious with non-specific symptoms. The current standard for diagnosing SLE is based on the ACR classification criteria. A diagnosis of definite SLE is made when a patient has met 4 of the 11 criteria, which may take years to fulfill. Patients who have met less than 4 ACR criteria may have pre-SLE and may go on to develop definite SLE, in whom serious organ damages might have occurred unnecessarily due to the missed opportunity of early treatment. Our recent studies have shown that cell-bound complement activation products (CB-CAP), particularly cell-bound C4d, can serve as unique biomarkers not only for diagnosis but also for disease activity monitoring in patients with SLE. We hypothesize that profiling the CB-CAP patterns in patients at risk for developing SLE may provide a “window” that may allow physicians to identify patients at an early stage of SLE and institute appropriate treatment accordingly.

Methods: To verify this hypothesis, a cross-sectional study investigating C4d levels on various circulating cells was conducted using blood samples taken from 429 patients with definite SLE, 51 patients with pre-SLE, 285 patients with other immune-inflammatory diseases, and 196 healthy individuals. Seven circulating cell types, including erythrocytes, reticulocytes, platelets, T and B lymphocytes, monocytes, and granulocytes, were detected and analyzed for surface-bound C4d by flow cytometry. Cell-bound C4d measure on each cell type was also classified in a binary positive (score = 1) and negative (score = 0) fashion and a cumulative CB-C4d score (ranging from 0 to 7) was derived for each study subject.

Results:

The results showed that C4d levels on all 7 circulating cell types were significantly elevated in patients with definite SLE or pre-SLE, compared to patients with other immune-inflammatory diseases, and healthy controls. However, the CB-C4d levels, with the exception for T cell- and B cell-bound C4d, were statistically indistinguishable between patients with definite SLE and patients with pre-SLE. When the cumulative CB-C4d scores of individual patients were calculated and compared, patients with definite SLE and pre-SLE were inclined to accrue higher CB-CAP scores (with an average score of 2.44 and 2.12, respectively) than did patients with other immune-inflammatory diseases (average score 0.72). Moreover, high CB-C4d scores were more prevalent in patients with definite SLE and pre-SLE than in patients with other immune-inflammatory diseases. The frequency distribution of CB-C4d scores within the patient group of pre-SLE resembled that within the patient group of definite SLE, but was considerably different from that within the patient group of other diseases.

Conclusion:

Collectively, the results suggest that CB-CAP generation may occur early during the pathogenic process of SLE. CB-CAP profiling may help identify patients at risk for developing full-blown SLE and thus provide preventative care to minimize disease progression.

Disclosure: C. C. Liu, Exagen Dgnostics, 7; **X. Tang**, None; **S. Manzi**, Exagen Dagnostics, 7; **J. Ahearn**, Exagen Diagnostics, 7.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/cell-bound-complement-activation-products-cb-cap-profiles-in-patients-with-pre-systemic-lupus-erythematosus

Abstract Number: 819

Upregulation of Complement C3 and Alpha-2-Macroglobulin in Cerebrospinal Fluid of Neuropsychiatric Systemic Lupus Erythematosus

Tomoyuki Asano[1], Shuzo Sato[1], Hiroko Kobayashi[1], Yoshinobu Kariya[2], Hiromi Ito[2], Kyoka Hoshi[2], Akioh Yoshihara[3], Yoshikazu Ugawa[3], Minoru Takahashi[4], Hideharu Sekine[4], Shunsei Hirohata[5], Hiroshi Watanabe[1], Hiromasa Ohira[1] and Yasuhiro Hashimoto[2], [1]Gastroenterology and Rheumatology, Fukushima Medical University School of Medicine, Fukushima, Japan, [2]Biochemistry, Fukushima Medical University School of Medicine, Fukushima, Japan, [3]Neurology, Fukushima Medical University School of Medicine, Fukushima, Japan, [4]Immunology, Fukushima Medical University School of Medicine, Fukushima, Japan, [5]Rheumatology and Infectious Diseases, Kitasato University School of Medicine, Kanagawa, Japan

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Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose: Various autoantibodies have been identified in cerebrospinal fluids (CSF) of neuropsychiatric systemic lupus erythematosus (NPSLE). They are supposed to form immune complex with complement to induce inflammatory responses. We therefore measured the 3rd component of complement (C3) and other inflammation-related molecules in CSF of NPSLE patients.

Methods: This study included 51 SLE patients. According to the 1999 ACR definition criteria, 43 patients were diagnosed with NPSLE whereas 8 patients were diagnosed with non-NPSLE. We measured levels of C3, alpha-2-Macroglobulin (α2MG) and IL-6, in CSF or serum by sandwich ELISA.

Results: Quantitative ELISA revealed that the IL-6 levels in CSF of NPSLE (441.9 ± 1233 pg/ml) were significantly higher than that of non-NPSLE (3.36 ± 2.58 pg/ml) ($p = 0.0010$), which is consistent with the previous observation reported by Hirohata *et al*. (Clin Rheumatol. 2009). IL-6 is a primary cytokine, which induces various inflammatory responses including complement activation. We examined C3 expression in CSF of NPSLE patients. C3 levels in CSF of NPSLE (4.94 ± 3.79 μg/ml) were significantly higher than that of non-NPSLE (1.92 ± 1.14 μg/ml) ($p = 0.0071$). It is possible that elevation of C3 in CSF is due to upregulation of serum C3. We therefore analyzed serum levels of C3. No significant difference in serum C3 levels was observed between NPSLE (645 ± 311 μg/ml) and non-NPSLE (824 ± 374 μg/ml) ($p = 0.2767$). In addition, correlation of C3 levels between CSF and serum was weak in NPSLE ($r = 0.2885$, $p = 0.0380$), suggesting that upregulation of C3 in CSF is independent of C3 levels in serum. Another inflammatory protein we analyzed was α2MG, which is a protease inhibitor for localizing proteolytic

responses in the inflammatory focus. Quantitative ELISA revealed that levels of α2MG in NPSLE (2.90 ± 3.69 μg/ml) were significantly higher than that of non-NPSLE (0.72 ± 0.26 μg/ml) ($p = 0.0010$). In contrast, serum levels of α2MG were similar in both specimens. Correlation of α2MG levels between CSF and serum was weak ($r = 0.2582$, $p = 0.0674$), suggesting independence of α2MG concentration between CSF and serum. It was notable that CSF levels of C3 and α2MG showed strong correlation ($r = 0.6990$, $p < 0.0001$). In addition, that CSF levels of IL-6 was correlated with that of C3 and α2MG, ($r = 0.5102$, $p = 0.0003$) and ($r = 0.5662$, $p < 0.0001$), respectively, suggesting that IL-6 upregulates C3 and α2MG in CSF.

Conclusion: We demonstrated the increase of IL-6 in CSF of NPSLE patients. IL-6 may upregulate C3 and α2MG in CSF as "local" inflammatory response.

Disclosure: T. Asano, None; **S. Sato**, None; **H. Kobayashi**, None; **Y. Kariya**, None; **H. Ito**, None; **K. Hoshi**, None; **A. Yoshihara**, None; **Y. Ugawa**, None; **M. Takahashi**, None; **H. Sekine**, None; **S. Hirohata**, None; **H. Watanabe**, None; **H. Ohira**, None; **Y. Hashimoto**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/upregulation-of-complement-c3-and-alpha-2-macroglobulin-in-cerebrospinal-fluid-of-neuropsychiatric-systemic-lupus-erythematosus

Abstract Number: 820

Peripheral Blood and Disease Features Associated with Complement Components C3 and C4 in SLE

Mikhail Olferiev, David Fernandez, Leila Khalili, Dina Greenman, Mary K. Crow and Kyriakos A. Kirou, Mary Kirkland Center for Lupus Research, Hospital for Special Surgery, New York, NY

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Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose: Decreases in peripheral blood levels of complement components of C3 and C4 are associated with SLE and often indicate a lupus flare. The aim of this study is to identify the biologic events that underline changes in complement levels and their clinical implications by characterizing peripheral blood features that are associated with low C3 or C4 levels in patients with SLE.

Methods: PBMC samples and multiple clinical and laboratory parameters were collected longitudinally for 71 patients that met ACR criteria for SLE. C3 and C4 were measured by nephelometry (the normal ranges for C3 and C4 were 79–152 mg/dl and 16–38 mg/dl, respectively). Longitudinal PBMC gene expression data were generated by microarray (2-8 visits/patient) for 22 SLE patients from the above group. Based on the data obtained, we built separate statistical models (linear mixed model) for C3 and C4. The relationships of C3 and C4 with the studied parameters were obtained, the p value threshold was set at 0.05 and a multiple testing correction was applied.

Results: C3 and C4 fluctuated during the disease course and from patient to patient. C3 and C4 showed a significant relationship ($p<0.05$) with each other. Both C3 and C4 correlate positively with serum albumin, alkaline phosphatase and calcium. C3 is positively correlated with WBC, RBC, serum albumin and C-reactive protein, and is negatively correlated with disease activity, as determined by SELENA-SLEDAI or BILAG2004. C3 was lower in patients with high serum creatinine, chloride, proteinurea (by definition of SLEDAI), DNA binding and lymphopenia. Based on longitudinal microarray data, C3 and C4 showed either positive or negative relationships with 1147 transcripts and 37 transcripts, respectively. There were 29 genes correlating with both C3 and C4. The functional analysis of selected transcripts indicates important categories, such as regulation of innate immune response and RNA preprocessing. Transcripts negatively correlating with C3 and C4 include NFATC1, MAP3K8, EGR1 that mediate T cell activation; or such important molecules as NF1, TNFAIP3, BTG1, DUSP2, CXCR4, NEDD and SHARPIN.

Conclusion: Our data confirmed the usefulness of C3 and C4 for monitoring disease activity in SLE and indicate that C3 might have better prognostic potential than C4. Patients with low C3 tend to have more prominent kidney involvement. Interestingly, C3 showed a better correlation with PBMC gene transcript expression than C4, and low C3 was associated with increased expression of transcripts involved in T cell activation, among other immune activation pathways. The results point to important molecular mechanisms that are associated with SLE disease activity.

Disclosure: M. Olferiev, None; **D. Fernandez**, None; **L. Khalili**, None; **D. Greenman**, None; **M. K. Crow**, Novartis Pharmaceutical Corporation, 5,BMS, 5,GlaxoSmithKline, 5; **K. A. Kirou**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/peripheral-blood-and-disease-features-associated-with-complement-components-c3-and-c4-in-sle

Abstract Number: 821

Elevated Serum Levels of Soluble CD146 in Patients with Systemic Sclerosis

Kazunori Kato[1], Tomoko Ito[2], Naoto Tamura[2], Sayuri Okuda[1], Masakazu Matsushita[2], Kurisu Tada[2], Ken Yamaji[2] and Yoshinari Takasaki[2], [1]Department of Biomedical Engineering, Toyo University, Saitama, Japan, [2]Department of Internal Medicine and Rheumatology, Juntendo University School of Medicine, Tokyo, Japan

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SESSION INFORMATION

Session Date: Sunday, November 8, 2015

Session Title: Systemic Sclerosis, Fibrosing Syndromes and Raynaud's - Clinical Aspects and Therapeutics Poster I

Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose: CD146 is a transmembrane glycoprotein belonging to Ig-superfamily. Human endothelial cells, activated fibroblasts and Th17 cells express CD146 that involved in angiogenesis, fibrosis and inflammation. CD146+ T cells secrete IL-17, IFN-g, and TNF-a. CD146 also exists as a soluble form (sCD146) that has biological activity. The aim of this study is to establish an enzyme-linked immunosorbent assay (ELISA) for detecting sCD146 , and to determine the serum levels of sCD146 in patients with systemic sclerosis (SSc), and examine the relationship with the clinical manifestations.

Methods: We used two non-cross-blocking CD146 mAbs to develop a sandwich ELISA for measuring serum sCD146. Recombinant sCD146 was used to obtain the standard curve. IRB approved blood sampling and measuring protocol was established at the Juntendo University School of Medicine and Toyo University and enrolled healthy controls. Blood samples were drawn from patients fulfilling criteria for SSc proposed by the 2013 classification criteria for SSc (ACR/EULAR). Levels of sCD146 were quantified in 40 serum samples from patients with SSc by the ELISA and compared with those of 14 healthy controls. The clinical manifestation and laboratory data of the patients were also examined.

Results: We established a sensitive and specific ELISA system for testing sCD146. Systemic sclerosis was focused from the result of screening various SCTDs for serum sCD146. The levels of sCD146 were significantly higher in 40 patients with SSc (14.12 ng/ml) than those in 14 healthy controls (6.73 ng/ml; $p<0.001$) [Figure]. However, there was no statistical correlation between sCD146 and the clinical manifestations, such as lung fibrosis and area of skin fibrosis. But the level of sCD146 was significantly correlated with the level of E-selectin, a marker of vascular damage. In addition,serum levels of sCD146 were decreased in SSc patients treated with glucocorticoid.

Conclusion: We identified the presence of sCD146 in SSc serum. It is suggested that sCD146 is involved in inflammation through vascular endothelial cells as well as E-selectin. The pathogenic and clinical significance of sCD146 in SSc should be further examined.

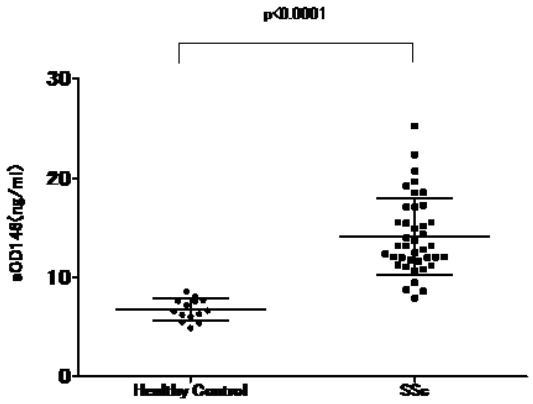

Figure.Serum sCD146 in SSc

Disclosure: K. Kato, None; **T. Ito**, None; **N. Tamura**, None; **S. Okuda**, None; **M. Matsushita**, None; **K. Tada**, None; **K. Yamaji**, None; **Y. Takasaki**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/elevated-serum-levels-of-soluble-cd146-in-patients-with-systemic-sclerosis

Abstract Number: 822

Beneficial Effect of Botulinum Toxin-a on Raynaud's Phenomenon in Japanese Patients

with Systemic Sclerosis: A Prospective, Open-Label Trial

Sei-ichiro Motegi[1], Kazuya Yamada[1], Sayaka Toki[1], Akihiko Uchiyama[1], Tetsuya Nakamura[2] and Osamu Ishikawa[1], [1]Department of Dermatology, Gunma University Graduate School of Medicine, Gunma, Japan, [2]Clinical Investigation and Research Unit, Gunma University Graduate School of Medicine, Gunma, Japan

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Session Title: Systemic Sclerosis, Fibrosing Syndromes and Raynaud's - Clinical Aspects and Therapeutics Poster I

Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose: Systemic scleroderma (SSc) is a generalized connective tissue disease characterized by fibrosis of the skin and internal organs, vascular dysfunction and immune disorder. Patients with SSc typically develop Raynaud's phenomenon (RP) and persistent digital ischemia, and often develop digital ulcers (DU). Currently, there is no satisfactory treatments for RP in SSc. Recently, it was reported that botulinum toxin A (BTX-A) injection was effective for the treatment of RP in SSc patients. Objective was to assess the efficacy and safety of BTX-A on RP in Japanese SSc patients.

Methods: In the prospective, open-label trial, 10 Japanese SSc patients with RP received 10U of BTX-A injections into the hand. The change in severity of RP, including the frequency of attacks/pain, color changes, duration time of RP and the severity of pain was assessed by the Raynaud score and pain VAS at each visits during 16 weeks. The recovery of skin temperature 20 minutes after cold-water stimulation was examined by thermography at baseline and 4 weeks after injection. The number of DU and adverse events were assessed at each visits.

Results: BTX-A injection decreased Raynaud's score and pain VAS from 2 weeks after injection, and the suppressive effect was continued until 16 weeks after injection. The symptoms of RP in 10 SSc patients without BTX-A treatment remained unchanged 4 weeks after injection, however, those in 10 patients with BTX-A injection were significantly improved. Skin temperature recovery after cold-water stimulation at 4 weeks after injection was significantly elevated compared to that before injection. All DU in five patients were healed within 12 weeks after injection. Neither systemic nor local adverse events was observed in all patients.

Conclusion: We conclude that BTX-A injection significantly improved the activity of RP in SSc patients without any adverse events, suggesting that BTX-A might have possible long-term preventive and therapeutic potentials for RP and RP-related DU in Japanese SSc patients.

Disclosure: S. I. Motegi, None; **K. Yamada**, None; **S. Toki**, None; **A. Uchiyama**, None; **T. Nakamura**, None; **O. Ishikawa**, None.

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Abstract Number: 823

Anti-IFI16 Antibodies in Scleroderma Are Associated with Digital Gangrene

Zsuzsanna McMahan[1], Ami A. Shah[2], Dhananjay Vaidya[3], Fredrick M. Wigley[4], Antony Rosen[5] and Livia Casciola-Rosen[6], [1]Rheumatology, Johns Hopkins University, Baltimore, MD, [2]Rheumatology, Johns Hopkins University School of Medicine, Baltimore, MD, [3]Medicine, School of Medicine, Johns Hopkins, Baltimore, MD, [4]Rheum Div/Mason F Lord, Johns Hopkins University School of Medicine, Baltimore, MD, [5]Mason Lord Bldg Ctr Tower, Johns Hopkins University, School of Medicine, Baltimore, MD, [6]Division of Rheumatology, Johns Hopkins University School of Medicine, Baltimore, MD

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Session Time: 9:00AM-11:00AM

Background/Purpose: Our aim was to examine and confirm the association between anti-IFI16 antibodies and clinical features of scleroderma.

Methods: Sera from a discovery sample of 94 scleroderma patients and 47 healthy controls were assayed for anti-IFI16 antibodies by ELISA, and associations were examined using regression analyses. As anti-IFI16 autoantibodies strongly associated with digital gangrene in the discovery sample, a subsequent 1:1 disease-duration matched case-control study was designed to further explore this association. Cases were patients with scleroderma and digital gangrene, while controls were patients with scleroderma and Raynaud's alone (n=52 pairs). Nonparametric

unadjusted matched-pair analyses, univariate and multivariable conditional logistic regression were performed.

Results: Anti-IFI16 antibodies in the discovery sample were more prevalent in scleroderma than in healthy controls (18% vs. 2%; p=0.01). Patients with anti-IFI16 antibodies were more likely to have limited scleroderma (77% vs. 46%; p=0.03), longer disease duration (15.2 [10.6-18.3] vs. 6.0 [3.4-13.8] years; p <0.01), digital gangrene (24% vs. 4%; p=0.02), and a low DLCO (p <0.01). In the matched case-control study, 38/104 (37%) were anti-IFI16 positive. Anti-IFI16 antibody levels were found to be significantly higher in cases than matched controls (p=0.02). Adjusted for age, cutaneous subtype, smoking, and DLCO, high anti-IFI16 antibody levels associated significantly with digital gangrene case status (adjusted OR 2.4; 95% CI 1.0, 5.4).

Conclusion: Anti-IFI16 antibodies are associated with digital gangrene in scleroderma. Longitudinal prospective studies exploring the role of anti-IFI16 antibodies as a scleroderma disease biomarker, and biological studies investigating the pathogenicity of these antibodies, are warranted.

Disclosure: Z. McMahan, None; **A. A. Shah**, None; **D. Vaidya**, Consumable Science, Inc, 5; **F. M. Wigley**, None; **A. Rosen**, None; **L. Casciola-Rosen**, None.

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Abstract Number: 824

Familial Risk of Systemic Sclerosis and Co-Aggregation of Autoimmune Diseases in Affected Families: A Nationwide Population Study

Chang-Fu Kuo[1], Matthew J. Grainge[2], Ana Valdes[3], Shue-Fen Luo[4], Lai-Chu See[5], Kuang-Hui Yu[6], Weiya Zhang[7] and Michael Doherty[8], [1]Division of Rheumatoplogy, Allergy and Immunology, Chang Gung Memorial Hospital, Tayuan, Taiwan, [2]Division of Epidemiology and Public Health, School of Community Health Sciences, University of Nottingham, Nottingham, United Kingdom, [3]Division of Rheumatology, Orthopaedics and Dermatology, University of Nottingham, Nottingham, United Kingdom, [4]Rheumatology, Chang Gung Memorial Hosp, Taipei, Taiwan, [5]Biostatistics Core Laboratory, Molecular Medicine Research Center, Chang Gung University, Taoyuan, Taiwan, [6]Division of Rheumatoplogy, Allergy and Immunology, Chang Gung Memoria Hospital, Tayuan, Taiwan, [7]Academic Rheumatology, School of Clinical Sciences, University of Nottingham, Nottingham, United Kingdom, [8]Academic Rheumatology, City Hospital, Nottingham, United Kingdom
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Background/Purpose:

To investigate familial aggregation of systemic sclerosis and the relative risks (RRs) of other autoimmune disease in relatives of affected patients.

Methods:

We identified 23,658,577 beneficiaries registered with the National Health Insurance in 2010, of whom 1,891 individuals had systemic sclerosis. We identified 21,009,551 parent-child relationships and 17,168,340 full sibling pairs. The familial risks of systemic sclerosis, rheumatoid arthritis and systemic lupus erythematosus, familial transmission and expected proportion of sporadic cases were estimated.

Results:

The prevalence of systemic sclerosis was 7.99 (95% confidence interval [CI], 7.64–8.36) per 100,000 people in the general population of Taiwan in 2010; in comparison, the prevalence was 387.60 (95% CI, 46.97–1393.06) per 100,000 people. The adjusted RR (95% CI) for systemic sclerosis was 81.21 (11.40–579.72) for siblings of systemic sclerosis patients. The familial transmission (heritability plus shared environmental contribution) was 0.72; despite this, 84.1% of patients was expected to be sporadic cases. The RR (95% CI) in first-degree relatives of systemic sclerosis patients was 7.43 (2.42–22.86) for rheumatoid arthritis; 9.82 (3.76–25.70) for systemic lupus erythematosus.

Conclusion:

The risk of systemic sclerosis and other autoimmune diseases is increased in relatives of people with systemic sclerosis and family factors explain over two-thirds the phenotypic variance of the disease. Despite this, the majority of patients were expected to be sporadic cases.

Disclosure: **C. F. Kuo**, None; **M. J. Grainge**, None; **A. Valdes**, None; **S. F. Luo**, None; **L. C. See**, None; **K. H. Yu**, None; **W. Zhang**, None; **M. Doherty**, None.

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Abstract Number: 825

Subclinical Atherosclerosis and Estimation of Cardiovascular Risk in Systemic Sclerosis

Gulsen Ozen[1], Fatmanur Korkmaz[2], Murat Sunbul[3], Rabia Deniz[4], Kursat Tigen[3], Pamir Atagunduz[1], Nevsun Inanc[1] and Haner Direskeneli[1], [1]Department of Rheumatology, Marmara University Faculty of Medicine, Istanbul, Turkey, [2]Department of Internal Medicine, Marmara University Faculty of Medicine, Istanbul, Turkey, [3]Department of Cardiology, Marmara University Faculty of Medicine, Istanbul, Turkey, [4]Marmara University Faculty of Medicine, Istanbul, Turkey

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Session Title: Systemic Sclerosis, Fibrosing Syndromes and Raynaud's - Clinical Aspects and Therapeutics Poster I

Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose: During the last decade, it has been shown that cardiovascular disease (CVD) in systemic sclerosis (SSc) is increased and accounts for ~30% of the SSc mortality. However, whether this is due to accelerated atherosclerosis and how to detect patients with high risk are still unclear. In this study we aimed to determine the frequency of subclinical atherosclerosis in patients with SSc compared to rheumatoid arthritis (RA) and to determine the ability of CV risk indices in detecting those SSc patients with high CV risk.

Methods: Eighty one SSc patients (F/M=74/7; mean age 49.7±12.1 years) and 80 age- and sex-matched RA patients (F/M=73/7; mean age 50.1±10.5 years) without a history of CVD were assessed. All patients were evaluated with carotid ultrasonography (US). Carotid intima-media thickness (cIMT) > 0.90 mm and/or carotid plaques were used as the gold standard test for subclinical atherosclerosis and high CV risk (US+). Systematic Coronary Risk Evaluation (SCORE), QRisk II and 2013 American College of Cardiology/American Heart Association (ACC/AHA) 10-year atherosclerotic CV disease risk (ASCVD) indices were calculated.

Results: Fifteen patients (18.5%) in SSc group and 19 patients (23.8%) in RA group were US+ and the presence of subclinical atherosclerosis and the mean cIMT were similar in SSc and RA patients (P=0.41, P=0.74, respectively) (Table 1). None of the CV risk factors in SSc patients were worse than RA patients except for lower HDL-chol levels (Table 1). However atherogenic index (Total-chol/HDL-chol) were not different (3.6±0.9 vs 3.5±1.1, P=0.67). When US+ and US- SSc patients were compared, it was observed that US+ SSc patients were older, had significantly more pulmonary arterial hypertension (PAH), elevated ESR, HT and less immunsuppressive usage than US- patients. In multivariable logistic regression analysis, age (OR=1.1, 95% CI [1.02-1.8], P=0.014), elevated ESR (OR=9.3, 95% CI [1.6-55.5], P=0.014) and PAH (OR=4.8, 95% CI [1.12-20.8], P=0.035) were independently associated with subclinical atherosclerosis. Concerning CVD risk indices, all 3 CV risk indices for general population failed to identify patients with subclinical atherosclerosis. Of the 15 US+ patients only 0 (0%), 1 (6.7%) and 3 (20%) patients were classified as high CV risk according to SCORE, QRisk II and ACC/AHA 10-year ASCVD risk, respectively.

Conclusion: Subclinical atherosclerosis in SSc is as frequent as in RA in which accelarated atherosclerosis is clearly defined. Atherosclerosis in SSc is independently associated with age, elevated ESR and PAH. However CV risk indices for general population, SCORE, QRisk II and ACC/AHA 10-year ASCVD risk are considerably insufficient to detect those patients with subclinical atherosclerosis. In future studies, elevated ESR and presence of PAH may be helpful in the SSc-specific CV risk estimation.

Table 1. CV risk factors of SSc and RA patients

	SSc patients (n=81)	RA patients (n=80) (n=80)	*P*
Disease duration, years	9.7±8.7	10.9±7.8	**0.10**
Obesity, n(%)	16 (19.8)	28 (35)	**0.03**
Ever smoked, n (%)	28 (34.6)	24 (30)	**0.53**
Hypertension, n (%)	21 (25.9)	28 (35)	**0.21**
Diabetes mellitus, n (%)	6 (7.4)	10 (12.5)	**0.28**
LDL-chol	106.5±37.3	113.0±33.9	**0.25**
HDL-chol	54.0±18.5	61.1±16.6	**0.011**
Triglycerides	122.4±58.4	117.7±61.6	**0.63**
Metabolic syndrome, n (%)	24 (29.6)	24 (30)	**0.95**

The values were presented as mean±SD

Disclosure: G. Ozen, None; **F. Korkmaz**, None; **M. Sunbul**, None; **R. Deniz**, None; **K. Tigen**, None; **P. Atagunduz**, None; **N. Inanc**, None; **H. Direskeneli**, None.

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Abstract Number: 826

Systemic Sclerosis Inpatient Mortality Has Not Improved from 1995-2011. Results from a National Irish Audit of Scleroderma Co-Morbidities.

Len Harty[1], Deirdre Fitzgerald[2], Michael Henry[2], John Ryan[3] and Sinead Harney[3], [1]Cork University Hospital, Cork, Ireland, [2]Respiratory, Cork University Hospital, Cork, Ireland, [3]Rheumatology, Cork University Hospital, Cork, Ireland

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Session Time: 9:00AM-11:00AM

Background/Purpose: Despite the advent of potent immunosuppressive and vasoactive therapies it is not clear that longevity of patients with systemic sclerosis (SSc) has improved. Therefore we sought to evaluate the age of death of SSc inpatients (inpts) relative to general inpts, the number of hospital inpt days and comorbidities in SSc patients.

Methods: The Hospital In-Patient Enquiry system was evaluated from 57 Irish hospitals from 1995-2011 for patients admitted with a diagnosis of SSc. Age, length of stay (LOS), gender and admitting indication were recorded. **Results** are shown as totals and mean (Standard deviation). Trends were examined by logistic regression analysis; Mann –Whitney U was used to compare groups. $p<0.05$ was considered statistically significant.

Results: 2667 inpt admissions occurred; 4:1, F:M, mean age 59yrs (15). On average 157 (15) admissions occurred annually for SSc patients, without variation (p=0.7). 146 patients died in hospital at average 65yrs (5) without annual improvement ($r^2=0.03$, p=0.5). SSc age of death was younger than general inpts ($p<0.0001$), whose longevity improved from 72 to 74yrs ($r^2=0.9$, $p<0.0001$). Male SSc inpts were average 6yrs younger than female at death (60yrs (10) v 66 yrs (6); $p<0.01$) in contrast to general inpts when men were average 3yrs younger than women at death (70 yrs v 73 yrs). SSc LOS increased from 11 to 14 days ($r^2=0.3$, p=0.03), as did age of admission ($r^2=0.4$, $p<0.01$). Autoimmune disease (predominantly scleroderma) was the commonest admitting diagnosis (n=945). Lung disease accounted for 383 admissions (170 infection, 62 PAH), CVS disease n=397 (236 limb / cardiac / cerebral ischaemic events, 51 heart failure, 32 arrhythmia), GI n=301, Rehab n= 151, MSK n=120, Haematological n=89 (52 anaemia), Renal n= 85 (51 Failure, 19 infection). 16 pregnancies were recorded with 2 spontaneous abortions, 3 pre-eclampsia incidents, and 9 unspecified complications. Imaging was the commonest principal procedure (n=346), followed by IV therapy (n=297), allied health professional intervention (n=277), gastroscopy (n=208) with 62 patients undergoing limb amputation and 9 having kidney

transplants.

Conclusion: Age of death among SSc inpts is not improving in contrast to unaffected inpts whose age of death is increasing, worse in men. SSc LOS is increasing in contrast to unaffected inpts whose LOS is decreasing. Cardiopulmonary comorbidity predominates among Irish SSc inpts supporting the need for more awareness and therapeutics to address this aspect of SSc.

Disclosure: L. Harty, None; **D. Fitzgerald**, None; **M. Henry**, None; **J. Ryan**, None; **S. Harney**, None.

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Abstract Number: 827

Reliability of the Quantitative Assessment of Peripheral Blood Perfusion By Laser Speckle Contrast Analysis in a Systemic Sclerosis Cohort

Valérie Lambrecht[1], Maurizio Cutolo[2], Filip De Keyser[3], Saskia Decuman[4], Barbara Ruaro[2], Alberto Sulli[5], Ellen Deschepper[6] and Vanessa Smith[7], [1]Department of Rheumatology, Ghent University Hospital, Ghent, Belgium, [2]Research Laboratory and Academic Division of Clinical Rheumatology, Department of Internal Medicine, University of Genova, Genova, Italy, [3]Rheumatology, Ghent University Hospital, Ghent, Belgium, [4]Department of Rheumatology, UGent, Ghent, Belgium, [5]Research Laboratory and Academic Division of Clinical Rheumatology, Department of Internal Medicine, Genova, Italy, [6]Biostatistics Unit, Biostatistics Unit, Ghent University, Ghent, Belgium, [7]Department of Rheumatology, Ghent University Hospital, Ghent University, Ghent, Belgium

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Background/Purpose:

Laser speckle contrast analysis (LASCA) is an innovative technique to quantify peripheral blood perfusion (PBP) over a given area. Quantification of blood flow might be of interest in diseases with affection of the microcirculation e.g. systemic sclerosis (SSc). In order to be used as an outcome measure, first reliability of LASCA needs to be attested. This study investigates the reliability of the quantitative assessment of PBP by LASCA between two raters in a SSc cohort.

Methods:

Two independent raters evaluated PBP in 40 consecutive patients with SSc (all fulfilling the 2013 ACR/EULAR classification criteria) using LASCA (Pericam PSI, Perimed, Jarfalla). PBP was measured at the level of the fingertips, dorsal and volar bilaterally, for 30 sec each. Measurements were performed under standardized conditions (acclimatization in a temperature controlled darkened room at 25°C for 20 min; seated position; hand at heart level on flat underground; working distance 14.3-14.8 cm; no movement or speaking during measurement; time interval between two raters maximal 30 min). PBP values were reported as perfusion units (PU) by creating regions of interest with fixed 1 cm diameter at central area of 2nd, 3rd, 4th and 5th fingertips. Mean PU per finger, left and right, dorsal and volar, per rater was calculated. Inter-rater agreement was assessed by calculation of intraclass correlation coefficients (ICC). Patients with flexion contractures (n=6) were excluded because they could not meet the standardization requirements.

Results:

The mean PBP values (in PU) are described in Table 1. ICC (95% confidence interval) for PBP values measured by the two raters varied from 0.82 (0.67 to 0.91) to 0.91 (0.83 to 0.96) for the dorsal fingertips, and from 0.74 (0.55 to 0.86) to 0.86 (0.74 to 0.93) for the volar fingertips (Table 2).

Conclusion:

This is the first study to demonstrate reliability of the quantitative assessment of peripheral blood flow by LASCA in a SSc cohort between two raters, performed under standardized patient, instrumental and environmental conditions. Reliability of LASCA is essential for further use of this tool in SSc trials.

Tabel 1 Mean (SD) PBP values (in PU) measured at level of fingertips in a SSc cohort

	Rater 1	Rater 2
Dorsal		
Left		
F2	86.98 (49.57)	89.05 (47.44)
F3	80.89 (48.71)	85.68 (46.90)
F4	86.80 (54.94)	92.26 (56.81)
F5	92.36 (56.39)	96.26 (56.43)
Right		
F2	109.25 (48.49)	109.74 (48.90)
F3	93.52 (50.87)	96.30 (50.27)
F4	98.33 (57.63)	104.16 (57.54)
F5	102.83 (53.61)	103.94 (58.73)
Volar		
Left		
F2	127.47 (73.57)	129.66 (76.51)
F3	115.35 (67.89)	117.61 (70.52)
F4	119.13 (62.82)	124.70 (71.90)
F5	116.15 (64.79)	119.01 (65.05)
Right		
F2	149.91 (84.07)	153.95 (76.38)
F3	130.96 (71.12)	137.88 (71.81)
F4	142.42 (81.25)	150.51 (79.41)
F5	142.85 (76.89)	154.97 (79.48)

PBP, peripheral blood perfusion; PU, perfusion units; SSc, systemic sclerosis; F, fingertip.

Tabel 2 ICC (95% CI) for PBP measured by LASCA by two independent raters

	ICC	95% CI
Dorsal		
Left		
F2	0.85	0.71;0.92
F3	0.89	0.79;0.94
F4	0.89	0.80;0.95
F5	0.83	0.68;0.91
Right		
F2	0.91	0.83;0.96
F3	0.90	0.81;0.95
F4	0.88	0.77;0.94
F5	0.82	0.67;0.91
Volar		
Left		
F2	0.86	0.74;0.93
F3	0.85	0.72;0.92
F4	0.84	0.70;0.92
F5	0.80	0.63;0.89
Right		
F2	0.84	0.70;0.91
F3	0.76	0.58;0.87
F4	0.74	0.55;0.86
F5	0.81	0.66;0.90

ICC, intraclass correlation coefficient; CI, confidence interval; PBP, peripheral blood perfusion; LASCA, laser speckle contrast analysis; F, fingertip.

Disclosure: V. Lambrecht, None; **M. Cutolo**, None; **F. De Keyser**, None; **S. Decuman**, None; **B. Ruaro**, None; **A. Sulli**, None; **E. Deschepper**, None; **V. Smith**, None.

Abstract Number: 828

Development of a Disease Damage Index in Systemic Sclerosis Using Consensus and Data Driven Methods

Nava Ferdowsi[1], Molla Huq[1], Jodie Burchell[2], Sam Mancuso[2], Tien Tay[1,3], Wendy Stevens[4], Candice Rabusa[4], Marie Hudson[5], Vijaya Sundararajan[2], David Prior[6], Susanna Proudman[7], Murray Baron[8] and Mandana Nikpour[9,10], [1]Rheumatology, The University of Melbourne at St Vincent's Hospital, Melbourne, Australia, [2]Medicine, The University of Melbourne at St Vincent's Hospital, Melbourne, Australia, [3]41 Victoria Parade, Fitzroy, St Vincent's Hospital, Melbourne, Australia, [4]Rheumatology, St. Vincent's Hospital, Melbourne, Australia, [5]Medicine, McGill University, Montreal, QC, Canada, [6]Cardiology, St Vincent's Hospital, Melbourne, Australia, [7]Rheumatology Unit, Royal Adelaide Hospital North Terrace, Adelaide, Australia, [8]Rheumatology, McGill University, Jewish General Hospital, Montreal, QC, Canada, [9]St Vincent's Hospital, Melbourne, Australia, [10]Medicine, The University of Melbourne at St. Vincent's Hospital, Melbourne, Australia

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Background/Purpose: As there is currently no existing index for quantifying organ damage in systemic sclerosis (SSc), we sought to develop a disease damage index in SSc (SSc-DI) for use in interventional and observational studies.

Methods: The SSc-DI working group, together with patient partners and expert advisors from disciplines other than rheumatology, has developed the initial SSc-DI using the following steps: (1) Definition of the concept of damage in SSc using consensus methods in survey form (Figure 1); (2) Item generation and definition through systematic literature review; (3) Item reduction using an online survey distributed to over 300 SSc experts internationally, together with Rasch modelling. (5) Univariable and multivariable regression modelling to (i) determine the relationship between the reduced list of items and death and (ii) to weight the items, using prospectively acquired data from the Australian Scleroderma Cohort Study (ASCS).

Results: A total of 83 items from 7 domains (organ systems) were included in the online survey. A total of 93 responses from SSc experts representing Australasia, North America and Europe were analysed. 58/83 items were retained based on the Delphi survey responses (³60% experts deemed item appropriate). A further 27 items were dropped after Rasch modelling, leaving 31 items to be considered for inclusion in the SSc-DI. Eight of the 31 remaining items were not collected in the ASCS and therefore were unable to be analysed in regression models. The cohort data set consisted of 1,544 patients, with 172 deaths (11.4%). The univariable relationship with death was statistically significant in 16 items. The final SSc DI with weighted scores can be seen in Table 1. Four items, although dropped in the Rasch analysis, were included in the final index by the investigators as they were felt to reflect damage and conferred a mortality risk. The model demonstrated good discrimination and calibration power (area under ROC curve = 0.83 and Hosmer-Lemeshow p = 0.54)

Conclusion: The combined use of consensus and data driven methods has resulted in a weighted 16-item Damage Index that predicts mortality. Further work includes creation of a separate index reflective of morbidity and external validation of these indices using prospective cohort data.

Figure 1: Consensus definition of "damage" in SSc

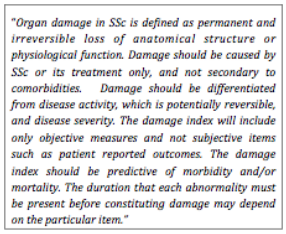

Table 1: Systemic Sclerosis Damage Index (SSc-DI)

Damage Item	Univariable p value	Multivariate p value	Coefficient	Weighted Score
Digital amputation	0.037	0.52	0.20	1
GORD based on symptoms and confirmed on endoscopy*	0.05	0.29	0.24	1
History of SRC	0.18	0.71	0.20	1
Small joint contracture	0.036	0.55	0.34	2
Esophageal stricture confirmed on endoscopy or barium swallow	0.031	0.13	0.46	2
Gastric antral vascular ectasia confirmed on endoscopy	0.10	0.41	0.30	2
Digital ulcerations	<0.001	0.39	0.41	2
Pseudo-obstruction with symptoms and dilatation of the small and/or large bowel on imaging	0.13	0.48	0.35	2
Scleroderma myocardial disease based on clinical features and supported by MRI and/or endomyocardial biopsy	0.031	0.34	0.55	3
ILD based on > 25% extent of lung disease on HRCT chest	0.031	0.31	0.81	4
Need for supplemental oxygen	0.031	0.36	0.78	4
Moderate to severe right ventricular dysfunction on TTE	0.031	<0.001	0.88	4
Pulmonary arterial hypertension defined as mean pAP > 25 mmHg and wedge pressure < 15mmHg	0.031	<0.001	0.97	5
Low BMI of < 18.5 kg/m2 and/or weight loss of > 10% in the last 12 month	0.031	<0.001	0.98	5
ILD with FVC < 70% predicted	0.031	0.33	0.93	5
Six minute walk distance < 250 meters	0.031	<0.001	1.3	7
Total				50

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/development-of-a-disease-damage-index-in-systemic-sclerosis-using-consensus-and-data-driven-methods

Abstract Number: 829

Fecal Incontinence and Association with Bowel Dysfunction in Systemic Sclerosis: A Canadian Multicenter Study

Nicolas Richard[1,2], Marie Hudson[2], Genevieve Gyger[2], Murray Baron[3], Evelyn Sutton[4], Nader A. Khalidi[5], Janet E. Pope[6], Nathalie Carrier[1], Maggie J. Larche[5], Alexandra Albert[7], Paul R. Fortin[7], Carter Thorne[8], Ariel Masetto[9] and Canadian Scleroderma Research Group, [1]Université de Sherbrooke, Centre Hospitalier Universitaire de Sherbrooke, Sherbrooke, QC, Canada, [2]McGill University, Jewish General Hospital, Montreal, QC, Canada, [3]Rheumatology, McGill University, Jewish General Hospital, Montreal, QC, Canada, [4]Rheumatology, Dalhousie University, Nova Scotia Rehabilitation Centre, Halifax, NS, Canada, [5]McMaster University, St Joseph's Healthcare Hamilton, Hamilton, ON, Canada, [6]Monsignor Roney Bldg/Rheum, University of Western Ontario, St Joseph Health Care, London, ON, Canada, [7]Université Laval, CHU de Québec, Québec, QC, Canada, [8]Southlake Regional Health Centre, Newmarket, ON, Canada, [9]Department of Medicine/Division of Rheumatology, Université de Sherbrooke, Centre Hospitalier Universitaire de Sherbrooke, Sherbrooke, QC, Canada

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Background/Purpose: Gastrointestinal (GI) tract involvement is a common and serious complication of systemic sclerosis (SSc). However, the prevalence of fecal incontinence (FI) and its relationship with other GI symptoms in SSc remain largely unknown. In this study, we aimed to establish the prevalence and severity of FI in an SSc cohort, to study the association between FI and constipation, small intestinal bacterial overgrowth (SIBO) and other potential predictors of FI, and to determine the impact of FI on health-related quality of life (HRQoL) in SSc.

Methods: We performed a multicenter, cross-sectional study of 271 patients with SSc followed in the Canadian Scleroderma Research Group registry (CSRG). In addition to the standardized data collection protocol, participants were asked to complete three validated questionnaires: Bristol stool scale (BSS; measuring consistency of stool from 1, being hardest, to 7, being completely liquid stool), Jorge-Wexner score (JWS; FI severity score ranging from 0-20, with 20 being most severe), and Fecal Incontinence Quality of Life scale (FIQOL; measuring 4 domains: lifestyle, coping/behaviour, depression/self perception, embarrassment). The Rome III criteria were used to define constipation. Descriptive statistics and multivariate regression analyses were generated to determine associations between the JWS and other clinical variables.

Results: Mean age was 59.3±12.1 years, 87.4% were women, median (interquartile range, IQR) disease duration was 10.3 (6.6-17.8) years and 30.0% had diffuse cutaneous SSc. Median BSS was 4.0 (3.0-4.0), 103 (39.6%) subjects met the criteria for constipation and 34 (13.2%) had been treated with antibiotics for SIBO since disease onset. FI, defined as a JWS ≥5, was identified in 74 (27.3%) subjects; among them 33 (12.2%) were mild (score 5-9) and 41 (15.1%) moderate to severe (score ≥10).

In multivariate logistic regression analyses, variables associated with FI were (OR (95% confidence interval)): loose (BSS≥6) vs well-formed (3≤BSS<6) stools (5.93 (1.81-19.42), p=0.003); history of forcep use at time of delivery (2.37 (1.13-4.94), p=0.022); constipation (3.21 (1.46-7.06), p=0.004) and history of antibiotic use for SIBO (4.82 (1.88-12.32), p=0.001). Other variables associated with FI in univariate but not multivariate analyses included advancing age (p=0.031), female gender (p=0.002), urinary incontinence (p<0.001), use of stool softeners

(p=0.022) and domperidone (p=0.034). No difference was found with disease duration (p=0.918), limited or diffuse cutaneous disease subsets (p=0.670) or SSc-specific antibodies (all p >0.4). HRQoL decreased significantly as severity of fecal incontinence increased (correlation coefficients of JWS with all 4 domains of FIQOL between -0.6 and -0.7, all p<0.001).

Conclusion: In this multicenter study, FI was common and often severe in SSc. Loose stools, SIBO, as well as constipation were strongly associated with FI. FI had a strong negative impact on HRQoL. These data can inform the design of future interventional studies aimed at improving the management of FI and HRQoL in SSc.

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Abstract Number: 830

Calcinosis Is Associated with Digital Ulcers and Osteoporosis in Patients with Systemic Sclerosis

Antonia Valenzuela[1], Murray Baron[2], Ariane L. Herrick[3], Susana Proudman[4], Wendy Stevens[5], Tatiana Sofia Rodriguez-Reyna[6], Alessandra Vacca[7], Thomas A. Medsger Jr.[8], Monique Hinchcliff[9], Vivien Hsu[10], David Fiorentino[11], Lorinda Chung[12] and the Canadian Scleroderma Research Group, and the ASIG rubric, [1]Stanford University School of Medicine, Stanford, CA, [2]Rheumatology, McGill University, Jewish General Hospital, Montreal, QC, Canada, [3]Centre for Musculoskeletal Research, University of Manchester, Manchester Academic Health Science Centre, Manchester, United Kingdom, [4]Rheumatology Unit, Royal Adelaide Hospital North Terrace, Adelaide, Australia, [5]Department of Rheumatology, St. Vincent's Hospital Melbourne, Melbourne, Australia, [6]Immunology and Rheumatology, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico, [7]University Hospital of Cagliari, Rheumatology Unit, Monserrato, Italy, [8]Department of Medicine/Rheumatology, University of Pittsburgh, Pittsburgh, PA, [9]Rheumatology, Northwestern University, Chicago, IL, [10]Rheumatology, RWJ Med Schl Scleroderma Prog, New Brunswick, NJ, [11]Department of Dermatology, Stanford University School of Medicine, Palo Alto, CA, [12]Stanford University, Palo Alto, CA

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Background/Purpose: Calcinosis is a debilitating complication of systemic sclerosis (SSc). We sought to determine the clinical factors associated with calcinosis in an international multi-center collaborative effort with the Scleroderma Clinical Trials Consortium (SCTC).

Methods: This is a retrospective cohort study of 5180 patients with SSc from 9 centers within the US, Australia, Canada, United Kingdom, Italy, and Mexico. Calcinosis was determined by physical examination and/or radiography. Logistic regression was used to obtain odds ratios (OR) relating calcinosis to various clinical features in multivariate analyses adjusted for disease duration, gender, and modified Rodnan skin score (mRSS).

Results: A total of 1290 patients (24.4%) had calcinosis. In univariate analyses (Table), not correcting for multiple comparisons, patients with calcinosis were older than patients without calcinosis, more likely to be female, and had longer disease duration from first non-Raynaud symptom. Patients with calcinosis were more likely to have digital ulcers, telangiectasias, and acro-osteolysis, cardiac disease, pulmonary hypertension, gastrointestinal involvement, and arthritis, but less likely to have myositis. Osteoporosis was much more common in patients who had calcinosis. Scl-70, RNA-polymerase-III, and RNP autoantibodies were significantly less common in patients with calcinosis, while anticentromere (ACA), PM-1, and anticardiolipin were more frequent. In multivariate analysis, the strongest associations with calcinosis were digital ulcers (OR 3.7, 95%CI 2.6-5.3, p<0.0001), and osteoporosis (OR 3.9, 95%CI 2.1-7.4, p<0.0001). After controlling for steroid use and body mass index in the model, the association with osteoporosis persisted in stratified analyses in non-obese patients (OR 6.5, 95%CI 1.8-23.8, p=0.004).

Conclusion: Almost one quarter of patients with SSc have calcinosis. Our data support a strong association of calcinosis with digital ulcers and osteoporosis in non-obese patients. We were successfully able to gather data from many sources, which markedly increased the power of our study in this rare disease. Our study sets a precedent for future studies of calcinosis in SSc and our results may guide the development of future therapies.

Table. Non-stratified univariate and multivariate analyses (calcinosis is the dependent variable).

	n (%)	Univariate analysis			Multivariate analysis		
		OR	95%CI	p-value	OR	95%CI	p-value
Age at last visit	4929 (93.4)	1.02	1.01 – 1.02	<0.0001			
Disease duration	5052 (95.7)	1.05	1.04 – 1.05	<0.0001	-	-	-
Female	5218 (98.8)	1.6	1.3 – 1.9	<0.0001	2.8	1.4 – 5.7	0.0038
Obese	3473 (65.8)	0.8	0.6 – 0.9	0.0133			
Steroids use ever	3503 (66.3)	0.7	0.6 – 0.8	<0.0001			
mRSS >11	4978 (94.3)	1.1	0.98 – 1.3	0.0759	-	-	-
Raynaud's phenomenon	5199 (98.5)	2.9	1.7- 4.9	<0.0001			
Digital ulcers	4992 (94.5)	3.6	3.2 – 4.2	<0.0001	3.7	2.6- 5.3	<0.0001
Digital pitting scars	5182 (98.1)	3.0	2.7 - 3.5	<0.0001			
Loss of digital pulp	3452 (65.4)	2.9	2.5 - 3.4	<0.0001			
Nailfold capillary changes	3826 (72.5)	2.7	2.3- 3.2	<0.0001			
Puffy fingers	4922 (93.2)	0.8	0.7 - 0.9	0.0232	0.6	0.4 - 0.9	0.0179
Sclerodactyly	5204 (98.6)	1.6	1.3 - 2.0	<0.0001			
Acroosteolysis	1156 (21.9)	3.5	2.5 – 4.9	<0.0001			
Telangiectasias	4888 (92.6)	4.1	3.4 – 4.9	<0.0001	3.5	2.1 – 5.7	<0.0001
Osteoporosis	2127 (40.3)	10.2	6.9 – 15.0	<0.0001	3.9	2.1 – 7.4	<0.0001
Cardiac disease	4907 (92.9)	1.6	1.3 – 1.9	<0.0001	1.9	1.1 – 3.0	0.0136
PAH	4990 (94.5)	1.2	1.0 – 1.5	0.0231			
GI disease	5179 (98.1)	1.7	1.4 – 1.96	<0.0001	1.9	1.1 – 2.5	0.0265
Myositis	4580 (86.7)	0.7	0.6 – 0.9	0.001	-	-	-
Arthritis	4606 (87.2)	1.2	1.0 – 1.4	0.0416	1.5	1.0 - 2.2	0.0323
Positive Scl-70	4578 (86.7)	0.6	0.5 - 0.8	<0.0001			
Positive anticentromere	3370 (63.8)	1.7	1.4 – 2.0	<0.0001	2.4	1.6 – 3.5	<0.0001
Positive PM-1	1825 (34.6)	1.8	1.2 – 2.5	0.0028			
Positive RNA polymerase III	2414 (45.7)	0.8	0.6 - 0.9	0.0159			
Positive RNP	4286 (81.2)	0.5	0.4 - 0.8	0.0002			
Positive Anticardiolipin	949 (18.0)	1.7	1.2 – 2.2	0.0005			

Abbreviations: mRSS=modified Rodnan skin score, PAH=pulmonary artery hypertension, GI=gastrointestinal, ACA=anticentromere, RNP= Ribonucleoprotein

Multivariate model included: disease duration from first non-Raynaud symptoms, gender, modified Rodnan skin score (mRSS), digital ulcers, puffy fingers, telangiectasias, osteoporosis, cardiac disease, GI disease, myositis, arthritis, and anticentromere antibody.

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Mycophenolate Decreases the Frequency of Endoscopic Therapy for Gastric Antral Vascular Ectasia in Patients with Systemic Sclerosis

Tiffany Lin[1], James Bena[2], Shannon Morrison[2] and Soumya Chatterjee[3], [1]Rheumatology, Cleveland Clinic Foundation, Cleveland, OH, [2]Quantitative Health Sciences, Cleveland Clinic Foundation, Cleveland, OH, [3]Cleveland Clinic Foundation, Cleveland, OH

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Background/Purpose: Gastric antral vascular ectasia (GAVE) is an increasingly recognized cause of upper gastrointestinal bleeding in patients with systemic sclerosis (SSc). These patients may require frequent interventions, which negatively impact quality of life. There is currently no defined role for immunosuppressive therapy in the treatment of GAVE. The goal of this study was to determine whether immunosuppressive therapy, used for any indication, also has a role in reducing the frequency of interventions for GAVE in patients with SSc.

Methods: A retrospective chart review was performed on patients that were seen within the past 10 years at our institution who had SSc complicated by GAVE. Data on demographic and clinical characteristics were collected. Types of immunosuppressive therapies and the time periods used were recorded. Intervention rates (hospitalizations, blood transfusions, and endoscopic therapies) were compared using repeated measures Poisson regression models to account for the different medication periods for each patient.

Results: Forty-eight patients with SSc complicated by GAVE were identified (Table 1). Twenty-nine received immunosuppressive therapy. Those who received immunosuppressive therapy had anti-centromere antibodies less often than those who did not receive therapy (17.2% versus 52.6%, p=0.010). Other patient characteristics were not significantly different between the two groups. The most commonly used therapy was mycophenolate (n=14), followed by glucocorticoids (n=11), hydroxychloroquine (n=7), cyclophosphamide (n=4), intravenous immunoglobulin (n=3), methotrexate (n=3), and azathioprine (n=1). When receiving immunosuppressive therapy, patients required therapeutic endoscopies less frequently (0.51/year versus 1.37/year, p=0.009) (Table 2). This decrease in frequency was more pronounced with mycophenolate in particular (0.25/year versus 1.37/year, p=0.013). There were no significant differences in hospitalization or blood transfusion frequencies.

Conclusion: Mycophenolate may have the potential to alter the course of disease in patients who have GAVE associated with SSc, and can be considered in those who require frequent therapeutic endoscopies. Further studies are needed to confirm these findings.

Table 1. Demographic and clinical characteristics of patients with SSc complicated by GAVE who never received immunosuppressive therapy compared to those who received immunosuppressive therapy

	Overall (N=48)		Never Treated (N=19)		Treated (N=29)		
Factor	N	Summary	N	Summary	N	Summary	p-value
Age (years)	48	65.0 (35.0, 86.0)	19	67.0 (35.0, 79.0)	29	64.0 (48.0, 86.0)	0.72[b]
Race	48		19		29		0.97[c]
Caucasian		30 (62.5)		12 (63.2)		18 (62.1)	
African American		3 (6.3)		1 (5.3)		2 (6.9)	
Unknown / Not Reported		15 (31.3)		6 (31.6)		9 (31.0)	
Gender	48		19		29		0.053[c]
Female		39 (81.3)		18 (94.7)		21 (72.4)	
Male		9 (18.8)		1 (5.3)		8 (27.6)	
Co-morbidities							
Chronic renal failure	48	2 (4.2)	19	0 (0.0)	29	2 (6.9)	0.51[d]
Congestive heart failure	48	2 (4.2)	19	1 (5.3)	29	1 (3.4)	0.99[d]
Sjogren's disease	48	5 (10.4)	19	4 (21.1)	29	1 (3.4)	0.072[d]
Hypothyroidism	48	6 (12.5)	19	3 (15.8)	29	3 (10.3)	0.67[d]
Subtype of systemic sclerosis	44		17		27		0.063[c]
Diffuse		18 (40.9)		4 (23.5)		14 (51.9)	
Limited		26 (59.1)		13 (76.5)		13 (48.1)	
Other organ involvement							
Pulmonary arterial hypertension	44	13 (29.5)	18	4 (22.2)	26	9 (34.6)	0.38[c]
Interstitial lung disease	44	11 (25.0)	18	3 (16.7)	26	8 (30.8)	0.29[c]
Gastroesophageal reflux disease	46	37 (80.4)	19	16 (84.2)	27	21 (77.8)	0.59[c]
Antibody subtype							
ANA only (no subtype)	48	5 (10.4)	19	3 (15.8)	29	2 (6.9)	0.37[d]
Scl-70	48	0 (0.0)	19	0 (0.0)	29	0 (0.0)	NA
Centromere	48	15 (31.3)	19	10 (52.6)	29	5 (17.2)	***0.010***[c]
RNA polymerase III	48	15 (31.3)	19	3 (15.8)	29	12 (41.4)	0.061[c]
U3-RNP	48	1 (2.1)	19	0 (0.0)	29	1(3.4)	0.99[d]
PM-Scl	48	1 (2.1)	19	0 (0.0)	29	1 (3.4)	0.99[d]
U1-RNP	48	3 (6.3)	19	0 (0.0)	29	3 (10.3)	0.27[d]
SS-A	48	10 (20.8)	19	5 (26.3)	29	5 (17.2)	0.45[c]
Years since GAVE diagnosis	48	2.0 (0.14, 13.2)	19	2.2 (0.14, 10.3)	29	1.9 (0.34, 13.2)	0.76[b]
Years of follow-up	48	2.0 (0.14, 13.2)	19	2.2 (0.14, 10.3)	29	1.9 (0.34, 13.2)	0.76[b]

Values presented as Median (min, max) or N (column %)
p-values: b=Wilcoxon rank sum test, c=Pearson's chi-square test, d=Fisher's exact test

Table 2. Intervention rates and relative risks during time periods not on immunosuppressive therapy (1st column) compared to time periods on immunosuppressive therapy (2nd and 3rd columns) and specifically mycophenolate (4th and 5th columns)

	Not on Therapy (112.8 person years)		Immunosuppressive Therapy (51.19 person years)		Immunosuppressive Therapy vs. Not on Therapy		Mycophenolate (23.60 person years)		Mycophenolate vs. Not on Therapy	
Measure	n	Rate per year (95% CI)	n	Rate per year (95% CI)	Relative Risk	p-value	n	Rate per year (95% CI)	Relative Risk	p-value
All interventions	198	1.74 (1.08, 2.84)	44	0.86 (0.49, 1.51)	0.49 (0.23, 1.04)	0.064	9	0.38 (0.11, 1.36)	0.22 (0.06, 0.85)	***0.028***
Hospitalizations	27	0.24 (0.11, 0.50)	9	0.18 (0.07, 0.44)	0.73 (0.24, 2.24)	0.59	1	0.04 (0.01, 0.32)	0.18 (0.02, 1.56)	0.12
Blood transfusions	16	0.14 (0.06, 0.32)	9	0.18 (0.08, 0.37)	1.24 (0.46, 3.32)	0.67	2	0.08 (0.02, 0.33)	0.60 (0.12, 2.92)	0.53
Endoscopic therapies	155	1.37 (0.85, 2.23)	26	0.51 (0.31, 0.84)	0.37 (0.18, 0.78)	***0.009***	6	0.25 (0.07, 0.88)	0.19 (0.05, 0.70)	***0.013***

n = total count of each type of intervention

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The Validity and Reliability of Online Obituaries As a Source of Mortality Data

Medha Soowamber[1], John T. Granton[2], Fatemeh Bavaghar-Zaeimi[3] and Sindhu R. Johnson[4,5], [1]Rheumatology, University of Toronto/ Toronto Western Hospital, Toronto, ON, Canada, [2]Medicine, Univeristiy Health Network Pulmonary Hypertension Programme, Toronto General Hospital and University of Toronto, Toronto, ON, Canada, [3]Rheumatology, Toronto Scleroderma Program, Toronto Western Hospital and Mount Sinai Hospital, Toronto, ON, Canada, [4]Toronto Scleroderma Program, Division of Rheumatology, Toronto Western Hospital, Mount Sinai Hospital, Institue of Health Policy, Management and Evaluation, University of Toronto, Toronto, ON, Canada, [5]Institute of Health Policy, Management and Evaluation,, University of Toronto, Toronto, ON, Canada

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Background/Purpose: Loss to follow-up is a major threat to the conduct of chronic disease cohort research. Tracking the survival status of patients who are lost to follow-up is limited by restricted access to death certificate data and patients moving. One strategy to gather mortality data is to use online obituaries. Although commonly used clinically, it is uncertain if this is appropriate for research. The primary objective of this study was to evaluate the reliability and validity of online obituaries as a source of mortality data in 2 chronic diseases, systemic sclerosis (SSc) and idiopathic pulmonary arterial hypertension (IPAH).

Methods: Patients whose survival status was known were randomly selected from the Toronto Scleroderma Program and the University Health Network Pulmonary Hypertension Program. Five commonly used online obituaries were evaluated. Two investigators, blinded to survival status, independently entered the first and last name of each patient in each website. If the patient was identified as deceased, other matching variables (date of birth, postal code, disease) were used to verify the patient. Pearson's correlation coefficient (r) was used to evaluate the correlation between the website finding and actual survival status. Intra-rater and inter-rater reliability was evaluated using the intra-class correlation coefficient (ICC).

Results: We studied 365 patients (273 females, 92 males) including 219 SSc (171 females, 48 males) and 146 IPAH (102 females, 44 males) patients. There was a significant positive correlation between website 1 and the actual survival status ($r = 0.36$ (95%CI 0.27, 0.45, $p<0.001$)) and was similar across diseases, SSc ($r=0.34$ (95%CI 0.21, 0.45, $p<0.001$) and IPAH ($r=0.41$ (95% CI 0.26, 0.53, $p<0.001$). The ICC for the intra-rater reliability of websites 1 and 3 were 0.95 (95%CI 0.93, 0.96) and 0.96 (95%CI 0.95, 0.97) respectively, which were higher compared website 2, 4, 5 (0.77 (95%CI 0.72, 0.80), 0.75 (95%CI 0.71, 0.80) and 0.21 (95%CI 0.11, 0.31) respectively). The ICC for inter-rater reliability was strong (0.82 (95%CI 0.78, 0.85).

Conclusion: Use of selected online obituaries is a valid and reliable method to gather mortality data. They could be used in clinical research to track patients who are lost to follow up.

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Safety and Immunogenicity of Pneumococcal Vaccine in Patients with Systemic Sclerosis and Healthy Controls

Johanna Nagel[1], Tore Saxne[2], Pierre Geborek[3], Lillemor Scattum[4], Roger Hesselstrand[5] and **Meliha C. Kapetanovic**[3], [1]Department of Clinical Sciences, Lund, Section of Rheumatology, Lund University and Skåne University Hospital, Lund, Sweden, Lund, Sweden, [2]Dept of Clinical Sciences, Lund, Section of Rheumatology, Lund University, Lund, Sweden, [3]Department of Clinical Sciences Lund, Section of Rheumatology Lund University and Skåne University Hospital, Lund, Sweden, [4]Department of Laboratory Medicine, Section of Microbiology, Immunology and Glycobiology, Lund University, Lund, Sweden, [5]Department of Clinical Sciences, Section of Rheumatology, Lund University, Lund, Sweden

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Background/Purpose: Studies investigating the immunogenicity of pneumococcal vaccine in patients with systemic sclerosis (SSc) are scarce. We aim to investigate the impact of SSs disease and treatment with disease modifying antirheumatic drugs (DMARDs) on antibody response elicited by either 13-valent pneumococcal conjugate vaccine (PCV13) or 23-valent pneumococcal polysaccharide vaccine (PPV23) in patients with SSc compared to healthy controls (HC).

Methods: In total, 44 SSc patients receiving standard of care treatment and 49 HC were vaccinated with a single dose of either PCV13 or PPV23. of 44, 12 SSc patients received DMARDs (mycophenolate mofetil=7; azathioprine=4 and azathioprine+hydroxychloroquine=1). Response to two pneumococcal capsular polysaccharides (6B and 23F) were measured in serum before and 4-6 weeks after vaccination using standard ELISA. Geometric mean levels (GML) were calculated from log transformed pre- and postvaccination antibody levels and then compared using paired T-test. Antibody responses between vaccines were also compared.

Results: Both vaccines were generally well tolerated. Number of patients, percentage female (%), mean age and mean disease duration (years) at vaccination were: 32, 94%, 57.5 and 11.4 years in SSs without DMARDs; 12, 100%, 55.5 and 6.2 years in SSc patients on DMARDs and 49, 63% and 50.6 years in HC. Numbers of patients immunized with PCV13 or PPV23 and GML (95% CI) for both serotypes tested are shown in Table. Prevaccination antibody levels to both serotypes did not differ between three groups (Mann-Whitney U-test). Prevaccination antibody levels for both serotypes increased significantly in SSc without DMARDs and HC ($p<0.001$) but not in SSc patients on DMARDs ($p=0.115$ for 6B and $p= 0.091$ for 23F). Compared to HC and SSc without DMARDs patients with SSc treated with DMARDs had lower postvaccination antibody levels for both serotypes. There were no significant differences in antibody levels between SSc patients without DMARDs and HC. When pre- and postvaccination antibody levels for 6B and 23F were compered between individuals immunised with PCV13 and those immunised with PPV23, no significant difference was seen within the same treatment group or within the whole study population.

Conclusion: Pneumococcal vaccination using either PCV13 or PPV23 yielded satisfactory antibody response in SSc patients not treated with DMARDs but decreased levels in patients treated with synthetic DMARDs suggesting a need of vaccination before start of treatment. Type of pneumococcal vaccine (conjugate vs polysaccharide) did not have a significant impact on the vaccination response.

ClinicalTrials.gov Identifier: NCT02240888

Table. Numbers of patients immunized with PCV13 or PPV23 and GML (95% CI) for serotypes 6B and 23F

		13-valent PCV antibody levels GML (95% CI)		**23-valent PPV antibody levels GML (95% CI)**	
Treatment groups (number of patients)	Serotypes	**before vaccination**	**after vaccination**	**before vaccination**	**after vaccination**
SSc without DMARDs (n=32)*	6B	0.7 (0.3-1.6)	2.8 (1.6-4.9)	0.4 (0.1-1.4)	3.1(0.7-14)
	23F	0.5 (0.3-0.9)	1.4 (0.7-2.8)	0.4 (0.1-2.5)	7.3 (2.7-20)
SSC on DMARD (n=12)**	**6B**	**0.3 (0-3.4)**	**1.5 (0.4-5.8)**	**0.5 (0.1-4.0)**	**0.6 (0-15)**
	23F	**0.3 (0.1-0.7)**	**0.8 (0.2-3.5)**	**0.5 (0-9.3)**	**0.6 (0-18)**
Healthy controls (n=49)***	6B	0.9 (0.5-1.6)	2.8 (1.7-4.8)	0.3 (0.1-0.7)	5.9 (0.9-40)
	23F	0.6 (0.4-1.0)	3.4 (2.0-5.7)	0.5 (0.1-3.3)	3.1 (0.2-45)

*25 patients received PCV13 and 7 patients received PPV23; **SSC 6 patients received PCV13 and 6 patients received PPV23; *** 44 patients received PCV13 and 5 patients received PPV23

Disclosure: J. Nagel, None; **T. Saxne**, None; **P. Geborek**, None; **L. Scattum**, None; **R. Hesselstrand**, None; **M. C. Kapetanovic**, None.

Abstract Number: 834

The Efficacy of Rituximab in Systemic Sclerosis Joint Disease: A Pilot Study

Helena Borrell Paños[1], Javier Narváez[2], Juan José Alegre[3], Ivan Castellvi[4], Gloria Albert Espi[3], Sergi Heredia[1], Elide Toniolo[4] and Joan Miquel Nolla[1], [1]Department of Rheumatology, Hospital Universitario de Bellvitge, Barcelona, Spain, [2]Rheumatology, Hospital Universitario de Bellvitge, Barcelona, Spain, [3]Rheumatology Department, Hospital Universitario Doctor Peset, Valencia, Spain, [4]Rheumatology Unit. Hospital de la Santa Creu i Sant Pau, Barcelona, Spain

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Session Title: Systemic Sclerosis, Fibrosing Syndromes and Raynaud's - Clinical Aspects and Therapeutics Poster I

Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose:

Between 16 and 20% of patients with systemic sclerosis (SS) have arthritis, which is occasionally erosive. In addition, between 1 and 5% of patients show syndrome overlap with rheumatoid arthritis (RA).

The initial management of this complication is typically similar to RA, with the use of methotrexate as a first-choice DMARD. In refractory cases, anti-TNF therapies could be useful. However, many of these patients develop diffuse interstitial lung disease (DILD), which contraindicates the use of these drugs.

Our objective was to evaluate the efficacy and safety of rituximab (RTX) in the treatment of joint disease in patients with SS.

Methods:

An ambispective study of 13 patients with SS (ACR/EULAR 2013 criteria) and severe polyarticular disease treated with RTX was performed. The primary efficacy outcome was an improvement of joint counts, as evaluated by DAS28-ESR at the end of the follow-up period

Results:

Of the 13 patients included (12 women), seven (54%) had diffuse SS and six had a limited form of the disease. The mean age (± SD) was 54 ± 11 years, and the time of evolution (median) was 7 ± 12 years. Two (15%) patients had positive ACPA and fulfilled the criteria for RA classification. The baseline DAS28-ESR score was 6.4 ± 1.8.

The main clinical characteristics and response to treatment are shown in the following table.

Indication	DAS28 at the beginning	Time tracking (months)	Number of cycles	DAS28 at last visit	Previous treatments
Polyarthritis + DILD	6.55	12	2	2.21	MTX, LEF, Etanercept
Polyarthritis (overlap RA)	6.47	18	3	3.01	MTX, LEF, D-penicilamina
Polyarthritis	6.61	18	3	2.45	MTX, LEF, D-penicilamina
Polyarthritis + DILD	7.92	18	3	2.31	CFM, MMF
Polyarthritis	6.78	12	2	2.41	MTX, SZP, MMF
Polyarthritis	7.88	6	1	6.66	MTX, SZP, LEF, HCQ
Polyarthritis	7.05	18	3	3.43	MTX, CFM, SZP, MMF
Polyarthritis + DILD	4.47	27	4	3.06	MMF
Polyarthritis + DILD	4.38	16	2	1.89	MMF
Polyarthritis + DILD + calcinosis	3.39	16	2	2.52	MMF
Polyarthritis + DILD + severe skin disease	4.85	48	4	2.12	MMF, Imatinib
Polyarthritis + DILD + severe skin disease + calcinosis	4.36	24	4	3.20	CFM
Polyarthritis + DILD	3.49	30	3	1.19	CFM, MMF

RTX treatment was only ineffective in one patient (8%) and was suspended at six months because of ineffectiveness. In the remaining 12 patients (92%), a good control of joint counts was achieved, and at the end of the follow-up period (median ± SD) of 18 ± 10 months (range, 12-48), the mean DAS28-ESR score decreased to 2.8 ± 1.3 (% improvement: mean -46.89%; range, -70.83% to -15.48%). In eight patients (61%), joint

disease remission (DAS28 < 2.6) was achieved. Three patients (23%) had low activity (DAS28 ≤ 3.2), and one (8%) had moderate activity.

The frequency of adverse effects was low, occurring in only two (15%) patients: one patient had two episodes of transient neutropenia (one feverish, prompting hospitalization), and the other had several mild infections (gastroenteritis, a urinary tract infection, and a respiratory infection). In neither of the two cases was it necessary to discontinue RTX treatment. In the patients with concomitant DILD, no worsening was observed in lung function tests.

Conclusion:

In our experience, RTX is a safe and effective drug for the treatment of joint disease in patients with SS

Disclosure: H. Borrell Paños, None; **J. Narváez**, None; **J. J. Alegre**, None; **I. Castellvi**, None; **G. Albert Espi**, None; **S. Heredia**, None; **E. Toniolo**, None; **J. M. Nolla**, None.

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Abstract Number: 835

A Meta-Analysis to Determine If the Prevalence of Scleroderma Renal Crisis Decreasing with Time

Matthew Turk[1] and Janet E. Pope[2], [1]Medicine/Rheumatology, University of Western Ontario, London, ON, Canada, [2]University of Western Ontario, London, ON, Canada

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Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose:

Systemic sclerosis (scleroderma, SSc) is an autoimmune connective tissue disease with increased mortality from various internal organ involvement. Scleroderma renal crisis (SRC) usually occurs in the diffuse cutaneous systemic sclerosis (dcSSc) subset. It causes acute severe hypertension and acute renal failure. In recent years, it has been treated with angiotensin-converting enzyme (ACE) inhibitors with great success and improved mortality. The prevalence of SRC since its classification in the early 1970s was determined as it is our impression that SRC prevalence is decreasing over time.

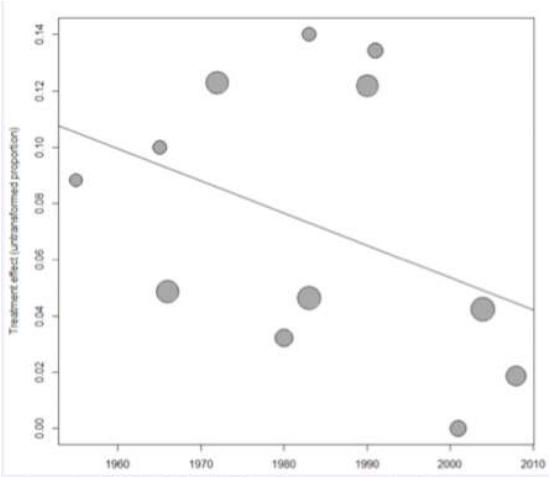
Methods:

A review of published articles and unpublished data was conducted up to May 2015 using MEDLINE, EMBASE, CINAHL, and Cochrane databases. Articles were included if they pertained to the prevalence of SRC in a cohort of patients. Articles were excluded if they were not in English, did not have a cohort of at least 50 dcSSC patients, if they were review articles, or solely abstracts.

Results: Of the 5306 citations identified, only 11 qualified. They were from Europe, USA, Australia, UK, and India. Years of publication were from 1983 to 2011 and cohort size varied from 68 to 3656 patients with SSc totaling 11,139 patients (4,536 [40.7%] with dcSSc). Dividing data by year of publication, before and including 1990, SRC occurred in 13.5% of dcSSc, from 2002 to 2007, SRC was in 7.9% and in 2010 and 2011, SRC had was infrequent at 2.4% (Figure). In lcSSc the range was from 0 to 4% with no obvious decreasing over time.

Conclusion:

It appears that SRC remains very uncommon in lcSSc and the rate in this group may be stable over time. However, the frequency of SRC has dropped dramatically in the dcSSc subset. The reasons for this are not known, especially as there is longer survival in SSc. Prophylactic use of ACE inhibitors does not seem to decrease the risk of SRC (observed in other studies) so it may be the changing etiology of SSc over time.



Graph of SRC in dcSSc by year of cohort

Disclosure: M. Turk, None; **J. E. Pope**, None.

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Abstract Number: 836

Influence of B Cell Depletion By Monoclonal Anti CD20 Antibodies in Systemic Sclerosis: Results of a Randomized Placebo Controlled Trial

Samira Ben Said-Bouyeri[1], Jessica Meijs[1], Nina Ajmone Marsan[2], Anne A. Schouffoer[1], Maarten K. Ninaber[3], Hans Ulrich Scherer[4], Femke Bonte-Mineur[5], T. W. J. Huizinga[1] and Jeska K. de Vries-Bouwstra[1], [1]Rheumatology, Leiden University Medical Center, Leiden, Netherlands, [2]Cardiology, Leiden University Medical Center, Leiden, Netherlands, [3]Pulmonology, Leiden University Medical Center, Leiden, Netherlands, [4]Department of Rheumatology, Leiden University Medical Center, Leiden, Netherlands, [5]Maasstad Hospital, Rotterdam, Rotterdam, Netherlands
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Session Title: Systemic Sclerosis, Fibrosing Syndromes and Raynaud's - Clinical Aspects and Therapeutics Poster I

Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose: Systemic sclerosis (SSc) is a severe, systemic auto-immune disease with limited treatment options. Previous observational studies showed possible efficacy of Rituximab (RTX), a monoclonal antibody against CD20. Our objective was to evaluate safety and efficacy of RTX in patients with SSc.

Methods: In this randomized, double-blind, placebo-controlled, single centre trial, patients with SSc (ACR 1980 criteria), diagnosed less than 2 years ago, were assigned to receive either 1000mg RTX or placebo on day 1, 15 and at 6 months. Patients were followed for 2 years with 3 monthly evaluation of modified Rodnan Skin Score (mRSS) , pulmonary function, laboratory tests and 6 monthly evaluation of high resolution CT thorax and cardiac ultrasound. Primary endpoints of the study were treatment related mortality, treatment related toxicity and clinical efficacy reflected by progression-free survival. Adverse events (AE) and serious adverse events (SAE) were recorded every visit. Progression was defined as ³ 10% drop in Forced Vital Capacity (FVC)of predicted, and/or ³ 15% drop in Diffuse Capacity of the Lung for Carbon Monoxide (DLCO) of predicted, and/or ³ 15% drop in left Ventricle Ejection fraction (LVEF), and/or ³ 15% drop in body weight, and/or ³ 30% drop in creatinine clearance, and/or ³ 30% increase in mRSS on 2 consecutive visits.

Results: Seventeen patients, including 14 females (82%), 11 Caucasians (65%), mean aged 39 (SD 14) years and a mean mRSS of 13 (SD 10), were included. One patient did not start treatment due to disease progression within 2 weeks after screening. Of the remaining patients, 8 received RTX and 8 received placebo. At baseline, patients characteristics were comparable between the groups. Two patients dropped out after 6 months, n = 1 (RTX) at own request, and n = 1 (placebo) due to active disease. This patient eventually died of a renal crisis after autologous stem cell transplantation.

After a median follow-up of 22 months (19-26 IQR), in total 90 AE (n=54 AE in n=8 for RTX; n=36 AE in n =8 for placebo; p=0,442) were reported of which 11 SAE (n=6 SAE in n= 5 for RTX; n=5 SAE in n=2 patients for placebo; p=0.335; none could be related to RTX). With placebo, disease progression according to prespecified criteria was observed in 1 patient (T= 18 months; based on ³ 30% increase in mRSS) ,

while progression free survival was 100% with RTX (p=0.13). Over time, no significant differences in mean mRSS, FVC, DLCO, LVEF and creatinine clearance were observed between the groups (Table 1: mean mRSS).

Conclusion: These preliminary results show that treatment with RTX is well tolerated by SSc patients. Although no differences in clinical parameters were observed between the groups, progression free survival was 100% with RTX and 75% with placebo. More detailed analyses on clinical and serological parameters, and functional ability scores, are currently being performed to evaluate efficacy of RTX.

Table 1: Efficay on skin (mRSS)				
mRSS		**Placebo**	**Rituximab**	
(mean (SD)/median (IQR))		**n=8**	**n=8**	
	Baseline	14 (11) / 16 (3-22)	16 (12) / 14 (9-20)	
	T=3 months	10 (9) / 7 (3-17)	17 (14) / 13 (9-23)	
	T=6 months	11 (9) / 11 (3-18)	15 (16) / 8 (6-24)	
	T=9 months	7 (5) / 6 (2-13)	9 (3) / 8 (8-12)	
	T=12 months	4 (7) / 2 (0-7)	9 (7) / 6 (4-18)	
	T=18 months	8 (11) / 3 (1-24)	9 (5) / 11 (5-14)	
	T=24 months	7 (8) / 6 (0-15)	9 (8) / 8 (3-18)	
mRSS: modified Rodnan Skin Score; SD: standard deviation; IQR: interquartile range; n=number of patients; T=follow up time				

Disclosure: S. Ben Said-Bouyeri, None; **J. Meijs**, Actelion Pharmaceuticals Nederland bv, 2; **N. Ajmone Marsan**, None; **A. A. Schouffoer**, None; **M. K. Ninaber**, None; **H. U. Scherer**, Roche, 8; **F. Bonte-Mineur**, None; **T. W. J. Huizinga**, Merck, UCB, Bristol Myers Squibb, Biotest AG, Pfizer, GSK, Novartis, Roche, Sanofi-Aventis, Abbott, Crescendo Bioscience, Nycomed, Boeringher, Takeda, Zydus, Epirus and Eli Lilly, 5; **J. K. de Vries-Bouwstra**, Actelion Pharmaceuticals Nederland bv, 5.

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Abstract Number: 837

Exposure to ACE Inhibitors Prior to Onset of Scleroderma Renal Crisis Is Not Associated with Increased Risk of Mortality in a Large Retrospective Cohort Study

Sindhu R. Johnson[1], Mohamed Elarabi[2], Susanna Proudman[3], Tracy M. Frech[4], Joanne Sahhar[5], Wendy Stevens[6], Jane Zochling[7], Zareen Ahmad[8], Murray Baron[9], Marie Hudson[9] and Canadian Scleroderma Research Group, [1]Medicine, Toronto Scleroderma Program, Toronto Western Hospital, Toronto General Hospital, Mount Sinai Hospital, and University of Toronto, Toronto, ON, Canada, [2]Toronto Scleroderma Program, Toronto Western Hospital, Toronto General Hospital, Mount Sinai Hospital, and University of Toronto, Toronto, ON, Canada, [3]Rheumatology Unit, Royal Adelaide Hospital North Terrace, Adelaide, Australia, [4]Div of Rheumatology, University of Utah, Salt Lake City, UT, [5]Department of Rheumatology, Monash Medical Centre, Melbourne, Australia, [6]Rheumatology, St. Vincent's Hospital, Melbourne, Australia, [7]Royal Hobart Hospital, Tasmania, Australia, [8]Division of Rheumatology, Toronto Scleroderma Program, Toronto Western Hospital, Toronto General Hospital, Mount Sinai Hospital, and University of Toronto, Toronto, ON, Canada, [9]Jewish General Hospital, Lady Davis Institute and McGill University, Montreal, QC, Canada

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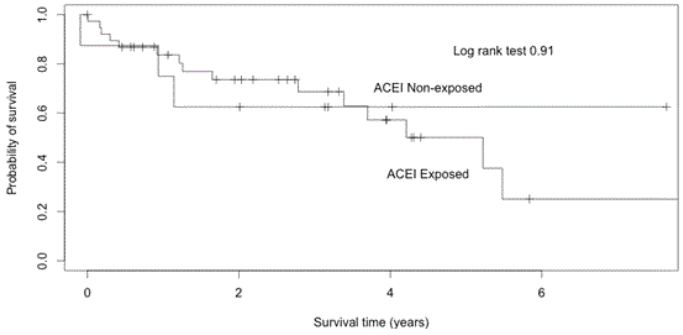
Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose: Scleroderma renal crisis (SRC) is a life-threatening complication of systemic sclerosis (SSc). Since the advent of angiotensin converting enzyme inhibitors (ACEI), the outcome of SRC has improved. There has also been more liberal use of ACEI to treat Raynaud's phenomenon and systemic hypertension in SSc. There is some evidence suggesting that exposure to ACEI prior to the onset of SRC may be associated with worse outcomes. The objective of this study is to evaluate the risk of death in SSc patients with SRC who were and were not exposed to ACEI prior to the onset of SRC.

Methods: We conducted an international multicenter retrospective cohort study of incident SSc patients with SRC. The exposure was treatment with ACEI prior to SRC. The primary outcome was time to death. Cox proportional hazards models were used to estimate risk in those exposed and not exposed to ACEI prior to SRC expressed as hazard ratios (HR).

Results: More than 3000 SSc patients were screened to identify 48 incident SSc patients with SRC, with a mean age of 59.4 years. Forty-one (85.4%) were female, 41 (85.4%) had diffuse SSc and 19/27 (70.3%) had RNA polymerase III antibodies. Prior to SRC, 18 (39.1%) subjects had systemic hypertension, and mean creatinine was 78.5 umol/L. Eight (17.4%) patients were on an ACEI. Post SRC, 30 (63.8%) subjects had new hypertension, mean creatinine was 262.5 umol/L, and 41 (85.4%) were on an ACE inhibitor. Post SRC, there were 19 (39.6%) deaths, 3 (37.5%) in the ACEI exposed group and 16 (40%) in the ACEI non-exposed group. The probability of 1-year survival was 75.0% (95% CI 50.3%, 100%) in the ACEI exposed compared to 83.6% (95% CI 72.4%, 96.6%) in the ACEI non-exposed. Kaplan Meier analysis found no difference in survival curves (log rank test p=0.91). In the unadjusted model for survival, ACEI prior to SRC had a HR 0.93 (95% CI 0.27, 3.23). Adjusting for baseline hypertension, the HR for ACEI exposure was 0.73 (95% CI 0.19, 2.88). Interestingly, in the unadjusted model for survival, calcium channel blocker (CCB), exposure prior to SRC had a HR 1.12 (95% CI 0.43, 2.87). Adjusting for baseline hypertension, the HR for CCB exposure was 1.06 (95% CI 0.40, 2.78).



Conclusion: Exposure to ACE inhibitors prior to onset of scleroderma renal crisis was not associated with increased mortality. Some limitations of this study include the design, which may be associated with left truncation, and low power, as evidenced by the wide confidence intervals. Further international efforts will be required to definitely resolve this important clinical question.

Disclosure: S. R. Johnson, None; **M. Elarabi**, None; **S. Proudman**, None; **T. M. Frech**, None; **J. Sahhar**, None; **W. Stevens**, None; **J. Zochling**, None; **Z. Ahmad**, None; **M. Baron**, None; **M. Hudson**, None.

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Abstract Number: 838

Impaired Quality of Life in Systemic Sclerosis and Patient Perception of the Disease: A Large International Survey

Camelia Frantz[1], Jerome Avouac[1], Oliver Distler[2], Fazia Amrouche[1], Dominique Godard[3], Ann Kennedy[4], John Varga[5], Marco Matucci-Cerinic[6] and Yannick Allanore[7], [1]Paris Descartes University, Rheumatology A department, Cochin Hospital, Paris, France, [2]Division of Rheumatology, University Hospital And Eular Scleroderma Trials And Research (EUSTAR) Board, Zurich, Switzerland, [3]Association des Sclérodermie de France, Auxerre, France, [4]Federation of European Scleroderma Associations (FESCA), Tournai, Belgium, [5]Division of Rheumatology, Northwestern University, Feinberg School of Medicine, Chicago, IL, [6]Rheumatology Department, University of Florence And World Scleroderma Foundation, Florence, Italy, [7]Paris Descartes University, Rheumatology A department, Cochin Hospital, And Eular Scleroderma Trials And Research (EUSTAR) Board, Paris, France

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Background/Purpose: Systemic sclerosis (SSc) is recognized as one of the most fatal rheumatic diseases, but it also promotes many detrimental effects on health-related quality of life (HRQOL). However, previous studies on HRQOL in SSc have lacked power, due to the difficulties involved in recruiting large samples for such a rare condition. Indeed, most previous studies focused on the outcome of patients in the early stages of disease or with DcSSc. The purpose of this study was to assess HRQOL and disease perception in a large, international group of SSc patients using validated questionnaires.

Methods: We conducted an international cross-sectional survey supported by EUSTAR, FESCA and Scleroderma US Foundation, from December 2013 to April 2014. We designed a standardized questionnaire translated and available on a website, including: Socio-demographic information, disease characteristics and self-assessment questionnaires namely Short Form 36 (SF-36) and Revised Illness Perception Questionnaire (IPQ-R).

Results: 1902 SSc patients from 60 countries were included with a mean±standard deviation (SD) age of 54±16 years and a mean±SD disease duration of 13±12 years. 712 (34.4 %) patients had DcSSc, 853 (44.8 %) had limited cutaneous SSc (LcSSc) and 122 (6.4 %) had SSc sine scleroderma.

HRQOL was found to be strongly impaired in SSc; in physical health (PCS, mean±SD 43.4±23.4; 100=best health) but also in mental health (MCS, mean±SD 52.3±23.1; 100=best health). SSc patients also had strongly perceptions about the chronic nature and negative consequence of the disease, and experienced negative emotions due to SSc.

Patients with DcSSc had a poorer HRQOL than those with LcSSc, for both physical (PCS, mean±SD 46.6±23.7 vs. 39.8±22.3; $p<0.0001$) and mental components (MCS, mean ± SD 53.8±23.0 vs. 50.3±23.2; $p=0.003$). They also had a more negative perception of their disease. Late-stage SSc patients were more likely to perceive their disease chronic ($p<0.0001$), less controllable ($p=0.03$) and with more consequences ($p=0.008$), but they also had a better understanding of their disease and experienced fewer negative emotions due to SSc.

Raynaud's phenomenon was the organ involvement with the most severe impact on daily life, associated with the most negative perception of illness severity followed by gastrointestinal complications, musculoskeletal and skin lesions.

Non-European SSc patients reported greater impacts on QOL, particularly for the physical component (PCS, mean±SD 39.9±22.6 vs. 46.0±23.7; $p<0.0001$), and they had a more negative perception of their illness than European SSc patients, but they had a better understanding of their disease and experienced fewer negative emotions.

Conclusion: This study provides unique information about the patients' perception of the disease and its impact on QOL, according to disease subset, disease duration and various geographical origins. The key message overall is the major impact on QOL and the negative perceptions of their disease expressed by SSc patients. Nevertheless, perceptions of the illness tended to improve with disease duration, suggesting the development of effective coping strategies. These results should be taken into account in patient management and future trials.

Disclosure: C. Frantz, None; **J. Avouac**, None; **O. Distler**, None; **F. Amrouche**, None; **D. Godard**, None; **A. Kennedy**, None; **J. Varga**, None; **M. Matucci-Cerinic**, None; **Y. Allanore**, None.

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Abstract Number: 839

Occupational Exposures in Patients with Systemic Sclerosis Associated with Increased Frequency of Interstitial Lung Disease and Primary Pulmonary Hypertension

Brandi E. Stevens[1,2], Mary Lucas[3], Thomas A. Medsger Jr.[4] and Robyn T. Domsic[5], [1]Division of Rheumatology, Children's Hospital of Pittsburgh of UPMC, Pittsburgh, PA, [2]Medicine-Rheumatology, University of Pittsburgh, Pittsburgh, PA, [3]Division of Rheumatology, University of Pittsburgh, Pittsburgh, PA, [4]Department of Medicine/Rheumatology, University of Pittsburgh, Pittsburgh, PA, [5]Medicine - Rheumatology, University of Pittsburgh, Pittsburgh, PA

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Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose: Systemic sclerosis (SSc) has been linked with environmental and occupational exposures. Silica and solvent exposure have the strongest known correlation with SSc. Other agents, notably aerosolized particles, may have a potential role in pathogenesis. To date, there has been limited information on how these exposures relate to disease phenotype. The objective of this study was to evaluate associations between occupational exposures and SSc phenotypes.

Methods: We used a large, prospectively enrolled, single-center SSc cohort for analysis. At the first visit, self-reported occupational exposure data is routinely collected. We reviewed this occupational exposure data on all patients seen between January 1, 2000 and December 31, 2014. Exposure was categorized as: none, solvent, silica/dust, other exposure (examples include fumes, aerosols), or ≥ 2 categories. We evaluated associations with disease phenotypes including cutaneous subtype (diffuse vs. limited), serum autoantibody (anti-Scl70, anti-RNA polymerase 3, anti-centromere and other) profile, and pulmonary involvement. Pulmonary arterial hypertension (PAH) was defined as a mean pulmonary artery pressure (PAP) > 25 mmHg on right heart catheterization or transthoracic echocardiogram with PAP > 45mmHg and PAH diagnosed by a cardiologist. Interstitial lung disease (ILD) required the presence of radiographic fibrosis. Chi-square analysis was used to compare groups by exposure status.

Results: The total cohort (n=746) was 78% female, 99% Caucasian and average age was 54 years. Of the 746 patients, 135 reported an occupational exposure. There were no differences between the exposed and unexposed groups in age or race, although there were more males compared to females in the exposed group (57% vs 14%, p <0.001). There was no difference in exposure between cutaneous subtype or serum autoantibodies. ILD was more frequent in the exposed (51%) vs. unexposed (37%) group (p=0.004). Subanalysis of the exposed groups found individuals with dust/silica exposure have a significantly higher rate of ILD than unexposed individuals (p=0.007). There was no difference between the exposed and unexposed group in PAH prevalence (p=0.29). However among the exposed group, those with "other" had a markedly higher rate of PAH at 32% (p=0.01).

Table 1: Prevalence of PAH and ILD by Occupational Exposure Group

	No Exposure n=611	Solvent n=47	Silica/Dust n=46	Other Exposure n=31	≥ 2 Exposures n=11
Pulmonary arterial hypertension	64 (10.5%)	4(8.5%)	4 (8.7%)	10 (32.3%)	1 (9.1%)
Interstitial lung disease	228 (37.3%)	22 (46.8%)	27 (58.7%)	13 (41.9%)	7 (63.6%)

Conclusion: Males had higher rates of occupational exposure. There was no relationship between exposure and cutaneous or autoantibody subtype. Silica/dust exposure was significantly associated with an increased frequency of ILD, whereas an increased frequency of PAH was seen in those who reported an occupational exposure that was not solvent or silica. These descriptive findings suggest that further investigation into occupational exposures and relationship to SSc-ILD and SSc-PAH is warranted.

Disclosure: B. E. Stevens, None; **M. Lucas**, None; **T. A. Medsger Jr.**, None; **R. T. Domsic**, Biogen-Idec, 5,Bayer, 5.

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Abstract Number: 840

Skin Telangiectasia Identify a Subset of Systemic Sclerosis Patients with Severe Vascular Phenotype

Jerome Avouac[1], Charlotte Hurabielle[2], Gemma Lepri[3], Tullia De Risi[4], Andre Kahan[5] and Yannick Allanore[6], [1]Rheumatology A department and INSERM U1016, Paris Descartes University, Cochin Hospital, Paris, France, [2]Rheumatology A department, paris Descartes University, Cochin Hospital, Paris, France, [3]Department of Internal Medicine, Rheumatology Section, Transition Clinic, University of Florence, Italy, Florence, Italy, [4]Rheumatology A department, Paris Descartes University, Cochin Hospital, Paris, France, [5]Rheumatology A, Cochin Hospital, Paris Cedex 14, France, [6]Paris Descartes University, Rheumatology A department, Cochin Hospital, And Eular Scleroderma Trials And Research (EUSTAR) Board, Paris, France

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Session Time: 9:00AM-11:00AM

Background/Purpose: Cutaneous Telangiectasia (CT) are common in systemic sclerosis (SSc) patients but their input to risk stratify the patients is poorly known. The aims of our study were to determine whether the number and size of CT i) were related to the pattern of microvascular lesions assessed by nailfold videocapillaroscopy (NVC) and ii) were associated with other disease characteristics, and more particularly with markers reflecting the severity of SSc-related vasculopathy.

Methods: We performed a cross-sectional study including consecutive SSc patients over a 6-month period. We considered three subsets of patients according to the number of hand or face CT: absence of CT, ≤10 hand or face CT (minor to moderate CT) or >10 CT (profuse CT). Pseudotumoral CT were also taken into account and were defined as CT with > 5mm diameter. NVC was performed and classified as early, active and late patterns.

Results: 87 patients were included (69 females), with median age of 57 years (range 19-89 years), and median disease duration of 11 years (range 0-53 years). 52 patients (60%) had the limited cutaneous subset. 75 patients (86%) had CT: 27 (36%) had profuse CT, and 19 (25%) pseudotumoral CT.

In univariate analysis, patients with profuse and pseudotumoral CT were more likely to have the late NVC pattern (p=0.003 and p=0.001 respectively). Profuse and pseudotumoral CT were also associated with capillary loss (5.09±1.25 vs. 7.73±2.1 capillaries/digit, p<0.001, and 5.34±1.11 vs. 7.34±2.03 capillaries/digit, p=0.002, respectively) and neoangiogenesis (p=0.009 and p=0.003 respectively).

Regarding disease characteristics, patients with profuse or pseudotumoral CT were significantly older than patients without these lesions (p=0.018 and p=0.037, respectively); patients with profuse or pseudotumoral CT were also more likely to have increased sPAP on echocardiography (>40mmHg, p=0.007 and p=0.004, respectively) and increased plasma HS-cTnT levels (>14 ng/L, p<0.001 and p=0.025, respectively). The likelihood of pseudotumoral CT was significantly higher in patients with precapillary pulmonary arterial hypertension (PAH) (p=0.008). A trend was observed for an association between profuse CT and past or current digital ulcers (DU) (p=0.055).

Then, a logistic regression analysis was performed including profuse or pseudotumoral CT as outcomes together with covariates reflecting the severity of vascular involvement. This analysis revealed that profuse CT were independently associated with past or current DU (odds ratio, OR: 2.95, 95% confidence interval, CI: 1.09-16.93, p=0.034), and above the cut-off value of HS-cTnT (OR: 7.66. 95% CI: 1.07-54.85, p=0.043). Pseudotumoral CT were independently associated with late NVC pattern (OR: 4.84, 95% CI 1.32-26.19, p=0.018) and precapillary PAH (OR: 12.60, 95% CI 1.68-94.53, p=0.014).

Conclusion: We demonstrate that the number and size of CT are associated with the most severe NVC pattern. In addition, profuse and pseudotumoral CT identify a subset of patients with a more severe vascular phenotype. Thus, the number and size of CT may reflect the vasculopathy of SSc and could represent a clinical biomarker for vascular disease.

Disclosure: J. Avouac, None; **C. Hurabielle**, None; **G. Lepri**, None; **T. De Risi**, None; **A. Kahan**, None; **Y. Allanore**, None.

Abstract Number: 841

Prevalence of Systemic Sclerosis in Primary Biliary Cirrhosis Using the New ACR/EULAR Classification Criteria

Boyang Zheng[1], Catherine Vincent[2], Marvin J. Fritzler[3], Jean-Luc Senécal[4], Martial Koenig[5] and France Joyal[5], [1]Division of Internal Medicine, Centre Hospitalier de l'Université de Montréal, Montreal, QC, Canada, [2]Division of Hepatology, Centre hospitalier de l'Université de Montréal, Montreal, QC, Canada, [3]Medicine, University of Calgary, Calgary, AB, Canada, [4]Department of Medicine, Division of Rheumatology, Centre Hospitalier de l'Université de Montréal, Montreal, QC, Canada, [5]Department of Medicine, Division of Internal Medicine, Centre Hospitalier de l'Université de Montréal, Montreal, QC, Canada

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Session Time: 9:00AM-11:00AM

Background/Purpose:

Systemic sclerosis (SSc) is a well established disease associated with primary biliary cirrhosis (PBC), however original 1980 American College of Rheumatology (ACR) criteria have poor sensitivity, especially for detection of earlier SSc in previous studies. The objective is to evaluate the prevalence of SSc in PBC patients using more sensitive 2001 LeRoy criteria and the recent 2013 ACR/European League Against Rheumatism (EULAR) classification criteria, and secondarily the frequency of individual clinical features.

Methods:

100 PBC patients without previously diagnosed SSc were recruited over 18 months from a tertiary care gastroenterology clinic. All patients underwent a clinical, biological, and capillaroscopic evaluation. Fulfillment of the three different criteria sets were analyzed.

Results:

1% of the PBC patients met the ACR 1980 criteria. 22% met the 2001 LeRoy's criteria for early SSc and 16% the 2013 ACR/EULAR criteria. Raynaud phenomenon, SSc related antibodies and SSc nailfold capillaroscopy changes were the most prevalent findings with the highest

sensitivities to help guide future screening.

Conclusion:

Our data show a high prevalence of SSc and possible underestimation of previous studies using the original ACR 1980 criteria. SSc based on newly described criteria may lead to improved detection and increased benefits of earlier treatment in ameliorating SSc related morbidity and mortality.

Disclosure: B. Zheng, None; **C. Vincent**, None; **M. J. Fritzler**, None; **J. L. Senécal**, None; **M. Koenig**, None; **F. Joyal**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/prevalence-of-systemic-sclerosis-in-primary-biliary-cirrhosis-using-the-new-acreular-classification-criteria

Abstract Number: 842

Clinical Utility of Serial KL-6 Measurement in Interstitial Lung Disease Associated with Systemic Sclerosis

Yuichiro Shirai[1], Tsutomu Takeuchi[2] and Masataka Kuwana[3], [1]Department of Allergy and Rheumatology, Nippon Medical School, Tokyo, Japan, Tokyo, Japan, [2]Keio University School of Medicine, Tokyo, Japan, [3]Department of Allergy and Rheumatology, Nippon Medical School Graduate School of Medicine, Tokyo, Japan

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Background/Purpose: Interstitial lung disease (ILD) is the leading cause of mortality in patients with systemic sclerosis (SSc). KL-6, a mucin-like glycoprotein highly expressed on type II pneumocytes, is known as a circulating biomarker for lung injury and various forms of ILD. Previous cross-sectional studies have shown that circulating KL-6 level is elevated in patients with SSc-ILD and is inversely correlated with percent predicted forced vital capacity (%FVC). We have recently found that elevated KL-6 level at baseline is an independent predictor of %FVC decline and mortality, although information on serial changes of KL-6 during the course of SSc is scarce. In **this study, we investigated clinical utility of serial KL-6 measurement in patients with SSc-ILD using a prospective cohort.**

Methods: We enrolled 58 consecutive patients who were diagnosed as having SSc between 2006 and 2012. These patients were selected from our SSc database, based on fulfillment of 1980 American College of Rheumatology preliminary criteria, disease duration ≤8 years at diagnosis, follow-up period >2 years, availability of pulmonary function test (PFT) and chest high-resolution CT (HRCT) at diagnosis, and availability of serial PFT results in an interval of <2 years. Serum KL-6 was measured using a monoclonal antibody-based kit (Eidia, Japan) at every visit. Clinically meaningful change of KL-6 levels was defined as 20% increase or decrease from the baseline. All clinical information had been prospectively recorded on the database.

Results: Twenty-three patients (40%) were classified as having diffuse cutaneous SSc, and 39 (67%) had ILD detected by HRCT at diagnosis. Baseline serum KL-6 level was significantly elevated in SSc patients with ILD than in those without ($P = 0.001$), and was higher in extensive than in limited disease in patients with ILD ($P < 0.001$). In 19 patients without ILD at diagnosis, KL-6 was below 500 U/ml at baseline, and was pretty stable during disease course. In contrast, baseline KL-6 level was highly variable in patients with ILD: 51% <500 U/ml, 18% 500-1000 U/ml, and 31% >1000 U/ml. KL-6 levels changed with variation in patients with ILD: 7 increase, 19 unchanged, and 13 decrease during 4.5 ± 1.1 years (range 2.0 - 6.3 years), regardless of the treatment. Yearly change of %FVC was inversely correlated with both the final KL-6 level and the final to initial KL-6 ratio ($p = 0.047$ and <0.001, respectively). Moreover, 20 patients who showed sustained increase of KL-6 (>500 U/ml) experienced significantly higher %FVC deterioration than those who did not ($p = 0.03$). Eleven patients with ILD received treatment with oral or intravenous cyclophosphamide during disease course. In these patients, KL-6 level significantly reduced at 12 months after initiation of the treatment ($p = 0.045$).

Conclusion: Serial measurement of KL-6 may be useful in predicting progression of pulmonary function and in evaluating treatment response of cyclophosphamide in patients with SSc-ILD.

Disclosure: Y. Shirai, Eidia, 2; **T. Takeuchi**, None; **M. Kuwana**, Eidia, 2.

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Abstract Number: 843

Natriuretic Peptide Predicts Mortality in Systemic Sclerosis

Christophe Meune[1], Andras Komocsi[2], Serena Vettori[3], Eric Hachulla[4], Jerome Avouac[5], Nicolas Hunzelmann[6], Jorg HW. Distler[7] and **Yannick Allanore**[8], [1]Cardiology department, Université Paris XIII, Hôpitaux Universitaires Paris-Seine-Saint-Denis, Bobigny, France, [2]Heart Institute, University of PECS, Pecs, Hungary, [3]Department of Clinical and Experimental Medicine, Rheumatology Unit, Second University of Naples, Naples, Italy, [4]CHU Lille, Lille, France, [5]Rheumatology A department and INSERM U1016, Paris Descartes University, Cochin Hospital, Paris, France, [6]Department of Dermatology, University of Cologne, Cologne, Germany, [7]Department of Internal Medicine 3 and Institute for Clinical Immunology, University of Erlangen-Nuremberg, Erlangen, Germany, [8]Paris Descartes University, Rheumatology A department, Cochin Hospital, And Eular Scleroderma Trials And Research (EUSTAR) Board, Paris, France

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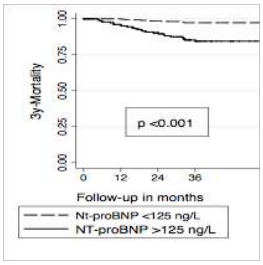
Session Time: 9:00AM-11:00AM

Background/Purpose: Heart involvement both of primary origin or secondary to lung disease is a key contributor to morbidity and mortality in systemic sclerosis (SSc). While Echocardiography is a primary tool of assessment in this setting, we have already reported that N-terminal Pro-brain natriuretic peptide (NT-proBNP) allows the reliable detection of reduced left and/or right ventricular ejection fraction (LVEF and RVEF) and of pulmonary arterial hypertension (PAH). Whereas NT-proBNP could predict mortality is SSc patients remains unknown.

Methods: This is a longitudinal, multicenter study that included 523 patients with SSc: mean age = 54±13 years, 323 women (61.8%), 8±9 years disease duration, diffuse cutaneous form in 168. Plasma NT-proBNP was measured at baseline and patients were followed up annually to 5 years. **Results:** At baseline, 37 patients had manifestations of cardiac involvement, including 17 with proven (PAH) and 20 with reduced LVEF<55%. 32 patients (7%) died within 3 years of follow-up and 59 (16%) within 5 years. NT-proBNP concentration was increased in SSc who died within 3 years versus those who survived (203 [129-514] versus 88 [47-167] ng/l respectively, p<0.001). Similar results were observed for a 5-years follow-up period (p<0.001), or after the exclusion of patients having PAH or reduced LVEF at baseline (p=0.001). Using a 125 ng/l cutoff value, NT-proBNP reliably predicts 3-y and 5-y mortality (respective sensitivities of 78.1% and 59.3%) (Figure 1). Negative predictive values for 3-y and 5-y mortality of a NT-proBNP concentration <125 ng/l were 97.6% and 90.0% respectively). Receiver-operating-characteristics analysis confirmed that NT-proBNP reliably predicted mortality (area under the curve 0.76). Of the most interest, in multivariate analyses, elevated NT-proBNP was an independent predictor of mortality at 3 years (p=0.03) such as pulmonary functional tests (FVC, p=0.008 and DLCO/VA, p= 0.01).

Conclusion: NT-proBNP reliably and independently predicted 3- and 5-years mortality in patients with SSc. Remarkably, our data show that NT-proBNP levels provide additional prognostic information that is independent of the one offered by common characteristics of the disease. Therefore, NT-proBNP may be considered as a first-line tool for prognostic assessment in SSc patients. This adverse prognostic marker might be considered as a potential eligibility criterion for risk stratifying SSc patients and for investigational or high-risk interventions.

Figure 1 : Kaplan Meier representation of 3y mortality according to NT-proBNP concentration (cox model for analysis)



Disclosure: C. Meune, None; **A. Komocsi**, None; **S. Vettori**, None; **E. Hachulla**, None; **J. Avouac**, None; **N. Hunzelmann**, None; **J. H. Distler**, None; **Y. Allanore**, None.

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Abstract Number: 844

Identification of Subclinical Skin Involvement By High Frequency Ultrasound in Systemic Sclerosis Patients

Barbara Ruaro, **Alberto Sulli**, Elena Bernero, Marco A. Cimmino, Sabrina Paolino and Maurizio Cutolo, Research Laboratory and Academic Division of Clinical Rheumatology, Department of Internal Medicine, IRCCS A.O.U. San Martino-IST, University of Genova, Genoa, Italy, Genoa, Italy

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Session Time: 9:00AM-11:00AM

Background/Purpose: Skin involvement may be evaluated in systemic sclerosis (SSc) by modified Rodnan skin score (mRSS), the validated method to distinguish between patients with limited (lcSSc) or diffuse (dcSSc) cutaneous skin involvement (1). In lcSSc the skin involvement is confined to the extremities (hands, forearms, feet, legs and face), whilst it is present also on arms, chest, abdomen and thighs in dcSSc patients (2). However, mRSS is unable to identify slight alterations in dermal thickness (DT) (3), and several studies report the utility of high frequency skin ultrasound (US) for early identification of skin involvement in SSc patients (4,5). DT was found progressively higher in SSc patients with worsening pattern of nailfold microangiopathy (5).

The aim of this study was to measure DT by US in both SSc patients and healthy subjects, looking for differences between the groups and correlations between US and mRSS.

Methods: Forty-eight SSc patients (ACR/EULAR criteria) (mean age 64±11SD years, mean disease duration 6±5 years) and 20 healthy subjects (mean age 66±14 years) were enrolled, after informed consent (1). Dermal thickness (DT) was evaluated by both mRSS and US transducer with 22 MHz frequency (Esaote, Genoa, Italy) at the level of the usual seventeen skin areas (cheeks, fingers, dorsum of hands, forearms, arms, chest, abdomen, thighs, legs, feet) in both SSc patients and healthy subjects. Nailfold videocapillaroscopy (NVC) was also performed to detect and classify SSc patients into the proper pattern of nailfold microangiopathy (“early”, “active” or “late”) (6).

Results: By US, DT was found significantly higher in both dcSSc and lcSSc patients than in healthy subjects in all the seventeen skin areas (median total DT 21.5 vs 19.1 vs 14.9 millimetres, respectively; $p<0.01$). Of great importance, lcSSc patients showed a statistically significant higher DT than healthy subjects in all the skin areas even with normal mRSS (mRSS=0), in contrast with the classificative diagnosis of lcSSc (median DT 1.20 vs 0.86 for right arm, 1.10 vs 0.86 for left arm, 1.30 vs 1.13 for chest, 1.40 vs 1.13 for abdomen, 1.40 vs 1.10 for right thigh, 1.40 vs 1.10 for left thigh, respectively; $p<0.01$). A significant progressive increase of DT was observed by US in SSc patients with different NVC pattern of microangiopathy at the level of all areas (median total DT 17.53 vs 21.20 vs 21.43 millimetres respectively for "early", "active", or "late" pattern, $p<0.05$). Finally, a statistically significant positive correlation was found between mRss and US in DT evaluation ($r=0.67$, $p<0.0001$).

Conclusion: This study demonstrates the utility of high frequency skin US to detect the subclinical diffuse dermal involvement even where the mRSS is normal in patients with lcSSc. This observation could make a contribution for future classification of the disease.

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Disclosure: B. Ruaro, None; **A. Sulli**, None; **E. Bernero**, None; **M. A. Cimmino**, None; **S. Paolino**, None; **M. Cutolo**, None.

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Abstract Number: 845

Modelling of Longitudinal Changes in Lung Function in Patients with Systemic Sclerosis and Their Association with Development of Pulmonary Hypertension

Svetlana I. Nihtyanova[1], Voon H. Ong[1] and Christopher P. Denton[2], [1]Rheumatology, UCL Division of Medicine, London, United Kingdom, [2]Rheumatology and Connective Tissue Diseases, University College London, London, United Kingdom

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Session Time: 9:00AM-11:00AM

Background/Purpose:

The majority of published models for prediction of PH use cross-sectional data, while studies exploring the use of repeated measurements of lung function tests (PFTs) are lacking. Gas transfer factor (DLCO) and forced vital capacity (FVC) are among the most powerful predictors of development of pulmonary hypertension (PH) in patients with systemic sclerosis (SSc).

We examine the changes in FVC and DLCO over time in a large unselected cohort of SSc patients and to explore their association with development of PH.

Methods:

We identified subjects with SSc with follow-up data for over 10 years and PFTs performed on at least two occasions. Linear mixed models were used to look for associations between repeated measurements of FVC and DLCO and development of PH over the follow-up period.

Results:

In this study we included 371 SSc subjects – 13% of those were male, 36% had diffuse cutaneous (dc)SSc. The cohort demonstrated antibody frequencies similar to other previously published studies - 27% had anti-centromere antibody (ACA), 20% had anti-topoisomerase I antibody, 8% had anti-RNA polymerase antibodies (ARA) and 6% had anti-U3RNP antibodies. Of the whole cohort, 15% had developed PH at the end of follow-up and its cumulative incidence was 4% at 5 years and 13% at 10 years. PFTs were performed on average every 15 months, between 2 and 20 times (median 6 times).

The extrapolated average FVC and DLCO of the cohort at the time of disease onset (baseline) were 86% and 68% respectively. Overall, FVC tended to increase over time by an average of 0.5% per year (SD 1.29) while DLCO decreased by an average of 1% per year (SD 1.3).

Without adjusting for other factors, patients who developed PH had 8.5% lower baseline FVC, compared to those who did not develop PH ($p=0.008$). Over time, FVC decreased by 0.4 % per year in PH while in non-PH subjects it increased by 0.6% on average ($p<0.001$). As expected, the rate of change in FVC was influenced by a number of other clinical characteristics (Table 1.). Even after adjustment, baseline FVC was on average 7.1% lower in PH subjects compared to non-PH ($p=0.014$). While in non-PH patients FVC increased by about 1% per year, in those who developed PH, the increase was <0.1% ($p=0.003$).

Similarly, unadjusted analysis demonstrated that PH subjects had on average 12.6% lower baseline DLCO, compared to non-PH ($p<0.001$). In PH patients, DLCO decreased by 2.6% per year, while in non-PH, the yearly decrease was 0.8% ($p<0.001$). When adjusting for other covariates, PH was still associated with a substantially lower baseline DLCO (11.2% difference, $p<0.001$) and this decreased by 1.9% per year compared to 0.2% ($p<0.001$) in non-PH patients, when keeping all other covariates constant (Table 1).

Conclusion:

Our findings confirm the particular value of serial measurements of lung function in the identification of patients at risk of PH. Subjects who develop PH have lower baseline FVC and DLCO levels with increased rates of DLCO reduction over time.

Table 1. Multivariable mixed models for FVC and DLCO change over time

FVC	β	95% CI for β		p-value
Time (yrs)	0.96	0.74	1.17	<0.001
PH	-7.08	-12.7	-1.46	0.014
PF	-18.98	-23.39	-14.58	<0.001
PH x time(yrs)	-0.88	-1.46	-0.3	0.003
PF x time(yrs)	-1.35	-1.77	-0.94	<0.001
ACA	4.31	0.42	8.2	0.030
U3RNP	-7.58	-14.69	-0.48	0.036
Cardiac SSc	-10.92	-19.76	-2.09	0.015
Age at onset	0.28	0.14	0.41	<0.001
Hb (centered at 12 g/dL)	1.38	0.26	2.51	0.016
Constant	77.53	70.68	84.39	<0.001
DLCO	**β**	**95% CI for β**		**p-value**
Time (yrs)	-0.2	-0.49	0.09	0.176
PH	-11.22	-16.48	-5.97	<0.001
PF	-15.76	-19.91	-11.6	<0.001
PH x time(yrs)	-1.72	-2.29	-1.14	<0.001
PF x time(yrs)	-1.11	-1.56	-0.67	<0.001
ACA	4.89	0.62	9.15	0.025
ARA	7.79	1.8	13.78	0.011
ACA x time(yrs)	-0.58	-1.01	-0.14	0.009
ARA x time(yrs	-0.76	-1.36	-0.17	0.012
Hb (centered at 12 g/dL)	1.7	0.68	2.73	0.001
Constant	71.01	68.07	73.95	<0.001

Disclosure: S. I. Nihtyanova, None; **V. H. Ong**, None; **C. P. Denton**, GlaxoSmithKline, 2,Actelion Pharmaceuticals US, 5,GlaxoSmithKline, 5,Serono, 5,Inventiva, 5,CSL Behring, 2,Bayer, 5.

Abstract Number: 846

Nationwide Trends in in-Hospital Mortality and Hospitalization Associated with Systemic Sclerosis (SSc)

Sara R. Schoenfeld[1], Na Lu[1], Flavia V. Castelino[2], Marcy B. Bolster[2] and Hyon K. Choi[1], [1]Rheumatology, Allergy and Immunology, Massachusetts General Hospital, Harvard Medical School, Boston, MA, [2]Rheumatology, Allergy, Immunology, Massachusetts General Hospital, Harvard Medical School, Boston, MA

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Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose:

Patients with systemic sclerosis (SSc) experience high rates of morbidity and mortality, but few studies have evaluated health care utilization such as hospitalization rates and in-hospital mortality associated with SSc. Moreover, it is unclear if and how these domains have changed over time and how they compare to other systemic rheumatic conditions. To address this knowledge gap, we evaluated in-hospital mortality and overall hospitalization trends in patients with SSc between 1999 and 2011 using a US nationwide inpatient database.

Methods:

The US National Inpatient Sample (NIS) contains all discharge data from a sample of hospitals from 44 states, making it the largest publicly

available all-payer inpatient health care database in the US. We studied all hospitalizations between 1999 and 2011 of adults (≥18 years) with a primary discharge diagnosis of SSc, identified by ICD-9 CM code 710.1. We evaluated in-hospital mortality and hospitalization rates over time and compared these rates to those of the overall hospitalized population and other systemic rheumatic conditions. All analyses were performed using hospital-level sampling weights provided by the NIS to obtain US national estimates.

Results:

Between 1999 and 2011, the rate of in-hospital mortality for patients admitted with SSc decreased from 9.6% to 5.8% (p for trend, <0.001), representing a yearly relative decrease of 4.0% (95% CI -7.2% to -0.8%) (**Figure 1**). Despite this decline, the in-hospital mortality rate in 2011 for patients with SSc (5.8%) remained substantially higher than for other systemic rheumatic conditions, including systemic lupus erythematosus (SLE) (0.93%) and granulomatosis with polyangiitis (2.6%), as well as than for the overall hospitalized population (2.1%). Among patients with a primary diagnosis of SSc who died during their hospitalization, the five most common secondary diagnoses were lower respiratory disease, fluid and electrolyte disorders, respiratory failure, pulmonary vascular disease and renal failure. These diagnoses did not change substantially during the study period, with the exception of congestive heart failure, which was replaced by renal failure. From 1999 to 2011, the rate of overall hospitalizations for SSc decreased slightly from 1.06 to 0.81 per 100,000 persons.

Conclusion:

Based on nationally representative inpatient data, our findings indicate a decrease in SSc in-hospital mortality between 1999 and 2011, suggesting that clinical care of SSc patients may be improving. Despite this encouraging trend, the in-hospital mortality rate remains approximately 6%, which is considerably higher than that of both the overall hospitalized population and any other systemic rheumatic condition. This highlights the need for continued improvement in the care of patients with SSc, including the development and implementation of effective therapeutic modalities.

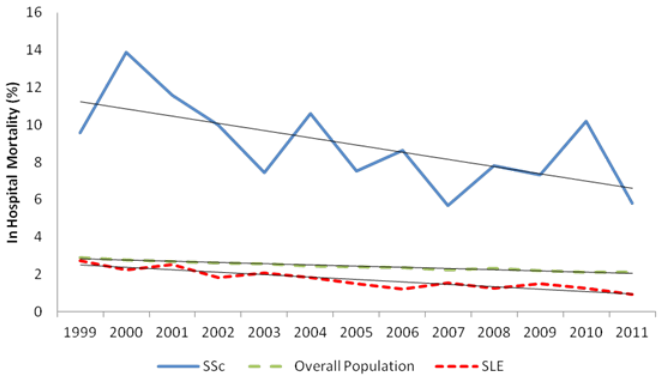

Figure 1. Trends in In-hospital Mortality for Patients Hospitalized With a Primary Diagnosis of SSc Versus Overall US Hospitalizations and SLE as a Primary Diagnosis. Black lines represent trend lines for each diagnosis.

Disclosure: S. R. Schoenfeld, None; **N. Lu**, None; **F. V. Castelino**, None; **M. B. Bolster**, Johnson and Johnson, 1,Eli Lilly and Company, 2,American College of Rheumatology, 6,Rheumatology Research Foundation, 6; **H. K. Choi**, None.

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Abstract Number: 847

Troponin T and NT-Probnp Are Prognostic Cardiac Disease Biomarkers in Patients with Systemic Sclerosis without Pulmonary Arterial Hypertension

Silvia Laura Bosello[1], Giacomo De Luca[1], Franca Forni[2], Clara Di Mario[3], Federico parisi[1], Giovanni Canestrari[1], Giorgia Berardi[1], Manuela Rucco[1], Francesca Gabrielli[4], Leonarda Galiuto[4], Francesco Loperfido[4] and Gianfranco Ferraccioli[1], [1]Division of Rheumatology, Catholic University of the Sacred Heart, Rome, Italy, [2]Department of Laboratory Medicine, Catholic University of the Sacred Heart, Rome, Italy, [3]Division of Rheumatology, Institute of Rheumatology, Catholic University of the Sacred Heart, Rome, Italy, [4]Division of Heart Failure and Cardiac Rehabilitation, Catholic University - Rome, Rome, Italy

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SESSION INFORMATION

Session Date: Sunday, November 8, 2015

Session Title: Systemic Sclerosis, Fibrosing Syndromes and Raynaud's - Clinical Aspects and Therapeutics Poster I

Session Type: ACR Poster Session A
Session Time: 9:00AM-11:00AM

Background/Purpose:

Heart involvement is common in Systemic Sclerosis (SSc), even if often clinically silent, and represents one of the leading cause of death in these patients. Recently it has been reported the role of NT-proBNP and high sensitivity Troponin T (cTnT) in patients with SSc-related pulmonary arterial hypertension (PAH), but their prognostic role is lacking in primary cardiac involvement. The aim of our study was to define the role of cardiac troponin T (cTnT) and NT-proBNP to identify cardiac involvement in SSc.

Methods: High sensitivity cTnT and NT-proBNP were measured in 200 consecutive SSc patients and in matched healthy controls. Patients with renal failure and with PAH on right heart catheterization were excluded. Data regarding disease subtype and organ involvement were available and all SSc-related deaths were registered. Classical cardiovascular risk factors were also considered. A mean follow-up of 48.6±20.6 months was reached.

Results:

cTnT levels and NT-proBNP values were higher in scleroderma patients (cTnT: 0.03±0.06 ng/ml and NTproBNP: 507.3±1718.9 pg/ml) than in healthy controls (cTnT: 0.006±0.0004 ng/ml and NT-proBNP: 90.6 ± 70.9, pg/ml,$p<0.00001$ for both comparisons).

cTnT levels were upper the normal limit in 65 SSc patients (32.5%), 72.6% complained cardiac symptoms, while 27.4% was completely asymptomatics. At multivariate analysis diffuse skin involvement (RR: 2.1 [1.2-4.4] and the presence of right bundle branch block (RBBB) on ECG (RR: 8.1 [1.4-45.5]) emerged as indipendent predictors of elevation of cTNT. NT-proBNP levels were above the cut-off limit of 125 ng/ml, recommended by the manufacturer, in 66 patients (33.3%), 72% of whom complained cardiac symptoms, while 28% was asymptomatic. Thirty-eight patients (19.0%) presented either an increase of cTnT either of NT-proBNP. At multivariate analysis diffuse skin involvement (RR: 2.3 [1.1-4.9]) and age (RR: 1.2 [1.03-1.09]) were indipendent predictors of elevation of NT-proBNP.

During the follow-up, 12 SSc-related death occurred; 8 of these were directly related to cardiac involvement (sudden cardiac death or heart failure). Cumulative survival estimated by Kaplan-Mayer curve was worse in patients with increased baseline levels of cTnT (X^2=10.2, p=0.001) and NT-proBNP (X^2=11.1, p=0.001), but patients with increase of cTnT and NT-proBNP had the worst outcome (X^2=13.5, p=0.003).

Conclusion:

cTnT and NT-proBNP are useful markers to identify symptomatic and asymptomatic SSc patients with a subclinical heart disease and a bad cardiac outcome.

Disclosure: S. L. Bosello, None; **G. De Luca**, None; **F. Forni**, None; **C. Di Mario**, None; **F. parisi**, None; **G. Canestrari**, None; **G. Berardi**, None; **M. Rucco**, None; **F. Gabrielli**, None; **L. Galiuto**, None; **F. Loperfido**, None; **G. Ferraccioli**, None.

Abstract Number: 848

Nitroglycerin Patch Application in Systemic Sclerosis: Evaluation By Laser Doppler Imaging

Georgiana Bentea, Aurelien Wauters, Jean-Claude Wautrecht and Elie Cogan, Erasme Hospital, Brussels, Belgium
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SESSION INFORMATION
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Session Title: Systemic Sclerosis, Fibrosing Syndromes and Raynaud's - Clinical Aspects and Therapeutics Poster I
Session Type: ACR Poster Session A
Session Time: 9:00AM-11:00AM

Background/Purpose:

Systemic sclerosis (SSc) is a complex autoimmune disease, commonly associated with Raynaud phenomenon (RP). The aim of this study was to characterize the microvascular reactivity to nitroglycerin (NTG) patch application in SSc patients by Laser Doppler imaging (LDI), and investigate predictive markers of the NTG response.

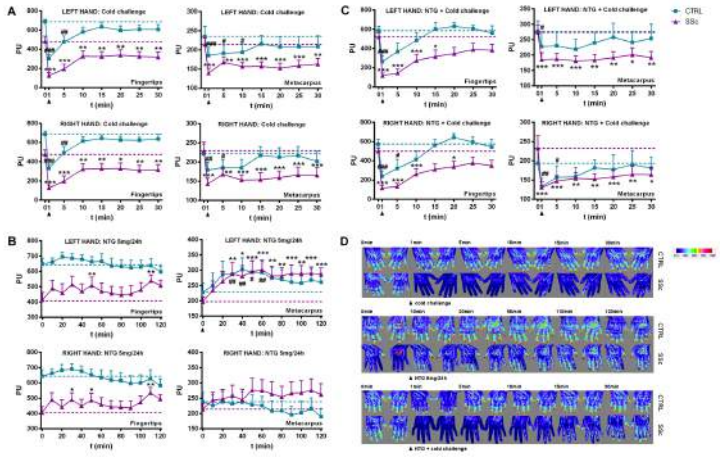
Methods:

The study included 21 SSc patients and 13 age-matched healthy volunteers. The SSc patients recruited from Erasme Hospital, Brussels, Belgium, met the American College of Rheumatology criteria for SSc, and presented with secondary RP. Blood flow was evaluated by LDI, and expressed in perfusion units (PU), as well as the area under the perfusion-time curve normalized for baseline flux (AUC). Microvascular morphology was evaluated by nailfold capillaroscopy (NC). Baseline measurements were complemented by dynamic studies analyzing microvascular function following application of a NTG 5mg/24h patch (left hand metacarpus, during 120 min). Subjects also underwent a cold challenge (both hands, 1 min at 15^{o}C) in the absence of, and following NTG application.

Results:

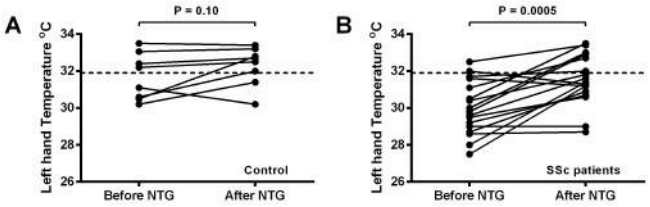
LDI measurements revealed decreased fingertip baseline perfusion in SSc patients compared to control. Moreover, SSc patients demonstrated a stronger vasoconstrictor response to a cold challenge, at both hands (Fig 1A).

Figure 1.



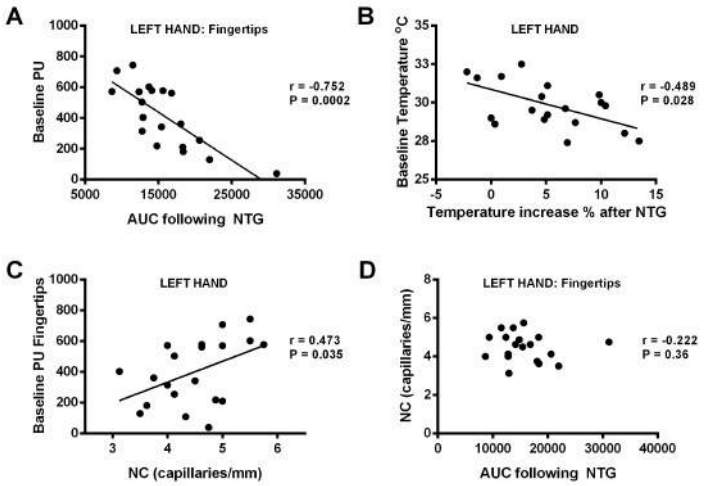
Metacarpal application of NTG patch led to an increase in blood flow and hand temperature in SSc patients but not in controls (Fig 1B, Fig 2). Furthermore, NTG administration led to a faster reperfusion after cold challenge (Fig 1C).

Figure 2.



Correlations analyses revealed that the magnitude of the vasodilatory response following NTG was inversely related with baseline fingertip perfusion and hand temperature (Fig 3A, B), but unrelated with structural microvascular features assessed using NC (Fig 3D).

Figure 3.



Conclusion:

We provide evidence of a vasodilatory reaction following application of a NTG patch in SSc patients using LDI. Furthermore, the magnitude of the response to NTG was related with functional, but not structural, features. In particular, SSc patients that showed decreased baseline condition (lower fingertip perfusion and hand temperature) benefited the most after NTG application. Our results support a further evaluation of the NTG patch as a possible effective treatment for SSc-associated RP.

Disclosure: G. Bentea, None; **A. Wauters**, None; **J. C. Wautrecht**, None; **E. Cogan**, None.

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A Computational Tool for Individualized Prognosis of Percent of Predicted Forced Vital Capacity Trajectories in Systemic Sclerosis

Peter Schulam[1], Colin Ligon[2], Robert Wise[3], Laura K. Hummers[4], Fredrick M. Wigley[5] and Suchi Saria[1,6], [1]Department of Computer Science, Johns Hopkins University, Baltimore, MD, [2]Rheumatology, Johns Hopkins University School of Medicine, Baltimore, MD, [3]Department of Pulmonology, Johns Hopkins University School of Medicine, Baltimore, MD, [4]Johns Hopkins University School of Medicine, Baltimore, MD, [5]Rheum Div/Mason F Lord, Johns Hopkins University School of Medicine, Baltimore, MD, [6]Departments of Biostatistics, and Health Policy and Management, Bloomberg School of Public Health, Baltimore, MD

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Session Title: Systemic Sclerosis, Fibrosing Syndromes and Raynaud's - Clinical Aspects and Therapeutics Poster I

Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose: Interstitial lung disease (ILD) is a common cause of mortality in systemic sclerosis (Ssc). Decreased forced vital capacity (FVC) in Ssc-ILD is associated with increased dyspnea, is predictive of more rapid development of clinically significant pulmonary fibrosis, and is associated with increased mortality. **Methods** are needed to prospectively identify patients at risk for progressive ILD to guide clinical trial enrollment and early treatment.

Methods: Continuous curves indicating the most likely future FVC values of a given individual are predicted using clinical data (see Fig. 1). Our model uses individual characteristics including demographic (gender and race) and serologic measurements (ACA and Scl-70 antibody positivity). In addition, it uses the FVC history of the individual to dynamically update predictions. Key to our approach is the idea of disease subtypes: subgroups of individuals with similar lung disease trajectories [1]. These trajectories are derived with a statistical learning algorithm (see for example [2]) using prospectively collected data. Individual-specific model parameters further personalize predictions. Our algorithm is being adapted to a web-based interface, allowing practitioners to obtain personalized estimates of a patient's future disease course.

Results: Figure 1 shows two individuals who test positive for Scl-70 antibodies and diffuse skin disease—both typically associated with development of progressive ILD. The two most probable subtypes are shown. Baseline FVC levels are comparable across both patients. After one year of followup, indicated by points (A) and (B), our model is able to correctly predict that the FVC in the individual in the first row will remain stable, while the other will experience FVC decline. After a transient decrease in FVC in the top patient resulting from an episode of cholecystitis, the predicted FVC trajectory appropriately continued to predict a largely stable course of ILD. After 4 years of data the confidence in each prediction is strengthened in spite of the sharp consecutive drop that both individuals exhibit—indicated by points (C) and (D). Using 10-fold cross validation on 672 patients, our model achieves mean absolute errors of 10.37, 8.95, and 6.98 when predicting pFVC values between 8-12 years of followup using 1, 2, and 4 years of data respectively.

Conclusion: Our prognostic model allows dynamic prediction of an individual's FVC trajectory from limited initial demographic and serologic data, and could inform recruitment of patients with similar expected ILD course into clinical trials. Incorporation of the model into a web-based decision-support tool could provide real-time prognostic data for widespread clinical practice.

References:

[1] Saria and Goldenberg, IEEE Intelligent Systems, 2015

[2] Schulam et al., Proc. of AAAI, 2011

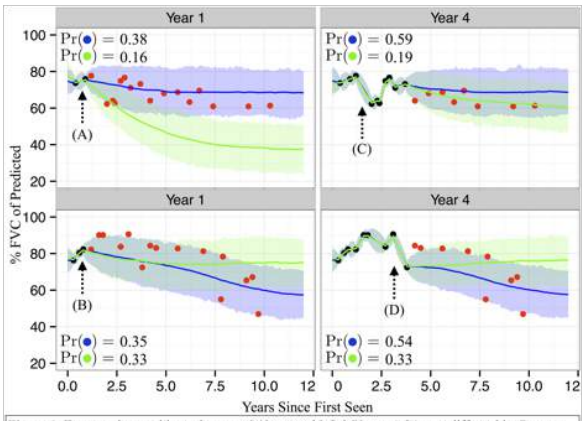

Figure 1: Top row shows white male, around 40 years old, Scl-70 pos, ACA neg, diffuse skin. Bottom row shows African American male, around 50 years old, Scl-70 pos, ACA neg, diffuse skin. Black dots indicate observed points at time of prediction, red dots indicate actual future points. The blue area represents the most likely predicted trajectory. The light green area represents the second most likely trajectory. Pr(*) = confidence in trajectory expressed as a probability.

Disclosure: P. Schulam, None; **C. Ligon**, None; **R. Wise**, None; **L. K. Hummers**, None; **F. M. Wigley**, None; **S. Saria**, None.

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Abstract Number: 850

Incidence and Predictors of Severe Heart Disease in Systemic Sclerosis

Serena Vettori[1], Yannick Allanore[2], Laszlo Czirjak[3], Francesco Del Galdo[4], Christopher P. Denton[5], Oliver Distler[6], Ivan Foeldvari[7], Marc Frerix[8], Veronika K. Jaeger[9], Brigitte Krummel-Lorenz[10], Marco Matucci Cerinic[11], Carina Mihai[12], Ulf Müller-Ladner[13], Gabriela Riemekasten[14], Tim Schmeiser[15], Ingo H. Tarner[8], Ulrich A. Walker[9], Gabriele Valentini[16] and EUSTAR Group and DeSScipher Consortium, [1]Department of Internal and Experimental Medicine, Rheumatology Unit, Second University of Naples, Naples, Italy, [2]Department of Rheumatology, University Paris Descartes and Cochin Hospital, Paris, France, [3]Rheumatology and Immunology Medical School, University of Pécs, Pécs, Hungary, [4]Division of Musculoskeletal Diseases, University of Leeds, Leeds, United Kingdom, [5]Department of Rheumatology, Royal Free and University College Medical School, London, United Kingdom, [6]Department of Rheumatology and Center of Experimental Rheumatology, University Hospital Zurich, Zurich, Switzerland, [7]Hamburg Center for Pediatric and Adolescent Rheumatology, Hamburg, Germany, [8]Justus-Liebig-University of Giessen, Kerckhoff-Klinik, Bad Nauheim, Germany, [9]Department of Rheumatology, University Hospital Basel, Basel, Switzerland, [10]Rheumatologist, Frankfurt, Germany, [11]Department of Internal Medicine, Division of Rheumatology, University of Florence, Florence, Italy, [12]Internal Medicine and Rheumatology Departement, Cantacuzino Hospital, Carol Davila University of Medicine and Pharmacy, Bucharest, Romania, Bucharest, Romania, [13]Internal Medicine and Rheumatology, Justus-Liebig-University of Giessen, Kerckhoff-Klinik, Bad Nauheim, Germany, [14]Rheumatology and Clinical Immunology, Charité – University Hospital, Berlin, Berlin, Germany, [15]Internistic Rheumatology, Krankenhaus St. Josef, Wuppertal, Germany, [16]Internal and Experimental Medicine, Rheumatology Unit, Second University of Naples, Naples, Italy

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Session Title: Systemic Sclerosis, Fibrosing Syndromes and Raynaud's - Clinical Aspects and Therapeutics Poster I

Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose: Heart disease occurs in most patients with systemic sclerosis (SSc), as emerged by autopsy and imaging studies. It can cause cardiac blocks (CBs), ventricular arrhythmias (VA), Q waves, and congestive heart failure (CHF), referred to as "severe heart disease" (SHD), as they may require a pacemaker/defibrillator implant (PM/DF) or ensue in death/sudden death (SD) in about 20% of cases. In a retrospective study, SHD has been recently found in 211/1119 SSc patients from the European Scleroderma Trial and Research (EUSTAR) database at first visits. We aimed to look for SHD incidence in a large SSc cohort and to identify SHD-related predictors.

Methods: SSc patients prospectively enrolled by 14 centers into the EUSTAR database from April 16 2013 to April 30 2015 with at least 1 follow-up (FU) visit were analyzed. At baseline, the prevalence of SHD manifestations was calculated. Incidence rates of SHD manifestations and their associations with demographics, disease features, and vasodilatory treatment were also calculated (study protocol at *www.clinicaltrials.gov;* NCT01836263).

Results:

Out of 449 patients meeting the new ACR/EULAR criteria for SSc with complete data on SHD, 284 (63%) had at least 1 FU visit (median FU 1.01 years, range 0.18-1.99) and were analyzed. Eighty-seven % were females; median age was 57 years (range 13-86); median disease duration 8 (range 0-61); 26% had diffuse cutaneous SSc; 74% limited cutaneous SSc. ANA were positive in 98% of patients (42% ACA; 34% anti-Scl-70; 5% anti-RNA polymeraseIII; 3% anti-PmScl; 3% anti-U1RNP). At baseline, 65/284 (23%) patients had at least 1 SHD manifestation: 52/280 (19%) had CBs, 2/267(1%) VA, 9/269 (3%) CHF, 6/262 (2%) Q waves, and PM/DF had been applied in 3/269 (1%). There was no statistical difference in any demographic and disease feature nor in the prevalence of SHD manifestations between the whole cohort and the patients investigated. During FU, 32 patients had a new SHD manifestation (20 CBs, 7 VA, 4 CHF, 2 Q waves, 1 PM/DF), with incidence rates of 11/100 patient*year for any SHD, 7/100 patient*year for CBs, 2.5/100 patient*year for VA, 1.43/100 patient*year for CHF, 0.7/100 patient*year for Q waves, and 0.4/100 patient*year for PM/DF. In univariate analysis, newly developed SHD manifestations were associated with baseline SHD, dyspnea, chest X-ray fibrosis, FVC and DLCO<80% of predicted, echo-assessed pulmonary hypertension (PH), modified Rodnan Skin Score (mRSS) and active disease (European Scleroderma Study Group Activity Index). At multivariate Cox-regression analysis, mRSS (HR 1.1, 95%CI 1.03-1.21) and echo-assessed PH (HR 17, 95%CI 4.4-66) were independent predictors of new SHD manifestations. New cases of CHF were only observed in patients with preexisting SHD.

Conclusion: To our knowledge, this is the first study investigating the incidence of all SHD manifestations in SSc. Our results suggest that mRss and echocardiographic PH mark an increased risk of new SHD manifestations over time and that CHF only develops in patients with preexisting SHD.

Aknowledgements. Funded by the European Community's Framework Programme 7 (FP7-HEALTH-2012.2.4.4-2 - Observational trials in rare diseases); grant n. 305495.

Disclosure: S. Vettori, None; **Y. Allanore**, Actelion, Bayer, Biogen, Bristol-Meyers Squibb, Inventiva, Medac, Pfizer, Roche/Genentech, Sanofi-Aventis, Servier, 2,Actelion, Bayer, Biogen, Bristol-Meyers Squibb, Inventiva, Medac, Pfizer, Roche/Genentech, Sanofi-Aventis, Servier, 5; **L. Czirjak**, None; **F. Del Galdo**, None; **C. P. Denton**, GlaxoSmithKline, 2,Actelion Pharmaceuticals US, 5,GlaxoSmithKline, 5,Serono, 5,Inventiva, 5,CSL Behring, 2,Bayer, 5; **O. Distler**, Consultancy relationships and/or has received research funding from Actelion, Pfizer, Ergonex, BMS, Sanofi-Aventis, United BioSource Corporation, Medac, Biovitrium, Boehringer Ingelheim, Bayer Pharma AG, Novartis, 4D Science and Active Biotech in the area, 2; **I. Foeldvari**, None; **M. Frerix**, None; **V. K. Jaeger**, None; **B. Krummel-Lorenz**, None; **M. Matucci Cerinic**, None; **C. Mihai**, None; **U. Müller-Ladner**, None; **G. Riemekasten**, None; **T. Schmeiser**, None; **I. H. Tarner**, None; **U. A. Walker**, None; **G. Valentini**, None.

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Abstract Number: 851

Does the Clinical Context Improve the Reliability of Rheumatologists Grading Digital Ulcers in Systemic Sclerosis?

Michael Hughes[1], Chris Roberts[2], Andrew Tracey[1], Graham Dinsdale[1], Andrea Murray[1] and Ariane L. Herrick[1], [1]Centre for Musculoskeletal Research, University of Manchester, Manchester Academic Health Science Centre, Manchester, United Kingdom, [2]Centre for Biostatistics, Institute of Population Health, University of Manchester, Manchester, United Kingdom

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Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose:

Digital ulcers (DUs) are often a primary end point in SSc clinical trials, although the reliability of rheumatologists grading DUs is poor to moderate at best. This is of concern as DUs are often a primary outcome measure in SSc clinical trials. DU assessment in recent trials has been based upon visual inspection alone, which potentially misses ‘real-world' clinical contextual information (e.g. pain and discharge). Our aim was to investigate whether this clinical information improves the reliability of rheumatologists grading DUs.

Methods:

80 photographs of a range of digital lesions were collected from patients with SSc-spectrum disorders (mainly SSc). The following clinical information was collected for each image: duration of the lesion (patient reported), pain associated with the lesion on a visual analogue score (100 being most severe) and its temporal relationship (whether the pain was less, the same or worse than a week ago), and the presence of discharge (both patient reported and clinician observed). A custom web-based interface was constructed to display the images and record the grading. Rheumatologists were invited to participate through SSc-specialist networks and were randomised to receive all images either with or without context. Lesions were graded on an ordinal scale of severity: ‘no ulcer', ‘inactive ulcer' or ‘active ulcer'. Reliability was assessed using a weighted kappa coefficient, with bootstrapping to generate estimates of confidence intervals. Ordinal logistic regression was used to investigate the relationship between the clinical context and grading.

Results:

51 rheumatologists completed the study (25 with and 26 without context), from 15 countries (mainly the US, UK, Canada and Italy). A total of 4590 (4080 unique and 510 repeated) image gradings were obtained. The intra and inter-rater reliability both without and with the context is presented in Table 1. There was no significant increase in the overall intra- or inter-rater reliability with the clinical context. There was a trend towards an increase in intra-rater reliability for ‘no ulcers' vs. ‘inactive ulcers' and ‘no ulcers' vs. ‘inactive'/'active ulcers', and a decrease for ‘inactive ulcers' vs. ‘active ulcers'. Patient reported discharge (OR= 2.67, 95% c.i. 2.02 to 3.53, P = <0.001) and pain VAS (OR= 1.02, 95% c.i. 1.01 to 1.03, P = <0.001) were associated with increased lesion severity, and lesion duration with reduced severity (OR= 0.81, 95% c.i. 0.76 to 0.86, P = <0.001).

Conclusion:

1. The overall intra and inter-rater reliability did not significantly improve with added clinical context.

2. There was a trend that clinicians may use the clinical context to help classify lesions as ‘no ulcer'.

3. Patient reported discharge and pain were associated with increased lesion severity and duration with reduced severity.

Table 1: Intra- and inter-rater reliability without and with context.

		INTRA-RATER RELIABILITY (95% CI)		INTER-RATER RELIABILITY (95% CI)	
		Without context	With context	Without context	With context
Overall		0.64 (0.53, 0.75)	0.71 (0.64, 0.78)	0.32 (0.25, 0.39)	0.36 (0.28, 0.44)
Pairwise	No ulcers vs. inactive ulcers	0.36 (0.08,0.60)	0.67 (0.50,0.84)	-0.07 (-0.17,0.02)	-0.03 (-0.12,0.05)
	No ulcers vs. active ulcers	0.95 (0.90,1.0)	0.90 (0.84,0.95)	0.42 (0.34,0.51)	0.44 (0.35,0.53)
	Inactive vs. active ulcers	0.53 (0.38,0.67)	0.41 (0.22,0.60)	0.22 (0.14,0.30)	0.21 (0.12,0.30)
Dichotomised	No ulcers vs. inactive/active ulcers	0.71 (0.60, 0.81)	0.82 (0.75, 0.89)	0.22 (0.16, 0.27)	0.26 (0.21, 0.31)
	No ulcers/inactive ulcers vs. active ulcers	0.74 (0.66, 0.82)	0.72 (0.65, 0.79)	0.32 (0.25, 0.39)	0.35 (0.27, 0.43)

Abstract Number: 852

Health-Related Quality of Life in Early Systemic Sclerosis

Marie Hudson[1], Murray Baron[2], Mianbo Wang[3], Candice Rabusa[4], Susanna Proudman[5], Mandana Nikpour[6], Wendy Stevens[4] and Canadian Scleroderma Research Group (CSRG), Australian Scleroderma Cohort Study (ASCS), [1]McGill University, Jewish General Hospital, Montreal, QC, Canada, [2]Jewish General Hospital, Lady Davis Institute and McGill University, Montreal, QC, Canada, [3]Lady Davis Institute for Medical Research, Montreal, QC, Canada, [4]Rheumatology, St. Vincent's Hospital, Melbourne, Australia, [5]Rheumatology Unit, Royal Adelaide Hospital North Terrace, Adelaide, Australia, [6]University of Melbourne Department of Medicine, Melbourne, Australia

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Session Time: 9:00AM-11:00AM

Background/Purpose:

Health-related quality of life (HRQoL) research is a priority in systemic sclerosis (SSc). Yet, much of the data comes from prevalent cohorts with established disease. There is a paucity of HRQoLdata in early SSc. The objective of this study was to estimate the magnitude of impairment in HRQoL, measured using the Medical Outcomes Trust Short Form-36 (SF-36), and the clinical correlates of physical and mental HRQoLin an inception SSc cohort.

Methods:

Cross-sectional study of incident SScsubjects (defined as < 2 years since onset of first non-Raynaud's disease symptom) enrolled in the International Systemic Sclerosis Inception Cohort (INSYNC) cohort. Subjects were assessed at entry with standardized clinical histories, medical examinations, and self-administered questionnaires and data were entered and harmonized in a central Redcap database. Multiple linear

regression was used to assess the relationship between selected demographic and clinical variables and the SF-36 Physical Component Summary (PCS) and Mental Component Summary (MCS) scores, adjusting for age, gender and race/ethnicity. Norm based scoring, where the mean score for the general population is 50 with a standard deviation (SD) of 10, was used to score SF-36 domain and summary scores. Values below 50 therefore indicate worse and above 50 better HRQoL, and each point is one tenth of a SD, compared to the general population.

Results:

The study included 483 incident SSc subjects (81% woman, mean (+SD) age 54.1+13.1 years, 89% White). Almost half (48.7%) of the cohort had diffuse cutaneous SSc (dcSSc), 27% interstitial lung disease (ILD), 6.0% pulmonary arterial hypertension (PAH) and 5.1% scleroderma renal crisis (SRC).

There were considerable impairments in all 8 SF-36 domains, with the worst scores for physical functioning (mean 36.5±12.7), role physical (36.4±13.9) and general health (38.6+10.8). Impairment was almost 1.5 SD below that of the general population in the SF-36 PCS (37.2± 12.0) and almost half of a SD below in the SF-36 MCS (45.7+12.7).

In multiple linear regression analysis, dcSSc (β -7.3, 95% confidence interval (CI) -10.0; -4.5, p<0.001), PAH (β -10.8, 95% CI -17.0; -4.6, p=0.001) and SRC (β -5.8, 95% CI -11.5; -0.15, p=0.04), but not ILD, were significant independent correlates of the SF-36 PCS score. The model explained 15% of the variance in the SF-36 PCS. On the contrary, ILD (β-4.1, 95% CI -7.6; -0.7, p=0.019), but not dcSSc, PAH or SRC, was a significant independent correlate of the SF-36 MCS. This model explained 4.7% of the variance in the SF-36 MCS.

Conclusion:

This study provides robust evidence of the magnitude and correlates of impairment in HRQOL in early SSc. Effective therapies are urgently needed to improve HRQoL in SSc.

Disclosure: M. Hudson, None; **M. Baron**, None; **M. Wang**, None; **C. Rabusa**, None; **S. Proudman**, None; **M. Nikpour**, None; **W. Stevens**, None.

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Abstract Number: 853

Evaluation and Validation of Case-Finding Algorithms for the Identification of Patients with Granulomatosis with Polyangiitis in Large Healthcare Administrative Databases

Antoine G. Sreih[1], Narender Annapureddy[2], Kevin Byram[3], George Casey[4], Vince Frangiosa[5], Michael George[6], Sapna Sangani[7], Rebecca Sharim[5] and Peter A. Merkel[8], [1]Department of Rheumatology, University of Pennsylvania, Philadelphia, PA, [2]Rheumatology and Immunology, Vanderbilt University, Nashville, TN, [3]Internal Medicine, Vanderbilt University, Nashville, TN, [4]The Vasculitis Foundation, Kansas City, MO, [5]Rheumatology, University of Pennsylvania, Philadelphia, PA, [6]Department of Rheumatology, Hospital of the University of Pennsylvania, Philadelphia, PA, [7]Penn Vasculitis Center, Division of Rheumatology, University of Pennsylvania, Philadelphia, PA, [8]Division of Rheumatology, University of Pennsylvania, Philadelphia, PA

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SESSION INFORMATION

Session Date: Sunday, November 8, 2015

Session Title: Vasculitis Poster I

Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose: To facilitate clinical care and research, validated algorithms are needed to accurately identify patients with granulomatosis with polyangiitis (GPA; Wegener's). This study, sought to evaluate and validate case-finding algorithms for GPA in 2 large health administrative databases.

Methods: 250 patients were randomly selected from 2 large healthcare systems (125 patients per system) using the International Classification of Diseases version 9 (ICD9) code for GPA: 446.4. Because eosinophilic granulomatosis with polyangiitis (Churg-Strauss) shares the same ICD9 code with GPA, patients who have ever had ICD9 codes 288.3 (eosinophilia) or 493.* (asthma) were excluded. 30 case-finding algorithms were constructed using a combination of ICD9 code, encounter type (1 inpatient ICD9 code on 3 consecutive days or 2 outpatient ICD9 codes 3 months apart), physician specialty (Rheumatology, Nephrology, Pulmonology, or Otorhinolaryngology), use of immunosuppressive medications, and whether an ANCA test was ordered. 2 time periods for ICD9 code submission were examined: 1 year and 2 years. The diagnosis was confirmed by chart review using the modified ACR classification criteria or the Chapel Hill Consensus Conference definitions for GPA. Patients who did not have a clear diagnosis were excluded from the analysis.

Results: 97 patients from the first healthcare system (site 1) and 98 patients from the second system (site 2) were included in the analysis after

excluding patients with unclear diagnosis. 38/97 (39%) patients had a confirmed diagnosis of GPA at site 1 and 66/98 (67%) patients at site 2. Table 1 shows the positive and negative predictive values of the studied algorithms in each healthcare system. An algorithm excluding patients with eosinophilia or asthma and including the encounter type and the physician specialty had the highest average positive predictive value (PPV: 87.1%). An algorithm excluding patients with eosinophilia or asthma and including the physician specialty had the highest average negative predictive value (NPV: 83.1%). There were no differences between the 2 time periods with regards to the algorithms' PPV or NPV.

Conclusion: Case-finding algorithms can accurately identify patients with GPA using large administrative databases. A simple algorithm excluding patients with eosinophilia or asthma and including the encounter type and the physician specialty has the highest positive predictive value. Similarly, an algorithm excluding patients with eosinophilia or asthma and including the physician specialty has the highest negative predictive value. These algorithms can be used to assemble population-based cohorts of patients with GPA and facilitate future research in healthcare use, outcomes, and comparative effectiveness.

Table 1. Test characteristics of the GPA algorithms in both healthcare systems

GPA Algorithms	Site 1 (n=97)		Site 2 (n=98)	
	PPV	NPV	PPV	NPV
ICD9+	46.2	94.1	72.9	69.2
Encounter	58.3	79.6	90.8	78.8
Specialty**	77.1	82.3	91.0	83.9
Medications	64.4	82.7	78.5	78.9
ANCA	68.0	70.8	82.5	66.7
ICD9+Encounter+				
Specialty*	82.1	78.3	92.1	77.1
Medications	71.0	75.8	90.8	78.8
ANCA	78.8	70.5	91.5	69.2
Specialty+Medications	80.0	75.0	92.1	77.1
Specialty+ANCA	82.4	70.0	91.5	69.2
Medications+ANCA	75.0	67.9	91.5	69.2
Specialty+Medications+ANCA	80.0	68.3	81.8	79.7
ICD9+Specialty+				
Medications	77.4	78.8	91.0	83.9
ANCA	78.9	70.5	90.3	72.2
Medications+ANCA	81.2	69.1	90.3	72.2
ICD9+Medications+				
ANCA	70.0	68.8	83.6	67.7
ICD9+Encounter+				
(1 year)	52.4	69.6	89.8	66.7
(2 years)	52.4	70.9	89.8	66.7
Specialty (1 year)	78.3	73.0	91.4	67.5
Specialty (2 years)	79.2	74.0	91.4	67.5
Medications (1 year)	67.9	72.5	89.8	66.7
Medications (2 years)	67.9	72.5	89.8	66.7
ANCA (1 year)	75.0	67.9	90.7	61.4
ANCA (2 years)	76.5	68.8	90.7	61.4
Specialty+Medications (1 year)	77.3	72.0	91.4	67.5
Specialty+Medications (2 years)	77.3	72.0	91.4	67.5
Specialty+ANCA (1 year)	80.0	68.3	90.7	61.4
Specialty+ANCA (2 years)	81.2	69.1	90.7	61.4
Specialty+Medications+ANCA (1 year)	80.0	68.3	90.7	61.4
Specialty+Medications+ANCA (2 years)	80.0	68.3	90.7	61.4

* Algorithm with the highest average PPV ** Algorithm with the highest average NPV.

PPV: positive predictive value. **NPV:** negative predictive value. **ICD9:** ICD9 code 446.4 excluding ICD9 code 288.3 (eosinophilia) or ICD9 code 493.* (asthma). **ENCOUNTER:** 1 inpatient ICD9 code on 3 consecutive days or 2 outpatient ICD9 codes 3 months apart. **SPECIALTY:** a Rheumatologist, Pulmonologist, Otorhinolaryngologist, or a Nephrologist involved in the care of the patient. **MEDICATIONS:** an immunosuppressive medication used. **ANCA:** ANCA test ordered.

1 year: encounter ICD9 codes submitted within 12 months. **2 years:** encounter ICD9 codes submitted within 24 months.

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None; **R. Sharim**, None; **P. A. Merkel**, None.

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Abstract Number: 854

Nationwide Incidence of Anti Neutrophil Cytoplasmic Antibody (ANCA) Associated Vasculitis in Iceland

Þórunn Bjarnadóttir[1], Árni Jón Geirsson[2], Kristján Steinsson[3], Jóhannes Björnsson[4], Gunnar Tomasson[5] and **Björn Rúnar Lúdvíksson**[6,7], [1]Landspitali University Hosptital, Reykjavík, Iceland, [2]Rheumatology, Department of Rheumatology, Landspitali - The National University Hospital of Iceland, Reykjavik, Iceland, [3]Rheumatology, Univ. Hospital, Reykjavik, Iceland, [4]Department of Pathology, Akureyri Hospital, Akureyri, Iceland, [5]Rheumatology Section, Boston University, Boston, MA, [6]Department of Immunology, University of Iceland, Reykjavik, Iceland, [7]Landspitali University Hosptital, Reykjavik, Iceland
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Background/Purpose: The Icelandic population is geographically isolated, genetically homogenous and with distinct environmental exposures. Deviations in disease occurrence compared to other Western countries might provide clues with respect to etiology of disease. ANCA-associated vasculitis (AAV) is a collective term for three rare small vessel vasculitides: Granulomatosis with Polyangiits (GPA), microscopic polyangiitis (MPA) and eosinophilic granulomtosis with polyangiitis (EGPA). The objective was to assess the incidence of AAV in the Icelandic Population.

Methods: Data from the Landspitali University Hospital and Akureyri Regional Hospital were used. Together, these hospitals provide care within the specialities of rheumatology, nephrology and immunology for the entire Icelandic population. The electronic medical records at those hospitals were search for ICD-9 and ICD-10 diagnoses corresponding to AAV from 1996-2006. Individual patient records were pulled for review. Final determination of AAV status was made if information in the patient record guided fulfilled the ACR classification criteria or the Chapel Hill nomenclature for systemic vasculitis. Information age, sex, ANCA measurements and organ involvement were obtained from the medical record. Numerical information on the size of the Icelandic population were obtained from the National Statistics Office. Incidence rate of AAV is expressed as number of new cases of AAV per million person-years of the Icelandic population during the study period.

Results: During the study period, 32 individual were diagnosed with AAV, an IR=10.30 (95% CI 6.7-13.9). Most subjects had GPA (N=20, IR=6.44(95%CI 2.9-10.0)) and 6 subjects had MPA and EGPA respectively. Mean age of patients was 54.7 years (range 20-87) and 20 (62.5%) of patients were women. Among patients with GPA, 65% had PR3-ANCA and 15% had MPO-ANCA. Among patients with MPA, 83% had MPO-ANCA and among patients with EGPA, 50% had MPO-ANCA.

Conclusion: The incidence of AAV is lower in Iceland that in most other Northern-European countries with an uneven female:male ratio. Prevalence and specificity of ANCA is similar as in other cohorts.

Disclosure: Bjarnadóttir, None; **J. Geirsson**, None; **K. Steinsson**, None; **J. Björnsson**, None; **G. Tomasson**, None; **B. R. Lúdvíksson**, None.

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Abstract Number: 855

Seasonality in ANCA-Associated Vasculitis

Luciano Enrique Pompermayer[1], Marina Scolnik[1], Valeria Scaglioni[2], Maria de los Angeles Gallardo[1] and Enrique R. Soriano[3], [1]Rheumatology Unit, Internal Medicine Service, Hospital Italiano de Buenos Aires, Instituto Universitario Hospital Italiano de Buenos Aires, and Fundacion PM Catoggio, Buenos Aires, Argentina, [2]Rheumatology, Hospital Italiano, Buenos Aires, Argentina, [3]Internal Medicine, Hospital Italiano de Buenos Aires, Buenos Aires, Argentina
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Background/Purpose: pathogenesis of ANCA-associated vasculitis (AAV) is multifactorial and most likely involves the interaction of environmental and genetic factors. Environmental seasonal exposures may play a role in the manifestation of the disease and incidence of relapses. Our objective was to investigate whether there are different clinical manifestations according to the seasonal period of the beginning of symptoms and if frequency of relapses differs in seasons in patients with ANCA vasculitis.

Methods: Patients with diagnosis of ANCA vasculitis (Chapel Hill 2012) (Granulomatosis with polyangiitis [GPA], Eosinophilic granulomatosis with polyangiitis [EGPA], Microscopic polyangiitis [MPA], and renal limited ANCA vasculitis [RLV]) seen between years 2000 and 2014 were included. Medical records we reviewed and dates of beginning of symptoms (symptoms included in the Birmingham vasculitis activity score attributed to the disease) and dates of relapses (recurrence of symptoms or new symptom attributed to vasculitis) were identified. Clinical and serological manifestations of ANCA vasculitis in patients beginning their disease in autumn-winter were compared with those beginning in spring-summer. Rate of relapses in the different seasonal periods was also compared.

Results: one hundred patients with AAV were included (females 70%, CI 60.9-79.1; mean age at diagnosis 58.4, SD 18.8, GPA=38, MPA=19 EGPA=15, RLV, =28). Forty seven patients began their vasculitis symptoms in autumn-winter, and another 47 in spring-summer. Dates of initial symptoms could not be established in 6 patients. Patients' characteristics at disease onset are compared in table 1. Clinical manifestations were similar in patients beginning their disease in different seasons except for sinus involvement that was more frequent in those starting symptoms in autumn-winter. A total of 26 patients (26%, GPA= 11, EGPA=7, MPA=4 and RLV=4) had relapses of AAV during follow-up, with a total of 30 relapses. Relapses were more frequent in autumn-winter (n=21) than in spring-summer (n=9) (p=0.004) for all patients, and in particular in GPA (p=0.03) and EGPA (p=0.03) (table 2).

Conclusion: no disease characteristic pattern at disease onset was observed according to seasonal period of the beginning of AAV. Relapses were more frequent in autumn-winter in GPA and EGPA, suggesting that environmental seasonal exposures may trigger them.

Table 1. ANCA vasculitis patients grouped by season of beginning of symptoms

	Beginning of symptoms in autumn-winter (n=47)	Beginning of symptoms in spring-summer (n=47)	P
Females, % (CI95)	74.5 (61.7-87.2)	63.8 (49.8-77.9)	0.264
Age at diagnosis, media (SD)	58.9 (SD 19.2)	59.1 (18.2)	0.98
Follow up, years, median (IQR)	6.9 (2.5-9.7)	6 (1.7-9.4)	0.54
GPA, n (%)	18 (38.3)	16 (34)	0.67
EGPA, n (%)	8 (17)	6 (12.7)	0.44
MPA, n (%)	8 (17)	11 (23.4)	0.56
LRV, n (%)	13 (27.7)	14 (29.8)	0.82
ANCA C positive, % (CI)	34.8 (20.7-48.9)	34.1 (19.7-48.5)	0.94
ANCA P positive, % (CI)	47.9 (35.2-62.8)	52.1 9 (0.7-70.4)	0.6
Initial clinical manifestations, % (CI)	66 (52-79.8)	68.1 (54.4-81.7)	0.83
- Renal	27.7 (14.6-40.8)	27.7 (14.6-40.8)	1
- Pulmonar infiltrates	10.6 (1.6-19.7)	8.5 (0.3-16.7)	0.73
- Alveolar Hemorrhage	21.3 (9.3-33.3)	23.4 (11-35.8)	0.8
- Fever	31.9 (18.3-45.6)	36.2 (22.1-50.2)	0.66
- Constitutional	4,3 (1.7-10.2)	4,3 (1.7-10.2)	1
- Ocular	40.4 (26.1-54.8)	21.3 (9.3-33.3)	**0.04**
- Sinus	10.6 (1.6-19.7)	14.9 (4.5-25.3)	0.54
- Hearing loss	12.8 (3-22.5)	14.9 (4.5-25.3)	0.77
- Neuropathy	8.5 (0.3-16.7)	14.9 (4.5-25.3)	0.34

Table 2. Relapses of ANCA vasculitis grouped by season

Disclosure: L. E. Pompermayer, None; **M. Scolnik**, None; **V. Scaglioni**, None; **M. D. L. A. Gallardo**, None; **E. R. Soriano**, Abbvie; Janssen; UCB; Roche; Bristol Myers Squibb, 2,Abbvie; UCB; Janssen; Roche; Bristol Myers Squibb; Pfizer; Novartis, 8.

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Abstract Number: 856

Elderly Versus Younger Patients with ANCA-Associated Vasculitis

Maria de los Angeles Gallardo[1], Marina Scolnik[1], Luciano Enrique Pompermayer[1], Valeria Scaglioni[2] and Enrique R. Soriano[3], [1]Rheumatology Unit, Internal Medicine Service, Hospital Italiano de Buenos Aires, Instituto Universitario Hospital Italiano de Buenos Aires, and Fundacion PM Catoggio, Buenos Aires, Argentina, [2]Rheumatology, Hospital Italiano, Buenos Aires, Argentina, [3]Internal Medicine, Hospital Italiano de Buenos Aires, Buenos

- Cutaneous			
Relapses during follow up, % (CI)	31.9 (18.3-45.6)	21.3 (9.3-33.3)	0.243

	Relapses in autumm-winter (n=21)	Relapses in spring-summer (n=9)	P
Total of ANCA vasculitis relapses, n	21	9	**0.004**
GPA, n	11	4	**0.03**
EGPA, n	6	1	**0.03**
MPA, n	3	1	0.5
LRV, n	1	3	0.5

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Background/Purpose: Clinical characteristics of elderly patients with ANCA- associated vasculitis (AAV) have not been fully elucidated. Advancing age is a risk factor for treatment-related side effects and mortality in AAV patients. Also comorbidities at time of AAV diagnosis have been associated with reduced patients and renal survival. Our objective was to analyze clinical features and outcomes in older patients with AAV compared with younger ones.

Methods: All patients seen at our hospital between years 2000 and 2014 with diagnosis of Granulomatosis with polyangiitis (GPA), Eosinophilic granulomatosis with polyangiitis (EGPA), Microscopic polyangiitis (MPA) and renal-limited ANCA vasculitis (RLV) were included. Patients were divided in an elderly group (age >=65 years) and a younger group (age <65 years). Clinical features, comorbidities, treatments, renal outcome and mortality were analyzed.

Results: one hundred patients were included (females 70%, mean age at diagnosis 58.4, SD 18.8). Younger patients (n=55) were compared with older ones (n=45) (table 1). Vasculitis renal involvement was significantly more frequent in older patients (p=0.045). No other clinical differences were found between both groups. Hypertension and dyslipidemia were more frequent in patients over 65 years. While relapses were more frequent in the younger group (p=0.02), mortality was increased in the older group (p=0.03). In a logistic regression analysis, chronic renal insufficiency was the only variable associated with mortality (OR 7, CI 1.18-41.7, p=0.032).

Conclusion: elderly patients with AAV had more renal involvement, hypertension and dyslipidemia and increased mortality. Relapses were more frequent in younger patients. Chronic renal insufficiency was independently associated with mortality in the whole group.

Table 1. Comparison between young and elderly patients with ANCA associated vasculitis

	Young ANCA-associated Vasculitis group (< 65 y) (n=55)	Elderly ANCA-associated Vasculitis group (>= 65 y) (n= 45)	P value
Females, % (CI)	69% (56.5-81.7)	71.1% (57.3-84.9)	0.83
Age at diagnosis, mean (SD)	45.2 (14.9)	74.6 (6.2)	<0.0001
Type of vasculitis, n (%)	24 (43.6)	14 (31.1)	0.23
- GPA	7 (12.7)	12 (26.7)	0.11
- MPA	10 (18.2)	5 (11.1)	0.35
- EGPA	14 (25.5)	14 (31.1)	0.49
- RLV			
ANCA positivity, n (%)	17 (32.7)	17 (38.6)	0.54
- C ANCA	27 (51.9)	24 (53.3)	0.89
- P ANCA			
Follow-up, years median (IQR)	3.9 (1.7-9.3)	7.6 (3.2-9.4)	0.15
Comorbidities, % (CI 95)	38.2 (25.1-51.3)	71.1 (57.6-84.7)	**0.001**
- Hypertension	3.6 (1.4-8.7)	11.1 (1.7-20.5)	0.15
- Diabetes	14.5 (5-24)	42.2 (27.4-57)	**0.002**
- Dyslipidemia	25.9 (14-37.9)	15.6 (4.7-26.4)	0.21
- Ever Smoker			
Initial involvement	56.4 (43-69.8)	75.6 (62.7-88.4)	**0.045**
- Renal	27.3 (15.2-39.3)	31.1 (17.3-45)	0.67
- Pulmonar infiltrates	10.9 (2.5-19.3)	6.7 (0.8-14.1)	0.46
- Alveolar hemorrhage	18.2 (7.8-28.6)	26.7 (13.4-39.9)	0.31
- Fever	25.5 (13.7-37.2)	40 (25.3-54.7)	0.12
- Constitutional	38 (25-51.3)	22.2 (9.8-34.7)	0.09
- Sinusal	5.5 (0.7-11.6)	4.4 (1.7-10.6)	0.82
- Eye	14.6 (5-24)	11.1 (1.7-20.5)	0.61
- Hearing loss	18.2 (7.8-28.6)	8.9 (0.4-17.4)	0.18
- Arthritis	9.1 (1.3-16.9)	15.6 (4.7-26.4)	0.32
- Cutaneous	14.5 (5-24)	13.3 (3.2-23.5)	0.98
- Mono or polyneuropathy			
Initial treatment, % (CI)	70.9 (58.6-83.2)	73.3 (60.1-86.6)	0.66
- Methylprednisolone IV	10.9 (2.5-19.3)	6.8 (0.8-14.4)	0.48
- Plasmapheresis	76.4 (65-87.8)	81.9 (70.1-93.4)	0.51
	14.6 (5-24)	15.9 (4.8-27)	0.85

- Cyclophosphamide - Dyalisis at diagnosis			
Duration of corticosteroids treatment, months, median (IQR)	36 (15-60)	15 (8-30)	**0.0006**
Major cardiovascular event during follow up, % (CI)	5.5 (0.6-11.6)	13.3 (0.3-23.5)	0.17
Cancer development during follow up, % (CI)	5.5 (0.6-11.6)	4.4 (1.7-10.6)	0.82
Infections requiring hospitalization or IV antibiotics during follow up, % (CI)	20 (9.2-30.8)	31.1 (17.3-45)	0.2
Relapses, % (CI)	36.4 (23.4-49.4)	15.6 (4.7-26.4)	**0.02**
Renal outcome, % (CI) - Chronic renal insufficiency - End stage renal disease	30.9 (18.4-43.4) 9.1 (1.3-16.9)	44.4 (29.6-59.3) 4.4 (1.7-10.6)	0.16 0.37
Vasculitis Damage Index at the end of follow up, media (SD)	1.3 (1.4)	1.7 (1.4)	0.14
Mortality, % (CI)	6.1 (0.8-13)	22.2 (8.2-36.2)	**0.03**

Abstract Number: 857

Prognosis Value of Geriatric Assessment Scales in Older Adults with New Onset ANCA--Associated Vasculitis: A Pilot Retrospective Study

Antoine Néel[1], Josephine Thomazeau[1], Christelle Volteau[2], Laure De Decker[3], Christian Agard[1], Marie Lino[4], Julie Graveleau[1], Fadi Fakhouri[4] and **Mohamed Hamidou**[1], [1]Internal Medicine Department, Nantes University Hospital, Nantes, France, [2]Clinical Research Department, Nantes University Hospital, Nantes, France, [3]Department of Geriatrics, Nantes University Hospital, Nantes, France, [4]Nephrology, Nantes University Hospital, Nantes, France

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Background/Purpose: 1/to assess the prognostic value of comorbidities, frailty and dependency as measures by dedicated geriatric scales, in older adults with ANCA-associated vasculitis (AAV). 2/ to identify factors that predict functional decline in Instrumental Activities of Daily Living.

Methods: Retrospective single center study of patients diagnosed with AAV after 65 y between 2000 and 2013. Comorbidities, frailty and dependency were measured using the Charlson Index, the CSHA Clinical Frailty Scale (CFS) and the Instrumental Activities of Daily Living 4 items (IADL4). These score were evaluated at 3 time points: 1 year prior to AAV diagnosis (baseline), at AAV diagnosis and 1 year after AAV diagnosis. Multivariate analysis was performed using Cox model.

Results: Fourty four patients were analysed, including 33 with MPA and 11 with GPA. Mean age was 76 years. Mean eGFR was

49ml/min/1.73m^2. As first line, 29 patients (66%) were treated with corticosteroids plus cyclophosphamide. Overall, a significant improvement of CFS and IADL were seen between disease onset and year 1 after the diagnosis. In multivariate analysis mortality was higher in patient with PR3 ANCA (HR=4.2), palliative care (HR:3.5) and worse baseline IADL4 (HR:1.84). Relapse-free survival was longer in patients with worse baseline CFS score (HR=0.41) and those with MPA (HR=0.25). IALD4 was the only factor that predicted infection-free survival (HR=1.95). Predictive factor of functional decline at 1 year were PR3 ANCA (HR=85), Charlson comorbidity index (3.2) and IADL4 at time of diagnosis (HR=3.9).

Conclusion: Geriatric assessment scales appear to have high prognostic value in older adults with AAV. These simple tools can be better predictors of outcome than age or some usual biological parameters such as eGFR. Multicenter prospective studies are needed to confirm our results. These tools may help identify at risk patients who may require more intensive supportive care.

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Abstract Number: 858

Stimulated Renal Glomerular Endothelial Cells Were Damaged By Fiber-like NETs Released By Neutrophils in ANCA-Associated Vasculitis

Yoshinori Komagata[1], Kanako Murakami[1], Chimako Kida[1], Kazuhito Fukuoka[1], Miho Karube[2], Shinya Kaname[1] and Yoshihiro Arimura[1], [1]First Department of Internal Medicine, Kyorin University School of Medicine, Tokyo, Japan, [2]Kyorin University School of Medicine, Tokyo, Japan

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Background/Purpose:

NETosis, a unique form of cell death of neutrophils, is characterized by the active release of chromatin fibers called NETs, that trap and kill invading microbes extracellularly. Although NETosis plays a crucial role in host defense, excessive NETs formation becomes self-defeating by promoting tissue injury and organ damage.

It has been known that NETs are implicated also in the pathogenesis of autoimmune diseases such as SLE, RA and ANCA –associated vasculitis (AAV). We observed NETs formation of neutrophils from MPO-AAV patients which is a majority type of AAV in Asia, and examined the effects of immunosuppressive therapy on the release of NETs in order to investigate the role of NETs in MPO-AAV. We also observed the damage of human renal glomerular endothelial cells (HRGECs) by neutrophils in order to investigate the role of NETs in AAV.

Methods:

Isolated peripheral blood neutrophils from healthy donors, pre/post-treatment MPO-AAV patients were incubated with phorbol myristate acetate (PMA), which is known as a strong inducer of NETs, PMA plus anti-MPO antibody or PMA plus anti-PR3 antibody. Neutrophils were stained with Hoechst 33342,SYTOX Green and the percentage of NETs producing cells were calculated. Brd-U labeled HRGECs stimulated by PMA were co-cultured with neutrophils. A cellular DNA fragmentation ELISA was used to quantitatively determine HRGECs damage.

Results:

Neutrophils from pre-treatment MPO-AAV patients produced much more fiber-like NETs than neutrophils from controls and the shape of fiber-like NETs were different from controls. Anti-MPO antibody increased the release of fiber-like NETs both in controls and MPO-AAV patients. The release of fiber-like NETs decreased in tandem with the decrease of ANCA titer after initial treatment and increased with the rise of ANCA titer in some MPO-AAV patients.

Although PMA-stimulated HRGEC were damaged in the presence of neutrophils, HRGEC without PMA stimulation were not damaged. When HRGEC and neutrophils were separated by transwell chamber, damage of HRGEC by neutrophils were substantially suppressed.

Conclusion:

Neutrophils from pre-treatment MPO-AAV patients released different type of fiber-like NETs and the amount of fiber-like NETs correlated with

the activity of AAV. HRGECs stimulated with PMA were damaged in the presence of neutrophils. It is suggested that both some soluble factors and fiber-NETs released from neutrophils are involved in the damage of HRGECs. These data suggest the release of fiber-like NETs by neutrophils at vascular endothelium is important for the pathogenesis of AAV.

Disclosure: Y. Komagata, None; **K. Murakami**, None; **C. Kida**, None; **K. Fukuoka**, None; **M. Karube**, None; **S. Kaname**, None; **Y. Arimura**, None.

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Abstract Number: 859

Predictors of Renal Histopathology in Antineutrophil Cytoplasmic Antibody Associated Glomerulonephritis

Sophia Lionaki[1], **Clio Mavragani**[2], George Liapis[3], George Somarakis[4], John Boletis[1], Alexandros A. Drosos[5], Athanasios G. Tzioufas[6] and Haralampos M. Moutsopoulos[6], [1]Nephrology, Laiko Hospital, Department of Nephrology, Athens, Greece, [2]Physiology, Department of Physiology, School of Medicine, National Kapodistrian University of Athens, Athens, Greece, [3]Pathology, Laiko Hospital, Department of Pathology, Athens, Greece, [4]Rheumatology Clinic, Department of Internal Medicine, Medical School, University of Ioannina, 45110, University of Ioannina, Rheumatology Clinic, Ioannina, Greece, [5]Dept of Internal Medicine, University of Ioannina, Rheumatology Clinic, Ioannina, Greece, [6]Department of Pathophysiology, Medical School of Athens, Department of Pathophysiology, Athens, Greece
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SESSION INFORMATION
Session Date: Sunday, November 8, 2015
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Background/Purpose:

Prompt, aggressive therapy is vital for anti-neutrophil cytoplasmic antibody (ANCA)-associated glomerulonephritis (GN). In this regard, we aimed to identify predictors of distinct renal histopathological classes at the time of clinical diagnosis.

Methods: An inception cohort of patients with biopsy proven ANCA-associated GN was studied retrospectively. Demographics, clinical, laboratory, serological and radiological parameters were analyzed. Patients were classified on the basis of renal histopathology, according to the report by Berden (1) et al into: focal class (≥50% normal glomeruli that were not affected by the disease process), crescentic class (≥50% of glomeruli with cellular crescents), sclerotic class (≥50% of glomeruli with global sclerosis), while all remaining biopsies were by definition not characterized by any of the predominant glomerular phenotypes and were classified as mixed class. Clinical phenotypes were assigned according to the second Chapel Hill vasculitides nomenclature Consensus Conference (2). A risk score was developed for each histopathological class using univariate and logistic regression analyses.

Results:

Of 147 eligible patients (136 from the University of Athens and 11 from the University of Ioannina), 105 had biopsy proven renal involvement. None of these patients had received any kind of immunosuppressive treatment at the time of kidney biopsy. Twenty out of the 105 pateints with renal involvement were excluded as they were younger than 16 years and had inadequate biopsy specimens (<10 glomeruli). Thus, the final study population consisted of 85 ANCA positive patients with biopsy proven GN.

Variables independently associated with focal class included disease duration up to diagnosis < 8 weeks, absence of red blood cell (RBC) casts by urine microscopy and eGFR > 49ml/min/1.73m^2; with crescentic class > 40 erythrocytes/hpf, identification of RBC casts in urine, ear nose and throat (ENT) involvement and eGFR < 49ml/min/1.73m^2; with mixed class age > 54 years, male gender, and absence of ENT involvement. In the presence of 2 or 3 risk factors a predictive risk score of each histopathological class was calculated: odds ratio (OR), 95% confidence intervals (CI), for focal class (≥2 risk factors) 17.5 (95% CI) [4.9-62.9], 38.0 [6.8-213.7] for crescentic class (≥3 risk factors), and 8.3 [1.0-67.5] (≥2 risk factors) for mixed class.

Conclusion: We propose a predictive algorithm of specific histolopathological classes of ANCA-associated GN, which might provide a crude estimation of the disease activity in the glomeruli at presentation. This tool might assist the clinician in making decisions regarding the level of intensity of inductive immunosuppressive therapy at clinical diagnosis.

References:

1.Berden AE, Ferrario F, Hagen EC, Jayne DR, Jennette JC, Joh K, et al. Histopathologic classification of ANCA-associated glomerulonephritis. *Journal of the American Society of Nephrology* : 2010;21(10):1628-36.

Disclosure: S. Lionaki, None; **C. Mavragani**, None; **G. Liapis**, None; **G. Somarakis**, None; **J. Boletis**, None; **A. A. Drosos**, None; **A. G. Tzioufas**, None; **H. M. Moutsopoulos**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/predictors-of-renal-histopathology-in-antineutrophil-cytoplasmic-antibody-associated-glomerulonephritis

Abstract Number: 860

Neutrophil/Lymphocyte Ratio: Could It be a Prognostic Indicator for Renal Outcome in Patients with Granulomatosis with Polyangiitis?

Berna Goker[1], Seminur Haznedaroglu[1], Hamit Kucuk[1], Ozkan Varan[1], Berivan Bitik[1], Abdurrahman Tufan[1], Ridvan Mercan[1] and Yasemin Erten[2], [1]Internal Medicine-Rheumatology, Gazi University Medical School, Ankara, Turkey, [2]Internal Medicine-Nephrology, Gazi University Medical School, Ankara, Turkey

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Background/Purpose: Neutrophil/lymphocyte ratio (NLR) has recently been extensively studied as a prognostic indicator in various malignancies, as well as an indicator of severity in cardiovascular disorders, including coronary arterial disease and hypertention. Its prognostic value in vasculitic disorders remains to be investigated. Aim of the study was to investigate NLR and its association with renal outcome in patients with granulomatosis with polyangiitis.

Methods: We studied 41 patients (mean±SD age 50±14 and M/F 23/17) with granulomatosis with polyangiitis. Data were obtained retrospectively from medical records. 17 patients had renal involvement of the vasculitis. Baseline C-reactive protein (CRP) levels, erythrocyte sedimentation rate (ESR), neutrophil and lympocyte counts were recorded. NLRs were calculated using the formula (neutrophil count/lymphocyte count). Serum creatinine levels at baseline and at 6-month follow-up were also recorded. Non-parametric tests were used for analyses.

Results: Median NLR of the entire group at baseline was high (4,5 [IQ range 5,8]). NLR at baseline correlated significantly with ESR and CRP levels (r=0,402, p<0,001 and r=0,481, p<0,001, respectively). Patients with NLR greater than 8.3 (the highest quartile) had significantly higher creatinine at baseline, as well as at 6 month follow-up (Mann-Whitney test p=0.002 and p=0.05, respectively). Patients with vasculitic renal involvement had higher NLR at baseline compared to those with non-renal vasculitis (5,0 [IQ range 10,9] vs 2,9 [IQ range 7,7], p=0,05). In the subgroup with renal involvement, baseline NLR correlated significantly with baseline creatinine levels (r=0,52, p=0,026). Moreover, in this subgroup, those with NLR at the highest quartile had significantly higher baseline, as well as 6-month follow-up creatinine (p=0,011 and 0,037, respectively) compared to those with renal involvment but lower NLR.

Conclusion: Results suggest that NLR at baseline correlates with renal function and those with a higher NLR at baseline have worse kidney outcome at 6 month follow-up. Further studies are needed to elucidate the function of neutrophils in the pathogenesis of tissue damage in a lymphocyte-mediated disease, such as granulomatosis with polyangiitis.

Disclosure: B. Goker, None; **S. Haznedaroglu**, None; **H. Kucuk**, None; **O. Varan**, None; **B. Bitik**, None; **A. Tufan**, None; **R. Mercan**, None; **Y. Erten**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/neutrophillymphocyte-ratio-could-it-be-a-prognostic-indicator-for-renal-outcome-in-patients-with-granulomatosis-with-polyangiitis

Abstract Number: 861

ANCA-Associated Pauci-Immune Glomerulonephritis: ¿Always Pauci-Immune?

Valeria Scaglioni[1], Marina Scolnik[1], Luis J. Catoggio[1], Carlos Federico Varela[2], Gustavo Greloni[2], Silvia Christiansen[3] and Enrique R. Soriano[4], [1]Rheumatology Unit, Internal Medicine Service, Hospital Italiano de Buenos Aires, Instituto Universitario Hospital Italiano de Buenos Aires, and Fundacion PM Catoggio, Buenos Aires, Argentina, [2]Nephrology Service. Hospital Italiano de Buenos Aires, Buenos Aires, Argentina,

[3]Pathology Service. Hospital Italiano de Buenos Aires, Buenos Aires, Argentina, [4]Internal Medicine, Rheumatology Unit, Internal Medicine Service, Hospital Italiano de Buenos Aires, Instituto Universitario Hospital Italiano de Buenos Aires, and Fundacion PM Catoggio, Buenos Aires, Argentina

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Background/Purpose:

Anti-neutrophil cytoplasmic antibody (ANCA)-associated glomerulonephritis (GN) is considered a “pauci-immune” disease, characterized by absent or mild glomerular tuft staining for immunoglobulin and/or complement. However, it is not unusual for renal biopsies in such cases to exhibit some immune complex (IC) deposition within glomeruli on immunofluorescence (IF) and/or electron microscopic study. Their potential pathologic and clinical significance is not clear, although a possible synergistic effect between immune complexes and ANCA in producing more severe glomerulonephritis is suggested by some authors. The aim of this study was to evaluate the prevalence and clinical significance of immune deposits in ANCA-associated pauci-immune GN.

Methods:

We included retrospectively all patients with biopsy-proven ANCA GN: granulomatosis with polyangiitis (GPA), granulomatosis with polyangiitis and eosinophilia (GPAE), microscopic polyangiitis (PAM) and renal limited vasculitis (RLV) between January 2002 and May 2013. Patients were divided into 2 groups: Group A: biopsy without IC deposits (less than 2+ intensity of immunostaining) and Group B: biopsy with IC deposits (more than 2+ intensity of immunostaining). IF included Ig (IgG, IgA and IgM) and complement components (C3 and C1q). Serum creatinine, estimated glomerular filtration rate (eGFR) at time of the biopsy, amount of proteinuria and hematuria, requirement of dialysis and extra renal involvement were recorded.

Results:

Fifty-three patients (75.4% females) were included. The mean age at the time of the biopsy was 66.3 (SD: 14.3). Typical pauci-immune GN was found in 39 patients (73.5%, group A). In 14 patients (26.4%, group B) histopathological examination revealed substantial deposition of Ig or complement in the mesangium and/or along the glomerular capillary wall. IC deposition was more frequent in GPA and GPAE compared with PAM and RLV. C3 deposition on the capillary wall was the most frequent finding (64.2%), followed by C3 + IgG (21.4%) and IgG alone (14.2%). No patient presented positive staining for C1q. IgM and IgA were found only in two patients but along with C3. Compared with patients in group A, those in group B demonstrated significantly more 24 h proteinuria (mean 0.8 (SD: 7.6) vs 1.6 (SD: 10.7), p= 0.0036). No differences between groups were found related to age, gender, renal function, extra renal organ involvement at the time of biopsy, and in response to induction therapy (table 1).

Conclusion:

Our results confirm that in ANCA GN a substantial percentage of patients have evidence of Ig or C3 deposition in renal biopsies (26.4%). In this subgroup, IC deposition was associated with a significantly greater degree of proteinuria. Further clinical and basic research is needed to elucidate the significance of IC deposition in ANCA GN.

TABLE 1. DIFFERENCES BETWEEN THE GROUPS

	GROUP A, N=39 (less than 2+ intensity of immunostaining)	GROUP B, N=14 (more than 2+ intensity of immunostaining)	p
Mean age (SD)	67.6 (15.4)	62.6 (10.1)	.26
Females, n (%)	29 (72.5)	10 (76.2)	.75
Diagnosis, n (%) - GPA - GPAE - PAM - RLV	9 (60) 3 (60) 9 (90) 18 (78)	6 (40) 2 (40) 1 (10) 5 (22)	
Mean Baseline Creatinine mg/dl, (SD)	3 (28.2)	3.4 (23.5)	.69
Extra-renal involvement; n, (%)	19 (48.7)	7 (50)	.93
Mean Proteinuria g/24 h, (SD)	0.8 (7.6)	1.6 (10.7)	**.0036**
Remission after induction treatment; n (%)	26 (74.2)	11 (68.7)	.68

Disclosure: V. Scaglioni, None; **M. Scolnik**, None; **L. J. Catoggio**, None; **C. F. Varela**, None; **G. Greloni**, None; **S. Christiansen**, None; **E. R. Soriano**, Abbvie; Janssen; UCB; Roche; Bristol Myers Squibb, 2,Abbvie; UCB; Janssen; Roche; Bristol Myers Squibb; Pfizer; Novartis, 8.

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Abstract Number: 862

Discriminative Performance of Nasal Endoscopic Findings and History Items in Patients with Granulomatosis with Polyangiitis

Erdem Eren[1], Toygar Kalkan[2], Secil Arslanoglu[1], Mustafa Ozmen[3], Kazim Onal[1], Emine Figen Tarhan[3] and **Servet Akar**[4], [1]Head and Neck Surgery, Izmir Ataturk Research and Training Hospital, Izmir, Turkey, [2]Internal Medicine, Izmir Ataturk Research and Training Hospital, Izmir, Turkey, [3]Rheumatology, Izmir Ataturk Research and Training Hospital, Izmir, Turkey, [4]Department of Internal Medicine, Division of Rheumatology, Izmir Katip Celebi University School of Medicine, Izmir, Turkey

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Background/Purpose:

Granulomatosis with polyangiitis (Wegener's granulomatosis, GPA) is a systemic vasculitis of unknown etiology. It is characterized by necrotizing granulomatous inflammation and affects predominantly small vessels. Upper respiratory tract is involved in some phase of the disease in about 90% of the patients and most frequently at the beginning of the disease. Median diagnostic delay was reported as 4-17 months and it was most remarkable in patients with head and neck symptoms. Up to now clinical manifestations of GPA were described retrospectively and discriminative ability of nasal history and examination findings was never systematically evaluated before. Therefore we aimed to determine the predictive value of history items and nasal endoscopic examination findings in the diagnosis of GPA.

Methods: Seventeen GPA patients (12 [67%] male; mean age 49,3 ± 13,9), 29 patients with rheumatologic disease other than GPA (8 [28%] male; mean age 46.8 ± 16.3) and 67 healthy subjects (28 [42%] male; mean age 47,3 ± 15,2) were included in the study. Patients' history was taken by a physician blinded to diagnosis and each patient was examined with flexible nasal endoscope and nasal endoscopic images are recorded and evaluated blindly. The following history items were noted and graded as present or absent; sneezing, rhinorrhea, nasal obstruction, cough, postnasal drip, facial pain, taste disturbance, decreased smell, epiphora, epistaxis, saddle-nose. Nasal endoscopic findings noted were edema of middle meatus, nasal secretion, polypoid changes of middle meatus mucosa, nasal polyposis, hypertrophy of inferior turbinate, septal

perforation, nasal crusting, adhesions, granuloma, hemorrhagic fragile nasal mucosa.

Results: Regarding the history items univariate analysis revealed that rhinorrhea (p=0,003), postnasal drip (p=0,022), epistaxis (p<0,001), and saddle nose deformity (p=0,046) were statistically significantly different between groups. However in binary logistic regression analysis none of these history items have a statistically significant predictive role in selecting patients with GPA. A univariate analysis demonstrates that the following endoscopic findings demonstrates statistically significant difference; nasal secretion (p=0,003), nasal septal perforation (p < 0,001), nasal crusting (p< 0,001), nasal adhesion (p < 0,001), nasal granuloma (p=0,046), polypoid changes of middle meatus mucosa (p=0,42), and hemorrhagic fragile nasal mucosa (p < 0,001). In regression analysis hemorrhagic fragile nasal mucosa (p< 0,001, OR=41) was the only significant predictor for GPA.

Conclusion: The results of the present study suggest that patients with hemorrhagic fragile nasal mucosa should alert the physician about the possibility of GPA. The role of the other nasal mucosal findings in the differential diagnosis of GPA needs to be verified by larger studies.

Disclosure: E. Eren, None; **T. Kalkan**, None; **S. Arslanoglu**, None; **M. Ozmen**, None; **K. Onal**, None; **E. F. Tarhan**, None; **S. Akar**, None.

Abstract Number: 863

Contribution of MPO-/PR3-ANCA Tests to the Diagnosis of ANCA-Associated Vasculitis in a Community Hospital: Evaluation of 2,782 Samples

Eishi Uechi, Chiai Nakata, Tomoo Murayama and Yoshiki Shiohira, Rheumatology, Tomishiro Central Hospital, Okinawa, Japan
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Session Time: 9:00AM-11:00AM

Background/Purpose:

The purpose of this study was to evaluate the contribution of MPO-/PR3-ANCA tests to the diagnosis of ANCA-associated vasculitis (AAV).

Methods:

We extracted patients who underwent MPO-/PR3-ANCA tests during the 5-year period from June 2009 to July 2014 using an electronic medical record system of a general hospital that has Departments of Rheumatology, Nephrology, Respiratory Diseases, Neurology, Cardiology, General Internal Medicine, and Dermatology in Okinawa, Japan. In the extracted patients, the clinical diagnosis and patients' background were confirmed using this system.

Results:

From June 2009 to July 2014, 2,782 samples obtained from 2,019 subjects were presented to the MPO-ANCA and PR3-ANCA tests (CLEIA method). MPO-ANCA and PR3-ANCA were positive in 107 (5%) and 36 (2%) subjects, respectively, of whom 50 (48.0%) and 3 (8.3%), respectively, had AAV, and 12 (11.2%) and 12 (33.3%), respectively, had infection. In the MPO-ANCA-positive patients, those with AAV showed a significantly higher MPO-ANCA level than the non-AAV patients (p = 0.001). In the PR3-ANCA-positive patients, the PR3-ANCA level did not differ between AAV and non-AAV patients. In this study, the sensitivity, specificity, positive predictive value, and negative predictive value of the MPO-ANCA test in AAV diagnosis were 0.85, 0.69, 0.47, and 0.93, respectively, and those of the PR3-ANCA test were 0.25, 0.79, 0.08, and 0.93, respectively.

Conclusion:

In daily practice in the Department of Rheumatology and the other departments, many samples had been presented for MPO-/PR3-ANCA tests. However, the percentage of patients positive for each test was low (< 10%). In this study, the positive predictive values of both MPO-ANCA and PR3-ANCA tests were low. Most ANCA-positive patients had diseases other than AAV, including many with infection. These results suggest that the results of the ANCA tests in daily practice should be carefully interpreted, and differential diagnosis between AAV and other diseases such as infection is important. The MPO-ANCA level was higher in the AAV group than in the non-AAV group. However, both the MPO-ANCA and PR3-ANCA values markedly varied in each group, and AAV diagnosis based on the ANCA level was difficult. In a previous large-scale study, the sensitivity and specificity of the MPO-ANCA test for MPA were 58 and 91%, respectively, and those of the PR3-ANCA test for GPA were 65-67 and 86-89%, respectively. The low specificity of the MPO-ANCA test based on data in this hospital suggests the presence of many patients with ANCA-negative MPA. In addition, compared with the previous study, the sensitivity and positive predictive value of PR3-

ANCA were extremely low. These results may reflect the low prevalence of GPA in Japan.When samples are presented for ANCA tests, patients in whom the pre-test probability of AAV is high should be selected, and the results of the test should be carefully interpreted even when samples are positive.

Disclosure: E. Uechi, None; **C. Nakata**, None; **T. Murayama**, None; **Y. Shiohira**, None.

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Abstract Number: 864

Anticytokine Autoantibody Profiling in Five Types of Systemic Vasculitis

Sarthak Gupta[1,2], Seema K. Patel[2], Mary Blake[2], Massimo G. Gadina[2], Wanxia L. Tsai[2], Simon Carette[3], David Cuthbertson[4], Gary S. Hoffman[5], Nader A. Khalidi[6], Curry L. Koening[7], Carol A. Langford[5], Carol A. McAlear[8], Larry W. Moreland[9], Paul A. Monach[10], Christian Pagnoux[3], Philip Seo[11], Ulrich Specks[12], Antoine G. Sreih[13], Steven R. Ytterberg[14], Sarah K. Browne[1,15], Steven M. Holland[1], Mariana J. Kaplan[2], Peter A. Merkel[16], Peter C. Grayson[2] and Vasculitis Clinical Research Consortium, [1]Laboratory of Clinical Infectious Diseases, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD, [2]National Institute of Arthritis and Musculoskeletal and Skin Diseases, National Institutes of Health, Bethesda, MD, [3]Division of Rheumatology, Mount Sinai Hospital, University of Toronto, Toronto, ON, Canada, [4]Biostatistics and Informatics, Department of Pediatrics, University of South Florida, Tampa, FL, [5]Rheumatology, Cleveland Clinic, Cleveland, OH, [6]Division of Rheumatology, St. Joseph's Health Care, McMaster University, Hamilton, ON, Canada, [7]Division of Rheumatology, University of Utah, Salt Lake City, UT, [8]Division of Rheumatology, University of Pennsylvania, Philadelphia, PA, [9]Rheumatology & Clinical Immunology, University of Pittsburgh, Pittsburgh, PA, [10]Rheumatology, Boston University School of Medicine, Boston, MA, [11]Division of Rheumatology, Johns Hopkins University, Baltimore, MD, [12]Division of Pulmonary and Critical Care Medicine, Mayo Clinic College of Medicine, Rochester, MN, [13]Department of Rheumatology, University of Pennsylvania, Philadelphia, PA, [14]Rheumatology Division, Mayo Clinic, Rochester, MN, [15]Office of Vaccines Research and Review, Center for Biologics Evaluation and Research, US Food and Drug Administration, Silver Spring, MD, [16]Penn Vasculitis Center, Division of Rheumatology, University of Pennsylvania, Philadelphia, PA

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Background/Purpose:

Anticytokine autoantibodies (ACAs) are pathogenic in many hematologic, pulmonary and infectious diseases. Evaluation in autoimmune diseases, including systemic lupus erythematosus (SLE), shows that ACAs are biologically active and may contribute to disease pathogenesis. The prevalence of ACAs and their correlation to circulating cytokine levels in vasculitis has not been characterized and was the focus of this study.

Methods:

Patients with various forms of vasculitis were selected from a multicentered, observational cohort and fulfilled modified ACR classification criteria for the respective diseases. All patients had active disease at the time of sample collection and had not received cyclophosphamide or rituximab within 6 months prior to sample collection. Plasma samples from patients with 5 types of vasculitis (n=149) and healthy controls (n=25) were tested for autoantibodies against 34 cytokines using a multiplex bead-based assay. For each ACA concentrations above two standard deviations of the mean of healthy controls and more than 1000 fluorescence intensity were classified as positive. Cytokine measurements were done using Human 25-Plex Panel (Invitrogen, Inc). Data were acquired on a Bio-Plex 100 instrument. Spearman's correlation coefficients were calculated to detect potential associations between levels of cytokines and the relevant ACA.

Results:

The majority of patients (57%) had at least one ACA; however, the prevalence of individual ACA ranged from 0 to 33% (Table 1). Autoantibodies against TNF and LT**a** were seen in the setting of anti-TNF monoclonal therapy. Compared to other types of vasculitis, an increased prevalence of autoantibodies against Th2 cytokines (IL-4, 5, 10, 13, up to 17%) were seen in Takayasu's arteritis and autoantibodies against G-CSF (15%) and IL-2 (23%) were detected in granulomatosis with polyangiitis (GPA). No autoantibodies against IL-6 were seen. Significant correlations were identified in 2 of 18 relevant pairings between ACAs and corresponding cytokine levels. IL-12 levels correlated weakly with anti-IL-12 autoantibodies ($r=0.21$, $p<0.01$), and soluble IL-2R levels, but not IL-2, negatively correlated with anti-IL-2 autoantibodies ($r=0.23$, $p<0.01$). Plasma IL-2R levels were significantly higher in patients with GPA compared to the other types of vasculitis

(668.3 vs 288.8 ng/ml, p<0.01); among patients with GPA IL-2R levels were 2-fold lower in patients with anti-IL-2 autoantibodies.

Conclusion:

ACAs occur at differing frequencies across the spectrum of vasculitis. Interestingly, autoantibodies directed against IL-2 were observed in a subset of patients with GPA and were negatively correlated with plasma IL-2R levels, suggesting that these autoantibodies may play a functional role in disease pathogenesis. Functional studies of candidate ACAs in vasculitis are warranted.

Table 1: Distribution of Anticytokine Autoantibodies in Patients with Vasculitis

	GPA n=40	EGPA n=30	PAN n=19	GCA n=30	TAK n=30
≥ 1 Autoantibody	22 (55%)	12 (40%)	10 (53%)	24 (80%)	17 (57%)
Anti-EPO	5 (13%)	1 (3%)	0 (0%)	3 (10%)	0 (0%)
Anti-G-CSF	6 (15%)	2 (7%)	2 (11%)	4 (13%)	2 (7%)
Anti-GM-CSF	1 (3%)	1 (3%)	0 (0%)	1 (3%)	1 (3%)
Anti-M-CSF	0 (0%)	1 (3%)	0 (0%)	0 (0%)	1 (3%)
Anti-TNF	4 (10%)	3 (10%)	0 (0%)	10 (33%)	6 (20%)
Anti-LTα	7 (18%)	3 (10%)	4 (21%)	7 (23%)	7 (23%)
Anti-TL1a	0 (0%)	1 (3%)	0 (0%)	1 (3%)	0 (0%)
Anti-APRIL	0 (0%)	1 (3%)	0 (0%)	0 (0%)	0 (0%)
Anti-IFN α	0 (0%)	1 (3%)	1 (5%)	1 (3%)	3 (10%)
Anti-IFN β	2 (5%)	2 (7%)	0 (0%)	2 (7%)	2 (7%)
Anti-IFN ω	2 (5%)	4 (13%)	2 (11%)	3 (10%)	3 (10%)
Anti-IFN γ	0 (0%)	0 (0%)	1 (5%)	0 (0%)	0 (0%)
Anti-IFN λ 1	0 (0%)	1 (3%)	2 (11%)	1 (3%)	3 (10%)
Anti-IFN λ 2	2 (5%)	1 (3%)	1 (5%)	2 (7%)	1 (3%)
Anti-IFN λ 3	1 (3%)	2 (7%)	0 (0%)	0 (0%)	3 (10%)
Anti-IL-1α	0 (0%)	1 (3%)	0 (0%)	1 (0%)	0 (0%)
Anti-IL-2	9 (23%)	2 (7%)	0 (0%)	3 (10%)	1 (3%)
Anti-IL-4	2 (5%)	2 (7%)	0 (0%)	1 (3%)	5 (17%)
Anti-IL-5	0 (0%)	1 (3%)	1 (5%)	2 (7%)	5 (17%)
Anti-IL-6	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Anti-IL-7	1 (3%)	1 (3%)	0 (0%)	1 (3%)	0 (0%)
Anti-IL-8	0 (0%)	1 (3%)	0 (0%)	1 (3%)	1 (3%)
Anti-IL-10	1 (3%)	1 (3%)	1 (5%)	0 (0%)	5 (17%)
Anti-IL-12	0 (0%)	1 (3%)	0 (0%)	0 (0%)	0 (0%)
Anti-IL-13	2 (5%)	3 (10%)	1 (5%)	3 (10%)	5 (17%)
Anti-IL-15	0 (0%)	1 (3%)	0 (0%)	0 (0%)	0 (0%)
Anti-IL-17A	2 (5%)	1 (3%)	0 (0%)	2 (7%)	1 (3%)
Anti-IL-17F	2 (5%)	0 (0%)	1 (5%)	2 (7%)	1 (3%)
Anti-IL-18	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Anti-IL-21	0 (0%)	1 (3%)	0 (0%)	0 (0%)	2 (7%)
Anti-IL-22	2 (5%)	2 (7%)	1 (5%)	1 (3%)	5 (17%)
Anti-IL-23	1 (3%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Anti-IP-10	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Anti-Leptin	0 (0%)	1 (3%)	1 (5%)	1 (3%)	6 (20%)

Results are reported for number (%) of patients. GPA: granulomatosis with polyangiitis; EGPA: eosinophilic granulomatosis with polyangiitis; PAN: polyarteritis nodosa; GCA: giant cell arteritis; TAK: Takayasu's arteritis; EPO: erythropoietin; G-CSF: granulocyte-colony stimulating factor; GM-CSF: granulocyte monocyte-colony stimulating factor; M-CSF: macrophage-colony stimulating factor; TNF: tumor necrosis factor; LT α : lymphotoxin- α ; APRIL: a proliferation-inducing ligand; IFN: interferon; IL: interleukin; IP-10: interferon-inducible-protein-10.

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Abstract Number: 865

Abdominal Visceral Adipose Tissue Measured By Dual Energy X-Ray Absorptiometry (DXA) As a Novel Surrogate Marker of Cardiovascular Risk in Primary Necrotizing Vasculitides

Bertrand Dunogué[1], Karine Briot[2], Sami Kolta[2], Alexis Regent[1], Pascal Cohen[1], Alice Berezne[1], Xavier Puéchal[1], Claire Le Jeunne[1], Luc Mouthon[1], Christian Roux[2], Loïc Guillevin[1] and Benjamin Terrier[1], [1]Internal Medicine, National Referral Center for Rare Systemic Autoimmune Diseases, Hôpital Cochin, Paris, France, [2]Rheumatology B Department, Hôpital Cochin, Paris, France

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Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose: Studies have shown a strong prevalence of cardiovascular events among patients with systemic necrotizing vasculitides (SNV). Recent studies indicate that visceral adipose tissue (VAT) is highly associated with cardiovascular events. The aim of this study was to assess the relevance of abdominal adipose tissue measurement by Dual energy X-ray Absorptiometry (DXA) as a potential surrogate marker for cardiovascular risk in patients with SNV.

Methods: Patients with SNV seen in our department were prospectively included in a cross-sectional study assessing cardio-vascular complications and risk factors, and other sequelae. DXA was performed to evaluate body composition and abdominal adipose tissue (both subcutaneous (SAT) and visceral (VAT)).

Results: One hundred and twenty consecutive patients with SNV were analyzed (66 female and 54 male, mean age 53±18 years, median disease duration of 54 months). Diagnoses were granulomatosis with polyangiitis in 61 patients, eosinophilic granulomatosis with polyangiitis in 30, polyarteritis nodosa in 14, microscopic polyangiitis in 13, and cryoglobulinemia vasculitis in 2. The median daily dose of glucocorticoids was 8.5 mg/day (0-80), with an estimated total cumulative dose of 15000±10000 mg of glucocorticoids.

High cardiovascular risk, as defined by the NCEP-ATPIII, was present in 28 (23.3%) patients, including 15 (12.5%) with previous cardiovascular disease. Variables significantly associated with high cardiovascular risk after multivariate analysis were an increased age [OR 1.04 (1.00-1.08); P=0.048] and an increased VAT/SAT ratio [OR 1.06 (1.03-1.09); P<0.0001]. The VAT/SAT ratio was significantly higher in patients with high cardiovascular risk (66.3±21.2 vs. 39.4±18.2%, P<0.0001), particularly those with previous cardiovascular history (75.2±13.4 vs. 41.1±19.5%, P<0.0001). A higher VAT/SAT ratio was independently associated with increased age (P<0.0001), male gender (P<0.0001), and elevated levels of triglycerides (P=0.01), glycated hemoglobin (P=0.007) and troponin (P=0.05).

The Framingham cardiovascular risk score, predicting a subject's risk of developing an ischemic cardiac disease in the next 10 years, was strongly correlated with the VAT/SAT ratio in our patients (r=+0.60, P<0.0001), but also with the 10-year probability of major osteoporotic (r=+0.35, P=0.0009) and hip (r=+0.51, P<0.0001) fractures using the FRAX.

Conclusion: This is the first study showing a significant association between a high VAT/SAT ratio assessed by DXA and cardiovascular risk in patients with SNV. The measurement of the abdominal adipose tissue seems to be an accurate and independent surrogate marker of cardiovascular risk in these patients. Finally, cardiovascular and osteoporotic fracture risks were strongly associated suggesting that optimal management of both risks is crucial in these patients.

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Abstract Number: 866

High Rate and Bimodal Pattern of Severe Infection in a Selected ANCA Associated Vasculitis Cohort

Esra Aydın[1], Bahtiyar Toz[2], Burak Erer[2], Mustafa Erelel[3], Ahmet Gocmez[4], Ahmet Gul[5], Murat Inanc[2], Lale Ocal[5] and Sevil Kamali[2], [1]Department of Internal Medicine,, istanbul faculty of medicine, istanbul, Turkey, [2]Department of Internal Medicine, Division of Rheumatology, Istanbul University, Istanbul Faculty of Medicine, Istanbul, Turkey, [3]Department of Pulmonology, Istanbul University Istanbul Faculty of Medicine Department of Pulmonology, istanbul, Turkey, [4]Department of Radiology, Istanbul University Istanbul Faculty of Medicine, istanbul, Turkey, [5]Department of Internal Medicine, Rheumatology Division, Istanbul University, Istanbul Faculty of Medicine, Istanbul, Turkey
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Background/Purpose : Increased rate of severe infection (SI) in patients who exposed to immunosuppressive drugs has been a well-known complication in inflammatory rheumatic diseases. However, there are few reports on SI complicating AAV course.

Methods: We retrospectively investigated the characteristics of "SI requiring hospitalization" in AAV patients with lung involvement who were previously included into a study evaluating lung damage. Data were collected from hospital records between 2000-2014. Demographics, data on infection investigation including blood, sputum and urine cultures, viral serology, PPD/QTB tests, procalcitonin, imaging and biopsy findings,

comorbidites, vasculitis activity and damage scores, cumulative dose of glucocorticoid (GC), cyclophosphamide (CYC) and rituximab (RTX) were noted into a predefined protocol. Infections that could not be revealed by cultures but succesfully treated with antibiotics were categorized as unidentified (UI). We compared the demographic and clinical data, presence of comorbidities, initial BVAS and cumulative VDI scores and GC/CYC doses according to the presence of SI by Mann-Whitney U test.

Results: Fifty-one AAV patients with lung involvement (25 female) (40 GPA, 8 MPA, 3 e-GPA) who were diagnosed according to ACR and CHCC criteria were included into the study. Age at diagnosis and total duration of follow-up were as follows: 49 ± 13 years (med 51), 67 ± 52 mo (med 47). Lung (100%), kidney (78 %), ENT (72 %), nervous system (25 %) were the involved organs. ANCA positivity was 94% (66% cANCA/anti-PR3, 34% p-ANCA/anti-MPO). Initial BVAS and cumulative VDI scores were 22±7 (4-38) (med 23), 3,4±2,2 (0-9) (med 3), respectively. Twenty-nine relapses occurred in 15 (29%) patients. Cumulative dose of GC and CYC were 16±9 g (med 14), 17± 25 (med 6), respectively. RTX was used in 17 patients. Diabetes (18%), chronic kidney failure (25%) were the major comorbidities and 7% had ESRD. Influenza and pneumococcal vaccination and TMP-SMX prophylaxis were applied in one forth and two-thirds of AAV cohort, respectively. Five patients (10%) had neutropenia (4 severe, 1 moderate) and suffered from SI. Eightyseven SI noted in 25 (52%) patients. Identified and unidentified SI in AAV cohort were shown in Table-1. Recurrent SI occurred in 27% of pulmonary and 33% of non-pulmonary groups. SI was associated with relapse in 16%. Serum

procalcitonin level increased in 93% (3.5±16.5, med 0.26, (0.5-95)) of 33 AAV patients. SI proportion was found to be increased during the first six months (%35) and after the 60th month of follow-up (30%). There were no significant difference between the patients with or without SI according to the risk factors.

Bacterial (35%) n=30	Pulmonary	M.tuberculosis (1), Klebsiella (3), Pseudomonas (6), S.pneumoniae (1), E.coli (3), S.marcescens (1)
	Urinary	E.coli (3), S.marcescens (1), Acinetobacter spp. (1)
	Catheter infection	MRCNS (1), MSSA (1)
	Musculo-skeletal	S.aureus (1)-septic arthritis, Nocardia (1)-Muscle abscess
	Peritonsillar abscess	Corynebacterium spp. (1)
	Choroiditis	M.tuberculosis (1)
Fungal (21%) n=19	Pulmonary	Aspergillus (2)
	Esophagitis	Candida albicans (15)
	Otitis media	Aspergillus (1)
	Urethritis	Candida albicans (1)
Viral (9%) n=8	Shingles	HZV (4)
	Esophagitis	CMV (2), HZV (1)
	Chorioretinitis	CMV (1)
Unidentified (35%) n=30	Pulmonary (21), Cellulitis (1), Oral mucositis (1), Tonsillitis (1), Sinusitis (2), Ventriculoperitoneal shunt infection (1), Epididymo-orchitis (1), Mesenteric lymphadenitis with intraabdominal infection (1), Pelvic inflammatory disease (1)	

Conclusion: Prevalence of SI was high and had a bimodal pattern in the early and late phase of AAV. SI was found to have a high proportion of re-occurrence. SI complicated disease relapses in a small group of patients

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Abstract Number: 867

Simultaneous Measurement of 25-Hydroxyvitamin D and Procalcitonin in Granulomatosis with Polyangiitis (GPA): Differentiation of Activity from Infection?

Mariana O Perez[1], Ricardo M. Oliveira[2], Valéria Caparbo[3,4], Mauricio Levy-Neto[5], Eloisa Bonfá[4] and Rosa M R Pereira[3], [1]Rheumatology Divison, Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil, [2]RDO Diagnósticos Médicos, São Paulo, Brazil, [3]Faculdade

de Medicina da Universidade de São Paulo, São Paulo, Brazil, [4]Rheumatology Division, Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil, [5]Rheumatology DIvision, Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil
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Background/Purpose: Vitamin D acts as innate and adaptive immune response immunomodulator. 25-hydroxyvitamin D (25OHD) deficiency was reported to be associated with autoimmune diseases flares and also with increased frequency of viral and bacterial infections. Procalcitonin (PCT) is a marker of bacterial and fungal infection and high levels may be related to disease activity in autoimmune diseases. There is no study evaluating simultaneously 25OHD and PCT serum levels in GPA patients and the association with disease activity and infections. The objective of this study is to determine the possible association of 25OHD and PCT serum concentrations with disease activity and respiratory infections in patients with GPA.

Methods: Thirty-two GPA patients were evaluated in winter/spring (n=32) and summer/autumn (n=27). 25OHD and PCT were measured by electrochemiluminescence. Disease activity was assessed using the Birmingham Vasculitis Activity Score (BVAS≥1) and ANCA. Airways respiratory infection was defined according to the CDC (Centers For Disease Control and Prevention) criteria. T-student, Mann Whitney and Fischer exact tests were performed for statistical analyses, with $p < 0.05$ considered significant.

Results: Fifty three percent (17/32) of patients were women, 65.6% (21/32) were caucasian, with a mean age of 46.2 ± 13yrs, disease duration of 8.9 ± 4.2yrs and 71.8% (23/32) presented generalized form of GPA. Of the 59 samples, 39 (66%) were in vitamin D replacement (800-7,000 U/day). There was no difference between 25OHD concentrations of those with (34.87 ± 12.51 ng/mL) or without (36.31 ± 12.81 ng/mL) vitamin D supplementation. In winter/spring season concentrations of 25OHD were lower compared to summer/autumn (32.31 ± 13.10 vs. 38.98 ± 10.97 ng/mL, p=0.04). Seven patients were diagnosed with airway infections, 5 of them in autumn/winter, with a predominance of tracheobrochitis (71.4%). Patients with airway infection had lower 25OHD concentrations compared with those without infection (24.51 ± 11.81 vs. 36.82 ± 11.98 ng/mL, p=0.01) whereas no difference was observed for PCT serum levels (0.07 ± 0.06 vs. 0.04 ± 0.03 ng/mL, p=0.26). With regard to activity, higher PCT serum levels was observed in patients with concomitant BVAS≥1 and positive ANCA compared with patients BVAS=0 and ANCA negative (0.07 ± 0.06 vs. 0.03 ± 0.01 ng/mL, p=0.02). Further analysis regarding the follow-up of ten patients that presented PCT ≥ 0.05 ng/mL and BVAS ≥ 1, five of them evolved for remission (BVAS = 0) and a decline of PCT was observed; 2 patients remained with active disease and PCT levels remained high (PCT > 0.10). Of note, 25OHD levels were comparable in patients with and without disease activity (BVAS≥1 and positive ANCA), (33.60 ± 11.84 vs. 36.19 ±12.89 ng/mL, p=0.46).

Conclusion: The observed association of low 25OHD levels with airway infection and high PCT levels with activity in patients with GPA suggests that simultaneous measurements of these markers may be helpful to distinguish disease activity from infection in GPA patients.

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Abstract Number: 868

Risk Factors for Cytomegalovirus Reactivation in Patients with Antineutrophil Cytoplasmic Antibody -Associated Vasculitis

Yuichiro Ota[1], Yuko Kaneko[2], Takahiko Kurasawa[3], Kunihiro Yamaoka[4], Katsuya Suzuki[4] and Tsutomu Takeuchi[5], [1]Division of Rheumatology, Department of Internal Medicine., Keio University School of Medicine., Tokyo, Japan, [2]Division of Rheumatology, Keio University School of Medicine, Tokyo, Japan, [3]Division of Rheumatology and Clinical Immunology, Department of Internal Medicine, Saitama Medical Ctr, Kawagoe, Japan, [4]Division of Rheumatology, Department of Internal Medicine, Keio University School of Medicine, Tokyo, Japan, [5]Keio University School of Medicine, Tokyo, Japan
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Background/Purpose: Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is a disease entity characterized by inflammatory cell infiltration and necrosis of blood vessel walls. AAV usually needs intensive immunosuppressive treatment for remission induction, that sometimes brings about serious infection. Cytomegalovirus (CMV) reactivation is one of the opportunistic infections for immunosuppressed patients, therefore, identifying patients at risk for CMV reactivation is of importance. This study was to investigate risk factors relevant with CMV in patients with AAV during remission induction therapy.

Methods: All patients with AAV including microscopic polyangiitis (MPA), granuromatosis with polyangiitis (GPA), and eosinophilic granulomatosis with polyangiitis (EGPA) in Keio University from April 2008 until May 2015 were retrospectively reviewed. Clinical information during remission induction therapy were collected from their medical charts. CMV reactivation was defined by the detection of detecting pp65 antigen in polymorphonuclear leukocytes from peripheral blood. Mean values and proportions were compared by Student's t-test and chi-square test, respectively, and multivariate logistic analysis was performed.

Results: Seventy AAV patients (MPA 33, GPA 19, and EGPA 18) were enrolled in this study. In total of 102 cases were treated with glucocorticoid and/or immunosuppressive agents as a remission induction therapy irrelevant of new onset or recurrence. We analyzed 67 cases (MPA 34, GPA 21, and EGPA 12) in whom CMV pp65 antigen was regularly measured during the treatment course. Patient characteristics were as following; mean age 65.5 ± 13.7 years old, female 35 (52%), disease duration 70.1 ± 142.9 weeks, and recurrence case 20 (31%). The mean initial dose of prednisolone (PSL) was 44.7±14.7 mg. Steroid pulse therapy was conducted in 11 patients (30%) and intravenous cyclophosphamide (IVCY) therapy in 30 patients (42%).

CMV was reactivated in 28 cases (42%). Six cases were treated with antiviral agents including 2 cases with organ involvement (CMV retinitis, and CMV colitis). While mean age and baseline performance status were not significantly different between the CMV-positive group (n = 28) and the CMV-negative group (n = 38), the initial prednisolone dose was higher (50.4 ± 11.4 mg vs. 40.6 ± 15.5 mg, $p = 0.007$), methylprednisolone pulse therapy (43% vs. 21%, $p = 0.049$) and IVCY (68% vs. 23%, $p < 0.001$) were more frequently conducted, and baseline serum creatinine level was higher (1.3 ± 0.8 mg/dl vs. 0.9 ± 0.3 mg/dl, $p = 0.004$) in CMV-positive group. Multivariate logistic analysis identified initial PSL dose ≥ 40 mg/day ($p = 0.031$), IVCY therapy ($p = 0.005$), recurrence case ($p = 0.018$), and higher Brinkmann index ($p = 0.033$) as independent risk factors for CMV reactivation. Correspondingly, all six cases treated with anti-CMV agents were treated with IVCY.

Conclusion: Initial PSL dose, IVCY, recurrence case, and high Brinkmann index are risk factors for CMV reactivation during induction therapy for AAV. Patients with those risks require a particular attention.

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Abstract Number: 869

Lymphoma in Patients with Granulomatosis with Polyangiitis

Karin Hjorton[1], Erik Hellbacher[1], Christer Sundstrom[2], Eva Baeckstrom[1] and Ann Knight[1], [1]Department of Medical Sciences, Section of Rheumatology, Uppsala University, Uppsala, Sweden, [2]Department of Genetics and Pathology, Uppsala University, Uppsala, Sweden
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Background/Purpose:

The risk of malignancy in patients with Granulomatosis with Polyangiitis (GPA) is increased, as shown in several previous studies. The risk of lymphoma has been described as high as 4-5-fold increased. In addition, lymphoma in the sinonasal region, especially NK/T-cell lymphoma, has been reported to mimic GPA localized to the ear-throat-nose (ENT) region. Several previous publications report cases where a sinonasal lymphoma initially was misdiagnosed as GPA. We therefore had a particular interest in investigating the presence of lymphoma localized in the

ENT-region. Our aim in this study was to assess the clinical characteristics and treatment of patients with GPA complicated by lymphoma and to describe the lymphoma types, sites and prognosis in a population-based setting.

Methods:

From the Swedish population based patient register all individuals with a diagnosis of GPA between 1964 and 2012 were identified (n=3,224). Through linkage with the Swedish cancer register all lymphoproliferative malignancies (ICD7:200-202) registered after the first discharge listing GPA were identified. The medical records of all patients with GPA and lymphoma were collected and the GPA diagnosis was evaluated using the EMEA Consensus Algorithm for Classification of Vasculitis (1). To confirm the lymphoma diagnosis all lymphoma tissues were retrieved and classified according to the latest WHO classification. Clinical data of both GPA and lymphoma were collected from the medical files.

Results:

In all, 24 GPA-patients with malignant lymphoma were identified. 20 of these were B-cell lymphomas, and only two T-cell lymphomas (Table). Only one of the lymphomas was localized to the ENT-area, a diffuse large B-cell lymphoma in the hard palate. The majority of the patients had generalized GPA disease, most (75%) had been treated with cyclophosphamide for their GPA, many for long periods and with high doses; the median cumulative dose was 40g. The mean time from GPA to lymphoma diagnosis was 10 years (0-22). The majority of the lymphomas were aggressive and the median survival after lymphoma diagnosis was only 4 months.

Conclusion:

The findings in this population-based setting indicate that the lymphomas developing in patients with GPA are aggressive with a poor prognosis. T-cell lymphoma or lymphoma localized to the ENT-area are not a prominent finding. The study emphasizes the need for awareness of lymphoma and long-term follow-up of patients with GPA.

1. Watts, R et al. Ann Rheum Dis, 2007

Type of lymphoma	Total (n=24)	Median survival time from lymphoma diagnosis (months)
B-cell lymphoma	20	4
Diffuse large B-cell lymphoma	6	4
Chronic lymphocytic leukemia	3	2
Mantle cell lymphoma	4	1.5
High grade B-cell lymphoma	4	26.5
Low grade B-cell lymphoma	1	0
Undifferentiated B-cell lymphoma	2	6.5
NK/T-cell lymphoma	2	3
High grade T-cell lymphoma	1	2
Peripheral T-cell lymphoma	1	4
Other	2	1.5
Undifferentiated High grade lymphoma	2	2
Undifferentiated Non-Hodgkins lymphoma	2	1

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Abstract Number: 870

Development of an Anti-Neutrophil Cytoplasmic Antibody-Associated Vasculitis Patient-Reported Outcome Measure: Identification of Salient Themes and Candidate Questionnaire Item Development

Joanna Robson[1], Susan Ashdown[2], Jill Dawson[3], Ebony Easley[4], Don Gebhart[5], Katherine Kellom[6], Georgia Lanier[7], Carol McAlear[8], Nataliya Milman[9], Jacqueline Peck[10], Judy A. Shea[11], Gunnar Tomasson[12], Raashid Luqmani[13], Peter F. Cronholm[4] and Peter A. Merkel[8], [1]Nuffield Department of Orthopaedics Rheumatology and Musculoskeletal Sciences, University of Oxford, University of Oxford, Oxford, United Kingdom, [2]NONE, Banbury, United Kingdom, [3]Nuffield Department of Population Health HSRU, University of Oxford, Oxford, United Kingdom, [4]Department of Family Medicine and Community Health, The University of Pennsylvania, Philadelphia, PA, [5]NONE, Columbus, OH, [6]PolicyLab, Children's Hospital of Philadelphia, Philadelphia, PA, United Kingdom, [7]NONE, Framingham, MA, [8]Penn Vasculitis Center, Division of Rheumatology, University of Pennsylvania, Philadelphia, PA, [9]Division of Rheumatology, University of Ottawa, Ottawa, ON, Canada, [10]NONE, Oxford, United Kingdom, [11]Division of General Internal Medicine, University of Pennsylvania, Philadelphia, PA, United Kingdom,

[12]Rheumatology Section, Boston University, Boston, MA, [13]Nuffield Department of Orthopaedics Rheumatology and Musculoskeletal Sciences, University of Oxford, Oxford, United Kingdom
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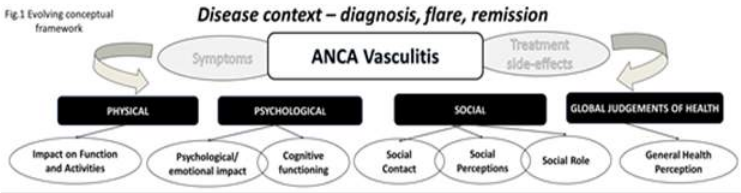
Background/Purpose: Patients with anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitides (AAVs), including granulomatosis with polyangiitis (Wegener's, (GPA), eosinophilic granulomatosis with polyangiitis (Churg-Strauss, EGPA), and microscopic polyangiitis (MPA), can face persistent disease activity, disease-associated damage, or adverse treatment effects, all of which may impact on health related quality of life. There is currently no disease-specific patient-reported outcome (PRO) for AAV. The development of a PRO should be in compliance with FDA recommendations and involves: (i) Questionnaire item development; (ii) Item reduction and scale generation; and (iii) Testing scale properties - reliability, validity and responsiveness. Following these principles, a multi-national collaboration of researchers and patient-partners from the UK, USA and Canada has been conducting the first stage of questionnaire item development with the aim of creating a tool with content validity (and cultural/linguistic equivalence) appropriate for use in all three countries.

Methods: Exploratory semi-structured patient interviews were performed in the UK, USA, and Canada. The aim was to identify salient dimensions of quality of life and perceived problems of health status related to having AAV. The overall sample size was determined by the point at which no new themes emerged from interviews (saturation), and was also guided by a purposive sampling framework to ensure a range of participants were included (for example differing disease presentations, age and genders). Researchers (within and across research groups) independently scrutinised interview transcripts for relevant themes. Themes identified from transcripts were then re-cast as candidate questionnaire items. Regular teleconferences maintained equivalence of methods and exchange of relevant themes.

Results: Forty-nine semi-structured interviews of patients with AAV were conducted. After transcription and scrutiny, 60 distinct themes related to having AAV were identified, these included symptoms (related to condition or treatment) and the ways in which these symptoms influenced patients' ability to work, activities of daily living, engagement in social activities, and state of mind. The interaction between these factors is demonstrated in the evolving conceptual framework for the PRO, shown in Figure 1.

Conclusion: A list of themes and candidate items, drawn directly from patient experience, has been used to inform the development of a PRO for AAV. A parallel survey of~500 patients in the UK and US is currently underway and will produce an instrument with appropriate scale structure, measurement properties, and scoring algorithms. This will be followed by a multi-centred prospective validation study.



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Abstract Number: 871

Clinicians' Perspective on Aspects of ANCA-Associated Vasculitis That Influence Patients' Function and General Health: A Delphi Exercise Based on the International Classification of Function, Disability and Health

Nataliya Milman[1], Peter Tugwell[2], Annelies Boonen[3] and Peter A. Merkel[4], [1]Division of Rheumatology, University of Ottawa, Ottawa, ON, Canada, [2]Center For Global Health, Institute of Population Hlth, Ottawa, ON, Canada, [3]Maastricht University Medical Center, Maastricht, Netherlands, [4]Penn Vasculitis Center, Division of Rheumatology, University of Pennsylvania, Philadelphia, PA
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SESSION INFORMATION

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Background/Purpose:

ANCA-associated vasculitis (AAV) is a multisystem condition that results in significant level of morbidity and functional limitations for many patients. Previous studies showed that patients and clinicians prioritize aspects of AAV differently. This study was conducted to determine which aspects of AAV are considered by clinicians most relevant to determining patients' function and general health.

Methods:

International vasculitis experts were identified by consulting with 3 major vasculitis societies and invited to participate in an email-based three-round Delphi exercise. The International Classification of Function, Disability and Health (ICF) was used to describe the studied aspects of AAV. The ICF is a general health status framework that describes health in terms of hierarchically organized categories from 4 interacting "components": body functions (BF), body structures (BS), activities and participation (AP), and contextual factors (personal (PF) and environmental (EF)).

In the first open-ended round of the exercise participants were asked to list up to 30 items they considered most relevant to determining patients' overall health for each of the ICF's 4 components of health. The participants of the second and third rounds selected those aspects of AAV they consider most important, given the results of the previous rounds. Categories identified by at least 80% of participants of either of the 3 rounds were selected as representative of the clinicians' perspective.

Results:

82 clinicians were invited to participate in this study and 44 responded; 27 clinicians participated in the first Delphi round, 30 in the second, and 36 in the third. Participants came from 17 countries and several relevant medical specialties (rheumatology, nephrology, pulmonology, otorhinolaryngology, internal medicine, immunology, and allied health professions).

After the third round 20 ICF categories were identified as important by > 80% of participants: 6 BF (energy level, seeing, hearing, pain, respiratory functions and renal function), 7 BS (eyes, ears (especially middle ear), nose (especially saddle nose and nasal crusting specifically), sinuses, lungs (also subglottic stenosis), kidneys, and peripheral nerves, 2 AP (carrying out daily routine and remunerative employment), and 3 EF (side effects of medications, support and relationships, and health services, systems and policies).

Conclusion:

This study identified aspects of AAV considered by clinicians as most relevant for determining the overall health of affected patients. The use of the standardised ICF classification allows comparison of these results across different perspectives. Among the categories identified in this study, "side effects of medications" is the only aspect of AAV that is not sampled by currently accepted core set of outcome measures for AAV which was recently subjected to an ICF-based analysis. An ongoing ICF-based study of the patient perspective on the most important aspects of AAV will allow for direct comparison of perspectives of patients and clinicians and help revise and enhance disease assessment in AAV for use in clinical research and routine care.

Disclosure: N. Milman, None; **P. Tugwell**, None; **A. Boonen**, None; **P. A. Merkel**, None.

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Abstract Number: 872

Work Limitations and Disability in Patients with Systemic Vasculitis

Emma Ali Bateman[1], Sherry Rohekar[2], Christian Pagnoux[3] and **Lillian Barra**[1], [1]Medicine, Division of Rheumatology, Western University, London, ON, Canada, [2]Western University, London, ON, Canada, [3]Mount Sinai Hospital, Toronto, ON, Canada
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Background/Purpose:

Despite recent advances in the treatment of systemic vasculitis (SV), direct consequences of the disease leading to impairments in physical and mental function can cause disability, which is an understudied aspect of SV. The objective of this research was to assess work limitations and disability in patients with SV.

Methods:

Patients aged >18 years old with SV (anti-neutrophilic cytoplasmic antibody-associated vasculitis (AAV), polyarteritis nodosa, large vessel vasculitis, IgA vasculitis, Behcet's syndrome or cryoglobulinemic vasculitis) were recruited from a tertiary care Rheumatology clinic (London, Canada). Work disabled (WD) was defined as not working, early retirement, or reduced hours at work due to SV. Participants who were working at the time of enrolment completed the Work Limitations Questionnaire (WLQ). Other work-related measures were self-reported by questionnaire. At the time of enrolment, the Vasculitis Damage Index (VDI) was also obtained.

Results: 103 participants completed the study (mean age 58±17, 60% females, 48% with AAV, 26% LVV and 26% other). 52 (51%) subjects were WD or retired for reasons other than SV and were excluded from further analyses; 22 (21%) were WD secondary to SV and 29 (28%) did not report any disability. SV-related WD subjects were more likely to have a diagnosis of AAV and a lower level of education ($p<0.01$) than non-WD subjects. Mean VDI scores were higher in SV-related WD vs. non-WD subjects (1.9±2.7 vs. 2.9±1.4; $p=0.015$). Involvement of musculoskeletal, peripheral vascular, ocular and neuropsychiatric systems was more common in WD. 38 subjects were working and completed the WLQ; their productivity loss was 8.9±7.2%, higher than control patients from the same center with Rheumatoid Arthritis and Ankylosing Spondylitis (4.5% and 5.8%, respectively).

Conclusion: SV-related work disability occurred in 21% of patients and was associated with a diagnosis of AAV, lower levels of education, higher disease activity and damage scores.

Disclosure: E. A. Bateman, None; **S. Rohekar**, None; **C. Pagnoux**, None; **L. Barra**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/work-limitations-and-disability-in-patients-with-systemic-vasculitis

Abstract Number: 873

The ANCA-Vasculitis Index of Damage (AVID): Performance of a New Damage Instrument

Eli Miloslavsky[1,2], Na Lu[3], Sebastian Unizony[3], Hyon K. Choi[3], Peter A. Merkel[4], Philip Seo[5], Robert F. Spiera[6], Carol A. Langford[7], Gary S. Hoffman[7], Cees Kallenberg[8], E. William St.Clair[9], Nadia Tchao[10], Fernando Fervenza[11], Paul A. Monach[12], Ulrich Specks[13] and John H. Stone[14], [1]Division of Rheumatology, Massachusetts General Hopsital, Boston, MA, [2]Division of Rheumatology, Allergy and Immunology, Massachusetts General Hospital, Boston, MA, [3]Rheumatology, Allergy and Immunology, Massachusetts General Hospital, Harvard Medical School, Boston, MA, [4]Penn Vasculitis Center, Division of Rheumatology, University of Pennsylvania, Philadelphia, PA, [5]Division of Rheumatology, Johns Hopkins, Baltimore, MD, [6]Rheumatology, Hospital for Special Surgery, New York, NY, [7]Rheumatology, Cleveland Clinic, Cleveland, OH, [8]Rheumatology/Clin Immunol AA21, Univer Med Center Groningen, Groningen, Netherlands, [9]Rheumatology and Immunology, Duke University, Durham, NC, [10]ITN, San Francisco, CA, [11]Mayo Clinic, Rochester, MN, [12]Rheumatology, Boston University School of Medicine, Boston, MA, [13]Division of Pulmonary and Critical Care Medicine, Mayo Clinic College of Medicine, Rochester, MN, [14]Massachusetts General Hospital Rheumatology Unit, Harvard Medical School, Boston, MA

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Background/Purpose:

Damage related to active disease or its treatment is an important outcome measure in ANCA-associated vasculitis (AAV). The Vasculitis Damage Index (VDI), the principal damage measure in AAV, was not designed specifically for AAV. The VDI may also underestimate toxicity from therapies for vasculitis, particularly glucocorticoids (GC). The AAV Index of Damage (AVID) was designed to be a more comprehensive tool for the assessment of damage in AAV, both due to disease and its treatment. We compared the performance of AVID to that of the VDI in the context of a large randomized, double-blind, placebo-controlled trial.

Methods:

We analyzed the VDI and AVID in 197 patients enrolled in the Rituximab in AAV (RAVE) trial. Disease damage was measured prospectively at baseline, 6, 12, 18 months, and end of follow-up by both the VDI and AVID.

The VDI is composed of 11 categories (e.g., musculoskeletal, pulmonary) and 64 individual damage items. The AVID has 12 categories and 112 items (Table 1). Twenty-five of the AVID items pertain to treatment-related damage (20 related to GC toxicity), compared to only 13 in the VDI (9 related to GC toxicity). Each item was counted as one point in the total score.

Results:

AVID captured 184 more damage-related items at baseline compared with the VDI. During the course of the trial, AVID identified 358 new items compared with only 201 identified by the VDI (Table 1). Renal and ear/nose/throat categories accounted for the most damage in both instruments. 188 (27%) of the new AVID items pertained to GC-associated damage as compared to 81 (18%) of the VDI items (Table 2).

The sum of GC-related AVID items was greater among the patients in the highest quartile of cumulative GC use (mean dose 9.2g) compared to the lowest quartile (mean dose 3.7g) (51 versus 22, $p<0.01$). In contrast, there was no significant difference in VDI scores between these two groups (24 versus 14, $p=0.08$). Changes in neither the AVID, nor the VDI scores correlated with baseline disease severity, the number of relapses during follow-up, or changes in quality-of-life as measured by the Short Form 36 Health Survey.

Conclusion:

In this prospective, head-to-head comparison of the AVID and VDI, AVID captured substantially more items of damage caused by either active AAV or its treatment. GC-related damage was captured more comprehensively by AVID, which was able to differentiate between high and low GC users. The inclusion of item weighting may improve the correlation of disease damage scores with baseline disease severity and patient quality-of-life scores.

Table 1 – VDI and AVID scores by category

	VDI		AVID	
Category	Baseline	End of follow-up	Baseline	End of follow-up
Musculoskeletal	11	20	16	27
Skin	3	5	16	33
Ocular	17	29	28	57
Ear/Nose/Throat	84	124	150	232
Pulmonary	20	44	9	27
Cardiovascular	21	45	39	80
Peripheral vascular disease	3	8	-	-
Gastrointestinal	1	1	1	1
Renal	30	84	42	108
Neuropsychiatric	16	37	-	-
Neurological	-	-	41	67
Psychiatric	-	-	6	9
Endocrine	-	-	23	32
Hematology/Oncology	-	-	1	3
Other	24	34	42	96
Total	230	431	414	772

Table 2 – Glucocorticoid-related VDI and AVID items

	VDI		AVID	
Item	Baseline	End of follow-up	Baseline	End of follow-up
Osteoporosis/vertebral collapse	9	12	-	-
Osteoporosis	-	-	9	13
Bone fracture	-	-	3	5
Muscle atrophy	-	-	4	8
Avascular necrosis	0	1	0	1
Striae	-	-	3	9
Easy bruising	-	-	6	11
Cataract	5	11	5	9
Glaucoma	-	-	1	5
Angina	1	2	1	2
Myocardial infarction	1	1	1	1
Percutaneous coronary intervention	-	-	1	1
Coronary artery bypass grafting	-	-	1	1
Subsequent myocardial infarction	0	0	-	-
Carotid artery disease	-	-	1	2
Hypertension	18	40	25	55
Diabetes	10	14	9	14
Impaired fasting glucose	-	-	3	6
Psychosis	0	0	-	-
Anxiety	-	-	3	7
Mood disorder	-	-	3	3
Weight gain	-	-	12	35
Total	44	81	91	188

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Abstract Number: 874

The Short Term Damage Burden in Vasculitis and Vasculitis Mimics As Measured By the

Vasculitis Damage Index

Alberto Floris[1,2], Jan Sznajd[3,4], Katarzyna Wawrzycka-Adamczyk[1,5], Joanna Robson[6], Anthea Craven[7], Peter A. Merkel[8], Richard A. Watts[9], **Raashid Luqmani**[3] and DCVAS investigators, [1]Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences, University of Oxford, Oxford, United Kingdom, [2]Rheumatology Unit, University Clinic, Cagliari, Italy, Monserrato, Italy, [3]Nuffield Department of Orthopaedics Rheumatology and Musculoskeletal Sciences, University of Oxford, Oxford, United Kingdom, [4]Jagiellonian University Medical College, Kraków, Poland, [5]Jagiellonian University Medical College, Cracow, Poland, [6]Rheumatology, University of Oxford, Oxford, United Kingdom, [7]Nuffield Department of Orthopaedics Rheumatology and Musculoskeletal Sciences, Botnar Research Centre, University of Oxford, Oxford, United Kingdom, [8]Division of Rheumatology, University of Pennsylvania, Philadelphia, PA, [9]Rheumatology Department Ipswich Hospital, University of East Anglia, Ipswich, United Kingdom

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Background/Purpose: Damage in vasculitis, which is due to both the vasculitic process itself and the complications of treatment, accumulates over time and accounts for significant morbidity across a variety of organs and body systems. It is not known whether comparator conditions mimicking vasculitis are associated with a similar spectrum and extent of damage. The aim of this study was to compare short term damage accrual in vasculitis and vasculitis mimics using the Vasculitis Damage Index (VDI).

Methods: We used data available from patients recruited into the ACR/EULAR Diagnostic and Classification Criteria in Vasculitis Study (DCVAS). VDI is recorded at 6 months from diagnosis in patients with vasculitis and also in patients with comparator conditions. We analysed total VDI score, system scores, and individual damage items in granulomatosis with polyangiitis (GPA), eosinophilic granulomatosis with polyangiitis (EGPA), microscopic polyangiitis (MPA), polyarteritis nodosa (PAN), giant cell arteritis (GCA), Takayasu's arteritis (TAK), and their clinical context-specific comparator conditions. The diagnosis supplied by the recruiting physician (with recorded confidence > 75%) was used as the gold standard. We used predetermined criteria to identify comparator conditions for each of the vasculitides; some of the comparators were used for analyses with more than one type of vasculitis. Comparator conditions for each vasculitis are shown in table 1.

Results: We analysed data from 1254 patients with vasculitis and 507 comparators. The vasculitis group was older (median age 64.1 (50.8-74.0) vs 58.1 (45.7-68.8) years; $p<0.0001$) and had shorter duration of symptoms (median 10.6 (7.9-16.4) vs 11.6 (7.8-21.7) months; $p=0.0379$). The median (IQR) number of VDI items was higher in all types of vasculitis vs comparators 1 (0-2) vs 0 (0-1), as well as for each form of vasculitis separately: GPA 1 (0-3) vs 0 (0-2); EGPA 2 (1-4) vs 0 (0-2); MPA 2 (0-3) vs 1 (0-2); PAN 1 (0-2) vs 0 (0-1) with $p< 0.0001$ for all; for TAK 2 (0-2) vs 0 (0-1) ($p<0.0004$); for GCA 0 (0-1) vs 0 (0-1) ($p=0.0054$). On multivariate analysis, average VDI scores were significantly higher in the vasculitides than comparators, except for GCA. Data on the individual damage items which were seen more frequently in each type of vasculitis, in comparison with the corresponding comparators, are presented in Table 2.

Conclusion: Patients with vasculitis accrue more damage in the first 6 months than disease comparators. A focus on reducing this early damage should be a key target of management in these patients.

Table 1. Comparator conditions for each form of vasculitis

	GPA	EGPA	MPA	PAN	GCA	TAK

	controls	controls	controls	controls	controls	controls
Dermatologic	4%	7%	4%	9%	2%	0%
Endocrine/Metabolic	1%	1%	1%	0%	1%	0%
Gastrointestinal	4%	4%	5%	2%	0%	0%
Genitourinary	2%	1%	4%	2%	0%	0%
Haematology	3%	5%	3%	4%	2%	6%
Infectious disease	9%	7%	8%	6%	5%	6%
Malignancy	4%	6%	3%	0%	4%	0%
Neurologic	8%	3%	8%	6%	35%	21%
Ophthalmologic	4%	1%	2%	0%	15%	0%
Respiratory	10%	14%	9%	2%	2%	0%
Rheumatologic*	46%	40%	50%	67%	24%	41%
Vascular	2%	1%	4%	6%	5%	26%
Toxic	0%	0%	0%	0%	0%	0%
Other	11%	14%	11%	7%	9%	0%

*Most frequent rheumatologic diseases included systemic lupus erythematosus, myositis, sarcoidosis, antiphospholipid syndrome.

Table 2. VDI items significantly more frequent in vasculitides than comparators

	GPA (n=397)		Controls (n=364)		p value
Nasal blockage/chronic discharge/crusting	111	28%	9	2%	<0.0001
Hearing loss	88	22%	6	2%	<0.0001
Estimated/measured GFR < 50%	63	16%	13	4%	<0.0001
Proteinuria > 0.5g/24h	43	11%	8	2%	<0.0001
Chronic sinusitis/radiological damage	40	10%	6	2%	<0.0001
Peripheral neuropathy	38	10%	14	4%	0.0022
Nasal bridge collapse/septal perforation	30	8%	3	1%	<0.0001
Osteoporosis/vertebral collapse	16	4%	5	1%	0.0274
	EGPA (n=106)		**Controls (n=134)**		**p value**
Peripheral neuropathy	59	56%	5	4%	<0.0001
Chronic asthma	47	44%	4	3%	<0.0001
Nasal blockage/chronic discharge/crusting	17	16%	8	6%	0.0202*
Chronic sinusitis/radiological damage	15	14%	5	4%	0.0045
Cardiomyopathy	8	8%	2	1%	0.0243*
Myocardial infarction	5	5%	0	0%	0.0159*
Proteinuria > 0.5g/24h	4	4%	0	0%	0.0368*
	MPA (n=161)		**Controls (n=185)**		**p value**
Estimated/measured GFR < 50%	62	39%	8	4%	<0.0001
Proteinuria > 0.5g/24h	47	29%	8	4%	<0.0001
Peripheral neuropathy	27	17%	11	6%	0.0024
Diastolic BP > 95 or requiring antihypertensive	22	14%	6	3%	0.0008
Osteoporosis/vertebral collapse	17	11%	2	1%	<0.0001
Diabetes	12	7%	5	3%	0.0480*
End stage renal disease	10	6%	2	1%	0.0150
Nasal bridge collapse/septal perforation	8	5%	1	1%	0.0140
Cataract	6	4%	0	0%	0.0010
	PAN (n=39)		**Controls (n=54)**		**p value**
Peripheral neuropathy	13	33%	4	7%	0.0022
Gut infarction/resection	6	15%	0	0%	0.0043
	GCA (n=458)		**Controls (n=127)**		**p value**
Diabetes	31	7%	1	1%	0.0006
Osteoporosis/vertebral collapse	26	6%	0	0%	0.0025
	TAK (n=93)		**Controls (n=34)**		**p value**
Claudication > 3 months	44	47%	4	12%	0.0002
Major vessel stenosis	42	45%	4	12%	0.0004
Absent pulses in one limb	41	44%	4	12%	0.0007

p values were calculated using Chi-squared or Fisher's exact test.

*non-significant after Benjamini-Hochberg correction for multiple comparisons with false discovery rate of 0.25 and total number of variables 64. Correction was performed for each subgroup analysis.

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Abstract Number: 875

Differences in Early Damage Patterns in Various Forms of Primary Systemic Vasculitis

Katarzyna Wawrzycka-Adamczyk[1,2], Joanna Robson[3], Alberto Floris[1,4], Jan Sznajd[2,5], Anthea Craven[6], Richard A. Watts[7], Peter A. Merkel[8], **Raashid Luqmani**[5] and DCVAS investigators, [1]Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences, University of Oxford, Oxford, United Kingdom, [2]Jagiellonian University Medical College, Kraków, Poland, [3]Rheumatology, University of Oxford, Oxford, United Kingdom, [4]Rheumatology Unit, University Clinic, Cagliari, Italy, Monserrato, Italy, [5]Nuffield Department of Orthopaedics Rheumatology and Musculoskeletal Sciences, University of Oxford, Oxford, United Kingdom, [6]Nuffield Department of Orthopaedics Rheumatology and Musculoskeletal Sciences, Botnar Research Centre, University of Oxford, Oxford, United Kingdom, [7]Rheumatology Department Ipswich Hospital and University of East Anglia, Ipswich, United Kingdom, [8]Division of Rheumatology, University of Pennsylvania, Philadelphia, PA
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Background/Purpose: Immunosuppressive agents have changed the outcome of the systemic vasculitides from invariably fatal to chronic conditions associated with damage as a result of disease, its treatment or comorbidity. The Vasculitis Damage Index (VDI) is a validated and standardized tool to measure damage occurring since the onset of disease.

Methods: We compared patterns of damage amongst patients with 8 forms of primary vasculitis, using data obtained from the ACR/EULAR Diagnosis and Classification Criteria of Vasculitis study (DCVAS). VDI was evaluated at the follow up visit, at least 6 months from diagnosis. Total VDI scores, systems involvement and individual damage items were compared across different types of vasculitis.

Results: The distribution of damage items was measured in 1371 adult patients with giant cell arteritis (GCA, n=453; median age 74 years [Inter Quartile Range 66-79]; Male:Female ratio 153:150), granulomatosis with polyangiitis (GPA; n=395; age 56 [43-65]; M:F 199:196), microscopic polyangiitis (MPA; n=158; age 65 [57-74]; M:F 70:88), eosinophilic granulomatosis with polyangiitis (EGPA; n=106; age 58 [44-65]; M:F 58:48), Takayasu's arteritis (TAK; n=93; age 33 [27-44]; M:F 21:72), IgA vasculitis (IgAV; n=86; age 46 [29-69]; M:F 49:37), Behçet's disease (BD; n=42; age 33 [28-39]; M:F 22:20), and polyarteritis nodosa (PAN; n=39; age 52 [34-61]; M:F 22:17). The median VDI score for all patients was 1.5 [0-11], measured at a mean of. 241±143 days after diagnosis. Levels of damage in different forms of vasculitis were defined as: low (IgAV and GCA, median VDI of 0; range 0-7), intermediate (PAN, GPA and BD, median VDI of 1; range 0-8) or high (TAK and EGPA, median VDI of 2; range 0-11). The most frequent VDI systems involved differed for each of the vasculitides included as follows: GCA: eyes (23%, $p<0.001$) and musculoskeletal (10%, $p=0.82$); GPA: ear, nose and throat (46%, $p<0.001$) and kidneys (22%, $p<0.001$); MPA: kidneys (53%, $p<0.001$) and lungs (25%, $p<0.001$); EGPA: lungs (58%, $P<0.001$) and neurological (57%, $P<0.001$); TAK: peripheral vessels (73%, $p<0.001$) and cardiovascular (27%, $p<0.001$); IgAV: kidneys (17%, $p=0.46$) and cardiovascular (6%, $p=0.21$); BD: skin/mucosa (56%, $p<0.001$) and eyes (21%, $p=0.06$); PAN: neurological (36%, $p<0.001$) and gut (20%, $p<0.001$). The most frequent individual items recorded in VDI per diagnosis are shown in Table 1.

Conclusion: Damage is detected early across the spectrum of systemic vascultides evaluated in this study, suggesting that patients suffer long term consequences of having a diagnosis of vasculitis. The amount and pattern of damage differs between individual diseases. EGPA and TAK are associated with the highest levels of damage; IgAV and GCA have the lowest levels. These patterns could serve as a basis for evaluating the impact of new or existing therapies on outcomes in vasculitis.

Table 1 Most frequent items of damage recorded, six months after diagnosis of vasculitis

The top 3 most frequent VDI items recorded for each disease

	Item	Frequency	P-value compared to all other forms of vasculitis
Giant cell arteritis n=453	1. Visual impairment/diplopia	11%	p<0.001
	2. Blindness in one eye	8%	p<0.001
	3. Diabetes	7%	p=0.028
Granulomatosis with polyangiitis n=395	1. Nasal blockage/discharge/crusting	29%	p<0.001
	2. Hearing loss	22%	p<0.001
	3. eGFR<50%	15%	p<0.001
Microscopic polyangiitis n=158	1. eGFR<50%	38%	p<0.001
	2. Proteinuria>0.5grams/24 hours	28%	p<0.001
	3. Peripheral neuropathy	16%	p=0.007
Eosinophilic granulomatosis with polyangiitis n=106	1. Peripheral neuropathy	56%	p<0.001
	2. Chronic asthma	44%	p<0.001
	3. Chronic breathlessness	20%	p<0.001
Takayasu's arteritis n=93	1. Claudication>3months	47%	p<0.001
	2. Major vessel stenosis	45%	p<0.001
	3. Absent pulses in one limb	44%	p<0.001
IgA vasculitis n=86	1. Proteinuria>0.5grams/24 hours	16%	p=0.004
	2. Cutaneus ulcers	5%	p<0.001
	3. Osteoporosis	3%	p=0.46
Behçet's disease n=42	1. Mouth ulcers	52%	p<0.001
	2. Visual impairment/diplopia	17%	p=0.002
	3. Cataract	9%	p=0.048
Polyarteritis nodosa n=39	1. Peripheral neuropathy	33%	p<0.001
	2. Gut infarction	15%	p<0.001
	3. Cutaneus ulcers	8%	p<0.001

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View Abstract and Citation Information Online - http://acrabstracts.org/abstract/differences-in-early-damage-patterns-in-various-forms-of-primary-systemic-vasculitis

Abstract Number: 876

Damage Develops Early and Is Common in Children with Chronic Systemic Vasculitis

Lorraine O'Neill[1], Marinka Twilt[2], Susanne Benseler[3], Dirk Föll[4], David A. Cabral[5] and Raashid Luqmani[6], [1]University of Oxford, Oxford, United Kingdom, [2]Division of Rheumatology, The Hospital for Sick Children, Toronto, ON, Canada, [3]Pediatrics, University of Calgary, Toronto, ON, Canada, [4]University of Muenster, Muenster, Germany, [5]Pediatrics/Rm K4-121, BC Children's Hospital, Vancouver, BC, Canada, [6]Nuffield Department of Orthopaedics Rheumatology and Musculoskeletal Sciences, University of Oxford, Oxford, United Kingdom

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Session Time: 9:00AM-11:00AM

Background/Purpose:

The chronic primary systemic vasculitides are a group of rare conditions with affected patients subject to a significant burden of morbidity from both the disease itself and its treatment. In adult vasculitides, the Vasculitis Damage Index (VDI) is a validated damage assessment tool and an integral outcome measure. The lack of such a validated index in childhood vasculitis has contributed to the paucity of outcome data in children with vasculitis. The aim of this study was to use a modification of the adult VDI to assess damage accrual in a cohort of children with primary systemic vasculitis recruited to A Registry of Childhood Vasculitis (ARCHiVe), a web-based registry founded in 2007 by the Canadian/US based Childhood Arthritis and Rheumatology Research Alliance (CARRA).

Methods:

A multi-centre cohort study of children enrolled into ARCHiVe was conducted. Children were included if they were followed for at least 12 months and had a PVDI completed.

Results:

A total of 74 children were included in the study. 65% were female. The mean age was 11.8 years (range 2-18). Granulomatosis with polyangiitis (GPA) was the most frequently encountered diagnosis (Table 1). At baseline, the median Paediatric Vasculitis Activity Score (PVAS) was 12 (range 2-31). At 12 months, 39/74 children (52.7%) had accumulated at least one item of damage (PVDI=1 in 18 patients, PVDI=2 in 14, PVDI=3 in 4, PVDI=4 in 1 and PVDI=5 in 2). The most commonly recorded damage items were in the "Other" section (consisting of significant striae [16.2%], chronic cough [5.4%] and vocal cord paralysis [5.4%]), followed by "Renal" due to end stage renal failure (9.5%) and proteinuria (9.5%) and "Pulmonary" due to impaired lung function (9.5%) as shown in Figure 1.

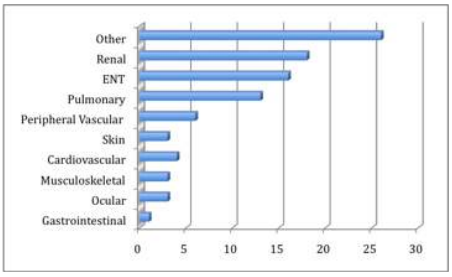
Conclusion:

Within the first year of disease more than 50% of children with systemic vasculitis have accumulated damage. The information gained from this study provides a useful data driven basis for future development and validation of a damage assessment tool in paediatric vasculitis.

Table 1

Diagnosis	No of Patients	Percentage %
Granulomatosis with Polyangiitis (GPA)	43	58.1
Limited Granulomatosis with Polyangiitis	8	10.8
Takayasu Arteritis	7	9.5
Eosinophilic Granulomatosis with Polyangiitis (EGPA)	5	6.8
Microscopic Polyangiitis (MPA)	3	4
Isolated Renal Microscopic Polyangiitis	3	4
Polyarteritis Nodosa	3	4
Unclassified Primary Vasculitis	1	1.4
ANCA positive pauci-immune glomerulonephritis	1	1.4

Figure 1



Number of patients with systemic vasculitis showing items of damage using the provisional pediatric modification of the VDI

Disclosure: L. O'Neill, None; **M. Twilt**, None; **S. Benseler**, None; **D. Föll**, None; **D. A. Cabral**, None; **R. Luqmani**, GSK, 5,Chemocentryx, 5,Roche Pharmaceuticals, 5.

Abstract Number: 877

Improved Survival in Granulomatosis with Polyangiitis: A Population-Based Study

Ju Ann[1], Hyon K. Choi[2], Sharan K. Rai[3], Eric C. Sayre[4] and **J Antonio Avina-Zubieta**[5,6], [1]Experimental Mediine, University of British Columbia, Richmond, BC, Canada, [2]Rheumatology, Allergy and Immunology, Massachusetts General Hospital, Harvard Medical School, Boston, MA, [3]Experimental Medicine, University of British Columbia, Vancouver, BC, Canada, [4]Arthritis Research Canada, Richmond, BC, Canada, [5]Arthritis Research Canada / University of British Columbia, Vancouver, BC, Canada, [6]Medicine, University of British Columbia, Department of Medicine, Division of Rheumatology, Vancouver, BC, Canada

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Background/Purpose: Granulomatosis with Polyangiitis (GPA) is associated with an increased risk of mortality. However, recent mortality trends in GPA are largely unknown, particularly in the general population. Our objectives were to assess mortality trends among GPA patients between January 1, 1997 and December 31, 2012 in a general population context.

Methods: Using an administrative health database from the province of British-Columbia, Canada (4.7 million), we identified all incident cases of GPA and up to 10 (6 were available) non-GPA controls matched on sex, age, and calendar year of study entry, between 1997 and 2012. All GPA cases required the use of glucocorticoids, immunosuppressives or methotrexate, during the period one-month before and six-months after the date of study entry as part of the case definition. The GPA cohort was then divided in two cohorts based on year of GPA diagnosis (i.e., 1997-2004 and 2005-2012) to evaluate changes in mortality. We calculated hazard ratios (HR) for death using a Cox proportional hazard and the rate differences using an additive hazard model, while additionally adjusting for potential confounders (e.g., Charlson Comorbidity Index, number of outpatient visits, hospitalization, cardiovascular drugs, glucocorticoids and NSAIDs).

Results: The early cohort (1997-2004) GPA patients had a considerable higher mortality rate than the late cohort (2005-2012) (i.e., 150.1 cases vs. 51.1 cases per 1000 person-years), as compared with only a moderate improvement in comparison cohorts between the two periods (24.0 to 15.9 per 1000 person-years). The corresponding absolute mortality rate differences were 88.2 (95% CI 55.1, 121.4) and 7.1 (95%CI -9.6, 23.8) cases per 1000 person years (p-value for interaction <0.001).

The corresponding adjusted HRs for mortality were 3.54 (95% CI, 2.42-5.18) and 1.72 (95% CI, 1.17-2.53), respectively (p for interaction = 0.003)

Conclusion: This population-based study shows that survival of GPA patients has improved over the past decade, suggesting the new treatments and improved management of the disease and its complications may be providing substantial benefits.

Table 1: Incidence Rates and Hazard Ratios (HR) for Associations between GPA and Death According to Cohort

	GPA Status	N	Deaths	Mean Follow-up (years)	Incidence Rate (cases per 1000 person-years)	Age, Sex and Entry-Time Matched IRR (95% CI)	Fully Adjusted HR (95% CI)
Total	Yes	586	175	4.04	73.93	3.52 (2.93-4.21)	2.60 (2.03, 3.33)
	No	3,516	412	5.57	21.02	1.00	1.00
Female	Yes	307	84	3.91	70.00	3.61 (2.76-4.68)	3.73 (2.60, 5.37)
	No	1842	193	5.40	19.41	1.00	1.00
Male	Yes	279	91	4.18	77.96	3.44 (2.66-4.41)	2.13 (1.50, 3.04)
	No	1674	219	5.77	22.68	1.00	1.00

Disclosure: J. Ann, None; **H. K. Choi**, None; **S. K. Rai**, None; **E. C. Sayre**, None; **J. A. Avina-Zubieta**, None.

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Abstract Number: 878

1997-2004	Yes	195	72	2.46	150.12	6.25 (4.55-8.55)	3.54 (2.42, 5.18)
	No	1176	100	3.54	24.01	1.00	1.00
2005-2012	Yes	390	60	3.01	51.14	3.21 (2.32-4.40)	1.72 (1.17, 2.53)
	No	2340	126	3.38	15.93	1.00	1.00

Significance of Interstitial Pneumonitis in Microscopic Polyangiitis

Kensuke Nakanishi and Mitsuyo Kinjo,
Rheumatology, Okinawa Chubu Hospital, Uruma, Japan

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Background/Purpose: Microscopic polyangiitis (MPA) is often associated with lung involvement, including alveolar hemorrhage and interstitial pneumonitis (IP). Clinical characteristics of IP in MPA have not been well described. The aim of this study was to determine the prevalence and clinical course of IP in MPA.

Methods: We retrospectively identified MPA patients at a tertiary medical center in Japan between 2002-2014. MPA patients with positive perinuclear anti-neutrophil cytoplasmic antibody (p-ANCA) who presented with renal involvement, including glomerulonephritis, acute and chronic renal failure, or lung disease such as alveolar hemorrhage or IP were selected. Data were collected on clinical features, medications, radiographic imaging (chest X-ray and computed tomography), and clinical outcome

Results: We identified 39 Japanese patients with MPA (Table). Median age was 69 (16-87); 51% were female; median observation period was 33 months (range 3-158). Among 27/39 (69%) who had IP, IP preceded diagnosis of MPA in 9 (33%), was seen upon diagnosis in 15 (56%), and occurred after diagnosis in 3 (11%). IP was not diagnosed in 33% of patients with MPA, over a median observation period of 74 months (range 45-138). Thirty-seven (95%) patients were treated with steroids or immunosuppressants. Acute exacerbation of IP was seen in 4 (15 %), and no radiographic change in 9 (33%) or minimal worsening of IP without clinical significance in14 (52%) on was found. All-cause mortality or death due to pulmonary complication in MPA did not differ between subjects with or without IP.

Conclusion: IP often precedes other manifestations of MPA. Clinical characteristics and outcomes are similar to those without IP.

Table. Clinical Characteristics of Microscopic Polyangiitis, by Interstitial Pneumonitis status.

Clinical characteristics	Interstitial pneumonitis present	Interstitial pneumonitis absent	P
n	27	12	
Age, years (range)	70 (56-87)	68 (15-86)	0.16
Female (n, %)	14 (52)	6 (50)	1
Observation period, months, median(range)	33 (3-159)	31 (18-77)	0.76
Tobacco (n, %)	15 (56)	8 (67)	0.73
Renal involvement (n, %)	23 (85)	12 (100)	0.29
Fever (n, %)	15 (56)	5 (42)	0.5
Skin involvement (n, %)	1 (4)	3 (25)	0.08
Peripheral neuropathy (n, %)	3 (11)	2 (17)	0.63
Alveolar hemorrhage (n, %)	5 (19)	4 (33)	0.42
Steroids (n, %)	25 (93)	12 (100)	1
Immunosuppressants* (n, %)	17 (63)	6 (50)	0.5
All-cause mortality (n, %)	12 (44)	3 (25)	0.31
Deaths due to pulmonary complication (n, %)	6 (22)	2 (17)	1

*Cyclophosphamide, azathioprine, cyclosporine, methotrexate and rituximab.

Disclosure: K. Nakanishi, None; **M. Kinjo**, None.

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Abstract Number: 879

Diffuse Alveolar Hemorrhage Secondary to ANCA-Associated Vasculitis: Predictors of Respiratory Failure and Clinical Outcomes

Rodrigo Cartin-Ceba[1], Fernando Fervenza[2], Steven R. Ytterberg[3] and Ulrich Specks[4], [1]Pulmonary and Critical Care Medicine, Mayo Clinic, Rochester, MN, [2]Mayo Clinic, Rochester, MN, [3]Rheumatology Division, Mayo Clinic, Rochester, MN, [4]Division of Pulmonary and Critical Care Medicine, Mayo Clinic College of Medicine, Rochester, MN

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Session Time: 9:00AM-11:00AM

Background/Purpose: The interpretation of the literature on diffuse alveolar hemorrhage (DAH) secondary to ANCA-associated vasculitis (AAV) has been complicated by the small size of reported cohorts, variable and unclear definitions of DAH used, and insufficient description of respiratory failure and its predictors. In addition, patients with severe DAH requiring mechanical ventilation were excluded from the only randomized controlled trial that comprised a sizable number of patients with DAH. In a well-defined cohort of patients with DAH secondary to AAV, we sought to identify predictors of respiratory failure and to describe the therapeutic efficacy of plasma exchange (PLEX) and rituximab versus cyclophosphamide in patients with or without respiratory failure.

Methods: Single center historical cohort study of all consecutive patients presenting with DAH secondary to AAV evaluated over a 15 year period. Respiratory failure was defined as the need for mechanical respiratory support. The main outcome was complete remission at 6 months (BVAS/WG=0 and off corticosteroids). Logistic regression models were developed to examine the predictive role of the baseline clinical characteristics for the development of respiratory failure, and also for the role of PLEX and induction of remission therapy on the main outcome. To account for potential unequal distribution of important covariates between groups resulting from the lack of random assignment in this observational study (sicker patients received PLEX), a propensity score analysis was performed to assess the probability of receiving PLEX.

Results: Seventy-three patients with DAH were identified of whom 34 patients developed respiratory failure. Degree of hypoxemia upon initial presentation, higher neutrophil percentage in the bronchoalveolar lavage fluid cell count, and higher C-reactive protein levels were independently associated with the development of respiratory failure. Complete remission at 6 months was achieved in 23 of 32 (72%) patients treated with PLEX versus 32 of 41 (78%) patients treated with no PLEX, p=0.54. After adjustment for important covariates, PLEX therapy was not found to be associated with achieving complete remission at 6 months (OR 0.49, 95% CI 0.12-1.95, p=0.32). Complete remission at 6 months was achieved in 33 of 37 (89%) patients treated with rituximab versus 21 of 31 (68%) patients treated with cyclophosphamide, p=0.02. After adjustment for important covariates, rituximab therapy was independently associated with increased odds of achieving complete remission at 6 months (OR 6.45, 95% CI 1.78-29, p=0.003). There was no difference in long-term survival between patients treated with rituximab compared to those treated with cyclophosphamide.

Conclusion: The most important predictor of respiratory failure in these patients seems to be the degree of hypoxemia upon presentation. A clear benefit of PLEX added to standard remission induction therapy could not be demonstrated. Patients with DAH secondary to AAV, including those requiring mechanical ventilation, achieved complete remission by 6 months at a higher rate with rituximab than with cyclophosphamide.

Disclosure: R. Cartin-Ceba, None; **F. Fervenza**, None; **S. R. Ytterberg**, None; **U. Specks**, Genentech and Serendex., 5.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/diffuse-alveolar-hemorrhage-secondary-to-anca-associated-vasculitis-predictors-of-respiratory-failure-and-clinical-outcomes

Abstract Number: 880

Extra-Corporeal Membrane Oxygenation and Diffuse Alveolar Haemorrhage: A Single Centre Case Series and Analysis of the ELSO Database

Chai Yiing Ling[1], Thomas Simpson[2], Guy Glover[2], Chris Meadows[3], Nicholas Ioannou[3], Boris Lams[3] and David P. D'Cruz[4], [1]Louise Coote Lupus Unit, Guy's & St Thomas' Hospital, London, United Kingdom, [2]Critical Care, Kings Health Partners, Guy's and St Thomas' NHS Foundation Trust, London, United Kingdom, [3]Kings Health Partners, Guy's and St Thomas' NHS Foundation Trust, London, United Kingdom, [4]Louise Coote Lupus Unit, Guy's and St Thomas' Hospital, London, United Kingdom

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Background/Purpose:

Diffuse alveolar haemorrhage (DAH) is a rare and potentially fatal complication of the systemic vasculitides and may present directly to the intensivist as a severe acute respiratory distress syndrome (ARDS) with reported mortality of 12- 60%. Whilst a severe respiratory failure (SRF) therapy strategy incorporating extracorporeal membrane oxygenation (ECMO) improves outcomes in ARDS, use of ECMO in DAH is often considered to be relatively contraindicated due to the requirement for systemic anticoagulation.

Methods:

We present a case series of 4 patients with DAH due to underlying ANCA-associated vasculitides diagnosed and / or managed by a standardised diagnostic pathway and ARDS treatment algorithm in a single, UK SRF centre, between 2012-13. We analysed the Extracorporeal Life Support Organisation (ELSO) database using ICD-9 codes 446.2, 446.21, 446.4, 446.6 and report on the current international experience of DAH and ECMO.

Results:

The case series is described in table 1. Median lung injury score (LIS) was 3.5. Three patients required ECMO (median duration 8 days) and all received immunosuppression. One patient received normal heparin protocol to target APTTr 1.5-2 whilst two patients had 48 hours of ECMO with no heparin followed by sub-therapeutic low dose heparin. ICU survival was 100% and six months survival was also 100%. There were no exacerbations of pulmonary haemorrhage, no new events of extra-pulmonary haemorrhage and no clotting complications.

Gender	Age (years)	Diagnosis	Lung Injury Score	Duration MV before referral (days)	Respiratory support (duration in days)	ECMO complic-ations	Treatment	Predicted ICU mortality (APACHE II)	ICU survival (LOS in days)	6 month survival
Male	73	GPA	3.5	1	VV-ECMO (8)	Nil	PEx, MEP, HD, CYC	25	Yes (17)	Yes
Male	61	GPA	3.5	3	VV-ECMO (8)	Nil	PEx, MEP, CYC	18	Yes (14)	Yes
Female	54	MPA	3.5	1	HFOV, Prone	N/A	MEP, CYC	17	Yes (15)	Yes
Male	46	GPA	3.25	1	VV-ECMO (5)	Nil	PEx, MEP, HD, CYC	20	Yes (21)	Yes

Table 1. MV, mechanical ventilation; LOS, length of stay; GPA, Granulomatosis and Polyangiitis (Wegener's Granulomatosis); MPA, Microscopic Polyangiitis; PEx, Plasma exchange; MEP, methylprednisolone; HD, Continuous veno-venous haemodialysis; CYC, Cyclophosphamide

The ELSO database contains 78 patients (adult, 59; paediatric, 19) with pulmonary vasculitides who received ECMO. 43 had a diagnosis of Granulomatosis and Polyangiitis (GPA), whereas the remaining diagnoses included hypersensitivity angiitis, Goodpasture's syndrome and thrombotic microangiopathy. The median age was 23 years (IQR 16-47). The median duration of ECMO was 190 hours (IQR 146-282) and ICU survival was 82%. Twelve patients (15%) were reported to have thrombotic ECMO circuit complications in the context of likely conservative heparinisation.

Conclusion:

In this case series, ECMO offers an excellent survival rate in SRF due to ANCA-associated DAH. ELSO registry data supports our case series and suggests that DAH related to vasculitis should not be considered a contraindication. ECMO should be considered as adjunctive therapy in DAH patients with SRF not responsive to conventional therapy.

Disclosure: C. Y. Ling, None; **T. Simpson**, None; **G. Glover**, None; **C. Meadows**, None; **N. Ioannou**, None; **B. Lams**, None; **D. P. D'Cruz**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/extra-corporeal-membrane-oxygenation-and-diffuse-alveolar-haemorrhage-a-single-centre-case-series-and-analysis-of-the-elso-database

Abstract Number: 881

ANCA Associated Vasculitis with Hypocomplementemia Has More Diffuse Alveolar Hemorrhage and a Poor Prognosis

Shoichi Fukui[1], Naoki Iwamoto[2], Masataka Umeda[2], Ayako Nishino[2], Yoshikazu Nakashima[2], Tomohiro Koga[2], Shin-ya Kawashiri[2], Kunihiro

Ichinose[2], Yasuko Hirai[1], Mami Tamai[3], Hideki Nakamura[1], Tomoki Origuchi[4] and Atsushi Kawakami[1], [1]Nagasaki University, Nagasaki, Japan, [2]Department of Immunology and Rheumatology, Nagasaki University, Nagasaki, Japan, [3]Transitional Med/Immun/Rheum, Nagasaki University, Nagasaki, Japan, [4]Department of Rehabilitation Sciences, Nagasaki University, Nagasaki, Japan

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Background/Purpose:

ANCA associated vasculitis (AAV) is known as a systemic vasculitis with unknown etiology. Recently, relationship between AAV and complement have been shown and complement have an important role in the pathogenesis of AAV (1). Regarding clinical feature of AAV, hypocomplementemia is reported to be associated with a poor prognosis in a study with a small number of patients (2). However, the clinical characteristics of AAV with hypocomplementemia still remain unclear. In this study, we tried to show the clinical characteristics of AAV with hypocomplementemia.

Methods:

We retrospectively analyzed patients in Nagasaki University Hospital who were newly diagnosed with AAV from April 2008 to June 2015. We analyzed the baseline variables, laboratory data, clinical symptoms and therapeutic outcomes after treatments including episodes of relapses, initiation of dialysis and death using medical records. All patients were classified as AAV based on the Chapel Hill Consensus Conference (CHCC) criteria and the European Medicines Agency (EMA) algorithm. The patients consist of all types of AAV including eosinophilic granulomatous polyangiitis (EGPA), granulomatous polyangiitis (GPA), microscopic polyangiitis (MPA), and renal limited vasculitis. We defined hypocomplementemia as the state which at least one of each complement 3 (C3), complement 4 (C4), or total complement activity (CH50) was lower than lower limits of normal range of each complements.

Results:

We included 82 patients with AAV (11 EGPA, 14 GPA, 54 MPA and 3 renal limited vasculitis) who were newly diagnosed. The median onset age was 71. Forty eight patients (59%) were female. Median follow up duration was 40 months. Seventeen patients (21%) had hypocomplementemia at diagnosis of AAV. Compared to AAV without hypocomplementemia, AAV with hypocomplementemia had significantly higher rates of occurrences of diffuse alveolar hemorrhage (DAH) (7 (41%) vs 5 (8%), $p<0.01$), thrombotic microangiopathy (TMA) (3 (18%) vs 0 (0%), $p<0.01$) and skin lesions (9 (53%) vs 8 (12%), $p<0.01$). Of 17 patients who had hypocomplementemia, only one patient fulfilled American college of rheumatology revised criteria for classification of systemic lupus erythematosus (SLE) concomitantly. Assessed by life-table analysis using the Kaplan-Meier method, hypocomplementemia at disease onset was associated with a poor prognosis ($p=0.012$).

Conclusion:

Our result suggested that hypocomplementemia in AAV might become risk factor for DAH and TMA. Moreover hypocomplementemia was a poor prognostic factor in AAV in this study. Therefore it is significantly important to pay attention to the levels of complement at the diagnosis of AAV.

References:

1. Nat Rev Rheumatol. 2014;10(8):463-73.

2. Nephron Clin Pract. 2014;126(1):67-74.

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Abstract Number: 882

Lung Damage in ANCA Associated Vasculitis Assessed By Vasculitis Damage Index: Recurrent Pulmonary Infections Have a Significant Contribution

Esra Aydın[1], Bahtiyar Toz[2], Burak Erer[3], Nilufer Alpay Kanitez[2], Mustafa Erelel[4], Ahmet Gocmez[5], Ahmet Gul[3], Murat Inanc[3], Lale Ocal[3] and **Sevil Kamali**[3], [1]Department of Internal Medicine,, istanbul faculty of medicine, istanbul, Turkey, [2]Department of Internal Medicine, Division of

Rheumatology, Istanbul University, Istanbul Faculty of Medicine, Istanbul, Turkey, [3]Department of Internal Medicine, Rheumatology Division, Istanbul University, Istanbul Faculty of Medicine, Istanbul, Turkey, [4]Department of Pulmonology, Istanbul University Istanbul Faculty of Medicine Department of Pulmonology, istanbul, Turkey, [5]Department of Radiology, Istanbul University Istanbul Faculty of Medicine, istanbul, Turkey
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Background/Purpose: Vasculitis damage index (VDI) is a validated comprehensive damage tool which has been developed as an outcome measure and consists of different types of lung damage items. We aimed to investigate lung damage in AAV by using VDI.

Methods: We analysed 51 patients (25 female) with AAV (40 GPA, 8 MPA, 3 e-GPA) and lung involvement who met ACR criteria and followed-up from a single tertiary center, between 1998-2014. Demographic and clinical features, smoking and exposure history, severe infections (SI) requiring hospitalization, relapse rates and immunsuppressive doses were recorded. Initial BVAS scores and imaging findings were noted. Severe pulmonary infections requiring hospitalization were recorded. Pulmonary function tests (PFT), 6MWT, HRCT and VDI scores were obtained. Correlation analysis was performed for BVAS and VDI scores. VDI scores were compared between the groups stratified in accordance to the presence and recurrence of severe pulmonary infections by Mann-Whitney U test.

Results: Lung involvement was investigated by imaging (X-Ray/HRCT) (100%), histopathology (15%) or bronchoscopy (25%). ANCA positivity was found in 94% (66% C-ANCA/anti-PR3, 34% p-ANCA/anti-MPO). Mean age at diagnosis, time between the first symptom and diagnosis and total follow-up time were 49±13 y (med 51), 4,8±5,8 mo,(med 3) and 66,5±52 mo (med 47), respectively. 28 patients were smokers. Kidney was the most frequently involved organ (78%) with lung. Initial total and lung BVAS were 22±7 (4-38) (med 23) and 4,6±2,8, respectively.The frequency of BVAS items were as follows: Nodules/cavities 80%, infiltration 52%, massive haemoptysis/alveolar haemorrhage 19%, respiratory failure 11%, pleural effusion/pleurisy 5%, endobronchial involvement 3 %. Respiratory failure developed in 11% at presentation. Cumulative total and lung VDI scores were 3,4±2,2 (0-9) (med 3), 0.4±0.8 (0-4) (med 1) respectively. The frequency of VDI lung items were 21% for impaired lung function, 7% for pulmonary fibrosis, 5% for chronic breathlesness, 1% for pulmonary hypertension. AAV patients had 1 (24%), 2 (12%) or 4 (1%) items of VDI. VDI scores of lung items in AAV subgroups were shown in Table-1. One of four patients who suffered from respiratory failure died. Severe pulmonary infections (>1 SI in 33%) were detected in 44%. VDI was higher in patients who suffered from pulmonary infection but, it was statistically insignificant (4.1±.4 vs 3±1.9, p>0.05). The patients with recurrent severe pulmonary infections had significantly high VDI scores when compared to the patients with only one infection (4.8±2.7 vs 3±1.9, p= 0.02). No significant correlation was found between BVAS and VDI scores.

VDI items	GPA n (%)	MPA n (%)	e-GPA n (%)
Pulmonary Hypertension	-	-	1 (2)
Pulmonary Fibrosis	1 (2)	3 (6)	-
Pulmonary Infarct	-	-	-
Pleural Fibrosis	-	-	-
Chronic Asthma	-	-	2 (4)
Chronic Breathlesness	2 (4)	-	1 (2)
Impaired Lung Function	5 (10)	3 (6)	3 (6)

Conclusion: VDI is a useful tool to demonstrate lung damage in AAV. Lung damage has been demonstrated in almost 40% of AAV patients. Recurrent pulmonary infections seem to be an important contributor to the lung damage in AAV.

Disclosure: E. Aydın, None; **B. Toz**, None; **B. Erer**, None; **N. Alpay Kanitez**, None; **M. Erelel**, None; **A. Gocmez**, None; **A. Gul**, None; **M. Inanc**, None; **L. Ocal**, None; **S. Kamali**, None.

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Abstract Number: 883

Evaluation of Thiopurine Metabolites Monitoring in Patients Treated with Azathioprine for Rheumatic Diseases

Aurélie Chapdelaine[1], Maxime Doré[2], Yves Troyanov[3] and Anne-Marie Mansour[1], [1]Internal Medicine, Université de Montréal, Montréal, QC,

Canada, [2]Pharmacy, Université de Montréal, Montréal, QC, Canada, [3]Rheumatology, Université de Montréal, Montréal, QC, Canada
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SESSION INFORMATION

Session Date: Sunday, November 8, 2015

Session Title: Vasculitis Poster I

Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

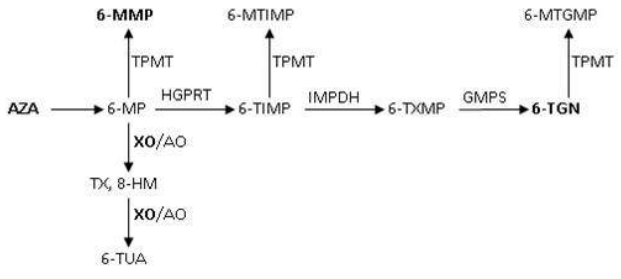
Background/Purpose: The thiopurine azathioprine (AZA) is an inactive pro-drug that undergoes complex metabolic transformations leading to the formation of 6-thioguanine nucleotide (6-TGN), the active metabolite, and 6-methylmercaptopurine (6-MMP), an inactive and potentially hepatotoxic metabolite (Figure). Evidence in inflammatory bowel disease (IBD) suggests that there is a weak correlation between the thiopurine dose and the 6-TGN blood concentration. In a subgroup of patients, production of 6-MMP predominates over production of active 6-TGN. This phenomenon is called hypermethylation. These patients are identified as shunters and are known to be thiopurine resistant unless combined with allopurinol. Current data in IBD support the clinical usefulness of 6-TGN and 6-MMP monitoring to improve the effectiveness and the safety profile of thiopurines. There are few data regarding the clinical benefits of thiopurine metabolites monitoring in patients with rheumatic diseases. The aims of the study were to evaluate the thiopurine doses used to treat diseases other than IBD, to estimate the correlation between the thiopurine dose and the 6-TGN blood concentration, to identify shunters and to describe their management.

Methods: Patients were identified using the central laboratory database and data were retrospectively collected. Spearman's correlation coefficient was used to estimate the correlation between the thiopurine dose (mg/kg) and the blood concentration of 6-TGN (pmol/8×10^8 erythrocytes).

Results: Seventy-one patients were included. Twenty-nine patients (41%) received AZA for vasculitis, 26 (37%) for connective tissue disease, 9 (13%) for myositis, and 7 (10%) for various conditions. Correlation between the thiopurine dose (mg/kg) and the blood concentration of 6-TGN has been estimated at the first thiopurine metabolites assay and at the greatest dose of thiopurine. Spearman's correlation coefficients are 0.337 (p=0.004) and 0.270 (p=0.023), respectively. For the subgroup of non-shunters, the correlation was consistent with that observed for the overall patient sample with Spearman's correlation coefficients of 0.319 (p=0,026) and 0.399 (p=0.005), respectively. Twenty-two patients (31%) were identified as shunters and 6 of them developed significant aminotransferase elevations (>1.5 times the normal upper limit). The AZA-allopurinol combination therapy was used in 9 shunters and allowed a shift toward 6-TGN production in 8 of them.

Conclusion: In this retrospective study, the correlation between the thiopurine dose and the 6-TGN blood concentration was weak. Thirty-one percent of the patients were identified as shunters. Consequently, thiopurine metabolites monitoring demonstrated its clinical usefulness and it should be routinely used to guide thiopurine therapy in patients treated for rheumatic diseases.

Figure. Azathioprine and 6-mercaptopurine metabolism pathway



6-MP, 6-mercaptopurine; **6-MMP, 6-methylmercaptopurine**; 6-MTGMP, 6-methylthioguanosine monophosphate; 6-MTIMP, 6-methylthioinosine monophosphate; **6-TGN, 6-thioguanine nucleotide**; 6-TIMP, 6-thioinosine monophosphate; 6-TUA, 6-thiouric acid; 6-TXMP, 6-thioxanthosine monophosphate; 8-HM, 8-hydroxymercaptopurine; AO, aldehyde oxidase; **AZA, azathioprine**; GMPS, guanine monophosphate synthetase; HGPRT, hypoxanthine-guanine phosphoribosyltransferase; IMPDH, inosine monophosphate deshydrogenase; TPMT, thiopurine *S*-methyltransferase; TX, thioxanthine; **XO, xanthine oxidase**

Disclosure: A. Chapdelaine, None; **M. Doré**, None; **Y. Troyanov**, None; **A. M. Mansour**, None.

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Abstract Number: 884

Patient Perceptions of Treatment with Glucocorticoids in ANCA-Associated Vasculitis

Joanna Robson[1], Susan Ashdown[2], Jill Dawson[3], Ebony Easley[4], Don Gebhart[5], Katherine Kellom[6], Georgia Lanier[7], Nataliya Milman[8], Jacqueline Peck[9], Judy A. Shea[10], Peter F. Cronholm[4] and Peter A. Merkel[11], [1]Nuffield Department of Orthopaedics Rheumatology and Musculoskeletal Sciences, Botnar Research Centre, University of Oxford, Oxford, United Kingdom, [2]NONE, Branbury, United Kingdom, [3]Nuffield Department of Population Health HSRU, University of Oxford, Oxford, United Kingdom, [4]Department of Family Medicine and Community Health, The University of Pennsylvania, Philadelphia, PA, [5]NONE, Columbus, OH, [6]PolicyLab, Children's Hospital of Philadelphia, Philadelphia, PA, United Kingdom, [7]NONE, Framingham, MA, [8]Division of Rheumatology, University of Ottawa, Ottawa, ON, Canada, [9]NONE, Oxford, United Kingdom, [10]Division of General Internal Medicine, University of Pennsylvania, Philadelphia, PA, United Kingdom, [11]Penn Vasculitis Center, Division of Rheumatology, University of Pennsylvania, Philadelphia, PA

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SESSION INFORMATION

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Session Title: Vasculitis Poster I

Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

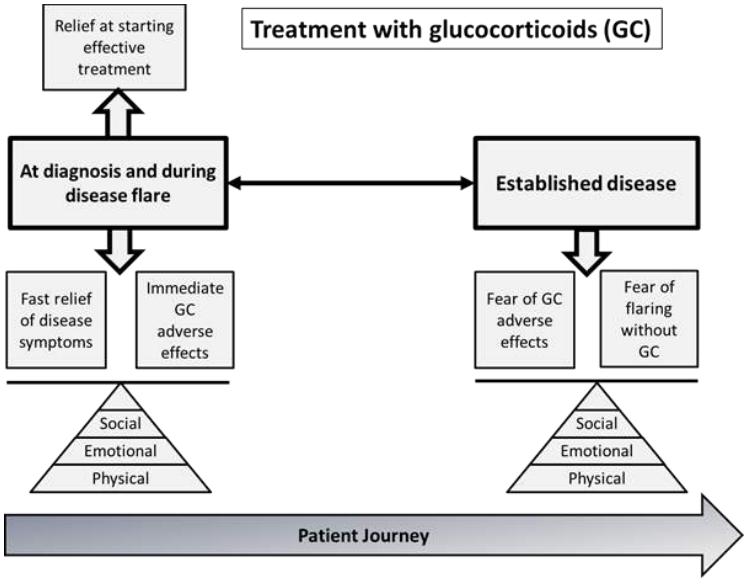
Background/Purpose: Granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA) and eosinophilic granulomatosis with polyangiitis (EGPA) comprise a group of multisystem diseases of the small blood vessels known as antineutrophil cytoplasm antibody (ANCA)-associated vasculitis (AAV). Inflammation can occur throughout the body and patients demonstrate significant impairments in mental and physical health. Treatment with glucocorticoids, often in high doses and in combination with other immunosuppressive therapy, is the cornerstone of management. However, glucocorticoids have substantial physical and psychological adverse effects.

Methods: Patients with AAV from the UK, USA, and Canada were interviewed about their disease and treatment. Patients were purposively sampled to include the spectrum of diseases, chronicity of disease (diagnosis or flare < 2 years previously or > 2 years), age, sex, and organ involvement. The project steering committee, which included patient-partners, defined a set of neutral, nondirective interview prompts and cues on the patient experience of AAV and its treatment, and any impact on health-related quality of life. Interviews were recorded and transcribed verbatim, anonymised and systematically analysed to establish themes grounded in the data. As themes emerged, a collaborative code book was developed. The final transcript yielded no new codes, indicating data saturation. Earlier transcripts were checked for the emerging new codes. A treatment-related code was used to identify all ideas related to experience of treatment; sub codes within the treatment code related to glucocorticoids were defined, grouped into categories, and then grouped into overarching themes.

Results: Forty-nine interviews were conducted. Individual sub codes related to glucocorticoid therapy were identified and grouped into 3 themes: i) Glucocorticoids are effective at the time of diagnosis and during relapse; withdrawal can potentiate a flare, ii) Glucocorticoids are associated with salient emotional, physical and social effects (depression, anxiety, irritation, weight gain and change in appearance, diabetes mellitus); and iii) Balancing the pros and cons of glucocorticoids (symptom relief versus long-term effects). The interaction between these themes is described in Figure 1.

Conclusion: Patients are generally positive about treatment with glucocorticoids in terms of rapidity of onset and efficacy, but anxious about potential long-term adverse effects and the uncertainty of the weaning process. Psychological effects predominated among adverse effects experienced. The results of this study will inform the development of a disease-specific PRO for AAV and a deeper understanding of the risks and benefits of this extremely common form of treatment.

Figure 1. Patient experiences of therapy with glucocorticoids (GC)



Disclosure: J. Robson, None; **S. Ashdown**, None; **J. Dawson**, Isis Innovations- University of Oxford, 5,Isis Innovations- University of Oxford, 7; **E. Easley**, None; **D. Gebhart**, None; **K. Kellom**, None; **G. Lanier**, None; **N. Milman**, None; **J. Peck**, None; **J. A. Shea**, None; **P. F. Cronholm**, None; **P. A. Merkel**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/patient-perceptions-of-treatment-with-glucocorticoids-in-anca-associated-vasculitis

Abstract Number: 885

a Retrospective Analysis of Low Dose Cyclophosphamide Therapy in Systemic Vasculitides

Antigoni Grigoriou[1], Shirish Sangle[2], Chai Ling[2] and David P. D'Cruz[3], [1]Rheumatology, St George's Univeristy Hospitals NHS Foundation Trust, London, United Kingdom, [2]Louise Coote Lupus Unit, Guy's and St Thomas' Hospital, London, UK, London, United Kingdom, [3]Louise Coote Lupus Unit, Guy's and St Thomas' Hospital, London, United Kingdom

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SESSION INFORMATION

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Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose:

The 'Euro-Lupus' low dose cyclophosphamide (CPM) protocol has been validated for use in lupus nephritis patients in randomised controlled trials. A recent controlled study of this protocol by the French vasculitis group has shown favourable results in ANCA positive vasculitis. Our aim is to assess the efficacy and safety of low dose CPM in systemic vasculitides patients.

Methods:

We retrospectively assessed 26 patients with systemic vasculitis at the Louise Coote lupus Unit at Guy's and St Thomas' Hospital who received low dose CPM induction therapy along with corticosteroids during the last 15 years. All patients fulfilled the ACR/Chapel Hill classification criteria for Granulomatosis with Polyangiitis, eosinophilic Granulomatosis with Polyangitis and Microscopic Polyangitis. All patients received 3 pulses of methylprednisolone 500mg and 6 pulses of CPM infusion 500 mg with mesna fortnightly as induction therapy. Subsequently Azathioprine, Methotrexate or Mycofenolate Mofetil were used as remission maintaining agents. Data regarding inflammatory markers Erythrocyte Sedimentation Rate (ESR) and C-reactive protein (CRP), Birmingham Vasculitis Activity Score (BVAS) and Vasculitis Damage Index (VDI) scores were assessed at baseline and after 6, 12, 24, 60, 120 and 180 months. Data on all relapses, organ involvement, duration of remission, corticosteroid requirement, repeat CPM infusions, Rituximab and adverse events were recorded.

Results:

26 patients (13 males, 13 females) were assessed. 22 were Caucasians, 2 mixed ethnicity and 2 Asians. Median age was 54 years. 20 patients had positive ANCA antibodies (15 anti-PR3, 5 anti-MPO). 6 were ANCA negative. The median disease duration prior to induction therapy was 3.12

years. 10 patients had pulmonary involvement (pulmonary hemorrhages, haemoptysis, cavitating lung lesions, nodules), 9 necrotizing crescentic glomerulonephritis, 1 myocarditis, 7 neurological manifestations (raised ICP, occipital masses, mononeuritis multiplex), 3 orbital granulomas, 1 necrotizing scleritis, 2 otitis media with hearing loss and 1 bowel ischaemia. Co-morbidities were antiphospholipid syndrome (2 patients), positive lupus anticoagulant (2), type 2 diabetes mellitus (1), past Tuberculosis (1) and sleep apnoea (1). All patients received tapered doses of oral prednisolone (median dose 30 mg) following the induction regimen.

Median duration of remission was 2.40 years. There was improvement in BVAS, CRP and ESR. 10 patients had relapses over 5 years. 5 patients required repeat CPM pulses for flares and 7 received Rituximab. 12 adverse events were recorded. Renal function remained stable over the years. 1 death has been recorded (See Table)

Conclusion:

Low dose intravenous infusion of CPM in combination with steroids may be effective in achieving remission in systemic vasculitides. This regimen may have fewer adverse events than conventional therapy with high dose CPM.

Table:

Time (1/12=1month)	Pre therapy	6/12	12/12	24/12	60/12	120/12	180/12
BVAS	15.52 (n=23)	4.54 (n=22)	5.42 (n=19)	9.00 (n=9)	4.40 (n=5)	2.00 (n=3)	2.00 (n=2)
ESR (mm/hr)	28.77 (n=22)	18.26 (n=19)	24.52 (n=17)	31.00 (n=6)	9.60 (n=5)	8.50 (n=2)	8.50 (n=2)
CRP (mg/L)	45.54 (n=22)	15.21 (n=19)	12.84 (n=19)	16.50 (n=6)	7.60 (n=5)	1.00 (n=2)	1.00 (n=2)
Creatinine (umol/L)	84.52 (n=21)	91.50 (n=20)	94.20 (n=20)	107.28 (n=7)	105.83 (n=6)	129.50 (n=2)	139.00 (n=2)
e GFR (ml/min)	79.15 (n=20)	76.56 (n=16)	74.78 (n=18)	67.50 (n=8)	70.75 (n=4)	46.00 (n=2)	44.00 (n=2)
PCR	72.44 (n=16)	20.75 (n=12)	17.62 (n=8)	31.00 (n=4)	0 (n=1)	342.00 (n=1)	181.00 (n=1)
Remission (BVAS =0)		N=4	N=3	N=1	N=1	N=1	N=1
Prednisolone dose (mg)	30 (n=21)	14 (n=20)	13 (n=21)	14 (n=8)	9 (n=5)	6 (n=2)	7.5 (n=2)
Relapses		N=2	N=5	N=1	N=2		N=1
Rituximab therapy		N=2	N=3	N=2		N=1	
Repeat CYP therapy		N=3	N=2	N=1			
VDI (median)	1.76 (n=21)	2.60 (n=20)	2.67 (n=18)	3.62 (n=8)	2.4 (n=5)	1.33 (n=3)	1.00 (n=2)
Adverse events		UTIs (recurrent) (n=1), SCC (n=1), cataract (n=1)	Reactivation of varicella zoster/ Shingles (n=1)	Death (n=1), steroid induced diabetes/ pancreatitis (n=1)	Squamous cell carcinoma (n=1)	MI (n=1)	Hurtle cell tumour (n=1

Disclosure: A. Grigoriou, None; **S. Sangle**, None; **C. Ling**, None; **D. P. D'Cruz**, None.

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Abstract Number: 886

Rituximab As a Cyclophosphimide Sparing Agent for Patients with Multi-Relapsing

Antineutrophil Cytoplasmic Antibody Associated Small Vessel Vasculitis

Sophia Lionaki[1], **George Fragoulis**[2], Aliki Venetsanopoulou[2], Panayiotis Vlachoyiannopoulos[2], John Boletis[1], Haralampos M. Moutsopoulos[2] and Athanasios G. Tzioufas[2], [1]Nephrology, Laiko Hospital, Department of Nephrology, Athens, Greece, [2]Pathophysiology, School of Medicine, National University of Athens, Athens, Greece

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SESSION INFORMATION

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Session Title: Vasculitis Poster I

Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose:

To evaluate the long term outcomes, of patients with multi-relapsing Antineutrophil Cytoplasmic Antibody (ANCA) associated Vasculitis (AAV), who received induction therapy with a rituximab regimen upon disease relapse versus a control group who received the standard regimen.

Methods:

We studied patients with biopsy proven AAV, and a history of frequent relapses of the disease, who were treated with a rituximab regimen upon relapsing vasculitis. Rituximab was typically used in combination with the standard regimen for patients with major relapses or with glucocorticoids alone for minor relapses. A control group consisted of patients from the era prior to the initiation of rituximab in the treatment of AAV, was selected, using the following criteria; history of relapse, organ involvement at relapse, treatment with the standard regimen (cyclophosphamide plus glucocorticoids). Patients and controls were also matched for age, gender, and disease duration. Comparisons of outcomes, along with the frequency and severity of adverse events were performed between groups.

Results:

Of 147 patients with biopsy proven AAV and a mean total follow up time of 78.2 months, we identified 18 patients (12.2%), who received induction treatment with rituximab for disease relapse. A control group of equal size was selected. Organ involvement and disease activity were similar between groups at entry. The mean number of relapses per patient was significantly higher in this group for the same period compared to the control group. 13/18 patients in the rituximab group received the standard regimen in addition to rituximab as inductive therapy. Patients in both groups achieved remission in similar rates but patients in the rituximab group showed a significant decline in the number of relapses per patient [median, (range): 2(1-4)] compared to the number of relapses per patient in the period prior to therapy with rituximab [0(0-1), $p<0.001$]. As a result, the subsequent exposure to cyclophopshamide was radically decreased in this group [median, (range): 21.75 grams (4.0-177.0) vs. 3(0.0-10.5), $p<0.0001$].

Conclusion:

In our experience, rituximab was shown efficacious in achievement of long term remission in patients with a history multiple relapsing AAV and allowed us to minimize the ultimate exposure to cyclophosphamide in these patients, avoiding further accumulation of toxicity.

Disclosure: S. Lionaki, None; **G. Fragoulis**, None; **A. Venetsanopoulou**, None; **P. Vlachoyiannopoulos**, None; **J. Boletis**, None; **H. M. Moutsopoulos**, None; **A. G. Tzioufas**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/rituximab-as-a-cyclophosphimide-sparing-agent-for-patients-with-multi-relapsing-antineutrophil-cytoplasmic-antibody-associated-small-vessel-vasculitis

Abstract Number: 887

Intravenous Immunoglobulin As Immunomodulating Agent in ANCA-Associated Vasculitides: A French Nationwide Study of 92 Patients

Etienne Crickx[1], Irène Machelart[2], Estibaliz Lazaro[3], Jean-Emmanuel Kahn[4], Fleur Cohen[5], Thierry Martin[6], Alexandre Mania[7], Pierre-Yves Hatron[8], Gilles Hayem[9], Claire Blanchard-Delaunay[10], Claire De Moreuil[11], Guillaume Le Guenno[12], Frédéric Vandergheynst[13], Francois Maurier[14], Bruno Crestani[15], Robin Dhote[16], Nicolas Martin Silva[17], Yann Ollivier[18], Anas Mehdaoui[19], Bertrand Godeau[20], Xavier Mariette[21], Jacques Cadranel[22], Pascal Cohen[23], Xavier Puéchal[23], Claire Le Jeunne[24], Luc Mouthon[25], Loïc Guillevin[26] and **Benjamin Terrier**[23], [1]Internal Medicine, Cochin Hospital, Paris, France, [2]Hôpital Pellegrin, Pessac, France, [3]Hôpital Haut-Lévêque, Pessac, France, [4]Internal Medicine, Foch Hospital, Suresnes, France, [5]Internal Medicine Dpt 2, Pitié-Salpêtrière Hospital, APHP, Paris, France, [6]Cnrs UPR9021, IBMC, Strasbourg, France, [7]Hôpital Gabriel Montpied, Clermont-Ferrand, France, [8]Service de Médecine Interne, Centre National de

Référence des Maladies Systémiques Rares, Hôpital Claude Huriez, CHRU Lille, Lille, France, [9]Hôpital Ambroise Paré, Boulogne Billancourt, France, [10]Internal Medicine, Centre Hospitalier, Niort, France, [11]CHU, Brest, France, [12]Internal Medicine department, Clermont-Ferrand, France, [13]Hôpital Erasme, Bruxelles, Belgium, [14]HP Metz Belle Isle Hospital, Department of Internal Medicine, Metz, France, [15]Pneumology, Bichat Claude-bernard, Universitary Hospital, APHP, Paris, France, [16]Internal Medicine, Hospital Avicenne, Bobigny, France, [17]CHU Caen, caen, France, [18]Hôpital Cote de Nacre, Caen, France, [19]Hôpital Eure Seine, Evreux, France, [20]Henri Mondor, Créteil, France, [21]Université Paris-Sud, AP-HP, Hôpitaux Universitaires Paris-Sud, Paris, France, [22]Hôpital Tenon, Paris, France, [23]Internal Medicine, National Referral Center for Rare Systemic Autoimmune Diseases, Hôpital Cochin, Paris, France, [24]Department of Internal Medicine, Hotel-Dieu Hospital, AP-HP, Paris, Paris, France, [25]Department of Internal Medicine, Department of Internal Medicine, Cochin Hospital, Referent Center for Necrotizing Vasculitis and Systemic Sclerosis, Paris-Descartes University, AP-HP, Paris, France, [26]Internal Medicine, Hopital Cochin, Paris, France
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SESSION INFORMATION

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Session Type: ACR Poster Session A
Session Time: 9:00AM-11:00AM

Background/Purpose:

Despite recent therapeutic advances in treating ANCA-associated vasculitides (AAVs), some patients relapse or require long-term immunosuppression, leading to significant morbidity and mortality. IVIg represents a therapeutic alternative for AAVs, but its efficacy has been evaluated in only 2 small prospective trials. This study aimed to evaluate IVIg efficacy and safety for AAVs.

Methods:

We conducted a nationwide retrospective study (1990–2014) on patients with AAVs, including granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA) and eosinophilic granulomatosis with polyangiitis (EGPA), who received IVIg immunomodulation (dose >1 g/kg/cycle). Patients given a substitution dose (<1 g/kg/cycle) for hypogammaglobulinemia were excluded.

Results:

Ninety-two patients (mean age: 51 years) with GPA (68%), EGPA (23%) or MPA (9%) received at least 1 IVIg cycle; 72% were ANCA-positive (immunofluorescence assay). IVIg were used as median 3rd-line therapy (range: 1-8), for AAV relapse (83%), the first AAV flare (11%) or dependency on initiated treatments (6%).

The main clinical manifestations at IVIg onset were: ENT (61%), pulmonary (37%), constitutional symptoms (32%), arthralgias (28%), glomerulonephritis (20%), skin (16%), peripheral neuropathy (15%), central nervous system (13%), asthma (12%). The Five-Factor Score (FFS) was 0 (75%), 1 (21%) or 2 (4%). Mean BVAS was 9.4 (range: 0–34).

IVIg was given for a median of 6 (1–156) months (M), combined only with corticosteroids for 21% or with other immunosuppressants/another immunosuppressant for 77%.

IVIg efficacy was assessed for the whole population and a subset of 34 patients with unmodified background therapy; their respective remission rates at M3 and M6 were 49% and 62%, and 44% and 62%, with respective refractory disease rates of 23% and 25%.

Mean BVAS declined from 9.4±6.3 at baseline to 3.0±4.1 at M3, 2.3±4.5 at M6, 1.8±3.6 at M9 and 1.1±2.2 at M12. Similarly, mean CRP and mean prednisone dose also declined during the first year after starting IVIg.

Comparing patients achieving remission (n=43) versus those with only partial responses (n=24) or refractory disease (n=20) at M3, no significant differences were found for age, sex, AAV subtype, FFS, ANCA status or organ involvement at baseline, or IVIg-associated therapeutic regimens. Baseline BVAS was lower for patients who entered remission (7.6±6.8) versus those with partial responses (11.1±4.2, P=0.001) or treatment failures (10.9±6.1, P=0.017).

Adverse events occurred in 33%, among which 12% were serious and led to IVIg discontinuation for 7%.

Conclusion:

The results of this large study showed IVIg's clinical benefit as adjunctive therapy, with an acceptable tolerance profile, supporting its use for patients with refractory or relapsing AAVs.

Disclosure: E. Crickx, None; **I. Machelart**, None; **E. Lazaro**, None; **J. E. Kahn**, None; **F. Cohen**, None; **T. Martin**, None; **A. Mania**, None; **P. Y. Hatron**, None; **G. Hayem**, None; **C. Blanchard-Delaunay**, None; **C. De Moreuil**, None; **G. Le Guenno**, None; **F. Vandergheynst**, None; **F. Maurier**, None; **B. Crestani**, None; **R. Dhote**, None; **N. Martin Silva**, None; **Y. Ollivier**, None; **A. Mehdaoui**, None; **B. Godeau**, None; **X. Mariette**, Biogen Idec, 2,Pfizer Inc, 2,Bristol-Myers Squibb, 5,Pfizer Inc, 5,AstraZeneca, 5,GlaxoSmithKline, 5; **J. Cadranel**, None; **P. Cohen**, None; **X. Puéchal**, None; **C. Le Jeunne**, None; **L. Mouthon**, None; **L. Guillevin**, None; **B. Terrier**, LFB, 5.

Abstract Number: 888

Plasma Exchanges to Treat Primary Systemic Necrotizing Vasculitides: Data from a French Nationwide Study

Gonzalo De Luna[1], Dominique Chauveau[2], Julien Aniort[3], Pierre-Louis Carron[4], Pierre Gobert[5], Alexandre Karras[6], Sylvain Adam-Marchand[7], Francois Maurier[8], Pierre-Yves Hatron[9], Alexandre Mania[10], Guillaume Le Guenno[11], Stéphane Ballly[12], Boris Bienvenu[13], Eric Cardineau[14], Tiphaine Goulenok[15], Noémie Jourde-Chiche Sr.[16], Maxime Samson[17], Antoine Huart[18], Jacques Pourrat[19], Aurelien Tiple[20], Olivier Aumaître[21], Xavier Puéchal[22], Farhad Heshmati[23], Claire Le Jeunne[24], Luc Mouthon[25], Loïc Guillevin[26] and **Benjamin Terrier**[22], [1]Medecine Interne, Cochin University Hospital, Paris, France, [2]CH Toulouse, Toulouse, France, [3]CHU, Clermont-Ferrand, France, [4]Internal Medicine, Centre Hospitalier de Grenoble, Grenoble, France, [5]Nephrology, Centre Hospitalier d'Avignon, Avignon, France, [6]George Pompidou European Hospital, Paris, France, [7]Pneumology, Centre Hospitalier Universitaire de Tours, Tours, France, [8]HP Metz Belle Isle Hospital, Department of Internal Medicine, Metz, France, [9]Service de Médecine Interne, Centre National de Référence des Maladies Systémiques Rares, Hôpital Claude Huriez, CHRU Lille, Lille, France, [10]Hôpital Gabriel Montpied, Clermont-Ferrand, France, [11]Internal Medicine department, Clermont-Ferrand, France, [12]CH, Chambéry, France, [13]Internal Medicine, Hospital Caen, Caen, France, [14]CH, Alencon, France, [15]University Paris Diderot - APHP - Bichat Hospital, aris, France, [16]Nephrology, Aix-Marseille Université - APHM, Marseille, France, [17]Department of Internal Medicine and Clinical Immunology, Dijon University Hospital, Dijon, France, [18]CHU, Toulouse, France, [19]Nephrology, Rangeuil Hospital, Paris, France, [20]Nephrology, CHU, Clermont-Ferrand, France, [21]Department of Internal Medicine 2. Referal center for SLE/APS, CHU Pitié-Salpêtrière, Paris, France, [22]Internal Medicine, National Referral Center for Rare Systemic Autoimmune Diseases, Hôpital Cochin, Paris, France, [23]Cochin Hospital, Paris, France, [24]Department of Internal Medicine, Hotel-Dieu Hospital, AP-HP, Paris, Paris, France, [25]Department of Internal Medicine, Department of Internal Medicine, Cochin Hospital, Referent Center for Necrotizing Vasculitis and Systemic Sclerosis, Paris-Descartes University, AP-HP, Paris, France, [26]Internal Medicine, Hopital Cochin, Paris, France

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Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose:

Plasma exchange (PE) is usually used to treat severe primary systemic necrotizing vasculitides (SNVs) and/or virus-induced vasculitides. Only severe renal insufficiency (serum creatinine (SCR) >500 µmol/l) was validated but long-term outcomes remain poor. In practice, PE may be used in clinical situations without literature input. This study aimed to identify practical PE indications for nonviral SNVs and evaluate short-term and long-term prognoses.

Methods:

This multicenter retrospective study (2005–2014) included PE-treated patients with AAV or nonviral polyarteritis nodosa (PAN) meeting ACR criteria, EMA algorithm and/or Chapel Hill nomenclature. For each indication, analysis of short- and long-term outcomes compared baseline (M0) vs post-PE parameter values.

Results:

Diagnoses of the 152 patients [94 men, 58 women; median age 64 (range 17–89) yr] were: 87 granulomatosis with polyangiitis (GPA), 56 microscopic polyangiitis (MPA), 5 PAN and 4 eosinophilic granulomatosis with polyangiitis (EGPA). ANCA were positive in 142/147 (97%, never PAN): 55% PR3-ANCA+ and 45% MPO-ANCA+.

PE was used for rapidly progressive glomerulonephritis (RPGN) in 126 (83%) [mean SCR 465±257 µmol/l; including <250, 250–500 and >500 µmol/l in one-third each], 64 (42%) alveolar hemorrhage most often RPGN-associated, 23 (15%) with extensive and severe multiple mononeuropathy, usually of acute onset (<4 weeks) and severe motor weakness, and 7 (5%) with extensive skin necrosis. M0 median BVAS was 18. Median (range) PE was 7 (1–12) sessions over a median of 11 (1–43) days.

After median follow-up of 22 (range 1–125) months post-PE onset, 18 (12%) had died, including 11 within M1–6. Renal function of 126 PE-treated RPGN patients improved significantly, as assessed by estimated glomerular filtration rate (eGFR) using MDRD, reaching a plateau between M3 and M6 post-PE onset, and maintaining eGFR through follow-up M24. According to M0-SCR (µmol/l) subgroup, M0-to-M6 eGFR

(ml/min), respectively, rose from 33.3 to 47.3 (P<0.0001) for <250, from 13.5 to 34.7 (P<0.0001) for 250–500, and from 6.9 to 32.9 (P<0.0001) for >500. PE-session numbers were similar for the 3 M0-SCR subgroups, with eGFR improving as that number rose, suggesting a PE dose-dependent effect on eGFR recovery.

PE resolved alveolar hemorrhages in all 64 patients, enabling O_2-therapy or MV discontinuation, after a median of 15 days.

Motor weakness regressed markedly in 23 PE-treated extensive mononeuritis patients. Severe motor-weakness (MRC <3/5) declined from M0 52% to 23%, 19% and 12.5% at M3, M6 and M12 post-PE onset.

End-stage renal disease and/or mortality rates were similar among M0-SCR groups but higher for MPO- than PR3-ANCA+ patients. PE-attributable adverse events occurred in 63%. No one died during PE.

Conclusion:

Our results highlight PE indications for SNVs. Different organ involvements seem to benefit from PE. For RPGN patients, the PE number seemed to correspond to the degree of eGFR recovery. These findings support using PE in conditions less severe than previously validated.

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Abstract Number: 889

Central Nervous System Involvement of Eosinophilic Granulomatosis with Polyangiitis (Churg-Strauss): Retrospective Analysis of 26 Cases and Review of the Literature

Raphael André[1], Chahéra Khouatra[2], Jean-Luc Saraux[3], Francois Maurier[4], Gilles Blaison[5], Boris Bienvenu[6], Pascal Cathebras[7], Nathalie Costedoat-Chalumeau[8], Robin Dhote[9], Aurélie Foucher[10], Helder Gil[11], Joelle Lapouarie[12], David Launay[13], Edouard Pertuiset[14], Valentine Loustau[15], Thierry Zenone[16], Claire Le Jeunne[17], Luc Mouthon[18], Loïc Guillevin[19] and **Benjamin Terrier**[20], [1]Cochin Hospital, Paris, France, [2]CHU Lyon, Lyon, France, [3]CH Eaubonne, Eaubonne, France, [4]HP Metz Belle Isle Hospital, Department of Internal Medicine, Metz, France, [5]Internal medicine, CHR, Colmar, France, [6]Internal Medicine, Hospital Caen, Caen, France, [7]Internal Medicine, University Hospital St Etienne, St Etienne, France, [8]Internal Medicine Department, Cochin Hospital, "René-Descartes Paris V" University, Paris, France, [9]Internal Medicine, Hospital Avicenne, Bobigny, France, [10]CHU, Saint Pierre de la Réunion, France, [11]CHU, Besancon, France, [12]CHU, Pau, France, [13]Service de Médecine Interne, Centre National de Référence des Maladies Systémiques Rares, Hôpital Claude Huriez, CHRU Lille, Lille, France, [14]CH René Dubos, Pontoise, France, [15]Hôpital Henri Mondor, Créteil, France, [16]CH de Valence, Valence, France, [17]Department of Internal Medicine, Hotel-Dieu Hospital, AP-HP, Paris, Paris, France, [18]Department of Internal Medicine, Department of Internal Medicine, Cochin Hospital, Referent Center for Necrotizing Vasculitis and Systemic Sclerosis, Paris-Descartes University, AP-HP, Paris, France, [19]Internal Medicine, Hopital Cochin, Paris, France, [20]Internal Medicine, National Referral Center for Rare Systemic Autoimmune Diseases, Hôpital Cochin, Paris, France

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Background/Purpose:

Eosinophilic granulomatosis with polyangiitis (EGPA) is characterized by asthma, blood and tissue eosinophilia, vasculitis-related peripheral neuropathy, glomerulonephritis or skin symptoms. Although peripheral nervous system involvement occurs frequently, usually as multiple mononeuropathy, exceptional central nervous system (CNS) disease, severe and associated with poor prognosis according to the 1996 Five-Factor Score, has been described. This study aimed to describe CNS involvement in EGPA.

Methods: This retrospective, observational, multicenter study included patients with EGPA meeting ACR criteria and/or Chapel Hill definitions, and CNS involvement affecting cranial nerves, brain or spinal cord. We also undertook a systematic literature review.

Results:

We analyzed 26 patients (50% women, mean age 57±15 years) and 62 reported EGPA-CNS cases (52% women, mean age 47±16 years). At EGPA diagnosis, their main manifestations included: asthma in 97%, hypereosinophilia in 98% with median eosinophil count 7500/mm^3, sinonasal abnormalities in 66%, peripheral neuropathy in 55%, pulmonary infiltrates in 52% and biopsy with eosinophilic infiltration in 46%; 41% had cardiac involvement, including myocarditis (27%), pericarditis (16%), endomyocardial fibrosis (8%) and cardiac arrhythmia (2%). 38/71 (55%) were ANCA-positive, with a perinuclear-labeling pattern and/or anti-MPO specificity.

The CNS was involved in 86% at EGPA diagnosis, preceded EGPA in 2%, and occurred during follow-up in 12% after a median of 24 months. The main neurological signs were: 46 (52%) ischemic cerebrovascular lesions, 21 (24%) intracerebral hemorrhage or subarachnoid hemorrhage, 28 (32%) visual acuity loss (15 with retrobulbar optic neuritis, 10 occluded central retinal artery or 4 cortical blindness), and 18 (20%) cranial nerves palsies; 25 patients had ≥1 of these clinical CNS signs.

Patients with visual acuity loss and cranial nerve palsies had similar clinical-biological parameters. In contrast, patients with intracerebral or subarachnoid hemorrhage compared to those with ischemic cerebrovascular lesions were younger (43 vs 52 years), had less frequent myocarditis (10% vs 35%), more frequent peripheral neuropathy (67% vs 41%), glomerulonephritis (29% vs 13%) and ANCA (79% vs 52%); and had higher median eosinophil counts (12850 vs 7500/mm^3).

All patients were treated with corticosteroids, associated with cyclophosphamide in 63%, azathioprine in 4% or methotrexate in 1%. Among the 81 patients with assessable neurological responses, 43% had complete responses without sequelae, 43% had partial responses with long-term sequelae and 14% refractory disease. After a mean follow-up of 36 months, 11 patients died, half of intracerebral hemorrhages.

Conclusion: The main EGPA-CNS manifestations form 4 distinct neurological pictures: ischemic lesions, intracerebral hemorrhages, cranial nerve palsies and optic neuritis- or central retinal artery occlusion-related visual acuity loss. Such manifestation should prompt practitioners to consider an EGPA diagnosis in such conditions. Neurological sequelae were common.

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Abstract Number: 890

Anti-IgE Monoclonal Antibody in Refractory and/or Relapsing Eosinophilic Granulomatosis with Polyangiitis (Churg-Strauss): Data from 17 Patients

Marie Jachiet[1], Maxime Samson[2], Vincent Cottin[3], Jean-Emmanuel Kahn[4], Guillaume Le Guenno[5], Philippe Bonniaud[6], Laurence Bouillet[7], Anne Gondouin[8], Fatma Makhlouf[7], Nadine Meaux Ruault[9], Helder Gil[8], Hervé Devilliers[10], Boris Bienvenu[11], André Coste[12], Violaine Giraud[13], Stephane Dominique[14], Bertrand Godeau[15], Xavier Puéchal[16], Chahéra Khouatra[17], Marc Ruivard[18], Claire Le Jeunne[19], Luc Mouthon[20], Loïc Guillevin[21] and **Benjamin Terrier**[16], [1]Dermatology, Cochin Hospital, Paris, France, [2]Department of Internal Medicine and Clinical Immunology, Dijon University Hospital, Dijon, France, [3]Division of Pneumology, Hôpital Louis-Pradel, Hospices Civils de Lyon, Lyon 1, Lyon, France, [4]Internal Medicine, Foch Hospital, Suresnes, France, [5]Internal Medicine department, Clermont-Ferrand, France, [6]CHU, Dijon, France, [7]CHU, Grenoble, France, [8]CHU, Besancon, France, [9]Internal Medicine and Clinical Immunology, CHU de Besançon, Besançon, France, [10]Department of Internal Medicine and Systemic Diseases, Dijon University Hospital, Dijon, France, [11]Internal Medicine, Hospital Caen, Caen, France, [12]CHI, Créteil, France, [13]Hôpital Ambroise Paré, Boulogne Billancourt, France, [14]Pneumology, Rouen University Hospital, Rouen, France, [15]Henri Mondor, Créteil, France, [16]Internal Medicine, National Referral Center for Rare Systemic Autoimmune Diseases, Hôpital Cochin, Paris, France, [17]CHU Lyon, Lyon, France, [18]CHU Clermont-Ferrand, Clermont–Ferrand, France, [19]Department of Internal Medicine, Hotel-Dieu Hospital, AP-HP, Paris, Paris, France, [20]Department of Internal Medicine, Department of Internal Medicine, Cochin Hospital, Referent Center for Necrotizing Vasculitis and Systemic Sclerosis, Paris-Descartes University, AP-HP, Paris, France, [21]Internal Medicine, Hopital Cochin, Paris, France

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Background/Purpose:

Omalizumab, an anti-IgE monoclonal antibody, has proven efficacy for the treatment of moderate-to-severe and severe-persistent allergic asthma and allergic rhinitis, with a favorable safety profile. Only rare and contrasting results have been reported for eosinophilic granulomatosis with polyangiitis (EGPA).

Methods:

To describe omalizumab efficacy and safety in patients with refractory and/or relapsing EGPA, we conducted a nationwide retrospective study on EGPA patients who had received omalizumab in these situations. Complete response was defined as the absence of asthma and/or sinonasal exacerbations with a prednisone dose ≤7.5 mg/day, and partial response as the absence of exacerbations with a prednisone dose >7.5 mg/day.

Results: Seventeen patients (median age: 45 years) took omalizumab for severe steroid-dependent asthma (88%) and/or sinonasal involvement (18%), always combined with only corticosteroids, (53%) or with adjunction of other immunosuppressive agents/another immunosuppressant (47%). After median follow-up of 22 months, 6 (35%) patients achieved complete responses, 5 (30%) had partial responses and 6 (35%) showed no improvement. Overall median BVAS dropped from 2.5 at baseline to 1 and 0.5 at 6 and 12 months, respectively. Median numbers of exacerbations decreased from 1/month at baseline to 0 at 6 and 12 months, and median forced expiratory volume in 1 second increased from 63% at baseline to 82% and 85% of the average predicted value at 6 and 12 months, respectively. Median prednisone dose decreased from 16 mg/day at baseline to 11 and 9 mg/day at 6 and 12 months, respectively. Eight patients stopped omalizumab, 25% because of remission, 25% for refractory disease or 50% for relapse. Relapses included EGPA-attributable retrobulbar optic neuritis (n=2) and severe asthma attacks (2 others). No other severe adverse events occurred.

Conclusion:

Results of this study suggest that omalizumab provides mild efficacy and corticosteroid-sparing effect in EGPA with asthmatic and/or sinonasal manifestations. Severe flares occurred in a quarter of the patients raising the question of its safety in this setting.

Disclosure: M. Jachiet, None; **M. Samson**, None; **V. Cottin**, None; **J. E. Kahn**, None; **G. Le Guenno**, None; **P. Bonniaud**, None; **L. Bouillet**, None; **A. Gondouin**, None; **F. Makhlouf**, None; **N. Meaux Ruault**, None; **H. Gil**, None; **H. Devilliers**, None; **B. Bienvenu**, None; **A. Coste**, None; **V. Giraud**, None; **S. Dominique**, None; **B. Godeau**, None; **X. Puéchal**, None; **C. Khouatra**, None; **M. Ruivard**, None; **C. Le Jeunne**, None; **L. Mouthon**, None; **L. Guillevin**, None; **B. Terrier**, None.

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Abstract Number: 891

Long-Term Use of Rituximab for Eosinophilic Granulomatosis with Polyangiitis

David Theis[1], Carol A. Langford[2], Gary S. Hoffman[3] and Alexandra Villa-Forte[4], [1]Orthopaedic and Rheumatologic Institute, Cleveland Clinic, Cleveland, OH, [2]Rheumatology, Cleveland Clinic, Cleveland, OH, [3]Center for Vasculitis Care and Research, Cleveland Clinic Foundation, Cleveland, OH, [4]Rheumatology, Cleveland Clinic Foundation, Cleveland, OH

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Session Time: 9:00AM-11:00AM

Background/Purpose:

Eosinophilic granulomatosis with polyangiitis (EGPA) often presents with persistently active disease requiring chronic glucocorticoid therapy or it may have a relapsing course with partial or no response to traditional immunosuppressive agents. Severe disease frequently responds to cyclophosphamide but its use is limited by the significant toxicity associated with prolonged therapy. The maintenance of disease remission presents a challenge, as patients often require unacceptable doses of glucocorticoids to control asthma or active disease. Rituximab (RTX) is an effective agent used for granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA). Recent retrospective reports have suggested that RTX may also be effective for EGPA. The role of RTX for EGPA is still unclear, including whether repeated courses of RTX may benefit individuals with relapsing disease.

Methods:

We present our experience using RTX for EGPA and present the available worldwide data on RTX for EGPA.

Results:

We identified 56 patients meeting ACR or Revised International Consensus Criteria for EGPA at our institution, 6 of whom received RTX. Five of 6 patients (83%) treated with RTX significantly improved. The remaining patient experienced respiratory distress during the first infusion and did not complete the infusion. These 5 patients had long follow-up (mean 53 months) and received multiple courses of RTX (mean 4.6 courses) for either disease relapse or remission maintenance. We identified 65 cases of EGPA treated with RTX published in the literature with 83-95% response rate using variable outcome measures. These patients received fewer courses of RTX (mean 1.6) and had shorter follow-up (mean 15 months). There were 3 infusion reactions (5%) and 18 infections (28%), 8 of which were severe (12%). Patients from our cohort and from the literature were able to reduce prednisone dose from a mean baseline of 28mg/day to 6.6mg/day and from 18.9mg/day to 8.1mg/day, respectively.

Discussion:

This series provides data on the use of multiple courses of RTX for EGPA. It is also the first series to provide follow-up beyond 3 years for RTX use in EGPA. It is noteworthy that further reductions in prednisone were observed in patients who received repeated courses of RTX as ongoing therapy.

Conclusion:

Although the role of RTX for EGPA is still unclear, a small but growing number of reports suggest that RTX may be an effective treatment option for EGPA that is severe, relapsing or refractory to other medications. Long-term treatment of EGPA using multiple courses of RTX may allow for further reductions in prednisone and thereby reduce associated morbidity. A multicenter prospective trial should be considered to better define both the short-term and long-term efficacy and safety of RTX in patients with EGPA.

Disclosure: D. Theis, None; **C. A. Langford**, None; **G. S. Hoffman**, None; **A. Villa-Forte**, None.

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Abstract Number: 892

Autoimmune Associated Orbital Inflammatory Masses and Response to Immunosuppressive Therapy

Alina Casian[1], Shirish Sangle (joint first author)[2], Ritu Malaiya[3], Pamela Lutalo[4], Louise Nel[5], Bina Menon[6], Hema Varma[7], Miles Stanford[8] and David P. D'Cruz[5], [1]Louise Coote Lupus Unit, Guy's and St Thomas' Hospital, London, UK, London, United Kingdom, [2]Louise Coote Lupus Unit, Guy's and St. Thomas' Hospital, London, United Kingdom, [3]Louise Coote Lupus Unit, Louise Coote Lupus Unit, St Thomas' Hospital, London, United Kingdom, [4]Rheumatology, St. George's Hospital, London, United Kingdom, [5]Louise Coote Lupus Unit, Guy's and St Thomas' Hospital, London, United Kingdom, [6]Rheumatology, Guy's Hospital, London, United Kingdom, [7]Radiology, Guy's and St. Thomas' Hospital, London, United Kingdom, [8]Ophthalmology, Guy's and St. Thomas' Hospital, London, United Kingdom

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Background/Purpose: To characterize a single centre retrospective case series of patients with orbital inflammatory masses associated with autoimmune diseases including granulomatosis with polyangiitis(GPA)(formerly Wegener's granulomatosis), eosinophilic granulomatosis with polyangiitis(eGPA) or Immunoglobulin G4 related disease(IgG4-RD).

Methods: We identified 30 patients with orbital inflammatory masses on MRI imaging. Clinical and laboratory data was collected from electronic clinical records. Comprehensive Diagnostic Criteria were used for IgG4-RD and Chapel Hill criteria for GPA and eGPA. Statistical analysis was performed by GraphPad software; continuous variables were compared between IgG4-RD and GPA groups using non-parametric Mann-Whitney test and categorical variables were compared by Fisher's exact test.

Results:

The study included 21 Caucasian, 6 Asian and 3 patients of African descent. There were 19 female and 11 male patients. The median age was 44 years(range 29-76).

14 patients were diagnosed with GPA, 11 patients had IgG4-RD, 1 patient with IgG4 lymphoma, 1 with eGPA, 1 unspecified vasculitis, 1 IgA dacryoadenitis, 1 non-specific granuloma.

7/11 patients with IgG4-RD had isolated orbital masses whereas all 14 GPA patients suffered extra-ocular manifestations (p=0.01), usually sino-nasal or pulmonary disease.

11/14 GPA patients had positive ANCA vs 2/11 patients with Ig4-RD (p=0.04). IgG4 levels were elevated pre-treatment in IgG4 RD patients (median 2.46 g/l (range 1.2-23.7)) and dropped to 1.25 g/l (range 0.37-10.4) after therapy(p=0.05); immunoglobulin subclasses were not checked routinely in GPA.

All 11 patients with IgG4-RD underwent diagnostic orbital biopsy vs 3/14 GPA (p=0.0001).

All 30 patients were treated with corticosteroids (used alone in 3/11 IgG4-RD patients). The median number of DMARDs ever used to treat GPA was 3 vs 1 DMARD for IgG4-RD (p=0.001). Rituximab was effectively administered to 10/14 GPA patients vs 3/11 IgG4-RD (p=0.04), is planned for 2 further IgG4-RD patients and approval was refused for 1 case. Surgical debulking was undertaken in 6/11 IgG4-RD vs 1/14 GPA (p=0.02). All 30 patients had subsequent MRI to assess response to therapy.

Conclusion: IgG4-RD is an important differential diagnosis of orbital inflammation, especially if ANCA is negative. Unlike GPA which was associated with extra-ocular manifestations in all patients, IgG4-RD was more likely to present with isolated orbital inflammation and to require biopsy or surgical debulking as the diagnosis was initially uncertain. Treatment with corticosteroids +/- DMARDs was effective, however the majority were left with some chronic visual damage. Serial imaging is useful to document clinical response. Rituximab can specifically deplete autoreactive B lymphocytes producing IgG4 and future systematic studies are required to establish the optimum therapeutic strategy.

Patient Group	Granulomatosis with polyangiitis	IgG4 asociated disease	P value
Number of patients	14	11	
Median age (years)	46	38	0.16
Gender distribution	8 female: 6 male	7 female: 4 male	1
Ethnic distribution	10 Caucasian/3 Asian/1 African	6 Caucasian/ 3 Asian/ 2 African	0.4
ANCA status	11 ANCA+ / 3 ANCA negative	2 ANCA+ /9 ANCA negative	0.04
Bilateral orbital inflammation	4/14	2/11	0.7
Extra-ocular manifestations	14/14	5/11	0.03
Orbital biopsy	3/14	11/11	0.0001
Median number of DMARDs	3 (range 1-5)	1 (range 0-3)	0.001
Rituximab treatment	10/14	3/11	0.04
Surgical debulking	1/14	6/11	0.02
Chronic damage (visual loss, diplopia, orbital pain /swelling)	8/14	5/11	0.7
Improvement of orbital inflammation on MRI	9/14	10/11	0.2

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Epidemiological Features of Childhood IgA Vasculitis (Henoch-Schönlein) in a French County: A Population-Based Survey

Maryam Piram[1], Carla Maldini[2], Sandra Biscardi[3], Nathalie De Suremain[4], Christine Orzechowski[5], Emilie Georget[6], Delphine Regnard[7], Isabelle Koné-Paut[1] and **Alfred Mahr**[2], [1]Pediatric Rheumatology, CHU Bicêtre, Le Kremlin Bicêtre, France, [2]Internal Medicine, Hospital Saint-Louis, Paris, France, [3]Pediatrics, Centre Hospitalier Intercommunal Créteil, Créteil, France, [4]Pediatrics, CHU Trousseau, Paris, France,

[5]Pediatrics, CH Sainte Camille, Bry-sur-Marne, France, [6]Pediatrics, Centre hospitalier de Villeneuve-Saint-Georges, Villeneuve Saint Georges, France, [7]Pediatrics, CHU Bicêtre, Le Kremlin Bicêtre, France
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Session Type: ACR Poster Session A
Session Time: 9:00AM-11:00AM

Background/Purpose: IgA vasculitis (IgAV, Henoch–Schönlein) is the most common childhood vasculitis in western countries. Population-based studies mainly carried out in Europe over the last 4 decades reported annual incidence rates of 3 to 27 per 100,000 children. The etiology of IgAV remains unclear. Incidence peaks in the colder months suggested an infectious underpinning, although genetic susceptibility and other environmental triggers might also play a role. More epidemiological studies are required to determine potential changes over time in the epidemiological characteristics of IgAV. This study aimed at describing the epidemiological characteristics of childhood IgAV in a large French population.

Methods: Cases were prospectively collected in Val de Marne county, a southeastern suburb of Paris, with 262,124 residents < 15 years old. Children with incident IgAV living in this area from 2012 to 2014 were identified by 4 sources of case notification (emergency departments, pediatrics departments, private practice pediatricians, general practitioners). Diagnoses were verified against the EULAR/PRINTO/PRES criteria. We calculated 95% confidence intervals (95% CIs) for incidence rates under the assumption of a Poisson distribution. Four-source capture–recapture analysis (CRA) was performed using log-linear modeling to estimate the completeness of case finding. Seasonal variations in IgAV incidence were investigated by comparing observed to expected frequencies by chi-square testing.

Results: The survey identified 151 incident cases meeting the study criteria, including 79 (52%) boys and 72 (48%) girls with a mean age of 6.7 years (standard deviation: 2.7 years; range 2.2–15.7 years). The overall annual incidence (per 100,000 children) was 19.2 (95% CI: 16.2–22.4), with 19.7 (95% CI: 15.6–24.5) for boys and 18.7 (95% CI: 14.6–23.5) for girls. CRA estimated the completeness of case finding at 61.9% (95% CI: 50.0–81.2). The annual distribution of diagnoses (spring: 29%, summer: 12%, fall: 26%, winter: 33%) significantly deviated from a random distribution ($P<0.01$) and indicated a higher incidence in fall or winter as compared with spring or summer ($P<0.01$). Clinical manifestations at presentation included purpura (100%), urticaria (12%), arthralgias/arthritis (93%), acral edema (72%), abdominal involvement (59%), scrotal edema (13%) and renal involvement (21%). Abdominal manifestations included pain (55%), vomiting (26%), diarrhea (13%), hemorrhage (7%) and intussusception (2%). Renal involvement was mostly mild and diagnosed from findings of proteinuria and hematuria; only 3 children (2%) underwent renal biopsy.

Conclusion: The annual incidence rate of 19.2 per 100,000 children, gender distribution and seasonal variation we observed are in line with data reported from other geographic areas and time periods. In contrast, the small proportion and mild presentation of IgAV-associated renal disease supports the rather benign profile of IgAV at the population level.

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Abstract Number: 894

Late-Onset IgA Vasculitis in Adult Patients Exhibits Distinct Clinical Characteristics and Outcomes

Seokchan Hong[1], Soo Min Ahn[1], Doo-Ho Lim[2], Byeongzu Ghang[3], Wook Jang Seo[4], Yong-Gil Kim[1], Chang-Keun Lee[1] and Bin Yoo[2], [1]Division of Rheumatology, Department of Internal Medicine, University of Ulsan College of Medicine, Asan Medical Center, Seoul, South Korea, [2]Division of Rheumatology, Department of Internal Medicine, Department of Rheumatology, University of Ulsan College of Medicine, Asan Medical Center, Seoul, South Korea, [3]Division of Rheumatology, Department of Internal Medicine, Univerisy of Ulsan College of Medicine, Asan Medical Center, Seoul, South Korea, [4]Internal Medicine, Seoul Veterans Hospital, Seoul, South Korea
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Background/Purpose:

To determine whether adult IgA vasculitis patients who developed disease at an older age differ from early-onset patients in terms of clinical features and outcomes.

Methods:

All consecutive adult patients who were diagnosed with IgA vasculitis between January 1997 and December 2014 were reviewed retrospectively. Patients who developed the disease at an older age (¡Ã60 years) were compared with those with an earlier onset of disease. Renal insufficiency was defined as an estimated glomerular filtration rate <60 ml/minute.

Results:

In total, 100 adult patients were diagnosed with IgA vasculitis (mean age, 45.61 ¡¾ 17.24 years), of whom 31 (31%) had late-onset disease. Compared to early-onset patients, late-onset patients were less likely to have a preceding upper respiratory tract infection (0/31, 0.0% *vs.* 14/69, 20.3%; p=0.004), and more likely to have renal insufficiency at presentation (14/31, 45.2% *vs.* 7/69, 10.1%; p=0.000). At the last follow-up visit, late-onset patients were more likely to have chronic renal insufficiency, including end-stage renal disease (18/28, 64.3% *vs.* 7/62, 11.3%; p=0.000). Multivariate Cox analysis revealed that late-onset was a significant risk factor for renal insufficiency at follow-up (odds ratio, 12.886, 95% confidence intervals, 3.653–45.457; p=0.000) (Table 1).

Conclusion:

Patients with late-onset IgA vasculitis in adults exhibit distinct clinical features characterized by greater renal involvement and worse renal outcomes. Thus, more intensive treatment might be needed for adult IgA vasculitis patients, in particular those with late-onset disease.

Table 1. Clinical factors that predict the development of chronic renal insufficiency, as measured by multivariate analysis

	OR	95% CI	P-value
Renal insufficiency at presentation[a]	1.947	0.760–4.991	0.165
Proteinuria (>1g/day) at presentation	0.611	0.233–1.601	0.316
Hematuria at presentation[b]	10.854	1.348¡©–87.393	**0.025**
Late-onset disease (¡Ã60 years)	12.886	3.653¡©–45.457	**0.000**

[a]Renal insufficiency was defined as an estimated glomerular filtration rate <60 mL/minute.

[b]Hematuria was defined as ¡Ã10 red blood cells per high-power field in urine analysis.

CI: confidence interval; OR: odds ratio.

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Relapses and Predictive Factors in Henoch-SchÖnlein Purpura. study of 417 Patients

Natalia Palmou[1], Vanesa Calvo-Río[1], Javier Loricera[1], Enar Pons[2], Patricia Fuentevilla[3], Jose L. Hernández[4], Cristina Mata-Arnaiz[5], L. Martín[6], Francisco Ortiz-Sanjuán[1], L Alvarez[7], Carmen Gonzalez-Vela[8], Domingo González-Lamuño[9], Hector Fernandez-Llaca[10], MA González López[11], S. Armesto[10], M Arias[12], Miguel Angel Gonzalez-Gay[1] and Ricardo Blanco[1], [1]Rheumatology, Hospital Universitario Marqués de Valdecilla. IDIVAL, Santander, Spain, [2]RHEUMATOLOGY, Hospital Universitario Marqués de Valdecilla. IDIVAL. Santander. Spain, SANTANDER, Spain, [3]Rheumatology, Hospital Universitario Marqués de Valdecilla. IDIVAL. Santander. Spain, santander, Spain, [4]Internal Medicine, Hospital Universitario Marqués de Valdecilla. IDIVAL, Santander, Spain, [5]Rheumatology, Hospital Laredo, Santander, Spain, [6]Nephrology, Hospital Universitario Marqués de Valdecilla. IDIVAL. Santander. Spain, Santander, Spain, [7]PEDIATRIC, Hospital Universitario Marqués de Valdecilla. IDIVAL. Santander. Spain, SANTANDER, Spain, [8]Pathology, Hospital Universitario Marqués de Valdecilla. IDIVAL, Santander, Spain, [9]Pediatrics, Hospital Universitario Marqués de Valdecilla. IDIVAL. Santander. Spain, Santander, Spain, [10]Dermatology, Hospital Universitario Marqués de Valdecilla. IDIVAL. Santander. Spain, Santander, Spain, [11]Dermatology, Hospital Universitario Marqués de Valdecilla. IDIVAL. Santander. Spain, santander, Spain, [12]nephrology, Hospital Universitario Marqués de Valdecilla. IDIVAL. Santander. Spain,

santander, Spain
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Background/Purpose: Although the prognosis of Henoch-Schönlein purpura (HSP) is usually favorable, relapses are relatively frequent.

Objectives: Our aim was to analyze the frequency, type and risk factors for relapses in a large series of unselected patients with HSP.

Methods: Retrospective study of 417 patients from a single center, diagnosed with HSP according to the criteria proposed by Michel et al. (J Rheumatol 1992; 19: 721-28). Relapse was defined as a new outbreak of HSP in a previously asymptomatic patient (at least for one month). Quantitative variables were expressed as mean ± SD or as median (interquartile range), and compared with the Student t-test or the Mann-Whitney U-test, as appropriate. Dichotomous variables were expressed as percentages and compared by using the chi-square test. The variables associated with HSP relapse in the univariate analysis entered into a stepwise multivariate logistic regression. Statistical analysis was performed using SPSS 15.0.

Results: 417 patients (240 men/177 women) were studied; median age, 7.5 years (IQR [5.3 to 20.1]). 315 (75.5%) were children or young people (≤20 years) and 102 (24.5%) adults. Clinical manifestations (onset/HSP established,%) were: skin lesions (55.9/100), nephropathy (24/41.2), gastrointestinal involvement (13.7/64.5), joint symptoms (9.1/63.1) and fever (6.2/20.4). Corticosteroids were the most frequently used drugs (35%), followed by NSAIDs (14%), and cytotoxic agents (5%).

After a median follow-up of 12 (IQR [2-38]) months, complete recovery was observed in most cases (n=346; 83.2%) and persistent and usually mild nephropathy, in 32 patients (7.7%). Relapses occurred in almost one third of the patients (n=133; 31.9%). Clinical manifestations during relapses were: cutaneous (89.6%); abdominal (27.1%); renal (25.9%) and articular (16.8%). The median number of relapses was 2.4 (IQR [1-3]). The main risk factors for the development of HSP relapse in univariate analysis are shown in the TABLE.

After multivariate analyses the most powerful predictive factors for relapse were joint manifestations at disease onset, gastrointestinal manifestations during the course of the disease, and corticosteroid treatment at the time of the first episode of HSP (TABLE).

TABLE. Univariate and multivariate analyses of the risk of relapses in a series of 417 patients with Henoch-Schönlein Purpura.

Variable	OR (CI 95%)	p
Univariate analysis		
Male gender	1.51 (0,98-2,32)	0,058
Joint manifestations at the beginning	2.60 (1,31-5,15)	0,006
Palpable purpura duration> 7 days	1.89 (1,04-3,42)	0,037
Abdominal pain	1.66 (1,05-2,60)	0,029
Gastrointestinal manifestations	1.60 (1,02-2,50)	0,042
Nephropathy in the course of HSP	1.61 (0,94-2,76)	0,085
Drug-intake	1.61 (1,06-2,45)	0,026
Corticosteroids	1.71 (1,12-2,64)	0,014
Prednisone doses> 30 mg / day	2.61 (1,06-6,41)	0,036
Duration corticosteroids (per month)	1,08 (0,99-1,16)	0,058
Multivariate analysis		
Joint manifestations at the beginning	2.63 (1,.31-5,30)	0,007
Gastrointestinal symptoms in the course	1.66 (1,05-2,62)	0,031
Treatment with corticosteroids	1.65 (1,06-2,55)	0,026

Conclusion: HSP is usually a benign entity but relapses are not uncommon. Patients with articular symptoms at onset or presenting with gastrointestinal manifestations during the course of the disease or those needing corticosteroids to control the initial episode of HSP, are more prone to develop relapses.

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Abstract Number: 896

Herpes Zoster and the Short Term Risk for Ischemic Stroke in Patients with Autoimmune Diseases

Leonard H. Calabrese[1], Fenglong Xie[2], Huifeng Yun[3], Kevin L. Winthrop[4], John Baddley[5], Cassandra Calabrese[6] and Jeffrey R. Curtis[7], [1]Rheumatic & Immunologic Dis, Cleveland Clinic Foundation, Cleveland, OH, [2]Rheumatology & Immunology, University of Alabama at Birmingham, Birmingham, AL, [3]Epidemiology, University of Alabama at Birmingham, Birmingham, AL, [4]Oregon Health and Science University, Portland, OR, [5]Infectious Diseases, University of Alabama, Birmingham, AL, [6]Cleveland Clinic Foundation, Cleveland, OH, [7]University of Alabama at Birmingham, Birmingham, AL

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Background/Purpose: Herpes zoster (HZ) is an opportunistic infection caused by Varicella Zoster Virus (VZV); HZ is observed with increasing frequency in patients on immunosuppressive therapies. HZ is not only a morbid condition but is associated with a variety of complications. Prior literature has suggested that the risk of stroke may increase shortly after an incidence of HZ, but little is known about this association for patients with autoimmune (AI) disease who are at increased risk both for zoster and stroke compared to the general population.

Methods:

Medicare data (2006-2012) was used to identify patients with incident herpes zoster (HZ), defined by at least one ICD9 diagnosis code 053.xx from hospital discharge or outpatient HZ with a prescription for zoster drug within 7 days. Within the preceding 12 months ('baseline'), they also must have had consecutive coverage with Medicare parts A, B, and D and could not have had any diagnosis code or treatment for HZ. They must also have had ankylosing spondylitis (AS), inflammable bowel disease (IBD), psoriasis (PSO), psoriatic arthritis (PSA), or rheumatoid arthritis (RA) based on 2+ diagnoses from physician visits. Patients with prior stroke or the occurrence of HZ and stroke on the same day were excluded.

Follow-up started at the date of HZ diagnosis + 1 day. The outcome of interest was hospitalized ischemic stroke. The hypothesis tested was that the incidence of stroke immediately following HZ was increased compared to the incidence of stroke at later time points. Incidence rate of hospitalized ischemic stroke in risk windows of 6 and 12 months following the HZ event were evaluated. Poisson regression was to compute incidence rate ratios (IRRs) and to control for multiple potential confounders potentially associated with stroke, comparing the 1, 6 and 12 month periods after HZ to subsequent time periods.

Results:

A total of 50,929 patients with autoimmune diseases and incident HZ were eligible for analysis. The crude incidence rate of hospitalized ischemic stroke was 9.8/1000py in the 6 months after HZ, compared to 8.7/1000py in years 2-6. After multivariable adjustment for multiple stroke-related factors, the IRR for the risk in the first year compared to the second was 1.30 (1.05 – 1.61) compared to month 12-18. Examining the shorter risk window of 30 days after HZ, the IRR was 1.50 (1.06 – 2.12) compared to the pooled rate in years 2-6. Age, diabetes, hypertension, atrial fibrillation, prior TIA, and higher glucocorticoid doses were also significantly associated with higher stroke risk.

Conclusion:

In patients with autoimmune diseases, incident herpes zoster was associated with a 50% increase risk for stroke in the subsequent month. These data provide urgency for developing strategies to reduce the risk of VZV in vulnerable immunosuppressed patients.

Abstract Number: 897

Intra-Articular Corticosteroids Are Safe and Have No Major Effect on Structural Progression of Synovitic Knee OA: A 2-Year Randomized Controlled Trial of 3-Monthly Triamcinolone Hexacetonide

Jeffrey Driban[1], Michael P. Lavalley[2], Lori Lyn Price[3], William F. Harvey[4] and **Timothy E. McAlindon**[4], [1]Tufts Medical Center, Boston, MA, [2]Biostatistics, Boston University, Boston, MA, [3]Clinical Care Research, Tufts Medical Center, Boston, MA, [4]Rheumatology, Tufts Medical Center, Boston, MA

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Background/Purpose: Synovitis is common in knees with OA, and is associated with structural progression. Intra-articular corticosteroids are widely used and could reduce knee OA cartilage damage associated with synovitis, but might also have adverse effects on cartilage health and periarticular bone. Our objective was to test the potential for disease modification of synovitic knee OA by triamcinolone hexacetonide (THA) in a clinical trial with comprehensive measurement of effects on cartilage and subchondral bone using MRI and DXA.

Methods: This was a 2-year NIH-funded, randomized, placebo-controlled, double-blind, clinical trial of intra-articular THA (40 mg) versus saline in people with symptomatic OA (KL grade 2 or 3) with ultrasonic evidence of synovitis. Randomization was blocked and stratified by gender and KL grade. We administered the intervention every 12 weeks over 2 years (8 doses). Assessments included WOMAC pain and function at each visit, annual knee MRI (Philips Achieva X-Series 3.0 Tesla using cartilage volume and morphology sequences) and knee/hip DXA scans. We evaluated MRI cartilage damage using a validated quantitative Cartilage Damage Index (primary structural outcome), area of denudation, and a semi-quantitative feature score (fissures, delamination, superficial fibrillation, signal change). We measured bone marrow lesion and synovial fluid volume quantitatively. Readers for quantitative structural measurements had good reliability (ICCs > 0.81). We compared change in outcomes for the groups over the observation period using regression adjusting for randomization stratification factors and malalignment. Skewed outcomes were log-transformed. We did additional repeated measures analyses using random effects mixed models.

Results: Of the 140 participants, 54% were women, 35% were nonwhite; mean BMI was 31.2 Kg/m2. Completion rates were high (≥90%) in both groups. There was no significant difference between groups in mean change in WOMAC pain (THA -2.2, placebo -2.8; p=0.3) or function (THA -7.1, placebo -9.2; p=0.4), chair stand (THA -1.1, placebo -1.6; p=0.8), or walk time (THA -0.5, placebo -0.03; p=0.5). There were also no significant differences in any of the quantitative or semiquantative structural endpoints, except for CDI (greater loss in the THA group; Table), and progression of fibrillation (THA 11%, placebo 24%; p=0.04). Rates of hypertension and hyperglycemia were low (3% overall for each) and did not differ significantly.

Conclusion: Intra-articular corticosteroids administered every 3 months over 2 years appear relatively safe but do not significantly reduce the progression of structural damage or patient outcomes over the long term. The greater rate of loss of cartilage thickness detected by the CDI in the treated group was small in magnitude and of uncertain clinical significance.

IA THA vs. Saline: Quantitative MRI and DXA structural outcomes

	SALINE		TRIAMCINOLONE		
	Baseline	*Change/yr*	*Baseline*	*Change/yr*	*p**
Cartilage Damage Index					
TOTAL	1168 (473)	-17.8 (71.3)	1246 (347)	-52.1 (108)	**0.03**
Tibia	401 (149)	-3.5 (34.0)	445 (121)	-14.1 (37)	0.09
Femur	768 (352)	-14 (57)	801 (252)	-38 (81)	0.06
Cartilage Denudation (log)					
TOTAL (mm^2)	2.6 (2.4)	0.3 (0.8)	2.1 (2.2)	0.3 (0.8)	0.8
Femur (mm^2)	2.4 (2.3)	0.3 (0.7)	1.9 (2.1)	0.3 (0.9)	0.9
Tibia (mm^2)	1.4 (2.2)	0.2 (0.9)	1.0 (1.7)	0.2 (0.8)	0.9
Subchondral Bone					
Tibial DXA					
Medial (g/cm^2)	1.1 (0.2)	0.0 (0.06)	1.1 (0.2)	0.0 (0.05)	0.5
Lateral (g/cm^2)	0.9 (0.2)	0.0 (0.06)	0.9 (0.2)	0.0 (0.05)	0.7
BML volume (Log) (mm^3)	5.9 (4.4)	0.5 (1.9)	6.5 (4.4)	1.0 (2.3)	0.2
Medial Tibial BVF	0.5 (0.2)	0.02 (0.15)	0.5 (0.21)	-0.01 (0.08)	0.3
Effusion volume (log, mm^3)	10.7 (0.8)	-0.08 (0.41)	10.6 (0.6)	-0.04 (0.48)	0.6

*adjusted for gender, KL grade and malalignment. DXA dual energy xray absorptiometry; BML = bone marrow lesion; BVF = bone volume fraction. Values are presented as mean (SD).

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Abstract Number: 898

A Randomized Double-Blind Study of Denosumab Compared with Zoledronic Acid in Postmenopausal Women with Osteoporosis Previously Treated with Oral Bisphosphonate

PD Miller[1], N Pannacciulli[2], JP Brown[3], E Czerwinski[4], BS Nedergaard[5], MA Bolognese[6], J Malouf[7], HG Bone[8], JY Reginster[9], A Singer[10], C Wang[2], RB Wagman[2] and SR Cummings[11], [1]Colorado Center for Bone Research, Lakewood, CO, [2]Amgen Inc., Thousand Oaks, CA, [3]Laval University and CHU de Québec (CHUL) Research Centre, Québec City, QC, Canada, [4]Krakow Medical Center, Krakow, Poland, [5]Center for Clinical and Basic Research, Aalborg, Denmark, [6]The Bethesda Health Research Center, Bethesda, MD, [7]Hospital de la Santa Creu i Sant Pau, Barcelona, Spain, [8]Michigan Bone and Mineral Clinic, Detroit, MI, [9]University of Liège, Liège, Belgium, [10]Georgetown University Medical Center, Washington, DC, [11]San Francisco Coordinating Center, CPMC Research Institute, San Francisco, CA

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Background/Purpose: Oral bisphosphonates are the most common osteoporosis treatment, but inconvenient dosing regimens and side effects lead to low adherence. Less frequently dosed bisphosphonates, eg, once yearly zoledronic acid (ZOL), are part of the treatment algorithm for patients who have failed or are intolerant to oral bisphosphonates. Yet there is no evidence that cycling through bisphosphonates offers therapeutic benefit.

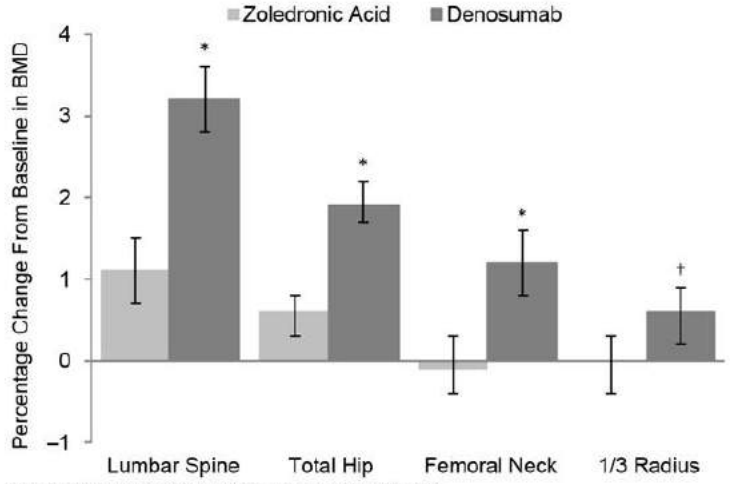
Denosumab (DMAb) has shown bone mineral density (BMD) increases in subjects previously treated with oral bisphosphonates, in contrast to ZOL (McClung et al. *Bone* 2007). This study evaluated DMAb compared with ZOL in postmenopausal women with osteoporosis previously treated with oral bisphosphonates.

Methods: This was a 12-month, multicenter, randomized, double-blind, double-dummy study in postmenopausal women aged ≥ 55 years who had received oral bisphosphonates for ≥ 2 years; had a BMD T-score ≤ –2.5 at the lumbar spine, total hip, or femoral neck; and a serum C-telopeptide of type 1 collagen (sCTX) ≤ 0.5 ng/mL. Subjects were randomized 1:1 to DMAb 60 mg every 6 months (Q6M) + placebo (intravenous [IV] once yearly) or ZOL 5 mg IV once yearly + placebo (subcutaneous Q6M) for 12 months, and received calcium and vitamin D daily. Endpoints included percentage change from baseline in BMD at the lumbar spine (primary endpoint), total hip, femoral neck, and 1/3 radius at month 12. sCTX and procollagen type 1 N-terminal propeptide (P1NP) were measured post baseline in a subset of subjects. Safety was also assessed.

Results: A total of 643 subjects were randomized (321 DMAb; 322 ZOL). Mean (SD) age was 69 (7) years, mean (SD) lumbar spine BMD T-score was –2.7 (0.8), and mean (SD) duration of prior oral bisphosphonates use was 6.3 (3.8) years. BMD change from baseline at month 12 was significantly greater with DMAb compared with ZOL at the lumbar spine (3.2% vs 1.1%; $p < 0.0001$; Figure) and all other measured skeletal sites (Figure). Median decrease from baseline was greater with DMAb compared with ZOL for sCTX at months 1 (–78% vs –68%), 6 (–63% vs –22%), and 12 (–63% vs 2%; all $p < 0.01$), and for P1NP at months 6 (–48% vs –30%) and 12 (–50% vs 4%; both $p < 0.01$). Overall and serious adverse events were similar between groups. There were no cases of osteonecrosis of the jaw, hypocalcemia, or delayed fracture healing. Three events consistent with the definition of atypical femoral fracture were observed (2 DMAb; 1 ZOL).

Conclusion: In postmenopausal women with osteoporosis previously treated with oral bisphosphonates, DMAb treatment increased BMD at all measured skeletal sites and reduced bone remodeling more than ZOL. No new safety risks were identified.

Figure. Percentage Change From Baseline in BMD at Month 12



*$p < 0.0001$ and †$p < 0.02$ denosumab vs zoledronic acid.
Data displayed are least-squared means and 95% CIs based on an ANCOVA model adjusting for treatment, sCTX stratification variable (< 0.3 ng/mL vs 0.3–0.5 ng/mL), baseline BMD, DXA machine type, and baseline value by DXA machine–type interaction.

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Abstract Number: 899

HA20: A Novel Autoinflammatory Disease Caused By Haploinsufficiency of A20, Encoded By TNFAIP3

Qing Zhou[1], Hongying Wang[2], Daniella M. Schwartz[3], Monique Stoffels[4], Yong Hwan Park[2], Yuan Zhang[5], Erkan Demirkaya[6], Masaki

Takeuchi[2], Jonathan J. Lyons[5], Xiaomin Yu[5], Claudia Ouyang[7], Amanda K. Ombrello[2], Deborah L. Stone[2], Patrycja Hoffmann[2], Anne Jones[2], Helen L. Leavis[8], Annet van Royen-Kerkhof[8], Ahmet Gül[9], Seza Ozen[10], Richard Siegel[11], Massimo Gadina[12], JaeJin Chae[2], Ronald Laxer[13], Daniel L. Kastner[2] and Ivona Aksentijevich[2], [1]Inflammatory Disease Section, National Human Genome Research Institute, Bethesda, MD, [2]National Human Genome Research Institute, Bethesda, MD, [3]Rheumatology fellowship and training branch, National Institute of Arthritis and Musculoskeletal and Skin Diseases, Bethesda, MD, [4]National Human Genome Research Institute, National Institutes of Health, Bethesda, MD, [5]National Institute of Allergy and Infectious Diseases, Bethesda, MD, [6]Pediatric Rheumatology, Gulhane Military Medical Academy, FMF Arthritis Vasculitis and Orphan disease Research Center (FAVOR),, Ankara, Turkey, [7]National Institute of Arthritis and Musculoskeletal and Skin Diseases, Bethesda, MD, [8]University Medical Center Utrecht, Utrecht, Netherlands, [9]Istanbul University, Istanbul Faculty of Medicine, Istanbul, Turkey, [10]Pediatric Nephrology and Rheumatology, Hacettepe University, Ankara, Turkey, Ankara, Turkey, [11]National Institute of Arthritis and Musculoskeletal and Skin Diseases, National Institutes of Health, Bethesda, MD, [12]NIAMS/NIH, Bethesda, MD, [13]The Hospital for Sick Children, Toronto, ON, Canada

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Background/Purpose:

We describe a new autoinflammatory syndrome caused by high penetrance heterozygous germline mutations in the NFκB regulatory protein TNFAIP3 (A20) in six unrelated families with early onset systemic inflammation. The syndrome resembles Behçet's disease (BD), which is typically considered a polygenic disorder with onset in early adulthood. Previously, low-penetrance common variants of *TNFAIP3* have been associated with a number of autoimmune and inflammatory diseases in multiple GWAS studies.

Methods:

We performed whole-exome and candidate gene sequencing in the patients and their unaffected family members. Targeted sequencing of *TNFAIP3* was performed in 384 Turkish and 384 Japanese patients with BD that were used for GWAS. We used overexpression experiments in 293T cells and Jurkat cells to establish the causality of candidate variants. Patient samples were analyzed using immunoblotting, immunohistochemistry, flow cytometry, real-time PCR, and cytokine profiling.

Results:

We identified 5 high-penetrance dominantly inherited frameshift and nonsense *TNFAIP3* mutations in 11 patients from 5 families who presented with early-onset systemic inflammation, arthralgia/arthritis, oral and genital ulcers, and ocular inflammation. Targeted sequencing of *TNFAIP3* identified one patient from the GWAS cohort with a novel frameshift mutation. None of the mutations have been reported in any public database. Expression of wild type (WT) A20 was reduced in patients' PBMCs and fibroblasts. A20 is a potent inhibitor of the NFκB signaling pathway. Over-expressed mutant proteins failed to suppress TNF-induced NFκB activity in comparison to WT A20, while co-transfection with the WT A20 normalized the NFκB activity. A20 restricts cellular activation by cleaving K63-linked ubiquitin chains (Ub) from target substrates such as NEMO, RIP1, and TRAF6. Cells transfected with A20 mutants showed a marked defect in the deubiquitination of each of these target molecules. This defect was partially rescued by co-transfection with wild-type A20, mimicking the situation in the patients. These experiments suggest haploinsufficiency as a likely mechanism of disease.

Stimulated patients' cells showed increased phosphorylation of IKKα/β, increased degradation of IκBα, and increased nuclear translocation of p65. Patients' PBMCs displayed weak association of A20 with the TNFR complex and a defect in the deubiquitination of A20 target molecules. Patient cells had a sustained higher K63-ubiquitinaton level of NEMO and RIP1 and accumulated high-molecular weight Ub-aggregates. These results indicate that inefficient deubiquitination of A20 target proteins might explain a higher NFκB signaling activity in mutant cells. Levels of IL-1β, TNF-α, IP-10, IL-17, and IL-9 were substantially increased in patients' serum and in the supernatants of stimulated PBMCs relative to healthy controls. Patients' cells showed constitutive activation of the NLRP3 inflammasome. Initial experience with agents targeting pro-inflammatory cytokines has been encouraging.

Conclusion:

This study provides the first example of the effects of germline high-penetrance heterozygous truncating mutations in the *TNFAIP3* gene.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/ha20-a-novel-autoinflammatory-disease-caused-by-haploinsufficiency-of-a20-encoded-by-tnfaip3

Abstract Number: 900

A Multidimensional Immunomics Approach Annotates an Immunome Shaped By the Interplay Between the Periphery and the Skin Microenvironment in Systemic Sclerosis

Hari Balaji Venkatanarayanan[1,2], Andrea Low[3], Raymond Ong Jr.[4], Liyun Lai[1,2], Juntao Li[2,5], Chie Hwee Ang[1,2], Suzan Saidin[1,2], Camillus Chua[1,2], Jing Yao Leong[1,2], Agnieszka Maliszewska[1,2], Lakshmi Ramakrishna[1,2], Julian Thumboo[6] and Salvatore Albani[1,2], [1]SingHealth Translational Immunology and Inflammation Centre, Singapore Health Services Pte Ltd, Singapore, Singapore, [2]Duke-National University of Singapore Graduate Medical School, Singapore, Singapore, [3]Division of Rheumatology, Singapore General Hospital, Singapore, Singapore, [4]Singhealth Translational Immunology and Inflammation Centre (STIIC), Singapore Health Services Pte Ltd, Singapore, Singapore, [5]SingHealth Translational Immunology and Inflammation Centre (STIIC), Singapore Health Services Pte Ltd, Singapore, Singapore, [6]Department of Rheumatology and Immunology, Singapore General Hospital, Singapore, Singapore

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Background/Purpose: Systemic sclerosis (SSc), is a chronic autoimmune disorder of the connective tissue. There is an unmet need to define precise immune correlates involved in SSc pathogenesis. The interplay between the tissue microenvironment such as the skin and the periphery in potentiating an inflammatory response remains to be elucidated. This knowledge gap is a major impediment for development of therapeutic interventions.

Methods: Our Immunomics platform integrates highly multiplexed technologies with the objective of identifying unique immune signatures that cluster meaningfully at the single-cell level. 1) Gene expression studies using Nanostring - Human dermal fibroblasts stimulated with culture supernatants of blood and skin derived DNA Topoisomerase I (Topo I, an autoantigen relevant in SSc) specific T cell lines (TCLs) 2) Mass spectrometry (CyTOF) analysis of peripheral blood using 35+ phenotypic and intracellular markers. 3) Next-gen, RNA-seq analysis of the the whole transcriptome, including TCR usage of Topo I specific TCLs. Using this approach, we interrogated samples from SSc subjects stratified (according to modified Rodnan skin score, MRSS) as patients with ILD (n=13), No ILD (n=13) and compared to healthy controls (n=8). The dense data sets generated from these high throughput measurements were analysed using computational tools such as Automatic Classification of Cellular Expression by Nonlinear Stochastic Embedding (ACCENSE), Principal Component Analysis (PCA) and Ingenuity Pathway Analysis (IPA).

Results: Skin derived Topo I specific TCLs expressed significantly higher amounts of IL-17A and IL-13 (p value $< .001$) compared to blood derived Topo I specific TCLs. Nanostring gene expression studies revealed that IL-1a, IL-1β, IL-6, IL-8, IL-11, CCL2, CXCL2, CXCL10, CSF3 and TNFSF14 were significantly (p value $< .05$) in the human dermal fibroblasts stimulated with culture supernatants from skin-derived TCLs. Gene expression was also confirmed at the protein level using Enzyme linked immunosorbent assay (ELISA). IPA gene ontology studies annotated IL-17A as a top upstream regulator of these genes. CyTOF analysis showed that CD4+CD45RO+CD161+CCR4+CCR6+ Th17 cells were increased (p value $< .03$) in SSc subjects with No ILD compared to patients with ILD and healthy controls. Finally, unique clonotypes of Topo I specific CD4+ T cells could be identified.

Conclusion: We have defined an Immunome in SSc that circumscribes an altered frequency of Th17 cell subset in patients with ILD as compared to No ILD. IL-17A was identified as the top regulator of genes upregulated by Topo I specific T cells in human dermal fibroblasts. Interestingly, cytokines encoded by some of these genes such as IL-1a, IL-1β, IL-6 and IL-11 are known to be involved in Th17 polarisation. We hypothesise that skin homing Topo I specific T cells secreting IL-17A upregulates inflammatory cytokines in SSc skin, perpetuating inflammation and polarizing a cutaneous Th17 response. These results annotate an interplay between the skin microenvironment and the periphery in shaping the Immunome relevant in SSc pathogenesis

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Abstract Number: 901

Novel B Cell-Derived Peptide Regulation of Homeostatic T-Cell Trafficking Is Subverted in Rheumatoid Arthritis

Helen McGettrick[1], Myriam Chimen[2], Ashley Martin[3], Francesca Barone[4], Andrew Filer[5], Karim Raza[6], Christopher Buckley[4], Parth Narendran[7] and G. Ed Rainger[2], [1]Rheumatology Research Group, Institute of Inflammation and Ageing, University of Birmingham, Birmingham, United Kingdom, [2]Institute of Cardiovascular Sciences, University of Birmingham, Birmingham, United Kingdom, [3]School of Cancer Sciences, University of Birmingham, Birmingham, United Kingdom, [4]University of Birmingham, Rheumatology Research Group, Birmingham, United Kingdom, [5]University of Birmingham, Birmingham, United Kingdom, [6]University of Birmingham, Rheumatology Research Group, Institute of Inflammation and Ageing, United Kingdom, Birmingham, United Kingdom, [7]Institute of Metabolism and Systems Research, University of Birmingham, Birmingham, United Kingdom

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Session Time: 2:30PM-4:00PM

Background/Purpose: In rheumatoid arthritis (RA), inappropriate recruitment of T-cells into the joint contributes to disease pathogenesis and joint destruction. We examined the ability of adiponectin to regulate the migration of T-cells.

Methods: Peripheral blood lymphocytes were isolated from healthy donors and from patients with newly presenting RA fulfilling the 1987 ACR criteria at the time of initial assessment. Lymphocyte migration across TNFα+IFNγ stimulated endothelial cells was assessed *ex vivo* using phase-contrast microscopy. *In vivo*, lymphocyte migration was assessed in a model of zymosan-driven peritoneal inflammation.

Results: Adiponectin inhibited the migration of human lymphocytes across inflamed endothelium in a dose dependent manner. This effect was lost when B-cells were absent, but could be regained by the addition of supernatants from adiponectin-stimulated B-cells. Mass spectrometry identified the adiponectin induced B-cell-derived agent as a small peptide, subsequently named PEPITEM. *In vitro*, PEPITEM blocks T-cell migration by stimulating endothelial cells to release sphingosine-1-phosphate, a known regulator of T-cell migration. In zymosan-induced peritonitis, T-cell recruitment was significantly increased in B-cell deficient animals compared to wild-type controls, and this was ameliorated by treatment with synthetic PEPITEM. B-cells isolated from patients with RA expressed lower levels of adiponectin receptors compared to healthy controls and were unable to respond to adiponectin. Consequently, T-cells from patients with RA were released from the inhibitory effects of adiponectin on transmigration. Excitingly the full effect of adiponectin was rescued by the therapeutic use of exogenous PEPITEM.

Conclusion: We have identified a novel endogenous peptide (PEPITEM) mediated pathway that suppresses T-cell recruitment across inflamed endothelium, which is dysfunctional in patients with RA. Thus, deregulation of the adiponectin-PEPITEM axis during early development and/or progression of disease could directly contribute to pathology in RA. Re-establishing PEPITEM function to "turn off" pathological recruitment of T-cells represents a novel and potentially powerful approach to treating patients with early rheumatoid arthritis.

Disclosure: H. McGettrick, Pfizer Inc, 2; **M. Chimen**, None; **A. Martin**, None; **F. Barone**, None; **A. Filer**, None; **K. Raza**, None; **C. Buckley**, None; **P. Narendran**, None; **G. E. Rainger**, None.

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Abstract Number: 902

Inhibitor of DNA Binding 1 As a Fibroblast Derived Inflammatory Angiogenic Agonist in Rheumatoid Arthritis

Gautam Edhayan[1], Christine M. Ha[1], Ray A. Ohara[1], Takeo Isozaki[1], M. Asif Amin[1], Ali S. Arbab[2], Phillip L. Campbell[1], Rachel Morgan[1], W. Alexander Stinson[3], Sean C. Friday[1], David A. Fox[1] and Jeffrey H. Ruth[1], [1]Internal Medicine, Division of Rheumatology, University of Michigan Medical Center, Ann Arbor, MI, [2]Georgia Regents University, Augusta, GA, [3]Division of Rheumatology, University of Michigan Medical Center, Ann Arbor, MI

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Background/Purpose: Inhibitor of DNA binding 1 (Id1) is a nuclear protein containing a basic helix-loop-helix (bHLH) domain that regulates cell growth by selective binding and prevention of gene transcription. We have shown that Id1 exhibits pleiotropic activity, is highly expressed in rheumatoid arthritis (RA) synovial tissues (STs) and effusions, and is primarily fibroblast derived. Soluble Id1 acts as a potent inducer of angiogenesis and may contribute to vasculogenesis and angiogenesis by independent mechanisms. This suggests that fibroblast-like synoviocytes (FLS) produce Id1, which induces blood vessel growth after release from FLS through an unknown mechanism.

Methods: Histologic analysis of RA STs and K/BxN mice ankles was conducted to reveal the cell types expressing Id1 in these tissues and how Id1 expression correlates with disease severity. FLS from RA, osteoarthritis (OA), and normal (NL) STs were plated and cell supernatants were measured for Id1 expression by ELISA. Supernatants were subjected to ultracentrifugation to isolate and purify exosomes. Nanoparticle Tracking Analysis was used to quantify the size and concentration of particles within the exosome fractions. Whole and lysed (0.5% Triton X-100) exosome fractions were then measured for Id1. For signal transduction analysis, human dermal microvascular endothelial cells (HMVECs), endothelial progenitor cells, and FLS were plated and stimulated with human Id1 to assess the kinetics of protein phosphorylation. Finally, we confirmed the effects of Id1 signaling on angiogenesis using silencing RNA (siRNA) to inhibit HMVEC signaling pathways in the mouse Matrigel plug assay. Further studies of Id1 as a secreted factor included electroporation of RA FLS with a clustered regularly interspaced short palindromic repeats (CRISPR)/Cas9 plasmid with a guideRNA targeting the Id1 gene. Successful expression of this plasmid will cause error-prone nonhomologous end joining (NHEJ) repair at the start codon of the Id1 gene, likely causing a nonsense mutation, resulting in an Id1 knockout cell.

Results: Histologic analysis revealed that Id1 expression correlated well with disease severity in RA STs and in K/BxN mouse ankles. We confirmed that >70% of particles in the exosome fraction of RA FLS supernatants were between 25-135 nm in diameter, which is the expected size of exosomes. We found that >80% of the Id1 released by RA FLS was encapsulated within these exosomes. Cell signaling assays showed the JNK pathway was consistently upregulated by Id1 in the cell types tested. Furthermore, we showed that inhibiting HMVEC associated JNK with siRNA reversed Id1 induced vessel formation in Matrigel plugs. Finally, we confirmed Cas9 mediated NHEJ at the start codon of the Id1 gene via Sanger sequencing and T7 endonuclease activity. These Id1 knockout FLS showed a 40% decrease in cell proliferation compared to sham transfected cells.

Conclusion: Id1 is a pleotropic molecule that has significant effects on angiogenesis, vasculogenesis, and FLS proliferation. Our data shows that Id1 is not only an important nuclear protein, but that it is also released from FLS, primarily in exosomes, thus expanding its role in the orchestration of inflammatory lesions through trans-cellular effects.

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View Abstract and Citation Information Online - http://acrabstracts.org/abstract/inhibitor-of-dna-binding-1-as-a-fibroblast-derived-inflammatory-angiogenic-agonist-in-rheumatoid-arthritis

Abstract Number: 903

CGEN-15001, a Novel B7-like Protein, Controls Inflammation in a Translational Rheumatoid Arthritis (RA) Assay and Induces Treg Driven Long-Term Remission in an Autoimmune Disease Model

Iris Hecht[1], Ashley Gilmour[2], Clare Tange[2], Donna McIntyre[2], Joseph R. Podojil[3], Kay McNamee[4], Galit Rotman[5], Eyal Neria[5], Mariola Kurowska-Stolarska[2], Richard O. Williams[4], Stephen D. Miller[3] and Iain B. McInnes[2,6], [1]Therapeutic Proteins, Compugen Ltd., Tel Aviv, Israel, [2]Institute of Infection, Immunity and Inflammation, College of Medical, Veterinary and Life Sciences, University of Glasgow, Glasgow, United Kingdom, [3]Microbiology-Immunology, Northwestern University, Chicago, IL, [4]Kennedy Institute of Rheumatology, University of Oxford, Oxford, United Kingdom, [5]Compugen Ltd., Tel Aviv, Israel, [6]Institute of Infection, Immunity and Inflammation, College of Medicine, Veterinary Medicine and Life Sciences, University of Glasgow, Glasgow, United Kingdom

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Background/Purpose:

CGEN-15001 is an Fc fusion protein composed of the extracellular domain of a novel B7-like protein. Therapeutic CGEN-15001 treatment is effective in collagen induced arthritis and potentially re-establishes immune tolerance. This is supported by long lasting efficacy in autoimmune disease models, and by establishment of tolerance to donor graft in a bone marrow transplantation model. CGEN-15001 inhibits T cell activation and induces Th1/Th17 to Th2 shift, IL-10 secretion and regulatory T cell (Treg) differentiation.

As Tregs have key role in tolerance, their involvement in the effects of CGEN-15001 was studied in the EAE (experimental autoimmune encephalomyelitis) model of multiple sclerosis by blocking IL-10 or TGFβ which play critical roles in Treg differentiation, or upon transient Treg inactivation by anti-CD25.

The therapeutic potential of CGEN-15001 for RA was studied in co-cultures of cytokine activated T cells (TcK) and macrophages (Mϕ) from RA patients and healthy donors. Such co-cultures mimic the interaction of cells in RA synovium that lead to aberrant cytokine production and provide a translational tool to evaluate potential therapies.

Methods:

CD4+ T cells and monocytes were isolated from healthy donors or RA patients' blood and cultured for 6 days with TNFα, IL-6 and IL-15 to induce TcK or with M-CSF to induce Mϕ differentiation, respectively. Autologous TcK and Mϕ were co-cultured in the presence of CGEN-15001 or controls for 24hrs. Cytokines were evaluated by luminex.

EAE was induced in SJL mice primed with $PLP_{139-151}$ in CFA. Mice were treated from onset of remission, 3 times/week for 2 weeks. Anti-IL-10 or anti-TGFβ were injected concomitantly with CGEN-15001. Alternatively, 2 injections of anti-CD25 were given 2 days before treatment with CGEN-15001 or 2 weeks after last treatment. Disease severity was followed.

Results:

In synovial-like Mϕ: TcK co-cultures, CGEN-15001 abrogated secretion of pro-inflammatory cytokines including TNFα, IL-17, IFNγ, GM-CSF, RANTES and MIP-1α. Similarly, inhibition in TNFα secretion was observed in co-cultures from RA patients' cells.

In EAE, durable remission was induced by a short course of therapeutic treatment. This effect was abrogated by concomitant treatment with anti-TGFb or anti-IL-10, demonstrating a central role for Treg supporting pathways in the therapeutic effects of CGEN-15001. Transient inactivation of Tregs by anti-CD25 before CGEN-15001 treatment did not affect the durable remission achieved by CGEN-15001, however, administration of anti-CD25 2 weeks after the last treatment resulted in transient disease relapse, suggesting that Treg functionality is crucial for the durable effects of CGEN-15001, while at early stages Th1/Th17 to Th2 skew may control the disease.

Conclusion:

The anti-inflammatory activity of CGEN-15001 in a translational assay mimicking RA synovium supports its therapeutic potential in RA. The long remission maintained by active Tregs in the EAE model supports a novel mechanism of re-establishing tolerance to autoantigens. Therefore, these results support the therapeutic potential of CGEN-15001 to reduce inflammation and maintain long-term remission in autoimmune diseases and RA in particular.

Disclosure: I. Hecht, Compugen Ltd., 3; **A. Gilmour**, None; **C. Tange**, None; **D. McIntyre**, ; **J. R. Podojil**, Compugen, 2; **K. McNamee**, None; **G. Rotman**, Compugen, 3; **E. Neria**, Compugen, 3; **M. Kurowska-Stolarska**, Compugen, 2; **R. O. Williams**, None; **S. D. Miller**, Compugen, 2; **I. B. McInnes**, Compugen, 2.

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Abstract Number: 904

Intracerebroventricular Tweak (TNF-like weak inducer of apoptosis) Induces Depressive-like Behavior and Cognitive Dysfunction in Non-Autoimmune Mice

Jing Wen[1], Christopher Chen[1], Ariel Stock[1], Jessica Doerner[1], Maria Gulinello[1] and **Chaim Putterman**[1,2], [1]Albert Einstein College of Medicine, Bronx, NY, [2]Division of Rheumatology, Albert Einstein College of Medicine, Bronx, NY

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Background/Purpose:

Neuropsychiatric lupus (NPSLE) is a common disease manifestation in lupus patients; however, the underlying mechanisms are not fully understood. TWEAK is a cytokine member of the TNF superfamily; the TWEAK receptor, Fn14, is inducibly expressed in the central nervous system (CNS) in endothelial cells, astrocytes, microglia, and neurons. Previously, we had found that Fn14 knockout MRL/lpr lupus mice have

significantly attenuated neuropsychiatric manifestations. To establish whether this improvement in disease is secondary to inhibition of TWEAK-Fn14 signaling within the CNS rather than in the periphery, and determine whether TWEAK-mediated neuropsychiatric effects are strain dependent, we performed short term intra-cerebroventricular injections (ICV) of Fc-TWEAK to C57Bl6/J (B6) mice.

Methods:

ICV injection of Fc-TWEAK (2 µg, n=12) or isotype control (P1.17, 2 µg, n=11) was conducted twice a week in B6 mice at 8 weeks of age for a total of 5 injections, according to the following stereotaxic coordinates: anteroposterior: -0.34 mm, mediolateral: -1.0 mm; dorsal ventricular: 2mm. Three days after the last injection, neurobehavioral tests including open field, object placement, object recognition, anhedonia, and forced swim were performed, after which the mice were sacrificed. To evaluate whether ICV administration of Fc-TWEAK modulates changes in blood brain barrier (BBB) integrity, extravascular fibronectin, aquaporin-4, and iNOS expression were evaluated by Western blot, immunofluorescence staining and qRT-PCR, respectively. Complement activation was assessed by measuring the expression of C3 by qRT-PCR and Western blot. TUNEL staining was employed to analyze for apoptosis in brain cells.

Results:

We found that Fc-TWEAK injected non-autoimmune mice developed significant depressive-like behavior and cognitive dysfunction (impaired spatial memory). Inflammatory mediators associated with lupus brain disease, including MCP-1, C3, and iNOS, were significantly elevated in the brains of Fc-TWEAK treated mice. Furthermore, Fc-TWEAK directly increased BBB permeability, as demonstrated by increased fibronectin deposition and reduced aquaporin-4 expression in the brain of Fc-TWEAK treated mice. Finally, mice injected with Fc-TWEAK exhibited increased apoptotic cell death in the cortex and hippocampus.

Conclusion:

TWEAK can contribute to lupus-associated neurobehavioral deficits including depression and cognitive deficits by acting within the CNS to enhance production of inflammatory mediators, promote permeability of the BBB, and induce apoptosis in resident brain cells. Our study provides further support that the TWEAK/Fn14 signaling pathway may be a potential therapeutic target for neuropsychiatric manifestations in SLE.

Disclosure: J. Wen, None; **C. Chen**, None; **A. Stock**, None; **J. Doerner**, None; **M. Gulinello**, None; **C. Putterman**, NIH, LRI research grant, 2.

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Abstract Number: 905

Citrullinated Epithelial-Derived Neutrophil-Activating Peptide 78 (ENA-78/CXCL5) Induces Monocyte Migration Via JNK and NFκB Signaling Pathways

Ray A. Ohara[1], **Nicholas Lepore**[2], W. Alexander Stinson[3], Gautam Edhayan[3], Phillip L. Campbell[1], Sarah Arwani[1], Rachel Morgan[1], Jeffrey H. Ruth[1], Alisa E. Koch[1,4], David A. Fox[1] and M. Asif Amin[1], [1]Internal Medicine, Division of Rheumatology, University of Michigan Medical Center, Ann Arbor, MI, [2]University of Michigan, Division of Rheumatology, University of Michigan Medical Center, Ann Arbor, MI, [3]Division of Rheumatology, University of Michigan Medical Center, Ann Arbor, MI, [4]Eli Lilly and Company, Indianapolis, IN

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Background/Purpose: Rheumatoid arthritis (RA) is a chronic autoimmune disorder characterized by monocyte (MN) infiltration into the synovium. Citrullination is a post-translational modification of arginine to citrulline mediated by peptidyl arginine deiminase (PAD). Previously, we have shown that citrullination converts epithelial-derived neutrophil-activating peptide 78 (ENA-78/CXCL5) from a neutrophil recruiter to a MN recruiter. In this study, we investigated the signaling pathways involved in MN recruitment by citrullinated ENA-78/CXCL5 (citENA-78/CXCL5).

Methods: Recombinant human (rh) ENA-78/CXCL5 was citrullinated by incubation with rhPAD enzyme. To confirm the citrullination sites, citENA-78/CXCL5 was analyzed using liquid chromatography-tandem mass spectrometry (LC-MS/MS). To determine the signaling pathways involved, MN chemotaxis assay was performed with citENA-78/CXCL5 in modified Boyden chambers with chemical signaling inhibitors. MNs were also transfected with JNK silencing RNA (siRNA). Three mutants (R45K, R48K and R45/48K) of rhENA-78/CXCL5 were generated by transmutation of arginines to lysines and were used in MN chemotaxis assays. To assess citENA-78/CXCL5-induced MN migration *in vivo*, a mouse subcutaneous air pouch model was used. The exudates from the air pouch were collected after 24 hours and immunofluorescence was

performed to detect MNs/macrophages using anti-F4/80 antibody. MNs were stimulated with citENA-78/CXCL5 for 15 minutes and Western blots were performed to evaluate phosphorylation of signaling molecules. We also assessed the crosstalk between the signaling pathways after incubating with chemical signaling inhibitors before citENA-78/CXCL5 stimulation.

Results: LC-MS/MS analysis confirmed citrullination of citENA-78/CXCL5. CitENA-78/CXCL5-induced MN migration was significantly reduced by JNK and NFκB inhibitors, but not by inhibitors of Src, p38, and Erk1/2. JNK siRNA-transfected MNs displayed decreased citENA-78/CXCL5-induced MN migration compared to control transfected MNs. CitR45K and citR48K mutations significantly reduced MN chemotaxis, suggesting that citENA-78/CXCL5-induced MN migration is dependent, at least partially, on both citrulline residues. The mouse air pouch model showed marked MN recruitment in response to citENA-78/CXCL5 compared to the controls, suggesting that citENA-78/CXCL5 increases MN ingress *in vivo*. CitENA-78/CXCL5-stimulated MNs showed increased expression of phosphorylated-JNK and phosphorylated-NFκB (p-NFκB) which was inhibited by signaling inhibitors. Moreover, a JNK inhibitor reduced the level of p-NFκB, suggesting that JNK is upstream of NFκB in citENA-78/CXCL5-stimulated MNs.

Conclusion: We found that citENA-78/CXCL5 induces MN migration via JNK and NFκB signaling pathways. MN chemotaxis induced by citENA-78/CXCL5 is partially dependent on both citrulline residues. CitENA-78/CXCL5 plays an important role in MN migration *in vivo* in the air pouch inflammatory model. Our data suggest that citENA-78/CXCL5 induces JNK and NFκB signaling pathways with JNK upstream of NFκB. Targeting citENA-78/CXCL5 and its signaling pathways may be a novel approach to treat MN-dependent diseases.

Disclosure: R. A. Ohara, None; **N. Lepore**, None; **W. A. Stinson**, None; **G. Edhayan**, None; **P. L. Campbell**, None; **S. Arwani**, None; **R. Morgan**, None; **J. H. Ruth**, None; **A. E. Koch**, None; **D. A. Fox**, None; **M. A. Amin**, None.

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Abstract Number: 906

Distinct Expression of IL-36Î±, β, Î³ and Their Antagonists IL-36Ra and IL-38 in Psoriasis, Rheumatoid Arthritis and Crohn's Disease

Marie-Astrid Boutet[1], Géraldine Bart[2], Jérôme Amiaud[1], Bénédicte Brulin[3], Céline Charrier[3], Franck Morel[4], Jean-Claude Lecron[4], Malvyne Rolli-Derkinderen[5], Arnaud Boureille[6], Cem Gabay[7], Gaby Palmer[8], Benoit Le Goff[2] and Frédéric Blanchard[9], [1]Laboratoire de physiologie de la résorption osseuse, Inserm UMR 957, Nantes, France, [2]Rheumatology, Nantes University Hospital, Nantes, France, [3]Inserm UMR 957, Nantes, France, [4]EA 4331, Poitiers, France, [5]Inserm UMR 913, Nantes, France, [6]Hepato-Gastroenterology Unit, Nantes University Hospital, Nantes, France, [7]Rheumatology, Geneva University Hospital, Geneva, Switzerland, [8]Geneva University Hospital, Geneva, Switzerland, [9]Laboratoire de Physiopathologie de la Résorption Osseuse et Thérapie des Tumeurs Osseuses Primitives, Inserm UMR 957, Nantes, France

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SESSION INFORMATION

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Session Type: ACR Concurrent Abstract Session

Session Time: 2:30PM-4:00PM

Background/Purpose: The IL-36 family of cytokines comprises three agonists, IL-36α, IL-36β and IL-36g, an antagonist IL-36Ra, as well as IL-38, another potential IL-36 inhibitor. IL-36 agonists are highly expressed in skin and are involved in the pathogenesis of psoriasis while antagonists limit uncontrolled inflammation. The expression and role of IL-36 cytokines in other chronic inflammatory diseases is currently debated. In this study, we compared the expression profile of IL-36 cytokines in psoriasis, RA and Crohn's disease (CD).

Methods: Skin, joint and colon inflammation was induced in mice according to standard protocols. Skin, synovial and colonic biopsies from patients respectively with psoriasis (n=15), RA (n=21) or CD (n=16) were collected with corresponding control samples. Synovial fluids from patients with RA (n=30) or osteoarthritis (n=29) were also collected. These samples were analyzed for cytokine expression by RT-qPCR, ELISA, multiparametric Luminex assays, immunohistochemistry and confocal microscopy. The cell sources of IL-36 cytokines were confirmed in cell cultures after stimulation with inflammatory cytokines and TLR agonists by RT-qPCR.

Results: During imiquimod-induced mouse skin inflammation and in human psoriasis, expression of IL-36α, g and IL-36Ra, but not IL-36β and IL-38, was induced and correlated with Th17 cytokines (IL-17A, IL-22, IL-23, CCL20), IL-1β, Oncostatin M, IFNg and IL-8. In mice with collagen-induced arthritis and in the synovium of patients with RA, IL-36α, β, g, IL-36Ra and IL-38 were all elevated and correlated with IL-1β, myeloid cytokines such as CCL3, CCL4 and MCSF, but not with Th17 cytokines, TNFα or IL-6. In mice with dextran sulfate sodium-induced colitis and in patients with CD, only IL-36α, g and IL-38 were induced at a relatively low level. Only a minor subgroup of patients with RA (17-29%) or CD (25%) had an elevated IL-36 agonists/antagonists ratio, versus 93% of patients with psoriasis. By IHC and in cell cultures, the different IL-36 cytokines were produced at different levels by human keratinocytes, $CD68^+$ inflammatory macrophages, dendritic/Langerhans cells, and $CD79\alpha^+$ plasmocytes. Endothelial cells and $CD55^+$ fibroblasts could also participate, but enterocytes were poor producers.

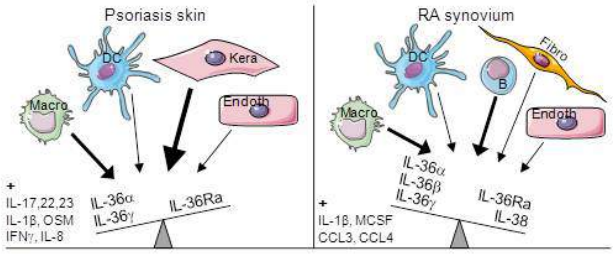

Figure: Proposed model for the distinct expression of IL-36 cytokines in psoriasis versus RA.

Conclusion : Expression of the different IL-36 cytokines is differently regulated and their cell sources are distinct. This helps to explain the different expression profiles observed in three chronic inflammatory diseases and why only a minor subgroup of RA and CD patients have an elevated IL-36 agonists/antagonists ratio. Additional studies are necessary to better identify these patients and to investigate whether they would benefit from IL-36 neutralization.

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Abstract Number: 907

The Natural History of an Inception Cohort of Patients with Inflammatory Polyarthritis Followed for 20 Years: Disease Activity, Disability and Surgery

James Gwinnutt[1], Deborah P.M. Symmons[1], Alex J Macgregor[2], Jacqueline Chipping[2], Tarnya Marshall[2] and Suzanne M. Verstappen[1], [1]ARC Epidemiology, Stopford Building, ARC Epidemiology Unit, the University of Manchester, Manchester, United Kingdom, [2]Rheumatology, Norfolk and Norwich University Hospital, Norwich, United Kingdom

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Background/Purpose: There is little data on the 20 year outcome of patients with inflammatory polyarthritis (IP). Hence the aim of this study was to describe patients with IP over long term follow up, including disease activity, disability and surgery.

Methods: Adults, aged ≥16 with ≥2 swollen joints for ≥4 weeks, recruited from 1990-1994 to the Norfolk Arthritis Register (NOAR) were included in this study. Baseline assessments included demographics, 51 swollen / tender joint counts and HAQ. RF, ACPA and CRP were measured from stored blood samples taken every 5 years; DAS28-CRP scores were calculated. Patients were re-assessed at years 1-3, 5, 7, 10, 15 and 20 years and self-report major orthopaedic surgeries data were also collected at these visits. Differences in the progression of disability over time based on gender and other baseline characteristics were assessed using a random effects model. The association between demographics, disability and disease activity and risk of first surgery was assessed using the Cox proportional hazard model. Censoring occurred when patients left the cohort. Mortality rates were calculated, using 15th December 2014 as censor date.

Results: Of 1022 patients (60.1% met the 2010 ACR RA criteria) included at baseline, 354 (34.6%) completed 20 years follow-up. 404 (39.5%) died during follow up (mortality rate: 22.6 / 1000 patient years). At baseline, median (IQR) swollen / tender joint counts were 6 (2-13) / 7 (3-16), and HAQ was 0.8 (0.3-1.4). After baseline, median joint counts improved and remained low (see table). The median HAQ (IQR) score dropped to 0.5 (0.0 -1.3) after 1 year before increasing to 0.9 (0.3-1.6) at 10 years and 1.0 (0.3-1.8) at 20 years. Median DAS28-CRP showed a similar trend. In total, 237 (23.2%) patients underwent at least 1 major joint surgery. The probabilities of patients completing 10 / 20 years of follow-up without surgery were 0.84 and 0.70 respectively. Higher age at onset (HR 1.01; 95% CI 1.00-1.02 per year), baseline HAQ (HR 1.35; 95% CI 1.03 -1.78) and baseline CRP level (HR 1.01; 95% CI 1.00-1.01 per mg/l) were associated with an increased risk of first surgery. The median (IQR) number of surgeries per patient was 2 (1-3). Men were older than women at baseline (mean 55.7 vs 55.2 years, p = 0.0012) whilst women had worse median HAQ scores (0.9 vs 0.5, p<0.0001) and more swollen (7 vs 4, p<0.0001) and tender joints (8 vs 6, p=0.0016).Women had higher HAQ scores than men over 20 year follow up (β coef. 0.007; p<0.001) using a random effects model.

Conclusion: Over 20 years patients' disease activity was well controlled. Median disability rose progressively but slowly after 5 years. Higher baseline HAQ and disease activity scores were associated with joint surgery during follow-up.

Table – Characteristics of the cohort at baseline and follow up years 5, 10, 15 and 20

	Baseline		5 years		10 years		15 years		20 years	
Variable	N	Mean (SD)§ / Median (IQR)‡	N	Mean (SD)§ / Median (IQR)‡	N	Mean (SD)§ / Median (IQR)‡	N	Mean (SD)§ / Median (IQR)‡	N	Mean (SD)§ / Median (IQR)‡
Attended FU	1022	-	782	-	607	-	477	-	354	-
Gender										
Men	360	-	255	-	185	-	153	-	103	-
Women	662		527		422		324		251	
Age at FU (years)	1022	53.4 (16.3) §	782	58.4 (15.1) §	607	61.4 (14.1) §	476	63.5 (13.38) §	354	66.0(12.2) §
Swollen joints (51)	1022	6 (2-13) ‡	554	1 (0-4) ‡	601	1 (0-4) ‡	477	1 (0-3) ‡	354	0 (0-2) ‡
Tender joints (51)	1022	7 (3-16) ‡	554	1.5 (0-6) ‡	601	2 (0-11) ‡	477	3 (0-10) ‡	354	2 (0-10) ‡
Both S+T (51)	1022	3 (0-8) ‡	554	0 (0-2) ‡	601	0 (0-2) ‡	477	0 (0-2) ‡	354	0 (0-10) ‡
DAS28-CRP	817	4.0 (2.9-5.0) ‡	509	2.5 (1.7-3.4) ‡	375	3.1 (2.3-4.0) ‡	352	3.0 (2.2-4.0) ‡	- ξ	-
HAQ	1010	0.8 (0.3-1.4) ‡	779	0.8 (0.1-1.6) ‡	597	0.9 (0.3-1.6) ‡	474	1 (0.3-1.8) ‡	347	1 (0.3-1.9) ‡
RF	891			-		-		-		-
Positive (%)	252 (28.3%)									
Negative (%)	639 (71.1%)									
Anti-CCP	797			-		-		-		-
Positive (%)	216 (27.1%)									
Negative (%)	581 (72.9%)									

ξ - *CRP not yet measured at 20 year follow up, thus DAS28-CRP not calculated*

Disclosure: J. Gwinnutt, None; **D. P. M. Symmons**, None; **A. J. Macgregor**, None; **J. Chipping**, None; **T. Marshall**, None; **S. M. Verstappen**, None.

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Abstract Number: 909

Smoking Behavior Changes after Rheumatoid Arthritis Diagnosis and Risk of Mortality during 36 Years of Prospective Follow-up

Jeffrey A. Sparks[1], Uyen Sa D.T. Nguyen[2,3], Shun-Chiao Chang[4,5], Yuqing Zhang[6], Hyon Choi[7] and Elizabeth W. Karlson[4], [1]Division of Rheumatology, Immunology, and Allergy, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, [2]Clinical Epidemiology Research &Training Unit, Boston University School of Medicine, Boston, MA, [3]Orthopedics and Physical Rehabilitation, University of Massachusetts Medical School, Worcester, MA, [4]Division of Rheumatology, Immunology and Allergy, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, [5]Channing Division of Network Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, [6]Clinical Epidemiology Research and Training Unit, Boston University School of Medicine, Boston, MA, [7]Division of Rheumatology, Allergy and Immunology, Massachusetts General Hospital, Harvard Medical School, Boston, MA

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Background/Purpose: Smoking is a major preventable cause of death and cessation is recommended for the general population. However, it is unclear whether being diagnosis with RA affects smoking cessation and whether continuing to smoke contributes to the excess mortality of RA. We aimed to describe smoking behavior changes after RA diagnosis and to evaluate the effect of smoking on mortality after RA diagnosis.

Methods: We investigated smoking and mortality among women diagnosed with RA during follow-up in the Nurses' Health Study (NHS). The NHS is composed of 121,700 women aged 30-55 years at baseline in 1976 and followed with biennial questionnaires. RA diagnosis was validated by medical record review according to the 1987 ACR criteria by two rheumatologists who identified the date of RA diagnosis. Smoking status and intensity (never, current, or past; cigarettes/day) were reported biennially during follow-up and cumulative smoking pack-years were calculated for each follow-up cycle. We categorized smoking at each follow-up cycle as occurring before or after the date of RA diagnosis. Deaths were identified by the National Death Index up to 2012. Cox regression models estimated HRs for all-cause mortality according to smoking pack-years after RA diagnosis, adjusting for sociodemographic, behavioral, and clinical factors.

Results: We analyzed 923 women diagnosed with RA during follow-up in the NHS with detailed prospective data available on smoking before and after RA diagnosis. There were 288 deaths in 16,111 person-years of follow-up. At RA diagnosis, mean age was 59.5 (SD 9.9) years, 52% were obese, and 60% consumed alcohol. In the cycle prior to RA diagnosis, 36% were never smokers, 43% were past smokers, and 21% were current smokers. Among current smokers just prior to RA diagnosis, 16% immediately quit smoking after RA diagnosis and maintained cessation, 21% continued to smoke throughout follow-up, 49% continued smoking for at least two cycles after RA but quit later, and 1% quit smoking after RA diagnosis then started smoking again later. Compared to never smokers after RA diagnosis, women who smoked >5 pack-years after RA diagnosis had significantly increased mortality (HR 2.69, 95% CI 1.33-5.46, **Table**) after adjustment for age, smoking pack-years prior to RA diagnosis, and other confounders. When analyzing only ever smokers at RA diagnosis, smoking >5 pack-years remained significantly associated with mortality compared to those who never smoked after RA diagnosis (HR 4.35, 95% CI 1.81-10.44).

Conclusion: Despite the known harmful effects of smoking in chronic diseases, only 16% of smokers quit after diagnosis with RA and maintained smoking cessation during follow-up. Smoking >5 pack-years after RA diagnosis was associated with increased mortality, independent of smoking before RA diagnosis. Interventions promoting cessation of smoking for patients newly diagnosed with RA may diminish the excess mortality of RA.

Table. Hazard ratios for all-cause mortality by cumulative smoking after RA diagnosis during 36 years of prospective follow-up in the Nurses' Health Study, 1976-2012.

Cumulative smoking after RA diagnosis, N=923	Deaths/Person-years	Incidence (per 100,000)	Age and pre-RA smoking adjusted HR (95% CI)*	Multivariable HR (95% CI)**
Never/past/current smoker before RA and never smoker after RA diagnosis	184/12,307	1,529	1.00 (Ref)	1.00 (Ref)
>0-5 pack-years after RA diagnosis	44/2,070	2,126	1.49 (0.85-2.60)	1.42 (0.71-2.82)
>5 pack-years after RA diagnosis	60/1,734	3,460	2.98 (1.70-5.22)	2.69 (1.33-5.46)
Subgroup analysis: Cumulative smoking after RA diagnosis among ever smokers, N=590	Deaths/Person-years	Incidence (per 100,000)	Age and pre-RA smoking adjusted HR (95% CI)*	Multivariable HR (95% CI)**
Past/current smoker before RA and never smoker after RA diagnosis	113/6,172	1,831	1.00 (Ref)	1.00 (Ref)
>0-5 pack-years after RA diagnosis	44/2,070	2,126	1.50 (0.80-2.81)	1.68 (0.74-3.82)
>5 pack-years after RA diagnosis	60/1,734	3,460	3.88 (2.01-7.45)	4.35 (1.81-10.44)

*Adjusted for age, questionnaire period, and cumulative smoking prior to RA diagnosis (never, >0-10, >10-20, >20 pack-years)

**Additionally adjusted for median family income (<$40K, ≥$40K), body mass index category (underweight/normal, overweight, or obese), postmenopausal hormone (PMH) use (premenopausal or postmenopausal/never PMH use, postmenopausal/ever PMH use), physical activity (continuous METs-hours/week), alcohol consumption (0, >0-<5, ≥5 g/d), Alternate Healthy Eating Index without alcohol component (tertiles), cardiovascular disease, and aspirin use.

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Abstract Number: 910

Tumor Necrosis Factor-Alpha Inhibitor Use and the Risk of Incident Hypertension in Patients with Rheumatoid Arthritis: A Retrospective Cohort Study

Rishi J. Desai[1], Daniel H. Solomon[2], Sebastian Schneeweiss[3], Goodarz Danaei[4], Katherine Liao[5] and Seoyoung C. Kim[6], [1]Division of Pharmacoepidemiology and Pharmacoeconomics, Brigham & Women's Hospital, Harvard Medical School, Boston, MA, [2]Rheumatology, Brigham and Women's Hospital, Boston, MA, [3]Division of Pharmacoepidemiology, Brigham and Women's Hospital, Boston, MA, [4]Harvard School of Public Health, Boston, MA, [5]Division of Rheumatology, Immunology, and Allergy, Brigham & Women's Hospital, Boston, MA, [6]Div. of Pharmacoepidemiology and Pharmacoeconomics, Div. of Rheumatology, Immunology and Allergy, Brigham and Women's Hospital, Boston, MA

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Session Time: 2:30PM-4:00PM

Background/Purpose: Results from several small studies support the potential blood pressure lowering effect of tumor necrosis factor (TNF)-a inhibitors in rheumatoid arthritis (RA) patients. Yet, no study has compared the effect of TNF-a inhibitors with non-biologic disease-modifying

anti-rheumatic drugs (nbDMARDs) on the development of incident hypertension in a population-based cohort of RA patients. Therefore, the objective of this study was to compare the risk of incident hypertension between initiators of TNF-α inhibitors and initiators of nbDMARDs in a cohort of RA patients taking methotrexate monotherapy who are free from cardiovascular diseases or hypertension.

Methods: We conducted a cohort study using insurance claims data (2001-2012) from the US. We identified initiators of either TNF-α inhibitors or nbDMARDs. Subsequent exposure to these agents was measured monthly in a time-varying manner. The outcome of interest was incident hypertension, defined by a diagnosis and a prescription for an anti-hypertensive drug. Marginal structural models (MSM) estimated hazard ratios (HR) adjusted for both baseline and time-varying confounders. To validate the primary analysis examining TNF-α inhibitors and hypertension association, we designed a verification analysis to evaluate a known association between leflunomide and hypertension using similar methodology.

Results: We identified 4,822 initiations of TNF-α inhibitors and 2,400 of nbDMARDs. Crude incidence rates of hypertension per 1,000 person-years of follow-up were 36.1 (95%CI 31.8-40.7) for the TNF-α inhibitor group and 41.2 (95%CI 33.0-50.8) for the nbDMARDs. The crude HR of TNF-α inhibitors versus nbDMARDs for the risk of incident hypertension was 0.85 (95%CI 0.67-1.09). After adjusting for both baseline and time-varying covariates in MSM, the HR was 1.01 (95%CI 0.78-1.31). In the verification analysis, the adjusted HR of incident hypertension was 2.33 (95% CI 1.75-3.09) in leflunomide initiators compared with methotrexate initiators.

Conclusion: Treatment with TNF-α inhibitors was not associated with a reduced risk of incident hypertension compared with nbDMARDs in RA patients.

Table: Incidence rates and relative risks of hypertension in initiators of TNF-alpha inhibitors compared to the initiators of non-biologic DMARDs for RA

	nbDMARDs	TNF-α inhibitors
Hypertension Events	88	258
Follow-up (person-years)	2137	7155
Crude incidence rates/1000 person-years (95% CI)	41.2 (33.0-50.8)	36.1 (31.8-40.7)
Unadjusted HR	1	0.85 (0.67-1.09)
Adjusted HR for only time-fixed covariates*	1	0.94 (0.74-1.25)
Adjusted HR for time-fixed and time-varying covariates using IPTW† in MSM**	1	1.01 (0.78-1.31)

Abbreviations: CI- Confidence interval, HR- Hazard ratio, IPTW- Inverse probability treatment weights, MSM- Marginal structural models, nbDMARDs- non biologic disease modifying anti-rheumatic drugs, TNF- tumor necrosis factor

*Time-fixed covariates (measured at initiation of either TNF-inhibitor of non-biologic DMARDs): gender, diabetes, hyperlipidemia, lipid-lowering agent use, anti-diabetic medication use, obesity, smoking, combined comorbidity score.

**Time-varying covariates (updated monthly post-initiation of either TNF-inhibitor of non-biologic DMARDs): use of NSAIDs, injectable steroids, cumulative dose of oral steroids, methotrexate use, leflunomide or cyclosporine use, other non-TNF biologic use, hospitalizations, emergency room visits, office visits, and number of distinct drugs, and age (updated every year in the study).

† IPTW were truncated at the 1st percentile (0.53) and 99th percentile (1.85). Mean (SD) of the weights were 0.97 (0.19) after truncation.

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Abstract Number: 911

Patients with Rheumatoid Arthritis Are at Increased Risk of Both Ischemic and Non-Ischemic Heart Failure

Ängla Mantel[1], Marie Holmqvist[1], Daniel Andersson[2,3], Lars Lund[2,3] and Johan Askling[4,5], [1]Dept of Medicine, Clinical Epidemiology Unit, Dept of Medicine, Karolinska Institutet, Stockholm, Sweden, [2]Department of medicine, Karolinska Institutet, Cardiology Unit, Dept of Medicine, Karolinska Institutet, Stockholm, Sweden, [3]Karolinska university hospital, Cardiology Unit, Karolinska University Hospital, Stockholm, Sweden, [4]Rheumatology Unit, Rheumatology Unit, Karolinska University Hospital, Stockholm, Sweden, [5]Clinical Epidemiology Unit, Department of Medicine, Karolinska Institutet, Stockholm, Sweden

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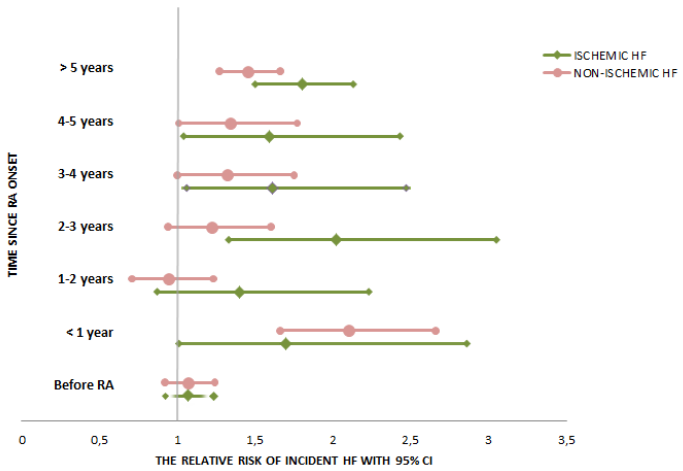
Background/Purpose: Studies among unselected patients with rheumatoid arthritis (RA) suggest increased risks of both ischemic and non-ischemic heart failure (HF). Since the risk of these two subtypes of HF have not been assessed simultaneously within the same cohort of RA-subjects, let alone in relation to time before/after RA diagnosis, the objectives of this study were to assess the relative risk (RR) of HF by subtype and to determine RR in different time periods since RA onset, in one and the same cohort.

Methods: We identified all subjects above 18 years of age with incident RA within the *Swedish Rheumatology Quality register (SRQ)*. All RA subjects were matched with up to 10 general population comparator subjects based on sex, age, and area of residency. The date of diagnosis was defined as the index-date; comparators received the same index-date as their corresponding RA patient. Ischemic HF was defined on the basis of ICD codes from linkage to the nationwide Patient Register as i) a diagnosis of any HF after a diagnosis of IHD or ii) a main diagnosis of ischemic HF, and was investigated in all subjects free of any HF at the index-date. Non-ischemic HF was defined as a diagnosis of HF in individuals without prior IHD-diagnosis, and was assessed in all subjects free of HF at index date and free of IHD by the date of the HF outcome. Study subjects were followed from the index-date until Dec 31st 2012 and censored at death, first migration, IHD and ischemic HF (when the outcome was non-ischemic HF), and HF (without antedating IHD) when the outcome was ischemic HF. Crude rates were calculated and presented as numbers of events per 1,000 person-years. As a measure of the RR of HF, hazard ratios (HRs) were obtained using cox regression models, and odds ratios were calculated using logistic regression as a measure of RR prior to the index-date.

Results: In total**,** 15,572 RA subjects and 132,018 comparators were free of HF at the index-date, and 14,581 RA subjects and 12,4406 comparators were free of both HF and/or IHD at index date. During follow-up 566 (6.7/1000 person-years) RA subjects and 3413 (4.5/1000 person-years) comparators developed a first non-ischemic HF, corresponding to a 40% risk increase for the RA subjects (HR 1.43 [95% CI 1.30-1.56]). 259 (2.9/1000 person years) RA subjects and 1,254 (1.6/1000 person-years) comparators developed ischemic HF during the follow-up, translating into an 80% risk increase for the RA subjects (HR 1.77 [95% CI 1.55-2.03]). For both HF subtypes, stratification by sex did not reveal any differences between sexes, HRs were higher for RF-positive compared to RF-negative patients. For both subtypes, the RR went from null prior to the index-date to increased risks soon after start of follow-up.

Conclusion: RA is associated with an increased risk of both ischemic and non-ischemic HF. Differences in when and how, in relation to RA onset the risks develop may suggest that several mechanisms mediate HF risks in RA.

Figure 1. The relative risk of subtypes of HF within different time periods since RA onset.



Disclosure: Mantel, None; **M. Holmqvist**, None; **D. Andersson**, None; **L. Lund**, None; **J. Askling**, None.

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Abstract Number: 912

Secondary Preventive Pharmacotherapy and Longterm Outcomes Following Acute Coronary Events in Patients with Prevalent Rheumatoid Arthritis

Ängla Mantel[1], Marie Holmqvist[1], Tomas Jernberg[2], Solveig Wållberg-Jonsson[3] and Johan Askling[4,5], [1]Dept of Medicine, Clinical Epidemiology Unit, Dept of Medicine, Karolinska Institutet, Stockholm, Sweden, [2]Section of Cardiology, Department of medicine, Karolinska University Hospital, Stockholm, Sweden, [3]Rheumatology, Institution of Public health and clinical medicine/ Rheumatology, University of Umeå, Umeå, Sweden, [4]Rheumatology Unit, Rheumatology Unit, Karolinska University Hospital, Stockholm, Sweden, [5]Clinical Epidemiology Unit, Department of Medicine, Karolinska Institutet, Stockholm, Sweden

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SESSION INFORMATION

Session Date: Sunday, November 8, 2015

Session Title: Epidemiology and Public Health I: RA Comorbidities and Mortality

Session Type: ACR Concurrent Abstract Session

Session Time: 2:30PM-4:00PM

Background/Purpose: Suboptimal use of secondary preventive pharmacotherapies after acute coronary syndrome (ACS) in patients with rheumatoid arthritis (RA) has been suggested to contribute to an increased risk of deaths and recurrent events following ACS. The objectives of this study were therefore to investigate whether (i) use of secondary preventive pharmacotherapies, (ii) long term mortality risk and (iii) risk of recurrent ACS after incident ACS differ in patients with prevalent RA and compared to general population comparators.

Methods: Using the Swedish national patient register, patients with prevalent RA and matched general population comparators with incident ACS between 2007 and 2010 were identified. After the ACS, information on dispensed secondary preventive drugs (antiplatelets, β-blockers, statins and RAS-blockers) was retrieved from the prescribed drug register and analyzed during 4 consecutive time periods the year following the ACS. Information on deaths and recurrent ACS was also retrieved and analyzed at 1 year and complete follow-up period, until the end of 2011, using cox regression models stepwise adjusted for preexisting comorbidities and ACS-type.

Results*:* 1135 (0.9%) of the RA-patients and 3184 (0.5%) of the comparators were listed with an incident ACS between 2007 and 2010 and remained eligible for analysis as exposed cases (RA-cases) and unexposed cases (Population-cases) . Among cases diagnosed with transmural myocardial infarction (MI), there were no differences in dispensed drugs within any of the time periods studied. Among RA-cases diagnosed with subendocardial and unspecific MI, the proportion dispensed antiplatelets were lower compared to population-cases within the first two time periods studied, but during the last two time periods these discrepancies disappeared. RA-cases had higher case-fatality rates the year following the ACS and during the complete follow-up period. The relative mortality risk was increased by 60% at 1 year (HR1.59 [95% CI 1.39-1.82]) and 70% during the complete follow-up period (HR 1.73 [95% CI 1.55-1.93]). RA-cases also had higher recurrence rates at 1 year and during the complete follow-up period, corresponding to an increased relative risk of approx. 30% (1 year HR 1.35 [95% CI 1.09-1.68]; Follow-up HR 1.34 [95% CI 1.12-1.60]), which remained stable after adjusting for previous comorbidities and infarct-type.

Conclusion: Despite similar usage of secondary preventive pharmacotherapies, patients with prevalent RA suffer increased risk of recurrent events and death after ACS compared to general population comparators.

Figure 1. Kaplan-Meier survival curves from time of Acute coronary Syndrome.

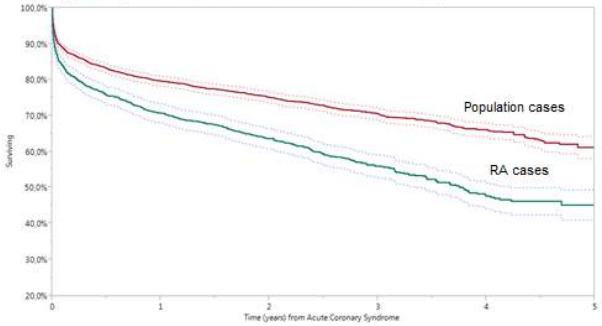
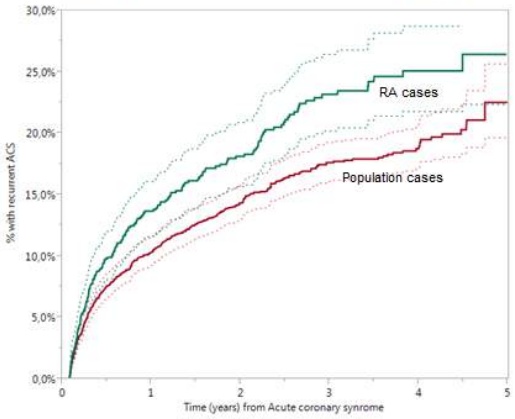


Figure 2. Recurrent ACS among RA-cases and population-cases with incident ACS.



Disclosure: Mantel, None; **M. Holmqvist**, None; **T. Jernberg**, None; **S. Wållberg-Jonsson**, None; **J. Askling**, None.

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Abstract Number: 913

A Comparison of Physician Based and Patient Based Criteria for the Diagnosis of Fibromyalgia

Frederick Wolfe[1], Mary-Ann Fitzcharles[2], Don Goldenberg[3], Winfried Häuser[4], Robert S. Katz[5], Philip J. Mease[6], Anthony Russell[7], Jon Russell[8] and Brian Walitt[9], [1]National Data Bank, Wichita, KS, [2]MGH, Montreal, QC, Canada, [3]Newton-Wellesley Hospital, Newton, MA, [4]Department of Psychosomatic Medicine and Psychotherapy, Technische Universität München, Munich, Germany, [5]Rush University Medical Center, Chicago, IL, [6]Department of Rheumatology, Swedish Medical Center and University of Washington, Seattle, WA, [7]Medicine, University of Alberta, Edmonton, AB, Canada, [8]Fibromyalgia Research and Consulting, San Antonio, TX, [9]National Institutes of Health, National Institute of Nursing Research, Bethesda, DC

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SESSION INFORMATION

Session Date: Sunday, November 8, 2015

Session Title: Fibromyalgia: Insights Into Diagnostic Criteria and Symptom Epidemiology

Session Type: ACR Concurrent Abstract Session

Session Time: 2:30PM-4:00PM

Background/Purpose: The American College of Rheumatology (ACR) 2010 preliminary criteria for the diagnosis of fibromyalgia requires ascertainment of pain extent and symptoms by physicians. The 2011 ÒsurveyÓ or ÒresearchÓ criteria modified the 2010 requirements by ascertaining criteria items entirely by patient self-report. Various concerns have been raised about potential problems with validity and reliability of the 2011 criteria. We used previously unreported patient data collected simultaneously from 514 patients in the ACR 2010 criteria study to compare physician based (MD) (2010) and patient based (PT) (2011) criteria.

Methods: From the 2010 study, we used data collected separately by physicians and patients for the widespread pain index (WPI), the symptom severity scale (SS), polysymptomatic distress scale (PSD) scale, and for fibromyalgia diagnosis using 2010 and 2011 study rules. A physician tender point count and determination of fibromyalgia by 1990 ACR criteria was also evaluated.

Results: The tender point count was strongly associated with the MD PSD scale (r=0.779) and PT PSD scale (r=0.702). Similar associations were noted with the MD WPI (r=0.751) and PT WPI (r=0.672). The area under the receiver operating curve (ROC) between tender point count and MD and PT diagnosis of fibromyalgia was 0.893 and 0.855. The MD and PT diagnostic agreement was substantial (83.4%, kappa = 0.67. PSD scores differed slightly: 12.3 (SD 7.7) for MD and 12.8 (SD 7.8) by PT, a difference of 0.42 units (p=0.213). The Bland-Altman 95% limits of agreement (LOA) for PSD was -8.5 and 7.7, with a standard error of the measurement of 2.9, and bias of -0.42 (Figure 1) [N.B. We will actually use Figure 2, below, for this ACR abstract].

Conclusion: MD and PT diagnosis and criteria items were strongly associated with tender points. Overall, there was good agreement in MD (2010) and PT (2011) fibromyalgia diagnosis and other measures. The low bias scores indicate consistent results for the physician and patient measures, but the large values for LOA indicate many widely discordant pairs. FM diagnostic agreement is greatest at high and low values of PSD, but becomes more uncertain as the 12-13 border line for diagnosis approaches There is acceptable agreement in diagnosis and PSD for research, but insufficient agreement for clinical decisions and diagnosis. If questionnaires are used to obtain clinical data for patient diagnosis, we recommend adjudication of symptom data by patient and physicians, as recommended by the 2010 ACR criteria.

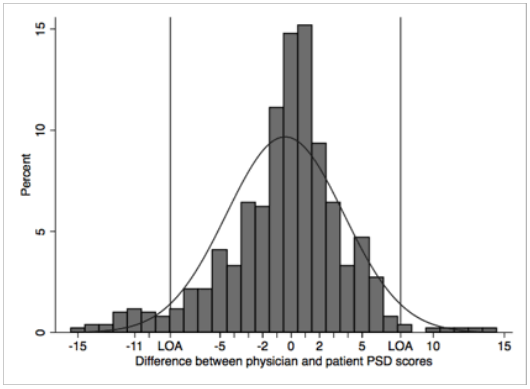

Figure 1. Bland-Altman 95% Limits of Agreement (LOA) histogram. Mean difference (bias) is -0.42, Although PSD difference is close to 0, lack of agreement at individual physician-patient level is evident.

Disclosure: F. Wolfe, None; **M. A. Fitzcharles**, Amgen, 5,Abbott Laboratories, 5,Lilly, 5,Bristol-Myers Squibb, 5,Purdue Pharma L.P., 5,Lilly, 8,Johnson & Johnson, 8,Janssen Pharmaceutica Product, L.P., 8,Pfizer Inc, 5,Johnson & Johnson, 5,Janssen Pharmaceutica Product, L.P., 5,Abbvie, 9; **D. Goldenberg**, Pfizer Inc, 5,Pfizer Inc, 6; **W. Häuser**, None; **R. S. Katz**, None; **P. J. Mease**, None; **A. Russell**, None; **J. Russell**, Pfizer Inc, 2,Lilly, 2,Theravance, 2; **B. Walitt**, None.

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Abstract Number: 914

When Fibromyalgia Criteria Misclassify

Frederick Wolfe[1] and Winfried Häuser[2], [1]National Data Bank, Wichita, KS, [2]Department of Psychosomatic Medicine and Psychotherapy, Technische Universität München, Munich, Germany

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Background/Purpose : The 2010 American College of Rheumatology (ACR) preliminary criteria for the diagnosis of fibromyalgia (FM2010) and its extension for clinical research by patient self-report questionnaire (FM2011) broke with previous 1990 criteria (ACR1990) by eliminating tender points, but also by eliminating the requirement that pain be widespread (4 quadrant + axial) (WSP). By changing the definition of fibromyalgia (FM), the 2010 and 2011 criteria created an expected and natural discordance with the 1990 criteria. In addition, some researchers indicated that elimination of WSP could lead to misclassification by including cases that did not have generalized pain (ACR1990 regions = 5) into the FM definition; and thereby introducing bias favoring psychological symptoms. In the ACR 2010 criteria paper, WSP was absent in 6%-7% of those with FM.

Methods: From 17,385 mixed rheumatic disease patients, we studied 4,964 (28.6%) who satisfied FM2011 criteria, and we evaluated the presence of WSP, and widespread pain index (WPI) scores (0-19) and the Symptom severity scales (SSS) (0-12). FM is diagnosed when (WPI ≥7 AND SS ≥5) OR (WPI 3–6 AND SS ≥9). We also calculated the number of painful regions (0-5: 4 quadrants + axial) from ACR1990. We determined the proportion of patients meeting FM2011 criteria who did not meet the ACR1990 widespread pain definition

Results: Among patients FM2011 (+) 6.6% did not have WSP. 3.5% those FM2011 (+) who had WPI <7did not have WSP. As shown in Table 1, 93.4% of FM2011 (+) had 5 ACR1990 painful regions; 5,3% had 4, and only 1.3% had <4. For the 0-19 WPI, 7% had scores between 4 and 6. Overall, those not meeting the ACR1990 definition, and those perhaps appropriately (regions = 4) not meeting the criteria, were few.

Conclusion: FM criteria may be used 1) for differential diagnosis in which fibromyalgia is the best clinical diagnosis to explain a patient's symptoms; or 2) for concomitant diagnosis in which the several illness are identified, one of which is fibromyalgia. FM2010 and FM2011 were designed for optimal diagnosis in the setting of usual rheumatic disease presentation and usual clinic prevalence. When used in settings where non-WSP and regional or psychiatric diagnoses are substantially increased, FM criteria will "misclassify" persons. This occurs because there is no reliable gold standard fibromyalgia definition. The solution to this type of misclassification is to use the most appropriate clinical diagnosis (e.g., regional arm pain or rheumatoid arthritis) and indicate the patient also satisfied fibromyalgia criteria. In a general or rheumatic disease clinic setting few people will meet FM2011 criteria without WSP, but most will also have many painful regions.

Table 1. Relation between Widespread Pain index and Widespread Pain Regions (ACR1990) and Fibromyalgia Criteria Status

Widespread Pain Index (WPI)	FM2011 (-)	FM2011 (+)	Widespread Pain Regions	FM2011 (-)	FM2011 (+)
0	2,157	0	0	2,256	0
%	17.4	0	%	18.2	0
1	1,691	0	1	0	0
%	13.6	0	%	0	0
2	1,726	0	2	1,942	4
%	13.9	0	%	15.6	0.1
3	1,610	77	3	1,839	61
%	13.0	1.6	%	14.8	1.2
4	1,421	76	4	2,468	262
%	11.4	1.5	%	19.9	5.3
5	1,199	89	5	3,916	4,637
%	9.7	1.8	%	31.5	93.4
6	996	105			
%	8.0	2.1			

Disclosure: F. Wolfe, None; **W. Häuser**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/when-fibromyalgia-criteria-misclassify

Abstract Number: 915

Defining Pain for Fibromyalgia Criteria: Multi-Site or Widespread? an Analysis of Data from Four UK Population-Based Studies

Gary J. Macfarlane[1], Linda E. Dean[1], Robert Bennett[2], Leslie J. Crofford[3], Abimbola Ayorinde[1], Elisa Fluess[1], Daniel J. Clauw[4], Mary-Ann Fitzcharles[5], Don Goldenberg[6], Eduardo Paiva[7], Roland Staud[8] and Lesley Arnold[9], [1]Musculoskeletal Research Collaboration (Epidemiology Group), University of Aberdeen, Aberdeen, United Kingdom, [2]SN-Office of Research & Development, Oregon Health & Science Univ, Portland, OR, [3]Medicine, Vanderbilt University, Nashville, TN, [4]Anesthesiology, University of Michigan, Ann Arbor, MI, [5]MGH, Montreal, QC, Canada, [6]Newton-Wellesley Hospital, Newton, MA, [7]Sociedade Brasileira de Reumatologia, São Paulo, Brazil, [8]University of Florida, Gainesville, FL, [9]University of Cincinnati, Cincinnati, OH

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Background/Purpose: The 1990 criteria for fibromyalgia (FM) remain the only set approved by the American College of Rheumatology (ACR). They require that pain be both widespread (i.e. occurs in contralateral body quadrants and in the axial skeleton) and have been present for three months. Subsequent preliminary ACR criteria in 2010 and modification for self-report require only that the pain be multi-site. As part of the Analgesic, Anesthetic, and Addiction Clinical Trial Translations, Innovations, Opportunities, and Networks (ACTTION) initiative developing a new taxonomy for pain conditions, we have investigated whether associations with features are stronger in persons with chronic widespread pain (CWP) compared to multi-site pain (MSP).

Methods: We have used four population-based studies conducted in the UK: 1958 Birth Cohort study, EpiFunD, SHAMA and WHeSt. In all studies participants were asked "Have you experienced pain in the past month lasting at least a day" - those responding positively shaded the site(s) of pain on 4-view body manikins and indicated if pain had been present for ≥ 3 months. Manikins were coded for pain at 35 individual sites. We determined the number of pain sites indicated and whether subjects met the ACR 1990 criteria definition of CWP. Information was collected across at least two studies on each of: fatigue (Chalder Fatigue or SF-36 vitality scale), Sleep (Sleep Problem Scale or 2010 modified preliminary ACR criteria question) and mood (General Health Questionnaire, Hospital Anxiety and Depression Scale, PROMIS). Relationships with pain reporting were determined by logistic regression, specifically comparing amongst those with MSP, persons with and without CWP.

Results:

There were a total of 28,789 subjects across studies (mean age 42-55 years; males 43-52% [WHeSt was conducted only in females]). Prevalence of CWP, across studies was 12-17%, and in each study the equivalent prevalence was obtained by defining multi-site pain (MSP) as ≥8 sites. Amongst persons with MSP, the proportion also with CWP varied between 62-72%. Those with CWP were more likely to report sleep problems (SHAMA: $OR_{CWP\ vs.\ no\ CWP}$2.99, 95% CI 1.66-5.38; EpiFunD: 2.26, 1.69-3.02), have depression/high levels of distress (1958 Birth cohort: 1.51, 1.15-1.98; WHeSt 3.00, 95% CI 1.42-6.31; EpiFunD 1.99, 1.32-2.98) and be more likely to report fatigue (SHAMA: OR 2.85, 95% CI 1.54-5.26; WHeSt: 1.23, 0.80-1.88).

Conclusion:

We have found that a definition of MSP as at least 8 (of 35) pain sites consistently results in a similar population prevalence to that of CWP, and that the defined groups are similar but not the same. The results suggest that amongst persons with MSP, those with CWP are significantly more likely to exhibit features typical of fibromyalgia.

Disclosure: G. J. Macfarlane, None; **L. E. Dean**, None; **R. Bennett**, None; **L. J. Crofford**, None; **A. Ayorinde**, None; **E. Fluess**, None; **D. J. Clauw**, Abbott Laboratories, 5,Cerephex, 5,Eli Lilly and Company, 5,Forrest Laboratories, 5,Johnson & Johnson, 5,Merck Pharmaceuticals, 5,Pfizer Inc, 5,Purdue Pharma L.P., 5,Samumed, 5,Theravance, 5,Tonix, 5,UCB, 5,Zynerba, 5,Abbott Laboratories, 6,Cerephex, 6,Eli Lilly and Company, 6,Forest Laboratories, 6,Johnson & Johnson, 6,Merck Pharmaceuticals, 6,Pfizer Inc, 6,Purdue Pharma L.P., 6,Samumed, 6,Theravance, 6,Tonix, 6,UCB, 6,Zynerba, 6; **M. A. Fitzcharles**, Abbvie, 5,Amgen, 5,Janssen Pharmaceutica Product, L.P., 5,Bristol-Myers Squibb, 5,Johnson & Johnson, 5,Janssen Pharmaceutica Product, L.P., 8,Eli Lilly and Company, 8,Johnson & Johnson, 8; **D. Goldenberg**, Pfizer Inc, 5,Pfizer Inc, 6; **E. Paiva**, Pfizer Inc, 8; **R. Staud**, None; **L. Arnold**, Pfizer Inc, 2,Eli Lilly and Company, 2,Forest Laboratories, 2,Daiichi Pharmaceutical Co, 2,Theravance, 2,Tonix, 2,Pfizer Inc, 5,Forest Laboratories, 5,Daiichi Pharmaceutical Co., 5,Theravance, 5,Innovative Med Concepts, 5,Ironwood, 5,Zynerba, 5,Pfizer Inc, 8.

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Abstract Number: 916

Assessing Alternative Selection Criteria for Fibromyalgia Patients within a Multicenter Chronic Pain Claims Database

Mark Gostine[1], Fred Davis[1], Bradley Roberts[2], Rebecca Risko[2], Joseph Cappelleri[3], Michael Asmus[4], **Andrew Clair**[5] and Alesia Sadosky[6], [1]Michigan Pain Consultants, PC, Grand Rapids, MI, [2]ProCare Systems, Inc., Grand Rapids, MI, [3]Biostatistics, Pfizer, Inc., Groton, CT, [4]North American Medical Affairs, Pfizer, Inc., Middleton, WI, [5]Pfizer Inc., New York, NY, [6]Pfizer Inc,, New York, NY

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Session Type: ACR Concurrent Abstract Session

Session Time: 2:30PM-4:00PM

Background/Purpose: Diagnosing FM is difficult because there is no specific laboratory test to confirm the disorder. Billing practices dictate that physicians assign ICD-9-CM (Corresponding International Classification of Diseases, Ninth Revision, Clinical Modification) codes based on the procedure for which they use to treat patients. Since FM pain encompasses many regions of the body and associated problems, physicians

commonly do not assign 729.1. Instead, patients may receive an ICD-9-CM code based on a procedure performed for pain relief, or some other diagnosis commonly associated with a symptom of FM. One of the objectives of this study was to develop a method to identify FM patients who do not meet the inclusion criteria of the 729.1 diagnosis assigned at least twice in a span greater than 12 months apart.

Methods: The FM predictive model was developed using different techniques. Among the 9,758 patients, there were 183,540 patient touch points, defined as a distinct time for which information could be obtained from the patient (Physician Health Assessment (PHA) questionnaire, office visits, medication prescriptions, and surgeries). Over 150 possible predictors were entered into a random forest as a second step for variable reduction. In place of the FM ICD-9-CM code, patients were required to have some type of procedure or visit within the same time frame. A logistic regression model identified the four predictors: musculoskeletal procedures, total unique medications, total unique diagnoses, and days between touch points. The model was validated by using *10*-fold cross validation. Propensity score 1:1 matching based on gender, age, length of treatment, and physician was then used to identify a control group of non-malignant chronic pain but without FM group. A two-sample *t*-test was used to assess differences between cases and controls for patient variables including total number of procedures, diagnoses, medications, and days between touch points.

Results: There were 15 diagnoses highly associated with FM that were distinguished by moderate to large effect sizes (Cohen's $d > 0.5$). The diagnoses included chronic pain syndrome, latex allergy, muscle spasm, fasciitis, cervicalgia, thoracic pain, shoulder pain, rheumatoid arthritis, cervical disorders, cystitis, cervical degeneration, anxiety, joint pain, lumbago, and cervical radiculitis. There was a significant association between FM patients and the region where they receive procedures. Specifically, FM patients are more than four times as likely to receive a procedure in the shoulder (3.55, 5.67) or neck (3.50, 5.02) as non-malignant chronic pain patients. Overall, FM patients are more likely to receive more procedures encompassing six of the seven regions used for analysis: shoulder, neck, arm, chest, knee, thoracic area (all $p < 0.05$).

Conclusion: The predictive model allows a larger selection of FM patients and, by doing so, may assist in accurately targeting more patients for appropriate treatment. This project gives new insights into the diagnosis, co-morbidities, and treatments associated with FM patients in a pain management setting.

Disclosure: M. Gostine, Pfizer, Inc. 235 E 42nd Street, New York, NY, 2; **F. Davis**, Pfizer, Inc., 235 E 42nd St., New York, NY, 2; **B. Roberts**, ProCare Systems, Inc., 3; **R. Risko**, ProCare Systems, Inc., 3; **J. Cappelleri**, Pfizer Inc, 3; **M. Asmus**, Pfizer, Inc., 235 E 42nd Street, New York, NY, 3; **A. Clair**, Pfizer Inc, 1,Pfizer Inc, 3; **A. Sadosky**, Pfizer Inc, 3,Pfizer Inc, 1.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/assessing-alternative-selection-criteria-for-fibromyalgia-patients-within-a-multicenter-chronic-pain-claims-database

Abstract Number: 917

Chronic Widespread Pain in Adolescents Is Highly Associated to Stress and Anxiety

Stefan Bergman[1,2,3], Ann Bremander[1,3,4], Anna-Carin Bergman[5] and Sofia Brorsson[6], [1]FoU Spenshult, Halmstad, Sweden, [2]Primary Health Care Unit, Department of Public Health and Community Medicine, The Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden, [3]Department of Clinical Sciences, Lund, Section of Rheumatology, Lund University, Lund, Sweden, [4]School of Business, Engineering and Science, Halmstad University, Halmstad, Sweden, [5]Sannarpsgymnasiet, Halmstad, Sweden, [6]Health and Welfare, Dalarna University, Falun, Sweden

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Session Type: ACR Concurrent Abstract Session

Session Time: 2:30PM-4:00PM

Background/Purpose: Chronic widespread pain (CWP), one of the hallmarks of fibromyalgia, is not uncommon in adolescents and it has previously been shown that adolescents with pain often become young adults with pain. CWP often co-varies with anxiety, depression, and stress symptoms in adults, but the knowledge regarding this is small in youth and young adults.

The aim was to study the associations between CWP, anxiety, depression and stress in adolescents attending first year of high school.

Methods: A computerized questionnaire to 296 adolescents attending Swedish high school, with validated questions regarding presence and distribution of pain (Epipain mannequin), stress symptoms (ELO question), anxiety and depression (Hospital Anxiety and Depression Scale – HADS), and health related quality of life (HRQL as measured by EQ5D). Pain was considered chronic when persistent for more than three months, and the subgroup CWP was defined according to the 1990 ACR criteria for fibromyalgia. Statistical analyses in SPSS v21 with comparison of means by Student's t-test and proportions by chi2-test or Fischer's exact test.

Results: 257 (87%) out of 296 eligible students, mean (SD) age 16.1 (0.7) and 65.8% girls, responded to the questionnaire. Prevalence of chronic pain was 20.8% and that of the subgroup CWP was 4.7%, without any gender differences (boys 18.2% vs girls 22.2%; p=0.224, and 3.4% vs 5.4%; p=0.692). High level (4 or 5 on a 5 point scale) of stress symptoms were less common in boys (16.0% vs 28.2%; p=0.015), as

was possible or probable anxiety (17.1% vs 44.4%; p<0.001), but not depression (10.3% vs 12.5%; p=0.764). Students with high level of stress reported CWP five times more often than those with less stress (30.4% vs 5.8%; p=0.001). Students with probable anxiety reported CWP ten times more often than students with no anxiety (17.6% vs 1.8%; p=0.001), and CWP was also more common, but not statistically significant, in students with probable depression (20.0% vs 3.1%; p=0.163). Those reporting CWP had significantly lower HRQL (0.58 vs 0.87; p=0.038) than students with no chronic pain.

Conclusion: The high prevalence of chronic pain and the strong associations between CWP and reports of stress and anxiety in adolescents highlights that a multifactorial background to chronic pain must be considered early in life. An apparent lower score in EQ5D also indicates that the presence of CWP has an marked impact on HRQL also in adolescents.

Disclosure: S. Bergman, None; **A. Bremander**, None; **A. C. Bergman**, None; **S. Brorsson**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/chronic-widespread-pain-in-adolescents-is-highly-associated-to-stress-and-anxiety

Abstract Number: 918

Assessment of the Temporal Variation of the Fibromyalgia Patient Profile Between 2005 and 2013: Do Guidelines Inform Clinical Care?

Angeliki Karellis[1,2], Emmanouil Rampakakis[1], Peter A. Ste-Marie[3], Yoram Shir[3], John S. Sampalis[1,4] and **Mary-Ann Fitzcharles**[3,5], [1]JSS Medical Research, St-Laurent, QC, Canada, [2]Department of Surgery, McGill University, Montreal, QC, Canada, [3]Alan Edwards Pain Management Unit, McGill University Health Centre, Montreal, QC, Canada, [4]McGill University, Montreal, QC, Canada, [5]Division of Rheumatology, McGill University Health Centre, Montreal, QC, Canada

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Background/Purpose:

In the last decade, interest in fibromyalgia (FM) has increased with the publication of revised diagnostic criteria and clinical guidelines. The 2010 and revised 2011 ACR criteria emphasized the polysymptomatic nature of FM. National FM guidelines (Germany, Canada & Israel) showcased the importance of sustained functionality, multimodal therapy ideally targeting the primary symptom/s and cautioned the likely modest effect for most drug treatments. Whether recommendations influenced clinical care remains speculative. We examined the profile and clinical care of FM Canadian patients in two time periods to assess the effect of this paradigm change.

Methods:

FM patients followed prospectively at a Montreal university based tertiary care pain clinic from 2005 to 2013 were recruited. Disease severity was measured with pain visual analog scale (VAS), patient global assessment (PGA), McGill Pain Questionnaire (MPQ), Pain Disability Index (PDI), Pain Catastrophizing Scale (PCS), Fibromyalgia Impact Questionnaire (FIQ), Health Assessment Questionnaire (HAQ) and Arthritis Impact Measurement Scales (AIMS) the latter including anxiety and depression subscales. Differences between enrolment period groups (2005-08 vs 2009-13) were assessed for statistical significance with the chi-square test for categorical variables and the independent-samples t-test for continuous variables.

Results:

Table 1 presents the profile of 248 FM patients stratified by enrolment period: 147 patients in 2005-08 and 101 patients in 2009-13. The mean ± SD age of patients was 47.9 ± 10.3 years (2005-08 vs 2009-13: 49.3 ± 9.71 vs 45.9 ± 10.94; p=0.012). The majority (91.1%) of patients were female (p=0.179). Mean ± SD disease duration was 10.8 ± 9.80 years (p=0.851). Significant between-group differences (2005-08 vs 2009-13) of mean ± SD scores were observed for PDI (36.1 ± 15.10 vs 40.0 ± 13.21; p=0.036), FIQ (65.1 ± 18.24 vs 69.8 ± 14.18; p=0.029) and AIMS depression (5.1 ± 1.64 vs 4.5 ± 2.05; p=0.005). Statistical trends were observed in regard to medication use: 2005-08 patients used more analgesics (24.5% vs 15.8%; p=0.114) and NSAIDs (26.5% vs 17.8%, p=0.126) but less antiepileptics (27.9% vs 38.6%, p=0.097). Exercise activity was more prevalent among 2009-13 patients (23.8% vs 39.6%; p=0.011). The 2009-13 group had lower disability rates (39.5% vs 18.8%; p=0.001), higher employment rates in manual and service areas (37.2% vs 16.3%) and lower rates in health care or educational areas (31.9% vs 58.1%) (p<0.001).

Conclusion: FM patient profile changes in the past decade may have been informed by recent guidelines. Despite similar pain durations at presentation and generally greater symptom severity, FM management has trended away from traditional analgesic medication use. Maintained

function with more patients employed and participating in exercise activity reflects the evolving concept of FM care.

Table 1 Clinical Features of FM Patients According to Enrolment Period

Parameter	Enrolment Period		P-value	Total
	2005 - 2008	2009 - 2013		
Age, years, mean ± SD	49.3 ± 9.71	45.9 ± 10.94	**0.012**	47.9 ± 10.3
Gender				
Female (%)	93.2	88.1	0.179	91.1
Male (%)	6.8	11.9		8.9
Marital Status				
Single (%)	21.1	23.7	0.720	22.1
Married (%)	62.6	62.9		62.7
Divorced (%)	11.6	11.3		11.5
Widowed (%)	4.8	2.1		3.7
Education level				
Less than high school (%)	44.2	34.3	*0.128*	40.2
College (%)	29.3	41.4		34.1
University (%)	26.5	24.2		25.6
Employment Status				
Employed or Unemployed due to other reasons (%)	60.5	81.2	**0.001**	69.0
Disabled (%)	39.5	18.8		31.0
Type of Occupation				
Manual or Service (%)	37.2	16.3	**0.012**	31.4
Education, Health, Office, Professional or Student (%)	62.8	83.7		68.6
Analgesic use (%)	24.5	15.8	*0.114*	21.0
NSAID use (%)	26.5	17.8	*0.126*	23.0
Antiepileptic use (%)	27.9	38.6	*0.097*	32.3
Tricyclic antidepressant use (%)	23.1	18.8	0.435	21.4
Other antidepressant use (%)	40.1	49.5	0.154	44.0
Alternative product use (%)	4.8	5.9	0.775	5.2
Medication count, mean ± SD	2.3 ± 1.39	2.1 ± 1.58	0.493	2.2 ± 1.47
Chiropractor/ osteopath/ massage (%)	17.0	11.9	0.283	14.9
Acupuncture (%)	6.1	2.0	0.208	4.4
Exercise (%)	23.8	39.6	**0.011**	30.2
Physiotherapy (%)	10.9	10.9	>0.999	10.9
Alternative medicine (%)	4.8	6.0	0.774	5.3
Pain duration, mean ± SD	10.9 ± 9.71	10.7 ± 9.97	0.851	10.8 ± 9.80
Pain VAS, mean ± SD	6.4 ± 2.33	6.7 ± 2.22	0.299	6.5 ± 2.3
PGA, mean ± SD	6.5 ± 2.42	6.7 ± 1.94	0.439	6.6 ± 2.24
MPQ, mean ± SD	41.5 ± 15.87	39.8 ±14.32	0.394	40.8 ± 15.25
PDI, mean ± SD	36.1 ± 15.10	40.0 ± 13.21	**0.036**	37.7 ± 14.46
PCS, mean ± SD	29.3 ± 12.19	29.6 ± 12.26	0.836	29.4 ± 12.20
FIQ, mean ± SD	65.1 ± 18.24	69.8 ± 14.18	**0.029**	67.0 ± 16.83
HAQ, mean ± SD	1.1 ± 0.67	1.1 ± 0.64	0.652	1.1 ± 0.66
AIMS anxiety, mean ± SD	6.2 ± 1.86	6.6 ± 1.80	*0.086*	6.3 ± 1.85
AIMS depression, mean ± SD	5.2 ± 1.64	4.5 ± 2.05	**0.005**	4.9 ± 1.84

AIMS, Arthritis Impact Measurement Scales; FIQ, Fibromyalgia Impact Questionnaire; HAQ; Health Assessment Questionnaire; MPQ, McGill Pain Questionnaire; NSAID, nonsteroidal anti-inflammatory drug; PCS, Pain Catastrophizing Scale; PDI, Pain Disability Index; PGA, patient global assessment; VAS, visual analog scale.

Statistically significant ($p<0.05$) results in bold; statistical trends ($p<0.15$) in italic.

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Abstract Number: 919

Automated Case Identification of Lupus from an Electronic Health Record Using Novel Informatics Approaches

Sara G. Murray[1], Chris Tonner[2], Ben J. Marafino[3], Sarah Haserodt[4], Gabriela Schmajuk[5] and Jinoos Yazdany[3], [1]Medicine, University of California, San Francisco, San Francisco, CA, [2]Rheumatology, University of California, San Francisco, San Francisco, CA, [3]University of California, San Francisco, San Francisco, CA, [4]Internal Medicine, California Pacific Medical Center, San Francisco, CA, [5]San Francisco VA Medical Center, University of California, San Francisco, San Francisco, CA

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Background/Purpose: Systemic lupus erythematosus (SLE) can be difficult to study given the relatively low prevalence of the disease. While we are now collecting a multitude of data in the electronic health record (EHR) that can be used to answer important research questions, there are no validated algorithms for SLE case-identification. In this study, we aimed to establish an algorithm to identify individuals with SLE from an EHR. We compared algorithms using structured terminologies for SLE with those based on novel machine learning (ML) algorithms that are capable of analyzing clinical free text in conjunction with structured data.

Methods: We created a data repository of "possible SLE" by extracting structured EHR data and clinical notes for patients who either had a relevant ICD-9 code OR positive dsDNA or Smith antibodies OR a mention of "SLE" or "lupus" in the text of clinical notes. We identified 18,357 individuals meeting this criteria, and selected 300 patients for review: 150 randomly and 150 enriched for positive serologies (to capture enough true SLE for ML). Via chart review performed by domain experts, we identified definite SLE cases as patients with ≥4 documented American College of Rheumatology (ACR) criteria. Next, we calculated the test characteristics for various definitions of SLE using only structured data. Finally, we compared this to a series of supervised ML algorithms based on support vector machines (SVMs) which used text features extracted from clinical notes in addition to structured fields. All SVM algorithms were trained and validated using 10-fold cross-validation.

Results: 121 of 300 patients reviewed met ACR criteria for SLE. The test characteristics of both the structured and supervised ML algorithms are shown in the Table. While a single ICD-9 code for 710.0 was near 100% sensitive for a diagnosis of SLE, additional criteria including a SLE-related medication and any positive serology increased the specificity with minimal loss in sensitivity (94%). ML algorithms slightly outperformed traditional definitions. The text features extracted from clinical notes that were strong predictors of SLE are graphically represented in the Figure.

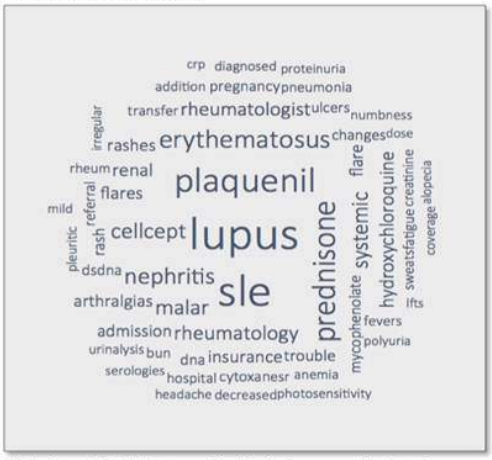
Conclusion: In an EHR-based data repository, a single ICD-9 710.0 was highly sensitive for SLE. ML algorithms processed a multitude of structured and unstructured EHR data, allowing increased specificity with minimal loss in sensitivity. These findings should be validated in other cohorts to lay the foundation for multi-institutional lupus research and creation of large national registries.

Table. Performance of traditional structured definitions and supervised machine learning algorithms in case identification of SLE in the electronic health record.

Structured Definitions				Supervised Machine Learning			
	Recall (Sensitivity)	Specificity	Precision (PPV)		Recall (Sensitivity)	Specificity	Precision (PPV)
Single ICD-9 710.0	1.00	0.72	0.71	All ICD-9 codes and counts[1]	1.00	0.72	0.71
Single ICD-9 710.0 + any lupus medication	0.97	0.80	0.77	All ICD-9 codes and counts + clinical notes[2]	0.98	0.76	0.74
Single ICD-9 710.0 + any lupus medication + any positive lupus serology	0.94	0.82	0.78	All ICD-9 codes and counts + clinical notes + all serologic data[3] + all medication data	0.99	0.84	0.78
				All ICD-9 codes and counts + clinical notes + all serologic data + all medication data + demographics[4]	0.90	0.94	0.82

[1]Supervised machine learning (ML) algorithms included all available ICD-9 codes for patients as well as counts and locations in the medical record in which they were found (clinical encounters, problem lists, medication orders, etc.).
[2]All free text data from clinical notes associated with a patient's medical record were included in the ML algorithm.
[3]Serologic data included ANA and antibodies to dsDNA, Smith, RNP, SSA and SSB.
[4]Demographic information included age, gender, race/ethnicity, insurance status, and employment status.

Figure. Word cloud of text data-elements that predict of a diagnosis of lupus in clinical notes extracted from the electronic health record.



*Text elements listed above were identified using our machine learning algorithms with the addition of penalization to restrict the predictor set so that it included only the most relevant text features. Size is directly proportional to weights identified by these algorithms.

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Abstract Number: 920

Patient Preferences for the Development of a Mobile Health (mHealth) Application (App) for Systemic Lupus Erythematosus (SLE) Patients: A Qualitative Study

Alana B. Levine[1], Adena Batterman[2], VP Bykerk[1], Aislinn Crank[3], Su Jin Kim[4], Juliette Kleinman[5], Laura Leuenberger[1], Laura Robbins[6], Jillian A. Rose[3], Jane E. Salmon[1,3], Nadine Spring[1], My-Lan Tran[7] and Roberta Horton[2], [1]Rheumatology, Hospital for Special Surgery, New York, NY, [2]Social Work Programs, Hospital for Special Surgery, New York, NY, [3]Hospital for Special Surgery, New York, NY, [4]School of Social Work, Columbia University, New York, NY, [5]Patient Care & Quality, Hospital for Special Surgery, New York, NY, [6]Education & Academic Affairs, Hospital for Special Surgery, New York, NY, [7]Department of Social Work Programs, Hospital for Special Surgery, New York City, NY

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Background/Purpose: SLE patients face many challenges due to lupus, including pain, fatigue, managing medications and appointments, and emotional impact. Patients employ various strategies to manage these challenges. mHealth offers the opportunity to improve self-management and self-efficacy and could prove effective in helping SLE patients manage their disease. Patient input is critical to the development of an SLE-specific mHealth tool; our aim was to explore patient preferences and interest related to development of an mHealth app for SLE patients.

Methods: Subjects ≥15 years old who met ACR SLE criteria were recruited from a diverse patient population at a large, urban SLE referral center. A standardized focus group methodology was developed by an expert panel of rheumatologists and social workers. Focus group sessions, moderated by clinical social workers trained in this methodology, were audio recorded, transcribed, and analyzed using NVivo in an iterative process to develop thematic categories. Questions explored challenges due to SLE, current coping strategies, how an SLE app could help with disease self-management, app format and design, and priorities for app content.

Results: 57 subjects participated in 8 focus groups. Participants were mostly female (84%), well-educated (68% had at least some college education), and 46% self-identified as belonging to a minority group. Mean SLEDAI was 3.7 (range 0-10) and mean SLICC-DI was 1.3 (range 0-7). Subjects identified physical manifestations (pain, fatigue, hair loss, change in weight), emotional/psychological issues (stress, frustration, unpredictability of disease, depression), and medications (adherence issues, pill burden) as current challenges in managing lupus; scheduling, exercise, sleep, relaxation, and social networking helped to manage those challenges. Regarding how the app could help, six key themes emerged

(Table): 1) track symptoms, 2) manage medications, 3) manage appointments, 4) communicate with providers, 5) nutrition and exercise tips, and 6) manage emotional/psychological issues. Ease of use, simplicity, and customizability were deemed critical to uptake of the app; finger pain, Raynaud's, denial/avoidance of illness, and technological complexity were identified as potential deterrents to use. 98% of participants said they would use an app to help manage lupus.

Conclusion: Participants were overwhelmingly interested in an mHeatlh app designed to help manage SLE and identified challenges an app could help them manage. These patient-generated themes can be used in platform development and assessment of a lupus-specific mHealth app.

How an App Can Help: Emerging Themes	Selected Illustrative Quotes
1. Track symptoms	[You could record] symptoms for the day, because sometimes when I go to the doctor I don't remember certain symptoms I had during the month and if I have a place to write that down, like how I was feeling certain days, I think it would help.
2. Manage medications	It would be great if you could put in your meds and your doses and time of day and it alerted you like, "Okay, it's time to take something." And then also… we'd get to the doctor and they say, "What have you been taking?" It's like, there.
3. Manage appointments	There are many different aspects of planning…The appointment reminder might be two days before the appointment, because I find that if I don't write it down, I will forget… I need time to process a day or two before.
4. Communicate with providers	Sometimes when we're at the appointment, we sometimes forget what was wrong at that moment, so when [the doctors] ask us a question, we're just like, "Oh, no, no, everything is fine…" and then you leave and remember, "Ok, I should have said this and I should have said that!"
5. Nutrition and exercise recommendations	So…we see what we're getting in terms of diet and what we're eating, how it affects the symptoms, that could be helpful, and it would help everybody.
6. Resources to manage emotional/psychological issues	The initial diagnosis can be very traumatic and I think if you have an app that can guide you through processing those emotions as well as learning how to accept help and communicating effectively what the illness does to you, I think it would be a helpful app.

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Abstract Number: 921

Poverty Associated with Increase in Damage in SLE over Two-Year Period

Edward H. Yelin[1], Laura Trupin[2], Jinoos Yazdany[2] and Stephanie Rush[3], [1]University of California, San Francisco, San Francisco, CA,

[2]Rheumatology, UCSF, SF, CA, [3]UCSF, SF, CA
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Background/Purpose: Prior research has shown that persons with SLE in poverty have fewer physician visits for SLE and receive lower technical quality of care. The current study evaluates the impact of poverty at baseline on longitudinal change in SLE outcomes, including disease activity, accumulated damage, and overall physical health.

Methods: We analyzed data from the UCSF Lupus Outcomes Study, a national sample of persons with SLE interviewed annually using a structured telephone survey. The annual survey collects data to assess whether individuals are ≤ 125% of the Federal poverty level (POV) as well as validated self-reported batteries of disease activity, the Systemic Lupus Activity Questionnaire (SLAQ); accumulated damage, the Brief Index of Lupus Damage (BILD); and the SF36 physical health component (PCS). We used linear regression to analyze the impact of POV in the 2012-2013 LOS annual wave on change in SLAQ, BILD, and PCS between 2012-2013 and 2014-2015. Models were adjusted for age, gender, race/ethnicity, level of educational attainment; disease duration; number of physician visits; kind of health care (public and private managed care or fee-for-service), specialty of physicians for SLE, and quality of care (pass rate of ≥ 85% on technical quality of care indicators vs. not and summary of ratings of interactions with providers and health systems).

Results: 524 persons with SLE responded to the annual LOS interviews in both 2012-2013 and 2014-2015 who had no missing values on variables in analysis; 10 with missing values were omitted from analysis. Mean age was 53.0 ± 12.5 yrs., mean duration was 20.1 ± 8.5 yrs., 36.6% were non-whites, and 12.6% met study definition of POV. In 2012-2013, mean SLAQ was 10.7 ± 7.0; BILD 2.9 ± 2.6; and PCS 39.3 ± 12.1. By 2014-2015, mean change in SLAQ was -0.27 ± 4.21; in BILD was 0.44 ± 0.75; and in PCS was -0.65 ± 7.22. Table 1 shows the unadjusted and adjusted values of the outcome measures by POV and indicates that poverty is associated with increased levels of BILD, but not SLAQ or PCS.

Conclusion: Poverty is associated with an increase in accumulated damage in SLE over two years, an effect only partially explained by sociodemographic and disease characteristics, number of physician visits, and kind, quantity, and quality of health care. Reducing the impact of poverty on damage will require increased attention to factors outside of health care as well as on-going improvements in treatment.

Table 1. Impact of Poverty Status on Change in Disease Activity (SLAQ), Damage (BILD), and Physical Health Status (PCS)

	Change in SLAQ*			Change in BILD**			Change in PCS***		
	Not Poor	Poor	Diff (95% CI)	Not Poor	Poor	Diff (95% CI)	Not Poor	Poor	Diff (95% CI)
Unadjusted	-0.24	-0.50	0.26 (-0.83, 1.36)	0.40	0.73	-0.33 (-0.52,- 0.14)	-0.62	-0.90	0.29 (-1.58, 2.16)
Adjusted‡	-0.98	-1.14	0.16 (-1.05, 1.37)	0.41	0.65	-0.24 (-0.45, -0.04)	0.64	-0. 01	0.65 (-1.40 , 2.70)

* SLAQ scored 0-47, higher scores indicate greater level of disease activity; positive change scores represent more disease activity.

** BILD scored 0-18, higher scores indicate greater level of accumulated damage; positive change scores represent more damage.

*** PCS scored 0-100, higher scores indicate better physical health status; negative change scores represent declining physical health status.

‡ Models adjusted for age, gender, race/ethnicity, educational attainment, disease duration, # MD visits in past year, kind of health care, specialty of SLE physicians, technical quality of care pass rate, and ratings of interactions with health systems and providers.

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View Abstract and Citation Information Online - http://acrabstracts.org/abstract/poverty-associated-with-increase-in-damage-in-sle-over-two-year-period

Abstract Number: 922

Factors Associated with Performance on Quality Measures Pertaining to Assessment of

Disease Activity in Juvenile Idiopathic Arthritis

Lara H. Huber[1,2], Murray H. Passo[3], Kristen Morella[1], **Natasha M. Ruth**[4] and Pediatric Rheumatology Care and Outcomes Improvement Network, [1]Pediatrics, Medical University of South Carolina, Charleston, SC, [2]Rheumatology & Immunology, Medical University of South Carolina, Charleston, SC, [3]Division of Rheumatology PTD, Medical University of South Carolina, Charleston, SC, [4]Pediatric Rheumatology, Medical University of South Carolina, Charleston, SC

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Background/Purpose:

Assessment of disease activity is a critical step in the management of patients with juvenile idiopathic arthritis (JIA). The American College of Rheumatology provisional criteria for clinical inactive disease (CID) are a widely accepted measure of disease activity for JIA. The aim of this study is to determine the frequency at which patients are fully assessed for disease activity using the Pediatric Rheumatology Care and Outcomes Improvement Network (PR-COIN) registry and to identify which component of disease activity is most often not evaluated. We also aim to identify patient and institutional factors associated with assessment of CID.

Methods:

Visits between January 2011 and February 2015 were evaluated for assessment of CID. Full assessment of CID was considered to have been performed if all components of CID were completed. (Table 1) The number of visits with full assessment of CID was calculated as a percentage of the total number of visits. The principal investigator of each PR-COIN site completed a survey regarding institutional characteristics. Hierarchical mixed model logistic regression was used to model full assessment of CID using patient and institutional factors.

Results:

There were 11,249 patient visits; 2,261 visits were excluded due to missing data. Assessment of CID occurred at 47% of patient visits. The component of CID most commonly not evaluated was assessment for uveitis. (Figure 1) Male gender, a positive ANA, and younger age were associated with full assessment of CID. Patients with systemic JIA, RF+ polyarticular JIA, and enthesitis related arthritis were more likely to have been fully assessed for CID. Having a full time coordinator was associated with better performance than having no coordinator. (Table 2)

Conclusion:

Evaluation of CID in patients with JIA does not occur consistently. Assessment for uveitis drives this low performance rate. While younger patients and patients with a positive ANA were more likely to be fully assessed, patients with JIA subtypes at highest risk for uveitis were the least likely to have been assessed for CID and to have had appropriate uveitis screening.

Table 1. Quality Measures Used to Determine Performance of Assessment of CID
1. A full joint count should be done at every visit.
2. A Physician's Global Assessment (PGA) of disease activity should be done at every visit.
3. Either the American Academy of Pediatrics (AAP) or modified Heiligenhaus guidelines for eye examinations should be followed for patients with any category of JIA. Documentation of compliance with the guidelines should be performed at every visit at least 3 months apart.
4. Duration of morning stiffness should be assessed at every visit.
5. The presence of active systemic arthritis features should be assessed at every visit for patients with systemic JIA.

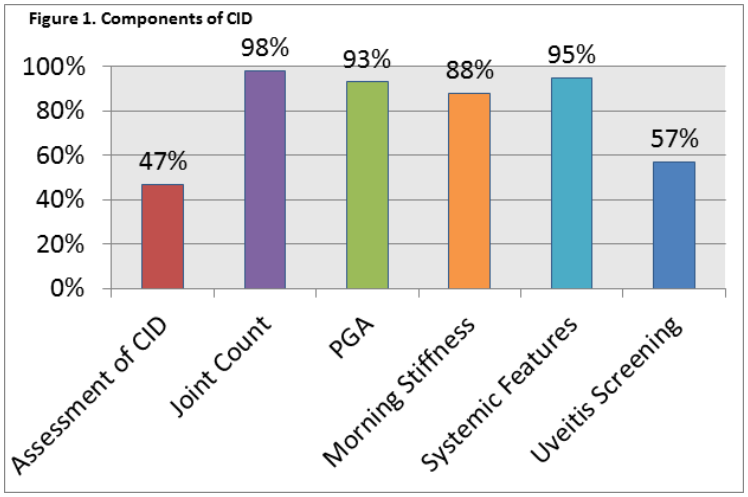

Table 2. Logistic Regression Model				
Variables		p-value	Odds Ratio	95% Confidence Interval
Time (3 month intervals)		0.0043	1.034	1.011 - 1.059
Gender		0.0126		
	Female		0.694	0.521 - 0.925
	Male		Reference	
Age (1 year intervals)		0.0157	0.969	0.945 – 0.994
ANA Status		<0.0001		
	Positive		131.465	90.641 - 190.677
	Negative		Reference	
JIA subtype		<0.0001		
	Systemic JIA		120.192	32.579 - 443.422
	Polyarticular RF (-)		1.911	0.559 - 6.530
	Polyarticular RF (+)		149.778	40.169 - 558.474
	Oligoarticular persistent		2.361	0.686 - 8.120
	Oligoarticular extended		3.007	0.858 - 10.536
	Psoriatic Arthritis		1.684	0.455 - 6.230
	Enthesitis Related Arthritis		95.606	26.163 - 349.370
	Undifferentiated Arthritis		Reference	
% Effort of Coordinator		<0.0001		
	76-100%		5.309	3.287 - 8.572
	26-50%		1.477	0.915 - 2.386
	1-25%		0.655	0.481 - 0.892
	No Coordinator		Reference	
Number of Providers at Institution		<0.0001	1.276	1.197 - 1.360
Pre-Visit Planning		<0.0001	0.359	0.224 - 0.575
Race and Insurance status were evaluated and not found to be significant.				

Disclosure: L. H. Huber, None; **M. H. Passo**, None; **K. Morella**, None; **N. M. Ruth**, None.

Abstract Number: 923

Perceptions of Infectious Risk of Immunosuppressive Medications Among Treating Physicians

Rebecca Sharim[1], Leny Mathew[2], Michael George[3], Preethi Thomas[4] and Misha Rosenbach[5], [1]Rheumatology, Hospital of the University of Pennsylvania, Philadelphia, PA, [2]Children's Hospital of Philadelphia, Philadelphia, PA, [3]Medicine, Hospital of the University of Pennsylvania, Philadelphia, PA, [4]Department of Rheumatology, Hospital of the University of Pennsylvania, Philadelphia, PA, [5]Dermatology, Hospital of the University of Pennsylvania, Philadelphia, PA

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Background/Purpose: Physicians often encounter patients who are treated with immunosuppressive agents and must consider the risk of infection that the medications may pose. We explored physician perceptions of the infectious risk of commonly used immunosuppressive therapies, hypothesizing that they vary by specialty and level of experience.

Methods: All physicians in seven departments at a single tertiary care institution were asked to complete a web-based survey. Data regarding medical specialty, level of experience, years of experience post medical school, frequency of prescribing immunosuppressant medications, and comfort level with issues related to immunosuppressant medications were collected. Respondents were asked to rate medications from 0 to 100 on their perception of the one-year risk of infection attributable to that medication if used as monotherapy. To facilitate comparisons, scores were divided into three groups, with 0 to 33 labeled low risk, 34 to 66 medium risk, and 67 to 100 high risk. Experienced physicians were defined as those with five years of experience post medical school who also reported that they prescribed immunosuppressant medications sometimes or frequently.

Results: The survey was distributed to 634 physicians; 197 physicians completed the survey. There was a significant difference in the median rating between specialties for 8 of 15 medications (Table 1). Compared to less experienced providers, the experienced providers (n=43) generally rated hydroxychloroquine, dapsone, and anti-TNF therapy lower in terms of infection risk (Figure 1). In contrast, 66% of experienced physicians compared to 52% of less experienced physicians rated prednisone 10-20 mg as medium or high risk. The majority of less experienced physicians (55%) identified anti-TNF therapy as high risk, while experienced physician perceptions were split nearly evenly among low (32%), medium (32%), and high risk (37%).

Conclusion: There is wide variability in physician perception of the infectious risk of many immunosuppressive medications by specialty and level of experience. Among experienced physicians who prescribe these agents, level of concern about commonly used therapies such as anti-TNF therapy range broadly. Less experienced physicians may perceive a lower risk of intermediate doses of prednisone and a higher risk of dapsone and hydroxychloroquine compared to more experienced physicians. Resources to better define and communicate the risks of immunosuppressive medications would facilitate better care of patients who require these drugs.

Table 1: Physician Reported Median Scores of Risk of Infection Using a 0 to 100 Visual Analogue Scale

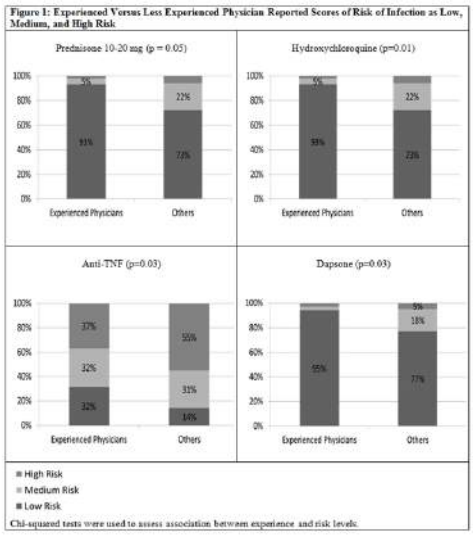
	Derm n=41	EM n=25	FM n=11	ID n=19	IM (O) n=19	IM (I) n=60	Rheum n=22	p value*
Prednisone < 10mg	22	15	16	16	15	18	18	0.91
Prednisone 10-20mg	40	20	44	38	29	35	40	0.53
Prednisone 21-59mg	69	42	73	73	50	70	75	<0.01
Prednisone ≥ 60mg	80	64	93	87	65	83	90	<0.01
Hydroxychloroquine	5	48	25	10	15	25	1	<0.01
Azathioprine	53	60	58	37	50	55	46	0.21
Methotrexate	30	55	34	30	46	52	50	0.02
Mycophenolate	59	70	75	55	59	63	59	0.13
Cyclosporine	62	71	71	62	53	66	57	0.13
Rituximab	52	65	72	60	60	72	70	0.08
Anti-TNF	52	61	85	66	64	79	68	<0.01
Cyclophosphamide	70	65	73	63	51	76	81	<0.01
IVIG	15	32	50	15	15	38	16	0.02
Dapsone	10	24	46	5	10	15	7	0.02
Thalidomide	10	34	33	10	27	40	31	0.08

Visual Analogue Scale was used to answer the question: "For a patient who has been taking each listed therapy as monotherapy regularly for one year (unless otherwise stated), please rate your concern that the patient will develop a medication-related infection within the next year. Please choose a number between 0 and 100, with 0 being "not at all concerned for a medication-related infection in the next year" and 100 being "extremely concerned for a medication-related infection in the next year."

*Median score compared across specialties using Kruskal-Wallis test.

Medication Dosages: prednisone as oral dose daily, hydroxychloroquine 400 mg oral daily, azathioprine 150 mg oral daily, methotrexate 20 mg subcutaneous weekly, mycophenolate mofetil 2 g oral daily, cyclosporine 5 mg/kg oral daily, rituximab 1 g intravenously given twice, 2 weeks apart, within 6 months; anti-TNF therapy at standard dose and frequency, cyclophosphamide 1000 mg intravenously monthly over the past 6 months; Intravenous Immunoglobulin 2g/kg divided over 4 days monthly; dapsone 100 mg oral daily, thalidomide 200 mg oral daily

Specialties: Derm = Dermatology; EM = Emergency Medicine; FM = Family Medicine; ID = Infectious Disease; IM(O) = Internal Medicine, primarily outpatient; IM(I) = Internal Medicine, primarily inpatient; Rheum = Rheumatology



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Abstract Number: 924

Patient and Provider Factors in Optimal Gout Management

Brian Coburn[1], Kayli Bendlin[2], Harlan Sayles[1] and Ted R. Mikuls[1], [1]Omaha VA Medical Center and University of Nebraska Medical Center, Omaha, NE, [2]Pharmacy Service, Veterans Affairs Nebraska-Western Iowa Health Care System, Omaha, NE

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SESSION INFORMATION

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Session Title: Health Services Research I: Digital Health and Patient, Provider Factors in Rheumatic Disease

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Session Time: 2:30PM-4:00PM

Background/Purpose:

Gout is the most common inflammatory arthritis worldwide. Despite its prevalence and the availability of effective therapies, studies have consistently characterized gout quality of care to be suboptimal. Suboptimal care has largely been defined by adverse events or gaps in care while few studies have identified factors to optimize gout care. The objective of this study was to develop a model of modifiable patient and provider factors associated with a well-accepted treatment target in gout, achievement of a serum urate (SU) < 6.0 mg/dL.

Methods:

For this cross-sectional study, we sent a questionnaire to 1437 gout patients receiving an allopurinol prescription during a 1-year period. Of these, 886 (62%) responded and 612 were included for the primary analysis after exclusions. Questionnaire data was linked to medical and pharmacy records. We hypothesized that five patient/provider factors would be associated with SU goal attainment < 6.0 mg/dL. The Patient Activation Measure (PAM^{TM}) was used to measure, on a 0-100 scale, the patient's knowledge, skills and confidence to engage in their own care. The proportion of days covered (PDC) was used to determine allopurinol adherence with a PDC ≥ 0.8 considered adherent. For providers, we considered dose escalation of allopurinol, anti-inflammatory prophylaxis during allopurinol initiation and low starting dose of allopurinol (≤ 100 mg/dL). Logistic regression was used to model both medication adherence and SU goal attainment. The Akaike Information Criterion (AIC) was used to determine the best model, with lower AIC values indicative of improved model performance.

Results:

Gout participants were older (mean age 72 ± 11 years), primarily Caucasian (89%) and men (98%). A vast majority (73%) were adherent to allopurinol over one year of observation. Factors associated with nonadherence in adjusted analysis were older age (p<0.001), higher BMI (p =0.007) and thiazide use (p=0.037). Considering SU goal, medication adherence (OR 2.06), a low allopurinol starting dose (OR 0.23), and dose escalation (OR 2.58) were each independently associated with attainment (Table). Importantly, a rheumatologist as the initial prescriber (OR

3.88) was associated with SU goal attainment whereas the PAM score was marginally associated and produced a lower AIC for the model.

Conclusion:

SU goal attainment with the use of allopurinol appears to be largely driven by factors related to medication dosing, such as low starting dose or dose escalation, and medication adherence. While higher patient activation did trend toward greater SU goal attainment in this study and improved model performance, it did not reach statistical significance in adjusted analyses. This study suggests that initial efforts to improve outcomes would benefit most from focus on proper dosing practices and medication adherence before addressing patient activation more broadly.

Table Multivariable Associations with Serum Urate Goal Attainment

	Coefficient (95% CI)	P
Patient Factors		
Adherence, PDC ≥ 0.8	2.06 (1.32 to 3.23)	0.002
PAM, 0 to 100 scale	1.02 (1.00 to 1.04)	0.09
Provider Factors		
Low Starting Dose	0.23 (0.14 to 0.37)	<0.001
Dose Escalation	2.58 (1.53 to 4.33)	<0.001
Anti-inflammatory Prophylaxis†	-	-
Other Factors		
GFR, mL/min/1.73 m^2	1.02 (1.01 to 1.03)	<0.001
Rheumatologist as Initial Prescriber	3.88 (1.40 to 10.7)	0.009

* Models were determined by the Akaike Information Criterion (AIC). † Anti-inflammatory prophylaxis was the only hypothesized provider factor excluded by the AIC. Proportion of days covered (PDC); serum urate (SU); confidence interval (CI); Patient Activation Measure (PAM); body mass index (BMI); glomerular filtration rate (GFR).

Disclosure: B. Coburn, None; **K. Bendlin**, None; **H. Sayles**, None; **T. R. Mikuls**, None.

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Abstract Number: 925

Musculoskeletal Ultrasound (MSK-US): Innovation or Overutilization?

Gurjit S. Kaeley[1], Dale Kraemer[2], Carmen Smotherman[3] and Sunita Dodani[4], [1]Rheumatology, University of Florida College of Medicine, Jacksonville, Jacksonville, FL, [2]Center for Health Equity and Quality Research, Department of Neurology, University of Florida College of Medicine, Jacksonville, Jacksonville, FL, [3]Center for Health Equity and Quality Research,, University of Florida College of Medicine, Jacksonville, Jacksonville, FL, [4]Cardiology and Epidemiology, University of Florida College of Medicine, Jacksonville, Jacksonville, FL

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Background/Purpose:

MSK-US use has risen in the USA with recent disturbing findings suggesting greater utilization of interventional ultrasound by non-noradiologists compared to Radiologists. (1) This study evaluated utilization of diagnostic and interventional MSK-US within the Medicare population in the USA from 2011 – 2013. Our objectives were to estimate the rate of MSK-US utilization by MSK specialties, compare the cumulative growth of services and payments as well as determine time trends of utilization within the study period.

Methods:

A retrospective cross-sectional analysis of Medicare Physician Supplier Payment Summary (PSPS) files from 2011 – 2013 was used to tabulate services and total payments on utilization. PSPS data is aggregated by multiple factors but excludes technical costs such as those billed by Radiology. Therefore, service count data more accurately reflects utilization across specialties. CPT 76881, 76882; and 76942 were coded as diagnostic ultrasound and interventional ultrasound respectively. Non-duplicative billing claims of these codes were summed for each years and provider specialty. Descriptive and statistical (ANOVA) analysis was conducted using SAS® for Windows Ver. 9.4.

Results:

There was greater utilization of interventional than diagnostic ultrasound among all MSK providers except Podiatry. (Table, Fig) Amongst non-radiology groups, a cumulative growth of up to 205% and 273% was seen in interventional and diagnostic ultrasound respectively, while there was a decrease in Radiology interventional services. Orthopedics and Rheumatology had higher mean number of services and payments compared to all other non-radiology specialties ($p<0.05$). (Fig)

Conclusion:

Marked dissociation of interventional MSK-US services from diagnostic services was seen in most MSK specialties. Orthopedics ranked highest for MSK-US interventional services. Lack of corresponding diagnostic billing could be due to bundling of diagnostic services or inability to acquire and bill diagnostic ultrasound. Although the rapid rise of utilization of interventional MSK-US could reflect innovation in care, it is not clear if addition of MSK-US ultrasound guidance on a population level leads to better value care. Medicare reimbursement of interventional MSK-US procedures has been reduced which may lead to a better value proposition and moderated utilization.

References:

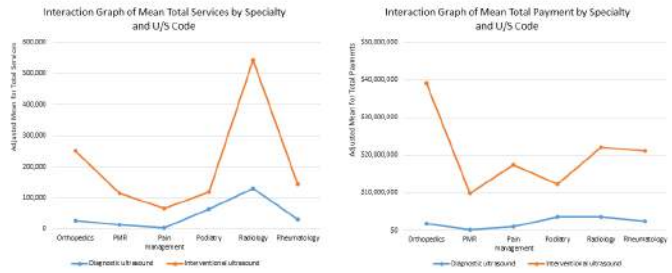
1. Sharpe RE, Jr., Nazarian LN, Levin DC, Parker L, Rao VM. The increasing role of nonradiologists in performing ultrasound-guided invasive procedures. Journal of the American College of Radiology : JACR. 2013;10(11):859-63.

Table: Stratified Services and Payments for Diagnostic and Interventional US: 2011-2013

Specialty	*Diagnostic Code*	*Year*	*Total Payment*	*Cumulative Percentage*	*Total Services*	*Cumulative Percentage*
Orthopedics	Diagnostic Ultrasound	2011	$1,201,095		17844	
Orthopedics	Diagnostic Ultrasound	2012	$1,884,973	57%	26688	50%
Orthopedics	Diagnostic Ultrasound	2013	$2,248,942	87%	33895	90%
Orthopedics	Interventional Ultrasound	2011	$18,265,453		110194	
Orthopedics	Interventional Ultrasound	2012	$38,291,935	110%	228527	107%
Orthopedics	Interventional Ultrasound	2013	$55,519,275	204%	336541	205%
PM-R	Diagnostic Ultrasound	2011	$745,724		10058	
PM-R	Diagnostic Ultrasound	2012	$978,527	31%	13806	37%
PM-R	Diagnostic Ultrasound	2013	$1,221,637	64%	18191	81%
PM-R	Interventional Ultrasound	2011	$10,989,414		67400	
PM-R	Interventional Ultrasound	2012	$15,845,584	44%	98488	46%
PM-R	Interventional Ultrasound	2013	$22,228,861	102%	138697	106%
Pain Management	Diagnostic Ultrasound	2011	$94,576		1370	
Pain Management	Diagnostic Ultrasound	2012	$181,131	92%	2719	98%
Pain Management	Diagnostic Ultrasound	2013	$313,524	232%	5137	275%
Pain Management	Interventional Ultrasound	2011	$5,018,728		33399	
Pain Management	Interventional Ultrasound	2012	$9,116,122	82%	59247	77%
Pain Management	Interventional Ultrasound	2013	$14,923,597	197%	97988	193%
Podiatry	Diagnostic Ultrasound	2011	$3,298,051		65383	
Podiatry	Diagnostic Ultrasound	2012	$3,572,297	8%	63065	-4%
Podiatry	Diagnostic Ultrasound	2013	$3,703,380	12%	66055	1%
Podiatry	Interventional Ultrasound	2011	$7,292,693		46368	
Podiatry	Interventional Ultrasound	2012	$8,946,745	23%	55801	20%
Podiatry	Interventional Ultrasound	2013	$9,936,656	36%	61593	33%
Radiology	Diagnostic Ultrasound	2011	$2,556,759		106228	
Radiology	Diagnostic Ultrasound	2012	$2,929,720	15%	117416	11%
Radiology	Diagnostic Ultrasound	2013	$3,263,319	28%	133003	25%
Radiology	Interventional Ultrasound	2011	$21,546,181		526409	
Radiology	Interventional Ultrasound	2012	$18,250,551	-15%	409151	-22%
Radiology	Interventional Ultrasound	2013	$15,563,707	-28%	296064	-44%
Rheumatology	Diagnostic Ultrasound	2011	$2,062,204		27170	
Rheumatology	Diagnostic Ultrasound	2012	$2,310,484	12%	29506	9%
Rheumatology	Diagnostic Ultrasound	2013	$2,706,841	31%	36021	33%
Rheumatology	Interventional Ultrasound	2011	$16,564,800		102421	
Rheumatology	Interventional Ultrasound	2012	$18,777,939	13%	113144	10%
Rheumatology	Interventional Ultrasound	2013	$20,782,347	25%	125579	23%

PM-R – Physical Medicine and Rehabilitation (includes Sports Medicine), Pain Management includes interventional pain management, Orthopedics includes Hand Surgery, Radiology includes interventional radiology.

Fig: Interaction Graphs by Specialty, Services and Payments



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Abstract Number: 926

Development of an Ultrasound Joint Inflammation Score for Rheumatoid Arthritis through a Data-Driven Approach

Anna-Birgitte Aga[1], Elisabeth Lie[2], Inge C Olsen[2], Hilde Berner Hammer[3], Till Uhlig[4], Désirée van der Heijde[5,6], Tore K. Kvien[2], Espen A. Haavardsholm[2] and the ARCTIC study group, [1]Department of Rheumatology, Diakonhjemmet Hospital, Oslo, Norway, [2]Dept. of Rheumatology, Diakonhjemmet Hospital, Oslo, Norway, [3]Postboks 23 Vinderen, Diakonhjemmet Hospital, Oslo, Norway, [4]Diakonhjemmet Hospital, Oslo, Norway, [5]Department of Rheumatology, Leiden University Medical Center, Leiden, the Netherlands, Leiden, Netherlands, [6]Rheumatology, Diakonhjemmet Hospital, Oslo, Norway

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Background/Purpose: No consensus exists regarding which joints and tendons should be systematically assessed by ultrasonography (US) to assess inflammation in rheumatoid arthritis (RA). Validity and responsiveness must be weighted against feasibility. Our group has previously developed and validated a US joint inflammation score (Aga et al, Ann Rheum Dis 2015). The objective of this study was to optimize the score in terms of sensitivity to change and feasibility, and to perform comparative analyses versus formerly proposed US scores in a longitudinal study.

Methods: DMARD-naïve early RA patients (pts) with <2 yrs symptom duration fulfilling the 2010 ACR/EULAR classification criteria were recruited between Sept 2010 and April 2013 and started on methotrexate. Extensive US examination were performed by experienced sonographers at baseline (BL) and after 3 and 6 months, using a validated grey-scale (GSUS) and power Doppler (PDUS) semi-quantitative scoring system with scores 0-3 for GSUS and PDUS in each of the following 36 joints and 4 tendons: MCP1-5, PIP2-3, radiocarpal, distal radioulnar, intercarpal, elbow, knee, talocrural, MTP1-5, extensor carpi ulnaris and tibialis posterior (TP) tendons, bilaterally. An US atlas was used as reference (Hammer et al, Ann Rheum Dis 2011). We performed principal component factor analyses (PCA) of GSUS and PDUS changes from BL to 3 months (ΔGSUS and ΔPDUS) to identify joint groups with high internal correlation. Based on these analyses we identified several joints/tendons candidate sets to be further tested. Standardised response means (SRMs) with 95% CI (bootstrapping) were estimated at 3 and 6 months for the candidate sets and formerly proposed scores.

Results: 117 early RA pts were included; 81.2% anti-CCP pos, mean(SD) age 50.3 (13.3) yrs, median(IQR) disease duration (from onset of swollen joint) 5 (3-9) months, mean(95% CI) 36-joint GSUS score 23(21-25) and PDUS score 11(10-12). Based on the PCA 12 groups of joint/tendons were identified (Table 1). Elbow, TP-tendon and MTP1 came out as separate factors, but were omitted from the scores due to low SRMs. Table 2 shows the 3- and 6-month SRMs for the previously published candidate sets (A, B), one of the new candidate sets (C) and the formerly proposed scores.

Conclusion: We used a data-driven approach to further develop an ultrasound joint inflammation score in RA. We propose a novel candidate set of joints/tendons with improved sensitivity to change, which is feasible, and performed numerically better than formerly proposed scores. Our results show that a reduced US assessment may efficiently contribute to disease assessment in RA.

Table 1: Joint/tendon groups identified by principal component factor analyses of ΔGSUS and ΔPDUS scores after 3 months with methotrexate treatment in early RA

Group 1	Group 2	Group 3	Group 4	Group 5	Group 6	Group 7	Group 8	Group 9	Group 10	Group 11	Group 12
Radiocarpal*	MCP3*	MTP2*	Elbow	MCP2*	MCP1*	MTP3*	TP-t	ECU-t*	PIP2*	PIP3*	MTP1
Intercarpal	MCP4					MTP4					
DRUJ	MCP5					MTP5					

DRUJ = distal radioulnar joint; MTP = metatarsophalangeal; MCP = metacarpophalangeal; PIP = proximal interphalangeal joints; TP-t = tibialis posterior tendon; ECU-t = extensor carpi ulnaris tendon. *Joints/tendon included in the new candidate set C

Table 2: 3- and 6- month standardised response means (SRMs) for candidate set A, B, C and formerly proposed ultrasound joint scores for RA

GSUS	**SRM*(95%CI) 3 months**	**SRM*(95%CI) 6 months**
12-joint score Naredo[1]	- 1.01 (- 1.17 to - 0.84)	- 0.92 (- 1.08 to - 0.76)
7-joint score Backhaus[2]	- 1.10 (- 1.30 to - 0.90)	- 1.15 (- 1.36 to - 0.94)
6-joint score Perricone[3]	- 0.99 (- 1.19 to - 0.78)	- 0.97 (- 1.15 to - 0.79)
Candidate set A score[4]	- 1.04 (- 1.23 to - 0.84)	- 1.06 (- 1.29 to - 0.84)
Candidate set B score[5]	- 1.06 (- 1.27 to - 0.87)	- 1.14 (- 1.35 to - 0.94)
Candidate set C score[6]	**- 1.25 (- 1.48 to - 1.02)**	**- 1.25 (- 1.47 to - 1.02)**

PDUS	**SRM*(95%CI) 3 months**	**SRM*(95%CI) 6 months**
12-joint score Naredo[1]	- 0.74 (- 0.89 to - 0.58)	- 0.74 (- 0.89 to - 0.60)
7-joint score Backhaus[2]	- 0.90 (-1.07 to - 0.74)	- 1.01 (- 1.16 to - 0.87)
6-joint score Perricone[3]	- 0.70 (- 0.87 to - 0.52)	- 0.78 (- 0.93 to - 0.62)
Candidate set A score[4]	- 0.90 (- 1.12 to - 0.68)	- 1.06 (- 1.27 to - 0.87)
Candidate set B score[5]	- 0.90 (- 1.11 to - 0.69)	- 1.08 (- 1.30 to - 0.88)
Candidate set C score[6]	**- 0.97 (- 1.18 to - 0.77)**	**- 1.08 (- 1.26 to - 0.92)**

*SRM (standardised response mean) = mean change divided by the standard deviation of the change. CI = confidence interval; GSUS = grey-scale ultrasound; PDUS = power Doppler ultrasound. Patients in the early RA cohort with data on 3 months (n=113) and 6 months (n=109).

[1]**12-joint score Naredo et al:** MCP2, MCP3, wrist, elbow, knee, ankle and TP tendon bilaterally (Naredo et al, Arthritis Rheum 2008).

[2]**7-joint score Backhaus:** MCP2, MCP3, PIP2, PIP3, wrist, MTP2, MTP5 and ECU tendon dominant side (Backhaus et al, Arthritis Rheum 2009).

[3]**6-joint score Perricone:** MCP2, wrist, knee bilaterally (Perricone et al, Rheumatology 2012).

[4]**Candidate set A score:** MCP1, MCP2, PIP3, radiocarpal, elbow, MTP1, MTP2, tibialis posterior (TP) tendon group and extensor carpi ulnaris (ECU) tendon bilaterally (Aga et al, Ann Rheum Dis 2015).

[5]**Candidate set B score:** same as candidate set A with addition of MCP5 and MTP5 (Aga et al, Ann Rheum Dis 2015).

[6] **Candidate set C score:** MCP1, MCP2, MCP3, PIP2, PIP3, radiocarpal, MTP2, MTP3 and ECU tendon bilaterally.

Disclosure: A. B. Aga, None; **E. Lie**, None; **I. C. Olsen**, None; **H. B. Hammer**, None; **T. Uhlig**, None; **D. van der Heijde**, None; **T. K. Kvien**, None; **E. A. Haavardsholm**, AbbVie, 2,Pfizer Inc, 2,MSD, 2,Roche Pharmaceuticals, 2,UCB, 2.

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Abstract Number: 927

Ultrasound Assessment of Heel Entheses in Spondyloarthritis Patients: A Comparative Study with Radiography and Magnetic Resonance Imaging

Rodrigo Aguila Maldonado[1], Santiago Ruta[2], Claudia Elizabeth Pena[1], Maria Laura Valuntas[3], Gisela Pendón[4], Dora Pereira[4] and Mercedes Argentina García[5], [1]Rheumatology Unit, HIGA San Martín La Plata, La Plata, Argentina, [2]Rheumatology Unit, Internal Medicine Service, Hospital Italiano de Buenos Aires, Buenos Aires, Argentina, [3]Servicio de Tomografía Computada y Resonancia Magnética, Sanatorio IPENSA, La Plata, Argentina, [4]Hospital Ricardo Gutierrez, La Plata, La Plata, Argentina, [5]Rheumatology Unit, HIGA San Martín, La Plata, Argentina

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Background/Purpose: enthesitis is one of the main hallmarks of Spondyloarthritis (SpA), being heel entheses frequently involved. Different imaging modalities, such as conventional radiography (CR), ultrasound (US) and magnetic resonance imaging (MRI) are commonly used for the detection of enthesopathy. The aim was to determine the agreement between US, CR and MRI for the detection of enthesopathy in SpA.

Methods: forty patients with a diagnosis of SpA (axial or peripheral ASAS criteria) were included. All patients underwent all imaging modalities in the same day, in order to assess bilaterally both Achilles tendon and plantar fascia insertions into the calcaneous bone.

US examinations were performed using a MyLab 60 machine (6-18 MHz multifrequency broad band linear transducer). The following US findings indicative of enthesopathy were dichotomously assessed: thickening, structural changes (hypoechoic areas with loss of the typical "fibrillar" echotexture), bursitis, abnormal vascularization by power Doppler (PD), bone erosions and enthesophytes.

MRI were performed with a Signa HDe 1.5 Tesla machine (General Electric) and read by a radiologist. The following MRI findings indicative of enthesopathy were dichotomously assessed: thickening, signal intensity changes of the entheses (structural changes), adjacent bone marrow edema, bursitis, bone erosions and enthesophytes.

CR were read by a rheumatologist in order to assess the presence of bone erosions and/or enthesophytes.

Both rheumatologists and the radiologist were blinded to clinical and to the others imaging data.

Results: a total of 160 heel entheses were examined. At least one sign indicative of enthesopathy was found in 68.1% (109/160), 65.6% (105/160) and 26.9% (43/160) entheses with MRI, US and CR, respectively. Tables 1 and 2 show a detailed description about the agreement between US and MRI and between CR, US and MRI, respectively. Among non-comparable findings, US detected abnormal vascularization by PD in 57 out of 160 (35,6%) entheses while MRI revealed adjacent bone marrow edema in 36 out of 160 (22,5%) entheses.

Table1. Agreement between US and MRI, unweighted kappa (k) values (95% coefficient interval) and absolute agreement (%).

Thickenning		**US**		
		absence	presence	
MRI	absence	108	4	**k= 0.80**
	presence	9	39	**(0.69-0.90),**
				(91,8%)
Structural changes		**US**		
		absence	presence	
MRI	absence	123	7	**k= 0.66**
	presence	9	21	**(0.51-0.81),**
				(90%)
Bursitis		**US**		
		absence	presence	
MRI	absence	66	0	**k= 0.68**
	presence	6	8	**(0.45-0.91),**
				(92,5%)
Bone erosions		**US**		
		absence	presence	**k= 0.69**
MRI	absence	103	10	**(0.57-0.82),**
	presence	10	37	**(87,5%)**
Enthesophytes		**US**		
		absence	presence	
MRI	absencee	96	10	**k= 0.70**
	presence	11	43	**(0.58-0.82),**
				(86,9%)

Table 2. Agreement between CR with US and MRI, unweighted kappa (k) values (95% coefficient interval) and absolute agreement (%).

Bone erosions		CR		
		absence	presence	
US	absence	104	9	**k= 0.45**
	presence	24	23	**(0.29-0.60),**
				(79,5%)
Enthesophytes		**CR**		
		absence	presence	**k= 0.78**
US	absence	102	4	
	presence	11	43	**(0.68-0.88),**
				(90,6%)
Bone erosions		**CR**		
		absence	presence	
MRI	absence	102	11	**k= 0.38**
	presence	26	21	**(0.22-0.54),**
				(76,9%)
Enthesophytes		**CR**		
		absence	presence	**k= 0.76**
MRI	absence	102	5	
	presence	11	42	**(0.66-0.87),**
				(91,2%)

Conclusion: a good agreement between US and MRI was found for all abnormal comparable findings at heel entheses in SpA patients. Agreement was also good between the three imaging modalities concerning detection of enthesophytes, with a lower agreement in the recognition of bone erosions.

Disclosure: R. Aguila Maldonado, None; **S. Ruta**, None; **C. E. Pena**, None; **M. L. Valuntas**, None; **G. Pendón**, None; **D. Pereira**, None; **M. A. García**, None.

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Abstract Number: 928

The Value of Early Ultrasound-Detected Osteophytes in Hand Osteoarthritis: Predicting the Future

Alexander Mathiessen[1], Barbara Slatkowsky-Christensen[2], Tore K. Kvien[3], Ida K. Haugen[4] and Hilde Berner Hammer[2], [1]Department of Rheumatology, Diakonhjemmet Hospital, Oslo, Norway, [2]Rheumatology, Diakonhjemmet Hospital, Oslo, Norway, [3]Dept. of Rheumatology, Diakonhjemmet Hospital, Oslo, Norway, [4]P.O. Box 23, Diakonhjemmet Hospital, Vinderen, Norway

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Background/Purpose: Ultrasound is more sensitive than conventional radiographs in detecting small osteophytes in hand osteoarthritis (OA). Osteophytes can be seen prior to joint space narrowing (JSN), may be an early risk factor for OA progression, and is associated with pain. However, previous studies on the predictive value of osteophytes on disease progression is limited in numbers, have shown inconsistent results, and none of these have included ultrasound.

We believe that ultrasound can be used to detect OA at an earlier stage than conventional radiographs. Hence, the aim of this longitudinal study was to examine whether ultrasound-detected osteophytes in joints with concurrent normal radiographs at baseline could predict incident radiographic hand OA five years later.

Methods: We included 78 participants (71 women, mean (SD) age 67.8 (5.2) years) from the Oslo Hand OA cohort. The presence of ultrasound-detected osteophytes was examined at baseline by two sonographers in collaboration. In the present analysis we included the joints most likely to develop OA (the first carpometacarpal joint and the interphalangeal joints bilaterally). One reader scored the radiographs with known time sequence according to the Kellgren-Lawrence (KL) scale and the Osteoarthritis Research Society International (OARSI) atlas for osteophytes and JSN.

Associations between baseline ultrasound-detected osteophytes (independent variable) and incident radiographic OA features (dependent variables) were explored only in joints without radiographic OA at baseline (i.e. KL grade = 0 and no osteophytes or JSN) by use of Generalized Estimating Equations (GEE), expressed as odds ratio (OR) with 95% confidence intervals (CI). Analyses were adjusted for age, sex, body mass index and follow-up time, with significance level 0.05.

Results: Mean (SD) follow-up time was 4.7 (0.4) years. In total 301 joints were assessed as being normal on conventional radiographs at baseline, of which 86 had concurrent osteophytes on ultrasound; most of these were small (score 1 = 79%).

Ultrasound-detected osteophytes at baseline were strong predictors for incident radiographic OA during follow-up (table). N=40 (47%) of the joints with preliminary sonographic osteophytes had developed radiographic OA (i.e. KL score increased from 0) at follow-up, as opposed to only 17% of the joints without baseline osteophytes. The strongest association was seen for incident JSN development (OR=5.3, 95% CI 2.1-13.4).

Conclusion: In the current analysis, we demonstrated that ultrasound-detected osteophytes in joints assessed as normal on radiographs were a strong predictor for development of radiographic OA in the same joint five years later. These results support the use of ultrasound as a promising clinical tool for early detection of hand OA.

Table

Ultrasound-detected osteophytes at baseline as a predictor for development of radiographic osteoarthritis (OA)

Baseline ultrasound osteophytes	Radiographic OA development at follow-up, n (%)*	Odds ratio (95% CI) Crude	Adjusted†
	Global OA (Kellgren-Lawrence)		
Grade 0 (n=215)	37 (17.2)	1.0	1.0
Grade 1-3 (n=86)	40 (46.5)	2.9 (1.6–5.4)	4.1 (2.0–8.1)
	Radiographic joint space narrowing		
Grade 0 (n=215)	9 (4.2)	1.0	1.0
Grade 1-3 (n=86)	15 (17.4)	4.2 (1.8–10.2)	5.3 (2.1–13.4)
	Radiographic osteophytes		
Grade 0 (n=215)	28 (13.0)	1.0	1.0
Grade 1-3 (n=86)	31 (36.0)	2.9 (1.6–5.4)	4.2 (2.1–8.5)

Generalized Estimating Equations presented as odds ratios for new OA features at follow-up with separate models for each radiographic feature. CI=confidence interval. *Number and percentage of joints with/without incident OA. †Adjusted for age, sex, body mass index, follow-up time.

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Abstract Number: 929

Diurnal Variation of Power Doppler in Metacarpophalangeal Joints of Patients with Rheumatoid Arthritis

Marwin Gutierrez[1], Emeline Minichiello[2], Alarico Ariani[1], Salima Challal[2], Emilio Filippucci[1], Marie-Christophe Boissier[2,3,4], Walter Grassi[1] and **Luca Semerano**[2,3,4], [1]Clinica Reumatologica, Università Politecnica delle Marche, Jesi, Italy, [2]Service de Rhumatologie, Assistance Publique – Hôpitaux de Paris (AP-HP) Groupe hospitalier Avicenne - Jean Verdier – René Muret, Bobigny, France, [3]Inserm UMR 1125, Bobigny, France, [4]Sorbonne Paris Cité - Université Paris 13, Bobigny, France

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Background/Purpose: In a preliminary study on 10 patients with active rheumatoid arthritis (RA) we showed for the first time that Power

Doppler ultrasonography (PDUS) signal of metacarpophalangeal (MCP) joints has a clear diurnal variation. To test whether PDUS signal of MCP joints in RA patients actually varies according to the time of day, we undertook a larger study involving 50 patients with active RA

Methods: A total of 500 MCP joints from 50 patients with active RA were evaluated at three different times during the same day T1: between 7 and 10 a.m.; T2: 4-6 hours after T1; T3: 4-6 hours after T2. All joints were evaluated for both presence/absence of PDUS signal and according to a semiquantitative score (from 0 to 3). The results at T1, T2 and T3 were compared for each joint. The day of examination, factors that could potentially influence PDUS signal were avoided or controlled (smoke, alcohol, corticosteroids, NSAIDs, vasoactive drugs intake, room temperature, hand position). Within-patient PDUS score variation was quantified as the sum of the differences between PDUS scores in each joint at the three different examinations for each patient. Semiquantitive PDUS scores were compared with Friedman's test. Categorical data (PDUS presence/absence) were compared with Cochran's Q test

Results: Globally, 46 out of 50 patients (92%; CI : 84.48% to 99.52%) displayed some circadian variation of PDUS signal. There was a significant variation in the number of PDUS-positive MCP joints during the day ($p<0.05$), with more PDUS positive MCP joints at T0 (156) vs. T1 (144) and T2 (129) ($p<0.05$). Fifteen patients (30%; 95CI 17.3% to 42.7%) had at least one joint in which PDUS signal appeared or disappeared at different. Semiquantitative PDUS scores were significantly higher at T1 ($p<0.05$ vs. T2 and T3) with a subsequent reduction at T2 ($p<0,05$ vs. T1 and T3) and further reduction at T3 ($p<0,05$ vs. T1 and T2). This pattern of variation was not univocal and single patients and even single joints in the same patient could show higher scores at T2 or, more rarely, at T3. Median within-patient PDUS score variation was 4 (range 0 to 34). Patients with higher than the median PDUS variation had higher DAS28 ($p<0.05$), but no higher CRP vs. those with lower variation. Within-patient variation was moderately correlated with DAS28 ($r=0.4$, $p=0.01$) but not with CRP

Conclusion: PDUS signal varies significantly through the day, being higher in the morning and progressively lowering in early afternoon and evening. PDUS signal variation involved about 90% of patients, independent of disease activity. Patients with higher disease activity displayed greater variation of PDUS signal

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Abstract Number: 930

Evaluation of Temporomandibular Joint Arthritis with Ultrasound in Juvenile Idiopathic Arthritis

Edward J. Oberle[1,2], James Nocton[3] and Arthur Meyers[4], [1]Pediatrics, Ohio State University, Columbus, OH, [2]Pediatric Rheumatology, Nationwide Children's Hospital, Columbus, OH, [3]Pediatrics, Medical College of Wisconsin, Milwaukee, WI, [4]Radiology, Children's Hospital of Wisconsin, Milwaukee, WI

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Background/Purpose: Temporomandibular joint (TMJ) arthritis is a common yet widely under recognized feature of Juvenile Idiopathic Arthritis (JIA). It is often clinically silent and difficult to diagnose without the use of Magnetic Resonance Imaging (MRI). The primary objective of this study was to describe the TMJ as seen on ultrasound (US) and determine the ability to detect arthritic changes as a means to develop a rapid, bedside screening tool to aid rheumatologists in the early diagnosis of TMJ arthritis.

Methods: Subjects were recruited from the Children's Hospital of Wisconsin. The control group consisted of healthy volunteers presenting to the dermatology clinic for routine care of non-rheumatologic conditions. The study group was composed of children and adolescents with a prior diagnosis of JIA seen at the rheumatology clinic for ongoing care. US was performed in both clinics by the same pediatric rheumatologist trained in musculoskeletal ultrasonography. Images were reviewed for pathology at a later date by the ultrasonographer and a blinded radiologist. JIA patients had their TMJs examined by their primary rheumatologist with their subtype of JIA, active and previously affected joints, and history of TMJ symptoms blinded to the ultrasonographer. The dermatology patients had their TMJs examined by the ultrasonographer after the completion of the ultrasound study. All subjects filled out a questionnaire about TMJ symptoms at the completion of the study with the results blinded to the study staff until after ultrasound studies were assessed.

Results:

Full evaluations were performed on 40 subjects (80 TMJs) including 20 JIA patients and 20 healthy controls. 12 females and 8 males were

evaluated in each group with a similar age distribution (range 5-18 years old). The subset of JIA patients evaluated included 2 oligoarticular-persistent, 3 oligoarticular-extended, 4 polyarticular rheumatoid factor (RF) negative, 5 polyarticular RF positive, 1 systemic onset, 4 enthesitis related, and 1 psoriatic arthritis patient. 10 patients had active arthritis at the time of the study in at least 1 non-TMJ joint.

US revealed a small window of the laterosuperior TMJ. In JIA TMJs (N=40), abnormalities visible included erosions (30%) or irregularities (18%) of the bony contour of the mandibular condyle, hyperemia (13%), effusion (5%), and prominent synovium (25%). Doppler signal within the TMJ space correlated to symptoms 80% of the time. 6 patients (30%) with TMJ abnormality on US had active arthritis in a peripheral joint. 10 TMJs (25%) were abnormal on US in 8 asymptomatic patients (40%). 12 TMJs (30%) were abnormal on US in 9 patients with normal TMJ physical exams (45%).

Irregularity in the contour of the condyle was observed in 9 (23%) control TMJs (N=40). An erosion was noted in 1 TMJ (3%). Doppler activity was noted on two control studies (5%) on the lateral portion of the condyle.

Conclusion: Point of care US in the rheumatology clinic has potential use to screen for arthritic changes to the TMJ in JIA patients. Abnormalities to the condyle contour regularly are seen in JIA patients, some of whom are asymptomatic. This is also the first study to demonstrate Doppler signal may be an indicator of active TMJ arthritis.

Disclosure: E. J. Oberle, None; **J. Nocton**, None; **A. Meyers**, None.

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mTOR Complex 1 Signaling Is Required for the Steady-State in Vivo Development of Inflammatory Monocytes

Pui Y. Lee[1], David Sykes[2], Sarah Ameri[3], Allyn Morris[4] and Peter A. Nigrovic[5], [1]Division of Immunology, Boston Children's Hospital, Boston, MA, [2]Massachusetts General Hospital, Boston, MA, [3]Division of Rheumatology, Immunology, and Allergy, Brigham and Women's Hospital, Boston, MA, [4]Brigham and Women's Hospital, Boston, MA, [5]Department of Medicine, Division of Rheumatology, Immunology and Allergy, Brigham and Women's Hospital, Harvard Medical School, Boston, MA

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Background/Purpose: Monocytes and macrophages are essential to innate immunity but also propagate the inflammatory response in autoimmune arthritis and lupus nephritis. Spontaneous development of inflammatory monocytes ($Ly6C^{hi}$ $CCR2^{+}$) and subsequent differentiation to residential monocytes ($Ly6C^{lo}$ CX_3CR1^{hi}) from murine bone marrow precursor cells is an enigmatic process that involves numerous transcription factors. Understanding the signaling pathways involved in myeloid development could help identify novel treatment targets for inflammatory diseases.

Methods: We developed a murine myeloid progenitor cell line with $CCR2^{RFP}$ CX_3CR1^{GFP} reporters to track monocyte differentiation. Small molecule library screen was used to identify biological pathways involved in monocyte development. Activation of mTOR substrates was measured by intracellular flow cytometry. Key findings were confirmed using pharmacologic inhibition and genetic disruption.

Results: Using a novel progenitor cell line that recapitulates the monocyte development continuum, we identified an essential role of mechanistic target of rapamycin complex 1 (mTORC1) on the generation of inflammatory monocyte through a small molecule library screen. Basal mTORC1 signaling was more prominent in monocytes than other cell subsets in wild-type mice and humanized mice. Inhibition of mTORC1 by rapamycin or disruption of Raptor (an essential component of mTORC1) impaired monocyte development, while deletion of TSC-1 (a negative regulator of mTORC1) accelerated the differentiation into mature macrophages. Correspondingly, Raptor $^{fl/fl}$ UBC-cre/ERT2 mice susceptible to tamoxifen-mediated deletion of Raptor demonstrated a rapid, inducibe depletion of circulating inflammatory monocytes, confirm an essential non-redundant role of mTORC1 in monocyte development *in vivo*. Curiously, Raptor-deficient progenitors in the bone marrow spontaneously differentiated into $Ly6C^{lo}$ CX_3CR1^{low} myeloid cells with characteristics of alternatively-activated macrophages.

Conclusion: Using a combination of *in vitro* and *in vivo* approaches, we identified a previously unrecognized role of mTORC1 in the normal development of inflammatory monocytes. These findings support the potential utility of mTORC1 inhibitors in monocyte- and macrophage-mediated inflammatory diseases.

Disclosure: P. Y. Lee, None; **D. Sykes**, None; **S. Ameri**, None; **A. Morris**, None; **P. A. Nigrovic**, None.

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Abstract Number: 932

IRF4-Dependent and IRF4-Independent Pathways Contribute to DC Dysfunction in Lupus

Michela Manni[1], Sanjay Gupta[2], Briana G. Nixon[3] and Alessandra B. Pernis[4], [1]Autoimmunity and Inflammation Program, Hospital for Special Surgery, New York, NY, [2]Autoimmunity & Inflammation Research Program, Hospital for Special Surgery, New York, NY, [3]Graduate Program in Immunology and Microbial Pathogenesis, Weill Cornell Graduate School of Medical Sciences, New York, NY, [4]Autoimmunity & Inflammation, Hospital for Special Surgery, Weill Cornell Medical College, New York, NY

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Background/Purpose: Interferon Regulatory Factors (IRFs) play fundamental roles in dendritic cell (DC) differentiation and function. In particular IRFs are critical transducers of Toll-like Receptors (TLR) signaling and their dysregulation is associated with the development of autoimmune disorders. While several IRFs are expressed in DCs, their relative contribution to the aberrant phenotypic and functional characteristics that DCs acquire in lupus has not been fully delineated. Mice deficient in DEF6 and SWAP-70 (=Double-knock-out or DKO mice), two members of a unique family of molecules that restrain IRF4 function, spontaneously develop systemic lupus erythematosus (SLE)-like disease in C57BL/6 mice. Although autoimmunity in DKO mice is accompanied by dysregulated IRF4 activity in both T and B cells, SWAP-70 is also known to regulate multiple aspects of DC biology. Here we thus explored whether DEF6 and SWAP-70 regulate IRF4 activity in DCs and investigated the contribution of IRF4 to DC dysfunction in the DKO mouse model.

Methods: $CD11b^+$ and $CD8^+$DCs were analyzed *in vivo* in WT and DKO mice by FACS. We investigated the expression of Blimp-1 and IL-10 in DCs *in vivo* by using a double reporter mouse model of these markers. Bone marrow derived DCs (BMDCs) were generated *in vitro* followed by TLR-4 and TLR-9 activation. BMDC activation markers, cytokine production and gene expression were analyzed by FACS, ELISA and qPCR. CD11c-Cre $IRF4^{fl/fl}$ WT and DKO conditional knock out mice were also generated and analyzed *in vivo* and *in vitro*.

Results: We demonstrated that *in vivo* $CD11b^+$ DCs in DKO mice are expanded and express higher levels of CD86 and PDL2 compared to WT mice. By using a dual reporter mouse model we determined that $CD11b^+$DCs in DKO mice exhibit dysregulated IL-10 production, which is accompanied by aberrant Blimp1 expression in the spleen but not in skin draining lymph nodes. PDL2 expression was also upregulated in IL-10 producing DCs independently of Blimp-1 expression. Similar to our *in vivo* results, BMDCs from DKO mice show higher levels of CD86 and PDL2 compared to WT BMDCs and are hyper-responsive to multiple TLR ligands as assessed by their aberrant IL-10 and IFN-b expression. By using CD11c-Cre $IRF4^{fl/fl}$ WT and DKO mice we also demonstrated that IRF4 plays a differential role in these responses by being required for the TLR4- but not the TLR9-mediated upregulation of IL-10. Finally *in vivo* deletion of IRF4 using the CD11c-Cre transgene led to a decrease in the $CD11b^+$ DC population without any significant effects on the $CD8^+$ DC subset. The lack of IRF4 did not significantly affect the upregulation of PDL2 and CD86 or the abnormal expansion of T_{FH}, Tregs, GC B cells and plasma cells that characterize DKO mice.

Conclusion: We demonstrated that $CD11b^+$ DCs from DKO mice exhibit enhanced expression of Blimp1, PDL2 and dysregulated IL-10 production *in vivo*. Similar to other SLE mouse models, DCs from DKO mice were hyper-responsive to TLR stimulation. Deletion of IRF4 in DKO DCs *in vivo* and *in vitro* revealed that this phenotype is driven by an unexpected degree of molecular heterogeneity whereby lack of IRF4 corrected the TLR4-mediated hyper-responsiveness but exerted no effects on the TLR9-induced dysfunction.

Disclosure: M. Manni, None; **S. Gupta**, None; **B. G. Nixon**, None; **A. B. Pernis**, Kadmon Corporation, 2.

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Abstract Number: 933

DEK-Targeting DNA Aptamers As Novel Therapeutics for Inflammatory Arthritis

Nirit Mor-Vaknin[1], Anjan K. Saha[2], Maureen Legendre[1], Carmelo Carmona-Rivera[3], M. Asif Amin[4], Bradley J. Rabquer[5], Marta J. Gonzalez-Hernandez[6], Julie M. Jorns[7], Srilakshmi Yalavarthi[8], Smriti Mohan[9], Dave Pai[10], Kristine Angevine[11], Barbara Adams[12], Jason S. Knight[8], Alisa E. Koch[13,14,15], David Fox[14], Dave Engelke[16], Mariana J. Kaplan[17] and David Markovitz[4], [1]Infectious Diseases, University of Michigan, Ann Arbor, MI, [2]Medical School, University of Michigan, Ann Arbor, MI, [3]Systemic Autoimmunity Branch, National Institute of Arthritis and Musculoskeletal and Skin Diseases, National Institutes of Health, Bethesda, MD, [4]Internal Medicine, University of Michigan, Ann Arbor, MI, [5]Albion College, Ann Arbor, MI, [6]Graduate Program in Immunology, University of Michigan, Ann Arbor, MI, [7]Pathology, University of Michigan, Ann Arbor, MI, [8]Division of Rheumatology, University of Michigan, Ann Arbor, MI, [9]Pediatric Rheumatology, University of Michigan, Ann Arbor, MI, [10]Scripps Research Institute, San Diego, CT, [11]Appistry, Inc, St. Louis, MO, [12]Pediatric Rheum PTD, Univ of Michigan Hlth System, Ann Arbor, MI, [13]VA Medical Service, Ann Arbor, MI, [14]Internal Medicine, Division of Rheumatology, University of Michigan Medical Center, Ann Arbor, MI, [15]Internal Medicine, Veteran's Affairs and University of Michigan, Ann Arbor, MI, [16]Biochemistry, University Michigan, Ann Arbor, MI, [17]Systemic Autoimmunity Branch, NIAMS, National Institutes of Health, Bethesda, MD

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Background/Purpose:

Aptamers are short single stranded DNA or RNA oligonucleotides that are specifically selected to bind and neutralize a wide range of biomedically relevant proteins. Aptamers are being used in the clinic for the treatment of macular degeneration while eight others are in clinical trials. Aptamers are particularly useful in targeting cell surface and extracellular proteins. We have previously demonstrated that the nuclear chromatin binding protein DEK is actively secreted by human macrophages, serves as a chemoattractant for neutrophils, can be taken up by adjacent cells in a bioactive form, and is abundant in the inflamed synovia of patients with juvenile arthritis (JA). We now demonstrate that targeting DEK with specific anti-DEK aptamers can prevent joint inflammation induced by zymosan.

Methods:

DEK-targeting aptamers were selected from a pool of random-sequence oligonucleotides by SELEX (Systematic Evolution of Ligands by Exponential Enrichment). Two single-stranded DNAs, 40 and 42 nucleotides long with high affinity to DEK were identified. 129/B6 wild type (WT) and DEK null (KO) mice were injected with zymosan through the suprapatellar ligament into the joint cavity to induce inflammatory arthritis. To neutralize DEK, WT mice were additionally injected with either control or DEK-targeting aptamers. Neutrophils were isolated from the blood of healthy human volunteers, synovial fluid of JA patients, or mouse bone marrow. Neutrophil extracellular traps (NETs) were detected *in vivo* and *in vitro* by immunofluorescence with elastase, LL-37, myeloperoxidase (MPO) and DEK antibodies. DEK-targeting aptamers were used to neutralize DEK during *in vitro* induction of NETs.

Results:

DEK KO mice display significantly less joint inflammation than wild-type mice in a zymosan-induced arthritis model (ZIA). Targeting DEK in the joints with specific aptamers significantly reduced joint inflammation induced by zymosan. Indeed, we found a significant reduction in NET formation in joints treated with DEK-targeting aptamers compared to joints treated with control aptamers. Moreover, activation of DEK KO neutrophils demonstrated appreciably reduced NET formation compared to WT neutrophils. Interestingly, NET formation could be rescued in DEK KO neutrophils with the addition of exogenous recombinant DEK. NETs released by synovial neutrophils from JA patients stained prominently for DEK. Similar to the mouse studies, NET release from human neutrophils was drastically abrogated by treatment with DEK-targeting aptamers.

Conclusion:

These results show that the nuclear DNA-binding protein DEK is a major factor in the development of joint inflammation. Specifically, DEK is implicated in the formation of NETs, in addition to its already established role as a leukocyte chemoattractant. These results strongly support the pro-inflammatory function of extracellular DEK, a protein that is crucial to both intracellular and extracellular chromatin structure. Targeting DEK with the newly developed anti-DEK aptamers is a promising therapeutic strategy for the treatment of local and systemic inflammatory conditions such as arthritis.

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Abstract Number: 934

Platelet-Independent Role of Megakaryocytes in Antibody-Mediated Murine Arthritis

Pierre Cunin[1], Loka Penke[2], Jonathan Thon[3], Paul A. Monach[4], Tatiana Jones[5], Mary Chen[2], Yoichiro Iwakura[6], Jerry Ware[7], Michael Gurish[2], Joseph Italiano[3], Eric Boilard[8] and Peter A. Nigrovic[2,9], [1]Rheumatology, Immunology and Allergy, Department of Medicine, Division of Rheumatology, Immunology and Allergy, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, [2]Department of Medicine, Division of Rheumatology, Immunology and Allergy, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, [3]Department of Medicine, Hematology Division, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, [4]Rheumatology, Boston University School of Medicine, Boston, MA, [5]Department of Clinical Laboratory and Nutritional Science, University of Massachusetts Lowell, Lowel, MA, [6]Center for Experimental Medicine, Institute of Medical Science, University of Tokyo, Tokyo, Japan, [7]Department of Physiology and Biophysics, University of Arkansas for Medical Sciences, Little Rock, AR, [8]Centre de Recherche en Rhumatologie et Immunologie, Centre de Recherche du Centre Hospitalier Universitaire de Québec, Faculté de Médecine de l'Université Laval, Quebec, QC, Canada, [9]Department of Medicine, Division of Immunology, Boston Children's Hospital, Harvard Medical School, Boston, MA

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Background/Purpose: Mice bearing mutations affecting *Kit* (stem cell factor receptor) exhibit multiple hematologic phenotypes, including mast cell deficiency, and have been used to assess the role of mast cells in K/BxN arthritis. We observed that arthritis susceptibility in disease-resistant $Kit^{W/Wv}$ mice could be rescued not only by engraftment of cultured mast cells, but also by marrow from mast cell-deficient $Kit^{Wsh/Wsh}$ mice, implicating another lineage in addition to mast cells in the $Kit^{W/Wv}$ phenotype.

Methods: Unirradiated $Kit^{W/Wv}$ were engrafted with bone marrow from mice deficient in key lineages determinants ($GFI^{-/-}$, $IL\text{-}1^{-/-}$, $NF\text{-}E2^{-/-}$, and $GPVI^{-/-}$). 14 days after transfer, arthritis was initiated with i.p. injection of 150µl of serum from K/BxN mice on day 0 and day 2. Arthritis was graded on a 0-12 clinical scale. In other experiments, $Kit^{W/Wv}$ were engrafted i.v. with lineages of interest, including bone marrow neutrophils, platelets, and megakaryocytes (MK), prior to arthritis induction. MK were generated by culturing bone marrow cells with medium supplemented with 1% supernatant from the TPO-producing fibroblast cell line GP122.

Results: Neutrophils transfer failed to restore arthritis in $Kit^{W/Wv}$, yet transfer of marrow from neutrophil-deficient mice $GFI\text{-}1^{-/-}$ restored arthritis as well as WT B6 marrow, confirming that neutropenia is not a critical basis for arthritis resistance in $Kit^{W/Wv}$. Instead, overcoming arthritis resistance in $Kit^{W/Wv}$ required donor marrow expressing IL-1 and the platelet/MK lineage determinants GP-VI and NF-E2 (Figure 1A-B), suggesting that platelet is the lineage that restores arthritis in $Kit^{W/Wv}$. However, $Kit^{W/Wv}$ mice are not thrombocytopenic, and platelet transfer failed to restore arthritis in these mice (Figure 1C). Because $Kit^{W/Wv}$ are megakaryocytopenic, we considered the possibility that restoration of arthritis might be mediated directly by MK. Indeed, we found that MK produce IL-1 rich microparticles capable of stimulating fibroblast-like synoviocytes in manner dependent on IL-1 receptor expression. In confirmation, we found that engraftment of MK relatively incompetent in platelet production could fully restore arthritis susceptibility in $Kit^{W/Wv}$ (Figure 1D).

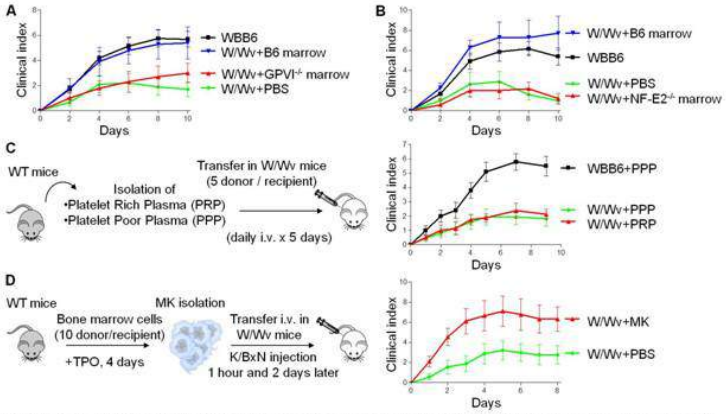

Figure 1. Megakaryocyte restore arthritis susceptibility in W/Wv mice. (A-B) W/Wv mice transferred i.v. with whole bone marrow (1 donor per 2 recipients), or corresponding WBB6 controls, were treated i.p. with K/BxN serum 150ul on days 0 and 2. (A) Clinical score after transfer of GPVI$^{-/-}$ and control B6 marrow. (B) Clinical score after transfer of NF-E2$^{-/-}$ and control B6 marrow. (C) Platelet rich plasma (PRP) and platelet poor plasma (PPP) were purified from B6 donors and transferred into recipient mice i.v. (5 donors/recipient/day on days 0-4) along with K/BxN serum 150μL i.p. on days 0 and 2. (D) W/Wv mice were injected i.v. with PBS or 2x10^5 MK cultured from pooled bone marrow. After 60 minutes, and again on day 2, mice were treated with K/BxN serum 150μL i.p. p=0.0282.

Conclusion: This study identifies megakaryocytes – likely independent of daughter platelets, but potentially mediated by MK microparticles – as a previously unrecognized participant in arthritis, and more generally, as a highly novel actor in IL-1-mediated systemic disease.

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Abstract Number: 935

Microrna-146a Provides Feedback Regulation of Monosodium Urate-Induced Gouty Arthritis in Mice By Targeting Tumor Necrosis Factor Receptor Associated Factor 6 and Interleukin-1 Receptor-Associated Kinase 1

Quan-Bo Zhang[1,2], Jing-Guo Zhou[3], Cong-Cong Yin[1], Yu-Feng Qing[4], Chang-Gui Li[5], Li Zhou[1] and Qing-Sheng Mi[6], [1]Immunology Program, Department of Dermatology, Henry Ford Health System, Detroit, MI, [2]Geriatrics, Affliated hospital of North Sichuan Medical College, Nanchong, China, [3]Department of Rheumatology and Immunology, Affliated hospital of North Sichuan Medical College, Nanchong, China, [4]Affiliated Hospital of North Sichuan Medical College, Sichuan 637000, China, Nanchong, China, [5]Affiliated Hospital of Qingdao University, Qingdao, China, [6]Immunology, Dermatology, Henry Ford Health System, Detroit, MI

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Session Time: 2:30PM-4:00PM

Background/Purpose: MicroRNAs (miRNAs) have been shown to serve as important regulators for inflammatory and immune responses and are implicated in several immune disorders including gouty arthritis. The expression of miR-146a is upregulated in peripheral blood mononuclear cells in patients with intercritical gout compared to normouricaemic and hyperuricaemic controls and those with acute gout flares. However, the role of miR-146a in gout development remains unknown. Here, we use miR-146a knockout (KO) mice to test miR-146a function in monosodium urate (MSU) -induced gouty arthritis.

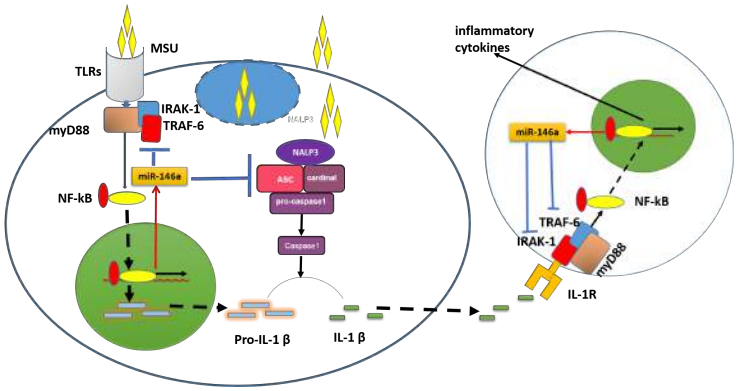
Methods: miR-146a KO and WT control mice were injected with MSU suspension into the foot pad (1mg/40ul) or ankle (0.5mg/20ul), respectively to induce the acute gouty arthritis. The bone marrow-derived macrophages (BMDM) were stimulated with 250ug/ml MSU and miR-146a, interleukin 1 beta (IL-1β), tumor necrosis factor-α (TNF-α) and NACHT, LRR and PYD domains-containing protein 3 (NALP3)

inflammasome gene expression were evaluated by qRT-PCR. The TNF-α and IL-1β protein level in BMDM were detected by FACS staining and western blot. Gene and protein levels of TRAF-6 and IRAK-1, the targets of miR-146a, were measured with qRT-PCR and western blot.

Results: MiR-146a expression in BMDM from C57/B6 mice was dramatically upregulated (160-folds compared to unstimulated cells) at 4 hours post MSU crystal stimulation. Significantly increased paw swelling index was observed in miR-146aKO mice compared to WT controls at 6h and 24h after MSU treatment (37.18±6.47% vs 27.03±8.03 at the 6h, $p<0.05$; 61.87±6.50% vs 37.78±3.38% at 24h, $p<0.05$, N=10 for each group). Consistent with increased paw swelling, miR-146aKO mice showed more severe ankle joint swelling compared to WT mice (40.38±2.19% vs 15.14±2.54% at 6h, $P<0.01$; 32.69 ±2.85% vs 24.75±3.96% at 24h and 8.74±3.27% vs 3.36±2.98% at 48h, $p<0.05$, N=10 for each group). The expression of IL-1β, TNF-α and NALP3 inflammatory, including of NALP3, ASC and caspase-1 were upregulated in BMDM after exposed to MSU crystals for 4 hours, compared to wild type mice. Consistent with the gene expression, the IL-1β and TNF-α protein were up-regulated in miR-146aKO mice. Finally, the qRT-PCR and western blot results showed that miR-146a targets, TRAF-6 and IRAK-1, were dramatically upregulated in BMDMs from miR-146 KO mice compared to that from WT.

Conclusion: Collectively, our data suggests that miR-146a provides feedback regulation of gout arthritis development and lack of miR-146a enhances gouty arthritis through upregulating TRAK-6/IRAK-1 and NALP3 inflammsome function (figure 1).

Figure 1. miR-146a provides feedback regulation of gout arthritis development through regulation of TRAK-6/IRAK-1 and NALP3 inflammsome



Disclosure: Q. B. Zhang, None; **J. G. Zhou**, None; **C. C. Yin**, None; **Y. F. Qing**, None; **C. G. Li**, None; **L. Zhou**, None; **Q. S. Mi**, None.

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Abstract Number: 936

IL-1 Receptor Antagonist Maintains Intestinal Microbial Homeostasis to Prevent Overt Toll-like Receptor 4-Dependent Intestinal Th17 Differentiation and Autoimmune Arthritis

Rebecca Rogier[1], Tom Ederveen[1], Jos Boekhorst[2], Harm Wopereis[3], Johan Garssen[4], Peter van der Kraan[5], Sacha van Hijum[2], Marije Koenders[6], Wim van den Berg[6] and **Shahla Abdollahi-Roodsaz**[7,8], [1]Rheumatology Research and Advanced Therapeutics, Radboud University Nijmegen Medical Center, Nijmegen, Netherlands, [2]Centre for Molecular Bioinformatics Nijmegen (CMBI), Radboud university medical center, Nijmegen, Netherlands, [3]Danone Research, Wageningen, Netherlands, [4]Danone Nutricia Research, Utrecht, Netherlands, [5]Rheumatology Research & Advanced Therapeutics, Radboud University Nijmegen Medical Centre, Nijmegen, Netherlands, [6]Experimental Rheumatology, Radboud university medical center, Nijmegen, Netherlands, [7]Medicine, NYU School of Medicine, New York, NY, [8]Rheumatology, Radboud university medical center, Nijmegen, Netherlands

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Background/Purpose: Interleukin-1 (IL-1) plays a pivotal role in inflammation and immunity. Activation of IL-1 receptor is physiologically inhibited by the IL-1 receptor antagonist (IL-1Ra). Mice lacking the IL-1Ra gene (*Il1rn*$^{-/-}$) are prone to several autoimmune diseases including arthritis; however, the mechanisms by which IL-1Ra provides protection against autoimmune disease remain unknown. Given recent evidence suggesting association of microbiome with autoimmunity, we investigated the role of IL-1Ra in regulation of the intestinal microbiome and the involvement of specific microbiota in development of arthritis.

Methods: Intestinal microbiota were characterized in wild-type and *Il1rn*$^{-/-}$ mice using high-throughput 16S rRNA pyrosequencing. Involvement of (intestinal) microbiota in arthritis dvelopment was investigated in germ-free (GF) mice and using oral broad-spectrum and selective antibiotic treatments combined with re-colonization with specific commensals. Intestinal T cell differentiation was assessed by multicolor flow cytometry on lamina propria (LP) mononuclear cells to evaluate potential correlations with arthritis. Cytokine production was determined in supernatants of LP, spleen and lymph node cells cultured with phorbol myristate acetate/ionomycin and preparations of fecal microbiota.

Results: Sequencing data showed that IL-1Ra critically maintains the diversity and the homeostatic composition of intestinal microbiota in mice. IL-1Ra deficiency caused specific taxonomic alterations characterized by overrepresented *Helicobacter* and underrepresented *Ruminococcus* and *Prevotella*. These alterations potentiated T helper 17 (Th17), but not Th1 and regulatory T cell, differentiation in intestinal lamina propria (LP). Notably, the increased LP Th17 proportion was observed in the absence of the major previously described Th17 inducers segmented filamentous bacteria (SFB). Importantly, LP Th17 expansion preceded the development and positively correlated with the severity of arthritis. The disease was markedly suppressed under germ-free condition, paralleled by a significant and specific reduction of IL-17 production in LP, spleen and lymph nodes draining the inflamed joints. Inhibition of arthritis was also achieved upon short-term treatment with broad-spectrum oral antibiotics. Interestingly, this protection was reversed by specific Th17, but not Th1, induction in LP upon colonization with SFB. In conventional *Il1rn*$^{-/-}$ mice lacking SFB, indigenous Gram-negative microbiota were surprisingly identified as disease inducers. Ablation of both IL-1Ra and Toll-like receptor 4 (TLR4) recognizing Gram-negative bacteria revealed that microbial TLR4 activation mediates intestinal and systemic Th17 differentiation and promotes arthritis by inducing mucosal IL-1β, TNFα and IL-23 while leaving IL-6 unaffected.

Conclusion: These findings outline a fascinating regulatory interplay between IL-1Ra, commensal microbiota, TLR4 and Th17 differentiation in the context of autoimmune arthritis. The data suggest a potential role for intestinal microbial TLR4 activation in the development of arthritis in addition to its previously described activation by endogenous agonists.

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Abstract Number: 937

Safety and Efficacy of Canakinumab in Patients with CAPS: Interim Results from the Beta-Confident Registry

Jasmin B. Kuemmerle-Deschner[1], Hal M. Hoffman[2], Philip N. Hawkins[3], T. van der Poll[4], Ulrich A. Walker[5], Antonio Speziale[6] and Hugh H. Tilson[7], [1]University Hospital Tuebingen, Tuebingen, Germany, [2]Division of Rheumatology, Allergy, and Immunology, University of California at San Deigo, La Jolla, CA, [3]University College London Medical School, London, United Kingdom, [4]Academic Medical Center, University of Amsterdam, Amsterdam, Netherlands, [5]Rheumatology, University Hospital, Basel, Basel, Switzerland, [6]Novartis Pharma AG, Basel, Switzerland, [7]University of North Carolina, Gillings School of Global Public Health, Chapel Hill, NC

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SESSION INFORMATION

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Session Type: ACR Concurrent Abstract Session

Background/Purpose: Cryopyrin-associated periodic syndrome (CAPS), is a rare autoinflammatory disease encompassing a spectrum of 3 phenotypes with an estimated population frequency ranging from 1-3 per million.[1,2] The β -confident Registry is a multicenter, long-term, observational study with an enrollment period of 5 years and a 1-year follow-up period to monitor the long-term safety and efficacy of canakinumab (CAN) for CAPS. The primary objective of the Registry is to monitor the overall safety of CAN, focusing on SAEs including serious infections, vertigo, malignancies, and hypersensitivity reactions. Here we report interim data of CAN in CAPS patients from the enrollment period.

Methods: The registry protocol does not mandate any visits or procedures; however, all observed and reported AEs and SAEs or AEs potentially related to CAN are recorded. Cumulative safety data are reported as incidence rate per 100 patient-years (IR/100 pyr) from the enrollment of the first patient (Nov 19, 2009) until the current data cut-off date (Dec 31, 2014). The enrollment is now complete and follow-up will continue through Dec 2015. Although only partial data are available for 11 patients owing to the cut-off date for the analysis, the data will be updated later. Efficacy was measured using physician global assessments (PGA).

Results: Overall, 288 patients were enrolled at 39 sites across 13 countries with mean patient exposure duration of 2.8 years. Of these, 21 (7.3%) discontinued CAN: 5 each due to AEs, poor efficacy, and patient preference; and 6 due to unknown reasons. The IR/100 pyr for overall AEs was 100.0. Patients with familial cold autoinflammatory syndrome (FCAS) had the lowest IR/100 pyr (60.9) compared to patients with Muckle–Wells syndrome (MWS) (IR/100 pyr 107.2), and chronic infantile neurologic cutaneous and articular (CINCA) syndrome/neonatal onset multisystem inflammatory disease (NOMID) (IR/100 pyr 120.3). The most common AEs were infections and infestations (IR/100 pyr, 36.7).

Vertigo was reported by 19 patients (IR/100 pyr, 3.7). Overall, 117 SAEs were reported by 62 patients (IR/100 pyr, 15.0), most commonly, infections (IR/100 pyr, 4.1). One death (metastatic rectal adenocarcinoma in 76-year-old MWS patient) was reported. Of 18 patients that received pneumococcal vaccination (PPV), 13 (72%) reported local post-PPV injection site reactions, of which 5 were considered as serious. Based on PGA, nearly half the patients had no disease activity, whereas most of the others experienced mild/moderate disease activity. Similarly, disease activity was mostly absent in patients with *NLRP3* mutation negative CAPS (n=14) treated with CAN. No evidence of loss of effect was observed with time. Further analyses of this cohort are ongoing.

Conclusion: The β -confident Registry is the largest CAPS cohort documented in a registry. Canakinumab demonstrated a safety profile consistent with that observed in the clinical trial program and provided continued effectiveness in patients with CAPS for up to 5 years. Canakinumab therapy was also effective in patients with *NLRP3* mutation negative CAPS.

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Disclosure: J. B. Kuemmerle-Deschner, Novartis Pharmaceutical Corporation, 8,Novartis and Sobi, 5; **H. M. Hoffman**, Novartis Pharmaceutical Corporation, 8,Novartis and Sobi, 5; **P. N. Hawkins**, Novartis Pharmaceutical Corporation, 5; **T. van der Poll**, None; **U. A. Walker**, Novartis Pharmaceutical Corporation, 5; **A. Speziale**, Novartis, 3; **H. H. Tilson**, Novartis Pharmaceutical Corporation, 5.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/safety-and-efficacy-of-canakinumab-in-patients-with-caps-interim-results-from-the-beta-confident-registry

Abstract Number: 938

Long-Term Efficacy and Safety of Canakinumab in Patients with Active Recurrent or Chronic TNF Receptor-Associated Periodic Syndrome

Marco Gattorno[1], Marco Cattalini[2], L. Obici[3], Roberto Barcellona[4], Antonio Speziale[5], Yolandi Joubert[5], Guido Junge[5] and Helen Lachmann[6], [1]Pediatric Rheumatology, G. Gaslini Institute, Genova, Italy, [2]Pediatric Clinic, University of Brescia, Brescia, Italy, [3]Amyloid Centre, Policlinico S. Matteo, Pavia, Italy, [4]Hospital of Sciacca, Sciacca, Italy, [5]Novartis Pharma AG, Basel, Switzerland, [6]UK National Amyloidosis Centre, University College London Medical School, London, United Kingdom

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Background/Purpose: Tumor necrosis factor (TNF) receptor-associated periodic syndrome (TRAPS) is a rare, dominantly inherited periodic fever syndrome characterized by recurrent attacks of fever associated with rash, musculoskeletal and abdominal pain, conjunctivitis, and periorbital edema.[1] Nonsteroidal anti-inflammatory drugs and high-dose corticosteroids are often used for acute symptomatic relief but are limited by their well-known side effects. TNF inhibitors have been shown to be effective in some patients, however, their efficacy tends to decrease over time.[2–4] Here we present the long-term safety and efficacy of canakinumab (CAN) in patients with active TRAPS. The primary objective was to assess if CAN induces complete or almost complete response in patients on Day 15. Secondary objectives included clinical and serological remission, changes in signs and symptoms of TRAPS and physician's global assessment (PGA) over time, as well as assessment of adverse events (AEs) and serious AEs (SAE) reported.

Methods: This was an open-label single treatment arm study with a 4-month treatment period, a 5-month follow-up period (treatment withdrawal), and a 24-month long-term treatment period. Patients with active TRAPS received monthly CAN 150 mg (2 mg/kg for patient ≤40 kg) subcutaneously.

Results: At baseline, PGA of TRAPS activity showed 13 (65%) patients with mild, 6 (30%) with moderate and 1 (5%) with severe TRAPS; with chronic TRAPS being present in 11 (55%) patients. Of all the 20 patients who received CAN, 18 (90%) completed the study. On day 15, 19 patients (95%) achieved a complete or almost complete response, while 20 (100%) and 12 (60%) patients had clinical and serological remission, respectively (Table). Disease activity decreased in the long-term treatment period, and most patients experienced absent, minimal, or mild disease activity. At the end of the long-term period, all patients had absent (84.2%) or minimal (10.5%) disease activity. CRP and SAA levels were highest at baseline and decreased rapidly with treatment. In total, 12 patients (60%) experienced study drug-related AEs, predominantly upper respiratory tract infections. Seven patients (35%) experienced SAEs; none were related to the study drug. There were no AEs leading to discontinuation and no deaths were reported during the study.

Table. Clinical and serological remission on Days 8 and 15		
Response criteria	**Canakinumab N=20, n (%)**	**95% CI***
Complete or almost complete response (Day 8)	16 (80)	(56.3, 94.3)
Complete or almost complete response (Day 15)	19 (95)	(75.1, 99.9)
Proportion of patients with complete clinical remission (PGA score ≤1; Day 8)	18 (90)	(68.3, 98.8)
Proportion of patients with complete clinical remission (PGA score ≤1; Day 15)	20 (100)	(83.2, 100.0)
Proportion of patients with both CRP and SAA ≤10 mg/L (Day 8)	7 (35)	(15.4, 59.2)
Proportion of patients with both CRP and SAA ≤10 mg/L (Day 15)	12 (60)	(36.1, 80.9)
Proportion with complete or almost complete response on Day 15 in the patient subgroup without complete or almost complete response on Day 8	4 (100)	(39.8, 100.0)
Complete response: Clinical (PGA ≤minimal) and serological (CRP and/or SAA <10 mg/L) remission Almost complete response: Clinical (PGA ≤minimal) and partial serological (≥70% reduction of baseline CRP and/or SAA) remission *95% CI (Clopper–Pearson) CI, confidence interval; CRP, C-reactive protein; PGA, physician's global assessment; SAA, serum amyloid A		

Conclusion: Canakinumab demonstrated rapid disease control in terms of clinical signs and symptoms, and serological response in patients with active TRAPS through the treatment and long-term treatment periods. No new safety signals were reported during this long-term study. Safety profile was consistent with those reported in other canakinumab studies.

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Disclosure: M. Gattorno, Novartis Pharmaceutical Corporation; SOBI, 2,Novartis Pharmaceutical Corporation; SOBI, 8; **M. Cattalini**, Novartis Pharmaceutical Corporation: SOBI, 5,Novartis Pharmaceutical Corporation, 8; **L. Obici**, Novartis Pharmaceutical Corporation, 5,Novartis Pharmaceutical Corporation, 8; **R. Barcellona**, None; **A. Speziale**, Novartis, 3; **Y. Joubert**, Novartis Pharmaceutical Corporation, 3; **G. Junge**, Novartis., 3; **H. Lachmann**, Novartis Pharmaceutical Corporation, 5.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/long-term-efficacy-and-safety-of-canakinumab-in-patients-with-active-recurrent-or-chronic-tnf-receptor-associated-periodic-syndrome

Abstract Number: 939

Long-Term Efficacy and Safety of Canakinumab in Active Hyperimmunoglobulinemia D with Periodic Fever Syndrome

Juan Ignacio Arostegui[1], Jordi Anton[2], Inmaculada Calvo-Penedes[3], Angel Robles[4], Antonio Speziale[5], Yolandi Joubert[5], Guido Junge[5] and Jordi Yagüe[6], [1]Department of Immunology-CDB, Hospital Clínic, Barcelona, Spain, [2]Unitat de Reumatologia Pediàtrica, Hospital Sant Joan de Déu, Barcelona, Spain, [3]Hospital de La Fe, Valencia, Spain, [4]Hospital La Paz, Madrid, Spain, [5]Novartis Pharma AG, Basel, Switzerland, [6]Immunology Department, Hospital Clinic Barcelona, Barcelona, Spain

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SESSION INFORMATION

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Session Type: ACR Concurrent Abstract Session

Background/Purpose: Hyperimmunoglobulinemia D with periodic fever syndrome (HIDS) is a recessively inherited disorder characterized by periodic episodes of high fever, abdominal distress, joint pain, and skin rashes.[1] Previous reports suggested interleukin (IL)-1 blockade as a potential therapy in HIDS.[2,3] Here we report the final results of a 36-month study assessing the efficacy and safety of the anti-IL-1β human monoclonal antibody canakinumab in patients with active HIDS and biallelic mevalonate kinase *(MVK)* mutations.

Methods: This was an open-label single treatment arm study with a 6-month treatment period (6mo-TP), an up-to 6-month follow-up period (6mo-FP), and a 24-month long-term treatment period (24mo-LTTP). The 6mo-TP included canakinumab administration (4 mg/kg q6w, max 300 mg, subcutaneously), with one permissible dose up-titration to 6 mg/kg (max, 450 mg) if a flare occurred in the first 6 weeks. In the 24mo-LTTP, patients received the same canakinumab dose administered at the last visit of the 6mo-TP. The primary objective of the study was to assess the reduction in frequency of flares during the 6mo-TP compared with a 6-month historical treatment-free period. Secondary objectives were evaluated for the entire study and included assessment of reduction in frequency of flares, changes in flare duration, changes in physician's global assessment (PGA) of flare severity and disease control, changes in plasmatic inflammatory markers, and adverse events (AEs).

Results: All enrolled patients (n=9) completed both the 6mo-TP and the 6mo-FP. Eight patients also completed the 24mo-LTTP. The median number of flares decreased from 5 (3-12) in the historical period to 0 (0-2) during the 6mo-TP, and persisted (0-3) until the end of the study. During the 24mo-LTTP, the median flare duration was 3.5 days (2-8) in the first year and 8.5 days (6-11) in the second. PGA of flare severity was “mild” to “moderate” at baseline (n=9) and remained the same through the TP (n=2) and 6mo-FP (n= 7). Flare severity reduced to “mild” or “minimal” and “mild” or “without signs/symptoms” in the first (n=4) and second years (n=2) of the 24mo-LTTP, respectively. PGA disease control scores improved in all patients from either “no” or “poor” control at baseline to “good” or “excellent” control by Day 4, which persisted until the end of the study. Plasma levels of C-reactive protein and serum amyloid A normalized by Day 15 and remained in normal values until the end of the study. The most frequent AEs were infections. No deaths were registered. No AE led to study discontinuation. Four patients experienced 14 serious AEs (mild to moderate), none considered as drug-related.

Conclusion: Canakinumab treatment substantially reduced the frequency of flares in active HIDS and provoked a rapid control of signs and symptoms as well as normalization of plasmatic inflammatory markers. No unexpected safety findings were observed through the study, and safety profile was consistent with those reported in other canakinumab studies.

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Disclosure: J. I. Arostegui, Novartis Pharmaceutical Corporation, 2; **J. Anton**, Novartis Pharmaceutical Corporation, 2,Novartis Pharmaceutical Corporation, 5,Novartis Pharmaceutical Corporation, 8; **I. Calvo-Penedes**, Novartis Pharmaceutical Corporation;Pfizer Inc; Abbvie; Roche Pharmaceuticals, 2,Novartis Pharmaceutical Corporation; Abbvie; Gebro; Roche, 8; **A. Robles**, None; **A. Speziale**, Novartis, 3; **Y. Joubert**, Novartis Pharmaceutical Corporation, 3; **G. Junge**, Novartis., 3; **J. Yagüe**, Novartis Pharmaceutical Corporation, 2.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/long-term-efficacy-and-safety-of-canakinumab-in-active-hyperimmunoglobulinemia-d-with-periodic-fever-syndrome

Abstract Number: 940

NOD2-Associated Autoinflammatory Disease: Therapy and Outcomes

Qingping Yao[1] and Bo Shen[2], [1]Cleveland Clinic, Cleveland, OH, [2]Gastroenterology, Cleveland Clinic, Cleveland, OH

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SESSION INFORMATION

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Background/Purpose:

NOD2-associated autoinflammatory disease, now redesignated as Yao Syndrome(YS) is a newly described and increasingly recognized entity. It is characterized by periodic fever, dermatitis, polyarthritis, sicca-like and gastrointestinal symptoms, and genotypically associated with *NOD2* mutations. Our aim was to evaluate the treatment and outcomes of the disease.

Methods:

A cohort of 52 adult patients with autoinflammatory phenotypes diagnosed with YS were enrolled at the Cleveland Clinic between November

2009 and March 2015. All patients were genotyped for the *NOD2*mutations. These patients were prospectively studied for treatment outcomes.

Results: All 52 patients were whites, with female accounting for 72%. The mean age at diagnosis was 38.0±12.0 years and the disease duration was 8.8±5.8 years. The clinical phenotypes included periodic occurrence, weight loss (42%), fever (67%), dermatitis (90%), inflammatory arthritis (79%), leg swelling (30%), gastrointestinal symptoms (65%), sicca-like (58%), oral ulcers (27%), and pericarditis/pleuritis (8%). All 52 patients carry *NOD2* gene mutations, including IVS8+158(98%) and/or R702W (19%). The majority (90%) of patients tried nonsteroidal anti-rheumatic drugs without obvious benefits. Nineteen (36%) received prednisone for flares, including a short course (30-40 mg/day x1-3 days) in 9 patients, with a marked reduction in disease severity and interval. Twenty-two (42%) received sulfasalazine (2g/day), with significant symptomatic improvement. Methotrexate and hydroxychloroquine were tried without noticeable benefits. For frequent flares, particularly high fever and inflammatory arthritis, three patients received infliximab with only partial clinical response in one. Two patients received anakinra with partial response in one. Two patients received canakinumab and both had partial response. One patient received tocilizumab with good response. During nearly 9 years of the disease course, most patients had intermittent disease flares. Only one patient had mild joint deformity. No inflammatory bowel disease or primary Sjögren's syndrome was found. Five patients had mild anemia, and no patients developed nephritis, liver, lung parenchymal or central nervous system disease. Seven patients had low levels of immunologobulins, four of whom had recurrent infections, and one received intravenous immunoglobulin infusions. One patient had monoclonal gammopathy of undetermined significance. Associated comorbidities with YS included fibromyalgia in 11 patients, asthma in seven, renal stones in three, and ventricular hypertrophy in two. Seven of the 52 patients had impaired physical functionality. No mortality was found.

Conclusion: Our study demonstrates that YS is a systemic autoinflammatory disease without major solid organ involvement, though it may lead to chronic pain and potential functional impairment. Glucocorticoids and sulfasalazine are effective, and IL-1 and IL-6 antagonists may be beneficial. Further study of the disease mechanisms and a search for more effective drugs are warranted.

Disclosure: Q. Yao, None; **B. Shen**, None.

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Abstract Number: 941

Relationship Between Colchine Plasma Level and Frequency of Familial Mediterranean Fever Attacks

Fadime Canbolat[1], **Gulsen Ozen**[2], Selma Ozilhan[1], Samet Gulturk[3], Ayse Ozcetin[4], Ali Ugur Unal[2], Nevsun Inanc[2], Pamir Atagunduz[2], Haner Direskeneli[2] and Tuncel Ozden[1], [1]Department of Pharmacology, Uskudar University Pharmacogenetic Laboratory, Istanbul, Turkey, [2]Department of Rheumatology, Marmara University Faculty of Medicine, Istanbul, Turkey, [3]Department of Molecular Biology and Genetics, Uskudar University, Istanbul, Turkey, [4]Department of Neuroscience, Uskudar University, Istanbul, Turkey

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Background/Purpose: Colchicine is the mainstay of Familial Mediterranean Fever (FMF) treatment that reduces the frequency of attacks and prevents amyloidosis in the majority of patients. Colchicine, despite its narrow therapeutic window, is a well-tolerated oral drug that is rapidly absorbed by the gastrointestinal tract. However not all patients respond to colchicine and the response is not universal at the same doses. Therefore some patients require higher doses of colchicine to suppress their attacks. In this study we aimed to investigate the relationship between colchicine plasma levels and clinical response to colchicine in FMF patients.

Methods: Forty FMF patients with normal renal and hepatic functions, receiving colchicine regularly (steady state dose for at least 3 months with good compliance) were enrolled to the study in a 6 month-period. Blood samples were collected 30 minutes before the next colchicine dose. Colchicine plasma levels have been measured by using the device consecutive high performance liquid chromatography-mass spectrometry (LCMS-MS). Internal standard was added to plasma and the solution was extracted with ether:dichlormethane. Organic phase was evaporated to dryness under nitrogen. The residue dissolved in methanol was injected into the system. Quantitation was based on monitoring precursor ion and product ion for colchicine m/z 400.2 > 310.3, and for internal standart colchicine- d3 m/ z 403.3> 359.2. The assay was linear for colchicine over the range of 0.25-8 ng/ ml, $r^2$is 0.997.

Results: Of the 40 patients using colchicine, 24 were receiving 1.5 mg/day and 16 were receiving 2 mg/day. The mean plasma colchicine concentration of the entire cohort was 1.097±0.42 ng/mL and was within the therapeutic range (0.5-3ng/mL). The mean plasma colchicine concentrations of patients who were on 1.5 mg/day (1.05 ng/mL) and 2 mg/day (1.17 ng/mL) colchicine treatment were not significantly different (P=0.40). Plasma colchicine concentrations positively correlated with daily oral colchicine dose. Before colchicine treatment, the mean attack number was 24.947±3.22 /year and after colchicine treatment was 1.631±0.42/year (P<0.0001). The patients who were on 1.5 mg/day and 2 mg/day colchicine treatment had similar % of decrease in attack frequency (85.6% vs 89.2 %, P= 0.43). Optimal clinical response (decrease in the frequency of attacks) was observed at oral doses of 1.5-2 mg/day, corresponding to plasma levels of approximately 1.097±0.42ng/ml.

Conclusion: These data indicate that colchicine plasma levels correlate with daily oral doses of colchicine. FMF patients receiving 1.5 mg/day and 2 mg/day colchicine doses have similar plasma colchicine concentrations and also similar decrease in attack frequency. To evaluate the role of colchicine metabolism and plasma concentrations on the different dose requirements for optimal suppresion of attacks and on the colchicine-refractory FMF, further data is currently being studied by our group.

Disclosure: F. Canbolat, None; **G. Ozen**, None; **S. Ozilhan**, None; **S. Gulturk**, None; **A. Ozcetin**, None; **A. U. Unal**, None; **N. Inanc**, None; **P. Atagunduz**, None; **H. Direskeneli**, None; **T. Ozden**, None.

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Abstract Number: 942

Update in the Management of Biologic Response Modifiers and Disease-Modifying Antirheumatic Drugs Following Coccidioidomycosis

Usman Ajaz[1], Neil M. Ampel[2], Varun Bhalla[3], Jeffrey R. Lisse[4] and Dominick Sudano[5], [1]Department of Medicine, University of Arizona, Tucson, AZ, [2]Department of Infectious Disease, Southern AZ VA Medical Center, Tucson, AZ, [3]University of Arizona, Tucson, AZ, [4]Arizona Arthritis Center, University of Arizona, Tucson, AZ, [5]Rheumatology, University of Arizona, Tucson, AZ

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Background/Purpose: In the Southwestern United States, Coccidioidomycosis (cocci) or Valley fever is an endemic fungal infection. It typically presents as a self-limited pulmonary illness. Patients with autoimmune diseases on disease-modifying antirheumatic drug (DMARD) or biologic response modifier (BRM) are at higher risk of more severe infection or infection disseminated outside the thoracic cavity. Currently, there are no management guidelines for cocci in such patients; however, retrospective data from the largest cohort of patients followed longitudinally suggests that retreatment of the rheumatic disease may be safe in some patients, and a management strategy based on cocci disease activity has been developed and implemented.

Methods: A retrospective chart review was performed and identified patients at two centers in Tucson, Arizona, who developed cocci on DMARD and/or BRM therapy. Patients were seen at least once between 2007 and 2014. Review emphasized the underlying rheumatic disease, manifestations of cocci, antifungal therapy, outcome, and management of BRM/DMARD therapy.

Results: 71 patients on DMARD and BRM therapy were identified. Among these patients, 19 were on BRM therapy, 16 were on DMARD and 36 were on combination therapy. Coccidioidomycosis was asymptomatic with positive serologies only in 19; 41 had pulmonary disease; while 10 were disseminated. BRM and DMARD therapy was stopped in 37 while in 14, BRM was stopped but DMARD continued. There was no change in immunosuppressive therapy in 20 patients. 52 patients were initially treated with antifungal therapy for 3 months or longer. Two of the patients with pulmonary illness and 12 patients with asymptomatic infection did not receive any antifungal therapy.

64 patients had follow up, out of which 50 patients continued BRM and/or DMARD therapy, and 22 received antifungal therapy. Four patients with disseminated disease restarted BRM therapy. Persistent positive serology and disseminated disease were the most common reasons for continuing antifungal therapy. Conversion to negative serology was the most common reason for stopping antifungal therapy. Patients were followed for a median of 29 months (range 2-141). There was one death from the group who was on DMARD and corticosteroid therapy. The deceased patient had disseminated coccidioidomycosis and was on antifungal treatment. There have been no deaths in the last three years. One patient with history of coccidioidal meningitis had relapse of disease, which was most likely related to his non-adherence with antifungal therapy.

Conclusion: Retreating or continuing DMARD and/or BRM therapy after cocci infection appears to be safe in some patients with close monitoring. If Cocci is asymptomatic, continuation of DMARD and/or BRM can be considered. In patients with pulmonary or disseminated infection, immunosuppressive therapy should be stopped and antifungal therapy should be continued until there is evidence of control of the infection. The management strategy implemented may be effective in guiding therapy.

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Abstract Number: 943

Development of an Internationally Agreed Minimal Dataset for Juvenile Dermatomyositis (JDM) for Clinical and Research Use

Liza J. McCann[1], Lucy R Wedderburn[2], Clarissa Pilkington[3], Adam M. Huber[4], Angelo Ravelli[5], Jamie Kirkham[6], Paula Williamson[6] and Michael W. Beresford[7], [1]Paediatric Rheumatology, Alder Hey Children's NHS Foundation Trust, Liverpool, United Kingdom, [2]Infection, Inflammation and Rheumatology Section, UCL Institute for Child Health, London, United Kingdom, [3]Department of Rheumatology, Great Ormond Street Hospital for Children NHS Trust, London, United Kingdom, [4]Pediatric rheumatology, IWK Health Centre, Halifax, NS, Canada, [5]Pediatria-II, IRCCS G. Gaslini and University of Genova, Genova, Italy, [6]Department of Biostatistics, University of Liverpool, MRC North West Hub for Trials Methodology Research, Liverpool, United Kingdom, [7]Alder Hey Children's NHS Foundation Trust Hospital, Institute of Translational Medicine (Child Health), University of Liverpool, Liverpool, United Kingdom

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Session Time: 2:30PM-4:00PM

Background/Purpose: Juvenile dermatomyositis (JDM) is a rare disease. International collaboration is essential for scrutiny of sufficient patient numbers. We aim to develop a core set of data for all clinicians/ researchers to collect in a standardized way, with international agreement.

Methods: Comparing variables in existing clinical registries led to a provisional minimal dataset.[1] A two-stage e-mail Delphi-process engaged the opinion of a large number of key stakeholders via established international paediatric rheumatology/ myositis organizations. Consensus that each outcome should be included in the dataset was defined by ≥70% of participants scoring 'critical for decision making'. This, together with a formalized patient / parent participation process (ongoing) informed a consensus meeting of internationally representative myositis experts. Nominal group technique was used, with agreement of ≥80% consensus required for each variable to be included. The resulting dataset will be tested for feasibility within existing databases and sent to all internationally representative collaborators for final comment.

Results: Delphi responses from healthcare professionals (n=181 in round 1, 146 in round 2; 12% attrition), patients (n=14) and parents (n=20) were used to inform a consensus meeting of experts. The expert group (n=18) determined the need to include a measure of improvement /worsening of disease as well as binary documentation (feature 'present / absent'). A visual analogue scale (VAS) was thus included for each major domain. 74 variables were included in the proposed dataset (Table 1 & 2) with further damage items under consideration. 'Optimal dataset' replaced the term 'minimal dataset'. The dataset will be developed further after testing accuracy of data capture in clinical practice and analyzing additional patient/parent questionnaires.

Conclusion: An internationally agreed optimal dataset has the potential to significantly enhance collaboration, provide a standard of care and enable analysis of the largest possible number of JDM patients to provide a greater understanding of this disease. The final approved core dataset could be rapidly incorporated into national/international collaborative efforts.

Table 1: Variables to be collected at first visit only (diagnosis):

Section headings	**Variables to be collected**
Personal factors (demo-graphics)	Date of birth
	Sex
	Age / date at first symptom of myositis
	Age / date at diagnosis of JDM
Diagnostic factors	MRI scan at diagnosis (if done) consistent with myositis
	Muscle biopsy (if done) consistent with myositis
	Myositis specific antibodies (MSA) positive at diagnosis – if taken
	Myositis associated antibodies (MAA) positive at diagnosis – if taken
Treatments received prior to diagnosis	Has this patient received systemic glucocorticoids prior diagnosis of JDM – yes / no
	Has this patient received any synthetic or biologic disease modifying anti-rheumatic drug prior to the diagnosis?

Table 2: Variables to be collected at every visit:

Section headings	Variables to be collected (details not shown)
Growth & development	Height, weight, puberty self assessment
Muscular	Symmetrical muscle weakness, Childhood Myositis Assessment Scale (CMAS), Manual Muscle Testing (MMT8)
Cutaneous	Features included in abbreviated Cutaneous Assessment Tool (CAT) score
Skeletal	Arthritis / contractures & Visual Analogue Scale (VAS) for skeletal activity
Gastrointestinal	Dysphagia, abdominal pain, gastrointestinal ulceration & VAS for gastrointestinal
Pulmonary	Pulmonary involvement / interstitial lung disease, dysphonia & VAS for pulmonary activity
Cardiovascular	Cardiovascular involvement, blood pressure & VAS for cardiovascular activity
Constitutional features	Fever, weight loss, fatigue & VAS for constitutional activity
Physician Global	Physician global VAS & extra-muscular activity VAS
Patient / parent outcome	Patient / Parent measure of function & participation
Investigations	Muscle enzymes & other specimens available
Treatment	Drug treatment & exercise routine: range of movement & muscle strength
Outcome / disease impact	Malignancy / death
Damage items (annual)	To include damage items across domains

References: 1. McCann LJ et al. Pediatric Rheumatology 2014. 12: 31

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Abstract Number: 944

Activity of Type I and Type II Interferons in Dermatomyositis Skin Is Correlated with Characteristic Pathologic Features

Hayley W. Leatham[1], Kerri Rieger[2], Lorinda Chung[3], Shufeng Li[1], Brandon W. Higgs[4], Yihong Yao[4], Kavita Sarin[1] and David Fiorentino[1], [1]Dermatology, Stanford University, Stanford, CA, [2]Dermatopathology, Stanford University, Stanford, CA, [3]Division of Immunology and Rheumatology, Stanford University School of Medicine, Stanford, CA, [4]Translational Sciences, MedImmune, LLC, Gaithersburg, MD

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Session Time: 2:30PM-4:00PM

Background/Purpose :

Interferon (IFN) signaling is upregulated in dermatomyositis (DM) skin, but the relationship to classic histopathologic features is unknown.

Methods :

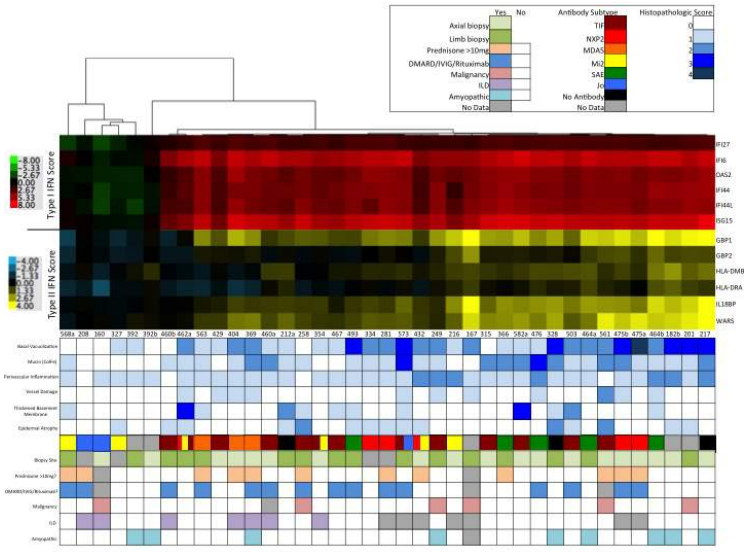
Thirty-nine skin biopsies from patients with dermatomyositis underwent gene expression analysis using Affymetrix arrays, as well as histologic analysis by a blinded dermatopathologist. Biopsies were scored for severity of several cardinal histopathologic features, including basal vacuolar change (BV), dermal mucin deposition, and perivascular inflammation. Type I and type II IFN scores were generated based on the average relative expression of selected genes previously demonstrated to be upregulated by IFN-alpha and IFN-gamma, respectively. Expression levels of IFN transcripts were measured by quantitative PCR. Univariate analysis was performed to evaluate the association between IFN scores and IFN transcripts with key histopathologic features, with subsequent multivariate models constructed to include potentially confounding variables such as biopsy site, medication use, age, and length of disease.

Results :

Skin biopsies were highly heterogeneous regarding both histopathologic features as well as type I or II IFN scores. Type I IFN scores correlated strongly with IFN beta expression ($r=0.75$, $p<0.0001$) but not other type I (alpha, kappa, omega) or type II IFN transcript levels. In univariate analysis, keratinocyte injury (reflected by BV score) was found to be associated with both type I and type II IFN scores ($p=0.0014$ and $p=0.004$, respectively); these associations remained significant in multivariate analysis. In contrast, dermal mucin deposition was highly correlated with the type I IFN ($p<0.0001$) but not type II IFN ($p=0.071$) activity. However, lymphocytic dermal inflammation was associated with type II IFN score ($p=0.0413$), but not the type I IFN score ($p=0.3088$). Additional histologic features, including epidermal atrophy, basement membrane thickening, and vessel damage were not statistically associated with either IFN score.

Conclusion :

Our results highlight that IFN signaling in DM skin likely represents a combination of at least type I and II IFN activity. Furthermore, our data suggest that type I and II signaling are each associated with shared as well as distinct pathologic processes in DM skin. Keratinocyte injury, the sine qua non finding in DM skin, is associated with both type I and II IFN activity. Finally, our results imply that IFN beta is the relevant IFN driving type I IFN signaling in DM skin and point to both IFN beta and IFN gamma as potential targets of pharmacologic inhibition in cutaneous DM.



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Abstract Number: 945

Anti-Hmgcr Antibodies As Specific Marker for Immune Mediated Necrotizing Myopathies

Lucile Musset[1], Chelsea Bentow[2], Marvin J. Fritzler[3], Jiri Vencovsky[4], Olivier Benveniste[5], Ignacio Garcia de la Torre[6], Franco Franceschini[7], Katalin Danko[8], Qinglin Peng[9], Sophie Hue[10], Olivier Boyer[11], Nicola Bizzaro[12], Yoshinao Muro[13], Xavier Bossuyt[14], Anna Ghirardello[15] and **Michael Mahler**[16], [1]Immunology, Immunochemistry & Autoimmunity Laboratory, Pitié-Salpêtrière University Hospital, Paris, France, [2]Research, Inova Diagnostics, San Diego, CA, [3]Medicine, University of Calgary, Calgary, AB, Canada, [4]Institute of Rheumatology, Charles University, Prague, Czech Republic, [5]Department de Internal Medicine and Clinical Immunology, Hôpital Pitié-Salpêtrière, AP-PH, UPMC, Paris, France, [6]Hospital General de Occidente, Zapopan, Mexico, [7]Rheumatology and Clinical Immunology, Spedali Civili and University of Brescia, Brescia, Italy, [8]Division of Clinical Immunology, 3rd Department of Internal Medicine, Medical and Health Science Center, University of Debrecen, Debrecen, Hungary, Co-Author, Debrecen, Hungary, [9]Department of Rheumatology, China-Japan Friendship Hospital, Beijing, China, [10]CHU Henri Mondor, APHP, Créteil, France, [11]Immunology, INSERM, U905 & Normandy University, Institute for Research and Innovation in Biomedicine, Rouen University Hospital, Rouen, France, [12]Laboratory of Clinical Pathology, San Antonio Hospital, Tolmezzo, Italy, [13]Dermatology, Division of Connective Tissue Disease & Autoimmunity, Nagoya University Graduate School of Medicine, Nagoya, Japan, [14]Laboratory Medicine, University Hospitals Leuven, and Department of Microbiology and Immunology, Catholic University of Leuven, Leuven, Belgium, [15]Department of Medicine-DIMED, University of Padova, Padova, Italy, [16]Inova Diagnostics, San Diego, CA

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SESSION INFORMATION

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Session Type: ACR Concurrent Abstract Session

Session Time: 2:30PM-4:00PM

Background/Purpose :

Autoantibodies are important biomarkers in the diagnosis of idiopathic inflammatory myopathies (IIM) including polymyositis (PM) and dermatomyositis (DM), inclusion body myositis (IBM) as well as overlap syndromes. Recently, it was reported that the prevalence of necrosis in patients with IIM is increasing and that the majority of the patients with necrosis exhibit autoantibodies to 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR), the molecular target of statins. This is the first international multi-center study on anti-HMGCR antibodies in a large cohort of patients.

Methods:

A total of 1906 samples from IIM patients and controls were collected at 12 different sites from nine different countries. Among patients with IIM (n=1250), 69 had immune mediated necrotizing myopathies (IMNM), 406 had PM, 525 had DM, 10 had PM/Scleroderma overlap syndrome, 45 had juvenile dermatomyositis (JDM), 18 had myositis overlap syndromes (MOS), 53 had amyopathic dermatomyositis (ADM), 49 had antisynthetase syndrome (ASS), 64 had cancer-associated myositis and 11 had IBM. All samples were tested for anti-HMGCR antibodies by ELISA.

Results:

Anti-HMGCR antibodies were present in 44.9% of IMNM, 4.4% of PM, 1.9% of DM, 6.7% of JDM, in 1.2% of primary Sjögren`s syndrome (pSS) and in 0.4% of systemic lupus erythematosus patients (see Table 1).

Table 1 Prevalence of anti-HMGCR antibodies in different disease cohorts

Disease Group	N=	Prevalence	95% CI
Immune Mediated Necrotizing Myopathy (IMNM)	31/69	44.9%	33.8-56.6%
Polymyositis (PM)	18/406	4.4%	2.8-6.9%
Dermatomyositis (DM)	10/525	1.9%	1.0-3.5%
Juvenile Dermatomyositis (JDM)	3/45	6.7%	2.3-17.9%
Primary Sjögren's Syndrome (pSS)	1/81	1.2%	0.02-6.7%
Systemic Lupus Erythematosus (SLE)	1/226	0.4%	0.01-2.5%

Among the IMNM patients, statin exposure was known for 45 patients. Patients tested positive for the anti-HMGCR were more frequently statin users (21 vs. 10; $p<0.0001$), showed a higher prevalence of necrosis ($p<0.0001$) and were older ($p=0.0001$) compared to ant-HMGCR negative patients. Receiver operating characteristic analyses showed good discrimination between IMNM and controls, and between IMNM and other forms of IIM. The prevalence of anti-HMGCR antibodies was highest in statin exposed elderly individuals (>50 years) diagnosed as IMNM reaching 76.5%.

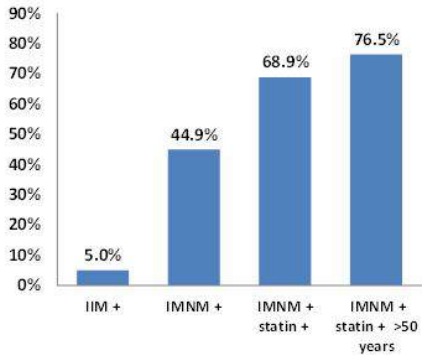

Figure 1 **Incremental prevalence of anti-HMGCR antibodies in different patient subsets**

Conclusion:

Anti-HMCGR antibodies characterize a subpopulation of IMNM patients previously exposed to statin and were significantly associated with an older age. However, it is important to note that not all patients with those autoantibodies had a history of exposure to statins indicating that different phenotypes and mechanisms exist.

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Abstract Number: 946

Novel Tripartite Motif Proteins Linked to Membrane Integrity As Biomarkers of Dermatomyositis and Polymyositis

Kevin McElhanon[1], Jenna Alloush[1], Nicholas A. Young[2], Zarife Sahenk[3], Rohit Aggarwal[4], Chester V. Oddis[5], Wael N. Jarjour[2] and Noah Weisleder[1], [1]Department of Physiology and Cell Biology, Davis Heart and Lung Research Institute, The Ohio State University College of Medicine, Columbus, OH, [2]Immunology and Rheumatology, The Ohio State University Wexner Medical Center, Columbus, OH, [3]Neurology, Research Institute at Nationwide Children's Hospital, Columbus, OH, [4]Department of Medicine / Rheumtology, University of Pittsburgh Medical Center, Pittsburgh, PA, [5]Rheum/Clinical Immunology, University of Pittsburgh, Pittsburgh, PA

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Session Time: 2:30PM-4:00PM

Background/Purpose:

The mechanisms that contribute to the pathogenesis of the idiopathic inflammatory myopathies remains largely unknown. This heterogeneous group of diseases involve autoimmunity toward muscles that results in tissue destruction. Previous studies on the synaptotagmin VII-knockout (Syt VII$^{-/-}$) mouse model revealed these mice develop myositis that could be exacerbated by combining the Syt VII$^{-/-}$ model with regulatory T-cell deficiency (FoxP3$^{-/Y}$) by adoptively transferring into immunodeficient (RAG1$^{-/-}$) recipients. Other studies indicate that Syt VII$^{-/-}$ mice have impaired sarcolemmal membrane resealing capacity, a defect that results in increased membrane permeability and resulting exposure of intracellular antigens to the extracellular space. Additional genes have been linked to membrane resealing, including members of the large tripartite motif (TRIM) gene family, where deletion of these genes result in myopathy. Our previous studies show that TRIM72/MG53 is essential for sarcolemmal membrane repair in striated muscles. Alteration of the expression levels of, or autoantibody responses to, TRIM72/MG53 and related TRIM proteins levels could alter membrane repair in the context of myositis and contribute to progression of the disease. Here, we examined protein expression levels of several related novel TRIM proteins in muscle tissue from this myositis mouse model and human myositis patients. Additional studies screened for autoantibody responses to these TRIM proteins in serum samples from other human myositis patients.

Methods: Muscle biopsies from myositis patients were collected and analyzed by standard Western immunoblotting and by

immunohistochemistry. Overexpression constructs for target TRIM proteins tagged with a green fluorescent protein (GFP) tag were transfected into HEK293 cells and resulting protein extracts were enriched for the TRIM proteins using co-immunoprecipitation approaches. Enriched extracts were used for Western immunoblotting using myositis patient serum samples as the primary antibody.

Results: We identified multiple TRIM family proteins that display altered expression in myositis muscle from both mice and humans. TRIM72/MG53 and other related TRIM proteins displayed altered expression in muscle extracts from both a myositis mouse model and human myositis patients. In particular, TRIM27 showed increased expression in myositis muscle from both humans and mice. We next examined if we could detect antibodies against these TRIM family proteins in the serum of human myositis patients. Autoantibodies were detected in the serum against TRIM72/MG53, TRIM27 and TRIM2 in multiple myositis patients but not in healthy controls

Conclusion: We have identified altered expression of TRIM proteins in skeletal muscle in a myositis mouse model and in muscle biopsies from human myositis patients. Autoantibodies targeting some of these TRIM proteins could be detected in the blood serum of myositis patients. These results highlight an association of decreased sarcolemmal membrane integrity in the development of myositis and suggest a mechanism that could be targeted for diagnostics and therapeutics in these diseases.

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Abstract Number: 947

Cohesin Complex Is a New Myositis Autoantigen

Shin Tanaka[1], S. John Calise[2], Yurie Satoh[3], Yoshiya Tanaka[4], Monica Vazquez-Del Mercado[5], Gabriel Medrano-Ramírez[6], Eric S. Sobel[7], Westley H. Reeves[8], Edward K.L. Chan[9] and Minoru Satoh[10], [1]Human, Information and Sciences, University of Occupational and Environmental Health, Japan, Kitakyushu, Japan, [2]Department of Oral Biology, University of Florida, Miami, FL, [3]First Department of Internal Medicine, University of Occupational and Environmental Health, KItakyushu, Japan, [4]The First Dept. of Internal Medicine, University of Occupational & Environmental Health, Kitakyusyu, Japan, [5]Servicio de Reumatología, División de Medicina Interna, Hospital Civil Dr. Juan I. Menchaca, Guadalajara, Mexico, [6]Rheumatology, Hospital General de Mexico, Secretaria de Salud, Mexico City, Mexico, [7]Medicine/Div of Rheumatology, University of Florida, Gainesville, FL, [8]Medicine, University of Florida, Gainesville, FL, [9]Dept of Oral Biology, University of Florida, Gainesville, FL, [10]Department of Clinical Nursing, School of Health Sciences, University of Occupational and Environmental Health, Kitakyushu, Japan

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SESSION INFORMATION

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Session Title: Muscle Biology, Myositis and Myopathies I

Session Type: ACR Concurrent Abstract Session

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Background/Purpose:

Each myositis specific autoantibodies (MSA) are associated with unique clinical subset and useful biomarkers in polymyositis/dermatomyositis (PM/DM). Identifying new MSA will help in monitoring PM/DM patients as evidenced recently by reports on anti-TIF1gamma (transcription intermediary factor-1gamma) associated with malignancy and anti-MDA5 associated with clinically amyopathic DM with rapidly progressive interstitial lung disease (ILD). Although new autoantibody specificities have been added, ~50% of patients with PM/DM are still without known MSA, thus identifying additional MSA is relevant. A set of 3 proteins of ~120 -160kD recognized by serum from patients with DM were noticed and the antigens and clinical features of patients with this autoantibody specificity were characterized.

Methods:

A set of 3 proteins of ~120 -160kD recognized by a prototype serum was purified and identified by mass spectrometry. Sera from ~2200 patients with various diagnosis including 434 SLE, 119 scleroderma, and 514 PM/DM from 4 countries were tested by immunoprecipitation of ^{35}S-methionine labeled K562 cell extract. Sera that immunoprecipitated the same set of proteins were searched and identity of specificity was verified by immunoprecipitation and western blot using mouse monoclonal antibodies (mAb). Clinical information was from database and charts.

Results: Many peptides covering 50+% of the whole sequence for cohesion subunit SA-1, SA-2 and SMC3 (structural maintenance of chromosome) were detected from purified ~120-160kD proteins. Identity of the proteins immunoprecipitated by human autoimmune sera was confirmed by probing immunoprecipitated proteins by mouse mAb to components of cohesion complex, SA-1, SA-2, SMC1 and Rad21. IP pattern of 3 bands by anti-SA-2 mAb appeared to be same as that by human autoimmune sera. Based on these findings, it was concluded that the set of

proteins recognized by the autoimmune sera was cohesion complex, which is known to regulate the separation of sister chromatids during cell division, and also involved in various functions such as controlling gene expression, DNA replication and DNA repair. All 4 anti-cohesin autoimmune sera showed fine speckled nuclear staining sparing nucleoli by immunofluorescence antinuclear antibodies. Despite localization of cohesion on chromosomes, staining of mitotic chromosomes was not clear. Four cases with anti-cohesin were identified; 3 females (2 African Americans, 1 Latin) and a male (Japanese). A Japanese patient was amyopathic DM with ILD. A Latin patient had DM and an African American patient had PM-SSc overlap syndrome with ILD and positive for anti-U1RNP and Su/Argonaute2 antibodies. Another American patient had Raynaud's phenomenon and skin ulcer/gangrene. None of these patients had cancer or coexisting MSA or SSc-specific autoantibodies. This specificity was not found in SLE, scleroderma, or other conditions.

Conclusion: Anti-cohesin complex is a new autoantibody specificity that appears to be associated with PM/DM and ILD. Whether it has association with unique features will need to be evaluated in future studies.

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Autoimmune Myopathies: Effects of Intravenous Immunoglobulin Therapy on Muscle Strength and Predictors of Response

Arash Lahoutiharahdashti[1], Iago Pinal-Fernandez[2], Jemima Albayda[1], Julie J. Paik[3], Sonye K. Danoff[4], Andrew Mammen[5] and Lisa Christopher-Stine[6], [1]Rheumatology, Johns Hopkins University School of Medicine, Baltimore, MD, [2]Autoimmune Systemic Diseases Unit, Vall D'Hebron University Hospital, Universitat Autònoma de Barcelona, Barcelona, Spain, [3]Division of Rheumatology, Johns Hopkins University School of Medicine, Baltimore, MD, [4]Medicine/Pulmonary, Johns Hopkins School of Medicine, Baltimore, MD, [5]Center Tower Ste 5300, Johns Hopkins University School of Medicine, Baltimore, MD, [6]Ste 4100 Rm 409, Johns Hopkins University School of Medicine, Baltimore, MD

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Background/Purpose:

There is a variable response rate to Intravenous immunoglobulin (IVIG) in patients with autoimmune myopathies. The aim of this study was to determine whether the presence of individual myositis-specific autoantibodies (MSA) predicts improved muscle strength in response to IVIG.

Methods:

A total of 378 adult subjects with a diagnosis of polymyositis or dermatomyositis based on the Bohan & Peter criteria, who presented to our Center between 2004 and 2014, had been treated with IVIG. Modified MRC scores for the 16 proximal muscle groups were summed to yield a composite score of muscle strength (range 0-160). The following groups of subjects were excluded from the study: those with minimal weakness at the initiation of IVIG therapy (composite score > 156/160) (n=30), those with inadequate data on the efficacy of IVIG including those who were on IVIG therapy at presentation to our Center (n=143), those with inadequate follow-up (<5 months) (n=57), patients who did not receive a standard dose (2 g/kg, given in 2-5 days/month, for a period of 3-6 months) (n=45), and patients for whom the existing therapies had been increased or a new medication had been added during IVIG therapy (n=36). All patients were tested for MSAs by three reference laboratories using previously validated immunoprecipitation methods. A positive response was defined by a ≥4 point increase in composite score. Fisher's exact test was used to examine the effects of each MSA. Exact logistic regression was used to calculate the odds ratio.

Results:

Among the 67 subjects included in this study, 17 (25.4%) were non-responders and 50 (74.6%) were responders (Table 1). 54/67 (80.6%) of subjects had a detectable MSA. The response to IVIG was different between statin-exposed and statin-naïve anti-HMG-CoA reductase (HMGCR) subjects. All 14 (100%) statin-exposed anti-HMGCR+ patients responded but only 4 of 7 (57.1%) statin-naïve anti-HMGCR+ patients were responsive to IVIG (p=0.026) (Table2). Overall, anti-HMGCR in statin-exposed patients predicted a higher response rate to IVIG (p=0.014). In contrast, anti-SRP antibody was associated with lack of response (p=0.001). Of note, all anti-TIF-1γ positive patients responded to IVIG therapy (p=0.055). The odds ratio of response to IVIG was 8.8 (95%CI: 1.34 - [+infinity]) for anti-HMGCR+ and 0.04 (95%CI: 0-0.31) for anti-SRP positive patients.

Conclusion:

MSAs may predict a characteristic response to certain ISs. Our results indicate that while anti-SRP antibody predicts a poor response, statin-exposed anti-HMGCR+ patients are more likely to respond to IVIG therapy.

Table 1- Demographics and baseline characteristics of the study patients			
	IVIG responder (n=50)	**IVIG non-responder (n=17)**	**P Value**
Age at diagnosis, mean (SD), year	52.3 (13.9)	44.8 (12.8)	0.054
Duration from onset of symptoms to initiation of IVIG therapy, median (Q1-Q3), month	26 (6-41)	13 (7-18)	0.10
Ethnicity (%)			
White	74.0	52.9	0.23
African-American	18.0	35.3	
Other[a]	8.0	11.8	
Male (%)	30.0	23.5	0.76
Malignancy (%)	18.0	5.9	0.43
Initial CPK, median (Q1-Q3)	3500 (760-11000)	7000 (3000-13000)	0.18
Mean (SD) composite muscle strength at the beginning of IVIG therapy	136.0 (14.9)	143.2 (17.3)	0.101
Number of immunosuppressive medications prior to IVIG therapy, median (IQR)	1 (1-3)	2 (1-2)	0.63
Dysphagia (%)	58.0	82.4	0.09
Fever at onset (%)	12.0	5.9	0.67
Raynaud's phenomenon (%)	30.0	35.3	0.76
Bohan & Peter classification (%)			
Dermatomyositis			0.58
Definite	40.0	23.5	
Probable	10.0	11.8	
Possible	6.0	0.0	
Polymyositis			
Definite	34.0	47.1	
Probable	8.0	17.7	
Possible	2.0	0.0	

Table2- Myositis-specific autoantibodies and IVIG response			
Autoantibody	**IVIG responsive (%) n=50**	**IVIG non-responsive (%) n=17**	**P Value**
HMGCR			
Statin exposed	14 (28.0)	0 (0.0)	0.014
Statin unexposed	4 (8.0)	3 (17.7)	0.36
SRP	0 (0.0)	5 (29.4)	0.001
Anti-synthetase [a]	7 (14.0)	4 (23.5)	0.45
NXP-2	2 (4.0)	3 (17.7)	0.099
TIF-1γ	10 (20.0)	0 (0.0)	0.055
Mi-2	2 (4.0)	0 (0.0)	1.0
MSA-negative [b]	11 (22.0)	2 (11.8)	0.49

a Anti-synthetase antibodies included anti-jo-1 (n=10) and anti-OJ (n=1)

b Patients with a negative test for any of the following antibodies were considered MSA-negative: anti-HMGCR, anti-SRP, anti-NXP2, anti-TIF-1γ, anti-Mi2, anti-MDA5, and anti-synthetase autoantibodies (anti-Jo1, anti-EJ/OJ, anti-PL7/PL12)

Disclosure: A. Lahoutiharahdashti, None; **I. Pinal-Fernandez**, None; **J. Albayda**, None; **J. J. Paik**, None; **S. K. Danoff**, None; **A. Mammen**, None; **L. Christopher-Stine**, Walgreen, 6.

Abstract Number: 949

The Metabolic Syndrome, Its Elements and Knee Osteoarthritis: The Framingham Osteoarthritis (OA) Study

Jingbo Niu[1], Mary Clancy[2], Piran Aliabadi[3] and David T. Felson[1], [1]Clinical Epidemiology Research and Training Unit, Boston University School of Medicine, Boston, MA, [2]Clinical Epidemiology, BUSM, Boston, MA, [3]Radiology, Brigham and Women's Hospital, Boston, MA

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Background/Purpose: Recent studies have suggested an association between knee OA and the metabolic syndrome (MetS), but in these studies the relationship of this syndrome to OA has often vanished after adjustment for BMI. Since BMI adjusts for the effect of loading on the knee, adjustment for BMI is appropriate and any association of MetS elements with OA should be present after this adjustment. In defining the MetS, its elements are dichotomized and any association of these elements with OA is more likely to be detected if they are examined over their range and not just as dichotomous measures. We used data from the Framingham Osteoarthritis Study to assess the association between MetS and each of its elements to radiographic knee OA (ROA).

Methods: The Framingham Osteoarthritis Study recruited subjects from the Offspring Cohort. At exam 7 (2002-2005), we carried out a cross sectional evaluation of MetS and OA. MetS was defined by National Cholesterol Education Program criteria as having at least three out of the five elements: waist circumference >102 cm in men and >88 cm in women), hypertriglyceridemia (>150 mg/dL), low HDL (<40 mg/dL in men and <50 mg/dL in women), high blood pressure (systolic BP >130 mmHg, diastolic BP >85 mmHg or treatment), and hyperglycemia (fasting glucose >100mg/dL or diagnosis of diabetes). ROA was defined as having KL>2 in the tibiofemoral joint on PA view radiograph, patellofemoral OA on the lateral view radiograph, or knee replacement. Among subjects 50 years and older, we used binary regress to assess the relation of MetS and each of its elements to the prevalence of ROA in men and women separately. We tested each element of MetS as dichotomous measures, quartiles, and continuous measures. Age, history of knee injury and surgery were included as covariates. We tested models with and without controlling BMI to show how the effect of MetS was affected by excessive weight. Generalized estimating equations were used to control for the correlation between two knees of a subject.

Results: Among 1091 subjects (mean age: 62.0 years, BMI 28.1 kg/m^2, 55.5% women), 41.4% of men and 28.6% of women had MetS. When adjusting for covariates other than BMI, large waist circumference, high tryglyceride and high systolic blood pressure were related to higher prevalence of ROA in both men; MetS, large waist circumference, high systolic blood pressure, and hyperglycemia were related to higher prevalence of ROA in women. After further adjusting for BMI, men with high waist circumference and tryglyceride tended to have a higher prevalence of ROA; while none of the above associations was observed in women **(Table)**.

Conclusion: The association between MetS and radiographic knee OA observed in women can be explained by excessive weight. The relation of its elements, i.e., waist circumference, high blood pressure, and hyperglycemia, to radiographic knee OA was also due to excessive weight.

Table. Metabolic syndrome and prevalent knee OA				
	Women		**Men**	
	Adjusted RR (95% CI)[1]	Adjusted RR (95% CI)[2]	Adjusted RR (95% CI)[1]	Adjusted RR (95% CI)[2]
metabolic syndrome yes vs. no	1.5 (1.1, 1.9) **	0.9 (0.6, 1.1)	1.3 (0.9, 1.7)	1.0 (0.7, 1.4)
waist circumference >102/88cm (m/w) yes vs. no	1.9 (1.3, 2.8) ***	1.0 (0.6, 1.5)	1.5 (1.1, 2.0) *	1.1 (0.7, 1.6)
2nd vs. lowest quartile	1.4 (0.8, 2.3)	1.1 (0.6, 1.8)	2.2 (1.3, 3.6) **	1.9 (1.2, 3.2) *
3rd vs. lowest quartile	1.5 (0.9, 2.5)	0.9 (0.6, 1.6)	2.0 (1.2, 3.3) **	1.6 (0.9, 2.8)
highest vs. lowest quartile	3.4 (2.1, 5.3) ***	1.3 (0.7, 2.4)	2.7 (1.7, 4.3) ***	1.8 (0.9, 3.6)
continuous, 10 units	*1.35 (1.27, 1.44)* ***	*0.94 (0.76, 1.16)*	*1.26 (1.12, 1.41)* ***	*1.00 (0.77, 1.31)*
triglyceride >150 mg/dL yes vs. no	1.2 (0.9, 1.6)	0.9 (0.7, 1.2)	1.0 (0.8, 1.4)	1.0 (0.7, 1.4)
2nd vs. lowest quartile	1.2 (0.8, 1.8)	0.9 (0.6, 1.2)	1.7 (1.0, 2.6) *	1.5 (1.0, 2.4)
3rd vs. lowest quartile	1.0 (0.7, 1.5)	0.8 (0.5, 1.1)	1.9 (1.2, 2.9) **	1.6 (1.0, 2.6) *
highest vs. lowest quartile	0.8 (0.6, 1.3)	0.8 (0.5, 1.2)	1.5 (0.9, 2.4)	1.3 (0.8, 2.2)
continuous, 10 units	*1.00 (0.98, 1.01)*	*0.98 (0.96, 1.00)* *	*1.01 (1.00, 1.03)*	*1.01 (0.99, 1.03)*
HDL <40/50 mg/dL (m/w) yes vs. no	1.2 (0.9, 1.6)	0.9 (0.7, 1.2)	0.9 (0.6, 1.2)	0.8 (0.6, 1.1)
lowest vs. highest quartile	1.2 (0.8, 1.8)	0.9 (0.6, 1.2)	0.9 (0.6, 1.4)	0.8 (0.5, 1.2)
2nd vs. highest quartile	1.0 (0.7, 1.5)	0.8 (0.5, 1.1)	1.0 (0.7, 1.5)	0.9 (0.6, 1.4)
3rd vs. highest quartile	0.8 (0.6, 1.3)	0.8 (0.5, 1.2)	0.8 (0.5, 1.2)	0.8 (0.5, 1.2)
continuous, 10 units	*0.97 (0.89, 1.05)*	*1.05 (0.97, 1.14)*	*0.97 (0.86, 1.10)*	*1.01 (0.89, 1.14)*
blood pressure SBP >130 mmHg, DBP >85 mmHg yes vs. no	1.2 (0.9, 1.7)	0.9 (0.7, 1.2)	1.1 (0.8, 1.5)	0.9 (0.7, 1.3)
SBP, 2nd vs. lowest quartile	1.2 (0.8, 2.1)	1.0 (0.6, 1.6)	1.6 (0.9, 2.8)	1.4 (0.8, 2.5)
SBP, 3rd vs. lowest quartile	1.8 (1.2, 2.8) *	1.3 (0.9, 2.0)	1.8 (1.1, 3.0) *	1.5 (0.9, 2.6)
SBP, highest vs. lowest quartile	1.5 (0.9, 2.4)	1.1 (0.7, 1.7)	1.7 (1.0, 2.9) *	1.5 (0.9, 2.5)
SBP, continuous, 10 units	*1.07 (1.01, 1.15)* *	*1.03 (0.96, 1.11)*	*1.08 (1.00, 1.16)* *	*1.07 (0.98, 1.15)*
DBP, 2nd vs. lowest quartile	1.0 (0.7, 1.4)	0.9 (0.6, 1.2)	1.4 (0.9, 2.1)	1.3 (0.9, 2.0)
DBP, 3rd vs. lowest quartile	1.1 (0.7, 1.5)	0.9 (0.7, 1.3)	1.5 (1.0, 2.3)	1.4 (1.0, 2.2)
DBP, highest vs. lowest quartile	1.1 (0.7, 1.6)	0.9 (0.6, 1.3)	1.3 (0.8, 2.1)	1.3 (0.8, 2.0)
DBP, continuous, 10 units	*1.06 (0.94, 1.21)*	*1.00 (0.89, 1.14)*	*1.14 (0.99, 1.32)*	*1.12 (0.97, 1.30)*
Blood glucose Fasting glucose >100mg/dL or diagnosis of diabetes, yes vs. no	1.5 (1.1, 1.9) **	0.9 (0.7, 1.2)	1.2 (0.9, 1.7)	1.1 (0.8, 1.5)
2nd vs. lowest quartile	1.4 (0.9, 2.3)	1.3 (0.8, 2.1)	1.2 (0.8, 1.8)	1.0 (0.7, 1.6)
3rd vs. lowest quartile	1.7 (1.1, 2.7) *	1.2 (0.8, 1.9)	1.3 (0.9, 2.0)	1.1 (0.7, 1.8)
highest vs. lowest quartile	2.0 (1.3, 3.2) **	1.2 (0.7, 1.8)	1.1 (0.7, 1.7)	0.9 (0.6, 1.4)
continuous, 10 units	*1.07 (1.03, 1.12)* **	*1.00 (0.96, 1.05)*	*0.97 (0.91, 1.03)*	*0.94 (0.87, 1.01)*

[1]adjusting for age, history of knee injury and surgery,

[2]adjusting for age, BMI, history of knee injury and surgery

*p-value <0.05, **p-value <0.01, ***p-value <0.001

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Abstract Number: 950

In a Two-Year Double-Blind Randomized Controlled Multicenter Study, Chondroitin Sulfate Was Significantly Superior to Celecoxib at Reducing Cartilage Loss with Similar Efficacy at Reducing Disease Symptoms in Knee Osteoarthritis Patients

Jean-Pierre Pelletier[1], Jean Pierre Raynauld[2], André Beaulieu[3], Louis Bessette[4], Frédéric Morin[5], Artur J Fernandes[6], François Abram[7], Marc Dorais[8] and Johanne Martel-Pelletier[9], [1]Rheumatology, Institut de recherche en rhumatologie de Montréal (IRRM), Montréal, QC, Canada, [2]Osteoarthritis Research Unit, CRCHUM, Montreal, Montreal, QC, Canada, [3]Centre de rhumatologie St-Louis, St. Louis, QC, Canada, [4]Groupe de Recherche en Rhumatologie et Maladies Osseuses, Quebec, Quebec, QC, Canada, [5]Centre de Recherche Musculo-squelettique, Trois-Rivières, Trois-Rivières, QC, Canada, [6]Centre de Recherche Musculo-squelettique, Trois-Rivières, 6Rheumatology Division, Sherbrooke, Sherbrooke, QC, Canada, [7]Medical Imaging Research & Development, ArthroLab Inc, Montreal, QC, Canada, [8]StatSciences Inc., Montreal, Canada, Montreal, QC, Canada, [9]Osteoarthritis Research Unit, University of Montreal Hospital Research Centre (CRCHUM),, Montreal, QC, Canada

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Background/Purpose: In osteoarthritis (OA) treatment, although chondroitin sulfate (CS) was found in a number of studies using radiography to have a structure modifying effect, to date the question is still under debate. A clinical study using quantitative magnetic resonance imaging (qMRI) is therefore of the utmost importance.

The present study has the objective to explore, as the first aim, in a two-year randomized, controlled double-blind clinical study (RCT) using qMRI, the disease modifying effect of CS treatment versus celecoxib (CE) on cartilage volume loss (CVL) in knee OA. The second aim was to investigate and compare the effect of CS and celecoxib on symptoms.

Methods: Symptomatic primary knee OA patients according to ACR criteria with Kellgren-Lawrence grades 2-3 and synovitis were included and treated with CS (1200 mg a day) or CE (200 mg once daily) for 24 months. Patients at high risk for cardiovascular and/or gastrointestinal disease were not included. MRI was performed at baseline, 12 and 24 months. CVL, bone marrow lesion (BML) size, and synovial membrane thickness were evaluated using qMRI, and presence of joint swelling and effusion clinically evaluated. Clinical symptoms were also assessed by validated questionnaires. Statistical analyses were done on the intention-to-treat (ITT) population (n=194 patients), per protocol set (n= 195) and the according-to-protocol completer population (n=120) using Student's t-test, Wilcoxon Mann-Whitney test, and ANCOVA.

Results: In the ITT population, OA patients treated with CS (n=97) had a reduction in CVL at 12 months (p=0.017) and 24 months in the medial tibiofemoral compartment (p=0.013) and global knee at 12 (p= 0.034) and 24 months (p=0.054) compared to CE (n=97). No difference in change in synovial thickness or BML size between the two treatment groups was observed over time. A marked reduction in the incidence of patients with joint swelling plus effusion was observed in both the CS (51%, 59 vs 6 patients) and celecoxib (39%, 55 vs 11 patients) groups from baseline to 24 months, without differences between treatments. Both therapeutic groups experienced a reduction in disease symptoms (WOMAC total, pain, and function, and VAS pain) over time: reduction in VAS pain at 24 months for CS and celecoxib was 48% and 55% respectively, and for WOMAC pain 43% and 54%. The overall daily consumption of rescue analgesic (acetaminophen) was not different between CS and celecoxib (584 vs 472 mg/day) groups. The incidence of adverse events was similar in both treatment groups.

Conclusion: This trial demonstrated, for the first time, the superiority of CS over CE at reducing the long term progression of knee OA structural changes. Moreover, both drugs were found equally effective at reducing the symptoms of OA. These findings have important implications regarding the usefulness of CS for long term management of knee OA and its impact on disease outcome.

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Abstract Number: 951

Comparative Effectiveness of Tai Chi Versus Physical Therapy in Treating Knee Osteoarthritis: A Randomized, Single-Blind Trial

Chenchen Wang[1,2], Christopher Schmid[3], Maura D. Iversen[4], William F. Harvey[2], Roger A. Fielding[5], Jeffrey B. Driban[2], Lori Lyn Price[6], John B. Wong[7,8], Kieran Reid[5], Ramel Rones[9] and Timothy E. McAlindon[2], [1]Rheumatology, Tufts Medical Center, Bosotn, MA, [2]Rheumatology, Tufts Medical Center, Boston, MA, [3]Brown University School of Public Health, Providence, RI, [4]Northeastern University,, Boston, MA, [5]Nutrition, Exercise Physiology and Sarcopenia Laboratory, Jean Mayer USDA Human Nutrition Research Center on Aging, Tufts University, Boston, MA, [6]Clinical Care Research, Tufts Medical Center, Boston, MA, [7]Tufts Medical Center, Boston, MA, [8]Clinical Decision Making, Tufts Medical Center, Boston, MA, [9]Center for Mind–Body Therapies, Boston, MA

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Background/Purpose: Knee osteoarthritis (OA) causes long-term pain and no effective treatments currently exist. Previous trials demonstrated that Tai Chi can improve both physical and mental health among patients with knee OA. However, it has not been compared against a standard of care therapy for knee OA. We designed this novel randomized, single-blind trial to test the superiority of Tai Chi compared to a standard physical therapy (PT) regimen for treatment of symptomatic and radiographic knee OA. The study was also powered to detect differences in outcomes among different Tai Chi instructors as an important secondary objective.

Methods: Adults ≥ 40 years old satisfying ACR criteria for Knee OA were randomized to 12 weeks of classical Yang style Tai Chi (2x/week) or to the standard PT regimen (2x/week for 6 weeks, followed by 6 weeks of rigorously monitored home PT). Clinical outcomes assessments were blinded to treatment allocation. The primary outcome was change in WOMAC pain subscale (0-500) at 12 weeks. Secondary outcomes included change in pain at 24 and 52 weeks as well as change in WOMAC function scores, patient global assessment (VAS, 0-10 cm), depression (Beck II, 0-63), chronic pain self-efficacy (0-10), 20 meter walk test (sec) and 6 min walk test (meters), quality of life (SF-36, 0-100), pain medication usage and comparisons of all outcomes by instructor assignment at 12, 24 and 52 weeks. We used an intent-to-treat analysis.

Results: We randomized 204 participants: 106 to Tai Chi and 98 to PT. The mean age 60 years, disease duration 8 years, BMI 33 kg/m^2; 70% were female; and 53% were white. Treatment groups did not differ in baseline characteristics, including participant expectation of treatment benefit. At 12 weeks, WOMAC pain scores improved by 167 points (95% CI: 145, 190) in the Tai Chi group and 143 points (95% CI: 119, 167) in the PT group. There was no significant difference between groups in WOMAC pain improvement (p = 0.16). A significantly greater improvement in the Tai Chi group was found in the SF-36 Physical Component score 3.2 (95% CI: 0.8, 5.5; p=0.01) and the Beck depression score 2.7 (95% CI, 0.7, 4.8, p=0.008). No differences between groups were found for other outcomes at 12 weeks. There were no serious adverse events. Pain medication use was reduced compared to baseline at all follow-up times in both groups, but the reductions did not differ between groups. Changes in WOMAC pain did not differ among the four Tai Chi instructors (p = 0.81), though differences approached significance comparing physical therapists (p=0.05).

Conclusion: Both Tai Chi and PT led to similar improvements in pain and other outcomes for persons with symptomatic knee OA, and the benefits of Tai Chi did not differ by instructor, suggesting that standardizedTai Chi can be used as a viable therapeutic alternative to treat knee OA.

Table. Changes in Primary and Secondary Outcomes

Variables	Groups	Baseline Mean (SD)	At 12 week Change (95% CI)	95% CI and P-value for D between group
WOMAC pain (0-500)	Tai Chi	254.8 (95.5)	-167.2 (-190.4,-144.9)	-24.2 (-57.9, 9.6)
	PT	252.9 (101.9)	-143.0 (-167.4,-118.6)	P=0.16
WOMAC function (0-1700)	Tai Chi	912.1 (338.5)	-608.3 (-695.3,-521.4)	-114.1 (-240, 118)
	PT	884.7 (368.1)	-494.2 (-585.3,-403.2)	P=0.08
Patient Global (10-cm VAS)	Tai Chi	0.5 (0.2)	-0.3 (-0.3, -0.2)	-0.7 (-0.15, 0.02)
	PT	0.5 (0.2)	-0.2 (-0.3, -0.2)	P=0.06
Chronic Pain Self-Efficacy (10-cm)	Tai Chi	6.1 (2.0)	1.3 (0.8, 1.8)	0.4 (-0.3, 1.2)
	PT	6.3 (2.2)	0.8 (0.3, 1.4)	P=0.22
20 meter walk test (sec)	Tai Chi	19.6 (6.3)	-1.6 (-2.4, -0.8)	-0.5 (-1.7, 0.7)
	PT	18.4 (3.9)	-1.1 (-2.0, -0.2)	P=0.40
6 min walk test (meters)	Tai Chi	391.2 (91.7)	28.6 (17.9, 39.2)	2.5 (-13.1, 18.0)
	PT	400.1 (88.7)	26.1 (14.9, 37.4)	P=0.76
SF-36: PCS	Tai Chi	36.5 (8.3)	6.3 (4.6, 7.9)	3.2 (0.8, 5.5)

Disclosure: C. Wang, National Institutes of Health, 2; **C. Schmid**, National Institutes of Health, 2; **M. D. Iversen**, National Institutes of Health, 2; **W. F. Harvey**, National Institutes of Health, 2; **R. A. Fielding**, National Institutes of Health, 2; **J. B. Driban**, National Institutes of Health, 2; **L. L. Price**, National Institutes of Health, 2; **J. B. Wong**, National Institutes of Health, 2; **K. Reid**, National Institutes of Health, 2; **R. Rones**, National Institutes of Health, 2; **T. E. McAlindon**, National Institutes of Health, 2,Tufts MCPO, 3.

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Abstract Number: 952

Cost-Effectiveness of Opioids for

(0-100)	PT	36.7 (10.0)	3.1 (1.4, 4.8)	P=0.01
SF-36: MCS	Tai Chi	52.6 (9.3)	1.6 (-0.1, 3.2)	1.6 (-0.8, 3.9)
(0-100)	PT	52.4 (9.2)	-0.03 (-1.7, 1.7)	P=0.18
Beck II Depression	Tai Chi	7.8 (9.0)	-2.2 (-3.7, -0.9)	-2.7 (-4.8, -0.7)
(0-60)	PT	7.5 (8.3)	0.5 (-1.0, 2.0)	P=0.008

Western Ontario and McMaster Universities =WOMAC. VAS= Visual Analogue Scale; SF-36 (PCS) =Short-Form health survey (physical component summary). SF-36 (MCS) = Short-Form health survey (mental component summary) PT= Physical Therapy.

the Treatment of Knee Osteoarthritis: Impact of Chronic Opioid Use on Total Knee Arthroplasty Outcomes

Savannah R. Smith[1], **Jeffrey N. Katz**[2], Jamie E. Collins[3] and Elena Losina[4], [1]Orthopedic and Arthritis Center for Outcomes Research, Brigham and Women's Hospital, Boston, MA, [2]Brigham and Women's Hospital and Harvard Medical School, Boston, MA, [3]Orthopaedic and Arthritis Center for Outcomes Research, Department of Orthopedic Surgery, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, [4]Orthopedics, Brigham and Women's Hospital, BU School of Public Health and Harvard Medical School, Boston, MA

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SESSION INFORMATION

Session Date: Sunday, November 8, 2015

Session Title: Osteoarthritis - Clinical Aspects: Treatments and Epidemiology

Session Type: ACR Concurrent Abstract Session

Session Time: 2:30PM-4:00PM

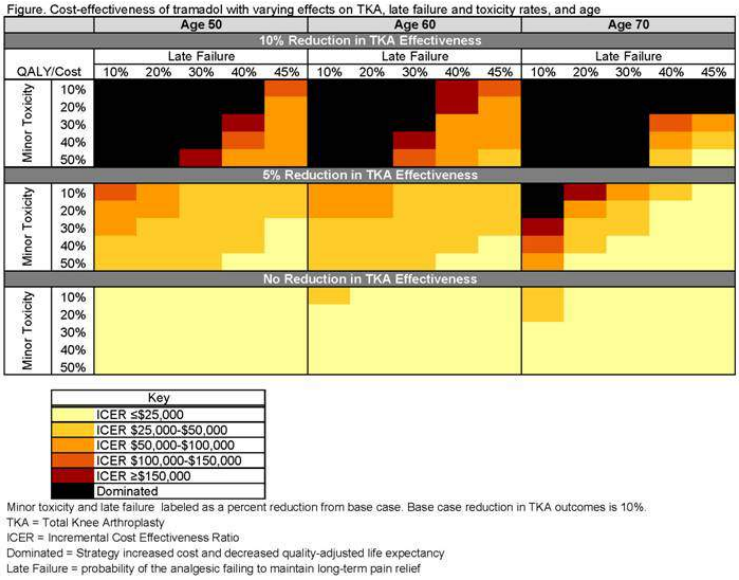
Background/Purpose: The US spends over $1 billion annually on opioids for persons with knee OA. We evaluated whether the use of opioids offers good value for money by conducting a formal cost-effectiveness analysis of the use of tramadol or oxycodone in OA patients.

Methods: We used the Osteoarthritis Policy Model, a validated computer simulation of knee OA, to evaluate long-term clinical and economic outcomes of knee OA patients with mean age 60 and no prevalent comorbidities, whose pain persists after initial treatment with non-steroidal antiinflammatory drugs (NSAIDs), physical therapy (PT), and corticosteroid injections. We evaluated 3 strategies: 1) opioid-sparing (OS, acetaminophen as needed until total knee arthroplasty [TKA]); 2) tramadol (T); and 3) tramadol followed by oxycodone for those who failed tramadol (T+O). Toxicity and efficacy were estimated from published literature. Mean WOMAC Pain change was 15 points for tramadol and 16 for oxycodone. Annual costs for tramadol ($600) and oxycodone ($2,700) included drug costs (Red Book), office visits, and, for oxycodone, diversion. Toxicities included gastrointestinal (GI) and cardiovascular (CV) events. Based on published literature, in the base case analysis we decreased the efficacy of TKA in strategies T and T+O by 10%. We adopted a societal perspective, discounting outcomes at 3%/year, and assumed a willingness to pay (WTP) threshold of $100,000 per quality adjusted life year (QALY). Strategies with incremental cost-effectiveness ratios (ICERs) below WTP were considered cost-effective. We conducted sensitivity analyses on the impact of opioid use on TKA outcomes, age at opioid initiation, and toxicity and discontinuation rates.

Results: In the base case, tramadol-treated patients were on tramadol for 2.4 years and oxycodone-treated patients were on oxycodone for 2.9 years, on average. The T and T+O strategies led to reduction in TKA use by 4% and 10% respectively and revision TKA use by 24% and 40%. In the base case, both opioid-based strategies increased cost and decreased QALYs compared to the opioid-sparing strategy. Tramadol cost-effectiveness was highly sensitive to its effects on TKA outcomes. When efficacy of TKA was reduced by 5% (base case 10%), tramadol had an ICER of $67,000/QALY (Figure). When TKA was not a treatment option, tramadol, but not tramadol + oxycodone, became a cost-effective strategy.

Conclusion: Opioids do not appear to be cost-effective in OA patients if they have an adverse effect on TKA outcomes. Despite reductions in TKA use, costs of opioids and toxicities led to an overall increase in cost for the T and T+O strategies compared to OS. Tramadol may be cost-effective in patients averse to TKA or if additional data show that its effects on TKA outcomes are minimal. The influence of chronic opioid use on TKA should be considered a research priority in order to understand the value of opioids in knee OA treatment.

Figure. Cost-effectiveness of tramadol with varying effects on TKA, late failure and toxicity rates, and age



Minor toxicity and late failure labeled as a percent reduction from base case. Base case reduction in TKA outcomes is 10%.
TKA = Total Knee Arthroplasty
ICER = Incremental Cost Effectiveness Ratio
Dominated = Strategy increased cost and decreased quality-adjusted life expectancy
Late Failure = probability of the analgesic failing to maintain long-term pain relief

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Abstract Number: 953

Effectiveness of a Progressive Resistence Strength Programme on Hand Osteoarthritis: A Randomized Crontrolled Trial

Michele V. Nery[1], Anamaria Martinez[2], Fabio Jennings[3], Marcelo Souza[2] and Jamil Natour[2], [1]Rheumatology Division, Universidade Federal de Sao Paulo, Sao Paulo, Brazil, [2]Rheumatology Division, Federal University of Sao Paulo, Sao Paulo, Brazil, [3]Disciplina de reumatologia, Universidade Federal de São Paulo, Sao Paulo, Brazil

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Session Time: 2:30PM-4:00PM

Background/Purpose: Hand osteoarthritis (OA) is highly prevalent, affecting 55-70% of the population over 55 years with an age-related progressive increase. The OA of interphalangeal (IF) and carpometacarpaljoints may have varying degrees of deformity associated with pain, decreased of grip and pinch strength, decreased range of motion and functional impairment. Systematic reviews and meta-analyzes have shown the beneficial effect of exercise for lower limb OA, however for hand OA exercise is still used based on recommendations based on clinical experience and low quality studies, not allowing a conclusion about the effects of exercise in pain, function and strength in hand OA patients. The purpose of this study was to assess the effectiveness of progressive resistance strength training program on pain, function and strength in hand OA patients.

Methods: diagnostic of hand OA according to ACR of at least 1year, age over 55 years, both genders, pain in IF joints between 3-8 cm on a 10-cm numerical pain scale (NPS). Sixty patients who meet the eligibility criteria were randomized into exercise group (EG) and control group (CG). Both groups performed a session regarding joint protection and energy conservation before randomization. The EG performed a progressive resistance strength training program for intrinsic muscles of the hand for 12 weeks. The outcome measures were NPS; *Australian*/Canadian (AUSCAN) Hand Osteoarthritis Index and Cochin Hand Functional Scalefor hand function; grip and pinch strengthening using the *Jamar*Hydraulic Hand*Dynamometer and a pinch gauge dynamometer* and satisfaction with the treatment using a Likert scale. A blinded evaluator performed the evaluations at baseline, 6 and 12 weeks after treatment baseline.

Results: The groups were homogeneous at baseline except for the key pinch strength for non-dominant hand and palmar pinch strength for both hands. The comparison between groups using repeated measures ANOVA shows an statistically difference between groups in AUSCAN (total score, $p = 0.005$; pain, $p = 0.006$ and function, $p = 0.047$), COCHIN ($p = 0.042$) and Likert scale ($p = 0.001$) with better results for the EG.

Conclusion: This progressive resistance strength training program was effective for pain, function, and treatment satisfaction for patients with

hand OA.

Table 1 – Between-groups comparison for pain, function and strength

	T0		T6		T12		
	CG	**EG**	**CG**	**EG**	**CG**	**EG**	**p**
NPS							
Dominant hand	6.13 ± 1.63	6.33 ± 1.67	4.63 ± 2.71	4.40 ± 2.49	5.10 ± 2.68	3.80 ± 2.43	0.085
Non-dominant hand	5.93 ± 1.70	5.67 ± 1.69	4.73 ± 2.63	4.20 ± 2.47	5.10 ± 2.58	3.77 ± 2.53	0.295
AUSCAN							
Pain	8.47 ± 3.01	7.90 ± 4.49	8.93 ± 3.56	5.73 ± 4.24	8.23 ± 4.42	4.97 ± 4.07	0.006*
Stiffness	2.20 ± 2.16	1.97 ± 1.00	2.33 ± 1.73	1.73 ± 1.51	2.13 ± 1.28	1.17 ± 1.15	0.386
Function	14.0 ± 7.05	12.67 ± 7.99	15.00 ± 7.08	11.77 ± 7.60	13.80 ± 7.42	8.77 ± 7.40	0.047*
Total score	24.70 ± 9.66	22.50 ± 12.10	26.30 ± 10.02	19.10 ± 10.47	24.13 ± 12.02	14.23 ± 10.47	0.005*
COCHIN	15.73 ± 10.37	14.53 ± 13.83	18.00 ± 12.26	12.30 ± 12.10	15.17 ± 11.71	8.90 ± 12.09	0.042*
GRIP STRENGTH							
Dominant hand	15.18 ± 4.20	17.70 ± 5.2	14.90 ± 4.10	18.70 ± 5.10	15.60 ± 5.10	19.10 ± 4.70	0.052
Non-dominant t hand	14.70 ± 4.20	16.50 ± 5.10	14.10 ± 3.80	16.90 ± 5.20	14.90 ± 4.50	17.80 ± 5.00	0.307
PINCH STRENGTH							
Tip							
Dominant hand	4.11 ± 1.28	4.51 ± 1.20	4.21 ± 0.95	4.44 ± 1.29	4.10 ± 1.16	4.54 ± 1.21	0.586
Non-dominant t hand	3.87 ± 1.10	5.39 ± 5.71	3.91 ± 1.12	4.48 ± 1.21	3.76 ± 1.00	4.31 ± 1.15	0.372
Key							
Dominant hand	5.78 ± 1.27	6.36 ± 1.12	5.69 ± 1.32	6.30 ± 1.14	5.95 ± 1.52	6.54 ± 1.06	0.984
Non-dominant hand	5.18 ± 1.07	5.88 ± 1.00	5.26 ± 1.05	6.00 ± 0.98	5.33 ± 1.12	7.76 ± 8.98	0.308
Palmar							
Dominant hand	4.53 ± 1.24	5.18 ± 1.18	4.79 ± 1.18	5.18 ± 1.17	4.71 ± 1.18	5.12 ± 1.05	0.387
Non-dominant hand	4.16 ± 1.25	4.89 ± 1.12	4.42 ± 1.38	4.92 ± 0.97	4.40 ± 1.10	4.99 ± 1.01	0.502

T0= baseline; T6= evaluation after 6 weeks; T12= evaluation after 12 weeks; CG= control group; EG= exercise group;

ANOVA= analysis of variance for repeated measures; NPS= numerical pain scale; AUSCAN= Australian and Canadian Hand

Osteoarthritis Index; pinch and grip strength (Kg/f); *Statistically significant p value (<0,05).

Disclosure: M. V. Nery, None; **A. Martinez**, None; **F. Jennings**, None; **M. Souza**, None; **J. Natour**, None.

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Abstract Number: 954

The Relationship Between Osteoarthritis and Cardiovascular Disease: Results from a Population-Based Cohort

Lauren King[1], Tetyana Kendzerska[1,2,3] and Gillian Hawker[1,2,3], [1]Department of Medicine, University of Toronto, Toronto, ON, Canada, [2]Women's College Research Institute, Women's College Hospital, University of Toronto, Toronto, ON, Canada, [3]Institute for Clinical Evaluative Sciences, Toronto, ON, Canada

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SESSION INFORMATION

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Session Title: Osteoarthritis - Clinical Aspects: Treatments and Epidemiology

Session Type: ACR Concurrent Abstract Session

Session Time: 2:30PM-4:00PM

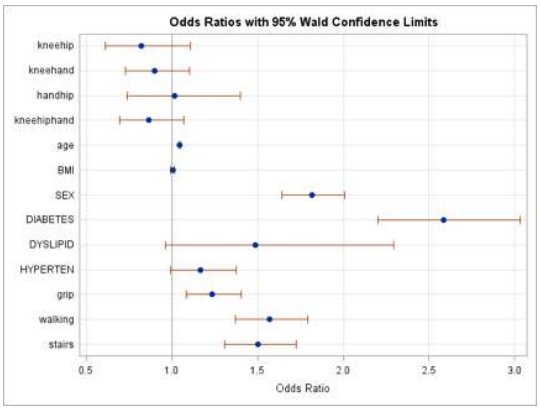
Background/Purpose: Symptomatic osteoarthritis (OA) and cardiovascular disease (CVD) commonly co-exist. Our aim was to determine the extent to which this relationship is explained by common risk factors (age and obesity), metabolic factors and self-reported functional limitations.

Methods: A population cohort aged ³55 years was recruited from 1996-98 from two communities. Age, sex, height and weight, self-reported medical comorbidities, joint complaints and functional limitations (difficulty with stair climbing, walking, and gripping) were collected by survey. Subjects with inflammatory arthritis, rheumatic disease and medical neurological conditions associated with functional disability were excluded. OA was defined as (1) swelling, pain, or stiffness in any joint lasting 6 weeks in the past 3 months; and (2) indication on the homunculus that a knee, hand and/or hip was "troublesome". CVD was defined as self-reported angina, heart disease, myocardial infarction, coronary reperfusion, heart failure, stroke, transient ischemic attack and/or carotid disease. Participants were classified into 8 mutually exclusive joint groups based on the presence/absence of knee, hand and hip complaints. Using logistic regression, we examined the relationship of CVD with knee, hand, and hip complaints, controlling for the following variables added to our model incrementally: (1) age and body mass index (BMI); (2) sex and metabolic factors (diabetes, hypertension and dyslipidemia); and (3) functional limitations (stairs, walking, grip).

Results: 20,501 participants were included: mean age 68.2±8.5 years, 58.5% female, 51.8% rural-dwelling and mean BMI of 25.9±4.5 kg/m^2. Controlling for age and BMI, the prevalence of self-reported CVD was significantly higher among individuals with a combination of knee, hand and hip OA (adj odds ratio [OR] 1.42, 1.16 – 1.72, p<0.01); combination of knee and hand OA (adj OR 1.37, 1.13 – 1.66, p<0.01); and combination of hand and hip OA (adj OR 1.46, 1.07 – 1.97, p=0.02). Further adjustment for sex and metabolic factors did not substantially impact these relationships. When functional limitations were entered into the model, the above associations were attenuated and became non-significant (Figure 1).

Conclusion: In a large population cohort aged ³55 years, the previously documented relationship between symptomatic OA (knee, hand, hip) and CVD was confirmed. This relationship remained robust after controlling for common risk factors and metabolic factors, but became non-significant after controlling for functional limitations, suggesting that the predominant mechanism driving cardiovascular risk in people with OA is functional disability. Further work is needed to investigate effective ways to improve functional limitations in people with established OA.

Figure 1: Correlates of Self-Reported CVD by Multivariable Logistic Regression Model



Disclosure: L. King, None; **T. Kendzerska**, None; **G. Hawker**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/the-relationship-between-osteoarthritis-and-cardiovascular-disease-results-from-a-population-based-cohort

Abstract Number: 955

Cancer Risk in 5,108 Patients with Juvenile Idiopathic Arthritis (JIA)

Omid Zahedi Niaki[1], Ann E. Clarke[2], Rosalind Ramsey-Goldman[3], Rae S.M. Yeung[4], Kristen Hayward[5], Kiem Oen[6], Ciarán M. Duffy[7], Alan M. Rosenberg[8], Kathleen O'Neil[9], Emily von Scheven[10], Laura Schanberg[11], Jeremy Labrecque[12], Jennifer LF Lee[13] and **Sasha Bernatsky**[14], [1]Medicine, McGill University, Montreal, QC, Canada, [2]Immunology/Epidemiology, Montreal General Hospital, Montreal, QC, Canada, [3]Northwestern University Feinberg School of Medicine, Chicago, IL, [4]Pediatrics, Immunology and Medical Science, The Hospital for Sick Children, University of Toronto, Toronto, ON, Canada, [5]Pediatric Rheumatology, University of Washington & SCH, Seattle, WA, [6]Department of Pediatrics and Child Health, University of Manitoba; Head, Section of Pediatric Rheumatology, Children's Hospital, University of Manitoba, The Children`s Hospital Foundation of Manitoba, Winnipeg, MB, Canada, [7]Children's Hospital of Eastern Ontario and University of Ottawa, Ottawa, ON, Canada, [8]Pediatrics, University of Saskatchewan, Saskatoon, SK, Canada, [9]Pediatric Rheumatology, RIley Hospital for Children, Indianapolis, IN, [10]Dept of Pediatric Rheumatology, Univ of California San Francisco, San Francisco, CA, [11]Pediatrics, Duke Medical Center, Durham, NC, [12]Clinical Epidemiology, McGill UHC/RVH, Montreal, QC, Canada, [13]Clinical Epidemiology Rheum, McGill UHC/RVH, Montreal, QC, Canada, [14]Rheum/Clin. Epid., McGill MUHC/RVH, Montreal, QC, Canada

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Session Time: 2:30PM-4:00PM

Background/Purpose: Given suspected links between inflammation and malignancy, several groups have attempted to elucidate the baseline risk of cancer in various inflammatory or autoimmune conditions, including rheumatoid arthritis, where there is an increased risk of hematological malignancies (lymphoma in particular). However, there are very few studies of cancer risk in large pediatric-onset rheumatic disease cohorts. The purpose of our study was to further investigate cancer risk in JIA, based on a very large multi-centre clinical population.

Methods: We examined data from 4 pediatric rheumatology clinic cohorts in Canada and 2 in the United States, across 1971-2011. We linked patients to regional cancer registries to detect observed cancers (O) occurring after cohort entry, defined as date first seen in the JIA clinic cohort. End of follow-up was defined as the date of cancer registry linkage (thus was not truncated once subjects reached adulthood). The expected number of malignancies (E) was obtained by multiplying the person-years in the cohort (defined from cohort entry to end of follow-up) by the geographically matched age, sex, and calendar year-specific cancer rates, and summing overall person-years.

The standardized incidence ratio (SIR; ratio of cancers observed to expected) was generated, along with 95% confidence intervals (CIs), based on the assumption of cancer occurrence as a Poisson-distributed variable. **Results** were also stratified by age group of person-time (categorized into 0-19 and >20 years of age).

Results: A total of 5,108 JIA patients were studied. The mean age at cohort entry was 8.9 years (standard deviation, SD 5.0). The majority were female (68.0%) and the sample was predominantly Caucasian, reflecting the source populations. The most common JIA subtype was oligoarticular. The mean duration of follow-up (time from cohort entry to end of follow-up) was 6.7 years, resulting in 34,224 patient-years of observation.

During total follow-up, 9 invasive cancers were observed, compared to 10.1 expected, for an over-all SIR of 0.89, 95% CI 0.41-1.69. Three of these were hematological (1 Hodgkin's lymphoma, 1 Non-Hodgkin lymphoma, and 1 leukemia). For all hematological malignancies, the SIR was 1.33 (95% CI 0.27-3.88).

When stratifying SIR estimates, for the 0-19 age group, seven cancers occurred, for an SIR of 1.69 (95% CI 0.68-3.48) for all cancers and a SIR of 2.01 (95% CI 0.41-5.87) for hematological cancers.

Conclusion: Our study is one of the largest examining the relationship between malignancy risk and JIA. Cancer was a relatively infrequent outcome, and most of the cancers observed occurred during the years when patients were aged 0-19 years. Further follow-up over time, of the subjects in this JIA cohort, would be necessary to capture accurately cancer risk for JIA in the adult years.

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Abstract Number: 956

The Addition of One or More Biologics to Methotrexate in Children with Juvenile Idiopathic Arthritis Increases the Incidence of Infections and Other Adverse Events

Joost Swart[1], Angela Pistorio[2], Francesca Bovis[3], Ekaterina Alexeeva[4], Michael Hofer[5], Susan Nielsen[6], Jordi Anton[7], Alessandro Consolaro[8], Violeta Vladislava Panaviene[9], Valda Stanevicha[10], Maria Trachana[11], Constantin Ailioaie[12], Florence Uettwiller[13], Fabrizio De Benedetti[14], Elena Tsitsami[15], Berit Flato[16], Pavla Dolezalová[17], Tamás Constantin[18], Troels Herlin[19], Sylvia Kamphuis[20], Sujata Sawhney[21], Despoina Maritsi[22], Veronika Vargova[23], Luca Villa[8], Chiara Pallotti[8], Angelo Ravelli[3], Alberto Martini[24], Nico Wulffraat[25], Nicolino Ruperto[26] and on behalf of for PRINTO, [1]Pediatric Rheumatology, Wilhelmina Children's Hospital/ UMC Utrecht, Utrecht, Netherlands, [2]Servizio di Epidemiologia e Biostatistica, Istituto Giannina Gaslini, Genoa, Italy, [3]Istituto Giannina Gaslini, Genoa, Italy, [4]Rheumatology, Scientific Center of Children's Health of RAMS, Moscow, Russia, [5]Pediatrie, Unité Romande de Rhumatologie Pédiatrique, Hospitalier Universitaire Vaudois, Lausanne, Switzerland, [6]Pediatric Rheumatology Unit, Juliane Marie Centret, Rigshospitalet, Copenhagen, Denmark, [7]Unitat de Reumatologia Pediàtrica, Hospital Sant Joan de Déu, Barcelona, Spain, [8]Pediatria II - Reumatologia, PRINTO, Istituto Giannina Gaslini, Genoa, Italy, [9]Centre of Pediatrics, Vilnius University, Vilnius, Lithuania, [10]Department of Paediatrics, Riga Stradins University, Riga, Latvia, [11]1st Department of Pediatrics, Aristotle University, Thessaloniki, Greece, [12]II Pediatric Clinic, Private Medical Clinic, IASI, Romania, [13]Unité d'Immunologie, Hématologie et Rhumatologie Pediatrique, Université Paris-Descartes, IMAGINE Institute, Hôpital Necker-Enfants Malades, Paris, France, [14]Reumatologia, Ospedale Pediatrico Bambino Gesù, Roma, Italy, [15]First Department of Pediatrics, Children Hospital Aghia Sophia, Athens, Greece, [16]Rheumatology, Oslo University Hospital, Oslo, Norway, [17]Pediatric Rheumatology Unit, Department of

Pediatrics and Adolescent Medicine, General University Hospital in Prague, Prague, Czech Republic, [18]Unit of Paediatric Rheumatology, 2nd Dpt of Pediatrics, Semmelweis University, Budapest, Hungary, [19]Department of Pediatrics, Aarhus University Hospital, Aarhus N, Denmark, [20]Pediatric Rheumatology, Erasmus MC Sophia Children's Hospital, Rotterdam, Netherlands, [21]Paediatric rheumatology, Sir Ganga Ram Hospital, New Delhi, India, [22]2nd Department of Academic Pediatrics, Athens Medical School, university of Athens, Athens, Greece, [23]1st Department of Paediatrics and Adolescent Medicine, Šafarik University and Children Faculty Hospital in Košice, Kosice, Slovakia, [24]Istituto G. Gaslini, Pediatria II, PRINTO, and University of Genoa, Genoa, Italy, [25]Pediatric rheumatology, Wilhelmina Children's Hospital/ UMC Utrecht, Utrecht, Netherlands, [26]Istituto G. Gaslini, Pediatria II, PRINTO, Genoa, Italy

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Background/Purpose:

Treatment of juvenile idiopathic arthritis (JIA) has greatly changed in the past 15 years thanks to the introduction of biologic agents but little is known on the long-term safety profiles.

Methods:

Pharmachild is an ongoing, multicenter, non-interventional, retrospective/prospective observational registry of patients with JIA treated with either methotrexate (MTX) alone or in combination with one or more biologic agents as part of their standard clinical care. Three treatment groups of patients were considered: MTX only (± other synthetic DMARD or corticosteroids), MTX followed by 1 biologic agent (1Bio±MTX) and treated with more sequentially given biologic agent (>1Bio±MTX). For the purpose of the analysis we divided drug exposure into 3 phases based on the starting date of each drug: MTX phase (11239 PY), 1 bio (9158 PY), > 1 bio (2814 PY). Safety was re-coded by certified assessors according to the Medical Dictionary for Regulatory Activities (MedDRA). True incidence rate events x100 patient-years (PY) for events of special interest (ESI) or at least moderate other adverse events (AE) were calculated for all MedDRA System Organ Class (SOC).

Results:

5862/7250 (81%) of the JIA patients in the database for a total of 23211 PY, were analyzed. There were 601 (10%) systemic, 1198 (20%) oligo persistent and 865 (15%) oligo extended, 2042 (35%) poly RF neg and pos and 1156 (20%) other JIA categories. Out of 5862 JIA patients, 1674 (23%, median disease duration, DD 4 years) were treated primarily with MTX (no biologics), 3025 (42%, DD 6 years) with 1 Bio±MTX (66% etanercept, 18.5% adalimumab, infliximab/tocilizumab 5% each) and 1163 (16%, DD 8 years) with >1Bio±MTX (30% etanercept, 27% adalimumab, 14% infliximab, 9% tocilizumab).

The incidence rates (Table) of AE increase with the addition of at least 1 biologic agent (10.7, 13.9, 19.5). A similar trend was observed for infections (2.9, 4.6, 4.8) and serious infections rates (0.7, 1.4, 2.0). Incidence rates for injury, poisoning and procedural complications (such as infusion/injection related reaction) and blood and lymphatic system (such as MAS) were higher in the group treated with more than 1 biologic agent. Incidence rates for gastrointestinal and hepatobiliary disorders (e.g. Hypertransaminasaemia) were higher for the MTX only group when compared to the other 2 (1.7, 0.9, 0.5).

Conclusion:

The introduction of one or more sequential biologic agent increase the rate of adverse events, infection and serious infections, when compared to the treatment with MTX alone. This risk can be 3 times higher during the use of a second or further biological.

Exposure: Person-years at last follow-up Total number of events	MTX only phase 11239 1207				1 BIO ± MTX 9158 1270				MORE BIO ± MTX 2814 550			
	No. AE	Rates	95% CI		No. AE	Rates	95% CI		No. AE	Rates	95% CI	
Infections and infestations	323	2.9	2.6	3.2	417	4.6	4.1	5.0	135	4.8	4.0	5.7
Serious infections and infestations	77	0.7	0.5	0.9	124	1.4	1.1	1.6	56	2.0	1.5	2.6
Injury, poisoning and procedural complications	32	0.3	0.2	0.4	94	1.0	0.8	1.3	84	3.0	2.4	3.7
Gastrointestinal disorders	161	1.4	1.2	1.7	107	1.2	1.0	1.4	33	1.2	0.8	1.6
Blood and lymphatic system disorders	46	0.4	0.3	0.5	72	0.8	0.6	1.0	49	1.7	1.3	2.3
Eye disorders	48	0.4	0.3	0.6	75	0.8	0.6	1.0	23	0.8	0.5	1.2
Skin and subcutaneous tissue disorders	44	0.4	0.3	0.5	62	0.7	0.5	0.9	34	1.2	0.9	1.7
General disorders and administration site conditions	68	0.6	0.5	0.8	73	0.8	0.6	1.0	29	1.0	0.7	1.5
Musculoskeletal and connective tissue disorders	34	0.3	0.2	0.4	35	0.4	0.3	0.5	25	0.9	0.6	1.3
Surgical and medical procedures	59	0.5	0.4	0.7	42	0.5	0.3	0.6	21	0.7	0.5	1.1
Hepatobiliary disorders	196	1.7	1.5	2.0	82	0.9	0.7	1.1	14	0.5	0.3	0.8
Nervous system disorders	22	0.2	0.1	0.3	42	0.5	0.3	0.6	17	0.6	0.4	0.9
Respiratory, thoracic and mediastinal disorders	16	0.1	0.1	0.2	22	0.2	0.2	0.4	14	0.5	0.3	0.8
Investigations	25	0.2	0.1	0.3	19	0.2	0.1	0.3	16	0.6	0.3	0.9
Psychiatric disorders	30	0.3	0.2	0.4	32	0.3	0.2	0.5	10	0.4	0.2	0.6
Renal and urinary disorders	17	0.2	0.1	0.2	17	0.2	0.1	0.3	8	0.3	0.1	0.5
Endocrine disorders	49	0.4	0.3	0.6	16	0.2	0.1	0.3	8	0.3	0.1	0.5
Immune system disorders	3	0.03	0.01	0.1	8	0.1	0.0	0.2	9	0.3	0.2	0.6
Metabolism and nutrition disorders	18	0.2	0.1	0.2	14	0.2	0.1	0.2	7	0.2	0.1	0.5
Vascular disorders	7	0.1	0.03	0.1	6	0.1	0.03	0.1	3	0.1	0.03	0.3
Reproductive system and breast disorders	1	0.01	0.001	0.04	11	0.1	0.1	0.2	5	0.2	0.1	0.4
Cardiac disorders	2	0.02	0.004	0.1	4	0.04	0.01	0.1	2	0.1	0.01	0.2
Ear and labyrinth disorders	1	0.01	0.001	0.04	3	0.03	0.01	0.1	1	0.04	0.003	0.2
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1	0.01	0.001	0.04	4	0.04	0.01	0.1	0	-	-	-
Social circumstances	1	0.01	0.001	0.04	4	0.04	0.01	0.1	0	-	-	-
Congenital, familial and genetic disorders	2	0.02	0.004	0.1	5	0.1	0.02	0.1	1	0.04	0.003	0.2
Pregnancy, puerperium and perinatal conditions	1	0.01	0.001	0.04	4	0.04	0.01	0.1	2	0.1	0.01	0.2
Total number of events	**1207**	**10.7**	**10.1**	**11.4**	**1270**	**13.9**	**13.1**	**14.6**	**550**	**19.5**	**18.0**	**21.2**

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Double Blind Placebo Controlled Randomized Trial of Probiotics in Enthesitis-Related-Arthritis Category of JIA: Effect on Clinical and Immunological Parameters

Anuj Shukla[1], Priyanka Gaur[2] and Amita Aggarwal[1], [1]Clinical Immunology, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, India, [2]Department of Clinical Immunology, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, India

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Background/Purpose: Gut microflora influences the development and homeostasis of the immune system. Dysbiosis has been reported in various immuno-inflammatory diseases. Pathogenesis of enthesitis-related-arthritis (ERA) category of JIA suggests an interaction between the gut and joints. Thus we studied the effect of probiotic therapy on immune and clinical parameters in children with ERA.

Methods: Forty-six children with active JIA-ERA were randomized to probiotic (VSL3 capsules) therapy or placebo along with NSAIDs for 12-weeks (CTRI/2012/08/002871). Patients, assessor and statistician were blinded to the allocation. Patients were assessed using a 6-point composite index of disease activity based on morning stiffness, joint count, enthesitis count, sacroilitis/inflammatory-back-pain, uveitis and ESR/CRP. Th1, Th2, Th17 and T-regulatory (Treg) cell frequencies were determined in blood using flow-cytometry. Cytokines IFNγ, IL4, IL17, IL10, TNFα and IL6 were measured in the serum by flow-cytometry using cytometric bead array (BD Biosciences) kit.

Results:

The average age of 46 children (44 boys) at enrollment was 15±2.5 year and duration of disease was 3.5±3 years. Most of the children were HLA-B27 positive (93.5%). All children had peripheral arthritis and 65% had associated enthesitis. 52% children had sacroilitis, 26% had inflammatory-back-pain, 9% had history of uveitis and 22% had a family member having spondyloarthritis.

There was no significant difference between the two groups at baseline. There were 2 dropouts in the probiotic-group while 4 in the placebo-group. There was a significant clinical response in both probiotic and placebo group after 12-weeks of therapy (Table) but probiotic group failed to show a significant clinical response compared to the placebo (Table). The immune parameters showed an increase in Th2 and IL-10 levels in placebo and a decrease in IL-6 with probiotics after 12 weeks (Table) but again the difference between the groups was significant only for IL10 levels (Table).

Adverse effects in the probiotic and the placebo groups were diarrhea (36 vs. 45%), abdominal pain (9 vs. 20%), minor infections (4.5 vs. 20%) and flatulence (23 vs. 15%) respectively. Two patients were withdrawn due to side effects 1 in placebo due to severe diarrhea and one in the probiotic-group due to tuberculosis.

Conclusion: Probiotic therapy in JIA-ERA children is well tolerated but failed to show any significant immunological or clinical effects over NSAID-therapy.

Table - Changes in Immune and clinical parameters in the probiotic (n=21) and the placebo groups (n=19). All values are expressed as median

with interquartile range, *p<0.05, **p<0.01 represent significance in the same group after 12 weeks. CI-ESR and CI-CRP – Composite index based on ESR and CRP respectively, PGI - patient reported global improvement, EMS – early morning stiffness, TJC – tender joint count, SJC – swollen joint count)

	Probiotic group (N=21)			Placebo group (N=19)			Difference between the groups (p values) Mann-Whitney test
	Baseline	After 12 weeks	Median change	Baseline	After 12 weeks	Median change	
Disease activity parameters							
CI-ESR	3 (2-4.5)	2 (1.5-4)	-0.5 (-2 to 0)*	3.5 (2.5-4)	2 (1-2.5)	-2 (-2.5 to -1)**	0.06
CI-CRP	3 (2.3-4.5)	1.5 (1-4)	-1 (-2.8 to 0)**	3.5 (2.5-5)	1.5 (0.5-2.5)	-2 (-2.5 to -1.5)**	0.16
PGI %	-	-	70 (35 to 80)	-	-	70 (25 to 90)	0.8
EMS (min)	30 (0-83)	2 (0-18)	-10 (-60 to 5)*	45 (15-60)	0 (0-15)	-30 (-60 to 0)	0.6
TJC (0-68)	3 (2-5)	1 (0-4)	-1 (-3.5 to 1.5)	3 (2-5)	0 (0-1)	-2 (-4 to -2)**	0.06
SJC (0-66)	2 (1.5-3.5)	0 (0-1.5)	-1 (-2.5 to -1)**	2 (2-3)	0 (0-1)	-2 (-3 to -1)**	0.15
Enthesitis count	2 (0.5-4.5)	2 (0.5-3.5)	0 (-2 to 1.5)	0 (0-3)	1 (0-2)	0 (0 to 2)	0.5
ESR mm	80 (39-120)	42 (30-80)	-15 (-61 to 10)	80 (40-100)	30 (22-45)	-40 (-66 to 2) **	0.35
CRP mg/dl	8 (2.4-10.4)	0.7 (0.3-6)	-3.3 (-8.3 to 0)*	2.8 (1.4-6.8)	1.1 (0.3-1.9)	-1.5 (-4 to -0.2) **	0.36
Immune parameters							
Th1 %	6.6 (4.9-8.9)	7.0 (3.8-8.9)	0.1 (-1.9 to 2.5)	6.5 (3.3-9.3)	5.9 (3.0-8.6)	0.8 (-3.3 to 3.5)	0.7
Th2 %	0.6 (0.2-1.2)	0.8 (0.3-1.5)	0.2 (-0.2 to 0.6)	0.3 (0.1-0.5)	0.6 (0.3-1.7)	0.3 (-0.1 to 1)*	0.5
Th17 %	1.5 (0.7-1.7)	1.0 (0.4-1.8)	-0.07 (-0.8 to 0.45)	1.2 (0.7-1.8)	1.2 (0.6-2.2)	0.4 (-0.4 to 0.8)	0.3
Treg %	2.6 (1.8-3.4)	2.6 (1.8-4.0)	0.4 (-1.6 to 1.3)	2.7 (1.3-3.7)	3.2 (2.4-4.2)	1.1 (-0.4 to 1.9)	0.2
IL-6 pg/ml	53 (12-15)	11.4 (6.6-21)	-37 (-102 to -1.7)*	33 (21-127)	13.5 (9-116)	-9.2 (-40 to 16.8)	0.13
TNFα pg/ml	0.9 (0.4-2.8)	0.41 (0-7.8)	-0.75 (-2.3 to 0.5)	1 (0.3-4.2)	0.8 (0.2-1.6)	0.14 (-2.2 to 0.9)	0.5
IFNγ pg/ml	0 (0-2.2)	0 (0 -0)	0 (-1.2 to 0)	0 (0-2.4)	0 (0-0)	0 (-2.4 to 0)	0.5
IL-4 pg/ml	0 (0-0)	0 (0 -1.64)	0 (0 to 1)	0 (0-1.85)	0 (0-1.6)	0 (-8.6 to 0.5)	0.3
IL-17 pg/ml	36 (2.7-58)	34 (14-63)	2.8 (-26 to 29)	44 (20-62)	24.3 (10-44)	-20 (-42 to 6)	0.26
IL-10 pg/ml	1 (0.5-2.2)	0.5 (0-1.35)	-0.75 (-2 to 0.6)	1.0 (0.7-1.6)	2 (0-3.4)	1 (-0.6 to 1.9)**	0.013*

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Abstract Number: 958

The Time Spent in Inactive Disease before MTX Withdrawal Is Relevant with Regard to the Recurrence of Active Disease in Juvenile Idiopathic Arthritis (JIA) Patients

Jens Klotsche[1], Gerd Ganser[2], Ivan Foeldvari[3], Hans Huppertz[4], Rolf M. Kuester[5], Angelika Thon[6], Kirsten Minden[7] and Gerd Horneff[8], [1]Epidemiology unit, German Rheumatism Research Center, Berlin, Germany, [2]Pediatric Rheumatology, Sankt Josef Stift, Sendenhorst, Germany, [3]Hamburger Zentrum für Kinder-und Jugendrheumatologie, Hamburg, Germany, [4]Prof Hess Children's Hospital, Bremen, Germany, [5]Asklepios Rheumazentrum Hamburg, Hamburg, Germany, [6]Kinderklinik der Medizinischen Hochschule Hannover, Hannover, Germany, [7]Children's

University Hospital Charite/German Rheumatism Research Centre Berlin, Berlin, Germany, [8]Asklepios Klinik Sankt Augustin GmbH, Sankt Augustin, Germany
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Background/Purpose: Methotrexate (MTX) is the most widely used disease modifying antirheumatic drug (DMARD) in JIA and regarded to be a safe drug, effective in around 70% of JIA cases. Therefore, strategies of withdrawing MTX therapy have become a challenging question.

Methods: Data from 1514 patients enrolled with MTX monotherapy in the national JIA biologic register BiKeR between 2005 and 2011 and prospectively observed into adulthood in the follow-up register JuMBO were considered for this analysis. Clinical characteristics, therapy, date and reasons for discontinuation of MTX were half-yearly reported by the treating physician. A recurrence of an active disease (AD) after attaining inactive disease (ID) under MTX monotherapy was defined as cJADAS-10 (Juvenile Arthritis Disease Activity Score) above five or the start of a therapy with MTX and/or a biologic DMARD. ID was defined as cJADAS-10 of lower or equal one. The time to recurrence of AD in patients withdrawing MTX due to ID was examined by a multivariable Cox-proportional hazard model.

Results: The mean age of the patients at JIA onset was 7.6 ± 4.6 years and their mean disease duration was 2.1 ± 2.8 years at inclusion in BiKeR. 27% had persistent oligoarthritis, 27% rheumatoid-factor (RF) negative polyarthritis and 68% were female. MTX was discontinued in 65% after a mean treatment duration of 2.0 ± 1.5 years during a mean follow-up of 3.5 ± 2.1 years. Reasons for MTX discontinuation were ineffectiveness including the switch to a biologic DMARD (23%), patients' request (16%), an adverse event (10%) and ID (20%). MTX was withdrawn due to ID (n=303) after a mean treatment duration of 2.3 ± 1.0 years. Among those, 172 (56.4%) experienced AD after 11.8 ± 14.9 months. Patients who had an ID for at least 12 months before discontinuation of MTX had a significantly lower recurrence rate of AD (49.4%, HR=0.67, p=0.013) than those with ID for at least 6 months (54.2%, HR=0.85, p=0.491) compared to those with ID for less than 6 months (61%) before drug discontinuation, respectively. Patients with systemic JIA (44.4%, OR=0.33, p=0.03) and patients with psoriatic arthritis (42.3%, OR=0.31, p=0.013) had the lowest recurrence of AD compared to patients with extended oligoarthritis having the highest recurrence rate of AD (70.5%).

Conclusion: Half of the patients had recurrence of active disease after MTX withdrawal, what confirms the high flare rate in JIA. Recurrence of active disease was less common in patients who spent at least 12 months in ID before MTX discontinuation, as compared to those with shorter time in ID before drug withdrawal. Thereafter, the rate of disease recurrence seems lower in prolonged MTX therapy.

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Results from the Childhood Arthritis and Rheumatology Research Alliance Systemic JIA Consensus Treatment Plans Pilot Study

Yukiko Kimura[1], Timothy Beukelman[2], Esi Morgan-DeWitt[3], Kelly L. Mieszkalski[4], Thomas Brent Graham[5], Maria F. Ibarra[6], Norman Ilowite[7], Marisa S. Klein-Gitelman[8], Karen Onel[9], Sampath Prahalad[10], Marilynn G. Punaro[11], Sarah Ringold[12], Dana Toib[13], Heather Van Mater[14], Pamela F. Weiss[15], Laura Schanberg[16] and the CARRA Registry Investigators, [1]Pediatric Rheumatology, Joseph M Sanzari Children's Hospital, Hackensack University Medical Center, Hackensack, NJ, [2]Rheumatology, University of Alabama at Birmingham, Birmingham, AL, [3]Pediatric rheumatology, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, [4]Rheumatology, Duke University Medical Center, Durham, NC, [5]Pediatric Rheumatology, Vanderbilt Children's Hospital, Nashville, TN, [6]Pediatric Rheumatolgy, Children's Mercy Hospital, Kansas City, MO, [7]Division of Pediatric Rheumatology, Children's Hospital at Montefiore, Bronx, NY, [8]Division of Rheumatology, Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, IL, [9]Pediatric Rheumatology, Univ of Chicago, Chicago, IL, [10]Rheumatology, Emory University, Atlanta, GA, [11]Texas Scottish Rite Hospital, Dallas, TX, [12]Pediatrics, Seattle Children's Hospital, Seattle, WA, [13]Pediatric Rheumnatology, St. Christopher's Hospital for Children, Philadelphia, PA, [14]Duke Pediatric Rheumatology, Duke University Medical Center, Durham, NC, [15]Rheumatology, Children's Hospital of Philadelphia, Philadelphia, PA, [16]Duke University, Durham, NC
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Session Time: 2:30PM-4:00PM

Background/Purpose:

Systemic JIA (sJIA) in usual practice is commonly treated with several agents, including glucocorticoids (GC), methotrexate (MTX) and biologic agents, most commonly IL1 or IL6 inhibitors, which may be given alone or in combination with GC. The most effective treatment for new onset sJIA is not known. The Childhood Arthritis and Rheumatology Research Alliance (CARRA) developed standardized consensus treatment plans (CTPs) for new onset sJIA to study the comparative effectiveness of these treatments using an observational registry. A pilot study was conducted to assess the feasibility of using the CTPs for this purpose.

Methods:

New onset untreated sJIA patients (pts) enrolled in the CARRA Registry at one of 15 pilot sites were treated according to the CTP selected by the treating physician (GC alone; MTX ± GC; IL1 inhibitor (IL1i) ± GC; IL6 inhibitor (IL6i) ± GC). Deviations from the chosen CTP could occur for inadequate response at any time. If GC was started, the CTPs suggested an aggressive taper (<50% of the starting dose by 3 months). Data were collected at standard intervals consistent with usual practice and the primary outcome of clinically inactive disease (CID) and successful cessation of GC was assessed at the 9 month visit. The CTPs were compared using chi square, Fisher's exact, and Wilcoxon rank sum tests.

Results:

30 patients were enrolled and completed the study (Table). There were not major differences between patients in each CTP, but patients treated with GC CTP alone tended to be older, non-white, have oligoarthritis, and be more likely to have very high ferritin levels. 83% of the MTX CTP treated patients had physicians who reported that they always select this treatment, as did 42% of the patients in the IL1i CTP. The study outcome was achieved by 37% of patients overall. No patients in the GC or MTX CTP achieved the study outcome, while 42% and 60% in the IL1i and IL6i CTPs did, respectively. There were 2 serious adverse events; both were infections that occurred while receiving IL1i. There were 2 episodes of macrophage activation syndrome: 1 each in IL1i and IL6i CTPs. All patients recovered.

Conclusion:

The CARRA sJIA CTP pilot study was successfully completed. The patients enrolled appeared reasonably balanced at baseline. The study outcome was achieved by 37% of patients treated with a biologic, and by none treated with GC alone or MTX. Having demonstrated feasibility of the CTPs, additional patients will be enrolled as part of a larger comparative effectiveness study to determine the most appropriate treatment strategy for new onset SJIA.

Table: sJIA Patients Enrolled in CTP Pilot Study and their Outcomes

Characteristic	GC	MTX	IL1i	IL6i	Total	p value
N	2	6	12	10	30	
Age (median)	12.5	3.3	3.9	9.0	5.5	0.044
Female (%)	50%	67%	92%	90%	83%	0.3
White (%)	0%	83%	33%	80%	57%	0.03
Disease duration (median)	116.5	38.0	31.0	55.0	42.5	0.21
Polyarthritis (%)	0%	50%	67%	80%	63%	0.2
Number of active joints at enrollment (median)	1	4.5	5	5.5	4.5	0.3
Hemoglobin (median)	8.9	9.6	9.6	10.8	10.1	0.09
ESR >3x ULN (%)	100%	67%	91%	43%	73%	0.3
CRP >3x ULN (%)	100%	83%	91%	40%	79%	0.3
Ferritin (median)	12,874	1,394	1,062	627	783	0.09
CHAQ (median)	0.9	1.3	1.9	0.8	1.4	0.6
Patient pain score (median)	3	6.5	6	7.5	6	0.6
Physician global (median)	4	7	5	5	5.5	0.1
Results						
CID at 9 months (%)	0%	33%	42%	60%	48%	0.4
GC cessation at 9 months (%)	50%	17%	83%	80%	67%	0.03
CID+ GC cessation at 9 months (%)	0%	0%	42%	60%	37%	0.07

Disclosure: Y. Kimura, Novartis Pharmaceutical Corporation, 2,Novartis Pharmaceutical Corporation, 5,SOBI, 5; **T. Beukelman**, UCB, 5,Genentech/Roche, 5,Novartis Pharmaceutical Corporation, 5; **E. Morgan-DeWitt**, None; **K. L. Mieszkalski**, None; **T. B. Graham**, None; **M. F. Ibarra**, None; **N. Ilowite**, Novartis Pharmaceutical Corporation, 5,SOBI, 5,Pfizer Inc, 5; **M. S. Klein-Gitelman**, None; **K. Onel**, None; **S. Prahalad**, None; **M. G. Punaro**, None; **S. Ringold**, None; **D. Toib**, None; **H. Van Mater**, None; **P. F. Weiss**, None; **L. Schanberg**, UCB, 5,Novartis Pharmaceutical Corporation, 2,SOBI, 5.

Abstract Number: 960

Efficacy of Canakinumab in Systemic Juvenile Idiopathic Arthritis Patients Previously Exposed to Biologics

Hermine I. Brunner[1], Nicolino Ruperto[2], Pierre Quartier[3], Tamas Constantin[2], Yackov Berkun[2], Inmaculada Calvo-Penedes[2], Müferet Erguven[2], Laurence Goffin[2], Michael Hofer[2], Tilmann Kallinich[2], Sheila Oliveira[2], Yosef Uziel[2], Stefania Viola[4], Kiran Nistala[2], Carine Wouters[2], Karolynn Leon[5], Antonio Speziale[6], Karine Lheritier[6], Guido Junge[6], Daniel Lovell[1,7] and Alberto Martini[2], [1]PRCSG, Cincinnati, OH, [2]PRINTO-Istituto Gaslini, Genova, Italy, [3]Necker-Enfant Malades Hospital, Paris, France, [4]Istituto G Gaslini, Pediatria II, Reumatologia, Genova, Italy, [5]Novartis Pharmaceuticals Corporation, East Hanover, NJ, [6]Novartis Pharma AG, Basel, Switzerland, [7]Rheumatology, Cincinnati Children's Hospital Medical Center, Cincinnati, OH

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Session Type: ACR Concurrent Abstract Session

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Background/Purpose: Efficacy and safety of canakinumab (CAN) in systemic juvenile idiopathic arthritis (SJIA) have been demonstrated in two phase III trials.[1] In these trials, over 60% of the patients (pts) had received a previous biologic and were switched to CAN for either lack of efficacy or safety reasons and may be more refractory to another biologic therapy. Here, we examine CAN efficacy in CAN-naïve SJIA pts, previously exposed to anakinra (ANK) and tocilizumab (TCZ).

Methods: This was an open-label extension study with details reported earlier.[2] Adapted (a) ACR 30/50/70/90/100 responses with CAN were assessed at Day 29 and 12 months. Pts with prior exposure to ANK or TCZ exposure were compared to biologic naïve pts. Reasons for discontinuation of ANK and TCZ were recorded and safety noted.

Results: Among the 123 pts considered in this analysis, 51 pts (42%) previously received ANK and 31 (25%) TCZ, respectively. The main reason for ANK/TCZ discontinuation was lack of efficacy (ANK, 21%; TCZ, 21%). At Day 29, aACR 30/50 response rates were similar for both ANK-naïve pts and those who discontinued ANK for lack of efficacy(Table); aACR30 but not aACR50 response rates were slightly higher in ANK-naïve vs those who discontinued ANK for lack of efficacy. In the TCZ-exposed pts, aACR 30 response rates were comparable at Day 29 in TCZ naïve pts vs those who discontinued TCZ for lack of efficacy. At month 12, aACR 50 response rates were higher in pts who discontinued TCZ due to lack of efficacy vs TCZ naïve pts.

Table. Percentage of patients with adapted JIA ACR (aACR) response* at Day 29 and Month 12

	Exposure to Biologics, Anakinra							
	Day 29, n (n/m %)				Month 12, n (n/m %)			
	Group 1 (N=26)	Group 2 (N=12)	Group 3 (N=13)	Group 4 (N=72)	Group 1 (N=26)	Group 2 (N=12)	Group 3 (N=13)	Group 4 (N=72)
	m=21	m=12	m=13	m=68	m=18	m=7	m=8	m=52
aACR 30	18 (86)	10 (83)	12 (92)	58 (85)	16 (89)	7 (100)	8 (100)	50 (96)
aACR 50	16 (76)	10 (83)	12 (92)	52 (77)	16 (89)	7 (100)	8 (100)	46 (89)
	Exposure to Biologics, Tocilizumab							
	Day 29, n (n/m %)				Month 12, n (n/m %)			
	Group 1 (N=26)	Group 2 (N=3)	Group 3 (N=2)	Group 4 (N=92)	Group 1 (N=26)	Group 2 (N=3)	Group 3 (N=2)	Group 4 (N=92)
	m=25	m=3	m=2	m=84	m=21	m=3	m=2	m=59
aACR 30	21 (84)	3 (100)	2 (100)	72 (86)	20 (95)	3 (100)	2 (100)	56 (95)
aACR 50	18 (72)	2 (67)	2 (100)	68 (81)	20 (95)	3 (100)	1 (50)	53 (90)

*aACR response =ACR response level plus absence of fever; n= number of patients who satisfy the criteria; m=number of patients with an assessment in the time period; If a patient has more than one assessment in the time period, their last value is taken

Group 1: Patients who discontinued anakinra/tocilizumab due to lack of efficacy; Group 2: Patients who discontinued anakinra/tocilizumab for safety/tolerability reasons; Group 3: Patients who discontinued anakinra/tocilizumab due to other reasons; Group 4: Never exposed to anakinra/tocilizumab

Conclusion: There is a comparable initial and 12 month aACR-JIA response to CAN among SJIA patients who switched from ANK or TCZ due to lack of efficacy compared to those without previous use. These results support the consistent efficacy of CAN across different patient subtypes and demonstrate efficacy in prior biologic non-responders.

References:

1. Ruperto N, et al. *N Engl J Med* 2012;367(25):2396–406.

2. Ruperto et al. *Ann Rheum Dis*. 2015;74(2):608

Disclosure: H. I. Brunner, Novartis, Roche, Pfizer, UCB, Celgene, Regeneron, Amgen, Astrazeneca, GSK, BMS, 5,Novartis, Roche, 8; **N. Ruperto**, Abbott, BMS, "Francesco Angelini", GlaxoSmithKline (GSK), Hoffman-La Roche, Italfarmaco, Janssen, Novartis, Pfizer, Sanofi Aventis, Schwarz Biosciences, Sobi, Xoma, Wyeth, 2,Abbott, AbbVie, Amgen, Biogenidec, Astellas, Alter, AstraZeneca, Boehringer, BMS, CD-Pharma,Celgene, CrescendoBio, EMD Serono,Hoffman-La Roche, Italfarmaco, Janssen, MedImmune, Medac, Novartis, Novo Nordisk, Pfizer, Sanofi Aventis, Servier, Takeda, Vertex, 8; **P. Quartier**, Abbvie, BMS, Chugai-Roche, Novartis, Pfizer, SOBI, 2,Abbvie, Novartis, Servier, SOBI, 5,Abbvie, BMS, Chugai-Roche, Medimmune, Novartis, Pfizer, SOBI, 8; **T. Constantin**, None; **Y. Berkun**, Novartis, 5; **I. Calvo-Penedes**, Roche, Abbvie, Novartis, Pfizer, 2,Roche, Abbvie, Gebro, Novartis, 8; **M. Erguven**, Novartis, 2; **L. Goffin**, None; **M. Hofer**, Abbvie, 2,Abbvie and Novartis Pharmaceutical Corporation, 5; **T. Kallinich**, None; **S. Oliveira**, Novartis, 2; **Y. Uziel**, Novartis, 5,Novartis, 8; **S. Viola**, None; **K. Nistala**, None; **C. Wouters**, GSK, Novartis, Roche, 2; **K. Leon**, Novartis Pharmaceutical Corporation, 3; **A. Speziale**, Novartis, 3; **K. Lheritier**, Novartis, 1,Novartis, 3; **G. Junge**, Novartis., 3; **D. Lovell**, National Institutes of Health, 2,Astra-Zeneca, Bristol Meyers Squibb, AbbVee, Pfizer, Roche, Novartis, UBC, Forest Research Institute, Horizon, Johnson & Johnson, Biogen, Takeda, Genentech, Glaxo Smith Kline, Boehringer Ingelheim, Celgene, Jannsen, 5,Genentech, Roche, Novartis, 8; **A. Martini**, Abbott, BMS, "Francesco Angelini", GlaxoSmithKline (GSK), Hoffman-La Roche, Italfarmaco, Janssen, Novartis, Pfizer, Sanofi Aventis, Schwarz Biosciences, Sobi, Xoma, Wyeth, 2,Abbott, Abbvie, Amgen, Biogenidecm Bristol MyersSquibb, Astellas, Behringer, Italfarmaco, Janssen, MedImmune, Novartis, NovoNordisk, Pfizer, Sanofi, Roche, Servier, Takeda., 8.

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Abstract Number: 961

Altered Th Cell Plasticity Favors Th17 Cells in Rheumatoid Arthritis

Jan Leipe[1], Fausto Pirronello[2], Hendrik Schulze-Koops[2] and Alla Skapenko[2], [1]Division of Rheumatology, University of Munich, Munich, Germany, [2]Division of Rheumatology and Clinical Immunology, University of Munich, Munich, Germany

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Session Type: ACR Concurrent Abstract Session

Session Time: 2:30PM-4:00PM

Background/Purpose: Previously, T helper (Th) cell subsets have been regarded as irreversibly differentiated endpoints. However, evidence suggests that Th cell differentiation is a plastic process in response to certain (e.g. inflammatory) conditions. Mechanisms leading to the pathogenetic important predominance of Th17 cells in rheumatoid arthritis (RA) are not yet understood. Therefore, we investigated plasticity and underlying molecular mechanisms to address the question if an altered T cell plasticity contributes to the shift towards the Th17 phenotype in RA.

Methods: A unique cohort of 40 patients with early, active and untreated RA (to exclude effects of immunosuppressive drugs on T cells) and 41 age- and sex- matched healthy controls (HC) were studied. Viable *in vivo*-originated Th1, Th2 and Th17 cells were FACS-sorted and trans-differentiated under Th1-, Th2- or Th17-inducing conditions. The cytokine Th profile of the trans-differentiated cells was assessed by flow cytometry. Epigenetic modifications including histone modifications and DNA methylation of Th cell-associated cytokine and transcription factor gene loci were analyzed by ChiP assay and bisulfite sequencing. Relative expression of cytokine and transcription factors were measured by ELISA and qRT-PCR.

Results: Th17 cells from RA patients cultured under Th1 and Th2 conditions showed a strikingly diminished trans-differentiation capacity into both Th1 and Th2 phenotypes and retained their IL-17 expression to a significantly higher degree compared to Th17 cells from HC. Vice versa, RA Th1 and Th2 cells demonstrated an enhanced capacity to re-differentiate into Th17 cells. We found higher *RORC* expression in RA Th1 cells that were trans-differentiated under Th17 conditions as a basis for increased re-differentiation of Th1 to Th17 cells in RA. With regard to epigenetic regulation, less permissive histone modifications H3K4 methylation and H3 actetylation over the repressive H3K27 methylation was found in the *Tbx21* locus of RA Th1 cells consistent with the shift from Th1 to Th17 cells. Moreover, DNA methylation of the IL-17 gene promoter was decreased in RA Th17 cells compared to HC enabling higher IL-17 expression.

Conclusion: Our data indicate that *in vivo*-originated Th17 cells from RA patients are resistant to changes in their phenotype, whereas other Th subsets are prone to Th17 cell trans-differentiation. Increased RORC expression, less DNA methylation at the IL-17A gene, and less permissive histone modifications of the Tbx21 gene might contribute to the altered Th plasticity in RA, thereby contributing to the pathogenic Th17 shift.

Disclosure: J. Leipe, None; **F. Pirronello**, None; **H. Schulze-Koops**, None; **A. Skapenko**, None.

Abstract Number: 962

Profiling at the Single-Cell Level Reveals Evidence for Antigen-Driven Oligoclonal Expansion of Citrullinated Vimentin-Specific CD4+ T Cells in Peripheral Blood of Rheumatoid Arthritis (RA) Patients

Soi Cheng Law[1], Hendrik Nel[1], Jamie Rossjohn[2,3], Hugh H Reid[3], Nicole L La Gruta[4] and Ranjeny Thomas[1], [1]The University of Queensland Diamantina Institute, Translational Research Institute, Princess Alexandra Hospital, Brisbane, Australia, [2]Institute of Infection and Immunity, Cardiff University, School of Medicine, Heath Park, Cardiff, England, [3]Department of Biochemistry and Molecular Biology, School of Biomedical Sciences, Monash University, Clayton, Melbourne, Australia, [4]Department of Microbiology & Immunology, Peter Doherty Institute for Infection and Immunity, University of Melbourne, Melbourne, Australia

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Session Time: 2:30PM-4:00PM

Background/Purpose:

RA is associated with shared epitope (SE)+ HLA-DRB1 alleles, including HLA-DRB1*0401, and development of anti-citrullinated protein autoantibodies. The preferential binding of citrullinated vimentin to HLA-DRB1*0401 and the correlation between disease activity and the frequency of citrullinated vimentin-specific T cells suggest that citrullinated vimentin selects and expands antigen-experienced T cells in SE+ RA patients. TCR diversity is generated through gene rearrangement, insertions and deletions of the genes encoding the Vα and Vβ chains. TCR Complementarity Determining Regions (CDR) interact directly with peptide-HLA (pHLA). If selection bias has occurred as a result of TCR-pHLA interactions, different individuals may share a similar TCR repertoire to a given pHLA. While deep sequencing synovial tissue has demonstrated oligoclonality, the antigens recognised by these clones are unknown. To obtain more direct evidence that presentation of citrullinated-vimentin shapes the repertoire in SE+ individuals, we profiled TCR repertoire diversity among single vimentin(59-71)cit-64-specific CD4+ T cells.

Methods: Single vimentin(59-71)cit-64-specific CD4+ T cells were sorted from peripheral blood mononuclear cells (PBMC) of 8 HLA-DRB1*0401+ RA patients and 6 HLA-DRB1*0401+ healthy controls (HC), based on staining with fluorescent pHLA tetramers. Sorted cells were simultaneously analysed for expression of CD25 and CD127. At sampling, 2 of the 8 patients had been treated for 18 and 41 months, respectively, 1 had recent-onset untreated RA and 5 had recent-onset RA. PBMC were collected pre- and 1-9 months post-treatment with disease modifying anti-rheumatic drugs. Paired TCR TRAV and TRBV sequences were analysed using multiplex, nested PCR and sequencing.

Results:

A total of 486 vimentin(59-71)cit-64-specific CD4+ T cells with productive TRAV and TRBV sequences were analysed from 8 patients and 6 HC (255 TRAV and 370 TRBV from RA patients; 97 TRAV and 116 TRBV from HCs). Among these T cells, the repertoire encoding TCRα and TCRβ was highly diverse in all patients and HC, and included a large number of unique CDR3 sequences. However, TCR usage in the epitope-specific population differed between RA patients and HC. In RA patients, TRAV26-1 (8%) and TRBV20-1 (13%) predominated while in HC, TRAV13-2 (12%) and TRBV20-1 (12%) were dominant. We did not observe preferential usage in the length of CDR3α or CDR3β. Repeated sequences of individual clonotypes were observed in 3/8 RA patients, but in none of the 6 HC. This oligoclonality was present in pre- and post-treatment samples, and in some cases the same sequences were observed in the same individual across time-points. The repeated sequences were exclusively derived from CD25+CD127+ effector CD4+ T cells.

Conclusion: These data demonstrate a wide range of possible TCRs available for recognition of the vimentin(59-71)cit-64 epitope in PB CD4+ T cells of RA patients and HC. While CD4+ T cells recognising citrullinated self-antigens are present in RA patients and HC carrying HLA-DRB1*0401, repeated clonotypic sequences only among RA patients suggests selective citrullinated self-antigen-driven oligoclonal effector T cell expansion in disease.

Disclosure: S. C. Law, None; **H. Nel**, None; **J. Rossjohn**, None; **H. H. Reid**, None; **N. L. La Gruta**, None; **R. Thomas**, None.

Abstract Number: 963

Ectopic Lymphoid Tissue in the Lung Is Associated with Serum Rheumatoid Arthritis-Related Autoantibodies Even in Absence of Clinically Apparent Rheumatoid Arthritis

Lindsay E. Brown[1], M. Kristen Demoruelle[2], Mark C. Parish[3], Marie L. Feser[2], Peter B. Sachs[4], David E. Heinz[5], Carlyne D. Cool[1] and Kevin D. Deane[6], [1]University of Colorado School of Medicine, Aurora, CO, [2]Division of Rheumatology, University of Colorado School of Medicine, Aurora, CO, [3]Rheumatology, University of Colorado Anschutz Medical Campus, Aurora, CO, [4]Department of Radiology, University of Colorado School of Medicine, Aurora, CO, [5]Pathology, University of Colorado School of Medicine, Aurora, CO, [6]Division of Rheumatology, U Colo Denver, Aurora, CO

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Background/Purpose: Lung disease has been associated with elevations of RA and Sjogren's-related autoantibodies (Abs), even in the absence of extrathoracic features of these diseases (Fischer 2010). In particular, in classifiable RA organized ectopic lymphoid tissue in the lung has been associated with RA related Abs (Rangel-Moreno 2006). Herein we examine the association of Abs and lung histopathology in subjects with RA lung disease, as well as subjects with non-RA lung disease.

Methods: Using materials from the NIH's Lung Tissue Resource Consortium (LTRC) we evaluated lung tissue and matched serum samples from 75 subjects with lung disease who for clinical care required lung biopsy: 10 subjects with RA and interstitial lung disease (ILD), and 65 subjects with ILD or emphysema in absence of RA based on evaluation at the time of lung biopsy. Serum was tested for Abs CCP3.1, RF isotypes IgA, IgM and IgG, and SSA and SSB. Lung tissue was evaluated by microscopy (H&E) to determine the presence of organized ectopic lymphoid tissue defined as germinal centers (GCs) by a pulmonary pathologist blinded to subjects' Ab status. Multivariate analyses were used to determine associations of Abs and GCs.

Results: The patients' characteristics grouped based on the presence of GCs are presented in the Table. RA was significantly associated with the presence of GCs, and there was a trend towards increasing age being inversely associated with GCs; smoking was not associated with the presence of GCs. In analyses adjusting for RA and age, serum positivity for CCP3.1 was strongly associated with the presence of GCs (OR 4.1, 95% CI 1.2-14.4; p=0.03). In adjusted analyses there were no significant associations with RF's or SSA/B with GCs as single Abs; however, an increasing number of positive Abs was associated with GCs. Specifically, for every increase by 1 in number of serum Abs (+), there was a 60% increase in risk of having GCs (OR 1.6, 95% CI 1.1-2.4; p=0.03).

Conclusion: In this unique sample set from the LTRC, we confirm a strong relationship between serum Abs and the presence of organized ectopic lymphatic tissue/GCs in the lung, even after adjusting for the presence of clinically apparent RA. The strongest associations were observed for anti-CCP and increasing total number of Abs. The findings suggest a mechanistic link between GCs in the lung and circulating Abs, and in particular anti-CCP, that may be due to in-situ generation of Abs within GCs in the lung or that circulating Abs perpetuate the immune response by forming organized lymphoid tissue in the lung. Future studies should assess these potential mechanisms as well as evaluate the potential that Abs may be a marker for lung GCs that could be used to understand disease prognosis and response to treatment.

Table. Characteristics of subjects with and without germinal centers			
	Germinal Center (+) N=16	Germinal Center (-) N=59	p-value
Age, median (range)	53 (40-73)	63 (40-80)	0.06
Female (%)	63%	56%	0.78
Non-Hispanic White (%)	75%	78%	0.20
Ever smoker (%)	75%	73%	1.00
Rheumatoid arthritis diagnosis (%)	**31%**	**9%**	**0.03***
Autoantibodies			
RF-IgA	25%	15%	0.46
RF-IgM	**44%**	**10%**	**<0.01***
RF-IgG	38%	24%	0.34
CCP3.1	**56%**	**22%**	**0.01***
SSA	13%	7%	0.60
SSB	6%	2%	0.38
Antibody Count	**1.5 (0-5)**	**0 (0-6)**	**<0.01***
*In analyses adjusted for age and diagnosis of RA, CCP3.1 positivity and Antibody Count were significantly associated with the presence of Germinal Centers; however, RF-IgM was not. For CCP3.1 adjusted OR 4.08, 95% CI 1.16-14.37; p=0.03. For Antibody Count adjusted OR 1.59, 95% 1.06-2.40; p=0.03.			

Abstract Number: 964

Neutrophil Extracellular Traps Are Not Only Targets for ACPA-Positive IgG from Rheumatoid Arthritis Patients but Also Directly Trigger Pro- and Anti-Inflammatory Effects Partly Mediated By the C1q Complement Protein

Matthieu Ribon[1], Sarra Seninet[1], Katarzyna Matyja[1], Mireille Sebbag[2], Cyril Clavel[2], Julie Mussard[1], Guy Serre[2], Marie-Christophe Boissier[3] and **Patrice Decker**[1], [1]Inserm UMR 1125, Li2P, University of Paris 13, Sorbonne Paris Cité, Bobigny, France, [2]University of Toulouse, UMR 5165 CNRS-1056 Inserm, Toulouse, France, [3]Rheumatology Department, Avicenne Hospital, AP-HP, Bobigny, France

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Background/Purpose: Activated neutrophils (PMN) form neutrophil extracellular traps (NET). Those structures are expelled chromatin fibers composed of DNA and associated proteins. The process, NETosis, is dependent on citrullination, and has been suggested to be pathogenic in rheumatoid arthritis (RA). RA is characterized by the production of anti-citrullinated protein autoantibodies (ACPA) which are specific for the disease. Although RA PMN show enhanced NETosis and RA autoantibodies recognize NET, the potential pathogenic mechanisms triggered by NET are not elucidated. Therefore, we have analyzed the antigenic and inflammatory properties of NET in RA.

Methods: PMN and monocytes were purified from the blood. We have used primary cells freshly isolated from 115 independent healthy donors and RA patients. IgG were purified from healthy donors, from ACPA-positive RA patients and from ACPA-negative patients with rheumatic diseases. Monocytes were differentiated into macrophages by culturing in the presence of M-CSF. Cell purity and IgG binding were estimated by flow cytometry. NETosis was induced *in vitro* by PMA on adherent PMN and was analyzed by fluorescence microscopy, together with IgG

binding. To produce soluble NET, NET were detached from glass by mild nuclease digestion. They were enriched, quantified by fluorescence and spectrophotometry, and characterized by SDS-PAGE and agarose gel. Macrophages/PMN were cultured with soluble NET in the presence/absence of LPS, IgG, NH_4Cl or C1q. C1q receptor expression and cell activation were estimated by flow cytometry and by measuring cytokine secretion by ELISA.

Results: Only low binding of IgG was observed by flow cytometry on untreated freshly isolated PMN. Upon NETosis, a strong recognition by ACPA+ IgG was observed, specifically on the NET structures, as demonstrated by fluorescence microscopy. The NET staining with ACPA from RA patients was stronger than with ACPA-negative IgG in 15 out of 19 experiments (79 %; $p < 0.05$) and normal NET were as antigenic as RA NET. Soluble NET activated both steady-state macrophages and PMN, leading to IL-8 secretion and CD11b up-regulation, independently of ACPA+ IgG. The stimulatory activity of soluble NET on macrophages was increased in the presence of C1q, whereas PMN activation was not influenced by inhibition of endosomal acidification. Soluble NET from both healthy donors and RA patients induced cell activation and have similar immuno-modulatory properties. Likewise, both PMN and macrophages from healthy donors and RA patients responded to soluble NET. On the contrary, soluble NET specifically inhibited LPS-induced IL-6 secretion by macrophages.

Conclusion: ACPA+ IgG from RA patients strongly and specifically recognize NET and not untreated PMN. NET are antigenic and possess both pro- and anti-inflammatory properties depending on the cell type, the activation level and the presence of co-factors like C1q or high expression of its receptors but independently of endolysosomal activity or ACPA. Therefore, an excess of NETosis rather than altered NETosis may be pathogenic in RA and trigger ACPA. This is probably the largest analysis comparing RA/normal NET on RA/normal cells reported so far.

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Abstract Number: 965

Crystal Structure of Porphyromonas Gingivalis peptidylarginine Deiminase: Implications for Autoimmunity in Rheumatoid Arthritis

Anna B. Montgomery[1], Jolanta Kopec[2], Leela Shresha[2], Marie-Laetitia Thezenasc[3], Nicola A. Burgess-Brown[2], Roman Fischer[3], Wyatt W. Yue[2] and Patrick J. Venables[1], [1]Kennedy Institute of Rheumatology, University of Oxford, Oxford, United Kingdom, [2]Structural Genomics Consortium, University of Oxford, Oxford, United Kingdom, [3]Target Discovery Institute, University of Oxford, Oxford, United Kingdom

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Session Title: Rheumatoid Arthritis - Human Etiology and Pathogenesis I

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Background/Purpose: Anti-citrullinated protein antibodies (ACPA) are the main autoantibody system in rheumatoid arthritis (RA), and due to high sensitivity and specificity testing using the anti-CCP2 assay is the gold standard in RA diagnosis. Citrullinated proteins are formed when arginine residue(s) are converted to citrulline residue(s) by peptidylarginine deiminase (PAD) enzymes. Five known human PAD isoforms (PAD1-4 &6) catalyse citrullination constitutively in numerous healthy tissues, and the process is essential for many pathways. It is unknown what causes the breach of tolerance to these native proteins. Periodontitis (PD) is a known risk factor for RA, and there is increasing evidence that the link between the two diseases is due to citrullination by a unique prokaryotic PAD enzyme expressed by the keystone PD pathogen *Pophyromonas gingivalis* (PPAD). PPAD and mammalian PADs have distinct substrate specificities and low sequence homology, thus making PPAD a prime candidate for inhibition. However, the precise mechanism by which PPAD could generate potentially immunogenic peptides has remained controversial due to lack of information about the structural and catalytic mechanisms of the enzyme. By solving the 3D structure of PPAD we aim to characterize activity and elucidate potential mechanisms involved in breach of tolerance to citrullinated proteins in RA.

Methods: A library of PPAD clones was synthesized, expressed and purified from *E.coli*. Candidates for crystallization were identified based on high solubility and activity. A highly active clone $tPPAD^{WT}$ was identified and crystallized, alongside a catalytically inactive mutant $tPPAD^{C351A}$ of corresponding sequence- with the exception of a single amino acid substitution within the active site- and their 3D crystal structures solved. Both enzymes were crystallized with bound arginine containing ligands. Key residues identified from 3D structures were examined by mutations. Fibrinogen and α-enolase were incubated with $tPPAD^{WT}$ and *P.gingivalis*arginine gingipain (RgpB) and citrullinated peptides formed were sequenced and quantified by mass spectrometry.

Results: Here, we solve the crystal structure of a truncated, highly active form of PPAD, and confirm catalysis is mediated by the following residues: Asp130, His236, Asp238, Asn297 and Cys351. In addition, we identify Arg152 and Arg154 as involved in substrate binding, and using a number of mutations demonstrate they may determine the substrate specificity of PPAD for C-terminal arginines. We show RA autoantigens are

favorable substrates for PPAD and demonstrate the formation of 37 C-terminally citrullinated peptides from fibrinogen and 11 from α-enolase following incubation with $tPPAD^{WT}$and RgpB.

Conclusion: PPAD displays an unequivocal specificity for C-terminal arginine residues not shown by mammalian PAD2 or PAD4. PPAD readily citrullinates peptides from key RA autoantigens to form novel peptides, which could be involved in the breach of tolerance to native citrullinated peptides in RA. The lack of sequence homology to mammalian PADs makes PPAD and ideal target for inhibition, and this high-resolution crystal data presented here could pave the way for this.

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Abstract Number: 966

In Rheumatoid Arthritis, Smoking Is Not Associated with Anti-Citrullinated Protein Antibodies per Se, but with the Concurrent Presence of Rheumatoid Factor, Anti-Citrullinated Protein Antibodies and Anti-Carbamylated Protein Antibodies

Tineke van Wesemael[1], Ammar Muhammad[1], Sofia ajeganova[2,3], Jennifer Humphreys[4], Deborah P.M. Symmons[5,6], Alex J Macgregor[7], Ingiäld Hafström[2], Leendert Trouw[1], T. W. J. Huizinga[1], Björn Svensson[8], René E. M. Toes[1], Suzanne M. Verstappen[9] and Diane van der Woude[1], [1]Rheumatology, Leiden University Medical Center, Leiden, Netherlands, [2]Rheumatology, Department of Medicine Karolinska Institutet at Karolinska University Hospital Huddinge, Stockholm, Sweden, [3]Rheumatology, Leiden University Medical Center, LEIDEN, Netherlands, [4]Manchester Academic Health Science Centre, Arthritis Research UK Epidemiology Unit,, Manchester, United Kingdom, [5]Centre for Musculoskeletal Research, University of Manchester, Arthritis Research UK Centre for Epidemiology, Manchester, United Kingdom, [6]NIHR Manchester Musculoskeletal Biomedical Research Unit, Central Manchester University Hospitals NHS Foundation Trust, Manchester, United Kingdom, [7]Rheumatology, Norfolk and Norwich University Hospital, Norwich, United Kingdom, [8]Section of Rheumatology, Department of Clinical Sciences,, University of Lund, Lund, Sweden, [9]Arthritis Research UK Epidemiology Unit, The University of Manchester, Manchester, United Kingdom

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Background/Purpose *:* In rheumatoid arthritis (RA) a biological hypothesis has been proposed linking smoking with citrullination, the development of anti-citrulline autoimmunity and anti-citrullinated protein antibodies (ACPA) and subsequently RA[1]. The fact that smoking is associated with several autoantibodies in other autoimmune diseases raised the question if in RA smoking is solely associated with ACPA or with autoantibodies in general.

Objectives*:* To investigate if in patients with RA, smoking is specifically associated with ACPA or with the presence of other autoantibodies as well.

Methods *:* Patients from three independent early arthritis cohorts were used: the Leiden Early Arthritis Clinic (n=767), the British Norfolk Arthritis Register (n=761) and the Swedish Better Anti-Rheumatic Fharmaco Therapy cohort (n=795). All patients fulfilled the 1987 RA criteria and had symptom duration of less than two years. Smoking (ever versus never) and autoantibody status: rheumatoid factor (RF), ACPA and anti-carbamylated protein antibodies (anti-CarP), were determined at inclusion into this studies. A meta-analysis was performed calculating odds ratios and 95% confidence intervals to assess the association between number of autoantibodies and smoking, using 2x2 comparison with seronegative RA patients as reference category. In the Leiden EAC, interaction between smoking and shared epitope (SE) was assessed using the three measures of biological interaction: relative excess risk due to interaction, the attributable proportion due to interaction and the synergy index.

Results: There was no significant association between smoking and seropositive RA in patients who were positive for one autoantibody only (n=406). However, smoking was significantly associated with double (n=429) and triple autoantibody-positivity (n= 606) (figure 1). Furthermore, interaction measures between smoking and SE were not significant for patients with one autoantibody, partly significant for patients with two autoantibodies, whereas all three measures were significant in the triple-positive group (table 1).

Conclusion: Smoking and the interaction between smoking and SE is not solely associated with ACPA-positive RA, but with the concurrent

presence of all three RA-associated autoantibodies. These data indicate that current hypotheses on the role of smoking in the pathophysiology of RA may need to be refined by taking the presence of other auto-antibodies into account.

References

1. Klareskog et al. 2006 Arthritis Rheum. 54:38

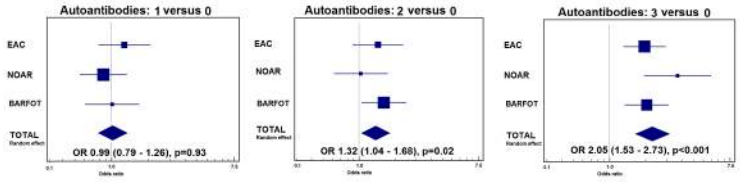

Figure 1. Meta-analysis of association of smoking and number of autoantibodies

Interaction measure	relative excess risk due to interaction	attributable proportion due to interaction	synergy index
0 autoantibodies	(referent)	(referent)	(referent)
1 autoantibody	-0.65 (-2.96 – 1.65)	-0.21 (-0.99 – 0.57)	0.77 (0.31 – 1.89)
2 autoantibodies	42.94 (-0.45 – 86.33)	**0.57 (0.34 – 0.81)**	**2.39 (1.35 – 4.23)**
3 autoantibodies	**357.58 (143.52 – 571.63)**	**0.95 (0.92 – 0.97)**	**19.37 (12.01 – 31.25)**

Table 1. Interaction measures for smoking and shared epitope with number of autoantibodies in Leiden early arthritis clinic

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Abstract Number: 967

Safety, Tolerability, and Pharmacodynamics of ABT-122, a Dual TNF- and IL-17-Targeted Dual Variable Domain (DVD)-IgTM in Subjects with Rheumatoid Arthritis

Roy Fleischmann[1], Frank Wagner[2], Alan J. Kivitz[3], Heikki T. Mansikka[4], Nasser Khan[4], Jia Liu[4], Jacob Gagnon[4], Feng Hong[5], Melanie Ruzek[4] and Robert J. Padley[4], [1]University of Texas Southwestern Medical Center at Dallas, Dallas, TX, [2]Charité Research Organisation GmbH, Berlin, Germany, [3]Altoona Center for Clinical Research, Duncansville, PA, [4]AbbVie Inc., North Chicago, IL, [5]AbbVie Inc., Worcester, MA

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Background/Purpose: TNF and IL-17 independently contribute to the pathophysiology of rheumatoid arthritis (RA) acting synergistically to induce mediators of inflammation and joint destruction. Selective dual neutralization of TNF and IL-17 confers superior protection vs inhibition of either alone in mouse arthritis models. ABT-122 is a novel dual variable domain immunoglobulin (DVD-Ig™) targeting both human TNF and IL-17A and is hypothesized to provide greater clinical responses in patients with RA.

Objective: Investigate safety, tolerability and exploratory pharmacodynamics of multiple doses of ABT-122 in subjects with stable RA

Methods: Two Phase 1, placebo-controlled, multiple dose studies randomized 43 subjects with stable RA while receiving stable doses of methotrexate (7.5–25 mg/wk). Subjects were subcutaneously administered either one of 4 dose regimens of ABT-122, 1 mg/kg every other week (4 doses), or 0.5, 1.5, or 3.0 mg/kg weekly (8 doses); or placebo and evaluated through 45 days following last dose. Serum samples for a panel of inflammation markers, and chemokines based on preclinical studies with dual TNF and IL-17 neutralization, were collected at baseline through day 92 and analyzed by multiplex assays.

Results: No clinically significant safety findings were observed in subjects with RA. Rates of treatment-emergent AEs were similar in ABT-122 and placebo treatment groups with no evidence of a dose response. There were no AE or serious AE trends, systemic hypersensitivity reactions

or dose limiting toxicities with ABT-122. Infections, consistent with expectations in RA, were reported with no apparent patterns related to etiology, type, or dose in rates with ABT-122 vs placebo and no subject discontinued the study due to infection. There were no clinically significant laboratory, vital sign, or ECG abnormalities. For CXCL9 and CXCL10, rapid decreases relative to placebo occurred within 3d of ABT-122 administration (−25% and −30% from baseline for CXCL9 and CXCL10, respectively). Maximal decreases occurred by d15 (−60% and −45% for CXCL9 and CXCL10, respectively) and persisted through 14d after last dose. Serum CCL23 also decreased following ABT-122 with maximal decreases (−30%) at d64 and continued through d92. Consistent with anti-TNF inhibition, soluble E-selectin levels decreased following ABT-122 , persisting through d92 for the 3.0 mg/kg group.

Conclusion: ABT-122 demonstrated a well tolerated safety profile in subjects with RA through 8 weeks of dosing up to 3 mg/kg, consistent with previous observations in the first-in-human study in healthy subjects. Because CXCL9, CXCL10, and CCL23 are involved in lymphocyte and myeloid cell recruitment into inflamed tissues, decreases in these chemokines indicate that ABT-122 rapidly modulates potential pathophysiologic pathways in RA patients, with evidence for persistent effects after cessation of dosing. These results suggest that dual neutralization of TNF and IL-17 may provide an opportunity to control inflammation and its clinical manifestations in RA subjects and in other immune-mediated inflammatory diseases.

Disclosure: R. Fleischmann, AbbVie, 2,AbbVie, 5; **F. Wagner**, None; **A. J. Kivitz**, AbbVie, 2; **H. T. Mansikka**, AbbVie, 1,AbbVie, 3; **N. Khan**, AbbVie, 1,AbbVie, 3; **J. Liu**, AbbVie, 1,AbbVie, 3; **J. Gagnon**, AbbVie, 1,AbbVie, 3; **F. Hong**, AbbVie, 1,AbbVie, 3; **M. Ruzek**, AbbVie, 1,AbbVie, 3; **R. J. Padley**, AbbVie, 1,AbbVie, 3.

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Abstract Number: 968

Certolizumab Pegol in Combination with Methotrexate in DMARD-Naïve Patients with Active, Severe, Progressive Rheumatoid Arthritis: Results from a Randomized, Double-Blind, Controlled Phase 3 Study

Michael Weinblatt[1], Clifton Bingham[2], Gerd Burmester[3], VP Bykerk[4], Daniel E. Furst[5], Xavier Mariette[6], Désirée van der Heijde[7], Daljit Tatla[8], Catherine Arendt[9], Irina Mountian[10], Brenda VanLunen[11] and Paul Emery[12], [1]Rheumatology Immunology & Allergy, Brigham and Women's Hospital, Boston, MA, [2]Johns Hopkins University, Baltimore, MD, [3]Department of Rheumatology and Clinical Immunology, Charité - Universitätsmedizin Berlin, Berlin, Germany, [4]Rheumatology, Hospital for Special Surgery, New York, NY, [5]Medicine, University of California, Los Angeles, David Geffen School of Medicine, Los Angeles, CA, [6]Université Paris-Sud, AP-HP, Hôpitaux Universitaires Paris-Sud, Paris, France, [7]University Hospital, Maastricht, Netherlands, [8]8010 Arco Corporate Dr, UCB Pharma, Raleigh, NC, [9]Global Medical Affairs, UCB Pharma, Brussels, Belgium, [10]UCB Pharma, Brussels, Belgium, [11]UCB Pharma, Raleigh, NC, [12]Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds, Leeds, United Kingdom

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Session Time: 2:30PM-4:00PM

Background/Purpose:

Early stages of rheumatoid arthritis (RA) may provide a therapeutic window in which biologic agents are most effective.[1] C-EARLY (NCT01519791) is a phase 3 study in DMARD-naïve patients (pts) with severe, active, progressive RA assessing efficacy and safety of certolizumab pegol (CZP)+MTX vs placebo (PBO)+MTX treatment in inducing and maintaining sustained clinical response and inhibiting radiographic damage.

Methods:

Pts in this multicenter double-blind randomized study had RA <1 year since diagnosis at baseline (BL) fulfilling the 2010 ACR/EULAR criteria; ≥4 swollen and ≥4 tender joints; DAS28(ESR)≥3.2; CRP≥10 mg/L and/or ESR≥28 mm/hr, rheumatoid factor or ACPA positive. 879 pts were randomized 3:1 to CZP (400 mg at Weeks [Wks] 0,2,4, 200 mg every 2 wks to Wk52)+MTX or PBO+MTX Q2W. MTX was initiated at 10 mg/wk and increased to 25 mg/wk by Wk8; the maximum tolerated dose per pt (optimized dose) was maintained to Wk52 in both treatment arms. Pts who could not tolerate ≥15 mg/wk MTX by Wk8 were withdrawn. Sustained DAS28(ESR) remission (sREM), defined as DAS28[ESR]≤2.6 at both Wk40 and Wk52, was the primary endpoint; sustained low disease activity (sLDA), defined as DAS28[ESR]≤3.2 at both Wk40 and Wk52, was a key secondary endpoint. Secondary efficacy variables included in the hierarchical testing were ACR50 response at Wk52, change from BL in HAQ-DI at Wk52 and change from BL at Wk52 in van der Heijde modified total Sharp score (mTSS). Pts with and without rapid

radiographic progression at Wk52 (defined as change from BL mTSS>3 or >5 based on linearly extrapolated scores)[2] were assessed post hoc.

Results:

BL characteristics were balanced between arms (Table A). 96.5% pts had high disease activity (DAS28[ESR]>5.1), median diagnosis time was 2.6 months.[3]

All hierarchical endpoints were statistically significant (Table B); 28.9% of CZP+MTX vs 15% of PBO+MTX in sREM ($p<0.001$); 43.8% of CZP+MTX vs 28.6% of PBO+MTX in sLDA ($p<0.001$). Approximately 3 times more pts progressed rapidly by >3 and >5 mTSS points in PBO+MTX vs CZP+MTX (23.3% vs 7.4% and 15.3% vs 4.2%). AE incidence rates were similar for both arms. Infections were higher with CZP+MTX vs PBO+MTX (71.8 vs 52.7/100 pt-yrs), but similar for serious infections (3.3 vs 3.7/100 pt-yrs). 2 deaths were reported with CZP+MTX (1 stroke, considered not related to study drug; 1 systemic tuberculosis, considered related to study drug); 1 with PBO+MTX (respiratory failure, considered not related to study drug). No new safety signals for CZP were reported.

Conclusion:

CZP+MTX treatment of DMARD-naïve pts with active, severe, progressive RA resulted in a greater proportion of pts in sREM and sLDA; greater improvements in RA signs and symptoms; and inhibition of structural damage vs PBO+MTX. Safety profile of CZP+MTX was similar to PBO+MTX.

References:

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2. Bruynesteyn K. Arthristis Rheum 2002; 46(3): 913–20
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Table A: Patient characteristics at baseline

	PBO+MTX n=213 [a]	CZP+MTX n=655 [a]
Mean (SD), unless otherwise stated		
Age, years	51.2 (13.0)	50.4 (13.6)
Female, n (%)	170 (79.8)	497 (75.9)
Mean BMI kg/m^2	28.8 (6.4)	28.0 (6.0)
DAS28(ESR)	6.8 (0.9)	6.7 (0.9)
DAS >5.1, n (%)	203 (95.3)	635 (96.9)
SDAI	44.8 (13.9)	43.5 (13.6)
CDAI	42.6 (12.9)	41.3 (12.5)
HAQ-DI	1.7 (0.7)	1.6 (0.6)
TJC (28 joints)	16.2 (6.5)	15.6 (6.5)
SJC (28 joints)	13.0 (5.6)	12.4 (5.5)
ESR (mm/hour)	50.8 (22.2)	50.2 (24.7)
CRP (mg/L)	21.5 (27.9)	21.7 (29.5)
Dx ≤4 months, n (%)	157 (73.7)	502 (76.6)
RF positive, [b] n (%)	206 (96.7)	634 (96.8)
ACPA positive, [c] n (%)	182 (85.4)	546 (83.4)
mTSS	8.8 (19.9)	7.2 (13.9)
Erosion score	5.0 (10.3)	4.4 (8.0)
Joint space narrowing	3.8 (10.6)	2.9 (6.8)
Erosions present, n (%)	169 (79.3)	506 (77.3)

[a] 213 PBO+MTX and 655 CZP+MTX pts were included in the full analysis set (FAS; pts with BL and post-BL DAS28[ESR]); 163 PBO+MTX pts and 528 CZP+MTX pts were included in the radiographic analysis set (FAS pts with valid BL and post-BL radiographs); [b] ≥14 IU/mL; [c] ≥7 IU/mL. ACPA: anticyclic citrullinated peptide antibody; Dx: time since diagnosis; RF: rheumatoid factor.

Table B: Clinical and radiographic outcomes at Week 52

Outcome at Week 52	PBO + MTX n=213	CZP + MTX n=655	Statistical analysis
Hierarchical endpoints			
sREM, [a] n (%)	32 (15.0)	189 (28.9)	OR: 2.3, p<0.001
sLDA, [b] n (%)	61 (28.6)	287 (43.8)	OR: 2.0, p<0.001
ACR50, [c] n (%)	113 (53.1)	408 (62.3)	OR: 1.4, p=0.023
LS mean change from BL HAQ-DI, [d] (SE)	-0.8 (0.04)	-1.0 (0.03)	p<0.001 [e]
Mean change from BL mTSS, [f] (SD)	1.9 (4.8) [n=163]	0.2 (3.3) [n=528]	p<0.001 [g]
Additional endpoints			
mTSS rapid progression, n (%) [h]	n=163	n=528	
Change from BL mTSS >3			
Patients with progression	38 (23.3)	39 (7.4)	
Patients without progression	125 (76.7)	489 (92.6)	OR: 3.9, p<0.001
Change from BL mTSS >5			
Patients with progression	25 (15.3)	22 (4.2)	
Patients without progression	138 (84.7)	506 (95.8)	OR: 4.2, p<0.001

[a] Sustained remission defined as DAS28(ESR)<2.6 at both Wk40 and Wk52, NRI; [b] Sustained low disease activity defined as DAS28(ESR)≤3.2 at both Wk40 and Wk52, NRI; [c] NRI; [d] LOCF; [e] ANCOVA model with factors for treatment, region, time since diagnosis, and BL rank as covariate; [f] Pts who withdrew before Wk52 and had radiographs taken at their Withdrawal Visit were included, Wk52 score estimated by linear extrapolation; [g] Rank ANCOVA including factors for treatment, region, time since diagnosis, and BL rank as covariate; [h] Rapid radiographic progression defined as change from BL mTSS>3 or >5 based on linearly extrapolated scores. OR: odds ratio CZP+MTX/PBO+MTX (and p-value) from a logistic regression model with factors for treatment, region, and time since RA diagnosis (≤4 months vs >4 months); mTSS: modified Total Sharp Score.

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Abstract Number: 969

Namilumab, an Anti-Granulocyte Macrophage-Colony Stimulating Factor (GM-CSF) Monoclonal Antibody: Results of the First Study in Patients with Mild-to-Moderate Rheumatoid Arthritis (RA)

T. W. J. Huizinga[1], Anastas Batalov[2], Rumen Stoilov[3], Eric Lloyd[4], Thomas Wagner[5], Didier Saurigny[6], Bernard Souberbielle[6] and Ehsanollah Esfandiari[6], [1]Rheumatology, Department of Rheumatology, Leiden University Medical Center, Leiden, Netherlands, [2]UMHAT Kaspela, Plovdiv, Bulgaria, [3]University Hospital (MHAT) St Ivan Rilski, Sofia, Bulgaria, [4]Takeda Pharmaceuticals, Deerfield, IL, [5]Takeda Pharmaceuticals, Zurich, Switzerland, [6]Takeda Pharmaceuticals, London, United Kingdom

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Background/Purpose: GM-CSF mediates a range of immunological processes, such as stimulating the production of inflammatory mediators and differentiation of proinflammatory T-helper 17 cells, and may play an important role in the pathogenesis of inflammatory diseases including RA. Namilumab (AMG203) is an investigational monoclonal antibody with high affinity for the GM-CSF ligand. The aim of this Phase Ib study (PRIORA; NCT01317797) was to evaluate the safety and tolerability, pharmacokinetics/pharmacodynamics and preliminary efficacy of namilumab in patients with active RA.

Methods: This was a double-blind, placebo-controlled, randomised, dose-escalating study in patients with mild-to-moderate RA (according to ACR 1987 revised criteria) receiving stable MTX doses for ≥12 weeks prior to randomisation. Patients received 3 single subcutaneous injections of namilumab 150 or 300 mg or matching placebo on Days 0, 15 and 29, with 12 weeks' follow-up. Clinical efficacy was an exploratory endpoint and originally measured by DAS44; a pre-defined *post hoc* efficacy analysis was performed to evaluate the effect of namilumab on signs and symptoms of RA using DAS28, swelling joint counts, tender joint counts, and patient outcome measures.

Results: 24 patients were enrolled (71% female, mean age 55.9 years): Cohort 1 (n=13; namilumab 150 mg, n=8; placebo, n=5); and Cohort 2 (n=11; namilumab 300 mg, n=7, placebo, n=4). Disease activity at baseline was moderate (mean DAS28-ESR: placebo = 4.7; namilumab 150 mg = 4.9; namilumab 300 mg = 4.4). Namilumab was generally well tolerated. A total of 49 treatment-emergent adverse events (TEAEs) were observed in 14 patients (58%). The most common TEAEs were nasopharyngitis (n=4; 17%), exacerbation/worsening of RA (n=3; 13%) and musculoskeletal pain (n=2; 8%). The percentage of patients with any TEAE was similar (namilumab 150 mg: 63%; namilumab 300 mg: 57%; placebo: 56%). There was no evidence of immunogenicity. Median time to maximum observed plasma concentration (t_{max}) after the third dose of namilumab was 5–6 days. Dose-normalised exposure (C_{max}/D and AUC_{tau}/D) was similar at both namilumab dose levels. Accumulation was ongoing after the third injection (Day 43), as expected given the observed mean $t_{1/2}$ of ~3 weeks. The *post hoc* efficacy analysis included 21 patients (1 patient on namilumab 150 mg and 2 patients on placebo were excluded due to major protocol violations). In general, improvements in DAS28 scores (ESR and CRP) and joint counts were greater with namilumab than placebo as early as Day 29. Both namilumab groups were associated with greater improvements in DAS28-CRP than placebo from Day 27 until the end of the study. Furthermore, the difference in mean DAS28-CRP changes from baseline between namilumab and placebo favoured namilumab at all time points.

Conclusion: Results of PRIORA show that namilumab was generally well tolerated in active RA and preliminary efficacy was demonstrated; further evaluation is needed due to the small sample size. Two Phase II studies have been initiated in patients with moderate-to-severe RA (NEXUS, NCT02379091; TELLUS, NCT02393378).

Disclosure: T. W. J. Huizinga, Dutch Arthritis Foundation, 2,EU Arthritis Foundation, 2,Merck Pharmaceuticals, 5,UCB, 5,Bristol-Myers Squibb, 5,Biotest AG, 5,Pfizer Inc, 5,Novartis Pharmaceutical Corporation, 5,Roche Pharmaceuticals, 5,Sanofi-Aventis Pharmaceutical, 5,Abbott Immunology Pharmaceuticals, 5,Crescendo Bioscience, 5,Nycomed, 5,Boehringer Ingelheim, 5,Takeda Pharmaceuticals, 5,Eli Lilly and Company, 5,Leiden University Medical Center, 3,UCB, 8,Bristol-Myers Squibb, 8,Roche Pharmaceuticals, 8; **A. Batalov**, None; **R. Stoilov**, None; **E. Lloyd**, Takeda Pharmaceuticals International, 3; **T. Wagner**, Takeda Pharmaceuticals International GmbH, 3; **D. Saurigny**, Takeda Pharmaceuticals International, 1,Takeda Development Centre Europe Ltd, 3; **B. Souberbielle**, Takeda Pharmaceuticals International, 1,Takeda Pharmaceuticals International, 3; **E. Esfandiari**, Shareholder of: Takeda Pharmaceuticals International, 1,Takeda Pharmaceuticals International; Takeda Europe; London, 3.

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Abstract Number: 970

Efficacy and Safety of Sarilumab in Combination with Csdmards in Patients with Active Rheumatoid Arthritis Who Were Inadequate Responders or Intolerant of Anti–TNF-Î± Therapy: Results from a Phase 3 Study

Roy Fleischmann[1], Geraldo Castelar-Pinheiro[2], Jan Brzezicki[3], Pawel Hrycaj[4], Yong Lin[5], Janet van Adelsberg[6], Neil Graham[7], Hubert van Hoogstraten[5], Deborah Bauer[5] and Gerd Burmester[8], [1]University of Texas Southwestern Medical Center, Dallas, TX, [2]Discipline of Rheumatology, Rio de Janeiro State University, Rio de Janeiro, Brazil, [3]Centrum Kliniczno-Badawcze, Elblag, Poland, [4]Poznan University of Medical Sciences, Poznan, Poland, [5]Sanofi, Bridgewater, NJ, [6]Clinical Science, Regeneron Pharmaceutials, Inc., Tarrytown, NY, [7]Regeneron Pharmaceuticals, Inc., Tarrytown, NY, [8]Department of Rheumatology and Clinical Immunology, Charité - Universitätsmedizin Berlin, Berlin, Germany

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Session Title: Rheumatoid Arthritis-Small Molecules, Biologics and Gene Therapy I: Biologics

Session Type: ACR Concurrent Abstract Session

Session Time: 2:30PM-4:00PM

Background/Purpose: The investigational agent sarilumab is a human mAb directed against the IL-6 receptor. The phase 3 MOBILITY study (NCT01061736) evaluated the efficacy and safety of Sarilumab in combination with MTX in RA patients with inadequate response to MTX.[1] The objectives of the phase 3 TARGET study were to evaluate efficacy and safety of addition of sarilumab to non-biologic DMARD(s) (csDMARDs) in patients (pts) with active RA.

Methods: Adults with active, moderate-to-severe RA with inadequate response or intolerance to ≥1 TNF inhibitor(s) were randomized to placebo (Pbo) (n=181), sarilumab 150 mg q2w (n=181), or sarilumab 200 mg q2w (n=184) subcutaneously + background csDMARD(s) for 24 wks of treatment in a double-blind fashion. Pts who did not respond adequately to treatment, starting at wk 12, were rescued with sarilumab 200 mg q2w. Coprimary endpoints were proportion of pts achieving ACR20 response at wk 24 (nonresponder imputation) and change from baseline in HAQ-DI at wk 12 (before rescue for inadequate response). Pts were stratified by region and number of previous anti-TNFs.

Results: Baseline demographic and disease characteristics (intention-to-treat population, n=546) were balanced among treatment groups. A significantly greater proportion of pts receiving either dose of sarilumab achieved ACR20 responses and significantly improved HAQ-DI scores (Table). Similar observations were made in the proportion of ACR50, ACR70, and HAQ-DI responders (HAQ-DI ≥0.22 improvement) at wk 24.

	Placebo + csDMARD (n=181)	**Sarilumab 150 mg q2w + csDMARD (n=181)**	**Sarilumab 200 mg q2w + csDMARD (n=184)**
Primary endpoints			
ACR20 at week 24, %	34	56	61
P value vs placebo		<0.0001	<0.0001
Change from baseline in HAQ-DI at week 12, mean (SD)	-0.29 (0.54)	-0.50 (0.64)	-0.49 (0.56)
P value vs placebo		0.0007	0.0004
Other endpoints			
ACR50 at week 24, %	18	37[a]	41[a]
ACR70 at week 24, %	7	20[b]	16[b]
HAQ-DI ≥0.22 at week 24, %	35	48[b]	56[a]
q2w, every 2 wks; SD, standard deviation. [a]*P*<0.0001 vs placebo. [b]*P*<0.025 vs placebo (to adjust for multiplicity, *P* values <0.025 are considered statistically significant).			

Treatment-emergent adverse events (TEAEs; safety population, n=546) were more frequent in sarilumab groups (66% and 65% in sarilumab 150 mg q2w and 200 mg q2w vs 50% in Pbo). Although incidence of SAEs was higher than Pbo (3.3%) in the sarilumab 200-mg q2w group (5.4%), they were similar to Pbo in the 150-mg q2w group (3.3%). Infection was the most frequently reported SAE. The most frequent events leading to treatment discontinuation were infection and low absolute neutrophil count (ANC). ANC <1.0 Giga/L was observed in 9.8% of pts in the sarilumab 200-mg q2w group, 7.7% in the sarilumab 150-mg q2w group, and 0.6% in the Pbo group and was not associated with serious infection. Laboratory abnormalities included elevations in lipids and transaminases. One death due to a car accident occurred in the Pbo group.

Conclusion: In this phase 3 study, sarilumab demonstrated efficacy in pts with active RA who were inadequate responders or intolerant of anti-TNFs, as evidenced by improvements vs Pbo in signs and symptoms of RA and in physical function. TEAEs leading to treatment discontinuation were more frequent in the sarilumab-treated groups. SAEs were more frequent in the sarilumab 200-mg q2w group. Laboratory findings were consistent with IL-6 blockade and observations from the MOBILITY study.

1. Genovese et al. *Arthritis Rheumatol*. 2015;67:1424-1437.

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Abstract Number: 971

Safety and Tolerability of Subcutaneous Sarilumab Compared to Intravenous Tocilizumab in Patients with RA

Paul Emery[1], Juan Rondon[2], Anju Garg[3], Hubert van Hoogstraten[3], Neil Graham[4], Ming Liu[5], Janie Parrino[6], Alberto J. Spindler[7] and Nancy Liu[5], [1]Division of Rheumatic and Musculoskeletal Disease, University of Leeds, Leeds, United Kingdom, [2]Elite Research Institute, Miami, FL, [3]Sanofi, Bridgewater, NJ, [4]Regeneron Pharmaceuticals, Inc., Tarrytown, NY, [5]Regeneron Pharmaceuticals, Tarrytown, NY, [6]Merck & Co., Inc., Whitehouse Station, NJ, [7]Rheumatology, Hospital Padilla, Tucuman, Argentina

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Session Time: 2:30PM-4:00PM

Background/Purpose: The investigational drug sarilumab is a human mAb directed against the IL-6 receptor. In previous studies, sarilumab + MTX demonstrated efficacy in patients (pts) with moderate-to-severe RA and was generally well tolerated.[1] Sarilumab and tocilizumab have the same mechanism of action. Two studies, Study 1309 (NCT02097524) and ASCERTAIN (NCT01768572), described the safety and tolerability of sarilumab and tocilizumab in adults with RA.

Methods: In the 6-wk Study 1309 (N=101), adult RA pts on background MTX were randomized 1:1:1:1 to receive a single dose of sarilumab 150 mg subcutaneously (SC), sarilumab 200 mg SC, tocilizumab 4 mg/kg intravenously (IV), or tocilizumab 8 mg/kg IV. In the 24-wk ASCERTAIN study (N=202), RA pts on background DMARDs with inadequate response to or intolerant of TNF antagonists were randomized 1:1:2 to sarilumab 150 or 200 mg SC every 2 wks or tocilizumab every 4 wks starting at 4 mg/kg with an increase to 8 mg/kg if needed, based on clinical response.

Results: Study 1309 and ASCERTAIN enrolled RA patients who were predominantly female (>80%), with a mean age of 55 and 52 yrs, respectively. In ASCERTAIN, 61% of pts on tocilizumab increased their dose from 4 to 8 mg/kg during the treatment period; 42% of pts increased their dose at wk 4. Incidence of treatment-emergent adverse events (TEAEs) was similar for the sarilumab and tocilizumab groups in each study (Table). Upper respiratory tract infections and neutropenia were among the most frequently reported TEAEs. Laboratory changes in both studies included increases in lipids and transaminases and decreases in neutrophil counts. Mean changes in absolute neutrophil count (ANC) in the sarilumab groups were within the ranges observed in tocilizumab groups. There was no association between decreased ANC and incidence of infection. Study 1309 demonstrated that time to onset for decreased ANC and magnitude of decrease were comparable across the sarilumab and tocilizumab groups for all doses (Figure).

Conclusion: Overall, there was no clinically meaningful difference between the treatment groups with regards to clinical adverse events. Laboratory changes noted in the sarilumab groups were within the same range as those noted in the tocilizumab groups. Differences in incidence of ANC <1.0 Giga/L between the sarilumab and tocilizumab groups in ASCERTAIN may reflect differences in dosing interval and sampling schedule.

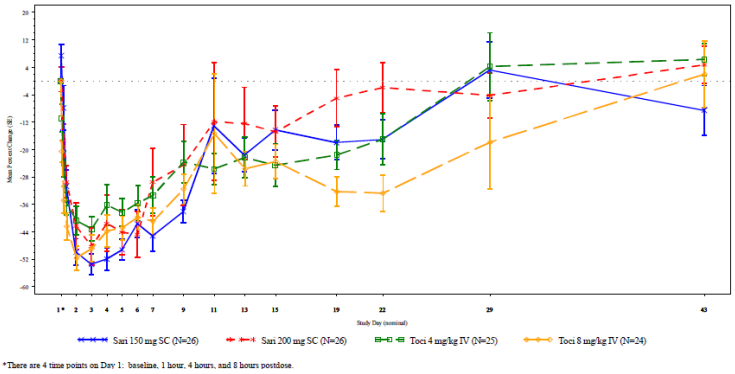
1. Genovese et al. *Arthritis Rheumatol*. 2015;67:1424-1437.

Table. Overview of Adverse Events and Laboratory Parameters in Study 1309 and ASCERTAIN

	Study 1309				ASCERTAIN		
	Patients, n (%)				Patients, n (%)		
	Tocilizumab IV 4 mg/kg (n=25)	Tocilizumab IV 8 mg/kg (n=24)	Sarilumab SC 150 mg (n=26)	Sarilumab SC 200 mg (n=26)	Tocilizumab IV 4 mg/kg (n=102)	Sarilumab SC 150 mg (n=49)	Sarilumab SC 200 mg (n=51)
Overview							
TEAEs	8 (32%)	12 (50%)	10 (39%)	12 (46%)	68 (67%)	33 (67%)	36 (71%)
SAEs	0	1 (4%)	0	0	7 (7%)	1 (2%)	3 (6%)
Serious infections	0	0	0	0	2 (2%)	0	1 (2%)
TEAEs leading to death	0	0	0	0	1 (1%)	0	0
Laboratory parameters							
Absolute neutrophil counts[a]							
<1.0 Giga/L	3 (12%)	6 (25%)	4 (15%)	7 (27%)	1 (1%)	3 (6%)	5 (10%)
ALT[b]							
>3 times ULN	0	2 (8%)	0	1 (4%)	3 (3%)	2 (4%)	3 (6%)
Total cholesterol[c]							
≥6.2 mmol/L	9 (36%)	6 (25%)	9 (35%)	11 (42%)	50 (50%)	27 (56%)	23 (45%)

ALT, alanine aminotransferase; IV, intravenously; SAE, serious adverse event; SC, subcutaneously; TEAE, treatment-emergent adverse event; ULN, upper limit of normal. [a]1309: 17 post-baseline ANC sampling time points over 43 days; ASCERTAIN: 12 post-baseline ANC sampling time points over 24 weeks. [b]1309: 5 post-baseline LFT sampling time points over 43 days; ASCERTAIN: 9 post-baseline LFT sampling time points over 24 weeks. [c]1309: 2 post-baseline lipid sampling time points over 43 days; ASCERTAIN: 5 post-baseline lipid sampling time points over 24 weeks.

Figure. Mean percent change from baseline in ANC by treatment and visit. ANC, absolute neutrophil count; IV, intravenously; SC, subcutaneously.



Disclosure: P. Emery, Abbvie, BMS, Lilly, MSD, Novartis, Pfizer, Roche, Samsung, Sandoz, UCB, 2,Abbvie, BMS, Lilly, MSD, Novartis, Pfizer, Roche, Samsung, Sandoz, UCB, 5; **J. Rondon**, None; **A. Garg**, Sanofi-Aventis Pharmaceutical, 1,Sanofi-Aventis Pharmaceutical, 3; **H. van Hoogstraten**, Sanofi-Aventis Pharmaceutical, 1,Sanofi-Aventis Pharmaceutical, 3; **N. Graham**, Regeneron, 1,Regeneron, 3; **M. Liu**, None; **J. Parrino**, Regeneron, 1,Regeneron, 3; **A. J. Spindler**, None; **N. Liu**, Sanofi-Aventis Pharmaceutical, 3.

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Abstract Number: 972

A Phase 2b Study Evaluating the Efficacy and Safety of Subcutaneously Administered Tregalizumab in Subjects with Active Rheumatoid Arthritis (RA) Despite Treatment with Methotrexate (MTX)

Ronald F. van Vollenhoven[1], Edward C. Keystone[2], Vibeke Strand[3], Cesar Pacheco-Tena[4], Jiri Vencovsky[5], Frank Behrens[6], Daniela Zipp[7], Faiza Rharbaoui[8], Ralf Wolter[9], Rolf-Dietrich Tiemann[10], Luise Knierim[11], Rainer Schmeidl[11], Xuefei Zhou[12], Silke Aigner[8,13], Benjamin Daelken[14] and Andrea Wartenberg-Demand[8,12], [1]Department of Medicine, Unit for Clinical Therapy Research, Inflammatory Diseases (ClinTRID), The Karolinska Institute, Stockholm, Sweden, [2]Mount Sinai Hospital, University of Toronto, Toronto, ON, Canada, [3]Biopharmaceutical Consultant, Portola Valley, CA, [4]Universidad Autónoma de Chihuahua, Chihuahua, Mexico, [5]Institute of Rheumatology, Prague, Czech Republic, [6]CIRI/Rheumatology & Fraunhofer TMP, Goethe University, Frankfurt, Germany, [7]Landseinerstr 5, Biotest AG, Dreieich, Germany, [8]Biotest AG, Dreieich, Germany, [9]Corporate Clinical Research, L, Biotest AG, Dreieich, Germany, [10]Data Management and Outsourcing, Biotest AG, Dreieich, Germany, [11]Cooperate Drug Safety, Biotest AG, Dreieich, Germany, [12]Cooperate Clinical Research, Biotest AG, Dreieich, Germany, [13]Landsteinerstrasse 5, Biotest AG, Dreieich, Germany, [14]Project Managerment Office, Biotest Pharmaceuticals Corporation, Boca Raton, FL

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Session Type: ACR Concurrent Abstract Session

Session Time: 2:30PM-4:00PM

Background/Purpose:

In autoimmune diseases reduced numbers and functional impairment of regulatory T cells (Tregs) have been observed (1). Tregalizumab (BT-061) is a humanized, anti-CD4 mAb, inducing selective Treg activation in vitro. Previous trials suggested efficacy in RA at doses ≥25 mg subcutaneously (SC). In a population PK/PD analysis, down-modulation of CD4 expression was identified as a biomarker to monitor CD4 target engagement in humans.

Methods:

This two-part, Phase 2b randomized controlled trial (RCT) included subjects with active RA for ≥6 months despite MTX (≥15mg/wk), with ≥6/28 TJC, ≥6/28 SJC and elevated CRP or ESR. Subjects were randomized to receive 25 mg, 100 mg, 200 mg, or PBO once-weekly SC injection + MTX over 24 wks. Primary endpoint was ACR20 at wk 12. At wk 12 (end of Main part I), non-responders were re-randomized to active treatment or higher doses. Subjects responding at wk 24 (end of Main part II) could extend treatment for an additional 24 wks. A data safety monitoring board (DSMB) was established for safety evaluation throughout the study.

Results:

Of 321 subjects enrolled from Europe, USA, Canada, Russia and Mexico, 37 (11.5%) withdrew at ≤ wk 12. Demographics and baseline disease characteristics were well balanced across groups: mean SJC and TJC 16 and 24, respectively; CRP 11.7 mg/L, DAS (ESR) 6.58 and HAQ-DI 1.56. ACR20 responders at wk 12 (42.3%/47%/44.3% vs. 35.2% in 25 mg, 100 mg, 200 mg groups and PBO, respectively), ACR20 responders at wk 24 and secondary endpoints did not differ significantly between tregalizumab groups and PBO. However, dose dependent modulation of CD4 expression on T cells occurred rapidly with BT-061 treatment, as predicted from previous analyses.

Through wk 12, TEAE (39.4% and 37.5%) and serious TEAEs rates (2.1% and 1.3%) were similar between BT-061 and PBO. For responder at wk 24, TEAEs (48.3% and 52.3%) were similar between BT-061 and PBO. Serious TEAEs were only reported in BT-061 treated subjects (2%). Three deaths occurred considered unrelated to treatment (car accident, acute coronary syndrome, death of unknown cause in a war area). There was no difference in infections between tregalizumab and PBO. One serious infection (peritonitis) occurred at wk 22 in the 25 mg dose group. Apart from acute coronary syndrome with fatal outcome, no further MACE events, Tuberculosis, opportunistic infections nor malignancies were reported.

Figure

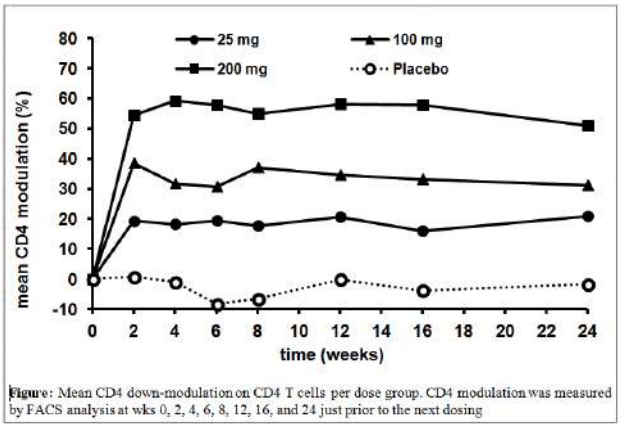

Figure: Mean CD4 down-modulation on CD4 T cells per dose group. CD4 modulation was measured by FACS analysis at wks 0, 2, 4, 6, 8, 12, 16, and 24 just prior to the next dosing

Conclusion:

No tested doses of tregalizumab demonstrated significant efficacy improving signs and symptoms of active RA based on ACR20 responses at wk 12 and 24 despite dose dependent down-modulation of CD4 expression. Tregalizumab was generally well tolerated.

Disclosure: R. F. van Vollenhoven, Amgen, BMS, GSK, Pfizer, Roche, UCB, 2,AbbVie, Biotest, BMS, Crescendo, GSK, Janssen, Lilly, Merck, Pfizer, Roche, UCB, Vertex, 5; **E. C. Keystone**, AbbVie Laboratories, Amgen Inc., AstraZeneca Pharmaceuticals LP, Baylis Medical, Bristol-Myers Squibb, F. Hoffmann-La Roche, Janssen Inc, Lilly Pharmaceuticals, Novartis Pharmaceuticals, Pfizer Pharmaceuticals, Sanofi-Aventis, UCB, 2,AbbVie Laboratories, AstraZeneca Pharma, Biotest, Bristol-Myers Squibb, F. Hoffmann-La Roche Inc, Genentech Inc, Janssen Inc, Merck, Nycomed, Pfizer Pharmaceuticals, UCB, 5; **V. Strand**, Biotest, 5; **C. Pacheco-Tena**, Abbvie, BMS, Roche, UCB, Janssen, Amgen, Astra-Zeneca, Pfizer, GSK, Ely Lilly, Sanofi, Celltrion, Vertex, Novo-Nordisk., 5; **J. Vencovsky**, None; **F. Behrens**, Roche, Pfizer, Chugai - Research grant/support; AbbVie, Biotest, BMS, Janssen, Lilly, Pfizer, UCB, Novartis, Genzyme, AstraZeneca, MSD/Merck, 5; **D. Zipp**, Biotest, 3; **F. Rharbaoui**, Biotest, 3; **R. Wolter**, Biotest, 3; **R. D. Tiemann**, Biotest, 3; **L. Knierim**, Biotest, 3; **R. Schmeidl**, Biotest, 3; **X. Zhou**, Biotest, 3; **S. Aigner**, Biotest, 3; **B. Daelken**, Biotest, 3; **A. Wartenberg-Demand**, Biotest, 3.

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Abstract Number: 973

The Effect of TNF Inhibitor Treatment on Occurrence of Anterior Uveitis in Ankylosing Spondylitis: Results from the Swedish Biologics Register

Elisabeth Lie[1,2], Ulf Lindström[2], Tatiana Zverkova-Sandström[2], Inge C Olsen[1], Helena Forsblad-d'Elia[3], Johan Askling[4], Lars Erik Kristensen[5,6] and Lennart TH Jacobsson[2], [1]Dept. of Rheumatology, Diakonhjemmet Hospital, Oslo, Norway, [2]Dept. of Rheumatology and Inflammation Research, Sahlgrenska Academy at University of Gothenburg, Gothenburg, Sweden, [3]Departments of Public Health and Clinical Medicine, Rheumatology, Umeå University, Umeå, Sweden, [4]Clinical Epidemiology Unit & Rheumatology Unit, Dept. of Medicine, Karolinska Institutet, Stockholm, Sweden, [5]Musculoskeletal Statistics Unit, The Parker Institute, Dept. of Rheumatology, Copenhagen University Hospital, Bispebjerg and Frederiksberg, Copenhagen, Denmark, [6]Section of Rheumatology, Department of Clinical Sciences, Lund University, Malmö, Sweden

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Background/Purpose: Anterior uveitis is a relatively frequent extra-articular manifestation in ankylosing spondylitis (AS), with a prevalence of 25.8% in a recent meta-analysis. TNF inhibitor (TNFi) treatment has been shown to reduce the rates of uveitis in this patient group. Some studies have suggested a greater protective effect with the anti-TNF monoclonal antibodies infliximab (IFX) and adalimumab (ADA) than with etanercept (ETN). Our objective was to study the effect of ADA, ETN or IFX treatment on occurrence of anterior uveitis in a cohort of patients (pts) with AS.

Methods: Data on AS pts starting ADA, ETN or IFX as their first TNFi from Jan 2003 through Dec 2010 were extracted from the Swedish Biologics Register ARTIS (follow-up data available through Dec 2011). Data on anterior uveitis, available from Jan 2001, were obtained by linkage to the National Patient Register as visits to an ophthalmologist with ICD-10 codes indicating anterior uveitis (H20, H22.1). We applied two main analytical approaches: (1) Comparison of uveitis rates (per 100 patient-years) before TNFi start (follow-up time pre-Rx 2-10 yrs) and during TNFi treatment for each TNFi, analysing (by Poisson regression): (a) total numbers of uveitis visits, (b) uveitis flares defined by a 60-day penalty from the index visit of one uveitis flare for a new flare to be counted, and (c) uveitis flares defined by a 90 day penalty from last uveitis flare follow-up visit for a new flare to be counted. (2) Cox regression analysis comparing hazard of first uveitis flare for ADA, ETN or IFX in a subgroup of pts who were uveitis-free during the 2 yrs before TNFi start, +/- adjustment for potential confounders (age, sex, prescription year, level of education, disease duration, presence of IBD, baseline CRP and use of DMARD co-medication, prednisolone and NSAIDs).

Results: 1365 AS pts were included (406 ADA, 354 ETN, 605 IFX). IFX pts more often used DMARD co-medication; ADA pts had lower baseline CRP. ADA was more frequently used towards the end of the study period. IFX doses tended to be lower than 5 mg/kg (at baseline/last registration 62%/50% used <=200 mg). A clear reduction in uveitis rates was observed for ADA, a slight reduction for IFX and a marked increase for ETN, irrespective of the method for counting flares (Table). 1127 pts were uveitis-free 2 yrs prior to TNFi start and included in the Cox regression analyses. In the adjusted analysis ADA and IFX were superior vs. ETN (Table).

Conclusion: In this large register-based study of AS pts we found reduction in uveitis rates with ADA treatment, a slight reduction with IFX and increased rates with ETN. In a subgroup free of recent uveitis, ADA and IFX were associated with significantly lower hazard for first uveitis flare than ETN. Potential caveats of this study include residual confounding, the relatively low doses of IFX used, reporting bias, and the possibility that the required uveitis-free period for pts included in the Cox regression analysis was too short.

Table. Comparative analysis of uveitis rates before and during TNFi treatment, and occurrence of first flare after start of TNFi in a subgroup of patients who were uveitis-free 2 years before TNFi start

(1) All patients (N=1365):	**ADA N=406**		**ETN N=354**		**IFX N=605**	
	Events per 100 pt-yrs (95% CI)		**Events per 100 pt-yrs (95% CI)**		**Events per 100 pt-yrs (95% CI)**	
	Before Rx	**On Rx**	**Before Rx**	**On Rx**	**Before Rx**	**On Rx**
Uveitis visits total (a)	29.9 (28.0-31.8)	15.7 (13.1-18.3)	23.1 (21.1-25.1)	55.2 (50.8-59.6)	31.7 (29.9-33.4)	25.9 (23.5-28.3)
Uveitis flares definition 1 (b)	12.9 (11.7-14.2)	7.7 (5.9-9.6)	9.6 (8.4-10.9)	20.2 (17.5-22.8)	12.7 (11.5-13.8)	11.7 (10.1-13.3)
Uveitis flares definition 2 (c)	9.5 (8.4-10.5)	6.0 (4.4-7.7)	7.7 (6.5-8.8)	15.0 (12.8-17.3)	9.1 (8.1-10.0)	8.0 (6.7-9.3)
(2) Uveitis-free 2 yrs pre-Rx (N=1127):	**ADA N=328**		**ETN N=296**		**IFX N=503**	
	HR (95% CI)		**HR (95% CI)**		**HR (95% CI)**	
Cox regression unadjusted	Ref.		4.12 (2.00-8.46)		2.00 (0.96-4.17)	
Cox regression adjusted*	Ref.		3.69 (1.61-8.46)**		1.67 (0.69-4.04)**	

*Adjusted for age, sex, prescription year, level of education, disease duration, presence of IBD, BL CRP and use of DMARD co-medication, prednisolone and NSAIDs

**HR (95% CI) 2.21 (1.25-3.89) for comparison ETN vs. IFX

See abstract text for definitions of (a), (b) and (c)

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Abstract Number: 974

Secukinumab Significantly Improves Signs and Symptoms of Active Ankylosing Spondylitis: 52-Week Results from a Randomized, Double-Blind, Placebo-Controlled Phase 3 Trial with Subcutaneous Loading and Maintenance Dosing

Juergen Braun[1], Atul A. Deodhar[2], Joachim Sieper[3], Maxime Dougados[4], Brian Porter[5], Mats Andersson[6] and Hanno Richards[6], [1]Rheumazentrum Ruhrgebiet, Herne, Germany, [2]Division of Arthritis & Rheumatic Diseases, Oregon Health & Science University, Portland, OR, [3]University Clinic Benjamin Franklin, Berlin, Germany, [4]Université Paris René Descartes and Hôpital Cochin, Paris, France, [5]Novartis Pharmaceuticals Corporation, East Hanover, NJ, [6]Novartis Pharma AG, Basel, Switzerland

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Background/Purpose: In MEASURE 2 (NCT01649375), subcutaneous (s.c.) secukinumab, an anti–interleukin-17A antibody, improved the signs and symptoms of ankylosing spondylitis (AS) through 16 weeks (wks) of therapy.[1] Here we report the long-term (52 wk) efficacy and safety of secukinumab in this study.

Methods: 219 patients (pts) with active AS, classified by modified New York criteria, despite therapy with NSAIDs, were randomized to s.c. secukinumab 150 or 75 mg or placebo (PBO) at baseline, Wks 1, 2, and 3, and every 4 wks from Wk 4. At Wk 16, PBO-treated pts were re-randomized to receive secukinumab 150 or 75 mg s.c. every 4 wks. The primary endpoint was the proportion of pts achieving an ASAS20 response at Wk 16. The secondary endpoints were ASAS40, hsCRP, ASAS 5/6, BASDAI, SF-36 PCS, ASQoL, and ASAS partial remission. Primary and secondary endpoints were assessed through Wk 52 using a non-responder imputation (binary variables) and mixed-model repeated measures analysis (continuous variables). A predefined hierarchical hypothesis testing strategy was used in statistical analyses at Wk 16 to adjust for multiplicity of testing.

Results: Overall, 181 pts (82.6%) completed 52 wks of treatment. ASAS20 response rates at Wk 16 were 61.1% with secukinumab 150 mg vs 28.4% with PBO (P=0.0001). Secukinumab 150 mg also significantly improved ASAS40, hsCRP, ASAS 5/6, BASDAI, SF-36 PCS, and ASQoL at Wk 16 vs PBO. Clinical responses with secukinumab 75 mg did not reach statistical significance for any of the pre-specified endpoints based on hierarchical testing. Improvements with secukinumab 150 mg were sustained through Wk 52 (Table). Using a more conservative estimate of efficacy with non-responder imputation, ASAS20/40 response rates with secukinumab 150 mg at Wk 52 were 62.5/48.6%; rates with observed data were 73.8/57.4%. ASAS20/40 response rates in pts originally randomized to PBO who received secukinumab 150 mg at week 16 (n=34) were 70.6%/52.9% at Wk 52 (non-responder imputation). Over the entire study period, exposure-adjusted SAE rates (mean secukinumab exposure: 425.8 days; mean PBO exposure: 107.6 days) were 6.6, 7.7, and 14.0. per 100 pt-years with secukinumab 150 mg, 75 mg, and PBO, respectively. The most common SAEs were infections; no pt discontinued therapy due to an infection. Three pts on secukinumab had a Candida infection (1 on 150 mg and 2 on 75 mg), 1 had a fatal myocardial infarction (75 mg), 2 had AEs of Crohn's disease (1 on 150 mg [de novo] and 1 on 75 mg [flare]), and 1 had an AE of uveitis (150 mg). There were no suicidality-related AEs with secukinumab.

Conclusion: Secukinumab 150 mg s.c. provided sustained improvements over 52 weeks in the signs and symptoms of AS, reducing inflammation, and improving physical function and health-related quality of life. Secukinumab was well tolerated; safety findings were consistent with previous reports.

References:

1. Sieper J, et al. *Arthritis Rheumatol.* 2014;66(11Suppl):S232

Table: Primary and Secondary Endpoint Results at Weeks 16 and 52				
		Secukinumab 150 mg s.c. (n = 72)	**Secukinumab 75 mg s.c. (n = 73)**	**Placebo (n = 74)**
ASAS20, %	Wk 16	61.1†	41.1	28.4
	Wk 52	62.5	53.4	N/A
ASAS40, %	Wk 16	36.1†	26.0	10.8
	Wk 52	48.6	34.2	N/A
hsCRP, post-baseline/baseline ratio	Wk 16	0.55†	0.61	1.13
	Wk 52	0.46	0.58	N/A
ASAS 5/6, %	Wk 16	43.1†	34.2	8.1
	Wk 52	52.8	39.7	N/A
BASDAI, mean change from baseline (MCID = 1)	Wk 16	-2.19†	-1.92	-0.85
	Wk 52	-2.85	-2.47	N/A
SF-36 PCS, mean change from baseline (MCID = 2.5)	Wk 16	6.06†	4.77	1.92
	Wk 52	6.82	6.11	N/A
ASQoL, mean change from baseline (MCID = 1.8)	Wk 16	-4.00µ	-3.33	-1.37
	Wk 52	-4.80	-3.88	N/A
ASAS partial remission, %	Wk 16	13.9	15.1	4.1
	Wk 52	22.2	15.1	N/A

†$P<0.001$ µ$P < 0.01$ for comparisons vs PBO. *P*-values at Wk 16 were adjusted for multiplicity of testing. NRI (binary variables) and MMRM (continuous variables) data are presented.

ASAS, Assessment of Spondyloarthritis International Society response criteria; ASQoL, Ankylosing Spondylitis Quality of Life; BASDAI, Bath Ankylosing Spondylitis Disease Activity; hsCRP, high sensitivity C-reactive protein; MCID, minimum clinically important difference; N/A, not applicable; SF-36 PCS, Short Form-36 item Health Survey Physical Component Summary

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Abstract Number: 975

The Effect of TNF Inhibition on Radiographic Progression in Ankylosing Spondylitis: An Observational Cohort Study of 374 Patients

Walter Maksymowych[1], Yufei Zheng[2], Stephanie Wichuk[1], Sasha Bernatsky[3], Praveena Chiowchanwisawakit[4] and Robert G Lambert[5], [1]Medicine, Medicine, University of Alberta, Edmonton, AB, Canada, [2]Alberta Institute of Health Economics, Edmonton, AB, Canada, [3]Rheum/Clin. Epid., McGill MUHC/RVH, Montreal, QC, Canada, [4]Rheumatology, Medicine, Siriraj Hospital, Mahidol University, Bangkok, Thailand, [5]Radiology, Radiology, University of Alberta, Edmonton, AB, Canada

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Background/Purpose: An analysis of radiographic progression in an observational cohort has suggested that anti-TNF therapy lessens radiographic progression, especially when treatment is introduced within 5 years of AS onset, although development of new syndesmophytes was not reported[1]. We aimed to assess the impact of anti-TNF therapy on radiographic progression in an observational cohort of AS by analyzing propensity-matched patients.

Methods: In the FOllow-up Research Cohort in AS (FORCAST), 374 patients with AS from Northern Alberta attending community and academic rheumatology practices have been assessed over a mean follow up of 3.1 years for clinical and laboratory outcomes every 6 months, and had spinal radiography at baseline and follow up. Patients received standard (n=147) or anti-TNF therapy (n=227). Radiographs were scored by two readers using the mSASSS with adjudication by a third reader according to pre-specified rules. The impact of anti-TNF therapy was assessed using univariate and multivariate Tobit regression for mSASSS data and Poisson regression for development of new syndesmophytes. Propensity matching was based on a caliper of 0.1 in a logistic model using age, gender, disease duration, smoking, mSASSS, and pre-treatment BASDAI and CRP. Multiple propensity score analysis based on multinomial logistic regression was used to compare treatment groups according to disease duration before start of anti-TNF. Missing values were imputed using the multiple imputation by chained equations (MICE) method.

Results: Subjects were predominantly males (74.9%) of mean (SD) age 43.0 (11.9) years, mean (SD) disease duration 21.4 (11.6) years, mean (SD) baseline mSASSS of 17.1 (18.4), mean (SD) radiographic progression of 0.97 (1.31) mSASSS unit/year, and 38.4% developed a new syndesmophyte. After propensity matching using baseline covariates 218 and 230 patients could be included in the post-match analysis of mSASSS progression and new syndesmophytes, respectively. These numbers were 158 and 190, respectively, after tighter matching using pre-treatment covariates. In univariate analyses of propensity-matched cases, significant predictors were baseline mSASSS and pre-treatment,ASDAS for mSASSS progression, and baseline mSASSS and age for new syndesmophyte. In the final multivariable Tobit and Poisson regression models using propensity-matched data, only pre-treatment ASDAS was a significant predictor of mSASSS progression (β=0.40 [95%CI: 0.08-0.72]; p=0.014). Multiple propensity score adjusted analyses demonstrated significantly less radiographic progression in patients who received anti-TNF within 5 years of disease onset versus those on standard therapy or treated with anti-TNF after >10 years of disease (Table).

Conclusion: A beneficial effect of anti-TNF treatment may be evident in AS patients receiving treatment within 5 years of disease onset.

1. Haroon et al. Arthritis Rheum 2013; 65: 2645-54.

Significant variables in multiple propensity analysis	Coefficient	95% CI	P value
Baseline mSASSS	0.018	0.003 - 0.032	0.015
Baseline ASDAS	0.24	0.031 - 0.45	0.024
Time between disease onset and anti-TNF start: No anti-TNF <5 years 5-10 years >10 years	REF -1.41 -0.34 -0.17	-2.56 - - 0.25 -1.30 – 0.62 -0.70 – 0.36	0.017 0.49 0.53
Time between disease onset and anti-TNF start: No anti-TNF <5 years 5-10 years >10 years	0.17 -1.24 -0.17 REF	-0.36 – 0.70 -2.45 - - 0.022 -1.16 – 0.82	0.53 0.046 0.74

Disclosure: W. Maksymowych, Abbvie, Amgen, Boehringer Ingelheim, Eli Llilly and Company, Janssen Pharmaceutica Product, L.P., Pfizer, UCB, 5,Abbvie, 2; **Y. Zheng**, None; **S. Wichuk**, None; **S. Bernatsky**, None; **P. Chiowchanwisawakit**, None; **R. G. Lambert**, None.

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Abstract Number: 976

The Reason of Discontinuation of a First TNF Inhibitor Affects Drug Retention of a Second Anti-TNF Agent in Axial Spondyloarthritis

Adrian Ciurea[1], Pascale Exer[2], Ulrich Weber[3,4], Giorgio Tamborrini[5], Beate Steininger[1], Rudolf O. Kissling[6], Jürg Bernhard[7] and Almut Scherer[8], [1]Rheumatology, University Hospital Zurich, Zurich, Switzerland, [2]Private rheumatology practice, Basel, Switzerland, [3]Institute of Regional Health Research, University of Southern Denmark, Odense, Denmark, [4]Department of Research, King Christian 10th Hospital for Rheumatic Diseases, Graasten, Denmark, [5]Department of Rheumatology, University Hospital, Zurich, Switzerland, [6]Division of Rheumatology, Balgrist University Hospital, Zurich, Switzerland, [7]Rheumatology and Rehabilitation, Bürgerspital Solothurn, Solothurn, Switzerland, [8]SCQM Foundation, Zurich, Switzerland

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Background/Purpose: Conflicting results have been demonstrated in axial spondyloarthritis (axSpA) with regard to whether effectiveness of a second (2°) TNFi depends on the reason of discontinuation of the first (1°) TNFi.

Methods: Patients with a clinical diagnosis of axSpA initiating a 2° TNFi in the Swiss Clinical Quality Management (SCQM) cohort were included. 2° TNFi drug maintenance and the proportion of patients achieving a moderately active or inactive disease state according to defined Ankylosing Spondylitis Disease Activity Score (ASDAS) cut-offs at 1 year (±6mo) were compared by the reason of discontinuation of the 1° TNFi (primary or secondary lack of response (PLR or SLR, defined as discontinuation of the 1° TNFi due to insufficient effectiveness before or after 6 months, respectively), adverse events (AE) or other reasons). LUNDEX values were used to indicate the proportion of patients adhering to treatment and achieving a response criterion.

Results: A 2° TNFi was started in 591 patients after inclusion into SCQM. Drug retention of 2° TNFi stratified by the reason of discontinuation of the 1° TNFi was significantly reduced after PLR in comparison to all other reasons of discontinuation, log-rank $p<0.001$ (Figure 1). Median (IQR) drug retention after PLR and SLR were 0.94 (0.58; 2.13) and 3.92 (2.46; 3.20) years, respectively. The proportion of patients achieving an ASDAS <2.1 and <1.3, respectively, in patients still on treatment (n=384) with complete follow-up visits at 1 year (n=176) are shown in Table 1. Response rates were slightly lower in patients having previously experienced PLR and AE in comparison to SLR and highest in patients having switched due to “other” reasons (e.g. remission, personal preferences). These differences were partially more pronounced after LUNDEX adjustment. An ASDAS<1.3 was reached by 2-12% of patients following a previous PLR, SLR or AE.

Conclusion: Previous PLR is associated with a strongly reduced retention of the 2° TNFi. Only a minority of patients on a 2° TNFi having previously experienced PLR, SLR or AE achieve an inactive disease state at 1 year. These findings might help guiding treatment choices after discontinuation of a 1° TNFi, as new treatment options with other modes of action will be available.

Figure 1. Retention of 2nd TNFi by the reason of discontinuation of the 1st TNFi

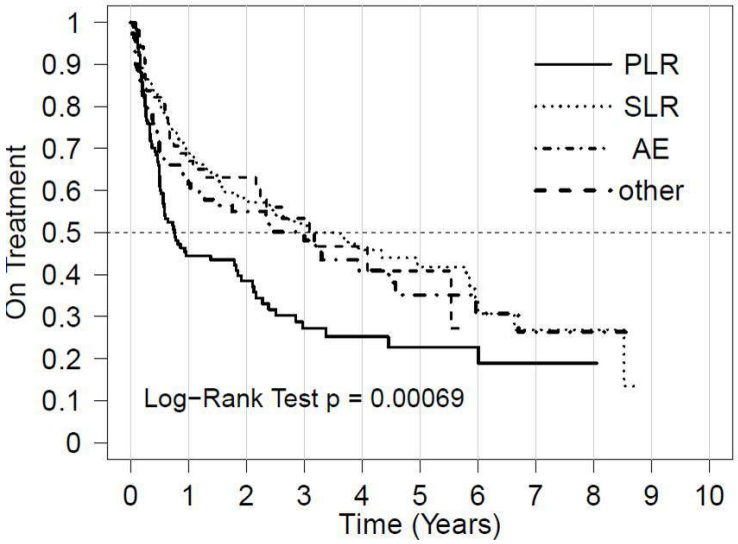

Table 1. Proportion of patients on a second TNFi achieving a moderately active or inactive disease state after 1 year (with and without LUNDEX adjustement of treatment responses for drop-outs). #Fisher's test; µNon-parametric permutation test.

	All	PLR	SLR	AE	Other	P
	N=176	N = 35	N= 87	N=36	N=18	Value
ASDAS<2.1	40%	34%	43%	31%	61%	0.16#
ASDAS<2.1 LUNDEX	28%	19%	31%	21%	44%	0.11µ
ASDAS<1.3	14%	13%	16%	3%	28%	0.052#
ASDAS<1.3 LUNDEX	10%	8%	12%	2%	20%	0.055µ

Disclosure: A. Ciurea, Abbvie, 2,Abbvie, 5,Celgene, 5,Eli Lilly and Company, 5,Janssen Pharmaceutica Product, L.P., 5,MSD, 2,MSD, 5,Novartis Pharmaceutical Corporation, 5,Pfizer Inc, 2,Pfizer Inc, 5,UCB, 2,UCB, 5; **P. Exer**, None; **U. Weber**, Abbvie, 5,MSD, 5; **G. Tamborrini**, None; **B. Steininger**, None; **R. O. Kissling**, None; **J. Bernhard**, MSD, 5,Pfizer Inc, 5; **A. Scherer**, None.

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Abstract Number: 977

A Randomized, Double-Blind, Active- and Placebo-Controlled Phase 3 Study of Efficacy and Safety of Ixekizumab, Adalimumab, and Placebo Therapy in Patients Naïve to Biologic Disease Modifying Anti-Rheumatic Drugs with Active Psoriatic Arthritis

Philip J. Mease[1], Désirée van der Heijde[2], Christopher T. Ritchlin[3], Raquel Cuchacovich[4,5], Catherine L. Shuler[5], Chin H. Lee[5], Suvajit Samanta[5], Chen-Yen Lin[5], Dafna D. Gladman[6] and Harald Vangerow[5], [1]Department of Rheumatology, Swedish Medical Center and University of Washington, Seattle, WA, [2]Department of Rheumatology, Leiden University Medical Center, Leiden, the Netherlands, Leiden, Netherlands, [3]Allergy Immunology & Rheumatology, University of Rochester Medical Center, Rochester, NY, [4]School of Medicine, Rheumatology Division, Indiana University, Indianapolis, IN, [5]Eli Lilly and Company, Indianapolis, IN, [6]Department of Medicine, Division of Rheumatology, University of Toronto, Toronto, ON, Canada

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Background/Purpose: Psoriatic arthritis (PsA) is a chronic immune-mediated inflammatory disease associated with psoriasis which includes peripheral arthritis, enthesitis, dactylitis, and spondylitis manifestations. Ixekizumab, under investigation for PsA treatment, is an IgG4 monoclonal antibody that binds with high affinity and specificity to the proinflammatory cytokine IL 17A.

Methods: In a phase 3 trial, 417 biologic disease-modifying antirheumatic drug (bDMARD)-naive patients with active PsA were randomized to up to 24 weeks of placebo (N=106); adalimumab 40 mg (N=101) once every 2 weeks (Q2W; active control); or ixekizumab 80 mg Q2W (N=103) or Q4W (N=107) following 160 mg initial dose at Week 0. Endpoints included American College of Rheumatology 20 response (ACR20) at Week 24 (primary), ACR50, ACR70, a 75/90/100% improvement in Psoriasis Area and Severity Index (PASI 75/PASI 90/PASI 100), Disease Activity Score (28 joint count) based on C-reactive protein (DAS28-CRP), Leeds Dactylitis Index (LDI-B) and Enthesitis Index (LEI), Health Assessment Questionnaire – Disability Index (HAQ-DI), and Van der Heijde modified Total Sharp (mTSS) score at 12 and 24 weeks. Efficacy variables were evaluated using the intent-to-treat population. Continuous data were evaluated using mixed-effects model for repeated measures. Categorical data were compared using a logistic regression model with missing values imputed by non-responder imputation, which treats inadequate responders as non-responders.

Results: A total of 382 patients completed 24 weeks of the study. A significantly greater percentage of patients treated with ixekizumab 80 mg Q2W or Q4W achieved ACR 20, ACR50, ACR70 and PASI 75/90/100 responses than with placebo at 12 and 24 weeks ($p<.01$) (Table 1). Both ixekizumab groups experienced significantly greater reductions than placebo for measures of dactylitis (LDI-B) at 12 and 24 weeks but not for enthesitis (LEI). Disease activity (DAS28-CRP) and functional disability (HAQ-DI) improved and inhibition of radiographic progression of joint structural damage (mTSS) was demonstrated with both ixekizumab doses compared to placebo ($p<.025$). Efficacy results with adalimumab versus placebo were significant on most measures, thus validating the study design. At 24 weeks, the incidence of treatment-emergent adverse events (TEAE) was greater ($p<.05$) and the rate of serious adverse events was higher ($p>.27$) with ixekizumab and adalimumab compared to placebo. Discontinuation due to a TEAE was similar across groups. No deaths occurred.

Conclusion: In bDMARD-naive patients with active PsA, ixekizumab showed significant, clinically meaningful improvements of disease activity and physical function, reduction in dactylitis, greater skin clearance of plaque psoriasis, and inhibition of structural progression. Ixekizumab was well tolerated with no unexpected safety findings.

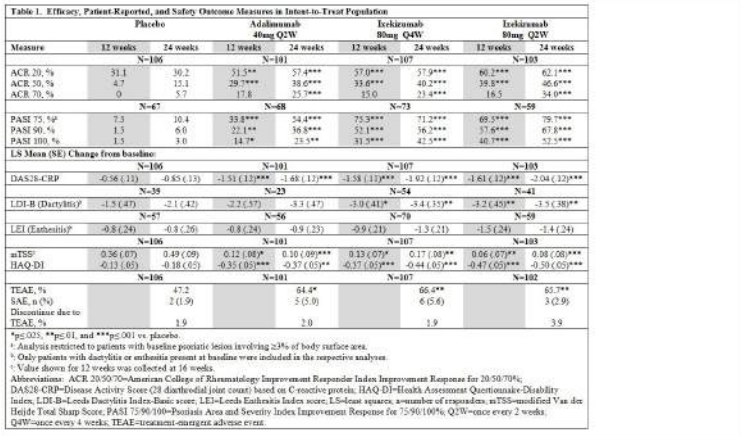

Table 1. Efficacy, Patient-Reported, and Safety Outcome Measures in Intent-to-Treat Population

	Placebo		Adalimumab 40mg Q2W		Ixekizumab 80mg Q4W		Ixekizumab 80mg Q2W	
Measure	**12 weeks**	**24 weeks**	**12 weeks**	**24 weeks**	**12 weeks**	**24 weeks**	**12 weeks**	**24 weeks**
	N=106		N=101		N=107		N=103	
ACR 20, %	31.1	30.2	51.5**	57.4***	57.0***	57.9***	60.2***	62.1***
ACR 50, %	4.7	15.1	29.7***	38.6***	33.6***	40.2***	39.8***	46.6***
ACR 70, %	0	5.7	17.8	25.7***	15.0	23.4***	16.5	34.0***
	N=67		N=68		N=73		N=59	
PASI 75, %[a]	7.3	10.4	33.8***	54.4***	75.3***	71.2***	69.5***	78.7***
PASI 90, %	1.5	6.0	22.1**	36.8***	52.1***	36.2***	57.6***	67.8***
PASI 100, %	1.5	3.0	14.7*	23.5**	31.5***	42.5***	40.7***	52.5***
LS Mean (SE) Change from baseline:								
	N=106		N=101		N=107		N=103	
DAS28-CRP	-0.56 (.13)	-0.85 (.13)	-1.51 (.13)***	-1.68 (.13)***	-1.58 (.13)***	-1.92 (.13)***	-1.61 (.12)***	-2.04 (.12)***
	N=35		N=23		N=54		N=41	
LDI-B (Dactylitis)[b]	-1.5 (.47)	-2.1 (.42)	-2.2 (.57)	-3.3 (.47)	-3.0 (.41)*	-3.4 (.35)**	-3.2 (.45)**	-3.5 (.38)**
	N=57		N=56		N=70		N=59	
LEI (Enthesitis)[b]	-0.8 (.24)	-0.8 (.26)	-0.8 (.24)	-0.9 (.23)	-0.9 (.21)	-1.3 (.21)	-1.5 (.24)	-1.4 (.24)
	N=106		N=101		N=107		N=103	
mTSS[c]	0.36 (.07)	0.49 (.09)	0.12 (.08)*	0.10 (.09)***	0.13 (.07)*	0.17 (.08)**	0.06 (.07)**	0.08 (.08)***
HAQ-DI	-0.13 (.05)	-0.18 (.05)	-0.35 (.05)***	-0.37 (.05)***	-0.37 (.05)***	-0.44 (.05)***	-0.47 (.05)***	-0.50 (.05)***
	N=106		N=101		N=107		N=102	
TEAE, %		47.2		64.4*		66.4**		65.7**
SAE, n (%)		2 (1.9)		5 (5.0)		6 (5.6)		3 (2.9)
Discontinue due to TEAE, %		1.9		2.0		1.9		3.9

*p≤.025, **p≤.01, and ***p≤.001 vs. placebo.
[a] Analysis restricted to patients with baseline psoriatic lesion involving ≥3% of body surface area.
[b] Only patients with dactylitis or enthesitis present at baseline were included in the respective analyses.
[c] Value shown for 12 weeks was collected at 16 weeks.
Abbreviations: ACR 20/50/70=American College of Rheumatology Improvement Responder Index Improvement Response for 20/50/70%; DAS28-CRP=Disease Activity Score (28 diarthrodial joint count) based on C-reactive protein, HAQ-DI=Health Assessment Questionnaire-Disability Index, LDI-B=Leeds Dactylitis Index-Basic score, LEI=Leeds Enthesitis Index score, LS=least squares, n=number of responders, mTSS=modified Van der Heijde Total Sharp Score, PASI 75/90/100=Psoriasis Area and Severity Index Improvement Response for 75/90/100%, Q2W=once every 2 weeks, Q4W=once every 4 weeks, TEAE=treatment-emergent adverse event.

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Abstract Number: 978

Continuous Versus on Demand Treatment of Ankylosing Spondylitis with Diclofenac over 2 Years Does Not Prevent Radiographic Progression of the Spine: Results from a Randomized Prospective Multi-Center Trial

Joachim Sieper[1], Joachim Listing[2], Denis Poddubnyy[1], In-Ho Song[1,3], Kay-Geert Hermann[1], Johanna Callhoff[2], Jürgen Braun[4] and Martin Rudwaleit[1,5], [1]Charité Universitätsmedizin Berlin, Berlin, Germany, [2]German Rheumatism Research Centre, Berlin, Germany, [3]Abbvie, Chicago, IL, [4]Rheumazentrum Ruhrgebiet, Herne, Germany, [5]Klinikum Bielefeld, Bielefeld, Germany

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SESSION INFORMATION

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Session Title: Spondylarthropathies and Psoriatic Arthritis - Clinical Aspects and Treatment: Treatment of AS

Session Type: ACR Concurrent Abstract Session

Session Time: 2:30PM-4:00PM

Background/Purpose:

Previously it was shown that non-steroidal antiinflammatory drugs (NSAIDs) given continuously reduce radiographic progression compared to an on demand therapy over 2 years in patient with ankylosing spondylitis (AS). A similar effect was found in an analysis from a prospective AS cohort (GESPIC). In the current study we tested whether such an effect of NSAIDs could be confirmed in another prospective randomized trial.

Methods:

AS patients were randomized to be treated with either continuous (at least 50% per day of the maximum dose of 150 mg) or on demand diclofenac for 2 years. Switching to another NSAID was possible in case of side effects or inefficacy. Eligible patients had active disease that justified the start or continuation of an NSAID and had no contraindications for an NSAID therapy. TNF-blockers were not allowed during the whole study period. Primary outcome was the difference in the increase of radiographic progression in the spine measured by the mSASSS, scored by two readers blinded to treatment arm and time point.

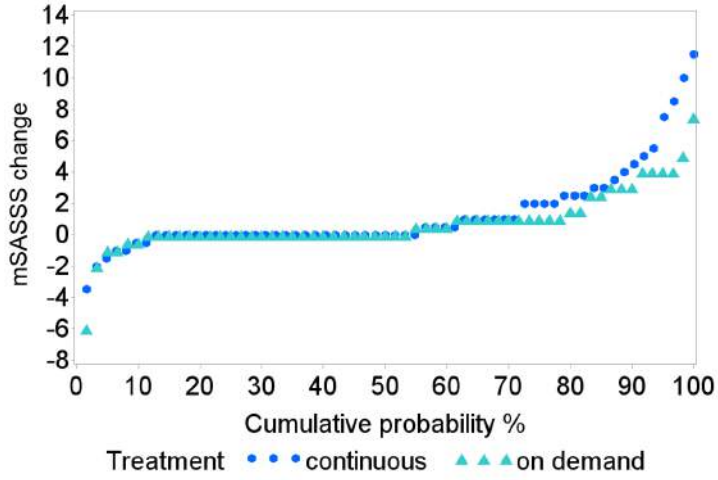
Results:

62 of 85 patients enrolled in the continuous arm (mean age 42 years, BASDAI 4.2, CRP 8.4 mg/l, disease duration 12.2 y, 74% male, mSASSS 11.3, HLA-B27 positivity 83.5%) and 60 of 82 enrolled in the on demand arm (mean age 44 years, BASDAI 4.5, CRP 12.9 mg/l, disease duration 15.2 y, 68% male, mSASSS 14.0, HLA-B27 84%) completed the study. Surprisingly, the mSASSS progression was numerically higher in the continuous group compared to the on demand group (1.28; 95%CI 0.68-1.92 vs 0.79; 95%CI 0.17-1.38 in the completer population), although this difference was not statistically significant (figure). When only patients were analysed who were CRP positive at baseline (54% cont., 58% demand) or had syndesmophytes at baseline (55% cont., 57% on demand), both known risk factors for radiographic progression, again there was numerically a higher radiographic progression in the continuous vs the on demand group: 1.68 vs 0.83 and 2.1 vs 0.89, respectively. We used the ASAS NSAIDs index (0-100) [3] to quantify NSAIDs intake over the 2 years, which was 75 (mean) for the continuous and 44 (mean) for the on demand group. At the end of year 2, 73% of the patients were still on diclofenac and had not switched to another NSAID. There were no differences between the 2 treatment groups regarding side effects: 19 serious adverse event occurred in the continuous group vs 19 in the on demand group.

Conclusion:

In our study continuous vs on demand treatment with diclofenac over 2 years did not prevent radiographic progression in AS. It is highly unlikely that the results would have been different with a higher number of patients because we found even a trend for less progression in the on demand group. Since 73% of patients were still on diclofenac at the end of the study we do not know whether other NSAIDs such as Celecoxib would have had a different effect on radiographic progression in our patients.

Figure. Radiographic spinal progression in the completer population (n = 62 in the continuous arm and n = 60 in the on demand arm)



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Abstract Number: 979

HLA Class I Genes As Susceptibility Markers of Psoriatic Arthritis in Patients with Psoriasis – a Meta-Analysis

Lihi Eder[1], Fatima Abji[2], Cheryl Rosen[3], Muhammad Haroon[4], Vinod Chandran[1], Rubén Queiro[5], Shelley Bull[6], Richard J. Cook[7], Proton Rahman[8], Robert Winchester[9], Oliver FitzGerald[10] and Dafna D. Gladman[1], [1]Rheumatology, University of Toronto, Toronto Western Hospital, Toronto, ON, Canada, [2]University of Toronto, Toronto Western Hospital, Toronto, ON, Canada, [3]Dermatology, University of Toronto, Toronto Western Hospital, Toronto, ON, Canada, [4]Kerry General Hospital, Tralee, Ireland, [5]Rheumatology Service, Hospital Universitario Central de Asturias, Oviedo, Spain, [6]School of Public Health, Mount Sinai Hospital, Toronto, ON, Canada, [7]Statistics and Actuarial Science, University of Waterloo, Waterloo, ON, Canada, [8]Computer Sciences, Memorial University of Newfoundland, St. John's, NF, Canada, [9]Columbia University, New York, NY, [10]Department of Rheumatology, St Vincent's University Hospital, Dublin, Ireland

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Session Type: ACR Concurrent Abstract Session

Session Time: 2:30PM-4:00PM

Background/Purpose:

Genes that differentiate patients with psoriatic arthritis (PsA) from those with psoriasis alone may serve as markers for the development of PsA in psoriasis patients. Psoriatic disease risk is strongly associated with variation within the HLA class I region. In this large-scale study we aimed to strengthen evidence about previously reported HLA risk alleles for PsA and to identify novel susceptibility markers to the disease.

Methods:

1677 PsA, 702 psoriasis without arthritis and 2275 healthy controls of European ethnicity from 4 sites in Canada, Ireland and Spain were included in the study. *HLA-B* and *–C* alleles were genotyped using sequence specific primers. Differences in allelic distribution for each *HLA* locus were compared using the Likelihood Ratio test by regression models with site indicator. The False Discovery Rate (FDR) approach was employed to assess the impact of multiple testing. Logistic regression analysis was performed to account for linkage disequilibrium between *HLA-B* and *-C* alleles. The association between amino acids encoded by the identified *HLA*genes and PsA was assessed using logistic regression analysis.

Results:

The following HLA alleles were confirmed as independent susceptibility markers of PsA in psoriasis patients in the multivariate analysis: *B*08* (Odds Ratio (OR) 1.48, p=0.002), *B*27* (OR 3.69, p=2.8x10^{-12}), *B*38* (OR 1.68, p=0.005), *B*39* (OR 1.80, p=0.01) and *C*06* (OR 0.47, p=6.8x10^{-13}). The following HLA alleles were confirmed as susceptibility markers for PsA in the general population: *B*27* (OR 2.37, p=2.5x10^{-13}), *B*38* (OR 3.81, p=2.5x10^{-13}), *B*39* (OR 2.17, p=9.5x10^{-6}), *B*57* (OR 2.06, p=3.6x10^{-7}) and *C*06* (OR 1.29, p=0.02). The frequency of the following alleles was reduced in PsA compared to healthy controls: *B*07*, *B*44*, *B*40*, *B*15*, *B*49*, *B*51*, *B*55*, *C*04* and *C*08*. PsA susceptibility was also associated with the presence of cysteine at position 67 (*B*27*, *B*39*, *B*38*), methionine at position 67 (*B*57*), aspartate at position 9 (*B*08*) and glutamine at position 45 (*B*08*, *B*39*, *B*38*, *B*27*). However, after inclusion of the specific *HLA* risk alleles these associations were not statistically significant.

Conclusion:

PsA susceptibility is associated with several *HLA* class I alleles. *HLA-B*38*, *B*39, B*08* and *B*27* confer an increased risk for PsA compared to psoriasis. In contrast, *HLA-C*06*, the strongest psoriasis susceptibility gene, is associated with a lower risk of developing PsA in patients with psoriasis.

Disclosure: L. Eder, None; **F. Abji**, None; **C. Rosen**, None; **M. Haroon**, None; **V. Chandran**, None; **R. Queiro**, None; **S. Bull**, None; **R. J. Cook**, None; **P. Rahman**, None; **R. Winchester**, None; **O. FitzGerald**, None; **D. D. Gladman**, None.

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Abstract Number: 980

Association of Platelet Endothelial Cell Adhesion Molecule-1 and ß1 Integrin Gene Polymorphisms with Uveitis Development in Ankylosing Spondylitis

Seung-Cheol Shim[1], In-Seol Yoo[2], Su-Jin Yoo[1], Young Kim[1], Mi-Kyoung Lim[3], Dong-Hyuk Sheen[4] and Jinhyun Kim[5], [1]Rheumatology, Chungnam National University School of Medicine, Daejeon, South Korea, [2]Department of Internal Medicine, Chungnam National University School of Medicine, Daejeon, South Korea, [3]Medicine, Eulji University Hospital, Daejeon, South Korea, [4]Rheumatology, Eulji University Hospital, Daejeon, South Korea, [5]Internal medicine, Chungnam National University School of Medicine, Daejeon, South Korea

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Session Type: ACR Concurrent Abstract Session

Session Time: 2:30PM-4:00PM

Background/Purpose:

Genetic factors provide over 90% of the overall susceptibility to ankylosing spondylitis (AS) and recent studies have focused on non-major histocompatibility complex genes. The etiology of uveitis in AS has been suggested to involve two adhesion molecules including intercellular adhesion molecule (ICAM)-1 and leukocyte functional antigen (LFA)-1.

Platelet-endothelial cell adhesion molecule 1 (PECAM1) is a member of the immunoglobulin superfamily which is expressed on endothelial cells. There is emerging evidence that PECAM1 may be an important regulator of activation of lymphocytes. The β1 integrin (ITGB1) can associate with different membrane proteins and cause signal transduction by interactions in the extracellular and trans-membrane domain. Therefore, we examined the association of PECAM1 and ITGB1 gene polymorphisms with development of uveitis in patients with AS.

Methods:

We conducted a case–control study where 223 AS patients who met the Modified New York criteria and 239 ethnically matched controls were genotyped for 9 single nucleotide polymorphisms (SNPs) in the PECAM-1 promoter and gene. Genomic DNA was isolated from peripheral blood leukocytes by a standard phenol–chloroform method and a GoldenGate assay (Illumina, http://www.illumina.com) was used for genotyping.

Results:

Conditional logistic regression was used to evaluate the association between the PECAM1 or ITGB1 SNPs with susceptibility to AS, and no significant association was found on both genes. However, in the subgroup analyses between AS patients with uveitis and those without, seven SNPs in PECAM1 gene were associated with the presence of uveitis, including rs1050382 (dominant model (DM), p=0.022), rs2812 (recessive model (RM), p=0.013), rs4968721 (DM, p=0.016), rs6808 (DM, p=0.011), rs6809 (DM, p=0.013), rs9899806 (DM, p=0.013) and rs9913080

(DM, p=0.019). In addition, seven polymorphisms in ITGB1 gene including rs11009147 (DM, p=0.012; co-dominant model (CDM), p=0.034), rs17468 (DM, p=0.012; CDM, p= 0.019), rs2153875 (CDM, p= 0.030), rs2230396 (DM, p=0.012), rs2488330 (DM, p=0.004), rs3780871 (DM, p=0.031) and rs7079624 (RM, p=0.004) were associated with uveitis development.

Conclusion:

This is the first analysis of the PECAM1 and ITGB1 gene polymorphisms in AS, demonstrating a clear association with uveitis in AS. Larger studies are warranted to elucidate the association of PECAM-1 and ITGB1 in the pathogenesis of uveitis in AS.

Table 1. Logistic analysis of PECAM1 polymorphisms and the risk of uveitis among AS patients

rs No.	Dominant Model		Recessive Model		Co-dominant Model	
	Odds (95% CI)	P.Value (adj.P.)	Odds (95% CI)	P.Value (adj.P.)	Odds (95% CI)	P.Value (adj.P.)
rs1050382	2.170 (1.116-4.219)	0.022 (0.027)	0.456 (0.129-1.611)	0.223 (0.262)	1.314 (0.824-2.095)	0.250 (0.294)
rs11079538	1.623 (0.745-3.537)	0.222 (0.261)	1.289 (0.568-2.924)	0.543 (0.571)	1.345 (0.821-2.202)	0.238 (0.297)
rs2812	2.190 (0.620-7.736)	0.223 (0.247)	0.424 (0.215-0.837)	0.013 (0.024)	0.732 (0.457-1.173)	0.195 (0.300)
rs4968721	2.302 (1.167-4.541)	0.016 (0.022)	0.412 (0.117-1.446)	0.166 (0.237)	1.304 (0.820-2.075)	0.261 (0.290)
rs6808	2.406 (1.220-4.743)	0.011 (0.020)	0.456 (0.129-1.611)	0.223 (0.278)	1.379 (0.862-2.205)	0.178 (0.298)
rs6809	2.354 (1.193-4.641)	0.013 (0.020)	0.456 (0.129-1.611)	0.223 (0.297)	1.364 (0.852-2.184)	0.195 (0.279)
rs8065316	1.124 (0.490-2.578)	0.781 (0.822)	1.774 (0.908-3.468)	0.093 (0.155)	1.360 (0.848-2.180)	0.201 (0.268)
rs9899806	2.354 (1.193-4.641)	0.013 (0.022)	0.509 (0.143-1.813)	0.297 (0.330)	1.414 (0.876-2.283)	0.155 (0.282)
rs9913080	2.252 (1.141-4.443)	0.019 (0.025)	0.392 (0.112-1.373)	0.143 (0.220)	1.270 (0.800-2.016)	0.310 (0.326)

Table 2. Logistic analysis of ITGB1 polymorphisms and the risk of uveitis among AS patients

rs number	Dominant Model		Recessive Model		Co-dominant Model	
	Odds (95% CI)	P.Value (adj.P.)	Odds (95% CI)	P.Value (adj.P.)	Odds (95% CI)	P.Value (adj.P.)
rs11009147	0.436 (0.226-0.839)	0.012 (0.021)	0.712 (0.273-1.858)	0.488 (0.596)	0.582 (0.353-0.960)	0.034 (0.046)
rs1187078	0.873 (0.261-2.921)	0.826 (0.865)	0.919 (0.486-1.737)	0.796 (0.834)	0.926 (0.560-1.532)	0.767 (0.804)
rs17468	0.436 (0.226-0.839)	0.012 (0.019)	0.563 (0.249-1.272)	0.167 (0.245)	0.589 (0.377-0.918)	0.019 (0.030)
rs2153875	0.527 (0.249-1.117)	0.094 (0.122)	0.465 (0.202-1.071)	0.072 (0.113)	0.582 (0.356-0.949)	0.030 (0.044)
rs2230396	0.436 (0.226-0.839)	0.012 (0.020)	0.712 (0.273-1.858)	0.488 (0.565)	0.582 (0.353-0.960)	0.034 (0.044)
rs2298141	1.340 (0.702-2.559)	0.374 (0.457)	3.718 (1.126-12.28)	0.031 (0.052)	1.508 (0.906-2.511)	0.113 (0.131)
rs2488330	0.390 (0.203-0.748)	0.004 (0.008)	0.712 (0.273-1.858)	0.488 (0.631)	0.546 (0.330-0.901)	0.017 (0.032)
rs2503997	1.278 (0.659-2.477)	0.466 (0.540)	1.308 (0.586-2.920)	0.511 (0.562)	1.205 (0.778-1.865)	0.401 (0.441)
rs3780871	0.268 (0.081-0.888)	0.031 (0.042)	0.745 (0.390-1.424)	0.374 (0.514)	0.662 (0.398-1.103)	0.113 (0.139)
rs7079624	1.403 (0.538-3.662)	0.488 (0.536)	2.560 (1.335-4.909)	0.004 (0.008)	1.830 (1.109-3.021)	0.017 (0.030)

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Abstract Number: 981

Anti-IL-17A Treatment Blocks Inflammation, Destruction and New Bone Formation in Experimental Spondyloarthritis in HLA-B27 Transgenic Rats

Melissa van Tok[1,2], Leonie van Duivenvoorde[1,3], Ina Kramer[4], Peter Ingold[4], Joel Taurog[5], Frank Kolbinger[4] and Dominique Baeten[1,2], [1]Amsterdam Rheumatology and Immunology Center, Amsterdam, Netherlands, [2]Department of Clinical Immunology and Rheumatology and Department of Experimental Immunology, Academic Medical Centre/University of Amsterdam, Amsterdam, Netherlands, [3]Experimental Immunology, Department of Clinical Immunology and Rheumatology and Department of Experimental Immunology, Academic Medical Centre/University of Amsterdam, Amsterdam, Netherlands, [4]Novartis Institutes for Biomedical Research, Basel, Switzerland, [5]Internal Medicine, Rheumatic Diseases Division, UT Southwestern Medical Center, Dallas, TX

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Session Type: ACR Concurrent Abstract Session

Session Time: 2:30PM-4:00PM

Background/Purpose:

The IL-17 axis has been identified as a crucial pathophysiological pathway in spondyloarthritis (SpA). Targeting the IL-17 axis significantly suppressed inflammation and halted bone and cartilage destruction in clinical trials with secukinumab (anti-IL17A), brodalumab (anti-IL17RA),

and ustekinumab (anti-IL23/IL12p40) in ankylosing spondylitis and psoriatic arthritis. The potential impact of IL-17A inhibition on new bone formation, the major form of structural damage in SpA, remains unknown. Assessment of this feature requires large patient numbers treated for an extended period and appropriate control groups. Therefore, we aimed to assess the impact of anti-IL17A on new bone formation in a validated animal model of SpA.

Methods:

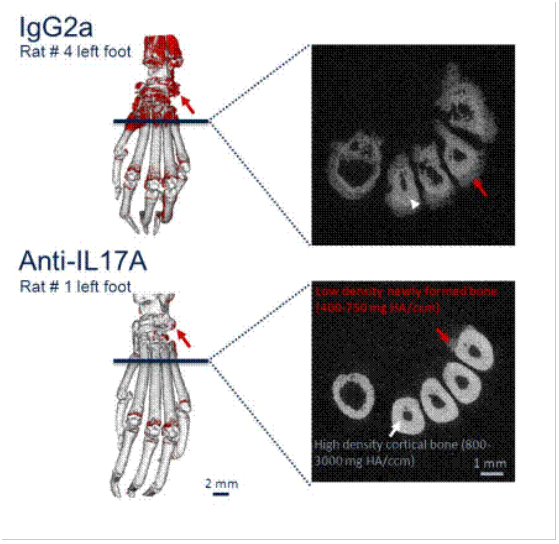
6 weeks old, orchiectomized, HLA-B27/huβ2m tg rats (23-1x283-2) were immunized with 45 µg heat-inactivated *M. tuberculosis*/IFA. Before the start of clinical symptoms, rats (n=6/group) were treated weekly with an anti-mouse/rat IL-17A antibody or IgG2a isotype control at 15mg/kg i.p for 5 weeks. Clinical measurements included weight, clinical scores for spondylitis and arthritis, and hind limb swelling (plethysmometry). After 6 weeks, rats were sacrificed for skeletal analysis by mCT imaging and histology.

Results:

In the control group, spondylitis and arthritis were observed in 100% of the rats at day 31 and day 19, respectively, after immunization. In contrast, only 83% and 33% of the anti-IL-17A treated rats developed spondylitis and arthritis at these time points. There was also a significant delay in the mean appearance of spondylitis (day 28 vs day 14; $p<0.05$) and arthritis (day 27 vs day 14; $p<0.05$) in treated versus control animals. Arthritis severity was lower in the anti-IL-17A-treated group compared to the controls, both by clinical scoring ($p<0.05$) and by plethysmometry ($p<0.05$). Quantitative analysis of structural damage by mCT of foot and ankle joints (figure 1) showed a significantly higher total bone volume in anti-IL-17A treated rats compared to controls (17% more, $p<0.05$), suggesting decreased bone loss. Moreover, the total volume of low density bone, reflecting newly formed bone, was significantly lower in the anti-IL-17A treated rats than in controls ($p<0.05$). Histological analysis confirmed a significant difference in structural damage in the peripheral joints, especially with respect to periosteal new bone formation, which was significantly less after anti-IL-17A treatment ($p<0.01$). In the axial joints there was a tendency towards less inflammation, destruction and new bone formation in the anti-IL-17A treated rats.

Conclusion:

IL-17A blockade significantly suppressed spondylitis and arthritis in the *M. tub*-induced diseased HLA-B27 tg rat model of SpA. Moreover, mCT data and histology indicated that IL-17A blockade also impacts structural damage, including pathological new bone formation.



Disclosure: M. van Tok, None; **L. van Duivenvoorde**, None; **I. Kramer**, Novartis Pharmaceutical Corporation, 3; **P. Ingold**, Novartis Pharmaceutical Corporation, 3; **J. Taurog**, None; **F. Kolbinger**, Novartis Pharmaceutical Corporation, 3; **D. Baeten**, Boehringer Ingelheim, Janssen, MSD, Novartis, Pfizer, 2,AbbVie, Boehringer Ingelheim, BMS, Eli Lilly, Janssen, MSD, Novartis, Pfizer, Roche, UCB, 5.

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Abstract Number: 982

CD4+CD146+ T Cells: The Primed IL-17 Secreting Cells in the Pathogenesis of Psoriatic Arthritis

Siba Raychaudhuri[1] and Smriti K. Raychaudhuri[2], [1]Med/Rheumatology, Univ California Davis/VA Sacramento, Davis, CA,

[2]Rheumatology/Immunology, VA Sacramento Medical Center, Davis, CA
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Session Type: ACR Concurrent Abstract Session

Session Time: 2:30PM-4:00PM

Background/Purpose: CD146, also called melanoma cell adhesion molecule (MCAM), is a cell surface adhesion molecule. A small minority of the T cell population also express MCAM. The ligand for MCAM is laminin 411. T cells expressing MCAM, are mainly responsible for IL17 production ex vivo. Furthermore, MCAM enriches for cells secreting IL-22 and IFN-γ. Thus, T cells expressing MCAM are uniquely capable of producing multiple cytokines responsible for psoriatic pathogenesis. Currently, CD4+ T cells with the capacity to secrete IL-17 (Th17 cells) have been viewed as a primary driver for psoriatic arthritis (PsA) and psoriasis; there are role for Th1 (IFN-γ) and Th22 (IL-22) T cells also. Thus it is likely that these pathologic CD4+T cells of psoriatic disease need to express CD146 for migration and localization at the disease site. Circulating CD146+ T cells have been reported to be elevated in several inflammatory diseases including in psoriasis; whether these cells play a role at the disease site of active inflammation in psoriatic arthritis remains unknown. **We hypothesized** that, in PsA, the synovial fluid and synovial tissue will be enriched with CD3+CD146+ T cells.

Methods: We studied synovial fluid mononuclear cells (SFMC), synovial tissues and psoriasis plaques from PsA (n=10) patients and have used osteoarthritis (OA) patients (n=10) as controls. Hi-D FACS studies were done to identify CD4+CD146+ and CD8+CD146+ T cells in the synovial fluid and PBMC of PsA patients. Double labeled IF study was done in synovial tissues from PsA patients and psoriasis plaques to identify CD3+CD146+ T cells.

Results: PsA patients showed significantly more CD4+CD146+ T cells in PBMC compared to OA (8 ± 2.8% vs 3.96 ± 0.6% respectively, p <0.01). Also SF of PsA had a significant higher level of CD4+CD146+ T cells (18 ± 3.1%; p <0.01) compared to PBMC. CD8+CD146+ T cells in PBMC and SFMC of PsA patients were <1%; CD146+ T cells were not identifiable in the SF of OA. CD146+ T cells were abundant within the psoriasis plaques and PsA synovial tissues and rare in non-lesional psoriatic skin.

Conclusion: 1. Here we observed that CD4+CD146+ T cells are enriched at the site of synovial inflammation in PsA (Fig 1). As CD146+ T cells are the primary source of the lesional Th-17 cytokines it is likely enrichment of these pathologic cells are critical for the disease process of PsA. 2. Also this opens up a new avenue for therapy of PsA and other autoimmune diseases. Rather than targeting individual cytokines, which often have redundant effects, targeting MCAM provides the possibility of the inhibiting the pathogenic cell itself, regardless of whether that cell is Th1, Th22 or Th17.

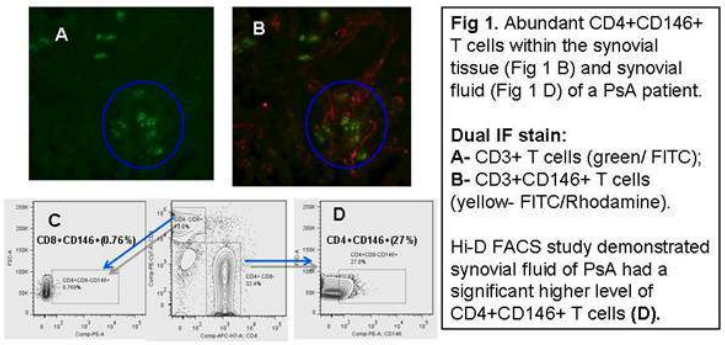

Fig 1. Abundant CD4+CD146+ T cells within the synovial tissue (Fig 1 B) and synovial fluid (Fig 1 D) of a PsA patient.

Dual IF stain:
A- CD3+ T cells (green/ FITC);
B- CD3+CD146+ T cells (yellow- FITC/Rhodamine).

Hi-D FACS study demonstrated synovial fluid of PsA had a significant higher level of CD4+CD146+ T cells **(D).**

Disclosure: S. Raychaudhuri, None; **S. K. Raychaudhuri**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/cd4cd146-t-cells-the-primed-il-17-secreting-cells-in-the-pathogenesis-of-psoriatic-arthritis

Abstract Number: 983

ERAP1 Deficiency Protects HLA-B27 Transgenic Rats from Arthritis

Tri M. Tran[1], Sohee Hong[2], Tejpal Gill[1], Joshua Bennett[1], Keith Sikora[1] and Robert A. Colbert[3], [1]NIAMS/NIH, Bethesda, MD, [2]Bldg 10 Crc

10 Center Dr, NIAMS/NIH, Bethesda, MD, [3]National Institute of Arthritis and Musculoskeletal and Skin Diseases, National Institutes of Health, Bethesda, MD

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Background/Purpose: HLA-B27 (B27) confers a strong predisposition to spondyloarthritis (SpA), but accounts for < 25% of overall heritability of ankylosing spondylitis. Rats transgenic for HLA-B27 and human beta-2-microglobulin (B27-TG) develop SpA-like disease with gut inflammation and arthritis. Common variants in ERAP1, which trims peptide cargo for HLA class I molecules in the ER, have been associated with SpA in B27(+) and some B27(-) individuals, although the influence on heritability is much smaller than for B27. Protective variants have been associated with lower enzymatic activity and lower expression of ERAP1, although analysis of entire allotypes suggests that many AS patients express very active variants. The objective of this study is to determine how ERAP1 loss-of-function affects SpA-like disease in rats.

Methods: The first exon of the rat ERAP1 gene was edited using TALEN technology (Transposagen) causing a deletion of 29-nucleotides. The resulting frame-shift results in 3 in-frame stop codons in the first exon. ERAP1 protein expression was assessed by Western blotting, which revealed complete lack of detectable protein in ERAP1-/-, and about 50% expression in ERAP1+/- rats. ERAP1-/- or ERAP1+/- Sprague-Dawley (SD) rats (disease permissive background) were crossed with B27-TG Lewis rats to generate cohorts of B27-TG with ERAP1+/+, ERAP1+/-, and ERAP1-/- genotypes. B7-TG rats and WT rats with ERAP1+/+, +/- or -/- were used as controls. Rats were observed for arthritis, fecal scores and other disease manifestations for up to 6 months of age. Gut inflammation was accessed by histology score of gut collected from 2, 4 and 6 months old rats.

Results: B27+ males with either ERAP1+/+ or ERAP1+/- genotype developed arthritis with a frequency of 29% (5/17), and 36% (8/22), respectively, with comparable arthritis severity scores (2.0) and age of onset (4.1 months), whereas only 6.7% (1/15) of rats with an ERAP1-/- genotype developed arthritis (P=0.02). Only 13.4% of B27+ERAP1+/- females developed arthritis with arthritis score of 1.25, while ERAP1+/+ and ERAP1-/- females remained healthy. Furthermore, B7-TG and WT rats were healthy regardless of the ERAP1 genotype, except one WT ERAP1+/- male that developed arthritis. All B27+ rats developed gut inflammation as assessed by histology, with increased fecal scores, in animals that were ERAP1+/- or ERAP1-/- with an increase in frequency (i.e. 3/16 (19%) for ERAP1+/+, 6/16 (38%) for ERAP1+/-, and 3/9 (33%) for ERAP1-/-), and histology scores were slightly higher in the complete absence of ERAP1 .

Conclusion: Complete absence of ERAP1 protected B27-TG rats from arthritis, but led to an increase in gut inflammation, suggesting different effects on pathogenic mechanisms involved in arthritis and colitis. B27-TG rats heterologous for ERAP1 exhibited higher incidence of arthritis concomitant with lower inflammation in the gut as compared to ERAP1-/- .This novel model provides an opportunity to better understand the mechanism(s) by which HLA-B27 contributes to SpA pathogenesis

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Disclosure: T. M. Tran, None; **S. Hong**, None; **T. Gill**, None; **J. Bennett**, None; **K. Sikora**, None; **R. A. Colbert**, None.

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Abstract Number: 984

Tofacitinib Inhibits Inflammation and New Bone Formation in Murine Spondyloarthritis but Does Not Adversely Inhibit Normal Human MSC Function

Rik Lories[1], Katelijne De Wilde[2], Kerri Heritage[1], Richard Cuthbert[3], Elena Jones[3], Karlijn Debusschere[4], Dennis McGonagle[3] and **Dirk Elewaut**[5], [1]Laboratory of Tissue Homeostasis and Disease, Skeletal Biology and Engineering Research Center, KU Leuven and University Hospitals Leuven., Leuven, Belgium, [2]Laboratory for Molecular Immunology and Inflammation; Department of Rheumatology,, VIB, Ghent University and Ghent University Hospital, Ghent, Belgium, [3]Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds, Leeds, United Kingdom, [4]Laboratory for Molecular Immunology and Inflammation; Department of Rheumatology, VIB, Ghent University and Ghent University Hospital, Ghent, Belgium, [5]Laboratory for Molecular Immunology and Inflammation, Department of Rheumatology, VIB, Ghent University and Ghent University Hospital, Ghent, Belgium

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Background/Purpose:

Inflammation and new bone formation at entheseal sites are hallmarks of spondyloarthritis (SpA). As TNF inhibition has only limited impact on new bone formation, there is a clear need for new SpA targets.

Objectives: To assess the role of JAK-STAT inhibition in *in vitro* and *in vivo* models that mimic specific SpA aspects with special emphasis on entheseal inflammation and new bone formation.

Methods:

Mice with a specific deletion of A20 (inhibitor of the NF-kB signaling pathway) in myeloid cells ($A20^{myelKO}$) were administered tofacitinib twice a day for 14 days in one experiment and for 21 days in a second experiment. They were scored clinically and afterwards sacrificed for histopathological analysis. Reporter assays with STAT- and NF-kB dependent reporters were conducted in presence or absence of A20. Synovial fibroblasts of A20 deficient mice were stimulated with TNF and the ability of tofacitinib to modulate release of a number of proinflammatory mediators including IL-6, MMP-3, MMP-13 was monitored. Entheseal inflammation, cell proliferation and new bone formation leading to joint ankylosis was studied in the spontaneous arthritis model in aging male DBA/1 mice. Mice were treated with tofacitinib at week 10 of age and continued for 14 weeks and evaluated for clinical signs of arthritis bi-weekly. In addition the effect tofacitinib on inflammation associated new bone formation was studied in the collagen-antibody induced arthritis(CAIA) model. pSTAT3 expression was determined in injured human entheses and the effect of tofacitinib was evaluated in normal human MSC induced osteogenesis.

Results:

We found that the earliest signs of inflammation in $A20^{myelKO}$ mice occur at the synovio-entheseal complex of the hindpaws with clear signs of enthesitis. In addition to its previously described role as negative regulator of NF-kB, we found an inhibitory role for A20 on Stat-1 induction. pSTAT3 expression was demonstrated by IHC at injured human entheses. We therefore assessed the role of JAK-STAT inhibition with tofacitinib and found a profound reduction of enthesitis by histopathology ($p<0.05$). In addition, tofacitinib completely suppressed TNF induced release of known proinflammatory mediators such as IL-6, MMP-13 and MMP-3. In the spontaneous ankylosing enthesitis model we noticed a steady increase in incidence and severity in the control group, but the incidence was delayed in the tofacinitib treated groups in a dose-dependent way. Severity of disease was significantly different with the high dosage of tofacitinib compared to control mice. Furthermore, we observed a significant effect of tofacitinb on the amount of new bone formation in the resolution phase collagen antibody induced arthritis ($p<0.05$). However, no adverse effect of tofocitinib was evident during in vitro MSC osteogenic differentiation.

Conclusion:

Our results highlight the potential of JAK-STAT inhibition to modulate inflammation and new bone formation in SpA. Interestingly, enthesitis occurring in $A20^{myelKO}$ mice proceeds independently from TNF, which highlights that the effects of JAK-STAT inhibition also occur beyond TNF.

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Abstract Number: 985

Improved Survival in Systemic Lupus Erythematosus: A Population-Based Study

Kateryna Vostretsova[1], Sharan K. Rai[2], Eric C. Sayre[3], Hyon K. Choi[4], JM Esdaile[5] and **J Antonio Avina-Zubieta**[6], [1]Rheumatology, Arthritis Research Centre, Vancouver, BC, Canada, [2]Experimental Medicine, University of British Columbia, Vancouver, BC, Canada, [3]Arthritis Research Canada, Richmond, BC, Canada, [4]Rheumatology, Allergy and Immunology, Massachusetts General Hospital, Harvard Medical School, Boston, MA, [5]Rheumatology, Arthritis Research Canada, Richmond, BC, Canada, [6]Medicine, University of British Columbia, Department of Medicine, Division of Rheumatology, Vancouver, BC, Canada

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Background/Purpose: Systemic Lupus Erythematosus (SLE) is associated with an increased risk of mortality. However, recent mortality trends of SLE are unknown, particularly at the general population level. Our objectives were to assess mortality trends among SLE patients between January 1, 1997 and December 31, 2012 in a general population context.

Methods: Using an administrative health database from the province of British-Columbia, Canada (4.5 million), we identified all incident cases of SLE and up to 10 (3 were selected) non-SLE controls matched on sex, age, and calendar year of study entry, between 1997 and 2012. The SLE cohort was then divided in two cohorts based on year of SLE diagnosis (i.e., 1997-2004 and 2005-2012) to evaluate changes in mortality. We calculated hazard ratios (HR) for death using Cox proportional hazard model and the rate difference using an additive hazard model, while additionally adjusting for possible confounders (i.e. Charlson Comorbidity Index, number of outpatient visits, hospitalization, cardiovascular medications, glucocorticoids and NSAIDs at baseline).

Results: The early cohort (1997-2004) SLE patients had a considerably higher mortality rate than the late cohort (2005-2012) (i.e., 67.33 cases vs. 25.98 cases per 1000 person-years), as compared with only a moderate improvement in comparison cohorts between the two periods (11.39 to 7.23 per 1000 person-years, respectively). The corresponding absolute mortality rate differences were 40.3 (95% CI 33.0, 47.7) and 6.4 (95%CI 2.9, 9.9) cases per 1000 person years (p-value for interaction <0.001). The corresponding adjusted HRs for mortality were 3.95 (95% CI, 3.24, 4.83) and 2.41 (95% CI, 2.01, 2.89), respectively (p for interaction = < 0.001).

Conclusion: This population-based study shows that survival of SLE patients has improved over the past decade, suggesting the new treatments and improved management of the disease and its complications may be providing substantial benefits.

Table 1: Incidence Rates and Hazard Ratios (HR) for Associations between SLE and Death According to Cohort

	SLE Status	N	Deaths	Mean Follow-up (years)	Incidence Rate (cases per 1000 person-years)	Age, Sex and Entry-Time Matched IRR (95% CI)	Fully Adjusted HR (95% CI)
Total	Yes	5,304	821	4.65	**33.28**	3.56 (3.23, 3.93)	**2.80 (2.49, 3.16)**
	No	15,912	836	5.63	9.34	1.00	1.00
Female	Yes	4,521	611	4.81	**28.11**	3.60 (3.21, 4.03)	2.77 (2.41, 3.18)
	No	13,563	603	5.69	7.82	1.00	1.00
Male	Yes	783	210	3.75	**71.52**	3.80 (3.14, 4.59)	2.95 (2.33, 3.75)
	No	2,349	233	5.27	18.84	1.00	1.00
1997-2004	Yes	1,656	334	3.00	**67.33**	5.91 (4.96, 7.06)	**3.95 (3.24-4.83)**
	No	5,022	209	3.65	11.39	1.00	1.00
2005-2012	Yes	3,630	287	3.04	**25.98**	3.59 (3.03, 4.26)	**2.41 (2.01-2.89)**
	No	10,890	262	3.33	7.23	1.00	1.00

Disclosure: K. Vostretsova, None; **S. K. Rai**, None; **E. C. Sayre**, None; **H. K. Choi**, None; **J. Esdaile**, None; **J. A. Avina-Zubieta**, None.

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Abstract Number: 986

Application of New EULAR Definitions of Remission in SLE: Durable 1-Year Remission Is Rare

Theresa Fischer[1], Laurence S Magder[2] and Michelle Petri[3], [1]Charité-Universitätsmedizin, Berlin, Germany, [2]University of Maryland School of Medicine, Baltimore, MD, [3]Rheumatology, Johns Hopkins University Hospital, Baltimore, MD

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Background/Purpose:

Developing definition(s) of remission in SLE is one of the primary recommendations on the research agenda of the treat-to-taget international task force. Definitions of remission were agreed upon by an international task force of the EULAR working group. We applied these definitions to a large clinical cohort to determine, time to remission, durability and predictors of remission.

Methods:

1555 patients with disease activity at cohort entry were followed until their first remission. 740 (48%) achieved remission. Of those who did not achieve remission, the median follow-up was 2.6 years. Remission was defined as clinical Systemic Lupus Disease Activity Index (SLEDAI) =

0, Physician Global Assessment (PGA) ² 0.5, prednisone ² 5 mg per day and no other immunosuppressants. Remission on treatment (ROT) was defined as SLEDAI = 0, PGA ² 0.5, prednisone ² 5 mg per day and allowance for immunosuppressive drugs. Hydroxychloroquine was allowed for remission and ROT. The Kaplan-Meier approach was used to estimate the time to remission. In addition, for patients on treatment, we identified variables that were predictive of remission at the next two visits.

Results:

Median time to remission was 2.8 years in women and 5.7 in men, median time to ROT was 1.3 years in women and 2.1 in men. Of those who satisfied the definition of remission, 52% had a relapse at a clinic visit within the next 90 days, and 15% more had a relapse from 90 to 180 days post remission (see table 1). Only 16% had a remission lasting over one year and only 2% over five years. Considering patients treated with immunosuppressives or prednisone greater than 5 mg/day at one visit, 2.8% successfully tapered treatment and achieved remission over the next two visits. Table 2 below shows rates of remission in various subgroups.

Conclusion:

50% of women and men with SLE achieve remission within 2.8 years and 5.7 years, respectively. However, most of them experience a relapse within the next 90 days. This reflects the relapsing-remitting nature of SLE for many patients. Remission and remisson on treatment are frequent in SLE. Durable remission is rare. Only 16% will have durability of more than one year. African-American ethnicity, anti-dsDNA and low complement predict against achieving remission. Our results provide further insights into the nature of remission in SLE and contribute towards applying the treat-to-target principle to SLE.

Table 1: Estimates of the distribution of duration of remission.

Duration of Remission	Probability
0-90 days	52%
90-180 days	15%
180-270 days	11%
270-365 days	6%
1-2 years	8%
2-5 years	6%
>5 years	2%

Table 2: Proportion of patients with treatment at one visit (i.e. immunosuppressives or prednisone greater than 5) who taper treatment at the next visit and satisfy the definition of remission at a third visit.

Variable	Proportion (%) achieving remission	Odds Ratio (95% CI)	P-value
All	696/24,871 (2.8%)		
Sex	641/22,541 (2.8%)	1.0 (Ref)	0.22
Female	55/2,330 (2.4%)	0.8 (0.6, 1.1)	
Male			
Race	365/10,620 (3.4%)	1.0 (Ref)	<0.0001
White	278/12,551 (2.2%)	0.6 (0.5, 0.8)	0.53
Black	53 (3.1%)	0.9 (0.6, 1.3)	
Other			
Education	82/3,507 (2.3%)	1.0 (Ref)	0.22
<High School	220/8,001 (2.8%)	1.2 (0.9, 1.7)	0.72
High School	160/6,538 (2.5%)	1.1 (0.7, 1.5)	0.021
Some College	234/6,825 (3.4%)	1.5 (1.1, 2.1)	
College Grad			
Low C3	535/17,103 (3.1%)	1.0 (Ref)	<0.0001
No	161/7,768 (2.1%)	0.7 (0.6, 0.8)	
Yes			
Low C4	574/18,854 (3.0%)	1.0 (Ref)	0.0001
No	122/6,017 (2.0%)	0.7 (0.6, 0.8)	
Yes			
Anti-dsDNA	498/15,711 (3.2%)	1.0 (Ref)	<0.0001
No	177/8,402 (2.1%)	0.7 (0.6, 0.8)	
Yes			

Disclosure: T. Fischer, None; **L. S. Magder**, None; **M. Petri**, None.

Abstract Number: 987

Pre-Emptive Renal Transplantation Among End Stage Renal Disease Patients with and without SLE

Anna R. Broder[1], Wenzhu Mowrey[2], Ladan Golestaneh[3], Mimi Kim[4], Karen H. Costenbader[5] and Chaim Putterman[6], [1]Rheumatology-Forchheimer 701N, Albert Einstein College of Medicine/Montefiore Medical Center, Bronx, NY, [2]Department of Epidemiology and Population Health/Division of Biostatistics, Albert Einstein College of Medicine, Bronx, NY, [3]Medicine/Nephrology, Albert Einstein College of Medicine, Bronx, NY, [4]Biostatistics and Research Design Resource, Albert Einstein Coll Med, Bronx, NY, [5]Rheumatology, Brigham & Women's Hospital, Boston, MA, [6]Division of Rheumatology, Albert Einstein College of Medicine, Bronx, NY

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Background/Purpose: Lack of evidence-based recommendations about pre-emptive renal transplantation in systemic lupus erythematosus (SLE) patients with end stage renal disease (ESRD) may be unnecessarily delaying transplantation in these patients. We compared rates and factors associated with pre-emptive transplantation between incident ESRD patients with and without SLE enrolled in the United States Renal Disease Systems (USRDS).

Methods: There were 561,038 individuals in the US with new onset ESRD of any cause between 1/1/2005 and 12/31/2009**.** Adult patients with incident ESRD SLE 2005-2009 were identified from the ICD-9 code 710.0 for SLE in the Medical Evidence report. They were frequency matched by age, sex and race to 4,830 patients with incident non-SLE ESRD (type 1 diabetes, type 2 diabetes, hypertension, and other causes). Pre-emptive transplantation was defined as the initial renal replacement modality without any intervening dialysis. Multivariable logistic regression models, adjusted for socio-demographic factors and comorbidities, were used to compare the odds of pre-emptive renal transplantation in SLE and non-SLE, and to evaluate associated factors in each group.

Results:

4,830 SLE subjects and 4,830 matched non-SLE subjects were included in the final analysis. SLE patients were less likely to have atherosclerotic heart disease, congestive heart failure (CHF), peripheral vascular disease (PVD), and chronic obstructive pulmonary disease (COPD). The proportions of patients with past cerebrovascular accidents (CVA) or transient ischemic attacks (TIA) were similar (p=0.12). SLE patients were more likely to be employed, and to have private insurance.

The overall adjusted odds ratio of pre-emptive transplantation were similar in SLE and non-SLE: OR = 0.85 (95% CI: 0.67, 1.01), p=0.2. However, when comparing specific non-SLE causes of ESRD to SLE, the adjusted OR for pre-emptive transplantation was 0.19 (95% CI: 0.09, 0.42) for type 2 diabetes, 0.42 (95% CI: 0.23, 0.75) for hypertension, 1.67 (95% CI: 1.10, 2.54) in type 1 diabetes, and 2.06 (95% CI: 1.55, 2.74) for “others” (Table). Over 70% of all pre-emptive transplants were form living donors. The rates of pre-emptive transplantation were significantly higher among patients with pre-ESRD nephrology care. In contrast to non-SLE, younger SLE patients were less likely to receive a pre-emptive kidney transplant.

Conclusion: The odds of pre-emptive transplantation vary by ESRD cause. Improving pre-ESRD nephrology care and access to living donor transplants, as well as addressing disease-specific barriers to pre-emptive transplantation, may increase a likelihood of pre-emptive transplantation.

Table: Adjusted Odds Ratios (OR) and 95% Confidence Intervals (95%CI) from the Logistic Regression Model for Pre-emptive Transplantation among ESRD patients with and without SLE.

Variable	OR	OR 95% CI		P value
Primary cause of ESRD				
SLE	1.00			
Type 1 diabetes	1.67	1.10	2.54	0.02
Type 2 diabetes	0.19	0.09	0.42	<.0001
Hypertension	0.42	0.23	0.75	0.003
Other	2.06	1.55	2.74	<.0001
Age at ESRD onset, per year increase	1.00	0.99	1.01	0.76
Sex				
Men	1.00			
Women	1.38	1.00	1.89	0.05
Race				
White	1.00			
Asian	0.45	0.27	0.76	0.003
Black	0.18	0.13	0.24	<.0001
BMI				
Normal weight	1.00			
Obese	0.96	0.71	1.31	0.80
Overweight	1.44	1.08	1.91	0.01
Underweight	1.44	0.82	2.52	0.20
Comorbidities				
Atherosclerotic heart disease	0.26	0.08	0.84	0.02
Cancer	0.20	0.06	0.66	0.008
CHF	0.06	0.01	0.24	<.0001
COPD	0.73	0.22	2.48	0.62
CVA/TIA	1.40	0.76	2.58	0.28
Diabetes	0.57	0.31	1.04	0.07
Drug abuse	0.47	0.06	3.61	0.47
Hypertension	0.75	0.56	1.00	0.049
Inambulatory	0.28	0.10	0.78	0.01
PVD	0.59	0.21	1.66	0.31
Smoking	0.51	0.23	1.12	0.09
Insurance				
Private	1.00			
Medicare/Medicaid	0.36	0.27	0.50	<.0001
None	0.15	0.07	0.30	<.0001
Other	0.84	0.56	1.25	0.39
Employment				
Employed	1.00			
retired	0.59	0.43	0.81	0.001
Student	0.78	0.45	1.33	0.36
Unemployed	0.44	0.32	0.61	<.0001
Geographic region				
Northeast	1.00			
Midwest	0.78	0.55	1.11	0.17
South	0.59	0.42	0.82	0.001
West	0.50	0.35	0.71	0.0001

Abstract Number: 988

Factors Associated with Renal Remission, Relapse and Long-Term Renal Function Decline in Lupus Nephritis Treated with Combined Prednisolone and Mycophenolate Mofetil (MMF) or Tacrolimus (Tac)

Chi Chiu Mok[1], Ling Yin Ho[2], Chi Hung To[3] and Kar Li Chan[1], [1]Medicine, Tuen Mun Hospital, Hong Kong, Hong Kong, [2]Dept of Medicine,

Tuen Mun Hospital, Hong Kong SAR, Hong Kong, [3]Medicine, Pok Oi Hospital, Hong Kong, Hong Kong
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SESSION INFORMATION

Session Date: Sunday, November 8, 2015

Session Title: Systemic Lupus Erythematosus - Clinical Aspects and Treatment I: Epidemiology and Prognosis

Session Type: ACR Concurrent Abstract Session

Session Time: 2:30PM-4:00PM

Background/Purpose:

To study the factors associated with renal remission, relapse and renal function decline in patients with lupus nephritis treated with combined steroid and MMF or Tac.

Methods:

Data were extracted from a RCT of the efficacy of MMF vs Tac for induction treatment of lupus nephritis. All patients recruited were treated with high-dose prednisolone with either MMF (2-3g/day) or Tac (0.1-0.06mg/kg/day) for 6 months. Patients with good clinical response were shifted to azathioprine (AZA) for maintenance. Rescue therapies were given to patients who did not respond to induction. Factors associated with complete renal response (CR), relapse and renal function decline at 5 years were studied by regression analyses.

Results:

150 patients (92% women) with lupus nephritis were studied (Class III±V 36%; IVG/S±V 46; pure V 19%; age 35.5±12.8 years; SLE duration 50.2±62 months). At baseline, 59(39%) patients were hypertensive and 67% patients had CrCl <90ml/min. At 6m, 61% patients achieved CR, 24% had partial response (PR) but 15% patients had no response (NR). Logistic regression revealed that the baseline urine P/Cr ratio (OR 0.75[0.57-0.99]; p=0.04) and the presence of membranous feature on renal histology (OR 0.25[0.07-0.91]; p=0.04) were independently associated with CR at 6m. AZA maintenance was given to 59 (78%) MMF-treated (dose 82.5±24 mg/day) and 60 (81%) TAC-treated patients (dose 86.5±21 mg/day; p=0.32). Patients with NR were re-induced with CYC (N=20), low-dose combination of MMF and TAC (N=5), cross-over to TAC or MMF (N=6). After a follow-up of 60.8±26 months, proteinuric and nephritic renal flares occurred in 24% and 18% of patients treated initially with MMF and 35% and 27% in those treated with TAC, respectively. In patients who achieved CR or PR after initial treatment, Cox regression showed that the female sex (HR 10.9[1.19-101]; p=0.04), positive anti-dsDNA at month 6 (HR 4.95[1.64-14.9]; p=0.005) and the use of ACE inhibitor after 6 month (HR 8.86[1.28-61.2]; p=0.03) were independently associated with renal flares (proteinuric or nephritic). The cumulative incidence of a composite outcome of decline of CrCl by ≥30%, development of CKD stage 4/5 or death at 5 years was 21% in patients treated with MMF and 22% in those treated with TAC. Factors significantly associated with this outcome were first time lupus nephritis (HR 0.21[0.05-0.82]; p=0.03), creatinine clearance (CrCl) at 6 month (HR 0.97[0.95-0.99]; p=0.005) and the use of AZA maintenance (HR 0.23[0.49-4.30]; p=0.046). Repeat renal biopsy in 23 patients with renal flares showed that the increase in chronicity score was similar between the MMF (1.3±3.0) and TAC (1.8±2.0) groups of patients (p=0.42).

Conclusion:

Tac is non-inferior to MMF for induction therapy of lupus nephritis. More proteinuria at baseline and the presence of histological membranous features are unfavorably associated with good renal response after induction treatment. Female patients and persistent elevation of anti-dsDNA after induction therapy are associated with renal flares. Lower creatinine clearance at 6 months and the absence of AZA maintenance are associated with renal function deterioration after 5 years.

Disclosure: C. C. Mok, None; **L. Y. Ho**, None; **C. H. To**, None; **K. L. Chan**, None.

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Abstract Number: 989

Economic Evaluation of Lupus Nephritis in an International Inception Cohort: Comparing the Hospitalization, Medication, Dialysis, and Procedure Costs of Those with and without Nephritis

Megan Barber[1], John G. Hanly[2], Aidan O'Keeffe[3], Li Su[4], Murray Urowitz[5,6], Yvan St. Pierre[7], Juanita Romero-Diaz[8], C. Gordon[9], Sang-Cheol Bae[10], Sasha Bernatsky[11], Daniel J Wallace[12], Joan T. Merrill[13], David A. Isenberg[14], Anisur Rahman[15], Ellen M. Ginzler[16], Paul R. Fortin[17], Dafna D. Gladman[18], Jorge Sanchez-Guerrero[19], Michelle Petri[20], Ian N. Bruce[21], Mary Anne Dooley[22], Rosalind Ramsey-Goldman[23], Cynthia Aranow[24], Graciela S. Alarcon[25], W. Winn Chatham[26], Kristján Steinsson[27], Ola Nived[28], Gunnar K. Sturfelt[29], Susan Manzi[30], Munther Khamashta[31], Ronald F. van Vollenhoven[32], Asad Zoma[33], Manel Ramos-Casals[34], Guillermo Ruiz-Irastorza[35], S. Sam Lim[36], Thomas Stoll[37],

Murat Inanc[38], Kenneth C. Kalunian[39], Diane L. Kamen[40], Peter Maddison[41], Christine A. Peschken[42], Søren Jacobsen[43], Anca Askanase[44], Jill P. Buyon[45], Chris Theriault[46], Kara Thompson[46], Vernon Farewell[47] and **Ann E. Clarke**[48], [1]Division of Rheumatology, University of Calgary, Caglary, AB, Canada, [2]Rheumatology, Division of Rheumatology, Capital Health and Dalhousie University, Halifax, NS, Canada, [3]Statistical Science, University College London, London, United Kingdom, [4]MRC Biostatistics Unit, Institute of Public Health, University Forvie Site, Cambridge, UK, Cambridge, United Kingdom, [5]Rheumatology, University of Toronto, Toronto Western Hospital, Toronto, ON, Canada, [6]Rheumatology, U of Toronto, Toronto Western Hospital, Toronto, ON, Canada, [7]Clinical Epidemiology, Research Institute of the McGill University Health Centre, Montreal, QC, Canada, [8]Immunology and Rheumatology, Instituto Nacional de Ciencias Medicas y Nutrición, Mexico City, Mexico, [9]School of Immunity and Infection, College of Medical and Dental Sciences, University of Birmingham, Birmingham, United Kingdom, [10]Rheumatology, Hanyang University Hospital for Rheumatic Diseases, Seoul, South Korea, [11]Rheum/Clin. Epid., McGill MUHC/RVH, Montreal, QC, Canada, [12]Cedars-Sinai Medical Center, West Hollywood, CA, [13]Clinical Pharmacology, Oklahoma Medical Research Foundation, Oklahoma City, OK, [14]Rayne Institute, Centre for Rheumatology Research, UCL Division of Medicine, London, United Kingdom, [15]Centre for Rheumatology Research,Rayne Institute, 4th Floor, University College London, London, United Kingdom, [16]Medicine/Box 42, SUNY-Downstate, Brooklyn, NY, [17]Rheumatology, University of Laval, Quebec, QC, Canada, [18]Department of Medicine, Division of Rheumatology, University of Toronto, Toronto, ON, Canada, [19]Rheumatology, Toronto Western Hospital, Toronto, ON, Canada, [20]Division of Rheumatology, Johns Hopkins University, Baltimore, MD, [21]Stopford Building, Arthritis Research UK Centre for Epidemiology, Centre for Musculoskeletal Research, Institute of Inflammation and Repair, Manchester Academic Health Science Centre, The University of Manchester, Manchester, United Kingdom, [22]UNC Kidney Centre, Chapel Hill, NC, [23]Northwestern University Feinberg School of Medicine, Chicago, IL, [24]Feinstein Institute for Medical Research, Mahasset, NY, [25]Medicine, University of Alabama at Birmingham, Birmingham, AL, [26]Medicine/Clinical Immunology and Rheumatology, University of Alabama at Birmingham, Birmingham, AL, [27]Centre for Rheumatology Research, Landspital University Hospital, Reykjavik, Iceland, [28]Rheumatology, Inst of Clinical sciences, Lund, Sweden, [29]Department of Rheumatology, Univ Hospital Lund, Lund, Sweden, [30]Division of Rheumatology, University of Pittsburgh School of Medicine, Pittsburgh, PA, [31]Graham Hughes Lupus Research Laboratory, The Rayne Institute, St Thomas' Hospital, London, United Kingdom, [32]Department of Medicine, Unit for Clinical Therapy Research, Inflammatory Diseases (ClinTRID), The Karolinska Institute, Stockholm, Sweden, [33]Lanarkshire Centre for Rheumatology, Hairmyres Hospital, East Kilbride, United Kingdom, [34]Department of Autoimmune Diseases, ICMiD, Hospital Clínic, Sjögren Syndrome Research Group (AGAUR), Laboratory of Autoimmune Diseases Josep Font, Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Barcelona, Spain, [35]Autoimmune Disease Research Unit, Service of Internal Medicine, Hospital de Cruces, UPV/EHU, Barakaldo, Spain, [36]Emory University School of Medicine, Atlanta, GA, [37]Abteilung Rheumatologie/Rehab, Kantonsspital Schaffhausen, Schaffhausen, Switzerland, [38]Department of Internal Medicine, Division of Rheumatology, Istanbul University, Istanbul Faculty of Medicine, Istanbul, Turkey, [39]Division of Rheumatology, Allergy & Immunology, UCSD School of Medicine Center for Innovative Therapy, La Jolla, CA, [40]Medicine, Medical University of South Carolina, Charleston, SC, [41]Musculoskeletal Medicine, Bangor University, Bangor, United Kingdom, [42]Rheumatology, Univ of Manitoba, Winnipeg, MB, Canada, [43]Department of Rheumatology,, Copenhagen University Hospital, Rigshospitalet, Copenhagen, Denmark, [44]Columbia University College of Physicians & Surgeons, New York, NY, [45]Medicine, Division of Rheumatology, New York University School of Medicine, New York, NY, [46]Medicine, Queen Elizabeth II Health Sciences Centre and Dalhousie University, Halifax, NS, Canada, [47]Medicine, Division of Rheumatology, Capital Health and Dalhousie University, Halifax, NS, Canada, [48]Division of Rheumatology, University of Calgary, Calgary, AB, Canada

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SESSION INFORMATION

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Session Type: ACR Concurrent Abstract Session

Session Time: 2:30PM-4:00PM

Background/Purpose:

Little is known about the long-term costs of lupus nephritis (LN). The annual and long-term healthcare costs were compared between SLE patients with and without LN.

Methods:

Patients from 32 centres in 11 countries were enrolled in the Systemic Lupus International Collaborating Clinics (SLICC) inception cohort within 15 months of diagnosis and provided annual data on renal function, hospitalizations, dialysis, and utilization of medications and selected procedures. LN was diagnosed by renal biopsy or fulfillment of the American College of Rheumatology (ACR) SLE classification criteria renal item. Renal function was also assessed annually based on estimated glomerular filtration rate (eGFR) or proteinuria (ePrU). Annual health resource utilization was costed using 2012 Canadian prices. Annual costs associated with renal function states were obtained from multiple regressions adjusting for age, race/ethnicity, disease duration, SLICC centre location, SLEDAI-2K and SLICC/ACR Damage Index (excluding renal components), and the SF-36. 5-year cumulative costs were estimated by determining annual costs associated with each renal function state and then forecasting the expected duration in each state. Durations were estimated using a relative risk regression model.

Results:

1645 patients participated, 89.2% females, 48.8% Caucasian, mean age at diagnosis 34.8 years (SD 13.4), mean disease duration at enrollment 0.5 years (SD 0.3), and mean follow up 6.1 years (SD 3.3). LN was diagnosed in 39.4% over follow up. Health resource utilization and annual costs (after adjustment using regression) were markedly higher in those with an eGFR < 30 ml/min or with LN (Table 1).

Table 1. Predicted Annual Health Costs Stratified by State of Renal Function

eGFR		ePrU		Lupus Nephritis	
State	Costs, Mean 95% CI 2012 CDN$	State	Costs, Mean 95% CI 2012 CDN$	State	Costs, Mean 95% CI 2012 CDN$
eGFR >60 ml/min	2234 (1503, 2965)	ePrU< 0.25g/d	2247 (1406, 3088)	No Lupus Nephritis	1588 (726,2450)
eGFR 30-60ml/min	3014 (1636, 4392)	ePrU 0.25-3.0g/d	3424 (2287, 4561)	Lupus Nephritis	3876 (2949,4803)
eGFR < 30 ml/min	12551 (10301, 14801)	ePrU > 3.0 g/d	4703 (2128, 7278)		

5-year cumulative costs stratified by baseline renal function state were calculated by multiplying the annual costs associated with each state by the expected duration in that state (eGFR example in Table 2).

Table 2. Expected Duration in Each Renal State over 5 Years

		Expected Duration in each State over 5 years		
Baseline State	Annual Costs 2012 CDN$	eGFR >60 ml/min	eGFR 30-60 ml/min	eGFR < 30 ml/min
eGFR >60 ml/min	2234	4.74 yrs	0.22 yrs	0.04 yrs
eGFR 30-60 ml/min	3014	2.60 yrs	1.88 yrs	0.52 yrs
eGFR < 30 ml/min	12551	1.03 yrs	1.09 yrs	2.88 yrs

Five year cumulative costs were greater in those with severely impaired eGFR or with LN at baseline (Table 3).

Table 3. Predicted 5-Year Cumulative Health Costs Stratified by Baseline State of Renal Function

eGFR		ePrU		Lupus Nephritis	
Baseline State	Costs, Mean 95% CI 2012 CDN$	Baseline State	Costs, Mean 95% CI 2012 CDN$	Baseline State	Costs, Mean 95% CI 2012 CDN$
eGFR >60 ml/min	11763 (7904, 15622)	ePrU< 0.25 g/d	12070 (7594, 16547)	No Lupus Nephritis	8663 (4331, 12995)
eGFR 30-60 ml/min	18008 (12348, 23667)	ePrU 0.25-3.0 g/d	13834 (8758, 18909)	Lupus Nephritis	19380 (14745, 24015)
eGFR < 30 ml/min	41732 (32998, 50467)	ePrU > 3.0 g/d	15627 (9192, 22061)		

Conclusion:

Patients with an eGFR <30ml/min and LN incur higher annual and 5-year cumulative costs. By estimating the expected duration in each renal function state and incorporating associated annual costs, disease severity at presentation can be used to anticipate future healthcare costs, critical knowledge for cost effectiveness evaluations of novel LN therapies.

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Abstract Number: 990

Performance of the Systemic Lupus International Collaborating Clinic Classification Criteria Versus the 1982 and Revised 1997 American College of Rheumatology Classification Criteria for Systemic Lupus Erythematosus: A Population-Based Study

Patompong Ungprasert[1], Cynthia S. Crowson[2] and Vaidehi Chowdhary[1], [1]Rheumatology, Mayo Clinic, Rochester, MN, [2]Health Sciences Research, Mayo Clinic, Rochester, MN

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Session Title: Systemic Lupus Erythematosus - Clinical Aspects and Treatment I: Epidemiology and Prognosis

Session Type: ACR Concurrent Abstract Session

Session Time: 2:30PM-4:00PM

Background/Purpose: Systemic lupus erythematosus (SLE) is an autoimmune disease with heterogeneous presentations. Therefore, classification criteria are required to help improve diagnostic accuracy in clinical practice and particularly in research. This study aimed to compare the performance of 1982 and revised 1997 ACR classification criteria to the newer 2012 SLICC classification criteria.

Methods: Potential cases of incident SLE from 1993 to 2005 in a predominantly Caucasian, geographically well-defined population were identified from the health-care network diagnostic codes. Comprehensive individual medical record review was performed to determine the presence or absence of the ACR and SLICC criteria. An incident case of SLE was defined as an individual who fulfilled at least 4 out of 11, 1982 or revised 1997 ACR criteria or met at least 4 SLICC criteria (with at least 1 clinical and 1 laboratory criteria) or had biopsy-proven lupus nephritis with positive ANA or ds-DNA and had been a resident for at least 1 year prior to the first physician diagnosis of SLE. Cases with isolated cutaneous lupus, drug-induced lupus and overlapping diseases were excluded. Overall incidence was age- and sex-adjusted to the 2000 US white population.

Results: There were 59 incident cases who fulfilled the SLICC criteria, corresponding to the adjusted incidence of 3.8 per 100,000 population (95% CI, 2.8 – 4.8). The incidence was significantly higher than that of the 1982 (45 cases; 2.9 per 100,000 population; p=0.004) and revised 1997 ACR criteria (46 cases; 2.9 per 100,000 population; p=0.046). The average age of 42.8 +/- 18.6 years in the SLICC cohort was not significantly different compared to 40.9 +/- 18.0 years in the 1982 ACR cohort and 41.1 +/- 17.9 years in the revised 1997 ACR cohort (p=0.11). Arthritis (56%), followed by acute cutaneous lupus (46%), renal involvement (25%) and serositis (24%) were the most frequently observed clinical criteria while positive ANA (93%), followed by positive ds-DNA (63%) and hypocomplementemia (36% for C3, 42% for C4 and 22% for total complement) were the most common immunologic criteria. Three cases were diagnosed based on renal biopsy and positive ANA or ds-DNA without fulfilling 4 out of 17 SLICC criteria.

Conclusion: The 2012 SLICC classification criteria may be more sensitive than the 1982 and revised 1997 ACR classification criteria in

identifying patients with SLE at population level.

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Abstract Number: 991

CaMK4 Facilitates Recruitment of IL-17 Producing Cells to Target Organs through the CCR6/CCL20 Axis in Th17-Driven Inflammatory Diseases

Tomohiro Koga[1,2], Kotaro Otomo[3], Masayuki Mizui[2], Nobuya Yoshida[4], José C. Crispin[2], Atsushi Kawakami[5] and George C. Tsokos[4], [1]Department of Immunology and Rheumatology, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan, [2]Medicine/Rheumatology, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, [3]Rheumatology, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, [4]Division of Rheumatology, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, [5]Department of Immunology and Rheumatology, Nagasaki University, Nagasaki, Japan

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SESSION INFORMATION

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Session Title: T cell Biology and Targets in Autoimmune Disease I

Session Type: ACR Concurrent Abstract Session

Session Time: 2:30PM-4:00PM

Background/Purpose:

The recruitment of IL-17 producing T helper (Th17) cells to the inflammatory sites has been implicated in the development of organ damage in inflammatory and autoimmune diseases. We have previously reported that IL-17 is important in the expression of anti-glomerular basement membrane Ab-induced glomerulonephritis (AIGN) (1). We have also shown that the blockage of Calcium/calmodulin-dependent protein kinase IV (CaMK4) ameliorates experimental autoimmune encephalomyelitis (EAE) and autoimmunity in lupus-prone mice (2). We have hypothesized that CaMK4 activation facilitates Th17 cells recruitment to target tissues in inflammatory settings through chemokines.

Methods:

To determine the role of CaMK4 in the infiltration of inflammatory cells to target tissues, we induced experimental AIGN in *Camk4*-sufficient or -deficient mice and compared the kidney injury, including Th17 related chemokine expressions, and the number of IL-17 producing cells in both groups. We also evaluated the efficacy of KN-93, a CaMK4 antagonist in this AIGN model. In addition, we investigated the effect of CaMK4 on the expression of CCR6 in memory CD4 T cells.

Results:

Camk4 deficient mice displayed less glomerular injury and less proteinuria at day 21 after induction of AIGN (Figure 1). Although there is no significant difference in the percentage of IL-17 producing T cells in the spleen or lymph nodes, kidney infiltration by IL-17 producing CD4 T cells along with CCR6 and CCL20 expression were decreased significantly in *Camk4* deficient mice. This observation implies that CaMK4 facilitates AIGN damage by promoting local inflammatory Th17 cells accumulation through the CCR6/CCL20 axis. In line with these observations, KN-93 treatment of mice prior to exposure to AIGN improved clinical and pathological finings in a dose-dependent manner. Finally, the expression of CCR6 in memory CD4 T cells in the peripheral blood was decreased among *Camk4* deficient mice.

Conclusion:

Collectively our results indicate that CaMK4 inhibition represents a novel therapeutic strategy for the treatment of Th17 cells-mediated tissue damage in inflammatory diseases.

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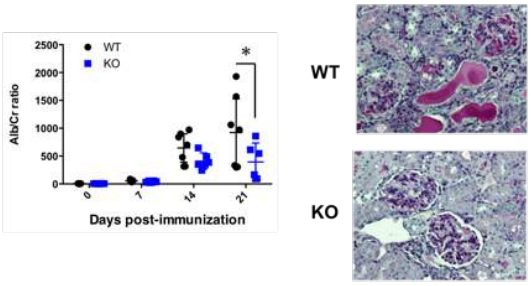

Figure 1. CaMK4 deficiency ameliorates AIGN

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Abstract Number: 992

Therapeutic Targeting of CD4+ T Cell Metabolism in Murine Models of Lupus

Laurence Morel[1], Seung-Chul Choi[2], Zhiwei Xu[2], Elisabeth Adkins[3], Byron Croker[2] and Derry Roopenian[3], [1]Pathology, Immunology, and Laboratory Medicine, University of Florida, Gainesville, FL, [2]University of Florida, Gainesville, FL, [3]The Jackson Laboratory, Bar Harbor, ME

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SESSION INFORMATION

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Session Title: T cell Biology and Targets in Autoimmune Disease I

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Session Time: 2:30PM-4:00PM

Background/Purpose: Cellular metabolism controls T cell functions, with TCR-mediated activation enhancing metabolism, and substrate utilization modulating effector functions. Autoreactive CD4 T cells are key effectors in lupus by providing help to B cells to produce high-affinity class-switched autoantibodies. We have previously shown that CD4 T cells from B6.*Sle1.Sle2.Sle3* (TC) and BWF1 lupus-prone mice, as well as from lupus patients, have an elevated mitochondrial oxidation (OXPHOS) and glycolysis. A combination of metformin and 2DG, two metabolic inhibitors which target OXPHOS and glucose metabolism, respectively, normalized the cellular metabolism of these T cells *in vitro*, and *in vivo*treatments reversed all disease phenotypes in TC and BWF1 mice. These two models are genetically related and their T cells are characterized by a high production of IFNγ. In this study, we investigated the efficacy of metabolic inhibitors in BXSB.Yaa mice, an unrelated model driven by type I Interferons.

Methods: Two month old TC or BXSB.Yaa mice were treated with yhree single metabolic inhibitors for 8 weeks (N = 10-22): metformin, 2DG, or dichloroacetate (DCA, an inhibitor of glycolysis) and compared to untreated controls (N = 27). T cell glycolysis and OXPHOS were measured with an extracellular fluid analyzer. Lymphocyte activation and effector subset distribution were measured by flow cytometry. Disease progression was assessed by ELISA and ANA staining for autoantibodies and histology for renal pathology. CD4 T cells from lupus mice and controls were polarized under Th1 conditions in the presence of metformin, 2DG, or DCA, and IFNγ production was measured by flow cytometry.

Results: CD4 T cells from BXSB.Yaa mice have a significantly higher glycolysis and OXPHOS than control mice. However, OXPHOS was significantly lower in BXSB.Yaa than in TC CD4 T cells, indicating a lower contribution of OXPHOS to BXSB.Yaa T cell metabolism. All 3 metabolic inhibitors significantly reduced renal pathology, the most effective being 2DG in both strains. DCA was more effective that metformin in BXSB.Yaa mice while the reverse was true in TC mice. All 3 metabolic inhibitors also reduced lymphoid expansion and T cell activation, with again 2DG having the greatest effect. 2DG and metformin, but not DCA prevented autoantibody production in TC mice. BXSB.Yaa autoantibody results are pending. *In vitro* Th1-polarized BXSB.Yaa CD4 T cells produced significantly more IFNγ than BXSB controls, but significantly less than TC CD4 T cells. Both 2DG and metformin decreased IFNγ production from polarized cells, but DCA, which increases pyruvate oxidation, also increased IFNγ production. This is consistent with their reduced OXPHOS, which supports which IFNγ production.

Conclusion: These results showed that inhibitors of glucose metabolism are effective in murine models in which lupus arise from different etiology. They suggest however that targeting mitochondrial oxidation may have better outcomes in IFNγ-driven disease while targeting glycolysis may be more effective type I IFN-driven disease. Further investigation of these models will lead to tailored pre-clinical models that target T cell metabolism for lupus treatment.

Disclosure: L. Morel, None; **S. C. Choi**, None; **Z. Xu**, None; **E. Adkins**, None; **B. Croker**, None; **D. Roopenian**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/therapeutic-targeting-of-cd4-t-cell-metabolism-in-murine-models-of-lupus

Abstract Number: 993

Failure in Nutrient Sensing Supports mTOR Hyperactivity and Proinflammatory Functions in T Cells from Patients with Rheumatoid Arthritis

Zhen Yang[1], Eric L. Matteson[2], Jison Hong[3], Jorg Goronzy[1] and Cornelia M. Weyand[4], [1]Medicine: Immunology and Rheumatology, Stanford University School of Medicine, Stanford, CA, [2]Division of Rheumatology, Department of Internal Medicine and Department of Health Sciences Research, Mayo Clinic, Rochester, MN, [3]Medicine/Immunology & Rheumatology, Stanford University, Palo Alto, CA, [4]Medicine, Stanford University School of Medicine, Stanford, CA

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SESSION INFORMATION

Session Date: Sunday, November 8, 2015

Session Title: T cell Biology and Targets in Autoimmune Disease I

Session Type: ACR Concurrent Abstract Session

Session Time: 2:30PM-4:00PM

Background/Purpose: Rheumatoid arthritis (RA) is a T cell dependent disease in which chronically activated immune cells cause progressive damage of articular cartilage and bone. RA T cells adapt their metabolic programs to support their chronic energy needs in a disease-specific pattern. Unlike healthy T cells, RA T cells fail to upregulate glycolytic flux due to suppression of the glycolytic enzyme PFKFB3, produce low concentrations of lactate and ATP and are energy deprived. The energy status of cells is monitored by AMP-activated protein kinase (AMPK), a nutrient-sensing "master-regulator" that enforces quiescence under conditions of energy stress by restraining mTORC1 activity. Here, we have explored how energy deficiency affects signaling pathways in RA T cells and how it shapes their effector functions.

Methods: Purified naïve CD4 T cells from RA patients and age-matched controls were stimulated with anti-CD3/CD28. Transcripts of AMPK components and autophagy-related genes were measured by RT-PCR. AMPK activity was assessed by Western blot analysis of AMPK targets, including p-p70-S6K and pACC1. Autophagic flux was measured by immunoblotting for LC3 conversion. Treg cells were induced under polarizing conditions with TGF-β1 and IL-2. $FoxP3^+$cells were quantified by flow cytometry 7 days after polarization.

Results: Compared to healthy CD4 T cells, RA T cells had reduced levels of p-AMPKα(Thr172) ($p<0.05$) indicating insufficient activation of the AMPK signaling axis. Protein subcomponents of AMPK, including AMPKα, β and γ were intact. Functional evidence for insufficient AMPK signaling in RA T cells came from the demonstration that mTORC1 activity was inappropriately high, captured by protein levels of p-p70-S6K ($p<0.05$) and pACC1 ($p<0.05$). Also, autophagy, an AMPK-dependent energy supply mechanism, was impaired in RA T cells ($p<0.05$).

To test whether AMPK was able to respond to stress signals, we deprived T cells of glucose by culturing them in the glucose analogue 2-DG. AMPK activation induced by energy stress was reduced in RA. To examine whether additional AMPK-dependent pathways were impaired, we examined the induction of anti-inflammatory Treg cells from naive RA T cells. Compared to healthy control T cells, RA T cells failed to differentiate into $FoxP3^+$Tregs.

Conclusion: RA T cells are energy deprived and are unable to correct their energy status due to defective responsiveness of the nutrient sensor AMPK. Functional consequences of insufficient AMPK activation include the failure of autophagy, defective upregulation of glycolysis, insufficient inhibition of lipogenesis and, most importantly, chronic hyperactivity of the immune activator mTORC1.

Disclosure: Z. Yang, None; **E. L. Matteson**, Novartis/Sanofi/Centocor-Jansen/Celgene/Amgen/Roche/Genentech/Mesoblast/Pfizer, 2; **J. Hong**, None; **J. Goronzy**, None; **C. M. Weyand**, None.

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Abstract Number: 994

Th17/Tfh Cell Predict Disease Severity in Rheumatoid Arthritis Patients Receiving TNF Inhibitor Therapy

Deepika Singh[1], Matthew Henkel[2], Juan (June) Feng[3], Jason Lyons[4], Heather Eng[5], Larry W. Moreland[6] and **Mandy J. McGeachy**[2],

[1]Rheumatology, Children's Hospital of Pittsburgh, Pittsburgh, PA, [2]Medicine, University of Pittsburgh, Pittsburgh, PA, [3]Epidemiology Data Center, University of Pittsburgh, Graduate School of Public Health, Pittsburgh, PA, [4]School of Public Health, Department of Epidemiology, University of Pittsburgh, Pittsburgh, PA, [5]Epidemiology, Univ of Pittsburgh, Pittsburgh, PA, [6]Rheumatology & Clinical Immunology, University of Pittsburgh, Pittsburgh, PA

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Session Time: 2:30PM-4:00PM

Background/Purpose: In autoimmunity, T follicular helper cells (TfH) are considered drivers of autoantibody production, and T helper 17 (Th17) cells are implicated in tissue-specific inflammation. In juvenile dermatomyositis patients, the Ueno lab showed that the ratio of TfH cells expressing markers of Th17 cells was increased relative to Th1, and this Th17/TfH ratio correlated with disease activity. Although patients with rheumatoid arthritis (RA) feature joint-specific inflammation and autoantibody production, TfH cell subsets have not been well-studied in context of disease activity or therapy.

Methods: We identified seropositive RA patients receiving stable TNF inhibitor (TNFi) therapy (n = 26) or non-biologic DMARDs (n = 35), who were enrolled in the RA Comparative Effectiveness Research (RACER) registry at University of Pittsburgh. Treatment groups were matched for age, gender, ethnicity, concomitant DMARD and steroid use. 8 healthy controls were also enrolled. A second cohort of 6 subjects were identified who showed a good response following initiation of TNFi. PBMC were isolated and CD4+CD45RO+ T cell subsets analyzed by flow cytometry using chemokine receptors as functional subset markers.

Results: There were no significant differences in blood memory cell frequency between RA and healthy controls. Total Th1 (CXCR3+) and TfH (CXCR5+) cells did not differ between RA treatment groups or controls. However, the proportion of TfH cells that co-expressed the Th17 marker CCR6 (termed Th17/TfH) was increased compared to healthy controls ($p = 0.044$, t-test). Surprisingly, Th17/TfH cell negatively correlated with disease activity in the TNFi group, as assessed by CDAI (Spearman $r = -0.72$, $p = 0.0001$) and DAS28crp ($r = -0.6844$, $p = 0.0001$). However, no correlation between disease activity and Th17/TfH cells was observed in patients receiving non-biologic DMARD therapy ($r = 0.175$, $p = 0.25$ for CDAI; $r = 0.059$, $p = 0.745$ for DAS28crp). While CXCR3-expressing Th1/TfH cells showed a trend towards being decreased in RA subjects, Th1/TfH cells did not correlate with disease activity in either treatment group. Analysis of longitudinal samples from TNFi subjects showed strong correlations between visits for Th17/TfH cell frequencies ($r = 0.818$, $p = 0.006$). To confirm these cross-sectional results, we analyzed a second longitundinal cohort (n = 6) of subjects initiating TNFi therapy and showing a subsequent good clinical response. Indeed, Th17/TfH cell frequencies remained stable after TNFi therapy ($r = 0.943$, $p = 0.017$).

Conclusion: Th17/TfH cells correlate with disease activity in RA subjects receiving TNFi, but not DMARDS alone. Th17/TfH frequencies remained remarkably stable over time for each individual. These data indicate that Th17/TfH cells are not directly affected by TNFi, but rather that proportions of these cells serve as a predictor of future disease severity for patients receiving TNFi therapy. Hence different levels of Th17/TfH cell contribution to RA pathogenesis in individuals could be one factor underpinning the clinical problem of heterogeneity in RA therapy responses.

Disclosure: D. Singh, None; **M. Henkel**, None; **J. Feng**, None; **J. Lyons**, None; **H. Eng**, None; **L. W. Moreland**, None; **M. J. McGeachy**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/th17tfh-cell-predict-disease-severity-in-rheumatoid-arthritis-patients-receiving-tnf-inhibitor-therapy

Abstract Number: 995

In Rheumatoid Arthritis Only a Few Expanded T-Cell Clones Dominate in Joint Inflammation: A Study in Seven RA Patients Undergoing Paired Synovial Tissue Biopsies in Multiple Joints

Anne Musters[1], Paul L. Klarenbeek[1,2], Marieke E. Doorenspleet[1,2], Rebecca E.E. Esveldt[1,2], Barbera D.C. van Schaik[3], Sander W. Tas[1,2], Antoine H.C. van Kampen[3], Frank Baas[4] and Niek de Vries[1,2], [1]Dept. of Clinical Immunology & Rheumatology, Amsterdam Rheumatology and immunology Center | Academic Medical Center/University of Amsterdam, Amsterdam, Netherlands, [2]Dept. of Experimental Immunology, Academic Medical Center/University of Amsterdam, Amsterdam, Netherlands, [3]Bioinformatics Laboratory, Department of Clinical Epidemiology, Biostatistics and Bioinformatics, Academic Medical Center/University of Amsterdam, Amsterdam, Netherlands, [4]Dept. of Genome Analysis, Academic Medical Center/University of Amsterdam, Amsterdam, Netherlands

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Background/Purpose: Previously we found a strong enrichment of highly expanded T-cell clones in rheumatoid arthritis (RA) synovial tissue of inflamed joints. To gain more insight into the potential role of these expanded clones in the inflammatory polyarthritis in this disease, we studied the distribution of these T-cell clones: Are they present only locally in the inflamed synovium? If not, to what extent are they also present in synovial biopsies taken from a different location in the same joint, or from a different joint?

Methods: In seven RA-patients we simultaneously obtained synovial tissue (ST) biopsies from two inflamed joints (N=7; ankle or knee) via mini-arthroscopy together with paired peripheral blood (PB; N=7) and synovial fluid samples (SF; N=5). ST biopsies were obtained from ankle (N=1) or from the infrapatellar region of the knee (N=6). In 6 patients we took additional independent suprapatellar (SP) biopsies within the same knee joint. Samples were processed for RNA-based next generation sequencing (NGS). T-cell clones were identified by their unique T-cell receptor β-chain sequence, the degree of expansion being expressed as a percentage of the total number of NGS reads. (Paired) student T-tests or Wilcoxon (matched-pair) signed rank test were performed where applicable.

Results: We identified 904,631 clones in 6,955,333 TCR-sequences. Of the top-25 most expanded clones in ST only a limited number were retrieved as top-25 clone in SF (18%; SEM 6.3) and in PB (24%, SEM 5.1). In contrast, considerable overlap was seen if we analyzed cellular infiltrate in synovial tissue biopsies from different regions of the same joint: 49% (SEM 6.2) of the top-25 ST clones were also retrieved as a top-25 clone in the suprapatellar biopsy of the same joint ($p<0.005$). When comparing different joints in the same patient, we noted that 52% (SEM 5.0) of the top-25 clones from the 1st joint were also amongst the top-25 clones in the 2nd joint (see figure 1).

Conclusion: Synovial fluid T-cells do not fully reflect the repertoire of dominant clones in the synovial tissue. Synovial tissue biopsies from different locations within the same joint or taken from different joints show substantial overlap of the most dominant T-cell clones in patients with active RA. Given the evidence pointing to T-cell involvement in the pathogenesis of RA this suggests that in individual patients a limited number of T-cell clones dominate the adaptive immune response. Detailed cellular characterization of these clones seems warranted, and may help to devise more selective strategies for therapeutic targeting.

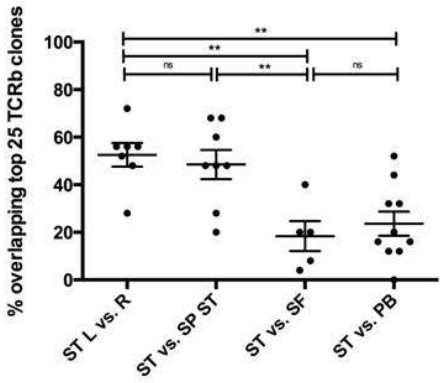

Figure 1 | percentage of overlapping top 25 TCRb clones. ST= synovial tissue; L= left; R= right; SP; suprapatellar region; SF= synovial fluid; PB= peripheral blood. ** = $p<0.005$; ns= not significant.

Disclosure: A. Musters, None; **P. L. Klarenbeek**, None; **M. E. Doorenspleet**, Patent on "Method for diagnosing IgG4 related diseases", application number PCT/ EP2013/070384, publication number WO/2014/049177, 9; **R. E. E. Esveldt**, BTCURE, 2; **B. D. C. van Schaik**, None; **S. W. Tas**, None; **A. H. C. van Kampen**, None; **F. Baas**, None; **N. de Vries**, None.

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Abstract Number: 996

Metabolic Control of Invariant Natural Killer T Cell Function

Kevin Wei[1], Deepak A. Rao[2], Pui Y. Lee[3], Anqi Gao[4], Peter A. Nigrovic[5] and Michael Brenner[6], [1]Rheumatology, Immunology & Allergy, Brigham & Women's Hospital, Boston, MA, [2]Internal Medicine/Rheumatology, Brigham & Womens Hospital, Boston, MA, [3]Division of Immunology, Boston Children's Hospital, Boston, MA, [4]Division of Rheumatology, Immunology, and Allergy, Brigham and Women's Hospital, Boston, MA, [5]Department of Medicine, Division of Rheumatology, Immunology and Allergy, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, [6]Division of Rheumatology, Immunology, and Allergy, Brigham and Women's Hospital, Harvard Medical School, Boston, MA

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Session Type: ACR Concurrent Abstract Session

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Background/Purpose:

Invariant Natural Killer T (iNKT) cells are a unique subset of T cells that shape an inflammatory response through rapid production of large amounts of cytokines following activation. Perturbation in frequency and proliferative response of peripheral blood iNKT cells have been described in rheumatoid arthritis and systemic lupus erythematosus, however the mechanism is not well understood. Metabolic reprogramming from oxidative phosphorylation to aerobic glycolysis is crucial for T cell proliferation and cytokine production. The aim of this study is to characterize metabolic reprogramming during iNKT cell activation.

Methods:

Peripheral blood iNKT cell frequency from rheumatoid arthritis patients and healthy controls were measured by flow cytometry. Cultured mouse iNKT cells were used for metabolic analysis. iNKT cell oxygen consumption and extracellular acidification were measured using a Seahorse XFe24 analyzer. Specific pharmacologic inhibitors 2-deoxyglucose (glycolysis) and oligomycin (oxidative phosphorylation) tested specific metabolic pathways for iNKT cell function.

Results:

Compared with healthy controls, rheumatoid arthritis patients had a decreased frequency of peripheral blood iNKT cells. Metabolic analysis of murine iNKT cell revealed predominant reliance on oxidative phosphorylation at basal state. Upon stimulation with the cognate lipid antigen alpha-galactosylceramide, iNKT cells exhibit significantly enhanced glycolysis and glycolytic capacity. In contrast, oxidative phosphorylation was only modestly elevated while spare respiratory capacity was suppressed following activation. Glycolysis, but not oxidative phosphorylation, has been shown to be essential for interferon-gamma production in MHC-restricted T-cells. In contrast, inhibition of either glycolysis or oxidative phosphorylation in iNKT cells resulted in dose-dependent suppression of interferon-gamma production, suggesting differential metabolic control in iNKT cells

Conclusion:

In summary, peripheral blood iNKT cells are significantly reduced in rheumatoid arthritis patients. Our data suggest that metabolic reprogramming and glucose utilization play a crucial role in iNKT cell function. Further characterization of iNKT cell metabolic state in rheumatoid arthritis patients may shed light on mechanisms of altered iNKT cell function during chronic inflammation.

Disclosure: K. Wei, None; **D. A. Rao**, None; **P. Y. Lee**, None; **A. Gao**, None; **P. A. Nigrovic**, None; **M. Brenner**, None.

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Abstract Number: 997

Feasibility and Influential Factors in Performing Self-Evaluation of DAS28 with Smart System of Disease Management (SSDM) By RA Patient in China

Mu Rong[1], Fei Xiao[2], Chun Li[3], Jianlong Guan[4], Yan Shen[4], Dongbao Zhao[5], Xia Xu[6], Lindi Jiang[7], Huiyong Chen[7], Li Su[8], Yuhua Jia[2], Li Zhang[2], Yuan Liu[2] and Zhan-Guo Li[3], [1]Department of Rheumatology and Immunology, People's Hospital, Beijing University Medical School, Beijing, China, [2]Gothic Internet Technology Corporation, Shanghai, China, [3]Department of Rheumatology & Immunology, People's Hospital, Beijing University Medical School, Beijing, China, [4]Huadong Hospital Affiliated to Fudan University, Shanghai, China, [5]ShangHai ChangHai Hospital, ShangHai ChangHai Hospital, ShangHai, China, [6]Department of Rheumatology and Immunology, Changhai Hospital,Second Military Medical University,, Shanghai, China, [7]Zhongshan Hospital, Fudan University, Shanghai, China, [8]Longhua Hospital Shanghai University of TCM, Shanghai, China

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Background/Purpose: Regular evaluations of rheumatoid arthritis (RA) disease activities with disease activity score in 28 joints (DAS28) are critical steps to reach the goal of "Treat to Target". However, over-load of RA patients and short supply of rheumatologists in China made these steps impossible in the clinic. An option is to realize self-disease-evaluation by RA patient. Due to the smart phone being widely used in 66% of Chinese people, a user-friend platform of the Smart System of Disease Management (SSDM) is a potential resolution for regular evaluations of RA disease activities. SSDM includes applications of self-evaluation of DAS28, HAQ, and digital records of medication and lab test results. SSDM is developed in IOS, Android and Web format with patient and physician's interfaces. After patient entries the data, it synchronizes with the interface of authorized doctor in real time mode.

To verify the feasibility and influential factors in performing self-evaluation on DAS28 with SSDM by RA patients.

Methods: From December 14, 2014 to February 2, 2015, two phases of studies were performed and total 103 patients enrolled, with 55 and 48 patients in each phase, respectively. All patients met the 1987 ACR criteria for diagnosis of RA. Ten rheumatologists and two nurses from five hospitals in Beijing and Shanghai participated in the study.

Education courses were held in hospitals. Patients were taught how to do self-evaluations on DAS28 and HAQ with SSDM. After practice and passing the exam, the self-evaluation of DAS28 was performed and data was recorded in SSDM. The same patient was evaluated by doctor or nurse simultaneously.

Statistical analysis was performed using SAS software, version 9.4. Intra-observer reliability of tender joint counts (TJCs) and swollen joint counts (SJCs) were expressed through the intra-class correlation coefficient (ICC).

Results: Among 103 RA patients, Mean age was 55.20 ± 13.26 (23 to 72) years, mean disease duration was 8.91 ± 8.25 (1 to 34) years.

As of December 31, 2014 for phase I, the ICCs of TJCs and DAS28 scores were 0.93 and 0.94, but the ICC of SJCs was 0.68. The analysis showed that the duration of disease was the only associate factor with significant difference ($P<0.05$). Stratified analysis showed that the result of SJCs matched between patients and health professionals was in the group with disease duration of 6.86 ± 5.78 years, but mismatched group was 14.18 ± 10.26 years in disease duration which group of patients under valuated their SJCs.

In Phase II of 48 patients, the education courses were more emphasized in identification of swollen joints. As a result, the ICCs of SJCs, TJCs and DAS28 were improved to 0.93, 0.93 and 0.92, respectively.

The average time for patients to do self-evaluation on a composite of DAS28 and HAQ with SSDM was 7.11 ± 5.21 (2-30) minutes, median time for 5 minutes; and the corresponding time for health professionals was 6.55 ± 4.26 (1-20) and 2 minutes, respectively.

Conclusion: Through improving education, RA patients in China can master SSDM and perform accurate self-evaluation on DAS28 and HAQ. SSDM may serve as a valuable platform for assisting rheumatologists in rationally managing RA patients in order to reach the goal of "Treat to Target".

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Abstract Number: 998

A Psychometric Analysis of the Social Interaction Anxiety Scale (SIAS-6) in Systemic Sclerosis: Results from the Scleroderma Patient-Centered Intervention Network (SPIN) Cohort

Shadi Gholizadeh[1], Sarah D. Mills[2], Rina S. Fox[2], Lisa Jewett[3,4], Linda Kwakkenbos[3,4], Marie-Eve Carrier[5], Brett D. Thombs[3,5], Scott C. Roesch[2,6], Vanessa L. Malcarne[2,6], Karen Gottesman[7] and SPIN Investigators, [1]Psychoogy, SDSU/UC San Diego Joint Doctoral Program in Clinical Psychology, San Diego, CA, [2]SDSU/UC San Diego Joint Doctoral Program in Clinical Psychology, San Diego, CA, [3]McGill University, Montreal, QC, Canada, [4]Lady Davis Institute for Medical Research, Jewish General Hospital, Montréal, QC, Canada, [5]Lady Davis Institute for Medical Research, Jewish General Hospital, Montreal, QC, Canada, [6]Psychology, San Diego State University, San Diego, CA, [7]Scleroderma Foundation, Los Angeles, CA

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Background/Purpose: The experience of living with a serious illness, such as systemic sclerosis (SSc), can pose challenges for an individual's self-concept and social roles. This can necessitate new patterns of interacting with others, which may lead to social anxiety. Research on the social impacts of SSc is limited, and there are few validated measures in this area. The Social Interactions Anxiety Scale (SIAS-6) was developed to assess social interactional anxiety, or distress experienced when interacting with others. The instrument has demonstrated good measurement properties, but has not been tested in SSc. The present study has the following two aims: 1) to assess the reliability and validity of the SIAS-6 in a sample of SSc patients, and 2) to explore whether scores can be meaningfully compared across the limited and diffuse subtypes of the disease.

Methods: Confirmatory factor analysis (CFA) was used to evaluate the structural validity of the one factor model of the SIAS-6 in sample of patients with SSc ($N = 596$; 59.1% limited, 40.9% diffuse) enrolled in the Scleroderma Patient-centered Intervention Network (SPIN) Cohort. Multiple group confirmatory factor analysis (MGCFA) was used to evaluate the comparability of the factor structures of the SIAS-6 for patients with limited and diffuse disease subtypes. The MGCFA evaluated configural invariance (i.e., baseline model fitting a one-factor solution for both groups), metric invariance (i.e., factor loadings constrained to equivalence), and factor variance invariance (i.e., factor loadings and variances constrained to equivalence) models. Internal consistency reliability was examined via Cronbach's coefficient alpha. Convergent validity was examined via Pearson product-moment correlations with measures of depression, body image dissatisfaction/avoidance, fear of negative evaluation, and social anxiety.

Results: Per descriptive fit indices using CFA, a one-factor model was found to fit the data (Comparative Fit Index [CFI] = 0.99, Standardized Root Mean Residual [SRMR] = 0.02, Root Mean Square Error of Approximation [RMSEA] = 0.06). The MGCFA demonstrated that the metric invariance model best fit the data (i.e., equivalent factor loadings but different variances across disease groups) based on the descriptive indices of CFI, SRMR, and RMSEA; change in CFI; and the Satorra-Bentler X^2 difference test. Internal consistency reliability was good for limited ($\alpha = 0.86$) and diffuse ($\alpha = 0.92$) groups. Convergent validity testing demonstrated significant, moderate to strong correlations in the expected directions with measures of depression ($r = 0.48$, $p < .01$), body image dissatisfaction, avoidance, and concerns ($r = 0.51$, $r = 0.42$, $r = 0.54$, respectively, all $ps < .01$), fear of negative evaluation ($r = 0.57$, $p < .01$), and social anxiety ($r = 0.58$, $p < .01$) in the total sample.

Conclusion: The present study demonstrates that the SIAS-6 can be confidently used as a one-factor measure of social interaction anxiety in patients with both limited and diffuse subtypes of SSc.

Disclosure: S. Gholizadeh, None; **S. D. Mills**, None; **R. S. Fox**, None; **L. Jewett**, None; **L. Kwakkenbos**, None; **M. E. Carrier**, None; **B. D. Thombs**, None; **S. C. Roesch**, None; **V. L. Malcarne**, None; **K. Gottesman**, None.

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Abstract Number: 999

Development of Quality Indicators for Hip and Knee Arthroplasty Rehabilitation

Marie Westby[1], Deborah Marshall[2], Jane Squire Howden[3] and C. Allyson Jones[4], [1]School of Public Health, University of Alberta, Edmonton, AB, Canada, [2]University of Calgary, Calgary, AB, Canada, [3]Edmonton Musculoskeletal Centre, Edmonton, AB, Canada, [4]Physical Therapy, University of Alberta, Edmonton, AB, Canada

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Background/Purpose: Rehabilitation before and after total hip (THA) and knee arthroplasty (TKA) surgery has been shown to decrease pain and impairment, and improve mobility, activity and participation. Yet there are reports of marked variation in clinical practices, outcomes and resources allocated for rehabilitation services. This project aimed to develop core sets of quality indicators (QIs) reflecting the minimum acceptable standard of rehabilitation care before and after elective THA and TKA for osteoarthritis.

Methods: We assembled an 18-member Canada-wide panel of clinicians, researchers and patients and used a modified RAND-UCLA Delphi approach to establish consensus on 82 proposed QIs (40 for THA, 42 for TKA). Indicators were derived from the authors' previous work and the literature and reflected the rehabilitation continuum (pre-operative, acute care and post-acute up to 1 year post-surgery). Panelists completed 2 rounds of rating using an online survey interspersed by a moderated online discussion forum over a 3-month period. Prior to rating, panelists received a synthesis of high quality evidence (practice guidelines, systematic reviews, randomized controlled trials) supporting each QI. They were instructed to review the evidence before accessing the survey. Each QI was rated for its importance and validity on a 9-point Likert scale.

Individual and group ratings from Round 1 were summarized and provided to panelists in order to inform the subsequent online discussion. During Round 2, panelists were asked to participate in the forum anonymously, share their views on the proposed QIs and debate each others' comments. This was immediately followed by the final round of ratings. Those QIs with median ratings of 7 or higher for both importance and validity, and with no disagreement were included in the final sets.

Results: Fifteen panelists representing 7 provinces and varied practice settings completed the Delphi process. Of the 82 proposed QIs, 67 (82%) were rated as both important and valid (31 for THA, 36 for TKA). For THA, 14 pre-op, 6 acute and 8 post-acute QIs were accepted. For TKA, 16 pre-op, 10 acute and 8 post-acute indicators were accepted. The majority of these QIs address assessment and screening activities (74%) while the remainder pertain to rehabilitation interventions. Three 'across-continuum' QIs were rated appropriate for THA and 2 of 3 for TKA. Engagement was high with 83% of panelists participating in the discussion forum.

Conclusion: These QIs represent an important first step in addressing rehabilitation practice and outcome variation and will serve as a tool with which to measure, report and benchmark quality of care in patients receiving rehabilitation before and after THA/TKA surgery. Online technology facilitated broad geographical representation, panelist anonymity and engagement, and decreased panelist burden and administration costs compared to the traditional RAND/UCLA method. The QIs will be further tested for reliability and feasibility before being widely disseminated in clinical settings and used to assess care gaps.

Disclosure: M. Westby, None; **D. Marshall**, CIHR, Arthritis Society, AIHS, CIORA, 2,University of Calgary, 3,Abbvie, 5,Pfizer Inc, 5,Novartis Pharmaceutical Corporation, 5,Johnson & Johnson, 5; **J. Squire Howden**, None; **C. A. Jones**, None.

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Abstract Number: 1000

Obesity and Foot Problems in the Framingham Foot Study: Does Foot Structure or Foot Function Protect Against Hallux Valgus?

Alyssa B. Dufour[1], Elena Losina[2], Michael P. Lavalley[3], David Gagnon[4,5], Hylton B. Menz[6] and Marian T. Hannan[7], [1]Institute for Aging Research, Hebrew SeniorLife, Harvard Medical School & Beth Israel Deaconess Medical Center, Boston, MA, [2]Orthopaedic and Arthritis Center for Outcomes Research, Department of Orthopaedic Surgery, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, [3]Biostatistics, Boston University, Boston, MA, [4]Biostatistics Department, Boston University School of Public Health, Boston, MA, [5]MAVERIC, VA Boston Health Care, Boston, MA, [6]Musculoskeletal Research Centre, La Trobe University, Bundoora, VIC, Australia, [7]Institute for Aging Research, Hebrew SeniorLife, Dept. of Medicine Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA

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Session Time: 2:30PM-4:00PM

Background/Purpose: Obesity and foot problems are common in older adults and associated with many negative health outcomes. There is limited evidence examining the relation between foot problems and obesity from a population perspective. Previous studies have found higher BMI to be linked with reduced odds of hallux valgus, a common foot disorder, but no study has determined the reason for this unexpected relation. The purpose of this study was to describe the associations between obesity categories, with foot pain and foot disorders (hallux valgus, claw, hammer, overlapping toes), and to determine if these associations differ by foot structure or by foot function in a community-based, cross-sectional study of older men and women.

Methods: We included 2445 participants (contributing 4888 feet) from the Framingham Foot Study between 2002 and 2008. A podiatric-trained examiner performed a validated examination of participantsÕ feet to determine the presence of foot disorders on each foot by comparing the foot to a laminated depiction of the disorder. Foot pain was defined by the question ÒOn most days, do you have pain, aching or stiffness in either foot?Ó Body mass index (BMI, kg/m^2) was determined at the time of the foot exam and categorized as normal (<25, referent), overweight (25-30), moderately obese (30-35) and severely obese (35+). Foot structure (cavus, planus) and foot function (pronated, supinated) were defined using the Tekscan Matscan pressure system as the modified arch index and the center of pressure excursion index, respectively. We used sex-specific logistic regression, adjusting for within person correlation, to examine the relation between foot pain and each foot disorder with obesity categories, adjusting for age and further stratified by foot structure and foot function categories in a foot-specific analysis.

Results: Average age was 68 (SD 11) years, 56% were female, BMI was 28 (SD 5) kg/m^2. 18% of feet had pain, 25% hallux valgus, 2% claw toes, 18% hammer toes, 7% overlapping toes. Severely obese men were more likely to have foot pain (OR=2.4; 95% CI: 1.4-4.3) and claw toes (OR=3.4; 95% CI: 1.1-10.7) compared to normal weight men. In women, there was an increased odds of foot pain with all categories of obesity (Table). Severely obese women were 40% less likely to have hallux valgus (OR=0.61; 95% CI: 0.4-0.9) compared to normal weight women. We

saw the same effect in men although it did not reach statistical significance. Patterns of association were the same stratified by foot structure or function in men or in women.

Conclusion: Women are more prone to foot pain and obese women, even more so. Reducing weight may reduce pain and potentially reduce foot problems. Foot structure and foot function do not change the associations between foot problems and obesity. Further studies are needed to determine the mechanism behind these associations and the role of longitudinal trajectories of BMI on foot problems.

Table. Per-foot analysis of the association between obesity categories (referent group BMI < 25 kg/m^2) and foot pain and foot disorders, adjusting for age.

	Obesity category	Men 2150 feet; 1076 people		Women 2738 feet; 1369 people	
		N	OR(95% CI)	N	OR(95% CI)
Foot pain	Normal (referent)	50/300	1.0	140/569	1.0
	Overweight	116/300	1.06 (0.67,1.67)	192/567	1.49 (1.09,2.03)**
	Moderately obese	82/300	1.17 (0.71,1.91)	139/567	2.01 (1.43,2.81)**
	Severely obese	52/300	2.44 (1.38,4.33)**	96/567	3.21 (2.15,4.79)*
Hallux valgus	Normal (referent)	71/323	1.0	350/919	1.0
	Overweight	150/323	1.01 (0.68,1.50)	338/919	0.97 (0.76,1.24)
	Moderately obese	81/323	0.84 (0.54,1.31)	168/919	0.81 (0.61,1.09)
	Severely obese	21/323	0.61 (0.31,1.18)	63/919	0.61 (0.40,0.93)*
Claw toes	Normal (referent)	8/44	1.0	25/65	1.0
	Overweight	16/44	1.23 (0.46,3.27)	24/65	1.05 (0.49,2.24)
	Moderately obese	13/44	1.89 (0.65,5.49)	11/65	0.97 (0.38,2.45)
	Severely obese	7/44	3.37 (1.06,10.66)*	5/65	1.14 (0.33,3.91)
Hammer toes	Normal (referent)	79/369	1.0	198/501	1.0
	Overweight	146/369	0.93 (0.64,1.35)	158/501	0.78 (0.58,1.05)
	Moderately obese	103/369	1.11 (0.74,1.66)	97/501	0.94 (0.66,1.33)
	Severely obese	41/369	1.37 (0.79,2.37)	48/501	1.13 (0.72,1.76)
Overlapping toes	Normal (referent)	28/112	1.0	82/212	1.0
	Overweight	44/112	0.86 (0.47,1.57)	74/212	0.97 (0.65,1.44)
	Moderately obese	30/112	1.03 (0.53,1.99)	43/212	1.15 (0.70,1.88)
	Severely obese	10/112	1.06 (0.43,2.62)	13/212	0.87 (0.40,1.88)

* p<0.05; ** p<0.01;

N = number in the BMI group with the foot problem divided by the number with the foot problem

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Abstract Number: 1001

What Is the Most Cost-Effective Physical Therapy Strategy to Treat Knee Osteoarthritis?

Allyn Bove[1], Ken Smith[2], Christopher Bise[1], Julie Fritz[3], John Childs[4], Gerard P. Brennan[5], J. Haxby Abbott[6] and G. Kelley Fitzgerald[1], [1]Physical Therapy, University of Pittsburgh, Pittsburgh, PA, [2]Division of Internal Medicine; Institute for Clinical Research Education, University of Pittsburgh, Pittsburgh, PA, [3]Department of Physical Therapy, University of Utah, Salt Lake City, UT, [4]US Army-Baylor University, Schertz, TX, [5]Rehabilitation Services, Intermountain Healthcare, Murray, UT, [6]Centre for Musculoskeletal Outcomes Research, Department of Surgical Sciences, University of Otago, Dunedin, New Zealand

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Background/Purpose: The American College of Rheumatology (ACR) strongly recommends exercise therapy as a first-line conservative treatment for individuals with knee osteoarthritis (OA).[1] Evidence supporting manual therapy for knee OA has shown varying levels of effectiveness.[1] In this population, there is minimal research regarding the use of "booster" physical therapy (PT) sessions-- visits spaced across a longer period of time to supplement initial treatments.[2]The purpose of this study was to compare the cost-effectiveness of combinations of exercise therapy and manual therapy with or without booster sessions in individuals with knee OA.

Methods: Data were collected as part of a 2-year multi-site study of 300 individuals who met ACR criteria for knee OA. A Markov model was constructed to compare 4 PT treatment strategies: (1) 12 visits of exercise therapy alone (EX); (2) 9 visits of exercise therapy plus 3 booster sessions spaced across a 12-month period (EX+B); (3) 12 visits of exercise therapy plus manual therapy (EX+MT); (4) 9 visits of exercise therapy plus manual therapy and 3 booster sessions (EX+MT+B). Total health care costs were estimated from the societal perspective using patient reported outcome measures as well as data from the Healthcare Utilization Project and the Medicare physician fee schedule. Utilities were measured using the U.S. version of the Euroqol-5-Dimension tool. Incremental cost-effectiveness ratios (ICERs) are expressed in Quality-Adjusted Life Years (QALYs).

Results: In the 2-year base case analysis, the booster strategies (EX+MT+B and EX+B) dominated (lower health care costs and greater effectiveness) the no-booster strategies (EX+MT and EX). EX+MT+B had the lowest total health care costs. The EX+B group cost $1,061 more and gained 0.082 more QALYs compared with EX+MT+B, for $12,900/QALY gained. In 1-way sensitivity analyses of all parameters, EX+B continued to be cost-effective (<$100,000/QALY gained) compared with EX+MT+B, unless the likelihood of staying in good or poor function was varied to a degree that would be highly improbable given what was observed in this study. In a preliminary model projecting costs and utilities over a 5-year period, the EX+B strategy remained well within the range that most would consider to be cost-effective by third-party payers.

Conclusion: Spacing exercise-based PT sessions over 12 months using periodic "booster" sessions was less costly and more effective over 2 years than strategies not containing "booster" sessions. Among booster strategies, the group receiving manual therapy in addition to exercise therapy (EX + MT + B) had lower costs but lower gains in QALYs than the EX + B group.

1. Hochberg MC, Altman RD, April KT, et al. American College of Rheumatology 2012 recommendations for the use of nonpharmacologic and pharmacologic therapies in osteoarthritis of the hand, hip, and knee. *Arthritis Care Res* 2012;64(2):465-74.
2. Bennell KL, Kyriakides M, Hodges PW, Hinman RS. Effects of two physiotherapy booster sessions on outcomes with home exercise in people with knee osteoarthritis: a randomized controlled trial. *Arthritis Care Res* 2014;66(11):1680-7.

Disclosure: A. Bove, None; **K. Smith**, None; **C. Bise**, None; **J. Fritz**, None; **J. Childs**, None; **G. P. Brennan**, None; **J. H. Abbott**, None; **G. K. Fitzgerald**, None.

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Abstract Number: 1002

Aiming for Remission in Early RA: Impact on Pain during the First Year of Treatment

Ellen Moholt[1], Anna-Birgitte Aga[1], Inge C Olsen[1], Hilde Berner Hammer[2], Till Uhlig[3], Anne Katrine Kongtorp[4], Heidi Lunoe[4], Elin Mejdell Styrmoe[4], Tore K. Kvien[1], Espen A. Haavardsholm[1] and the ARCTIC study group, [1]Dept. of Rheumatology, Diakonhjemmet Hospital, Oslo, Norway, [2]Department of Rheumatology, Diakonhjemmet Hospital, Oslo, Norway, [3]Diakonhjemmet Hospital, Oslo, Norway, [4]Dept of Rheumatology, Diakonhjemmet Hospital, Oslo, Norway

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Session Time: 2:30PM-4:00PM

Background/Purpose: Pain is the symptom people with rheumatoid arthritis (RA) have prioritized highest for improvement [1]. Treating to target

and aiming for remission in early RA may reduce pain, but there is limited knowledge about the impact of pain in RA patients classified using the 2010 ACR/EULAR criteria and treated according to modern treatment strategies. The objective of this study was to explore and describe changes in the degree of pain in early RA during the first year after starting treatment with DMARDs.

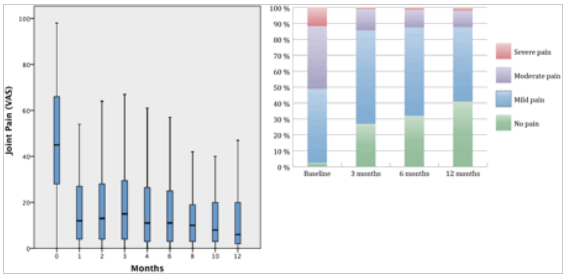
Methods: Patients from 11 rheumatology centers who fulfilled the 2010 ACR/EULAR classification criteria for RA, with symptom duration (from first swollen joint) less than 2 years, and were DMARD naïve with indication for DMARD treatment, were followed for 1 year. Treatment target was remission, and DMARD was prescribed according to international recommendations. Pain was recorded on a Visual Analog Scale (VAS 0-100 mm) at every visit, and grouped according to Jensen et al. [2] with cut points for no pain set at 0-4 mm, mild 5-44 mm, moderate 45-74 mm and severe pain 75-100 mm. Short Form 36 (SF-36) bodily pain was recorded, and transformed to a scale from 0-100, where high score indicates low bodily pain.

Results: A total of 205 early RA patients were included: 61.5% female, 82.4% ACPA positive, mean (SD) age 52.2 (13.4) years**.** At initiation of DMARD treatment the mean (SD) 44-swollen joint count was 10.2 (7.2), Ritchie Articular Index 8.14 (6.5), ESR 24 (19) mm/hr and Patient Global Assessment 49 (24) mm. DAS was mean (SD) 3.4 (1.1): 20.1% were in low DAS, 47.1% in moderate DAS and 32.8% in high DAS. VAS pain at baseline was median (IQR) 45 (27-68) mm, and decreased to 12 (4-27) mm after 1 month, and after 1 year to 6 (2-20) mm; see fig. 1A for details. Mean (SD) SF-36 bodily pain at baseline was 40 (21), and 73 (23) after 1 year. At baseline less than 3% of patients reported no pain, after 3/6/12 months this proportion increased to 27/32/41%, and after 12 months more than 87% of patients reported either mild or no pain (fig. 1B).

Conclusion: In this cohort of early DMARD-naïve RA patients treated according to modern treatment strategies aiming for remission, there was a significant reduction of pain after 1 month, and pain is decreased further during 12 months follow-up. Early intervention and treating to target in this population fulfills the patients' prioritized goal of minimizing pain, leading to a decreased burden of pain in RA.

Image/graph: Figure 1A. VAS pain 0-100 mm median and interquartile range

Figure 1B. VAS pain group proportion at baseline, 3, 6 and 12 months.



References:

1. Heiberg, T. et al. Arthritis Care Res 2002.

2. Jensen, M.P. et al. The Journal of Pain, 2003.

Disclosure: E. Moholt, None; **A. B. Aga**, None; **I. C. Olsen**, None; **H. B. Hammer**, None; **T. Uhlig**, None; **A. K. Kongtorp**, None; **H. Lunoe**, None; **E. Mejdell Styrmoe**, None; **T. K. Kvien**, None; **E. A. Haavardsholm**, AbbVie, 2,Pfizer Inc, 2,MSD, 2,Roche Pharmaceuticals, 2,UCB, 2.

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Abstract Number: 1003

Use of Nsaids Correlates with the Risk of Venous Thromboembolism in Knee OA Patients: A UK Population-Based Case-Control Study

Taeyeon Lee[1], Na Lu[1,2], David T. Felson[3], Hyon K. Choi[4], Deepan S Dalal[1], Yuqing Zhang[1] and Maureen Dubreuil[5,6], [1]Boston University School of Medicine, Boston, MA, [2]Division of Rheumatology, Allergy & Immunology, Massachusetts General Hospital, Harvard Medical School, Boston, MA, [3]Clinical Epidemiology Research and Training Unit, Boston University School of Medicine, Boston, MA, [4]Rheumatology,

Allergy and Immunology, Massachusetts General Hospital, Harvard Medical School, Boston, MA, [5]Rheumatology, Boston University School of Medicine, Boston, MA, [6]Rheumatology, VA Boston Healthcare System, Boston, MA
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Session Title: Osteoarthritis - Clinical Aspects I: Imaging and Epidemiology

Session Type: ACR Concurrent Abstract Session

Session Time: 4:30PM-6:00PM

Background/Purpose : The association between NSAIDs use and myocardial infarction has been demonstrated in many studies. However, the relation between NSAIDs use and venous thromboembolism (VTE) remains controversial. We aimed to examine whether the current users of specific NSAIDs have an increased risk of VTE among knee OA patients.

Methods : We conducted a population-based case-control study using The Health Improvement Network (THIN), a database of patient records from general practices in the UK. For every VTE case, we identified 5 controls matched on age, sex, and calendar year of study enrolment. We used conditional logistic regression to assess the association between current use of specific NSAIDs and risk of VTE relative to remote NSAID users.

Results : Among knee OA patients with at least one NSAID prescription, we identified 4020 incident cases of VTE and 20059 matched controls. Adjusted odd ratios (OR) relative to the remote users were 1.38 (95% CI 1.32 - 1.44) for the recent users and 1.43 (95% CI 1.36 - 1.49) for current users. Among the current NSAID users, the risk of VTE was increased with diclofenac (OR 1.63 [95% CI 1.53 - 1.74], ibuprofen (OR 1.49 [1.38 - 1.62]), meloxicam (OR 1.29 [1.11 - 1.50]) and coxibs (celecoxib OR 1.30 [95% CI 1.11 - 1.51]; rofecoxib OR 1.44 [95% CI 1.18 - 1.76]); naproxen did not increase VTE risk (OR 1.00 [95% CI 0.89 - 1.12]).

Conclusion : Compared with the remote users of NSAIDs, the risk of VTE increased for current users of diclofenac, ibuprofen, and coxibs, but not for naproxen, in the knee OA population.

Table 1. Baseline Characteristics of the VTE Cases and matched controls

	VTE Cases	Controls
	(n=4020)	(n=20059)
Female - %	2431 (60.5%)	12137 (60.5%)
Age (years)		
Mean ± S.D.	72.7 ± 10.1	72.8 ± 10.0
< 60	479 (11.9%)	2357 (11.8%)
60 - 69	968 (24.1%)	4840 (24.1%)
≥ 70	2573 (64.0%)	12862 (64.1%)
BMI category (kg/m^2)		
< 18.5	15 (0.4%)	97 (0.5%)
18.5 – 24.9	574 (15.9%)	4079 (22.7%)
25 – 29.9	1346 (37.2%)	7420 (41.3%)
≥ 30	1682 (46.5%)	6373 (35.5%)
Major risk factors for VTE		
Surgery	338 (8.4%)	1522 (7.6%)
Any trauma	274 (6.8%)	1133 (5.6%)
Cancer	632 (15.7%)	2276 (11.3%)
Smoking		
None	2319 (60.4%)	11408 (59.4%)
Past	1114 (29.0%)	5544 (28.8%)
Current	408 (10.6%)	2267 (11.8%)
Alcohol		
None	877 (24.3%)	4113 (22.8%)
Past	97 (2.7%)	426 (2.4%)
Current	2634 (73.0%)	13489 (74.8%)
Other comorbidities		
Stroke	375 (9.3%)	1768 (8.8%)
Ischemic heart disease	788 (19.6%)	3525 (17.6%)
Chronic kidney disease	468 (11.6%)	2062 (10.3%)
Liver disease	98 (2.4%)	476 (2.4%)
Hypertension	2012 (50.0%)	9980 (49.8%)
Diabetes	484 (12.0%)	2365 (11.8%)
Hyperlipidemia	1298 (32.3%)	6654 (33.2%)
Inflammatory conditions[a]	594 (14.8%)	2516 (12.5%)
Rheumatoid arthritis	110 (2.7%)	477 (2.4%)
NSAID use		
Remote user (any NSAID)	2114 (52.6%)	12208 (60.9%)
Recent user (any NSAID)	950 (23.6%)	3991 (19.9%)
Current diclofenac user	396 (9.9%)	1433 (7.1%)
Current ibuprofen	218 (5.4%)	861 (4.3%)
Current naproxen user	96 (2.4%)	550 (2.7%)
Current meloxicam user	57 (1.4%)	250 (1.2%)
Current celecoxib user	59 (1.5%)	248 (1.2%)
Current rofecoxib user	34 (0.8%)	129 (0.6%)
Current other coxib user	25 (0.6%)	100 (0.5%)
Current other NSAIDs user	71 (1.8%)	289 (1.4%)
Other medication use		
Glucocorticoids	445 (11.1%)	1459 (7.3%)
Aspirin	1147 (28.5%)	5319 (26.5%)
Hormone replacement therapy	141 (3.5%)	689 (3.4%)
Medical service utilization		
Specialist referral	1547 (38.5%)	6670 (33.3%)
GP visits	5.6 ± 4.4	4.8 ± 3.9
Hospitalizations	0.37 ± 1.0	0.28 ± 0.8

Table 2. Risk of VTE with usage of specific NSAIDs compared with remote usage of any NSAID

	Cases	Controls	Crude OR[b] (95% CI)	Adjusted OR[c] (95% CI)
Remote use (any NSAID)	2114	12208	1 (reference)	1 (reference)
Recent use (any NSAID)	950	3991	1.40 (1.34 - 1.47)	1.38 (1.32 - 1.44)
Current use	956	3860	1.47 (1.40 - 1.53)	1.43 (1.36 - 1.49)
Diclofenac	396	1433	1.66 (1.56 - 1.77)	1.63 (1.53 - 1.74)
Ibuprofen	218	861	1.49 (1.37 - 1.61)	1.49 (1.38 - 1.62)
Naproxen	96	550	1.02 (0.91 - 1.14)	1.00 (0.89 - 1.12)
Meloxicam	57	250	1.34 (1.16 - 1.56)	1.29 (1.11 - 1.50)
Celecoxib	59	248	1.43 (1.23 - 1.66)	1.30 (1.11 - 1.51)
Rofecoxib	34	129	1.60 (1.32 - 1.95)	1.44 (1.18 - 1.76)
Other coxibs	25	100	1.46 (1.17 - 1.83)	1.45 (1.15 - 1.83)
Other NSAIDs	71	289	1.46 (1.27 - 1.67)	1.34 (1.17 - 1.54)

[a]Seronegative Spondyloarthropathy/Psoriasis, Connective Tissue Disease, Vasculitidies, and Crystal Arthropathies.

[b] Adjusted for age, sex, and calendar year.

[c] Adjusted for age, sex, calendar year, surgery, trauma, cancer, BMI, smoking, ischemic heart disease, hypertension, diabetes, hyperlipidemia, inflammatory conditions, glucocorticoid use, number of GP visits, specialist referral, and hospitalizations.

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Abstract Number: 1004

Prevalence and Cross-Sectional Risk Factors of Ankle Osteoarthritis in a Community-Based Cohort

Shahmeer Lateef[1], Yvonne M. Golightly[2], Jordan B. Renner[3], Joanne M. Jordan[1] and Amanda E. Nelson[1], [1]Thurston Arthritis Research Center, University of North Carolina, Chapel Hill, NC, [2]Epidemiology, University of North Carolina, Chapel Hill, NC, [3]Radiology, University of North Carolina, Chapel Hill, NC

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Session Type: ACR Concurrent Abstract Session

Session Time: 4:30PM-6:00PM

Background/Purpose: Historically, ankle osteoarthritis (OA) has been considered uncommon, and its development has been thought of as a consequence of primarily ankle injury. Other etiologies have not been extensively analyzed in community-based samples. Therefore, we examined the frequency of ankle OA and determined associations between body-mass index (BMI), sex, race, and other participant characteristics with the presence of ankle OA.

Methods: Complete data on OA, pain, and injuries of the ankle, as well as participant characteristics, were available for 856 participants (mean age 71 years, mean BMI 31.0 kg/m^2, 68% women, 34% African Americans) in the Johnston County OA Project. Lateral and mortise views of the ankle were obtained in standing and read for Kellgren-Lawrence grade (KLG) by a musculoskeletal radiologist (JBR). Presence of ankle OA was defined one of two ways: KLG>=2 (primary) or KLG>=1 (secondary). Ankle symptoms were considered present based on an affirmative response to the question: ÒOn most days of any one month in the last 12 months did you have pain, aching or stiffness in your left/right ankle?Ó History of ankle injury was self-reported. Chi-square statistics for categorical variables and t-tests for continuous variables were used to compare all participant characteristics by the presence or absence of ankle OA. Multiple logistic regression models were performed to examine the associations of each participant characteristic with ankle OA, adjusting for all other factors.

Results: Among the 856 participants, 56 (7%) had ankle OA, defined as a KLG of >=2, in at least one ankle. There was no significant age difference between participants with and without ankle OA (Table). Participants with ankle OA had a higher mean BMI than those without (p<0.01). Additionally, individuals with a history of ankle injury and those with ankle symptoms, were more likely to have ankle OA (p<=0.05). In adjusted models, for every 1 unit increase in BMI, the odds of having ankle OA (KLG>=2), increased by 3%. Self-reported ankle injury was associated with 80% higher odds, while the presence of ankle symptoms was associated with more than twice the odds, of ankle OA. Results were similar when ankle OA was defined as KLG>=1 (n=634, 74%), but there were also differences by race (African Americans 40% lower odds) and sex (women 60% lower odds) in associations with ankle OA .

Conclusion: In this first community-based study of radiographic ankle OA including African American and Caucasian men and women, we found that ankle OA, defined as either KLG>=2 or KLG>=1, was not uncommon, and higher BMI and ankle symptoms were important factors. The association between increased BMI and more frequent ankle OA suggest that not only post-injury changes, but also individual characteristics of BMI or ankle symptoms, should be considered in the process of ankle OA.

Table. Participant Characteristics by Ankle OA.

Characteristic	Category	Either ankle KLG≥2 N=56 (6.5%)	Both ankles KLG<2 N=800 (93.4%)	p-value*	Adjusted ** Odds Ratio (95% Confidence Interval)	Either ankle KLG≥1 N=638 (74.5%)	Both ankles KLG<1 N=218 (25.5%)	p-value*	Adjusted ** Odds Ratio (95% Confidence Interval)
Age (mean years, SD)	--	72.6 (7.3)	71.1 (7.6)	0.14	1.03 (0.99, 1.07)	71.0 (7.4)	71.7 (8.0)	0.24	1.00 (0.98, 1.02)
BMI (mean kg/m², SD)	--	33.6 (6.7)	30.8 (7.5)	<0.01	1.03 (1.00, 1.06)	31.8 (7.9)	28.6 (5.5)	<0.01	1.10 (1.06, 1.13)
Sex, n (%)	Women	38 (67.9)	545 (68.1)	0.97	1.00 (0.55, 1.82)	409 (64.1)	174 (79.8)	<0.01	0.43 (0.29, 0.62)
	Men	18 (32.1)	255 (31.9)		referent	229 (35.9)	44 (20.2)		referent
Race, n (%)	African American	17 (30.4)	270 (33.8)	0.60	0.90 (0.49, 1.67)	202 (31.7)	85 (39.0)	0.05	0.63 (0.45, 0.90)
	Caucasian	39 (69.6)	530 (66.3)		referent	436 (68.3)	133 (61.0)		referent
Either ankle injured, n (%)	Yes	11 (19.6)	86 (10.8)	0.04	1.80 (0.88, 3.69)	81 (12.7)	16 (7.4)	0.03	1.68 (0.94, 3.01)
	No	45 (80.4)	712 (89.2)		referent	556 (87.3)	201 (92.6)		referent
Either ankle symptoms, n (%)	Yes	19 (33.9)	124 (15.5)	<0.01	2.60 (1.43, 4.75)	122 (19.2)	21 (9.6)	<0.01	1.69 (1.01, 2.82)
	No	37 (66.1)	675 (84.5)		referent	515 (80.9)	197 (90.4)		referent

* Chi-square tests for categorical variables; t-tests for continuous variables
** Adjusted for all other factors

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Abstract Number: 1005

Association of Baseline Knee Sagittal Dynamic Joint Stiffness during Gait and 2-Year Cartilage Damage Progression in Knee Osteoarthritis (OA)

Alison H. Chang[1], Joan S. Chmiel[2], Orit Almagor[3], Kirsten C. Moisio[3], Laura Belisle[3], Yunhui Zhang[3], Karen W. Hayes[4] and Leena Sharma[5], [1]PT & Human Movement Sciences, Northwestern University Feinberg School of Medicine, Chicago, IL, [2]Preventive Medicine, Northwestern University Feinberg School of Medicine, Chicago, IL, [3]Northwestern University Feinberg School of Medicine, Chicago, IL, [4]Department of Physical Therapy and Human Movement Sciences, Northwestern University Feinberg School of Medicine, Chicago, IL, [5]Rheumatology, Northwestern University Feinberg School of Medicine, Chicago, IL

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Background/Purpose: While patellofemoral (PF) OA has been found to have substantial impact on pain and function, most studies continue to

focus on tibiofemoral (TF) OA. These compartments differ in pathomechanics and the profile of factors contributing to disease course. Depending on where and how it is transmitted, increased joint stress, force transmitted through the joint averaged over articular contact area, may overload and injure cartilage in either compartment. Knee sagittal plane dynamic joint stiffness (DJS) is the interaction between the external knee flexion moment and knee flexion joint excursion during gait. In theory, greater knee sagittal DJS may increase joint stress and accelerate disease progression through elevated external knee flexion moment, reduced sagittal joint excursion and contact area, or both. We hypothesized that greater baseline knee sagittal DJS is associated with cartilage damage progression in PF and TF compartments 2 years later in persons with knee OA.

Methods: Participants all had knee OA (KL grade ³ 2) in at least one knee. Three-dimensional knee kinematics and kinetics during walking on a 35 x 4 foot walkway were captured at a rate of 120 Hz, using external passive reflective markers, an 8-camera Digital Real-Time Eagle motion analysis system, and 6 AMTI force plates. Baseline sagittal DJS of both knees was computed as the slope of the linear regression line for external knee flexion moments vs. flexion angles during the loading response phase of gait. Participants underwent 3.0T MRI of both knees at baseline and 2 years later using double oblique coronal and axial FLASH sequences, coronal T1-weighted spin-echo (SE), and sagittal, coronal and axial fat-suppressed turbo spin echo sequences. Cartilage damage progression was defined as WORMS score worsening for whole, medial, or lateral TF and PF. We assessed the association between baseline DJS and 2-year cartilage damage progression (yes vs. no), using logistic regression with GEE to account for correlations between knees, adjusting for demographics and disease covariables. **Results** are shown as odds ratios (ORs) and 95% confidence intervals (CIs).

Results: The study sample consisted of 391 knees from 204 persons: mean age 64.2 years (SD 10.0); BMI 28.4 kg/m^2 (5.7); 156 (76.5%) women. Table 1a shows the percentage of knees with cartilage damage progression. Table 1b shows the ORs for progression unadjusted, then adjusted for covariables. Greater baseline DJS was strongly associated with 2-year structural progression in the PF, specifically the lateral surface, but not in the TF.

Conclusion: Elevated baseline knee sagittal DJS was associated with increased risk of PF disease progression. Unlike frontal-plane joint mechanics, which predominantly influence the medial-lateral TF load distribution, sagittal knee mechanics during ambulation may determine PF load and disease course.

Table 1a. Number (percentage) of knees with baseline-to-2-year cartilage damage progression in each compartment (n = 391 knees; 204 persons)

Compartment:	Whole TF	Medial TF	Lateral TF	Whole PF	Medial PF	Lateral PF
Number (%)	100/391 (25.6%)	61/391 (15.6%)	48/391 (12.3%)	53/391 (13.6%)	29/391 (7.4%)	28/391 (7.2%)

Table 1b. Association between baseline predictor of sagittal DJS (%body weight*height/degree) and baseline-to-2-year TF and PF cartilage damage progression dichotomized outcomes in each compartment (n = 391 knees; 204 persons)

Unadjusted odds ratio (95% CI)	0.06 (0.001, 2.92)	0.01 (0.00, 1.15)	0.65 (0.12, 3.51)	**2.57 (1.09, 6.03)**	0.05 (0.00, 11.48)	**4.27 (2.04, 8.91)**
Odds ratio (95% CI), adjusted for age, gender, gait speed, and disease severity	0.04 (0.0005, 3.27)	**0.002 (0.00, 0.53)**	0.77 (0.19, 3.20)	**3.70 (1.79, 7.65)**	0.83 (0.14, 4.97)	**5.70 (2.62, 12.39)**
Odds ratio (95% CI), adjusted for age, gender, gait speed, disease severity, WOMAC pain, and pain meds	0.07 (0.001, 5.54)	**0.002 (0.00, 0.61)**	1.05 (0.30, 3.59)	**3.51 (1.63, 7.55)**	0.79 (0.11, 5.44)	**5.37 (2.33, 12.41)**

Bold odds ratio indicates that the associated 95% CI excludes 1
TF = tibiofemoral joint; PF = patellofemoral joint; CI = confidence interval

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Incident Frequent Knee Pain Is Associated with Changes in Semi-Quantitative Imaging Biomarkers of Inflammation

C.Kent Kwoh[1], Michael J. Hannon[2], Tomoko Fujii[3], Frank W Roemer[4], Ali Guermazi[5], David Hunter[6], Felix Eckstein[7] and Robert M. Boudreau[8], [1]Department of Medicine, The University of Arizona Arthritis Center and Division of Rheumatology, Tucson, AZ, [2]Department of Medicine, University of Pittsburgh School of Medicine, Pittsburgh, PA, [3]University of Pittsburgh, Pittsburgh, PA, [4]Department of Radiology, Boston University School of Medicine, Boston, MA, [5]Boston University School of Medicine, Boston, MA, [6]Rheumatology, Institute of Bone and Joint Research, Kolling Institute, University of Sydney, Sydney, Australia, [7]Paracelsus Med Univ, Chondrometrics GmbH, Salzburg, Austria, [8]Epidemiology, University of Pittsburgh, Pittsburgh, PA

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Background/Purpose: The cause of knee pain in osteoarthritis (OA) is multi-factorial, and there is increasing evidence of the role of inflammation in OA. The goal of this study was to examine the association between development of incident frequent knee pain or improvement of frequent knee pain with changes in semi-quantitative (SQ) MRI imaging biomarkers of inflammation.

Methods: Data from the Osteoarthritis Initiative (OAI) study was used for this analysis. Knees from the OAI that were at risk of developing incident radiographic OA through the 48-month OAI visit were included if they had SQMRI readings and data on frequent knee pain (KP) on at least two successive OAI annual visits. MRIs were read according to the MRI Osteoarthritis Knee Score (MOAKS) system, unblinded to order of acquisition but blinded to clinical data. Frequent knee pain was defined as "pain on most days of the past 30 days". For each pair of successive annual time points where KP was absent at the first time point, we examined the potentially increased odds of transitioning to KP (no KP to KP+) predicted by whether Hoffa synovitis (HS) had a concurrent change from absent (no HS) to present (HS+) vs other HS patterns. Concurrent effusion synovitis (ES) vs KP transition patterns were analogously compared. We also compared the HS and ES concurrent transitions when a knee went from KP+ to no KP. State transition modeling was used to estimate the odds of transitioning from no KP to KP+ in successive years predicted by HS or ES transitions. The absence of Hoffa synovitis or effusion synovitis at both time points was the referent group. Random effects mixed models were used to account for clustering of knees within a person and multiple time points for each knee. Models were adjusted for age, gender and BMI.

Results: We included 345 knees from 313 participants, 66% female and with a mean age of 60 years; 62% of knees were KLG 1 and 38% were KLG 0 at baseline (Table 1). No ES to ES+ and no HS to HS+ were the only changes associated with the transition from no KP to KP+ in multivariate analyses. When stratified by sex, the association of no HS to HS+ with the transition of no KP to KP+ was stronger for men (aOR=7.37, 95% CI: 1.54-35.32) than for women (aOR=3.95, 95% CI: 1.47-10.61), whereas for no ES to ES+, the association with transition of no KP to KP+ was significant only in men (aOR=3.98, 95% CI: 1.39-11.38), but not women (aOR=1.78, 95% CI: 0.84 -3.74). There were no significant associations of these SQMRI biomarkers with the transition from KP+ to no KP.

Conclusion: Incident frequent knee pain was associated with the presence of new Hoffa synovitis or effusion-synovitis, and these associations varied by sex. These SQMRI biomarkers of inflammation are potential targets for therapeutic interventions for pain in knee OA.

Table 1. Association between semi-quantitative MRI biomarkers of inflammation and incident knee pain

Exposure (effusion-synovitis, Hoffa synovitis transitions from one time point to the next)	**Incident Knee Pain*** aOR (95%CI)**	P-value
No effusion-synovitis to No effusion-synovitis	**Reference**	
No effusion-synovitis to effusion-synovitis+	2.22 (1.23-4.01)	0.0083
Effusion-synovitis+ to No effusion-synovitis	0.83 (0.36-1.92)	0.4248
Effusion-synovitis+ to effusion-synovitis+	1.21 (0.76-1.95)	0.4248
No Hoffa synovitis to No Hoffa synovitis	**Reference**	
No Hoffa synovitis to Hoffa synovitis+	4.65 (2.03-10.68)	0.0003
Hoffa synovitis+ to No Hoffa synovitis	0.78 (0.08-7.78)	0.8283
Hoffa synovitis+ to Hoffa synovitis+	1.06 (0.68-1.65)	0.8138

*From No KP to KP+ at next time point

**adjusted for age, gender, BMI

Disclosure: C. K. Kwoh, None; **M. J. Hannon**, None; **T. Fujii**, None; **F. W. Roemer**, Boston Imaging Core Lab, 1; **A. Guermazi**, Boston Imaging Core Lab, LLC, 1,TissueGene, 5,OrthoTrophix, 5,MerckSerono, 5,Genzyme Corporation, 5; **D. Hunter**, None; **F. Eckstein**, Chondrometrics GmbH, 1,Merck Serono, 5; **R. M. Boudreau**, None.

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Change in Semi-Quantitative Imaging Biomarkers Predicts Knee Osteoarthritis Progression: Data from the Fnih OA Biomarkers Consortium

Jamie E. Collins[1], Elena Losina[2], Michael C. Nevitt[3], Frank W. Roemer[4], Ali Guermazi[4], John A. Lynch[5], Jeffrey N. Katz[2], C. Kent Kwoh[6], Joanne M. Jordan[7], Virginia Kraus[8] and David Hunter[9], [1]Orthopaedic and Arthritis Center for Outcomes Research, Department of Orthopedic Surgery, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, [2]Brigham and Women's Hospital and Harvard Medical School, Boston, MA, [3]University of California, San Francisco, San Francisco, CA, [4]Boston University School of Medicine, Boston, MA, [5]University of California San Francisco, San Francisco, CA, [6]University of Arizona, Tucson, AZ, [7]Thurston Arthritis Research Center, University of North Carolina, Chapel Hill, NC, [8]Duke Molecular Physiology Institute, Duke University School of Medicine, Durham, NC, [9]University of Sydney, Sydney, Australia

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Background/Purpose: Semi-quantitative scoring of magnetic resonance images (MRIs) is a valuable method for performing multi-feature assessment of the knee joint. The goal of this study was to investigate the ability of change in semi-quantitative knee MRI biomarkers over 24 months to predict knee osteoarthritis (OA) progression over 48 months.

Methods: This analysis was done as a part of the fNIH-funded OA Biomarkers Consortium case-control study. We selected a predetermined number of index knees, one knee per subject, in four different knee outcome groups: 1) knees with both radiographic and pain progression; 2) knees with radiographic but not pain progression; 3) knees with pain but not radiographic progression; 4) knees with neither radiographic nor pain progression. For the purposes of this analysis we used the single comparison, comparing knees with both radiographic and pain progression (cases) vs. everybody else (controls). MRIs were read according to the MRI Osteoarthritis Knee Score (MOAKS) scoring system in sequential order unblinded to time point of acquisition but blinded to group assignment. This analysis focused on change in several joint features: 1) bone marrow lesions (BMLs), 2) cartilage thickness, 3) cartilage surface area, 4) effusion-synovitis, 5) meniscus morphology, 6) meniscus extrusion, 7) osteophytes size, and 8) Hoffa-synovitis. We used logistic regression to examine the association between each biomarker and case status. Multivariable models were built in a hierarchical fashion, with the best performing biomarkers from univariate analyses added to the model first (performance based on p-value, OR and c-statistics). **Results:** We used the data from 194 cases and 406 controls, mean age 62 years, 59% females, 51% K-L 2 and 37% K-L 3. All joint features considered were significantly associated with case status in univariate analyses, and all features were progressed to multivariable modeling. We built several hierarchical models with c-statistics ranging from 0.686 to 0.725 (Table). Results of multivariable modeling revealed that changes from baseline to 24 months in cartilage thickness, cartilage surface area, meniscal morphology, effusion-synovitis, and Hoffa-synovitis independently predicted knee OA progression (case status). BMLs, osteophytes, and meniscal extrusion did not exhibit a statistically significant association with being a case in multivariable models when cartilage thickness and surface area and meniscal morphology were included in the model.

Conclusion: Both loss of cartilage thickness and cartilage surface area worsening over 24 months were independently associated with knee OA progression over 48 months. In addition, changes over 24 months in semi-quantitative measures on MRI related to meniscus morphology, effusion-synovitis, and Hoffa-synovitis were associated with progression of knee OA in multivariable models.

Table. Association between select knee joint features measured by semi-quantitative MRI (MOAKS) and case status: results from multivariable modeling. P-values, odds ratios (95% confidence intervals) presented in cells.

	Model 1: Include Cartilage	Model 2: Model 1 + Meniscus	Model 3: Model 2 + Effusion	Model 4: Model 3 + Synovitis – Meniscal Extrusion
C-statistic	0.686	0.711	0.725	0.725
Cartilage: number of areas with loss in thickness	P=0.0004	P=0.0028	P=0.0087	P=0.0120
None	REF	REF	REF	REF
1 subregion	1.7 (1.1, 2.6)	1.6 (1.0, 2.6)	1.6 (1.0, 2.5)	1.5 (0.9, 2.4)
2 subregions	2.5 (1.4, 4.2)	2.2 (1.3, 3.9)	2.0 (1.1, 3.5)	1.9 (1.1, 3.4)
3+ subregions	3.2 (1.6, 6.5)	2.8 (1.4, 5.8)	2.8 (1.3, 5.7)	2.7 (1.3, 5.7)
Cartilage: number of areas with worsening in surface area affected	P=0.0003	P=0.0291	P=0.0804	P=0.0719
None	REF	REF	REF	REF
1 subregion	1.3 (0.8, 2.1)	1.2 (0.8, 2.0)	1.2 (0.8, 1.9)	1.2 (0.8, 2.0)
2 subregions	1.9 (1.1, 3.3)	1.6 (0.9, 2.9)	1.5 (0.8, 2.7)	1.5 (0.8, 2.6)
3+ subregions	3.3 (1.9, 5.6)	2.3 (1.3, 4.2)	2.1 (1.2, 3.9)	2.2 (1.2, 3.9)
Meniscal Morphology: Any regions with worsening		P=0.0420 1.8 (1.0, 3.0)	P=0.0416 1.8 (1.0, 3.0)	P=0.0042 2.1 (1.3, 3.5)
Meniscal Extrusion Medial worsening		P=0.0304 1.9 (1.1, 3.3)	P=0.1249 1.6 (0.9, 2.8)	
Effusion-synovitis : Change in Effusion-synovitis Category			P=0.0010	P=0.0012
Improvement			0.7 (0.4, 1.3)	0.7 (0.4, 1.3)
No change			REF	REF
Worsening			2.0 (1.3, 3.1)	2.0 (1.3, 3.1)
Hoffa-Synovitis: Change in Hoffa-Synovitis Category				P=0.0695
No change/improve				REF
Worsening				1.8 (1.0, 3.3)

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Abstract Number: 1008

Morphometric Study of Algerian Hips: An Etiological Study to Explain the Low Prevalence of Hip Osteoarthritis in Algeria

Samy Slimani[1], Aicha Ladjouze-Rezig[2], Khalid Testas[3], Imen Bencharif[4], Mohamed Boukredera[5] and Riad Chiheub[5], [1]Department of Medicine, University of Batna, Batna, Algeria, [2]Department of Rheumatology, EHS Ben Aknoun, Algiers, Algeria, [3]Department of Medicine, Khroub Hospital, Constantine, Algeria, [4]Department of Medicine, University of Constantine 1, Constantine, Algeria, [5]Rheumatology office, Constantine, Algeria

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Background/Purpose: In western countries, hip osteoarthritis (OA) is the third osteoarthritic location in terms of prevalence, with a ratio hip/knee OA of 1:2 to 1:3. However, in Asian/African countries, this ratio is much lower, of 1:27 in Algeria and 1:40 in China. A comparative study between American and Chinese hips in elderly women found more impingement and asphericity in hips of white women. We conducted this study to find out morphometric differences between Algerian and American hips that may explain such differences in hip OA prevalence.

Methods: A morphometric study was performed on 200 hips of 100 Algerian healthy female subjects, aged ³ 60 years and compared with values of 200 American female hips of the Study of Osteoporotic Fractures (SOF). Were mesured and compared the following dysplasia and impingement parameters: lateral center-edge angle, impingement angle, acetabular slope, femoral head-to-femoral neck ratio and crossover sign. Comparisons were made using t tests for continuous variables and z tests for proportions. Inta- and inter-observer intraclass correlation for Algerian measures were calculated.

Results: The intra- and inter-observer intraclass correlation were good to excellent (0.91 to 0.97 and 0.79 to 0.89, respectively). Different values are exposed on table 1.

Parameter	**Algerian subjects** **n=100, 200 hips**	**American subjects** **n=100, 200 hips**	***P value***
Age (mean ± SD) (years)	66.6 ± 6.4	71.0 ± 4.8	< **0.0001**
BMI (mean ± SD) (Kg/cm^2)	29.1 ± 5.7	26.8 ± 4.2	**0.0014**
Lateral center-edge angle (Wiberg) (°)	41.4	30.4	0.075
Impingement angle (°)	62.6	83.6	**0.029**
Femoral head-to-femoral neck ratio	0.91	0.89	0.505
Acetabular slope of T™nnis (°)	2.7	3.8	0.663
Wiberg > 35° (%)	77.5	23.1	< **0.0001**
Wiberg < 20° (%)	0.0	7.0	**0.0001**
T™nnis < 0° (%)	16.5	13.0	0.323
T™nnis > 15° (%)	0.0	1.0	0.156
Impingement angle < 70° (%)	78.0	12.1	< **0.0001**
Femoral head-to-femoral neck ratio > 1.35 (%)	0.5	4.0	**0.018**
Crossover sign (%)	3	81	< **0.0001**

Conclusion: Compared with American women > 60 years, Algerian women have distinct differences in their morphometric values, with lower mean impingement angles and more important Lateral center-edge angles. These data suggest a more common asphericity and impingement in Algerians, which theoritically predisposes to more hip OA lesions. We think that this abnormality is largely offset by the almost total lack of acetabular retroversion in Algerians (only 3% in Algerians VS 81% in Americans), which may play a protective role against the anterior femoroacetabular impingement.

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Abstract Number: 1009

Promoting Professional Development of Medical Educators in Rheumatology: Perspectives of Clinician Scholar Educators

Juliet Aizer[1] and Jeanne Bitterman[2], [1]Rheumatology, Hospital for Special Surgery, New York, NY, [2]Adult Learning and Leadership, Teachers College, Columbia University, New York, NY

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Background/Purpose:

Recognizing the importance of supporting educators to improve patient care, the Rheumatology Research Foundation (RRF) offers competitive awards for Clinician Scholar Educators (CSE) in rheumatology. CSE awards have provided project-based funding since 1999 and evolved to provide additional financial support for professional development (PD). By analyzing the experiences of CSE awardees we aimed to identify approaches to support PD for educators in rheumatology.

Methods:

With IRB approval, each of the 53 rheumatologists who had completed CSE awards by 2014 were invited by email to contribute his or her perspective on PD of medical educators in focus groups or individual interviews. Parallel semi-structured formats were used, probing motivation for study participation, motivation for PD, descriptions and impacts of PD, and suggestions for how to support medical educators' PD. Focus groups and interviews were audio-recorded and transcribed. The authors independently reviewed transcripts using a general inductive approach and developed codes sensitized by theories of adult learning. Investigators compared and contrasted findings, arriving at an expanded and then condensed set of themes.

Results:

In November 2014, 20 rheumatologists participated in 1-hour focus groups at the American College of Rheumatology (ACR) Annual Scientific Meeting. Focus group size ranged from 3-7 participants. Between December 2014 and May 2015, 6 rheumatologists participated in individual telephone interviews, 25-35 minutes in duration. In total, perspectives of 49% (26/53) of CSE awardees were captured. Gender distribution of participants (54% women) was similar to that of awardees (47% women). A similar number of participants had received the award in the first 7 years the CSE award was offered as in the subsequent years (12 versus 14).

Interviews captured greater detail than focus groups; overall themes from the focus groups were corroborated in the interviews. Participants cited commitment to supporting medical education, medical educators, the community of CSE awardees, an individual CSE awardee, and the ACR/RRF as motivating factors for study participation. A minority attended to hear others' experiences. PD experiences before, during and after CSE award funding were described.

Participants emphasized the value of communities of educators, including the community of CSE awardees, as well as communities of program directors, course directors, educators in formal education programs, and members of Academies of Medical Educators. PD was often triggered by new or desired responsibilities. Mentorship, collaborations, feedback, inquiry and leadership roles emerged as experiences with critical impact; these were recommended for other educators.

Conclusion:

Experiences reported by CSE awardees as having positive PD impact align most closely with theories of adult development within a constructivist paradigm. Communities of medical educators can be a key source of opportunities for mentorship, team learning, collaborative or collegial inquiry, and leadership roles to promote development of medical educators.

Disclosure: J. Aizer, Hospital for Special Surgery Academy of Medical Educators, 2; **J. Bitterman**, Teachers College, Columbia University, 3.

Abstract Number: 1010

Differing Perspectives Between Doctor, Nurse and Patient Views on Professionalism and Empathy: An Inter-Professional 360-Degree Rheumatology Objective Structured Clinical Examination

Jessica Berman[1], Juliet Aizer[2], Meng Zhang[3], Anne R. Bass[2], Irene Blanco[4], Anne Davidson[5], Theodore R. Fields[2], Jane Kang[6], Leslie Kerr[7], Deana M. Lazaro[8], Stephen A. Paget[9] and Michael H. Pillinger[10], [1]Rheumatology, Hospital for Special Surgery, Weill Cornell Medical College, New York, NY, [2]Rheumatology, Hospital for Special Surgery, New York, NY, [3]Epidemiology and Biostatistics, Hospital for Special Surgery, New York, NY, [4]Medicine, Albert Einstein College of Medicine, Bronx, NY, [5]Autoimmunity and Musculoskeletal Diseases, Feinstein Inst for Med Rsch, Manhasset, NY, [6]Medicine, Columbia School of Medicine, New York, NY, [7]Associate Professor of Medicine & Geriatrics, Mount Sinai Medical Ctr, New York, NY, [8]Rheumatology, Box 42, SUNY Downstate Medical Center, Brooklyn, NY, [9]Division of Rheumatology, Hospital for Special Surgery, New York, NY, [10]Medicine/Rheumatology, NYU School of Medicine/NYU Hospital for Joint Diseases, New York, NY

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SESSION INFORMATION

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Session Title: Education
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Session Time: 4:30PM-6:00PM

Background/Purpose: The New York City Rheumatology Objective Self Assessment Clinical Exam (NYC-ROSCE) annually assesses 1st and 2nd year fellow competencies in areas such as professionalism and communication skills in a patient-interactive setting. This year's exam used inter-professional evaluators to allow for a complete 360-degree comparison of ratings from physician-evaluators (MD), nurse-evaluators (RN) and patient-actors (PT).

Methods: The 2015 NYC-ROSCE included 5 patient-centered stations focusing on rheumatic diseases. The stations focus on psychosocial dilemmas that occur in the context of clinical care in order to assess fellow professionalism and other elements of the patient-doctor relationship. Rheumatology fellows (n=25), faculty MD-evaluators (n=25) and RN-evaluators (n=25) from 7 rheumatology training programs participated. Professional actors (n=25) were trained to role-play patients. Written quantitative assessments of the fellows were made at each station (9-point Likert scale) by MD-, RN- and PT-evaluators in the areas of maintaining composure, professionalism, and empathy. Immediate oral feedback was given to each fellow by all three evaluators following each encounter. Repeated measures ANOVA was performed to compare the mean ratings among the evaluators in all three areas. Tukey's method was used to preserve the overall Type I error when making multiple comparisons. Spearman correlation coefficient was calculated to assess the relationship between ratings for professionalism and empathy at each station for each type of evaluator.

Results: When assessing the areas of professionalism, composure and empathy, there was a statistically significant difference between evaluators' mean ratings, with RN-evaluators rating fellows the lowest and patient-actors the highest, suggesting that physicians, nurses and patients may apply different criteria when assessing competencies during observed encounters (table1). The ratings for professionalism and empathy were highly correlated for all evaluators at the majority of stations (data not shown).

Conclusion: The introduction of the RN-evaluator to the MD-evaluator and patient-actor to our yearly ROSCE offered a unique inter-professional 360-degree perspective of the patient-physician encounter. When assessing specific competencies, the MD-, RN-evaluators' and patient-actors' scores were disparate, likely reflecting their differing professional experiences and the way in which those affect how they value/rate the same event. The ultimate “true” evaluation is likely a composite of these individual perspectives. As this is the first subspecialty inter-professional ROSCE to compare raters, further research will be needed to understand the significance of the differing assumptions and expectations of MDs, RNs and patients vis-à-vis the patient-physician interchange.

Table 1. Multiple Comparisons of Mean Ratings among Evaluators

	Mean Ratings (Standard error)			Adjusted P-value		
	RN	MD	PT	RN vs. MD	RN vs. PT	MD vs. PT
Professionalism	6.51 (0.12)	6.96 (0.12)	7.72 (0.12)	0.01	<.0001	<.0001
Composure	6.42 (0.13)	6.79 (0.13)	7.37 (0.13)	0.07	<.0001	0.002
Empathy	6.25 (0.17)	6.74 (0.17)	7.06 (0.17)	0.02	<.0001	0.20

Disclosure: J. Berman, None; **J. Aizer**, None; **M. Zhang**, None; **A. R. Bass**, None; **I. Blanco**, None; **A. Davidson**, None; **T. R. Fields**, None; **J. Kang**, None; **L. Kerr**, None; **D. M. Lazaro**, None; **S. A. Paget**, MedScape, 8; **M. H. Pillinger**, None.

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Abstract Number: 1011

Impact of a Musculoskeletal "Mini-Residency" Continuing Professional Education Program on Knee MRI Orders By Primary Care Providers

Matthew Call[1,2], Andrea M. Barker[3], Grant W. Cannon[4], Phillip Lawrence[5] and Michael J. Battistone[6], [1]Rheumatology, University of Utah, Salt Lake City, UT, [2]Salt Lake City VA Medical Center and University of Utah, Salt Lake City, UT, [3]General Internal Medicine, Salt Lake City VA Medical Center and University of Utah, Salt Lake City, UT, [4]Division of Rheumatology, Salt Lake City VA Medical Center and University of Utah, Salt Lake City, UT, [5]Pharmacology, Salt Lake City VA Medical Center and University of Utah, Salt Lake City, UT, [6]Rheumatology, Salt Lake City VA Medical Center and University of Utah, Salt Lake City, UT

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Session Type: ACR Concurrent Abstract Session

Session Time: 4:30PM-6:00PM

Background/Purpose:

The US Department of Veterans Affairs (VA) has developed a national continuing professional development program to train primary care providers (PCPs) in the evaluation and management of patients with common musculoskeletal (MSK) conditions. Although the initial phase of this project emphasized the development of providers' proficiency to perform joint injections, the appropriate use of advanced imaging technology (e.g., magnetic resonance imaging (MRI)) in evaluating knee pain is an important additional objective of this national educational initiative. The aim of this study was to investigate the impact of this educational program on providers' utilization of MRI in the evaluation of knee pain.

Methods:

Twenty-six PCPs from the Salt Lake City VA Health Care System participated in the MSK "Mini-Residency between April 2012 and October 2014. All orders for knee MRIs submitted by these providers over the 12-months prior to their participation in the mini-residency (pre-training) were reviewed, as well as all orders submitted over the 12-months following their participation (post-training). MRIs were categorized as follows:

"Inappropriate": No prior weight-bearing x-rays done within the preceding 12 months

"Probably inappropriate": Findings of OA described on x-ray report

"Possibly appropriate": No findings of OA described on x-ray report

The number of MRIs in each category was recorded for the pre-training and post-training period specific to each provider, and the number of MRIs in each category was tallied. Differences in the numbers of MRIs that were ordered post-training as compared to pre-training for each of the three categories were evaluated using Student's t-test (2—tailed).

Results:

	Pre-training	Post-training	Change (n, % of change; p)
Completed MRIs (n, % of total)	114 (100%)	62 (100%)	-52 (-54.4%; p < 0.001)
Inappropriate	70 (61.4%)	33 (53.2%)	-37 (-47.1%; p = 0.03)
Probably Inappropriate	30 (26.3%)	16 (25.8%)	-14 (-53.3%; p = 0.03)
Possibly Appropriate	14 (12.3%)	13 (21%)	-1 (-7.1%; p = NS)

Conclusion:

Following participation in the MSK Mini-Residency program, the overall number of MRI orders decreased by over 50%. The reduction in total number of MRIs is completely attributable to a decrease in orders that were categorized as either inappropriate or probably inappropriate. The number of MRIs that were categorized as possibly appropriate did not change. These findings suggest that the cost effectiveness of the MSK mini-residency program is even greater than earlier estimates, which did not consider cost savings due to more appropriate use of imaging.

Disclosure: M. Call, None; **A. M. Barker**, None; **G. W. Cannon**, None; **P. Lawrence**, None; **M. J. Battistone**, None.

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Abstract Number: 1012

Use of Social Media By Rheumatology Fellows in North America

Jonathan S. Hausmann[1,2], Jayanth Doss[3] and Laura Cappelli[4], [1]Rheumatology, Boston Children's Hospital, Boston, MA, [2]Rheumatology, Beth Israel Deaconess Medical Center, Boston, MA, [3]Division of Rheumatology, Vanderbilt University Medical Center, Nashville, TN, [4]Ste 4500, Johns Hopkins University, Baltimore, MD

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Background/Purpose:

Social media, now used by 79% of US adults with internet access, has the potential to change the way in which physicians, patients, and medical organizations communicate about health-related issues. What remains unclear is to what extent physicians use social media in their professional lives. The benefits of using social media professionally include connecting physicians with common interests from geographically disparate areas, collaborating on research projects, and obtaining and sharing scientific information. It is assumed that younger physicians are more involved in social media, although it is not known whether this reflects personal or professional use.

To date, only a few small studies have systematically assessed physicians' professional use of social media. We examined the use of social media for personal and professional purposes by rheumatology fellows in North America.

Methods:

Rheumatology fellows attending the 2014 ACR Annual Meeting were invited to participate. After the Fellows-In-Training educational session, Quick Response (QR) codes and web links to an online survey were provided. The survey evaluated the educational session and assessed use of and attitudes towards social media.

Results:

375 fellows attended the Fellows-In-Training educational session, and 235 (62.7%) of these fellows completed the survey. Year of training and specialty are shown in Table 1. 88.5% of fellows use social media for personal use, while 40.9% use it professionally at least

once monthly (Table 2).

Conclusion:

Facebook was the most commonly used platform, with 82% of fellows using it for personal use. Twitter, for either personal or professional use, was reported by 18% of fellows, significantly less than surveys of adults with a college education, where the rates of use are 30%.

For professional use, LinkedIn was the most commonly used platform, utilized by 20% of rheumatology fellows. This is less than in national studies, in which 50% of internet users with a college education use LinkedIn.

It is possible that warnings about potential harms of social media within healthcare institutions have made rheumatology fellows less likely to engage on these platforms. Future studies should examine the barriers to professional use of social media, as well as educate physicians about its potential benefits.

Table 1: Level and type of training of rheumatology fellows.

Year in training	n (%)
First year	113 (48)
Second year	105 (45)
Third year	16 (7)
Fourth year	1 (0)
Specialty	**n (%)**
Pediatric rheumatology	40 (17)
Adult rheumatology	190 (81)
Combined pediatric and adult rheumatology	5 (2)

Table 2: Frequency of social network use by rheumatology fellows.

Social network	Never	Once a month	Once a week	Most days	Once a day	Several times a day
Professional Use n (%)						
Blogs	222 (95)	5 (2)	4 (2)	2 (1)	2 (1)	0
Doximity	217 (92)	15 (6)	2 (1)	0	1 (0)	0
Facebook	198 (84)	13 (6)	8 (3)	4 (2)	7 (3)	5 (2)
Google+	208 (89)	2 (1)	2 (1)	3 (1)	5 (2)	12 (5)
LinkedIn	187 (80)	34 (15)	7 (3)	4 (2)	1 (0)	2 (1)
Twitter	218 (93)	8 (3)	3 (1)	3 (1)	2 (1)	1 (0)
Personal Use n (%)						
Blogs	195 (83)	16 (7)	10 (4)	5 (2)	4 (2)	5 (2)
Doximity	220 (94)	11 (5)	2 (1)	1 (0)	0	1 (0)
Facebook	43 (18)	23 (10)	33 (14)	38 (16)	42 (18)	56 (24)
Google+	157 (67)	27 (12)	11 (5)	10 (4)	11 (5)	19 (8)
LinkedIn	182 (78)	35 (15)	11 (5)	3 (1)	2 (1)	2 (1)
Twitter	199 (85)	18 (8)	6 (3)	4 (2)	2 (1)	6 (3)

Disclosure: J. S. Hausmann, None; **J. Doss**, None; **L. Cappelli**, None.

Abstract Number: 1013

The Fellow As Clinical Teacher Curriculum: Improving Rheumatology Fellows' Teaching Skills during Inpatient Consultation

Eli Miloslavsky[1], Lisa Criscione-Schrieber[2], Beth Jonas[3], Kenneth S. O'Rourke[4], Jakob McSparron[5] and Marcy B. Bolster[6], [1]Division of Rheumatology, Massachusetts General Hopsital, Boston, MA, [2]Rheumatology, Duke University Medical Center, Durham, NC, [3]Thurston Arthritis Research Ct, UNC-Chapel Hill, Chapel Hill, NC, [4]Section on Rheumatology and Immunology, Wake Forest University School of Medicine, Winston-Salem, NC, [5]Divsion of Pulmonary and Critical Care Medicine, Beth Israel Deaconess Medical Center, Boston, MA, [6]Massachusetts General Hospital, Boston, MA

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Background/Purpose:

Enhancing rheumatology fellows' teaching skills in the setting of inpatient consultation may have a broad positive impact. Such efforts may improve fellows' clinical skills and overall patient care. Most importantly, effective resident-fellow teaching interactions may not only increase residents' knowledge of rheumatology, but may influence their career choice. However, a number of barriers to the resident-fellow teaching interaction have been identified, including fellows' teaching skills. We developed the Fellow As Clinical Teacher (FACT) curriculum in order to enhance fellows' teaching skills during inpatient consultation.

Methods:

The FACT curriculum was delivered over two 45-minute workshops during the three-day Winter Meeting of the Carolina Fellows Collaborative. We evaluated its effect with self-assessment surveys and fellow performance on the Objective Structured Teaching Exercise (OSTE) before and after participation in the curriculum.

Results:

Nineteen fellows from four rheumatology training programs participated in the pre and post-curriculum OSTEs. Of the 8 OSTE rating items, fellows scored higher on 5 items and the total score in the post-curriculum OSTE as compared to the pre-curriculum OSTE (Table 1). Fellows' ability to listen to the learner, encourage learner to participate actively in the discussion, evaluate learner's ability to synthesize information, present well organized material and give feedback were all rated higher during the post-curriculum OSTE. The average total OSTE score increased after participation in the FACT curriculum (35.7 versus 29.5, $p<0.01$).

Eighteen fellows completed pre and post-curriculum surveys. Following the completion of the FACT curriculum fellows reported more confidence in their ability to teach in the setting of consultation and in their ability to give feedback (Table 2). Fellows rated the curriculum highly (4.1 out of 5) and 17 of 18 fellows (94%) stated that they would teach more frequently during consultation after participating in the FACT curriculum.

Conclusion:

The FACT curriculum, focused on teaching during consultation, improved fellows teaching skills and attitudes towards teaching. Improving and increasing fellow teaching, particularly in the setting of consultation, may impact patient care, resident and fellow learning, teaching skills of future faculty and could potentially influence trainees' career choice.

Table 1 – Performance on pre and post-curriculum Objective Structured Teaching Exercise (OSTE)

Item	Pre-curriculum N=19	Post-curriculum N=19	p-value
Listened to learner	3.95	4.84	<0.01
Encouraged learner to participate actively in the discussion	3.75	4.32	0.04
Evaluated learner's knowledge of factual medical information	3.53	4.16	0.11
Evaluated learnrer's ability to analyze or synthesize knowledge	3.18	3.84	0.03
Presented well organized material	4.00	4.55	<0.01
Paced the session	3.92	4.24	0.22
Explained to learner why he/she was correct/incorrect	3.38	4.60	<0.01
Overall teaching effectiveness	3.75	4.16	0.13
Total score	29.46	34.71	<0.01

Table 2 – Self-assessment of teaching skills

Item	Pre-curriculum N=18	Post-curriculum N=18	p-value
Teach in the setting of consultation	2.86	3.75	<0.01
Assess learner	3.94	4.17	0.30
Determine teaching objectives	4.06	4.28	0.10
Teach within time constraints	3.72	4.17	0.06
Give feedback	3.61	4.2	<0.01

Disclosure: E. Miloslavsky, Genentech Inc., 2; **L. Criscione-Schreiber**, None; **B. Jonas**, None; **K. S. O'Rourke**, unlisted, 9; **J. McSparron**, None; **M. B. Bolster**, Johnson and Johnson, 1,Eli Lilly and Company, 2,ACR, Committee on Training and Workforce, Chair, 6,ACR Board of Directors, Member, 6,RRF Board of Directors, Member, 6,ABIM Council, Member, 6,ABIM Rheumatology Specialty Board, Chair, 6,ABIM, Rheumatology Exam Writing Committee, Chair, 6.

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Abstract Number: 1014

Improvement in Mentoring Associated with Implementation of an Inter-Institutional Mentoring Program within Pediatric Rheumatology

Lakshmi N. Moorthy[1], Eyal Muscal[2], Meredith Riebschleger[3], Marisa S. Klein-Gitelman[4], Lise E. Nigrovic[5], Kelly A. Rouster-Stevens[6], Polly J. Ferguson[7], B. Anne Eberhard[8], Hermine I. Brunner[9], Sampath Prahalad[10], Rayfel Schneider[11] and Peter A. Nigrovic[12], [1]Pediatric Rheumatology, Rutgers-Robert Wood Johnson Medical School, New Brunswick, NJ, [2]Pediatric Rheumatology, Baylor College of Medicine, Texas Children's Hospital, Houston, TX, [3]Pediatric Rheumatology & Health Services Research, University of Michigan, Ann Arbor, MI, [4]Division of Rheumatology, Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, IL, [5]Division of Emergency Medicine, Boston Children's Hospital, Boston, MA, [6]Pediatric Rheumatology, Emory Univ School of Medicine, Atlanta, GA, [7]Dept of Pediatrics--Rheum, University of Iowa, Iowa City, IA, [8]Schneider Children's Hospital, New Hyde Park, NY, [9]Pediatric Rheumatology Collaborative Study Group, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, [10]Emory University School of Medicine and Children's Healthcare of Atlanta, Atlanta, GA, [11]Division of Rheumatology, The Hospital for Sick Children and University of Toronto, Toronto, ON, Canada, [12]Department of Medicine, Division of Rheumatology, Immunology and Allergy, Brigham and Women's Hospital, Harvard Medical School, Boston, MA

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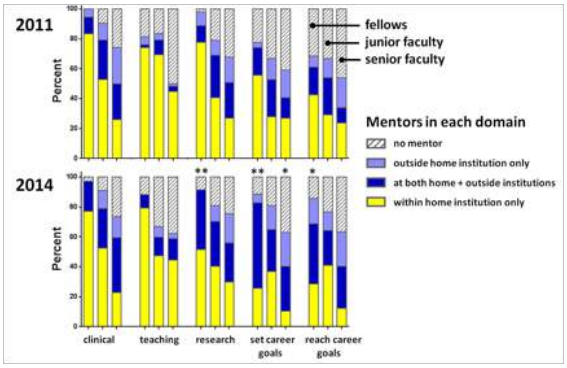
Background/Purpose: Mentoring is a key contributor to success in academic medicine. In pediatric rheumatology, surveys have repeatedly identified mentoring as a major career unmet need of fellows and junior faculty. In response, in 2011 the American College of Rheumatology (ACR) and the Childhood Arthritis & Rheumatology Research Alliance (CARRA) launched a subspecialty-wide inter-institutional mentoring program for pediatric rheumatologists, the ACR/CARRA Mentoring Interest Group (AMIGO). Our objective is to evaluate if implementation of AMIGO was associated with improved access to mentoring in pediatric rheumatology.

Methods: US and Canadian pediatric rheumatology fellows, junior faculty (assistant professor and below) and senior faculty (associate professors and above) were surveyed in 2011 (pre-AMIGO) and again in 2014 (post-AMIGO). Participants were asked to report access to mentoring in domains relevant to academic rheumatology: clinical practice, teaching, research, setting career goals, and identifying how to achieve career goals. Respondents reported whether mentoring in each domain was available at the home institution, at an outside institution, at both or neither, and were asked to rate overall satisfaction with career mentoring.

Results: Respondents to each survey included >50% of pediatric rheumatologists in the US and Canada (n=277 in 2011; n=177 in 2014 and 59% AMIGO participants). By 2014, 86% of fellows and 31% of junior faculty were AMIGO mentees. In 2011, fellows were substantially less likely than senior faculty to have mentoring outside the home institution. This difference resolved by 2014. By 2014, the proportion of fellows with outside mentors increased markedly in the domains of research, setting career goals, and achieving career goals (Figure 1). No change was observed in clinical or teaching domains. Overall, fellows but not junior faculty reported an increase in satisfaction with career mentoring between 2011 and 2014.

Conclusion: The implementation of AMIGO was associated with improved access to mentoring beyond the home institution for fellows in pediatric rheumatology as well as an increase in satisfaction with career mentoring measureable at the level of the whole community. These findings support the efficacy of the subspecialty-wide AMIGO mentoring program, and suggest that AMIGO may serve as a model for mentoring programs in adult rheumatology and in other domains of medicine.

Figure 1: Access to Mentoring in 2011 and in 2014



Disclosure: **L. N. Moorthy**, None; **E. Muscal**, None; **M. Riebschleger**, None; **M. S. Klein-Gitelman**, None; **L. E. Nigrovic**, None; **K. A. Rouster-Stevens**, None; **P. J. Ferguson**, None; **B. A. Eberhard**, None; **H. I. Brunner**, None; **S. Prahalad**, None; **R. Schneider**, None; **P. A. Nigrovic**, None.

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Abstract Number: 1015

Contribution of TNF and Type I Interferon to the Development of Persistent Post-Inflammatory Mechanical Allodynia in Arthritic Mice

Sarah Woller[1], Cody Ocheltree[2], Tony Yaksh[1] and Maripat Corr[2], [1]Anesthesiology, UCSD, La Jolla, CA, [2]Division of Rheumatology, Allergy, and Immunology, UCSD, La Jolla, CA

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Background/Purpose: Male C57Bl/6 (WT) mice develop transient inflammation in response to K/BxN serum transfer and show a corresponding pain state, which persists beyond the resolution of inflammation. The current studies first examined the role of spinal cytokines, specifically TNF and IFNβ in the transition to a persistent, post-inflammatory pain state, which is mediated through Toll-like receptor (TLR) 4 signaling. Importantly, the contribution of TLR4 to pain states has been found to differ between male and female animals. Thus, our second aim was to examine whether female WT mice respond similarly to K/BxN serum transfer, and to examine whether TLR4 signaling associated spinal cytokines were involved in the development of tactile allodynia (TA) in female animals.

Methods: K/BxN sera (100µl) was injected into male and female WT, *Tnf*$^{-/-}$, *Tlr4*$^{-/-}$, and *Ifnar1*$^{-/-}$ mice on Days 0 and 2. Ankle width and withdrawal thresholds were examined over 28 days and then analyzed in the peak inflammatory (d3-10) and post-inflammatory (d13-18) phases. Spinal cords were collected from WT and *Tlr4*$^{-/-}$ arthritic mice and changes in gene expression were measured using qPCR.

Results: We examined spinal cords for differences in TNF and IFNβ gene transcripts on day 10 post K/BxN serum transfer, relative to day 0. IFNβ transcripts decreased in WT mice (average fold change: 0.41) and were increased in *Tlr4*$^{-/-}$ mice (average fold change: 18.84). In contrast, TNF transcripts increased in WT mice (average fold change 1.33), and remained unchanged in *Tlr4*$^{-/-}$ mice (average fold change 0.96). Next, we assessed the development of TA in male *Ifnar1*$^{-/-}$ and *Tnf*$^{-/-}$ mice. The early, inflammatory phase of pain is attenuated in *Ifnar1*$^{-/-}$ mice (1.18g threshold relative to 0.5g in WT males, $p < .05$); however these mice develop persistent pain while the late phase of pain is reduced in *Tnf*$^{-/-}$ mice (1.29g threshold, relative to 0.74g in WT males, $p < .05$).

Next, we examined female WT mice after K/BxN serum transfer. To our surprise, female mice developed an initial tactile allodynia that is indistinguishable from males (0.72g relative to 1.97g at baseline), but do *not* develop a persistent pain state (post-inflammatory threshold: 1.36g, $p < .05$). The behavioral phenotype of female WT mice resembled that of *Tlr4*$^{-/-}$ males, and we assessed whether similar cytokine signaling contributed to the K/BxN pain phenotype. Both female *Ifnar1*$^{-/-}$ and *Tnf*$^{-/-}$ mice were indistinguishable from their male counterparts in terms of both ankle inflammation and pain ($p > .05$). We then determined whether TNF and IFNβ transcripts change over

time (days 0, 3, 10, 18, and 28) by qPCR in male and female WT mice. Males showed a general increase in spinal TNF mRNA expression, and a decrease in IFNβ. Although the female mice also showed an increase in TNF transcripts, they had a transient decrease in IFNβ and then recovered to initial levels.

Conclusion: These results show persistent pain in male WT animals is associated with differential modulation by TNF and type I IFN. Female WT animals, however, fail to develop persistent pain, and show a recovery of IFNβ transcription indicating that co-modulation is important to prevent the development of persistent, post-inflammatory TA.

Abstract Number: 1016

Collagen Antibodies Induce Pain-like Behavior in Mice Independent of Inflammation and Complement Activation but Requires FcÎ³rs

Gustaf Wigerblad[1], Katalin Sandor[1], Kutty Selva Nandakumar[2], Rikard Holmdahl[3] and Camilla Svensson[1], [1]Department of Physiology and Pharmacology, Karolinska Institutet, Stockholm, Sweden, [2]Medical Biochemistry and Biophysics, Karolinska Institutet, Stockholm, Sweden, [3]Department of Medical Biochemistry and Biophysics, Karolinska Institutet, Stockholm, Sweden
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Background/Purpose:

Collagen Antibody Induced Arthritis (CAIA) is an acute mouse model of rheumatoid arthritis (RA). It is induced by an intravenous injection of a cocktail of monoclonal antibodies (mAb) against collagen type II (CII), producing a transient inflammation that typically starts around day 6-9 and peaks around day 12-15. Interestingly, in our studies aimed at characterizing pain-like behavior in the CAIA model we found that the mice displayed clear signs of nociception prior to the onset of inflammation. Thus, the purpose of this study was to characterize the pre-RA phase from a pain perspective and to investigate what drives anti-CII antibody-induced nociception.

Methods:

Male B10.RIII, B10.Q, and B10.Q $C5^{-/-}$ mice were injected i.v. with 4 mg/mouse of anti-CII mAbs cocktail, isotype control IgG, CII Ab Fab fragments, EndoS-treated CII mAbs, or CIIF4 mAbs and monitored for 5 days. Arthritis was examined by visual scoring of the paws (0-60), histological examination (H&E), and gene expression (qPCR) analysis of the ankle joints. MMP activity in the paws was visualized using MMPsense680. Pain-like behavior was monitored by measuring mechanical hypersensitivity with von Frey filaments day 0-5 and locomotion parameters by Comprehensive Lab Animal Monitoring System the night between days 2-3. Mice were injected subcutaneously (s.c.) with a peptide inhibitor (PMX53, 3 mg/kg/day) of the receptor for complement component 5a (C5aR).

Results:

Over the 5 days after injection of anti-CII mAb cocktail, only minor visual signs of inflammation (score: <10) in 3 of 14 mice was observed. Minor cell infiltration and bone erosion (in 2 and 1 mouse, respectively), while no cartilage destruction, change in mRNA expression (of examined cytokines, mast cell proteases, or MMPs), or MMP enzymatic activity was detected day 5. In contrast, all mice injected with CII mAbs, but not control mAbs, displayed a significant reduction in mechanical thresholds day 2, which remained low through day 5 and a significant decrease in ambulation, rearing, and total movement night 3. Mice lacking the C5 protein are resistant to CAIA. However, $C5^{-/-}$ mice and mice treated with C5aR inhibitor still developed anti-CII mAb-induced mechanical hypersensitivity and reduction in locomotion. The CIIF4 mAb bind cartilage but protects against arthritis, when injected with the CAIA mAbs. Injection of CIIF4 alone induced mechanical hypersensitivity to a similar degree as the anti-CII mAb cocktail. Injection of anti-CII mAbs lacking the Fc-part or the glycan at Asp297 did not induce hypersensitivity or reduce locomotion.

Conclusion:

No correlation between the arthritis scores, histological changes, gene expression of inflammatory factors, complement activation, and nociception (evoked or ongoing) was found. However, antibody treatment that diminishes the ability of the antibodies to associate with FcγRs prevented nociceptive behavior, indicating that antibody-Fc interaction is necessary for *in vivo* pain-behavior. Thus, our current work suggests that certain RA-associated antibodies have the capacity to evoke pain through mechanisms that are dependent on their binding to FcγRs but not by inducing inflammation.

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Abstract Number: 1017

A Novel Mechanism of Arthritis-Induced Pain: Activation of Sensory Neurons By Autoantibodies

Duygu Bas[1], Alex Bersellini Farinotti[1], Jon Sinclair[2], Gustaf Wigerblad[3], Kutty Selva Nandakumar[4], Rikard Holmdahl[5], Bo Rydqvist[2] and Camilla Svensson[3], [1]Physiology and Pharmacology, Karolinska Institutet, Stockholm, Sweden, [2]Karolinska Institutet, Stockholm, Sweden, [3]Department of Physiology and Pharmacology, Karolinska Institutet, Stockholm, Sweden, [4]Department of Biochemistry and Biophysics, Karolinska Institutet, Stockholm, Sweden, [5]Department of Medical Biochemistry and Biophysics, Karolinska Institutet, Stockholm, Sweden

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Background/Purpose: Joint pain is one of the main reasons for patients with rheumatoid arthritis (RA) to seek medical care. Collagen type II (CII) antibodies (Abs) are detectable in serum and synovial fluid of many RA patients and are thought to contribute to the inflammatory process in the joint. A common view is that factors produced during inflammation are the major cause of joint pain in RA. However, pain can appear prior to diagnosis and continue to be a significant problem even when the disease is under medical control. Earlier, we have shown that while injection of CII Abs in mice induces transient joint inflammation, pain-like behavior not only outlasts the inflammation but also precedes the onset of inflammation. Moreover, Fc gamma receptors (FcγRs), which are activated by immune complexes (ICs) on inflammatory cells, are also present on peripheral sensory neurons. The aim of this study is to examine if antibodies can directly activate sensory neurons via neuronally expressed FcγRs and thus act as pain-inducing molecules.

Methods: Male BALB/c mice (10-12 weeks) were used to prepare dorsal root ganglia (DRG) primary neuronal cell cultures. Neuronal expression of FcγRI was evaluated by immunocytochemistry. The effect of stimulation with CII mAb cocktail, control IgG2b and CII (all 1 µg/ml) and ICs formed by CII mAb cocktail and CII (CII-IC; 0.1-10 µg/ml) on neuronal excitability were examined by a) calcitonin-gene related peptide (CGRP) release in wild type (WT) and Fcγ-chain deficient mice b) electrophysiology and c) calcium imaging

Results: FcγRI expression was detected in DRG neurons and co-localized with PGP9.5, a neuronal marker. The levels of CGRP, a pain-associated neurotransmitter were increased in a bell shaped fashion in supernatants from WT DRG neurons stimulated with CII-IC, peaking at 1 µg/ml. Note that, 1 µg/ml concentration was used in subsequent studies. No increase in CGRP was detected after stimulation with CII mAb cocktail, CII or control IgG2b. CGRP release was induced by capsaicin (Cap; 50 nM), a ligand for transient receptor potential vanilloid 1 (TRPV1), was used as a positive control. In contrast, while DRG cultures from Fcγ-chain deficient mice responded to Cap, stimulation with CII-IC did not evoke CGRP release. Electrophysiological recordings in voltage clamp mode showed ionic current changes in the presence of CII-IC. Of 114 cells, 52 cells gave inward current response to Cap and 42% (22) of the Cap^+ cells gave response to CII-IC. In control experiments, none of the Cap^+ cells (18) responded to IgG2b. Calcium influx assessed by calcium imaging increased in DRG neurons stimulated with CII-IC and KCl (50 mM) (positive control to detect functional neurons) but not control IgG2b. Among the 1555 cells, 1119 cells gave response to KCl and 22.1% (247) of the KCl^+ cells responded to CII-IC, but not to control IgG2b (<1%).

Conclusion: The present study demonstrates for the first time that CII Abs in immune complex formation, presumably via activation of FcγRs expressed on DRG neurons directly contribute to nociception. These findings have the potential to define new roles for antibodies in pain transmission and open new avenues for treatment of pain in RA and other autoimmune diseases.

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Abstract Number: 1018

A 32-Mer Aggrecan Fragment Generated through Adamts-4/5 and MMP-Mediated Cleavage Can Directly Excite Nociceptive Neurons

Rachel E. Miller[1], Richard J. Miller[2], Abdelhak Belmadani[3], Suzanne Golub[4], Amanda J. Fosang[4] and **Anne-Marie Malfait**[5], [1]Biochemistry, Rush University Medical Center, Chicago, IL, [2]Molecular Biochemistry and Pharmacology, Northwestern University, Chicago, IL, [3]Northwestern University, Chicago, IL, [4]University of Melbourne, Melbourne, Australia, [5]Rush University Medeical Center, Chicago, IL

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Background/Purpose:

Cleavage of aggrecan in the interglobular domain (E^{373}-^{374}A) by ADAMTS-4/5 is an early event in osteoarthritis pathogenesis. Further cleavage by MMPs (N^{341}-^{342}F) releases a 32-amino-acid fragment, FFGVGGEDDITIQTVTWPDLELPLPRNVTEGE. We recently reported that this 32-mer acts as a TLR2-dependent damage-associated molecular pattern on chondrocytes and synovial fibroblasts. Here, we hypothesized that this aggrecan fragment may directly excite nociceptors.

Methods:

DRG cells (L3-L5) were isolated from adult C57BL/6 wild-type, *Tlr4*-null, or *Tlr2*-null mice and cultured. Direct effects of synthetic 32-mer on DRG neurons were monitored by examining intracellular calcium (Ca)i mobilization or production of MCP-1. For Ca mobilization assays, cells were loaded with Fura-2 and responses to 32-mer or scrambled peptide recorded in >100 neurons. For MCP-1 stimulation assays, cells were treated overnight with 32-mer (0.3-30 μM) or with scrambled control. Supernatants were collected for MCP-1 ELISA, because we have previously shown that MCP-1 is a key mediator of pain in experimental OA.

For *ex vivo* imaging assays, intact DRG were isolated from Pirt-GCaMP3 mice, which express the fluorescent calcium indicator, GCaMP3, in 90% of sensory neurons through the Pirt promoter. Explants, placed in a perfusion chamber and imaged using a spinning disk confocal microscope, were stimulated by injecting 10 μL of 1 mM 32-mer into a continuously running perfusion chamber with a 1 mL-volume. ImageJ analysis was performed to determine change in fluorescence intensity with time.

Results:

Cultured DRG neurons rapidly responded to 32-mer, but not scrambled control peptide, as indicated by increased (Ca)i in 20% of neurons. This suggests that DRG neurons express excitatory receptors for this protein fragment. Responses were mostly seen in small-to-medium-diameter neurons (nociceptors) that were also responsive to capsaicin, which demonstrates that TRPV1-expressing nociceptors are capable of responding to 32-mer. In order to show that 32-mer responses are not an artifact of cell culture, calcium imaging was also performed using intact DRG from Pirt-GCaMP3 mice. Within DRG explants, 7% of neurons responded to 32-mer peptide, while scrambled peptide elicited no responses.

Overnight stimulation of cultured DRG cells with either 3 or 30 μM 32-mer peptide resulted in significant upregulation in MCP-1 protein production compared to unstimulated cells (3.1-fold (3 μM) and 3.5-fold (30 μM), $p<0.001$). The highest concentration of scrambled peptide (30 μM) did not induce MCP-1 production (0.8-fold, $p=0.09$ vs. unstimulated).

In order to investigate which receptor mediates the upregulation of MCP-1, DRG cells were cultured from *Tlr2* null or *Tlr4* null mice. Stimulation with 32-mer peptide (3 μM) produced increased MCP-1 in *Tlr4* null DRG cells compared to unstimulated cells (3.3-fold, $p<0.01$), but not in *Tlr2*null cells (0.9-fold, $p=0.5$), suggesting that these effects are mediated through TLR2.

Conclusion:

Nociceptors can respond to a specific 32-mer cleavage product of aggrecan through TLR2. This pathway may contribute to the development of OA-associated pain, a hypothesis currently being tested in *in vivo* models.

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Abstract Number: 1019

Brain Functional Connectivity Differentially Predicts Response to Two Centrally Acting Analgesics in Fibromyalgia

Eric Ichesco[1], Johnson Hampson[2], Lynne Pauer[3], Andrew Clair[4], Tobias Schmidt-Wilcke[5], David A. Williams[6], Daniel J. Clauw[2] and Richard E. Harris[1], [1]Anesthesiology, U. Michigan, Ann Arbor, MI, [2]Anesthesiology, University of Michigan, Ann Arbor, MI, [3]Pfizer Inc, New London, CT, [4]Pfizer Inc., New York, NY, [5]Bergmannsheil, Bochum, Germany, [6]Anesthseiology, University of Michigan, Ann Arbor, MI

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Background/Purpose: Recently, several functional brain imaging techniques including functional magnetic resonance imaging (fMRI) have been proposed to be useful in probing the mechanisms of action of centrally acting analgesics. In parallel, our group has utilized brain resting state functional connectivity (fcMRI) outcomes to predict clinical pain response in fibromyalgia (FM) to pregabalin (PGB) and milnacipran (MLN), two known efficacious compounds. While preclinical work suggests that the mechanisms of action of these drugs may differ, a key hurdle in the identification of novel acting central analgesics would be the ability to differentially predict clinical response to different compounds in humans.

Methods: 29 female FM patients were included in this study: 14 underwent a double-blind placebo-controlled crossover study with the administration of PGB, and15 were enrolled in a similar study with MLN. All patients underwent a 6 minute fcMRI scan pre-treatment for both the drug and placebo periods. Patients also reported clinical pain pre- and post-treatment using a 0-10 rating scale. fcMRI data were analyzed with an *a priori* regions of interest approach using the Conn toolbox running through SPM8 and Matlab. Regions previously identified as predictive for PGB and MLN in isolation were cross-utilized in both data sets. Seeds included: the insula, rostral and genual anterior cingulate, dorsal lateral prefrontal cortex (DLPFC), periaqueductal gray, and amygdala. Prediction results were analyzed in SPM8 with a multiple regression that included seed-to-whole brain correlation maps with clinical pain difference scores. **Results** were significant on the cluster level with a false discovery rate p value < 0.05 derived from an uncorrected voxel level p value < 0.001.

Results: Reduced functional connectivity between the right DLPFC (seed) to both the inferior parietal lobule ($r = 0.94$ $p < 0.001$) and inferior/mid temporal gyrus ($r = 0.88$, $p < 0.001$) was associated with greater subsequent reduction in clinical pain for MLN, but not PGB. In contrast, greater connectivity between the rostral ACC (seed) to the subgenual ACC ($r = – 0.91$, $p < 0.001$) and the left amygdala (seed) to the left insula/sensory motor cortex ($r = - 0.96$, $p < 0.001$) and the primary motor cortex ($r = - 0.89$, $p=0.01$) was associated with subsequent reduction in pain for PGB, but not MLN. Furthermore, connectivity between the right periaqueductal gray (seed) to the precuneus ($r = - 0.89$, $p = 0.02$) and between the right anterior insula (seed) to the precuneus ($r = -0.86$, $p = 0.042$) was associated with reduction in pain to PGB, but not MLN.

Conclusion: These data demonstrate that fcMRI can differentially predict clinical response to two efficacious analgesics in FM, thus providing evidence that these compounds may have differing mechanisms of action. As suspected from preclinical data, it appears that SNRIs such as milnacipran may be acting partly by increasing fcMRI to brain regions involved in anti-nociception, whereas gabapentinoids such as pregabalin may be acting by decreasing fcMRI to pro-nociceptive regions. This provides some rationale for the common clinical practice of using these two classes of drugs in chronic pain states.

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Abstract Number: 1020

Abnormal Resting State Functional Connectivity in Chronic Fatigue Syndrome Patients: An Arterial Spin-Labeling fMRI Study

Roland Staud[1], Song Lai[2], Donald Price[3], Michael Robinson[4], Jason Craggs[5] and **Jeff Boissoneault**[6], [1]Rheum, Univ of Florida, Gainesville, FL, [2]Radiation Oncology, University of Florida, Gainesville, FL, [3]Oral Surgery, Univ of Florida, Gainesville, FL, [4]Clin and Health Psychology, Univ of Florida, Gainesville, FL, [5]Clinical & Health Psychology, University of Missouri, Columbia, MO, [6]University of Florida, Gainesville, FL

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Background/Purpose: Myalgic encephalitis/chronic fatigue syndrome (CFS) is a debilitating disorder characterized by disabling fatigue and cognitive dysfunction. However, little is known regarding the neural mechanisms underlying fatigue in CFS. Recent work from our laboratory utilizing arterial spin labeling functional magnetic resonance imaging (ASL fMRI) indicates CFS patients have lower resting state regional cerebral blood flow (rCBF) in several areas associated with memory and attentional functioning, including parahippocampal gyrus, superior frontal gyrus, and anterior cingulate gyrus. This regional hypoperfusion may underlie CFS pathogenesis. The current report uses functional connectivity analysis to determine relationships between fatigue related brain regions in CFS patients compared healthy controls.

Methods: Participants were 16 CFS patients (M_{age}=52.33 years, SD=10.6) and 19 age/sex matched healthy controls (HC; M_{age}=48.74 years, SD=11.74). CFS was diagnosed in all patients using 1994 CDC criteria. All participants underwent T1-weighted structural MRI as well as a 6-minute pseudo-continuous arterial spin labeling (pCASL) sequence. pCASL allows the non-invasive quantification of CBF by magnetically labeling blood as it enters the brain. Imaging data were preprocessed in MATLAB 2011b using SPM version 12 and ASL tbx. 4D ASL images were realigned and coregistered to structural MRI prior to pairwise subtraction of control and label images to obtain the perfusion time series. Perfusion signal time series were then masked and normalized, and CBF was computed using the single-compartment ASL perfusion model (Wang et al., 2005). Functional connectivity analysis was conducted using the CONN toolbox. All effects noted below are significant at $p<0.01$.

Results: ROI-to-ROI functional connectivity analysis utilizing the regions previously identified as being hypoperfused in CFS patients and regions associated with affective, cognitive, and motor function indicated differential patterns of functional connectivity between CFS patients and HC for several areas. Right parahippocampal gyrus connectivity with left medial temporal gyrus was higher in CFS patients than HC, whereas left parahippocampal gyrus connectivity to parietal operculum was lower in CFS patients than controls. Left superior frontal gyrus connectivity to right lingual gyrus was higher in CFS patients than HC, but connectivity to right frontal operculum was lower. Finally, anterior cingulate connectivity to the superior parietal lobule was higher in CFS patients than controls.

Conclusion: Results of our ASL based analyses demonstrated hypoperfusion in several brain regions of CFS patients associated with higher cognitive functions. Additionally, these regions also demonstrate altered functional connectivity in CFS patients compared to their healthy counterparts. Although preliminary, additional results also suggest abnormal relationships between functional connectivity as reflected by ASL fMRI and CFS symptoms (e.g., self-reported fatigue ratings).

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Abstract Number: 1021

Nucleic Acids Sensing Receptors RIG-I and MDA5 As Potential Amplifiers of the Interferon Signature in Childhood Onset Systemic Lupus Erythematosus

Naomi I Maria[1], M. Javad Wahadat[1], Cornelia G. van Helden-Meeuwsen[1], Annette van Dijk-Hummelman[2], Radboud JEM Dolhain[3], Sylvia Kamphuis[2] and Marjan A. Versnel[1], [1]Immunology, Erasmus Medical Center, Rotterdam, Netherlands, [2]Pediatric Rheumatology, Eramus MC Sophia Children's Hospital, Rotterdam, Netherlands, [3]Rheumatology, Erasmus Medical Center, Rotterdam, Netherlands
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Background/Purpose: Defective or sustained activation of Interferon (IFN) signaling has been associated with enhanced susceptibility to systemic lupus erythematosus (SLE). The cytosolic RIG-I-like receptors (RLRs), RIG-I (DDX58) and MDA5 (IFIH1) are intracellular pattern recognition receptors involved in the recognition of double-stranded RNA, leading to production of IFN type I. It is thought that overexpression of these receptors potentially promotes autoimmunity and contributes to the systemic IFN overactivation. Recent evidence showed a gain-of-function mutation in the IFIH1-gene, supporting the role of these cell-intrinsic sensors in autoimmune disease [Funabiki *et al*., Immunity 2014]. Childhood onset SLE (cSLE) is an incurable systemic autoimmune disease and medication is by far not effective enough, leaving children with significant side effects, especially due to prednisone. The aim of this study was to determine the prevalence of the IFN type I signature in cSLE, in relation to disease activity and the expression of the cytosolic RLRs.

Methods: In 34 healthy controls (HC), and 22 cSLE patients fulfilling ≥ 4 ACR criteria, whole blood (Paxgene) samples were collected. cSLE patients with a mean disease duration of 2.7 (± 1.6) years were followed-up prospectively and disease activity was assessed using the SELENA-SLEDAI score, including Physician Global Assessment and Flare-scores. Whole blood expression levels of 14 IFN-inducible genes, as determined by real-time quantitative PCR, were submitted to a principle component analysis (PCA) to identify 5 genes explaining >95% of the total variance. The IFNscore, a quantitative measure for total IFN type I bioactivity, was calculated using expression levels of the 5 indicator genes - IFI44, IFIT1, IFIT3, Ly6e and MX1 - to define the whole blood IFN type I signature in cSLE. cSLE patients positive for the IFN type I signature (IFNscore >10) were compared with patients negative for the IFN signature (IFNscore <10). Additionally, mRNA expression of the RLRs was assessed.

Results: We identified the presence of an IFN type I signature in 54.5% (12/22) of the cSLE patients. At time of inclusion, we found no significant difference in disease activity between IFNpositive and IFNnegative cSLE patients (p=0.0744). Disease activity and other biological markers are being assessed longitudinally. Interestingly the RLRs, RIG-I (p<0.001) and MDA5 (p<0.001) were significantly upregulated in IFNpositive cSLE compared to HC and IFNnegative cSLE patients. Furthermore, RIG-I (p<0.0001; r=0.954) and MDA5 (p<0.0001; r=0.904) highly correlated with the IFNscore.

Conclusion: The prevalence of the IFN type I signature in cSLE was 54.5%. Interestingly, overexpression of RIG-I and MDA5 is evident in cSLE, and strongly related to the presence of the IFN signature. Further investigating the role of these RLRs in disease pathogenesis is warranted and might offer new opportunities for selective therapeutic targeting.

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Abstract Number: 1022

Identification of Shared Genomic Regions in Distantly Related Pairs of Cases with Juvenile Idiopathic Arthritis

Sampath Prahalad[1], K. Alaine Broadaway[2], John F. Bohnsack[3], Ann Dodd[2], Aimee O. Hersh[4], Sheila T. Angeles-Han[1], Se Ryeong Jang[1], Marc Sudman[5], Susan D. Thompson[6], Michael Zwick[7], Karen Conneely[2] and Michael Epstein[2], [1]Emory University School of Medicine and Children's Healthcare of Atlanta, Atlanta, GA, [2]Emory University School of Medicine, Atlanta, GA, [3]Pediatrics, University

of Utah Health Sciences Center, Salt Lake City, UT, [4]Pediatrics/Rheumatology, University of Utah, Salt Lake City, UT, [5]Divison of Rheumatology, Childrens Hospital Med Ctr, Cincinnati, OH, [6]Rheumatology Dept, Childrens Hospital Med Ctr, Cincinnati, OH, [7]Human Genetics, Emory University School of Medicine, Atlanta, GA

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Background/Purpose: Juvenile idiopathic arthritis (JIA) is a complex genetic trait. While several risk variants have been identified using genome wide studies, a substantial component of the genetic risk is unexplained by known variants. We hypothesized that distantly related JIA cases might share genomic regions that harbor susceptibility variants.

Methods: Using probabilistic linking of children with JIA to the Utah Population Database, we identified distantly related JIA cases among descendants of founders with 4 or more descendants affected with JIA. We also identified distantly related controls whose degrees of relationship matched our cases. We genotyped subjects using Affymetrix 6.0 microarrays, and after stringent quality control, analyzed them using the Refined IBD program in Beagle. We identified segments greater than 1000 basepairs shared pairwise among cases. We then used GraphIBD to test for single nucleotide polymorphisms (SNPs) that fell within shared regions of case/case pairs more often control/control or case/control pairs.

Results: We identified 296 distantly related cases and 300 distantly related controls. In all 194 founders had significantly excessive number of descendants with JIA (range 4-17). We genotyped 218 cases and 148 controls, of whom 190 cases and 139 controls met our rigorous quality control inclusion criteria (excluding individuals with <95% call rate or heterozygosity outliers, close relatives, and population stratification outliers). Although no SNPs demonstrated association at genome wide thresholds of significance, many demonstrated associations at $p < 1X10^{-4}$ (Figure). Of the top 500 SNPs, 120 were on chr 6, corresponding to a gene *EYS,* (best $p < 1.8X10^{-5}$) which is implicated in retinitis pigmentosa, and acute uveitis associated with ankylosing spondylitis. Variants on chr 20, corresponding to the gene *PTPRT*, implicated in rheumatoid arthritis were also associated ($p < 8\ X10^{-5}$). Other regions of interest included *NFKRB* on chr 11, and two novel transcripts on chr 4 and 15.

Conclusion: Using a novel approach, we found variants in *EYS* and other loci that are shared more often among distantly related JIA case pairs, although the modest sample size limited our power. Investigating distantly related JIA case pairs offers a complementary approach to the search for genes underlying JIA risk. Analysis stratifying subjects by presence of uveitis, and replication of high priority variants in an independent cohort of JIA are underway.

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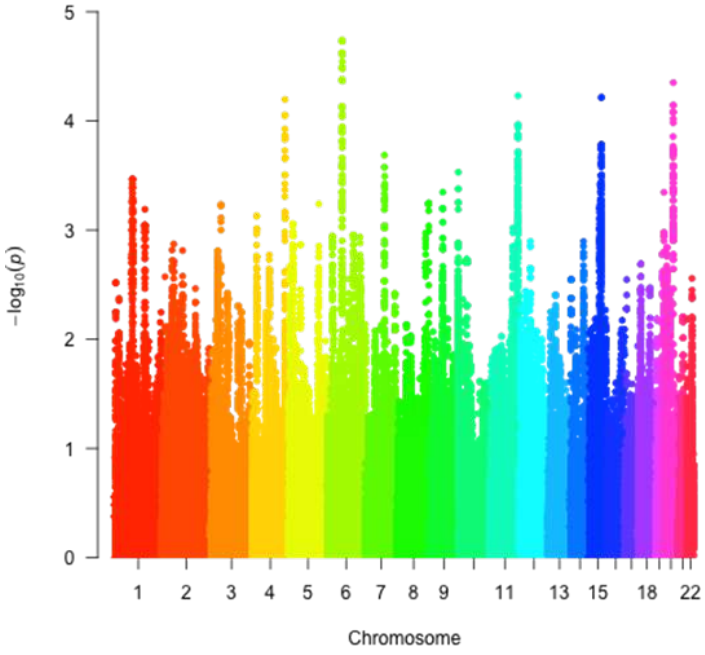

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Abstract Number: 1023

Tumor Necrosis Factor-a (TNF-a) and Interferon Gamma Inducible Protein-10 (IP-10) As Predictors of Active Disease Status in Localized Scleroderma

Kathryn S. Torok[1], Jonathan Yabes[2], Qi Mi[3], Christina Kelsey[1] and Kelsey Magee[4], [1]Pediatric Rheumatology, Univ of Pittsburgh Med Ctr, Pittsburgh, PA, [2]Department of Medicine, University of Pittsburgh, Pittsburgh, PA, [3]Department of Sports Medicine and Nutrition, University of Pittsburgh, Pittsburgh, PA, [4]Pediatrics, University of Pittsburgh, Pittsburgh, PA

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Background/Purpose: Localized scleroderma has both inflammatory and fibrotic components contributing to its effect on the skin and underlying tissue. The extent and duration of inflammation during the active phase of the disease is thought to be the major contributor to long-term disease damage and disability in LS. Therefore, accurately identifying the active disease state is imperative, which may not always be apparent in subtypes with deeper tissue involvement or slowly progressive changes, such as with the Parry Romberg subtype. Current commercially available serological markers of disease activity, such as ESR and CRP, are rarely elevated in LS. Therefore, identifying new circulating biologic markers reflecting active disease status would be helpful for patient management; especially when deciding when to initiate or discontinue therapy in unclear cases.

Methods: Forty-five LS subjects with ≥ 2 serial serum samples who had active disease (Physician Global Assessment - Activity > 0) at the first sera collection and had subsequently entered inactive disease state at follow-up (remission) were included in a 31

cytokine/chemokine Luminex panel (T_H1 / 2 / 17 associated panels) run on 72 total LS subjects. The cytokine profile of active vs. inactive disease state was analyzed utilizing both statistical modeling and data mining techniques. Unadjusted and adjusted mixed effects logit models were fitted using activity status as the outcome and each of the cytokines as the primary predictor. Covariates for adjustment were included one at a time. Cytokine levels were categorized into quartiles and Association Rules Mining (web-based analyses) and Bayesian Network assessment were used as alternative analytical strategies.

Results: In unadjusted analyses, the cytokines/chemokines that were significantly elevated at the baseline active disease visit compared to the inactive disease state at follow-up were IP-10 (Odds Ratio (OR) [95% confidence interval] = 2.1 [1.4, 3.2], p <0.001), TNF-α (OR = 1.8 [1.1, 3.0], p = 0.016), and MCP-1 (OR = 2.0 [1.1, 3.9], p = 0.034). After adjusting one at a time for several clinical covariates, such as age at first sample, disease duration, gender, mLoSSI, LoSDI, ANA, Anti-ssDNA and AHA antibodies, IP-10 remained significant for all adjustments, TNF-α significant for all except mLoSSI, and MCP-1 significant for all except disease duration. Data mining approaches demonstrated similar results with elevation of IP-10 and TNF-α in the peripheral blood (4^{th} quartile) showing the strongest links in the active disease node, followed by other T_H1 associated cyto/chemokines and T_H17 associated cytokines.

Conclusion: IP-10 and TNF-α were identified as inflammatory mediators that predict disease activity when comparing paired active and inactive LS serologic cytokine/chemokine profiles. These data support earlier findings of correlations of IP-10 and TNF-α with disease activity parameters in a cross-sectional Luminex plasma study. These may serve to augment clinical decision making when disease activity status is not straightforward by clinical examination. Further study with additional longitudinal serological data points is underway.

Disclosure: K. S. Torok, None; **J. Yabes**, None; **Q. Mi**, None; **C. Kelsey**, None; **K. Magee**, None.

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Abstract Number: 1024

Disruptions in Folate Homeostasis May Lead to Increased Risk for Methotrexate Intolerance in Juvenile Idiopathic Arthritis

Mara L Becker[1], Leon van Haandel[2], Ryan Funk[3], Rodger Gaedigk[4] and J.S. Leeder[5], [1]Rheumatology, Children's Mercy Kansas City, Kansas City, MO, [2]Clinical Pharmacology, Medical Toxicology, and Therapeutic Innovation, Children's Mercy Kansas City, Kansas City, MO, [3]University of Kansas Medical Center, Kansas City, KS, [4]Clinical Pharmacology, medical Toxicology and Therapeutic Innovation, Children's Mercy Kansas City, Kansas City, MO, [5]Clinical Pharmacology, Medical Toxicology and Therapeutic Innovation, Children's Mercy Kansas City, Kansas City, MO

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Background/Purpose: Despite widespread use, there remain no clear predictors of methotrexate (MTX) response or toxicity in Juvenile Idiopathic Arthritis (JIA). With the utilization of new assessment tools, the prevalence of MTX intolerance may be higher than previously recognized. We explore cellular folate and genotype as potential predictors of MTX intolerance.

Methods: This is a single center prospective cohort study of newly treated JIA patients on standardized doses of MTX (15mg/m^2) and folic acid (1mg/day). After obtaining informed consent, samples for assessment of intracellular erythrocyte folate ([folate]; comprised of 5-methyl-tetrahydrofolate + 5-10 methenyl-tetrahydrofolate) and MTX polyglutamate (MTXGlu) measurements by UPLC-tandem mass spectrometry are collected prior to and after 3 and 6 months on therapy. Genotype analysis for 41 SNPs, indels and repeats in 23 folate related genes are assessed by established methods. Clinical data are collected at each time point and include the methotrexate intolerance severity score (MISS) in a subset of patients (n=26). Statistical significance was tested using ANOVA, simple linear regression, and chi square, utilizing Wilcoxon Rank Sum or Spearman's correlations in non-normally distributed data

Results:

MISS scores ranged from 0-11, and the median (IQR) score was 2 (0, 5) in the 26 patients with data at 3 months; of these, 4/26 (15%) had a score of 6 or greater. Higher pretreatment RBC [folate] was associated with lower 3 month MISS scores (β: -0.005, p=0.008, R^2 0.28). Greater decreases in RBC [folate] from baseline were also associated with lower 3 month MISS scores (β: -3.033, p=0.05, $R^2$0.17).

When MISS scores were dichotomized at a cutoff of 6, patients with scores less than 6 had higher mean baseline RBC [folate] compared to patients with scores of 6 or greater (1107.5 (± 306) nmol/L vs. 767.2 (± 184) nmol/L, $p<0.05$). There were no correlations between 3 month MISS scores and MTXGlu.

The presence of at least 1 variant allele in methionine synthase reductase (MTRR) A>G (rs 1801394) appeared protective based on lower mean MISS scores (1.4 vs. 5.3, p=0.005) and decreased probability of a MISS score of ≥6 (0% vs. 50%, p=0.02). Homozygous variant patients had higher mean baseline RBC [folate] (1152.7 (± 379) nmol/L vs. 897.4 (± 304) nmol/L, p=0.01) and higher 3 month RBC [folate] (807.4 (± 241) nmol/L vs. 656.9 (± 241) nmol/L, p=0.02).

Conclusion: MTX intolerance is associated with lower baseline folate and reduced folate depletion after MTX initiation, suggesting a difference in folate homeostasis in intolerant children. Genetic variation in MTRR (rs 1801394) appears to be protective and reflects its important regulatory role in the folate pathway, restoring the activity of methionine synthase (MTR), crucial for transformation of homocysteine to methionine and important for one-carbon metabolism. The 'Methyl-trap' has been described with decreased MTR/MTRR activity due to depletion of the B_{12} cofactor, resulting in a functionall folate depleted state. Our data suggest that MTRR AA patients may be at risk for a similar 'methyl trap' state, further exacerbated with the introduction of MTX, resulting in increased intolerance.

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Abstract Number: 1025

Interstitial Lung Disease in Sting-Associated Vasculopathy with Onset in Infancy (SAVI): Genotype-Phenotype Correlation

Louise Malle[1], Bernadette Marrero[1], Yin Liu[2], Gina A. Montealegre Sanchez[1], Dawn C. Chapelle[1], Hanna Kim[1,3], Michelle O'Brien[1], Suzanne Ramsey[4], Gregor Dueckers[5], Seza Ozen[6,7], Helmut Wittkowski[8], Dirk Föll[9], Klaus Tenbrock[10], Olcay Y. Jones[11], Steven M. Holland[12], Joseph Fontana[13], Yan Huang[1], Benito Gonzalez[14], Paul Brogan[15], Juergen Brunner[16], Athimalaipet V Ramanan[17], Tom Hilliard[17], Laisa Santiago[18], AnneMarie Brescia[19], Amy Paller[20], Stephen Brooks[21], Zuoming Deng[22], Adriana Almeida de Jesus[1] and Raphaela Goldbach-Mansky[1], [1]Translational Autoinflammatory Diseases Section, NIAMS, NIH, Bethesda, MD, [2]Scientific Review Branch, NIAMS, NIH, Bethesda, MD, [3]Pediatric Rheumatology, Alfred I duPont Hospital for Children, Wilmington, DE, [4]Pediatric Rheumatology, IWK Health Centre, Halifax, NS, Canada, [5]Helios Kliniken - Kinderklinik, HELIOS Klinikum Krefeld, Krefeld, Germany, [6]Paediatric Rheumatology International Trials Organization (PRINTO), Istituto Giannina Gaslini, Genova, Italy, [7]Pediatric Nephrology and Rheumatology, Hacettepe University, Ankara, Turkey, Ankara, Turkey, [8]Pediatrics, University of Muenster, Muenster, Germany, [9]University of Muenster, Muenster, Germany, [10]University Aachen, Aachen, Germany, [11]Rheumatology, George Washington University, Washington, DC, [12]Laboratory of Clinical Infectious Disease, NIAID, NIH, Bethesda, MD, [13]NHLBI, NIH, Bethesda, MD, [14]Luis Calvo Mackenna Hospital, Santiago, Chile, [15]UCL Institute of Child Health and Great Ormond Street Hospital NHS Foundation Trust, London, United Kingdom, [16]Universitätsklinik für Kinder- u. Jugendheilkunde, Innsbruck, Austria, [17]Bristol Royal Hospital for Children, Bristol, United Kingdom, [18]All Children's Hospital Rheumatology, Saint Petersburg, FL, [19]Jefferson Medical College/ A.I. Dupont Hospital for Children, Willmington, DE, [20]Departments of Dermatology and Pediatrics, Feinberg School of Medicine, Northwestern University, Chicago, IL, USA;, Chicago, IL, [21]NIAMS/NIH, Bethesda, MD, [22]Biodata Mining & Discovery, NIAMS/NIH, Bethesda, MD
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Background/Purpose:

STING-Associated Vasculopathy with Onset in Infancy (SAVI) is an IFN-mediated disease caused by gain-of-function mutations in *TMEM173*, the gene encoding the stimulator of interferon genes (STING). SAVI is a member of a subclass of interferon-mediated autoinflammatory disorders caused by chronic Type-I interferon (IFN) production. To evaluate genetic causes of the variable disease severity of the interstitial lung disease (ILD) in SAVI patients, we hypothesized that the severity of the interstitial lung disease may be

modulated by a common SNP (R232H, rs1131769) that is functionally associated with decreased *IFNB1* transcription.

Methods:

Twelve SAVI patients, with N154S, V155M, V147L, or V147M *TMEM173* mutations, were evaluated. Lung involvement was assessed by chest computed tomography (CT) and pulmonary function tests (PFTs) for all patients; lung biopsies were available for seven patients. Peripheral blood genomic DNA samples were obtained and *TMEM173* (NM_198282.3) gene was sequenced by Sanger technique. STING function was evaluated in the different *TMEM173* haplotypes by *IFNB1* Luciferase Reporter assays performed with cells transfected with wildtype or mutant *TMEM173* on the R232 and the H232 backgrounds.

Results:

Of twelve SAVI patients, nine had evidence of severe ILD characterized by moderate to severe abnormalities on chest CT, PFTs and/or lung biopsy. Four out of the nine patients with severe ILD succumbed to pulmonary complications. Two patients presented with mild ILD and one did not have any evidence of ILD. The only patient without ILD was homozygous for the H232 allele (H232/H232) and the two patients with mild ILD were heterozygous (R232/H232) for the SNP. On contrast, 8 out of the 9 patients with severe ILD were homozygous for R232 (R232/R232) and one was heterozygous for the SNP. Thus, the severity of interstitial lung disease seems to correlate with the STING haplotype. Transfection of HEK293T cells with the R232 *TMEM173* haplotype with or without SAVI-causing mutations results in significantly increased *IFNB1* expression in the presence of both low affinity and high affinity STING stimulator cGAMP in comparison with cells transfected with the H232 haplotype. These findings suggest that the H232 haplotype background may be protective from the development of ILD and that gain-of-function of STING in the R232 background seems to provoke a more severe lung phenotype.

Conclusion:

The variable severities of ILD in SAVI patients are associated with the *TMEM173* haplotype at amino acid position 232. Our functional data suggest that common polymorphisms can modify organ-specific disease expression and provide insights to understanding the variable disease phenotype in other IFN-mediated diseases.

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Abstract Number: 1026

Microrna-125a-5p Has Increased Expression in Active Systemic Juvenile Idiopathic Arthritis and Is an Essential Modulator of Regulatory Macrophage Phenotypes in Vitro

Grant Schulert[1], Ndate Fall[2], Nan Shen[3], Sherry Thornton[2] and Alexei A. Grom[4], [1]Pediatric Rheumatology, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, [2]Division of Rheumatology, Cincinnati Children's Hospital, Cincinnati, OH, [3]Center for Autoimmune Genomics and Etiology, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, [4]Division of Rheumatology, Cincinnati Children's Hospital Medical Center, Cincinnati, OH

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Background/Purpose: Systemic juvenile idiopathic arthritis (SJIA) is an autoinflammatory disease of childhood, characterized by a predominance of mononuclear phagocytic effector cells, compared to the lymphocyte driven pathogenesis in other autoimmune JIA subtypes. Monocytes respond to their cytokine milieu by adopting polarization phenotypes with distinct functions, including M1 (classical) activation and several forms of alternative activation, including M2b and M2c which have potent immunoregulatory properties. Previous

data has shown that monocytes in SJIA patients have a novel phenotype, with features of both classical activation and immunoregulatory phenotypes. Controlling factors of monocyte/macrophage differentiation in SJIA are unknown. MicroRNAs are transcriptional negative regulators which fine-tune gene expression, and have been implicated in the differentiation of monocytes/macrophages. However, microRNA expression in SJIA has not been examined.

Methods: CD14+ monocytes were isolated from children with active SJIA and clinically inactive disease (CID), and miRNA expression quantified using TaqMan MicroRNA Array. Primary human monocytes or THP1 macrophage-like cells were polarized using LPS and interferon-γ (M1), IL-4 (M2a), LPS plus immune complexes (M2b), and IL-10 or TGF-β (M2c). THP1 cells were treated with either miR-125a-5p-specific or negative control antagomir or transfected with miR-125a-5p or negative control mimic prior to polarization. Gene expression was determined using real-time PCR or TaqMan assays.

Results: We identified miR-125a-5p as the most highly upregulated microRNA in monocytes from children with active SJIA compared to those with CID. Expression of miR-125a-5p significantly correlated with markers of disease activity, including serum ferritin and white blood cell count, and systemic features such as rash and hepatomegaly. Expression of miR-125a-5p was significantly increased in both primary human monocytes and THP1 cells after polarization with M2b or M2c conditions, but not by M1 polarization. Interestingly, we found that miR-125a-5p was dispensable for M1 polarization, as treatment with a specific microRNA antagomir did not alter expression of MIG, I-TAC, TNF-α or IL-6. However, miR-125a-5p was essential for M2b polarization, as antagomir treatment significantly reduced expression of the M2b-specific chemokine CCL1 by 56%. Conversely, transfection of miR-125a-5p mimic resulted in enhanced M2b polarization with increased expression of CCL1, IL-6, and CD163. In contrast, miR-125a-5p overexpression diminished M2c polarization, and altered M1 polarization by increasing production of some M2-associated markers.

Conclusion: Our data demonstrated increased miR-125a-5p expression in active SJIA and correlation with disease activity. We also showed that miR-125a-5p serves as an essential regulator of the polarization of M2b regulatory macrophages, and may impact the balance between different forms of alternative activation. Taken together, these data suggest that miR-125a-5p could serve as an important diagnostic and therapeutic target in SJIA.

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Abstract Number: 1027

Rheumatoid Arthritis Disease Activity Assessment Frequencies in Clinical Practices Do Not Support Treat-to-Target Care

David Sikes[1], James Bower[2], Drew Johnson[3], J. Timothy Harrington[2], Rafia Khalil[4], Edmund LaCour[5], Michael Naarendorp[6], Hillary Norton[7] and Kathleen Thomas[8], [1]Rheumatology, Florida Medical Clinic PA, Zephyrhills, FL, [2]Joiner Associates LLC, Madison, WI, [3]Crescendo Bioscience, Inc., South San Francisco, CA, [4]Rafia Khalil Arthritis & Rheumatology Center, PC, Port Huron, MI, [5]Dothan Medical Associates PC, Dothan, AL, [6]Harlem Rhematology, LLC, New York, NY, [7]Rheumatology, Santa Fe Rheumatology, Santa Fe, NM, [8]Community Rheumatology, Noblesville, IN

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Background/Purpose: Treat-to-Target (T2T) recommendations for rheumatoid arthritis (RA) care include standardized frequencies of disease activity (DA) assessment based on DA level. For this study, "on time" is defined as three-month intervals for patients with moderate or high disease activity and six-month intervals for those with controlled or low disease activity. These assessments are generally performed during provider-patient encounters using a variety of clinical and laboratory measures. The actual frequencies of DA assessments in clinical practices are investigated in this study.

Methods: The Rheumatoid Arthritis Practice Performance (RAPP) Project is a voluntary collaboration of U.S. clinician rheumatologists whose goal is to provide T2T care and optimal RA disease outcomes. Of the 168 participants in the RAPP Project, 86 have enrolled their entire RA population (ICD-9 code 714.0) in a HIPAA-compliant disease population registry to this point and are entering their preferred

DA measures. Sorting these DA measures by date allows an analysis of "on-time" and "overdue" percentages in each population. The 15 RA populations in this analysis have one or more DA measures entered on at least 45% of the enrolled population, including RAPID3, a 0-10 Provider Global Assessment (PGA), Clinical Disease Activity Index (CDAI), and/or a multi-biomarker (MB) test. The on-time/overdue analysis for each registry uses multi-biomarker results, as this measure is entered for the greatest number of patients (N=11,332). The reasons for overdue DA assessments were analyzed separately in 20 practices using a visit capacity analysis methodology (provider visit slots available per month compared to slots needed for on-time assessment).

Results:

On-time DA Assessment Analysis	**Median**	**Ranges (N,%)**
Patients enrolled/registry (N,%)	662/100%	413-2120
Patients assessed/registry (N,% of enrolled)	636/81%	204-1560
DA distribution in 15 RA registry populations		
Controlled and Low DA (% of assessed)	22%	16-36
Moderate DA (% of assessed)	39%	35-45
High DA (% of assessed)	39%	28-47
On-time assessment rates (% of DA cohorts)		
Controlled and Low DA assessed within 6 months	10%	3-21
Moderate and high DA assessed within 3 months	29%	14-52

Similar on-time percentages were obtained for other DA measures.

Capacity Analysis showed that most practices had insufficient visit slots available to provide on-time DA assessments for their population.

Conclusion: 1. RA disease activity assessments in clinical practices are not being provided as frequently as recommended for T2T care. 2. Until DA assessments are on time, treatment cannot be optimized. 3. Population registries and different practice workflows are required to provide and document on-time DA assessments.

Disclosure: D. Sikes, Crescendo Bioscience, 5; **J. Bower**, Crescendo Bioscience, 5; **D. Johnson**, Crescendo Bioscience, 3; **J. T. Harrington**, Crescendo Bioscience, 5; **R. Khalil**, Crescendo Bioscience, 5; **E. LaCour**, Crescendo Bioscience, 5; **M. Naarendorp**, Crescendo Bioscience, 5; **H. Norton**, Crescendo Bioscience, 5; **K. Thomas**, Crescendo Bioscience, 5,Crescendo Bioscience, 8.

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Abstract Number: 1028

Improving Pneumococcal Immunization Rates Among Immunocompromised Adolescent Patients at a Tertiary Care Children's Hospital

Michal Feldon[1], Adam Furnier[2], Corinne Lehmann[3], Bradford Fletcher[4], Jack Kues[5], Barbara Speer[5], Sandy Kramer[6], Pamela Morgan[7], Lois Siegle[8], Rebecca Brady[9] and Jennifer L. Huggins[6], [1]Pediatric Rheumatology, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, [2]Quality Improvement Systems, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, [3]Division of adolescent and transitional medicine, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, [4]Division of pharmacy, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, [5]Continuing medical education department, University of Cincinnati, Cincinnati, OH, [6]Division of Rheumatology, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, [7]Division of gastroenterology, hepatology and nutrition, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, [8]department of gastroenterology, hepatology and nutrition, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, [9]Division of infectious diseases, Cincinnati Children's Hospital Medical Center, Cincinnati, OH

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Background/Purpose: *Streptococcus pneumoniae* is a leading cause of severe infections, including pneumonia and meningitis, among immunocompromised patients. The administration of both the 13-valent pneumococcal conjugate vaccine (PCV13) and the 23-valent pneumococcal polysaccharide vaccine (PPSV23) is indicated for patients with immunocompromising conditions per U.S. Advisory Committee on Immunization Practices (ACIP) guidelines.

The SMART aim of this project was to increase the percentage of immunocompromised patients 11 years and older seen in the Rheumatology and Inflammatory Bowel Disease (IBD) clinics at Cincinnati Children's Hospital Medical Center (CCHMC) who receive PCV13 vaccine from 20% to 80%.

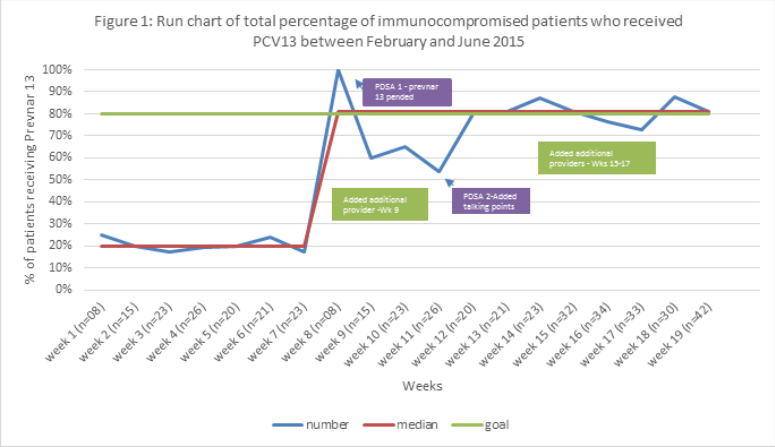
Methods: Providers from various specialty clinics at CCHMC recognized common barriers related to immunization administration, including knowledge gaps, access to immunization records, identification of the immunocompromised patient, sharing responsibility of vaccine administration between the primary care provider (PCP) and the specialist and the appropriate timing of vaccines.

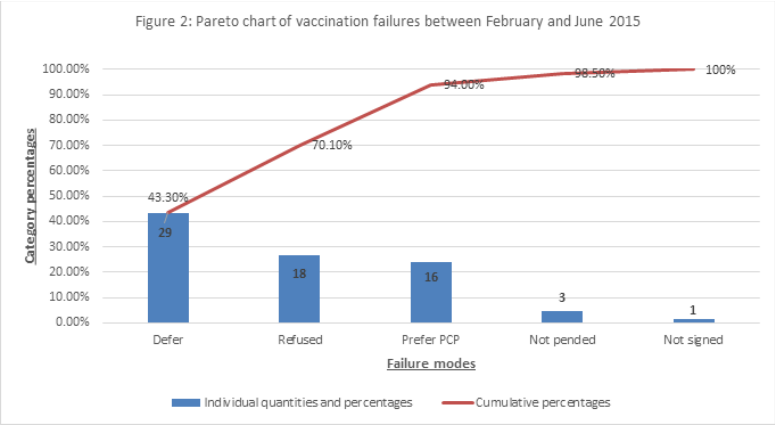
Eligible patients included adolescents defined as immunocompromised according to Center for Disease Control and Prevention (CDC) guidelines, between 11-18 years of age, who were seen in the Rheumatology and IBD clinics between February and June 2015.

Interventions that were implemented during the study included education of clinic providers and nurses; the development of physician "talking points" for patients; easy clinic access to vaccines and pre-visit planning that included a visual reminder to the provider and a pended order for the vaccine.

Results: During the 19-week study period, 443 eligible patients were seen in both clinics. The pre-intervention immunization rate for PCV13 ranged from 0% - 20%. Pending the vaccine order increased the percentage to ~60% [Figure 1] and the addition of provider "talking points" increased it further to 80%. In total, 376 patients (84.8%) received the PCV13. At the initiation of the project, most failures were related to the preference to receive vaccine in the PCP's office. With the institution of the "talking points", the main reason for failure was a request to defer the vaccine to a later visit with the specialist (Figure 2).

Conclusion: We have demonstrated that with a few key interventions, it is possible to increase the PCV13 vaccination rate to over 80% in a heterogeneous group of immunocompromised patients. These same measures can be easily implemented in other clinics for different vaccinations.





Disclosure: M. Feldon, None; **A. Furnier**, Pfizer Inc, 2; **C. Lehmann**, Pfizer Inc, 2; **B. Fletcher**, None; **J. Kues**, Pfizer Inc, 2; **B. Speer**, Pfizer Inc, 2; **S. Kramer**, None; **P. Morgan**, None; **L. Siegle**, None; **R. Brady**, Pfizer Inc, 2; **J. L. Huggins**, Pfizer Inc, 2.

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Abstract Number: 1029

Improving Gout Outcomes Using a Disease Management Program within an Integrated Health System

David Bulbin[1], Carson Maynard[2], Tarun Sharma[1], Alfred E. Denio[3], Jason Brown[4], Andrea Berger[5], H. Lester Kirchner[5] and William T. Ayoub[6], [1]Rheumatology, Geisinger Medical Center, Danville, PA, [2]Internal Medicine, Geisinger Medical Center, Danville, PA, [3]Dept of Rheumatology, Geisinger Medical Center, Danville, PA, [4]Henry Hood Center for Clinical Research, Geisinger Health System, Danville, PA, [5]Biostatistics, Geisinger Center for Health Research, Danville, PA, [6]Rheumatology, Geisinger Medical Group, State College, PA
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Background/Purpose: Gout is a chronic inflammatory arthritis which can be effectively managed. The American College of Rheumatology published evidenced based gout management guidelines. These guidelines are often not followed leading to unnecessary morbidity and cost. We piloted a gout management quality improvement project at one primary care site and the rheumatology department within our integrated health system.

Methods: The primary care site included 3 internal medicine providers, 11 family medicine providers, and 441 gout patients. We surveyed primary care providers for their preferred quality improvement strategies. These strategies included live or online continuing medical education (CME), electronic medical record reminders, nursing staff protocols, and a monthly National Quality Forum based outcome measure report card for each provider comparing their performance with peers. The Rheumatology Department included 15 rheumatologists and 800 gout patients. An exit survey again asked for the providers' preferred quality improvement strategies. Lastly, we compared the intervention primary care clinic results to a usual care control: another clinic that was matched for providers and gout patients. Performance data for gout patients 6 months before and after intervention were compared. Binary logistic regression models were used to obtain estimates of odds ratios with their 95% confidence intervals (CI). Post-intervention performance in the pilot site was compared to the control site.

Results: Data analysis pre- and post- intervention is presented in Table 1. Odds Ratios with their 95% confidence intervals for primary care intervention site versus usual care control are presented in figures 1 and 2. Survey results showed primary care providers rated live CME and electronic health record reminders the highest with an average 4/5 (5 being most effective). Rheumatologists chose audit and feedback of their own performance compared with peers highest at 4/5.

Conclusion: Gout management significantly improved with primary care and rheumatology intervention, education and accountability. There were significant improvements in both monitoring ($P<0.0001$) and goal uric acid level ($P<0.0001$). Gout outcome measures improved significantly in the intervention primary care site compared to the usual care site. The provider survey suggests that CME, EHR reminders and report card feedback were the most effective at changing provider behavior. We plan a system wide implementation of this gout quality improvement project.

Table 1: Odds Ratios and their 95% Confidence Intervals for Comparisons

	OR	95% CI		P-value
		Lower Bound	Upper Bound	
Primary Care Intervention Site: Average Effect Post Intervention vs. Average Effect Pre-Intervention				
Treated with urate lowering therapy	1.16	1.04	1.30	0.0089
Monitored Uric Acid in past 2 years	3.76	3.17	4.45	< 0.0001
At Goal (Uric Acid < 6.0)	2.44	2.01	2.96	< 0.0001
Rheumatology: Average Effect Post Intervention vs. Average Effect Pre-Intervention				
Treated with urate lowering therapy	1.07	0.95	1.22	0.2539
Monitored Uric Acid in past 2 years	5.67	5.08	6.33	< 0.0001
At Goal (Uric Acid < 6.0)	3.16	2.88	3.48	< 0.0001
Primary Care Intervention Site vs. Usual Care Control Site for May 2015 Performance				
Treated with urate lowering therapy	1.37	1.03	1.83	0.0329
Monitored Uric Acid in past 2 years	3.32	2.18	5.06	< 0.0001
At Goal (Uric Acid < 6.0)	1.94	1.29	2.91	0.0014

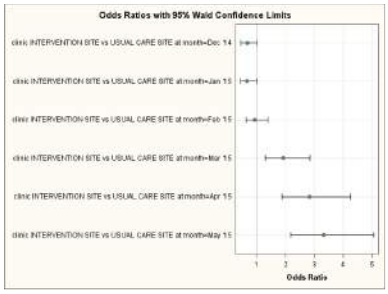

Figure 1: Odds Ratios and their 95% Confidence Limits by Month for Gout Patients monitored for uric acid level in the past 2 years at the Intervention Site versus the Usual Care Site.

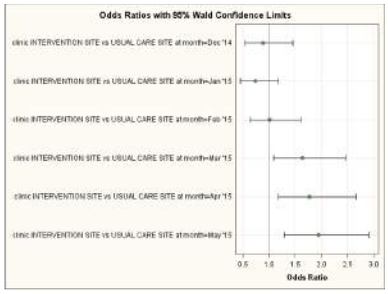

Figure 2: Odds Ratios and their 95% Confidence Limits by Month for Gout Patients at goal (uric acid < 6.0) at the Intervention Site versus the Usual Care Site

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Abstract Number: 1030

Unwanted Variations in Rheumatology Clinic Rooming: A Time Study Tool and Analysis

Brad Stroik[1], **Christie M. Bartels**[2], Diane Lauver[3], Patrick McBride[4], Jon Arnason[2], Sarah Loring[3] and Edmond Ramly[5,6], [1]University of Wisconsin School of Medicine and Public Health, Madison, WI, [2]Medicine, Rheumatology, University of Wisconsin School of Medicine and Public Health, Madison, WI, [3]University of Wisconsin-Madison School of Nursing, Madison, WI, [4]Cardiology/Medicine, University of Wisconsin School of Medicine and Public Health, Madison, WI, [5]Department of Medicine, University of Wisconsin-Madison, Madison, WI, [6]Industrial and Systems Engineering, University of Wisconsin-Madison College of Engineering, Madison, WI
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Background/Purpose: Facing fixed time for specialty visits, the time staff spends on rooming patients is a premium, but remains poorly understood. We conducted a time study, a basic systems engineering approach, to examine the frequency and duration of all visit related tasks performed by clinic staff (medical assistants (MA) or nurses) between the waiting room and the entry of the rheumatologist.

Methods: We developed a time study tool using health system policies and procedure documents, interviews and observations of pre-visit rooming. The tool measured 25 pre-determined tasks at a resolution of 15s=0.25 min. Trained engineering and medical observers measured 190 rooming sequences for a total of 1419 minutes at three rheumatology clinics in an academic multispecialty practice during Fall 2014-Spring 2015. Rooming was performed by nurses or MA at 2 sites, but otherwise by MAs. Scheduled visits varied from 20-30 minutes. We calculated descriptive statistics on tasks and times, compared frequencies using Fischer's exact test, and times using analysis of variance. We developed a task taxonomy and described variations in tasks.

Results: We observed 18 additional actions beyond 25 expected tasks. We then grouped 15 labeled tasks in 5 categories based on the sequence they occurred and clinical objectives for each task (Table 1). Total rooming time varied widely (2.5-22 min). Mean rooming time was 7.5 ± 3.1 min across clinics (Table 1) and varied between clinics, at 8.8, 6.7, and 7.6 minutes ($p<0.001$).

Vital signs (1.9 ± 0.6 min) and medication reconciliation (1.7 ± 1.3 min) accounted for half of the total rooming time. Maximum time variation was associated with questionnaire administration (±1.8 min), medication reconciliation (±1.3 min), and other conversations (± 1.2 min). Only 4 tasks were observed in >90% of the rooming sequences: initiation, pulse, blood pressure measurement, and medication reconciliation. For other tasks, frequencies varied by clinic. For instance, prescription refills occurred in 3 vs. 46% of clinic visits, and pain scores in 17 vs. 98% of visits when stratified by clinic ($p=<0.001$). Five of nine tasks with high frequency variation were identified to benefit from standardization: height, weight measurement, prescription refill cueing, pain assessment, questionnaire administration (disease activity, new patient) and tobacco history.

Conclusion: Using time study we developed a practical tool for measuring time spent on each rooming task, and created a taxonomy of rooming tasks. We found that the frequency and timing of rooming tasks varied among encounters and clinics. Implications of this work beyond our institution include methods for (A) identifying and prioritizing opportunities for standardization, (B) offering a platform for decisions regarding changing standards and (C) comparing baseline data for new scheduling or care quality initiatives.

Table 1. Duration and frequency of tasks in rooming sequence in rheumatology clinic visits

	ALL VISITS		Clinic A	Clinic B	Clinic C	Between Clinics	
TASKS	n= 190 Mean± SD	(%)	n=41 (%)	n=86 (%)	n= 63 (%)	p % of visits	p time
TOTAL TIMES	**7.5 ± 3.1**		**8.8 ± 2.5**	**6.7 ± 3.3**	**7.6 ± 2.8**	-	<0.001
Initiation: ID and Walk Patient to Room	**0.8 ± 0.4**	**99**	**100**	**99**	**100**		
Vitals (Wt/HT/P/BP/Temp)	**1.9 ± 0.6**	**100**	**100**	**100**	**100**		0.002
Weight Measurement	0.3 ± 0.2	81	88	66	95	*	
Height Measurement	0.4 ± 0.2	22	5	21	33	*	
Pulse Measurement	0.5 ± 0.2	94	98	92	94		0.02
Blood Pressure Measurement	1.1 ± 0.4	99	100	99	98		0.002
Temperature Measurement	0.3 ± 0.1	8	0	19	0	*	
Allergies/Med Reconciliation/Pharmacy	**2.1 ± 1.4**	**100**	**100**	**100**	**100**		
Allergies	0.3 ± 0.1	83	93	76	87	*	
Med Reconciliation	1.7 ± 1.3	98	100	98	98		
Pharmacy Specification	<15s†	83	85	76	92	*	
Refill Cuing	0.5 ± 0.3	18	46	3	21	*	
Chronic Disease Management	**0.8 ± 1.1**	**75**	**100**	**47**	**98**	*	
Pain Assessment	0.6 ± 0.4	61	98	17	95	*	
Questionnaires	0.8 ± 1.8	35	7	nr	57	*	<0.001
Vaccination History & Offer	0.5 ± 0.4	11	5	8	19		
Tobacco History	<15s†	43	56	38	41	*	
Other Questions or Conversation	**1.3 ± 1.2**	**84**	**93**	**78**	**86**		0.04
TOTAL OBSERVATION TIME = 1419 minutes							

*p<0.05. †<15s, no SD calculated. nr=Not recorded, administered in lobby.

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Abstract Number: 1031

Quantifying the Delays to Rheumatologist Consultation and Treatment Among Patients with Systemic Inflammatory Rheumatic Diseases

Jessica Widdifield[1], Sasha Bernatsky[2], J Carter Thorne[3], Claire Bombardier[4], R. Liisa Jaakkimainen[5], Vandana Ahluwalia[6], J. Michael Paterson[7], Noah Ivers[4], Debra Butt[8] and Karen Tu[8], [1]McGill University, Montreal, QC, Canada, [2]Rheum/Clin. Epid., McGill MUHC/RVH, Montreal, QC, Canada, [3]Southlake Regional Health Centre, Newmarket, ON, Canada, [4]University of Toronto, Toronto, ON, Canada, [5]Preventive Med and Biostatisti, University of Toronto, Toronto, ON, Canada, [6]Past President, Ontario Rheumatology Association, Brampton, ON, Canada, [7]ICES, Toronto, ON, Canada, [8]Institute for Clinical Evaluative Sciences, Toronto, ON, Canada

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Background/Purpose: Optimal care for systemic inflammatory rheumatic diseases often hinges upon early referral from primary care physicians (PCP) to rheumatologists. Our aim was to quantify the time from symptom onset (T_0) to 1st PCP visit related to the complaint (T_1) to PCP referral to rheumatologist (T_2) to 1st rheumatologist visit (T_3), and to treatment (T_4).

Methods: We employed a novel approach to identify 1st-time rheumatology referrals from the primary care Electronic Medical Record Administrative data Linked Database (EMRALD), representing comprehensive EMR data from 168 PCPs across Ontario, Canada (32 rural, 39 suburban and 97 urban physicians). Using a standardized data abstraction tool, PCP and rheumatology consultation records were reviewed to identify diagnoses and treatments associated with each referral. Administrative data were used to identify accurate dates of the 1st rheumatologist visit subsequent to the date of referral identified in the EMR. The time in days from the date of each component of the care pathway was determined overall and for each diagnostic category.

Results: Among 2430 patients with 1st-time referrals, we identified 745 patients with systemic inflammatory rheumatic diseases (31%): RA (16%), other inflammatory arthritis (22%), connective tissue diseases (18%), gout/crystal arthropathies (16%), spondyloarthropathies (10%), psoriatic arthritis (6%), polymyalgia rheumatica (9%), and vasculitis (3%). Overall, 21% and 70% of patients were seen by rheumatologists within 3 months of symptom onset and PCP referral, respectively. Wait-time measures varied by condition (table). Comparing to established Canadian wait-time measures (target being 100%), only 38% of RA patients were seen within 4 weeks from the date of referral, 63% of AS/SpA patients were seen within 3 months; and 34% of PsA patients were seen within 6 weeks. For RA patients, the median time to be seen by rheumatologists from symptom onset and referral was 327 and 66 days, respectively. Within the 1st year, 93% of RA patients had a documented treatment initiated by a rheumatologist, and of these, 95% were prescribed DMARDs, 26% oral steroid, 15% steroid injection, and 6% biologic. The average time to DMARD was 56 days from date of first rheumatology consultation.

Conclusion: Our representative sample of PCPs revealed longer wait-times than previous reports that sampled patients from urban rheumatology clinics and exceed current Canadian recommendations. Most of the delay occurs prior to referral, where targeted efforts are needed to optimize care for more timely consultations.

Table.

Proportion of Patients seen by rheumatologists within		**RA n=120**	**IA n=167**	**Crystal n=122**	**PMR n=66**	**AS/SpA n=76**	**PsA n=44**	**Vasculitis n=19**	**CTDs/Other n=131**
1 mo. from	Referral	38%	35%	27%	47%	22%	25%	53%	27%
	Symptom onset	#	#	5%	#	#	#	#	#
3 mo. from	Referral	71%	70%	64%	71%	63%	59%	74%	62%
	Symptom onset	24%	21%	16%	28%	14%	#	28%	17%
6 mo. from	Referral	79%	80%	83%	82%	83%	86%	74%	76%
	Symptom onset	42%	46%	35%	53%	34%	34%	39%	30%
9 mo. from	Referral	84%	83%	88%	86%	86%	96%	79%	77%
	Symptom onset	50%	59%	45%	63%	39%	43%	44%	42%
12 mo. from	Referral	87%	86%	89%	88%	86%	98%	79%	82%
	Symptom onset	59%	66%	47%	72%	41%	49%	56%	47%
Median (IQR) Time (in days)	Symptom onset (T_0) to PCP (T_1)	173 (16-189)	102 (10-112)	188 (4-192)	63 (14-77)	716 (14-730)	228 (17-245)	128 (3-131)	208 (14-222)
	PCP visit (T_1) to Referral (T_2)	115 (14-128)	125 (11-136)	353 (20-373)	123 (15-138)	173 (7-181)	513 (15-528)	73 (7-80)	181 (7-188)
	Symptom onset (T_0) to Referral (T_2)	326 (49-375)	259 (41-300)	1326 (48-1374)	238 (55-293)	1342 (63-1405)	627 (90-7167)	293 (33-325)	855 (44-899)
	Referral (T_2) to Rheumatologist (T_3)	66 (15-81)	55 (17-71)	69 (24-93)	53 (11-64)	62 (29-91)	88 (30-117)	28 (11-39)	62 (22-83)
	Symptom onset (T_0) to Rheumatologist (T_3)	327 (83-410)	260 (91-350)	1312 (111-1423)	240 (81-321)	1262 (112-1374)	680 (125-805)	608 (59-667)	940 (113-1053)

Abbreviations: RA: Rheumatoid Arthritis; IA: Inflammatory Arthritis – other (e.g., undifferentiated); Crystal: Gout and other crystal arthropathies; PMR: Polymyalgia Rheumatica; AS/SpA: Ankylosing Spondylitis and other spondyloarthropathies; PsA: Psoriatic Arthritis; CTDs: Connective Tissue Diseases and other systemic autoimmune rheumatic diseases (e.g., lupus, scleroderma, SjogrenÕs, RaynaudÕs); IQR: interquartile range; # not reported due low count

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Ahluwalia, None; **J. M. Paterson**, None; **N. Ivers**, None; **D. Butt**, None; **K. Tu**, None.

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Abstract Number: 1032

Adherence Patterns to American Academy of Ophthalmology Guidelines for Hydroxychloroquine Baseline Screening: Quality Assurance Assessment Utilizing Highmark Claims Data

Christina Payne[1], Patricia Gladowski[2], James Byers Jr.[2], Amy Tang[3] and Mary Chester M. Wasko[4], [1]Allegheny General Hospital Department of Medicine, Allegheny Health Network, Pittsburgh, PA, [2]Enterprise Knowledge Discovery, Highmark Health, Pittsburgh, PA, [3]Asthma, Allergy and Autoimmunity Institute, Allegheny Health Network, Pittsburgh, PA, [4]Lupus Center, Pittsburgh, PA

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Background/Purpose: Hydroxychloroquine (HCQ) is an antimalarial agent used commonly to treat selected autoimmune rheumatic diseases because of its therapeutic benefits, low cost, and favorable safety profile. While minor side effects may occur, the most feared toxicity is retinal thinning with irreversible loss of vision. The February 2011 American Academy of Ophthalmology (AAO) Revised Recommendations on Screening for Hydroxychloroquine Retinopathy advise a three-component baseline evaluation prior to initiation of therapy: 1)retinal exam, 2)Humphrey 10-2 visual-fields, and 3)either multifocal-electroretinogram, spectral-domain optical coherence tomography or fundus autofluorescence.

Methods: In this descriptive study, we utilized Highmark medical and pharmacy claims data to examine adherence to baseline screening recommendations in rheumatic disease patients initiating HCQ. We also explored ophthalmologic screening patterns in patients with ≥1 risk factor for development of retinal toxicity ("high risk" patients) and in rheumatic disease diagnostic subsets.

Results: From March 2011 through June 2014, 952 rheumatic disease patients initiated HCQ; 10% received the recommended 3 component ophthalmology screening, 44% completed partial screening, and 46% had no baseline eye evaluation (Table 1). Patients with commercial type insurance are more likely to complete screening than those with other types (Table 1). Of the 367 "high risk" patients, 13% had full screening, 53% had partial screening, and 34% had no baseline evaluation (Figure 1). Adherence patterns did not substantially differ by diagnostic subsets. In multivariable logistic regression analysis, the only predictor of full baseline screening was a history of retinal disease (Table 2).

Conclusion: Adherence rates to AAO recommendations for retinal baseline screening in rheumatic disease patients initiating HCQ are quite low, though somewhat better in those with risk factors for retinal toxicity. Our findings suggest that education of practitioners and patients is warranted to improve adherence to screening guidelines and optimize safe prescribing patterns.

Table 1: Six Month Pre and Post First Hydroxychloroquine Prescription - Testing Pattern Analysis

Testing Type	March 2011 – February 2012 Newly Identified Members (N = 274 / 1,622,759)	March 2012 – February 2013 Newly Identified Members (N = 244 / 1,644,542)	March 2013 – February 2014 Newly Identified Members (N = 313 / 1,531,030)	March 2014 – February 2015 (end Jun 2014)* Newly Identified Members (N = 121 / 1,931,913)	All Years Combined (by Testing Cohort) Newly Identified Members (N = 952 / 2,636,699)
Baseline Exam & Humphrey Visual Field Testing & either mfERG, SD-OCT and/or FAF	22 (8%) Commercial – 15 MA – 6 Other - 1	29 (12%) Commercial – 24 MA – 4 Other - 1	37 (12%) Commercial – 26 MA – 10 Other - 1	11 (9%) Commercial – 9 MA – 2 Other - 0	99 (10%) Commercial – 74 MA – 22 Other - 3
Any Other Combination of Testing	131 (48%) Commercial – 101 MA – 23 Other - 7	105 (43%) Commercial – 70 MA – 31 Other - 4	129 (41%) Commercial – 109 MA – 19 Other - 1	54 (45%) Commercial – 48 MA – 2 Other - 4	419 (44%) Commercial – 328 MA – 75 Other - 16
No Testing	121 (44%) Commercial – 103 MA – 16 Other - 2	110 (45%) Commercial – 96 MA – 10 Other - 4	147 (47%) Commercial – 128 MA – 16 Other - 3	56 (46%) Commercial – 49 MA – 5 Other - 2	434 (46%) Commercial – 376 MA – 47 Other - 11
Total Each Year (Without Regard to Testing Cohort)	274 Commercial – 219 MA – 45 Other - 10	244 Commercial – 190 MA – 45 Other - 9	313 Commercial – 263 MA – 45 Other - 5	121 Commercial – 106 MA – 9 Other - 6	N = 952 Commercial – 778 MA – 144 Other – 30

Figure 1: High Risk vs. Non-High Risk Member Testing Pattern Comparison

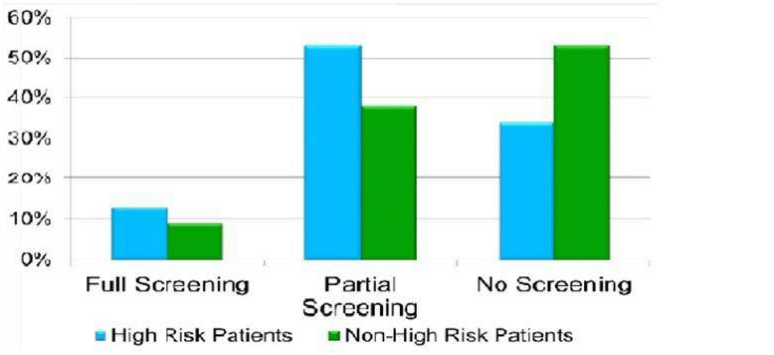

Table 2: Multivariate Regression Model Analysis of Retinal Toxicity Screening on High Risk Members

	Odds Ratio (95% CI)	P-Value
Age (≥65)		
<65 vs ≥65 (All Required Testing)	1.2 (0.54-2.7)	0.693
<65 vs ≥65 (Partial Screening)	1.1 (0.61-1.9)	0.826
Retinal Disease		
<65 vs ≥65 (All Required Testing)	5.5 (2.5-12.1)	**<0.0001**
<65 vs ≥65 (Partial Screening)	2.3 (1.4-3.9)	**0.002**
CKD		
<65 vs ≥65 (All Required Testing)	1.3 (0.52-3.1)	0.585
<65 vs ≥65 (Partial Screening)	1.2 (0.69-2.3)	0.465
Diabetes		
<65 vs ≥65 (All Required Testing)	1.05 (0.50-2.2)	0.901
<65 vs ≥65 (Partial Screening)	1.2 (0.71-2.0)	0.477

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Abstract Number: 1033

Novel Ligand-Independent Peptide Inhibitors of Triggering Receptor Expressed on Myeloid Cells 1 (TREM-1) and T Cell Receptor (TCR): Efficacy in a Collagen-Induced Arthritis Model Suggests New Targeted Treatment for Rheumatoid Arthritis

Zu T. Shen and **Alexander B. Sigalov**, SignaBlok, Inc., Shrewsbury, MA

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Background/Purpose: Macrophages and T cells are central to the pathophysiology of autoimmune diseases. Synovial macrophages, synovial fibroblasts and infiltrating T lymphocytes are the most abundant cell populations found in the synovium of patients diagnosed with rheumatoid arthritis (RA). Activation of these cells leads to the production of proinflammatory cytokines and mediators. Triggering Receptor Expressed on Myeloid Cells 1 (TREM-1) and T cell receptor (TCR), expressed on macrophages and T cells, respectively, play a critical role in the signal transduction pathways leading to the onset and development of RA. In this study, novel ligand-independent peptide inhibitors of TREM-1 and TCR were rationally designed by employing a new model of immune signaling, the Signaling Chain HOmoOLigomerization (SCHOOL) model, and these inhibitors, for the first time, were evaluated in a mouse collagen-induced arthritis (CIA) model.

Methods: CIA was induced by immunizing male DBA/1J mice on days 0 and 21 by bovine type II collagen in Freund's complete adjuvant. On day 24, animals were weighed, randomized across study groups and given daily intraperitoneal (IP) doses of SCHOOL TREM-1 inhibitory peptide GF-9 or TCR inhibitory peptide MG-11 in free and targeted nanoparticle-bound forms, at doses of 25 mg/kg and 2.5 mg/kg, respectively. The mice were weighed every second day and all paws were scored daily for clinical signs of arthritis.

Results: Mice treated with GF-9 or MG-11 showed a significant delay in arthritis onset as well as a striking reduction in disease severity. This effect is specific as administration of the control peptide did not affect disease onset or severity. Targeted delivery of SCHOOL peptides utilizing self-assembling lipid-peptide nanoparticles significantly increased peptide dosage efficacy.

Conclusion: This study provides clear data demonstrating that inhibition of TREM-1 and TCR signal transduction pathways using short synthetic peptides that employ a novel ligand-independent mechanism of action (SCHOOL peptides) may represent a new, targeted, and non-toxic treatment for RA. Importantly, this ligand-independent mode of TREM-1 inhibition may significantly decrease the risk of failure in clinical development because of the unknown nature of the TREM-1 ligand(s).

Disclosure: Z. T. Shen, None; **A. B. Sigalov**, None.

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Abstract Number: 1034

Immunomodulation By a Second-Generation Peptidyl Arginine Deiminase Inhibitor Abrogates Collagen-Induced Arthritis in a Therapeutic Protocol

Anne-Marie Quirke[1], Joanna Kawalkowska[2], Fatemeh Ghari[3], Venkataraman Subramaniam[4], Paul Thompson[5], Richard O. Williams[1], Nick La Thangue[3] and Patrick J. Venables[1], [1]Kennedy Institute of Rheumatology, University of Oxford, Oxford, United Kingdom, [2]Kennedy Institute for Rheumatology, University of Oxford, Oxford, United Kingdom, [3]Department of Oncology, University of Oxford, Oxford, United Kingdom, [4]Biochemistry and Molecular Pharmacology, University of Massachusetts, Worcester, MA, [5]University of Massachusetts, Worcester, MA

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Background/Purpose: Citrullination is a post translational modification of arginine catalysed by peptidyl arginine deiminases (PADs) and may be important in generating pathogenic autoantibodies to citrullinated proteins in rheumatoid arthritis. However citrullination may control inflammation by other mechanisms, including transcriptional modulation of cytokines and generation of proinflammatory

extracellular proteins. In previous studies, the PAD inhibitor Cl-amidine was shown to have a modest anti-inflammatory effect, when given prophylactically at high doses. While much of this benefit was thought to be due to inhibition of PAD4, recent studies have highlighted the proinflammatory effects of PAD2. Therefore the objective of this study is to examine the PAD inhibitor (BB-Cl-amidine), which is 10 fold more active than Cl-amidine against PAD2. We chose collagen-induced arthritis (CIA) as a reproducible and predictive model of immune-mediated arthritis and used a therapeutic, rather than prophylactic, treatment protocol, which could be translated into human disease.

Methods: CIA was induced by immunization with bovine type II collagen (CII) in DBA/1 mice. After the onset of arthritis, mice were scored daily for severity (0-3 for each paw) and hind paw swelling using calipers. Mice were treated daily with vehicle (n=12) or BB-Cl-amidine (1 or 10 mg/kg, n=12) intraperitoneally for 9 days post onset. On day 10 post onset, mice were culled, and paws, blood and inguinal lymph nodes collected for further analysis. Cytokines were measured in serum and lymph node culture supernatants using a multiplex platform, and serum IgG1 and IgG2a anti-CII antibodies by ELISA. The phenotypes of lymph node T cells and their response to anti-CD3 antibody stimulation were determined via flow cytometry.

Results: Therapeutic administration of 10 mg/kg BB-Cl-amidine after the onset of arthritis, reversed its development. Compared with vehicle treated mice, there was reduced clinical scoring ($p<0.0001$ from 5 days treatment), paw swelling ($p<0.0001$ from 6 days treatment), with a partial response in all measures to 1 mg/kg. Histological changes were almost completely normalised by BB-Cl-amidine at 10mg/kg with significant reduction in histology scores ($p<0.01$). These effects were accompanied by a significant increase in anti-collagen IgG1 ($p<0.0001$) and no change in IgG2a antibody levels. Unexpectedly, while pro-inflammatory cytokine levels in serum remained unaffected by BB-Cl-amidine, IL-4 and IL-5 were significantly elevated. In line with this, IL-4-expressing Th2 cells were increased in the lymph nodes of BB-Cl-amidine treated mice. Further analysis revealed a significant decline in Th1 and Th17 numbers with BB-Cl-amidine treatment.

Conclusion: Our study demonstrates that BB-Cl-amidine is therapeutic in CIA. The effect appears more due to immunomodulation than simple immunosuppression, by supporting anti-inflammatory Th2 responses, while inhibiting pro-inflammatory Th1 and Th17 responses. We propose that targeting PADs is now a realistic strategy for the treatment of rheumatoid arthritis and other chronic inflammatory diseases.

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Abstract Number: 1035

Synovium-Derived microRNAs Inhibit Bone Formation in Rheumatoid Arthritis

Ellen M. Gravallese[1], Yukiko Maeda[2], Nicholas H Farina[3], Paul Fanning[4] and Jane Lian[3], [1]Lazare Research Bldg Ste 223, University of Massachusetts Medical School, Worcester, MA, [2]Medicine, University of Massachusetts Medical School, Worcester, MA, [3]Department of Biochemistry, University of Vermont, Burlington, VT, [4]Department of Orthopedics, University of Massachusetts Medical School, Worcester, MA

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Background/Purpose: Articular bone erosion in rheumatoid arthritis (RA) is a consequence of synovial inflammation that leads to disability for patients. Cells within the synovium secrete inflammatory cytokines, RANKL, and Wnt signaling inhibitors, promoting osteoclastogenesis and inhibiting osteoblast function and bone formation. MicroRNAs (miRNAs) are key regulators of skeletal remodeling and also play a role in RA pathogenesis. Therefore, we hypothesized that miRNAs derived from synovial tissues may regulate the erosive process in RA at least in part through effects on osteoblasts.

Methods: To address whether synovium-derived miRNAs regulate osteoblast differentiation and bone formation, we used the serum transfer model of RA. We performed Fluidigm high-throughput expression profiling of 750 miRNAs in pooled synovial samples from non-arthritic and arthritic mice. We also performed gene array (Affymetrix) analysis in these same RNA samples and compared gene expression and miRNA expression from array data. To identify miRNAs regulating skeletal pathways, we collected target genes of up-regulated and down-regulated miRNAs using TargetScan. We restricted downstream analysis to targets differentially expressed by gene

array. Finally, we transfected a selected miRNA in murine calvarial osteoblasts to examine its role in cellular differentiation.

Results: Our comparative analysis identified 417 up-regulated genes that are predicted targets of 72 down-regulated miRNAs (1.5 fold or >), and 536 down-regulated genes that are predicted targets of 59 up-regulated miRNAs. Gene ontology analysis of the miRNA-targeted genes revealed significant enrichment of skeletal pathways involved in osteoblast function, including Wnt/β-catenin signaling. Of the 22 most significantly regulated (ANOVA $p<0.01$) miRNAs between non-arthritic and arthritic mice, 11 were predicted to target numerous Wnt and BMP signaling pathway components. We validated their expression in isolated synovial fibroblasts and in whole synovium by qPCR and showed that 4 of these miRNAs were downregulated by TNF. Some of the target genes of these miRNAs, including GSK3β, Sfrp2 and Tob1, were up-regulated at erosion sites in bone. Among the 11 miRNAs, miR-221 was significantly up-regulated during peak inflammation. Since miR-221 is known to be up-regulated in RA synovial tissues (Pandis et al., 2012), we examined the role of miR-221 in osteoblasts. Transfection of miR-221 into primary murine calvarial osteoblasts suppressed osteoblast differentiation and mineralization. Expression of a predicted target gene of miR-221 that is essential for bone mineralization, DKK2, is suppressed by miR-221 at the protein level. Tcf-1, a downstream target of Wnt signaling, is also down-regulated by miR-221.

Conclusion: We have identified several miRNAs expressed in inflamed synovium that potentially regulate skeletal pathways, including osteoblast differentiation. Of these, miR-221 inhibits osteoblast differentiation. These results support the hypothesis that miRNAs derived from inflamed synovial tissue may regulate skeletal pathways and osteoblast function in RA.

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Abstract Number: 1036

Important Role of microRNA-146a in Inflammatory Arthritis By Controlling Local Bone Destruction

Victoria Saferding[1], Antonia Puchner[2], Eliana Goncalves-Alves[3], Melanie Hofmann[3], Emine Sahin[4], Silvia Hayer[5], Philippe Georgel[6], Marije M. Koenders[7], Gernot Schabbauer[4], Josef S. Smolen[3], Guenter Steiner[8], Kurt Redlich[3] and Stephan Blüml[3], [1]Rheumatology, Medical University of Vienna, Vienna, Austria, [2]Department of Rheumatology, Medical University of Vienna, Vienna, Austria, [3]Division of Rheumatology, Medical University of Vienna, Vienna, Austria, [4]Vascular Biology and Thrombosis research, Medical University Vienna, Vienna, Austria, [5]Waehringer Guertel 18-20 A-A09, Medical University of Vienna, Vienna, Austria, [6]Centre de Recherche en Immunologie et Hématologie, Université de Strasbourg, Strasbourg, France, [7]Medical Center, Radboud University Nijmegen, Nijmegen, Netherlands, [8]Internal Medicine III, Division of Rheumatology, Medical University of Vienna, Vienna, Austria
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Background/Purpose: MicroRNA (MiR-) 146a is a key regulator of the innate immune response and has also been shown to suppress cancer development in myeloid cells. Although in late stages of arthritis elevated expression of miR-146a in synovial tissue of rheumatoid arthritis patients was detected, the level of this miRNA was found to be down regulated in early disease, but its role in the development of inflammatory arthritis is yet unknown.

Methods: We induced K/BxN serum transfer arthritis in wild type and miR-146a$^{-/-}$ mice. As a second inflammatory arthritis model we crossed miR-146a deficient into hTNFtg mice. Disease severity was assessed clinically and histologically in both arthritis models. Blood of arthritis animals was analyzed by flow cytometry. Serum cytokine levels were measured by Elisa. RNA expression levels were measured by qPCR.

Results: Absence of miR-146a leads to increased clinical signs of the induced serum transfer arthritis. In line, higher serum levels of the proinflammatory cytokines IL-12 and TNF were measured in miR146a deficient compared to wt mice. When we crossed miR-146a$^{-/-}$ into hTNFtg mice, histological examination revealed a significant increase in synovial inflammation and even more striking a more than twofold increase in local bone destruction due to increased generation of osteoclasts in the tarsal joints in miR-146a$^{-/-}$/hTNFtg mice compared to hTNFtg mice. Interestingly, systemic bone loss was comparable in hTNFtg compared to miR-146a$^{-/-}$/hTNFtg mice, suggesting

an important local role of miR-146a. Indeed, we detected increased levels of IL-1β and RANKL and decreased expression of OPG locally in the paws of miR-146a$^{-/-}$/hTNFtg compared to hTNFtg mice. Analysing the content of myeloid cells in the blood of arthritis diseased mice, revealed significantly increased numbers of circulating CD11b^{+} as well as CD11c^{+}cells in mice lacking miR-146a. Bone marrow transplants demonstrated a pivotal role for miR-146a in mesenchymal cells in controlling local osteoclast generation and bone destruction.

Conclusion: These data demonstrate an important mitigating role of the miR-146a in inflammatory arthritis, most importantly in local bone destruction, by controlling mesenchymal expression of osteoclastogenic factors. This shows an important anti-inflammatory role of miR-146a, which might possibly be exploited for therapeutic purposes.

Disclosure: V. Saferding, None; **A. Puchner**, None; **E. Goncalves-Alves**, None; **M. Hofmann**, None; **E. Sahin**, None; **S. Hayer**, None; **P. Georgel**, None; **M. M. Koenders**, None; **G. Schabbauer**, None; **J. S. Smolen**, None; **G. Steiner**, None; **K. Redlich**, None; **S. Blüml**, None.

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Abstract Number: 1037

Impaired Regulatory T Cell Survival in the Pathogenesis of Autoreactive Arthritis Mediated By CD11c-Deletion of Flip

Qi Quan Huang[1], Renee E. Doyle[1], Robert Birkett[2], Deyu Fang[3], Syamal K. Datta[1] and Richard M. Pope[1], [1]Medicine/Rheumatology, Northwestern University Feinberg School of Medicine, Chicago, IL, [2]Division of Rheumatology, Department od Medicine, Northwestern University Feinberg School of Medicine, Chicago, IL, [3]Department of Pathology, Northwestern University Feinberg School of Medicine, Chicago, IL

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Background/Purpose: We have generated a mouse line with Flip conditionally deleted in CD11c-cre expressing cells (CD11c-Flip-KO, named HUPO), which spontaneously develops erosive arthritis resembling rheumatoid arthritis (RA). HUPO mice exhibit significantly reduced conventional dendritic cells (cDC), especially its CD8α^{+} subset, as well as a reduction in the number and percent of CD4^{+} T regulatory cells (Tregs). The reduced Tregs contribute to disease pathogenesis in HUPO mice, permitting the expansion of autoreactive CD4^{+}T cells, plasmablasts, and joint specific autoantibodies. This study is focused on discovering the cause for the reduced Tregs in the HUPO mice.

Methods: Immune cell phenotyping and apoptosis/necrosis were assessed by antibody-flow cytometric analysis. HUPO mice were crossed with *Rag*$^{-/-}$ generated HUPO-*Rag*$^{-/-}$ double mutant line. Cells were adoptively transferred intravenously. Cytokines were determined by quantitative ELISA. Tregs were identified as CD4^{+}CD25^{+}Foxp3^{+}.

Results: HUPO-*Rag*-/- mice developed a very mild arthritis, which was not erosive, mediated by macrophages. Whole spleen T and B cells were isolated from 3-5 month old control or HUPO mice and adoptively transferred into *Rag*$^{-/-}$ or HUPO-*Rag*$^{-/-}$ mice. After 3 weeks, there was no difference in the percent Tregs when control lymphocytes were transferred to *Rag*$^{-/-}$ or HUPO-*Rag*$^{-/-}$ mice. Further, no difference in Tregs was observed when HUPO lymphocytes were transferred to *Rag*$^{-/-}$ mice. In contrast, when HUPO lymphocytes were transferred into HUPO-*Rag*$^{-/-}$ mice, after 3 weeks Tregs were significantly reduced compared to all the other groups. Next, isolated control CD45.1^{+}CD4^{+}CD25^{+} T cells transferred into CD45.2 HUPO mice resulted in reduced CD45.1^{+}Foxp3^{+}Tregs after 2-3 weeks compared to transfer into control mice. These data suggest that both HUPO Tregs and the in vivo environment of the HUPO mouse contribute to the reduction of Tregs. To define the potential mechanisms, in vitro culture of the total splenocytes for 7 days resulted in significantly reduced IL-2 in the HUPO, compared with the littermate control, culture supernatants. Further, significantly reduced Tregs were present in the HUPO, compared with the control, cultures. Interestingly, supplement of the culture medium with IL-2 prevented the loss of Tregs in the cultures from the HUPO, but not the control mice. The reduction of IL-2 was not due to cDCs, however, the production of immuno-reactive TGFβ, important for Treg differentiation, was significantly reduced with BM differentiated DCs from HUPO, compared with control, mice

Conclusion: HUPO mice represent a novel arthritis model that may provide insights into the mechanisms that contribute to the initiation of RA. This study suggests that the mechanisms for the reduction of Tregs in HUPO mice are multifactorial and include a reduction of cDC TGFβ and a reduction of IL-2 which is essential for maintenance of Tregs. Many earlier studied documented the reduction of IL-2 in patients with RA. Our observations suggest that IL-2 may be an effective treatment strategy in the HUPO mouse model of RA.

Disclosure: Q. Q. Huang, None; **R. E. Doyle**, None; **R. Birkett**, None; **D. Fang**, None; **S. K. Datta**, None; **R. M. Pope**, None.

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Abstract Number: 1038

Tumor Necrosis Factor Alpha and Peptidylarginine Deiminase 4 in Lung and Joint Inflammation

Mandar Bawadekar[1], Annette Gendron-Fitzpatrick[2], Thomas F. Warner[3], Lennart K.A. Lundblad[4], Paul Thompson[5] and **Miriam A. Shelef**[1,6], [1]Medicine, University of Wisconsin, Madison, WI, [2]Comparative Pathology Laboratory of the Research Animal Resources Center and Pathobiological Sciences, University of Wisconsin, Madison, WI, [3]Department of Pathology and Laboratory Medicine, University of Wisconsin, Madison, WI, [4]Medicine, The University of Vermont, Burlington, VT, [5]University of Massachusetts, Worcester, MA, [6]Medicine, William S. Middleton Memorial Veterans Hospital, Madison, WI
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Background/Purpose: The relationship between lung and joint inflammation in rheumatoid arthritis is poorly understood. About 10% of people with rheumatoid arthritis develop interstitial lung disease and people who have early rheumatoid arthritis or anti-citrullinated protein antibodies (ACPAs) without clinical arthritis have increased rates of subclinical lung disease. Also, citrullinated proteins can be found in diseased lungs similar to inflamed joints. Taken together, these observations suggest that one or both of two possible lung/joint relationships may exist. Lung inflammation may be an inciting event in rheumatoid arthritis development possibly by triggering ACPA formation and/or lung inflammation and arthritis may be two manifestations of a similar underlying pathology. However the true mechanism is unknown. Overexpression of TNFα in mice causes both an inflammatory destructive arthritis similar to rheumatoid arthritis as well as severe lung inflammation. We have previously shown that the citrullinating enzyme peptidylarginine deiminase 4 (PAD4) contributes to arthritis in these mice, but its role in lung disease is unknown. Here, we employ mice that overexpress TNFα to address several basic questions about the relationship between TNFα, citrullination, PAD4, arthritis, and lung inflammation.

Methods: Ankle joint and lung tissue from mice that systemically overexpress TNFα (TNF^+) and wild type littermates as well as $TNF^+PAD4^{+/+}$ and $TNF^+PAD4^{-/-}$ littermates were flash frozen and homogenized. Protein lysates were diluted in trichloroacetic acid, incubated with Rh-PG (a citrulline detection probe), quenched, washed, subjected to gel electrophoresis, imaged, stained with Coomassie, and re-imaged to determine the extent of total protein citrullination. Lungs from $TNF^+PAD4^{+/+}$ and $TNF^+PAD4^{-/-}$ littermates were fixed, sectioned, stained with hematoxylin and eosin (H&E), and scored in a blinded manner for the severity of several characteristics of lung inflammation. Ankle joints from 22 month old mice that overexpress TNFα only in the lung under the control of the surfactant promoter and littermate controls were fixed, sectioned, stained with H&E, and scored for arthritis severity.

Results: TNF^+ mice have increased gross protein citrullination in their joints and lungs at 5 months of age, but not 2 or 3.5 months of age compared to wild type. There was no difference between $TNF^+PAD4^{+/+}$ and $TNF^+PAD4^{-/-}$ mice in gross protein citrullination in either joints or lungs at 5 months of age, however $TNF^+PAD4^{-/-}$ mice had reduced lung disease severity compared to $TNF^+PAD4^{+/+}$ mice. No arthritis was detected in the mice that overexpress TNFα only in the lungs.

Conclusion: PAD4 contributes to both lung and joint inflammation downstream of TNFα, without having a required role in generalized protein citrullination in these tissues. Further, TNFα induced lung inflammation does not drive arthritis in mice.

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Abstract Number: 1039

The Safety and Effect on Disease Activity of Tocilizumab in Combination with MTX Versus Tocilizumab Monotherapy in Patients with Mild to Moderate RA: An Attempt to Optimise the Treatment Response

Burkhard Leeb[1,2], Raimund Lunzer[3], Peter Fasching[4], Manfred Herold[5], O. Zamani[6], Winfried Graninger[7] and OPTIMISE trial Investigators, [1]2nd Dept. of Medicine, State Hospital Stockerau, Center for Rheumatology Lower Austria, Stockerau, Austria, [2]Department of Clinical Rheumatology, Karl Landsteiner Society, Stockerau, Austria, [3]Department of Internal Medicine, Hospital Barmherzige Brüder Graz-Eggenberg, Graz, Austria, [4]Department of Internal Medicine V, Wilhelminen Hospital Vienna, Vienna, Austria, [5]Internal Medicine VI, Medical University of Innsbruck, Austria, Innsbruck, Austria, [6]Rheumazentrum Favoriten, Wien, Austria, [7]Rheumatology and Immunology, Medical University of Graz, Graz, Austria

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Session Title: Rheumatoid Arthritis - Clinical Aspects I - Treatment Advances and Strategies

Session Type: ACR Concurrent Abstract Session

Session Time: 4:30PM-6:00PM

Background/Purpose:

An Austrian multi-center study of the effect on disease activity and the safety of Tocilizumab (TCZ) in combination with Methotrexate (MTX) versus TCZ Monotherapy in patients with mild to moderate rheumatoid arthritis (RA), with inadequate response to MTX – The OPTIMISE trial (EUDRACT No. 2011-001863-39)

As only limited data are available on the efficacy of biologicals in Rheumatoid Arthritis (RA) patients in mild to moderate disease activity, particularly with respect to Tocilizumab (TCZ), this study was performed to assess the influence on disease activity of TCZ+MTX versus TCZ-monotherapy in patients with mild to moderate RA.

Methods:

Seventy-seven patients with mild to moderate RA and an inadequate response (DAS28 < 4.5 and >2.6) to a stable dose of MTX (15 – 25 mg/wk) were enrolled into the first phase and received three infusions of TCZ (8 mg/kg) iv every 4 weeks + MTX. If the patients achieved a good/moderate EULAR response after 3 months they were randomized into group A (TCZ 8 mg/kg iv/mth plus MTX) or group B (TCZ 8 mg/kg iv/mth plus Placebo (PBO) MTX). The primary endpoint was the change in DAS28 score from week 12 (time of randomization) to week 24. Secondary endpoints were the proportion of patients achieving DAS28 remission, CDAI remission, SDAI remission and RADAI-5 remission at week 24 as well as the improvement in physical & mental health and satisfaction with treatment using different questionnaires.

Results:

Sixty-five patients (84.4%; 51 female/14male; mean age 57.5 +/- 11.3 yrs) achieved a EULAR response and were included into the blinded phase of the trial. The mean DAS28 (ITT-population) at wk 12 in the MTX group (n=32) was 1.51, and in the PBO group (n=33) 1.72. The change in DAS28 score from wk 12 to wk 24 was statistically not significant between group A and group B (0.17 ± 0.83 in the MTX group vs. -0.16 ± 1.13 in the PBO group (n = 33); 95% CI for the difference [-0.16; 0.82], p =0,188). All secondary endpoints, namely the proportion of patients in remission, improvement of function, mental health, and satisfaction with treatment proved to be statistically not significantly different between MTX or PBO treated patients. Regarding tolerability no new signals could be detected.

Conclusion:

Additional TCZ treatment led to significant improvement in patients with mild to moderate RA and an inadequate response to MTX. TCZ-Monotherapy was seen as effective as combination with MTX to preserve the level of disease activity achieved at wk12.

Abstract Number: 1040

Factors Associated with Long Term Rituximab Use in Rheumatoid Arthritis – Results from the British Society of Rheumatology Biologics Register

Alexander G.S. Oldroyd[1], Deborah P.M. Symmons[1], Lianne Kearsley-Fleet[1], Kath Watson[1], Mark Lunt[2], Jamie Sergeant[1], Kimme L. Hyrich[1] and on behalf of the BSRBR-RA, [1]Arthritis Research UK Centre for Epidemiology, The University of Manchester, Manchester, United Kingdom, [2]Manchester Academic Health Sciences Centre, Arthritis Research UK Centre for Epidemiology, The University of Manchester, Manchester, United Kingdom

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Session Time: 4:30PM-6:00PM

Background/Purpose:

Analysis of long term continuation of biologics in rheumatoid arthritis (RA) is considered a valid surrogate for treatment effectiveness and safety. Only a small number of studies have investigated the long-term persistence with rituximab (RTX) in RA. Analysis of long term continuation of biologics in rheumatoid arthritis (RA) is considered a valid surrogate for treatment effectiveness and safety. Only a small number of studies have investigated the long-term persistence with rituximab (RTX) in RA.

Methods: This analysis included all patients enrolled with the British Society for Rheumatology Biologics Register for RA when starting RTX between 2008 and 2011. Baseline characteristics (demographic, disease and treatment-related data) were compared between bio-naive and experienced cohorts. RTX treatment discontinuation was defined at start of alternative biologic, death or 1 year following the most recent RTX infusion, whichever came first. Kaplan-Meier curves were used to study discontinuation rates over time and by reason, both as a whole cohort and stratified by past biologic treatment experience; discontinuation rates at 1, 2, 3 and 4 years following treatment initiation were ascertained. The association of baseline variables (age, gender, smoking status, presence of comorbidities, disease duration, DAS-28 score, HAQ score, steroid use, methotrexate (MTX) use, previous biologic use) with RTX discontinuation after 4 years was assessed using multivariate Cox-proportional hazards models.

Results: In total, 1629 patients were included (1371 [84.2%] bio-experienced patients and 258 [15.8%] bio-naïve). Bio-experienced patients tended to be younger, but have longer disease duration than bio-naïve patients (Table 1). Treatment persistence at 4 years was 43% (95% CI 40, 45) and was similar between bio-naïve and bio-experienced patients (Figure 1). For the whole cohort, baseline variables associated with RTX discontinuation after 4 years were low DAS28 score (HR 0.91 [95% CI 0.85, 0.98]), RhF negativity (HR 0.84 [0.72, 0.99]) and younger age (HR 0.99 [0.98, 0.99] per year). Higher number of previously used biologics was associated with RTX discontinuation for the bio-experienced cohort (HR 1.28 [CI 1.08, 1.50]) and smoking history was associated for the bio-naïve cohort only (HR 1.82 [1.06, 3.12]). Tocilizumab was the most commonly used subsequent biologic for both the naive and experienced cohorts: 12 (41.4%), 133 (56.8%), respectively.

Conclusion: Just over half of patients were no longer receiving RTX after 4 years, which was similar in both bio-naïve and experienced patients. In bio-experienced patients, those who started RTX after 2 or more past TNFi failures were more likely to discontinue treatment compared to only 1, which may be identifying a more refractory patient cohort. The role of risk factors in predicting treatment outcomes on RTX is again supported by these data.

Variable		All RTX patients n = 1629	Biologic naïve patients n = 258	Biologic experienced patients n = 1371	p-value
Mean age/years (SD)		59.5 (12.1)	62.5 (11.3)	58.9 (12.2)	<0.01
Women, n (%)		1243 (76.3)	174 (67.4)	1069 (78.0)	<0.01
Current smoker (%)		226 (13.9)	56 (21.7)	170 (12.4)	<0.01
Comorbidities, n (%)	0	612 (37.6)	102 (39.5)	510 (37.2)	0.53
	1	518 (31.8)	77 (29.8)	441 (32.2)	0.49
	2	326 (10.0)	54 (20.9)	272 (19.8)	0.71
	3+	173 (10.6)	25 (9.7)	148 (10.8)	0.66
ILD, n (%)		91 (5.6)	47 (18.2)	44 (3.2)	<0.01
Previous TB, n (%)		64 (3.9)	10 (3.9)	54 (3.9)	0.99
Previous cancer, n (%)		215 (13.2)	81 (31.4)	134 (9.8)	<0.01
Median disease duration/ years (IQR)		12 (6, 20)	10 (4, 20)	13 (7, 20)	<0.01
Median DAS28 (IQR)		6.1 (5.4, 6.8)	6.1 (5.5, 6.7)	6.1 (5.4, 6.9)	0.99
Median HAQ (IQR)		2.0 (1.6, 2.4)	1.9 (1.5, 2.3)	2.1 (1.6, 2.4)	<0.01
Current steroids, n (%)		670 (41.1)	123 (47.7)	547 (40.0)	0.02
RhF positive, n (%)		953 (58.5)	175 (67.8)	778 (56.7)	0.89
Concurrent MTX, n (%)		247 (15.2)	233 (90.3)	1149 (83.8)	0.01
Leflunomide, n (%)		129 (7.9)	27 (10.5)	102 (7.4)	0.12
No concurrent DMARD, n (%)		167 (10.2)	11 (4.3)	156 (11.4)	<0.01
Previous biologics, n (%)					
	1			1029 (75.1)	
	2			222 (16.2)	
	3+			27 (2.0)	
KM estimate after year (95% CI)	1	95 (94, 96)	95 (93, 98)	95 (94, 96)	
	2	71 (69, 73)	76 (71, 81)	70 (67, 72)	
	3	55 (53, 58)	61 (55, 67)	54 (52, 57)	
	4	43 (40, 45)	44 (38, 51)	43 (40, 45)	
Median follow-up time in study/ years (IQR)		4.5 (3.6, 5.4)	4.5 (3.6, 5.3)	4.5 (3.6, 5.4)	
Adverse events by 4 years, n (%)		235 (14.4)	51 (19.8)	184 (13.4)	
Inefficacy by 4 years, n (%)		270 (16.6)	31 (12.0)	239 (17.4)	
Started subsequent biologic, n (%)		263 (16.6)	29 (11.2)	234 (17.1)	
No biologic treatment, n (%)		249 (15.3)	53 (20.5)	196 (14.3)	

Disclosure: A. G. S. Oldroyd, None; **D. P. M. Symmons**, None; **L. Kearsley-Fleet**, None; **K. Watson**, None; **M. Lunt**, None; **J. Sergeant**, None; **K. L. Hyrich**, None.

Abstract Number: 1041

Methotrexate Monotherapy and Methotrexate Combination Therapy with Traditional and Biologic Dmards for Rheumatoid Arthritis: A Cochrane Systematic Review and Network Meta-Analysis

Glen S. Hazlewood[1,2], Cheryl Barnabe[3], George A. Tomlinson[4], Deborah Marshall[5], Daniel Devoe[5] and Claire Bombardier[6], [1]Institute of Health, Policy, Management and Evaluation, University of Toronto, Toronto, ON, Canada, [2]Medicine, University of Calgary, Calgary, AB, Canada, [3]Cumming School of Medicine, University of Calgary, Calgary, AB, Canada, [4]Institute for Health Policy, Management and Evaluation, University of Toronto, Toronto, ON, Canada, [5]University of Calgary, Calgary, AB, Canada, [6]18 Strathearn Blvd, University of Toronto, Toronto, ON, Canada

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Background/Purpose: To compare methotrexate based disease-modifying anti-rheumatic drug (DMARD) treatments for rheumatoid arthritis in patients naïve to or after an inadequate response (IR) to methotrexate.

Methods: We conducted a systematic review and Bayesian random-effects network meta-analysis of trials assessing methotrexate used alone or in combination with other conventional synthetic DMARDs (csDMARDs), biologics (bDMARDs) or tofacitinib in adult patients with rheumatoid arthritis. The major outcomes were ACR50 response (major clinical improvement), radiographic progression and withdrawals due to adverse events (WDAE). Trials were identified from MEDLINE, EMBASE and CENTRAL databases from inception to August 13, 2014, abstracts from 2 major rheumatology meetings from 2009-2014, 2 trial registers, and hand-searches of Cochrane reviews. The risk of bias of each study was evaluated using the Cochrane risk of bias tool, separately for each outcome. Trials judged at high overall risk of bias were excluded.

Results: 150 trials with over 34,000 patients were included. Methotrexate naïve: In methotrexate-naïve patients, 'triple therapy' (the combination of methotrexate + sulphasalazine + hydroxychloroquine), and methotrexate + several bDMARDs (abatacept, adalimumab, etanercept, infliximab, rituximab, tocilizumab) were similar to each other and significantly superior to oral methotrexate for ACR50 response. There was a 61% probability of an ACR50 response with triple therapy (moderate quality evidence), which was similar to the probability of an ACR50 response for the MTX + bDMARDs that were statistically significantly superior to oral MTX (range: 55%-67%, moderate to high quality evidence). Only methotrexate + adalimumab and methotrexate + etanercept were significantly superior to oral MTX for inhibiting radiographic progression. Triple therapy had significantly fewer WDAE compared to methotrexate + infliximab. Methotrexate-IR: In methotrexate-IR patients, several treatments were significantly superior to oral methotrexate for ACR50 response, including csDMARD combinations (triple therapy, methotrexate + hydroxychloroquine, methotrexate + leflunomide, methotrexate + intramuscular gold), methotrexate + most bDMARDs, and methotrexate + tofacitinib. There was a 61% probability of an ACR50 response with MTX + sulphasalazine + hydroxychloroquine, compared to 27% to 65% for the MTX + bDMARDs that were statistically significantly superior to oral MTX. No treatment was significantly superior to oral methotrexate for inhibiting radiographic progression. Methotrexate + abatacept had fewer WDAE than several treatments.

Conclusion: Triple therapy and most regimens combining biologic DMARDs with methotrexate were similarly effective in controlling disease activity and all generally well tolerated in both methotrexate-naive and methotrexate-exposed patients. Given cost considerations, these findings support a therapeutic trial of low-cost triple therapy prior to using biologic DMARDs.

Disclosure: G. S. Hazlewood, None; **C. Barnabe**, Roche, Amgen, Abbott, 5; **G. A. Tomlinson**, None; **D. Marshall**, CIHR, Arthritis Society, AIHS, CIORA, 2,University of Calgary, 3,Abbvie, 5,Pfizer Inc, 5,Novartis Pharmaceutical Corporatio, 5,Johnson & Johnson, 5; **D. Devoe**, None; **C. Bombardier**, Abbvie, Amgen, Bristol Myers Squibb, Hospira, Janssen, Roche, Pfizer, UCB, 2.

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Abstract Number: 1042

Pragmatic Multicenter Open-Label Randomized Controlled Trial of Stopping TNF-Inhibitors in Rheumatoid Arthritis Patients in Remission or Stable Low Disease Activity in the Netherlands

Marjan Ghiti Moghadam[1], Harald E. Vonkeman[2], Peter M. ten Klooster[3], Janneke Tekstra[4], Dirkjan van Schaardenburg[5], Mirian Starmans-kool[6,7], Elisabeth Brouwer[8], Reinhard Bos[9], Willem F. Lems[10], Edgar Colin[11], Cornelia F. Allaart[12], Inger L. Meek[13], Robert B.M. Landewé[14], Hein J. Bernelot Moens[15], Piet van Riel[13], Mart A.F.J. van de Laar[16], Tim Jansen[17] and on behalf of the Dutch National POET Collaboration., [1]rheumatology, Medisch Spectrum Twente - Arthritis Center Twente, Enschede, Netherlands, [2]Ariensplein 1, Medisch Spectrum Twente - Arthritis Center Twente, Enschede, Netherlands, [3]Pcgr, University of Twente, Enschede, Netherlands, [4]Dept. Rheumatology & Clinical Immunology, University Medical Center Utrecht, Utrecht, Netherlands, [5]Jan van Breemen Research Institute, Amsterdam, Netherlands, [6]Rheumatology, Orbis Medical Center, Geleen-Sittard, Netherlands, [7]Rheumatology, Atrium Medical center, Heerlen, Netherlands, [8]Rheumatology, University Medical center Groningen, Groningen, Netherlands, [9]Rheumatology, Medical Center Leeuwarden, Leeuwarden, Netherlands, [10]Rheumatology, Amsterdam Rheumatology and immunology Center, VU University medical center, Amsterdam, Netherlands, [11]Rheumatology, Erasmus MC, Rotterdam, Netherlands, [12]Department of Rheumatology, Leiden Universitary Medical Center, Leiden, Netherlands, [13]Rheumatology, Radboud University Nijmegen Medical Centre, Nijmegen, Netherlands, [14]Department of Rheumatology, Amsterdam Rheumatology Center, Amsterdam, Netherlands, [15]rheumatology, Ziekenhuisgroep Twente, Almelo, Netherlands, [16]Rheumatology, Medisch Spectrum Twente - Arthritis Center Twente, Enschede, Netherlands, [17]VieCuri Medical Center, Venlo, Netherlands

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SESSION INFORMATION

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Session Title: Rheumatoid Arthritis - Clinical Aspects I - Treatment Advances and Strategies

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Background/Purpose: TNF-inhibitors (TNFi) are effective treatments of rheumatoid arthritis (RA). It is not clear if patients in remission or stable low disease activity need to continue their TNFi. Issues of polypharmacy and the relatively high costs of TNFi make it important to examine whether patients in remission or stable low disease activity can stop their TNFi. If patients stop TNFi and consequently flare, it is unclear whether TNFi can be restarted effectively and safely.

Methods: Pragmatic multicenter open-label randomized controlled trial. Inclusion criteria: patients diagnosed with RA according to the ACR 1987 criteria, patients using a TNFi for at least 1 year with stable dose DMARDs over the last 6 months, DAS28 <3.2 over the last 6 months. Patients were randomized to either stop or continue their current TNFi in a 2:1 ratio. Flare was defined as DAS28 ≥3.2 with an increase ≥0.6 compared to the previous DAS28. In case of flare in the stop group, TNFi could be restarted at the discretion of the treating rheumatologist.

Results: In total 817 patients from 47 centers were included: 531 patients (65%) in the stop group and 286 patients (35%) in the continuation group. At 6 months, significantly more patients in the stop group (212/531 [31.5%]) had experienced a flare than in the continuation group (36/286 [9.8%], p<0.001). At 12 months these were 267/531 [50.3%] vs 52/286 [18.2%], respectively (p<0.001). The hazard ratio for flare after stopping TNFi was 3.41 (95% CI: 2.53–4.59). Mean DAS28 scores in the stop group were significantly increased throughout the follow-up period compared with the continuation group (p<0.001). Of the 195 patients that restarted TNFi within 26 weeks, 165 (84.6%) had regained low disease activity (DAS28 < 3.2) 6 months later and median time to regained low disease activity was 12 weeks (95% Cl: 10.8-13.2).

SAEs in stop vs. continuation groups: Deaths 0 vs. 1 (0.3%) and hospitalization due to infections 11 (2%) vs. 4 (1,4%), respectively. There were no allergic reactions among the patients in the stop group that restarted TNFi.

Conclusion: Stopping TNFi treatment in RA patients in remission or stable low disease activity results in substantially more flares than continuing.

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Abstract Number: 1043

Enhancing Comparative Effectiveness Research By Combining Observational and Randomized Trial Data to Personalize the Choice Between Methotrexate and Triple Therapy for Methotrexate-Naïve Patients with Early Rheumatoid Arthritis

Glen S. Hazlewood[1,2], Cheryl Barnabe[3], Gilles Boire[4], Carol Hitchon[5], Edward C. Keystone[6], Boulos Haraoui[7], J Carter Thorne[8], Diane Tin[9], Janet E. Pope[10], Daming Lin[11], VP Bykerk[12] and CATCH investigators, [1]Institute of Health, Policy, Management and Evaluation, University of Toronto, Toronto, ON, Canada, [2]Medicine, University of Calgary, Calgary, AB, Canada, [3]Cumming School of Medicine, University of Calgary, Calgary, AB, Canada, [4]Department of Medicine/Division of Rheumatology, Université de Sherbrooke, Sherbrooke, QC, Canada, [5]University of Manitoba, Winnipeg, MB, Canada, [6]Mount Sinai Hospital, University of Toronto, Toronto, ON, Canada, [7]Institut de Rhumatologie, Montreal, QC, Canada, [8]Southlake Regional Health Centre, Newmarket, ON, Canada, [9]The Arthritis Program, Southlake Regional Health Centre, Newmarket, ON, Canada, [10]University of Western Ontario, London, ON, Canada, [11]Rheumatology, Mount Sinai Hospital, University of Toronto, Toronto, ON, Canada, [12]Hospital for Special Surgery, Weill Cornell Medical College, New York, NY

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Background/Purpose: Randomized controlled trials (RCTs) are considered the gold standard for comparing efficacy of treatments, but the results may be less generalizable to clinical practice than observational studies. We have recently completed a Cochrane network meta-analysis that included all available RCT evidence and found a statistically significant increase in the odds of ACR50 response for triple therapy relative to methotrexate (MTX) alone in MTX-naïve patients. The objective of this study was to convert these relative treatment effects (odds ratios) into the expected probability of response for patients with different baseline characteristics, using data from an observational cohort. The overall aim was to enhance the knowledge required to achieve informed decision-making in practice.

Methods: We estimated the probability of an ACR50 response at 6 months for patients with ERA (2010 ACR criteria, symptoms ≤1-year), initiating methotrexate therapy (oral or subcutaneous) for patients in the multicenter, prospective Canadian Early Arthritis Cohort (CATCH). A multivariable logistic regression model with a candidate list of variables feasible to collect in clinic visits was developed to determine patient characteristics associated with ACR50 response. The final model was used to estimate the probability of ACR50 response with MTX monotherapy for patients with different baseline characteristics. We then determined the probability of ACR50 response for triple therapy, using the odds ratio derived from a completed Cochrane network meta-analysis of 150 trials.

Results: The population for the multivariable model included 666 patients with ERA: mean age 53 yrs, 74% female, mean DAS28 5.5, mean HAQ 1.1, swollen joint count 9.4. The mean starting dose of methotrexate was 19 mg/week. In the multivariable model, younger age, lower HAQ-DI and higher swollen joint counts were each independently associated with a higher odds of ACR50 response. The expected probability of an ACR50 response with MTX alone versus triple therapy for different patient characteristics is shown in Table 1. As the baseline chance of an ACR50 response increased, the absolute difference between MTX and triple therapy also increased.

Conclusion: By combining a predictive model from a large, prospective cohort with treatment effects from a network meta-analysis of all available RCTs, probabilities of treatment response with MTX and triple therapy can be estimated and may help inform evidence-based treatment choices for individual patients.

Table 1: Estimated probability of ACR50 response for methotrexate and triple therapy based on variable baseline characteristics

Change in baseline variables	Expected probability of ACR50 response		Absolute difference (95% CI)
	Methotrexate	Triple therapy (95% CI)	
Age increased (HAQ=1; SJC=10)			
Age 20	32%	53% (37 to 70)	21% (5 to 38)
Age 40	25%	43% (28 to 61)	18% (4 to 36)
Age 60	18%	33% (21 to 51)	16% (3 to 33)
Age 80	13%	26% (15 to 42)	13% (2 to 29)
SJC increased (Age=55, HAQ=1)			
SJC 5	14%	26% (16 to 43)	13% (2 to 29)
SJC 10	20%	36% (22 to 54)	16% (3 to 34)
SJC 15	27%	46% (31 to 64)	19% (4 to 37)
SJC 20	37%	57% (41 to 74)	20% (4 to 37)
HAQ increased (Age=55, SJC=10)			
HAQ 0.5	24%	42% (28 to 61)	18% (4 to 36)
HAQ 1.0	20%	36% (23 to 54)	16%(3 to 34)
HAQ 1.5	16%	30% (18 to 47)	14% (3 to 31)
HAQ 2.0	12%	24% (14 to 40)	12% (2 to 28)

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Abstract Number: 1044

Many Patients with Early Rheumatoid Arthritis Want Triple Therapy: An Analysis Combining Comparative Effectiveness Research and Patients Preferences to Inform

Treatment Recommendations

Glen S. Hazlewood[1,2], Claire Bombardier[3], George A. Tomlinson[4] and Deborah Marshall[5], [1]Institute of Health, Policy, Management and Evaluation, University of Toronto, Toronto, ON, Canada, [2]Medicine, University of Calgary, Calgary, AB, Canada, [3]Toronto General Hospital Research Institute, University Health Network, Toronto, ON, Canada, [4]Medicine, University Health Network, Toronto, ON, Canada, [5]University of Calgary, Calgary, AB, Canada
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Background/Purpose: Growing evidence supports the efficacy of triple therapy (methotrexate + sulphasalazine + hydroxychloroquine) for controlling disease activity in patients with early rheumatoid arthritis (ERA), but it requires multiple pills and appears to be less effective than methotrexate + anti-TNF therapy for preventing joint damage. The GRADE approach for developing treatment recommendations has been adopted by the ACR and requires that treatment recommendations integrate the estimated treatment effects for key outcomes and patients' preferences, but methods for doing this have not been defined. The objective of this study was to apply a novel approach for jointly considering the comparative benefits and harms of treatment options and patients' preferences to estimate the preferred treatment for patients with ERA.

Methods: We determined the preferred treatment for patients with moderate-severe ERA (<2 years since diagnosis) separately for methotrexate-naïve patients (choice of triple therapy versus methotrexate) and for patients who have had an inadequate response to methotrexate (choice of triple therapy versus methotrexate + anti-TNF therapy). We used patients' preferences that we elicited through a discrete choice experiment to apply weights to 3 key outcomes from a network meta-analysis (ACR50 response, radiographic progression, withdrawals due to adverse events) and other important considerations (dosing, rare adverse events). The preferred treatment was the one that had the highest total value, which was calculated as a sum of the preference-weighted treatment characteristics. We incorporated uncertainty in both the treatment effects and individual patients' preferences by averaging the results across 10,000 samples from Bayesian models for both the network meta-analysis outcomes and the patients' preferences.

Results: Triple therapy was the most preferred treatment in methotrexate-naive patients (78% preferred triple therapy to methotrexate) or after an inadequate response to methotrexate (58% preferred triple therapy to methotrexate + anti-TNF therapy). In methotrexate-naïve patients, triple therapy provided a higher chance of benefit (ACR50 response) than methotrexate alone based on the network meta-analysis, which was most important to patients and outweighed the additional pills or other inconveniences. After failing methotrexate, triple therapy provided a similar chance of ACR50 response to anti-TNF therapy based on the network meta-analysis, but did not require injections or have an increased risk of infection/ possible increased risk of skin cancers as with anti-TNF therapy. For most patients, these issues outweighed any benefit of anti-TNF therapy on preventing joint damage.

Conclusion: Based on estimates of the comparative benefits and harms of methotrexate-based treatment options for ERA and patients' preferences, many patients would prefer triple therapy to methotrexate as initial therapy and triple therapy to methotrexate + anti-TNF therapy after an inadequate response to methotrexate. Explicitly considering patients' preferences may affect treatment recommendations made using GRADE.

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Abstract Number: 1045

Baricitinib, Methotrexate, or Baricitinib Plus Methotrexate in Patients with Early Rheumatoid Arthritis Who Had Received Limited or No Treatment with Disease-Modifying Anti-Rheumatic Drugs (DMARDs): Phase 3 Trial Results

Roy Fleischmann[1], Tsutomu Takeuchi[2], Douglas E. Schlichting[3], William L. Macias[3], Terence Rooney[3], Sirel Gurbuz[3], Ivaylo Stoykov[3],

Scott D. Beattie[3], Wen-Ling Kuo[3] and M Schiff[4], [1]Rheumatology, Metroplex Clinical Research Center, Dallas, TX, [2]Keio University School of Medicine, Tokyo, Japan, [3]Eli Lilly and Company, Indianapolis, IN, [4]School of Medicine, University of Colorado, Denver, CO
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SESSION INFORMATION

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Session Title: Rheumatoid Arthritis-Small Molecules, Biologics and Gene Therapy II: Small Molecular Targeted Therapies
Session Type: ACR Concurrent Abstract Session
Session Time: 4:30PM-6:00PM

Background/Purpose:

In 2 completed phase 3 studies, baricitinib (bari) improved disease activity with a satisfactory safety profile in patients (pts) with moderately-to-severely active RA who were inadequate responders to either conventional synthetic[1] or biologic[2]DMARDs. This abstract reports results from a phase 3 study of bari administered as monotherapy or in combination with methotrexate (MTX) to pts with early active RA who had limited or no prior treatment with DMARDs. MTX monotherapy was the active comparator.

Methods: Pts with active RA (TJC & SJC ≥6, hsCRP ≥3.6 mg/L) and no previous DMARD treatment other than ≤3 doses of MTX were randomized 4:3:4 to MTX, bari 4 mg once daily (QD; bari monotherapy), or bari 4 mg QD + MTX for up to 52 wks. MTX dose, with or without bari, was up-titrated from 10 to 20 mg once weekly over 8 weeks (wks). Rescue was not allowed prior to Wk 24, the time point for primary and all major secondary efficacy endpoints. The primary objective evaluated non-inferiority of bari 4 mg monotherapy to MTX on ACR20 at Wk 24 (using a 12% margin).

Results: Of 584 randomized pts, 87%, 91%, and 89% of pts completed Wk 24 in the MTX, bari 4 mg monotherapy, and bari 4 mg + MTX groups, respectively. ACR20 response at Wk 24 was higher with bari 4 mg monotherapy vs. MTX (77% vs. 62%, p≤.01). Compared to MTX, bari 4 mg monotherapy produced significantly greater improvements in multiple secondary measures of disease activity (Table 1), many as early as Wk 1. MTX in combination with bari 4 mg did not appear to increase the benefit observed with bari 4 mg monotherapy. Clinical remission was seen in a significantly higher proportions of pts treated with bari 4 mg alone or in combination with MTX compared to MTX alone (Table 1). Rates of treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs) were similar across groups (Table 2). Through 24 wks, 2 (1.0%), 6 (3.8%) and 14 (6.5%) pts discontinued the study because of an adverse event in the MTX, bari 4 mg monotherapy, and bari 4 mg + MTX groups, respectively. No GI perforations occurred during the study. Laboratory abnormalities were generally less frequent in the bari 4 mg group compared to either the MTX or bari 4 mg + MTX groups (Table 2).

Conclusion:

In pts with early RA, all treatment groups experienced improvements in disease activity with bari 4 mg monotherapy producing significantly larger and more rapid improvements and higher rates of clinical remission compared to MTX monotherapy, with a satisfactory safety profile. MTX addition to bari 4 mg did not increase the benefit observed with bari monotherapy, while it appeared to increase the frequency of laboratory abnormalities.

	Wk 12			Wk 24		
Table 1 Efficacy Measures	**MTX (N=210)**	**Bari 4 mg (N=159)**	**Bari 4 mg + MTX (N=215)**	**MTX (N=210)**	**Bari 4 mg (N=159)**	**Bari 4 mg + MTX (N=215)**
ACR20	59	79***	77***	62	77**	78***
ACR50	33	55***	60***	43	60**	63***
ACR70	16	31***	34***	21	42***	40***
DAS28-CRP ≤3.2	30	47***	56***	38	57**	60***
DAS28-CRP <2.6	16	28**	36***	24	40**	41***
DAS28-ESR ≤3.2	15	21	34***	23	36*	39**
DAS28-ESR <2.6	7	13*	18**	12	21*	25**
CDAI ≤10	30	43**	51***	39	60***	59***
CDAI ≤2.8	7	14*	19***	11	21*	22**
SDAI ≤11	30	45**	54***	40	62***	61***
SDAI ≤3.3	6	14*	20***	11	22**	23**
HAQ-DI MCID ≥0.22	67	86***	80**	70	81*	78
FACIT-F MCID ≥3.56	64	79**	72	65	75*	70
Data are % pts achieving response (NRI); *p≤.05, **p≤.01, ***p≤.001 vs. MTX						

Table 2 Safety Measures through Wk 24	MTX (N=210)	Bari 4 mg (N=159)	Bari 4 mg + MTX (N=215)
TEAEs	137 (65.2)	101 (63.5)	145 (67.4)
Infections*	58 (27.6)	43 (27.0)	74 (34.4)
Herpes Zoster	1 (0.5)	3 (1.9)	3 (1.4)
SAEs	8 (3.8)	5 (3.1)	8 (3.7)
Serious infections	3 (1.4)	1 (0.6)	4 (1.9)
Malignancy	0	0	2 (0.9)
Non-melanoma skin cancer	0	0	1
Adrenocortical carcinoma	0	0	1
Deaths	1 (0.5)	0	0
CTCAE Grade Shift (≥1 increase in grade from baseline)**			
Hemoglobin	51 (24.8)	45 (28.3)	66 (31.1)
Lymphocyte	45 (21.8)	15 (9.4)	38 (17.9)
ALT	54 (26.2)	19 (11.9)	52 (24.5)
Data are n(%) pts. CTCAE = Common Terminology Criteria for Adverse Events. *1 *Pneumocystis carinii* pneumonia and 1 esophageal candidiasis were reported (bari 4 mg + MTX). **% of pts with laboratory grade shifts are based on n-observed for analyte.			
Citations: [1]Dougados M et al. Ann Rheum Dis 2015;74(S2):79; [2]Genovese M et al. Ann Rheum Dis 2015;74(S2):75-76			

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Abstract Number: 1046

Previous Biologic Disease-Modifying Antirheumatic Drug (bDMARD) Exposure and Efficacy and Safety Analysis from a Phase 3 Study of Baricitinib in Patients with Rheumatoid Arthritis and an Inadequate Response to Tumor Necrosis Factor Inhibitors

Mark C. Genovese[1], Joel M. Kremer[2], Cynthia Kartman[3], Douglas E. Schlichting[3], Li Xie[3], Tara Carmack[4], William L. Macias[3] and Josef S. Smolen[5], [1]Division of Rheumatology, Stanford University Medical Center, Palo Alto, CA, [2]Center for Rheumatology, Albany, NY, [3]Eli Lilly and Company, Indianapolis, IN, [4]Quintiles, Durham, NC, [5]Department of Rheumatology, Medical University of Vienna, Vienna, Austria

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Session Time: 4:30PM-6:00PM

Background/Purpose: Baricitinib, an oral inhibitor of JAK1/JAK2, improved disease activity with an acceptable safety profile in a phase 3 study (RA-BEACON) of patients with active rheumatoid arthritis (RA) and an inadequate response to tumor necrosis factor inhibitors (TNFi).[1] Oral baricitinib once-daily (QD) produced improvements that were sustained through 24 weeks. The objective of this analysis was to evaluate the effect of prior bDMARD exposure on the efficacy and safety of baricitinib in RA-BEACON.

Methods: 527 patients with moderately-to-severely active RA despite previous use of ≥1 TNFi for ≥3 months were randomized 1:1:1 to

receive placebo (PBO) or 2 or 4 mg baricitinib QD for 24 weeks. All bDMARDs were discontinued ≥28 days prior to treatment. Patients were enrolled with a history of receiving multiple TNFi including non-TNFi bDMARDs. Post hoc subgroups defined by prior biologic use [1 TNFi only, >1 TNFi (but no non-TNFi), and ≥3 bDMARDs] were assessed for evidence of qualitative and quantitative treatment interactions utilizing modified intent to treat analysis (mITT) and nonresponder imputation (NRI). The treatment-by-subgroup interaction comparing each baricitinib group to PBO was tested at the 0.1 significance level.

Results: Across the treatment arms, ~38% of patients had a history of previous treatment with ≥1 non-TNFi bDMARD, including abatacept 20%, tocilizumab 19%, and rituximab 17%. Table 1 shows the ACR20 response rate for baricitinib vs PBO in patients with prior exposure to a non-TNFi by type of biologic. Improvements in ACR response rates and proportion of patients achieving DAS28-CRP ≤3.2 were demonstrated at Weeks 12 and 24 with baricitinib in subgroups defined by prior biologic use (Table 2). Significant interaction p values were observed infrequently and inconsistently indicating minimal treatment heterogeneity across subgroups defined by prior biologic use. As with the overall study, more treatment emergent adverse events occurred in patients receiving baricitinib 2 or 4 mg vs PBO with prior exposure to 1 or 2 biologics (65%, 74%, 62%, respectively) or ≥3 biologics (84%, 87%, 70%, respectively). Serious infections were infrequent, and no TB or opportunistic infections were seen.[1]

Conclusion: In this post-hoc, exploratory analysis of prior bDMARD use in the TNFi-inadequate responder population, a beneficial treatment effect was observed across subgroups irrespective of prior bDMARD use (number or nature). In general, a consistent treatment effect was observed across the strata with no evidence of a qualitative interaction.

[1]Genovese et al. *Ann Rheum Dis* 2015;74(Suppl2):75-76

Table 1. ACR20 Response at Weeks 12 and 24 in patients with prior exposure to nonTNFi (NRI)

	Week 12			Week 24		
n/N (%)	PBO	Baricitinib 2 mg QD	Baricitinib 4 mg QD	PBO	Baricitinib 2 mg QD	Baricitinib 4 mg QD
Abatacept	9/37 (24)	12/34 (35)	16/36 (44)	10/37 (27)	10/34 (29)	12/36 (33)
Rituximab	3/23 (13)	16/33 (49)**	14/34 (41)*	2/23 (9)	12/33 (36)*	9/34 (27)
Tocilizumab	2/36 (6)	12/36 (33)**	14/30 (47)***†	3/36 (8)	14/36 (39)**†	11/30 (37)**

Data are n/N (%) patients achieving response (NRI); *p≤.05, **p≤.01, ***p≤.001 vs PBO

N = number of mITT patients in the specified subgroup; n = number of patients in the specified category, subgroups are not mutually exclusive

†Significant interaction among patients ever treated or never treated with tocilizumab

Table 2. Efficacy Response at Weeks 12 and 24 by prior bDMARD use (NRI)							
		Week 12			Week 24		
	n/N (%)	PBO	Baricitinib 2 mg QD	Baricitinib 4 mg QD	PBO	Baricitinib 2 mg QD	Baricitinib 4 mg QD
1 TNFi only	ACR20	22/69 (32)	32/61 (53)*	40/63 (64)***	21/69 (30)	27/61 (44)	40/63 (64)***
	ACR50	8/69 (12)	15/61 (25)	25/63 (40)***	12/69 (17)	14/61 (23)	29/63 (46)***
	ACR70	1/69 (1)	12/61 (20)***	12/63 (19)***	2/69 (3)	9/61 (15)*	20/63 (32)***
	DAS28-CRP ≤3.2	8/69 (12)	15/61 (25)	27/63 (43)***	10/69 (15)	12/61 (20)	31/63 (49)***
>1 TNFi, no nonTNFi	ACR20	10/30 (33)	18/33 (55)	17/33 (52)	9/30 (30)	15/33 (46)	13/33 (39)
	ACR50	1/30 (3)	8/33 (24)*	7/33 (21)	4/30 (13)	10/33 (30)	7/33 (21)
	ACR70	1/30 (3)	5/33 (15)	2/33 (6)	2/30 (7)	5/33 (15)	2/33 (6)†
	DAS28-CRP ≤3.2	2/30 (7)	10/33 (30)*	8/33 (24)	3/30 (10)	8/33 (24)	8/33 (24)
≥3 prior bDMARDs	ACR20	6/47 (13)	19/50 (38)**	24/45 (53)*** ‡	5/47 (11)	16/50 (32)*	16/45 (36)**
	ACR50	1/47 (2)	5/50 (10)	9/45 (20)**	3/47 (6)	10/50 (20)	11/45 (24)*
	ACR70	0/47 (0)	3/50 (6)	5/45 (11)*	1/47 (2)	6/50 (12)	5/45 (11)
	DAS28-CRP ≤3.2	1/47 (2)	9/50 (18)*	12/45 (27)***	3/47 (6)	8/50 (16)	11/45 (24)*
Data are n/N (%) patients achieving response (NRI); *p≤.05, **p≤.01, ***p≤.001 vs PBO							
N = number of mITT patients in the specified subgroup; n = number of patients in the specified category							
†Significant interaction between 1 TNFi and >1 TNFi							
‡Significant interaction between <3 bDMARDs and ≥3 bDMARDs							

Disclosure: M. C. Genovese, AbbVie, Astellas, Eli Lilly and Company, Galapagos, Pfizer, Vertex, 2,AbbVie, Astellas, Eli Lilly and Company, Galapagos, Pfizer, Vertex, 5; **J. M. Kremer**, AbbVie, Amgen, Bristol-Myers Squibb, Eli Lilly and Company, Genentech, Pfizer, and UCB, 2,Corrona, 3,Eli Lilly and Compnay, 5; **C. Kartman**, Eli Lilly and Company, 1,Eli Lilly and Company, 3; **D. E. Schlichting**, Eli Lilly and Company, 1,Eli Lilly and Company, 3; **L. Xie**, Eli Lilly and Company, 1,Eli Lilly and Company, 3; **T. Carmack**, None; **W. L. Macias**, Eli Lilly and Company, 1,Eli Lilly and Company, 3; **J. S. Smolen**, Abbvie, Janssen, Eli Lilly and Company, MSD, Pfizer, Roche, 2,Abbvie, Amgen, Astra-Zeneca, Astro, Celgene, Glaxo, ILTOO, Janssen, Eli Lilly and Company, Medimmune, MSD, Novartis-Sandoz, Novo-Nordisk, Pfizer, Roche, Samsung, Sanofi, UCB, 5.

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Abstract Number: 1047

Characterization of Changes in Lymphocyte Subsets in Baricitinib-Treated Patients with Rheumatoid Arthritis in Two Phase 3 Studies

Paul Emery[1], Iain McInnes[2], Mark C. Genovese[3], Josef S. Smolen[4], Joel Kremer[5], Maxime Dougados[6], Douglas E. Schlichting[7], Terence Rooney[7], Maher Issa[7], Stephanie de Bono[7], William L. Macias[7], Veronica Rogai[7], Steven H. Zuckerman[7] and Peter C. Taylor[8], [1]Division of Rheumatic and Musculoskeletal Disease, University of Leeds, Leeds, United Kingdom, [2]Glasgow Biomedical Research Centre, Glasgow, United Kingdom, [3]Division of Rheumatology, Stanford University Medical Center, Palo Alto, CA, [4]Department of Rheumatology, Medical University of Vienna, Vienna, Austria, [5]Albany Medical College, Albany, NY, [6]Paris-Descartes University, Paris, France, [7]Eli Lilly and Company, Indianapolis, IN, [8]Kennedy Institute of Rheumatology, Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences, University of Oxford Botnar Research Centre, Oxford, United Kingdom

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Session Title: Rheumatoid Arthritis-Small Molecules, Biologics and Gene Therapy II: Small Molecular Targeted Therapies

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Background/Purpose: Baricitinib (bari) is an oral, reversible inhibitor of Janus kinase (JAK)1/JAK2 being developed as QD treatment for patients (pts) with RA. In phase (ph) 1 studies, transient increases in total lymphocyte count were seen within hours of dosing and returned to baseline prior to the next daily dose;[1] ph 3 data were consistent with these observations.[2,3] The objective of this analysis was to examine changes over time in lymphocyte subsets in RA pts treated with bari or placebo (PBO) in ph 3 RA-BUILD and RA-BEACON studies.

Methods: Pts had active RA with insufficient response (IR) to conventional synthetic DMARDs (csDMARDs) (RA-BUILD; N=684) or TNF inhibitors (TNFi) (RA-BEACON; N=527). Pts were randomized 1:1:1 to receive PBO or 2 or 4mg bari QD for 24 weeks (wks). Lymphocyte subsets and natural killer (NK) cells were quantified by flow cytometry at baseline and Wks 4, 12, and 24. Total lymphocyte count was measured at all study visits. Change from baseline and differences vs PBO were evaluated. At Wks 12 and 24, phlebotomy was conducted before administering study drug (reflecting trough concentration).

Results: Compared to PBO, significant improvements in disease activity were seen for bari in both studies[2,3]. Total lymphocyte increases seen at Wk 4 for bari were generally within normal ranges. Compared to PBO, change in total lymphocyte count was similar at Wks 12 and 24, respectively, for the bari groups. Increased T cells, B cells, and NK cells were seen at Wk 4, while decreased T cells and NK cells and increased B cells were seen at Wks 12 and 24 for the bari groups (Table 1). These changes were generally within normal ranges. Changes in other T- and B-cell populations were somewhat variable, but generally reflected these patterns (Table 1). Decreased NK cell count did not appear to be associated with an increased incidence of infection (Table 2).

Conclusion: In ph 3 studies, QD oral bari produced significant clinical improvements in disease activity in csDMARD-IR and TNFi-IR RA patients. These improvements were accompanied by a variety of changes in lymphocyte counts, predominantly within normal ranges, including transient increases from baseline in total lymphocyte count, transient increases followed by decreases from baseline in T cells and NK cells, and sustained increases from baseline in B cells. Similar lymphocyte subset and NK cell assessments will be available in a long-term extension study that receives pts from the bari ph 3 RA program.

1. Shi JG, et al. *J Clin Pharmacol*. 2014;54:1354-61

2. Dougados M et al. *Ann Rheum Dis*. 2015;74:Suppl(2)79

3. Genovese M, et al. *Ann Rheum Dis* 2015;74:Suppl(2)75

Table 1. Changes in Lymphocyte Subset Counts at Weeks 4, 12, and 24

LS mean Δ from baseline	Placebo			Baricitinib 2 mg			Baricitinib 4 mg		
	Week 4	Week 12	Week 24	Week 4	Week 12	Week 24	Week 4	Week 12	Week 24
RA-BUILD									
Lymphocytes, 10^3 cells/mm^3	-0.04	-0.01	0.06	0.30***	0.04	-0.01	0.26***	-0.05	-0.05
T cells, cells/μL	-77.0	-7.6	21.3	158.3***	-20.9	-117.2**	124.1***	-87.6	-83.4*
B cells, cells/μL	-10.0	1.1	-2.0	66.7***	65.0***	24.3	82.9***	75.1***	55.2***
NK cells, cells/μL	5.0	3.3	4.2	59.5***	-36.7***	-41.2	46.2***	-57.0***	-53.4
RA-BEACON									
Lymphocytes, 10^3 cells/mm^3	-0.09	-0.07	-0.06	0.08**	0.02	-0.09	0.30***	0.00	-0.02
T cells, cells/μL	-83.1	-45.1	7.5	22.6*	0.7	-128.1*	170.7***	-33.1	-53.8
B cells, cells/μL	-12.2	-9.8	0.2	36.8***	49.3***	22.6	74.3***	70.2***	65.0***
NK ells, cells/μL	2.1	-6.0	-9.2	36.8**	-22.0	-45.0**	77.0***	-22.7	-40.9*

*p=0.05 vs. placebo, **p=0.01 vs. placebo, ***p=0.001 vs. placebo
Reference ranges (all are age and gender dependent): Lymphocytes = 0.8 – 4.28; T cells = 603-2990; B cells = 107-698; NK cells = 95-640

Table 2. Treatment-Emergent Abnormalities in Absolute Lymphocyte Subset Counts Through Week 24

% of patients with abnormality at any time	Placebo	Baricitinib 2 mg	Baricitinib 4 mg
RA-BUILD			
TE high Lymphocytes	2	9	9
TE low T Cells	9	9	8
TE high B Cells	0	5	3
TE low NK Cells	10	16	22
RA-BEACON			
TE high Lymphocytes	4	14	16
TE low T Cells	7	3	6
TE high B Cells	2	1	6
TE low NK Cells	16	14	16

TE=treatment emergent
Reference ranges (all are age and gender dependent): Lymphocytes = 0.8 – 4.28; T cells = 603-2990; B cells = 107-698; NK cells = 95-640

Disclosure: P. Emery, Pfizer Inc, MSD, AbbVie, BMS, UCB, Roche, Novartis, Samsung, Eli Lilly and Company, takeda, 5; **I. McInnes**, Eli Lilly and Company, Pfizer, Galapagos, AbbVie, UCB, Janssen, Novartis, 5,Pfizer, UVCB, Janssen, Astra Zeneca, 2; **M. C. Genovese**, AbbVie, Astellas, Eli Lilly and Company, Galapagos, Pfizer, Vertex, 2,AbbVie, Astellas, Eli Lilly and Company, Galapagos, Pfizer, Vertex, 5; **J. S. Smolen**, AbbVie, Janssen, Eli Lilly and Company, MSD, Pfizer, Roche, 2,Abbvie, Amgen, Astra-Zeneca, Astro, Celgene, Glaxo, ILTOO, Janssen, Lilly, Medimmune, MSD, Novartis-Sandoz, Novo-Nordisk, Pfizer, Roche, Samsung, Sanofi, UCB, 5; **J. Kremer**, Eli Lilly and Company, AbbVie, Amgen, BMS, Genetech, Pfizer, UCB, 2,Eli Lilly and Company, 5,Corrona, 3; **M. Dougados**, Eli Lilly and Company, Pfizer, Roche, UCB, Mercki, BMS, AbbVie, 5,Eli Lilly and Company, Pfizer, Roche, UCB, Mercki, BMS, AbbVie, 2; **D. E.**

Schlichting, Eli Lilly and Company, 1,Eli Lilly and Company, 3; **T. Rooney**, Eli Lilly and Company, 1,Eli Lilly and Company, 3; **M. Issa**, Eli Lilly and Company, 3,Eli Lilly and Company, 1; **S. de Bono**, Eli Lilly and Company, 3,Eli Lilly and Company, 1; **W. L. Macias**, Eli Lilly and Company, 1,Eli Lilly and Company, 3; **V. Rogai**, Eli Lilly and Company, 1,Eli Lilly and Company, 3; **S. H. Zuckerman**, Eli Lilly and Company, 1,Eli Lilly and Company, 3; **P. C. Taylor**, Eli Lilly and Company, Pfizer, Galapagos, 5,UCB, 2.

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Abstract Number: 1048

Filgotinib (GLPG0634), an Oral JAK1 Selective Inhibitor Is Effective in Combination with Methotrexate in Patients with Active Rheumatoid Arthritis: Results from a Phase 2B Dose Ranging Study

R Westhovens[1], Rieke Alten[2], Dace Pavlova[3], Favio Enríquez-Sosa[4], Minodora Mazur[5], Maria Greenwald[6], Annegret Van der Aa[7], Frédéric Vanhoutte[7], Chantal Tasset[7] and Pille Harrison[7], [1]Skeletal Biology and Engineering Research Center, Department of Development and Regeneration, KU Leuven, Leuven, Belgium, KU Leuven, Leuven, Belgium, [2]Internal Medicine, Rheumatology & Clinical Immunology, Schlosspark-Klinik, University Medicine Berlin, Berlin, Germany, [3]LTD M & M Centrs, Carnikava, Latvia, [4]CLINSTILE, S.A. DE C.V, Mexico, Mexico, [5]IMSP Institul de Cardiologie, Chisinau, Moldova, [6]Desert Medical Advances, Palm Desert, CA, [7]Galapagos NV, Mechelen, Belgium
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Session Time: 4:30PM-6:00PM

Background/Purpose: Filgotinib (GLPG0634) is a novel oral, potent and selective JAK1 inhibitor that has previously demonstrated efficacy in combination with methotrexate (MTX) in treating rheumatoid arthritis (RA) in 4-week phase 2A studies with an acceptable safety profile. The purpose of this study was to evaluate efficacy and safety of different doses and dose regimens of filgotinib versus placebo (PBO) in patients with active RA with inadequate response to MTX.

Methods: Patients with active RA on stable dose of MTX were randomized 1:1:1:1:1:1:1 in a double blinded manner to receive either PBO or one of three doses of filgotinib (50mg, 100mg or 200mg) as once (qd) or twice daily (bid) regimen for 24 weeks (DARWIN 1 study). The primary endpoint was the proportion of patients achieving ACR 20 response at week 12. Reported data are from the planned 12 weeks analysis.

Results: Of 594 randomized and treated patients, 76-86% were females with a mean age across groups of 52-55 years, mean duration of RA of 7-10 years and DAS28(CRP) at baseline ranging from 6.0-6.2. Patients were well distributed across different geographical regions. At week 12, a statistically significant higher ACR20 response versus PBO was observed with 200mg daily dose. For other key efficacy endpoints (ACR50, ACR-N, DAS28(CRP), CDAI, SDAI) all doses showed significant differences versus PBO. No statistically significant difference between qd and bid regimens was seen. By week 12, 24-50% of patients on filgotinib achieved low disease activity (DAS28(CRP)≤ 3.2) in a dose dependent manner, compared to 14% on PBO. Onset of efficacy was rapid for ACR-N, DAS28(CRP) and SDAI with significant differences seen from week 1 onwards at 200mg daily dose.

Table 1. Summary of the ACR/DAS28(CRP)/CDAI responses after 12 weeks treatment:

		Once-daily dosing			Twice-daily dosing		
	Placebo *n=86*	50mg *n=82*	100mg *n=85*	200mg *n=86*	25mg *n=86*	50mg *n=85*	100mg *n=84*
ACR20, NRI[1], %	45	56	62	69*	57	59	80***
ACR50, NRI, %	15	32*	39**	43***	28*	34*	55***
ACR70, NRI, %	8	16	20	24*	14	19	31**
ACR-N, LOCF[2], %	23	34*	38**	42***	33*	36*	51***
DAS28(CRP), mean change from BL[3], LOCF	-1.2	-1.8*	-2.2***	-2.5***	-1.9**	-2.1***	-2.8***
CDAI[4], mean change from BL, LOCF	-17	-20	-24**	-26***	-21*	-23**	-29***

* p< 0.05 vs. placebo; ** p<0.01 vs. placebo; *** p<0.001 vs. placebo; ACR scores based on ITT analysis. [1]Non-responder imputation. [2] Last observation carried forward.[3] Baseline. [4]Clinical Disease Activity Index.

Conclusion: Over 12 weeks, filgotinib in combination with MTX demonstrated consistent efficacy on signs and symptoms of active RA with a rapid onset of action. The safety profile was overall favorable and consistent with previous studies conducted in RA with filgotinib.

Disclosure: R. Westhovens, Roche Pharmaceuticals, 2,Bristol-Myers Squibb, 8,Janssen, Galapagos, 5; **R. Alten**, None; **D. Pavlova**, None; **F. Enríquez-Sosa**, None; **M. Mazur**, None; **M. Greenwald**, None; **A. Van der Aa**, Galapagos, 3; **F. Vanhoutte**, Galapagos NV, 3; **C. Tasset**, Galapagos, 3; **P. Harrison**, Galapagos, 3.

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Abstract Number: 1049

Filgotinib (GLPG0634), an Oral JAK1 Selective Inhibitor Is Effective As Monotherapy in Patients with Active Rheumatoid Arthritis: Results from a Phase 2B Dose Ranging Study

Arthur Kavanaugh[1], Lucia Ponce[2], Regina Cseuz[3], Olga Reshetko[4], Mykola A Stanislavchuk[5], Maria Greenwald[6], Annegret Van der Aa[7], Frédéric Vanhoutte[7], Chantal Tasset[7] and Pille Harrison[7], [1]University of California San Diego, La Jolla, CA, [2]Consulta Privada Dra. Lucia Ponce, Temuco, Chile, [3]Revita Reumatologiai Rendelo, Budapest, Indonesia, [4]Regional Clinical Hospital, Saratov, Russia, [5]Vinnitsa Regional Clinical Hospital n.a. Pirogov, Vinnitsa, Ukraine, [6]Desert Medical Advances, Palm Desert, CA, [7]Galapagos NV, Mechelen, Belgium

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Session Type: ACR Concurrent Abstract Session

Session Time: 4:30PM-6:00PM

Background/Purpose: Filgotinib (GLPG0634) is a novel oral, potent and selective JAK1 inhibitor that has previously demonstrated efficacy in combination with methotrexate (MTX) in treating rheumatoid arthritis (RA) in 4-week phase 2A studies with an acceptable safety profile. The purpose of this study was to evaluate efficacy and safety of different doses of filgotinib as monotherapy versus placebo (PBO) in patients with active RA with inadequate response to MTX.

Methods: Patients with active RA were randomized 1:1:1:1 in a double blinded manner to receive either PBO or one of three doses of filgotinib (50mg, 100mg or 200mg) as once daily regimen for 24 weeks (DARWIN 2 study). The primary endpoint was the proportion of patients achieving ACR20 response at week 12. Reported data are from the planned 12 weeks analysis.

Results: Of 283 randomized and treated patients, 76-87% were females with mean age across groups of 52-53 years, mean duration of RA of 9 years and DAS28(CRP) at baseline ranging from 6.0-6.2. Patients were well distributed across geographical regions. At week 12, a statistically significant higher ACR20 response versus PBO was observed with all three doses tested versus PBO. For other key efficacy endpoints (ACR50, ACR-N, DAS28 (CRP), CDAI, SDAI) all doses showed significant difference versus PBO. By week 12, 24-45% of patients on filgotinib achieved low disease activity (DAS28(CRP)≤ 3.2) in a dose dependent manner, compared to 14% in PBO. Onset of efficacy was rapid for ACR-N and DAS28(CRP) with statistically significant differences at 100mg and 200mg daily dose seen from week 1 onwards.

Table 1. Summary of the ACR/DAS28(CRP)/CDAI responses after 12 weeks treatment:

	Placebo *n=72*	50mg *n=72*	100mg *n=70*	200mg *n=69*
ACR20, NRI[1], %	31	67***	66***	73***
ACR50, NRI, %	11	36**	34**	44***
ACR70, NRI, %	4	8	19*	13
ACR-N, LOCF[2], %	16	35***	37***	41***
DAS28(CRP), LOCF, mean change from BL[3]	-1.0	-1.7***	-2.0***	-2.3***
CDAI[4] mean change from BL, LOCF	-11	-21***	-24***	-25***

*p< 0.05 vs. placebo; **p<0.01 vs. placebo; ***p<0.001 vs. placebo. ACR scores based on ITT analysis. [1]Non-responderimputation. [2]Last observation carried forward. [3]Baseline. [4]Clinical Disease Activity Index

Over 12 weeks, Serious Adverse events (2%) and Treatment-Emergent Adverse events (TEAE) were distributed across the groups including placebo: 38% patients on PBO and 31-42% in the filgotinib groups experienced TEAES. Most of the TEAEs were mild. In the filgotinib groups, a dose dependent decrease in mean neutrophil as well as a small reduction in platelet counts was seen without discontinuations and mild increase in mean creatinine concentration was apparent. Notably, a dose dependent increase in haemoglobin concentration was detected and no meaningful difference in transaminase changes was encountered with filgotinib.

Conclusion: Over 12 weeks, filgotinib as monotherapy demonstrated clear efficacy in treating the signs and symptoms of active RA with a rapid onset of action. Overall safety profile was favorable and consistent with previous studies conducted in RA with filgotinib.

Disclosure: A. Kavanaugh, Galapagos NV, 5; **L. Ponce**, None; **R. Cseuz**, None; **O. Reshetko**, None; **M. A. Stanislavchuk**, None; **M. Greenwald**, None; **A. Van der Aa**, Galapagos, 3; **F. Vanhoutte**, Galapagos NV, 3; **C. Tasset**, Galapagos, 3; **P. Harrison**, Galapagos, 3.

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Abstract Number: 1050

Response to Baricitinib at 4 Weeks Predicts Response at 12 and 24 Weeks in Patients with Rheumatoid Arthritis: Results from Two Phase 3 Studies

Joel Kremer[1], Maxime Dougados[2], Mark C. Genovese[3], Paul Emery[4], Lili Yang[5], Stephanie de Bono[5], Thorsten Holzkaemper[5], Noriko Iikuni[5], Douglas E. Schlichting[5] and Josef S. Smolen[6], [1]The Center for Rheumatology, Center for Rheumatology, Albany Medical College, Albany, NY, [2]Service de Rhumatologie B, GHU Cochin, F-75014 France, PARIS, France, [3]Division of Rheumatology, Stanford University Medical Center, Palo Alto, CA, [4]Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds, Leeds, United Kingdom, [5]Eli Lilly and Company, Indianapolis, IN, [6]Department of Rheumatology, Medical University of Vienna, Vienna, Austria
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Background/Purpose: Baricitinib (bari), an oral, reversible inhibitor of Janus kinase (JAK)1/JAK2, improved signs and symptoms in phase 3, placebo (PBO)-controlled studies in patients (pts) with active RA despite treatment with conventional synthetic DMARDs (RA-BUILD)[1] or TNF inhibitors (RA-BEACON)[2]. In both studies, statistically significant improvements in multiple measures of disease activity were observed for bari 4 mg QD as early as Week (Wk) 1 and were maintained through Wk 24. The objective of this analysis was to determine if clinical response to bari 4 mg at Wk 4 is highly likely to predict disease state at Wk 12 or 24.

Methods: 684 pts in RA-BUILD and 527 pts in RA-BEACON were randomized 1:1:1 to receive PBO or 2 or 4 mg bari QD for 24 wks. Improvement from baseline (BL) to Wk 4 in a number of clinical response variables, including DAS28-ESR (DAS28) and the Clinical Disease Activity Index (CDAI), was used to predict low disease activity (LDA; DAS28 ≤3.2) or remission (DAS28 <2.6) at Wk 12 or 24. Decreases from BL to Wk 4 of 0.6 to 1.2 for DAS28 and 3 to 12 for CDAI were investigated.

Results: Compared to PBO, treatment with bari 4 mg was associated with a rapid decrease in DAS28 and CDAI as early as Wk 1 ($p \leq 0.001$ for both endpoints in both studies). Across both studies, decreases from BL to Wk 4 of ≥0.6 for DAS28 or ≥6 for CDAI were the minimum levels of improvement associated with an increased probability of achieving LDA or remission at Wk 12 or 24 compared to LDA and remission rates observed in pts not experiencing these levels of improvement (Table 1). Approximately 81% and 79% of pts on bari 4 mg had a decrease in DAS28 ≥0.6 and 80% and 80% had a decrease in CDAI ≥6 in RA-BUILD and RA-BEACON, respectively. The negative predictive value (NPV) for LDA or remission at Wk 12 or 24 associated with a <0.6 decrease in DAS28 or <6 in CDAI from BL to Wk 4 almost always exceeded 90%, indicating that patients with this low degree of improvement were highly unlikely to achieve LDA or remission (Table 2). Inclusion of an acute phase reactant in the disease activity score did not appear to increase the NPV over that seen with CDAI.

Conclusion: In RA-BUILD and RA-BEACON, lack of early clinical response to bari 4 mg QD, as indicated by a failure to achieve a decrease in DAS28 ≥0.6 or CDAI ≥6 after 4 wks of treatment, was associated with very low rates of LDA or remission at 12 or 24 wks. Larger decreases in DAS28 or CDAI at Wk 4 were associated with improved clinical responses. Early identification of pts (at 4 wks) who are not likely to achieve LDA or remission may be useful in tailoring therapy to individual pts.

Table 1. Low Disease Activity and Remission After 12 and 24 Weeks of Baricitinib 4 mg Treatment in RA-BUILD[1] and RA-BEACON[2]

	LDA (DAS28-ESR ≤ 3.2)		Remission (DAS28-ESR < 2.6)	
Decrease from Baseline to Week 4	Week 12	Week 24	Week 12	Week 24
	RA-BUILD			
DAS28-ESR				
<0.6	3/39 (7.7)	5/36 (13.9)	2/39 (5.1)	3/36 (8.3)
≥0.6	45/168 (26.8)	62/159 (39.0)	19/168 (11.3)	32/159 (20.1)
CDAI				
<6	2/41 (4.9)	2/37 (5.4)	2/41 (4.9)	2/37 (5.4)
≥6	44/166 (26.5)	65/159 (40.9)	18/166 (10.8)	32/159 (20.1)
	RA-BEACON			
DAS28-ESR				
<0.6	1/31 (3.2)	1/28 (3.6)	1/31 (3.2)	1/28 (3.6)
≥0.6	20/126 (15.9)	29/125 (23.2)	9/126 (7.1)	15/125 (12.0)
CDAI				
<6	1/33 (3.0)	2/30 (6.7)	1/33 (3.0)	1/30 (3.3)
≥6	19/125 (15.2)	27/125 (21.6)	8/125 (6.4)	14/125 (11.2)

Data presented are n/N (%) of patients achieving clinical outcome of interest.

Table 2. Predictive Values (%) of Low Disease Activity and Remission After 12 and 24 Weeks of Baricitinib 4 mg Treatment in RA-BUILD[1] and RA-BEACON[2]

	LDA (DAS28-ESR ≤ 3.2)		Remission (DAS28-ESR < 2.6)	
Decrease from Baseline to Week 4	Week 12	Week 24	Week 12	Week 24
	RA-BUILD			
DAS28-ESR				
<0.6 (NPV)	92.3	86.1	94.9	91.7
≥0.6 (PPV)	26.8	39.0	11.3	20.1
CDAI				
<6 (NPV)	95.1	94.6	97.0	96.7
≥6 (PPV)	26.5	40.9	10.8	20.1
	RA-BEACON			
DAS28-ESR				
<0.6 (NPV)	96.8	96.4	96.8	96.4
≥0.6 (PPV)	15.9	23.2	7.1	12.0
CDAI				
<6 (NPV)	95.1	94.6	95.1	94.6
≥6 (PPV)	15.2	21.6	6.4	11.2

NPV=negative predictive value; PPV=positive predictive value

[1]Dougados M et al, Ann Rheum Dis 2015;74(S2):79
[2]Genovese M et al, Ann Rheum Dis 2015;74(S2):75-76

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Abstract Number: 1051

Serum Calprotectin As Biomarker of Carotid Atherosclerosis in Patients with Primary Sjögren's Syndrome

Gabriela Moreira Balarini[1], Eliana Zandonade[2], leandro tanure[3], gilda Aparecida ferreira[3], Wildner Mardegan Sardenberg[4], Érica Vieira Serrano[4], Cléia Coelho Dias[5], Túlio Pinho Navarro[3], João Felipe Tonini[4], Hilde H Nordal[6], Piotr Mydel[7], Johan Gorgas Brun[8], Karl Albert Brokstad[9], Eva Gerdts[8], Roland Jonsson[10,11] and **Valeria Valim**[4,12], [1]Department of Medical Clinic, Federal University of Espírito Santo (UFES), Brazil., cachoeiro de itapemirim, Brazil, [2]Department of Statistic, Federal University of Espírito Santo (UFES), Brazil., vitória, Brazil, [3]Department of Locomotor System, Federal University of Minas Gerais, Brazil., belo horizonte, Brazil, [4]Department of Medical Clinic, Federal University of Espírito Santo (UFES), Brazil., vitória, Brazil, [5]Department of Medical Clinic, Federal University of Espírito Santo (UFES), Brazil., vila velha, Brazil, [6]Broegelmann Research Laboratory/University of Bergen, Norway, bergen, Norway, [7]Clinical Science, Broegelmann Research Laboratory, Bergen, Norway, [8]Department of Clinical Science, University of Bergen, Norway, bergen, Norway, [9]Department of Clinical Science, University of Bergen, Norway., bergen, Norway, [10]Broegelmann Research Laboratory, Department of Clinical Science, University of Bergen, Bergen, Norway, [11]Broegelmann research laboratory, Bergen, Norway, [12]Rheumatology, Universidade Federal do Espírito Santo, Vitória, Brazil
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SESSION INFORMATION

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Background/Purpose: The relationship between atherosclerosis, traditional risk factors, disease activity and biomarkers is not well explored. We aimed to identify the association of carotid atherosclerosis with traditional risk factors, disease features, cytokine profile and calprotectin in patients with pSS.

Methods: 63 patients primary pSS and 63 age-sex-matched healthy controls underwent carotid ultrasound, clinical and laboratorial evaluation. Presence of carotid plaques was taken as carotid atherosclerosis. Covariates of carotid atherosclerosis were identified in univariate and multivariate regression. Financing from CAPES (Higher Education Personnel Improvement Coordination-Brazil) and Broegelmann Research Laboratory-Bergen.

Results: Patients with pSS had higher prevalence of carotid atherosclerosis (13% vs. 2%, p<0.05), calprotectin, tumoral necrosis factor receptor 2 (TNF-R2), Hepatocyte growth factor (HGF), and monocyte chemoattractant protein-1 (MCP-1) than controls, while sex, menopause and prevalences of traditional cardiovascular risk factors including smoking, hypertension, diabetes, dyslipidemia, obesity and metabolic syndrome (MetS) did not differ (all p>0.05). In univariate analyses, serum calprotectin (2945.16 ± 1793.36 vs. 1407.09 ± 990.66, p=0.002), most traditional cardiovascular (age, male sex, MetS, hypertension, hypertriglyceridemia, and serum creatinine), and some disease-associated risk factors (glucocorticoid or saliva substitute use, ESSDAI constitutional domain) were associated with higher risk for plaque (Table 1). In multivariate analysis, disease itself and calprotectin were independent risk factors for carotid atherosclerosis. Higher serum calprotectin was associated with carotid atherosclerosis independent of serum creatinine and systolic blood pressure (Table 2).

Conclusion: In patients with pSS, calprotectin is a biomarker of carotid atherosclerosis, which in pSS patients is modulated by traditional cardiovascular risk factors as well as the disease itself.

Table 1. Cardiovascular risk factors for carotid atherosclerosis in primary Sjögren's syndrome (pSS).

Risk Factor	OR	OR 95%CI	p-value
pSS disease	9.02	1.09-94.41	0.040
Gender	6.4	1.05-39.86	0.040
Age (years)	0.86	0.78-0.95	0.002
Metabolic Syndrome	8.92	1.06-74.86	0.040
Hypertension	5.6	1.11-28.16	0.044
Hypertriglyceridemia	5.8	1.37-24.64	0.017
Familiar history of myocardial infarct	10.27	1.22-86.33	0.002
Glucocorticoid use	11.76	2.68-51.59	0.001
Framingham score	0.84	0.73-0.93	0.009
Serum creatinine (mg/dL)	0.04	0.01-0.55	0.016
Calprotectin (ng/mL)	1.001	0.999-1	0.002

Table 2. Sjögren's syndrome and calprotectin as independent risk factor for carotid atherosclerosis after adjusting for traditional risk factors.

Model	Risk factor	OR	95% CI Lower Limit	95% CI Upper Limit	p-value
1	Sjögren's syndrome	28.76	1.689	490.19	0.020
	Age	0.820	0.721	0.940	0.004
	Hypertension	1.890	0.273	13.05	0.519
	Hypertriglyceridemia	10.074	1.162	87.33	0.036
	Serum creatinine	1.072	0.005	23.058	0.965
2	Hypertension	1.040	0.99	1.09	0.004
	Serum creatinine	10.204	0.60	166.666	0.055
	Calprotectin	1.001	1.000	1.001	0.023

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Identification of Novel Sjogren's Syndrome Risk Loci in the Regions of TNFAIP3 and PRDM1

Christopher J. Lessard[1,2], He Li[1,2], John Ice[2], Indra Adrianto[3], Astrid Rasmussen[2], Kiely Grundahl[4], Jennifer A. Kelly[5], Corinne Miceli[6], Simon Bowman[7], Susan Lester[8], Johan G. Brun[9,10], Lasse G. Goransson[11], Erna Harboe[11], Joel M. Guthridge[2], Kenneth M. Kaufman[12,13], Per Eriksson[14], Maija-Leena Eloranta[15], Marika Kvarnström[16], Deborah S. Cunninghame-Graham[17], A. Darise Farris[2], Michael T. Brennan[18], James Chodosh[19], Raj Gopalakrishnan[20], Andrew J.W. Huang[21], Pamela Hughes[22], David M. Lewis[23], Lida Radfar[24], Michael D. Rohrer[25], Donald U. Stone[26], Timothy J. Vyse[17], Patrick M. Gaffney[2], Judith A. James[1,5,27], John B. Harley[12,28], Roald Omdal[11], Marie Wahren-Herlenius[16], Gabor G. Illei[29], Torsten Witte[30], Roland Jonsson[10,31], Maureen Rischmueller[32,33], Lars Rönnblom[34], Xavier Mariette[35], Juan-Manuel Anaya[36], Wan-Fai Ng[37], Gunnel Nordmark[34], Courtney G. Montgomery[2], Nelson L.

Rhodus[38], Barbara M. Segal[39], R. Hal Scofield[2,27,40] and Kathy L. Sivils[1,2], [1]Department of Pathology, University of Oklahoma Health Sciences Center, Oklahoma City, OK, [2]Arthritis and Clinical Immunology Research Program, Oklahoma Medical Research Foundation, Oklahoma City, OK, [3]Oklahoma Medical Research Foundation, Oklahoma City, OK, [4]Arthritis and Clinical Immunology Research Program, Oklahoma Medical Research Foundation, Oklahoma CIty, OK, [5]Arthritis & Clinical Immunology Research Program, Oklahoma Medical Research Foundation, Oklahoma City, OK, [6]Rheumatology, PARIS, France, [7]Rheumatology Dept, University Hospital Birmingham, Birmingham, United Kingdom, [8]Queen Elizabeth Hospital, Adelaide, Australia, [9]Institute of Internal Medicine, University of Bergen, Bergen, Norway, [10]Department of Rheumatology, Haukeland University Hospital, Bergen, Norway, [11]Clinical Immunology Unit, Department of Internal Medicine, Stavanger University Hospital, Stavanger, Norway, [12]US Department of Veterans Affairs Medical Center, Cincinnati, OH, [13]Division of Rheumatology, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, [14]Department of Clinical and Experimental Medicine, Rheumatology/AIR, Linköping University, Linköping, Sweden, Linköping, Sweden, [15]Department of Medical Sciences, SciLife Lab, Rheumatology, Uppsala University, Uppsala, Sweden, Uppsala, Sweden, [16]Department of Medicine, Karolinska Institutet, Stockholm, Sweden, [17]Department of Medical and Molecular Genetics, King's College London, London, United Kingdom, [18]Department of Oral Medicine, Carolinas Medical Center, Charlotte, NC, [19]Ophthalmology, Massachusetts Eye and Ear Infirmary, Harvard Medical School, Boston, MA, [20]Diagnostic and Biological Sciences, Division of Oral Pathology, University of Minnesota, Minneapolis, MN, [21]Department of Ophthalmology and Visual Sciences, Washington University, St Louis, MO, [22]Division of Oral and Maxillofacial Surgery, Department of Developmental and Surgical Science, University of Minnesota School of Dentistry, Minneapolis, MN, [23]College of Dentistry, Department of Oral and Maxillofacial Pathology, University of Oklahoma Health Sciences Center, Oklahoma City, OK, [24]Oral Diagnosis and Radiology Department, University of Oklahoma Health Sciences Center College of Dentistry, Oklahoma City, OK, [25]Hard Tissue Research Laboratory, University of Minnesota School of Dentistry, Minneapolis, MN, [26]Department of Ophthalmology, University of Oklahoma Health Sciences Center, Oklahoma City, OK, [27]Department of Medicine, University of Oklahoma Health Sciences Center, Oklahoma City, OK, [28]Center for Autoimmune Genomics and Etiology (CAGE), Cincinnati Children's Hospital Medical Center, Cincinnati, OH, [29]National Institute of Dental and Craniofacial Research, NIH, Bethesda, MD, [30]Hannover Medical School, Hanover, Germany, [31]Broegelmann Research Laboratory, The Gade Institute, University of Bergen, Bergen, Norway, [32]University of Adelaide, Adelaide, Australia, [33]Department of Rheumatology, The Queen Elizabeth Hospital, Adelaide, Australia, [34]Rheumatology, Department of Medical Sciences and Science for Life Laboratory, Uppsala University, Uppsala, Sweden, [35]AP-HP, Hopitaux Universitaires Paris-Sud, Université Paris-Sud, Paris, France, [36]Center for Autoimmune Diseases Research (CREA), Universidad del Rosario, Bogotá, Colombia, [37]Institute of Cellular Medicine, Newcastle University, Newcastle upon Tyne, United Kingdom, [38]Department of Oral Surgery, University of Minnesota School of Dentistry, Minneapolis, MN, [39]Division of Rheumatology, University of Minnesota Medical School, Minneapolis, MN, [40]US Department of Veterans Affairs Medical Center, Oklahoma City, OK
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SESSION INFORMATION

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Background/Purpose: Sjögren's syndrome (SS) is a complex autoimmune disease with both environmental and genetic factors playing important roles in its pathophysiology. The goal of this study was replicate suggestive loci that failed to exceed the genome-wide significance (GWS) threshold of 5x10E-8 in our previously published work. This list included: *TNFAIP3, PTTG1, PRDM1, DGKQ, FCGR2A, IRAK1BP1, ITSN2,* and *PHIP*.

Methods: Our previous study included 1638 SS cases and 6754 population controls typed either on Illumina Omni1 or ImmunoChip arrays. In the current study, we typed an additional 212 SS cases and 2150 population controls on OmniExpress arrays yielding a combined total of 1850 SS cases and 8904 population controls for analysis. The Omni1 data and the ImmunoChip data were imputed using IMPUTE2 with the 1000 Genomes reference panels. Analysis was done using logistic regression accounting for ancestry and gender. and the results were combined using a weighted Z-score method.

Results: Two regions that have not been previously reported were found to exceed the GWS threshold. Association has been previously established with SS to a risk haplotype that spans the *TNFAIP3* coding region originally describe in lupus; however, in the current study we identified a novel effect ~230kb 5' of the TNFAIP3 coding region (rs6933404, P_{meta}= 7.79x10E-9, OR= 1.28, 95% CI=1.14-1.44), which was originally describe as a risk effect for rheumatoid arthritis. Association was observed for the haplotype previously established with SS spanning the *TNFAIP3* coding region; however, the signal peaks at rs58721818 (P=4.77x10E-4), which is correlated (r2>0.8) with rs7749323, a variant previously described in lupus. Logistic regression analysis adjusting for rs6933404 found that this variant accounted for all association in the *TNFAIP3* region. Bioinformatics data provided only limited evidence that rs6933404 might be the true functional/causal variant in this region; however, another variant on this haplotype also surpassing GWS, rs6927172, has been shown to modify 8 transcription factor binding sites, 13 bound proteins in various cell lines by ENCODE, and is located within an enhancer element in $CD4^+CD25^-IL17^+$ PMA-Ionomycin stimulated Th17 primary cells by the Epigenetics Road Map Project. The second region to surpass the GWS threshold was *PRDM1*, which peaked at rs526531 (P_{meta}= 1.24x10E-8, OR= 1.25, 95% CI=1.12-1.39). Logistic regression

adjusting for rs526531 found it accounted for all association in this region. Two additional variants on this haplotype exceeded GWS, but no clear candidate functional/causal variant has emerged based on bioinformatics data. Of the 6 remaining suggestive regions, *PTTG1*, *DGKQ*, and *FCGR2A* continue trending towards GWS.

Conclusion: These data now establish 2 new SS risk haplotypes, *TNFAIP3* and *PRDM1*. *TNFAIP3*, which codes for the protein A20, is a negative regulator of NF-kB responses. *PRDM1*, which codes for the protein BLIMP1, is an important transcription factor in regulation of the interferon-beta locus and plasma cell differentiation. Additional studies are needed to determine how these association signals function in the human genome and contribute to SS pathophysiology.

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Phosphatidylinositol-3-Kinase Delta Pathway a Novel Therapeutic Target for Sjogren's Syndrome

Saba Nayar[1], Joana Campos[1], Christopher Buckley[1], Rodger Allen[2], W.A. Fahy[2], Andrew Payne[2] and Francesca Barone[1], [1]University of Birmingham, Rheumatology Research Group, Birmingham, United Kingdom, [2]UCB Pharma, Slough, United Kingdom

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Background/Purpose: Sjögren's syndrome (SS) is a chronic autoimmune disease characterized by B cell hyper-activation and exocrine gland infiltration that results in loss of glandular function, systemic manifestations and autoantibody production. The phosphatidylinositol 3–kinase delta isoform (PI3Kδ) belongs to a large family of intracellular lipid kinases that regulate metabolism, survival, proliferation, apoptosis, growth, and cell migration. The PI3Kδ pathway has been successfully targeted in B cell malignancies. Given the central role of the B cell in the pathogenesis of Sjögren's syndrome we investigated evidence for the engagement of the PI3Kδ pathway in SS and the functional consequences of blocking PI3Kδ in an animal model of SS.

Methods: PI3K pathway activation was investigated in paraffin embedded salivary glands from patients with Sjogren's Syndrome and non-specific chronic sialoadenitis (NSCS). Staining for phosphorylated ribosomal protein S6 (pS6) was performed in combination with several cellular markers. UCB5857, a small molecule inhibitor of PI3Kδ, was used *in vivo* in an inducible model of ectopic lymphoneogenesis in murine salivary glands that mimics Sjögren's syndrome. Wild type (C57BL/6) murine salivary glands were cannulated with AdV5 (10^8 p.f.u.). UCB5857 or vehicle was administered by daily gavage, prophylactically or therapeutically, starting at either day 0, day 3 or day 5 p.c. 6 mice were used per group. Flow cytometry, immunofluorescence (IF) and quantitative real time PCR was used on the murine isolated salivary gland to evaluate the samples at peak of inflammation which is day 15 p.c. for all groups analyzed.

Results: Histological staining for PI3Kδ pathway activation protein, pS6 in human tissues, showed significant expression of pS6 in SS samples, as compared to non-specific sialoadenitis control, confirming engagement of the PI3K pathway. pS6 was detected within the lymphoid aggregates in both T and B cell areas and on the periphery of the lymphoid foci. Interestingly, pS6 staining was predominantly found on CD138+ plasma cells in salivary glands of SS patients.

In vivo, we observed a decrease in the number of T and B cells in cannulated salivary glands of mice prophylactically treated with UCB5857, as compared to vehicle treated mice, confirmed both by flow cytometry on isolated lymphocytes and IF. A reduction in total number of $CD45^+$, CD3, (both CD8 and $CD4^+$cells) and B cells was observed. The gene expression profile of tertiary lymphoid organ (TLO)-associated genes (CXCL13, CCL19, CCL21) was also significantly impaired in mice treated with UCB5857. This decrease was

also observed in mice treated therapeutically from day 3 or day 5 pc. Aggregates in these mice were characterized by decrease in focus score, smaller size of lymphoid aggregates and reduced T/B cell follicular organization.

Conclusion: Preliminary data suggest that PI3Kδ is engaged in several cells present in the salivary glands of patients with SS and might contribute to disease pathogenesis. Accordingly, prophylactic and therapeutic blocking of PI3Kδ results in disaggregation of the inflammatory foci and resolution of salivary gland inflammation in an animal model of SS.

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A Potential Role of Type III Interferon in the Glandular Involvement of Sjögren's Syndrome

Tania Mora[1], Felipe Alonso Masso Rojas[2], Araceli Paez[2], Mariana Patlan[3], Misael Gómez-Mondragón[2], Alberto Aranda-Frausto[4], Maya Chacón Pérez[5] and Luis M. Amezcua-Guerra[6,7], [1]Rheumatology, National Institute of Cardiology, Mexico City, Mexico, [2]Department of Cell Physiology, National Institute of Cardiology, Mexico City, Mexico, [3]Department of Immunology, National Institute of Cardiology, Mexico City, Mexico, [4]Department of Pathology, National Institute of Cardiology, Mexico City, Mexico, [5]National Institute of Cardiology, Mexico City, Mexico, [6]Immunology, National Institute of Cardiology, Mexico City, Mexico, [7]Mexican Accreditation Council of Rheumatology, A.C., Mexico City, Mexico

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Background/Purpose:

Primary Sjögren's syndrome (pSS) is an autoinmune disorder characterized by lymphocytic infiltration of salivary and lachrymal glands. Recently, it has been showed that plasmacytoid dendritic cells (pDC, main cell source of type I IFNs) are reduced in the circulation of pSS patients, although its numbers are substantially increased in the salivary glands. This suggests that pDCs migrate and are housed into the glandular tissue following a specific antigenic stimulus, possibly a viral infection.

Type III IFNs are a novel family of cytokines mainly produced by cytotoxic cells which share many biological activites with type I IFNs. Epithelial tissues are the primary target to IFN-lambda3, which possess the highest activity of all type III IFNs. The possible role that IFN-lambda3 plays in pSS pathogenesis is unknown.

Methods:

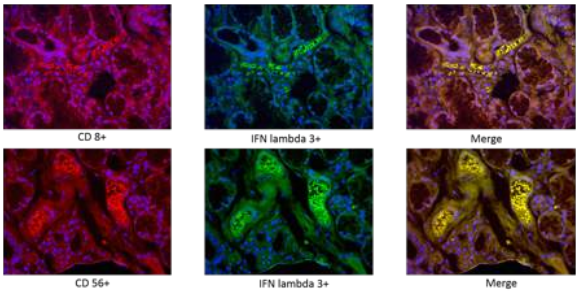
Peripheral blood mononuclear cells (PBMC) from patients with pSS and healthy controls were analyzed by conventional flow cytometry to determine the number of T cytotoxic cells (CD8+ T cells and CD56+ Natural Killers) that were also positive for IFN-lambda3. In addition, biopsies of minor salivary gland from 6 pSS and 6 non-pSS were evaluated by immunofluorescence with antibodies against CD8, CD56, and IFN-lambda3.

Results:

PBMC from 14 pSS patients and 8 healthy volunteers were included. Flow cytometry counts are presented in the Table.

Cell subtype	pSS (n=14)	Healthy (n=8)	*P*
CD8+ total cells/1«10^6 PBMC	104,757 (25,300-226,200)	71,200 (18,600-165,200)	0.3
CD8+IL28+ total cells/1«10^6 PBMC	1,478 (300-3,700)	2,742 (900-5,900)	0.06
CD8+IL28+ % of total CD8+ cells	1.73% (0.19%-5.9%)	3.96% (2.53%-6.7%)	***0.002***
CD56+ total cells/1«10^6 PBMC	39,950 (4,500-161,300)	18,085 (11,300-38,800)	0.3
CD56+IL28+ total cells/1«10^6 PBMC	871 (100-3,100)	2,900 (900-5,300)	***0.009***
CD56+IL28+ % of total CD56+ cells	3.2% (0.43-11.6%)	16% (7.8%-23.7%)	***0.0005***

On immunofluorescence, salivary tissues from pSS patients were extensively infiltrated by CD8+, CD56+, and IFN-lambda3+ cells. As noted, IFN-lambda3+ was in tightly co-localization with both CD8+ and CD56+ cells. This was not noticed in salivary glands from non-pSS individuals.



Conclusion:

The number of circulating cytotoxic cells producing IFN-lambda3 is decreased in the peripheral blood of pSS patients; however, an intense infiltration of cytotoxic cells with high expression of IFN-lambda3 was found in salivary tissue from pSS patients. This suggest the existence of an important stimulus so far unknown (probably a viral infection), causing the migration and homing of cytotoxic cells highly producing IFN-lambda3 from peripheral blood to target tissues.

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Abstract Number: 1055

Expansions of Salivary Gland CD4+ T Cells from Sjögren's Syndrome Patients: Single-Cell Repertoire Analysis and Correlation with Clinical Measures of Disease

Michelle L. Joachims[1], Kerry M. Leehan[2,3], Christina M. Lawrence[3], Astrid Rasmussen[3], Lida Radfar[4], David M. Lewis[5], Glen D Houston[6], Kiely Grundahl[3], Donald U. Stone[7,8], Kimberly Hefner[9], R. Hal Scofield[2,10,11], Kathy L. Sivils[2,3], Linda F. Thompson[12] and **A. Darise Farris**[1,2], [1]Arthritis and Clinical Immunology, Oklahoma Medical Research Foundation, Oklahoma City, OK, [2]Department of Pathology, University of Oklahoma Health Sciences Center, Oklahoma City, OK, [3]Arthritis and Clinical Immunology Program, Oklahoma

Medical Research Foundation, Oklahoma City, OK, [4]Oral Diagnosis and Radiology Department, University of Oklahoma Health Sciences Center College of Dentistry, Oklahoma City, OK, [5]College of Dentistry, Department of Oral and Maxillofacial Pathology, University of Oklahoma Health Sciences Center, Oklahoma City, OK, [6]Heartland Pathology, Oklahoma City, OK, [7]Department of Ophthalmology, Johns Hopkins University, Baltimore, MD, [8]King Khaled Eye Specialist Hospital, Riyadh, Saudi Arabia, [9]Hefner Eye Care and Optical Center, Oklahoma City, OK, [10]College of Medicine, Section of Endocrinology and Diabetes, University of Oklahoma Health Sciences Center, Oklahoma City, OK, [11]Arthritis and Clinical Immunology Research Program, Oklahoma Medical Research Foundation, Oklahoma City, OK, [12]Immunobiology and Cancer Program, Oklahoma Medical Research Foundation, Oklahoma City, OK
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Session Title: Sjögren's Syndrome I: Basic Insights
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Background/Purpose: $CD4^+$ T cells predominate in salivary gland (SG) focal lymphocytic infiltrates in primary Sjögren's syndrome (pSS). However, their antigen specificity, degree of clonal expansion and relationship to clinical disease features remain unknown. Here, we determined the T cell receptor (TCR) repertoire of $CD4^+$ memory T cells in SG and peripheral blood (PB) of pSS patients and assessed whether the frequencies of clonally expanded SG T cells correlate with specific measures of disease.

Methods: Multiplex single cell RT-PCR was used to amplify both the α and β TCR sequences from individual memory $CD4^+$ T cells sorted from SG lip biopsy tissue and PB of 10 patients fulfilling both the 2002 Revised American European Consensus Group Criteria and the 2012 Provisional ACR Criteria for pSS. Percentages of T cells that were part of SG clonal expansions were calculated and correlated with various measures of disease.

Results: Over 3,000 TCR sequences were obtained from 50-115 (median 91) individual SG and 75-121 (median 108) individual PB $CD4^+$ memory T cells per patient. The percentages of cells that were part of clonal expansions were significantly higher in SG (median 12%, range 0-28%) compared to PB (median 0.9%, range 0-7%, p=0.002). The TCR sequences of expanded memory $CD4^+$ T cells in SG were largely distinct from those in PB and were enriched for cells expressing dual productive TCRα transcripts ($\chi 2$=4.42, p=0.036). Sequence analysis revealed: 1) highly homologous CDR3s among different expanded SG T cell clones within single patients, suggesting antigen-driven expansion and 2) unique cases of convergent recombination among unrelated patients, where different V segments/additions/deletions were utilized to make identical CDR3 amino acid sequences. The percentages of clonally expanded $CD4^+$ memory T cells in SG correlated significantly with reduced whole unstimulated salivary flow (r=-0.758, p=0.015) and increased degree of SG fibrosis (r=0.661, p=0.044) but not with systemic features of disease.

Conclusion: SG clonal expansions detected in this study likely identify T cells involved in recognition of common antigen(s) and glandular dysfunction.

Disclosure: M. L. Joachims, None; **K. M. Leehan**, None; **C. M. Lawrence**, None; **A. Rasmussen**, None; **L. Radfar**, None; **D. M. Lewis**, None; **G. D. Houston**, None; **K. Grundahl**, None; **D. U. Stone**, None; **K. Hefner**, None; **R. H. Scofield**, None; **K. L. Sivils**, None; **L. F. Thompson**, None; **A. D. Farris**, None.

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Abstract Number: 1056

Aquaporin Gene Therapy Corrects Bone Morphogenetic Protein 6 Associated Exocrine Gland Dysfunction in Mouse Model of Sjögren's Syndrome

Hongen Yin[1], Zhennan Lai[2], Javier Cabrera-Perez[3], Patricia Glenton[4], Ankur Patel[5], William Swaim[5], Changyu Zheng[5], Maria Guimaro[5], Sandra Afione[6], Cuong Nguyen[5], Fred Nyberg[7] and John A. Chiorini[2], [1]NIDCR, NIH, Bethesda, MD, [2]Mptb, NIH/NIDCR, Bethesda, MD, [3]Molecular Physiology and Therapeutics Branch, National Institute of Dental and Craniofacial Research, National Institutes of Health, Bethesda, Bethesda, MD, [4]Department of Pathology and Infectious Diseases, University of Florida, Gaineville, FL, [5]Molecular Physiology and Therapeutics Branch, National Institute of Dental and Craniofacial Research, National Institutes of Health, Bethesda, MD, [6]National Institute of Dental and Craniofacial Research, Bethesda, MD, [7]Department of Pharmaceutical Bioscience, Division of Biological Research on Drug Dependence, Uppsala University, Uppsala, MD, Sweden
First publication: September 29, 2015

SESSION INFORMATION

Session Title: Sjögren's Syndrome I: Basic Insights

Session Type: ACR Concurrent Abstract Session

Background/Purpose: Loss of secretory epithelial function is a hallmark of primary Sjögren's syndrome (pSS). Previously we reported that bone morphogenetic protein 6 (BMP-6) inhibits cell volume regulation and is associated with the loss of salivary gland dysfunction in human and experimental pSS. The objective of this study is to understand the mechanism associated with BMP-6 induced salivary gland hypofunction and develop a novel treatment based on this to restore salivary flow.

Methods: Correlative gene expression analysis was used to identify gene expression changes that were induced by BMP6 expression. Adeno-associated vector (AAV) mediated AQP-5 and AQP-1 were transferred in BMP-6 treated human salivary gland cell (HSG) lines and membrane water permeability was detected by regulated volume decrease (RVD) assay. AAV mediated AQP-1 was delivered to either BMP-6 overexpression induced xerostomia animal model or C57BL/6.NOD-Aec1Aec2 Sjögren's mouse model.

Results: Correlation analysis identified AQP-5 expression as changing with BMP-6 induced loss in cellular regulated volume decrease. Confocal imaging confirmed a correlation between an increase in BMP6 expression and a decrease in AQP5 expression. Exogenous expression of AQP-1 or AQP-1 in HSG cells can restore the water permeability that was decreased by BMP-6. Salivary gland AAV-AQP-1 local gene therapy in animal models restored secretory function in both salivary and lacrimal glands, accompanied with decreased sailadenitis and systemic inflammation markers.

Conclusion: AAV mediated AQP-1 local gene therapy in salivary gland is a promising treatment for salivary and lacrimal epithelial hypofunction and systemic symptoms associated with pSS.

Disclosure: H. Yin, None; **Z. Lai**, None; **J. Cabrera-Perez**, None; **P. Glenton**, None; **A. Patel**, None; **W. Swaim**, None; **C. Zheng**, None; **M. Guimaro**, None; **S. Afione**, None; **C. Nguyen**, None; **F. Nyberg**, None; **J. A. Chiorini**, None.

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Abstract Number: 1057

Are Ankylosing Spondylitis, Psoriatic Arthritis and Undifferentiated Spondylarthritis Associated with an Increased Risk of Cardiovascular Disease?

Karin Bengtsson[1], Helena Forsblad-d'Elia[2], Elisabeth Lie[1], Eva Klingberg[1], Mats Dehlin[1], Sofia Exarchou[3], Ulf Lindström[1], Johan Askling[4] and Lennart TH Jacobsson[1], [1]Department of Rheumatology and Inflammation Research, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden, [2]Departments of Public Health and Clinical Medicine, Rheumatology, Umeå University, Umeå, Sweden, [3]Section of Rheumatology, Department of Clinical Sciences, Malmö, Lund University, Malmö, Sweden, [4]Clinical Epidemiology Unit and Rheumatology Unit, Department of Medicine, Karolinska Institute, Stockholm, Sweden

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SESSION INFORMATION

Session Date: Sunday, November 8, 2015

Session Title: Spondylarthropathies and Psoriatic Arthritis - Clinical Aspects and Treatment: Clinical Aspects and CoMorbidities

Session Type: ACR Concurrent Abstract Session

Session Time: 4:30PM-6:00PM

Background/Purpose: It is unclear whether and to what extent different phenotypes of spondylarthritis (SpA) are associated with an increased risk of cardiovascular events such as acute coronary syndrome (ACS), stroke and venous thromboembolism (VTE). Studies have indicated that ankylosing spondylitis (AS) and psoriatic arthritis (PsA) are associated with an increased risk of cardiovascular morbidity, but the results have been divergent and for undifferentiated spondylarthritis (uSpA) it has not been studied. Our objective was to investigate the incidence and risk of these cardiovascular outcomes in patients with AS, PsA and uSpA compared to each other and to general population (GP) comparators.

Methods: The study design was a prospective nationwide population-based cohort study, including an AS cohort (n=6228), a PsA cohort (n=16039), an uSpA cohort (n=4795) and a GP cohort (n=269815). The cohorts were identified between 2001 and 2009 in the Swedish Patient and Population registers. Patients with diagnoses for more than one SpA phenotype (n=1943) were excluded. The follow-up began January 1, 2004 or at the date of first diagnosis thereafter in previously undiagnosed cases and extended until the first outcome occurrence, death, emigration or December 31, 2012, whichever occurred first. Subjects with a history of each of the cardiovascular outcomes of

interest were excluded from the analysis of that outcome. Number of outcomes, person-years at risk, crude rates and age- and sexstandardized rates to the GP cohort were calculated for each outcome and cohort. Age- and sexadjusted hazard ratios (HRs) were calculated using Cox proportional hazard regression analysis.

Results: Age-and sexadjusted HRs for ACS and stroke events were significantly increased in PsA (HR (95% CI) 1.71 (1.56-1.88) and 1.41 (1.29-1.54)) and in AS (HR 1.47 (1.26-1.73) and 1.33 (1.14-1.55)), and non-significantly increased in uSpA compared to the GP cohort. For VTE the age-and sexadjusted HRs for both AS, PsA and uSpA were equally and significantly increased with about 50% compared to the GP cohort. Patients with uSpA had a significantly lower HR for ACS than patients with PsA, otherwise no significant differences in HRs were noted between the SpA phenotypes (Table).

	AS	**PsA**	**uSpA**	**GP**
Acute coronary syndrome				
Subjects at risk, n	5987	15516	4707	262002
Incident events, n	161	481	62	7144
Crude rates	4.0 (3.4-4.6)	4.8 (4.3-5.2)	2.0 (1.5-2.5)	3.2 (3.2-3.3)
Standardized rates*	4.1 (3.3-4.9)	5.4 (4.9-5.9)	4.3 (2.9-5.7)	na
Hazard ratio† (GP as ref.)	1.47 (1.26-1.73)	1.71 (1.56-1.88)	1.26 (0.98-1.62)	1
Hazard ratio† (PsA as ref.)	0.86 (0.72-1.03)	1	0.75 (0.57-0.98)	na
Stroke				
Subjects at risk, n	6051	15576	4726	261953
Incident events, n	172	532	74	9877
Crude rates	4.2 (3.6-4.9)	5.3 (4.8-5.7)	2.4 (1.9-3.0)	4.5 (4.4-4.6)
Standardized rates*	5.5 (4.4-6.6)	5.9 (5.4-6.4)	5.6 (3.9-7.2)	na
Hazard ratio† (GP as ref.)	1.33 (1.14-1.55)	1.41 (1.29-1.54)	1.22 (0.97-1.53)	1
Hazard ratio† (PsA as ref.)	0.97 (0.81-1.16)	1	0.90 (0.70-1.15)	na
Venous thromboembolism				
Subjects at risk, n	6124	15705	4721	266418
Incident events, n	105	289	56	4762
Crude rates	2.5 (2.1-3.0)	2.8(2.5-3.1)	1.8 (1.4-2.3)	2.1 (2.1-2.2)
Standardized rates*	3.3 (2.4-4.1)	3.0 (2.6-3.4)	3.1 (2.1-4.2)	na
Hazard ratio† (GP as ref.)	1.52 (1.25-1.84)	1.48 (1.31-1.67)	1.49 (1.14-1.94)	1
Hazard ratio† (PsA as ref.)	1.13 (0.90-1.43)	1	1.01 (0.75-1.35)	na

Rates are presented as number of events/1000 person-years. All rates and hazard ratios are calculated with 95 % confidence interval given in parenthesis. *Age- and sexadjusted with the GP cohort as reference. †Age- and sexadjusted.

Conclusion:

We found that patients with AS or PsA had a significantly higher risk of having a first event of ACS and stroke compared to GP comparators. Both AS, PsA and uSpA patients had a nearly 50% increased risk of experiencing a first event of VTE compared to the GP. There were no significant differences between the SpA phenotypes, except for a lower risk for ACS in uSpA patients compared to PsA patients.

Disclosure: K. Bengtsson, None; **H. Forsblad-d'Elia**, None; **E. Lie**, None; **E. Klingberg**, None; **M. Dehlin**, None; **S. Exarchou**, None; **U. Lindström**, None; **J. Askling**, None; **L. T. Jacobsson**, None.

Abstract Number: 1058

Prevalence of Comorbidities in Spondyloarthritis and Evaluation of Their Monitoring: Results of the International Cross-Sectional ASAS-Comospa Study

Anna Moltó[1], Adrien Etcheto[1], Désirée van der Heijde[2], Robert B. M. Landewé[3], Filip van Den Bosch[4], Maxime Dougados[5] and on behalf of the ASAS-COMOSPA task force, [1]Paris Descartes University, Rheumatology Department, Cochin Hospital, AP-HP. INSERM (U1153): Clinical Epidemiology and Biostatistics, PRES Sorbonne Paris-Cité,, Paris, France, [2]Department of Rheumatology, Leiden University Medical Center, Leiden, the Netherlands, Leiden, Netherlands, [3]Department of Rheumatology, Amsterdam Rheumatology Center, Amsterdam, the Netherlands, Amsterdam, Netherlands, [4]Univ Hosp, Ghent, Belgium, [5]Université Paris René Descartes and Hôpital Cochin, Paris, France

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SESSION INFORMATION

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Session Title: Spondylarthropathies and Psoriatic Arthritis - Clinical Aspects and Treatment: Clinical Aspects and CoMorbidities

Session Type: ACR Concurrent Abstract Session

Session Time: 4:30PM-6:00PM

Background/Purpose:

Increased risk of cardio-vascular disease, and osteoporosis is documented in SpA. Some of these comorbidities (e.g. cardiovascular disease risk) are subject to recommendations, with specific components relevant to rheumatic inflammatory diseases (e.g. yearly evaluation of BP, LDL-cholesterol). However, it is known that a gap exists between recommendations and their implementation in practice. The aim of this study was to evaluate: 1) the prevalence of SpA co-morbidities and risk factors for these comorbidities in different countries worldwide, 2) the gap between available recommendations and daily practice concerning prevention/management of these co-morbidities and 3) the number of risk factors detected due to the present initiative

Methods: International, cross-sectional study of consecutive SpA patients in routine care. Data comprise SpA characteristics, plus relevant cardiovascular, infection, cancer, osteoporosis and gastro-intestinal disorders.

Results:

Twenty-two participating countries (from 4 continents) included 3984 patients. Age: 44±14 years, disease duration 8±9 years, male gender: 65%, past or current axial (89%) and articular peripheral (56%) involvement; ASDASCRP: 2.0±1.1, BASFI 3.2±2.7, NSAID intake during last 3 months 68% and any past or current intake of methotrexate (33%), sulfasalazine (44%) or biologicals (44%). The most frequent diseases (past or current) found were osteoporosis (13%), gastro-duodenal ulcus (11%), cardiovascular events (myocardial infarction or stroke) (4%), solid cancers (3%), and hepatitis B infection (3%). The most frequent risk factors for these diseases were hypertension (34%), smoking (current or past (<3years)) 29%, dyslipidaemia (27%) and family history of cardiovascular disease and breast cancer (each 15%). Substantial inter-country variability was observed for the screening of co-morbidities (e.g. LDL-cholesterol measured at least in the last year from 8% (Taiwan) to 98% (Germany) or dentist visit in the last year from 0% (China) to 85% (Netherlands)). Evaluation of comorbidities and risk factors as part of this study unveiled previously undetected abnormalities [e.g. elevated blood pressure (14%), hyperglycemia (4%)] and emphasized the sub-optimal management of co-morbidities.

Conclusion:

This study suggests a) a high prevalence of co-morbidities in SpA, b) a substantial inter-country variability c) a highly variable detection of relevant risk factors. This study strongly suggests that rigorous application of systematic evaluation of co-morbidities may permit earlier detection, which ultimately may result in an improved outcome of patients with SpA.

Acknowledgements: This study was conducted under the umbrella of ASAS and thanks to an unrestricted grant from Abbvie, Pfizer and UCB.

Abstract Number: 1059

Increased Risk of Atrioventricular Block, Atrial Fibrillation and Pacemaker Implantation in Ankylosing Spondylitis, Undifferentiated Spondylarthritis and Psoriatic Arthritis Compared to the General Population

Karin Bengtsson[1], Helena Forsblad-d'Elia[2], Elisabeth Lie[1], Eva Klingberg[1], Mats Dehlin[1], Sofia Exarchou[3], Ulf Lindström[1], Johan Askling[4] and Lennart TH Jacobsson[1], [1]Department of Rheumatology and Inflammation Research, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden, [2]Departments of Public Health and Clinical Medicine, Rheumatology, Umeå University, Umeå, Sweden, [3]Section of Rheumatology, Department of Clinical Sciences, Malmö, Lund University, Malmö, Sweden, [4]Clinical Epidemiology Unit and Rheumatology Unit, Department of Medicine, Karolinska Institute, Stockholm, Sweden

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Session Type: ACR Concurrent Abstract Session

Session Time: 4:30PM-6:00PM

Background/Purpose: There is a known association between conduction disturbances and ankylosing spondylitis (AS). The risk of conduction disturbances in other phenotypes of spondylarthritis (SpA) is less well studied. Studies have also indicated that SpA patients have an increased risk of cardiovascular morbidity. Atrial fibrillation (AF) is both an expression of cardiac disease and a risk factor for stroke. Our objective was to investigate the incidence of atrioventricular (AV) block and AF in patients with AS, undifferentiated spondylarthritis (uSpA) and psoriatic arthritis (PsA) compared to each other and to general population (GP) comparators. We also investigated the incidence of pacemaker implantation, a possible consequence of severe arrhythmia.

Methods: The study design was a prospective nationwide population-based cohort study, including an AS cohort (n=6228), an uSpA cohort (n=4795), a PsA cohort (n=16039) and a GP cohort (n=269815). The cohorts were identified between 2001 and 2009 in the Swedish patient and population registers. Patients with diagnoses for more than one SpA phenotype (n=1943) were excluded. The follow-up began January 1, 2004 or at the date of first diagnosis thereafter in previously undiagnosed cases and extended until the first outcome occurrence, death, emigration or December 31, 2012, whichever occurred first. Subjects with a history of each of the outcomes of interest were excluded from the analysis of that outcome. Number of outcomes, person-years at risk, crude rates and age- and sexstandardized rates to the GP cohort were calculated for each outcome and cohort. Age- and sexadjusted hazard ratios (HRs) were calculated using Cox proportional hazard regression analysis.

Results: Age-and sexadjusted HRs for AV block, AF and pacemaker implantation were significantly increased in both AS, uSpA and PsA compared to the GP cohort. AS patients had not only a 2-fold increase in HRs for AV block and pacemaker implantation compared to GP but also a significantly increased HR compared to patients with PsA. The increased HR for AV block was most pronounced for men in both the AS and uSpA cohort, with an over 3-fold increase compared to GP comparators (Table).

	AS	uSpA	PsA	GP
Atrioventricular block				
Subjects at risk, n	6170	4773	15990	269125
Incident events, n	47	19	68	1329
Crude rates	1.1 (0.8-1.4)	0.6 (0.3-0.9)	0.6 (0.5-0.8)	0.6 (0.5-0.6)
Standardized rates*	1.1 (0.8-1.5)	1.2 (0.5-1.9)	0.7 (0.5-0.9)	na
Hazard ratio† (GP as ref.)	2.75 (2.05-3.69)	2.71 (1.72-4.27)	1.45 (1.14-1.86)	1
Hazard ratio† (PsA as ref.)	1.70 (1.16-2.49)	1.74 (1.03-2.92)	1	na
Male hazard ratio# (GP as ref.)	3.01 (2.21-4.11)	3.77 (2.29-6.20)	1.66 (1.23-2.23)	1
Female hazard ratio# (GP as ref.)	1.65 (0.68-4.00)	1.07 (0.34-3.33)	1.16 (0.75-1.78)	1
Atrial fibrillation				
Subjects at risk, n	5983	4720	15568	263558
Incident events, n	204	82	625	11669
Crude rates	5.1 (4.4-5.8)	2.7 (2.1-3.3)	6.2 (5.7-6.7)	5.3 (5.2-5.4)
Standardized rates*	7.2 (5.8-8.6)	6.1 (4.4-7.9)	7.1 (6.5-7.7)	na
Hazard ratio† (GP as ref.)	1.43 (1.25-1.65)	1.26 (1.01-1.56)	1.49 (1.38-1.62)	1
Hazard ratio† (PsA as ref.)	0.99 (0.84-1.17)	0.83 (0.66-1.05)	1	na
Pacemaker implantation				
Subjects at risk, n	6165	4769	15972	268806
Incident events, n	70	24	140	2429
Crude rates	1.7 (1.3-2.1)	0.8 (0.5-1.1)	1.3 (1.1-1.6)	1.1 (1.0-1.1)
Standardized rates*	2.1 (1.4-2.7)	1.5 (0.7-2.2)	1.5 (1.2-1.7)	na
Hazard ratio† (GP as ref.)	2.19 (1.73-2.79)	1.76 (1.17-2.63)	1.60 (1.35-1.90)	1
Hazard ratio† (PsA as ref.)	1.43 (1.07-1.93)	1.13 (0.73-1.76)	1	na

Rates are presented as number of events/1000 person-years. All rates and hazard ratios are calculated with 95 % confidence interval given in parenthesis. *Age- and sexadjusted with the GP cohort as reference. †Age- and sexadjusted. #Age-adjusted.

Conclusion: Patients with AS, uSpA and PsA had a significantly increased risk of AV block, AF and pacemaker implantation compared to GP comparators. Male AS and uSpA patients had a more than 3-fold increased risk of AV-block compared to GP. These results demonstrate both similarities and differences in subtypes of SpA, which were partly sex-specific.

Disclosure: K. Bengtsson, None; **H. Forsblad-d'Elia**, None; **E. Lie**, None; **E. Klingberg**, None; **M. Dehlin**, None; **S. Exarchou**, None; **U. Lindström**, None; **J. Askling**, None; **L. T. Jacobsson**, None.

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Abstract Number: 1060

The View of Healthy Persons on the Impact of Spondyloarthritis on Functioning and Health: Results of a Best-Worst Scaling Based on the ASAS Health Index

Ivette Essers[1,2], Mickaël Hiligsmann[3], Uta Kiltz[4], Nick Bansback[5], Juergen Braun[4], Désirée van der Heijde[6] and Annelies Boonen[1,7], [1]School for Public Health and Primary Care (CAPHRI), Maastricht University, Maastricht, Netherlands, [2]Rheumatology, Maastricht University Medical Center, Maastricht, Netherlands, [3]Department of Health Services Research, University of Maastricht, Maastricht,

Netherlands, [4]Rheumazentrum Ruhrgebiet, Herne, Germany, [5]School of Population and Public Health, University of British Columbia, Vancouver, BC, Canada, [6]Rheumatology, Leiden University Medical Center, Leiden, Netherlands, [7]Maastricht University Medical Center, Maastricht, Netherlands

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Session Time: 4:30PM-6:00PM

Background/Purpose: The ASAS Health Index (HI) is a disease-specific questionnaire (QoL) for patients with spondyloarthritis (SpA) aiming to measure functioning and health. The ASAS HI can serve as a starting point to develop a disease-specific utility reflecting the value or preference for health states specific for patients with SpA. Although it is important to measure health utility from the perspective of the patient, it is recommended worldwide to base decisions about resource allocation on utilities representing the perspective of the general population. In a first step towards a disease specific utility for the societal perspective, it is necessary to know which of the 17 aspects of health impairments included in the ASAS HI have the most influence on health according to subjects from general population and to understand whether there are differences in ratings among European countries.

Methods: An online survey was performed to conduct a best-worst experiment (BWS) based on the items of the ASAS HI in a random sample of persons from the general population from the UK, France, Germany, the Netherlands, Spain and Italy. In the BWS experiment, persons answered 17 choice tasks, each consisting each time of 4 different items of the ASAS HI. In each task, persons had to indicate which item they considered the most important and the least important for functioning and health. The mean relative importance for each item of the ASAS HI could then be generated using the estimated hierarchical Bayes method. Differences in subgroups by country, gender and age were explored. Construction of the tasks and data-analysis were performed using the Sawtooth software.

Results: In total, 3,039 (around 500/country) persons from the general population (age 46.5 years (SD 15.2), 1556 women (52.2%)) contributed to the analysis. The 5 most important aspects were pain (9.97, 95%-CI 9.79 to 10.14), sleeping (9.50, 95%-CI 9.31 to 9.69), being exhausted (8.03, 95%-CI 7.88 to 8.19), overcome difficulties (7.55, 95%-CI 7.39 to 7.70), and being able to concentrate (6.78, 95%-CI 6.63 to 6.93). The 5 least important items were washing hair (2.28, 95%-CI 2.18 to 2.39), running (3.65, 95-CI 3.50 to 3.80), driving (3.94, 95%-CI 3.80 to 4.08), contact with people (4.16, 95%-CI 4.02 to 4.29), and travelling (4.42, 95-CI 4.29 to 4.56). Figure 1 shows results and illustrates the consistency of findings across countries, age-categories and sex.

Conclusion: This study provides information of the relative impact of the items of the ASAS HI on overall health from the societal perspective. The general population states that pain, sleeping problems and being exhausted are the most important aspects of SpA that influence functioning and health. The results were comparable across sex, age and countries. This study is the first step towards a disease specific utility for health in SpA.

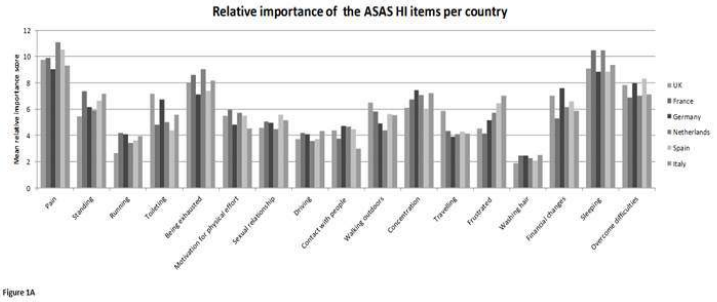

Figure 1A

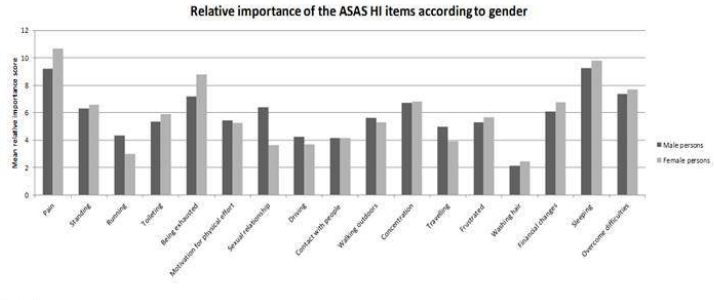

Figure 1 B

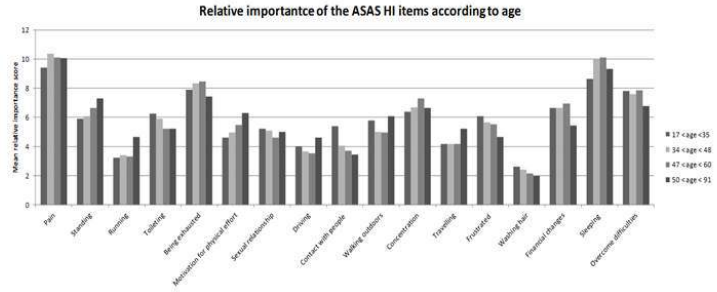

Figure 1 C

Figure 1: Relative importance of the ASAS HI items according to the general population
Figure 1A: relative importance per country; Figure 1B: relative importance according to gender; Figure 1C: relative importance according to age

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Abstract Number: 1061

Patients with Fibromyalgia (FM) Do Not Fulfill Classification Criteria for Axial Spondyloarthritis (axSpA) but Patients with Axspa May Fulfill Classification Criteria for FM

Xenofon Baraliakos[1], Andrea Regel[1], Uta Kiltz[1], Hans-Jürgen Menne[2], Friedrich Dybowski[3], Manfred Igelmann[4], Ludwig Kalthoff[3], Dietmar Krause[5], Ertan Saracbasi[1], Elmar Schmitz-Bortz[6] and Jürgen Braun[1], [1]Rheumazentrum Ruhrgebiet, Herne, Germany, [2]Rheumatology practice, Dortmund, Germany, [3]Private rheumatology office, Herne, Germany, [4]Private Rheumatology office, Bochum, Germany, [5]Internistische und rheumatologische Gemeinschaftspraxis, Gladbeck, Germany, [6]Rheumatology practice, Hattingen, Germany
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Session Type: ACR Concurrent Abstract Session

Session Time: 4:30PM-6:00PM

Background/Purpose: Both patients with axial spondyloarthritis (axSpA) and patients with fibromyalgia (FM) are suffering from pain. The new ASAS classification criteria for axSpA have been recently challenged by arguing that FM patients could easily fulfill the clinical arm of the criteria, which could lead to overdiagnosis of axSpA and wrong treatment decisions. In this study we examined similarities and differences between axSpA and FM using different sets of classification criteria and to assess the severity of wide-spread pain in both diseases.

Methods: In this prospective study, patients were consecutively included if they were diagnosed with axSpA, or FM by a rheumatologist. Patients with rheumatoid arthritis (RA) were also included as an inflammatory control group. Patients on anti-TNF treatment were not included. Established classification and outcome parameters as well as standardized instruments were used in all patients. MRI performed in all axSpA and 20 FM patients. All axSpA and FM patients had radiographs. The Mann-Whitney-U test was used for statistical comparisons between groups.

Results: A total of 214 patients was included: 93 with FM (7.5% HLA B27+), 91 with axSpA (79.1% HLA-B27+) and 30 with RA (53.3% seropositive). The mean age was 50.7±9.1, 43.0±12 and 58.4±11.9 years, respectively, and the mean symptom duration was comparable between groups: 6.6±6.9, 6.4±7.8 and 6.2±11.3, respectively. Expectedly, the gender ratio differed: FM and RA patients were mostly female (93.4% and 76.7%, respectively), as compared to axSpA patients (28.3%). The ASAS classification criteria were not fulfilled by any FM patient. In contrast, the 1990 and 2010 FM criteria were fulfilled by 98.3% and 100% of patients with FM, but also by 14.3% and 34.1% of axSpA (no differences between AS and nr-axSpA) and 30% and 46.7% of RA patients, respectively. The Fibromyalgia impact questionnaire (FIQ) values were 69.5±13.0, 45.4±19.3 ($p<0.001$) and 49.9±22.8, respectively, while the Health Assessment Questionnaire (HAQ) values were 1.7±0.5, 1.2±0.5 ($p<0.001$) and 1.6±0.8, for FM, axSpA and RA, respectively. FM patients reported the highest pain scores on a 0-10 numeric rating scale: 7.0±1.7 vs. 6.0±1.9 and 6.1±1.9 in axSpA and RA patients, respectively, while mean CRP values (mg/dl) were higher in axSpA (1.1±1.3) and RA (0.6±0.9) patients vs. FM (0.4±0.4) (both $p<0.001$).

Conclusion: Importantly, no FM patients fulfilled ASAS classification criteria. Only a small proportion of patients with axSpA fulfilled any of the FM classification criteria. There was less overlap between patients with FM, axSpA and RA using the 1990 criteria as compared to the more sophisticated 2010 FM criteria. FM patients reported higher pain scores and more functional deficits. Some patients with widespread pain may have underlying axSpA - this differential diagnosis needs to be taken into account when dealing with the diagnosis of FM in daily practice.

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Abstract Number: 1062

Predictive Validity of the ASAS-Classification Criteria for Axial and Peripheral Spondyloarthritis – a Final Analysis

Robert Landewé[1], Alexandre Sepriano[2,3], Martin Rudwaleit[4], Joachim Sieper[4,5], Désirée van der Heijde[6] and on behalf of ASAS , [1]Department of Rheumatology, Amsterdam Rheumatology Center, Amsterdam, The Netherlands, Amsterdam, Netherlands, [2]Rheumatology, Department of Rheumatology, Leiden University Medical Center, Leiden, the Netherlands, Leiden, Netherlands, [3]Rheumatology, Hospital de Egas Moniz - CHLO, Lisbon, Portugal, Lisbon, Portugal, [4]Rheumatology, Charité - Campus Benjamin Franklin, Berlin, Germany, Berlin, Germany, [5]German Rheumatism Research Centre, Berlin, Germany, Berlin, Germany, [6]Department of Rheumatology, Leiden University Medical Center, Leiden, the Netherlands, Leiden, Netherlands

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Background/Purpose: The Assessment of SpondyloArthritis international Society (ASAS) cohort has been established to validate the ASAS criteria for axial spondyloarthritis (axSpA) and peripheral spondyloarthritis (pSpA), which have been released in 2009 and 2011 respectively. Since then, the criteria have received broad international acceptance, but were criticized for potential misclassification (clinical arm) and lacking data about predictive validity. Our aim was to establish the predictive validity of an ASAS SpA, pSpA or axSpA classification by either the 'imaging arm' or the 'clinical arm' at baseline, by comparing these classifications with the final diagnosis after follow up.

Methods: The ASAS-cohort included 975 patients collected from 29 ASAS centers worldwide. 22 of the original ASAS centres (N=909) participated in the follow-up study, with 10 having more than 75% of complete follow-up data. Eligible patients had either chronic (>3 months) back pain of unknown origin and age of onset below 45 years (N=658) or had peripheral arthritis and/or enthesitis and/or dactylitis (N=251). From these, 345 attended a follow-up visit and of an additional 219 information was obtained by phone [mean (range) follow-up time: 4.4 (1.9; 6.8) years]. Baseline-classification according to the ASAS criteria were tested against the rheumatologist's diagnosis at follow-up. For patients evaluated by phone, self-reported (change in) diagnosis was recorded.

Results: In total 564 patients (57.8% of the original cohort, 62.0% of the participating centers) were assessed at follow-up. 396/564 patients received a diagnosis of SpA by the rheumatologist (280 predominantly axial, 116 predominantly peripheral). Patients with- and without follow-up data available were comparable regarding the number of baseline SpA features [mean 2.5 (SD 1.4) *vs* mean 2.2 (1.4)] irrespective of the proportion of patients followed in each center. 335 patients fulfilled axSpA or pSpA criteria at baseline and of these, 309 were diagnosed by their rheumatologist as 'SpA' after follow-up (PPV SpA criteria: 92.2%). Similarly, the PPV of the axSpA and pSpA criteria was 93.3% and 89.5% respectively. 190 of the 240 (79.2%) patients fulfilling the axSpA criteria had sacroiliitis on imaging (X-ray and/or MRI) reflecting the prominent place of imaging in the criteria. Fulfillment of only the 'clinical arm' of the axSpA criteria (thus: imaging negative) yielded a PPV of 88.0%. When only considering centers with more than 75% of follow-up data available (N=291), PPV was similarly high, which pleas against 'channeling bias'.

Conclusion: The positive predictive value of both the axSpA and pSpA criteria to forecast an expert's diagnosis of 'SpA' after more than 4 years follow up is excellent. The 'imaging arm' and the 'clinical arm' of the axSpA criteria have similar predictive validity and are truly complementary.

Table: Predictive validity of the ASAS classification criteria, by testing the classification at baseline against the rheumatologist's diagnosis at follow-up (on average 4.4 years).

Criteria	Predictive values		Classification at baseline	Rheumatologist diagnosis at follow-up		
	PPV (%)	NPV (%)		SpA	No-SpA	
SpA*	92.2	62.0	Positive	309	26	335
			Negative	87	142	229
				396	168	564
pSpA	89.5	58.7	Positive	85	10	95
			Negative	31	44	75
				116	54	170
axSpA	93.3	63.6	Positive	224	16	240
			Negative	56	98	154
				280	114	394
axSpA: Imaging arm	94.7	51.0	Positive	180	10	190
			Negative	100	104	204
				280	114	394
axSpA: Clinical arm	96.0	48.9	Positive	168	7	175
			Negative	112	107	219
				280	114	394
axSpA: Imaging arm alone	86.2	31.9	Positive	56	9	65
			Negative	224	105	329
				280	114	394
axSpA: Clinical arm alone	88.0	31.4	Positive	44	6	50
			Negative	236	108	344
				280	114	394

*Combination of ASAS criteria for axSpA (in patients with predominant back pain with or without peripheral manifestations) and criteria for pSpA for patients with peripheral manifestations only. axSpA, axial spondyloarthritis; pSpA, peripheral spondyloarthritis; PPV, positive predictive value; NPV, negative predictive value.

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Abstract Number: 1063

Admissions and Readmissions of Patients with Systemic Lupus Erythematosus Is a Major Cause of Direct and Indirect Health Care Costs

Allen P. Anandarajah[1], Ugo Awa[2], Christine Izzo[3], Kate Burns[4], Ummara Shah[5], Jennifer H. Anolik[6] and Christopher T. Ritchlin[7], [1]Dept of Rheumatology, Univ of Rochester Medical Ctr, Rochester, NY, [2]Medicine, University of Rochester Medical Center, Rochester, NY, [3]Rheumatology, University of Rochester Medical Center, Rochester, NY, [4]Allergy, Immunology and Rheumatology, University of Rochester, Rochester, NY, [5]Medicine, Strong Memorial Hospital, University of Rochester, Rochester, NY, [6]University of Rochester Medical Center, Rochester, NY, [7]Allergy, Immunology and Rheumatololgy Division, University of Rochester Medical Center, Rochester, NY

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Background/Purpose: Systemic Lupus Erythematosus (SLE), a chronic autoimmune disease that can affect multiple organ systems and is associated with high morbidity. Reports estimate that the cost of direct health care for patients with SLE is 3-fold higher than the national capital average. Limited data are available on the cost of in-patient care for SLE patients.

Objective: To calculate the cost of admissions, rate of readmissions and potential cost of readmissions of SLE patients at a large tertiary care center.

Methods: We conducted a financial analysis of all admissions for systemic lupus erythematosus at the 2 major hospitals affiliated with the University of Rochester of Medical Center between the July 1st of 2013 and June 30th of 2014. In-patient care for the 2 hospitals, Strong Memorial Hospital (>750 beds) and Highland Community hospital (> 120 beds) are solely provided by faculty in the Department of Allergy, Immunology and Rheumatology. The total number of admissions for the diagnosis code 710.0 as primary or secondary diagnosis, regardless of rheumatology consults, was calculated. We also estimated the total cost of admissions based on total charges and the revenue generated. Additionally, we recorded the length of stay for all admissions for SLE. To confirm the findings from the financial data search at the two hospitals, we also analyzed our admission log, maintained for all rheumatology consults received for the fiscal year from July 2013 to June 2014, based on primary diagnosis at time of admission and at discharge.

Results: The total number of SLE admissions for the year was 274, with a total cost estimated to be between $6,213,812.00 and $ 12, 182,166.00 and accounted for 2576 days of admission for all cases. The cost per admission was therefore between $22,678.15 and $ 44,460.46 and the average of length of stay per admission was calculated to be 9.4 days. The cost represented 25.5% of all rheumatology in-patient care. Moreover, 86 SLE consults recorded in the fiscal year 2014, represented about 19% of all in-patient rheumatology admissions, second only to vasculitis as a cause for admission. Of the 86 patients consulted, 12 (14%) were readmitted on multiple occasions accounting for a total of 26 admissions. Readmissions were between 1 and 5 months in duration and were estimated to cost between $317,494.10 and $622,446.44. The most common reason for readmission among these patients was lupus nephritis followed by lupus flare.

Conclusion: Hospitalization of patients with SLE is a major driver of health care costs and readmission rates for SLE are high. Development of methods to provide coordinated outpatient care and improve outpatient access and counseling are needed to optimize outcomes and decrease cost of care for these patients.

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Abstract Number: 1064

Feasibility and Validity of Patient Reported Outcome Measurement Information System (PROMIS) in SLE

Shanthini Kasturi[1], Jayme C. Burket[2], Jessica Berman[1], Kyriakos A. Kirou[1], Alana B. Levine[1], Lisa R. Sammaritano[1] and Lisa Mandl[1,3], [1]Rheumatology, Hospital for Special Surgery, New York, NY, [2]Healthcare Research Institute, Hospital for Special Surgery, New York, NY, [3]Department of Rheumatology, Hospital for Special Surgery, New York, NY
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Background/Purpose: Accurate measurement of patient reported outcomes (PROs) is particularly important in SLE, a heterogeneous disease in which similar symptoms can have disparate impact across patients. PROMIS offers dynamic computer adaptive tests (CATs) to

precisely and efficiently measure PROs in a variety of relevant domains. The aims of this study were to: 1) assess the feasibility of administering PROMIS CATS serially to SLE outpatients; 2) correlate PROMIS CATs with legacy PRO measures, SLE disease activity and organ damage; 3) assess retest reliability of PROMIS CATs.

Methods: Adults meeting ACR SLE classification criteria were recruited from a SLE Center of Excellence. Subjects completed the Short Form-36 (SF-36), LupusQoL-US, and selected PROMIS CATs. SLE disease activity, flare, and damage were evaluated with the SELENA-SLEDAI and SLICC-ACR damage index. PROMIS domains were compared with disease activity, damage, and similar domains in legacy instruments using Spearman correlations. Retest reliability was evaluated among subjects reporting stable SLE activity at two assessments a week apart using intraclass correlation coefficients (ICC).

Results: Of 114 patients approached, 101 (89%) completed at least one assessment (Table 1), 81 (80%) completing it remotely. 91 (90%) completed a retest. Most PROMIS domains showed moderate to strong correlations with similar domains in both legacy instruments, although social function and fatigue CATs showed poor, non-significant correlations with similar SF-36 domains (Table 2). On average, flaring subjects scored a clinically meaningful half standard deviation worse on PROMIS pain and social function CATs ($p < 0.05$). However, correlations between PROMIS and SLEDAI were overall weak (mean $r = 0.24$, $p < 0.05$). SLICC scores did not consistently correlate with PROMIS. PROMIS retest ICCs were 0.78 to 0.89.

Conclusion: To our knowledge, this is the first study to assess the feasibility and validity of administering PROMIS CATs to adult SLE outpatients. These data show that PROMIS CATs can be successfully administered to diverse SLE patients at the point of care or remotely, and are valid, reliable and responsive for many SLE relevant domains. The weak correlations of social function and fatigue CATs with corresponding SF-36 domains point to a knowledge gap and the need for further study. Importantly, PROMIS scores did not correlate well with the SLEDAI. This disconnect between objective signs and symptoms and the subjective patient disease experience underscores the crucial need to integrate PROs into clinical care to ensure optimal disease management.

Table 1. Baseline Demographics and SLE Characteristics

	Enrolled (n = 101)	**Not Enrolled (n = 13)**	**P Value**
Age: mean ± SD years, (range)	40.1 ± 13.9, (19 -73)	45.3 ± 12.7, (24 - 71)	0.20
Disease Duration: mean ± SD years, (range)	11.8 ± 8.3, (0 - 48)	21.5 ± 13.9, (6 - 39)	**0.02***
Female: n (%)	90 (89.1)	12 (92.3)	> 0.99
Race: n (%)			0.53
White	32 (31.7)	6 (46.2)	
Black	31 (30.7)	2 (15.4)	
Asian	16 (15.8)	2 (15.4)	
Other	22 (21.8)	3 (23.1)	
Ethnicity: n (%) Hispanic/Latino	31 (30.7)	4 (30.8)	0.60
Insurance: n (%)			**0.02***
Medicaid	34 (33.7)	7 (53.8)	
Medicare	13 (12.9)	4 (30.8)	
Private	54 (53.5)	2 (15.4)	
Disease Characteristics:			
Physician Global Assessment: mean ± SD, (range)	0.82 ± 0.64 (0 - 2)		
SLEDAI: mean ± SD, (range)	5.3 ± 4.56 (0 - 24)		
SELENA-SLEDAI Flare: n (%)	21 (20.2)		
SLICC: mean ± SD, (range)	2.0 ± 2.94 (0 - 16)		

*Non-enrolled patients had significantly longer disease duration and were more likely to be insured by Medicaid.

Table 2. Instrument Correlations			
Domain	**PROMIS CAT Domain**	**Legacy Instrument Domain**	**Spearman's *r***
Physical Function	Physical Function	SF-36/Physical Function	0.84
	Physical Function	SF-36/Role Physical	0.67
	Physical Function	SF-36/PCS	0.58
	Physical Function	Lupus QoL-US/Physical Health	0.84
	Mobility	SF-36/Physical Function	0.86
	Mobility	SF-36/Role Physical	0.57
	Mobility	SF-36/PCS	0.54
	Mobility	Lupus QoL-US/Physical Health	0.80
Pain	Pain Behavior	SF-36/Bodily Pain	0.73
	Pain Behavior	Lupus QoL-US/Pain	-0.78
	Pain Interference	SF-36/Bodily Pain	0.78
	Pain Interference	Lupus QoL-US/Pain	-0.82
Fatigue	Fatigue	SF-36/Vitality	0.04 (p = 0.67)
	Fatigue	Lupus QoL-US/Fatigue	0.79
Emotional Health	Anger	SF-36/Mental Health	-0.28
	Anger	SF-36/Role Emotional	-0.55
	Anger	SF-36/MCS	-0.63
	Anger	Lupus QoL-US/Emotional	-0.74
	Anxiety	SF-36/Mental Health	-0.30
	Anxiety	SF-36/Role Emotional	-0.48
	Anxiety	SF-36/MCS	-0.58
	Anxiety	Lupus QoL-US/Emotional	-0.76
	Depression	SF-36/Mental Health	-0.20 (p = 0.05)
	Depression	SF-36/Role Emotional	-0.56
	Depression	SF-36/MCS	-0.60
	Depression	Lupus QoL-US/Emotional	-0.76
Social Function	Ability to Participate in Social Roles	SF-36/Social Function	0.09 (p = 0.35)
	Satisfaction with Social Roles	SF-36/Social Function	0.03 (p = 0.67)
All p values < 0.0001 unless otherwise noted.			

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Abstract Number: 1065

Atherosclerotic Vascular Events in a Multinational SLE Inception Cohort: Description and Predictive Risk Factors over a 15 Year Period

Murray Urowitz[1,2], Dafna Gladman[1], Nicole Anderson[3], Jiandong Su[1] and Systemic Lupus Erythematosus International Collaborating

Clinics (SLICC), [1]Rheumatology, University of Toronto, Toronto Western Hospital, Toronto, ON, Canada, [2]Rheumatology, U of Toronto, Toronto Western Hospital, Toronto, ON, Canada, [3]Division of Rheumatology, University of Toronto, Toronto Western Hospital, Toronto, ON, Canada

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Background/Purpose: A large multicentre multinational inception cohort was established to study risk factors for atherosclerosis (AS) in SLE. We aim to describe all vascular events and determine the predictors of atherosclerotic vascular events (AVE) in this prospectively followed cohort over a 15 year period

Methods: Patients enter the cohort within 15 months of SLE diagnosis (≥4 ACR criteria). Clinical and laboratory features of SLE are collected in a standardized protocol at yearly intervals between 2000 and 2015. Vascular events are described and attributed on a specialized form. Events recorded include myocardial infarction (MI), angina, congestive heart failure (CHF), intermittent claudication (PVD), transient ischemic attack (TIA), and stroke. Diagnosis of an event was confirmed using standard clinical criteria, relevant laboratory data and imaging where appropriate. Attribution to AS was made on the basis of lupus disease being inactive at the time of the event, and/or the presence of typical AS changes on imaging or pathology and/or evidence of AS elsewhere. Factors associated with AVE were analyzed using time to event analysis with time dependent covariates and cox proportional hazard model.

Results: Since 2000, 1848 patients have been entered into the cohort (86.8%F, age at SLE 34.7 ± 13.4 years, disease duration at enrolment 5.6±4.2 months, mean follow-up of 6.1 ± 3.9 years). Thus far there have been 202 vascular events in 142 patients. These include: MI (21), angina (29), CHF (49), pacemaker insertion (8), PVD (16), TIA (29) and stroke (50). 89 of the events were attributed to active lupus and 40 to other causes.

73 events in 51 patients were attributed to AS including: MI (15), angina (24), CHF (12), pacemaker (5), PVD (7), TIA (7), and stroke (3). Thirteen patients in the AS group had more than one event. Lupus duration at first AS event was 3.2 ± 2.9 years.

Table 1. Predictive Factors at Enrolment - Univariate Analysis

Characteristic	Patient that had a VE (N=51)	Patients that did not have a VE (N=1331)	p value
Male	17 (33.3%)	126 (9.5%)	<.001
Caucasian	37 (72.5%)	643 (48.3%)	<.001
Age at SLE diagnosis (Mean ± SD)	52.34 ± 15.05	33.99 ± 12.96	<.001
Smoking	32 (62.7%)	453 (34.0%)	<.001
Hypertension	30 (58.8%)	427 (32.1%)	<.001
Diabetes	4/48 (7.8%)	45/1320 (3.4%)	<.001
Obese	24/49 (47.1%)	371/1287 (28.8%)	0.01
Hypercholesterolemia	27 (52.9%)	458 (34.4%)	0.024
Family history of CAD	24 (47.1%)	289 (21.7%)	<.001
SLEDAI-2K (Mean ± SD)	3.57 ± 3.82	5.37 ± 5.34	0.017
Total ACR Criteria (Mean ± SD)	5.00 ± 1.22	4.91 ± 1.05	0.532
Serositis	21 (41.2%)	352 (26.4%)	0.02
Renal Disorder	14 (27.5%)	377 (28.3%)	0.892
Neurologic Disorder	4 (7.8%)	60 (4.5%)	0.266
Immunologic Disorder	43 (84.3%)	1016 (76.3%)	0.186
Anticardiolipin	9/35 (17.6%)	116/898 (8.7%)	0.088
Lupus Anticoagulant	13/36 (25.5%)	184/928 (13.8%)	0.057
Treated with oral steroids	37 (72.5%)	928 (69.7%)	0.666
Average daily steroid dose (Mean ± SD)	14.31 ± 16.59	16.49 ± 17.09	0.371
Treated with antimalarials	31 (60.8%)	913 (68.6%)	0.239
Treated with immunosuppressives	21 (41.2%)	530 (39.8%)	0.846
Treated with antihypertensives	25 (49.0%)	363 (27.3%)	<.001
Treated with antihyperlipidemia	17 (33.3%)	123 (9.2%)	<.001

Table 2. Predictive Factors at Enrolment – Multivariate Analysis

Predictor	Hazard Ratio	95% Confidence Interval	p value
Male	2.21	1.10, 4.40	0.025
Age at SLE diagnosis	1.08	1.06, 1.10	<.0001
ACR Criteria - Serositis	2.52	4.38, 4.60	0.0026
ACR Criteria – Neurological Disorder	2.74	0.97, 7.73	0.057

Conclusion: Over the follow-up of an inception cohort with SLE there were 202 vascular events but only 73 were attributable to AS (cardiac, peripheral, CNS). Only male sex, age, and lupus disease factors (serositis) at inception remain significant risk factors of AVE in a multivariate analysis of a multicentre inception cohort followed for 7 or more years. Traditional cardiovascular risk factors likely become important over time.

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Abstract Number: 1066

Temporal Trends and Outcomes of Acute Myocardial Infarction in Systemic Lupus Erythematosus Hospitalizations

Narender Annapureddy[1], Achint Patel[2], Rabi Yacoub[3], Krishna Pakanati[4], Shiv Agarwal[5], Priya Simoes[6], Sunil Kamat[7], Alexandre Benjo[8] and Girish Nadkarni[9], [1]Rheumatology and Immunology, Vanderbilt University, Nashville, TN, [2]Public Health, Icahn School of Medicine at Mount Sinai, New York, NY, [3]Icahn School of Medicine at Mount Sinai, New York, NY, [4]Gateway Medical Center, Clarksville, TN, [5]Cardiology, University of Arkansas Medical Sciences, Little Rock, AR, [6]Internal Medicine, St.Lukes Roosevelt Hospital Center at Mount Sinai, New York, NY, [7]Critical Care, Kokilaben Dhirubhai Ambani Hospital and Medical Research Institute, Mumbai, India, [8]Ochsner Clinic Foundation, New Orleans, NY, [9]Nephrology, Icahn School of Medicine at Mount Sinai, New York, NY
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SESSION INFORMATION

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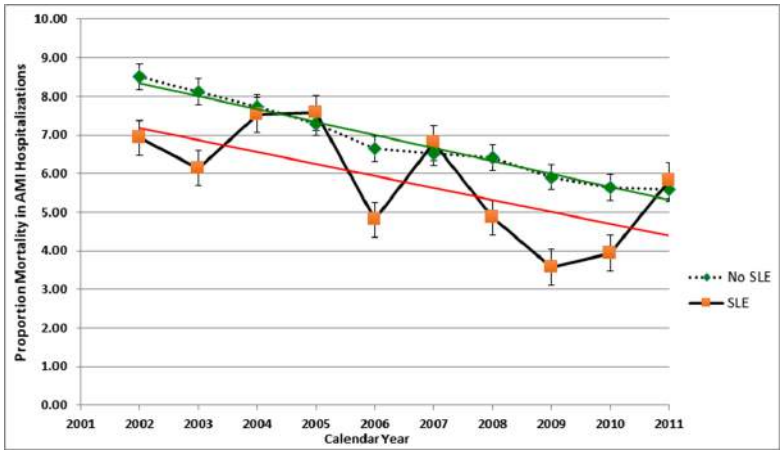
Background/Purpose: Cardiovascular disease remains the most common cause of mortality in Systemic lupus erythematosus (SLE). Some studies suggest that mortality due to acute myocardial infarction (AMI) in SLE has decreased. We aimed to evaluate temporal trends of incidence and mortality of SLE in AMI hospitalizations in a nationally representative sample.

Methods: We reviewed Nationwide Inpatient Sample (NIS) data over 10 year period from 2002-2011 for adult AMI hospitalizations as a primary diagnosis with SLE as secondary diagnosis using validated ICD9-CM codes. We calculated unadjusted proportions of mortality yearly and used survey logistic regression to calculate adjusted odds ratios (aOR) for hospital mortality overall and after stratifying for age (≤50 vs. >50).

Results: We identified a total of 6588743 AMI hospitalizations from 2002-2011 of which 20508 (0.31%) had a diagnosis for SLE. The proportion of patients with SLE in AMI hospitalizations increased from 0.27% in 2002 to 0.39% in 2011. SLE hospitalizations were younger (60.5 vs. 67.8 years<0.01); more female (80.4% vs. 40.1%; p<0.01); with a higher proportion of African-Americans (21.4% vs. 9.2%; p<0.01) and a higher Charlson comorbidity index (Mean 2 vs. 1.5; p<0.01). The unadjusted mortality rates in SLE hospitalizations yearly were similar to hospitalizations without SLE (Figure 1). After adjusting for age, gender, race, Charlson comorbidity index, hospital level characteristics, cardiac procedures, SLE hospitalizations had similar odds-ratio for hospital mortality (aOR=0.98; 95% CI= 0.83-1.16; p=0.54) compared to non-SLE hospitalizations. In hospitalizations ≤50 years, there was no significant difference in the adjusted odds of hospital mortality (aOR=0.88; 95% C 0.56-1.37; p=0.57)

Conclusion: In hospital mortality in SLE hospitalizations with AMI was similar to non-SLE hospitalizations. This could be related to better disease recognition, newer modalities, risk modification and increased life expectancy in SLE patients.

Figure 1 Proportion of Mortality in AMI Hospitalizations Stratified by Systemic Lupus Erythematosus Status



Disclosure: N. Annapureddy, None; **A. Patel**, None; **R. Yacoub**, None; **K. Pakanati**, None; **S. Agarwal**, None; **P. Simoes**, None; **S. Kamat**, None; **A. Benjo**, None; **G. Nadkarni**, None.

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Abstract Number: 1067

Sex Differences in Rates of End-Stage Renal Disease and Death Among Medicaid Patients with Incident Lupus Nephritis

Anna R. Broder[1], **Candace H. Feldman**[2], Anand Kumthekar[3], Michail Alevizos[4], Hongshu Guan[5], Medha Barbhaiya[6] and Karen H. Costenbader[7], [1]Rheumatology-Forchheimer 701N, Albert Einstein College of Medicine/Montefiore Medical Center, Bronx, NY, [2]Division of Rheumatology, Immunology and Allergy, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, [3]Medicine, Albert Einstein College of Medicine/Jacobi Medical Center, Bronx, NY, [4]Medicine, Albert Einstien College of Medicine/Jacobi Medical Center, Bronx, NY, [5]Rheumatology, Immunology and Allergy, Brigham and Women's Hospital, Boston, MA, [6]Internal Medicine, Weill Cornell Medical College, New York, NY, [7]Rheumatology, Brigham & Women's Hospital, Boston, MA

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Background/Purpose:

Prior studies suggest that males with lupus nephritis (LN) may have worse outcomes than females. However, the majority of these studies, are from tertiary-care centers and there are few large cohort studies of sex differences in LN outcomes. We thus investigated risks of ESRD and death by sex in a nationwide cohort of patients with incident LN.

Methods:

Within the Medicaid Analytic eXtract (MAX) with billing claims from 47 US states and D.C., we identified individuals aged 5-65 with incident LN from 2000-4 using a previously described algorithm (>3 ICD-9 codes for SLE and > 2 codes for acute renal disease all >30 days apart, following > 12 months with none of these codes). MAX data were linked by the Centers for Medicare and Medicaid Studies (CMS) to the US Renal Datasystem (USRDS) to identify ESRD onset and subsequent deaths. The index date was the date that the incident LN definition was met. We followed individuals in the linked dataset through 12/31/2006. Deaths were captured in MAX prior to ESRD and in USRDS after ESRD. We examined baseline sex differences in sociodemographics and SLE comorbidities in the 12 months prior to the index date. We used Fine and Gray proportional hazards models to determine the subdistribution hazard ratios (HR) for ESRD by sex, accounting for the competing risk of death. Multivariable Cox proportional hazards regression models were used to estimate HRs for death by sex. To test the proportional hazards assumption, we included an interaction term for sex and follow-up time. The interaction term was statistically significant in our ESRD model and we therefore stratified follow-up time at <2 vs. >2 years post-index date where survival curves diverged.

Results: Of the 2576 Medicaid patients with incident LN, 230 (9%) were male. Mean age was 30 years (+16) among males and 34 years (+14) among females (p<0.001). More males than females were White (32% vs. 20%), and fewer Black (23% vs. 32%), p 0.02. There was no significant difference in the SLE comorbidity index (p 0.11). Mean follow-up was 2.8 (+1.5) years for both sexes (p 0.62). Among 200 females and 27 males who developed ESRD, median time to ESRD was 1.35 (range 0.11-4.62) years and 2.02 (range 0.11-4.02) years. 216 females and 17 males died in follow-up (including 31 females and 4 males who died after ESRD onset). While the HR for ESRD was similar within 2 years of incident LN, it was significantly elevated among males (HR 2.87, 95%CI 1.48, 5.24) at > 2 years after incident LN. (**Table**). HR for death did not differ by sex.

Conclusion: ESRD risk was comparable in both sexes within 2 years of LN onset, but higher among males thereafter. Mortality rates were similar in males and females. To our knowledge, this is one of the largest incident LN cohorts followed for long-term outcomes by sex. However, the relatively small number of males limits conclusions. Further study of LN outcomes by sex should be pursued.

Table. Hazard Ratios for Development of End-Stage Renal Disease (ESRD) and Death in Males vs. Females among Medicaid Patients with Incident Lupus Nephritis	
Outcome	**Hazard Ratio*** (95% CI)**
ESRD within < 2 years of Lupus Nephritis Onset*	0.94 (0.57, 1.56)
ESRD > 2 years following Lupus Nephritis Onset*	**2.87 (1.48, 5.24)**
Death following Lupus Nephritis Onset**	0.98 (0.63, 1.52)
* Subdistribution proportional hazards models, accounting for the competing risk of death in ESRD models. As the interaction between sex and follow-up time was significant (p 0.03), we stratified follow-up at the 2 year mark (< 2 years vs. > 2 years after index date). **The interaction between sex and follow-up time was not significant for analyses of death ***Mutivariable model adjusted for age, sex, race/ethnicity, calendar year of LN onset, US region, zip code-based socioeconomic status (Ward MM, *J Rheum,* 2007) and SLE Comorbidity Index (Ward MM, *J Rheum*, 2000). Females = referent.	

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Abstract Number: 1068

Assessment of 10-Year Risk of Myocardial Infarction or Stroke in SLE

Michelle Petri[1] and Laurence S Magder[2], [1]Johns Hopkins University School of Medicine, Baltimore, MD, [2]University of Maryland School of Medicine, Baltimore, MD

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B

Background/Purpose: In 2013 the American College of Cardiology (ACC) and the American Heart Association (AHA) developed a new formula to estimate the 10-year risk of an adverse cardiovascular event based on traditional cardiovascular risk factors. In contrast to previous formulae, this new formula focused on risk of "hard" events of myocardial infarction or stroke. Using a large cohort of patients with SLE, we derived a formula for estimating the 10-year risk of hard cardiovascular events (CVE) among patients with SLE based on both traditional and SLE-related risk factors, and compared our findings to the ACC/AHA risk estimates.

Methods: This analysis is based on data from the Hopkins Lupus Cohort since 1987. A CVE was defined as the first occurrence of a stroke or myocardial infarction (MI). Patients who had a CVE prior to cohort entry or within the first two years of cohort participation were exluded from the analysis. There were 1513 patients included, 92% female, 54% Caucasian, 39% African-American, median age at baseline was 35 and median duration of follow-up was 8 years. To derive the score, risk factors were calculated based on variables measured in the first two years of cohort participation. Cox Proportional Hazards models were constructed to determine the variables that affected the risk of a subsequent CVE. Using the results, a formula to calculate the risk of a CVE within the next 10 years was derived.

Results: 100 CVE were observed: 63 strokes, 36 MI, and 1 diagnosed with both stroke and MI. Table 1 shows the results of a multivariable Cox model used to estimate 10 year risk.

Table 1: Association between predictors and risk of a CVD event among patients with SLE.

	Hazard Ratio (95% CI)	P-value
Age (per decade)	1.3 (1.1, 1.5)	0.0050
Male (vs. female)	1.5 (0.8, 2.8)	0.17
Systolic Blood Pressure (per 10 mmHg)[1]	1.3 (1.1, 1.6)	0.0010
Cholesterol (per 25 mg/dl)[1]	1.1 (1.0, 1.2)	0.11
Current Smoking	1.6 (1.0, 2.6)	0.055
Diabetes	1.5 (0,9, 2.6)	0.12
SLEDAI (per unit increase)[1]	1.1 (1.0, 1.2)	0.028
History of Lupus Anticoagulant	2.2 (1.4, 3.3)	0.0003
Low Mean C3[1]	1.8 (1.1, 2.9)	0.027

[1] Based on mean during the first two years of cohort participation.

Table 2 shows how the estimated 10-year risk for CVE based on this model compares to the risk from the ACC/AHA risk assessment tool for selected subgroups.

Table 2: Estimated 10-year risk based on our formula, and the ACC/AHA formula for selected subgroups.

Risk Profile	Estimated 10-year risk based on our formula	Estimated 10-year risk based on 2013 ACC/AHA score[1]
White Woman, age 40, SBP=120 (treated), Chol=150, HDL=40, No other risk factors	2.6%	0.7%
White Woman, age 60, SBP=120 (treated), Chol=150, HDL=40, No other risk factors	4.2%	3.9%
White Woman, age 60, SBP=120 (treated), Chol=150, HDL=40, Mean SLEDAI=3, No other risk factors	6.9%	3.9%
White Woman, age 60, SBP=120 (treated), Chol=150, HDL=40, Low C3, No other risk factors	7.4%	3.9%
White Woman, age 60, SBP=120 (treated), Chol=150, HDL=40, Hx of Lupus Anticoagulant, No other risk factors	9.1%	3.9%

[1] Calculated at http://tools.cardiosource.org/ASCVD-Risk-Estimator/

Conclusion: Patients with SLE are generally at increased risk for myocardial infarction or stroke, especially at younger ages. The ACC/AHA score underestimates the true risk. The excess risk is highest among those with low complement, lupus anticoagulant, or high levels of disease activity. Our risk assessment tool can be useful in guiding efforts to reduce traditional and SLE-related risk factors for "hard" cardiovascular events among patients with SLE.

Disclosure: M. Petri, None; **L. S. Magder**, None.

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Abstract Number: 1069

Child's HLA-DRB1 Genotype Increases Maternal Risk of Systemic Lupus Erythematosus: Results from the Mother-Child Immunogenetic Study in Autoimmunity

Giovanna I. Cruz[1], Xiaorong Shao[2], Hong L. Quach[2], Janelle Noble[3], Nikolaos Patsopoulos[4], Michael Busch[5], Darrell Triulzi[6], Wendy

S.W. Wong[7], Benjamin Solomon[7], John Niederhuber[7], Lindsey A. Criswell[8] and Lisa F. Barcellos[2], [1]School of Public Health, University of California, Berkeley, Berkeley, CA, [2]Genetic Epidemiology and Genomics Laboratory, University of California, Berkeley, Berkeley, CA, [3]Children's Hospital Oakland Research Institute, Oakland, CA, [4]Division of Genetics, Department of Medicine, Brigham & Women's Hospital, Harvard Medical School, Boston, MA, [5]Blood Systems Research Institute, San Francisco, CA, [6]Institute of Transfusion Medicine, University of Pittsburgh, Pittsburgh, PA, [7]Division of Medical Genomics, Inova Translational Medicine Institute, Falls Church, VA, [8]Rosalind Russell / Ephraim P. Engleman Rheumatology Research Center, University of California, San Francisco, San Francisco, CA

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Background/Purpose: SLE [MIM 152700] disproportionately affects women of reproductive age and pregnant patients are more likely to experience flares. Fetal microchimerism (FMC), or the persistence of a small population of cells in the mother, is a natural consequence of pregnancy. Risk of SLE is possibly increased through fetal HLA-antigen molecular mimicry. The causes of SLE are unknown but genetic and environmental factors, including Epstein-Barr virus (EBV) infection, are suspected. The strongest genetic association is with *HLA-DRB1* alleles **03:01, *15:01, *08:01*. We hypothesize that compared to controls, SLE cases are more likely to have children with a) *DRB1*-associated risk alleles and/or b) *DRB1*04:01*that encodes a homologous amino acid sequence to EBV.

Methods: We investigated mother-child HLA relationships in 218 SLE and 349 control mothers (and their 881 children) from the Mother-Child Immunogenetic Study (MCIS). The MCIS is a study with over 9,000 individuals: cases were recruited at UC San Francisco; controls were recruited from the Blood Centers of the Pacific, the Institute for Transfusion Medicine at the University of Pittsburgh, and from studies at the Inova Translational Medicine Institute (ITMI). Comprehensive MHC region SNP genotyping was conducted using the Illumina MHC, ImmunoChip, and 660K arrays for MCIS participants and whole genome sequencing for ITMI controls. Classical two-field HLA alleles were imputed using SNP2HLA. Clinical data were abstracted from medical records. We selected mothers of European ancestry using multidimensional scaling and ancestry informative markers to minimize any impact of population stratification. We used logistic regression models to estimate odds ratios (ORs) and 95% confidence intervals (CIs) for the association between SLE and having any children who carry *DRB1* risk alleles or *DRB1*04:01*.

Results: Initial findings reveal an increased risk of SLE among mothers with children who carry *DRB1*15:01* (OR 2.26; 95% CI, 1.39-3.66) and **04:01* (OR 1.73; 95% CI, 1.14-2.64), both adjusted for maternal genotype. Furthermore, we observed a stronger association between children who carry *DRB1*15:01*and the SLE complication lupus nephritis compared to controls (OR 2.75; 95% CI, 1.12-6.76, n=383).

Conclusion: These findings support the hypothesis that a child's genotype influences a mother's risk of disease, independent of the mother's genotype. This is the first study to demonstrate an association between a child's *DRB1* genotype and risk of SLE in the mother.

Disclosure: G. I. Cruz, None; **X. Shao**, None; **H. L. Quach**, None; **J. Noble**, None; **N. Patsopoulos**, None; **M. Busch**, None; **D. Triulzi**, None; **W. S. W. Wong**, None; **B. Solomon**, None; **J. Niederhuber**, None; **L. A. Criswell**, None; **L. F. Barcellos**, None.

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Abstract Number: 1070

CD 14(C-159T) Polymorphism and Soluble CD14 Are Associated with Increased Disease Activity and Nephritis in SLE

Sarit sekhar Pattanaik[1], Aditya kumar Panda[2], Rashmi ranjan Sahoo[1], Rina Tripathy[3] and Bidyut kumar Das[1], [1]Medicine, SCB Medical College, Cuttack, India, [2]Centre for Life science, Central University of Jharkand, Ranchi, India, [3]Biochemistry, SCB Medical College, Cuttack, India

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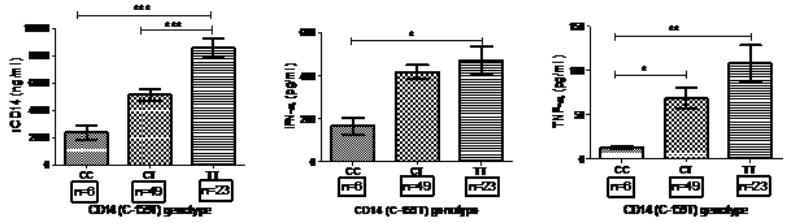
Session Time: 4:30PM-6:00PM

Background/Purpose: Cluster of differentiation 14 (CD14) plays an important role in innate immune system as a co-receptor in TLRs (2, 4, 7 and 9) signaling. Host innate receptor TLR7 and 9 recognizes nucleic acids as a ligand and produce type I IFN which is believed to be associated in the pathogenesis of SLE. TLR7 and 9 require CD14 for effective signaling, we hypothesized that CD14 polymorphism and soluble CD14 levels would correlate with disease susceptibility and disease activity in SLE.

Methods: In a case control hospital based study, 130 female SLE patients fulfilling the ACR criteria and 140 age, sex matched healthy controls were enrolled. CD14 (C-159T) polymorphism was genotyped by PCR-RFLP. In 78 SLE patients and 46 healthy controls plasma sCD14, TNF-α, IFN-α levels were quantified by ELISA. Clinical, serological and other markers of disease activity (C3, C4 and anti-dsDNA) were measured by standard laboratory procedures.

Results: Prevalence of mutant genotypes (CT and TT) and allele T were significantly higher in patients of SLE. Mutants (CT and TT) for CD14(C-159T) polymorphism were associated with higher plasma sCD14, IFN-α and TNF-α compared to wild type CC. Plasma sCD14 levels were significantly high in SLE patients compared to healthy controls (P<0.001).Plasma sCD14 correlated with SLEDAI(P = 0.002, r = 0.34), proteinuria (P=0.001, r = 0.34) and negatively correlated with C3 (P = 0.003, r = -0.33) and C4 (P < 0.0001, r = -0.50). Patients with lupus nephritis displayed higher plasma levels of sCD14, and IFN-α

Conclusion: CD14 (C-159T) polymorphism is associated with SLE. Higher soluble CD14 levels is significantly associated with SLE disease activity and lupus nephritis making it a promising biomarker.



Association of CD14(C-159T) polymorphism with plasma sCD14, IFN-α and TNF-α.

Plasma concentrations (mean ± standard error of mean) of sCD14, IFN-α and TNF-α were measured by commercial kit. Plasma of 78 SLE patients were quantified for sCD14 (A), IFN-α (B) and TNF-α (C) and correlated with CD14(C-159T) polymorphism. Numbers of samples from each genotype are shown in box. Mean plasma levels in different genotypes were compared by Kruskal-Wallis test followed by Dunns post test. *P* value less than 0.05 was considered as significant. **P*<0.05, ***P*<0.01, ****P*<0.001

Disclosure: S. S. Pattanaik, None; **A. K. Panda**, None; **R. R. Sahoo**, None; **R. Tripathy**, None; **B. K. Das**, None.

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Abstract Number: 1071

Single-Cell RNA Sequencing of Human Podocytes, Endothelial Cells, and Tubular

Cells Identifies Markers and Gene Profiles Differentiating Class IV and Class V Renal Disease in Lupus Nephritis

Evan Der[1], Kemal Akat[2], Robert Clancy[3], Beatrice Goilav[4], Anna R. Broder[5], H. Michael Belmont[6], Peter M. Izmirly[7], Nicole Jordan[8], Tao Wang[9], James Pullman[10], Daniel Schwartz[10], Ming Wu[11], Thomas Tuschl[2], Jill P. Buyon[3] and Chaim Putterman[12], [1]Albert Einstein College of Medicine, Bronx, NY, [2]Rockefeller University, New York, NY, [3]Medicine, Division of Rheumatology, New York University School of Medicine, New York, NY, [4]Division of Nephrology, Children's Hospital at Montefiore, Bronx, NY, [5]Rheumatology-Forchheimer 701N, Albert Einstein College of Medicine/Montefiore Medical Center, Bronx, NY, [6]Hosp for Joint Disease, New York, NY, [7]Rheumatology, NYU School of Medicine, New York, NY, [8]Montefiore Medical Center, New York, NY, [9]Department of Epidemiology & Population Health, Albert Einstein College of Medicine, Bronx, NY, [10]Pathology, Albert Einstein College of Medicine, Bronx, NY, [11]Pathology, New York University School of Medicine, New York, NY, [12]Division of Rheumatology, Albert Einstein College of Medicine, Bronx, NY

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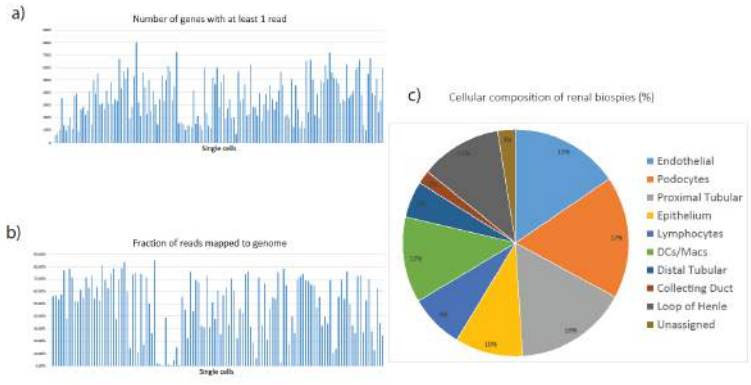
Background/Purpose: Currently, classification and treatment decisions in lupus nephritis (LN) are largely based on renal histology. Transcriptome analysis may accurately differentiate types of renal involvement, and better inform treatment outcome and prognosis. Single-cell RNAseq is an emerging technology that allows for resolution of differential gene expression at the single-cell level, thus facilitating the detection of expression changes that would be unnoticed in conventional bulk-tissue RNAseq. Our objectives were to determine if single-cell RNAseq can differentiate among various cell types in LN kidney, and distinguish between LN class IV and V.

Methods: RNAseq was performed on ~2 mg kidney tissue from consented clinically indicated renal biopsies in 5 SLE patients, using Fluidigm C1 Integrated Fluidic Circuits and the C1 Single-Cell Auto Prep. cDNA libraries were prepared using the Nextera XT DNA Library Prep Kit followed by HiSeq 2500 (Illumina) sequencing. Sequence-read alignments were conducted using the STAR aligner, and uniquely mapped reads were summarized at the gene level using the featureCounts software. Differential expression analysis was performed using the DESeq2 package for R version 3.2.0.

Results: A total of 155 single cells were characterized from LN kidney biopsies (n=36 pure class IV and n=108 pure class V). An average of 3500 genes/cell were identified (Fig. 1a), with 50% of reads mapping to the reference genome (Fig. 1b). Through transcriptome analysis and utilization of standard lineage markers, major renal resident and infiltrating cell types including podocytes, endothelial cells, tubular cells, macrophages, dendritic cells, and lymphocytes could be identified (Fig. 1c). Comparison of gene expression between cells from class IV and class V biopsies revealed that class IV podocytes and endothelial cells expressed significantly higher levels of complement C7 than class V cells ($p=.001$ and .01, respectively). Podocytes from class IV kidney expressed significantly higher IL-1b ($p<.01$) and TLR3 ($p<.001$) as well as IFN-γ receptor ($p<.001$) and TNF receptor ($p<.05$). Similarly, endothelial cells from class IV kidney demonstrated significant upregulation of several inflammatory molecules including NF-κB ($p=.005$), CXCL8 ($p<.05$), and IL-1b ($p<.05$). Proximal tubular cells from class IV patients expressed significantly higher levels of CXCL12 ($p<.05$) than those isolated from class V patients.

Conclusion: These findings demonstrate that single-cell RNAseq is feasible and informative in cell specific transcriptome analysis from fresh renal biopsy tissue in SLE. In this pilot study, single-cell RNAseq correlates well with histologic classification, and shows changes in gene expression that could directly drive or be influenced by disease pathogenesis. If confirmed, this novel approach may identify new therapeutic targets and track clinical responses.



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Abstract Number: 1072

Baseline Gene Expression Profiles in 1760 Patients from Two Phase III Trials of BAFF/BLyS Blockade in SLE

Robert W Hoffman[1], Joan T Merrill[2], Marta E. Marta Alarcón Riquelme[3], Michelle Petri[4], Ernst R Dow[5], Eric Nantz[6], Laura K Nisenbaum[5], Krista M Schroeder[6], Wendy J Komocsar[6], Narayanan B Perumal[5], Matthew D Linnik[6], Guilherme V Rocha[6] and Richard E Higgs[6], [1]Immunology-Medical, Eli Lilly and Company, Indianapolis, IN, [2]OMRF, Oklahoma, OK, [3]Oklahoma Medical Research Foundation, Oklahoma City, OK, [4]Johns Hopkins Lupus Center, Johns Hopkins University School of Medicine, Baltimore, MD, [5]Eli Lilly and Company, Indiananpolis, IN, [6]Eli Lilly and Company, Indianapolis, IN
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Session Time: 4:30PM-6:00PM

Background/Purpose: Elevated Type-I interferon (IFN) signature characterizes at least 50% of adults with SLE and has been associated with autoantibodies and more severe disease in single-center studies, but association with disease severity in clinical trials of diverse populations has been controversial (Kennedy Lupus Sci Med. 2015 28;2). Therefore, we examined gene expression profiles of 1,760 randomly selected SLE patients from two worldwide Phase III trials of the anti-BAFF, IgG4 monoclonal antibody, tabalumab in SLE.

Methods: Total RNA was extracted from whole blood, collected at baseline in Tempus tubes, using the PerfectPure RNA Blood Kit. RNA quality was assessed using Ribogreen and a Bioanalyzer RNA chip. The Affymetrix WT Plus Kit was utilized for cDNA prep and labeling, and labelled cDNA was hybridized to the GeneChip Human Transcriptome Array 2. The Affymetrix HTA2.0 array has 70,753 transcript clusters. Annotation data were retrieved from Affymetrix's na34 build (www.Affymetrix.com). Only transcript clusters that represented a single protein coding gene were considered in this analysis (n=19,818). A literature review yielded 163 reported interferon responsive genes and a subset of 34 was selected to form a pre-specified signature for analysis. Kaplan-Meier time to event analysis and Cox proportional hazards regression with backward elimination (p-leave=0.05) were conducted using baseline covariates: Type-I IFN signature, SELENA-SLEDAI, low C3, elevated anti-dsDNA antibody, race and geographic region.

Results: Using the pre-specified Type-I IFN gene signature, 75% of SLE patients in the tabalumab trials had an elevated Type-I IFN

response gene signature at baseline. Type-II IFN-associated genes were also upregulated in SLE vs controls to a much lesser extent. As expected, the baseline Type-I IFN signature was associated with anti-dsDNA antibodies, low C3, low C4 and SELENA-SLEDAI score. Severe flare, as measured by the SELENA-SLEDAI Flare Index, was observed in 16.3% and 15.8% of patients in Trial-1 and Trial-2, respectively. The Type-I IFN signature at baseline was associated with risk of developing a severe SELENA-SLEDAI flare over the ensuing 52W and time to flare was highly significant in Trial-1 ($p<0.0001$) and Trial-2 ($p<0.001$). Baseline Type-I or Type-II IFN signature was not associated with SRI-5 response to either standard of care or standard of care + tabalumab. Using Cox proportional hazard analysis, the time to SELENA-SLEDAI flare predicted by the Type-I IFN signature was found to be an independent risk factor from baseline anti-dsDNA antibodies, low C3, low C4 or baseline SELENA-SLEDAI score in both Trial-1 ($p=0.0015$) and Trial-2 ($p=0.0002$).

Conclusion: 75% of SLE patients in the tabalumab trials had elevated Type-I IFN signature at baseline, associated with anti-dsDNA antibodies, low C3, low C4, SELENA-SLEDAI score and time to SELENA-SLEDAI severe flare. Time to SELENA-SLEDAI severe flare predicted by the Type-I IFN signature was found to be an independent risk factor using a Cox proportional hazard model. SRI-5 response to tabalumab could not be predicted by the IFN signature status at baseline.

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Abstract Number: 1073

B Cell Subsets Are Epigenetically and Transcriptionally Dysregulated in Systemic Lupus Erythematosus

Emily Blalock[1], Chris Scharer[2], Ben Barwick[2], Scott Jenks[3], Bridget Neary[3], Jeremy Boss[2] and Ignacio Sanz[3,4], [1]Emory University School of Medicine, Atlanta, GA, [2]Microbiology and Immunology, Emory University School of Medicine, Atlanta, GA, [3]Rheumatology, Emory University School of Medicine, Atlanta, GA, [4]Medicine, Emory University, Atlanta, GA

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Session Title: Systemic Lupus Erythematosus - Human Etiology and Pathogenesis: Genetics, Gene Expression, and Epigenetics

Session Type: ACR Concurrent Abstract Session

Session Time: 4:30PM-6:00PM

Background/Purpose: Systemic lupus erythematosus (SLE) is characterized by multiple B cell abnormalities, including the production of autoantibodies, a major contributing factor to disease pathogenesis. Epigenetic modifications that drive the early molecular events leading to the activation of autoreactive B cells in SLE remain unclear. Therefore, we investigated the epigenetic and transcriptional signatures of SLE B cell subsets including activated naïve (aN), resting naïve (rN), late transitional (T3), switched memory (SM), and double negative (DN) B cells.

Methods: We simultaneously profiled the methylome and transcriptome of B cell subsets from SLE and healthy control (HC) African American females utilizing reduced representation bisulfite sequencing (RRBS) and RNA-seq, respectively. In addition, chromatin accessibility in SLE and HC B cells subsets was determined using assay for transposase-accessible chromatin (ATAC)-seq.

Results: Global DNA methylation analysis of total B cells identified 2,686 SLE-disease specific differentially methylated loci surrounding 951 genes. Demethylated genes in SLE B cells included IFN response genes as well as negative regulators of the viral response, while cell-cell signaling and calcium transmembrane transport genes were methylated. SLE and HC aN B cells gained DNA methylation at 2,952 loci and lost DNA methylation at 82,313 loci when compared compared to rN B cells, indicating a loss of DNA methylation during the transition from a rN to an aN B cell state. Transcriptome analysis of total B cells identified 334 differentially regulated genes in SLE patients. In individual B cell subsets, 953 genes were differentially regulated between B cell types; these cell-type transciptomes diverged from one another as cells differentiated from rN to aN to DN B cells. Integrated analysis of the methylome and transcriptome data sets identified 85 genes, 35 of which were IFN-regulated genes, whose DNA methylation changes inversely correlated with SLE disease-specific changes in gene expression.

Conclusion: DNA methylation analysis indicated the largest differences between cell types with aN B cells undergoing a genome-wide hypomethylation. Transcriptionally aN and rN B cells are more similar to each other, whereas DN B cells are more disparate. This could

reflect the cell stage of activation/differentiation, as we hypothesize that differentiation occurs in a linear manner from rN to aN to DN B cells. Although the largest differences were observed between B cell types, there were consistent SLE-specific gene expression differences (i.e.: IFN). Our results indicate that SLE B cells are epigenetically and transcriptionally distinct from HC B cells, suggesting that SLE B cells may be pathogenically programmed at an early stage of maturation.

Disclosure: E. Blalock, None; **C. Scharer**, None; **B. Barwick**, None; **S. Jenks**, None; **B. Neary**, None; **J. Boss**, None; **I. Sanz**, None.

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Abstract Number: 1074

DNA Methylation Patterns in Naïve CD4+ T Cells Identify Epigenetic Susceptibility Loci for Malar Rash and Discoid Rash in Systemic Lupus Erythematosus

Paul Renauer[1], Patrick Coit[1], Matlock A. Jeffries[2], Joan T. Merrill[3], W Joseph McCune[4], Kathleen Maksimowicz-McKinnon[5] and Amr H. Sawalha[6], [1]Division of Rheumatology, University of Michigan, Ann Arbor, MI, [2]Rheumatology, University of Oklahoma Health Sciences Center, Oklahoma City, OK, [3]Oklahoma Medical Research Foundation, Oklahoma City, OK, [4]Int Med/ Rheum, University of Michigan, Ann Arbor, MI, [5]Rheumatology, Henry Ford Hospital, Detroit, MI, [6]Rheumatology, University of Michigan, Ann Arbor, MI
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Session Date: Sunday, November 8, 2015
Session Title: Systemic Lupus Erythematosus - Human Etiology and Pathogenesis: Genetics, Gene Expression, and Epigenetics
Session Type: ACR Concurrent Abstract Session
Session Time: 4:30PM-6:00PM

Background/Purpose: Systemic lupus erythematosus (SLE) is a complex autoimmune disease characterized by heterogeneous clinical manifestations, autoantibody production, and epigenetic dysregulation in T cells. We sought to investigate the epigenetic contribution to the development of cutaneous manifestations in SLE.

Methods: We performed genome-wide DNA methylation analyses in SLE patients stratified by a history of malar rash, discoid rash, or neither cutaneous manifestation, and age, sex, and ethnicity matched healthy controls. We characterized differentially methylated regions (DMRs) in naïve CD4+ T cells in each disease subset, and assessed functional relationships between DMRs using bioinformatic approaches.

Results: We identified 36 and 37 unique DMRs that contribute to the epigenetic susceptibility to malar rash and discoid rash, respectively. These DMRs were primarily localized to genes mediating cell proliferation and apoptosis. Hypomethylation of *MIR886* and *TRIM69,* and hypermethylation of *RNF39* were specific to lupus patients with a history of malar rash. Hypomethylation of the cytoskeleton-related gene *RHOJ* was specific to SLE patients with a history of discoid rash. In addition, discoid rash-specific hypomethylated DMRs were found in genes involved in antigen-processing and presentation such as *TAP1* and *PSMB8*. Network analyses showed that DMRs in SLE patients with but not without a history of cutaneous manifestations are associated with TAP-dependent processing and MHC-class I antigen cross-presentation ($P = 3.66x10^{-18}$ in malar rash, and $3.67x10^{-13}$ in discoid rash).

Conclusion: We characterized DNA methylation changes in naïve CD4+ T cells specific to malar rash and discoid rash in patients with SLE. These data suggest unique epigenetic susceptibility loci that predispose to or are associated with the development of cutaneous manifestations in SLE.

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Abstract Number: 1075

The Scleroderma Lung Study II (SLS II) Shows That Both Oral Cyclophosphamide

(CYC) and Mycophenolate Mofitil (MMF) Are Efficacious in Treating Progressive Interstitial Lung Disease (ILD) in Patients with Systemic Sclerosis (SSc)

Philip J. Clements[1], Donald Tashkin[1], Michael Roth[1], Dinesh Khanna[2], Daniel E. Furst[3], Chi-hong Tseng[1], Elizabeth R. Volkmann[1] and Robert Elashoff[4], [1]Medicine, University of California Los Angeles, David Geffen School of Medicine, Los Angeles, CA, [2]Medicine, University of Michigan, Ann Arbor, MI, [3]Medicine, University of California, Los Angeles, David Geffen School of Medicine, Los Angeles, CA, [4]Biomath, University of California Los Angeles, David Geffen School Of Medicine, Los Angeles, CA
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SESSION INFORMATION

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Session Type: ACR Concurrent Abstract Session
Session Time: 4:30PM-6:00PM

Background/Purpose: Demonstrate that the course of forced vital capacity (FVC) over 2-years was better in SSc patients with symptomatic ILD treated with oral MMF for two years than with oral CYC for one year followed by placebo during the second year in a blinded randomized controlled trial.

Methods: Entry criteria: 1980 ACR criteria for SSc; disease duration of =< 7 years from 1st non-Raynaud sign or symptom; moderate dyspnea (Level 2 of the Magnitude of Task scale of the Mahler Baseline Dyspnea Index [BDI]; %FVC between 45% and 80%; and any ground-glass opacification on chest high-resolution computed tomography (HRCT).

At baseline and every 3 months during the 2-year trial, physical exams (including modified Rodnan skin scoring or MRSS), lung function testing and patient-reported outcomes were completed: Scleroderma Health Assessment Questionnaire (disability index [HAQ-DI] and 5 100-mm visual analogue scales); SF-36, and transition dyspnea index (TDI).

Patients were randomized to Arm A (oral CYC 2 mg/kg/day for one year followed by matching placebo for the second year) or Arm B (matching MMF up to 1500 mg BID for 2 years).

Results: 142 patients were randomized; 106 completed the 2-year evaluation. With the exception of MRSS, which was higher in the MMF group (15.3 in MMF vs 14.1 in CYC, p=xxx) the baseline characteristics were not different between treatment groups.

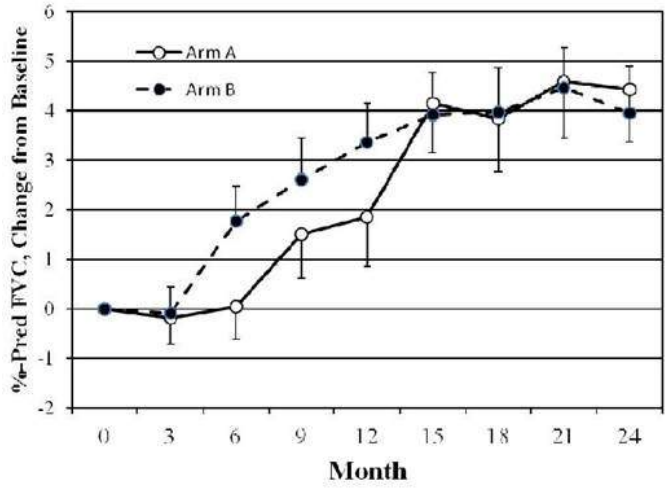
In preliminary analyses, -the course of FVC showed comparable improvement in both treatment groups at 24 months (see figure). Improvements in both treatment groups were noted in TDI (increase of 2.24 in CYC vs 1.86 in MMF,) and in MRSS (decline of 6.1 units in CYC vs 2.9 units in MMF).

More patients in the CYC arm withdrew from study treatment prematurely (36 in CYC and 20 in MMF) (p=0.019).Of all the subjects with end-point data 23% assigned to CYC received alternative therapy after stopping study treatment (MMF in 8, Rituximab in 1, tocilizimab in 1 and IV-CYC in 2) and 4% assigned to MMF received alternative treatment (po CYC in 1 and IV-CYC in 1) after stopping study treatment..

Weight loss (NS) and leukopenia/thrombocytopenia ($p<0.05$) occurred more frequently in the CYC arm

Conclusion: In this large, double blind, RTC, we found: 1) At 24 months the improvement in %FVC was comparable in the two treatment groups. 2) The TDI and MRSS improved in both treatment arms but there was a trend favoring improvements in the CYC group. 3) Significantly fewer premature withdrawals were noted in the MMF arm. 4) Leukopenia/thrombocytopenia were noted significantly less frequently in the MMF arm5) It is unclear how the use of alternative medications in SSc patients who withdrew prematurely from study treatments, particularly in the CYC patients, could have influenced the results.

In summary both CYC and MMF are efficacious for treatment of SSc-ILD.



Disclosure: P. J. Clements, None; **D. Tashkin**, None; **M. Roth**, None; **D. Khanna**, Bristol-Myers Squibb, 2,EMD Serono, 2,Genentech and Biogen IDEC Inc., 2,Bayer, 5,Biogen Idec, 5,Cytori, 5,EMD Serono, 5,Forward, 5,Genentech and Biogen IDEC Inc., 5,Gilead, 5,Lycera, 5,Seattle Genetics, 5; **D. E. Furst**, Gilead, 2,GlaxoSmithKline, 2,NIH, 2,Novartis Pharmaceutical Corporation, 2,Pfizer Inc, 2,Roche Pharmaceuticals, 2,Genentech and Biogen IDEC Inc., 2,UCB, 2,Abbvie, 5,Actelion Pharmaceuticals US, 5,Amgen, 5,Bristol-Myers Squibb, 5,Cytori, 5,Janssen Pharmaceutica Product, L.P., 5,Gilead, 5,GlaxoSmithKline, 5,NIH, 5,Novartis Pharmaceutical Corporation, 5,Pfizer Inc, 5,Roche Pharmaceuticals, 5,Genentech and Biogen IDEC Inc., 5,UCB, 5,Abbvie, 8,Actelion Pharmaceuticals US, 8,Bristol-Myers Squibb, 2,Amgen, 2,Actelion Pharmaceuticals US, 2,Abbvie, 2,UCB, 8; **C. H. Tseng**, None; **E. R. Volkmann**, None; **R. Elashoff**, None.

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Abstract Number: 1076

Safety and Tolerability of Cyclophosphamide Versus Mycophenolate for Systemic Sclerosis-Related Interstitial Lung Disease

Elizabeth R. Volkmann[1], Michael Roth[2], Robert Elashoff[3], Philip J. Clements[1], Daniel E. Furst[2], Dinesh Khanna[4], Jonathan Goldin[5], Donald Tashkin[1] and Scleroderma Lung Study II Group, [1]Medicine, University of California Los Angeles, David Geffen School of Medicine, Los Angeles, CA, [2]Medicine, University of California, Los Angeles, David Geffen School of Medicine, Los Angeles, CA, [3]Biomathematics, University of California, Los Angeles, Los Angeles, CA, [4]Medicine, University of Michigan, Ann Arbor, MI, [5]David Geffen School of Medicine, University of California, Los Angeles, Los Angeles, CA

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Session Type: ACR Concurrent Abstract Session

Session Time: 4:30PM-6:00PM

Background/Purpose: Interstitial lung disease (ILD) is the leading cause of death in patients with systemic sclerosis (SSc). Although cyclophosphamide (CYC) demonstrated beneficial treatment effects at one year on FVC and self-reported dyspnea (1), these benefits came at the expense of a high degree of adverse effects. Uncontrolled studies have demonstrated that mycophenolate (MMF) may improve SSc-ILD; however, no studies have directly compared outcomes of CYC and MMF in SSc-ILD. The present double-blind, randomized, placebo-controlled trial (RCT) compared the effects of CYC versus MMF in patients with SSc-ILD.

Methods: Between September 2009 and January 2013, 142 SSc-ILD patients from 14 US centers were randomized to receive MMF (titrated as tolerated to 3.0 g/day in divided doses) for 2 years or oral CYC (titrated as tolerated to 2 mg/kg daily) for 1 year followed by 1

year on placebo. Inclusion criteria were age ≥18 years, duration of disease ≤7 years from onset of the first non-Raynaud's SSc symptom, FVC 40-80% predicted, DLCO ≥40% predicted (or 30-39% predicted if no evidence of pulmonary hypertension on echocardiogram and/or right heart catheterization), and evidence of *any* ground glass opacity on HRCT. The primary endpoint was treatment responsiveness as measured by the course of the FVC% predicted over 24-months.

Results: Among 142 participants (Mean [SD] age 52.3 [9.7] years), 74% were female and 59% had diffuse cutaneous involvement. The mean disease duration was 2.6 [1.8] years. Baseline pulmonary function was as follows (All Mean [SD]% predicted): FVC 66.5 [9.1]; TLC 65.9 [10.9]; DLCO 54.0 [12.7]. Baseline quantitative lung fibrosis (QLF) scores were 32.5 [23.8] and 8.6 [6.8], for the zone of maximum involvement and whole lung, respectively. By 24 months, approximately half (49%) of the participants assigned to CYC (N=73) went off drug, compared with 29% of participants assigned to MMF (N=69). A greater proportion of participants assigned to MMF reached the required dosage compared with CYC, and the time to reach the maximum targeted dose was significantly longer in the CYC arm (152 days) compared with the MMF arm (92 days). Participants assigned to CYC experienced more serious adverse events (SAEs) considered to be drug-related by a morbidity and mortality committee compared with patients assigned to MMF (22% versus 7%, respectively), although the majority of SAEs were deemed to be related to underlying ILD (Table 1). During the study period, there were 11 deaths (15%) in the CYC group and 5 deaths (7%) in the MMF group.

Conclusion: The present findings demonstrate that treatment with MMF is associated with fewer SAEs deemed to be drug-related and fewer deaths compared with treatment with CYC in patients with SSc-ILD. Moreover, MMF appears to be better tolerated than CYC.

References:

1. Tashkin DP, et al. NEJM 2006;354:2655-2666.

Table 1. Summary of serious adverse events (SAEs) for participants assigned to CYC (N=73) versus MMF (N=69).

	CYC	MMF
Total Number of SAEs	36	42
SAEs due to drug (%)	22.2%	7.1%
SAEs due to underlying disease (%)	44.4%	38.1%
SAEs due to other causes (%)	31.6%	52.4%
SAE not yet reviewed (%)	2.8%	2.4%

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Abstract Number: 1077

High Levels of CCL-18 Are Associated with Deterioration of Lung Function, Increased Annual Fibrosis Progression Rate and Decreased Survival in Systemic Sclerosis

Anna-Maria Hoffmann-Vold[1,2], Anders Heiervang Tennøe[2], Oyvind Midtvedt[1], Torhild Garen[3], May Brit Lund[4], Trond Mogens Aalokken[5], Cathrine Brunborg[6], Thor Ueland[2] and Øyvind Molberg[7], [1]Rheumatology, Oslo University Hospital, Oslo, Norway, [2]Institute of clinical medicine, University of Oslo, Oslo, Norway, [3]Rheumatology, Department of Rheumatology, Oslo University Hospital, Oslo, Norway, [4]Respiratory Diseases, Oslo University Hospital, Oslo, Norway, [5]Radiology, Oslo University Hospital, Oslo, Norway, [6]Biostatistics, Epidemiology and Health Economics, Oslo University Hospital, Oslo, Norway, [7]Department of Rheumatology, Institute of Clinical Medicine, Oslo University Hospital, Oslo, Norway

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Background/Purpose: Systemic sclerosis (SSc) carries high risk for progressive interstitial lung disease (ILD), but biomarkers for individual risk stratification are largely missing. There is an ongoing discussion about the potential of chemokine CCL18 or pulmonary and activation regulated chemokine (PARC) as a marker for (progressive) ILD in SSc. The aim of this study was to examine associations between ILD parameters and serum levels of CCL18 in a large and unselected SSc cohort with complete and data sets on pulmonary function and lung fibrosis extent by HRCT.

Methods: Sera from the prospective Oslo University Hospital SSc cohort (n=298) and healthy blood donor controls (HC; n=100) were analysed for CCL18 by enzyme immunoassay. CCL18 levels were defined as high or low using [mean 2SD] in HC sera as cut-off value. Paired pulmonary function tests and HRCT images were obtained at baseline and follow-up. All patients in the SSc cohort met the 2013 ACR/EULAR classification criteria.

Results: CCL18 was increased in SSc compared to HC, and high levels of CCL18 (>53 ng/ml) were identified in 105/298 (35%) of the SSc patients. Patients with high and low CCL18 did not differ regarding demographics, SSc subtype or auto-antibody profile (Table 1). Analysis of ILD parameters showed that high CCL18 was associated with low Forced Vital Capacity (FVC) at baseline, decline in FVC across the observation period and lung fibrosis progression; expressed as annual fibrosis progression rate (Table 2). Multivariate analyses showed associations between CCL18, FVC decline and FVC <70% at follow up (Table 3). Finally, Kaplan-Meyer analyses showed that patients with high CCL18 levels had reduced 5-and 10 year survival compared to the CCL18 low subset; (85% and 74% compared to 97% and 89%, log rank: 0.004).

Conclusion: In this prospective SSc cohort, high levels of CCL18 were associated with deterioration of lung function, higher annual fibrosis progression rate and decreased survival. Our results support the notion that circulating CCL18 has potential as marker for progressive ILD in SSc.

Table1: Demographics and clinical findings in the SSc cohort stratified by level of CCL18

	Total SSc cohort (n=298)	**Low CCL 18 (n=193)**	**High CCL18 (n=105)**	**p-value***
Age at disease onset, yrs (SD)	48 (15.4)	47 (15.1)	51 (16.6)	0.064
Time disease onset to sampling, yrs (SD)	5.9 (6.1)	6.4 (6.1)	5.2 (6.1)	0.111
Total observation period, yrs (SD)	11.5 (8.0)	11.7 (7.2)	11.2 (9.3)	0.635
Males, no (%)	55 (13.8)	29 (15.0)	26 (24.8)	0.038
Ever smoker, no (%)	107 (26.9)	71 (39.4)	36 (37.5)	0.752
Deceased, no (%)	67 (16.8)	33 (17.1)	34 (32.4)	0.003
Diffuse cutaneous SSc, no (%)	78 (19.6)	48 (24.9)	30 (28.6)	0.488
Pulmonary hypertension, no (%)	52 (13.1)	25 (13.0)	27 (25.7)	0.006
Anti-topoisomerase antibodies, no (%)	47 (11.8)	27 (15.3)	20 (21.1)	0.427
Anti-centromere antibodies, no (%)	127 (31.8)	83 (46.6)	44 (46.3)	0.902

Tabl2: Lung fibrosis and lung function in the SSc cohort stratified by level of CCL18

	Total SSc cohort (n=298)	Low CCL 18 (n=193)	High CCL18 (n=105)	p-value*
Baseline lung fibrosis, % mean SD	6.6 (12.7)	5.5 (10.5)	8.6 (15.8)	0.105
Annual fibrosis progression rate % mean	0.5 (2.3)	0.2 (1.9)	0.9 (2.9)	0.028
Baseline FVC, % mean SD	94.7 (20.5)	96.6 (19.6)	91.2 (21.8)	0.031
Total FVC decline, % mean SD	4.3 (13.7)	2.4 (10.9)	8.0 (17.4)	0.004
FVC >10%, no (%)	76 (26.6)	36 (19.0)	40 (41.2)	<0.000
FVC <70% at follow up, no (%)	53 (18.5)	25 (13.2)	28 (28.9)	0.001
Baseline DLCO, % mean SD	68.2 (21.7)	71.4 (20.9)	62.0 (22.0)	<0.000
DLCO decline, % mean SD	8.4 (14.8)	8.0 (14.1)	9.1 (16.0)	0.553
DLCO decline >15%, no (%)	85 (29.9)	54 (28.7)	31 (32.2)	0.535

Table 3: Multivariate analyses with FVC <70% at follow up, FVC decline and annual fibrosis progression rate as primary outcomes

	Primary outcomes					
	FVC <70%	p-value	FVC decline >10%	p-value	Annual fibrosis progression	p-value
CCL 18 OR (95% CI)	3.8 (1.27-11.55)	0.017	3.1 (1.66-5.57)	<0.001	1.7 (0.80-3.71)	0.169
Anti-centromere OR (95% CI)	0.3 (0.08-1.09)	0.068	0.3 (0.19-0.66)	<0.001	0.49 (0.19-1.19)	0.116
Baseline FVC OR (95% CI)	0.9 (0.82-0.91)	<0.001	0.34 (0.99-1.03)	0.057	1.01 (0.99-1.04)	0.302
Baseline fibrosis OR (95% CI)	1.06 (1.01-1.09)	0.050			1.2 (1.08-1.25)	<0.001

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Abstract Number: 1078

CXCL4 Does Not Predict Extent or Progression of Interstitial Lung Disease in Systemic Sclerosis

Elizabeth R. Volkmann[1], Donald P. Tashkin[1], Michael Roth[1], Chi-hong Tseng[1], Holly LeClair[2], Philip J. Clements[1], Daniel E. Furst[3], Maureen D Mayes[4], Julio Charles[5], Dinesh Khanna[6], Robert Elashoff[7], Shervin Assassi[8] and Scleroderma Lung Study II Group, [1]Medicine, University of California Los Angeles, David Geffen School of Medicine, Los Angeles, CA, [2]University of California Los Angeles, David Geffen School of Medicine, Los Angeles, CA, [3]Medicine, University of California, Los Angeles, David Geffen School of Medicine, Los Angeles, CA, [4]University of Texas - Houston Medical School, Houston, TX, [5]Internal Medicine/Rheumatology, University of Texas - Houston Medical School, Houston, TX, [6]University of Michigan, Ann Arbor, MI, [7]Biomathematics, University of California, Los Angeles, Los Angeles, CA, [8]Rheumatology, University of Texas Medical School at Houston, Houston, TX

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Background/Purpose: Increased circulatory levels of the chemokine CXCL4 have been associated with the presence of pulmonary fibrosis (PF) by HRCT in an observational study of patients with systemic sclerosis (SSc)[1]. In addition, higher baseline levels of CXCL4 predicted faster decline in DLCO in a subgroup of patients from this study[1]. No studies have evaluated whether CXCL4 can predict both extent and progression of PF in SSc patients, all of whom have well-characterized PF and all of whom are receiving aggressive therapy with either mycophenolate (MMF) or cyclophosphamide (CYC).

Methods: Between September 2009 and January 2013, 142 SSc-PF patients from 14 US centers were randomized to receive MMF (titrated as tolerated to 3.0 g/day in divided doses) for 2 years or oral CYC (titrated as tolerated to 2 mg/kg daily) for 1 year followed by 1 year on placebo. Plasma samples were obtained at baseline, 1 and 2 years. Baseline plasma samples were examined by validated, commercially available ELISA kits (Human CXCL4/PF4 Quantikine Kit - R&D Systems). CXCL4 levels were compared between SSc-PF patients (N=136) and age- and gender-matched healthy control patients (N=67) using a Student's t test. Correlations were performed between CXCL4 levels and baseline measures of extent of PF, as well as change in DLCO (from baseline) at 12, 18, and 24 months.

Results: Among 136 participants with baseline plasma samples, 94% were ANA positive, 46% were Scl-70 positive, 13% were Anti-RNA polymerase III positive. Baseline pulmonary function was as follows (All Mean [SD]% predicted): FVC 66.5 [9.1]; TLC 65.8 [11.1]; DLCO 54.0 [12.7]. Baseline quantitative lung fibrosis (QLF) scores were 22.8 [19.6] and 8.6 [6.9], for the zone of maximum involvement (ZM) and whole lung (WL), respectively. Baseline modified Rodnan skin score (mRSS) was 14.7 [10.5] and Baseline Dyspnea Index (BDI) was 7.2 [2.2]. Baseline CXCL4 levels were higher in SSc-PF patients compared with healthy controls (Mean [SD]: 2699 [1489] versus 2233.4 [1351.1], respectively; P=0.03). There were no significant correlations between baseline CXCL4 levels and extent of PF as measured by FVC, TLC, DLCO, QLF-ZM, QLF-WL, BDI (all P-values >0.2), and extent of cutaneous sclerosis as measured by the mRSS (P=0.2). There were also no significant correlations between baseline CXCL4 levels and change in DLCO at 12 (P =0.6), 18 (P =0.4), or 24 months (P=0.6).

Conclusion: Consistent with prior studies,[1] levels of CXCL4 were higher in patients with SSc-PF compared with controls. However, CXCL4 levels were not correlated with extent of PF and progression of PF as measured by change in DLCO in patients with SSc-PF.

References:

1. van Bon L, Affandi AJ, Broen RB, et al. Proteome-wide Analysis and CXCL4 as a Biomarker in Systemic Sclerosis. NEJM 2014;370:433-43.

Disclosure: E. R. Volkmann, None; **D. P. Tashkin**, None; **M. Roth**, None; **C. H. Tseng**, None; **H. LeClair**, None; **P. J. Clements**, None; **D. E. Furst**, Gilead, 2,GlaxoSmithKline, 2,NIH, 2,Novartis Pharmaceutical Corporation, 2,Pfizer Inc, 2,Roche Pharmaceuticals, 2,Genentech and Biogen IDEC Inc., 2,UCB, 2,Abbvie, 5,Actelion Pharmaceuticals US, 5,Amgen, 5,Bristol-Myers Squibb, 5,Cytori, 5,Janssen Pharmaceutica Product, L.P., 5,Gilead, 5,GlaxoSmithKline, 5,NIH, 5,Novartis Pharmaceutical Corporation, 5,Pfizer Inc, 5,Roche Pharmaceuticals, 5,Genentech and Biogen IDEC Inc., 5,UCB, 5,Abbvie, 8,Actelion Pharmaceuticals US, 8,Bristol-Myers Squibb, 2,Amgen, 2,Actelion Pharmaceuticals US, 2,Abbvie, 2,UCB, 8; **M. D. Mayes**, None; **J. Charles**, None; **D. Khanna**, Bristol-Myers Squibb, 2,EMD Serono, 2,Genentech and Biogen IDEC Inc., 2,Bayer, 5,Biogen Idec, 5,Cytori, 5,EMD Serono, 5,Forward, 5,Genentech and Biogen IDEC Inc., 5,Gilead, 5,Lycera, 5,Seattle Genetics, 5; **R. Elashoff**, None; **S. Assassi**, None.

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The Potential Effect on Recruitment of Restricting Skin Scores Eligibility Criteria in Early Diffuse Scleroderma Trials

Robyn T. Domsic[1], Dinesh Khanna[2], Mary Lucas[3], Virginia D. Steen[4], Daniel E. Furst[5], Robert Lafyatis[6] and Thomas A. Medsger Jr.[7], [1]Medicine - Rheumatology, University of Pittsburgh, Pittsburgh, PA, [2]Division of Rheumatology, University of Michigan, Ann Arbor, MI, [3]Medicine, University of Pittsburgh Scleroderma Center, Pittsburgh, PA, [4]Rheumatology, Georgetown University Medical Center, Washington, DC, [5]Medicine, University of California, Los Angeles, David Geffen School of Medicine, Los Angeles, CA, [6]Boston University School of Medicine, Boston, MA, [7]Department of Medicine/Rheumatology, University of Pittsburgh, Pittsburgh, PA

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Background/Purpose: There is increasing interest in cohort enrichment for clinical trials of early diffuse SSc (dcSSc). Recent EUSTAR database analysis (Maurer et al. 2015) suggests that patients with a low modified Rodnan skin score (mRss)< 22 and short disease duration (< 15 months from first non-Raynaud symptom) have the highest probability of worsening (defined as progressive skin involvement) at one year. The autoantibody profile in the US dcSSc population is different than Europe, with greater percentages of patients with anti-RNA polymerase III (RNAP) antibody in the US. Anti-RNAP positive patients often present with higher skin scores. If an upper threshold skin score is used as an inclusion criterion thenmany RNAP positive patients could be excluded. The objective of this study was to examine the effect of restricting mRss in early diffuse SSc clinical trials with respect to: 1)the percentage of patients experiencing a significant change in mRss and 2) recruitment in a US population.

Methods: We used a single-center cohort of prospectively followed early dcSSc patients seen for an initial visit between Jan. 1, 1980 and Dec. 31, 2013 at a US Scleroderma Center. Early was defined as < 18 months from the first non-Raynaud symptom. Patients had to have at least two mRss within one year of the first SScCenter visit. After descriptive baseline statistics, time to peak skin score, and the percentage of patients who had improvement or worsening of mRss over one year were calculated. Data is presented by skin score at presentation.

Results: Among 304 eligible patients, mean age at the first SSc Center visit was 51.8 ±13.5 years. The cohort was 76% female and 93%Caucasian. Overall patients were 58% RNAP positive, 21% anti-Scl70 positive, 11% other SSc-autoantibody positive and 10% unknown. The percentage of patients with improving or worsening mRss by ≥5 points,≥5 points and 25% change, and the times to peak skin score are shown in Table 1. Including patients with higher baseline skin score did not change the overall % of patients improving or worsening their mRss within one year. The median time to peak skin score was nearly identical in the patient groups. By restricting our inclusion criterion to mRss< 25 points, 27-40% of patients with worsening mRss would have been excluded with different progression.

Table 1: Skin score change at one year by baseline mRss at presentation

mRss at first SSc Center visit	N	mRssworsened by ≥5 points	mRss improved by ≥5 points (%)	< 5 point change in mRss	Median (IQR) time to peak mRss from first visit
10-25	176	87 (49%)	47 (27%)	42 (24%)	0.45 (0.00, 0.64)
10-30	217	110 (51%)	55 (25%)	52 (24%)	0.46 (0.16,0.67)
10-35	253	127 (50%)	69 (27%)	57 (23%)	0.45 (0.15, 0.66)
10-40	284	142 (50%)	82 (29%)	60 (21%)	0.42 (0.07, 0.66)
10-45	304	143 (47%)	90 (30%)	71 (23%)	0.40 (0.00, 0.63)
	N	**mRssworse ≥5 points and 25%**	**mRss improved by ≥5 points and 25%**	**< 5 point and 25% change in mRss**	
10-25	176	84 (47%)	44 (25%)	58 (33%)	
10-30	217	97 (45%)	49 (22%)	71 (33%)	
10-35	253	108 (43%)	61 (24%)	84 (33%)	
10-40	284	115 (41%)	69 (24%)	100 (35%)	
10-45	304	115 (38%)	71 (23%)	118 (36%)	

Conclusion: In one US SSc Center population expanding the allowable mRss from ≥22 to ≤45 did not decrease the percentof patients changing their mRss. Restricting mRss at≤ 22 may significantly limit our potential to recruit patients in the US. Further study of this issue should be undertaken with additional modeling and consideration to different autoantibody frequencies in geographic regions. Limitations of our data include that it is single center population.

References: Maurer et al., Annals Rheum Dis. 2015; 74: 1124.

Disclosure: R. T. Domsic, Biogen-Idec, 5,Bayer, 5; **D. Khanna**, Bristol-Myers Squibb, 2,EMD Serono, 2,Genentech and Biogen IDEC Inc., 2,Bayer, 5,Biogen Idec, 5,Cytori, 5,EMD Serono, 5,Forward, 5,Genentech and Biogen IDEC Inc., 5,Gilead, 5,Lycera, 5,Seattle Genetics, 5; **M. Lucas**, None; **V. D. Steen**, None; **D. E. Furst**, Gilead, 2,GlaxoSmithKline, 2,NIH, 2,Novartis Pharmaceutical Corporation, 2,Pfizer Inc, 2,Roche Pharmaceuticals, 2,Genentech and Biogen IDEC Inc., 2,UCB, 2,Abbvie, 5,Actelion Pharmaceuticals US, 5,Amgen, 5,Bristol-Myers Squibb, 5,Cytori, 5,Janssen Pharmaceutica Product, L.P., 5,Gilead, 5,GlaxoSmithKline, 5,NIH, 5,Novartis Pharmaceutical Corporation, 5,Pfizer Inc, 5,Roche Pharmaceuticals, 5,Genentech and Biogen IDEC Inc., 5,UCB, 5,Abbvie, 8,Actelion Pharmaceuticals US, 8,Bristol-Myers Squibb, 2,Amgen, 2,Actelion Pharmaceuticals US, 2,Abbvie, 2,UCB, 8; **R. Lafyatis**, Shire, Sanofi, Regeneron, Genentech, UCB, HGS, Precision Dermatology, Biogen, BMS, Inception, Stromedix, PRISM, Pfizer, 2,Shire, Sanofi, Regeneron, Roche/Genentech, Biogen, Lycera, Novartis, Celgene, BMS, Amira, Celdara, Celltex, Dart Therapeutics, ldera, Inception,

Intermune, Medimmune, Precision Dermatology, Promedior, Zwitter, PRISM, UCB, Actelion, EMD Sereno, Akros, E, 5; **T. A. Medsger Jr.**, None.

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Modified Rodnan Skin Score Thresholds for the Optimization of Cohort Enrichment in Clinical Trials in Skin Fibrosis in Patients with Diffuse Cutaneous Systemic Sclerosis

Rucsandra Dobrota[1], Britta Maurer[1], Nicole Graf[2], Suzana Jordan[3], Carmen Marina Mihai[4], Otylia Kowal-Bielecka[5], Yannick Allanore[6], Oliver Distler[1] and EUSTAR co-authors, [1]Division of Rheumatology, University Hospital Zurich, Zurich, Switzerland, [2]graf biostatistics, Winterthur, Switzerland, [3]Department of Rheumatology, University Hospital Zurich, Zurich, Switzerland, [4]Department of Internal Medicine and Rheumatology, Cantacuzino Hospital, Carol Davila University of Medicine and Pharmacy, Bucharest, Romania, [5]Department of Rheumatology and Internal Medicine, Medical University of Bialystok, Bialystok, Poland, [6]Department of Rheumatology, University Paris Descartes and Cochin Hospital, Paris, France

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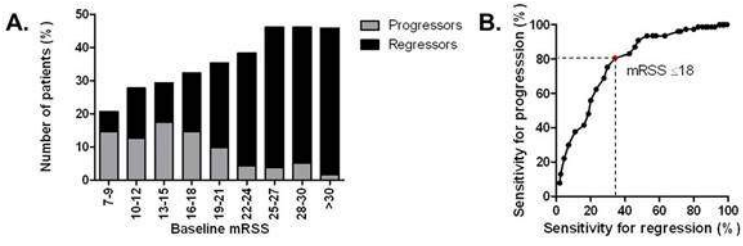
Background/Purpose: The modified Rodnan skin score (mRSS) is the major outcome measure for skin fibrosis in clinical trials (CT) in diffuse cutaneous scleroderma (dcSSc). Traditionally, CT in skin fibrosis included mostly severe patients with higher mRSS. This approach is challenged by recent data showing that patients with lower baseline skin scores are more likely to progress during 1 year of follow-up (1). In this study, we explored baseline mRSS as a predictor of change in skin fibrosis in patients with dcSSc. **Methods:** This longitudinal analysis included 704 patients from the EUSTAR registry. The inclusion criteria were: expert-diagnosis of dcSSc, fulfillment of ACR1980 criteria, mRSS≥7 at baseline and available data for mRSS at 12±2 months follow-up. Skin improvement and skin progression were defined as a decrease/increase in mRSS of >5 points AND ≥25 % within 1 year, respectively (1). A comparison of the baseline mRSS in patients with/without skin improvement/progression after 1 year was performed (Wilcoxon rank sum test). Further, we explored the interdependence between different mRSS cut-offs and progression/regression of skin fibrosis. **Results:** A total of 155/704 (22%) patients showed skin improvement, whereas 77/704 (11%) showed skin progression after 1 year (Figure 1A). High baseline mRSS was strongly associated with skin improvement ($p<0.001$), with the best sensitivity and specificity for prediction of skin regression at a cut-off of 17.5 points (area under the curve 0.708). A lower baseline mRSS was confirmed as predictor of skin progression after 1 year ($p<0.001$). We analysed different mRSS cut-offs and their sensitivity for progression and regression of skin fibrosis (Figure 1B). In this cohort, an upper baseline mRSS cut-off value of 18 points performed best, including the highest proportion of progressors (80.5%) and the lowest proportion of regressors (34.2%, Figure 1B). For feasibility reasons, higher thresholds were also analyzed and, overall, a baseline mRSS between 18 and 25 allowed the inclusion of a reasonably high rate of progressors over regressors. **Figure 1. A.** Percentage of progressors and regressors per baseline mRSS range. **B.** Sensitivity for progression and regression depending on different cut-off values for baseline mRSS.



Conclusion: These results argue for a paradigm shift regarding mRSS thresholds used as inclusion criteria in CT in skin fibrosis in dcSSc. In order to preferentially include progressive patients over those prone to improve as part of the natural history of the disease, a lower mRSS at baseline should be considered. Further analyses on other cohorts will add valuable data to support the choice of a specific threshold. **References:**

1. Maurer B, Graf N, Michel BA, et al. Prediction of worsening of skin fibrosis in patients with diffuse cutaneous systemic sclerosis using the EUSTAR database. Ann Rheum Dis. 2015;74(6):1124-31.

Disclosure: R. Dobrota, Pfizer Inc, 2; **B. Maurer**, None; **N. Graf**, Medac, Boehringer Ingelheim Pharma, Bayer, 5; **S. Jordan**, None; **C. M. Mihai**, Actelion/Geneva Romfarm, Abbvie, 5; **O. Kowal-Bielecka**, None; **Y. Allanore**, Actelion, Bayer, Biogen, Bristol-Meyers Squibb, Inventiva, Medac, Pfizer, Roche/Genentech, Sanofi-Aventis, Servier, 2,Actelion, Bayer, Biogen, Bristol-Meyers Squibb, Inventiva, Medac, Pfizer, Roche/Genentech, Sanofi-Aventis, Servier, 5; **O. Distler**, Actelion, Pfizer, Pharmacyclics, Ergonex, BMS, Sanofi-Aventis, United BioSource Corporation, Roche/Genentech, Medac, Biovitrium, Boehringer Ingelheim Pharma, Novartis, 4D Science, Active Biotec, Bayer-Schering, Sinoxa, Serodapharm, EpiPharm, Biogen, Inven, 5,Actelion, Pfizer, Pharmacyclics, Ergonex, BMS, Sanofi-Aventis, United BioSource Corporation, Roche/Genentech, Medac, Biovitrium, Boehringer Ingelheim Pharma, Novartis, 4D Science, Active Biotec, Bayer-Schering, Sinoxa, Serodapharm, EpiPharm, Biogen, Inven, 2.

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Abstract Number: 1081

Administration of Patient Reported Outcome Measurement Information System (PROMIS) Instruments By Computer Adaptive Testing in Patients with Systemic Vasculitis

Gunnar Tomasson[1], John T. Farrar[2], David Cuthbertson[3], Carol McAlear[4], Susan Asdown[5], Don Gebhart[6], Georgia Lanier[7], Nataliya Milman[8], Jacqueline Peck[9], Joanna Robson[10], Simon Carette[11], Gary S. Hoffman[12], Nader A. Khalidi[13], Curry L. Koening[14], Carol A. Langford[12], Larry W. Moreland[15], Paul A. Monach[16], Christian Pagnoux[11], Ulrich Specks[17], Antoine G. Sreih[18], Steven R. Ytterberg[19] and Peter A. Merkel[4], [1]Dept of Public Health Sciences, University of Iceland, Reykiavik, Iceland, [2]Universitiy of Pennsylvania, Philadelphia, PA, [3]Biostatistics and Informatics, Department of Pediatrics, University of South Florida, Tampa, FL, [4]Penn Vasculitis Center, Division of Rheumatology, University of Pennsylvania, Philadelphia, PA, [5]NONE, Branbury, United Kingdom, [6]NONE, Columbus, OH, [7]NONE, Framingham, MA, [8]Division of Rheumatology, University of Ottawa, Ottawa, ON, Canada, [9]Oxford University, Oxford, United Kingdom, [10]Nuffield Department of Orthopaedics Rheumatology and Musculoskeletal Sciences, University of Oxford, University of Oxford, Oxford, United Kingdom, [11]Mount Sinai Hospital, Toronto, ON, Canada, [12]Rheumatology, Cleveland Clinic, Cleveland, OH, [13]McMaster University, Hamilton, ON, Canada, [14]Division of rheumatology, George E. Wahlen Department of Veterans Affairs Medical Center Salt Lake City and University of Utah, University of Utah School of Medicine, Salt Lake City, UT, [15]Rheumatology & Clinical Immunology, University of Pittsburgh, Pittsburgh, PA, [16]Rheumatology, Boston University School of Medicine, Boston, MA, [17]Division of Pulmonary and Critical Care Medicine, Mayo Clinic College of Medicine, Rochester, MN, [18]Department of Rheumatology, University of Pennsylvania, Philadelphia, PA, [19]Rheumatology Division, Mayo Clinic, Rochester, MN
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Background/Purpose: Currently-used outcome measures in vasculitis insufficiently capture the life impact of systemic vasculitis from patients' perspectives. The Patient Reported Outcome Measurement Information System (PROMIS) is a collection of item banks designed to cover a broad range of self-reported health. This study assessed the feasibility and construct validity of selected PROMIS instruments in a longitudinal cohort of patients with vasculitis.

Methods: Data from a multicenter longitudinal cohort of subjects with systemic vasculitis from May 2014 to February 2015 were used. Instruments from 10 PROMIS item banks were selected (Table 1) with direct involvement of patient research partners and added to ongoing disease assessments. Each subject completed PROMIS instruments from 6 item banks. PROMIS instruments were administered using computer adaptive testing (CAT) intended to allow for a more precise estimate while minimizing burden on study subjects. The Short Form 36 (SF-36) and physician and patient global assessments for disease activity were also measured on an 11 point scale (0-10). Active disease was defined as a physician global assessment >0. Cross-sectional construct validity was assessed by calculating the correlations of PROMIS scores with the other disease measures at baseline and longitudinal construct validity was assessed by correlations of between-study visit differences in PROMIS scores with differences in other disease measures.

Results: 604 study subjects came for 899 study visits. PROMIS assessments were completed at 796 (88%) of the visits. The median

time to complete the set of PROMIS assessments was 8.7 minutes (IQR 6.1-12.1) for the total cohort, 15.2 minutes (IQR 11.9-19.2) for those older than 80, and 6.7 (IQR 4.9-9.6,)) minutes for those younger than 40. Mean PROMIS scores at baseline are shown in Table 1. PROMIS instruments correlated cross-sectionally with the individual scales of the SF-36, most strongly with subscales of the SF-36 addressing the same domain as the PROMIS instrument. Weaker correlations were observed in differences of scores longitudinally. The differences in all PROMIS scores during active disease vs. remission were in the expected direction for each domain (Table 2).

Conclusion: PROMIS measures have cross-sectional construct validity and help discriminate between active disease and remission. Inclusion of PROMIS instruments in disease assessment in vasculitis would enhance capture of patients' perspectives of disease burden and complement traditional physician-based outcome measures.

Table 1. PROMIS scores from CAT instruments across different forms of vasculitis expressed as mean (standard deviation)

	Forms of Vasculitis					
PROMIS Instrument	EGPA N=77	GCA N=119	GPA N=277	MPA N=35	PAN N=29	TAK N=67
Fatigue	54.8 (9.8)	53.7 (9.5)	54.1 (9.4)	55.7 (10.6)	56.2 (11.4)	54.9 (10.5)
Physical Function	44.9 (8.6)	41.4 (8.1)	45.2 (9.2)	42.2 (8.3)	44.6 (10.1)	44.6 (10.0)
Pain Interference*	57.3 (7.8)	57.5 (7.7)	57.9 (7.4)	53.9 (5.8)	60.9 (6.1)	60.0 (5.4)
Applied Cognitive Abilities	50.4 (9.7)	50.5 (7.5)	49.6 (7.6)	49.7 (7.6)	47.7 (10.8)	49.0 (9.7)
Sleep Disturbance	50.6 (10.3)	49.8 (11.5)	51.2 (9.1)	58.7 (8.0)	55.1 (8.2)	53.8 (10.3)
Ability to Participate Social Activities	52.3 (9.9)	49.2 (7.9)	50.4 (8.8)	46.4 (6.7)	48.3 (9.1)	48.4 (8.8)
Sleep-Related Impairment	56.9 (9.3)	50.4 (10.2)	53.6 (11.3)	51.0 (12.4)	56.5 (10.6)	51.6 (12.6)
Anger	51.7 (9.1)	48.2 (9.5)	49.8 (8.2)	49.0 (9.5)	52.8 (10.2)	49.8 (9.6)
Social Isolation	44.7 (9.2)	44.8 (8.9)	45.5 (9.8)	39.7 (6.5)	50.1 (9.2)	45.1 (10.5)
Anxiety	51.3 (8.9)	51.5 (6.7)	51.9 (9.5)	48.0 (7.4)	57.5 (16.4)	54.0 (10.1)

PROMIS = Patient Reported Outcomes Measurement Information System.
All PROMIS instruments are designed to follow a normal distribution and are calibrated to have a mean of 50 and standard deviation of 10 in the US population.
CAT = computer adaptive testing, EGPA = eosinophillic granulomatosis with polyangiitis,
GCA = giant cell arteritis, GPA = granulomatosis with polyangiitis,
MPA = microscopic polyangiitis, PAN = polyarteritis nodosa, TAK = Takayasu's arteritis.
*Only administered to those admitting to have experienced some pain.

Table 2. Differences between PROMIS instruments scores during visits at active disease (n=63) vs. remission (n=658).

PROMIS Instruments	Difference between active disease and remission
Fatigue	5.76 (3.30;8.21)
Physical function	-3.28 (-5.60;-0.95)
Pain Interference	3.00 (0.40;5.60)
Applied cognitive abilities	-3.07 (-5.17;-0.98)
Sleep disturbance	5.29 (0.90;9.67)
Social Participation	-2.10 (-6.05;1.85)
Sleep Impairment	4.00 (-0.01;8.01)
Anger	1.27 (-2.12;4.66)
Social isolation	-1.15 (-7.29;4.98)
Anxiety	0.24 (-5.54;6.02)

Positive values denote higher scores during active disease and negative values denote higher scores during remission.

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ANCA-Negative and Myeloperoxidase-ANCA-Positive Patients with Granulomatosis with Polyangiitis: Clinical Manifestations and Risk of Relapse

Eli Miloslavsky[1], Na Lu[2], Sebastian Unizony[3], Hyon K. Choi[3], Peter A. Merkel[4], Philip Seo[5], Robert F. Spiera[6], Carol A. Langford[7], Gary S. Hoffman[7], Cees Kallenberg[8], E. William St.Clair[9], Nadia Tchao[10], Fernando Fervenza[11], Paul A. Monach[12], Ulrich Specks[13] and John H. Stone[14], [1]Division of Rheumatology, Allergy and Immunology, Massachusetts General Hospital, Boston, MA, [2]Division of Rheumatology, Allergy and Immunology, Massachusetts General Hospital, Harvard Medical School, Boston, MA, [3]Rheumatology, Allergy and Immunology, Massachusetts General Hospital, Harvard Medical School, Boston, MA, [4]Penn Vasculitis Center, Division of Rheumatology, University of Pennsylvania, Philadelphia, PA, [5]Division of Rheumatology, Johns Hopkins, Baltimore, MD, [6]Rheumatology, Hospital for Special Surgery, New York, NY, [7]Rheumatology, Cleveland Clinic, Cleveland, OH, [8]Rheumatology/Clin Immunol AA21, Univer Med Center Groningen, Groningen, Netherlands, [9]Rheumatology and Immunology, Duke University, Durham, NC, [10]ITN, San Francisco, CA, [11]Mayo Clinic, Rochester, MN, [12]Rheumatology, Boston University School of Medicine, Boston, MA, [13]Division of Pulmonary and Critical Care Medicine, Mayo Clinic College of Medicine, Rochester, MN, [14]Massachusetts General Hospital

Rheumatology Unit, Harvard Medical School, Boston, MA
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Session Time: 4:30PM-6:00PM

Background/Purpose:

Recent studies in ANCA-associated vasculitis (AAV) have suggested that classification based on ANCA type (PR3 versus MPO) may represent a more clinically relevant division than the traditional disease type categorization (granulomatosis with polyangiitis [GPA] versus microscopic polyangiitis [MPA]). The differences between these two classifications are driven primarily by patients with GPA who are MPO-ANCA+ or ANCA-negative. However, little scrutiny of these patient subsets has been described in the literature. We analyzed the clinical features and treatment outcomes of MPO-ANCA+ patients with GPA and ANCA-negative patients with GPA enrolled in the Wegener's Granlomatosis Etanercept Trial (WGET) or the Rituximab in AAV (RAVE) trial.

Methods:

We performed a pooled analysis of patients enrolled in the WGET and RAVE trials. We compared both MPO-ANCA+ and ANCA-negative patients with GPA to two well-defined AAV subgroups: 1) PR3-ANCA+ patients with GPA and, 2) MPO-ANCA+ patients with MPA.

Results:

Among the 365 patients analyzed, 273 had PR3-ANCA+ GPA (75%), 33 had MPO-ANCA+ GPA (9%), 15 had ANCA-negative GPA (4%) and 44 had MPO-ANCA+ MPA (12%).

MPO-ANCA+ patients with GPA

MPO-ANCA+ patients with GPA were more often female than PR3-ANCA+ patients with GPA and were younger than MPO-ANCA+ patients with MPA (Table 1). The clinical features and frequency of granulomatous inflammation confirmed by histopathology were similar between MPO-ANCA+ GPA and PR3-ANCA+ patients with GPA. However, MPO-ANCA+ patients with GPA showed a complete absence of scleritis and endobronchial lesions though these differences did not reach significance. MPO-ANCA+ patients with GPA also differed from MPO-ANCA+ patients with MPA in having more frequent manifestations typically associated with GPA. The rate of relapsing disease at trial entry and relapse rate during the trial in patients with MPO-ANCA+ GPA was similar to that of PR3-ANCA+ GPA but higher than MPO-ANCA+ patients with MPA.

ANCA-negative patients with GPA

ANCA-negative patients with GPA were similar in age and sex distribution to PR3-ANCA+ patients with GPA but had lower BVAS/WG scores at trial entry (4.5 vs 7.7, $p<0.01$). Renal involvement was less frequent, while granulomatous features on histology and relapsing disease at trial entry were more frequent in ANCA-negative patients with GPA than their PR3-ANCA+ GPA counterparts.

Conclusion:

In this population of patients enrolled in clinical therapeutic trials of AAV, MPO-ANCA+ patients with GPA did not differ significantly from PR3-ANCA+ patients with GPA with respect to clinical manifestations or rate of relapse. ANCA-negative patients with GPA had more frequent relapsing disease at study entry than PR3-ANCA+ patients with GPA. This data adds to the debate on the contribution of ANCA type and disease type to clinical manifestations and treatment outcomes in AAV.

Table 1 – Patient characteristics and relapse rates of MPO-ANCA+ patients with GPA

	MPO-ANCA+ GPA (N=33)	PR3-ANCA+ GPA (N=273)	ANCA-negative GPA (N=15)	MPO-ANCA+ MPA (N=44)	MPO-GPA versus PR3-GPA	MPO-GPA versus MPO-MPA	ANCA-negative GPA versus PR3-GPA
Age (mean)	53	50	50	61	0.28	0.02	0.81
Male	42%	61%	33%	36%	0.04	0.59	0.03
BVAS/WG	8.2	7.7	4.5	7.2	0.36	0.16	<0.01
VDI	0.9	1.3	2.0	0.9	0.19	0.96	0.08
Clinical characteristics							
Granulomatous features on histology	14/30 (47%)	95/209 (45%)	12/14 (86%)	0/33 (0%)	0.90	<0.01	<0.01
Ear/Nose/Throat	25 (76%)	217 (79%)	11 (73%)	8 (18%)	0.62	<0.01	0.57
Bloody nasal discharge	18 (55%)	184 (67%)	10 (67%)	7 (16%)	0.14	<0.01	>0.99
Sinus involvement	13 (39%)	133 (49%)	10 (67%)	1 (2%)	0.31	<0.01	0.18
Subglottic inflammation	3 (9%)	31 (11%)	0 (0%)	0 (0%)	>0.99	0.07	0.38
Hearing loss-conductive	3 (9%)	61 (22%)	4 (27%)	0 (0%)	0.11	0.07	0.70
Mucous membranes/eyes	9 (27%)	94 (34%)	5 (33%)	6 (14%)	0.41	0.13	0.93
Conjunctivitis/episcleritis	5 (15%)	56 (21%)	3 (20%)	3 (7%)	0.47	0.66	>0.99
Uveitis	0 (0%)	3 (1%)	0 (0%)	0 (0%)	>0.99	-	>0.99
Scleritis	0 (0%)	22 (8%)	1 (7%)	1 (2%)	0.15	>0.99	>0.99
Retro-orbital mass/proptosis	2 (6%)	11 (4%)	1 (7%)	0 (0%)	0.58	0.18	0.48
Heart	0 (0%)	4 (2%)	0 (0%)	0 (0%)	>0.99	-	>0.99
Gastrointestinal tract	0 (0%)	4 (2%)	0 (0%)	1 (2%)	>0.99	>0.99	>0.99
Pulmonary	20 (61%)	170 (62%)	10 (67%)	18 (41%)	0.85	0.09	0.73
Endobronchial involvement	0 (0%)	28 (10%)	1 (7%)	0 (0%)	0.06	0.36	>0.99
Nodules or cavities	11 (33%)	92 (34%)	5 (33%)	1 (2%)	0.97	<0.01	0.98
Alveolar hemorrhage	7 (21%)	65 (24%)	1 (7%)	8 (18%)	0.83	0.74	0.20
Cutaneous	8 (24%)	66 (24%)	1 (7%)	7 (16%)	0.99	0.36	0.20
Renal	22 (67%)	170 (62%)	3 (20%)	38 (86%)	0.62	0.04	<0.01
GFR (MDRD mL/min/1.73 m^2)	56.9	66.7	76.3	47.9	0.18	0.23	0.37
Nervous System	9 (27%)	44 (16%)	2 (13%)	9 (20%)	0.11	0.48	>0.99
Sensory neuropathy	6 (18%)	36 (13%)	2 (13%)	9 (20%)	0.42	0.80	>0.99
Motor mononeuritis	3 (9%)	12 (4%)	1 (7%)	6 (14%)	0.21	0.54	0.51
Relapse rate							
Relapsing disease at trial entry	19 (58%)	156 (57%)	13 (87%)	8 (18%)	0.96	<0.01	0.02
Relapse at 6 months	8 (24%)	71 (26%)	6 (40%)	4 (9%)	0.82	0.07	0.23
Severe relapses	1 (0%)	23 (9%)	0 (0%)	2 (5%)	0.49	>0.99	0.62
Relapse at 12 months	12 (36%)	127 (47%)	8 (53%)	5 (11%)	0.12	<0.01	0.61
Severe relapses	5 (15%)	44 (17%)	1 (16%)	3 (7%)	0.89	0.28	0.48
Relapse at 18 months	15 (45%)	148 (54%)	9 (60%)	8 (18%)	0.34	<0.01	0.66
Severe relapses	7 (21%)	63 (23%)	3 (20%)	5 (9%)	0.81	0.24	0.78

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View Abstract and Citation Information Online - http://acrabstracts.org/abstract/anca-negative-and-myeloperoxidase-anca-positive-patients-with-granulomatosis-with-polyangiitis-clinical-manifestations-and-risk-of-relapse

Abstract Number: 1083

Nationwide Trends in Hospitalization and in-Hospital Mortality Associated with Granulomatosis with Polyangiitis (GPA)

Zachary Wallace[1], John H. Stone[2], Hyon K. Choi[3], Na Lu[3], Sebastian Unizony[3] and Eli Miloslavsky[4], [1]Division of Rheumatology, Allergy and Immunology, Massachusetts General Hospital, Boston, MA, [2]Massachusetts General Hospital Rheumatology Unit, Harvard Medical School, Boston, MA, [3]Rheumatology, Allergy and Immunology, Massachusetts General Hospital, Harvard Medical School, Boston, MA, [4]Division of Rheumatology, Massachusetts General Hopsital, Boston, MA

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SESSION INFORMATION

Session Date: Sunday, November 8, 2015

Session Title: Vasculitis I

Session Type: ACR Concurrent Abstract Session

Session Time: 4:30PM-6:00PM

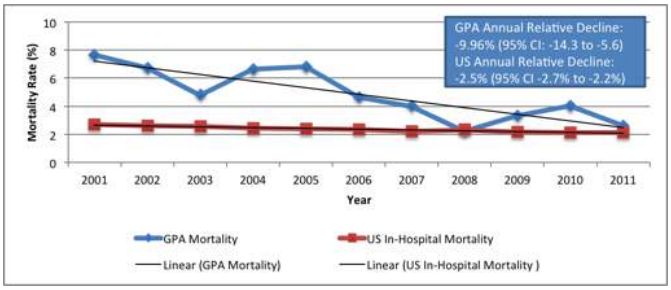
Background/Purpose: Granulomatosis with polyangiitis (GPA) is associated with severe end-organ damage (e.g., renal failure) and treatment-related complications (e.g., severe infection) which often lead to hospitalization with major resource use. However, no data on hospitalization trends and associated mortality are available. We evaluated recent trends in nationwide hospitalization and in-hospital mortality among patients with GPA.

Methods: We used the National Inpatient Survey (NIS) which is the largest all-payer inpatient database in the US and includes data and sampling weights from over 1,200 hospitals across 44 states. We studied all hospitalizations of adults (³18 years) with a primary discharge diagnosis of GPA (ICD 9: 446.4) between 2001 and 2011. We investigated trends in hospitalization and mortality by comparing GPA to overall inpatient hospitalization trends. All analyses were performed using hospital-level sampling weights provided by the NIS to obtain US national estimates.

Results: From 2001 to 2011, the rate of hospitalization for GPA remained stable from 0.76/100,000 persons to 0.78/100,000 persons. The mean age tended to get younger from 56.9 yrs to 55.1 yrs and there was a slight male predominance (40.6% +/- 3.1 vs. 50.0% +/- 2.9; P-for-trend=0.0001) over the study period. From 2001 to 2011, the mean length of stay remained stable, between 9.7 +/- 0.6 and 8.6 +/- 0.5 days (P-for-trend 0.24), but there was a significant decline in in-hospital death from 7.7% (+/-2.7%) in 2001 to 2.6% (+/-1.5%) in 2011 **(Figure 1)** (P-for-trend < 0.0001). Overall, the annual relative change in GPA mortality was -9.96% (95% CI: -14.3 to -5.6) and the annual absolute change was -0.46% (95% CI: -0.66% to -0.25%). This was a significantly greater decline than overall inpatient hospitalization mortality (annual relative change of -2.5% 95% CI -2.7% to -2.2% and annual absolute change of -0.06%, 95% CI: -0.06% to -0.05%). Among those who died during a hospitalization when GPA was the primary diagnosis in 2011, the most common secondary diagnoses were respiratory failure, chronic kidney disease, and lower respiratory disease.

Conclusion: Between 2001 and 2011, hospitalization and length of stay for GPA remained stable but in-hospital mortality declined in this dataset representative of all US hospitalizations. This decline was significantly greater than that of the background US in-hospital mortality rate. The declining in-hospital mortality rate may be due to earlier recognition of GPA, shifts in treatment that emphasize less cyclophosphamide use and more tempered use of glucocorticoids, and secular trends in the management of infections and end-organ complications.

FIGURE 1: Nationwide Trends in In-Hospital Mortality of GPA Patients



Disclosure: Z. Wallace, None; **J. H. Stone**, Roche, Genentech, 2,Genentech, 5; **H. K. Choi**, None; **N. Lu**, None; **S. Unizony**, None; **E. Miloslavsky**, Genentech Inc., 2.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/nationwide-trends-in-hospitalization-and-in-hospital-mortality-associated-with-granulomatosis-with-polyangiitis-gpa

Abstract Number: 1084

Improved Survival in Granulomatosis with Polyangiitis: A General Population-Based Study

Zachary Wallace[1], Sebastian Unizony[2], Na Lu[2], Hyon K. Choi[2] and John H. Stone[3], [1]Division of Rheumatology, Allergy and Immunology, Massachusetts General Hospital, Boston, MA, [2]Rheumatology, Allergy and Immunology, Massachusetts General Hospital, Harvard Medical School, Boston, MA, [3]Massachusetts General Hospital Rheumatology Unit, Harvard Medical School, Boston, MA
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Background/Purpose: Granulomatosis with polyangiitis (GPA) is associated with an increased risk of mortality. Advances in diagnosis and treatment strategies are thought to improve outcomes in GPA. While prior reports estimate a standardized mortality rate (SMR) of 2.1-

4.8, recent GPA mortality trends in a general population context are unknown.

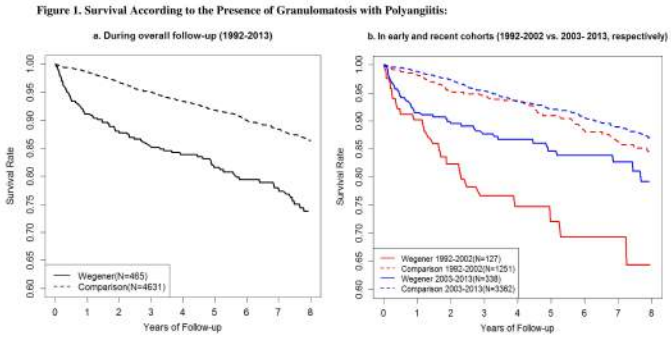
Methods: We conducted a matched-cohort study using data from an electronic medical record database representative of the UK general population, collected from 1992 to 2013. GPA was defined using Read codes for GPA. Cox proportional hazard regression models were used to estimate the hazard ratio (HR) of mortality among patients with GPA compared to sex-, age-, and entry time-matched non-GPA individuals, adjusting for lifestyle factors, comorbidities, medication use, and other potential confounders. The cohort was divided into two sub-groups based on the year of diagnosis (1992-2002 and 2003-2013) to evaluate changes in mortality with time; these time periods were chosen based on the timing of publications between 2000 to 2003 studying the safety and efficacy of different treatment strategies. We calculated the absolute rate difference using an additive hazard model for the two sub-cohort follow-ups and tested the additive interaction between GPA and time period.

Results: We identified 474 cases of GPA (average age 60.2 +/- 14.6 years; 52.1% male). The incidence rate of death (per 1000 person-years) in the GPA group was 43.5 (95% CI 35.4-52.9) compared to 19.3 (95% CI 17.6 to 21.0) in the control group, which resulted in a multivariate HR of 2.5 (95% CI 1.9-3.3). Patients with GPA were at the greatest risk of death in the first year following diagnosis. There was no apparent difference in the mortality HR between males and females and those older and younger than 65 years of age.

The early cohort (1992-2002) GPA patients had considerably higher mortality rates than the recent cohort (2003-2013) patients (72.0 vs. 35.7 cases per 1000 person-years), as compared with a moderate improvement in mortality rates in the comparison cohorts between the two periods (19.8 vs 17.0 cases per 1000 person-years, **Figure 1**). The HR for mortality was 4.34 (95%, 2.72-6.92) in the early cohort in contrast to 2.41 (95%, 1.74-3.34) in the recent cohort (p for interaction = 0.043).

Conclusion: In this large cohort representative of the UK population, we demonstrate that GPA survival has improved considerably over the past two decades. This trend is coincident with changes in management that minimized exposure to cyclosphophamide and emphasized earlier introduction of steroid-sparing agents.

Figure 1: Survival According to the Presence of Granulomatosis with Polyangiitis



Disclosure: Z. Wallace, None; **S. Unizony**, None; **N. Lu**, None; **H. K. Choi**, None; **J. H. Stone**, Roche, Genentech, 2,Genentech, 5.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/improved-survival-in-granulomatosis-with-polyangiitis-a-general-population-based-study

Abstract Number: 1085

Levamisole Triggers Neutrophil Extracellular Trap Formation through Muscarinic Receptors in Patients with Drug-Induced Vasculitis

Peter C. Grayson[1], Carmelo Carmona-Rivera[2], Meryl Waldman[3], Karran Phillips[4], Venkataraman Subramaniam[5], Paul Thompson[6], Jonathan D. Graf[7] and Mariana J. Kaplan[1], [1]National Institute of Arthritis and Musculoskeletal and Skin Diseases, National Institutes of Health, Bethesda, MD, [2]Systemic Autoimmunity Branch/ NIAMS, National Institutes of Health, Bethesda, MD, [3]NIDDK, National

Institutes of Health, Bethesda, MD, [4]NIDA, National Institutes of Health, Baltimore, MD, [5]Biochemistry and Molecular Pharmacology, University of Massachusetts, Worcester, MA, [6]Biochemistry and Molecular Pharmacology, University of Masshachussetts, Worcester, MA, [7]Rosalind Russell / Ephraim P. Engleman Rheumatology Research Center, University of California, San Francisco, San Francisco, CA
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Background/Purpose:

Levamisole, an anti-helminth drug, has been implicated in cases of drug-induced autoimmunity in humans exposed to adulterated cocaine. Clinical manifestations of levamisole-induced autoimmunity include cutaneous vasculitis and specific autoantibodies (e.g. anti neutrophil cytoplasmic antibodies, ANCA; antinuclear antibodies, ANA). Neutrophil extracellular trap (NET) formation is a novel cell death mechanism implicated in certain idiopathic autoimmune diseases. Proteins commonly found within NETs include the specific targets of ANCA and ANA. The objective of this study was to determine the role of NET formation in the pathogenesis of levamisole-induced autoimmunity.

Methods: Human and mouse neutrophils were exposed to graded concentrations of levamisole. NET formation was visualized and quantified by fluorescence microscopy. To assess the pathways involved in levamisole-induced NETosis, in some experiments the following inhibitors were added diphenylene iodonium (DPI), an inhibitor of reactive oxygen species, and Cl-amidine, an inhibitor of peptidylarginine deiminase (PAD) enzymes. Involvement of Akt and Raf-MEK-ERK kinase pathways was tested by Western blot. The role of Toll-like receptors (TLRs) and muscarinic receptors (MR) in levamisole-induced NETosis was investigated. Pharmacologic inhibitors and MR knockout mice were used to study specific MR subtypes implicated in NETosis. MR subtype receptors on neutrophils from patient samples were assessed by flow cytometry. Autoantibodies against specific NET-components were examined among cocaine users with no overt sign of autoimmune disease.

Results: Levamisole induced prominent NETs in human and murine neutrophils that contained myeloperoxidase and proteinase 3, the targets of ANCA. NET formation induced by levamisole was dependent on phosphorylation of Akt and Raf-MEK-ERK kinase pathways. DPI and Cl-amidine significantly abrogated levamisole-induced NETosis, highlighting that levamisole stimulates NETs via generation of reactive oxygen species and activation of PAD enzymes. Both levamisole and acetylcholine induced NETs through MR engagement on the surface of neutrophils and not through stimulation of TLRs. Atropine, a non-selective MR antagonist, blocked levamisole mediated NETosis. Screening experiments with pharmacologic inhibitors and neutrophils from MR knockout mice demonstrated that levamisole-induced NETosis was mediated through engagement of M3 muscarinic receptor. In a cohort of 21 patients actively using cocaine, 100% had quantifiable levamisole in urine, and sera from these patients demonstrated novel autoantibodies against NET components. In longitudinal observations, ex-vivo spontaneous NET formation correlated with periods of active cocaine use.

Conclusion: Levamisole induces NETosis through engagement of M3 muscarinic receptors on the surface of neutrophils. These findings implicate a novel interaction between the cholinergic nervous system and innate immunity in the pathogenesis of levamisole-induced autoimmunity.

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Abstract Number: 1086

Does Adding Azathioprine to Glucocorticoid Induction Increase the Remission Rate and Prevent Relapses in Patients with Systemic Necrotizing Vasculitides without Poor-Prognosis Factors? a Multicenter, Double-Blind Randomized Controlled Trial

Xavier Puéchal[1], Christian Pagnoux[2], Gabriel Baron[3], Thomas Quémeneur[4], Antoine Néel[5], Christian Agard[5], François Lifermann[6], Eric Liozon[7], Marc Ruivard[8], Pascal Godmer[9], Nicolas Limal[10], Arsène Mékinian[11], Thomas Papo[12], Anne-Marie Ruppert[13], Anne Bourgarit-Durand[14], Boris Bienvenu[15], Loïck Geffray[16], Jean-Luc Saraux[17], Elisabeth Diot[18], Bruno Crestani[12], Xavier Delbrel[19],

Laurent Sailler[20], Pascal Cohen[1], Véronique Le Guern[21], Benjamin Terrier[1], Matthieu Groh[21], Claire Le Jeunne[21], Luc Mouthon[21], Philippe Ravaud[3] and Loïc Guillevin for The French Vasculitis Study Group[21], [1]Internal Medicine, National Referral Center for Rare Systemic Autoimmune Diseases, Hôpital Cochin, Paris, France, [2]Mount Sinai Hospital, Toronto, ON, Canada, [3]Hôpital Hôtel Dieu, Paris, France, [4]CH Valenciennes, Valenciennes, France, [5]CHU Nantes, Nantes, France, [6]CH Dax, Dax, France, [7]CHU Limoges, Limoges, France, [8]CHU Clermont-Ferrand, Clermont–Ferrand, France, [9]CH Vannes, Vannes, France, [10]CHU Créteil, Créteil, France, [11]Service de médecine interne. Hôpital Saint-Antoine., Paris, France, [12]CHU Bichat, Paris, France, [13]CHU Tenon, Paris, France, [14]CHU Bondy, Bondy, France, [15]Internal Medicine, Hospital Caen, Caen, France, [16]CH Lisieux, Lisieux, France, [17]CH Eaubonne, Eaubonne, France, [18]CHU Tours, Tours, France, [19]CH Pau, Pau, France, [20]CHU Toulouse, Toulouse, France, [21]National Referral Center for Rare Systemic Autoimmune Diseases, Hôpital Cochin, AP–HP, Université Paris Descartes, Paris, France
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Background/Purpose: Glucocorticoids (GC) achieve remission in most patients with systemic necrotizing vasculitides (SNVs) without poor-prognosis factors based on the 1996 Five-Factor Score (FFS; comprising creatininemia >140 µmol/L, proteinuria >1 g/24 h, specific gastrointestinal, cardiomyopathy and CNS involvement). However, more than a third of them relapse, mainly during the first 2 years after treatment onset. This study aimed to determine whether combined GC and azathioprine (AZA) could achieve higher remission and lower relapse rates than GC alone in patients with newly diagnosed eosinophilic granulomatosis with polyangiitis (EGPA), microscopic polyangiitis (MPA) or polyarteritis nodosa (PAN), without increasing adverse events.

Methods: All patients included in this multicenter, prospective, randomized, double-blind trial received GC, initially 1 mg/kg/day, then gradually tapered over 12 months (asthmatic patients' doses were lowered as much as possible while controlling asthma symptoms) and were randomly assigned to receive concomitant 12 months of oral AZA (2 mg/kg/day, increased after 3 months to 3 mg/kg/day for insufficient responses, defined as BVAS >6, persistently elevated acute-phase reactants, eosinophilia >1x10^9/L or manifestations, with FFS always 0) or placebo. Patients were followed for another 12 months, for 24 months of follow-up. The primary endpoint was combined remission-induction failures and minor or major relapses at month (M) 24. Analyses used a modified intent-to-treat strategy and were adjusted according to the vasculitis.

Results: Among the 101 eligible patients, 95(51 EGPA, 25 MPA, 19 PAN) met the inclusion criteria and received at least 1 dose of AZA (n=46) or placebo (n=49). At endpoint, 21 (45.6%) AZA-arm patients had remission-treatment failures and/or relapses compared to 24 (49.0%) placebo recipients (odds ratio [OR], 0.96; [95% CI, 0.41–2.24]). Secondary endpoints were also comparable between arms: initial remission rate (80.4% vs. 81.6%; OR, 0.90 [0.31–2.70]) and numbers of patients with minor (26.7% vs. 25.0%) or major relapses (13.3% vs. 10.4%) (OR, 1.45 [0.61–3.44]). Two (4.1%) AZA-arm patients died (1 sudden death at M12 while in complete remission, 1 86-year-old died of congestive heart failure). Mean and cumulative GC doses and area under the curve for GC use were also comparable between arms. At least 1 serious treatment-related adverse event occurred in 8 (17.4%) AZA-arm and 3 (6.1%) placebo-arm patients (OR, 3.22 [0.69-14.29]). For EGPA patients, neither the primary endpoint nor the numbers with exacerbated asthma/rhinosinusal disease differed between arms.

Conclusion: At study M24, AZA adjunction to GC induction did not lower the absolute risk of treatment failure or relapse in patients with non-severe SNVs, compared to GC alone, had no steroid-sparing effect, and, did not reduce EGPA patients' rate of asthma/rhinosinusal disease exacerbations (*CHUSPAN2 trial was funded by French Ministry of Health PHRC P060243 and sponsored by AP–HP; ClinicalTrials.gov number, NCT00647166*).

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Abstract Number: 1087

“It Was Just My Right Pace”: A Qualitative Study Exploring Yoga Practice in Adults with Rheumatoid Arthritis

Heather Greysen, School of Nursing, University of California San Francisco, San Francisco, CA
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SESSION INFORMATION

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Background/Purpose: Physical activity is reported to improve physical function and reduce disease symptoms in adults with rheumatoid arthritis (RA); however adults with RA are less likely to participate in physical activity than adults with other chronic diseases. The dynamic mind-body physical activity of yoga may be an acceptable and beneficial way for RA adults to increase physical activity. However, little is known about how patients with RA are practicing yoga in the community and about the benefits they experience. The objective of this qualitative study was to explore yoga practice characteristics in addition to perceived benefits and facilitators of yoga practice in adults with RA.

Methods: A convenience sample of 17 adults, with rheumatologist-diagnosed RA, who had participated in yoga within the previous year, completed a semi-structured telephone interview. An interview guide was used to explore: the decision to start, continue and stop yoga; perceived benefits of yoga; importance of components of a yoga session; and general thoughts about yoga as it relates to RA. Thematic analysis was used to analyze interview transcripts.

Results: The majority of the 17 participants were white (71%), female (94%), employed full-time (53%), had mean age of 56 years, had an average disease duration of 21 years, and had bachelor’s or graduate degrees (65%). The primary style of yoga practiced was Vinyasa and Restorative/Gentle (47% combined). Four main themes were identified: (1) Facilitators, (2) Barriers, (3) Benefits, and (4) Harms of yoga practice. Facilitators included: socialization, physical fitness, and improving practice. Barriers included: finances and class mismatch. Benefits included: increased coping abilities and improved sleep, flexibility, energy, strength, balance, pain, mood, and physical function. Harms included RA flares and muscle strain injuries. There were many styles of yoga practiced and participants described various ways to adapt or change an existing yoga practice to meet the physical and emotional needs of the practitioner on any particular day. Study participant quotes illustrated how the dynamic exercise of yoga, which can be gentle with breath exercises, meditation, and relaxing stretches or can be a vigorous exercise with fast moving strenuous poses, suited their dynamic needs as a person with fluctuating symptom burden.

Conclusion: In this study RA patients described how yoga practice helped improve physical function and numerous RA disease symptoms. Yoga practice can provide many benefits for adults with RA when it is practiced at the right pace for the individual. Yoga practices vary and yoga may not be beneficial for every adult with RA, in fact it may be harmful if practiced inappropriately. Next steps include further investigating the role of the yoga teacher and the physical yoga practice environment as facilitators and barriers to practice.

Table 1. Main Themes and corresponding yoga participant quotes		
Key Theme	**SubTheme**	**Quote**
Facilitators	Desire for physical fitness	*"... I thought that it would help me stretch out and um, hopefully give me more mobility."*
	Being influenced by others	*"...the Pain Management Program, they suggested that I get into yoga"* *"...my friends said, 'why don't you give it a try'"*
	Increased benefits	*"in the beginning, my joint stuff was really bad, it was kind of hard for me to do all the poses, but as I started doing it, I did notice that there were certain poses like the triangle pose, and stuff, that, I hated at one point, but then I was able to do it, so I noticed that my flexibility did improve."*
Barriers	Financial issues	*"She recommends that I have it twice a week, but financially I just can't do that."*
	Yoga class mismatches	*"I think I would like to try yoga again but it would have to be in a therapeutic environment, meaning, I would need, probably pillows or other things that would help me to do the exercises, you know."*
Benefits	Physical and mental	*"it just helps me with my overall mobility, I just feel like I am able to move so much better...I have improvement in all of those things, pain, energy, mood…I really, really like it, I feel it's so worth it, I do enjoy it very much."* *"Well, it just made me feel better, more flexible, it made me feel, um, more calm, more better inside, stronger….it helps my mood, outlook and energy"*
	Psychosocial	*"It was, the fellowship, the people. You know, you get hear somebody else griping about their toes hurting and their elbow hurtin, and then you know, we all get in there and we start doing our exercises and stuff and then we're talking about grandkids, you know, catchin crab or salmon and we start talkin about other stuff instead of you know, whatever hurts, so that part of it is a big uplift."*
	Pride and achievement	*"I was pretty proud of myself for getting through it…when I do certain moves, I can feel pretty good about myself"*
	A tool to cope	*"I think the breathing and the meditation are a big part …it's just, when you have RA you can get a lot of negative thinking and this really helps with that…yoga is really helpful, like a tool to turn to."*
Harms	RA Flares	*"I had to stop doing yoga because of my RA. I needed something more gentle, so I do Qigong now. I actually tried yoga again recently, but it caused a flare, so I said, okay, well, I've got to stop doing that."*

Disclosure: H. Greysen, None;

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/it-was-just-my-right-pace-a-qualitative-study-exploring-yoga-practice-in-adults-with-rheumatoid-arthritis

Abstract Number: 1088

Effect of Training on Knee Torsional Stiffness and Its Relationship to Tibial Compressive and Anterior Shear Forces in Recreational Female Runners

Bhushan Thakkar[1] and D. S. Blaise Williams III[2], [1]PHYSICAL THERAPY, VIRGINIA COMMONWEALTH UNIVERSITY, RICHMOND, VA, [2]Physical Therapy, Virginia Commonwealth University, Richmond, VA

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SESSION INFORMATION

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Session Time: 4:30PM-6:00PM

Background/Purpose: 42 million Americans participate annually in running. In 2014, the half marathon was the most popular distance with a total of 61% females (1.2 million) finishing these races. Further, there has been a 2% increase annually in new female runners

completing a half marathon. Because medial knee osteoarthritis (MOA) is more prevalent among women, it is reasonable to investigate the mechanical impact of females training for a half marathon. Knee stiffness is related to leg stiffness which is significantly greater in individuals with MOA during walking. However, it is currently unknown how knee mechanics may be impacted by running and training for a half marathon distance. Therefore, the purpose of this study is to determine the relationship between shear and compressive forces and torsional stiffness at the knee with training.

Methods: A 16 week half-marathon training program was completed. Pre- and post-training analyses were completed. 3D gait analysis was performed during a 30-second treadmill run at self-selected pace. Retroreflective markers were placed on bilateral lower extremities. Kinematic data were collected at 240 Hz with a 5-camera motion analysis system. Commercial software was used to reconstruct 3-D coordinates for each marker and generate kinematic and kinetic variables. Torsional stiffness was calculated as the slope between the net joint moment and the angular displacement at the knee joint in the sagittal plane. Univariate regression analyses were calculated for stiffness and shear, stiffness and compression (pre and post). Welch 2 sample t tests were used to compare pre and post stiffness and pre and post shear.

Results: 21 female recreational runners between 33-56 years. (μ=47.6±8.1 yrs).There were significant differences found between pre and post stiffness (p= 0.03), pre and post compression (p=0.01), pre and post joint moment (p=0.04) and pre and post stride frequency (p=0.02). Regression models predicted a significant relationship between joint moment and shear (pre) ($p=<0.01, r^2=0.19$), and joint moment and compression (post) ($p=<0.01, r^2=0.44$). In addition, stride frequency was increased after training.

Conclusion:

With training, torsional stiffness at the knee increased but shear and compressive forces decreased. The change in joint moment was significant but there was no change in joint angle**.**We suggest that the joint moment changes existed due to a different position of vertical ground reaction force (VGRF) relative to the knee joint center, as there were no changes in magnitude of VGRF. This change in position is likely related to the increase in stride frequency and subsequent decrease in stride length. The modulation of knee stiffness in women may be protective against passive joint loading (sparing the compressive and shear forces) by increasing quadriceps muscle activation (active generation of force). Quantification of quadriceps muscle activity may aid in development of adjunct training programs for female runners

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Disclosure: B. Thakkar, None; **D. S. B. Williams III**, None.

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Abstract Number: 1089

Responsiveness of Physical Activity Measures Following Exercise Intervention in Individulas after Total Knee Arthroplasty

Gustavo J. Almeida[1], James J. Irrgang[2] and Sara R. Piva[1], [1]Physical Therapy, University of Pittsburgh, Pittsburgh, PA, [2]Orthopaedic Surgery, University of Pittsburgh, Pittsburgh, PA

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Background/Purpose: Few instruments that measure physical activity (PA) can accurately quantify PA performed at light and moderate intensities, which is particularly relevant to older adults with OA of the lower extremities. However, evidence of their ability to capture change over time in PA is limited. Also, responsiveness has not been compared across instruments that measure PA. Such investigation would allow for a well-educated choice of tools to assess changes in PA behavior over time. Our aim was to determine and compare the responsiveness of the Actigraph (ACT), Sensewear Armband (SWA) and Community Healthy Activities Model Program for Seniors (CHAMPS) questionnaire in assessing PA from light to moderate intensities after an exercise intervention in individuals following total knee arthroplasty (TKA).

Methods: Baseline and 6 months data on PA from subjects participating in an intervention to promote PA were analyzed. Internal (distribution based) and external (anchor based) responsiveness were assessed. Changes in duration in light and moderate intensity PA from baseline to 6 months and the standardized response mean (SRM) were calculated to assess internal responsiveness, and were compared across instruments. External responsiveness was assessed by comparing changes in PA to changes perceived by the subjects

using the global rating of change in PA that was administered at 6 months. In addition, agreement between instruments on identifying subjects who were less, the same or more active based on standard error of the measurement was performed using weighted Kappa.

Results: Thirty subjects (67±6 years old, 73% female and obese [BMI=30±4 kg/m^2]) were included in the analysis. Changes in PA measured by each instrument after the intervention were small and did not reach statistical significance (Table). SRMs indicated low degree of responsiveness (SRM < 0.30) across PA intensity levels measured by each instrument. Based on the external anchor, all subjects reported being more active after the intervention, while the distribution of the changes in PA showed that some of them were less active. Using the measurement error as a threshold for change in PA, the ACT identified 37% of subjects as less active, 33% as more active, and 30% who stayed the same. Data from SWA identified 30%, 37% and 33% respectively. Data from CHAMPS identified 40%, 37% and 23% respectively. The ACT and SWA agreed on identifying changes beyond error in moderate PA (Kappa = 0.60) and number of steps (Kappa = 0.63). There was no agreement between CHAMPS and the activity monitors (Kappa ² 0.22).

Conclusion: Distribution-based method may not be appropriate to investigate changes in PA after an intervention since there were no changes on a group basis. However, as individuals, we observed relevant changes in PA. Using the measurement error as a threshold for changes in PA may be useful since it allowed for identifying those who became more or less active after an intervention.

TABLE. Daily duration of physical activity (PA) measured by the Actigraph (ACT), Sensewear Armband (SWA) and CHAMPS questionnaire, and the magnitude of changes. Data represents means ± standard deviation, unless otherwise indicated.

N=30	PA categories	BASELINE	FOLLOW-UP	Changes in PA (95% CI)	p-value	SRM (95%CI)[à]
ACT	Light-to-moderate	81.5±44.4	75.3±47.3	-6.2±36.6 (-19.9; 7.4)	0.358	-0.17 (-0.50; 0.20)
	Light	69.6±35.1	62.4±36.2	-7.2 ±27.5 (-17.5; 3.1)	0.163	-0.26 (-0.57; 0.11)
	Moderate	11.9±13.4	12.6±16.2	0.6±14.3 (-4.7; 6.0)	0.814	0.04 (-0.33; 0.40)
	Number of Steps	4676±2151	4667±2109	9.1±1525.7 (-607.1; 625.4)	0.976	0.01 (-0.35; 0.37)
SWA	Light-to-moderate	163.6±104.7	158.6±108.3	-5.0±70.5 (-31.4; 21.3)	0.698	-0.14 (-0.48; 0.23)
	Light	119.3±77.4	117.1±88.8	-2.3±60.2 (-24.7; 20.3)	0.844	-0.08 (-0.43; 0.29)
	Moderate	44.2±37.8	41.4±36.7	-2.8±37.0 (-16.6; 11.1)	0.686	-0.12 (-0.46; 0.25)
	Number of Steps	6003±3311	5960±2995	-42.8±2266.3 (-889.1; 803.5)	0.918	-0.05 (-0.40; 0.32)
CHAMPS	Light-to-moderate	121.7±70.4	110.1±53.4	-11.6±64.6 (-35.7; 12.6)	0.335	-0.18 (-0.51; 0.19)
	Light	68.4±57.9	67.0±37.5	-1.4±46.0 (-18.5; 15.8)	0.870	-0.03 (-0.39; 0.33)
	Moderate	53.4±33.3	44.2±31.8	-9.1±46.5 (-26.5; 8.2)	0.290	-0.20 (-0.52; 0.17)

p-value from paired t test; à SRM: Standardized response mean and its respective 95% confidence intervals.

Disclosure: G. J. Almeida, None; **J. J. Irrgang**, None; **S. R. Piva**, None.

Abstract Number: 1090

Characteristics and Trajectories of Child Pain, Function, and Psychological Outcomes Associated with Conversion Disorder in Intensive Interdisciplinary Pediatric Pain Rehabilitation

Cara Hoffart[1] and Dustin Wallace[2], [1]Rheumatology and Integrative Pain Management, Children's Mercy Hospital, Kansas City, MO, [2]Integrative Pain Management and Developmental and Behavioral, Children's Mercy Hospital, Kansas City, MO

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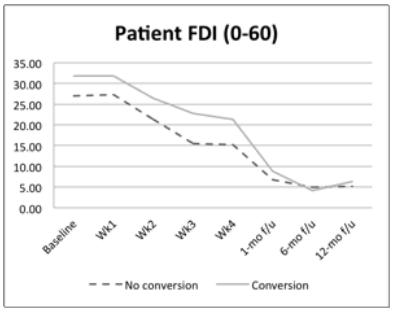
Background/Purpose: Given the degree of compromise in quality of life, there is a critical need to identify the natural history of pain and disability in association with conversion symptoms. While there is increasing recognition of comorbid conversion disorder in pediatric chronic pain, few studies investigate the effect of interdisciplinary treatment on outcomes in children with chronic musculoskeletal pain and conversion disorder. We hypothesized youth with conversion disorder would have greater pain, disability, and anxiety at baseline and throughout treatment, leading to worse function, pain, and psychological outcomes.

Methods: This outpatient program provides 5-6 hours of daily intensive PT and OT in addition to self-regulation, and behavioral health intervention. 69 participants age 11-18 (58 female) with chronic musculoskeletal pain completed Functional Disability Inventory (FDI), PROMIS anxiety, depression, and peer relationships, PRCQ-catastrophizing, CPAQ-A, and reported pain using a 100mm Visual Analog Scale (VAS 0-100) at program start, end of each week, and at 1, 6, and 12-mos follow-up. Hierarchical linear modeling (HLM) software was used to conduct time-series analyses.

Results: 19 participants (15 female) had conversion disorder. Patients with conversion had greater physical disability upon program entry (P=.02). Functional differences decreased during the program, with trends toward faster improvement among those with conversion (P=.089), and these differences resolved by follow-up. All patients significantly improved function from baseline to program end (P<.001) and continue to improve following treatment (P=.002). Similar patterns were found for peer relationships and pain acceptance. Patients with conversion had similar pain severity (M=61.5) as those without conversion (M=58.4) at baseline (P=.48) and throughout. Both groups demonstrated significant decrease in pain through follow-up (P=.001). There were no differences between groups in depression, anxiety, or catastrophizing.

Conclusion: Children with chronic pain and comorbid conversion disorder have increased disability, poorer peer relationships, and decreased pain acceptance compared to those without conversion at baseline, though differences resolve post-treatment. Patients with conversion have similar pain severity and no differences in depression, anxiety, or catastrophizing to those without conversion. Both groups demonstrate significant improvement in function, pain, and psychological outcomes post-treatment. Prospective studies are warranted to determine best practices for diagnosis and treatment of comorbid conversion symptoms in children with chronic pain.

Figure: Patient Functional Disability Inventory (FDI) demonstrates increased disability in patients with conversion at baseline (P=.02). Functional differences resolved by follow-up.



Disclosure: C. Hoffart, None; **D. Wallace**, None.

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Abstract Number: 1091

Effectiveness of Multidisciplinary Pain Rehabilitation Programs for Patients with Fibromyalgia Syndrome: A Systematic Review

Niall Halliday[1,2], Caroline Treanor[2], Rose Galvin[3] and Jason Brooks[4], [1]Medicine, Dentistry and Biomedical Sciences, Queens University Belfast, Belfast, Northern Ireland, [2]Physiotherapy, Beaumont Hospital, Dublin, Ireland, [3]Clinical Therapies, University of Limerick, Limerick, Ireland, [4]Medicine, Dentistry and Biomedical Sciences, Queens University Belfast, Belfast, Ireland
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Background/Purpose:

Fibromyalgia syndrome (FMS) is a common, chronic pain condition with complex multiple symptoms. Combinations of therapies in a multidisciplinary pain rehabilitation program (MPRP) are recommended by several international guidelines for the management of FMS. A number of primary research studies have evaluated the impact of MPRPs. However, no study has evaluated the totality of evidence regarding the effectiveness of MPRP's for FMS.

The aim of this systematic review with meta-analysis was to examine the impact of MPRP's on levels of impairment, activity limitation and participation restriction in people with FMS.

Methods:

An electronic search was conducted and included PubMed (1950 to present)

EMBASE (1980 to present), CINAHL (1982 to present), Science Direct (1985 and Databases of existing reviews such as The Cochrane Database of Systematic Reviews (*The Cochrane Library*, latest issue) The Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library*, latest issue) as well as electronic dissertation/theses databases and a grey literature search. The references of identified articles and reviews were checked, clinical trial registers and the Science Citation Index searched. Content experts were also contacted for additional or unpublished studies.

Studies were considered eligible for inclusion if they met the following inclusion criteria: *study design*; randomized controlled trials (RCTs), *population*; individuals with FMS, *intervention*; MPRP with involvement from a physician and two other health professionals, *comparison*; less intensive MPRP or no intervention, *outcomes;* impairment, activity limitation and participation restriction.

Studies were screened based on title/abstract and irrelevant studies eliminated. Two reviewers extracted the data and assessed the methodological quality of the studies using the Cochrane risk of bias tool. Finally, both a meta-analysis and a narrative synthesis were performed to evaluate the level of scientific evidence for the effectiveness of MPRP's.

Results:

After screening 11,280 abstracts, nine RCT's (1216 patients) met the inclusion criteria. The mean age of participants was 47.1 years, the mean duration FMS was 10.29 years and the population was 90.4% female. All MPRP's consisted of both a physical and a psychological intervention. Comparison groups included waiting list control with exercise, pharmacological treatment, less intensive MPRP's, and no intervention. The methodological quality of the studies was variable. A meta-analysis revealed that MPRP's are effective in the long term at reducing to pain levels ([FEM, SMD=-0.27 (95% CI -0.45, -0.10), $p<0.01$ I^2=45%]) and disease impact [FEM, MD=-6.24 (95% CI -9.32, -5.95), $p<0.01$ I^2=47%]. The narrative synthesis revealed moderate to low quality evidence in support of MPRP's FMS.

Conclusion:

These findings suggest that MPRP have a positive impact on long-term pain levels and disease impact in people with FMS. There is also

some indication that the tailoring of treatments to specific subgroups of patients may be the most effective method of delivery. Future research should be directed towards analyzing such sub-groups analysis.

Disclosure: N. Halliday, None; **C. Treanor**, None; **R. Galvin**, None; **J. Brooks**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/effectiveness-of-multidisciplinary-pain-rehabilitation-programs-for-patients-with-fibromyalgia-syndrome-a-systematic-review

Abstract Number: 1092

Illicit Drug Use in US Adults with Chronic Low Back Pain: Nhanes 2009-2010

Anna Shmagel[1] and Robert Foley[2], [1]Rheumatic & Autoimmune Diseases, University of Minnesota Medical School, Minneapolis, MN, [2]Renal Diseases and Hypertension, University of Minnesota, Minneapolis, MN

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Background/Purpose: Addictive medications, such as opiates and benzodiazepines are frequently prescribed to patients with chronic low back pain (cLBP). Little is known about illicit drug use among Americans with cLBP.

Methods: We used data from the back pain survey, administered to a representative sample of US adults aged 20-69 (N = 5103) during the 2009-2010 cycle of the National Health and Nutrition Examination Survey (NHANES). Participants who reported pain in the area between the lower posterior margin of the ribcage and the horizontal gluteal fold at the time of survey with a history of pain lasting almost every day for at least 3 months were classified as having cLBP (N = 700). The drug use questionnaire included data on lifetime and current use of marijuana or hashish, cocaine, heroin, and methamphetamine. Questions were self-administered in a private room using the Audio Computer-Assisted Self-Interviewing system. Chi-square tests, analysis of variance and logistic regression models, adjusted for age, gender, race and level of education, were used for comparisons.

Results: US adults with cLBP were older, less educated, and more often Caucasian than those without cLBP. They had higher odds of unemployment, poverty, and depression. 46.5% of US adults with cLBP used marijuana vs 42% of those without cLBP (aOR 1.36, 95% CI 1.06-1.74, p=0.016). 22% vs 14% used cocaine (aOR 1.85, 95% CI 1.47-2.34, p<0.0001), 9% vs 5% used methamphetamine (aOR 2.03, 95% CI 1.30-3.16, p=0.002), and 5% vs 2% used heroin (aOR 2.43, 95% CI 1.44-4.11, p=0.001).

Conclusion: Community-based US adults with chronic low back pain had higher odds of using marijuana, cocaine, heroin, and methamphetamine than the general population. Particular caution should be exercised when prescribing medications with abuse potential to cLBP patients.

Disclosure: A. Shmagel, None; **R. Foley**, None.

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Abstract Number: 1093

Activation of Syk-Btk Signal in Peripheral Blood B Cells in Patients with Rheumatoid Arthritis: A Potential Target for Abatacept Therapy

Shigeru Iwata[1], Shingo Nakayamada[2], Shunsuke Fukuyo[1], Sheau-Pey Wang[1], Satoshi Kubo[2], Maiko Yoshikawa[1], Kazuyoshi Saito[3] and Yoshiya Tanaka[3], [1]The First Department of Internal Medicine, University of Occupational and Environmental Health, Japan, Kitakyushu, Japan, [2]First Department of Internal Medicine, University of Occupational and Environmental Health, Japan, Kitakyushu, Japan, [3]The First Department of Internal Medicine, University of Occupational and Environmental Health, Kitakyushu, Japan

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SESSION INFORMATION

Session Date: Monday, November 9, 2015

Session Title: B cell Biology and Targets in Rheumatolid Arthritis and other Autoimmune Disease Poster

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: B cells play a pivotal role in the pathogenesis of autoimmune diseases. Although Syk function as a key molecule in BCR signaling, the pathological role of Syk in B cells in RA remains unclear. The purpose of this study was to assess the relevance of activation of Syk in B cells to RA pathology and responsiveness to treatment with biologics.

Methods: Healthy subjects (n=36) and patients with moderate or severe RA disease activity (n=70) were studied. The phosphorylation of Syk in peripheral blood B cells was measured by flow cytometry, and the correlation with clinical characteristics and changes after administration of biological products were evaluated.

Results: Syk phosphorylation in B cells was significantly higher in RA patients compared with the control (p-Syk-positive $CD19^+$ B cells (%): control, 11.9±8.2; RA, 27.7±23.2, p=0.0019). The expression levels of p-Syk in all different treatment groups of RA patients were significantly higher than the control (control; 10.7±1.3%, treatment-naïve RA (n=12); 21.6±7.7%, MTX-treated (n=36); 24.8±3.3%, MTX+biologics-treated (n=9); 30.8±10.0%, p=0.0036). Although Btk is well-known as downstream of Syk, Btk phosphorylation in B cells was also higher in patients with RA compared with the control (mean MFI of p-Btk in $CD19^+$ B cells: control, 144±73.4; RA, 224±171, p=0.031). Syk phosphorylation was significantly higher in B cells of patients strongly positive for ACPA (p-Syk-staining among $CD19^+$ B cells (%): negative for ACPA, 22.2±24.9; positive, 19.5±21.5; strongly positive, 32.6±23.5; p=0.0335), but not correlated with indexes of RA disease activity, such as tender joints, swollen joints, CRP, ESR, MMP-3, DAS28-CRP, DAS28-ESR, CDAI, and SDAI. Autoantibody production by B cells requires the involvement of T cells and abatacept can inhibit T cell activation. Based on this background, we hypothesized that abatacept inhibits Syk phosphorylation in B cells. Interestingly, the rate p-Syk-positive cells among $CD19^+$ B cells diminished from 21.4±30.9 to 3.3±3.8 (from week 0 to week 24, p=0.0341) in the abatacept group, and from 30.0±23.1 to 42.0±34.8 (p=0.1255) in the TNF inhibitors group. Although Th1 cells ($CD4^+CXCR3^+$ cells) were not changed, abatacept significantly reduced the proportion of Tfh cells ($CD4^+CXCR5^+PD\text{-}1^+$ cells) from 5.7±5.7 at week 0 to 3.4±4.7 % at week 4 (p=0.0206).

Conclusion: Our results demonstrated that significantly high levels of Syk phosphorylation in B cells were strongly related to ACPA in RA patients. Our data suggested that abatacept seems to inhibit Syk-Btk signal in B cells as well as development of T follicular helper cells, highlighting the relevance of B-T cell interaction as a potential target of abatacept therapy in RA.

Disclosure: S. Iwata, None; **S. Nakayamada**, None; **S. Fukuyo**, None; **S. P. Wang**, None; **S. Kubo**, None; **M. Yoshikawa**, None; **K. Saito**, None; **Y. Tanaka**, Mitsubishi-Tanabe, Eisai, Chugai, Abbott Japan, Astellas, Daiichi-Sankyo, Abbvie, Janssen, Pfizer, Takeda, Astra-Zeneca, Eli Lilly Japan, GlaxoSmithKline, Quintiles, MSD, Asahi-Kasei, 5,Bristol-Myers, Mitsubishi-Tanabe, Abbvie, MSD, Chugai, Astellas, and Daiichi-Sankyo, 2.

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Abstract Number: 1094

Increased IgA Plasmablasts Are Associated with Rheumatoid Arthritis-Related Autoantibodies in the Absence of Inflammatory Arthritis

Jennifer Kinslow[1], Lisa Blum[2], Kevin D. Deane[3], Kristen Demoruelle[4], Mark C. Parish[5], Sarah Kongpachith[6], Lauren J. Lahey[7], Jill M. Norris[8,9], William H. Robinson[10] and V. Michael Holers[11], [1]Rheumatology, University of Colorado, Aurora, CO, [2]Stanford University, Palo Alto, CA, [3]Division of Rheumatology, U Colo Denver, Aurora, CO, [4]Division of Rheumatology, University of Colorado School of Medicine, Aurora, CO, [5]Rheumatology, University of Colorado Anschutz Medical Campus, Aurora, CO, [6]Medicine, Division of Immunology and Rheumatology, Stanford University School of Medicine, Stanford, CA, [7]Medicine, VA Palo Alto HealthCare System and Stanford University, Palo Alto, CA, [8]University of Colorado Denver, Aurora, CO, [9]Epidemiology, Colorado School of Public Health, Aurora, CO, [10]Division of Immunology and Rheumatology, Stanford University School of Medicine, Stanford, CA, [11]Rheumatology Division, Univ of Colorado School of Med, Aurora, CO

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Session Type: ACR Poster Session B
Session Time: 9:00AM-11:00AM

Background/Purpose: Rheumatoid Arthritis (RA) autoimmunity starts years before clinically apparent inflammatory arthritis (IA) develops, and elevated disease-specific autoantibodies, including anti-citrullinated protein antibodies (ACPA) and rheumatoid factor (RF), can be detected in this period. Early responses to known and/or novel autoantigens likely drive the eventual production of pathogenic autoantibodies. We hypothesized that through characterization of circulating plasmablasts one can identify the specific antigens to which early tolerance has been broken in at-risk individuals who exhibit autoantibodies associated with future RA onset but who are currently without IA.

Methods: We have investigated the antibody-secreting plasmablasts of a characterized cohort of seropositive (Ab+) individuals (ACPA and/or RF) in comparison to seronegative (Ab-) individuals, patients recently diagnosed seropositive RA (<1 yr), and healthy controls. Plasmablasts were identified by flow cytometric analysis and defined as CD19+CD3-CD33-CD14-CD20-CD27+CD38^{hi}. As IgG-producing plasmablasts have low surface BCR expression, 'IgG+' cells were identified by the absence of IgA and IgM staining, while IgA+ plasmablasts were identified by IgM-IgA+ surface staining. The antibody repertoires of at-risk subjects were analyzed using a DNA barcode-based method of paired heavy- and light-chain gene sequencing. Cells were single-cell sorted into 96-well plates prior to adding cell-specific DNA barcodes by template switching during reverse transcription, followed by adding plate-specific DNA barcodes by PCR. Samples underwent Roche 454 sequencing or 2 x 300 MiSeq analysis. Data were demultiplexed using a custom software pipeline to separate reads from each single cell according to its unique compound (plate + well) barcode ID. The isotype of sorted cells was confirmed by gene-specific PCR and by identification of isotype-specific sequences in the final data.

Results: Total plasmablast levels were not elevated in Ab+ individuals (1%) compared to controls (0.4-1.6%). However, fitting with prior studies supporting a potential role for mucosal immune responses in RA initiation in the preclinical period, we observed markedly increased frequencies of IgA+ vs. IgG+ plasmablasts in Ab+ individuals (39% IgA+, 37% IgG+ plasmablasts) as compared to all other groups (1-9% IgA+, 71-87% IgG+ plasmablasts). Furthermore, sequencing of paired antibody heavy and light chains from Ab+ subjects revealed the presence of cross-isotype clonal families as well as similar sequence characteristics between the IgA and IgG plasmablast repertoires of seropositive subjects.

Conclusion: The IgA plasmablast dominance in these Ab+ individuals suggests that a subset of antibodies may arise from both systemic as well as mucosal immune responses which may drive clinical disease development in individuals who are at-risk for developing RA. We intend to identify and characterize antigens to which these dual isotype antibodies react with the immediate goal of identifying known and novel autoantigens, and a potential future goal of using tolerizing therapies to these autoantigens that could be effective in prevention or early treatment strategies.

Disclosure: J. Kinslow, None; **L. Blum**, None; **K. D. Deane**, None; **K. Demoruelle**, None; **M. C. Parish**, None; **S. Kongpachith**, None; **L. J. Lahey**, None; **J. M. Norris**, None; **W. H. Robinson**, Atreca, Inc, 5,Atreca, Inc, 4; **V. M. Holers**, Shared patent with Stanford University for use of biomarkers to predict clinical phenotypes in rheumatoid arthritis., 7.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/increased-iga-plasmablasts-are-associated-with-rheumatoid-arthritis-related-autoantibodies-in-the-absence-of-inflammatory-arthritis

Abstract Number: 1095

Identification of Carbamylated Alpha-1-Anti-Trypsin (A1AT) As an Antigenic Target of Anti-Carp Antibodies in Patients with Rheumatoid Arthritis

Marije K. Verheul[1], Alvin Yea[2], Andrea Seaman[2], Robert A. Cordfunke[3], Jan W. Drijfhout[4], George M. Janssen[4], Arnoud de Ru[3], Peter A. van Veelen[4], René E. M. Toes[5], Michael Mahler[2] and **Leendert A. Trouw**[1], [1]Department of Rheumatology, Leiden University Medical Center, Leiden, Netherlands, [2]Inova Diagnostics, San Diego, CA, [3]IHB, Leiden University Medical Center, Leiden, Netherlands, [4]Immunohematology and Bloodbank, Leiden University Medical Center, Leiden, Netherlands, [5]Leiden University Medical Center, Leiden, Netherlands

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Session Time: 9:00AM-11:00AM

Background/Purpose:

Antibodies targeting carbamylated proteins (anti-CarP) were recently identified in serum samples from patients with rheumatoid arthritis (RA). The presence of anti-CarP antibodies was associated with a more severe disease course in RA patients and correlated with the development of RA in arthralgia patients and healthy blood donors. It may therefore serve as a new biomarker in the management of early RA. Carbamylated-fetal calf serum (Ca-FCS), a complex mixture of proteins, is currently used in ELISA to identify anti-CarP antibodies. It is not yet clear which of the proteins in Ca-FCS are responsible for the reactivity of the anti-CarP antibodies. Therefore, we set out to investigate which protein(s) within the Ca-FCS mixture may function as an antigen for anti-CarP antibodies. This might serve as a method to optimize the ELISA, using a known and consistent antigen and may provide novel insights in the pathophysiological mechanisms of anti-CarP antibodies.

Methods:

Ca-FCS was fractionated using anion-exchange chromatography. Fractions containing sufficiently high protein concentrations were coated onto ELISA plates and used for the detection of anti-CarP antibodies. Fractions containing a high anti-CarP antibody binding capacity and low protein content were selected and analysed by SDS-PAGE gel-electrophoresis. Coomassie stained bands were excised and analysed by mass-spectroscopy. Human A1AT was obtained from commercial sources, carbamylated and used in ELISA. Receiver operating characteristic (ROC) analysis was used to analyse the discriminatory power of different assays.

Results:

We observed high anti-CarP binding capacity in several fractions obtained after fractionation of Ca-FCS using anion-exchange chromatography. The fraction with the best signal (ELISA) to protein concentration ratio was further separated by SDS-PAGE gel-electrophoresis, proteins bands were excised and analysed by mass-spectrometry. The most promising band was identified as bovine alpha 1 anti-trypsin (A1AT). Purified human A1AT from commercial sources was *in-vitro* carbamylated and used as antigen to coat ELISA plates. In sera of RA patients, we found a strong reactivity towards Ca-A1AT and only limited reactivity against non-modified A1AT. We detected anti-CarP antibodies directed against Ca-A1AT in around 45% of the ACPA positive RA patients. Importantly, as for the anti-CarP FCS assay, we observed around 14% anti-Ca-A1AT positive patients in the ACPA negative stratum. Using ROC analyses comparing RA patients to healthy controls we observed for anti-Ca-A1AT an AUC of 0.72 (0.65-0.78) as compared to an AUC of 0.69 (0.63-0.76) for anti-Ca FCS. We observed a good quantitative correlation between anti-Ca-FCS and anti-Ca-A1AT reactivity of anti-CarP antibodies (r=0.76 (0.67-0.86)), making A1AT a suitable new antigen for the detection of anti-CarP antibodies.

Conclusion:

Carbamylated-A1AT is a promising antigenic target of anti-CarP antibodies as an aid in the diagnosis of RA.

Disclosure: M. K. Verheul, None; **A. Yea**, Employee of Inova Diagnostsics, 3; **A. Seaman**, Employee of Inova Diagnostics, 3; **R. A. Cordfunke**, None; **J. W. Drijfhout**, Received a research grant from Inova Diagnostics, 2; **G. M. Janssen**, None; **A. de Ru**, None; **P. A. van Veelen**, Recieved a research grant from Inova Diagnostics, 2; **R. E. M. Toes**, Received a grant from Inova Diagnostics, 2; **M. Mahler**, Employee of Inova Diagnostics, 3; **L. A. Trouw**, Received a reasearch grant from Inova Diagnostics, 2.

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Abstract Number: 1096

B Cells Are Prime Producers of Tumor Necrosis Factor Alpha in Rheumatoid Arthritis

Victor Wang[1], Nida Meednu[1], Wen Sun[2], Javier Rangel-Moreno[3], Lianping Xing[2] and Jennifer H. Anolik[1], [1]Medicine- Allergy, Immunology and Rheumatology, University of Rochester Medical Center, Rochester, NY, [2]Pathology & Lab Medicine, University of Rochester Medical Center, Rochester, NY, [3]Medicine- Allergy, Immunology, and Rheumatology, University of Rochester Medical Center, Rochester, NY

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Background/Purpose: Rheumatoid arthritis (RA) is a systemic autoimmune disease, which causes joint inflammation and bone loss. Inflammation-mediated joint damage is linked to the imbalance of bone-resorbing osteoclast (OC) and bone-depositing osteoblast (OB) activity. Pro-inflammatory cytokines present in the synovium have been shown to directly or indirectly stimulate OC differentiation. Although the effect of T cell, macrophage and synoviocyte-derived cytokines on bone resorption is well characterized, less is known about the impact of B cell-derived cytokines. Tumor necrosis factor α (TNFα) is a pro-inflammatory cytokine that promotes osteoclastogenesis and inhibits OB differentiation. In this study, we examined TNFα expression by B cells in RA patients and healthy controls.

Methods: PBMCs were isolated from peripheral blood of healthy controls (HC) or RA patients (n=6 each) by Ficoll-Hypaque density gradient centrifugation. RA patients fulfilled 1987 American College of Rheumatology diagnostic criteria and were CCP+. B cells were isolated by CD19+ magnetic bead selection from peripheral blood and stimulated with α-Igs (α-IgA, α-IgG, and α-IgM) and CpG2006 for 4 or 24 hours. TNFα production was measured by qPCR, flow cytometry, and ELISA. Statistical significance was determined by Mann-Whitney test. B cell populations were categorized based on the differential expression of CD27 and IgD, as naïve (CD19+CD27-IgD+), double negative (CD19+CD27-IgD-), unswitched (CD19+CD27+IgD+) and switched memory B cells (CD19+CD27+IgD-). RA synovial biopsies were immuno-stained with antibodies against CD20, CD27 and TNF.

Results: Short-term stimulation of healthy control (HC) B cells with α-Igs and CpG2006 (4 hours) induced significant production of TNFα compared to unstimulated B cells at both the mRNA (64.4±8.2 fold, $P<0.001$) and secreted protein level (ng/uL TNFα: 2.86±0.60 vs. 0.0124±0.0047, $P<0.02$) at 4 hours. At 24 hours, the secreted protein level did not further increase (ng/uL TNFα: 3.032±.40 for stimulated vs. 0.0078±0.0023 for unstimulated, $P<0.005$), and the mRNA levels were actually lower (9.1 fold over unstimulated control), suggesting the mRNA concentration peaks closer to the 4 hour time point. There was no statistically significant difference in TNFα production by HC vs. RA B cells at the mRNA (64.4±8.2 fold in HC vs 52.4±14.5 fold in RA, n=6) or protein level at 4 hours (ng/uL TNFα: 2.86±0.60 in HC vs 2.23±0.84 in RA, n=5) or 24 hours (ng/uL TNFα: 3.032±0.40 in HC vs 2.66±0.69 in RA, n=6). The synovium was enriched for memory B cells (CD27+IgD- memory 55.15±10.41 vs naïve 8.47±2.64, n=7, $P<0.001$) expressing TNFα on immuno-staining. In agreement with memory B cells being the prime producers of TNFα, preliminary data indicates that peripheral blood memory B cells have an increased propensity to produce TNFα under stimulation compared to the double negative or naïve B cell subsets (%TNFα+: 17.1 vs 8.4 and 1.2, respectively).

Conclusion: Our results suggest that TNF- producing memory B cells are enriched in the RA synovial microenvironment, potentially stimulating OC production/activity and thus enhancing bone erosion.

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Disclosure: V. Wang, None; **N. Meednu**, None; **W. Sun**, None; **J. Rangel-Moreno**, None; **L. Xing**, None; **J. H. Anolik**, None.

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Abstract Number: 1097

Pre-Clinical Development of a Novel, Potent and Selective BTK Inhibitor for Autoimmune Disease and Inflammation Including Arthritis

Stephen Morris, Alain Laurent, Lori Jerome, Alain Boudreault, Helen Ashdown, Yannick Rose, Patrick Bureau, Shou-Yun Yin, Patrick Cleroux, Delphine Labit, Nicholas Henry, Marie-Noelle Tremblay, Marlyna Guerard, Emilie Dumas Bérubé and Kosta Spathis, Pharmascience Inc., Ville St-Laurent, QC, Canada

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Background/Purpose: Bruton's tyrosine kinase (BTK) is an important component of B cell and Fc receptor signaling and has been shown to be critical for B-cell proliferation and differentiation. Expression of BTK in cell types that are dysregulated or which play a pathological role in arthritis suggests that inhibition of BTK may be therapeutically advantageous in the treatment of rheumatoid arthritis. For use in chronic disease settings such as arthritis highly specific inhibitors are desired. However, the ATP binding site of kinases is highly conserved and it is often difficult to design competitive inhibitors exhibiting a high degree of selectivity. One approach taken by our group and others to develop highly specific BTK inhibitors is to target a cysteine residue immediately outside the ATP binding pocket. Unfortunately, the position of this cysteine is conserved in 11 kinases within the human kinome including, for example, EGFR.

Consequently many BTK inhibitors also inhibit those cysteine-containing kinases.

Methods: A novel and selective BTK inhibitor was identified using in vitro kinase assays. The compound was further characterized using in vitro ADME assays and cellular assays. In vivo efficacy was monitored using the collagen-induced arthritis model in B10 mice.

Results: We report here the characterization of AEG42766, a highly potent and selective BTK inhibitor with an apparent IC50 of 8nM against purified BTK and no significant activity against EGFR. AEG42766 inhibits IgM-mediated proliferation of murine splenocytes and purified human B cells with EC50s of 0.8nM and 0.4nM, respectively. AEG42766 shows good stability in human liver microsomes. In vivo PO administration in mice indicates oral bioavailability of >25% and results in robust, long duration inhibition of BTK. Consistent with profound inhibition of BTK, in vivo pharmacology studies demonstrate that AEG42766 is active in models of reverse passive anaphylaxis and collagen-induced arthritis.

Conclusion: AEG42766 is a highly potent BTK inhibitor suitable for further development as a candidate to treat rheumatoid arthritis and other diseases.

Disclosure: S. Morris, Pharmascience Inc., 3; **A. Laurent**, Pharmascience Inc., 3; **L. Jerome**, Pharmascience Inc., 3; **A. Boudreault**, Pharmascience Inc., 3; **H. Ashdown**, Pharmascience Inc., 3; **Y. Rose**, Pharmascience Inc., 3; **P. Bureau**, Pharmascience Inc., 3; **S. Y. Yin**, Pharmascience Inc., 3; **P. Cleroux**, Pharmascience Inc., 3; **D. Labit**, Pharmascience Inc., 3; **N. Henry**, Pharmascience Inc., 3; **M. N. Tremblay**, Pharmascience Inc., 3; **M. Guerard**, Pharmascience Inc., 3; **E. Dumas Bérubé**, Pharmascience Inc., 3; **K. Spathis**, Pharmascience Inc., 3.

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Abstract Number: 1098

Interleukin-1 Reciprocally Regulates Interferon-Gamma Induced B Cell Activating Factor of the Tumor Necrosis Factor Family (BAFF) and Interleukin-6 in Human Synovial Fibroblasts

Georg Pongratz[1], Rainer Straub[2] and Torsten Lowin[3], [1]Rheumatology - Hiller Research Center Rheumatology, University Hospital Düsseldorf, Düsseldorf, Germany, [2]Laboratory of Experimental Rheumatology and Neuroendocrine Immunology, Department of Internal Medicine, University Hospital Regensburg, Regensburg, Germany, [3]Internal Medicine I, University Hospital Regensburg, Regensburg, Germany

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Background/Purpose: B cell activating factor of the tumor necrosis factor family (BAFF) and interleukin-6 (IL-6) are cytokines important for the stimulation and survival of autoreactive B cells and plasma cells, respectively, and play a role in several autoimmune diseases, e.g. autoimmune arthritis. It is known that synovial fibroblasts (SFs) are capable of producing BAFF and IL-6 and therefore provide survival signals to autoreactive B cells and plasma cells in the joint. Therefore, we wanted to better characterize inflammatory stimuli that modulate BAFF and IL-6 in SFs.

Methods: Fibroblasts isolated from synovial tissue of RA (n=10) and OA (n=10) patients were cultured in the presence or absence of different stimuli (interferon (IFN)g and interleukin (IL)-1). BAFF was determined by ELISA. Levels of phosphorylated and total STAT1 and STAT3 were determined by western blotting.

Results: IFN in a concentration-dependent manner induced BAFF and IL-6 in RA and OA fibroblasts. Since inflammation usually leads to hypoxic conditions, we also compared IFN-g-induced cytokine production in RA and OA SFs under normoxic and hypoxic (oxygen content 2%) culture conditions. IFN-induced BAFF was augmented in OA ($p<0.001$) and RA ($p<0.01$) SFs under hypoxic conditions, whereas there was no oxygen dependency of IFN-induced IL-6. IFN leads to a strong phosphorylation of STAT1 but to a reduction in phosphorylated STAT3 in RA and OA SFs. However, it has been suggested that concomitant phosphorylation of STAT3 further augments BAFF production. Therefore, we wanted to test if concomitant IL-1, which leads to phosphorylation of STAT3, further increases IFN-induced BAFF and/or IL-6 in SFs. However, in the presence of IL-1, INF-induced BAFF was inhibited ($p>0.001$), whereas IFN-induced

IL-6 was increased ($p<0.001$) in a concentration dependent manner independent of oxygen content in both, OA and RA fibroblasts. Furthermore, inhibition of pSTAT3 resulted in further augmentation of IFN-induced BAFF ($p=0.003$) and decrease of IFN-induced IL-6 ($p=0.04$).

Conclusion: Taken together, BAFF and IL-6 production in synovial fibroblasts are induced by IFN and reciprocally regulated by IL-1 in a STAT3 dependent manner. In contrast to IL-6, IFN-induced BAFF can be further augmented by hypoxia. These results give further insight in local regulation of the microenvironment provided for B cells in the arthritic joint.

Disclosure: G. Pongratz, None; **R. Straub**, None; **T. Lowin**, None.

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Abstract Number: 1099

Single Cell RNA-Seq Analysis of Citrullinated Alpha-Enolase Peptide-Specific B Cells in RA

Yogita Ghodke-Puranik[1], Na Zhang[2], Jessica M. Dorschner[1], Anna Shmagel[3], Zhongbo Jin[1], Philip Titcombe[4], Timothy B. Niewold[1] and **Daniel Mueller**[5], [1]Division of Rheumatology and Department of Immunology, Mayo Clinic, Rochester, MN, [2]Medicine, University of Minnesota Medical School, Minneapolis, MN, [3]Rheumatic & Autoimmune Diseases, University of Minnesota Medical School, Minneapolis, MN, [4]University of Minnesota Medical School, Minneapolis, MN, [5]Medicine/Rheumatic & Autoimmune Diseases, University of Minnesota Medical School, Minneapolis, MN

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Background/Purpose:

The high prevalence of citrullinated protein antibodies and improvement following rituximab anti-CD20 therapy both suggest that B cells are important in the pathogenesis of RA. Nonetheless, this has been difficult to study due of the rarity of citrullinated protein-specific B cells and the lack of tools to physically isolate them. We recently developed citrullinated alpha-enolase peptide tetramer technology to identify and capture autoreactive blood B cells in RA, and now report the first whole transcriptome analysis of these autoreactive B cells.

Methods:

A female CCP+/RF+ RA patient previously shown to produce IgG against the citrullinated alpha-enolase peptide CEP-1 (CKIHA-X-EIFDS-X-GNPTVEC, where X represents citrulline) donated 60 ml of blood for further investigation (U. of Minnesota IRB Code Number: 9712M00072). CEP-1 peptide-specific B cells were then captured from PBMC using anti-phycoerythrin Miltenyi beads and a combination of CEP-1 [peptide-streptavidin-phycoerythrin] and native alpha-enolase EP-1 (CKIHAREIFDSRGNPTVEC) [peptide-streptavidin-phycoerythrin-AF647] decoy tetramers, as previously described in Taylor JJ et al., J Exp Med. 2012 Oct 22;209(11):2065-77. Both autoreactive CEP-1 tetramer- and control EP-1 tetramer-bound B cell fractions were purified by FACSAria flow cytometry, differentially stained, mixed, and loaded into a Fluidigm C1 small-cell chip. The Fluidigm C1 autoprep system was used for single cell capture and RNA from each cell was converted to cDNA. Barcoded cDNA libraries were sequenced on an Illumina Hi-Seq sequencer. Differential gene expression between autoreactive CEP-1 peptide-specific B cells and decoy tetramer-bound control B cells was analyzed using Omics office software embedded in Tibco Spotfire version 6.5.2. False discovery rate (FDR) was controlled at 0.05 using the Benjamini-Hochberg procedure, and gene lists were analyzed using Ingenuity Pathway Analysis (IPA) software to detect significantly over-represented canonical pathways.

Results:

We found 119 genes which were differentially expressed between the captured autoreactive CEP-1 peptide-specific B cells and decoy EP-1 peptide tetramer-specific sorted B cells which withstood FDR correction ($q<0.05$). Of these, only one transcript was down-regulated in autoreactive cells (IFI44L), whereas all the other 118 transcripts were up-regulated. Transcripts that were up-regulated in the autoreactive cells included genes involved in B cell receptor and calcium signaling (CALM2), B cell activation, differentiation and transmembrane signaling (CD53), and cell cycle progression (CDKN2D). Using Ingenuity Pathways Analysis, 38 of 115 mapped genes were found to be

involved with cellular proliferation (p = 0.004). Other over-represented canonical pathways included protein ubiquitination and integrin signaling.

Conclusion:

In an RA patient demonstrating serological reactivity to citrullinated alpha-enolase, a CEP-1 peptide tetramer allowed for the capture of autoreactive B cells that demonstrated an activated and proliferative gene expression signature. These results illustrate that novel analytic approaches can now be applied to isolated autoreactive RA B cells.

Disclosure: Y. Ghodke-Puranik, None; **N. Zhang**, None; **J. M. Dorschner**, None; **A. Shmagel**, None; **Z. Jin**, None; **P. Titcombe**, None; **T. B. Niewold**, None; **D. Mueller**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/single-cell-rna-seq-analysis-of-citrullinated-alpha-enolase-peptide-specific-b-cells-in-ra

Abstract Number: 1100

Citrullinated Antigen-Specific B Cells in Peripheral Blood and Synovial Fluid of Patients with Rheumatoid Arthritis: Identification and Phenotypic Characterization

Priscilla Kerkman[1], Ellen I.H. van der Voort[1], Arnaud Zaldumbide[2], Emeline Fabre[1], Yoann Rombouts[1], Theo Rispens[3], Gertjan Wolbink[4], Rob Hoeben[2], Hergen Spits[5], Dominique Baeten[6], T. W. J. Huizinga[1], René E. M. Toes[1] and **Hans Ulrich Scherer**[1], [1]Department of Rheumatology, Leiden University Medical Center, Leiden, Netherlands, [2]Department of Molecular Cell Biology, Leiden University Medical Center, Leiden, Netherlands, [3]Sanquin Research, Amsterdam, Netherlands, [4]Immunopathology, Sanquin Research, Amsterdam, Netherlands, [5]Department of Cell Biology and Histology, Amsterdam Rheumatology and Immunology Center, Amsterdam, Netherlands, [6]Amsterdam Rheumatology and Immunology Center, Amsterdam, Netherlands
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Background/Purpose: Rheumatoid arthritis (RA) is characterized by the presence of anti-citrullinated protein antibodies (ACPA) in the majority of patients. ACPA represent highly disease-specific biomarkers that predict disease onset in patients with arthralgia. Experimental data suggest that ACPA could be involved in disease pathogenesis. Of interest, however, depletion of $CD20^{+}$B cells is effective in reducing disease activity, while ACPA serum titres remain rather stable. Also, interference with plasma cell development seems clinically ineffective. Therefore, we hypothesized that ACPA could be surrogate markers for a (potentially pathogenic) auto-reactive B cell response and set out to identify citrullinated antigen-specific B cells in peripheral blood and synovial fluid of patients with RA.

Methods: We generated differentially labelled streptavidin and extravidin tetramers conjugated to biotinylated CCP2 or control antigens to identify citrullinated antigen-specific B cells in peripheral blood and synovial fluid by flow cytometry. Blocking and fluorescence activated cell sorting experiments followed by in-vitro stimulation and culture were used to confirm specificity of the staining approach. Cells were further phenotypically characterized by flow cytometry.

Results: The combination of differentially labelled CCP2 and control tetramers allowed the successful separation of ACPA-expressing B cells from non-specific background signals. Tetramer-positive B cells, but not tetramer-negative cells, produced large amounts of ACPA upon stimulation. Interestingly, phenotypic analysis revealed that citrullinated antigen-specific B cells are mainly class-switched, post-germinal centre memory B cells and plasma blasts/cells expressing IgG or IgA. Only few cells exhibited a naïve phenotype. We observed a remarkably high frequency of memory B cells (up to 1 in 500) in peripheral blood, which correlated with ACPA serum titres and spontaneous ACPA production in culture.

Conclusion: We developed a novel technology that identifies ACPA-expressing B cells in peripheral blood and synovial fluid of patients with RA, providing the basis for a detailed characterisation of this immune response on a single cell level. First analyses show the presence of a high frequency of memory B cells, which is remarkable considering the continuous presence of citrullinated antigens. These data pave the path for a detailed understanding of the development and maintenance of citrullinated antigen-reactive B cells and could lead to the identification of targets for novel therapeutic interventions.

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Abstract Number: 1101

Matrix Metalloproteinase-10 (Stromelysin 2) Is a Target of Robust Autoimmune T and B Cell Responses in Antibiotic-Refractory Lyme Arthritis, but Not in Rheumatoid Arthritis

Jameson T. Crowley[1], Elise E. Drouin[2], Annalisa Pianta[1], Klemen Strle[1], Qi Wang[3], Catherine E. Costello[3] and Allen C. Steere[4], [1]Center for Immunology and Inflammatory Diseases, Massachusetts General Hospital, Harvard Medical School, Boston, MA, [2]Medicine, Center for Immunology and Inflammatory Diseases, Massachusetts General Hospital, Harvard Medical School, Boston, MA, [3]Center for Biomedical Mass Spectrometry, Boston University School of Medicine, Boston, MA, [4]Center for Immunolgy and Inflammatory Diseases, Massachusetts General Hospital, Harvard Medical School, Boston, MA

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Background/Purpose:

Infection-induced autoimmunity has been hypothesized to have a pathogenic role in antibiotic-refractory Lyme arthritis (LA). We previously identified 3 autoantigens, endothelial cell growth factor, annexin A2, and apolipoprotein B-100, that are targets of T and B cell responses in Lyme disease patients. However, only about half of patients with antibiotic-refractory LA have one or more of these autoimmune responses. In the current study, we again used discovery-based proteomics and translational research to identify another novel autoantigen, matrix metalloproteinase-10 (MMP-10), in antibiotic-refractory LA.

Methods:

HLA-DR-presented peptides were isolated and identified from the synovial tissue of a patient with antibiotic-refractory LA. Immunogenicity of the peptides was measured using the case patient's PBMC in an IFN-γ ELISpot assay. Reactive peptides and their source proteins were then tested for T and B cell reactivity in large numbers of patients with early or late manifestations of Lyme disease, rheumatoid arthritis (RA), or healthy controls (HC). To gain insights into autoantibody-associated pathology, rankings of histologic findings in synovia were correlated with the magnitude of autoantibody responses.

Results:

Of the 124 HLA-DR-presented self-peptides identified from the synovial tissue of a patient with antibiotic-refractory LA, one peptide derived from MMP-10 caused his PBMC to secrete IFN-γ. When tested in additional patients, only 1 patient each with erythema migrans (EM), an early disease manifestation, or with antibiotic-responsive LA had low-level T cell reactivity with MMP-10 peptides, though 26% of patients with EM and 14% of those with antibiotic-responsive LA had autoantibody responses to full-length MMP-10. In contrast, 5 of 20 patients (25%) with antibiotic-refractory LA had robust T cell responses to MMP-10 peptides, and 25 of 114 patients (22%) with refractory arthritis had autoantibody responses to MMP-10. No HC and only 6% of RA patients had minimal autoantibody responses to this protein. Furthermore, only a few patients with LA had antibody reactivity to MMP-3 (stromelysin 1), a protein with 78% amino acid sequence homology to MMP-10, further demonstrating the specificity of reactivity with MMP-10. In refractory patients, the magnitude of the MMP-10 antibody response positively correlated with synovial lining layer thickness and fibroblast proliferation, and with greater staining for CXCL13 and larger numbers of plasma cells, suggestive of local antibody production.

Conclusion:

Identification of a single HLA-DR-presented peptide (T cell epitope) provided a bridge to the discovery of a broadly immunogenic autoantigen, MMP-10, in Lyme disease. B cell reactivity with this protein may develop early in the illness. Later in the infection, patients

with antibiotic-refractory LA may have both T and B cell responses to MMP-10, and in these patients, the autoantibody response appears to become pathogenic. The specificity of this response (not found in RA) suggests that initial interaction between the spirochete and host at disease onset is critical in immunogenicity, and not simply abundance of MMP proteins.

Disclosure: J. T. Crowley, NIH NIAID (R01 A1-110175), 2; **E. E. Drouin**, None; **A. Pianta**, NIH NIAID (R01 A1-110175), 2; **K. Strle**, NIH K (K01AR062098), 2,Arthritis Foundation, 2; **Q. Wang**, None; **C. E. Costello**, None; **A. C. Steere**, NIAID (AI-101175), 2,Rolland Foundation, 2,Littauer Foundation, 2,Eshe Fund, 2.

Abstract Number: 1102

CD19+CD24-CD38hi B-Cell Subset: A Potential Biomarker for IgG4-Related Disease

Wen Zhang[1,2], Wei Lin[3], Yu Chen[4], Yunjiao Yang[4], Hua Chen[4], QingJun Wu[4], Yunyun Fei[4], Chaojun Hu[4], Yongzhe Li[3], Xuan Zhang[3], Yan Zhao[4], Fengchun Zhang[3], Xiaofeng Zeng[4] and Peter E. Lipsky[5], [1]Rheuamtology, Peking Union Medical College Hospital, Beijing, China, [2]Peking Union Medical College Hospital, Chinese Academy of Medical Science & Peking Union Medical College, Beijing, China, [3]Peking Union Medical College Hospital, Beijing, China, [4]Rheumatology, Peking Union Medical College Hospital, Beijing, China, [5]Bldg 10 Rm 6d47c, National Institutes of Health, Bethesda, MD

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SESSION INFORMATION

Session Date: Monday, November 9, 2015

Session Title: B cell Biology and Targets in Rheumatolid Arthritis and other Autoimmune Disease Poster

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose:

To investigate a B-cell subpopulation, exhibiting CD19+CD24-CD38hi phenotype, can be a biomarker for diagnosis and disease activity in IgG4 related disease (IgG4-RD).

Methods:

Circulating B-cell subsets from 42 untreated IgG4-RD patients, including CD19+CD24-CD38hi, CD19+CD24+CD38-, CD19+CD24intCD38int and CD19+CD24hiCD38hi B cells, were sorted by flow cytometry and their gene expression was measured by microarray. Characterizing of CD19+CD24-CD38hi B cell subset was confirmed by testing surface markers such as CD27, CD95 and HLA-DR, et al. In addition, supernatant IgG4 concentrations were measured by Cytometric Bead Array (CBA).

Results:

In untreated IgG4-RD patients, expanded CD19+CD24-CD38hi B-cell subset exhibited a significant different gene expression pattern compared with the other three B cell subsets, which showed much higher expression of Blimp-1 and IRF4, and the lower expression of PAX5 and BCL-6. In addition, CD27, CD95 and HLA-DR were highly expressed on CD19+CD24-CD38hi B-cell subset from IgG4-RD peripheral B cells. Furthermore, CD19+CD24-CD38hi B-cell subset expressed more surface IgG4 and secreted more IgG4. Finally, the level of CD19+CD24-CD38hi B-cells was decreased after therapy, which correlates with disease remission.

Conclusion:

Circulating CD19+CD24-CD38hi B-cell subset is elevated in active IgG4-RD, which shows the morphological as well as the phenotypical characteristics of plasmablasts (PB) and decreases during IgG4-RD remission. This B-cell subset might be a potentially useful biomarker for diagnosis and assessing response to treatment.

Disclosure: W. Zhang, None; **W. Lin**, None; **Y. Chen**, None; **Y. Yang**, None; **H. Chen**, None; **Q. Wu**, None; **Y. Fei**, None; **C. Hu**, None; **Y. Li**, None; **X. Zhang**, None; **Y. Zhao**, None; **F. Zhang**, None; **X. Zeng**, None; **P. E. Lipsky**, None.

Abstract Number: 1103

Phosphatidylserine Outer Layer Translocation Is Implicated in IL-10 Secretion By Human Regulatory B Cells

Charlotte Hua[1], Rachel Audo[2], Michael Hahne[2], Bernard Combe[3], Jacques Morel[3] and Claire I. Daien[3], [1]Department of Rheumatology, Lapeyronie Hospital and Montpellier University, Montpellier, France, [2]IGMM-CNRS UMR5535, Montpellier, France, [3]Department of rheumatology, Lapeyronie Hospital and Montpellier University, Montpellier, France

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Background/Purpose:

B cells can have a negative regulatory role, mainly mediated by interleukin 10 (IL-10) and we recently showed that IL-10 producing B cells (B10 cells) are deficient in patients with rheumatoid arthritis (RA). However, B10 cells still remain to be better characterized and finding new markers of B10 cells is an important challenge. Annexin V (AnV) is a protein binding to phosphatidylserine (PS), a phospholipid usually located on the inner leaflet of the plasma membrane that could be externalized during some process such as apoptosis. Previous works have suggested that AnV staining, a known marker for apoptosis, could also be expressed on viable and stimulated B cells. We therefore aimed to explore the relationship between PS exposure (assessed by AnV staining) and B10 cells.

Methods:

We used PBMCs from 6 healthy controls and 7 RA patients. AnV staining was compared between human B10 cells and IL-10 non-producing B cells. Levels of CpG induced B10 cells from flow cytometry sorted AnV^{pos} and AnV^{neg} B cells were compared. Apoptosis was studied in AnV^{pos} and AnV^{neg} B cells, using different methods: DAPI staining, cellular cycle study with propidium iodide (PI) and DiOC6 staining. PS was then blocked using biotynilated AnV and glyburide to evaluate the impact on B cell IL-10 production.

Results: B10 cells externalized more PS than IL-10 non-producing B cells with respectively 27.75 [17.03-44.38]% and 12.35 [9.49-14.20]% of AnV^{pos} B cells (p= 0.03; n= 6 healthy controls). In RA patients, the proportion of AnV^{pos} B cells was also significantly higher among B10 cells than among IL-10 non-producing B cells (p= 0.03; n= 6). After CpG stimulation, the differentiation into B10 cells was more important for AnV^{pos} B cells than for AnV^{neg} B cells (5.50 [2.21-8.80]% vs 2.50 [0.75-6.09]% respectively, p= 0.03; n= 6 healthy controls). This exposure of PS does not seem to be related to apoptosis since proportions of dead cells (DAPI+) were similar between AnV^{pos} and AnV^{neg} B cells (p= 0.3; n= 6 healthy controls). Moreover, the proportions of B cells in an early apoptotic stage (DiOC6-) were similar between AnV^{pos} and AnV^{neg} B cells (p= 0.4; n=4 healthy controls). Lastly, cellular cycle study showed that, compared to AnV^{neg} B cells, AnV^{pos} B cells have a higher proliferation index (p= 0.03; n= 6 healthy controls). PS blockade decreased the levels of B10 cells with 6.59 [3.71-8.12]% of B10 cells for culture medium alone; 2.99 [1.15-5.61]% with biotynilated AnV and 3.20 [1.26-4.80]% with glyburide (p= 0.03 and p= 0.06 for biotynilated AnV vs media and glyburide vs media respectively, n= 6 healthy controls).

Conclusion: This study showed that a positive AnV staining is observed on viable B cells suggesting that AnV is not only a marker for apoptosis. In healthy controls and RA patients, B10 cells have an increased AnV staining. These AnV^{pos} B cells differentiate more into B10 cells and phosphatidylserine (PS) blockade inhibits B10 cells generation. These results strongly suggest a link between PS exposure and B10 cells. This could be useful to generate B10 cells in future therapeutic issues, for example for RA patients.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/phosphatidylserine-outer-layer-translocation-is-implicated-in-il-10-secretion-by-human-regulatory-b-cells

Abstract Number: 1104

Mouse B Cells Require Glucose and Free Fatty Acids As Carbon Sources for Cytokine and Chemokine Secretion

Doujiao Wu[1], Dongyue Huang[2], Edward Pearce[1] and **Alfred Kim**[2], [1]Pathology & Immunology, Washington University School of Medicine, Saint Louis, MO, [2]Rheumatology, Washington University School of Medicine, Saint Louis, MO
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Background/Purpose: B cells contribute to disease pathophysiology through several mechanisms, including cytokine and chemokine secretion. A wide variety of stimuli can activate B cells including B cell receptor (BCR) and Toll-like receptor (TLR) engagement. Recently, numerous observations have demonstrated the requirement of various metabolic pathways in establishing the diverse array of immune cell functions. Here, we examine the metabolic requirements of *in vitro*B cell cytokine and chemokine secretion.

Methods: B cells were isolated from the spleens of 129 mice using negative selection and magnetic bead separation. B cells were activated overnight individually by the following agents: anti-μ antibody (B cell receptor), anti-CD40 agonist antibody, poly(I:C) (TLR3), LPS (TLR4), and CpG (TLR9). Supernatants were collected and analyzed for the quantification of cytokines using the Bioplex Pro Mouse Cytokine 23-plex assay.Real-time analysis of extracellular acidification rates (ECAR) and oxygen consumption rates (OCR) of activated B cells were performed using the XF-96 Extracellular Flux Analyzer (Seahorse Bioscience).

Results: High-dose LPS and CpG activation of B cells generated the highest levels and widest breadth of cytokines and chemokines (Table 1). In addition, these stimuli generated high OCR and ECAR values, reflecting the need for oxidative phosphorylation and glycolysis respectively. Both LPS and CpG required free fatty acids and glucose as a carbon sources, as addition of etomoxir (inhibitor of fatty acid oxidation) and UK-5099 (inhibitor of pyruvate transfer into the mitochondria) abrogated both cytokine and chemokine secretion and oxidative phosphorylation. The other stimulatory agents tested minimally generated cytokine or chemokine release and did not induce oxidative phosphorylation in B cells.

Conclusion: We catalogued the breadth of cytokines and chemokine secreted by B cells via various stimulatory agents. High-dose LPS and CpG required free fatty acids and glucose for the elaboration of LPS or CpG-induced cytokine production. These data suggest that B cell cytokine and chemokine secretion can be manipulated by altering the local metabolic environment, and may represent an interesting therapeutic approach for modulating B cells in autoimmune diseases.

	Unstimulated	BCR (medium/high)	CD40 (all concentrations)	TLR3 (all concentrations)	TLR4 (low)	TLR4 (medium/high)	TLR9 (medium/high)
Eotaxin	+	+	+	+	+	+	++
MIP-1β	++	++++	+	++++	+++	+++	++++
TNF-α	0	++	0	0	0	0	+
IL-12 (p70)	0	+	0	+	0	0	+
MIP-1α	0	+	0	+	0	+	+++
RANTES	0	0	0	+++	0	++	+
IL-6	0	0	0	0	0	+	+++
IL-9	0	0	0	+	+	+	++
IL-10	0	0	0	0	0	+	++
IL-1β	0	0	0	0	0	0	++
IL-13	0	0	0	0	0	0	++
GM-CSF	0	0	0	0	0	0	+
MCP-1	0	0	0	0	0	0	+
	0=not detected	+=5-100 pg/mL	++=100-250 pg/mL		+++=250-1000 pg/mL		++++=>1000 pg/mL

Table 1. Cytokines secreted by isolated B cells from 129 mice following stimulation.

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Abstract Number: 1105

The IgG/IgG4 mRNA Ratio By Quantitative PCR Accurately Diagnoses IgG4-Related

Disease and Predicts Treatment Response

Lowiek Hubers[1], Marieke Doorenspleet[2], Paulus Klarenbeek[3], Emma Culver[4], Lucas Maillette de Buy Wenniger[5], Roger Chapman[4], Stan Van de Graaf[6], Joanne Verheij[7], Thomas Van Gulik[8], Frank Baas[9], Ellie Barnes[4], Ulrich Beuers[1] and Niek De Vries[3], [1]Dept. of Gastroenterology & Hepatology and Tytgat Institute of Liver and Intestinal Research, Dept. of Gastroenterology & Hepatology and Tytgat Institute of Liver and Intestinal Research, Academic Medical Center/University of Amsterdam, Amsterdam, Netherlands, [2]Dept. of Clinical Immunology & Rheumatology, Amsterdam Rheumatology and immunology Center | Academic Medical Center/University of Amsterdam, Amsterdam, Netherlands, [3]Dept. of Clinical Immunology & Rheumatology, Amsterdam Rheumatology and immunology Center, Academic Medical Center/University of Amsterdam, Amsterdam, Netherlands, [4]Translational Gastroenterology Unit and NDM Oxford University, Translational Gastroenterology Unit and NDM Oxford University, John Radcliffe Hospital/Oxford University, Oxford, United Kingdom, [5]1Dept. of Gastroenterology & Hepatology and Tytgat Institute of Liver and Intestinal Research, Dept. of Gastroenterology & Hepatology and Tytgat Institute of Liver and Intestinal Research, Academic Medical Center/University of Amsterdam, Amsterdam, Netherlands, [6]Dept. of Gastroenterology & Hepatology and Tytgat Institute of Liver and Intestinal Research,, Dept. of Gastroenterology & Hepatology and Tytgat Institute of Liver and Intestinal Research, Academic Medical Center/University of Amsterdam, Amsterdam, Netherlands, [7]Dept. of Pathology, Dept. of Pathology, Academic Medical Center/University of Amsterdam, Amsterdam, Netherlands, [8]Dept. of Surgery, Dept. of Surgery, Academic Medical Center/University of Amsterdam, Amsterdam, Netherlands, [9]Dept. of Genome Analysis, Academic Medical Center/University of Amsterdam, Amsterdam, Netherlands

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Session Time: 9:00AM-11:00AM

Background/Purpose : IgG4-associated cholangitis (IAC) and autoimmune pancreatitis (AIP) are major manifestations of IgG4-related disease (IRD). Misdiagnosis and inadequate treatment are common since IAC and AIP mimic other inflammatory and malignant pancreatobiliary diseases and accurate diagnostic biomarkers are lacking. Moreover, relapse after tapering of immunosuppressive therapy is seen in 50% of patients, underscoring the need for biomarkers monitoring disease activity. Recently, using Next-Generation Sequencing, we found that dominant IgG4+ B-cell receptor clones in peripheral blood distinguish patients with active IAC/AIP from primary sclerosing cholangitis (PSC) and pancreatobiliary malignancies (CA) [Hepatology 2013;57:2340]. Therefore, we aimed to develop a quantitative PCR (qPCR) protocol for diagnosing IAC/AIP and monitoring disease activity before and after treatment.

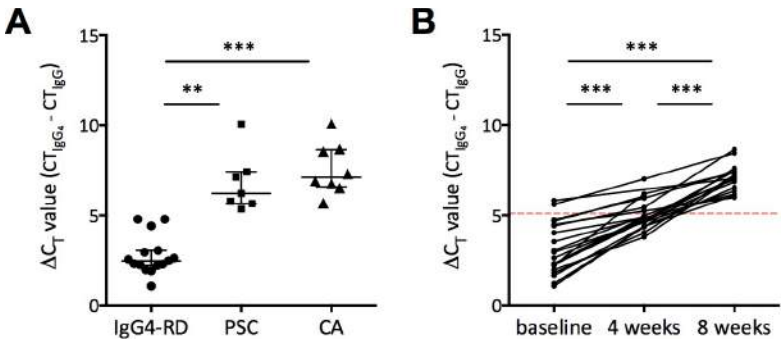
Methods : 15 patients with IAC and/or AIP according to HISORt criteria, 7 patients with PSC and 8 with CA formed the test cohort. Intra- and extramural replication cohorts consisted of 16 IAC/AIP, 5 PSC and 13 CA patients (Dutch cohort), and 8 IAC/AIP and 8 PSC patients (British cohort). From 20 Dutch IAC/AIP patients, follow-up samples after 4 and 8 weeks of corticosteroid therapy were available. RNA was isolated, and a forward primer amplifying all IgG subtypes, together with a generic reverse primer for all IgG subtypes and a specific reverse primer for IgG4 were used to amplify the constant region of the B-cell receptor. The ratio total IgG/IgG4 mRNA was calculated and expressed as ΔC_T.

Results : ΔC_T as measure of IgG/IgG4 mRNA expression in peripheral blood of the test cohort was 2.8±1.1 (mean+SD) in IAC/AIP patients, compared to 6.8±1.6 in PSC and 7.6±1.4 in CA (Figure 1A, $p<0.0001$). ROC analysis revealed a ΔC_T cut-off value of 5.1 in the test cohort distinguishing all cases from controls. In the replication cohort sensitivity was 95% and specificity 100% ($p=8.6*10^{-21}$). ΔC_T increased after 4 weeks (5.1±0.8) and 8 weeks (7,1±0.7) of corticosteroid treatment, compared to pre-treatment (mean 3.1±1.4, $p<0.0001$, Figure 1B).

Conclusion : IgG4-related disease of the biliary tree and pancreas can accurately be distinguished from PSC or pancreatobiliary malignancies by ΔC_T based on an affordable qPCR test. ΔC_T can also be used as a marker for treatment response and disease activity in IgG4-related disease.

Acknowledgement: This study was supported by grants from German and American PSC patient organizations (to UB).

Figure 1



Disclosure: **L. Hubers**, None; **M. Doorenspleet**, Patent on "Method for diagnosing IgG4 related diseases", application number PCT/ EP2013/070384, publication number WO/2014/049177, 9; **P. Klarenbeek**, None; **E. Culver**, None; **L. Maillette de Buy Wenniger**, Patent on "Method for diagnosing IgG4 related diseases", application number PCT/ EP2013/070384, publication number WO/2014/049177, 9; **R. Chapman**, None; **S. Van de Graaf**, None; **J. Verheij**, None; **T. Van Gulik**, None; **F. Baas**, None; **E. Barnes**, None; **U. Beuers**, Patent on "Method for diagnosing IgG4 related diseases", application number PCT/ EP2013/070384, publication number WO/2014/049177, 9,Research grants from German and American PSC patient organizations, 2; **N. De Vries**, Patent on "Method for diagnosing IgG4 related diseases", application number PCT/ EP2013/070384, publication number WO/2014/049177, 9.

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Abstract Number: 1106

Efficacy of Abbv-105, a Selective and Irreversible Inhibitor of Bruton's Tyrosine Kinase (BTK), in Multiple Models of Inflammation

Christian Goess[1], Candace Graff[2], Ting Ting Zhang[2], Gregory Preston[2], Richard McCarthy[1], Matthew Perham[1], Jacqueline Loud[1], Christopher M. Harris[1], Sara Murdock[1], Erik Sampson[3], Michael Hoemann[4], Michael Friedman[4], Robert Talanian[3], Jeremy Edmunds[4] and Andrew Long[1], [1]Immunology Pharmacology, AbbVie Inc, AbbVie Bioresearch Center, Worcester, MA, [2]DMPK, AbbVie Inc, AbbVie Bioresearch Center, Worcester, MA, [3]AbbVie Inc, AbbVie Bioresearch Center, Worcester, MA, [4]Chemistry, AbbVie Inc, AbbVie Bioresearch Center, Worcester, MA

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Background/Purpose: Bruton's Tyrosine Kinase (BTK) is a non-receptor tyrosine kinase required for intracellular signaling pathways downstream of several key immunoreceptors, including the B cell receptor, Fc receptors, and the GPVI collagen receptor. Due to its involvement in multiple mechanisms of inflammatory disease pathogenesis, targeting BTK may be a useful strategy for indications like rheumatoid arthritis and lupus. ABBV-105 is a covalent, irreversible inhibitor that alkylates Cys481 specifically, resulting in durable BTK inhibition *in vitro* and *in vivo*. Only 10 other kinases have a cysteine at this position and ABBV-105 has greater than 30-fold selectivity versus these kinases.

Methods: To evaluate the effects and specificity of BTK inhibition *in vitro* we evaluated ABBV-105 in BTK dependent cell assays including FCεR-mediated basophil degranulation, FCγR-mediated monocyte activation, and TLR9 agonist-mediated activation of PBMC. As a consequence of the covalent nature of the binding, target engagement can be assessed both *in vitro* and *in vivo* by measuring the amount of unbound BTK associated with a biotinylated probe derived from a related covalent Btk inhibitor. BTK occupancy can be calculated by comparing the free BTK levels in a sample with or without ABBV-105 treatment. To understand the effects of BTK inhibition on inflammatory processes *in vivo*, we evaluated ABBV-105 in a rat collagen-induced arthritis (CIA) model and in an IFNα-accelerated lupus nephritis model in NZB/W mice.

Results: ABBV-105 potently and selectively inhibits the BTK enzyme and multiple BTK dependent cell-based assays including FCεR-mediated basophil degranulation, FCγR-mediated monocyte activation, and TLR9 agonist-mediated activation of PBMCs. Following oral administration of ABBV-105 *in vivo*, there is a rapid clearance of ABBV-105 in plasma while BTK occupancy of ABBV-105 in both

spleen and peripheral blood leukocytes remains. In rat CIA, ABBV-105 fully inhibits paw swelling and bone destruction comparable to prednisolone. ABBV-105 also significantly reduces proteinuria, prolongs survival, and reduces anti-dsDNA autoantibody titers in an IFNα-accelerated lupus nephritis model. Efficacy in both models correlates with BTK splenic occupancy in a dose- and exposure-dependent manner.

Conclusion: Taken together, our data confirm that selective and covalent inhibition of BTK is effective in ameliorating disease pathogenesis in preclinical models of rheumatoid arthritis and lupus and may provide a therapeutic benefit to patients.

Disclosure: C. Goess, Abbvie, 3; **C. Graff**, AbbVie, 1; **T. T. Zhang**, Abbvie, 3; **G. Preston**, Abbvie, 3; **R. McCarthy**, Abbvie, 3; **M. Perham**, Abbvie, 3; **J. Loud**, Abbvie Bioresearch Center Inc., 3; **C. M. Harris**, Abbvie, 3; **S. Murdock**, Abbvie, 3; **E. Sampson**, AbbVie, 1,AbbVie, 3; **M. Hoemann**, Abbvie, 3; **M. Friedman**, Abbvie, 3; **R. Talanian**, Abbvie, 3; **J. Edmunds**, Abbvie, 3; **A. Long**, Abbvie, 3.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/efficacy-of-abbv-105-a-selective-and-irreversible-inhibitor-of-brutons-tyrosine-kinase-btk-in-multiple-models-of-inflammation

Abstract Number: 1107

Inhibition of B Cell Activation and Plasma Cell Differentiation By Epratuzumab, a Humanized Monoclonal Antibody Targeting CD22

Natalia V. Giltiay[1], Geraldine L. Shu[2], Anthony Shock[3] and Edward A. Clark[1,2], [1]Division of Rheumatology, Department of Medicine, University of Washington, Seattle, WA, [2]Department of Immunology, University of Washington, Seattle, WA, [3]UCB Pharma, Slough, United Kingdom

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Background/Purpose:

Systemic lupus erythematosus (SLE) is characterized by B cell hyperactivity and production of autoantibodies. Treatment of patients with moderate-to-severe SLE with epratuzumab, a humanized monoclonal antibody that targets CD22, has resulted in clinically relevant, sustained improvements in disease activity. While epratuzumab is thought to modulate B cell function, its mechanism of action has not been completely elucidated. This study was undertaken to determine how epratuzumab affects the activation of different B cell subsets in response to Toll-like receptor (TLR) and/or B cell receptor (BCR) stimulation.

Methods:

$CD20^+$ B cell subsets were isolated from human tonsils using magnetic bead cell separation and cell sorting based on their relative expression of CD10, CD27, IgD, CD38 and other surface markers. Cells were treated with anti-IgM and/or R848 (a TLR7 agonist) in the presence of epratuzumab or a human IgG control. Changes in mRNA levels of *PRDM1*, the gene encoding B lymphocyte-induced maturation protein 1 (Blimp-1), and a variety of other genes associated with B cell activation were analyzed by RT-PCR 12–24 hours after stimulation. Cell survival and plasma cell differentiation were assessed by flow cytometry after 3–5 days of *in vitro* cell culture.

Results:

Treatment of $CD20^+CD27^-CD10^-$ B cells with R848, anti-IgM, or a combination of R848 plus anti-IgM led to a significant (2–10-fold) increase in *PRDM1* expression 12 hours after stimulation. Epratuzumab dramatically inhibited *PRDM1* mRNA levels, but had no effect on the expression of a number of other genes, including *AICDA*, *PAX5*, *BCL6, XBP1*, and *ETS1*. In cell culture experiments R848, anti-IgM, or a combination of R848 plus anti-IgM stimulation did not have a significant effect on $CD20^+CD27^+CD10^-IgD^-$ (switched memory cells), or $CD20^+CD27^-CD10^-IgD^+$ (naïve B cells), but significantly induced the activation of $CD20^+CD27^-CD10^-IgD^-$ cells, as evidenced by increased cell proliferation and by the appearance of blasting $CD27^{hi}CD38^{hi}$ (pre-plasma) cells. Epratuzumab significantly inhibited CD38 expression and the generation of pre-plasma cells without significantly affecting cell survival.

Conclusion:

These results suggest that one therapeutic effect of epratuzumab may be via inhibiting the expression of *PRDM1* (Blimp-1). Since Blimp-1 is required by B cells to mature into antibody-producing cells, epratuzumab-mediated inhibition of Blimp-1 may reduce autoantibody production in SLE patients. Epratuzumab inhibits the activation of $CD20^{+}CD27^{-}CD10^{-}IgD^{-}$ tonsillar B cells, which appear highly responsive to stimulation via TLR7. This population of cells might correspond to $CD27^{-}$ memory B cells, found to be substantially increased in SLE patients. These data may have implications for understanding the effects of epratuzumab treatment on B cell function in SLE patients.

Disclosure: **N. V. Giltiay**, None; **G. L. Shu**, None; **A. Shock**, UCB Pharma, 3; **E. A. Clark**, UCB Pharma, 2.

Abstract Number: 1108

Epratuzumab, a Monoclonal Antibody Targeting CD22 on B Cells, Stimulates the Phosphorylation of Upstream Inhibitory Signals of the B Cell Receptor

Simon Lumb[1], **Sarah J. Fleischer**[2], Capucine Daridon[2], Alison Maloney[1], Anthony Shock[1] and Thomas Dorner[2], [1]UCB Pharma, Slough, United Kingdom, [2]Charité University Medicine Berlin, CC12, Dept. Medicine/Rheumatology and Clinical Immunology and German Rheumatism Research Center Berlin (DRFZ), a Leibniz Institute, Berlin, Germany

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Background/Purpose:

Epratuzumab, a humanized monoclonal antibody targeting CD22, is currently in phase 3 clinical trials in patients with systemic lupus erythematosus (SLE). Previous work suggests epratuzumab down-modulates B cell receptor (BCR) function.[1,2] Inhibitory co-receptors of the BCR complex, such as CD22 and the inhibitory Fc receptor CD32B, prevent overstimulation of B cells by signaling through tyrosine (Tyr) based inhibitory motifs (ITIMs). Phosphorylation of Tyr residues on CD22 results in the recruitment of adaptor and inhibitory signaling molecules eg. Tyr^{822} binds SHP-1 and Tyr^{807} binds Grb2. In contrast CD32B contains a single ITIM motif (Tyr^{292}) that down-regulates activating signals. In this study the effects of epratuzumab on the phosphorylation of inhibitory motifs within CD22 and CD32B were assessed.

Methods:

Fluorescence-activated cell sorting (FACS) was conducted on peripheral blood mononuclear cells from healthy donors. After addition of epratuzumab (10 µg/ml; n=6) or anti-BCR (12 µg/ml; n=8) for various durations, cells were fixed, permeabilized and analyzed using a phospho-Tyr^{822} antibody and B cell markers CD19/CD20/CD27. Confocal microscopy assessed co-localization of CD22 with SHP-1 (n=3) using specific fluorescently-labelled antibodies. For immunoprecipitation (IP) experiments, B cells from human tonsils or Daudi B cells were treated ± epratuzumab or anti-BCR (both at 10 mg/mL), lysed and IP'd with epratuzumab or CD32B antibodies. Captured proteins were identified by Western blotting. Phosphorylated Tyr residues were detected using phospho-specific antibodies against p-Tyr^{807} and p-Tyr^{822} on CD22, and p-Tyr^{292} on CD32B. Signals were detected using HRP-linked secondary antibodies.

Results:

FACS experiments showed that anti-BCR induced a rapid (<5 min) increase in CD22 Tyr^{822} phosphorylation in both naïve (CD27-) and memory (CD27+) B cells. Epratuzumab stimulated Tyr^{822} phosphorylation in a similar time frame, albeit to a lesser extent than anti-BCR (52% less phosphorylation). In keeping with this, epratuzumab induced SHP-1 co-localization with CD22. An increase in CD22 Tyr^{822} phosphorylation with epratuzumab was detected in IP experiments in Daudi cells. These experiments showed increased CD22 Tyr^{807} phosphorylation at early (<10 min) time points in tonsil B cells and Daudi cells, although to a lesser extent than anti-BCR. Finally, epratuzumab induced a modest increase in CD32B ITIM Tyr^{292} phosphorylation on B cells peaking at approximately 10 min.

Conclusion:

Epratuzumab directly induced phosphorylation of inhibitory ITIM motifs within key negative regulatory B cell molecules. On CD22, these included Tyr^{822}, with a concomitant increase in SHP-1 co-localization and Tyr^{807}, both of which would inhibit BCR-driven signaling. Finally, epratuzumab induced Tyr^{292} phosphorylation on the inhibitory Fc receptor CD32B, potentially dampening a hyper-reactive B cell response. Overall, the data provide further evidence that epratuzumab down-modulates B cell activation events, of potential relevance to the treatment of SLE patients with epratuzumab.

References:

1. Sieger N. Arth Rheum 2013;65:770

2. Rossi E. Blood 2013;122:3020

SL and SF contributed equally to this work.

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Abstract Number: 1109

Co-Crystal Structure of TACI and APRIL-BAFF-BAFF Heteromer Suggests That Charged Residues in APRIL and BAFF Dictate Their Receptor Binding Affinities

Xuliang Jiang[1], Thomas Tan[2], Klaus Maskos[3], Alfred Lammens[3], Pascal Schneider[4] and Wolf Palinksy[5], [1]Research and Development Institute, EMD Serono, Billerica, MA, [2]EMD Serono Research, Billerica, MD, [3]Proteros Biostructures GmbH, Planegg, Germany, [4]Biochemistry, University of Lausanne, Epalinges, Switzerland, [5]Global Biotech Development, Merck Serono, Aubonne, Switzerland
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SESSION INFORMATION
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Background/Purpose: The human B cell survival factor, B cell activation factor (BAFF), and its closely related homologue, a proliferation-inducing ligand (APRIL), modulate B cell functions by binding to three receptors, BAFFR, TACI and BCMA. APRIL binds more strongly to BCMA than to TACI while the opposite is true for BAFF. In addition, BAFF, but not APRIL, binds to BAFFR with high affinity. Both BAFF and APRIL are known to form homotrimers and heterotrimers, which display different affinities for their cognate receptors.

Methods: We used X-ray crystallography to determine the structural elements of the APRIL, BAFF and TACI binding sites.

Results: To understand the structural basis underlying the different binding affinities, we solved the crystal structure of the APRIL-BAFF-BAFF heterotrimer, either alone or bound to TACI.

Conclusion: Analysis of these structures and comparative analysis of previously solved structures of BAFF and APRIL in complex with BAFFR, TACI or BCMA revealed that the charged residues of BAFF and APRIL are crucial determinants of receptor binding affinities, conferring homotrimers and heterotrimers with a variety of signaling strength to modulate responses of immune cells.

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Abstract Number: 1110

A Proliferative Inducing Ligand (APRIL) Promotes IL-10 Production of Human B Cells

Charlotte Hua[1], Rachel Audo[2], Nataliya Yeremenko[3], Dominique Baeten[4], Michael Hahne[2], Bernard Combe[5], Jacques Morel[5] and Claire I. Daien[5], [1]Department of Rheumatology, Lapeyronie Hospital and Montpellier University, Montpellier, France, [2]IGMM-CNRS UMR5535, Montpellier, France, [3]Academic medical center, University of Amsterdam, Amsterdam, France, [4]1Academic Medical Center / University of Amsterdam, Amsterdam, Netherlands, [5]Department of rheumatology, Lapeyronie Hospital and Montpellier University, Montpellier, France

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Background/Purpose: B cells may have a negative regulatory role, mainly mediated by interleukin 10 (IL-10). We recently showed that regulatory B-cell functions are impaired in patients with rheumatoid arthritis (RA) and that mice transgenic for a proliferation-inducing ligand (APRIL) are protected against collagen-induced arthritis. We aimed to explore the effect of APRIL on human B-cell production of IL-10.

Methods: CpG induced IL-10 B-cell production was compared in presence or absence of APRIL and B lymphocyte stimulating factor (BLys). The expression of the BLyS and APRIL receptor transmembrane activator and CAML interactor (TACI) and of BLyS specific receptor (BAFF-R) was compared between IL-10 producing and non-producing B cells. The effect of APRIL stimulated B cells on T cell cytokine production was analyzed after 3 days of co-culture. Signaling pathways of B cells activated by CpG and APRIL were analyzed by western blot. Similar experiments were performed on cells of RA patients.

Results: IL-10 production by B cells was greater with APRIL than BLyS treatment or control medium (9.5 [6.8-13.2]% vs 6.2 [3.9-7.0]%, p=0.007, and 4.2 [3.3-8.0]%, p=0.002, respectively, n= 11 controls). This increase was abrogated by co-culture with APRIL inhibitors (8.4 [3.7-13.8]% vs 3.5 [1.9-8.8]%, p<0.01, n=8 controls). APRIL did not stimulate IL-10 production of monocytes and T cells. TACI expression was greater in IL-10 producing than non-IL-10–producing B cells (1.9 [1.3-4.4]% vs 0.4 [0-2.3]%; p=0.031, n= 7 controls) whereas BAFF-R expression was lower (2.3 [2.0-2.5] vs 2.7 [2.3-2.8] of mean fluorescence intensity; p=0.021, n= 7 controls). When compared with non-stimulated B cells, APRIL-stimulated B cells decreased the secretion of TNF-α (-36±13%, p=0.02) and IFN-γ (-14±3%; p=0.02) by T cells but not IL-17 (-14±14%; p=0.31, n= 8 controls). APRIL further stimulated CpG-activated STAT3 and STAT3 inhibition specifically decreased IL-10 production by B cells (-28±3%, p<0.05, n= 7 controls). APRIL also promoted IL-10 production by B cells in 11 RA patients (7.0 [4.1-11.8]% vs 6.1 [3.1-9.8]%, p= 0.024 and 3.6 [2.2-7.3]%, p= 0.009 for APRIL, BLyS and control medium respectively). Similar pattern of APRIL and BLyS receptors on IL-10 producing B cells were observed between the controls and 7 RA patients.

Conclusion: APRIL but not BLyS promotes IL-10 production by B cells and enhances the regulatory role of B cells on T cells by decreasing T-cell secretion of TNF-α and. IFN-γ. IL-10 producing B cells in RA patients are responsive to APRIL, which suggests a possible therapeutic application of APRIL for expanding IL-10 producing B cells in these patients. This could also explain the difference of clinical efficacy observed between belimumab and atacicept in RA.

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View Abstract and Citation Information Online - http://acrabstracts.org/abstract/a-proliferative-inducing-ligand-april-promotes-il-10-production-of-human-b-cells

Abstract Number: 1111

Relapse of Lupus after B-Cell Depletion Therapy Is Associated with Loss of Apoptotic Cell Clearance and Elevated Type I Interferon Responses in Lupus Prone BXD2

Hui-Chen Hsu[1,2], Zhaoqi Yan[3], PingAr Yang[2], Qi Wu[1,2], Jennie Hamilton[4], Jun Li[5], Hao Li[6], Bao Luo[6], Laurie Harrington[3] and John Mountz[7], [1]Department of Medicine, University of Alabama at Birmingham, Birmingham, AL, [2]Department of Medicine, Clinical Immunology & Rheumatology, University of Alabama at Birmingham, Birmingham, AL, [3]Cell, Developmntl & Integrative Biology, University of Alabama at Birmingham, Birmingham, AL, [4]University of Alabama at Birmingham, Birmingham, AL, [5]Medicine, University of Alabama at Birmingham, Birmingham, AL, [6]Division of Clinical Immunology and Rheumatology, Department of Medicine, University of Alabama at Birmingham, Birmingham, AL, [7]Dept of Med/Rheumatology Div, University of Alabama at Birmingham and Birmingham VA Medical Center, Birmingham, AL

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Background/Purpose: B-cell depletion therapy (BCDT) is a promising therapy for autoimmune diseases but relapse can occur. In rheumatoid arthritis, patients who did not respond well to rituximab exhibited higher levels of type I interferon (IFN) signature gene expression in PBMCs but the underlying mechanisms remain unknown. Spleen marginal zone macrophages (MZMs) are essential for tolerogenic clearance of apoptotic cells (ACs). Maintenance of MZMs requires MZ B cells. The purpose of this study is to determine if anti-CD20 depletion of MZ B cells promotes the loss of MZMs, leading to excessive uncleared ACs and stimulation of autoreactive B cells by type I IFN in autoimmune BXD2 mice.

Methods: BXD2 mice and normal B6 mice were administered anti-CD20 (clone 5D2, IgG2a) or isotype control (250 µg/single dose iv). B-cell depletion and repopulation were determined over 9 weeks of time. The distribution of MZMs in the spleen was examined by confocal microscopy. The expression of type I IFN signature genes, *Usp18* and *Oasl*, in repopulated B cells was determined by quantitative PCR. The development of autoantibody titers and autoAb producing B cells was determined by ELISA and ELISPOT assays.

Results: Administration of anti-CD20 resulted in nearly complete depletion of B cells in the PBMCs but there was less complete depletion of B cells in the spleen. In the spleen, the deepest depletion occurred at week (wk) 2 and this was associated with a dramatic decline in MZMs of both strains but uncleared ACs were observed in only BXD2 but not B6 spleen. By wk 5, the spleen B-cell repopulation rate was 69% in BXD2 but was only 26% in B6 mice and MZM and AC clearance defects were found for both strains. By wk 9, there was >85% repopulation of spleen B cells in both strains. In BXD2 mice, at wk 5, there was a 1.7-fold increase in the number of $PNA^{+}Fas^{+}$ $CD19^{+}$ spleen germinal center (GC) B cells and an increased number of IgG anti-DNA and anti-histone producing B cells in the BCDT group, compared to the control group. This is associated with an increased expression of *Usp18* and *Oasl* in repopulated MZ precursor (MZ-P) B cells in the BCDT group, compared to the control group. At wk 9, serum titers of IgG autoantibodies against DNA, histone, and malondialdehyde, a lipid peroxidation product associated with apoptotic blebs, were markedly increased in the BCDT group, compared to the control group. Interestingly, despite the relatively slower repopulation of B cells and MZMs in anti-CD20 treated B6 mice, there was no elevation in GC B cells and autoantibody titers when B cells were repopulated.

Conclusion: Although BXD2 mice responded to BCDT, anti-CD20 induced repopulation of GC and autoreactive B cells. The relapse was associated with the functional loss of tolerogenic AC clearance. This is consistent with our previous findings that normal MZ B cells are required to maintain normal tolerogenic function of MZMs. The results suggest that measurement of AC by-production and type I IFN responses should be considered as biomarkers for therapeutic efficacy and timing of repeated BCDT (This worked was supported by the NIH (RO1-AI-071110, RO1-AI-083705, P30-AR-048311 and P30-AI-027767) and the VA Merit Review 1I01BX000600-01. Anti-CD20 and isotype control are generous gifts from Genentech Inc.).

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Abstract Number: 1112

Obinutuzumab Outperforms Rituximab at Inducing B-Cell Cytotoxicity in Vitro through Fc-Mediated Effector Mechanisms in Rheumatoid Arthritis and Systemic Lupus Erythematosus

Venkat Reddy[1], Christian Klein[2], David A. Isenberg[3], Geraldine Cambridge[4], Martin Glennie[5], Mark Cragg[6] and Maria J. Leandro[1], [1]Rheumatology, University College London, London, United Kingdom, [2]Roche Pharmaceutical Research & Early Development Oncology Discovery & Translational Area, Roche Glycart AG, Schlieren, Switzerland, [3]Centre for Rheumatology, Division of Medicine, University College London, London, United Kingdom, [4]Rheumatology, Centre for Rheumatology and Bloomsbury Rheumatology Unit, University College London, London, United Kingdom, [5]Antibody and Vaccine group, Southampton University, Southampton, United Kingdom, [6]Antibody and Vaccine group, Cancer Sciences Unit, Faculty of Medicine, Southampton University, Southampton, United Kingdom
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Background/Purpose:

Obinutuzumab (OBZ, a Type II anti-CD20 monoclonal antibody [mAb] with afucosylated Fc portion and enhanced affinity for Fcγ receptor III) is more efficient than Rituximab (RTX, a Type I mAb) at inducing malignant B cell cytotoxicity and is approved by the Food and Drug Administration for use in chronic lymphocytic leukemia. Here we compared their effects against B cells from patients with Rheumatoid Arthritis (RA) and Systemic Lupus Erythematosus (SLE).

Methods:

We used flow cytometry to perform: in vitro whole blood B cell depletion assays to compare the efficiency of OBZ and RTX in depleting target B cells; surface fluorescence-quenching assays to determine the extent of mAb internalization; complement dependent cellular cytotoxicity (CDC) assays to assess the ability to recruit complement and lyse target cells; NK cell degranulation assays to assess surface expression of CD107a as a measure of antibody-dependent cellular cytotoxicity (ADCC); and neutrophil activation assays assessing the surface expression of CD62L and CD11B. OBZ-gly (OBZ with Fc glycosylation similar to RTX) was used to assess the effects of afucosylation. All mAb were used at 1µg/mL except for the CDC assay (10µg/mL).

Results:

Obinutuzumab (OBZ) was > 2 fold more efficient than Rituximab (RTX) at inducing cytotoxicity in B cells from patients with RA (n=31) and SLE (n=34) in whole blood assays (Figure 1A). It was also internalized by isolated B cells from SLE patients (n=6) to a significantly lower extent than RTX with a median surface accessible mAb of 75% and 59%, respectively, after 6 hours of incubation (Figure 1B). OBZ was at least twice as efficient at inducing NK cell activation, Figure 2 in RA (n=13) and SLE (n=19); and also activated neutrophils more efficiently than RTX in SLE (n=15) (Figure 3). In contrast, RTX was significantly more efficient than OBZ at evoking CDC of isolated B cells (SLE, n=6) (Figure 1C).

Conclusion:

Obinutuzumab is more efficient than rituximab at inducing B cell cytotoxicity in vitro in both RA and SLE samples. Enhanced direct cell death, reduced CD20 internalization and superior FcR-mediated effector mechanisms are observed, while complement mediated cytotoxicity is reduced. These data provide a mechanistic basis for considering obinutuzumab as an alternative B cell depleting agent in RA and SLE.

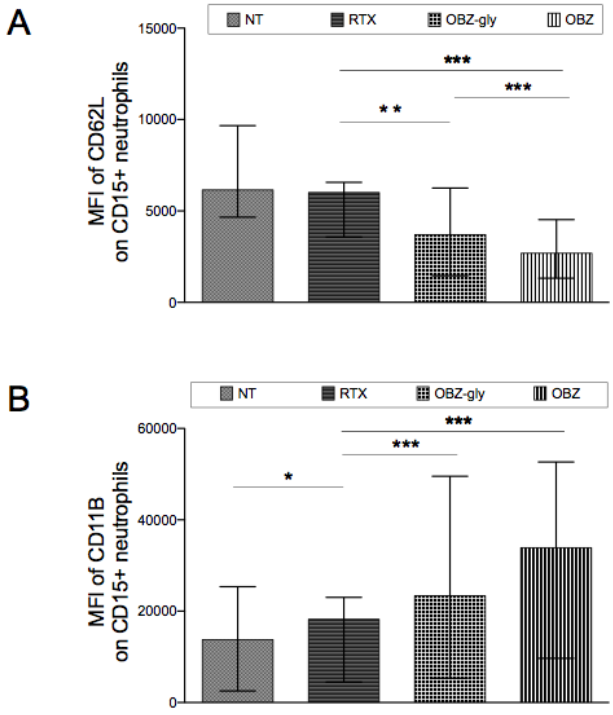

Figure 3. Obinutuzumab is more efficient than Rituximab at Activating Neutrophils in Rheumatoid Arthritis and Systemic Lupus Erythematosus. A) After 24 hour incubation of whole blood samples with mAbs at 1µg/mL, the mean fluorescence intensity (MFI) of CD62L was lower and B) that of CD11B was higher on CD15+ neutrophils, in samples incubated with mAbs when compared with samples incubated without mAbs (NT, not treated) suggesting activation of neutrophils by mAbs. The Median and interquartile ranges are represented by the error bars. There was a hierarchy in changes such that the MFI of CD62L was lowest for OBZ < OBZ-gly < RTX whereas the MFI of CD11B was highest for OBZ > OBZ-gly > RTX. RTX, rituximab, OBZ, Obinutuzumab and OBZ-WT, Obinutuzumab wild-type. * p<0.05; **, p<0.005; ***, p<0.0001.

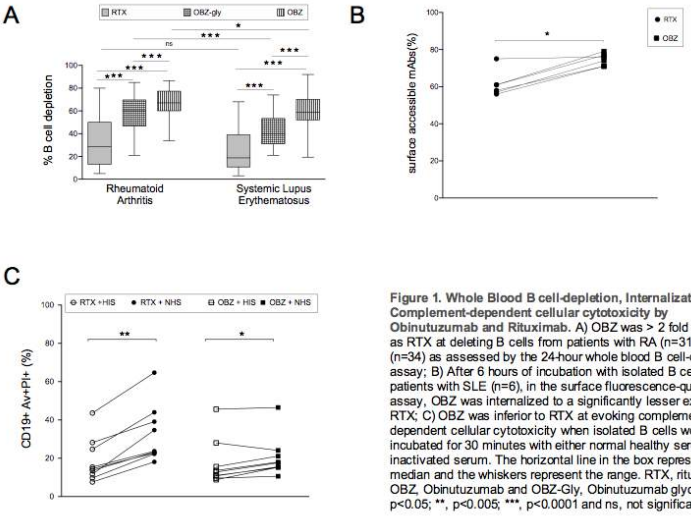

Figure 1. Whole Blood B cell-depletion, Internalization and Complement-dependent cellular cytotoxicity by Obinutuzumab and Rituximab. A) OBZ was > 2 fold as efficient as RTX at deleting B cells from patients with RA (n=31) and SLE (n=34) as assessed by the 24-hour whole blood B cell-depletion assay; B) After 6 hours of incubation with isolated B cells from patients with SLE (n=6), in the surface fluorescence-quenching assay, OBZ was internalized to a significantly lesser extent than RTX; C) OBZ was inferior to RTX at evoking complement-dependent cellular cytotoxicity when isolated B cells were incubated for 30 minutes with either normal healthy serum or heat inactivated serum. The horizontal line in the box represents the median and the whiskers represent the range. RTX, rituximab, OBZ, Obinutuzumab and OBZ-Gly, Obinutuzumab glycosylated. * p<0.05; **, p<0.005; ***, p<0.0001 and ns, not significant.

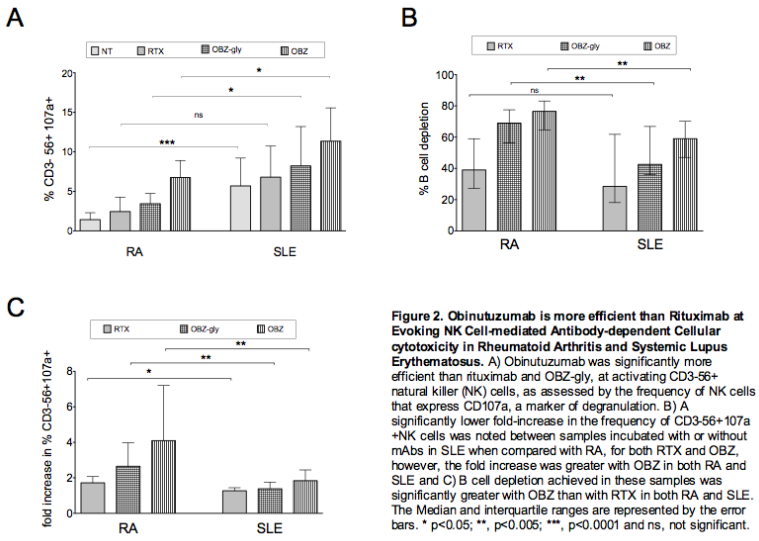

Figure 2. Obinutuzumab is more efficient than Rituximab at Evoking NK Cell-mediated Antibody-dependent Cellular cytotoxicity in Rheumatoid Arthritis and Systemic Lupus Erythematosus. A) Obinutuzumab was significantly more efficient than rituximab and OBZ-gly, at activating CD3-56+ natural killer (NK) cells, as assessed by the frequency of NK cells that express CD107a, a marker of degranulation. B) A significantly lower fold-increase in the frequency of CD3-56+107a +NK cells was noted between samples incubated with or without mAbs in SLE when compared with RA, for both RTX and OBZ, however, the fold increase was greater with OBZ in both RA and SLE and C) B cell depletion achieved in these samples was significantly greater with OBZ than with RTX in both RA and SLE. The Median and interquartile ranges are represented by the error bars. * p<0.05; **, p<0.005; ***, p<0.0001 and ns, not significant.

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Abstract Number: 1113

B Cell Signature Profiling in Systemic Lupus Erythematosus Patients on Belimumab

Michelle T. Ngo[1], Abigail Benitez[2], Kimberly J. Payne[2], Michael De Vera[3], Terry Ann Milford[2] and Karina Marianne D. Torralba[4], [1]Rheumatology, Loma Linda University, Loma Linda, CA, [2]Loma Linda University, Loma Linda, CA, [3]Transplant Surgery, Loma Linda University, Loma Linda, CA, [4]Division of Rheumatology, Department of Internal Medicine, Loma Linda University, Loma Linda, CA
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Background/Purpose: The B cell pool is composed of subsets with different phenotypes and functions that mainly have effector functions to maintain immunologic tolerance. These subsets and their proportions are an individual's "B cell signature" (BCS). Systemic lupus erythematosus (SLE) is a clinically heterogeneous autoimmune disease. BCS SLE studies reveal altered immature and unswitched memory B cell numbers when compared to healthy controls (HC). BCS potentially can be a biomarker for monitoring SLE disease activity. Belimumab is B-cell activating factor inhibitor approved for use in SLE. For this study, we will determine the effect of belimumab on BCS in SLE patients.

Methods: PBMCs and plasma were collected from 5 SLE patients on belimumab, 13 SLE patients conventional non-B cell-standard therapy (ST) and 12 HC. Demographic data, medication history, disease activity and damage measurements were collected. B cell subsets including transitional, naive and memory were assessed using 7-color flow cytometry and Flowjo Analysis software. Plasma BAFF levels were evaluated using ELISA. Subset percentages within the B cell pool (CD19+) and BAFF levels were correlated with clinical parameters. Student t test to analyze differences between groups was used.

Results: Altered BCS in belimumab patients were observed. CD21/CD24 co-expression model for nonmemory subsets showed significant increase in T1 cells ($P < 0.001$) while T2 cells were significantly decreased ($P < 0.0001$) in HC and belimumab groups. When comparing HC to ST, a significant decrease in T2 cells comparable to belimumab was noted. Number of T2 derived naïve cells between HC and SLE was not significant. A significant difference in the number of naive cells between belimumab and ST ($P < 0.01$) was noted. Using IgD/CD27 co-expression to evaluate memory subsets, significant decreases in unswitched memory cells (IgD+) in both ST and belimumab compared to HC ($P < 0.01$), respectively, was noted. Assessment of switched memory cells showed significant decreases ($P > 0.01$) in ST

compared to HC, yet belimumab displayed a significant increase ($P > 0.01$) in switched memory cells compared to ST. Assessment of double negative memory (CD27neg) noted a significant increase in belimumab compared to HC ($P > 0.01$).

Conclusion: This is the first clinical belimumab study using the translational model CD21/CD24 to thoroughly evaluate B cell subsets for BCS. The model was derived from mouse studies evaluating the effect of BAFF on T1 and T2 in promoting the development of auto-reactive naive B cells. Evaluating the effect of belimumab on BCS can serve as a biomarker for patient response. Individual BCS may also allow clinicians to tailor a treatment regimen in either induction and/or maintenance therapy that is specific to their patients in the future.

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Abstract Number: 1114

Profiling Circulating Plasmablasts from Anti-Ro Positive Mothers of Children with Congenital Heart Block to Identify Antigenic Targets Conferring Pathogenicity

Sarah Kongpachith[1], WH Robinson[1], Sara Rasmussen[2], Robert Clancy[3] and Jill P. Buyon[3], [1]Medicine, Division of Immunology and Rheumatology, Stanford University School of Medicine, Stanford, CA, [2]Department of Medicine, Division of Rheumatology, New York University School of Medicine, New York, NY, [3]Medicine, Division of Rheumatology, New York University School of Medicine, New York, NY

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Background/Purpose: Neonatal lupus (NL) is an uncommon autoimmune disease classically manifest as permanent complete heart block and/or transient cutaneous lesions. By definition of NL, there is universal exposure to maternal autoantibodies reactive with the Ro/La ribonucleoprotein complex; however, only 2% of women with these antibodies will have an affected child. Accordingly, this study was initiated to address the hypothesis that antigen agnostic approaches (i.e. those that are antigen-independent) will have utility for identifying important functional antibodies and their targets.

Methods: Peripheral blood mononuclear cells were obtained from 10 Anti-Ro (plus or minus)/La positive mothers (asymptomatic, pauci-symptomatic, SLE, or Sjogren's Syndrome) of children with complete heart block (5 of whom died). Circulating plasmablasts were single-cell sorted and their IgH and IgL chains tagged with cell-specific DNA barcodes before sequencing with Illumina Miseq. Phylogenetic trees of the antibody repertoire were generated via binning the reads from each B cell based on the barcodes. Antibodies representative of clonal families were recombinantly expressed. Profiling of the recombinant antibodies was done by immunofluorescence (IF) using the HEp-2 cell line and ELISAs using native Ro60, recombinant Ro52 and recombinant La.

Results: From inspection of the phylogenetic usage of IgH and IgL in NL mothers, the approach captured a profile inclusive of highly mutated antibodies. Twenty three expressed antibodies representing the repertoires of two mothers were further evaluated. For the majority of monospecific immunoglobulin IgG (16/23), there was strong nuclear and/or cytoplasmic staining which correlated with reactivity on ELISA. Several antibodies showed polyreactivity for multiple antigens by ELISA. In one mother with mild dry eyes and identification of anti-Ro only after the diagnosis of heart block in her fetus, there was evidence of a convergent autoimmune-specific antibody HCDR3 signature. Interestingly, while the antibodies showing evidence of this convergent signature were both positive by IF, they were discordant regarding Ro/La reactivity.

Conclusion: While prior studies used approaches involving preselecting Ro/La antigens to further identify pathogenic autoantibodies, this is the first to define candidates based on clonal families identified through mining the plasmablast antibody repertoires in mothers with the pathogenic antibodies by virtue of their having a child with NL. Monospecific antibodies, particularly the subset with convergent specific antibody signatures, provide a platform for identifying the "pathoepitope" leading to cardiac injury.

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Abstract Number: 1115

B Cell-Intrinsic Interferon Gamma Signals Promote the Development of Systemic Lupus Erythematosus By Enhancing the Formation of Spontaneous Autoimmune Germinal Centers

Shaun Jackson, Nicole Scharping, Holly Jacobs, Tanvi Arkatkar, Socheath Khim and David Rawlings, Seattle Children's Research Institute, Seattle, WA

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Background/Purpose: Type 1 interferon (IFN) is strongly implicated in lupus pathogenesis, and SLE patients frequently express a "type 1 IFN gene signature". The type 2 interferon, IFN gamma (IFN-γ), has also been implicated in lupus development via direct activation of autoreactive T cells. Although B cells are critical in lupus pathogenesis, whether these cytokines exert cell-intrinsic impacts on autoantibody-producing B cells has not been studied. We recently developed a chimeric murine lupus model in which Wiskott-Aldrich syndrome protein (WAS)-deficient B cells promote spontaneous humoral autoimmunity (Jackson, et al. *J Immunol* 2014). An important advantage of the WAS chimera model is that dysregulated immune responses are limited to the B cell compartment, allowing genetic manipulation in a B cell-intrinsic fashion. In the current study, we contrast the impact B cell-intrinsic type 1 interferon and IFN-γ signals on serum autoantibody titers, systemic inflammation and the development of lupus nephritis.

Methods: Using the WAS chimera model of spontaneous humoral autoimmunity, we deleted the type 1 IFN receptor (IFNAR) or IFN-γ receptor (IFNgR) on all hematopoietic cells ("global deletion"), or specifically on B cells ("B cell-intrinsic"). Chimeras were analyzed for autoantibodies, immune activation and immune-complex glomerulonephritis (IC GN) by ELISA, flow cytometry and immunohistochemistry.

Results: Surprisingly, although type 1 IFN enhanced B cell responses *in vitro*, B cell-intrinsic IFNAR deletion exerted minimal impacts on lupus pathogenesis. To address whether other cytokines promote B cell activation in this model, we quantified cytokine production *ex vivo*, and noted prominent CD4 T cell IFN-γ production in diseased WAS chimeras. Consistent with this, global IFNγR deletion prevented autoantibody (Ab) production and systemic inflammation in WAS chimeras. Strikingly, cell-intrinsic deletion of IFN-γR on either T cells or B cells recapitulated the phenotype of global IFNγR deficiency. Mechanistically, deletion of IFNγR on B cells prevented the formation of spontaneous germinal centers (GCs), required for class-switched Ab formation. Consistent with lack of serum autoantibodies, lupus nephritis was abrogated in B cell IFNγR-null chimeras.

In addition to Ab formation, B cells promote autoimmunity via antigen presentation and production of cytokines. Based on prominent B cell IFN-γ production in this model, we hypothesized that B cell-derived IFN-γ enhances spontaneous GC formation. In contrast, rendering B cells unable to produce IFN-γ did not alter the development of murine lupus suggesting that other cellular IFN-γ sources compensate for lack of B cell-derived IFN-γ.

Conclusion: We report the novel observation that IFN-γ, and not type 1 IFN, signals promote systemic lupus via direct actions on B cells. Mechanistically, IFN-γ promotes the formation of spontaneous autoimmune GCs via reciprocal activation of GC B cells and T follicular helper cells. To our knowledge, this study is the first to directly address the impact of B cell IFN-γ activation in murine lupus, of relevance to both the understanding of disease pathogenesis and to efforts to target IFN-γ therapeutically in SLE.

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Abstract Number: 1116

Decreased Expression of Negative Regulators of Toll-like Receptor Signaling and Increased TLR7 Responsiveness in Expanded IgD- CD27- B Cells from Systemic

Lupus Erythematosus Patients

Scott Jenks[1], Benjamin Barwick[2] and Ignacio Sanz[3], [1]Allergy, Immunology, and Rheumatology, Emory University School of Medicine, Atlanta, GA, [2]Emory University, Altanta, GA, [3]Medicine, Emory University, Atlanta, GA
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Background/Purpose:

B cell homeostasis is perturbed in SLE patients; in particular many patients with active disease have a large expansion of IgD- CD27- B cells (DN). The DN population is heterogeneous for CXCR5 expression, and CXCR5- DN are a the majority population in SLE patients with expanded DN but not in HCD. To further understand how these expanded cells differ from other B cells subsets and how they may be dysregulated in SLE, we analyzed gene transcription through RNA sequencing of sorted purified naïve, switched memory (SWM), CXCR5+ DN and CXCR5- DN (DNN) B cells from HCD and SLE patients with expanded DNN.

Methods:

RNA from sorted B cells subsets was isolated, amplified and sequenced. The resulting reads were aligned to the human genome and transcripts were assembled and quantified using edgeR. Transcripts are expressed as reads per kilobase per million (RPKM), genes that showed at least a two fold difference and a false discover rate < 0.05 were considered differentially expressed. TLR7 signalling after stimulation with R848 was measured by staining with anti- phospho-tyrosine specific anti-ERK. Changes in gene expression were evaluated by flow cytometry of purified B cells after overnight R848 stimulation.

Results:

Genes differentially regulated between SLE and HCD B cells were primarily interferon regulated genes and were up-regulated in all B cell subsets, including several positive regulators of viral pathogen sensing and TLR signaling. DNN showed several commonalities in gene expression with naïve B cells that differentiated them from memory B cells and CXCR5+ DN. These included higher expression of BCL6, IL21 receptor, and CD72 and decreased expression of the high affinity IL2 receptor, CD25, and genes associated with active cell division. Significantly, a negative regulator of TLR signaling, TRAF5, was uniquely down regulated in DNN in both HCD and SLE patients. Consistent with decreased expression of negative regulators of TLR signaling, DNN had enhanced *in vitro* sensitivity to TLR7 antagonist R848 as measured by ERK phosphorylation. Furthermore, R848 increased expressions of genes necessary for antigen presentation including HLA-DR and CD86 but decreased expression of the inhibitory receptors CD32b and CD72 in DN B cells but not naïve B cells.

Conclusion:

DNN represent a separate B cell lineage with a distinct origin and function as they differed from other B cells subsets both in uniquely expressing several genes and and a lack expression of other genes. One of the genes that is down regulated in DNN relative to all other B cell subsets is TRAF5, which in mice has been shown to negatively regulate TLR responses in B cells. Supporting the hypothesis that this gene may have a similar function in human B cells, both TLR7 signaling and responsiveness was enhanced in DNN. RNA from apoptotic cells can be internalized as immune complexes and through B cell receptors specific for auto-antigens. These antigens are powerful stimulants of TLR7 and DNN are uniquely sensitive to this signal. Furthermore, increased expression of HLA-DR and CD86 in DNN after TLR will enhance antigen presentation to CD4 T cells. DNN likely play an important role in SLE pathogenesis by linking innate TLR signaling with B cell mediated adaptive immunity.

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Abstract Number: 1117

The B Cell Survival Cytokine BAFF Promotes Systemic Lupus Erythematosus Via Activation of TACI, Not BAFF Receptor

Holly Jacobs[1], Christopher Thouvenel[1], Tanvi Arkatkar[1], Nicole Scharping[1], David Rawlings[2] and **Shaun Jackson**[1], [1]Seattle Children's Research Institute, Seattle, WA, [2]Pediatrics/Immunology, Washington, Seattle, WA
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Background/Purpose: Systemic lupus erythematosus (SLE) is a multisystem autoimmune disease characterized by polyclonal B cell activation and production of class-switched antinuclear antibodies (ANA). Transgenic mice (Tg) overexpressing B cell activating factor of the TNF family (BAFF, also known as BLyS) develop an autoimmune disease resembling human SLE. Consistent with this, lupus nephritis patients have increased serum BAFF levels and the BAFF-targeted monoclonal Belimumab is an approved SLE therapy. BAFF binds to distinct receptors expressed on B cells, the BAFF receptor (BAFF-R) and transmembrane activator and CAML interactor (TACI). Because BAFF-R deletion results in a loss of mature B cells, this receptor has been suggested to explain the autoimmune phenotypes in BAFF-Tg mice. However, potential important roles for TACI in lupus pathogenesis have not been addressed.

Methods: To test the impact of TACI on BAFF-driven autoimmunity, we crossed BAFF-Tg and *Taci-/-* mice. Serum autoantibodies, peripheral B cell development, splenic immune activation and development of immune-complex glomerulonephritis (IC GN) was assessed by ELISA, flow cytometry and immunohistochemistry.

Results: Surprisingly, deletion of TACI abrogated serum anti-nuclear autoantibodies (ANA) in BAFF-Tg mice. In addition, lack of TACI prevented autoantibodies targeting RNA- and DNA-associated self-antigens, including Sm/RNP and dsDNA, across all immunoglobulin isotypes and subtypes, including IgM, IgG, IgA, IgG2b, IgG2c, IgG3. Lack of autoantibodies was not explained by alterations in peripheral B cell development, since both BAFF-Tg and *Taci*$^{-/-}$.BAFF-Tg mice exhibited similar B cell hyperplasia, with equivalent expansion of the follicular (FM) and marginal zone (MZ) compartments.

Aged BAFF-Tg mice develop prominent immune-complex glomerulonephritis, characterized by mesangial expansion, glomerular basement membrane thickening and capillary occlusion. Consistent with the lack of serum autoantibodies, *Taci-/-*.BAFF-Tg were completely protected from murine lupus nephritis, as evidenced by lack of albuminuria and restoration of renal histology.

Conclusion: We report the novel observation that TACI, not BAFF-R, is the predominant B cell receptor promoting BAFF-mediated murine lupus nephritis. These findings suggest that TACI may be an important therapeutic target in SLE, particularly in patients with high serum BAFF levels.

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Abstract Number: 1118

Role of the Chemokine Receptor CXCR3 in the Function of Regulatory B Cells in Patients with SLE

Shun-ichiro Ota[1,2], Hiroaki Niiro[3], Naoko Ueki[2,4], Yuri Hirosaki[2], Hirofumi Tsuzuki[2], Siamak Jabbarzadeh-Tabrizi[2], Tsuyoshi Nakayama[2], Koji Mishima[2], Ayako Takaki[2], Hiroki Mitoma[2], Mitsuteru Akahoshi[2], Yojiro Arinobu[2], Hiroshi Tsukamoto[2] and Koichi Akashi[2], [1]Department of Rheumatology, Internal medicine and connective tissue disorders, Shimonoseki City Hospital, Shimonoseki, Japan, [2]Department of Medicine and Biosystemic Science, Kyushu University Graduate School of Medical Sciences, Fukuoka, Japan, [3]Clinical Education Center, Kyushu University Hospital, Fukuoka, Japan, [4]Division of Nephrology and Rheumatology, Fukuoka University, Fukuoka, Japan
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Background/Purpose: The emerging application of B-cell directed therapies in autoimmune diseases has led to the discovery of a novel B cell population, referred to as regulatory B cells (Bregs), that exerts regulatory functions via IL-10 production. We previously showed that human Bregs are strongly induced in IgM-memory (IgMM) B cell subsets following TLR9 stimulation and Breg functions are impaired due to attenuated induction of Blimp1 in systemic lupus erythematosus (SLE). It remains, however, largely elusive about the underlying mechanisms of this phenomenon in SLE patients. Given a critical role of C-X-C chemokine receptor type 3 (CXCR3) in inflammation, in the present study we have tested whether the migratory potential of Bregs is associated with their regulatory functions in healthy donors and patients with SLE.

Methods: Human B cell subsets in healthy donors and patients with SLE were enriched by cell sorting and subjected to the analysis of gene and protein expression by quantitative PCR, ELISA and flow cytometry.

Results: CXCR3, the chemokine receptor for CXCL10 and CXCL11, is predominantly expressed on T helper type 1 cells, a T-cell subset which plays a pivotal role in the initiation and perpetuation of inflammation. In human B cells CXCR3 was mainly expressed on memory subsets. We first tested Breg potential of CXCR3+ and CXCR3- IgMM B cells in healthy donors, and found that both subsets exhibited comparable potential in IL-10 production, suggesting that CXCR3 expression itself does not affect Breg function. Intriguingly, however, stimulation of CXCL10 and CXCL11 exerted inhibitory and stimulatory effects, respectively, on IL-10 production along with alteration of Blimp1 expression. Consistent with previous findings that the serum levels of CXCL10 are elevated in patients with SLE, CXCR3+ IgMM B cells in patients exhibited decreased potential in IL-10 expression compared with this subset in healthy donors, suggesting that aberrant expression of chemokine ligands is associated with crippled Breg function in patients with SLE.

Conclusion: Together, these findings uncover not only a new aspect of regulation of Breg function in humans, but also a novel clue to the revitalization of Bregs for the treatment of SLE.

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Abstract Number: 1119

High Resolution Motif Mapping of in Situ Anti-Native-Vimentin Antibodies in Lupus Tubulointerstitial Nephritis

Andrew Kinloch[1], Yuta Asano[2], Balazs Banfai[3], Gregor Dernick[3], Carole Henry Dunand[4], Nirit Mor-Vaknin[5], Maureen Legendre[5], David Markovitz[5], Thomas Schindler[6] and Marcus R. Clark[7], [1]University of Chicago, Chicago, IL, [2]Committee of immunology, University of Chicago, Chicago, IL, [3]Translational Technologies and Bioinformatics, Roche, Basel, Switzerland, [4]Rheumatology and Knapp Center for Lupus and Immunology Research, University of Chicago, Chicago, IL, [5]University of Michigan, Ann Arbor, MI, [6]Roche Innovation Center Basel, Roche, Basel, Switzerland, [7]Rheumatology and Knapp Center for Lupus Research, University of Chicago, Chicago, IL
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Background/Purpose: Severe lupus tubulointerstitial nephritis (TIN) is prognostic of renal failure and characterized by an *in situ* autoantibody response. By characterizing monoclonal antibodies engineered from *in situ* activated B cells and plasmablasts using mass spectrometry and whole protein arrays we identified vimentin as the dominant antigen targeted by this *in situ* immune response. Direct binding of mAbs and TIN serum IgG to vimentin, together with multi-color confocal microscopy of lupus kidney samples confirmed autoantibody reactivity and that vimentin was a dominant autoantigen expressed in the inflamed tubulointerstitium. To understand the origin and evolution of this anti-vimentin antibody response we mapped the specific epitopes these antibodies recognized and, by reversion to germline, identified their original antigenic specificities.

Methods: Twelve IgG1 mAbs previously cloned from the inflamed tubulointerstitium of 6 lupus patients were expressed. Those with the highest anti-vimentin immunoreactivity were reverted to germ-line. Selected antibodies were then screened for immunoreactivity against purified bovine vimentin, recombinant human vimentin expressed in bacteria and vimentin that had been citrullinated (and confirmed as such by mass spectrometry) by PAD4. Nimblegen peptide arrays covering the entire human proteome as overlapping 12mers were probed.

Results: Previously characterized anti-vimentin antibodies bound directly to recombinant human vimentin and this binding was strongly inhibited by *in vitro* citrullination. Immunoreactivity with recombinant human vimentin and purified bovine vimentin was similar suggesting that no post-translational modifications were required for antibody binding. Using the Nimblegen arrays, we identified two epitopes within vimentin that both contained arginines and which were potential sites of citrullination. When anti-vimentin antibodies were reverted to germline, they still recognized vimentin but with a relative affinity significantly less than the mutated parent antibody.

Conclusion: These data indicate that the *in situ* humoral immune response in lupus tubulointerstitial nephritis is specific for vimentin that has not been citrullinated and therefore is fundamentally different than that associated with rheumatoid arthritis. Furthermore, this immune response arises from a naïve repertoire already reactive with vimentin and not with the nuclear antigens most often associated with systemic lupus erythematosus. These data suggest that unique mechanisms of *in situ* antibody selection drive local inflammation in lupus tubulointerstitial disease.

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Abstract Number: 1120

Analysis of SLE Plasmablasts By High Throughput Pairing of the Immunoglobulin Heavy and Light Chain (VH-VL)

Deepak Tomar[1], Christopher Tipton[1] and Ignacio Sanz[2], [1]Medicine/Rheumatology, Emory University School of Medicine, Atlanta, GA, [2]Rheumatology, Emory University School of Medicine, Atlanta, GA

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Background/Purpose: In-depth analysis of the molecular and antigenic properties of antibody secreting cells (ASC) is critical for our understanding of autoimmune diseases. This goal however has been hampered by technological barriers imposed by low-throughput technologies to interrogate the ASC at the single cell level. We describe here the incorporation of a high throughput methodology for linking the B cell receptor's heavy and light chain variable region (VH and VL) for analyzing the plasmablast B cell population from a SLE patient. Conventional techniques for sequencing of genomic DNA or cDNA from single cells are limited by low efficiency and low cell throughput (<200–500 cells), whereas >2 x 10^6B cells per experiment can be analyzed by this single-cell, emulsion-based technology for sequencing antibody VH-VL repertoires.

Methods: We use a flow focusing apparatus to encapsulate the single B cells in to the emulsion droplets containing the lysis buffer and oligo dT magnetic beads for capturing the mRNA, followed by an emulsion RT-PCR for generating the VH and VL linked products for next generation sequencing. Approximately 50,000 plasmablasts (CD19+IgD-CD27^{high}CD38^{high}CD138^{neg}) from a SLE patient were flow sorted and VH and VL transcript were linked using emulsion RT-PCR. IgH, IgL and linked transcripts were sequenced via Illumina MiSeq.

Results: 20,000 different sequences representing over 2,200 different clonotypes were identified, thereby demonstrating a very polyclonal PB repertoire during Lupus flares. High concordance was shown with Illumina miseq data obtained from bulk PB obtained from a separate aliquot of the same blood draw. Both experiments also demonstrated the presence of substantial clonal expansions of the SLE-associated VH4-34 clones.

Conclusion: We have incorporated a high-throughput methodology of linking immunoglubulin heavy and light chain variable region (VH-VL) transcripts prior to amplification and repertoire analysis via NGS. The ability of this approach to combine deep sequencing with single cell antibody generation should greatly enhance our understanding of the antigenic triggers involved in the pathogenesis of SLE and

other autoimmune diseases.

Disclosure: D. Tomar, None; **C. Tipton**, None; **I. Sanz**, None.

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Abstract Number: 1121

Breach of B Cell Anergy in New Zealand Black Congenic Mice

Kieran Manion[1,2], Yuriy Baglaenko[1,2], Nan-Hua Chang[3] and Joan Wither[3], [1]Immunology, University of Toronto, Toronto, ON, Canada, [2]Genetics and Development, Toronto Western Research Institute, University Health Network, Toronto, ON, Canada, [3]University Health Network, Toronto, ON, Canada

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Background/Purpose: Anti-DNA B cells are a primary cause of pathology in individuals with systemic lupus erythematosus (SLE), producing autoantibodies that deposit in diverse tissues and cause extensive inflammatory damage. Congenic mice generated through the introgression of New Zealand Black (NZB) chromosome 1 (C1) susceptibility loci onto the non-autoimmune C57BL/6 (B6) strain are an effective way of modelling lupus and parsing its pathogenesis. Our laboratory has previously provided evidence that a B cell defect instrumental in autoantibody production localizes to the C1d (170.8-181 Mb) region of the NZB C1 and we have further shown that additional T cell and dendritic cell (DC) defects map to the C1b-d (124-181 Mb) locus. Since B cells from both C1d and C1b-d mice with transgenes for hen egg lysozyme (HEL)-specific immunoglobulin and soluble HEL demonstrated a breach of anergy, we hypothesized that the C1d interval alone would be sufficient to breach tolerance to nuclear antigen. Here, we have used a knock-in model of anergy to ssDNA to address this question.

Methods: Genes for the 3H9 heavy chain (IgH^a) and Vκ8 light chain were knocked into their proper loci in the C1d and C1b-d congenic strains in order to generate mice with homogeneous, ssDNA-specific B cell repertoires. Female B6, C1d and C1b-d Vκ8/3H9 and wild type mice were aged to 8 months, at which time sera, splenocytes and bone marrow were collected. Serum levels of anti-nuclear autoantibody production were measured by ELISA, while T and B cell activation and localization were assessed using flow cytometry and immunofluorescence microscopy.

Results: C1d.Vκ8/3H9 mice produce significantly higher levels of anti-ssDNA $IgG2a^a$ autoantibodies compared to their B6 counterparts. In line with this increased $IgG2a^a$ production, these mice also have a significant increase in the proportion of germinal centre B cells and plasma cells compared to B6 Vκ8/3H9 mice. As anticipated, C1b-d.Vκ8/3H9 mice show an even stronger breach of anergy, with significant increases in anti-ssDNA IgG, IgM and $IgG2a^a$ autoantibodies as well as significantly higher proportions of germinal centre B cells than their B6 counterparts. These changes mirror the observed increase in the number of follicular helper and IFNγ-producing T cells, which are thought to provide support for germinal centre B cell development and subsequent autoantibody production. C1d and C1b-d mice also show evidence of defective receptor editing, with significantly lower proportions of B cells with the Igλ1 light chain in the bone marrow compared to B6 counterparts. In agreement with our previous observations of increased survival and peripheral expansion of autoreactive B cells in the HEL model, the proportions of $Ig\lambda1^+$ B cells normalize in the spleen, further supporting the observed breach of anergy.

Conclusion: Our results confirm the presence of a B cell defect to nuclear antigen in the C1d interval and further imply that this defect involves perturbation of both central and germinal centre tolerance.

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Abstract Number: 1122

B Cell Phenotypic Changes in Anti-Nuclear Antibody Positive Individuals Prior to the Onset of Systemic Autoimmune Rheumatic Disease

Joan Wither[1], Nan-Hua Chang[1], Babak Noamani[2], Dennisse Bonilla[1], Sindhu R. Johnson[3], Larissa Lisnevskaia[4], Earl Silverman[5], Arthur Bookman[1] and Carolina Landolt-Marticorena[1], [1]University Health Network, Toronto, ON, Canada, [2]Genetics and developmental biology, University Health Network, Toronto, ON, Canada, [3]Toronto Scleroderma Program, Toronto Western Hospital, Mount Sinai Hospital, University of Toronto, University Health Network Pulmonary Hypertension Programme, Toronto, ON, Canada, [4]Lakeridge Health Services, Oshawa, ON, Canada, [5]The Hospital for Sick Children, Toronto, ON, Canada
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Background/Purpose: Patients with systemic autoimmune rheumatic diseases (SARD) often have a prolonged pre-clinical phase during which they are anti-nuclear antibody $(ANA)^+$ but lack clinical symptoms. It has been proposed that progression from asymptomatic autoimmunity to clinical disease is accompanied by immunologic changes that could be used as predictors of disease development. However, little is known about the cellular derangements that accompany the transition from benign to pathological autoimmunity. Previous studies indicate that a number of B cell phenotypic changes are seen in SARD patients including changes in the proportions of various naïve and memory B cell subsets, increased B cell activation and elevated levels of plasmablasts/plasma cells. Here we examined whether ANA^+individuals who lack sufficient symptoms for a SARD diagnosis share any of the B cell phenotypic changes seen in early SARD.

Methods: ANA^+individuals who: 1) lacked clinical symptoms of SARD (ANS); 2) had a least one clinical symptom of SARD (UCTD); or 3) had a recently diagnosed steroid and immunosuppressive naïve SARD (SLE, SS, SSc, MCTD, DM) were recruited from clinics at UHN/MSH hospitals. Healthy controls (HC) were also recruited. PBMCs were isolated over a Ficoll gradient, stained with various combinations of fluorescently labeled antibodies and analyzed by flow cytometry. ANAs were measured through the hospital laboratory.

Results: B cell phenotypes were examined for 35 HC, 40 ANS, 24 UCTD, and 53 early SARD (22 SS, 19 SSc, 7 SLE, 2 MCTD, 1 DM) patients. Although significantly increased proportions of $CD19^{lo/-}CD38^{+++}CD27^{+++}$ plasmablasts/plasma cells were seen in all SARD patients (except those with SSc), these were not seen in ANS and UCTD patients and significant increases in $CD138^+$ plasma cells were not seen in any of the ANA^+ subsets except SS. Patients with early SARD had a number of changes in their naïve and memory B cell subsets, as previously reported for patients with established disease including: increased proportions of mature naïve B cells (SSc); increased proportions of T1T2 cells (SLE and SS); and decreased proportions of switched memory B cells ($CD27^+IgD^-$) in all SARD. However, in contrast to some reports no changes were seen in the proportion of $CD27^+IgD^+$ un-switched or $CD27^-IgD^-$ memory cells. Similar decreases in the proportion of switched memory B cells were seen in ANS and UCTD patients, and as seen for the SARD patients these cells were activated with elevated levels of CD86 as compared to HC. Significantly increased activation of the $CD27^-IgD^-$ memory compartment was also seen in ANS, SLE and SS patients, with trends observed for the other patient subsets. When all ANA^+ individuals were examined there was a significant association between ANA titer and the proportion of $CD19^{lo/-}CD38^{+++}CD27^{+++}$ and $CD138^+$plasmablast/plasma cells as well as the reduced size and increased activation of the switched memory B cell compartment. This was also seen when the ANS subset was examined alone.

Conclusion: B cell phenotypic abnormalities appear to precede the onset of clinical disease in ANA^+ individuals and correlate with autoantibody levels as reflected by the ANA titer.

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Abstract Number: 1123

Regulatory B Cells Regulate Skin and Lung Fibrosis and Immunological Abnormalities in a Topoisomerase I and Complete Freund's Adjuvant-Induced Scleroderma Model Via an Antigen-Specific Manner

Ayumi Yoshizaki[1], Takashi Taniguchi[1], Kouki Nakamura[1], Ryosuke Saigusa[1], Takashi Yamashita[1], Takehiro Takahashi[1], Tetsuo Toyama[1], Yohei Ichimura[1], Yoshihide Asano[2] and Shinichi Sato[1], [1]Dermatology, University of Tokyo Graduate School of Medicine, Tokyo, Japan, [2]University of Tokyo Graduate School of Medicine, Tokyo, Japan
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Background/Purpose: Immune cells play a critical role in systemic sclerosis (SSc). B cells have more functions than producing antibodies, including antigen-presentation, various cytokine production, and T cell differentiation. In addition, abnormal B cell function can drive the development of autoimmunity. However, specific B-cell subsets can also play a protective role during T cell-mediated inflammation and have been termed regulatory B cells. Regulatory B cells with the ability to express the inhibitory cytokine interleukin (IL)-10 have been identified. Mice subcutaneously injected with topoisomerase-I and complete Freund's adjuvant (CFA) develop skin and lung fibrosis and inflammatory infiltration with anti-topoisomerase I antibody and fibrogenic cytokine production, which more closely mimics the features of human SSc than traditional models, such as tight-skin mouse. However, the contribution of regulatory B cells and the mechanisms underlying suppression effects of immunological abnormalities in topoisomerase I and CFA-induced SSc remain unknown. Therefore, we investigated the role of regulatory B cells, in the development of fibrosis and autoimmunity induced by topoisomerase I and CFA.

Methods: Topoisomerase I and CFA were injected 4 times subcutaneously into the shaved back of the mice at an interval of 2 weeks. To assess the antigen-specific regulatory B cell function, wild type and activation-induced cytidine deaminase (AID)-deficient mice were used. AID is important molecules for inducing immunoglobulin class switch and somatic hypermutation. CD5+ and CD1dhi regulatory B cells were obtained from topoisomerase I and CFA-induced SSc model mice and adoptively transferred to these mice. Skin and lung sections were assessed histologically. Protein and mRNA levels of IL-4, IL-6, IL-17, tumor necrosis factor-α, transforming growth factor-β, and interferon-γ were measured using ELISA and real-time RT-PCR.

Results: In AID deficient mice, topoisomerase I and CFA treatment induced lower number of topoisomerase I-specific regulatory B cells than those in wild type mice. Furthermore, regulatory B cells obtained from wild type mice significantly attenuated the development of skin and lung fibrosis, skin expression of fibrogenic cytokines, especially IL-4, IL-6, and IL-17, and hyper-g-globulinemia compared with those from AID deficient mice.

Conclusion: Regulatory B cells are potent negative regulators of antigen-specific inflammation and T-cell-dependent autoimmunity in topoisomerase I and CFA-induced SSc model mice. This study revealed fist that regulatory B cells ameliorate fibrosis and immunological abnormalities via an antigen-specific manner in SSc.

Disclosure: A. Yoshizaki, None; **T. Taniguchi**, None; **K. Nakamura**, None; **R. Saigusa**, None; **T. Yamashita**, None; **T. Takahashi**, None; **T. Toyama**, None; **Y. Ichimura**, None; **Y. Asano**, None; **S. Sato**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/regulatory-b-cells-regulate-skin-and-lung-fibrosis-and-immunological-abnormalities-in-a-topoisomerase-i-and-complete-freunds-adjuvant-induced-scleroderma-model-via-an-antigen-specific-manner

Abstract Number: 1124

Bruton's Tyrosine Kinase Levels Are Increased in B Cells from Patients with Primary Sjögren's Syndrome

Odilia B.J. Corneth[1], Gwenny Verstappen[2], Marjolein de Bruijn[1], Erlin A. Haacke[3], Arjan Vissink[4], Hendrika Bootsma[5], Frans G.M. Kroese[2] and Rudi W. Hendriks[1], [1]Pulmonary Medicine, Erasmus MC, Rotterdam, Netherlands, [2]Rheumatology and Clinical Immunology, University Medical Center Groningen, Groningen, Netherlands, [3]Pathology, University Medical Center Groningen, Groningen,

Netherlands, [4]Oral and Maxillofacial Surgery, University Medical Center Groningen, Groningen, Netherlands, [5]Department of Rheumatology and Clinical Immunology, University Medical Center Groningen, Groningen, Netherlands
First publication: September 29, 2015

SESSION INFORMATION

Session Date: Monday, November 9, 2015

Session Title: B cell Biology and Targets in Rheumatolid Arthritis and other Autoimmune Disease Poster

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: Upon B cell receptor stimulation, B cells increase protein expression levels of the key downstream signaling molecule Bruton's tyrosine kinase (BTK). BTK-transgenic mice that overexpress BTK exclusively in B cells, spontaneously develop antinuclear autoantibodies and SLE/Sjögren-like autoimmunity. These mice exhibit increased levels of T follicular helper (Tfh) cells and T regulatory (Treg) cells in lymphoid tissues and develop lymphoid infiltrates in salivary glands and lungs, which contain ectopic germinal centers. Therefore, we aimed to investigate whether BTK expression is also dysregulated in B cells from patients with primary Sjögren's syndrome (pSS).

Methods: Twenty-six treatment-naïve pSS patients, which fulfilled the revised AECG criteria, and 26 sex- and age-matched healthy controls were included in this study. Fifteen pSS patients were treated with abatacept (i.v.) for 24 weeks. Peripheral blood mononuclear cells (PBMCs) and serum were collected from 26 patients at baseline, and from 15 treated patients at 4, 12, 24, 36 and 48 weeks after the first dose of abatacept. B and T cells were analyzed by 12-color flow cytometry. (auto-)Antibodies were measured by ELISA. Histopathological analysis was performed on parotid gland biopsies from 15 pSS patients before and after abatacept treatment.

Results: Flow cytometry analysis of PBMCs from pSS patients and healthy controls revealed that in 16 of 26 of the patients, BTK expression levels were increased in B cells, compared to levels in healthy controls ($p=0.032$). Excitingly, these levels were consistently higher in all B cell subsets, including naïve B cells. In pSS patients with high BTK expression levels, serum RF levels were also increased ($p=0.035$) and a trend towards increased levels of Ro52 and Ro60 (SSA) was found. There was no correlation between BTK levels in B cells from pSS patients and total serum immunoglobulins (IgG, IgA, IgM). Treatment of pSS patients with abatacept, which targets co-stimulation of T cells, resulted in a decrease of the elevated BTK expression levels in circulating B cells to levels in healthy controls ($p=0.003$). We further observed that abatacept treatment reduced absolute numbers of circulating Tfh and Treg cells, while numbers of Th1, Th2 and Th17 were not affected. Although abatacept did not influence the amount of infiltrate in parotid gland tissue, the number of germinal centers declined, illustrating the Tfh cell dependency of these structures.

Conclusion: We show that BTK levels in circulating B cells are increased in a large proportion of pSS patients. High BTK levels may reduce thresholds for B cell activation, and thereby contribute to B cell autoreactivity. In pSS patients, this is reflected by the positive association of elevated BTK levels in B cells with serum RF levels. The observation that abatacept treatment reduced BTK levels in pSS patients implies that high BTK levels are -at least partly- dependent on T cell co-stimulation. Our data may further suggest that Tfh cells play a pivotal role in T cell dependent BTK expression. Together, this study underlines the importance of interfering with B-T cell interaction in the treatment of pSS.

Disclosure: O. B. J. Corneth, None; **G. Verstappen**, None; **M. de Bruijn**, None; **E. A. Haacke**, None; **A. Vissink**, None; **H. Bootsma**, Roche Pharmaceuticals, 2,Bristol-Myers Squibb, 2; **F. G. M. Kroese**, None; **R. W. Hendriks**, None.

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Abstract Number: 1125

Next-Generation Sequencing Demonstrates Dynamic Recirculation of B Cell Clones in Ectopic Lymphoid Structures of Sjögren's Syndrome

William Murray-Brown[1], Emanuela Carlotti[1], Anwar Tappuni[2], Nurhan Sutcliffe[3], Costantino Pitzalis[4] and **Michele Bombardieri**[5], [1]Centre for Experimental Medicine and Rheumatology, William Harvey Research Institute, QMUL, London, United Kingdom, [2]Oral Medicine Department, Institute of Dentistry, QMUL, London, United Kingdom, [3]Rheumatology, Barts Health NHS Trust, London, United Kingdom, [4]Centre for Experimental Medicine & Rheumatology, Queen Mary's School of Medicine and Dentistry, London, United Kingdom, [5]Experimental Medicine and Rheumatology, Queen Mary University of London, London, United Kingdom
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Session Title: B cell Biology and Targets in Rheumatolid Arthritis and other Autoimmune Disease Poster

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: B cells play a central role in Sjogren's syndrome (SS) pathogenesis whereby autoreactive B-cells populate ectopic germinal centres (eGC) in SS-salivary glands (SG) and undergo somatic hypermutation (SHM) and class-switch recombination of the immunoglobulin (Ig) genes. However, the capacity of specific B cell clones to seed eGC in different SG and undergo clonal diversification is unclear. Here we aimed to unravel the dynamics of B cell recirculation among adjacent minor SG (mSG) biopsies, by investigating immunoglobulin heavy chain (IgH) gene rearrangements and SHM using a high-throughput next-generation sequencing approach.

Methods: IgH gene usage and SHM were investigated in four pairs of mSG biopsies from 4 pSS patients with high B cell infiltration and eGC. Retro-transcription of 100 ng total RNA using constant domain Ig-l, -c and -a specific primers yielded Ig-specific cDNA for use as template in producing libraries representing B cell Ig-gene rearrangements in SS mSGs. Sequencing was performed using the Roche GS-FLX titanium platform.

Results: We generated ~166,000 reads >350 bp in total, and detected 1631 clonotypes (defined as reads with the same IgHV and IgHJ gene usage and equal CDR3 length) across all eight samples. Between 5 and 9 shared clonotypes were observed among paired SG biopsies in all four patients, demonstrating the same B cell can recirculate between different glands. Lineage tree analysis revealed three different patterns of B cell circulation across the biopsies: a) unidirectional circulation of B cell clones from one biopsy to another; b) circulation between the two biopsies – circulating in both directions; c) an undefined pattern with a less-mutated and unidentified precursor migrating from one site to the other.

Conclusion: We show that B cells recirculate between mSG in SS and undergo further rounds of SHM in adjacent glands. These findings demonstrate the dynamic nature of B cell affinity maturation in SS within eCG.

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Abstract Number: 1126

Pyrrolopyrimidine Derivatives That Inhibit BAFF Binding to Its Receptor, BR3, Decrease IgG Production By B Cells in Vitro and in Vivo Model of Autoimmune Diseases

Keiko Yoshimoto[1], Eriko Ishioka[2], Ayumi Nishikawa[1], Katsuya Suzuki[1], Kunio Sugahara[3] and Tsutomu Takeuchi[4], [1]Division of Rheumatology, Department of Internal Medicine, Keio University School of Medicine, Tokyo, Japan, [2]Division of Rheumatology, Department of Internal medicine, Keio University School of Medicine, Tokyo, Japan, [3]Department I, Immunology, Pharmacology Research laboratories I, Research Division, Mitsubishi Tanabe Pharma Corporation, Yokohama, Japan, [4]Keio University School of Medicine, Tokyo, Japan

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Session Time: 9:00AM-11:00AM

Background/Purpose: We have found that the expression level of BAFF receptor (BR3) is abnormally enhanced in peripheral monocytes of patients with pSS, and BAFF robustly increases IL-6 production in vitro by pSS monocytes. In addition, the proportion of BR3-positive monocytes to total monocytes was positively and significantly correlated with the serum IgG level of pSS patients. These data collectively suggest that the elevated expression of BR3 on monocytes is involved in the pathogenesis of pSS which is often accompanied with hypergammaglobulinemia (HgG). Our findings suggest that BR3 is a therapeutic target to treat pSS. In our previous study, we have successfully discovered two pyrrolopryimidine derivatives, BIK12 and BIK13, which inhibit binding of BAFF to BR3, by our original

high-throughput screening (HTS) system. In this study, we investigated inhibitory effects of these compounds on BAFF signaling pathways. To this end, we measured not only IL-6 production by monocytes, but also IgG production by B cells co-cultured with BAFF-stimulated monocytes. In addition, we analyzed the effects of the compounds on serum level of an anti-dsDNA antibody in autoimmune disease model mice received these compounds.

Methods: Peripheral monocytes were stimulated with soluble BAFF (sBAFF) and cultured in vitro with or without peripheral B cells in the presence of BIK-12 or BIK-13. IL-6 production by monocytes and IgG production by B cells were measured by ELISA. For examination of the effects of these compounds in vivo, MRL/lpr and NZBWF1 mice were treated with these compounds three times a week at a dose of 1 mg/kg or 0.2 mg/kg for 6 months. The titer of an anti-ds DNA antibody was measured by ELISA.

Results: sBAFF-induced IL-6 production by peripheral monocytes was significantly suppressed by BIK12 and BIK13 in a dose dependent manner. Similarly, IgG production by B cells cultured with sBAFF-stimulated peripheral monocytes was significantly suppressed by these compounds, while sBAFF itself did not increase IgG production by B cells. These data suggest that inhibition of BAFF binding to BR3 on monocytes suppressed IgG production by co-cultured B cells. Interestingly, the titer of an anti-dsDNA antibody in both MRL/lpr and NZBWF1 mice received BIK13 was lower as compared to control mice after 16 weeks of treatment, indicating that the compound was also efficacious in vivo.

Conclusion: We discovered pyrrolopyrimidine derivatives by HTS which inhibited BAFF signaling, and found that the compounds suppressed IgG production by B cells through affecting monocytes. Our findings strongly suggest that BR3 is a therapeutic target to treat autoimmune diseases which accompany HgG, such as pSS. Moreover, these compounds may provide novel tools to explore the pathological mechanism of the development of autoimmune diseases.

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Abstract Number: 1127

Downregulation of nuclear Factor-Erythroid 2-Related Factor (Nrf2)/Heme Oxygenase-1 Axis in Diabetic Cartilage: Towards a Better Phenotyping of diabetes-Related Osteoarthritis

Carlos Vaamonde Garcia[1,2], Ayah Langar[2], Marie-Charlotte Laiguillon[2], Alice Courties[2], Xavier Houard[2], Saadia Kerdine-Romer[3], Francis Berenbaum[2,4] and Jeremie Sellam[2,4], [1]Tissue Engineering and Cellular Therapy Group. Medicine Department. University of A Coruña, A Coruña, Spain, [2]Inserm UMRS_938, CDR St-Antoine, Univ Paris 06 UPMC, Paris, France, [3]UniverSud, Paris-Saclay, INSERM UMR-S 996, Châtenay-Malabry, France, [4]Department of Rheumatology, Assistance Publique – Hôpitaux de Paris, Saint-Antoine Hospital, Paris, France

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SESSION INFORMATION

Session Date: Monday, November 9, 2015

Session Title: Biology and Pathology of Bone and Joint Poster I: Osteoarthritis Pathogenesis

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: Epidemiological findings support the hypothesis that type 2 diabetes (DB) is an independent risk factor of osteoarthritis (OA). Likewise, we have recently reported a higher responsiveness to inflammatory stress of OA cartilage from DB patients and enhanced IL-1β-induced inflammation in cultured chondrocytes in a high glucose (HG) environment[1]. To investigate whether the antioxidant defense system may participate in this dysregulation, we investigated the involvement of nuclear factor-erythroid 2-related factor (Nrf-2), the master transcriptional regulator of antioxidant responses, and heme oxygenase-1 (HO-1), one of its main target gene, in OA cartilage from DB and non-DB patients, and in normal murine chondrocytes subjected to HG exposure.

Methods: Human cartilage was obtained at the time of knee replacement of DB and non-DB OA patients (with similar age and body mass index). Cartilage explants were incubated for 24h and Nrf-2 and HO-1 tissue levels were assayed by western blot (WB). Articular chondrocytes in primary culture isolated from newborn C57Bl6 mice were stimulated at 72h w/o IL-1β (5 ng/mL) under a normal (5.5 mM; NG) or a high (25 mM; HG) glucose environment. Nuclear translocation of Nrf-2 (30 min) was analyzed by WB. Gene and protein expression of Nrf-2, HO-1 and IL-6 were assessed by RT-qPCR and WB, respectively. ROS production was measured using DCFDA. To

determine the mechanistic pathways involved in cell activation by HG ± IL1β, a HO-1 inducer (CoPP; 10μM) and sulforaphane (SFN; 5mM), a natural Nrf-2 translocation activator, were used, and experiments were also performed in $Nrf2^{-/-}$ mice generated from inbred C57BL/6J background Nrf2 heterozygous mice.

Results: *Ex vivo* experiments indicated that Nrf-2 and HO-1 expressions were reduced in OA cartilage from DB patients (n=7, 0.57-fold [Nrf-2] and 0.34-fold [HO-1]) compared to non-DB patients (n=8, $p<0.05$). HO-1 expression was positively correlated with Nrf-2 levels ($p<0.05$).

In vitro, IL-1β-stimulated chondrocytes exposed to HG had lower Nrf-2 nuclear levels (0.61-fold) than those incubated in NG (n=5, $p<0.05$). In agreement, total protein expression of Nrf-2 by IL-1ß-stimulated cells was also reduced in presence of HG versus NG (0.82-fold; n=5, $p<0.05$). A decreased HO-1 protein levels (0.49-fold) was also observed (n=5, $p<0.05$). HO-1 expression was positively correlated with Nrf-2 ($r = 0.35$; $p<0.05$) and negatively with IL-6 levels ($r= -0.35$; $p<0.05$) using PCR.

CoPP reduced ROS production (-75%) and IL-6 expression (-74%) detected in HG + IL-1ß condition ($p<0.05$). The decrease of HO-1 and increase of IL-6 induced by HG was reversed in IL-1ß-stimulated chondrocytes from $Nrf-2^{-/-}$mice. SFN rescued HO-1 levels and reduced ROS production (-20%) triggered by HG + IL-1ß stimulation ($p<0.05$).

Conclusion: Nrf2/HO-1 axis is disturbed in diabetic OA cartilage and is a critical pathway involved in the hyperglucidic-mediated dysregulation of articular chondrocytes. The impairment of this anti-oxydant system could explain the higher inflammatory responsiveness observed in cartilage from DB patients and may open new opportunities for treating patients with a diabetes-related OA phenotype.

[1]Laiguillon MC et al Osteoarthritis &Cartilage 2015 in press

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Disclosure: C. Vaamonde Garcia, None; **A. Langar**, None; **M. C. Laiguillon**, None; **A. Courties**, None; **X. Houard**, None; **S. Kerdine-Romer**, None; **F. Berenbaum**, None; **J. Sellam**, None.

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Abstract Number: 1128

Insulin-Induced Cartilage Degradation in Osteoarthritis Is Associated to Defective Autophagy

Beatriz Carames[1], Madalena Ribeiro[1,2], Paloma Lopez de Figueroa[1], Alexandrina Mendes[2] and Francisco J. Blanco[1], [1]Cartilage Biology Group. Rheumatology Division, INIBIC-Hospital Universitario A Coruña, A Coruña, Spain, [2]Centre for Neuroscience and Cell Biology, University of Coimbra; Faculty of Pharmacy, University of Coimbra, Coimbra, Portugal

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Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose:

Autophagy, a key cellular quality control mechanism, is defective in Osteoarthritis (OA) and Type 2 Diabetes (T2D). T2D has been proposed as a risk factor for OA. Although epidemiological studies suggest a strong association between these diseases, how T2D may have an effect on the deterioration of articular cartilage is still unknown. *The objective of this study is to understand the role of autophagy in the articular cartilage function under diabetic conditions.*

Methods:

Human chondrocyte cell line (TC28a2) and primary human chondrocytes (HC) were cultivated in DMEM high glucose (25 mM) and treated with Insulin (10, 100, 500 nM) for 2, 6 and 24 hours. Activity of LC3-II, Akt and rpS6 was evaluated by Western blotting (WB). To investigate whether autophagy activation protects from diabetic conditions, autophagy was induce by Rapamycin (10 μM). Human cartilage explants were cultivated in DMEM 25mM glucose and insulin (100, 500, 1000nM) for 24 hours to evaluate histopathological changes. MMP-13 and IL-1β expression was determined by immunohistochemistry and WB, respectively. Expression of LC3 and p-rpS6 was determined by WB in human chondrocytes from Non Diabetic-OA and Diabetic-OA patients.

Results:

In the presence of high glucose and increased doses of insulin autophagy was decreased in a dose dependent-manner in human chondrocytes, as indicated by LC3II expression, the main marker of autophagy activation (TC28-a2; $p< 0.05$ at 6 hours post-treatment; HC; $p < 0.01$ at 24 hours post-treatment). To investigate the mechanism by which autophagy is reduced by insulin, Akt and rpS6 phosphorylation was analyzed. We observed a significant increase in p-AKT and p-rpS6 activity, suggesting that insulin effect is mediated by AKT/mTOR pathway (TC28-a2 $p< 0.05$ at 6 hours; HC; $p< 0.01$ at 2 hours). Autophagy activation by Rapamycin reversed insulin effects on LC3 and p-rbS6 expression (Tc28a2 and HC:$p < 0.05$), indicating that autophagy induction prevents insulin-mediated autophagy signaling downregulation. To evaluate the impact of insulin-mediated autophagy regulation in the context of articular cartilage biology, cartilage explants were treated with insulin (100, 500 and 1000 nM) for 24 hours. Histological analysis indicated a loss of proteoglycans and increased MMP-13 and IL-1β expression ($p<0.01$) after insulin treatment. Remarkably, chondrocytes from OA-diabetic patients showed decreased LC3 and increased p-rpS6 expression compared to Non-Diabetic OA patients.

Conclusion:

Our findings demonstrate that diabetic conditions decrease autophagy by an AKT/mTOR dependent mechanism. Pharmacological activation of autophagy might protect against T2D in human chondrocytes. Our data also indicate that chondrocytes from OA-diabetic patients exhibit a deficient autophagy. Taking together, these results suggest that impaired autophagy might be one of the mechanisms by which T2D diabetes accelerates cartilage degradation.

Disclosure: B. Carames, None; **M. Ribeiro**, None; **P. Lopez de Figueroa**, None; **A. Mendes**, None; **F. J. Blanco**, Pfizer, Bioiberica, and Gebro Pharma, 5.

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Abstract Number: 1129

Transthyretin Deposition Accelerates the Development of Experimental Osteoarthritis in Mice

Tokio Matsuzaki[1], Oscar Alvarez-Garcia[2], Yukio Akasaki[3], Natalia Reixach[4], Joel Buxbaum[2] and Martin K. Lotz[5], [1]Molecular and Experimental Medicine, The Scripps Research Institute, La Jolla, CA, [2]The Scripps Research Institute, La Jolla, CA, [3]Kyushu University, Fukuoka, Japan, [4]Department of Molecular and Experimental Medicine, The Scripps Research Institute, La Jolla, CA, [5]Division of Arthritis, The Scripps Research Institute, La Jolla, CA

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Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose:

Deposition of amyloid is a common aging-associated phenomenon and a key factor in the pathogenesis of several aging-related diseases. Osteoarthritis (OA) is the most prevalent joint disease and aging is its major risk factor. Transthyretin (TTR) is an amyloidogenic protein. We previously reported that amyloid and TTR deposition were increased in human OA cartilage with aging and OA grade. In addition, amyloidogenic TTR affected chondrocyte survival and induced the OA related genes such as ADAMTS4, interleukin 6 and inducible nitric oxide synthase. Here we investigated the role of TTR in vivo. Transgenic mice for wild-type human TTR (hTTR TG mice) were analyzed using an experimental OA model.

Methods:

TTR in cartilage and chondrocytes was analyzed by immunohistochemistry and Western blotting. OA was surgically induced by destabilizing the medial meniscus of the hTTR TG mice (n=26) and control mice (n=22). Mice were sacrificed 10 weeks after surgery. To investigate the effects of TTR on cartilage, 6-month-old mice were sacrificed and examined by immunohistochemistry, real-time PCR and Western blotting. In addition, quantitative analysis of cell number in cartilage was examined in 6-, 12-month-old mice, and surgical model. OA-related tissue changes were evaluated using the Glasson's semi-quantitative cartilage scoring system and Krenn's synovitis score.

Results:

TTR protein was detected in cartilage in hTTR TG mice, but chondrocytes did not express TTR mRNA, the transgene was highly overexpressed in the liver. ADAMTS4 and MMP13 mRNA were significantly elevated in cartilage in 6 month-old hTTR TG mice compared with control mice. Immunohistochemical and Western blotting analysis showed increased MMP13 expression in the hTTR TG mice 10 weeks after surgery compared with control mice. In addition, nuclear factor-κB (NF-κB) p65 and Phospho-NF-κB p65 was elevated in hTTR TG mice. In the surgical model, both histological OA score and synovitis score were significantly increased in hTTR TG mice. Additionally, cellularity was significantly lower in the 6-month-old hTTR TG mice and hTTR TG mice with surgical OA compared with control mice.

Conclusion:

These findings are the first to show that TTR deposition accelerated the development of OA in the surgically-induced murine OA model. Our observations suggested that reducing TTR amyloid formation can be a new therapeutic approach for OA.

Disclosure: T. Matsuzaki, None; **O. Alvarez-Garcia**, None; **Y. Akasaki**, None; **N. Reixach**, None; **J. Buxbaum**, None; **M. K. Lotz**, None.

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Abstract Number: 1130

Global DNA Methylation Analysis of Osteoarthritic Subchondral Bone Reveals Significant Regional Variation and Similarity to Overlying Cartilage

Matlock A. Jeffries[1,2], Madison Andrews[3], Mary Beth Humphrey[1], Judith A. James[4] and Amr H. Sawalha[5], [1]Rheumatology, University of Oklahoma Health Sciences Center, Oklahoma City, OK, [2]Arthritis and Clinical Immunology, Oklahoma Medical Research Association, Oklahoma City, OK, [3]Department of Medicine, University of Oklahoma Health Sciences Center, Oklahoma City, OK, [4]Arthritis & Clinical Immunology Research Program, Oklahoma Medical Research Foundation, Oklahoma City, OK, [5]Univers, Oklahoma City, OK
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SESSION INFORMATION
Session Date: Monday, November 9, 2015
Session Title: Biology and Pathology of Bone and Joint Poster I: Osteoarthritis Pathogenesis
Session Type: ACR Poster Session B
Session Time: 9:00AM-11:00AM

Background/Purpose: Osteoarthritis (OA) is a leading cause of chronic disability affecting a majority of individuals over age 70. Outside of cartilage, little is known regarding changes in DNA methylation that occur regionally within OA joints. Herein, we performed global DNA methylation analysis of subchondral bone underlying eroded and intact regions of the OA hip joints and compared it to our previous analysis of OA cartilage.

Methods: Twelve femoral heads were obtained from hip arthroplasty for primary OA. From eroded and intact areas of each joint, articular cartilage and 1cm-deep cores of underlying subchondral bone were dissected, frozen in liquid nitrogen, and DNA extracted. Methylation profiling of >485,000 sites was performed using Illumina HumanMethylation450 arrays; differential methylation was defined as FDR-corrected $p<0.01$ with absolute methylation difference of at least 15%. Pyrosequencing confirmed the four most differentially methylated sites.

Results: We identified 5477 hypo- and 1839 hypermethylated CpG sites in subchondral bone underlying eroded cartilage compared to intact tissue, corresponding to 2290 and 621 genes, respectively. The most hypomethylated genes included the RISC component EIF2C2, ERGIc1, the cell adhesion molecule LPP, and the MAPK deactivator DUSP1, whereas the most hypermethylated genes were HOXA7, CD4, CD6, and CD28. Pathway analysis revealed genes involved in cancer (n=96, p=1.38E-12), axonal guidance (n=104, $p=4x10^{-11}$), NFAT signaling (n=55, $p=4x10^{-10}$), and ERK/MAPK signaling (n=55, $p=1x10^{-9}$). The most highly associated upstream regulators included TGFβ1 ($p=3x10^{-39}$), TNF ($p=1x10^{-27}$), and p53 ($p=8x10^{-24}$). Comparing subchondral bone results to our OA cartilage data, 153 methylation sites from 420 genes were differentially methylated in both OA cartilage and subchondral bone. Significant overlap in upstream regulators and many shared pathways were found including ERK/MAPK-, NFAT-, IGF-1-, and PTEN-signaling. Among upstream regulators, TGFβ, miR-124, angiotensinogen, RANKL, and p38 MAPK were all highly associated with differentially methylated genes in both cartilage and subchondral bone. Four previously-identified OA susceptibility genes, COL11A2, FTO, LRP5, and NCOR2,

were differentially methylated in both subchondral bone and overlying cartilage.

Conclusion: Our data implicate epigenetic dysregulation of several genes and pathways in localized areas of subchondral bone underlying OA damage. Although relatively few differentially methylated sites were shared among cartilage and subchondral bone, there was substantial overlap among pathways and upstream regulators. Our work strengthens the notion that a dysregulated epigenome among subchondral bone and cartilage are intimately linked in the pathogenesis of OA, and reiterates that OA represents a disease of the entire joint organ.

Disclosure: M. A. Jeffries, None; **M. Andrews**, None; **M. B. Humphrey**, None; **J. A. James**, None; **A. H. Sawalha**, None.

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Abstract Number: 1131

A Histone Deacetylase Inhibitor SAHA Induce MCPIP1 Expression and Suppress IL-6 Expression By Upregulating Cebpα Expression and Downregulating the Expression of Mir-9 in Human OA Chondrocytes

Mohammad Shahidul Makki[1] and Tariq Haqqi[2], [1]4209 St Rt 44 PO Box 95, Northeast Ohio Medical University, Rootstown, OH, [2]Anatomy & Neurobiology, Northeast Ohio Medical University, Rootstown, OH

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Background/Purpose: Histone deacetylase inhibitors (HDACi) are a class of compounds that inhibits the histone deacetylase activity. MCPIP1 is a negative regulator of IL-6 expression and is expressed at low levels in human osteoarthritis (OA) cartilage. In the present study we tested the effects of class I and class II HDACi on the expression of MCPIP1 and IL-6 in OA chondrocytes.

Methods: OA chondrocytes were isolated by enzymatic digestion of cartilage samples obtained from OA patients who underwent total knee arthroplasty. Primary OA chondrocytes were treated with IL-1β in the absence or presence of SAHA-a class I & II HDACi. Gene expression and protein levels were measured by TaqMan assay and Western blot respectively. Expression of miR-9 was quantified by TaqMan assay. Secreted IL-6 levels were determined by ELISA. MCPIP1 promoter or 3' UTR reporter vector activity was assayed using dual luciferase reporter assay system. MCPIP1 promoter deletion mutants were generated by PCR and cloned into reporter vectors. PCR based Nuclear run-on assay was employed for the analysis of ongoing transcription. Transcription factor binding to the MCPIP1 promoter was determined by ChIP assay performed with ChIP grade antibodies.

Results: Treatment of OA chondrocytes with SAHA robustly induced the expression of MCPIP1 and inhibited the expression of IL-6 mRNAs upon IL-1β stimulation and reduced the secreted IL-6 protein level in the culture medium by ~70%. Treatment of OA chondrocytes with SAHA inhibited the IL-1b-induced expression of miR-9 by ~70%. Luciferase reporter vectors containing the 3'UTR of the MCPIP1 mRNA which contains the miR-9 "seed sequence" exhibited 25% increased luciferase activity in OA chondrocytes upon SAHA treatment compared to controls treated with IL-1β alone. Nuclear run-on assays using nuclei prepared from OA chondrocytes treated with IL-1β alone or IL-1b + SAHA demonstrated increased expression of MCPIP1 (1.4 fold) in OA chondrocytes compared to IL-1β alone-stimulated OA chondrocytes. Using MCPIP1 promoter deletion mutants a 156bp fragment was identified that encompassed sequences sufficient to enhance luciferase activity in OA chondrocytes stimulated with SAHA. *In-silico* analyses identified CEBPa binding site in the 156 bp promoter region and expression of CEBPα was significantly increased upon SAHA treatment in OA chondrocytes. Ectopic overexpression of CEBPα was sufficient to enhance the expression of MCPIP1 and increased the luciferase activity of the reporter vectors containing either the full length MCPIP1 promoter or the 156bp promoter fragment. Recruitment of CEBPα to the MCPIP1 promoter was significantly increased upon SAHA treatment. Finally we found reduced expression of CEBPa in damaged OA cartilage compared to smooth cartilage, which suggests that low level of MCPIP1 expression could be due to the reduced expression of CEBPα in damaged OA cartilage.

Conclusion: These data indicate that HDACi SAHA upregulates MCPIP1 expression and suppress IL-6 expression in IL-1β treated OA chondrocytes via upregulation of CEBPa and inhibition of miR-9 expression. Results of the present study propose a novel therapeutic role for HDACi SAHA for the management of OA.

Disclosure: M. Shahidul Makki, None; **T. Haqqi**, None.

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Abstract Number: 1132

Altered Histone 3 Dynamics at the Matrix Metalloproteinase 1 (MMP1) Transcription Start Site Contributes to MMP1 Suppression in Betaine Supplemented Synovial Fibroblasts in Rheumatoid Arthritis

Selene Glück[1], Niharika Gaur[1], Michelle Trenkmann[1,2], Emmanuel Karouzakis[1], Fangfang Sun[1], Christoph Kolling[3], Beat A. Michel[1], Renate E. Gay[1], Steffen Gay[1], Michel Neidhart[1] and Mojca Frank Bertoncelj[1], [1]Center of Experimental Rheumatology, University Hospital Zurich, University Zurich, Zurich, Switzerland, [2]St. Vincent's University Hospital, Centre for Arthritis and Rheumatic Diseases, Dublin Academic Medical Centre, Dublin 4, Ireland, [3]Schulthess Clinic, Zurich, Switzerland, Zurich, Switzerland
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Background/Purpose:

Synovial fibroblasts (SF) produce elevated levels of matrix degrading enzymes, including matrix metalloproteinase 1 (MMP1), in the joints of rheumatoid arthritis (RA) patients, leading to irreversible joint damage. The aggressive behavior of RASF has been associated with epigenetic alterations, including global DNA hypomethylation and altered histone methylation. Supplementation of SF with re-methylating agents, such as betaine, may attenuate the destructive behavior of SF. Here, we investigated the role of betaine in the regulation of MMP1 expression in SF focusing on histone dynamics at the MMP1 transcription start site.

Methods:

RASF (passages 5-8) were supplemented with 50 mM betaine for two weeks and were cultured for an additional week without betaine. The levels of HOTAIR and MMP1 mRNA were quantified by SYBR Green real time qPCR. The amount of MMP1 protein in cell culture supernatants was assessed by ELISA and normalized to the cell number. SF were transfected with HOTAIR siRNA (72h) using Lipofectamine 2000. The Roadmap Epigenomics database was used to determine regions enriched for histone 3 lysine 4 trimethylation (H3K4me3) and histone 3 lysine 27 trimethylation (H3K27me3) at the promoters of HOTAIR and MMP1 and in the region 500 bp downstream of their transcription start sites. The levels of H3, H3K4me3 and H3K27me3 were assessed using chromatin immunoprecipitation. Adhesion to cell culture plates and proliferation of SF were monitored with xCELLigence RTCA DP Instrument. Apoptosis was analyzed by flow cytometry using the Annexin V/PI assay.

Results:

The levels of HOTAIR (0.7±0.03 vs. 1 in untreated, p=0.005 n=3), MMP1 mRNA (0.54±0.27, p=0.008, n=6) and MMP1 protein (0.4±0.3, p=0.02, n=6) were significantly reduced in SF supplemented with 50 mM betaine for two weeks and were down regulated by 10%±7.8% (n=3) after an additional week without betaine. Moreover, betaine supplemented SF adhered less strongly to the cell culture plate (cell index=0.7±0.1 vs. 1 in untreated SF, n=3) and proliferated slower than untreated SF (doubling time=1.4±0.3 vs.1 in untreated SF, n=3). The number of apoptotic cells did not increase after supplementation. Silencing of HOTAIR resulted in significant up regulation of MMP1 mRNA (2.6±0.8 vs. 1 in control transfected, p<0.0001, n=8), indicating that HOTAIR is not involved in MMP1 repression in betaine supplemented SF. In contrast, the levels of activating H3K4me3 mark 74 to 220 bp downstream the transcription start site of MMP1 (0.66±0.23 vs. 1 in untreated, n=2) and at the HOTAIR promoter (-1908-2008 bp, 0.66±0.09 vs. 1 in untreated, n=2) were reduced in betaine supplemented SF, whereas the repressive H3K27me3 mark was significantly increased 74 to 220 bp downstream the transcription start site of MMP1 (2.4±0.2 vs. 1 in untreated, p=0.046, n=2). Of interest, the levels of H3 at the HOTAIR promoter diminished in supplemented SF, suggesting that betaine induced eviction of H3.

Conclusion:

We provide the first evidence that, by altering the histone dynamics at gene regulatory sites, betaine supplementation may regulate the

transcription of RA-relevant genes such as MMP1, thus significantly reducing the matrix destructive behavior of RASF.

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Abstract Number: 1133

Microrna-128 Interference Mitigates the Progression of Keen Osteoarthritis By Regulating Sirtuin-1

Feng-Sheng Wang[1], Yi-Chih Sun[1], Yu-Shan Chen[1] and Jih-Yang Ko[2], [1]Core Facility for Phenomics & Diagnostics, Department of Medical Research, Core Facility for Phenomics & Diagnostics, Department of Medical Research, Kaohsiung Chang Gung Memorial Hospital, Taiwan, Kaohsiung, Taiwan, [2]Department of Orthopedic Surgery, Department of Orthopedic Surgery, Kaohsiung Chang Gung Memorial Hospital, Taiwan, Kaohsiung, Taiwan

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Background/Purpose: MicroRNAs, non-coding small RNAs, reportedly regulate development, remodeling and pathogenesis activities in various tissues through silencing mRNA targets and protein translation. This study is undertaken to analyze comparative microRNA expression profiles, characterize the biological role of candidate microRNA-128 (miR-128) in articular cartilage integrity and investigate whether knockdown of miR-128 attenuated cartilage erosion, synovial remodeling, subchondral bone deterioration and osoteophyte accumulation during the pathogenesis of knee OA.

Methods: Left knees of male Spargue-Dwley rats underwent medial parapatellar arthrotomy and anterior cruciate ligament transaction (ACLT) to induce OA. Arthrography of cartilage injury and synovitis were visualized by 9.4T μMRI. Articular cartilage damage was scored by OARSI scale. Subchondral bone microarchitecture and osteophyte formation were quantified by μCT. Comparative microRNA expression of injured joints was analyzed by Megaplex™ microRNA arrays and verified by quantitative RT-PCR and in situ hybridization.

Results: miR-128 expression was increased with intensive articular cartilage destruction and chondrocyte apoptosis in the development of knee OA. Intra-articular injection of lentivirus-mediated exogenous miR-128 led to intact knee joints progressively had severe chondrocyte loss and exacerbated cartilage breakdown that recapitulated OA histopathology. Of note, intra-articular administration of exogenous miR-128 antisense oligonucleotide (miR-128-AS) attenuated the ACLT-mediated chondrocyte apoptosis, proteinase expression (MMP3, MMP9 and ADAMTS5), cartilage matrix degradation and microstructure impediment. The miR-128-AS treatment lessened the provoking effects on synovial thickening, fibroblast activation, macrophage infiltration and inflammatory regulator expression (IL-1β, TNFα, CXCL-9 and COX-2). This administration also simultaneously ameliorated subchondral plate damage, trabecular microarchitecture loss and osteophyte deposition. miR-128 decreased sirtuin-1 (SIRT1) mRNA and protein expression through targeting the 3'-UTR of sirtuin-1 in chondrocytes. miR-128-AS treatment restored SIRT1 signaling and stabilized cartilage transcription factor SOX9 through regulating acetylation state of SOX9 in affected knee joints.

Conclusion: miR-128 aggravated joint integrity in the pathogenesis of knee OA. Interruption of miR-128 maintained chondrocyte viability and metabolism through regulating SIRT1 signaling and thereby alleviated the pathogenesis of cartilage erosion, synovitis, subchondral plate damage and osteophyte development. This study sheds a new light on miR-128 deterioration of articular cartilage homeostasis and highlights the therapeutic potential of miR-128 interference for curtailing knee OA pathogenesis.

Disclosure: F. S. Wang, None; **Y. C. Sun**, None; **Y. S. Chen**, None; **J. Y. Ko**, None.

of-keen-osteoarthritis-by-regulating-sirtuin-1

Abstract Number: 1134

Identification of Novel Micro-RNAs in IL-1β-Stimulated OA Chondrocytes By Next-Generation Sequencing

Mohammad Shahidul Makki[1] and Tariq Haqqi[2], [1]4209 St Rt 44 PO Box 95, Northeast Ohio Medical University, Rootstown, OH, [2]Anatomy & Neurobiology, Northeast Ohio Medical University, Rootstown, OH

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Background/Purpose: Osteoarthritis (OA) is a chronic and debilitating disease of articulating joints. Mechanical stress, genetic and environmental factors play critical role in the pathogenesis of OA. Micro-RNAs (miRNA) are endogenous, short ~22-nucleotides non-coding single stranded RNAs, that act as a regulator of gene expression. In order to understand the role of miRNAs in OA pathogenesis we employed deep sequencing technology to comprehensively profile the miRNA population in OA chondrocytes.

Methods: Chondrocytes were prepared from human cartilage samples obtained from OA patients at the time of knee arthroplasty and were treated with IL-1β (2ng/ml) for 1, 12, 24 h. Total RNA was isolated using miRNeasy Mini kit (Qiagen) and a small RNA library was prepared using TrueSeq Small RNA Library Preparation Kit (Illumina). RNA purity, integrity and library integrity and purity was verified using Agilent 2100 Bioanalyzer. Cluster generation and sequencing was performed on MiSeq (Illumina). The small RNA-Seq reads were aligned to genomic reference (hg19) and subsequently miRNAs were annotated to generate the miRNA abundance profile and novel miRNA sequences from NGS data using Strand NGS software. Data was normalized followed by differential expression analyses in control and treated samples using Strand NGS software. Expression of selected miRNAs was verified by TaqMan assays. Differentially regulated miRNAs were used to construct the signaling pathways that were enriched by the treatment using DIANA-mirPath open web tool.

Results: We obtained 2.0-2.5 million reads per sample and more than 95% reads pass the quality filter. We identified 1548 miRNAs in our sequencing reads that were unique. miRNAs with less than 5 sequencing reads were excluded from the analyses which left 511 differentially expressed miRNAs. In chondrocytes, expression of 10 miRNAs (miR-100, 26a, 22, 148a, 27b,125b, 99b, 21, let-7a and 7b) on average constitute ~70% of all miRNAs expression across the samples. Differentially expressed miRNAs were identified across different time points by using 1.5 fold as cut-off criteria. We identified 46 miRNA that were upregulated and 41 miRNAs that were downregulated compared to untreated control sample at all the time points analyzed. Highest upregulated miRNA was miR-146a (30 fold) which has been implicated in OA pathogenesis and most downregulated miRNA was miR-452 (5 fold). Some miRNAs exhibited dynamic expression pattern. Fifteen miRNAs were identified as potential novel miRNAs by the Strand NGS software. One sequence (newgene 105) annotated in bovine as bta-miR-2904 was also found to be expressed in human chondrocytes. Several of the differentially expressed miRNAs were predicted to target mRNAs associated with MAPK signaling, PI3K-AKT signaling, focal adhesion and regulation of actin cytoskeleton.

Conclusion: Deep sequencing revealed several novel miRNAs in OA chondrocytes. Expression of Newgene 105 (miR-2904 in *Bos taurus*) has been documented for the first time in human chondrocytes. These newly identified miRNAs could have novel functions in OA pathogenesis. Our work deliver a clear picture of miRNA profile and associated regulatory network in OA chondrocytes.

Disclosure: M. Shahidul Makki, None; **T. Haqqi**, None.

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Abstract Number: 1135

Krüppel-like Factors (Klfs), Novel Transcriptional Regulators of Articular Chondrocytes That Are Abnormally Expressed in Osteoarthritic Cartilage

Takeshi Teramura[1], Joe Hasei[2], Hiroshi Asahara[1,3,4] and Martin K. Lotz[5], [1]Molecular and Experimental Medicine, The Scripps Research Institute, La Jolla, CA, [2]Molecular and Exerpimental Medicine, The Scripps Research Institute, La Jolla, CA, [3]Tokyo Medical and Dental University, Tokyo, Japan, [4]National Research Institute for Child Health and Development, Tokyo, Japan, [5]Division of Arthritis, The Scripps Research Institute, La Jolla, CA
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Background/Purpose:

Krüppel-like factors (Klfs) are known to play key roles in cell cycle regulation, definition of cell fate and regulation of terminal differentiation. There is no information on expression and function of Klfs in cartilage. The objectives of this study were to analyze expression of Klfs in normal and OA cartilage and study their role in regulating chondrocyte functions.

Methods:

Klf expression in normal and OA human cartilage and in developing mouse limb buds was examined by next generation RNA sequencing and qPCR. Klf4 function in normal human chondrocytes and TC28 immortalized chondrocytes was analyzed by gene overexpression and knock down. Overexpression of Klf4 mutants and reporter constructs were used to determine critical motifs for Klf regulation of gene expression.

Results:

Next generation RNA sequencing showed that Klf2, 4, 5, 9, 10 and 15 are significantly suppressed in OA cartilage. Quantitative real time PCR for mouse limb buds showed significantly increased Klf2, 4 and 5 expression from E11.5 to E15.5. Over expression-based screening in the immortalized human chondrocyte cell line TC28 revealed that only Klf4 strongly enhanced Col2A1 and Acan gene expression. Conversely, knockdown of Klf4 resulted in suppression of Col2A1 and Acan genes in human primary chondrocytes. Luciferase reporter assays showed that Klf4 binds to consensus sequences of Col2A1 and Acan promoters and activates their expression. ChIP-qPCR for Col2A1 promoter and Co-IP study revealed that Klf4 could interact with Sox9 directly. Klf4 C-terminus, which contains three tandem zinc fingers, which are critical for this interaction are required for activation of the target genes. Finally, we demonstrated that induction of Klf4 expression could induce Col2A1 and Acan expression in various cell types including dedifferentiated chondrocytes, and the magnitude of upregulation of the target genes was attenuated by reduction of Sox9 expression.

Conclusion:

These results are the first to show that Klf factors have a tissue specific expression in articular cartilage and that OA is associated with dysregulated expression of several Klfs. Among the Klfs, Klf4 expression pattern is most closely linked with chondrogenic markers. Klf4 promotes expression of chondrocyte specific genes, in part through direct interaction with Sox9. Collectively, these findings implicate abnormal expression of Klfs as a novel mechanism of abnormal chondrocyte differentiation and activation in OA.

Disclosure: T. Teramura, None; **J. Hasei**, None; **H. Asahara**, None; **M. K. Lotz**, None.

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Abstract Number: 1136

IL-1β-Induced Stress Granules Sequester COX-2 mRNA and Regulates Its Expression in Human OA Chondrocytes

Mohammad Ansari[1] and Tariq Haqqi[2], [1]Anatomy & Neurobiology, Northeast Ohio Medical University, Roostown, OH, [2]Anatomy & Neurobiology, Northeast Ohio Medical University, Rootstown, OH
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Background/Purpose:

Stress granules (SGs) are ribonucleoprotein complexes assembled in the cytoplasm of eukaryotic cells to respond adequately to stress (e.g. heat shock, UV irradiation, oxidative stress etc.). SGs sequester mRNAs to enable the cell to reprogram its translational repertoire via mRNA triage. Translational stalling of selective mRNA populations by SGs has been shown to be critical in the pathogenesis of neurodegenerative diseases. Here we studied the induction and formation of SGs in response to inflammatory stimuli, translational stalling of COX-2 mRNAs by SGs, and the mechanism of SGs clearance in human osteoarthritis (OA) chondrocytes.

Methods:

Primary human OA chondrocytes were isolated from smooth cartilage obtained from OA patients who underwent total knee arthroplasty. Chondrocytes were treated with IL-1β (10ng/ml) for different periods of time. Chondrocyte lysate was prepared in RIPA buffer supplemented with protease and phosphatase inhibitors. Immunoblotting was done using specific antibodies. Activation of the integrated stress response (ISR) was determined by studying GRP78 expression levels, phosphorylation of eIF2α by Western immunoblotting, and formation and duration of SGs by immunofluorescence staining of G3BP1, TIA-1, TIAR, Staufen1 and HuR. Association of COX-2 mRNA with SGs was determined by FISH and RNA immunoprecipitation. mRNA decay was analyzed using Actinomycin-D chase assay. Role of specific proteins in IL-1b-induced SGs formation was assessed by RNAi mediated knockdown of target mRNAs. ROS generation was measured by flow cytometry using CellROX dye. Treatment with ammonium chloride and Bafilomycin was used to block SGs clearance via autophagy. Production of PGE_2 was determined by ELISA.

Results:

Human OA chondrocytes stimulated with IL-1β showed enhanced ROS production and the expression of the ER stress marker GRP78 and activation of the ISR through phosphorylation of eIF2α and the assembly of SGs. Immunofluorescence staining using antibodies specific for G3BP1, TIA-1, TIAR, Staufen1 and HuR as well as by transient transfection with the G3BP1-GFP plasmid showed robust assembly of SGs in IL-1b-stimulated OA chondrocytes. COX-2 mRNAs were mainly localized in SGs in complex with the RNA binding protein HuR. Sequestration in SGs stalled COX-2 mRNA translation and COX-2 protein levels increased only after the disassembly of SGs. Formation of SGs was TIA-1-dependant as its knockdown resulted in loss of SGs assembly and promoted early and enhanced translation of COX-2 mRNA and protein expression. Production of PGE_2 mirrored the COX-2 protein expression. Inhibition of autophagy blocked SGs clearance and inhibited COX-2 protein expression without affecting the COX-2 mRNA levels in OA chondrocytes.

Conclusion: To our knowledge, this is the first report showing IL-1β induced assembly of SGs in human OA chondrocytes and describes a novel function of SGs in controlling the pro-inflammatory stimulus in in OA chondrocytes through subcellular trafficking of COX-2 mRNAs to SGs. These data demonstrate the importance of RNA binding proteins and SGs assembly in OA pathogenesis and identify specific RBPs/SGs as potential therapeutic targets

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Disclosure: M. Ansari, None; **T. Haqqi**, None.

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Abstract Number: 1137

Low Molecular Weight Polyphenol Harpagoside Inhibits IL-1β-Induced Expression of IL-6 By Blocking the Expression and Activity of c-Fos in Primary Human Osteoarthritis Chondrocytes

Abdul Haseeb[1,2], Mohammad Ansari[3] and Tariq Haqqi[1], [1]Anatomy & Neurobiology, Northeast Ohio Medical University, Rootstown, OH, [2]Anatomy and Neurobiology, Northeast Ohio Medical University (NEOMED), Rootstown, OH, [3]Anatomy & Neurobiology, Northeast Ohio Medical University, Roostown, OH

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Background/Purpose: Osteoarthritis (OA) is a multifactorial disease and is characterized by focal degradation of articular cartilage. Several components of the inflammatory pathway, such as IL-6, are found to be highly expressed in OA joints. There is growing evidence to support the involvement of IL-6 in OA progression and severity. Harpagoside is a natural compound isolated principally from the secondary roots of *Harpagophytum procumbens (Hp)*. In the present study we used an *in vitro* model of joint inflammation to study the therapeutic potential of harpagoside in OA.

Methods: Primary human OA chondrocytes were isolated from the non-affected cartilage obtained from OA patients who underwent total knee arthroplasty. Human OA chondrocytes were cultured and pre-treated with harpagoside (300 µg/ml) and then cultured with and without IL-1β (1-10 ng/ml). Chondrocyte viability was assayed using CytoTox 96® Non-Radioactive Cytotoxicity Assay (Promega). mRNA levels of 92 chemokines and chemokine-associated genes were measured by TaqMan human chemokine PCR array (Life Technologies). Secreted levels of IL-6 in the culture supernatants were assayed by ELISA and immunoblotting. Total protein levels and phosphorylation status of proteins were measured by immunoblotting using specific antibodies. mRNA levels of individual genes were quantified using the TaqMan assays (Life Technologies). Subcellular localization of c-FOS and IL-6 was studied using confocal microscopy (Olympus FV1000 microscope). Activation of transcription factor c-FOS/AP-1 was analyzed by ELISA (Active Motif). Data were analyzed and plotted using Origin 6.1 software and $P<0.05$ was considered significant.

Results: Harpagoside significantly modulated the IL-1β-induced expression of a number of chemokines in primary human OA chondrocytes. Several of the genes, including IL-6, that showed robust expression in response to IL-1β were markedly downregulated by treatment with harpagoside. Treatment with IL-1β markedly stimulated the mRNA expression as well as protein secretion of IL-6 in the culture supernatants. In contrast, OA chondrocytes pre-treated with harpagoside showed a significant reduction ($p<0.05$) in IL-1β-induced expression of IL-6. Importantly, harpagoside did not inhibit the IL-1b-induced activation of NF-κB and C/EBPb but specifically suppressed the IL-1β-triggered over-expression, phosphorylation and activity of c-FOS, one of the major components of AP-1. Further, we show here that harpagoside imparts its inhibitory effect on c-FOS activity and IL-6 production partially through suppression of IL-1β induced ROS production in human OA chondrocytes.

Conclusion: Taken together, our data showed that harpagoside markedly inhibited the IL-1β-induced expression and production of IL-6 in human OA chondrocytes. Importantly, a novel mechanism of IL-6 suppression by harpagoside which involves the inhibition of c-FOS expression was identified. These data provide strong evidence that harpagoside may have a chondroprotective effect and may be a potential therapeutic choice to prevent and/or to slow down the progression of OA.

Disclosure: A. Haseeb, None; **M. Ansari**, None; **T. Haqqi**, None.

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Abstract Number: 1138

Suppressor of Cytokine Signaling 1 Inhibits Interleukin-1β Induced Matrix Metalloproteinases Expression in Human Chondrocytes By Modulating p38-CREB-C/Ebpβ Pathway

You Jung Ha[1], **Yong Seok Choi**[2], Eun Ha Kang[3], Kichul Shin[4], Jaehyung Hur[1], Yeong Wook Song[5] and Yun Jong Lee[2], [1]Division of Rheumatology, Department of Internal Medicine, Seoul National University Bundang Hospital, Seongnam-si, South Korea, [2]Internal Medicine, Seoul National University Bundang Hospital, Seongnam-si, South Korea, [3]Department of Internal Medicine, Seoul National University Bundang Hospital, Seongnam-si, South Korea, [4]Rheumatology, SMG-SNU Boramae Medical Center, Seoul, South Korea, [5]Department of Molecular Medicine and Biopharmaceutical Sciences, Graduate School of Convergence Science and Technology and College of Medicine Seoul National University, Seoul, South Korea

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Background/Purpose: CAAT/enhancer-binding protein-beta (C/EBPb) is known to be a transcription factor regulating IL-1b-induced catabolic pathways, including the expression of matrix metalloproteinases (MMPs), in chondrocytes. Suppressor of cytokine signaling 1 (SOCS1) was reported to inhibit interleukin (IL)-1b signaling in chondrocytes. However, the effect of SOCS1 on C/EBPb has not been explored.

Methods: To investigate the interaction between SOCS1 and C/EBPb, we established human chondrocyte-like SW1353 cell lines with overexpression or knockdown of SOCS1 or C/EBPb. MMP-1, MMP-3, MMP-13, and C/EBPb transcripts were measured by using quantitative real-time PCR. The expression of C/EBPb and cAMP response element-binding protein (CREB) protein was evaluated by immunoblot. To evaluate the binding of C/EBPb to MMP-13 promoter, chromatin immunoprecipitation (ChIP) assay was performed.

Results: Both SOCS1 and C/EBPb were involved in transcription of MMP-3 and MMP-13. When SW1353 cells were stimulated with IL-1b, C/EBPb levels were significantly increased by SOCS1 knockdown and decreased by SOCS1 overexpression (Fig. 1). Also, the same change in IL-1b induced C/EBPb expression was observed in SOCS1 transfected human articular chondrocytes (Fig. 1). But, C/EBPb overexpression or knockdown did not change the levels of IL-1b-inducible SOCS1 (Fig. 1). SOCS1 did not affect the ubiquitination of C/EBPb, but it regulated the levels of C/EBPb mRNA and suppressed the phosphorylation of CREB1, an active transcription factor of C/EBPb (Fig. 2). In addition, p38 MAPK, a target of SOCS1, was involved in the phosphorylation of CREB1. The ChIP assay confirmed that SOCS1 overexpression resulted in reduced binding of C/EBPb to MMP-13 promoter.

Conclusion: These results demonstrate that SOCS1 down-regulates p38-CREB-C/EBPb pathway resulting in suppression of MMPs expression in chondrocytes.

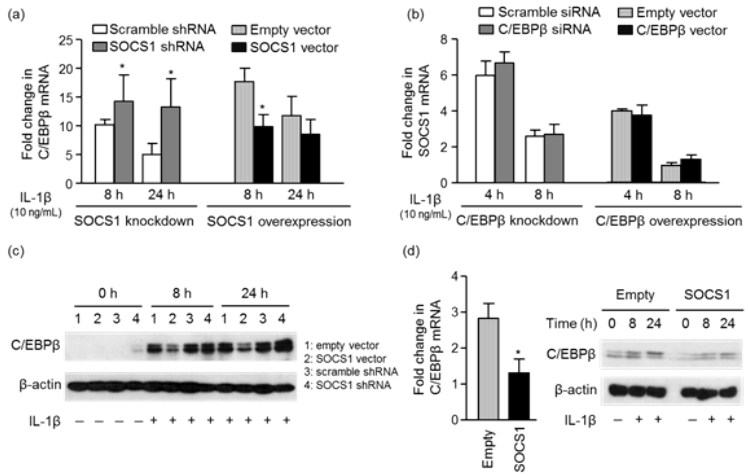

Fig. 1. SOCS1 knockdown increased and SOCS1 overexpression decreased IL-1b induced C/EBPb mRNA and protein expression in SW1353 cells (a, c), but C/EBPb knockdown or overexpression showed no alteration in SOCS1 transcript levels (b). In SOCS1-overexpressed human articular chondrocytes, IL-1b-induced C/EBPb mRNA and protein expression showed the same trends (d).

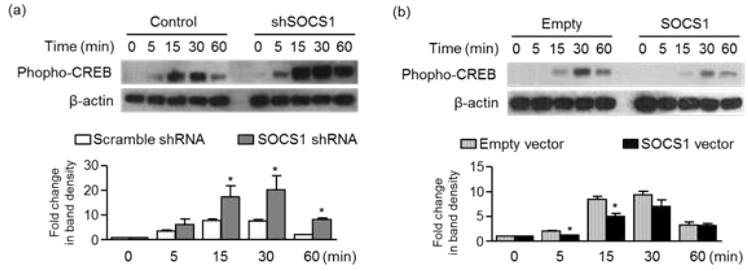

Fig. 2. Effects of SOCS1 on phosphor-CREB levels in SW1353 cells.

Disclosure: Y. J. Ha, None; **Y. S. Choi**, None; **E. H. Kang**, None; **K. Shin**, None; **J. Hur**, None; **Y. W. Song**, None; **Y. J. Lee**, None.

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Abstract Number: 1139

Differential Inflammatory Profile in Experimental Models of Arthritis

Ana C. Ortiz[1], Anne Crilly[1], Lynette Dunning[1], Carmen Huesa[1], C. S. Goodyear[2], John C. Lockhart[1], William R. Ferrell[2] and Iain B. McInnes[2], [1]Institute of Biomedical and Environmental Health Research, University of the West of Scotland, Paisley, United Kingdom, [2]Institute of Infection, Immunity and Inflammation, College of Medicine, Veterinary Medicine and Life Sciences, University of Glasgow, Glasgow, United Kingdom

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Background/Purpose: While osteoarthritis (OA) in humans is characterized by cartilage degradation, osteophyte formation and joint remodeling, inflammation and synovitis are now recognized to contribute to joint pathology. Two experimental models of OA, destabilization of the medial meniscus (DMM) and section of the anterior cruciate ligament (ACL), are commonly used in the study of OA. While these models mimic many of the changes observed in human OA, the role of synovitis and inflammation remains unclear. To address this, inflammation in DMM and ACL models was evaluated.

Methods: All murine procedures were Home Office (UK) approved. OA was induced in 10 week old C57BL/6 male mice by DMM or ACL. SHAM operated and naïve animals were used as controls. Freund's complete adjuvant (FCA) monoarthritis model was used as a positive control of inflammatory joint disease. Knee joint diameter was assessed prior to induction of arthritis and then every three days thereafter. IVIS technology was used to assess myeloperoxidase activity. After 4 weeks synovium was harvested and used for explant culture. Supernatants were collected after 4 hours and analyzed by Luminex for the presence of inflammatory mediators. In parallel experiments, joints were collected for histological analysis of CD3+ and F4/80+ cells. Data were expressed as mean ± SEM with $p<0.05$ taken as the criterion of significance, tested using 1 or 2 way ANOVA.

Results: There was no significant change in the knee joint diameter between naïve, SHAM, DMM and ACL at 4 week time point. However, knee joint diameter significantly increased in FCA compared to all other groups (figure 1A) and it was the only model demonstrating elevated myeloperoxidase activity. Also, elevated levels of IL-1β, IFNγ, RANTES and IL-10 were only detected in FCA explant cultures. While histological analysis of the joints demonstrated an absence of CD3+ T cells in both DMM and ACL models, F4/80+ cells were observed within/adjacent to the anterior cruciate ligament in ACL and at the medial collateral ligament in DMM. Importantly, MIP-1β/CCL4 was significantly increased in FCA and OA surgical models compared to naïve (figure 1B). IL-33 was elevated in FCA and ACL models but did not attain significance for DMM (figure 1C).

Conclusion: This study demonstrates that the OA inflammatory milieu within the DMM and ACL synovium differs substantially from the FCA model. Nevertheless, the presence of F4/80+ cells and high levels of MIP-1β/CCL4 within the synovium as well as elevated IL-33 suggests an ongoing low-grade inflammatory process in these OA models.

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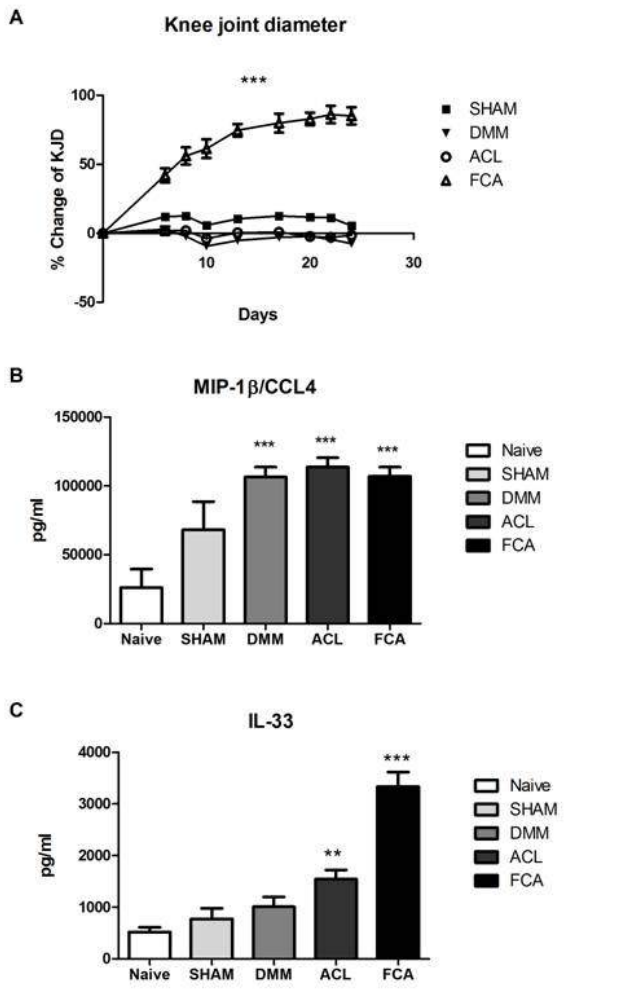

Figure 1. (A) Knee joint diameter measurements. Analysis by 2 way ANOVA test *** p<0.001, FCA vs other groups. Levels of MIP-1β/CCL4 (B) and IL-33 (C) in synovium explant cultures. Analysis by 1 way ANOVA test with Bonferroni's posthoc test ** p<0.02, *** p<0.001 vs. naive. Data are expressed as mean± SEM, n=6 per group.

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Abstract Number: 1140

Resident Non-Classical Monocytes Are Critically Important for Tissue Destruction in Arthritis

Antonia Puchner[1], Victoria Saferding[2], Eliana Goncalves-Alves[3], Michael Bonelli[3], Silvia Hayer[4], Carl-Walter Steiner[2], Birgit Niederreiter[5], Josef S. Smolen[1], Kurt Redlich[3] and Stephan Blüml[3], [1]Department of Rheumatology, Medical University of Vienna, Vienna, Austria, [2]Rheumatology, Medical University of Vienna, Vienna, Austria, [3]Division of Rheumatology, Medical University of Vienna, Vienna, Austria, [4]Department of Internal Medicine III, Division of Rheumatology, Medical University of Vienna, Vienna, Austria, [5]Rheumatology, Internal Medicine III, Medical University of Vienna, Vienna, Austria

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Background/Purpose: Bone destruction in rheumatoid arthritis is mediated by osteoclasts, which are derived from precursor cells of the myeloid lineage. Although there is much known about mature osteoclasts, the identity of an osteoclast precursor population and its regulation by inflammatory cytokines during arthritis is poorly understood.

Methods: HTNFtg mice were clinically scored once per week for grip strength and swelling. In addition, blood was collected every other week starting on week 4. Mice were sacrificed at week 10 - blood, spleen and bone marrow were collected for flow cytometry analysis. K/BxN Arthritis was induced in wild type mice, blood and spleen were collected 14 days after disease induction. HTNFtg/CCR2$^{-/-}$and hTNFtg mice were analyzed histologically. Different monocyte subsets were Facs-sorted and cultured in the presence of RANKL and MCSF to induce osteoclasts.

Results: Here we show that during TNF-driven arthritis monocytes, in particular resident non-classical monocytes (CD115^{+}Ly6C^{low}CCR2^{-}), are elevated in blood before the onset of clinical symptoms and remain elevated throughout. Upon sorting resident and inflammatory monocytes (CD115^{+}Ly6C^{high}CCR2^{+}) from blood, we demonstrate that resident monocytes are more potent to form osteoclasts *ex vivo*. In addition, the number of resident monocytes in blood positively correlated with histological signs of joint destruction, such as area of erosion and number of osteoclasts in arthritic hind paws, while the number of inflammatory monocytes did not correlate at all with those parameters. Of note, we observed a similar correlation of resident monocytes with histological markers of tissue damage also in another model of inflammatory arthritis, K/BxN serum transfer arthritis. Next, we crossed CCR2 deficient mice, which lack circulating inflammatory monocytes, into hTNFtg animals. In line with our hypothesis that resident monocytes are mediating local bone destruction, hTNFtg mice lacking CCR2 showed no decrease but even enhanced local bone erosion and osteoclast generation.

Conclusion: Resident non classical monocytes with osteoclastogenic potential are elevated during chronic inflammatory arthritis and the numbers in blood correlate with histological markers of joint destruction in models of inflammatory arthritis in two models of arthritis. Therefore these cells may provide a biomarker for erosive inflammatory arthritis and even a possible target for therapeutically intervention.

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Abstract Number: 1141

Synovial Ultrasound Power Doppler Enhancement Reflects Multiple Cytokine Expression in Synovial Tissue, Distinguishing Distinct High Macrophage-Associated and Low Inflammation Profiles

Lorraine Yeo[1], Dagmar Scheel-Toellner[2], Christian Ludwig[3], Ilfita Sahbudin[2], Maria Juarez[2], Christopher Buckley[4], Karim Raza[5] and **Andrew Filer**[6], [1]Rheumatology Research Group, Centre for Translational Inflammation Research, College of Medical and Dental Sciences, University of Birmingham, Birmingham B15 2TT, UK, Birmingham, United Kingdom, [2]University of Birmingham, Rheumatology Research Group, Institute of Inflammation and Ageing, Birmingham, United Kingdom, [3]University of Birmingham, Institute of Cancer Studies, Birmingham, United Kingdom, [4]University of Birmingham, Rheumatology Research Group, Birmingham, United Kingdom, [5]University of Birmingham, Rheumatology Research Group, Institute of Inflammation and Ageing, United Kingdom, Birmingham, United Kingdom, [6]University of Birmingham, Birmingham, United Kingdom
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Background/Purpose:

Power doppler ultrasound provides joint level data on the risk of erosive progression in patients with inflammatory arthritis. Understanding the synovial tissue correlates of ultrasound variables may reveal factors that drive erosive disease. The purpose of this study was to examine the relationship between ultrasound variables, tissue histological variables and cytokine profiles in DMARD naïve inflammatory arthritis patients.

Methods:

Ultrasound guided synovial biopsies were obtained from patients with at least one clinically swollen joint at presentation to the Birmingham Early arthritis Cohort (BEACON) and followed for 18 months to confirm outcome as either rheumatoid arthritis fulfilling 2010 criteria (RA: n=29, median symptom duration 10 weeks), or spontaneously resolving disease (RES: n=9, median symptom duration 5 weeks). All patients underwent baseline ultrasound, clinical and serological assessment. Fractional Power Doppler pixel quantification (USPD) was performed using a custom Matlab application. Ultrasound Greyscale (USGS) synovial hypertrophy was graded on a 4 point semiquantitative scale. Synovial tissue histology variables were assessed by blinded pathologists. Synovial cellular populations were quantified by blinded cell counts of fluorescence stained tissue sections. Synovial mRNA expression of 119 cytokines was quantified using low density PCR array techniques.

Results:

Histological grading of leukocyte infiltrate complexity in biopsies correlated with USGS synovial hypertrophy (RA $p<0.05$, RA+RES combined $p<0.01$), but not USPD. Lining layer thickness did not correlate with USGS or USPD in any group. Neither infiltrate complexity nor lining layer thickness was significantly different between diagnostic groups. After correction for multiple comparisons, mRNA levels of key cytokines and chemokines were positively correlated with PDUS in RA, including IL-6 (p=0.007), IL-32 (p=0.0.025) and the chemokines CCL2 (p=0.007), CCL7 (p=0.0002), CCL8 (p=0.0161), CCL19 (p=0.024) and CXCL13 (p=0.045), while key mediators of low inflammation pathways were negatively correlated with PDUS, including IGFBP5 (P=0.048), Galectin-3 (P=0.002) , Galectin12 (P=0.043) and SFRP-1 (P=0.01). A similar pattern was seen in the RES group, and combining groups resulted in a total of 30 genes correlated with PD. Correlation of PDUS with CD68-positive joint counts in synovial biopsies revealed a positive relationship for combined groups (RA+RES p=0.03, RA alone P=0.05).

Conclusion:

Infiltrate complexity correlates most closely with the extent of synovial hypertrophy, rather than hyperaemia measured by PD. However US power doppler fraction correlates positively with key inflammatory macrophage related cytokines, chemokines, growth factors and tissue CD68 positive cell counts, providing an explanation for the link beween power doppler and joint damage.

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Abstract Number: 1142

Joint Specific Function of Synovial Fibroblasts – Integrating Positional Transcriptomes and Anatomic Patterns of Arthritis

Mojca Frank Bertoncelj[1], Michelle Trenkmann[1], Kerstin Klein[1], Emmanuel Karouzakis[1], Christoph Kolling[2], Andrew Filer[3], Christopher Buckley[4], Beat A. Michel[1], Renate E. Gay[1], Steffen Gay[1] and **Caroline Ospelt**[1], [1]Center of Experimental Rheumatology, University Hospital Zurich, University Zurich, Zurich, Switzerland, [2]Upper Extremity Dept., Schulthess Clinic Zurich, Zurich, Switzerland, [3]University of Birmingham, Birmingham, United Kingdom, [4]University of Birmingham, Rheumatology Research Group, Birmingham, United Kingdom

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Background/Purpose:

Synovial fibroblasts (SF) profoundly influence physiological and pathological processes in the joint such as reaction to inflammatory stimuli and production of extracellular matrix. We recently reported that SF from different joints exhibit site specific gene expression patterns; more than 20% of all detected transcripts in RNA sequencing significantly differed between knee, shoulder and hand SF. Here we investigated how these substantial differences in transcriptional programs translate into joint specific function of SF.

Methods:

SF were isolated from synovial tissues of hip, knee, shoulder, elbow and metacarpophalangeal (MCP) joints of RA and OA patients undergoing joint replacement surgery. MetaCore (Thomson Reuters, log2 ratio=2, p=0.05) was used for pathway enrichment analysis of RNA sequencing data (Illumina HiSeq 2000). Basal and TNF-α-induced MMP1 secretion from SF was analyzed with ELISA. Transwell plates (5mm polycarbonate membrane, Corning Costar) were used to measure migration (16h) of leukocytes from healthy donors (n=2) towards supernatants of cultured SF. Adhesion to tissue culture plates 16h after seeding and proliferation of SF were measured in real time with the xCELLigence RTCA DP Instrument (ACEA Biosciences, Inc.). Synovitis was quantified in synovial tissues from hands (n=17), elbows (n=6), shoulders (n=7), knees (n=8) and hips (n=4).

Results: Pathway enrichment analysis of RNA sequencing data between joint localizations (knee, shoulder, MCP) revealed joint specific enrichment of several arthritis-relevant biological processes, such as chemotaxis, proliferation, cell adhesion and matrix degradation. SF from hands, elbows and shoulders (n=4 each) secreted higher levels of MMP1 protein compared to knee SF (n=8) under basal conditions (hand 1808±1008, elbow 1773±1450, shoulder 2073±1083 vs. knee 449±883 pg/ml) and TNF-α stimulation (hand 8431±2339, elbow 8216±2110, shoulder 7176±1428 vs. knee 5369±1515 pg/mL). While adhesion was significantly stronger in shoulder vs. hand SF (cell index 0.9±0.2 vs. 0.6±0.2, p=0.01, n=7 each), shoulder SF (doubling time: 67±15h, p=0.03, n=5) showed a significantly lower proliferative potential than hand (39±3h, n=4) and knee SF (45±9h, n=6). More leukocytes migrated towards the supernatants from cultured knee and hand SF (x fold both: 1.4±0.03 vs. control cell culture medium=1) than shoulder SF (x-fold: 1.2±0.1). The total synovitis score composed of changes in stroma, synovial lining thickness and leukocyte infiltration showed an increased value in hands and elbows (6.2±1.8, 6.2±1.3 vs. shoulder 4.4±2.8, knee 4.1±2.3, hip 4.3±1.5, p=0.06), but the influx of immune cells was significantly enhanced into the synovium of hands versus shoulders and hips (hands 2.1±0.6; shoulders 1±0.4; hips 0.8 ±0.5, p=0.02).

Conclusion:

SF from joints of different anatomic sites are functionally distinct cells and create a unique and specialized microenvironment in each joint localization. Since hand SF secrete higher amounts of MMP1 and exhibit stronger proliferative and chemotactic properties compared with SF from other joints, they may in particular contribute to joint destruction occurring in hand arthritides.

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Abstract Number: 1143

Reduced Hydrogen Sulfide Synthesis in the Joint, a New Player in the Pathogenesis of Osteoarthritis

Angela Vela-Anero[1], Lucia Gato-Calvo[2,3], Cristina Ruiz-Romero[2,3], Rosa Meijide-Failde[1], Francisco J. Blanco[3] and Elena F. Burguera[3,4], [1]Grupo de Terapia Celular y Medicina Regenerativa. Instituto de Investigación Biomédica de A Coruña (INIBIC). Complexo Hospitalario Universitario de A Coruña (CHUAC). Sergas. Universidade de A Coruña (UDC), A Coruña, Spain, [2]Grupo de Bioingeniería Tisular y Terapia Celular (GBTTC-CHUAC). CIBER-BBN/ISCIII. Instituto de Investigación Biomédica de A Coruña (INIBIC). Complexo Hospitalario Universitario de A Coruña (CHUAC). Sergas. Universidade de A Coruña (UDC), A Coruña, Spain, [3]Servicio de Reumatología. Instituto de Investigación Biomédica de A Coruña (INIBIC). Complexo Hospitalario Universitario de A Coruña (CHUAC). Sergas. Universidade de A Coruña (UDC), A Coruña, Spain, [4]Grupo de Bioingeniería Tisular y Terapia Celular (GBTTC-CHUAC). CIBER-BBN/ISCIII. Instituto de Investigación Biomédica de A Coruña (INIBIC). Complexo Hospitalario Universitario de A Coruña (CHUAC). Sergas. Universidade de A Coruña (UDC), A Coruna, Spain

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Background/Purpose: Hydrogen sulfide (H_2S) is, next to NO and CO, the third endogenous gasotransmitter. It has been shown that in some pathologies, such as hypertension, cardiovascular disease or diabetes type II, H_2S endogenous levels or biosynthesis are significantly reduced and that exogenous administration might be helpful. Previous experiments by our group have demonstrated that H_2S releasing compounds have anti-inflammatory and anti-catabolic effects on IL1β-stimulted OA chondrocytes. Therefore our hypothesis in the present work was that OA patients might also have lower endogenous H_2S levels.

Methods: Joint tissues and blood samples were obtained from patients of the Orthopedic or Rheumatology Services of the University Hospital A Coruña (CHUAC), or volunteers (blood only), after written informed consent. The mRNA expression of the H_2S production enzymes, cystathionine β-synthase (CBS), cystathionine γ-lyase (CTH) and mercaptopyruvate sulfurtransferase (MPST) was analyzed in cartilage, synovial membrane and subchondral bone. Immunohistochemistry and quantification with ImageJ was performed to evaluate the location and abundance of the CBS, CTH and MPST. Hydrogen sulfide concentration was measured using a selective ion microelectrode. Direct H_2S concentration was measured in 200 µL of fresh serum after incubation with 200 µL of an antioxidant buffer (AB) for 1h. Likewise, H_2S production from cartilage was measured by incubating cartilage disks in 200 µL of the same AB for 2 h.

Results: We found that all three enzymes, CBS, CTH and MPST were expressed in all tested joint tissues. CBS was slightly reduced in the OA cartilage, but no statistically significant differences were detected for this enzyme, nor CTH, in any tissue. Notably, however, MPST mRNA expression was significantly reduced in OA cartilage with respect to normal controls. Immunohistochemistry also showed decreased levels of this enzyme in cartilage. On the other hand, statistically significant differences were also found in the H_2S production measured from OA with respect to non OA cartilage samples. Indeed, OA cartilage H_2S production was 0.105 ± 0.042 nmoles/g of cartilage (mean ± SE, n=13) in OA tissue while that of healthy cartilage was 0.433 ± 0.110 nmoles/g of cartilage (mean ± SE, n=5), $p<0.05$. These differences, however, were not reflected in the H_2S concentrations in blood serum samples, where no statistically significant differences were found (OA serum: 56.48 ± 7.24 µM (mean ± SE, n=38) vs. N serum: 72.18 ± 10.66 µM (mean ± SE, n=28), $p>0.05$).

Conclusion: Local H_2S biosynthesis is reduced in the OA joint. This is the result, at the least, of a reduced mRNA expression and protein abundance of MPST. Since MPST is predominantly a mitochondrial enzyme, this deficit might be another factor that causes the mitochondrial dysfunction that is known to contribute to OA pathogenesis.

Disclosure: A. Vela-Anero, None; **L. Gato-Calvo**, None; **C. Ruiz-Romero**, None; **R. Meijide-Failde**, None; **F. J. Blanco**, Pfizer, Bioiberica, and Gebro Pharma, 5; **E. F. Burguera**, None.

Abstract Number: 1144

Effect of PEP-1-Glrx-1 on Catabolic Gene Expression in Human Articular Chondrocytes and in Mouse Carrageenan-Induced Paw Edema Model

In young Park[1], Hyun Sook Hwang[1], Dae Won Kim[2], Soo Young Choi[2] and **Hyun Ah Kim**[3], [1]Division of rheumatology, Hallym University Sacred Heart Hospital, Kyunggi, South Korea, [2]Institute for Skeletal Aging, Hallym University, Chunchon, South Korea, [3]Internal Medicine, Hallym Univ Sacred Heart Hosp, Anyang, South Korea
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Background/Purpose:

Excessive production of reactive oxygen species (ROS) of the chondrocyte plays an important role of cartilage degradation, inflammation, and increased chondrocyte death in the development and progression of osteoarthritis (OA). Recently, many studies have demonstrated that the transduction of a therapeutic protein using protein transduction domain (PTD), which targets the lipid bilayer directly can be utilized

for therapeutic applications. GLRX (Glutaredoxins) are endogenous antioxidant systems and key players in the balance of cellular redox homeostasis. In this study we sought to investigate whether PEP-1-GLRX-1, a fusion protein of GLRX-1 with PEP-1 peptide, one of protein transduction domains, could suppress catabolic responses in primary human chondrocytes and carrageenan-induced paw edema mouse model.

Methods:

Human articular chondrocytes were enzymatically isolated from articular cartilage and cultured in monolayer. The transduction efficiency of PEP-1-GLRX1 into articular chondrocytes was measured by Western blot and immunochemistry analysis. The effect of PEP-1-GLRX1 on MMP expression and catabolic factor expressions in interleukin-1β (IL-1β)- and lipopolysaccharide (LPS)-treated chondrocytes were analyzed by real-time quantitative reverse transcription-polymerase chain reaction and Western blot analysis. The effect of PEP-1-GLRX1 on mitogen activated protein kinase (MAPK) and NF-κB signaling pathway were analyzed by Western blot analysis. The inhibitory effect of PEP-1-GLRX-1 on MMP13 production was measured in carrageenan-induced edema mouse model.

Results:

PEP-1- Efficient penetration of GLRX-1 into human and mouse cartilage was demonstrated by western blot and immunochemistry analysis. PEP-1-GLRX-1 in interleukin-1β (IL-1β)- and lipopolysaccharide (LPS)-treated chondrocytes significantly suppressed the expressions of matrix metalloproteinase (MMP)-13 and inducible NO synthase (iNOS), at both mRNA and protein levels compared with GLRX-1. In addition, PEP-1-GLRX-1 decreased IL-1β- and LPS-induced activation of mitogen activated protein kinase (MAPK) and NF-κB. In a mouse model of carrageenan-induced paw edema, PEP-1-GLRX-1 significantly suppressed carrageenan-induced MMP-13 production as well as paw edema.

Conclusion:

Therefore, these results showed that PEP-1-GLRX-1 can be efficiently transduced *in vitro* and *in vivo* and down-regulate catabolic responses in chondrocytes and in arthritis animal model through inhibiting activation of MAPK and NF-κB. PEP-1-GLRX-1 has a potential to reduce catabolic responses in chondrocytes and cartilage.

Disclosure: I. Y. Park, None; **H. S. Hwang**, None; **D. W. Kim**, None; **S. Y. Choi**, None; **H. A. Kim**, None.

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Abstract Number: 1145

Expression of Xylosyltransferase-1 Is Modulated By Fibronectin Fragment in Human Articular Chondrocytes

Mi Hyun Lee[1], Min Ha Choi[1], Hyun Sook Hwang[1] and **Hyun Ah Kim**[2], [1]Division of rheumatology, Hallym University Sacred Heart Hospital, Kyunggi, South Korea, [2]Internal Medicine, Hallym Univ Sacred Heart Hosp, Anyang, South Korea

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Background/Purpose:

Xylosyltransferase-1 (XT-1), encoded by *xylt1* gene, is an essential anabolic enzyme to catalyze the initial and rate-determining step in glycosaminoglycan chain synthesis. The effect of fibronectin fragments (FN-fs), generated by proteolytic cleavage of FN and known as damage-associated molecular pattern (DAMP) molecules, on cartilage metabolism was poorly characterized. In this study we examined 29-kDa amino-terminal fibronectin fragment (29-kDa FN-f)-mediated XT-1 expression mechanism and its signaling pathway, determining the role of 29-kDa FN-f in cartilage matrix synthesis

Methods:

Human articular chondrocytes were enzymatically isolated from articular cartilage and cultured in monolayer. In 29-kDa FN-f-stimulated chondrocytes, the relative levels of mRNA and protein for XT-1 were analyzed by real-time quantitative reverse transcription-polymerase

chain reaction and Western blot analysis, respectively. In order to investigate the effects of 29-kDa FN-f on XT-1, human chondrocytes were transfected with small interfering RNAs (siRNAs) targeting TLR-2.

Results:

The level of aggrecan and XT-1 in human osteoarthritis cartilage was significantly decreased compared to normal cartilage. XT-1 expression in cultured primary articluar chondrocytes showed a periodic oscillation in both mRNA and protein level. 29-kDa FN-f significantly suppressed the mRNA and protein levels of XT-1 at 14 h and 24 h, respectively. Inhibition of mitogen activated protein kinase and nuclear factor-κB signaling pathway restored 29-kDa FN-f-inhibited XT-1 expression. Knockdown of toll like receptor-2 (TLR-2) using small interference RNA revealed that the decrease of XT-1 expression by 29-kDa FN-f is mediated by TLR-2 signaling pathway. In addition, Sp3, a repressor of XT-1 promoter, was up-regulated by 29-kDa FN-f. Knockdown and overexpression experiments revealed that XT-1 expression was modulated by 29-kDa FN-f-stimulated Sp3 in primary articular chondrocytes

Conclusion:

These results demonstrated that 29-kDa FN-f plays a detrimental role in the regulation of cartilage extracellular matrix formation including XT-1 expression.

Disclosure: M. H. Lee, None; **M. H. Choi**, None; **H. S. Hwang**, None; **H. A. Kim**, None.

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Abstract Number: 1146

Deficiency of TLR2 and TLR4 Impairs Autophagic Flux in Chondrocytes

Yun Wang[1], Robert Terkeltaub[2] and **Ru Liu-Bryan**[3], [1]Medicine-Rheumatology, VA Medical Ctr/UCSD, San Diego, CA, [2]Medicine-Rheumatology, VA Medical Ctr/University of California San Diego, San Diego, CA, [3]Medicine-Rheumatology, VA Medical Center/University of California San Diego, San Diego, CA

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Background/Purpose:

We have previously demonstrated that chondrocyte deficient in both TLR2 and TLR4 almost completely abolished pro-catabolic responses to rHMGB1 and LMW-HA, which are known to be present in OA joints. Since both TLR2 and TLR4 signaling can modulate autophagy, and autophagy plays an important role in cartilage homeostasis, we investigated the role of TLR2 and TLR4 in chondrocytes *in vitro*.

Methods:

Immature knee chondrocytes were isolated from TLR2/TLR4 double knockout (dKO) and the wild type (WT) mice. Microtubule-associated protein 1 light chain 3 (LC3) conversion (LC3-I to LC3-II) was examined by Western blotting. To monitor autophagic flux (the rate at which autophagic vacuoles are processed by lysosomes), the TLR2/TLR4 dKO and WT chondrocytes were transfected with a tandem fluorescent-tagged LC3 (mRFP-EGFP-LC3). Green and red fluorescent proteins have different pH stability. The acidic environment (pH<5) inside lysosome quenches the fluorescent signal of EGFP. The transfected cells were treated with HBSS containing 1% DMEM high (for starvation to induce autophagy) or chloroquine (an inhibitor of autophagic flux by inhibition of fusion of autophagosome with lysosome) for 1-2 hours and then subjected to flow cytometry analysis for fluorescence intensity of GFP and RFP or Western blot analysis for GFP or RFP expression levels.

Results: Basal level of LC3 conversion was higher in TLR2/TLR4 dKO chondrocytes, and basal level of mean fluorescence intensity (MFI) of GFP and RFP in TLR2/TLR4 dKO chondrocytes was 2.3 and 1.9 fold higher than that in WT chondrocytes. Western blot analysis also showed significantly higher level of GFP in TLR2/TLR4 dKO chondrocytes compared to WT chondrocytes. As expected, the MFI of GFP and RFP was increased by 34.8% and 19.3% respectively by chloroquine, but was decreased by 12% and 18% respectively by starvation, compared to non-treatment control in WT chondrocytes, indicating that there was autophagic flux. In contrast, despite that chloroquine was still able to increase the MFI of GFP and RFP by 27.3% and 23% respectively, starvation did not decrease the MFI of

GFP and RFP at all, compared to non-treatment control in TLR2/TLR4 dKO chondrocytes. These data suggested that autophagic flux was impaired in TLR2/TLR4 dKO chondrocytes.

Conclusion:

Chondrocytes deficient in TLR2 and TLR4 exhibit impairment of autophagic flux. Given that autophagy is a cellular homeostasis mechanism for the removal of dysfunctional organelles and macromolecules, and autophagic pathways are constitutively targets intracellular cytosolic components for lysosomal degradation, and is essential for maintaining cellular energy and metabolic homeostasis, the diminished efflux of products from autolysosomes is likely to induce a state of metabolic insufficiency and accumulates dysfunctional organelles and aggregates of macromolecules. The fact that TLR2 and TLR4 deficiency show little chondroprotection in mouse OA model may partially result from impairment of autophagic flux in chondrocytes.

Disclosure: Y. Wang, None; **R. Terkeltaub**, None; **R. Liu-Bryan**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/deficiency-of-tlr2-and-tlr4-impairs-autophagic-flux-in-chondrocytes

Abstract Number: 1147

TGFß1 Blocks Chondrocyte Hypertrophy and Increases Cell Viability in Cultured Cartilage Explants but Does Not Protect Against Proteoglycan Loss

Arjan van Caam, Wojciech Madej, Henk van Beuningen, Esmeralda Blaney Davidson and Peter van der Kraan, Experimental Rheumatology, Radboud university medical center, Nijmegen, Netherlands

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Background/Purpose:

In osteoarthritis, cartilage degradation is partly due to chondrocytes gaining a hypertrophy-like phenotype. TGFβ1 is considered to be a protective factor for articular cartilage by blocking this hypertrophy and by inducing production of matrix molecules like proteoglycans (e.g. aggrecan). However, these functions of TGFβ1 have been identified using very young cartilage whereas TGFβ1-signaling is known to change upon maturation (ageing). Therefore, we investigated in healthy mature cartilage the effect of TGFβ1 on chondrocyte phenotype, viability and total amount of glycosaminoglycans (GAGs, as measure for proteoglycans) in long term *ex vivo* culture.

Methods: Articular cartilage explants were isolated from the metacarpophalangeal joint of healthy 5 yr old adult cows. Subsequently, explants were cultured in DMEM/F12 alone or supplemented with either 10% Fetal Calf Serum (FCS), rhTGFβ1 or rhIGF1 for the duration of 2 weeks. To investigate via which TGFβ1 receptor, ALK1 or ALK5, the observed TGFβ1 effects run, the ALK5-kinase inhibitor SB-505124 (5 µM) was used. Sulfated-GAGs were measured using dimethylmethylene blue (DMB). Cellular viability was measured with the use of XTT. To correct for the amount of cells, total DNA content of explants was measured using PicoGreen. Furthermore, gene expression of chondrocyte hypertrophy markers was measured using qPCR.

Results: Two weeks of *ex vivo* explant culture resulted in GAG loss; total GAG content was reduced from approximately 4% of wet weight in freshly isolated explants to 1% of wet weight in cultured explants. Addition of 10% FCS fully prevented this GAG loss. In contrast, TGFβ1 (10 ng/ml) was unable to inhibit GAG loss. Replacement of 10% FCS with 20 ng/ml of IGF1 also prevented GAG loss, but surprisingly, when IGF1 was combined with TGFβ1, TGFβ1 inhibited the positive effect of IGF1 on total GAG content. Compared to freshly isolated samples, expression of the chondrocyte-hypertrophy markers *Col10a1* and *Mmp13* was profoundly upregulated in explants cultured for 2 weeks. The addition of 10% FCS to the medium did not inhibit the upregulation of these genes, and even induced expression of Alkaline phosphatase (*Alpl*), another marker of chondrocyte hypertrophy. In contrast, addition of TGFβ1 (1 ng/ml or 10 ng/ml) fully blocked induction of *Col10a1* and *Mmp13* expression, and lowered expression of *Alpl* 4-fold. Additionally, TGFβ1 induced *Col2a1* expression 16-fold. TGFβ1 also enhanced chondrocyte viability, because after 2 weeks, mitochondrial activity was 50% higher in TGFβ1 treated samples compared to 10% FCS treated samples. All these effects of TGFβ1 were blocked by 5 µM of the ALK5-kinase inhibitor SB-505124.

Conclusion:

Based on our results, we conclude that in adult cartilage TGFβ1 is a potent inhibitor of chondrocyte hypertrophy and that this inhibition runs via ALK5. Additionally, TGFβ1 profoundly induced *Col2a1* production, and maintained chondrocyte viability in long term culture. In contrast, TGFβ1 was not able to counteract GAG depletion over time and even inhibited the beneficial effect of IGF1 on total GAG-content in cartilage, demonstrating that TGFβ1 does not positively regulate GAG content in adult cartilage.

Disclosure: A. van Caam, None; **W. Madej**, None; **H. van Beuningen**, None; **E. Blaney Davidson**, None; **P. van der Kraan**, None.

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Abstract Number: 1148

The Role of TRPC6 in CXCR2-Mediated Chondrocyte Phenotypic Stability

Joanna Sherwood[1], Jessica Bertrand[1], Francesco Dell'Accio[2] and Thomas Pap[3], [1]Institute for Experimental Musculoskeletal Medicine, University Hospital Münster, Münster, Germany, [2]EMR, Queen Mary's School of Medicine and Dentistry, London, United Kingdom, [3]Institute of Experimental Musculoskeletal Medicine, University Hospital Münster, Münster, Germany
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Background/Purpose: We have recently demonstrated that ELR+ CXC chemokines signaling via the CXCR2 receptor, are produced by healthy chondrocytes and are retained within the cartilage matrix via interactions with heparan sulfate proteoglycans. They act to support articular cartilage homeostasis by increasing AKT phosphorylation, thus promoting SOX9 expression, extracellular matrix production and chondrocyte survival, particularly during conditions of physiological challenge, indicated by increased chondrocyte apoptosis and cartilage degradation in $CXCR2^{-/-}$ mice following destabilization of the medial meniscus. Importantly, the transient receptor potential channel 6 (TRPC6) mechanosensitive ion channel has been shown to be a specific mediator of CXCR2 driven cell migration via AKT signaling. This project aims to investigate whether TRPC6 activity is required for chondrocyte phenotypic stability and is involved in the mechanism of CXCR2-mediated cartilage homeostasis.

Methods: Costal chondrocytes were isolated from $CXCR2^{-/-}$ mice, $TRPC6^{-/-}$ mice and their wild type littermates and expanded in standard conditions. Gene expression was assessed using real time RT-PCR. Sulfated proteoglycan content and mineralization of micromass cultured chondrocytes was measured using Alcian blue or alizarin red staining and spectrophotometric quantification. CXCR2 was activated using murine CXCL6 whilst TRPC6 was specifically activated using hyp9, a stabilized derivative of the TRPC6-selective activator hyperforin. Intracellular calcium was chelated by treating cells with BAPTA-AM prior to receptor activation. AKT phosphorylation was analyzed using Western blot. Calcium mobilization in chondrocytes was measured using a fura-2 assay.

Results: TRPC6 mRNA was detected in wild type murine chondrocytes. Chondrocytes lacking either TRPC6 or CXCR2 expressed lower levels of the chondrocyte differentiation markers SOX9 and type II collagen in comparison to wild type. Culture of chondrocytes in micromass resulted in significantly less sulfated proteoglycan production and increased mineralization by $TRPC6^{-/-}$ chondrocytes in comparison to chondrocytes obtained from wild type littermates. Activation of CXCR2 in articular chondrocytes resulted in increased intracellular calcium mobilization. In vitro activation of TRPC6 using hyp9 led to an increased AKT phosphorylation, whereas chelation of intracellular calcium inhibited CXCL6-induced phosphorylation of AKT. Finally, activation of TRPC6 resulted in a significant increase in SOX9 and type II collagen mRNA expression, together with a decrease in type X collagen mRNA expression.

Conclusion: TRPC6 calcium channel activity is required for chondrocyte phenotypic stability. In vitro TRPC6 activation is sufficient to increase AKT phosphorylation and the expression of key chondrocyte phenotypic markers in murine chondrocytes, indicating that TRPC6 may be an ideal therapeutic target aimed at preventing cartilage degradation during osteoarthritis.

Disclosure: J. Sherwood, None; **J. Bertrand**, None; **F. Dell'Accio**, None; **T. Pap**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/the-role-of-trpc6-in-cxcr2-mediated-chondrocyte-phenotypic-stability

Abstract Number: 1149

The Active Metabolite of Fostamatinib, R406, Only Decreases the Inflammation-Driven Extracellular Matrix Turnover of the Joint at High Concentrations Ex Vivo

Cecilie F. Kjelgaard-Petersen[1,2], Christian S. Thudium[1], Anne Sofie Siebuhr[1], Thorbjørn G. Christiansen[3], Morten Asser Karsdal[1], Per Hägglund[2] and Anne C. Bay-Jensen[4], [1]Biomarkers and Research, Nordic Bioscience, Herlev, Denmark, [2]Systems Biology, Technical University of Denmark, Kgs. Lyngby, Denmark, [3]Gentofte University Hospital, Orthopaedicsurgery unit, Gentofte, Denmark, [4]Biomarkers and Research, Rheumatology, Nordic Bioscience, Herlev, Denmark

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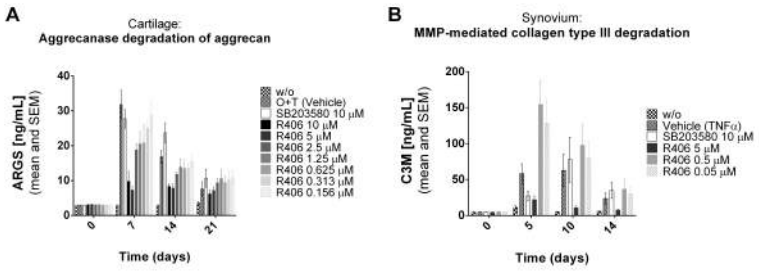
Background/Purpose: Osteoarthritis (OA) and rheumatoid arthritis are degenerative diseases of the whole joint. The extracellular matrix (ECM) turnover is highly regulated in response to the inflammatory status. This leads to an increased degradation of collagen type III in the synovium and an increased degradation of collagen type II and aggrecan in cartilage. The spleen tyrosine kinase (Syk) is involved in pro-inflammatory signaling and R406, the active metabolite of the anti-inflammatory drug, Fostamatinib inhibits Syk. Fostamatinib has been tested in both phase II and phase III clinical trials with mixed results. The aim of this study was to investigate R406 effects on the ECM turnover of the synovium and cartilage under inflammatory conditions *ex vivo*.

Methods: Cartilage turnover was investigated using a bovine cartilage explant (BEX) model. Synovial tissue turnover was investigated using a human synovial membrane OA explant (SME) model. **BEX:** BEX was cultured 3 weeks without (w/o) treatment, or in the presence of 2 ng/mL TNFα + 10 ng/mL OSM (O+T), or O+T with R406 in 7 different concentrations from 10 µM to 0.156 µM. **SME:** The explants were cultured for 2 weeks w/o treatment, or in the presence of 10 ng/mL TNFα, or TNFα with 5 µM, 0.5 µM or 0.05 µM R406. Both models were cultured with O+T or TNFα with the p38 inhibitor 10 µM SB203580. The tissue turnover was assessed with the biomarkers; C2M, C3M, acMMP3 the ARGS neo-epitope in the supernatant with ELISA.

Results: BEX) O+T increased the MMP-mediated degradation of collagen type II (C2M) after 14 days and ARGS after 7 days compared to w/o ($p<0.0001$). All concentrations of R406 inhibited the release of C2M in a dose depended manner. R406 at 10 µM ($p<0.0001$), 5 µM ($p<0.0001$) and 2.5 µM ($p = 0.0281$) decreased the release of ARGS compared to O+T, whereas lower concentrations of R406 did not affect ARGS (Figure 1A). SB202580 at 10 µM decreased C2M ($p<0.0001$), but did not affect the ARGS release compared to O+T. **SME)** TNFα increased the released of the MMP-mediated degradation of collagen type III (C3M) ($p=0.0400$) and activated MMP3 (acMMP3) ($p=0.0371$) compared to w/o. R406 at 5 µM tended to decrease the release of C3M, while R406 at 0.5 µM ($p=0.0219$) increased and 0.05 µM tended to increased C3M compared to TNFα. (Figure 1B). R406 tended to decrease the release of acMMP3 at 5 µM and had no effect at 0.5 µM and 0.05 µM compared to TNFα. SB203580 did not affect C3M or acMMP3 compared to TNFα.

Conclusion: These data show that R406 can inhibit pro-inflammatory ECM joint degradation at concentrations higher than 0.5 µM, but at 0.5 µM or lower R406 increased the inflammatory degradation of collagen type III and had no effect on aggrecan degradation. In contrast, the p38 inhibitor SB203580 had no effect on synovial ECM turnover or aggrecan degradation, underlining the importance of understanding the differences between inhibitors of pro-inflammatory mediators and their effect on the joint tissue.



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decreases-the-inflammation-driven-extracellular-matrix-turnover-of-the-joint-at-high-concentrations-ex-vivo

Abstract Number: 1150

Novel Chitosan Hydrogels for the Treatment of Osteoarthritis: Mechanical Support, Lubrication and Prevention of Cartilage Degradation in a Rabbit Model of Osteoarthritis

Yves Henrotin[1,2], Frédéric Oprenyeszk[1], Fanny Comblain[3], Jean-Emile Dubuc[4], Christelle Boileau[5], Mickaël Chausson[6], Renaud Lecler[6], Guillem Rocasalbas[6], Pierre Douette[6] and Sandrine Gautier[6], [1]Bone and Cartilage Research Unit, Arthropôle Liege, University of Liege, Liege, Belgium, [2]Physical Therapy and Rehabilitation Department, Princess Paola Hospital, Marche-en-Famenne, Belgium, [3]University of Liège, Bone and Cartilage Research Unit, Arthropôle Liege, University of Liege, Liege, Belgium, [4]Clinical University Saint Luc, Orthopaedic Department, Clinical University Saint Luc, Brussels, Belgium, [5]Artialis S.A.,11 Avenue de l'Hôpital, Tour Giga+3, Liege, Belgium, [6]Synolyne Pharma, rue Haute Claire 4, Herstal, Belgium
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Session Type: ACR Poster Session B
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Background/Purpose:

Chitosan, a glucosamine polysaccharide, is a good candidate for viscosupplementation in OA joints. Herein, we report the physico-chemical properties and the effects of an innovative chitosan hydrogels in the rabbit anterior cruciate ligament model ACLT model of OA.

Methods:

The mechanical and rheological properties of animal-free ultrapure chitosan hydrogels (Vegetech inside™, Synolyne Pharma, Belgium) were characterized using a mechanical compression equipment (Instron, US) and the Discovery Hybrid DHR-2 rheometer (TA Instruments, US). The properties were compared with those of synovial fluids and of hyaluronan: injection force, capacity to absorb shocks at walk frequency, ability to lubricate (viscosity at rest), and biodegradation kinetics. In addition, the chitosan hydrogels were mixed with patient synovial fluid (in a 1:1 ratio, v/v), and the ex vivo rheological properties of the mix were characterized.

OA was surgically induced by the transection of the anterior cruciate ligament (ACLT) in female HYLA albino rabbits. One week after surgery, animals were randomly divided into 2 groups. One group (n=9) was injected intra-articularly (right knee) with 600ml saline solution (control) and the other group (n=10) with 600ml of a chitosan hydrogel (VI002, Synolyne Pharma, Belgium). X-rays from the right knee were performed at the time of sacrifice and scored with the Kellgren and Lawrence (K&L) scale. Animals were euthanized 9 weeks after surgery and a macroscopic evaluation of cartilage was done. Histological sections of cartilage areas and of synovial membrane were evaluated according to the OARSI histopathology initiative.

Results:

Chitosan hydrogels were less prone to in vitro oxidative biodegradation than crosslinked and non crosslinked hyaluronan viscosupplements. Their mechanical and lubrication capacity are higher than those of synovial fluid and of hyaluronan viscosupplements. In addition, chitosan hydrogels were easily injected through 25G to 27G needles, with an injection force lower than that of a highly cohesive hyaluronan viscosupplement. Interestingly, when the chitosan hydrogels were mixed with the synovial fluid of OA patients, the mechanical and lubrication capacity were found to be restored.

The X-rays analysis showed a significant decrease ($p=0.0079$) of the K&L score in rabbits injected with the VI002 chitosan hydrogel (0.40±0.30) compared with control (1.78±0.32). The macroscopic OA cartilage lesions significantly decreased in the lateral compartment in animals treated with VI002 compared to control (21.40±2.67 with VI002 vs. 36.89±3.79 with control; $p=0.0041$). The synovitis histological scores, mostly synoviocytes hyperplasia and inflammatory infiltrate criteria, were significantly reduced by VI002 (13.25±0.51 with VI002 vs. 14.79±0.35 with control, $p=0.0040$). Finally, the injection of VI002 hydrogel significantly improved the structure of cartilage (6.54±0.35 with VI002 vs. 8.42±0.38 with control; $p =0.0017$).

Conclusion:

These results are confirming the high potential of the *mono-dose viscosupplementation* with non crosslinked chitosan hydrogels

specifically designed to protect cartilage and decrease the symptoms associated with OA.

Disclosure: Y. Henrotin, Artialis, Bioiberica, Danone, Expanscience, Ibsa, Merck, Pierre Fabre, Synolyne Pharma, Tilman, 5,Founder and President of Artialis SA and Synolyne Pharma, two spin-off companies of the University of Liege, 9; **F. Oprenyeszk**, None; **F. Comblain**, None; **J. E. Dubuc**, None; **C. Boileau**, Artialis S.A., 3; **M. Chausson**, Synolyne Pharma, 3; **R. Lecler**, Synolyne Pharma, 3; **G. Rocasalbas**, Synolyne Pharma, 3; **P. Douette**, Synolyne Pharma, 3; **S. Gautier**, Synolyne Pharma, 3.

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Abstract Number: 1151

The Proteomic Profile of Histological Samples Derived from a Surgical Mouse Model of Osteoarthritis Reveals an Unexpected Mode of Action for the Anti-Aggrecanase-2 Monoclonal Antibody CRB0017

Gianfranco Caselli[1], Riccardo Chiusaroli[2], Michela Visintin[3], Tiziana Piepoli[2], Ornella Letari[2], Adriana Grotti[2], Marco Lanza[2], Antonella De Palma[4], Dario di Silvestre[4], Pierluigi Mauri[4] and Lucio Claudio Rovati[2], [1]Pharmacology & Toxicology, Rottapharm Biotech Srl, Monza, Italy, [2]Rottapharm Biotech Srl, Monza, Italy, [3]Rottapharm Biotech Srl, Trieste, Italy, [4]Institute for Biomedical Technologies - CNR, Segrate, Italy

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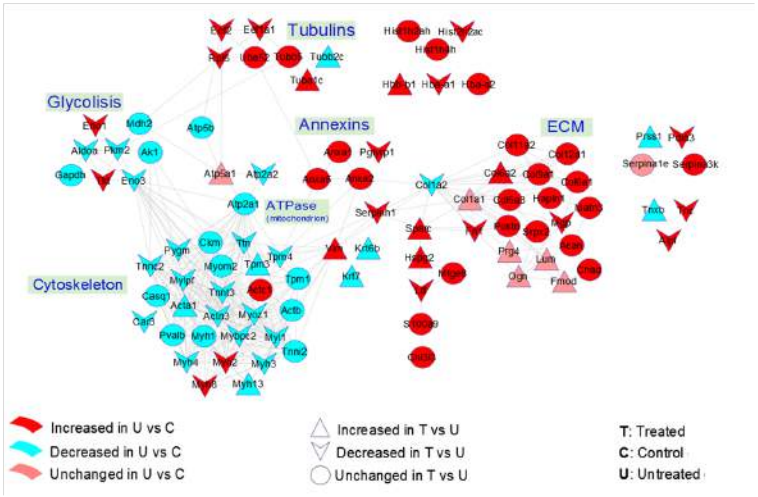
Background/Purpose : CRB0017 is a novel therapeutic monoclonal antibody that recognizes the spacer domain of aggrecanase-2, a key enzyme in the degradation of extracellular matrix (ECM) in osteoarthritis (OA). CRB0017 showed a marked cartilage protection in different models of OA in rodents (accompanying abstract by Caselli et al). Because CRB0017 does not recognize the catalytic domain of aggrecanase-2 and, therefore, does not simply inhibit the cleavage of aggrecan, its molecular mode of action on ECM proteins is not fully understood. So, we performed the proteomics analysis of histological samples derived from a surgical model of OA, the Destabilization of Medial Meniscus (DMM) in mice, in which intra-articularly injected CRB0017 had markedly counteracted cartilage degradation (in vivo results in the accompanying abstract by Caselli et al).

Methods : DMM was performed in C57BL/6J mice (10 weeks old at surgery; CRB0017 injection [72 µg in 4 µL] 1 week after surgery, injection repeated after 1 and 2 months, sacrifice at 3 months). At sacrifice, the femorotibial joints were explanted and processed for histology. Histological samples in paraffin from sham, DMM vehicle and DMM CRB0017 mice (9 samples/group) were processed for proteomics analysis. Briefly, samples were deparaffinized, trypsinized and analyzed by LC-MS, and lists of identified proteins were evaluated by MAPROMA cluster and network analyses.

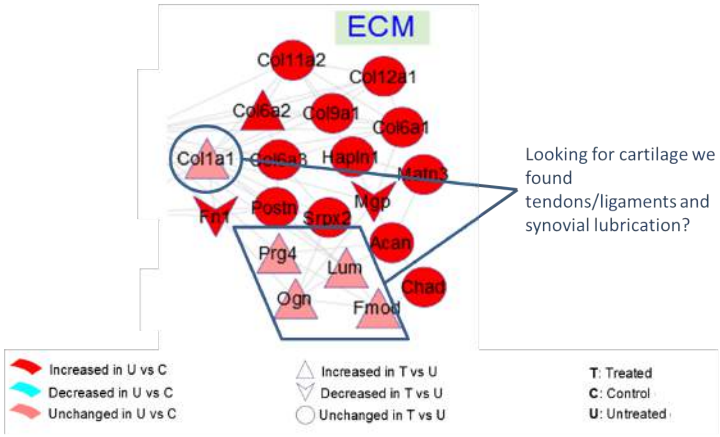
Results : About 400 proteins were identified, and the differential proteomics analysis of sham and DMM animals revealed the expected changes (i.e. general increase in ECM protein turnover, as depicted in Figure 1), confirming the validity of the selected protocol.

Figure 1 – Network analysis of differentially expressed proteins in histological samples from the femorotibial joints of sham operated control mice (**C**), DMM mice untreated (**U**) or DMM mice treated with CRB0017 (**T**)



The differential analysis between DMM mice treated with vehicle or CRB0017 revealed that the latter affected a series of proteins that have not been associated so far with aggrecanase-2 activity. In particular, (as shown in the enlarged particular in Figure 2) CRB0017 seems to preserve a homogeneous class of ECM proteins, the small leucine-rich repeat proteoglycans (SLRPs) fibromodulin, lumican and osteoglycin, and the levels of lubricin, one the most relevant components of joint lubrication.

Figure 2 – Zoom-in of Figure 1 on ECM proteins differentially expressed between DMM mice treated with CRB0017 (**T**) and untreated DMM mice (**U**); **C** are sham operated control mice.



Col1a1 = alpha-1 type I collagen; Fmod = fibromodulin; Lum = lumican; Ogn = osteoglycin; Prg4 = lubricin

Conclusion : Proteomics analysis of histological samples from joints of DMM mice treated with CRB0017 revealed that this monoclonal antibody against the spacer domain of aggrecanase-2 can modulate a series of proteins whose association with aggrecanase has not been codified yet (besides fibromodulin), but whose contribution to OA progression is well documented. These data, therefore, point out a new potential mode of action for therapeutic anti-aggrecanase antibodies.

Disclosure: G. Caselli, Rottapharm Biotech Srl, 3; **R. Chiusaroli**, Rottapharm Biotech Srl, 3; **M. Visintin**, Rottapharm Biotech Srl, 3; **T. Piepoli**, Rottapharm Biotech Srl, 3; **O. Letari**, Rottapharm Biotech Srl, 3; **A. Grotti**, Rottapharm Biotech Srl, 3; **M. Lanza**, Rottapharm Biotech Srl, 3; **A. De Palma**, Rottapharm Biotech Srl, 5; **D. di Silvestre**, Rottapharm Biotech Srl, 5; **P. Mauri**, Rottapharm Biotech Srl, 5; **L. C. Rovati**, Rottapharm Biotech Srl, 3.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/the-proteomic-profile-of-histological-samples-derived-from-a-surgical-mouse-model-of-osteoarthritis-reveals-an-unexpected-mode-of-action-for-the-anti-aggrecanase-2-monoclonal-antibody-crb0017

Abstract Number: 1152

Comprehensive Novel Proteomic Analysis of RA Synovial Fluid Highlights the Distinct Protein Profiles of Bone and Cartilage Metabolism

Yasushi Kondo[1], Katsuya Suzuki[1], Masaru Takeshita[2], Yoshiaki Kassai[3], Keiko Koga[3], Yuumi Gotou[4], Takahiro Miyazaki[3], Rimpei Morita[5], Yasuo Niki[6], Atsuko Murota[1], Ayumi Nishikawa[1], Hironari Hanaoka[1], Yuko Kaneko[7], Hidekata Yasuoka[7], Kunihiro Yamaoka[1], Akihiko Yoshimura[5] and Tsutomu Takeuchi[8], [1]Division of Rheumatology, Department of Internal Medicine, Keio University School of Medicine, Tokyo, Japan, [2]Division of Rheumatology and Clinical Immunology, Department of Internal Medicine, Keio University School of Medicine, Tokyo, Japan, [3]Inflammation Drug Discovery Unit, Pharmaceutical Research Division, Takeda Pharmaceutical Company Ltd., Kanagawa, Japan, [4]Inflammation Drug Discovery Unit, Pharmaceutical Research Division, Takeda Pharmaceutical Company Limited, Tokyo, Tokyo, Japan, [5]Department of Microbiology and Immunology, Keio University School of Medicine, Tokyo, Japan, [6]Department of Orthopaedic Surgery, Keio University, Tokyo, Japan, [7]Division of Rheumatology, Keio University School of Medicine, Tokyo, Japan, [8]Dept. of Internal Medicine, School of Medicine Keio University, Tokyo, Japan
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SESSION INFORMATION

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Background/Purpose:

Growing interest has arisen in the search for specific pathophysiology and biomarker for rheumatoid arthritis (RA) utilizing synovial fluid (SF) proteomic analysis. However the difference of protein profiles between SF and serum is still unclear. The objective of this study was to clarify the difference of protein signatures in RASF and serum.

Methods:

SF was collected from 10 untreated RA patients and 10 osteoarthritis (OA) patients. Serum was collected from 30 untreated RA patients and 30 healthy controls (HC). Total of 1128 proteins were quantitatively measured by comprehensive high-throughput proteomics assay using nucleic acid aptamers (SOMAscan™ Assay; Somalogic Inc., CO, USA). Comparison pathway analysis was performed with Ingenuity Pathway Analysis (IPA; Ingenuity system, CA, USA) and statistically extracted differentially up- or down-regulated proteins (fold change >1.5 or <0.66, $p<0.05$) in RA SF compared to OA SF and RA serum compared to HC serum.

Results:

A total of 167 of known pathways were extrapolated from RA SF, while only 23 pathways were extrapolated from RA serum ($p<0.01$ in the Benjamin-Hochman's multiple testing correction). The inflammatory signaling pathway was extrapolated from both, RA SF and serum, however osteoblast, osteoclast and chondrocyte signaling pathway was uniquely extrapolated from RA SF (-log p value=13.2). Focusing on the SF proteins associated with bone and cartilage metabolism, bone morphogenic protein (BMP)-6, 7 which proteins promote osteogenesis and RANKL/RANK/OPG signaling proteins including osteoprotegerin were significantly lower in RA SF compared to OA SF. ($p<0.05$) Unexpectedly, dickkopf (Dkk)-1 and -4 those that negatively regulated Wnt signaling pathway were significantly suppressed in RASF. ($p<0.05$) Futhermore, BMP and Dkk family proteins negatively correlated with pro-inflammatory cytokines in RA SF especially IL-6 (range of $r=-0.613$ to -0.400, $p<0.05$).

Conclusion:

Novel proteomic analysis of the RA synovial fluid revealed the clear difference of protein expression in serum and SF, especially highlighting the distinct protein profiles of aberrant bone metabolic turnover and cartilage formation in RA affected joint.

Disclosure: Y. Kondo, None; **K. Suzuki**, None; **M. Takeshita**, None; **Y. Kassai**, Takeda Pharmaceutical Company Ltd, 3; **K. Koga**, Takeda Pharmaceutical Company Ltd, 3; **Y. Gotou**, Takeda Pharmaceutical Company Ltd, 3; **T. Miyazaki**, Takeda Pharmaceutical Company Ltd, 3; **R. Morita**, None; **Y. Niki**, None; **A. Murota**, None; **A. Nishikawa**, None; **H. Hanaoka**, None; **Y. Kaneko**, Abbvie, 5,Abbvie, Eisai Pharmaceutical, Chugai Pharmaceutical, Bristol Myers Squibb, Astellas Pharmaceutical, Mitsubishi Tanabe Pharma Corporation, Pfizer, Janssen, UCB., 8,Eisai Pharmaceutical, Chugai, Pharmaceutical, Astellas Pharmaceutical, Mitsubishi Tanabe Pharma Corporation, Pfizer, 9; **H. Yasuoka**, None; **K. Yamaoka**, Pfizer, Chugai Pharma, Mitsubishi-Tanabe Pharma, Takeda Industrial Pharma, GlaxoSmithKline, Nippon Shinyaku, Eli Lilly, Janssen Pharma, Eisai Pharma, Astellas Pharma and Actelion Pharmaceuticals., 8; **A. Yoshimura**, None; **T. Takeuchi**, Astellas Pharma, Bristol–Myers K.K., Chugai Pharmaceutical Co, Ltd., Daiichi Sankyo Co., Ltd., Eisai Co.,Ltd., Mitsubishi Tanabe Pharma Co., Pfizer Japan Inc., Santen Pharmaceutical Co., Ltd., Takeda Pharmaceutical Co.,Ltd., Teijin Pharma Ltd., AbbVie GK,, 2,Astra Zeneca K.K., Eli Lilly Japan K.K., Novartis Pharma K.K., Mitsubishi Tanabe Pharma Co., and Asahi Kasei Medical K.K.,abbivie GK, Daiichi Sankyo Co.,Ltd., Bristol–Myers K.K., Nipponkayaku Co.Ltd., 5,Mitsubishi Tanabe Pharma Co., Eisai Co., Ltd., Abbivie GK, 9,bbVie GK., Bristol–Myers K.K., Chugai Pharmaceutical Co,. Ltd., Eisai Co., Ltd., Janssen Pharmaceutical K.K., Mitsubishi Tanabe Pharma Co., Pfizer Japan Inc., and Takeda Pharmaceutical Co., Ltd., Astellas Pharma, and Diaichi Sankyo

Co.,Ltd. ,Celtrion , Ni, 8.

Abstract Number: 1153

Colonic Intraepithelial Lymphocytes Produce IL-6 in Response to Resident Bacteria to Modulate Epithelial Barrier Function

Gaurav Mehta[1], Emilie H. Regner[2], Neha Ohri[2], Sean P. Colgan[2] and **Kristine A. Kuhn**[2], [1]Division of Rheumatology, University of Colorado School of Medicine, Aurora, CO, [2]University of Colorado School of Medicine, Aurora, CO
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Background/Purpose: Dysbiosis of colon bacteria has emerged as a likely contributor to diseases such as rheumatoid arthritis and spondyloarthropathies. Interactions between the microbiota and distal gut are critical for human health. These interactions are focused at the level of the colonic mucosa, and intestinal epithelial homeostasis is regulated by multiple signals emanating from both microbes and immune cells. As intraepithelial lymphocytes (IELs) are positioned within the epithelial barrier, we hypothesized that colon bacteria can modulate epithelial barrier function through interactions with IELs.

Methods: Epithelial cells were harvested from wild type C57Bl/6 mice, and lymphocytes evaluated by flow cytometry for T cell surface markers or magnetically sorted and stimulated ex vivo with mitogen for evaluation of cytokine production by ELISA. To model dysbiosis, mice were treated with ampicillin, metronidazole, neomycin, and vancomycin in the drinking water. Recolonization of mice occurred by cohousing antibiotic treated mice with unmanipulated littermates. Epithelial barrier integrity was evaluated by paracellular permeability of indigestible FITC-dextran in vivo and in vitro using the model human colonic cell line T84. Contact of host bacteria with the epithelium was performed by FISH using a universal bacterial probe. Protein and RNA analyses were done by Western blot and qRT-PCR, respectively.

Results: Our data demonstrate the major subpopulation of IELs in the mouse colon are CD3+, CD4-CD8-, and TCRβ+, express cell surface markers consistent with activated lymphocytes, and produce large amounts of IL-6 under mitogenic stimulation. Administration of significantly decreased the number of activated, IL-6-secreting IELs. This was reversible, as recolonization resulted in normalization of the IEL numbers, IL-6 secretion, and epithelial barrier integrity. The epithelial barrier in *IL-6*$^{-/-}$ and antibiotic-treated mice was noted to have increased paracellular permeability and closer interaction with luminal bacteria. IL-6 was found to signal in colonic epithelial cells and resulted in increased epithelial barrier integrity and claudin 1 expression in model epithelia.

Conclusion: We conclude that the host microbiota provides a homeostatic role through regulation of IEL derived IL-6. In turn, IL-6 participates in a barrier protective role in which it stimulates increased tight junction protein expression and decreased contact between luminal bacteria and the host. We postulate that dysbiosis, through the loss of IEL-derived IL-6, in combination with genetic risk, results in increased immune activation at the mucosal barrier, leading to downstream autoimmune responses.

Disclosure: G. Mehta, None; **E. H. Regner**, None; **N. Ohri**, None; **S. P. Colgan**, None; **K. A. Kuhn**, None.

Abstract Number: 1154

Ajulemic Acid Is a Novel Cannabinoid That Suppresses the Secretion of TNF-α and IFN-α from the Peripheral Blood Mononuclear Cells of DM Patients In Vitro

Paul Alves[1,2], Elizabeth Robinson[1,2], Muhammad Bashir[1,3], Rui Feng[4] and Victoria P. Werth[1,2], [1]Dermatology, Veterans Affairs Medical

Center, Philadelphia, PA, [2]Dermatology, University of Pennsylvania, Philadelphia, PA, [3]Department of Dermatology, University of Pennsylvania, Philadelphia, PA, [4]Biostatistics and Epidemiology, University of Pennsylvania, Philadelphia, PA
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Background/Purpose:

DM is an autoimmune disease with cutaneous symptoms often accompanied by inflammatory muscle and/or lung disease. Current therapies for DM are often toxic and ineffective. Ajulemic acid (AJA) is a synthetic, non-psychoactive cannabinoid potentially useful for treating DM. Experiments presented here quantify the capacity of AJA to suppress the secretion of TNF-α and IFN-α, two pro-inflammatory cytokines implicated in the pathogenesis of DM, from the peripheral blood mononuclear cells (PBMCs) of DM patients.

Methods:

PBMCs were isolated from the blood of 22 DM patients and then treated with 0, 3, 10 and 15 μM concentrations of AJA and incubated at 37°C and 5.0% CO_2 for 18 hours both with and without lipopolysaccharide (LPS) in the case of TNF-α and with and without CpG oligonucleotides (CpG) in the case of IFN-α. LPS and CpG were used to stimulate secretion of TNF-α and IFN-α, respectively, in order to ensure sufficient production for quantifying the effects of AJA via ELISA. Statistical analyses were performed on TNF-α and IFN-α secretion values normalized by natural log transformation, and unstimulated TNF-α secretion values below 2 pg/ml were excluded from analysis as outliers.

Results:

The LPS-stimulated PBMCs treated with 0 (n=17), 3 (n=16), 10 (n=16) and 15 (n=15) μM AJA secreted mean (standard deviation = SD) TNF-α values of 7.37 (1.33), 7.73 (1.03), 5.60 (1.91) and 4.20 (1.92) pg/ml, respectively. There was a statistically significant difference between the means using one-way ANOVA analysis ($p<0.0001$). In the *post hoc* analysis, AJA suppressed the secretion of TNF-α from LPS-stimulated PBMCs at 10 μM AJA (adjusted $p=0.0115$) and 15 μM AJA (adjusted $p<0.0001$), but not at 3 μM AJA (adjusted $p=0.9098$), when compared to LPS-stimulated PBMCs not treated with AJA. Unstimulated PBMCs treated with 0 (n=11), 3 (n=9), 10 (n=9) and 15 (n=7) μM AJA secreted mean (SD) TNF-α values of 2.27 (1.40), 2.47 (1.75), 1.83 (1.57) and 0.14 (1.72) pg/ml, respectively. Analysis by one-way ANOVA found a statistically significant difference between the means ($p=0.0303$). In the *post hoc* analysis, AJA suppressed the secretion of TNF-α from unstimulated PBMCs at 15 μM AJA (adjusted $p=0.0444$), but not at 3 μM AJA (adjusted $p=0.9925$) or 10 μM AJA (adjusted $p=0.9274$), when compared to unstimulated PBMCs not treated with AJA.

CpG-stimulated PBMCs treated with 0 (n=8), 3 (n=7), 10 (n=8) and 15 (n=7) μM AJA secreted mean (SD) IFN-α values of 5.33 (0.77), 1.38 (2.19), 1.06 (0.78) and -0.03 (1.68) pg/ml, respectively. There was a statistically significant difference between the means using one-way ANOVA analysis ($p<0.0001$). In the *post hoc*analysis, AJA suppressed IFN-α secretion from CpG-stimulated PBMCs at 3 μM AJA (adjusted $p=0.0004$), 10 μM AJA (adjusted $p=0.0010$) and 15 μM AJA (adjusted $p=0.0003$) when compared to CpG-stimulated PBMCs not treated with AJA. Unstimulated PBMCs secreted too little IFN-α to test the effects of AJA.

Conclusion:

AJA is a novel, non-psychoactive cannabinoid that suppressed secretion of TNF-α and IFN-α from the PBMCs of DM patients *in vitro*. Thus, AJA may offer patients with DM an effective therapy with less toxicity than other treatments currently available.

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Abstract Number: 1155

Free Fatty Acids Promote Inflammation in Bone of Rheumatic Patients Via Osteoblast

Klaus W. Frommer[1], Andreas Schäffler[2], Uwe Lange[1,3], Stefan Rehart[4], Jürgen Steinmeyer[5,6], Markus Rickert[7], Ulf Müller-Ladner[1,8] and Elena Neumann[1], [1]Internal Medicine and Rheumatology, Justus-Liebig-University of Giessen, Kerckhoff-Klinik, Bad Nauheim,

Germany, [2]Department of Internal Medicine III, Endocrinology, Diabetes, Metabolism, Justus-Liebig-University of Giessen, Bad Nauheim, Germany, [3]Internal Medicine and Rheumatology, Justus-Liebig-University Giessen, Kerckhoff-Klinik, Bad Nauheim, Germany, [4]Orthopedics and Trauma Surgery, Markus-Hospital, Frankfurt, Germany, [5]Experimental Orthopedics, Justus-Liebig-University of Giessen, Giessen, Germany, [6]Dept Orthopedics and Experimental Orthopedics, University Hospital of Giessen and Marburg, Giessen, Germany, [7]Dept of Orthopedics and Orthopedic Surgery, University Hospital of Giessen and Marburg, Gießen, Germany, [8]Internal Medicine/Rheumatology, Justus-Liebig-University of Giessen, Internal Medicine and Rheumatology, Kerckhoff-Klinik, Bad Nauheim, Germany
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Background/Purpose:

A pathophysiological link of free fatty acids (FFA) to inflammation is supported by the observation that chronically elevated serum FFA levels as found in obese patients are associated with numerous inflammatory cardiovascular and metabolic diseases. Also, FFA have been shown to induce signaling cascades and changes in gene expression in monocytes, adipocytes and hepatocytes *in vitro*. However, the influence of FFA on cells of bone metabolism is largely unknown so far. As obesity is associated with a higher risk of osteoarthritis also in non-weight bearing joints and increased amounts of visceral fat are associated with lower bone density, FFA may also play a role in bone metabolism.

Therefore, our main objective was to analyze the effect of FFA on cells of bone metabolism, specifically osteoblasts, in the context of rheumatic diseases. A further objective was to examine whether Wnt or TLR signaling is involved in FFA-mediated effects in osteoblasts.

Methods:

Primary osteoblasts were isolated from cancellous bone of rheumatoid arthritis (RA) or osteoarthritis (OA) patients undergoing knee joint surgery. The osteoblasts were stimulated with saturated and unsaturated FFA. Immunoassays were used to quantify protein secretion. mRNA expression levels were quantified by real-time PCR. Mineralization activity was measured by alizarin red S staining of mineralized matrix.

Results:

FFA induced a strong secretion of the proinflammatory cytokine IL-6 and the chemokine IL-8 in cultured osteoblasts, while showing a high variability between patients (IL-6: up to 9.1-fold ↑; IL-8: up to 221-fold ↑). On the other hand, RANKL and OPG, important regulators of osteoclastogenesis and osteoclast activity, osteoblast activity markers (ALP and collagen type I) and markers of osteoblast differentiation (SOX9, RunX2, osterix, osteocalcin) were not affected by FFA stimulation. Mineralization activity of FFA stimulated osteoblasts did not change significantly. The expression of Wnt signaling molecules (axin-2 and β-catenin) also remained unchanged. However, FFA-induced IL-8 secretion could significantly be reduced by blocking TLR4 but not by blocking TLR2. Of note, both saturated and unsaturated FFA caused a pro-inflammatory response in osteoblasts.

Conclusion:

Inflammation is centrally involved in many rheumatic diseases. Increased inflammatory activity is associated with decreased bone density. Our data therefore suggest that locally increased FFA levels may promote inflammation and thus inflammation-mediated degradation of bone via osteoblasts. These effects are at least in part mediated by TLR4, while TLR2 and Wnt signaling appear not to be involved.

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Abstract Number: 1156

Th17 Cytokines Regulate Osteoclastogenesis in Rheumatoid Arthritis

MIN-YOUNG JUNG[1], Hae-Rim Kim[2], HYUN-SOOK KIM[3], HO-YOUN KIM[1] and Sang Heon Lee[4], [1]Konkuk university hospital, Seoul, South Korea, [2]Division of Rheumatology, Konkuk University School of Medicine, Seoul, South Korea, [3]Soonchenhyang university school of medicine, Seoul, South Korea, [4]Konkuk University Hospital, Seoul, South Korea
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Background/Purpose: This study aimed to determine the regulatory effect of Th17 cytokines on osteoclastogenesis in rheumatoid arthritis (RA).

Methods: The expression of interleukin (IL)-17 and receptor activator of nuclear factor kappa-B ligand (RANKL) was determined in synovial tissue, fibroblast-like synoviocytes (FLS), and synovial fluids of RA patients using immunohistochemical staining, ELISA and real-time PCR. Th17 cytokines-induced RANKL expression was studied in RA FLS by using real-time PCR, luciferase activity assays, and western blot. Human peripheral blood monocytes were cultured with macrophage colony-stimulating factor (M-CSF) and Th17 cytokines, following which osteoclastogenesis was evaluated by counting the number of tartrate-resistant acid phosphatase (TRAP)-positive multinucleated cells. Osteoclastogenesis was also evaluated after human monocytes were co-cultured with IL-17-prestimulated FLS.

Results: There was significant correlation between RANKL and IL-17 levels in RA synovial fluid. IL-17, IL-21, and IL-22 increased the expression of RANKL mRNA in RA FLS and the IL-17-induced RANKL expression decreased by the inhibition of Act1, TRAF6, NF-κB and AP-1. Th17 cytokines and IL-17-prestimulated FLS induced osteoclastogenesis from monocytes in the absence of exogenous RANKL. The osteoclastic effect was reduced by inhibition of TNF-a.

Conclusion: Th17 cytokines have a dual effect on osteoclastogenesis in RA: direct induction of osteoclastogenesis from monocytes and upregulation of RANKL production in RA FLS. This Th17 cytokine/RANKL axis could be a potential therapeutic target for bone destruction in RA.

Abstract Number: 1157

Specific Profile of Serum Free Fatty Acids Is Found in Rheumatoid Arthritis Patients

Javier Rodríguez-Carrio[1], Mercedes Alperi-López[2], Patricia López[1], Javier Ballina-García[2] and Ana Suárez[1], [1]Area of Immunology, Department of Functional Biology, University of Oviedo, Oviedo, Spain, [2]Department of Rheumatology, Hospital Universitario Central de Asturias, Asturias, Spain
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Background/Purpose: Lipidomics is an emerging field in biomedical research. Free Fatty Acids (FFA) are important mediators of the lipid metabolism which can play a role in a number of biological functions other than energetic ones. FFA have been described to affect gene expression patterns in monocytes and macrophages, as well as modulation of CD4+ T-cell function. Since a role for FFA in the pathogenesis of rheumatic diseases can he hypothesized, we aimed to evaluate the serum FFA profile in Rheumatoid Arthritis (RA) patients.

Methods: serum FFA (palmitic, stearic, oleic, palmitoleic, linoleic –LA–, a-linolenic –ALA–, g-linolenic –GLA–, eicosapentanoic –EPA–, docosahexanoic –DHA– and arachidonic –AA–), were quantified by LC-MS/MS chromatography after a methyl-*tert*-butylether

extraction protocol in samples from 69 healthy controls and 129 RA patients. Moreover, 13 prospectively-followed RA patients undergoing TNFa-blockade were included. IFNg, TNFa and MCP1 serum levels were quantified by immunoassays.

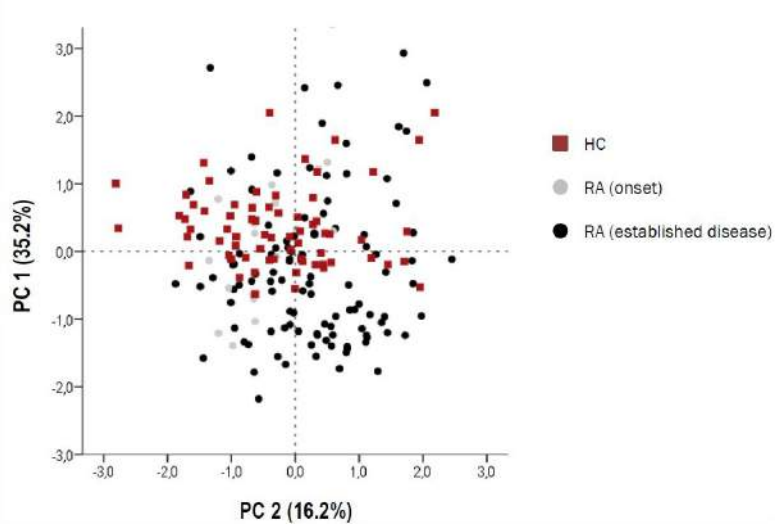
Results: Lower levels of palmitic ($p<0.0001$), oleic ($p=0.005$), palmitoleic ($p=0.003$), ALA ($p=0.023$), EPA ($p<0.0001$), DHA ($p<0.0001$) and AA ($p=0.031$) were found in RA patients. Although w3-polyunsaturated FFA were mainly decreased, there was not a general pattern of FFA associated with the chain length or the degree of desaturation, but individual FFA within a given class seems to exhibit a particular pattern. Principal Component Analysis supported this observation (Figure 1). These differences were more pronounced in patients with two copies of the shared epitope (SE) compared to patients with a single copy or SE-negative. No associations with disease activity or autoantibodies status were found.

Decreased FFA were associated with disease duration, whereas stearic acid exhibited a positive correlation ($r=0.431$, $p<0.001$). Additionally, stearic acid was positively correlated with IFNg levels ($r=0.408$, $p<0.0001$), whereas EPA and DHA negatively did ($r=-0.226$, $p=0.016$ and $r=-0.237$, $p=0.011$, respectively). Equivalent results were observed with MCP-1 levels, but no associations were found with TNFa. No differences by glucocorticoid or methotrexate usage were found.

Finally, decreasing DHA, EPA and AA levels (all $p<0.050$) were found in patients who exhibited no response upon TNFa-blockade, whereas no changes were found among good-responders ($n=5$; $p>0.05$ in all cases).

Conclusion: RA patients exhibited a different serum FFA profile associated to disease duration and inflammatory cytokines. Specific FFA were found to be decreased, independently of their chemical characteristics. Decreased levels of some FFA were associated with poor clinical outcome upon TNFa-blockade. These findings could support the use of fatty acid supplementation in RA and prove this field worthy or further research.

Figure 1: Principal Component Analysis of serum FFA in RA patients and HC.



Disclosure: J. Rodríguez-Carrio, None; **M. Alperi-López**, None; **P. López**, None; **J. Ballina-García**, None; **A. Suárez**, None.

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Abstract Number: 1158

Active Non-Canonical NF-Kappab Signaling in Microvessels of Atherosclerotic Lesions in Coronary Arteries Is Associated with Inflammatory Cell Infiltration and Myocardial Infarction

Chrissta X. Maracle[1], Rabia Agca[2], Boy Helder[1], Hans W. Niessen[3], Mike T. Nurmohamed[2] and Sander W. Tas[4], [1]Clinical Immunology and Rheumatology, Amsterdam Rheumatology and immunology Center | Academic Medical Center, Amsterdam, Netherlands, [2]Rheumatology, Amsterdam Rheumatology and immunology Center, VU University medical center, Amsterdam, Netherlands, [3]Pathology, VU University Medical Center, Amsterdam, Netherlands, [4]Clinical Immunology and Rheumatology, Amsterdam Rheumatology and immunology Center | Academic Medical Center/University of Amsterdam, Amsterdam, Netherlands

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Background/Purpose:

Patients with chronic inflammatory diseases (CID) have higher risk of developing cardiovascular disease which may be in part due to increased systemic inflammatory burden. In atherosclerosis, extensive neovascularization is associated with plaque instability and an increased chance for myocardial infarction (MI). We have established that the non-canonical NF-κB pathway, with its central regulator NF-κB inducing kinase (NIK), in endothelial cells (EC) contributes to pathological angiogenesis in synovial tissue of patients with various forms of arthritis, including rheumatoid arthritis (RA). Thus, we hypothesized that NIK^+EC may also contribute to neovascularization in atherosclerotic lesions.

Objective:

Evaluate expression of NIK in microvessels in atherosclerotic lesions from patients with and without CID and determine if it is associated with inflammatory cell influx, systemic inflammation or involvement of coronary arteries in MI.

Methods:

We obtained atherosclerotic coronary arteries from 11 individuals with CID (5 RA, 4 psoriasis, 2 inflammatory bowel disease) along with 11 matched controls without CID, all of whom died of fatal MI. Coronary arteries were immunohistochemically stained with antibodies against NIK, CD31/34 (EC), myeloperoxidase (neutrophils), CD45 (lymphocytes), CD68 (macrophages) and tryptase (mast cells). NIK positive vessel density (VD) (NIK^+ vessels/mm2) and immune cell density (ICD cells/mm2) were calculated for right coronary artery (RCA) (internal control; remote area) and left anterior descending artery either implicated in MI (LAD+) or not (LAD-). Differences in NIK^+ vessel density and cell densities in CID and controls, and between LAD+, LAD- and RCA, were analyzed using non-parametric Spearman's Rank correlation or non-parametric Mann-Whitney U test.

Results:

NIK^+ EC were present in atherosclerotic lesions of all coronary arteries. NIK^+VD significantly correlated with ICD of all characterized immune cells: leukocytes ($r=0.5227$; $p<0.0001$), macrophages ($r=0.3397$, $p<0.0001$), mast cells ($r=0.4205$, $p<0.0001$) and neutrophils ($r=0.2129$, $p=0.0016$). No significant differences were found in NIK^+VD in CID patients versus healthy, however, influx of leukocytes and macrophages per NIK^+ microvessel was significantly higher in CID lesions. An increase in NIK^+microvessels was also noted in LAD+ as compared to LAD- tissues ($p=0.0139$) in both healthy and CID patients.

Conclusion:

NIK^+ microvessels are present in high numbers in atherosclerotic lesions and are strongly associated with the influx of inflammatory cells. Systemic inflammation is not a prerequisite for activation of this pathway in EC in atherosclerotic lesions, but our findings suggest that non-canonical NF-κB signaling is more pronounced in patients with CID resulting in the attraction of more immune cells that may further enhance progression of atherosclerotic lesions. Since activation of the non-canonical NF-κB pathway in EC induces angiogenesis and NIK^+ vessels are increased in coronary arteries associated with MI, non-canonical NF-κB signaling in EC may drive neovascularization and plaque instability, thus increasing the chance of developing a (fatal) MI.

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Abstract Number: 1159

Transcription Factor SOX5 Promotes Rheumatoid Arthritis Synovial Fibroblast Migration and Invasion By Regulating MMP9 Expression

Wenfeng Tan[1], Yumeng Shi[2], Xiaoke Feng[2], Fang Wang[2], Xiaoxi Wang[2], Qiuyue Peng[2], Wenhua Xuan[2] and zhang miaojia[3], [1]Rheumatology, the First Affiliated Hospital of Nanjing Medical University, Nanjing, China, [2]the First Affiliated Hospital of Nanjing

Medical University, Nanjing, China, [3]the First Affiliated Hospitial of Nanjing Medical University, Nanjing, China
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Background/Purpose:

SOX5 is known as a transcription factor which primarily involved in in the regulation of embryonic development, cell fate, and chondrogenesis. To date, little is known the effect of SOX5 on rheumatoid arthritis (RA). We previously reported a RANKL promoter SNP confers an elevated promoter activity after stimulation via binding to a SOX family transcription factor SOX5 and is associated with younger age at onset of rheumatoid arthritis (RA) *(Arthritis Rheum 2010; 62(10):2864-75.)*. Subsequently, we confirmed that SOX5 could up-regulate RANKL expression in RA synovial fibroblast(SF) and participate in the bone erosion of RA. Here, we examine the effect of SOX5 on the migration and invasive characteristics of RA synovial fibroblasts.

Methods:

Rheumatoid synovial fibroblasts cell line MH7A were treated with SOX5 small interfering RNA (SOX5-siRNA) and recombinant Adenovirus SOX5 expression vectors (Ad-SOX5). Migration and invasion and of RASF was assessed by transwell matrigel^{TM}invasion chambers and collagen gel assays. Modulation of MMP9 expression in RASF was analyzed by real-time PCR, western blot and luciferase assay. Collagen-induced arthritis (CIA) DBA/1 mouse locally injected with lentivirus-shSOX5 was used to examine the effect of SOX5 on MMP9 expression in vivo.

Results:

Overexpression of SOX5 significantly promoted cell migration, invasion and MMP-9 expression in RASF. Migration and invasion of RASF was markedly decreased by silencing SOX5 expression in RASF but could be reverted by added the recombinant MMP9 cytokine into RASF. Overexpression of SOX5 enhanced the promoter activity of MMP9 in Hela cell. Local silencing SOX5 in CIA mice inhibited the synovitis and bone erosion and accompanied by the reduced MMP9 expression in synovium of CIA mice.

Conclusion:

These findings indicate transcription factor SOX5 plays an important role in regulating RASF migration and invasion by modulation MMP9 expression, suggesting SOX5 as a potential therapeutic target for the treatment of RA.

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Abstract Number: 1160

DNA Hydroxylmethylation Regulates Pro-Inflammatory Cytokine Expression in Macrophages

Fangfang Sun[1,2], Renate E. Gay[1], Beat A. Michel[1], Shuang Ye[2], Steffen Gay[1], Michel Neidhart[1] and Emmanuel Karouzakis[1], [1]University Hospital Zurich, Center of Experimental Rheumatology, Switzerland, Zurich, Switzerland, [2]Department of Rheumatology, South Campus, Renji Hospital, School of Medicine, Shanghai Jiao Tong University, China, Shanghai, China
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Background/Purpose:

Activated macrophages are found in the inflamed and hyperplasic synovial RA tissues. Macrophages are the main producers of high levels of pro-inflammatory cytokines such as TNF-a and IL-6. Our group has already reported a persistent global hypomethylation in RA tissues and RA synovial fibroblasts (RASF). Recent findings showed that the 5-methylcytosine (5-mC) modification of DNA can be converted to 5-hydroxymethylcytosine (5-hmC) through the activation of the family of Ten-Eleven-Translocation (TET1-3) enzymes which may explain the genomic hypomethylation in RA. In the current study, we investigated the 5-hmC modification in monocyte derived macrophages stimulated with lipopolysaccharide (LPS), and characterized the function of TET1-3 enzymes during inflammation.

Methods:

The leukemic monocytic cell line THP-1 was differentiated into macrophages in the presence of 50nM phorbol myristate acetate (PMA). Primary human monocytes were isolated using CD14 magnetic beads from peripheral blood mononuclear cells (PBMCs). Next, macrophages were prepared by culturing the CD14 monocytes with macrophage colony stimulating factor (M-CSF) for 6 days. THP-1 derived macrophages and human primary macrophages were stimulated with 100 ng/ml LPS for 2 hours. At different time points, the mRNA levels of TETs were analysed by quantitative Real-time PCR. The global 5-hmC levels were quantified by DNA dot blot assay and presented as chemiluminescence intensity in arbitrary units (AU). Hydroxymethylated DNA immunoprecipitation (hMeDIP) was applied to analyse the levels of 5-hmC in different areas of the TNF-a (TNF-a 1-4) and IL-6 promoter. THP-1 derived macrophages were transfected with TET1 siRNA and then stimulated with 100ng/ml LPS. TNF-a and IL-6 levels were measured in the supernatants by ELISA.

Results:

Global 5-hmC levels were significantly up regulated during differentiation from THP-1 cells to macrophages (Dot blot: ratio to ssDNA 0h 0.59, 48h 4.13 AU). After 48 hours of differentiation, we observed an increase of 5-hmC enrichments in four different regions of the TNF-a. (hMeDIP: TNF-a1: 2.42, TNF-a2: 2.25, TNF-a3: 2.03, TNF-a4: 2.08, fold enrichment, n=3). Stimulation of the macrophages with LPS for 0.5h showed a significant increase of TET1 mRNA (TET1: 0.5h 1.93±0.7, fold change, n=4, p=0.03). Interestingly, LPS stimulation increased 5-hmC levels in the promoter of TNF-a and IL-6 in primary human macrophages (hMeDIP: TNF-a 1.64±0.2, n=3, p=0.03; IL-6 1.74±0.2, n=3, p=0.03). Since, TET1-3 enzymes catalyze the synthesis of 5-hmC, we knocked down TET1 with siRNA in THP differentiated macrophages and found that TNF-a and IL-6 production was reduced by 46% and 44% respectively (n=4).

Conclusion:

For the first time, we showed that TET1 contributes to the activation of macrophages through the regulation of 5-hydroxymethylation in the promoter of pro-inflammatory cytokine genes. The TET1 enzyme could be a promising therapeutic target to inhibit the persistent inflammation caused by macrophages in RA.

Disclosure: F. Sun, None; **R. E. Gay**, None; **B. A. Michel**, None; **S. Ye**, None; **S. Gay**, None; **M. Neidhart**, None; **E. Karouzakis**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/dna-hydroxylmethylation-regulates-pro-inflammatory-cytokine-expression-in-macrophages

Abstract Number: 1161

Synovial Th9 Cells Prolong Neutrophil Survival and Functionally Enhance the Infiltrating T Cells in Rheumatoid Arthritis

Dipendra Kumar Mitra[1] and Kaustav Chowdhury[2], [1]Transplant Immunology & Immunogenetics, All India Institute of Medical Sciences, Delhi, India, [2]TRANSPLANT IMMUNOLOGY AND IMMUNOGENETICS, ALL INDIA INSTITUTE OF MEDICAL SCIENCES, New Delhi, India

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SESSION INFORMATION

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Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: Th-9 cells are distinct T cell subset secreting IL-9 and associated with allergic and parasitic diseases and

produced by Th9 cells. Contribution of these cells autoimmune colitis (1, 2), uveitis (3) and experimental autoimmune encephalomyelitis (EAE) has ben reported recently. However, reports on their presence or enrichment at the pathologic sites and impact on the local inflammatory cascade in rheumatoid arthritis (RA) remain unknown. Functional relevance of newly described IL-9 producing CD4+ T cells is not yet been clearly described in RA. This study is an attempt to determine the status of Th9 cells in the disease site in RA patients. Here for the first time, we show that Th9 cells or IL-9 can modulate survival of neutrophils and T cell function and enhances the local inflammatory cascade in RA inflicted joints.

Methods: We recruited treatment naïve active RA patients (n=26) with DAS28-ESR >3.5. Polymorphonuclear (PMNs/Neutrophil) and mononuclear cells (MNCs) were isolated both from the peripheral blood (PBL) and synovial fluid (SF). Neutrophils were cultured in presence of recombinant IL-9 (rIL-9), synovial fluid of RA patients (RA SF), IL-9 neutralizing antibody (aIL-9). MNCs were cultured with plate bound anti-CD3 & anti-CD28 along with rIL-9, RA SF, aIL-9. To easure apoptosis neutrophils were stained for Annexin V and their lysate was immunobloted for expression of anti-apoptotic protein MCL-1. MNCs were stained with CD4 and IL-9 to determine the frequency and function of Th9 cells. Frequencies of other cytokine (IFN-γ, TNF-α, IL-17) producing CD4+ T cells were evaluated by intracellular cytokine staining.

Results: Significant enrichment of Th9 cell was noted in synovial fluid (SF) of RA patients. Recombinant IL-9 (rIL-9) and RA SF reduced the spontaneous apoptosis of neutrophils along with higher expression of survival protein MCL-1. Blocking endogenous IL-9 of SF decreased their survival and rescued their apoptosis, suggesting the critical role of IL-9 in prolonged neutrophil survival in RA. IL-9 and RA SF also increased the frequencies of TNF-α+, IFN-γ+, IL-17+ CD4+ T cells. Interestingly, both synovial and peripheral Th9 cell frequency showed significant correlation with disease activity DAS-28 ESR score.

Conclusion: Th9 cells or IL-9 plausibly mediate synovial inflammation by prolonging the neutrophil survival and enhancing inflammatory cytokine producing T cells in the RA joint. So blocking IL-9 by specific antibody could be a possible therapy in RA. Frequency of Th9 cell may serve as objective disease severity biomarker for joint inflammation in RA patients

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Disclosure: D. K. Mitra, None; **K. Chowdhury**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/synovial-th9-cells-prolong-neutrophil-survival-and-functionally-enhance-the-infiltrating-t-cells-in-rheumatoid-arthritis

Abstract Number: 1162

IL37 Reduces Pro-Inflammatory Cytokine and Catabolic Enzyme Production in Human Chondrocytes: A Protective Role in Osteoarthritis?

Ellen van Geffen[1], Arjan van Caam[2], Elly Vitters[2], Henk van Beuningen[2], Esmeralda Blaney Davidson[2] and Peter M. van der Kraan[2], [1]Experimental Rheumatology, Radboud university medical center, Nijmegen, Netherlands, [2]Experimental Rheumatology, Radboud university medical center, Nijmegen, Netherlands

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Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: Osteoarthritis (OA) is the most common joint disease, primarily characterized by progressive articular cartilage degradation. Cartilage destruction is assumed to be mediated by pro-inflammatory cytokines, including IL-1β, IL-6, IL-8 and TNFα via induction of matrix degrading enzymes, such as matrix metalloproteinases (MMPs) and A Disintegrin-like and Metalloproteinases with Thrombospondin Motifs (ADAMTS). Recently, IL37 has come into view as an anti-inflammatory cytokine with inhibitory properties on innate immune responses by decreasing the production of pro-inflammatory cytokines. In this study we investigated if IL37 is able to reduce the expression and secretion of pro-inflammatory cytokines and catabolic enzymes in human OA chondrocytes.

Methods: Cartilage was obtained from eight OA patients undergoing total knee or hip joint arthroplasty. First IL37 expression was analyzed by immunohistochemistry. To determine if IL37 expression is responsive to pro-inflammatory cytokines, chondrocytes were stimulated with IL-1β (10 ng/ml). IL37 gene expression was measured using qPCR. The functionality of IL37 was tested in primary human OA chondrocytes by overexpression of human IL37 via an adenovirus. Subsequently, chondrocytes were stimulated with IL-1β to create an OA-like environment. The effect of IL37 on the production and secretion of pro-inflammatory cytokines and enzymes in this environment was analyzed by qPCR, Western Blot and Luminex.

Results: In cartilage of OA patients, immunohistochemical analysis indicated that IL37 protein was indeed expressed by chondrocytes. Furthermore, we found that in primary OA chondrocytes the production of IL37 is significantly *(p<0.0076)* induced through IL-1β stimulation. After overexpression, IL37 was effective to suppress IL-1β-induced gene expression of the pro-inflammatory cytokines *IL-1β (p<0.0007)*, *IL-6 (p<0.0043)*, *IL-8 (p<0.0002)* and the catabolic enzymes *MMP3 (p<0.0010)* and *ADAMTS5 (p<0.0104)* gene expression levels. In addition to gene expression analysis, we also studied the protein expression of pro-inflammatory cytokines in response to IL37 in primary OA chondrocytes. IL37 significantly reduced IL-1β-induced IL-6 *(p<0.0111)* and IL-8 protein *(p<0.0001)* levels in the supernatant of primary OA chondrocyte cultures. Furthermore, on Western blot analysis IL37 showed a reduction in IL-1β-induced IL-1β protein level.

Conclusion: In the present study, we showed basal IL37 protein expression and IL-1β- induced IL37 gene expression in human OA cartilage. This is the first study, demonstrating the enhanced expression of IL37 by primary human OA chondrocytes in an inflammatory environment. Furthermore, IL37 potently reduced the IL-1β-induced production and secretion of pro-inflammatory cytokines and catabolic enzymes. Clearly, these data implicate IL37 as a potent protective cytokine against cartilage degradation.

Disclosure: E. van Geffen, None; **A. van Caam**, None; **E. Vitters**, None; **H. van Beuningen**, None; **E. Blaney Davidson**, None; **P. M. van der Kraan**, None.

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Abstract Number: 1163

Dynamic Regulation of Enhancers and Super-Enhancers in Rheumatoid Arthritis Synovial Finroblasts

Sung-Ho Park[1], Christopher Sohn[1], Konstantinos Loupasakis[2], Angela Lee[3], Eugenia Giannopoulou[1], Lionel B. Ivashkiv[3] and **George D. Kalliolias**[1], [1]Hospital for Special Surgery, New York, NY, [2]Rheumatology, Hospital for Special Surgery Weill Cornell Medical College, New York, NY, [3]Medicine, Hospital for Special Surgery, New York, NY

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Session Time: 9:00AM-11:00AM

Background/Purpose: Enhancers are regulatory elements that modulate transcriptional rates of genes. Super-enhancers (SupE) are extremely large enhancers associated primarily with highly expressed genes that have critical functions in health and disease. The purpose of this study was to map typical enhancers and super-enhancers (SupE) in rheumatoid arthritis (RA) synovial fibroblasts (FLS).

Methods: Chromatin immunoprecipitation sequencing (ChIPseq) was used to evaluate H3K27 acetylation (Ac) genome-wide in control and TNF-stimulated FLS. Typical enhancers and SupE, were identified by H3K27Ac signal, using HOMER in a similar manner to the method described in Whyte et al. Cell 2013;153(2):307-19.

Results: The number and distribution of typical enhancers and SupE in FLS is modulated by TNF-stimulation in a time-dependent manner (Figure 1A-B). In some loci TNF-stimulation induces SupE (Figure 1C-D) and in others, baseline SupE are down-regulated or abrogated (Figure 1E). SupE-associated genes display significantly higher expression levels, compared to typical-enhancer-associated genes, in control and TNF-stimulated cells (Figure 2A). 16 RA-associated Single Nucleotide Polymorphisms (SNPs) are localized within SupE in RA FLS (Figure 2B).

Conclusion: The enhanceosome and super-enhanceosome is highly dynamic in RA FLS. TNFa has a genome-wide impact on FLS chromatin, suggesting that during the course of synovitis inflammatory mediators induce a pathogenic behavior by altering the landscape of enhancers and SupE in FLS. RA-associated SNPs are enriched in SupE of RA FLS, supporting the critical role of FLS in RA pathogenesis.

Figure 1

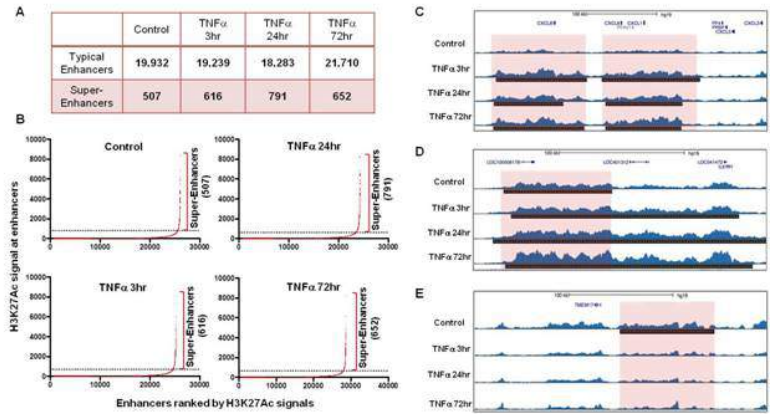
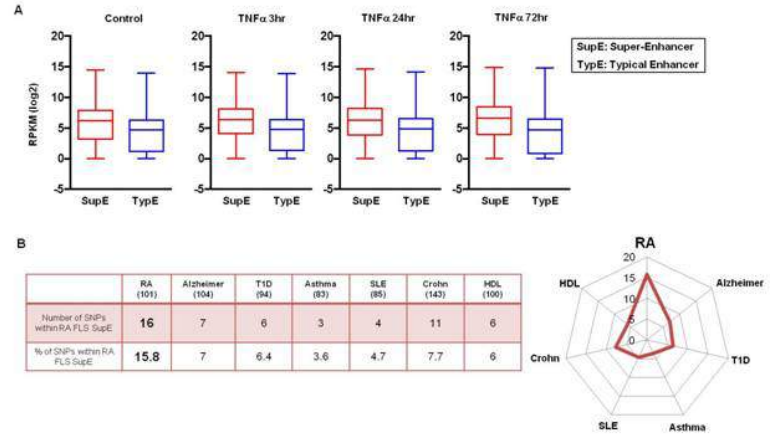


Figure 2



Disclosure: S. H. Park, None; **C. Sohn**, None; **K. Loupasakis**, None; **A. Lee**, None; **E. Giannopoulou**, None; **L. B. Ivashkiv**, None; **G. D. Kalliolias**, None.

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Abstract Number: 1164

Four Types of Calcium Pyrophosphate Crystals Differentially Induce IL-1beta Production By Monocytes through ATP/Potassium Efflux/ROS Dependent Pathways

Laure Campillo-Gimenez[1], Pierre Gras[2], Félix Renaudin[3], Marion Renaud[3], Lorène Télot[4], Amine Mellouk[5], Pierre Bobé[5], Jean-Michel Camadro[4], Christèle Combes[2], Martine Cohen-Solal[3,6], Frederic Liote[3,6] and Hang-Korng Ea[3,6], [1]Hôpital Lariboisière, Centre Viggo Petersen, INSERM UMR1132, Paris Diderot University, Paris, France, [2]ENSIACET, CIRIMAT, INPT-UPS-CNRS, Toulouse, France, [3]INSERM UMR1132, Paris Diderot University, Paris, France, [4]CNRS UMR7592, Jacques Monod Institute, Paris Diderot University, Paris, France, [5]INSERM UMRS757, Paris Sud University, Orsay, France, [6]AP-HP, Lariboisière Hospital, Rheumatology Department, Paris, France

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Session Time: 9:00AM-11:00AM

Background/Purpose:

Monoclinic and triclinic calcium pyrophosphate (m- and t-CPP) crystals are the 2 types of CPP crystals observed in human joints. Frequently asymptomatic, it can give rise to acute arthritis. Interleukin (IL-) 1β plays a pivotal role in CPP crystal-induced inflammation but how they induce IL-1β production remains unknown. IL-1β secretion occurs after its maturation by caspase-1 which is activated by NLRP3 inflammasome. NLRP3 inflammasome can be stimulated by potassium (K^+) efflux, reactive oxygen species (ROS) generation, lysosomal or mitochondrial alterations. In this study we aimed to decipher how CPP crystals initiate IL-1β production.

Methods:

Four types of CPP crystals were synthesized *in vitro*: m- and t-CPP dihydrate (m- and t-CPPD), amorphous CPP (a-CPP) and m-CPP tetrathydrate (m-CPPT) [1]. The effects of CPP and monosodium urate (MSU) crystals – the later used as control – were assessed in human THP-1 cell line and bone marrow-derived monocytes (BMDM) from wild type (wt) and P2X7 receptor knock-out ($P2X7^{-/-}$) mice. Cells were primed before stimulation with crystals. *In vivo*, m- and t-CPPD crystal effects were evaluated in the murine air pouch model.

IL-1β production was measured in cell culture supernatants and air pouch lavages by ELISA. Expression of inflammatory mediator genes was analyzed by qPCR. ROS production and mitochondrial membrane potential were evaluated by microscopy and flow cytometry, using fluorescent probes (CellRox® and JC-1, respectively). Extracellular ATP (ATP_e) concentration was quantified in cell culture supernatants.

Results:

In vitro, we showed that m-, t-CPPD and MSU crystals differentially induced IL-1β secretion and IL-1β, IL-6, IL-8, TNF-α, COX2 gene expression (m-CPPD > MSU > t-CPPD) while a-CPP and m-CPPTβ crystals had no effect; IL-1β production was not correlated with CPP crystal specific surface area. Similarly, these 3 inflammatory crystals induced *in vivo* IL-1β secretion, neutrophil and monocyte influx into the air pouch. Then, we assessed the mechanisms of CPP crystal-induced IL-1β production. First, we found that m- and t-CPPD crystals brought on an ATP release and that IL-1β production was partially inhibited by oxidized ATP. Second, m- or t-CPPD-induced IL-1β secretion was completely abrogated when K^+ efflux was inhibited (cell culture with a K^+-enriched medium). Although ATP_e can trigger K^+ efflux through P2X7 receptor opening, crystal-mediated IL-1β production was identical between wt and $P2X7^{-/-}$BMDM. Finally, we demonstrated an early decrease in mitochondrial membrane potential following crystal stimulation combined with a higher intracellular ROS level. Moreover, ROS scavenger dramatically decreased IL-1β release (75% inhibition) induced by CPPD crystals.

Conclusion:

CPP crystals displayed different inflammatory properties, m-CPPD crystals being the most potent one. CPPD crystal-induced IL-1β maturation occurs through three major mechanisms including ATP release, P2X7 receptor-independent K^+efflux, and mitochondrial disruption/ROS production.

[1] Gras P. et al, Eur. J. Inorg. Chem., 2013

Disclosure: L. Campillo-Gimenez, None; **P. Gras**, None; **F. Renaudin**, None; **M. Renaud**, None; **L. Télot**, None; **A. Mellouk**, None; **P. Bobé**, None; **J. M. Camadro**, None; **C. Combes**, None; **M. Cohen-Solal**, None; **F. Liote**, None; **H. K. Ea**, None.

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Abstract Number: 1165

Age-Dependent Effects of HLA-B27/β2m Expression on Host Immunity and the Intestinal Microbiota

Mark Asquith[1], Phoebe Lin[2], Sean Davin[3], Patrick Stauffer[4], Stephen R. Planck[5] and James T. Rosenbaum[6], [1]OHSU, Portland, OR, [2]Casey Eye Institute, Oregon Health and Science University, Portland, OR, [3]Oregon Health and Science University, Portland, OR, [4]Oregon Health & Science University, Portland, OR, [5]Casey Eye Institute, Oregon Health & Science University, Portland, OR, [6]Devers Eye Institute, Legacy Hospital system, Portland, OR

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Background/Purpose: The HLA-B27/β2m transgenic rat is a leading model of Anklylosing Spondylitis (AS) and other B27-associated spondyloarthopathies. The development of both bowel and joint inflammation is dependent on the presence of intestinal bacteria and we have shown previously that adult HLA-B27/β2m rats have an altered intestinal microbiota. In this study we sought to better define age-dependent changes to immune function, host gene expression and the development of dysbiosis in this system.

Methods: Ileal, cecal and colonic contents were collected from WT and HLA-B27/β2m+ rats during the post-weaning period (3 and 6 weeks), at disease onset (10 wks) and after the establishment of disease (16wks). Microbial community structure was determined by 16s sequencing and qRT-PCR. Mucosal and systemic Th1, Th17 and Treg responses were analyzed by flow cytometry. Flow cytometry was also used to determine the frequency of IgA-coated bacteria in intestinal contents. Host expression of inflammatory cytokines and antimicrobial peptides (AMPs) was determined in intestinal tissue by qRT-PCR. Histopathological evaluation was performed on H&E stained intestinal and joint sections.

Results: Both HLA-B27/β2m rats and controls exhibited a highly age-dependent intestinal microbiota. The microbiota of these rats diverged from that of controls by 10wks of age. *Akkermansia muciniphila* was greatly expanded in the intestinal mucosa of transgenic animals. Notably, an inflammatory cytokine signature and elevated AMP expression during the post-weaning period preceded the development of clinical bowel inflammation and dysbiosis. An early and sustained expansion of the Th17 pool was specifically observed in cecal and colonic mucosa of HLA-B27/β2m rats, whereas FoxP3 +ve Treg and Th1 cells were either unchanged or decreased at these tissue sites. By contrast, CD4+FoxP3+ T cells were significantly expanded in both mesenteric lymph node and spleen of HLA-B27/ β2m rats. Strikingly, a vast expansion in the frequency of IgA-coated intestinal bacteria (30-fold over controls) was observed at a late stage (16 weeks) concurrent with the age of arthritis onset in these animals.

Conclusion: HLA-B27/β2m expression renders the host hyper-responsive to microbial antigens from infancy. Early activation of innate immunity and expansion of a mucosal Th17 signature is soon followed by dysbiosis in HLA-B27/β2m+ve animals. The study of mucosal immune response and dysbiotic changes to the intestinal microbiota strongly merit further study in both pre-diseased and diseased SpA patient populations. IgA-coating has been reported to identify colitogenic bacteria in CD patients. Efforts are ongoing to identify sIgA+ve bacteria observed in the presence of HLA-B27 expression and their arthritogenic potential.

Disclosure: M. Asquith, None; **P. Lin**, None; **S. Davin**, None; **P. Stauffer**, None; **S. R. Planck**, None; **J. T. Rosenbaum**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/age-dependent-effects-of-hla-b272m-expression-on-host-immunity-and-the-intestinal-microbiota

Abstract Number: 1166

Expression and Function of Proviral Integration Site for Moloney Murine Leukemia Virus 1 (PIM-1) Kinase in Rheumatoid Arthritis Fibroblast-like Synoviocytes

Yong Seok Choi[1], You Jung Ha[2], Jaehyung Hur[3], Eun Ha Kang[4], Yeong Wook Song[5] and Yun Jong Lee[2], [1]Internal Medicine, Seoul National University Bundang Hospital, Seongnam-si, South Korea, [2]Division of Rheumatology, Department of Internal Medicine,Seoul National University Bundang Hospital, Seongnam, South Korea, [3]Division of Rheumatology, Department of Internal Medicine, Seoul National University Bundang Hospital, Seongnam-si, South Korea, [4]Department of Internal Medicine, Seoul National University Bundang Hospital, Seongnam-si, South Korea, [5]Division of Rheumatology, Department of Internal Medicine, Seoul National University Hospital, Seoul, South Korea

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Background/Purpose: The Proviral Integration site of Moloney murine leukemia virus (PIM) kinases are important mediators of cell survival and considered as attractive targets in cancer chemotherapy. Their implication has not been studied in the function of rheumatoid arthritis (RA)-fibroblast-like synoviocytes (FLS).

Methods: Immunoblot or quantitative real-time RT-PCR was performed to investigate the expression of 3 isoforms of PIM kinases (PIM-1, PIM-2, and PIM-3) in of RA- and osteoarthritis (OA)-FLS. The presence of PIM-1 was confirmed using immunostaining on synovial

tissue from RA and OA patients. After knockdown of PIM-1 using siRNA, proliferation and migration assay were carried out. Additionally, matrix metalloproteinases (MMPs) and interleukin (IL)-6 secretion was measured using ELISA from RA-FLS transfected with control or PIM-1 siRNA.

Results: Among PIM kinases, PIM-1 was most strongly induced by IL-6 stimulations in RA-FLS. The expression of PIM-1 protein was higher in RA-FLS than in OA-FLS. In the synovial tissues from RA patients, PIM-1 was immunostained in the synovial lining layer and mononuclear cells (Fig. 1). When RA-FLS with PIM-1 knockdown were stimulated with TNF-a, RA-FLS proliferation or migration was significantly decreased (Fig. 2). Moreover, the production of MMP-1, MMP-3, and MMP-13 was significantly suppressed in RA-FLSs with PIM-1 knockdown (Fig. 2). IL-6 production from PIM-1 knockdown RA-FLS was also reduced, but statistically insignificant.

Conclusion: These results suggest that PIM-1 is involved in the survival, migration, and matrix-degradation of RA-FLS and PIM-1 could be a potential target for RA treatment.

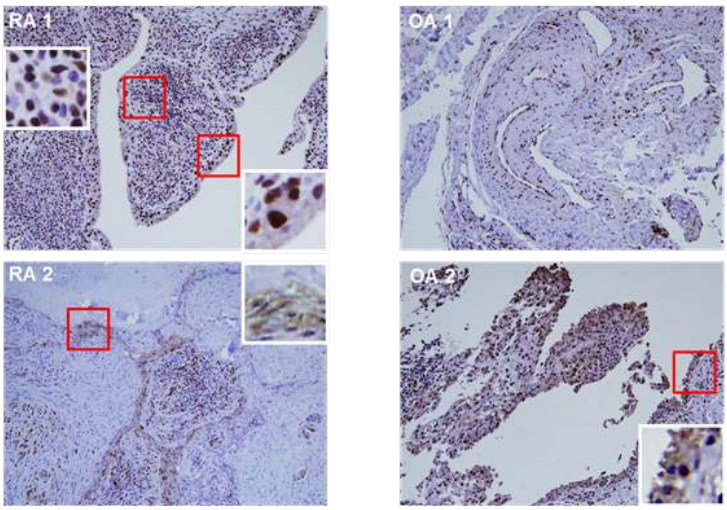

Fig. 1. The immunohistochemical staining of PIM-1 kinase in the synovial tissue from 2 RA and 2 OA patients.

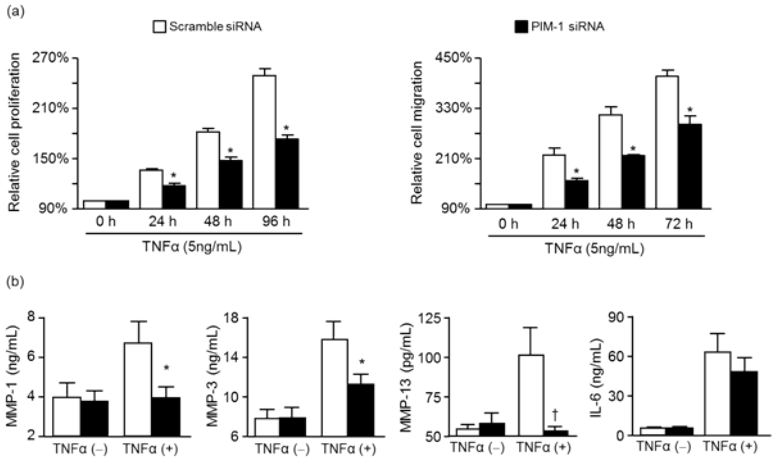

Fig. 2. The effect of PIM-1 on RA-FLS. (a) Under the stimulation with TNF-a, proliferation and migration was significantly inhibited in PIM-1 siRNA-transfected RA-FLS. (b) PIM-1 knockdown also significantly suppressed the secretion of MMP-1, MMP-3, and MMP-13 from RA-FLS stimulated with TNF-a in serum-free media.

Disclosure: Y. S. Choi, None; **Y. J. Ha**, None; **J. Hur**, None; **E. H. Kang**, None; **Y. W. Song**, None; **Y. J. Lee**, None.

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Abstract Number: 1167

Treating Experimental Arthritis with Adenoviral Overexpression of IL-22 or with Blocking Antibodies Against Endogenous IL-22 Both Reduces Inflammation and

Destruction

Marije I. Koenders[1], Debbie M. Roeleveld[1], Loreto Parga[1], Shahla Abdolahi-Roodsaz[1], Fons A.J. van de Loo[1], Jay K. Kolls[2] and Peter M. van der Kraan[1], [1]Experimental Rheumatology, Radboud university medical center, Nijmegen, Netherlands, [2]Richard King Mellon Foundation Institute for Pediatric Research, Children's Hospital of Pittsburgh of UPMC, Pittsburgh, PA

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Background/Purpose: Interleukin-22 (IL-22) is an IL-10 family cytokine member that was recently discovered to be mainly produced by Th17 cells. Previous studies have indicated the importance of IL-22 in host defense against Gram-negative bacteria in gut and lung. Recently, there is emerging evidence that IL-22 plays a dual role in the pathogenesis of several autoimmune diseases like psoriasis and multiple sclerosis. In this study we aimed to unravel the pathogenic effects of IL-22 on joint inflammation and destruction, and its therapeutic potential during experimental arthritis.

Methods: First, endogenous IL-22 was blocked using neutralizing antibodies during collagen-induced arthritis (CIA), and the effects were studied on X-ray and by histology. To further investigate the pathogenic effects of IL-22, an adenoviral construct overexpressing murine IL-22 (AdIL-22) or a control virus was intra-articularly injected into naïve knee joints of C57Bl/6 mice, and at various time points the knee joints were clinically and histologically assessed for inflammation and destruction. Synovial biopsies and washouts were obtained for analysis of cytokines, chemokines and MMPs on mRNA expression (RT-QPCR) and protein levels (Luminex). In addition, in vitro stimulated fibroblasts were used to confirm these IL-22 effects. Finally, IL-22 was overexpressed during experimental arthritis induced by the injection of bacterial (SCW) fragments into the knee joint, to study IL-22's contribution as Th17 cytokine in the aggravation of an acute joint inflammation.

Results: Anti-IL-22 treatment after the onset of CIA significantly reduced arthritis progression, and had even more dramatic therapeutic effects on radiographic destruction. Adenoviral overexpression of IL-22 in naïve and arthritic joints was used to further investigate the pathogenic effects of IL-22. Overexpression of IL-22 in a naïve knee joint resulted in an acute joint inflammation which was relatively mild and short-lasting in comparison to other proinflammatory cytokines like TNF and IL-1. The increased influx of cells by AdIL-22 was accompanied by elevated levels of the chemokines MCP-1 and KC, as well as IL-6 and S100A9. Overexpression of IL-22 induced significant proteoglycan depletion from the articular cartilage, but did not cause severe and irreversible destruction to cartilage and bone, in contrast to the significant upregulation of MMP3, MMP9 and RANKL in the synovial tissue and by the in vitro stimulated fibroblasts. We therefore expected that in synergy with other inflammatory stimuli during SCW-induced arthritis, IL-22 overexpression would become far more potent and destructive. Surprisingly, however, IL-22 overexpression during experimental arthritis significantly suppressed joint inflammation, suggesting a more complex mechanism of action of this dual cytokine.

Conclusion: Since both overexpression of IL-22 as well as blocking endogenous IL-22 with neutralizing antibodies provide protection against further disease progression in experimental arthritis, the exact mechanism of action of IL-22 needs to be identified before IL-22-based treatments can be applied in clinical treatment of RA.

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Abstract Number: 1168

MiR125a-5p Mediates Angiogenic Mechanisms in Inflammatory Arthritis

Mary Connolly[1], **Sarah Wade**[1], Douglas J. Veale[2] and Ursula Fearon[1], [1]St. Vincent's University Hospital, Centre for Arthritis and Rheumatic Diseases, Dublin Academic Medical Centre, Dublin 4, Ireland, [2]St Vincent's University Hospital, Centre for Arthritis and Rheumatic Diseases, Dublin Academic Medical Centre, Dublin 4, Ireland

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Background/Purpose: MicroRNAs (miRNA) belong to a class of small, evolutionarily conserved, noncoding RNAs that function as post-transcriptional repressors of gene expression. An accumulating body of evidence suggests that up to 50% of the human genome is regulated by miRNAs. The aim of this study was to examine expression, regulation and function of miRNA-125a-5p in inflammatory arthritis (IA).

Methods: Synovial tissue biopsies and primary synovial fibroblasts (SFC) were obtained from patients with Psoriatic arthritis (PsA), Rheumatoid Arthritis (RA) and osteoarthritis (OA). MiR125a-5p levels were analyzed by real-time PCR and data was calculated by the deltaCt method using RNU6B as an endogenous control. To examine possible factors involved in regulating miR125a-5p expression, primary synovial fibroblasts (SFC) and microvascular endothelial cells (HMVEC) were cultured with candidate pro-inflammatory stimuli including; TLR ligands (PAM, PolyIC, LPS), pro-inflammatory cytokines (TNFa, IL-1b, IL-17) and growth factors (VEGF, Ang2). Overexpression/silencing of miR-125a-5p was analysed using a synthetic precursor of Pre or Anti-miR™-125, respectively. Cell invasion, tube formation and migration were examined using transwell invasion, angiogenic and wound repair assays, and pro-inflammatory mediators were quantified by ELISA.

Results: Expression of miR125a-5p was significantly higher in PsA and RA synovial biopsies and/or synovial fibroblasts compared to OA ($p<0.05$; $p<0.05$), with highest expresson observed in PsA ($p<0.05$). Angiogenic growth factor Ang2 induced miR125a-5p in synovial fibroblasts and HMVEC ($p<0.05$), with no effect observed for TLR ligands or pro-inflammatory cytokines. Silencing of miR by transfection with anti-miR-125a-5p resulted in inhibition of cell invasion, angiogenic tube formation and IL-6 expression. This is consistent with *in silico* analysis where prediction algorithms identified members of the IL-6 signalling pathway (IL-6R, gp130) as potential targets of miR-125a-5p.

Conclusion: Our data provides evidence that miR125a-5p is significantly increased in the inflammed joint, particularly in PsA. High miR125a-5p expression in PsA and regulation by key angiogenic factor Ang2, is consistent with a possible role for miR125a-5p in the regulation of angiogenic mechanisms. MiR125a-5p also mediated cell migration, angiogenesis and IL-6 expression, key processes involved in the pathogenesis of PsA and RA. In conclusion, miR-125a-5p may be an important regulator of pathogenic mechanisms in inflammatory arthritis and may represent a potential novel target for future therapeutic strategies.

Disclosure: M. Connolly, None; **S. Wade**, None; **D. J. Veale**, None; **U. Fearon**, None.

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Abstract Number: 1169

Crossregulatory Mechanisms Between Synovial Fibroblasts and Macrophages Relevant in RA Pathogenesis

Jennifer Ding[1], Lionel B. Ivashkiv[2] and Laura T. Donlin[1], [1]Arthritis and Tissue Degeneration Program and the David Z. Rosensweig Genomics Research Center, Hospital for Special Surgery, New York, NY, [2]Medicine, Hospital for Special Surgery, New York, NY
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Background/Purpose:

Macrophages and synovial fibroblasts function as key drivers of inflammation in rheumatoid arthritis (RA). We have developed a co-culture system that aims to define how these two cell types crossregulate within an inflammatory setting. Previously, we have shown that soluble synovial fibroblast factors suppress the macrophage TNF-induced Type I Interferon response. Here we aimed to understand the impact of macrophages on synovial fibroblasts and have identified a novel crossregulatory epidermal growth factor (EGF) pathway that is also expressed in synovial macrophages from RA patients. Through studying this EGF pathway we aim to identify potential therapeutic targets to resolve long-term inflammation in the RA synovium.

Methods:

Primary RA synovial fibroblast cell lines were plated in permeable transwell culture inserts and placed above wells with or without human blood-derived macrophages. The co-cultures were then incubated for 2 days with or without exogenous TNF. PolyA selected RNA was processed for paired-end RNAseq using the Tru-seq kits (Illumina) and Illumina HiSeq 2500. The Ingenuity Pathway Analysis and Gene Set Enrichment Analysis programs provided pathway analytics. Synovial fibroblasts were plated in Matrigel transwell invasion assays with TNF and macrophages in the chamber below. The number of invading fibroblasts was scored in the absence or presence of EGFR inhibitors erlotinib and gefitinib.

Results:

Upon TNF exposure, macrophages responding in close proximity to synovial fibroblasts altered the expression of ~1,200 fibroblast genes. Pathway analysis identified an activated EGF pathway that contributed to this altered fibroblast transcriptome. While fibroblasts are commonly considered a predominant source of growth factors, further work determined it was the macrophages that directly produced the EGF ligands responsible for the fibroblast EGF response. The rare non-canonical EGF ligands produced by the fibroblast-trained macrophages are related to a recently described macrophage activation state found in chronic inflammation, which is distinct from both the prototypical pro-inflammatory (M1) and alternative (M2) polarization states. We have detailed the mechanism by which signalling crosstalk induced massive amounts of fibroblast-generated prostaglandins that drives this unique macrophage activation state and non-canonical EGF ligand production. Synovial macrophages from RA patients exhibited increased production of non-canonical EGF ligands, suggesting this crossregulatory EGF response is present in RA synovium and supporting the disease-relevance of these results. Ultimately, the fibroblast-trained macrophages increased the invasive potential of synovial fibroblasts via the EGF response, thereby increasing pathologic fibroblast activity found in RA joints.

Conclusion:

We have identified a novel functional cross-coupling between macrophages and synovial fibroblasts that modulates TNF responses to drive production of rare non-canonical EGF ligands, which in turn induces the invasiveness of synovial fibroblasts. Our data support targeting of the EGF pathway as a possible therapeutic approach in the treatment of inflammatory diseases such as RA.

Disclosure: J. Ding, None; **L. B. Ivashkiv**, None; **L. T. Donlin**, None.

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Abstract Number: 1170

The Alarmins S100A8/A9 Induce Canonical Wnt Signaling in Naïve Joints and Experimental OA

Martijn H. van den Bosch[1], Arjen Blom[1], Rik Schelbergen[2], Thomas Vogl[3], Johannes Roth[4], Wim van den Berg[1], Peter van der Kraan[1] and Peter van Lent[1], [1]Experimental Rheumatology, Radboud university medical center, Nijmegen, Netherlands, [2]Radboud university medical center, Nijmegen, Netherlands, [3]Institute of Immunology, University of Muenster, Munster, Germany, [4]Institute of Immunology, University of Münster, Münster, Germany

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Background/Purpose: Many osteoarthritis (OA) patients show synovial activation, which is thought to be involved in joint destruction. Previously, we found increased expression of both the alarmins S100A8/A9 and members of the Wnt signaling pathway in the joints during experimental OA. Active roles in the development of the OA pathology are attributed to both groups of proteins. In this study, we investigated whether S100A8/A9 induced canonical Wnt signaling and if S100 effects run *via* activation of Wnt signaling.

Methods: Gene expression was measured in the destabilization of the medial meniscus (DMM) and collagenase-induced OA (CIOA) experimental OA models. Selected Wnts were overexpressed and expression levels of S100A8/A9 were measured. Activation of canonical Wnt signaling was determined after intra-articular injection of S100A8 into naïve mouse knee joints and after induction of CIOA in S100A9-deficient mice. Expression of Wnts was tested in macrophages and fibroblasts after stimulation with S100A8. To

determine if the effects of S100A8 injections run *via* activation of Wnt signaling, canonical Wnt signaling was inhibited *in vivo* by feeding inducible DKK-1 Tg mice a diet supplemented with doxycycline to induce overexpression of the DKK-1 transgene.

Results: qPCR analysis showed increased and coinciding expression of the alarmins S100A8/A9 and several members of the canonical Wnt signaling pathway in experimental OA models. This gave rise to the question if an interrelationship existed between these factors. Therefore, we overexpressed Wnt8a and Wnt16, two canonical Wnts, with the use of adenoviral vectors. However, this did not result in increased expression of S100A8 and S100A9, both on RNA and protein level. In contrast, we found that injection of S100A8 increased the expression of Wnt16 in the synovium and accumulation of β-catenin, a hallmark of canonical Wnt signaling, in both cartilage and synovium. In addition, the downstream mediator of canonical Wnt signaling WISP1, was increased. Furthermore, we found reduced β-catenin accumulation in the cartilage and synovium after induction of the CIOA model in S100A9 deficient mice. However, differences in inflammation as the result of divergent S100 levels could possibly explain the differences in canonical Wnt signaling. Therefore, we stimulated both murine and human macrophages and fibroblasts with S100A8 *in vitro* and found increased expression of Wnt16 and WISP1 in macrophages, but not in fibroblasts. Finally, we determined if activation of canonical Wnt signaling was required for the effects of S100A8. Therefore, we injected S100A8 into knee joints of DKK-1 Tg mice that were fed a standard diet or a diet supplemented with doxycycline, which led to overexpression of DKK-1. Injection of S100A8 significantly induced the expression of MMP3, IL-6, MIP1α and KC. However injection of S100A8 in mice overexpressing DKK-1, therefore having reduced canonical Wnt signaling, did not result in significantly induced expression of MMP3, IL-6 KC but not MIP1α.

Conclusion: The alarmins S100A8/A9 induce canonical Wnt signaling in macrophages and murine knee joints. In addition, effects of S100A8/A9 partially run via activation of canonical Wnt signaling.

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Abstract Number: 1171

Plasma Soluble ST2 Levels Are Independently Associated with Both Carotid Atherosclerosis and Compromised Cortical Volumetric Bone Mineral Density and Microstructure in Patients with Psoriatic Arthritis

Jiayun Shen[1], Qing Shang[1], Edmund Li[1], Tracy Y. Zhu[2], Ling Qin[2] and Lai-Shan Tam[1], [1]Department of Medicine & Therapeutics, The Chinese University of Hong Kong, Hong Kong, China, [2]Department of Orthopaedics & Traumatology, The Chinese University of Hong Kong, Hong Kong, China

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Background/Purpose: Patients with PsA have both increased risk of subclinical atherosclerosis and lower cortical volumetric BMD (vBMD) compared with the general population, probably as a result of the dysregulated molecular pathways. We have reported that inflammation induced by the IL-33/ST2 axis was associated with carotid plaque progression in RA. Emerging data suggest that this axis may also be involved in bone homeostasis and osteoclastogenesis. In this study, we studied the association among IL-33/ST2 pathway, carotid plaque, and vBMD/bone microstructure in PsA patients.

Methods: 80 PsA patients (44 males; 53±10 years) without unstable cardiovascular diseases (CVD) or disorders that could affect bone metabolism were included. Carotid plaque was determined by ultrasound. vBMD and microstructure of the distal radius were measured using high-resolution peripheral quantitative CT (HR-pQCT). Plasma IL-33 and its decoy receptor soluble ST2 (sST2) levels were determined by ELISA.

Results: Plasma sST2 levels were significantly higher in 33 (41%) patients with carotid plaques (11.2±4.5 vs 7.7±3.7 ng/ml, $p<0.001$). The patients with plaques were also older (57±9 vs 50±10 years, $p=0.002$), had longer PsA duration (17±7 vs 12±7 years, $p=0.006$), and an increased prevalence of high CVD risk (Framingham 10-year CVD risk >10%: 64% vs 34%, $p=0.013$). The prevalence of hyperlipidemia was higher (36% vs 19%, $p=0.085$) and more patients were put on statins (27% vs 11%, $p=0.046$). After adjusting for these confounding factors, sST2 was an independent explanatory variable associated with the presence of carotid plaques (odds ratio: 1.3,

95% confidence interval [CI]: [1.2, 1.5]; p=0.003). Using linear regression, plasma sST2 level was negatively associated with cortical vBMD (coefficients: -5.4, 95%CI: [-8.6, -2.3], p=0.001), and positively associated with cortical porosity index (0.25, [0.12, 0.38], p<0.001) and cortical pore volume (3.0, [1.4, 4.6], p<0.001). The associations remained significant after adjusting for confounding factors[1](Table 1). On the other hand, plasma IL-33 levels were not associated with the presence of carotid plaque or vBMD/microstructure.

Conclusion: Plasma sST2 levels are independently associated with both carotid plaque and compromised cortical vBMD/microstructure in PsA patients, indicating that IL-33/ST2 axis may contribute to both atherosclerosis and bone loss. The detailed mechanism should be further investigated.

1. Zhu TY, et al. Osteoporos Int. 2015;26:261-72.

Table 1. Univariate and multivariate linear regression analysis for the correlations among plasma sST2 level and HR-pQCT parameters

	Unadjusted Coefficients (95%CI)	*p*	Adjusted* Coefficients (95%CI)	*p*
Ct. vBMD	-5.406 (-8.550, -2.263)	0.001	-2.918 (-6.111, 0.275)	0.073
Ct. TMD	-2.538 (-4.540, -0.536)	0.014	-0.723 (-2.808, 1.363)	0.492
Ct. thickness	0.009 (-0.007, 0.024)	0.257		
Ct. Po	0.248 (0.116, 0.380)	<0.001	0.184 (0.042, 0.325)	0.012
Ct. PoV	2.973 (1.371, 4.575)	<0.001	2.247 (0.434, 4.060)	0.016
Ct. Po. Dm	-0.001 (-0.002, 0.001)	0.410		

* Adjusted for age, gender, body mass index, hypertension, diabetes, ESR and CRP.
Ct., cortical; vBMD, volumetric BMD; TMD, tissue mineral density; Po, porosity index; PoV, pore volume; Po. Dm, pore diameter.

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Abstract Number: 1172

Single Cell Sequencing of Non-Lesional Non-Sun Exposed Skin from SLE Patients with Proteinuria Supports Widespread Endothelial Activation

Robert Clancy[1], Evan Der[2], Kemal Akat[3], Anna R. Broder[4], H. Michael Belmont[5], Peter M. Izmirly[6], Beatrice Goilav[7], Thomas Tuschl[3], Chaim Putterman[8] and Jill P. Buyon[1], [1]Medicine, Division of Rheumatology, New York University School of Medicine, New York, NY, [2]Albert Einstein College of Medicine, Bronx, NY, [3]Rockefeller University, New York, NY, [4]Rheumatology-Forchheimer 701N, Albert Einstein College of Medicine/Montefiore Medical Center, Bronx, NY, [5]New York University School of Medicine, New York, NY, [6]Rheumatology, NYU School of Medicine, New York, NY, [7]Division of Nephrology, Children's Hospital at Montefiore, Bronx, NY, [8]Division of Rheumatology, Albert Einstein College of Medicine, Bronx, NY
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Background/Purpose:

Given the widespread vasculopathy present in SLE, endothelial cell activation in the renal tubulointerstitium in lupus nephritis (LN) may be accompanied by similar activation in other tissue beds, even non-lesional skin. Faithful reflection of a relevant pathway in renal tissue by a more readily accessible compartment would be an advance. Single-cell transcriptional states as performed in this study may provide a framework for understanding how in vivo biological function emerges from complex cell ensembles. Accordingly, this study utilized single-cell RNAseq as a novel approach to identify whether non-lesional non-sun exposed skin reflects diffuse activation of the microvasculature in patients with LN.

Methods:

Single-cell RNAseq was performed on cell suspensions prepared from ~2 mm punch biopsies of non-lesional non sun-exposed skin from the buttocks of 5 SLE patients with proteinuria and known ISN/RPS Class and 1 healthy control. The libraries were prepared on the Fluidigm C1 platform followed by sequencing on an Illumina HiSeq 2500. We generated 192 single-cell data sets with on average 3500 genes/cell and 50% of reads mapping to the reference genome. The profile of differential expression analysis was used to assign in vivo cell-type compositions through unsupervised sampling and modeling of transcriptional states in single cells. Data are expressed as transcripts per million.

Results:

Based on expression of PROCR, F2R, VWF, CD34, SERPINE1, ESAM and MCAM (CD146), assignments yielded 36 endothelial cells from 5 patients. From the two Class II subjects there were 10 single-cell transcriptomes. The other three subjects (1- Class IV,V; 1- Class V, 1-Class IV) yielded 26 single cell transcriptomes. Further consideration used evaluations of broad signatures involving the NFkB pathway (reflected by expression of SELE, ICAM1 & VCAM1) and IFNa response/Stat genes (IFI27, IFI44L, IFIH1, IFIT1, IFIT3, CXCL14 & SOCS3). The endothelial cells from patients with Class II had a significantly lower expression of NFkB-related genes compared to those with more advanced disease (4 of 10, i.e. 4 cells expressed at least one transcript and 6 none, vs 20 of 26, $p<0.001$). Both groups strongly expressed at least one IFNa response gene (10 of 10 vs 26 of 26). In addition, standard lineage markers identified the major skin resident and infiltrating cell types including keratinocytes, and lymphocytes. In contrast to the endothelial cells, these cells all displayed low expression of NFkB transcripts, independent of biopsy Class. However, IFNa responsive genes were strongly represented in all 5 patients. The skin biopsy from the healthy control showed neither NFkB nor IFNa responsive genes.

Conclusion:

Single-cell RNAseq is feasible and informative in cell specific transcriptome analysis of fresh non-lesional skin biopsies from SLE patients with a spectrum of active renal disease. Insidious expression of endothelial activation and genes reflective of cytokine exposure support application of this novel approach to study readily accessible tissue. Insight into disease progression should facilitate earlier identification and treatment, critical to tissue survival in organs such as the kidney.

Disclosure: R. Clancy, None; **E. Der**, None; **K. Akat**, None; **A. R. Broder**, None; **H. M. Belmont**, None; **P. M. Izmirly**, None; **B. Goilav**, None; **T. Tuschl**, None; **C. Putterman**, None; **J. P. Buyon**, None.

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Abstract Number: 1173

G Protein Coupled Receptor Kinase 3 Regulation of Inflammatory Arthritis

Matthew J. Billard[1], Roman Timoshchenko[2], D. Stephen Serafin[2] and Teresa K. Tarrant[3], [1]Medicine, University of North Carolina, Chapel Hill, NC, [2]Thurston Arthritis Research Center, University of North Carolina, Chapel Hill, NC, [3]Rheumatology, University of North Carolina, Chapel Hill, NC

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Background/Purpose: Chemokine receptors are G Protein Coupled Receptor (GPCR) family members that direct cell migration, differentiation, and survival in inflammatory conditions, but neutralization strategies have had mixed results in autoimmunity and even less efficacy in Rheumatoid Arthritis (RA). This has been partially attributed to chemokine receptor/ligand redundancy in inflammation, and it

has been proposed that a regulator of GPCR signaling should be targeted rather than neutralization of singular chemokines or their receptors. G protein coupled receptor kinase 3 (GRK3) activity negatively regulates GPCR activation, but also helps recruit downstream signaling machinery to coordinate leukocyte responses. GRK3-deficient mice were previously shown to be protected from disease in two acute models of inflammatory arthritis (K/BxN serum transfer and Collagen Antibody Induced Arthritis) by altering granulocyte migration and innate responses. In this study, we examine the effects of GRK3 knockdown in the chronic, HLA-restricted Collagen Induced Arthritis (CIA) model.

Methods: The Collagen-Induced Arthritis (CIA) model of inflammatory arthritis was used to test *in vivo* disease progression in GRK3-deficient DBA mice. To examine the biological basis for protection in GRK3 knockout mice, an interdisciplinary approach was used. Traditional migration and survival assays were performed on leukocytes *ex vivo* and a mathematical model of GRK3 signal regulation was developed.

Results: Results showed that GRK3-deficient DBA mice are protected from developing CIA *in vivo*. Serum antibody is decreased in GRK3-deficient mice and PCR of the joint revealed greatly reduced levels of IL-17, IL-23, TNFα, and IL-1β transcript expression, suggesting a lack of inflammatory cell infiltration. *Ex vivo* assays describe altered migration and survival of immune cells. A mathematical model was created to further examine and test the mechanisms of signal regulation.

Conclusion: Proinflammatory functions of leukocytes critical to RA development require GRK3 function. Having a single protein target for RA therapeutic intervention that appears to selectively prevent infiltration into the joint represents a compelling target for therapeutic attempts at single cytokine or chemokine neutralization.

Disclosure: M. J. Billard, None; **R. Timoshchenko**, None; **D. S. Serafin**, None; **T. K. Tarrant**, None.

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Abstract Number: 1174

Class 3 Semaphorins Modulate the Invasive Capacity of Rheumatoid Arthritis Fibroblast-like Synoviocytes

Samuel Garcia Perez[1], Bea Malvar Fernandez[1], Simon P. Newsom[2], Man Wai Tang[2], T.R.D.J. Radstake[3], Dominique Baeten[2], Paul P. Tak[2,4] and Kris A. Reedquist[1], [1]Department of Rheumatology and Clinical Immunology and Laboratory of Translational Immunology, University Medical Center Utrecht, Utrecht, Netherlands, [2]Clinical Immunology and Rheumatology, Academic Medical Center, University of Amsterdam, Amsterdam, Netherlands, [3]Department of Rheumatology & Clinical Immunology, University Medical Center Utrecht, Utrecht, Netherlands, [4]University of Cambridge and GlaxoSmithKline, Stevenage, United Kingdom
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Background/Purpose:

The semaphorin family is a large group of proteins initially described as axon guidance molecules that play crucial roles in the development of the nervous system. However, semaphorins also play a role in other processes such as the regulation of immunity, angiogenesis, apoptosis and cell migration and invasion. Moreover, semaphorins have been related with the pathogenesis of diseases like multiple sclerosis, myocarditis, atherosclerosis and cancer. Importantly, class 3 semaphorins Sema3B and Sema3F have been defined as important tumor suppressors. However, the potential role of class 3 semaphorins in rheumatoid arthritis (RA) remains unknown.

The aim of this study is analyze the role of class 3 semaphorins in the pathology of RA.

Methods: mRNA expression of class 3 semaphorins in the synovial tissue of early, DMARD-naive arthritis patients was analyzed by low-density (q)uantitative PCR array. RA FLS were stimulated for 4h with IL-1β (1 ng/ml), TNF (10 ng/ml) or LPS (1 μg/ml). RNA was isolated, transcribed to mRNA and expression of class 3 semaphorins was analyzed by qPCR. FLS were stimulated with Sema3A, Sema3B or Sema3F (100 ng/ml) in the presence or absence of PDGF (10 ng/ml) and cell migration and invasion were determined using wound closure motility and transwell invasion assays, respectively.

Results: mRNA expression of class 3 semaphorins in the synovial tissue of early arthritis patients negatively and significantly correlated with the mRNA expression of inflammatory mediators and the disease activity parameters of these patients. Moreover, Sema3B, Sema3C, Sema3F and Sema3G mRNA expression was significantly lower in early arthritis patients who developed persistent diseases compared with patients with self-limiting disease after two year follow-up. Also, Sema3F and Sema3B expression was significantly lower in the patients that after 2 years of follow-up progressed to RA compared to those who remained as undifferentiated arthritis patients. FLS expression of Sema3A was significantly induced after IL-1, TNF or LPS stimulation, while the expression of Sema3B and Sema3F was down-regulated. Finally, functional assays showed that Sema3A significantly induced the migration and invasion of FLS. In contrast, Sema3B and Sema3F reduced spontaneous FLS migration and PDGF-induced cell invasion.

Conclusion: these data show that class 3 semaphorins are differently expressed in the synovium of early patients depending of the severity and the progression of the disease and that Sema3A, Sema3B and Sema3F play an important role in the invasiveness ability of RA FLS. Together, class 3 semaphorins and their receptors could be useful biomarkers and promising therapeutic targets for the treatment of RA.

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Abstract Number: 1175

Blood Outgrowth Endothelial Cells Isolated from Systemic Sclerosis Patients Exhibit a Pro-Inflammatory Phenotype

Robert Good[1], Sarah L. Trinder[2], Christopher P. Denton[3], David Abraham[4] and **Alan M. Holmes**[1], [1]Centre for Rheumatology and Connective Tissue Diseases, UCL Medical School, London, United Kingdom, [2]Centre for Rheumatology and Connective Tissue Diseases, UCL, London, United Kingdom, [3]Rheumatology and Connective Tissue Diseases, University College London, London, United Kingdom, [4]Centre for Rheumatology and Connective Tissue Disease, University College London, London, United Kingdom

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Background/Purpose:

Vascular complications are a key pathological feature of systemic sclerosis (SSc) affecting the microcirculation and arterioles. Under normal circumstances the endothelium acts as a biological barrier supporting controlled permeability, immune surveillance and cellular trafficking. In SSc endothelial damage, contributes to barrier dysfunction and elevated immune cell infiltration and inflammation. The cause(s) of the initial endothelial dysfunction in SSc is unclear. Blood outgrowth endothelial cells (BOECs) are thought to home to sites of vascular injury and differentiate into endothelial cells, aiding the repair and restoration of normal endothelial functions. Circulating levels of BOECs have been shown to be reduced in SSc patients, and recent studies suggest that BOECs may be dysfunctional in vascular diseases. Here we sought to assess SSc-BOECs and their contribution to vascular dysfunction in SSc.

Methods:

BOECs were established from peripheral blood PBMCs from healthy donors (HD) and SSc patients. BOECs from HD (n=5) and SSc patients (n=6) were profiled using Illumina HT12 gene arrays and secreted inflammatory cytokines profiled by meso discovery scale (MSD) arrays. The capacity of SSc-BOECs (n=4) and HD-BOECs (n=4) to: 1) Establish biological barriers alone or in co-culture with mature endothelial cells, was assessed using electric cell-substrate impedance sensing (ECIS); 2) Support PBMC (n=4) trans-endothelial migration, by forming monolayers in 24-well transwell inserts stimulated with or without TNFα (10ng/ml).

Results: Using gene set enrichment analysis, it was determined that SSc-BOECs exhibit a significantly altered gene expression profile including inflammatory chemokines and cytokines. In addition SSc-BOECs exhibited significantly elevated pro-inflammatory cytokine secretion compared to HD-BOECs, including IL-6 ($P<0.05$; 0.003ng/ml vs 0.73ng/ml) and IL-8 ($P<0.01$; 0.294ng/ml vs 1.7ng/ml). SSc and HD-BOECs exhibited a similar paracellular and transcellular barrier functions alone or in co-culture with mature endothelial cells as determined by ECIS. In contrast SSc-BOECs supported significantly elevated basal trans-endothelial PBMC migration ($P<0.05$) compared HD-BOECs. Whereas TNFα significantly induced trans-endothelial cell migration in both BOEC cell types ($P<0.01$ HD vs $P<0.05$ SSc).

Conclusion:

We have demonstrated that BOECs isolated from SSc patients exhibit a significantly altered gene profile compared to that of BOECs isolated from HC donors. Additionally, SSc-BOECs exhibit a pro-inflammatory profile, secreting high levels of cytokines including IL-6 and IL-8.BOECs isolated from SSc patients exhibited a similar capacity to form biological barriers compared to those from HDs. Conversely, SSc-BOEC monolayers supported a higher level of immune cell trans-endothelial migration. Our data suggests that BOECs integrated into the endothelium in SSc patients are dysfunctional and may promote immune cell infiltration and exacerbate the pro-inflammatory environment in vascular fibrotic lesions in SSc patients.

Disclosure: R. Good, None; **S. L. Trinder**, None; **C. P. Denton**, None; **D. Abraham**, None; **A. M. Holmes**, None.

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Abstract Number: 1176

Interleukin-37 Prevents New-Onset Joint Inflammation but Does Not Inhibit Existing Experimental Arthritis

Marije I. Koenders[1], Debbie M. Roeleveld[1], Charles Dinarello[2], Peter M. van der Kraan[1] and Leo Joosten[3], [1]Experimental Rheumatology, Radboud university medical center, Nijmegen, Netherlands, [2]Department of Medicine, Division of Infectious Diseases, University of Colorado, Denver, CO, [3]Internal Medicine, Radboud university medical center, Nijmegen, Netherlands
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Background/Purpose: Interleukin-37 (IL-37) is a recently identified cytokine with potent anti-inflammatory and immunosuppressive functions. This cytokine has been shown to be expressed in synovial tissue of patients with rheumatoid arthritis (RA) as well as osteoarthritis (OA), and plasma levels of IL-37 in RA have been correlated with TNF, IL-17, and disease activity during DMARD treatment. The objective of this study was to investigate the therapeutic potential of IL-37 in various mouse models and stages of experimental arthritis.

Methods: Mice transgenic for human IL-37 (IL-37tg) were generated on a C57Bl/6 background and antigen-induced arthritis (AIA) was elicited by two immunizations with methylated bovine serum albumin (mBSA) as an antigen in Freund's complete adjuvant, and subsequently intra-articular injection with mBSA. This mono-arthritis was studied by ^{99m}Technetium measurements to detect joint swelling in the arthritic knee joint, and synovial washouts were collected to assess cytokine and chemokine production by Luminex. Second, recombinant IL-37 protein was administered either prophylactic or therapeutic during collagen-induced arthritis (CIA) in DBA-1J mice (1ug/mouse/day i.p. for 2 weeks), and arthritis development was scored macroscopically three times per week. In addition, joints were collected for radiographic and histological analysis.

Results: Mice transgenic for human IL-37 demonstrated suppressed joint swelling compared to C57Bl/6 control mice early after AIA induction. In addition, these IL-37tg mice had reduced synovial levels of IL-6 and KC compared to wild-type controls, and showed a trend towards suppressed IL-17. In line with this protective effect of IL-37, exogenous recombinant IL-37 administered before onset of collagen-induced arthritis resulted in significant protective effects on the macroscopic clinical scores, although these effects were not observed on radiographic analysis. Luminex to detect serum cytokine levels demonstrated an 80% reduction in systemic IL-6 levels, while anti-TNF treatment only caused a 50% suppression. In addition, serum levels of KC seemed to be slightly reduced (P=0.06). In contrast, a therapeutic approach with exogenous IL-37 after the onset of CIA did not have any beneficial effects on further disease progression, suggesting that the therapeutic window of IL-37 treatment in arthritis is limited to new-onset or early arthritis.

Conclusion: This study is the first to show that the anti-inflammatory effect of IL-37 during experimental arthritis is limited to new-onset disease, and that IL-37 is not capable to block arthritis progression during an existing inflammation.

Disclosure: M. I. Koenders, None; **D. M. Roeleveld**, None; **C. Dinarello**, None; **P. M. van der Kraan**, None; **L. Joosten**, None.

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Abstract Number: 1177

Characterization of Different Phosphorylation Sites of Mcl-1 in Human Rheumatoid Arthritis Synovial Fibroblasts and Their Correlation with RA Pathogenesis

Nahid Akhtar and Salahuddin Ahmed, Department of Pharmaceutical Sciences, Washington State University College of Pharmacy, Spokane, WA

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Background/Purpose:

Myeloid cell leukemia (Mcl-1), a Bcl-2 family anti-apoptotic protein, is a critical determinant of rheumatoid arthritis synovial fibroblasts (RA-FLS) resistance to apoptosis. Phosphorylation of Mcl-1 at different sites may influence its stability and function, however, it's implication on RA pathogenesis is not fully studied. In the present study, we evaluated the expression levels of phospho- and total Mcl-1 in FLS from RA, osteoarthritis (OA), and non-diseased (NL) donors and in the joints of rat adjuvant induced arthritis (AIA) model.

Methods:

FLS were obtained from RA (n=10) and OA (n=6) patients undergoing synovectomy or joint replacement surgery. NL samples (n=9) were obtained at the time of autopsy/amputation with no known history of OA or RA. Basal cell lysates (n=6) from NL-, OA-, and RA-FLS were prepared and analyzed for phosphorylated and total Mcl-1, and its endogenous regulators such as Noxa, Bak, and Bax using Western immunoblotting. Correlation between Noxa and Mcl-1 mRNA expression in NL-, OA-, and RA-FLS (n=6) and in synovial tissues (ST; n=5) was determined using qRT-PCR. A Bcl-2/Mcl-1 inhibitor (AT101; 1μM) was used as a control. Findings from human RA-FLS were further validated in rat AIA model. $p<0.05$ was considered significant.

Results:

Our results showed that Mcl-1 mRNA and protein expression was significantly higher, whereas Noxa expression was markedly reduced in OA- and RA-FLS compared to NL-FLS. In addition, a significantly higher Mcl-1/Noxa mRNA ratio (~20-fold) was also observed in RA-ST suggesting the resistance of RA-FLS to apoptosis compared to NL-ST. Studies in the rat AIA model showed an increase in Mcl-1 (~88%) and a decrease in Noxa (~55%) expression in the joints of AIA rats on day 18 compared to the naïve group. Studies suggest that the phosphorylation of Mcl-1 at Thr163 inhibits its anti-apoptotic activity and phosphorylation at Ser159 destabilizes Mcl-1. Our results showed a significantly lower phosphorylation state of Mcl-1 at Ser159/Thr163 (~63%) and specifically at Mcl-1 Ser159 (~60%) sites in RA-FLS indicating their pro-survival nature compared to NL-FLS. RA-FLS also showed an increase in p-Mcl-1 Ser64 protein expression which enhances its anti-apoptotic property. A similar decrease in p-Mcl-1 Ser159/Thr163 and p-Mcl-1 Ser159, and an increase in p-Mcl-1 Ser64 was observed in the joints of AIA rats compared to the naïve group. Pretreatment of RA-FLS with AT101 markedly inhibited TNF-α-induced Mcl-1 as well as pSer159/Thr163, pSer159 and pSer64 protein expression in RA-FLS. Moreover, this increase in Mcl-1 expression was in contrast to the paucity in the expression of pro-apoptotic proteins Bak and Bax in RA-FLS and in the joints of AIA rats compared to their respective controls.

Conclusion:

This study provides a novel evidence for higher Mcl-1/Noxa ratio and increased phosphorylation of Mcl-1 at Ser64 as a potential mechanisms of Mcl-1 stability and RA-FLS survival in RA pathogenesis.

Disclosure: N. Akhtar, None; **S. Ahmed**, None.

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Abstract Number: 1178

Educational Impact of a Clinical Anatomy Workshop on 1st-Year Orthopedic and Rheumatology Fellows and a Comparison of Scores Between Specialties in Mexico

Miguel A. Saavedra[1,2], Pablo Villaseñor Ovies[3,4], Luis A. Harfush[5], José E. Navarro-Zarza[6], Juan J Canoso[7,8,9], Pilar Cruz-Dominguez[10,11], Angelica Vargas Guerrero[12], Cristina Hernández-Diaz[13], Karla Chiapas-Gasca[14], Javier Camacho-Galindo[5], José Alvarez-Nemegyei[15] and Robert A. Kalish[9,16], [1]Rheumatology, Centro Médico Nacional La Raza IMSS, México, Mexico, [2]Universidad Nacional Autónoma de México, Distrito Federal, Mexico, [3]Medicina, Hospital Angeles de Tijuana, Baja California, Mexico, [4]Ciencias de la Salud, Universidad Autónoma de Baja California, Tijuana, Mexico, [5]Orthopedics, ABC Medical Center, Mexico City, Mexico, [6]Medicine, Hospital General Raymundo Abarca Alarcón, Chilpancingo, Mexico, [7]Medicine/Rheumatology, ABC Medical Center, Mexico City, Mexico, [8]ABC Medical Center, Mexico City, Mexico, [9]Medicine, Tufts University School of Medicine, Boston, MA, [10]Centro Médico Nacional La Raza IMSS, México, Mexico, [11]Research Division, Mexico, DF, Mexico, [12]Rheumatology, National Institute of Cardiology, Mexico City, Mexico, [13]Ultrasonography Laboratory, National Institute of Rehabilitation, Mexico City, Mexico, [14]Rheumatology, Hospital Lic. Adolfo López Mateos ISSSTE, Mexico City, Mexico, [15]Unidad de Investigación, Hospital Regional de Alta Especialidad de la Península de Yucatán, Merida, Mexico, [16]Medicine, Tufts Medical Center, Boston, MA

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Background/Purpose: Office orthopedics, and community-based rheumatology overlap in the care of patients with regional pain syndromes. A thorough understanding of these syndromes requires proficiency in clinical anatomy. Previous data indicated a deficient knowledge of clinical anatomy among rheumatologists and rheumatology fellows. In this study, we compared the level of anatomic knowledge between orthopedic and rheumatology trainees and studied the educational impact of a clinical anatomy workshop in both groups of fellows.

Methods: All first-year rheumatology fellows and a convenience sample of first-year orthopedic fellows from Mexico City, all in the 9th month of training, were invited to the workshop. Fourteen of 15 orthopedic fellows and 17 of 20 rheumatology fellows agreed to participate. A pre- and the post- workshop test consisted of 20 questions in which fellows identified or demonstrated relevant anatomical structures in a live human body. These questions, arranged by anatomical regions, were identical in the pre- and post-workshop tests and implemented in 5 stations.

Results: (Table) Overall, the 31 participants showed an increase in correct answers, from a median of 6 (range 1 to 12) of 20 in the pre-workshop test, to a median of 14 (range 7 to 19) in the post-workshop test. Orthopedic fellows scored a median of 7 (range 2-12) and rheumatology fellows 5 (range 1 to 10) in the pre-workshop test. Corresponding scores in the post-workshop test were 15 (10 to 19) and 12 (7 to 18). Intra-group comparisons showed a statistically significant improvement in both the orthopedic and the rheumatology fellows. Inter-group comparisons, from comparable scores in the pre-workshop test, favored the orthopedic group in the post-workshop test.

Conclusion: We found baseline knowledge in clinical anatomy to be deficient in both orthopedic and rheumatology fellows in their first year of training. Our clinical anatomy workshop was useful, in the short term, as a teaching instrument for both groups of trainees. There is a need for a better training in clinical anatomy in orthopedic and rheumatology programs.

	Pre-workshop test, median (range)	Post-workshop test, median (range)	p
Overall (N=31)	6 (1-12)	14 (7-19)	p<0.001*
Orthopedic fellows (n=14) †	7 (2-12)	15 (10-19)	p<0.001*
Rheumatology fellows (n=17) †	5 (1-10)	12 (7-18)	p<0.001*
	p=0.297 †	p=0.026 †	

†Mann-Whitney U test comparing orthopedic and rheumatology fellows in the pre-workshop and the post-workshop tests

*Wilcoxon signed rank test

Disclosure: M. A. Saavedra, None; **P. Villaseñor Ovies**, None; **L. A. Harfush**, None; **J. E. Navarro-Zarza**, None; **J. J. Canoso**, None; **P. Cruz-Dominguez**, None; **A. Vargas Guerrero**, None; **C. Hernández-Diaz**, None; **K. Chiapas-Gasca**, None; **J. Camacho-Galindo**,

None; **J. Alvarez-Nemegyei**, None; **R. A. Kalish**, None.

Abstract Number: 1179

An Evidence-Based Analysis and Revision of a Pediatric Rheumatology Academic Half-Day Program

Mercedes Chan[1] and Kristin Houghton[2], [1]Pediatrics, Division of Pediatric Rheumatology, University of Alberta, Edmonton, AB, Canada, [2]Rheumatology/Pediatrics, British Columbia's Children's Hospital, Vancouver, BC, Canada

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Background/Purpose:

The pediatric rheumatology (PR) academic half-day (AHD) is a weekly 2-hour block of protected time in our training program for trainees to discuss topics relevant to their future practice. Topics reflect the Royal College of Physicians and Surgeons of Canada's (RCPSC) objectives of training and are covered in a 1-year curriculum. Instructional formats vary with trainees' preference. Weekly topics are assigned to trainees who lead discussions using PowerPoint, cases, or articles with faculty supervision. Medical education practices recommend regular evaluation of curricula to ensure they meet objectives and align with educational theory and evidence-based patient care. As part of a medical education quality assurance exercise, we aimed to:

1) Evaluate a PR AHD curriculum.

2) Make evidence-based recommendations for AHD program development using feedback from curriculum analyses and an instructional design model.

Methods:

The AHD program was evaluated using Posner's framework for curriculum analysis to determine its strengths and weaknesses. Data collected: curriculum descriptions (origin, content), program evaluations, and interviews with staff and trainees regarding teaching and learning experiences. Hidden curricula and epistemological assumptions were elicited.

Feedback from analyses was used to guide plans for a formally structured AHD program based on the Dick and Carey instructional model (instructional goals, learner characteristics, performance objectives, instructional strategy).

Results:

Strengths: flexible learning formats, identified core topics, learner independence, regular assessments.

Weaknesses: inconsistent structure, lack of level-specific tasks for junior/senior learners, vague performance objectives.

A revised AHD program was developed around a 2-year spiral curriculum based on RCPSC core topics. Topics are organized into units of 1-4 modules, e.g., a lupus unit includes modules on neonatal lupus, lupus nephritis, outcome measures, and cutaneous disease. Modules are case-based to situate learning, have junior/senior-level goals, and include performance objectives based on authentic tasks, requiring learners seek out the latest evidence behind practice.

E.g., You are a pediatric rheumatologist recommending a joint injection for a child with monoarticular juvenile idiopathic arthritis. What drug will you use to inject and what risks/benefits will this have for the child?

Modules end with a quiz based on the principle that assessment drives learning. Each AHD session concludes with a request for staff and trainees to write instructional objectives and questions on the current topic. In this way, the AHD modules are continuously updated and participants are engaged in the development of the curriculum.

Conclusion:

Regular curriculum analyses can reveal strengths and weaknesses of programs to guide revision of instructional strategies. The caveat exists that new instructional designs undergo piloting and evaluation for efficacy (improved knowledge, patient care) and acceptability, and are regularly revised to maintain currency.

Disclosure: M. Chan, None; **K. Houghton**, None.

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Abstract Number: 1180

Effective Knowledge Transfer: A Demonstration of Video Illustration in the Immunology Curriculum for Rheumatology Trainees

Dharini Mahendira[1], Arthur A. M. Bookman[2], Heather McDonald-Blumer[3], Jerry Won[4] and Carolina Landolt-Marticorena[5], [1]Rheumatology, St. Michael's Hospital, University of Toronto, Toronto, ON, Canada, [2]Rheumatology,, Toronto Western Hospital, University of Toronto, Toronto, ON, Canada, [3]Rheumatology,, Mount Sinai Hospital, University of Toronto, Toronto, ON, Canada, [4]Biomedical Sciences, University of Toronto, Toronto, ON, Canada, [5]Rheumatology, Toronto Western Hospital and University of Toronto, Toronto, ON, Canada

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Background/Purpose: A proper foundation in immunology is essential for the understanding and management of rheumatic conditions. An effective immunology curriculum is required for rheumatology trainees to meet the core competencies mandated by the Royal College of Physicians and Surgeons of Canada. However, we have demonstrated that Canadian Rheumatology Program Directors and trainees believe that current immunology curricula, teaching and resources require significant improvement. We have developed a short video clip highlighting a well-defined immunology topic and assessed its role in facilitating relevant knowledge acquisition in rheumatology trainees.

Methods: We enlisted an Education Information Technology (EIT) student to create a five-minute immunology video clip on T cell development. The topic was identified as “high yield” by rheumatology Program Directors and trainees across Canada. Adobe Illustrator and After Effects were used to design the video. Immunology and rheumatology experts assisted in the creation of the video content. The video was piloted on adult and pediatric rheumatology trainees at the University of Toronto and semi-structured qualitative feedback was obtained. Additionally, a quiz based on contents of the video was administered to the trainees before and after its viewing. The teaching effectiveness of this tool was evaluated by comparing pre and post video scores.

Results: A total of fourteen rheumatology trainees (eleven adult and three pediatric) participated in the video testing. All participants identified the immunology video as easy to follow and stimulating. Participating residents described the immunology video as “engaging, excellent and effective.” All trainees agreed that similar immunology video clips would be a valuable addition to their current immunology curriculum. There was a significant improvement observed between pre and post-testing ($p < 0.0001$). The average pre-test score was 50.6% (+/- 26.9), compared to an average post test score of 85% (+/- 14.9). There was an average improvement in scores of 34.4% (+/- 22.2) with a 95% confidence interval of 22.7%-46.0%. While only 5/14 participants received a passing score as set by our departmental guidelines (≥ 70%) on the pre-test, 13/14 participants successfully passed the post-test. Thirteen rheumatology trainees (10 adult and 3 pediatric) participated in repeat post-testing approximately three months later. Knowledge retention was demonstrated, with an average quiz score of 77.15 % (+/- 14.61).

Conclusion: Our pilot immunology video clip was an effective tool for improving short-term comprehension of a focused immunology topic amongst rheumatology trainees. Furthermore, knowledge was retained three months thereafter. These results are encouraging, and support the development of further immunology videos. This teaching aid has great potential as an educational deliverable, helping to improve and standardize immunology training.

Disclosure: D. Mahendira, None; **A. A. M. Bookman**, None; **H. McDonald-Blumer**, None; **J. Won**, None; **C. Landolt-Marticorena**, None.

Abstract Number: 1181

Ambulatory Rheumatology Curriculum: Effect of Fellow Teaching Multimodal Simulation Curriculum Enhancement

Oana E. Zaha[1], Susan A. Harwell[2], Cecilia P. Chung[3], Mario A. Davidson[4], D. Alan Johnstone[5], Laura A. Skaug[5], Charlene M. Dewey[6] and Susan F. Kroop[2], [1]Rheumatology and Immunology, Vanderbilt University School of Medicine, Nashville, TN, [2]Division of Rheumatology, Vanderbilt University School of Medicine, Nashville, TN, [3]Division of Rheumatology & Immunology, Vanderbilt University School of Medicine, Nashville, TN, [4]Department of Biostatistics, Vanderbilt University School of Medicine, Nashville, TN, [5]Center for Experiential Learning and Assessment, Vanderbilt University School of Medicine, Nashville, TN, [6]Internal Medicine, Vanderbilt University School of Medicine, Nashville, TN

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Background/Purpose:

Internal medicine (IM) trainees should be proficient in rheumatologic knowledge and skills. Our prior data show that a curriculum including an attending-led multimodal simulation training session (MSTS) improves residents' self-confidence in rheumatologic history, physical exam, procedures, and patient care. This academic year, we elected to have the second year rheumatology fellows lead the MSTS. To assess effectiveness, we conducted pre/post self-assessment surveys of residents completing the rheumatology curriculum and compared them to the prior year.

Methods:

All Post Graduate Year 1(PGY 1) IM residents rotating on the ambulatory rheumatology block during the 2014 and 2015 academic years participated in a two-part training session. Residents performed a rheumatologic history and exam on a standardized patient presenting with knee pain and practiced knee joint aspiration with a mannequin. In 2015, second year rheumatology fellows completed a six session teaching training period. After this training, fellows directed the MSTS program for PGY1 trainees.

All PGY 1 residents completed an online, self-assessment survey on self-confidence (0=not confident, 100=extremely confident) in performing a rheumatologic history, physical examination, common procedures, and interpreting rheumatologic lab tests pre/post their rheumatology block in addition to a MSTS evaluation. We compared the pre/post survey results in residents' self-assessed confidence from the 2014 and 2015 academic years using the Wilcoxon signed-rank test. The Institutional Review Board approved the study.

Results:

A total of 40/44 (91%) and 25/29 (86%) PGY1 trainees from 2014 and 2015 respectively completed the pre/post-surveys. Both cohorts increased their self-assessed confidence ratings from pre to post in all variables (Table 1). There was no significant difference in improved self-confidence levels on pre/post rotation in performing a rheumatologic history or exam and in interpreting common rheumatologic labs. However, compared to the 2015 fellow-taught cohort, the 2014 faculty-taught cohort had a significantly higher improvement in median self–assessed confidence in performing knee injection [median 44; IQR (20-57.5) vs. 26; IQR (16-37)] and knee aspiration [median 50, IQR (25-64) vs. 25; IQR(3-40)] (Table 1). In both cohorts, over 98% of PGY1 IM residents strongly agreed or agreed that the MSTS was a valuable training exercise.

Conclusion:

Our results indicate that the fellow-led MSTS enhanced curriculum is as effective as an attending-led MSTS enhanced curriculum in

improving residents' self-confidence in performing a rheumatologic history and exam, but not in knee aspiration and injection. These results suggest that a fellow-led MSTS program can be effective, however, alternative methods for training fellows to teach joint injections and aspirations should be investigated.

Table 1: Comparison of Change in Median Self-assessed Confidence Levels of PGY1 IM Residents: Faculty vs. Fellow-led MSTS Enhanced Curriculum

	2014 Change in Median (IQR) Faculty-led	2015 Change in Median (IQR) Fellow-led	Difference of change in median (95% CI)
Self-assessed confidence in performing:			
Rheumatology history	31 (20, 52)	35 (22, 55)	2 (-10, 15)
Rheumatology exam	34 (24, 51)	34 (20, 53)	-2 (-12, 9)
Knee injection	44 (20, 58)	26 (16, 37)	-17 (-29, -3)
Knee aspiration	50 (25, 64)	25 (3, 40)	-22 (-34, -5)
Shoulder injection	13 (1, 29)	17 (-1, 27)	-2 (-12, 8)
Trochanteric bursa injection	13 (0, 32)	13 (0, 27)	-1 (-11, 6)
Self-assessed confidence in interpreting:			
ESR	10 (3, 19)	10 (-4, 19)	-2 (-11, 6)
CRP	12 (4, 18)	10 (-4, 19)	-4 (-12, 4)
ANA	14 (4, 23)	12 (5, 32)	1 (-8, 11)
RF	20 (9, 30)	20 (3, 34)	-1 (-10, 9)
Anti-CCP	23 (12, 41)	23 (5, 41)	-1 (-11, 12)

Visual analog scale (0=not confident, 100=extremely confident) ; IQR: interquartile range

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Disclosure: O. E. Zaha, None; **S. A. Harwell**, None; **C. P. Chung**, None; **M. A. Davidson**, None; **D. A. Johnstone**, None; **L. A. Skaug**, None; **C. M. Dewey**, None; **S. F. Kroop**, None.

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Abstract Number: 1182

Rheumatology Training Experience – European Survey Among Rheumatology Trainees & Newly Qualified Specialists

Francisca Sivera[1], Sofia Ramiro[2], Nada Cikes[3], Maxime Dougados[4], Laure Gossec[5], Tore K. Kvien[6], Ingrid E. Lundberg[7], Peter Mandl[8], Arumugam Moorthy[9], Sonia Panchal[9], J.A.P. da Silva[10], Johannes W J Bijlsma[11] and Working Group on Training in Rheumatology across Europe , [1]Reumatología, Hospital General Universitario de Elda, Alicante, Spain, [2]Rheumatology, Leiden University Medical Center, Leiden, Netherlands, [3]University Hospital Centre Zagreb, Zagreb, Croatia, [4]Hôpital Cochin; PRES Sorbonne Paris-Cité, Université Paris Descartes, INSERM (U1153): Epidemiologie Clinique et Biostatistiques, Paris, France, [5]AP-HP, Hôpital Pitié Salpêtrière, Rheumatology Department; Sorbonne Universités, UPMC Univ Paris 06, Paris, France, [6]Diakonhjemmet Hospital, Oslo, Norway, [7]Karolinska University Hospital, Rheumatology Unit, Department of Medicine, Solna, Karolinska Institutet, Stockholm, Sweden, [8]Dpt Rheumatology, Medical University of Vienna, Vienna, Austria, [9]Rheumatology, University Hospitals of Leicester, Leicester, United Kingdom, [10]Centro Hospitalar e Universitário de Coimbra - Hospitais da Universidade de Coimbra, EPE, Coimbra, Portugal, [11]Rheumatology and Clinical Immunology, ARC Amsterdam; UMC Utrecht, Utrecht, Netherlands

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Background/Purpose:

To describe the confidence and training experience acquired during rheumatology training in 21 core competences across the different European countries.

Methods:

As part of a European project to evaluate the differences and similarities in training in rheumatology across Europe, we developed an online survey to assess the training experience. The target population was trainees in rheumatology and rheumatologists certified in the past 5 years. We selected 21 competences, core to rheumatology clinical practice, from the UEMS European curriculum framework (1). For each competence, respondents were asked to assess the confidence in their abilities (0-10 numerical rating scale), the existence of formal education (yes/no), the experience with patients (0; 1-10; 11-50; 51-100; 101-150; >150) and the existence of an assessment (yes/no) where appropriate. All questions referred to the training period. The survey (June-December 2014) was disseminated in each country by a national PI.

Results:

We gathered 1433 answers to the survey of which 1079 could be included in the analysis (24% of overall target population). Respondents came from the 41 EULAR countries with rheumatology training (30% male, 52% trainees). A summary of the results is presented in Table 1.

Competence	Confidence mean (SD)	Very low confidence (NRS<3)	Education (yes)	Limited practical experience (<10)**	Assessment (yes)
MSK exam	8.97 (1.5)	3 (0.3%)	785 (75%)		517 (51%)
Detect synovitis	9.04 (1.4)	4 (0.4%)	783 (75%)		521 (52%)
Inerpret lab tests	9.38 (1.1)	2 (0.2%)	836 (81%)		578 (58%)
Disease activity measures	8.90 (1.5)	10 (0.9%)	802 (77%)		537 (54%)
Monoarthritis*	9.10 (1.4)	3 (0.3%)	831 (80%)	126 (12%)	569 (57%)
OA*	8.90 (1.6)	7 (0.7%)	764 (74%)	70 (7%)	519 (52%)
Gout*	9.12 (1.4)	3 (0.3%)	855 (83%)	144 (14%)	544 (54%)
Early RA*	9.04 (1.4)	3 (0.3%)	925 (89%)	97 (10%)	604 (60%)
SpA*	9.00 (1.4)	2 (0.2%)	939 (91%)	83 (8%)	597 (60%)
CTD*	8.02 (1.9)	17 (1.6%)	821 (79%)	214 (21%)	568 (57%)
Vasculitis*	7.45 (2.2)	37 (3.5%)	768 (74%)	450 (44%)	513 (51%)
OP*	8.66 (1.6)	7 (0.7%)	816 (79%)	93 (9%)	536 (53%)
bDMARD*	8.84 (1.8)	18 (1.7%)	814 (78%)	170 (17%)	527 (52%)
Knee aspiration	8.96 (2.0)	35 (3.3%)	828 (80%)	186 (18%)	483 (48%)
Hand X-ray	8.15 (1.9)	18 (1.7%)	725 (70%)	104 (10%)	473 (47%)
Crystal ID	6.07 (3.8)	285 (26.6%)	545 (53%)	622 (61%)	295 (29%)
MSK US	5.83 (3.4)	252 (23.8%)	721 (70%)	391 (39%)	434 (43%)
Multidisciplinary team	8.11 (2.3)	47 (4.4%)			376 (37%)
Interpret research paper	7.84 (2.1)	26 (2.4%)	648 (62%)		407 (41%)
Presentations	8.06 (2.1)	28 (2.6%)	618 (59%)	408 (40%)	472 (47%)
Communication	8.94 (1.5)	8 (0.7%)	547 (53%)		418 (42%)

* Questions on diseases referred to the management of a patient with a given rheumatic disease

** Practical experience refers to patients managed during training. Managing was defined as having some degree of responsibility in their treatment and/or follow-up.

SD: standard deviation; NRS: numerical rating scale; ID: identification

For any given competence, mean confidence was higher in respondents who had received formal education than in those who had not. Similarly, for all clinical competences and rheumatologic techniques, mean confidence was also higher amongst those who had a higher patient experience than in those who managed ≤10 patients during their training with that given disease. Mean acquired confidence was also higher in respondents who had a longer training period (internal medicine plus rheumatology) than in those with a shorter training period for all competences except osteoporosis and hand Xray interpretation. The level of confidence was also higher for specialists (vs trainees).

Conclusion:

The acquired confidence in competences during the rheumatology training program considered core for rheumatology practice is variable, but high for most competences. Most of the trainees seem to receive formal education and have some patient experience in all competences, though only around half are assessed in each competence.

References: 1. European Board of Rheumatology (a section of UEMS). The European Rheumatology Curriculum Framework. http://dgrh.de/fileadmin/media/Praxis_Klinik/european_curriculum_uems_april_2008.pdf

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Disclosure: F. Sivera, None; **S. Ramiro**, None; **N. Cikes**, None; **M. Dougados**, None; **L. Gossec**, None; **T. K. Kvien**, None; **I. E. Lundberg**, None; **P. Mandl**, None; **A. Moorthy**, None; **S. Panchal**, None; **J. A. P. da Silva**, None; **J. W. J. Bijlsma**, None.

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Abstract Number: 1183

The Country Where You Perform Your Rheumatology Training Is Associated with the Acquired Confidence, the Education Received and the Assessment in Core Competences

Francisca Sivera[1], Sofia Ramiro[2], Nada Cikes[3], Maxime Dougados[4], Laure Gossec[5], Tore K. Kvien[6], Ingrid E. Lundberg[7], Peter Mandl[8], Arumugam Moorthy[9], Sonia Panchal[9], J.A.P. da Silva[10], Johannes W J Bijlsma[11] and Working Group on Training in Rheumatology across Europe, [1]Reumatología, Hospital General Universitario de Elda, Alicante, Spain, [2]Rheumatology, Leiden University Medical Center, Leiden, Netherlands, [3]University Hospital Centre Zagreb, Zagreb, Croatia, [4]Hopital Cochin, Paris Descartes University, Paris, France, [5]AP-HP, Hôpital Pitié Salpêtrière, Rheumatology Department; Sorbonne Universités, UPMC Univ Paris 06, Paris, France, [6]Dept. of Rheumatology, Diakonhjemmet Hospital, Oslo, Norway, [7]Karolinska University Hospital, Rheumatology Unit, Department of Medicine, Solna, Karolinska Institutet, Stockholm, Sweden, [8]Dpt Rheumatology, Medical University of Vienna, Vienna, Austria, [9]Rheumatology, University Hospitals of Leicester, Leicester, United Kingdom, [10]Centro Hospitalar e Universitário de Coimbra - Hospitais da Universidade de Coimbra, EPE, Coimbra, Portugal, [11]Rheumatology and Clinical Immunology, ARC Amsterdam; UMC Utrecht, Utrecht, Netherlands

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Background/Purpose:

To assess the association between the country where rheumatology training takes place and the acquired confidence, exposure to education, practical experience and competence assessments in 21 core competences

Methods:

As part of a European project to evaluate the differences in training in rheumatology across Europe, we developed an online survey to assess the training experience. The target population was rheumatology trainees and rheumatologists certified in the past 5 years. We selected 21 competences, core to rheumatology: 13 clinical (MSK examination, detecting synovitis, managing a patient with monoarthritis, lab test interpretation, managing a patient with OA, gout, early RA/undifferentiated arthritis, SpA, CTD, vasculitis, OP, with a biologic DMARD, using disease activity measures), 4 procedures (knee arthrocentesis, crystal identification, hand X-ray interpretation, performing an MSK US) and 4 generic competences (engaging in a multidisciplinary team, interpreting a research paper, performing a scientific presentation, and patient communication). For each competence, respondents were asked to assess the confidence in their abilities (0-10), the exposure to formal education (yes/no), the amount of patient experience (0; 1-10; 11-50; 51-100; 101-150; >150) and assessment (yes/no) where appropriate. For each competence, regression models (linear or logistic, as appropriate) were developed to assess the influence of country of training on the level of confidence, education, practical experience and assessment for that given competence.

Results:

1079 answers were included in the analysis (30% male, 52% trainees) from the 41 EULAR countries that offer rheumatology post-graduate training. For all given competences, the country of training was significantly associated with the acquired confidence. For example, trainees from the UK (arbitrary reference) had on average 1.4 points higher confidence in their ability to manage a patient with early RA than a trainee from France (Table 1). Education and managing >10 patients were also associated with the acquired confidence for all competences. The existence of an assessment was associated to the level of confidence for only some competences (MSK exam, managing a patient with CTD, with vasculitis, crystal ID, MSK US, multidisciplinary team and interpreting a paper).

		Regression coefficient	95% CI
Age	≤ 25 years	Reference	
	26-30 years	0.73	0.06, 1.39
	31-35 years	0.72	0.03, 1.40
	36-40 years	0.79	0.07, 1.51
	>40 years	0.71	-0.05, 1.46
Gender	Male vs female	-0.20	-0.37, -0.03
Trainee vs rheumatologist		0.25	0.06, 0.44
Country*	UK	Reference	
	1 - Albania	-2.62	-3.55, -1.69
	2 - Armenia	-1.05	-3.45, 1.34
	3 - Austria	-0.12	-0.81, 0.57
	4 - Belarus	0.15	-1.27, 1.56
	5 - Belgium	-0.55	-1.26, 0.16
	6 - Bosnia	0.42	-0.56, 1.41
	7 - Bulgaria	-0.14	-1.06, 0.78
	8 - Croatia	-0.49	-1.46, 0.48
	10 - Czech Rep	-0.92	-1.49, -0.36
	11 - Denmark	-0.08	-0.54, 0.38
	12 - Estonia	-0.21	-1.15, 0.72
	13 - Finland	-0.49	-1.26, 0.28
	14 - France	-1.44	-1.91, -0.97
	15 - Georgia	-0.55	-1.62, 0.52
	16 - Germany	-0.20	-0.88, 0.48
	17 - Greece	-0.87	-1.40, -0.33
	18 - Hungary	-0.86	-1.41, -0.32
	20 - Ireland	0.11	-0.58, 0.80
	21 - Israel	-0.43	-1.11, 0.24
	22 - Italy	-0.86	-1.58, -0.14
	23 - Lebanon	-0.06	-1.03, 0.92
	24 - Latvia	-2.55	-3.96, -1.14
	25 - Lithuania	-0.69	-1.75, 0.36
	26 - Macedonia	-0.19	-1.31, 0.92
	27 - Malta	-0.90	-2.61, 0.81
	28 - Moldova	-1.75	-4.13, 0.63
	30 - Netherlands	-0.03	-0.63, 0.57
	31 - Norway	-0.20	-0.73, 0.32
	32 - Poland	-1.24	-1.74, -0.74
	33 - Portugal	-0.10	-0.64, 0.44
	34 - Romania	-0.82	-1.32, -0.31
	35 - Russia	-1.16	-1.81, -0.50
	37 - Serbia	-0.97	-1.71, -0.24
	38 - Slovakia	-0.41	-1.11, 0.28
	39 - Slovenia	0.04	-0.79, 0.87
	40 - Spain	-0.51	-0.99, -0.03
	41 - Sweden	-0.29	-0.94, 0.36
	42 - Switzerland	-0.16	-0.76, 0.44
	43 - Turkey (GIM)	-0.80	-1.34, -0.27
	44 - Turkey (Physical therapy)	-0.40	-1.17, 0.38
	46 - Ukraine	-1.54	-2.95, -0.13
Education (yes vs no)		0.54	0.28, 0.81
Assessment (yes vs no)		-0.05	-0.22, 0.12
Patient exposure (>10 vs ≤10)		0.88	0.60, 1.15
* $p<0.0001$ for overall effect of country variable (with all dummies in the model)			

The country of training was also associated with a higher odds of receiving formal education, of being exposed to >10 patients and of being assessed in a given competence (all separate multivariable models).

Conclusion:

The European country where rheumatology postgraduate training is performed is associated with the level of confidence acquired, the odds of receiving formal education, the odds of acquiring patient experience and the odds of being assessed in core rheumatic competences. Further attempts are needed to harmonize educational outcomes of rheumatology training across Europe.

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Abstract Number: 1184

Addressing Medical Non-Adherence from Lack of Finances in an Observed Structured Clinical Exam of Rheumatology Fellows

Irene Blanco[1], Ravi Sutaria[2], Juliet Aizer[3], Anne R. Bass[3], Anne Davidson[4], Theodore R. Fields[3], Jane Kang[5], Leslie Kerr[6], Deana M. Lazaro[7], Stephen A. Paget[8], Michael H. Pillinger[9] and Jessica Berman[10], [1]Rheumatology, Albert Einstein College of Medicine, Bronx, NY, [2]Medicine, North Central Bronx, Bronx, NY, [3]Rheumatology, Hospital for Special Surgery, New York, NY, [4]Autoimmunity and Musculoskeletal Diseases, Feinstein Inst for Med Rsch, Manhasset, NY, [5]Rheumatology, University of Pennsylvania, Philadelphia, PA, [6]Associate Professor of Medicine & Geriatrics, Mount Sinai Medical Ctr, New York, NY, [7]Brooklyn VA, Brooklyn, NY, [8]Division of Rheumatology, Hospital for Special Surgery, New York, NY, [9]Medicine/Rheumatology, NYU School of Medicine/NYU Hospital for Joint Diseases, New York, NY, [10]Medicine, New York Presbyterian Weill Cornell Medical College, New York, NY
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Background/Purpose: Patients have many reasons for medical non-adherence. Finances often contribute where even the insured may find the cost of medications prohibitively high. In rheumatology, with the advent of multiple biologic medications, the cost of treatment regimens has soared. We therefore devised a structured clinical encounter for rheumatology fellows to assess how well they address non-adherence in a patient that has stopped his/her biologic medication secondary to a loss of insurance.

Methods: The 9thannual 2013 New York City Rheumatology Objective Self Assessment Clinical Exam (NYC-ROSCE) featured 5 stations each focusing on rheumatic diseases. In one of the stations we devised a scenario where a trained actor portrayed a patient with rheumatoid arthritis that had previously been well controlled on a biologic medication. The patient though in the encounter now comes into the office with a disease flare after having stopping their regimen because of unemployment and losing his/her insurance. The actor was instructed to be embarrassed at addressing this awkward financial issue. The fellows were then asked to assess why the patient had now become non-adherent with their biologic and offer potential solutions to the patient.

Results: 24 fellows participated from 7 NYC-area rheumatology fellowships. Fellows were observed and evaluated on a 9-point Likert scale (9:excellent) by both a patient-actor and an MD evaluator. At this station, the mean patient-actor scores for composure (7.38), partnering with the patient (7.29), professionalism (7.67) and empathy (7.04) were high and not significantly different from the MD evaluators. Fellows were also evaluated on a 4-point scale as to how well they assessed financial burden and whether the patient-actors felt judged regarding their financial status (1: not at all, 4: extensively). On average all fellows addressed finances to a certain extent (2.95) and the patient-actors did not feel very judged (1.8). Interestingly though only 58% of the patient-actors felt that the fellows truly found the cause of the non-adherence v 92% of the MD evaluators (p=0.02). If assistance with finances was offered, patient-actors were most offered a referral to social work (11/24), referral to a patient assistance program (11/24) and a referral to the Medicaid office (7/24).

Conclusion: In our OSCE encounter, while the fellows were all very professional, the patient-actors felt that only 58% of them had truly addressed the root cause of non-adherence: a lack of insurance. All of the fellows addressed finances to a some extent which is perhaps

why the MD evaluators felt that more fellows addressed the cause of non-adherence when compared to the actors. This difference in perception is key given that potentially fellows may not be sufficiently trained to examine the psychosocial issues that lead to non-adherence.

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Abstract Number: 1185

Assessment of a Rheumatology Curriculum Utilizing Multiple Learning Modalities

Joshua Scott[1] and Daniel Battafarano[2], [1]Internal Medicine/Rheumatology, San Antonio Military Medical Center, JBSA - Ft Sam Houston, TX, [2]Rheumatology, San Antonio Military Medical Center, JBSA - Ft Sam Houston, TX

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Background/Purpose: Graduate medical education has evolved to incorporate more interactive learning modalities, such as audience response, problem based learning, and patient encounters. We have incorporated these modalities into the rheumatology series of the internal medicine (IM) residency didactic sessions at our institution. This curriculum was assessed utilizing survey data from participants evaluating self-assessment of rheumatology knowledge and preference of learning modality.

Methods: Over a 4 week period IM residents attended 12 hours of didactic sessions dedicated to rheumatology education taught by the rheumatology department. The didactic sessions were divided into lecture, interactive lecture with audience response, rheumatology patient encounters, case based learning, and arthrocentesis simulation lab (Table 1). The effectiveness of our curriculum was measured utilizing survey data collected from participants evaluating pre-curriculum and post-curriculum self-assessment of rheumatology knowledge on a 10 point Likert scale (0=very poor, 10=very good). The survey tool also evaluated preferred learning modality on a 10 point Likert scale (0=not preferred, 10=most preferred). The learning modality preference data was analyzed utilizing a four factor repeated measures ANOVA and Bonferroni corrected post hoc analysis between modalities.

Table 1 Rheumatology Curriculum for IM residents

	Day 1	*Day 2*	*Day 3*	*Day 4*
Hour 1	Lecture[1]	Interactive Lecture[3]	Lecture	Case Based Learning
Hour 2	Arthrocentesis Simulation Lab[2]	Patient Encounter[4]	Case Based Learning	Case Based Learning
Hour 3	Arthrocentesis Simulation Lab	Case Based Learning[5]	Patient Encounter	Interactive Lecture

Definitions: [1]Lecture is a PowerPoint style. [2]Arthrocentesis Simulation Lab utilizes joint models to teach arthrocentesis/injection. [3]Interactive Lecture is a PowerPoint style with audience response or knowledge bowl style. [4]Patient Encounter is interaction with a patient who has a rheumatic disease and discussion led by rheumatology staff/fellow. [5]Case based learning is a small group discussion of ACR Rheum2Learn modules.

Results: A total of 65 participants attended the didactic sessions, 44/65 (67.7%) completed the survey. The participant's pre-curriculum self-assessment mean was 3.98 and post assessment mean was 6.61. This increase of 2.63 was statistically significant ($p < 0.001$). The results of the learning modality assessment are presented in table 2, the most preferred learning modality was rheumatology patient encounters and least preferred was lecture.

Table 2 Learning Modality Preference Results

	Mean (n=44)	Range	p-value*
Lecture	6.07	1-9	-
Arthrocentesis Simulation Lab	6.75	3-10	0.196
Interactive Lecture	6.93	3-9	<0.001
Rheumatology Patient Encounter	8.07	3-10	<0.001
Case Based Learning	7.55	3-10	<0.001

*from post-hoc comparison of each modality to lecture

Conclusion: IM residents found a curriculum utilizing multiple educational modalities very effective to improve rheumatology knowledge. IM residents prefer interactive teaching modalities to basic lecture. The most preferred method of instruction included the use of direct patient encounters guided by a rheumatology interview, examination, and discussion.

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Abstract Number: 1186

Musculoskeletal Ultrasound Education Among Rheumatology Fellowship Programs in the United States

Karina Marianne D. Torralba[1], Amy C. Cannella[2], Eugene Y. Kissin[3], Marcy B. Bolster[4], Jay B. Higgs[5], Jonathan Samuels[6], Midori Jane Nishio[7], Gurjit S. Kaeley[8], Amy M. Evangelisto[9], Paul J. DeMarco[10] and Minna J. Kohler[11], [1]Division of Rheumatology, Department of Internal Medicine, Loma Linda University, Loma Linda, CA, [2]Section of Rheumatology, University of Nebraska Med Ctr, Omaha, NE, [3]Boston University School of Medicine, Boston, MA, [4]Massachusetts General Hospital, Boston, MA, [5]Rheumatology Service, Brooke Army Medical Center, San Antonio, TX, [6]Rheumatology, NYU - Hospital for Joint Diseases, New York, NY, [7]Private Practice - Walnut Creek CA, Walnut Creek, CA, [8]Rheumatology, University of Florida College of Medicine, Jacksonville, Jacksonville, FL, [9]Arthritis, Rheumatic and Back Disease Associates, Voorhees, NJ, [10]Arthritis& Rheumatism Assoc PC, Wheaton, MD, [11]Rheumatology, Allergy, and Immunology, Massachusetts General Hospital / Harvard Medical School, Boston, MA

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Background/Purpose:

A 2008 survey involving 46 responding rheumatology fellowship program (RFP) directors (PDs) (46/135, 33% responder rate) found that 41% included some aspect of musculoskeletal ultrasound (MSUS) in their training. Although not a RFP requirement, more programs have since incorporated MSUS training. Our goal was to assess the current state and ascertain the needs for MSUS education among RFPs, in addition to determining methods of curricular integration.

Methods:

Two surveys (S1, S2) were developed and sent via the online survey tool Qualtrics™. S1 is a 13-item needs assessment [ultrasound (US) machine accessibility, faculty training, and institutional support] sent to all PDs of current RFPs. S2 is a 32-item curricular assessment sent to lead MSUS faculty designated by PDs.

Results:

S1: Out of 113 currently active RFPs, 103 (91%) PDs responded; 94% of RFPs are currently offering some form of MSUS training. Lead MSUS faculty were identified as: key clinical faculty (KCF) (44%), PDs (24%), and other non-KCF (15%). US machine access was reported as follows: owns (76%), leases (5%), shares with another division (15%), no access (5%). 84% of RFPs reported at least 1

faculty competent in MSUS. Of 6 programs not engaged in MSUS, all would like to eventually offer training. 66 (63%) of PDs felt that inclusion of MSUS into the RFP curriculum should be optional; 33 (32%) preferred for it to be mandatory, while 4 (3.8%). felt it should be excluded.

S2: Out of 97 RFPs offering MSUS training, 71 (73%) responded. Of the respondents, 41% have a formal written curriculum. 81% would share curricula, and 69% would collaborate in curriculum development. At least 1 faculty member in each RFP has been described as having received MSUS training (34%), certification (32%), and are actively teaching fellows MSUS (52%). Overall, ACR certification was obtained by 88%. Common training avenues were the: ACR Fundamentals Course (52%), USSONAR Train-the-Trainers Course (38%), and faculty instruction (39%). Common curriculum topics were anatomy, procedures, image optimization, and sonopathology. Common instructional strategies were hands-on-clinic-teaching (HOCT), USSONAR fellowship program, and online materials. Procedure logs were the most common evaluation method. HOCT was accomplished via dedicated faculty US clinic in 49%. Fellow access to machines was available in continuity clinics, dedicated US clinics, and faculty clinics. Of 65 programs with an identified MSUS clinic, more teaching emphasis was on diagnostic US (41%), US-guided procedures (22%), or an equal emphasis in both areas (41%). While 86% of RFPs reported time for self-directed learning/practice, this occurred primarily in the second year of training in 54%. MSUS is a graduation requirement in 7% of programs. The major barriers to MSUS integration were inadequate clinic time, and lack of training funding for faculty and fellows.

Conclusion:

MSUS has become prevalent in RFPs. Most programs have access to equipment and educators. Curricular integration is heterogeneous. Curricular and assessment tool standardization is widely desired among PDs. Information from these surveys will inform educators moving forward.

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Abstract Number: 1187

Comprehensive Musculoskeletal Exam Curriculum for Rheumatology Fellows

Sonali Narain, Shanthini Kasturi and VP Bykerk, Rheumatology, Hospital for Special Surgery, New York, NY

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Background/Purpose: The musculoskeletal exam (MSKE) is an integral part of rheumatology training, both as a diagnostic aid, and as a predictor of disease activity. Formal structured training in MSKE is not given priority at various levels of medical education including rheumatology fellowship. Our aim was to design and implement a formal structured program in MSKE for rheumatology trainees that would: 1) improve fellows' comfort and confidence in performing joint examinations and assessing disease activity and 2) improve fellows' knowledge of the diagnosis of MSK pathology through physical exam.

Methods: Applying Fleming's Visual Auditory Kinesthetic model, we devised a structured program covering a systematic approach to examination of all major joints/joint areas as well as inflammatory arthritis disease activity indices. Adult and pediatric rheumatology fellows at a single teaching hospital were invited to participate. Success of the curriculum was measured by the likelihood of attendees to recommend the training and by an overall rating of >5 on a 10 point scale. Participants also completed pre- and post-curriculum questionnaires containing subjective (comfort and confidence) and objective (knowledge) domains. Content knowledge was assessed using validated questions in the literature, many of which had an orthopedic focus.

Results: Of the 8 fellows who participated in the program, 75% reported no prior formal MSKE training. All participants felt that training in the MSKE should be part of fellowship and over 80% of fellows were likely or extremely like to recommend the course to others. The

average rating of the curriculum was 8/10. The post-curriculum assessment showed: 1) modest increase in the percentage of fellows endorsing comfort in their exam skills and confidence in their ability to assess disease activity; 2) decrease in the percentage of participants endorsing confidence in diagnosing MSK pathology (Figure 1a); 3) slight improvement in objective scores (Figure 1b).Over 60% of participants felt they could benefit from more practice time.

Conclusion: We successfully implemented a structured MSKE curriculum that was received with enthusiasm and engagement among participants as reflected in their overall rating of the program. The modest improvement in both subjective and objective components of the post course assessment questionnaire may have been due to limitations of the questionnaire. The decline in the participants' confidence in diagnosing MSK pathology may reflect fellows' heightened awareness of limitations in their knowledge at the end of the curriculum. An observed structured clinical assessment may more effectively measure skills relevant to rheumatology and thus improve trainees' confidence.

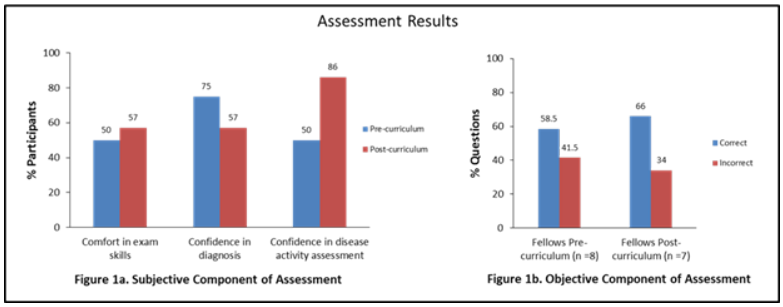

Figure 1a. Subjective Component of Assessment

Figure 1b. Objective Component of Assessment

Disclosure: S. Narain, None; **S. Kasturi**, None; **V. Bykerk**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/comprehensive-musculoskeletal-exam-curriculum-for-rheumatology-fellows

Abstract Number: 1188

Comprehensive Musculoskeletal Course Improves Post-Graduate Trainees' Confidence in Performing Joint Injections

Erica Jaffe[1], Andrea M. Barker[2], Grant W. Cannon[3], J. Peter Beck[4] and Michael J. Battistone[5], [1]Internal Medicine, Salt Lake City VA Medical Center and University of Utah, Salt Lake City, UT, [2]General Internal Medicine, Salt Lake City VA Medical Center and University of Utah, Salt Lake City, UT, [3]Division of Rheumatology, Salt Lake City VA Medical Center and University of Utah, Salt Lake City, UT, [4]Orthopaedics, Salt Lake City VA Medical Center and University of Utah, Salt Lake City, UT, [5]Rheumatology, Salt Lake City VA Medical Center and University of Utah, Salt Lake City, UT

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SESSION INFORMATION

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Session Title: Education Poster I

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose:

Developing confidence in procedural skills is an important aspect in improving procedural competency. Although a number of studies have explored effective methods to teach arthrocentesis, the relationship between the number of injections performed and confidence in injection skills has not been researched. We investigated the number of subacromial (SA) and knee injections required for a learner to become confident in procedural skills.

Methods:

Internal Medicine (IM) interns at our program participate in a week-long musculoskeletal skills course that takes place at a VA Medical Center. The course is open to post-graduate residents of other specialties. During the course SA and knee injection techniques are introduced through didactics and reinforced through simulation, peer-teaching and supervised ambulatory experiences. A total of 45 trainees participated in the course in 2014-15 (IM (32), physical medicine & rehabilitation (6), occupational medicine (5), orthopedics (2)). The number of SA and knee injections performed by each trainee was tallied. Before and after the course participants used a 5-point

Likert scale to rate confidence in performing joint injections. Data were divided into two categories for analysis (1-4 = less confident, 5 = highly confident). Chi squared analysis was used to compare the number of injections performed versus post-course self-assessment of confidence.

Results:

In addition to simulator training, trainees performed an average of 1.1 SA injections (range 0-3, median 1) and 1.6 knee injections (range 0-5, median 2). Mean confidence scores markedly increased from 2.4 pre-course to 4.5 post-course for SA injections and from 2.7 to 4.3 for knee injections. Of the participants who started as less confident in SA injections, only 1 (2%) decreased in confidence; 5 (11%) did not change. Of the participants who started as less confident in knee injections, only 1 (2%) decreased in confidence; 2 (4%) did not change. Table 1 shows association between the number of supervised joint injections performed and self-reported confidence post-course.

Table 1. Association of Number of Supervised Joint Injections with Self-Reported Confidence Post-Course

		Number of Joints Injected		
		≤ 1	≥2	Total
Subacromial	Less Confident	20 (44.4%)	5 (11.1%)	24 (53.3%)
	Highly Confident	7 (15.6%)	13 (28.9%)	21 (46.7%)
	Total	27 (60%)	18 (40%)	45 (100%)
				p=0.0022
Knee	Less Confident	9 (20%)	10 (22.2%)	19 (42.2%)
	Highly Confident	13 (28.9%)	13 (28.9%)	26 (57.8%)
	Total	22 (48.9%)	23 (51.1%)	45 (57.8%)
				p= NS

Conclusion:

Our MSK course increased confidence in performing SA and knee injections. Participants who performed at least 2 SA injections had a statistically significant association with ranking themselves as highly confident post-course. There was no statistical significance association between the number of knee injections performed and self-assessment as highly confident post-course. Our next step will be confirming that the self-assessment of confidence is valid by comparing scores to external measures (e.g. objective structured clinical exam).

Disclosure: E. Jaffe, None; **A. M. Barker**, None; **G. W. Cannon**, None; **J. P. Beck**, None; **M. J. Battistone**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/comprehensive-musculoskeletal-course-improves-post-graduate-trainees-confidence-in-performing-joint-injections

Abstract Number: 1189

Internal Medicine Subspecialty Fellows' Attitudes Towards Teaching and Learning How to Teach: A Needs Assessment

Eli Miloslavsky[1] and Jakob McSparron[2], [1]Division of Rheumatology, Massachusetts General Hopsital, Boston, MA, [2]Divsion of Pulmonary and Critical Care Medicine, Beth Israel Deaconess Medical Center, Boston, MA

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Background/Purpose:

Clinical fellows can have a major educational impact on students and residents. However, a number of barriers to teaching during inpatient consultation exist in the hospital environment, making it challenging to initiate teaching interactions, provide a positive environment for learning and deliver effective teaching. Improving fellows' teaching skills has been proposed as a strategy to enhance teaching during consultation. Within Internal Medicine (IM) subspecialties, fellows' attitudes towards teaching and interest in programs to improve teaching skills has been largely unexplored. We conducted a needs assessment to evaluate IM subspecialty fellows' interest in teaching and improvement of their teaching skills.

Methods:

379 IM subspecialty fellows from three academic medical centers (Massachusetts General Hospital, Brigham and Women's Hospital, Beth Israel Deaconess Medical Center) were invited to complete a survey assessing their attitudes towards teaching, assessment of barriers to teaching during consultation, interest in training related to teaching skills, and the current practices of assessment and improvement of teaching skills during fellowship.

Results:

179 fellows from ten subspecialties responded to the survey (47% response rate), including 15 rheumatology fellows. 80% of fellows anticipate teaching during their careers, and 22% plan to participate in medical education scholarship (Table 1). Fellows reported a strong interest in teaching and programs aimed at improving their teaching skills (Table 2). Fellows who anticipated teaching during their career had more interest in teaching and teacher training. However, the majority of subjects (68%) reported no specific training focused on teaching skills during their fellowship and 37% have never received feedback about their teaching.

Conclusion:

Among a large sample of IM fellows participating in this study, the majority anticipate teaching during their careers. Fellows expressed a strong interest in programs aimed at improving their teaching skills. However, the majority of fellows did not have the opportunity to participate in such programs during fellowship and a significant minority reported that they did not receive feedback on their teaching. A need exists among fellows for programs focused on improving their teaching skills.

Table 1 – Fellows' anticipated career activities

Activity	Total (n=179)	Percentage
Patient care	152	84.9%
Teaching	143	79.9%
Clinical research	123	68.7%
Basic science research	63	35.2%
Administration	45	25.1%
Medical education scholarship	40	22.3%
Not sure	7	3.9%

Table 2 – Fellows' attitudes towards teaching

Question	Planning to teach during career		Not planning to teach during career		p-value
	Disagree-neutral	Agree or strongly agree	Disagree-neutral	Agree or strongly agree	
I enjoy teaching residents and medical students	6 (4.3%)	134 (95.7%)	5 (14.3%)	30 (85.7%)	0.04
If I had more time I would do more teaching	4 (2.9%)	135 (97.1%)	5 (13.9%)	31 (86.1%)	0.02
My teaching skills can be improved	6 (4.3%)	134 (95.7%)	7 (19.4%)	29 (80.6%)	<0.01
I want to receive more feedback about my teaching	31 (22.1%)	109 (77.9%)	15 (42.7%)	21 (58.3%)	0.02
I am interested in receiving training to improve my teaching skills	32 (23.0%)	107 (77.0%)	12 (33.3%)	24 (66.7%)	0.2

Disclosure: E. Miloslavsky, None; **J. McSparron**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/internal-medicine-subspecialty-fellows-attitudes-towards-teaching-and-learning-how-to-teach-a-needs-assessment

Abstract Number: 1190

Developing an Introductory Musculoskeletal Ultrasound Curriculum for Rheumatology Fellows

Ekaterini Zapantis and Maria-Louise Barilla-LaBarca, Rheumatology, North Shore - Long Island Jewish Health System, Great Neck, NY
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Background/Purpose: Musculoskeletal ultrasound has been increasingly recognized as a cost-effective, sensitive diagnostic bedside tool that rheumatologists can utilize across a wide spectrum of inflammatory and non-inflammatory diseases. It is rapidly becoming a highly requested elective during fellowship, though few curricular components exist for fellows not enrolled in a dedicated year-long course of training track. We report on our newly designed curriculum that features intermittent, short intense bursts of interactive teaching exercises that utilize formative assessment, flanking each session as a means to not only assess effectiveness of learning across several months, but also to reinforce important concepts from previous weeks and lead to a more durable retention of material when daily practice is not feasible.

Methods: Six two-hour teaching sessions were developed over a four month period of time. Fellows personal goals were assessed initially to guide the curriculum development. Each session focused on a different joint area and consisted of a de-identified pre-assessment and cumulative assessment, short framing lecture, modeling of scanning technique, hands on scanning (with a 1:1 or 2:1 fellow:machine ratio), and post-assessment. All questions were reviewed with the fellows at the conclusion of every session. The cumulative assessment consisted of 10 multiple choice questions related to key concepts from prior sessions and the pre-assessment contained 5 multiple choice questions about the day's session. The post-test consisted of 5 multiple choice questions which covered the sessions's content. A final assessment was administered about a month after the last session which consisted of 53 multiple choice questions to assess retention of knowledge.

Results: Three rheumatology fellows (two first years, one second year) with at most minimal experience, participated in the curriculum. Participants' personal goals included understanding the mechanics of ultrasound as well as identifying normal structures and pathology. A poll after the course revealed that all objectives were met. The average score of the six pre-assessments was 43.5% and 85% on the post-assessments with an average percent improvement of 41.5%. The cumulative pre-assessments (not including the final assessment) average score was 71%. The final assessment average was 80%. It was observed that the fellows scored equally on first order and higher order questioning.

Conclusion: Effective implementation of a musculoskeletal ultrasound curriculum can be easily introduced into a training program where routine daily practice is not possible. Intermittent, short intense bursts in coordination with spiraling content review, was shown to be a successful teaching method with fellows demonstrating durability of knowledge.

	Pre-Assessment Average (%)	Post Assessment Average (%)	Cumulative Assessment Average (%)
Session One (Introduction) Time zero	58	81	
Session Two (Knee) 3 weeks	28	94	80 (Range: 70-90)
Session Three (Hand and Foot) 6 weeks	39	94	70 (Range: 50-90)
Session Four (Wrist) 7 weeks	20	53	80
Session Five (Elbow) 10 weeks	60	90	55 (Range: 40-70)
Session Six (Shoulder) 14 weeks	56	100	80 (Range: 77-85)
	43.5	85	71

Disclosure: E. Zapantis, None; **M. L. Barilla-LaBarca**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/developing-an-introductory-musculoskeletal-ultrasound-curriculum-for-rheumatology-fellows

Abstract Number: 1191

Validity Evidence for Two Objective Structured Clinical Examination Stations to Assess Core Examination Skills of the Shoulder and Knee

Michael J. Battistone[1], Andrea M. Barker[2,3], J. Peter Beck[4], Robert Z. Tashjian[5] and Grant W. Cannon[6], [1]Rheumatology, Salt Lake City VA Medical Center and University of Utah, Salt Lake City, UT, [2]General Internal Medicine, Salt Lake City VA Medical Center and University of Utah, Salt Lake City, UT, [3]Family and Preventative Medicine, University of Utah School of Medicine, Salt Lake City, UT, [4]Orthopaedics, Salt Lake City VA Medical Center and University of Utah, Salt Lake City, UT, [5]Division of Orthopaedics, Salt Lake City VA and University of Utah, Salt Lake City, UT, [6]Division of Rheumatology, Salt Lake City VA Medical Center and University of Utah, Salt Lake City, UT

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Validity Evidence for 2 Objective Structured Clinical Examination Stations to Assess Core Examination Skills of the Shoulder and Knee **Background/Purpose:** A multi-disciplinary group developed two objective structured clinical examination (OSCE) stations to train and assess trainee's skills in the evaluation and management of shoulder pain and knee pain. Our objective was to examine the validity of these two OSCEs. **Methods:** *Content* Two orthopaedists, two rheumatologists, and a primary care provider developed checklists of physical exam maneuvers and criteria for guiding rater observations. Content was proposed by faculty, supplemented by literature review, and finalized through a modified Delphi process. Simulated cases representing common causes of shoulder pain and knee pain were constructed. *Response Process* A multi-disciplinary cohort of 69 trainees participated in the OSCEs in 2014-15. To promote accuracy of the simulated patient (SP) responses to assessment prompts, one faculty member served as SP and another as rater; ratings were recorded in real time. *Internal Structure* Two faculty members independently rated a portion of the cases. Percent agreement was calculated and Cohen's kappa corrected for chance agreement on binary outcomes. *Relationship to Other Variables* Relationship to self-assessment of ability to evaluate shoulder pain and knee pain was explored by written surveys utilizing a 5-point Likert scale. Responses were stratified into 3 categories – low, medium, and high – and compared with similarly stratified OSCE scores. **Results:** Checklists were developed for the shoulder (21 items) and knee (26 items); scoring rubrics converted each checklist to a 5-point scale. Using the examination approach in the checklists, trainees correctly identified rotator cuff pathology 61/69 (88%) and meniscal disease 62/69(89%) of the time. Inter-rater agreement was 89% for the knee (k = 0.55) and 96% for the shoulder (k = 0.51). Relationship of stratified self-assessment and OSCE scores is shown in Table 1; Pearson's coefficient indicated no correlation for either shoulder (0.02) or knee (-0.07). Table 1.

SHOULDER		OSCE Rating			
		Low	Med	High	Total
Self-Assessment Rating	Low	0	0	5	5
	Med	4	5	20	29
	High	5	5	25	35
	Total	9	10	50	69
KNEE		OSCE Rating			
		Low	Med	High	Total
Self-Assessment Rating	Low	0	0	2	2
	Med	11	12	12	35
	High	10	13	9	32
	Total	21	25	23	69

Conclusion: The two station OSCE is responsive and consistency in test performance across a range of trainees over time, with good inter-rater reliability. Lack of correlation with self-assessment suggests that these OSCEs measure a construct that is different than learners' self-confidence to support the continuing use of these two shoulder and knee OSCE stations in a structured educational program. The next steps will search for additional validity evidence of these experiences.

Disclosure: M. J. Battistone, None; **A. M. Barker**, None; **J. P. Beck**, None; **R. Z. Tashjian**, None; **G. W. Cannon**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/validity-evidence-for-two-objective-structured-clinical-examination-stations-to-assess-core-examination-skills-of-the-shoulder-and-knee

Abstract Number: 1192

The F-Word: Why Is Talking about Fatigue so Hard?

Ruth Hart[1], Katie Hackett[2], Julia Newton[3], Wan-Fai Ng[3,4] and Ben Thompson[4,5], [1]Institute of Health and Society, Newcastle University, Newcastle upon Tyne, United Kingdom, [2]Institute of Cellular Medicine, Newcastle University, Newcastle upon Tyne, United Kingdom, [3]Newcastle University, Newcastle upon Tyne, United Kingdom, [4]Newcastle-upon-Tyne Hospitals NHS Foundation Trust, Newcastle upon Tyne, United Kingdom, [5]Newcastle University, Newcastle-upon-Tyne, United Kingdom
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SESSION INFORMATION
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Background/Purpose: Fatigue is a common symptom for people with inflammatory arthritis and associated auto-immune conditions. Its impact is wide-ranging and significantly reduces health-related quality of life. Research evidence, however, suggests that neither clinicians nor patients consistently raise the issue in clinic. In-depth discussion of fatigue and support from professionals to manage its impacts are rare. Arthritis Research UK developed a booklet, 'Fatigue and Arthritis', intended to help patients help themselves. Our study has explored patients' approaches to managing fatigue and the impact this booklet has upon them.

Methods: Twelve patients from a rheumatology outpatient service in north-east England took part in in-depth, qualitative interviews before and after being given the 'Fatigue and Arthritis' booklet. Patients were recruited purposively to ensure variation in diagnosis (rheumatoid arthritis (RA), ankylosing spondylitis (AS), and primary Sjögren's Syndrome (pSS)), fatigue severity, and demographic characteristics. Data, in the form of transcripts, was analysed thematically using coding, mapping and memoing techniques.

Results: This study confirms both the impact of fatigue and evidence that neither clinicians nor patients routinely raise the matter in consultations. Our data suggests patients face significant barriers to communicating their fatigue, including: reliance on a diverse, colloquial vocabulary to define the problem; uncertainty how it relates to their condition; doubts to its place on the consultation agenda; and a belief that nothing can be done about it. These barriers affect both if and how patients raise their concerns and are reinforced where clinicians' responses do not invite elaboration.

None of our participants, even those who had discussed fatigue with a clinician, reported having seen the 'Fatigue and Arthritis' booklet before. Not all found it of practical help in improving their day-to-day management and experience of fatigue (criticisms including the familiarity and/or unsuitability of advice). However, most reported gaining something from the booklet. Benefits included: improved understanding of a distressing symptom; validation of their concerns; and a sense that things could be done to manage fatigue. These gains made it easier to discuss fatigue and its impacts with clinicians and with family, friends and colleagues.

Conclusion: Our research adds to the limited evidence on barriers to fatigue communication in the rheumatology clinic. In detailing patients' difficulties, it reinforces prior recommendations that clinicians need to be prepared both to initiate discussions and respond sensitively to concerns about fatigue. It suggests that information materials such as the booklet featuring in this study may be a useful tool for improving communication. We encourage clinicians to give this booklet (or a similar resource) to patients reporting fatigue, and to commit to discussing it at future appointments. More effective communication about fatigue would improve clinicians' understanding of the burden of disease individual patients bear and facilitate improved (shared) decision-making about management options.

Disclosure: R. Hart, None; **K. Hackett**, None; **J. Newton**, None; **W. F. Ng**, None; **B. Thompson**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/the-f-word-why-is-talking-about-fatigue-so-hard

Abstract Number: 1193

The Effectiveness of Low-Impact Exercise Program on Musculoskeletal Health of Asian Older Adults

Huijuan Huang[1], Titilayo Ologhobo[1], Vicky Jin[1], Sandra Goldsmith[2] and Laura Robbins[1], [1]Education & Academic Affairs, Hospital for Special Surgery, New York, NY, [2]Public and Patient Education, Hospital for Special Surgery, New York, NY
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Background/Purpose:

The Center for Disease Control and Prevention (CDC) showed that in 2010-2015, 50% of adults 65 years or older reported an arthritis diagnosis. Studies have shown that participation in low-impact physical activity improves pain, function, mood and quality of life without worsening arthritis symptoms or disease severity. Despite this, the people with arthritis are less likely to be physically active. Nearly 44% of adults with arthritis report no leisure-time physical activity. In 2010, 25% of Asian seniors age 65 and older in NYC lived in poverty and were affected by musculoskeletal conditions. Asian women are at increased risk for developing osteoporosis since they tend to be slender with lower bone mass and avoid consuming dairy due to lactose intolerance. To help Asian seniors in underserved communities better manage musculoskeletal conditions, Hospital for Special Surgery developed its Asian Community Bone Health Initiative (ACBHI) in 2011. This study attempts to show that ACBHI improves musculoskeletal outcomes in Asian older adults.

Methods:

This eight week low-impact exercise program led by bilingual certified instructors, is held once a week in community-based organizations largely serving Asian older adults. Program impact was evaluated with a pre-post design using validated instruments to assess musculoskeletal outcomes. The 11-point Numeric Pain Rating Scale quantified the intensity of muscle or joint pain. Pain interference on seven daily activities was measured using the 11- point Brief Pain Inventory. The SF-36 measured physical function, while the 6-item self-efficacy scale for managing chronic disease was used to measure self-efficacy to exercise. Stiffness and fatigue levels were measured on an 11- point Numeric Rating Scale and 11- point Brief Fatigue Inventory respectively. Demographics such as age, gender and race/ethnicity were also collected. Paired t-test and chi square tests were used for statistical analysis.

Results:

Between 2011 and 2014, there were 311 participants in the exercise program; 175 responded to bilingual (English/Chinese) surveys. Respondents were mostly female (91%) between 65 and 84 years (75%). Physical function improved with a 69% increase in participants who could lift and carry groceries ($p < 0.001$); 88% increase in participants that could climb several flights of stairs ($p < 0.001$); 67% increase in participants who could bend, kneel, or stoop ($p < 0.001$). Participants' muscle and joint pain decreased by 32% ($p < 0.001$). The mean pain intensity rating reduced from 5.6 to 4.4 ($p < 0.001$). Mean fatigue level dropped from 3.9 to 2.3 ($p < 0.001$) while the mean stiffness level also dropped from 3.8 to 2.6 ($p < 0.001$). Reductions in mean pain interference were seen in all seven daily activities. Participants reported that their exercise confidence increased from 6.9 to 8.5 ($p <0.001$).

Conclusion:

Results indicate that this community-based low-impact exercise program is successful in helping Asian seniors in underserved communities improve musculoskeletal outcomes. Providing free exercise programs to the community can play an important role in improving exercise, and managing musculoskeletal disorders.

Disclosure: H. Huang, None; **T. Ologhobo**, None; **V. Jin**, None; **S. Goldsmith**, None; **L. Robbins**, None.

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Abstract Number: 1194

Support for Community-Based Programs for Managing Hip and Knee Osteoarthritis: Results of a Public Survey

Aileen Davis[1], Marvilyn Palaganas[2] and Linda Li[3], [1]Health Care and Outcomes Rsrch, Toronto Western Research Institute, Toronto, ON, Canada, [2]Health Care and Outcomes Research, Toronto Western Research Institute, University Health Network, Toronto, ON, Canada, [3]Arthritis Research Canada, Richmond, BC, Canada

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Background/Purpose: Treatment guidelines for the management of mild to moderate hip and knee osteoarthritis (OA) recommend exercise, weight management and pain medication as first-line treatment to manage and limit symptoms, structural damage and disability. However, delivery of programs within the context of these guidelines by health professionals, such as physiotherapists, poses significant challenges in many countries, largely related to access and cost, as many health care systems do not provide or provide very limited coverage for rehabilitation services. While linking the wellness and health sectors provides an opportunity to increase the availability of programs for people with OA, there is a need to determine if people are willing to participate in programs delivered by trainers delivered in community centers and gyms. The purpose of this survey was to elicit public opinion related to interest in and willingness to attend such community programs, including willingness to pay.

Methods: We conducted an online public survey during September and October 2014. Our sample included the general public in Canada, >30 years of age experiencing hip or knee pain. The 15 question survey could be completed in less than five minutes and included: age; sex; language spoken at home; province/territory of residence and proximity of community/fitness centers; no/yes to pain, aching or discomfort in or around one or both knees/hips/shoulders, hands, neck, back on most days of the past three months; ever told you have arthritis; ever told you have OA or 'wear and tear' in your joints; ever had a hip or knee replacement surgery; membership at a community or fitness center; frequency of exercise at a center or at home; interest in attending a program twice a week for 6 weeks; and, amount willing to pay for such a program. We calculated descriptive statistics with 95% confidence intervals for all variables. Chi-square tests were used to evaluate factors that might be associated with willingness to pay.

Results: After removing duplicate records, 751 completed the survey. 363 (51%) reported knee pain and 247 (34%) reported hip pain. Pain in other joints was reported by 482 (65%). Fifty-seven percent (423) reported that they had been told they had arthritis and 374 (51%) reported OA. Most respondents (79%) resided in British Columbia, 10% in Ontario, with the remainder in the other Canadian provinces. Those with hip or knee replacement surgery (73, 10%) were excluded from further analysis. The results were similar irrespective of joint for the remaining 408 likely to have hip and/or knee OA. Age ranged from 30 to >75 years with 260 (63.7%) aged 45 to 64 years. 86% were female. Only 2 (<1%) reported it took more than an hour to drive to a community center. 156 (38%) reported they currently had a center membership with 203 (50.4%) reporting exercise 3 days/week, 120 (29.8%) <3 days and 80 (19.9%) reporting no exercise. 297 (73.7%) were willing to attend a program and, of these, 26% were willing to pay 100 Cdn$ or more.

Conclusion: Targeted programs delivered in community/fitness centers may be a viable option to support people in managing their hip and or knee OA.

Disclosure: A. Davis, None; **M. Palaganas**, None; **L. Li**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/support-for-community-based-programs-for-managing-hip-and-knee-osteoarthritis-results-of-a-public-survey

Abstract Number: 1195

Rheumatology Nurse Advice Line in Singapore Tertiary Hospital – Pilot Study

Sow Ling Yee[1], Xiaohui Xin[2], Rong Fang Zhang[3], Hui Yang[4] and Siaw Ing Yeo[5], [1]Nursing, Singapore General Hospital, Singapore, Singapore, [2]Academic Clinical Programme, Division of Medicine, Singapore General Hospital, Singapore, Singapore, [3]Nursing, Singapore General Hospital, S, Singapore, [4]Division of Medicine, Singapore General Hospital, Singapore, Singapore, [5]Department of Rheumatology & Immunology, Singapore General Hospital, Singapore, Singapore
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Background/Purpose:

To evaluate the role of the rheumatology nurse advice line service and the patterns of calls for patient management in an outpatient setting.

Methods:

This is a prospective descriptive study. The rheumatology nurse advice line service is meant for addressing non-emergency queries from patients. This service is delivered through an answerphone service. Response times to the calls are kept within 24 hours. Administrative data and patient demographics (November 2013 to May 2015) were collected. The service utilization rate, purpose of call and time taken to respond to patients were also collected and analyzed to assess the demand and the benefit of this service for patients.

Results:

Forty-seven calls were received over the study duration with 79% (37) of the calls made by patients themselves. Seventy-two percent (34) of the calls made were related to clinical issues, while the rest were administrative enquiries. The top three reasons for utilizing this service were: disease-related symptoms (32%), side effect from drugs(19%), and enquiry on procedures or medications(15%). Sixty-eight percent (32) of the cases were made by patients diagnosed with Rheumatoid Arthritis with 50% of their queries pertaining to disease flare and side effects related to immunosuppressive therapy. The mean time taken to respond to a patient's enquiry was 527 min / 8 hours 47 min.

Conclusion:

These results suggest that there is a need for clinical advice pertaining to disease flares and medication side effects as provided by the rheumatology nurse advice line in the management of rheumatoid arthritis patients in an outpatient setting. These interventions may play a significant role in encouraging adherence to therapy, prevent major flares, promote self-management in patients, and improve patient satisfaction. We plan to study the relationship between availability of the rheumatology nurse advice line with management of mild disease flare and adherence to medications.

The current uptake is low as the RNA is a new service and recruitment was not open to all patients. To improve the uptake, we plan to allow access to all patients and increase the awareness of this advice line of referring physicians.

Disclosure: S. L. Yee, None; **X. Xin**, None; **R. F. Zhang**, None; **H. Yang**, None; **S. I. Yeo**, None.

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Abstract Number: 1196

Patient Education in Spondyloarthritis Should be Guiding, Reliable and Available and Presented in Varied Formats

Emma Haglund[1,2,3], Ann Bremander[1,2,3], Stefan Bergman[1,3,4] and Ingrid Larsson[3,5], [1]Department of Clinical Sciences, Lund, Section of Rheumatology, Lund University, Lund, Sweden, [2]School of Business, Engineering and Science, Halmstad University, Halmstad, Sweden, [3]Spenshult Research and Development Center, Halmstad, Sweden, [4]Primary Health Care Unit, Department of Public Health and Community Medicine, The Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden, [5]School of Health and Welfare, Halmstad University, Halmstad, Sweden

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Session Title: Education Poster (ARHP): Education/Community Programs

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Background/Purpose:

The treatment target for axial spondyloarthritis (SpA) is to maximize health-related quality of life (HRQoL) by controlling disease activity and improving functioning. The treatment cornerstones are a combination of patient education, pharmacological and non-pharmacological treatment. Health professionals are familiar with providing patient education but the knowledge is scarce concerning how this education is experienced by the patients.

The aim was to describe patients' experiences of education in SpA management.

Methods:

The study had a descriptive design with a qualitative conventional content analysis approach performed in seven steps in accordance with Graneheim & Lundman (1). The analysis aimed to describe and preserve contextual meanings. After coding and subgrouping meaningful parts of the text were merged into categories. Eleven interviews were conducted between 2014-2015 in patients with SpA based on a strategic sampling in order to achieve variation with regard to sex (7 men, 4 women), age (38-66 years), subdiagnoses (5 patients with AS, 6 with USpA), quality of life (EQ5D 0.29-1.0), disease activity (BASDAI 1-6), physical function (BASFI 0-5), and global health (BASG 0-7) .

Results:

Three categories representing patients' experiences of patient education in disease management emerged; guiding education, reliable education and available education. *Guiding education* comprised SpA management including disease knowledge such as symptoms, prognosis, treatment, self-management, climate impact, heredity, and assisting devices. *Reliable education* meant how and by whom the education was communicated and was considered reliable if it was based on science and communicated by specialists, for example by physician, nurse, PT, dietician and senior patients with experience of rheumatic diseases. The patients experienced difficulties in assessing the large flow of education coming from various sources. Individualized education also increased the reliability. *Available education* meant that the education can and should be presented in varied formats, and that the amount of information could be chosen. The education could be given orally (through meetings, videos, lectures), in writing (by pamphlets, e-mails, journals, webpages) or obtained through own personal experiences. There were requests to utilize newer media like skype, video and chat forums. Furthermore, individual contacts with healthcare professionals when needed were of importance.

Conclusion:

This study highlights the importance of obtaining a guiding, reliable and available patient education for management of SpA. Health care professionals need to consider the importance of presenting varied formats of education based on patients' experiences and expectations.

References:

1.Graneheim UH, Lundman B. Qualitative content analysis in nursing research: concepts, procedures and measures to achieve trustworthiness. Nurse education today 2004;24(2):105-12.

Disclosure: E. Haglund, None; **A. Bremander**, None; **S. Bergman**, None; **I. Larsson**, None.

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Abstract Number: 1197

Two Strategies for Recruiting Rural Faith-Based Organizations for a Fall-Prevention Exercise Intervention in a Population with High Rates of Arthritis

Dina L. Jones[1], Rachael E. Whitley[2] and Jennifer L. Eicher[1], [1]Orthopaedics, West Virginia University, Morgantown, WV, [2]Marshall University, Huntington, WV

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Background/Purpose: Rates of falls are higher in older adults, rural areas, and people with chronic conditions such as arthritis. Translating evidence-based, fall-prevention programs into practice is a public health priority in these populations. The Tai Ji Quan: Moving for Better Balance (MFBB) program is an evidence-based, community-delivered, fall-prevention exercise intervention for older adults. There is a need to translate MFBB into more diverse settings, such as faith-based organizations (FBOs). A sample of 237 older adults, of which 63% had arthritis, enrolled in a 16-week translational study of MFBB in 20 rural FBOs. This study describes the methods and outcomes of the 2 strategies used to recruit the FBOs.

Methods: The FBOs in 7 rural counties were eligible to participate if they could secure a space for the class, identify a leader, host a 16-week class, recruit up to 15 class participants, and wanted to continue class after the study ended. The intervention was delivered in 2 rounds. The FBOs in round 1 were identified via mailing lists, internet and newspaper searches, Chambers of Commerce, Extension Service Agents, a Community Partnership Board, and a faith-based consultant. We used multi-stage purposeful random sampling to select

55 of the 164 FBOs in round 1 to receive a recruitment packet by mail. A follow-up mailing was sent to non-responders, as well as the 109 FBOs not targeted in the first mailing. Due to low response rates, we switched to a non-probability sampling method, snowball sampling, which relied on networking and word-of-mouth. We "knocked on doors" of community constituents (e.g., clergy, congregants, fitness centers, senior centers, etc…) and attended church/prayer services, ministerial association meetings, and festivals, and volunteered at potluck dinners and food pantries. We tracked response rates to the mailings, the number of trips and miles traveled, and the number of communications needed to recruit the FBOs.

Results: The study counties had higher rates of rural older adults and arthritis as compared to the US average. Only 6% and 2% of FBOs responded to the first and second mailings, respectively, which resulted in 3 (15%) of the 20 needed FBOs enrolling in the study. Snowball sampling took 12 months, during which we made 289 telephone calls, sent 193 e-mails and 215 mailings, distributed brochures to 69 FBOs, and held 118 meetings, all to recruit the remaining 17 (85%) FBOs. This process involved 20 trips over 31 days for a total of 8933 miles traveled. It took between 1 and 280 days (average 62 days) to recruit a FBO. The FBOs were predominantly Mainline Protestant churches/organizations (70%). Two-thirds of the FBOs were small with fewer than 100 members.

Conclusion: There is a need for fall-prevention interventions in rural older adults with arthritis. In this study, FBO recruitment rates were greater when relying on networking and word-of-mouth rather than mailings. The snowball sampling approach, however, took 1 year to complete with substantial investments in time and travel. Future studies may want to factor in the additional time and costs associated with recruiting FBOs using this method during the planning phase of the study.

Disclosure: D. L. Jones, None; **R. E. Whitley**, None; **J. L. Eicher**, None.

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Abstract Number: 1198

Design and Implementation of a Patient-Centered Navigator Program to Improve Adherence to Disease-Modifying Antirheumatic Drugs

Candace H. Feldman[1], Anarosa Campos[2], Alyssa Wohlfahrt[2], Yuanyu Lo[2], Joshua Gagne[3], Maura D. Iversen[4], Elena Massarotti[5] and Daniel H. Solomon[1], [1]Division of Rheumatology, Immunology and Allergy, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, [2]Rheumatology, Immunology and Allergy, Brigham and Women's Hospital, Boston, MA, [3]Pharmacoepidemiology and Pharmacoeconomics, Brigham and Women's Hospital, Boston, MA, [4]Northeastern University, Department of Physical Therapy, and Brigham & Women's Hospital, Harvard Medical School, Boston, MA, [5]Rheumatology, Immunology and Allergy, Brigham and Women's Hospital, Harvard Medical School, Boston, MA

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Background/Purpose: Adherence is a complex behavior and rates among patients with rheumatic diseases are especially poor. To date, the impact of interventions on adherence and disease outcomes has been inconsistent. We developed a patient-centered intervention using navigators, college-educated individuals trained to provide education, advocacy, mental health support and care coordination services tailored to each patient's needs, to understand and improve adherence to disease modifying antirheumatic drugs (DMARDs).

Methods: Two board-certified rheumatologists designed a training curriculum for the navigators that included education about systemic rheumatic diseases. Collaborating with a pharmacist, materials were developed on DMARD pharmacokinetics, administration, drug interactions, monitoring, and adverse effects. The drug and disease-specific training consisted of three two-hour modules. A health behavior epidemiologist provided a two-day motivational interviewing training. To familiarize the navigators with available resources, meetings were arranged with a social worker, psychiatry department leadership, a financial counselor, clinic administrators and outpatient pharmacists. Individual structured interviews were conducted between the navigators and four rheumatologists to better understand the needs and perspectives of providers. The navigators also shadowed nurse practitioners during medication education sessions and rheumatologists during clinic visits.

Results: We identified and trained three patient navigators, one of whom is fluent in Spanish. Patients receiving care at an academic medical center with a rheumatic disease who recently started an oral DMARD were eligible. Patients could self-refer, be referred by their

rheumatologist, or be identified by electronic medical record review and were contacted after approval from their rheumatologist. 25 of the 32 practicing rheumatologists referred patients. We sent letters to 553 patients, 313 of whom were reached by a navigator. Of these, 114 enrolled and 102 completed baseline surveys. During the ongoing two-year study, patients are followed for a 6-month period. There have been 360 patient encounters (phone calls or in person meetings) and 20 patients have completed the 6-month intervention. Navigators have established a rapport with rheumatologists and opened a channel of communication between patients and providers. They have identified medication errors, recognized and addressed mental health issues and adverse events, and coordinated care across providers to facilitate adherence to rheumatologists' recommendations. They developed a system with the psychiatry department to expedite referrals based on needs they uncover and routinely work with pharmacies, insurance companies and the financial counselor to ensure that patients obtain their prescribed medications.

Conclusion: A patient navigator program is a feasible strategy to facilitate care coordination and promote adherence to oral DMARDs. Next steps include evaluation of the impact of rheumatology-specific navigators on clinical outcomes and long-term adherence.

Disclosure: C. H. Feldman, Pfizer Inc, 2; **A. Campos**, None; **A. Wohlfahrt**, None; **Y. Lo**, None; **J. Gagne**, None; **M. D. Iversen**, None; **E. Massarotti**, None; **D. H. Solomon**, None.

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Abstract Number: 1199

The Charla De Lupus (Lupus Chat)® Program: An Evaluation of a Lupus Support Program for Teens, Young Adults and Parents

Melissa T. Flores[1], Jillian A. Rose[1], Roberta Horton[1], Dariana M. Pichardo[1], Lillian Mendez[1] and Lisa F. Imundo[2], [1]Social Work Programs, Hospital for Special Surgery, New York, NY, [2]Assoociate Professor of Pediatrics in Medicine - Rheumatology, Columbia University Medical Center, New York, NY

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Background/Purpose:

Research shows that chronic illnesses such as lupus have a multi-level impact on the entire family; it can be challenging for both patients & caregivers to find support, cope & manage the illness. An evaluation was conducted of a monthly hospital-based psychoeducation program, ongoing since 1994, for teens & young adults with lupus & their loved ones. The program provides a platform for support strategies for coping with lupus. Each 2-hour program includes a professionally-led presentation, hands-on workshop or open discussion on a lupus-related topic.

Methods:

A 46-item survey with Likert scale & open-ended questions was mailed to 290 members. Items included demographics, topic choices, satisfaction, impact & areas for program improvement. Separate analyses on satisfaction & impact were conducted for teens/young adults (Ts/YAs) & parents (Ps).

Results:

53 surveys (18%) were returned. Over half (55%) of the respondents identified as Ts/YAs, 41% Ps & 4% support persons. 86% were female, 63% Latino(a), 26% African American, 7% Asian, and 7% White. 58% attended some college or some high school. 23% reported annual income < $5,000. 92% had health insurance; average # years since diagnosis was 6.

100% of respondents were satisfied with the group overall & the group staff. 98% strongly agree/agree they were satisfied with the topics overall; 96% of respondents strongly agree/agree that the topics presented contributed to their understanding of lupus-related issues. 88% of Ts/YAs strongly agree/agree that the topics helped them cope with lupus.

Satisfaction rated by topic was high overall, but Ps consistently reported higher satisfaction than Ts/YAs. 92% of respondents were satisfied with topic "Caring for the Caregiver" (100% Ps, 86% Ts/YAs); 90% satisfied with "Kidneys and Lupus" (94% Ps, 86%

Ts/YAs); 85% satisfied with "Body Image and Lupus" (94% Ps, 77% Ts/YAs); 89% satisfied with "Lupus, Tattoos & Piercings" (100% Ps, 82% Ts/YAs).

We assessed impact for Ts/YAs group in 4 areas: coping, support, knowledge & management of lupus as a result of group participation. 79% strongly agree/agree they were better able to cope with their illness. 97% strongly agree/agree they had a better support system. 89% strongly agree/agree they know more about lupus & treatments. 93% strongly agree/agree they can better manage lupus. For parents, 88% agree they have a better support system & 83% agree they know more about lupus & treatments.

Results demonstrate the key role that the program plays in providing support & education not only to Ts/YAs but also their caregivers. The high levels of satisfaction & agreement reported by parents highlight the benefit of using a family model in support programs. Responses to open-ended questions underscored that parents value "information & sense of family," "the interaction, support & fellowship," & "knowledge to know how to treat lupus."

Conclusion:

Despite limitations due to a small sample size, our results underscore the success of the program & next steps for program enhancement. The evaluation of this family model of support provides lessons to rheumatology health professionals who work with teens/young adults with lupus to help improve overall quality of life for the entire family.

Disclosure: M. T. Flores, None; **J. A. Rose**, None; **R. Horton**, None; **D. M. Pichardo**, None; **L. Mendez**, None; **L. F. Imundo**, None.

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Abstract Number: 1200

Use of Focus Groups and Patient Partners to Revise an Internet Self-Management Program

Sharon Newbill[1], Dinesh Khanna[2], Jennifer Serrano[3], Josephine Battyany[4], Dana Rosson[5], Cynthia Maxwell[6], Mary Alore[7], Laura Dyas[8], Saville Kellner[9], Luke Evnin[10], Dennis Raisch[11], Richard Silver[12] and **Janet L. Poole**[13], [1]University of New Mexico, Albuquerque, NM, [2]Division of Rheumatology, University of Michigan, Ann Arbor, MI, [3]University of Michigan, Ann Arbor, MI, [4]Scleroderma Foundation Southern California, Culver City, CA, [5]Medical University of South Carolina, Charleston, SC, [6]Patient Partner, Charleston, SC, [7]Patient Partner, Shelby Township, MI, [8]Scleroderma Foundation Michigan Chapter, Southfield, MI, [9]Scleroderma Research Foundation, Henderson, NV, [10]Scleroderma Research Foundation, San Francisco, CA, [11]College of Pharmacy, University of New Mexico, Albuquerque, NM, [12]Division of Rheumatology and Immunology, Medical University of South Carolina, Charleston, SC, [13]Health Sciences Ctr OT Program, 1 University of New Mexico, Albuquerque, NM

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Background/Purpose: Taking Charge of Systemic Sclerosis (TOSS) is an internet self-management program developed for people with systemic sclerosis (SSc). The purpose of this qualitative study was to engage patient partners, stakeholders and people with SSc in focus groups to assess whether the current program has the information people with SSc perceived they need to manage and effectively cope with their disease.

Methods:

Six focus groups with a total of 30 participants with SSc were conducted: 2 telephone groups and 4 face-to-face groups. Prior to the focus group meetings, participants reviewed the current website. A semi-structured interview guide was used to elicit participants' responses about additional content needed. Interviews were audio-recorded and transcribed verbatim. Content analysis of de-identified open transcripts occurred in two stages: 1) initial coding by the qualitative researcher to create a coding structure using NVIVO version 10 software that conformed to the topics in the interview and/or focus group guides and 2) an iterative team process which verified and expanded the original coding into emergent themes and categories. The principal investigator conducted an independent review of transcripts. Edits of the initial coding structure, internal audits and member checking were conducted through one discussion.

Results:

The participants were 63% female, 70% Caucasian, 23.3 % African American, 67% had diffuse systemic sclerosis, the mean age was 48.8 years, mean disease duration was 11.4 years, and the mean education level was 15.8 years. Each focus group lasted 2.0-2.5 hours in duration. Dominant themes for additions to the current website: format changes and additional pictures, additional materials on affect and positive affirmation; disease and symptom management; self-advocacy; information for use by caregivers, families, coworkers and strangers; tracking systems for medical records, tests and symptoms; and information about local support groups. Although the focus group questions concentrated primarily on additional content needed, participants were positive regarding the audio voice over, exercise module, content, and the logs and checklists.

Conclusion:

Persons with SSc identified additional content to improve the internet self-management program. Many of the suggestions will be incorporated into the current program as modifications and additions to existing modules, patient testimonials, worksheets, resources sheets, and/or links to additional websites.

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Abstract Number: 1201

A Short Training on Solution Focused Approach May be Helpful in Providing Psychological Support Skills to Nurses Involved in Rheumatoid Arthritis

Mie Fusama[1], Tomoko Shiratori[2], Kayoko Higashi[1] and Hideko Nakahara[1,2], [1]NTT West Osaka Hospital, Osaka, Japan, [2]Kansai Health Administration Center, NTT West Corporation, Osaka, Japan

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Background/Purpose:

Patients with rheumatoid arthritis (RA) often suffer from psychological problems, which may exacerbate pain and disease activity [1]. Bad emotional reaction to the diagnosis of RA contributes to the onset of depression symptoms [2]. However, hospitals cannot readily provide psychological support for patients because of insufficient specialists. Therefore, based on EULAR's recommendations, nurses should acquire the necessary skills to provide psychological support in busy clinical settings.

The aim of this study is to assess if nurses who receive a single short training session from a clinical psychologist can attain confidence and competence in providing psychological support for patients.

Methods:

A clinical psychotherapist provided psychological support training to the participants only once for a period of one hour. This lecture was divided into 2 parts: (1) basic attitudes toward patients, such as "agreeableness", "acceptance" and "empathic understanding"; (2) Solution Focused Approach (SFA), a new method in the RA field, consisting of the miracle, coping and scaling questions.

We evaluated nurses' opinions regarding their confidence and competence in providing psychological support for patients by utilizing a 0-10 scale (0 = none, 10 = full agreement). Participants were asked regarding the necessity and feasibility of psychological support by nurses and their motivation for training. Client Satisfaction Questionnaire-8 (CSQ-8J) was utilized to assess satisfaction with the lecture; while the General Self-Efficacy Scale(GSES)was used to evaluate self-efficacy of nurses. Data analyses were performed with the Paired t-test and Wilcoxon rank sum test.

Results: Nurses involved in treatment of patients with RA were selected randomly between May and June, 2015. 55 nurses (0 male/ 55 female) were included in this study. The average of ages, clinical experience and clinical experience in RA were 42.4 years old, 17.8 and 5.8 years, respectively. Agreement about necessity and motivation was high and there were no statistically significant differences before and after the lecture (mean±SD; necessity: 9.55±1.07, 9.43±1.36, respectively, p=0.591, motivation: 9.24±1.4, 9.14±1.74, respectively, p=0.481). However, agreement regarding feasibility after the lecture was statistically significantly higher than that before the lecture (mean ±SD; 7.88±2.07, 7.16±2.19, respectively, p<0.05). Nurses showed high levels of satisfaction with the lecture. The only question for which satisfaction was low concerned short length and lack of more detailed explanations. There were no statistically significant differences in nurses' evaluations of self-efficacy before and after the lecture.

Conclusion: This is the first study indicating that even short training may be helpful in providing nurses with psychological support and SFA skills. This strategy could be appropriate in busy clinical settings. Further studies of repeated training and of nurses' application of the skills acquired in such training are ongoing.

References:

[1] Rathbun AM, et al. Rheumatology (Oxford) 2013; 52: 1785-94.

[2] Sheehy C, et al. Rheumatology (Oxford) 2006; 45: 1325-7.

Disclosure: M. Fusama, None; **T. Shiratori**, None; **K. Higashi**, None; **H. Nakahara**, None.

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Abstract Number: 1202

Knowledge and Perception of Cardiovascular Disease Risk in Patients with Psoriatic Disease

Dennis Wong[1], Daniel Pereira[2], Sutha Shanmugarajah[1], Renise Ayearst[2], Dafna Gladman[2], Cheryl Rosen[3] and Vinod Chandran[2], [1]University of Toronto, Toronto Western Hospital, Toronto, ON, Canada, [2]Rheumatology, University of Toronto, Toronto Western Hospital, Toronto, ON, Canada, [3]Dermatology, University of Toronto, Toronto Western Hospital, Toronto, ON, Canada
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Background/Purpose: The prevalence of cardiovascular diseases (CVD) is higher in patients with psoriatic disease. Psoriatic disease is known to be an independent risk factor for the development of CVD. CVD knowledge and risk perception is a key predictor of patients' likelihood of adopting a healthy lifestyle. However, it is not clear whether patients with psoriatic disease have adequate knowledge and what the barriers are that prevent them from understanding CVD risk. Thus, the aim of this cross-sectional study was to assess psoriatic patients' knowledge and perception of CVD and examine their relationship with demographic and clinical characteristics.

Methods: Psoriatic arthritis (PsA) patients, who have had psoriasis diagnosis confirmed by a dermatologist, were recruited from the PsA clinic. Patients with psoriasis without PsA (PsC), were diagnosed by a dermatologist and evaluated by a rheumatologist to exclude PsA. All patients completed the knowledge level questionnaire based on the validated Heart Disease Fact Questionnaire for Rheumatoid Arthritis (HDFQ-RA), and risk perception was measured by the validated Perception of Risk of Heart Disease Scale (PRHDS). Framingham Risk Score was calculated as a measure of the estimated risk of CVD. The relationships between CVD knowledge and variables such as perceived risk, estimated risk, demographic and clinical characteristics were examined with Spearman correlation.

Results: 200 patients (102 PsA and 98 PsC), who did not have a history of CVD, completed the questionnaire (Mean age = 51.9±13.6 years, 53% females and 78% Caucasians). The mean score in CVD knowledge among psoriatic patients was 60.4% (SD±15.5). Patients scored significantly lower ($p < 0.001$) in questions addressing psoriatic-specific risk factors and CVD symptoms (Mean score = 42.2% and 43.4%, respectively) as compared to questions on traditional risk factors and diet (Mean score = 68.8% and 71.5%, respectively). CVD knowledge was found to have a significant correlation with education level (Spearman's rho $r_s = 0.271$, $p < 0.001$). Significant difference in knowledge level was found between patients who only completed grade school (Mean score = 43%) and those who completed post-secondary degrees (Mean score = 62.7%) ($p = 0.001$). Furthermore, CVD knowledge level and perception of risk has a

weak but significant positive correlation ($r_s = 0.277$, $p < 0.001$). No significant correlation between patients' perceived risk and estimated CVD risk was found ($r_s = 0.157$, $p = 0.221$).

Conclusion: Improving CVD knowledge and risk perception and developing CVD risk reduction interventions are imperative for psoriatic patients. Educational programs on psoriatic-specific risk factors and CVD symptoms might help encourage active participation in disease management and maintenance of healthy lifestyle, particularly among patients with lower education level.

Disclosure: D. Wong, None; **D. Pereira**, None; **S. Shanmugarajah**, None; **R. Ayearst**, None; **D. Gladman**, None; **C. Rosen**, None; **V. Chandran**, None.

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Abstract Number: 1203

Patient Satisfaction and Outcomes of a NOVEL Ankylosing Spondylitis Education and Self-Management Project

Jean McQuade[1], Christina Johnston[2], **Charles Inderjeeth**[3,4,5,6], Kathy Briffa[7], Jack Edelman[8], Nicola Cook[9] and Warren Raymond[10], [1]Arthritis WA, Wembley, Australia, [2]Arthritis and Osteoporosis WA, Perth, Austria, [3]Rehabiltation and Aged care and Rheumatology, Sir Charles Gairdner Hospital and University of Western Australia, Nedlands, Australia, [4]North Metropolitan Health Service, University of Western Australia, Perth, WA, Australia, [5]Subiaco Rheumatology Clinic, Subiaco, Australia, [6]Linear Clinical Research Ltd, Perth, Australia, [7]School of Physiotherapy and Exercise Science, Curtin University, Perth, Australia, [8]Rheumatology, Sir Charles Gairdner Hospital, Perth, Australia, [9]Royal Perth Hospital, Perth, Australia, [10]Rheumatology and Geriatric Medicine, Sir Charles Gairdner Hospital and University of Western Australia, Nedlands, Australia

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Background/Purpose : Disease specific self-management interventions are rare. After a needs assessment, focus group discussions, and *Plan, Do, Study, Act* (PDSA) model we developed and tested the *Self Management for Ankylosing Spondylitis* (SMAS) program, for people with Ankylosing Spondylitis (AS). We examined the benefits of an SMSA program for people with AS regarding change in health status, quality of life, and disease activity.

Methods: 134 people were recruited in this case cohort intervention. Exclusion criteria: <18yo; non-English speaking; co-morbid inflammatory musculoskeletal disease; and/or visual, auditory, or cognitive impairment. Participants attended a weekly 2.5 hour self-management education session facilitated by same two health professionals over 6 weeks. The scripted content included multidimensional strategies including stretches; and optional 7th week supervised exercise class.

Demographic, AS disease management characteristics, medication patterns, and outcomes were measured at baseline, 6 weeks, 3 and 6 months using repeated measures ANOVA for: back pain (VAS), fatigue (MAF), anxiety and depression (HAD), health distress (HDq), fatigue severity scale (FSS), pain self-efficacy (PSEQ), quality of life (SF-36) and Evaluating Ankylosing Spondylitis Qol (EASIQol), global perceived health (GPH), patients disease global assessment (PDGA). AS outcomes were analysed using repeated measures ANOVA for: Bath Ankylosing Spondylitis – Global, Disease Activity Index, and Functional Index (BAS-G, BASDAI, & BASFI), and Ankylosing Spondylitis QoL (ASQol).

Results: At baseline, 43.3% were male, and the mean age was 47.2 ± 15.1 years. The median time to AS diagnosis from the index

symptom experience was 3 years with an IQR (1-6). The BAS-G improved between baseline and 3 months (p=0.011) and were sustained at 6 months (p=0.039). The BASDAI improved between baseline and 3 months (p=0.01) and were sustained at 6 months (p=0.009). The ASQol improved between baseline and 6 months (p=0.051). A positive trend were seen for the MAFs GFI, back pain (i.e. nocturnal and total), and the PDGA over the 6 months although these trends were not statistically significant. The composite SF-36 (physical and mental), HADs, HDq, FSS, composite Easiqol (physical, disease activity, wellbeing, and social), PSEQ demonstrated no improvement over the study. There was no significant change in medication usage over the 6 months.

Conclusion:

SMAS for AS is independently effective in improving AS specific Disease activity, but global QOL scores did not change.

Table 1: Repeated Measures ANOVA for Quality of Life and Disease Activity tools over time.

Repeated Measures ANOVA	Baseline	WK6	WK6-BL	3MO	3M-BL	6MO	6MO-BL	Within-Subjects Contrasts
	Mean (SE)	Mean (SE)	p-value	Mean (SE)	p-value	Mean (SE)	p-value	p-value
AS Specific Tools								
BAS-G Score	6.09 (0.40)	5.83 (0.36)	0.548	4.89 (0.37)	0.011	5.03 (0.40)	0.039	0.004
BASDAI	5.30 (0.36)	4.83 (0.37)	0.107	4.36 (0.35)	0.01	4.30 (0.37)	0.009	0.005
AS Qol	8.83 (1.08)	8.17 (1.00)	0.409	7.50 (0.88)	0.104	7.03 (1.01)	0.051	0.059
BASFI	4.06 (0.40)	4.03 (0.34)	0.94	3.62 (0.31)	0.118	3.80 (0.40)	0.446	0.266
General Intervention Assessments								
MAFs - GFI	26.14(2.33)	26.50 (2.43)	0.853	23.91 (2.67)	0.333	21.79 (2.67)	0.081	0.06
Back Pain Nocturnal	4.72 (0.41)	4.10 (0.41)	0.142	4.28 (0.42)	0.317	3.97 (0.43)	0.092	0.151
Back Pain Total	5.59 (0.45)	5.21 (0.38)	0.383	4.90 (0.36)	0.091	4.59 (0.46)	0.076	0.143
PDGA	5.24 (0.38)	5.07 (0.42)	0.634	4.66 (0.39)	0.176	4.55 (0.42)	0.081	0.246
SF 36 (Composite)	102.24 (2.07)	103.52 (1.74)	0.429	103.59 (1.59)	0.446	104.31 (1.76)	0.265	0.552
HADS	14.90 (1.62)	14.83 (1.64)	0.962	14.52 (1.43)	0.799	13.69 (1.54)	0.417	0.741
HDq	2.35 (0.25)	2.30 (0.27)	0.858	2.15 (0.26)	0.443	2.00 (0.26)	0.172	0.396
FSS	40.88 (1.87)	41.86 (1.69)	0.517	No Data	No Data	41.29 (1.93)	0.79	0.79
EasiQol (Composite)	35.78 (6.04)	36.11 (3.19)	0.950	30.44 (3.86)	0.228	30.33 (6.18)	0.492	0.544
PSEQ	36.62 (2.51)	36.31 (2.20)	0.861	36.66 (1.97)	.987	37.17 (2.59)	0.832	0.978

Disclosure: J. McQuade, None; **C. Johnston**, None; **C. Inderjeeth**, None; **K. Briffa**, None; **J. Edelman**, None; **N. Cook**, None; **W. Raymond**, None.

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Abstract Number: 1204

Measuring the Effectiveness of Patient Education of Patients Receiving Injectable Biologic Medications

Victoria Ruffing[1], Ana-Maria Orbai[2] and Clifton O. Bingham III[3], [1]Medicine JHAAC, Johns Hopkins University, Baltimore, MD, [2]Rheumatology, Johns Hopkins University, Baltimore, MD, [3]Johns Hopkins University, Baltimore, MD

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SESSION INFORMATION

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Session Title: Education Poster (ARHP): Education/Community Programs

Session Type: ACR Poster Session B
Session Time: 9:00AM-11:00AM

Background/Purpose: Injectable biologic medications have become part of the routine treatment rheumatoid arthritis (RA), and other inflammatory arthritides. These medications are associated with potentially serious risks. Patients must receive adequate education on disease states, medication administration, common and side effects, and when to contact a health care professional with problems. Aim: Examine the sources from which information concerning biological drug safety is obtained by patients. Identify specific knowledge gaps concerning biologic drug administration and crucial aspects of safety

Methods: Surveys were administered to a random group of patients receiving injectable biological therapies and seen at 2 different clinical settings. We captured basic demographics, disease characteristics, and current and past biologics used. We assessed the type, and method of education received regarding drugs and disease, satisfaction with education, and the level of retained medical knowledge concerning critical aspects of injectable biologics. Questions covered injection technique, storage and handling, side effects, signs of infection, and what to do for elective surgery. Questions were asked using Visual Analog Scales (VAS), Likert scales, with additional comments recorded. Frequencies were compared using Chi-square (X^2) tests. We calculated odds ratios of satisfactory medication safety knowledge (answered all questions correctly) using logistic regression adjusted for demographics (age, sex, race).

Results: Table 1. Participants correctly identified appropriate injection sites, technique, and storage and handling of biologics 100% of the time. There was considerable variability in knowledge concerning basic aspects of relevance to biologic safety. Among the overall group 30% were unable to correctly answer all 4 knowledge questions concerning biologic safety issues related to infections, elective surgery, and when to contact the rheumatologist. Level of education (≤HS vs >HS) was not associated with medication safety knowledge (X^2 1.05, p=0.31). Patients who had received their education from a nurse were more likely to answer all questions correctly (X^2 8.20, p<0.01). Safety knowledge was significantly associated with receiving biologic education from a nurse (OR 8.9, 95%CI 1.9, 42.4, p=0.006) after adjustment for demographic characteristics.

Conclusion: Critical gaps in knowledge exist regarding safe use of biologics. HCPs bear responsibility for educating patients about the safety aspects of biologic medications. In this small study, education provided by a nurse was associated with greater knowledge by patients. Further study is needed to identify the optimal methods of delivering patient education that will be applicable across care settings and to develop a standardized patient curriculum.

Table 1

Covariates	Patients per group (n)	OR	95% CI	p-value
RN				
No (ref)	23			
Yes	25	42.9	3.2-575.9	0.005
Sex				
Male (ref)	6			
Female	42	1.7	0.2-19	0.65
Ethnicity				
African-American (ref)	6			
Caucasian	39	83.5	1.8-3974	0.03
Hispanic	3	8.2	0.1-578	0.33
Education				
HS or less (ref)	22			
More than HS	26	0.5	0.1-4	0.5
Arthritis type				
Other (ref)	16			
Rheumatoid	32	0.1	0.0-1	0.07
First biologic				
No (ref)	13			
Yes	35	1.1	0.1-8.8	0.9

Disclosure: V. Ruffing, None; **A. M. Orbai**, None; **C. O. Bingham III**, Janssen R & D, LLC, 2.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/measuring-the-effectiveness-of-patient-education-of-patients-receiving-injectable-biologic-medications

Abstract Number: 1205

The Spectrum of Early RA Practice Across the Globe: Results from a Multinational

Cross Sectional Survey

Elena Nikiphorou[1], James Galloway[2,3], Piet L van Riel[4], Andrew Östör[5], Glenn Haugeberg[6,7], Feride Gogus[8,9], Markku Kauppi[10], Yusuf Yazici[11] and Tuulikki Sokka-Isler[12], [1]Jyvaskyla Central Hospital, Jyvaskyla, Finland, [2]Academic Department of Rheumatology, King´s College London, London, United Kingdom, [3]King's College Hospital, Department of Rheumatology, London, London, United Kingdom, [4]Scientific Institute for Quality of Healthcare, Radboud University Medical Center, Nijmegen, Netherlands, [5]Addenbrooke's Hospital, Cambridge, United Kingdom, [6]Rheumatology, The Norwegian University of Science and Technology, Trondheim, Norway, [7]Head of the Department of Rheumatology, Martina Hansens Hospital, Bærum, Norway, [8]University of Gazi, Ankara, Turkey, [9]Gazi University, Faculty of Medicine, Ankara, Turkey, [10]Rheumatology, Päijät-Häme Central Hospital, Lahti, Finland, [11]Rheumatology, Hospital for Joint Diseases and Medicine, NYU Langone Medical Centre, New York, NY, [12]Rheumatology, Jyvaskyla Central Hospital, Jyvaskyla, Finland

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Session Title: Epidemiology and Public Health Poster II: Pathogenesis and Treatment of Systemic Inflammatory Diseases

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose:

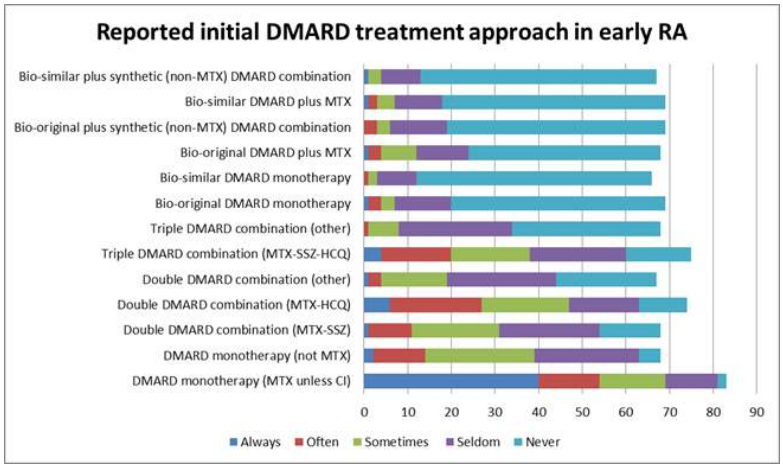
Early diagnosis & treatment are crucial to the management of rheumatoid arthritis (RA). Despite this, the approach to early RA management appears to be inharmonious across countries, although this has not been systematically evaluated.

Methods:

An online survey was emailed to practising rheumatologists in all QUEST-RA countries & also made accessible on social media platforms between April & May 2015. Questions (n=38) assessed the structure & setting of early RA clinics, times to diagnosis & treatment, patient monitoring, use of guidelines & data recording.

Results:

Participants: 212 from 39 countries (76% European). 62% had an early RA clinic based at a university hospital. Patient referral to rheumatology was mainly (78%) via primary care. 44% had an agreed early RA local referral pathway, 15% a national pathway; 27% no pathway. 71% reviewed early RA patients in general rheumatology clinics. Only 16% had dedicated clinics, 76% of which were practitioners in European countries (64% northern Europe) who had access to local or national referral pathways. 42% collected patient data for research purposes. Over 50% reported patients being seen within 4 weeks from primary care referral, a third within 2 weeks. DMARD initiation at first review & within 4 weeks was reported by 47% & 31% respectively. The rheumatologists' satisfaction levels significantly differed by clinic appointment duration (P=.005) satisfaction increasing with longer duration. 43% had radiographs of the hands & feet available at the patient's first review. MSK US was 'always' provided on site by a rheumatologist (18%) or when considered necessary (37%). Over 50% reported having ESR/CRP & antibody results available at the first patient visit. Guidelines were followed by the majority of rheumatologists, especially European (P<=.001). Treatment decisions were reported to be influenced by international &/or national guidelines in 71% & 61%. Figure 1 shows the initial treatment strategies used. Steroid use was reported as 'always'/'often' per os by 26/24% & intra-articularly by 2/11%.



Conclusion:

These data are the first to provide comparative benchmark information regarding the global provision of early RA care. Substantial variations exist in referral & early assessment pathways. Guidelines play a key role, although their impact is most apparent in Northern Europe. This survey is the first of its kind providing invaluable insights that could help harmonize early RA management across countries.

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Abstract Number: 1206

Presence of ACPA in a Large (>40.000) Population Based Cohort from the Netherlands

Elisabeth Brouwer[1], Suzanne Arends[2], Hendrika Bootsma[1], Caroline Roozendaal[3], Pieter C Limburg[4], Fiona Maas[1], René E. M. Toes[5], T. W. J. Huizinga[6], LA Trouw[7] and Annemirthe Van Zanten[1], [1]Rheumatology and Clinical Immunology, University Medical Center Groningen, University of Groningen, Groningen, Netherlands, [2]Rheumatology, Medical Center Leeuwarden, Leeuwarden, Netherlands, [3]Laboratory Medicine, University Medical Center Groningen, Groningen, Netherlands, [4]Laboratory Medicine, University Medical Center Groningen, University of Groningen, Groningen, Netherlands, [5]Department of Rheumatology, Leiden University Medical Center, Leiden, Netherlands, [6]Leiden University Medical Center, Leiden, Netherlands, [7]Rheumatology, Leiden University Medical Centre, Leiden, Netherlands

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Session Time: 9:00AM-11:00AM

Background/Purpose: Anti-citrullinated protein antibodies (ACPA) status provides important information regarding the diagnosis and prognosis of Rheumatoid Arthritis (RA). By using samples from blood bank donors that later developed RA it was shown that ACPA can already be present many years prior to the clinical onset of RA. However, little information is available on the presence of ACPA in the general population and the actual predictive power of ACPA positivity towards development of RA in the future. In this study, we determined the prevalence of ACPA in 40.227 participants from the LifeLines (LL) population based study (1).

Methods: The LifeLines cohort consists of 167.729 persons divided over 3 generations in the northern provinces of The Netherlands. Participants were recruited with help of general practitioners from both rural and non-rural areas and from different economic classes.For this cross-sectional study, 40.136 LL participants were tested for serum levels of ACPA from March 2012 until September 2013 The detection of ACPA was performed by measuring anti-CCP2 (by EliA-CCP test) on the Phadia 250 analyzer. ACPA levels ≥ 5 U/ml are considered positive. An extensive questionnaire on demographic and clinical information, including smoking, periodontal health, and early symptoms of musculoskeletal disorders was sent around as well in 2012 and 2013. RA was defined by a combination of self-reported RA, medication use (DMARDs, NSAIDs and/or steroids) for the indication of rheumatism and visiting a medical specialist within the last year. Mann-Whitney U and Chi-square tests were performed to assess differences between the ACPA positive and negative and LL participants.

Results: Of the total 40.136 individuals, 666 (1.7%) had an ACPA level ≥ 5 U/ml and 306 (0.8%) had an ACPA level ≥ 10 U/ml. Of the participants with ACPA level ≥ 5 U/ml, 14.4% had self-reported RA and 9.3% were defined as having RA.Within the group of self-reported and defined RA patients, ACPA-positivity (≥ 5 U/ml) was seen in 96 (11.5%) and 62 (44.9%) participants, respectively. In participants without self-reported/defined RA, 570 (1.5%) were ACPA positive. ACPA-positive participants reported significantly more pack years of smoking, were more often female and were significantly older compared to ACPA-negative participants (Table 1). When excluding all RA patients, differences in gender and smoking remained statistically significant, whereas age was comparable between both groups (data not shown).

Table 1 baseline characteristics of all participants				
	All (n=40.136)	ACPA-positive (≥ 5 U/mL) (n=666)	ACPA-negative (n=39,470)	P-Value
Age (yrs)	44(18-92)	46(19-80)	44(18-92)	< 0.001
Gender (female)	58%	65%	58%	< 0.001
Smoking Pack years	0.00(0-139)	0.90(0-86)	0.00(0-139)	< 0.001
Smoking status never	49%	43%	49%	0.006
Smoking status former	30%	32%	30%	
Smoking status current	21%	25%	21%	
Self-reported RA	2.0%	14.0%	1.9%	< 0.001
Defined RA	0.3%	9.3%	0.2%	< 0.001
BMI, alcohol use, periodontitis, first degree relatives of RA patients, and in women, nulliparity, menopausal status, early menarche and regular menses were not significantly associated with ACPA status.				

Conclusion: In this large population based study, the prevalence of ACPA levels ≥ 5 U/ ml as estimated by the Phadia analyzer was 1.7% for the total group and 1.5% when excluding RA patients. Smoking, female gender and older age were more frequently present in ACPA-positive LL participants.

References: 1. Scholtens S et al Int J Epidemiol. 2014 Dec 14. pii: dyu229. [Epub ahead of print]

Disclosure: E. Brouwer, Abbvie, 2,Pfizer Inc, 2; **S. Arends**, Pfizer Inc, 2,Abbvie, 2; **H. Bootsma**, Roche Pharmaceuticals, 2,Bristol-Myers Squibb, 2; **C. Roozendaal**, None; **P. C. Limburg**, None; **F. Maas**, None; **R. E. M. Toes**, None; **T. W. J. Huizinga**, Merck, UCB, BMS, Biotest AG, Pfizer, GSK, Novartis, Roche, Sanofi-Aventis, Abbott, Crescendo Bioscience, Nycomed, Boehringer, Takea, Zydus, and Eli Lilly., 5,Roche & Abbott, 9; **L. Trouw**, None; **A. Van Zanten**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/presence-of-acpa-in-a-large-40-000-population-based-cohort-from-the-netherlands

Abstract Number: 1207

Predictive Utility of Anti- Citrullinated Peptide Antibodies and Rheumatoid Factor – a Retrospective Dataanalysis

Miriam Gärtner, Mathias Schneeweiss, Josef S. Smolen and Klaus Machold, Department of Rheumatology, Medical University of Vienna, Vienna, Austria

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SESSION INFORMATION

Session Date: Monday, November 9, 2015

Session Title: Epidemiology and Public Health Poster II: Pathogenesis and Treatment of Systemic Inflammatory Diseases

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: Antibody profiling encompassing rheumatoid factor (RF) and anti-citrullinated peptide antibodies (ACPA) supports diagnosis in patients with Rheumatoid arthritis (RA). However, RF and ACPA are not specific for RA, and predictive values of tests depend heavily on the population in which such tests are performed. Because testing for these antibodies is frequently ordered by non-Rheumatologists, at substantial costs, we sought to determine the predictive values of such testing in patients of a large tertiary hospital.

Methods: Results of all RF and ACPA tests performed in the Vienna General Hospital between 2006 and 2012 were obtained from the Department of Laboratory Medicine and the ordering departments were determined. Diagnoses were extracted from the hospital-wide database. Positive and negative predictive values (PPV and NPV) of RF and ACPA were evaluated.

Results: Between 2006 and 2012 50.138 RF and ACPA tests in 5496 patients were performed. Among these, 31.2% were positive for RF,

23.5% for ACPA and 21.6% were positive for both antibodies. For 3146 patients (57% of all patients in whom RF/ACPA was tested) the tests were not ordered by the Department of Rheumatology. The tests were requested by the Departments of Infectiology (32%), Angiology (11%), Nephrology (8%), Cardiology (4%), Gastroenterology (3%), Oncology (3%), Endocrinology (2%), Pneumology (1%), Hematology (1%), Pediatrics (2%), Ophthalmology (2%), Dermatology (6%), Pediatric Psychiatry (5%) and the Department of Orthopedics (8%). 2251 of the 3146 patients had a documented diagnosis. (Figure 1).

Among the 3146 patients 218 (8.8%) were positive for RF, 118 (3.2%) for ACPA and 56 (2.3%) patients tested positive for both antibodies. PPV and NPV for the presence of musculoskeletal diseases were 31.7% and 80.9% for RF and 42.4% and 81.5% for ACPA testing. However, for presence of chronic inflammatory musculoskeletal diseases (ICD-10-Codes M05.X to M09.X and M30.X to M35.X) PPV were only 16.1% for RF and 30.5% for ACPA. NPV were 94.7% and 94.4%, respectively.

Conclusion: RF and ACPA testing was frequently ordered by non-Rheumatologists. In this patient group, we found a relatively high NPV (95%) but a very low PPV of 16-30%. Thus, >70% of positive tests did not contribute to a diagnosis of inflammatory musculoskeletal disease. This observation underscores the necessity to use such testing only in the appropriate clinical context.

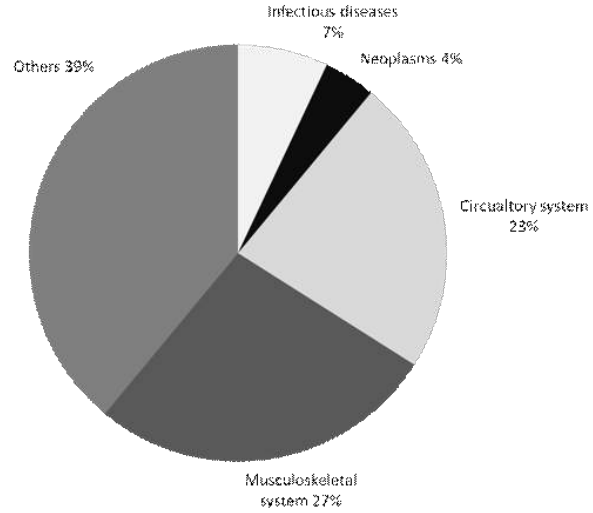

Figure 1: Distribution of the main diagnostic groups among "Non Rheumatology" patients tested for RF and ACPA (n=2251)

Disclosure: M. Gärtner, None; **M. Schneeweiss**, None; **J. S. Smolen**, None; **K. Machold**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/predictive-utility-of-anti-citrullinated-peptide-antibodies-and-rheumatoid-factor-a-retrospective-dataanalysis

Abstract Number: 1208

How Well Do Acpas Discriminate and Predict RA in the General Population – a Study Based on 12,590 Population-Representative Swedish Twins

Aase Haj Hensvold[1], Thomas Frisell[2], Johan Askling[2] and **Anca I Catrina**[1], [1]Rheumatology Unit, Department of Medicine, Karolinska Institute, Karolinska University Hospital, Stockholm, Sweden, [2]Clinical Epidemiology Unit, Department of Medicine, Karolinska Institutet, Stockholm, Sweden

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Background/Purpose: Anti citrullinated protein antibodies (ACPA) are highly specific for rheumatoid arthritis (RA), but the distribution

and diagnostic accuracy of ACPA in general population has not been thoroughly investigated. We aimed to evaluate the distribution and diagnostic accuracy of ACPA in in the general population.

Methods:

Unselected serum samples from a large population-based twin cohort consisting of 12 590 individuals were analyzed for the presence of ACPA using anti-CCP2 ELISA. All ACPA-positive samples (n=350) were further tested for four peptide-specific ACPAs. C reactive protein (CRP), information on SE and smoking were also available. RA cases were identified by linkage to the Swedish National Patient Register.

Results:

Three hundred fifty individuals had a positive ACPA test and 102 of these ACPA-positive individuals had an RA diagnosis at the time of blood donation (prevalent ACPA positive RA). Among the remaining 248 ACPA positive individuals an additional 22 individuals developed RA between blood donation and diagnosis follow-up (incident ACPA negative RA). 53 individuals had an RA diagnosis without testing positive for ACPA at the time of blood donation (prevalent ACPA negative RA) and an additional number of 15 individuals developed ACPA negative RA between blood donation and diagnosis follow-up (incident ACPA negative RA).

Beside smoking and SE, female sex was an important factor associated with ACPA positivity independent of RA diagnosis. The proportion of females was 55% in the entire cohort, 61% among ACPA-positive individuals without RA and 71% among those with prevalent ACPA-positive RA. Female sex was associated with ACPA occurrence (OR=1.6, 95% CI 1.2-2.0) and increased the risk of also having ACPA-positive RA (OR=1.8, 95% CI 1.1-3.1). ACPA-positive individuals without RA had lower ACPA titers and fewer peptide specific ACPAs than both individuals that later developed (incident) ACPA-positive RA and those having prevalent ACPA-positive RA. ACPA-positive individuals had also higher CRP levels than ACPA-negative individuals without RA.

Based on the distribution of ACPA positivity among the 155 cases of prevalent RA at the time point of blood donation, the sensitivity and specificity of ACPA for RA was 66% and 98%, respectively. ACPA high test had a sensitivity of 62% and a specificity of 99%. The positive predictive value (PPV) was 29% (95% CI: 24-34) for ACPA overall, and 48% (95% CI: 41-54) for ACPA high test. The negative predictive values (NPVs) were similar for ACPA test and ACPA high test (99.5% and 99.6 respectively).

Conclusion:

ACPAs associate with female sex and have a high diagnostic accuracy for an RA diagnosis in a population setting.

Disclosure: A. H. Hensvold, None; **T. Frisell**, None; **J. Askling**, None; **A. I. Catrina**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/how-well-do-acpas-discriminate-and-predict-ra-in-the-general-population-a-study-based-on-12590-population-representative-swedish-twins

Abstract Number: 1209

Associations Between Rheumatoid Arthritis (RA)-Related Autoimmunity, Joint Symptoms, and Physical Activity in First-Degree Relatives without RA in a Prospective Cohort

Jan M. Hughes-Austin[1], Joachim H. Ix[2], Samuel R. Ward[3], Michael H. Weisman[4], James R. O'Dell[5], Ted R. Mikuls[5], Jane H. Buckner[6], Peter K. Gregersen[7], Richard M. Keating[8], Kevin D. Deane[9], V. Michael Holers[10] and Jill M. Norris[11], [1]Department of Family and Preventive Medicine, University of California, San Diego, La Jolla, CA, [2]University of California, San Diego, La Jolla, CA, [3]Radiology, Orthopaedic Surgery, and Bioengineering, University of California, San Diego, La Jolla, CA, [4]Rheumatology, Cedars-Sinai Medical Center, Los Angeles, CA, [5]University of Nebraska Medical Center, Omaha, NE, [6]Benaroya Research Institute at Virginia Mason, Seattle, WA, [7]Robert S. Boas Center for Genomics and Human Genetics, Feinstein Institute for Med Res, Manhasset, NY, [8]Division of Rheumatology, Scripps Health, La Jolla, CA, [9]Division of Rheumatology, U Colo Denver, Aurora, CO, [10]Rheumatology Division, Univ of Colorado School of Med, Aurora, CO, [11]University of Colorado Denver, Aurora, CO

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Background/Purpose: Physical activity in RA patients is significantly less than in counterparts without RA, and many live just above the muscle strength threshold needed for activities of daily living. It is not known whether physical activity declines prior to the onset of RA, potentially because of joint swelling and tenderness or because of the inflammatory processes associated with preclinical autoimmunity. Therefore, we first sought to determine whether RA-related autoantibodies, and joint tenderness and swelling, were associated with physical activity in first-degree relatives (FDRs) of RA patients, a population at increased risk for future RA.

Methods: In the Studies of the Etiology of RA (SERA) (a multicenter prospective study of preclinical RA), we evaluated associations between RA-related autoantibodies (Abs), swollen and tender joint count (SJC, TJC) and hours of physical activity in 233 FDRs. We defined RA-related autoantibody positivity as being positive (+) for any of 5 RA-related Abs: rheumatoid factor (RF), RF isotypes – IgM, IgG, IgA, or anti-cyclic citrullinated peptide (anti-CCP2). Positivity for a High-Risk Profile (HRP) was defined as being (+) for anti-CCP2 and/or 2 or more RF isotypes (IgM, IgG, IgA), which has been shown to be 96% specific for future RA. Hours sleeping, sitting, and engaging in slight, moderate, or heavy activity during a typical 24-hour day were obtained through questionnaire, weighted to reflect metabolic expenditure, and calculated as follows: PA score = $(1.0*h_{sleep} + 1.1*h_{sedentary} + 1.5*h_{slight} + 2.4*h_{moderate} + 5.0*h_{heavy})$. ANCOVA was used to evaluate associations between continuous PA score and Ab and HRP positivity, adjusting for age, sex, race, body mass index (BMI), smoking, and TJC. These same methods were used to evaluate associations between SJC and TJC and PA score. Logistic regression was used to evaluate associations between the dichotomous median-and-above (versus < median) PA score and Ab and HRP positivity adjusted for these same covariates.

Results:

Mean age was 47±17 years. 70% were female, 67% were White, 25% were Ab+, and 7% were HRP(+). Mean SJC was 0.3±1 and mean TJC was 1±2 for all FDRs. Average PA score was 37.4. Neither Ab(+) status nor HRP(+) status were associated with PA score or median-and-above PA score in fully adjusted analysis (PA Score: $\beta_{Ab(+)}$=0.20±1.3, p=88; $\beta_{HRP(+)}$=-0.27±0.6, p=0.66) (Median-and-above PA Score Odds Ratios (ORs): $OR_{Ab(+)}$=1.33, 95% CI=0.67-2.67; $OR_{HRP(+)}$=0.43, 95% CI=0.14-1.30)

Neither SJC nor TJC were significantly associated with PA score in fully adjusted analysis (PA Score: β_{SJC}= -0.54±0.6, p=0.38 β_{TJC}= 0.03±0.3, p=0.91).

Conclusion:

In FDRs of RA patients, neither the number of swollen and tender joints nor autoantibody status was associated with physical activity in cross-sectional analysis.

Disclosure: J. M. Hughes-Austin, None; **J. H. Ix**, None; **S. R. Ward**, None; **M. H. Weisman**, None; **J. R. O'Dell**, None; **T. R. Mikuls**, None; **J. H. Buckner**, None; **P. K. Gregersen**, None; **R. M. Keating**, None; **K. D. Deane**, None; **V. M. Holers**, Shared patent with Stanford University for use of biomarkers to predict clinical phenotypes in rheumatoid arthritis., 7; **J. M. Norris**, None.

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Abstract Number: 1210

Genetic, Environmental, and Serologic Risk Factors for Inflammatory Joint Signs Among First-Degree Relatives without Rheumatoid Arthritis in a Prospective Cohort

Jeffrey A. Sparks[1], Shun-Chiao Chang[2], Kevin D. Deane[3], Ryan W. Gan[4], Kristen Demoruelle[3], Marie L. Feser[3], LauraKay Moss[3], Jane H. Buckner[5], Richard M. Keating[6], Karen H. Costenbader[7], Peter K. Gregersen[8], Michael H. Weisman[9], Ted R. Mikuls[10], James R. O'Dell[10], V. Michael Holers[3], Jill M. Norris[4] and Elizabeth W. Karlson[2], [1]Division of Rheumatology, Immunology, and Allergy, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, [2]Division of Rheumatology, Immunology and Allergy, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, [3]Division of Rheumatology, University of Colorado School of Medicine, Aurora, CO, [4]Epidemiology, Colorado School of Public Health, Aurora, CO, [5]Benaroya Research Institute at Virginia Mason, Seattle, WA, [6]Division of Rheumatology, Scripps Health, La Jolla, CA, [7]Rheumatology, Immunology and Allergy, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, [8]Feinstein Insititute for Medical Research, Manhasset, NY, [9]Rheumatology, Cedars-Sinai Medical Center, Los Angeles, CA, [10]Veteran Affairs Nebraska-Western Iowa Health Care System and University of Nebraska Medical Center, Omaha, NE

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Background/Purpose: Family history of RA in a first-degree relative increases RA risk 4-fold. Determining risk factors for inflammatory joint signs (IJS) in this high risk population may elucidate the transition from genetic susceptibility to inflammatory arthritis in pre-clinical RA. We examined whether genetic, environmental, and serologic RA factors were associated with IJS among relatives without RA.

Methods: We evaluated RA factors and IJS in a prospective cohort of first-degree relatives in the Studies of the Etiology of RA (SERA). At enrollment, subjects in SERA did not have RA according to the 1987 ACR criteria by clinical exam. Genetic RA risk factors, including 5 *HLA-DRB1* (**04* or **01*) shared epitope alleles and 45 risk alleles validated among Caucasian populations, were combined into a weighted genetic risk score (GRS50). Smoking, BMI, education, parity, CCP, and RF were assessed at baseline. Physical examination at baseline (n=966) and 2-year follow-up (n=396) assessed IJS as tender or swollen joints at sites typical for RA (**Table)**. We evaluated the association of RA factors with IJS at baseline and follow-up using logistic regression, adjusting for confounders and tested for effect modification.

Results: We analyzed 966 non-Hispanic Caucasian subjects at baseline. In addition, incident IJS at 2-year follow-up was analyzed in 262 subjects after excluding 134 with IJS at baseline. At baseline, mean age was 47.2 years (SD 15.5), 71% were female, 55% were shared epitope-positive, 18% smoked >10 pack-years, and 8% were CCP/RF positive. Smoking >10 pack-years was associated with IJS at baseline (OR 1.59, 95% CI 1.09-2.32) and incident IJS at 2 years (OR 2.66, 95% CI 1.01-7.03). Current (OR 2.12, 95% CI 1.33-3.38) and past smokers (OR 1.61, 95% CI 1.12-2.33) had significantly higher odds of baseline IJS. BMI, education, sex/parity, GRS50, and RF/CCP were not associated with IJS at baseline or follow-up. Among those aged <50 years, subjects who smoked >10 pack-years had 4-fold increased odds of IJS (OR 4.39, 95% CI 2.22-8.66, **Figure**) compared to never smokers (*p*, interaction 0.02).

Conclusion: In a high-risk cohort of first-degree relatives without RA, smoking was associated with both prevalent and incident inflammatory joint signs at sites typical for RA. Those <50 years old who smoked >10 pack-years had the highest risk of IJS with a significant interaction between smoking and age. Neither genetic nor serologic RA factors were significantly associated with IJS in this sample. These results suggest that smoking plays a role in inflammatory arthritis development. Longitudinal studies are needed to further investigate transitions of pre-clinical RA phases.

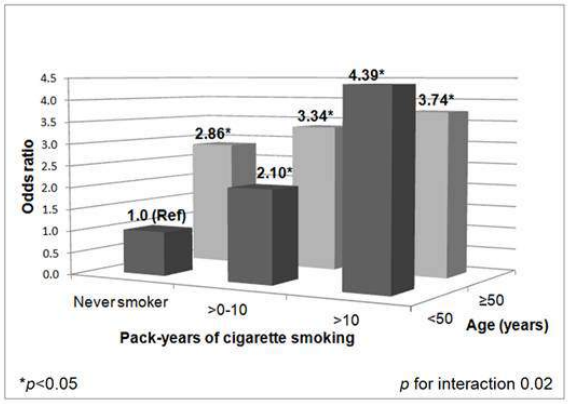
Table. Age-adjusted odds ratios for inflammatory joint signs at sites typical for RA[1] at baseline (n=966) and two-year follow-up among relatives without inflammatory joint signs at baseline (n=262) among first-degree relatives without RA in the Studies of the Etiology of RA.

Model	Covariates	OR (95% CI)[2] at baseline visit (n=966)	OR (95% CI)[2] at two-year follow-up visit (n=262)
Age	Per year	**1.03 (1.02-1.04)**	**1.05 (1.02-1.08)**
Cigarette smoking	Never to ≤10 pack-years	1.0 (Ref)	1.0 (Ref)
	>10 pack-years	**1.59 (1.09-2.32)**	**2.66 (1.01-7.03)**
Body mass index category	Normal/underweight	1.0 (Ref)	1.0 (Ref)
	Overweight/obese	0.93 (0.68-1.28)	1.49 (0.61-3.64)
Education	≤High school graduate	1.0 (Ref)	1.0 (Ref)
	Some college or greater	0.76 (0.53-1.10)	1.37 (0.42-4.46)
Sex/Parity	Female/parous	1.0 (Ref)	1.0 (Ref)
	Female/nulliparous	1.21 (0.76-1.95)	2.52 (0.76-8.35)
	Male	0.77 (0.54-1.11)	0.91 (0.34-2.44)
RA GRS50[3]	Low (≤Median)	1.0 (Ref)	1.0 (Ref)
	High (>Median)	0.99 (0.73-1.35)	1.25 (0.55-2.83)
RA-related antibodies	CCP2 ≤5 units and negative RF	1.0 (Ref)	1.0 (Ref)
	CCP2 >5 units or positive RF	1.20 (0.66-2.19)	1.62 (0.55-4.80)

[1]Inflammatory joint signs were considered as any tender or swollen joints at metacarpophalangeal, proximal interphalangeal, wrist, elbow, and metatarsophalangeal joints. First metacarpophalangeal or first metatarsophalangeal joints and findings deemed to be due to trauma or degenerative disease by the examiner were not included.
[2]All models were adjusted for age in continuous years.
[3]RA GRS50: 5 *HLA* shared epitope alleles and 45 non-*HLA* single nucleotide polymorphisms weighted by known RA risk. GRS5 (5 *HLA* shared epitope alleles), GRS45 (45 non-*HLA* single nucleotide polymorphisms), and shared epitope positivity were not significantly associated with inflammatory joint signs at baseline or follow-up.

CCP2, anti-cyclic citrullinated peptide (2nd generation); CI, confidence interval; GRS, genetic risk score; OR, odds ratio; RA, rheumatoid arthritis; RF, rheumatoid factor. Bolding indicates $p<0.05$.

Figure. Combined effect of age and cigarette smoking on inflammatory joint signs at sites typical for RA among first-degree relatives without RA at baseline in the Studies of the Etiology of RA (n=966).



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Shift of Rheumatoid Arthritis Onset Toward Old Age in Japan Based on a Nationwide Cohort Database

Eri Kimura[1], Tetsuji Sawada[2], Koichiro Tahara[1], Haeru Hayashi[1], Mayu Tago[1], Hiroaki Mori[1], Toshihiro Matsui[3], Jinju Nishino[4] and Shigeto Tohma[5], [1]Rheumatology, Tokyo Medical University, Tokyo, Japan, [2]Rheumatology, Tokyo Medical University, Shinjuku Tokyo, Japan, [3]Department of Rheumatology, National Hospital Organization Sagamihara Hospital, Sagamihara, Kanagawa, Japan, [4]Department of Orthopaedic Surgery, Faculty of Medicine, The University of Tokyo, Tokyo, Japan, [5]Department of Rheumatology, National Hospital Organization Sagamihara Hospital, Kanagawa, Japan

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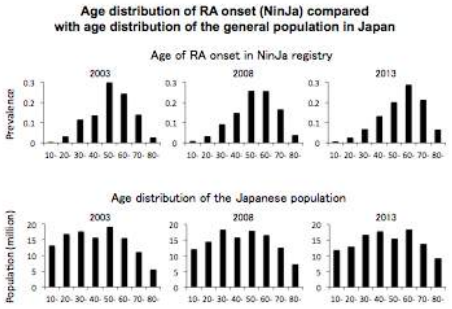
Background/Purpose: Previous studies from Western countries have demonstrated that the incidence of rheumatoid arthritis (RA) increases with age and the age of RA onset was about 59 years. However, in Japan, Imanka et al demonstrated that it increased from 37.5 years of age in the period of from 1960 to 1965 to 46.9 years of age in the period of from 1985 to 1990. Japan has faced a demographic change with a rapidly aging population in recent decades. In our experience in daily clinical practice over the past decade, we felt that we have encountered more patients who developed RA late in life than previously. In the present study, we aimed to determine whether there was a shift in the age of RA onset toward elderly onset based on a nationwide cohort database (National Database of Rheumatic Diseases by iR-net in Japan, NinJa) between 2003 and 2013.

Methods: We analyzed the data of RA patients who were newly registered in the NinJa database as early RA (disease duration of less than 2 years) in 2003, 2008 and 2013. The numbers of patients who developed RA in 2002–2003, 2007–2008 and 2012–2013 were 536, 812 and 1,864, respectively. The age composition of the Japanese population in the corresponding periods was obtained from the database of the Ministry of Internal Affairs and Communications. Student's t-test was used to compare the average ages.

Results: The average age of RA onset increased significantly over the past decade from 55.7 years in 2003 to 57.0 years and 59.9 years in 2008 and 2013, respectively. Regarding the distribution of the age of RA onset, the peak age shifted from the 50s in 2003 to the 60s in 2013 (Figure). There was no difference in the age of RA onset between male and female RA patients. It should also be noted that the

prevalence of RA was disproportionately higher in persons in their 50s in 2003, which included the so-called first baby boomers who were born after the world war, compared with persons in their 30s and 40s, even with consideration of the shift in age distribution of the general population.

Conclusion: We have clearly demonstrated that the age of RA onset has significantly increased over the last decade in Japan. This may be attributed to the increase in the aging population, as a birth cohort effect. However, the smoking rate is higher among the first baby boomers than among persons of the following generations. Thus, in addition to the birth cohort effect, alteration of environmental factors, such as cigarette smoking, may contribute to the shift of age of RA onset in Japan.



Disclosure: E. Kimura, None; **T. Sawada**, None; **K. Tahara**, None; **H. Hayashi**, None; **M. Tago**, None; **H. Mori**, None; **T. Matsui**, None; **J. Nishino**, None; **S. Tohma**, None.

Abstract Number: 1212

Investigation of Vitamin D Supplement Use, Rheumatoid Arthritis-Related Autoimmunity and Joint Signs Among Those at Increased Risk for the Development of Rheumatoid Arthritis

Elizabeth A. Bemis[1], Ryan W. Gan[2], Marie L. Feser[3], Michael H. Weisman[4], James R. O'Dell[5], Ted R. Mikuls[5], Jane H. Buckner[6], Peter K. Gregersen[7], Richard M. Keating[8], M. Kristen Demoruelle[9], Kevin D. Deane[10], V. Michael Holers[11] and Jill M. Norris[12], [1]Epidemiology, Epidemiology, Colorado School of Public Health, Aurora, CO, [2]Colorado School of Public Health, University of Colorado Denver, Aurora, CO, [3]Division of Rheumatology, University of Colorado School of Medicine, Aurora, CO, [4]Rheumatology, Cedars-Sinai Medical Center, Los Angeles, CA, [5]University of Nebraska Medical Center, Omaha, NE, [6]Benaroya Research Institute at Virginia Mason, Seattle, WA, [7]Feinstein Insititute for Medical Research, Manhasset, NY, [8]Division of Rheumatology, Scripps Health, La Jolla, CA, [9]Rheumatology, University of Colorado School of Medicine, Aurora, CO, [10]Division of Rheumatology, U Colo Denver, Aurora, CO, [11]Rheumatology Division, Univ of Colorado School of Med, Aurora, CO, [12]University of Colorado Denver, Aurora, CO
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Background/Purpose: Vitamin D has immunomodulatory properties, and could be a protective factor against rheumatoid arthritis (RA). Anti-cyclic citrullinated peptide (anti-CCP) autoantibodies and swollen small joints of the hand (wrist and metacarpophalangeal [MCP] joints) are characteristics of RA that can be present years prior to the development of classifiable RA by established criteria. We investigated the associations between anti-CCP2 positivity and swollen joint symptoms with self-reported vitamin D supplement use in a population without RA, but at risk for development of RA.

Methods: The multicenter Studies of the Etiology of RA (SERA) cohort study recruited subjects who are classified as RA-free at visit,

but at increased genetic and/or family risk for RA. At baseline, we assessed the association between self-reported vitamin D supplement use over the past year and presence of the two preclinical outcomes, anti-CCP2 positivity and having >= 1 swollen wrist and/or MCP joint. Three vitamin D exposure variables were created including a yes or no response, source of vitamin D (none, multivitamin or single supplement), and total months of use (0 months, 1-12 months or >12 months [i.e. those taking more than one vitamin D supplement]). These self-reported variables were found to be associated with 25-hydroxyvitamin D (25OHD) plasma concentrations that were available in a subset of the study population. Logistic regression models were used to estimate the independent association between the three exposure variables and the two outcomes, adjusting for age, sex, race, shared epitope, current smoking, cohort (first degree relative vs not), site of recruitment and use of other supplements.

Results: The analysis cohort (n=2,383 at-risk subjects) was 69% female, 80% non-Hispanic white, with a mean age of 44.6 years. We identified 44 anti-CCP2 subjects and 57 subjects with >= 1 swollen joint at baseline. Vitamin D supplement use was not associated with anti-CCP2 positivity (Table). A marginally significant association was seen with joint signs, where those with >= 1 swollen joint were about half as likely to have been taking vitamin D supplements in the previous year (Table).

Table: Odds ratios (OR) for anti-CCP2 positivity and >=1 swollen joint in relation to each vitamin D exposure variable.

	Outcome			
	Anti-CCP2 n=44 positive subjects		**>= 1 swollen joint*** n=57 positive subjects	
Any Vitamin D Supplement	**OR (95% CI)**	**p-value**	**OR (95% CI)**	**p-value**
No	1.00	Ref	1.00	Ref
Yes	1.92 (0.47-7.92)	0.37	0.47 (0.22-1.01)	0.07
Vitamin D Source				
No vitamin D supplement	1.00	Ref	1.00	Ref
From a Multivitamin only	1.80 (0.43-7.55)	0.42	0.47 (0.22-1.04)	0.08
From a Single supplement containing vitamin D	2.37 (0.49-11.43)	0.28	0.47 (0.17-1.32)	0.19
Vitamin D Duration				
0 Months (no vitamin D supplement)	1.00	Ref	1.00	Ref
1-12 Months	1.15 (0.26-5.05)	0.85	0.46 (0.22-1.05)	0.07
>12 Months	2.45 (0.46-13.08)	0.29	0.45 (0.14-1.38)	0.16

Adjusted for age, sex, race, cohort, recruitment site, current smoking status, Shared Epitope, and other supplement use.

*The sample size for the joint outcome analysis is n=1955, which is reduced because our off-site visits did not include a joint examination.

Conclusion: Vitamin D supplement use was not associated with RA-related autoimmunity in at-risk subjects. An inverse trend between joint signs and vitamin D supplement use suggests the need for further research to examine the role of vitamin D in the later stages of pre-clinical RA.

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Abstract Number: 1213

Prospective Study of Dietary Patterns and Risk of Rheumatoid Arthritis in Women

Bing Lu[1], Yang Hu[2], Jeffrey A. Sparks[3], Karen H. Costenbader[4], Frank Hu[5] and Elizabeth W. Karlson[1], [1]Division of Rheumatology, Immunology and Allergy, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, [2]Nutrition, Harvard School of Public Health, Boston, MA, [3]Division of Rheumatology, Immunology, and Allergy, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, [4]Rheumatology, Immunology and Allergy, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, [5]Harvard School of Public Health, Boston, MA

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Background/Purpose: Although some individual dietary factors have been identified to be associated with the development of rheumatoid arthritis (RA), few studies have examined the effects of overall eating patterns on RA. We examined overall dietary patterns in relation to the risk of RA in a large prospective cohort, the Nurses' Health Study II (NHSII).

Methods: We prospectively followed 93,859 women free of RA at baseline who provided dietary data from 1991 to 2011 in the NHS II. Dietary data were obtained from validated food frequency questionnaires in 1991 and every 4 years during follow-up. Two dietary patterns were identified using principal component analysis: the Prudent dietary pattern characterized by high intakes of fruit, vegetables, legumes, whole grains, poultry, and fish; the Western pattern characterized by high intakes of red meats, processed meats, refined grains, French fries, desserts and sweets, and high-fat dairy products. The cumulative average pattern scores over time were categorized into quartiles. Incident RA cases were validated by medical record review. Time-varying Cox proportional hazards models were used to calculate hazard ratios (HR) after adjusting for age, census-track income, smoking, body mass index (BMI), total calories, alcohol use and physical activity.

Results : During 1,509,033 person-years of follow-up, 626 incident cases of RA developed with the mean diagnosis age of 49. In the multivariable adjusted model, the Prudent pattern was associated with a reduced risk of RA, while the Western pattern was associated with an increased risk of RA (Table). The HRs (95% CI) across increasing quartiles of the Prudent pattern score were 1.00, 0.81(0.60,1.09),0.69(0.51,0.95), and 0.71(0.52,0.98) (p trend 0.04), and for the Western pattern, HRs ((95% CI) were 1.00, 1.41(1.01,1.98), 1.61(1.14,2.27), and 1.57(1.09,2.67) (p trend 0.03). After additional adjustment for BMI, the associations were attenuated.

Conclusion: In this female cohort study, dietary patterns were association with RA risk. A negative association was found between a Prudent diet rich in fruit, vegetables, and fish, and the risk of RA, whereas a positive association was found between a Western diet rich in refined grains, processed and red meats, desserts, and French fries, and the risk of RA. Further analysis of BMI as a potential confounder or mediator of these associations is warranted.

Table. Hazard ratios (95% CIs) of rheumatoid arthritis according to dietary pattern scores in the Nurses' Health Study II (1991-2011)[1]

	Dietary pattern scores (quartiles)				p for trend[2]
	Q1	Q2	Q3	Q4	
Prudent Pattern					
Cases/ Person-years	93 / 368,986	84 / 379,428	77 / 382,024	87 / 378,595	
Age-adjusted HR (95% CI)	1.00	0.81(0.60,1.09)	0.72(0.53,0.97)	0.78(0.58,1.05)	0.11
Multivariable HR (95% CI)[3]	1.00	0.81(0.60,1.09)	0.69(0.51,0.95)	0.71(0.52,0.98)	0.04
Multivariable HR (95% CI)[4]	1.00	0.82(0.60,1.10)	0.72(0.52,0.98)	0.74(0.54,1.02)	0.08
Western Pattern					
Cases/ Person-years	60/371125	85/378,206	97/381,583	99/378,119	
Age-adjusted HR (95% CI)	1.00	1.40(1.00,1.94)	1.60(1.16,2.21)	1.70(1.23,2.34)	<0.01
Multivariable HR (95% CI)[3]	1.00	1.41(1.01,1.98)	1.61(1.14,2.27)	1.57(1.09,2.67)	0.03
Multivariable HR (95% CI)[4]	1.00	1.35(0.96,1.90)	1.49(1.06,2.11)	1.40(0.96,2.03)	0.13

[1]Hazard ratios were calculated by using time-varying Cox proportional hazards models.

[2]p for trend was derived from tests of linear trend across categories of dietary pattern scores by treating the median value of each category as a continuous variable.

[3] Adjusted for age, smoking (pack-years), total calories intake. Additional adjustment for census tract median family income, alcohol use and physical activity did not change the statistical significance.

[4]Additional adjustment for BMI (kg/m^2; <25, 25–29.9, or ≥30).

Disclosure: B. Lu, None; **Y. Hu**, None; **J. A. Sparks**, None; **K. H. Costenbader**, None; **F. Hu**, None; **E. W. Karlson**, None.

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Abstract Number: 1214

Rheumatoid Arthritis in Female Spouses in the Agricultural Health Study:

Associations with Pesticides and Other Farm Exposures

Christine G. Parks[1], Jane Hoppin[2], Karen H. Costenbader[3] and Dale Sandler[4], [1]Epidemiology Branch, National Institute of Environmental Health Science, Research Triangle Park, NC, [2]Biological Sciences, North Carolina State University, Raleigh, NC, [3]Rheumatology, Immunology and Allergy, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, [4]Epidemiology Branch, NIH/NIEHS, Research Triangle Park, NC

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Background/Purpose: Farming has been associated with rheumatoid arthritis (RA), but the role of pesticides is not known. We examined associations between RA, pesticides and other exposures among female spouses of licensed pesticide applicators in the Agricultural Health Study.

Methods: Women were enrolled 1993-1997 and followed through 2010. RA cases (n=275 total, 132 incident) were confirmed by a physician or self-reported use of specific disease modifying anti-rheumatic drugs, and were compared with non-cases (n=24,019) who never reported RA. Pesticide use was self-reported at enrollment. We estimated odds ratios (OR) and 95% Confidence Intervals (CI) using logistic regression models adjusted for age, state (NC/IA) and smoking pack-years.

Results: A suggestive association with RA was seen for use of any pesticides (overall OR=1.2; 95%CI 0.97, 1.6; incident only OR=1.4; 95%CI 0.99, 2.1). Of 15 pesticides examined, higher RA risk was associated with the fungicide maneb/mancozeb (OR=3.3; 95%CI 1.5, 7.1) and the herbicide glyphosate (OR=1.4; 95%CI 1.0, 2.1). Elevated (OR ≥1.5) but non-significant associations were seen for RA with the insecticides permethrin and DDT and the fungicide captan. DDT was significantly associated with RA in women who grew up on a farm (65% of cases, 61% of non-cases; OR=2.0; 95%CI 1.0, 4.2). RA risk was also associated with chemical fertilizers (OR=1.7; 95%CI 1.1, 2.7) and solvents for cleaning (OR=1.6; 95%CI 1.1, 2.4), but inversely associated with livestock exposure both as a child and adult (OR=0.48; 95%CI 0.24, 0.98) compared with no animal exposure.

Conclusion: Our results suggest that specific agricultural pesticide and fertilizer exposures may increase risk of RA in women, while others related to animal handling may be protective. These findings warrant replication and future studies including information on timing of exposures.

Abstract Number: 1215

Air Pollution and the Rheumatic Diseases: A Systematic Review and Meta-Analysis

Gavin Sun[1], Glen Hazlewood[2], Sasha Bernatsky[3], Gilaad Kaplan[4], Bertus Eksteen[5] and Cheryl Barnabe[2], [1]Department of Internal Medicine, University of Calgary, Calgary, AB, Canada, [2]Division of Rheumatology, University of Calgary, Calgary, AB, Canada, [3]Rheum/Clin. Epid., McGill MUHC/RVH, Montreal, QC, Canada, [4]Division of Gastroenterology, University of Calgary, Calgary, AB, Canada, [5]Division of Hepatology, University of Calgary, Calgary, AB, Canada

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Background/Purpose: Environmental risk factors, such as air pollution, have been studied in relation to the risk of development of

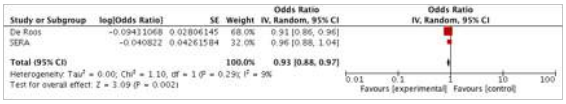
rheumatic diseases, including rheumatoid arthritis (RA), systemic autoimmune rheumatic diseases (SARDs), vasculitis and juvenile idiopathic arthritis (JIA). We have performed a systematic literature and meta-analysis to summarize the existing knowledge.

Methods: Medline (1950 to May 2015) and EMBASE (1980 to May 2015) databases and rheumatology conference abstracts (2012-2015) were searched using MeSH terms and keywords to identify cohort and case-control studies reporting risk estimates (hazard ratios, relative risks, odds ratios) for the development of select rheumatic diseases in relation to exposure to measured air pollutants. Meta-analysis was completed using the generic inverse-variance approach with random effects models using RevMan version 5.3.

Results: A total of 103 non-overlapping publications were identified of which 20 underwent full-text review, with 9 studies included in qualitative synthesis and 2 studies used for meta-analysis. Three studies included subjects with RA (one cohort study, two case-control studies) and examined associations with exposure to nitrogen dioxide (NO_2), sulfur dioxide (SO_2) and particulate matter up to 10 micrometers in size (PM_{10}). An association with particulate matter up to 2.5 micrometers in size ($PM_{2.5}$) was studied in the RA cohort study, and additional pollutants (carbon monoxide, nitrous oxide, ozone and black carbon) in one case-control study. In the RA cohort study, there was no definite evidence for increased RA risk related to NO_2, SO_2, PM_{10} or $PM_{2.5}$ exposures. In the case-control studies, there was no evidence of an increased risk for the development of RA with exposure to NO_2 (pooled OR 0.93, 95%CI 0.86 to 1.01) or SO_2 (pooled OR 0.94, 95%CI 0.82 to 1.08), but possibly a protective effect with exposure to PM_{10} (pooled OR 0.93, 95%CI 0.88 to 0.97, Figure 1). Both case-control studies in SARDs indicated higher odds of having SARDs in relation to increasing $PM_{2.5}$ exposure. Two studies examined vasculitis conditions (ANCA vasculitis and PM_{10} exposure, Kawasaki Disease and $PM_{2.5}$ exposure) but were unable to draw definitive conclusions regarding associations. One study of found an increased relative risk for JIA related to $PM_{2.5}$ exposure but only in American children <5.5 years of age; the results were inconclusive when studying a broader JIA population in America and Canada.

Conclusion: The existing studies do not support an association between air pollutant exposures and the development of RA, SARDs, or vasculitis, and uncertain effects in JIA. The measurement of cumulative and time-varying exposures are important considerations for future studies.

Figure 1. Meta-Analysis of Association Between RA Development and PM_{10} Exposure



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Abstract Number: 1216

The Clinical and Ultrasonographic Presentation of Seronegative RA Is More Severe Compared to Seropositive RA in an Inception Cohort of DMARD-Naïve Patients Classified According to the 2010 ACR/EULAR Criteria

Lena B. Nordberg[1], Siri Lillegraven[1], Elisabeth Lie[1], Anna-Birgitte Aga[2], Inge C Olsen[2], Hilde Berner Hammer[3], Till Uhlig[1], Désirée van der Heijde[4], Tore K. Kvien[1], Espen A. Haavardsholm[1] and the ARCTIC Study Group, [1]Dept. of Rheumatology, Diakonhjemmet Hospital, Oslo, Norway, [2]Department of Rheumatology, Diakonhjemmet Hospital, Oslo, Norway, [3]Dept of Rheumatology, Diakonhjemmet Hospital, Oslo, Norway, [4]Dept. of Rheumatology, Leiden University Medical Center, Leiden, Netherlands
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Background/Purpose: The development of the 2010 ACR/EULAR classification criteria for rheumatoid arthritis (RA) has led to a

redefinition of the patient population, including classification of seropositive versus seronegative patients. Studies have yielded conflicting results on whether seropositive and seronegative RA represent different disease entities.

Our aim was to compare the disease characteristics of seropositive and seronegative DMARD-naïve early RA patients classified according to the 2010 ACR/EULAR criteria.

Methods: RA patients who fulfilled the 2010 ACR/ EULAR classification criteria were recruited at 11 rheumatology centers between 2010 and 2013. All patients had symptom duration (from first swollen joint) <2 years, and were DMARD naïve with indication for DMARD treatment.

Patients were stratified as seropositive (rheumatoid factor (RF)+, anti-citrullinated peptide antibody (ACPA)+, or both) or seronegative (both RF- and ACPA-) and disease characteristics were compared across the groups using t-test or Mann-Whitney U test as appropriate.

Results: A total of 237 patients were included with mean (SD) age 51.5 (13.7) years, median [25-75 percentiles] disease duration 5.7 [2.8-10.2] months and 61.6% female gender. Thirty-five patients (14.8%) were seronegative.

The seronegative patients were older (mean age 56.9 yrs) than seropositive patients (50.5 yrs, p=0.01), while gender distribution was similar. 43% of the seronegative patients and 31% of the seropositive patients did not fulfill the 1987 ACR criteria for RA (p=0.17). Ultrasonography (US) scores, number of swollen joints, DAS44 and Physician Global were significantly higher in seronegative subjects compared to seropositive. However, Richie articular index and patient reported outcome measures were similar between groups.

	Seronegative RA n=35	**Seropositive RA** n=202	**p**
Disease duration[1], months	4.5 [2.5-10.5]	6.0 [3.0-10.0]	0.37
DAS[2, 4]	3.9 (1.1)	3.4 (1.1)	**0.02**
PD score[1, 3]	14 [7-29]	6 [2-12]	**<0.001**
GS score[1, 3]	36 [21-52]	16 [10-24]	**<0.001**
Tot US score[1, 3]	62 [34-70]	22 [14-36]	**<0.001**
SJC[1]	18 [11-25]	8 [4-13]	**<0.001**
CRP[1], mg/L	9 [5-34]	7 [3-18]	0.15
ESR[1], mm/hr	15 [10-30]	20 [12-32]	0.40
Ritchie Articular Index[1]	8 [3-16]	7 [4-12.5]	0.54
Physician Global[2], mm	52.1 (20.9)	38.2 (20.0)	**<0.001**
Patient Global[2], mm	52.1 (27.3)	49.2 (23.7)	0.53
EQ-5D[1]	0.59 [0.06-0.73]	0.66 [0.23-0.72]	0.22
Pain VAS[2], mm	47.7 (27.0)	47.7 (23.5)	>0.99
Fatigue VAS[2], mm	41.6 (30.1)	40.0 (28.8)	0.78
RAID score[2]	4.9 (2.4)	4.4 (2.1)	0.21

[1]Median [25-75 percentiles]. [2]Mean(SD). [3]US examinations were performed by experienced sonographers using a validated gray-scale (GS) and power-Doppler (PD) semi-quantitative scoring system with ranges 0-3 for GS and PD in 32 joints. [4] Original DAS-ESR based on 44-SJC and Ritchie articular index.

Conclusion: In this cohort of DMARD naïve early RA patients classified according to the 2010 ACR/ EULAR criteria, only 15% of patients were seronegative. We found that the seronegative patients had higher disease activity, assessed both clinically and by US, than

seropositive patients. This may in part be due to the strong weighting of RF and ACPA status in the 2010 criteria, requiring seronegative patients to have involvement of many joints, and thus high disease activity, to fulfill the criteria.

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Abstract Number: 1217

Phenome-Wide Association Study of Novel Anti-Citrullinated Peptide Antibodies in Rheumatoid Arthritis

Katherine Liao[1], Jeffrey A. Sparks[1], Boris Hejblum[2], I-Hsin Kuo[1], Jing Cui[1], Lauren J. Lahey[3], Andrew Cagan[4], Vivian Gainer[4], Weidong Liu[5], Tony Cai[6], Jeremy Sokolove[7] and Tianxi Cai[2], [1]Division of Rheumatology, Immunology, and Allergy, Brigham & Women's Hospital, Boston, MA, [2]Biostatistics, Harvard School of Public Health, Boston, MA, [3]Medicine, VA Palo Alto HealthCare System and Stanford University, Palo Alto, CA, [4]Research Computing, Partners HealthCare, Charlestown, MA, [5]Institute of Natural Sciences, Shanghai Jiao Tong University, Shanghai, China, [6]Statistics, University of Pennsylvania, Philadelphia, PA, [7]Medicine, VA Palo Alto Health Care System and Stanford University, Palo Alto, CA

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Background/Purpose:

RA patients develop autoantibodies against a spectrum of antigens. However, the clinical significance of these autoantibodies after RA diagnosis is unclear. The Phenome-Wide Association Study (PheWAS) is one approach to studying the clinical significance of novel biomarkers. The PheWAS was designed to analyze biomarker data linked with electronic medical records (EMR), allowing for high-throughput screening of potential associations between biomarkers and phenotypes. Using the PheWAS approach, we examined the association between variations in autoantibodies and subphenotypes of RA.

Methods:

We conducted this study in an electronic medical record (EMR) based RA cohort with patients from 2 large academic institutions. Using a validated multiplex bead assay, we measured 36 autoantibodies targeting epitopes from 10 antigens (citrullinated & non-citrullinated) implicated in RA (Figure). We extracted all unique ICD9 codes for each subject. ICD9 codes were then grouped using a published method into disease categories or PheWAS codes. For example, Felty's syndrome (ICD9 714.1) was included in the 'RA' PheWAS code along with RA (ICD9 714.0), while juvenile idiopathic arthritis (ICD9 714.3) was not. Autoantibody data were grouped by antigen target, e.g. fibrinogen. We studied all PheWAS codes with ≥3% prevalence in the cohort. Association analyses were performed between each autoantibody group and all PheWAS codes, adjusting for age, gender, race and correlation between individual autoantibody tests. A false discovery rate (FDR) <0.1 was considered significant. For significant associations, we reviewed the medical records of 50 subjects with each PheWAS code to determine the positive predictive value (PPV) of the PheWAS code.

Results:

We studied 1006 RA subjects, mean age 61 years (SD 12.9) and 79% female. The RA cohort had 3,568 unique ICD9 codes grouped into 625 PheWAS codes; 206 PheWAS codes had a prevalence of ≥3%. The PheWAS grouped by autoantibody target identified 13 associations with FDR<0.1 (Figure). Among the associations, the PheWAS code with the highest PPV (96%) on chart review was 'Other alveolar and parietoalveolar pneumopathy', which included diagnoses of cryptogenic organizing pneumonia, obliterative bronchiolitis, lipoid pneumonia, and alveolitis. These data suggest a link between autoantibodies targeting fibrinogen, both citrullinated & non-citrullinated, with chronic inflammatory lung diseases ($p=2.6x10^{-4}$) in RA.

Conclusion:

We demonstrated the application of a bioinformatics method, the PheWAS to screen for the clinical significance of novel autoantibodies in RA. The PheWAS identified a potential link between autoantibodies targeted at fibrinogen and inflammatory lung conditions in RA. These findings are of particular interest since pulmonary disease is recognized as a major cause of mortality in RA.

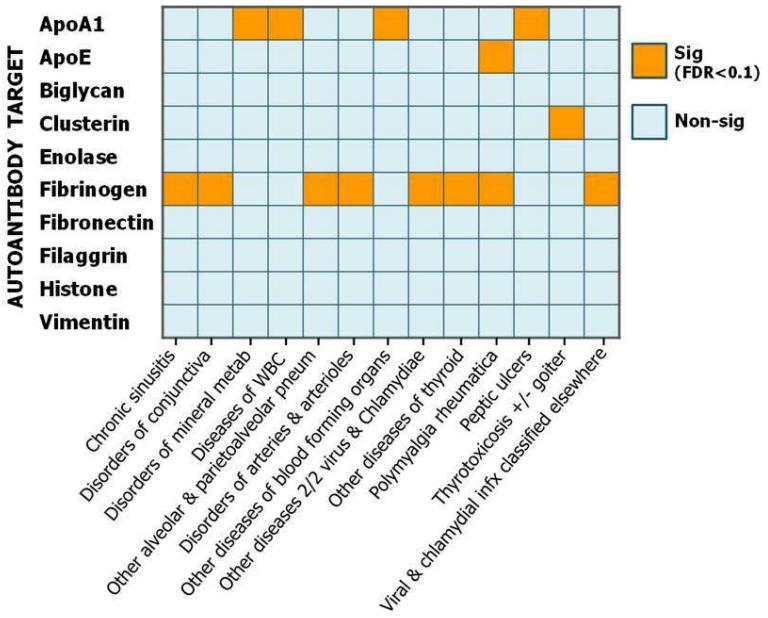

Figure. Results from PheWAS analysis of autoantibodies grouped by antigen target in an RA cohort.

Disclosure: K. Liao, None; **J. A. Sparks**, None; **B. Hejblum**, None; **I. H. Kuo**, None; **J. Cui**, None; **L. J. Lahey**, None; **A. Cagan**, None; **V. Gainer**, None; **W. Liu**, None; **T. Cai**, None; **J. Sokolove**, Novimmune, 5; **T. Cai**, None.

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Abstract Number: 1218

Higher Education Is Associated with a Better Rheumatoid Arthritis Outcome Concerning Pain and Function but Not Disease Activity: Results from Swedish Registers

Xia Jiang[1], Maria Sandberg[2], Saedis Saevarsdottir[3], Lars Alfredsson[4], Lars Klareskog[5] and Camilla Bengtsson[6], [1]Karolinska Institutet, Stockholm, Sweden, [2]Unit of Cardiovascular Epidemiology, Institute of Environmental Medicine, Karolinska Institutet, Karolinska Institutet, Stockholm, Sweden, [3]Rheumatology Unit, Karolinska University Hospital, Karolinska Institutet, Stockholm, Sweden, [4]Unit of Cardiovascular Epidemiology, Institute of Enviornmental Medicine, Karolinska Institutet, Karolinska Institutet, Stockholm, Sweden, [5]Rheumatology Unit, Karolinska University Hospital, Stockholm, Sweden, [6]The Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden

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Background/Purpose:

To investigate the influence of education (achieving university/college degree (high) or not (low)) on the outcomes of early RA, in terms of disease activity, pain, and functional impairment.

Methods:

We used DMARD-naïve RA patients recruited in the Epidemiological Investigation of RA (EIRA) study with outcomes followed in the Swedish Rheumatology Quality (SRQ) register (N=3021). Outcomes were categorized in three ways: 1) scores equal to/above median *vs.* below median; 2) DAS28-based low disease activity, good response, remission; 3) scores decreased over the median *vs.* less than median. Associations between education and outcomes were calculated by Poisson regressions, at diagnosis and at each of the three (3, 6, 12 months) follow-up visits.

Results:

High and low educated patients had similar symptom durations (195 days) and anti-rheumatic therapies at baseline, and comparable treatment patterns during follow-up. Higher educated patients had less pain, less functional disability at baseline and throughout the whole follow-up period (VAS-pain: baseline: 49 (28-67) *vs.* 53 (33-71), p<0.0001; 1-year-visit: RR=0.81 (95% CI 0.73-0.90). HAQ: baseline: 0.88 (0.50-1.38) *vs.* 1.00 (0.63-1.50), p=0.001; 1-year-visit: 0.84 (0.77-0.92)). They also had greater chances to achieve pain remission (VAS-pain≤20) after one year (1.17 (1.07-1.28)). Adjustments for smoking and BMI altered the results only marginally. Education did not influence DAS28-based outcomes.

Conclusion:

In Sweden, with tax-financed, general health-care system, higher educated RA patients experienced less pain, less functional disability, and achieved pain remission more often during the first year receiving standard care. Education affected neither time to referral to rheumatologists nor anti-rheumatic treatments.

Disclosure: X. Jiang, None; **M. Sandberg**, None; **S. Saevarsdottir**, None; **L. Alfredsson**, None; **L. Klareskog**, None; **C. Bengtsson**, None.

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Abstract Number: 1219

Prevalence and Clinical Characteristics of Rheumatoid Arthritis in Poland: First Nationwide Study

Bogdan Batko[1], Marcin Stajszczyk[2], Jerzy Swierkot[3], Filip Raciborski[4] and Piotr Wiland[3], [1]Rheumatology, J. Dietl Specialist Hospital, Krakow, Poland, [2]Department of Reumatology and Autoimmune Diseases, Silesian Rheumatology Center, Ustron, Poland, [3]Department of Rheumatology and Internal Medicine, Wroclaw Medical University, Wroclaw, Poland, [4]Department of Epidemiology and Health Promotion, Institute of Rheumatology, Warsaw, Poland

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Background/Purpose:

The prevalence of rheumatoid arthritis (RA) in Europe varies from a geographical standpoint. Knowledge of the occurrence of RA is valuable for policy makers and health professionals. There are no reliable data regarding the prevalence of RA in Poland.

Methods:

The study consists of two independent stages. The first stage is a survey on a nationwide representative sample of 3000 people (ages 15 and over), covering RA related symptoms, risk factors, and treatment. The questionnaire is validated for Polish RA population. The second stage of the study is a survey for characteristics of RA patients evaluated by a retrospective analysis of a group of 1957 RA patients in routine clinical practice.

Results:

The overall RA prevalence in Poland was 0.9% (95% CI 0.6-1.2%), 1.06% in women, 0.74% in men. A total of 1957 patients with RA were analyzed: 78% were female, mean age 56, and mean disease duration approximately 7 years. The most frequently associated diseases were: hypertension, 49%; ischemic heart disease, 22%; diabetes, 17%; interstitial lung disease, 7%. The ratio of employed to unemployed patients from the ages of 51-60 was almost 1:1; however, younger patients (<50) remained professionally active in approximately 90% of cases. Over 30% of patients were diagnosed within 3 months of first RA symptoms, while for 16% of patients diagnosis took more than one year. 56% of newly diagnosed patients were characterized by a high disease activity of DAS-28>5.1. Presently, low disease activity of DAS-28<3.2 could be found in approximately 40% of patients; however, there was still a majority with DAS-28>3.2. In Poland, 94% of patients have been treated with NSAID (Nonsteroidal anti-inflammatory drugs), and diclofenac was most frequently prescribed. Almost 80% of patients have been treated with glucocorticoids, and 56% of patients have continued with this treatement. Our study confirms that Methotrexate is an anchor drug in Poland.

Conclusion:

This is the first cross-sectional population-based epidemiological study regarding RA in the adult Polish population. The results demonstrate a high prevalence of RA, however they fall within the upper bound estimates for Europe. Retrospective analysis of RA patients indicates that despite ongoing treatment, the majority still have moderate to high disease activity.

Disclosure: B. Batko, None; **M. Stajszczyk**, None; **J. Swierkot**, None; **F. Raciborski**, None; **P. Wiland**, None.

Abstract Number: 1220

Oral Glucocorticoid Prescribing Patterns in UK Primary Care for Patients with Rheumatoid Arthritis

Rachel J Black[1,2], Rebecca M Joseph[3,4], Mohammad Movahedi[2], Mark Lunt[2] and **William G Dixon**[2,5], [1]Department of Medicine, The University of Adelaide, Adelaide, Australia, [2]Manchester Academic Health Sciences Centre, Arthritis Research UK Centre for Epidemiology, The University of Manchester, Manchester, United Kingdom, [3]Manchester Academic Health Science Centre, Arthritis Research UK Centre for Epidemiology, The University of Manchester, Manchester, United Kingdom, [4]NIHR Manchester Musculoskeletal Biomedical Research Unit, Manchester, United Kingdom, [5]Manchester Academic Health Sciences Centre, Health e-Research Centre, Farr Institute for Health Informatics Research, The University of Manchester, Manchester, United Kingdom

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Background/Purpose:

Oral glucocorticoids (GCs) are commonly used in the treatment of rheumatoid arthritis (RA). Although GPs don't typically alter DMARD prescriptions, changes to GC therapy are commonly made in primary care. It is important to assess how GCs are used in this setting, including variability in dose and duration of treatment, so that rheumatologists understand how their patients are being treated. The objective of this study was to describe the patterns of GC prescribing for patients with RA in primary care.

Methods:

Patients with incident RA were identified from the Clinical Practice Research Datalink, a large UK general practice database. For patients who received GCs, the mean, minimum and maximum prednisolone equivalent doses were calculated. To determine the population distribution, the median of these values across all treated patients was then calculated. A GC course was defined as back-to-back GC prescriptions where the end date of the first prescription was not more than one calendar day different from the start date of the next prescription. The median number of courses per year was then determined. The proportion of patients to receive greater than 5mg, 10mg, 20mg, 30mg, 50mg and 75mg per day was determined as was the proportion of total time on GCs these doses were prescribed for.

Results:

Of the 16 536 patients with incident RA, 7749 patients (47%) received at least one GC prescription during the follow up period. The mean

duration of follow up was 4.8 years per patient. In GC users, the median proportion of time spent on GCs was 24.3% (IQR 36.2%-64.2%). Of those receiving GCs, the population distribution was a median of 7.5mg per day (IQR 5-15.7mg) for the mean dose, 5mg per day (IQR 2.5-7.5mg) for the minimum dose and 15mg per day (IQR 7.5-30mg) for the maximum dose.

Of those that received GCs, the median number of courses per year was 1.4 (IQR 0.4-3.0) and 39.4% received more than 2 GC courses per year. The median duration of each GC course was 46 days (IQR 28-81).

Of those that were prescribed GCs during follow up, 79.9% received a prednisolone equivalent daily dose of more than 5mg per day and 56.2% received more than 10mg per day. 38.2% received more than 20mg per day, 17.3% received more than 30mg per day, 3.5% received more than 50mg per day and 1.4% received more than 75mg per day. The median proportion of total time on GCs that patients received these doses is shown in the table below.

	Proportion of total time on GCs (%)
Dose per day	Median (IQR)
>5mg	58.0 (19.5-100)
>10mg	25.7 (5.5-100)
>20mg	20.0 (3.2-100)
>30mg	12.7 (2.3-66.7)
>50mg	5.6 (1.0-24.1)
>75mg	5.9 (1.0-28.8)

Conclusion: Half the patients with incident RA were prescribed GCs in primary care. They received GCs for 25% of the time they were observed. Of those who received GCs, 80% received doses greater than 5mg per day and 40% more than 20mg/day. Patients spent 60% of their total duration on GCs taking doses greater than 5mg per day. The extent of GC prescribing for RA patients in primary care may be surprising to many rheumatologists and highlights the need to be aware of GC use in this setting in order to avoid excess exposure and associated side effects.

Disclosure: R. J. Black, None; **R. M. Joseph**, None; **M. Movahedi**, None; **M. Lunt**, None; **W. G. Dixon**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/oral-glucocorticoid-prescribing-patterns-in-uk-primary-care-for-patients-with-rheumatoid-arthritis

Abstract Number: 1221

Characteristics and Outcomes of RA Patients Who Start Biosimilar Infliximab in South Korea

Yoon-Kyoung Sung[1], Soo-Kyung Cho[1], Soyoung Won[2], Chan-Bum Choi[3], So-Young Bang[4], Seung-Jae Hong[5], Hyoun-Ah Kim[6], Eunmi Koh[7], Hye-Soon Lee[8], Chang-Hee Suh[9], Dae-Hyun Yoo[10], Sang-Cheol Bae[1] and BIOPSY investigators, [1]Department of Rheumatology, Hanyang University Hospital for Rheumatic Diseases, Clinical Research Center for Rheumatoid Arthritis (CRCRA), Seoul, South Korea, [2]Clinical Research Center for Rheumatoid Arthritis (CRCRA), Seoul, South Korea, [3]Hanyang University Hospital for Rheumatic Diseases, Clinical Research Center for Rheumatoid Arthritis (CRCRA), Seoul, South Korea, [4]Hanyang University Guri Hospital, Guri, South Korea, [5]Division of Rheumatology, Department of Internal Medicine, Kyung Hee University Hospital, Seoul, South Korea, [6]Ajou University Hospital, Suwon, South Korea, [7]Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea, [8]Department of Rheumatology, Hanyang University Guri Hospital, Guri, South Korea, [9]Department of Rheumatology, Ajou University Hospital, Suwon, South Korea, [10]Department of Rheumatology, Hanyang University Hospital for Rheumatic Diseases, Seoul, South Korea

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Background/Purpose: Recently biosimilar infliximab was approved in South Korea and it has been commonly used for rheumatoid

arthritis (RA) patients who are resistant to conventional DMARDs. The biosimilar infliximab have been shown to be equivalent to original infliximab in equivalent efficacy and safety in RA through several clinical trials, but its effectiveness and safety in daily practice has not yet been reported. This study aims to compare the characteristics of RA patients who use biosimilar infliximab with those of patients who start original infliximab and to identify the effectiveness and safety of biosimilar infliximab for RA patients in clinical practice.

Methods: Using the prospective biologic DMARDs registry in Korea: BIOlogics Pharmacoepidemiologic StudY (BIOPSY), we selected RA patients who started either biosimilar or original infliximab. Baseline characteristics including sociodemographics, disease activity, previous or concurrent medications, and comorbidities of two groups were compared. Treatment outcomes such as DAS28-ESR and HAQ-DI scores observed in 6 or 9 months after starting infliximab were compared between two groups. Drug retention rates of both groups were also compared using Kaplan-Meier analysis and the reasons of discontinuation were described in each group.

Results: A total of 98 RA patients who started either original or biosimilar infliximab were included in this analysis; 52 for biosimilar infliximab users (33.8 PY) and 46 of original infliximab users (50.2 PY). Baseline characteristics of two groups were quite similar in age, disease duration, and previous or current medications. Although baseline DAS28-ESR and HAQ-DI scores were not differed between two groups, swollen joints count was lower in biosimilar users than original users (6.1 ± 4.9 vs. 8.2 ± 5.4, *P*=0.05). Biologics-naïve patients were more common in biosimilar users but not significant statistically (92.3 % vs. 84.8 %, *P*=0.39). Early DAS28-ESR remission rate observed in 6 or 9 months after starting biosimilar and original infliximab were 18.6% and 15.6%, respectively (*P* =0.75). HAQ-DI changes were not different between two groups (0.4 ± 0.8 vs. 0.4 ± 0.7 P=0.85). The drug retention rates during 20 months were higher in biosimilar users, but there was no statistical significance (68.4% in biosimilar users vs. 53.1% in original users, p=0.16 by log-rank test). The most common reason of drug discontinuation was ineffectiveness in both groups (61.5% in biosimilar and 68.2% in original infliximab). Discontinuation due to infusion related reaction was only one case in each group.

Conclusion: There was no significant difference in baseline characteristics of biosimilar infliximab users compared to original infliximab users in South Korea. Drug persistency of biosimilar infliximab for 20 months was comparable to that of original infliximab, and the reasons of drug discontinuation were similar between two groups.

Disclosure: Y. K. Sung, None; **S. K. Cho**, None; **S. Won**, None; **C. B. Choi**, None; **S. Y. Bang**, None; **S. J. Hong**, None; **H. A. Kim**, None; **E. Koh**, None; **H. S. Lee**, None; **C. H. Suh**, None; **D. H. Yoo**, None; **S. C. Bae**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/characteristics-and-outcomes-of-ra-patients-who-start-biosimilar-infliximab-in-south-korea

Abstract Number: 1222

The Risk of Tuberculosis (TB) in Rheumatoid Arthritis Patients Treated with TNF Inhibitors and the Safety of Resuming Biologic Dmards for Patients Who Developed TB after Anti-TNF Treatment

Soo-Kyung Cho[1], Dam Kim[1], Hye-Jin Jeong[2], Il Woong Sohn[2], Soyoung Won[3], Minkyung Han[3], Jiyoung Lee[3], Eun Jin Jang[4], Sang-Cheol Bae[1] and **Yoon-Kyoung Sung**[1], [1]Department of Rheumatology, Hanyang University Hospital for Rheumatic Diseases, Clinical Research Center for Rheumatoid Arthritis (CRCRA), Seoul, South Korea, [2]Hanyang University Hospital for Rheumatic Diseases, Seoul, South Korea, [3]Clinical Research Center for Rheumatoid Arthritis (CRCRA), Seoul, South Korea, [4]Information Statistics, Andong National University, Andong-si, South Korea

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Background/Purpose: The association between TNF inhibitor (TNFI) treatment and the development of tuberculosis (TB) has been confirmed through several observational studies. Current guidelines strongly recommend latent tuberculosis infection (LTBI) screening treatment before starting TNFI and they might reduce the risk of development of active TB in TNFI users. However, there is still limited evidence of the risk of TB in RA patients who used TNFI after introduction of LTBI screening and treatment guidelines. Moreover, the safety of resuming biologic DMARDs for RA patients who developed TB after anti-TNF treatment has not been well-known. This study aims to estimate the incidence of TB in RA patients who used TNFI after introduction of LTBI screening and treatment guidelines and to evaluate the safety of resuming biologic DMARDs for patients who developed TB after anti-TNFtreatment.

Methods: A retrospective cohort of RA patients who started TNFI was established using Korean national healthcare claims database between January 2009 and December 2013. There was 1 year wash-out period of biologic DMARDs to determine the incident users of biologic DMARDs. After excluding the patients who started biologics other than TNFI, we made an inception cohort for RA patients who started TNFI as a first biologic DMARD. Patients were followed for the development of TB or the last observational date (December 31, 2013). The development of the TB was defined as the appearance of ICD 10 code of TB plus at least 3 among 4 agents of isoniazid, rifampin, ethambutol, and pyrazinamide. Through this definition, the incidence rate (IR) per 100,000 person-year (PY) and standardized incidence ratio (SIR) of TB for TNFI starters based on total RA patients were calculated. We also classified the patients who developed TB into two groups; resuming biologic DMARD group vs. conventional DMARD group. After comparing the characteristics between two groups, the TB relapse rate among patients who resumed biologic DMARDs was estimated.

Results: We included 4,638 RA patients who had started TNFI as the first biologic DMARD, contributing 8,542 PYs of follow-up. A total of 81 patients had been developed TB infection during follow-up. The IR and the SIR of TNFI users based on total RA patients were 1,100 per 100,000 PY [860-1,340/100,000 PY, 95% confidence interval (CI)] and 2.04 (1.62-2.54, 95% CI). If we restrict the maximal follow-up period in 1 year, the IR and SIR of TNFI starters increased to 1,660/100,000 PY and 3.08, respectively. Among the 81 patients who developed TB during follow-up, 30 patients (37.0%) had continued or resumed biologic DMARDs. Mean interval between TB development and resuming biologic DMARDs was 3.3 months. Two cases of TB were developed in 30 patients with observational period of 45.7 PY.

Conclusion: The risk of TB in RA patients who start TNFI is still higher than that of total RA patients after introduction of LTBI treatment guidelines. Resuming biologic DMARDs after TB development should be undertaken with careful monitoring of TB relapse.

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Abstract Number: 1224

Infection Rate in HIV Patients Who Received TNF-a Inhibitor Therapy for Concomitant Autoimmune Diseases

Sintawat Wangsiricharoen[1], Colin Ligon[2], Ahmad Dehrab[3], Lydia Gedmintas[4], Marisa Tungsiripat[5], Clifton Bingham[6], Carlos J. Lozada[7] and Leonard H. Calabrese[8], [1]Chiang Mai University, Chiang Mai, Thailand, [2]Rheumatology, Johns Hopkins University School of Medicine, Baltimore, MD, [3]Rheumatology, University of Miami Jackson Memorial Hospital, Miami, FL, [4]Rheumatology, Brigham's Women's Hospital, Boston, MA, [5]Infectious Disease, Cleveland Clinic Foundation, Cleveland, OH, [6]Johns Hopkins University, Baltimore, MD, [7]University of Miami Miller School of Medicine, Miami, FL, [8]Rheumatic & Immunologic Dis, Cleveland Clinic Foundation, Cleveland, OH

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Background/Purpose:

Few HIV-infected patients have been treated with tumor necrosis factor (TNF)-α inhibitor therapy for autoimmune diseases refractory to conventional therapies. Evidence supporting the safety of TNF-α inhibitor therapy in HIV-infected individuals is limited and based on isolated case reports and small series.

Objective:

To estimate the incidence of serious infections in patients with HIV infection who are treated with TNF-α inhibitors therapy for concomitant autoimmune diseases, and to compare these rates between certain CD4+ cell count and viral load levels.

Methods:

Using a unified search strategy of the electronic medical record EPIC, four centers identified HIV infected patients exposed to TNF-α

inhibitors. Patient characteristics and infection data were assessed via chart review in all HIV-infected patients who are ≥ 18 years old and have received TNF-α inhibitor therapy after HIV diagnosis between January 1999 and March 2015.

Results:

The inclusion criteria were met in 23 patients with 26 uses of TNF-a inhibitor therapy, 16 treated with Etanercept, 6 with Adalimumab and 4 with Infliximab. The median (range) age was 47 (20-66). The median (range) CD4+ cell count and viral load at therapy initiation was 541.5 (1-1100) and undetectable (undetectable to 298,281), respectively at time of biologic therapy initiation. These individuals provided 86.7 person-years of followup. Two (8.7%) experienced at least 1 serious infection episode (SIE) (pneumonia with empyema and MSSA chest tube infection), an overall incidence rate for all treatment courses of 2.3 per 100 patient-years (95% CI [Confidence Interval] 0.26-8.33). Both of them were on Etanercept before infectious episodes; at the time of the infection in both, viral load was < 50 and CD4+ cell count was increased from the time of TNF inhibitor initiation (209 and 804 cells/mm3 at time of SIE). There were no opportunistic infections. The incidence rate per 100 patient-years was 3.28 (95% CI 0.04-18.26) among patients with viral load > 500 copies/mL at therapy initiation and 2.08 (95% CI 0.03-11.6) among patients with viral load ≤ 500 copies/mL. One of them was on TNF inhibitor monotherapy while the other was on low-dose corticosteroid.

Conclusion:

This study suggests that TNF-α inhibitor therapy may have reasonable rates of SIEs in the range of those observed in registry data bases when used in patients with HIV infection under active care.

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Abstract Number: 1225

Long-Term Use of Biological Therapy and Discontinuation Rates in Rheumatoid Arthritis – Real World Patient Data

Laurent Chanroux, Joan Casellas and Fara Mboge, Therapy Watch, Research Partnership, London, United Kingdom
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Background/Purpose:

Biologics (bDMARDs) have been shown to control disease progression in RA however there is still no cure for the disease and in many cases long-term use of these agents is required. Their cost and toxicity can be problematic over time and immunogenicity may cause their efficacy to diminish.

The aim of our research is to better understand long-term bDMARD survival to guide disease strategies and maximise patient outcomes.

Methods:

We used data collected as part of an online treatment survey conducted among a panel of 288 US rheumatologists between July 2011 and December 2014. We analysed a total of 6,113 patient forms and focused our research on 4,557 bDMARD patients with complete treatment information and analysed their current DAS, joint count and perceived disease severity to assess their response to therapy over time. A discriminant analysis was also performed to understand the relationship between four different groups of patients (based on their time on a bDMARD) and a number of patient characteristics to understand their associated with sustained response to bDMARDs.

Results:

The 1st stage of our analysis showed that on average patients spent 29.5 months on their bDMARD (21.3 for switch patients). We observed

differences in the mean drug survival of bDMARDs: 36.1 months for etanercept, 28.2 for adalimumab, 42.2 for infliximab, 23.1 for rituximab, 21.7 for abatacept, 11.9 for tocilizumab, 16.6 for certolizumab pegol and 15.1 for golimumab. The reported drug survival rates at 1, 2, 3, 4 and 5 years were 60.8%, 40.2%, 27.5%, 19.7% and 14.0% respectively. These results matched the primary reasons given for switching bDMARD. Lack of long-term efficacy (> 6 months) was the most common reason (36.0%) followed by lack of initial response defined as ≤ 6 months (14.6%). Safety/tolerability issues were only chosen as a primary reason for switching in 10.9% of cases and immunogenicity was reported for 0.9% of patients.

We saw little significant difference between patients based on their length of time on treatment. Patients on bDMARDs for ≤ 12 months were significantly more likely to be aged below 24 years ($p<0.05$) while those who had been treated for > 12 months were more likely to be aged > 60. The latter were also significantly more likely to be retired. However, patients treated for > 6 months were more likely to be considered to have mild RA by their Dr and while patients treated for > 12 months had higher mean DAS they typically had lower mean joint counts.

The discriminate function showed a significant association between groups and the patient variables, accounting for 51.1% of between group variability. Closer analysis of the structure matrix showed only 2 significant associations, time since 1st ever bDMARD initiation (.832) and time since diagnosis (.712). The cross validated classification showed that 60.7% of cases were correctly classified.

Conclusion:

Our research emphasizes the fact that long-term response to bDMARDs varies considerably by patient and by drug. Lack of long-term efficacy is the most common reason for switching away from a bDMARD but immunogenicity is chosen in <3% of all cases (total reasons). More research is needed to better understand how to ensure sustained response with bDMARDs and optimise patient outcomes.

Disclosure: L. Chanroux, None; **J. Casellas**, None; **F. Mboge**, None.

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Abstract Number: 1226

Assessing the Possible Association of Anti-TNF Use with New Neoplasms: An Important Methodological Consideration

Yesim Ozguler[1], Yusuf Yazici[2], Gulen Hatemi[1] and **Hasan Yazici**[3], [1]Division of Rheumatology, Department of Internal Medicine, Cerrahpasa Medical Faculty, University of Istanbul, Istanbul, Turkey, [2]Department of Medicine, Division of Rheumatology, New York University School of Medicine, New York, NY, [3]Rheumatology, Istanbul University, Cerrahpasa Medical Faculty, Istanbul, Turkey
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Background/Purpose: Whether anti- TNF agents increase the frequency of neoplasms remains debated. The drug regulatory agencies still mandate black boxes on the related package inserts or drug advertisements. We hypothesized that one important reason for this continuing concern was that the majority of studies addressing this issue had methodological weaknesses. Specifically, we had the impression that tabulating the number of cancers in the comparator groups (CGs), the expected number of cancers, was especially problematic. In observational studies when the CG is a national registry like SEER, the expected cancer incidence is given as new cancers/number of population rather than the number of patients with a new cancer which is the common method in assessing the observed incidence. Since multiple primary cancers, (around 1/6th) of all new cancers in the general population (1), are not separately tabulated as such in the national registries, a fair comparison of the cancer incidence between a patient cohort and a national registry is prone to important error. This potential error is further compounded by the fact patients with a previous history of cancer are not usually prescribed anti-TNF agents. Thus we set out to formally test our impression that the issue of multiple primary cancers is not accounted for in the debate about whether anti-TNF agents increase the incidence of neoplasms.

Methods: To test our hypothesis we first selected a recent comprehensive review (2) related to this debate which had concluded that anti-TNF agents did not increase cancer rate. All references to human studies were reanalyzed by 2 independent observers seeking whether the issue of multiple primary cancers was considered in studies which used cancer rates in the background general population as comparator. Any discrepancies between observers were to be settled by combined reassessment.

Results: Thirty-six references were selected for analyses. 24 were observational studies and 12 were meta-analyses or systematic reviews of controlled clinical trials and/or observational studies. 19 studies used national general population databases such as SEER as CGs. In none of these studies the issue of multiple primary cancers in the national database was addressed, causing a potential decrease in SIR for cancers in the anti-TNF using group, due to counting patients with multiple cancers in the general population more than once. There were no discrepancies in data assessment between the 2 observers.

Conclusion: The important issue of multiple primary cancers have not been given due consideration in studies comparing the cancer incidence associated with anti-TNF use. We propose that all previous related studies which had used this problematic methodology should be reanalyzed and reinterpreted.

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Disclosure: Y. Ozguler, None; **Y. Yazici**, Samumed, 3; **G. Hatemi**, None; **H. Yazici**, None.

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Abstract Number: 1227

Discrepancies Between Registered and Published Primary Outcomes in Randomized Controlled Trials of Rheumatoid Arthritis

Sheila Lezcano[1], Saha Sajib[2], Ashley Fan[3], Mohini Pathria[3], Karina Marianne D. Torralba[4] and Nasim A. Khan[5], [1]Internal Medicine, Loma Linda University, Loma Linda, CA, [2]Internal Medicine, University of California-Riverside, Riverside, CA, [3]Loma Linda University, Loma Linda, CA, [4]Division of Rheumatology, Department of Internal Medicine, Loma Linda University, Loma Linda, CA, [5]Rheumatology, University of Arkansas for Medical Sciences and Central Arkansas Veterans Healthcare System, Little Rock, AR

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Background/Purpose: Selective outcome reporting may bias treatment effect estimates of clinical trials. Registration of clinical trials was established to improve transparency in their conduct and reporting. We studied the discrepancies between the registered and published primary outcomes (PO) of rheumatoid arthritis (RA) randomized controlled trials (RCTs).

Methods: RA RCTs that were registered at ClinicalTrials.gov (CTG) with completion date before January 1, 2010 and ≥ 1 publication in a peer-reviewed journal were studied. Registered and published POs were extracted, and two authors independently categorized presence and type of PO discrepancies using standardized method (see Table) with resolution of differences by consensus. Associations of presence of PO discrepancies with RCT characteristics were assessed by Chi-square or Fisher's Exact test.

Results: Among 95 eligible RCTs, 56 (58.9%) had identical registered and published POs. PO discrepancies could not be assessed for 10 RCTs (3 had missing PO in CTG records; while ambiguous/unclear PO were recorded in 4 CTG records and 3 manuscripts). 29 (30.5%) had explicit discrepancies between the registered and published POs (Table). Discrepant or ambiguous PO reporting was associated with funding source [Industry funding (21/65, 32.3%) vs non-profit source funding (18/30, 60%), p = 0.011). No association was found with study phase; year of study registration; and number of study centers. Among 39 RCTs with ambiguous/explicit PO changes, discrepancies were considered to be clinically relevant in 8 RCTs [7 with shorter published PO assessment time (5 non-profit & 2 industry funded); 1 with statistically significant published PO but insignificant CTG PO (industry funded)]; not clinically relevant in 12 RCTs (both CTG and published POs had identical statistical significance); and were unable to assess clinical relevance in 19 RCTs (10 with missing or ambiguous PO, 7 where only difference was published PO time assessment specification, and 2 with statistically significant published POs not specified in CTG).

Conclusion: More than quarter of RA RCTs had ambiguous or explicit PO discrepancies, and 8 (5.6%) were clearly considered to be of

potentially clinical relevance. Industry funding was associated with less likelihood of ambiguous/discrepant PO reporting. Improvement in reporting of registered and published POs is needed to improve utility of trial registries.

Table. Types of discrepancies between CTG registered and published POs.

Type of PO discrepancy	n (%) of RCTs (N = 95)*
None	56 (56.8)
Unable to assess	10 (10.5)
PO assessment time discrepancy	9 (9.5)
PO assessment time explicitly specified in manuscript	7 (5.1)
Deletion of ≥ 1 CTG efficacy PO	6 (6.3)
Deletion of ≥ 1 CTG safety PO	5 (3.5)
PO completely different than CTG PO reported in manuscript	4 (4.2)
Published PO described as secondary outcome in CTG	1 (0.7)

*5 RCTs had > 1 PO discrepancies, hence total (%) RCTs > 95 (100%)

Ref: Arthritis Rheumatol. 2014;66:2664-74

Disclosure: S. Lezcano, None; **S. Sajib**, None; **A. Fan**, None; **M. Pathria**, None; **K. M. D. Torralba**, None; **N. A. Khan**, None.

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Abstract Number: 1228

Estimating Under-Diagnosis of Rheumatoid Arthritis in Primary Care Data from the UK Clinical Practice Research Datalink

Julian Gardiner[1], Bowen Su[1], Benjamin Ellis[2] and **Michael Soljak**[1], [1]Department of Primary Care and Public Health, Imperial College London, London, United Kingdom, [2]Arthritis Research UK, London, United Kingdom

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Background/Purpose:

The prevalence of rheumatoid arthritis (RA) in primary care electronic health records (EHRs) is much lower than patient self-reports from population surveys, which may be due to under-diagnosis. The objectives of this study were to identify possible RA cases using a diagnostic algorithm developed from the 2010 EULAR/ACR criteria, and to compare them with EHR RA diagnosis cases, in order to estimate potential under-diagnosis rates.

Methods:

Patients' EHRs in the UK Clinical Practice Research Datalink (CPRD) contain diagnostic, clinical and test information. We extracted relevant data to identify patients with diagnosed RA and possible additional RA cases using an algorithm consisting of four parts, including joint involvement and symptom duration, acute phase reactants, and serology tests. Clinical findings, diagnostic labels and results of tests

ordered by consultant rheumatologists are not available in CPRD. In the EULAR/ACR classification criteria patients can score up to five points for any joint involvement, up to three points for positive serology, one point for positive acute phase reactants and one point if the duration of symptoms is greater than six weeks. In line with the classification criteria we defined those with a score of six or more as "algorithm-diagnosed RA cases". The incidence of RA was calculated from the number of CPRD patients receiving a new RA diagnosis in that year divided by the denominator. The prevalence was calculated from the cumulative number of patients receiving an RA diagnosis up to and including a given year (as far back as CPRD records allow, with patients who have died being removed).

Results:

A total of 88,299 patients had a primary care EHR diagnosis of RA, and an additional 12,928 were defined as algorithm-diagnosed RA cases. The prevalence of RA was 0.49% for EHR-diagnosed RA, rising to 0.58% if algorithm diagnosed cases are included (**Table 1.**). This has risen steadily over time, possibly because of more complete diagnostic coding. The incidence of EHR-diagnosed RA is approximately 30.4/100,000 over the period 2005-14 compared with 6.0/100,000 algorithm-diagnosed cases, an overall incidence rate of 36.4/100,000. There were 3,091 patients diagnosed by both a doctor and the algorithm. The mean age of EHR-diagnosis patients was 60.2 years compared with 57.7 years for the algorithm-diagnosis group, which may suggest diagnostic delay.

Table 1. Incidence and prevalence of RA in the CPRD. Figures are per 100,000 people.

Year	Incidence of doctor diagnosed RA	Incidence of algorithm diagnosed RA	Total incidence of RA	Prevalence of doctor diagnosed RA	Prevalence of algorithm diagnosed RA	Total prevalence of RA	Denominator
2000	21.16	4.55	25.71	220.46	18.65	239.12	11,915,756
2001	24.19	5.29	29.48	236.13	23.89	260.02	11,982,172
2002	24.99	5.94	30.93	252.24	29.63	281.86	12,042,662
2003	27.10	7.13	34.22	269.58	36.47	306.05	12,096,190
2004	31.78	6.96	38.74	290.88	42.94	333.82	12,151,149
2005	30.49	6.92	37.41	310.31	49.56	359.87	12,204,412
2006	29.50	6.67	36.17	329.37	55.67	385.03	12,258,669
2007	28.40	6.43	34.84	346.74	61.35	408.09	12,311,226
2008	27.83	7.12	34.95	363.32	67.65	430.97	12,363,171
2009	28.15	6.37	34.52	380.32	73.05	453.37	12,411,546
2010	25.79	6.14	31.93	394.83	78.38	473.21	12,457,701
2011	25.96	5.65	31.60	409.49	83.02	492.51	12,499,758
2012	27.90	5.50	33.40	427.27	87.48	514.75	12,535,602
2013	38.84	4.87	43.71	455.23	91.19	546.42	12,563,940
2014	41.01	4.10	45.11	487.74	94.21	581.94	12,585,816

Conclusion:

The algorithm developed from the 2010 ACR/EULAR criteria identified a significant number of possible RA cases, or patients who may be at high risk of developing RA, in addition to those with a coded diagnosis. Insufficiently accurate coding of joint involvement by general practitioners prevented more precise scoring and classification. Delayed or under-diagnosis has implications for prognosis in these patients.

Disclosure: J. Gardiner, None; **B. Su**, None; **B. Ellis**, None; **M. Soljak**, None.

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Abstract Number: 1229

Regional Variation in Measured Detection of Ankylosing Spondylitis

Jason Shafrin[1], Jin Joo Shim[1], Caroline Huber[1], **Jenny Griffith**[2], Arijit Ganguli[2] and Wade Aubry[3], [1]Precision Health Economics, Los Angeles, CA, [2]AbbVie Inc., North Chicago, IL, [3]University of California, San Francisco, San Francisco, CA

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Background/Purpose:

Patients suffering from ankylosing spondylitis (AS) often receive a delayed or mis-diagnosis, as this condition is frequently confused with mechanical back pain from other causes. If AS is not properly identified, patients can receive inadequate care, delaying disease-specific treatment, which may contribute to decreased physical functioning, quality of life, excessive use of narcotic analgesics, and disease progression. This study looks at regional variation in AS detection and examines whether regions that are better able to detect AS also are less likely to provide inappropriate care.

Methods:

A large commercial claims database covering the years 2008 through 2013 was used to measure geographic variation in AS and back pain detection and potentially inappropriate health resource utilization. All adults with 12 months of continuous eligibility in the dataset were included. Measured detection was defined as the prevalence of AS (ICD-9 codes: 720.0) and measured detection for back pain was defined as (720.1-720-.9, 721.x, 722.x, 723.0-723.8, 724.x, 739.1x-739.4x, 846.x, 847.x). We measured the share of patients with back pain who used narcotic analgesics and corticosteroid injections as a proxy for unnecessary healthcare utilization, as well as medical and pharmacy costs within each metropolitan statistical area (MSA) using generalized linear models adjusting for age, gender, and comorbidities. Geographic variation across MSAs was evaluated using standard deviation (SD), interquartile range (IQR) and coefficient of variation (CV).

Results:

In the data, 21,215,151 patients were diagnosed with back pain or AS. Nationally, 37 per 100,000 (0.037%, SD: 0.023%, IQR: 0.024%-0.043%) individuals were diagnosed with AS. A majority of MSAs (74.9%, 293 of 391 MSAs) had AS measured detection below the average in the data, and all MSAs (391 of 391) had AS measured detection below the 0.55% US AS prevalence estimate from the 2009-2010 National Health and Nutrition Examination Survey (NHANES). The CV for AS measured detection (0.631) was almost 2.5 times higher than the CV for measured detection of back pain alone (0.256). Based on our regression model, moving from an MSA at the 10^{th} percentile of AS measured detection to one at the 90^{th}percentile would decrease the share of patients using narcotic analgesics (-1.0%) and steroids (-7.9%), but would increase spending on disease-modifying antirheumatic drugs (+14.4%). The net effect would be a decrease in both total pharmacy costs (-7.1%) and total costs (-2.1%).

Conclusion:

Detection of AS varies dramatically across MSAs in the US and is significantly below prevalence estimates from large national surveys. Further, areas with higher rates of AS measured detection were less likely to use narcotic analgesics and steroids, suggesting that patients with back pain from AS who are not accurately diagnosed with AS may be receiving inadequate care. Increased patient and provider awareness regarding the treatment of inflammatory conditions—such as AS—that cause back pain is needed to ensure appropriate and timely care.

Disclosure: J. Shafrin, Precision Health Economics, 5; **J. J. Shim**, Precision Health Economics, 5; **C. Huber**, Precision Health Economics, 5; **J. Griffith**, AbbVie, 3,AbbVie, 1; **A. Ganguli**, AbbVie, Inc., 3; **W. Aubry**, Precision Health Economics, 5.

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Abstract Number: 1230

Only One-Third of Patients with Spondyloarthritis Are Managed By Rheumatologists

Linda E. Dean, Gary J. Macfarlane and Gareth T Jones, Musculoskeletal Research Collaboration (Epidemiology Group), University of Aberdeen, Aberdeen, United Kingdom

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Background/Purpose: The prevalence of Ankylosing Spondylitis (AS) in Europe has been estimated in a number of studies, some based on clinic populations, others from general population surveys, and prevalence has been shown to range between 9 and 49/10,000. However, to date, none have attempted to determine the prevalence in primary and secondary care within the same population. Knowing, not only the prevalence, but also the proportion of patients managed in specialist services has important implications in terms of health service planning and resource allocation. Thus, the aim of the current study was (a) to determine, in a single population, the prevalence of AS plus the proportion of patients actively managed in secondary care; and (b) to examine differences in basic characteristics of these patients.

Methods: Data from the Primary Care Clinical Informatics Unit (PCCIU) and the Scotland Registry for Ankylosing Spondylitis (SIRAS) were utilised to estimate the prevalence of AS in Scotland, in primary and secondary care respectively.

Established in April 2000, and covering around a third of the entire population, the PCCIU collected data from a representative sample of general practices across Scotland, UK, via Read Codes: a coded thesaurus of clinical terms used to document all diseases (including AS). SIRAS is a registry collecting clinical and patient-reported outcomes on all patients with a clinical diagnosis of AS being seen within secondary care clinics in Scotland. Patients were identified via clinic lists, if available, or through a review of recent physician correspondence for evidence of an AS diagnosis.

Data for the denominator was taken either from the PCCIU database (total patients) or the mid-year population estimate for Scotland, published by the National Records of Scotland.

Results: In April 2007, the PCCIU comprised 1,469,688 persons, of whom 1,964 had received a diagnostic code for AS (prevalence: 13.4 per 10,000; 95%CI 12.8-14.0 per 10,000). The SIRAS registry identified 1,686 patients in secondary care; from a population of 3,578,984 (prevalence: 4.7 per 10,000; 4.5-4.9 per 10,000).

There was no difference in sex between the two populations, although patients managed in secondary care were more likely to be younger (mean age 51 vs 62yrs; $p<0.001$), received their diagnosis earlier (mean age 35 vs 38yrs; $p<0.001$) and were more likely to experience extra-spinal manifestations of disease (uveitis 34% vs 22%, inflammatory bowel disease 12% vs 6% and psoriasis 14% vs 6%; all $p<0.001$).

Conclusion: As far as we are aware, this is the first study to estimate the prevalence of AS simultaneously in primary and secondary care, in the same population. We have shown that nearly two-thirds of AS patients in Scotland are managed solely in primary care, without rheumatology input. This group are less likely to have extra-spinal manifestations, but are older with a longer time since diagnosis. This, not only has important ramifications in terms of health service resource planning, but highlights the importance, in a progressive disease, of ascertaining whether some of these individuals have serious spinal pathology that is currently inadequately managed.

Disclosure: L. E. Dean, Pfizer Inc, 2; **G. J. Macfarlane**, Abbvie, 2,Pfizer Inc, 2; **G. T. Jones**, Abbvie, 2,Pfizer Inc, 2.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/only-one-third-of-patients-with-spondyloarthritis-are-managed-by-rheumatologists

Abstract Number: 1231

The Prevalence of Non-Radiographic Axial Spondyloarthritis Among Patients with Inflammatory Back Pain in Rheumatology Practices

Rubén Burgos-Vargas[1], James Wei[2], Mahboob U Rahman[3], Nurullah Akkoc[4], Syed A. Haq[5], Mohammed Hammoudeh[6], Ehab Mahgoub[7], Ena Singh[8], Lyndon Llamado[9], Khalid Shirazy[10], Sameer Kotak[11], Connie Hammond[7], Ronald Pedersen[12], Qi Shen[13] and Bonnie Vlahos[13], [1]Rheumatology, Hospital General de Mexico, Mexico city, Mexico, [2]Division of Allergy, Immunology and Rheumatology, Chung Shan Medical University Hospital, Taichung, Taiwan, [3]Perelman School of Medicine, University of Pennsylvania, Philadephia, PA, [4]Department of Rheumatology, Dokuz Eylul University, Faculty of Medicine, Izmir, Turkey, [5]Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh, [6]Medicine, Hamad Medical Corporation, Doha, Qatar, [7]Pfizer, Collegeville, PA, [8]500 Arcola Road, Pfizer, Collegeville, PA, [9]Pfizer, Makati, Philippines, [10]Pfizer, Dubai, United Arab Emirates, [11]Global Health and Value, Pfizer, New York, NY, [12]Department of Biostatistics, Pfizer, Collegeville, PA, [13]GIPB - Clinical Sciences, Pfizer, Collegeville, PA

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SESSION INFORMATION

Session Date: Monday, November 9, 2015

Session Title: Epidemiology and Public Health Poster II: Pathogenesis and Treatment of Systemic Inflammatory Diseases

Session Type: ACR Poster Session B
Session Time: 9:00AM-11:00AM

Background/Purpose: The diagnosis of Ankylosing Spondylitis (AS) is delayed by >10 years after the symptoms develop, as by definition the modified NY criteria for classification of AS requires radiographic sacroiliitis (X-ray SI). However, patients continue to suffer and have similar disease burden even before radiographic changes are evident. The new Assessment of SpondyloArthritis international Society (ASAS) classification criteria for non-radiographic axial spondyloarthritis (nr-axSpA) helps to identify many of these patients. The purpose of this epidemiological study was to estimate the prevalence of nr-axSpA among patients with inflammatory back pain (IBP) presenting to rheumatology clinics in Latin America, Africa, Europe, and Asia.

Methods: Consecutive patients with IBP from 51 participating rheumatology clinics in 19 countries were enrolled. Data were collected using medical records, self-completed questionnaires, physician evaluation (for SpA features), magnetic resonance imaging (MRI), X-ray SI, human leukocyte antigen B27 (HLA-B27), and CRP results. Patients with IBP were classified as nr-axSpA or AS using the ASAS and modified New York criteria, respectively. In addition, ASDAS - ESR and CRP, BASDAI, BASFI, and BASMI were evaluated.

Results: Data from 914 patients with IBP were collected; of which 266 (27.3%) had nr-axSpA with the highest prevalence in Asia (36.5%). HLA-B27 results were available for 544 (59.5%) patients with IBP; 135/189 (71.4%) with nr-axSpA patients were HLA-B27 positive. Baseline characteristics of patients with nr-axSpA, and the efficacy assessments are shown in Table 1. The BASFI and BASMI scores were lower among patients with nr-axSpA than those observed in patients with AS. However, considerable disease burden (as measured by ASDAS and BASDAI) was noted in patients with nr-axSpA (Table 1).

Conclusion: Approximately 30% of patients referred to rheumatology clinics with IBP in all regions studied met the classification criteria for nr-axSpA. The prevalence of nr-axSpA varies by region, with the highest in Asia and the lowest in Africa, possibly due to limited access to MRI and HLA-B27 testing in these regions. The overall disease burden in nr-axSpA is substantial and similar to AS. These findings justify the need for intensive therapy, which may have positive long-term benefits. However, as this was an epidemiological study, these data may have some selection bias and should be interpreted with caution.

Table 1. Baseline characteristics, and clinical and patient-reported outcomes among patients with inflammatory back pain					
Parameter	**Total IBP (n=914)**	**nr-axSpA (n=266)**	**AS (n=491)**	**Other IBP (n=157)**	**P-value[a]**
Age, years	38.7±12.0	34.8±10.0	39.0±11.4	44.3±14.5	<0.001
Males, n (%)	588 (64.3)	169 (63.5)	350 (71.3)	69 (44.0)	<0.001
Duration of IBP, years	5.4±8.0	5.2±7.7	6.5±8.5	5.2±8.3	0.747
Age of IBP onset, years	28.8±9.7	27.8±7.3	27.0±7.7	36.2±14.2	<0.001
Positive HLA-B27, n/N* (%)**	397/544 (73.0)	135/189 (71.4)	250/302 (82.8)	12/53 (22.6)	<0.001
Family history of SpA, n/N* (%)**	220/870 (25.3)	70/250 (28.0)	132/475 (27.8)	18/145 (12.4)	<0.001
ASDAS score – ESR	2.9±1.1	2.6±1.2	3.0±1.1	2.9±1.0	0.003
ASDAS score – CRP	2.8±1.2	2.5±1.2	2.9±1.2	2.8±1.2	0.002
BASDAI	4.4±2.2	4.0±2.3	4.6±2.2	4.8±2.3	0.010
BASFI	4.1±2.6	3.20±2.5	4.4±2.6	4.4±2.5	<0.001
BASMI (11-point)	3.6±2.0	2.4±1.5	4.1±2.1	3.3±1.8	<0.001

AS, ankylosing spondylitis; ASDAS, Ankylosing Spondylitis Disease Activity Score; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index, BASFI, Bath Ankylosing Spondylitis Functional Index; BASMI, Bath Ankylosing Spondylitis Metrology Index; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; HLA-B27, human leukocyte antigen B27; IBP, inflammatory back pain; nr-axSpA, non-radiographic axial spondyloarthritis; SpA, spondyloarthritis

Data are mean (±SD) unless stated otherwise.

[a]Across group comparison

*N represents number of patients with available data. **Percentage calculated based on the number of patients

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Abstract Number: 1232

Prevalence of Idiopathic Inflammatory Myopathies in Sweden in 2012 – a National Register Study

John Svensson[1], Anna Tjärnlund[2], Ingrid E. Lundberg[3] and Marie Holmqvist[4], [1]Karolinska Institutet, Stockholm, Sweden, [2]Rheumatology Unit, Department of Medicine, Karolinska University Hospital in Solna, Karolinska Institutet, Stockholm, Sweden, [3]Medicine, Department of Medicine, Rheumatology Unit, Karolinska University Hospital, Karolinska Institutet S-171 76, Stockholm, Sweden, Stockholm, Sweden, [4]Dept of Medicine, Clinical Epidemiology Unit, Dept of Medicine, Karolinska Institutet, Stockholm, Sweden

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Background/Purpose:

Overall prevalence of idiopathic inflammatory myopathies (IIM) is commonly reported at 10 per 100,000 but worldwide estimates vary between 1 and 25 per 100,000 depending on region, population, sub-diagnosis, methodological considerations and case sources. In this study we aimed at assessing the prevalence of IIM in Sweden on January 1st, 2012, using population-based registers.

Methods:

Linking of multiple national registers was possible using each Swedish resident's unique personal identification number. Through this linkage we identified all individuals with an inpatient- or non-primary outpatient visit with an ICD-10 code indicating IIM, relevant IIM medication dispensation or registration in the Swedish Rheumatology Quality Register (SRQ).

IIM cases were defined by three progressively strict definitions; *(1) liberal* requiring ≥1 relevant specialist[1] visit, *(2) base case* requiring ≥2 specialist visits and *(3) strict,* also requiring dispensation of glucocorticoids or DMARDs. If a patient was registered in the SRQ he/she fulfilled all three definitions.

Prevalence was calculated for respective case definition and stratified by age group, sex, and clinical sub-diagnosis, in addition to county of residence for the base case definition. Corresponding Swedish population as of January 1st2012, retrieved from census data at Statistics Sweden was used in the denominator.

Results:

Overall prevalence varied between 35 (liberal), 19 (base case) and 13 (strict) per 100,000. Using the base case definition, overall female to male ratio was 1.4 and varied between 0.6, for inclusion body myositis (IBM), to 2.6, for juvenile dermatomyositis (JDM)**.** Prevalence per clinical sub-diagnosis was 8, 6, 4, 2 and 1 per 100,000 for polymyositis (PM), unspecified myositis, dermatomyositis (DM), IBM and JDM respectively.

Prevalence increased with age and peaked between 70-79 years (44 per 100,000). Overall women to men ratio was 1,5 and prevalence was highest in women for all age groups except for 70-79 and >80 year groups. Regional variations were observed between the 25 different Swedish counties (between 11 and 24 per 100,000 for Gotland and Västmanland county respectively).

Conclusion:

Estimated prevalence, 19 per 100,000 for the base case definition, was higher than what have been historically reported for IIM but corresponded well to results from recently published register studies. One challenge with this study was to determine which ICD-10 codes correspond to, primarily IIM, but also to correct clinical subgroups.

[1] Rheumatologist, neurologist, internal medicine, pediatric-clinic

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Disclosure: J. Svensson, None; **A. Tjärnlund**, None; **I. E. Lundberg**, None; **M. Holmqvist**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/prevalence-of-idiopathic-inflammatory-myopathies-in-sweden-in-2012-a-national-register-study

Abstract Number: 1233

Epidemiology of GCA in Bergen (Western Norway) 1972-2012

Lene K Brekke[1], Andreas P Diamantopoulos[2], Elisabet L Esperø[1], Bjørg-Tilde Fevang[3,4], Johan G Brun[3,4] and Clara G Gjesdal[3,4], [1]Haugesund Hospital for Rheumatic Diseases, Haugesund, Norway, [2]Rheumatology, Haugesund Hospital for Rheumatic Diseases, Haugesund, Norway, [3]Department of Rheumatology, Haukeland University Hospital, Bergen, Norway, [4]Department of Clinical Science, University of Bergen, Bergen, Norway

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Session Time: 9:00AM-11:00AM

Background/Purpose:

Giant cell arteritis (GCA) is the most common systemic vasculitis in persons older than 50 years. The highest incidence rates of the disease have been reported in the Scandinavian countries. However, the epidemiology is changing as the elderly population is increasing. The aim of this study was to investigate the epidemiology of GCA in an expected high-incidence region over time.

Methods:

This is a retrospective cohort study of patients diagnosed with GCA in the hospitals of Bergen Health Area (Helse Bergen) during 1972-2012. The International Classification of Diseases (ICD)-coding system was used to identify patients from hospital records, ICD-8 (446.4) for 1972-1987, ICD-9 (446.5) for 1987-1998 and ICD-10 (M31.5-6) for 1999-2012. The diagnosis was verified according to ACR classification criteria by review of patient charts. The 820 patients who satisfied these criteria were selected for initial analyses. Long term patient outcomes were documented by review of patient charts from time of diagnosis until time of death or end of study (31 Dec 2012). Information on time and cause of death was collected from the Norwegian Cause of Death Registry. Incidence was calculated by using population data for Hordaland County from Statistics Norway.

Results:

Among 820 identified GCA patients there were 585 females (mean age 73.4 years, SD 8) and 235 males (mean age 71.7, SD 9). Five-hundred twenty-eight patients (64 %) had a positive temporal artery biopsy and 206 patients (25 %) had a negative biopsy. For the remaining 86 patients (11 %) biopsy was not performed or biopsy results were inconclusively or insufficiently reported. Patient characteristics and outcomes are presented in table 1.

The average annual incidence rate for GCA was 15.7 per 100 000 > 50 years (females 20.4 and males 9.9). There were large fluctuations in incidence according to year of diagnosis with a tendency of progressive increase. The highest annual incidence rate observed was 35.1 in 2007. The lowest annual incidence rate was 2.6 in 1976 and 1978. Yearly distribution of incidence rates is displayed in figure 1.

Four-hundred forty-three patients (54 %) of our cohort died during the follow-up period.

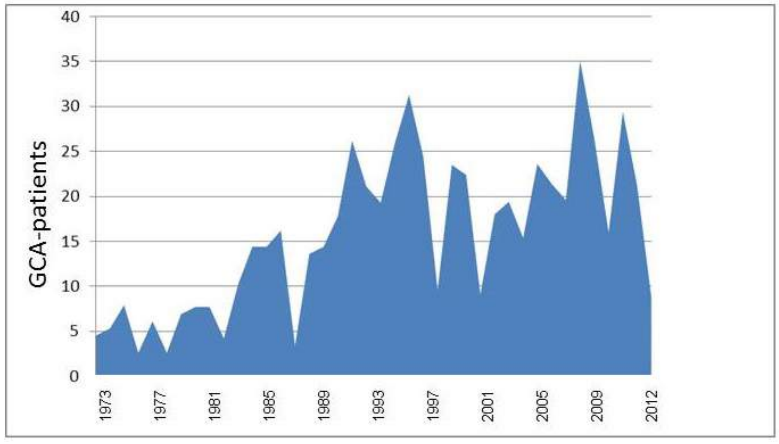
Conclusion:

An increasing cumulative incidence throughout the period 1972-2012 was observed in our study. Higher awareness of GCA among clinicians could be an explanation. This interesting finding warrants further investigation.

Table 1. Patient characteristics and outcomes

	Overall	Female	Male
	n=820	**n=585**	**n=236**
Mean age at onset of GCA (SD)	72.9 (8.7)	73.4 (8.4)	71.7 (9.3)
ACR criteria fulfilled (%)	820 (100)		
Age ≥ 50 at disease onset (%)	816 (99.5)	583 (99.7)	233 (99.1)
New onset headache (%)	592 (72.2)	418 (71.5)	174 (74.0)
Temporal artery tenderness (%)	378 (46.1)	265 (45.3)	113 (48.1)
Decreased temporal pulse(%)	230 (28)	170 (29.1)	60 (25.5)
ESR ≥ 50 (%)	740 (90.2)	525 (89.7)	215 (91.5)
Biopsy showing vasculitis (%)	528(64.4)	378 (64.6)	150 (63.8)
Giant cells in biopsy (%)	243 (29.6)	185 (31.6)	58 (24.7)
Mean ESR (SD) n=810	84.1 (27.6)	83.7 (27.9)	85.1 (27.0)
Mean CRP (SD) n=626	90.3 (63.4)	87.5 (62.3)	97.7 (65.2)
Jaw claudication (%)	181 (22.1)	134 (22.9)	47 (20)
Polymyalgia Rheumatica (%)	246 (30)	195 (33.3)	51 (21.7)
Peripheral Arthritis (%)	35 (4.3)	25 (4.3)	10 (4.3)
Visual disturbance (%)	149 (18.2)	106 (18.1)	43 (18.3)
Blindness one or both eyes (%)	33 (4)	24 (4.1)	9 (3.8)
Scalp necrosis (%)	6 (0.7)	4 (0.7)	2 (0.9)
Number of deaths 1972-2012 (%)	443 (54)	311 (53.2)	132 (56.2)

Figure 1: Annual incidence rate of GCA per 100 000 persons age > 50 years



Disclosure: L. K. Brekke, None; **A. P. Diamantopoulos**, None; **E. L. Esperø**, None; **B. T. Fevang**, None; **J. G. Brun**, None; **C. G. Gjesdal**, None.

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Abstract Number: 1234

Epidemiology of Sarcoidosis 1976-2013: A Population-Based Study

Patompong Ungprasert[1], Eva M. Carmona Porquera[2], James P. Utz[2], Jay H. Ryu[3], Cynthia S. Crowson[4] and Eric L. Matteson[5], [1]Rheumatology, Mayo Clinic, Rochester, MN, [2]Pulmonary and Critical Care Medicine, Mayo Clinic, Rochester, MN, [3]Division of Pulmonary and Critical Care Medicine, Mayo Clinic, Rochester, MN, [4]Health Sciences Research, Mayo Clinic, Rochester, MN, [5]Division of Rheumatology, Department of Internal Medicine and Department of Health Sciences Research, Mayo Clinic, Rochester, MN

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SESSION INFORMATION

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Session Time: 9:00AM-11:00AM

Epidemiology of Sarcoidosis 1976-2013: A Population-Based Study

Background/Purpose: The epidemiology of sarcoidosis is not well-described. Only coding-based studies with point estimates over relatively short periods, without detailed case information or verification based on individual medical record review have been reported. This study aimed to characterize the epidemiology of sarcoidosis, with emphasis on annual incidence and mortality, from 1976 to 2013.

Methods: An inception cohort of patients with incident sarcoidosis in 1976-2013 in a geographically well-defined population was identified based on comprehensive individual medical record review. Inclusion required physician diagnosis supported by histopathology and radiologic features of intrathoracic sarcoidosis, compatible clinical presentation, and exclusion of other granulomatous diseases. Tissue samples are considered positive if they demonstrate non-caseating granuloma without evidence of acid-fast bacilli or fungi. The only exception to the requirement of histopathological confirmation was stage I pulmonary sarcoidosis that required only radiographic evidence of symmetric bilateral hilar adenopathy. Isolated granulomatous disease of the skin without other features of sarcoidosis was not considered. Incidence rates were age and sex adjusted to the US white 2010 population.

Results: In 1976-2013, 345 incident cases of sarcoidosis were identified (mean age 45.6 years and 50.4% female). The annual incidence of sarcoidosis was 10.8 per 100,000 population (11.0 per 100,000 population in female and 10.5 per 100,000 population in male). The peak incidence was observed in those who were 35 to 64 years old. The numbers of minorities were too low to establish separate estimates by self-assigned ethnicity. Significant changes of incidence over time were not observed (Figure 1).

97% of cases had intra-thoracic involvement (87% intra-thoracic lymphadenopathy and 50% pulmonary parenchymal infiltration). Only 43% of patients had respiratory symptoms. The most common extra-thoracic manifestations were skin rash, arthralgia, ophthalmologic and hepatic involvement (18%, 14%, 7% and 6%, respectively). Isolated extrapulmonary sarcoidosis was diagnosed in 10 (3% of patients).

During median follow-up of 12.2 years (5002 total person-years), 50 patients died. The overall mortality of patients with sarcoidosis was not different from general population (standardized mortality ratio: 0.85; 95% CI, 0.63-1.13). Significant changes of mortality over time were not observed as well.

Conclusion: Sarcoidosis occurred in about 11 persons per 100,000 per year. Most of the patients had intra-thoracic involvement, although less than half had respiratory symptoms. Overall mortality was not different from general population.

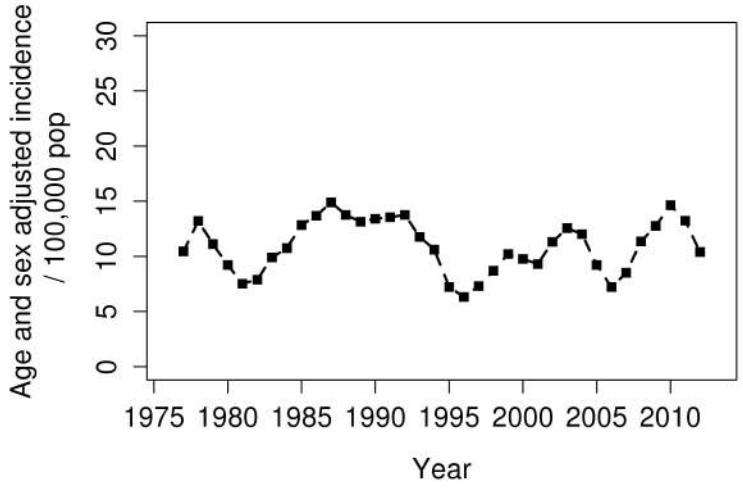

Figure 1. Trends in incidence of sarcoidosis 1976-2013 overall

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Abstract Number: 1235

Epidemiology of Kikuchi-Fujimoto Disease in Martinique and Characteristics in an Afro-Caribbean Population: Close Relation with Lupus

Florence MOINET[1], Vincent MOLINIE[2], Katlyne Polomat[1], Nadege Cordel[3], Guillaume BERAUD[4], Dominique SAINTE MARIE[5], Olivier DUFFAS[6], Charlène BOMAHOU[7], Serge ARFI[1], Jean-come MENIANE[8], Suzy DUFLO[9], Yves HATCHUEL[10] and **Christophe Deligny**[1], [1]Rheumatology and Internal Medicine, Zobda Quitman Hospital, Fort de France, Martinique, [2]pathology, Zobda Quitman Hospital, Fort de France, Martinique, [3]Infectious diseases, dermatology and internal medicine, Centre Hospitalier universitaire de Guadeloupe, Pointe à Pitre, Guadeloupe, [4]Internal medicine and infectious disease, CHU de Poitiers, Poitiers, France, [5]Dermatologie, Centre Hospitalier André Rosemon, Cayenne, French Guiana, [6]ENT, Zobda Quitman Hospital, Fort de France, Martinique, [7]Internal medicine, Hopital Européen Georges Pompidou, Paris, France, [8]Hematology, Zobda Quitman Hospital, Fort de France, Martinique, [9]ENT, Centre Hospitalier universitaire de Guadeloupe, Pointe à Pitre, Guadeloupe, [10]Pediatry, Zobda Quitman Hospital, Fort de France, Martinique

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Background/Purpose:

Kikuchi-Fujimoto disease (KFD) is a rare histiocytic necrotizing lymphadenitis affecting mainly Asian young women, associated to systemic lupus (SLE) in less than 25% of the cases. There is no epidemiology and no series devoted to African descent patients. Our objectives were to study (1) the incidence in the population of Martinique, (2) the characteristics of KFD afro-Caribbean patients from the 3 French American dependencies.

Methods:

A retrospective study including all patients with KFD compatible pathology report during a first episode or a recurrence in Martinique between 1991 and 2013 by three sources: (1) database of the two pathology units in the island (one public, one private), (2) the healthcare coding system of the academic hospital, (3) the departments of internal medicine, rheumatology, hematology and otorhinolaryngology files. In a second time, for a more comprehensive description of the disease's characteristics, we explored by the same way two other overseas French departments (Guadeloupe, French Guiana) and also included more afro-Caribbean patients in the cohort. Inclusion criteria were a biopsy with compatible pathology report for the epidemiology in Martinique, adding for the whole series description, an auto-declared afro-Caribbean ethnicity. SLE was defined by the presence of 1997 ACR criteria.

Results: Thirty-six cases of KFD were included, all afro-Caribbean: 26 from Martinique, 8 from Guadeloupe, 2 from French Guiana. The mean age at KFD diagnosis was 30.5 years (range: 5-59) and the female/male sex ratio was 3/1 (27 females, 9 males). Initial features were: fever (25/30; 83.3 %), asthenia (19/26; 73 %), weight loss (16/25; 64.4 %). Lymph nodes were cervical in 88.8 % (32/36), inguinal in 16.1% (5/31), only axillary in 8.3%, only abdominal in 2.8 %. Lupus was underlying in 4/36 patients (11.1%), diagnosed concomitantly with KFD in 6 (16.7%) and after KFD in 1 (2.8%). Recurrence was noted in 9 (25 %) of the patients but 15 KFD (14 non SLE related and 1 SLE related) were lost to follow up. At the time of KFD diagnosis, ANA were available for 22 patients, and 12 were ≥ 1/320 (54.5 %). The evolution was a spontaneous regression in 16/29 (55.1%) and 12/28 (42.8 %) of the patients received oral steroids. 11/30 KFD cases (36.6 %) were associated with lupus: 9 SLE (30%) and 2 pure cutaneous lupus (6.6%). Twenty four cases were diagnosed in Martinique between 1991 and 2013 (women: n=16, men: n=8): the crude average annual incidence was 2.77 cases for 10^6inhabitants (95%CI: 1.73-3.93), 3.5 for women (95%CI: 1.97-5.25) and 1.96 for men (95%CI: 0.74-3.43). Other autoimmune diseases were associated to KFD:

primary Sjögren syndrome (n=1) and juvenile idiopathic arthritis (n=1, her mother had SLE).

Conclusion:

We report here the first KFD epidemiology. This study confirms: (1) the presence of KFD in the afro-Caribbean population, to be confirmed in other African heritage populations, (2) the strong association with autoimmune diseases (mainly lupus) in our black population. But, KFD epidemiology is difficult to carry out because of the usual transient nature of this disease, leading to no lymph node biopsy and frequent lost to follow up after diagnosis.

Disclosure: F. MOINET, None; **V. MOLINIE**, None; **K. Polomat**, None; **N. Cordel**, None; **G. BERAUD**, None; **D. SAINTE MARIE**, None; **O. DUFFAS**, None; **C. BOMAHOU**, None; **S. ARFI**, None; **J. C. MENIANE**, None; **S. DUFLO**, None; **Y. HATCHUEL**, None; **C. Deligny**, None.

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Abstract Number: 1236

Google-Driven Search for Autoimmune Big Data Links Air Pollution and Younger Age at Diagnosis of Systemic Lupus Erythematosus: Geoepidemiological Analysis of 171,000 Adult Patients

Manuel Ramos-Casals[1], Pilar Brito-Zerón[1], Belchin Kostov[2], **Soledad Retamozo**[1], Antoni Sisó-Almirall[2], Xavier Bosh[3], David Buss[4], Courtney Grant[5], Daphne Superville[6], Antoni Trilla[7], Yehuda Shoenfeld[8], John H. Stone[9] and Munther Khamashta[10], [1]Department of Autoimmune Diseases, CELLEX-IDIBAPS, Hospital Clínic, Barcelona, Barcelona, Spain, [2]Primary Care Research Group, Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Primary Care Centre Les Corts, CAPSBE, Barcelona, Spain, [3]Department of Internal Medicine, ICMiD, Hospital Clínic, Barcelona, Spain, [4]Department of Autoimmune Diseases, ICMiD, Hospital Clínic, Department of Autoimmune Diseases, CELLEX-IDIBAPS, Hospital Clínic, Barcelona, Barcelona, Spain, [5]University of Glasgow, Glasgow, United Kingdom, [6]Massachusetts Institute of Technology (MIT), Cambridge, MA, [7]Preventive Medicine and Epidemiology Unit, Hospital Clínic-Universitat de Barcelona-Barcelona Centre for International Health Research, Barcelona, Spain, [8]Zabludowicz Center for Autoimmune Diseases, Chaim Sheba Medical Center, Tel Hashomer, Israel Incumbent of the Laura Schwarz-Kipp Chair for Research of Autoimmune Diseases, Sackler Faculty of Medicine, Tel-Aviv University, Tel Aviv, Israel, [9]Massachusetts General Hospital Rheumatology Unit, Harvard Medical School, Boston, MA, [10]Lupus Research Unit, The Rayne Institute, St Thomas Hospital, Kings College London School of Medicine, London, United Kingdom

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Background/Purpose:

Systemic autoimmune diseases (SAD) are characterized by a wide spectrum of demographic patterns with respect to the age at diagnosis, gender distribution and ethnic differences. Studying the distribution of these diseases across geographic regions and ethnic groups using a big data-driven approach may facilitate understanding of the corresponding genetic and environmental underpinnings, and help obtain a more "high-definition resolution" of these complex diseases.

Methods:

We explored the potential of the Google search engine to collect and merge cohorts (>100 patients) of patients with systemic lupus erythematosus (SLE) reported in the Pubmed library. We made a text-word search in Google (www.google.com) between 8th and 15th May 2015 using the following text algorithm: "systemic lupus erythematosus" and "100...100000000 patients" and "site:http://www.ncbi.nlm.nih.gov/pubmed". We analyzed potential links between epidemiological features (age, gender ratio), ethnic distribution and geographical variables (total population, nominal gross domestic product –GPD-, the pollution index –PI- and the exponential pollution index –expPI- of the country of origin of each cohort of SLE patients).

Results:

We merged the data of 133 SLE cohorts including 171,000 patients; gender was detailed in 130 cohorts: 150,937 (88%) women and 17,958 (12%) men (female: male ratio, 8,4). mean age at onset (29.89 ± 3.48), at diagnosis (32.33 ± 2.99), and at protocol (40.57 ± 5.01). SLE was diagnosed according to ACR criteria in 89% of cohorts, and according to ICD codes in 11%. The countries contributing the most cohorts were the USA (31), Japan (8) and Spain (5). A higher female: male ratio was found in cohorts with a higher frequency of Asian patients (r = 0.386, p=0.015), a higher number of participant countries (ratio of 14.5 in cohorts from more than one country vs. 10.7 in cohorts from one country), cohorts from countries with a greater population (r=0.189, p=0.043), cohorts that recruited patients in the 21st century (ratio of 11.7 vs. 8.9 in cohorts that recruited patients in the 20th century) and cohorts in which the time of recruitment was < 10 years (11.7 vs. 8.9 in cohorts with a time of recruitment > 10 years). The PI (r=-0.416, p=0.035) and the expPI (r=-0.414, p=0.036) were inversely associated with the mean age at diagnosis of SLE.

Conclusion:

This analysis is the first to show the potential benefits of a combined search using Google and Pubmed to seek geographical factors that influence the phenotypic expression of SLE. This approach is an example of multidisciplinary collaboration that could involve clinical researchers, epidemiologists, mathematicians, and health informatics experts. The approach used here is a first, exploratory step which will require significant improvement and refinement. Using a "big data" approach enabled hitherto unseen connections between the environment and SAD to emerge.

Disclosure: M. Ramos-Casals, Bristol-Myers Squibb, 2; **P. Brito-Zerón**, None; **B. Kostov**, None; **S. Retamozo**, None; **A. Sisó-Almirall**, None; **X. Bosh**, None; **D. Buss**, None; **C. Grant**, None; **D. Superville**, None; **A. Trilla**, None; **Y. Shoenfeld**, None; **J. H. Stone**, Roche, Genentech, 2,Genentech, 5; **M. Khamashta**, None.

Abstract Number: 1237

The Incidence and Prevalence of Systemic Lupus Erythematous in a Defined Population in United Arab Emirates

Ali Al Dhanhani[1], Omran Bakoush[2], Mukesh Agarwal[3] and Yusra Othman[4], [1]Dept. Internal Medicine,, Assistant profesor, UAE University, Al Ain, United Arab Emirates, [2]Internal Medicine, Associate Professor , UAE University, Al Ain, United Arab Emirates, [3]Professor, UAE University, Al Ain, United Arab Emirates, [4]Tawam Hospital, Al Ain, United Arab Emirates

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Session Time: 9:00AM-11:00AM

Background/Purpose: There is a paucity of information about the incidence and prevalence of systemic lupus erythematosus (SLE) in United Arab Emirates (UAE) and Arab countries. The aim of this study was to determine the incidence of SLE and point prevalence among native population of Al Ain city, UAE.

Methods: Al-Ain city population are provided with health services in 2 major hospitals and multiple primary health care clinics all belong to a governmental Abu Dhabi Health Services (SEHA) and are linked with one Health Information System (HIS). New cases of SLE (2009-2012) were identified using hospital records and a serology database as follows: 1) the two major hospitals inpatients and outpatients medical records (2009-2012) were searched for patients with ICD-9 codes related to diagnosis of SLE , and discoid lupus ; 2) electronic records for patients with a positive DsDNA test (ELISA, cutoff value of 50 U/ml) , or two positive ANA test (one hospital provide all the immunological testing for the city); 3) we searched the skin and renal biopsy records for diagnosis of SLE, discoid lupus or lupus nephritis. The electronic charts of these cases identified were reviewed for fulfilling the American College of Rheumatology (ACR) criteria for SLE. Incidence and prevalence were calculated based on the yearly census of Al Ain city (Statistics Center- Abu Dhabi). The standardized age incidence ratio was estimated using WHO standard population as a reference.

Results: Sixteen new cases (13 females and 3 males) fulfilled the ACR SLE criteria and were diagnosed between January 2009 and December 2012. The point prevalence of SLE among native population in Al Ain city according to 2012 population was 23.7/100,000. The incidence ratio for each year is shown in (Table 1). The mean age at time of diagnosis was 28.6 ± 12.4 years (range of 4 to 47). Age-

standardized incidence per 100,000 population is shown in Figure 1. Most common manifestations during the first year of diagnosis were positive ANA and positive immunological tests (anti-DsDNA, anti-Smith, anti-cardiolipin or lupus anticoagulant) which were present in all patients (100%) followed by arthritis (62.5%) and malar rash (56%).

Conclusion: This is the first population-based incidence and prevalence report of SLE in UAE. Although the prevalence of SLE is higher than reported from a similar Arab population from Saudi Arabia, it is similar to Caucasian populations.

Table 1. The Incidence of SLE in Al Ain city, UAE, between 2009 and 2012

Year	No. of cases		Native Population	Incidence per 100,000		
	Male	Female		Male	Female	Overall
2009	2	4	170,400	2.3	4.6	3.5
2010	0	2	177,100	-	2.2	1.1
2011	1	3	186,000	1.1	3.3	2.1
2012	0	4	194,200	-	4.2	2.1

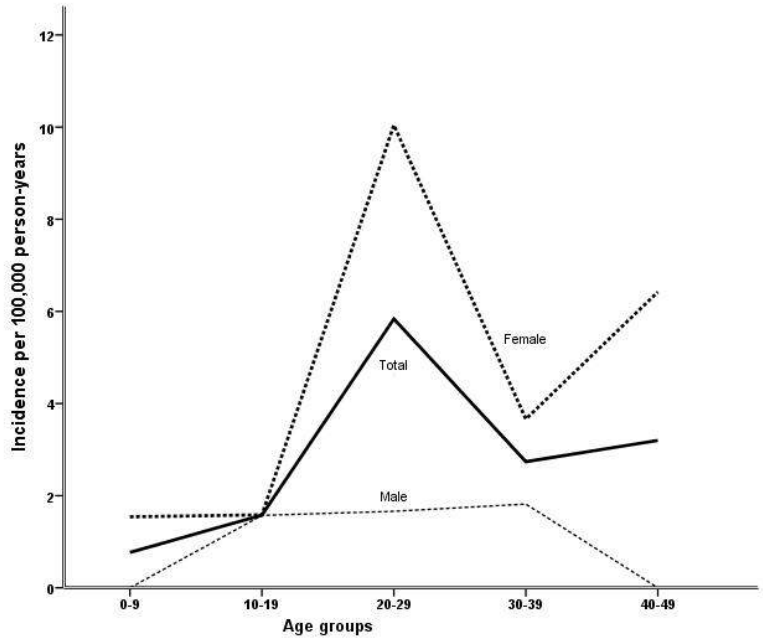

Fig. 1, The age-standardized incidence per 100,000 population over 4 years among males, females and overall.

Disclosure: A. Al Dhanhani, None; **O. Bakoush**, None; **M. Agarwal**, None; **Y. Othman**, None.

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Abstract Number: 1238

Incident Systemic Lupus Erythematosus in Males in a Northern California County Hospital

Jorge A. Uribe[1], Julia F Simard[2], Laura Tarter[3] and Thomas M. Bush[1], [1]Medicine/Rheumatology, Santa Clara Valley Medical Center, San Jose, CA, [2]Division of Epidemiology, Health Research and Policy Department, and Division of Immunology & Rheumatology, Department of Medicine, Stanford School of Medicine, Stanford, CA, [3]Rheumatology, Stanford University Hospital, Stanford, CA
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Background/Purpose: Little is known about males with systemic lupus erythematosus (SLE), particularly among those with a recent diagnosis. To better understand the presentation and outcomes of adult males with SLE we describe the demographic, clinical and immunological manifestations, and treatment profiles in a small inception cohort of men with SLE at Santa Clara Valley Medical Center (SCVMC), a 574-bed medical center in Santa Clara County.

Methods: Electronic records were searched to identify adult males diagnosed with SLE at SCVMC between January 2004 and August 2014 with at least 2 rheumatology clinic visits and documented SLE diagnosis within one year of their initial visit. Medical record review of these incident cases confirmed the diagnosis using ACR classification criteria. Additional data collected included socio-demographic variables, history of comorbidities at diagnosis (e.g. myositis, hypertension), clinical and immunological SLE manifestations, clinical events after diagnosis (e.g. avascular necrosis, cerebrovascular event, pulmonary embolism) and treatment profiles. Individuals were followed until either the end of follow-up (August 2014), death, or loss to follow-up.

Results: Of the 16 incident male SLE patients identified, the average age at diagnosis was approximately 32 years and the majority of patients were Hispanic (69%). At initial presentation the majority of patients had arthritis (81%), history of hyperlipidemia (69%), and history of hypertension (63%). 44% had a documental serum creatinine >1.5mg/dl with biopsy-confirmed lupus nephritis (LN) in 6 patients (2 with class 3/4 and 4 with class 5). In the first year 81% were prescribed hydroxychloroquine, 75% corticosteroids, 38% mycophenolate mofetil, and 31% cyclophosphamide. Among the 15 contributing more at least 2 years of follow-up the use of most of these medications increased (93% hydroxychloroquine, 80% corticosteroids, 47% mycophenolate mofetil, and 20% (n=3) started azathioprine) and no patients remained on cyclophosphamide (the one patient with less than 1yr follow-up was not on this). Of the 6 men with documented cyclophosphamide treatment during follow-up, all 6 had LN plus 2 had vasculitis and 2 had myositis. Nine of 16 (56%) men had a notable clinical or catastrophic event during follow-up (Table 1).

Conclusion: In this case series of 16 men with recently onset SLE nearly half of the patients had elevated serum creatinine documented and 37.5% biopsy confirmed LN. This is similar to reported LN incidence (44.8%) among a Spanish subset of male SLE patients (Casas I, et al. ACR Abstract 2014 #2622). More than half experienced at least one catastrophic event and over 37% of subjects required cyclophosphamide at one point. This is one of the first studies to look at treatment of male SLE and more information is needed both with respect to sex differences and male SLE outcomes.

Table 1. Documented clinical outcomes and catastrophic events during follow-up among SCVMC males with incident SLE (n=16), presented as %

Myocardial infarction	0
CAD/ischemia	0
Avascular necrosis	12.5
Cerebrovascular accident/TIA	18.8
CHF	6.3
Blindness	0
APLS	12.5
History of hemodialysis	12.5
Pulmonary embolus	12.5
Death	6.3

Disclosure: J. A. Uribe, None; **J. F. Simard**, None; **L. Tarter**, None; **T. M. Bush**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/incident-systemic-lupus-erythematosus-in-males-in-a-northern-california-county-hospital

Abstract Number: 1239

Significant Impact of Microrna-Target Gene Networks on the Genetics of Rheumatoid Arthritis

Yukinori Okada[1,2] and Toshihiro Tanaka[3,4], [1]Department of Human Genetics and Disease Diversity, Graduate School of Medical and Dental Sciences, Tokyo Medical and Dental University, Tokyo, Japan, [2]Laboratory for Statistical Analysis, RIKEN Center for Integrative Medical Sciences, Yokohama, Japan, [3]Bioresource Research Center, Department of Human Genetics and Disease Diversity, Tokyo Medical and Dental University, Tokyo, Japan, [4]Laboratory for Cardiovascular Diseases, RIKEN Center for Integrative Medical Sciences, Yokohama, Japan

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Background/Purpose: MicroRNA (miRNA), a short endogenous noncoding RNA, has a major role in the degradation and translational repression of a specific gene through its binding to 3' UTR of such target mRNA. While biological contribution of miRNA has been reported, its impact on the genetics of human complex traits, especially in the context of miRNA-target gene networks, has not been assessed.

Methods: We developed a novel analytical method that comprehensively evaluates enrichment of genome-wide association study (GWAS) signals in miRNA-target gene networks. We obtained GWAS results of the 19 human complex traits, that comprises in total >1.75 million subjects. The association signals of the SNPs (i.e. p-values) were converted into the gene-based or miRNA-based association signals, adjusted by local linkage disequilibrium structures and gene/miRNA sizes. Relative enrichment of the association signals between miRNAs and target genes predicted by the multiple public databases (miRDB, miRmap, PITA, and TargetScan) was evaluated through permutation test (x10,000 iterations).

Results: Of the 19 evaluated human complex traits, rheumatoid arthritis (RA), estimated glomerular filtration rate (eGFR), and adult height showed significant enrichment of the association signals in miRNA-target gene networks ($P < 0.05/19 = 0.0026$; **Figure 1**). RA demonstrated the most significant results with 1.77-fold relative enrichment compared to the null hypothesis ($P = 1.7 \times 10^{-4}$ [illegible] G**Figures 1** and **2**). Our method also provides a list of miRNA and target gene pairs with excess genetic association signals, part of which included drug target genes.

Conclusion: Our method clearly indicated significant impacts of miRNA-target gene networks on the genetics of human complex traits, especially implying their important roles in biology and drug discovery of RA.

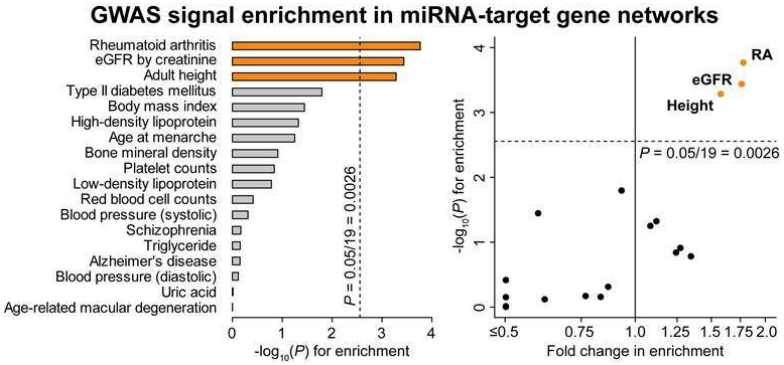

Figure 1 GWAS signal enrichment in miRNA-target gene networks.

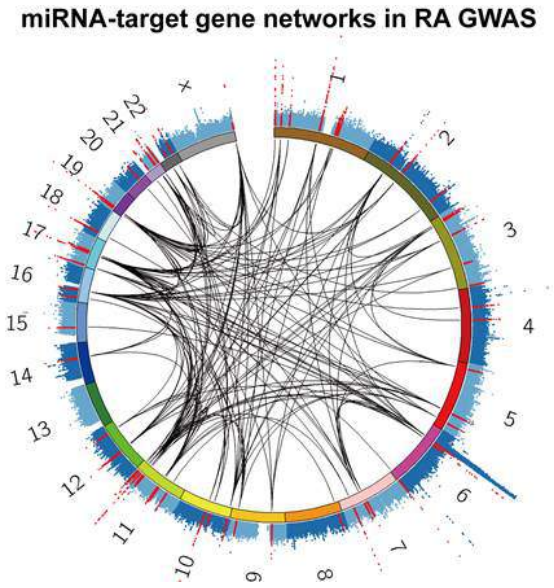

Figure 2 miRNA-target gene networks in RA GWAS

Disclosure: Y. Okada, None; **T. Tanaka**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/significant-impact-of-microrna-target-gene-networks-on-the-genetics-of-rheumatoid-arthritis

Abstract Number: 1240

Systematic Protein-Protein Interaction and Pathway Analyses in the Idiopathic Inflammatory Myopathies

Joanna Parkes[1], Simon Rothwell[2], Philip Day[1,3], Neil J McHugh[4], Zoë Betteridge[5], Robert Cooper[6], William E. Ollier[1], Hector Chinoy[2], Janine Lamb[7] and MYOGEN, [1]Centre for Epidemiology, University of Manchester, Manchester, United Kingdom, [2]Centre for Musculoskeletal Research, University of Manchester, Manchester, United Kingdom, [3]Manchester Institute of Biotechnology, University of Manchester, Manchester, United Kingdom, [4]Rheumatology, Bath Institute of Rheumatic Diseases, Royal National Hospital for Rheumatic Diseases, Bath, United Kingdom, [5]Bath Institute of Rheumatic Diseases, Bath Institute of Rheumatic Diseases, Royal National Hospital for Rheumatic Diseases, Bath, United Kingdom, [6]MRC/ARUK Institute of Ageing and Chronic Disease, University of Liverpool, Liverpool, United Kingdom, [7]Centre for Integrated Genomic Medical Research, University of Manchester, Manchester, United Kingdom
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Background/Purpose:

The idiopathic inflammatory myopathies (IIM) are autoimmune diseases characterised by acquired proximal muscle weakness, inflammatory cell infiltrates in muscle and myositis-specific/associated autoantibodies (MSA/MAA). The cornerstone of IIM treatment is prompt control of inflammation with immunosuppressive therapy, before irreversible tissue damage ensues from muscle atrophy and fatty replacement of tissue. Despite treatments, many patients become progressively disabled with co-morbidities due to both the underlying disease and treatment. There is thus a clear need to identify pathways involved in IIM pathogenesis to develop future treatment approaches. We therefore conducted protein-protein interaction and pathway analyses using myositis autoantibody targets and gene products of IIM associated loci.

Methods:

Protein-protein interactions were analysed using Disease Association Protein-Protein Link Evaluator (DAPPLE). Gene ontology and pathway analyses were conducted using Database for Annotation Visualisation and Integrated Discovery (DAVID) and Gene Relationships Across Implicated Loci (GRAIL). Three analysis strategies were used, including: i) the targets of all published MSAs and the MAA anti-PMScl-75/100; ii) significant and suggestive single nucleotide polymorphisms (SNPs) from a recently reported IIM association study; iii) SNPs plus MSA/MAA targets combined.

Results:

The protein-protein interaction networks formed by MSA/MAA targets and associated SNPs showed significant direct and/or indirect connectivity. Inclusion of both MSA/MAA targets and associated SNPs resulted in more significant indirect and common interactor connectivity than the separate networks, identifying TRAF6 as a hub protein, and suggesting interaction between MSA/MAA targets and proteins encoded by IIM associated loci. Protein-protein interaction analysis of associated loci also identified *UBE3B, HSPA1A, HSPA1B* and *PSMD3*as genes with significant connectivity. DAVID pathway analyses confirmed previous knowledge of MSA target involvement in translational processes. 'Ubiquitin' was the sole keyword strongly linking significant genes in each region in all three GRAIL analyses of MSA/MAA targets and IIM associated SNPs.

Conclusion:

Autoantibody targets and associated loci in IIM show significant connectivity and inter-relatedness and identify several key genes in IIM pathogenesis, possibly mediated via the ubiquitination-proteasome pathway.

Disclosure: J. Parkes, None; **S. Rothwell**, None; **P. Day**, None; **N. J. McHugh**, None; **Z. Betteridge**, None; **R. Cooper**, None; **W. E. Ollier**, None; **H. Chinoy**, Novartis, Janssen, Pfizer, UCB, Abbvie, Celgene, Servier, Roche, MSD, and aTyr, 5,Novartis, Janssen, Pfizer, UCB, Abbvie, Celgene, Servier, Roche, MSD, and aTyr, 2; **J. Lamb**, None.

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Abstract Number: 1241

Identification and Validation of Diagnostic and Activity Urinary Metabolomic Biomarkers in Immune-Mediated Inflammatory Diseases

Arnald Alonso[1], Jesús Tornero[2], Antonio Fernandez-Nebro[3], Juan D. Cañete[4], Eugeni Domènech[5], Javier P. Gisbert[6], Carlos Ferrándiz[5], Eduardo Fonseca[7], Valle García[8], Francisco Blanco[7], Jesus Rodriguez[9], Jordi Gratacós[10], Patricia E. Carreira[11], Antonio Julià[1], Raül Tortosa[1], Maria López-Lasanta[12], Xavier Correig[13] and Sara Marsal[1], [1]Rheumatology Research Group, Vall d'Hebron Hospital Research Institute, Barcelona, Spain, [2]Rheumatology Department, Hospital Universitario Guadalajara, Guadalajara, Spain, [3]Rheumatology, Hospital Universitario Carlos Haya, Malaga, Spain, [4]Unitat d'Artritis, Servei de Reumatologia, Hospital Clínic de Barcelona and Institut d'Investigacions Biomèdiques August Pí i Sunyer, Barcelona, Spain, [5]Hospital Universitari Germans Trias I Pujol, Badalona, Spain, [6]Hospital Universitario de la Princesa, Madrid, Spain, [7]Complejo Hospitalario Juan Canalejo, A Coruña, Spain, [8]Hospital Universitario Reina Sofía, Córdoba, Spain, [9]Rheumatology, Hospital Universitari de Bellvitge, Barcelona, Spain, [10]Hospital Parc Taulí, Sabadell, Spain, [11]Rheumatology, Hospital Universitario 12 de Octubre, Madrid, Spain, [12]Vall d'Hebron Hospital Research Institute, Barcelona, Spain, [13]CIBERDEM, Metabolomics Platform, Reus, Spain
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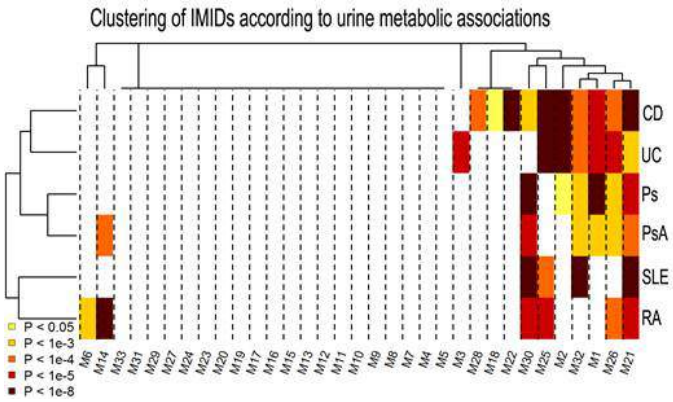
Background/Purpose: The recent advances in metabolomics have allowed the study of the regulatory processes linked to metabolism. The comprehensive analysis of the metabolome in biological samples can provide new insights to identify pathological processes and to develop new biomarkers. The present study represents the first high-throughput metabolomics analysis of immune-mediated inflammatory diseases (IMIDs). The objective of the study is the identification and validation of diagnostic and activity biomarkers through the analysis of the urine metabolome within two independent cohorts of >2,500 individuals including healthy controls

and IMID patients.

Methods: The metabolomics analysis was performed using nuclear magnetic resonance on 2 independent cohorts. The discovery cohort included 100 controls and 200 patients per IMID: rheumatoid arthritis (RA), psoriatic arthritis (PsA), psoriasis (Ps), ulcerative colitis (UC), Crohn's disease (CD), and systemic lupus erythematosus (SLE). The validation cohort included 200 controls and 200 patients per IMID. The patients of each IMID were selected to define 2 groups: low and high disease activity patients. A total of N=37 metabolites were accurately quantified. The association analyses were performed at 3 levels: diagnostic -comparing each IMID vs controls-, differential -comparing similar IMIDs between them-, and activity -comparing low and high activity patients of each IMID-. The statistical analysis was performed using linear regression adjusted by epidemiological and sample collection variables.

Results: The diagnostic analysis identified n=28 metabolic associations, from which n=26 were replicated in the validation cohort. These associations involved n=10 different metabolites from which n=6 were jointly associated to ≥3 IMIDs. When analyzing differences between IMIDs, we validated n=3 associations when comparing CD vs UC. At the nominal level, n=2 further associations were validated when comparing RA vs PsA. The analysis of disease activity identified and validated n=3 associations related with disease activity in CD patients. We also validated at the nominal level n=2 associations in UC and n=1 association in PsA, SLE and CD.

Conclusion: We have identified and validated significant differences in metabolite concentrations when comparing IMID patients vs healthy controls. CD, UC and RA gathered the largest number of metabolic associations. Relevantly, n=6 metabolites were associated to ≥3 IMIDs. These metabolites are then candidate proxies for the physiopathological processes shared by these diseases. Regarding to the discrimination between related IMIDs, the urine metabolome has shown significant differences when comparing CD vs UC and RA vs PsA. The disease activity analysis also identified significant associations but with a lower impact than that from the diagnostic analysis.



Disclosure: **A. Alonso**, None; **J. Tornero**, None; **A. Fernandez-Nebro**, None; **J. D. Cañete**, None; **E. Domènech**, None; **J. P. Gisbert**, None; **C. Ferrándiz**, None; **E. Fonseca**, None; **V. García**, None; **F. Blanco**, None; **J. Rodriguez**, None; **J. Gratacós**, None; **P. E. Carreira**, None; **A. Julià**, None; **R. Tortosa**, None; **M. López-Lasanta**, None; **X. Correig**, None; **S. Marsal**, None.

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Abstract Number: 1242

Germ Line DNA Methylation Profiling Provides Novel Insights into the Parent-of-Origin Effect in Psoriatic Disease

Remy Pollock[1], Darren O'Reilly[2], Proton Rahman[3], Vinod Chandran[4] and Dafna Gladman[4], [1]University of Toronto, Toronto Western Hospital, Toronto, ON, Canada, [2]Memorial University of Newfoundland, St. John's, NF, Canada, [3]Computer Sciences, Memorial University of Newfoundland, St. John's, NF, Canada, [4]Rheumatology, University of Toronto, Toronto Western Hospital, Toronto, ON, Canada

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Background/Purpose: Parent-of-origin effects refer to the differential risk or pathogenicity of a disease that depends on the sex of the disease-transmitting parent. Excessive paternal transmission has been described in psoriasis and psoriatic arthritis (PsA) patients. Genomic imprinting or other germ line epigenetic phenomena have been hypothesized to mediate this effect. This study aimed to investigate the presence of germ line epigenetic variants associated with psoriasis and PsA.

Methods: Male psoriasis (n=24) and PsA (n=13) patients were recruited from the University of Toronto Psoriatic Disease Program. Psoriasis patients were diagnosed by a dermatologist and examined by a rheumatologist to verify the absence of PsA. PsA patients were diagnosed by a rheumatologist and satisfied the CASPAR criteria. Unaffected male controls (n=19) with no family history of psoriasis or PsA were also recruited. Sperm cells were isolated from semen samples and genomic DNA was extracted and bisulfite converted. DNA methylation was measured at 485,577 CpG sites using Illumina HumanMethylation 450k arrays. Methylation differences were assessed by Student's t-test using M-values and then converted to percent differences in methylation (β diff) between groups.

Results: Differential methylation analysis performed on 331,258 unique CpG sites retained after filtering identified 57 differentially methylated CpG sites between psoriasis patients and controls, and 97 between PsA patients and controls ($p<0.05$). Top hits in psoriasis patients vs. controls included CpG sites near the long non-coding RNA *TINCR* (β diff=0.14, p=0.03) and *IRF6* (β diff=0.16, p=0.03), which are necessary for epidermal differentiation. Top CpG sites in PsA vs. controls were located near *LCP1* (β diff=0.16, p=0.01), which regulates polarization and migration of chemokine-stimulated T lymphocytes, and PsA susceptibility locus *HLA-B* (β diff=-0.25, p=0.03) on 6p21.3. The inflammasome component *NLRP13* was differentially methylated in both PsA (β diff=0.11, $p=1.8x10^{-3}$) and psoriasis (β diff=0.09, $p=7.6x10^{-3}$) patients compared to controls. There were 84 differentially methylated CpGs between PsA vs. psoriasis patients ($p<0.05$). Top CpGs were located near *TPPP* (β diff=0.25, $p=1.4x10^{-4}$), involved in tubulin polymerization, and *HCG26*, a non-coding RNA that lies between *MICA* and *MICB* on 6p21.3 (β diff=-0.22, $p=4.0x10^{-3}$). Upon combining the results of all three analyses, five hits mapped to a 2.1 Mb interval on chromosome 8p23.3 that we previously identified as differentially methylated in whole blood of PsA patients with paternally vs. maternally-transmitted disease. Hits in this region were located near the genes *ERICH1-AS1*, *MYOM2, CSMD1*, and *DLGAP2*, which has been computationally identified as a putative paternally imprinted gene.

Conclusion: We identified several differentially methylated CpG sites in the germ line of psoriasis and PsA patients. These preliminary results require further experimental verification and replication in somatic tissues, to determine their relevance to the parent-of-origin effect and the aetiopathogenesis of psoriasis and PsA.

Disclosure: R. Pollock, None; **D. O'Reilly**, None; **P. Rahman**, None; **V. Chandran**, None; **D. Gladman**, None.

Abstract Number: 1243

Identification of the Gene Expression Signatures Predicting the Responses to Three Biologics (infliximab, tocilizumab, and abatacept) in Rheumatoid Arthritis

Seiji Nakamura[1], Hiroshi Iijima[1], Yuko Hata[2], Yohei Ishizawa[2], Chun Ren Lim[2], Ryo Matoba[2], Katsuya Suzuki[3], Koichi Amano[4] and Tsutomu Takeuchi[3], [1]Kanagawa, DNA Chip Research Inc., Yokohama, Japan, [2]DNA Chip Research Inc., Yokohama, Japan, [3]Division of Rheumatology, Department of Internal Medicine, Keio University School of Medicine, Tokyo, Japan, [4]Rheumatology and Clinical Immunology, Saitama Medical Center, Saitama Medical University, Kawagoe, Japan

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Background/Purpose: Employing genome-wide gene transcription on a unified platform, to identify molecular signatures for predicting therapeutic effects for rheumatoid arthritis (RA) with three biologics, infliximab (IFX), tocilizumab (TCZ), and abatacept (ABT).

Methods: Two hundred and three RA patients who were methotrexate-inadequate response and the first biologic administered were enrolled (IFX: 139, TCZ: 34, ABT: 30). Whole blood gene transcription data of each patient were obtained using a unified platform, Agilent Whole Genome Microarray 44K prior to administration of drugs. Using gene set enrichment analysis (GSEA), a priori defined functional set of genes, such as Reactome pathways and blood cell subtype-specific transcripts, were analyzed to find the difference of biological characteristics between remittors and non-remittors based on CDAI at 6th month of treatment. "Signature scores" of the gene sets

derived from the GSEA results was calculated for each patient and then was reviewed using logistic regression and ROC analysis.

Results: Based on GSEA, innate immunity pathways (inflammasomes and negative regulators of RIG-I/MDA5 signaling) were significantly upregulated in baseline peripheral blood of non-remitters in IFX (table 1). In TCZ, genes specifically expressed in B or T cells were significantly upregulated in remitters. Apoptosis related or NK cells-specific genes were related with ABT treatment outcome. Univariate logistic regression of signature scores supported the GSEA results. Multivariate logistic regression adjusting to clinical background showed inflammasomes genes for IFX, CD19 cells-specific genes for TCZ, CD56 cells-specific genes for ABT as significant independent predictive factors. The AUCs of ROC curve of each signature score were 0.638 (95% CI: 0.538-0.739), 0.769 (95% CI: 0.596-0.943), and 0.764 (95% CI: 0.575-0.953) for IFX, TCZ, and ABT, respectively.

Table 1 GSEA results
IFX, infliximab; TCZ, tocilizumab; ABT, abatacept.
SIZE: Number of genes found in the gene set from expression dataset.
NOM p-val: Statistical significance of the enrichment score. Nominal p value is not adjusted for gene set size or multiple hypothesis testing.
FDR q-val: False discovery rate; that is, the estimated probability that the normalized enrichment score represents a false positive finding. A FDR q-val <0.25 was considered statistically significant.

Reactome gene sets	IFX	Up-regurated in non-remittors at baseline			
		Gene set name	SIZE	NOM p-val	FDR q-val
		Inflammasomes	16	0.0020	0.1854
		Negative regulators of RIG-I/MDA5 signaling	30	0.0042	0.2431
	ABT	Up-regurated in non-remittors at baseline			
		Gene set name	SIZE	NOM p-val	FDR q-val
		Regulation of apoptosis	54	0.0039	0.1008
Blood cell gene sets	TCZ	Up-regurated in remittors at baseline			
		Gene set name	SIZE	NOM p-val	FDR q-val
		Specific-CD19 (Watkins 2009)	140	0.0101	0.0487
		T cells-induced (Allantaz 2012)	25	0.0243	0.0735
		B cells-induced (Allantaz 2012)	56	0.0359	0.0966
	ABT	Up-regurated in non-remittors at baseline			
		Gene set name	SIZE	NOM p-val	FDR q-val
		NK cells-induced (Allantaz 2012)	78	0.0021	0.0157
		Specific-CD56 (Watkins 2009)	51	0.0265	0.0430

Conclusion: We have shown a long sought objective means to predict the therapeutic effects of biologics using multiple expression markers expressed in peripheral blood. Each signature is shown to be associated with biological function underlying the therapeutic mechanism.

Disclosure: S. Nakamura, DNA Chip Research Inc., 3; **H. Iijima**, DNA Chip Research Inc., 3; **Y. Hata**, DNA Chip Research Inc., 3; **Y. Ishizawa**, DNA Chip Research Inc., 3; **C. R. Lim**, DNA Chip Research Inc., 3; **R. Matoba**, DNA Chip Research Inc., 3,DNA Chip Research Inc., 1; **K. Suzuki**, None; **K. Amano**, None; **T. Takeuchi**, None.

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Abstract Number: 1244

Extracellular MicroRNAs in Synovial Fluid Reveal a Marked Proliferative Signature in Patients with Antibiotic-Refractory Lyme Arthritis

Robert B. Lochhead, Nancy D. Kim, Sheila Arvikar, Klemen Strle and Allen C. Steere, Division of Rheumatology, Allergy & Immunology, Massachusetts General Hospital, Harvard Medical School, Boston, MA

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Background/Purpose:

Lyme arthritis (LA), caused by a tick-borne spirochete *Borrelia burgdorferi*, usually resolves appropriately with antibiotic treatment, called antibiotic-responsive LA. However, in some patients, arthritis persists for months or years after spirochetal killing with oral and IV

antibiotic therapy, called antibiotic-refractory LA. Synovial lesions in these patients show marked synovial proliferation, inflammation, and vascularization, accompanied by pathogenic autoimmunity. MicroRNAs (miRs) regulate many biological processes including inflammation, immune responses, and cell proliferation, and are effective biomarkers that may reveal molecular mechanisms of disease. Our objective here was to identify extracellular miRs (ex-miRs) in synovial fluid (SF) that distinguish regulated (responsive) from dysregulated (refractory) immune responses in LA, thereby providing insights into underlying biological processes and potential diagnostic biomarkers to distinguish between these disease courses.

Methods:

Using an unbiased systems approach, SF was screened for the expression of 372 ex-miRs commonly found in biofluids, using qPCR, in patients with responsive LA (n=6) or refractory LA (n=5), and for comparison, in those with rheumatoid arthritis (RA, n=4) or osteoarthritis (OA, n=4). A cluster analysis algorithm (Qiagen) was used to identify ex-miR signatures present in one or more patient groups. Statistically significant differences in miR expression between groups were determined by ANOVA ($p<0.05$).

Results:

In SF from patients with responsive or refractory LA or RA, miRs reflective of an inflammatory signature (miR-146a, miR-155) and a vascularization signature (miR-30fam) were significantly up-regulated compared with that of OA patients. Furthermore, up-regulation of the inflammatory ex-miR signature was more pronounced (~4-6-fold higher) in patients with refractory LA than in those with responsive LA, consistent with the greater expression of inflammatory cytokines in SF of refractory patients. However, the most novel finding in refractory LA was marked up-regulation of a cell proliferation signature, which included miR-223, miR-142, and miR-17-92fam, miRs associated with oncogenesis. For miR-223 and miR-142, two of the most abundant ex-miRs, the amounts were ~3-to-6-fold greater in refractory LA compared with that in responsive LA and OA, and similar to the levels observed in RA SF. Preliminary cell culture experiments suggest that some of these ex-miRs are transferred to fibroblast-like synoviocytes where they alter target gene expression.

Conclusion:

Cell proliferation ex-miR signatures were a key component that distinguished antibiotic-refractory LA or RA from antibiotic-responsive LA or OA. Thus, in antibiotic-responsive LA, a localized inflammatory response to *B. burgdorferi* infection is down-regulated appropriately, whereas in antibiotic-refractory LA, the greater inflammatory response in joints appears to activate marked synovial proliferation that persists after spirochetal killing. It will be important to determine whether miR-223 and miR-142 may be used as biomarkers to identify patients at risk for a refractory disease course.

Disclosure: R. B. Lochhead, NIAMS (T32 AR007258-36A1), 2; **N. D. Kim**, None; **S. Arvikar**, Rheumatology Research Foundation, 2; **K. Strle**, NIH K (K01AR062098), 2,Arthritis Foundation, 2; **A. C. Steere**, NIAID (AI-101175), 2,Rolland Foundation, 2,Littauer Foundation, 2,Eshe Fund, 2.

Abstract Number: 1245

Differential DNA Methylation Associated with Lupus Nephritis Shows Enrichment in Genes Involved in Regulation of TH2 Differentiation and Renal Development

Renuka Nayak[1], Sharon A. Chung[2], Joanne Nitiham[3] and Lindsey A. Criswell[3], [1]Department of Medicine, UCSF, Rosalind Russell / Ephraim P. Engleman Rheumatology Research Center, University of California, San Francisco, San Francisco, CA, [2]Russell/Englemen Rheumatology Research Center, Rosalind Russell / Ephraim P. Engleman Rheumatology Research Center, University of California, San Francisco, San Francisco, CA, [3]Rosalind Russell / Ephraim P. Engleman Rheumatology Research Center, University of California, San Francisco, San Francisco, CA

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Background/Purpose: Genetic and epigenetic factors contribute to the progression of systemic lupus erythematosus (SLE). We have the ability to identify these factors and their influence on SLE manifestations. Few studies have examined epigenetic marks associated with

lupus nephritis. In contrast to genetic polymorphisms which are heritable and fixed, epigenetic modifications are heritable but also modifiable by environmental factors. Therefore epigenetic modifications can provide new insights into the development and progression of SLE nephritis. The focus of this study is to determine whether differentially methylated DNA sites are associated with lupus nephritis.

Methods: We previously enrolled 326 consecutive Caucasian non-smokers with SLE, 80 (25%) of whom met the ACR classification criterion for lupus nephritis (LN) or had evidence of LN on renal biopsy. We used the Illumina Infinium HumanMethylation450 BeadChip to examine ~480,000 epigenetic marks (i.e. methylation marks) on the genomic DNA of each patient. This high-throughput array profiles CpG sites in ~23,000 genes and assesses methylation for sites in promoters, 5' and 3' regions, gene bodies, CpG islands, CpG island shores, and outside of CpG islands.

Results: Using multivariate analysis controlling for age, disease duration and other variables, we previously identified 7 methylation sites that were significantly differentially methylated among patients with LN compared to those without LN ($p<1 \times 10^{-6}$). These 7 sites were present in 4 unique genes (*PRR4*, *HIF3A*, *KLF13*, and *SYNGR1*), with *HIF3A* having three methylation sites that were significantly associated with LN. None of these genes have been previously associated with lupus nephritis. However, *HIF3A* has been implicated in renal cell carcinoma and *KLF13* has been previously associated with lupus. We also examined candidate genes that are known to play roles in the development of SLE or LN and found differential methylation of sites in *HIVEP3* ($p=0.006$) and in *FRMD4A* ($p=9.05 \times 10^{-5}$). Here, we extended our analysis to include additional significant methylation marks (top 6,000) and found functional enrichment for: "response to interferon gamma," "regulation of Th2 differentiation" and "positive regulation of kidney development." We compared our results to those of a smaller study examining differential methylation in naive CD4+ T cells in LN patients and were able to replicate a significant number of their differentially methylated genes in our study ($p<0.001$).

Conclusion: These results demonstrate that DNA methylation levels are reproducibly associated with lupus nephritis. Additionally, pathogenesis of LN may involve epigenetic modification of the interferon gamma pathway, Th2 differentiation and genes involved in renal development. These findings may be useful in stratifying patients to determine their risk of lupus nephritis.

Disclosure: R. Nayak, None; **S. A. Chung**, None; **J. Nitiham**, None; **L. A. Criswell**, None.

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Abstract Number: 1246

Gene Expression Analysis of Adult Onset Still's Disease and Systemic Juvenile Idiopathic Arthritis Suggest a Single Disease Continuum

N. Nirmala[1], Arndt Brachat[2], Eugen Feist[3], Norbert Blank[4], Christof Specker[5], Matthias Witt[6], Jan Zernicke[7], Alberto Martini[8] and Guido Junge[9], [1]Novartis Institutes for Biomedical Research, Cambridge, MI, [2]Novartis Institutes for Biomedical Research, Basel, Switzerland, [3]Rheumatology and Clinical Immunology, Charite University Hospital, Berlin, Germany, [4]University of Heidelberg, Heidelberg, Germany, [5]Kliniken Essen Süd, Essen, Germany, [6]Division for Rheumatology, University of Munich, Munich, Germany, [7]Department of Rheumatology and Clinical Immunology, Charité University Medicine, Berlin, Germany, [8]Department of Pediatrics, G Gaslini Institute, Genova, Italy, [9]Novartis Pharma AG, Basel, Switzerland

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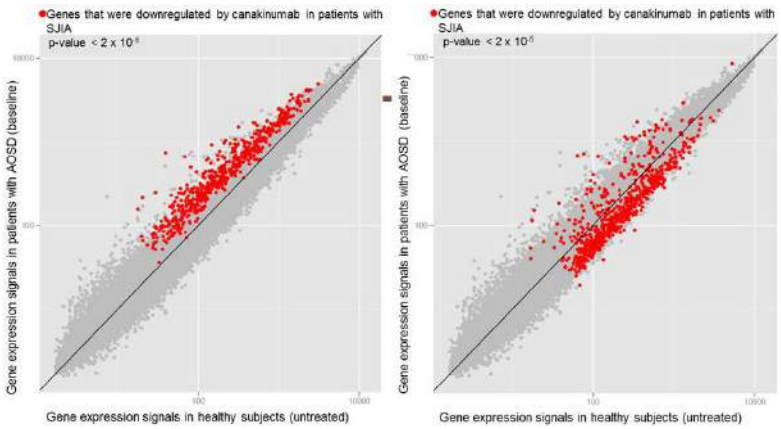
Background/Purpose: Adult-onset Still's disease (AOSD) is a rare auto-inflammatory disorder.[1] The superimposable systemic clinical features of AOSD and the pediatric syndrome known as systemic juvenile idiopathic arthritis (SJIA) suggest both clinical phenotypes represent the same disease continuum with different ages of onset. Previous reports have shown that canakinumab repressed several inflammation- and innate immunity-related genes, including those in interleukin (IL)-1 signaling pathways in SJIA patients.[2] To evaluate if AOSD may be also an IL–1-driven condition, we investigated how genes that respond to canakinumab in patients with SJIA behave in patients with active AOSD, relative to healthy subjects.

Methods: For the gene expression analysis, blood samples were obtained from 17 patients with active AOSD and 19 healthy controls. Gene expression profiles were compared using Affymetrix U133Plus 2 DNA microarrays. The probe sets identified in the blood samples

of patients with SJIA were used for supervised visualization of gene expression levels in untreated patients with AOSD and healthy subjects. The data were median-centered per gene for clearer visualization of the direction of differential expression.

Results: An analysis of the average gene regulation in overall patients showed that genes that were downregulated in patients with SJIA following canakinumab treatment were upregulated in patients with active AOSD, relative to healthy subjects (**Figure**). Comparison of the gene expression patterns with neutrophil counts showed a correlation between elevated neutrophil numbers and upregulation of canakinumab-responsive genes. Most genes that were upregulated following canakinumab treatment in patients with SJIA were downregulated in a majority of patients with AOSD (**Figure**).

Figure. Comparison of gene expression data in patients with Adult Onset Still's Disease prior to canakinumab treatment and healthy subjects



Conclusion: The results of this gene expression analysis are consistent with and further support the concept of a Still's disease continuum that includes both pediatric/juvenile (SJIA) and adult (AOSD) onset of the disease. Genes that respond to canakinumab treatment in patients with SJIA appear to be inversely dysregulated in those with AOSD. These findings support further clinical evaluation of anti-IL-1β therapy in patients with AOSD.

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[2]Brachat A, et al. Ann Rheum Dis 2014;73(Suppl2):62.

Disclosure: N. Nirmala, Novartis Pharmaceutical Corporation, 3; **A. Brachat**, Novartis Pharmaceutical Corporation, 3; **E. Feist**, Novartis Pharmaceutical Corporation, 2,Novartis Pharmaceutical Corporation, 5,Novartis Pharmaceutical Corporation, 8; **N. Blank**, Novartis Pharmaceutical Corporation, SOBI, Amgen, BMS, Pfizer, Roche, Abbvie and others, 2,Novartis Pharmaceutical Corporation, SOBI, Amgen, BMS, Pfizer, Roche, Abbvie and others, 8; **C. Specker**, None; **M. Witt**, None; **J. Zernicke**, None; **A. Martini**, Novartis Pharmaceutical Corporation,Abbott, Bristol Myers and Squibb,Francesco Angelini S.P.A., Glaxo Smith & Kline, Janssen Biotech Inc, Pfizer Inc,Roche,Sanofi Aventis, Schwarz Biosciences GmbH, 2,Novartis Pharmaceutical Corporation, Bristol Myers and Squibb, Centocor Research & Development,Glaxo Smith & Kline,Pfizer Inc, Roche, Sanofi Aventis, Schwarz Biosciences GmbH, 5,Novartis Pharmaceutical Corporation, Abbott, Abbvie, Amgen, Biogenidecm Bristol MyersSquibb, Astellas, Behringer,Italfarmaco, Janssen, MedImmune,NovoNordisk, Pfizer, Sanofi, Roche, Servier, 8; **G. Junge**, Novartis., 3.

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Abstract Number: 1247

Methylation Analysis of HLA-B Locus in Familial Behçet Syndrome

Eda Tahir Turanli[1], Pelinsu Koprulu[2], Serdal Ugurlu[3], Hasan Yazici[4] and Emire Seyahi[3], [1]Molecular Biology and Genetics Department, Istanbul Technical University, Istanbul, Turkey, [2]Molecular Biology Genetics and Biotechnology Program, Istanbul Technical University,

Istanbul, Turkey, [3]Division of Rheumatology, Department of Internal Medicine, Cerrahpasa Medical Faculty, University of Istanbul, Turkey, Istanbul, Turkey, [4]Division of Rheumatology, Department of Internal Medicine, Cerrahpasa Medical Faculty, University of Istanbul, Istanbul, Turkey

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Background/Purpose: Our focus has been on the potential role of the epigenetic processes, mainly of the methylation, on the development of Behçet syndrome (BS) using family data. We have previously studied global methylation in a group of concordant and disconcordant 8 BS twins (4 monozygotic, 4 dizygotic) along with healthy controls twins and found no difference within or between groups (average dC:5-mdC ratio=0.032 sd=0.0006 for BS twins, and average dC:5-mdC ratio=0.030 sd=0.0001 for control twins). Further analysis on the role of HLA-B51 carrier risk and its methylation mark using locus specific methylation analysis on HLA-B region had indicated indicated increased methylation levels of BS twins compared to healthy controls (p=0.0024) (Ozkõlõnc M. et.al., Methylation Pattern of Twin Groups with Behçet Syndrome. International Congress- ASHG Annual Meeting 2012, San Francisco, California, USA).

In this study, we wanted to take further our preliminary findings among familial BS cases and more directly examine the influence of HLA-B51 frequency and its methylation upon the presence of the clinical phenotype.

Methods: : About 850 BS patients seen consecutively at the Cerrahpasa Medical Faculty, rheumatology outpatient clinic between 2013 and 2015 were asked if they had an affected relative with BS. About 150 cases were familial and we studied 15 index patients including their BS relatives (n=17) and their healthy relatives (n=16). All were ³ 20 years of age. Age-gender matched healthy controls were also included (n=25). Peripheral blood samples were collected and genomic DNA was isolated from leukocytes. HLA-B51 genotyping was performed by sequence-specific PCR and random samples were confirmed with Sanger sequencing. HLA-B locus specific methylation levels were analysed using Real-Time based OneStep qMethyl Kit. Chi-square tests were performed to determine significance levels of genotyping results among groups. Statistical analyses were performed using Graphpad Prism 6th Version programme (GraphPad Software, La Jolla California USA).

Results: HLA-B51 carrier rate was significantly higher among index patients (13/15), affected relatives (13/17) and healthy relatives (13/16) compared to healthy controls (8/25), ($p<0.0001$). As seen in the Table 1, both index BS patients and their affected relatives had statistically higher methylation levels for exon-1-intron-1-exon-2 region of HLA-B gene compared to their healthy relatives and healthy controls ($p=0.0044$). Methylation levels of index patients and affected relatives were similar. This was also true for the methylation level of healthy relatives and healthy controls.

Conclusion: These findings point to a role of allele-specific methylation on BS pathogenesis and deserve further scrutiny.

Table 1: Mean methylation levels and mean age for four groups.

	Mean age	**Mean Methylation Levels** (exon-1-intron-1-exon-2 region of HLA-B gene) **(%)**	**95 % CI values**
Index patients (n=15)	37.3 ± 7.0	112.4 ± 14.5	82.66 - 142.2
Affected relatives (n=17)	44 ± 8.5	122.0 ± 15.4	90.72-153.3
Healthy relatives (n=16)	39.8 ± 15.3	70.5 ± 7.5	55.14-85.79
Healthy controls(n=20)	40.7 ± 7.5	69.3 ± 7.3	54.61-84.00

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Abstract Number: 1248

Discovery of Novel Serum Biomarkers for Osteoarthritis Using Affinity Proteomics

Lucía Lourido[1,2], Burcu Ayoglu[3], Juan Fernández-Tajes[4], Frauke Henjes[3], Jochen M. Schwenk[3], Cristina Ruiz-Romero[1,5], Peter Nilsson[3] and Francisco J. Blanco[2], [1]Rheumatology Division. ProteoRed-ISCIII. Proteomic Group, Inibic- C. Hospitalario Universitario A Coruña, A Coruña, Spain, [2]RIER-RED de Inflamación y Enfermedades Reumáticas, INIBIC-CHUAC, A Coruña, Spain, A Coruña, Spain, [3]Affinity Proteomics, SciLifeLab, School of Biotechnology, KTH - Royal Institute of Technology, Stockholm, Sweden, Stockholm, Sweden, [4]Wellcome Trust Centre For Human Genetics, McCarthy's Group, University of Oxford, Roosevelt Drive, Oxford OX3 7BN, United Kingdom, Oxford, England, [5]CIBER-BBN Instituto de Salud Carlos III, INIBIC-CHUAC, A Coruña, Spain, A Coruña, Spain
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Background/Purpose:

Osteoarthritis (OA) is the most common rheumatic disease. Despite active research in the OA biomarker field, no single protein is sufficiently reliable for its use in diagnosis. This is mainly due to the lack of validation studies in large populations, which makes the findings questionable to be considered as robust biomarkers.

In this work we have undertaken a large-scale study in order to find novel serum proteins that could serve as potential indicators of OA.

Methods:

Antibody suspension bead arrays were applied to profile serum samples from patients with OA (n=288), and compare them to patients with rheumatoid arthritis (RA, n=288), psoriatic arthritis (PSA, n=288) and control (n=96) subjects. The serum protein content was labelled and the protein profiles were obtained using 174 antibodies from the Human Protein Atlas, targeting 78 different proteins. The panel of proteins proposed and analysed for this study was selected on the basis of previous protein profiling studies in the context of rheumatic diseases. A focused bead array was then built to further profile 46 selected protein targets as a replication of the first findings, and also to validate these results in an independent cohort of samples composed by patients with OA (n=196), RA (n=192), PSA (n=192) and control individuals (n=92). For the statistical analysis, a lineal regression analysis adjusting by sex, age and BMI was applied to observe differences in protein profiles between groups. These were denoted statistically significant if they concordantly revealed p.values < 0.05 in the different assays and cohorts.

Results:

Four proteins were found elevated in serum from OA patients compared to controls: S100 calcium binding protein A6 (S100A6), leptin (LEP), Complement 3 (C3) and Inter-Alpha-Trypsin Inhibitor Heavy Chain (ITIH1); and two proteins, Apolipoprotein A-I (APOA1) and Vitamin D-binding protein (GC) were significantly increased in controls compared to OA patients. C3 protein levels also can discriminate among OA, RA and PSA patients being increased in OA patients. ITIH1, a hyaluronic protein carrier, also shows higher protein levels in OA sera compared to RA serum samples. Interestingly, S100A6, a protein involved in chondrocyte differentiation, was also found increased in K&L>2 scores compared to controls (K&L 0 and 1) in both cohorts of samples.

Conclusion:

Broad-scale profiling of protein levels in serum enables the discovery of potential novel biomarkers in osteoarthritis. Using antibody suspension bead arrays we have defined an interesting panel of seven biomarker candidates, which allows distinguishing serum samples from control individuals, OA patients and patients from other rheumatic diseases. The alterations of these proteins provide new potential serum biomarkers of disease, bringing new insights to the OA biomarker field and contributing to a better understanding of OA pathology. Moreover, we have found that S100A6 can be a novel potential early biomarker in OA.

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Differential Expression of SLE Susceptibility Genes By Interferon-Alpha and the HLA-DRB1*03:01 Haplotype in Ex Vivo B Cells

Carolina Duarte[1], Lora Boteva[2], Timothy Vyse[1] and Michelle Fernando[1], [1]Division of Genetics and Molecular Medicine and Division of Immunology, Infection and Inflammatory Disease, King's College London, London, United Kingdom, [2]MRC Human Genetics Unit, University of Edinburgh, Edinburgh, United Kingdom

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Background/Purpose: Systemic lupus erythematosus (SLE) is a complex genetic autoimmune disease characterized by autoantibody production and up-regulation of type 1 interferons (IFNs). The strongest genetic association in Europeans is tagged by the *HLA-DRB1*03:01* extended haplotype, located in the MHC region on chromosome 6. Due to tight linkage disequilibrium and high polymorphism, the molecular mechanisms underlying the *DRB1*03:01* association remain elusive. Coding and non-coding variants arising from this haplotype may play a role in disease susceptibility through regulating gene expression in a context-specific manner.

We therefore sought to investigate the effect of the SLE susceptibility factors (i) IFN-α and (ii) the *DRB1*03:01* haplotype on gene expression in *ex vivo* B cells.

Methods: Fifty healthy European women harbouring *DRB1*03:01* homozygous (n=17), heterozygous (n=3) and non-*DRB1*03:01* (n=30) haplotypes were included in the study. RNA was extracted from negatively-selected *ex vivo*B cells at rest (n=49) and after stimulation with IFN-α (n=33). Genome-wide gene expression levels were quantified using the Affymetrix Human Exon 1.0 ST array and TaqMan qPCR. Differential expression was calculated using an ANOVA in Partek Genomics Suite and R (FDR<1%).

Results: Thirty-three per cent (5,163 / 15,468) of genes genome-wide are differentially expressed between resting and IFN-α-treated cells. Forty per cent of SLE ($p=4x10^{-2}$) and 53% ($p=6x10^{-6}$) of RA susceptibility genes from genome-wide association studies are significantly enriched in this data set, compared to IBD (30%, p=0.07).

As expected, these include members of the type 1 IFN pathway, such as the SLE risk genes *IRF7* (fold change, FC=7.2) and *STAT4* (FC=6.8). Interestingly, a number of SLE genes outside canonical type 1 IFN pathways are significantly down-regulated in response to IFN-α, including *FCGR2B* (FC=-2.7), *ETS1* (FC=-1.7) and *NCF2* (FC=-2.3). In addition, IFN-α decreases the expression of genes implicated in familial SLE, such as the B cell survival gene, *PRKCD* (FC=-1.2).

Furthermore, we find that the MHC class II gene, *HLA-DPB1*, is significantly up-regulated in *DRB1*03:01* haplotypes compared to non-*DRB1*03:01*haplotypes at a similar level in resting cells and IFN-α-stimulated cells (FC=1.2).

Conclusion: Stimulation of B cells with IFN-α significantly alters expression of genes associated with idiopathic and familial SLE not previously reported to be involved in the type 1 IFN response. Down-regulation of a number of these genes by IFN-α parallels previously reported loss-of-function polymorphisms associated with SLE susceptibility. We also report a *cis*-eQTL (expression quantitative trait locus) between the *DRB1*03:01* haplotype and *HLA-DPB1*, implicating a role for this haplotype in gene regulation. These data shed light into the role of IFN-α in the aetiopathogenesis of SLE and implicate *HLA-DPB1* as an additional candidate gene underlying the *DRB1*03:01* association with autoimmunity.

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Abstract Number: 1250

DNA Methylation and Its Relation to Immunological Phenotypes in Peripheral Blood: A Study of Anti-CCP Antibody Positivity from a Population-Based Pool

Sasha Bernatsky[1], Xiaojian Shao[2], Marie-Michelle Simon[2], Marvin J. Fritzler[3], Philip Awadalla[4,5], Marie Hudson[6], Ines Colmegna[7], Tony Kwan[2] and Tomi Pastinen[2], [1]Divisions of Rheumatology and Clinical Epidemiology, McGill University Health Centre, Montreal, QC, Canada, [2]Department of Human Genetics, McGill University and Génome Québec Innovation Centre, Montreal, QC, Canada, [3]Medicine, University of Calgary, Calgary, AB, Canada, [4]Medicine, Université de Montreal, Montreal, QC, Canada, [5]Ontario Institute for Cancer Research, Toronto, ON, Canada, [6]McGill University, Jewish General Hospital, Montreal, QC, Canada, [7]Rheumatology, McGill University Health Centre, Montreal, QC, Canada
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Background/Purpose: DNA methylation represents an important potential mediator of environmental influences on autoimmunity, including rheumatoid arthritis (RA). Genome-wide methylation in the context of clinical phenotypes is most commonly performed using Illumina Human 450K methylation arrays. These assay only about 1% of dynamic methylome in the genome and underestimate the impact of methylation differences distal to CpG-rich regions as well as intergenic functional elements. To overcome these limitations, we developed a comprehensive approach to study blood (immune cell) methylomes. We used this to compare DNA methylation in subjects positive vs. negative for anti-cyclic citrullinated peptide (anti-CCP, a key serological marker of RA risk).

Methods: Using banked serum from a random subset of a general population cohort, we identified 22 subjects who were anti-CCP positive and 24 who were anti-CCP negative. Custom capture of target regions by SeqCap Epi (Roche) allows targeting of desired genomic regions as we described earlier (Allum et al. Nat Comm. 2015) to conduct genome-wide bisulphite sequencing. For this study we have established an "immune-methylome" panel that targets regulatory elements in approximately 20 immune cell subsets along with content of 450K arrays and regions genetically associated with autoimmune/inflammatory diseases. Altogether approximately 120Mb of genomic DNA harboring 4.6M CpG sites were interrogated by our assay.

Results: First-pass data analyses in peripheral blood of 22 anti-CCP positive and 24 anti-CCP negative subjects (sequenced to 10-15x average depth) show the clear advantages of comprehensive methylome assessment. We detected 2600 significant CpGs, of which only about 8% were represented in Illumina 450K arrays. The variation among the groups was depleted at proximal promoters and enriched in gene distal regions. The annotation of immunologic signatures by GREAT for the differentially methylated sites show distinct gene sets impacted by relative hyper- or hypo-methylation in anti-CCP positive vs. negative subjects.

Conclusion: These novel methods represent a comprehensive tool to assess methylation variation and its relation to immunological phenotypes in peripheral blood, with clear differences being shown in anti-CCP positive vs. negative subjects.

Disclosure: S. Bernatsky, None; **X. Shao**, None; **M. M. Simon**, None; **M. J. Fritzler**, None; **P. Awadalla**, None; **M. Hudson**, None; **I. Colmegna**, None; **T. Kwan**, None; **T. Pastinen**, None.

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Abstract Number: 1251

Physiological Evidence for Diversification of the IFNα- or IFNβ-Mediated Response Programs in Different Autoimmune Diseases

Tamarah D. de Jong[1], Saskia Vosslamber[1], Elise Mantel[1], Sander de Ridder[1], John G. Wesseling[1], Tineke C.T.M. van der Pouw Kraan[2], Joep Killestein[3], Ingrid E. Lundberg[4], Jiri Vencovsky[5,6], Irene E.M. Bultink[7], Alexandre E. Voskuyl[8], Michiel Pegtel[1], Conny J. van der Laken[9], Johannes W. Bijlsma[8] and Cornelis L. Verweij[1], [1]Pathology, VU University medical center, Amsterdam, Netherlands, [2]Molecular Cell Biology and Immunology, VU University medical center, Amsterdam, Netherlands, [3]Neurology, VU University medical center, Amsterdam, Netherlands, [4]Rheumatology Unit, Karolinska University Hospital, Solna, Karolinska Institutet, Stockholm, Sweden, [5]Rheumatology, Institute of Rheumatology and Department of Rheumatology, 1st Faculty of Medicine, Charles University, Prague, Czech Republic, [6]Institute of Rheumatology and Department of Rheumatology, 1st Faculty of Medicine, Charles University, Prague, Czech Republic, Prague, Czech Republic, [7]Amsterdam Rheumatology and immunology Center, location VU University medical center, Amsterdam, Netherlands, [8]Rheumatology, Amsterdam Rheumatology and immunology Center, location VU University medical center,

Amsterdam, Netherlands, [9]Rheumatology, VU University medical center, Amsterdam, Netherlands
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Background/Purpose: Presence of a type I interferon (IFN) signature is described for several autoimmune diseases, including systemic lupus erythematosus (SLE), multiple sclerosis (MS), myositis (IIM) and rheumatoid arthritis (RA). While IFNα contributes to SLE pathology, IFNβ therapy is beneficial for many MS patients, implying different immunoregulatory roles for these IFNs. This study aims to investigate potential diversification of the IFNα- and IFNβ-mediated response programs in autoimmune diseases.

Methods: Peripheral blood gene expression of 23 known type I IFN response genes (IRGs) was determined in healthy controls (n=54), SLE (n=47), IFNβ-treated MS (3 months, n=72), untreated MS (n=164), IIM (n=78) and RA patients (n=76) by multiplex qPCR. An IFN score was calculated and patients with a type I IFN signature –defined as an IFN score above the mean+2SD in HC– were selected for analysis.

Results: Unsupervised cluster analysis of SLE (IFNα-driven) and IFNβ-treated MS patients showed excellent separation based on two IRG clusters. Statistical testing revealed increased expression of 5 IRGs in SLE (Gene cluster (GC-)A, $p \leq 0.006$) and 13 IRGs in IFNβ-treated MS (Gene cluster (GC-)B, $p \leq 0.044$), believed to reflect IFNα- and IFNβ-specific response programs, respectively. Concordantly, the GC-A/GC-B log-ratio was positive for all SLE patients and negative for virtually all IFNβ-treated MS patients.

Using this information, we determined the nature of type I IFN signature in IIM, RA and untreated MS. IIM displayed relative GC-A dominance as reflected by positive GC-A/GC-B log-ratios, indicating predominant IFNα activity in this disease. The GC-A/GC-B log-ratio in RA was lower and approached zero in part of the patients, implying relative importance of both clusters. Remarkably, GC-A/GC-B log-ratios appeared most heterogeneous in untreated MS; half of the patients displayed GC-A (IFNα) dominance, whereas others showed GC-B (IFNβ) dominance or log-ratios near zero.

We confirmed these results for SLE, RA and MS using two public microarray datasets containing 22 SLE patients, 112 RA patients, 58 IFNβ-treated MS patients and 62 untreated MS patients.

Exploring functional differences between GC-A and GC-B genes revealed enrichment of the ISGF3-binding response element ISRE and IRF8 binding sites only in GC-B, suggesting that IFNβ is more potent in activating these transcription factors than IFNα.

Conclusion: We provide physiological evidence for diversification of the type I IFN response in SLE (IFNα-driven) and IFNβ-treated MS patients. Using this information we demonstrate that IIM appears IFNα-driven, supporting the previously described pathogenic role of IFNα in IIM. RA patients exhibited less distinct IFNα/IFNβ dominance. Untreated MS patients displayed interindividual variation in GC-A or GC-B dominance, suggesting a different pathogenic role of the type I IFNs in these patients.

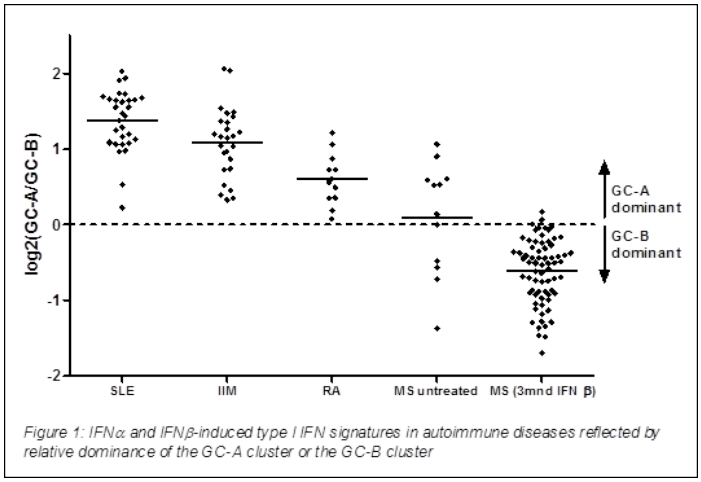

Figure 1: IFNα and IFNβ-induced type I IFN signatures in autoimmune diseases reflected by relative dominance of the GC-A cluster or the GC-B cluster

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or-ifn-mediated-response-programs-in-different-autoimmune-diseases

Abstract Number: 1252

Serum Biomarkers Associated with Disease Activity and Response to Ustekinumab in Patients with Ankylosing Spondylitis

Bidisha Dasgupta[1], Shannon Telesco[2], Joachim Sieper[3] and Denis Poddubnyy[4], [1]Janssen Research & Development, LLC., Spring House, PA, [2]Janssen R & D, LLC, Spring House, PA, [3]University Clinic Benjamin Franklin, Berlin, Germany, [4]Rheumatology, Charité - Campus Benjamin Franklin, Berlin, Germany

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Background/Purpose: A recent POC, open label trial (TOPAS)[1] showed efficacy of ustekinumab (a monoclonal antibody against IL12 and IL23p40 in pts with active AS. To identify novel serum biomarkers associated with disease activity and response to ustekinumab treatment in pts with AS.

Methods: We profiled 20 AS pts from the TOPAS study[1] (treated with 90 mg ustekinumab SC at baseline, wk 4 and wk 16) and compared to an independent cohort of 30 healthy normal volunteers (HNV). Samples collected at wk0 and wk24 were assayed using the SOMAmer^{TM} (Slow Off-rate Modified Aptamer)-based proteomic assay[2], which measured 1129 analytes. A general linear model was applied to identify analytes that differed between AS and HNV and within subjects before and after treatment using a fold change (FC) cutoff of $|FC|>1.3$ and p value cutoff of $p<0.05$. Correlation between serum markers and disease activity scores was evaluated by the Spearman rank correlation test. **Results** were interpreted via Ingenuity Pathway Analysis (IPA). Disease activity was specified by Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Ankylosing Spondylitis Disease Activity Score (ASDAS) and Osteitis MRI Scores (Berlin method) for sacroiliac joints and spine. Clinical response to ustekinumab was defined as 50% improvement in BASDAI at wk24 as compared to baseline.

Results: 113 analytes were differentially expressed in AS compared to HNV. The top dysregulated pathways were Acute Phase Response Signaling, Role of Macrophages, Fibroblasts and Endothelial Cells and Inflammation. Following ustekinumab treatment, proteins involved in Acute Phase Response Signaling were significantly modulated and C-reactive Protein (CRP) decreased (p=0.009) in BASDAI 50 responders but not non-responders. At baseline, Stanniocalcin-1 (STC1, p = 0.0012), Thyroid Stimulating Hormone (p=0.0051), Tumor Necrosis Factor Receptor Superfamily 2 (TNFRSF2, p=0.0132) and Spondin-1 (SPON1, p= 0.0135) correlated to BASDAI score, and Interleukin 13 Receptor alpha 1 (IL13RA1, p=0.0019), and Bone Morphogenetic Protein Receptor 1A (BMPR1A, p= 0.0036) correlated to ASDAS. Chk protein kinase 1 (CHEK1, p=0.0017), and ADAM metallopeptidase 5 (ADAMST5, p=0.0024) correlated to baseline osteitis on MRI and markers known to be involved in bone remodeling i.e. Dickkopf Like Protein 1 (DKKL1, p=0.0092), Semaphorin 3E (SEMA3E, p= 4.29E-05), SPON1 (p= 0.0002), ADAM12 (p=0.0002), and CLIC1 (p= 0.0003) correlated with wk24 change in osteitis and spinal osteitis scores. Baseline levels of acute phase markers showed a trend for association with response. BASDAI 50 responders had decreased Complement component 3 (C3, p=0.0120) and fibronectin (FN, p=0.0131), increased Haptoglobin (HP, p=0.0095) and predicted inhibition of Colony Stimulating Factor 1 (CSF-1, implicated in osteoclast differentiation) at baseline.

Conclusion: Evidence for significant dysregulation of inflammatory pathways and bone remodeling can be demonstrated from the serum of AS patients. Novel serum markers associated with AS disease activity and response to ustekinumab, were identified. We plan for future assessment of these markers in an expanded placebo controlled cohort.

[1]Ann Rheum Dis 2014;73:817–823. [2]PLoS ONE 5: e15004

Disclosure: B. Dasgupta, Janssen R & D, LLC, 3; **S. Telesco**, Janssen R & D, LLC, 3; **J. Sieper**, Janssen R & D, LLC, 2; **D. Poddubnyy**, Janssen R & D, LLC, 2.

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Abstract Number: 1253

Identification and Validation of Novel Putative Salivary Proteomic Biomarkers in Sjögren's Syndrome and Different Disease Subsets

Chiara Baldini[1], Daniela Martini[1], Nadia Ucciferri[2], Silvia Rocchiccioli[2], Letizia Mattii[3], Antonietta Raffaella Maria Sabbatini[3], Francesca Sernissi[1], Francesco Ferro[1], Nicoletta Luciano[1], Leonardo Lorenzini[1], Marta Mosca[4], Stefano Bombardieri[1] and Antonella Cecchettini[3], [1]Rheumatology Unit, University of Pisa, Italy, Pisa, Italy, [2]Institute of Clinical Physiology, Pisa, Italy, Pisa, Italy, [3]Department of Clinical and Experimental Medicine, University of Pisa, Italy, Pisa, Italy, [4]University of Pisa, Pisa, Italy
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Background/Purpose: Salivary proteomics has recently appeared as a promising tool for the identification of novel diagnostic biomarkers for primary Sjögren's syndrome (SS). However, to date the vast majority of the studies have focused the attention essentially on a restricted panel of high-abundance proteins, partially limiting the diagnostic potentiality of salivary proteomics. Moreover, the clinical inter-subject variability of SS seem to be reflected in the variability of the proteomic profiling. Aims of this study were: 1) to identify and validate putative salivary biomarkers in SS by using LC-MS/MS. 2) to highlight a specific fingerprint able to discriminate between different SS phenotypes, defined on the basis of the focus score (FS) and on the variation of the salivary flow rate (USFR).

Methods: USFR was collected from 18 patients with SS (AECG criteria, 2002). Six patients presented a high focus score (FS≥3) and normal USFR (group A), six patients presented a FS≥3 and an USFR<1.5 ml/15 (Group B), and 6 patients a low focus score (FS<3) and USFR <1.5 ml/15 (group C). Six healthy volunteers (CTRL) represented the controls. ProteoPreop Immunoaffinity Albumin and IgG depletion kit (Sigma) was used for high-abundance proteins removal. A high-throughput liquid chromatography tandem mass spectrometry (LC-MS/MS) was used for the proteomic analysis. Western Blotting (WB) and immunohistochemistry on minor salivary gland biopsies were used to validate proteomics results. Principal component analysis (PCA) was utilized for statistical analysis.

Results: Overall, 100 differentially expressed candidate biomarkers were identified. When compared to CTRL, the salivary proteomic profile of SS patients was characterized by 20 proteins which were significantly decreased and 113 proteins which were significantly increased. Among the differentially expressed proteins, of interest were: proline-rich proteins, cystatins, calcium-binding proteins, antigen binding proteins, profilin and other cell motion-related proteins, proteins involved in apoptosis, defence- and inflammatory-response. PCA distinctively discriminate between CTRL and SS patients stratified as previously described. Preliminary validation by WB and immunohistochemistry of prolactin-inducible protein precursor, cystatins C, S and SA, S-100A7 protein, kallikrein-6 and histhidine-rich glycoprotein indicated similar expression profile trends to those identified by LC-MS/MS.

Conclusion: The proteomics workflow was able to detect novel candidate biomarkers potentially related to specific phenotypes of SS disease. These candidate biomarkers might be useful to improve SS non-invasive diagnosis and clinical stratification.

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Abstract Number: 1254

Deciphering the Immunome of Clinically Effective Immune Tolerization in Rheumatoid Arthritis

Jing Yao Leong[1,2], Raymond Ong Jr.[3], Juntao Li[4], Theodorus van den Broek[5], Roberto Spreafico[4], Maura Rossetti[1] and Salvatore Albani[1,2], [1]SingHealth Translational Immunology and Inflammation Centre, Singapore Health Services Pte Ltd, Singapore, Singapore, [2]Duke-National University of Singapore Graduate Medical School, Singapore, Singapore, [3]Singhealth Translational Immunology and Inflammation Centre (STIIC), Singapore Health Services Pte Ltd, Singapore, Singapore, [4]SingHealth Translational Immunology and Inflammation Centre (STIIC), Singapore Health Services Pte Ltd, Singapore, Singapore, [5]Translational Research Unit, Sanford-Burnham

Medical Research Institute, La Jolla, CA
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Background/Purpose:

We have previously described (*Nature Medicine, PNAS, A&R, Nature Rheum, Lancet*) how oral treatment with the pro-inflammatory, heat shock protein-derived dnaJP1 peptide induces detectable clinical amelioration in Phase I and IIa clinical studies in rheumatoid arthritis. In previous work, we have also identified T effector (Teff) immune deviation and an increase in PD-1 Treg subsets as some of the immune mechanisms leading to clinical improvement. Clinical and immunological data also emphasized a synergistic effect with hydroxychloroquine (HCQ). Our previous studies, however, did not capture, yet, the complexity of the dynamic interactions among subsets of immune cells. Here, we apply a novel approach aiming at addressing this unmet need.

Methods:

Patient selection, randomization treatment and assessment of clinical outcomes were previously described (Koffeman, et al 2009, Arthritis & Rheumatism). Antibody panels were designed, based on previous specific experience and data, to encompass the major subsets of immune cells and employed to study by flow cytometry PBMCs from two treatment cohorts: (a) dnaJP1-HCQ responders (n=6) (b) Placebo HCQ Non Responders (n=10) We have substantially modified and adapted for use in translational research the clustering software ACCENSE (Shekhar, et al, 2014, PNAS). The work flow is presented in Fig. 1, and FD is defined as fold difference percentage of responders over non responders cells.

Results:

T cell subsets which were significantly more represented in dnaJP1 responders were antigen experienced, activated T cells which displayed tolerogenic/regulatory characteristics ($CD4^{+}CD45RO^{+}TGF\text{-}B^{int}CD69^{int}$, FD= 17) and ($CD4^{+}HLA\text{-}DR^{hi}GITR^{int/high}$, FD = 27). Intriguingly we also detected $FoxP3^{hi}$ T cells which may represent regulatory subsets transiting between inflammatory ($CCR5^{hi}CXCR3^{hi}$, FD = 9) and mucosal ($CD103^{hi}CD27^{hi}CD62L^{hi}$, FD = 7) compartments.

Analysis of the antigen presentation cells (APCs) compartment revealed two functionally distinct subsets which are significantly elevated in dnaJP1 clinical responders, both subsets probably the outcome of cross talk between tolerized/regulatory T cells and APC: (a) $CD14^{+}CD16^{+}CD303^{hi}CD141^{hi}$ (FD = 10) monocytes that exhibit $CD86^{hi}$ expression, which has been described to relate to and augment Treg function, (b) APCs which manifest a mature phenotype ($CD83^{+}$), subdivided into 3 lineages (i) $CD19^{hi}$ B cells (FD = 9), (ii) dendritic cells $CD1c^{hi}$ (FD = 72) and (iii) $CD1c^{lo}$ (FD = 19).

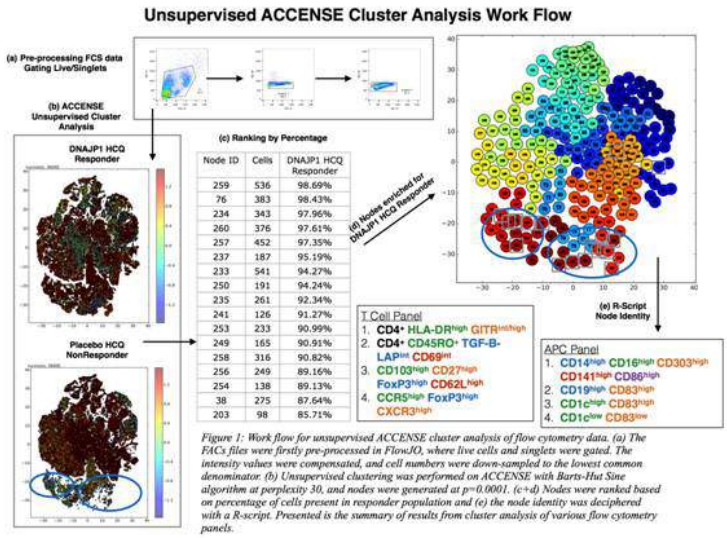

Figure 1: Work flow for unsupervised ACCENSE cluster analysis of flow cytometry data. (a) The FACs files were firstly pre-processed in FlowJO, where live cells and singlets were gated. The intensity values were compensated, and cell numbers were down-sampled to the lowest common denominator. (b) Unsupervised clustering was performed on ACCENSE with Barts-Hut Sine algorithm at perplexity 30, and nodes were generated at p=0.0001. (c+d) Nodes were ranked based on percentage of cells present in responder population and (e) the node identity was deciphered with a R-script. Presented is the summary of results from cluster analysis of various flow cytometry panels.

Conclusion:

A holistic approach to the immunome confirmed the specificity and complexity of the immune tolerization mechanism, which relies on the interplay between effector and regulatory T cells and APC. This approach has a dual translational value, as it provides mechanistic knowledge and also potential biomarkers directly related to the therapeutic intervention.

Disclosure: J. Y. Leong, None; **R. Ong Jr.**, None; **J. Li**, None; **T. V. D. Broek**, None; **R. Spreafico**, None; **M. Rossetti**, None; **S. Albani**, Patent, 9.

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Abstract Number: 1255

Genome-Wide DNA Methylation Patterns in CD4+ T Reveal Significant Contribution of DNA Methylation to Rheumatoid Arthritis

Shicheng Guo[1,2], Ting Jiang[1,2], Rongsheng Wang[1,2], Yi Shen[1,2], Xiao Zhu[3], Fengmin Bai[1,2], Qin Ding[1,2], Guangjie Chen[4] and Dongyi He[1,2], [1]Department of Rheumatology, Shanghai Guanghua Hospital of Integrated Traditional and Western Medicine, Shanghai, China, [2]Arthritis Institute of integrated Traditional and Western medicine, Shanghai Chinese Medicine Research Institute, Shanghai, China, [3]Guangdong Provincial Key Laboratory of Medical Molecular Diagnostics, Guangdong Medical University, Guangzhou, China, [4]Department of Immunology and Microbiology, Shanghai JiaoTong University School of Medicine, Shanghai, China
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Background/Purpose: Rheumatoid arthritis (RA) is an autoimmune disease that causes chronic inflammation of the joints. Recent evidence showed more and more importance of the epigenetic contribution, especially the DNA methylation, to the pathogenesis of rheumatoid arthritis. Identification of aberrant DNA methylation regions in RA would provide important for the comprehensively understand to the pathogenesis of rheumatoid.

Methods: We performed a genome-wide DNA methylation study in CD4+ T cells in 12 rheumatoid arthritis patients compared to 12 matched normal healthy controls. CD4+ T cells were prepared from freshly isolated PBMCs by depleting cells expressing CD8, CD14, CD16, CD19, CD36, CD56, CD123, γ/δ T cell receptors, and glycophorin A using No-Touch T cell isolation kits (Miltenyi Biotec). The purity of the CD4+ T cells was 95–98%, as determined by flow cytometry using specific antibodies.Cytosine methylation status was quantified with Illumina methylation 450K microarray (HM450K, 485512 CpG sites). Beta-mixture quantile normalization, batch effect correction, outlier probe imputation were applied in the data pre-processing to keep the data creditable for the follow analysis.

Results: We identified 810 hypomethylated and 392 hypermethylated CG sites in RA CD4+ T cells compared to normal controls, representing 383 and 785 genes hypermethylated and hypomethylated in RA patients ($P<3.4\times10^{-7}$). Cluster analysis based on significantly differential methylated loci showed distinct separation between RA and normal controls. Gene ontology analysis showed alternative splicing ($P=1.2\times10^{-7}$, FDR) and phosphoprotein (1.7×10^{-2}, FDR) were significantly aberrant in RA patients, indicating the abnormal of transcript alternative splicing and protein modification mediated by DNA methylation might play important role in the pathogenesis of rheumatoid arthritis. What's more, the result showed human leukocyte antigen (HLA) region was frequently hypomethylated in RA patients, including HLA-DRB6, HLA-DQA1 and HLA-E, however, HLA-DQB1 showed different methylation profiles with significant hypermethylation in CpG island region and hypomethylation in CpG shelf region. Outsite of the MHC region, the most hypermethylated genes in RA included HDAC4, NXN, TBCD and TMEM61 while the most significant hypomethylated genes included ITIH3, TCN2, PRDM16, SLC1A5 and GALNT9.

Conclusion: Genome-wide DNA methylation patterns revealed significant DNA methylation change in CD4+ T cells from patients with rheumatoid arthritis which might provide contribution to the pathogenesis of rheumatoid arthritis

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Disclosure: S. Guo, None; **T. Jiang**, None; **R. Wang**, None; **Y. Shen**, None; **X. Zhu**, None; **F. Bai**, None; **Q. Ding**, None; **G. Chen**, None; **D. He**, None.

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reveal-significant-contribution-of-dna-methylation-to-rheumatoid-arthritis

Abstract Number: 1256

Gas Chromatography/Time-of-Flight-Mass Spectrometry-Based Metabolomic Profiling in Cultured Fibroblast-like Synoviocytes from Rheumatoid Arthritis

Joong Kyong Ahn[1], Sooah Kim[2], Jiwon Hwang[1], Jungyeon Kim[2], Young Hee Eun[3], Hyemin Jeong[4], Ji-Min Oh[5], Hyungjin Kim[3], Jaejoon Lee[3], Eun-Mi Koh[3], Kyoung Heon Kim[2] and Hoon-Suk Cha[6], [1]Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, Seoul, South Korea, [2]Department of Biotechnology, Korea University Graduate School, Seoul, South Korea, [3]Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea, [4]Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea, [5]Anyang SAM Hospital, Anyang, South Korea, [6]Division of Rheumatology, Department of Internal Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea
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Background/Purpose: Rheumatoid arthritis (RA) is a chronic systemic autoimmune disease characterized by synovial inflammation and hyperplasia. Fibroblast-like synoviocytes (FLS) in RA exhibit a tumor cell-like aggressive phenotype and have a major role in the initiation and perpetuation of joint inflammation. The metabolomic approach enables the elucidation of the current physiological or pathological states of individual cells that result from the interactions between genes and the environment. A systematic characterization of the metabolic pathways in transformed RA FLS is currently lacking. Thus, gas chromatography/time-of-flight-mass spectrometry (GC/TOF-MS) was employed to identify the characteristic metabolic profiling of RA FLS compared to that of osteoarthritis (OA) FLS.

Methods: Metabolite profiling of RA FLS and OA FLS ($N = 6$, respectively) was performed using GC/TOF-MS in conjunction with univariate and multivariate statistical analyses. We performed metabolite set enrichment analysis (MSEA) to establish which pathways are affected.

Results: A total of 129 metabolites were identified and were classified into sugars and sugar alcohols (20.9% of identified metabolites), amino acids (20.2%), organic acids (19.4%), fatty acids (15.5%), amines (10.9%), phosphates (7.0%), and miscellaneous compounds (6.2%). A principal component analysis based on cellular metabolites showed very clear discrimination between the intracellular metabolite profiles of the two groups ($R^2X = 53.9\%$ and $Q^2 = 59.5\%$). The levels of 35 metabolites that belonged to the amines, fatty acids, phosphates, and organic acids class were significantly increased in RA FLS compared to those in OA FLS. Also, the levels of 26 metabolites that belonged to the amino acids, sugars, and sugar alcohols class were significantly decreased in RA FLS compared to those in OA FLS. MSEA demonstrated that the sugar metabolic pathways such as glycolysis, galactose metabolism, gluconeogenesis, and the pentose phosphate pathway; the amino acid metabolism pathways such as tyrosine, phenylalanine, and catecholamine biosynthesis; protein biosynthesis, and the urea cycle were severely disturbed in RA FLS compared to OA FLS.

Conclusion: Our metabolic results suggested that the alteration of sugar metabolism, lipolysis, and amino acid metabolism in RA FLS is related to synovial hyperplasia and inflammation. This is the first metabolomic study to determine metabolic changes characteristic of RA FLS, which will provide valuable information to gain in-depth insights into the pathogenesis of RA.

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View Abstract and Citation Information Online - http://acrabstracts.org/abstract/gas-chromatographytime-of-flight-mass-spectrometry-based-metabolomic-profiling-in-cultured-fibroblast-like-synoviocytes-from-rheumatoid-arthritis

Abstract Number: 1257

Genome-Wide DNA Methylation Signatures of Salivary Gland Inflammation in Sjögren's Syndrome

Michael Cole[1], Diana Quach[1], Hong L. Quach[1], Lisa F. Barcellos[1] and **Lindsey A. Criswell**[2], [1]Genetic Epidemiology and Genomics Laboratory, University of California, Berkeley, Berkeley, CA, [2]Rosalind Russell / Ephraim P. Engleman Rheumatology Research Center, University of California, San Francisco, San Francisco, CA
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Background/Purpose: Sjögren's Syndrome (SS, OMIM #270150) is a chronic, multi-system autoimmune disease characterized by progressive destruction of the exocrine glands, with subsequent mucosal and conjunctival dryness. A growing body of evidence indicates that many epigenetic changes are associated with disease status and that epigenetic marks can provide unique insights into complex disease mechanisms. We report on results of a case-control study of DNA methylation (DNAm) differences within labial salivary gland tissue, using biopsies sampled from 13 severe SS cases and 13 controls in the Sjögren's International Collaborative Clinical Alliance (SICCA; http://sicca.ucsf.edu/; HHSN268201300057C) registry.

Methods: We have methylotyped gland tissue and sorted PBMCs from these subjects using the Illumina HumanMethylation450 (450k) BeadChip platform. In addition to standard background correction and normalization techniques, we applied an adaptive normalization scheme to adjust for residual associations between DNAm and control measures.

Results: Principal component analysis (PCA), applied to the 404,353 CpG sites passing strict QC criteria, clearly distinguishes glands of primary SS cases from those of controls. We find over 10,000 significant differentially methylated positions (DMPs) that show significant overlap with the promoters of genetic risk loci as a whole, with particular enrichment seen in the promoters of *CXCR5* and *BLK*. We also observe an extended region of differential methylation surrounding *PSMB8* and *TAP1* in the MHC class II region. Despite a previous report of association between global DNAm and ICAM1 expression in the context of SS, we fail to detect differential methylation in the promoter of the *ICAM1* locus. On the other hand, differential methylation patterns surrounding several non-coding RNAs suggest many indirect consequences of the observed salivary gland *hypo*-methylation in SS. Transcription factor motif enrichment analysis highlights the specific nature of these methylation differences, demonstrating co-localization of DMPs with interferon- stimulated response element (ISRE) and PU-Box motifs. DNAm signatures derived from sorted PBMCs show that disease-associated changes in DNAm are linearly correlated with cell-type specific patterns, resolving differential lymphocyte proportions.

Conclusion: Our results emphasize the utility of CpG methylation not only as a biomarker of disease status, but also as an independent probe of underlying disease processes.

Disclosure: M. Cole, None; **D. Quach**, None; **H. L. Quach**, None; **L. F. Barcellos**, None; **L. A. Criswell**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/genome-wide-dna-methylation-signatures-of-salivary-gland-inflammation-in-sjogrens-syndrome

Abstract Number: 1258

Identification of a Spectrum of Therapeutic Targets of a New Treatment for Osteoarthritis Composed By Curcuminoids Extract, Hydrolyzed Collagen and Green Tea Extract

Fanny Comblain[1], Cécile Lambert[1], Isabelle Lesponne[2], Christelle Sanchez[1], Jean-Emile Dubuc[3] and **Yves Henrotin**[4,5], [1]University of Liège, Bone and Cartilage Research Unit, Arthropôle Liege, University of Liege, Liege, Belgium, [2]Royal Canin Research Center, Aimargues, France, [3]Clinical University Saint Luc, Orthopaedic Department, Clinical University Saint Luc, Brussels, Belgium, [4]Physical Therapy and Rehabilitation Department, Princess Paola Hospital, Marche-en-Famenne, Belgium, [5]Bone and Cartilage Research Unit, Arthropôle Liege, University of Liege, Liege, Belgium
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Background/Purpose: The goal of treatment in OA is to reduce pain and improve function. There is no cure for the disease, but some attempts to slow the progression of the disease. We have previously demonstrated that a mixture of curcuminoids extract, hydrolyzed collagen and green tea extract (COT) inhibited inflammatory and catabolic mediator's synthesis by osteoarthritic human chondrocytes in monolayer [1]. The objective of this study was to identify new targets of COT using genomic and proteomic approaches.

Methods: Enzymatically isolated primary human chondrocytes were cultured in monolayer until confluence and then incubated for 24 or 48 hours in the absence or in the presence of human interleukin-1β (10^{-11} M) and with or without COT, each compound at the concentration of 4 µg/ml. Microarray gene expression profiling between control (ctrl), COT, IL-1β and COT IL-1β conditions was performed. The biological relevance of regulated genes was determined with Ingenuity Pathway Analysis. Immunoassays (ELISA) were used to confirm the identified genes that were differentially expressed.

Results: 2549 genes were differentially expressed between ctrl and IL-1β conditions, 2280 genes were differentially expressed between IL-1β and COT IL-1β conditions and 1907 genes were differentially expressed between ctrl and COT conditions. The key regulated pathways were related to inflammation, cartilage metabolism and angiogenesis. In the inflammatory pattern, the IL 1β stimulated chemokine (C-X-C motif) ligand 6 (CXCL6) gene expression and protein production were strongly down-regulated by COT ($p<0.001$). The most IL-1β up-regulated enzyme in the catabolic pattern was matrix metalloproteinase-13 (MMP-13). Both gene and protein were significantly down regulated by COT ($p<0.001$). The IL 1β-stimulated bone morphogenetic protein-2 (BMP-2) gene expression and protein production were down-regulated by COT ($p=0.001$). In the angiogenesis pathway, one of the most up-regulated factors by IL-1β was stanniocalcin 1 (STC1) ($p=0.005$). This IL 1β stimulating effect was significantly down regulated by COT ($p<0.001$). Moreover, COT significantly decreased STC1 production in basal condition ($p=0.030$). Finally, serpin E1 gene expression and protein production were down-regulated by IL 1β ($p<0.001$). COT fully reversed the inhibitory effect of IL-1β ($p=0.028$). Serpin E1 gene expression was up-regulated by COT in basal condition ($p<0.001$).

Conclusion: The mixture COT has beneficial effect on OA physiopathology by regulating the synthesis of key catabolic, inflammatory and angiogenesis factors. These findings give a scientific rationale for the use of these natural ingredients in the management of OA.

1. Comblain F, Sanchez C, Lesponne I, Balligand M, Serisier S, Henrotin Y. Curcuminoids Extract, Hydrolyzed Collagen and Green Tea Extract Synergically Inhibit Inflammatory and Catabolic Mediator's Synthesis by Normal Bovine and Osteoarthritic Human Chondrocytes in Monolayer. PLoS One. 2015;10(3):e0121654.

Disclosure: F. Comblain, Royal Canin SAS, 2; **C. Lambert**, None; **I. Lesponne**, RandD Scientific Support Manager Royal Canin SAS, 3; **C. Sanchez**, None; **J. E. Dubuc**, None; **Y. Henrotin**, Artialis, Bioiberica, Danone, Expanscience, Ibsa, Merck, Pierre Fabre, Synolyne Pharma, Tilman, 5,Founder and President of Artialis SA and Synolyne Pharma, two spin-off companies of the University of Liege, 9.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/identification-of-a-spectrum-of-therapeutic-targets-of-a-new-treatment-for-osteoarthritis-composed-by-curcuminoids-extract-hydrolyzed-collagen-and-green-tea-extract

Abstract Number: 1259

Verification of Haptoglobin and Von Willebrand Factor As Potential Biomarkers of Knee Osteoarthritis Using a Targeted Proteomics Approach in Serum

Patricia Fernandez-Puente[1], Valentina Calamia[1], Jesús Mateos[1], Lucia Lourido[1], Beatriz Rocha[2], Cristina Ruiz-Romero[1] and Francisco J. Blanco[1], [1]Grupo de Proteomica-PBR2-ProteoRed/ISCIII-Servicio de Reumatologia. Instituto de Investigación Biomédica de A Coruña (INIBIC), Complexo Hospitalario Universitario de A Coruña (CHUAC), Sergas. Universidade da Coruña (UDC). As Xubias, 15006., A Coruña, Spain, [2]Rheumatology Division, Proteomics Group-ProteoRed/ISCIII, INIBIC-CHUAC, A Coruña, Spain
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Background/Purpose:

The current diagnosis of osteoarthritis (OA) relies on the description of pain symptoms, affected joint stiffness, and radiography used as the reference technique for determining the grade of joint destruction. Limitations of the presently available diagnostic tests have provided an impetus for the substantial increase in interest in finding new specific biological markers for OA to facilitate the early diagnosis, evaluate disease progression and improve disease prognosis. Recently, there has been a remarkable development in mass spectrometry-based methodologies for the verification and validation of biomarkers with high specificity and sensitivity, since the multiple reaction monitoring (MRM) assay can measure several targets (peptides) with high sensitivity and throughput in biological samples. The aim of this work was to verify a panel of OA biomarker candidates in serum samples using the MRM technology.

Methods:

Serum samples were obtained from OA patients at different stages of the disease (K/L grade II=38, K/L grade IV=39 and control donors=39). Proteins were quantified and digested with trypsin. The peptide mixture was separated by nano-LC coupled to a 5500 QTRAP mass spectrometer. A single multiplexed MRM assay was used to quantify the levels of seven proteins (identified as putative OA biomarker candidates in shotgun proteomics experiments performed previously by our group) at different stages of OA, and compared to control donors: Pigment epithelium derived factor, Haptoglobin, Von Willebrand factor, Fructose-bisphosphate aldolase A, Insulin-like growth factor-binding protein complex acid labile subunit, C-type lectin domain family 3 member A and matrix metallopeptidase 2. Von Willebrand factor and Haptoglobin were found quantitatively altered in the serum of OA patients compared to control donors. The relative quantification values of peptides were determined by calculating the ratio of peak areas from transitions of target peptides in OA and control samples, normalized to the peak area of the internal standard. Data analysis was performed using the Skyline software. Kruskal–Wallis and Mann–Whitney *U* test were used for the statistical analysis.

Results:

Haptoglobin was found to discriminate between the different K/L grades of OA, and it was found to be altered between early OA compared to controls with a significant p-value. Therefore, this protein could be a putative diagnostic biomarker. On the other hand, Von willebrand factor was found altered in OA vs control samples with a significant p-value ($p<0,05$), but showed no differences between the different K/L grades of OA.

Conclusion:

A multiplexed method for the simultaneous quantification of a panel of seven proteins in serum has been developed, which is based on liquid chromatography-multiple reaction monitoring (LC-MRM) mass spectrometry. By these means, two novel putative OA serum protein biomarkers, Von Willebrand factor and Haptoglobin, were verified in a cohort of individual serum samples. Further qualification studies will be necessary to establish their usefulness for OA diagnosis and progression studies.

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Abstract Number: 1260

Differential DNA Methylation and Reduced Expression of Transcription Factors in Human OA Cartilage

Oscar Alvarez-Garcia[1], Kathleen M. Fisch[1], Ryuichiro Akagi[2,3], Masahiko Saito[4], Takahisa Sasho[4], Andrew I. Su[5] and Martin K. Lotz[6], [1]The Scripps Research Institute, La Jolla, CA, [2]The Scripps Research Institute, San Diego, CA, [3]Department of Orthopaedic Surgery, School of Medicine, Chiba University, Chiba, Japan, [4]Orthopaedic Surgery, Chiba University, Chiba, Japan, [5]Molecular and Experimental Medicine, The Scripps Research Institute, La Jolla, CA, [6]Division of Arthritis, The Scripps Research Institute, La Jolla, CA
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Background/Purpose:

DNA methylation is the most characterized epigenetic mechanism and has been recently linked to knee osteoarthritis (OA) pathogenesis. The present study was design to comprehensively compare the methylome and transcriptome of normal and OA knee articular cartilage using the Illumina Infinium HumanMethylation450 beadchip array and next generation RNA sequencing, respectively. Furthermore, we used different *in vitro*approaches to experimentally validate the link between DNA methylation and gene expression in human chondrocytes.

Methods:

Genomic DNA was isolated from human macroscopically preserved (N=11) and OA (N=12) knee articular cartilage. After bisulphite treatment, DNA was profiled using the Illumina Infinium HumanMethylation450 beadchip. For transcriptomic analysis, RNA isolated from normal (N=8) and OA (N=10) knee articular cartilage was sequenced using the Illumina HiSeq 2000 platform. In both cases, normalized data was analyzed using a custom-made R bioconductor package. For *in vitro*experiments, primary chondrocytes isolated from donors with normal (N=5) cartilage, and TC28 immortalized chondrocytes were used. Cells were cultured in monolayer until confluence, treated with different doses of the DNA methylation inhibitor 5-Aza-2-deoxycytidine (5'Aza) or vehicle, and gene expression was assessed by qPCR.

Results: DNA methylation profiling revealed 2833 differentially methylated sites (DMS) between normal and OA cartilage ($p<0.05$, FDR<1%, delta β-value>0.15). DMS were significantly enriched in gene bodies and enhancer regions of the genome, and comprised a total of 1279 genes. Among these, 102 transcription factors that harbored DMS were identified. Integrative analysis and subsequent validation showed a subset of 8 transcription factors that were significantly hypermethylated and downregulated in OA cartilage (ATOH8, FOXO3, KLF15, MAFF, NCOR2, RARA, TBX4, and ZBTB16). Upon 5'Aza treatment, TC28 cells showed a significant increase in gene expression for all eight transcription factors. In primary chondrocytes, ATOH8, FOXO3 and TBX4 were increased after 5'Aza treatment

Conclusion:

Our findings reveal that normal and OA knee articular cartilage have significantly different methylomes. The identification of a subset of epigenetically regulated transcription factors with reduced expression in OA may represent an important mechanism to explain changes in the chondrocyte transcriptome and function during OA pathogenesis.

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Abstract Number: 1261

Molecular Analysis of Vascular Smooth Muscle Cells from Patients with Giant Cell Arteritis: Targeting Endothelin-1 Receptor to Control Proliferation

Alexis Regent[1], Kim Heang Ly[2], Matthieu Groh[3], Chabha Khifer[4], Sebastien Lofek[5], Mathieu Tamby[6], Guilhem Clary[7], Philippe Chafey[7], Véronique Baud[8], Cédric Broussard[9], Christian Federici[7], Francois Labrousse[10], Laura Mesturoux[11], Claire Le Jeunne[12], Elisabeth Vidal[13], Antoine P. Brezin[14], Veronique Witko-Sarsat[15], Loïc Guillevin[12] and Luc Mouthon[15], [1]Service de médecine interne, Hôpital Cochin, Paris, France, [2]CHU Dupuytren, Limoges, Limoges, France, [3]National Referral Center for Rare Systemic Autoimmune Diseases, Hôpital Cochin, AP–HP, Université Paris Descartes, Paris, Paris, France, [4]Institut Cochin, INSERM U1016, CNRS UMR 8104, Université Paris Descartes, Paris, France, Paris, France, [5]Université Paris Descartes, Paris, France, [6]Institut Cochin, U1016, Paris, France, [7]Institut Cochin, INSERM U1016, CNRS UMR 8104, Université Paris Descartes, Paris, France, [8]Institut cochin, U1016, Paris, France, [9]Inserm U 567, CNRS UMR 8104, Cochin Institute, Paris, France, [10]Department of Pathology, Limoges University Hospital, Limoges, France, [11]CHU Limoges, Limoges, France, [12]Internal Medicine, National Referral Center for Rare Systemic Autoimmune Diseases, Hôpital Cochin, Paris, France, [13]Internal Medecine, Limoges hospital, Paris, France, [14]Université Paris Descartes, Hôpital Cochin, Paris, France, [15]Labex Inflamex, Université Sorbonne Paris Cité, Paris, France

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Background/Purpose:

Vascular remodeling play a major role in the pathophysiology of giant cell arteritis (GCA) and the mechanisms underlying it are poorly understood.

Methods:

Vascular smooth muscle cells (VSMC) were cultured from temporal artery biopsies (TAB) obtained from patients suspected of GCA: patients with biopsy proven GCA (TAB^+-GCA), patients with biopsy-negative GCA (TAB^--GCA), and patients with another diagnosis than GCA (GCA-control). Two-dimension DIGE (2D-DIGE) and affymetrix chips were used in order to analyze proteomes and gene expression profile of VSMC from the different groups. Normal human aorta VSMC (HAoSMC) were used as control in proteomic experiments. Proliferation of VSMC was analysed using a BrdU proliferation assay ELISA kit. Immunohistochemistry with ET-1, ET_AR and ET_BR were also performed on temporal artery biopsies from TAB^+-GCA and GCA-control patients.

Results:

2D-DIGE analysis of VSMC protein extracts revealed 16, 30 and 2 protein spots differentially expressed between TAB^+-GCA and GCA-control patients, between TAB^+-GCA and TAB^--GCA patients and between TAB^--GCA and GCA-control patients, respectively (fold change$\geq$1.5 and p-value$\leq$0.05). Among the 153 differentially expressed between VSMC from TAB^+-GCA and HAoSMC, a lot of them were linked with endothelin-1.

Genes differentially expressed between VSMC from patients with TAB^+-GCA, TAB^--GCA and GCA-control were involved in proliferation. Endothelin-1 was also identified as a link between genes of interest. Proliferation of VSMC from TAB^+-GCA patients was reduced in the presence of macitentan, an endothelin receptor antagonist and its active metabolite and was not modified with bosentan or ambrisentan. Interestingly, in immunochemistry analysis, patients who had a transmural expression of endothelin-1 on TAB received a significantly increased glucocorticoid daily dose after a 6-month follow-up.

Conclusion:

Inhibition of the increased proliferation of VSMC during GCA with macitentan might represent a promising therapeutic approach in patients with GCA, in combination with glucocorticoids.

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Abstract Number: 1262

Epigenome-Wide DNA Methylation Patterns Associated with Fatigue in Primary Sjögren's Syndrome

Katrine B Norheim[1], Juliana Imgenberg-Kreuz[2], Kristin Jonsdottir[3], Emiel Janssen[4], Ann-Christine Syvänen[2], Johanna K Sandling[2], Gunnel Nordmark[5] and Roald Omdal[6], [1]Dept of Internal Medicine, Clinical immunology Unit, Stavanger, Norway, [2]Molecular Medicine and Science for Life Laboratory, Department of Medical Sciences, Uppsala University, Uppsala, Sweden, [3]Dept. of Pathology, Stavanger University Hospital, Stavanger, Norway, [4]Dept. of Pathology, Stavanger university Hospital, Stavanger, Norway, [5]Rheumatology and Science for Life Laboratory, Department of Medical Sciences, Uppsala University, Uppsala, Sweden, [6]Department of internal medicine, Clinical Immunology unit, Stavanger, Norway

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Background/Purpose:

Chronic fatigue is a common, often disabling, and poorly understood phenomenon of many diseases. Recent studies indicate that epigenetic mechanisms may be involved in the expression of fatigue, which is a prominent feature of primary Sjögren's syndrome (pSS), a chronic autoimmune disease. The aim of this study was to investigate whether DNA methylation profiles of whole blood are associated with fatigue in patients with pSS.

Methods:

48 pSS patients with high (n=24) or low (n=24) fatigue were included. Genome-wide DNA methylation was investigated using the Illumina HumanMethylation450 BeadChip array. After quality control, a total of 383 358 CpG sites remained for further analysis. Age, sex, and differential cell count estimates were included as covariates in the association model. A false discovery rate–corrected $p<0{\cdot}05$ was considered significant, and a cut-off of 3% average difference in methylation levels between high- and low-fatigue patients was applied.

Results:

251 differentially methylated CpG sites were associated with fatigue (166 hypomethylated sites annotated to 117 genes and 85 hypermethylated sites annotated to 65 genes). The CpG site with the most pronounced hypomethylation in pSS high fatigue compared with pSS low fatigue annotated to the SBF2-antisense RNA1 gene. The most distinct hypermethylation was observed at a CpG site annotated to the lymphotoxin alpha gene. Functional pathway analysis of genes with differently methylated CpG sites in subjects with high versus low fatigue revealed enrichment in several pathways associated with innate and adaptive immunity.

Conclusion:

Some genes involved in regulation of the immune system and in inflammation are differently methylated in pSS patients with high versus low fatigue. These findings point to functional networks that may underlie fatigue. Epigenetic changes could constitute a fatigue-regulating mechanism in chronic inflammatory diseases such as pSS.

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Abstract Number: 1263

Applications of Protein Microarray for Saliva Diagnostics in Autoimmune Diseases

Yeon-Ah Lee[1], Yong-Gil Kim[2], Seung-Jae Hong[1] and Paul J. Utz[3], [1]Division of Rheumatology, Department of Internal Medicine, School of Medicine, Kyung Hee University, Seoul, South Korea, [2]Division of Rheumatology, Department of Internal Medicine, University of Ulsan College of Medicine, Asan Medical Center, Seoul, South Korea, [3]Medicine, Stanford University School of Medicine, Stanford, CA
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Background/Purpose:

There have been many reports showing that saliva could be a source of biomarkers capable of detecting certain diseases. However, very few studies have been conducted to profile autoantibody isotypes in the saliva of various autoimmune diseases except Sjogren's syndrome. This study was performed to establish protein microarray for saliva diagnostics in autoimmune diseases and to identify distinct profiles of salivary autoantibody in patients with systemic lupus erythematosus (SLE).

Methods:

We constructed antigen microarrays and probed healthy saliva spiked with commercial antibodies (Abs) (monoclonal mouse anti-La, anti-Ro52 and anti-Ro60 and polyclonal rabbit anti-U1-70). To investigate whether saliva destroys Abs existing in patients' serum, we used serum from clinically confirmed SLE and mixed connective tissue disease (MCTD) patients diluted from 250 to 8000 fold with healthy

saliva and PBST containing 5% fetal calf serum. Following proof-of-concept experiments, we developed another array with a panel of canonical antigens of SLE as well as cytokines (interferon α-2b, interferon γ, BAFF and CXCL13) to characterize autoantibodies in matched saliva and serum derived from 17 SLE patients and 13 healthy controls. The autoantibody IgG and IgA isotypes were assayed using goat anti-human IgG (AF647 conjugated) and goat anti-human IgA (Cy3 conjugated). The Axon Scanner and GenePix Pro 7.0 were used to determine median fluorescence intensities (MFI) of features and background. Data were analyzed using MultiExperiment Viewer and Significance Analysis of Microarray (SAM) algorithm.

Results:

The dynamic range of detection on the array was 1-10^4 ng/mL for commercial Abs spiked into saliva. We observed a high degree of specificity and each Ab was specific for its target antigen. In the experiments investigating the effect of saliva on the reactivity of Abs existing in patients' serum (anti-Ro52 and anti-La in SLE, anti-U1-70 and anti-U1-A in MCTD), saliva made the MFI signals a little bit weaker than buffer, but it was not significantly different. The optimal dilution rate of saliva for protein microarray turned out to be 1:4 to 1:8. Matched saliva and serum samples from 17 SLE patients and healthy controls were incubated with anti-IgG and anti-IgA secondary Abs. IgG Ab reactivity against specific antigens was found mainly in serum, while IgA Ab reactivity to given antigens was predominant in saliva, suggesting the possibility of isotype switching between saliva and serum. SAM identified 7 antigens including BAFF, Ro60, U1-A and Sm/RNP that were significantly more reactive to IgA Ab in the saliva of SLE patients than in healthy controls (false discovery rate<0.01). The hierarchical clustered heat-map successfully placed SLE patients into close subgroups.

Conclusion:

Protein microarrays facilitate detection of autoantibody in human saliva as well as serum. Saliva profiling revealed that elevated IgA autoantibody reactivity to several targets including BAFF was associated with SLE compared with controls. The noninvasive nature of saliva collection with protein microarray highlights the efficacy of pursuing saliva as a diagnostic medium.

Disclosure: Y. A. Lee, None; **Y. G. Kim**, None; **S. J. Hong**, None; **P. J. Utz**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/applications-of-protein-microarray-for-saliva-diagnostics-in-autoimmune-diseases

Abstract Number: 1264

Residential Proximity to Highways, DNA Methylation and Systemic Lupus Erythematosus

Cristina Lanata[1], Renuka Nayak[2], Joanne Nitiham[1], Kimberly Taylor[3], Lisa F. Barcellos[4], Sharon A. Chung[5] and Lindsey A. Criswell[6,7], [1]Medicine, University of California, San Francisco, Rosalind Russell / Ephraim P. Engleman Rheumatology Research Center, San Francisco, CA, [2]Department of Medicine, UCSF, Rosalind Russell / Ephraim P. Engleman Rheumatology Research Center, University of California, San Francisco, San Francisco, CA, [3]University of California, San Francisco, Rosalind Russell / Ephraim P. Engleman Rheumatology Research Center, San Francisco, CA, [4]Genetic Epidemiology and Genomics Laboratory, University of California, Berkeley, Berkeley, CA, [5]School of Medicine, University of California, San Francisco, Rosalind Russell / Ephraim P. Engleman Rheumatology Research Center, San Francisco, CA, [6]Rheumatology, UCSF, SAN FRANCISCO, CA, [7]Rosalind Russell / Ephraim P. Engleman Rheumatology Research Center, University of California, San Francisco, San Francisco, CA

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Background/Purpose:

Systemic lupus erythematosus (SLE) is a heterogeneous disease characterized by autoantibody formation in which multiple genetic, epigenetic and environmental risk factors have been implicated. We previously demonstrated that methylation levels differ significantly among SLE patients according to auto-antibody status and presence/absence of lupus nephritis. The study of epigenetics provides a mechanistic bridge to understand the effects of environmental exposures with disease risk and outcome. Air pollution has been linked not only to an increase in overall mortality but also to an increased incidence of rheumatoid arthritis. There are few studies evaluating air pollution and SLE development and outcomes. However, anti-dsDNA antibody titers have been associated with high levels of air

particulate matter. The goal of this study was to evaluate methylation differences in relation to residential proximity to highways in patients with SLE.

Methods:

We studied 307 Caucasian females with SLE, all non-smokers, who were previously enrolled in a Lupus Genetics Project. Residence at the time of blood draw was recorded and geocoded. The distance to the nearest roads from the geocoded locations were calculated for the four major Tele Atlas Feature Class Codes (FCC) road classes. The Geographic Data Technology, Inc. (GDT) road network data were used for these calculations. Genome-wide methylation profiling was performed using the Illumina Infinium HumanMethylation 450 BeadChip. After quality control measures 467,314 CpG sites were analyzed.

Results:

Patients residing within a 300 meter radius from a major highway were defined as at high risk for significant hazardous health outcomes[1]. Thirty-eight patients (12.4%) were residing in a high risk area. Multivariate analysis did not reveal any statistically significant association between proximity to highways and disease phenotypes, however there was a trend for higher incidence of malar rash (OR 2.4, CI[1.1, 5]) and photosensitivity (OR 2.7, CI[1.2, 5.9]). Analysis of genome-wide methylation data revealed 3 methylation sites that were significantly hypomethylated in patients who resided in a high risk zone (P value <**1.7 E-07).** These three sites belonged to a single gene, *UBE2U,* which encodes one of the E2 enzymes involved in the ubiquitination of proteins and histones, as well as DNA repair. Genome wide association studies (GWAS) in SLE have identified a risk variant at *UBE2L3*, also an E2 ubiquitination enzyme. In a large ongoing GWAS marked overexpression of UBE2L3 was seen in plasmablasts of patients of SLE with an associated upregulation of NF-κB.

Conclusion:

Hypomethylation of *UBE2U* was associated with residing close to a highway in our cohort of SLE patients. To our knowledge, this study represents the first genome-wide assessment of DNA methylation in relationship to residential proximity to highways. Additional work is warranted to confirm these findings, examine other potentially relevant exposures, and determine whether these epigenetic changes are associated with SLE severity and outcome.

1. Residential proximity to major highways - United States, 2010. *MMWR Surveill Summ*. 2013;62 Suppl 3:46-50.

Disclosure: C. Lanata, None; **R. Nayak**, None; **J. Nitiham**, None; **K. Taylor**, None; **L. F. Barcellos**, None; **S. A. Chung**, None; **L. A. Criswell**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/residential-proximity-to-highways-dna-methylation-and-systemic-lupus-erythematosus

Abstract Number: 1265

Genetic and Epigenetic Mapping of Very Early RA Synovial Fibroblasts

Emmanuel Karouzakis[1], Andrew Filer[2], Stephen Eyre[3], Karim Raza[4], Christoph Kolling[5], Renate E. Gay[1], Beat A. Michel[1], Jane Worthington[3], Christopher Buckley[6], Steffen Gay[1], Michel Neidhart[1] and Caroline Ospelt[1], [1]University Hospital Zurich, Center of Experimental Rheumatology, Switzerland, Zurich, Switzerland, [2]University of Birmingham, Birmingham, United Kingdom, [3]University of Manchester,Institute of Inflammation and Repair, United Kingdom, Manchester, United Kingdom, [4]University of Birmingham, Rheumatology Research Group, Institute of Inflammation and Ageing, United Kingdom, Birmingham, United Kingdom, [5]Upper Extremity Dept., Schulthess Clinic Zurich, Zurich, Switzerland, [6]University of Birmingham, Rheumatology Research Group, Birmingham, United Kingdom

First publication: September 29, 2015

SESSION INFORMATION

Session Date: Monday, November 9, 2015

Session Title: Genetics, Genomics and Proteomics Poster II

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose:

Genome wide association studies (GWAS) studies from rheumatoid arthritis patients have identified SNPs, which are associated with changes in gene expression levels. Recent studies revealed epigenetic changes in DNA methylation associated with rheumatoid arthritis

synovial fibroblasts (RASF). Now, we want to identify genetic variations in RASF that are associated with quantitative changes in DNA methylation at very early disease state of RA.

Methods:

SF were obtained from patients with undifferentiated arthritis (symptom duration <3 months). Patients were classified as resolving arthritis or very early RA (VeRA) depending on whether they fulfilled the ACR criteria for classification within the subsequent 18 months. Methylation immunoprecipitation (MeDIP) and high throughput sequencing was used for the analysis of differentially methylated regions (DMRs) between resolving and very early RA (n=2). The DMRs were visualized with Integrative genome viewer (IGV) and biological pathway analysis was performed by DAVID bioinformatics tools. Rheumatoid arthritis single nucleotide polymorphisms (SNPs) associated with CpG sites were mapped together with the DMRs sequencing data.

Results:

The high throughput methylome sequencing of samples from VeRA versus resolving arthritis revealed >1000 DMRs that are associated with nearby gene promoters or introns. The gene ontology analysis of the DMRs showed significant enrichment of extracellular matrix, cell adhesion and joint development pathways. Genomic loci of WNT6, WNT8A and WNT1 secreted proteins were found to be altered by DNA methylation in very early RA disease. Next, we mapped genotypic data from RA associated CpGs SNPs with the DMRs sequences of very early RASF. Thereby, we found that the region containing the IL6R introning SNPs rs4576655 and rs4537645 were hypomethylated in VeRASF versus resolving arthritis SF.

Conclusion:

In this study, we clearly show that changes in DNA methylation in RASF occur even before diagnosis and differ between RA and resolving arthritis. The overlap of DMR with RA risk SNPs suggests that genetic/epigenetic interactions play a role in disease development.

Disclosure: E. Karouzakis, None; **A. Filer**, None; **S. Eyre**, None; **K. Raza**, None; **C. Kolling**, None; **R. E. Gay**, None; **B. A. Michel**, None; **J. Worthington**, None; **C. Buckley**, None; **S. Gay**, None; **M. Neidhart**, None; **C. Ospelt**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/genetic-and-epigenetic-mapping-of-very-early-ra-synovial-fibroblasts

Abstract Number: 1266

Rheumatologic Diagnoses, Characteristics and Needs of Somali Patients Referred to a Rheumatology Clinic Serving the Somali Population

Elizabeth Miller[1], Elie Gertner[2], Rosemary Quirk[1] and Maribet McCarty[1], [1]Hennepin County Medical Center, Minneapolis, MN, [2]Section of Rheumatology, Regions Hospital and University of Minnesota, St. Paul, MN

First publication: September 29, 2015

SESSION INFORMATION

Session Title: Health Services Research Poster II (ACR): Healthcare Access, Patterns of Medication Use and Workforce Considerations

Session Type: ACR Poster Session B

Background/Purpose: With the growing immigrant and refugee population in the United States, the landscape of medicine is constantly changing. In order to provide quality healthcare, it is crucial that we investigate disease patterns and continue to monitor the quantity and quality of resources available. Somali immigrants live in many areas of the United States with the largest number in the Minneapolis-St Paul area. There are no data available to define rheumatologic disease or attendance with rheumatology specialists in this population in the United States. To better characterize the disease patterns for an emergent immigrant community, we investigated the clinical characteristics of Somali patients referred to the principal rheumatology clinic serving this population over a 5-year period. We evaluated the rheumatologic and non-rheumatologic diagnoses made after referral in this cohort as well as follow-up.

Methods: A retrospective chart review from 2010-2014 for patients of Somali origin presenting to Hennepin County Medical Center (HCMC) rheumatology clinic in Minneapolis, MN. We collected data from one hundred consecutive Somali patients seen in clinic, including population characteristics, diagnoses and follow up (see table 1).

Results: Over a 5-year period, 100 patients of Somali origin were referred to the clinic. 81% were female. 1/3 (33/100) did not have a rheumatologic syndrome. 1/3 (32/100) had OA or myofascial pain. 1/3 (35/100) had an inflammatory or immunologic CVD. Coexisting mental health disorders were present in 44% of those with OA or myofascial pain. In addition, an average of 90% of patients had low vitamin D levels. Of all 100 patients, 64% were asked to return to clinic for follow up and over half did not. See tables 1-3.

Conclusion: Of 100 Somali patients referred to our rheumatology clinic, 1/3 had no rheumatologic disease. Additionally, 1/3 had non-inflammatory conditions (OA and myofascial pain). These also had a high incidence of mental health diagnoses (44%). Hypovitaminosis D was highly prevalent. The no-show rate for return visits was more than 50%. More effort is needed in education of primary care physicians regarding non-rheumatological disease, OA and myofascial pain as well as hypovitaminosis D in this population. Awareness of mental health issues and provision of such services as well as working with the community to improve attendance at clinic is important

TABLE 1 Demographics and Comorbidities in rheumatologic vs non-rheumatologic diagnostic groups

Column1	Rheumatologic Diagnoses (n= 67)	Non Rheumatologic Diagnoses (n = 33)
Mean Age	50	50
% Female	81% (67)	90 (30)
Mental Health Disorder	24% (16)	15% (5)
Hypovitaminosis D	92% (46 of 50 checked)	80% (19 of 24 checked)

TABLE 2a Rheumatologic Diagnoses

Rheumatologic Diagnoses		Mental health disorders
Rheumatoid Arthritis	7	0
Spondylarthropathies	6	0
SLE	6	2
Connective Tissue Disease NOS	5	0
Gout	9	0
Antiphospholipid antibody syndrome	2	0
Osteoarthritis	11	5
Myofascial Pain	21	9
Total	67	16

TABLE 2b Non-rheumatologic Diagnoses

Non-rheumatologic Diagnoses		Mental Health Disorders
Joint Pain/Arthralgia	26	5
Other	7	0
Total	33	5

TABLE 3 Patient Follow Up based on diagnoses category

	Rheumatologic Diagnoses	Non-rheumatologic Diagnoses
Number of patients with recommended FU	46	18
Number of patients who no showed	23	11
No show rate	50%	61%

Disclosure: E. Miller, None; **E. Gertner**, None; **R. Quirk**, None; **M. McCarty**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/rheumatologic-diagnoses-characteristics-and-needs-of-somali-patients-referred-to-a-rheumatology-clinic-serving-the-somali-population

Abstract Number: 1267

Drug Survival of Second Biologic DMARD Therapy in Patients with Rheumatoid Arthritis: Comparison of a Second Anti-TNF with a Second Non-Anti-TNF after Discontinuation of a First Anti-TNF

T Wilke[1], S Mueller[1], I Majer[2], M Heisen[2], A Fuchs[3] and U Maywald[3], [1]Institut für Pharmakoökonomie und Arzneimittellogistik (IPAM), Hochschule Wismar, Germany, [2]Pharmerit International, Rotterdam, Netherlands, [3]AOK PLUS, Dresden, Germany
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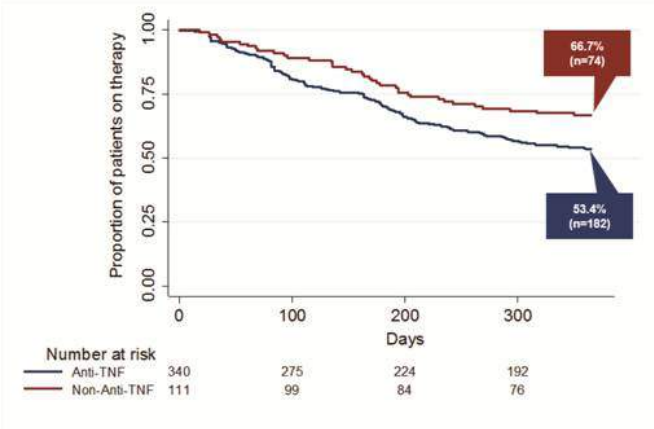
SESSION INFORMATION
Session Title: Health Services Research Poster II (ACR): Healthcare Access, Patterns of Medication Use and Workforce Considerations
Session Type: ACR Poster Session B

Background/Purpose: There is limited information on drug survival (i.e., continuation versus discontinuation of drug treatment) of RA patients who received a 2nd bDMARD therapy after 1st anti-TNF therapy. The objective of this study was to compare continuation, discontinuation, re-start and switch rates of RA patients who received an anti-TNF versus a non-anti-TNF as 2nd bDMARD. **Methods:** Our analysis was based on a German claims data set (AOK PLUS) that included all insured RA patients (at least one RA diagnosis: ICD-10 M05 or M06; aged >18 years). RA patients were included if they received at least one anti-TNF and, additionally, one 2nd bDMARD (anti-TNF or non-anti-TNF) during 01/01/2010–31/12/2012 with a requested follow-up of at least 12 months. Percentages of patients who discontinued (treatment gap >90 days), switched to a 3rd bDMARD, re-started (at least one prescription of the 2nd bDMARD after discontinuation) or continued therapy during a 12-month follow-up were analyzed. A multivariate Cox regression model, adjusting for baseline confounding variables (age, sex, Charlson Comorbidity Index [CCI], prior and concomitant medications, anti-TNF/non-anti-TNF as 2nd biologic treatment), was used to assess factors associated with discontinuation or switch (combined outcome, irrespective of a later re-start) of 2nd bDMARD. In all analyses, patients who had received rituximab (RTX) as a 2nd bDMARD were excluded because this agent is not given on a continuous basis after the initial two doses. **Results:** 3140 RA patients received at least one prescription of an anti-TNF. Of these, 451 patients received at least one prescription of a 2nd non-RTX bDMARD (340 anti-TNF: 116 adalimumab, 42 certolizumab, 120 etanercept, 46 golimumab, 16 infliximab; 111 non-anti-TNF: 40 abatacept, 3 anakinra, 68 tocilizumab). Mean age of the anti-/non-anti-TNF groups was 52.6/55.9 years (p=0.053) and 77.4/79.3% were female (p=0.792), respectively. After 12 months, 53.4% of patients receiving a 2nd anti-TNF vs 66.7% (p=0.016) receiving a 2nd non-anti-TNF continued their therapy, 3.8 vs 1.8% (p=0.387) re-started their therapy after discontinuation, 14.1 vs 19.8% (p=0.179) discontinued the therapy without re-start, and 28.7 vs 11.7% (p<0.001) had switched to a 3rd bDMARD. Figure 1 presents the Kaplan–Meier curves for the two patient groups showing time to switch or discontinuation. In the multivariate Cox regression model, independent variables significantly associated with earlier therapy discontinuation or switch were higher CCI (hazard ratio [HR]=1.127 per CCI score point; 95% CI: 1.036, 1.226), concomitant gout medication (HR=1.444; 95% CI: 1.046, 1.993) and prescription of an anti-TNF as 2nd bDMARD (HR=1.513; 95% CI: 1.052, 2.175).

Conclusion: Our results suggest that patients are at higher risk of treatment discontinuation or switch to a 3rd bDMARD after 12 months if they have received an anti-TNF versus a non-anti-TNF as 2nd bDMARD therapy.

Figure 1: Drug survival of 2nd bDMARD



	Estimated mean survival time[a]	Std. Error	p-value[b]
Anti-TNF	264 days (8.7 months)	6.8	0.016
Non-anti-TNF	295 days (9.7 months)	10.5	

a. Main outcome of this analysis is percentage of patients still continuing 2nd bDMARD therapy (separately for anti-TNF/non-anti-TNF). Patients were assumed to discontinue treatment if a gap >90 days (irrespective of whether therapy was later re-started) or a switch to a 3rd DMARD was observed. Patients having died during the follow-up were censored. Patients still on the treatment were censored at 1 year of follow-up.
b. Test of equality of survival distributions for the two treatment groups (log-rank/mantel cox).

Disclosure: T. Wilke, LEO Pharma, Bayer, Bristol-Myers Squibb, GlaxoSmithKline, Johnson & Johnson, Boehringer Ingelheim, Merck, Abbvie, Pharmerit, 9; **S. Mueller**, Bristol-Myers Squibb, 5; **I. Majer**, Bristol-Myers Squibb, 5; **M. Heisen**, Bristol-Myers Squibb, 5; **A. Fuchs**, None; **U. Maywald**, None.

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Abstract Number: 1268

Utilization of Viscosupplementation: 2011 – 2013

Gurjit S. Kaeley[1], Myint Thway[1] and Sunita Dodani[2], [1]Rheumatology, University of Florida College of Medicine, Jacksonville, Jacksonville, FL, [2]Cardiology and Epidemiology, University of Florida College of Medicine, Jacksonville, Jacksonville, FL
First publication: September 29, 2015

SESSION INFORMATION

Session Title: Health Services Research Poster II (ACR): Healthcare Access, Patterns of Medication Use and Workforce Considerations

Session Type: ACR Poster Session B

Background/Purpose:

Viscosupplementation (VS) is approved in the USA as an option for knee osteoarthritis (OA) pain. Recent American Academy of Orthopedic Surgeons (AAOS) guidelines have strongly recommended against use of hyaluronic acid because of lack of clinical improvement compared with placebo. (1) OA has a higher prevalence and impact in the elderly population necessitating use of therapies to relieve pain and maintain mobility. Use of VS as one of the therapies for knee OA may be an important cost driver for Medicare. **Objective**: To estimate and compare the prevalence and cost of VS utilization amongst Medicare Beneficiaries from 2011 -2013.

Methods:

A retrospective cross-sectional analysis of Medicare (CMS) Physician Supplier Payment Summary (PSPS) files from 2011 – 2013 was used to tabulate volume and total payments on utilization. Non-duplicative billing claims for five types of VS were calculated for all three years by provider specialty and by State. Aggregated specialties that billed the majority of the services were included as shown in Table. Number of services submitted were standardized to reflect unique doses (One dose of Synvisc=16mg, Synvisc One = three doses). Descriptive summary analysis was conducted using R-Studio (Version 0.98.1102).

Results:

Orthopedists received 63% of the VS payments from 2011-2013, and compared to 2011, the rate of growth in payments was 12% (Table). Strikingly, there was minimal increase in utilization amongst Rheumatologists from 2011 to 2013 whereas other provider groups showed a payment growth from 24% - 56%. Amongst the five brands, Synvisc and Hyalgan were the most utilized. 2.1 million doses of each drug was used over the three years. Payments for Synvisc were $322.6 million and Hyalgan $146 million. The overall payments for VS over 3 years was $708,675,805. Utilization in the Top 10 States with the greatest number of payments is presented in Figure 1. Orthopedists were the dominant providers and Synvisc payments predominated in these states.

Conclusion:

This study highlights the significant cost of VS in the Medicare population. Orthopedists and Physician assistants were the greatest utilizers of these drugs whereas three other provider groups show robust increases in utilization. In view of the negative recommendations by the AAOS against the use of Hyaluronic acid joint injections, the current trajectory of use of Hyaluronic acid may not represent optimal value care.

References:

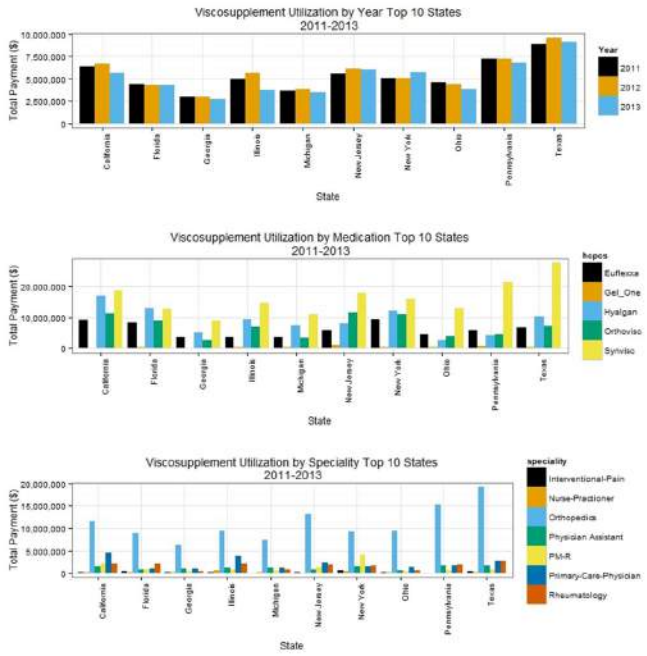
1. AAOS Guideline: Treatment of Knee Osteoarthritis. http://wwwaaosorg/Research/guidelines/TreatmentofOsteoarthritisoftheKneeGuidelinepdf.

Table: Utilization of Viscosupplementation (VS) by Provider Types and Year.

Specialty	*Year*	*Sum Total Doses (Percent Total per Year)*	*Cumulative Percentage Change*	*Sum Payment (Percent Total per Year)*	*Cumulative Percentage Change*
Interventional-Pain	2011	20633 (1%)		$1,978,621 (1%)	
	2012	22128 (1%)	7%	$2,194,488 (1%)	11%
	2013	25463 (1%)	23%	$2,503,846 (1%)	27%
Nurse-Practitioner	2011	34500 (2%)		$3,793,010 (2%)	
	2012	45414 (2%)	32%	$5,022,975 (2%)	32%
	2013	53923 (2%)	56%	$5,882,256 (2%)	55%
Orthopedics	2011	1161990 (62%)		$138,315,121 (65%)	
	2012	1233721 (60%)	6%	$151,186,847 (63%)	9%
	2013	1254420 (58%)	8%	$155,098,032 (61%)	12%
Physician Assistant	2011	164884 (9%)		$18,866,953 (9%)	
	2012	204459 (10%)	24%	$23,958,332 (10%)	27%
	2013	239000 (11%)	45%	$28,019,650 (11%)	49%
PM-R	2011	97627 (5%)		$10,194,646 (5%)	
	2012	129163 (6%)	32%	$13,610,284 (6%)	34%
	2013	149486 (7%)	53%	$15,927,569 (6%)	56%
Primary-Care-Physician	2011	212824 (11%)		$21,714,180 (11%)	
	2012	237861 (12%)	12%	$24,542,318 (11%)	13%
	2013	273328 (13%)	28%	$27,026,111 (8%)	24%
Rheumatology	2011	171547 (9%)		$19,271,040 (9%)	
	2012	171549 (8%)	0%	$19,764,371 (8%)	3%
	2013	172837 (8%)	1%	$19,805,155 (8%)	3%

(PM-R: Physical Medicine and Rehabilitation (including Sports Medicine).
Primary Care Physician – includes Internal Medicine, Family Practice, General Practice)

Figure 1: Relative Utilization of Viscosupplemention (VS) in the Top 10 States with the Greatest Number of Payments.



Disclosure: G. S. Kaeley, None; **M. Thway**, None; **S. Dodani**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/utilization-of-viscosupplementation-2011-2013

Abstract Number: 1269

Measuring the Rheumatologist Workforce in Canada: Preliminary Results of the Stand up and be Counted Survey

Claire E H Barber[1], Lauren Jewett[2], Vandana Ahluwalia[3], Cory Baillie[4,5], Dianne Mosher[6], Michel Zummer[7], J Carter Thorne[8], Janet Ellsworth[9], Henry Averns[10], Cheryl Barnabe[11], Alfred Cividino[12], Janet E. Pope[13], Elizabeth M. Badley[14,15], Deborah M. Levy[16], Thanu Ruban[14], Katie Lundon[17], Robert McDougall[18], Julie Brophy[1], Diane Lacaille[19], Deborah Marshall[2] and The Canadian Rheumatology Association (CRA) Human Resources Committee, [1]Rheumatology, University of Calgary, Calgary, AB, Canada, [2]University of Calgary, Calgary, AB, Canada, [3]William Osler Health Center, Brampton, ON, Canada, [4]Canadian Rheumatology Association (President), Winnipeg, MB, Canada, [5]University of Manitoba, Winnipeg, MB, Canada, [6]Med, University of Calgary, Calgary, AB, Canada, [7]Université de Montréal, Quebec, QC, Canada, [8]Southlake Regional Health Centre, Newmarket, ON, Canada, [9]University of Alberta, Edmonton, AB, Canada, [10]Consultant Rheumatologist Kingston Ontario, Kingston, ON, Canada, [11]Cumming School of Medicine, University of Calgary, Calgary, AB, Canada, [12]Department of Medicine, McMaster University, Hamilton, AB, Canada, [13]University of Western Ontario, London, ON, Canada, [14]University of Toronto, Toronto, ON, Canada, [15]Toronto Western Research Institute, Toronto, ON, Canada, [16]Rheumatology, The Hospital for Sick Children, Toronto, ON, Canada, [17]Medicine, University of Toronto, Toronto, ON, Canada, [18]University of Saskatchewan, Regina, SK, Canada, [19]Arthritis Research Centre, University of British Columbia, Vancouver, BC, Canada

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SESSION INFORMATION

Session Title: Health Services Research Poster II (ACR): Healthcare Access, Patterns of Medication Use and Workforce Considerations

Session Type: ACR Poster Session B

Background/Purpose: Given the rising burden of arthritis care, there is concern about access to rheumatologists in many regions. To better characterize the rheumatologist workforce, the Canadian Rheumatology Association (CRA) launched the Stand Up and Be Counted survey in March 2015.

Methods: Following a literature review of existing workforce studies to identify gaps in knowledge, a working group including the research team, CRA staff and adult and pediatric rheumatologists from academic and community practices developed and pilot-tested English and French versions of the survey. The survey consisted of 63 questions including demographic and practice information, questions on provision of care to rural and remote communities, and allocation of time for clinical care. The survey was distributed to the CRA membership, with non-CRA members identified through the Royal College of Physicians and Surgeons, provincial licensing bodies, and snowball recruitment from other CRA members. To increase survey uptake, periodic electronic reminders were sent out to non-respondents and study updates were provided at regional meetings.

Results: The survey was sent to 657 individuals of whom 456 were expected to be practicing rheumatologists (400 adult, 56 pediatric) based on CRA membership information. As of May 2015 there were 320 respondents (49%), of which 33 were excluded, as they were not actively practicing rheumatologists or did not complete enough of the survey to determine this. There were 287 respondents included in this preliminary analysis, including 244 adult rheumatologists, and 43 pediatric rheumatologists, representing 61% and 76% of the expected respondents respectively. The median age was 50 years and nearly a third (90, 31%) plan to retire within the next 10 years. Sixty percent were affiliated with a university: 136 had a university-based clinic and an additional 37 had an academic appointment but practiced in a private community-based setting. Of the remaining respondents, 103 had community-based clinics and 11 reported other types of practice settings. Thirty-one percent of rheumatologists did not use an electronic medical record. With respect to rheumatologists' clinical practices and workload: the majority of the respondents' caseloads were comprised of patients with inflammatory arthritis (70%) and the median number of ½ day clinics offered per week was 8. The majority of rheumatologists' time was devoted to clinical practice (70%) while the remainder was spent on research, teaching or administration activities (10% each). Two-thirds participate in a call roster within their centers. To provide care to rural and remote communities 48 rheumatologists offer travelling clinics (16%), and 42 participate in Telehealth or eConsultations (15%).

Conclusion: The Stand Up and Be Counted survey is the first CRA national rheumatology workforce survey in Canada. The results highlight an ongoing need for training rheumatologists given that 1/3 of the workforce will be retiring in the next 10 years. Adoption of alternative models of care may be an option to increase clinical capacity, and enhanced use of technology to deliver care to remote and rural populations should be considered.

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Abstract Number: 1270

Low Socioeconomic Status As a Predictor of Long-Term Direct Medical Costs Following Diagnosis of Granulomatosus with Polyangiitis: A General Population-Based Cohort Study

Natalie McCormick[1], Carlo Marra[2] and J Antonio Avina-Zubieta[3], [1]Faculty of Pharmaceutical Sciences, University of British Columbia/Arthritis Research Canada, Vancouver, BC, Canada, [2]Pharm Sciences, Univ of British Columbia, Vancouver, BC, Canada, [3]Arthritis Research Canada / University of British Columbia, Vancouver, BC, Canada
First publication: September 29, 2015

SESSION INFORMATION
Session Title: Health Services Research Poster II (ACR): Healthcare Access, Patterns of Medication Use and Workforce Considerations
Session Type: ACR Poster Session B

Background/Purpose:

Estimates of the healthcare costs of Granulomatosus with polyangiitis (GPA) and predictors of costs are scarce. In particular, while socioeconomic status (SES) is associated with costs in general populations, its impact in GPA is unknown. To address these gaps, we estimated the incremental (extra) direct medical costs of a general population-based cohort of incident GPA for the first five years after diagnosis, and examined the relationship between SES at diagnosis, and medical costs in GPA.

Methods:

Data Source: Our administrative data captured all provincially-funded outpatient encounters and hospitalizations (1990-2010) and all dispensed medications for ALL residents of the province of British Columbia, Canada.

Sample: We assembled a population-based cohort of all cases of GPA who had a new diagnosis of GPA from at least one hospitalization or rheumatologist visit, or two non-rheumatologist visits, between Jan 1996 and Dec 2010, and no prior GPA diagnosis between Jan 1990 and Dec 1995. Ten controls matched by age at diagnosis (±2 years), sex, and calendar year of diagnosis were selected for each case from the general population. SES was defined from Statistics Canada neighbourhood income quintile data for the year of GPA diagnosis.

Cost Calculation: Outpatient and prescription costs were summed directly from billing data. Case-mix methodology was used for hospitalizations.

Statistical Analysis: We estimated the unadjusted incremental costs of GPA (difference in per-patient-year (PY) costs between cases and controls). Generalized linear models were then used to:

1. Further adjust for differences in SES, urban/rural residence, and Charlson-Romano comorbidity index between cases and controls; and
2. Evaluate the relationship between SES and direct medical costs among GPA cases.

Results: We matched 441 incident GPA cases to 4,410 controls (54% female, mean age 61 ±16.0 years, median comorbidity score=1).

Unadjusted incremental costs of GPA for the first 5 years after diagnosis averaged $81,603 per-PY (2010 Canadian), with 80% from hospital, 15% from outpatient, and 5% from medications. 74% of cases (vs. 17% of controls) were hospitalized during the first year after diagnosis, with GPA cases averaging 0.86 more admissions per-PY than controls (excluding the index admission). Following adjustment, costs for GPA cases were 5.3-times higher than matched controls (95% CI: 4.6-6.1).

Amongst GPA cases, age ($p < 0.001$), comorbidity score ($p < 0.001$), and being in the lowest SES group (vs. the highest, $p < 0.001$) were significantly associated with higher costs. This was driven mainly by hospitalizations for GPA (see **Table**). Predicted mean costs for lowest SES cases ($121,358/PY) were 1.9-times greater than the highest-SES.

Conclusion:

The medical costs of GPA cases over 5 years are substantial (averaging $81,603/PY more than matched controls from the general population), with lower SES a predictor of higher costs.

Unadjusted Mean Per-Patient-Year (PY) Costs for the First Five Years After GPA Diagnosis (2010 Canadian) (95% CI)						
Socioeconomic Status (SES) at GPA Diagnosis						
	All GPA Cases	**1=Lowest SES Cases**	**2**	**3=Middle SES Cases**	**4**	**5=Highest SES Cases**
N Cases	441	82	110	84	82	83
Mean Per-Patient-Year Outpatient Costs	$16,466 ($15,042-$17,891)	$17,260 ($13,570-$20,949)	$18,376 ($15,150-$21,602)	$14,099 ($11,348-$16,850)	$17,765 ($14,075-$21,455)	$14,265 ($11,895-$16,636)
Mean Per-Patient-Year Medication Costs	$7,611 ($6,505-$8,717)	$9,280 ($4,686-$13,875)	$7,299 ($5,502-$9,095)	$6,172 ($4,494-$7,851)	$6,924 ($5,218-$8,630)	$8,512 ($6,675-$10,350)
Mean Per-Patient-Year Hospitalization Costs (amongst all cases)	$75,945 ($62,557-$89,334)	$97,809 ($52,083-$143,535)	$88,274 ($62,831-$113,716)	$67,041 ($35,491-$98,591)	$75,058 ($49,154-$100,962)	$47,894 ($30,627-$65,161)
Mean Per-Patient-Year Overall Costs	$100,023 ($85,760-$114,286)	$124,349 ($75,700-$172,998)	$113,948 ($86,386-$141,511)	$87,313 ($54,815-$119,810)	$99,747 ($71,801-$127,692)	$70,671 ($51,952-$89,391)
Breakdown of Five-Year Mean Per-Patient-Year Hospitalization Costs Amongst Hospitalized Cases (95% CI)						
	All GPA Cases	**1=Lowest SES Cases**	**2**	**3=Middle SES Cases**	**4**	**5=Highest SES Cases**
Hospitalizations with GPA as a primary or secondary diagnosis	$84,304 ($67,227-$101,381)	$105,940 ($51,531-$160,349)	$96,580 ($63,600-$129,559)	$89,611 ($42,856-$136,365)	$77,992 ($46,937-$109,047)	$44,304 ($26,231-$62,376)
Hospitalizations with no GPA diagnosis recorded	$38,667 ($28,679-$48,656)	$44,970 ($10,432-$79,509)	$44,718 ($26,025-$63,411)	$24,015 ($12,174-$35,855)	$31,827 ($14,397-$49,258)	$43,976 ($17,528-$70,424)

Disclosure: N. McCormick, None; **C. Marra**, None; **J. A. Avina-Zubieta**, None.

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Abstract Number: 1271

Cost Savings and Interest in Pediatric Rheumatology Telemedicine Visits

Elizabeth A Kessler[1], Chelsey Smith[1], Ashley Sherman[2] and Mara L Becker[1], [1]Rheumatology, Children's Mercy Kansas City, Kansas City, MO, [2]Research Development and Clinical Investigation, Children's Mercy Kansas City, Kansas City, MO
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Session Type: ACR Poster Session B

Background/Purpose: Nearly 1 in 250 children live with arthritis, yet less than 300 board certified, practicing pediatric rheumatologists exist in the United States, approximately 90% of whom are located in large cities. Clinic travel can be a significant time and monetary commitment for families. Telemedicine (TM) may improve patient access to pediatric rheumatology (PR) clinics and reduce the cost of care. The objective of this study is to describe the cost to families associated with PR visits and identify interest in TM.

Methods: Surveys were offered to parents and patients aged 18 or older in PR clinics in Kansas City, Missouri (KC) and at a TM outreach site 160 miles away, in Joplin, Missouri. Survey questions included the distance traveled to the appointment, amount of work and school missed, meal and lodging costs, and interest in a TM clinic. Joplin patients were asked to answer the survey questions in relation to

appointments located currently in Joplin as well as previously in KC. Statistical analyses were conducted on patients seen in KC (n=256) and Joplin (n=24), as well as on a subsample of the KC respondents living at least 50 miles from the KC clinic. Different survey versions resulted in a variable number of total responses for each question. Descriptive and inferential analyses were performed using SPSS 20 and SAS 9.4, including chi-square and Wilcoxon rank sum tests for categorical and continuous variables, respectively.

Results: At the main KC clinic, the median distance traveled one-way was 41 miles [IQR=20-82]. Sixty-one percent of respondents missed work for the appointment, 52% purchased meals and 6% spent money on lodging. Overall, 42% were interested in a TM option. When stratified by distance, respondents living at least 50 miles from the KC clinic were more interested in TM than those less than 50 miles away (63% vs. 28%, $p<0.0001$). Among respondents who missed work, those who spent more hours away from work were more likely to endorse interest in TM ($p=0.004$). The number of hours of school missed and amount of money spent were not associated with increased interest in TM.

In the Joplin sample, the median distance traveled was 60 miles [IQR=20-85] when seen via TM vs. 175 miles [IQR=160-200] when seen in KC ($p<0.0001$). Thirty-eight percent spent money on food related to the TM visit in contrast to 92% with a KC visit ($p<0.0001$). Joplin respondents were more likely to spend money collectively on food, lodging and/or child care when traveling to KC as compared to Joplin (92% vs. 38%, $p<0.0001$). Respondents missed an average of 5.5 ± 3.4 hours of work when seen in TM vs. 8.7 ± 1.6 hours when traveling to KC ($p=0.018$). Patients missed a mean of 4.8 ± 2.8 hours of school when seen via TM in Joplin compared to 8.4 ± 2.3 hours for an appointment in KC ($p=0.001$).

Conclusion: Children with rheumatic diseases often travel substantial distances to receive subspecialty care and incur significant costs with this travel. Interest in TM is associated with greater distance traveled and more time away from work. In our established TM Joplin clinic, respondents were less likely to spend money on travel, food, and lodging as well as time away from work and school. TM is an effective way to lessen financial burden for families that travel considerable distances for PR care.

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View Abstract and Citation Information Online - http://acrabstracts.org/abstract/cost-savings-and-interest-in-pediatric-rheumatology-telemedicine-visits

Abstract Number: 1272

Utilization of Ambulatory Physician Encounters, Emergency Room Visits and Hospitalizations By SLE Patients: A 13 Year Population Health Study

John G. Hanly[1], Chris Skedgel[2] and Kara Thompson[3], [1]Rheumatology, Division of Rheumatology, Capital Health and Dalhousie University, Halifax, NS, Canada, [2]Division of Rheumatology, Dalhousie University and Capital Health, Halifax, NS, Canada, [3]Nova Scotia Rehab Site, Division of Rheumatology, Capital Health and Dalhousie University, Halifax, NS, Canada

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Session Type: ACR Poster Session B

Background/Purpose: Resource utilization has been examined in various geographic locations and utilizing different research methodologies including secondary use of heath care administrative data. Our objective was to determine total physician encounters, emergency room visits and hospitalizations in an incident cohort of systemic lupus erythematosus (SLE) cases and matched controls over 13 years.

Methods: A retrospective cohort study was performed utilizing administrative health care data from approximately 1 million people with access to universal healthcare. Using ICD-9 and ICD-10 diagnostic codes, 7 SLE case definitions were used and each SLE case was matched by age and gender to four randomly selected controls. Information on physician billings, emergency room visits and hospital discharges over 13 years was obtained. Analysis included descriptive statistics, linear regression and negative binomial models to examine differences in utilization between cases and controls. Models were also adjusted for the index year of utilization.

Results: The number of incident SLE cases varied from 564 to 4,494 depending upon the case definition. The mean ± SD age was 50.4 ± 16.4 with 77.9% females. For all case definitions there was significantly higher utilization of all physician groups by SLE cases compared

to controls (p<0.001). For SLE cases the utilization was highest in the index year and fell thereafter, although never to the level of utilization in the matched controls. By the fourth year, encounters with subspecialty physicians fell by 60% (Rheumatologists), 50% (Internal medicine) and 31% (other physicians). In contrast, visits to family physicians fell by only 9%. Regardless of which case definition for SLE that was used, visits to the emergency room were significantly more frequent for SLE cases (P<0.001). This was most apparent early in the disease and fell to within the range seen in the controls by the end of the study. Likewise, the hospital admission rate for SLE cases was significantly higher (P<0.001) than controls, especially early in the disease course.

Conclusion: In SLE patients, health care utilization is highest in the first few years following the diagnosis, which coincides with the highest frequency of visits to rheumatologists. Utilization declines over time and encounters with patient's family physicians predominate over other physician groups.

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Abstract Number: 1273

Uptake of the First Biosimilar Infliximab Since Its Approval in South Korea

Seoyoung C. Kim[1], Nam-Kyong Choi[2], Joongyub Lee[2], Kyoung-Eun Kwon[3], Wesley Eddings[4], Yoon-Kyoung Sung[5], Hong Ji Song[6], Aaron K. Kesselheim[4] and Daniel H. Solomon[7], [1]Div. of Pharmacoepidemiology and Pharmacoeconomics, Div. of Rheumatology, Immunology and Allergy, Brigham and Women's Hospital, Boston, MA, [2]Seoul National University Hospital, Seoul, South Korea, [3]Seoul National University College of Medicine, Seoul, South Korea, [4]Division of Pharmacoepidemiology and Pharmacoeconomics, Brigham and Women's Hospital, Boston, MA, [5]Hospital for Rheumatic Disease, Hanyang Univ Medical Center, Seoul, South Korea, [6]Hallym University Sacred Heart Hospital, Anyang, South Korea, [7]Division of Rheumatology, Immunology and Allergy, Brigham and Women's Hospital, Harvard Medical School, Boston, MA
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SESSION INFORMATION
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Session Type: ACR Poster Session B

Background/Purpose: Development of tumor necrosis factor (TNF) inhibitors has been a major advance in treatment of systemic inflammatory diseases, such as rheumatoid arthritis. While TNF inhibitors are highly effective in controlling systemic inflammation, their high cost limits their use in developing countries and raises concerns in the U.S. as well. The FDA is currently considering an application for a biosimilar version of infliximab, which has been available in South Korea since November 2012.

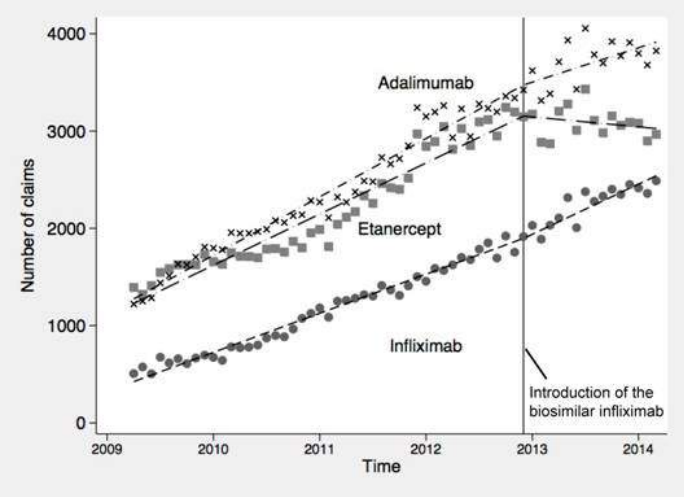
Methods: Using the medical claims data (4/2009-3/2014) of the Korean Health Insurance Review and Assessment Service database, which includes the entire Korean population, we assessed the uptake of biosimilar infliximab. A segmented linear regression was used to examine utilization patterns of infliximab (the branded and biosimilar) and other branded TNF inhibitors (adalimumab and etanercept) before and after the introduction of biosimilar infliximab. The model included the number of claims by drug each month as the outcome variable, as well as an intercept and two slope terms that described the trend in use of TNF inhibitors per month before and after the introduction of biosimilar infliximab in November 2012.

Results: We identified a total of 20,976 patients with mean age of 44 (SD 16) years who used adalimumab, etanercept, infliximab, or biosimilar infliximab during the study period. Since its introduction, there were 983 users of biosimilar infliximab. Among all the claims for any infliximab version, the proportion of biosimilar infliximab claims increased to 19% through 3/2014. The use of all TNF inhibitors increased significantly with the number of claims approximately tripling from 3,117 in April 2009 to 9,278 in March 2014. Prior to introduction of biosimilar infliximab, each month there were 33 (95%CI, 32-35) more infliximab claims, 44 (95%CI, 40-48) more etanercept claims, and 50 (95%CI, 47-53) more adalimumab claims (**Figure**). After the introduction of biosimilar infliximab, there was a significant change in the slopes with an additional increase in the use of both branded and biosimilar infliximab (9 claims/month, 95%CI, 2-17) and a decrease in the use of etanercept (-52 claims/month, 95%CI, -66 to -38) and adalimumab (-21 claims/month, 95%CI, -35 to -

6).

Conclusion: During the 15 months since its introduction in South Korea, one-fifth of all infliximab claims were for the biosimilar. Our results show that introduction of biosimilar infliximab may affect the use of other TNF inhibitors. These results suggest that an approved biosimilar infliximab product could have a major impact in the U.S., where about 40% of rheumatoid arthritis patients get treated with a biologic drug.

Figure. Trends in use of all TNF-α inhibitors before and after market introduction of biosimilar infliximab



Infliximab after the red vertical line includes both the branded and biosimilar.

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Abstract Number: 1274

Factors That Impact Job Selection in Pediatric Rheumatology

Mara L Becker[1], Meredith Riebschleger[2], Holly S. Ruch-Ross[3], 'Laura Laskosz[4], Carrie Radabaugh[5], Polly J. Ferguson[6], Kenneth N. Schikler[7] and Sandy D. Hong[8], [1]Rheumatology, Children's Mercy Kansas City, Kansas City, MO, [2]Pediatric Rheumatology & Health Services Research, University of Michigan, Ann Arbor, MI, [3]Independent Research and Evaluation Consultant, Evanston, IL, [4]Division of Technical and Medical Services, The American Academy of Pediatrics, Elk Grove Village, IL, [5]Department of Education, American Academy of Pediatrics, Elk Grove Village, IL, [6]Dept of Pediatrics--Rheum, University of Iowa, Iowa City, IA, [7]Pediatrics, University of Louisville, Louisville, KY, [8]Pediatrics-Rheumatology, U of Iowa Children's Hosp, Iowa City, IA
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Session Type: ACR Poster Session B

Background/Purpose: There remain valid concerns about the capability of the pediatric rheumatology (PR) workforce to meet the clinical needs of U.S. children and to absorb the imminent retirement of senior practitioners. The American Academy of Pediatrics Section on Rheumatology (AAPSORh) performed a survey to characterize current PR work force patterns and identify factors in employment

selection.

Methods: Eligible PR survey recipients were identified using the AAP SORh member list and American Board of Pediatrics certified PR practitioners. An electronic survey was fielded from 9/2014-12/2104. Survey domains included demographics, training, practice characteristics, distribution of professional time, call responsibilities, and plans for retirement. Respondents reporting current PR practice were eligible for analyses. Descriptive analyses utilized frequency distributions and measures of central tendency as appropriate. Statistical significance was tested using ANOVA for comparison of means and chi square for cross tabulations.

Results: 151/317 (48%) identified PR responded to the survey, however, 137 (55% female) identified important factors in employment selection and were included in this analysis. Of factors listed, location (59%) was ranked most frequently and salary (18%) was ranked least frequently as "most important" by respondents (Table 1). Females significantly rated "mentorship" as a very important factor compared to males (37% v 17%, p=.02) (Figure 1). Many factors were significantly correlated with one another and could be grouped including: "Life" factors which included: location and spouse/partner employment; "University" factors which included: research, university affiliation, and mentorship; and "Job" factors which included: salary and practice size. Although there was a clear order of importance, there was overlap between groups (Table 1). Significantly more females than males rated one or more "Life" factors as very important (80% v 60%, p=.01).

Conclusion: As the PR current and future workforce plays an important role in access to care, understanding what fuels employment decisions may assist in the development of workforce initiatives. The current PR workforce survey suggests "Life" factors as most important in decision making about employment. Incentivizing practice locations, making larger efforts in spouse/partner recruitment, and targeting future trainees from underrepresented areas to return to these areas may be worthwhile investments for future workforce priorities.

Figure 1:

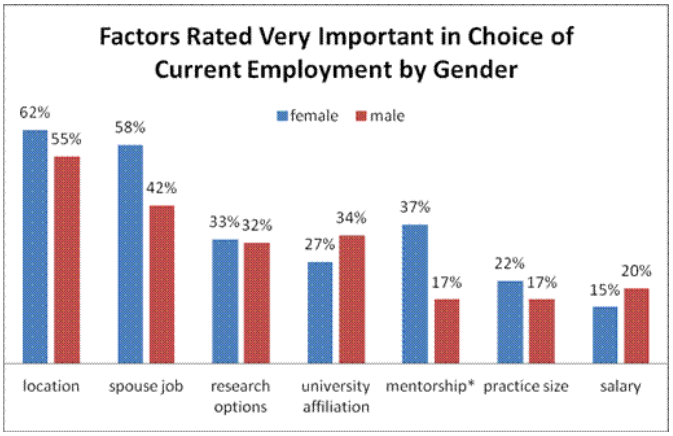

Table 1

	Factors in order of frequency with which they were rated "very important"	Rated "very important"		
		N	%	
Life	Location	81	59.1%	67% rated at least one of these "very important;" 31% said both
	Spouse/partner employment	67	50.4%	
University	Research opportunities	44	33.1%	About 50% rated at least one of these "very important;" 26% said 2 or more
	University affiliation	41	30.4%	
	Mentorship	39	28.9%	
Job	Size of practice/number of partners	27	19.9%	30% rated at least one of these "very important;' 4% said both
	Salary/benefits	24	17.8%	

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Abstract Number: 1275

Pediatric Rheumatology Work Force and Patients Status in Latin America. a Snap Shot Web Based Survey

Zoilo Morel[1], Graciela Espada[2], Clara Malagón[3], Claudia Magalhaes[4], Luis Lira[5], Raúl Gutiérrez[6], Mabel Ladino[7], Ruth Erazo[8], Ivonne Arroyo[9], Flavio Sztajnbok[10] and Carlos Rose[11], [1]Pediatrics, Hospital de Clinicas. Facultad de Ciencias Medicas. Universidad Nacional de Asuncion. UNA., Asuncion, Paraguay, [2]Rheumatology Section, Childrens Hosp Ricardo Gutierrez, Buenos Aires, Argentina, [3]Pediatric

Rheumatology. Universidad El Bosque, Bogota, Colombia, [4]Pediatric Rheumatology Division. UNESP. Botucatu Medical School., Botucatu, Brazil, [5]Pedro De Valdivia #295, Pediatric Rheumatology. Chilean Society of Rheumatology., Santiago, Chile, [6]Pediatric Rheumatology. Hospital Shriners para niños., Mexico DF, Mexico, [7]Pediatric Rheumatology. Hospital San Juan de Dios. University of Chile., Santiago, Chile, [8]Hospital Pablo Tobon, Medellin, Colombia, [9]San Jorge Medical Building, Santurce, PR, [10]Pediatric Rheumatology Division, Adolescent Health Care Unit, Universida de do Estado do Rio de Janeiro., Rio de Janeiro, Brazil, [11]Pediatric Rheumatology Division . Nemours/Alfred I. duPont Hospital for Children. Wilmington., Delaware, DE
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SESSION INFORMATION

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Session Type: ACR Poster Session B

Background/Purpose:

Developing countries face serious socioeconomics problems, and pediatric rheumatic illnesses are not seen as priority by health programs. The PANLAR Pediatric Rheumatology Study Group conducted a web based survey in order to assess the specific reality in Pediatric Rheumatology care in Latin America (LA), to gather individual data from all Pediatric Rheumatologists (PRs) in LA, their training history, practice, and characteristics of Juvenile Idiopathic Arthritis (JIA) patients as well as access to drug therapy and other health services.

Methods:

An international wide web based survey involving LA PRs. All performed a baseline evaluation, including 54 questions to assess in the following domains: demographics, practice status, training history, functional status of JIA and access to treatment and monitoring resources. Data captured began December 30, 2014 and closed on February 28, 2015.

Results:

A total of 169 (47%) responded to the survey sent to 356 PRs in LA, from Argentina, Bolivia, Brazil, Chile, Colombia, Cuba, Ecuador, El Salvador, Guatemala, Mexico, Nicaragua, Paraguay, Peru, Puerto Rico, Dominican Republic, Uruguay, Venezuela. There were: 16 countries without PRs, all from Antilles and some countries of Central America. The largest number (68%) of PRs works in countries with larger populations and training centers as Argentina, Brazil, Colombia and Mexico. Forty five percent of PRs has been in practice for less than 10 years. Twenty percent of LA children are seen by a Rheumatologist untrained in Pediatrics. Most PRs work in urban areas and under the Public Health System. Of the total available time, 90% is spent in patient care and 10% in research. JIA subtypes distribution matches other series. The median time from the beginning of first symptoms to diagnosis was 6 (3-11) months in 50% of LA JIA patients. A Steinbrocker functional class III and IV was observed in 18% of patients at presentation. In almost 50% of countries, PRs are solo practitioners. Full adherense to treatment is around 61%; DMARDs requirement: 70%; Biologics use: 40%. Access to biological therapy was graded as “very difficult” in 20% and covered by State or Social Security in 80%.

Conclusion:

The Survey data suggest a need to: 1. increase the number of pediatric rheumatologists, 2. Improve PR training, 3. Foster access to care, earlier referral and availability of effective medication. A cross sectional study of functional status in JIA is needed. With adequate funding PANLAR is well positioned to promote development of educational programs and to carry on epidemiologic prospective research.

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Abstract Number: 1276

Improvement in Work and Household Productivity for Patients with Rheumatoid Arthritis and Ankylosing Spondylitis Treated with Anti-TNFs in Routine Clinical Practice in Turkey

Sebnem Ataman[1], Mehmet Kirnap[2], Buminhan Seferoglu[3], Zuhal Altay[4], Aylin Rezvani[5], Omer Kuru[6,7], Erhan Capkin[8], Nazli Derya Bugdayci[9], Ilhan Sezer[10], Hasan Fatih CAY[11] and Akinci Tan[12], [1]Rheumatology Department, Ankara University Faculty of Medicine, Ankara, Turkey, [2]Department of Physical Medicine and Rehabilitation, Erciyes University, Kayseri, Turkey, [3]Physical Medicine and

Rehabilitation, Ataturk University Medical School, Erzurum, Turkey, [4]ELAZIG KARAYOLU UZERI, Inonu University, Turgut Ozal Medical Center, Malatya, Turkey, [5]Department of Physical Medicine and Rehabilitation, Bezmialem Foundation University, İstanbul, Turkey, [6]Kurupelit Mevkii Kurupelit 552, Ondokuz Mayis Univ.Tip Fak.Has.-Fizik Tedavi, Samsun, Turkey, [7]Physical Medicine and Rehabilitation, Ondokuz Mayis University, Samsun, Turkey, [8]PM&R AND RHEUMATOLOGY, Karadeniz Tecnical University, Faculty of Medicine, TRABZON, Turkey, [9]Physical Treatment and Rehabilitation, Istanbul Physical Treatment and Rehabilitation Training and Research Hospital, Istanbul, Turkey, [10]Rheumatology, Physical Medicine and Rheabilitation, Antalya Education and Research Hospital, Antalya, Turkey, [11]Rheumatology, Physical Medicine&Rehabilitation, Antalya Education and Research Hospital, Antalya, Turkey, [12]Physical Med & Rehab, Hacettepe Univ, Ankara, Turkey
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Background/Purpose:

The impact of rheumatoid arthritis (RA) and ankylosing spondylitis (AS) on paid work is measured on the basis of employed people missing time from work (absenteeism) and reduced performance while at work (presenteeism) which leads to reduced routine working hours through changing or even losing jobs (employment status change). Work loss due to disabling rheumatic conditions is an important medical and social issue and various epidemiological studies explored the impact on the productivity, but there are few studies conducted in Turkey. We planned a non-interventional study on the basis of geo-demographic representation and explored the effects of treatment.

Methods:

In this study work disability and productivity loss was investigated through collecting data on worked hours per week and lost hours per week for paid work and household activity in RA and AS patients treated with anti-TNFs. Work and household productivity was also measured with Work Productivity and Activity Impairment Index (WPAI) scores. A total of 713 patients who were >18 years of age and with proven diagnosis of AS or RA in accordance with ACR and Modified New York Criteria were analysed. Additional parameters of quality of life (QoL) measurements by SF-36 (RA and AS), ASQoL (AS); disease scores by DAS-28 (RA) and BASDAI (AS) and functional assessments by HAQ-DI (RA), BASFI (AS) were evaluated.

Results:

A total of 713 patients enrolled (481 AS, 232 RA patients) where AS patients were younger compared to RA patients (37.6 + 10.0 versus 48.7 + 11.7 years, ns). Absenteeism decreased (14.1 hours to 3.3 hours for RA, 18.9 hours to 6.4 hours for AS patients) during 15 months follow-up and presenteeism increased towards the end of the study ($p<0.001$). WPAI evaluations also revealed significant decreases in four assessed parameters for RA and AS ($p<0.001$) except for missed hours in AS patients ($p=0.006$). During follow-up, both RA and AS patients experienced major and significant improvements in their health and quality of life with anti-TNF treatment combined with DMARDs and with or without NSAIDs. Disease activity scores of DAS-28 and BASDAI were significantly improved ($p<0.001$). Health related information by means of patient reported outcomes (SF-36 for AS and RA, ASQoL for AS, and HAQ-DI for RA) showed significant improvements in all parameters for both group of patients at 15 months ($p<0.001$). Disease related functional assessment were evaluated by means of BASFI in AS patients and improvements in all functional disability categories were reported ($p<0.001$). Treatments were well tolerated, cessation of anti-TNF treatment due to adverse events were infrequent (3.0% in AS and 1.6% in RA patients).

Conclusion:

In this study we have shown that overall work loss was significantly reduced with anti-TNF treatment during the follow-up period along with improvements in disease activity scores, QoL surveys and in disease related functional assessment outcomes.

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Abstract Number: 1277

US Adult Rheumatologists Perspective on the Transition Process for Young Adults

with Rheumatic Conditions

Devy Zisman[1,2], Patience White[3], Peter Chira[4], Stacy P. Ardoin[5], Erica F. Lawson[6], Emily von Scheven[7], Idit Lavi[8], Laura Tarter[9] and Elizabeth D. Mellins[10], [1]Technion, The Ruth and Bruce Rappaport Faculty of Medicine, Haifa, Israel, [2]Carmel Medical Center, Haifa, Israel, [3]Department of Medicine, Division of Rheumatology, The George Washington University, Washington, DC, [4]Pediatric Rheumatology, University of California San Diego, Rady Children's Hospital, San Diego, CA, [5]Pediatric & Adult Rheumatology, Ohio State University, Columbus, OH, [6]Pediatrics, University of California San Francisco, San Francisco, CA, [7]Dept of Pediatric Rheumatology, Univ of California San Francisco, San Francisco, CA, [8]Department of Community Medicine and Epidemiology, Carmel Medical Center, Haifa, Israel, [9]Rheumatology, Stanford University Hospital, Stanford, CA, [10]Dept of Pediatrics CCSR, Stanford University Med Ctr, Stanford, CA

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Background/Purpose: To assess the attitudes and common practices of adult rheumatologists in US regarding transition of young adults with rheumatic diseases from pediatric to adult care.

Methods: An online survey was sent to adult and combined adult and pediatric rheumatologist members of the ACR who practice in U.S. The anonymous questionnaire included demographic data, questions about attitudes and common practices regarding the transition process.

Results: 203 of 4064 (5%) rheumatologists completed the survey. Among them, 178 (87.7%) were board certified in rheumatology and 11 (5.4%) were certified in adult and pediatric rheumatology; 14 (16.9%) were fellows. 92 (45.7%) work in a university clinic and 85 (42.9%) in private practice, 67 (34%) had practiced <10 years and 113 (57.6%) >15 years. 88 (45.1%) were never trained in transition practices, and 133 (74.7%) were not familiar with the American Academy of Pediatrics consensus statement about transition care for youth with special healthcare needs. 71 (37%) had not developed a plan for integrating former pediatric patients into their practice; 43 (22.4%) do not have a written transition policy, but follow an informal procedure and 27 (14.1%) do not think that a transition policy is needed. Only 105 (56.15%) feel comfortable caring for former pediatric patients. The vast majority do not have a multidisciplinary team to integrate new young adults into their practice [175 (90.7%)]; 165 (86.8%) do not have a designated staff responsible for coordinating the integration. For 153 (80.1%), the patient is referred by a pediatric rheumatologist, or adult primary care [111; (58.1%)] for 106 (55.5%), the patient is self-referred. The median age of transition is 18-20 years. Time from last pediatric rheumatology visit to first adult rheumatology visit is 3-6 months in 70 (40.7%) and between 6-12 months in 67 (38.9%). The physicians were dysatisfied with the following data received: previous treatments 85 (48.9%), hospitalization history 83 (48%), disease activity index 78 (45.1%), medical history summary 76 (43.9%), co-morbidities 63 (36.4%), medication list 59 (34.1%) and disease classification 56 (32.6%). Only a minority were satisfied with the current integration process [12 (7.14%)], have sufficient resources and personnel [15 (8.93%)] and time in clinic [22 (13.1%)]. The 3 major barriers to the integration process are lack of insurance reimbursement [57 (33.9%)], lack of knowledge about community resources to support patients [52 (31.3%)] and lapse in care between primary provider and specialist [47 (28%)]. The vast majority need tools to facilitate transition 133 (79.6%) and desire a specific rheumatology consensus statement with guidelines for transitioning adolescent rheumatology patients to adult-centered care 141 (83.9%). No significant differences were noted between practitioners in university clinics vs private practice or between those practicing for less or more than 15 years.

Conclusion: This survey of rheumatologists caring for adults demonstrated substantial gaps in knowledge and resources regarding transition from pediatric to adult care for young adults with rheumatic diseases. Practice guidelines may be an effective way to address these gaps.

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Abstract Number: 1278

An Underlying Diagnosis of Osteoarthritis Is Associated with Better Outcomes after Total Hip Arthroplasty Than Avascular Necrosis of Bone

Jasvinder A. Singh[1], Jason Chen[2], Maria Inacio[2], Robert Namba[2] and Elizabeth Paxton[2], [1]University of Alabama at Birmingham,

Birmingham, AL, [2]Kaiser Permanente, San Diego, CA
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Background/Purpose:

We recently showed that underlying diagnosis of RA was associated with higher readmission rate compared to osteoarthritis. Studies of adequate sample size assessing post-THA outcomes in patients with avascular necrosis are lacking. The objective of our study was to examine whether avascular necrosis as an underlying diagnosis was associated with a higher adjusted risk of complications and readmissions after primary THA, compared to OA.

Methods:

: We analyzed prospectively collected data from an integrated healthcare system Total Joint Replacement Registry of adults with avascular necrosis (AVN) vs. osteoarthritis (OA) undergoing unilateral primary THA during 2001-2012. We examined mortality (90-day), revision (ever), deep (1 year) and superficial (30-day) surgical site infection (SSI), venous thromboembolism (VTE, 90-day), and unplanned readmission (90-day). Age, gender, race, body mass index, American Society of Anesthesiologists class, and diabetes prevalence were evaluated as confounders. Logistic and Cox regression models were fit with variables significant in univariate models for each outcome. Odds ratios (OR) and hazard ratios with 95% confidence intervals (CI) were calculated.

Results:

Of the 47,523 primary THA cases, 45,252 (95.2%) had OA, and 2,271 (4.8%) had AVN. Compared to the OA cohort, the AVN patient cohort was younger (median age 55 vs. 67 years), had more male (57.5% vs. 41.7%), and less White (59.8% vs. 77.4%). Compared to the OA cohort, the AVN cohort had higher crude incidence of 90-day mortality (0.7% vs. 0.3%), revision (3.1% vs. 2.4%), SSI (1.2% vs. 0.8%), and unplanned readmission (9.6% vs. 5.2%). After multivariable-adjustment for significant factors, AVN patients had a higher likelihood of mortality (OR:2.48; 95% CI:1.31-4.72), SSI (OR:1.67, 95%CI:1.11 - 2.51), and unplanned readmissions (OR:2.20; 95% CI:1.67-2.91) than OA patients.

Conclusion:

OA was associated with better outcomes than AVN post-THA. Detailed discussion with AVN patients regarding the risk of complications is needed during the informed consent.

Disclosure: J. A. Singh, Takeda, Savient, 2,Takeda, Savient, merz, Regeneron, Allergan, Crealta, Bioiberica, 5; **J. Chen**, None; **M. Inacio**, None; **R. Namba**, None; **E. Paxton**, None.

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Abstract Number: 1279

Racial Variation in Total Knee Replacement in a Diverse Community-Based Clinical Trial

Lindsey MacFarlane[1], Nancy Cook[2], I-Min Lee[2], Jeffrey N. Katz[3] and Karen H. Costenbader[4], [1]Rheumatology, Brigham and Women's Hospital, Boston, MA, [2]Department of Medicine, Brigham and Women's Hospital, Boston, MA, [3]Brigham and Women's Hospital and Harvard Medical School, Boston, MA, [4]Rheumatology, Immunology and Allergy, Brigham and Women's Hospital, Harvard Medical School, Boston, MA
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Background/Purpose:

Total knee replacement (TKR) surgery is common with > 700,000 surgeries performed annually in the United States. Racial variation in TKR utilization has been documented in population-based studies, however, there is a paucity of prospective data on disparities in TKR use in patients with osteoarthritis (OA). We aimed to evaluate racial disparity in incident TKRs in a cohort of patients with physician-diagnosed OA followed in a current clinical trial.

Methods:

Vitamin D and Omega-3 Trial (VITAL) is an ongoing nationwide, racially diverse, community-based, randomized controlled trial of 25,874 males age ≥50 and females age ≥55. We identified a knee pain subgroup with probable knee OA based on: a) self-reported knee pain symptoms in walking 2-3 blocks; b) pain > 1 day/week for > 1 year; and c) a doctor's diagnosis of OA. This subgroup completed a modified Western Ontario and McMaster's Universities Osteoarthritis Index (WOMAC) questionnaire, and reported prior TKR and laterality (103 people with bilateral TKR at baseline were excluded.) Participants reported new TKR, laterality and date, over the 2 year follow-up. We compared baseline WOMAC scores by race using t-tests. In multivariable-adjusted logistic regression analyses, we investigated the association of race with TKR risk, adjusting for potential confounders including age, sex, race, geographic location, WOMAC pain, function and stiffness, body mass index, income, education level, and self-reported depression.

Results:

At baseline, 1508 (5.8%) of trial participants were eligible for the knee pain cohort. Of those, 1241 (94.7% of mailed) returned a baseline knee pain questionnaire and 1019 (82%) returned a follow-up questionnaire, a mean of 27 (±4) months after baseline. Within this group, 133 (13%) reported TKR in follow-up. Among those who underwent TKR, mean age was 68 (±7) years, 65% were female, and 13% were Black. Among those who did not have TKR, mean age was 67 (±7) years, 66% were female and 24% Black. All baseline WOMAC score means were significantly higher among Black than White patients. (**Table)**In multivariable logistic regression analyses, only race and WOMAC pain score were related to TKR incidence. The odds ratio of TKR among Black compared to White patients was 0.40 (95% CI 0.22, 0.74). After adjustment for baseline WOMAC pain and stiffness scores, the odds of TKR among Black patients was further reduced to 0.32 (0.18, 0.58).

Conclusion:

Despite having worse self-reported worse knee pain, function and stiffness at baseline, and having demonstrated a high level of engagement by virtue of volunteering for a large randomized trial, Black patients had much reduced odds of undergoing TKR compared to White patients. This community-based, racially diverse cohort is unique as subjects have physician-diagnosed OA, and have been followed prospectively. Our data highlights the need for further efforts to correct this large racial disparity.

Table. Baseline WOMAC Scores in Black vs. White Patients

	Blacks	Whites	p**
WOMAC Pain score*, mean (SD)	44.81(20.94)	32.21 (15.79)	p<0.0001
WOMAC Function score*, mean (SD)	44.39 (21.15)	32.12 (17.54)	p<0.0001
WOMAC Stiffness score*, mean (SD)	51.46 (22.87)	40.19 (20.69)	p<0.0001

Odd Ratios for TKR in Black vs. White Patients

	Multivariable Model 1*** Odds Ratio (95% CI)	Multivariable Model 2*** Odds Ratio (95% CI)
Black vs. White Race	0.40 (0.22, 0.74)	0.32 (0.18, 0.58)

CI; confidence interval

* WOMAC pain, function and stiffness scores on 0 (best)-100 (worst) scale

** paired t-test

***Model 1: adjusted for age, sex, race, geographic location, body mass index (kg/m2), income, education level, and self-reported depression

***Model 2: adjusted for baseline WOMAC pain and function scores

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Comparison of Health Service Utilization Costs Between Aboriginal and Non-Aboriginal Patients with Rheumatoid Arthritis Requiring Biologic Therapy

Cheryl Barnabe[1], Yufei Zheng[2], Arto Ohinmaa[2], Brenda Hemmelgarn[3], Gilaad Kaplan[4], Liam Martin[5] and Walter Maksymowych[6], [1]Cumming School of Medicine, University of Calgary, Calgary, AB, Canada, [2]Institute of Health Economics, Edmonton, AB, Canada, [3]Division of Nephrology, University of Calgary, Calgary, AB, Canada, [4]Division of Gastroenterology, University of Calgary, Calgary, AB, Canada, [5]Medicine, University of Calgary, Calgary, AB, Canada, [6]Medicine, Medicine, University of Alberta, Edmonton, AB, Canada

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Background/Purpose: Logistical issues and poor cultural environments in tertiary care create barriers to specialized care for Aboriginal patients with rheumatoid arthritis (RA). Aboriginal patients are thus more likely than non-Aboriginal patients to see a primary care provider and less likely to see a rheumatologist for their RA care, and may result in differences in disease management and clinical outcomes. We used health services data to estimate the effect of these differences reflected in health system costs.

Methods: The Alberta Biologics Pharmacosurveillance Program (ABioPharm) is a longitudinal RA cohort study, linked to population-based administrative databases. These databases capture hospitalization, emergency room, and outpatient clinic visits which have an associated clinical modifier group, and physician visits which have an associated claim cost, from which health service utilization costs are estimated. Given the skewed nature of the data and that it may contain many zero values, we used a two-part modeling strategy for mixed discrete-continuous outcomes. In the first part, a binary choice model was estimated for the probability that the patient has had (or not had) health costs (dichotomous). In the second part, a generalized linear model with gamma family (with propensity score analysis) was used to estimate the difference in health costs between Aboriginal and non-Aboriginal groups, conditional on a cost having been incurred. Costs were adjusted for inflation to 2011/2012 using the Canadian Consumer Price Index from Statistics Canada.

Results: The cohort included 1,545 patients (n=83 Aboriginal) with 8,145 person-years of follow-up. Mean and median total costs and specific RA-related costs for hospitalizations, emergency room, outpatient clinic and physician costs are presented in Table 1, demonstrating the skewed nature of the data. Emergency room costs were higher in Aboriginal patients using standard analysis (median $1,003 CAD (IQR 2,833) vs $262 CAD (IQR 1,071) per patient per year, Mann-Whitney $p<0.001$). In the two-part model (Table 1), cost estimates for Aboriginal patients showed a numerical trend to lower hospital, outpatient clinic and physician visit total and RA-related costs, but with higher emergency room costs compared to non-Aboriginal patients, although not reaching statistical significance.

Conclusion: Health service utilization costs did not vary between Aboriginal and non-Aboriginal patients, although with limitations of sample size. Differences in health service use may explain disparate clinical outcomes observed in our cohort, which could be remedied by increased collaboration with primary care providers, and creating health care environments that deliver culturally competent care.

Table 1. Health Service Utilization Costs (annual cost per patient), in Canadian Dollars (CAD)

	Hospital	Emergency Room	Outpatient Clinic	Physician Visits
Total Costs, mean (SD)	$14,152 (43,111)	$1,114 (2,556)	$4,565 (7,569)	$7,731 (8,427)
Total Costs, median (IQR)	$0 (0)	$280 (1,162)	$2,631 (4,917)	$5,280 (7,721)
RA-Related Costs, mean (SD)	$5,860 (19,950)	$323 (757)	$1,431 (2,495)	$3,301 (3,477)
RA-Related Costs, median (IQR)	$0 (0)	$0 (272)	$539 (1,756)	$2,027 (3,419)
Model Coefficient*, Total Costs (95%CI) p value	-5,406 (-11,552 to 740) p=0.08	660 (-38 to 1,357) p=0.06	-1,037 (-2,300 to 226) p=0.1	-1,072 (-2,986 to 843) p=0.2
Model Coefficient*, RA-Related Costs (95%CI) p value	-2,561 (-5,315 to 193) p=0.06	163 (-50 to 375) p=0.1	-295 (-731 to 141) p=0.1	-107 (-972 to 758) p=0.8

* Aboriginal vs non-Aboriginal; a negative value indicates lower costs in Aboriginal patients

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Abstract Number: 1281

Reduction in Rural-Urban Disparity in Discharge Disposition to Home after Total Knee Arthroplasty in the U.S

Jasvinder A. Singh and Rekha Ramachandaran, University of Alabama at Birmingham, Birmingham, AL
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Background/Purpose:

Rural-urban disparities in outcomes after total joint arthroplasty are of great interest, given the differences in health care access and social support between those two settings. Our objective was to compare the discharge disposition after Total Knee Arthroplasty (TKA) in a nationally representative sample of patients.

Methods:

We used the U.S. Nationwide Inpatient Sample from 2003-2010 to compare outcomes after total knee arthroplasty (TKA). The study period was divided into two, 2003-2006 and 2007-2010 to assess changes in outcomes over time. Rural versus urban residence was determined based on patient's residence at the time of surgery. We compared post-TKA outcomes including discharge disposition and the length of hospitalization by rural vs. urban patient residence. Patient discharge was categorized as home (with or without home health care) or to an inpatient facility (short term hospital, skilled nursing facility, intermediate care facility or another type of inpatient facility). Unadjusted and adjusted logistic regression and analyses of variance (ANOVA) were used to make rural-urban comparisons. We adjusted for age, race, gender, Charlson score and hospital TKA volume.

Results:

Overall, 61.3% of patients undergoing TKA in 2003-2010 were discharged to home and the mean length of stay was 3.6 days. During the 2003-2006 period, significantly higher proportion of patients residing in rural locations were discharged to home compared to urban location, 61.6% vs. 54.3%. Differences were still significant in 2007-2010 period, 69.6% vs. 65.1%, but the rural-urban disparity decreased significantly from 2003-2006 to 2007-2010 (p<0.0001; Table 1). There were no significant differences in hospital length of stay between rural and urban residents in 2003-2006 or 2007-2010 and no significant changes were noted over time (Table 1).

Table 1. Rural-urban differences in TKA outcomes and time-trends

	All combined	Rural		Urban			
	2003-2010	2003-2006	2007-2010	2003-2006	2007-2010	Unadjusted p-value	Adjusted p-value*
Discharged home, n (%)	532,618 (61.3%)	50,527 (61.6%)	76,480 (69.6%)	157,201 (54.2%)	241,452 (65.1%)	<0.0001 <0.0001 <0.0001	<0.0001 <0.0001 <0.0001
Length of stay, mean (SD or range)	3.6 (1.9)	3.9 (0, 70)	3.4 (0, 108)	3.8 (0, 172)	3.4 (0, 215)	0.78 0.61 0.59	0.16 0.17 0.69

*Adjusted for age, race, gender, Charlson score, hospital TKA volume

For p-values: first p-value denotes rural/urban disparity in 2003 -2006; second the rural/urban disparity in 2007 -2010 and the third denotes the change in the disparity magnitude between 2003 – 2006 and 2007 – 2010.

Conclusion:

In this study, we noted rural-urban disparity in post-TKA discharge to home. This disparity decreased over time. Future studies should investigate the factors responsible for this favorable time-trend in discharge disposition, and continue to investigate whether further improvements can be made in the proportion discharged to home.

Disclosure: J. A. Singh, Takeda, Savient, 2,Takeda, Savient, merz, Regeneron, Allergan, Crealta, Bioiberica, 5; **R. Ramachandaran**, None.

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Abstract Number: 1282

Persistence with Osteoporosis Therapies in Postmenopausal Women in a Large US National Health Plan

Benjamin Chastek[1], Lung-I Cheng[2], John C. White[3], Leslie Spangler[4], Darshan Mehta[5] and Richard Barron[6], [1]Optum Insight, Eden Prairie, MN, [2]Amgen, Thousand Oaks, CA, [3]Optum Life Sciences, Eden Prairie, MN, [4]Amgen Inc., Thousand Oaks, CA, [5]University of Southern California, Los Angeles, CA, [6]Amgen, Inc., Thousand Oaks, CA

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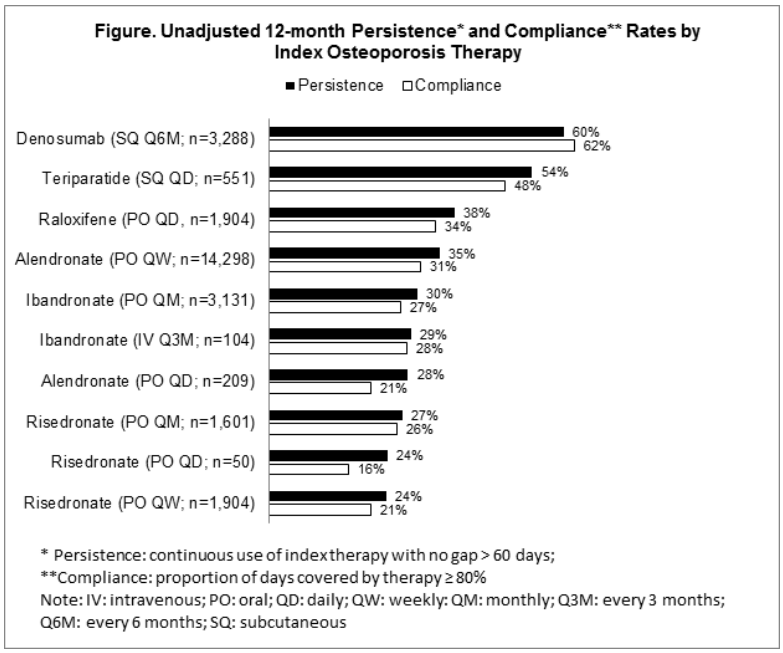
Background/Purpose: Persistence and compliance with oral osteoporosis therapies are generally suboptimal; however, limited persistence data exist for newer injectable therapies that have become available in recent years. The objective of this study is to examine persistence and compliance of osteoporosis therapies using real-world data from a large national health plan in the United States (US).

Methods: Women affiliated with a large US national health plan who newly initiated an osteoporosis medication (alendronate, denosumab, ibandronate, raloxifene, risedronate, or teriparatide) between January 2012 and December 2012 were identified using the Optum Research Database. The index date was the first qualifying claim date. Patients were required to be ≥ 50 years of age at index and have ≥ 12 months of pre-index and ≥ 12 months of post-index continuous enrollment in the health plan. Patients with Paget's disease of the bone, osteogenesis imperfecta, hypercalcemia, malignant cancer and metastasis, HIV, and patients receiving preventive treatment for risk of breast cancer were excluded. Persistence (continuous use of index therapy with no gap > 60 days) and compliance (proportion of days covered by therapy ≥ 80%) were assessed during the 12-month follow-up period. Multivariable logistic regression models were used to estimate and compare persistence and compliance for the therapies of interest, adjusting for demographic and clinical characteristics (reference = group with highest persistence/compliance).

Results: A total of 27,040 patients were eligible and included in the study (mean [SD] age: 67.2 [10.1] years). 12-month persistence was highest for denosumab (subcutaneous every 6 months) at 59.9% and lowest for risedronate (oral weekly) at 23.8%; 12-month compliance was highest for denosumab at 62.2% and lowest for risedronate (oral daily) at 16.0% (Figure). The multivariable logistic regressions showed that the odds of being persistent and compliant across treatments favored denosumab (odds ratios from 1.4 to 4.9, $p<0.001$ for persistence; 1.9 to 8.8, $p<0.001$ for compliance).

Conclusion: In a large US national health plan, persistence and compliance over 12 months were higher among patients initiating denosumab compared to those initiating other osteoporosis therapies.



Disclosure: B. Chastek, Optum, 3; **L. I. Cheng**, Amgen Inc., 1,Amgen Inc., 3; **J. C. White**, Optum, 3; **L. Spangler**, Amgen Inc., 1,Amgen Inc., 3; **D. Mehta**, Amgen Inc., 9; **R. Barron**, Amgen Inc., 1,Amgen Inc., 3.

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Abstract Number: 1283

The Burden of Non-Radiographic Axial Spondyloarthritis from the Employer Perspective: A Real World European Study

Tim Holbrook[1], Robert Wood[1], **Christopher Black**[2], Xiaohan Hu[2] and Sumesh Kachroo[2], [1]Adelphi Real World, Macclesfield, United Kingdom, [2]CORE, Merck & Co., Inc., Rahway, NJ

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Background/Purpose: Non-radiographic axial spondyloarthritis (nr-axSpA) is a burdensome disease to both the patient and the healthcare system, as previous research has indicated. However, the societal burden is less well understood, particularly from the employer perspective. The aim of this analysis was to quantify the burden nr-axSpA patients have on employers.

Methods: Data were taken from the 2014 nr-axSpA Disease Specific Programme a cross-sectional, multi-national survey of nr-axSpA patients and their rheumatologists conducted in France, Germany, Italy, Spain and the UK. Rheumatologists completed patient record forms containing patient demographics and treatment history. These patients completed patient self-completion (PSC) forms containing the Work Productivity and Activity Impairment questionnaire and annual income. Patients who were biologic treatment naïve, yet were considered eligible for biologic treatment by the physician, were compared to patients who had been receiving their current biologic treatment for 6 months or more. Questions regarding income had banded responses and so the midpoint was used in all calculations. Observations were weighted to ensure findings were more representative of the patient population. The weight was applied when calculating all percentages, means and SDs. The human capital method was applied in order to calculate the burden of productivity-loss.

Results: A total of 310 patients were included in the analysis (mean age 42.5±11.8 [SD], 74.8% male), with 123 biologic-naïve patients and 187 patients currently receiving a biologic. Only 76 patients completed a PSC in total. Over half (59.8%) of biologic-naïve patients were employed compared to 78.8% of the biologic-treated patients. The most frequently stated reason for having not yet prescribed biologic treatment in a candidate was “Very recent diagnosis” (32.5%). Biologic-naïve patients had greater overall work impairment

compared to biologic-treated patients (means: 37.1% vs. 18.8%; diff.=18.4%). The mean annual income for the biologic-naïve cohort was 30,171.83€ and the mean duration between diagnosis and first biologic to be prescribed was 17.4 months for the biologic-treated cohort. Therefore, productivity-loss associated with biologic-naïve patients compared to biologic-treated patients equates to 10,834.92€ from the employer perspective, per-patient.

Conclusion: The burden on the economy due to productivity-loss per nr-axSpA patient is substantial. This burden is avoidable to some extent where patients are eligible for biologic treatment. Moreover, biologic treatment was withheld in a third of eligible patients due to a recent diagnosis, suggesting earlier initiation of biologic treatment could be considered.

Disclosure: T. Holbrook, Merck Pharmaceuticals, 5; **R. Wood**, Merck Pharmaceuticals, 5; **C. Black**, Merck Pharmaceuticals, 3; **X. Hu**, Merck Pharmaceuticals, 3; **S. Kachroo**, Merck Pharmaceuticals, 3.

Abstract Number: 1284

Burden of Illness Associated with Non-Radiographic Axial Spondyloarthritis: A European Real World Database Analysis from the Clinical and Healthcare System Perspective

Tim Holbrook[1], Robert Wood[1], **Christopher Black**[2], Xiaohan Hu[2] and Sumesh Kachroo[2], [1]Adelphi Real World, Macclesfield, United Kingdom, [2]CORE, Merck & Co., Inc., Rahway, NJ

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Background/Purpose: Whilst the burden of axial spondyloarthritis (axSpA) is well known, non-radiographic (nr)-axSpa has only recently been identified as a distinct spondyloarthritic indication with its own associated burden. As such, evidence demonstrating the clinical and healthcare system burden of illness is sparse.

Methods: Data were taken from the 2014 nr-axSpA Disease Specific Programme (DSP) a cross-sectional, multi-national survey of nr-axSpA patients and their rheumatologists in France, Germany, Italy, Spain and the UK. Rheumatologists completed patient record forms containing patient demographics, clinical results, symptomology, information on acute episodes and consultations and hospitalisations in the last 12 months. Patients were defined to be non-responsive to current treatment if they were currently experiencing an acute episode, or had worsened in severity or remained severe since initiation of current therapy, or the physician was dissatisfied with their current level of control. Responders were defined as the inverse of non-responders. To adjust for the design bias of the DSP, the number of consultations in the last 12 months was used as an inverse probability weight. The weight was applied to all percentages, means and standard deviations.

Results: A total of 631 patients were included in the analysis (mean age 41.8±12.0 [SD], 70.4% male). Mean age at onset was 35.0±11.2, while 27.3% were classified as having moderate or severe disease state. Over half (56.7%) of patients were currently suffering from inflammatory back pain (IBP) ranging from 43.4% in Spain to 68.4% in Germany, and 18.1% were asymptomatic. On average patients were receiving 1.7 pharmacological products, with little variation across countries. Mean number of consultations with a primary care provider in the last 12 months varied from 1.0 in the UK to 3.2 in Italy. The UK also had the lowest mean number of consultations with a specialist while Germany had the highest (1.8 vs. 3.6). Minimal time was spent in hospital as a result of nr-axSpA with only 0.1 nights spent in hospital on average. Under a quarter (22.9%) of patients were defined to be non-responders. Only 22.5% of non-responders were currently receiving biologic therapy compared to 43.2% of responders.

Conclusion: Nr-axSpa patients suffer from various chronic and acute symptoms and associated pain, while a considerable proportion of patients were non-responsive to their nr-axSpA treatment. Inter-country patient management differences were observed, and may be associated with corresponding unmet clinical needs.

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Abstract Number: 1285

Markers of Non-Compliance with ASAS/EULAR Management Recommendations Among Early Spa Patients: Evidence over 3 Years in the DESIR Cohort

Stephanie Harvard[1,2], Daphne Guh[3], Nick Bansback[4], Maxime Dougados[5], Aslam H. Anis[6] and Bruno Fautrel[7,8], [1]School of Population and Public Health, University of British Columbia, Vancouver, BC, Canada, [2]GRC08, Sorbonne Universités, UPMC Univ Paris 06, Paris, France;, Paris, France, [3]St. Paul's Hospital, Centre for Health Evaluation and Outcome Sciences, Vancouver, BC, Canada, [4]Centre for Health Evaluation and Outcome Sciences, Vancouver, BC, Canada, [5]Medicine Faculty, Paris-Descartes University, Paris, UPRES-EA 4058, Cochin Hospital, Rheumatology B, Paris, France, [6]School of Population and Public Health, Univ of British Columbia, Vancouver, BC, Canada, [7]GRC08, Sorbonne Universités, UPMC Univ Paris 06, Paris, France, Paris, France, [8]AP-HP, Rheumatology Dept, Pitié Salpétrière University Hospital, Paris, France;, Paris, France

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Background/Purpose: We previously published quantitative definitions of the ASAS AS management recommendations designed for use with observational data.[1] The definitions, developed by consensus with expert rheumatologists, are comprised of one or more clinical actions considered to be markers of 'non-compliance with' ASAS recommendations. The DESIR cohort, a longitudinal study of early SpA patients, provides 3 years of observational data suitable for measuring non-compliance according to these definitions.

Methods: We used DESIR cohort data to describe the number of patients with markers of non-compliance at each of 6 follow-up visits (months 0, 6, 12, 18, 24, 36) and at any point over 3 years. We calculated the number of patients with any marker of non-compliance; any 'core' marker of non-compliance (i.e., markers applicable to all patients at all times); any marker of non-compliance minus that pertaining to physiotherapy (for which consensus was not achieved); the number of follow-up visits at which patients had at least one marker of non-compliance; and the total number of markers of non-compliance in each patient at each visit. Non-compliance pertaining to anti-TNF agents was analyzed among patients satisfying ASAS criteria for anti-TNF agents. The analysis included all DESIR patients who satisfied ASAS criteria for axial SpA.

Results: A total of 486 patients satisfied ASAS criteria for axial SpA and were included in the analysis. The most frequently observed marker of non-compliance pertained to lack of physiotherapy, noted among 236 patients (48.6%). When including physiotherapy, 311 patients (64.0%) had at least one marker of non-compliance over 3 years; when excluding physiotherapy, 137 patients (28.2%) had at least one marker of non-compliance over 3 years. Among 153 patients who satisfied ASAS criteria for anti-TNF agents, the marker of non-compliance (i.e., failure to receive an anti-TNF when indicated) was noted among 88 (57.5%). Markers of non-compliance unrelated to physiotherapy or anti-TNF agents were infrequently observed.

Conclusion: In a cohort of early SpA patients, almost half had not had physiotherapy in the first 12 months, while over half of those satisfying the criteria for anti-TNFs did not receive one as soon as indicated. This study suggests areas for improvement in SpA care.

[1]Harvard S, Gossec L, Pham T, Richette P, Dougados M, Anis A,

Fautrel B. Measurable definitions of ankylosing spondylitis management recommendations are needed for use in observational studies. Joint Bone Spine. 2015 Mar 13.

Table 1. Quantitative Definitions of ASAS Recommendations as Markers of Non-Compliance

ASAS Recommendation Category	Marker(s) of Non-Compliance in Category	Marker Included in Analysis?	Marker Number (Label)
Non-Pharmacological Therapy	a. If by the 12-month follow-up visit, patient has had 0 visits to the physiotherapist	Yes	1 (Physiotherapy)
Extra-Articular Manifestations and Co-	a. If at a given study visit, a patient has a new	Yes	2 (Ophthalmologist)

Morbidities	diagnosis of uveitis AND has not had an opthamologist consult by the next study visit		
	b. If at a given study visit, a patient has a new diagnosis of psoriasis AND has not had a dermatologist consult by the next study visit	Yes	3 (Dermatologist)
	c. If at a given study visit, a patient has a new diagnosis of pustulosis AND has not had a dermatologist consult by the next study visit	No (insufficient data)	4 (NA)
	d. If at a given study visit, a patient has a new diagnosis of IBD AND has not had a gastroenterologist consult by the next study visit	Yes	5(Gastroenterologist)
	e. If at a given study visit, a patient has a new cardiovascular event and has not had a cardiologist consult by the next study visit	No (too few cardiovascular events)	6 (Cardiologist)
Non-Steroidal Anti-Inflammatory Drugs	a. If patient received their first DMARD before their first NSAID	Yes	7 (DMARD)
	b. If patient has diagnosis of renal insufficiency (i.e., creatinine clearance < 30 ml/ min) and NSAID use is not interrupted within 15 days of that diagnosis (as assessed at next study visit)	No (insufficient data)	8 (NA)
	c. If patient has history of GI event other than	Yes	9 (PPI)

	dyspepsia and receives an NSAID or Cox inhibitor without a concomitant PPI		
Glucocorticoids	a. If at a given study visit, a patient is receiving oral prednisone or equivalent and has no history of uveitis, peripheral arthritis or inflammatory bowel disease	Yes	10 ('Prednisone')
Disease-Modifying Anti-Rheumatic Drugs	a. If patient has synovitis ³3 at two consecutive visits and is not prescribed a DMARD at either of these visits	No (too few synovitis ³3)	11 (NA)
	b. If at a given study visit, a patient is receiving MTX and has no history of peripheral arthritis or psoriasis	Yes	12 (MTX)
	c. If at a given study visit, a patient is receiving SSZ and has no history of peripheral arthritis, IBD, or uveitis	Yes	13 (SSZ)
Anti-TNF Agents	a. If at two consecutive study visits, patient has had at least 2 adequate therapeutic trials of NSAIDs (i.e., minimum two NSAIDs over a 4-week period in total since symptom onset), BASDAI is ³4, Physician's Global Assessment of Disease is ³4 AND an anti-TNF agent has	Yes	14 (Anti-TNF)

	not been prescribed at the 3rd visit		
	b. If patient is receiving a biological agent other than anti-TNF (*EXCEPTION: psoriatic patients may receive a biologic other than anti-TNF, but then cannot receive a concomitant anti-TNF)	No (0 patients receiving other biologics)	15 (NA)

Table 2. DESIR Patients with Markers of Non-Compliance Over 3 Years of Follow-Up

	Number of patients with non-compliance by time point						
Marker	**Baseline**	**6M**	**12M**	**18M**	**24M**	**36M**	**Ever**
1: Physiotherapy			236 (48.6%)	236 (48.6%)	236 (48.6%)	236 (48.6%)	236 (48.6%)
2: Ophthalmologist	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.2%)	1 (0.2%)
3: Dermatologist	0 (0.0%)	7 (1.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	18 (3.7%)	18 (3.7%)
5: Gastroenterologist	0 (0.0%)	0 (0.0%)	1 (0.2%)	1 (0.2%)	2 (0.4%)	3 (0.6%)	3 (0.6%)
7: DMARD	0 (0.0%)	23 (4.7%)	27 (5.6%)	27 (5.6%)	27 (5.6%)	27 (5.6%)	27 (5.6%)
9: PPI	6 (1.2%)	16 (3.3%)	17 (3.5%)	19 (3.9%)	19 (3.9%)	20 (4.1%)	20 (4.1%)
10: Prednisone	3 (0.6%)	11 (2.3%)	8 (1.6%)	5 (1.0%)	3 (0.6%)	8 (1.6%)	23 (4.7%)
12: MTX	1 (0.2%)	2 (0.4%)	2 (0.4%)	5 (1.0%)	5 (1.0%)	6 (1.2%)	6 (1.2%)
13: SSZ	2 (0.4%)	5 (1.0%)	4 (0.8%)	4 (0.8%)	4 (0.8%)	3 (0.6%)	7 (1.4%)
14: Anti-TNF			33 (6.8%)	42 (8.6%)	49 (10.1%)	53 (10.9%)	53 (10.9%)
Any Core Marker (1, 7, 10, 12, 13,14)	6 (1.2%)	40 (8.2%)	275 (56.6%)	281 (57.8%)	283 (58.2%)	288 (59.3%)	298 (61.3%)
Any Marker Excluding Physiotherapy	12 (2.5%)	57 (11.7%)	83 (17.1%)	92 (18.9%)	100 (20.6%)	124 (25.5%)	137 (28.2%)
Any Marker	12 (2.5%)	57 (11.7%)	281 (57.8%)	287 (59.1%)	290 (59.7%)	302 (62.1%)	311 (64.0%)

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Abstract Number: 1286

Persistent Individual and Neighborhood Poverty Are Independent Risk Factors for Accumulated Lupus Damage

Laura Trupin[1], Stephanie Rush[2], Jinoos Yazdany[3] and Edward H. Yelin[4], [1]Medicine/Rheumatology, University of California San Francisco, San Francisco, CA, [2]UCSF, SF, CA, [3]University of California, San Francisco, San Francisco, CA, [4]Medicine/Rheumatology, UC San Francisco, San Francisco, CA

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Title: Persistent Individual and Neighborhood Poverty Are Independent Risk Factors for Accumulated Lupus Damage

Background/Purpose: Previous research in systemic lupus erythematosus (SLE) has shown that individual poverty and living in an area of concentrated poverty are both associated with poor health outcomes. The present study evaluates whether persistent poverty or persistently living in a neighborhood with a high concentration of poverty is associated with accumulated disease damage in SLE, in comparison to those who are intermittently or never in those circumstances.

Methods: Data derive from the UCSF Lupus Outcomes Study, a national cohort of persons with SLE interviewed annually since 2003. Interview data were augmented through geocoding with data from participants' census block group (600-3000 residents), the study definition of a neighborhood. The survey includes measures of demographic characteristics, socioeconomic status, technical and interpersonal quality of healthcare, and disease status. Individual poverty status was calculated annually, defined as household income ≤125% of the Federal poverty level (<FPL). Concentrated poverty was calculated for each address, and defined as living in a census block group in which >30% of households <FPL. Persistent individual and neighborhood poverty were defined as being poor or in a poor neighborhood at each of the five or more interview years. The Brief Index of Lupus Damage (BILD), a validated self-report measure, was collected in 2012-13 and 2014-15. We modeled the 2 year change in BILD as a function of the proportion of interviews in which participants' incomes were <FPL, and the proportion in which they lived in concentrated poverty, controlling for gender, age, racial/ethnic minority status, disease duration, education, and two measures of quality of care (pass rate of ≥ 85% on technical quality of care indicators vs. not and summary of ratings of interactions with providers and health systems).

Results: Analysis included 501 participants with ≥ 5 interviews and complete data on all variables of interest. Mean age was 54 ± 12 yrs., mean duration 20 ± 9 yrs., 35% were non-white, 25% had ≥ 1 year in individual poverty, and 14% lived in a concentrated poverty neighborhood for ≥ 1 year. Mean BILD score at baseline was 2.9 ±2.6 (range 0-18); mean 2-year change in BILD was 0.44 ± 0.75 (range 0-5). Persistence in both individual and neighborhood poverty were associated with increased BILD scores. Results from the multivariable linear regression model shown in table.

Conclusion: In this national sample of individuals with SLE followed for up to 11 years, persistent individual and neighborhood poverty were independently predictive of increased accumulated lupus damage, even after adjustment for other characteristics known to affect SLE outcomes. Persistent individual and neighborhood poverty are strong markers for future accumulation of damage.

Adjusted mean change (95% Confidence Intervals; CI) in Brief Index of Lupus Damage (BILD) scores over 2 years, by proportion of study years spent in household or neighborhood poverty.

	Household poverty		Neighborhood poverty	
% of time in poverty	n	Mean BILD change (95%CI)	n	Mean BILD change (95%CI)
Never	375	0.58 (0.41, 0.74)*	433	0.56 (0.43, 0.70)*
<50% of years	73	0.57 (0.36, 0.78)*	17	0.53 (0.17, 0.90)
>50% of years	23	0.80 (0.53, 1.08)	26	0.84 (0.54, 1.14)
All years (persistent)	20	0.94 (0.59, 1.29)	25	0.95 (0.64, 1.26)

Means adjusted for both poverty measures, age, gender, race/ethnicity, education, disease duration, technical and interpersonal quality of care.
*p<0.05 compared to 'persistent' group.

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Impact of Participation in Adalimumab Patient Support Program (PSP) on Clinical Outcomes and Predictors of PSP Utilization Among Patients with Rheumatoid Arthritis

Filip van Den Bosch[1], Siegfried Wassenberg[2], Andrew Östör[3], Nupun A. Varothai[4], Vishvas Garg[4] and Jasmina Kalabic[4], [1]Ghent University Hospital, Ghent, Belgium, [2]Fachkrankenhaus, Ratingen, Germany, [3]Addenbrooke's Hospital, Cambridge, United Kingdom, [4]AbbVie, North Chicago, IL

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Background/Purpose: Adalimumab (ADA) treated rheumatoid arthritis (RA) patients (pts) are offered patient support programs (PSP) to manage their disease. The purpose of this study is to assess the impact of PSP utilization on clinical outcomes of ADA treated RA pts and examine the predictors of PSP utilization among pts in clinical settings.

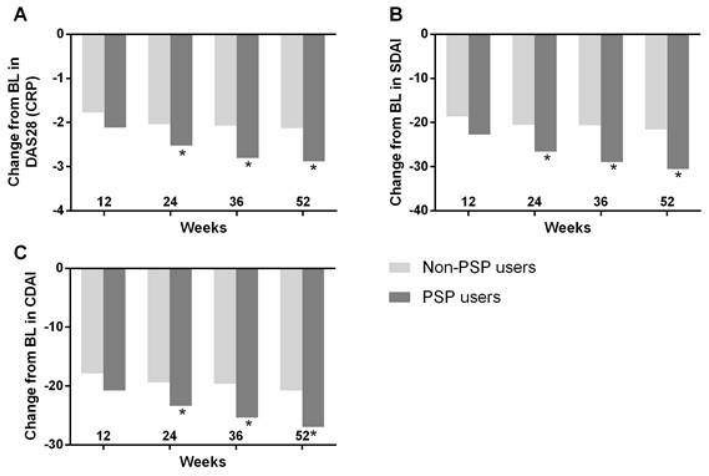
Methods: This is a post-hoc analysis based on interim data from PASSION (NCT01383421); a post-marketing observational study of pts with moderate to severe RA with an insufficient response to ≥1 disease-modifying antirheumatic drug (DMARD) and initiated ADA at participating sites in the EU, Israel, Mexico, Puerto Rico, and Australia. Pts had to be ADA-naïve and treated with ≤1 prior biologic

DMARD. Pts were prescribed ADA according to the local product label and had an option to utilize the PSP while participating in the study. The elements of PSP comprised of starter pack, call center/hotline, nursing services, educational material, injection guide, refill reminders, email, newsletters, support groups, home delivery, and financial assistance. Using multiple regression analysis DAS28, SDAI, and CDAI (mean change at week 52 from baseline [BL]) were compared between PSP-users and PSP non-users from 1-year time-horizon, after adjusting for the pts demographics (age, gender, race) and clinical characteristics (RA duration , prior biologic DMARD use, HAQ-DI, TJC28, SJC28, CRP [mg/l]) at the BL. In a separate multivariate logistic regression analysis, the following variables were assessed as the predictors of PSP usage among ADA treated RA pts: age, race, gender, RA duration , BL DAS28(CRP), BL HAQ-DI, prior biologic DMARD use, and PAM-13 level.

Results: A Total of 852 pts were included in this analysis of which 49.9% were PSP-users while treated with ADA. The mean age at BL was 54.1 y; 76.1% were female, and the mean duration of RA was 7.8 y. Mean BL disease scores were 5.3 for DAS28(CRP), 35.8 for SDAI, and 33.4 for CDAI. Prior biologic DMARD exposure was 17.4%. As shown in the figure, after adjusting for pts BL demographics and clinical characteristics, significant higher improvements ($P \leq 0.005$) from BL to wk 52 were observed for PSP-users vs PSP non-users in DAS28(CRP), SDAI, and CDAI scores. Independent predictors of PSP utilization were found to be: white race (3.856, [2.092, 7.108]), male gender (0.630, [0.426, 0.934]), higher BL HAQ (1.321, [1.019, 1.717]) and DAS28 (1.016, [1.016, 1.379]) values and use of prior biologic DMARD (2.331, [1.484, 3.660]).

Conclusion: Moderate to severe RA pts who were treated with ADA and used PSP showed significantly better clinical outcomes compared to ADA treated PSP non-users. Several demographic and clinical characteristics independently predicted PSP utilization. These findings indicate toward the potential role of ADA PSP in better disease management among moderate to severe RA pts.

Figure: Changes from baseline in DAS28 (CRP) (A), SDAI (B) and CDAI (C) over time between Non-PSP and PSP users.



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Abstract Number: 1288

Dual Care Utilization in Patients Enrolled in the Veterans Affairs Rheumatoid Arthritis Registry

Pascale Schwab[1], Harlan Sayles[2], Debra Bergman[3], Grant W. Cannon[4], Kaleb Michaud[5], Ted R. Mikuls[2] and Jennifer Barton[1], [1]VA Portland Health Care System, Portland, OR, [2]University of Nebraska Medical Center, Omaha, NE, [3]Rheumatology, University of Nebraska Medical Center, Omaha, NE, [4]Division of Rheumatology, Salt Lake City VA Medical Center and University of Utah, Salt Lake City, UT, [5]Rheumatology & Immunology, University of Nebraska Medical Center and National Data Base for Rheumatic Diseases, Omaha, NE
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Background/Purpose: While use of multiple health care systems may allow rapid access to medical care, the practice results in fragmented and redundant treatments at a higher cost. A common source of dual care in the US is characterized by health care provided by both the Veterans Affairs (VA) Healthcare System and any additional federal or private health care coverage. In a 2010 survey of VA enrollees, 75% of those 65 or older and 51% of those under 65 received dual care. The objective of this study was to evaluate dual care use by patients enrolled in the Veterans Affairs Rheumatoid Arthritis Registry (VARA), a longitudinal multi-site disease registry and to compare patient characteristics of dual users (DUs) and non-dual users (NDUs).

Methods: A questionnaire based on the National Data Bank for Rheumatic Diseases inquiring about dual care utilization was sent to veterans with RA enrolled in VARA at 3 sites characterized by beneficiaries from both urban and rural settings (Oregon, Nebraska, and Utah). Veterans reported medical services from a non-VA primary care provider or non-VA subspecialist. Information on co-morbidities, non-VA medications, and non-VA hospitalizations was also collected. T-tests for continuous variables and Pearson chi-square tests for categorical variables were performed to compare characteristics of DUs versus NDUs. Fisher's exact test was used to compare comorbidities between the two groups.

Results: Of 526 veterans surveyed, 310 (59%) responded (74%, 69%, and 52% in Oregon, Nebraska, and Utah respectively). Data on the initial 251 responders are presented here. Approximately one-fourth (26%) of enrollees reported having a non-VA primary care physician, 22% reported having a non-VA subspecialist (a third of these were cardiologists) and 5% reported having a non-VA rheumatologist. With respect to medication use, 24% of respondents received non-VA non-RA medications and only 5% reported receiving a non-VA synthetic DMARD, biologic DMARD, or corticosteroids. Overall, nearly 1 in 10 veterans had been hospitalized at a non-VA facility within 6 months prior to the survey. A comparison of patient characteristics revealed that DUs were older, had more years of education, and were more likely to have never been smokers compared to NDUs; additionally, DUs reported more comorbidities and orthopedic procedures than NDUs (Table).

Conclusion: VARA participants have a lower rate of dual care utilization than previously reported for the overall VA population, with very few patients receiving dual rheumatology care or non-VA RA medications. This survey suggests that the majority of US veterans enrolled in VARA utilize the VA as their single source of RA care.

Characteristics of US Veterans with Rheumatoid Arthritis: Dual Users v. Non-Dual Users

Characteristic	Dual User (n=99)	Non-Dual User (n=152)	P-value
Age, mean years (SD)	71 (10)	67 (8)	<0.001
Male, N (%)	91 (92)	142 (93)	0.65
Caucasian, N (%)	91 (92)	138 (91)	0.76
Education, mean years (SD)	14 (2)	13 (2)	0.04
Never smoker, N (%)	28 (29)	25 (16)	0.03
Comorbidities, N (%)			
- Heart condition	17 (17)	12 (8)	0.03
- Stroke	4 (4)	0 (0)	0.02
- Cancer	25 (25)	21 (14)	0.03
- Cataract	33 (33)	30 (20)	0.02
- Thyroid disorder	24 (24)	19 (13)	0.03
- Any orthopedic procedure	26 (26	18 (11)	0.004

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Abstract Number: 1289

Healthcare Utilization Differences According to Sex Among Children and Adults in Medicaid with Incident Lupus Nephritis

Candace H. Feldman[1], Anna R. Broder[2], Hongshu Guan[3], Anand Kumthekar[4], Michail Alevizos[5], Jinoos Yazdany[6] and Karen H. Costenbader[7], [1]Division of Rheumatology, Immunology and Allergy, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, [2]Rheumatology-Forchheimer 701N, Albert Einstein College of Medicine/Montefiore Medical Center, Bronx, NY, [3]Rheumatology, Immunology and Allergy, Brigham and Women's Hospital, Boston, MA, [4]Medicine, Albert Einstein College of Medicine/Jacobi Medical Center, Bronx, NY, [5]Medicine, Albert Einstien College of Medicine/Jacobi Medical Center, Bronx, NY, [6]Rheumatology, University of

California, San Francisco, San Francisco, CA, [7]Rheumatology, Immunology and Allergy, Brigham and Women's Hospital, Harvard Medical School, Boston, MA

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Background/Purpose: Past studies suggest that males with lupus nephritis (LN) may have increased rates of end-stage renal disease (ESRD) and mortality compared to females. Most prior studies have focused on biological differences and few have examined variations in healthcare use and access. We investigated potential sex differences in healthcare utilization in the period surrounding onset of LN in a nationwide incident LN cohort.

Methods: We utilized the Medicaid Analytic eXtract (MAX) with billing claims from 47 U.S. states and Washington, D.C.to identify children and adults ages 5-65 with incident LN from 2000-2004. We used a previously validated ICD-9 code algorithm for LN (PPV 80%), and required 12 months without any LN codes to define incident cases. MAX data were linked to the US Renal Data System to identify ESRD onset. The index date was the date the incident LN definition was met and we followed individuals in both datasets through 2006. Subjects were censored at death, ESRD, Medicaid disenrollment, or end of follow-up. We evaluated sociodemographics by sex and calculated sex-specific proportions of SLE and renal medication use, renal biopsies and preventive care in the period 3 months prior through 12 months after the index date. We estimated incidence rates of all emergency department, outpatient, and inpatient visits during this period. We used Poisson regression models to calculate incidence rate ratios for healthcare utilization by sex, adjusting for baseline sociodemographic and clinical characteristics.

Results: Of 2576 patients with incident LN, 230 (9%) were male. Mean follow-up was 2.8 (±1.5) years for both sexes. Mean age was 30 years (±16) among males and 34 years (±14) among females (p<0.001). More males were White (32% vs. 20% of females) and fewer Black (23% vs. 32%, p 0.02). Geographically, a higher proportion of males lived in the West (p 0.006) and in higher socioeconomic status areas (p 0.02). There was no significant difference in the SLE comorbidity index (p 0.11). 31% of men and 37% of women underwent renal biopsy (p 0.06), while 10% of males and 16% of females received azathioprine (p 0.02). There were no statistically significant differences by sex in use of immunosuppressives overall, hydroxychloroquine, glucocorticoids, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, erythropoetin, or in influenza or pneumoccocal vaccine uptake. Incidence rates of inpatient admissions were similar for both sexes, but the rates of outpatient and emergency department visits were significantly lower among males (**Table**).

Conclusion: In this large incident LN cohort, males had modestly lower rates of outpatient and emergency department visits than did females. Further studies are needed to understand whether the observed variation is related to differences in SLE activity or in health-seeking behavior, and how it relates to long-term outcomes.

Table. Incidence Rates and Adjusted Rate Ratios for Healthcare Utilization among Medicaid Patients with Incident Lupus Nephritis, by Sex

	Female (N=2346)			Male (N=230)			Adjusted IRR* (95% CI) Female=referent
	Events	Person-years	IR (95%CI)	Events	Person-years	IR (95%CI)	
Emergency Department Visits	8619	2719.4	316.9 (310.2-323.6)	722	262.4	275.2 (255.1-295.2)	**0.81 (0.68-0.98)**
Outpatient Visits	33964	2719.4	1248.9 (1235.6-1262.2)	2973	262.4	1133.2 (1092.5-1174.0)	**0.88 (0.79-0.99)**
Inpatient Admissions	5958	2719.4	219.1 (213.5-224.7)	726	262.4	276.7 (256.6-296.9)	1.13 (0.98-1.31)

IR, incidence rate per 100 person-years; IRR, incidence rate ratio

*Poisson regression analyses adjusted for age, race/ethnicity, calendar year, U.S. region, zip-code based socioeconomic status based on 7 US census indicators (Ward MM,J Rheum, 2007), and SLE Risk Adjustment Index (Ward MM, J Rheum, 2000)

Disclosure: C. H. Feldman, None; **A. R. Broder**, None; **H. Guan**, None; **A. Kumthekar**, None; **M. Alevizos**, None; **J. Yazdany**, None; **K. H. Costenbader**, None.

Abstract Number: 1290

Burden of Rheumatoid Arthritis in the US Elderly Population: Comorbidities, Healthcare Resource Utilization, and Cost

Chieh-I Chen[1], Li Wang[2], Wenhui Wei[3], Huseyin Yuce[4] and **Kristine Phillips**[5], [1]Regeneron Pharmaceuticals, Inc., Tarrytown, NY, [2]Director, Analytic Research, STATinMED Research, Plano, TX, [3]Sanofi-Aventis, Bridgewater, NJ, [4]New York City College of Technology (CUNY), New York, NJ, [5]Rheumatology, University of Michigan, Ann Arbor, MI
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SESSION INFORMATION
Session Title: Health Services Research Poster II (ACR): Healthcare Access, Patterns of Medication Use and Workforce Considerations
Session Type: ACR Poster Session B

Background/Purpose: Rheumatoid arthritis (RA) is a systemic inflammatory disease resulting in significant healthcare resource utilization (HRCU) and cost. Data on elderly RA patients are generally limited. This study aimed to estimate the burden of RA in the US elderly by comparing comorbidities, HCRU, and cost among elderly RA patients with elderly non-RA patients.

Methods: Using Medicare fee-for-service claims data from 2010 through 2013, this was a retrospective study of RA patients aged ≥ 65 years with ≥ 2 medical claims with a diagnosis of RA (ICD-9-CM 714.xx) and ≥ 1 pharmacy claim for a disease-modifying antirheumatic drug (DMARD, biologic and/or conventional synthetic), and a control cohort of non-RA elderly patients, 1:1 matched on age, gender, race, and region. The index date was the date of the first prescription DMARD for RA patients, and randomized assigned for non-RA patients. Prevalence of comorbidities was assessed for a 12-month period prior to the index. All-cause and RA-related (defined based on RA diagnosis and treatment) HCRU and costs during the 12-month post-index period were compared between elderly patients with RA and matched controls.

Results: The matched cohorts included a total of 231,734 patients (elderly RA, n = 115,867; control, n = 115,867) with average age 75.2 years, 79.4% women, 86.2% Caucasian, and 41.3% living in the South. Compared with non-RA elderly, RA elderly had significantly greater overall comorbidity burden (Charlson Comorbidity Index excluding RA: 1.86 vs. 1.00, $P < 0.0001$) and individual baseline comorbidities including hypertension, hyperlipidemia, diabetes, respiratory disease, osteoporosis, and cardiovascular diseases (all $P < 0.0001$). The top 5 non-bone/joint-related diagnoses among RA patients were essential hypertension, disorders of lipid metabolism, general symptoms, symptoms involving the respiratory system and other chest symptoms, and other disorders of soft tissue (Figure). Elderly RA patients had significantly more HCRU than non-RA patients, resulting in nearly 3-fold higher annual healthcare costs, with half being RA-related (Table). After controlling for differences in patient characteristics and comorbidities, the adjusted total mean annual costs for RA patients were still more than double as that of non-RA patients ($16,374 vs. $6,712, $P < 0.0001$).

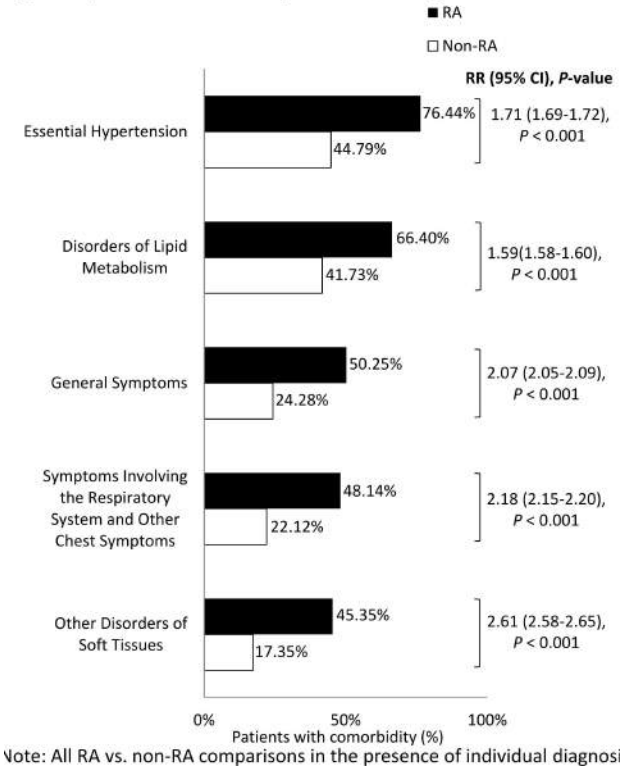
Conclusion: Among US elderly patients, RA was associated with significantly greater burden of comorbidities, HCRU and costs, as compared with elderly patients without RA. RA was a major driver of the overall healthcare use and cost.

Table. Annual Healthcare Resource Utilization and Cost

	Case Group (RA)		Control Group (Non-RA)
	All-cause	RA-related	All-cause
	Mean (SD)	Mean (SD)	Mean (SD)
Annual Healthcare Utilization			
No. of Inpatient/ER Visits	0.96 (1.75)	0.49 (1.11)	0.40 (1.13)
No. of Outpatient Visits	31.28 (19.83)	9.17 (6.97)	11.99 (16.99)
No. of Prescription Fills	35.64 (19.83)	12.52 (7.05)	22.29 (17.89)
Length of Hospital Stay(days)	4.38 (16.20)	2.66 (10.77)	0.97 (4.92)
Annual Healthcare Costs			
Inpatient/ER Costs	$6,103 ($17,134)	$4,198 ($13,050)	$2,142 ($9,757)
Outpatient Costs	$9,022 ($9,795)	$4,719 ($8,964)	$2,607 ($6,315)
Pharmacy Costs	$5,794 ($8,969)	$2,670 ($6,755)	$2,449 ($4,263)
Total Costs	$20,919 ($23,888)	$11,587 ($16,920)	$7,197 ($15,094)

Note: All RA vs. non-RA comparisons were statistically significant at the 0.001 level. ER = emergency room

Figure. Top 5 Baseline Non-Bone/Joint Related Diagnosis in RA Patients



Note: All RA vs. non-RA comparisons in the presence of individual diagnosis were statistically

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Disclosure: C. I. Chen, Regeneron Pharmaceuticals, Inc., 1,Regeneron Pharmaceuticals, Inc., 3; **L. Wang**, Statinmed, 3,Sanofi US, 9; **W. Wei**, Sanofi US, 1,Sanofi US, 3; **H. Yuce**, None; **K. Phillips**, Sanofi US, 5.

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Abstract Number: 1291

The Pediatric Rheumatology Workforce in 2015: A Survey of Pediatric Rheumatologists

Meredith Riebschleger[1], Mara L Becker[2], Holly S. Ruch-Ross[3], 'Laura Laskosz[4], Carrie Radabaugh[5], Polly J. Ferguson[6], Kenneth N. Schikler[7] and Sandy D. Hong[8], [1]Pediatric Rheumatology & Health Services Research, University of Michigan, Ann Arbor, MI, [2]Rheumatology, Children's Mercy Kansas City, Kansas City, MO, [3]Independent Research and Evaluation Consultant, Evanston, IL, [4]Division of Technical and Medical Services, The American Academy of Pediatrics, Elk Grove Village, IL, [5]Department of Education, American Academy of Pediatrics, Elk Grove Village, IL, [6]Dept of Pediatrics--Rheum, University of Iowa, Iowa City, IA, [7]Pediatrics, University of Louisville, Louisville, KY, [8]Pediatrics-Rheumatology, U of Iowa Children's Hosp, Iowa City, IA

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SESSION INFORMATION

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Session Type: ACR Poster Session B

Background/Purpose: Pediatric Rheumatology (PR) is among the smallest pediatric subspecialties, with only ~300 clinically active board-certified Pediatric Rheumatologists in the US. To better characterize the work patterns of the US PR workforce, the American Academy of Pediatrics (AAP) performed a survey of Pediatric Rheumatologists.

Methods: A list of Pediatric Rheumatologists was generated using the membership list of the AAP Section on Rheumatology and the PR certification list of the American Board of Pediatrics. An electronic survey was fielded 9/2014-12/2014. Survey domains included demographics, practice characteristics, distribution of professional time, and future plans. Only respondents reporting current PR practice were eligible for analyses. SPSS 18.0 was used for analyses, including frequency distributions, measures of central tendency, ANOVA,

and χ^2.

Results: 151/317 (48%) identified Pediatric Rheumatologists responded to the survey. 138 respondents reported current PR practice and were included in analyses. Of those, 25 (18%) reported part-time PR practice. Part-time respondents worked fewer hours/week than full-time respondents (mean 44 vs. 52 hours/week, p<.001), but % clinical time, half-day clinic sessions/week, and patients seen/week were not significantly different between the two groups (table 1). Overall, 99% of respondents reported spending time in direct patient care, 78% reported time in administration, 88% reported time in teaching, and 75% reported time in research. The breakdown of apportioned time for part- and full-time respondents is detailed in table 1. For all respondents combined, hours worked/week was inversely related to % time spent in direct patient care (table 2, p=.016).

Conclusion: A significant minority of the PR workforce report part-time PR practice, and more than half of full-time respondents spend ≤60% of their time in direct patient care. Providers who spend more time on non-clinical duties average more hours of work/week, illustrating the extra time required for an academic career. As most Pediatric Rheumatologists work in medical school/University affiliated practices, with academic requirements for promotion, it is critical to account for non-clinical time in estimates of future PR workforce requirements.

Table 1 – Comparison of part-time and full-time Pediatric Rheumatology respondents

	Respondents reporting PART-TIME PR practice (N=25)	Respondents reporting FULL-TIME PR practice (N=113)	All respondents (N=138)	p-value (part-time vs. full-time)
Sex				NS
Male	52 (48%)	8 (32%)	60 (45%)	
Female	57 (52%)	17 (68%)	74 (55%)	
Practice type				NS
Medical school / University hospital	21 (84%)	90 (80%)	111 (80%)	
Other	4 (16%)	23 (20%)	27 (20%)	
Clinics per week Mean (SD)	3.6 (2.0)	4.1 (2.4)	4.0 (2.3)	NS
Hours per week Mean (SD)	44.2 (13.5)	55.2 (9.4)	53.2 (11.0)	<.001
Patients seen per week Mean (SD)	26.4 (20.6)	31.0 (22.3)	30.1 (22.0)	NS
Apportioned time				
Direct patient care Mean percent time	59.9	52.9	54.1	NS
Administration Mean percent time	8.9	10.9	10.5	NS
Teaching Mean percent time	11.6	8.2	8.8	NS
Research Mean percent time	11.3	22	20.1	.055

Table 2 – Measures of clinical productivity and work hours compared with percent clinical time (Includes both full-time and part-time Pediatric Rheumatology respondents, combined)

	0-20% (N=21)	21-40% (N=24)	41-60% (N=15)	61-80% (N=35)	81-100% (N=41)	p-value
Number half-day clinic sessions per week Mean (SD)	1.7 (1.7)	2.3 (1.2)	3.3 (0.9)	5.0 (1.4)	5.7 (2.3)	<.001
Total number of patients seen per week Mean (SD)	14.0 (20.1)	16.3 (9.3)	29.9 (12.1)	35.0 (14.2)	43.4 (27.2)	<.001
Total hours worked per week Mean (SD)	58.1 (8.7)	55.3 (10.5)	52.7 (10.0)	54.6 (12.7)	48.9 (10.3)	.016

Disclosure: M. Riebschleger, None; **M. L. Becker**, None; **H. S. Ruch-Ross**, None; **Laskosz**, American Academy of Pediatrics, 3; **C. Radabaugh**, American Academy of Pediatrics, 3; **P. J. Ferguson**, None; **K. N. Schikler**, None; **S. D. Hong**, None.

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Abstract Number: 1292

What Is the Effect of TNF Inhibitors on Employment Status in Rheumatoid Arthritis Patients and What Are the Predictors of Progression to Unemployment?

Andrew Chow[1], Regan Arendse[2], Wojciech Olszynski[2], John Kelsall[3], Milton F. Baker[4], William G Bensen[5], Philip Baer[6], Anna Jaroszynska[7], Denis Choquette[8], Suneil Kapur[9], Jacqueline Stewart[10], Emmanouil Rampakakis[11,12], Eliofotisti Psaradellis[12], Francois Nantel[13], Susan Otawa[14], Cathy Tkaczyk[14], Allen J Lehman[14] and Karina Maslova[13], [1]University of Toronto/McMaster University, Mississauga, ON, Canada, [2]University of Saskatchewan, Saskatoon, SK, Canada, [3]Mary Pack Arthritis Centre, Vancouver, Vancouver, BC, Canada, [4]VIHA, Victoria, BC, Canada, [5]St Joseph's Healthcare Hamilton, Hamilton, ON, Canada, [6]Section on Rheumatology, Ontario Medical Association/Journal of the Canadian Rheumatology Association, Toronto, ON, Canada, [7]Private Practice, Burlington, ON, Canada, [8]Rheumatology Department, Institut de Rhumatologie de Montréal and University of Montreal, Montreal, QC, Canada, [9]Rheumatology, University of Ottawa, Ottawa, ON, Canada, [10]Penticton Regional Hospital, Penticton, BC, Canada, [11]JSS Medical Research, St-Laurent, QC, Canada, [12]JSS Medical Research, Montreal, QC, Canada, [13]Janssen Inc., Toronto, ON, Canada, [14]Medical Affairs, Janssen Inc., Toronto, ON, Canada

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SESSION INFORMATION

Session Title: Health Services Research Poster II (ACR): Healthcare Access, Patterns of Medication Use and Workforce Considerations

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Background/Purpose:

Rheumatoid arthritis (RA) is a chronic, progressive inflammatory disease which has been associated with an increased incidence of disability and unemployment over time. The aim of this analysis was to evaluate the prevalence of unemployment due to work disability in RA patients initiating treatment with infliximab (IFX) or golimumab (GLM) and to identify determinants of disability.

Methods:

BioTRAC is an ongoing, prospective registry of patients initiating treatment for RA, AS, or PsA with IFX or GLM as first biologics or after having been treated with a biologic for <6 months. Data were obtained from RA patients treated with IFX (2002-2014) or GLM (2010-2014). Between employment group differences were assessed for statistical significance with the independent samples t-test or the chi-square. Time to employment and time to unemployment were assessed with the Kaplan-Meier (KM) estimator of the survival function. Cox regression was used to identify predictors of time to unemployment.

Results:

A total of 581 RA patients were included; 374 (64.4%) employed and 207 (35.6%) unemployed due to disability. The following baseline parameters were associated with significantly increased likelihood of being unemployed due to disability: female vs. male gender (40.1% vs. 27.6%; P=0.006), earlier enrolment period (2002-05 vs. 2006-09 vs. 2010-14: 49.3% vs. 30.5% vs. 22.4%; P<0.001), insurance type (provincial vs. private vs. both: 54.9% vs. 23.8% vs. 20.0%; P<0.001), older age (P=0.033), and increased disease activity as evidenced by the higher DAS28 (P<0.001), SJC (P<0.001), TJC (P<0.001), HAQ (P<0.001), MDGA (P<0.001), PtGA (P<0.001), CDAI (P<0.001), SDAI (P<0.001), pain (P<0.001), and ESR (P<0.001).

Among disabled patients, 10.1% were able to return to work upon treatment with TNF a mean KM-based duration of 119.5 months from baseline; whereas 6.4% of employed patients became disabled (2002-05 vs. 2006-09 vs. 2010-14: 7.0% vs. 10.1% vs. 1.7%; P=0.021) with a mean time to unemployment of 113.4 months. Multivariate survival analysis showed that, upon adjusting for enrolment period, higher baseline HAQ [HR (95%CI): 3.59 (1.64, 7.87), P=0.001], and higher baseline SJC [HR (95%CI): 1.09 (1.02, 1.16), P=0.011] were significant predictors of unemployment due to disability.

Conclusion:

A significant proportion of RA patients are unemployed due to disability in Canada. At anti-TNF initiation, work disability was associated with higher disease activity, female gender, earlier enrolment period, and provincial insurance. Increased HAQ and higher SJC were significant predictors of progression to unemployment highlighting the importance of early anti-TNF initiation in order to prevent work disability. Anti-TNF treatment was effective in enabling a considerable portion of disabled patients to return to employment.

Disclosure: A. Chow, Janssen Inc., 5; **R. Arendse**, Janssen Inc., 5; **W. Olszynski**, Janssen Inc., 5; **J. Kelsall**, Janssen Inc., 5; **M. F. Baker**, Janssen Inc., 5; **W. G. Bensen**, Janssen Inc., 5; **P. Baer**, Janssen Inc., 5,AbbVie, 5,Amgen, 5,BMS, 5,Pfizer Inc, 5,Roche Pharmaceuticals, 5; **A. Jaroszynska**, Janssen Inc., 5; **D. Choquette**, Janssen Inc., 5,AbbVie, 5,Amgen, 5,Celgene, 5,BMS, 5,Pfizer Inc, 5; **S. Kapur**, Janssen Inc., 5; **J. Stewart**, Janssen Inc., 5; **E. Rampakakis**, JSS, 3; **E. Psaradellis**, JSS Medical Research, 3; **F. Nantel**, Janssen Inc., 3; **S. Otawa**, Janssen Inc., 3; **C. Tkaczyk**, Janssen Inc., 3; **A. J. Lehman**, Janssen Inc., 3; **K. Maslova**, Janssen Inc., 3.

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Abstract Number: 1293

A Comparison of Prenatal Care in Mothers with and without JIA: Association with Outcomes

Debbie Ehrmann Feldman[1], Anick Bérard[2], Evelyne Vinet[3], Ciarán M. Duffy[4], Elizabeth Hazel[5], Marie-Pierre Sylvestre[6], Garbis Meshefedjian[7] and Sasha Bernatsky[8], [1]School of Rehabilitation, Université de Montréal, Montreal, QC, Canada, [2]Université de Montréal, Montréal, QC, Canada, [3]Divisions of Rheumatology and Clinical Epidemiology, McGill University Health Centre, Montreal, QC, Canada, [4]Children's Hospital of Eastern Ontario and University of Ottawa, Ottawa, ON, Canada, [5]Rhematology, McGill University Health Centre, Montreal, QC, Canada, [6]Université de Montréal, Montreal, QC, Canada, [7]Public Health Department of Montreal, Montreal, QC, Canada, [8]Rheum/Clin. Epid., McGill MUHC/RVH, Montreal, QC, Canada

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SESSION INFORMATION

Session Date: Monday, November 9, 2015
Session Title: Health Services Research Poster (ARHP)
Session Type: ACR Poster Session B
Session Time: 9:00AM-11:00AM

Background/Purpose:

Women who had JIA in childhood and adolescence may be at higher risk for adverse neonatal and maternal outcomes. Our objective was to examine aspects of prenatal care in women who had JIA versus those who did not have JIA, and to evaluate the association between prenatal care and risk of adverse outcomes.

Methods:

We designed a cohort study using data from physician billing and hospitalization data covering Québec, Canada. The cohort contained all females with JIA with a first-time birth between 01/01/1983 and 12/31/2010 (n=1681) and a control cohort of first-time mothers without JIA from the same administrative data, matching 4:1 for date of first birth, age of mother and area of residence (n=6724). Using the revised

G-INDEX (which is based on the American College of Obstetricians and Gynecologists recommendations for prenatal visits for low risk pregnant women), we determined prenatal care as adequate, intermediate, inadequate, and a group with no care or missing data. This latter group may contain those mothers that receive no prenatal care or those that see salaried physicians, midwives or nurses whose services are not recorded in the physician billing data. We described and compared prenatal care in mothers with JIA and those who did not have JIA and used logistic regression analysis to determine the association between prenatal care levels and adverse outcomes (prematurity, small for gestational age, and major congenital malformations) adjusted for maternal age, education and socioeconomic status (deprivation index).

Results:

In our entire cohort 1.4% of mothers in the JIA group and 4.6% in the non JIA group were classified as receiving inadequate care. Adequate, and intermediate care were 32.9 and 8.4% respectively in the JIA group and 57.7 and 21.9% in the non-JIA group. Nearly a quarter of our cohort (24.1%) had missing data or received no prenatal care, and this was substantially higher in the JIA group (57.4% vs 15.8% in the non-JIA group). We were unable to detect an increased risk of an adverse event in the JIA or non-JIA group when comparing adequate/intermediate care to inadequate prenatal care . However, being in the no care/ missing group was associated with having a child with a major congenital malformation in both the JIA group (adjusted Relative Risk (RR), 1.95; 95% Confidence Interval (CI) 1.37,2.79) and non-JIA groups (adjusted RR 1.81; 95% CI 1.14,2.87).

Conclusion:

Mothers with a history of JIA differ from those without JIA in terms of prenatal care patterns. In both groups, having no record of prenatal care was associated with having an adverse birth outcome.

Disclosure: D. Ehrmann Feldman, None; **A. Bérard**, None; **E. Vinet**, None; **C. M. Duffy**, None; **E. Hazel**, None; **M. P. Sylvestre**, None; **G. Meshefedjian**, None; **S. Bernatsky**, None.

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Abstract Number: 1294

Infection and Screening Costs Related to Tumor Necrosis Factor-Alpha Inhibitor Use

Elizabeth G. Salt[1], Amanda T. Wiggins[1], Mary Kay Rayens[1], David Mannino[2], Huaman Joo Moises[3], Allison R. Jones[4], Scott A. Merkley[5], Philip Schwieterman[6] and Leslie J. Crofford[7], [1]College of Nursing, University of Kentucky, Lexington, KY, [2]Colege of Medicine and Public Health, University of Kentucky, Lexington, KY, [3]College of Medicine- Infectious Disease, Univesity of Kentucky, Lexington, KY, [4]University of Kentucky, Lexington, KY, [5]Lexington Clinic, Lexington, KY, [6]College of Pharmacy, University of Kentucky, Lexington, KY, [7]Medicine, Vanderbilt University, Nashville, TN

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Session Time: 9:00AM-11:00AM

Background/Purpose: Bacterial and fungal infections (e.g., tuberculosis, histoplasmosis) have been associated with the use of TNF-α inhibitors (TNFI). Although screening for specific infections prior to initiating TNFI has been recommended, the costs associated with screenings and treatment of these infections has not been well described in the literature. Thus, the study aim was to describe the costs associated with screenings for and the treatment of targeted fungal or mycobacterial infections in patients taking TNFI.

Methods: A case-control study ($N = 436$) was conducted using deidentified patient health claims information from a dataset representing a commercially-insured, U.S. population of 15 million patients annually (1/1/2007-12/31/2009). To begin, all patients who obtained a TNFI for any indication were extracted from the dataset which resulted in 25,949 unique patients. These patients were then followed forward in time and defined as a case if they received medical care (inpatient or outpatient) for one (or more) targeted fungal or mycobacterial infections (i.e., tuberculosis, histoplasmosis, unspecified mycosis, coccidioidomyocosis, cryptococcal) and 124 unique patients were identified. Fifteen of these patients had cancer and were excluded from the analyses; thus, 109 patients were defined as cases. Controls were randomly selected to frequency match cases on age and length of follow-up in a 3:1 ratio. Descriptive statistics were used to summarize standardized costs of screening and medical treatments attributed to targeted infections.

Results: Of the 436 patients in our sample the median cost for screening was $23.05 (Interquartile Ranges: Q1 = $10.20, Q3 = $46.73) for the total sample; $20.40 (Q1 = $10.20, Q3 = 46.73) for controls and $32.52 (Q1 = $10.2, Q3 = $46.73) for cases. See Table 1 for the cost per screening procedure. The median cost of infection treatment was $100.97 (Q1 = $45.12, Q3 = $276.56). See Table 2 for the cost per infection.

Conclusion: Although few patients in this study were diagnosed with a targeted infection (0.48%), from a cost perspective, the high cost of these infections relative to the low cost of the more frequently used screenings likely warrants their continued use in clinical practice.

Table 1. Standardized Cost Per Screening (Total Sample = 436; Screened = 126)

Screening	Median (Interquartile Ranges)
Bronchoalveolar lavage (*n* = 1)	$619.60
CT of the chest (*n* = 7)	$375.97 (Q1 = $375.97; Q3 = $555.36)
Interferon gamma release assay (*n* = 1)	$61.75
Fungal cultures (*n* = 3)	$27.40 (Q1 = $27.40; Q3 = $116.02)
Chest x-ray (*n* = 63)	$45.12 (Q1 = $16.65; Q3 = $45.12)
Coccidioidal serologic test IgG and IgM (*n* = 8)	$25.78 (Q1 = $27.78; Q3 = 34.37)
Tuberculin skin test (*n* = 84)	$10.20 (Q1 = $10.20; Q3 = $10.20)
Crytococcal serum antigen (*n* = 0)	-
Histoplasmosis culture/serologic specific antibodies (*n* = 0)	-
Histoplasmosis polymerase chain reaction (*n* = 0)	-
Urine/serum/broncholavage for histoplasmin antigen (*n* = 0)	-

Table 2. Aggregated Standardized Cost Per Infection

Targeted Infection	Median (Interquartile Ranges)
Tuberculosis (*n* = 46)	$79.11 (Q1 = $45.12; Q3 = $156.30)
Histoplasmosis (*n* = 46)	$154.42 (Q1 = $62.84, Q3 = $1103.30)
Fungal Culture Unspecified (*n* = 10)	$56.13 (Q1 = $48.88, Q3 = $351.25)
Coccidioidomyocosis (*n* = 6)	$124.47 (Q1 = $33.30; Q3 = $259.43)
Cryptococcal (*n* = 2)	$379.19 (Q1 = $256.73; Q3 = $501.65)

Disclosure: E. G. Salt, None; **A. T. Wiggins**, None; **M. K. Rayens**, None; **D. Mannino**, None; **H. J. Moises**, None; **A. R. Jones**, None; **S. A. Merkley**, None; **P. Schwieterman**, None; **L. J. Crofford**, None.

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Abstract Number: 1295

Online Consultation for Rheumatic Disease Patients Based on Smart System of Disease Management (SSDM) Mobile Tools: A Study of Medical Economics

Fei Xiao[1], Xiangyuan Liu[2], Hua Wei[3], Zhijun Li[4], Yanhong Huang[5], Yaohu Jiang[6], Huiqiong Zhou[7], Jie Shen[8], Yuhua Jia[1], Li Zhang[1], Yuan Liu[1], Minjun Wang[1] and Fengchun Zhang[9], [1]Gothic Internet Technology Corporation, Shanghai, China, [2]Department of Rheumatology and Immunology, Peking University Third hospital, Bei jing, China, [3]No 98,Nantong West Rd,Yangzhou, Northern Jiangsu People's Hospital, Yangzhou, China, [4]The First Affiliated Hospital of Bengbu Medical College, Bengbu, China, [5]Beijing Jishuitan Hospital, Beijing, China, [6]Renji Hospital Shanghai Jiaotong University School of Medicine, Shanghai, China, [7]The First Affiliated Hospital of PLA General Hospital, Beijing, China, [8]University of Rochester, Rochester, NY, [9]Department of Rheumatology, Peking Union Medical college Hosptial, Beijing, China

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Background/Purpose: China has no primary medical care and referral system. Patients can choose any hospitals or any doctors they like to seek medical care. As a result, most patients with rheumatic diseases rushed to a few large cities on their own cost.

Survey shows more than 40% of the rheumatic disease patients are unnecessary to go to hospital and they only need advices from specialist.

Smart System of Disease Management (SSDM) is a series of applications for chronic diseases management, which develop the interaction between doctors and patients online with mobile device. The study shows that, after training, the rheumatoid arthritis (RA) patients can master the SSDM and perform self-management, including DAS28 and HAQ evaluations, as well as medication and lab test data entries.

To evaluate the feasibility and benefit of the medical economics of online consultations based on SSDM by rheumatologists.

Methods: The rheumatologists implemented the education and training programs on using SSDM for rheumatic disease patients and assist them in downloading SSDM APP in clinic.

The SSDM includes doctors' application and patients' application. The patient application includes self-assessment (DAS28, HAQ), medication management, adverse events management and laboratory records. After data entry, patients can synchronize data to the authorized doctor. On the basis of understanding of the disease activities, medication and laboratory test results, the rheumatologists can accept the request from their patients and practice consultation in the form of texting or telephone call.

Results: Between February 14, 2015 and June 22, 2015, 8 rheumatologists supplied 55 patients with 64 times free and 12 paid consultations. Paid consulting included 8 times text Q&A and four telephone consultations. The consulting fee ranged from RMB 50 to 300 yuan (USD:RMB =1:6.1) each in average of 220.83 ± 72.17 yuan, which rate match the registration fee in hospital. The total collection of fee for consultations was 2,650 yuan.

75% patients receiving online consultation lived in different city with the rheumatologists, the mean distance was 925.71 ± 803.65 (58 - 3,150) kilometers. If patients seek medical in hospital, in addition to the registration fees and medical expenses, the mean cost of transportation, accommodation, meals and lost wages was 922.37 ± 686.94 (200 - 2,000) yuan. The total of cost for all patients would have been 70,100 yuan, which is 26.45 times compare with the cost of online. Through the SSDM system for online consultations, patients can save 96.22% of the cost. Survey shows all patients were satisfied and 87.5% of them were "very satisfied" with the consultations.

Conclusion: Using SSDM system to obtain online consultation, Chinese patients with rheumatic disease can enjoy reducing cost with high rate of satisfaction. In the era lack of primary care system in China, SSDM may serve a complimentary platform to control medical care cost, as well as relieve the tensions between health care professionals and patients.

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Abstract Number: 1296

Evaluating Inter-Rater Reliability in Joint Count to Promote Quality and Trust in a Clinical Arthritis Care Team

Diane Tin[1], Lorna J. Bain[1], **J Carter Thorne**[2], Meen Jae Lee[2,3], Lois Derrick[1,4], E Jean Painter[1], Annabelle Estaban[1], Nooshin Samadi[2], Sue Charette[1], Sherry Hartnett[1], Carolyn Bornstein[1], Edward Ng[2] and Michael Aubrey[2], [1]The Arthritis Program, Southlake Regional Health Centre, Newmarket, ON, Canada, [2]Southlake Regional Health Centre, Newmarket, ON, Canada, [3]Pharmacology, McGill University, Montreal, QC, Canada, [4]The Arthritis Society, Toronto, ON, Canada
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Background/Purpose:

Joint count assessment is essential for the diagnosis and ongoing evaluation of Rheumatoid Arthritis (RA) disease activity. In our team based, interprofessional approach to arthritis care, the attending rheumatologist must be able to trust the joint count of fellow rheumatologists and allied health care providers (AHPs). Congruency and accuracy in joint count is imperative for effective collaboration to occur.

Inter-rater variability in assessing tender and swollen joint counts has been well documented, especially with a lack of consistency in swollen joint count (SJC), (ICC range 0.29 to 0.95)1. As part of continuous quality improvement, we undergo annual joint count intervalidation. In the Spring 2015, a joint count intervalidation event was held with all team members who routinely perform joint counts. The aim of this study was two-fold: 1) to estimate the agreement between team members, and 2) to provide training for standardizing joint count assessments.

Despite a growing interest to use patient-reported joint counts as an outcome measure, some argue (and we concur) that the physician/clinician joint count should remain the standard of care on which treatment decisions are based, and as such a joint count should be conducted at every visit.

Methods:

Ten assessors (4 rheumatologists, 2 physical therapists, 3 occupational therapists, 1 kinesiologist) and six patient volunteers with RA (2 diagnosed within past 12 months, 4 have longer term disease) attended the intervalidation session. Patients were informed that the purpose of this event was quality assurance, not clinical care. Assessors were instructed to be as objective as possible, by neglecting the historical comparison of joint status, and to measure counts based on swollen vs. not swollen. All assessors and patient volunteers attended a debrief session afterwards when SJCs were compared and assessment techniques were discussed. A survey was administered to both assessors and patients to gather their feedback on the event.

Results:

Overall, inter-rater reliability between the 10 assessors on SJC for the 6 RA patients was moderate (ICC: 0.51, 95% CI: 0.30-0.91), with no difference between short and longer-term patients with RA ($p>0.05$). Nonetheless, post-event questionnaires revealed that 100% of the rheumatologists and AHPs agreed or strongly agreed that intervalidation was a critical quality assurance initiative and a collaborative process for learning. All 4 rheumatologists reported increased confidence to co-manage RA patients with AHPs after attending the intervalidation session.

Conclusion:

This is a unique quality assurance initiative designed to foster trust amongst a large interprofessional arthritis care team in a clinical care setting. In the framework of shared care and treat to target approaches, joint count intervalidation within networks of arthritis care providers may be valuable. Further research is necessary to identify opportunities to improve inter-rater agreement and more fully understand how assessor and patient-level factors may contribute to these findings.

1. Cheung PP. et al: Reliability of joint count assessment in rheumatoid arthritis: A systemic literature review. Semin Arthritis Rheum 2014; 43:721-9

Disclosure: D. Tin, None; **L. J. Bain**, None; **J. C. Thorne**, None; **M. J. Lee**, None; **L. Derrick**, None; **E. J. Painter**, None; **A. Estaban**, None; **N. Samadi**, None; **S. Charette**, None; **S. Hartnett**, None; **C. Bornstein**, None; **E. Ng**, None; **M. Aubrey**, None.

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Abstract Number: 1297

Improving the Medication Prior Authorization Process in a University Based Rheumatology Practice

Jessica King[1], Megan E. B. Clowse[2], Stephanie Puryear[3] and Steven Collins[3], [1]Rheumatology, Duke University Health System, Hillsborough, NC, [2]Rheumatology & Immunology, Duke University, Durham, NC, [3]Rheumatology, DUHS, Durham, NC

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Background/Purpose: The vast majority of medications prescribed to treat rheumatologic conditions now require insurance prior authorization (PA) before the medication will be paid for by insurance and available to a patient. We found increasing clinical staff and physician time being devoted to obtaining PA's. We initiated a quality improvement project with the goal of decreasing the time between PA initiation and completion and the effort dedicated by clinical staff to completing each PA.

Methods: In our university-based rheumatology practice, we evaluated 10 PA's from 4 time periods to assess the change in the total days between initiation and completion of each PA. We also assessed the number of entries in the electronic medical record (EMR) about the PA, whether it was approved or denied, and whether an appeal was made. Inclusion criteria for evaluated PA's included: DMARD or biologic medication, on-label use, and sufficient information in the EMR to determine PA status. We reviewed 4 time periods: **1. Baseline**; **2. Covermymeds®** when multiple clinic employees were assigned to submit PA's electronically using covermymeds®, provided a PA form, and in a percentage of patients provided a real time approval/denial; **3. Insurance specialist** when we were no longer allowed to use covermymeds®, an insurance specialist from our clinic would obtain and complete the correct PA form from the insurance company and complete needed follow-up; **4. Phone line** when a dedicated phone line and full-time clinical staff member responded to both patients and insurance companies; in addition, a patient education hand-out and educational tools were developed for both clinical staff and providers.

Results: Over a 10 month period, 9,943 patient visits in the university rheumatology clinic resulting in 2,835 prescriptions requiring a PA. Approximately 29% of arrived patient visits in our clinic require a PA during this time period. The duration between PA initiation and completion as well as the number of EMR notes required per PA varied over the time periods with improvements seen with the use of covermymeds® and a dedicated phone line and staff member. The approval rate for the on-label use prescriptions was high and few appeals were needed.

Conclusion: Our findings suggest that submitting PA's electronically, minimizing the number of staff members involved in the PA process, education related to the PA process, and having a dedicated telephone line, have had the biggest impact on improving our success. This level of support requires a full-time clinical staff member, increasing our personnel cost. We suspect that a systematic change on both a state and notional level within the healthcare system will be required to force change.

Time Period	Time Period	Total days for PA process mean (range)	EMR notes mean (range)	Approval Rate	Appeal Initiated
1. Baseline	8/5/14-11/6/14	13.1 (0-26)	5.3 (1-15)	70%	1
2. Covermymeds	1/2/15-2/20/15	8 (0-27)	2.1 (1-3)	100%	0
3. Insurance specialist	2/21/15-4/17/15	24.4 (3-82)	5.3 (2-12)	90%	0
4. Phone line	4/24/15-6/11/15	3.7 (0-19)	1.9 (1-4)	100%	0

Disclosure: J. King, None; **M. E. B. Clowse**, None; **S. Puryear**, None; **S. Collins**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/improving-the-medication-prior-authorization-process-in-a-university-based-rheumatology-practice

Abstract Number: 1298

Advocating for Rheumatoid Arthritis and Cardiovascular Health (ARCH): A Collaborative and Systems-Based Approach to Improve Access to Care

Barbara Goldstein and JoAnn Zell, Medicine, National Jewish Health, Denver, CO
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Background/Purpose: Patients with rheumatoid arthritis (RA) have an increased risk of cardiovascular disease (CVD) as compared to the general population. The European League Against Rheumatism (EULAR) recommends that rheumatologists engage in assessing the CVD risks in RA patients. Multiple barriers such as limited time and lack of familiarity of CVD screening guidelines challenge the feasibility of this practice. Furthermore, recent data suggest that primary care providers fail to assess RA patients consistently or aggressively. At a tertiary referral center, we implemented an innovative system to provide RA patients direct access to cardiology for a CVD risk assessment. In the new RA-CVD clinic workflow, the rheumatologist can screen for CVD risk factors during a clinical visit and refer RA patients using a prescribed order set. Next, the patient is evaluated by cardiology and the 10-year risk for atherosclerotic cardiovascular disease (ASCVD) score is calculated to help guide therapy decisions. In this study, we examined patient access, lipid profiles and medication use before and after the intervention.

Methods: We devised an order set within the electronic medical record (EMR) that was available to all rheumatologists starting January 2015. The order set included a referral to the RA-CVD clinic, electrocardiogram, lipid profile or vertical auto profile (VAP), and hemoglobin A1C. For this study, we reviewed all RA patients presenting to our hospital for new or follow up appointments pre- and post-implementation of the program. Chart review was performed to identify elevated lipid profiles (LDL>130) and statin use. Our cardiology team devised a specific protocol to best risk assess these patients per EULAR guidelines.

Results: Since the launch of our program, 722 RA patients have been seen by the rheumatology practice, 99 (14%) of these patients agreed and were then referred to the RA-CVD clinic. Screening for diabetes and hypercholesterolemia has improved by 60% with the implementation of the program. To date, 13 patients have undergone full risk assessment, however not all patients have been seen partially due to cardiology appointment lag time. Of these patients, 5/13 (38%) patients were started on a statin based on their ASCVD score.

Conclusion: Our study suggests that the creation of a RA-CVD workflow significantly increased the rates of risk factor screening and appeared to provide a forum for necessary interventions. However, lack of cardiology access may limit the strength this program.

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Abstract Number: 1299

Can Bone Marrow Lesions be Scored More Reliably and Responsively in Knee Osteoarthritis Using a Web-Based Overlay System (KIMRISS) Than By Standard MRI Osteoarthritis Knee Scoring (MOAKS)? Data from the Osteoarthritis Initiative and a Prospective Trial of Adaluminab Therapy

Jacob Jaremko[1], Mark Buller[2], Dean Jeffery[2], David McDougall[3], Benjamin Smith[2], Robert G Lambert[1] and Walter Maksymowych[4], [1]Radiology, Radiology, University of Alberta, Edmonton, AB, Canada, [2]Radiology & Diagnostic Imaging, University of Alberta, Edmonton, AB, Canada, [3]Radiology, University of Alberta, Edmonton, AB, Canada, [4]Medicine, University of Alberta, Edmonton, AB, Canada

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Background/Purpose:

Bone marrow lesions (BML) relate to pain and prognosis in knee osteoarthritis. The Knee Inflammation MRI Scoring System (KIMRISS) offers simple template-assisted binary BML scoring via a web-based interface. We tested whether KIMRISS was more reliable and responsive to change than the commonly used MRI Osteoarthritis Knee Score (MOAKS) system, particularly for naïve readers.

Methods:

The KIMRISS web-based overlay system separates the knee into multiple small regions, each scored 0 (no BML) or 1 (BML present). The reader scrolls through sagittal fluid-sensitive MRI slices and mouse-clicks (or contacts a touch-screen) each region in which BML is present. Scores are tabulated and exported automatically. In contrast, MOAKS BML grading is performed in 9 larger knee regions based

on the number of lesions present and percentages of the region containing edema and cystic change.

Exercise 1 assessed reliability, in observational data from the Osteoarthritis Initiative. We had 40 subjects at baseline and 1 year follow-up (80 MRI). Expert readings were performed by two radiologists (6 and 11 years experience) familiar with KIMRISS, and consensus score computed as the average of these readings. Two radiology residents naïve to KIMRISS and MOAKS reviewed a 55-slide presentation describing KIMRISS, three scored reference cases, and a published manuscript describing MOAKS. These readers then scored the same data by KIMRISS and MOAKS. All readers were blinded to scan time point (baseline vs. follow-up).

Exercise 2 assessed responsiveness, using data from an open-label pilot study testing adalimumab (Humira) knee OA therapy. Two blinded experienced readers scored BML by MOAKS and KIMRISS at enrolment and 12 weeks post-therapy in all 16 patients (32 MRI).

Reliability statistics were calculated using intra-class correlation coefficients (ICC), with differences significant at $p<0.05$ when the 95% confidence intervals of ICC did not overlap. To assess responsiveness in Exercise 2, we computed standardized response means (SRM).

Results:

Subjects were primarily older adults (average 62 and 58 years for Exercises 1 and 2 respectively), and female (80% and 65%), with moderate OA (K-L grade 3 or 4 in 73% and 75%).

In Exercise 1, reliability of KIMRISS and MOAKS was high and similar for baseline BML (ICC 0.89-0.98 vs 0.85-0.89). However, changes in BML were significantly more reliably detected by KIMRISS than MOAKS, whether comparing expert readings (ICC 0.82 vs. 0.53) or comparing naïve readings to expert consensus (ICC 0.87-0.92 KIMRISS vs. 0.32-0.51 MOAKS).

In Exercise 2, decrease in BML was visually obvious post treatment in most patients. This decrease in BML was statistically significant when scored by KIMRISS (mean change from 37.3 to 29.8, SRM=-0.69, p=0.015), but not by MOAKS (6.25 to 6.06, SRM=-0.12, p=0.63).

Conclusion:

Comparing two semi-quantitative MRI BML scoring systems, KIMRISS was more responsive to change in BML than MOAKS, and detected change with better reliability than MOAKS for expert and naïve readers. KIMRISS scoring may be useful in observational and therapeutic trials for knee OA.

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Abstract Number: 1300

Comparison Between Semiquantitative and Quantitative Methods for the Assessment of Knee Synovitis Using Non-Enhanced and Gadolinium-Enhanced MRI

Michel D. Crema[1], Frank Roemer[2], Ling Li[3], Laura B. Rosen[4], Amanda Dudley[5], Robert Alexander[6] and **Ali Guermazi**[7], [1]Department of Radiology, Boston University School of Medicine, Boston, MA, [2]Radiology, Boston University School of Medicine, Boston, MA, [3]Dana-Farber Cancer Institute, Boston, MA, [4]AstraZeneca Neuroscience Innovative Medicines, Cambridge, MA, [5]AstraZeneca Neuroscience Innovative Medicines, Cambridge, United Kingdom, [6]Pfizer Neuroscience, Cambridge, MA, [7]Boston University School of Medicine, Boston, MA

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Background/Purpose: There is evidence that the presence of synovitis in knee osteoarthritis (OA) is clinically relevant since it is

associated with pain and structural damage. As several methods are available on MRI to assess and quantify synovitis in knee OA, our aim was to compare different semiquantitative and quantitative methods using both non-enhanced and gadolinium-enhanced MRI.

Methods: End-stage clinical OA knees in patients undergoing a total knee replacement surgery were included in this cross-sectional study. MRI was performed and included non-enhanced (triplanar fat suppressed (FS) intermediate-weighted sequences with fat suppression) as well as gadolinium-enhanced sequences (sagittal and axial T1-weighted FS sequences). Using non-enhanced MRI, we semiquantitatively assessed two features widely used as surrogate for synovitis: "effusion-synovitis" (ES), representing a combination of joint effusion and synovial thickening; and "Hoffa-synovitis" (HS), representing ill-defined high-signal intensity of Hoffa's fat pad at the intercondylar region, both graded from 0 to 3. Using gadolinium-enhanced sequences, we semiquantitatively assessed synovial thickness (ST) in 11 regions of the knee, graded from 0 to 2. Then, we summed the scores for the 11 regions and graded whole-knee synovitis as: grade 0 (total score<5), grade 1 (5-8), grade 2 (9-12), and grade 3 (>12). Using manual segmentation we quantitatively evaluated the total synovial volume (SV) on gadolinium-enhanced sequences, in mm^3, and defined 3 grades of SV as: grade 1 (<30mm^3), grade 2 (30-60 mm^2), and grade 3 (>60 mm^3). As synovitis is ideally evaluated using gadolinium-enhanced sequences, we assessed the correlations of synovitis grades of ES and HS with synovitis grades of ST and SV, applying Spearman correlation analysis. Furthermore, we compared the sum of scores of ST with SV as continuous variables using Pearson correlation analysis.

Results: A total of 104 subjects (1 knee per subject) were included; mean age 67 ± 7; 64 females (61.4%); mean body mass index 30 ± 5. The number of knees exhibiting the different grades of ES, HS, ST, and SV is presented in Table 1. Using gadolinium-enhanced sequences, the mean summed score for "ST" synovitis was 15.0 ± 3.8; the mean "SV" synovitis was 56.0 ± 17.1 mm^3. A positive and significant correlation was found between ES and ST (r=0.41; p<.0001), as well as between HS and ST (r=0.32; p<.001). A positive and significant correlation between the summed scores of ST and total SV was found using gadolinium-enhanced sequences (r=0.53; p<.0001).

Conclusion: ES showed a better correlation with ST assessed on gadolinium-enhanced sequences, and should be preferred over HS as a surrogate marker for synovitis in knee OA studies in which gadolinium-enhanced sequences are not available. Using gadolinium-enhanced sequences, both ST and SV methods may be applied to assess knee synovitis.

Table 1. Distribution of synovitis grades in knees using both non-enhanced and gadolinium-enhanced MRI.

	N	%
Hoffa-Synovitis (non-enhanced MRI)		
0	11	10.6
1	56	53.8
2	31	29.8
3	6	5.8
Effusion-Synovitis (non-enhanced MRI)		
0	0	0
1	27	26
2	59	56.7
3	18	17.3
Synovial Thickness (sums- gadolinium-enhanced MRI)		
0	0	0
1	5	4.8
2	26	25
3	73	70.2
Synovial Volume (gadolinium-enhanced MRI)		
1	34	32.7
2	35	33.7
3	35	33.7

Disclosure: M. D. Crema, Boston Imaging Core Lab, 1; **F. Roemer**, Boston Imaging Core Lab, 4; **L. Li**, None; **L. B. Rosen**, AstraZeneca Neuroscience Innovative Medicines, 3; **A. Dudley**, AstraZeneca Neuroscience Innovative Medicines, 3; **R. Alexander**, Pfizer Neuroscience, 3; **A. Guermazi**, Boston Imaging Core Lab, LLC, 1,TissueGene, 5,OrthoTrophix, 5,MerckSerono, 5,Genzyme Corporation, 5.

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Abstract Number: 1301

Pain Central Sensitization Assessed By Functional Magnetic Resonance Imaging in Patients with Knee Osteoarthritis

Jordi Monfort[1], Jesus Pujol[2], Marina Lopez[3], Jone Llorente[3], Gerard Martinez[2], Didac Macià[2], Francisco Montañés[3], Miguel Angel Campillo[3], Pedro Benito Ruiz[4] and Joan Deus[2], [1]Rheumatology Department, Hospital del Mar, Barcelona, Spain, [2]Magnetic Ressonance Imaging Unit, Barcelona, Spain, [3]Rheumatology Department, Barcelona, Spain, [4]Rheumatology Service, Hospital del Mar, Barcelona, Spain

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Background/Purpose: An important aspect in chronic pain is central sensitization (CS) which involves increased responsiveness of the central neurons and it is clinically expressed like hyperalgesia and allodynia. CS is common in patients with OA and may reduce anti-inflammatory treatment effects and increase clinical severity. The aim of this study was to typify brain changes related to pain sensitization by functional MRI (fMRI) in patients suffering from chronic knee OA.

Methods: We designed a cross-sectional, single blind study and compared OA patients following clinical and radiological ACR criteria vs healthy controls. All participants were selected during one year and a half in the OA Unit in the Hospital del Mar (Barcelona). Presence of CS was assessed in OA group. CS was clinically defined based on the evidence of regional spread of pain (spreading sensitization assessed by an extended version of the ArendtNielsen peripatellar map[1]) and increased pain response to repeated stimulation (temporal summation). The fMRI paradigm included 3 painful test: direct painful stimulation of the knee (articular interline) using a pressure of 2.5kg/cm^2, painful stimulation on the anterior tibial surface of the leg (sensitized site) by exerting a pressure of 4kg/cm^2, and painful heat stimulation on the forearm using 45º Celsius peaks.

Results: We included 60 OA patients (66.7 +/ 7.8yrs) and 30 controls (62.8 +/ 7.7yrs). A total of 33 patients showed some evidence of CS which 19 met all criteria of CS. At interline test, there was no difference on fMRI outcomes. At tibial test we found significant differences on brain activity which involved greater activation, in sensitized patients, in primary somatosensory area, supramarginal gyrus, sensorymotor cortex and basal ganglia. Correlation between brain response and clinical CS assessment was significant on somatosensory cortex, suppramarginal gyrus, anterior cingulated cortex and ventral putamen nucleus, bilaterally. No significant differences were found on brain activation between groups on the painful heat stimulation.

Conclusion: The presence of pain CS in chronic knee OA patients was very frequent. The pressure at medial interline has shown not to be an appropriate test to discriminate sensitized patients, since it is a maneuver with direct impact on the damaged structures in the disease. In contrast, relevant clinical pain in sensitized patients and increased brain response was produced by the pressure stimulation on the anterior tibial surface of the leg. Pain brain sensitization was related to a widespread activation of sensory cortices suggesting that sensitization is expressed mostly as an enhanced sensory phenomenon. At correlation maps, the changes in frontosubcortical structures may speculatively suggest that pain CS also involves alterations of elements implicated in associative painrelated learning (e.g., associations of pain with everyday contexts). Finally, negative results in the painful heat stimulation test suggest that sensitization is not a general phenomenon that may not implicate superior limbs or the processing of heatelicited pain.

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Abstract Number: 1302

Inflammation Signs on Magnetic Resonance Imaging in Chronic or Recurrent

Gonarthritis Treated with Intra-Articular Infliximab or Corticosteroids

Gülsah Akdemir[1], Arie E. van der Bijl[2], Badelog J.E. de Lange-Brokaar[3], T. W. J. Huizinga[1], Cornelia F. Allaart[1] and Margreet Kloppenburg[3], [1]Rheumatology, LUMC, Leiden, Netherlands, [2]Isala Klinieken, Zwolle, Netherlands, [3]Rheumatology, Leiden University Medical Center, Leiden, Netherlands

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Background/Purpose: To evaluate synovial inflammation on magnetic resonance imaging (MRI) before treatment and changes after treatment with intra-articular (i.a.) infliximab (IFX) or methylprednisolone (MP) injections in relation to clinical response in chronic or recurrent gonarthritis patients.

Methods: In the RIA study (Remicade Intra Articularly), a prospective double-blind trial in chronic or recurrent gonarthritis patients randomized to i.a. IFZ or MP. T1 contrast enhanced MRI of the affected knee before and 4 weeks after treatment were scored for Hoffa synovitis using the MRI Osteoarthritis Knee Score (MOAKS), and for joint effusion using the Knee Osteoarthritis Scoring System (KOSS). Outcomes of MRIs were compared between the randomization groups. Associations between MRI outcomes pre- and post-treatment and baseline characteristics were analysed by logistic regression analysis.

Results: 19 patients had baseline MRIs available. Baseline MRI outcomes were not associated with baseline characteristics. 18 patients (20 knees; 14 IFX and 12 MP) had 2 consecutive MRIs. Hoffa synovitis scores pre- and post-treatment were not associated with patient characteristics. Pre-treatment effusion scores were associated with number of previous i.a. corticosteroid injections (OR (95% CI) 0.74 (0.55;0.99)); post-treatment no associations were found. At baseline, MRI scores were similar in the randomization groups (table 2). After four weeks, Hoffa synovitis scores and effusion scores had decreased significantly in IFX injected knees (delta Hoffa synovitis score -1 (-1;0), p=0.021 and delta effusion score 0 (-1;0), p=0.007, respectively), but not in MP injected knees (p=0.157 and p=0.102, respectively). After 6 months, a recurrence of arthritis occurred in all IFX treated knees, and in 50% of MP treated knees. Median (IQR) Hoffa synovitis scores and effusion scores before injection were similar in MP treated patients with or without recurrence 2.0 (2.0;3.0) and 2.0 (1.0;2.0), p=0.080 in patients with recurrence, and 3.0 (3.0;3.0) and 2.5 (1.8;3.0), p=0.617 in patients without recurrence, respectively. MP treated patients with or without recurrence also showed no difference in improvement in Hoffa synovitis scores and effusion scores (delta Hoffa synovitis score 0.0 (-1.5;0.5), p=0.414 and 0 (-1;0), p=0.157, delta effusion score 0.0 (-1.0;0.0), p=0.157 and 0.0 (-0.5;0.0), p=0.317, respectively.

Conclusion: An apparent statistically significant decrease in Hoffa synovitis and effusion scores on MRIs was seen in chronic or recurrent gonarthritis patients treated with IFX injections, but not after MP injections. This apparent reaction to treatment on MRI, however, appears not to be related to clinical outcome after 6 months: a recurrence of arthritis occurred in all IFX treated knees and in 50% of MP treated knees.

Table 1: MRI outcomes before and 4 weeks after treatment and clinical outcome 6 months after treatment in the randomization groups.

Time point	IFX n=14	MP n=12	p-value	p-value week 0 vs. 4 IFX	p-value week 0 vs. 4 MP
Hoffa synovitis score, median (IQR)					
Baseline	2.5 (1.8-3.0)	2.0 (2.0-2.0)	0.288		
Week 4	2.0 (1.0-2.3)	1.5 (1.0-2.0)	0.826		
Delta	-1 (-1-0)	0 (-1-0)		0.021	0.157
Effusion score, median (IQR)					
Baseline	2.5 (2.0-3.0)	3.0 (2.0-3.0)	0.286		
Week 4	1.0 (1.0-3.0)	2.0 (1.0-3.0)	0.186		
Delta	-1 (-1-0)	0 (-1-0)		0.007	0.102
6 months					
Sufficient response*, n (%)	0	6 (50)			
Insufficient response, n (%)	14 (100)	6 (50)	0.004		

IFX: infliximab; MP: methylprednisolone; n: number; IQR: interquartile range.
*no clinical recurrence of arthritis requiring therapeutic intervention within 6 months after injection

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Abstract Number: 1303

Is MRI More Sensitive Than Conventional Radiographs to Detect Hand Osteoarthritis Progression over 5 Years Follow-up?

Ida K. Haugen[1], Barbara Slatkowsky-Christensen[2], Karwan Faraj[3] and Tore K. Kvien[4], [1]P.O. Box 23, Diakonhjemmet Hospital, Vinderen, Norway, [2]Diakonhjemmet Sykehus, Revmatologisk Avd, Oslo, Norway, [3]Radiology, Diakonhjemmet Hospital, Oslo, Norway, [4]Dept. of Rheumatology, Diakonhjemmet Hospital, Oslo, Norway

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SESSION INFORMATION

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Background/Purpose : Conventional radiographs (CR) are currently the imaging modality of choice for evaluation of structural hand osteoarthritis (OA) progression. Lately Magnetic Resonance Imaging (MRI) has been introduced as a promising tool to detect both structural and inflammatory hand OA features. No studies have compared the detection of structural hand OA progression by MRI and CR. The aim was therefore to evaluate the agreement between 1.0T MRI and CR to detect structural hand OA progression as well as the sensitivity and specificity of MRI in comparison to CR.

Methods : We included 69 persons (91% women, mean (SD) age of 68.0 (5.5) years) from the Oslo hand OA cohort with 1.0T MRI scans and radiographs of the interphalangeal joints at baseline (2008-09) and 5-year follow-up (2013). Evaluating the paired radiographs (posteroanterior view) with known time sequence, the joints were scored for radiographic osteophytes (grade 0-3), joint space narrowing (JSN) (grade 0-3) and central erosions (absent/present). Similarly, the joints were scored for MRI-defined osteophytes (grade 0-3), cartilage space loss (grade 0-3) and erosive damage (grade 0-3) using a T1-weighted sequence in coronal and sagittal planes. Progression was defined as an increase of ³1 features. We evaluated the agreement to detect progression using kappa statistics. The sensitivity and specificity of MRI to detect progression was calculated using CR as reference. We repeated the analyses focusing on osteophytes and joint damage separately. Cartilage space loss/JSN and erosions were evaluated as one combined feature (joint damage) as erosions likely affect the joint space.

Results: We analysed 549 joints (3 joints missing), of which 131 (23.9%) and 144 (26.2%) showed structural progression by MRI and CR, respectively. We found moderate agreement between MRI and CR (Table). Structural progression was detected by both modalities in 79 (14.4%) joints, MRI only in 52 (9.3%) joints and CR only in 65 (11.8%) joints. The sensitivity of MRI was modest. In joints with radiographic progression only, progression of osteophytes was most commonly observed. The specificity of MRI was high, as most joints did not progress by neither MRI nor CR. In joints with MRI-progression only, progression of joint damage was most frequently seen.

We found similar results with modest sensitivity of MRI when looking into progression of individual features (Table). However, MRI detected more joints with incident erosions as compared to CR (35 vs. 25 joints) in joints without erosive changes neither on CR nor MRI at baseline.

Table: The detection of structural hand OA progression by MRI and CR

	Kappa	**Sensitivity***	**Specificity***
Structural hand OA progression	0.43	0.55	0.87
Osteophytes	0.33	0.40	0.91
Cartilage damage/JSN or erosions	0.49	0.58	0.91

* CR as reference. OA=osteoarthritis, JSN=joint space narrowing

Conclusion: 1.0T MRI is not more sensitive than CR to detect structural hand OA progression. CR will also assess more joints to a lower price, and should therefore be the imaging modality of choice rather than 1.0T MRI in clinical trials on therapies with potential effects on disease progression. Future studies should compare OA progression by CR and MRI with higher field strength.

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Abstract Number: 1304

Studying MR-Detected Inflammation in Symptom-Free Persons from the General Population to Generate Ramris-Based Reference Values

L. Mangnus[1], H.W. van Steenbergen[2], M. Reijnierse[3] and A.H.M. van der Helm- van Mil[1], [1]Rheumatology, Leiden University Medical Center, Leiden, Netherlands, [2]Leiden University Medical Center, Leiden, Netherlands, [3]Radiology, Leiden University Medical Center, Leiden, Netherlands

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Background/Purpose: It is recommended by an EULAR imaging taskforce that MR-detected inflammation is useful in the diagnostic process of Rheumatoid Arthritis. This recommendation is based on the sensitivity of MR to detect inflammation. The specificity is unknown, but knowledge on the prevalence of MR-detected inflammation in symptom-free persons is pivotal when considering MR for diagnostic purposes. This prompted us to perform this study.

Methods: From November 2013-December 2014 196 symptom-free persons were recruited from the general population. Inclusion criteria were: no history of inflammatory arthritis, no joint symptoms during the last month and no clinically detectable arthritis at physical examination. Contrast-enhanced 1.5T MR-images of the dominant MCP, wrist and MTP joints were made and scored by two readers according to RAMRIS. At categorisation, MR-inflammation was considered present if both readers scored positive.

Results: Of 193 persons scanned (age range 19-89 years), only 28% had no single inflammatory-feature. Higher age correlated with higher inflammation-scores ($p<0.001$). Individual lesions were mostly grade-1. Preferential locations for synovitis were MCP-3 (14% in persons aged 40-59 years, 17% if aged ≥60 years). MCP-2 (8%, 19% respectively), wrist joints (8-35% if aged ≥40 years) and MTP-1 (11-13% if aged ≥40 years). BME was frequent at all ages in the lunate (6-27%) and MTP-1 (10-23%). Tenosynovitis was infrequent, except for extensor carpi ulnaris (9% in persons aged 40-59 years; 12% if aged ≥60 years).

Conclusion: MR-detected inflammation is prevalent in the absence of symptoms, especially at higher age and at preferential locations. Tables with RAMRIS-based and age, location and inflammation-type dependent prevalences were constructed.

Disclosure: L. Mangnus, None; **H. W. van Steenbergen**, None; **M. Reijnierse**, None; **A. H. M. van der Helm- van Mil**, None.

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Abstract Number: 1305

Prevalence of MR-Detected Ramris-Defined Erosions in the General Population

L. Mangnus[1], H.W. van Steenbergen[2], M. Reijnierse[3] and A.H.M. van der Helm- van Mil[1], [1]Rheumatology, Leiden University Medical Center, Leiden, Netherlands, [2]Leiden University Medical Center, Leiden, Netherlands, [3]Radiology, Leiden University Medical Center, Leiden, Netherlands

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Background/Purpose: The diagnostic value of Magnetic Resonance (MR) imaging for Rheumatoid Arthritis (RA) is undetermined. The main value of MR is its sensitive depiction of inflammation. A EULAR-imaging taskforce suggested MR also for early detection of joint damage. Because, the specificity of MR-detected erosions for RA is unknown, we assessed in symptom-free persons of the general population (1) the prevalence of MR-detected erosions and of these erosions (2) the preferential anatomic locations, (3) the association with gender and age and (4) the simultaneously presence of local MR-detected inflammation.

Methods: From November 2013-December 2014 symptom-free persons were recruited via newspapers and websites. Inclusion criteria were: no history of inflammatory arthritis, no joint symptoms during the last month and no clinically detectable arthritis. Contrast-enhanced 1.5T-MR of the dominant MCP, wrist and MTP-joints was made. Erosions were assessed based on RAMRIS (presence on 2 planes, with cortical break on ≥1 plane).

Results: 193 persons fulfilled the criteria (mean age 49.8 years, range 19-89). 22% of persons had no erosions. The total erosion-score correlated with age (r=0.69 p<0.001) and not with gender. Preferential locations were MCP-2 (6% of persons aged <40, 33% if aged ≥60), MCP-3 (8% in persons aged <40, 17% if aged ≥60), scaphoid (37% in persons aged ≥60), distal ulna (23% in persons aged ≥60), MTP-1 (37% in persons aged ≥60) and MTP-5 (10% in persons aged ≥60). Part of the joints with erosions also showed MR-detected inflammation.

Conclusion: In symptom-free persons MR-detected RAMRIS-defined erosions are prevalent, especially at higher age.

Disclosure: L. Mangnus, None; **H. W. van Steenbergen**, None; **M. Reijnierse**, None; **A. H. M. van der Helm- van Mil**, None.

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Abstract Number: 1306

MRI Erosions in Undifferentiated Arthritis. Different Associations with the Collagen IIA N-Terminal Propeptide (PIIANP) and Galectin-3 in Pre-RA and Other Arthritides

Saida Farah Issa[1], Anne Duer[2], Mikkel Østergaard[3], Hanne Lindegaard[1], Kim Hørslev-Petersen[4], Merete Lund Hetland[5], Jakob M. Møller[6], Anne Friesgaard Christensen[7] and Peter Junker[1], [1]Department of Rheumatology, Odense University Hospital, Odense, Denmark, [2]Department of Rheumatology, Copenhagen University Hospital at Hvidovre, Hvidovre, Denmark, [3]Center for Rheumatology and Spine Diseases, Glostrup Hospital, Copenhagen Center for Arthritis Research (COPECARE), Center for Rheumatology and Spine Diseases, Rigshospitalet - Glostrup, University of Copenhagen, Denmark, Glostrup, Denmark, [4]Rheumatology, Research Unit at King Christian X Hospital for Rheumatic Diseases, Graasten, Denmark, [5]DANBIO, Center for Rheumatology and Spine Diseases, Glostrup Univ Hospital, Glostrup, Denmark, [6]Department of Radiology, Copenhagen University Hospital Herlev, Herlev, Denmark, [7]Department of Rheumatology, Vejle Hospital, Vejle, Denmark

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Background/Purpose: Galectin-3 has been implicated as a mediator of inflammation and erosive progression in animal arthritis and rheumatoid arthritis(RA). The type IIA procollagen peptide(PIIANP) is an emerging seromarker for cartilage collagen II synthesis and we have previously reported subnormal levels in patients with newly diagnosed, untreated RA.

The aims were to study A. Baseline galectin-3 and PIIANP in patients with undifferentiated arthritis and to compare the levels in pre-RA and other arthritides; B. The relationship between galectin-3 and PIIANP with disease phenotype and MRI findings.

Methods: Patients categorized with early, undifferentiated arthritis(n=116) were followed up for at least 12 months after which they were reclassified according to appropriate criteria(TUDAR)(1). Baseline variables included demographics, biochemical and clinical disease activity measures. Baseline MRI was obtained of the dominant wrist, MCP, PIP and MTP joints. One hundred and twenty individuals

served as controls. Galectin-3 and PIIANP were measured by ELISA(R&D, Millipore/Linco Research).

Results: Galectin-3 was significantly increased in patients with undifferentiated arthritis, 4.42 ng/ml (*95% CI 4.08;4.75*) vs. controls, 3.96 ng/ml (*95% CI 3.70;4.22*, p = 0.03), particularly in the pre-RA subset, 4.99 ng/ml (*95% CI 4.30;5.67*, p = 0.002). Conversely, galectin-3 in patients with other arthritides than future RA did not differ from healthy controls (fig 1a). PIIANP was also increased in the entire group, 1800 ng/ml (*IQR 1440;2250*) vs. healthy controls, 888 ng/ml (*IQR 742;1029,* p < 0.0001). However, when stratifying according to pre-RA and other kinds of arthritis, PIIANP was equally increased in these two subsets, 1752 ng/ml (*IQR 1483.5;2067,* p < 0.0001) and 1801 ng/ml (*IQR 1436;2260,* p < 0.0001). Galectin-3 and PIIANP did not associate with clinical disease activity measures. However, PIIANP correlated negatively with total MRI erosion score in patients with pre-RA, rho=-0.83 p = 0.009.

Figure 1.a Galectin-3 levels in controls, pre-RA and other arthritides

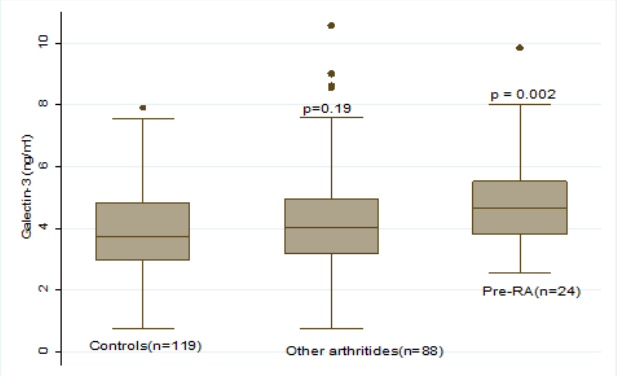
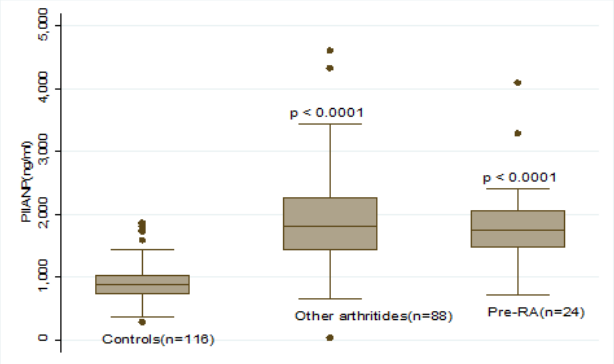


Figure 1.b PIIANP levels in controls, pre-RA and other arthritides



Conclusion : These findings indicate that synovitis of any origin elicits a regenerative chondrogenic response. However, the inverse correlation between PIIANP and baseline MRI erosion score in pre-RA indicates that cartilage collagen II metabolism is skewed towards a net catabolic state in this arthritis subset. This altered cartilage metabolic profile may relate to the increased galectin-3 expression in patients with pre-RA.

1 Duer-Jensen A et al. Arthritis Rheum. 2011;63:2192-202

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Abstract Number: 1307

Does Computerized Segmentation of Early Erosions on Magnetic Resonance Imaging Predict Functional Ability in Rheumatoid Arthritis?

Matthew Jessome[1], Michael Tomizza[1], Karen A. Beattie[2], William G. Bensen[2], Raja Bobba[2], Alfred Cividino[2], Patrick D. Emond[2], Chris Gordon[2], Lawrence Hart[2], George Ioannidis[2], Maggie Larche[2], Arthur Lau[3], Ruben Tavares[2], Stephen Tytus[2] and Jonathan D.

Adachi[2], [1]McMaster University, Hamilton, ON, Canada, [2]St Joseph's Healthcare Hamilton, Hamilton, ON, Canada, [3]Division of Rheumatology, McMaster University, Hamilton, ON, Canada

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Background/Purpose: Functional ability of rheumatoid arthritis (RA) patients is reduced by both acute (inflammatory) and chronic (joint damage) disease manifestations. However, the impact of early erosive damage in small joints is not yet fully appreciated. Advances in automated erosion segmentation of magnetic resonance (MR) images, such as Early Erosions in Rheumatoid Arthritis (EERA) software, enable more reliable and precise measurement of erosions. Our objective was to develop multiple linear regression models to determine how small amounts of erosive damage contribute to loss of functional ability.

Methods: From a single rheumatology clinic, 131 patients satisfying early RA referral criteria were included. Clinical examinations, laboratory tests, MR images of both hands, and the Health Assessment Questionnaire – Disability Index (HAQ-DI) were captured. A single reader used EERA software to compute the total erosive damage in the metacarpophalangeal (MCP) joints, in mm^3. A multiple linear regression model was constructed (Model 1), with HAQ-DI as the dependent variable, and age, sex, symptom duration < 1 year, DMARD or biologic use over preceding 3 months, 28 joint Disease Activity Score (DAS28), and MCP erosion volume as predictors. Model 2 was constructed identical to Model 1, except MCP erosion volume was categorized into: $0mm^3$, $0\text{-}50mm^3$, $50\text{-}100mm^3$ and $>100mm^3$.

Results: Patients were 78% female, 77% Caucasian, mean (standard deviation) age 55.9 (13.3) years, symptom duration 4.2 (5.1) years, DAS28 4.48 (1.40), HAQ-DI 0.81 (0.71), with 50% using DMARD or biologic over the preceding 3 months. Mean erosive damage was low at 32.3 (78.5) mm^3. Model 1 (R^2=0.296, p<0.001) and Model 2 (R^2=0.282, p<0.001) had similar parameter estimates. Each unit increase in DAS28 was associated with a 0.25 unit increase in HAQ-DI. DMARD or biologic use in the preceding 3 months was associated with 0.27 unit decrease in HAQ-DI. Age was significantly related to HAQ-DI in Model 1, but the effect was small (0.1 increase in HAQ-DI for 10 years age increase). Erosive damage to the MCP joints was not significantly related to HAQ-DI in either model.

Conclusion: Low amount of erosive damage was not associated with decreased functional ability. Low disease activity and concurrent DMARD or biologic therapy were associated with improved functional ability. Longitudinal models controlling for additional variables may help elucidate how early erosive damage influences functional ability.

Summary of Parameter Estimates for Model 1 and Model 2

	Model 1			Model 2		
Predictor	**Beta**	**Std. Error**	**p-value**	**Beta**	**Std. Error**	**p-value**
Constant	-0.6453	0.3405	0.060	-0.4678	0.3381	0.167
Age (years)	0.0095	0.0043	0.030*	0.0080	0.0043	0.067
Male Sex	-0.0048	0.1440	0.974	0.0306	0.1445	0.833
Symptom Duration > 1 year	0.2026	0.1256	0.109	0.1547	0.1264	0.223
DMARD or Biologic Use in Previous 3mo.	-0.2696	0.1188	0.025*	-0.2791	0.1216	0.023*
DAS28	0.2572	0.0408	<0.001*	0.2447	0.0413	<0.001*
MCP Erosion Volume (mm^3)	-0.0002	0.0004	0.693	N/A	N/A	N/A
**Erosion 0-50mm^3	N/A	N/A	N/A	-0.0589	0.1263	0.642
**Erosion 50-100mm^3	N/A	N/A	N/A	-0.2972	0.2188	0.177
**Erosion > 100mm^3	N/A	N/A	N/A	-0.0584	0.2183	0.790

DMARD, disease-modifying antirheumatic drug; DAS28, disease activity score on 28 joints; MCP, metacarpophalangeal; N/A, not applicable to the model.
* p < 0.05
**Reference level is Erosions $0mm^3$

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Abstract Number: 1308

MRI Measures of Disease Activity and Joint Damage Are Associated with Patient-

Reported Outcomes in Rheumatoid Arthritis

Joshua Baker[1], Philip G. Conaghan[2], Daniel Baker[3], Paul Emery[4] and Mikkel Østergaard[5], [1]Medicine/Rheumatology, University of Pennsylvania, Philadelphia, PA, [2]University of Leeds & NIHR Leeds Musculoskeletal Biomedical Research Unit, Leeds, United Kingdom, [3]Immunology, Centocor Inc., Malvern, PA, [4]Division of Rheumatic and Musculoskeletal Disease, University of Leeds, Leeds, United Kingdom, [5]Center for Rheumatology and Spine Diseases, Glostrup Hospital, Copenhagen Center for Arthritis Research (COPECARE), Center for Rheumatology and Spine Diseases, Rigshospitalet - Glostrup, University of Copenhagen, Denmark, Glostrup, Denmark
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Background/Purpose: We used data from a large clinical trial of golimumab (GO-BEFORE) to comprehensively assess associations between magnetic resonance imaging (MRI) measures of synovitis, osteitis, and bone erosion with patient-reported measures of physical functioning, pain, and global disease activity in rheumatoid arthritis (RA).

Methods: MRI of the dominant hand was performed and RAMRIS scores were determined at baseline, and at weeks 12, 24, 52. van der Heijde- Sharp scores (vdHS) were determined from radiography at baseline and 52 weeks. Standard patient-reported measures were recorded at these time-points including the Health Assessment Questionnaire (HAQ), as well as pain and patient global scores as measured by visual analogue scale. Spearman correlations as well as multivariable linear and logistic regression utilizing robust generalized estimating equations (GEE) were used to assess relationships between RAMRIS measures and patient-reported outcomes over all time-points.

Results: Correlations between all MRI measures and HAQ were noted at all time-points (Table 1). Pain and patient global scores were increasingly correlated at later follow-up times. In multivariate models incorporating all time-points, synovitis and bone erosion were associated with HAQ independent of clinical disease activity as measured by the DAS28. Greater synovitis was also associated with greater pain and greater patient global scores independent of C-Reactive Protein (CRP) and swollen/tender joint counts. Greater improvements in synovitis were correlated with improvements in HAQ at all time-points and associated with improvements in pain at early time-points (Table 2). Considering all intervals over which change could occur, changes in synovitis were associated with changes in HAQ ($p=0.001$), pain ($p=0.02$), and patient global scores ($p=0.02$). After adjusting for baseline HAQ, and baseline and 52-week change in synovitis, increases in erosion at 52 weeks (per unit) were associated with increases in HAQ (β: 0.038, $p=0.01$), pain (β: 0.18, $p=0.006$), and patient global scores (β: 0.17, $p=0.005$). In contrast increases in vdHS were not associated in similar models (all $p>0.7$).

Conclusion: Synovitis was associated with physical functioning, pain, and patient global scores, independently of measures of clinical disease activity. Improvements in synovitis correlated with improvements patient-reported outcomes, while increases in MRI erosion were associated with worsening. Changes in MRI findings are likely to have important implications for how patients experience their disease.

Table 1: Spearman correlations at 0, 12, 24, and 52 weeks between synovitis, bone edema, bone erosion, and HAQ, pain, and patient global.

HAQ

	Week 0	Week 12	Week 24	Week 52
Synovitis	0.24 ***	0.20 ***	0.26 ***	0.27 ***
Bone Edema	0.13 **	0.19 **	0.23 ***	0.22 ***
Bone Erosion	0.18 **	0.23 ***	0.27 ***	0.28 ***

Pain

	Week 0	Week 12	Week 24	Week 52
Synovitis	0.093	0.13 *	0.17 **	0.21 **
Bone Edema	0.0073	0.14 *	0.14 *	0.21 **
Bone Erosion	0.072	0.12 *	0.14 *	0.20 **

Patient Global

	Week 0	Week 12	Week 24	Week 52
Synovitis	0.14 *	0.16 **	0.18 **	0.24 ***
Bone Edema	0.046	0.16 **	0.14 *	0.23 ***
Bone Erosion	0.11	0.15 *	0.15 *	0.21 **

* p<0.05; ** p<0.01; *** p<0.001

Table 2: Spearman correlations of change in synovitis, bone edema, and bone erosion with change in HAQ, pain, and patient global scores over same time-period.

	HAQ	Pain	Patient Global
Synovitis			
Week 12	0.19 **	0.17 *	0.13
Week 24	0.17 **	0.17 *	0.10
Week 52	0.24 ***	0.14	0.16 *
Osteitis			
Week 12	0.030	0.081	0.075
Week 24	0.11	0.080	0.11
Week 52	0.090	0.074	0.076
Bone Erosion			
Week 12	0.067	0.058	0.10
Week 24	0.10	0.15 *	0.20 **
Week 52	0.13	0.17 *	0.17 *

* p<0.05; ** p<0.01; *** p<0.001

Disclosure: J. Baker, None; **P. G. Conaghan**, Abbvie, BMS, Novartis Non-remunerative, 5,Abbvie, BMS, Janssen, Roche, 8; **D. Baker**,

Janssen R & D, LLC, 3; **P. Emery**, Pfizer Inc, MSD, AbbVie, BMS, UCB, Roche, Novartis, Samsung, Eli Lilly and Company, takeda, 5; **M. Østergaard**, None.

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Abstract Number: 1309

Defining an Acceptable Level of MRI Inflammation in Rheumatoid Arthritis

Joshua Baker[1], Mikkel Østergaard[2], Daniel Baker[3], Paul Emery[4] and Philip G. Conaghan[5], [1]Medicine/Rheumatology, University of Pennsylvania, Philadelphia, PA, [2]Center for Rheumatology and Spine Diseases, Glostrup Hospital, Copenhagen Center for Arthritis Research (COPECARE), Center for Rheumatology and Spine Diseases, Rigshospitalet - Glostrup, University of Copenhagen, Denmark, Glostrup, Denmark, [3]Immunology, Centocor Inc., Malvern, PA, [4]Division of Rheumatic and Musculoskeletal Disease, University of Leeds, Leeds, United Kingdom, [5]University of Leeds & NIHR Leeds Musculoskeletal Biomedical Research Unit, Leeds, United Kingdom
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Background/Purpose: Imaging-detected inflammation persists in many rheumatoid arthritis (RA) patients despite therapy. We used data from two clinical trials of golimumab to determine thresholds for RA magnetic resonance imaging scores (RAMRIS) for synovitis and osteitis associated with a low risk of radiographic and MRI progression in structural damage.

Methods: MRI of the dominant hand was performed and RAMRIS scores were determined at weeks 0, 24, and 52. X-rays were also performed and van der Heijde-Sharp scores (vdHS) determined. .In a development cohort (GO-BEFORE) the changes in MRI erosion score and vdHS score were determined over the 24-week to 52-week interval. MRI erosion and vdHS progression were defined as a change of >0.5. We aimed to identify 24-week thresholds for synovitis (total possible score 21) and osteitis (possible score 230) that provided approximately 90% sensitivity for MRI erosion progression over the 24 to 52 week interval. Rates of progression were illustrated over the range of synovitis, osteitis, and a combination (total inflammation score) at the beginning of the interval. The performance of the cutoffs was then tested in a validation cohort (GO-FORWARD).

Results: In the development cohort, subjects who reached a synovitis or osteitis score <=5 by 24 weeks had a low probability of progression on MRI and X-ray between 24 and 52 weeks (8% and 9%, respectively). The coefficient for osteitis was stronger than that of synovitis in multivariable models predicting X-ray and MRI progression. Therefore, when these scores were combined into a single inflammation score, the score was weighted on osteitis (x2). In the validation cohort, subjects who reached an inflammation score of <=10 by 24 weeks had a low predicted probability of progression from 24 to 52 weeks (7%). In the validation cohort, there was a low rate of MRI progression between 24 and 52 weeks among those with low synovitis, osteitis, and inflammation scores (Table) independent of 24-week DAS28 or C-reactive protein. A lower risk of x-ray progression was observed between 0 and 52 weeks among 34% of subjects with a low inflammation score at baseline as well as among the 47% and 49% of subjects who reached a low inflammation score by weeks 12 or 24, respectively.

Conclusion: Patients that reach low levels of MRI inflammation by 3 or 6 months are substantially less likely to have structural damage progression independent of DAS28 response. A low score by 6 months is predictive of a low risk of radiographic progression over 52 weeks, suggesting that these outcomes might potentially be used as early dichotomous endpoints in clinical studies.

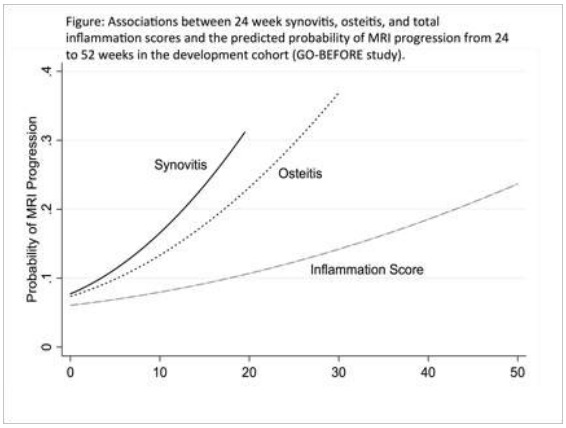

Table: Risk of progression among those above and below identified thresholds in the validation cohort (GO-FORWARD).

Percent with MRI Progression Between 24 to 52 Weeks by MRI Score

	Synovitis		Osteitis		Synovitis + (2*Osteitis)	
	Low (<=5)	Not Low	Low (<=5)	Not Low	Low (<=10)	Not Low
Week 24	11.3%	25.7%	12.0%	30.2%	6.9%	30.1%
	OR=0.36 (0.15, 0.91)*		OR=0.32 (0.14, 0.72)**		OR=0.17 (0.059, 0.47)**	

Percent with X-Ray Progression 0 to 52 Weeks by MRI Score

	Synovitis		Osteitis		Synovitis + (2*Osteitis)	
	Low (<=5)	Not Low	Low (<=5)	Not low	Low (<=10)	Not Low
Week 0	11.1%	28.0%	12.3%	34.2%	8.6%	27.9%
	OR= 0.32 (0.13, 0.78)*		OR=0.27 (0.13, 0.56)**		OR= 0.24 (0.089, 0.67)**	
Week 12	14.0%	31.6%	16.4%	40.0%	11.5%	34.0%
	OR= 0.35 (0.17, 0.74)**		OR= 0.29 (0.15, 0.58)**		OR= 0.25 (0.11, 0.55)**	
Week 24	13.2%	35.4%	16.2%	41.8%	11.1%	38.7%
	OR= 0.28 (0.12, 0.64)**		OR= 0.27 (0.13, 0.57)**		OR= 0.19 (0.083, 0.47)**	

*p<0.05, **p<0.01

Disclosure: J. Baker, None; **M. Østergaard**, None; **D. Baker**, Janssen R & D, LLC, 3; **P. Emery**, Pfizer Inc, MSD, AbbVie, BMS, UCB, Roche, Novartis, Samsung, Eli Lilly and Company, takeda, 5; **P. G. Conaghan**, Abbvie, BMS, Novartis Non-remunerative, 5,Abbvie, BMS, Janssen, Roche, 8.

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Abstract Number: 1310

Efficacy of Abatacept in Patients with Rheumatoid Arthritis Assessed By MRI Scans of Bilateral Hands

Yuji Kukida[1], Akiko Kasahara[1], Takahiro Seno[1,2], Yu Isoda[1], Tomoya Sagawa[1], Takuya Inoue[1], Naoka Kamio[1], Risa Sagawa[1], Takashi Kida[1], Amane Nakabayashi[1], Hidetake Nagahara[3], Ken Murakami[1], Aihiro Yamamoto[1], Satoshi Morita[4], Hirotoshi Ito[5], Masataka Kohno[1] and Yutaka Kawahito[1], [1]Inflammation and Immunology, Graduate School of Medical Science, Kyoto Prefectural University of Medicine, Kyoto, Japan, [2]Department of Rheumatic Diseases and Joint Function, Graduate School of Medical Science, Kyoto Prefectural University of Medicine, Kyoto, Japan, [3]Graduate School of Medical Science, Kyoto Prefectural University of Medicine, Kyoto, Japan, [4]Department of Biomedical Statistics and Bioinformatics, Kyoto University Graduate School of Medicine, Kyoto, Japan, [5]Department of Radiology, Kajiicho Medical Imaging Center, Kyoto, Japan

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Background/Purpose:

Previous radiographic and MRI studies have demonstrated that abatacept (ABT) can inhibit the progression of bone and joint destruction in patients with rheumatoid arthritis (RA), just like other biologic agents. However, the relations between MRI scores and other disease indexes are not well-known. And MRI scans of only single hand have been performed in previous reports. The aim of the present study is

to evaluate efficacy of ABT in patients with RA using MRI of bilateral hands and to investigate whether MRI scores are related to SDAI and HAQ scores in comparison with radiographic scores.

Methods:

Thirty-five RA patients who had not been received more than 1 biological agent were included in this study. MRI of bilateral hands was performed at baseline and 12 months of intravenous ABT treatment. MRI images were scored for synovitis (0-42), osteitis (0-138) and bone erosion (0-460) according to the Rheumatoid Arthritis MRI Scoring System. Conventional radiographs of hands and feet were also obtained at baseline and 12 months, and they were scored according to the van der Heijde modified total Sharp scoring system. These scores were read by two independent doctors, who were blinded to clinical data. Clinical assessment was performed at baseline and at 1, 3, 6, 9, 12 months. The primary endpoint was change from baseline in MRI-measured synovitis score (SS), osteitis score (OS) and bone erosion score (ES).

Results:

Thirty-one patients completed this study for 12 months. The mean SS and OS were significantly reduced at 12 months compared with the baseline (SS at baseline/ 12 months: 17.1±7.02/ 11.4±6.24 (p<0.0001), OS: 5.11±8.16/ 1.89±2.47 (p=0.003)). On the other hand, ES showed no change throughout the study (28.2±38.6/ 28.7±39.2 (p=0.380)). At 12 months, 57.1% of patients showed no progression in ES (deltaES≤0) and 63.6% of patients showed no progression in radiographic erosion score. Changes from baseline in SS (deltaSS) and ES (deltaES) were correlated with relative SDAI response (p=0.023/0.021), while radiographic scores were not correlated with SDAI score. SS, OS and ES at 12 months were correlated with HAQ score at 12 months (p=0.038/0.007/0.038), while radiographic scores were not correlated with HAQ score statistically. Patients achieving SDAI remission at 12 months (n=11) showed lower OS at 12 months (p=0.030) and lower deltaES (p=0.004) compared to those who didn't achieve SDAI remission (n=20), while radiographic scores didn't show significant differences between two groups. Patients achieving HAQ remission at 12 months (n=17) showed lower OS at 12 months (p=0.015), lower SS at 12 months (p=0.049), lower ES at 12 months (p=0.019) and lower deltaES (p<0.001) compared to those who didn't achieve HAQ remission (n=13).

Conclusion:

ABT reduced synovitis and osteitis score in MRI of bilateral hands at 12 months. Compared to radiographs, MRI of bilateral hands showed higher correlations with SDAI and HAQ scores.

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Abstract Number: 1311

Effect of a Non Biologic Treat-to-Target Strategy on MRI-Determined Inflammatory and Destructive Changes in Early Rheumatoid Arthritis – Results from a 2-Year Investigator-Initiated Double-Blind Randomized Controlled Clinical Trial

Signe Moller-Bisgaard[1,2], Bo Jannik Ejbjerg[2], Iris Eshed[3], Kim Horslev-Petersen[4], Merete Lund Hetland[5], Anne G. Jurik[6], Jørgen Vallø[7], Henrik Thomsen[8], Trine Torfing[9], Kristian Stengaard-Pedersen[10], Peter Junker[11], Niels Steen Krogh[12], Tine Lottenburger[13], Torkell Ellingsen[14], Lis Smedegaard Andersen[15], Ib Hansen[10], Henrik Skjødt[16], Anders Svendsen[14], Ulrik Tarp[10], Jan Pødenphant[15],

Jens Kristian Pedersen[7], Hanne Lindegaard[14] and Mikkel Østergaard[1], [1]Center for Rheumatology and Spine Diseases, Glostrup Hospital, Copenhagen Center for Arthritis Research (COPECARE), Center for Rheumatology and Spine Diseases, Rigshospitalet - Glostrup, University of Copenhagen, Denmark, Glostrup, Denmark, [2]Department of Rheumatology, Slagelse University Hospital, Slagelse, Denmark, [3]Department of Radiology, Sheba Medical Center, Tel Hashomer, Israel, [4]Reumatologi, Kong Christian X's Gigthospital, Grasten, Denmark, [5]DANBIO, Copenhagen Center for Arthritis Research, Center for Rheumatology and Spine Diseases, Rigshospitalet, Glostrup, Denmark, [6]Department of Radiology, Aarhus University Hospital, Aarhus, Denmark, [7]University Hospital at Southern Denmark, Odense, Denmark, [8]Department of Radiology, Copenhagen University Hospital Herlev, Copenhagen, Denmark, [9]Department of Radiology, University Hospital at Southern Denmark, Odense, Denmark, [10]Department of Rheumatology, Aarhus University Hospital, Aarhus, Denmark, [11]University of Southern Denmark, Odense, Denmark, [12]ZiteLab ApS, Copenhagen, Denmark, [13]Department of Rheumatology, University Hospital at Southern Denmark, Vejle, Denmark, [14]Department of Rheumatology, Odense University Hospital, Odense, Denmark, [15]Department of Rheumatology, Copenhagen University Hospital, Gentofte, Denmark, [16]Center for Rheumatology and Spine Diseases, Glostrup Hopital, Copenhagen Center for Arthritis Research (COPECARE), Center for Rheumatology and Spine Diseases, Rigshospitalet - Glostrup, University of Copenhagen, Denmark, Glostrup, Denmark
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Background/Purpose: MRI has proved to be more sensitive than clinical examination and x-ray for detection of inflammatory and destructive joint changes in early rheumatoid arthritis (RA) and to discriminate between treatment arms in clinical trials using the semi-quantitative Outcome Measures in Rheumatology Clinical Trials (OMERACT) RA MRI scoring (RAMRIS) system. We aimed to investigate whether MRI-determined measures of disease activity and joint destruction were suppressed in early RA patients following a treat-to-target strategy with methotrexate (MTX) and intraarticular (i.a.) betamethasone and to investigate whether concomitant cyclosporine (CYA) had an additional effect on MRI determined inflammatory and destructive findings over 2 years.

Methods: In the 2-year randomized, double-blind, multicenter, clinical, treat-to-target trial, CIMESTRA, 160 patients with early (<6 months) RA were treated with MTX, i.a. betamethasone and CYA/placebo CYA of wich129 patients participated in the MRI substudy. Patients had contrast-enhanced MRIs at months 0, 6, 12 and 24 that covered the non-dominant wrist (wrist-only group) and if technically possible both wrist and metacarpophalangeal (MCP) joints (wrist+MCP group). MRIs were evaluated by an experienced radiologist blinded to patient identity, clinical and biochemical data but not to chronology, using the RAMRIS scoring system assessing inflammatory (osteitis, synovitis, tenosynovisits) and destructive (bone erosion, joint space narrowing) changes. Observed data, without any data imputations, are reported. Non-parametric statistics were used. A value of $p<0.05$ was considered statistically significant.

Results: MRI-results from the wrist-only group are shown in table 1. The data in the wrist+MCP group were overall similar (data not shown). No statistically significant differences between the treatment groups were observed in any MRI characteristics at baseline or at any follow-up time point. Both the wrist-only group and the wrist+MCP group showed significant reductions compared to baseline in osteitis, synovitis and tenosynovitis at 6 months (all parameters) and 12 and 24 months (synovitis and tenosynovitis). Statistically significant, but numerically low, increases in erosion and JSN scores from baseline to 6, 12 and 24 months were seen.

Conclusion: A treat-to-target strategy with MTX and i.a. betamethasone reduced MRI inflammatory findings significantly, with no additional effect of CYA, but still minor structural damage progression was observed.

Table 1

MRI status scores - Wrist only group												
	Treatment group A **Methotrexate + placebo cyclosporine** n=58				Treatment group B **Methotrexate + cyclosporine** n=71				All n=129			
	Baseline	6 Months	12 Months	24 Months	Baseline	6 Months	12 Months	24 Months	Baseline	6 Months	12 Months	24 Months
MRI measures												
Osteitis *(0-24) n*	58	53	58	56	71	66	68	62	129	119	126	118
Mean +/- SD	2.6±6.6	1.8±5.4	2.4±6.8	2.0±5.7	3.1 ±9.3	1.1±1.8	2.0±5.5	1.3±2.2	3.0 ± 8.2	1.4 ± 3.8	2.2 ± 6.1	1.6 ± 4.3
Median(range)	0 (0-33)	0 (0-27) NS	0 (0-37) NS	0 (0-38) NS	0 (0-63)	0 (0-10) NS	0 (0-34) NS	0 (0-10) NS	0 (0-63)	0 (0-27)*	0 (0-37) NS	0 (0-38) NS
Synovitis *(0-9) n*	58	53	58	56	71	65	67	61	129	118	125	117
Mean +/- SD	4.8±3.1	2.9±2.8	3.3±2.9	2.5±2.8	4.4±3.1	3.1±2.7	2.7±2.3	2.2±2.4	4.6 ± 3.1	3.0 ± 2.7	3.0 ± 2.6	2.3 ± 2.6
Median(range)	5.5 (0-9)	2 (0-9)***	3 (0-9)***	1 (0-9)***	4 (0-9)	3 (0-9)***	2 (0-9)***	1 (0-9)***	5 (0-9)	3 (0-9)***	3 (0-9)***	1 (0-9)***
Tenosynovitis *(0-30) n*	58	53	58	56	71	65	67	61	129	118	125	117
Mean +/- SD	4.7±5.4	1.6±3.2	1.4±3.1	1.1±3.2	6.3±6.6	2.1±3.8	2.3±4.1	2.0±4.2	5.5 ± 6.1	2.1 ± 3.8	1.9 ± 3.7	1.6 ± 3.8
Median(range)	3 (0-27)	0 (0-15)***	0 (0-18)***	0 (0-20)***	5 (0-30)	0 (0-19)***	0 (0-17)***	0 (0-20)***	4 (0-30)	0 (0-19)***	0 (0-18)***	0 (0-20)***
Bone erosion *(0-150) n*	58	53	58	56	71	66	68	62	129	119	126	118
Mean +/- SD	1.9±4.3	2.3±5.3	3.0±6.0	3.3±6.4	1.5±2.4	1.9±3.5	1.9±3.5	2.3±3.5	1.7 ± 3.4	2.1 ± 4.4	2.4 ± 4.8	2.8 ± 5.1
Median(range)	0 (0-30)	0 (0-35)*	1 (0-34)***	1 (0-38)***	0 (0-13)	0.5 (0-23)*	0.5 (0-23)***	1 (0-18)***	0 (0-30)	0(0-35)**	1 (0-34)***	1 (0-38)***
JSN *(0-68) n*	58	53	58	56	71	66	68	62	129	119	126	118
Mean +/- SD	0.9±2.9	1±3.2	1.5±4.7	1.4±4.2	0.3±1.0	0.3±1.0	0.3±1.0	0.4±1.1	0.6 ± 2.1	0.6 ± 2.3	0.8 ± 3.3	0.9 ± 3.1
Median(range)	0 (0-19)	0 (0-20) NS	0 (0-27)*	0 (0-28)***	0 (0-7)	0 (0-7) NS	0 (0-27)*	0 (0-7)*	0 (0-19)	0 (0-20)*	0 (0-27)**	0 (0-28)***

Values for MRI status scores at baseline, 6, 12 and 24 months are presented as mean±SD and medians (range). NS, not significant; *p<0.05; **p≤0.005, *** p<0.0005 compared with baseline. Comparison between groups were carried out using Mann-Whitney U-test and comparisons between time points were carried out using Wilcoxon´s signed-rank test. JSN: Joint space narrowing.

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Abstract Number: 1312

Radiocarpal Cartilage Matrix Changes 3-Months after Anti-TNF Treatment for Rheumatoid Arthritis – Feasibility Study Using MR T1ρ Imaging

Eric Ku[1], Valentina Pedoia[2], Matthew Tanaka[3], Ursula Heilmeier[1], John Imboden[4], Jonathan D. Graf[5], Thomas M. Link[6] and Xiaojuan Li[7], [1]Department of Radiology & Biomedical Imaging, Musculoskeletal Quantitative Imaging Research, UCSF, San Francisco, CA, [2]Department of Radiology & Biomedical Imaging, Department of Radiology and Biomedical Imaging, University of California San Francisco, San Francisco, CA, [3]University of California Berkeley, Berkeley, CA, [4]Rheumatology, Rheumatology, University of California San Francisco, San Francisco, CA, [5]Rosalind Russell / Ephraim P. Engleman Rheumatology Research Center, University of California, San Francisco, San Francisco, CA, [6]Department of Radiology and Biomedical Imaging, Musculoskeletal Quantitative Imaging Research, UCSF, San Francisco, CA, [7]Radiology & Biomedical Imaging, Department of Radiology and Biomedical Imaging, University of California San Francisco, San Francisco, CA

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Background/Purpose:

Standard assessment of Rheumatoid Arthritis (RA) on MRI relies on semi-quantitative joint space narrowing scores that are not sensitive to cartilage focal lesions or early biochemical damage[1,2]. MRI T1ρ has been shown to quantitatively evaluate cartilage proteoglycan loss, collagen matrix changes, and water content[3]. The purpose of our study was to evaluate the feasibility of radiocarpal cartilage T1ρ as a biomarker in RA clinical trials.

Methods:

Nine patients were included in this study: 6 RA patients with active disease despite methotrexate (MTX) treatment started on certolizumab pegol (CZP) and 3 RA patients with low disease on MTX treatment alone. 3T MR was performed at baseline (immediately before CZP initiation) and after 3 months for all subjects. A coronal T1ρ sequence was used (Time of Spin-Lock = 0/10/20/50ms; spin lock frequency = 500Hz, resolution 0.21x0.21x3mm) for lunate, scaphoid, and radius cartilage segmentations. All echoes and follow-up images were registered to baseline images with piecewise rigid registration using individual bone masks (Fig. 1). Paired t-tests were used to compare T1ρ values at baseline and 3-month. Progression of T1ρ values (ΔT1ρ) were correlated (Spearman's rho) with progression of Disease Activity Scores, Michigan Hand Questionnaires, and Health Assessment Questionnaires.

Results:

Patient characteristics are presented in Tab. 1. MTX alone patients showed an increase in Global T1ρ (37.4±1.4 to 39.3±1.6 ms) after 3 months while CZP + MTX patients did not show any significant changes in T1ρ. A statistically significant correlation was found between ΔGlobal T1ρ and ΔDAS28-ESR, ΔMHQ, and ΔHAQ (Fig. 2).

Conclusion:

We previously reported excellent in vivo reproducibility of wrist cartilage T1ρ (1.42% – 5.62% CV) [4]. The overall non-significant change of cartilage T1ρ at 3 months for CZP + MTX patients suggests cartilage responds positively to anti-TNF treatment through joint structure protection. Despite the small sample size, there are already strong correlations between progression of cartilage T1ρ with DAS28, MHQ, and HAQ, encouraging further research with more patients and time points.

References:

[1] Dohn et al., J of Rheumatol 2014 [2] Duvvuri et al., Magn Reson in Med 1997 [3] Li et al., Osteoarthritis Cartilage 2007 [4] Pedoia et al., ACR Abstract 2014

Table 1: Patient characteristics at baseline and 3-month follow-up.

	MTX only (n = 3)		CZP + MTX (n = 6)	
	Baseline	**3-month**	**Baseline**	**3-month**
Demographics at Baseline				
Age, years†	71.3 (4.5)	-	45.3 (10.9)	-
Sex	2 Female, 1 Male	-	6 Female	-
Ethnicity	3 Hispanic	-	5 Hispanic, 1 Black	-
BMI	26.4 (8.8)	-	31.6 (7.1)	-
Time since RA onset†	9.0 (7.8)	-	1.5 (1.4)	-
Clinical Scores				
DAS28-ESR†	2.33 (0.74)	3.00 (0.55)	6.12 (0.72)	4.30 (1.02)*
Patient-Reported Outcomes				
MHQ†	71.6 (24.6)	78.8 (21.2)	34.3 (6.1)	65.1 (24.9)*
HAQ†	0.63 (0.45)	0.91 (0.93)	1.83 (0.33)	0.90 (0.65)*
T1ρ Cartilage Relaxation Times, ms				
Lunate	33.5 (1.54)	35.8(2.1)	35.1 (3.4)	35.6 (4.3)
Radius	37.7 (1.9)	39.6 (1.1)	38.6 (3.1)	39.0 (3.8)
Scaphoid	40.2 (4.6)	42.4 (5.4)	39.6 (3.4)	39.0 (3.0)
Global	37.1 (1.4)	39.3 (1.6)	37.8 (2.5)	37.9 (2.7)

Data is presented as mean (standard deviation)
*Statistically significant difference between baseline and 3-month follow-up.
†Statistically significant difference between Group I and Group II at Baseline.

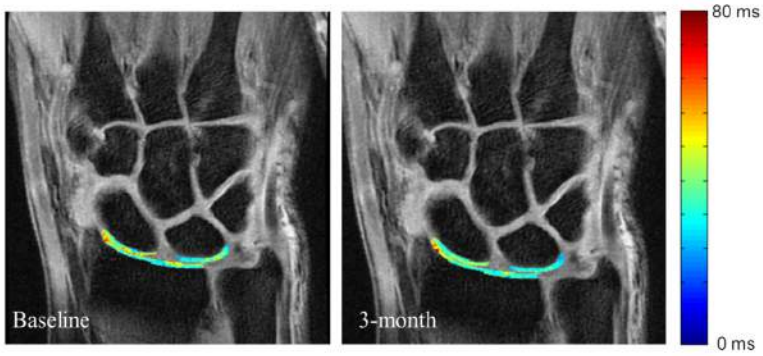

Figure 1: Cartilage T1ρ maps at baseline and 3-month follow-up (registered image) for a subject who achieved a good response to CZP+MTX treatment based on EULAR criteria.

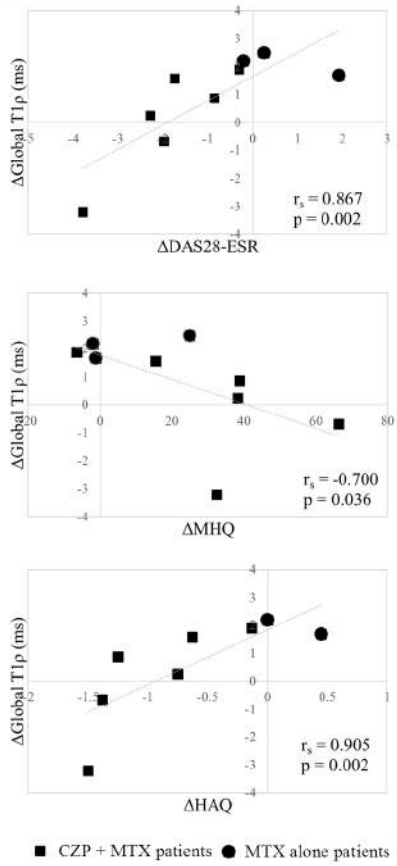

Figure 1: Correlation graphs of Global T1ρ progression with DAS28-ESR, HAQ, and MHQ progression. Circles correspond to MTX alone patients while squares correspond to CZP + MTX patients. Increased T1ρ: increased cartilage degeneration; increased DAS28: increased disease activity; increased MHQ: decreased disability; ncreased HAQ: increased disability.

Disclosure: E. Ku, None; **V. Pedoia**, None; **M. Tanaka**, None; **U. Heilmeier**, None; **J. Imboden**, None; **J. D. Graf**, None; **T. M. Link**, None; **X. Li**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/radiocarpal-cartilage-matrix-changes-3-months-after-anti-tnf-treatment-for-rheumatoid-arthritis-feasibility-study-using-mr-t1%ef%bf%bd-imaging

Abstract Number: 1313

Tumour Necrosis Factor Inhibitor Treatment Normalises Hand Bone Loss in a Minority of Rheumatoid Arthritis Patients Treated in Clinical Practice. Results from the Copenhagen Osteoarthritis Study and the Danbio Registry

Lykke Midtbøll Ørnbjerg[1], Mikkel Østergaard[1], Trine David Jensen[2], Pernille Bach Mortensen[2], Lars Hyldstrup[2], Pernille Boyesen[3], Anja Thormann[1], Ulrik Tarp[1], Wolfgang Bøhme[1], Hanne Lindegaard[1], Uta Engling Poulsen[1], Annette Hansen[1], Annette Schlemmer[1], Niels Graudal[1], Anne Rødgaard Andersen[1], Jakob Espesen[1], Gina Kollerup[1], Bente Glintborg[1], Ole Rintek Madsen[1], Dorte Vendelbo Jensen[1] and Merete Lund Hetland[1], [1]DANBIO, On behalf of Depts of Rheumatology, North, South, Central, Zealand and Capital Region, Copenhagen, Denmark, [2]Dept. of Endocrinology, Hvidovre Hospital, Copenhagen, Denmark, [3]Dept. of Rheumatology, Diakonhjemmet Hospital, Oslo, Norway

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SESSION INFORMATION

Session Date: Monday, November 9, 2015

Session Title: Imaging of Rheumatic Diseases Poster II: X-ray, MRI, PET and CT

Session Type: ACR Poster Session B
Session Time: 9:00AM-11:00AM

Background/Purpose: Rheumatoid arthritis (RA) is characterised by progressive joint destruction and loss of periarticular bone mass. Thus hand bone loss (HBL) has been proposed as an outcome measure for treatment efficacy. A definition of increased HBL adjusted for age- and gender-related bone loss is lacking. We aimed to establish a HBL reference material and investigate whether HBL normalises in RA patients during tumour necrosis factor inhibitor (TNFα-I) treatment in clinical practice.

Methods: Hand bone mass (DXR-BMD) was assessed by Digital X-ray Radiogrammetry (DXR), a computerised method of estimating cortical bone mineral density in the 2^{nd} – 4^{th}metacarpal bone, in a reference population and a patient cohort. The reference population was 1,487/ 2,541 randomly selected men/women who had hand x-rays done in the cross-sectional Copenhagen Osteoarthritis Study. Linear regression analyses were fitted to the data and mean age-related changes in DXR-BMD (ie. normal HBL) estimated for men and women.

The patient cohort comprised 135 patients in the DANBIO registry with hand x-rays obtained ~2 years prior to TNFα-I (pre-baseline, patients treated with conventional synthethic Disease-Modifying Anti-Rheumatic Drugs (csDMARD)), at start of TNFα-I (baseline) and ~ 2 years after TNFα-I start (follow-up). Annual HBL during csDMARD and TNFα-I treatment were calculated in the individual patients and compared with the lower 95% CI of normal HBL for the matching age and gender to assess if increased HBL was present.

Results: Table 1 presents the HBL reference material. The 135 RA patients (85% women, 71% IgM-RF positive, median age 55(range 23-84) years; median disease duration 5(range 1-53) years) had a median pre-baseline DAS28 of 4.3(range 1.6-6.9) and a baseline DAS28 of 5.3(1.4-8.2). TNFα-I treatment was infliximab (74%), etanercept (13%) or adalimumab (13%). At follow-up (DAS28 3.1(1.4-7.7) 59% received the initial TNFα-I, 27% had switched to another biological drug and 14% had withdrawn.

Compared to the reference population, 101 (75%) patients had increased HBL during csDMARD treatment while 79 (59%) patients had increased HBL during TNFα-I treatment (p = 0.17,Chi-Sq). In 38 patients with increased HBL during csDMARD treatment HBL was normalised during TNF-I. Sixteen patients had normal HBL during csDMARD treatment but increased HBL during treatment with TNFα-I.

Conclusion: We have established a reference material for HBL in the general population. Increased HBL was present in the majority of RA patients initiating TNFα-I treatment in clinical practice and was normalised in few patients during treatment.

Table 1

Age-related changes of DXR-BMD in 2,541 Danish women and 1,485 Danish men

Women			**Absolute 1 year change**	**Men**		**Absolute 1 year change**
Age (years)	N	BMD (g/cm^2), mean (SD)	Estimated hand bone loss (g/cm^2) (95 % CI)	N	BMD (g/cm^2), mean (SD)	Estimated hand bone loss (g/cm^2) (95 % CI)
18-29	41	0.597 (0.05)	0.00416 (0.00268 - 0.00564)	32	0.666 (0.06)	-0.00012 (-0.00095 - 0.00071)
30-34	51	0.599 (0.04)	0.00123 (0.00031 – 0.00213)	35	0.671 (0.06)	-0.00060 (-0.00128 - 0.00007)
35-39	84	0.601 (0.05)	- 0.00066 (-0.00122 - -0.00009)	45	0.679 (0.05)	-0.00098 (-0.00153 - -0.00042)
40-44	116	0.589 (0.04)	- 0.00224 (-0.00260 - -0.00189)	71	0.660 (0.05)	-0.00135 (-0.00179- -0.00090)
45-49	131	0.592 (0.05)	-0.00351 (-0.00379 - -0.00323)	98	0.668 (0.05)	-0.00172 (-0.00206 - -0.00138)
50-54	185	0.569 (0.05)	-0.00437 (-0.00470 - -0.00411)	133	0.653 (0.05)	-0.00202 (-0.00235 - -0.00184)
55-59	322	0.541 (0.05)	-0.00513 (-0.00543 - -0.00483)	209	0.636 (0.05)	-0.00247 (-0.00269 - -0.00225)
60-64	311	0.513 (0.06)	-0.00548 (-0.00575 - -0.00521)	198	0.623 (0.06)	-0.00284 (-0.00309- -0.00259)
65-69	430	0.486 (0.06)	-0.00552 (-0.00577 - -0.00527)	211	0.602 (0.06)	-0.00321 (-0.00354- -0.00288)
70-74	394	0.460 (0.05)	-0.00525 (-0.00559- -0.00492)	213	0.594 (0.06)	-0.00358 (-0.00401- -0.00316)
75-79	307	0.440 (0.05)	-0.00468 (-0.00525- -0.00410)	140	0.572 (0.06)	-0.00396 (-0.00450- -0.00342)
80-84	123	0.411 (0.05)	-0.00380 (-0.00472 - -0.00288)	68	0.563 (0.06)	-0.00432 (-0.00499- -0.00367)
85-93	46	0.400 (0.06)	-0.00261 (-0.00397- -0.00124)	32	0.534 (0.08)	-0.00470 (-0.00548- -0.00392)
Total	2541	0.505 (0.08)		1485	0.619 (0.08)	

DXR: Digital X-ray Radiogrammetry; BMD: Bone Mineral Density; CI: Confidence Interval.

Disclosure: L. M. Ørnbjerg, None; **M. Østergaard**, AbbVie, 8,Janssen Pfizer, 8,BMS, 8,Merck Pharmaceuticals, 8,Roche Pharmaceuticals, 8,UCB, 8,Abbvie, 2,Janssen Pharmaceutica Product, L.P., 2,BMS, 2,Merck Human Health, 2; **T. D. Jensen**, None; **P. Bach Mortensen**, None; **L. Hyldstrup**, None; **P. Boyesen**, None; **A. Thormann**, None; **U. Tarp**, None; **W. Bøhme**, None; **H. Lindegaard**, None; **U. E. Poulsen**, None; **A. Hansen**, None; **A. Schlemmer**, None; **N. Graudal**, None; **A. R. Andersen**, None; **J. Espesen**, None; **G. Kollerup**, None; **B. Glintborg**, None; **O. Rintek Madsen**, None; **D. V. Jensen**, None; **M. Lund Hetland**, None.

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Abstract Number: 1314

Quantitative MRI Measurement of Tenosynovitis Demonstrates Differing Responses of Synovitis and Tenosynovitis after RA Treatment

Michael A. Bowes[1], Gwenael Guillard[1], Graham R. Vincent[2], Jane E. Freeston[3], Edward M. Vital[4], Paul Emery[5] and Philip G. Conaghan[6], [1]Imorphics, Manchester, United Kingdom, [2]Imorphics Ltd, Manchester, United Kingdom, [3]LIMM Section of Musculoskeletal Disease, University of Leeds, Leeds, United Kingdom, [4]Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds, Leeds, United Kingdom, [5]Leeds Institute of Rheumatic and Musculoskeletal Medicine, Leeds Gen Infirmary, Leeds, United Kingdom, [6]University of Leeds & NIHR Leeds Musculoskeletal Biomedical Research Unit, Leeds, United Kingdom

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SESSION INFORMATION

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Session Time: 9:00AM-11:00AM

Background/Purpose: Inflammation of the tendon sheaths (tenosynovitis) is a recognised component of rheumatoid arthritis (RA). A comprehensive assessment of inflammation will require the inclusion of tenosynovitis as well as synovitis and osteitis, and consequently it is proposed to include a semi-quantitative assessment of wrist tenosynovitis in the OMERACT RAMRIS scoring system. Active appearance models (AAM) have been successfully used to develop an automatic quantitative version of the current RAMRIS methodology.

This study was a pilot investigation in established RA to assess whether AAMs can be used to produce an automatic tenosynovitis measure and compare the response to therapy of quantitative wrist tenosynovitis and synovitis measures.

Methods: MR images of the hand were acquired at 0, 3 and 6 months from 34 established, seropositive RA patients who received a cycle of rituximab therapy in an open label study. Pre- and post-contrast VIBE images with fat saturation were acquired, and searched with AAMs to identify bones and capsular structures and generate 3D regions of interest (ROIs). Volume which enhanced with contrast was calculated using a shuffle transform. AAMs of the flexor tendons were generated from an independent training set of hand MR images. Briefly, the process includes manual segmentation of the tendons by an expert, generating 3D surfaces using a marching cubes algorithm and the generation of AAMs for each tendon. Images were automatically searched using the AAM, and visually inspected to ensure that the search process had correctly identified the tendons. A 3D region of interest (ROI) around each tendon was created by inflating the tendon shape to form a halo which included the tendon sheath. Within the ROI the tenosynovitis volume was calculated using the shuffle transform method. For this pilot study only the wrist flexor tendons within the common synovial sheath were analysed. The amount of change for the 2 methods was judged using a paired t-test.

Results:

Tenosynovitis in the flexor tendons, and synovitis volume decreased at 3 and 6 months, in an approximately linear fashion. Change was significant at 6 months for both measures (Figure 2). Although the change in the population mean was linear for both measures, the slope of change in tenosynovitis volume for individual patients did not correlate with change in synovitis volume for the same patients ($r^2 = 0.29$).

Conclusion:

It is feasible to quantify tenosynovitis using AAMs. Tenosynovitis in the flexor tendons decreased over 6 months, and only correlated weakly with change in synovitis volume within the same patient. Tenosynovitis appears to be as responsive as synovial volume, but did not correlate with synovial change in individual patients in this small study. Tenosynovitis may therefore add new information to that already provided by measures of synovitis, though this will need confirmation with a fully developed tool in a larger RA population.

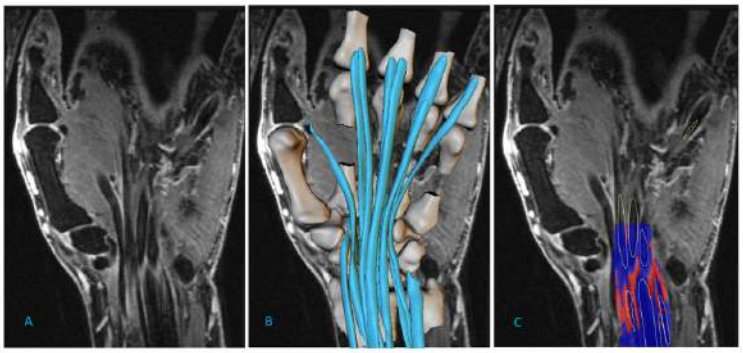

Figure 1. Using appearance models to automatically identify bone, and generate 3D regions of interest

Figure A shows a single slice in a typical post-contrast VIBE image from this study. The 3D image is searched using an active appearance model (AAM), which generates surfaces for all the bones and flexor tendons in the hand (B). C shows the areas which enhance with contrast in the 3D region of interest around the flexor tendons in the ulnar bursa group of flexor tendons (enhanced voxels coloured red, region of interest coloured blue

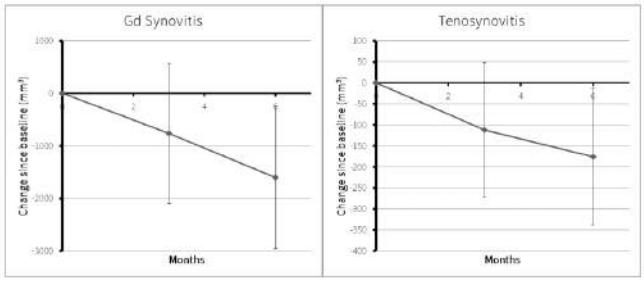

Figure 2: Change from baseline at 3 and 6 months

34 patients had images at all of 0,3 and 6 month time points. Graphs show change in synovitis volume (microliters or mm³) and tenosynovitis volume in the ulnar bursa, showing 95% confidence limits for change from baseline using a paired t-test

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Disclosure: M. A. Bowes, None; **G. Guillard**, None; **G. R. Vincent**, None; **J. E. Freeston**, Chugai, Pfizer, 5; **E. M. Vital**, Roche Pharmaceuticals, 2,Roche Pharmaceuticals, GSK, UCB, Chugai, 5; **P. Emery**, Abbvie, BMS, Lilly, MSD, Novartis, Pfizer, Roche, Samsung, Sandoz, UCB, 2,Abbvie, BMS, Lilly, MSD, Novartis, Pfizer, Roche, Samsung, Sandoz, UCB, 5; **P. G. Conaghan**, Abbvie, BMS, Novartis Non-remunerative, 5,Abbvie, BMS, Janssen, Roche, 8.

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Abstract Number: 1315

Detecting Subtle Changes in Bone Structure Following Three-Month Anti-TNF Theraphy Using High-Resolution Peripheral Quantitative Computed Tomography

Matthew Tanaka[1], Favian Su[2], Min Hee Lee[3,4], Andrew J. Burghardt[5], Thomas M. Link[4], Jonathan D. Graf[6], John Imboden[7] and Xiaojuan Li[8], [1]University of California Berkeley, Berkeley, CA, [2]Radiology and Biomedical Imaging, Musculoskeletal Quantitative Imaging Research, UCSF, San Francisco, CA, [3]Department of Radiology and Research Institute of Radiology, Asan Medical Center, University of Ulsan College of Medicine, Seoul 138-736, South Korea, [4]Department of Radiology and Biomedical Imaging, Musculoskeletal Quantitative Imaging Research, UCSF, San Francisco, CA, [5]Department of Radiology & Biomedical Imaging, Department of Radiology and Biomedical Imaging, University of California San Francisco, San Francisco, CA, [6]Rosalind Russell / Ephraim P. Engleman Rheumatology Research Center, University of California, San Francisco, San Francisco, CA, [7]Rheumatology, Rheumatology, University of California San Francisco, San Francisco, CA, [8]Radiology & Biomedical Imaging, Department of Radiology and Biomedical Imaging, University of California San Francisco, San Francisco, CA

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SESSION INFORMATION

Session Date: Monday, November 9, 2015

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Session Type: ACR Poster Session B

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Background/Purpose: Radiographs have been traditionally used to detect bone erosions and joint space narrowing (JSN) in rheumatoid arthritis (RA), but they are not sensitive to small erosions and subtle changes in erosions or JSN based on Sharp scoring, which requires at least 12 months to detect disease progression in clinical trials[1]. High-resolution peripheral quantitative computed tomography (HR-pQCT) is an emerging *in vivo* imaging technology that has an *in vivo* resolution 82 µm that allows us to detect smaller erosions[2], measure joint space width (JSW), quantify trabecular bone structure, and detect subtle changes in these measures. In this study, we examine the effects of anti-TNF on JSW and bone structure in a three-month period.

Methods: The wrists of 10 RA patients (54.8 ± 15.1 year., 8 female., DAS28-ESR: 4.97 ± 1.83) were scanned using HR-pQCT with an isotropic resolution of 82 µm. Patients were divided into two groups: Group I was given only methotrexate (MTX) (3 patients) and Group II was given certolizumab pegol (CZP) and MTX (7 patients). Scans were performed on metacarpophalangeal (MCP), and wrist joints at baseline (before anti-TNF initiation for Group II) and 3-month follow up. The second, third, and fourth MCP, and wrist JSW were measured, and the MCP and distal radius trabecular bone were quantified using previously developed methods[3]. Bone erosion dimensions were evaluated by measuring the maximal erosion dimensions on an axial 2-dimensional slice[4]. T-tests were performed to compare measures between the groups and within the groups from baseline to 3-month.

Results: DAS28-ESR of patients in Group II decreased significantly from baseline to 3-month ($p = 0.004$), and the decrease in MCP 3 JSW for Group II approached significance ($p = 0.055$). Eleven and 31 erosions were identified at baseline for Group I and II respectively, with 72.7% and 67.7% of these lesions increasing in size (change > 10%) at baseline and 3-month respectively. Six and 13 new erosions were identified at 3-month for Group I and II respectively.

Conclusion: The decrease of MCP 3 JSW in Group II may be due to decreased inflammation and less synovitis and effusion with anti-TNF treatment. We observed more than half of the erosions increased in size and the generation of new erosions for both groups within a very short time period (3 months) using HR-pQCT, indicating the high sensitivity of HR-pQCT detecting subtle changes in erosions as compared to radiographs. The significant decrease in DAS28-ESR for Group II suggests that although anti-TNF treatment suppresses the inflammation pathway, the process of structural joint damage may require more time to be arrested.

[1] Heijde et al, The Journal of Rheumatology. 1995. [2] Lee et al, International Journal of Rheumatic Diseases. 2013 [3] Yang et al, International Journal of Rheumatic Diseases. 2015 [4] Srikhum et al, The Journal of Rheumatology. 2013

Table 1: Patient characteristics at baseline and 3-month follow-up.

	MTX only (n = 3)		CZP + MTX (n = 7)	
Patient Characteristics	**Baseline**	**3-month**	**Baseline**	**3-month**
Patient Demographics at Baseline				
Age, years*	71.3 (4.5)	-	47.7 (10.9)	-
Sex	1 Female, 2 Male	-	7 Female	-
BMI	26.5 (8.8)	-	31.4 (6.5)	-
Clinical Scores				
DAS28-ESR*	2.33 (0.7)	3.00 (0.5)	6.10 (0.7)	4.14 (1.0) †
Joint Space Width, mm				
MCP 2	1.78 (0.2)	1.97 (0.1)	1.84 (0.1)	1.82 (0.1)
MCP 3	1.85 (0.1)	1.92 (0.1)	1.79 (0.1)	1.73 (0.1) ††
MCP 4	1.65 (0.2)	1.81 (0.1)	1.59 (0.1)	1.58 (0.1)
Radioulnar	1.36 (1.2)	1.41 (1.2)	1.58 (0.7)	1.57 (0.7)
Radioscaphoid	2.05 (0.1)	2.09 (0.1)	1.66 (0.8)	1.60 (0.8)
Radiolunar	2.27 (0.2)	2.19 (0.1)	1.92 (0.9)	1.90 (0.9)
Trabecular Bone Mineral Density, mg/cm^3				
MCP 2	254.3 (5.1)	258.7 (13.8)	261.6 (18.9)	263.3 (23.2)
MCP 3	243.4 (15.3)	246.7 (10.1)	285.4 (19.1)	286.5 (18.1)
MCP 4	238.8 (9.6)	241.6 (8.7)	250.3 (17.3)	249.7 (22.0)
Distal Radius	138.4 (12.3)	139.3 (14.4)	176.5 (29.5)	173.5 (26.4)
Bone Erosions				
Number identified	11	17 (6 new)	31	44 (13 new)
Number increased in size§	-	8	-	21
Number decreased in size§	-	2	-	8
Number stayed the same§	-	1	-	2

Data is presented as mean (standard deviation)
*Statistically significant difference between Group I and Group II at Baseline (Age: $p = 0.01$; DAS28-ESR: $p = 0.00004$).
†Statistically significant difference between baseline and 3-month follow-up ($p = 0.004$).
†† $p = 0.055$
§Determined using 10% difference threshold.

Disclosure: M. Tanaka, None; **F. Su**, None; **M. H. Lee**, None; **A. J. Burghardt**, None; **T. M. Link**, None; **J. D. Graf**, None; **J. Imboden**, None; **X. Li**, None.

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Abstract Number: 1316

Is MRI of Use in Identifying Which Undifferentiated Arthritis Patients Will Develop RA?

W.P. Nieuwenhuis[1], E.C. Newsum[1], H.W. van Steenbergen[2], L. Mangnus[1], T. W. J. Huizinga[1], M. Reijnierse[3] and A.H.M. van der Helm-van Mil[2], [1]Rheumatology, Leiden University Medical Center, Leiden, Netherlands, [2]Leiden University Medical Center, Leiden, Netherlands, [3]Radiology, Leiden University Medical Center, Leiden, Netherlands
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Background/Purpose:

The 2010 ACR/EULAR criteria for rheumatoid arthritis (RA) identify RA patients earlier than the 1987 ACR criteria. However, still a considerable amount of patients not fulfilling the 2010 criteria or other rheumatic diagnoses (i.e. undifferentiated arthritis, UA) develop RA.[1,2]Previous studies revealed that auto-antibodies and existing prediction rules fail to identify the UA patients that will progress to RA. In this observational study we studied the use of MRI-detected inflammation to identify these UA patients.

Methods:

202 patients presenting with 2010UA consecutively included in our early arthritis cohort were studied. Unilateral, 1.5T extremity MRI of the metacarpophalangeal, wrist and metatarsophalangeal joints was performed at baseline. Bone marrow edema (BME), synovitis and tenosynovitis were scored according the RA MRI scoring system by 2 independent readers blinded for clinical data. MRI positivity was defined as the presence of inflammation with a prevalence <5% in age matched symptom free controls. Clinical and laboratory findings were also recorded. Two outcome measures were studied; fulfilling the 1987 ACR RA criteria and initiation of DMARD therapy within the first year.

Results:

The 202 UA-patients had a median symptom duration of 8.7 weeks; 29 patients (14%) progressed to RA and 75 (37%) started DMARD therapy. A positive MRI for any MRI inflammation was associated with both RA development (OR 6.1 95%CI 1.4-26.8) as well as initiation of DMARD-therapy (OR 2.4 95%CI 1.2- 4.6). When assessing the MRI features BME, synovitis and tenosynovitis separately, only tenosynovitis was associated with RA development and initiation of DMARD-therapy (OR 5.4 95%CI 1.9-15.2 and OR 4.2 95%CI 2.3-7.8 respectively). When evaluating traditional inflammatory measures, the swollen joint count at baseline (SJC) and C-reactive protein level at baseline (CRP) were also associated with RA-development, in contrast to the presence of ACPA or RF. Multivariable analyses including SJC and CRP with RA-development as outcome, yielded ORs of 5.6 (95%CI 1.2-25.6) for any MRI detected inflammation and 6.3 (95%CI 2.1-19.3) for MRI detected tenosynovitis. Similar analyses with initiation of DMARD therapy as outcome yielded ORs of 1.8 (95%CI 0.9-3.6) and 3.6 (95%CI 1.9-6.9) respectively.

Conclusion:

Within 2010UA, a positive MRI was associated with RA development, independent of commonly used measures of inflammation (SJC, CRP). MRI detected tenosynovitis in particular was most predictive. The next step is to determine the clinical benefit of extremity MRI to enable an early diagnosis of RA.

References:

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View Abstract and Citation Information Online - http://acrabstracts.org/abstract/is-mri-of-use-in-identifying-which-undifferentiated-arthritis-patients-will-develop-ra

Abstract Number: 1317

Clinical Utility of Joint Space Width and X-Ray Radiogrammetry in RA: Markers for Early Radiographic Progression

Michael Platten[1], Yogan Kisten[2], Johan Kälvesten[3], Kristina Forslind[4] and Ronald F. van Vollenhoven[5], [1]Medicine, Karolinska Institutet, Huddinge, Sweden, [2]ClinTRID, Unit for Clinical Therapy Research, Inflammatory Diseases (ClinTRID), The Karolinska Institute, Stockholm, Sweden, [3]Sectra AB, Stockholm, Sweden, [4]Department of Medicine, Helsingborgs Lasarett, Section of Rheumatology, Helsingborg, Sweden, [5]Department of Medicine, Unit for Clinical Therapy Research, Inflammatory Diseases (ClinTRID), The Karolinska Institute, Stockholm, Sweden
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SESSION INFORMATION

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Session Type: ACR Poster Session B
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Background/Purpose:

Early prediction of radiographic progression is beneficial in rheumatoid arthritis (RA) patient management. The van der Heijde modified Sharp score (SHS) is currently the standard that quantifies radiographic progression. The digital joint space width (JSW) measurement (Kälvesten et. al, submitted 2015) is a quick method which may offer a remedy to observer dependency and measurement error. Likewise, objective quantification of hand osteopenia may be of value in the assessment of bone involvement in early RA.

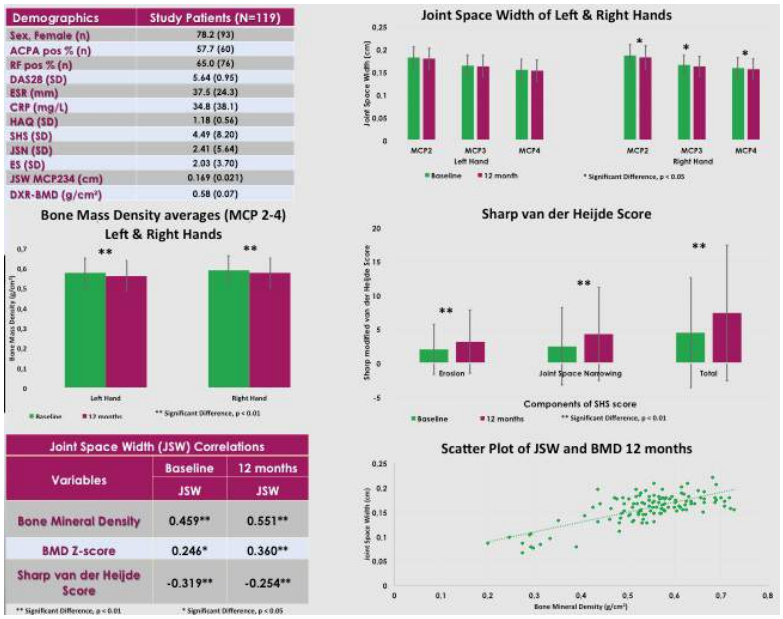
Methods:

Bilateral hand BMD and JSW measurements of the metacarpals (2, 3 & 4) and SHS of early RA patient data, acquired from the SWEFOT database were studied. Computer assisted automated measurements of the MCP joint spaces were calculated from the hand x-rays using dedicated software analysis. Hand BMD was assessed by digital x-ray radiogrammetry (DXR; Sectra, Linköping, Sweden) of the same hand radiographs, scored with SHS at baseline and at 12 months. The Z-score BMD was a calculated measure adjusted for age and gender. Measurement differences of the ΔJSW, ΔBMD scores, and ΔSHS were established and correlated.

Results:

We studied 119 early RA patients (78% female), with an average age of 53.6 years. In 714 joints (MCP2, 3 & 4 bilaterally), the automated JSW showed an average narrowing (ΔJSW) of -0.0492mm from baseline to 12 months. The BMD displayed an average bone loss of -0,0238g/cm^2 from baseline to 12 months. A highly significant correlation was evident for JSW and BMD averages (0.459, $p<0.01$; 0.551, $p<0.01$) at baseline and at 12-month follow-up respectively. Even the ΔJSW and ΔBMD over the 12 months demonstrated a highly significant correlation (0.417, $p<0.01$). BMD Z-Scores showed similar patterns with JSW (0.246, $p<0.05$, n=109; 0.360, $p<0.01$, n= 106) at baseline and 12 months respectively. A positive inverse relationship emerged between automated JSW and the joint space narrowing (JSN) component of SHS (-0.319, $p<0.01$; -0.254, $p<0.01$) at baseline and 12 months respectively. The average JSW measurements of both hands (n = 117) also revealed significant correlations (-0.224, $p<0.05$; -0.271, $p<0.01$) with total SHS at baseline and 12 months respectively. No significant correlation was found between JSW and SHS erosion score. The 12-month BMD displayed near significant correlations with the 12-month SHS erosion score (-0.174, p=0.060) and the 12-month total SHS (-0.157, p=0.090).

Image/graph:



Conclusion:

Automated analyses of JSW & BMD were technically feasible with reproducibility and agreement with the SHS. Correlations between JSW & BMD and JSW & SHS were noted. An inverse relationship between JSW and SHS narrowing score can be seen on individual female joints. These objective, digitally quantified measures of Joint Space Width and Bone Mineral Density may be useful as additional complementary markers for early destructive radiographic progression in RA.

Disclosure: M. Platten, None; **Y. Kisten**, None; **J. Kälvesten**, Sectra, 3; **K. Forslind**, None; **R. F. van Vollenhoven**, None.

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Abstract Number: 1318

Prediction of Large Joint Destruction in Patients with Rheumatoid Arthritis Using FDG-PET/CT: A Prospective Study

Takahito Suto, Koichi Okamura, Yukio Yonemoto, Chisa Okura and Kenji Takagishi, Department of Orthopaedic Surgery, Gunma University Graduate School of Medicine, Maebashi, Gunma, Japan

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Background/Purpose: The assessments of joint damage in patients with rheumatoid arthritis (RA) are mainly restricted to small joints in the hands and feet. However, the development of arthritis in RA patients often involves the large joints, such as the shoulder, elbow, hip, knee and ankle. Few studies have been reported regarding the degree of radiographic damage in large joints in patients with RA. 18F-fluorodeoxyglucose positron emission tomography combined with computed tomography (FDG-PET/CT) precisely visualizes the disease activity in large joints affected by RA. In this study, the associations between destruction of the large joints and the findings of FDG-PET/CT as well as laboratory parameters were investigated, and factors associated with large joint destruction after the administration of biological therapy were identified in patients with RA.

Methods: A total of 264 large joints in 23 RA patients (six males and 17 females; mean age of 66.9 ± 7.9 years) were assessed in this study. All patients were diagnosed according to the American College of Rheumatology criteria revised in 1987. FDG-PET/CT was performed at baseline and six months after the initiation of biological therapy. The extent of FDG uptake in large joints (shoulder, elbow, wrist, hip, knee and ankle) was analyzed using the maximum standardized uptake value (SUVmax). Radiographs of the 12 large joints per

patient obtained at baseline and after two years were assessed according to Larsen's method. A logistic regression analysis was performed to determine the factors most significantly contributing to the progression of joint destruction within two years.

Results: Among the 264 joints, radiographic progression of joint destruction was detected in 33 joints. The SUVmax at baseline and six months and the disease activity score (DAS) 28 – erythrocyte sedimentation rate (ESR) at six, 12 and 24 months were significantly higher in the group with progressive joint destruction. The SUVmax at baseline and DAS28-ESR at six months were found to be factors associated with joint destruction at two years ($p < 0.05$).

Conclusion: The FDG uptake in the joints with destruction was higher than that observed in the joints without destruction. The SUV max at baseline and the DAS28–ESR at six months after the biological treatment were identified to be significant factors predicting destruction of the large joints at two years.

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Disclosure: T. Suto, None; **K. Okamura**, None; **Y. Yonemoto**, None; **C. Okura**, None; **K. Takagishi**, None.

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Abstract Number: 1319

18F-Fluorodeoxyglucose Positron Emission Computer Tomography and Ultrasonography for Assessing Remission in Patients with Rheumatoid Arthritis

Charline Rinkin[1], Pacôme Fosse[2], Nathalie Chapelier[1], Laurence Seidel[3], Adelin Albert[3], Roland Hustinx[4] and Michel Malaise[1], [1]Rheumatology Department, CHU of Liège, Liège, Belgium, [2]Nuclear Medicine Department, CHU of Angers, Angers, France, [3]Biostatistic Department, CHU of Liège, Liège, Belgium, [4]Nuclear Medicine Department, CHU of Liège, Liège, Belgium

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Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose:

The disease activity score based on 28 joints (DAS-28) might not be sufficient to assess remission in rheumatoid arthritis (RA). Several studies have shown that patients in remission according to DAS-28 still evidence synovitis by Ultrasound (US) and Magnetic Resonance Imaging (MRI). Those patients could eventually develop irreversible joint damage. Although ^{18}F-Fluorodeoxyglucose Positron Emission Computer Tomography (^{18}F-FDG PET/CT) is known to be correlated with DAS-28 in patients with active RA, its role in assessing remission has not yet been evaluated.

Methods:

A cross-sectional study was performed on 63 RA patients. A total of 1764 joints was assessed. Clinical assessment (DAS-28), ^{18}F-FDG PET/CT and US were performed the same day. Patients were classified in 3 groups according to their disease status : 22 (35%) were in remission (DAS-28 < 2.6), 31 (49%) had a low or moderate disease activity (2.6 < DAS-28 ≤ 5.1) and 10 (16%) had a severe disease activity (DAS 28 > 5.1). PET/CT was analyzed first visually, then semiquantitatively by determining the Standardized Uptake Value (SUV) of the positive joints. Synovitis were considered as positive in US according to OMERACT criteria. Logistic regression analysis was applied to discriminate between severe and non-severe patients and between subjects with and without remission with respect to the

number of PET/CT (or US) positive joints. Cutoff levels were determined from receiver operating characteristic (ROC) curve analysis and efficacy by the area under the curve (AUC).

Results: Of the 1724 articulations, 373 (21.2%) were tender, 242 (13.7%) were swollen, 361 (20.5%) were PET/CT positive and 152 (8.6%) were US positive. Discrimination between severe and non-severe patients was significant for PET/CT (AUC=0.77, P=0.0046) and for US (AUC=0.84, P=0.0030). Cut-off levels were 8 positive joints for PET-CT, 17.8 for the cumulative SUV and 3 positive for US. By contrast, patients in remission could not be discerned from others: AUC ranging from 0.51 to 0.60 (P > 0.05). Among the 22 RA patients in clinical remission, only 6 (27%) did not show any PET/CT positive joint and 5 (23%) had no positive joint by US. Moreover, in the remission group, 4 (18%) patients had more than 8 PET/CT positive joints and 4 (18%) more than 3 US positive joints. US and PET/CT were positive in different joints, predominantly in small joints of the hands for PET/CT.

Conclusion:

Both ^{18}F-FDG PET/CT and US identify subgroups of patients with highly positive imaging findings and low clinical activity. A prospective analysis is needed, in order to define the potential clinical relevance of such infra-clinical disease.

Disclosure: C. Rinkin, None; **P. Fosse**, None; **N. Chapelier**, None; **L. Seidel**, None; **A. Albert**, None; **R. Hustinx**, None; **M. Malaise**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/18f-fluorodeoxyglucose-positron-emission-computer-tomography-and-ultrasonography-for-assessing-remission-in-patients-with-rheumatoid-arthritis

Abstract Number: 1320

Assessment of 18F-Fluoro-Deoxyglucose Uptake in the Ascending Aorta of Rheumatoid Arthritis Patients

Ayse Bag Ozbek[1], Jon Giles[1], Richard Weinberg[2], Mona Kinkhabwala[2], Afshin Zartoshti[1], Sabahat Bokhari[2] and Joan Bathon[1], [1]Rheumatology, Columbia University Medical Center, NY, NY, [2]Cardiology, Columbia University Medical Center, NY, NY

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Background/Purpose: Increased cardiovascular (CV) disease risk in RA has been attributed to traditional CV risk factors and/or to enhanced inflammation. Increased subclinical vascular inflammation has been demonstrated in a small sample of RA patients vs controls using ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT). We examined the feasibility and reproducibility of ^{18}F-FDG PET/CT in a large cohort of RA patients in order to assess RA characteristics associated with vascular FDG uptake.

Methods : 100 RA patients underwent ^{18}F-FDG PET/CT scanning between 2013-2015 as well as coronary artery calcium (CAC) assessment, laboratory studies and clinical evaluation. ^{18}FDG-uptake was determined by three independent readers (Reading Center 1) by calculation of the mean and maximum (max) standardized uptake value (SUV) of the total ascending aorta (SUVtotal), and of the most diseased segment (SUVmds) within the ascending aorta. Inter-reader correlation among the three readers at Reader Center 1 was evaluated in 10 of the 100 scans and calculated using ANOVA. 15 scans were also read at a second independent reading center (Center #2). Inter-reader correlations were also calculated between Reading Centers 1 and 2.

Results : 91 of the 100 scans were evaluable for aortic FDG uptake. The Inter-reader correlation among three readers at Center 1 for maxSUVtotal was 0.997. Inter-reader correlations for meanSUVtotal and maxSUVtotal between Centers 1 and 2 were 0.979 and 0.939, respectively. Of the 91 RA patients, 80% were female, median DAS28-CRP= 3.7(2.8-4.5), CDAI= 16(7.6-28), mean disease duration of 7.2 years(1.6-14.4), 65% seropositive (RF or anti-CCP), 33% on current steroid with median dose of 5mg (4-10) per day, 77% on any non-biologic DMARD(s), and 40% on any biologic DMARD(s)]. In multivariable analyses, body mass index, use of antihypertensives,

and rheumatoid nodules, were positively, while anti-CCP was inversely, correlated with meanSUVtotal and meanSUVmds measurements. For meanSUVtotal and meanSUVmds, 53% and 59% of the explainable variability in the measures, respectively, were accounted for by RA factors. In separate analyses, higher aortic FDG uptake was significantly correlated with higher echocardiographic E/E' (a measure of diastolic dysfunction), and lower end-diastolic and stroke volumes (data not shown).

Conclusion: FDG aortic wall uptake can be performed and reproducibly measured in relatively large numbers of RA patients, and may serve as a feasible surrogate measure for CVD in future RA clinical trials. These analyses suggest that both conventional CV risk factors and RA disease characteristics are independently associated with FDG uptake in the aorta.

Multivariate analysis for SUVmean values of total and MDS

Modeled Covariates	SUVmean (total)		SUVmean(MDS)	
	β	P value	β	P value
BMI	0.0212	0.003	0.0271	0.005
BP medications	0.141	0.093	0.153	0.076
CCP>60 units	-0.207	0.014	-0.215	0.0143
Nodules	0.384	0.010	0.443	0.004
R^2	0.197		0.202	
%Adjusted R^2 Explained by RA factors	53% (0.529)		59% (0.590)	

B coefficient represents the average change inn SUVmeanMDS per 1 unit higher of the covariate. R^2 represents the total explainable variability in the outcome in the model containing the given covariates.
SUV: Standardized uptake value, BMI: Body mass index, BP: Blood pressure, CCP: Cyclic citrullinated peptide antibody

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Disclosure: **A. Bag Ozbek**, None; **J. Giles**, None; **R. Weinberg**, None; **M. Kinkhabwala**, None; **A. Zartoshti**, None; **S. Bokhari**, None; **J. Bathon**, None.

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Abstract Number: 1321

Inter-Reader Agreement of a Novel Method of Radiographic Scoring of Rheumatoid Arthritis

Priyanka Vashisht[1], Abhijeet Danve[2], Harlan Sayles[3], Ted R. Mikuls[3] and Alan R. Erickson[4], [1]Division of Rheumatology and Department of Immunology, University of Nebraska Medical Center, Omaha, NE, [2]Rheumatology, University of Nebraska Medical Center, Omaha, NE, [3]University of Nebraska Medical Center, Omaha, NE, [4]Omaha VA Medical Center and University of Nebraska Medical Center, Omaha, NE

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Background/Purpose:

Although widely used in research studies, most of the radiographic scoring systems for Rheumatoid Arthritis (RA) are not feasible in routine clinical practice as they are time-intensive and require specialized expertise. We have developed a novel method [VARA (Veterans Affairs RA) scoring method] to evaluate for the disease activity/damage in the RA hand joints. Using the VARA registry, a

multi-center database of veterans with RA, our previous study found that VARA scoring method correlated well with the widely accepted Modified Sharp/van der Hejjde scoring method when assessed by a single experienced reader. In this study we evaluated the inter-rater reliability of the VARA method using an experienced reader and a pair of Rheumatology trainees.

Methods:

The VARA radiographic method involves assessment for the presence of erosions (E) and joint space narrowing (JSN) in 3 joint regions of the hand and wrist, metacarpophalangeal (MCP) and proximal interphalangeal (PIP) joints. The presence of E or JSN each gives a score of 1 and absence gives a score of 0. Hence, the maximum E or JSN score for each hand is 3 each with a minimum of 0. Total hand scores (E + JSN) for each hand could range from 0-6, for a total score of 0-12 across both hands. The experienced reader (AE) used a standardized 30-minute presentation to train the trainees (PV and AD) to assess hand radiographs using the VARA method.

The trainees and the experienced reader independently read the most recent bilateral hand x-rays of 25 randomly selected patients using the VARA scoring method. All readers were blinded to each other's scoring results. Comparisons were made using combined scores from both hands. Inter-rater reliability was assessed several ways using a series of two-way, random, absolute agreement type intraclass correlation coefficients with single measures [ICC2 (A,1)]. Measures of E, JSN, and E + JSN were assessed using each pair of the three raters and all three together. Estimates were made of the time needed for each rater to complete the scoring of a set of radiographs.

Results:

Inter-rater reliability measures, which are estimates of the proportion of variability in scores accounted for by differences in true scores, were fairly high with E + JSN scores for any pair of raters producing an ICC in the range of 0.680-0.807 and all three raters combined yielding an ICC of 0.765 (Table). The time needed for VARA scores by the expert was estimated to be 3.3 minutes and the time needed for the trainees was 3.5 minutes.

Conclusion:

The VARA method is a very practical method of radiographic scoring and may be particularly useful for observational studies and in clinical practice where quantitative assessments of joint damage at a single time point by a single rater are needed. It is easy to learn and practical to perform in regular clinical practice and the reliability of this measure is quite good.

Table

Raters	Measure	ICC2(A,1)	95% C.I.
AD, PV	E + JSN	0.807	0.609, 0.911
AD, PV	E	0.672	0.381, 0.841
AD, PV	JSN	0.823	0.638, 0.918
AE, PV	E + JSN	0.799	0.600, 0.906
AE, PV	E	0.754	0.518, 0.884
AE, PV	JSN	0.680	0.304, 0.857
AE, AD	E + JSN	0.680	0.400, 0.845
AE, AD	E	0.510	0.166, 0.747
AE, AD	JSN	0.582	0.201, 0.800
AE, AD, PV	E + JSN	0.765	0.603, 0.879
AE, AD, PV	E	0.650	0.445, 0.810
AE, AD, PV	JSN	0.683	0.458, 0.837

Disclosure: P. Vashisht, None; **A. Danve**, None; **H. Sayles**, None; **T. R. Mikuls**, None; **A. R. Erickson**, None.

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Abstract Number: 1322

How Can We Reduce the Time for Scoring Radiographic Joint Damage in Rheumatoid Arthritis? Initial Results with a New Computer-Based Documentation Tool

Alexander Langer[1], Joachim Böttcher[2], Diane M. Renz[3], Alexander Pfeil[4] and Hans-Eckhard Langer[5], [1]Department of Computer Science, RWTH Aachen University, Aachen, Germany, [2]Institute for Diagnostic and Interventional Radiology, SRH Waldklinikum, Gera, Germany, [3]Institute for diagnostic and Interventional Radiology, Jena University Hospital - Friedrich Schiller University, Jena, Germany, [4]Department of Internal Medicine III, Jena University Hospital - Friedrich Schiller University, Jena, Germany, [5]RHIO (Rheumatology, Immunology, and Osteology), Duesseldorf, Germany

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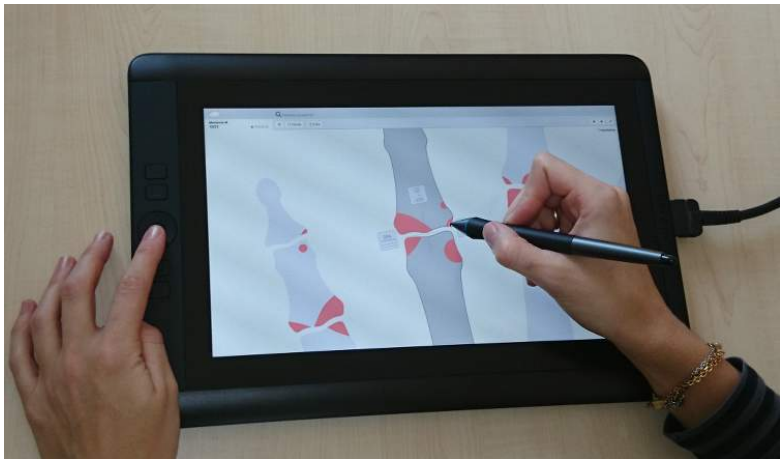
Background/Purpose:

Radiographic progression is a key outcome parameter in RA[1]. Manual scoring of joint damage based on the established scoring methods (e. g. Sharp Score) is a very time-consuming process with an average time of 30 minutes per image set[2]. The objective of this initial feasibility study is to evaluate a new tool for the computer based documentation of joint damage in RA.

Methods:

15 sets of X-rays of 15 patients with RA (12 female, mean age 70.9 ± 4.8 years) were read for bone erosions, joint space narrowing and bone mineralization in 54 hand areas and 28 feet areas as a consensus-reading by two experienced readers. A computer documentation system developed by the first author provides uniform templates of the hands and the feet, into which all identified erosions, joint space narrowing, (sub-)luxation and demineralization were transcribed with a stylus on a tablet (cf. Fig 1). The tool automatically computed the Ratingen[3] and Sharp/van der Heijde[4] scores from the documented structural changes. The time for the documentation in the computer was measured.



Results:

The mean time for the documentation of the structural changes in all areas was 16.0 ± 6.2 minutes (range 6-31 minutes; median: 15 minutes) per image set. The scores were automatically computed as 17.9 ± 14.1 points (range 1 - 50 points; median: 13 points) for the Ratingen score, as 32.5 ± 28.0 points (range 2 - 97 points; median: 27 points) for the erosion score segment and as 54.7 ± 27.0 points (range 11 -

105 points; median: 52 points) for the joint space narrowing segment of the Sharp/van der Heijde score.

Conclusion:

The tool allows for an easy and fast documentation. In this pilot study, the times to assess and document the structural changes on the hand and foot joints in patients with RA were significantly lower than those reported in the literature[2]. Multiple scores are computed automatically from the same source data by the system. These points might be of great potential and benefit for X-ray scoring over the time, especially in clinical and research settings.

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Abstract Number: 1323

Reaching Consensus – Volumetric Joint Space Width Calculations in Finger Joints of Arthritis Patients

Kathryn S. Stok[1,2], Andrew J. Burghardt[3], Stephanie Boutroy[4], Nicolas Vilayphiou[2], Xiaojuan Li[5], Hubert Marotte[6], Steven K. Boyd[7] and Cheryl Barnabe[7], [1]Institute for Biomechanics, ETH Zurich, Zurich, Switzerland, [2]Scanco Medical AG, Brüttisellen, Switzerland, [3]Department of Radiology & Biomedical Imaging, Department of Radiology and Biomedical Imaging, University of California San Francisco, San Francisco, CA, [4]INSERM UMR 1033, University of Lyon, Lyon, France, [5]Radiology & Biomedical Imaging, Department of Radiology and Biomedical Imaging, University of California San Francisco, San Francisco, CA, [6]INSERM 1059 / LBTO, Université de Lyon, Saint-Etienne; Rheumatology Department, Saint-Etienne, France, [7]Cumming School of Medicine, University of Calgary, Calgary, AB, Canada

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Background/Purpose: Joint space width (JSW) is suggested as an indirect measure of arthritis disease activity and could be used as a measure of radiographic progression with consequent narrowing and cartilage loss. The current gold standard for assessing rheumatoid arthritis (RA) radiographic damage is a semi-quantitative analysis by trained physicians where JSW is calculated from radiographs [Sharp, 2005]. Alternative methods include ultrasound [Möller, 2009] and magnetic resonance imaging [Peterfy, 2013] for radiation-free visualisation, and high resolution peripheral quantitative computed tomography (HR-pQCT) for three-dimensional (3D) quantification [Barnabe, 2013; Burghardt, 2013]. HR-pQCT is a novel imaging instrument for bony damage in RA, and is undergoing validation as an outcome measurement tool. In this work, three published techniques for high-throughput, robust, and reproducible measurement of JSW from HR-pQCT derived data are compared and contrasted, in order to reach consensus on a new standard in arthritis damage assessment.

Methods: The second and third metacarpophalangeal joints (MCP) of 30 RA and control subjects (n=60 joints) were imaged at three sites – 10 from the University of Lyon (LYN), 9 from the University of California San Francisco (SFR), and 11 from the University of Calgary (CLG) – using an XtremeCT I (Scanco Medical AG, Switzerland) and the agreed Study grouP for xtrEme Computed Tomography in

Rheumatoid Arthritis (SPECTRA) protocol [Barnabe, 2012]. The data was then segmented to remove bone from background, and 3D JSW was calculated using each of three in-house methods [Barnabe, 2013; Burghardt, 2013; Boutroy, 2013]. The minimum, maximum and mean JSW were compared, and the intraclass correlation coefficients (ICC) calculated.

Results: The results demonstrate a high ICC (upper 95%CI, lower 95%CI) for minimum JSW of 0.986 (0.978, 0.991) between the three methods, with the ICC for mean JSW at 0.981 (0.971, 0.988), and for maximum JSW at 0.910 (0.861, 0.944).

Conclusion: The high correlation between the 3D methods suggest that they all calculate a minimum JSW from approximately the same volume of interest, while variation increases for mean and maximum JSW values which is directly related to the volume of interest and segmentation methods used in the individual methods. The goal in developing these methods is to detect arthritis change through longitudinal monitoring of patients. In this work three methods for assessing JSW are compared in order to reach consensus on a high-throughput, robust, and reproducible measurement of JSW from HR-pQCT.

References: Sharp et al, J. Rheumatol, 32: 2456-61, 2005. Möller et al, Arthritis Care Res, 61: 435-41, 2009. Peterfy et al. Arthritis Res Ther 15: R44, 2013 Barnabe et al. Med Eng Phys 35: 1540-4, 2013. Barnabe et al, J Rheumatol, 39 : 1494-5, 2012. Burghardt et al. Ann Biomed Eng 41: 2553-64, 2013. Boutroy et al. Arthr Rheum 65(10):S840, 2013.

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Abstract Number: 1324

Simplified Larsen Erosion Score Is Compatible with the Classic Larsen Score but Less Time Consuming in Practice

Michael Ziegelasch[1], Alf Kastbom[2], Thomas Skogh[3], Kristina Forslind[4] and Alf Kastbom, [1]Rheumatology Department, Rheumatology/AIR, Linkoping, Sweden, [2]Department of Clinical and Experimental Medicine, Rheumatology/AIR, Linköping, Sweden, [3]IKE/Rheumatology, Linköping University, Linköping, Sweden, [4]Department of Medicine, Helsingborgs Lasarett, Section of Rheumatology, Helsingborg, Sweden

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Background/Purpose:

Untreated rheumatoid arthritis (RA) often leads to joint space narrowing (JSN) and erosions in synovial joints. Scoring systems like Sharp van der Heijde and Larsen are commonly used as outcome measures in clinical trials, but they are time consuming and thus not used in clinical practice. It would be important to introduce a simple radiographic measure to guide treatment decisions in clinical routine. For Sharp van der Heijde score the simplified score "SENS" (1) is available. As we use Larsen score in our studies, we wished to know if a simplified Larsen score would be feasible. Thus, we applied the "simplified Larsen erosion score" (SLES), documenting the number of joints with erosions, and evaluated whether or not it corresponds to radiological changes assessed by the total Larsen score.

Methods:

217 patients diagnosed with recent onset RA in the Swedish "TIRA-2" cohort participated in this study. All patients fulfilled the ACR 1987 criteria. Radiography of hands and feet were performed at diagnosis, 1, 2 and 3 years. The radiographs were scored by the classical Larsen score and by SLES where 32 joints (PIP 2-5, MCP 2-5, four quadrants in the wrist, MTP 2-5) are assessed – in Larsen score both JSN and erosions, in SLES only erosions. In Larsen score changes are graded from 0-5 (0= no changes, 5= mutilating changes). The total Larsen score range is 0-160. In SLES, erosions are graded only as present or not, i.e. 0= no change and 1= erosion(s). The SLES range is 0-32.

Results: Of the 217 patients included with radiographs at inclusion 155 had radiographs at 1 year, 119 at 2 years and 168 at 3 years. Using Spearman's Correlation test, SLES gave the same information as Larsen score regarding radiographic joint damage as well as the total

Larsen score (p<0,01) at all time points. (Table 1)

Table 1

	Total Larsen, mean	SLES, mean	Correlation coefficient	P-value
0 months	2.58	0.31	0.496	<0.01
12 months	2.83	0.40	0.433	<0.01
24 months	3.42	0.47	0.483	<0.01
36 months	4.27	0.51	0.494	<0.01

Conclusion:

Simplified Larsen erosion score provided similar information regarding radiographic changes as the total Larsen score among our patients with recent onset RA (<0.01). As being less time consuming, the SLES could be an applicable tool to rapid and easy assessment of radiographic damage.

Reference: 1. The usefulness of the Simplified Erosion Narrowing Score (SENS) in clinical practice for estimating joint damage in early rheumatoid arthritis. Forslind K; BARFOT Study Group. Scand J Rheumatol. 2011 Nov;40(6):497-8

Disclosure: M. Ziegelasch, None; **A. Kastbom**, None; **T. Skogh**, None; **K. Forslind**, None.

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Abstract Number: 1325

Age Effects Joint Space Narrowing in Early Active Rheumatoid Arthritis Patients

Xanthe M.E. Matthijssen[1], Gülsah Akdemir[1], Iris M. Markusse[2], Yvonne P. Goekoop-Ruiterman[3], K. Huub Han[4], Annekoos L. Huidekoper[5], Pit J.S.M. Kerstens[6], Willem F. Lems[7], T. W. J. Huizinga[1] and Cornelia F. Allaart[1], [1]Rheumatology, LUMC, Leiden, Netherlands, [2]LUMC, Leiden, Netherlands, [3]Rheumatology, HAGA hospital, The Hague, Netherlands, [4]Rheumatology, Maasstad hospital, Rotterdam, Netherlands, [5]Rheumatology, Bronovo hospital, The Hague, Netherlands, [6]Department of Rheumatology, Reade, Amsterdam, Netherlands, [7]Rheumatology, Amsterdam Rheumatology and immunology Center, VU University medical center, Amsterdam, Netherlands
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Background/Purpose:

Joint space narrowing (JSN) and erosions are the major radiologic markers of radiographic progression in rheumatoid arthritis (RA), as scored by the Sharp/van der Heijde score (SHS). JSN may also be a manifestation of (primary) osteoarthritis becoming more prominent with age. We hypothesize that the severity of JSN progression and predictors of JSN progression may differ between older and younger RA patients.

Methods:

Ten year follow-up data of the BeSt study, a randomized controlled treat-to-target (Disease activity score (DAS)≤2.4) trial in early RA were used. Annual X-rays of hands and feet from baseline to year 10 were scored with the SHS by two independent readers, blinded for patient identity and time order. Subgroups were defined by age at baseline: ≥55 (median age), ≥40<55 and <40 years. Poisson regression with multiple imputation for missing data (7% and 45% of the radiographs at baseline and year 10) was used to identify univariate predictors. Factors with p<0.2 were entered in a multivariate regression analysis. Post-hoc Bonferroni corrections were used to correct for multiple testing.

Results:

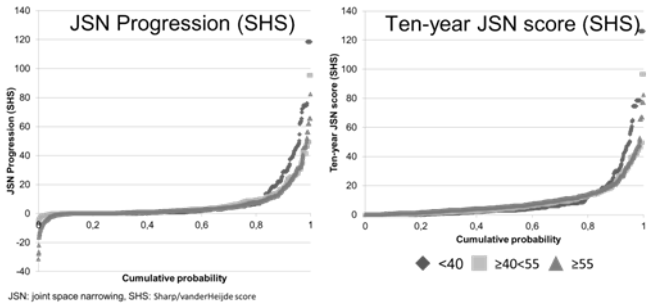
Baseline median (interquartile) SHS scores were higher in patients ≥55 compared to the other groups (≥55: 2.5 (1.0-7.4); ≥40<55: 1.0 (0.0-4.5); <40: 1.0 (0.0-3.0); p≤0.001). Also, higher baseline JSN was observed in patients ≥55 compared to the other groups: 2.0 (0.0-6.0), 1.0 (0.0-3.0) and 0.3 (0.0-3.0), p≤0.001, respectively. After ten years, total JSN and SHS scores were similar in all age-groups. Although fewer patients <40 years appear to have JSN progression, if they do show JSN progression it is more severe (figure 1).

Table 1 shows significant univariate risk factors. In the multivariate regression, in patients ≥55 mean erythrocyte sedimentation rate (ESR) over ten years follow-up (RR 1.02, 95% CI (1.00-1.03)) and the combined presence of rheumatoid factor and anti-citrullinated protein antibodies (RF+/ACPA+) (3.27 (1.25-8.53)) were significantly associated with JSN progression. In patients ≥40<55 no significant risk factors were revealed. In patients <40 baseline swollen joint count (SJC) (1.09 (1.01-1.18)) and mean ESR (1.04 (1.02-1.06)) were significantly associated.

Conclusion:

At baseline, RA patients ≥55 years had more JSN but after 10 years of DAS≤2.4 targeted treatment they do not show more often or more severe JSN progression. Independent risk factors for JSN progression were mean ESR in patients <40 and those ≥55 years, RF+/ACPA+ in patients ≥55 years and SJC in patients <40 years. This suggests that mechanisms leading to JSN progression vary between age groups.

Figure 1: JSN progression and total JSN score after ten years



JSN: joint space narrowing, SHS: Sharp/vanderHeijde score

Table 1: Univariate Poisson regression analysis

≥55 n=248	RR (95% C.I.)	≥40<55 n=179	RR (95% C.I.)	<40 n=81	RR (95% C.I.)
Mean ESR	1.02 (1.01-1.03)	Mean ESR	1.02 (1.00-1.04)	Mean ESR	1.04 (1.00-1.08)
RF+/ACPA+	4.19 (1.58-11.1)	RF+/ACPA+	3.41 (1.33-8.71)	RF+/ACPA+	5.39 (1.25-23.2)
Mean DAS	1.54 (1.05-2.28)	Baseline erosions	1.07 (1.01-1.12)	Baseline JSN	1.17 (1.01-1.35)
Smoking	2.00 (1.11-3.58)			SJC	1.11 (1.02-1.21)

OR: odds ratio, 95% C.I. 95% confidence interval, Mean ESR: mean erythrocyte sedimentation rate over ten years, DAS: 44-joint disease activity score, RF: rheumatoid factor, ACPA: anti–citrullinated protein antibodies JSN: baseline joint space narrowing, SJC: baseline total swollen joint count

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Abstract Number: 1326

Which Score to Use for Radiographic Damage Assessment of the Spine in (early) Axial Spondyloarthritis? Two-Year Data from the DESIR Cohort

Sofia Ramiro[1], Pascal Claudepierre[2], Rosaline van den Berg[3], Victoria Navarro-Compán[4], Antoine Feydy[5], Maria-Antonietta d'Agostino[6], Damien Loeuille[7], Maxime Dougados[8], Monique Reijnierse[9] and Désirée van der Heijde[1], [1]Rheumatology, Leiden University Medical Center, Leiden, Netherlands, [2]Rheumatology, Université Paris Est Créteil, Créteil, France, [3]Leiden University Medical Center, Leiden, Netherlands, [4]Rheumatology, University Hospital La Paz, Madrid, Spain, [5]Paris Descartes University, Radiology B department, Cochin Hospital, Paris, France, [6]Rheumatology, Versailles-Saint Quentin en Yvelines University, Boulogne-Billancourt, France, [7]Rheumatology, Nancy University Hospital, Nancy, France, [8]Rheumatology Department, Cochin hospital, Paris-Descartes University, Paris, France, [9]Radiology, Leiden University Medical Center, Leiden, Netherlands

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Background/Purpose: Several scores have been developed to assess radiographic damage in AS. However, we do not know how they perform in early phases of the disease. Our aim was to compare the performance of different radiographic scores of the spine in patients with early axial spondyloarthritis (axSpA).

Methods: Yearly radiographs from a 2-year follow-up of the DESIR cohort from patients fulfilling the ASAS axSpA criteria have been used. Spinal (cervical, thoracic and lumbar) and sacro-iliac (SI) radiographs were scored independently by two readers for the presence of the different damage aspects enabling the calculation of different scores: mSASSS (0-72), SASSS (0-72), RASSS (0-84) and BASRI-spine (0-12), using the averaged scores between readers per vertebral corner (VC)/SI joints. Additionally, a variation of the BASRI-spine was computed adding an overall score for the thoracic spine (0-16). Following the OMERACT proposal, scores were compared with regard to truth, discrimination (sensitivity to change and reliability) and feasibility. Status (at baseline of first x-ray available) and 2-year progression scores were calculated for each of the methods as well as the proportion of patients with any change (change>0).

Results: In total, 486 patients (mean age 33.0 (SD 8.6) years, 50% males) had at least one radiograph available. At baseline, scores ranged from 0 and 21.6 for the mSASSS (30% of the maximum of the scale), 20.6 for RASSS (25% of maximum), 6 for SASSS (8% of maximum), 8.5 for BASRI-spine (71% of maximum) and 10.25 for BASRI-spine with thoracic spine (64% of maximum). Status scores and 2-year progression scores available are shown in the table. The proportion of patients with any 2-year change was the following: 9.9% for mSASSS, 10.7% for RASSS, 6.9% for SASSS, 19.2% for BASRI-spine and 22.0% for BASRI-spine with thoracic spine. Absolute change scores (table) showed that the mSASSS and RASSS captured most change. 2-year RASSS progression occurred in a balanced way across segments (cervical, thoracic and lumbar), when taking the number of VCs included per segment. All scores had acceptable reliability. In what concerns feasibility, all scores seemed to be feasible, but the BASRI-spine (+/- thoracic spine) was more frequently missing (up to 15% of the cases), as it requires also the availability of SI joints.

Table - Status and 2-year progression for the different radiographic scoring methods

	mSASSS mean (SD) n = 481	RASSS mean (SD) n = 481	SASSS mean (SD) n = 483	BASRI spine mean (SD) n = 447	BASRI spine with thoracic mean (SD) n = 442
STATUS SCORES					
Total score	0.57 (2.37)	0.54 (2.34)	0.17 (1.03)	1.35 (1.62)	1.46 (1.80)
Cervical segment	0.36 (1.69)	0.34 (1.66)	--	0.16 (0.55)	0.17 (0.55)
Lumbar segment	0.21 (1.09)	0.16 (1.04)	0.17 (1.03)	0.18 (0.54)	0.19 (0.55)
Lumbar segment with thoracic segment included	--	0.19 (1.13)	--	--	--
Thoracic segment	--	0.03 (0.28)	--	--	0.09 (0.38)
Lumbar anterior	--	--	0.16 (1.03)	--	--
Lumbar posterior	--	--	0.00 (0.02)	--	--
SI joints	--	--	--	1.00 (1.13)	1.00 (1.13)
2-YEAR PROGRESSION SCORES					
	mSASSS n = 322	RASSS n = 319	SASSS n = 335	BASRI spine n = 287	BASRI spine with thoracic n = 268
Total score	0.27 (1.57)	0.36 (1.74)	0.15 (0.78)	0.05 (0.72)	0.07 (0.83)
Cervical segment	0.19 (1.16)	0.17 (1.18)	--	0.04 (0.36)	0.03 (0.35)
Lumbar segment	0.08 (0.63)	0.13 (0.66)	0.15 (0.78)	0.01 (0.40)	0.02 (0.35)
Lumbar segment with thoracic segment included	--	0.18 (0.84)	--	--	--
Thoracic segment	--	0.06 (0.38)	--	--	0.00 (0.32)
Lumbar anterior	--	--	0.13 (0.65)	--	--
Lumbar posterior	--	--	0.02 (0.33)	--	--
SI joints	--	--	--	0.01 (0.36)	0.01 (0.37)

Conclusion: The existing scoring methods to assess radiographic damage performed well in early phases of axSpA. The mSASSS and RASSS captured most change, but there was no gain in additionally scoring the thoracic spine for the RASSS. The mSASSS remains the most sensitive and most adequate scoring method in axSpA, including early phases of the disease.

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Abstract Number: 1327

Five-Year Follow-up of Radiographic Sacroiliitis: Progression As Well As Improvement?

Alexandre Sepriano[1,2], Martin Rudwaleit[3], Joachim Sieper[4,5], Rosaline van den Berg[6], Robert B. M. Landewé[7] and Désirée van der Heijde[8], [1]Rheumatology, Department of Rheumatology, Leiden University Medical Center, Leiden, the Netherlands, Leiden, Netherlands, [2]Rheumatology, Hospital de Egas Moniz - CHLO, Lisbon, Portugal, Lisbon, Portugal, [3]Rheumatology, Dept of Medicine, Charité - Campus Benjamin Franklin, Berlin, Germany, Berlin, Germany, [4]German Rheumatism Research Centre, Berlin, Germany, Berlin, Germany, [5]Rheumatology, Charité - Campus Benjamin Franklin, Berlin, Germany, Berlin, Germany, [6]Leiden University Medical Center, Leiden, Netherlands, [7]Department of Rheumatology, Amsterdam Rheumatology Center, Amsterdam, the Netherlands, Amsterdam, Netherlands, [8]University Hospital, Maastricht, Netherlands

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Background/Purpose: Detecting sacroiliitis on plain pelvic X-rays is known to be difficult, resulting in large variability regarding presence/absence of radiographic sacroiliitis. In addition, the number of patients with radiographic sacroiliitis in a cohort of patients with axial SpA can be expected to (slightly) increase or remain stable over time but certainly not decrease. We have investigated the change of pelvic X-ray abnormalities over time in the Assessment of SpondyloArthritis international Society (ASAS) validation cohort.

Methods: In the ASAS study, 975 patients with either chronic back pain (>3 months) of unknown origin beginning <45 years of age or undiagnosed peripheral arthritis, and/or enthesitis, and/or dactylitis were assessed at baseline. From these, 565 patients were followed and reassessed at follow-up [mean follow-up time 4.44 years (SD: 1.01)]. Patients with radiographs of the pelvis (X-SI) available at baseline and follow-up were included in this analysis (n=357). Readings were performed locally at both time points, either by the same or by a different reader. Positive cases were defined as definite radiographic sacroiliitis (grade ≥2 bilaterally or grade 3–4 unilaterally) according to the modified New York criteria (mNY).

Results: In total, 357 patients with follow-up visit had also baseline radiographs available. The mean age at baseline was 33.8 years (SD: 10.8), 47.9% were men, 50.2% had active inflammation of the sacroiliac joints on MRI and 48.7% were HLA-B27 positive. The proportion of patients fulfilling the radiographic mNY at baseline was 17.4% (62/357), whereas at follow-up 22.4% (80/357) of the patients fulfilled these criteria (table). However, more than half of the patients (36/62; 58.1%) with positive baseline X-SI were graded negative at follow-up. Moreover, 54/295 (18.3%) became positive at follow-up. However, given the percentage of the patients 'becoming negative', it is hard to decide what the real rate of progression is.

Conclusion: Our results confirm that radiographic sacroiliitis, defined by the mNY, is a poorly reliable method. Consequently, this method is difficult to use as an outcome measure to define progression in a cohort of patients, with and without treatment, although paired reading may improve the result.

Table: radiographic sacroiliitis according to the mNY at baseline and at follow-up (on average 4.4 years).

	Follow-up radiograph		
Baseline radiograph	Positive	Negative	**Total**
Positive	26	36	**62**
Negative	54	241	**295**
Total	**80**	**277**	**357**
PPV (%)	41.9		
NPV (%)	81.7		

mNY: modified New York criteria. PPV: positive predictive value; NPV: negative predictive value.

Heijde, None.

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Abstract Number: 1328

Pelvic Plain Radiograph, Thoraco-Abdominal and Pelvic CT Scan and MRI Compared to the CT of the Sacroiliac Joints Taken As Gold Standard in the Diagnosis of Structural Sacroiliitis

julian Melchior[1], Yusef Azraq[2], Isabelle Chary-Valkenaere[3], Anne-Christine Rat[4], Pedro Augusto Gondim Texeira[5], Alain Blum[6] and Damien Loeuille[7], [1]University Hospital of Nancy, Vandoeuvre-lès-Nancy, France, [2]radiology, University hospital of Hadassah, Jerusalem, Israel, [3]CHU de Nancy, Rheumatology, Nancy, France, [4]Rheumatology, Nancy Teaching Hospital, Nancy, France, [5]Radiology Imagerie Guilloz, University Hospital of Nancy, Nancy, France, [6]CHU de Nancy, Radiology, Nancy, France, [7]CHU nancy, Nancy, France
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Background/Purpose: To compare the respective performances of the pelvic plain radiograph (RX), thoraco-abdominal and pelvic CT (TAP-CT) and MRI of the sacroiliac joints (SIJ-MRI) to CT of the sacroiliac joints (SIJ-CT) for the diagnosis of structural sacroiliitis in a population suffering from spondyloarthritis (SpA) meeting the New York or ASAS criteria.

Methods: All radiographic or non-radiographic SpA patients eligible for biologic treatment who received a pretherapeutic check up including the four imaging techniques in the same year from 2005 to 2012 were selected. Sacroiliitis was assessed on Rx according to New York criteria independently by a rheumatologist and a radiologist and on TAP-CT, SIJ-MRI and SIJ-CT for the presence of erosion on at least two consecutive slices. A final diagnosis was established for conflicting exams.

Results: Of the 58 selected patients, sacroiliitis was diagnosed on RX, TAP-CT, SIJ-MRI and SIJ-CT in 32, 26, 34 and 35 times respectively. Inter-reader agreements were good for the grade of sacroiliitis (Kappas between 0.60 and 0.76) and moderate for the diagnosis of sacroiliitis (Kappas between 0.45 and 0.55) for the four imaging techniques. The sensitivities of RX, TAP-CT and SIJ-MRI in comparison to SIJ-CT were 82.8%, 71.4% and 85.7% respectively and the specificities were 86.9%, 100% and 82.6% respectively with SIJ-CT considered gold standard.

Conclusion: This study demonstrates the interest of SIJ-MRI and TAP-CT for the diagnosis of structural sacroiliitis in comparison with the SIJ-CT with the same level of performances as RX. These imaging techniques avoid redundant exams.

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Abstract Number: 1329

Impact of Repeating Imaging of the Sacroiliac Joints after One Year on the Classification of Patients According the ASAS Axial Spa Criteria

Pauline Bakker[1], Miranda van Lunteren[2], Zineb Ez-Zaitouni[2], Rosaline van den Berg[3], Manouk de Hooge[4], Karen M. Fagerli[5], Robert B. M. Landewé[6], Maikel van Oosterhout[7], Roberta Ramonda[8], Monique Reijnierse[9], Floris van Gaalen[1] and Désirée van der Heijde[10], [1]Rheumatology, Leiden University Medical Center, Leiden, Netherlands, [2]Leiden University Medical Centre, Leiden, Netherlands, [3]Leiden University Medical Center, Leiden, Netherlands, [4]Department of Rheumatology, Leiden University Medical Centre, Leiden,

Netherlands, [5]Rheumatology, Diakonhjemmet Hospital, Oslo, Norway, [6]Rheumatology, University Hospital Maastricht, Maastricht, Netherlands, [7]Rheumatology, GHZ Hospital, Gouda, Netherlands, [8]Cattedra, Voc Rheumatology, University of Padua, Padova, Italy, [9]Radiology, Leiden University Medical Center, Leiden, Netherlands, [10]University Hospital, Maastricht, Netherlands
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Background/Purpose: It is known that in axial spondyloarthritis (axSpA) inflammatory lesions on MRI of the SI joints (MRI-SI) can change over time. The usefulness of repeating imaging in the diagnostic process is unclear. By this study we aim to investigate how patients with short-term chronic back pain are classified by the ASAS axSpA- criteria at baseline and after 1-year follow-up, focussing on the role of imaging.

Methods: Patients in the SPACE-cohort (back pain: ≥ 3 months, ≤ 2 years, onset < 45 years) with (suspicion of) axSpA underwent MRI and X-rays of the SI-joints at baseline and 1-year follow-up. Patients with complete MRI- and X-SI data at both timepoints were included in the analysis (n=185). MRI-SI and X-SI were scored by 3 different well-calibrated readers independently according to the ASAS-definition for a positive MRI and the mNY-criteria, blinded for patient characteristics and time sequence. Fulfilment of ASAS-MRI or mNY-criteria was considered positive if 2/3 readers agreed. At each timepoint, patients were classified according the ASAS axSpA-criteria and grouped in the different arms (imaging arm: mNY+/- or MRI+/-; clinical arm, fulfilment of both arms and possible axSpA). At year one, in contrary to the normal application of the criteria, we grouped patients according to the finding at that timepoint, ignoring previous imaging findings.

Results: At baseline, 92/185 patients (49.7%) fulfilled the ASAS criteria (clinical arm: 53; imaging arm: 15, both arms: 24) (table). At 1 year, 14 additional patients fulfilled the criteria (8 clinical arm; 5 imaging arm only; 1 both arms). After 1 year, in 12 patients MRI-SI became positive. As a result,14/93 (15.1%) of the no SpA or possible SpA patients at baseline could be classified additionally as axSpA because of additional SpA features (n=8), a positive MRI (n=4) or sacroiliitis according to the mNY-criteria (n=2), On the other hand, MRI-SI became negative after 1 year in 12 other patients. Of these patients, 10 still fulfilled the ASAS criteria (clinical arm (n=7) or both arms (n=3)). Only 4 patients (classified as axSpA at baseline) would be missed if imaging would have been performed only at 1 year (due to negative MRI or x-ray findings).

Conclusion: In our cohort, a significant number of patients with no SpA or possible SpA at baseline developed (additional) SpA features leading to fulfilment of axSpA criteria at year one.

Table: impact of repeating imaging after 1 year on the ASAS axSpA classification of patients

	1 year										
Baseline	**ASAS classification** different arms		**No SpA**	**Possible SpA**	**Clinical arm +**	**Imaging arm +**			**Both arms +**			**Total**
						mNY+ MRI+	mNY+ MRI-	mNY- MRI+	mNY+ MRI+	mNY+ MRI-	mNY- MRI+	
	No SpA		18	12			1	1				32
	Possible SpA			49	8		1	2			1	61
	Clinical arm +				47					1	5	53
	Imaging arm +	mNY+ MRI+				2				1		3
		mNY+ MRI-	1	1			2			1		5
		mNY- MRI+	1	1	2	1					2	7
	Both arms +	mNY+ MRI+			1				2	1	2	6
		mNY+ MRI-			3				1		2	6
		mNY- MRI+			4				1	1	6	12
	Total		20	63	65	3	4	3	4	5	18	185

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Abstract Number: 1330

What Is the Reliability of Recognizing Structural MRI Lesions of Sacroiliac Joints in Patients with Recent Inflammatory Back Pain in Clinical Practice?

Charlotte Jacquemin[1], Roxana Rubio Vargas[2], Rosaline van den Berg[2], Salah Ferkal[1], Philippe Le Corvoisier[3], Alain Rahmouni[4], Damien Loeuille[5], Désirée van der Heijde[6] and Pascal Claudepierre[7], [1]Rheumatology, Hôpital Henri Mondor, Créteil, France, [2]Leiden University Medical Center, Leiden, Netherlands, [3]Clinical Investigation Center, Hôpital Henri Mondor, Créteil, France, [4]Radiology, Hôpital Henri Mondor, Créteil, France, [5]Rheumatology, Department of Rheumatology, CHRU Vandoeuvre les Nancy, Vandoeuvre les Nancy, France, [6]Rheumatology, Leiden University Medical Center, Leiden, Netherlands, [7]Hôpital Henri Mondor, Créteil, France
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Background/Purpose: Axial spondyloarthritis (axSpA) can be difficult to diagnose at an early stage of the disease. Identification of structural lesions of the sacroiliac joints (SIJ) on X-rays is often delayed for several years and remains very disputable, even for trained

readers. Inflammatory lesions on MRI are taken into account in classification criteria of axSpA but the validity of MRI in detecting structural lesions in clinical practice has not been assessed. The objective of this study was to evaluate the reliability of recognising structural lesions on MRI-SIJ in patients with inflammatory back pain (IBP) suggestive of axSpA in clinical practice compared to a central reading.

Methods: Patients aged 18-50, with recent (<3 years) and chronic (≥3 months) IBP, suggestive of axSpA were included in the DEvenir des Spondyloarthrites Indifférenciées Récentes (DESIR) cohort. MRI-SIJ structural lesions (erosions, fatty lesions, ankylosis) were scored by a local reader (non specifically trained radiologist or rheumatologist, with access to clinical data) and by two trained central readers (blinded for clinical data and other imaging modalities). Local readers scored each SIJ in 3 grades (0=normal, 1=doubtful, 2=definite) regarding the presence of structural lesions. A method similar to the SPARCC SIJ Structural Score was used for central reading.

The analyses were done based on the individual scores as well as the mean score of the two central readers.Agreement was calculated (kappa; % positive and negative agreement) between central readers regarding 9 possible definitions of a positive MRI-SIJ (table), and between local readers (3 definitions).

Results: In this analysis, 664/708 patients with complete available images were included. According to the central reading 39% had a least 1 erosion, fatty lesion or (partial) ankylosis, and according to the local reading, 35.4% patients had a positive MRI-SIJ based on structural lesions(at least unilateral 'doubtful' or 'definite structural lesion'). Agreement between central readers was "moderate" for 4 definitions MRI-SIJ structural lesions, and "fair" for the other 5 definitions (data not shown).When comparing local to central reading (both definitions 1) as external standard (table, mean score central readers), there were 13.1% false positive (overclassified) and 16.7% false negative classifications (not detected).Agreements improve when adding fat lesions to erosions in the definition of a positive MRI-SIJ.

Conclusion: In this study, agreement on positive MRI-SIJ based on the presence of structural lesions was fair to moderate between local and central readers, as well as between trained central readers. The reliability improved when fat lesions are combined with erosions. The diagnostic value of MRI structural lesions needs to be determined in longitudinal follow-up.

	MRI Central Reading (mean of the two central readers)					
	Definition 1: ≥1 erosion, fatty lesion or (partial) ankyosis		Definition 2: ≥1 erosion		Definition 3: ≥2 erosions	
MRI Local Reading	PPA	NPA	PPA	NPA	PPA	NPA
Definition 1 : At least 1 SI-joint with doubtful or definite structural lesions	59,9 K(95%CI): **0,36** (0,29 to 0,44)	76,3	57,8 K(95%CI): **0,35** (0,27 to 0,43)	77,2	48,6 K(95%CI): **0,31** (0,24 to 0,39)	80,5
Definition 2 : At least 1SI-joint with definite structural lesions	57,6 K(95%CI): **0,38** (0,31 to 0,46)	79,5	54,3 K(95%CI): **0,35** (0,27 to 0,43)	79,9	49,8 K(95%CI): **0,35** (0,27 to 0,43)	85,0
Definition 3 : Bilateral definite structural lesions	51,6 K(95%CI): **0,36** (0,29 to 0,42)	80,6	48,0 K(95%CI): **0,31** (0,24 to 0,39)	80,8	50,0 K(95%CI): **0,38** (0,30 to 0,47)	88,3
	Definition 4: ≥3 erosions		Definition 5: ≥1 fatty lesion		Definition 6: ≥2 fatty lesions	
Definition 1	38,0 K(95%CI): **0,24** (0,17 to 0,30)	80,2	55,9 K(95%CI):**0,35** (0,28 to 0,43)	79,0	52,3 K(95%CI): **0,36** (0,29 to 0,43)	81,8
Definition 2	40,8 K(95%CI): **0,28** (0,20 to 0,37)	85,6	56,5 K(95%CI):**0,40** (0,32 to 0,48)	83,3	54,2 K(95%CI): **0,41** (0,33 to 0,49)	86,3
Definition 3	46,4 K(95%CI): **0,37** (0,28 to 0,46)	90,1	52,1 K(95%CI): **0,38** (0,30 to 0,46)	85,1	56,9 K(95%CI):**0,47** (0,38 to 0,55)	89,9
	Definition 7: ≥3 fatty lesions		Definition 8: (partial) ankylosis		Definition 9: ≥3 erosions and/or fatty lesions	
Definition 1	46,9 K(95%CI): **0,34** (0,27 to 0,41)	82,9	19,0 K(95%CI): **0,01** (-0,05 to 0,08)	74,8	59,3 K(95%CI):**0,38** (0,31 to 0,46)	79,0
Definition 2	50,2 K(95%CI): **0,40** (0,31 to 0,48)	87,7	19,7 K(95%CI): **0,04** (-0,03 to 0,11)	81,0	58,8 K(95%CI):**0,42** (0,35 to 0,49)	82,8
Definition 3	56,2 K(95%CI):**0,48** (0,39 to 0,57)	91,8	19,9 K(95%CI): **0,06** (-0,02 to 0,15)	85,7	54,4 K(95%CI): **0,41** (0,33 to 0,48)	84,4

PPA/NPA= positive/negative percent agreement; K=Kappa

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Abstract Number: 1331

Change in MRI in Patients with Spondyloarthritis Treated with Anti-TNF Agents : Systematic Review of the Literature

Gisèle KHOURY[1], BG Combe[2] and Cédric Lukas[3], [1]Rheumatology, Hopital Lapeyronie, Montpellier, France, [2]Lapeyronie, Montpellier, France, [3]Hopital Lapeyronie, Montpellier, France
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Background/Purpose: The follow-up of axial spondyloarthritis (SpA) remains difficult in clinical practice, mainly based on patient-reported outcomes, whereas objective parameters in disease monitoring are often lacking, especially in axial manifestations. MRI of the spine and sacroiliac joints (SIJ) might be relevant for difficult cases, provided that its validity and correlation with clinical, biological parameters, functional and activity scores is ascertained.

The aim of this study was to assess the effect of TNF alpha inhibitors (TNF-) on MRI scoring of inflammation on spine and SIJ and to evaluate their correlation with the clinical and biological parameters used in daily practice.

Methods: A systematic review of the literature using PUBMED and the Cochrane library as well as proceedings from recent major relevant congresses was performed until January 2015. All randomized controlled trials and controlled cohorts reporting the effect of TNF- on spine and SIJ MRI scores (ASspiMRI, SPARCC, Berlin) were selected. Data were collected using a predetermined form. The outcomes were: the change in scores between baseline and follow up in TNF- and control groups, the correlation of theses changes with CRP, ESR, BASDAI, BASFI, ASDAS, pain and morning stiffness. When appropriate, statistical analysis determined the pooled therapeutic effect of TNF- on MRI scores computed by meta-analysis.

Results: Out of 365 screened references, 58 studies were included : 14 using ASspiMRI score, 8 using spine SPARCC score, 8 using SPARCC SIJ score, 7 using BERLIN spine score, 7 using BERLIN SIJ score and 14 using other scores. In ASspiMRi at 12 weeks and 2years follow up, and in SPARCC spine score at 12 weeks follow up a non significant difference in MRI score decrease between the TNF alpha inhibitor group and control group was reported. A significant decrease in the SPARCC SIJ score at 12 weeks in TNF alpha inhibitor group was reported. The correlation between MRI spine and SIJ scores on one side, and the clinical and biological data on the other side was very heterogeneous across the different reports. However, an association was usually reported between the MRI scores and CRP, ESR and ASDAS.

Conclusion: Considering our findings, MRI (especially MRI of the spine) seems to insufficiently reflect the axial activity of SpA patients to recommend its use in individual follow-up or assessment of patients. Regarding its diagnostic value or relevance in the apprehension of the pathophysiology of the disease however, it remains currently the most accurate tool.

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Assessing Radiographic Damage in Ankylosing Spondylitis: Variability in Reliability of the Modified Stoke Ankylosing Spondylitis Spine Score According to the Statistical Method

Sibel Z. Aydin[1], Esen Kasapoglu-Gunal[2], Esra Kurum[3], Servet Akar[4], Eyyup Mungan[5], Fatma Alibaz-Oner[6], Helena Marzo-Ortega[7], Dennis McGonagle[8], Robert G Lambert[9], Pamir Atagunduz[6] and Walter Maksymowych[10], [1]Department of Rheumatology, Koc University Faculty of Medicine, Istanbul, Turkey, [2]Internal Medicine, Istanbul Medeniyet University Goztepe Training and Research Hospital,

Istanbul, Turkey, [3]PhD,Department of Epidemiology of Microbial Diseases, Yale School of Public Health, New Haven, CT, [4]Department of Internal Medicine, Division of Rheumatology, Izmir Katip Celebi University School of Medicine, Izmir, Turkey, [5]Goztepe training and research hospital, MD, Istanbul, Turkey, [6]Rheumatology, Marmara University School of Medicine, Istanbul, Turkey, [7]Leeds Musculoskeletal Biomedical Research Unit and University of Leeds, Leeds, United Kingdom, [8]Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds, Leeds, United Kingdom, [9]Radiology, Radiology, University of Alberta, Edmonton, AB, Canada, [10]Medicine, University of Alberta, Edmonton, AB, Canada
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Background/Purpose: Conventional radiography is the main imaging modality to assess damage in the spine in ankylosing spondylitis. Modified Stoke Ankylosing Spondylitis Spine Score (mSASSS) has been endorsed by OMERACT as being more sensitive to change, therefore more commonly used in clinical trials. We aimed to compare the reliability of mSASSS on status scores by using different approaches to understand how different readers agree on overall scores and on the presence of individual findings included in mSASSS.

Methods: : The SPAR (The Spondyloarthritis Radiography) training module was used for the purpose of the study. After a standardization exercise, 4 investigators scored 68 plain radiographs of the cervical and lumbar spine of 34 patients at 2 time points with 2-year intervals. The anterior vertebral corners in lateral images were scored for erosions, sclerosis, squaring, syndesmophytes and ankylosis and a total mSASSS score was calculated. The reliability of the 4 readers was compared with 2 gold standard readers using ICC (intraclass coefficient). Additionally, the reproducibility of each finding in 1632 vertebral corners was calculated by kappa analysis and positive agreement rates.

Results: The reliability analysis using ICC revealed that all readers had excellent agreement with both gold standards with a range of ICC between 0.858-0.948. The kappa analysis showed worse agreement within lesions (table): For syndesmophytes agreement was between 0.394-0.677. The highest kappa values were detected for ankylosis, in a range between 0.624-0.889. The positive agreement rates showed that erosions were never detected at the same vertebral corner by 2 readers (positive agreement rate of 0%). The positive agreement rates for other score 1's were also very low (sclerosis mean for agreement (range): 5.2% (0-15); squaring: 22.6% (0-59.7)). Ankylosis had the highest positive agreement rate, between 77.8 % (66.1-89.6%) and syndesmophytes had a mean positive agreement of 48.9% (39.4-63.9).

Conclusion: Our results show that there is a poor agreement on grade 1's between readers which has a risk of increasing measurement error. The currently used definitions of reliability have a risk of overestimating the reproducibility (such as high ICC values) and the results of mSASSS should be interpreted with precaution.

vs gold

standard	**Sclerosis**		**Squaring**		**Erosions**		**Syndesmophytes**		**Ankylosis**	
	kappa	positive agreement	kappa	positive agreement	kappa	positive agreement	kappa	positive agreement	kappa	positive agreement
Reader 1	I	0.554-0.680	0	0.462-0.575	0	0.416-0.501	0	0.463-0.535	39.4	0.664-0.681	71.4
	II	0.525-0.623	7.5	0.33-0.584	0	0.649-0.728	0	0.394-0.416	28.3	0.690-0.739	75.1
Reader 2	I	0.678-0.690	0	0.594-0.612	13.7	0.483-0.510	0	0.621-0.649	56.5	0.765-0.776	80.4
	II	0.676-0.684	13.4	0.634-0.649	10.8	0.796-0.808	0	0.580-0.592	51.1	0.814-0.842	85.2
Reader 3	I	0.675-0.697	0	0.625-0.628	27.3	0.705-0.726	0	0.570-0.580	51.1	0.624-0.684	68.7
	II	0.645-0.672	15.0	0.590-0.681	21.2	0.486-0.517	0	0.495-0.547	48.1	0.637-0.666	66.1
Reader 4	I	0.713-0.736	0	0.696-0.711	59.7	0.492-0.503	0	0.670-0.677	63.9	0.801-0.802	86
	II	0.682-0.730	5.6	0.689-0.771	48.7	0.785-0.877	0	0.599-0.604	52.4	0.839-0.889	89.6

Table: The kappa values and positive agreement rates (%), given separately for all lesions and all readers, compared to gold standards I and II.

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Abstract Number: 1333

Assessment of Focal Fat Infiltration in Sacroiliac Joints in Patients with Spondyloarthritis By 1.5T Versus 3.0T Magnetic Resonance Imaging: Is the Field Strength Important to Contrast to Noise Ratios, Reproducibility and Total Scores?

Jakob M. Møller[1], Jelena Jankovic[1], Mikkel Østergaard[2], Inge Juul Sorensen[3], Rene Poggenborg[4], Ole Rintek Madsen[5], Henrik S Thomsen[1] and Susanne Juhl Pedersen[6], [1]Department of Radiology, Copenhagen University Hospital Herlev, Herlev, Denmark, [2]Rigshospitalet-Glostrup, Copenhagen Center for Arthritis Research, Center for Rheumatology and Spine Diseases, Rigshospitalet - Glostrup, Glostrup, Denmark, [3]Copenhagen Center for Arthritis Research, Center for Rheumatology and Spine Diseases, Rigshospitalet - Glostrup, Glostrup, Denmark, [4]Rheumatology, Copenhagen University Hospital at Gentofte, Gentofte, Denmark, [5]Department of Rheumatology/C, Department of Rheumatology/C, Copenhagen University Hospital Gentofte, Hellerup, Denmark, [6]Copenhagen Center for Arthritis Research, Glostrup Hospital, University of Copenhagen, Copenhagen, Denmark

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Background/Purpose:

Reporting of focal fat infiltrations (FFI) in sacroiliac joints (SIJs) is becoming more important in patients with axial spondyloarthritis (SpA) since this lesion has been shown to be an independent predictor of ankylosis. T1 relaxation times depend on magnetic field strength and hence T1 contrast behavior of bone marrow (i.e. the visualization of fat in the bone marrow) is magnetic field strengths dependent. Therefore FFI may be scored differently depending of the field strength.

Methods:

19 SpA patients (10 males age 42.8±13.8 years, 9 females age 42.5±12.5 years) and 3 healthy volunteers (1 male age 49 years, 2 females age 39.5±9.1 years) underwent MRI at 1.5T (Time to repeat (TR)/ time to echo (TE) 550/14 ms voxel dimension 1x1.5x4 mm) and 3T (TR/TE: 700/20 ms voxel dimension 1x1.5x4 mm). The cartilaginous part of the SIJs were divided into 8 quadrants and evaluated on 5 consecutive slices (1) and were analyzed for FFI in two ways: 1. If FFI was present the signal intensity (SI) was measured. On every slice normal bone marrow SI and standard deviation of the noise (SDn) was measured. Contrast to noise ratio (CNR) was calculated as the difference between normal SI and FFI SI divided by SDn. 2. All quadrants were scored for presence/absence of FFI according to the Spondyloarthritis Research Consortium of Canada (SPARCC) SIJ Structural Score (SSS)(1). The intra-observer variation of both methods was assessed in six patients and expressed as the Intraclass Correlation Coefficient (ICC). The paired t-test was used for comparing CNR results. SSS results were compared using the Wilcoxon Signed Rank test.

Results:

The ICC for CNR was 0.90 at 1.5T and 0.77 at 3T, and for SSS 0.96 at 1.5T and 0.94 at 3T. On both right and left side, CNR was higher at 3T ($p < 0.001$) compared to 1.5T. SDn was lower ($p < 0.001$) at 3T compared to 1.5T. For SSS the sum of scores was 160 (mean 7.3) at 1.5T and 169 (7.7) at 3T ($p = 0.87$)

Conclusion:

3T compared to 1.5T MRI provides a better contrast to noise ratio, but the intra-observer agreement and total scores of focal fat infiltration

are identical.

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Abstract Number: 1334

Bone Erosion in Gout: Relationship with Tophus Urate and Soft Tissue Volumes. a Conventional and Dual Energy CT Study

Mark Sapsford[1], Gregory Gamble[2], Opetaia Aati[2], Julie Knight[1], Anne Horne[2], Anthony Doyle[1] and Nicola Dalbeth[2], [1]University of Auckland, Auckland, New Zealand, [2]Department of Medicine, University of Auckland, Auckland, New Zealand

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Background/Purpose: Imaging and pathology studies have established the close relationship between intraosseous tophus and bone erosion in gout. The tophus is an organised structure consisting of urate crystals and a chronic inflammatory soft tissue response. It is currently unknown whether bone erosion in gout occurs due to direct effects of urate crystals or indirect effects of the soft tissue response. The aim of this work was to examine the relationship between bone erosion and each component of the tophus.

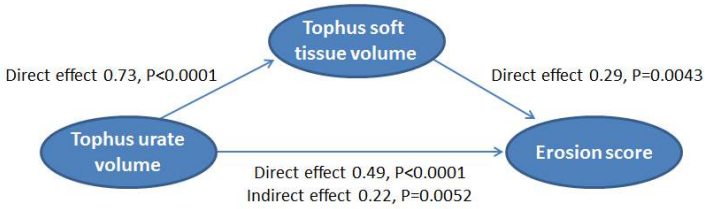
Methods: Plain radiographs and computed tomography (CT) scans of the feet were prospectively obtained from 92 people with tophaceous gout. The ten metatarsophalangeal joints were scored on XR for Sharp-van der Heijde erosion score (scale 0-10). Conventional CT and dual energy CT (DECT) images were assessed at each joint for the presence and total volume of tophus (using manual outlining analysis of conventional CT images) and the presence and volume of tophus urate deposition at the same joints (using automated volume DECT analysis). Tophus soft tissue volume was calculated by subtracting the DECT tophus urate volume from the total CT tophus volume. In total, 918 joints were available for analysis. The readers of the XR and CT/DECT were blinded to each other's scores and all clinical characteristics of the patients. Data were analysed using generalized estimating equations to account for repeated measures in participants, and mediation analysis to examine the direct and indirect effects of urate volume on bone erosion score.

Results: XR erosion was present at 261 (28.4%) joints. Mean (SD) XR erosion score was 1.2 (2.3) in all joints and 4.1 (2.5) in those with XR erosion. CT tophus was present at 447 (48.7%) joints and DECT tophus urate was present at 443 (48.3%) joints. CT tophus was adjacent to bone in 74.7% of all XR erosions (odds ratio (OR) 10.1 [95% CI 6.8-14.8]) and DECT tophus urate was adjacent to bone in 64.8% of all XR erosions (OR 10.6 [95% CI 7.1-15.8]).

Mean (SD) total tophus volume was 1.88 (4.25) cm^3, urate volume was 0.27 (0.80) cm^3, and soft tissue volume was 1.61 (3.63) cm^3. In mediation analysis, urate volume and soft tissue volume were directly associated with XR erosion score (Figure). About a third of the association of urate volume with XR erosion score was indirectly mediated through the strong association between urate volume and soft tissue volume.

Conclusion: Urate and soft tissue components of the tophus are strongly and independently associated with bone erosion in gout. These data suggest that tophi contribute to bone erosion in gout both through direct urate crystal effects and through indirect effects of soft tissue on bone.

Figure: Summary of the mediation analysis. Values represent standardized path coefficients (n=92). The directions of these associations were dictated by biological experience. R^2 for model =0.52.



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Abstract Number: 1335

Factors Associated with Progressive Radiographic Damage in Gout: A Prospective Observational Study

Alastair Eason[1], Meaghan House[2], Zoe Vincent[1], Julie Knight[1], Paul Tan[1], Anne Horne[2], Gregory Gamble[2], Anthony Doyle[1], William J. Taylor[3] and **Nicola Dalbeth**[2], [1]University of Auckland, Auckland, New Zealand, [2]Department of Medicine, University of Auckland, Auckland, New Zealand, [3]Department of Medicine, University of Otago Wellington, Wellington, New Zealand
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Background/Purpose: Radiographic damage is frequently observed in patients with longstanding gout. Although cross-sectional studies have described factors associated with joint damage in gout, there are very few prospective studies that have investigated radiographic progression. The aim of this prospective observational study was to determine the rate of progression and factors associated with progressive radiographic damage in gout.

Methods: People with gout according to the 1977 ARA criteria, with disease duration <10 years were recruited into this prospective observational study. At the baseline visit, detailed clinical assessment was undertaken in 295 participants including subcutaneous tophus count, joint counts, blood tests and plain radiographs of the hands and feet. Participants were invited to attend a further study visit with repeat testing three years after the baseline visit. Paired radiographs (XR) were scored for erosion and joint space narrowing (JSN) in chronological order by two readers according to the gout-modified Sharp van der Heijde XR damage score. Both readers were blinded to each other's scores and all clinical variables. Inter-reader intraclass correlation coefficient (95% CI) for the XR damage score was 0.91 (0.87-0.94). The mean scores for both readers were used in the analysis. Pearson correlation and stepwise linear regression models were used to identify variables independently associated with progressive XR damage.

Results: Paired XR were available for 135 participants. At baseline, mean (SD) erosion score was 4.9 (10.2), JSN score was 6.0 (8.6) and total XR damage score was 10.9 (16.9). At Year 3, mean (SD) erosion score was 7.7 (14.6), JSN score was 7.1 (9.7) and total XR damage score was 12.8 (19.2). Change in subcutaneous tophus count correlated with change in erosion score ($r=0.36$, $p<0.001$), change in JSN score ($r=0.33$, $p=0.001$), and change in total XR damage score ($r=0.53$, $p<0.001$). In stepwise linear regression analysis, baseline XR damage score and change in subcutaneous tophus count independently predicted change in total XR damage score over three years (model $R^2=0.48$, $p<0.001$), with the following baseline variables excluded from the model: tophus count, swollen joint count, tender joint count, C-reactive protein, and serum urate. Baseline XR score and change in subcutaneous tophus count also predicted change in the XR erosion and JSN scores when analysed as separate dependent variables in the regression models.

Conclusion : The presence of radiographic damage at baseline and development of new subcutaneous tophi are associated with progressive joint damage in people with gout. These data provide further evidence that the tophus plays a central role in joint damage in gout.

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Abstract Number: 1336

To PET or Not to PET in General Rheumatology Practice

Kavina Shah, Roshni Doshi, Joshua Balogun-Lynch, Henry Penn and Shahir Hamdulay, Rheumatology, Northwick Park Hospital, Middlesex, United Kingdom

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SESSION INFORMATION

Session Date: Monday, November 9, 2015

Session Title: Imaging of Rheumatic Diseases Poster II: X-ray, MRI, PET and CT

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose:

Fluoro-deoxy-glucose positron emission tomography with computerised tomography (PET/CT) is an imaging modality which identifies tissues with high metabolic activity. It is used in the diagnosis of patients with malignancy, infections, inflammatory diseases and pyrexia of unknown origin (PUO). Although useful, PET/CT has a high radiation dose of 14mSv and therefore should be used cautiously. We investigated the role of PET/CT in general rheumatology practice aiming to understand the indications, diagnostic yield and whether there was additional benefit to whole-body CT (WB-CT).

Methods:

PET/CT requests arranged by 8 rheumatologists between January 2008 and April 2015 were retrospectively reviewed for indication, inflammatory markers, PET/CT, WB-CT findings and final diagnoses. Definitions for analysis: true positive - PET/CT abnormality directly contributing to diagnosis, false positive - abnormality not contributing to diagnosis, true negative- normal scan, false negative- normal scan but disease process identified at 6 months follow-up. A final diagnosis was made by physician assessment, other investigations and tissue biopsy where indicated.

Results:

80 PET/CT requests were identified (55 females), mean age 63 years (range 24-86). A final diagnosis was established in 86%. Indications included large vessel vasculitis (34), disease activity progression (3), infection (2), malignancy (22), PUO (2), unexplained inflammatory response (18).

Two sub-groups were analysed; first presentation with no diagnosis (n=53) and prior established rheumatological diagnosis (n=27).

First presentation: PET/CT identified abnormalities in 23/53 (43%) cases, of which 10 (43%) contributed to diagnosis (malignancy-2, large vessel vasculitis-6, PMR-1 and infection-1). 13 (25%) identified non-specific abnormalities with no contribution to a final diagnosis. 16 (30%) were negative and no new diagnosis was apparent at 6 months follow-up. Ten patients did not reach a final diagnosis. The sensitivity in this setting was 45% and specificity 76%.

Established rheumatological diagnoses included myositis, rheumatoid arthritis, scleroderma, Takayasu's, GCA, JIA, lupus, PMR, undifferentiated and mixed connective tissue disease. PET/CT was positive in 15/27 cases (56%), identifying new diagnoses in 10 patients (5 aortitis, 1 Takayasu's, 1 Polymyositis, 2 infection, 1 vasculitic myositis) and increase in disease activity in 2 (inflammatory arthritis in scleroderma and JIA). Non-specific abnormalities were apparent in 3 cases. 12 had truly normal scans.

PET/CT added no further information to WB-CT in 31/45 (69%) patients including those diagnosed with malignancy. However PET/CT directly diagnosed Takayasu's arteritis in 1, aortitis in 3 cases and inflammatory arthritis in 2, which was not apparent on WB-CT. The mean ESR was 76 in patients with a truly positive scan versus 44 with a truly negative PET/CT.

Conclusion:

PET/CT has moderate diagnostic sensitivity and reasonable specificity in general rheumatology practice and often appears to provide no further information to WB-CT. Its main diagnostic advantage is for aortitis, and an elevated ESR may improve its diagnostic yield.

Disclosure: K. Shah, None; **R. Doshi**, None; **J. Balogun-Lynch**, None; **H. Penn**, None; **S. Hamdulay**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/to-pet-or-not-to-pet-in-general-rheumatology-practice

Abstract Number: 1337

Pulmonary Computed Tomography Changes in Patients with Rheumatoid Arthritis

Alexandra Balbir-Gurman[1], Ludmila Guralnik[2], Mordehai Yigla[3], Yolanda Braun-Moscovici[4], Anna Astrahan[5] and Emilia Hardak[6], [1]B. Shine Rheumatology Unit, Rambam Health Care Campus, Rappaport Faculty of Medicine, Technion - Institute of Technology, Haifa, Israel, [2]Department of Diagnostic Imaging, Rambam Health Care Campus, The Bruce Rappaport Faculty of Medicine, Technion-Institute of Technology, Haifa, Israel, [3]Division of Pulmonary Medicine, Rambam Health Care Campus, The Bruce Rappaport Faculty of Medicine, Technion-Institute of Technology, Haifa, Israel, [4]B Shine Department of Rheumatology, Rambam Health Care Campus,. Rappaport Faculty of Medicine, Technion, Haifa, Israel, [5]Rappaport Faculty of Medicine-Technion, Israeli Institute of Technology, Haifa, Israel, [6]Pulmonary Institute, Rambam Health Care Campus; Rappaport Faculty of Medicine-Technion, Israeli Institute of Technology, Haifa, Israel

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Session Time: 9:00AM-11:00AM

Background/Purpose: Lung involvement in RA it is often diagnosed in advanced stage. Chest CT is the main modality for assessment of ILD. To analyze chest CT changes in a cohort of RA patients followed at our center and their correlation with RA features and prognosis.

Methods: Chest CT scans performed by RA patients were retrospectively analyzed. CT findings were classified as RA-lung and non-RA-lung and correlated to patients data (age, sex, RA duration, smoking, death, DAS28, joint erosions, extra-articular features, CRP, RF, ACPA, FVC, DLCO), and treatment. The search of the MEDLINE was performed using keyword combinations: RA and chest CT; rheumatoid lung and chest CT; RA and ILD for the period from 1991 until 2015. Statistical analysis included logistic regression. P-value <0.05 was defined as significant.

Results: 48 out of 84 patients (57.2%) had RA-lung. Positive RF (p=0.018), joint erosions (p=0.003) and reduced DLCO (p=0.005) correlated with RA-lung. Treatment with DMARDs had protective effect against RA-lung (p=0.028). Analyzed published literature (100 original articles, reviews and case reports) on chest CT in RA reported on changes in the lung parenchyma, pleura, bronchial system, and the vasculature. CT changes were attributed to RA-lung (mainly ILD) or non-related to RA (new or existing lung pathology, drug induced pneumonitis, and conventional and opportunistic infections, especially in patients treated with synthetic and/or biological DMARDs).

Conclusion: Findings on chest CT attributed to ILD-RA in the literature are variable and difficult for interpretation and classification. Correlation of CT findings with clinical data according to analyzed literature is not fully estimated. There is an unmet need to design an algorithm for prediction of CT changes compatible with ILD-RA with a high probability. Our data indicates that in RA patients with high RF, erosive disease and reduced DLCO there is a high probability for abnormal chest CT study, especially for ILD-RA. Diagnosing of ILD-RA early could allow comprehensive approach to treatment with possible control of both, RA and RA-lung disease; early intervention may change the course of RA and ILD-RA with possible slowing and prevention the progression of ILD-RA toward pulmonary fibrosis.

Disclosure: A. Balbir-Gurman, None; **L. Guralnik**, None; **M. Yigla**, None; **Y. Braun-Moscovici**, None; **A. Astrahan**, None; **E. Hardak**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/pulmonary-computed-tomography-changes-in-patients-with-rheumatoid-arthritis

Abstract Number: 1338

Increased Aortic Wall Thickness for the Diagnosis of Aortitis: a Computed Tomography-Based Study

Gleb Slobodin[1,2,3], Afif Nakhleh[4], Doron Rimar[1], Vladimir Wolfson[5], Itzhak Rosner[1] and Majed Odeh[2,3], [1]Rheumatology, Bnai Zion Medical Center, Haifa, Israel, [2]Internal Medicine A, Bnai Zion Medical Center, Haifa, Israel, [3]Bnai Zion Medical Center, Haifa, Israel, [4]47 Golomb St, Bnai Zion Medical Center, Haifa, Israel, [5]Radiology, Bnai Zion Medical Center, Haifa, Israel

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Session Title: Imaging of Rheumatic Diseases Poster II: X-ray, MRI, PET and CT

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Session Time: 9:00AM-11:00AM

Background/Purpose: To evaluate the usefulness of computed tomography (CT)-measured aortic wall thickness (AWT) as a sole imaging finding for the confirmation of clinically suspected aortitis.

Methods: CT scans of 20 patients with the diagnosis of aortitis, endorsed by the abnormally thickened aortic wall, as a single imaging finding, and 250 patients without known aortitis were reviewed and AWT manually measured at the levels of thoracic descending aorta, upper abdominal aorta and infrarenal aorta, as well as the level of maximal AWT in patients with diagnosed aortitis. Patients' charts were analyzed and demographic data and data on co-morbidities extracted. Correlations of measured AWT with patients' demographic data and co-morbidities were calculated for the control patients. Age-dependent upper 97.5 percentile points for AWT were calculated for different age groups as a reference. AWT of patients, diagnosed with aortitis, was compared with these reference values.

Results: AWT had significant positive correlation with patient age ($p<0.001$), gender ($p<0.03$) and presence of aortic wall calcifications ($p<0.001$). In 9 of 20 patients, with diagnosed aortitis confirmed by the increased CT-measured AWT, the revised values of AWT were lower than calculated upper 97.5 percentile point for the relevant age group. In 4 of these patients, the values of the measured AWT were in the range of mean+SD for AWT for the same age.

Conclusion: The confirmation of suspected aortitis by the increased CT-measured AWT only may be equivocal and necessitate more specific imaging, particularly in elderly patients.

Fig 1. Correlation plots of AWT with patients' age

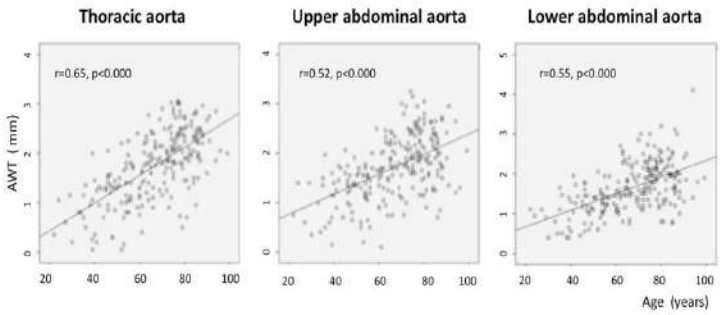

Table 1. AWT in different age groups

Age groups (years)	Thoracic Aorta		Upper Abdominal Aorta		Lower Abdominal Aorta	
	Mean SD¤	97.5¦	Mean SD¤	97.5¦	Mean SD¤	97.5¦
<50	0.998 0.49	1.96	1.188 0.46	2.08	1.063 0.42	1.89
50-70	1.544 0.57	2.66	1.535 0.53	2.57	1.504 0.47	2.43
>70	2.133 0.54	3.19	2.012 0.55	3.09	1.927 0.55	3.01

Mean value of aortic wall thickness (mm)

¤ Standard deviation

¦ Upper 97.5 percentile point

Table 2. Correlations of AWT with patients' demographic data and co-morbidities. Summary of the multivariate regression analysis (*p* values)

	Thoracic Aorta	Upper Abdominal Aorta	Lower Abdominal Aorta
Age	<0.001	<0.001	<0.001
Gender	0.03	0.029	<0.001
AW Calcifications	<0.001	<0.001	<0.001
Arterial Hypertension	0.179	0.830	0.329
Hyperlipidemia	0.656	0.758	0.375
Diabetes Mellitus	0.714	0.997	0.979
Coronary Artery Disease	0.866	0.144	0.459

Disclosure: G. Slobodin, None; **A. Nakhleh**, None; **D. Rimar**, None; **V. Wolfson**, None; **I. Rosner**, None; **M. Odeh**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/increased-aortic-wall-thickness-for-the-diagnosis-of-aortitis-a-computed-tomography-based-study

Abstract Number: 1339

Granulomatosis with Polyangiitis or Post Pulmonary Tuberculosis: Can CT Chest Help in Differentiating in a Tuberculosis Endemic Area?

Aman Sharma[1], Manphool Singhal[2], Mitali Sen[3], Manish Rathi[4], Varun Dhir[1], Kusum Sharma[5], Ranjana Minz[6], Surjit Singh[3], Pradeep Bambery[7] and Niranjan Khandelwal[2], [1]Internal Medicine (Rheumatology Unit), Postgraduate Institute of Medical Education and Research, Chandigarh, India, [2]Department of Radiodiagnosis, PGIMER,, Chandigarh, India, [3]Department of Internal Medicine,, PGIMER,, Chandigarh, India, [4]Department of Nephrology,, Postgraduate Institute of Medical Education and Research, Chandigarh, India, [5]Department of Medical Microbiology,, PGIMER,, Chandigarh, India, [6]Department of Immunopathology,, PGIMER,, Chandigarh, India, [7]Rheumatology, Bundaberg base hospital, University of Queensland, Bundaberg, Australia

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SESSION INFORMATION

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Session Type: ACR Poster Session B
Session Time: 9:00AM-11:00AM

Background/Purpose:

The data on the Computed tomography (CT) changes of chest in Granulomatosis with polyangiitis (GPA) is available mostly from low tuberculosis prevalence countries. We planned to study the CT findings in confirmed GPA patients from a tuberculosis endemic area and compared these with published CT chest findings of post primary tuberculosis.

Methods:

Clinical and CT chest data from 40 patients with GPA was reviewed. The CT findings were classified as pulmonary parenchymal and pleural abnormalities. Parenchymal lesions were further defined as nodules (round opacity with diameter less than 3 cm), mass like consolidation (opacity greater than 3 cm in diameter with obscured underlying vessels) and ground glass opacities (not obscuring the underlying vessels). Lesions were also classified as angiocentric, centrilobular or subpleural based on their location. Cavitation, when present, was documented based on type, centric or eccentric, shape of inner wall margin as well as wall thickness. Architectural distortion of the lung, honeycombing, traction bronchiectasis, pleural or pericardial involvement and hilar or mediastinal lymphadenopathy, if present, were also recorded. We then compared our finding with those reported from two large European cohorts (One from the French vasculitis group and the other from the German group), one cohort each from USA, Mexico, Japan and Korea, and China. We then compared our findings with well described and widely cited CT findings in non HIV patients with Post Primary Pulmonary Tuberculosis.

Results: CT abnormalities were noted in both lungs in 34 and were unilateral in six (right sided in five) GPA patients. The findings were nodules (lesions less than 3 cm in diameter) in 15 (37.5%), masses (lesions more than 3cm) in 11 (27.5%) and ground glass opacities, consolidations and septal thickening in 16 (40%) each, pleural involvement in seven (17.5%), mediastinal lymphadenopathy and pericardial involvement in two(5%) and parenchymal bands in one. Our patients had more consolidation and ground glass opacities, and much fewer parenchymal bands as compared to other series. While comparing the CT findings of GPA with Post primary tuberculosis, the consolidation in areas other than apical and posterior segment of upper lobe and superior segment of lower lobe, eccentric cavitation with smooth inner walls, widespread distribution of nodules with well-defined and clear margins along with the relative absence of mediastinal lymphadenopathy favoured GPA as compared to post primary tuberculosis.

Conclusion: Combination of CT chest findings can help in differentiating GPA from post primary tuberculosis in an endemic area.

Disclosure: A. Sharma, None; **M. Singhal**, None; **M. Sen**, None; **M. Rathi**, None; **V. Dhir**, None; **K. Sharma**, None; **R. Minz**, None; **S. Singh**, None; **P. Bambery**, None; **N. Khandelwal**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/granulomatosis-with-polyangiitis-or-post-pulmonary-tuberculosis-can-ct-chest-help-in-differentiating-in-a-tuberculosis-endemic-area

Abstract Number: 1340

Value of 18F-FDG PET for Therapeutic Assessment in Patients with Polymyalgia Rheumatica Treated in First Line By Tocilizumab

Xavier Palard[1], Solene Querellou[2], Maelenn Gouillou[3], Alain Saraux[4,5], Thierry Marhadour[6], Florent Garrigues[7], Ronan Abgral[8], Pierre-Yves Salaun[8] and Valerie Devauchelle[9,10], [1]Department of nuclear medicine, University hospital of Brest, Brest, France, [2]Department of nuclear medicine, Université Européenne de Bretagne; Université de Brest; EA3878 (GETBO) IFR148, Brest, French Polynesia, [3]Clinical Investigation Centre (CIC) 1412, CHU Cavale Blanche- Institut National de la Santé et de la Recherche Médicale (INSERM), Brest, France, [4]Department of rheumatology and unit of immunology (EA 2216), Université Brest Occidentale, Brest, France, [5]Rheumatology Department, CHU de la Cavale Blanche, Brest Cedex, France, [6]CHU La Cavale Blanche, Brest, France, [7]Radiology department, Cavale Blanche Hospital and Brest Occidentale University, Brest, France, [8]Department of nuclear medicine, Université Européenne de Bretagne; Université de Brest; EA3878 (GETBO) IFR148, Brest, France, [9]Service de Rhumatologie, CHU Brest, Brest, France, [10]Rheumatology, Brest university medical school, EA 2216, UBO and CHU de la Cavale Blanche,, Brest, France
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Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: To evaluate the interest of 18F-FDG positron emission tomography-computed tomography (PET-CT) for therapeutic assessment in polymyalgia rheumatica (PMR) patients undergoing tocilizumab (TCZ) therapy at first line.

Methods:

Patients were prospectively enrolled in a twenty four weeks open label longitudinal, prospective multicenter study assessing TCZ therapy on PMR patients (TENOR: Tolerance and Efficacy of tocilizumab iN pOlymyalgia Rheumatica). They underwent 18F-FDG positron emission tomography-computed tomography (PET-CT) at baseline, after the first infusion of TCZ (TCZ 1) and after the last infusion of TCZ (TCZ 3). PMR activity score (PMR-AS), C-Reactive Protein (CRP) and Erythrocyte Sedimentation Rate (ESR) lab tests were also assessed. Maximal standardized uptake value (SUVmax) was used for assessment of FDG uptake regions usually seen in PMR (spinous processes, hips, shoulders, sternoclavicular and ischial tuberosities). Wilcoxon test was applied to evaluate parameter's changes after infusions and Spearman's rank correlation test was applied to assess the correlation between SUVmax and PMR-AS, CRP and ESR.

Results: Eighteen patients were included. On baseline PET-CT, abnormal joint uptakes (upper than the liver background) were found most frequently in ischial tuberosities and hips regions (94% of patients) following by shoulders region (89%). Cervical spinous processes were the less frequently described (56% of patients). Bioclinical parameters decreased after TCZ 1 (PMR-AS: from 37 to 18, CRP: from 82 to 1 and ESR from 56 to 4, all $p<0.05$) as well as SUVmax (SUVmax: from 5.9 to 5.4, $p<0.05$). All parameters decreased also after TCZ 3 (PMR-AS from 37 to 4, CRP from 82 to 1 and ESR from 56 to 4; SUVmax from 5.9 to 4.6; $p<0.05$). On region based analysis, all SUVmax were significantly reduced after TCZ 3, except for cervical spinous processes and shoulders regions. Concerning correlations, DSUVmax on patient based analysis was significantly correlated with DPMR-AS after TCZ 1 ($r=0.5$, $p=0.04$) such as left hip DSUVmax with DCRP after TCZ 1 ($r=0.64$, $p=0.01$).

Conclusion: FDG PET-CT uptake decreased significantly after TCZ therapy in PMR patients and might reflect disease activity.

Disclosure: X. Palard, None; **S. Querellou**, None; **M. Gouillou**, None; **A. Saraux**, None; **T. Marhadour**, None; **F. Garrigues**, None; **R. Abgral**, None; **P. Y. Salaun**, None; **V. Devauchelle**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/value-of-18f-fdg-pet-for-therapeutic-assessment-in-patients-with-polymyalgia-rheumatica-treated-in-first-line-by-tocilizumab

Abstract Number: 1341

Imaging Growing Joints By Diffraction Enhanced-Computed Tomography Using a Synchrotron Light Source

Alan M. Rosenberg[1], Glendon Rhoades[2], Dean Chapman[3], George Belev[4], Sheldon Wiebe[3], David Cooper[3], Adelaine Wong[3] and Brian Eames[3], [1]Department of Pediatrics, University of Saskatchewan, Saskatoon, SK, Canada, [2]Biomedical Engineering, University of Saskatchewan, Saskatoon, SK, Canada, [3]University of Saskatchewan, Saskatoon, SK, Canada, [4]Canadian Light Source Inc, Ssasatoon, SK, Canada

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Session Title: Imaging of Rheumatic Diseases Poster II: X-ray, MRI, PET and CT

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose:

This project developed a new method for evaluating growing joints by employing diffraction enhanced imaging (DEI) with computed tomography (CT) using a synchrotron light source. DEI is a technique that, compared to conventional radiography, generates more detailed images with a lower radiation dose. DEI develops contrast both from absorption, the process involved in conventional radiography, and from x-ray refraction and diffraction reduction. We show that three-dimensional CT in combination with DEI yields more detailed images than DEI alone or than any other currently available conventional imaging modality. This project, the first to use DEI-CT for imaging intact growing joints, introduces a new tool for studying inflammatory joint diseases during growth.

Methods:

Explanted piglet stifle joints, which are anatomically similar to human knees, were imaged. Joints were from healthy 4-week old piglets which have skeletal maturation equivalent to a 10 month old child. Images were acquired at the Canadian Light Source synchrotron. The DEI-CT scanned slices were "stitched" together forming a three-dimensional (3D) dataset. To compare DEI-CT with other imaging modalities we imaged the stifle joint using planar DEI (with no CT) and conventional radiography, CT and MRI. To begin to explore pathology we imaged joints that were iatrogenically damaged with 200 µm diameter acupuncture needles. Bone and cartilage histology was correlated with DEI-CT features.

Results:

DEI-CT demonstrated bone and soft tissue detail within all joint tissues. Cartilage edges, cartilage-bone interfaces, cortical shell, trabecular bone, and ligaments were clearly displayed. Vascular canals within cartilage and traversing between bone and cartilage, characteristics of growing but not mature joints, were clearly visualized. Resolution of DEI-CT was more detailed than with other imaging modalities. The 200 µm traumatic sites were clearly discerned. Histological assessment confirmed the presence of vascularity in articular cartilage.

Conclusion:

This report documents DEI combined with CT and using synchrotron light yields more detailed 3D images of growing joints than conventional imaging modalities. Using DEI-CT in a large animal model during growth affords opportunities to better characterize both normal and pathologic growth. Studying inflammatory joint diseases in the piglet provides a valuable animal model to study pathology and treatment responses in juvenile arthritis. These results provide a basis and impetus for developing clinically accessible, non-synchrotron based DEI-CT technologies.

Disclosure: A. M. Rosenberg, None; **G. Rhoades**, None; **D. Chapman**, None; **G. Belev**, None; **S. Wiebe**, None; **D. Cooper**, None; **A. Wong**, None; **B. Eames**, None.

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Abstract Number: 1343

Mortality Due to Sepsis in Patients with Rheumatoid Arthritis

Orit Barrett[1], Ella Abramovich[2], Jacob Dreiher[3], Victor Novack[4] and **Mahmoud Abu-Shakra**[5], [1]Department of Medicine D, Soroka Medical Center and Ben-Gurion University, Beersheba, Israel, [2]Department of Medicine D, Soroka University Medical Center and Ben-Gurion University, Beersheba, Israel, [3]Clalit Health Services, Ben-Gurion University of the Negev, Beer Sheva,,, BeerSheba, Israel, [4]Clinical Research Center, Soroka Medical Center and Ben-Gurion University, Beersheba, Israel, [5]Rheumatic Diseases Unit, Soroka Medical Center and Ben-Gurion University, Beer-Sheva, Israel

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SESSION INFORMATION

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Session Title: Infection-related Rheumatic Disease: Poster Session

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: Severe infections contribute significantly to the morbidity and mortality of patients with rheumatoid arthritis.

The aim of the study was to identify the characteristics of patients with RA who were admitted to intensive care unit (ICU) with Sepsis, to determine whether RA is an independent risk factors for short- and long-term mortality in patients admitted to the ICU with sepsis and to identify variables associated with mortality among patients with RA

Methods: The study was based on the data of SEPSIS-ISR, an ongoing prospective study that collects data on all patients admitted the ICUs with the diagnosis of sepsis. 124 patients with RA and sepsis were found in the database.

Controls: Age-and-gender matched controls who were admitted to the ICU with diagnosis of Sepsis were selected in a ratio of 2:1.

Results: The mean age of the patients with RA and control was 71 years with 65% of them were women. The main comorbidity included hypertension (77%), diabetes mellitus (57%), congestive heart failure (35%), renal failure (35%), and chronic lung disease (27%).

Severe sepsis and septic shock were diagnosed in 92% vs. 84% (P=0.032) and 50% vs. 39% (P=0.059) in the RA patients and controls

respectively. Pneumonia (35% vs. 30%) and urinary tract infection (9% vs. 15%) were the most common site of infection.

The 30 days mortality was 48% vs. 43% (P=0.37) in the RA and controls and the 3 years survival was 18% vs. 30% in the RA patients vs. controls (P=0.02).

In univariate analyses Variables associate with 3 years mortality included: RA (OR=2.2, P=0.009), CHF (OR=5.3 P=0.001), DM (OR=2.4 P=0.002), Charlson's Score (OR=1.6 P=0.001), HTN (OR=1.86 P=0.036) and age (OR=1.03, P=0.017)

Multivariate analyses revealed that RA (OR=3.66 P=0.005) and Charlson's score (OR=1.9 P=0.001) were the only variables associated with 3 years mortality

Conclusion: RA is an independent risk factor for adverse results in sepsis including sever sepsis, septic shock and 3 years mortality. Long term survival of patients with RA admitted to the ICU with sepsis is related to higher Charlson's score. Other factors associated with higher mortality rates among patients with sepsis includes CHF, DM, HTN and advanced age.

Disclosure: O. Barrett, None; **E. Abramovich**, None; **J. Dreiher**, None; **V. Novack**, None; **M. Abu-Shakra**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/mortality-due-to-sepsis-in-patients-with-rheumatoid-arthritis

Abstract Number: 1344

The Positive Synovial Fluid Culture: Septic Arthritis or Contamination?

Clara Zhu[1], Mary Louise Fowler[2], Sarah B. Lieber[3], Andrew Moore[4], Robert H. Shmerling[5] and Ziv Paz[3], [1]Medical School, Boston University School of Medicine, Boston, MA, [2]School of Medicine, Boston University School of Medicine, Boston, MA, [3]Beth Israel Deaconess Medical Center, Boston, MA, [4]Medicine, Cambridge Health Alliance, Harvard Medical School, Cambridge, MA, [5]Medicine, Beth Israel Deaconess Medical Center, Boston, MA

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Background/Purpose: Isolation of bacteria from synovial fluid (SF) is the gold standard for the diagnosis of septic arthritis (SA). However, false positive culture results (contamination) can result in misdiagnosis and mismanagement. Little is known about the microbiologic profile of contaminated SF (cSF) cultures, the clinical presentation of such cases, outcomes and rates of alternative diagnoses. The purpose of this study is to characterize the demographic features, clinical characteristics, microbiology and outcomes of patients diagnosed withcSF and to compare them with patients with SA

Methods: We conducted a retrospective study including all patients ages 18 and older admitted to a single, tertiary-case hospital between 1998 and 2015 with suspected SA with positive SF cultures. The diagnosis of cSF was determined by infectious disease specialists involved in the patients' care.

Results: 371 patients with SA and 25 patients with cSF were identified. The groups were significantly different with regard to age (58.9 vs. 68.2; $p<0.01$). The most frequently involved joint was the knee but ankle involvement was relatively more common among those with cSF (Figure 1). The clinical presentations were different between the groups: 35.3% of the patients with SA and 16% of those with cSF presented with fever ($p<0.01$); ESR and CRP were significantly higher in the SA group (76.1 (mm/hr) vs. 52.3 (mm/hr) and 145.3 (mg/L) vs. 64.4 (mg/L) respectively; $p<0.01$ for each comparison). Similarly, the mean SF white blood cell count (in thousands) was higher in the SA group (89.2 vs. 36.7; $p< 0.01$). The mean number of days until the first positive culture results in the group with cSF was 3.2 days. The most common organism identified in the cSF group was coagulase-negative staphylococcus [Figure 2]. The mean length of stay (11 vs. 6.2), ICU admission rates (15.9% vs. 4%) and rates of alternative diagnoses (1.3% vs. 36%) within one year were significantly different ($p<0.01$ for all comparisons) between patients in the SA and cSF groups.

Conclusion: This study suggests that cSF is identified in up to 6% of patients with suspected SA and positive SF cultures . These patients present with less severe disease, better outcomes and an alternative diagnosis in 36% of the cases within one year. The unique characteristics of this group include their less severe presentation and delayed and minimal growth of organisms with low pathogenicity. Based on this study, we recommend a conservative approach for patient with suspected SA with mild disease manifestations and no growth of pathogenic organisms within the first 48 hours.

Figure 1: Distribution of joint involvement in patients with contaminated synovial fluid, in %

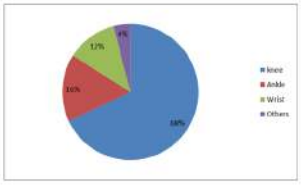
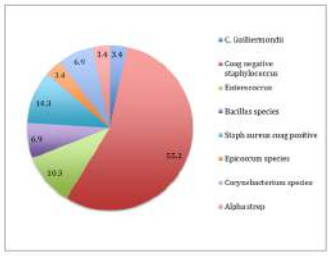


Figure 2: Distribution of bacteria in patients with contaminated synovial fluid, in %



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Abstract Number: 1345

The Impact of Prior Antibiotic Treatment on Culture Results of Patients with Septic Arthritis

Ziv Paz[1], Sarah B. Lieber[1], Andrew Moore[2], Clara Zhu[3], Mary Louise Fowler[4] and Robert H. Shmerling[5], [1]Beth Israel Deaconess Medical Center, Boston, MA, [2]Medicine, Cambridge Health Alliance, Harvard Medical School, Cambridge, MA, [3]Medical School, Boston University School of Medicine, Boston, MA, [4]School of Medicine, Boston University School of Medicine, Boston, MA, [5]Medicine, Beth Israel Deaconess Medical Center, Boston, MA

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Background/Purpose:

Synovial fluid culture and gram stain offer the most compelling proof of septic arthritis (SA); these tests are indicated in every suspected case. However, the sensitivity and specificity of these studies are not well established, especially among patient who have received antibiotic administration prior to synovial fluid sampling. The purpose of this study was to define the impact of prior antibiotic use on synovial fluid gram stain and culture results among patients with septic arthritis.

Methods:

We conducted a retrospective cohort study of patients 18 years and older admitted to a single tertiary care center from 1998 to 2015 with septic monoarthritis. The diagnosis of SA was defined by typical clinical presentation and positive blood culture, synovial gram stain and/or culture. Patients were stratified by the timing of antibiotic use with regard to joint aspiration and whether the involved joint was native or prosthetic.

Results:

Of 338 patients with SA, 207 had native joint involvement. The synovial fluid cultures were positive in 84.6% of cases while synovial fluid gram stain was positive in only 35%. Prior antibiotic use was associated with a significant reduction in synovial fluid culture positivity (90.5% without prior antibiotics vs. 67.5% with prior antibiotics; $p<0.01$) (Tables 1 and 2). There was no significant difference in the rate of gram stain positivity based on prior antibiotic treatment although there was a trend toward fewer positive gram stain results among those receiving prior antibiotics (Table 1).

Conclusion:

While it is well-known that prior antibiotic administration may affect the results of synovial fluid culture and gram stain, this is one of the few large studies that quantitate these effects. We found the most dramatic impact of prior antibiotic administration is a reduction of synovial fluid culture positivity. Further analysis is ongoing to assess the timing of prior antibiotic therapy on synovial fluid culture and gram stain results in SA.

Table 1: Culture results of septic native joint monoarthritis stratified by timing of antibiotics administration.

	Antibiotic treatment prior to joint aspiration (N= 80)	Antibiotic treatment after joint aspiration (N= 127)	P- value
Positive synovial fluid cultures, N (%)	54 (67.5)	115 (90.5)	<0.01
Positive synovial fluid gram stain, N (%)	22 (27.5)	50 (39.3)	0.14

Table 2: Culture results of septic prosthetic joint monoarthritis stratified by timing of antibiotics administration.

	Antibiotic treatment prior to joint aspiration(N=46)	Antibiotic treatment after joint aspiration (N=85)	P-value
Positive synovial fluid cultures, N (%)	34 (73.9)	77 (90.5)	0.02
Positive synovial fluid gram stain, N (%)	15 (32.6)	27 (31.7)	0.38

Disclosure: Z. Paz, None; **S. B. Lieber**, None; **A. Moore**, None; **C. Zhu**, None; **M. L. Fowler**, None; **R. H. Shmerling**, None.

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Abstract Number: 1346

The Presentation and Outcomes of Surgically Treated Septic Arthritis: the Impact of Culture Results

Ziv Paz[1], Mary Louise Fowler[2], Clara Zhu[3], Sarah B. Lieber[1], Andrew Moore[4] and Robert H. Shmerling[5], [1]Beth Israel Deaconess Medical Center, Boston, MA, [2]School of Medicine, Boston University School of Medicine, Boston, MA, [3]Medical School, Boston University School of Medicine, Boston, MA, [4]Medicine, Cambridge Health Alliance, Harvard Medical School, Cambridge, MA, [5]Medicine, Beth Israel Deaconess Medical Center, Boston, MA

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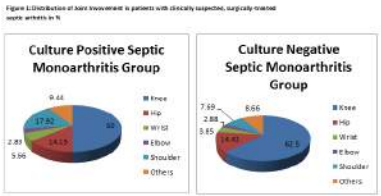
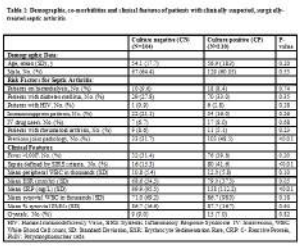
Background/Purpose: Clinically-suspected septic arthritis is culture-negative in 18-43% of cases. These patients are often treated surgically with associated morbidity, prolonged hospital stays and high medical costs. Patients with culture-negative (CN) septic arthritis may differ in important ways from their culture-positive (CP) counterparts, including the possibility that such patients could be successfully managed without surgery. The purpose of our study is to compare the clinical characteristics and outcomes between CN and CP patients with surgically-treated septic arthritis.

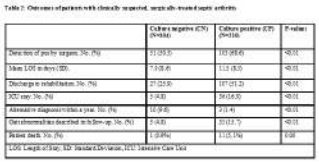
Methods: We conducted a retrospective study that included all patients ages 18 and older admitted to a single, tertiary-care hospital between 1998 and 2015 who were diagnosed with monoarticular septic arthritis and were treated with antibiotics and surgery. We excluded all cases of osteomyelitis and polyarticular or prosthetic joint infection.

Results: Of 314 patients with clinically suspected and surgically treated septic arthritis, 104 were CN and 210 were CP. The groups were similar with regard to age, gender and presence of associated comorbidities [Table 1]. Though, significantly more CP patients had known, pre-existing joint pathology (p=0.003). The most common joint affected was the knee, which was more frequently involved in the CN group (p=0.03), while the shoulder was more often involved in the CP group (p=0.01) [Figure 1]. The clinical presentations and outcomes differed significantly between the two groups with more severe disease [Table 1] and less favorable outcomes [Table 2] noted among those in the CP group. Nearly 10% of patients in the CN group were diagnosed with another cause of inflammatory arthritis within one year of follow-up.

Conclusion: This study suggests that patients presenting with suspected septic arthritis have less severe disease and better outcomes when their synovial fluid cultures are negative. Many CN patients are diagnosed with another cause of inflammatory arthritis in follow-up. Non-surgical treatment may be appropriate for patients with suspected septic arthritis when synovial fluid cultures are negative.







Disclosure: Z. Paz, None; **M. L. Fowler**, None; **C. Zhu**, None; **S. B. Lieber**, None; **A. Moore**, None; **R. H. Shmerling**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/the-presentation-and-outcomes-of-surgically-treated-septic-arthritis-the-impact-of-culture-results

Abstract Number: 1347

The Presentations and Outcomes of Prosthetic Joint Septic Arthritis: a Comparison of Culture-Positive and Culture-Negative Disease

Ziv Paz[1], Sarah B. Lieber[1], Andrew Moore[2], Clara Zhu[3], Robert H. Shmerling[4] and Mary Louise Fowler[5], [1]Beth Israel Deaconess Medical Center, Boston, MA, [2]Medicine, Cambridge Health Alliance, Harvard Medical School, Cambridge, MA, [3]Medical School, Boston University School of Medicine, Boston, MA, [4]Medicine, Beth Israel Deaconess Medical Center, Boston, MA, [5]School of Medicine, Boston University School of Medicine, Boston, MA

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Session Time: 9:00AM-11:00AM

Background/Purpose: Prosthetic joint septic arthritis (PJSA) may complicate joint replacement in approximately 1-2% of cases. Synovial fluid cultures are negative in up to 25% of cases making the diagnosis of PJSA and its management challenging. Most patients with suspected, but culture-negative (CN), PJSA are managed similarly to their culture positive (CP) counterparts. We hypothesized that

patients with CN PJSA are different in their clinical course and outcomes and might warrant a more conservative approach. The purpose of this study was to compare the demographic features, clinical characteristics and outcomes of CN and CP PJSA.

Methods: We conducted a retrospective study including all patients ages 18 and older admitted to a single, tertiary-care hospital between 1998 and 2015 diagnosed with PJSA and treated with antibiotics and surgery. We excluded all cases of osteomyelitis, polyarticular or native joint infection.

Results: 220 patients with PJSA were identified; 61 were CN and 161 were CP and all received antibiotic therapy and surgery. The groups were similar with regard to age and presence of associated comorbidities; however, there was a male predominance in the CP group (p=0.013) [Table 1]. The most frequently involved joint was the knee, particularly in the CN group (p=0.001); hip involvement was relatively more common in the CP group (p=0.005) [Figure 1]. The clinical presentations and outcomes differed significantly between the two groups, with less severe disease [Table 1] and better outcomes [Table 2] noted among those in the CN group. In addition, the CN patients with PJSA tended to have a shorter hospital stay (p=0.06) and more alternative diagnoses established within one year (p=0.08).

Conclusion: This study suggests that patients with CN PJSA have less severe disease and a trend toward better outcomes. Our observations support the need for a prospective, randomized trial of patients with CN PJSA comparing the outcomes of surgical and non-surgical management.

Figure 1: Distribution of Joint Involvement in patients with clinically suspected, surgically-treated septic arthritis in % [Note: in culture negative group n=0 for elbow and wrist; in culture positive group n=0 for wrist.]

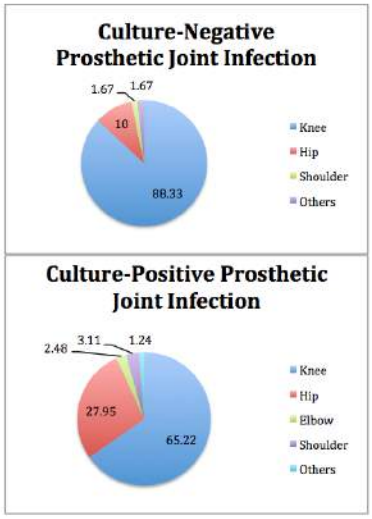

Table 2: Outcomes of patients diagnosed with septic arthritis distinguished by culture results

	Culture negative (N=61)	Culture positive (N=161)	P-value
Prosthetic joint removed, N (%)	19 (31.7)	73 (45.3)	0.07
Observation of pus by surgeon, N (%)	14 (23.3)	79 (49.1)	<0.01
Mean LOS in days,(SD)	8.3 (4.9)	10.4 (7.7)	0.06
Discharge to rehabilitation facility, N (%)	31 (51.7)	104 (64.6)	0.24
ICU stay, N (%)	4 (6.7)	23 (14.3)	0.17
Alternative Diagnosis Within One Year, N (%)	4 (6.7)	2 (1.2)	0.09
Gait Abnormalities as Described in Follow-Up Visits, N (%)	3 (5.2)	51 (37.2)	<0.01
Limited Range of Motion as Described in Follow-Up Visits, N (%)	23 (39.7)	56 (40.1)	<0.01
Expiration, N (%)	1 (1.7)	4 (2.5)	1.00

Conservative measures include antibiotics and serial joint taps; SD: Standard Deviation, LOS: Length of Stay, ICU: Intensive Care Unit

Table 1: Demographic, co-morbidities, and clinical features of patients with prosthetic joints and clinically suspected, surgically-treated septic arthritis

	Culture negative (CN) (N=61)	Culture positive (CP) (N=161)	P-value
Demographic Data:			
Age, mean (SD), y	62.6 (10.9)	61.6 (15.3)	0.65
Male, N (%)	20 (33.3)	84 (52.2)	0.01
Risk Factors for Septic Arthritis:			
Patients with diabetes mellitus, N (%)	20 (33.3)	48 (29.8)	0.61
Patients with HIV, N (%)	0 (0)	6 (3.7)	0.13
Immunosuppress patients, N (%)	6 (10.0)	17 (10.6)	0.90
IV drug users. N (%)	3 (5.0)	7 (4.4)	1.00
Patients with RA, N (%)	6 (10.0)	9 (5.6)	0.25
Previous septic arthritis, N (%)	9 (15.0)	38 (23.6)	0.17
Clinical Features			
Patients with fever >100F, N (%)	11 (18.3)	55 (34.2)	<0.01
Patients with sepsis defined by SIRS criteria, N (%)	7 (11.7)	42 (26.1)	<0.01
Mean Peripheral WBC in thousands (SD)	10.3 (4.9)	11.5 (5.1)	0.13
Mean Peripheral PMN (SD)	73.8 (12.0)	77.4 (10.7)	0.04
Mean ESR (mm/hr) (SD)	72.7 (33.1)	72.5 (37.5)	0.97
Mean CRP (mg/L) (SD)	95.3 (75.2)	128.9 (107.1)	0.06
Mean synovial WBC in thousands (SD)	26.7 (31.5)	92.5 (124.4)	<0.01
Mean % synovial PMN (SD)	76.6 (25.0)	89.7 (14.5)	<0.01
Crystals. N (%)	0 (0)	3 (1.9)	0.02

SD: Standard Deviation, HIV: Human Immunodeficiency Virus, RA: rheumatoid arthritis, SIRS: Systemic Inflammatory Response Syndrome IV: Intravenous, WBC: White Blood Cell count, PMN: Polymorph- ESR: Erythrocyte Sedimentation Rate, CRP: C- Reactive Protein

Disclosure: **Z. Paz**, None; **S. B. Lieber**, None; **A. Moore**, None; **C. Zhu**, None; **R. H. Shmerling**, None; **M. L. Fowler**, None.

Abstract Number: 1348

Clinical Characteristics and Outcomes of Patients with Septic Arthritis Treated without Surgery

Sarah B. Lieber[1], Andrew Moore[2], Clara Zhu[3], Robert H. Shmerling[4], Mary Louise Fowler[5] and Ziv Paz[1], [1]Beth Israel Deaconess Medical Center, Boston, MA, [2]Medicine, Cambridge Health Alliance, Harvard Medical School, Cambridge, MA, [3]Medical School, Boston University School of Medicine, Boston, MA, [4]Medicine, Beth Israel Deaconess Medical Center, Boston, MA, [5]School of Medicine, Boston University School of Medicine, Boston, MA

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Background/Purpose:

Septic arthritis (SA) is typically managed with antibiotics and surgery, though nonsurgical management may be appropriate in certain

circumstances. Little is known about how patients treated for SA with antibiotic therapy alone differ from their operatively managed counterparts. The purpose of this study is to compare clinical characteristics and outcomes of patients with SA managed with or without surgery.

Methods:

We conducted a retrospective cohort study of patients 18 years and older admitted to a single tertiary care center from 1998 to 2015 with culture-positive septic monoarthritis. Patients were stratified into operatively (OR+) and non-operatively (OR-) managed groups. Microbial profile, predisposing factors, sites of joint involvement, length of hospital stay (LOS), and 60-day readmission rate were determined.

Results:

434 patients with culture-positive SA were identified; 50 were OR- and 384 were OR+. In the OR- group, 45 patients were not offered surgery by the consulting surgeon while 5 patients declined surgery that had been recommended. The OR+ patients were older (63.8 vs. 58.6 years old; p =0.04) and the OR+ group had more pre-infection joint pathology (p<0.01); otherwise, the groups were similar with respect to baseline comorbidities [Table 1]. Prosthetic joint involvement was more commonly observed in the OR+ group (p<0.01). The knee was the most commonly involved joint in both groups, though more predominant in the OR+ group (p=0.01), and relatively more wrist involvement was noted in the OR- group (p<0.01) [Table 1]. The most commonly isolated organisms were methicillin-sensitive Staph aureus and methicillin-resistant Staph aureus. Clinical presentations and outcomes differed significantly between groups, with more severe disease [Table 1] and worse outcomes [Table 2] noted among those in the OR- group. All patients in the OR- group with prosthetic joint involvement (n=10) survived.

Conclusion:

On the basis of this large retrospective study**,** patients with culture-positive SA who were not taken to the operating room appeared to be much sicker than those who underwent surgery. Despite this, most survived, including all of those with prosthetic joint involvement. Based on these findings, future research should include randomized trials comparing conservative and operative therapy in selected patients with SA.

Table 1: Demographic and clinical features of patients with culture-positive monoarthritis stratified by operation status

	Operation Negative (OR-) (N=50)	Operation positive (OR+) (N=384)	P-value
Demographic Data:			
Age, mean (SD), y	63.8 (17.8)	58.6 (17.2)	0.04
Male, N (%)	25 (50)	168 (43.8)	0.01
Risk Factors for Septic Arthritis:			
Patients with diabetes mellitus, N (%)	20 (40)	122 (31.5)	0.22
Patients with HIV, N (%)	2(4)	12(3.1)	0.15
Immunosuppressed patients, N (%)	7 (14.0)	51 (13.1)	0.87
IV drug use, N (%)	1(2.0)	27 (6.9)	0.17
Patients with RA, N (%)	5(10.0)	21 (5.4)	0.19
History of joint pathology, N (%)	21 (42)	259 (66.9)	<0.01
Previous septic arthritis, N (%)	6 (12.0)	75 (19.3)	0.20
Joint involvement			
Native joint, N (%)	40 (80)	226 (58.4)	<0.01
Knee involvement, N (%)	19 (38.0)	258 (66.3)	0.01
Hip involvement, N (%)	7 (14.0)	79 (20)	0.28
Wrist involvement, N (%)	8 (16.0)	12 (3.1)	<0.01
Shoulder involvement, N (%)	9 (18.0)	45 (11.6)	0.19
Clinical Features			
Patients with fever >100F, N (%)	23 (46.0)	136 (35.1)	0.06
Patients with sepsis defined by SIRS criteria, N (%)	21 (42.0)	120 (30.7)	0.04
Mean Peripheral WBC in thousands (SD)	11.8(5.3)	13.7(5.5)	0.04
Mean Peripheral PMN (SD)	79.2(9.5)	77.9(10.7)	0.44
Mean ESR (mm/hr) (SD)	75 (41.4)	76.1 (27.3)	0.87
Mean CRP (mg/L) (SD)	122.3 (84.1)	144.2 (109.9)	0.35
Mean % synovial PMN (SD)	79.1 (14.1)	88.4 (15.8)	<0.01
Crystals, N (%)	7 (14)	19 (5.1)	0.04

SD: Standard Deviation, HIV: Human Immunodeficiency Virus, RA: rheumatoid arthritis, SIRS: Systemic Inflammatory Response Syndrome IV: Intravenous, WBC: White Blood Cell count, PMN: Polymorph - ESR: Erythrocyte Sedimentation Rate, CRP: C- Reactive Protein

Table 2: Outcomes of patients with culture-positive monoarthirtis stratified by operation status

	Operation Negative (OR-) (N=50)	Operation positive (OR+) (N=384)	P-value
Mean LOS in days,(SD)	10.5 (9.4)	10.49 (8.1)	0.72
Discharge to rehabilitation facility, N (%)	19 (39.5)	215 (55.5)	<0.01
ICU stay, N (%)	14 (28.0)	60 (15.5)	<0.01
Re-admission within 60 days, N (%)	8 (16)	74(19.1)	0.11
Expiration, N (%)	6 (12)	15 (3.8)	0.01

Conservative measures include antibiotics and serial joint taps; SD: Standard Deviation, LOS: Length of Hospital Stay, ICU: Intensive Care Unit

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Disclosure: S. B. Lieber, None; **A. Moore**, None; **C. Zhu**, None; **R. H. Shmerling**, None; **M. L. Fowler**, None; **Z. Paz**, None.

Abstract Number: 1349

Clinical Characteristics and Outcomes of Septic Bursitis

Sarah B. Lieber[1], Clara Zhu[2], Mary Louise Fowler[3], Andrew Moore[4], Robert H. Shmerling[5] and Ziv Paz[1], [1]Beth Israel Deaconess Medical Center, Boston, MA, [2]Medical School, Boston University School of Medicine, Boston, MA, [3]School of Medicine, Boston University School of Medicine, Boston, MA, [4]Medicine, Cambridge Health Alliance, Harvard Medical School, Cambridge, MA, [5]Medicine, Beth Israel Deaconess Medical Center, Boston, MA
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Background/Purpose:

Septic bursitis (SB) is a common condition that typically involves the olecranon and patellar bursae. It is unclear whether patients with SB treated surgically differ in their clinical presentation and outcomes from patients treated with antibiotics alone. Furthermore, it is unknown if preceding trauma is a risk factor for more severe disease and higher rates of surgical intervention. Finally, the factors distinguishing patients with olecranon SB from those with patellar involvement are not well understood. The purpose of this study is to describe the clinical features and outcomes of patients with SB and to address these uncertainties.

Methods:

We conducted a retrospective cohort study of patients 18 years and older admitted to a single tertiary care center from 1998 to 2015 with culture-proven olecranon and patellar (including prepatellar and infrapatellar) SB. Patients with concurrent septic arthritis or sterile bursal fluid cultures were excluded. Baseline characteristics and clinical features, microbial profile, rate of operative intervention, length of hospital stay (LOS), and 60-day readmission rate were determined. Patients were stratified by site of SB, presence or absence of preceding bursal trauma, and operative or non-operative management.

Results:

Of 44 cases of SB, 31 involved the olecranon bursa and 13 affected the patellar bursae. Patients with olecranon and patellar SB were similar with respect to age, male predominance and frequency of preceding bursal trauma. However, patients managed operatively were younger (mean 42.4 vs. 57.7 years; $p = 0.05$), as were those without preceding bursal trauma (mean 51.1 vs. 62.6 years; $p = 0.05$). Clinical features at presentation and presence of comorbidities were similar when patients were stratified by site of SB, history of preceding bursal trauma, or management strategy. The most common organisms isolated from bursal fluid were methicillin-sensitive Staph aureus (MSSA), methicillin-resistant Staph aureus (MRSA), and coagulase negative Staph. Patients managed operatively were discharged to rehabilitation less frequently ($p=0.04$) and had a lower rate of 60-day readmission than their conservatively managed peers ($p = 0.05$). A trend toward shorter mean LOS was observed among patients with preceding bursal trauma as compared to those without trauma (4.4 vs. 10.4 days; $p = 0.07$).

Conclusion:

In this study of SB, we were unable to identify factors that differentiate patients treated surgically from those treated conservatively. Similarly, there was no clear relationship between preceding trauma or site of SB and clinical course, management, or outcomes. Patients with SB treated surgically tended to be younger and have lower readmission rates. Additional study is needed to identify patients who would benefit from early surgical intervention for SB.

Disclosure: S. B. Lieber, None; **C. Zhu**, None; **M. L. Fowler**, None; **A. Moore**, None; **R. H. Shmerling**, None; **Z. Paz**, None.

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Abstract Number: 1350

Multi-Targeted Loop-Mediated Isothermal Amplification for Rapid Diagnosis of Osteoarticular Tuberculosis in 60 Minutes: Experience from North India

Kusum Sharma[1], Aman Sharma[2] and Mandeep Dhillon[3], [1]Department of Medical Microbiology,, PGIMER,, Chandigarh, India, [2]Internal Medicine, Postgraduate Institute of Medical Education and Research, Chandigarh, India, [3]Department of Ortho[aedics,, PGIMER,, Chandigarh, India

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Background/Purpose: Loop-mediated Isothermal Amplification (LAMP) is a promising nucleic-acid amplification assay. Prompt and accurate diagnosis of Osteoarticular tuberculosis (OATB) is required for early treatment, better patient outcomes and to prevent further joint destruction.The objective of the present study was to evaluate the LAMP test using IS6110 and MPB64 targets specific for *Mycobacterium tuberculosis* complex for rapid diagnosis of OATB. Comparison of results of IS6110 LAMP, MPB64 LAMP test with IS6110 PCR, culture and AFB smear

Methods:

LAMP assay using six pairs of primers (each for IS6110 and MPB64) specific for *Mycobacterium tuberculosis* were performed on synovial fluid/pus samples of 90 patients(10 confirmed, 80 suspected) of OATB and 30 non tuberculosis controls subjects.

Results:

Overall LAMP test (using any of two targets) had sensitivity and specificity of 100% for confirmed OATB cases. In 80 clinically diagnosed but unconfirmed OATB cases LAMP was positive in 71/80 (88.75%) cases. Senstivity of IS6110 LAMP, MPB64 LAMP and IS6110 PCR in clinically unconfirmed OATB cases was 81.75% (65/80), 86.25% (69/80) and 72.5%(58/80) respectively. The overall sensitivity of microscopy, culture, IS6110 PCR, IS6110LAMP, MPB64 LAMP and LAMP test (if any of the targets were used) were 3.33%, 11.1%, 73.33%, 83.33%, 87.77% and 90% respectively. Specificity of all the tests were100%.There were 4 cases which were missed by IS6110 LAMP assay and 2 cases were missed by MPB64 LAMP assay.

Conclusion:

LAMP assay using two targets is promising technique for rapid diagnosis of OATB in 60 minutes.

Disclosure: K. Sharma, None; **A. Sharma**, None; **M. Dhillon**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/multi-targeted-loop-mediated-isothermal-amplification-for-rapid-diagnosis-of-osteoarticular-tuberculosis-in-60-minutes-experience-from-north-india

Abstract Number: 1351

Long-Term Efficacy of Latent Tuberculosis Infection Screening in Juvenile Idiopathic Arthritis Patients Prior to Anti-TNF Treatment in an Endemic Area

Juliana Brunelli[1], Karina Bonfiglioli[2,3], Clovis A Silva[4], Katia T. Kozu[5], Cláudia Goldenstein-Schainberg[6], Eloisa Bonfá[1] and **Nadia E Aikawa**[4], [1]Rheumatology, Faculdade de Medicina da Universidade de São Paulo, Sao Paulo, Brazil, [2]Rheumatology Division, Faculdade de Medicina da Universidade de São Paulo, Sao Paulo, Brazil, [3]Rheumatology Division, Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil, [4]Pediatric Rheumatology, Faculdade de Medicina da Universidade de São Paulo, Sao Paulo, Brazil, [5]Pediatrics, Faculdade de Medicina da Universidade de São Paulo, Sao Paulo, Brazil, [6]Clínica Médica, Faculdade de Medicina da Universidade de São Paulo, Sao Paulo, Brazil

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Background/Purpose: We have demonstrated previously that latent tuberculosis infection (LTBI) screening is effective in adult rheumatoid arthritis (RA) patients prior to anti-TNF treatment. One study suggested that prevention of tuberculosis in JIA children receiving etanercept is efficient. However, the short-term evaluation and the absence of data regarding other TNF blockage classes precludes a definitive conclusion, particularly taking into consideration that a recent population-based study reported that tuberculosis (TB) risk is significantly higher in JIA patients. Objectives: To evaluate, in an endemic country, the long-term efficacy of LTBI screening and primary prophylaxis in patients with JIA receiving TNF blockers.

Methods: This was a prospective study that included JIA patients (ILAR classification criteria) regularly followed in the Rheumatology outpatient clinic of a tertiary university hospital of Sao Paulo city, Brazil and who were refractory to non-biologic DMARDs and were eligible to anti-TNF therapy. Patients were evaluated for disease activity before starting TNF inhibitor using Juvenile Arthritis Disease Activity Score (JADAS) (patients <19 years old) or Disease Activity Score 28-Joint Counts (DAS28) (patients ≥19 years old). All patients were screened for LTBI prior to anti-TNF treatment using the tuberculin skin test (TST), chest X-ray and history of exposure to TB. When indicated computerized chest tomography was performed. All subjects were regularly followed at 1- to 3-month intervals.

Results: Sixty-nine JIA patients were included and all patients were vaccinated with BCG during neonatal period. They had current age of 17.4 ± 5.8 years, 24 (34.8%) were males and the mean disease duration until anti-TNF initiation was 5.0 ± 4.9 years. Sixty-three (91.3%) patients were under NSAIDs, 31 (44.9%) prednisone, 60 (86.9%) methotrexate, 23 (33.3%) leflunomide and 13 (18.8%) cyclosporine. At baseline, JADAS was 13.4 ± 8.4 and DAS28 3.8 (1.9-6.1). Forty-seven (68.1%) patients were treated with a single anti-TNF agent, while 22 (31.9%) patients switched to another anti-TNF agent once or twice. At the end of follow-up, 33 (47.8%) patients had received adalimumab, 57 (82.6%) etanercept and 3 (4.3%) infliximab. LTBI screening was positive in three (4.3%) JIA patients: one had TST-positive and history of TB exposure and two had solely TST-positive. During follow-up, TST was repeated in two patients due to a long period (> 1 year) of anti-TNF interruption, and TST conversion was observed in one of them. LTBI patients were treated with isoniazid (10mg/Kg/day, up to 300mg/day) for 6 months, and none of them had TB. No active TB was diagnosed during the study period (median of follow-up during anti-TNF therapy was 7.9 years).

Conclusion: The frequency of LTBI in middle class JIA was low. Long-term evaluation revealed that LTBI screening and primary prophylaxis before anti-TNF treatment were effective and TST was the most sensitive parameter to identify these patients.

Disclosure: J. Brunelli, None; **K. Bonfiglioli**, None; **C. A. Silva**, None, 2; **K. T. Kozu**, None; **C. Goldenstein-Schainberg**, None; **E. Bonfá**, None, 2; **N. E. Aikawa**, None.

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Abstract Number: 1352

How Frequently Does Tuberculosis Screening Test Become Positive in Rheumatic Patients Treated with ANTI-Tumor Necrosis Factor-ALPHA Therapy? an Analysis of Risk Factors

Jorge Gaspar Ramos[1], Dafhne Miranda[2], Pilar Cruz-Dominguez[3], Luis Javier Jara[4] and Miguel A. Saavedra[5], [1]Rheumatology, Hospital de Especialidades, Dr. Antonio Fraga Mouret, Centro Medico Nacional La Raza, IMSS, Mexico City, Mexico, [2]Rheumatology, Rheumatology Unit, Hospital de Especialidades. Centro Médico La Raza, IMSS, Distrito federal, Mexico, [3]Centro Médico Nacional La Raza IMSS, México, Mexico, [4]Instituto Mexicano del Seguro Social, Mexico City, Mexico, [5]Reumatología, Centro Médico Nacional La Raza IMSS, México DF., México D.F., Mexico

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Background/Purpose: Anti-tumor necrosis factor-α (TNF-α) therapy is associated with an increased risk of mycobacterium tuberculosis infection. Tuberculosis (TB) reactivation can lead to severe complications in patients treated with anti-TNF-α therapy. There is little information regarding the reliability of repeated tuberculin skin tests (TST) in patients with rheumatic diseases on anti-TNF-α therapy. The aim was to assess the usefulness of repeat tuberculosis screening tests in patients with rheumatoid arthritis (RA), ankylosing spondylitis (AS), and psoriatic arthritis (PsA) on anti-TNF-α therapy, and to identify risk factors associated to positive TST conversion.

Methods: We performed a case-control retrospective study nested in a cohort of patients with rheumatic diseases on prolonged anti-TNF-α therapy (≥12 months) with baseline negative TST. The study period was from January 2009 to December 2014. Patients with at least one new TST ≥12 months on anti-TNF-α therapy were included. The patients were allocated in two groups: Group I, patients with positive TST (induration size ≥5 mm after 48-72 hours), and Group 2, patients with negative TST. We analyzed baseline variables that potentially had predictive value for TST conversion, including age, sex, rheumatic diseases, DMARD's therapy, glucocorticoid use, previous TB exposure, BCG vaccination, and anti-TNFα therapy. The statistical analysis included t-test and Chi square test. A logistic regression analysis was performed and odd ratios (OR) were calculated.

Results: We included 105 patients, 47 (56.6%) were female. The mean age was 44.3±11.1 years. The diagnoses included RA (n=53), AS (n=46), and PsA (n=6). Twenty-six patients (24.7%) had positive TST conversion. We observed a significant difference in disease evolution between Group 1 (95.42 ± 51.45 months) and Group 2 (140.66 ±104.3 months) (p=0.036). In the logistic regression analysis, infliximab use was the only associated variable with positive TST conversion (OR 2.2 [IC 95% 1.1-4.2], p=0.01) (Table).

Conclusion: Our study shows that about 25% of patients on anti-TNF-α treatment developed positive TST conversion. The incidence rate of positive TST conversion in patients on anti-TNF-α therapy seems to be high in our population, especially with the use of infliximab. The TST should be recommended in high risk population on anti-TNF-α during follow-up.

anti-TNF-α therapy		**Group 1 (TST +) n=26**	**Group 2 (TST -) n=79**	**OR (CI 95%)**	**p**
Adalimumab n (%)		5(20)	20(80)	1.07 (0.52-2.23)	0.839
Etanercept n (%)		6(16.7)	30(83.3)	0.86 (0.42-1.74)	0.680
Infliximab n (%)		15(34.1)	29(65.9)	2.2 (1.17-4.25)	0.015

Disclosure: J. G. Ramos, None; **D. Miranda**, None; **P. Cruz-Dominguez**, None; **L. J. Jara**, None; **M. A. Saavedra**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/how-frequently-does-tuberculosis-screening-test-become-positive-in-rheumatic-patients-treated-with-anti-tumor-necrosis-factor-alpha-therapy-an-analysis-of-risk-factors

Abstract Number: 1354

Whipple's Disease: The Diagnostic Utility of Synovial Fluid Tropheryma Whipplei Polymerase Chain Reaction

Zoran Kvrgic[1], Kelly Cawcutt[2], Robin Patel[3], Abinash Virk[2], Clement J. Michet Jr.[4], Eric L. Matteson[5] and Tim Bongartz[1], [1]Rheumatology, Mayo Clinic, Rochester, MN, [2]Infectious Diseases, Mayo Clinic, Rochester, MN, [3]Medicine, Mayo Clinic, Rochester, MN, [4]Mayo Clinic, Rochester, MN, [5]Division of Rheumatology, Department of Internal Medicine and Department of Health Sciences Research, Mayo Clinic, Rochester, MN

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Background/Purpose:

Inflammatory arthritis is a common, non-specific symptom of Whipple's disease. Recovery of the organism by conventional culture is often unsuccessful. Synovial fluid polymerase chain reaction (PCR) testing for *Tropheryma whippelii* may increase the diagnostic yield; however the diagnostic specificity of this approach is unclear. A high rate of detection of *T. whipplei* PCR in saliva of healthy individuals has been reported. To date, there has been no study of the performance of PCR for *T. whippelii* in synovial fluid PCR.

Therefore, we aimed to summarize our experience with a *T. whippelii* synovial fluid PCR test in patients seen at a single referral center and clarify whether utilization of this test in patients with inflammatory arthritis would result in a high rate of false-positive results.

Methods:

DNA was extracted from synovial fluid using the automated MagNA Pure LC instrument. Real-time PCR with FRET probe detection, targeting the heat shock protein gene of *T. whipplei*, was performed on amplified DNA. The total number of patients who had synovial fluid PCR testing for *T. whippelii* between 01/01/2003-04/01/2015 was determined using the clinical microbiology database. A detailed chart review was performed for all patients with positive PCR results. All patients were followed up for a minimum of one year.

Results:

Over the past 12 years, 302 patients underwent synovial fluid PCR testing for *T. whippelii* at our institution. The PCR was positive in only 4 patients. All PCR positive patients were middle-aged males who presented with chronic inflammatory arthritis and a variety of additional symptoms including fever, malaise, and peripheral edema and generalized weakness. They had been diagnosed and treated with various immunosuppressive drugs or antiinflammatories unsuccessfully. Small bowel biopsy to identify the organism was undertaken in 2 of the 4 patients with positive synovial fluid PCR. Tissue samples from these biopsies were negative for periodic acid Schiff stain (PAS) positive macrophages and by *T. whippelii* PCR.

All synovial fluid PCR positive patients (including the 2 with negative small bowel biopsies) were diagnosed with Whipple's disease by their medical team and subsequently treated with antibiotics (ceftriaxone 2g IV q24 for 2-4 weeks followed by trimethoprim-sulfamethoxazole 160/800 mg 1 tablet twice daily for 1 year), resulting in complete resolution of symptoms in all patients. No recurrences occurred during the follow-up period of at least 1 year.

Conclusion:

Our experience suggests that *T. whippelii* synovial fluid PCR testing in patients with inflammatory arthritis is a highly specific test for Whipple's disease. All patients who tested positive in our cohort had symptoms consistent with a diagnosis of Whipple's disease, had previously been unsuccessfully treated with immunosuppressive therapies, and had a dramatic and complete improvement after starting antibiotic therapy. No recurrences/alternative diagnoses emerged during the follow-up period. Synovial fluid PCR testing for *T. whippelii* appears to be a valuable diagnostic test in patients with inflammatory arthritis and suspected Whipple's disease even when the stain for PAS positive macrophages on small bowel biopsy is negative.

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View Abstract and Citation Information Online - http://acrabstracts.org/abstract/whipples-disease-the-diagnostic-utility-of-synovial-fluid-tropheryma-whipplei-polymerase-chain-reaction

Abstract Number: 1355

Ankle Periarthritis, a New Sign for Chikungunya : Ultrasound Study of Joint Lesions at the Acute Phase of Chikungunya

Lauren Brunier-Agot[1], Michel DeBandt[2], George Jean-Baptiste[3], Regis Duvauferrier[3], Catherine Lebris[3] and Andre Cabié[4], [1]Internal medicine and rheumatology, Zobda Quitman Hospital, Fort de France, Martinique, [2]Medicine, Abstract Medical Int'l, Boulogne, France, [3]Chu de Martinique, Fort de France, France, [4]infectious disease, Zobda Quitman Hospital, Fort de France, Martinique
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Background/Purpose: Chikungunya (CHIK) is a viral disease transmitted by the Aedes mosquito. The acute phase of the disease combines: fever, fatigue, arthralgia, arthritis, rash . Studies of humans and animal models have shown that disease signs and symptoms following infection are associated with viral infection of cells in musculoskeletal tissues, such as fibroblasts and osteoblasts, and infiltration of inflammatory cells.

Joint imaging studies in CHIK are rare, except one from Manimunda (3), showing joint effusion, bone edema, synovial thickening, tenosynovitis and erosions on MRI in patients with persistent pain beyond one month after the acute episode.

There are no data with ultrasound imaging.

Ultrasound showed interest in early diagnosis of rheumatoid arthritis (RA), by analogy between these two diseases (RA / Chik) we hypothesized that ultrasound could be relevant to study articular and juxta articular damage in early CHIK.

The EchoCHIK study is a prospective study part of the context of studies of CHIK - during the epidemy that began in Martinique in January 2014- aiming at describing ultrasound aspects of CHIK. Preliminary results allow a description of joint involvement during the acute phase.

Methods: patients with arthralgias and / or arthritis related to CHIK for less than 10 days were included. Confirmation of the diagnosis was made by serology or PCR. Exclusion criteria were: history of chronic inflammatory rheumatic disease, concomitant use of NSAIDs or steroids. Demographic data were recorded and clinical examination was performed by a rheumatologist. Joint ultrasound of the 3 most painful and / or swollen joints was performed in B-mode and Doppler power research, looking for subcutaneous infiltration, effusion, tenosynovitis, erosion and Doppler signal.

Results: 28 patients were enrolled, including 19 women and 9 men with a mean age of 50.75 years and mean diseases duration of 6.15 days.

At baseline, all patients had arthritis, 18 patients had fatigue, 12 had myalgia and 3 had a fever.

Mean VAS was 38.7, the average number of painful joints was 6.2 and the average number of swollen joints was 3.3.

Joint effusion and /or synovial hypertrophy were present in 92.8% of studied joints, with hand and wrist in 75%, ankle 50%, knees 35.7%, mostly unilateral (in 75% of cases). A positive Doppler signal was found in 28.3% of effusions.

Tenosynovitis were found in 2 patients only (unilateral in 1, bilateral in 2). None had erosion at that early visit.

Subcutaneous infiltration with ankles periarthritis was present in 28.6% of patients, unilateral in 3 and bilateral in 5.

2/28 patients with a confirmed diagnosis of CHIK had a normal ultrasound examination.

Conclusion: Ankle periarthritis has been described during acute sarcoïdosis in association with erythema nodosum. It's the first time ankle periarthritis is described with another acute arthritis. In epidemic situation of CHIK this finding may help the clinician diagnosis.

We describe for the first time ankle periarthritis as a new sign for acute Chik arthritis.

Disclosure: L. Brunier-Agot, None; **M. DeBandt**, None; **G. Jean-Baptiste**, None; **R. Duvauferrier**, None; **C. Lebris**, None; **A. Cabié**, None.

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Abstract Number: 1356

Autoimmune Manifestations in Hepatitis C: A Single-Centered Experience

Azza Ali[1], Reshma Khan[1], Kirthi Lilley[2], Paul Naylor[2], Rajaie Namas[1] and Malini Venkatram[1], [1]Rheumatology, Wayne State University, Detroit, MI, [2]Gastroenterology, Wayne State University, Detroit, MI

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Background/Purpose:

Hepatitis C infection (HCV) is a leading cause of chronic liver disease. It is associated with a plethora of autoimmune manifestations including clinical, serological and pathological abnormalities affecting different organs. Immune dysregulation in HCV is further indicated by the high prevalence of non-organ specific antibodies. We investigated the autoimmune manifestations in HCV including clinical, laboratory, imaging and pathological data with emphasis on serologies.

Methods:

We conducted a retrospective chart review in Rheumatology clinic on patients with HCV (confirmed by viral RNA) as a cofactor. We collected the demographic, clinical, laboratory, imaging and pathological data on these patients. We investigated the extent of autoimmune manifestations and its correlation to the degree of hepatic damage.

Results:

We obtained data on 29 patients of whom a limited number had available serological data. 41.3% had a coexisting autoimmune disease with Rheumatoid arthritis (RA) as the most common (33.3%). Arthralgia and Raynaud's were seen in 79.3% and 10.3% respectively. A positive ANA was demonstrated in 61.5% and ENA was demonstrated in 22.2%. Smith and RNP antibodies were detected in 25% and 50% respectively in the absence of clinical Lupus. ANCA was detected in 20% and cryoglobulins in 28% in the absence of clinical vasculitis. Rheumatoid Factor (RF) and Anti-CCP were seen in 45% and 22.2% respectively. 22.2% of patients with RF and 5.5% of patients with Anti-CCP did not have clinical RA. Antiphospholipid antibodies were seen in 40% in the absence of thromboembolic disease. Serologies were confounded by illicit drugs in 20%. The severity of autoimmune manifestations and serological abnormalities did not track the severity of hepatic damage.

Conclusion:

Significant autoimmune manifestations including serological abnormalities and cryoglobulinemia can be seen in hepatitis C in the absence of a clinical disease. Autoimmune manifestations do not parallel the degree of hepatic damage in hepatitis C.

Disclosure: A. Ali, None; **R. Khan**, None; **K. Lilley**, None; **P. Naylor**, Gilead Sciences, 2; **R. Namas**, None; **M. Venkatram**, None.

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Abstract Number: 1357

Cytomegalovirus (CMV) Infections in Patients with Rheumatic Diseases: Experience of a Referral Center

Yusuf Ziya Sener[1], Burak Yasin Aktas[1], Abdulsamet Erden[2], Levent Kilic[2], Berkan Armagan[2], Ahmet Cagkan Inkaya[3], **Omer Karadag**[2], Sule Apras Bilgen[2] and Sedat Kiraz[2], [1]Internal Medicine, Hacettepe University Faculty of Medicine, Ankara, Turkey, [2]Rheumatology, Hacettepe University Faculty of Medicine, Ankara, Turkey, [3]Infection Disease, Hacettepe University Faculty of Medicine, Ankara, Turkey
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Background/Purpose: CMV is a ubiquitous herpes virus associated with significant immunosuppression. Immunosuppressive treatments and ageing is well known risk factors for CMV reactivation. There are only a few case series about CMV disease in patients with rheumatologic diagnosis. In this report we present descriptive data of our rheumatic patients with CMV disease.

Methods: Database of our university hospital between 2000 and 2014 years was searched for CMV disease. Totally 34 (Female/Male: 25/9) patients with Rheumatic diseases were included into the further analysis. Patients' demographic data like age and gender, rheumatologic diagnoses, receiving immunosuppressive drugs at the admission, need of intensive care unit admission, clinical presentation type and outcomes were recorded. Confirmation of CMV disease was mainly based on CMV viral load in blood samples detected by

molecular techniques (PCR), pathological examination of biopsy specimens, eye fundoscopic evaluation and radiologic imaging.

Results: The mean age was 50.4±3.08 years. Most of the patients have vasculitis (44%). Ten patients (29%) had Systemic Lupus Erythematosus, and 5 patients (15%) had Rheumatoid arthritis. Other diagnoses were Still's disease, dermatomyositis and anti-synthetase syndrome. Patients are grouped according to their co-morbidities and 9 of them (27%) had a history of hypertension while 7 (21%) had diabetes and 8 (24%) had chronic renal disease. 5 patients were consuming tobacco at the time of appeal. Median dose of steroid treatment was 40 mg/day (0-60 mg). 13 (38%) were on pulse therapy. Except for one patient, all of the patients were using steroids at the time of CMV disease. 29 (85%) patients were using any additional immunosuppressive agent. Cyclophosphamide was the mostly used immunosuppressive agent (44%). Five patients were on anti-TNF therapy (infliximab:2, etanercept: 2, adalimumab: 1) and two patients were using rituximab. Other therapeutic agents were MMF (n=4), azathioprine (n=5), methotrexate (n=2) and leflunomide (n=1). Median time between the diagnosis of rheumatologic disease and CMV re-activation was 2.5 years (0-30 years), while mean time was 6.4±1.4 years. 26 (76%) patients required intensive care unit management. 19 (56%) of patients had died. There was no difference regarding between concomitant rheumatic diseases (p=0.66). Majority of patients were presented with pneumonia (59%). 5 patients (15%) had GIS involvement, 2 (%6) patients had retinitis, 1 patient had pneumonia and GIS involvement. In 6 patients (18%) the only symptom was high fever. Mortality was significantly high in patients with pneumonia (71%) and gastrointestinal involvement (67%), p=0.01).

Conclusion: In patients with rheumatic disease, CMV infections are very rare but have a high mortality rate. Corticosteroids, cyclophosphamide and biologic agents were the mostly used immunosuppressive agents in our patients. CMV disease should be kept in mind especially in rheumatic patients with respiratory failure and gastrointestinal bleeding.

Reference:

1. Kraft CS, Armstrong WS, Caliendo AM. Interpreting quantitative cytomegalovirus DNA testing: understanding the laboratory perspective. Clin Infect Dis. 2012 Jun;54(12):1793-7.

Disclosure: Y. Z. Sener, None; **B. Y. Aktas**, None; **A. Erden**, None; **L. Kilic**, None; **B. Armagan**, None; **A. C. Inkaya**, None; **O. Karadag**, None; **S. Apras Bilgen**, None; **S. Kiraz**, None.

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Abstract Number: 1358

Detection of a Unique Viral Infection in Salivary Glands of Sjögren's Syndrome Patients and Viral-Mediated Recapitulation of Disease in Vivo

Melodie Weller[1], Matthew Gardner[1], Zoe Bogus[1], Michael Smith[1], Elisa Astorri[2], Drew Michael[1], Changyu Zheng[1], Peter Burbelo[3], Paul A. Wilson[4], Zhennan Lai[1], Bill Swaim[1], Beverly Handelman[1], Sandra Afione[1], Michele Bombardieri[2] and John A. Chiorini[1], [1]Molecular Physiology and Therapeutics Branch, National Institute of Dental and Craniofacial Research, National Institutes of Health, Bethesda, MD, [2]Centre for Experimental Medicine and Rheumatology, William Harvey Research Institute, Queen Mary University of London, London, United Kingdom, [3]Clinical Dental Research Core, National Institute of Dental and Craniofacial Research, National Institutes of Health, Bethesda, MD, [4]National Intramural Database, Division of Enterprise and Custom Applications, Center for Information Technology, National Institutes of Health, Bethesda, MD

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Background/Purpose:

A viral infection is thought to be one of the triggers in the development of primary Sjögren's syndrome (pSS). Multiple studies have shown stimulation of antiviral response pathways in pSS tissues further suggesting the role viral infections may play in disease pathogenesis and/or progression. Yet with this data in hand, a true cause and effect relationship between a viral infection and development of Sjögren's syndrome had not been identified. Therefore, a study was designed to further define the viral landscape within the affected salivary gland tissue of Sjögren's syndrome patients and to identify potential viral-mediated triggers of this autoimmune disease.

Methods:

To better understand the viral signatures present in salivary gland tissue, a viral microarray was developed to assess the viral transcripts present in healthy salivary glands compared to patients diagnosed with primary Sjögren's syndrome. All pSS subjects studied met the American European criteria for pSS. Viral antigens were expressed in salivary glands of female C57BL/6 mice using adeno-associated viral vectors and monitored for changes in stimulated saliva flow, lymphocytic infiltrate formation and development of autoantibodies.

Results:

Two distinct viral profiles were identified by microarray analysis in the Sjögren's syndrome patients evaluated. One of the profiles identified the presence of hepatitis delta virus (HDV) in 50% of the primary Sjögren's syndrome cohort. Presence of HDV sequence and antigens were confirmed in two patient cohorts and HDV sequence was confirmed by an independent lab. Patients positive for HDV in salivary gland tissue were negative for detectible hepatitis B virus (HBV) antigen and antibody in serum and presented with normal transaminase levels. In vivo analysis of HDV antigen expression in salivary glands of female C57BL/6 mice resulted in a pSS-like phenotype including reduced saliva flow, increased lymphocytic infiltrates, and development of autoantibodies.

Conclusion:

Identification of HDV in Sjögren's syndrome patients and induction of a Sjögren's syndrome-like disease in vivo further support a viral-mediated etiopathology in Sjögren's syndrome.

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Abstract Number: 1359

Risk Factors for the Development of Gout in HIV Patients: A Retrospective Study

Bibi Ayesha, Rafeeq Ahmed, Richard Peralta, Syed Bokhari, Anupama Menon, Giovanni Franchin and Sridhar Chilimuri, Medicine, Bronx Lebanon Hospital Center, Bronx, NY

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Background/Purpose:

The interaction between human immunodeficiency virus (HIV) disease and rheumatic disorders has been described as "an unfortunate experiment of nature" that could provide insights into the pathogenesis of both disorders . Examples of this interaction have been described for many rheumatic conditions, but limited reports have explored the association with gout. Patients with HIV infection are characteristically hypouricemic due to malnutrition and defective renal handling of uric acid ; therefore, the coexistence of gouty arthritis and HIV would be unexpected. There have been limited studies evaluating potential risk factors for the development of gout in HIV patients. Because of the scarcity of published literature, additional data are warranted to determine risk factors for the development of gout in HIV positive patients.

Methods:

The primary objective of this study is to determine potential risk factors for the development of gout in HIV positive patients. The study is 1:2 retrospective case-control design. Study duration was for 14 years(2001-2014) which included 72 case patients and 144 control patients . Case patients included HIV positive patients who have at least 2 medical visits during the study period, in whom a subsequent diagnosis of gout has been made. Control patients included HIV positive patients who have at least 2 medical visits during the study period, in whom there is no diagnosis of gout . A standardized data collection instrument was created in an Excel spreadsheet and the Electronic Medical Records were utilized for all data collection. The demographic, clinical and medication exposure data was obtained. SPSS, version 22 was used for statistical analysis

Results:

During the 14 year study period, we found the following risk factors in the development of gout in HIV infected patients.

Protease inhibitors (p value 0.006) that included atazanavir (p value 0.047) and saquinavir (p value 0.035). Nucleoside reverse transcriptase inhibitors (p value 0.003) that included abacavir (p value < 0.0005), lamivudine (p value <0.005) and stavudine (<0.036). Additional risk factors were comorbidities like hyperlipidemia (p value 0.016), coinfection with hepatitis B (0.024), chronic kidney disease (p value < 0.0005), alcohol abuse (p value 0.021) and hydrochlorthiazide therapy (p value 0.042).

In the study group, the mean CD4 count was 468 and the mean uric acid level was 8.5 mg/dl at the time of diagnosis of gout in HIV patients. In the control group, the mean CD4 count was 395 and mean uric acid level was 5.4 mg/dl.

Conclusion:

In our study, risk factors for the development of gout in HIV Patients include therapy with protease inhibitors(atazanavir and saquinavir), nucleoside reverse transcriptase inhibitors (abacavir, lamivudine and stavudine), hyperlipidemia, hydrochlorthiazide therapy, coinfection with hepatitis B, chronic kidney disease and alcohol abuse.

Disclosure: B. Ayesha, None; **R. Ahmed**, None; **R. Peralta**, None; **S. Bokhari**, None; **A. Menon**, None; **G. Franchin**, None; **S. Chilimuri**, None.

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Abstract Number: 1360

Functional Consequences of NOD2 Gene Variants in Patients with NOD2-Associated Autoinflammatory Disease

Christine McDonald[1], Min Shen[1], Amrita Kabi[1], Craig Homer[1] and Qingping Yao[2], [1]Cleveland Clinic, Cleveland, OH, [2]Rheumatic and Immunologic Dis, Cleveland Clinic, Cleveland, OH

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SESSION INFORMATION

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Session Title: Innate Immunity and Rheumatic Disease Poster II

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: Yao Syndrome (YS) is a systemic autoinflammatory disease formerly termed Nucleotide-binding oligomerization domain 2 (*NOD2*)-associated AutoInflammatory Disease (NAID) due to its association with specific genetic variants in *NOD2*. This study examined the function of *NOD2* in YS patients.

Methods:

Study subjects (10 YS patients and 5 healthy individuals) were screened for *NOD2* variants by sequencing or TaqMan probes. Plasma cytokine levels, *NOD2* expression, and transcript splicing were measured by ELISA, qRT-PCR, and PCR, respectively. Functional assays were performed with peripheral blood mononuclear cells to assess *NOD2*activation in response to its ligand, muramyl dipeptide. The efficacy of tocilizumab therapy was examined in a YS patient.

Results: All YS patients were heterozygous for the *NOD2* IVS8^{+158} variant and 4 were compound heterozygous for R702W. Plasma levels of TNFα, IL-1β, IFNγ, and S100A12 were unaltered in YS patients as compared to healthy individuals. Splicing of intron 8 was unaffected by carriage of the IVS8^{+158} variant; however, *NOD2* expression was elevated in IVS8^{+158} heterozygous patients but not in IVS8^{+158}/R702W compound heterozygotes. MDP-stimulated NFκB activity was suppressed uniquely in compound heterozygotes and correlated with lower TNFα secretion. IL-6 secretion was enhanced specifically in IVS8^{+158} heterozygotes and anti-IL6 receptor antibody (tocilizumab) treatment of a YS patient with this *NOD2* genotype resulted in significant clinical improvement.

Conclusion:

Our findings indicate that YS is associated with dysfunction of *NOD2*, and specific *NOD2* genotypes associate with distinct functional

subtypes. This study suggests that *NOD2* genotype could be used as a biomarker in the selection of therapeutic modalities for YS and warrants further investigation in clinical trials.

Disclosure: C. McDonald, None; **M. Shen**, None; **A. Kabi**, None; **C. Homer**, None; **Q. Yao**, None.

Abstract Number: 1361

Synovial Macrophages Promote TGF-β Signaling but Protect Against Influx of S100A8/S100A9-Producing Cells after Intra-Articular Injections of Oxidized Low-Density Lipoproteins

Wouter de Munter[1], Martijn H. van den Bosch[1], Arjen Blom[1], Birgitte Walgreen[2], Monique Helsen[1], Leo Joosten[3], Johannes Roth[4], Thomas Vogl[5], Fons van de Loo[1], Marije Koenders[1], Wim van den Berg[1], Peter van der Kraan[1] and Peter van Lent[1], [1]Experimental Rheumatology, Radboud university medical center, Nijmegen, Netherlands, [2]Experimentel Rheumatology, Radboud university medical center, Nijmegen, Netherlands, [3]Internal Medicine, Radboud university medical center, Nijmegen, Netherlands, [4]Institute of Immunology, University of Münster, Münster, Germany, [5]University of Muenster, Muenster, Germany

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Background/Purpose: In previous studies we found that synovial macrophages regulate joint pathology during experimental osteoarthritis (OA). Recently, we found that high systemic levels of LDL aggravate joint pathology during experimental OA with synovitis. LDL in inflamed synovium is oxidized and taken-up by macrophages via scavenger receptor A and CD36, leading to an activated macrophage phenotype. In this study, we investigate whether direct injection of oxLDL into a normal murine knee joint induces joint pathology and elucidate the role of synovial macrophages in that process.

Methods: Knee joints of C57BL/6 mice were injected five consecutive days with 6 µl PBS, or PBS containing 1.2 mg/mL oxLDL or LDL. This same procedure was done in mice which were depleted of synovial macrophages by intra-articular injection of clodronate liposomes seven days prior to the (ox)LDL or vehicle injections. Joint pathology was investigated by immunohistochemistry and RNA expression and protein production by synovium were determined using RT-PCR and luminex, respectively. Active TGF-β was measured using a functional CAGA-luciferase assay. Data are depicted as mean ± standard deviation.

Results: LDL and oxLDL injection in naïve knee joints did not increase synovial thickening, or production of pro-inflammatory factors (IL-1β, IL-6 and S100A8/9) compared to LDL injection. Levels of active TGF-β in synovial wash-outs was, however, significantly increased by 33% (from 84.7 ± 14.4 ng/mL/g synovium to 113.0 ± 33.3 ng/mL/g synovium; $p<0.05$). Immunohistochemistry of knee joints showed that repeated injections of PBS caused low expression of aggrecanase- (NITEGE) and matrix metalloproteinase- (VDIPEN) induced neo-epitopes. Repeated injections of oxLDL could reduce expression of NITEGE and VDIPEN in areas that are prone to develop osteophytes, in contrast to LDL-injections (arbitrary VDIPEN score 0.33 ± 0.30 for oxLDL-injections and 0.96 ± 0.36 for LDL-injections; $p<0.05$).

In contrast, repeated injections of oxLDL in macrophage-depleted knee joints led to a 5.3 fold increase of synovial thickening (due to cell influx), compared to injection of LDL ($p<0.001$). Protein levels of S100A8/A9, markers for inflammation, were significantly increased in synovial wash-outs of oxLDL injected joints, compared to LDL-injection (fold increase 5.6; $p<0.05$). Protein and mRNA levels of chemokines CXCL1, CCL2 and CCL3 were also significantly upregulated after oxLDL-injections compared to LDL-injections. Further immunohistochemical investigation of infiltrating cells revealed that these were NIMP.R14-negative, mononuclear monocyte-like cells.

No raise in active TGF-β was measured in macrophage-depleted joints. Remarkably, NITEGE expression was increased in these joints at the synovial-cartilage contact areas after oxLDL injection (fold increase compared to LDL-injection 2.7; $p<0.05$).

Conclusion: Synovial macrophages promote anabolic effects after oxLDL injections in knee joints. In absence of synovial macrophages, however, oxLDL induces cell influx, production of pro-inflammatory mediators and aggrecanase activity.

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Abstract Number: 1362

Investigating the Role of Dendritic Cell Maturation & T Cell Activation within the Inflamed Synovium in Rheumatoid Arthritis

Mary Canavan[1], Micheal O'Rourke[2], Carl Orr[2], Sharee Basdeo[3], Jean Fletcher[3], Douglas J. Veale[4] and Ursula Fearon[5], [1]St. Vincent's University Hospital, Centre for Arthritis and Rheumatic Diseases, Dublin Academic Medical Centre, Dublin, Ireland, [2]Dublin Academic Medical Centre, Translational Rheumatology Research Group, St Vincent's University Hospital, Dublin, Ireland, [3]Trinity Biomedical Sciences Institute, School of Biochemistry and Immunology, Trinity College Dublin, Dublin, Ireland, [4]St Vincent's University Hospital, Centre for Arthritis and Rheumatic Diseases, Dublin Academic Medical Centre, Dublin 4, Ireland, [5]St. Vincent's University Hospital, Centre for Arthritis and Rheumatic Diseases, Dublin Academic Medical Centre, Dublin 4, Ireland

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Background/Purpose: Dendritic cells (DC) are a heterogeneous population of antigen presenting cells which link both innate & adaptive immunity. To date their classification within blood & skin has been well characterised however evidence identifying DC within other tissues, in particular in the context of autoimmunity is limited. In this study we aim to characterise the DC populations within the inflamed synovium & to elucidate the effect of the inflamed joint microenvironment on DC characterisation & function & subsequent effects on T cell activation.

Methods: Synovial tissue was obtained from RA patients through arthroscopy. For characterisation of tissue DC, biopsies were digested & gated on $CD45^+$ cells. DC were defined as $HLADR^+$, $Lineage^-$ & cell surface expression of CD11c, CD1c, CD141, CD123, CD80, CD83 & CD40 was assessed by flow cytometry. In parallel, RA synovial fluid (SF) & peripheral blood (PB) DC characterisation was also analysed in comparison to synovial tissue. To assess the effect of the inflamed microenvironment on DC activation & function, RA synovial tissue explants were cultured for 24hr allowing the spontaneous release of proinflammatory cytokines & mediators into the culture medium. MoDC were then cultured in the presence of RA explant conditioned media (ECM), RA SF under normoxia or hypoxia & the expression of CD80, CD83 & CD40 assessed. Furthermore MoDC were treated with RA SF & cocultured with $CD4^+$ T cells for 5 days, supernatants harvested & T cells restimulated with PMA (50ng/ml) & Ionomycin (500ng/ml) to examine intracellular expression of IFNγ.

Results: Phenotypic characterization of mDC in PB, SF & synovial tissue from RA patients demonstrated a significant increased gradient in DC maturation markers CD40 & CD80 as DC migrate from blood, to fluid & finally to the synovial tissue ($p<0.05$; $p<0.05$). This is consistent with our data showing that RA patients have a significant decrease ($p<0.05$) in CD11c mDC circulating in PB compared to age matched HC. A significant increase in $CD141^+$ DC in the SF compared to PB ($p<0.005$) was demonstrated. This DC population has not been previously identified in the joint. Furthermore analysis of RA synovial tissue DC demonstrated subpopulations of DC. CD1c DC were identified in the tissue however no CD141 DC were present which is in contrast to a strong CD141 population in the fluid. To mimic the joint microenvironment, MoDC were cultured in the presence of ECM or SF under normoxic or hypoxic conditions. A significant increase in CD80 expression in response to RA ECM or RASF was demonstrated ($p<0.05$; $p<0.0001$ respectively), furthermore hypoxia significantly potentiated the effect of ECM on CD80, CD40 & CD83 compared to basal (all $p<0.0001$). Finally, enhanced IFNγ production ($p<0.05$) & T cell proliferation was demonstrated in SF MoDC & $CD4^+$ T cells co-cultures compared media control.

Conclusion: In this study we identified differential DC subpopulations in the inflamed joint compared to systemic circulation. These cells display a more activated phenotype & can induce T cell function, effects of which are influenced by the RA joint microenvironment, through increased proinflammatory mediators & through the hypoxic nature of the joint.

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Abstract Number: 1363

Changes in Cyclooxygenase-2's Expression, and PGE2's and 6-Keto-PGF1α Levels in the Presence of the Muscarinic Acethylcholine Receptor Antibody in Primary Sjogren Syndrome

Micaela Ana Cosatti[1], Silvia Reina[2], Cecilia N. Pisoni[3], Alicia Eimon[4], Sabrina Ganzinelli[2] and Enri Borda[2], [1]Section Rheumatology and Immunology, CEMIC, CABA, Argentina, [2]Pharmacology Unit, School of Dentistry, University of Buenos Aires, Buenos Aires, Argentina; National Research Council of Argentina (CONICET), Buenos Aires, Argentina, [3]Lupus Research Unit, The Rayne Institute, St Thomas' Hospital and Kings College London, London, United Kingdom, [4]CEMIC, Buenos Aires, Argentina
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Background/Purpose: to assess the inflammatory process provoked by the M_3 muscarinic acetylcholine receptor antibody from primary Sjogren Syndrome (pSS) patient's sera in rat submandibular gland by measuring the expression of mRNA COX-2 and production of PGE_2 and PGI_2.

Methods:

The levels and the generation of PGE_2, 6-keto-$PGF_{1\alpha}$ by Enzyme-linked immunoabsorbent assay (ELISA), cyclic AMP (cAMP) by cAMPc-RIA kit and COX-2 mRNA gene's expression at Real Time PCR in rat submandibular gland acini's preparations were measured in the presence of the autoantibodies alone or after incubation with different inhibitors. PGE_2 and 6-keto-$PGF_{1\alpha}$ were also measured in serum from pSS patients.

Statistical analyses

The Student's "t" test for unpaired values was used to determine the level of significance. Differences between means were considered significant if $P<0.05$.

Results:

To determine the effect of pSS IgG anti M3 peptide on gland acini's we analyzed the time-course of COX-2 mRNA expression by Real Time-PCR. COX-2-mRNA was significantly ($P<0.001$) increased in the presence of pSS IgG anti M3 versus normal serum (control). When the autoantibody was incubated in the presence of DuP697 (1x10-6 M) [a specific COX-2 antagonist] under the same experimental conditions, it abrogated the increment of COX-mRNA's expression in a significant manner ($P<0.01$).

Primary Sjogren Syndrome IgG anti M3 antibody increased the production of both prostanoids PGE2 and 6-keto-PGF1α on submandibular gland acini's in a dose-response concentration curve reaching the maximal when the antibody concentration is 1x10-8 M. The increment in the generation of both prostanoids is abrogated, reaching values similar to basal ones, when the tissue preparations are incubated with prostanoid antagonists PF-04418948 2x10-9 M and RO3244794 5x10-8 M for PGE2 and 6-keto-PGF1α respectively, and in the presence of synthetic M3 peptide 5x10-6 M.

To ascertain if cAMP increment is caused by the generation of PGE2 and 6-keto-PGF1α in our preparation, we studied the action of both prostanoids on the production of this nucleotide. Both prostaglandins were able to increase cAMP production, whereas the selective prostanoids antagonists (PF-04418948 for PGE2 and RO3244794 for 6-keto-PGF1α) blunted the stimulatory action provoked by the prostaglandins.

The levels of PGE2 and 6-keto-PGF1α were studied in serum of 28 pSS patients and in 25 healthy individuals. The concentration of 6-keto-PGF1α and PGE2 in serum of pSS patients was two standard deviations higher than that in normal individuals ($P<0.001$).

Conclusion: The present study suggests a complex interplay between different factors involved in adaptativa autoimmunity in pSS patients

at the level of exocrine glands. The presence of anti M_3 IgG autoantibody from pSS sera was able to stimulate COX-2 mRNA gene's expression and the increment in the generation of PGE_2 and 6-keto-$PGF_{1\alpha}$ abolished by M_3 specific cholinergic antagonist. The prostanoids play an important role in the inflammatory process at exocrine gland level.

Disclosure: M. A. Cosatti, None; **S. Reina**, None; **C. N. Pisoni**, None; **A. Eimon**, None; **S. Ganzinelli**, None; **E. Borda**, None.

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Abstract Number: 1364

Treating Experimental Arthritis with the Innate Immune Inhibitor IL-37 Reduces Joint and Systemic Inflammation

Giulio Cavalli[1], Marije Koenders[2], Lorenzo Dagna[3], Alberto Mantovani[4], Cecilia Garlanda[4], Leo Joosten[5] and Charles Dinarello[1], [1]Department of Medicine, Division of Infectious Diseases, University of Colorado, Denver, CO, [2]Experimental Rheumatology, Radboud university medical center, Nijmegen, Netherlands, [3]Internal Medicine and Clinical Immunology, Vita-Salute San Raffaele University, Milano, Italy, [4]Research Institute Humanitas, Milan, Italy, [5]Internal Medicine, Radboud university medical center, Nijmegen, Netherlands
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Background/Purpose: Characterized as a fundamental inhibitor of innate inflammation, IL 1 family member IL 37 is expressed in the synovia of patients with rheumatoid arthritis. We investigated the role of IL 37 in joint inflammation and the effects of IL 37 treatment on joint pathology in a mouse model of experimental arthritis.

Methods: Wild type mice were subjected to acute arthritis and peritonitis by instillation of streptococcal cell wall (SCW) fragments, and treated with a recombinant form of the naturally occurring human IL 37. SCW induced arthritis was induced also in mice transgenic for human IL 37 (IL 37tg). The severity of joint and systemic inflammation, changes in IL 37 gene expression, joint histology, and local and systemic cytokine and chemokine production were determined.

Results: In wild type mice, low doses of recombinant IL 37 suppressed joint inflammation by 51.7% ($p<0.001$), and significantly decreased synovial IL 1β by 84%, IL 6 by 73%, TNFα by 33%, KC by 58%, and MPO by 60%. These effects were associated with reduced recruitment of neutrophils to the joint. The anti inflammatory effects of IL 37 treatment were confirmed in SCW induced peritonitis, and shown to require the IL 1 family decoy receptor IL 1R8/SIGIRR. In IL 37tg mice, synovial expression of IL 37 reached peak levels during the resolution phase of the arthritis, and was associated with a reduction of joint swelling.

Conclusion: IL 37 emerges as a key suppressor of joint and systemic inflammation. These findings demonstrate a role of IL 37 in the pathogenesis of arthritis, and indicate a potential for IL 37 in the treatment of rheumatoid arthritis.

Disclosure: G. Cavalli, None; **M. Koenders**, None; **L. Dagna**, None; **A. Mantovani**, None; **C. Garlanda**, None; **L. Joosten**, None; **C. Dinarello**, None.

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Abstract Number: 1365

Innate Lymphoid Cells. New Players in Systemic Sclerosis Correlate with Extent of Skin and Lung Fibrosis

Thomas Wohlfahrt[1], Stefanie Weber[1], Matthias Englbrecht[2], Clara Dees[3], Christian Beyer[3], Oliver Distler[4], Georg Schett[1], Jorg HW

Distler[1,3] and Andreas Ramming[1], [1]Department of Internal Medicine 3 and Institute for Clinical Immunology, University of Erlangen-Nuremberg, Erlangen, Germany, [2]Department of Internal Medicine 3, Rheumatology & Immunology, University of Erlangen-Nuremberg, Erlangen, Germany, [3]Department of Internal Medicine 3, University of Erlangen-Nuremberg, Erlangen, Germany, [4]Research of Systemic Autoimmune Diseases, Center of Experimental Rheumatology, University Hospital Zurich, Zurich, Switzerland
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Background/Purpose: Type 2 innate lymphoid cells (ILC2s), are recently identified as population of cells with lymphoid morphology lacking re-arranged antigen-specific receptors. Although findings in animal models of fibrotic diseases demonstrate increased numbers of ILC2s in fibrotic lesions, data on ILC2s in humans are mainly limited to allergic diseases. We aimed to evaluate the contributive role of ILC2s in the pathogenesis of systemic sclerosis (SSc), their levels and correlations with fibrotic manifestations in SSc.

Methods: Sixty-nine patients with SSc and 47 healthy controls were included into the study. Blood samples and skin sections were analyzed by flow cytometry and immunohistochemistry. ILC2 counts were correlated with clinical manifestations of SSc.

Results: Elevated numbers of ILC2s were detected in the skin (10-fold increase) as well as in the blood (4-fold increase) of SSc patients compared to healthy controls. As no single marker can sufficiently distinguish ILC2s from other cell population, we used two established sets of ILC2 markers to quantify ILC2 cells in the peripheral blood and the skin of SSc patients and healthy individuals, both of which yielded comparable results. Notably, activation markers are lacking on circulating ILC2s, however, after migration into the dermis ILC2s become activated as indicated by expression of IL-17RB and thymic stromal lymphopoietin protein (TSLP) receptor as well as by positive staining for the skin homing marker cutaneous lymphocyte antigen (CLA). Our data also suggest that ILC2s may be involved in the pathogenesis of fibrosis in SSc by showing multiple associations of ILC2 counts with fibrotic manifestations in SSc patients. Stratification of the SSc population in patients with limited (lcSSc) and diffuse cutaneous SSc (dcSSc) demonstrated increased levels of ILC2 in both subgroups with significantly higher frequencies in dcSSc compared to lcSSc. Moreover, dermal and circulating ILC2 counts correlated closely with the modified Rodnan skin score (mRSS). Increased ILC2 numbers were not only associated with more extensive skin fibrosis, but also with anti-topoisomerase antibodies and pulmonary fibrosis. ILC2 counts were highest in patients with extensive lung involvement assessed by CT scan. A comparison of circulating ILC2 frequencies between different cohorts of patients with rheumatoid arthritis, systemic lupus erythematosus and SSc demonstrated strong upregulation of ILC2s only in SSc patients.

Conclusion: Here, we provide first evidence for a role of ILC2s in the pathogenesis of rheumatic diseases by demonstrating increased ILC2 counts in the skin and blood of patients with SSc as compared to healthy individuals. Migration of circulating ILC2s into the skin, the activated state of dermal ILC2s and correlations of ILC2 counts with dermal and pulmonary fibrosis suggests a central role of ILC2s in the pathogenesis of fibrosis and encourage follow-up studies to further evaluate the potential of ILC2 as biomarkers in SSc patients.

Disclosure: T. Wohlfahrt, None; **S. Weber**, None; **M. Englbrecht**, None; **C. Dees**, None; **C. Beyer**, None; **O. Distler**, None; **G. Schett**, None; **J. H. Distler**, None; **A. Ramming**, None.

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Abstract Number: 1366

Natural Antibodies, Not B Cells, Contribute to Acute Cell Death-Induced Inflammation

Hiroshi Kataoka, Rheumatology and Clinical Immunology, Sapporo City General Hospital, Sapporo, Japan
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Background/Purpose: Alarmins, such as uric acid, released from dying cells activate inflammasomes and mediate dead cell-induced inflammation (Ref.). Since it is remains unknown whether or not local host immune factors contribute to the alarmin-related inflammatory response, we focused on the roles of B cells and immunoglobulins in Alarmin-related inflammation. The aim of this study is to test whether natural antibodies have a role in acute cell death-induced inflammation in two different models, acetaminophen-induced liver damage and dead cell-induced peritonitis.

Methods: First we looked at neutrophil infiltration into acetaminophen-damaged livers in mice genetically lacking B cells (μMT) and control wild-type (WT) C57BL/6 mice. Dead EL4 cells, murine T lymphoma cell line, that had been heat-shocked and frozen were injected intraperitoneally into μMT and controls, and the recruitment of neutrophils and monocytes to peritoneal cavity was also quantified by flow cytometry. Then, to see whether natural antibodies contribute to acute inflammation in these two settings, acute inflammatory cell recruitment was quantitated by flow cytometry in μMT mice given infusions of pooled normal serum that was collected from untreated WT mice into their tail veins in advance of commencing inflammation and compared to untreated control mice.

Results: $B220^{+}$ cells as well as neutrophils and monocytes were recruited into acetaminophen-damaged liver in WT mice, suggesting that multiple immune cells might contribute to the inflammation. The numbers of neutrophils and monocytes in damaged liver tissue were significantly reduced in μMT mice compared to WT controls (μMT:$2.6\pm1.9\times10^{5}$,$7.2\pm3.9\times10^{4}$, WT:$2.4\pm1.4\times10^{6}$,$1.0\pm0.8\times10^{6}$ (neutrophils, monocytes)), and the inflammatory response was substantially restored by reconstitution of natural antibody-containing normal serum without B cell co-transfer (figure 1). In another inflammation model, peritoneal recruitment of neutrophils and monocytes in response to injured EL4 cells was also markedly decreased in μMT mice (μMT:$2.9\pm0.4\times10^{5}$,$9.6\pm5.5\times10^{4}$, WT:$5.7\pm3.1\times10^{5}$,$2.4\pm1.5\times10^{5}$ (neutrophils, monocytes)), and also the neutrophilic response was successfully reversed by normal serum transfer to μMT to the WT level (figure 2).

Conclusion: Natural antibodies participate in neutrophil recruitment in acute cell death-induced inflammation. In contrast, B cells are also recruited to the inflammation site, but they may be dispensable for acute neutrophil response.

Reference: Rock KL, Kataoka H, Lai JJ. *Nat Rev Rheumatol* 9 (1):13-23

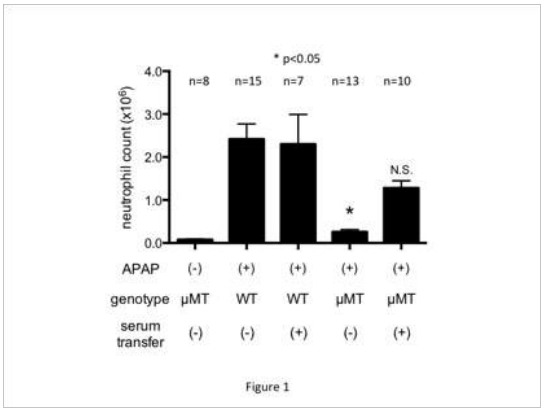

Figure 1

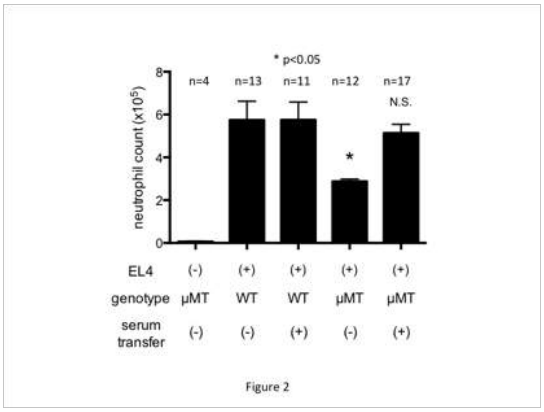

Figure 2

Disclosure: H. Kataoka, None;

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Abstract Number: 1367

Fibroblast-like Synoviocytes Shape and Perpetuate the Inflammatory Immune Responses Associated with Antibiotic-Refractory Lyme Arthritis.

Klemen Strle[1], Robert Locchead[2], Annalisa Pianta[3], Jameson T. Crowley[3], Sheila Arvikar[1] and John Aversa[4], [1]Division of Rheumatology, Allergy & Immunology, Massachusetts General Hospital, Harvard Medical School, Boston, MA, [2]Rheumatology, Allery and Immunology, Massachusetts General Hospital, Harvard Medical School, Charlestown, MA, [3]Center for Immunology and Inflammatory Diseases, Massachusetts General Hospital, Harvard Medical School, Boston, MA, [4]Yale Medical Group, Orthopaedics and Rehabilitation, Yale University School of Medicine, New Haven, CT

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Session Time: 9:00AM-11:00AM

Background/Purpose:

Antibiotic-refractory Lyme arthritis is defined as persistent synovitis for months to years after antibiotic therapy for *Borrelia burgdorferi*, the causative agent of Lyme disease. Rather than persistent infection, this condition is thought to result from inappropriate activation of inflammatory immune responses which are elicited by the spirochetes and further augmented by host genetics. Fibroblast-like synoviocytes (FLS) are the predominant cell type in hypertrophied synovial tissue, but their responses to *B. burgdorferi* are not well-defined. Here we assessed the inflammatory responses of FLS to a highly virulent *B. burgdorferi*RST1 strain and evaluated these responses according to a host TLR1-1805GG polymorphism, a risk factor for antibiotic-refractory Lyme arthritis.

Methods:

FLS were obtained from synovia of antibiotic-refractory Lyme arthritis patients who underwent synovectomies due to incomplete responses to treatment with antibiotics and then DMARDs. Protein levels of 8 matrix metalloproteinases and 21 cytokines and chemokines in *B. burgdorferi*-stimulated FLS were assessed using Luminex. mRNA expression in synovial biopsies and FLS was assessed using QuantiGene and whole-genome RNASeq analyses.

Results:

FLS sense and respond to *B. burgdorferi* by producing high levels of matrix metalloproteinases (MMP1, MMP2, MMP3, MMP9, and MMP13) which degrade cartilage and bone. In addition, *B. burgdorferi*-stimulated FLS produce large amounts of inflammatory mediators associated with both innate (IL-6, IL-8, IL-10, TNF, CCL2), and adaptive Th1-like responses (CXCL9, CXCL10). These responses corroborate in vivo findings in the joint fluid of patients with antibiotic-refractory Lyme arthritis, linking FLS to excessive joint inflammation. Moreover, FLS responded directly to stimulation with IFNγ, the prototypical Th1 effector cytokine, leading to high levels of CXCL9 and CXCL10, which are potent chemoattractants for $CD4^{+}$Th1 cells, the predominant T-effector cell type in joints of patients with refractory arthritis. These responses were amplified in FLS from patients with a TLR1-1805GG polymorphism, which leads to diminished TLR1 expression on the cell surface. Cells with 1805GG had altered SOCS3 mRNA expression suggesting that the greater inflammatory responses in the 1805GG group may be due to a loss of a regulatory pathway. In addition, RNASeq analysis revealed that a deficiency in TLR1 in patients with 1805GG also leads to increased expression of other pathogen-recognition receptors, including TLRs and NODs, which could further contribute to excessive inflammation in patients with 1805GG.

Conclusion:

FLS are an important cell type in the pathogenesis of antibiotic-refractory Lyme arthritis because of their ability to shape and perpetuate innate and adaptive immune responses. These responses are altered in patients with TLR1-1805GG polymorphism, a risk factor for antibiotic-refractory Lyme arthritis.

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Abstract Number: 1368

PMN Reactivity Contribute to Acute Onset Joint Inflammation By Increasing CXCL8 Production in Joints of RA Patients with Anti-Collagen II Antibodies

Vivek Anand Manivel[1], Azita Sohrabian[2] and Johan Rönnelid[3,4], [1]Immunology, Genetics and Pathology, Department of Immunology, Genetics and Pathology, Uppsala University, Uppsala, Sweden, [2]Department of Immunology Genetics and Pathology,Uppsala University, Uppsala, Sweden, [3]Department of Immunology, Genetics and Pathology,Uppsala University, Uppsala, Sweden, [4]4Unit of Rheumatology, Department of Medicine, Karolinska Institutet, Stockholm, Sweden

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Background/Purpose: RA patients with antibodies against collagen type II (CII) have a distinct acute onset RA phenotype, associated with cytokine induction by surface-bound anti-CII IC (Mullazehi A&R 2006, Mullazehi ARD 2007, Mullazehi ART 2012). PMN reactivity relate to early joint destruction in this phenotype (Manivel ART 2015). Hence we searched for CII-dependent mechanisms that might attract PMN to the joint.

Methods: Healthy donor PMN and peripheral blood mononuclear cells (PBMC) were stimulated together (co-cultures) and individually with surface-bound IC (anti-CII IC, tetanus toxoid (TT)/anti-TT IC, plate-bound IgG) or GM-CSF. Blocking and neutralizing studies were performed with antibodies against TLR4, FcgRIIa, FcgRIII and GM-CSF. Supernatant levels of TNF-a and CXCL8 were analyzed with ELISA.

Results: PMN alone produced negligible cytokine levels. TNF-a production was downregulated in all co-culture systems compared to PBMC cultures. CXCL8 levels were specifically upregulated in anti-CII IC-stimulated co-cultures compared to parallel PBMC cultures (fig 1). The anti-CII IC augmentation of CXCL8 was dependent on CII, as CXCL8 production was downregulated in co-cultures stimulated with the other IC; plate-bound IgG (fig 1) or TT/anti-TT IC (not shown). Blocking and neutralization studies showed that the increase of CXCL8 in anti-CII IC stimulated co-cultures was totally dependent on TLR4, partly on PMN enzymes (fig 2), FcgRIIa, FcgRIII (fig 3), and density of anti-CII in IC. Like anti-CII IC, GM-CSF alone also induced co-culture-dependent CXCL8 enhancement (fig 1), and GM-CSF neutralization abrogated the anti-CII IC-dependent CXCL8 enhancement (fig 3).

Conclusion: In anti-CII-positive RA patients, PMN amplify local inflammation by inducing CXCL8. This mechanism is dependent on TLR4, PMN enzymes, GM-CSF and the joint-specific autoantigen CII. Local TLR4 blockade, PMN enzyme inhibition or GM-CSF neutralization might be used to suppress acute joint inflammation.

Figure:1

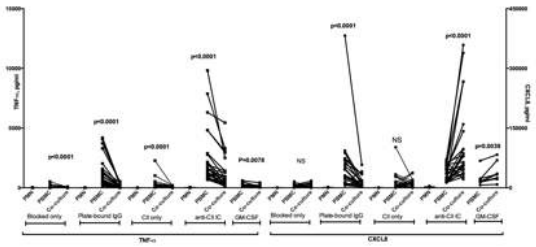


Figure:2

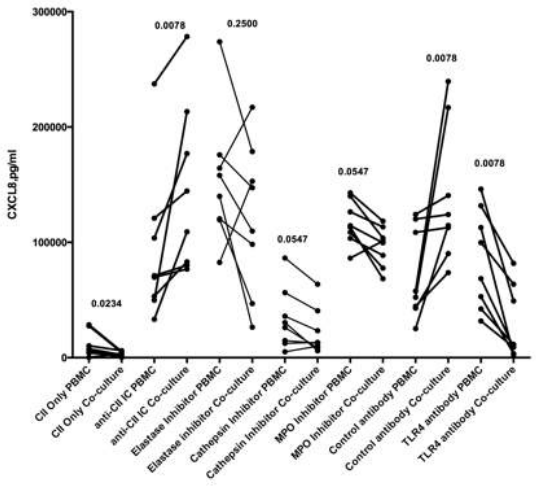
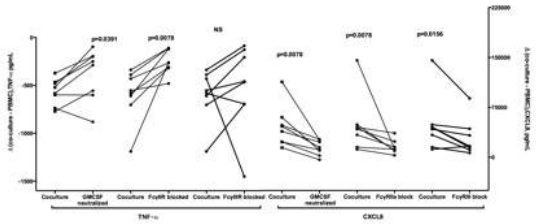


Figure:3



Disclosure: V. A. Manivel, None; **A. Sohrabian**, None; **J. Rönnelid**, None.

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Abstract Number: 1369

Enhanced Myelopoiesis Downstream of Toll-like Receptor 9 Activation Drives a Feed-Forward Inflammatory Response

Lehn K. Weaver[1] and Edward M. Behrens[2], [1]Pediatric Rheumatology, Children's Hospital of Philadelphia, Philadelphia, PA, [2]Pediatric Rheumatology, Childrens Hospital of Philadelphia, Philadelphia, PA

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Background/Purpose: Monocytes are myeloid cells important for the initiation of inflammation and have been implicated in the pathogenesis of autoimmunity. Monocytes interact with their environment through expression of cell-surface and endosomal pattern recognition receptors, including Toll-like receptors (TLRs), which are activated by endogenous and exogenous ‘danger’ signals. Persistent activation through TLRs is thought to drive chronic inflammation in multiple rheumatic diseases. However, the cellular mechanisms driving feed-forward inflammation downstream of repeated TLR stimulation remain unknown.

Methods: We treat C57BL/6 mice with repeated doses of CpG1826, a TLR9 agonist, to induce a feed-forward inflammatory response. Yet40 interleukin (IL)-12 reporter mice are used to identify the TLR9 responsive, IL-12 producing cells in this model. C-C chemokine receptor type 2 (CCR2)$^{-/-}$ mice are used to define CCR2- dependent and independent cell trafficking during TLR9-mediated inflammation. Flow cytometric identification of myeloid progenitor cells and *in vitro* myelopoiesis assays are used to characterize inflammation-induced myelopoiesis.

Results: We demonstrate that repeated stimulation through TLR9 leads to a feed-forward inflammatory response driven by the accumulation of TLR9 responsive inflammatory monocytes. Interestingly, TLR9-activated CCR2$^{-/-}$ mice are not protected from disease and accumulate similar numbers of peripheral blood and splenic inflammatory monocytes as wildtype mice, despite previous work demonstrating defective inflammatory monocyte egress from the bone marrow in CCR2$^{-/-}$ mice. Peripheral monocytosis does not coincide with an expansion of bone marrow myeloid progenitor cells, but rather correlates with an accumulation of myeloid progenitor cells in the spleen and liver of TLR9-activated mice. Furthermore, myeloid progenitor cell accumulation at peripheral sites of inflammation is independent of CCR2, implicating *in situ* generation of inflammatory monocytes as an explanation for the peripheral monocytosis seen in TLR9-activated CCR2$^{-/-}$ mice. Finally, repeated TLR9 activation *in vivo*reprograms extramedullary myeloid progenitor cells to have increased inflammatory monocyte production capacity demonstrating another mechanism driving feed-forward myelopoiesis downstream of repeated TLR9 activation.

Conclusion: Our data indicate that profound changes in extramedullary myelopoiesis occur during TLR9-driven inflammation leading to increased production of inflammatory monocytes. The accumulation of TLR9 responsive monocytes leads to enhanced inflammatory responses downstream of repeated TLR9 activation generating a feed-forward inflammatory loop. As extramedullary myeloid progenitor cells are found in patients with rheumatoid arthritis, systemic lupus erythematous, scleroderma, dermatomyositis, and psoriasis, it is intriguing to speculate that enhanced myelopoiesis downstream of repeated TLR activation is a critical factor driving systemic inflammatory responses in multiple rheumatic diseases.

Disclosure: L. K. Weaver, None; **E. M. Behrens**, None.

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Abstract Number: 1370

CD40/CD40L Pathway Is Associated with Increased Oxidative Burst and Neutrophil Extracellular Traps Release in Behcet´s Disease

Sandro F. Perazzio[1,2], Paulo Vitor Soeiro Pereira[3], Alexandre W.S. Souza[4], Antonio Condino-Neto[3] and Luis Eduardo C. Andrade[5], [1]Rheumatology Division, Universidade Federal de São Paulo, Sao Paulo, Brazil, [2]Fleury Medicine and Health, Sao Paulo, Brazil, [3]Immunology, ICB IV - Universidade de São Paulo, São Paulo, Brazil, [4]Rheumatology Division, Universidade Federal de Sao Paulo, Sao Paulo, Brazil, [5]Immunology Division, Fleury Medicine and Health, São Paulo, Brazil
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Background/Purpose: Previous studies suggested that unknown plasma factors increase oxidative burst in Behçet's disease (BD), but little is known about neutrophil extracellular traps (NET) formation. Herein, we investigated in patients with active (aBD) and inactive BD (iBD): soluble CD40L (sCD40L) plasma levels; the effect of CD40 pathway activation on NET release and oxidative burst; and the expression of CD40L and its receptors.

Methods: Neutrophils and PBMC were obtained from patients with aBD (n=30), iBD (n=31), and healthy controls (HC; n=30). For each group, a pool of plasma treated or not with recombinant CD40 (rhCD40) for sCD40L blockade was created. A pool of plasma from four CD40L-deficient patients was also obtained. sCD40L plasma concentration was measured by Luminex. NET formation was quantified on neutrophils plated onto circular coverslips, followed by labeling with Hoechst 123 and antibodies to histones and neutrophil elastase. H_2O_2/O_2^-production was determined by luminol/lucigenin luminescence intensity. Cells were treated with PMA, sCD40L or the pool of plasma. Flow cytometry analysis evaluated the expression of 1) CD40, Mac-1, α5β1-integrin and α2bβ3-integrin on neutrophils and monocytes; 2) CD40L on T cells; 3) CD40L on platelets.

Results:

sCD40L plasma levels were significantly higher in iBD (median/range=17,234/2,346-19,279) and aBD (18,288.50/412.58-19,883) compared to HC (47.45/33.68-26,743; p<0.001). NET formation was constitutively increased in BD compared to HC. Stimulation of in vitro NET formation by aBD plasma or sCD40L was inhibited by CD40L blockade (Table 1). Neutrophil and PBMC production of

O_2^-/H_2O_2 was higher after stimuli with sCD40L, aBD or iBD plasma than with HC plasma and decreased after CD40L blockade (Table 2). Mac-1 expression was constitutively increased in iBD (4,615/208-8,594) and aBD (2,018/891-6,533) neutrophils compared to HC (55.35/17.5-70.5; $p<0.01$). CD40, CD40L, α5β1- and α2bβ3-integrin expression were similar in the three groups.

Conclusion: Plasma from aBD patients exerts a stimulus on NET formation and oxidative burst, probably mediated by Mac-1. Increased concentration of sCD40L might be associated with neutrophil hyperactivity in BD.

Table 1 - Neutrophil extracellular traps (NETs) formation

	NET formation (μm²)		
	HC	**iBD**	**aBD**
No stimulus[a]	20.00±4.08*¨	146.50±15.58¨«»	207.75±51.99¨«
PMA	594.83±102.21¶	512.50±37.99¶	514.00±51.69¶
sCD40L	836.22±206.05¶	1443.42±92.10¶	1442.00±494.48¶
Plasma from HC[a]	62.33±11.91¨	161.83±31.80¨«»	210.50±32.30¨«
Plasma from HC + rhCD40	65.50±40.02	60.78±38.27†…	70.617±30.56…†
Plasma from iBD[a]	66.75±25.86¨	197±34.03*¨«	225±58.41¨«
Plasma from iBD + rhCD40	62.98±33.41	87.24±29.99…†	80.43±33.65…†
Plasma from aBD[a]	123.25±46.56¶	351±36.25¶»	304.75±20.12¶
Plasma from aBD + rhCD40	71.12±30.71†…	83.22±17.77†…	104.50±19.90…«†

Table 2 – Production of O_2^- and H_2O_2

Source of neutrophils	No stimulus[a] (RLU)	sCD40L (RLU)	Plasma from HIgM[a] (RLU)	Plasma from HC[a] (RLU)		Plasma from iBD[a] (RLU)		Plasma from aBD[a] (RLU)	
				rhCD40-	rhCD40+	rhCD40-	rhCD40+	rhCD40-	rhCD40+
O_2- production									
Healthy control	1,561 100 to 20,428¶	46,922 5,862 to 296,460¶	3,528 1,298 to 7,564	20,150 4,156 to 79,584	14,189 2,460 to 55,318	54,848 10,584 to 117,380*	23,212 8,109 to 124,484†…	56,996 6,880 to 232,802*	26,142 9,202 to 112,554†…
iBD	856 44 to 41,492¶	68,600 10,472 to 615,780¶	2,903 1,003 to 7,940	21,954 2,472 to 83,160	15,386 4,058 to 63,372	60,943 5,024 to 273,100*	27,098 10,034 to 165,606†…	57,408 7,956 to 233,104*	31,230 4,943 to 166,448†…
aBD	3,477 544 to 15,702¶	338,040 97,270 to 379,520*¶	7,093 1,439 to 8,292	33,648 5,836 to 93,952	10,256… 3,352 to 55,252†	69,549 12,580 to 165,444*	28,675 18,318 to 119,578†…	61,392 12,532 to 186,668*	27,633 13,633 to 141,624†…
H_2O_2 production									
Healthy control	1,607 344 to 6,216¶	244,833 48,636 to 358,276¶	3,298 1,135 to 8,082	39,888 5,484 to 137,424	34,391 3,690 to 290,354…†	76,170 10,054 to 290,000*¨	20,895 5,683 to 93,590…†	190,310 11,468 to 511,472*	55,608 6,444 to 410,401†…
iBD	944 368 to 14,632¶	318,768 58,234 to 489,016¶	2,767 1,154 to 5,861	33,764 5,148 to 210,644	33,896 2,610 to 340,022†…	87,432 8,020 to 341,972*	16,168 10,546 to 245,998…†	107,687 8,136 to 399,116*	93,528 16,494 to 441,561†…
aBD	2,684 620 to 8,789¶	452,846 155,338 to 1,270,000*¶	8,082 2,431 to 34,956	49,792 6,012 to 166,704	38,038 2,936 to 95,320…†	106,832 34,708 to 465,252*¨	47,282 5,038 to 148,932…†	365,877 33,556 to 1,779,106*	80,075 10,453 to 403,571†…

RLU: relative light units; [a] Figures correspond to median and range or mean±SD; * $p<0.05$ comparing to "stimulus with plasma from HC"; ¨ $p<0.05$ comparing to "stimulus with aBD plasma"; ¶ $p<0.05$ comparing to any form of stimulus; † $p<0.05$ comparing to the analogous pool of plasma without rhCD40.

Disclosure: S. F. Perazzio, None; **P. V. S. Pereira**, None; **A. W. S. Souza**, None; **A. Condino-Neto**, None; **L. E. C. Andrade**, None.

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Abstract Number: 1371

Complement-Mediated Neutrophil Lysis-a Mechanism Promoting Hypercitrullination in Rheumatoid Arthritis?

Tal Gazitt[1], Christian Lood[2], Jeffrey Ledbetter[3] and Keith B. Elkon[3], [1]Rheumatology, University of Washington, Seattle, WA, [2]University of Washington, Lund, Sweden, [3]Division of Rheumatology, University of Washington, Seattle, WA

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Background/Purpose:

Protein citrullination, the post-translational conversion of arginine to citrulline, mediated by peptidylarginine deiminase (PAD) enzymes, is considered a likely mechanism for the stimulation of anti-citrullinated protein antibodies (ACPA) in patients with rheumatoid arthritis (RA). Hypercitrullination, the citrullination of multiple intracellular proteins, was recently demonstrated in synovial fluid cells from RA patients but was not found in other physiologic processes involving citrullination, such as NETosis (Romero *et al., Sci Transl Med,* 2013). This unique form of citrullination is proposed to occur via immune-mediated, pore-forming membranolytic pathways causing neutrophil cell death; one mediated by cytotoxic cells through the perforin-granzyme pathway, and the other mediated by complement activation and formation of the membrane attack complex (MAC). Since the evidence to support this hypothesis was derived from simulated *in vitro* systems, we explored the naturally occurring humoral mechanisms required for induction of complement-mediated neutrophil lysis.

Methods:

Neutrophils (PMNs) isolated from synovial fluid (SF) or peripheral blood (PB) of RA patients as well as in healthy controls (HC) were exposed to the inflammatory milieu found in RA joints. PMNs isolated from SF (n=3) and PB (n=25) of ACPA-positive RA patients as well as PB of HC (n=10) were screened for anti-neutrophil binding IgG, C3bi and C5b-9 complement component deposition, as well as PMN viability using annexin V and propidium iodide staining by flow cytometry analysis. In addition, PMNs isolated from HC were incubated with serum or SF from RA patients or normal human serum from the same healthy controls.

Results:

In the periphery, in the majority of patient samples, RA PMNs had highly increased mean fluorescence intensity (MFI) ratio for C3bi cell-surface deposition as compared to healthy controls ($p<0.05$), but no differences were seen in MFI of C5b-9 deposition. However, in SF samples, PMNs had elevated MFI ratio of C5b-9 as compared to PB PMNs from HC ($p<0.05$) and paired RA patients ($P< 0.0001$). Complement deposition on SF PMNs was also associated with decreased cell surface expression of the complement regulatory molecule CD46, as well as increased cell death, with more than 50% of the SF PMNs undergoing secondary necrosis, consistent with the notion of complement-mediated killing of SF PMNs. Moreover, incubation of HC PMNs with 15% RA SF, but not 15% serum from paired RA patients or HC induced C3bi and C5b-9 deposition, reduction in CD46 expression, and PMN lysis via secondary necrosis.

Conclusion:

RA PMNs, in particular SF PMNs, demonstrate increased complement deposition associated with PMN cell death both *in vivo* and *in vitro*. Elucidating the cause of complement deposition and the role of complement regulatory proteins in promoting PMN lysis may help to uncover a mechanism for hypercitrullination, ACPA formation and RA disease propagation.

Disclosure: T. Gazitt, None; **C. Lood**, None; **J. Ledbetter**, None; **K. B. Elkon**, None.

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Abstract Number: 1372

Characterization of Synovial Mast Cells in Knee Osteoarthritis: Association with Clinical Parameters

Badelog J.E. de Lange-Brokaar[1], Margreet Kloppenburg[1], Stefan Andersen[1], Annemarie Dorjee[1], Erlangga Yusuf[1], Linda van Toorn[1], Herman Kroon[2], Anne-Marie Zuurmond[3], Vedrana Stojanovic-Susulic[4], Johan Bloem[2], Rob Nelissen[5], René E. M. Toes[6] and **Andreea Ioan-Facsinay**[1], [1]Rheumatology, Leiden University Medical Center, Leiden, Netherlands, [2]Radiology, Leiden University Medical Center, Leiden, Netherlands, [3]TNO, Leiden, Netherlands, [4]Janssen, Pharmaceutical Companies Johnson & Johnson, Springhouse, PA, [5]Orthopaedics, Leiden University Medical Center, Leiden, Netherlands, [6]Department of Rheumatology, Leiden University Medical Center, Leiden, Netherlands

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Background/Purpose: Synovial inflammation is a common feature of osteoarthritis (OA) and rheumatoid arthritis (RA) patients. Comparative studies indicated that synovitis, measured by histology or imaging, is more severe in RA than in OA, which is also reflected in more infiltrating immune cells in RA than in OA. Intriguingly, mast cell numbers were found in some studies to be equal or lower in RA than OA. Here, we wished to expand these findings using immunofluorescence and to assess the possible relevance of mast cells in OA by studying their association with clinical parameters, such as radiographic damage and pain.

Methods: Synovial tissues of 56 symptomatic OA and 49 RA patients were obtained from arthroscopy (early disease) (22 OA, 23 RA) or arthroplasty (late disease) (34 OA, 26 RA). Two to three paraffin slides were used to quantify inflammation using haematoxylin and eosin staining (synovitis score 0-9), and to quantify and determine degranulation state of mast cells (per 10 high-power fields) using double immunofluorescence for CD117 and tryptase. Average scores per patient were used for analysis. Knee radiographs of OA patients were scored according to the Kellgren and Lawrence (KL) system and self-reported pain was determined in OA patients by visual analogue scale at baseline.

Results:

Median (range) of mast cells was significantly higher in OA samples 45 (1-168) compared to RA samples 4 (1-47) (p-value < 0.001), despite a lower median (range) synovitis score in OA (2.5 (0-6.0)) compared to 4.6 (0-8.0) in RA samples. This held true when comparing the subgroups of early and late samples between diagnoses. Similar percentages of mast cells were degranulated in both diseases at all stages, indicating that the abundance of these cells rather than degranulation state could be relevant for the disease process. The synovitis score correlated with the number of mast cells both in OA (Spearman's rho = 0.3, p =0.023) and RA (Spearman's rho = 0.5,p < 0.001), indicating that mast cells could contribute to synovial inflammation in both diseases, although their contribution is probably moderate. Interestingly, the number of mast cells was associated with an increased KL-grade (p-value 0.05) in OA patients, independently of synovitis. No associations were found with self-reported pain.

Conclusion:

Prevalence of mast cells in OA synovial tissue is higher than in RA. Interestingly, it appears to be associated with synovial inflammation, as well as structural damage in OA patients, suggesting a role of mast cells in this disease.

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Abstract Number: 1373

Epigenetic Mechanisms Contribute to the Lack of LPS-Induced Tolerance in Rheumatoid Arthritis Synovial Fibroblasts

Kerstin Klein[1], Renate E. Gay[1], Christoph Kolling[2], Adrian Ciurea[1], Diego Kyburz[1], Beat A. Michel[1], Lih-Ling Lin[3], Steffen Gay[1] and Caroline Ospelt[1], [1]Center of Experimental Rheumatology, University Hospital Zurich, Zurich, Switzerland, [2]Upper Extremity Dept., Schulthess Clinic Zurich, Zurich, Switzerland, [3]Inflammation and Immunology Research Unit, Pfizer, Cambridge, MA
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Background/Purpose:

In macrophages, repeated stimulation of Toll-like receptor (TLR) 4 leads to a tolerant state of the cell which protects inflamed tissues from damage. We have recently shown that rheumatoid arthritis (RA) synovial fibroblasts (SF) lack these protective mechanisms and maintain the secretion of inflammatory cytokines and matrix degrading metalloproteinases also after repeated LPS stimulation. The objective was to

investigate mechanisms behind tolerizable and non-tolerizable effects in RASF.

Methods:

RASF, osteoarthtitis (OA) SF, and *in vitro* differentiated peripheral blood derived macrophages from healthy donors and RA patients were treated with LPS (100 ng/ml) for 24h and then re-stimulated with LPS (10 ng/ml) for another 24h. The expression levels of interleukin (IL) 6, IL8, chemokine (C-X-C mofif) ligand 10 (CXCL10), matrix metalloproteinases (MMP) 1 and MMP3, as well as retionoic acid-inducible gene 1 (RIG1) and 2`-5`-oligoadenylate synthetase (OAS1) were analyzed by quantitative Real-time PCR or ELISA. Nuclear factor-κB (NF-κB) and activator protein-1 (AP-1) promoter activities in RASF (n=4) were evaluated by Dual-Luciferase reporter assays after repeated stimulation with LPS. The levels of histone 3 (H3) and H4 acetylation (H3ac, H4ac) as well as H3 lysine 4 trimethylation (H3K4me3) in promotor regions of tolerizable (OAS1, CXCL10) and non-tolerizable (IL6, IL8, MMP1, MMP3) genes in SF (n=3) were analyzed by Chromatin Immune precipitation (ChIP).

Results:

As expected, the expression of IL6 decreased in double-stimulated (886 ± 596 pg/ml) compared to single-stimulated (2368 ± 315 pg/ml; $p<0.01$) macrophages from healthy donors (n=4) and RA patients (n=6, $p=0.06$). On the other hand, RASF (n=10) and OASF maintained their production of IL6 after repeated TLR4 stimulation (RASF: single stimulation: 13.2 ± 5.8 ng/ml, double stimulation: 12.4 ± 7.1 ng/ml). A lack of tolerizable effects of RASF was also found for MMP1 and MMP3, whereas the interferon-responsive genes OAS1, RIG1 and CXCL10 were tolerizable. RASF (n=5) secreted 531 ± 385 pg/ml CXCL10 after a single LPS stimulation and 111 ± 97 pg/ml CXCL10 after double stimulation ($p<0.05$). Reporter gene activities for NF-κB and AP-1 were similar in single and double stimulated RASF, excluding potential differences in the activation of these transcription factors as underlying mechanisms for tolerizable/non-tolerizable effects in RASF. Interestingly, the levels of the activating histone marks H4ac and H3K4me3 were decreased by LPS double compared to single stimulation of SF in different promoter regions of OAS1 and CXCL10, whereas these chromatin marks were not changed or even increased in promoter regions of IL6, IL8, MMP1 and MMP3. On the other hand, changes in the levels of H3ac after LPS double stimulation did not distinguish tolerizable from non-tolerizable genes.

Conclusion:

Epigenetic modifications on target gene promoters are likely to contribute to differences in tolerization between RASF and macrophages. Since many pro-inflammatory cytokines and MMPs are non-tolerizable genes in RASF, we conclude that the lack of tolerization in these cells keeps RASF aggressive in persistent inflammation.

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Abstract Number: 1374

Mucosal-Associated Invariant T- Cells Are Decreased and Functionally Immature in Peripheral Blood of Patients with Primary Sjögren Syndrome

Tatjana Banovic[1,2,3], Jing Jing Wang[4], Dimitra Beroukas[5], Pravin Hissaria[6] and Tom Gordon[2,6], [1]Immunology, Level 3, SA Pathology, Adelaide, Australia, [2]Flinders University, Adelaide, Australia, [3]Pediatrics, University of Adelaide, Adelaide, Australia, [4]Immunology, Flinders University, Adelaide, Australia, [5]SA Pathology, Adelaide, Australia, [6]Immunology, SA Pathology, Adelaide, Australia
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SESSION INFORMATION
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Background/Purpose: Primary Sjögren Syndrome (pSS) is characterized by organ-specific autoimmune destruction of salivary and lacrimal glands. Patients typically experience debilitating symptoms of dry mouth and eyes and commonly develop systemic complications including renal tubular acidosis, arthritis, polysynovitis, refractory pulmonary disease, mixed cryoglobulinaemia, polyclonal hypergammaglobulinaemia and lymphoma. The risk of developing lymphoma is 30-40 times higher in patients with pSS compared to the

general population. Autoimmune destruction of glandular tissue in pSS is mediated by conventional CD4+ T helper (Th) – cells but little is known about the involvement of non-conventional, innate-like T-cells in this process. Mucosal-Associated Invariant T (MAIT) - cells are a novel sub-population of unconventional T-cells at the frontier between innate and adaptive immunity. They comprise up to 10% of peripheral blood (PB) T-cells in humans. They accumulate primarily in the intestinal lamina propria and are endowed by a "natural memory" phenotype and function. MAIT cells are able to rapidly produce high levels of Th1, Th2 and Th17 cytokines. One of their proposed roles is protection of mucosal surfaces against vitamin B-metabolizing bacteria and yeasts. To our knowledge, the role of MAIT cells in the pathogenesis of primary Sjögren Syndrome (pSS) has not yet been explored.

Methods: We studied the frequencies, immunophenotype and function of MAIT-cells in the PB of patients with pSS (N=50) and healthy control subjects (HC, N= 22) by using 8- colour flow cytometry and in vitro stimulation assays.

Results: We showed that MAIT cells are significantly decreased in patients with pSS. Furthermore, the residual MAIT cells in pSS patients showed altered immunophenotype and function. While in the HC subjects MAIT cells were almost exclusively $CD8^+$ and expressed an effector memory immunophenotype, in pSS patients they were enriched in $CD4^+$and naïve subpopulations. This is consistent with our functional studies which demonstrated that MAIT cells from pSS showed a lower level of activation with reduced expression of CD69 and CD154 (CD40L), and a lower production of TNF and IFNγ.

Conclusion: We propose that the reduced frequencies and functional immaturity of MAIT cells in patients with pSS, may result in impaired protective mucosal barrier function and dysregulation of mucosal immunity with subsequent microbial damage to mucosal surfaces and initiation of the autoimmune response. A better understanding of the immunophenotype and function of this novel innate-like T-cell subpopulation in patients with pSS is required in order to evaluate their involvement in the evolution of severe mucosal damage and systemic complications in patients suffering from this debilitating disease.

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Abstract Number: 1375

S100A8/A9, a Serum and Imaging Biomarker for Assessing Joint Inflammation and Destruction in Experimental Seronegative Arthritis

Edwin J. W. Geven[1], Shahla Abdolahi-Roodsaz[1], Annet Sloetjes[1], Marije I. Koenders[1], Dirk Föll[2], Johannes Roth[3], Thomas Vogl[3] and Peter L. E. M. van Lent[1], [1]Experimental Rheumatology, Radboud university medical center, Nijmegen, Netherlands, [2]Department of Pediatric Rheumatology and Immunology, University of Münster, Münster, Germany, [3]Institute of Immunology, University of Münster, Münster, Germany

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SESSION INFORMATION

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Session Time: 9:00AM-11:00AM

Background/Purpose:

Seronegative joint diseases such as psoriatic arthritis and juvenile idiopathic arthritis are characterized by the lack of autoantibodies, potent biomarkers used for predicting disease activity and outcome in seropositive joint diseases. Promising alternative biomarkers for detecting disease activity in seronegative arthritis are the Damage Associated Molecular Patterns (DAMPs) S100A8 and S100A9 proteins specifically expressed and released by infiltrating phagocytes in the inflamed joint. In this study, we explore the biomarker potential of serum S100A8/A9 and in vivo imaging of synovial S100A8 to assess joint inflammation and damage in IL-1 receptor antagonist deficient ($IL\text{-}1Ra^{-/-}$) mice, a mouse model for seronegative arthritis in which serum autoantibodies are not correlated to disease activity.

Methods:

Serum of $IL\text{-}1Ra^{-/-}$and WT (BALB/c genetic background) mice was collected every two weeks starting at week 4 until end-point at week 16, and swelling in the hind paws was macroscopically scored on a scale of 0 to 4. Serum levels of IL-1β, IL-6 and TNFα were measured by Luminex technology and S100A8/A9 complex levels by ELISA. Hind paws were isolated and histologically scored for cell influx,

cartilage damage and bone erosion. Paraffin sections of the hind paws were also stained for S100A8 expression. Synovial S100A8 was imaged by injection of anti-S100A8-Cy7 antibody and 24 hour p.i. fluorescent images were acquired in the IVIS Lumina optical imaging system.

Results:

Starting at week 8 up to week 16, serum levels of S100A8/A9 in IL-1Ra$^{-/-}$ mice were significantly increased (1640 ± 1008 ng/ml at week 16) compared to basal levels in WT mice (429 ± 191 ng/ml, $P = 0.005$) and strongly correlated to joint swelling (r = 0.740, $P < 0.0001$). Histological analysis of hind paws showed that joint inflammation but also cartilage and bone destruction (r = 0.672 – 0.770, $P < 0.0001$) significantly correlated to serum S100A8/A9 levels, in contrast to levels of IL-1β, IL-6, and TNFα. Serum S100A8/A9 levels already correlated to joint swelling (r = 0.410, $P = 0.047$) as early as week 8 and high serum levels at week 10 were predictive for increased joint swelling at week 16 (r = 0.563, $P = 0.004$). Local expression of S100A8 within the synovium as detected by immunolocalisation correlated to joint damage and serum S100A8/A9 levels, indicating the activated synovial lining as the source of increased serum S100A8/A9. Imaging of S100A8 using specific anti-S100A8-Cy7 antibody showed a significant uptake in inflamed joints of IL-1Ra$^{-/-}$ mice when compared to a control isotype ($P = 0.044$). In non-arthritic IL-1Ra$^{-/-}$mice no specific S100A8 targeting was observed.

Conclusion:

High levels of serum S100A8/A9 correlate to joint inflammation and destruction in experimental seronegative arthritis and local synovial expression of S100-DAMPs can be monitored in vivo by molecular imaging. These findings underline the potential of S100-DAMPs as a serum and imaging biomarker for disease severity in seronegative arthritis.

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Abstract Number: 1376

Presence of the Interferon Signature in Anti-Nuclear Antibody Positive Individuals Prior to the Onset of Systemic Autoimmune Rheumatic Disease

Joan Wither[1], Tony Liu[1], Babak Noamani[2], Dennisse Bonilla[1], Sindhu R. Johnson[3], Earl Silverman[4], Arthur Bookman[1], Larissa Lisnevskaia[5] and Carolina Landolt-Marticorena[1], [1]University Health Network, Toronto, ON, Canada, [2]Genetics and developmental biology, University Health Network, Toronto, ON, Canada, [3]Toronto Scleroderma Program, Toronto Western Hospital, Mount Sinai Hospital, University of Toronto, University Health Network Pulmonary Hypertension Programme, Toronto, ON, Canada, [4]The Hospital for Sick Children, Toronto, ON, Canada, [5]Lakeridge Health Services, Oshawa, ON, Canada

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Background/Purpose: Patients with systemic autoimmune rheumatic diseases (SARD) often have a prolonged pre-clinical phase during which they are anti-nuclear antibody (ANA)$^{+}$ but lack clinical symptoms. It has been proposed that progression from asymptomatic autoimmunity to clinical disease is accompanied by immunologic changes that could be used as predictors of disease development. Elevated levels of interferon (IFN)-induced gene expression, termed the IFN signature, are found in several SARD conditions, and IFNs appear to play an important role in disease pathogenesis. In this study we examined whether ANA^{+}individuals who lack sufficient symptoms for a SARD diagnosis share the IFN-signature.

Methods: ANA^{+}individuals who: 1) lacked clinical symptoms of SARD (ANS); 2) had a least one clinical symptom of SARD (UCTD); or 3) had a recently diagnosed steroid and immunosuppressive naïve SARD (SLE, SS, SSc, MCTD, DM) were recruited from clinics at UHN/MSH hospitals. Healthy controls (HC) were also recruited. RNA was prepared from blood archived in Tempus tubes. Expression of 5 IFN-induced genes was quantified by NanoString, normalized to expression of housekeeping genes, and summed to generate an IFN5 score. ANAs, serum complements, and levels of specific autoantibodies were measured by the hospital laboratory.

Results: : To date we have measured the IFN signature on 96 individuals (17 HC, 24 ANS, 17 UCTD, 22 SS, 8 SSc, 6 SLE, 1 MCTD, 1 DM). Higher mean IFN scores were seen in all ANA+ sub-groups as compared to HC (mean ± SD: HC 5,380 ± 1,619; ANS 25,886 ± 34,092; UCTD 28,252 ± 24,827; SSc 34,940 ± 40,940; SS 61,877 ± 33,404; SLE 62,769 ± 50,233; MCTD/DM 97,716 ± 24,973), which achieved statistical significance for ANS, UCTD, SSc, SS, and SLE subsets (corrected $p = 0.0036$, 0.0006, 0.048, < 0.0001, 0.0054, respectively). Using a cutoff of 3 SD above the mean of HC as indicative of an elevated IFN5 score, 10/24 ANS, 10/17 UCTD, 5/7 SSc, 19/22 SS, 5/6 SLE, and 2/2 MCTD/DM participants had elevated IFN levels. Marked elevations of the IFN5 score were seen in a subset of ANS and UCTD participants, which could not be attributed to recent infection. Although there was a significant correlation between the ANA titer ($p = 0.0006$) and IFN5 score for all ANA^+ individuals, this was not seen in the ANS or UCTD subsets of this population. However the IFN5 score was positively correlated with the number of different ANA specificities present in the UCTD subset ($p = 0.026$) and all ANA^+ individuals ($p < 0.0001$). The IFN5 score was significantly higher in ANA^+ individuals who were anti-Ro antibody positive, as compared to those who were negative. Within the ANS subset, there was a strong correlation between the presence of anti-Ro/La antibodies with 6/10 $IFN5^{high}$ as compared to 1/14 IFN^{low}individuals being antibody positive ($p = 0.009$). There was no association between the IFN5 score and the presence or absence of other autoantibody specificities, or complement levels.

Conclusion: An IFN signature is seen in a subset of ANA^+ individuals prior to a confirmed diagnosis of SARD and appears to correlate with the number and type of specific ANAs rather than clinical disease.

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Abstract Number: 1377

IL-22 Drives the Proliferation and Differentiation of Human Bone Marrow Mesenchymal Stem Cells (MSCs); A Novel Pathway That May Contribute to Aberrant New Bone Formation in Human Spa and Beyond

Yasser El-Sherbiny[1], Ahmed Elzayadi[2], Evangelos M. Fragkakis[1], Richard Cuthbert[1], Thomas Baboolal[3], Elena Jones[1] and Dennis McGonagle[1], [1]Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds, Leeds, United Kingdom, [2]Obstetrics and Gynaecology, Mansoura University, Egypt, MD, MSc., Mansoura, Egypt, [3]PhD, Leeds, United Kingdom
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Background/Purpose:

The human spondyloarthropathies (SpA) are associated with single nucleotide polymorphisms (SNPs) in the IL-23 pathway and IL-23/17 axis therapy is effective in SpA. The SpAs are also associated with new bone formation that is to a degree independent of TNF blockade. Given that IL-23R receptor signaling in lymphoid cells is associated with IL-22 production and since IL-22 is a pivotal cytokine that maintains gut and skin stem cell function[1,2], we hypothesized that IL-22 might also drive skeletal stem cells and hence contribute to the SpA bone phenotype. Therefore we explored the effect of IL-22 on bone marrow mesenchymal stem cells (MSCs).

Methods:

Human Bone marrow MSCs were expanded and tested by multi-parameter flow cytometry for expression of the ISCT criteria for MSCS and IL-22R. IL-22R priming was undertaken with IFN gamma and TNF alpha prior to recombinant IL-22 exposure. MSC proliferation and migration were tested by colorimetric XTT assay and chamber migration assays. MSC osteogenic functional differentiation was performed with and without cytokines.

Results:

MSCs expressed low level IL22RA1 which was significantly up-regulated in combination with IFN gamma and TNF alpha, Mean

fluorescent intensity (MFI) increased 1.8±0.12 fold. MSCs proliferation and migration dramatically increased following IL-22 exposure after IFN gamma and TNF alpha combined priming compared to IL-22 alone or no cytokine (p= 0.0159 and 0.028). MSCs migration function was enhanced by IL-22 after priming with IFN gamma and TNF alpha compared to no cytokine (p= 0.0159). Osteogenic differentiation was significantly higher in MSCs exposed to IL-22 alone (p=0.002), but was depressed when IL-22 combined with IFN gamma and TNF alpha compared to IL-22 alone or no cytokine (p=0.002 and p=0.003).

Conclusion:

Given that IL-22 is exclusively produced by lymphoid cells and acts on non-lymphoid cells including stem cells, our findings confirm that IL-22 can drive bone marrow MSC osteogenesis. Furthermore, IL-22 boosted MSCs proliferation and migration after priming with IFN gamma & TNF alpha *in vitro* and had variable effects depending on the inflammatory milieu. Given the IL23 axis association with SpA this work opens up a novel pathway for exploring new bone formation in SpA related disease.

Disclosure: Y. El-Sherbiny, None; **A. Elzayadi**, None; **E. M. Fragkakis**, None; **R. Cuthbert**, None; **T. Baboolal**, None; **E. Jones**, None; **D. McGonagle**, None.

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Abstract Number: 1378

AMP-Activated Protein Kinase As an Anti-Inflammatory Target for Methotrexate

Cornelia Cudrici[1], Amma Agyemang[1], Martin Pelletier[1], Gregory Steinberg[2] and Richard M. Siegel[1], [1]NIAMS, Immunoregulation Section, Autoimmunity Branch, Bethesda, MD, [2]Department of Medicine, Division of Endocrinology,McMaster University, Hamilton, ON, Canada

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Background/Purpose:

Methotrexate (MTX) is a first-line medication effective in multiple forms of inflammatory arthritis. The anti-inflammatory effects of MTX are more prolonged than its plasma half-life might suggest and most likely are the result of accumulation of polyglutamate metabolites in tissues. Inhibition of 5-aminoimidazole-4-carboxamide ribonucleotide (AICAR) transformylase by methotrexate metabolites result in elevation of intracellular levels of AICAR, which is a potent inhibitor of AMP deaminase and adenosine deaminase. The consequent increase in intracellular and released adenosine has led to the hypothesis that adenosine mediates the anti-inflammatory effects of MTX. In addition to regulating nucleotide metabolism AICAR is also is also an endogenous activator of the intracellular energy sensor AMPK, a highly conserved protein kinase that exists in all eukaryotic cells. AMPK is activated by an increasing cellular AMP/ATP ratio secondary to metabolic stresses or accelerated ATP consumption, and promotes ATP production by promoting catabolism and autophagy and suppressing energy-consuming biosynthetic pathways. Parallel studies of immune cell metabolism have shown that activating catabolic pathways can have anti-inflammatory effects. We hypothesize that AMPK activation through AICAR may mediates a major portion of the anti-inflammatory effects of MTX, and that this may account for some of the efficacy of MTX in rheumatic diseases.

Methods:

Human monocytes derived macrophages (MDM) and murine bone marrow-derived macrophages were treated with MTX, AICAR, folic acid and A769662, a small-molecule that activates AMPK independently of AMP. AMPK phosphorylation and total AMPK was measured by Western blotting. We have also used compound C, a selective ATP-competitive inhibitor of AMPK in order to determine whether MTX exhibits anti-inflammatory through AMPK. Cells were then stimulated with LPS and production of pro-inflammatory cytokines were measured in the supernatant.

Results:

MTX induced AMPK phosphorylation in a time and dose-dependent manner, with effects comparable to the synthetic AMPK activator A769662 and AICAR. Mitochondrial oxygen consumption and the ATP/ADP ratio were not altered by MTX, suggesting that AMPK

activation by MTX was not due to suppression of ATP generation. MTX-induced AMPK activation was associated with a reduction in production of pro-inflammatory cytokines (IL-6 and TNF) in response to LPS. Compound C is able to partially reverse the effects of MTX on LPS-induced cytokine production, suggesting that AMPK activation is responsible for these anti-inflammatory effects.

Conclusion: Methotrexate is able to induces AMPK activation in both human and mouse macrophages, and suppress pro-inflammatory cytokines in a manner dependent on AMPK activity. These results are being confirmed genetically in macrophages deficient in AMPK subunits. Our findings raise the possibility that some anti-inflammatory effects of MTX are mediated by AMPK, suggest that AMPK may be a target for the action of current 'antimetabolite' anti-inflammatory agents and a target for the development of new anti-inflammatory drugs.

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Abstract Number: 1379

High Serum IgG4 Concentration Is a Risk Factor for Relapse in IgG4-Related Disease

Sho Sendo[1], Jun Saegusa[1], Akira Onishi[2], Ikuko Naka[1], Kosaku Tsuda[1], Takaichi Okano[1], Kengo Akashi[1], Soshi Takahashi[1], Miwa Nishida[1], Keisuke Nishimura[1], Yo Ueda[1], Yoshinori Kogata[3], Goichi Kageyama[1], Goh Tsuji[4], Shunichi Kumagai[5] and Akio Morinobu[1], [1]Department of Rheumatology, Kobe University Hospital, Kobe, Japan, [2]Department for Rheumatology, Kobe University Hospital, Kobe, Japan, [3]Department of Clinical Pathology and Immunology, Kobe University Hospital, Kobe, Japan, [4]Center for Rheumatic disease, Shinko Hospital, Kobe, Japan, [5]Center for Rheumatic Disease, Shinko Hospital, Kobe, Japan

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Background/Purpose: IgG4-related disease (IgG4-RD) is a recently recognized systemic fibro-inflammatory disease of unknown etiology with multi-organ involvement. Although the organ involvement in IgG4-RD usually improve with initial glucocorticoids (GC) therapy, relapse occurs frequently during GC tapering. This study was aimed to elucidate the factors influencing the relapse of IgG4-RD during GC therapy.

Methods: Thirty-five IgG4-RD patients were enrolled. They all met Comprehensive Diagnostic Criteria for the diagnosis of IgG4-RD and were treated with GC in Kobe university hospital or Shinko hospital, Kobe, Japan. "Relapse" was defined as recurrence or new appearance of organ involvement attributable to IgG4-RD which required increase in immunosuppressive therapy. Association of various clinical parameters and relapse was determined by Students' t-test or Welch's t-test. Relapse-free survival was compared by the Kaplan-Meier estimation.

Results: Ten female and 25 male patients were retrospectively analyzed. The mean age at the time of diagnosis was 63.9±10.2 years (range 45-81). All 35 patients were treated with GC, and 14 patients relapsed (40%). The mean duration from the initiation of GC therapy to relapse was 27.0±18.7 weeks. The baseline serum IgG4 levels before GC therapy was significantly higher in patients with relapse than in those without (P=0.017; median 843 to 426 mg/dl). Minimum serum IgG4 levels during GC therapy also tended to be higher in patients with relapse than that in patients without (P=0.055; median 185 to 102 mg/dl). In contrast, sex, age at the diagnosis, numbers of involved organs, initial GC dose, and GC dose in maintenance therapy were not different between patients with and without relapses. ROC curve analysis on baseline serum IgG4 level revealed that the best cut-off level which maximized sensitivity and specificity for the prediction of relapse was 532mg/dl. The patients with baseline serum IgG4 level less than 532 mg/dl ("baseline IgG4<532 group") showed better relapse-free survival than "baseline IgG4≥532 group" (Log-rank test, (X^2 = 5.94, P=0.015)) (Figure 1). In addition, when patients were divided into two groups according to whether their IgG4 levels declined below 135 mg/dl ("minimum IgG4<135 group") or not ("minimum IgG4≥135 group") during therapy, the former showed better relapse-free survival (Log-rank test, (X^2 = 4.85, P=0.027)) (Figure 2).

Conclusion: Higher serum IgG4 concentration before and during GC therapy are risk factors for predicting relapse in IgG4-RD. Serum IgG4 levels should be monitored during the therapy.

Figure 1

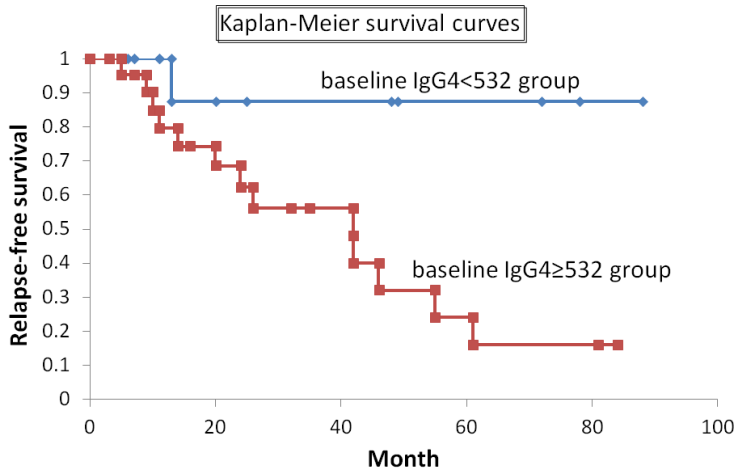
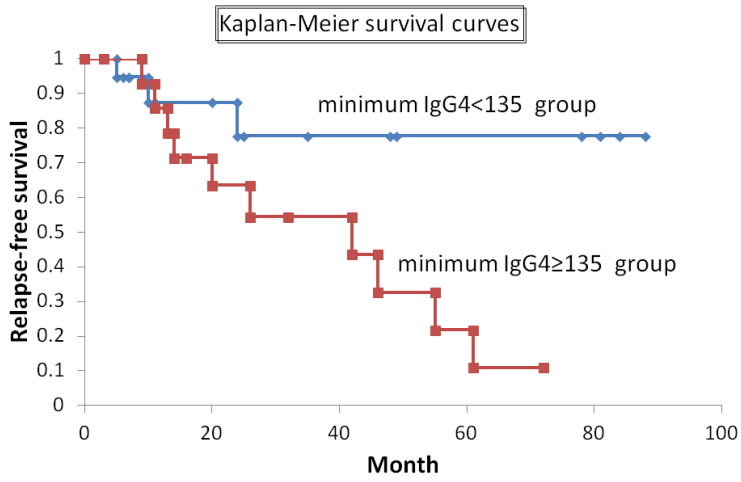


Figure 2



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Abstract Number: 1380

Characterization of Lymphocytes Subsets in Peripheral Blood of Untreated IgG4-Related Disease Patients

Aurélie Grados[1], Mikael Ebbo[1], Christelle Piperoglou[2], Matthieu Groh[3], Alexis Regent[4], Maxime Samson[5], Benjamin Terrier[6], Nathalie Morel[7], Sylvain Audia[5], Francois Maurier[8], Julie Graveleau[9], Mohamed Hamidou[10], Amandine Forestier[11], Sylvain Palat[12], Emanuelle Bernit[1], Gilles Kaplanski[13], Frederique Retornaz[14], Bernard Bonotte[5], Catherine Farnarier[15], Jean-Robert Harle[16], Nathalie Costedoat-Chalumeau[7], Frederic Vely[17] and Nicolas Schleinitz[1], [1]Internal Medicine, Aix-Marseille Université, AP-HM, Marseille, France,

[2]Immunology, CIML, AP-HM, Marseille, France, [3]National Referral Center for Rare Systemic Autoimmune Diseases, Hôpital Cochin, AP–HP, Université Paris Descartes, Paris, France, [4]Service de médecine interne, Hôpital Cochin, Paris, France, [5]Department of Internal Medicine and Clinical Immunology, Dijon University Hospital, Dijon, France, [6]Internal Medicine, National Referral Center for Rare Systemic Autoimmune Diseases, Hôpital Cochin, Paris, France, [7]Internal Medicine Department, Cochin Hospital, "René-Descartes Paris V" University, Paris, France, [8]HP Metz Belle Isle Hospital, Department of Internal Medicine, Metz, France, [9]Medecine Interne Hotel Dieu Nantes, Nantes, France, [10]Internal Medicine Department, Nantes University Hospital, Nantes, France, [11]Internal Medicine, Groupe Hospitalier Mutualiste de Grenoble, Grenoble, France, [12]Service de Medecine Interne, CHU limoges, Limoges, France, [13]Internal Medicine hopital conception, Aix-Marseille Université, Marseille, France, [14]Conseil General 13 cellule recherche, Marseille, France, [15]Laboratoire d'immunologie, Hopital de la Conception, Marseille, France, [16]Internal Medicine, Aix-Marseille Université, APHM, Marseille, France, [17]CIML, Laboratoire d'Immunologie Conception AP-HM, Aix-Marseille université, Marseille, France
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Background/Purpose: IgG4-related disease (IgG4-RD) is associated with characteristic pathological changes including lymphoplasmocytic infiltration with abundant IgG4 positive plasma cells, storiform fibrosis and obliterative phlebitis. The etiology of the disease is unknown but a chronic antigen driven process leading to the production of IgG4 and $IgG4^+$ plasmablasts is proposed. Various T cell subsets have been analyzed in the disease however in small studies. Their role remains unclear. We conducted a study to characterize peripheral blood immune cells subsets in patients with untreated IgG4-RD.

Methods:

Thirty patients with IgG4-RD were included prospectively in the study and compared to healthy controls (HC) and primary Sjögren syndrome (pSS) patients. Patients fulfilled the 2011 comprehensive IgG4-RD diagnostic criteria and the 2002 American-European Consensus Group criteria for pSS. PBMC of patients and controls were analyzed by flow cytometry on a BD FACS Canto II. T regulatory cells were characterized as $CD4^+$ $FoxP3^+$ $CD25^{high}CD127^{low}$, T cells were categorized as memory or naive by CD45RO and CD45RA expression, B cells were categorized as naive or switched memory by IgD and CD27 expression, plasmablasts were characterized as $CD19^+CD27^{high}CD38^{high}$, dendritic cells were categorized as plasmacytoid or myeloid by CD11c and CD123 expression, NK cells were characterized as $CD3^-$ $CD56^+CD16^+$.$CD4^+$ T helper subsets were analyzed after stimulation by intracellular staining for IL-4 (Th2), IFNg (Th1) and IL-17 (Th17). The cytokine production for IL-4, IL-10 and IL-17 was performed with the cytokine bead assay (CBA® kit, BD Biosciences) on supernatant of stimulated PBMC. Statistical analysis was performed on PRISM software.

Results:

The frequency and absolute number of total T cells, $CD4^+$ and $CD8^+$T cells, CD45RA and CD45RO, total DC, T regulatory cells, NK cells, B and naive B cells did not show any changes between IgG4-RD patients and HC. pDC were decreased in IgG4-RD compared with HC ($p=0.01$) and pSS ($p=0.01$). Plasmablasts frequency ($p=0.0003$) and absolute numbers ($p=0.0004$) were increased in IgG4-RD patients when compared to HC. T helper subsets analysis showed an increase of Th2 cells ($p=0.0004$), Th17 cells ($p=0.03$) but not Th1 cells when compared to HC. The cytokine production by PBMC showed an increased release of IL-4 ($p<0.0001$), IL-10 ($p=0.004$) and IL-17 ($p=0.001$) by IgG4-RD compared to HC.

Conclusion: Baseline changes of immune cells in peripheral blood of IgG4-RD patients is characterized by plasmablast expansion, as previously reported, a decrease of plasmacytoid DC and a T helper switch to Th2 IL-4 producing cells. We also show an increase in IL-10 release and an increase of both Th17 cells and IL-17 release. Further studies are required to elucidate the role of these different subsets in the pathogenesis of IgG4-RD.

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Abstract Number: 1381

The Relationship Between Serum Cholinesterase, Number of Organ Involvement and Fibrotic Markers in Japanese Patients with IgG4-Related Disease

Hirofumi Nishikawa[1], Yoshinori Taniguchi[1], Yoshiko Shimamura[1], Kosuke Inoue[1], Taro Horino[1], Susumu Nishiyama[2], Yasuhiko Yoshinaga[2] and Yoshio Terada[1], [1]Kochi University, Nankoku, Japan, [2]Kurashiki Medical Center, Kurashiki, Japan
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Background/Purpose: To evaluate the relationship between cholinesterase, number of organ involvement and serum fibrotic markers in Japanese patients with IgG4-related disease (IgG4-RD).

Methods: The clinical symptoms, laboratory, pathological and FDG-PET/CT findings of Japanese patients with IgG4-RD (n=20) were assessed. Several laboratory data of IgG4-RD with multiple organs' involvements (IRDMOI) (n=10), IgG4-RD with limited organ's involvement (IRDLOI) (n=10), ANCA-associated vasculitis (AAV) (n=10) and Sjogren syndrome (SjS) (n=10) were comparatively examined. Furthermore, we studied the relationship between the numbers of organ involvement (NOI) and several fibrotic markers (ELF score and serum Dkk-1) in IgG4-RD group.

Results: Serum cholinesterase (ChE) levels were significantly lower in IRDMOI group than IRDLOI, AAV and SjS groups. All cases did not show hepatic dysfunction in laboratory examinations. Serum albumin and IgG levels were significantly lower and CRP levels were significantly higher in AAV group, compared with IgG4-RD and SjS group. There were no significant differences in these levels between IRDMOI and SjS. In total IgG4-RD cases, ChE levels inversely correlated with NOI and fibrotic score, and fibrotic score positively correlated with NOI. Finally, Dkk-1, one of Wnt inhibitors, levels in IRDMOI were significantly lower than IRDLOI and healthy subjects ($p<0.05$).

Conclusion: The ELF score and serum Dkk-1 level might be a clinically useful indicators of active fibrosis and the extent of disease in Japanese patients with IgG4-RD. Notably, serum ChE levels could predict these phenomena.

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Abstract Number: 1382

Clinical and Serum IgG4 Characteristics of a Unique British Columbian IgG4-Related Disease Cohort

Luke Chen[1], Andre Mattman[2], Sujin Park[3], Brian Skinnider[4], Graham Slack[4] and **Mollie Carruthers**[5], [1]Hematology, University of British Columbia, Vancouver, BC, Canada, [2]Medical Biochemistry, University of British Columbia, Vancouver, BC, Canada, [3]University of British Columbia, Vancouver, BC, Canada, [4]Pathology, University of British Columbia, Vancouver, BC, Canada, [5]Rheumatology, University of British Columbia, Vancouver, BC, Canada
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Background/Purpose:

IgG4-related disease (IgG4-RD) is a fibro-inflammatory disorder that is known to have protean manifestations and variably elevated serum IgG4 concentrations. We present the serum IgG4 characteristics and clinical features of a unique cohort of IgG4-related disease patients in British Columbia. Anecdotally, Asians seem to have more exuberant immunoglobulin production but this has not been formally studied to date.

Methods:

All patients are residents of British Columbia and have biopsy proven IgG4-related disease according to consensus guidelines. Each patient underwent full history and physical examination by two IgG4-related disease physician experts. All patients underwent serum IgG4 levels by nephlometry. Unpaired t-test was used for serum IgG4 comparisons.

Results:

There were 19 patients with IgG4-related disease. The mean age at time of IgG4-RD diagnosis was 61 years old (range: 28-85) and the male:female ratio was 55:45. The time to diagnosis was lengthy at 9 years, on average, from start of symptoms. The organ involvement included salivary glands (n=7), lymph nodes (n=3), lacrimal gland (n=3), kidneys (n=2), genitourinary tumor (n=2), amongst others. Treatments included prednisone (n=10), rituximab (n=5), azathioprine (n=2), cyclosporine (n=2), fludarabine (n=1) and bortezomib (n=1). An additional 4 patients were undergoing observation only. Serum IgG4 levels were on average elevated at 10 g/L ± 9 (cutoff >1.25) as were IgG levels at 35 g/L ± 18 (cutoff >15.2). There was a statistically significant difference between IgG4-RD levels of Chinese and East Asians patients (n=10) averaging 13.8 g/L (range: 2.3-26.9) and Caucasians (n=9) averaging 3.0 g/dL (range: 0.418-9.75) (p=0.021).

Conclusion:

This is a unique multi-ethnic cohort of IgG4-related disease patients in Canada. There are statistically significant, possibly genetically related, differences in Asian and Caucasian serum IgG4 concentrations.

Disclosure: L. Chen, None; **A. Mattman**, None; **S. Park**, None; **B. Skinnider**, None; **G. Slack**, None; **M. Carruthers**, None.

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T-Cell Subset Analysis in IgG4-Related Disease and Lymphocyte-Variant Hypereosinophilic Syndrome

Mollie Carruthers[1], Bakul Dalal[2], Sujin Park[3], Graham Slack[2], Andre Mattman[4] and Luke Chen[5], [1]Rheumatology, University of British Columbia, Vancouver, BC, Canada, [2]Pathology, University of British Columbia, Vancouver, BC, Canada, [3]University of British Columbia, Vancouver, BC, Canada, [4]Medical Biochemistry, University of British Columbia, Vancouver, BC, Canada, [5]Hematology, University of British Columbia, Vancouver, BC, Canada

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Background/Purpose:

IgG4-related disease (IgG4-RD) and lymphocyte-variant hypereosinophilic syndrome (L-HES) share elevated peripheral eosinophilia and IgE levels as well as common clinical features including atopy, cutaneous lesions and lymphadenopathy. Distinguishing between these two diseases is a diagnostic challenge. L-HES is driven by an aberrant population of T lymphocytes characterized by an abnormal immunophenotype, clonal T-cell receptor rearrangements, or both. Determining whether there is overlap in the immunphenotype of T-cells in IgG4-RD with L-HES will be helpful in the diagnosing and understanding the pathophysiology of these conditions.

Methods:

IgG4-RD patients were biopsy proven according to consensus guidelines and HES patients fit WHO criteria for HES including persistent

blood eosinophilia >1,500/mm3 at a single Canadian academic center. There were 9 patients with L-HES and 11[p1] patients with IgG4-related disease. Peripheral blood T-cell immunophenotyping was performed by multicolor flow cytometry using an antibody panel consisting of CD2, 3, 4, 7, 8, 45 and 56. Polymerase chain reaction was used to analyze T-cell receptor clonality.

Results:

There were three IgG4-related disease patients with elevated CD4+/7- T-cell subsets median 14.5% (range 11-16.5; cut-off>10) and 6 additional IgG4-RD patients had normal subsets. Two IgG4-related disease patients had elevated NK cells. None of the IgG4-RD patients had a clonal T-cell receptor rearrangement by PCR. All nine L-HES patients had an abnormal phenotype, including increased CD4+/3- (n=4), CD4+/3-/8- (n=3), CD4+/7- (n=1) and increased NK cells (n=1). There were 5 HES patients, out of 8 total measured, with clonal T-cell receptor rearrangements by PCR, including the patient with an elevated CD4+/7- population.[p2]

Conclusion:

Five of eleven patients with IgG4-RD had immunophenotypic abnormalities of the T-lymphocytes which overlap with the immunophenotypic abnormalities seen in L-HES. However, none of the IgG4-RD patients had a clonal T-cell rearrangement by PCR, indicating that the expanded CD4+/7- and NK populations seen in this disease are likely a nonspecific finding also seen in other inflammatory/autoimmune disorders.

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Comparison of IgG4-Related and Non-IgG4-Related Retroperitoneal Fibrosis; A 12 Year Retrospective Study

Piyush Poddar[1,2], Steven Billings[3], Leonard H. Calabrese[4] and Carmen E. Gota[5], [1]Rheumatology, Sanford Medical center, Bismarck, ND, [2]Rheumatology, Cleveland Clinic, Cleveland, OH, [3]Department of Anatomic Pathology, Cleveland Clinic, Cleveland, OH, [4]Rheumatic & Immunologic Dis, Cleveland Clinic Foundation, Cleveland, OH, [5]Orthopedic and Rheumatologic Institute, Cleveland Clinic, Cleveland, OH

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Comparison of IgG4-related and Non-IgG4-related Retroperitoneal fibrosis; a 12 year Retrospective Study

Background/Purpose: Retroperitoneal fibrosis (RPF) is a rare disease characterized by a progressive proliferation of fibro-inflammatory tissue in the periaortic region leading to abdominal pain, back pain, renal failure, etc. Over 2/3rd cases of RPF are idiopathic. Prior studies, using various criteria to define IgG4 RPF, have suggested an association of idiopathic RPF (IRPF) with IgG4-related disease (IgG4RD) with a frequency between 28-58%, while little is known about the clinical outcome of these patients.

We were interested to determine the prevalence of IgG4-related RPF amongst IRPF and their clinical characteristics and outcomes compared to non-IgG4-related RPF.

Methods: Retrospective chart review of all biopsy proven cases of IRPF between 1/1/2003 to 4/3/2015 presenting at Cleveland Clinic. Data including demographics, history, labs, imaging, treatment and outcomes were collected. IgG4RD was defined as compatible clinical presentation along with characteristic HP – dense lymphoplasmacytic (LP) infiltrate; fibrosis, usually storiform and obliterative phlebitis (OP); with immunohistochemistry (IHC) showing ≥30 IgG4+ plasma cells/ HPF and IgG4+/IgG >40%. Statistical analysis was done using t-test and Fischer's exact test.

Results: 72 cases were identified and their charts were reviewed – 33 patients were found to have IRPF based on no identifiable secondary cause. Of these 6 (18%) met the criteria for IgG4RD. There was no statistical difference found in demographics, clinical features, labs, imaging, treatment modalities and outcomes in the 2 groups (see table 1 and 2). 30% needed surgical and 56% needed both surgical and medical management in non-IgG4-related RPF vs. 50% and 33.3%, respectively in the IgG4-related RPF. Two patients were on prednisone at the time of biopsy-one was IgG4-related and other was non-IgG4-related RPF. IgG4RD patients were statistically more likely to have OP, eosinophilia and lymphoid follicles than non-IgG4-related RPF; though none of these histologic features are sufficiently sensitive/specific for the diagnosis in the absence of immunostains for IgG4 to establish the diagnosis.

Conclusion: This is the largest reported cohort of biopsy proven IRPF cases presenting at one tertiary center. Only 18% cases of IRPF were IgG4RD compared to 28-58% reported in other series. There were no difference found in the treatment outcomes between IgG4-related RPF and non-IgG4-related RPF. OP, arteritis, eosinophilia and lymphoid follicles are suggestive of IgG4RD and should prompt additional testing

Table 1.

	Overall		Non-IgG4-related RPF		IgG4-related RPF		
	(N=33) N	Summary	(N=27) N	Summary	(N=6) N	Summary	p-value
DEMOGRAPHICS:							
Age (years)	33	57.33±13.1	27	55.6±13.6	6	65.3±6.5	0.10
Race	26/33	78.8%	20/27	74.1%	6/6	100%	0.16
. White	7/33	21.2%	7/27	25.9%	0/6	0%	
. Black or African American							
Gender	23/33	69.7%	18/27	66.7%	5/6	83.3%	0.69
. Male	10/33	30.3%	9/27	33.6%	1/6	16.7%	
. Female							
Duration of follow-up (months)	33	47.3±46	27	43.4±43.7	6	64.8±56	0.31
CLINICAL FEATURES:							
Abdominal pain	19/28	67.86%	15/22	68.2%	4/6	66.7%	0.94
Acute kidney injury	16/29	55.17%	13/24	54.17%	3/5	60%	1.0
Low back pain	10/27	37.04%	8/22	36.4%	2/5	40%	0.89
HISTORY:							
Smoker	10/33	30.3%	8/27	29.5%	2/6	33.3%	0.49
. Current	11/33	33.3%	8/27	29.5%	3/6	50%	
. Former	12/33	36.4%	11/27	40.7%	1/6	16.7%	
. Never							
Other fibrosing conditions	1/33	3%	1/27	3.7%	0/6	0%	0.62
LABS:							
Creatinine (mg/dL)	31	3.3±4.6	25	3±4.5	6	4.6±5.4	0.46
CRP (mg/dL)	10	4.8±5.1	9	5.3±5.1	1	0	0.35
WSR (mm/hr)	11	79.3±47.7	10	73.3±45	1	140	0.19
IgG4 serum (mg/dL)	9	48.2±53.8	7	57.5±58.3	2	15.5±2.1	0.36
IMAGING:							
Hydronephrosis	25/32	78.12%	20/26	76.9%	5/6	83.3%	0.73
Bilateral Hydronephrosis	23/32	71.9%	18/26	69.2%	5/6	83.3%	0.49
Maximal dimension (cm)	22	6.4±4.9	17	6±5.1	5	7.5±4.1	0.57
Abdominal aortic aneurysm	8/29	27.59%	6/24	25%	2/5	40%	0.49
Location of mass	8/33	24.4%	6/27	22.2%	2/6	33.3%	0.93
. Periaortic and periureteral	10/33	30.3%	9/27	33.3%	1/6	16.7%	
. Periaortic only	5/33	15.2%	4/27	14.8%	1/6	16.7%	
. Periureteral only							

Values presented as Mean±SD or percentage

p-values: t-test for continuous variables and Fisher's Exact test for non-continuous variables (ordinal and nominal)

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Table 2.

	Overall		Non-IgG4-related RPF		IgG4-related RPF		
	(N=33) N	Summary	(N=27) N	Summary	(N=6) N	Summary	p-value
Method of biopsy	11/33	33.3%	8/27	29.6%	3/6	50%	0.34
. CT guided	22/33	66.7%	19/27	70.4%	3/6	50%	
. Open							
HISTOPATHOLOGY:							
Lymphoplasmacytic infiltrate (0 to 3)	2/33	6.1%	2/27	7.4%	0/6	0%	0.56
. 0	11/33	33.3%	10/27	37%	1/6	16.7%	
. 1	6/33	18.2%	5/27	18.5%	1/6	16.7%	
. 2	14/33	42.4%	10/27	37%	4/6	66.7%	
. 3							
Storiform fibrosis	8/33	24.2%	6/27	22.2%	2/6	33.3%	0.46
Fibrosis	28/33	84.8%	23/27	85.2%	5/6	83.3%	0.90
Obliterative phlebitis	2/33	6.1%	0/27	0%	2/6	33.3%	0.002
Eosinophilia	9/33	27.3%	5/27	18.5%	4/6	66.7%	0.02
Arteritis	1/33	3%	0/27	0%	1/6	16.7%	0.03
Lymphoid follicles	6/33	18.2%	3/27	11.1%	3/6	50%	0.03
TREATMENTS:							
Treatment type	17/33	51.5%	15/27	55.6%	2/6	33.3%	0.09
. Medical and Surgical	4/33	12.2%	4/27	14.8%	0/6	0%	
. None	11/33	33.3%	8/27	29.6%	3/6	50%	
. Surgical	1/33	3%	0/27	0%	1/6	16.7%	
. Unknown							
Glucocorticoids	15/32	46.9%	13/27	48.1%	2/5	40%	0.74
Medical treatment for at least 6 months	16/32	50.0%	14/27	51.9%	2/5	40%	0.63
Treatment stents	24/32	75%	19/27	70.4%	5/5	100%	0.30
Treatment recurrent stents	19/31	61.3%	16/26	61.53%	3/5	60%	1.0
Treatment ureterolysis	22/32	68.75%	18/27	66.7%	4/5	80%	0.56
OUTCOMES:							
Outcome creatinine change (mg/dL)	30	-0.9±5.2	24	-1.2±5	6	0.4±6.3	1.0
Outcome WSR change (mm/hr)	9	-66.7±44.7	8	-59.1±41	1	-128	0.16
Outcome imaging change	10/33	30.3%	8/27	29.6%	2/6	33.5%	0.79
. Improved	3/33	9.1%	2/27	7.4%	1/6	16.7%	
. Resolution	9/33	27.3%	7/27	25.9%	2/6	33.3%	
. Stable	6/33	18.2%	5/27	18.5%	1/6	16.7%	
. Unknown	5/33	15.2%	5/27	18.5%	0/6	0%	
. Worse							
Steroids on last follow-up	3/16	18.75%	3/13	23.1%	0/3	0%	-
Off steroids	9/16	56.25%	7/13	53.8%	2/3	66.7%	1.0
On steroids	4/16	25%	3/13	23.1%	1/3	33.3%	
Unavailable data							
Stent/ nephrostomy on last follow-up	9/24	37.5%	8/19	42.1%	1/5	20%	0.36

Values presented as Mean±SD or percentage

p-values: t-test for continuous variables and Fisher's Exact test for non-continuous variables (ordinal and nominal)

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Efficacy and Tolerance of Rituximab in IgG4-Related Disease: A Retrospective Multicentric Study in 24 Patients

Mikael Ebbo[1], Aurélie Grados[1], Maxime Samson[2], Clarisse Carra-Dallière[3], Agnieszka Pozdzik[4], Pierre Labauge[3], Sylvain Palat[5], Jean-Marie Berthelot[6], Jean-Loup Pennaforte[7], Alain Wynckel[8], Celine Lebas[9], Thomas Quémeneur[10], Karine Dahan[11], Jean-Jacques Boffa[11], Bertrand Godeau[12], Nicolas Limal[12], Franck Carbonnel[13], Anne Herber[14], Gaëlle Leroux[15], Patrice Cacoub[16], Alexis Mathian[17], Eric Hachulla[18], Nathalie Costedoat-Chalumeau[19], Jean-Robert Harle[20] and Nicolas Schleinitz[1], [1]Internal Medicine, Aix-Marseille Université, AP-HM, Marseille, France, [2]Department of Internal Medicine and Clinical Immunology, Dijon University Hospital, Dijon, France, [3]Neurology, CHRU de Montpellier, Montpellier, France, [4]Nephrology, Erasme Hospital, Cliniques Universitaires de Bruxelles, Bruxelles, Belgium, [5]Service de Medecine Interne, CHU limoges, Limoges, France, [6]Rhumatologie, CHU Nantes, Nantes, France, [7]Internal Medicine, CHU de Reims, Reins, France, [8]Nephrolohy, CHU de Reims, Reims, France, [9]Nephrology, CHRU de Lille, Lille, France, [10]CH Valenciennes, Valenciennes, France, [11]Nephrology, Tenon Hospital, Paris, France, [12]Internal Medicine, Mondor Hospital, Creteil, France, [13]Gastro-enterology, CHU Bicêtre, Le Kremlin Bicêtre, France, [14]Gastro-enterology, CH de Chartres, Chartres, France, [15]Department of Internal Medicine 2. Referal center for SLE/APS, CHU Pitié-Salpêtrière, Paris, France, [16]Internal Medicine Department, University Hospital “Pitié-Salpêtrière”, “Pierre et Marie Curie Paris VI” University, Paris, France, [17]Internal Medecine Department, Pitie-Salpetriere Hospital, Paris, France, [18]FAI²R, Hôpital Claude Huriez, CHRU Lille, LILLE, France, [19]Internal Medicine Department, Cochin Hospital, “René-Descartes Paris V” University, Paris, France, [20]Internal Medicine, Aix-Marseille Université, APHM, Marseille, France

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Background/Purpose: IgG4-related disease (IgG4-RD) is a systemic fibroinflammatory condition with characteristic histopathological lesions. Nearly all anatomic sites can be involved with a risk of organ dysfunction. A dramatic response to steroids is usual but relapses are frequent and steroids sparing agents are frequently required. Favorable response to B-cell depletion by rituximab (RTX) has been suggested by case reports, small series and an open label trial. However data “in real life” with a long term follow-up are sparse, especially concerning the efficacy and tolerance. We analyzed rituximab use in a national multicentric cohort of IgG4-RD patients.

Methods: Patients included in a national multicentric cohort of IgG4-related disease and treated by RTX were included in this study. All patients fulfilled the 2011 comprehensive IgG4-RD diagnostic (CDC) criteria. All differential diagnosis were systematically ruled out. Clinical, biological, histological, radiological and therapeutic data were retrospectively collected in order to evaluate efficacy and tolerance of RTX in this indication.

Results: Twenty-four patients were included in this study. All patients fulfilled the 2011 CDC criteria, with a “definite” diagnosis in 15 cases, “probable” in 6 cases and “possible” in 3 patients. Median age at RTX was 57 years [extreme 36-84]. Median duration of the disease before RTX was 35.5 months [4-180], and mean number of previous medical treatments was 1.6 [0-4], with previous steroid use in all patients but one. Median number of organ involved was 5 [1-8], and organ involvement justifying use of RTX was mainly kidney in 6 patients (25%), biliary involvement in 6 (25%), pancreas in 5 (21%), retroperitoneal and/or aortic involvement in 4 (15%). Administration was 1gx2 d1-d15 in most patients (63%), and 375 mg/m2 in 6 (25%). A clinical efficacy was noted in 18/22 patients symptomatic at treatment initiation. A decrease of IgG4 serum levels was observed 13/14 evaluable patients with pre-treatment serum

IgG4 elevation. Imagery (conventional and/or metabolic) improvement was noted in 12/18 and stability was noted in 5 over 18 evaluable patients. Among 21 responders, 7 patients (33%) presented a relapse, with a median follow-up of 11 months [1-129]. Relapse occurred with a median delay of 18 months [9-36] after RTX treatment. Corticosteroids could be stopped in only 12/23 evaluable patients (52%). Infectious events were observed in 10 patients (42%), with severe infections in 2 patients with concomitant steroid therapy (septic shock in 1, and mitral endocarditis in 1). Hypogammaglobulinemia was observed in 2 patients, requiring immunoglobulin substitution in one case.

Conclusion: Rituximab appear to be effective in more than 80% of patients with IgG4-RD. Nevertheless, complete withdrawal of steroids was possible in only half of patients. One third of patients relapsed after 1 year of follow-up. Finally, infectious events and hypogammaglobulinemia are not rare and must be monitored, even if the responsibility of RTX is difficult to assess in these multitreated patients.

Disclosure: M. Ebbo, None; **A. Grados**, None; **M. Samson**, None; **C. Carra-Dallière**, None; **A. Pozdzik**, None; **P. Labauge**, None; **S. Palat**, None; **J. M. Berthelot**, None; **J. L. Pennaforte**, None; **A. Wynckel**, None; **C. Lebas**, None; **T. Quémeneur**, None; **K. Dahan**, None; **J. J. Boffa**, None; **B. Godeau**, None; **N. Limal**, None; **F. Carbonnel**, None; **A. Herber**, None; **G. Leroux**, None; **P. Cacoub**, None; **A. Mathian**, None; **E. Hachulla**, None; **N. Costedoat-Chalumeau**, None; **J. R. Harle**, None; **N. Schleinitz**, CSL behring Company France, 2,Roche France, 2,GlaxoSmithKline france, 2.

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Abstract Number: 1386

Malignancy Prevalence Is Increased Among Patients before the Onset of IgG4-Related Disease

Zachary Wallace[1], John H. Stone[2], Hyon K. Choi[3], Na Lu[3] and Carly Wallace[4], [1]Division of Rheumatology, Allergy and Immunology, Massachusetts General Hospital, Boston, MA, [2]Massachusetts General Hospital Rheumatology Unit, Harvard Medical School, Boston, MA, [3]Rheumatology, Allergy and Immunology, Massachusetts General Hospital, Harvard Medical School, Boston, MA, [4]Rheumatology Unit, Massachusetts General Hospital, Boston, MA

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SESSION INFORMATION

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Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: IgG4-related disease (IgG4-RD) is a systemic fibroinflammatory disease of unclear etiology. Studies have suggested that patients with IgG4-RD may be at increased risk of malignancy when followed prospectively. We have observed a frequent history of malignancy preceding the onset of IgG4-RD. If true, this may inform our understanding of the pathogenesis. We therefore evaluated this further in a well-described cohort of 125 patients by comparing the prevalence of malignancy to the general US population as well as that of age- and sex-matched controls from our Center.

Methods:

We reviewed the electronic medical records of the first 125 patients with IgG4-RD evaluated in our Center, all of whom were diagnosed by strict clinicopathologic criteria. We identified those with a history of invasive malignancy and collected details from the electronic medical record, confirming details with the patients. The indirect standardization method was used to compare the rate of malignancy between our cohort and that of the US population using the Surveillance, Epidemiology, and End **Results** (SEER) database of the National Cancer Institute (NCI). Furthermore, up to 5 age- and gender- matched controls were selected among patients with either osteoarthritis or fibromyalgia evaluated in the MGH Division of Rheumatology, Allergy, and Immunology (DRAI) and identified using the Research Patient Data Registry (RPDR) at Partners HealthCare. The age of control patients at their first visit in DRAI was matched to the age of cases at the onset of findings or symptoms attributed to IgG4-RD. Patients with immune-mediated conditions (e.g., SLE, RA) were excluded because of the putatively increased risk of malignancy in some of those patient subsets. Conditional logistic regression was used to compare the rate of malignancy between our cohort and that of the matched controls evaluated in DRAI.

Results:

Of the125 patients with IgG4-RD included, 60.8% was male and the average age of onset was 50.3+/-14.9 years. The mean number of

organs involved was 2.3 +/-1.3. Twenty patients (16%) had been diagnosed with 21 malignancies before the onset of IgG4-RD. Malignancy was diagnosed an average of 6.9 years (range 1-22) prior to the diagnosis of IgG4-RD. Prostate cancer (n=7) and lymphoma (n=4) were the most common malignancies. Compared to the general US population, the observed prevalence of malignancy in patients with IgG4-RD is 2.5 times higher than expected (95% CI: 1.1-3.6). Compared to patients evaluated in the MGH DRAI, patients with IgG4-RD had a significantly higher prevalence of malignancy than age- and gender-matched controls (OR 2.9, 95% CI 1.5-5.9).

Conclusion: Our findings, derived from two separate comparison groups, suggest that patients with IgG4-RD more often have a history of malignancy prior to their diagnosis. The reason(s) for this finding remains under investigation, but potential explanations include shared risk factors for the respective diagnoses and increase in the risk of IgG4-RD resulting from the treatment of cancer. Future studies may investigate potential pathogenetic, clinical, and prognostic differences between patients with and without a history of malignancy.

Disclosure: Z. Wallace, None; **J. H. Stone**, Roche, Genentech, 2,Genentech, 5; **H. K. Choi**, None; **N. Lu**, None; **C. Wallace**, None.

Abstract Number: 1387

Thoracic Paravertebral Masses and IgG4-Related Disease: Report of 8 Cases and Review of the Literature

Zachary Wallace[1], Sian Lim[1], John H. Stone[2], Micheal McInnis[3] and Amita Sharma[4], [1]Division of Rheumatology, Allergy and Immunology, Massachusetts General Hospital, Boston, MA, [2]Massachusetts General Hospital Rheumatology Unit, Harvard Medical School, Boston, MA, [3]Radiology Department, Thoracic Imaging, Massachusetts General Hospital, Boston, MA, [4]Department of Radiology, Thoracic Imaging, Massachusetts General Hospital, Boston, MA

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Background/Purpose:

IgG4-related disease (IgG4-RD) is an immune-mediated fibro-inflammatory condition that often leads to tumefactive lesions. We describe a common but under-recognized radiologic finding in this disease: the occurrence of paravertebral masses that may mimic a number of other inflammatory, infectious, and malignant disorders.

Methods:

The medical records of 143 subjects with IgG4-RD diagnosed by strict clinicopathologic correlation were examined to identify those with relevant imaging (n = 59). The available computed tomography (CT), 18F-fluorodeoxyglucose (18F-FDG) positron emission tomography (PET), and magnetic resonance imaging (MRI) studies were reviewed by thoracic radiologists. All images were reviewed and interpreted by board-certified radiologists. Demographic, clinical, and serological features were collected from the medical record.

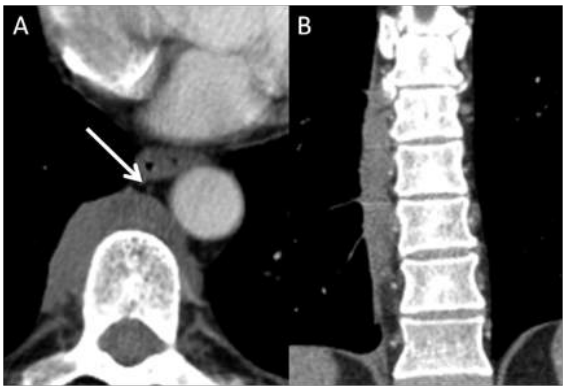
Results:

Of 59 patients with relevant imaging, 8 (14%) had a paravertebral mass. These lesions were typically detected on the right side, along the lower thoracic spine, and spanned multiple vertebral bodies (Figure 1). The lesions demonstrated contrast enhancement on CT and 18F-FDG avidity on PET. All patients not on treatment had elevated serum IgG4 concentrations. Multi-organ IgG4-RD was present in seven patients (88%). One of the four patients with imaging studies before and after treatment demonstrated resolution of the lesions.

Conclusion:

Paravertebral masses are often detected incidentally on pulmonary imaging in IgG4-RD. Our series of eight cases is, to our knowledge, the largest series of paravertebral masses associated with IgG4-RD reported in the literature. All of our cases had biopsy-proven IgG4-RD. Characteristic features of these lesions include their right-sided location, the extension across multiple vertebral bodies, and their common association with other manifestations of IgG4-RD.

Figure 1. (a) Axial contrast enhanced CT in a 59 year old man with IgG4-RD. The paravertebral mass is centered predominantly on the right side of the thoracic spine. The thoracic duct (arrow) can be identified anterior to, and separate from, the paravertebral mass. (b) Follow up CT with coronal reformats demonstrates the typical craniocaudal extent, spanning multiple vertebral bodies.



Disclosure: Z. Wallace, None; **S. Lim**, None; **J. H. Stone**, Roche, Genentech, 2,Genentech, 5; **M. McInnis**, None; **A. Sharma**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/thoracic-paravertebral-masses-and-igg4-related-disease-report-of-8-cases-and-review-of-the-literature

Abstract Number: 1388

Adalimumab in Patients with Inactive, Non-Infectious Uveitis Requiring Systemic Treatment

Quan Dong Nguyen[1], Shree Kumar Kurup[2], Pauline Merrill[3], John Sheppard[4], Joachim Van Calster[5], Andrew D Dick[6], Glenn Jaffe[7], Friederike Mackensen[8], **James T. Rosenbaum**[9,10], Ariel Schlaen[11], Anne Camez[12], Samir Tari[13], Martina Kron[12], Alexandra Song[13] and Antoine Brezin[14], [1]Truhlsen Eye Institute, University of Nebraska, Omaha, NE, [2]Wake Forest Baptist Medical Center, Winston-Salem, NC, [3]Rush University Medical Center, Chicago, IL, [4]Lions Medical Eye Bank of Eastern Virginia, Norfolk, VA, [5]University Hospitals Leuven, Leuven, Belgium, [6]Bristol Eye Hospital, Bristol, United Kingdom, [7]Duke University, Durham, NC, [8]Heidelberg University Hospital, Heidelberg, Germany, [9]Dever's Eye Institute, Legacy Hospital, Portland, OR, [10]Division of Rheumatology, Oregon Health and Science University, Portland, OR, [11]Austral University, Buenos Aires, Argentina, [12]Abbvie Deutschland GmbH & Co KG, Ludwigshafen, Germany, [13]AbbVie Inc., North Chicago, IL, [14]Université Paris Descartes, Hôpital Cochin, Paris, France
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Background/Purpose: To assess adalimumab (ADA) efficacy and safety in corticosteroid-dependent patients with inactive non-infectious, intermediate, posterior, or panuveitis enrolled in the international, double-masked trial, VISUAL II.

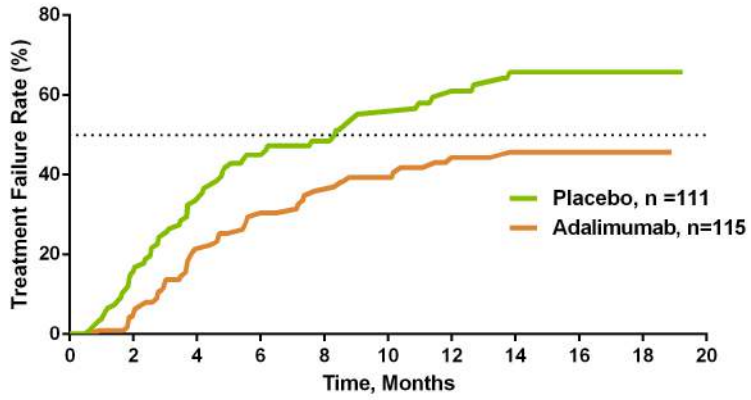
Methods: Patients aged ≥18 years with inactive, non-infectious, intermediate, posterior, or panuveitis requiring 10-35 mg oral prednisone to maintain an inactive state (no active, inflammatory chorioretinal and/or retinal vascular lesions, anterior chamber (AC) cell grade ≤0.5+ and vitreous haze (VH) grade ≤0.5+) were randomized 1:1 to receive placebo (PBO) or ADA (80 mg week 0, followed by 40mg every other week from week 1 for ≤80 weeks). From week 2, all patients underwent a mandatory prednisone taper to 0 mg by week 19 or earlier depending on the baseline dose. Primary endpoint was time to treatment failure (TF) in ≥1 eye at or after week 2. TF was defined as ≥1 of the following criteria: new active, inflammatory lesions; worsening of BCVA by ≥15 letters; 2-step increase in AC cell grade; 2-step increase in VH grade relative to baseline (BL). Secondary endpoints included change in AC cell grade, VH grade and BCVA from BL to the final visit, time to optical coherence tomography (OCT) evidence of macular edema (after week 2), and percent change in central retinal thickness (CRT) from BL to final visit. Adverse events (AEs) were monitored throughout the study.

Results: A total of 229 patients were randomized (female, 61%; mean age, 42.5 years; mean duration of uveitis 61.2 months); 21% had intermediate, 32% had posterior, 46% had panuveitis, and 1% had intermediate and posterior uveitis. Patients who received ADA were

less likely to have TF (hazard ratio=0.57; 95% CI, 0.39-0.84; P=0.004). Median time to TF was 8.3 months for PBO and not estimable for ADA, as more than half of the ADA-treated patients did not experience TF **(Figure)**. Secondary endpoints were numerically in favor of ADA, although significant differences between ADA and PBO were not observed. No significant differences were observed between SAEs, serious infections and the overall rate of AEs between ADA and PBO.

Conclusion: ADA significantly lowered the risk for uveitic flare or vision loss in patients with steroid-dependent inactive, non-infectious uveitis. No new safety signals were identified with ADA treatment in patients with inactive uveitis; the safety profile of ADA in this population was comparable to other approved indications. Similar results were observed in patients with active, noninfectious, intermediate, posterior, or panuveitis despite the use of corticosteroids, enrolled in the VISUAL I trial.

Figure: Rate of Treatment failure (Kaplan-Meier Curve)



Disclosure: Q. D. Nguyen, AbbVie, Santen, XOMA, Bausch & Lomb, and chairs the Steering Committee for the VISUAL studies., 9; **S. K. Kurup**, AbbVie, Allergan, Bayer, Clearside, Regeneron, and Xoma., 9; **P. Merrill**, consultant for Santen., 9; **J. Sheppard**, AbbVie, Alcon, Allergan, Aldeyra, Bausch & Lomb, Clearside, EyeGate, Tear Lab, Tear Science, Santen; investigator for Xoma, 9; **J. Van Calster**, consultant for MSD, 5; **A. D. Dick**, Abbvie, 9; **G. Jaffe**, AbbVie, 5; **F. Mackensen**, AbbVie and Merck Serono, 9; **J. T. Rosenbaum**, AbbVie, UCB, XOMA, Santen, Novartis, Medimmune, Cavtherx, Portage, Topivert, Regeneron, Allergan, and Sanofi, 5,Alcon Research Institute, 2; **A. Schlaen**, None; **A. Camez**, AbbVie, 1; **S. Tari**, AbbVie, 1; **M. Kron**, AbbVie, 1; **A. Song**, AbbVie, 1; **A. Brezin**, AbbVie, 9.

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Abstract Number: 1389

A Meta-Analysis of the Prevalence of the Ocular Manifestations in All Inflammatory Rheumatic Diseases

Jacqueline Hayworth[1] and Janet E. Pope[2], [1]Medicine, University of Western Ontario and U of Toronto, Toronto, ON, Canada, [2]University of Western Ontario, London, ON, Canada

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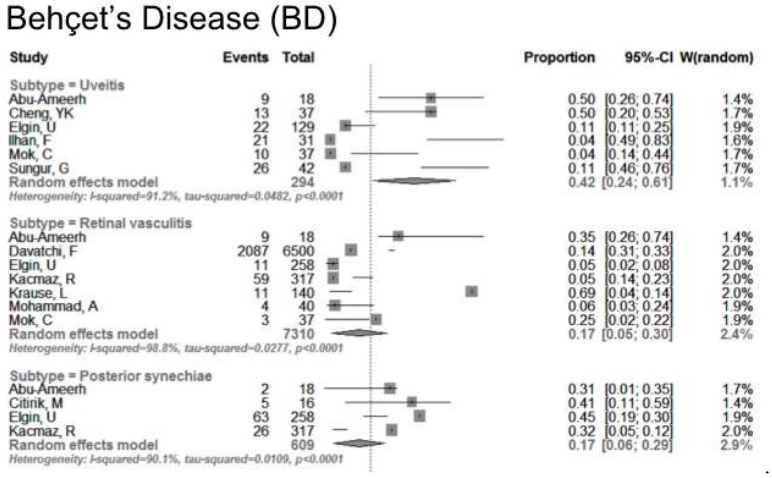
Background/Purpose: Many inflammatory rheumatic diseases (IRD) are associated with ocular involvement. The prevalence of these complications is not fully known. This meta-analysis was performed to systematically investigate the prevalence and type of ocular involvement in IRD.

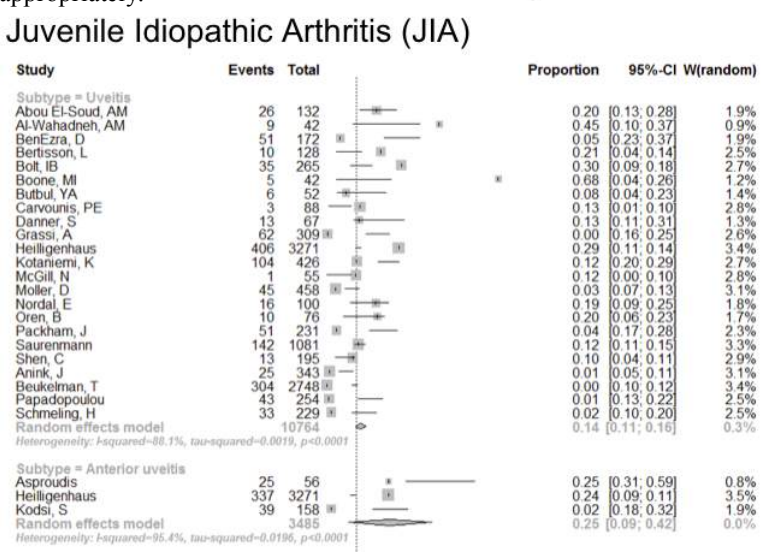
Methods: Medline, Web of Science and Cochrane databases were searched to July 2014, to identify publications related to IRD and associated ocular conditions. Disease terms included; juvenile arthritis (JIA), rheumatoid arthritis (RA), connective tissue disease, spondyloarthropathy (SpA), ankylosing spondylitis (AS) and Behcet's disease. For eye involvement terms were; conjunctivitis,

keratoconjunctivitis sicca, xeropthalmia, uveitis, eye hemorrhage, optic neuritis, papilledema, orbital disease, retinal artery/vein occlusion, macular edema, retinitis, chorioretinitis, scleritis, iridocyclitits, choroid hemorrhage, blindness and amaurosis fugax. Data regarding the rates of ocular complications were analyzed with a random effects model.

Results: 7124 studies were found with 263 for full review. There were 13 AS studies, 30 Behcet's disease (BD), 31 JIA, 12 PsA, 11 RA and 165 others. Pooled prevalence for commonly reported ocular manifestation were uveitis rates of: 22% (95% CI: 16-24%) in AS, Behcet's 55% (41-68%), JIA [oligoarthritis 36% (20-51%), polyarticular 13% (8-19%) systemic onset 3% (0-7%)], pediatric Behcet's 33% (0-74%), and PsA 15% (5-24%) for anterior uveitis and 0.2% for posterior uveitis. In RA, keratoconjunctivitis sicca occurred in 16% (8-25%), sicca symptoms in 31% (21-42%), marginal ulcerative keratitis in 1-3%, episcleritis in 1-2% and retinal vasculitis in 0.2%. In SLE 29% of patients had dry eyes. There may have been publication bias (over reporting due to selection bias of cohorts enriched for ocular complications such as patients from university clinics where complications could be higher, and several estimates had herterogeneity. Data were lacking on confounding variables (such as screening and treatment). Figure shows some uveitis rates.

Conclusion: Extra-articular manifestations of inflammatory rheumatic diseases frequently complicate the ocular health of afflicted individuals. Although the rates vary, an awareness of potential complications can aid in early identification and treatment of these rheumatic complications. Rates of ocular involvement may not be changing over time and therefore need to be recognized and treated appropriately.





Disclosure: J. Hayworth, None; **J. E. Pope**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/a-meta-analysis-of-the-prevalence-of-the-ocular-manifestations-in-all-inflammatory-rheumatic-diseases

Abstract Number: 1390

Hidradenitis Suppuritiva Is Associated with Inflammatory Eye Disease

Abrahim U. Syed[1], Didem Uzunaslan[2], Careen Y. Lowder[3], Sunil Srivastava[3], Juan J. Maya[1] and Rula A Hajj-Ali[4], [1]Internal Medicine, Cleveland Clinic, Cleveland, OH, [2]Cleveland Clinic, Cleveland, OH, [3]Cole Eye Institute, Cleveland Clinic, Cleveland, OH, [4]Rheumatic

and Immunologic Dis, Cleveland Clinic, Cleveland, OH
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Background/Purpose:

Hidradenitis Suppurativa (HS) is an inflammatory skin condition that can cause profound morbidity. Patients can present with recurrent nodules, sinus tract formation, abscesses and/or scarring, mainly affecting intertriginous skin areas. A variety of inflammatory disorders have been associated with HS, such as inflammatory bowel disease (IBD) and spondyloarthropathies. Case reports have documented coexistence between HS and inflammatory eye disease (IED), but associations have not been described. Herein, we aimed to assess the types of IED associated with HS, risk factors for developing IED in patients with HS, and treatment outcomes.

Methods:

Case identification was performed by including all cases within Cleveland Clinic Health System with a diagnosis of HS (ICD code 705.83) and any IED. Using this strategy, 483 patients were identified. With Cleveland Clinic electronic medical records, a retrospective chart review was done to identify demographics, IED patterns, associated conditions, treatments and outcomes. Ophthalmologic notes were reviewed by an independent ophthalmologist to ensure accuracy of IED diagnosis. Patients with episcleritis and sicca were excluded given their prevalence in the general population. Only those with chronic IED were included. A total of 20 patients with HS and IED met these criteria. Qualitative variables were described with measures of frequency.

Results:

16 patients were female (80%). 12 were African American (60%) and 7 Caucasian (35%). HS was diagnosed before IED in 11 patients (55%). Mean age when HS was diagnosed was 42.15; mean age when IED was diagnosed was 43.65.

13 patients had uveitis (65%), 6 had scleritis (30%) and 1 had peripheral ulcerative keratitis. 8 patients (40%) had a co-morbid IBD: 5 with Crohn's disease, 1 with ulcerative colitis, and 2 were undifferentiated. RA and common variable immunodeficiency were each diagnosed in 2 patients. There was 1 patient for each of the following conditions: sarcoidosis, AS, psoriasis, Behcet's disease, multiple sclerosis, SLE, lymphoma, and colon cancer.

Table 1: Treatment of IED with a diagnosis of HS

Treatment	Number of Patients	Number Achieving Remission
Topical Steroid	17	6 (35%)
Systemic Steroid	7	1 (14%)
Infliximab	4	3 (75%)
Adalimumab	4	2 (50%)
Methotrexate	7	2 (29%)
Periocular steroid injection	1	0

Conclusion:

HS should be included in the etiology of IED. Female gender and African American ethnicity are common in patients with both IED and HS. The pattern of IED most associated with HS was uveitis followed by scleritis. Among the co-morbidities, IBD is the most prevalent, especially the subset of Crohn's disease. While topical steroid remains first-line treatment, systemic immunosuppressive agents show promise for refractory eye disease, particularly anti-TNF-alpha biologics among this study group.

Disclosure: A. U. Syed, None; **D. Uzunaslan**, None; **C. Y. Lowder**, None; **S. Srivastava**, None; **J. J. Maya**, None; **R. A. Hajj-Ali**, None.

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Abstract Number: 1391

Differential Expression of Interferon Gamma in Exudate from Hidradenitis Suppurativa Lesions Compared to Chronic Wounds

Anirban Banerjee[1], Victoria K. Shanmugam[1,2], Sean McNish[1] and Kara Couch[1], [1]Division of Rheumatology, The George Washington University, Washington, DC, [2]Director, Division of Rheumatology, The George Washington University, Washington, DC

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Background/Purpose:

Hidradenitis suppurativa (HS) is a chronic recurrent inflammatory disease which affects 1% to 4% of young adults. The purpose of the current study was to investigate inflammatory cytokines and growth factors in the effluent from HS lesions compared to effluent from chronic wound specimens. In differentiating the inflammatory profile of HS lesions compared to chronic wounds we hope to identify potential local drivers of inflammation unique to HS over and above inflammatory responses seen in patients with chronic wounds.

Methods:

Wound fluid specimens from 8 patients with HS and 8 age-matched patients with chronic wounds were selected for analysis. Baseline demographics were obtained from the Wound Etiology and Healing (WE-HEAL) database. The Hidradenitis Suppurativa Score a validated HS disease activity score utilized in clinical trials was used to determine extent of HS activity at the time of specimen collection. The Meso Scale Discovery V-Plex cytokine panel 1 and the V-plex proinflammatory panel 1 were used to analyze proinflammatory cytokines in the fluid specimens.

Results:

There was no significant difference in race, sex, presence of diabetes, and cigarette smoking exposures in the HS compared to chronic wound cohorts. Mean HSS in the HS cohort was 68.88 (SD ±41.45) confirming moderately active disease. Interferon-gamma (IFN-γ) was significantly elevated in the HS wound fluid compared to chronic wound samples (Table 1, 1418 ± 1501 pg/ml compared to 102.5 ± 138 pg/ml, p 0.027). HS effluent also had significantly higher levels of TNF-β than chronic wound fluid (Table 1, 9.24 ± 7.22 pg/ml compared to 1.65 ± 2.14 pg/ml, p 0.03). There was no significant difference in any other proinflammatory cytokines including TNF-α, IL-1β, IL-12p70, IL-1α, IL-17A, IL-6, IL-16 and IL12/IL23p40. The anti-inflammatory cytokines IL-10, Il-4, and IL-13, the traditional proliferation cytokines, IL-2, IL-15, Il-7 and IL-5, and the growth factors GM-CSF and VEGF were not significantly different between HS effluent and chronic wound fluid.

Conclusion:

Local molecular drivers of HS are poorly understood. In this study we were able to show that when compared with effluent from chronic wounds HS effluent contains higher levels of the cytokines IFN-γ and TNF-β suggesting that IFN-γ and TNF-β may play a crucial role in driving and perpetuating the exuberant inflammation in HS.

		WOUND FLUID			
		HIDRADENITIS	CHRONIC WOUND	P value	
		(pg/mL)	(pg/mL)		
		N=8	N=8		
		Mean ±SD	Mean ±SD		
	AGE	41.61 ± 13.81	45.32 ± 10.43	0.55	NS
	INF-γ	1418 ± 1501	102.5 ± 138	0.027	*
	IL-12p70	9.412 ± 7.59	15.02 ± 27.28	0.609	NS
	IL-1β	862.5 ± 1076	1503 ± 3500	0.69	NS
	IL-1α	1126 ± 1746	2549 ± 5565	0.5291	NS
PRO-INFLAMMATORY	IL-17A	1006 ± 1652	32.7 ± 37.36	0.12	NS
	IL-6	2377 ± 1604	5451 ± 8180	0.32	NS
	TNF-α	83.26 ± 69.07	65.74 ± 105.4	0.70	NS
	TNF-β	9.24 ± 7.22	1.65 ± 2.14	0.03	*
	IL-16	15277 ± 18785	15586 ± 25553	0.97	NS

	IL12/IL23p40	488.3 ± 570.8	97.86 ± 67.06	0.07	NS
ANTI-INFLAMMATORY	IL-10	19.85 ± 18.74	34.74 ± 69.58	0.57	NS
	IL-4	6.56 ± 4.15	9.77 ± 13.98	0.54	NS
	IL-13	70.98 ± 48.16	55.61 ± 56.10	0.56	NS
PROLIFERATION	IL-2	18.97 ± 18.66	13.16 ± 22.15	0.60	NS
	IL-15	24.5 ± 37.29	5.61 ± 4.75	0.18	NS
	IL-7	22.29 ± 20.49	10.45 ± 6.28	0.14	NS
	IL-5	30.15 ± 33.63	9.314 ± 18.01	0.17	NS
GROWTH FACTOR	GM-CSF	78.45 ± 62.6	82.13 ± 208.8	0.96	NS
	VEGF	632.1 ± 757.4	1544 ± 1765	0.23	NS

Table 1: Comparison of cytokines profiles in HS and chronic wounds

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Disclosure: A. Banerjee, None; **V. K. Shanmugam**, None; **S. McNish**, None; **K. Couch**, None.

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Abstract Number: 1392

Azathioprine May be an Effective Steroid Sparing Agent in Patients with Isolated Recurrent Pericarditis

Adam Brown[1], Xiaobo Liu[2] and Soumya Chatterjee[3], [1]Rheumatology, Cleveland Clinic, Cleveland, OH, [2]Quantitative Health Sciences, Cleveland Clinic, Cleveland, OH, [3]Cleveland Clinic Foundation, Cleveland, OH

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SESSION INFORMATION

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Background/Purpose:

Isolated Recurrent pericarditis (IRP) is a disease with high morbidity. IRP refers to recurrent pericarditis not associated with an autoimmune rheumatic disease or cardiac surgery/injury. Conventional therapy for IRP is a combination of NSAIDs, colchicine and Glucocorticoids (GC) termed triple therapy. A major cause of morbidity in these patients is the predictable side effects of prolonged GC therapy to prevent and treat flares. There is some evidence to support the use of azathioprine (AZA) as an immunomodulating agent in this setting.[1]The purpose of our study was to evaluate whether AZA can be used as an effective steroid sparing agent in IRP. This goal was achieved by evaluating the average and cumulative GC requirement over 6 months before and after initiation of AZA in patients with IRP.

Methods:

To be eligible for the study patients had to be followed for at least 6 months after initiating AZA and had to have at least 2 recurrences of IRP prior to initiation of AZA. After evaluating all patients with IRP, 13 patients satisfied the inclusion criteria. Patients' charts were reviewed to determine the total dose of GC required in 2 week intervals over the course of 6 months. Each IRP flare (as defined by the cardiologist) was also documented. Since the onset of action of AZA is thought to be 2-3 months, the number of flares after starting AZA was documented between months 3 and 6. Paired t-tests and Wilcoxon rank sum tests were used for statistical analysis. All tests were performed at a significance level of 0.05.

Results:

Twenty-eight patients were excluded because of evidence of systemic rheumatic disease or prior immunomodulator therapy. Out of 13 IRP cases, 10 were considered idiopathic or post viral and 3 were post myocardial injury. IRP patients had an average disease duration of 17 months prior to the initiation of AZA and all had at least 5 months of continuous prednisone use prior to initiation of AZA (12 patients had prednisone for >6 months). The mean daily dose of prednisone prior to AZA was 21 mg, and cumulative dose was 4,004 mg over 6 months. The mean daily dose of prednisone post AZA was 13 mg (p= 0.003), and cumulative dose was 2,229 mg (p=0.012) over 6 months. The average number of flares while on triple therapy in the 6 months prior to AZA was 3, and number of flares between months 3 and 6 of AZA therapy was 0.3 (p=0.001). The average dose of AZA was 1.8 mg/kg. Three patients were not able to lower their prednisone dose after AZA initiation and 2 of these patients were on < 1.5 mg/kg of AZA/day.

Conclusion:

This is the first retrospective study that evaluated the average and cumulative dose requirement of GC in patients with IRP to maintain clinical remission before and after initiation of AZA. After the initiation of AZA, patients were able to have a significant reduction in the dose of GC required and had a significant reduction in the frequency of flares within a given time period. In conclusion, this study suggests AZA is an effective steroid sparing agent in IRP. Further studies are needed to confirm these findings.

1. Vianello F, et al. Int J Cardiol. 2011 Mar 17;147(3):477-8

Disclosure: A. Brown, None; **X. Liu**, None; **S. Chatterjee**, None.

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Abstract Number: 1393

Diagnostic Categorization of Ocular Sarcoidosis Based on the International Criteria Proposed By the First International Workshop on Ocular Sarcoidosis. a Case Series of 11 Spanish Patients

Carlos Francisco Meneses Villalba[1], Olga Maiz Alonso[1], Ana Blanco[2], César Antonio Egües Dubuc[1], Miren Uriarte Ecenarro[1], Nerea Errazquin Aguirre[1], Jesus A. Valero[1] and Joaquin Maria Belzunegui Otano[1], [1]Rheumatology, Donostia University Hospital, Donostia, Spain, [2]Ophthalmology, Donostia University Hospital, Donostia, Spain

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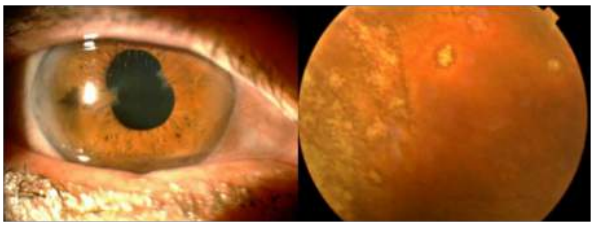
Background/Purpose: Sarcoidosis is a multisystemic disorder of unknown cause. About 30-60% of patients have ocular involvement consistent in bilateral uveitis. Recently, the clasification criteria proposed by the First International Workshop on Ocular Sarcoidosis (FIWOS) has been validated. The criteria classifies ocular sarcoidosis as definite (uveitis and biopsy positive), presumed (bilateral hilar lymphadenophaty and uveitis without biopsy), probable (3 ocular signs and 2 laboratory tests without biopsy and without bilateral hilar lymphadenopathy) and possible (4 ocular signs and 2 laboratory tests with negative biopsy) based of specific ophthalmological and laboratory findings. This classification is useful especially when a biopsy is not avalilable or when it is negative./Categorization of patients diagnosed with ocular sarcoidosis according to the criteria proposed by the FIWOS in the last five years in a uveitis unit of the University Hospital Donostia in Guipœzcoa, Spain.

Methods: The clinical records of patients diagnosed with ocular sarcoidosis were reviewed retrospectively. The variables measured were age, sex, systemic manifestations, pattern of uveitis, Quantiferon test, angiotensin converting enzyme, biopsy, chest radiography and treatment. The patients then were classified based on the criteria of the FIWOS.

Results: A total of 11 patients were diagnosed with sarcoid uveitis, 7 females (63.6%) and 4 males (36.3%). The median age was 58.0 years (SD 20.5). In 7 patients (63.3%) uveitis was the first manifestation of the disease, 5 of them later developed systemic symptoms and 2 showed isolated eye involvement. The remaining 4 patients (36.3%) showed systemic symptoms of: bilateral hilar adenopathy in 81.8%, respiratory symptoms 36.3%, peripheral adenopathy 18.1%, parotitis in 27.2% and erythema nodosum in 9.0%. The patterns of uveitis most frequently observed were bilateral panuveitis in 54.5%, chronic unilateral anterior uveitis in 27.2% and chronic bilateral anterior uveitis in 18.1%. The categorization of patients revealed a diagnosis of definite sarcoidosis in 4 (36.3%), presumed in 5 (45.4%), probable in 1 (9.0%) and possible in 1 patient (9.0%). The most common treatment was methotrexate in 45.4%. Two patients were treated withanti-TNF

Conclusion: 81.7% of our patients were categorized as having definite or presumed sarcoidosis. More than half of our patients who had no confirmatory biopsy were diagnosed of ocular sarcoidosis. Bilateral panuveitis and chronic anterior uveitis were the most frequent ocular patterns. Most patients with ocular involvement developed subsequently systemic symptoms.



A. B

A. Peripheral anterior synechiae after complicated uveitis.

B. Multiple chorioretinal lesions.

Disclosure: C. F. Meneses Villalba, None; **O. Maiz Alonso**, None; **A. Blanco**, None; **C. A. Egües Dubuc**, None; **M. Uriarte Ecenarro**, None; **N. Errazquin Aguirre**, None; **J. A. Valero**, None; **J. M. Belzunegui Otano**, None.

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Abstract Number: 1394

Clinical Characteristics of Sarcoid Arthropathy: A Population-Based Study

Patompong Ungprasert[1], Cynthia S. Crowson[2] and Eric L. Matteson[3], [1]Rheumatology, Mayo Clinic, Rochester, MN, [2]Health Sciences Research, Mayo Clinic, Rochester, MN, [3]Division of Rheumatology, Department of Internal Medicine and Department of Health Sciences Research, Mayo Clinic, Rochester, MN

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Background/Purpose: The epidemiology and clinical characteristics of sarcoid arthropathy are not well-described as only referral-based studies have been reported. This study aimed to use the data from a geographically well-defined population to characterize the clinical characteristics of sarcoid arthropathy.

Methods: An inception cohort of patients with incident sarcoidosis in 1976-2013 in a geographically well-defined population was identified based on comprehensive individual medical record review. Inclusion required physician diagnosis supported by histopathology and radiologic features of intrathoracic sarcoidosis, compatible clinical presentation, and exclusion of other granulomatous diseases. Tissue samples were considered positive if they demonstrate non-caseating granuloma without evidence of acid-fast bacilli or fungi. The only exception to the requirement of histopathological confirmation was stage I pulmonary sarcoidosis that required only radiographic evidence of symmetric bilateral hilar adenopathy. Patients with joint pain were then identified from this cohort. Data were collected on pattern of joint involvement, associated cutaneous and systemic symptoms, physical examinations and inflammatory markers.

Results: In 1976-2013, 345 incident cases of sarcoidosis were identified (mean age 45.6 years and 50.4% female). Symptoms of joint pain occurred in 42 patients (mean age 41.2 years and 57.1% female), and 35 patients had swollen joint(s) on physical examination. Most patients had arthralgia prior to the diagnosis of sarcoidosis with an average time to diagnosis of 21 days. Approximately half of patients had fever and elevated sedimentation rate at diagnosis (48% and 46%, respectively).

Of the 35 cases with objective evidence of synovitis, oligoarthritis (two to four joints) was the most common pattern (88%) followed by monoarthritis (6%) and polyarthritis (6%). Ankles were involved in 91% of cases (14% one ankle and 77% both ankles). In the majority of patients (88%), the arthritis resolved within 6 weeks.

The most common associated cutaneous manifestation was erythema nodosum followed by subcutaneous nodule/plaque (31% and 5%, respectively). The classic Lofgren syndrome (arthritis, erythema nodosum and hilar adenopathy) was observed in 11 patients (26%).

Conclusion: Inflammatory arthritis occurred in a minority of patients with sarcoidosis. Acute oligoarthritis with bilateral ankles involvement was the most common pattern of sarcoid arthropathy. A significant portion of patients also had systemic symptoms as well as

erythema nodosum.

Disclosure: P. Ungprasert, None; **C. S. Crowson**, None; **E. L. Matteson**, Novartis/Sanofi/Centocor-Jansen/Celgene/Amgen/Roche/Genentech/Mesoblast/Pfizer, 2.

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Abstract Number: 1395

Prevalence and Significance of MEFV GENE Mutations in Patients with Sarcoidosis

Senol Kobak[1], Fidan Sever[2], Ozlem Goksel[3], Tuncay Goksel[3], Mehmet Orman[4] and Afig Berdeli[5], [1]Rheumatology, Sifa University Faculty of Medicine, 35100, Turkey, [2]Chest Disease, Sifa University, Izmir, Turkey, [3]Chest Disease, Ege University, Izmir, Turkey, [4]Ege University Department of Statistic, Associated Professor, Izmir, Turkey, [5]Genetics and Molecular Medicine, Ege University, Izmir, Turkey
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Background/Purpose: Sarcoidosis is a chronic granulomatous disease. Pyrin, is encoded by the MEFV gene and has anti-inflammatory effects in the inflammasoma regulation. MEFV gene mutations affects the inflammatory cascade and cause familial Mediterranean fever. The relationship between different rheumatic diseases and MEFV gene mutations are shown in previous studies. **Aim:**The aim of this study was to determine the MEFV gene prevalence in Turkish patients with sarcoidosis and to determine the possible correlation between the occurrence of mutations and disease phenotype.

Methods: Seventy-eight sarcoidosis patients and age, gender and ethnicity compatible 85 healthy controls were included in the study. The most common eight MEFV gene mutations were investigated by PCR method.

Results: Among seventy-eight sarcoidosis patients MEFV gene mutation was detected in nine patients(%11.5). The distribution of the nine mutations; three (3.8%) V726A, two (2.5%) E148Q, two (2.5%) M680, a (1.3%) A744S, one (1.3%) of K695, respectively. None of the sarcoidosis patients were M694V, M694I, R761H and P369S and compound heterozygous carriers (Table 1). MEFV gene mutations frequency in the healthy control group was found to be 22.4%.The distribution of MEFV gene mutations in the healthy control were; E148Q 9 (10.6%), M694V 2 (2.3%), M694I 1 (1.2%), M680 1 (1.2%), V726A 2 (2.3%), A744S1 (1.2%), K695 2 (2.3%), P369S1 (1.2%), respectively, Compared with the control group, a lower carrier frequency of MEFV gene mutations were detected in patients with sarcoidosis, but it was not statistically significant(p=0.067). In the sarcoidosis group, while serum ESR and CRP levels were significantly higher in the mutation carrier group than those of the non-carrier group (p=0.01,p=0.04). In the sarcoidosis group, while arthritis,enthesitis and ankle arthritis were significantly more frequent in the mutation carrier group than those of the non-carrier group (p=0.028, p=0.05, p=0.05 respectively).

Conclusion:

In Turkish patients with sarcoidosis, we found a lower frequency of MEFV gene mutations compared with healthy control group. Sarcoidosis mutation carrier group were found to be associated with high serum acute phase response , arthritis and enthesitis. The presence of MEFV gene mutation may have a protective role for the development of sarcoidosis. Prospective studies with large patient series are need on this subject.

Disclosure: S. Kobak, None; **F. Sever**, None; **O. Goksel**, None; **T. Goksel**, None; **M. Orman**, None; **A. Berdeli**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/prevalence-and-significance-of-mefv-gene-mutations-in-patients-with-sarcoidosis

Abstract Number: 1396

Long Term Outcome of Neurosarcoidosis

Catherine Chapelon[1], Bastien Joubert[1], Lucie Biard[2], David Saadoun[3], Mathieu Resche Regon[4], Fanny Domont[1], Lea Savey[1], Didier Dormont[1] and **Patrice Cacoub**[5], [1]Hôpital Pitié Salpétrière, AP-HP, UPMC, Univ Paris 06, Paris, France, [2]Biostatistics, Saint-Louis Hospital, Paris, France, [3]Department of Internal Medicine and clinical Immunology. French National Reference Center for Autoimmune Diseases. DHU I2B (Inflammation, Immunotherapy and Biotherapy), UPMC, Paris VI, Hôpital Pitié Salpétrière, AP-HP, UPMC, Univ Paris 06, Paris, France, [4]biostatistics Saint Louis Hospital, paris, France, [5]Internal Medicine Department, University Hospital "Pitié-Salpêtrière", "Pierre et Marie Curie Paris VI" University, Paris, France
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Background/Purpose: Although clinical and imaging features of neurosarcoidois (NS) have been described, few studies have reported on the long-term outcome. We report the long-term outcome of a large series of NS, focusing on overall and relapse-free survival and dependency status.

Methods: Retrospective monocenter analysis of NS patients fulfilling international criteria for NS. All NS patients had an evaluation including physical examination, dependence scoring by Expanded Disability Status Scale (EDSS), cerebral spinal fluid (CSF) analysis, brain and/or spine MRI; and for thirty-four cases a pathological study of nerve/muscle tissue. Endpoints were rates of and factors associated with: (i) overall survival after NS diagnosis (OS), (ii) relapse-free survival after NS diagnosis (RFS), and (iii) dependence at the end of the follow-up (FU), as assessed by EDSS ≥2.5. The RFS was calculated using Kaplan-Meier estimator and a multivariate Cox proportional hazard ratio model was selected to assess prognostic factors of RFS.

Results:

Among a cohort of 690 sarcoidosis patients, 242 patients with NS were identified i.e. definite NS in 34 patients (14%), probable NS in 149 (62%) and possible in 59 (24%). Median age at NS diagnosis was 41 years (IQR 30; 52), 50% were female and 53% Caucasian. Multivisceral sarcoidosis was noted in 214/242 of NS (88%) including cardiac involvement in 85 patients. Symptoms of NS preceded extra-neurological involvement in 55/242 patients (23%), while neurological symptoms were concomitant or followed extra-neurological involvement in 135/242 (56%) and 52/242 (21%) patients, respectively.

Main neurological involvements of NS were central nervous system in 184/242 patients (76%) including spinal cord in 63 patients, cranial nerve in 85/242 (35%), and peripheral nerve and/or muscle in 42/242 (17%). Overall, 148/242 patients (61%) had more than one neurological involvement. Analysis of CSF showed unspecific abnormalities in 90/242 patients (37%). The initial EDSS score was ≥2.5 in 159/242 patients (36%). Steroids were given to 224/242 patients (93%) associated to i.v. cyclophosphamide in 90/242 (37%), methotrexate in 97/242 (40%), mycophenolate mofetil in 57/242 (24%) and infliximab in 23/242 (10%).

After a median FU of 96 months, 22/242 patients (9%) died including 6 patients with no NS relapse. The OS rates at 1, 5, and 10 years were 98.8%, 95.4%, and 91.3%, respectively. At the end of FU, 25% of patients had an EDSS ≥2.5. Factors independently associated with dependence were CSF protein ≥1g/l and presence of a CNS lesion at MRI ($p<0.05$). The RFS rates at 1, 5 and 10 years were 69.9%, 38.7% and 30.7%, respectively. Factors independently associated with poor RFS were older age at NS diagnosis, neurological signs preceding multivisceral sarcoidosis diagnosis and CSF protein ≥1g/L ($p<0.01$). There was no impact of international criteria on OS and RFS.

Conclusion: Neurosarcoidosis is a severe condition with low relapse-free survival rates. However, the overall survival rate is > 90% at 10 years. International criteria of NS showed no impact on overall or relapse-free survival rates.

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Abstract Number: 1397

Successful Treatment of Cardiac Sarcoidosis with Biologic and Immunosuppressive Combination Therapy

Maya Estephan[1], Mehrdad Maz[2], Mark Hamblin[3] and Julian Magadan[1], [1]Division of Allergy, Clinical Immunology, and Rheumatology, University of Kansas Medical Center, Kansas City, KS, [2]Division of Rheumatology, University of Kansas Medical Center, Kansas City, KS, [3]Pulmonary and Critical Care Medicine, ILD Clinic, University of Kansas Medical Center, Kansas city, KS
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Background/Purpose: Although cardiac involvement is symptomatic in only 5% of patients with sarcoidosis, it is considered an important prognostic factor and the second leading cause of death in patients with sarcoidosis. There are no formal guidelines for the diagnosis or management of cardiac sarcoidosis (CS). Due to the rarity of this disease, prospective clinical trials are lacking and difficult to conduct. Corticosteroids are the mainstay of treatment in CS. Steroid sparing agents mainly methotrexate, azathioprine, mycophenolate mofetil and TNF-alpha inhibitors (Tumor Necrosis Factor). Our aim is to report successful treatment of CS with a combination therapy consisting of a TNF-alpha inhibitors and an oral immunosuppressive agent.

Methods: This is a retrospective chart review of patients with sarcoidosis who were evaluated either by a rheumatologist or a pulmonologist at a tertiary academic medical center between January 1st2013 and December 31st 2014. Patients with biopsy proven sarcoidosis (with the exception of endomyocardial biopsy) were included. Presence of hypermetabolic activity on the cardiac fluorodeoxyglucose (FDG) positron emission tomography (PET) scan was used to establish the diagnosis of CS. PET scan was repeated after 6-12 months to assess response to therapy.

Results: The charts of 103 patients with a diagnosis of sarcoidosis were reviewed and only 81 patients with biopsy proven sarcoidosis were included. Fifteen out of 81 patients (18.5%) had cardiac FDG PET suggestive of CS. All cases had other manifestations of systemic sarcoidosis, with lymphadenopathy and pulmonary parenchymal involvement as the most common affected areas. Clinical manifestations of CS included chest pain with or without elevation of cardiac enzymes, a reduced ejection fraction, palpitations and conduction abnormalities on ECG. Out of 15 patients, 9 patients were treated with a combination regimen of TNF-alpha inhibitors (infliximab in 8 patients, adalimumab in 1 patient) and an oral immunosuppressive agent (mycophenolate mofetil in 7 patients, azathioprine in 2 patients). Prednisone was also used in all but one patient, with doses ranging from 10 mg to 60mg daily. Six patients were not included in our study as they were eventually managed elsewhere and immunosuppressive treatment was withheld in one patient due to pregnancy. A repeat Cardiac FDG PET scan after 6-12 months of therapy showed a marked improvement or resolution of the hypermetabolic activity in all 9 patients. Cardiac and extracardiac manifestations improved or resolved following treatment.

Conclusion: We describe the clinical presentation and treatment outcomes of 9 patients with cardiac sarcoidosis successfully managed with a combination of a TNF inhibitor and an oral immunosuppressive agent. To our knowledge, this is the largest series of cardiac sarcoidosis successfully treated with such a combination therapy.

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Abstract Number: 1398

Musculoskeletal and Serologic Findings in an Adult Cystic Fibrosis Clinic Population- a Systematic Review and Collation with Disease Status

Mohamed Elarabi[1,2], Katherine Griffin[3], Luxme Mahendira[1,4], Jenna Sykes[3], Erin Norris[1,2], Anne Stephenson[1,3], Elizabeth Tullis[1,3] and Laurence Rubin[1,5], [1]University of Toronto, Toronto, ON, Canada, [2]Rheumatology, Saint Michael's Hospital, Toronto, ON, Canada, [3]Respirology, Saint Michael's Hospital, Toronto, ON, Canada, [4]30 Bond Street, Saint Michael's Hospital, Toronto, ON, Canada, [5]Saint Michael's Hospital, Toronto, ON, Canada
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Background/Purpose:

Cystic fibrosis (CF) is a genetic disorder characterized by exocrine gland production of highly viscous mucus, leading to obstructive and inflammatory changes in the respiratory, digestive and reproductive systems. Musculoskeletal (MSK) burden in CF has historically been addressed in young adults when fewer therapies resulted in a greater infective and inflammatory pulmonary burden. Reported presentations included undifferentiated arthropathy, hypertrophic osteoarthropathy, fluoroquinolone induced arthropathy and osteoporosis. With an increasing lifespan and broader disease spectrum, the impact of CF on the MSK system warrants re-evaluation. Our objectives are to assess MSK burden, the prevalence of serologic and biochemical markers and the relationship of chronic infection to the MSK system in adult CF patients.

Methods:

We conducted a prospective cohort study of all adult patients in St. Michael's Hospital CF clinic (n>400). To date, 163 subjects were recruited. Subjects completed MSK specific questionnaires; multidimensional health assessment questionnaire (MDHAQ), WOMAC, Osteoporosis and Fracture History. They were examined for tender and swollen joints. Serology (RF, ANA, anti-cyclic Citrullinated peptide (anti-CCP) antibodies, ESR, CRP and carboxy-terminal collagen crosslinks were obtained. MSK specific data was linked with the Toronto CF database, a comprehensive record of pulmonary and nutritional status, microbiology, and CF genotype.

Results:

Median age was 32 years; 86 males, 77 females. Median Routine Assessment of Patient Index data 3 (Rapid3) score was 1.33 (normal range: 0-10) and median WOMAC score was 1 (normal range: 0-96). Four subjects had at least 1 swollen joint and 24 had at least 1 tender joint. Seven subjects were RF positive (21-224), 14 were anti-CCP positive (5.1-229.5) and 20 were ANA positive (1.1-6.1). Two subjects had swollen joints and positive antibodies (RF and/or anti-CCP). There was no difference in median age (p=0.55), forced expiratory volume in 1 second (FEV1) % predicted (p=0.40), or proportion of females (p=0.13) between the MSK cohort and overall CF clinic patients. There was no significant association between lung function (FEV1), and antibody status. Stenotrophomonas maltophilia infections were associated with a significantly higher anti-CCP titre (p=0.03).

Conclusion:

In adult CF, MSK manifestations are mild. However, the prevalence of confirmed seropositive inflammatory arthritis is slightly higher than the general population (1.22%). The relationship between Stenotrophomonas maltophilia and anti-CCP titre warrants further investigation.

Baseline characteristics of the cohort (n-163)

Variable	Frequency/Median	Proportion/Range
Gender		
	77	47.2%
Female		
	86	52.8%
Male		
Age at study visit	31.6	18.4-69.1
BMI	22.8	15.9-39
Genotype		
	72	44.2%
Heterozygous dF508		
	59	36.2%
Homozygous dF508		
	8	4.9%
Missing		
	24	14.70%
Other		
FEV1 % predicted	59.7	19.9-118.5
CF related diabetes	54	33.1%
Lung transplant	9	5.5%
Microbiology (n=144)		
	9	6.2%
Burkholderia cepacia complex		
	106	73.6%
Pseudomonas		
	63	43.8%
Staphylococcus aureus		
	35	24.3%
Stenotrophomonas maltophilia		
Joints (n=97)		
	4	4.1%
Swollen		
	24	24.7%
Tender		
Rapid 3 score (n=160)	1.33	0-6.86
WOMAC score (n=161)	1	0-68
Rheumatoid factor (n=150)		
	143	95.3%
<20		
	7	4.7%
>20		
Antinuclear antibodies (n=149)	0.5	0.1-6.1
Anti-cyclic Citrullinated peptide (n=150)	0.4	0-229.5
Carboxy-terminal collagen crosslinks (n=148)	286.8	40-1153
Vitamin D (n=150)	64.5	8-155.8
Fractures (n=158)	66	41.8%

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Abstract Number: 1399

Patterns of Arthropathy in Patients with Cystic Fibrosis

Amanda Schnell[1], Muhammad Imran[2], Michael Crosser[3] and Mehrdad Maz[4], [1]Internal Medicine, University of Kansas Medical Center, Kansas City, KS, [2]Rheumatology, University of Kansas Medical Center, Kansas City, KS, [3]Pulmonary and Critical Care, University of Kansas Medical Center, Kansas City, KS, [4]Division of Rheumatology, University of Kansas Medical Center, Kansas City, KS

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Background/Purpose: There are limited published studies about patterns of arthropathy seen in cystic fibrosis (CF) patients. The objective of this study was to determine the musculoskeletal involvement, clinical presentation, serological patterns, and treatments used in a cohort of CF patients.

Methods: This is a retrospective chart review of patients followed in the Pulmonary CF Clinic in a tertiary medical center from 2004 through 2014.

Results: Of 204 adult CF patients (age 18-67, median age 41, 100 males and 104 females), 88 patients presented with some form of musculoskeletal complaints. Of these, 66 had nonspecific arthropathy. Fourteen out of 66 had flare of arthralgia following CF pulmonary exacerbations. Ten out of 88 were diagnosed with CF arthropathy based on patterns described in other published cohorts (4.9%), 2 with osteoarthritis, 4 with fibromyalgia, and 6 with nonspecific myalgia/arthralgia. Of the 204 patients, ANA was measured in 25 patients and only 6 were elevated. RF was measured in 19 patients; 3 had low to moderate titers. CCP was negative in all 16 measured patients. None of the patients met the diagnostic or classification criteria for any rheumatologic diseases except for one who was diagnosed with Sjogren's syndrome with a positive ANA and SSA.

Six out of 10 CF arthropathy patients (7 women, 3 men, age 23-59) were seen by a rheumatologist and all 10 patients had polyarticular disease. Large joints in a symmetrical pattern were more often involved than small joints. Three patients not seen by a rheumatologist had documented 'generalized' polyarthralgia and a specific joint group was not identified. Only 1/10 had documented synovitis of a 4thPIP. Five out of 10 patients had x-rays of the affected joints which did not show erosions or deformities. Three out of 10 patients had elevated ANA and 1 had a positive SSA diagnosed as Sjogren's by a Rheumatologist. RF and CCP were measured in 5/10 and 4/10 patients, respectively, and all were negative. Of the 10 CF arthropathy patients, 6 had documented flares of arthralgia with CF pulmonary exacerbations; in 2 patients arthropathy did not correlate with CF exacerbations; and 2 patients did not have clear documented arthropathy with CF exacerbations. Arthralgia responded to NSAIDs in 7/10 patients. Arthralgia responded to 3/6 patients treated with varying doses of prednisone initiated either for arthropathy or for pulmonary symptoms. Four patients were treated with hydroxychloroquine and one with both hydroxychloroquine and sulfasalazine with some possible response. One patient who was managed by an outside rheumatologist was treated with leflunomide and previously with methotrexate and cyclosporine. Arthralgia improved in 2 patients treated with tramadol and in 1 patient treated with hydrocodone/acetaminophen. Arthralgia did not respond to acetaminophen alone in any of the patients.

Conclusion: In this large cohort of cystic fibrosis patients, CF arthropathy was diagnosed in about 5% of patients. Seronegative nonerosive noninflammatory polyarticular large joint disease was the dominant pattern. In some patients, the arthralgia appeared to respond to NSAIDs. The flare of arthropathy appeared to correlate with CF pulmonary exacerbations in some patients.

Disclosure: A. Schnell, None; **M. Imran**, None; **M. Crosser**, None; **M. Maz**, None.

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Abstract Number: 1400

Hyperferritinemia and Fever in Adults

Kensuke Nakanishi and Mitsuyo Kinjo, Rheumatology, Okinawa Chubu Hospital, Uruma, Japan

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Session Type: ACR Poster Session B

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Background/Purpose: Clinical associations of hyperferritinemia include: hepatocellular injury, hemophagocytic lymphohistiocytosis (HLH), hematologic malignancy, adult-onset Still's disease (AOSD), and iron overload. Fever of undetermined origin (FUO) may or may

not co-exist with hyperferritinemia in adults. The aim of this study was to describe the associations of with hyperferritinemia and FUO in adults.

Methods: We retrospectively identified patients >16 years old with serum ferritin levels > 5,000 µg/L at a tertiary medical center in Japan between 2002-2014. FUO was defined as temperature>38.3℃ with etiology undetermined after 3 days of in-hospital evaluation. Data were collected on clinical features, medications and mortality.

Results: We identified 156 Japanese patients with hyperferritinemia. Median age was 66 years (range, 16-95); 47% were female. Median serum ferritin level was 9,369µg/L (range, 5,000-170,202); Mortality during the admission was 42%. FUO was absent in 118/156 and present in 38/156 patients (Table). The most common diagnosis was hepatocellular injury, but this was rarely seen with FUO. Among those with FUO and elevated ferritin, hematologic malignancies, HLH, AOSD, and lupus (SLE) were diagnosed. HLH and AOSD remains most prevalent for patients with serum ferritin>10,000µg/L and FUO.

Conclusion: Although hyperferritinemia commonly indicates liver disease and hemochromatosis, clinicians should be aware that hyperferritinemia in conjunction with FUO is a reliable marker for more complex diagnoses such as HLH, AOSD or SLE, especially when ferritin levels are extremely high.

Table. Differential Diagnosis of Hyperferritinemia, by FUO status.

Diagnosis	No FUO No. (%)	With FUO No. (%)
Total	118	38
Hepatocellular injury	57 (48)	2 (5)
Iron overload	26 (22)	0 (0)
Hemophagocytic lymphohistiocytosis	0 (0)	8 (21)
Hematologic malignancies	12 (10)	9 (24)
Bacterial infection	9 (8)	0 (0)
Adult onset Still's disease	0 (0)	8 (21)
Systemic lupus erythematosus	0 (0)	4 (11)
Viral infection	2 (2)	0 (0)
Solid tumor	10 (8)	0 (0)
Other	0 (0)	4 (11)
Undetermined	1 (1)	3 (8)

* Castleman's disease (2), miliary tuberculosis (1), dermatomyositis (1).

Disclosure: K. Nakanishi, None; **M. Kinjo**, None.

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Abstract Number: 1401

Is There Any Difference Between Autoimmune or Hemato-Oncology Etiology of Macrophage Activation Syndrome?

César Antonio Egües Dubuc, Miren Uriarte Ecenarro, Nerea Errazquin Aguirre, Olga Maiz Alonso, Iñaki Hernando Rubio and Joaquin Maria Belzunegui Otano, Rheumatology, Donostia University Hospital, Donostia, Spain

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Background/Purpose: Macrophage activation syndrome (MAS) is a group of diseases, especially autoimmune (AI) and hemato-oncology (HO). So it will be interesting to find any clinical or analytical data to differentiate both.

Methods: Describe and compare demographics, clinical and laboratories features, mortality during hospital stay and after the discharge of

patients diagnosed with MAS secondary HO and AI diseases in the period December 2008 to January 2015, in Donostia University Hospital. A cohort of patients diagnosed with MAS was studied by reviewing medical records. We analyzed and compared only patients with AI and HO disease. The variable were diagnosis, sex, age, fever, organomegaly, hospital mortality and overall mortality (from diagnosis to the end of the study), analytical findings, hospital stay in days, days from admission to diagnosis and days from diagnosis to the end of the study (January 21, 2015) or death after discharge. Quantitative variables are shown with the median and interquartile range. For the bivariate analysis Wilcoxon and Chi square test was used. Survival in months and relative risk (RR) was calculated with the Kaplan Meier plot.

Results: 19 patients with different etiologies MAS were found, 6 and 9 were due to AI and HO diseases. Table 1 shows the etiologic diagnosis of SAM due to AI and HO diseases. Table 2 shows the descriptive analysis of 19 patients and the bivariate analysis between AI and HO group. The median survival of HO disease group was 1.2 months and AI disease group cannot be calculated. The mortality oh HO and AI disease was 77.8% and 16.7% respectively with a p equal to 0.04 by the log rank test. The RR of death among the group of HO against AI disease was 6.84.

Conclusion: In the present study the following statistically significant differences were found:

1) Patients with MAS due AI diseases have higher elevated liver enzymes compared to HO disease.

2) Patients with MAS due HO diseases have a greater pancytopenia compared to AI diseases, especially in leukocytes and neutrophils.

3) Patients with MAS due HO have a higher mortality and lower median survival after diagnosis compared to AI diseases.

Table 1: MAS secondary to AI and HO diseases.

MAS secondary to AI diseases	
Etiologic diagnosis	**Nº patients**
Systemic Lupus Erythematosus	3
Adult Still`s disease	2
IgG4 related disease	1
MAS secondary to HO diseases	
Acute myeloid leukemia	3
Non-Hodgkin lymphoma B cell spleen	2
Non-Hodgkin lymphoma T and B cells	1
Extranodal lymphoma Natural Killers cells	1
Mieodisplasico síndrome	1
Gastric plasmocytoma	1

Table 3: Descriptive analysis of all patients with MAS and bivariate analysis among the group of AI and HO diseases

	All patients (n=19)	**AI diseases (n=6)**	**HO diseases (n=9)**	***p* between AI y HO**
Age (years)	56 (32)	37.5 (26)	66 (15)	
Female sex	10 (52.6%)	4 (66.7%)	3 (33.3%)	0.205
Hospital stay	38 (69)	37.5 (46)	61 (59)	0.216
Days from admission to diagnosis	14.5 (15)	10.5 (12)	24.5 (23.5)	0.069
Days from diagnosis to discharge or hospital death	26.5 (33)	29 (35)	38.5 (51.5)	0.366
Days from diagnosis to death or study end	430 (1166)	1125 (554)	67.5 (410)	0.07
Fever	19 (100%)	6 (100%)	9 (100%)	1
Organomegaly	15 (78.9%)	5 (83.3%)	7 (77.8%)	0.792
Hemoglobin (mg/dl)	7.3 (1.6)	7.4 (2.5)	6.4 (1.1)	0.0866
Platelets (/ul)	8000 (15000)	11000 (66000)	2000 (15000)	0.0771
Leukocytes (/ul)	1010 (2990)	2840 (1850)	100 (590)	0.0022
Neutrophils (/ul)	360 (1770)	1068 (1120)	0 (20)	0.0074
Triglycerides (mg/dl)	382 (217)	414.5 (307)	341 (157)	0.44
Fibrinogen (mg/dl)	213 (304)	212 (346)	228 (302)	0.784
Ferritin (ug/L)	15971 (31603)	15329.5 (38936)	16750 (43203)	0.366
AST	144 (365)	796 (923)	91 (132)	0.0251
ALT	177 (302)	581 (409)	108 (157)	0.0451
Hospital mortality	8 /(42%)	1 (16.7%)	6 (66.7%)	0.057
Overall mortality	10 (52.6%)	1 (16.7%)	7 (77.8%)	0.02

Disclosure: C. A. Egües Dubuc, None; **M. Uriarte Ecenarro**, None; **N. Errazquin Aguirre**, None; **O. Maiz Alonso**, None; **I. Hernando Rubio**, None; **J. M. Belzunegui Otano**, None.

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Abstract Number: 1402

Development of Systemic Juvenile Idiopathic Arthritis Manifestations Following Remission of Hemophagocytic Lymphohistiocytosis

Baruch Goldberg[1], Eyal Muscal[2], Marietta De Guzman[3] and Carl Allen[4], [1]Pediatric Rheumatology, Texas Children's Hospital, Houston, TX, [2]Pediatric Rheumatology, Baylor College of Medicine, Texas Children's Hospital, Houston, TX, [3]Pediatric Immunology, Allergy, and Rheumatology, Baylor College of Medicine, Texas Children's Hospital, Houston, TX, [4]Pediatric Hematology and Oncology, Baylor College of Medicine, Texas Children's Hospital, Houston, TX
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Background/Purpose: Hemophagocytic lymphohistiocytosis (HLH) is a potentially fatal pathologic inflammatory process resulting from impaired immune function due to inherited gene mutations or secondary to viral infections or immune-mediated disease. Systemic Juvenile Idiopathic Arthritis (SoJIA) is also characterized by dysregulated pro-inflammatory cytokines and systemic inflammation. SoJIA can lead to Macrophage Activation syndrome (MAS), a life threatening cytotoxic T cell dysfunction, often resembling HLH. MUNC13-4 mutation are found in up to 30% of children with inherited HLH as well as some patients with MAS secondary to SoJIA. The phenotypic overlap of SoJIA, MAS and HLH may reflect shared pathways of immune dysregulation leading to overwhelming inflammation.

Methods: In an attempt to define the clinical spectra of MAS and HLH, we reviewed charts of children who met criteria for HLH (HLH-2004 criteria) and were later referred to Rheumatology for development of new immune-mediated disease. During the review period of 2008-2014, three children were referred for new symptoms of arthralgia or arthritis after completing HLH therapy. We abstracted clinical features, HLH associated biomarkers and genetic mutations both at HLH presentation and diagnosis of SoJIA by Rheumatology. We documented response to therapy and clinical outcomes.

Results: Three female patients (ages 16 months-14 years), met HLH criteria at presentation without prior history of autoimmune disease. All patients had fevers, bi-cytopenias, Ferritin levels > 20,000ng/ml (Range: 20,638 – 110,000), and Soluble IL2 receptor levels > 3,000units/ml (Range: 3545 – 10,271, normal 334-3,026). Two of the three patients had severely decreased or absent NK cell function at HLH diagnosis. One patient had hemophagocytosis on BM biopsy. A diagnosis of an autoimmune or autoinflammatory disease was ruled out at HLH diagnosis after Rheumatology evaluation. All patients were treated with dexamethasone and an additional immunosuppressive agent (etoposide or cyclosporine) as per HLH protocol. Only a teenage patient was found to have a disease-associated MUNC13-4 mutation.

All patients developed SoJIA features (fever, rheumatoid rash, and polyarthritis) within 7 months of HLH presentation (Range: 5 – 7 months). SoJIA features without laboratory evidence of MAS developed after HLH remission and corticosteroid discontinuation (range: 1.5 – 5 months). An HLH flare was excluded by oncology due to normal ferritin and Soluble IL2 receptor levels. SoJIA clinical features and systemic inflammation responded to IL-1 blockade with anakinra and canakinumab in 2 children. The teenage patient with bi-allelic MUNC13-4 mutations had SoJIA manifestations that were refractory to TNF-alpha, IL-1 and IL-6 blockade (etanercept, anakinra, and tocalizumab), and ultimately underwent allogeneic hematopoietic cell transplant.

Conclusion: HLH and MAS are life threatening inflammatory conditions with underlying immune dysregulation. We describe a novel cohort of children developing SoJIA features after achieving HLH remission. Ongoing clinical follow up and whole exome sequencing studies of these patients may elucidate shared immune-pathway dysfunction of SoJIA, MAS, and HLH.

Disclosure: B. Goldberg, None; **E. Muscal**, None; **M. De Guzman**, None; **C. Allen**, None.

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Abstract Number: 1403

Immune Related Adverse Events Associated with Immune Checkpoint Inhibitors in Cancer Patients: A Systematic Review of Case Reports

Noha Abdel-Wahab[1,2] and Maria E. Suarez-Almazor[3], [1]Rheumatology & Rehabilitation Department, Assiut University Hospital, Egypt, Assiut, Egypt, [2]The Department of General Internal Medicine, The University of Texas, MD Anderson Cancer Center, USA, Houston, TX, [3]General Internal Medicine, The University of Texas, MD Anderson Cancer Center, Houston, TX
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Background/Purpose:

Background: The recent discovery of the immune checkpoint blockade that targets the regulatory pathways in T cells to enhance antitumor immune responses has led to major advances in the strategy of cancer care. However, the occurrence of serious immune-related adverse events (irAEs) in the treated patients has been increasingly reported in the literature suggesting an aberrant autoimmune T cell activation. We conducted a systematic review of case reports documenting the development of irAEs in cancer patients following treatment with anti-cytotoxic T lymphocyte antigen (CTLA-4) or anti-programmed cell death 1 (PD-1), to identify the type of cancer, and the clinical scenario of the irAEs reported in these cases.

Methods: We searched Medline, EMBASE, Web of Science, PubMed ePubs, and Cochrane CENTRAL with no language restriction from inception through April 2015. We included case reports describing the occurrence of irAEs in cancer patients after being treated with anti CTLA-4 or anti PD-1/PD-L1 antibodies. Bibliography search of the included citations was also performed. We extracted data on the type of cancer, the type of immune checkpoint blockade, the nature of the irAEs and their reported outcome.

Results: Out of 2,109 unique citations identified, 152 publications met our inclusion criteria, reporting on 197 case reports. More than half of the reported cases were from the United States (56.4%). The mean age of the cases was 60.2 years (standard deviation, 12.3 years). One hundred and twenty three patients (62.4%) were male. Metastatic melanoma was reported in the majority of the cases (95.4%). Patients with metastatic prostatic cancer, lung cancer, and bladder cancer were seen in 3.0%, 1.0%, and 0.5% respectively. Patients were categorized according to the type of the immune checkpoint blockade. One hundred and eighty six patients (94.4%) were treated with anti CTLA-4 antibodies, either ipilimumab or tremelimumab. While only 11 patients (5.6%) were treated with anti PD-1 antibodies, either nivolumab or pembrolizumab. Frequency of adverse events are shown in the table. Complete resolution of the adverse events was observed in the majority of cases regardless of the type of the immune checkpoint blockade. However, persistent symptoms was reported in 13.7% of the reported cases. Death from complicated irAEs was seen in 4.1%, all of them reported in patients treated with ipilimumab.

Conclusion: Systematic reviews can help identify rare adverse events. Our findings suggest that following treatment with immune checkpoint blockade, irAEs are common. Further longitudinal studies should be conducted to better identify the incidence and quantify the risk of irAEs after treatment with these novel agents.

immune checkpoint blockade	irAEs (%)
Anti CTLA-4 antibodies (Ipilimumab/Tremelimumab = 186 cases)	
Colitis	28.0%
Hepatitis	6.5%
Dermatitis	20.4%
Endocrinopathies	32.7%
Neurological	9.7%
Ophthalmological	7.5%
Sarcoid like disease	5.4%
Vasculitis	2.2%
Lupus nephritis	0.5%
Dermatomyositis	0.5%
Autoimmune inflammatory myopathy	0.5%
Polyarthritis	0.5%
Vogt-Koyanagi-Harada like syndrome	0.5%
Celiac disease	0.5%
Multiple sclerosis	0.5%
Granulomatous inflammation of rectus abdominus muscle	0.5%
Anti PD-1/PD-L1 antibodies (nivolumab/pembrolizumab = 11 cases)	
Dermatitis	54.5%
Endocrinopathies	37.3%
Seronegative polyarthritis	18.2%
Rhabdomyolysis	9.1%
Polymyalgia rheumatica	9.1%

Disclosure: N. Abdel-Wahab, None; **M. E. Suarez-Almazor**, None.

Abstract Number: 1404

Death and Infection Rates Appear Reduced in a Modern Cohort of ICU Patients with Rheumatic Disease

Erin M. Wilfong[1], Sara G. Murray[2], Gabriela Schmajuk[3] and Jinoos Yazdany[4], [1]Division of Rheumatology, Department of Medicine, University of California, San Francisco, San Francisco, CA, [2]Medicine, University of California, San Francisco, San Francisco, CA, [3]San Francisco VA Medical Center, University of California, San Francisco, San Francisco, CA, [4]University of California, San Francisco, San Francisco, CA

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Background/Purpose:

Prior studies of patients with rheumatic diseases admitted to ICU care have been limited to case series; none included patients admitted after 2010. We examined a modern cohort of rheumatic disease patients admitted to a tertiary care center ICU. Given recent changes in the management of rheumatic diseases, we hypothesized that infection would be a leading cause of mortality compared to mortality from disease complications [e.g. interstitial lung disease (ILD), pulmonary hypertension (PH)].

Methods:

We queried the University of California, San Francisco electronic health record (EHR) to identify patients with rheumatic disease and an ICU admission between 6/13/2012-6/5/2015. We included patients with an ICD9 code for 1 of 11 rheumatologic diagnoses listed among admission diagnoses, hospital-problem lists, discharge diagnoses, or billing data for the encounter. We assessed in-hospital mortality (primary outcome) and other covariates including reason for ICU admission and immunosuppressive use via chart review of the EHR by 1 author. ICU encounters following elective surgeries, for the sole purpose of medication titration, or for the primary reasons of myocardial infarction and arrhythmia were excluded. The primary outcome was in-hospital mortality. EHR chart review was performed to confirm diagnoses, determine the cause of ICU admission, and identify immunosuppressive use.

Results:

239 ICU encounters for 204 patients were identified. Diagnoses are listed in the Table. 37 (15%) of encounters resulted from primary rheumatic disease flare, 48 (20%) from disease complications (e.g. ILD, PH), and 109 (46%) from presumably unrelated medical illnesses. 81 (34%) encounters were caused or complicated by sepsis. Overall in-hospital mortality for this cohort was 15%, with higher mortality among patients with a new rheumatic disease diagnosis made during that same admission (25%) and disease complications (23%), although these did not reach statistical significance. Additional results are shown in the Table. Sepsis-related mortality was not higher in patients receiving significant immunosuppression (10%, p=0.77) defined as prednisone > 15 mg/day or the use of another cytotoxic agent.

Conclusion:

To our knowledge, this is the largest study of patients with rheumatic disease admitted to the ICU. Compared with prior studies, this cohort had lower overall mortality (16% vs. 17-55% in prior reports), and infection was not the major cause of in-hospital death. Additional analyses are required to control for potential confounders. In the future, we plan to investigate the performance of traditional markers of ICU mortality (e.g. APACHE scores, vasopressors, ventilation) in this cohort and expand these methods (automated extraction of structured and unstructured (text) data) to construct a registry of critically ill rheumatic disease patients to guide future research.

Table 1. Mortality based on disease association and reason for ICU admission.

Disease	Overall	New Diagnosis	Disease Flare	Disease Complications	Unrelated illness	Sepsis
SLE						
total encounters (%)	58	6 (10)	13 (22)	8 (14)	26 (49)	19 (33)
died (%)	8 (14)	1 (13)	2 (25)	1 (13)	4 (50)	1 (12)
RA						
total encounters (%)	57	---	1 (2)	7 (12)	33 (47)	19 (33)
died (%)	8 (14)	---	---	3 (38)	4 (50)	1 (12)
Scleroderma						
total encounters (%)	34	4 (12)	6 (18)	16 (47)	8 (26)	13 (38)
died (%)	6 (18)	---	---	5 (83)	1 (17)	2 (33)
Vasculitis						
total encounters (%)	20	4 (25)	8 (50)	3 (15)	6 (30)	7 (35)
died (%)	4 (20)	2 (50)	2 (50)	---	---	2 (50)
Sarcoidosis						
total encounters (%)	17	---	2 (12)	2 (12)	9 (53)	4 (23)
died (%)	4 (24)	---	1 (25)	1 (25)	2 (25)	2 (25)
Spondyloarthropathy						
total encounters (%)	15	---	1 (7)	7 (47)	6 (40)	2 (13)
died (%)	1 (7)	---	---	1 (100)	---	---
Myositis						
total encounters (%)	13	4 (31)	5 (38)	2 (15)	5 (38)	6 (46)
died (%)	3 (23)	2 (67)	2 (67)	---	1 (33)	1 (33)
Sjogrens						
total encounters (%)	8	---	---	2 (35)	6 (75)	4 (50)
died (%)	1 (13)	---	---	---	1 (100)	---
PMR						
total encounters (%)	7	---	---	---	4 (57)	3 (43)
died (%)	1 (14)	---	---	---	---	1 (100)
JIA						
total encounters (%)	6	---	1 (17)	---	4 (67)	2 (33)
died (%)	2 (33)	---	---	---	2 (100)	1 (50)
Miscellaneous						
total encounters (%)	4	2 (50)	0	---	3 (75)	2 (50)
died (%)	---	---	---	---	---	---
Cumulative Mortality	15.9%	25.0% p=0.34	18.9% p=0.64	23.4% p=0.21	14.6% p=0.87	13.6% p=0.72

*Columns are not mutually exclusive.
** Total encounter percentages represent the percent of patients with that disease admitted to the ICU for a particular reason. % of patients died represents the percent of patients who died for a specific reason for that disease.

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Abstract Number: 1405

Tocilizumab Serum Levels and Antidrug Antibodies and Its Relationship with Disease Activity in Rheumatic Diseases

Samantha Rodriguez-Muguruza[1], Melania Martínez-Morillo[1], Juana Sanint[2], Bibiana Quirant Sr.[3], Aina Teniente Sr.[4], Agueda Prior[5], Anne Riveros-Frutos[6], Susana Holgado[7], Maria Lourdes Mateo[7], Alejandro Olivé[8], Jeronima Cañellas[5] and Xavier Tena[7], [1]Rheumatology, Hospital Universitario Germans Trias i Pujol, Barcelona, Spain, [2]Rheumatology, Hospital Universitario Germans Trias i Pujol, Badalona, Spain, [3]Immunology, Hospital Universitari Germans Trias i Pujol, Barcelona, Spain, [4]immunology, Hospital Universitari Germans Trias i Pujol, barcelona, Spain, [5]Rheumatology, Hospital Universitari Germans Trias i Pujol, Barcelona, Spain, [6]Microbiology, Hospital Universitario Germans Trias i Pujol, Badalona, Spain, [7]Rheumatology, Hospital Germans Trias i Pujol, Badalona, Spain, [8]Hospital Germans Trias i Pujol, Badalona, Spain
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Background/Purpose: Tocilizumab (TCZ) is a humanized anti-IL-6 receptor-blocking monoclonal antibody used for the treatment of rheumatoid arthritis (RA), idiopathic juvenile arthritis (IJA) and off-label in Adult Onset Still Disease (AOSD). The development of anti-TCZ antibodies could reduce treatment efficacy or induce treatment failure. Our aime was to analyse TCZ serum levels and antidrug antibodies (ADA) in a cohort of RA, IJA and AOSD patients treated with TCZ, and to evaluate its relationship with Disease Activity Score using a 28-joint count (DAS28), C-reactive protein (CRP) levels and the presence of combined treatment with glucocorticoids or DMARDs

Methods: Cross-section study including all patients undergoing chronic treatment with TCZ in a tertiary academic hospital. Referral area: 850,000 inhabitants. Twenty-two patients were included. TCZ serum and ADA levels were measured by ELISA (Theradiag) at baseline (before infusion), 15 days and 30 days after infusion.

Results: Twenty-two patients were studied: 18 RA, 3 IJA and 1 AOSD, 81.8% female; mean age and mean disease duration: 54.2 (±13) and 15.5 (±12) years respectively; 73% of the RA patients were positive for anti-CCP and 70% for rheumatoid factor, mean DAS28-CRP at day 0 and 30: 2.9 and 2.6 respectively. Fifteen patients were treated with TCZ for more than 1 year (range 12-58 months), 19 were treated with TCZ at 8 mg/kg, 2 at 6mg/kg, and one at 5mg/kg every 4 weeks due to low disease activity. Thirteen patients received TCZ in monotherapy, 9 received DMARDs combined treatment, 10 with glucocorticoids (mean dose 4mg/day, range 2-10mg) . TCZ serum levels were at baseline: 1.2- 61.7 µg/ml, 15 days: <1-130.1 µg/ml and 30 days: <1-97.1 µg/ml. No patient showed presence of ADA. No correlation was found with DAS28-CRP, but there was inversely relation between CRP and TCZ serum levels (p=ns) . The mean CRP levels were 14.4, 64.2 and 17.6 mg/dL at day 0, 15 and 30. TCZ Serum levels were higher in patients with combined therapy with DMARDs than those with monotherapy at day 15 and 30 (p=ns, 71 vs 55 µg/mL / 23 vs 12 µg/mL, respectively). Patients treated without glucocorticoids had high levels of TCZ (68.62 vs 59.96 µg/mL at day 15 and 20.2 vs 13.68 µg/mL at day 30, p=ns)

Conclusion: Levels of TZC were heterogeneous. Our patients showed no presence of ADA, this data suggest that TCZ has a low immunogenic potential. No correlation was found in disease activity and TCZ serum levels, but we found a relation with CRP levels. Patients with DAMRDs or without glucocorticoids showed higher levels of TCZ. We did not find correlation between combined treatment with DMARDs or glucocorticoids and levels of TCZ. Our study was limited due to a low sample size; we cannot exclude the correlation between TCZ and DAS28-CRP in a higher sample of patients.

Disclosure: S. Rodriguez-Muguruza, None; **M. Martínez-Morillo**, None; **J. Sanint**, None; **B. Quirant Sr.**, None; **A. Teniente Sr.**, None; **A. Prior**, None; **A. Riveros-Frutos**, None; **S. Holgado**, None; **M. L. Mateo**, None; **A. Olivé**, None; **J. Cañellas**, None; **X. Tena**, None.

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Abstract Number: 1406

The Treatment of Undifferentiated Arthritis: A Systematic Review and Meta-Analysis of Randomized Clinical Trials

Voké Kakpovbia[1], **Maria A. Lopez-Olivo**[2], Jude Des Bordes[3], Robin Christensen[4] and Maria E. Suarez-Almazor[2], [1]Baylor College of Medicine, Houston, TX, [2]General Internal Medicine, The University of Texas, MD Anderson Cancer Center, Houston, TX, [3]Department of General Internal Medicine, The University of Texas, MD Anderson Cancer Center, Houston, TX, [4]The Parker Institute, Department of Rheumatology, Copenhagen University Hospital, Bispebjerg and Frederiksberg, Copenhagen, Denmark

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Background/Purpose: While various studies have looked at possible RA therapies for undifferentiated arthritis (UA), there remains no consensus on optimal management strategies. We undertook a systematic review and meta-analysis to evaluate the efficacy of treatments used in patients with UA.

Methods: We searched in electronic databases (Medline, EMBASE, Web of Science, and The Cochrane Library) with no restrictions up to April 2014. We also searched the clinicaltrials.gov website and the list of references of relevant articles. Two reviewers independently screened citations and evaluated the risk of bias of the included studies. Data was extracted by one reviewer and cross-checked by another. We performed direct comparison meta-analyses.

Results:

Eight studies (nine publications) reporting on 931 participants were included. The majority (88%) had a low risk of performance and detection bias, but did not provide details to judge their risk of reporting bias. After reviewing the manuscripts, we decided to include five comparisons: (1) intra-articular triamcinolone combined with Sm-153 PHYP (a radiation synovectomy agent) versus triamcinolone alone, (2) methylprednisolone versus placebo, (3) methotrexate versus placebo/no intervention, (4) infliximab versus placebo, and (5) abatacept versus placebo. Patients on methylprednisolone were less likely to have started a DMARD compared to patients receiving placebo, at 6 months (RR 0.81, 95%CI 0.68-0.96). Patients on methylprednisolone had less swollen (MD -1.0; -1.6, -0.40) and tender joints (MD -1.0; -2.0, -0.05), improved physician global assessment (MD -6.1; -11.7, -0.52) and quality of life (measured by the EQ5D; MD 0.08; 0.01, 0.15) compared to placebo, at 2 weeks to 12 months; however, compared to placebo there were more patients reporting adverse events in the methylprednisolone group (RR 1.8, 95% CI 1.0-3.3). Patients treated with methotrexate were less likely to develop RA (RR 0.31, 95% CI 0.18-0.53) or have radiographic progression (RR 1.3 95% CI 1.0-1.5) compared to patients treated without methotrexate, at 12-18 months. However, this difference was not observed at 30 months (RR 0.76, 95% CI 0.50-1.1) or 60 months (RR 0.86, 95% CI 0.59-1.3). Higher ACR20 response rates (RR 3.7; 1.3, 10.6), reduced swollen (MD -5.0; -9.8, -0.17) and tender joint counts (MD -13.0; -23.5, -2.5) and fatigue (MD 35.0; 15.6, 54.4) were observed in patients receiving infliximab compared to placebo at 3-6 months. Similarly, patients receiving abatacept had better outcomes compared to patients receiving placebo including disease remission (RR 2.0; 1.1, 3.9), reduced swollen and tender joint count (RR 4.4; 1.5, 13.1), radiographic (MD -0.31; -0.40, -0.22) and MRI changes (MD -5.0; -7. 6, -2.4), at 6-12 months. No other statistically significant differences were found.

Conclusion: Treatment benefits were observed with all alternatives except for intra-articular use of a radiation agent plus triamcinolone versus triamcinolone alone. Transient delay of RA development was only observed with methotrexate compared to control.

Disclosure: V. Kakpovbia, None; **M. A. Lopez-Olivo**, None; **J. Des Bordes**, None; **R. Christensen**, None; **M. E. Suarez-Almazor**, None.

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Abstract Number: 1407

New Clinical Features of Pyogenic Arthritis, Pyoderma Gangrenosum, and Acne Syndrome

Patrycja Hoffmann[1], Amanda K. Ombrello[2], Deborah Stone[3], Anne Jones[4], Karyl Barron[5] and Daniel Kastner[6], [1]Inflammatory Disease Section, National Human Genome Research Institute, Bethesda, MD, [2]Inflammatory Diseases Section, National Human Genome Research Institute, National Institutes of Health, Bethesda, MD, [3]NIH/NHGRI, Bethesda, MD, [4]NHGRI/NIH, Bethesda, MD, [5]National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD, [6]Metabolic, Cardiovascular, and Inflammatory Disease Genomics Branch, NIH/NHGRI, Bethesda, MD

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Background/Purpose: The dominantly inherited pyogenic arthritis pyoderma gangrenosum and acne (PAPA) syndrome is caused by mutations in *PSTPIP1*. It is one of the least understood of the known monogenic autoinflammatory diseases, both from a pathogenic and treatment perspective. Associated symptoms include arthritis, cystic acne, and pyoderma gangrenosum without discernable infection. Therapy revolves around the suppression of the systemic inflammation, typically with corticosteroids, interleukin-1 receptor antagonists, and tumor necrosis factor inhibitors. This abstract documents the continued expansion of clinical manifestations of disease as two PAPA patients have recently presented with the features of noninfectious epiglottitis and sterile osteomyelitis.

Methods: A retrospective medical records review of not previously published rare complications of two patients with PAPA syndrome. Complete histories were obtained and physical exams were performed. Radiographic imaging, complete blood count with differential, CRP and ESR were examined.

Results: One patient with PAPA developed a severe sore throat, which upon further clinical and radiographic evaluation showed piriform sinus swelling consistent with supraglottitis. CRP and ESR were elevated, while WBC was normal. Treatment was initiated with IV clindamycin and ceftriaxone; doxycycline was later added. The patient continued to have severe sore throat and repeat radiographic findings showed ongoing swelling. Clindamycin was stopped and methylprednisolone as well as a scheduled dose of golimumab was initiated with significant improvement in symptoms and normalization of radiographic findings. CRP and ESR improved.

Another patient developed severe right wrist pain and swelling. MRI findings revealed distal right radial epiphysis marrow abnormalities consistent with osteomyelitis without synovitis. ESR and CRP were elevated and WBC was normal. The patient was treated with clindamycin without benefit in symptoms or improvement in MRI findings. Clindamycin was discontinued and methylprednisolone and anakinra were initiated which resulted in decreased pain and improvement in marrow inflammation on MRI. CRP and ESR improved.

Conclusion: Our findings indicate new clinical features in PAPA that include aseptic supraglottitis and non-bacterial osteomyelitis. Improvement in clinical symptoms, radiographic findings, and acute phase reactants as well as a normal WBC support an inflammatory rather than infectious process.

Disclosure: P. Hoffmann, None; **A. K. Ombrello**, None; **D. Stone**, None; **A. Jones**, None; **K. Barron**, None; **D. Kastner**, None.

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Abstract Number: 1408

Cogan Syndrome: Differential Response to Biologic Agents and Role of PET-CT in the Increased Diagnosis of Aortitis

Bahtiyar Toz[1], Burak Erer[2], Sevil Kamali[2], Ilknur Tugal-tutkun[3], Lale Ocal[2] and **Ahmet Gul**[4], [1]Department of Internal Medicine, Division of Rheumatology, Istanbul University, Istanbul Faculty of Medicine, Istanbul, Turkey, [2]Department of Internal Medicine, Rheumatology Division, Istanbul University, Istanbul Faculty of Medicine, Istanbul, Turkey, [3]Department of Ophthalmology, Istanbul Faculty of Medicine, Istanbul University, Istanbul, Turkey, [4]Department of Internal Medicine, Rheumatology Division, Istanbul University, Istanbul Faculty of Medicine,, Istanbul, Turkey
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Background/Purpose: Cogan syndrome (CS) is a rare inflammatory disorder typically characterized by interstitial keratitis and audiovestibular symptoms, and patients may also develop other inflammatory ocular symptoms, sensorineural hearing loss and systemic manifestations including aortitis, aortic insufficiency. We herein aimed to investigate the diagnostic and therapeutic characteristics of five CS patients followed-up in a tertiary referral center.

Methods: We retrospectively reviewed the charts of the five patients diagnosed with CS according to their clinical manifestations. All of

the clinical findings, laboratory and imaging results and treatment responses were recorded using a standard form. Because of the sample size, no statistical analysis was carried out, and results are summarized as descriptive findings.

Results: The mean age of the patients diagnosed with CS was 34 years, and the mean follow-up duration was 7.6 years. Demographic and clinical characteristics of CS patients are summarized in Table 1. Sensorineural hearing loss and intraocular findings were present in all patients. We observed variability in ocular findings, which included typical interstitial keratitis in three, and scleritis in two patients. Although aortitis has rarely been reported previously, diagnostic work-up included PET-CT imaging in three patients, and it revealed positive findings compatible with aortitis. One of our patients needed aortic valve replacement due to severe aortic regurgitation. All patients responded well to high dose corticosteroids, but complete remission was achieved in 1 patient with a mild disease course with methotrexate. Remaining 4 patients required biologic agents to control inflammatory activity. One patient with polyarthritis responded adalimumab and methotrexate combination. However, no response or even exacerbation of findings were observed in two patients with anti-TNF, and a partial or near-complete remission could be achieved with IL-1 blockade.

Table 1. Demographic and clinical features of Cogan syndrome patients.

Patient #	**Sex, age**	**Disease duration (year)**	**Disease Manifestations**					**Treatment (in order)**	**Treatment response**	**Outcome**
			ENT	Eye	Aortitis	Arhritis	Other			
1	F, 25	9	SNHL	Interstitial keratitis	Yes	Oligoarthritis	Aortic valve regurgitation	ANK, CAN	Partial	Deafness
2	M, 33	2	SNHL	Scleritis	Yes	Polyarthritis	Aortic valve regurgitation	TCZ, ETN, ADA, ANK, CAN	Partial	Aortic valve replacement
3	M, 30	9	SNHL	Interstitial keratitis, uveitis	Yes	-	-	MP, MTX	Complete	Hearing loss
4	F, 33	13	SNHL	Scleritis	-	Polyarthritis	Leukocytoclastic vasculitis	ADA, MTX	Complete	Hearing loss
5	F ,49	5	SNHL	Nodular scleritis, interstitial keratitis, and retinal vasculitis	-	-	Skin rash No mutation in NLRP3 gene	INF (exacerbation), ANK	Near complete	Deafness and scleritis sequelea

SNHL: sensorineural hearing loss ,MP: methylprednisolone; MTX: methotrexate; ANK: anakinra; CAN: canakinumab; ETN: etanercept; ADA: adalimumab; TCZ: tocilizumab.

Conclusion: Patients with CS comprise a heterogeneous group, which may include some yet undiagnosed hereditary autoinflammatory conditions. Aortic involvement has rarely been reported in CS patients, but PEY-CT imaging may help diagnosing asymptomatic patients with inflammatory imaging findings in aorta. Early and effective treatment may prevent organ damage, and a differential response to IL-1 blocking biologic agents requires further investigation for both understanding its pathogenesis and better management of refractory patients.

Disclosure: B. Toz, None; **B. Erer**, None; **S. Kamali**, None; **I. Tugal-tutkun**, None; **L. Ocal**, None; **A. Gul**, None.

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Abstract Number: 1409

Subglottic Stenosis: A Unique Inflammatory Disorder

Robert S. Katz[1] and Robert Bastian[2], [1]Rush University Medical Center, Chicago, IL, [2]Bastian Voice Institute, Downers Grove, IL

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Background/Purpose: Inflammatory subglottic stenosis may present with discomfort, stridor, and hoarseness. In these patients granulomatosis with angiitis needs to be ruled out.

A diagnosis using direct visualization and biopsy is made during videoendoscopy. Biopsy is often combined with a dilatation procedure performed in the operating room under general anesthesia. Inflammatory subglottic stenosis appears to always recur after dilatation, but intervals between dilatations may possibly be lengthened due to the use of corticosteroid AND immunosuppressive and biologic response modifier medication.

Methods: We describe 16 patients with inflammatory subglottic stenosis

Results: The patients were diagnosed and followed in a laryngology office. Mean age 35 (21-63). All patients presented with SOB and stridor. Ten also had nasal symptoms, 2 had saddle nose deformities. 3 pts were positive for cANCA and 4 had pANCA. The patients did not have symptoms of cutaneous or systemic vasculitis, sinusitis, pulmonary or renal involvement or other features of granulomatosis with polyangiitis. The patients all had biopsies showing acute and chronic inflammatory changes. Granulomas and vasculitis were not seen. All had dilation procedures. One had a cricotracheal resection. 3 pts had a tracheotomy. In cases of recurrent inflammatory subglottic stenosis, corticosteroids were very helpful in treatment. Five pts were treated with methotrexate, and one with cyclophosphamide. Almost all patients were negative for the presence of cytoplasmic antibodies.

Conclusion: Recurrent inflammatory subglottic stenosis is described in 16 patients. All experienced shortness of breath and stridor.

Inflammatory subglottic stenosis appears to be a unique entity, not related to granulomatosis with polyangiitis.

Treatment with corticosteroids was helpful, but did not avoid the eventual need for subsequent dilation. Methotrexate was moderately effective. One patient received cyclophosphamide. The use of TNF blockers as other biologic response modifiers is unknown.

Disclosure: R. S. Katz, None; **R. Bastian**, None.

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Abstract Number: 1410

Prolotherapy Versus Corticosteroid Injections and Phonophoresis for the Treatment of Plantar Fasciitis: A Randomized Controlled Trial

Gulseren Demir[1], Muyesser Okumus[2], Aynur Karagoz[3] and Turgut Kultur[4], [1]Clinic of PMR, Health Ministry Ankara Training and Research Hospital, Ankara, Turkey, [2]Department of Physical Medicine and Rehabilitation, Kirikkale University Faculty of Medicine, KÄ±rÄ±kkale, Turkey, [3]Dept of Physical Medicine and Rehabilitation, Ministry of Health, Ankara Training and Research Hospital, Ankara, Turkey, [4]University of Kirikkale, Faculty of Medicine, Department of Physical Medicine and Rehabilitation, Assistant Professor, Kirikkale, Turkey

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Background/Purpose: Proximal plantar fasciitis is the most common cause of plantar heel pain in adults. Plantar fasciitis is a degenerative syndrome of the plantar fascia resulting from repeated trauma at its origin on the calcaneus. Prolotherapy has evolved as a new treatment option for refractory Plantar Fascitis. In this study we compared the efficacy of prolotherapy versus corticosteroid injection and phonophorezis for the treatment plantar fasciitis.

Methods: A hundred and fifty patients with clinically determined plantar fasciitis were recruited. Patients were assigned to receive dextrose prolotherapy, corticosteroid injection or corticosteroid phonophoresis for treatment of plantar fasciitis. The first group underwent at baseline followed by a second injection 2 weeks later. The second group was performed local corticosteroid injection as single dose and the third group received phonophoresis. All patients were given an exercise program. Heel Sensitivity Index (THI), Visual Analogue Scale (VAS), Foot Function Index (FFI), Foot and Ankle Outcome Score (FAOS) and SF-36 were measured at baseline and at 1 and 3 months' follow-up. Besides plantar fascia thickness was measured by Ultrasonography (USG) before treatment, 1 and 3 months after treatment.

Results: Within each group, the analysis demonstrated statistically significant improvements in all parameters from baseline to 1 and 3 months ($p < 0.05$). There was no significant difference between groups in terms of efficacy of treatment ($p > 0.05$). Aside from injection-associated pain, no adverse reactions were reported. The plantar fascial thickness between the baseline and final measurements revealed a mean decrease in thickness, statistically significant difference ($p < 0.05$) in three groups. Between groups before treatment, 1 and 3 months after treatment in terms of plantar fascia thickness there was no statistically significant difference ($p > 0.05$). (Table 1)

Table 1. The Distribution of Plantar Fascia Thickness of between Treatment Groups and within Each Group

Plantar fascia thickness	Before treatment	A month after treatmant	Three months after treatment	p
	Mean±S	Mean±S	Mean±S	
Prolotherapy	5,45±1,04[bc]	3,43±1,33	3,53±1,41	**<0,001**
Corticosteroid Injection	5,31±1,07[bc]	3,22±1,24	3,74±1,36	**<0,001**
Phonophoresis	5,37±0,93[bc]	3,56±1,28	3,92±1,49	**<0,001**
p	0,728	0,369	0,451	

[b]In post-hoc pairwise comparisons result of "Post-Therapy First Month" with no significant difference was found.

[c] In post-hoc pairwise comparisons result of "Post-Therapy Third Month" with no significant difference was detected..

Conclusion: Prolotherapy, corticosteroid and phonophorosis therapies were generally well tolerated and appeared to provide benefit of patients with plantar fasciitis. As a result prolotherapy can be an effective way to treat plantar fasciitis

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Disclosure: G. Demir, None; **M. Okumus**, ..., 2; **A. Karagoz**, None; **T. Kultur**, None.

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Abstract Number: 1411

A Double-Blind, Randomized, Placebo-Controlled Trial of Mesenchymal Stem Cells for the Treatment of Patients with Full-Thickness Rotator Cuff Tears

Jose Ramon Lamas[1], Pilar Tornero-Esteban[2], Carlos García Fernández[3], Luis Rodriguez Rodriguez[2], Fernando Marco[4] and Benjamín Fernández-Gutiérrez[5], [1]Rheumatology Service, Hospital Clínico San Carlos, Instituto de Investigación Sanitaria del Hospital Clínico San Carlos (IdISSC), Madrid, Spain, [2]Rheumatology, Rheumatology Service, Hospital Clínico San Carlos, Instituto de Investigación Sanitaria del Hospital Clínico San Carlos (IdISSC), Madrid, Spain, [3]Ortopaedics Surgery and Traumatology Service, Hospital Clínico San Carlos, Instituto de Investigación Sanitaria del Hospital Clínico San Carlos (IdISSC), Madrid, Spain, [4]Traumatology, Ortopaedics Surgery and Traumatology Service, Hospital Clínico San Carlos, Instituto de Investigación Sanitaria del Hospital Clínico San Carlos (IdISSC), Madrid, Spain, [5]Department of Rheumatology, Hospital Clínico San Carlos, Madrid, Spain
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Background/Purpose:

Rotator cuff lesions cause shoulder pain and disability. The outcome after surgical repair of full-thickness rotator cuff tears has been controversial due to the high rate of re-rupture. New therapeutic alternatives are needed to overcome the limited tendon healing, including the use of growth factors, cytokines and/or tissue engineering approaches using mesenchymal stem cells (MSCs). The purpose of this study was to evaluate the safety and effectiveness of autologous MSCs implantation in patients with full-thickness rotator cuff tears.

Methods:

Thirteen patients were included in the study. They were double-blind randomized into two groups. Control group: (n=5) was treated with a

collagen type I implant (OrthADAPT™). Treatment group: (n=8) was treated with type I collagen membrane combined with $20x10^6$ autologous Bone Marrow-MSCs (BM-MSCs).

Bone marrow (BM) was aseptically drawn under local anesthesia from right posterior superior iliac spine and immediately anticoagulated by heparin. Collected bone marrow (50ml) was processed to isolate and to expand BM-MSCs in vitro. The day of surgery, $20x10^6$cells BM-MSCs were resuspended in 1ml of saline solution and seeded over the OrthADAPT™ for 10 minutes prior implantation into the patient.

Patients were evaluated preoperatively and at one year follow-up by: (1) tendon status by MRI (Magnetic Resonance Imaging), (2) functional recovery using the Constant Score (CS) and (3) pain score (10 cm visual analog score [VAS]). The primary endpoint of the study was to achieve a functional improvement of at least 20 points in the CS. Differences between groups were analyzed using the Mann-Whitney U test, values of $p \leq 0.05$ were considered significants. The study was registered (Eudra-CT: 2007-007630-19) and was in accordance with ethical standards for research on human subjects.

Results:

Only the treatment group met the clinical functional improvement criteria, registering differences of 31 points in the CS one year post-intervention (p=0.0073). Additionally, comparable reductions in mean VAS, re-tear rate and repair integrity were found in both groups.

Constant's Score	**Control group (n=5)**		**Treatment group (n=8)**	
	Preoperative	12 months	Preoperative	12 months
Contralateral Shoulder	81 [77.5−94.5]	84[75−91.5]	89 [79−91]	91 [87−96]
Injured shoulder	55 [42.5−58]	71 [49.75−78.5]	45.5 [35.25−51.75]	76.5 [62.25−85]a

Three patients enrolled in the treatment group (37.5%) and one in the control group (25%) developed postoperative complications. These 4 patients showed swelling and symptoms of recurrent tear including pain and reduced range of motion within 3 months post-operation. The 4 patients underwent surgery to remove the patch. Histological analysis revealed the existence of chronic synovitis with granulomatous tissue. Microbiological tests were negative in all cases. These complications were solved after additional surgery.

Conclusion:

These results provide preliminary satisfactory clinical outcomes related to the use of MSCs for the treatment of full thickness rotator cuff tears. Nevertheless, the occurrence of adverse events, likely related to patch instability indicated the need for further controlled studies.

Disclosure: J. R. Lamas, None; **P. Tornero-Esteban**, None; **C. García Fernández**, None; **L. Rodriguez Rodriguez**, None; **F. Marco**, None; **B. Fernández-Gutiérrez**, None.

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Abstract Number: 1412

Thread Carpal Tunnel Release (TCTR) Completely Divides the Transverse Carpal Ligament (TCL) As Well As Open and Endoscopic Surgery: A Cadaver Study

Nathan Wei, Arthritis Treatment Center, Frederick, MD

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Background/Purpose: The gold standard for definitive treatment of severe carpal tunnel syndrome is surgery, either endoscopic or open. Unfortunately, both surgical procedures have pitfalls including relatively long term recovery, complications, and lack of success, which often is due to incomplete transection of the TCL.

The Guo TCTR technique is an innovative method for releasing the carpal tunnel. Performed using local anesthetic with ultrasound needle guidance, a loop of proprietary metal-impregnated cutting thread is looped around the TCL. This is accomplished by inserting an 18 gauge spinal needle just proximal to the superficial palmar arterial arch (SPA) and guiding it proximally, superficial to the SPA, then deep, to pierce the proximal part of the palmar aponeurosis and run on the *deep* surface of the TCL. This needle is ultrasonographically guided proximally, until it surfaces through the skin at the exit point, 1 cm proximal to the proximal wrist crease, in the Nakamichi safe zone, between the median nerve and the ulnar artery. The thread is passed through this needle and the needle is removed. A second spinal needle is then passed through the same entrance and exit points, except that this 2nd needle is guided along the *superficial* surface of the TCL. When the 2ndneedle is in place, the proximal end of the thread is passed through it, and the needle is removed. This results in the thread looped around the TCL with both ends of the thread protruding through the skin at the initial entry point. The operator grasps the two ends of the thread, and uses a to-and-fro sawing motion. The thread cuts through the TCL.

Methods: To determine whether this method performed a complete TCL transection, we performed eight carpal tunnel release procedures in eight cadaver wrists. After each case, surgical dissection was done to directly view the results. Dissection of the first case performed with the entry point at the typical site of carpal tunnel release (trapezium/hamate line) showed incomplete distal release of the TCL and the proximal palmar aponeurosis, creating an incomplete release. The subsequent seven procedures used a more distal needle insertion point, and we added initial hydrodissection of the proximal palmar aponeurosis with a 27 gauge needle to move the "duck's beak" of the distal TCL edge to a more volar position. This permitted more exact placement of the thread loop to encompass the entirety of the distal TCL.

Results: All seven of the procedures using the revised more distal approach resulted in total TCL release from the proximal to the distal TCL border. No damage to neural or vascular structures occurred. Previous clinical experience with this method has shown excellent results with minimal morbidity. (Guo D, Tang Y, Ji Y, Sun T, Guo J, Guo D. A non-scalpel technique for minimally invasive surgery: percutaneously looped thread transection of the transverse carpal ligament. Hand. 2015; 10:40-48). **Conclusion:** The advantages of this procedure are the relative lack of invasiveness, use of local anesthetic only, shorter recuperation, decreased likelihood of complications, and greater assurance of complete transection of the TCL.

Disclosure: N. Wei, None;

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Abstract Number: 1413

Medial Meniscus Extrusion and Spontaneous Osteonecrosis of the Knee

Tadashi Yasuda, Soichiro Masuda, Yuka Miyazaki, Makoto Hayashi, Yusuke Yamawaki, Mutsumi Watanabe, Hisataka Takeuchi, Satoshi Ota, Satoshi Fujita, Eijiro Onishi, Koichi Iwaki and Hiroshi Yamamoto, Department of Orthopaedic Surgery, Kobe City Medical Center General Hospital, Kobe, Japan

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Background/Purpose:

Although the pathogenesis of spontaneous osteonecrosis of the knee (SONK) remains unclear, two main etiologies have been suggested in the pathogenesis of SONK: vascular and traumatic. Recently, the presence of medial meniscus tear has been proposed as a potential third etiology behind development of SONK. Meniscal extrusion is associated with the progression of osteoarthritis. However, there has been no information on correlation between meniscal extrusion and SONK. Our purpose was to determine whether the extent of meniscal extrusion is associated with the severity of SONK.

Methods:

We examined 12 knees in 12 patients with a diagnosis of SONK in the medial femoral condyle between November 2010 and April 2015. All patients were examined by plain radiography and magnetic resonance imaging (MRI), which confirmed the diagnosis of SONK. No patient had a history of taking steroids or excessive alcohol consumption. There were four men and eight women, with a mean age of 70 years (55 to 82). The stage of progression of SONK was determined according to the radiological classification system. After measurement of anteroposterior, mediolateral, and superoinferior dimensions of the lesion by magnetic resonance imaging (MRI), its ellipsoid volume was calculated from the three dimensions. The extent of medial meniscus extrusion and its degeneration and tear were

also evaluated by MRI.

Results:

The mean volume of the lesions in 12 patients with SONK was 2837 mm^3 (324 to 7464). Degeneration and tear of the medial meniscus were found in 12 and 11 patients, respectively. The mean extrusion of the medial meniscus was 6.7 mm (3.0 to 10.2). Of the 12 knees with SONK, 2 knees showed the radiographic stage 2 lesions, 7 knees the stage 3, and 3 knees the stage 4. When the ellipsoid volume of SONK lesion was compared among stages, the volume tended to increase with the stage progression (*P*=0.062 by ANOVA). Medial meniscal extrusion was likely to increase with the stage progression, although no statistically significant difference was found (*P*=0.234 by ANOVA). The simple linear regression of the ellipsoid volume of SONK lesion on medial meniscal extrusion showed a significant correlation (R=0.761, *P*=0.004).

Conclusion:

The extent of medial meniscal extrusion was significantly associated with the size of the lesion of SONK, which could determine the prognosis of the disease.

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Abstract Number: 1414

Comparison of Surgical and Conservative Therapy of Lumbar Disc Herniation with Radicular Signs and Symptoms in a Quality Management Program

Marinella Gugliotta[1], Bruno R. da Costa[2], Essam Dabis[3], Robert Theiler[4], Stephan Reichenbach[2], Peter Jüni[2], Hans Landolt[1] and **Paul Hasler**[3], [1]Neurosurgery, Kantonsspital Aarau, Aarau, Switzerland, [2]Clinical Epidemiology and Biostatistics, University of Bern, Bern, Switzerland, [3]Rheumatology, Kantonsspital Aarau, Aarau, Switzerland, [4]Rheumatology, Stadtspital Triemli, Zürich, Switzerland
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Background/Purpose: Current evidence for outcomes of surgical versus conservative treatment of lumbar disc herniation with nerve root compression is ambiguous. To compare the effectiveness of surgical versus conservative treatment in patients with symptomatic lumbar disc herniation we followed cases prospectively in a quality control setting.

Methods: Validated instruments (North American Spine Society (NASS) questionnaire and SF-36) were used to measure patient-reported back pain, physical function, neurogenic symptoms and quality of life. Primary outcomes were pain symptoms at 6 and 12 weeks after the end of the treatment. Conservative treatment encompassed ergonomic instruction, active physical therapy, education/counseling with instructions for home-based exercise, analgesia, physical therapy and periradicular infiltrations and/or radicular pulsed radiofrequency application. Surgical treatment consisted of standard open discectomy and the appropriate components of the conservative approach. Effectiveness was assessed at 6, 12, 52, and 104 weeks after the end of the treatment.

Only cases with non-missing primary outcome data were included in the analysis. Missing data was filled in with multiple imputations, and mixed-effects models were used to account for repeated measures within cases. Baseline group differences were adjusted for by inverse probability weighting.

Results: Three-hundred-and-seventy patients were consecutively sampled and assigned to surgical (n=297) or conservative (n=73) treatment. Patients receiving surgical treatment tended to have more severe neurogenic symptoms at baseline (P=0.098) and were more likely to be from a higher social class (P=0.065). There was no significant difference between groups for all variables at baseline after adjustment using inverse probability weighting (P≥0.72).

Patients receiving surgical treatment reported less back pain than those receiving conservative treatment at 6 week follow-up (-0.97; 95%

confidence interval -1.89 to -0.09), had a higher proportion with ≥50% decrease in back pain symptoms from baseline to 6 weeks (48% vs 17%, risk difference: 0.34; 95% confidence interval 0.16 to 0.47), and less physical function disability at 1 year follow-up (-3.7; 95% confidence interval -7.4 to -0.1). For other assessments, between-group differences were minimal for all outcomes, with confidence intervals including the null effect.

Conclusion: Surgical treatment appears to provide faster relief for back pain symptoms than conservative treatment in the management of patients with lumbar disc herniation. However, surgical treatment did not show a clear benefit over conservative treatment in mid- and long-term follow-up.

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Abstract Number: 1415

The Relationship Between Obesity and Low Back Pain and Disability Is Affected By Mood Disorders – a Population-Based, Cross-Sectional Study of Men

Louisa Chou[1], Sharmayne Brady[2], Donna Urquhart[2], Andrew Teichtahl[3,4], Flavia Cicutinni[2], Julie Pasco[5,6], Sharon Brennan-Olsen[5,6,7] and Anita Wluka[2], [1]Department of Epidemiology and Preventative Medicine, School of Public Health and Preventive Medicine, Monash University, Melbourne, Australia, [2]Department of Epidemiology and Preventive Medicine, School of Public Health and Preventive Medicine, Monash University, Melbourne, Australia, [3]Epidemiology and Preventive Medicine, School of Public Health and Preventive Medicine, Monash University, Melbourne, Australia, [4]Baker IDI Heart and Diabetes Institute, Melbourne, Australia, [5]School of Medicine, Deakin University, Geelong, Australia, [6]North-West Academic Centre, University of Melbourne, Melbourne, Australia, [7]Australian Institute of Musculoskeletal Sciences, Melbourne, Australia

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Background/Purpose: Low back pain and obesity are both major public health problems. Known risk factors for back pain include age, female gender, lower educational attainment, strenuous physical activity and mood disorders. Obesity has also been linked with low back pain with recent studies reporting an association between increased fat but not lean tissue mass and back pain. However, these studies predominantly examined women. The relationship between body composition and low back pain in men is unknown. Therefore, the aim of this study was to examine the relationship between body composition and low back pain and disability in a population-based sample of men.

Methods: 978 male participants from the Geelong Osteoporosis Study, which is a population-based Australian study designed to investigate the epidemiology of osteoporosis among adults, were invited to participate in a follow up study in 2006. Participants completed questionnaires on sociodemographics and health status. Low back pain was determined using the validated Chronic Back Pain Grade Questionnaire and the presence of mood disorders was assessed using the Hospital Anxiety Depression Scale. Body composition was measured using dual energy x-ray absorptiometry. Binary logistic regression and estimated marginal means were used to examine the relationships between obesity measures and body composition in participants with high intensity pain and disability compared to those with no or low pain and disability. Multivariate analyses included adjustments for age, mood disorder, education, mobility and body mass index (BMI). To examine the multivariate associations between body composition and back pain, adjustment was also made for the alternate body composition measure. Interactions between risk factors for low back pain and measures of obesity, including measures of body composition were also examined.

Results: Of the 820 respondents (84% response rate), 124 (15%) had high intensity low back pain and/or disability. Participants with high intensity pain and/or disability were older, more likely to have a mood disorder, less likely to have completed secondary school and more likely to have poor mobility than those with no or low back pain and disability ($p<0.002$ for all). Low back pain was associated with higher BMI (28.7±0.4 vs 27.3±0.2 kg/m^2, $p=0.02$) and waist-hip ratio (0.97±0.006 vs 0.96±0.006, $p=0.04$), with increased tendency towards having a higher fat mass index (8.0 vs 7.6 kg/m^2, $p=0.08$), but not fat-free mass index ($p=0.68$). The relationships between back pain and measures of obesity were stronger in those with a mood disorder, particularly for waist-hip ratio ($p=0.05$ for interaction) and fat

mass index (p=0.06 for interaction).

Conclusion: In a population-based sample of men, high intensity low back pain and/or disability were associated with increased levels of obesity, particularly in those with mood disorders. This provides evidence to support a biopsychosocial interaction between mood disorders and obesity with low back pain.

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Abstract Number: 1416

Postoperative Complications Rate in Orthopaedic Surgery Performed in Rheumatic Patients in Use of Biologic Agents

Clarissa Queiroz Pimentel[1], Luiz Eduardo de Paula[1], Ana Paula Luppino-Assad[2], Gilberto Luis Camanho[3], Eloisa Bonfá[4] and **Marco Antonio Gonçalves Pontes Filho**[1], [1]Division of Rheumatology, University of São Paulo Medical School, São Paulo, Brazil, [2]Division of Rheumatology, University of São Paulo, sao paulo, Brazil, [3]Division of Orthopedics, University of São Paulo Medical School, São Paulo, Brazil, [4]Rheumatology, University of São Paulo, São Paulo, Brazil, Sao Paulo, Brazil

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Background/Purpose: Biologic agents have been associated with an increased risk of infection, thrombosis and delayed wound healing. However, there is no definitive consensus on suspension or continuity in the perioperative period, with few data assessing the risk of complications in rheumatic patients in use of these medications. The aim of this study is to evaluate the rate of complications after orthopedic procedures in rheumatic patients, assessing the effect of the disruption of biological therapy and trying to identify other potential predictors of complications.

Methods: We retrospectively assessed a monocentric cohort of patients with autoimmune rheumatic diseases who underwent orthopedic surgery from January 2007 to December 2014.

Results: A total of 87 patients underwent orthopedic surgery in the period, accounting for 178 procedures. Baseline diagnosis were rheumatoid arthritis (54%), juvenile idiopathic arthritis (17.2%), psoriatic arthritis (5.7%), ankylosing spondylitis (18.4%), systemic lupus erythematosus (1.1%), enteropathic spondyloarthropathy (1.1%), adult onset Still's disease (1.1%) and reactive arthritis (1.1%). The main cause of surgery was osteoarthritis secondary to the underlying disease (57.4%). The main surgeries were total hip arthroplasty (40.4%) and total knee arthroplasty (14%). A hundred twenty six patients were on nonbiologic disease-modifying antirheumatic drugs (DMARDs) and 53 were on biological therapy. Infliximab accounted for the majority of cases (33.9%), followed by etanercept (26.4%), adalimumab (18.9%), abatacept (11.3%), rituximab (5.7%), and tocilizumab (3.8%). In almost all cases the biological therapy was suspended in the preoperative period (98%), from an average of 20 days. Seven patients had postoperative infectious complications (3.9%), including superficial wound infection to necrosis and amputation of the affected limb. Five patients (2.8%) had severe complications requiring hospitalization or intravenous antibiotics. From these 7 patients, 2 (28.6%) were on abatacept, 2 (28.6%) on infliximab, 1 (14.3%) on tocilizumab, 1 (14.3%) on adalimumab and 1 on DMARD only. DMARDs associated with infections were leflunomide (3 patients, 42.9%), methotrexate (1 patient, 14.3%) and azathioprine (1 patient, 14.3%); 2 patients were on biologic agents only. Primary hypertension, dyslipidemia, diabetes mellitus and chronic kidney disease were present in 85.7, 57.1, 42.8 and 14.3% of patients with complications, respectively.

Conclusion: In our cohort, the rate of postoperative complications in orthopedic surgery performed in rheumatic patients treated with biological therapy was low compared to the literature (3.9% vs. 6.5%). Patients with complications had a high prevalence of comorbidities, which may have contributed to this outcome. Biological therapy discontinuation occurred in the majority of cases and seems to be a safe strategy for this population, however the ideal period of the suspension should be subject of further studies.

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Abstract Number: 1417

Rural Residence Does Not Impact Total Ankle Arthroplasty Utilization and Outcomes

Jasvinder A. Singh and Rekha Ramachandaran, University of Alabama at Birmingham, Birmingham, AL
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Background/Purpose: It is not known whether there are rural-urban disparities in Total Ankle Arthroplasty (TAA), given that TAA is a relatively new procedure and is an elective procedure. Our objective was to assess whether patient's residence (rural vs. urban) was associated with any disparities in TAA utilization and TAA outcomes. We hypothesized the utilization rates will be lower and poor outcomes more common in rural residents, compared to urban residents.

Methods: We used the Nationwide Inpatient Sample (NIS) from 2003-11 to compare utilization and outcomes (post-arthroplasty discharge disposition, length of hospitalization and mortality) by rural vs. urban residence.

Results: 10,833 patients in urban and 3,324 patients in rural area underwent TAA. Compared to rural residents, urban residents had: lower mean age, 62.4 vs. 61.8 ($p < 0.0001$), higher percent of women, 49% vs. 56% ($p=0.0008$) and lower proportion of Whites, 93% vs. 86% ($p=0.0005$). There were rural-urban disparities in TAA utilization in 2003 (0.32 vs. 0.39/100,000; $p=0.021$), but not in 2011 (1.19 vs. 1.17/100,00; $p=0.80$). TAA outcomes did not differ by rural vs. urban residence: (1) 11.3% rural vs. 14.2% urban residents were discharged to an inpatient facility ($p=0.098$); (2) length of hospital stay above the median stay, 44.8% vs. 42.2% ($p=0.30$); and (3) mortality, 0.2% vs. 0.1%, respectively ($p=0.81$). Multivariable-adjusted logistic regression models did not show any significant differences in discharge to home, length of stay or mortality, by residence.

Conclusion: Our study demonstrated no evidence of rural-urban differences in TAA outcomes. The rural-urban differences in TAA utilization noted in 2003 were no longer significant in 2011.

Disclosure: J. A. Singh, Takeda, Savient, 2,Takeda, Savient, merz, Regeneron, Allergan, Crealta, Bioiberica, 5; **R. Ramachandaran**, None.

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Abstract Number: 1418

The Importance of Comorbidity in Understanding the 6-Month Trajectories of Pain and Function after Total Hip Arthroplasty

C. Allyson Jones[1], Gian S. Jhangri[2], Lauren A. Beaupre[1] and Maria E. Suarez-Almazor[3], [1]Physical Therapy, University of Alberta, Edmonton, AB, Canada, [2]School of Public Health, University of Alberta, Edmonton, AB, Canada, [3]General Internal Medicine, The University of Texas, MD Anderson Cancer Center, Houston, TX
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Background/Purpose:

Osteoarthritis (OA) is chronic condition associated with a number of other comorbidities which may affect the 6 month pattern of recovery of total hip arthroplasty (THA). It is not clearly understood which comorbidities affect 6-month pain relief and functional recovery. We looked at the pattern of recovery for THA to determine which comorbid conditions had the most impact on the recovery following THA in terms of pain relief and functional improvement.

Methods:

Longitudinal prospective inception cohort of 305 patients receiving elective primary THA were followed within a month prior to surgery, and then at 1, 3, 6 months after surgery. The outcome measures, hip pain and function were measured using the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC). Comorbid conditions were extracted from the chart and reported by the patient using a standardized list. Patients who reported conditions also rated the impact of the specific condition on routine activities. Health status was measured using a generic health measure, Health Utilities Index Mark3 (HUI3). The Center for Epidemiologic Studies-Depression (CES-D) was used to screen for depressive symptomology. Measurements were repeated at each of the follow-up interviews. Linear mixed models were developed for pain and functional recovery of THA to evaluate changes over time while adjusting for covariates.

Results:

The mean age of participants was 65.9 (SD10.1) yrs; 175(57%) were female. Mean pre-operative WOMAC pain improved from 56.0(SD 16.7) to 10.8 (SD 13.2) over the 6 months ($p<0.001$). The mean pre-operative WOMAC function improved from 54.7 (SD 16.4) to 18.7 (SD 12.8) over this time ($p<0.001$). At baseline, the mean overall HUI3 score was 0.42 (SD 0.26). At baseline, 101(33%) had low back pain, 80(26%) had chronic respiratory disease, 60 (20%) had depressive symptomology, and 77 (25%) urinary incontinence. After controlling for age, sex, baseline pain and time, depression score (coeff 2.2, p=0.06), low back pain (coeff 2.8, p<0.01), chronic respiratory disease (coeff 4.4, p<0.01) had a deleterious effect on pain relief. Urinary incontinence (coeff 2.0, p=0.03), after controlling above mentioned variables, affected functional improvement.

Conclusion:

Patients with low back pain, depression and chronic respiratory disease are likely to have slower pain relief after THA. Urinary incontinence had a deleterious effect on functional improvement over a 6 month recovery. Using patient-centered care in managing these conditions before surgery may help patients attain more favourable outcomes.

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Abstract Number: 1419

Increasing Comorbidity Is Associated with Worsening Physical Function during Intermediate-Term Follow-up of Primary Total Knee Arthroplasty

Maren Hilton[1], Terence Gioe[2] and **Jasvinder A. Singh**[3], [1]Arthritis and Rheumatology Consultants, Edina, MN, [2]Department of Orthopaedic Surgery, Minneapolis VA Medical Center, Minneapolis, MN, [3]University of Alabama at Birmingham, Birmingham, AL
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Background/Purpose:

Total knee arthroplasty (TKA) is associated with significant gains in function and pain improvement. However, decline in function has been noted in patients who have undergone TKA. We were interested in what factors, changing through time, may be associated with this decline in function. In this study, we examined the relationship of the change in comorbidity with the change in SF-36 and WOMAC

physical function and pain scores. To our knowledge, none of the previous studies have addressed this question.

Methods:

We performed a retrospective chart review of veterans who had completed Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) and Short Form-36 (SF36) surveys at regular intervals after primary TKA using structured data abstraction form. Comorbidity was assessed using a variety of scales: validated Charlson comorbidity score, local musculoskeletal morbidity (back and lower extremity), TKA complications and a novel Medical Comorbidity Severity Index, at multiple time-points post-TKA. We used mixed model linear regression to examine the association of worsening comorbidity, with worsening WOMAC and SF36 scores, controlling for age, length of follow-up, and repeated observations.

Results:

The study cohort consisted of 124 patients with a mean age of 71.7 years (range 58.6-89.2, standard deviation (SD) 6.9) followed for a mean of 4.9 years post-operatively (range 1.3-11.4; SD 2.8). We found that post-operative worsening of the Charlson Index was significantly associated with worsening SF-36 Physical Function (PF) ($p<0.0001$) and worsening WOMAC PF ($p=0.012$). Worsening scores on novel medical Comorbidity Severity Index scores were significantly associated with worsening SF-36 PF ($p<0.001$), and a non-significant trend of association with WOMAC PF ($p=0.056$). Local comorbidity index was significantly associated with SF-36 PF ($p<0.001$), WOMAC PF ($p<0.001$), and WOMAC Pain ($p=0.004$). TKA complications were not significantly associated with SF-36 or WOMAC domain scores.

Conclusion:

Worsening medical comorbidity was significantly associated with worsening physical function and worsening lower extremity and spine morbidity with declining physical function as well as worsening pain during intermediate term follow-up after primary TKA. Further studies should examine which comorbidity had the greatest impact on these outcomes.

Disclosure: M. Hilton, None; **T. Gioe**, None; **J. A. Singh**, Takeda, Savient, 2,Takeda, Savient, merz, Regeneron, Allergan, Crealta, Bioiberica, 5.

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Abstract Number: 1420

6-Month Change in Pain and Function By Pre-Surgery Pain and Function Among Patients Selected for Total Knee Replacement in the United States

Uyen Sa D.T. Nguyen[1], David Ayers[2], Wenjun Li[3], Leslie Harrold[4] and Patricia D. Franklin[5], [1]Orthopedics and Physical Rehabilitation, University of Massachusetts Medical School, Worcester, MA, [2]Orthopedics & Physical Rehab, University of Massachusetts Medical School, Worcester, MA, [3]Medicine, Division of Preventive Medicine, University of Massachusetts Medical School, Worcester, MA, [4]Department of Orthopedics and Medicine, University of Massachusetts Medical School, Worcester, MA, [5]Orthopedics & Physical Rehab, Univ of MA Med Schl, Worcester, MA

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Background/Purpose: In the US, the annual rate of TKRs in people 65 years or older increased almost 9-fold between 1979 and 2006, with similar if not greater growth in younger age groups. There is increasing debate regarding the appropriate utilization of TKRs. We examined change in pain and function, quality of life (QOL), and patient satisfaction at 6-month post-surgery stratified by their pre-surgery pain and function status.

Methods: We used data from the Function and Outcomes Research for Comparative Effectiveness in TJR (FORCE-TJR), a national cohort of TJR patients of more than 150 surgeons in 22 sites nationwide. Participants had: primary, unilateral TKRs indicated by osteoarthritis; surgeries between April 2011 and May 2014; completed pre-operative Knee Injury and Osteoarthritis Outcome Score (KOOS) including QOL items and Short-Form 36-item (SF-36) functional health survey; and the respective 6-month post-operative surveys, with satisfaction

measured by Self Evaluated Transitions items. We classified patients as having high or low pain (KOOS Pain<70 vs. ≥70), and low or high physical function (SF-36 PCS <40 vs. ≥40) and grouped then as follows: 1) Low pain-High function (LP-HF), 2) Low pain-Low function (LP-LF), 3) High pain-High function (HP-HF), and 4) High pain-Low function (HP-LF). Change from baseline to 1-year post-surgery pain and function scores were calculated. Cohen's unadjusted standardized differences in absolute post-op scores accounting for pooled SD were calculated with LP-HF as referent group.

Results: This study included 4,563 participants: 5% pre-op LP-HF, 20% either HP or LF, and 75% both HP-LF. By 6-month post-op **(Table)**, in Group 1, 85% remained the same but 4% became much worse among people with pre-op LP-HF: in Group 4, 18% remained the same and 52% achieved much improvement among people with pre-op HP-LF. Mean change (SD) in 6-month KOOS pain score in LP-HF group was 8.3 (14.6) compared with 37.2 (19.7) in the HP-LF group. Patients in LP-HF had the near highest absolute mean (SD) post-op pain score (88.9 (13.0)) and the HP-LF group the lowest (79.9 (17.3)); the unadjusted standardized effect size was 0.59. Similarly, the mean change in PCS function was 2.6 (7.8) in the LP-HF group, and was 11.9 (9.0) in the HP-LF group. The LP-HF group had the highest absolute mean 6-month post-surgery function of 50.0 (7.4) while the HP-LF group had the lowest score of 42.0 (9.5); the unadjusted standardized effect size was 0.94. The groups reported similar satisfaction, but QOL items indicated better QOL among the pre-surgery LP-HF than the HP-LF groups.

Conclusion: While TKR patients with low pain and high function pre-op achieved the smallest mean change in pain and function, they reported better absolute outcomes at 6-months. The majority of TKR patients with high pain and poor function achieved the greatest mean improvement in pain and function.

Table. 6 Month-Change in Pain and Function by Pre-Operative Pain and Function Status				
Characteristics	**Group 1** **Low Pain** **High Function** **n=234 (5%)**	**Group 2** **Low Pain** **Low Function** **n=173 (4%)**	**Group 3** **High Pain** **High Function** **n=718 (16%)**	**Group 4** **High Pain** **Low Function** **n=3288 (75%)**
Pain & Function Status 6-mth Post-KR				
Remained in Same Classification Group	85%	25%	11%	18%
Optimal Improvement -> (to Low Pain-High Function Group)	NA	65%	79%	52%
Worst Decline-> (to High Pain-Low Function Group)	4%	6%	7%	NA
Other Changes	9%	4%	3%	30%
6-month Change in Pain & Symptoms				
Pain, KOOS Mean (SD) – Pre	80.7 (7.9)	79.5 (7.6)	53.7 (11.0)	42.7 (11.6)
Pain, KOOS Mean (SD) – Post	88.9 (13.0)	89.6 (11.3)	84.2 (14.8)	79.9 (17.3)
Unadjusted 6-mth Change Mean (SD)	*8.3 (14.6)*	*10.2 (12.9)*	*30.5 (16.6)*	*37.2 (19.7)*
Unadjusted Standardized Differences *relative to Pooled SD***	*REF*	*0.06*	*0.34*	*0.59*
6-month Change in Function				
Function, SF36 PCS, Mean (SD)-Pre	47.4 (4.7)	34.0 (4.4)	44.5 (3.6)	30.1 (6.0)
Function, SF36 PCS, Mean (SD)-Post	50.0 (7.4)	44.1 (8.5)	49.3 (7.0)	42.0 (9.5)
Change over 6 months Mean (SD)	*2.6 (7.8)*	*10.2 (7.8)*	*4.8 (7.0)*	*11.9 (9.0)*
Unadjusted Standardized Differences *relative to Pooled SD***	*REF*	*0.74*	*0.10*	*0.94*
6-mth Post-TKR Satisfaction using Self-Evaluated Transitions				
Better Health compared to 1 year ago-	60%	54%	61%	63%
More Capable everyday physical activity	79%	80%	82%	82%
More able to accomplish daily work	78%	78%	77%	78%
Less often bothered by emotional problem	47%	43%	47%	52%
Better Health compared to before surgery	61%	57%	63%	64%
Pre- and Post-TKR QoL Issues				
Awareness Knee Problem Daily/Constantly-Pre*	86%	92%	98%	99%
Daily/Constantly-Post	46%	52%	54%	62%
General Difficulty with Knee				

NONE-Pre*	5.9%	4.0%	0.7%	0.2%
NONE-Post	50%	38%	35%	26%

* For Descriptive Purposes Only

**Cohen's d http://www.uccs.edu/~lbecker/: effect size: 0.2-small, 0.5-medium, 0.8-large

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Abstract Number: 1421

The Risk Factor of Preoperative Deep Vein Thrombosis in Patients Undergoing Total Knee Arthroplasty

Hiroki Wakabayashi[1], Masahiro Hasegawa[1], Sho Kato[1], Rui Niimi[1], Shinichi Miyazaki[1], Noriki Miyamoto[1] and Akihiro Sudo[2], [1]Department of Orthopaedic Surgery, Mie University Graduate School of Medicine, Tsu City, Japan, [2]Orthopaedic surgery, Mie University Postgraduate School of Medicine, Tsu-city, Japan

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SESSION INFORMATION

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Session Title: Orthopedics, Low Back Pain and Rehabilitation Poster

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Background/Purpose: Total knee arthroplasty (TKA) reliably relieves pain and improves function in patients with end-stage arthropathy of the knee such as rheumatoid arthritis (RA). The most common complication after knee arthroplasty is DVT. The significance of DVT lies in the possibility of PE and the occurrence of chronic venous insufficiency at a later stage. PE is a potentially life-threatening disorder and is among the most common causes of death postoperatively. Previous studies have reported elevated risks of DVT in patients with RA. If a high risk of DVT is identified in the patient's background and medical history, it might be useful in early diagnosis. It is not reported whether the prevalence of DVT in the RA patients undergoing TKA is higher compared with non-RA patients or not. Thus, we investigated the patient's background and medical history in patients admitted to hospital for TKA and identified the risk factors, including RA, for DVT development before TKA.

Methods:

Patients

From 2003 to 2013, 319 patients admitted for TKA at Mie University Hospital were eligible for the present retrospective study. The surgical diagnoses were degenerative osteoarthritis (OA) in 274 patients and rheumatoid arthritis (RA) in 45 patients. The patients' sex, weight, body mass index (BMI, weight in kilograms divided by the square of the height in meters), and data from the medical history and medical condition were recorded.

Diagnosis of DVT

B-mode ultrasonography with compression and color Doppler imaging were performed for bilateral common femoral veins, the superficial veins, the popliteal veins, and the calf veins.

Results:

The preoperative diagnosis was OA in 274 patients (85.9%) and RA in 45 patients. Moreover, admissions for joint replacement in this population were for primary procedures in 300 patients (94.0%) and revision TKA in 19 patients. The most frequent preoperative medical history or medical condition was hypertension (52.7%). The second most frequent preoperative medical history or medical condition was major surgery (50.5%), including a history of primary TKA and cancer surgery

Preoperative DVT was diagnosed in 57 of 319 (17.9%) patients overall. Significantly elevated risks of DVT were found in patients who were female ($p = 0.039$), who had RA ($p=0.006$), and who were admitted for revision TKA ($p=0.033$) using Fisher's exact test. Multiple linear regression analysis was performed to test the association of DVT with putative risk factors. The analysis showed that admission for

RA (p=0.049) and revision TKA (p=0.009) were significant independent risk factors for preoperative DVT.

Conclusion: RA and admission for revision TKA surgery were risk factors for DVT among those admitted to the hospital for TKA. The results also suggest that instrumental screening should be encouraged, at least in subgroups at higher risk for preoperative DVT.

Disclosure: H. Wakabayashi, None; **M. Hasegawa**, None; **S. Kato**, None; **R. Niimi**, None; **S. Miyazaki**, None; **N. Miyamoto**, None; **A. Sudo**, None.

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Abstract Number: 1422

Pain after Total Knee Arthroplasty: Poverty Modifies the Effect of Race and Education

Susan M. Goodman[1], Anne R. Bass[1], Michael Parks[2], Kelly McHugh[1], Meng Zhang[3], Joseph Nguyen[3], Yuo-Yu Lee[3], Mark P. Figgie[4] and Lisa Mandl[5], [1]Rheumatology, Hospital for Special Surgery, New York, NY, [2]Orthopedics, Hospital for Special Surgery, New York, NY, [3]Epidemiology and Biostatistics, Hospital for Special Surgery, New York, NY, [4]Orthopaedics, Hospital for Special Surgery, New York, NY, [5]Hospital for Special Surgery, New York, NY

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Pain after Total Knee Arthroplasty: Poverty Modifies the Effect of Race and Education

Background/Purpose: Race and education are important predictors of pain after total knee arthroplasty (TKA) in the United States (US). However, whether community poverty modifies the effect of race and education on pain following TKA is unknown. We assessed the interaction between poverty and race, and poverty and education on WOMAC pain 2 years after TKA.

Methods: Individual patient level variables were obtained from a single institution registry of TKA performed between 5/1/2007 and 7/1/2010 including demographics, baseline and 2 year WOMAC pain (0-100; 100 best), HSS Expectations Score (1-100, 100 best) and geocodable US addresses. Individual patient level variables were then linked to US Census Bureau data at the census tract level. Statistical models including both patient level variables and census tract level variables were constructed within multilevel frameworks. Two multivariate linear mixed effect models with separate random intercepts for each census tract were used to assess the interaction between race and census tract poverty level, and the interaction between education and census tract poverty level as predictors of WOMAC pain 2 years after TKA.

Results: 507/4225 (11.3%) of the TKA registry patients were non-white, and non-white patients were less likely to be college educated than whites (48.2 vs 62.8%, p-value≤0.0001). In univariate analysis, race, education and census tract poverty level (the percent of the community living below the poverty level) were significantly associated with WOMAC pain 2 years after TKA. In the first multivariate linear mixed effect model it was estimated that non-whites had worse WOMAC pain scores than whites and this difference increased with the increasing census tract poverty level (**Table 2**). The second multivariate linear mixed effect model showed that patients without college education had worse WOMAC pain 2 years after TKA than those with at least some college education, and this effect was magnified by greater levels of census tract poverty (**Table 3**).

Conclusion: Non-white race and a lack of college education are both associated with worse WOMAC pain 2 years after TKA and this effect is magnified by higher community poverty level. The differential impact of poverty, race, and education on pain after TKA needs more study.

Table 1: Patient characteristics				
Individual Level Variables	**Total (N=4225)**	**White (N=3970)**	**Non-White (N=507)**	**p-value**
Age, mean ± std	67.1 ± 9.7	67.2 ± 9.6	65.4 ± 10.0	0.0001
Female, %	61.8	60.9	70.7	<0.0001

Ethnicity				<0.0001
Hispanic, %	3.9	1.2	26.7	
Non-Hispanic ,%	96.1	98.9	73.3	
Co-morbidity				<0.0001
0 Comorbidities, %	71.4	72.8	61.3	
+1 Comorbidity, %	28.6	27.2	38.7	
Education				<0.0001
College above, %	61.3	62.8	48.2	
No college, %	38.7	37.2	51.8	
BMI, mean ± std	29.9 ± 5.9	29.8 ± 5.8	31.1 ± 6.4	<0.0001
Insurance				<0.0001
Medicare%	62.2	63.2	50.6	
Medicaid%	2.0	0.54	13.3	
Other%	35.8	35.8	36.1	
WOMAC pain at baseline, mean ± std	54.0± 17.7	54.7 ± 17.5	48.8 ± 19.5	<0.0001
HSS Expectations Score, mean ± std	78.6 ± 18.0	78.5 ± 18.0	78.3 ± 18.0	0.84

Table 2: Estimation based on a Linear Mixed Effects Model Assessing the Effect of Interaction between Race and Poverty at Census-tract Level on WOMAC Pain at 2 Years after TKA*

Race	Below poverty**	Estimated WOMAC Pain at 2 years	Standard Error	p-value	Estimated difference in 2 year WOMAC Pain: (Non-white vs. White)	Standard Error	p-value
Non-white	10%	**83.9**	0.96	<0.0001	**-3.01**	1.02	**0.0033**
White	10%	86.9	0.42	<0.0001			
Non-white	30%	**80.4**	1.54	<0.0001	**-5.13**	1.99	**0.0104**
White	30%	85.6	1.29	<0.0001			
Non-white	50%	**76.9**	2.85	<0.0001	**-7.25**	3.65	**0.0472**
White	50%	84.2	2.32	<0.0001			
Non-white	70%	**73.5**	4.25	<0.0001	**-9.37**	5.39	**0.0822**
White	70%	82.9	3.36	<0.0001			
Non-white	90%	**70.1**	5.68	<0.0001	**-11.49**	7.15	**0.1081**
White	90%	81.6	4.41	<0.0001			

TKA = total knee arthroplasty

*Linear mixed effect model controlling for age, gender, BMI, race, education, baseline WOMAC pain, expectations, Charlson-Deyo comorbidities, Percentage of population below poverty at census tract level (census tract poverty level) and interaction of census tract poverty level and race (Census tract poverty level x race); estimates were calculated based on the following: WOMAC pain=53.73; age=66.51; BMI= 29.99; expectation score= 78.49; gender=female; education=college-above; comorbidities=0

** percentage of population in census tract below poverty level

Table 3: Estimation based on a Linear Mixed Effects Model Assessing the Effect of Interaction between Education and Poverty at Census-tract Level on WOMAC Pain at 2 Years after TKA*							
Education	Below poverty**	Estimated WOMAC Pain at 2 years	Standard Error	p-value	Estimated difference in 2 year WOMAC Pain: (college-above vs. Non college)	Standard Error	p-value
College-above	10%	**87.4**	0.60	<0.0001	**4.05**	**0.69**	**<0.0001**
No college	10%	**83.4**	0.64	<0.0001			
College-above	30%	**86.8**	1.49	<0.0001	**6.92**	**1.99**	**0.0005**
No college	30%	**79.9**	1.35	<0.0001			
College-above	50%	**86.3**	2.66	<0.0001	**9.80**	**3.59**	**0.0065**
No college	50%	**76.5**	2.44	<0.0001			
College-above	70%	**85.7**	3.85	<0.0001	**12.67**	**5.22**	**0.0154**
No college	70%	**73.0**	3.57	<0.0001			
College-above	90%	**85.1**	5.05	<0.0001	**15.54**	**6.86**	**0.0237**
No college	90%	**69.6**	4.72	<0.0001			

TKA = total knee arthroplasty

*Linear mixed effect model controlling for age, gender, BMI, race, education, baseline WOMAC pain, expectations, Charlson-Deyo comorbidities, Percentage of population below poverty at census tract level (census tract poverty level) and interaction of census tract poverty level and education (Census tract poverty level x education); estimates were calculated based on the following: WOMAC pain=53.73; age=66.51; BMI= 29.99; expectation score= 78.49; gender=female; race=non-white; comorbidities=0

** percentage of population in census tract below poverty level

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Disclosure: **S. M. Goodman**, None; **A. R. Bass**, None; **M. Parks**, Zimmer, Inc, 5,Orthopeadic Research and Education Foundation, 6,American Academy of Orthopaedic Surgery Orthopaedic Learning Center, 6,New York State Society of Orthopaedic Surgeons, 6; **K. McHugh**, None; **M. Zhang**, None; **J. Nguyen**, None; **Y. Y. Lee**, None; **M. P. Figgie**, None; **L. Mandl**, Up To Date, 7,Annals of Internal Medicine, 9.

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Abstract Number: 1423

Racial Disparities in Pain and Function after Total Knee Arthroplasty in the United States: A Systematic Literature Review

Susan M. Goodman[1], Kelly McHugh[1], Michael Parks[2], Mark P. Figgie[3], Yuo-Yu Lee[4], Kara Fields[5], Rie Smethurst[6] and Anne R. Bass[1], [1]Rheumatology, Hospital for Special Surgery, New York, NY, [2]Orthopedics, Hospital for Special Surgery, New York, NY, [3]Orthopaedics, Hospital for Special Surgery, New York, NY, [4]Epidemiology and Biostatistics, Hospital for Special Surgery, New York, NY, [5]Medicine/Rheumatology, Hospital for Special Surgery, New York, NY, [6]Education - Academic Training, Hospital for Special Surgery, New York, NY

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Background/Purpose: Blacks in the United States (US) are less likely to undergo total knee arthroplasty (TKA) than whites, in part because they expect to benefit less. Whether their lower expectations are justified is unclear. The objective of this systematic literature review was to compare Health Related Quality of Life (HRQOL), pain, function, and satisfaction after TKA in US blacks andUS whites.

Methods: A librarian assisted search was performed on 12/14/2014 using PUBMED, EMBASE and the Cochrane Central Register. In addition, a hand search of journals focusing on disparities was performed. The following key terms were used: total knee replacement, quality of life, outcomes, and satisfaction. The search was limited to studies published during or after the year 2000. The population of interest was black US adults, the intervention was TKA, and the comparator was white US adults. Outcomes were HRQOL, pain, function and satisfaction following TKA. High quality observational cohorts with ≥ 6 month follow-up after TKA were included.

Results: 4781 studies were identified and screened by title, 346 by abstract, and 18 by full text. Only 7 studies met inclusion criteria and included race in the analysis. These studies represented a total of 4559 TKA patients of whom 482 (11%) were black. Because the studies used different outcome measures and were inconsistent in their adjustment for confounders, we could not perform a quantitative synthesis of the results. In 4 studies US blacks had worse pain, in 4 worse function, and in 1 less satisfaction 6 months-2 years after TKR.

Conclusion: US blacks may derive less benefit from TKA than whites as measured by HRQOL, pain, function and satisfaction, and this may contribute to lower rates of TKA utilization by blacks. Many large studies assessing predictors of patient related TKA outcomes fail to analyze race as a variable, which limited our study. More studies assessing the impact of race and socioeconomic factors on TKA outcomes are needed.

Table 1. Included Studies

Citation	Years	Duration follow up	Outcomes analyzed	Total	White	Black	Significantly worse in black patients	Adjusted					Notes
								Age	Sex	LOS	Comorbidity	SES	
Maratt Jo A[a] 2015	2001-2007	2 yrs	WOMAC Pain Stiffness Function	2322	2108	101	WOMAC pain	Ö	Ö	Ö	Ö	Ö	Large number of excluded patients may have biased results
Barrack CORR[b] 2014	NA	1-4 yrs	Function Residual symptoms Return to work UWSC satisfatction*	661	573	85	Pain Function**	Ö				Ö	Retrospective
Jacobs JoA[a] 2014	NA	2-5 yrs	Satisfaction†	989	830	49	Satisfaction	Ö	Ö			no	SES not analyzed
KamathCORR[b] 2010	2004	2-5 yrs	ROM KSS	185	87	90	KSS ROM		Ö			no	Retrospective
Lavernia CORR[b] 2011	1992-2007	2-16 yrs	ROM Radiographs QWB SF-36 WOMAC HSS KSKS HHS score MAP Score	1010	176	74	QWB SF-36 physical WOMAC pain WOMAC function		Ö			no	Single surgeon study
Lopez-Olivo ARD[c] 2011	2004-2005	6mo	WOMAC pain, function KSRS total KRS function	241	166	61	KSRS function				Ö	Ö	May not be generalizable
Styron JBJS[d] 2011		1,3,6 mo	KOOS, WOMAC SF-12 Time to return to work	162	137	22	KOOS ADL Pain KOOS QOL WOMAC pain WOMAC ADL	Ö	Ö				More blacks lost to follow up

*Survey designed by The University of Wisconsin Survey Center (UWSC); targeted satisfaction with overall knee function, ability to perform daily activities, and pain relief, using a 5 point Likert scale

**Questions worse in minority patients included: problems getting in and out of the car or chair, difficulty going up and down stairs, experienced pain in the last 30 days, limp while walking

†Patients were asked if they were satisfied with their surgery and given the options “yes” “no” or “I’m not sure” -“yes” were categorized as satisfied

KSS=Knee Society Score; WOMAC=Western Ontario and McMaster Universities Osteoarthritis Index, QWB= quality of well-being score, HSS=Hospital for Special Surgery; KSKS=Knee Society Knee Score; MAP score = Merle d'Aubigne´-Postel score

[a]JoA Journal of Arthroplasty; [b]CORR Clinical Orthropedic and Related Research; [c]ARD Annals of Rheumatic Disease; [d]JBJS Journal of Bone and Joint Surgery

Disclosure: S. M. Goodman, None; **K. McHugh**, None; **M. Parks**, Zimmer, Inc, 5,Orthopeadic Research and Education Foundation, 6,American Academy of Orthopaedic Surgery Orthopaedic Learning Center, 6,New York State Society of Orthopaedic Surgeons, 6; **M. P. Figgie**, None; **Y. Y. Lee**, None; **K. Fields**, None; **R. Smethurst**, None; **A. R. Bass**, None.

Abstract Number: 1424

Barriers to Primary Care Clinician Adherence to Clinical Guidelines for the Management of Low Back Pain: A Systematic Review and Meta-Synthesis of Qualitative Studies

Susan Slade[1], Peter Kent[2], Shilpa Patel[3], Tracey Bucknall[4] and **Rachelle Buchbinder**[1], [1]Monash Department of Clinical Epidemiology, Cabrini Institute and Monash University, Melbourne, Australia, [2]Department of Sports Science and Clinical Biomechanics, University of Southern Denmark, Odense, Denmark, [3]Warwick Clinical Trials Unit, The University of Warwick, Warwick, United Kingdom, [4]School of Nursing & Midwifery, Deakin University and Alfred Health, Melbourne, Australia

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Background/Purpose: Low back pain is the highest ranked condition contributing to years lived with disability according to the most recent Global Burden of Disease study and is associated with significant societal and individual cost. Despite the availability of consistent evidence-based treatment recommendations for low back pain, management in primary care remains suboptimal with overreliance on imaging and medical intervention. We performed a systematic review and meta-synthesis of qualitative studies that explored what primary care clinicians believe about clinical practice guidelines for low back pain, including perceived enablers and barriers to guideline adherence.

Methods: The study was registered with PROSPERO (CRD42014012961) and our methods conformed to Cochrane Collaboration guidelines, the PRISMA Statement and the COREQ Checklist. Studies investigating perceptions and beliefs about low back pain guidelines were included if participants were primary care clinicians and qualitative methods had been used for both data collection and analysis. Only English-language studies were included. Eight electronic databases were searched from inception until July 2014. Pairs of reviewers independently screened titles and abstracts, extracted data, appraised method quality using the CASP checklist, conducted thematic analysis and synthesized the results in narrative format.

Results: From a search yield of 1880 titles, 32 papers were read in full and 17 papers fulfilled inclusion criteria. Studies were conducted in UK, Canada, USA, Netherlands, Germany, Israel, New Zealand and Norway and included general practitioners, physical therapists, chiropractors, osteopaths and occupational therapists.

All studies reported research aims, a justification for qualitative methods and a purposive sampling strategy and the majority reported recruitment and data collection details. However, many studies failed to report other key study components to allow full method quality assessment. We identified three key themes: clinicians have beliefs/perceptions that influence guideline implementation and adherence; they have beliefs/perceptions about patient expectations within the clinician-patient relationship; and they have beliefs/perceptions that act as barriers to guideline adherence.

Clinicians believe that guidelines are categorical, prescriptive and constrain professional practice, that popular clinical practices supersede the guidelines, and imaging can be used to manage consultations. Their perceptions reflect lack of content knowledge and

understanding of how guidelines are developed.

Conclusion: Addressing misconceptions and other barriers to uptake of evidence-based guidelines for managing low back pain is needed to improve knowledge transfer and close the evidence-practice gap in the treatment of this common condition.

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Abstract Number: 1425

Current Tobacco Use and the Rates of Complications after Total Hip Arthroplasty

Jasvinder A. Singh, University of Alabama at Birmingham, Birmingham, AL

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Background/Purpose:

The risk of postoperative complication with tobacco use disorder and complication after total hip arthroplasty (THA) are not known. Our objective was to compare the rates of complications in current tobacco users and non-users who underwent primary THA.

Methods:

All patients who underwent primary THA at the Mayo Clinic from 2010 to 2013 were included. Current tobacco use was defined as the use of cigarettes, cigars, pipes or smokeless tobacco reported by the patients at the time of their surgery. We used Cox proportional hazards regression to assess the association of current tobacco use status with each post-THA complication, using hazard ratio (HR) and 95% confidence intervals (CI), and Kaplan-Meier survival to estimate the implant survival.

Results:

Tobacco use status was available for 3,649 patients (95%) and not available for 197 patients (5%); 3,312 (92%) were current tobacco users. Among current tobacco users, higher proportion were male ($p<0.001$), or were 71-80 or ≥80 years old ($p=0.02$ and $p<0.001$; reference ≤60); no differences were noted for BMI, cemented vs. uncemented implant, Charlson index or ASA class.

Compared to current tobacco non-users, the hazards were significantly higher in current tobacco users for deep infection, hazard ratio of 2.89 (95% CI: 1.26,6.64; $p=0.01$). Non-significant trends for higher hazards were noted for rates of any infection at 1.66 (0.78,3.49; $p=0.19$), and any revision, 1.66 (0.82,3.35; $p=0.16$). No significant differences were noted for superficial infection and periprosthetic fracture by current tobacco use.

Conclusion:

We noted that current tobacco use was associated with high risk of infection after primary THA. Future studies should determine the optimal time for tobacco use cessation before elective surgeries such as THA.

Endpoint	Variable	# events	1 year (95% CI)	2 years (95% CI)	HR (95% CI)	p-value
Any revision	Current tobacco user	9	94.1 (90.2,98.1)	94.1 (90.2,98.1)	1.66 (0.82,3.35)	0.16
	Past user or never used	61	97.5 (96.8,98.2)	96.7 (95.8,97.6)	1.0 (ref)	
Revision for aseptic loosening	Current tobacco user	0	100	100	0.56 (0.03,10.95)	0.70
	Past user or never used	10	99.5 (99.1,99.8)	99.3 (98.9,99.7)	1.0 (ref)	
Revision for infection	Current tobacco user	3	98.4 (96.5,100)	98.4 (96.5,100)	1.55 (0.46,5.21)	0.48
	Past user or never used	21	99.1 (98.7,99.5)	99.0 (98.5,99.4)	1.0 (ref)	
Revision for peri-prosthetic fracture	Current tobacco user	1	99.2 (97.7,100)	99.2 (97.7,100)	1.79 (0.21,15.19)	0.59
	Past user or never used	6	99.8 (99.6,100)	99.7 (99.4,100)	1.0 (ref)	
Complication deep infection	Current tobacco user	7	97.1 (94.9,99.2)	97.1 (94.9,99.2)	2.89 (1.26,6.64)	0.01
	Past user or never used	26	98.9 (98.5,99.4)	98.8 (98.3,99.3)	1.0 (ref)	
Complication superficial infection	Current tobacco user	1	99.6 (98.7,100)	99.6 (98.7,100)	0.41 (0.06,3.03)	0.38
	Past user or never used	25	98.9 (98.5,99.4)	98.9 (98.5,99.4)	1.0 (ref)	
Complication any infection	Current tobacco user	8	96.6 (94.3,99.0))	96.6 (94.3,99.0)	1.66 (0.78,3.49)	0.19
	Past user or never used	51	97.9 (97.3,98.5)	97.7 (97.1,98.4)	1.0 (ref)	
Complication wound complications	Current tobacco user	5	97.5 (95.3,99.8)	97.5 (95.3,99.8)	1.30 (0.51,3.28)	0.59
	Past user or never used	40	98.5 (98.0,99.0)	98.3 (97.7,98.8)	1.0 (ref)	
Complication peri-prosthetic fracture	Current tobacco user	8	97.5 (95.6,99.4)	97.5 (95.6,99.4)	0.78 (0.39,1.59)	0.50
	Past user or never	103	96.4 (95.7,97.1)	96.1 (95.4,96.9)	1.0 (ref)	

	used					

Disclosure: J. A. Singh, Takeda, Savient, 2,Takeda, Savient, merz, Regeneron, Allergan, Crealta, Bioiberica, 5;

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Abstract Number: 1426

The Effect of Anti-Interleukin-6 Receptor Antibody in Ovariectomized Mice

Sho Kato[1], Hiroki Wakabayashi[2], Taro Nakagawa[3], Yohei Naito[3], Takahiro Iino[4] and Akihiro Sudo[5], [1]Department of Orthopaedic Surgery, Mie University Graduate School of Medicine, Tsu City, Japan, [2]Orthopaedic Surgery, Mie University Graduate School of Medicine, Tsu City, Japan, [3]Department of Orthopaedic Surgery, Mie University Graduate School of Medicine, Tsu City, Mie, Japan, [4]Mie University Graduate School of Medicine, Mie University Graduate School of Medicine, Tsu City, Mie, Japan, [5]Orthopaedic surgery, Mie University Postgraduate School of Medicine, Tsu-city, Japan
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Session Time: 9:00AM-11:00AM

Background/Purpose: Osteoporotic patients with no evidence of fractures sometimes experience vague low back pain. Bone pain associated with bone metastasis may also be related to increased osteoclastic bone resorption suggesting that osteoporosis-related bone pain is caused by increased osteoclastic bone resorption. J.Mysliwiec et al suggested that Interleukin-6 (IL-6) plays a considerable role of in the pathogenesis of thyrotoxicosis-related disturbances of bone turnover in estrogen-deficient women. In prospective study, IL-6 receptor inhibitor (IL-6Ri) increased the BMD of RA patients who had osteopenia. In addition, anti-IL-6R antibody inhibits systemic bone loss in the collagen-induced arthritis model mice. In this study, we investigated the effect of anti-IL-6R antibody on pain-related behavior and bone morphometry in ovariectomized mice.

Methods: 8-week-old female ddY mice were ovariectomized (OVX) and assigned to 3groups; SHAM-operated mice treated with vehicle (SHAM), OVX mice treated with vehicle (OVX), OVX mice treated with anti-IL-6R antibody (IL-6Ri). Starting immediately after surgery, vehicle or 2mg anti-IL-6R antibody was injected subcutaneously once a week for 4 weeks. The bilateral proximal tibial metaphyses were analyzed three-dimensionally by μCT 4 weeks after surgery (each group; 8 mice). Mechanical sensitivity was tested using von Frey filaments 4 weeks after surgery. The frequency of the withdrawal response and the withdrawal threshold to the application of von Frey filaments to the planter surface of the hindpaws was examined. To evaluate the frequency of the withdrawal response, three von Frey filaments with forces of 0.4, 0.6 and 1.4 were applied 5 times each in ascending order of force, and the number and intensity of withdrawal responses were noted. **Results** were expressed as the percent response frequency of paw withdrawals. To evaluate the withdrawal threshold, each von Frey filament was applied once, starting with 0.008g and increasing until a withdrawal response was reached, which was considered a positive response. The lowest force producing a response was considered the withdrawal threshold.

Results:μCT analysis of the femoral distal metaphysis and the proximal tibial metaphysis showed that bone volume/tissue volume (BV/TV) and trabecular number (Tb.N) were significantly less in the OVX group than in the SHAM group, whereas trabecular separation (Tb.Sp) was significantly greater in the OVX group than in the SHAM group. IL-6Ri treatment was no effect on bone morphometry compared with OVX group. The withdrawal threshold was significantly lower in the OVX group than in the SHAM group, and was significantly improved in the IL-6Ri group than in the OVX group. The paw-withdrawal-frequency stimulated by von Frey filaments with strength of 0.4, 0.6 and 1.4 g was significantly higher in the OVX group than in the SHAM group, and von Frey filaments with strength of 1.4g was significantly higher in the OVX group than in the IL-6Ri group. Anti-IL-6R antibody improved mechanical hyperalgesia in hindlimbs.

Conclusion: In this study, anti-IL-6R antibody prevented mechanical hyperalgesia in hindlimbs in hindlims of OVX mice, but did not prevent ovariectomy-induced bone loss.

Disclosure: S. Kato, None; **H. Wakabayashi**, None; **T. Nakagawa**, None; **Y. Naito**, None; **T. Iino**, None; **A. Sudo**, None.

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Abstract Number: 1427

Analgesic Effects of the Novel Alpha-2-Delta Ligand Mirogabalin (DS-5565) in Experimental Animal Models of Fibromyalgia

Yuki Domon[1], Naohisa Arakawa[1], Shun-ichi Yasuda[2], Kensuke Saeki[2], Mayumi Kano[2], Masami Kato[2] and Yutaka Kitano[1], [1]Biological Research Laboratories, Daiichi Sankyo Co., Ltd., Tokyo, Japan, [2]Hashima Laboratory, Nihon Bioresearch Inc., Gifu, Japan
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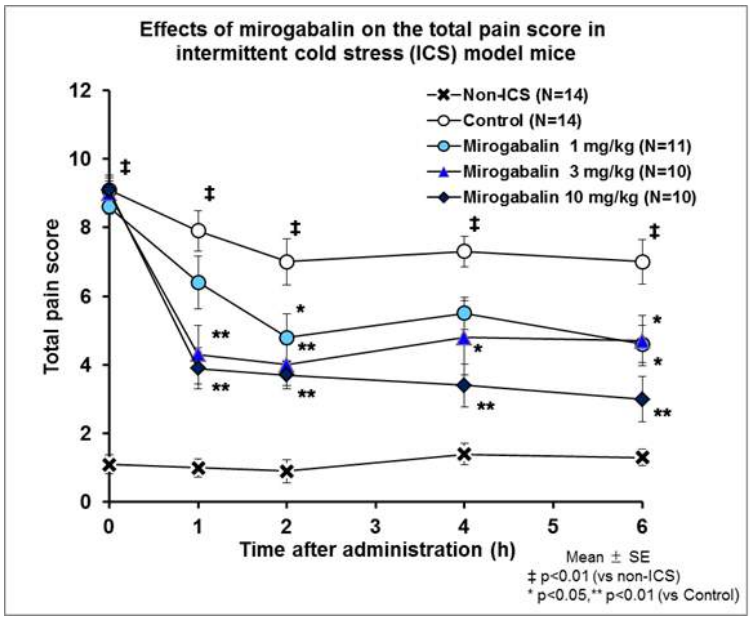
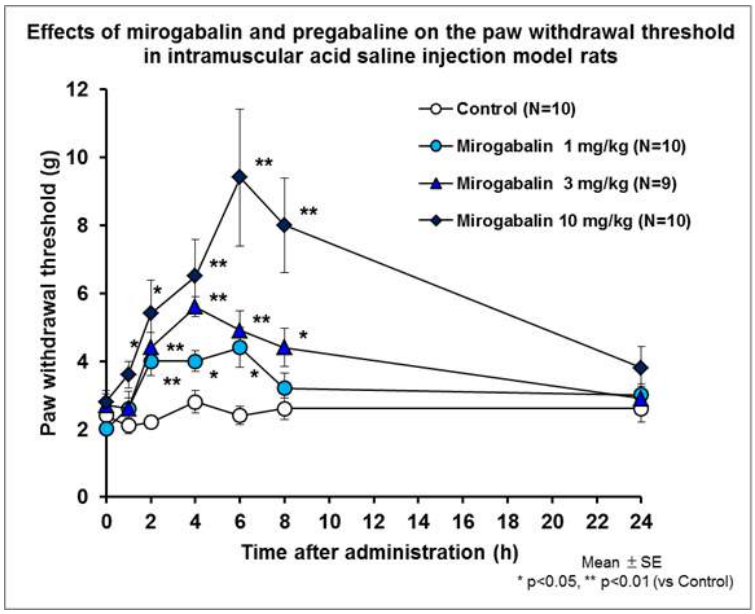
Background/Purpose: Mirogabalin (DS-5565) is a novel ligand of the $\alpha_2\delta$ subunit of voltage-gated calcium channels. Mirogabalin possesses unique binding characteristics to $\alpha_2\delta$ subunits, and potent and long-lasting analgesic effects in peripheral neuropathic pain models. Phase III clinical trials of mirogabalin in patients with postherpetic neuralgia, diabetic peripheral neuropathic pain and fibromyalgia are ongoing. In the present study, we investigated the analgesic effects of mirogabalin in two animal models of fibromyalgia, the intermittent cold stress model in mice and the intramuscular acid saline injection model in rats.

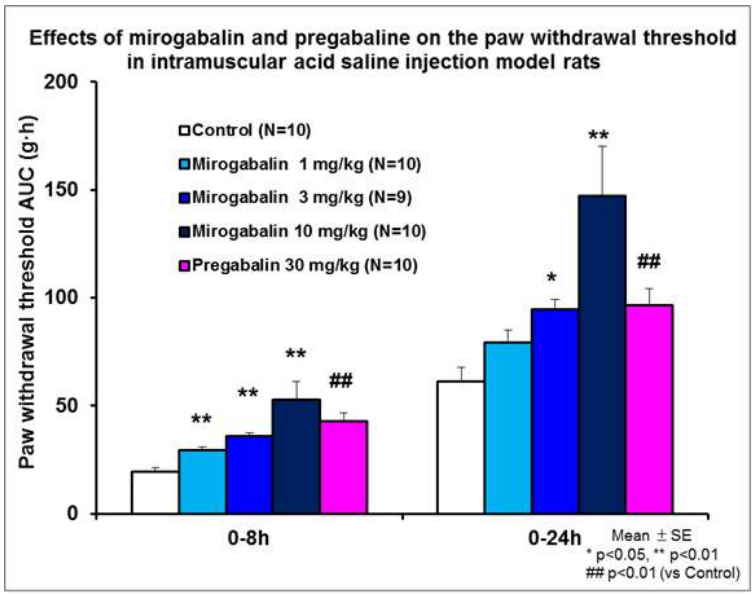
Methods: Female ddY mice were exposed to intermittent cold stress for three days, and male SD rats received two repeated intramuscular injections of acid saline (pH 4.0) into the gastrocnemius muscle. After development of hyperalgesia, the animals received the test compounds (mirogabalin and pregabalin) orally and the pain responses to mechanical stimulation were determined by von Frey test.

Results: In both models, mechanical hyperalgesia was demonstrated by increased pain scores or decreased pain thresholds to von Frey filaments. A single oral administration of mirogabalin (1, 3 and 10 mg/kg) significantly inhibited mechanical hyperalgesia in both models. The effects of mirogabalin were significant up to 6 or 8 hours after administration. Pregabalin, a standard $\alpha_2\delta$ ligand showed similar effects at 30 mg/kg.

Conclusion: Mirogabalin showed potent and long-lasting analgesic effects in two non-clinical models of fibromyalgia. Mirogabalin may provide effective pain relief for patients with fibromyalgia.







Disclosure: Y. Domon, None; **N. Arakawa**, None; **S. I. Yasuda**, None; **K. Saeki**, None; **M. Kano**, None; **M. Kato**, None; **Y. Kitano**, None.

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Abstract Number: 1428

Subchondral Bone Structure and Pain Behaviors in Complete Freund's Adjuvant (CFA) Monoarthritis in Mice Treated with Intra-Articular (IA) Neurotoxin

Hollis E. Krug[1,2], **Joseph Bert**[3], Fakhar Abbass[4], Christopher W. Dorman[5], Sandra Frizelle[5] and Maren L. Mahowald[1,2], [1]Medicine, Minneapolis VA Health Care System, Minneapolis, MN, [2]Medicine, University of Minnesota, Minneapolis, MN, [3]Internal Medicine, Division of Rheumatology, University of Minnesota, Minneapolis, MN, [4]Minneapolis VA Health Care System, Minneapolis, MN, [5]Research, Minneapolis VA Health Care System, Minneapolis, MN

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Background/Purpose:

Bone histomorphometry can define OA changes in rodents and in Antigen-Induced arthritis (AIA) in rats. We produced painful inflammatory monoarthritis in mouse knees with IA CFA. IA neurotoxins reduced pain behaviors in murine CFA arthritis. Ttreatment with anti-nerve growth factor in humans rarely produced rapid joint destruction requiring arthroplasty. We used micro CT of knees to correlate pain behaviors with histomorphometric bone changes and to determine whether IA neurotoxin treatment worsened changes.

Methods:

Chronic Inflammatory arthritis was produced by IA injection of 30 µl CFA into the left knee of C57BL6 male mice 3 weeks prior to pain behavior testing using evoked pain score (EPS) and automated dynamic weight bearing (ADWB) device. EPS was a tally of fights and vocalizations/min with knee palpation at 15.6 psi. Percent weight and time on each limb was measured with ADWB apparatus (Bioseb, Vitrolles, France). IA vanilloids resiniferatoxin (RTX) and capsaicin (CAP) (10µl each of 0.001%RTX, 0.003% RTX or 0.01% CAP) were given 7 days prior to pain testing. IA botulinum toxin A (10µl 0.02 IU) was injected 3 days before testing. Knees were imaged on a micro-CT scanner (micro-CT40; Scanco Medical AG, Bassersdorf, Switzerland). Subchondral trabecular bone volume fraction (BV/TV), trabecular thickness (Tb.Th in µm), trabecular spacing (Tb.S in µm), and number (Th.N in 1/mm) were calculated from coronal slices using 3D Calculator (Erasmus Medical Center, Rotterdam, Netherlands).

Results:

Arthritis pain behavior was low in naïve mice - EPS (0.5) and ADWB proportions for weight (40.9%) and time (97.4%) were normal. IA CFA arthritis significantly increased EPS (2.5) and decreased ADWB for weight (34.1) and time (92.3). Arthritic knees had significantly reduced BV/TV (42.4 vs 50.3%), Tb.Th (252 vs 352 µm), and increased Tb.S (183 vs 112 µm) compared to naive knees. There was a significant negative linear relationship between EPS and BV/TV (R^2= 0.626, $p<.05$) with higher EPS when BV/TV was lower. ADWB measures trended in the same direction but were not statistically significant. IA neurotoxin treatments did not decrease BV/TV or Tb.Th or increase Tb.S. High dose IA-RTX in CFA mice normalized Tb.Th but not Tb.S or BV/TV.

Conclusion:

We confirmed that IA CFA monoarthritis increased evoked and spontaneous pain behaviors. MicroCT measured significant changes in BV/TV proportion, Tb.Th and Tb.Sp in CFA inflammatory arthritis. These findings are consistent with bone histomorphometry in rats with AIA. IA neurotoxins treatments with BOT, RTX and CAP did not worsen these subchondral changes. Interestingly high dose IA-RTX actually normalized Tb.Th. The negative relationship between BV/TV proportion and pain behaviors (ie increased pain with lowest BV/TV) suggests that more severe arthritic subchondral structural changes may be associated with increased pain behaviors.

Disclosure: H. E. Krug, None; **J. Bert**, None; **F. Abbass**, None; **C. W. Dorman**, None; **S. Frizelle**, None; **M. L. Mahowald**, None.

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Abstract Number: 1429

The Effect of Gabapentin and Cyclooxygenase Inhibitors on Evoked and Ongoing Pain-like Behavior in Two Arthritis Models in Mice

Katalin Sandor[1], HueJung Park[2], Johanna McQueen[3], Sarah Woller[3], Maripat Corr[4], Camilla Svensson[1] and Tony Yaksh[3], [1]Department of Physiology and Pharmacology, Karolinska Institutet, Stockholm, Sweden, [2]College of Medicine, Department of Anesthesiology and Pain Medicine, The Catholic University of Korea, Seoul, South Korea, [3]Anesthesiology, UCSD, La Jolla, CA, [4]Division of Rheumatology, Allergy, and Immunology, UCSD, La Jolla, CA
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Background/Purpose:

Induction of K/BxN serum transfer arthritis and collagen antibody-induced arthritis (CAIA) leads to transient joint inflammation but persistent mechanical hypersensitivity lasting at least 2 weeks after the inflammation has resolved (late phase). While mechanical hypersensitivity during the inflammatory phase is reversed by analgesics such as ketorolac/diclofenac (cyclooxygenase inhibitors) and gabapentin (calcium channel blocker), only gabapentin has effect in the late phase. Assessment of mechanical hypersensitivity is based on a stimulus-evoked response. Non-evoked or "ongoing pain" is another aspect of pain in RA that is more difficult to monitor in animal models. A current question is if changes in spontaneous behavior can be used as a measure of ongoing pain-like behavior. The aim of this study was to examine if K/BxN and CAIA which induce mechanical hypersensitivity also induce changes in locomotor activity and condition place preference (CPP) and if those are similarly sensitive to treatment with cyclooxygenase inhibitors and/or gabapentin.

Methods:

K/BxN arthritis was induced in C57BL/6 mice by i.p. injection of 100 µl K/BxN serum and CAIA in BALB/c and B10.RIII mice by i.v. injection of 4 mg collagen type II antibody cocktail. Joint inflammation was assessed by visual scoring and mechanical hypersensitivity by von Frey filaments. Locomotor activity was recorded overnight using a Comprehensive Lab Animal Monitoring System. CPP was assessed by monitoring the number of crossings between distinctly different chambers (wall pattern and floor texture). CPP paradigm: 2 days adaptation with free access to all chambers, 2 days conditioning with restriction to one chamber (vehicle in morning and drug in afternoon), preference testing on day 5 with free access to all chambers. Effects of gabapentin (50 or 100 mg/kg) and cyclooxygenase inhibitors (ketorolac: 15 mg/kg; diclofenac: 30 mg/kg; naproxen 30 mg/kg) were assessed.

Results:

Gabapentin reversed mechanical hypersensitivity during both phases of the K/BxN and CAIA models. Ketorolac and diclofenac only attenuated mechanical hypersensitivity during ongoing inflammation in the K/BxN and the CAIA model, respectively, and had no effect in the late phase in both models. Ketorolac did not reduce CAIA-induced mechanical hypersensitivity. Locomotor activity was reduced in the early phase in the CAIA model (not assessed in the K/BxN model), which was normalized by naproxen, but not by gabapentin. Diclofenac reduced locomotion in naïve mice. A significant preference for both the gabapentin and ketorolac-paired compartment was observed in the early phase of the K/BxN model, while in the late phase only gabapentin treatment resulted in CPP. In the CAIA model, gabapentin produced a preference in the early phase and a trend in the late phase, whereas ketorolac was ineffective in both phases.

Conclusion:

We found that the K/BxN and the CAIA models induce changes in spontaneous behavior. Locomotor activity was affected by sedative side effects of the drugs. While somewhat different responses to cyclooxygenase inhibitors were noted in the two arthritis models, there was correspondence between the anti-hyperpathic pharmacology as defined by thresholds and CPP.

Disclosure: K. Sandor, None; **H. Park**, None; **J. McQueen**, None; **S. Woller**, None; **M. Corr**, None; **C. Svensson**, None; **T. Yaksh**, None.

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Abstract Number: 1430

Peripheral HMGB1 Regulates Arthrtis-Associated Pain-like Behaviour

Nilesh Agalave[1], Teresa Fernandez Zafra[2], Peter Lundback[3], Ulf Andersson[4], Helena E. Harris[3] and Camilla Svensson[5], [1]Physiology and Pharmacology, Karolinska Institutet, Stockholm, Sweden, [2]Physiology and pharmacology, Karolinska Institutet, Stockholm, Sweden, [3]Center for Molecular Medicine, Karolinska Institutet, Stockholm, Sweden, [4]Center for Molecular medicine, Karolinska Institutet, Stockholm, Sweden, [5]Department of Physiology and Pharmacology, Karolinska Institutet, Stockholm, Sweden

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Background/Purpose: HMGB1 has received attention for its emerging roles in the extracellular environment acting as damage associated molecular pattern molecule. The redox state of HMGB1 is key in determining which receptors HMGB1 activates and partially reduced HMGB1 (disulfide HMGB1) functions as a cytokine-inducing TLR4 ligand. Accumulating data indicate that HMGB1 plays important roles in the pathogenesis of inflammatory and autoimmune diseases. Blocking the action of HMGB1 with neutralizing antibodies ameliorates experimental arthritis in both mice and rats. Peripheral HMGB1 has also been linked to induction of pain-like behavior in experimental models of neuropathic and low back pain. However, the role of peripheral HMGB1 in pain hypersensitivity subsequent to development of arthritis has not been investigated. Thus the aim of the current study was to investigate if peripheral HMGB1 regulate arthritis-induced pain-like behavior.

Methods: BALB/c and C57BL/6 male and female mice (12-18 weeks) were used for this study. Collagen antibody-induced arthritis (CAIA) was induced by i.v. injection of anti-collagen antibody cocktail (1.5 mg/mice) followed by i.p. injection of LPS (25 ug). Disulfide HMGB1 (1 µg) was injected intraarticularly to the ankle joint. Mechanical hypersensitivity was assessed by von Frey filaments and the degree of joint inflammation by visual inspection and joint histology (H&E). The HMGB1 neutralizing antibody 2G7 (4 mg/kg) and the recombinant Abox protein (12 mg/kg) (blocks extracellular HMGB1 activities, although the exact mechanisms of action are unknown) were injected once/day for 6 consecutive days in both the inflammatory and late phase. Primary neuronal cultures were prepared from dorsal root ganglia and calcium flux subsequent to HMGB1 stimulation (100 nM) examined by calcium imaging. KCl (50 mM) was used as positive control to detect functional neurons.

Results: While CAIA mice developed transient joint inflammation with visual and histological arthritis scores, induction of mechanical hypersensitivity, which coincided with the inflammatory phase, did not resolve and remained pronounced throughout the study ("late phase" from day 38 to 51). Repeated systemic injection of 2G7 and Abox reversed CAIA-induced mechanical hypersensitivity in the inflammatory phase while in the late phase, Abox, but not 2G7, partially reversed the pain-like behavior. Intraarticular injection of dsHMGB1 in naïve mice induced mechanical hypersensitivity for at least 6h in both male and female mice. Stimulation of primary DRG neurons with dsHMGB1 did not evoke calcium flux in KCl responding neurons.

Conclusion:

Our findings suggest that extracellular HMGB1 is an important factor in arthritis-induced pain during ongoing inflammation, but that it has a less pronounced role in mechanisms that maintain nociception subsequent to a period of joint inflammation. The TLR4 activating redox form of HMGB1 has nociceptive properties in the joint in naïve conditions, most likely via actions on immune cells as dsHMGB1 does not directly activate DRG neurons. Future studies are warranted to define the mechanisms by which peripheral HMGB1 contribute to arthritis-induced pain.

Disclosure: N. Agalave, None; **T. Fernandez Zafra**, None; **P. Lundback**, None; **U. Andersson**, None; **H. E. Harris**, None; **C. Svensson**, None.

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Abstract Number: 1431

Age and Sex Impacts the Development of Hypersensitivity in the Murine Partial Medial Menisectomy Model of Osteoarthritis

Ada Delaney[1], Azar Barharpoor[1], Tianle Gao[1], Jie Su[1], NIlesh Agalave[1] and Camilla Svensson[2], [1]Dept. of Physiology & Pharmacology, Karolinska Institutet, Stockholm, Sweden, [2]Department of Physiology and Pharmacology, Karolinska Institutet, Stockholm, Sweden
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Background/Purpose:

Osteoarthritis (OA) is the leading cause of chronic pain in European adults (37%; painineurope.com). Pain is the foremost symptom of OA, with both episodes and severity becoming more constant or frequent with progression of the disease. Current therapies to reduce pain are often ineffective and have use limiting side effects. Thus the development of efficacious analgesics is crucial to improve the lives of individuals with OA, to this end the use of animal models is required to understand the underlying mechanisms of OA-induced chronic

pain. We aimed to further characterize the partial medial menisectomy model of OA, by assessing the development of hypersensitivity to mechanical stimulus, the impact on burrowing behaviour, and the response to Gabapentin a known analgesic used in the treatment of neuropathic pain, in both young and aged adult male and female mice.

Methods:

C57/Black6J male and female mice approx. 3-4 or 16-18 months of age at the time of surgery were randomized into partial medial menisectomy or sham surgery groups, all groups received post-operative analgesia of buprenorphine. Hypersensitivity to mechanical stimulus was assessed using von Frey filaments applied to the hindpaw, to determine secondary mechanical allodynia. Burrowing behaviour was used as an outcome measure of general wellbeing and is thought to reflect ongoing pain. All behaviour was monitored before and up to 16-30 weeks post-surgery. Mechanical allodynia was assessed following administration of Gabapentin (50mg/kg; i.p.). Osteoarthritic pathology of the knee joints were analyzed by hematoxylin and eosin and/or Safranin-O staining.

Results:

In both aged (14 weeks post-surgery) and young (27 weeks post-surgery) female groups significant development of mechanical hypersensitivity and signs of osteoarthritic pathology (cartilage loss) were observed. Mechanical hypersensitivity was not observed in young adult male mice and less pronounced in aged male compared to aged female mice. Mechanical hypersensitivity in female mice was significantly reversed by Gabapentin. No significant deficit in burrowing behaviour was noted between the groups.

Conclusion:

The partial medial menisectomy model is a slowly developing model of OA-induced mechanical hypersensitivity in adult female mice (with earlier onset in aged mice), which is reversible by Gabapentin. No deficit in burrowing suggests this model does not have a negative impact on the overall wellbeing or lead to ongoing pain for the mice. This model reflects the clinical condition and could aid the translation of preclinical findings into clinical outcomes.

Disclosure: A. Delaney, None; **A. Barharpoor**, None; **T. Gao**, None; **J. Su**, None; **N. Agalave**, None; **C. Svensson**, None.

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Abstract Number: 1432

Relationship Between Patient Reported Outcome Measures and Evoked Pain Measures in Knee Osteoarthritis

J. Ryan Scott[1], Steven E. Harte[1], David A. Williams[2,3], Daniel J. Clauw[4] and **Kristine Phillips**[5], [1]Department of Anesthesiology, University of Michigan, Ann Arbor, MI, [2]Chronic Pain & Fatigue Rsch Ctr, Univ of MI Hlth System-Lobby M, Ann Arbor, MI, [3]Anesthseiology, University of Michigan, Ann Arbor, MI, [4]Anesthesiology, University of Michigan, Ann Arbor, MI, [5]Internal Medicine, University of Michigan, Ann Arbor, MI

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Background/Purpose: Quantitative sensory testing (QST) can be used to assess pain processing mechanisms, and theoretically identify a subset of chronic pain patients that has central sensitization or centralized pain. However, measures of "evoked pain" from experimental stimuli obtained via QST typically are only marginally related to clinical pain reports. This study looked the relationship between manual algometry pressure-pain thresholds (PPT) at multiple sites and clinical pain measures in knee osteoarthritis (KOA) patients.

Methods: Fifty-four subjects meeting ACR criteria for osteoarthritis of the knee (mean age: 62.04 years; range: 37 – 83 years; 24 male, 34 female) presented for QST and a clinical pain battery including WOMAC, PainDETECT, Michigan Body Map (MBM), and Brief Pain Inventory (BPI). PPT was measured three times (Wagner FDX 25: 0.5 kg/s ramp rate, 20 inter-stimulus interval) bilaterally at four body sites: lateral patella (knee), tibialis anterior, trapezius and wrist. Associations between PPTs and clinical pain were assessed by Pearson's product-moment correlations (r) and partial correlations controlling for gender were assessed for significance using SPSS 22.

Results: WOMAC was significantly correlated to left and right knee PPT, r = -0.37 and -0.52 ($p < 0.05$), respectively. WOMAC pain, stiffness and functional limitation subscales were all significantly correlated to right knee PPT, r = -0.32, -0.39 and -0.52 (all $p < 0.05$), respectively; however, only functional limitation was significantly correlated to left knee PPT, r = -0.38, $p < 0.05$. PainDETECT was significantly correlated to all sites (knee, trapezius, tibialis anterior and wrist) and correlation coefficients for left and right side were r = -0.52, -0.51, -0.45, -0.34 and -0.59, -0.59. -0.50, -0.37 (all $p <0.05$), respectively. MBM, a measure of clinical pain distribution, correlated with both knee PPT (r = -0.33, $p < 0.05$) and trapezius PPT (r = -0.43, $p < 0.01$) on the right side; however, the left side was not significantly correlated. BPI severity and interference were not correlated to PPT at any body site (all $p > 0.31$). All correlations remained significant when controlling for gender.

Conclusion: These data suggest that the MBM and painDETECT assess pain quality associated with augmented central pain processing in patients with symptomatic knee OA. These results provide a foundation for future assessment of correlations between evoked and clinical pain measures. Additional studies are needed to determine the specific sites best suited for assessment of OA pain.

Table 1. Pearson correlation coefficients between PPT site and clinical pain measures

	Knee		Trapezius		Tibialis Anterior		Wrist	
	Left	Right	Left	Right	Left	Right	Left	Right
WOMAC	-0.37*	-0.50**	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
Pain	n.s.	-0.32*	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
Stiffness	n.s.	-0.39**	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
Functional Limitation	-0.38*	-0.52**	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
MBM	n.s.	-0.33*	n.s.	-0.43**	n.s.	n.s.	n.s.	n.s.
PainDETECT	-0.52**	-0.59**	-0.51**	-0.59**	-0.45**	-0.50**	-0.34*	-0.37*
BPI Severity	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
BPI Interference	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.

*Significance at $p <.05$ **Significance at $p <.01$

n.s. - not significant

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Abstract Number: 1433

Predicting Response to Osteoarthritis Treatment Based on Patient Reported Outcome Measures and Quantitative Sensory Testing

Kristine Phillips[1], David A. Williams[2], Arnold Gammaitoni[3], J. Ryan Scott[4], Steven E. Harte[4], Susan L. Murphy[5] and Daniel J. Clauw[6], [1]Internal Medicine, University of Michigan, Ann Arbor, MI, [2]Anesthseiology, University of Michigan, Ann Arbor, MI, [3]Zogenix, Inc, San Diego, CA, [4]Department of Anesthesiology, University of Michigan, Ann Arbor, MI, [5]Phyiscal Medicine & Rehabilitation, University of Michigan, Ann Arbor, MI, [6]Anesthesiology, University of Michigan, Ann Arbor, MI

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Background/Purpose:

Recent studies have suggested that a subset of individuals with arthritis have a component of sensitization to their pain. This subset of patients with centralized pain can theoretically be identified via self -report measures, quantitative sensory testing, or a combination of the two. This study examined whether phenotyping patients by self-report or QST measures of pain centralization predicted a differential response amongst OA patients to a centrally-acting (duloxetine) vs. peripherally-acting (topical diclofenac) analgesic, or both together.

Methods:

Fifty-two subjects meeting ACR criteria for osteoarthritis of the knee were enrolled in a double-blind crossover trial where each was treated with 20 mg of duloxetine or four times daily 1.5% topical diclofenac solution. Assessments included WOMAC, PainDETECT, Pain Quality Assessment Scale (PQAS), PROMIS physical function Short Form, Pressure Pain Threshold, and Conditioned Pain Modulation. Subjects were treated for eight weeks in a counter-balanced fashion, followed by a four-week washout period, and then another eight weeks of treatment. A subset of individuals entered a third treatment period of combined duloxetine and diclofenac. The primary endpoint was a change in the WOMAC pain subscale at eight weeks.

Results:

Treatment with duloxetine resulted in a significant decrease in WOMAC pain subscale whereas there was no significant improvement in the group means in the 1.5% diclofenac treatment period. Patient reported outcome measures predicted response to duloxetine, including total scores on PainDETECT and PQAS Intensity subscale. QST assessment for baseline pressure pain threshold predicted the response to duloxetine based on change in WOMAC pain subscale, but there was no association between QST measures of conditioned pain modulation and response to duloxetine. An increase in the PainDETECT score was associated with an increase in pain as measured by the WOMAC pain subscale by an average of 0.22 per unit increase in pain DETECT score (SE 0.059, p=0.0005). There were no differences in adverse events or rescue medication usage between the arms.

Conclusion:

PainDETECT, PQAS, and Pressure Pain Threshold predict response to duloxetine. Pain control in this cohort was most favorable for duloxetine alone or in combination with topical diclofenac.

Disclosure: K. Phillips, None; **D. A. Williams**, Health Focus Inc., 5; **A. Gammaitoni**, None; **J. R. Scott**, None; **S. E. Harte**, MAST Device, 4,Cerephex, 5,Analgesic Solutions, 5,Merck, 5,Regeneron, 5,deCode Genetics, 5; **S. L. Murphy**, None; **D. J. Clauw**, Abbott Laboratories, 5,Cerephex, 5,Eli Lilly and Company, 5,Forrest Laboratories, 5,Johnson & Johnson, 5,Merck Pharmaceuticals, 5,Pfizer Inc, 5,Purdue Pharma L.P., 5,Samumed, 5,Theravance, 5,Tonix, 5,UCB, 5,Zynerba, 5,Abbott Laboratories, 5,Cerephex, 5,Eli Lilly and Company, 5,Forest Laboratories, 5,Johnson & Johnson, 5,Merck Pharmaceuticals, 5,Pfizer Inc, 6,Purdue Pharma L.P., 6,Samumed, 5,Theravance, 5,Tonix, 5,UCB, 5,Zynerba, 5.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/predicting-response-to-osteoarthritis-treatment-based-on-patient-reported-outcome-measures-and-quantitative-sensory-testing

Abstract Number: 1434

Neuropathic Pain in Patients with Rheumatoid Arthritis: Relation with Clinical Variables

Ferda Kaygisiz[1], Pinar Borman[2] and Aynur Karagoz[3], [1]Dept of Physical Medicine and Rehabilitation, Ankara Training and Research Hospital, Ankara, Turkey, [2]Department of Physical Medicine and Rehabilitation, University of Hacettepe Faculty of Medicine, Ankara, Turkey, [3]Dept of Physical Medicine and Rehabilitation, Ministry of Health, Ankara Training and Research Hospital, Ankara, Turkey
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SESSION INFORMATION
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Background/Purpose:

There are few studies in the literature indicating that neuropathic pain occurs in rheumatoid arthritis (RA). The aim of this cross sectional

study was to evaluate frequency of neuropathic hand pain in RA patients and to determine the relation with clinical variables and occurrence of neuropathic pain.

Methods:

A hundred-nineteen RA patients, who were not having any comorbid disease and/or using drugs that would cause neuropathy, were recruited to the study. Demographic properties (age, sex, disease duration) and clinical characteristics (pain by VAS, functional status, disease activity and quality of life (QoL) assessed by HAQ, DAS28 and RAQoL respectively) were recorded. The neuropathic property of hand pain was assessed by both Leeds assessment of neuropathic symptoms and signs pain scale (LANSS), Douleur Neuropathique4 (DN4) and Pain-DETECT scales. Descriptive statistics was used for clinical variables and frequency of neuropathic pain. The difference of clinical variables between patients with and without neuropathic pain, were examined using t tests and chi square tests for continuous and categorical variables respectively. Correlation coefficients of clinical variables and neuropathic pain scores were analyzed with Spearman correlation analyses. The significance threshold was set as p values less than 0.05.

Results:

61 female, 58 male RA patients with a mean age of 50.51± 12.45 years, were included to the study. Neuropathic pain was detected in 76 (%63.9), 70 (%58.8), 61(%51.3) RA patients depending on the LANSS(scores>12), DN4(scores>4) and painDETECT(scores>12) questionnaires respectively. The mean levels of VAS-pain, HAQ and RAQoL scores were significantly higher in patients having neuropathic pain than in patients not having ($p<0.05$) (Table 1,2). The scores of the neuropathic pain scales were correlated with each other but not with the scores of disease activity.

Conclusion:

Neuropathic hand pain is determined in more than half of the patients with RA and related with pain intensity, functional status and QoL. Diagnosis and treatment of neuropathic pain are warranted in order to improve pain, disability and quality of life in RA patients.

Table-1. The clinical properties of patients having and lacking neuropathic pain, determined by LANSS.

	Neuropathic pain (+) **n=76**	**Neuropathic pain (-)** **n=43**	**p**
VAS	5.93±2.23	4.44±2.54	**0.001**
DAS28-ESH	3.10±0.91	2.96±0.84	0.424
RAQoL	16.46±7.65	11.28±6.82	**0.001**
HAQ	1.38±0.74	0.91±0.73	**0.001**

Table-2. The clinical properties of patients having and lacking neuropathic pain, determined by DN4

	Neuropathic pain (+) **n=70**	**Neuropathic pain (-)** **n=49**	**p**
VAS	5.77±2.47	4.85±2.33	**0.049**
DAS28-ESH	2.99±0.91	3.13±1.08	0.428
RAQoL	16.80±7.47	11.43±7.07	**<0.001**
HAQ	0.96±0.73	0.96±0.73	**0.002**

Disclosure: F. Kaygisiz, None; **P. Borman**, None; **A. Karagoz**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/neuropathic-pain-in-patients-with-rheumatoid-arthritis-relation-with-clinical-variables

Abstract Number: 1435

Central Pain Sensitization in Rheumatoid Arthritis – Role of ACPA?

Katarzyna Rogoz[1], **Teresa Fernandez Zafra**[1], Catia Cerqueira[2], Per Johan Jakobsson[3], Katalin Sandor[4], Erwan Le Maître[5], Magnus LA. Andersson[6], K. Lundberg[7], Camilla Svensson[4] and Jon Lampa[8], [1]Physiology and pharmacology, Karolinska Institutet, Stockholm, Sweden, [2]Rheumatology Unit, Department of Medicine, Karolinska Institutet, Stockholm, Sweden, [3]Department of Medicine, Unit of Rheumatology, Karolinska Institutet, Karolinska University Hospital, Stockholm, Sweden, [4]Department of Physiology and Pharmacology, Karolinska

Institutet, Stockholm, Sweden, [5]Department of Medicine, Karolinska Institutet, Stockholm, Sweden, [6]Dep of Neurology, Karolinska Institute, Stockholm, Sweden, [7]Karolinska Institute, Stockholm, Sweden, [8]Dep of Medicine, Rheumatology unit, Karolinska Institute, Karolinska Institute, Stockholm, Sweden
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Background/Purpose: Chronic pain continues to be a significant problem for patients with rheumatoid arthritis (RA), even when the disease is medically controlled or in remission. RA patients often develop a generalized increase in pain sensitivity at remote sites from the inflamed joint, suggesting that central sensitization may play an important role. We have previously shown that joint inflammation is associated with an upregulation of inflammatory mediators in the central nervous system (CNS) of humans and mice. Here we sought to investigate if anti-citrullinated protein antibodies (ACPA) can be detected in the cerebrospinal fluid (CSF) of RA patients and if ACPA can be linked to central pain sensitization.

Methods: Clinical study: CSF (via lumbar puncture) and serum was collected from 13 female RA patients with anti-CCP positive (+) ($ACPA^+$) antibodies. CSF from age-matched i) individuals with no neuroinflammatory or rheumatic disease (n=10) and ii) multiple sclerosis (MS) patients (n=26) was used as controls. ACPA IgGs were measured using a commercial anti-CCP2 ELISA according to the manufacturer's protocol (serum diluted 1:100, CSF undiluted).Experimental study: Purification of IgG from plasma and sera from 36 separate $ACPA^+$ patients was done by HiTrap Protein G columns and ACPA IgG was further purified using CCP2 affinity columns. IgG not binding to the CPP2-column was used as control and denoted flow through (FT). Balb/c/AnNRJ female mice (>12 weeks old) were used and ACPA or FT (100-300) µg was injected intrathecally into CSF by lumbar puncture. Mechanical hypersensitivity was assessed using von Frey filaments and cold sensitivity by the acetone test. Tissues were collected at day 20 for western blot analysis.

Results: Clinical study: 7/13 serum $ACPA^+$ RA patients had ACPA also in CSF (29-154 U/ml). ACPA levels in controls were significantly lower; non-inflammatory controls: 2.19 +/- 0.09U/ml, and MS patients: 2.54 +/- 0.16U/ml. In RA patients, there was a strong correlation between the presence of ACPA in CSF and significantly higher serum ACPA levels (1453 +/- 82U/ml in RA ACPA pos serum and CSF vs 90 +/- 46U/ml; ACPA neg CSF, $p<0.01$). Experimental study: Intrathecal injection of ACPA, but not FT, led to a reduction in mechanical thresholds from day 10 to day 18. In addition, 100 µg and 300 µg ACPA, but not FT, induced cold hypersensitivity at day 11. Western blot analysis showed a time dependent elimination of ACPA. Human IgG was not detectable in spinal cords or joints of ACPA injected mice 20 days post injection.

Conclusion: Our data show that ACPA can be detected in CSF of RA patients with high ACPA serum titers. We did not find indications of intrathecal ACPA production. In mice, intrathecal injection of ACPA induced pain-like behavior, indicating changes in spinal/brain facilitation of nociceptive signaling. Interestingly, the delayed onset of pain responses, and the long lasting effect being present despite clearance of antibodies, suggest antibody-induced secondary events at the spinal cord/brain level or redistribution of ACPA to peripheral sites. Altogether, these results give support to the hypothesis that ACPA may enter the CNS and possibly affect central pain mechanisms in RA.

Disclosure: K. Rogoz, None; **T. Fernandez Zafra**, None; **C. Cerqueira**, None; **P. J. Jakobsson**, None; **K. Sandor**, None; **E. Le Maître**, None; **M. L. Andersson**, None; **K. Lundberg**, None; **C. Svensson**, None; **J. Lampa**, None.

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Abstract Number: 1436

Characterization of Patient Reported Pain Medication in Early Vs. Established Rheumatoid Arthritis

Apoorva Kelkar, Angela Cesta, Xiuying Li and **Claire Bombardier**, Toronto General Hospital Research Institute, University Health Network, Toronto, ON, Canada
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Background/Purpose: Pain control in rheumatic diseases is complex and various pharmacotherapy approaches can be utilized for management of rheumatic pain. Currently, systematic clinical practice guidelines for pain management in Rheumatoid Arthritis (RA) are lacking; however, there are several evidence-based expert recommendations provided by a broad panel of rheumatologists from the 3e initiative[1]. Based on these recommendations, the aim of this study was to describe patient-reported pharmacotherapy regimens involved in the management of rheumatic pain in early vs. established RA.

Methods: Patient-reported medication data was collected from the Ontario Best Practices Research Initiative (OBRI), a clinical cohort of RA patients followed in routine care. As recommended by the 3e initiative, patients receiving NSAIDs, acetaminophen (APAP), opioids, antidepressants (AD) and neuromodulators (NM) at cohort-entry or while in the OBRI were selected (n = 1,470) and followed till a change in pain therapy was reported. Based on disease duration, patients were categorized into early RA (disease duration ≤1 year) or established RA (disease duration >1 year). For each group, patient demographics, common pharmacotherapy regimens and the number of patients receiving each regimen were determined.

Results: From the selected cohort, 384 patients met the criteria for early RA and 1,054 patients for established RA. 32 patients did not indicate their disease duration and were excluded. In early RA, the mean age ± SD of patients was 56.4±14.2 years, 73.2% were female and mean disease duration ± SD was 0.42±0.49 years. In established RA, the mean age ± SD of patients was 57.4±12.0 years, 80.0% were female and mean disease duration ± SD was 11.9±9.41 years. The most common pharmacotherapy regimens and % patients receiving each regimen are shown in figure 1.

Conclusion: Our study showed that NSAID use as monotherapy or in combination with other agents was highly prevalent across both groups. Patients with established disease were more likely to use a combination of NSAIDs + APAP and NSAIDs + opioids + APAP possibly due to worsening pain with disease progression. The use of NSAIDs + opioids was higher in early RA. Physicians may feel more comfortable prescribing opioids in early RA due to the advent of Ontario's Narcotic Monitoring System as well as better patient education and follow-up with dedicated pain clinics. Further work is required to determine the association between pain therapy regimens and disease activity measures in early vs. established RA.

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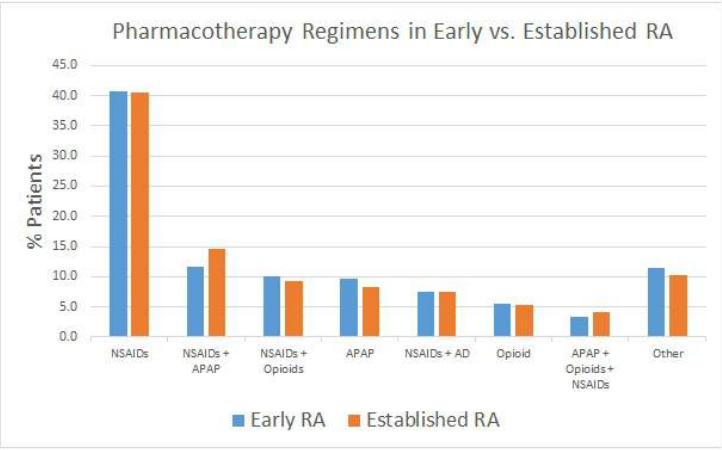

Figure 1 - Comparison of the most common patient-reported pain therapy regimens in early vs. established RA

Disclosure: A. Kelkar, None; **A. Cesta**, None; **X. Li**, None; **C. Bombardier**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/characterization-of-patient-reported-pain-medication-in-early-vs-established-rheumatoid-arthritis

Abstract Number: 1437

Prevalence of Pain, Its Impact and Management in a Population-Based Cohort of Patients with Rheumatoid Arthritis: Data from the Australian Rheumatology Association Database

Bethan Richards[1,2], Rachelle Buchbinder[3], Marissa N. Lassere[4] and Lyn March[5], [1]Sydney Medical School, University of Sydney, Sydney, Australia, [2]Royal Prince Alfred Hospital, Mulgrave, Vic, Australia, [3]Monash Department of Clinical Epidemiology, Cabrini Institute and Monash University, Melbourne, Australia, [4]Dept of Rheumatology, St George Hospital, Kogarah, Australia, [5]Department of Rheumatology, Northern Clinical School, Institute of Bone and Joint Research, Kolling Institute, University of Sydney & Department of Rheumatology, Royal North Shore Hospital, St Leonards, Sydney, Australia

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Background/Purpose: Despite advances in the treatments available for rheumatoid arthritis (RA), many patients continue to experience musculoskeletal pain. Untreated and under-treated pain are well known to increase disability and negatively impact overall well-being. Recently, multinational evidence based guidelines have been published in an attempt to improve overall pain management in these patients. To date, no studies have evaluated the prevalence and magnitude or impact of pain on Australian patients with RA. The pattern and type of analgesics used is also not known. The purpose of this study was to determine the prevalence and severity of pain and its impact on functional capacity and quality of life in Australian patients with RA and to describe current analgesic use.

Methods: We performed a descriptive analysis from the Australian Rheumatology Association Database (ARAD). ARAD is a voluntary registry that collects longitudinal health outcome data from Australian patients with inflammatory arthritis (RA, psoriatic arthritis, ankylosing spondylitis and juvenile idiopathic arthritis). The latest data entry point between 1st Januray 2014 and 31st December 2014 for all adult patients (≥18 years) with RA was used. Patient demographics, pain scores (VAS 0-100mm), medication use, responses to the HAQ, Assessment of Quality of Life (AQOL), and European Quality of Life-5 Dimensions (EQ-5D) were extracted and analysed. For the prevalence calculation pain was defined as being present if >4mm (0-100mm VAS).

Results: In 2014, 1548 patients with RA (76% female, mean age 60 years (range 21 to 90, mean disease duration 19 years) completed an ARAD questionnaire. 85% were receiving biological therapy. Mean HAQ was 0.94 (SD 0.75), EQ-5D 0.65 (0.24), AQOL 0.56 (SD 0.24). Overall 95% of patients reported pain (>4mm) in the preceding week (mean 41.1mm, SD 25.7) with 37% having mild pain (5-34mm), 39% moderate pain (35-69mm) and 19% severe pain (70-100mm) . Females reported higher mean pain (42.3mm versus 37.2mm, p =0.001), as did those using biological agents (41.7mm versus 36.4mm, p=0.02) or receiving the disability pension (53mm versus 39mm, p<0.0001). Seventy-three percent of patients reported taking an analgesic medication, most commonly paracetamol (60%), NSAID (37%), opioid (26%), and/or an antidepressant/neuromodulator (1%). A single analgesic medication was used by 49%, with 37% taking two and 14% consuming three or more. Higher pain scores were associated with use of a higher number of analgesic medications (F (3,1542) = 79.2, p<0.0001), poorer quality of life (lower EQ-5D (ß=-0.01, p<0.0001), lower AQOL (ß=-0.01, p<0.0001)) and poorer function (higher HAQ (ß=0.02, p>0.0001)).

Conclusion: Despite use of multiple analgesic medications, the prevalence of moderate to severe pain is high in patients with RA and is associated with lower levels of function and quality of life.

Disclosure: B. Richards, None; **R. Buchbinder**, None; **M. N. Lassere**, None; **L. March**, None.

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Abstract Number: 1438

Oral Potassium (K+) Reduces Pain in RA: A Randomized Active Control Study of Diet Based K+ Intervention

Toktam Kainifard[1], Manjit Saluja[2], Anuradha Venugopalan[3], Raju Rane[4] and Arvind Chopra[5], [1]Rheumatology, PhD fellow, Pune, India, [2]Clinical care, Center for Rheumatic Diseases, Pune, India, [3]Rheumatology, R & D, Lab, Center for Rheumatic Diseases, Pune, India,

[4]Pathology, Pathologist, Pune, India, [5]Rheumatology, Centre for Rheumatic Diseases, Pune 411001, India
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Background/Purpose:

National Health and Nutrition Survey III (1988-94,USA) data showed a low K+ body status in RA. Further information is scanty. K+ is critical to 'pain' [nociceptive processing, K+ ion channel downregulation (Tsantoulas. Trends Neurosci 2014; 37:146) and related process e.g. oxidant tissue damage and T lymphocytes function [K2P5.1 (Bitner. Arthritis Res Therapy 2011;13:R 21), Kv1.3 & KCa3.1 channels (Lam. Drug Dev Res 2011; 72: 573] and cortisol secretion. Using Indian standards (National Institute of Nutrition, Hyderabad) and controlled diet survey, we showed that K+ was low ($p<0.5$) in RA patients, more so in women (EULAR 2014).

Methods: 172 consenting chronic RA patients (ACR 1987 classified, mean age 49.9 years, 89 % women, mean duration 9.9 years,74% seropositive RF) with active pain(visual analogue scale > 4 cm) were randomized into an assessor blind, three arm study of 16 week duration in a community rheumatology center. Standardized oral K+ intake was based on K+ rich vegetarian balanced diet in Arm A (3.5-4 gm K+ daily) and an additional K+ supplement powder (K+ rich pulses & seeds plus oral rehydration salt(3 gm K+), Indian pharmacopeia) in Arm B (7.5-8 gm K+ daily); local diet preferences considered. Arm C was control (routine diet , 2-3 gm K+ daily). Patients continued pre-study suprvised standard rheumatology care/drugs (72% methotrexate, mean weekly dose 14 mg;60% prednisolone, mean4 mg daily); analgesic rescue permitted and monitored as per protocol. No other non-drug intervention advised. Standard efficacy/safety measures and diet intake were evaluated every month. Compliance check included urinary K+ assay. The study (80% power, significant $p<0.05$) was analyzed using SPSS; NS: p, not significant. Arms were well matched for several measures (for mean DAS 28: A=4.9; B=5.5; C=4.9) and withdrawals (A: 8.8%; B:12.1%; C: 8.8%).

Results:

Pain and several ACR efficacy measures improved ($P<0.05$) by intervention; difference was NS by intent to treat analysis/ITT (mean change pain VAS: A=-1.3 cm; B=2 cm; C= 1.2; p=0.17, ANOVA).But completer analysis showed significant change (p=0.04) in mean pain VAS in the B intervention arm (high K+ intake). B arm also showed best response (ITT, $P<0.05$) in proportion patients with at least 50% reduction and minimal clinical important difference in pain VAS on completion from baseline. Maximum improvement (NS) in HAQ (Indian validated version) and SF 36 physical score was seen in the B arm. There was reduction (NS) in the mean DAS 28 score by intervention (A:-1.4; B:-1.2; C: -0.9). Only mild AE were reported (<8% patients by study arm). On completion, B arm demonstrated a maximum serum cortisol (AM) increase. K+ intervention arms showed reduction in systolic BP. Ongoing medication, dietary factors and compliance, disease activity status may confound results.

Conclusion:

This pragmatic interventional control study in patients suffering from chronic symptomatic RA showed a clinically important pain reduction over and above standard drug treatment using dietary K+ augmentation. Other possible benefits were reduced disease activity and improved BP (cardiovascular) status. Overall, this seemed to be a gentle useful and safe adjunct therapy.

Disclosure: T. Kainifard, None; **M. Saluja**, None; **A. Venugopalan**, None; **R. Rane**, None; **A. Chopra**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/oral-potassium-k-reduces-pain-in-ra-a-randomized-active-control-study-of-diet-based-k-intervention

Abstract Number: 1439

Reducing Gastric Ulcers in Patients with a History of Gastrointestinal (GI) Ulcers Who Require Long-Term High-Dose Non-Steroidal Anti-Inflammatory Drug (NSAID) Therapy

John Fort[1], **Robert J. Holt**[2], Jeffrey D. Kent[3] and Alfonso Bello[4], [1]POZEN Inc., Chapel Hill, NC, [2]College of Pharmacy, University of Illinois-Chicago, Vernon Hill, IL, [3]Horizon Pharma USA, Inc., Deerfield, IL, [4]Illinois Bone & Joint Inst, Glenview, IL
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Background/Purpose: Patients ≥65 taking naproxen with previous GI symptoms have a 29% annual incidence of significant upper gastrointestinal events.(1) Those patients who are older, with previous ulcer history, and on low dose aspirin (LDA) are particularly at risk for gastric ulcers. Prophylaxis with gastroprotective agents can help reduce adverse GI effects. Here we report the comparative incidence of gastric ulcers (GUs) with a fixed combination of naproxen 500 mg/ esomeprazole 20 mg (NAP/ESO) versus naproxen 500mg (NAP) alone given twice daily to patients with a previous history of ulcers who required continued NSAID therapy.

Methods: We pooled data from two large randomized, placebo controlled trials (n=854) which reported a significant reduction in the incidence of cumulative GUs over 6 months with NAP/ESO (n=428) compared with NAP (n=426). (2) Efficacy in a subset with 1) a history of GU within 5 years, 2) aged ≥ 50 + history of GU, and 3) use of aspirin + history of GU were assessed. The CMH test was used to compare the treatment groups for differences at the 0.05 level. Relative Risk Reduction (RRR) and number-needed-to-treat (NNT) were calculated.

Results: In total, 69 patients (N=33, NAP/ESO, N=36, NAP) had a history of GUs (Figure 1). NAP/ESO use was found to statistically significantly reduce the risk for GUs over 6 months as compared with NAP alone in those 1) with a history of GU [RRR=0.81, NNT= 2.62], 2) aged ≥ 50 + history of GU [RRR=0.91, NNT=1.97]and 3) use of aspirin + a history of GUs [RRR=1, NNT=1.67].

Conclusion: The fixed combination of NAP/ESO significantly reduces the risk for gastric ulcers associated with high dose naproxen in those at high inherent risk. Numbers of patients needed to be treated to prevent one event were low (< 3).

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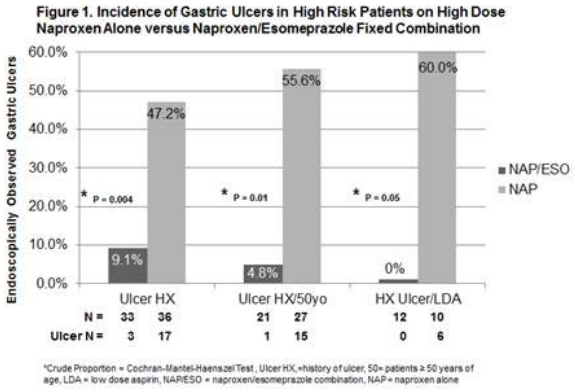

Disclosure: J. Fort, Pozen, Inc, 3; **R. J. Holt**, Horizon Pharma USA, Inc, 5; **J. D. Kent**, Horizon Pharma USA, Inc, 3; **A. Bello**, Horizon Pharma USA, Inc, 5.

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Abstract Number: 1440

Outcomes and Cost-Effectiveness of Shoulder Injections with Sonographic Needle Guidance

Timothy Moore[1], Wilmer Sibbitt Jr.[1], Cole Paffett[2], Dan Tandberg[3], Arthur Bankhurst[4], Roderick Fields[5] and Suzanne Emil[1],

[1]Rheumatology, University of New Mexico, Albuquerque, NM, [2]School of Medicine, Univeristy of New Mexico, Albuquerque, NM, [3]University of New Mexico, Albuquerque, NM, [4]Rheum/ MSC 105550, University of NM Med Ctr, Albuquerque, NM, [5]Rheumatology, University of New Mexico, Albquerque, NM

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Background/Purpose: Sonographic needle guidance (USG) of musculoskeletal injections has improved outcomes of intraarticular (IA) injections, but is associated with increased procedural costs. This practical randomized controlled pilot study was designed to determine: 1) the overall costs and cost-effectiveness of the USG technique of IA corticosteroid injections in the shoulder, and 2) provide preliminary power data to determine whether USG IA injections were more effective than the conventional anatomic landmark palpation-guided (ALMPG) method.

Methods: 29 patients with intractable shoulder pain (glenohumeral joint (GHJ) arthritis with tenderness to deep palpation anteriorly) were randomized to injection by either conventional ALMPG (15 patients) injection USG (14 patients) injection. A two-step technique was utilized for IA procedures using one needle and two syringes. The USG method comprised: 1) interrogation of the shoulder to find the GHJ, 2) needle introduction into the GHJ using the anterior approach under USG, 3) 3 ml 1% lidocaine injected with US visible dilation of the IA space, 4) a syringe exchange leaving the IA needle in place, and 5) injection of 80 mg triamcinolone acetonide (2 ml) through the IA needle. Demographics, baseline pain, procedural pain, pain at 2 weeks, pain at 24 weeks, therapeutic duration, physician satisfaction, total cost per procedure, and yearly cost per patient were collected and analyzed. Pain was measured with the 10 cm Visual Analogue Pain Scale (VAS).

Results: There were no complications in either treatment group. Both groups significantly improved at 2 weeks post-injection ($p<0.005$), supporting that both USG and ALMPG were both effective as has been previously demonstrated. There was no significant difference in total cost (yearly cost per patient) between US and non-US methods ($p<0.23$), despite increased upfront procedural costs. The USG data suggested potentially improved outcomes due to statistical trends for reduced post-procedural costs ($p<0.101$), reduced injection pain ($p<0.113$), and prolongation of time to next procedure ($p<0.06$). With the current subject numbers, compared to conventional ALMPG methods, USG injection did not demonstrate statistically significant improvement in pain at 2 weeks post-injection ($p<0.69$), pain at 24 weeks post-injection ($p<0.63$), pain from baseline compared to 2 weeks post-injection ($p<0.78$), pain from baseline to 24 weeks post-injection ($p<0.60$), or duration of therapeutic effect ($p<0.39$).

Conclusion: USG does not increase the overall costs of IA shoulder injections and with a trend of decreasing post-procedure costs, findings of importance for medical economics. Further, the present study trends suggest that USG may improve overall clinical outcomes of IA shoulder injections permitting power determination for future definitive studies

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Abstract Number: 1441

Marine Oil Supplements for Arthritis Pain: A Systematic Review and Meta-Analysis of Randomized Trials

Ninna Karsbæk Senftleber[1,2], **Sabrina Mai Nielsen**[3,4], Jens Rikardt Andersen[4], Henning Bliddal[5], Simon Tarp[3], Lotte Lauritzen[4], Daniel E. Furst[6], Maria E. Suarez-Almazor[7], Anne Lyddiatt[8] and Robin Christensen[5], [1]Musculoskeletal Statistics Unit, The Parker Institute, Department of Rheumatology, Copenhagen University Hospital, Bispebjerg and Frederiksberg, Frederiksberg and Bispebjerg, Denmark, [2]Department of Nutrition, Exercise and Sports, University of Copenhagen, Frederiksberg, Denmark, [3]Musculoskeletal Statistics Unit, The Parker Institute, Department of Rheumatology, Copenhagen University Hospital, Bispebjerg and Frederiksberg, Copenhagen, Denmark, [4]Department of Nutrition, Exercise and Sports, University of Copenhagen, Copenhagen, Denmark, [5]The Parker Institute, Department of Rheumatology, Copenhagen University Hospital, Bispebjerg and Frederiksberg, Copenhagen, Denmark, [6]Medicine, University of California, Los Angeles, David Geffen School of Medicine, Los Angeles, CA, [7]General Internal Medicine, The University of Texas, MD

Anderson Cancer Center, Houston, TX, [8]Musculoskeletal Group, Cochrane Collaboration, Ottawa, ON, Canada
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Background/Purpose: Marine oil supplements (MOS) are suggested to have anti-inflammatory properties, but there is no consensus regarding the efficacy of MOS in the management of arthritis. The objective was to evaluate whether oral MOS improve pain and other clinical features in patients with any type of arthritis.

Methods: Included in the systematic review were randomized trials comparing an MOS, with no marine oil supplementation (i.e., add-on designs) with trial duration of at least 2 weeks in patients with any type of arthritis, at any age and gender. Trials that collected some patient-reported pain outcome were considered eligible for meta-analysis. A systematic search was applied (02.24.15) to Medline, Web of Science, The Cochrane Central Register of Controlled Trials, EMBASE, ClinicalTrials.gov, and the World Health Organization International Clinical Trial Registry Platform portal. Assessment for inclusion, data extraction and bias assessment were done independently by 2 reviewers. Data were extracted using a standardized form. Risk of bias was assessed using the Cochrane Risk of Bias tool. Standardized mean differences (SMD) were calculated, using Hedges's adjustment. Random-effects meta-analysis was used to pool the trial data and heterogeneity was explored using REML-based meta-regression analysis (R software).

Results: From 65 potentially eligible trials included in the systematic review, 42 trials met inclusion criteria for the meta-analysis. Of these, 30 trials had complete data for inclusion, where data on 1509 patients, of whom 781 received an oral MOS, were used. Although substantial heterogeneity was present (I^2, 63%), the pooled SMD suggested a favorable association with MOS compared with control (SMD, -0.24; 95%CI: -0.42 to -0.07); corresponding to an improvement of 8 % on a VAS pain scale. Inclusion of the trials with non-complete data on pain outcome, and high risk of outcome reporting bias, using a null imputation, resulted in a lower effect size (42 trials; SMD, -0.16; -0.28 to -0.03). Meta-regression analysis on the trials with complete data showed a statistically significant effect in rheumatoid arthritis (RA) patients (22 trials; SMD, -0.21; -0.42 to -0.0043) but not in patients with osteoarthritis (OA) (5 trials; SMD, -0.17; -0.57 to 0.24); other/unclear/mixed diagnoses were described in three trials (-0.63; -1.2 to -0.06). Inadequate blinding of participants and high risk of attrition bias were associated with higher effect sizes, compared to those with an adequately reported procedure.

Conclusion: Meta-analytic pooling of all studies across arthritis conditions showed a statistically significant association between oral MOS and pain (SMD>0.20 indicating clinical significance). A statistically significant effect was seen in RA patients but not in OA patients. However, our confidence in the estimate(s) is rated to low-quality evidence due to heterogeneity, and the empirical evidence suggesting a high risk of bias.

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Descriptive Characteristics of Patients Prescribed Opioids for the Treatment of Chronic Pain

Jenna Goesling[1], Stephanie Moser[2], Afton L. Hassett[3], Chad Brummett[1] and Natalie Gulau[1], [1]Anesthesiology, University of Michigan, Ann Arbor, MI, [2]Department of Anesthesiology, University of Michigan, Ann Arbor, MI, [3]Anesthesiology, University of Michigan Medical School, Ann Arbor, MI
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Background/Purpose:

Opioids remain the cornerstone of acute pain therapy. However, there is little empirical evidence supporting the use of long-term opioid therapy for chronic pain. In clinic settings, one of the challenges faced by physicians is determining what to do with patients who were started on opioids for therapeutic use (i.e. pain relief) but who continue to use opioids even when benefit is not apparent. The goal of this study was to describe the unique characteristics of patients currently taking opioids. **Methods:**

This study included 150 new patients between the ages 18-70 seeking treatment for chronic pain at an outpatient tertiary pain clinic. As part of their visit, all patients completed self-report measures of pain severity (Brief Pain Inventory), physical functioning (PROMIS Short Form) and psychiatric symptoms (Hospital and Depression Scale). During the new patient visit, a research assistant approached eligible patients in an exam room and completed a structured interview developed by the investigative team. For patients reporting current opioid use, additional data was collected including duration of use, helpfulness of opioid across multiple domains, motivation to continue opioids, and interest in learning alternative ways to manage pain. The Opioids Difficulties Scale (PODS) and Domains of Change Opioid Scale (DCOS) were collected on all participants currently taking opioids. Chi-square and t-tests were conducted. **Results:**

Of the 150 patients, 55.26% (N=84) reported current opioid use. Current opioid use was associated with a worse clinical phenotype, including higher pain severity, worse physical functioning, and more symptoms of depression (See Table 1). Descriptive data on the characteristics of opioid use is presented in Table 2 and opioid related beliefs are presented in Table 3. **Conclusion:**

These data question the benefits of long term opioid use. For instance, 41% of patients report less than an hour of pain relief after taking an opioid. The data from this study also highlight important target areas for helping patients not benefiting from opioids taper off opioids. For instance, patients report low confidence in their ability to manage pain without opioids. Importantly, the majority of patients report interest in learning alternative strategies for managing their pain.

Table 1. Patients using opioids had a worse pain phenotype when compared to those not using opioids, including higher pain severity, worse physical function and higher symptoms of depression

	Opioid Use		p°
	Yes N=85	No N=66	
Gender (% Male)	41.67	40.91	0.93
Race (% Caucasian)	88.89	84.48	0.46
Age (years)	48.75 (11.8)	47.06 (13.4)	0.41
BPI Pain Severity (range = 0 – 10)	6.59 (1.8)	5.42 (2.1)	<0.001
PROMIS Physical Functioning (range = 22 – 62)	36.61 (7.6)	40.41 (7.8)	0.007
HADS Depression	8.49 (4.2)	7.05 (4.5)	0.065
HADS Anxiety	8.63 (4.9)	7.88 (4.4)	0.375

Note. BPI= Brief Pain Inventory; HADS=Hospital Anxiety and Depression Scale. Lower values on the PROMIS Physical functioning scale are t-scores and represent worse physical functioning. Chi-square tests were conducted for categorical variables and independent samples t-tests were conducted for continuous variables. Mean and standard deviation reported for continuous variables.

Table 2. Descriptive characteristics of opioid use

	N	%
Duration of current opioid use (%)		
< 90 days	18	21.95
90 days to < 1 year	23	28.05
1 year – 5 years	27	32.93
5 plus years	14	17.04
Schedule (%)		
Fixed only	25	30.49
Before pain starts only	5	6.10
After pain starts only	31	37.80
Combination of all three	21	25.61
Average duration of pain relief		
No relief	14	16.44
Less than 1 hour	18	24.66
1 to < 2 hours	9	12.33
2 to < 4 hours	10	13.70
4 to < 6 hours	14	19.18
6+ hours	10	13.70
	Mean	SD
Amount of pain relief (range 0 – 10)	4.98	2.41
Improvement in functioning (range 0 – 10)	4.41	2.88

Note. Amount of pain relief: "On a scale of 0 to 10 where zero is no relief and 10 is complete relief, what number best describes how much pain relief you get on average after taking this medication"; Improvement in functioning: "Thinking about your ability to do day to day activities, on a scale of 0 to 10 where 0 is no improvement and 10 is complete return to your normal activity level, what number best describes how much your ability to function improves after taking this medication".

Table 3. Patients' perceived effects of opioids and interest in continuing opioids

	Mean	SD	Median	IQR	Min	Max
Desire to continue taking an opioid	4.13	3.97	4	8	0	10
Confidence in managing pain without an opioid	3.52	3.57	2	5	0	10
Interest in learning alternative coping strategies	8.56	2.61	10	2	0	10
% pain improvement needed before considering stopping opioids	71.82	22.57	75	40	0	100
PODS scale (range 0 – 5)	1.01	0.70	0.72	1	0.19	2.6
DCOS Pain (range 0 – 6)	3.12	1.84	4	3	0	6
DCOS Physical Activity	2.78	1.55	3	2	0	6
DCOS Mood	2.95	1.10	3	1	0	6
DCOS Anxiety	2.80	1.10	3	1	0	6
DCOS Sleep	2.99	1.30	3	2	0	6

Note. "On a scale of 0-10 where 0 is no desire and 10 is full desire, which number best describes your want to continue taking an opioid for your current pain"; "On a scale of 0-10 where 0 is not at all confident and 10 is very confident, how confident are you in your ability to manage pain without opioids?"; "On a scale of 0-10 where 0 is no desire and 10 is full desire, which number best describes your interest in learning different ways of managing pain other than opioids? "; "What % of pain improvement would you need to experience before you would consider stopping use of your opioid medication?" PODS =The Perceived Opioids Difficulties Scale; Lower values on the PODS indicate patients have few difficulties with their opioids; DCOS= Domains of Change Opioid Scale; Higher values on the DCOS indicate that the domain has improved since the patient began taking opioids.

Disclosure: J. Goesling, None; **S. Moser**, None; **A. L. Hassett**, Bristol-Myers Squibb, 2,Lexicon Pharma, 5; **C. Brummett**, Tonix Pharmaceuticals, 5; **N. Gulau**, None.

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Abstract Number: 1443

A Multiple Ascending-Dose Study to Evaluate Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of Mirogabalin in Healthy Elderly Subjects

Karen Brown[1], Yoshihiro Kumagae[1], Shoichi Ohwada[2], Vance Warren[1], Hamim Zahir[1] and Victor Dishy[1], [1]Daiichi Sankyo Pharma Development, Edison, NJ, [2]Daiichi Sankyo Co., Ltd., Tokyo, Japan

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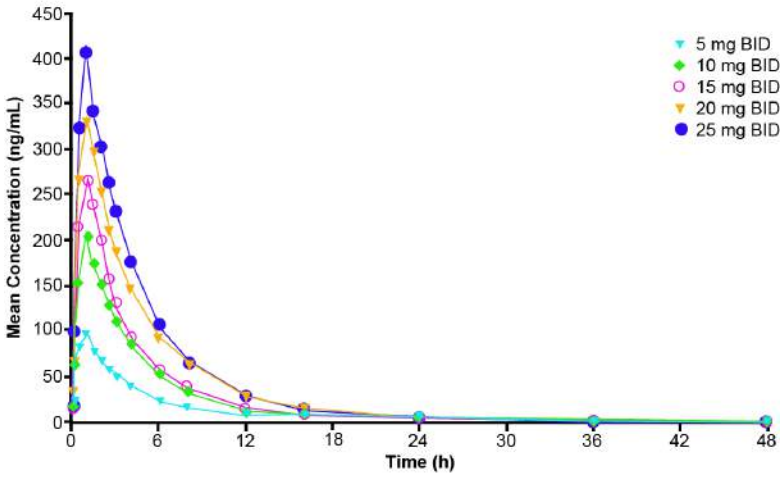
Background/Purpose: Mirogabalin (DS-5565) is a preferentially selective a2d-1 ligand intended for treatment of pain associated with fibromyalgia and neuropathic pain. We evaluated the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of mirogabalin after multiple doses in healthy elderly subjects to guide dose selection for further clinical development.

Methods: A randomized, double-blind, placebo- and active-controlled, multiple ascending-dose study was conducted in healthy subjects aged 55─75 years inclusive. Subjects were randomly assigned (6:2:2) to receive multiple oral doses of mirogabalin (5, 10, 15, 20, and 25 mg BID [25 mg QD followed by 25 mg BID]), pregabalin (75 mg followed by 150 mg BID), or placebo for 14 days. PK samples (blood and urine) were collected after each treatment, and PD assessments evaluated sedation, attention, dizziness, and ataxia. Safety was based on treatment-emergent adverse events (TEAEs), clinical laboratory evaluations, vital signs, suicidality, and physical examinations.

Results: In total, 48 subjects participated (6 subjects each received mirogabalin 5, 10, 15, 20, or 25 mg BID, 8 received pregabalin, and 10 received placebo). Mean mirogabalin concentrations increased with increasing doses (Figure), though exposure appeared to increase in a slightly less than proportional manner. Mean clearance and volume of distribution were comparable across all mirogabalin dose levels. Half-life of mirogabalin ranged from 3.6─7.5 h. There was no significant plasma accumulation of mirogabalin on day 14. Mirogabalin did not appear to increase sedation or decrease attention; however, subjects receiving 15, 20, or 25 mg BID reported increases in dizziness and ataxia from day 3; highest rates were in the 20 mg BID cohort. Mirogabalin 5, 10, and 15 mg BID doses were generally well tolerated, though 15 mg BID was associated with a higher incidence of dizziness/somnolence. Mirogabalin 20 and 25 mg BID doses were not well tolerated. One subject in the mirogabalin 10 mg BID group discontinued on day 8 due to a mild TEAE of elevated hepatic transaminases that subsequently resolved. Most common TEAEs after mirogabalin administration were somnolence (47%), constipation (33%), headache (27%), and dizziness (27%). Somnolence and dizziness tended to resolve within 4 days. Pregabalin PK and PD parameters were comparable to those previously reported for healthy subjects.

Figure. Mean mirogabalin concentration-time profiles after administration of mirogabalin 5 mg to 25 mg BID on study day 14.



Conclusion: Mirogabalin plasma concentrations increased with increasing doses, with no significant accumulation over 14 days of dosing. Doses up to 15 mg BID were well tolerated. Based on these data, 15 mg BID was selected as the highest target dose for clinical development. Somnolence and dizziness observed with mirogabalin were expected based on the mechanism of action but tended to resolve spontaneously, suggesting possible development of tolerance after repeated dosing.

Disclosure: K. Brown, Daiichi Sankyo, 1,Daiichi Sankyo, 3; **Y. Kumagae**, Daiichi Sankyo Pharma Development, 3; **S. Ohwada**, Daiichi Sankyo, Co. Ltd., 3; **V. Warren**, Daiichi Sankyo Pharma Development, 3; **H. Zahir**, Daiichi Sankyo Pharma Development, 1,Daiichi Sankyo Pharma Development, 3; **V. Dishy**, Daiichi Sankyo Pharma Development, 3.

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Abstract Number: 1444

Validation of a Revised Version of the Michigan Body Map

Chad Brummett[1], Rishi Bakshi[2], Daniel Leung[1], Jennifer Zollars[3], Jenna Goesling[1], Stephanie Moser[4], David A. Williams[5] and Afton L. Hassett[6], [1]Anesthesiology, University of Michigan, Ann Arbor, MI, [2]Physical Medicine and Rehabilitation, University of Michigan Medical School, Ann Arbor, MI, [3]Anesthesiology, University of Michigan Health System, Ann Arbor, MI, [4]Department of Anesthesiology, University of Michigan, Ann Arbor, MI, [5]Anesthseiology, University of Michigan, Ann Arbor, MI, [6]Anesthesiology, University of Michigan Medical School, Ann Arbor, MI
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Title: Validation of a Revised Version of the Michigan Body Map

Background/Purpose:

One of the hallmark features of fibromyalgia and other centralized pain states is widespread body pain. We developed the original Michigan Body Map (MBM) as a self-report measure to assess widespread body pain in clinical care and in epidemiological studies (Fig 1a). It is a one-sided body image with check boxes for 35 body areas and a box for "No Pain." Whereas patients preferred the original MBM to the Widespread Pain Index used to describe the body areas for the 2011 Survey Criteria for Fibromyalgia (FM), there were some issues with distinguishing left from right side body areas and some preferred the two-sided image from the Brief Pain Inventory. We developed a new body map (Fig 1b) that consists of the same 35 body areas, but is a two-sided image depicting front and back. The aim of the present study was to assess patients' understanding of and accuracy when completing the new MBM, as well as to assess preference when compared to the original MBM.

Methods:

80 patients from the University of Michigan's Physical Medicine and Rehabilitation Spine Center were included in this study. Written informed consent was obtained. Patients completed both the original MBM and the new MBM. Order of completion was counterbalanced across participants. Understanding, accuracy and preference between the two body maps were assessed.

Results:

Participants completed the original body map (34.5 sec) more quickly than the new map (44 sec) ($p = 0.003$). Compared to the original map, the new map was more frequently preferred, better allowed participants to show pain, and was easier to accurately show painful areas on left and right sides (Table 1). 12 (15%) participants incorrectly flipped left and right sides on the original MBM compared to only 4 (5%) participants on the new MBM ($p = .046$). Participants incorrectly endorsed an average of 2.5 body areas on the original body map compared to only 1.6 on the new map ($p = 0.004$). No differences were found in the calculation of the count of 19 body areas used in the 2011 survey criteria for FM in the original map (4.78 ± 3.01) compared to the new map (4.79 ± 3.3) ($p = 0.922$).

Conclusion:

Overall, participants demonstrated good understanding of the new MBM and generally preferred it to the original MBM. There were no significant differences in the FM survey scores between the old and new body maps suggesting that data from the two different versions can be combined when necessary.

Table 1. Preferences between the original and revised Michigan Body Map.

	Original MBM	New MBM	No Preference
Preference	31.25%	61.25%	7.5%
Best depicts areas of pain	25%	53.75%	21.25%
Easier to complete	46.25%	38.75%	15%
Best distinguishes left from right	32.5%	52.5%	15%

Participants preferred the revised (new) Michigan Body Map (MBM). Participants also felt the new MBM depicted areas of pain better, was easier to complete and better distinguished left from right.

Figure 1a) Original Michigan Body Map

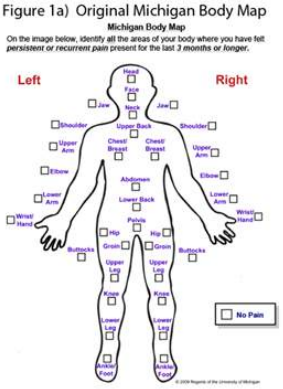
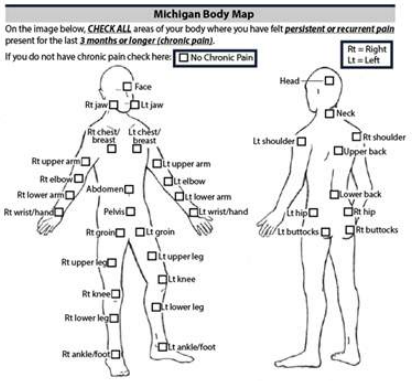


Figure 1b) New Michigan Body Map



Disclosure: **C. Brummett**, Tonix Pharmaceuticals, 5; **R. Bakshi**, None; **D. Leung**, None; **J. Zollars**, None; **J. Goesling**, None; **S. Moser**, None; **D. A. Williams**, Health Focus Inc., 5; **A. L. Hassett**, Bristol-Myers Squibb, 2,Lexicon Pharma, 5.

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Physicians' Perspectives on the Diagnosis and Treatment of Chronic Nonbacterial Osteomyelitis

Yongdong Zhao[1], Fatma Dedeoglu[2], Polly J. Ferguson[3], Sivia Lapidus[4], Ronald Laxer[5], Suzanne C. Li[6] and for the CARRA SVRD subcommittee, [1]Pediatric Rheumatology, Seattle Children's Hospital, Seattle, WA, [2]Rheumatology, Boston Children's Hospital, Boston, MA, [3]Dept of Pediatrics--Rheum, University of Iowa, Iowa City, IA, [4]Pediatric Rheumatology, Goryeb Children's Hospital, Morristown, NJ, [5]Division of Rheumatology, The Hospital for Sick Children, Toronto, ON, Canada, [6]Pediatrics, Joseph M Sanzari Children's Hospital, Hackensack University Medical Center, Hackensack, NJ

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Background/Purpose: Chronic nonbacterial osteomyelitis (CNO), also known as chronic recurrent multifocal osteomyelitis (CRMO), is an autoinflammatory bone disease of unknown cause that can result in persistent bone pain, destruction and pathological fractures. Currently, no guidelines exist in managing patients with CNO. Understanding the practices of pediatric rheumatologists in diagnosing and treating CNO would provide us with important information to refine the diagnostic criteria and guide the development of consensus treatment plans. The objectives of this study were to determine (1) which disease features physicians consider important for ordering a bone biopsy, (2) physicians' approaches in monitoring disease activity and (3) physicians' treatment choices.

Methods: After IRB approval, we surveyed members of the Childhood Arthritis and Rheumatology Research Alliance (CARRA) using a web-based questionnaire regarding diagnosis and management of CNO. Data was analyzed using descriptive statistics.

Results: 135 of 369 (38%) members responded to the survey and 124 completed the survey. Thirteen chose an early survey exit point because of lack of experience in managing CNO. 84.2% of responders were pediatric rheumatology attending physicians with 50% of responders having practiced >10 years, and 13.4 % were fellows. The majority of these providers cared for 1-4 patients (70.5%) and diagnosed 0-3 new cases (90.2%) each year. Most providers felt "very or moderately" confident with diagnosing (81.8%) and treating (86.6%) patients with CNO.

Reported bone biopsy frequencies were: never 0%, rarely 11.6%, sometimes 25.6%, often 39.7%, or always 23.1%. The top three reasons for performing a biopsy were constitutional findings (84.8%), unifocal bone lesions (82.6%), and nocturnal bone pain (57.6%). The top three reasons for not performing a biopsy were involvement of typical sites such as the metaphyses of long bones and clavicles (83.5%), presence of multiple bone lesions (79.1%), and presence of conditions known to be associated with CNO, such as psoriasis and inflammatory bowel disease (63.7%). Biopsy sites were usually determined by the orthopedic surgeon or interventional radiologists (67.5%).

Among all imaging modalities, regional MRI and X rays were most commonly used. 36.5% of responders used whole body MRI often or always. 53.3% of responders used imaging regularly to monitor disease activity, 53.1% of which monitored every 6 months and 25% of which obtained imaging every 12 months.

Almost all responders (98.3) routinely prescribed NSAIDs as initial therapy. For patients who failed NSAID treatment, methotrexate (68.6%), TNF inhibitors (66.9%) and bisphosphonates (46.6%) were the next most commonly used treatments. Presence of a spinal lesion increased the use of bisphosphonate treatment.

Conclusion: The diagnostic approach and disease activity monitoring for CNO varied among physicians. NSAIDs remained the first line treatment for CNO. Methotrexate, TNF inhibitors and bisphosphonates were most commonly used after NSAIDs failed. These findings provide important background to move forward with development of consensus treatment plans for CNO.

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Abstract Number: 1446

Long-Term Effectiveness and Safety of Abatacept in Juvenile Idiopathic Arthritis: Interim Results from the Abatacept in JIA Registry

Daniel J Lovell[1], N Ruperto[2], S Spalding[3], JA Dare[4], R Cimaz[5], V Stanevica[6], RK Vehe[7], N Tzaribachev[8], G Horneff[9], M Trachana[10], TA Simon[11], HI Brunner[12] and A Martini[2], [1]Cincinnati Children's Hospital Medical Center, Cincinnati, OH, [2]Istituto G. Gaslini Pediatria II Reumatologia, Genova, Italy, [3]Cleveland Clinic, Cleveland, OH, [4]University of Arkansas Medical Center, Little Rock, AR, [5]Azienda Ospedaliero-Universitaria Meyer, Florence, Italy, [6]Riga Stradins University, Riga, Latvia, [7]University of Minnesota, Minneapolis, MN, [8]Pediatric Rheumatology, Bad Bramstedt, Germany, [9]Asklepios Klinik Zentrum für Allgemeine Paediatrie und Neonatologie, Sankt Augustin, Germany, [10]Hippokration General Hospital, Thessaloniki, Greece, [11]Bristol-Myers Squibb, Hopewell, NJ, [12]Division of Rheumatology, Cincinnati Children's Hospital Medical Center, Cincinnati, OH

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Background/Purpose: Abatacept (ABA) is a widely approved and used biologic in children with juvenile idiopathic arthritis (JIA). The purpose of this study was to describe the longitudinal effectiveness and safety of ABA in JIA patients (pts). **Methods:** Using a standardized protocol, clinical sites in the Pediatric Rheumatology Collaborative Study Group (PRCSG) and Paediatric Rheumatology International Trial Organization (PRINTO) enrolled JIA pts currently on or starting ABA in this longitudinal registry. Planned duration of follow-up is 10 yrs. Visits are every 3 mths for Yr 1, every 6 mths for Yrs 2–5 and annually for Yrs 6–10. After ≥4 mths on ABA, pts remain in the registry even if ABA is stopped. Data shown are those collected through March 26, 2015 (up to 2 yrs follow-up). **Results:** *Overview*. Of 146 JIA pts enrolled, 133 provided data for this analysis (6 had no data entry; 7 discontinued the study: 1 lost to follow-up, 1 withdrew consent, 3 moved to other site, 2 other). The total person-yrs of observation were 79.4: 67.9 yrs on ABA, 11.5 after ABA. In this registry, 33% (44/133) of pts were new starts on ABA and 28% (38/133) were biologic naïve; 39% had received ABA treatment for 0–1 yrs and 28% for 1–2 yrs. ABA was continued during follow-up in 85% of pts (113/133). Reasons for ABA discontinuation were inefficacy (18), surgery (1) and therapy complete (1). *Baseline*. 86% of pts were female, mean/median: age at enrollment was 13.4/13.8 yrs, disease duration was 5.9/5.4 yrs, height percentile (WHO standards for healthy children) 47.9/52.8, weight percentile 50.8/48.2 and 3.0/1.0 active joints. Baseline clinical, functional and HRQoL scores are shown in the **Table**. 15% had a history of uveitis and 4% had active uveitis. JIA subtype was systemic 3%, oligoarticular 21%, polyarticular RF– 54%, polyarticular RF+ 10%, psoriatic 5%, enthesitis-related 2%, undifferentiated 6%. 86% were taking a concomitant JIA medication (64% MTX, 49% NSAIDs, 17% systemic steroids, 5% leflunomide, 5% hydroxychloroquine, 1% cyclosporine, 1% sulfasalazine). ABA was given IV every 4 weeks in 83% and SC weekly in 17%. *Follow-up effectiveness*. Results up to 2 yrs are shown in the **Table**. *Follow-up safety*. Eleven AEs were seen (10 serious; all single occurrences) in 10 pts (8% of study population) for an AE rate of 12.6 per 100 pt-yrs of exposure (95% CI 6.9, 21.0). There were 2 infections of special interest (1 non-serious, candida esophagitis; 1 serious, methicillin-resistant *Staphylococcus aureus* wound infection). 1/133 (<1%) discontinued ABA due to a safety event (anaphylaxis). No new autoimmune diseases, deaths, malignances or tuberculosis cases were reported.

Table. Follow-up effectiveness

Endpoints	Baseline n=133	3 months n=76	6 months n=52	12 months n=49	24 months n=3
Clinical					
MD Global	1.9/1.0	1.45/1.0	1.7/1.0	1.3/0.5	1.0/1.0
CID,[1] %	33	38	31	49	50
JADAS	7.3/4.5	6.6/4.5	6.3/3.5	6.8/2.5	2.0/1.0
JADAS ID, %	32	18	10	12	2
JAMAR Functional[2]	4.0/2.0	3.6/3.0	3.8/3.0	3.7/2.5	0.5/0.5
JAMAR HRQoL	6.5/3.0	5.9/5.0	6.4/6.0	5.3/3.0	1.4/1.0

Data are mean/median unless otherwise indicated

CID=clinical inactive disease (Wallace criteria); JADAS=Juvenile Arthritis Disease Activity Score (range 0–91); JADAS ID=Juvenile Arthritis Disease Activity Score Inactive Disease (JADAS ≤1); JAMAR Functional=Juvenile Arthritis Multidimensional Assessment Report Functionality Scale Child (range 0–15); JAMAR HRQoL=Juvenile Arthritis Multidimensional Assessment Report HRQoL Scale Child (range 0–15); MD Global=MD Global Disease Activity (VAS 0–10); VAS=visual analog scale

Conclusion: In this JIA cohort, abatacept demonstrated persistent effectiveness with low MD Global, low number of active joints and over 30% of pts were in CID. Abatacept was well tolerated and no new safety signals were seen.

1. Wallace C, et al. *Arthritis Care Res* 2011;**63**:929–36. 2. Filocamo G, et al. *J Rheumatol* 2011;**38**:938–53.

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Janssen, 5; **N. Ruperto**, Abbott, Bristol-Myers Squibb, "Francesco Angelini", GlaxoSmithKline, Hoffman-La Roche, Italfarmaco, Janssen, Novartis, Pfizer, Sanofi-Aventis, Schwarz Biosciences, Sobi, Xoma,Wyeth, 2,Abbott, AbbVie, Amgen, Biogen Idec, Astellas, Alter, AstraZeneca, Boehringer, Bristol-Myers Squibb, CD-Pharma, Celgene, Crescendo Bioscience, EMD Serono, Hoffman-La Roche, Italfarmaco, Janssen, MedImmune, Medac, Novartis, Novo Nordisk, Pfizer, Sanofi-Aven, 5,Abbott, AbbVie, Amgen, Biogen Idec, Astellas, Alter, AstraZeneca, Boehringer, Bristol-Myers Squibb, CD-Pharma, Celgene, Crescendo Bioscience, EMD Serono, Hoffman-La Roche, Italfarmaco, Janssen, MedImmune, Medac, Novartis, Novo Nordisk, Pfizer, Sanofi-Aven, 8; **S. Spalding**, None; **J. Dare**, AbbVie, AstraZeneca, Bristol-Myers Squibb, Horizon Pharma, Medac, Pfizer, Roche, UCB Biosciences, 2; **R. Cimaz**, None; **V. Stanevica**, None; **R. Vehe**, None; **N. Tzaribachev**, UCB, Pfizer, Janssen, Roche, 2; **G. Horneff**, Pfizer, Abbvie, Roche, 2; **M. Trachana**, Novartis, Roche, Pfizer, 5,Novartis, Abbvie, Bristol-Myers Squibb, 2; **T. Simon**, Bristol-Myers Squibb, 3; **H. Brunner**, Pfizer, Bristol-Myers Squibb, UCB, Janssen, Amgen, Celgene, AstraZeneca, Novartis, Genentech, 5,Novartis, Genentech, 8; **A. Martini**, Abbott, Bristol-Myers Squibb, "Francesco Angelini", GlaxoSmithKline, Hoffman-La Roche, Italfarmaco, Janssen, Novartis, Pfizer, Sanofi-Aventis, Schwarz Biosciences, Sobi, Xoma, Wyeth, 2.

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Abstract Number: 1447

Positive Power Doppler Signal Increases the Risk of Clinical Flare of Patients with Juvenile Idiopathic Arthritis in Clinical Remission: A Prospective Study

Vanessa B Miotto e Silva[1], **Octavio Peracchi**[2], Claudio A. Len[3], Sônia A.V. Mitraud[4], Rita NV Furtado[5], Jamil Natour[6] and Maria Teresa Terreri[7], [1]Pediatrics, Universidade Federal de São Paulo / UNIFESP, São Paulo, Brazil, [2]Pediatric Rheumatology, Assistent Doctor, Sao Paulo, Brazil, [3]Pediatrics, Universidade Federal de São Paulo, São Paulo,, Brazil, [4]Radiology and Diagnostic Imaging, Escola Paulista de Medicina/ Universidade Federal de São Paulo (EPM/UNIFESP), São Paulo, Brazil, [5]Medicine, Universidade Federal de Sao Paulo, Sao Paulo, Brazil, [6]Rheumatology Division, Federal University of Sao Paulo, Sao Paulo, Brazil, [7]Pediatrics, Universidade Federal de Sao Paulo, São Paulo, Brazil

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Background/Purpose: Prior ultrasound (US) studies in patients with juvenile idiopathic arthritis (JIA) in clinical remission have demonstrated the presence of subclinical synovitis. However, the significance of subclinical synovitis and positive power Doppler (PD) signal in these patients is still not well understood. The objectives of this study were to evaluate possible factors associated with clinical flare over a 30-month evaluation in a group of patients with JIA in remission and assess if the presence of US features could predict disease flares.

Methods: In this two years longitudinal, single-center study we performed clinical, laboratory (every 6 months) and US evaluations (initial, after 12 and 24 months) in 35 JIA patients in clinical remission according to Wallace criteria (34 joints/60 articular recesses). US parameters included synovial hypertrophy, PD signal and evidence of bone erosions. Subclinical synovitis was defined by the presence of synovial hypertrophy and/or positive PD signal. Flare was defined according to Wallace criteria.

Results: Of the 35 patients (80% female), 14 (40%) had persistent oligoarticular, 12 (34.3%) extended oligoarticular and 9 (25.7%) polyarticular JIA. Twenty patients (57.1%) were antinuclear antibodies (ANA) positive and none were rheumatoid factor (RF) positive. The mean age was 11.6 ± 3.8 years, the mean age of onset of JIA was 4.4 ± 3.2 years and the mean disease duration was 7.1 ± 3.5 years. Twenty-six (74.3%) patients were in remission on treatment and 9 (25.7%) were in remission off medication, for a median of 1.9 years. Twenty (57.1%) patients flared during the 30 months follow-up. Knees and ankles were most commonly affected. Eighteen (90%) were on treatment at the time of clinical flare. Of the 20 clinical flare patients, 7 (35%) had subclinical synovitis, 10 (50%) had synovial hypertrophy and 2 (10%) had positive PD signal at the time of flare. A Cox regression analysis found that both a positive PD signal ($p=0.046$) and the use of medications ($p <0.001$) were significantly associated with flare, and the risk of flare in patients with a positive PD signal was five times greater than in patients without a PD signal. Patients who were in remission on treatment showed a 14 times higher risk of clinical flare than patients off treatment.

Conclusion: The presence of subclinical synovitis detected by US in JIA patients in clinical remission did not predict flare of the disease. On the other hand, a positive PD signal showed a greater risk of JIA clinical flare. The remission on medication was also a risk factor for

JIA flare. Patients in remission on treatment with a positive PD signal should be cautiously tapered due to the higher risk of clinical flares.

Disclosure: V. B. Miotto e Silva, None; **O. Peracchi**, None; **C. A. Len**, None; **S. A. V. Mitraud**, None; **R. N. Furtado**, None; **J. Natour**, None; **M. T. Terreri**, None.

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Abstract Number: 1448

Progressive Pseudorheumatoid Arthropathy of Childhood (PPAC) – a Single Center Case Series

Renate Haefner, Boris Huegle and Johannes Peter Haas, German Center for Pediatric and Adolescent Rheumatology, Garmisch-Partenkirchen, Germany

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Background/Purpose: Progressive pseudorheumatoid arthropathy of childhood (PPAC, OMIM #208230) is a bone dysplasia caused by mutations in the WISP3 gene. Due to its presentation with joint stiffness and finger swelling, it is frequently misdiagnosed as polyarticular juvenile idiopathic arthritis (JIA). However, PPAC has some characteristics which distinguish it from JIA; early diagnosis avoids unnecessary treatments and allows adequate therapy for an optimum long-term outcome.

The objective of this study was to retrospectively document a single center cohort of PPAC and describe presentation and clinical course of this rare disease.

Methods: The database of the German Center for Pediatric and Adolescent Rheumatology was searched to identify all patients with a diagnosis of PPAC seen between 1997 and 2015. Clinical and molecular genetic data was extracted from patient files, and results were analyzed using descriptive statistics.

Results: 8 patients were included (6 male, 2 female), including 2 sibling pairs. Median age at presentation was 8 years (range 6 - 13 years), median follow-up was 8.5 years (range 3 – 18 years). Median age of first symptoms was 3 years (range 1 – 4 years). Four patients (50 %) were diagnosed as JIA prior to diagnosis of PPAC. Mutations in the WISP3 gene were detected in 5/5 tested patients. Typical symptoms at onset were abnormal gait (7/8 patients), swelling of the interphalangeal finger joints (4/8 patients) and muscular weakness (2/8 patients). All patients developed short stature with height below the 3rd percentile and an abnormally short trunk, mainly due to vertebral dysplasia which became apparent during elementary school in most cases. Other radiographic abnormalities included overgrowth of the epiphyses (8/8 patients), widening of the heads of the basal phalanges (8/8 patients) and malformation of vertebral bodies (8/8 patients). Functional impairment progressed in all cases, with severely impaired ambulation on last follow-up. Two patients regained longer walking distances after joint replacement of the hips, one patient also received knee arthroplasty. Avascular necrosis developed in 5/8 patients, involving the femoral head, the proximal tibia and the talus bone.

Conclusion: PPAC is frequently misdiagnosed as JIA, but history, typical symptoms and radiographs of the hands and spine can help to differentiate the two disease entities. Patients uniformly develop short stature and are at risk for avascular necrosis. Joint replacements can significantly improve function.

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The Effect of IL-1 Receptor Antagonist Anakinra (Kineret®) on Measures of Central

Nervous System Inflammation and Headaches in Pediatric Patients with Severe Cryopyrin-Associated Periodic Syndromes

Hans Olivecrona[1], Raphaela Goldbach-Mansky[2], Torbjörn Kullenberg[1] and **Mika Leinonen**[3], [1]Swedish Orphan Biovitrum, Stockholm, Sweden, [2]Translational Autoinflammatory Diseases Section, NIAMS, NIH, Bethesda, MD, [3]4Pharma AB, Stockholm, Sweden
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Background/Purpose: Cryopyrin-Associated Periodic Syndromes (CAPS) include a group of rare inherited autoinflammatory diseases consisting of Familial Cold Autoinflammatory Syndrome (FCAS), Muckle-Wells Syndrome and the most severe form, Neonatal-Onset Multisystem Inflammatory Disease (NOMID). Data on the effect of anakinra on measures of central nervous system (CNS) inflammation and headaches have been reported in a broad range of severe CAPS patients, showing that headaches and cerebrospinal fluid (CSF) leukocytosis improved dramatically during anakinra treatment[1,2]. The objective of this analysis is to evaluate the effect of anakinra on CNS inflammation and headache scores in CAPS children initiating anakinra treatment at an early age compared with adolescents/adults.

Methods: A prospective, open-label, long-term study of anakinra treatment in a total of 43 patients with severe CAPS was conducted at the National Institutes of Health[1,2]. The patients were treated with anakinra for up to 5 years. CNS inflammation was evaluated with CSF white blood cell (WBC) count and magnetic resonance imaging (MRI) was used to characterize different CNS lesions (presence of leptomeningeal enhancement). Headaches were assessed daily with diaries and scored on a scale from 0 (no symptoms) to 4 (severe symptoms). The patients were classified as children (age <12 years) or adolescents/adults (age ≥12 years) based on age at anakinra treatment start, including subgroup analysis in infants/toddlers (age <2 years at treatment start). The changes from baseline in children versus adolescents/adults were compared using Mixed Model for Repeated Measures. References: [1]Goldbach-Mansky R, et al. NEJM. 2006;355:581-592.[2]Sibley CH, et al. Arthritis Rheum. 2012;64:2375-2386.

Results: Children (N=22) and adolescents/adults (N=8) presented with comparable symptoms at baseline, as assessed by CSF WBC count and presence of leptomeningeal enhancement as well as headache scores. For CSF WBC count and leptomeningeal enhancement, both children and adolescents/adults showed significant decreases from baseline and had comparable low values throughout the treatment period. The average (standard error) headache scores at baseline were 0.8 (0.2) for children and 1.1 (0.4) for adolescents/adults. Following the initiation of anakinra treatment, the headache scores decreased significantly. The decrease among children (average score of 0.1 or lower for up to Month 60) was larger than in adolescents/adults (average score of 0.3 to 0.6 at different visits); p=0.026. Among the 4 infants/toddlers, the headaches were present in 2 patients at baseline and decreased or disappeared during the treatment.

Conclusion: Both children and adolescents/adults presented with comparable CNS inflammation measures and headache scores at baseline. All measures improved after initiation of anakinra treatment and the headache scores decreased even more in children compared with adolescents/adults. The headaches decreased or disappeared in infants/toddlers with symptoms at baseline. These data further suggest that every effort should be made for early diagnosis and treatment initiation to preserve normal organ function in children with CAPS.

Disclosure: H. Olivecrona, Swedish Orphan Biovitrum, 3; **R. Goldbach-Mansky**, SOBI, Novartis, Regeneron and Lilly, 2; **T. Kullenberg**, Swedish Orphan Biovitrum, 3; **M. Leinonen**, Swedish Orphan Biovitrum, 5.

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Abstract Number: 1450

Clostridium Difficile Infection-Associated Reactive Arthritis in a Pediatric Cohort

Daniel B. Horton[1,2,3], Brian L. Strom[1,3], Mary E. Putt[3], Carlos D. Rose[2], David D. Sherry[4] and Julia S. Sammons[5], [1]Rutgers Biomedical and Health Sciences, New Brunswick, NJ, [2]Pediatrics, Nemours A.I. duPont Hospital for Children, Division of Pediatric Rheumatology, Thomas Jefferson University, Wilmington, DE, [3]Biostatistics and Epidemiology, Center for Clinical Epidemiology and Biostatistics, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, [4]Pediatrics, Children's Hospital of Philadelphia, Division of

Pediatric Rheumatology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, [5]Pediatrics, Infection Prevention and Control, Division of Infectious Diseases, Children's Hospital of Philadelphia, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA

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Background/Purpose: The incidence of *Clostridium difficile* infection (CDI) has increased among children, and CDI is associated with significant morbidity and mortality. Cases of *C. difficile* infection-associated reactive arthritis (CDIAREA) in children have been described, but the epidemiology of this complication is poorly understood.

Methods: We performed a descriptive cohort and nested case-control study of CDIAREA in individuals aged 2-20 years using the electronic medical record of two large pediatric care networks from 2004-2013. Cases of CDIAREA were defined as presence of acute arthritis and/or tenosynovitis between ²4 weeks before and ³12 weeks after confirmed, symptomatic CDI with 1) no other apparent cause for arthritis and 2) negative synovial cultures (if obtained). Each case was compared to up to 4 controls with CDI without arthritis/tenosynovitis, randomly selected at the time of CDIAREA diagnosis ±3 months, using conditional logistic regression. Incidence of CDIAREA was calculated based on cases and unaffected children seen as an outpatient in the respective care network within the last 2 years. Attack rate was calculated as cases of CDIAREA per total number of CDIs during the same time period.

Results: We identified 26 cases of CDIAREA during the study period, with an incidence of 5.0 cases per million person-years (95% CI 3.0, 7.8) and an attack rate of 6.4 cases per 1000 CDIs (95% CI 3.6, 10.5). Among cases of CDIAREA, the acute onset of joint symptoms began a median of 11 days (IQR 7, 15) after gastrointestinal symptom onset. CDIAREA typically involved multiple joints (median 5, IQR 3, 8) in migratory fashion (77%), most commonly the hip and knee (Figure). About half of children with CDIAREA had fever (58%) or rash (54%). Among those with CDIAREA, 5 (19%) were treated for a presumed septic hip arthritis even though all had negative synovial cultures. All cases with CDIAREA and presumed septic hip arthritis had post-antibiotic diarrhea and/or other joints affected before surgical drainage. Not including those with hospital-onset CDI, cases with CDIAREA were more commonly treated in the emergency room and/or hospitalized (P=0.02), despite having fewer comorbidities and more community-onset CDI (Table). Treating providers made a diagnosis of CDIAREA in only 36% of cases (95% CI 18%, 57%).

Conclusion: CDIAREA is an acute, under-recognized, potentially morbid reactive arthritis associated with *C. difficile* infection that is often confused with septic arthritis. Better recognition of CDIAREA in children is needed.

Figure. Joint involvement for children with *C. difficile* infection-associated reactive arthritis.

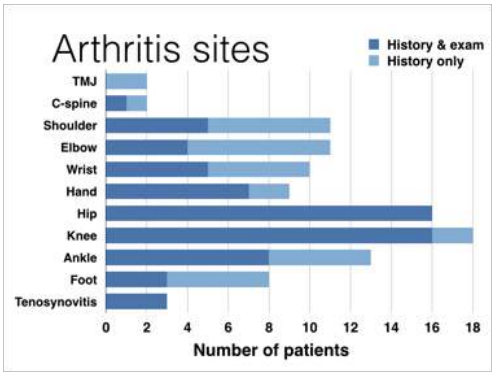

Table. Characteristics of children with *C. difficile* infection-associated reactive arthritis and controls with *C. difficile* infection without arthritis

Characteristic	Cases (N=26)	Controls (N=94)	P-value[a]
Age, median (IQR)	8 (6, 14)	8 (3, 13)	0.28
Female sex, N (%)	13 (50)	45 (48)	0.75
Race, N (%)	19 (73)	68 (72)	0.39[b]
White	3 (12)	18 (19)	
Black	4 (15)	8 (9)	
Other			
Number of medical comorbidities, median (IQR)	0 (0, 1)	1 (1, 2)	0.01
Autoimmune comorbidity, N (%)	3 (12)	16 (17)	0.58
Prior *C. diff* infection, N (%)	1 (4)	10 (11)	0.38
Antibiotic exposure in prior 2 months, N (%)	22 (85)	78 (84)	0.90
Community-onset *C. diff* infection[c], N (%)	26 (100)	69 (74)	0.004[b]
Hospitalized, N (%)	21 (81)	51 (55)	0.02
Hospitalized for *C. diff* symptoms or dehydration	6 (23)	27 (29)	0.77
Hospitalized for arthritis	17 (65)	0	-
Hospitalized for other reason	0	24 (36)	-
Seen in emergency room and/or hospitalized (any reason)	24 (92)	60 (64)	0.02
Seen in emergency room and/or acutely hospitalized for *C. diff* infection-related illness[d], N (%)	24 (92)	36 (38)	0.001

[a] P-values were obtained from conditional logistic regression model.

[b] P-value signifies overall chi-square.

[c] Symptom onset outside of the hospital or before hospital day 3.

[d] Hospitalization for abdominal symptoms, dehydration, or arthritis, not including prior hospitalization leading to hospital-associated *C. difficile* infection.

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Abstract Number: 1451

Neurologic Findings and Serial Neuroimaging in Patients with Linear Scleroderma En Coup De Sabre (ECDS) and Parry-Romberg Syndrome (PRS)

Rebecca Prengler[1], Stephanie Morris[1], Soe Mar[1], Andrew J. White[2] and Susan Bayliss[1], [1]St. Louis Children's Hospital, St. Louis, MO,

[2]Washington University, St. Louis Children's Hospital, St. Louis, MO
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Background/Purpose: To describe the evolution of neurologic symptoms and neuroradiologic findings in patients with ECDS and PRS.

Methods: The medical records database at St. Louis Children's Hospital was searched to identify patients diagnosed with "linear scleroderma" who had been evaluated by Rheumatology, Dermatology or Neurology between 1999 and 2015. Each chart was initially reviewed to identify children who had been diagnosed with ECDS or PRS. The resulting charts were then reviewed to characterize skin manifestations, identify associated neurologic symptoms and evaluate for neuroradiologic abnormalities.

Results:

15 patients with ECDS or PRS were identified. Mean age of cutaneous lesion onset was 7.5 years (0-16 years). 14 patients had brain MRI performed, with serial brain MRI available in 7 patients (50%) over an average of 3 years (1-4 years). Of the 14 patients, 6 had abnormal MRI findings which were ipsilateral to the cutaneous lesion in 5 patients. The most common findings were T2/FLAIR white matter hyperintensities (83%). Brain lesions remained stable in 4 patients (80%), while 1 patient had progression in the setting of non-compliance with mycophenolate mofetil, which restabilized with compliance. All patients with abnormal imaging had neurologic symptoms, including migraines (67%), developmental delay (50%), seizures (33%) and facial palsy (17%).

Conclusion: Unilateral and commonly ipsilateral T2/FLAIR white matter hyperintensities were the most common neuroradiologic abnormalities identified. Lesions remained stable or improved over time with treatment. All patients with abnormal imaging had neurologic symptoms. Our results emphasize that patients with ECDS or PRS would benefit from serial neuroimaging, neurocognitive testing and ongoing neurologic follow-up.

Disclosure: R. Prengler, None; **S. Morris**, None; **S. Mar**, None; **A. J. White**, None; **S. Bayliss**, None.

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Abstract Number: 1452

Pauciimmune and Immune Mediated Pulmonary Capillaritis in Children

Jennifer Soares[1,2], Gail Deutsch[2,3], BreAnna Kinghorn[2] and Anne M. Stevens[4], [1]Pediatric Pulmonary and Sleep Division, Seattle Children's Hospital, Seattle, WA, [2]School of Medicine, University of Washington, Seattle, WA, [3]Pathology, Seattle Children's Hospital, Seattle, WA, [4]Seattle Children's Res Inst, Seattle Children's Hospital, Seattle, WA
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Session Time: 9:00AM-11:00AM

Background/Purpose: Immune mediated and pauciimmune pulmonary capillaritis are rare causes of diffuse alveolar hemorrhage and associated childhood diffuse lung disease. As such ideal therapies and prognosis are unknown. The purpose was to review the clinical presentation and outcome in children with pulmonary capillaritis through a single institution review.

Methods: Retrospective review of children with biopsy proven pulmonary capillaritis at our institution between 1995-2015 was performed with case ascertainment through the pathology database and clinical billing queries. A modified Fan Survival-of-Illness score was calculated to measure risk of severe morbidity or death (Calculation measured 0-6; >3 indicates increased risk for severe

morbidity/death from disease).

Results: Of 74 biopsies reviewed, 7 cases of alveolar hemorrhage with capillaritis were identified. Median hematocrit at presentation was 21.7; interquartile range (IQR) of 16.3 and 31.9. Five subjects presented with respiratory symptoms; the other two presented with pallor and/or lethargy. Median age at presentation was 5.2 years (IQR 2.3, 8.2) while median age at follow up was 7.8 years (IQR 4.7,13). The median time between presentation and diagnosis was 0.08 years (0.08, 0.33). The Fan score decreased over the course of treatment in only two subjects. Five of the patients had bilateral opacities detected on chest roenterogram. Five of 6 subjects evaluated by chest computed tomography had ground glass opacities. Only 2 subjects had autoantibodies, leading to diagnoses of microscopic polyangiitis and antiphospholipid antibody syndrome. Five subjects were diagnosed with pauciimmune pulmonary capillaritis. All subjects received systemic steroids. Those with the most severe Fan scores (>3) received escalated therapy regardless of autoantibodies. Two subjects have had multiple relapses requiring hospitalization. Morbidities included restrictive lung disease, cataracts, pulmonary hypertension, sleep disturbance and exercise intolerance. At 0.5-5.8 years of follow up, transplant free survival was 100%.

Conclusion: Unlike other vasculitides, pulmonary capillaritis affected prepubescent males disproportionately. Patients presenting with more severe disease despite absence of disease-associated autoantibodies received escalated therapies including plasmapheresis with improvement. Normal hematocrit at presentation did not preclude the diagnosis of pulmonary capillaritis. Morbidity was moderate with risk of relapse in a subset of patients. Mortality risk appears favorable.

Table 1. Clinical characteristics of patients at diagnosis

Subject	Sex	Age at Diagnosis (years)	Hematocrit %	Bilateral opacities on CXR*	Ground glass opacities on Chest CT*	Autoantibodies	Other significant biopsy findings
1	M	3.4	15.3	Yes	Yes		Deficient growth, lymphoid hyperplasia
2	M	2.3	13.2	Yes	Yes		Pulmonary arteriopathy, deficient growth
3	M	1.9	21.7	Yes	ND*		Pulmonary arteriopathy, deficient growth
4	M	5.2	32.0	Yes	Yes		Lymphoid hyperplasia, remodeling
6	F	6.6	17.3	Yes	Yes		None
8	F	15.8	31.7	No	No	ANCA, ASO, MPO, PR3*	Pulmonary arteriopathy
9	M	10.4	34.9	No	Yes	Cardiolipin, B2 glycoprotein, Lupus anticoagulant	Arterial thrombi
Median		5.2	21.7				
IQR		2.9, 8.5	16.3, 31.9				

*CXR, chest X-ray; CT, Computed Tomography; ANCA, anti-neutrophil cytoplasmic antibody; ASO, Anti-streptolysin O antibody; MPO, myeloperoxidase; ND, Not Done

Table 2. Disease course: Treatment and outcomes

Subject	Fan Score at Presentation	Steroids	Immunosuppressive Therapy*	Rituximab	IVIG** and/or Plasmapheresis	Fan Score at Follow up	Time to last follow up from biopsy (years)
1	1	X	X	-	-	1	2.6
2	1	X	-	-	IVIG	1	0.9
3	5	X	X	-	Both	5	0.7
4	4	X	X	X	Both	2	2.7
6	2	X	-	-	-	1	3.3
8	2	X	X	X	-	2	0.5
9	1	X	X	-	-	1	5.8
Mean	2.29					1.85	
SD	1.6					1.46	
Median							2.6
IQR							0.8, 3

*Immunosuppression included cyclophosphamide, azathioprine, hydroxychloroquine;
**IVIG, intravenous immune globulin

Disclosure: J. Soares, None; **G. Deutsch**, None; **B. Kinghorn**, None; **A. M. Stevens**, None.

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Abstract Number: 1453

Surveillance of Periodic Fever Syndromes in Canada

Paul Dancey[1,2], Susanne Benseler[3], Marco Gattorno[4], Anne K Junker[5], Ronald Laxer[6], Paivi Miettunen[7] and Lesley Ann Turner[8], [1]Health Science Centre, Memorial University of Newfoundland, St Johns, NF, Canada, [2]Pediatrics, Janeway Children's Hospital, St. John's, NF, Canada, [3]Pediatrics/Alberta Children's Hospital, Department of Pediatrics/University of Calgary, Calgary, AB, Canada, [4]Pediatry, G. Gaslini Institute, Genova, Italy, [5]University of British Columbia, Vancouver, BC, Canada, [6]The Hospital for Sick Children, Toronto, ON, Canada, [7]University of Calgary, Calgary, AB, Canada, [8]Memorial University, St. John's, NF, Canada
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Session Time: 9:00AM-11:00AM

Background/Purpose: To estimate the incidence of periodic fever syndromes in the Canadian paediatric population, to describe the patterns of presentation, and to raise awareness in the medical community.

Methods: This study was initiated through the Canadian Paediatric Surveillance Program (CPSP), and was carried out over a three year period ending in September 2014. The case definition included patients less than 18 years of age presenting with a newly diagnosed periodic fever syndrome (PFS). Conditions under surveillance included Familial Mediterranean fever (FMF), Tumor necrosis factor receptor-associated periodic syndrome (TRAPS), Hyperimmunoglobulin D syndrome (HIDS), cryopyrin-associated periodic syndromes (CAPS), Periodic fever, aphthous stomatitis, pharyngitis, and adenitis (PFAPA), and Undefined periodic fever syndromes. The study protocol outlined established clinical and/or genetic criteria for diagnosis. Participating pediatricians and pediatric subspecialists across the country were sent monthly reporting forms. Detailed questionnaires were completed by physicians who report a recent diagnosis. Submissions were screened for accuracy and confirmed cases then entered into a database.

Results: Between September 2011 and August 2014 a total of 221 cases of PFS were reported. Detailed questionnaires were completed on 192 (87%), from which 13 were excluded. Of the 179 confirmed cases, 84 (47%) were PFAPA, 72 (40%) were undefined PFS, 17 (10%) were FMF, and the remaining 6 cases were CAPS, TRAPS, and HIDS. The mean age at diagnosis was 5.5 years (range 12 months - 16 years). On average symptom onset occurred 2.5 years before diagnosis (range 1-4 years). The majority of reporting physicians were rheumatologists (58%), and paediatricians (36%). Cases were identified in all provinces across Canada with the majority (103, 58%) from Ontario. For the 72 undefined PFS cases the reporting physicians described 36% as PFAPA-like, 10% FMF-like, 5% HIDS-like, 4% CAPS-like, and 1% TRAPS-like. Such cases had features of the specified PFS but either did not meet the full criteria, or confirmatory tests were not available at the time of reporting. Among all cases reported in the study, 58% had genetic testing completed as part of their diagnosis. The majority of cases without any genetic testing had been diagnosed as PFAPA.

Conclusion: Periodic fever syndromes represent rare forms of autoinflammatory disease, which affect many Canadian children. This CPSP study identified that the most common PFS diagnosed was PFAPA followed by undefined PFS and FMF. CAPS, HIDS, and TRAPS were rarely diagnosed. Children with PFS were seen by multiple physicians over an average of two to three years before a diagnosis was made. It is hoped that increased awareness of these rare conditions will facilitate earlier diagnosis and the initiation of effective treatments for these children.

Disclosure: P. Dancey, None; **S. Benseler**, None; **M. Gattorno**, None; **A. K. Junker**, None; **R. Laxer**, None; **P. Miettunen**, None; **L. A. Turner**, None.

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Abstract Number: 1454

Familial Mediterranean Fever in Childhood: a Single Center Experience

Kenan Barut[1], Ada Bulut Sinoplu[2], Gozde Yucel[3], Gizem Pamuk[2], Amra Adrovic[4], Sezgin Sahin[4] and **Ozgur Kasapcopur**[5], [1]Department of Pediatric Rheumatology, Cerrahpasa Medical School, Istanbul University., Fellow in Pediatric Rheumatology, Istanbul, Turkey, [2]Department of Pediatric Rheumatology, Cerrahpaşa Medical School, Istanbul University., Resident in Pediatrics, Istanbul, Turkey, [3]Department of Pediatric Rheumatology, CerrahpaÅŸa Medical School, Istanbul University., Resident in Pediatrics, Istanbul, Turkey, [4]Department of Pediatric Rheumatology, Cerrahpaşa Medical School, Istanbul University., Fellow in Pediatric Rheumatology, Istanbul, Turkey, [5]Istanbul University, Cerrahpasa Medical School, Department of Pediatric Rheumatology, Professor of Pediatric Rheumatology, Istanbul, Turkey

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Background/Purpose: Familial Mediterranean fever (FMF) is an autosomal recessively inherited autoinflammatory disease which is clinically manifested with periodic episodes of fever, polyserositis and arthritis. The severity of the disease depends mostly on the MEFV gene mutation variations. The objective of this study is to reveal a single center follow-up experience of a wide amount of childhood FMF patients from different regions around Turkey in terms of the demographic and clinical features, the genetic diversity and treatment response.

Methods: 708 children diagnosed with FMF and under treatment of colchicine for at least 6 months that are seen out patiently in our Pediatric Rheumatology Clinic between November 2014 and March 2015 were reviewed retrospectively with the data based on the patient records and also taken from the parents.

Results:

708 patients consisting 362 males and 246 females that are diagnosed with FMF were included in the study. The mean age of the patients by the time of the study was found to be 12,3±4,4 years, while the mean age at the onset of the disease was 4,8±3,4 years and at diagnosis was 7,3±3,8 years. The consanguinity rate was resulted to be %29,2 and positive family history was detected in 370 (52,3%) patients.

In 634 (89,5%) of patients, episodes of abdominal pain for at least 6 hours due to peritonitis; in 629, (88.8%) periods of fever for at least 12 hours and in 122(17,2%), chest pain probably due to pleuritis was found. 213 (30,1%) patients experienced erysipelas like erythema and 288 (40,7%) were diagnosed with findings of arthritis that last for at least a day. In 467 (66%) cases exertional leg pain and in 29(4,1%) myalgia are among the complaints and enthesitis was reported in 26(3,7%) patients. Pericarditis was developed only in 2(0,3%) patients. The mean duration of the attack was found to be 64,8±38,5 hours. In 38(53,4%) patients with appendectomy was performed due to unresolved episodes of abdominal pain.

The patients were investigated about the MEFV gene mutations and M694V homozygote mutation was found in 154(21,8%) and M694V heterozygote in 141 (19,8%) children. All the other mutations in exon 10 region (M680I, V726A, M694I) in a compound heterozygous manner with M694V mutation were detected to be in 90 (12,7%) cases and the rate of patients that is a carrier of only one copy of exon 10 region mutations other than M694V was 13%. The rest of the mutations (in exon 2,3,5 regions) were revealed in 45 (6,4%) children. In 45 (6,4%) of patients none of the so far known main mutations were shown.

Amyloidosis had been developed only in two cases both of whom were suffering from the disease process for at least 10 years and showing defective compliance to the colchicine treatment. One of them was a 20 years old M694V homozygote mutation carrier and the other was happened to be compound heterozygous with M694V/M680I mutations.

Conclusion:

The diagnosis of childhood FMF is frequently encountered in our country. The most severe clinical presentation occurs as a result of M694V and other exon 10 region mutations. With the absolute compliance to treatment; the episodes disappear and amyloidosis, the most dreadful complication of the disease, can be prevented.

Disclosure: K. Barut, None; **A. B. Sinoplu**, None; **G. Yucel**, None; **G. Pamuk**, None; **A. Adrovic**, None; **S. Sahin**, None; **O. Kasapcopur**, None.

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Abstract Number: 1455

Juvenile Spondyloarthropathies: a Single Center Experience

Kenan Barut[1], Metin Sezen[2], Sezgin Sahin[3], Amra Adrovic[3], Serdal Ugurlu[4], Huri Ozdogan[5] and **Ozgur Kasapcopur**[6], [1]Department of Pediatric Rheumatology, Cerrahpasa Medical School, Istanbul University., Fellow in Pediatric Rheumatology, Istanbul, Turkey, [2]Pediatric Rheumatology, Istanbul University, Cerrahpasa Medical Faculty, Istanbul, Turkey, [3]Department of Pediatric Rheumatology, Cerrahpaşa Medical School, Istanbul University., Fellow in Pediatric Rheumatology, Istanbul, Turkey, [4]Istanbul University, Cerrahpasa Faculty of Medicine, Istanbul, Turkey, [5]Division of Rheumatology, Department of Internal Medicine, Cerrahpasa Medical Faculty, University of Istanbul, Istanbul, Turkey, [6]Istanbul University, Cerrahpasa Medical School, Department of Pediatric Rheumatology, Professor of Pediatric Rheumatology, Istanbul, Turkey

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Background/Purpose: : Juvenile spondyloarthropathies (JSpA) are a group of chronic childhood rheumatic diseases which emerge especially before 16 and after 6 years-old. While enthesitis and oligoarthritis are the major signs of the early period, axial skeletal involvement and sacroiliitis are the late period signs. Although the diagnosis of the spondyloarthropathy is easy in adults, it is quite difficult in children. The aim of the study to determine clinical and demographical features of the JSpA cases that is followed-up in our department, and to evaluate treatment modalities and long term complications of disease together with the side effects of the drugs.

Methods: 107 children (21 female, 86 male) that admitted to our clinic with the diagnosis of JSpA between January 2005-December 2014 were involved in our study. Enthesitis related arthritis and Juvenile Ankylosing Spondylitis were included under the topic of JSpA. Clinical and laboratory variables were obtained from patient records.

Results: While the mean age of the disease onset and diagnosis were 11,4±3 years (range 3 -17 years) and 12,4±2,8 years (range 5-18 years) respectively, the mean duration of follow-up period was 2,7±2,5 years (range 2 months-12 years). Lower extremity arthritis (n=83, 77,6%), hip pain (n=63, 58,9%) and inflammatory low back pain (n=47, 43,9%) were the major clinical findings. The most seen involvement of the lower extremity was ankle joint arthritis (n=60, 72,3%) followed by enthesitis (n=76, 71%) and tarsitis (n=30, 28%). Axial skeletal involvement was noted in 57% (n=61) of patients and mean inflammatory low back pain duration was 8,3±6,9 months (range 1-24 months). Magnetic resonance imaging could be studied in 77 patients (72%) that imaging results of 52 children (48,6 %) were consistent with sacroiliitis. Lumbar movement limitation in Schober's test was seen in 42 cases (39.3%). Family history of spondylitis in 29 children (27.1%) and familial Mediterranean fever (FMF) in 4 cases. Furthermore, 5 patients diagnosed as FMF and treated with colchicine. None of the family history were consistent with inflammatory bowel disease. Uveitis was seen in 11 children (10.3). HLA-B27 was positive in 73.8 % (n=79) of the patients. First line therapies were methotrexate in 51 patients (47.5%) and sulphasalazine in 40 cases (37.4%). Anti-TNF alpha agents were used in 51 patients (47,7%) that were resistant to first line therapy. In the last medical visits we evaluated the patients in the terms of treatment modalities; 60.7% (n=65) of cases were noted as using drugs and in remission, 12.1% (n=13) gave up drugs and in remission, 16.8% (n=18) as minimally active and 6,5% (n=7) as active.

Conclusion: Initial signs of JSpA are usually lower extremity arthritis and enthesitis in children that is quite different from adults. JSpA should be strongly suspected in the case of a boy that is older than 6 years-old with lower extremity arthritis and the family history of spondyloarthropathy. Afterwards, axial skeletal evaluation must be investigated immediately and in order to prevent this complication true and efficient therapy must be started. FMF should be kept in mind in the differential diagnosis of JSpA in our country.

Disclosure: K. Barut, None; **M. Sezen**, None; **S. Sahin**, None; **A. Adrovic**, None; **S. Ugurlu**, None; **H. Ozdogan**, None; **O. Kasapcopur**, None.

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Abstract Number: 1456

Macrophage Activation Syndrome and Familial Hemophagocytic Lymphohistiocytosis: Is Their Clinical Phenotype Really Similar?

Francesca Minoia[1], AnnaCarin Horne[2], Sergio Davì[1], Francesca Bovis[1], Silvia Rosina[1], Kai Lehmberg[3], Sheila Weitzman[4], Antonella Insalaco[5], Carine Wouters[6], Susan Shenoi[7], Graciela Espada[8], Seza Ozen[9], Jordi Anton[10], Raju Khubchandani[11], Ricardo Russo[12], Nicolino Ruperto[13], Alberto Martini[1], Randy Q. Cron[14] and Angelo Ravelli[1], [1]Istituto Giannina Gaslini, Genoa, Italy, [2]Karolinska University Hospital Solna, Stockholm, Sweden, [3]University Medical Center, Hamburg, Germany, [4]The Hospital for Sick Children, Toronto, ON, Canada, [5]Ospedale Pediatrico Bambino Gesù, Rome, Italy, [6]University Hospital Gasthuisberg, Leuven, Belgium, [7]Seattle Children's Hospital, Seattle, WA, [8]Hospital de Ninos Ricardo Gutierrez, Buenos Aires, Argentina, [9]Hacettepe University, Ankara, Turkey, [10]Unitat de Reumatologia Pediàtrica, Hospital Sant Joan de Déu, Barcelona, Spain, [11]Jaslok Hospital and Research Center, Mumbai, India, [12]Hospital de Pediatria Garrahan, Buenos Aires, Argentina, [13]Istituto G. Gaslini, Pediatria II, PRINTO, Genoa, Italy, [14]University of Alabama at Birmingham, Birmingham, AL

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Diseases

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Background/Purpose: Macrophage activations syndrome (MAS) is a potentially life-threatening complication of systemic juvenile idiopathic arthritis (sJIA). It is common view that sJIA associated MAS bears a close clinical resemblance to the group of hemophagocytic lymphohistiocytosis (HLH), including familial HLH (FHL). This has led to suggest the use of the HLH-2004 guidelines to diagnose MAS in sJIA. However, MAS develops in the context of an underlying highly inflammatory condition, whereas FHL is a primary disorder with genetic basis. It is thus conceivable that some differences exist in the clinical expression and severity of the two conditions. However, their clinical picture has previously been compared only in small studies. The aim of our study was to compare the demographic, clinical, laboratory and histopathologic features of sJIA-associated MAS and FHL.

Methods : Data on sJIA associated MAS were collected by both pediatric rheumatologists and pediatric hemato-oncologists in a large multinational collaborative effort. Data on FHL patients were gathered from the HLH-94 and HLH-2004 trials. Clinical and laboratory features at disease onset were compared between by means of Mann-Whitney U test or chi-square/Fisher exact test, as appropriate.

Results : A total of 620 patients were enrolled: 362 (58.4%) sJIA-associated MAS and 258 (41.6%) FHL. The main differences in demographic, clinical, laboratory and histopathologic features between the two patient groups are presented in Table 1.

	sJIA-associated MAS (n = 362)	FHL (n = 258)	p value
Median age, yr	8.1	0.3	<.0001
Female, n (%)	208 (57.5)	128 (49.6)	0.05
Fever, n (%)	341/355 (96.1)	236/257 (91.8)	0.03
Lymphadenopathy, n (%)	178/346 (51.4)	28/110 (25.5)	<.0001
Hepatomegaly, n (%)	245/ 350 (70.0)	234/254 (92.1)	<.0001
Splenomegaly, n (%)	201/347 (57.9)	142/248 (96.2)	<.0001
CNS involvement, n (%)	122/349 (35.0)	89/253 (35.2)	0.96
Jaundice, n (%)	49/351 (14.0)	35/99 (35.4)	<.0001
Median laboratory values at onset			
Hemoglobin, g/dl	9.8	7.3	<.0001
Neutrophil count, x 10^3/l	5.4	0.6	<.0001
Platelet count, x 10^9/l	144	29	<.0001
Aspartate aminotransferase, U/l	134	171	0.01
Lactate dehydrogenase (LDH), U/l	1,203	696	<.0001
Triglycerides, mg/dl	234	325	<.0001
Fibrinogen, mg/dl	267	98	<.0001
Ferritin, ng/ml	5,352	2,919	0.003
Patients with hemophagocytosis	159/252 (63.1)	178/236 (75.4)	0.003

Conclusion : Although MAS and FHL showed similar clinical features and laboratory abnormalities, the frequency of most clinical manifestations and the severity and trend of laboratory changes were different. FHL patients had greater frequency of hepatosplenomegaly and more profound cytopenia, hypofibrinogenemia and hypertransaminasemia, whereas MAS patients had higher levels of ferritin and LDH. The prevalence of CNS disease was comparable between the two groups. Hemophagocytosis was detected more commonly in FHL. The observed differences suggest the use of different diagnostic criteria for the two conditions.

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Abstract Number: 1457

An Organ Based Diagnostic Approach to Macrophage Activating Syndrome in Children Demonstrates Impaired Reticuloendothelial System Clearance

King Soon Goh[1], Francesca Minoia[2], Angelo Ravelli[2], Randy Q. Cron[3] and Bita Shakoory[4], [1]Rheumatology, Temple University Hospital, Philadelphia, PA, [2]Istituto Giannina Gaslini, Genoa, Italy, [3]University of Alabama at Birmingham, Birmingham, AL, [4]Rheumatology, George Washington University, Washington, DC

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Background/Purpose:

Early recognition and treatment of Macrophage Activating Syndrome (MAS) can improve outcome. Various diagnostic criteria are available to optimize the diagnosis if suspected by the treating physicians. However, low index of suspicion and the non-specific nature of the criteria can present a barrier to prompt and early recognition. This study utilizes an established MAS dataset in a cohort of systemic juvenile idiopathic arthritis (sJIA) patients to determine organ based predictors of MAS by admitting physicians for early recognition.

Methods:

The data from international multicenter cohort of MAS (Minoia et. al. Arthritis Rheumatol. 2014; 66:3160-9) was used. Retrospective data was collected from 95 investigators in 33 countries, including 362 patients with sJIA with MAS, 404 patients with active sJIA without MAS, and 345 patients with systemic infection. The dataset included demographics, clinical, laboratory, and histopathological variables. Data describing dysfunction in heart, lung, and kidney function; elevations in serum ferritin and triglyceride (TG) levels were defined as > 3,000 ng/dL, and 250 mg/dL, respectively. Other organ dysfunctions were defined as below:

- Coagulopathy: fibrinogen level <100 mg/dL, platelet count <40,000 /mm^3, d-dimers >2-times the upper normal value.
- Hepatobiliary dysfunction (HBD): liver enzyme elevation at least 3-times the upper normal value or bilirubin > 5.8 mg/dL.
- Hematological dysfunction: counts below normal limits, or 50% reduction in hemoglobin or leukocytes.

Univariate and multivariate statistical analyses were performed to identify correlates of MAS, and entered into a logistic regression model to assess independent predictors of MAS.

Results:

A total of 1,111 patients were included. Despite the statistically significant association in Univariate analysis, logistic regression did not identify a meaningful association with kidney, lung, or cardiovascular system (CVS) dysfunction (Table-1). Six independent parameters strongly correlates with MAS includes: central nervous system dysfunction (CNS), HBD dysfunction, coagulopathy, hematologic dysfunction, elevated ferritin and TG. Presence of 2 out of these 6 parameters was considered suggestive of MAS and 3 out of these 6 parameters was found to be confirmatory.

Conclusion:

MAS is associated with dysfunctional reticuloendothelial clearance, manifesting as CNS, hematologic, hepatobiliary, and coagulation dysfunction, with high levels of ferritin and TG. Presence of MAS should be suspected when at least 2 of the 6 parameters are noted, which should prompt further investigation and early identification.

Table 1: Univariate and multivariate analyses show CNS dysfunction, HBD, coagulopathy, hematologic dysfunction, ferritin and TG as strongest independent parameters in predicting MAS.

	MAS (n=362) N(%)	Non-MAS (n=744) N(%)	Odds Ratio (95% CI)	P Value
Kidney	54 (15.3)	22 (2.95)	5.9 (3.5-9.9)	**<0.0001**
Lung	77 (21.9)	86 (11.5)	2.1 (1.5-3.0)	**<0.0001**
CVS	90 (25.5)	64 (8.6)	3.6 (2.6-5.2)	**<0.0001**
CNS	122 (34.9)	41 (5.5)	**9.2 (6.3-13.5)**	**<0.0001**
HBD	157 (43.4)	34 (4.5)	**16.1 (10.8-24.1)**	**<0.0001**
Coagulopathy	111 (30.7)	24 (3.2)	**13.4 (8.4-21.2)**	**<0.0001**
Hematologic	136 (37.6)	13 (1.7)	**34.1 (18.9-61.3)**	**<0.0001**
High TG >250	213 (58.8)	50 (6.7)	**19.9 (14-28.5)**	**<0.0001**
High Ferritin >3000	220 (60.8)	47l (6.3)	**23.1 (16.1-33.2)**	**<0.0001**

MAS: macrophage activation syndrome; CVS: cardiovascular system; CNS: central nervous system; HBD: hepatobiliary dysfunction; TG: triglycerides.

Table 2: diagnostic properties of predictors of MAS with sensitivity, specificity, positive predictive value, negative predictive value and accuracy, respectively.

Score	Sensitivity (%)	Specificity (%)	Positive PV (%)	Negative PV (%)	Accuracy (%)
1	94.3	76.7	65.5	96.6	82.3
2	77.4	**96.1**	**90.3**	**90.1**	**90.1**
3	49.9	**99.3**	**97.2**	80.9	83.5
4	29.8	**99.9**	**99**	75.2	77.5
5	11.5	**100**	**100**	70.7	71.7
6	2.0	**100**	**100**	68.5	68.7

MAS: macrophage activation syndrome; PV: predictive value

Disclosure: K. S. Goh, None; **F. Minoia**, None; **A. Ravelli**, None; **R. Q. Cron**, None; **B. Shakoory**, None.

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Abstract Number: 1458

Association of Chronic, Extreme Elevation of Serum IL-18 with the Development of Macrophage Activation Syndrome in a Cohort of Autoinflammatory Disease Patients: A Potential Diagnostic Biomarker?

Scott Canna[1], Adriana Almeida de Jesus[2], Yan Huang[3], Sushanth Gouni[1], Guangpu Shi[4], Igal Gery[4] and Raphaela Goldbach-Mansky[3], [1]Molecular Immunology and Inflammation Branch, NIAMS/NIH, Bethesda, MD, [2]Translational Autoinflammatory Disease Section, National Institute of Arthritis and Musculoskeletal and Skin Diseases, NIH, Bethesda, MD, [3]Translational Autoinflammatory Diseases Section, National Institute of Arthritis and Musculoskeletal and Skin Diseases, NIH, Bethesda, MD, [4]National Eye Institute/NIH, Bethesda, MD

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Background/Purpose: Macrophage Activation Syndrome (MAS) is a life-threatening systemic inflammatory syndrome that complicates several rheumatic diseases. Current MAS-related serum biomarkers (ferritin, neopterin, CD163, and CD25) mark active disease but normalize with quiescence and may lack specificity. Serum IL-18 elevation has been associated with many inflammatory and infectious diseases, but extremely high levels have been reported in Still's Disease and Systemic Juvenile Idiopathic Arthritis, particularly in patients with a history of MAS.

Methods: We measured serum levels of several cytokines across a complex cohort of patients with idiopathic or genetically-defined autoinflammatory diseases (NCT00059748). Samples were obtained from healthy adults (24 patients) and children (4), and patients with cryopyrinopathies (Neonatal Onset Multisystem Inflammatory Disease/NOMID (18) and Muckle-Wells Syndrome (1)), NLRC4-MAS (2), Non-infectious Osteomyelitis (3), Deficiency of IL-1 Receptor Antagonist (3), CANDLE (Chronic Atypical Neutrophilic Dermatosis with Lipodystrophy and Elevated Temperature (3), SAVI (STING-Associated Vasculopathy with onset in Infancy (2), XIAP-deficiency (2) and undifferentiated (11). Cytokines were measured by Bio-Plex Luminex technology, except IL-37 (adipogene) and IL-18BP (R&D systems).

Results: We examined 142 samples from 27 controls and 49 patients. Of these patients, 13 had a clinical history of one to 4 episodes of MAS (as determined by the investigators based on the criteria established by *Ravelli et al.*, J. Pediatr. 2005). Serum levels for total active IL-18, IL-18 binding protein (BP), and IL37 in healthy controls were 29-308, 3648-7889, and 40-505 pg/mL, respectively. Median serum IL-18 was 8773 (Interquartile Range (IQR) 1560-13581) pg/mL in patients with a history of MAS, and 176 (IQR 88-432) pg/mL in those without ($p<0.0001$, Mann-Whitney-U-test). Serum IL-18 levels did not correlate with disease activity or treatment, but stratified patients into normal, elevated (~10x normal), or extremely elevated (~100x normal) groups, with 12 of 13 MAS patients in the highest group. Levels of IL-18BP and IL-37, anti-inflammatory cytokines known to inhibit the bioactivity of IL-18 did not correlate with total IL-18. Interestingly, a patient with clinical NOMID but no *NLRP3* mutation developed recurrent MAS and was our only cryopyrinopathy patient with chronically highly elevated IL-18 levels.

Conclusion: Extraordinary serum IL-18 elevation, even during quiescence, is associated with a clinical history of MAS. The utility of this

biomarker in predicting MAS risk needs to be tested prospectively in patients at risk for developing MAS.

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Abstract Number: 1459

Racial Comparisons of Children with Idiopathic Uveitis: Results from the Childhood Arthritis and Rheumatology Research Alliance (CARRA) Registry

Sheila T. Angeles-Han[1,2,3], Curtis Travers[3], Mindy S. Lo[4], C. Egla Rabinovich[5], Sampath Prahalad[6] and and CARRA Registry Investigators, [1]Children's Healthcare of Atlanta, Atlanta, GA, [2]Ophthalmology, Emory University School of Medicine, Atlanta, GA, [3]Pediatrics, Emory University School of Medicine, Atlanta, GA, [4]Medicine/Immunology, Children's Hospital Boston, Boston, MA, [5]Duke University Medical Center, Durham, NC, [6]Emory University School of Medicine and Children's Healthcare of Atlanta, Atlanta, GA

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Background/Purpose: Childhood uveitis can lead to poor visual outcomes. Our data from single center studies suggests that non-Hispanic African American children (NHB) with non-inflammatory uveitis have increased ocular complications, and that African American race is a predictor of vision loss and blindness. Our aim is to characterize the epidemiology and clinical course of non-Hispanic White (NHW) and NHB children with idiopathic uveitis in the CARRA Registry.

Methods: There were 65 NHW and 11 NHB children with idiopathic uveitis enrolled in the CARRA Registry. Demographic and uveitis-related data were collected from time of diagnosis to enrollment. We compared clinical characteristics of NHB and NHW children using 2 sample t-tests and chi-square tests. Logistic regression was used to model risk factors for vision loss.

Results: The 11 (14.5%) NHB children had a mean age of uveitis onset of 8.4 ± 3.0 years, 6 (55%) were female, and 3 (30%) were ANA positive (Table 1). Uveitis was primarily anterior in location (73%) and bilateral (82%). Ocular complications were common (64%): cataracts (36%), increased intraocular pressure (27%), posterior synechiae (27%) and keratic precipitates (27%). Uncorrected abnormal or blind vision was reported in the right eye in 86%, and in 71% in the left eye.

Comparing NHW and NHB children (Table 1), there were no significant differences in gender, smoking exposure, ANA positivity, age of uveitis onset, location of uveitis, laterality, or presence and type of ocular complications. There were also no differences in insurance status, age at first rheumatology visit, or time to first rheumatology visit from disease onset. Medication use was similar except for increased use of oral methotrexate in NHW (p=0.003). There was a trend towards increased vision loss or blindness in NHB children overall, but this was only statistically significant in the right eye for uncorrected vision (85.7% vs. 36.4%, p = 0.034). This may be secondary to our sample size or to one eye being most affected. On logistic regression analysis, NHB race was a significant predictor of vision loss in the right eye (OR = 10.5, (95% CI 1.16-95.11). This was not significant in the left eye (OR = 3.61, (95% CI 0.63 – 20.71).

Conclusion: In the CARRA registry, 14% of children with idiopathic uveitis were NHB. The odds of developing vision loss were 10.5 times greater in NHB children compared to NHW. Although the numbers of NHB children in this registry are small, these results support our previous findings of racial differences in the visual outcomes of children with uveitis. This highlights the need for further exploration of the impact of race in a racially diverse cohort.

Table 1. Comparison of Non-Hispanic White and Black Children with Idiopathic Uveitis

Characteristics N = 76 unless otherwise specified N (%) unless otherwise specified	**Overall** **N = 76**	**Non-Hispanic whites** **N = 65**	**Non-Hispanic Blacks** **N = 11**	**p-value**
Demographics				
Age at baseline visit, *mean ± sd*	11.9 ± 3.7	11.9 ± 3.8	11.8 ± 3.7	0.929
Female	39 (51.3%)	33 (50.8%)	6 (54.6%)	1.00
Insured (N = 75)	74 (98.7%)	63 (98.4%)	11 (100.0%)	1.00
Smoker (N = 61)	3 (4.9%)	3 (5.5%)	0 (0.0%)	1.00
Smoking in Household (N = 38)	7 (18.4%)	5 (15.2%)	2 (40.0%)	0.223
Disease Characteristics				
Age at onset (years) (N = 74), *mean ± sd*	8.5 ± 3.6	8.5 ± 3.7	8.4 ± 3.0	0.900
Duration of uveitis (years) (N = 74), *mean ± sd*	3.5 ± 2.6	3.6 ± 2.7	2.8 ± 2.5	0.367
Age at 1st rheum visit (years) (N = 74), *mean ± sd*	9.2 ± 3.5	9.2 ± 3.6	9.1 ± 2.7	0.929
Time to 1st rheum visit (years) (N = 74), *mean ± sd*	0.7 ± 1.0	0.7 ± 1.1	0.7 ± 0.5	0.892
ANA, Positive (N = 61)	25 (41.0%)	22 (43.1%)	3 (30.0%)	0.505
Location				
Anterior	49 (64.5%)	41 (63.1%)	8 (72.7%)	0.936
Intermediate	11 (14.5%)	10 (15.4%)	1 (9.1%)	
Posterior	3 (3.9%)	3 (4.6%)	0 (0.0%)	
Panuveitis	13 (17.1%)	11 (16.9%)	2 (18.2%)	
Bilateral involvement	56 (73.7%)	47 (72.3%)	9 (81.8%)	0.717
Length of Current Episode				
In Remission	36 (47.4%)	32 (49.2%)	4 (36.4%)	0.244
< 3 months	9 (11.8%)	6 (9.2%)	3 (27.3%)	
> 3 months	31 (40.8%)	27 (41.5%)	4 (36.4%)	
Right Eye Uncorrected, Abnormal/Blind, (N = 51)	22 (43.1%)	16 (36.4%)	6 (85.7%)	0.034*
Right Eye Corrected, Abnormal/Blind, (N = 41)	7 (17.1%)	5 (13.9%)	2 (40.0%)	0.196
Left Eye Uncorrected, Abnormal/Blind, (N = 51)	23 (45.1%)	18 (40.9%)	5 (71.4%)	0.222
Left Eye Corrected, Abnormal/Blind, (N = 42)	6 (14.3%)	5 (13.5%)	1 (20.0%)	1.00
Ocular Complications	57 (75%)	50 (76.9%)	7 (63.6%)	0.496
Increased Intraocular Pressure	27 (35.5%)	24 (36.9%)	3 (27.3%)	0.737
Cataracts	25 (32.9%)	21 (32.3%)	4 (36.4%)	1.00
Posterior Synechiae	18 (23.7%)	15 (23.1%)	3 (27.3%)	1.00
Band Keratopathy	14 (18.4%)	12 (18.5%)	2 (18.2%)	1.00
Macular Edema	13 (17.1%)	13 (20.0%)	0 (0.0%)	0.194
Keratic Precipitates	11 (14.5%)	8 (12.3%)	3 (27.3%)	0.349
Medication Use, Ever				
Topical Steroid Drops (N = 72)	68 (94.4%)	59 (95.2%)	9 (90.0%)	1.00
Methotrexate Oral (N = 65)	38 (58.4%)	37 (66.1%)	1 (11.1%)	0.003*
Methotrexate Subcutaneous (N = 65)	41 (63.1%)	33 (58.9%)	8 (88.9%)	0.137
Biologics (N = 76)	40 (52.6%)	34 (52.3%)	6 (54.6%)	1.00
Infliximab (N = 40)	25 (62.5%)	22 (64.7%)	3 (50.0%)	0.654
Adalimumab (N = 40)	18 (45.0%)	15 (44.2%)	3 (50.0%)	1.00
**p <0.05*				

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Abstract Number: 1460

Association of Vitamin D Receptor Polymorphism with Juvenile Idiopathic Arthritis (JIA)

Fernanda Falcini[1,2], Francesca Marini[3], Stefano Stagi[4], Gemma Lepri[2], Donato Rigante[5], Marco Matucci-Cerinic[2] and M. L. Brandi[3], [1]Department of Internal Medicine, Rheumatology Section, Transition Clinic, University of Florence, Firenze, Italy, [2]Department of Internal Medicine, Rheumatology Section, Transition Clinic, University of Florence, Italy, Florence, Italy, [3]University of Florence, Dept. of Surgery and Translational Medicine, Florence, Italy, [4]Pediatric Endocrinology Unit, Anna Meyer Children's Hospital, University of Florence, Pediatric Endocrinology Unit, Anna Meyer Children's Hospital, Firenze, Italy, [5]Istitute of Pediatrics, Università Cattolica del Sacro Cuore, Rome, Italy

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Background/Purpose: JIA is the most common chronic arthritis of childhood. Vitamin D is a potential immuno-modulator in many conditions, including autoimmune diseases. Its influence in JIA is still unclear. Specific polymorphisms of vitamin D receptor gene (*VDR*) have recently been associated with different biologic responses to vitamin D itself.

Methods: 90 Italian children, adolescents and young adults with poli- or oligoarticular onset of JIA were studied. *VDR* polymorphisms were analysed by PCR-based sequencing (*CDX2* in the promoter region) and PCR-based enzymatic digestions (*FokI* in exon 2, *BsmI* and *ApaI* in intron 8, and *TaqI* in exon 9) in the genomic DNA from blood of patients. 2221 healthy Italian unrelated individuals have been used as controls for *VDR* polymorphism frequencies. Distribution of *VDR* polymorphisms has been evaluated in patients *vs* controls, in patients with active and inactive disease, and in patients with poli- or oligoarticular JIA.

Results: The distribution of *FokI*, *BsmI*, and *TaqI* polymorphisms did not show any significant difference between subjects with JIA and controls. Conversely, significant statistical differences in the distribution of *CDX2* and *ApaI* genotypes were found, respectively with the *CDX2* GG genotype (Yates-corrected chi-square 6.56; Odds ratio=1.80; p=0.0104) and the TT *ApaI* genotype (Yates-corrected chi-square 20.97; Odds ratio=2.67; p=0.0000), both more frequent in JIA than in controls. Also the G allele of *CDX2* (Yates-corrected chi-square 6.12; Odds ratio=1.60; p=0.0134) and the T allele of *ApaI* (Yates-corrected chi-square 19.69; Odds ratio=2.05; p=0.0000) was more frequent in JIA. No statistical differences were found for all the analysed *VDR* polymorphisms, between the poliarticular *vs* oligoarticular forms. No significant association was found between *VDR* polymorphisms and active or inactive forms of JIA, neither with osteopenic or normal bone mineral density status.

Conclusion: Pathogenetic mechanisms influencing the predisposition to JIA are poorly elucidated and autoimmune dysfunctions are strongly suspected. This genetic study found a significantly higher frequency of the GG genotype of *VDR CDX2* polymorphism and TT genotype of *VDR ApaI* polymorphism in patients with JIA. The *CDX2*polymorphism is located in the promoter region of the *VDR* gene and has been associated with *VDR* mRNA expression, while the ApaI polymorphism has been associated with the stability of *VDR* mRNA. Therefore, we can speculate that *CDX2* GG genotype and *ApaI* TT genotype can both influence the expression of the VDR protein, presumably resulting in a reduced receptor activity with subsequent decreased response to vitamin D and potential immunity deregulation, favouring the development of JIA. Conversely, *VDR* polymorphisms seem not to have any influence for patients' active or non-active status, both for the oligoarticular and poliarticular form of the disease.

Disclosure: F. Falcini, None; **F. Marini**, None; **S. Stagi**, None; **G. Lepri**, None; **D. Rigante**, None; **M. Matucci-Cerinic**, None; **M. L. Brandi**, None.

Abstract Number: 1461

Inflammatory Bowel Disease in Children with Systemic Juvenile Idiopathic Arthritis

Emily Fox[1], Joyce Hsu[2], Elizabeth Chalom[3,4], Sarah Sertial[5], KT Park[6], Julia F Simard[7], Pierre Quartier[8], Maria Teresa Terreri[9], Kevin Baszis[10], Charlotte Borocco[11], Sampath Prahalad[12], Adam Reinhardt[13], Dieneke Schonenberg[14], Elizabeth D. Mellins[15] and Devy Zisman[16], [1]Pediatric Rheumatology, Stanford, Palo Alto, CA, [2]Pediatric Rheumatology, Stanford University, Palo Alto, CA, [3]Pediatrics, St Barnabas Med Center-ACC, Livingston, NJ, [4]Pediatric Rheumatology, St. Barnabas Medical Center, West Orange, NJ, [5]Children's Hospital of New Jersey, Livingston, NJ, [6]Division of Gastroenterology, Stanford University School of Medicine, Stanford, CA, [7]Division of Epidemiology, Health Research and Policy Department, and Division of Immunology & Rheumatology, Department of Medicine, Stanford School of Medicine, Stanford, CA, [8]Hôpital Necker-Enfants Malades, Paris, France, [9]Pediatrics, Universidade Federal de Sao Paulo, São Paulo, Brazil, [10]Pediatrics, Division of Rheumatology, Washington University School of Medicine, St. Louis Children's Hospital, St. Louis, MO, [11]Necker Hospital for Sick Children, Paris, France, [12]Emory University School of Medicine and Children's Healthcare of Atlanta, Atlanta, GA, [13]Faculty of Physicians of the University of Nebraska Medical Center, College of Medicine, Nebraska, NE, [14]Department of Pediatric Rheumatology and Immunology, Emma Children's Hospital, Academic Medical Center, Amsterdam, Netherlands, [15]Dept of Pediatrics CCSR, Stanford University Med Ctr, Stanford, CA, [16]Rheumatology Unit, Carmel Medical CenterThe Ruth and Bruce Rappaport Faculty of Medicine, Technion, Israel, Haifa, Israel

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Background/Purpose: Systemic juvenile idiopathic arthritis (sJIA) is an autoinflammatory disease accompanied by systemic symptoms including lymphadenopathy, serositis, and hepatosplenomegaly. Recently, we encountered a patient previously diagnosed with sJIA three years ago who developed hematochezia and weight loss with endocscopy findings consistent with indeterminate colitis, a form of inflammatory bowel disease (IBD). This association is scantly known with only one case report detected in the literature search.

Methods: We distributed a survey to all members of the Childhood Arthritis and Rheumatology Research Alliance (CARRA) and the Pediatric Rheumatology Bulletin Board asking physicians to report their cases of patients with both sJIA and IBD. Demographic, clinical, laboratory, and therapeutic information were collected on identified patients to gain further insight into this possible association. The data was analyzed, using descriptive statistics, specifically, means, median, and ranges for continuous variables and frequencies and proportions for categorical variables.

Results: Our survey identified 14 patients with diagnoses of sJIA and IBD. 13 of the patients were first diagnosed with sJIA. Five patients were from the United States, 7 from Europe, and 2 from South America. The average age at sJIA diagnosis was 9.9 years (range 6-14.5 years). Nine patients had a persistent sJIA course; 4 patients had a monocyclic course and 1 patient had a polycyclic course. Prior to their IBD diagnosis, the majority of patients were treated with corticosteroids (79%), NSAIDs (79%), and methotrexate (71%) for sJIA. Seven patients received TNF-α inhibitor (etanercept in 5/7). 7 patients received anti-IL-1 therapy, and 4 patients received an IL-6 inhibitor. The average age of the patients at IBD diagnosis was 12.3 years (range 9-17 years). During the 3 months prior to the IBD diagnosis, 6 patients were in remission, 6 were in an active flare, one had not yet received the sJIA diagnosis, and one answer was missing from the survey. Ten patients were diagnosed with Crohn's disease and 4 with indeterminate colitis. 11/14 patients received a TNF-α inhibitor for IBD, with 10/11 demonstrating a full response to this class of medications. Other medications used in treatment include corticosteroids (57%), methotrexate (36%), azathioprine (43%), oral antibiotics (29%), and enteral formula therapy (36%). After both diagnoses were made in this cohort, 4 patients had quiescence of both sJIA and IBD diseases, 6 experienced an IBD flare with quiescent sJIA disease, 3 patients had a sJIA flare with quiet IBD, and one patient had a flare of both diseases.

Conclusion: IBD morbidity is rare in patients with sJIA. It is most commonly manifest as Crohn's disease with persistent sJIA. Its appearance and flares do not typically correlate with sJIA activity, and the majority of these patients respond to monotherapy with a monoclonal TNF-α inhibitor. The therapeutic implications, however, are notable, given that many children with sJIA with systemic features do not respond to TNF inhibition. The biology underlying the association of these two diseases and their response to therapy is not clear and warrants further study.

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Abstract Number: 1462

Farber Disease: Important Differential Diagnostic Information for JIA and Other Inflammatory Arthritis Phenotypes Is Revealed By Data from the Largest Clinical Cohort to Date

Alexander Solyom[1], Boris Huegle[2], Bo Magnusson[3], Balahan Makay[4], Nur Arslan[5], John Mitchell[6], Pranoot Tanpaiboon[7], Norberto Guelbert[8], Ratna Puri[9], Lawrence Jung[10], Giedre Grigelioniene[11], Karoline Ehlert[12], Michael Beck[13], Calogera Simonaro[14] and Edward Schuchman[15], [1]Pediatrics, University of Pecs, Pecs, Hungary, [2]Pediatric Rheumatology, German Center for Pediatric and Adolescent Rheumatology, Garmisch-Partenkirchen, Germany, [3]Pediatric Rheumatology, Karolinska University Hospital, Stockholm, Sweden, [4]Pediatric Rheumatology, Eylul University, Izmir, Turkey, [5]Eylul University, Izmir, Turkey, [6]Pediatric Endocrinology, Montreal Children's Hospital, Montreal, QC, Canada, [7]Genetics and Metabolism, Children's National Medical Center, Washington, DC, [8]Metabolic Diseases Section, Children's Hospital of Cordoba, Cordoba, Argentina, [9]Medical Genetics, Sir Ganga Ram Hospital, New Delhi, India, [10]Pediatric Rheumatology, Children's National Med Ctr, Washington, DC, [11]Clinical Genetics, Karolinska University Hospital, Stockholm, Sweden, [12]University Medical Center - Greifswald, Greifswald, Germany, [13]Institute of Human Genetics, University Medical Center - Mainz, Mainz, Germany, [14]Genetics and Genomic Sciences, Icahn School of Medicine at Mt. Sinai, New York, NY, [15]Genetics and Genomic Sciences, Icahn School of Medicine at Mount Sinai, New York, NY

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Background/Purpose:

Farber disease (Farber lipogranulomatosis; acid ceramidase deficiency) is a rare lysosomal storage disorder resulting from the inherited deficiency of the enzyme acid ceramidase due to mutations in the ASAH1 gene. Inheritance is autosomal recessive. The enzyme deficiency leads to accumulation of the potent pro-inflammatory and pro-apoptotic lipid substrate, ceramide. This, in turn, induces macrophage-driven inflammation in tissues, including synovitis and lipogranuloma formation. The phenotype generally includes joint swelling, contractures and pain. Farber patients do not usually have organomegaly and none have coarse facial features. The clinical similarity of the moderate Farber phenotypes to polyarticular juvenile idiopathic arthritis (JIA) can lead to misdiagnosis. Differential diagnosis can be made by accounting for progressive symmetric arthritis, presence of subcutaneous nodules, and an unusual, hoarse voice (due to nodule formation on the larynx) in Farber disease patients.

Methods: A cohort of 19 Farber disease patients who have not undergone hematopoietic stem cell transplantation (HSCT) provides insight into the phenotypic spectrum of the disease, as well as the clinical history, diagnostic evaluations, symptomatic treatments and their effects. Retrospectively, whenever possible, the presenting symptoms, clinical history, biochemical, and genetic diagnostic evaluations were recorded. Treatment modalities and response to treatment were registered.

Results: Patients in the cohort vary in age from 5 months to 25 years of age. Phenotypes range from infantile onset with systemic inflammation, to late childhood onset and very mild disease. All patients demonstrated the three typical symptoms of Farber disease (arthritis, subcutaneous nodules, dysphonia). However, in several cases years passed between the appearance of the individual symptoms. Treatment varied from biologics (incl. anti-TNFa and anti-IL-6), joint injections with corticosteroids, DMARDs, NSAIDs, intensive pain relief, to no chronic treatment at all.

Conclusion: This study represents the largest collection of clinical data on Farber disease to date. It is clear that the spectrum of phenotypes includes mild presentations not previously associated with Farber, and that in most cases a pediatric rheumatologist is involved in patient care. The fact that 19 patients can be referenced and potentially followed prospectively (30 patients including those

who have undergone HSCT) implies that the disease is not as rare as earlier supposed. These results also suggest that acid ceramidase deficiency may likely account for a larger number of polyarticular JIA patients than previously thought, with mild disease even possibly diagnosed in adulthood. Therapy with biologics may improve some symptoms, but will not resolve them completely. This shows that lack of adequate response to biologics can also contribute to the indication for Farber testing. It is therefore important to increase awareness of Farber disease among rheumatologists. Clinical screening studies and a natural history study are planned for the near future. Enzyme replacement therapy for Farber is currently under development.

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Abstract Number: 1463

Anti-Cyclic Citrullinated Peptide Antibody Subclass Phenotypes in Polyarticular Juvenile Idiopathic Arthritis

Hannah Peckham[1], Lauren Bourke[2,3], Anna Radziszewska[4], Maria Leandro[5], Debajit Sen[2], **Geraldine Cambridge**[6] and Yiannis Ioannou[7,8], [1]Adolescent Centre for Rheumatology Research, University College London, London, United Kingdom, [2]Arthritis Research UK Centre for Adolescent Rheumatology, University College London, London, United Kingdom, [3]Centre for Rheumatology Research, University College London, London, United Kingdom, [4]The Rayne Institute, Arthritis Research UK Centre for Adolescent Rheumatology at University College London, Great Ormond Street Hospital and UCLH, University College London, London, United Kingdom, [5]Centre for Rheumatology, University College London, London, United Kingdom, [6]Centre for Rheumatology, Department of Medicine, University College London, London, United Kingdom, [7]Arthritis Research UK Centre for Adolescent Rheumatology at University College London, Great Ormond Street Hospital and UCLH, University College London, London, United Kingdom, [8]Centre for Rheumatology Research, University College Hospital London, London, United Kingdom

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Session Time: 9:00AM-11:00AM

Background/Purpose:

Raised levels of Rheumatoid Factor (RhF) and antibodies to citrullinated proteins (ACPA), detected in the clinic using combinations of cyclic citrullinated peptides (CCP), are persistently demonstrated in adult Rheumatoid Arthritis (RA) serology. Multiple isotypes of both autoantibodies can be detected months or years prior to the onset of clinical manifestations. IgG-ACPAs are generally accepted as having greater diagnostic specificity than IgM-RhF, which are present in ~10% of the healthy population. IgG-ACPAs have also been detected in sera of patients with Juvenile Idiopathic Arthritis (JIA); in particular those with IgM-RhF+ve polyarticular JIA (poly-JIA), a subset often considered comparable to adult RA. The prevalence and predictive value of ACPA of IgG, IgM and IgA isotype has been extensively studied in adults with RA, but not, to our knowledge, in a juvenile population. This study profiles a large adolescent JIA cohort using CCP as substrate, with the aim to establish a distinct ACPA phenotype for RhF+ve poly-JIA patients, when compared to other JIA subtypes.

Methods:

Levels of anti-CCP antibodies from a total of 95 patients with poly-JIA (RhF–ve; n=67 and RhF+ve; n=24) were compared with age-matched disease controls (Enthesitis-Related Arthritis (ERA) n=29; Extended-Oligoarthritis (EOA) n= 38) and 31 age-matched healthy controls (HCs). Sera were tested for IgG, IgA and IgM isotypes of anti-CCP, using commercial ELISA plates, coated with second generation citrullinated peptides (CCP2). Cut-offs for positivity were defined by manufacturer's instructions for IgG-CCP (5U/ml). The median age of the poly-JIA patients was 17.4 yrs (IQ range 15.9 to 19.0), with a median disease duration of 8.6 years. RhF status of the poly-JIA cohort was determined from the clinical records. Statistical analysis determined by Mann-Whitney U test.

Results:

In the poly-JIA cohort 87.5% (21/24) of IgM-RhF +ve patients were IgG-CCP+ve, compared with only 6.0% (4/67) of IgM-RhF-ve patients. Furthermore, when compared to control groups, only 2.6% of EOA patients (1/38) and none of the ERA (0/29) or HCs (0/31) were IgG-CCP positive. When results for IgM-RhF+ve/IgG-CCP+ve (n=21) poly-JIA patients were compared with those of the seronegative poly- JIA cohort (IgM-RhF -ve/IgG-CCP–ve; n=67) levels of IgA-CCP (6.47 (IQ range 4.43-15.74) vs 2.95 (IQ range 2.48-4.37);p<0.0001) and IgM-CCP (69.03 (IQ range 38.03-180.5) vs 40.52 (IQ range 27.0-66.88);p=0.0223) were significantly higher in the seropositive (IgM-RhF+ve/IgG-CCP+ve) group.

Conclusion:

This is the first study to our knowledge that profiles autoantibodies against CCP in a large adolescent JIA patient cohort. Results suggested a significantly higher proportion of poly-JIA patients who are IgM-RhF +ve being IgG-CCP positive when compared to those who were IgM-RhF–ve. Additionally, patients who are IgM-RhF+ve/IgG-CCP+ve had significantly higher levels of both IgA-CCP and IgM-CCP antibodies when compared to patients who were IgM-RhF–ve/IgG-CCP–ve. This data suggests that the serological profile of IgM-RF +ve poly-JIA patients mirrors that described in seropositive adult patients with RA.

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Abstract Number: 1464

Assessment of Left Ventricle Functions in Children with Familial Mediterranean Fever with Tissue Doppler and Strain Echocardiography

Fatih Kelesoglu[1], Gafur Dogdu[2], Remzi Sarikaya[3], Adem Atici[3], Serra Karaca[4], Zeynep Sarac[5], Feyza Tiryaki[5], Omer Kumas[5], Zehra Bugra[6], Sevinc Emre[7] and Rukiye Omeroglu[8], [1]Pediatric Rheumatology, Istanbul Medical School, Pediatric Rheumatology, Istanbul, Turkey, [2]Pediatric Cardiology, Istanbul Medical School, Pediatric Cardiology, istanbul, Turkey, [3]Cardiology, istanbul Medical School, Cardiology, istanbul, Turkey, [4]Pediatric Rheumatology, istanbul Medical School, Pediatric Cardiology, istanbul, Turkey, [5]Student, istanbul Medical School, istanbul, Turkey, [6]cardiology, istanbul Medical School, Cardiology, istanbul, Turkey, [7]Istanbul Medical School, Pediatric Rheumatology, istanbul, Turkey, [8]Pediatric Rheumatology, Istanbul Medical School, Pediatric Rheumatology, istanbul, Turkey
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Session Time: 9:00AM-11:00AM

Assessment of Left Ventricle Functions in Children with Familial Mediterranean Fever with Tissue Doppler and Strain Echocardiography

Background/Purpose: The effects of Familial Mediterranean Fever (FMF) on cardiac functions are generally without typical symptoms. Global strain is a sensitive and relatively more objective indicator of early myocardial deformation due to various conditions. We aimed to evaluate cardiac functions in children with FMF using tissue Doppler and strain echocardiography methods.

Methods: This is a cross sectional study in 37 children with FMF with a mean follow up of 4 years (range: 1-13 years) and 29 healthy children. We performed tissue Doppler and strain echocardiography in addition to standard echocardiography in all of the subjects. We did longitudinal strain measurements using apical 2, 3, and 4 chamber views.

Results: Gender ratio and mean age were similar between the groups (Table 1). Left ventricular ejection fraction, similar between the patients and controls. Global strain (GS) was significantly worse in patients with FMF compared to controls. None of the patients or controls had an abnormal GS (>-15). The rate of borderline GS was more common in the FMF group. There was also a borderline significant difference between E'/A' ratio which was lower in patients with FMF. GS was significantly lower in males compared with females (-18.8±2.2 vs. -21±2, p<0.001). Mean ages of the male and female subjects were similar (12.5±4.1 vs. 13.5±3.2, respectively, p=0.3)

Global strain was significantly correlated with disease duration (r=0.33, p=0.046) in patients with FMF and with E/A ratio in the whole

group (r=0.34, p=0.005). There was also an inverse correlation between GS and ejection fraction (EF) in the whole group (r=-0.39, p=0.001). Linear regression analysis revealed independent correlates of GS (r^2 of the model 0.44) as FMF group (B=1.8 95%CI 0.83-2.7, p<0.001), ejection fraction (B=-0.08, 95%CI [-0.1]-[-0.04], p<0.001), and gender (B=1.4 95%CI 0.5-2.4, p=0.005). In patients with FMF, disease duration (B=0.2, 95%CI 0.03-0.4, p=0.023) and EF (B=-0.13, 95%CI [-0.2]-[-0.02], p=0.026) seemed to be independently associated with GS while there was no significant gender association.

Conclusion: Global strain was significantly worse in patients with FMF with no established cardiac problems. Male gender and a lower EF seemed to be other independent determinants of a worse GS. In patients with FMF, longer disease duration is another factor associated with a worse GS. These are our preliminary findings and this study is going on. No strict conclusions can be done because of the currently limited sample size.

Table 1. Comparison of the study groups

	FMF (37)	Controls (29)	P
Current age (years)	12.3 ± 4.1	13.1 ± 1.9	0.99
Gender (%female)	56.8	79.3	0.054
GS	-19.5 ± 2	-21.3 ± 2.3	**0.001**
Borderline GS (%)	43.2	13.8	**0.015**
Global EF	68.8±5.864.7±15.6	64.7±15.6	0.15
Stroke Volume	52.4±18.8	57.3±24.2	0.35
E	97.6±14.9	91.2±13.9	0.08
A	61.1±14.9	57.7±9	0.3
E/A	1.6±0.32	3.4±1.6	0.3
E'	12.5±2	12.1±2.7	0.5
A'	6.7±1.56	6.2±1.7	0.2
E'/A'	1.9±0.48	2.4±1.2	**0.049**

FMF: Familial Mediterranean fever, GS: global strain, EF: ejection fraction

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Disclosure: F. Kelesoglu, None; **G. Dogdu**, None; **R. Sarikaya**, None; **A. Atici**, None; **S. Karaca**, None; **Z. Sarac**, None; **F. Tiryaki**, None; **O. Kumas**, None; **Z. Bugra**, None; **S. Emre**, None; **R. Omeroglu**, None.

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Abstract Number: 1465

Musculoskeletal Anomalies in Children with Trisomy 21

charlene foley[1], Orla G killeen[1] and emma Jane macDermott[2], [1]Our Lady's Children's Hospital Crumlin, National Centre for Paediatric Rheumatology, Dublin, Ireland, [2]our Lady's Children's Hospital Crumlin, National Centre for Paediatric Rheumatology, Dublin, Ireland
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Background/Purpose: Musculoskeletal complications of Trisomy 21 (T21) are common. Almost all children with T21 have muscle hypotonia and joint laxity. The combination of this ligamentous laxity and low muscle tone contribute to an increased risk of a number of musculoskeletal disorders, a delay in acquisition of motor milestones and lower levels of physical activity. Inappropriately low expectations of physical activity and motor function from family, health care workers and self, and over-attributing motor difficulties to low tone and hypermobility may lead to missed pathology and misdiagnoses.

Objective(s)

1. To describe the musculoskeletal anomalies observed in a national cohort of children with T21
2. To calculate the average age children with T21 walked unaided in our cohort

Methods: Over an 18-month period, children with T21 were invited to attend for a musculoskeletal assessment by a paediatric doctor. Relevant musculoskeletal history and clinical findings were documented.

Results: 503 children with T21 were examined (56% male). Median age 8.1 years (0.6-19.2 years). ***Musculoskeletal Anomalies and Trisomy 21***. Pes Planus was the most common musculoskeletal anomaly detected, occurring in 91.1% of the children with T21 examined. Just under a quarter of these children did not avail of orthoses (23.6%). A range of other anomalies were observed, inflammatory arthritis (7.1%) and scoliosis (4.8%) occurring most frequently after pes planus. Other spinal abnormalities included the well-documented T21 associated c-spine instability, absent C2 vertebra and spondylolisthesis. Common hip and foot pathologies included dislocations, Perthes disease, slipped upper femoral epiphysis (SUFE) and hallux valgus. ***Ambulation and Trisomy 21***. The median age our cohort walked was 28 months (12-84 months). This is comparable to the literature that reports children with T21 walk at 23 months (range 13-48), compared with 12 months (range 9-17) for the general paediatric population.

Conclusion: Children with T21 are at increased risk of a number of potentially debilitating musculoskeletal problems. These conditions can present in a variety of ways, with differing symptoms and signs. Pes planus is common therefore early consideration of orthotics and life-long appropriate supportive footwear is advised. Significantly delayed ambulation is noted in children with T21. Early multi-disciplinary intervention is important to ensure these children obtain their full potential with regards to acquisition of walking unaided. Compulsory annual musculoskeletal assessment for all children with T21 would enable early detection of potential problems, allowing for timely intervention and in-turn better clinical outcomes.

Disclosure: C. foley, None; **O. G. killeen**, None; **E. J. macDermott**, None.

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Abstract Number: 1466

Assessment of Transition Readiness in Adolescents and Young Adults with Chronic Health Conditions

Paul Jensen[1,2], Gabrielle Paul[3], Stephanie LaCount[4], Brendan Boyle[5], Manmohan K. Kamboj[6] and Stacy P. Ardoin[7], [1]Rheumatology, Nationwide Children's Hospital, Columbus, OH, [2]Medicine, Ohio State University Medical Center, Columbus, OH, [3]College of Medicine, Ohio State University, Columbus, OH, [4]Pediatrics, Nationwide Children's Hospital, Columbus, OH, [5]Gastroenterology, Nationwide Children's Hospital, Columbus, OH, [6]Endocrinology, Nationwide Children's Hospital, Columbus, OH, [7]Pediatric & Adult Rheumatology, Ohio State University, Columbus, OH

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Background/Purpose:

The transition from pediatric to adult care is a vulnerable period associated with increased morbidity and mortality. Guidelines call for assessing patients' transition readiness to help individualize plans. Several measurement tools have been created, but none have been prospectively evaluated. The Transition Readiness Assessment Questionnaire (TRAQ) was developed to measure transition readiness with regards to self-management (Domain 1) and self-advocacy (Domain 2). Our aim was to evaluate the TRAQ's validity by assessing whether baseline score influenced successful transition over a 3 year period. We previously reported baseline demographic information and TRAQ scores. Here we report the transition outcomes after three years of follow up.

Methods:

89 adolescents and young adults with chronic diseases at a single pediatric center were enrolled. Participants completed a baseline survey which included demographic information, transition experience, and a TRAQ questionnaire. Study personnel conducted telephone interviews every six months for three years to determine participant health status and time at which they transitioned. Attendance at adult

subspecialty provider visit was confirmed by the adult providers. Successful transition was defined as attending at least one adult provider visit.

Results:

The 89 participants were mostly female, Caucasian, and non-Hispanic and had rheumatic (56%), gastrointestinal, (21%) or endocrine (22%) conditions. Each unit increase in TRAQ Domain 1 score increased the odds of successful transition by 1.28 (p=0.32) and each unit increase in Domain 2 score increased the odds by 1.67 (p=0.14). Of other variables measured (age, disease duration, gender, race, insurance status), only baseline age significantly predicted transition (p=0.028).

Conclusion:

This is the first study, to our knowledge, which prospectively measures the effectiveness of a transition assessment tool over a prolonged period of time. While increased baseline TRAQ scores were associated with increased odds of transition, the finding did not reach statistical significance. Additionally, disease duration, race, gender, and insurance status failed to predict transition. Although not statistically significant, the TRAQ domain 2 score predicted transition better than the domain 1 score which suggests that training in self-advocacy may help prepare the emerging adult for transition. Further research is necessary to determine optimal measurement of transition readiness in adolescents and young adults with chronic diseases.

Table 1 . Baseline TRAQ Scores

TRAQ Domain 1

Predictor	Levels	Mean (SE)	P-value*
Age group	16 to 18 years (N=52)	2.94 (0.94)	0.15
	19 to 20 years (N=29)	3.35 (0.91)	
	>= 21 years (N=8)	3.34 (1.35)	
Gender	Female (N=59)	3.12 (0.93)	0.91
	Male (N=30)	3.09 (1.08)	
Race	White (N=72)	3.10 (0.97)	0.78
	Non-white (N=17)	3.17 (1.05)	
Specialty	Rheumatology (N=50)	3.1 (1.03)	0.97
	Endocrinology (N=19)	3.16 (0.98)	
	Gastroenterology (N=20)	3.09 (0.89)	

TRAQ Domain 2

Predictor	Levels	Mean (SE)	P-value*
Age group	16 to 18 years (N=52)	3.58 (0.77)	0.02
	19 to 20 years (N=29)	3.88 (0.66)	
	>= 21 years (N=8)	4.27 (0.54)	
Gender	Female (N=59)	3.81 (0.63)	0.22
	Male (N=30)	3.60 (0.92)	
Race	White (N=72)	3.73 (0.80)	0.80
	Non-white (N=17)	3.78 (0.42)	
Specialty	Rheumatology (N=50)	3.69 (0.82)	0.31
	Endocrinology (N=19)	3.64 (0.62)	
	Gastroenterology (N=20)	3.96 (0.62)	

Table 2: Associations Between Successful Transition and Participant Baseline Characteristics After Three Years of Follow Up

Predictor	Mean Baseline Score		Odds Ratio of Successful Transition	95% CI	P-value
	Yes	No			
TRAQ domain 1 score					
Domain 1 score	3.22 ± 0.97	3.03 ± 0.83	1.28	0.79 – 2.10	0.32
Domain 2 score	3.90 ± 0.53	3.65 ± 0.86	1.67	0.85 – 3.27	0.14
Age (years)	18.77 ± 1.65	17.98 ± 1.49	1.39	1.04 – 1.86	0.028
Disease Duration (years)	5.21 ± 3.85	4.50 ± 4.04	1.05	0.94 – 1.17	0.42
Gender					
Female (N=56)	25 (45%)	31 (55%)	0.75	0.30 – 1.88	0.54
Male (N=27)	14 (52%)	13 (48%)	1.0		
Race					
White (N=68)	31 (46%)	37 (54%)	0.73	0.24 – 2.25	0.59
Non-white (N=15)	8 (53%)	7 (47%)	1.0		
Insurance type					
Private (N=58)	29 (50%)	29 (50%)	1.5	0.53 – 4.21	0.44
Public (N=20)	8 (40%)	12 (60%)	1.0		

Disclosure: P. Jensen, None; **G. Paul**, None; **S. LaCount**, None; **B. Boyle**, None; **M. K. Kamboj**, None; **S. P. Ardoin**, None.

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Abstract Number: 1467

Health Related Quality of Life Is Reduced in Pediatric Patients with Juvenile Idiopathic Arthritis and Juvenile-Onset Fibromyalgia

Michal Feldon[1], Catherine Donnelly[2], Hermine I. Brunner[3], Anne Louis Johnson[1], Lukasz Itert[4], Lisa G Rider[5] and Edward H. Giannini[3], [1]Pediatric Rheumatology, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, [2]Internal Medicine, University of Cincinnati, Cincinnati, OH, [3]Rheumatology, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, [4]Division of Pediatric Rheumatology, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, [5]Environmental Autoimmunity Group, NIEHS, NIH, Bethesda, MD
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Background/Purpose : A number of validated measures are now available for the evaluation of health related quality of life (HRQOL) in children with rheumatic diseases, but most are lengthy and not feasible for use in a clinical setting.

The objective of this study was to document the degree of HRQOL impairment in juvenile idiopathic arthritis (JIA) and juvenile-onset fibromyalgia (JFM) patients using the SF-10v2® questionnaire.

Methods : Patients ages 5-18 years with a diagnosis of JIA or JFM were recruited during routine clinic visits in Cincinnati Children's Hospital Medical Center (CCHMC) over 6 months. Demographic data as well as disease severity scores, including the physician's global, parental overall wellbeing and pain scores, were recorded from the patients' medical records. HRQOL was ascertained via the SF-10v2® Health Survey questionnaire. The SF-10v2® is a 10-item caregiver-completed, generic measure of children's functional health and wellbeing over the preceding 4 weeks; the SF10v2® features 2 summary measures - the physical summary score [PHS] and the psychosocial summary score [PSS].

This was an exploratory, cross-sectional descriptive study that examined the variation in HRQOL scores in relation to different patient and disease characteristics, and compared the scores of JIA and JFM patients to U.S age-and-gender-matched healthy and physically ill children.

Results : 133 JIA and 9 JFM patients were included in the analysis. For JIA patients, mean age at study entry and the mean duration of disease were 11.5 and 4.1 years, respectively; 63% were female and 90% were Caucasian. All JFM patients were Caucasian females with a mean age and mean duration of disease of 12.2 and 1 years, respectively.

Both summary scores of the SF-10v2® were lower among JFM patients compared to JIA patients and to the age-and-gender-matched healthy and physically ill populations. In contrast, the PHS only was lower for JIA patients compared with the healthy and physically ill populations (Table 1).

Among the different JIA categories, PHS scores for enthesitis-related arthritis (ERA) patients were lower than those for polyarticular RF (-) JIA patients (31.72 vs. 45.31 p=0.018). For the JIA patients, PHS scores were lower with active disease, abnormal parental scores and reported pain. Age, gender, race, disease duration and additional autoimmune disease were not associated with reduced scores (Table 2).

Conclusion : HRQOL was lower among JIA and JFM patients compared to healthy and physically ill children. Active disease and reported pain were the most important predictors of reduced HRQOL among JIA patients.

Table 1: One-way ANOVA of HRQOL summary scores of JIA and JFM patients relative to age-and-gender-matched healthy and other physically ill U.S. children

	Healthy*		**Physically ill***		**JIA**		**JFM**				**Tukey's post-hoc analyses**
	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	F	P	
PHS	1255	53.88 (5.2)	836	48.17 (11)	133	41.93 (14.83)	9	13.77 (11.84)	182	0.00	All comparisons were significant
PSS		54.61 (5.87)		53.1 (6.61)		53.61 (8.97)		42.77 (11.93)	18.61	0.00	Well vs. ill; Well vs. JFM; Physically ill vs. JFM; JIA vs. JFM – P=0.00 Well vs. JIA and Physically ill vs. JIA –_NS**

* The comparison populations were taken from a 2006 US general population sample with and without a parent-reported chronic condition, as provided by QualityMetric Inc.

**NS – non-significant

Table 2: Comparisons of PHS and PSS in relation to different patient and disease characteristics among JIA patients								
Variable		**N**	**Physical summary score (PHS)**			**Psychosocial summary score (PSS)**		
			Mean (SD)	T-score	p-value	Mean (SD)	T-score	p-value
Age	Age ≤ median	66	43.14 (15.24)	0.933	0.352	54.15 (8.83)	0.581	0.561
	Age > median	67	40.74 (14.42)			53.24 (9.2)		
Race	Caucasian	121	41.54 (15)	0.97	0.333	53.86 (9)	0.7	0.489
	Non-Caucasian	12	45.87 (11.62)			51.95 (8.9)		
Gender	Female	84	43.56 (14.44)	1.665	0.0982	53.77 (9.44)	0.129	0.897
	Male	49	39.15 (15.22)			53.56 (8.28)		
Duration of disease	Duration ≤ median	70	39.74 (15.5)	1.80	0.072	53.81 (8.4)	0.159	0.873
	Duration > median	63	44.36 (13.69)			53.56 (9.67)		
Autoimmune disease	Yes	27	43.47 (15.08)	0.6	0.548	46.24 (16.59)	0.77	0.439
	No	106	41.54 (14.81)			50.31 (10.66)		
Physician global score	<0.5	66	46.6 (12.02)	3.84	**0.0002**	53.36 (9.43)	0.16	0.872
	≥0.5	57	36.9 (15.9)			53.63 (9.04)		
Parental score	0	56	52.52 (5.15)	9.03	**<0.0001**	55.18 (6.07)	1.567	0.119
	>0	68	33.68 (14.88)			52.68 (10.58)		
Pain report	No pain	45	52.74 (5.45)	6.94	**<0.0001**	54.02 (6.94)	0.22	0.895
	>0	86	36.45 (15.2)			53.66 (9.73)		

-

Disclosure: M. Feldon, None; **C. Donnelly**, None; **H. I. Brunner**, None; **A. L. Johnson**, None; **L. Itert**, None; **L. G. Rider**, None; **E. H. Giannini**, None.

Abstract Number: 1468

The Proposed Outcome Parameters of the Multinational Interdisciplinary Working Group for Uveitis in Childhood (MIWGUC) with Uveitis Disability VAS Score Correspond Significantly with Uveitis "Classicaly Assessed" Uveitis Activity

Ivan Foeldvari[1], Sandra Schenck[2], Gabriele Simonini[3], Cinzia DeLibero[4], Gabriele Brumm[5], Kaisu Kotaniemi[6], Susan Mary Nielsen[7], Regitze Bangsgaard[7], Irene Pontikaki[8], Valeria Maria Gerloni[8], Elisabetta Miserocchi[9], Vasco Miranda[10], Margarida Guedes[11], Sheila T. Angeles-Han[12], Steven Yeh[13], Jordi Anton[14], Rosa Bou Torrent[15], Carmen García de Vicuña[16], Martina Niewerth[17] and Arnd Heiligenhaus[18], [1]Hamburger Zentrum für Kinder-und Jugendrheumatologie, Hamburg, Germany, [2]Deutsches Rheuma-Forschungszentrum, Berlin, Germany, [3]Pediatric Rheumatology, Pediatric Rheumatology Unit, Anna Meyer Children's Hospital-University of Florence, Firenze, Italy, [4]Ophthalmology Unit, Anna Meyer Children's Hospital, Florence, Italy, [5]Klinik und Polyklinikum für Augenheilkunde, Universitätsklinikum Hamburg-Eppendorf, Hamburg, Germany, [6]Ophthalmology Department, Rheumatism Foundation Hospital, Heinola, Finland, [7]Rigshospitalet, Copenhagen, Denmark, [8]Dipartimento di Reumatologia, Università di Milano - Istituto Gaetano Pini, Milano, Italy, [9]Department of Ophthalmology, Scientific Institute San Raffaele, University Vita-Salute, Milan, Italy, [10]Centro Hospitalar do Porto, Porto, Portugal, [11]Hospital de Santo António - Centro Hospitalar do Porto, Porto, Portugal, [12]Pediatrics, Emory Children's Center, Atlanta, GA, [13]Ophthalmology, Emory University School of Medicine, Atlanta, GA, [14]Unitat de Reumatologia Pediàtrica, Hospital Sant Joan de Déu, Barcelona, Spain, [15]Pediatrics Department, Pediatric Rheumatology Unit, Universitat de Barcelona, Hospital Sant Joan de Deu, Barcelona, Spain, [16]Universitat de Barcelona, Hospital Sant Joan de Deu, Barcelona, Spain, [17]Epidemiology, German Rheumatism Research Centre, Berlin, Germany, [18]Department of Ophthalmology at St. Franziskus Hospital Muenster, University of Duisberg-Essen, Muenster, Germany

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Background/Purpose:

Juvenile idiopathic arthritis (JIA) associated uveitis is one of the most severe comorbidities of JIA and occurs in around 10% of JIA patients. There are currently no specific established outcome measures for this specific uveitis. The Standardization of Uveitis Nomenclature (SUN) group made the first attempt to establish outcome measures for uveitis, which were not aimed at JIA associated Uveitis. Adopting part of it, we developed and proposed specific outcome measures for JIA associated Uveitis over a consensus process specific for JIA associated uveitis. Here we are presenting the results of the validation study.

Methods:

Patients were considered eligible, if they started a nonbiologic or biologic disease modifying agent , as indicated by active the uveitis. At baseline, follow up at 3 months and at 6 months following parameters were collected: demographics, rheumatologic assessment (JIA type, activity of arthritis, JIA-related disability), ophthalmologic assessment (duration of uveitis, activity and damage of uveitis,visual acuity, ocular complications, topical and systemic medications, surgical procedure, uveitis-related disability).

Results:

Sixtynine patients were included in the study and up till now 38 patients had a complete follow-up for 6 months. 50/69 (72.5%) of the patients were female. The mean age at inclusion into the study was 8.0 years (range 3-18 years). 98% of the patients were Caucasian. The JIA subset distribution was 56.3% oligoarticular, 14.1% extended oligoarticular, 18.8 % RF negative polyarticular and 4.7% enthesitis related. At inclusion the median disease duration of JIA was 55 months for arthritis and 32.5 months for uveitis. All patients had anterior uveitis. The left eye was more frequently involved (90.3%) then the right eye (83.6 %). Cellcount at baseline was +0.5 or more in 68.3 % of the right eyes and 62.3% of the left eyes, and at 6 months only 30.6% the left eyes. The cell count before dilatation ($p=0.005$) and after dilatation ($p<0.001$) improved significantly over time. Flare was ≥ 0.5+ (graded by SUN) at baseline in the right eyes in 76.7% and in the left eyes 70.2% and at 6 months at the right eyes in 21.2% and the left eyes in 23.5%. The flare grade according SUN ($p<0.001$) improved significantly comparing time point zero to 6 months. The flare grad according MIWGUC;flare >0.5 in 82.4% at time point 0 and after 6 months 35.3%, improved singifiacnatly to ($p=0.021$). The VAS score (0-100) for uveitis related disability decreased from 43.2 to 18.8 ($p=0.001$) and JIA associated disability, decreased from 33.3 to 8.0 ($p< 0.001$). The assessed complication of uveitis decreased from

86.7% to 61.9% after 6 months follow up (p=0.102).

Conclusion:

These results regarding the standardized assessment of the JIA associated uveitis are promising. The newly suggested Uveitis disability score showes significant correlation with cell count and flare grade after 6 months. Further evaluation of these items and the other suggested items will help to establish standardized measures to assess the activity of uveitis and the effecacy of a drug in treatment trials. The assessment of the newly published JIA associated Uveitis QOL is planned.

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Abstract Number: 1469

A Comparison of Pain and Disability, and Their Association Between Juvenile Primary Fibromyalgia Syndrome and Pediatric Rheumatic Diseases: Results from the Childhood Arthritis and Rheumatology Research Alliance Registry

Jennifer E. Weiss[1] and Mark Connelly[2], [1]Hackensack Univ Med Ctr, Hackensack, NJ, [2]Psychology, University of Kansas Medical Center, Kansas City, KS

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Background/Purpose: We aim to determine the extent to which pain severity differs between patients with JPFS and other rheumatic diseases and if the degree of association between pain and functioning is unique to JPFS.

Methods: We evaluated demographics, pain, functional measures (ACR functional class, current and worst, childhood (C) HAQ, health-related quality of life (HRQoL)) and health status scores from the baseline visits of patients in the CARRA Registry from 5/2010 – 6/2014. CHAQ assesses activities of daily living; 0 (no disability) to 3 (high disability). ACR functional class is a 4-point scale indicating patient's ability to do usual self-care. HRQoL is a 5-point scale ("excellent" to "very poor"). Subjective well-being is a 0-10 scale assessing how well patient is doing considering their disease. General linear models with Dunnett's post-hoc tests compared JPFS to other diseases on pain and function and Fisher's r-to-z transformation compared disease groups on the correlation between pain and function.

Results: 9523 patients from infancy to 33 years (M = 12.1, SD = 4.83) (Table 1). Pain ratings were 1.8±2.6 (Vasculitis) to 6.4±2.4 (JPFS), with pain being significantly higher in the JPFS group (score 6.4/10) than any other group (effect sizes = .22 to 1.05). Ratings on disability measures were significantly worse for JPFS patients (effect sizes = .62 to 1.06) regardless of physician-rated disease severity (Fig. 1). However, the *relationship* between pain severity and function/disability was in most cases significantly greater for rheumatic disease patients relative to JPFS and was highest among dermatomyositis, JIA, and MCTD patients (Fig. 2).

Conclusion: JPFS is unique with regard to the perceived severity of pain and disability, yet pain appears to be comparably or more highly associated with disability in other rheumatic diseases. Given the association of pain severity with functional ability across most rheumatic diseases, regardless of disease severity, pain needs further research and increased prioritization in treatment.

Table 1. Demographic data for JPFS and disease cohorts

Variable	JPFS Cohort (*n* = 180)	Rheumatic Disease Cohort (*n* = 9343)
Age (years)	9-21 (M = 15.4, SD = 2.2)	0-33 (M = 4.0, SD = 4.8)
Sex	85% female	73% female
Race	86% White	81% White
	6% Black/AA	9% Black/AA
	8% Other	10% Other
Ethnicity	16% Hispanic	13% Hispanic
Median income	$75-$100,000	$50-$75,000
Disease type		6538 (69.0%)
JIA		1004 (11.0%)
SLE		632 (7.0%)
Dermatomyositis		390 (4.1%)
Localizing scleroderma		192 (2.0%)
CNS vasculitis		139 (1.5%)
MCTD		103(1.1%)
Uveitis		92 (1.0%)
Autoinflammatory disorders		61 (0.6%)
Systemic sclerosis		49 (0.5%)
Sarcoidosis		27 (0.3%)
Sjögren's syndrome		116 (1.2%)
Unknown		

Figure 1. Functional measures as a function of disease

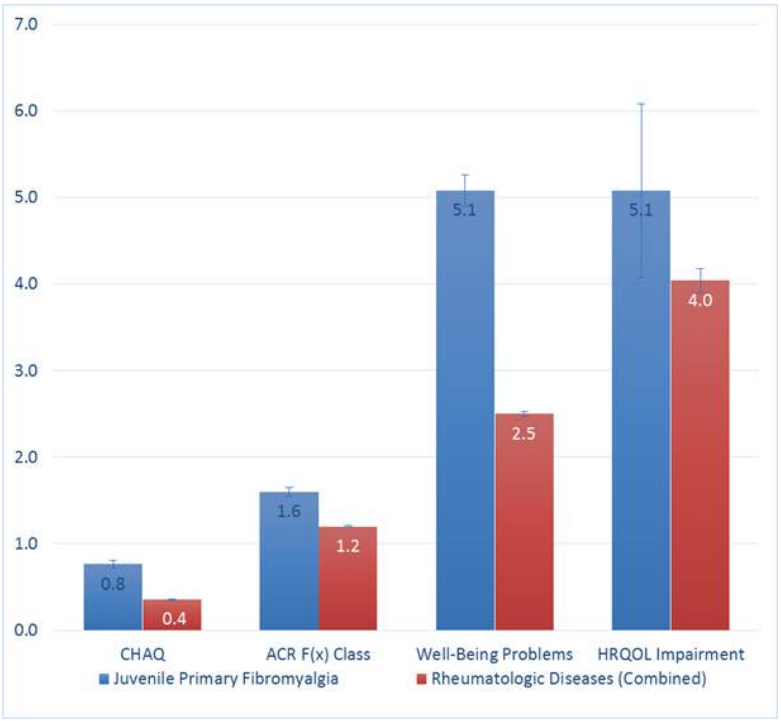
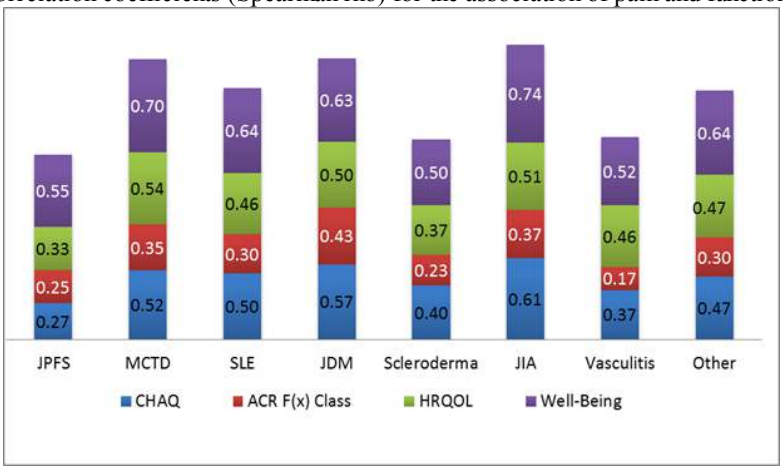


Figure 2. Correlation coefficients (Spearman rho) for the association of pain and function across disease cohorts (higher values = greater association)



Disclosure: J. E. Weiss, None; **M. Connelly**, None.

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Abstract Number: 1470

A Population-Based Study of Outcomes of Patients with Juvenile Idiopathic Arthritis (JIA) Compared to Non-JIA Subjects

Megan L. Krause[1], J.A. Zamora-Legoff[2], Cynthia S. Crowson[3], Thomas Mason II[1], Theresa Wampler Muskardin[2] and Eric L. Matteson[4], [1]Rheumatology, Mayo Clinic, Rochester, MN, [2]Division of Rheumatology, Mayo Clinic, Rochester, MN, [3]Health Sciences Research, Mayo Clinic, Rochester, MN, [4]Division of Rheumatology, Department of Internal Medicine and Department of Health Sciences Research, Mayo Clinic, Rochester, MN

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Background/Purpose: The impact of juvenile idiopathic arthritis (JIA) is not confined to joint involvement in children but rather widespread effects extending to adulthood. This study evaluated outcomes of patients with JIA compared to matched controls.

Methods: Population based cohorts of all residents of a geographically defined area who first met ILAR criteria for JIA in 1994-2013 and age- and sex-matched non-JIA comparator subjects were identified. Outcomes during childhood utilized all patients and outcomes during adulthood were evaluated in 38 pairs, with follow-up beyond age 18. Employment and educational status based on patient report were obtained via medical record review. Occurrences of hospitalizations and surgeries (both joint and non-joint related) were abstracted. Pregnancies and comorbidities including depression and malignancy based on physician diagnosis were collected and evaluated.

Hazard ratios (HR) with 95% confidence intervals (CI) adjusted for age, sex, and calendar year of incidence/index date were obtained from Cox models to evaluate differences in first occurrence of joint surgery, non-joint surgery, and hospitalization. Poisson methods were used to obtain rate ratios (RR) with 95% CI to compare rates of outcomes.

Results: Eighty-nine patients with JIA were identified with 89 non-JIA comparators. Each group had 57 (64%) females. The mean (standard deviation [SD]) age at diagnosis was 8.6 (5.1) years. The length of follow-up after age 18 in patients with JIA 8.0 (5.5) years and non-JIA 8.9 (5.7) was similar.

There was no difference in educational achievement; 25 (66%) versus 22 (58%) in patients with JIA versus not, respectively, had some education beyond high school (p=0.48). Similarly, there was no difference in employment status with only 3 (8%) in each group who were unemployed or disabled (p=1.0).

It was more common for patients with JIA to have a joint surgery as compared to non-JIA both as children and adults, RR 3.93 (1.18, 24.94) and 8.50 (2.27, 120.1). It is more likely for patients with JIA compared to non-JIA to have non-joint surgery as a child RR 1.90 (1.05, 3.67) and perhaps as adults, RR 1.92 (0.89, 4.57). Similarly, hospitalization rates were higher during childhood, RR 2.25 (1.04, 5.53), and somewhat during adulthood, RR 1.79 (0.69, 5.25), when comparing patients with JIA versus non-JIA.

There was an increased risk of developing depression during childhood following JIA diagnosis/index date with HR 2.49 (1.01, 6.13). However, in those who were not diagnosed with depression as children, there was no difference in depression during adulthood, HR 0.48 (0.10, 2.26).

No patients developed a malignancy over the course of follow-up.

There was no difference in the rates of pregnancies between JIA and non-JIA women, RR 0.68 (0.38, 1.20).

Conclusion: In a modern population based cohort of patients with JIA compared to non-JIA subjects, there were higher rates of joint surgery both as children and adults, non-joint surgery as children, and hospitalizations as children. The risk of depression during childhood was higher in JIA than non-JIA. There were no differences in educational or employment outcomes.

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Abstract Number: 1471

Phenotypic Differences Between HLA-B27 Positive and Negative Children with Enthesitis-Related Arthritis

Sabrina Gmuca[1], Timothy Brandon[2], Rui Xiao[3], Ilaria Pagnini[4], Tracey B. Wright[5], Timothy Beukelman[6], Esi Morgan-DeWitt[7] and Pamela F. Weiss[8], [1]Pediatric Rheumatology, The Children's Hospital of Philadelphia, Philadelphia, PA, [2]Pediatrics, Children's Hospital of Philadelphia, Philadelphia, PA, [3]Department of Biostatistics and Epidemiology, University of Pennsylvania, Philadelphia, PA, [4]Department of Paediatrics, University of Florence and Anna Meyer Children's Hospital, Florence, Italy, Florence, Italy, [5]Pediatrics/Rheumatology, UT Southwestern Medical Center, Dallas, TX, [6]Rheumatology, University of Alabama at Birmingham, Birmingham, AL, [7]Pediatric rheumatology, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, [8]Rheumatology, Children's

Hospital of Philadelphia, Philadelphia, PA
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Background/Purpose: The association of HLA-B27 with spondyloarthritis is well-established. Under the International League of Associations for Rheumatology (ILAR) criteria most children with spondyloarthritis are classified as enthesitis-related arthritis (ERA). It is unknown if the clinical features vary between children with ERA who are HLA-B27 positive (pos) versus HLA-B27 negative (neg). Therefore, we aimed to test whether ERA manifests differently in these serologically distinct populations.

Methods: We performed a retrospective multicenter cohort study that included subjects from 5 pediatric rheumatology centers who were diagnosed with ERA from 1989-2012. Baseline visit for patients was defined as the first rheumatology appointment at which the patient exhibited enthesitis, arthritis or acute, symptomatic uveitis. To be included in the study, patients had to have a documented HLA-B27 test result and had to fulfill the ILAR criteria for ERA within the first 6 months from baseline visit. Patient data collected included the following: demographics, clinical features, patient reported outcomes, and medications prescribed both at the time of diagnosis of ERA and over the following 12 months. Differences in clinical and demographic characteristics by HLA-B27 status were assessed using the Mann-Whitney or chi-squared test, as appropriate.

Results: Data was collected from 301 children and a total of 296 were included in the study. Patients were predominantly male (69%) and Caucasian (83%). Median age at diagnosis was 12 years (IQR: 10-14) and 53% were HLA-B27 pos. HLA-B27 positivity was associated with male gender ($p<0.01$) and older age at diagnosis ($p=0.03$). Symptom duration at time of diagnosis was shorter in the HLA-B27 neg group with a median of 6 versus 7 months, respectively ($p=0.04$). Table 1 shows the ILAR criteria, clinical features and patient reported outcomes at the time of diagnosis as well as the incidence of arthritis and enthesitis throughout the duration of the study, and compared between HLA-B27 pos and neg groups. Not only did a greater proportion of HLA-B27 neg patients have enthesitis at diagnosis (78% vs. 59%; $p<0.01$), but these children also had greater tender entheses counts at diagnosis ($p<0.01$) and a greater number of affected entheses during the first year after diagnosis ($p<0.01$). Sacroiliac tenderness and uveitis were not associated with HLA-B27 status. Disease activity scores and patient reported outcomes were not significantly different between the two groups.

Conclusion: In this retrospective cohort, the clinical phenotype of children with ERA differed significantly based on HLA-B27 status. In comparison to HLA-B27 pos children, HLA-B27 neg children are younger, more likely to be female, and have more peripheral enthesitis. Future studies should address differences in response to therapy and outcomes between these 2 groups.

Table. Patient Characteristics Based on HLA-B27 Status

	All (n=296)	HLA-B27 pos (n=158)	HLA-B27 neg (n=138)	P-value*
ILAR ERA criteria, N (%)				
Arthritis	260 (88)	143 (91)	117 (85)	0.13
Enthesitis	201 (68)	93 (59)	108 (78)	**<0.01**
Sacroiliac joint tenderness and/or inflammatory spinal pain	92 (31)	45 (28)	47 (34)	0.30
Acute, symptomatic uveitis	17 (6)	10 (6)	7 (5)	0.67
Onset of arthritis in a male > 6 years	172 (58)	107 (68)	65 (47)	**<0.01**
Family history of HLA-B27 pos associated disease† in a first degree relative	42 (14)	23 (15)	19 (14)	0.85
Clinical Features and Patient Reported Outcomes at Diagnosis, Median (IQR)				

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Abstract Number: 1472

Incidence and Mortality in a Population-Based Cohort of Patients with Juvenile Arthritis 1960-2013

Megan L. Krause[1], Cynthia S. Crowson[2], C. John Michet

(IQR)				
Active Joint Count	2 (1, 4)	2 (1, 4)	2 (1, 3)	**0.04**
Tender Entheses Count	2 (0, 4)	1 (0, 3)	2 (1, 4)	**<0.01**
Physician disease activity (VAS 0 - 10)	2.0 (2.0, 3.2)	2.0 (2.0, 3.0)	2.6 (2.0, 3.5)	0.09
Juvenile Spondyloarthritis Disease Activity Index (JSpADA) (0 – 8)	2.0 (1.0, 3.0)	2.0 (1.0, 3.0)	2.0 (1.0, 3.0)	0.79
Function (CHAQ) (0 – 3)	0.4 (0.0, 1.0)	0.4 (0.0, 1.0)	0.4 (0.0, 1.0)	0.44
Patient/parent pain (VAS 0 – 10)	4.0 (2.0, 7.0)	4.0 (2.0, 7.0)	4.0 (2.0, 6.0)	0.48
Patient/parent disease activity (VAS 0 – 10)	4.0 (2.0, 6.0)	4.0 (2.0, 6.0)	3.5 (2.0, 6.0)	0.42
Enthesitis/Arthritis Throughout Study Duration, Median (IQR)				
Maximum tender entheses count at any visit	2 (1, 4)	2(0, 4)	3(2, 6)	**<0.01**
Maximum active joint count at any visit	3(2, 5)	3(2, 5)	2(1, 4)	**0.04**
Total active joints^	3 (2, 6)	4 (2, 7)	3 (2, 5)	**0.02**
Total tender entheses^	2 (1,5)	2 (0, 4)	4 (2, 7)	**<0.01**

Legend. *Differences between HLA-B27 categories were compared using the Mann-Whitney or chi-squared test, as appropriate**.** † HLA-B27 possassociated disease defined as including: ankylosing spondylitis; inflammatory bowel disease; reactive arthritis or acute anterior uveitis. ^Number of unique joints with arthritis and unique affected entheses over the first year after diagnosis. ILAR: International League of Associations for Rheumatology; HLA: human leukocyte antigen; IQR: interquartile range; CHAQ: childhood health assessment questionnaire. Number of patients with patient-reported outcomes varied due to the retrospective nature of the study. The total number of patients available for each assessment at diagnosis was as follows: Physician disease activity (N=156); CHAQ (N=149); Patient/parent pain (N=160); Patient/parent disease activity (N=123).

III[1], Theresa Wampler Muskardin[3], Thomas Mason II[1] and Eric L. Matteson[1], [1]Rheumatology, Mayo Clinic, Rochester, MN, [2]Health Sciences Research, Mayo Clinic, Rochester, MN, [3]Division of Rheumatology, Mayo Clinic, Rochester, MN

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Background/Purpose: Information regarding incidence, prevalence, and mortality in juvenile rheumatoid arthritis is scarce, particularly since the advent of recent classification criteria for juvenile inflammatory arthritis (JIA). Estimates are based on varying populations, classification criteria, follow-up durations, and disease validation methodology.

Methods: Incident cases of juvenile arthritis were identified between January 1, 1994 and December 31, 2013 in a geographically well-defined population using individual medical record review for case validation. Cases meeting ACR criteria for juvenile rheumatoid arthritis (JRA) and ILAR criteria for juvenile idiopathic arthritis (JIA) were included. Individuals who met criteria for JRA were combined with a prior cohort of incident cases from 1960-1993.[1] Incidence and prevalence rates with 95% confidence intervals (CI) were sex- and age-adjusted to the 2010 U.S. white population. The standardized mortality ratio (SMR) with 95% CI was calculated with expected deaths based on age, sex and calendar year specific life tables for the U.S. population and displayed using Kaplan-Meier methods.

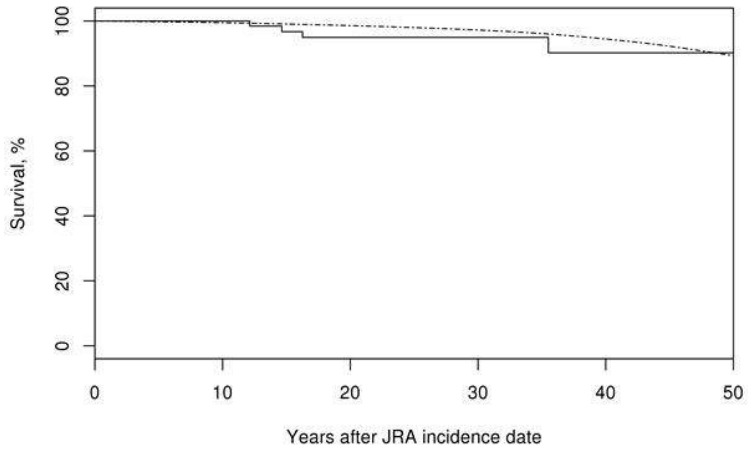
Results: Fifty-nine incident cases met JRA criteria in 1994-2013. Disease subtypes included 48 (81%) with pauciarticular disease, and 9 (15%) with polyarticular and 2 (3%) with systemic disease. These JRA patients were combined with the additional 59 patients from the previously identified 1960-1993 cohort for a total of 118 patients. There were no differences in the subtypes of JRA, age at diagnosis, sex, or time from symptoms to diagnosis comparing the 2 cohorts. The incidence of JRA in 1994-2013 was 9.5 per 100,000 (95% CI 7.1, 12.0). Prevalence of JRA on 1/1/2010 was 54.4 per 100,000 (95% CI 28.5, 80.2). There was no significant change in the incidence of JRA over the entire time period.

Utilizing JIA criteria, 71 incident cases were identified in 1994-2013. Incidence was 10.3 per 100,000 (95% CI 7.9, 12.7). Prevalence on 1/1/2010 was 57.6 per 100,000 (95% CI 31.0, 84.5). Oligoarthritis was the most common subtype accounting for 63%. Joint erosions were noted in 17% and eye involvement in 7%.

A total of 4 deaths occurred during 2180.7 person-years of follow-up in patients with JRA. No deaths have occurred in children with incident JRA in 1994-2013. None of the deaths were directly related to juvenile arthritis. The SMR was 1.50 (95% CI 0.41-3.83); the survival curve is shown in figure 1.

Conclusion: The incidence of JRA did not change significantly between 1960-2013. Incidence is higher when using the more inclusive criteria of JIA as compared to JRA. When specifically evaluating the more homogeneous group of patients who met ACR JRA criteria, there was no demonstrated increase in mortality compared to the general population.

[1]Peterson LS, et al. *Arthritis Rheum* 1996;39(8):1385-90.



Disclosure: M. L. Krause, None; **C. S. Crowson**, None; **C. J. Michet III**, None; **T. Wampler Muskardin**, None; **T. Mason II**, None; **E. L. Matteson**, Novartis/Sanofi/Centocor-Jansen/Celgene/Amgen/Roche/Genentech/Mesoblast/Pfizer, 2.

Abstract Number: 1473

Juvenile Psoriatic Arthritis Manifestations in a Cohort of 361 Patients from US and Canada

Devy Zisman[1,2], Matthew L Stoll[3], Dafna D. Gladman[4], Vibeke Strand[5], Idit Lavi[6], Joyce Hsu[7], Elizabeth D. Mellins[8] and for the CARRA Registry Investigators, [1]Technion, The Ruth and Bruce Rappaport Faculty of Medicine, Haifa, Israel, [2]Rheumatology Unit, Carmel Medical Center, Haifa, Israel, [3]Department of Pediatrics, Division of Rheumatology, University of Alabama at Birmingham, Birmingham AL, Alabama, AL, [4]Toronto Western Hospital, Toronto, ON, Canada, [5]Stanford University, Palo Alto, CA, [6]Department of Community Medicine and Epidemiology, Carmel Medical Center, Haifa, Israel, [7]Pediatric Rheumatology, Stanford University, Palo Alto, CA, [8]Dept of Pediatrics CCSR, Stanford University Med Ctr, Stanford, CA

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Background/Purpose: To assess the demographic, clinical, and radiographic manifestations, health questionnaire (HQ) scores (physician global assessment, Health-related Quality of Life, parent/subject overall well-being and parent/subject pain), family history and drug regimens at enrollment and after one year follow up (F/U), in children with juvenile psoriatic arthritis (JPsA) in an international registry.

Methods: The study population included all JPsA patients in the registry between May 2010 - December 2013. We analyzed cross-sectional data at enrollment visit, stratified according to the age at disease onset (< or ≥ 6 years) and compared with information at 1 year F/U. Chi square or Fisher's exact tests were used for categorical characteristics, t-tests for continuous variables, and Mann-Whitney-U tests for non-normally distributed variables. Comparison of binary variables between enrollment and F/U was performed using McNemar Test, and Wilcoxon Signed Rank Test for continuous variables. A multivariable logistic regression model was used to assess the influence of 1 year of treatment with DMARDs, biological DMARDs, NSAIDS or glucocorticoids (GCs) on objective outcome (improvement in ≥ 5 from the following: arthritis, dactylitis, enthesitis, skin psoriasis, sacroiliitis and nail pitting), and on subjective outcome (improvement in all 4 HQ scores) adjusted for age, gender, race and ethnicity.

Results: 361 children with JPsA were entered in the registry. The majority (93.9%) were white and not Hispanic (91.7%); 68.14% had symptom onset ≥ 6 years. Comparison between data in the two age groups at disease onset is presented in Table 1. Data after 1 year F/U were available for 222 patients. Statistically significant improvements were noted in the number of patients with ≥ 5 joints involved, nail pitting, dactylitis, psoriasis, enthesitis, sacroiliitis and uveitis [(126 (61.8%) vs 21 (10.2%,), (70 (35.9%) vs 31 (15%), (60 (30.9%) vs 5 (2.4%), (137 (68.2%) vs 73 (34.8%), (57 (29.5%) vs 17 (8.1%), (35 (18.1%) vs 13 (6.2%) (27 (15.1%) vs 8 (4.3%) P<0.0001 respectively]. Improvement in objective outcome was associated with disease onset < 6 years (OR 3.69, 95% CI 1.3-10.48), female gender (OR 2.44, 95% CI 1.07-5.56) and lack of biological DMARD (bDMARDS) therapy (OR 2.73 95% CI 1.16-6.44). Improvement in subjective outcome was associated with the presence of enthesitis (OR 4.14, 95% CI 1.12-15.25).

Conclusion: JPsA onset at or after age 6 is diagnosed earlier after symptom onset, with a male predominance and higher prevalence of psoriasis, nail pitting, enthesitis, sacroiliitis and less uveitis. This group is treated more often with daily NSAIDS and MTX and less often with intraarticular GCs. Females with disease onset before age 6 and not receiving bDMARDs have a better objective outcome, while patients with enthesitis had a better subjective outcome.

Table 1: Comparison between JPsA onset before and after the age of 6

Parameter	Total JPsA	JPsA < 6	JPsA ≥ 6	P value
	361 patients	115 patients	227 patients	
Demographics				
Age at onset of symptoms (years)	8.34±4.57	2.78±1.61	11.04±2.74	
Age at first rheumatology visit (years)	9.37±4.54	4.22±2.83	11.88±2.74	
Time between symptom onset and first rheumatology visit (years)	1.04±1.46	1.43±2.04	0.84±1.02	**<0.0001**
Gender (Male)	137 (38%)	35 (30.4%)	93 (227) 41%	0.057
Family History of psoriasis	113 (31.3%)	42 (36.5%)	67 (29.5%)	NS
Clinical Characteristics				
Oligoarthritis (N) (%)	160 (358) (44.7%)	56 (115) (48.7%)	96 (224) (42.9%)	NS
Polyarthritis (N) (%)	198 (358) (55.3%)	59 (115) (51.3%)	128 (224) (57.1%)	NS
Nail Pitting (N) (%)	128 (341) (37.5%)	30 (107) (28%)	86 (215) (40.0%)	**0.023**
Dactylitis (N) (%)	102 (344) (29.7%)	39 (108) (36.1%)	58 (217) (26.7%)	0.082
Psoriasis (N) (%)	233 (349) (66.8%)	60 (109) (55.0%)	164 (222) (73.9%)	**0.001**
Enthesitis (N) (%)	112 (342) (32.7%)	25 (107) (23.4%)	79 (217) (36.4%)	**0.018**
Sacroiliitis (N) (%)	57 (342) (16.7%)	9 (108) (8.3%)	44 (216) (20.4%)	**0.006**
Uveitis	39 (348) (11.2%)	19 (112) (17%)	18 (217) (8.3%)	**0.018**
Subjective Questionnaires				
Health Related Quality of life score	2.17±0.84	2.07±0.86	2.22±0.84	NS
Parent/subject overall well-being score	2.33±2.20	2.05±2.0	2.52±2.3	0.09
Parent/Subject pain scale score	2.58±2.64	2.23±2.5	2.78±2.73	0.06
Physician global assessment score	1.50±1.71	1.53±1.83	1.49±1.68	NS
Radiographic Characteristics				
Imaging evidence of joint damage (N) (%)	74 (301) (24.6%)	21(94) (22.3%)	46(189) (24.3%)	NS
Medications				
Non-biologics DMARDs ever (N) (%)	294 (361) (81.4%)	96 (115) (83.5%)	181 (227) (79.7%)	NS
Biological DMARDS ever (N) (%)	191 (361) (52.9%)	62 (115) (53.9%)	114 (227) (50.2%)	NS
Glucocorticosteroids (N) (%)	188 (361) (52.1%)	68 (115) (59.1%)	107 (227) (47.1%)	NS
Daily NSAIDs (N) (%)	160 (361) (44.3%)	40 (115) (34.8%)	116 (227) (51.1%)	**0.004**
Methotrexate (N) (%)	181 (361) (50.14%)	52(115) 45.2%	129 (227)56.8%	**0.042**
Intraarticular glucocorticosteroids (N) (%)	118 (361) (32.7%)	49(115) (42.6%)	59 (227) (26%)	**0.002**

N-actual number of patients

Disclosure: D. Zisman, None; **M. L. Stoll**, None; **D. D. Gladman**, None; **V. Strand**, Abbvie, Alder, Amgen, Anthera, AstraZeneca, BiogenIdec, Bristol-Myers Squibb, Genentech, GSK, Janssen, MerckSerono, Novartis, Pfizer Inc, Sanofi-Aventis, and UCB, 2; **I. Lavi**, None; **J. Hsu**, None; **E. D. Mellins**, Novartis, Glaxo-Smith-Kline, 2,Ascendent, Codexis, 5.

of-361-patients-from-us-and-canada

Abstract Number: 1474

8-Year Follow-up Study: Differences Between HLA-B27 Positive and Negative Children with Juvenile Idiopathic Arthritis in Finland

Suvi Peltoniemi[1], Ellen Berit Nordal[2,3], Pekka Lahdenne[4] and Kristiina Aalto[4], [1]Department of Pediatric Rheumatology, Children's Hospital, Helsinki University Hospital, Helsinki, Finland, [2]Department of Pediatrics, University Hospital of North Norway, Tromsø, Norway, [3]Department of Clinical Medicine, UIT The Arctic University of Norway, Tromsø, Norway, [4]Department of Pediatrics, Children's Hospital, Helsinki University Hospital, Helsinki, Finland

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Background/Purpose: Long-term studies have shown that many patients with juvenile idiopathic arthritis (JIA) still suffer from persistent inflammation and disability as adults. Because of the heterogeneity of JIA, there are not many clinical or laboratory parameters that could be used to clarify the prognosis of a single patient. The human leukocyte antigen HLA-B27 is known to be related to spondyloarthritides in adults. Some children with JIA have the antigen, but at least so far, it has a primary role in the classification. The aim of the study was to find out if there are major differences between HLA-B27 positive and negative children with JIA with respect to disease characteristics during 8-years' follow-up.

Methods: This study is part of a multicentre population-based cohort study in the Nordic countries based on consecutive patients with a new diagnosis of JIA according to ILAR criteria. They were enrolled 1997-2000 from a defined area of Southern Finland. Information regarding clinical data, serology, and disease activity was registered at certain intervals for 8 years.

Results: 163 of 187 children fulfilled the criteria for 8-year study. HLA-B27 was analysed in 141 patients. 20% of the children were HLA-B27 positive and 67% negative. The most common ILAR categories were enthesitis-related arthritis (41%) among the HLA-B27 positive patients and oligoarthritis (51%) among the negative, when combining the persistent and extended oligoarthritis categories together. At 8-years' time 41% of the antigen positive patients were not in remission vs. 33% of the antigen negative ones. Also the percentage of current users of biological agents was higher in the HLA-B27 positive group, 28 vs. 18%. The highest incidence of uveitis (30%) was among the HLA-B27 negative patients, who also had the maximum mean number (9) of cumulative joints. A larger proportion of HLA-B27 positive boys with older age at disease onset was found (p=0.004), which is consistent with the findings in other Nordic studies.

Conclusion: Some trends for differences were found regarding the presence of HLA-B27, including the main ILAR subgroups, rates of remission and use of biological agents. However, a statistically significant older age at disease onset was found in HLA-B27 positive boys.

Disclosure: S. Peltoniemi, None; **E. B. Nordal**, None; **P. Lahdenne**, None; **K. Aalto**, None.

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Abstract Number: 1475

Fatigue, Quality of SLEEP and PAIN in Children with Juvenile Idiopathic Arthritis

Ela Tarakci[1], Saime Nilay Baydogan[2], Kenan Barut[3] and **Ozgur Kasapcopur**[4], [1]Division of Physiotherapy and Rehabilitation, Faculty of Health Science, Istanbul University,, Associate Professor, Istanbul, Turkey, [2]Division of Physiotherapy and Rehabilitation, Faculty of Health Science, Istanbul University,, Assistant Professor, Istanbul, Turkey, [3]Pediatric Rheumatology, Istanbul University, Cerrahpasa Medical Faculty, Istanbul, Turkey, [4]Istanbul University, Cerrahpasa Medical School, Department of Pediatric Rheumatology, Professor of

Pediatric Rheumatology, Istanbul, Turkey
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Background/Purpose:

Juvenile Idiopathic Arthritis (JIA) is one of the most common rheumatic diseases in childhood, affecting at least 1 in 1000 children (1). Children with JIA, experience joint inflammation and swelling, pain and tenderness, morning stiffness, limited mobility. Also, children with JIA and their parents complain fatigue easily and sleep disturbances such as falling asleep, fragmented sleep with more nightly awakenings, and daytime sleepiness. The aim of this study to determine the prevalence of fatigue, disturbed sleep and pain in patients with JIA, at the same time to identify relationship between fatigue, pain, sleep quality and activity limitation and participation restriction.

Methods:

84 patients (51 female, 33 male) with JIA and their parents were enrolled in the study. The subjects were recruited in a pediatric rheumatology clinic. They were diagnosed with JIA by a pediatric rheumatologist based on the ILAR diagnostic criteria. Patients with recent diagnoses of JIA and those with mental deficits were excluded. PedsQL Multidimensional Fatigue Scale was used to evaluate fatigue.

Pittsburg sleep quality index (PSQI) was used to evaluate quality of sleep, daytime sleepiness. Pain was evaluated with 10 cm Visual Analog Scale (VAS). Childhood Health Assessment Questionnaire (CHAQ) was used to evaluate activity limitation and participation restriction.

Results:

Respectively, the mean age, disease duration and number of affected joint were 12.90±3.50 years, 5.70±3.76 years and 1.99±1.94. The mean of scores of CHAQ was 1.20±1.69, the mean of PSQI-daytime sleepiness was 0.76±0.81, the mean of PSQI-sleep quality was 0.89±0.74, the mean of PSQI-Total was 4.34±2.34 and the mean of scores was PedsQL-fatigue 66.21±23.27. The relationships of scores of VAS, PedsQL-fatigue, PSQI and CHAQ were demonstrated Table I.

Conclusion:

This study confirmed that patients with JIA suffer from pain, fatigue and sleep disturbances. In addition to, sleep disturbance and fatigue are strongly associated with increased pain. Due to this relationship, activity limitation and participation restriction may be observed in patients with JIA. Strategies aimed at improving sleep quality and reducing fatigue and pain should be studied as possible ways of improving participation in activities in children with JIA.

Table I. The correlations scores of VAS, CHAQ, PedsQL-fatigue, PSQI

	VAS	PSQI-Daytime	PSQI-Sleep Quality	PSQI-Total	PedsQL-Total	PedsQL-General Fatigue	PedsQL-Sleep/rest	PedsQL-Cognitive
CHAQ	0.283**	0.157	0.240*	0.230*	-0.546**	-0.501**	-0.440**	-0.506**
VAS		0.352**	0.212	0.351**	-0.372**	-.0289**	-0.387**	-0.317**
PSQI-Daytime			0.374**	0.726**	-0.418**	-0.430**	-0.411**	-0.283**
PSQI-Sleep Quality				0.615**	-0.478**	-0.439**	-0.442**	-0.394**
PSQI-Total					-0497**	-0.482**	-0.466**	-0.383**
PedsQL-Total						0.929**	0.870**	0.862**
PedsQL-General Fatigue							0.789**	0.692**
PedsQL-Sleep/rest								0.562**

Disclosure: E. Tarakci, None; **S. N. Baydogan**, None; **K. Barut**, None; **O. Kasapcopur**, None.

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Abstract Number: 1476

Improvement of the Long-Term Outcome in Greek Adult Patients with Juvenile Idiopathic Arthritis in the 21st Century

Despoina Dimopoulou[1], Maria Trachana[2], Polyxeni Pratsidou-Gertsi[2], Prodromos Sidiropoulos[3], Athina Theodoridou[1], Florence Kanakoudi-tsakalidou[2] and Alexandros Garyfallos[1], [1]4th Department of Internal Medicine, Aristotle University, Thessaloniki, Greece, [2]1st Department of Pediatrics, Aristotle University, Thessaloniki, Greece, [3]Rheumatology, University of Crete, Medical School, Heraklion, Greece

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Background/Purpose: During the last decade there is evidence of a rising improvement regarding the long-term outcome of patients with Juvenile Idiopathic Arthritis (JIA). The aim of the study was to compare long-term outcome between patients with disease onset before and after 2000.

Methods: Patients (pts) > 18 years with an established JIA, a disease onset >5 years and no history of > 6 months care from external rheumatologists, were enrolled in the study. Clinical, laboratory and radiographic examination were performed at the last follow-up visit, 17.2 years post-diagnosis. The outcome variables were: radiographic damage assessed by the Total modified Sharp/van der Heijde Score (TmSvdHS), articular and extra-articular damage by Juvenile Arthritis Damage Index (JADI-A and JADI-E) and physical ability by the Health Assessment Questionnaire-Disability Index (HAQ-DI). In the multivariate analysis, possible explanatory variables were characteristics present at onset and active disease duration within 5 years of onset.

Results: A total of 102 (72 F) pts were enrolled. The age at disease onset (mean ±SD) was 7.7 ±4 yrs, the interval from onset to last visit 17.2 ±6.7 yrs and the pts' current age 25 ±5.9 yrs. Twenty eight patients were diagnosed after 2000 (Group 1) and 74 patients before 2000 (Group 2). The 2 Groups didn't differ in demographic and clinical characteristics, as gender, type of disease onset and ACPA positivity. At the last follow-up visit, Group 1 had better TmSvdHS, better JADI-A and better JADI-E score as compared to Group 2 ($p<0.001$, $p<0.001$, $p=0.003$, respectively). In contrast, HAQ-DI score did not differ between the 2 Groups ($p=0.55$). Disease duration within 5 yrs of onset was longer in Group 2 ($p=0.02$). In the multivariate analysis, disease duration within 5 yrs of onset was a prognostic factor for joint damage [B (95%CI) 2.114 (0.206,4.022), $p=0.03$], cumulative % time spent in a state of active disease [B (95%CI) 0.007 (0.004,0.011), $p<0.001$] and cumulative time spent in a state of clinical remission off medication over the entire disease course [B (95%CI) -0.667 (-1.048,-0.286), $p=0.001$].

Conclusion: Patients diagnosed after 2000, had a better long term outcome as compared to those before 2000. Despite the difference in disease duration, active disease duration within 5 years of onset proved to be a critical prognostic factor, probably reflecting the availability of biologics nowadays and the treat-to-target strategies.

Disclosure: D. Dimopoulou, None; **M. Trachana**, None; **P. Pratsidou-Gertsi**, None; **P. Sidiropoulos**, None; **A. Theodoridou**, None; **F. Kanakoudi-tsakalidou**, None; **A. Garyfallos**, None.

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Abstract Number: 1477

Patterns of Enthesitis and Arthritis in Juvenile Idiopathic Arthritis

Florence A. Aeschlimann[1], Mira van Veenendaal[1], Simon Eng[2] and Rae S.M. Yeung[1], [1]Division of Rheumatology, The Hospital for Sick Children, Toronto, ON, Canada, [2]151 Beecroft Rd., Apt. 604, University of Toronto, Toronto, ON, Canada

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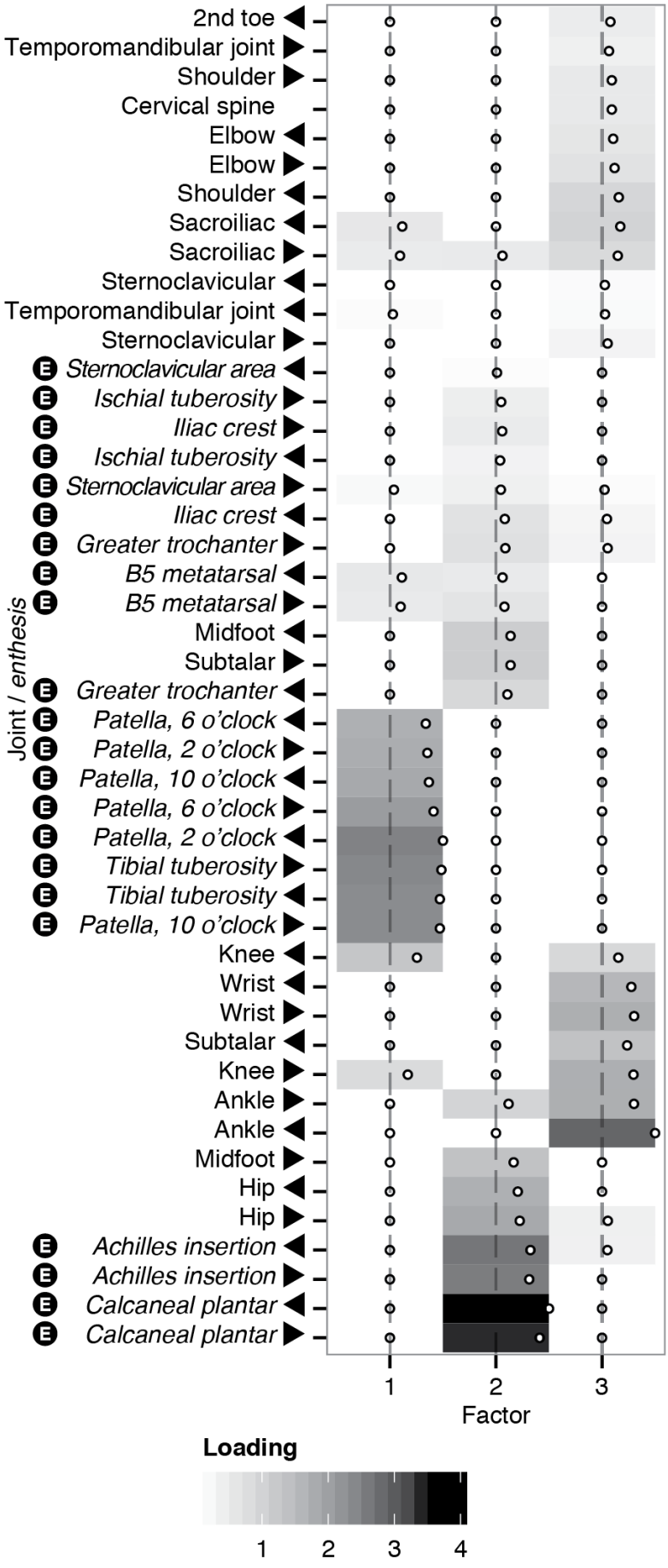
Background/Purpose: Juvenile idiopathic arthritis (JIA) encompasses a heterogeneous group of diseases characterized by chronic joint inflammation with presence of enthesitis as an important classification criteria. Although joint count and enthesitis are represented in the ILAR criteria, their pattern is not taken into consideration. We studied these patterns using data-driven pattern recognition techniques aiming at identifying homogeneous subgroups of children with JIA and enthesitis.

Methods: We included 116 patients from a Canadian multicenter prospective inception cohort. Inclusion criteria consisted of a diagnosis of JIA according to the ILAR criteria <3 months prior to study entry, treatment-naivety except for NSAIDs and enthesitis at baseline. Non-negative matrix factorization (NMF) was performed on baseline enthesitis and arthritis data to identify factors that describe major patterns distinguishing groups from each other. A feature of NMF is that each factor lends itself to a cluster.

Results: NMF identified 3 factors and clusters: (1) predominantly involvement of the knees, with symmetric involvement of enthesitis around the patella and tibial tuberosities and knee arthritis together with enthesitis at the base of the 5th metatarsal bone and sacroiliitis (38 patients); (2) foot/ankle and hip/pelvis involvement with enthesitis at the calcaneal insertion of the achilles tendon and the plantar fascia, arthritis of all the ankle joints and enthesitis at the pelvic bones, greater trochanter with arthritis in the hip and SI joints (43 patients); and (3) peripheral and axial polyarthritis with a non-specific pattern of enthesitis involvement (36 patients).

Conclusion: Using computer-driven analysis we detected distinct patterns of enthesitis and arthritis at presentation of disease. These will be helpful in characterizing homogeneous patient subgroups and disease trajectories and potentially identify predictors of treatment response and disease outcome.

Figure 1: Contributions of individual joints and entheses to factors. Shades of gray indicate the degrees to which individual joints and entheses (y-axis; entheses are marked with "E"s) contribute to factors (x-axis). Shades nearer black indicate stronger contributions. Traces (lines represent 0 loadings and dots indicating absolute loadings) provide an alternative means of visualizing the loadings. Arrows indicate the side of body.



Disclosure: F. A. Aeschlimann, None; **M. van Veenendaal**, None; **S. Eng**, None; **R. S. M. Yeung**, Novartis Pharmaceutical Corporation,

2.

Abstract Number: 1478

Comparison of JIA and RA Patients in the National Data Bank for Rheumatic Diseases

Melissa L. Mannion[1], Sofia Pedro[2,3], Timothy Beukelman[4], Jeffrey R. Curtis[5] and Kaleb Michaud[3], [1]Pediatrics, University of Alabama at Birmingham, Birmingham, AL, [2]Clinical and Translational Research Center, Bioepi, Oeiras, Portugal, [3]National Data Bank for Rheumatic Diseases, Wichita, KS, [4]Pediatric Rheumatology, University of Alabama at Birmingham, Birmingham, AL, [5]University of Alabama at Birmingham, Birmingham, AL

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Background/Purpose: We aimed to compare patient reported outcomes between adults with juvenile idiopathic arthritis (JIA) and adults with rheumatoid arthritis (RA) with similar disease duration and treatment era.

Methods: This cross sectional study used a random observation from JIA and RA participants in the National Data Bank for Rheumatic Diseases (NDB), a longitudinal cohort of patients that complete biannual questionnaires. Participants were included in the JIA group if they were <55 years old at enrollment and had a physician diagnosis of JIA, a self-diagnosis of JIA (with a physician diagnosis of arthritis), or a physician diagnosis of RA with symptoms prior to age 16. Each JIA patient was matched to 3 RA patients based on sex, calendar year of observation, and calendar year of diagnosis. This produced matching disease duration and treatment era while minimizing effects of comorbid conditions unrelated to arthritis. The demographics, patient reported outcomes, and disease characteristics were compared between the JIA and RA groups using Chi square or t tests. The SF-36 physical and mental component summary scores, the patient activity score (PAS), and PAS-II were compared between groups using stepwise reduced linear regression models.

Results: We identified 596 JIA patients who were matched to 1788 RA patients; 90% were female. The JIA patients had a mean (SD) age of 34.3 years (10.0) and 82% were white; the RA patients had a mean age 53.1 (7.4) and 86% were white. Patients with RA were more likely to have a history of total joint replacement, cancer, heart disease, liver disease, or cataract and have a higher rheumatic disease comorbidity index. Patients with JIA report higher pain scores, longer morning stiffness, have a higher PAS and PAS-II, and lower SF-36 MCS (Table 1). After including 18 potential confounders, JIA diagnosis was not significantly associated with the SF-36 PCS (beta 0.39, 95% CI -0.70, 1.49), MCS (beta 0.06, 95% CI -1.73, 1.86), PAS (beta -0.06, 95% CI -0.26, 0.13), or PAS-II (beta 0.09, 95% CI -0.12, 0.31). Each final model included 8-12 variables; variables with significant associations in all 4 models were the number of rheumatology visits in the prior 6 months, meeting fibromyalgia criteria, household income, having a total joint replacement in the prior 6 months, the rheumatic disease comorbidity index, and the cumulative number of biologic medications.

Conclusion: JIA patients have different disease characteristics and patient reported outcomes compared to RA patients matched on disease duration and treatment era. JIA patients had active disease in adulthood with similar number of visits to rheumatology and higher pain scores than RA patients. Comorbidities, disease severity, and fibromyalgia may explain the lower SF-36 MCS and higher PAS-II among JIA patients rather than age of diagnosis. This is the first study to compare patient reported outcomes of adult JIA patients to RA patients.

Table 1: Demographics, disease characteristics, and patient reported outcomes for JIA and matched RA patients in the NDB. Not all variables had 100% response rate. * indicates $p < 0.05$

	All JIA (n=596)	RA (n=1788)
Female (n,%)	539 (90.44%)	1617 (90.44%)
Age, years (mean, SD) *	34.30 (9.95)	53.08 (7.42)
Age of onset, years (mean, SD) *	10.41 (5.36)	30.34 (8.87)
Disease duration, years (mean, SD) *	23.88 (10.20)	22.75 (9.12)
Ethnic origin (%), White, not Hispanic *	81.88%	86.19%
Urban (n, %) *	106 (18.12%)	469 (26.71%)
Total Annual Income, US $ (mean, SD) *	48,364.09 (34,509.28)	54,955.26 (33,039.86)
Disabled (self-reported work status)	137 (24.08%)	475 (27.91%)
Rheumatology visits in prior 6 months (mean, SD)	2.44 (2.16)	2.26 (1.95)
Lifetime DMARD and biologic use, count (mean, SD) *	3.79 (2.49)	4.27 (2.58)
Lifetime biologic use, count (mean, SD) *	1.27 (1.28)	1.13 (1.21)
Lifetime Total Joint Replacement (n, %) *	136 (22.97%)	486 (27.27%)
Total Joint Replacement in prior 6 months (n, %)	30 (5.15%)	71 (4.01%)
HAQ (mean, SD)	1.05 (0.75)	1.12 (0.77)
Pain 0-10 VAS, (mean, SD) *	4.61 (2.80)	4.22 (2.87)
Patient Activity Score (mean, SD)	4.07 (2.30)	3.93 (2.30)
Patient Activity Score II (mean, SD) *	4.15 (2.31)	3.78 (2.33)
SF-36 Physical Component Score (mean, SD)	35.97 (11.17)	36.25 (12.54)
SF-36 Mental Component Score (mean, SD) *	45.17 (12.49)	47.46 (12.86)
Rheumatic Disease Comorbidity Index (mean, SD) *	1.58 (1.54)	1.74 (1.65)
Depression, ever (n, %)	281 (48.95%)	857 (50.26%)
Fibromyalgia (new and old NDB survey criteria) (n, %) *	201 (38.21%)	518 (31.70%)

Disclosure: M. L. Mannion, None; **S. Pedro**, None; **T. Beukelman**, UCB, 5,Genentech/Roche, 5,Novartis Pharmaceutical Corporation, 5; **J. R. Curtis**, Pfizer Inc, 2,Pfizer Inc, 5; **K. Michaud**, None.

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Abstract Number: 1479

Qualitative Assessment of Patient Important Long-Term Outcomes in Juvenile Idiopathic Arthritis

Melissa L. Mannion[1], Michelle Williams[2], Nataliya Ivankova[3], Gerald McGwin Jr.[4], Kenneth G. Saag[5] and Timothy Beukelman[6], [1]Pediatrics, University of Alabama at Birmingham, Birmingham, AL, [2]School of Public Health, University of Alabama at Birmingham, Birmingham, AL, [3]Health Services Administration, University of Alabama at Birmingham, Birmingham, AL, [4]Epidemiology, University of Alabama at Birmingham, Birmingham, AL, [5]University of Alabama at Birmingham, Birmingham, AL, [6]Pediatric Rheumatology, University of Alabama at Birmingham, Birmingham, AL

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Background/Purpose: The aim of this study was to identify and characterize the factors that JIA patients in young adulthood use to define a successful disease outcome, with the ultimate goal of creating an outcome assessment tool to provide a gold-standard for comparing different treatment approaches for JIA.

Methods: In depth personal interviews were conducted with adolescents (ages 14-18) and young adults (ages 19-40) with JIA and parents of children with JIA to generate themes regarding successful treatment, acceptable disease states, and optimal disease management outcomes for young adults with JIA. Interviews were recorded and transcribed; then they were coded using in vivo coding to generate mutually exclusive categories that were further combined into themes and quantized. The outcome topic categories were also quantized

based on the number of participants who mentioned the category. Outcome themes were compared to themes generated from interviews with pediatric rheumatologists. 4 adolescents with JIA, 6 young adults with JIA, and 10 parents of children with JIA were interviewed with representation of all US census regions. 13 pediatric rheumatologists from the US were interviewed.

Results: The initial in vivo codes were regrouped into 15 outcome topics and quantized; chronic arthritis/joint damage, physical/functional, medication, pain/fatigue, expectations, vocation/profession, social/participation, daily life/activities of daily living, health, vision, family, independence, appearance, mental health, and community. The categories with the most patient/parent codes were medication, social/participation, and community while the categories with the most physician codes were chronic arthritis/joint damage, physical/functional, and medication. The categories mentioned by all patients and parents were physical/functional, medication, social/participation, and community. The transcripts were recoded for description of outcomes resulting in 9 mutually exclusive categories; ability, active disease/remission, interference/burden, feel normal, everything that they want to do, understanding, satisfaction, indistinguishable from peers, and acceptance. The categories with the most patient/parent codes were interference/burden and indistinguishable from peers; the categories with the most physician codes were ability and interference/burden. Interference/burden was mentioned in all interviews, indistinguishable from peers was mentioned by all patients and parents and ability was mentioned by all physicians.

Conclusion: This study begins to characterize the factors that adolescents with JIA, young adults with JIA, and parents of children with JIA use to define a successful disease outcome for JIA in young adulthood. Patients prioritize medication burden and effects, social and participation impacts, and the idea of a supportive community in the definition of successful JIA management. With additional studies, the definition of a gold standard based on physician and patient input will enable patients to be better informed about their treatment options and expected future outcomes.

Disclosure: M. L. Mannion, None; **M. Williams**, None; **N. Ivankova**, None; **G. McGwin Jr.**, None; **K. G. Saag**, None; **T. Beukelman**, UCB, 5,Genentech/Roche, 5,Novartis Pharmaceutical Corporation, 5.

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Abstract Number: 1480

Adiposity in Children with Juvenile Psoriatic Arthritis (JPsA)

Aaida Samad[1], Matthew L. Stoll[2], Idit Lavi[3], Kriti Gupta[1], Joyce Hsu[4], Vibeke Strand[5,6], Elizabeth D. Mellins[7], Devy Zisman[8] and for the CARRA Registry Investigators, [1]Dept of Pediatrics CSSR, Stanford University Med Ctr, Stanford, CA, [2]University of Alabama at Birmingham, Birmingham, AL, [3]Department of Community Medicine and Epidemiology, Carmel Medical Center, Haifa, Israel, [4]Pediatric Rheumatology, Stanford University, Palo Alto, CA, [5]Stanford University, Palo Alto, CA, [6]Biopharmaceutical Consultant, Portola Valley, CA, [7]Dept of Pediatrics CCSR, Stanford University Med Ctr, Stanford, CA, [8]Rheumatology Unit, Carmel Medical CenterThe Ruth and Bruce Rappaport Faculty of Medicine, Technion, Israel, Haifa, Israel

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Session Time: 9:00AM-11:00AM

Background/Purpose: To assess the adiposity/BMI of children diagnosed with JPsA in a North American registry, examining differences between overweight and non-overweight patients with regard to demographic data, family history, clinical characteristics, radiological manifestations, and scores on Physician Global Assessment, Health-Related Quality of Life, parent/subject overall well-being (PSOWBS), parent/subject pain scale & the Childhood Health Assessment Questionnaire (CHAQ).

Methods: The study population included all JPsA patients in the Childhood Arthritis and Rheumatology Research Alliance (CARRA) registry for whom age, height and weight were recorded at baseline visit. We assessed adiposity according to CDC 2010 recommendations —in children < 2 years, the ratio of weight to length was plotted on WHO curves, and in children ≥ 2 years, BMI was calculated according to height, weight and age using the CDC/NCHS growth references. Children were divided into two groups: non-overweight including underweight (<2.3rd percentile for children < 2 years and calculated BMI < 5th percentile in children ≥ 2 years old) and normal weight (2.3rd - 97.7th percentile for children < 2 years and calculated BMI ≥ 5-85th percentile in children ≥ 2 years old) children and an overweight group including overweight (>97.7th percentile for children < 2 years and calculated BMI > 85th percentile in children ≥2 years old) and obese (BMI ≥ 95th percentile in children >2 years) children. Descriptive analysis of BMI subgroups was performed using

prevalence and percent for the categorical characteristics and mean ±standard deviation or median for continuous parameters. Comparisons of categorical characteristics between two independent groups (non-overweight and overweight) were done by Chi square or Fisher's exact test. Comparison of continuous parameters between BMI subgroups was performed by T-test or Mann Whitney test, as appropriate.

Results: 320 out of 361 (88.6%) children with JPsA were included in the study: 116 (36.3%) were overweight and 204 (63.8%) were non-overweight. The majority of patients were white (90.6%), non-Hispanic (91.3%) and female (64.7%). Between the two groups, children in the overweight category were significantly older at symptoms onset (9.26 ± 4.48 vs. 7.74 ±4.67 years, P=0.005). There were no significant differences between the two groups for other demographic parameters (race/ethnicity, gender, age at first rheumatology assessment), family history, number of joints involved, nail pitting, dactylitis, psoriasis, enthesitis, sacroiliitis, uveitis and radiological manifestations. In health assessment questionnaires, overweight patients scored worse on the PSOWBS (2.64 ± 2.32 vs 2.15 ± 2.15, p=0.04) and CHAQ (0.42 ± 0.52 vs 0.31 ± 0.47, p=0.05).

Conclusion: More than 1/3 of patients with JPsA from this registry were overweight and around 19% were obese. Patients who were overweight developed symptoms later and had worse patient reported outcomes as shown by PSOWBS and CHAQ scores. Not only does this JPsA subgroup feel subjectively worse, but patients with increasing adiposity/BMI also may have poorer long-term outcomes with regards to growth and health.

Disclosure: A. Samad, None; **M. L. Stoll**, None; **I. Lavi**, None; **K. Gupta**, None; **J. Hsu**, None; **V. Strand**, None; **E. D. Mellins**, Novartis, Glaxo-Smith-Kline, 2,Ascendent, Codexis, 5; **D. Zisman**, None.

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Abstract Number: 1481

A Description of the Transition Aged Population in the Childhood Arthritis and Rheumatology Research Alliance (CARRA) Registry

Aimee O. Hersh[1], Mary Beth Son[2] and Emily von Scheven[3], [1]Pediatrics/Rheumatology, University of Utah, Salt Lake City, UT, [2]Division of Immunology, Children's Hospital Boston, Boston, MA, [3]Dept of Pediatric Rheumatology, Univ of California San Francisco, San Francisco, CA

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Background/Purpose: The chronic and complex nature of pediatric-onset rheumatic diseases (PRD) necessitates the need for effective health care transition from pediatric to adult providers. Prior studies suggest suboptimal transition and health outcomes for patients with PRD. We utilized the Childhood Arthritis and Rheumatology Research Alliance (CARRA) registry to describe a large transition aged cohort with JIA and jSLE.

Methods: Baseline, cross-sectional data were obtained from the CARRA registry, a pediatric rheumatology database contributed to by 60 pediatric rheumatology centers in North America. Patients (pts) included were diagnosed with JIA or jSLE at ≤18 years (yrs) of age. Pts ≥18 yrs of age were considered "transition aged." Data abstracted included demographics, measures of disease activity (Systemic Lupus Erythematosus Disease Activity Index (SLEDAI), Childhood Arthritis Questionnaire (CHAQ), Health Related Quality of Life (HRQOL), parent or self-report pain scores with a Likert scale: 0 = no pain,10 = very severe pain) and current and past medications at baseline visit. Descriptive statistics and tests of comparison were used to compare the variables between pts younger and older than 18 yrs with JIA and jSLE.

Results:

Data from 6572 JIA and 1014 jSLE pts were analyzed; 466 (7.1%) JIA pts and 251 (24.7%) jSLE pts were ≥18 yrs old at baseline visit (Table 1).

Transition JIA pts were more likely than younger JIA pts to have enthesitis related arthritis or rheumatoid factor positive polyarticular JIA

subtypes and had higher pain scores (3.2 vs 2.6, p=0.000). There was no difference in insurance, CHAQ, or HRQOL between transition and younger JIA pts. Among the transition JIA pts, 13% were on oral steroids, 45% were on methotrexate and 67% were on a TNF inhibitor.

Transition jSLE pts had longer disease duration and were more likely to be uninsured than younger jSLE pts (6% vs. 2.8%, p=0.03), but there was no difference in CHAQ, HRQOL and pain scores. SLEDAI scores were moderate (median of 4.0, range 0-45), and younger pts had higher SLEDAI scores than transition pts (5.1 vs. 4.3, p=0.046). As in transition JIA pts, older jSLE pts demonstrated polypharmacy with 62% taking steroids, 48% taking mycophenalate mofetil, and 30% ever prescribed intravenous cyclophosphamide.

Disease measures in transition JIA and jSLE cohorts were also compared (Table 2).

Conclusion: In this large cohort of transition aged pts with PRD, there was significant disease activity and polypharmacy. This analysis highlights the need for comprehensive transitional support for disease management, medication monitoring and follow-up care.

Table 1.

	Transition cohort (n = 717)
JIA, n (%)	466 (65)
jSLE, n (%)	251 (35)
Median age at baseline visit, yrs (range)	19.1 (18-32)
Mean age at disease onset, yrs (SD)	11.6 (4.5)
Female, n (%)	532 (74)
Ethnicity	
Hispanic/Latino n (%)	130 (18)
Race, n (%)	
White	508 (72)
Black	125 (17)
Asian	55 (7.7)
Other	30 (7)
Uninsured, n (%)	27 (3.7)

Table 2.

	JIA (n=466)	jSLE (n=251)	p value
CHAQ score, median (range)	0.125 (0-3)	0 (0-3)	0.0015
HRQOL, n (%)			
Excellent/Very good/ Good	430 (92)	224 (89)	NS
Pain score, median (range)	3.26 (2.8)	2.7 (2.9)	0.0041

Disclosure: A. O. Hersh, None; **M. B. Son**, None; **E. von Scheven**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/a-description-of-the-transition-aged-population-in-the-childhood-arthritis-and-rheumatology-research-alliance-carra-registry

Abstract Number: 1482

Temporomandibular Pain in Patients with Juvenile Idiopathic Arthritis

Peter Stoustrup[1], **Marinka Twilt**[2], Bernd Koos[3], N Tzaribachev[4], Troels Herlin[5], Thomas Klit Pedersen[6] and Lynn R. Spiegel[7], [1]Section of Orthodontics, University of Aarhus, Aarhus C, Denmark, [2]Pediatric Rheumatology, Aarhus University Hospital, Aarhus, Denmark, [3]Orthodontics, University of Rostock, Rostock, Germany, [4]Pediatric Rheumatology, PRI - Pediatric Rheumatology Research Institute, Bad Bramstedt, Germany, [5]Pediatric Rheumatology Clinic, Department of Pediatrics, Aarhus University Hospital, Aarhus, Denmark, [6]orthodontics, Aarhus University Hospital/Dental school, Aarhus, Denmark, [7]Rheumatology/Pediatrics, The Hospital for Sick Children, Toronto, ON, Canada

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Background/Purpose:

Joint pain is a primary symptom in Juvenile Idiopathic Arthritis (JIA). Experience of pain has been shown to be a significant predictor of impaired physical and psychosocial function. Although pain in JIA overall is a well-known feature and pain-related beliefs were significantly associated with pain in children with JIA, perception and impact of pain of the temporomandibular joint (TMJ) in patients with JIA is not well researched. Therefore a TMJ specific pain questionnaire was developed by the Clinical Recommendation group of euroTMjoint, an international network established in 2010 to enhance multidisciplinary, multicenter TMJ research in JIA. The aim of this study is to report the frequency and pattern of pain in the TMJ area and describe the impact on TMJ function.

Methods:

A specific TMJ pain questionnaire was developed based on a Delphi study and systematic review. The following items were incorporated: pain frequency; pain intensity; pain location; TMJ function; TMJ symptoms; changes in facial or TMJ pain since last visit; changes in TMJ function since last visit. All consecutive JIA patients visiting one orthodontic clinic in Aarhus, Denmark, were included.

Results:

180 patients were approached to participate in the study. All patients agreed, however 8 did not complete the questionnaire, and were therefore excluded. 172 questionnaires were included. 58% (100/172) of patients reported the presence of TMJ pain with a median VAS of 3.6 (range 0.4-8.9). Imaging of the TMJ (CBCT or MRI) was available in 112 of the 172 patients (65%); 69% in patients with TMJ pain and 60% in patients without TMJ pain. Evidence of TMJ involvement on imaging was present in 61/69 (88%) of patients with TMJ pain and in 34/43 (79%) of patients without TMJ pain. The most frequent orofacial pain location was the masseter area followed by the TMJ region (58% and 46% respectively); and in both the masseter and TMJ regions in 15% of patients.Patients with TMJ pain reported significantly more functional problems, such as difficulty chewing, than those without pain. (70% compared to 7%, $p<0.0001$).

Conclusion:

More than half of JIA patients experience orofacial pain. Most frequently this involves the masseter and TMJ region. TMJ pain seems to be more frequent in patients with TMJ pathology on imaging, however is also present when imaging is normal. Pain in the TMJ area is significantly correlated with functional TMJ problems.

Disclosure: P. Stoustrup, None; **M. Twilt**, None; **B. Koos**, None; **N. Tzaribachev**, UCB, Pfizer, Janssen, Roche, 2; **T. Herlin**, None; **T. K. Pedersen**, None; **L. R. Spiegel**, None.

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Abstract Number: 1483

Pediatric Rheumatologists' Perceptions of Career Satisfaction, Confidence in Fulfilling Their Roles, and Burn-out

Lakshmi N. Moorthy[1], Rayfel Schneider[2], Meredith Riebschleger[3], Eyal Muscal[4], Marisa S. Klein-Gitelman[5], B. Anne Eberhard[6], Polly J. Ferguson[7], Kelly A. Rouster-Stevens[8], Hermine I. Brunner[9], Sampath Prahalad[8] and Peter A. Nigrovic[10], [1]Pediatric Rheumatology, Rutgers-Robert Wood Johnson Medical School, New Brunswick, NJ, [2]Division of Rheumatology, The Hospital for Sick Children and University of Toronto, Toronto, ON, Canada, [3]Pediatric Rheumatology & Health Services Research, University of Michigan, Ann Arbor, MI, [4]Pediatric Rheumatology, Baylor College of Medicine, Texas Children's Hospital, Houston, TX, [5]Division of Rheumatology, Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, IL, [6]Schneider Children's Hospital, New Hyde Park, NY, [7]Dept of Pediatrics--Rheum, University of Iowa, Iowa City, IA, [8]Emory University School of Medicine and Children's Healthcare of Atlanta, Atlanta, GA, [9]Cincinnati Child Hospital Medical Center (CCHMC) Division of Rheumatology, Cincinnati, OH, [10]Department of Medicine, Division of Rheumatology, Immunology and Allergy, Brigham and Women's Hospital, Harvard Medical School, Boston, MA

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Background/Purpose: Mentoring usually targets academic advancement in medicine, but it may also foster success in non-academic aspects of professional life, such as work-life balance. The American College of Rheumatology (ACR) and the Childhood Arthritis & Rheumatology Research Alliance (CARRA) developed the ACR/CARRA Mentoring Interest Group (AMIGO) in 2011 to foster mentoring in pediatric rheumatology. We assessed pre-AMIGO measures of career satisfaction in pediatric rheumatology, including career aspirations, confidence with professional tasks, and self-reported burn-out.

Methods: Internet-based survey of US and Canadian pediatric rheumatologists in 2011, before AMIGO implementation.

Results: Respondents included 277 pediatric rheumatologists, estimated at >75% of pediatric rheumatologists in the US and Canada. Of 129 who responded to the question about their "ideal job," 81% indicated that the ideal job included doing "primarily clinical work"; 61% reported it included "mentoring in clinic"; 57% reported "research," 20% reported "mentoring in research," and 5% reported "administration." About 50% responded that they were likely to obtain their ideal job.

Of the198 who responded to questions about confidence in work-related tasks, most respondents stated they were quite/extremely confident about advocating for patients, contributing to educational programs and meeting clinical productivity goals (Table 1). Most reported being somewhat/slightly/not at all confident in accessing grant funding, working with industry, achieving work-life balance, advocating for themselves at work, and managing their practices (Table1). Of 190 who responded to questions about burn out, 31% reported burn out at work at least once a week.

Conclusion: Most pediatric rheumatologists feel confident about meeting their clinical and educational responsibilities but a significant proportion have concerns about their ability to obtain grants, work with industry, manage administrative aspects of their jobs and achieve work-life balance. Burn-out is reported by a substantial fraction. Follow up evaluations of AMIGO mentees will assess whether improved access to mentoring through AMIGO has helped to address these needs. Further exploration of reasons behind burnout and work-life balance concerns is warranted.

Table 1: Data on confidence among pediatric rheumatologists

	Not confident at all	Slightly/ somewhat confident	Quite/ extremely confident	N/A
Meet goals for clinical productivity	2 (1%)	60 (30%)	128 (63%)	9 (5%)
Advocate for patients	2 (1%)	29 (15%)	158 (80%)	9 (5%)
Contribute to educational programs	2 (1%)	66 (33%)	128 (64%)	3 (1.5%)
Keep track of teaching activities	7 (4%)	90 (43%)	96 (48%)	6 (3%)
Access grant funding	61 (31%)	86 (43%)	37 (19%)	15 (8%)
Work with industry	52 (26%)	82 (41%)	28 (14%)	37 (19%)
Manage your practice	27 (14%)	76 (38%)	60 (30%)	36 (18%)
Advocate for yourself at work	18 (9%)	105 (53%)	76 (38%)	
Achieve success in your job (as defined by the person)	7 (4%)	87 (44%)	105 (53%)	
Work-life balance	19 (10%)	111 (56%)	66 (33%)	2 (1%)

Disclosure: L. N. Moorthy, None; **R. Schneider**, None; **M. Riebschleger**, None; **E. Muscal**, None; **M. S. Klein-Gitelman**, None; **B. A. Eberhard**, None; **P. J. Ferguson**, None; **K. A. Rouster-Stevens**, None; **H. I. Brunner**, None; **S. Prahalad**, None; **P. A. Nigrovic**, None.

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Abstract Number: 1484

Development and Validation of Juvenile Autoinflammatory Disease Multidimensional Assessment Report (JAIMAR)

Dilek Konukbay[1], Dilek Yildiz[1], Cengizhan Acikel[2,3], betul sozeri[4], Balahan Makay[5], Nuray Aktay Ayaz Sr.[6], Kenan Barut[7], Aysenur Kisaarslan[8], Yelda Bilginer[9], Harun Peru[10], Ozlem Aydog[11], Erbil Unsal[12], Ozgur Kasapcopur[13], Zubeyde Gunduz[8], Seza Ozen[14] and **Erkan Demirkaya**[15], [1]Gulhane Military Medical Faculty, Ankara, Turkey, [2]Biostatistics, Gulhane Military Medical Faculty, Ankara, Turkey, [3]Department of Bioistatistics, Gulhane Military Medical Academy, Ankara, Turkey, [4]Pediatric Rheumatology, Ege University Faculty of Medicine, Izmir, Turkey, [5]Pediatric Rheumatology, Eylul University, Izmir, Turkey, [6]Pediatric Rheumatology, Istanbul KSS Education and Research Hospital, Istanbul, Turkey, [7]Department of Pediatric Rheumatology, Cerrahpasa Medical School, Istanbul University., Fellow in Pediatric Rheumatology, Istanbul, Turkey, [8]Pediatric Rheumatology, Erciyes University Faculty of Medicine, Kayseri, Turkey, [9]Department of Pediatric Rheumatology, Hacettepe University Faculty of Medicine, Ankara, Turkey, [10]Pediatric Rheumatology, Selcuklu Medical Faculty, Konya, Turkey, [11]Pediatric Rheumatology, Dr. Sami Ulus Children's Hospital, Ankara, Turkey, [12]Pediatric Rheumatology, 9 Eylul University Faculty of Medicine, Izmir, Turkey, [13]Pediatric Rheumatology, Istanbul University Cerrahpasa Medical Faculty, Istanbul, Turkey, [14]Deptartment. of Pediatric Rheumatology, Hacettepe University, Ankara, Turkey, [15]Pediatric Rheumatology, Gulhane Military Medical Academy, FMF Arthritis Vasculitis and Orphan disease Research Center (FAVOR),, Ankara, Turkey

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Background/Purpose: There are lots of effects of auto-inflammatory diseases (e.g. pain, fatigue, fear of attack, lifelong drug use, being nervous and angry, problems at school) and those are quite important to patients but have not been measured with the outcome instruments currently included in clinical trials of auto-inflammatory diseases. The aim of this study is to develop and validate a new multidimensional questionnaire for assessment of children with auto-inflammatory disease (AID) in standard clinical care.

Methods: JAIMAR includes 16 parent or patient-centered measures and four dimensions that assess functional status, pain, therapeutic compliance and health-related quality of life (physical, social, school, emotional status) with disease outcome. The JAIMAR is proposed for use as both a proxy-report and a patient self-report, with the suggested age range of 8-18 years for use as a self-report. The study was conducted both children with FMF and their parents in seven different paediatric rheumatology centers from Turkey. To validate the JAIMAR, the Outcome Measures in Rheumatology Clinical Trials (OMERACT) filter for outcome measures in rheumatology was applied.

Results: The analysis data set was collected from the parents of 250 children with FMF in 351 visits and from 179 children in 187 visits. The median age of the children was 10.64 ± 4.38. The JAIMAR was found to be feasible and to possess face, content, criterion and construct validity. Completing and scoring of the JAIMAR is quick and can be finished approximately in 15 minutes. The Cronbach's alpha coefficient for internal consistency for the JAIMAR dimensions was between 0.507-0.998. Between the test-retest scale scores, there is a significant and a positive correlation from medium level to high level (0.607-0.966). For construct validity all the factor loadings are above 0.30. When the criterion validity is considered, we would say that the correlation level between the each subscale and the related scale spanned from medium ($r = 0.329$, $p < 0.0001$) to large ($r = 0.894$, $p < 0.0001$). Parents' proxy-reported and children's self-reported data were outstandingly concordant. Cronbach's alpha values were between 0.770-0.989.

Conclusion: The development of the JAIMAR introduces a new and a multi-dimensional approach in pediatric rheumatology practice. It is a valid tool for children with autoinflammatory disease and will help enhance the quality of care of in this group of patients.

Disclosure: D. Konukbay, None; **D. Yildiz**, None; **C. Acikel**, None; **B. sozeri**, None; **B. Makay**, None; **N. Aktay Ayaz Sr.**, None; **K. Barut**, None; **A. Kisaarslan**, None; **Y. Bilginer**, None; **H. Peru**, None; **O. Aydog**, None; **E. Unsal**, None; **O. Kasapcopur**, None; **Z. Gunduz**, None; **S. Ozen**, None; **E. Demirkaya**, None.

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Abstract Number: 1485

Efficacy of Yttrium-90 Radiosynovectomy in Camptodactyly-Arthropathy-Coxa Vara-Pericarditis Syndrome

Sulaiman M Al-Mayouf[1], Nora AlMutairi[2] and Khalid Alismail[3], [1]Pediatric Rheumatology, King Faisal Specialist Hospital & Research Center, Riyadh, Saudi Arabia, [2]Pedaitric Rheumatology, King Faisal Specialist Hospital & Research Center, Riyadh, Saudi Arabia, [3]Musculoskeletal Radiology, King Faisal Specialist Hospital & Research Center, Riyadh, Saudi Arabia

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Session Time: 9:00AM-11:00AM

Background/Purpose:

Camptodactyly-arthropathy-coxa-vara-pericarditis (CACP) syndrome is an autosomal recessive disorder caused by mutations in PRG4 gene that encodes for proteoglycan 4, the main lubricant for joints and tendon surfaces. It is non-inflammatory arthropathy, characterized by joint effusions and synovial hypertrophy. So far, there is no effective treatment for this disorder. We evaluated the effectiveness of yttrium-90 radiosynovectomy in arthropathy of patients with CACP syndrome

Methods:

Consecutive patients with CACP syndrome prospectively evaluated at the enrollment and 3 months after the right knee injection with yttrium-90. The outcome variables were patient/ parent and physician's global assessment measured by a 3-point scale, right knee swelling and range of motion on a 3-point scale, in addition to *Magnetic Resonance Imaging*(MRI) assessment of the right knee for bone, cartilage, fluid, synovial hypertrophy and soft tissue changes.

Results:

Six (3 boys, 3 girls) patients with mean age of 12 years and mean follow-up duration of 8.5 years completed a single right knee intra-articular yttrium-90 injection with 5 mCi. The procedure was well tolerated without adverse events apart from mild and transient joint pain in 2 patients. There was a minimal radioisotope leakage to soft tissue in 2 patients. During the 3 months follow-up interval, there was no improvement in the outcome variables. Patients and parents did not notice favorable therapeutic effects and global physician assessment was unsatisfactory. No difference in knee joint swelling or range of motion. Furthermore, MRI findings were unchanged. However, there was minimal increase in synovial fluid post injection.

Conclusion:

Yttrium-90 radiosynovectomy seems to be safe and well tolerated procedure, but with the given dose and interval time it didn't show a beneficial therapeutic effect in arthropathy of CACP syndrome.

Disclosure: S. M. Al-Mayouf, None; **N. AlMutairi**, None; **K. Alismail**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/efficacy-of-yttrium-90-radiosynovectomy-in-camptodactyly-arthropathy-coxa-vara-pericarditis-syndrome

Abstract Number: 1486

Comparative Study of Instruments to Assess Disease Activity in Fibrolyalgia

Susan Chrostowski[1], Barbara Gray[2] and Peggy Mancuso[2], [1]Rheumatology Associates of Texas, Dallas, TX, [2]Texas Woman's University, Dallas, TX

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Session Title: Quality Measures and Quality of Care Poster Session (ARHP): Clinical Practice/Patient Care

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Background/Purpose:

Clinical assessment instruments to accurately assess disease activity in the fibromyalgia population have been difficult to develop because of the subjective nature of the disease. The Symptom Severity (SS) scale is an instrument completed by the healthcare provider based on the provider's perception of the patient's symptoms. The Revised Fibromyalgia Impact Questionnaire (FIQR) is a tool completed by the patient and based on the patient's perception of their symptoms severity. The purpose of this study was to determine whether a provider-generated assessment tool, the SS scale, would provide comparable results to a patient-generated assessment tool, the FIQR, for evaluation of symptom severity in adults with an established diagnosis of fibromyalgia.

Methods:

One hundred fifty five participants were recruited from a convenience sample of adult patients at a private rheumatology office in the south central United States. The participants had an established diagnosis of fibromyalgia. After providing consent for study participation, the participants were provided with a copy of the FIQR to complete prior to their appointment with the medical provider. During the medical assessment, the healthcare provider completed the SS scale based on the provider's perception of the patient's symptoms. The assessment instruments were completed at the same clinic visit and kept separated and blinded from each other.

Results:

Spearman's rank-based correlation coefficients showed that SS-fatigue was weakly correlated with FIQR Domain 1 (ρ = .285) and moderately correlated with Domains 2 and 3 (ρ = .438; ρ = .447) and the FIQR total score (ρ = .420). Similarly, SS-waking unrefreshed was weakly correlated with FIQR Domain 1 (ρ = .250) and moderately correlated with Domains 2 and 3 (ρ = .353, ρ = .385) and FIQR total score (ρ = .358). SS-somatic symptoms and SS-total scores were moderately correlated with all three FIQR domains and the FIQR total score (ρs ranging from .371 to .527). FIQR scores were, on average, higher than were SS scores (M = .559 compared to M = .479), and the difference between them was statistically significant, t (154) = 5.094, p < .001.

Conclusion:

All five subscales of the Symptom Severity scale were significantly related to the four FIQR domains and the FIQR total score. Higher scores on the SS scale were associated with higher scores on the FIQR questionnaire. The strength of the relationships, however, was moderate. The FIQR completed by the patient had significantly higher total scores than the SS scale completed by the healthcare provider. These findings suggest that the study participants perceived their FM disease activity to be higher than was perceived by the healthcare provider.

Disclosure: S. Chrostowski, None; **B. Gray**, None; **P. Mancuso**, None.

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Abstract Number: 1487

Tocilizumab in Combination with Methotrexate in the Treatment of Rheumatoid Arthritis in Patients Who Have Failed to Disease-Modifying Antirheumatic Drugs: Long Term Results of the Brazilian Cohort

Wiliam Chahade[1], Cristiano Zerbini[2], Sebastiao Radominski[3], Morton Scheinberg[4], Walber P. Vieira[5] and Ana Paula Garcia Lucco[6], [1]Director-Rheumatology, Hospital Servidor Estadual, Sao Paulo, Brazil, [2]Centro Paulista de Investigação Clinica, São Paulo, Brazil, [3]Universidade Federal do Paraná, Curitiba, Brazil, [4]Clinical Research, Hospital Abreu Sodre-AACD, Sao Paulo, Brazil, [5]Hospital Geral de Fortaleza, Fortaleza, Brazil, [6]Produtos Roche Químicos e Farmacêuticos SA, São Paulo, Brazil

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Background/Purpose: Tocilizumab is a humanized monoclonal antibody that binds to IL-6 receptor, blocking its effects. The efficacy and safety of tocilizumab in rheumatoid arthritis (RA) patients were evaluated in a comprehensive global clinical development program with several phase III studies, following the initial development in Japan. The long-term efficacy of tocilizumab was also established based on the follow-up of prior pivotal studies. Although efficacy and safety of the drug is consistent in the literature, efficacy and safety data in Brazilian population are scarce. The RITMO study collected the long-term safety and efficacy of tocilizumab associated with methotrexate in patients with RA with inadequate response to disease-modifying antirheumatic drugs (DMARD) therapy. The Brazilian cohort of RITMO study followed patients over a period of 2 years. Therefore, the aim of the present study is to evaluate safety and efficacy of tocilizumab 8 mg/kg associated with methotrexate in the treatment of Brazilian patients with moderate to severe RA with inadequate response DMARDs therapy.

Methods: RITMO was an open-label, phase 3, single-arm study conducted in 10 countries from Latin America to evaluate follow-up of intravenous tocilizumab, in association with methotrexate, in patients with moderate to severe active RA with inadequate response to DMARDs. Brazilian patients were enrolled to the extension study and were followed during 2 years, receiving treatment for 96 weeks. Efficacy and safety-related outcomes were analyzed. This analysis includes only Brazil data. (Clinicaltrials.gov NCT00754572).

Results: 98 patients were included in this analysis. Patients presented early response to the study drug with rapid improvement, of which 32% of the patients achieved ACR20 response in the second week of treatment. In addition, the functional disability in patients decreased during the study, through reduction of HAQ-DI mean value from 1.6 ± 0.7 to 0.80 ± 0.40. After 24 weeks of treatment, patients achieved response rate of 77%, 57% and 39% for ACR20, ACR50 and ACR70, respectively; these response rates remained stable after this period. After 96 weeks, 46.1% of the patients met DAS28 remission criteria. Prevalence of adverse events was 115.6 events/100 patients-year, with 14 serious adverse events (2/100 patients-year); 145 infections in 63 patients (20.2/100 patients-year) were reported, of which 6 were serious infections (0.8/100 patients-year).

Conclusion: Tocilizumab associated with methotrexate in RA patients with inadequate response to DMARDs therapy was safe and effective. The analysis of the Brazilian cohort of RITMO study was consistent with prior reported phase III studies.

Disclosure: W. Chahade, None; **C. Zerbini**, None; **S. Radominski**, Roche Pharmaceuticals, 2; **M. Scheinberg**, None; **W. P. Vieira**, None; **A. P. Garcia Lucco**, Roche Pharmaceuticals, 3.

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Abstract Number: 1488

Following the American College of Rheumatology Quality Guidelines Can Enhance the Safety of Rheumatoid Arthritis Patients Treated with Disease Modifying Drugs

Delfina Bur[1] and Humeira M. Badsha[2], [1]Dr. Humeira Badsha Medical Clinic, Dubai, United Arab Emirates, [2]Rheumatology, Dr Humeira Badsha Medical Center, Dubai, United Arab Emirates
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Background/Purpose: Adverse events (AEs) and serious adverse events (SAEs) from disease modifying drugs (DMARDs) for Rheumatoid Arthritis (RA) can result in significant morbidity and even fatality. The American College of Rheumatology (ACR) has published drug safety disease modifying drug (DMARD) guidelines for doctors to follow so that they can monitor side effects. The aim of our study was to audit our practice to see if the ACR guidelines were followed and what impact that had on RA patients with AEs and SAEs.

Methods: We collected data on DMARD and biologic usage of 250 RA patients in a Musculoskeletal clinic in the United Arab Emirates (UAE) and audited the practice to see how many of the ACR drug safety guidelines were being followed. Subsequently we analyzed how

many patients suffered from AEs and SAEs (death, initial or prolonged hospitalization, persistent or significant disability, cardiac failure, or myocardial infarction). Outcomes of the AEs and SAEs were recorded.

Results: 518 DMARDs were prescribed to 250 patients (Methotrexate, Arava, Sulfazalazine, Imuran, Plaquenil, Enbrel, Humira, Xeljanz, Simponi, Acterma, and Mabthera). The average duration of DMARD use was 52.4 months. The average age was 47 years, 51 males (20.4%), 199 females (79.6%) and the ethnicities represented were 131 Asian (52.4%), 53 Arab (21.2%), 53 Caucasian (21.2%), 12 African (4.8%), and 1 other (0.4%). All six guidelines; informing patients about risk, prophylaxis for patients at risk for gastrointestinal bleeding, hemoglobin tests, serum creatinine tests, baseline studies, and drug toxicity monitoring were applied to 100% of the patients. 15.6% of all the patients experienced some sort of AE and 0.4% experienced a SAE. Of these patients 74.4% of them discontinued the medication that caused them to have an AE and changed to another DMARD. The reported AEs consisted of increased LFT (27.2%), intolerance (9.1%), infection (9.1%), allergy (9.1%), hair loss (7.3%), skin pigmentation (7.3%), chronic cough (5.5%), chronic low WBC (5.5%), severe injection site reaction (3.6%), discomfort in chest (1.8%), menorrhagia (1.8%), dizziness (1.8%), neoplastic lesion in thyroid (1.8%), psoriasis (1.8%), upper GI bleed (1.8%), asthma (1.8%), eye toxicity (1.8%) and pulmonary hemorrhage (1.8%). Of these AEs only pulmonary hemorrhage (1.8%) was deemed a SAE. All AEs were resolved due to early detection and careful monitoring.

Conclusion: Of the 250 patients administered with 518 drugs, 39 (15.6%) reported AEs of which 1.8% of them were deemed SAEs and 29 patients (74.4%) discontinued the DMARD. All adverse events were resolved with drug discontinuation and no patients had irreversible side effects. We believe that adherence to the ACR DMARD safety guidelines for RA treatment can limit the impact of AEs and SAEs and enhance the safety of patients.

Key Point: Strict adherence to the ACR drug safety guidelines results in patient safety and effective RA treatment.

Disclosure: D. Bur, None; **H. M. Badsha**, None.

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Abstract Number: 1489

Promoting Smoking Cessation Among Rheumatoid Arthritis Patients: What Motivations and Barriers Are Reported after Being Offered a Smoking Cessation Intervention?

Lisa K. Stamp[1], Megan Gath[1], Pip Aimer[1], Simon Stebbings[2] and Gareth Treharne[3], [1]Medicine, University of Otago, Christchurch, Christchurch, New Zealand, [2]Dunedin School of Medicine, University of Otago, Dunedin, New Zealand, [3]Department of Psychology, University of Otago, Dunedin, New Zealand

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Background/Purpose: Patients with rheumatoid arthritis (RA) may experience specific barriers to smoking cessation but may also be motivated to quit to improve their health, particularly if informed of the possible impact of smoking on disease activity, treatment efficacy, and outcomes. Qualitative research on the perspectives of smokers and ex-smokers with RA is needed to help design, implement, and evaluate smoking cessation interventions that can be applied in clinical practice if efficacious.

Methods: Semi-structured interviews were carried out with 29 ongoing smokers and 10 ex-smokers with RA who had previously been invited to participate in a randomized controlled trial of a novel RA-specific smoking cessation intervention (14/19 in the intervention group; 14/19 in the control group; 11/18 who had declined being in the trial). The interviews were led by a researcher with no involvement in the participants' clinical care. Interview transcripts were subjected to thematic analysis to investigate the motivations and barriers to smoking cessation that are most pertinent to RA patients, which led us to formulate themes outlining what we call ‘incentives' and ‘drives' to quit.

Results: Participants described five incentives to quit (health, arthritis, social relationships, coping mechanism, and costs) and four drives to quit (commitment, mental preparation, will power, and interventions). In particular, participants highlighted how their health (in general and relating to their RA) could provide an incentive to quit or be used as a rationalization for not having quit. Living with RA contributed to the stress and negative emotions experienced by participants and also limited the availability of coping methods that might be used in

places of smoking, particularly those coping methods requiring mobility. None of the 10 participants who had quit smoking mentioned having previously relied on smoking as a coping method.

Conclusion: When RA patients have been informed that continued smoking may impact on the outcomes of their RA it can provide an important incentive to quit smoking that may bolster other general incentives to quit. At the same time, RA patients experience stress and mobility difficulties that often make it difficult to quit smoking despite knowing the general and RA-specific health benefits. Overall, the incentives and drives revealed in this research also indicate ways that RA patients might be supported in developing the motivation to quit smoking and ways of overcoming barriers. RA patients who report using smoking to cope may benefit from psychological interventions to help them replace or reframe that coping method and bolster other psychological processes that can drive smoking cessation.

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Abstract Number: 1490

Can Patients Forget Their Artificial Joint after Arthroplasty?

Gizem Irem KINIKLI[1], Hande GUNEY[2], Sercan ONAL[2], Ceyda SARIAL[2], Dilara DONDER[2], Inci YUKSEL[2], Omur CAGLAR[3] and Gulay KINIKLI[4], [1]Department of Physiotherapy and Rehabilitation, Hacettepe University, Faculty of Health Sciences, Department of Physiotherapy and Rehabilitation, Ankara, Turkey, [2]Department of Physiotherapy and Rehabilitation, Hacettepe University, Faculty of Health Sciences, Ankara, Turkey, [3]Department of Orthopedics and Traumatology, Hacettepe University, Faculty of Medicine, Ankara, Turkey, [4]Department of Rheumatology, Ankara University, Faculty of Medicine, Ankara, Turkey
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Background/Purpose: Knee and hip osteoarthritis (OA) are the clinical outcome of a functional and structural failure resulting with pain and physical dysfunction. Total joint arthroplasty is increasingly utilised surgical treatment at the end stage (OA). The ultimate goal of arthroplasty surgery is for the patient to be able to forget the artificial joint during daily activities. The traditional main outcomes are clinically objective surgeon-reported endpoints. Patient-reported outcome assessment is the primary indicator of patient satisfaction with their operated joint results. The aim of this study is to investigate long-term patient functional outcomes and relationship with the ability to forget their artificial joint according to patients' perspective.

Methods: Consecutive 72 patients undergone unilateral cemented total hip arthroplasty or total knee arthroplasty (THA; n=42; TKA; n=30) for primary OA in Hacettepe University Hospital between January 2010 and January 2014, participated in the study. Patients were asked to complete the patient-reported outcome (PRO) assessments such as the Western Ontario and McMaster Universities (WOMAC) osteoarthritis index, Tampa Kinesiophobia Scale (TKS) and the Forgotten Joint Score (FJS-12). WOMAC Index was used to assess pain, stiffness and function. The TKS assessed the fear of movement. The FJS-12 consists of 12 questions where subjects were asked to rate their awareness of their joint arthroplasty during various activities.

Results: Average age 61.9 ± 14.6 years; 82% female, 50% obese (BMI>=30kg/m^2). Average time after surgery was 30.8±16.1 months. Mean post-operative WOMAC pain score was 13±3.2, WOMAC stiffness score was 7±1.4, WOMAC function score was 48±18.4. Mean TSK was 43.0±8.7 and mean FJS-12 score was 66.1±21.5. Correlations between FJS-12 and WOMAC and TKS scores were as follows: r=-0.68 for WOMAC-Pain, r=-0.53 for WOMAC-Stiffness, r=-0.65 for WOMAC-Function, and r=-0.63 for TKS in patients with TKA. Correlations between FJS-12 and WOMAC function score and TKS scores were as follows: r=-0.58 and r=-0.62 in patients with THA.

Conclusion: Assessing patients' perception about their artificial joint is becoming more important in clinical area following total joint arthroplasty. The true success of the surgery may not equate to the sum of a set outcome variables. Long-term follow-up with PROs showed that there is a need for a greater focus on understanding the perspectives of patients following arthroplasty surgery to improve the efficacy of interventions focused on better functional outcomes in TKA and THA recipients.

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2)Behrend H, Giesinger K, Giesinger JM, Kuster MS. The "forgotten joint" as the ultimate goal in joint arthroplasty: validation of a new patient-reported outcome measure.J Arthroplasty. 2012 Mar;27(3):430-436.

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Abstract Number: 1491

Effects of Drug Induced Toxicity on Patient Reported Outcomes in Early Rheumatoid Arthritis Treated-to-Target Using Conventional Triple DMARD Therapy

Nasir Wabe[1], Michael Sorich[2], Mihir Wechalekar[2,3], Leslie Cleland[3], Leah McWilliams[3], Anita Lee[4,5], Llew Spargo[4], Robert Metcalf[3], Cindy Hall[4], Susanna Proudman[4,5] and Michael D. Wiese[6], [1]School of Pharmacy and Medical Sciences and Sansom Institute for Health Research, University of South Australia, Adelaide, Australia, [2]Flinders University, Adelaide, Australia, [3]Royal Adelaide Hospital, Adelaide, Australia, [4]Rheumatology Unit, Royal Adelaide Hospital, Adelaide, Australia, [5]Discipline of Medicine, University of Adelaide, Adelaide, Australia, [6]University of South Australia, Adelaide, Australia

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Background/Purpose: While the introduction of the treat-to-target (T2T) strategy is associated with lower disease activity scores in rheumatoid arthritis (RA), the potential for increased toxicity due to more intensive use of concurrent DMARDs could adversely affect patient reported outcomes (PROs). The objective was to determine the effects of DMARD related toxicity on PROs in early RA patients treated according to T2T strategy for 3 years

Methods: A total of 149 patients from an inception cohort of recent onset RA were included. The occurrence and severity of toxicity were monitored at each clinic visit over three years. PROs studied were function (measured using health assessment questionnaire), helplessness (assessed using the rheumatology attitudes index), pain, fatigue and patient global assessment (PGA) all assessed using a 100mm visual analogue scale and health-related quality of life (HRQoL) (assessed using SF-36).

For each PRO, the effect of drug withdrawal was measured by comparing mean change from baseline among patients with no/temporary withdrawal *versus* those with permanent drug cessation. The effects of the frequency of minor side effects, frequency of drug withdrawals, weeks to withdrawal and number of drugs withdrawn were analysed using linear regression.

Results: After 3 years, 56 (37.6%) patients ceased at least one drug permanently due to toxicity. Patients with no/temporary withdrawal (n=93) achieved significantly greater improvement in function, pain, fatigue and PGA compared to their counterparts (n=56). Drug-related toxicity did not have a significant effect on HRQoL and helplessness (Table 1).

Table 1: Improvement in PROs, *mean change (SE),* according to withdrawal due to toxicity				
	No/temporary withdrawal (n=93)	Permanent withdrawal (n=56)	*Between group mean differences (95%CI)*	*P-value*
Function	-0.54 (0.06)	-0.31 (0.09)	-0.23 (-0.44 to -0.02)	0.033
Pain	-39.82 (3.44)	-25.02 (5.50)	-14.80 (-27.03 to -2.56)	0.018
Fatigue	-29.14 (3.43)	-14.76 (4.89)	-14.38 (-25.97 to -2.80)	0.015
PGA	-29.64 (3.16)	-17.00 (4.21)	-12.64 (-23.03 to -2.25)	0.018
Helplessness	-4.44 (0.62)	-3.69 (0.75)	-0.75 (-2.73 to 1.23)	0.455
SF-36 Summary				
Physical	10.85 (1.32)	6.84 (1.78)	4.01 (-0.36 to 8.38)	0.072
Mental	4.31 (1.38)	4.48 (1.83)	-0.17 (-4.71 to 4.37)	0.941

After adjusting for other relevant baseline variables, regression analysis indicated that higher frequency of withdrawals was associated with lesser improvements in function, pain, fatigue and PGA, while the number of drugs withdrawn and the time to withdrawal had lesser effects. The occurrence of minor side effects did not affect change in PROs (Table 2).

Table 2: Relationship between drug-related toxicities and improvement in PROs over 3 years.								
Nature of toxicity		Function	Pain	Fatigue	PGA	Helplessness	SF-36 Physical	SF-36 Mental
Frequency of minor side effects	β	-0.02	-1.34	0.14	-0.98	-0.04	-0.13	-0.21
	SE	0.01	0.71	0.75	0.62	0.11	0.28	0.29
	P-value	*0.262*	*0.061*	*0.854*	*0.119*	*0.701*	*0.630*	*0.474*
Frequency of withdrawals	β	-0.07	-4.17	-3.47	-4.12	-0.34	-1.04	-0.32
	SE	0.03	1.32	1.38	1.13	0.22	0.52	0.56
	P-value	*0.005*	*0.002*	*0.013*	*<0.000*	*0.124*	*0.05*	*0.573*
Weeks to first withdrawal	β	0.003	0.21	0.17	0.19	0.0	0.07	0.05
	SE	0.002	0.11	0.10	0.09	0.02	0.04	0.04
	P-value	*0.092*	*0.065*	*0.118*	*0.039*	*0.979*	*0.101*	*0.246*
No. of drugs withdrawn	β	-0.06	-4.29	-3.31	-4.15	-0.39	-0.32	-0.52
	SE	0.03	1.86	1.87	1.56	0.29	0.69	0.73
	P-value	*0.091*	*0.023*	*0.080*	*0.009*	*0.183*	*0.649*	*0.481*
The Beta sign indicates whether the PROs improved or not as a result of drug-induced toxicity. Negative scores indicate inverse relationship while positive scores indicate direct relationship.								

Conclusion: In the setting of a T2T strategy where use of multiple DMARDs and frequent dose escalation were common, DMARD withdrawal due to toxicity was significantly associated with less improvement in function, pain, fatigue and PGA while toxicity had little impact on helplessness and broader measures of HRQoL.

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Abstract Number: 1492

Implementation in Clinical Practice of a Medication Assessment Tool Specific for Rheumatoid Arthritis, Rhmat

Louise Grech[1,2], Anthony Serracino Inglott[1], Victor Ferrito[1] and Lilian M. Azzopardi[1], [1]Department of Pharmacy, University of Malta, Msida, Malta, [2]Clinical Pharmacy Practice Unit, Department of Pharmacy, Mater Dei Hospital, Msida, Malta
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Background/Purpose: The RhMAT is a medication assessment tool developed to specifically analyse pharmacotherapy adherence to evidence based medicine and guidelines on the management of rheumatoid arthritis. The RhMAT was developed to identify any gaps within management care plans. The objective of this study was to implement the innovative RhMAT within a pharmaceutical care plan model for rheumatoid arthritis patients.

Methods: Rheumatoid arthritis patients regularly attending the rheumatology clinic at Mater Dei Hospital who were 18 years or older, able to understand Maltese or English were eligible to participate in the study. The University of Malta Ethics approval and the patients' consent was obtained. The study was run between January and December 2014. The patients' medical notes were screened. Patient interviews were conducted where necessary to fill in gaps in the documentation. The RhMAT was completed for the patients taking part in the study. For each criterion given in the RhMAT the researcher can choose one of four options between adherence (yes), non adherence no justified, non adherence not justified, not applicable and insufficient data (table 1). The RhMAT adherence rate achieved was calculated. A score of 50% or less was determined as low adherence, a score between 51% and 74% showed intermediate adherence and a score of 75% or more was determined as high adherence to the RhMAT.

Results: A total of 78 patients (56 females, 22 males) were recruited for the study. More than half of the patients (55% n=43) were prescribed a traditional disease modifying antirheumatic drug (tDMARD) with 81% (n=35) being on monotherapy tDMARD. Methotrexate was the most commonly prescribed tDMARD whether monotherapy or in combination with other tDMARDs (n=29, 67%). Overall, a score of 75% or more, determined as high adherence rate, was achieved in 80% (n=62) and a score 51% to 74% or intermediate adherence rate was achieved in 19% (n=15). A low adherence score was achieved only in 1 patient.The mean score for the methotrexate section was 99.5% (n=54). The mean score for the biologic section was 97.9% (n=35). Time taken to complete each RhMAT for each patient was 15 minutes.

Conclusion: Methotrexate was the most common tDMARD prescribed. The average time taken to complete each RhMAT was realistic,practical and feasible for a busy clinic. The overall high adherence rate achieved indicates that the majority of the current pharmacotherapy of the study patient population is in agreement with established guidelines. A high adherence rate was also observed with respect to methotexte prescribing and monitoring and screening for biologic drugs. The RhMAT was useful in identifiying gaps in agreement to established guidelines thereby enabling the clinical pharmacist to discuss these issues with the clinicians further improving the quality of service offered.

Table 1. Extract from the RhMAT – Methotrexate section

	Methotrexate	N/A	Yes	No justified	No unjustified	Insufficient Data	Comments	Reference
1	Used as first line DMARD in the absence of contraindications							
2	Pre-treatment screening including Chest X ray, CBC, ESR, CRP, LFTs, U&Es, Creatinine have been completed							
3	Regular monitoring according to monitoring protocol schedule including mouth ulcers, nausea and vomiting and dyspnoea							
4	Contraindications namely pregnancy, breastfeeding, active local or systemic infection, bone marrow suppression excluded							
5	The patient has been prescribed methotrexate at a dose that is unambiguously expressed as a *ONCE A WEEK* administration							

Disclosure: L. Grech, None; **A. Serracino Inglott**, None; **V. Ferrito**, None; **L. M. Azzopardi**, None.

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Abstract Number: 1493

Adherence in Patients Who Are on Stable Doses of Methotrexate

Sandra M. Robinson[1], Peta S. Heslop[1], Stacey Duffy[2] and David Walker[3], [1]R&D, North Tyneside General Hospital, North Shields, United Kingdom, [2]R&D, Northumbria Healthcare NHS Foundation Trust, North Shields, United Kingdom, [3]Rake Lane, Northumbria Healthcare, Newcastle Upon Tyne, United Kingdom

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Background/Purpose:

Methotrexate has become the mainstay of DMARD treatment in Rheumatoid Arthritis and is also used in other rheumatological conditions. It is a drug that carries many tolerability problems with 56 to 85% prevalence of adverse symptoms, even in patients who continue on therapy (Robinson et al 2015). Adherence to drug regimes is not thought to be good with the WHO estimating that 40% of patients not being fully adherent. In a situation where there are also tolerability problems then adherence may be worse. We were interested to explore the

views of patients who were on stable ongoing doses of methotrexate about their adherence.

Methods: 450 patients from seven units spread across the UK and Ireland who were taking a stable dose of methotrexate, and planning to continue on it, were asked about how often they had either "forgotten" or "chosen" not to take their methotrexate and for how many weeks. Two centres surveyed 100 patients whilst the other five centres surveyed 50 patients. In four centres the patients were asked to complete the questionnaire by a doctor and in the other three by a nurse.

Results: A total of 48 (11%) patients revealed that they had chosen to miss one or more doses in the past year. This varied from 2 (4%) patients in the Barnsley centre to 13 (26%) patients in the North Tyneside centre. Patients reported forgetting to take their Methotrexate more readily; 95 (21%) of the whole group. The variation in this reporting was interesting – zero in Barnsley and 25 (50%) in Waterford the only difference being that the survey was carried out by a doctor in Barnsley and a nurse in Waterford.

Overall, in the 4 centres where the survey was completed by a doctor (300 patients were surveyed), 25 (8%) patients said they had chosen not to take their Methotrexate for at least 1 week and 36 patients (12%) said that they had forgotten to take it. In the 3 nurse centres, (150 patients were surveyed), the figures were higher; 23 (15%) patients said that they had chosen not to take their Methotrexate for 2 – 4 weeks and 59 (39%) patients said they had forgotten to take it for 1 – 6 weeks.

Conclusion: There is a substantial amount of missed Methotrexate. Patients seem more comfortable to admit to forgetting rather than choosing to miss drug. Patients seem more comfortable to admit to missing drug to nurses rather than doctors. Studies of adherence need to take account of how and who asks the questions.

Reference

Robinson et al 2015 A multi-centre Survey of Tolerability and Adherence for Patients on Regular Methotrexate *Rheumatology* 54 (suppl 1) i36-i37

Disclosure: S. M. Robinson, None; **P. S. Heslop**, None; **S. Duffy**, None; **D. Walker**, None.

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Abstract Number: 1494

The Role of a Nurse-Led Clinic in the Assessment and Prevention of Cardio-Vascular Risk

Nieves Martínez-Alberola[1], **Francisca Sivera**[2], Cristina Fernández-Carballido[3], Mariano Andrés[4], Raquel Martín-Doménech[1], Maria Paz Martínez-Vidal[1] and Alejandro SanMartin-Alvarez[1], [1]Rheumatology, Hospital General Universitario Elda, ELDA, Spain, [2]Reumatología, Hospital General Universitario de Elda, Alicante, Spain, [3]Rheumatology, Hospital General Universitario de Elda, Elda (Alicante), Spain, [4]Reumatologia, Hospital General Universitario Alicante, Alicante, Spain
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Background/Purpose:

Patients with chronic arthritis have a higher risk of cardiovascular (CV) events than the general population. This is possibly due to the combination of a high prevalence of classic cardiovascular risk factors (CVRF) and persistent inflammation due to their rheumatic disease. T2T approaches and other advances have increased our control of disease activity, however, classic CVRF are often monitored and treated exclusively by the GP.

Aim: To describe the implementation of a specific program for patients with chronic inflammatory arthritis based around a nurse-led clinic and aimed at:

1) Detecting classic CVRF and

2) Optimizing the treatment of these classic CVRF

Methods:

Following the EULAR 2010 recommendations, we developed a screening program for CVRF. Patients with the diagnosis of RA, SpA or PsA who were followed up at a single Rheumatology Department were offered participation in this program by their managing rheumatologist. In a single visit to a nurse-led clinic CV risk was evaluated through a clinical interview. Patients were asked about smoking status, diet, exercise, prior diagnosis of hypertension (HBP), diabetes (DM), dyslipemia (Dlp), personal and familial CV events, other comorbidities and their current treatment. Weight, height, BMI, and blood pressure were registered. Laboratory tests were then reviewed. SCORE tables were applied to calculate the CV risk; adjustment of the SCORE in RA patients was performed according to the EULAR recommendations. Those patients who did not achieve their target for the CVRF were sent to the rheumatologist for consultation. In the rheumatology nurse clinic, an educational program was initiated in order to modify diet, exercise, lifestyle and smoking cessation, where appropriate. The project is currently ongoing; preliminary results are presented.

Results:

133 patients (85 female) have been screened at the nurse-led clinic up to June 2015. Mean age was 59.1 years (SD 10.6). Diagnoses of the screened patients were 93 RA, 29 PsA and 11 SpA. At baseline, 11 patients had a history of CV events, 26 patients had a prior diagnosis of DM (9 (35%) with HbA1C>8%), 64 had HBP (32 (50%) with BP>140/90 at the nurse visit), 60 had Dlp (24 (40%) with cholesterol >220mg/dL). 42 patients were active smokers and 48 were obese (BMI>30).

In the patients without prior DM, the nurse clinic detected 4 patients (3/107, 4%) with glycemia ≥126mg/dL. In these patients a new blood test was ordered to confirm the diagnosis of DM. In patients without prior HBP 26 patients (26/69, 38%) had BP>140/90. In patients without prior Dlp 20 patients (18/73, 27%) had total cholesterol levels >220mg/dL and 37 (37/73, 51%) had LDL-cholesterol levels over their therapeutic target.

Overall, this screening strategy allowed the detection of classical CVRF which were previously undetected or poorly controlled (DM, HBP, Dlp) in 105/133 (79%) of the evaluated patients. In all patients, the nurse-led educational program was initiated.

Conclusion:

A nurse led single-visit screening program allows the detection of classic CVRF in a high proportion of patients. If proper treatment for the classic CVF is initiated, this might result in a decrease of CV events with a favorable impact on the general health of chronic arthritis patients.

Disclosure: N. Martínez-Alberola, None; **F. Sivera**, None; **C. Fernández-Carballido**, None; **M. Andrés**, None; **R. Martín-Doménech**, None; **M. P. Martínez-Vidal**, None; **A. SanMartin-Alvarez**, None.

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Abstract Number: 1495

Person-Centred Care Can Help Patients to Become More Effective Consumers in the Use of Health Information Than Regular Care – an RCT in Patients with Arthritis Undergoing Biological Therapy

Ingrid Larsson[1,2], Stefan Bergman[2,3,4] and Ann Bremander[2,3,5], [1]School of Health and Welfare, Halmstad University, Halmstad, Sweden, [2]FoU Spenshult, Halmstad, Sweden, [3]Department of Clinical Sciences, Lund, Section of Rheumatology, Lund University, Lund, Sweden, [4]Primary Health Care Unit, Department of Public Health and Community Medicine, The Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden, [5]School of Business, Engineering and Science, Halmstad University, Halmstad, Sweden
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Background/Purpose:

Person-centred care (PCC) is a holistic approach with respectful and individualized care allowing negotiation of care where persons with health problems are empowered to be involved in health decisions. Patients' illness narratives constitute a starting point for building a collaboration with health care professionals and to empower them to play an active role in their health care. Little is known of the impact of PCC vs. regular care on patients' skills as health care consumers. The aim was to study the impact on effective consumers' skills over 6 and 12 months as measured by the Effective Consumer Scale (EC17) in patients undergoing biological therapy and randomly assigned to either a nurse-led rheumatology clinic (NLC) based on PCC or to a rheumatologist-led clinic (RLC) based on regular care.

Methods:

A 12 month RCT in 107 patients with chronic inflammatory arthritis[1]. Inclusion criteria were ongoing biological therapy and a DAS28 ≤3.2. All patients met a rheumatologist at inclusion and after 12 months, while the 6 month follow-up was randomized to either at an NLC (PCC) or at an RLC (regular care). Outcome measure was the EC17, developed and endorsed by the OMERACT, including five subscales; 1. Use of health information, 2. Clarifying personal priorities, 3. Communicating with others, 4. Negotiating roles and 5. Deciding and taking action. EC17 total score ranges from 0-100, worse to best. Differences between and within NLC and RLC were analyzed with Friedmans' test or Mann Whitney U-test.

Results:

After 12 months 97 patients completed the RCT (NLC n=47, RLC n=50), mean (SD) age 55.4 (12.7) years, disease duration 16.7 (11.5) years, DAS28 2.1 (0.7), HAQ 0.54 (0.38), global health 20.4 (17.1), pain 21.1 (18.0) and 56% were women. There were no statistically significant differences within or between the two intervention groups at baseline nor in EC17 total score mean (SD) at baseline (NLC 83.5 (9.4) vs. RLC 83.2 (10.8), 6 months (NLC 85.4 (10.4) vs. RLC 82.9 (10.9) and 12 months (NLC 85.3 (11.1) vs. RLC 82.3 (10.9)). However, in NLC there was a statistically significant improvement in EC17 subscale "1. Use of health information" at both 6 and 12 months (p=0.041 and p=0.004 respectively).

Conclusion:

Replacing just one of three visits over 12 months to an NLC based on PCC instead of an RLC based on regular care resulted in more effective consumers concerning the use of health information. Larger studies over longer time frames focusing on PCC are needed to better understand its full impact on effective consumer skills measured by EC17.

References:

1. Larsson I, et al. Randomized controlled trial of a nurse-led rheumatology clinic for monitoring biological therapy. J Adv Nurs 2014;**70**:164-75.

Disclosure: I. Larsson, None; **S. Bergman**, None; **A. Bremander**, None.

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Abstract Number: 1496

Uncovering and Addressing Issues Related to Medication Adherence Among Patients with Rheumatic Diseases: A Patient Navigator Pilot Program

Anarosa Campos[1], Alyssa Wohlfahrt[1], Yuanyu Lo[1], Maura D. Iversen[2], Elena Massarotti[3], Daniel H. Solomon[4] and Candace H. Feldman[5], [1]Rheumatology, Immunology and Allergy, Brigham and Women's Hospital, Boston, MA, [2]Northeastern University, Department of Physical Therapy, and Brigham & Women's Hospital, Harvard Medical School, Boston, MA, [3]Rheumatology, Immunology and Allergy, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, [4]Division of Rheumatology, Immunology and Allergy, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, [5]Rheumatology, Immunology and Allergy, Brigham and Women's Hospital,Harvard Medical School, Boston, MA

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Background/Purpose: Poor adherence to medications is a common problem among rheumatology patients that can lead to irreversible negative outcomes. We piloted an intervention using patient navigators- laypeople trained in care coordination, basic rheumatology, and relevant pharmacology- to improve adherence to oral disease-modifying antirheumatic drugs (DMARDs). Navigators aimed to identify and understand barriers to adherence to DMARDs that may be missed during clinical encounters and to work with patients to develop personalized strategies to overcome these barriers.

Methods: We recruited patients ≥18 years old from a large academic Arthritis Center. Eligibility included a rheumatic disease diagnosis by a board certified rheumatologist and initiation of an oral DMARD within the prior 6 months. Navigators conducted baseline interviews to assess patients' understanding of their rheumatic disease and their adherence to DMARDs. Then, depending on need, navigators contacted patients once every 1-4 weeks by phone or in person, and these conversations were thoroughly documented. Navigators connected patients with hospital resources, provided education about diagnoses and medications, and developed individually tailored strategies to circumvent barriers. Five team members independently reviewed the documentation from patient call notes to categorize issues raised by participants and subsequent navigator actions. Multiple issues and actions could be recorded per patient but each was counted only one time per patient. Differences in coding were adjudicated by the team.

Results: Two navigators followed 88 patients for up to six months. Mean age was 54 years (SD 17) and 92% were female. 81% had inflammatory arthritis, 10% had lupus or mixed connective tissue disease, and 9% had other rheumatic diseases. Seven main categories of patient issues relevant to adherence were identified: adverse events (45%), challenges with medication acquisition (31%), concerns about medication effectiveness (30%), lack of knowledge about medications or diagnosis (20%), need for social support (14%), financial/insurance difficulties (11%), and interruptions in medication use (9%) (**Table**). 19% of patients raised no issues, 25% discussed one, and 56% ≥ 2 issues. The most common navigator actions included: facilitation of patient-doctor communication (33%), medication and diagnosis education (30%), development of individualized strategies to improve adherence (18%), and assistance with financial/insurance issues (11%) (**Table**).

Conclusion: Most patients described one or more issues related to their oral DMARD adherence or to their rheumatic disease. Navigators played a key role uncovering and addressing concerns not identified by routine clinical care. Further analyses will assess the impact of navigators on DMARD adherence and rheumatic disease-related outcomes.

Table. Patient issues and navigator actions related to medication adherence (N= 88)

Categories of Patient Issues	**N (%)**
Adverse events (e.g. alopecia, rash, gastrointestinal side effects)	40 (45%)
Challenges with medication acquisition (e.g. refills and prior authorizations)	27 (31%)
Concerns about medication effectiveness (e.g. onset of action)	26 (30%)
Lack of knowledge about medications or diagnosis	18 (20%)
Need for social support (e.g. expression of depressive symptoms)	12 (14%)
Financial/Insurance difficulties obtaining medications (e.g. high co-payments, billing errors)	10 (11%)
Interruptions in medication use (e.g. surgery, infections)	8 (9%)
Navigator Actions	**N (%)**
Facilitation of patient-doctor communication (e.g. notified rheumatologists of patients symptoms or concerns)	29 (33%)
Medication or diagnosis education (e.g. explained side effects, described expected timing of medication effects, helped manage side effects)	26 (30%)
Development of individualized strategies to improve adherence (e.g. pillboxes, text messages, set-up of automatic refills, magnet reminders)	16 (18%)
Assistance with financial and insurance issues (e.g. referral to financial counselor, interactions with insurance companies)	10 (11%)
Coordination of care (e.g. helped patients obtain referrals to other specialties)	8 (9%)
Provision of social and emotional support	7 (8%)
Facilitation of expedited mental health referrals	6 (7%)

Disclosure: A. Campos, None; **A. Wohlfahrt**, None; **Y. Lo**, None; **M. D. Iversen**, None; **E. Massarotti**, None; **D. H. Solomon**, None; **C. H. Feldman**, Pfizer Inc, 2.

Abstract Number: 1497

Panlar Consensus on Hand, Hip and Knee OA

Oscar Luis Rillo[1], Humberto Riera[2], Rolando Espinosa-Morales[3], Carlota Acosta[4], Veronica Liendo[5], Joyce Bolaños[6], Ligia Monterola[7], Edgar Nieto[8], Luisa M. Franco[9], Rodolfo Arape[10], Ana Antunez[11], Silvia Beatriz Papasidero[12], Mariflor Vera[13], Jorge Esquivel[14], Renee Souto[15], Jose F. Molina[16], César Rossi[17], Francisco Ballesteros[18], José Salas[19], Francisco Radrigan[20], Marlene Guibert-Toledano[21], Gil Reyes Llerena[22], Lorena Urioste[23], Walter Camacho[24], Abraham García[25], Isa Iraheta[26], Carmen E Gutierrez[27], Raúl Aragón[28], Margarita Duarte[29], Oswaldo Castañeda[30], Juan Angulo Solimano[31], Ibsen Coimbra[32], Roberto Munoz Louis[33], Carlos Vallejo[34], Ricardo Saenz[35], Francisco Giron[36], Anibal De León[37], Ramon Perez Acuna[38], Anthony M. Reginato[39] and **Maritza Quintero**[2], [1]Hospital General de Agudos “Dr. Ignacio Pirovano”, Buenos Aires, Argentina, [2]Unidad de Reumatología, Instituto Autónomo Hospital Universitario de Los Andes, Universidad de Los Andes, Mérida, Venezuela, [3]Mexican Board of Rheumatology, Mexico City, Mexico, [4]Ciudad Bolivar, Hospital Universitario "Ruiz y Páez, Bolivar, Venezuela, [5]Clínica Roosevelt, Caracas, Venezuela, [6]Hospital Perez Carreño, Caracas, Venezuela, [7]Clínica Colinas, Anzoátegui, Venezuela, [8]Traumatology, Instituto Autónomo Hospital Universitario de Los Andes, Universidad de Los Andes, Mérida, Venezuela, [9]Instituto Docente de Urología, Carabobo, Venezuela, [10]Centro Clínico La Isabelica, Carabobo, Venezuela, [11]Hospital Central Dr. URQUINAONA, Maracaibo, Venezuela, [12]Rheumatology Department, Hospital General de Agudos Dr. E. Tornú, Buenos Aires, Argentina, [13]Instituto Autónomo Hospital Universitario de Los Andes, Universidad de Los Andes, Mérida, Venezuela, [14]Universidad Autónoma de Nuevo León, Distrito Federal, Mexico, [15]Catedra de Reumatología de la Facultad de Medicina, Universidad de la Republica, Montevideo, Uruguay, [16]Centro Integral de Reumatologia Reumalab, Medellin, Colombia, [17]Cátedra de Reumatología de la Facultad de Medicina, Universidad de la República, Montevideo, Uruguay, [18]Departamento de Reumatología, Universidad de Chile, Santiago, Chile, [19]Reumacaribe, Barranquilla, Colombia, [20]Departamento de Reumatología, Universidad Católica de Chile, Santiago, Chile, [21]Rheumatology, Centro de Investigaciones Médico Quirúrgicas, Habana, Ciudad Habana, Cuba, [22]Servicio Nacional de Reumatología, Centro de Investigaciones Médico Quirúrgicas (CIMEQ), La Habana, Cuba, [23]Hospital Alfonzo Gumucio-Techo Académico Universidad Católica, San Pablo, Bolivia, [24]Servicio de Medicina Interna, Hospital Obrero N° 3 de la Caja Nacional de Salud, Santa Cruz, Bolivia, [25]Postgrado de Reumatología, Universidad Francisco Marroquí, Guatemala, Guatemala, [26]Rheumatology, Guatemalan Association against Rheumatic Diseases (AGAR), Guatemala City, Guatemala, [27]Instituto Salvadoreño del Seguro Social, San Miguel, El Salvador, [28]FACULTAD DE MEDICINA, UNIVERSIDAD DE EL SALVADOR., San Salvador, El Salvador, [29]Servicio de Reumatología, Hospital de Clínicas de Asunción, Universidad Nacional de Asunción, Asunción, Paraguay, [30]Clínica Angloamericana, Lima, Peru, [31]Rheumatology, Universidad Nacional Mayor San Marcos, Lima, Peru, [32]Departamento de Clínica Médica, Faculdade de Ciências Médicas da UNICAMP, Campinas, Brazil, [33]Reumatologia, Clinica Abreu - Hospital Docente Padre Billini, Santo Domingo, Dominican Republic, [34]FACULTAD DE MEDICINA. PONTIFICIA UNIVERSIDAD CATOLICA DEL ECUADOR., Quito, Ecuador, [35]Hospital Dr. Rafael A. Calderón Guardia, San José, Costa Rica, [36]IHSS Tegucigalpa, Tegucigalpa, Honduras, [37]Hospital Santo Tomás, Panama, Panama, [38]Zona franca ultrpark 6A, Zona franca ultrpark 6A, La Aurora de Heredia, Costa Rica, [39]Rheumatology, Rhode Island Hospital, The Warren Alpert School of Medicine at Brown University, Providence, RI
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Background/Purpose: The purpose of this Consensus is to update the PANLAR recommendations for hand, hip and knee osteoarthritis (OA) based on a combination of the available evidence and expert opinion.

Methods: Recommendations were developed by a group of 40 specialists of 18 countries of Latin America, and patients suffering from OA of the referred joints. A systematic review of articles, meta-analysis and guidelines published between 2008 and January 2014 was undertaken. The level of evidence and degree of recommendation were classified according to the Center for Evidence Based Medicine at Oxford or Jadad scale. Level of agreement was established through a Delphi technique.

Results: Both “strong” and “conditional” recommendations were made. In **hand OA** it is important to educate regarding joint protection

and to provide an exercise regimen that improves muscle strengthening and range of motion (IC). Topical NSAIDs are indicated in mild to moderate pain (IA). Acetaminophen (up to 3 g/day) is recommended as the oral analgesic of first choice (IA). If it is not effective, oral NSAIDs are recommended at the lowest effective dose and for the shortest time possible (IA). The use of chondroitin sulfate is recommended and may be used in the long-term (IA). The use of steroids or intra-articular hyaluronic acid might be considered for OA of the symptomatic TMC joint (IIaB). Surgery could be considered for severe rhizarthrosis in patients with strong pain and/or disability and after conservative treatment has failed (IIBB). For **Hip OA**, patients should be educated on the importance of changes in lifestyle (IB). Strengthening the extensors and abductors improves function and can prepare the patient before a hip implant (IB). In mild to moderate pain, acetaminophen (IB) is recommended. In cases of higher pain, high doses of NSAIDs or selective COX2 inhibitors could be indicated (IB). In patients who do not respond to NSAIDs or inhibitors of COX-2, or do not tolerate them or are contraindicated, weak opioids such as tramadol would be useful (IIbB). Total hip arthroplasty is indicated in patients with high pain, walking difficulty and loss of quality of life (IA). Finally in **Knee OA,** it is important to educate about lifestyle changes (IA). Acetaminophen is recommended up to 3 gr per day for mild pain (IA). For moderate pain, traditional and selective NSAIDs are indicated (IA). Topical NSAIDs may be indicated in patients with gastrointestinal risk (IA). In severe pain, the use of tramadol is recommended (IA).Treatment with chondroitin sulphate has demonstrated symptomatic effect in patients with knee OA and it may delay OA progression (IA). Combined use of glucosamine and chondroitin sulfate is indicated in patients with moderate to severe pain (IB). Benefits of intra-articular hyaluronic acid have been reported (IIaB). Arthroscopy is not beneficial (IIIA).Total knee arthroplasty may be indicated in knee OA (IIaB).

Conclusion:

These recommendations are based on the consensus judgment of clinical experts, informed by available evidence, balancing the benefits and harms of treatments, and incorporating their preferences and values. It is hoped that these recommendations will be useful in the management of OA patients.

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Abstract Number: 1498

Engaging Clinic Staff in Work System Redesign to Adapt a Hypertension Protocol for Rheumatology

Edmond Ramly[1], Diane Lauver[2] and Christie M. Bartels[3], [1]Industrial and Systems Engineering, University of Wisconsin-Madison College of Engineering, Madison, WI, [2]University of Wisconsin-Madison School of Nursing, Madison, WI, [3]Department of Medicine, University of Wisconsin (UW) School of Medicine and Public Health (SMPH), Madison, WI

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Background/Purpose: Despite routine blood pressure (BP) measurement by clinic staff, we reported that rheumatologists discussed elevated BPs in <1/3 of visits leading to missed opportunities for cardiovascular disease prevention. Staff-driven hypertension protocols in primary care reduce such variation by empowering clinic staff. Our objective was to engage clinic staff in work system redesign to develop and implement a blood pressure protocol adapted to specialty care. We report results of this process under the five work system domains: people, tools, organization, environment, and tasks.

Methods: Our multidisciplinary team engaged clinic staff (medical assistants (MA), nurses (RN), and schedulers) in work system redesign. Three discipline-specific one hour focus groups appraised pre-visit rooming and check-out workflows, our proposed protocol, and electronic health record (EHR) tools. Staff participated in a 45 min group session on BP, and one-on-one 15 min EHR training sessions. We audited fidelity through EHR data and provided monthly individual audit feedback. These brief sessions focused on goal-setting and staff-driven problem-solving. Three later focus groups offered us evaluative feedback and suggestions for improvements. We

also administered a retrospective anonymous 15 item staff questionnaire after pilot testing.

Results: Over 90% (9 MAs, 5 RNs, 4 schedulers) of staff participated in focus groups. Content analysis of the focus groups informed the development and implementation of work system redesign interventions (Table 1). The work system redesign included training (people), protocol and workflows adapted to specialty care (organization, tasks), a customized EHR alert for elevated BP and EHR follow-up order set (technology), and supportive physical cues like a desktop patient brochure linking rheumatologic conditions and heart risk (environment). Four monthly audit feedback sessions with 10 regular MAs or RNs identified barriers and solutions. All staff met progressively higher goals and achievement. In evaluative focus groups staff voiced satisfaction and suggested pragmatic changes including BP re-measurement red cue cards and EHR alert revisions. Questionnaires showed improved BP self-efficacy post intervention.

Conclusion: We engaged rheumatology clinic staff in participatory work system redesign to improve follow up for patients with elevated blood pressure. The collaborative redesign process resulted in successful modification and implementation of a blood pressure protocol for specialty care. Results suggest sound intervention feasibility including improved staff self-efficacy and demonstrate good intervention fidelity including improved BP re-measurement and follow up orders over time.

Table 1. Results of Participatory Work System Redesign

Work System Components	Before Redesign	After Redesign
People	Staff BP self-efficacy: 2.5 of 5	Staff BP self-efficacy: 4 of 5
Organization	No BP follow up policy	Standard protocol supported by staff and leadership
Technology	No prompts for elevated BP	EHR alert & order set for education and follow-up
Environment	No physical cues for BP follow up	Patient brochure, Staff red cue card for re-measuring BPs
Tasks	Re-measurement of elevated BPs: <1%	BP re-measurement: <50%(Q1), > 75% (Q2) BP follow up orders: Peak >20 per month
Staff Assessment:	*"There is no system. I don't ever know what happens." MA*	*"I think it's great. They are right in the moment of, "My blood pressure is high,"... we're capturing them at an important time." RN*

Disclosure: E. Ramly, Pfizer Inc, 2; **D. Lauver**, Pfizer Inc, 2; **C. M. Bartels**, Pfizer Inc, 2.

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Abstract Number: 1499

Patients Who Take Many Medications for Their Fibromyalgia Symptoms at the Initial Office Visit Tend to Have a Worse Clinical Course

Robert S. Katz[1], Alexandra Katz Small[1] and Hannah Leavitt[2], [1]Rush University Medical Center, Chicago, IL, [2]Rheumatology Associates S.C., Chicago, IL

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Background/Purpose: Fibromyalgia syndrome (FMS) patients taking a greater number of medications may identify those with a more challenging clinical course.

Methods: We evaluated patients at their initial rheumatology office visit to determine the number of medications they were taking for pain and other fibromyalgia symptoms, and later outcome based on HAQ scores for functional ability as well as visual analogue scales (VAS) for pain, fatigue, concentration and general health.

Results: The mean number of medications taken for fibromyalgia symptoms was 5.23, range 0-23. The mean number of non-prescription medication such as dietary supplements and over-the-counter drugs was 2.12, with a range of 0-10.

Conclusion: Those patients taking more prescription for their fibromyalgia symptoms at their initial office visit tended to have a worse clinical course, evidenced by higher HAQ scores, poor general health, and more pain and fatigue. Those FMS patients may be more difficult to care for.

Disclosure: R. S. Katz, None; **A. Katz Small**, None; **H. Leavitt**, None.

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Abstract Number: 1500

Impact of Menopause on Functional Impairment of Rheumatoid Arthritis Patients

Naglaa Hussein[1] and Abdelmoneim Helal[2], [1]physical medicine, rheumatology &rehabilitation, Alexandria university, Alexandria, Egypt, [2]Physical Medicine, Rheumatology & rehabilitation, Professor, Alexandria, Egypt

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Session Time: 9:00AM-11:00AM

Background/Purpose: Rheumatoid arthritis (RA) is an autoimmune disease which is predominant in female with female to male ration ranging between 2:1 to 3:1. The peak incidence of RA in women coincides with the time of menopause. When there are diminished production of estrogen , progesterone and adrenal androgen.

Aim : To assess the effect of menopause early versus late on the functional status of rheumatoid arthritis patients

Methods: this was retrospective study. Fifty patients with RA diagnosed according to 2010 American College of Rheumatology /European League Against Rheumatism classification criteria for RA from those have been treated at our outpatient clinic, provided that they had developed RA prior to the onset of menopause, all are non smoker and their records are available at our clinic archives. Twenty five of those patients had early onset menopause (<45years) constituted group I, while Group II was the remaining 25 patients with late onset menopause(≥45years).

All patients were subjected to history taking including history of the disease, drug history, gynecological history(age of menarche, age of menopause, parity), detailed musculoskeletal examination, current as well as previous Health Assessment Questionaire (HAQ) obtained from previous records that were taken prior to the onset of menopause to each patient. Current disease activity score 28(DAS28) was conducted to all patients.current Laboratory investigations including 1st hour erythrocyte sedimentation rate (ESR), C-reactive protein

Results: The mean age for group I patients was 51.76±9.21, and for group II 55.24±4.28. No significant difference in between groups regarding demographic data (age of menarche, marriage status, parity, occupation. The mean disease duration for group I was 8.58±7.88 and for group II 9.57±9.75 (p=0.838). Regarding the use of disease modifying antirheumatic drugs(DMARDS) ; 21 patients of group I(84%) and 23 patients (92%) of group II used DMARDS. For group I, the mean HAQ before menopause was 0.31±0.59 and that after menopause was 2.05±0.69(p=0.001). For group II the mean HAQ before menopause was 1.02±1.14 and that after menopause was 1.86±0.87(p=0.01). Before menopause, HAQ was significantly higher for group II (p=0.012) while after menopause there is no significant difference in between groups(p=0.496). After menopause, for those patients using DMARDS with both groups, the mean 1st hour ESR was 60.95±32.02 for group I and 52.74±30.93 for group II(p=0.35), the mean C reactive protein for group I was 64.62±72.75 and for groupII was 16.93±12 (p=0.238). The mean DAS for group I was 7.03±1.04, that of group II was 6.59±1.31(p=0.234)

Conclusion: Menopause significantly impairs the functional status of rheumatoid women whether this menopause is early or late. Early menopause tends to affect the disease activity more. Further studies with larger samples will help to document the impact of menopause on functional impairment as well as disease activity of rheumatoid arthritis

Study limitation: lack of previous laboratory studies and DAS28 prior to menopause limited the accuracy of results regarding menopause and disease activity.

Disclosure: N. Hussein, None; **A. Helal**, None.

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Abstract Number: 1501

Prevalence of Unassessed and Uncontrolled Cardiovascular Disease Risk Factors Among Rheumatoid Arthritis Patients in an Academic Rheumatology Practice

Darcy S. Majka[1], Eric M. Ruderman[2], Ji Young Lee[3], Elisha Friesema[4] and Stephen D. Persell[4], [1]Rheumatology, Northwestern University Feinberg School of Medicine, Chicago, IL, [2]Medicine, Division of Rheumatology, Northwestern University Feinberg School of Medicine, Chicago, IL, [3]Northwestern University Feinberg School of Medicine, Chicago, IL, [4]General Internal Medicine, Northwestern University Feinberg School of Medicine, chicago, IL

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Background/Purpose: Cardiovascular disease (CVD) is the leading cause of death in individuals with rheumatoid arthritis (RA). Patients with RA are at 1.5-2.0-fold increased risk of CVD morbidity relative to the general population. Despite the high burden of CVD and recommendations by the European League Against Rheumatism (EULAR) for routine cardiovascular risk assessment and management, it has recently been shown that both rheumatologists and primary care physicians identify and manage cardiovascular risk factors less often in RA patients compared with controls from the general population.

Methods: We queried our electronic health record (EHR) using Structured Query Language and used an accurate RA detection algorithm. We assessed whether patients had established CVD, and collected data for cholesterol, blood pressure, antihypertensive and lipid lowering therapy, and smoking and diabetes status. We calculated CVD risk (symptomatic coronary or cerebrovascular disease) using equations from the 2013 American College of Cardiology (ACC)/American Heart Association (AHA) risk assessment guideline. We identified RA patients with a CVD risk of ≥ 5% because at this level the ACC/AHA guideline recommends statin therapy be considered, and strongly recommends it at a level of ≥ 7.5%. In addition, RA patients with CVD risk estimated at 5% likely have a true level of risk exceeding 7.5% because CVD risk is increased approximately 1.5 fold in RA.

Results: Among 1414 RA patients, 83% were female and mean age was 56 years. Only half of RA patients had all major risk factors assessed (data missing for lipids [49%] and diabetes screening [8%]). Among those potentially eligible for a statin (known CVD or 10-year CVD risk of ≥ 5%), only 47% were treated with a moderate or high intensity statin and 46% were prescribed no statin. Most recent BP was <140/90 for 83% of the cohort. Diabetes and current smoking prevalences were low (9.9% and 5.3% respectively).

Conclusion: In this academic rheumatology practice, we found two major areas for CVD prevention improvement: promotion of complete risk factor assessment and the appropriate use of statins. This study demonstrates that system-based interventions are needed to improve CVD risk factor assessment and management among RA patients in this practice. Such interventions might include both rheumatology and generalist provider education, performance feedback, and point of care decision support tools within the rheumatology practice to improve risk factor measurement and referral for risk factor modification.

Table 1. Atherosclerotic Cardiovascular Disease (ASCVD) Risk Factors and Treatment among Study Site RA Patients*

Characteristic	Entire cohort	Known CVD	ASCVD risk ≥5%	Risk < 5%, with diabetes or LDL ≥ 190	Other
	N = 1414	N = 84	N = 299	N = 24	N = 1007
Age, mean, y	56.1	69.5	66.6	47.5	52.1
Female, %	83.2	69.1	74.6	95.8	86.7
Race, %					
African American	15.6	25.0	28.8	8.3	11.1
White	51.7	57.1	46.5	41.7	53.0
Asian	3.0	2.4	3.0	0	3.1
Other/missing	29.7	15.5	21.7	50.0	32.8
Hispanic/Latino, %	11.5	8.3	10.7	33.3	11.4
Current smoking, %	**5.3**	**3.6**	**8.7**	0	**4.6**
Drug treated hypertension, %	45.6	92.9	68.9	29.2	35.2
Uncontrolled blood pressure, %	**16.7**	**28.6**	**26.4**	**16.7**	**12.8**
Diagnosed diabetes, %	9.9	27.4	22.7	87.5	2.8
Anti-thrombotic drug use, %	24.0	94.1	32.4	25.0	15.6
Statin use, none, %	73.6	**16.7**	**53.9**	**50.0**	84.7
Low potency	4.0	**8.3**	**7.4**	0	2.7
Mid or High potency	22.5	75.0	38.8	50.0	12.6
Unmeasured cholesterol, %	**48.8**	**17.9**	0	0	**67.0**
Unmeasured glucose/HbA1c, %	**7.7**	**3.6**	**1.0**	0	**10.2**

*Bolded numbers indicate populations with potential targets for clinical intervention. Abbreviations: LDL, low density lipoprotein, HbA1c, hemoglobin A1c.

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Initiating Statin Medication and Risk of Fatigue in Rheumatoid Arthritis

James S. Andrews[1], Harlan Sayles[2], Kaleb Michaud[3] and Patricia P. Katz[4], [1]Rheumatology, University of California San Francisco, San Francisco, CA, [2]University of Nebraska Medical Center, Omaha, NE, [3]Internal Medicine, University of Nebraska Medical Center, Omaha, NE, [4]Rheumatology, UCSF, SF, CA

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Background/Purpose: Fatigue is common in Rheumatoid Arthritis (RA) and has a major impact on quality of life. Individuals with RA are also at increased risk of cardiovascular disease and are often prescribed statin medications. Recent data suggest that statins may be associated with increased fatigue symptoms (Golomb, Arch Intern Med, 2012; 172:1180), but the effect of statins on fatigue in RA has not been studied. This study tests whether statin initiation is associated with increased fatigue in RA.

Methods: Data were from the longitudinal National Data Bank for Rheumatic Diseases (NDB), for which participants complete questionnaires every 6 months. RA was physician confirmed. Medication use was self-reported. The primary exposure was first-ever initiation of a statin. Participants were classified as exposed if they 1) began taking a statin, 2) took this statin for at least 1 month, and 3) had never taken any statin in the past. Fatigue severity was measured by Visual Analogue Scale (range 0-10): "How much of a problem has fatigue or tiredness been for you in the past week?" The primary outcome was 6-month change in fatigue severity. We used a new-user nested cohort design. Subjects were analyzed as controls until the 6-month interval in which they initiated statin use, during which they were analyzed as exposed. To exclude prevalent statin users, participants were censored beginning in the 6-month interval after exposure. Generalized estimating equations, with a fixed effect term for 6-month interval and robust standard errors, were used to model the effect of statin initiation on change in fatigue, controlling for age, sex, baseline fatigue severity, depressive symptoms, sleep quality, HAQ score, comorbidities, BMI, and RA Disease Activity Index (RADAI) score. Secondary analysis examined the effect of initiation of "high-potency" statins (atorvastatin, rosuvastatin, and simvastatin) on change in fatigue.

Results: Of the 12,482 participants, 80% were female and the mean ±SD baseline characteristics were: age 63 ±12 years, RADAI score 2.4 ±1.4, fatigue 4.1 ±2.5. 3,617 participants (29%) initiated a statin, of which 91% were "high-potency." Mean 6-month change in fatigue was -0.001 (±0.6) among controls and 0.02 (±2.4) among statin new-users. In adjusted models, new use of a statin was not associated with a significant change in fatigue [(coefficient=0.01; (CI:-0.07,0.10); p=0.8]. Results were similar when analysis was limited to new use of high-potency statins [(coefficient=-0.01; (CI:-0.10, 0.08); p=0.8].

Conclusion: In this large longitudinal cohort of patients with RA, there was strong evidence that new use of a statin is not associated with significant risk of increased fatigue. Because the 95% confidence interval (-0.07, 0.10) includes the null and excludes all clinically meaningful values for change in fatigue, we conclude that new use of a statin does not have a clinically important effect on fatigue (Hoenig, American Statistician, 2001; 55:19). Given the importance of statin medications in reducing cardiovascular risk for individuals with RA, these findings have great clinical relevance.

Disclosure: J. S. Andrews, None; **H. Sayles**, None; **K. Michaud**, None; **P. P. Katz**, None.

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A Systematic Screening of Comorbidities By the Rheumatologist in Inflammatory Rheumatisms Impacts Chronic Disease Care

Claire I. Daien[1], Amandine Tubery[2], Guilhem du Cailar[3], Aurore Royanez[4], Thibault Mura[5], Marie-Christine Picot[6], Rodolphe Bourret[7], François Roubille[8], Jean Bousquet[9], Jacques Morel[1], Pierre Fesler[3] and Bernard Combe[10], [1]Department of rheumatology, Lapeyronie Hospital and Montpellier University, Montpellier, France, [2]Nîmes University Hospital, Rheumatology Department, Nimes, France, [3]Internal Medicine and Hypertension, Hopital Lapeyronie, Montpellier, France, [4]Rheumatology and Pharmacology, Montpellier, France, [5]CIC, Hopital Gui De Chauliac, Montpellier, France, [6]DIM, Montpellier, France, [7]Direction Teaching hospital, Montpellier, France, [8]Cardiology, Montpellier, France, [9]Pneumology, Montpellier, France, [10]Rheumatology, Hopital Lapeyronie, Montpellier, France

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Background/Purpose: Patients with inflammatory rheumatisms especially rheumatoid arthritis (RA) have a greater risk of cardiovascular diseases (CVD), infections, chronic respiratory diseases (CRD) and osteoporosis. As recommended by EULAR, rheumatologists start to perform systematic screening of CVD and comorbidities. Moreover, the 2015 EULAR guidelines recommend assessment of asymptomatic atherosclerotic plaques by carotid ultrasound. We aimed to determine the real impact of this strategy.

Methods: A screening was set up in an out-patient daily clinic of Rheumatology. It included 1) cardiovascular evaluation with modified SCORE calculation, supra-aortic trunks and abdominal aorta ultrasound and echocardiography, 2) CRD evaluation with spirometry; 3) osteoporosis with bone mineral density and FRAX calculation, and 4) check-up of vaccine calendar and recommended neoplasia screenings. Three months later, patients were called and the application of recommendation evaluated.

Results: 184 patients including 150 RA patients and 29 spondyloarthritis performed this screening. The mean rheumatism duration was

14±9 years and the mean age was 59±11 years. Unknown uncontrolled hypertension was diagnosed in 14% (n=26); dyslipidemia in 21% (n=38); diabetes in 8% (n=14) of the patients. 26% (n=47) patients were estimated at risk of chronic obstructive pulmonary disease or sleep apnea syndrome and were recommended to perform further explorations. Anti-osteoporosis drugs were prescribed in 11% (n=21) patients. Vaccinations and neoplasia screening updates were proposed for 53% (n=97) and 41% (n=75) patients. Only one clinically significant carotid stenosis requiring therapy was found (0.5%). Mild to moderate stenosis were found in 8/168 patients (4.7%). Abdominal aorta aneuvrysm requiring monitoring were detected in 8/168 patients (4.7%). Patients with detected carotid stenosis or aorta aneuvrym were significantly older (65±9 vs 58±11 years, p=0.01), more often male (58 vs 29%, p=0.01), with higher waist circumference (99±16 vs 92±14 cm, p=0.03) and mSCORE (4.4±3.6 vs 2.1±2.2, p<0.001). A mSCORE ≥4.5 would detect vascular Doppler abnormalities with a 88% sensitivity and a 43% specificity. Abnormal echocardiography was found in 30/184 patients (25 patients with valvular diseases, 3 hypokinesia and 5 left ventricular hypertrophia). Three months after screening, 84 patients were contacted by phone. 6/10 declared to have recommendation for hypertension, 5/8 for diabetes and 6/10 for osteoporosis. 14/29 declared to have performed the recommended CRD explorations, 30/40 the vaccines and 18/36 the neoplasia screenings.

Conclusion: A daily out-patient clinic for comorbidity screening helps to detect chronic diseases such as hypertension, diabetes, dyslipidemia, or osteoporosis requiring treatment in a 1/3 of patients. Chronic respiratory diseases were also detected in 26% patients. 50 to 75% of the recommendations proposed appeared to be applied. Profitability of systematic supra-aortic trunk doppler appears to be low with only 0.5% of clinically significant abnormalities. The use of systematic vascular ultrasonography should probably be limited to a more targeted population such as patients with a mSCORE≥4.5.

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Abstract Number: 1504

Increased Risk of Thromboembolism Among Patients with VTE Association with Rheumatoid Arthritis

Howard Amital[1,2] and Arnon-Dov Cohen[3], [1]Department of Medicine B, Center for Autoimmune Diseases, Sheba Medical Center, Tel-hashomer, Israel, [2]Department of Internal Medicine 'D', Sackler Faculty of Medicine, Tel-Aviv University, Kfar-Saba, Israel, [3]Chief Physician's Office, Clalit Health Services, Tel Aviv, Israel

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Increased risk of thromboembolism among patients with VTE association with Rheumatoid Arthritis

Background/Purpose: Rheumatoid arthritis (RA), is among most common autoimmune conditions manifested by progressive and irreversible joint destruction. Less is known about its hematological aspects.

The aim of this study was to assess whether an association exists between RA and venous thromboembolism (VTE); pulmonary embolism and/or deep vein thrombosis.

Methods: This study was a cross-sectional analysis performed utilizing the database of Clalit Health Services, the largest healthcare provider organization in Israel. All patients diagnosed with RA ['cases'] were compared with age and sex matched controls that did not have RA (by a ratio of 1:5). Data on health-related lifestyles and other comorbidities were collected. χ^2, *t*-tests, and logistic regression .models were used to compare the study groups

Results: This study included 11,782 patients with RA, in all ages, compared to 57,973 controls, which were age, Sex, BMI and (socioeconomic statue matched. The prevalence of VTE in people with RA was increased by a factor of 2.2 (CI 2.03-2.42

in comparison to control group in each category (P< 0.001). This factor contributed more than a history of smoking, increased BMI or older age (Table 1).

Conclusion: Our results significantly demonstrate that RA is associated with increased rates of VTE. Pathogenic mechanisms explaining this association should be explored.

Table 1

		O.R.	p-value	95% C.I.	
				Lower	Upper
	Sex (M:F)	0.76	<0.001	.681	.849
	Age	1.04	<0.001	1.036	1.043
	SES	0.98	<0.02	.959	.995
	RA	2.22	<0.001	2.028	2.424
	Smoking	1.06	0.25	.962	1.161
	BMI	1.04	<0.001	1.037	1.050

OR- Odd's ratio, CI – confidence interval, SES- Socioeconomical status,

RA – rheumatoid arthritis, BMI – Body mass index

Disclosure: H. Amital, None; **A. D. Cohen**, None.

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Abstract Number: 1505

Carotid Artery Atherosclerosis in Patients with Active Rheumatoid Arthritis: Predictors of Plaque Occurrence and Progression over 24 Weeks

Tatiana Nevskaya[1], Janet E. Pope[2], Lillian Barra[3] and Grace Parraga[4], [1]Medicine, Division of Rheumatology, University of Western Ontario, London, ON, Canada, [2]University of Western Ontario, London, ON, Canada, [3]Medicine, Division of Rheumatology, Schulich School of Medicine and Dentistry, Western University, London, ON, Canada, [4]University of Western Ontario, Robarts Research Institute, London, ON, Canada

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Background/Purpose: This study evaluated the prevalence and progression of subclinical carotid artery atherosclerosis in active rheumatoid arthritis (RA).

Methods: Carotid arteries of RA patients were scanned using high resolution 3D ultrasound at baseline and 24 weeks for vessel wall volume, intima-media thickness (IMT) and total plaque area, as well as arterial stiffness measured using pulse wave velocity. Variables related to inflammation, lipids and cardiovascular risk were assessed for associations with plaque progression. Of 195 screened patients, 31 met inclusion criteria (66 Swollen joint count (SJC) plus 68 Tender joint count (TJC)^{3}8 OR SJC plus TJC^{3}4 with elevated acute phase reactants) and were enrolled (27 female; mean age 59.3±9.8 years). Patients using lipid lowering drugs and uncontrolled comorbidities were excluded.

Results: Atherosclerotic plaque occurred in 35% and arterial wall hypertrophy (IMT^{3}0.6mm) in 86% of patients. Most (68%) had an atherogenic lipid profile characterized by reduced HDL and/or increased total cholesterol/HDL index, which was adversely affected by disease activity. Stepwise binary logistic regression analysis showed that Framingham risk score (OR=1.155, 95%CI:1.002-1.332, p=0.046) and ESR (OR=1.148, 95%CI:1.015-1.299, p=0.028) predicted plaque most strongly (table). Plaque progression was significantly associated with baseline higher hsCRP, ESR, and heavy smoking, but only hsCRP predicted plaque growth in multivariate regression analysis (p=0.004); and hsCRP was related to higher disease activity (r=0.443, p=0.016), LDL (r=0.544, p=0.007), and

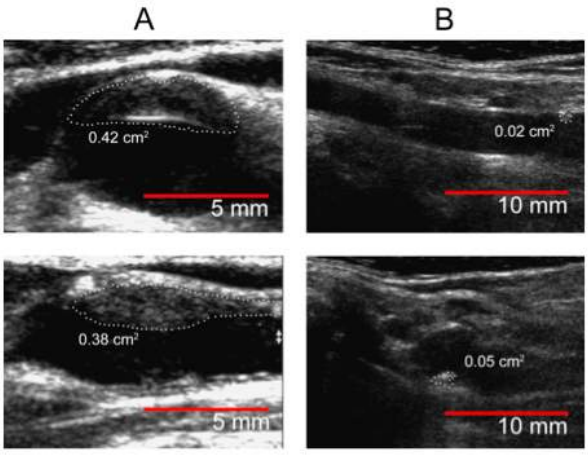
smoking (r=0.384, p=0.04). Figure shows carotid artery plaque with and without progression.

Conclusion:

RA-related inflammation contributed to augmented CV burden in RA and might mediate its effect on atherosclerosis through hsCRP and modulation of the traditional CV risk factors, such as dyslipidemia.

	RA patients with plaque, *n* = 11	**RA patients without plaque, *n* = 20**	***P*-value**
Clinical characteristics			
Age, years (SE)	63.2 (8.9)	57.1 (9.8)	0.1
Disease duration, years	18.1 (12.0)	13.8 (9.5)	0.29
DAS 28-ESR (SE)	4.9 (1.1)	4.8 (1.3)	0.81
DAS 28-CRP (SE)	4.5 (1.2)	4.6 (1.2)	0.86
Hypertension, n (%)	7 (64)	10 (50)	0.46
Body mass index-(SE)	27.6 (7.8)	30.6 (5.8)	0.36
Smoking history:			
Current smokers, n (%)	9(36)	6(30)	
Former smokers, n (%)	4 (36)	7(35)	0.53
Never smokers, n (%)	3 (28)	7 (35)	
Family history of cardiovascular disease, n (%)	5 (46)	5 (25)	0.24
Framingham risk score	19.2 (12.1)	10.5 (6.6)	0.005
Creatinine clearance (Cockcroft-Gault equation)	0.93 (0.36)	1.16 (0.19)	0.002
ESR, mm/hr (SE)	30.2 (14.2)	17.7 (15.4)	0.009
hsCRP, mg/l (SE)	9.5 (7.7)	6.7 (6.5)	0.33
Total cholesterol, mmol/l (SE)	4.9 (0.8)	5.1 (0.8)	0.64
LDL cholesterol, mmol/l (SE)	2.9 (0.6)	3.0 (0.7)	0.42
HDL cholesterol, mmol/l (SE)	1.52 (0.5)	1.4 (0.5)	0.52
Total/HDL cholesterol (AI) (SE)	3.6 (1.5)	4.1 (1.5)	0.42

Figure. Baseline 3D ultrasound measures of total plaque area (TPA) in two patients with rheumatoid arthritis indicative of atherosclerotic plaque occurrence (patient A; TPA -0.8mm^2) and normal carotid artery wall (patient B. TPA - 0.07mm^2). The cross-sectional area of each plaque was measured in the longitudinal view. TPA was the sum of all plaques between the clavicle and the angle of the jaw in both left and right carotid arteries.



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Abstract Number: 1506

EULAR Recommendations for Cardiovascular Risk Management in Patients with Rheumatoid Arthritis and Other Inflammatory Joint Diseases – 2015 Update

Michael T. Nurmohamed and on behalf of the EULAR task force "EULAR Recommendations for Cardiovascular Risk Management in patients with Rheumatoid Arthritis and other Inflammatory Joint Diseases", Rheumatology, Amsterdam Rheumatology and immunology Center, VU University medical center, Amsterdam, Netherlands

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Background/Purpose: Patients with rheumatoid arthritis (RA) (and other inflammatory joint diseases (IJD)) have an increased cardiovascular (CV) risk. In 2009 a EULAR taskforce recommended screening, identification of CV risk factors and cardiovascular risk management (CV-RM) largely based on expert opinion. In view of substantial new evidence, an update appeared timely with the aim of producing a more evidence base set of CV-RM recommendations.

Objectives:To 1) Review the presently available RA-specific cardiovascular risk prediction models and advise about the most appropriate model(s), 2a) Assess whether imaging techniques can improve CV risk prediction models, and b) advise whether routine screening with echocardiography before biologic therapy is initiated is indicated. 3) Give recommendations about lipid assessment, lipid lowering treatment and treatment targets, 4) Give recommendations about life style modifications. 5) Conduct a systematic literature update to determine the CV risk in AS and PsA and 6) Update the recommendation on NSAID/COXIB use in patients with IJD.

Methods: The multidisciplinary steering committee comprised 25 members including patients, rheumatologists, cardiologists, internists, epidemiologists and a health professional, representing 15 European countries. Systematic literature searches were done, evidence was categorized according to standard guidelines. The evidence was discussed and summarised by the experts in the course of a consensus finding and voting process and ultimately 10 evidence based recommendations for CV-RM were formulated.

Results: 1) Validated RA-specific CV-risk models have not yet been published, hence adjustment of general population risk models is still recommended 2) There are some suggestions that (imaging) biomarkers might improve risk prediction models. However, there are practical constraints for implementation. Echocardiographic screening before initiation of biologic treatment is not recommended. 3) Statins are at least as effective and safe in RA patients as in non-RA controls. 4) Exercise should be part of RA management, both to lower CV risk and improve disease outcomes. Counselling for smoking cessation should be considered 5) There is now more evidence for an increased CV-risk in patients with AS and PsA that is comparable to RA. Systemic inflammation enhances CV risk and adequate control of disease activity good control of disease activity is likely to be beneficial. 6) Current evidence does not support a strong association

between NSAID use and CVD in patients with IJD. As in the general population, the use of aspirin for the primary prevention of CV events in patients with IJD is not recommended. Level of agreement for the 10 recommendations varied but was generally high.

Conclusion: The present update confirms and further extends the evidence that the CV-risk in the whole spectrum of IJD is increased. This underscores the need for CV-RM in these patients. As these updated recommendations are based on a pan-European consensus it is hoped that they will facilitate CV-RM in daily clinical practice, ultimately leading to a decreased CV burden in our patients.

Disclosure: M. T. Nurmohamed, None;

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Abstract Number: 1507

Risk of Obstructive Sleep Apnea in Rheumatoid Arthritis Patients: The Frequency and Associated Disease Features

Fabian Dario Sinigaglia[1], Rafael Chaparro del Moral[1], Silvia Papasidero[1], Oscar Luis Rillo[1], José Angel Caracciolo[2], María Alejandra Medina[1], Analia Dellepiane[3], Cecilia Zaffarana[4], Maria de los Angeles Correa[5], Luciana Casalla[6], Lucía Zarate[6], Nieves Capozzi[7], María Victoria Martire[8], Marta Mamani[8], Damaris Alvarez[9], Eduardo Kerzberg[9] and José Luis Velasco Zamora[10], [1]Rheumatology Section, Hospital General de Agudos Dr. E. Tornú, Buenos Aires, Argentina, [2]Rhematology Section, Hospital General de Agudos Dr. E. Tornú, Buenos Aires, Argentina, [3]CEMEC, Santa Fe, Argentina, [4]Instituto de Rehabilitación Psicofísica, Buenos Aires, Argentina, [5]Rheumatology, Instituto de Rehabilitación Psicofísica, Buenos Aires, Argentina, [6]Rheumatology Section, Hospital Posadas, Buenos Aires, Argentina, [7]'Irigoyen 1418. CABA, Hospital Posadas, Buenos Aires, Argentina, [8]Rheumatology, Hospital Bernardino Rivadavia, Buenos Aires, Argentina, [9]Rheumatology Section, Hospital General de Agudos Dr. J. M. Ramos Mejía, Buenos Aires, Argentina, [10]Reumatología al Sur, Berazategui, Argentina

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Background/Purpose: Obstructive Sleep Apnea Syndrome (OSA) affects 2-4% of the population and it has been observed in rheumatoid arthritis (RA) patients in up to 30.8%. Besides, OSA has been determined as an independent risk factor for arterial hypertension (AHT) and has been associated with cardiovascular disease and stroke. There is little information in the literature about the relationship between this syndrome and the characteristics of RA, therefore the aim of this study is to investigate the risk of OSA in patients with RA and related factors.

Methods: We conducted a multicenter cross-sectional observational study that included consecutive RA patients (ACR 1987-ACR/EULAR 2010). Socioeconomic status, clinical data and comorbidities were recorded. OSA risk was assessed by the Berlin Sleep Apnea Questionnaire and daytime sleepiness by the Epworth Sleepiness Scale. Visual Analog Scale for pain (VAS pain), RAPID3, DAS28, HAQ-DI and Hospital Anxiety and Depression Scale (HADS A and HADS D) were also assessed. For data analysis descriptive statistics, X^2test, T-Test and binary logistic regression for multivariate analysis were applied, using OSA risk as dependent variable.

Results: Of 168 RA patients, OSA high risk was observed in 71 patients (42%) and daytime sleepiness in 50 patients (29.7%). Patients with high OSA risk showed higher BMI (29 ± 5 vs 26 ± 5, p <0.001), higher disease activity [DAS28 (4.5 ± 1.4 vs 3.7 ± 1.2, p <0.001) and RAPID3 (14 ± 7 vs 10 ± 6, p <0.002)], and worse functional capacity [HAQ (1.3 ± 0.7 vs 0.9 ± 0.7, p <0.01)]. The frequency of AHT was higher among patients with high OSA risk (42% vs 19%, p <0.002), as well as with daytime sleepiness (43% vs 25%, p <0.02), anxiety and depression disorders [HAD-A (9.2±4 vs 6.5 ± 4, p<0.001) and HAD-D (7.5±3 vs 5.4 ± 3, p<0.001)] than the low OSA risk group. In multivariate analysis, the independently variables associated with high OSA risk were BMI (OR 1.14, 95%CI: 1.052-1.235, p = 0.001) and DAS28 (OR 1.13, 95%CI: 1.006-2.459, p = 0.047).

Conclusion:

The risk of OSA was 42% in patients with RA and was associated with BMI and disease activity.

Disclosure: F. D. Sinigaglia, None; **R. Chaparro del Moral**, None; **S. Papasidero**, None; **O. L. Rillo**, None; **J. A. Caracciolo**, None; **M. A. Medina**, None; **A. Dellepiane**, None; **C. Zaffarana**, None; **M. D. L. A. Correa**, None; **L. Casalla**, None; **L. Zarate**, None; **N. Capozzi**, None; **M. V. Martire**, None; **M. Mamani**, None; **D. Alvarez**, None; **E. Kerzberg**, None; **J. L. Velasco Zamora**, None.

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Abstract Number: 1508

Lipid Target Achievement Among Patients with Recent-Onset Rheumatoid Arthritis during the First Six Years of Follow-up: Results from a French Multicenter Cohort of Early Arthritis

Anne Tournadre[1], Bruno Pereira[2], Jean-Jacques Dubost[3], Nathalie Rincheval[4], Anne-Christine Rat[5,6], Bernard Combe[7] and Martin Soubrier[3], [1]Rheumatology, UNH-UMR 1019 INRA University of Auvergne and Rheumatology department CHU Clermont-Ferrand, Clermont-Ferrand, France, [2]Biostatistics unit (DRCI), CHU Clermont-Ferrand, Clermont-Ferrand, France, [3]Rheumatology department CHU Clermont-Ferrand, Clermont-Ferrand, France, [4]Lapeyronie Hospital, Montpellier I University, UMR 5535, EA2415, Montpellier, France, [5]CHU Nancy, Clinical Epidemiology and Evaluation, Université de Lorraine, Paris Descartes University, APEMAC, EA 4360, Nancy, France, [6]CHU de Nancy, Rheumatology, Nancy, France, [7]Rheumatology, Hopital Lapeyronie, Montpellier, France
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Background/Purpose: Cardiovascular mortality is increased in rheumatoid arthritis (RA) and RA is an independent risk factor leading to a rapid increase in risk following diagnosis. Reduction of LDL-cholesterol (LDL-c) is essential to decrease CV risk. Between 2005 and 2010, French recommendations were based on the serum level of LDL-c, the target LDL-c depending on the number of risk factors. In 2006, it was recommended to consider RA as an additional cardiovascular risk factor (1). Our objective was to assess every year between 2005 and 2010 the proportion of patients with recent-onset RA achieving LDL-c objectives of national guidelines.

Methods : ESPOIR is a large, French, multicenter cohort of patients with early arthritis of less than 6 months' duration and a high probability of developing RA. 814 patients were included between 2002 and 2005. Repeated cross-sectional analysis for cardiovascular risk factors, LDL and HDL cholesterol levels were performed every year between 2005 and 2010 to determine the proportion of patients achieving the LDL-c goal according to the French guidelines considering RA as an additional risk factor since 2006.

Results : 689 patients were analyzed at the first point (age 49.6 ± 12.2 years, mean symptom duration was 1.83 ± 0.95 years), 77 % were female. At this first point, 495 patients (72 %) fulfilled the ACR criteria for RA. 3 % of the patients were being treated with statins which did not significantly vary during follow-up. The proportion of patients achieving the recommended LDL-c target decreased significantly following the publication of specific RA guidelines in 2006 but did not differ during the next 5 years of follow-up (89.5 % in 2005 ; 84.7 % in 2006 ; 81.5 % in 2007 ; 77.5 % in 2008 ; 80.6 % in 2009, 81.5 % in 2010). More males and more than half of patients with high CV risk did not reach the lipid target. The proportion of patients who did not achieve the LDLc target increased with the number of risk factors accounting for less than 8 % in patients with only one risk factor and for more than 58 % in patients with the highest risk (Table).

Conclusion: Regardless of specific recommendations for management of cardiovascular risk in RA patients and large cholesterol screening, management of dyslipidaemia remained suboptimal in particular among patients at highest risk. It is still unclear whether the expansion of the indications for statin therapy would expand lipid target achievement.

1. Pham T, Gossec L, Constantin A et al. Cardiovascular risk and rheumatoid arthritis: clinical practice guidelines based on published evidence and expert opinion. Joint Bone Spine. 2006;73:379-87

Proportion of patients in whom LDLc target was NOT achieved according to the level of cardiovascular risk.

Level of risk according to French Guidelines (LDLc target)	2005 (n=689)	2006 (n=620)	2007 (n=558)	2008 (n=530)	2009 (n=515)	2010 (n=486)
No associated risk	3/354	0/146	0/122	0/96 (0)	0/103	0/82 (0)

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No associated risk factors	3/334 (0.8)	0/140 (0)	0/122 (0)	0/90 (0)	0/103 (0)	0/82 (0)
(5.7 mmol/L = 2.2 g/L)						
1 associated risk factor	13/178 (7.3)	5/192 (2.6)	5/169 (3)	8/161 (5)	5/139 (3.6)	2/135 (1.5)
(4.9 mmol/L = 1.9 g/L)						
2 associated risk factors	10/81 (12.3)	27/165 (16.4)	30/141 (21.3)	28/137 (20.4)	34/148 (23)	23/140 (16.4)
(4.1 mmol/L = 1.6 g/L)						
≥ 3 associated risk factors	11/23 (47.8)	30/69 (43.5)	44/86 (51.2)	48/85 (56.5)	30/79 (38)	37/81 (45.7)
(3.4 mmol/L = 1.3 g/L)						
High risk	35/53 (66)	33/48 (69)	24/40 (60)	35/51 (68.6)	31/46 (67.4)	28/48 (58.3)
(2.6 mmol/L = 1 g/L)						

Abstract Number: 1509

Serum Nitrite Levels in Rheumatoid Arthritis and Relationship to Cardiovascular Risk Factors and Atherosclerosis Biomarkers

Kimberly P. Liang[1], Douglas P. Landsittel[2], Bernadette B. Sendon[3], Donald M. Jones[4], Rachel Gartland[3], Suresh R. Mulukutla[5], Steven E. Reis[6], Flordeliza S. Villanueva[5], Ali Hakim Shoushtari[7], Cameron Dezfulian[8] and Larry W. Moreland[4], [1]Department of Medicine, Division of Rheumatology and Clinical Immunology, University of Pittsburgh, Pittsburgh, PA, [2]Medicine, University of Pittsburgh, Pittsburgh, PA, [3]Rheumatology and Clinical Immunology, University of Pittsburgh, Pittsburgh, PA, [4]Rheumatology & Clinical Immunology, University of Pittsburgh, Pittsburgh, PA, [5]Division of Cardiology, University of Pittsburgh, Pittsburgh, PA, [6]Division of Cardiology and Department of Clinical and Translational Science, University of Pittsburgh, Pittsburgh, PA, [7]Clinical and Translational Science Institute, University of Pittsburgh, Pittsburgh, PA, [8]Critical Care Medicine and Clinical and Translational Science, University of Pittsburgh, Pittsburgh, PA

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Background/Purpose: Nitric oxide (NO) has been implicated in immune regulation, inflammation, arthritis and atherosclerosis. Raised levels of nitrite (NO_2) in serum and synovial fluid have been reported in rheumatoid arthritis (RA). However, impaired NO bioavailability is a hallmark of endothelial dysfunction, an early step in atherosclerosis. Premature atherosclerosis is known to exist in RA. Plasma NO_2 has been validated as an excellent measure of NO synthase activity and negatively correlated with CV risk factors in non-RA patients. This study aims to compare the levels of NO_2 in RA and controls, and to evaluate the relationship of NO_2 to traditional cardiovascular (CV) risk factors, subclinical atherosclerosis, and atherosclerosis biomarkers.

Methods: Traditional CV risk factors of smoking (current/ever vs. never), family history of CV disease, obesity, hypertension (HTN), hyperlipidemia, and diabetes were compared between RA subjects and controls using chi-squared or Fisher's exact tests. Carotid ultrasounds were performed with measurement of intima-media thickness (cIMT, using maximum of both sides) and plaque presence (of either side), and serum biomarkers (ICAM-1, VCAM-1, E-selectin, MPO, IL-6, CD40L, and MMP-9) were measured by ELISA in all subjects (78 RA cases and 92 controls). NO_2 was measured by chemiluminescence (39 RA and 50 controls). NO_2 was compared between cases and controls, and between those with and without plaque or individual CV risk factors (both overall and by case status), using t-tests. The relationship between NO_2 and each serum biomarker or cIMT was tested by Pearson correlations. The relationship between number of CV risk factors and NO_2 or each biomarker was tested by Spearman correlations.

Results: All traditional CV risk factors were similar between RA and controls except for HTN, which was higher in RA (44.9%) than controls (24.4%) (p=0.01). Mean ± SD NO_2 levels in RA (0.17 ± 0.08) were similar to levels in controls (0.15 ± 0.09; p=0.35). There were no significant differences in mean NO_2 between those with and without plaque either overall (p=0.86) or in the RA group only (p=0.78). NO_2 levels were not significantly associated with cIMT or any serum biomarker in RA group, but did have significant negative correlations with CD40L in controls (r -0.28, p=0.048) and with MMP9 in overall group (r -0.22, p=0.03). There were no significant differences in mean NO_2 between those with and without each CV risk factor, both overall and in the RA group. In the overall group, number of CV risk factors was slightly positively correlated with NO_2 (r_s 0.20, p=0.06), and significantly positively correlated with cIMT (r_s 0.24, p<0.01) and E-selectin (r_s 0.19, p=0.01), but these were not significant within the RA group. Number of CV risk factors was significantly positively correlated with MPO (r_s0.26, p=0.02) in the RA group.

Conclusion: NO_2 levels in RA are not lower than controls, and were similar in those with or without traditional CV risk factors or plaque.

Number of CV risk factors positively correlated with cIMT and E-selectin in the overall group, but not within RA patients. These findings suggest possible different pathways by which NO and CV risk factors mediate subclinical atherosclerosis in RA versus non-RA persons.

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Abstract Number: 1510

The Association Between HDL Cholesterol Efflux Capacity, Citrullinated ApoA1 and Anti-Citrullinated ApoA1 Antibodies in Rheumatoid Arthritis

Katherine Liao[1], Jing Cui[1], Christopher Rhodes[2], Lauren J. Lahey[2], Martin Playford[3], I-Hsin Kuo[1], Michelle Frits[1], Christine Iannaccone[1], Jonathan S. Coblyn[4], Michael Weinblatt[1], Nancy Shadick[5], Nehal N. Mehta[3] and Jeremy Sokolove[2], [1]Division of Rheumatology, Immunology, and Allergy, Brigham & Women's Hospital, Boston, MA, [2]Medicine, VA Palo Alto HealthCare System and Stanford University, Palo Alto, CA, [3]NHLBI, National Institutes of Health, Bethesda, MD, [4]Brigham & Women's Hospital, Boston, MA, [5]Division of Rheumatology, Immunology & Allergy, Brigham & Women's Hospital, Boston, MA

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Background/Purpose:

High density lipoprotein (HDL) cholesterol efflux capacity measures how well HDL particles remove cholesterol from lipid-laden macrophages, such as those found in atherosclerotic plaques. This function of HDL is an important predictor of cardiovascular (CV) risk, independent of traditional risk factors, and is impaired in RA. Apolipoprotein A1 (apoA1) is the component of HDL that mediates cholesterol efflux. Recently developed assays can measure citrullinated apoA1 (cit-apoA1) as well as antibodies against cit-apoA1 (anti-cit-apoA1) in human serum. Our objective was to study whether cit-apoA1 and anti-cit-apoA1 in RA subjects was associated with impaired HDL efflux capacity.

Methods:

We performed this study in a prospective RA cohort based at a large academic center. We focused on a subgroup of subjects who had HDL cholesterol efflux capacity and total apoA1 measured in a previous study. Subjects were included in the subgroup if they experienced a reduction in inflammation between two consecutive years. HDL cholesterol efflux capacity was measured using a cell based assay, and total apoA1 was measured in a clinical laboratory using standardized commercial methods. For the present study, we measured cit-apoA1 and anti-cit-apoA1 at baseline. Cit-apoA1 was measured using ELISA and anti-cit-apoA1 was measured using a multiplex bead assay. To test the association between cit-apoA1 and HDL efflux capacity, we studied cit-apoA1 as a proportion to total apoA1 levels: (cit-apoA1)/(total apoA1). We then constructed a linear regression model to examine the association between the proportion of cit-apoA1 with HDL efflux capacity at baseline, adjusted by age and gender. Additionally, we tested the association between cit-apoA1 with HDL efflux capacity, and total apoA1 with HDL efflux capacity in separate linear regression models. We constructed a linear regression model to study the association between the concentration of anti-cit-apoA1 with HDL efflux capacity at baseline, adjusted by age and gender.

Results:

The 90 subjects in the study had a mean age of 57.4 (SD 12.3), 90% were female, and 77.8% were anti-CCP positive. A higher proportion of cit-apoA1 in the serum was associated with impaired HDL efflux capacity [β=-46.0 (SE 22.0), p=0.039]. While there was no association between the absolute concentration of cit-apoA1 with HDL efflux capacity (p=0.47), a higher level of total apoA1 was associated with better HDL efflux capacity [β=-2.0x10^{-3} (SE 3.0x10^{-4}), p=<0.0001]. We found no significant association between the concentration of anti-cit-apoA1 and HDL efflux capacity [β=-3.0x10^{-4} (SE 2.0x10^{-4}), p=0.136].

Conclusion:

This study suggests that a higher proportion of citrullinated apoA1 is linked with impaired ability of HDL to remove cholesterol from lipid-laden macrophages. Larger studies are needed to further investigate this relationship and its potential impact on cardiovascular risk in RA.

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Abstract Number: 1511

Increased Prevalence of Anti-Nuclear and Anti-SSA Autoantibodies in African American Rheumatoid Arthritis Patients Versus Matched Caucasian Rheumatoid Arthritis Patients

Tyler Sevco[1], Douglas P. Landsittel[2], Chengli Shen[3], Bruce Rabin[4] and Larry W. Moreland[5], [1]Medicine, University of Pittsburgh School of Medicine, Pittsburgh, PA, [2]Medicine, University of Pittsburgh, Pittsburgh, PA, [3]University of Pittsburgh School of Medicine, Pittsburgh, PA, [4]Pathology, University of Pittsburgh Medical Center, Pittsburgh, PA, [5]Rheumatology & Clinical Immunology, University of Pittsburgh, Pittsburgh, PA

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Background/Purpose: African American (AA) patients with rheumatoid arthritis (RA) have worse Health Assessment Questionnaire (HAQ) scores and increased disease activity clinically compared to Caucasian (CAU) RA patients. Serologically, AA RA patients have a higher reported prevalence of antinuclear antibody (ANA) and anti-SSA compared to CAU RA patients in two established unmatched RA cohorts. However, no matched studies have been performed. In addition, RA and Sjogren's Syndrome can co-exist and this joint pathology is associated with worse clinical manifestations and increased ANA and anti-SSA positivity. We hypothesize that the increased disease activity of RA in AAs may be linked to an increased frequency of ANA and anti-SSA antibodies, causing increased disease activity and more severe RA in AA patients.

Methods: Plasma samples were assayed from matched AA and CAU RA patients in the Rheumatoid Arthritis Comparative Effectiveness Research (RACER) cohort at the University of Pittsburgh. Patients were matched for variables including age, gender, disease duration, and RF and Cyclic Citrullinated Peptide (CCP) antibody positivity. ANA testing was performed using Indirect Immunofluorescence and titers of $\geq$ 1:80 were classified as positive. Samples also underwent specific autoantibody testing, including anti-SSA testing, with the Bioplex 2200 Multiplex Bead Assay and titers $\geq$ 1:1.9 were considered positive. Differences in autoantibody prevalence between AA and CAU RA patients were assessed using chi-square and Fisher's exact tests.

Results: AA RA patients (N=94) were matched with CAU RA patients (N=93) for age, BMI, gender, RF positivity, anti-CCP positivity, and disease duration (Table 1). Anti-SSA was significantly more prevalent in the AA RA patients (11.70% vs. 3.23%; p=0.021). AA RA patients also had a higher prevalence of ANA (21.28% vs. 10.75%) and higher prevalences of systemic lupus associated antibodies including anti-RNP, anti-SM/RNP, and anti-chromatin compared to CAU RA patients (Table 2).

Conclusion: The increased disease severity observed in AA RA patients compared to CAU RA patients may be mediated by an increased prevalence of a serologically unique subset of RA patients who are ANA and anti-SSA positive.

Table 1: RACER Demographic Data

	African American (N=94)	Caucasian (N=93)	P-value
Mean Age (years)	60.39	58.72	0.394
Mean BMI (Kg/M2)	31.04	29.54	0.243
Female (%)	93.50%	95.60%	0.747
RF Positive	77.20%	82.80%	0.363
Anti-CCP Positive	75.00%	76.30%	0.864
Mean Disease Duration (Months)	14.00	13.04	0.520

Table 2: Autoantibody prevalence in AA and CAU Patients

	AA % Positive (N=94)	CAU % Positive (N=93)	P-value
ANA (≥1:80)	21.28% (20/94)	10.75% (10/93)	0.095
Anti-SSA	11.70% (11/94)	3.23% (3/93)	0.021
Anti-SSB	4.26% (4/94)	1.08% (1/93)	0.180
Anti-SSA AND/OR Anti-SSB	12.77% (12/94)	4.30% (4/93)	0.021
Anti-Double Stranded DNA	4.26% (4/94)	6.45% (6/93)	0.523
Anti-Smith	0.00%	0.00%	--
Anti-Smith/Anti-Ribonucleoprotein	3.19% (3/94)	1.08% (1/93)	0.317
Anti-Ribonucleoprotein	6.38% (6/94)	4.30% (4/93)	0.480
Chromatin	4.26% (4/94)	2.15% (2/93)	0.103
Ribosomal P	0.00%	0.00%	--
Centromere B	0.00%	2.15% (2/93)	0.157
Anti-Topoisomerase 1 (Scl-70)	1.06% (1/94)	0.00%	0.317
Anti-histidyl tRNA synthetase (Jo-1)	0.00%	0.00%	--

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Incidence of Co-Morbid Autoimmune Diseases in Patients with Rheumatoid Arthritis

TA Simon[1], H Kawabata[1], JM Esdaile[2], V Moorthy[3] and S Suissa[4], [1]Bristol-Myers Squibb, Hopewell, NJ, [2]Arthritis Research Canada, Vancouver, BC, Canada, [3]Mu Sigma, Northbrook, IL, [4]McGill University, Montreal, QC, Canada
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Background/Purpose: Rheumatoid arthritis (RA) is one of more than 80 different types of autoimmune diseases, many of which, including RA, share common pathogenic mechanisms, resulting in overlapping syndromes. Some autoimmune diseases, such as lupus and psoriasis, may also occur as a side effect of treatment. The purpose of this study was to quantify the incidence of autoimmune diseases in an RA population. For comparison, a population of patients was identified who had osteoarthritis (OA) and similar health care encounters to the RA population.

Methods: Patients were identified from the US MarketScan® Commercial and Supplemental Medicare databases. Patients with RA were age- and sex-matched 1:5 with a comparison cohort of patients with OA. Patients were required to have ≥180 days of continuous health plan enrollment before the qualifying RA or OA diagnosis between January 1, 2006 and September 30, 2013. Study index date corresponded to the first qualifying RA or OA diagnosis date during the study period. A single International Classification of Diseases, Ninth Revision diagnosis code of an autoimmune disease after the index date was considered an event. Over 28 autoimmune diseases were pre-specified. Patients were followed from their index date until the end of study period, end of enrollment, or occurrence of autoimmune disease, whichever occurred first. For the RA cohort, patients were censored if they developed OA during the follow-up period. Patients with an autoimmune disease in their 6-month baseline period were excluded when calculating incidence rates (IRs) for that specific autoimmune disease during follow-up. IRs with 95% CI for 28 pre-specified autoimmune diseases during the follow-up period were computed for both RA and OA populations.

Results: A total of 208,397 and 1,031,784 patients with RA and OA, respectively, were evaluated. Of the 28 pre-specified autoimmune diseases evaluated, lupus, psoriatic disease, and Sjögren's syndrome occurred most frequently among patients with RA, occurring in 5%, 3%, and 3% of the population, respectively, with corresponding IRs of 29, 19 and 17/1000 person-years. Corresponding IRs for the matched OA population were 2, 6 and 2/1000 person-years for lupus, psoriatic disease, and Sjögren's syndrome, respectively. Chronic urticaria and type 1 diabetes were the most frequently reported autoimmune diseases in the OA population (2% and 1.9%, respectively), with IRs of 8.7 and 8.4/1000 person-years, respectively. The IRs of autoimmune diseases were generally higher among the RA patients than the matched OA patients (except for type 1 diabetes). Selected co-morbid autoimmune diseases in either cohort are shown in the Table. **Conclusion:** Previous work showed that the prevalence of certain autoimmune diseases was greater in RA patients compared to those with OA. These results suggest that some autoimmune diseases occur more frequently among patients with RA than in closely matched patients with OA.

Table. Incidence of selected co-morbid autoimmune diseases in patients with RA or OA (by incidence in RA)								
	RA (N=208,397)				OA (N=1,031,784)			
Autoimmune disease	Patients evaluated (n)	Person-years	Incident events	IR per 1000 person-years (95% CI)	Patients evaluated (n)	Person-years	Incident events	IR per 1000 person-years (95% CI)
Systemic lupus erythematosus	201,443	357,799	10,500	29.35 (28.79, 29.91)	1,027,876	2,356,510	5273	2.24 (2.18, 2.30)
Psoriatic disease	200,664	361,762	6886	19.03 (18.59, 19.49)	1,024,827	2,335,570	13,187	5.65 (5.55, 5.74)
Sjögren's syndrome	205,664	373,755	6477	17.33 (16.91, 17.76)	1,030,217	2,364,584	3844	1.63 (1.57, 1.68)
Psoriatic arthritis	202,830	368,143	5325	14.46 (14.08, 14.86)	1,030,231	2,366,876	2718	1.15 (1.11, 1.19)
Psoriasis only	204,674	373,376	5149	13.79 (13.42, 14.17)	1,025,785	2,338,698	12,523	5.35 (5.26, 5.45)
Raynaud's syndrome	206,482	379,286	4082	10.76 (10.43, 11.10)	1,030,173	2,363,104	4697	1.99 (1.93, 2.05)
Chronic urticaria	206,352	378,995	3877	10.23 (9.91, 10.56)	1,026,381	2,327,235	20,255	8.70 (8.58, 8.82)
Pulmonary fibrosis	206,753	380,755	3568	9.37 (9.07, 9.68)	1,029,445	2,352,905	9657	4.10 (4.02, 4.19)
Graves' disease	206,749	380,802	3258	8.56 (8.26, 8.85)	1,025,493	2,330,011	16,351	7.02 (6.91, 7.13)
Type 1 diabetes mellitus	205,412	379,066	3046	8.04 (7.75, 8.33)	1,018,398	2,307,542	19,298	8.36 (8.25, 8.48)

Disclosure: T. Simon, Bristol-Myers Squibb, 3; **H. Kawabata**, Bristol-Myers Squibb, 1,Bristol-Myers Squibb, 3; **J. Esdaile**, None; **V. Moorthy**, None; **S. Suissa**, Bristol-Myers Squibb, Genentech, Roche, 5.

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Abstract Number: 1513

Reactivation of Hepatitis B-Infection in German Patients with Inflammatory Rheumatic Diseases Treated with Biologics – a Monocentric Analysis Involving 1107 Patients

Eva Christina Scharbatke[1], Sonja Kreissl-Kemmer[2], Hans-Peter Tony[3], Marc Schmalzing[4] and Andreas Geier[2], [1]Rheumatology/Immunology, University hospital Wuerzburg, Wuerzburg, Germany, [2]Hepatology, University hospital Wuerzburg, Wuerzburg, Germany, [3]University Hospital Würzburg, Würzburg, Germany, [4]Rheumatology/Clinical Immunology, University Hospital Würzburg, Würzburg, Germany

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Background/Purpose: Hepatitis B virus (HBV) reactivation is a common complication of immunosuppressive treatment in countries with a high prevalence of HBV infection. Biologics – and especially Rituximab – seem to cause this adverse event more commonly than conventional forms of treatment do. However, it is unclear how often patients suffer from HBV reactivation in a low prevalence country like Germany when treated with biologics for rheumatic diseases.

Methods: Using an electronic database (EMIL©; version 4.7.6.19), we were able to digitally search the files of patients treated in our Rheumatology out-patient unit between April 2008 and May 2015 (10.019 patients in total). Patients on immunosuppressive therapy screened for HBV infection have been included in the analysis. Clinical data of all patients are summarized in table 1.

Results: Between April 2008 and May 2015, 1107 patients were treated with biologics in our Rheumatology/Immunology out-patient department, 378 of which received Rituximab at least once. Of the 1107 biologics patients, 59 (5%) tested HBc antibody positive, indicating prior infection with HBV. One patient (1/59) suffered from an active HBV infection (HBs antigen positive). Only 2/59 patients, including the chronically infected patient mentioned above, received prophylactic antiviral treatment. There were no obvious HBV reactivations and no incidents of liver failure due to HBV, although in 2 patients, traces of HBV DNA could newly be detected under treatment with Infliximab in one case, and Rituximab in another case. After antiviral treatment HBV DNA became undetectable again in both cases.

Conclusion: HBV reactivation during antirheumatic therapy with biologics is a relatively rare event in German patients. Whilst both screening for prior or chronic HBV infection and close monitoring of affected patients is mandatory, prophylactic antiviral treatment does not seem to be necessary in every detected case of prior HBV infection.

Table: Clinical data of the patients involved in the current analysis

Total number of patients treated with biologics between April 2008 and May 2015 included in this analysis	**1107**
Number of patients receiving Rituximab at least once (not withstanding other biologic treatment). Reactivation under Rituximab	**378** **1/378**
Rheumatologic diagnosis	Rheumatoid arthritis: **663** Psoriatic arthritis: **113** Spondyloarthritis: **140** Connective Tissue Diseases (CTD)/Myositis: **50** Vasculitis: **54** Other: **87**
Hepatitis Bc antibody positive	**59**
HBs antigen positive	**1**
HBV DNA positive	**3**
Reactivation with Rituximab Reactivation with non-Rituximab treatment	**1/378 (0,3%)** **1/729 (0,1%)**
Antiviral treatment	Preemptive: **2** After increase of HBV DNA: **2**
Liver failure due to HBV infection	**0**

Disclosure: E. C. Scharbatke, Chugai Pharma, 2,Chugai Pharma, 5,AbbVie, 5,Baxter, 5,Roche Pharmaceuticals, 5; **S. Kreissl-Kemmer**, None; **H. P. Tony**, AbbVie, 5,AbbVie, 8,Roche Pharmaceuticals, 5,Chugai, 5,MSD, 5,Pfizer Inc, 5,UCB, 5; **M. Schmalzing**, AbbVie, 5,Actelion Pharmaceuticals US, 5,Chugai, 5,Pfizer Inc, 5,Roche Pharmaceuticals, 5,UCB, 5; **A. Geier**, AbbVie, 5,Gilead, 5,Janssen Pharmaceutica Product, L.P., 5,Falk, 5,Sequana, 5,Novartis Pharmaceutical Corporation, 5,BMS, 5.

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Abstract Number: 1514

Incidence and Risk Factors of Malignancy in a Cohort of Rheumatoid Arthritis Patients from Singapore

XR Lim[1], LZ Liu[2], X Gao[2], J W L Tan[1], L W Koh[3], TY Lian[1], W Q See[4], KP Leong[1], ET Koh[1] and TTSH RA Study Group, [1]Rheumatology, Allergy and Immunology, Tan Tock Seng Hospital, Singapore, Singapore, [2]Clinical Research and Innovation Office, Tan Tock Seng Hospital, Singapore, Singapore, [3]Department of Rheumatology, Allergy and Immunology, Tan Tock Seng Hospital, Singapore, Singapore, [4]Tan Tock Seng Hospital, singapore, Singapore
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Background/Purpose:

Patients with rheumatoid arthritis (RA) have been shown to have an increased risk of developing malignancies. This study was undertaken to determine the incidence and pattern of malignancy in RA patients and identify risk factors of malignancy among patients with RA.

Methods:

Patients from the TTSH RA Registry were followed up longitudinally and those who developed malignancies from 2001 to 2013 after the onset of RA were identified. Age-standardised rates (ASRs) of various cancers were analyzed and compared with the Singapore Cancer Registry data. Risk factors for developing malignancy, including demographics, disease characteristics and treatment history, were analyzed using Chi-squared test and student's t test.

Results:

Of the 1,134 patients in the registry, 81 patients developed malignancies at a mean interval of 15.1 (SD 9.7) years after the onset of RA. The mean age of the 81 patients was 65.9 (SD 10.8) years, of which 61 (75.31%) were females and 69 (85.19%) were Chinese. There were 70 (86.4%) with solid-organ tumours and 11 (13.6%) haematological malignancies.

The ASR of cancer in RA patients was 310.3 for males and 232.5 for females per 100,000 person-years, compared with 229.3 (95%CI 226.5-232) for males and 218.3 (95%CI 213.8-216.3) for females in the general population. By cancer type, there is an increased risk of lung cancer, lymphoid neoplasms and stomach cancer in RA compared with the general population.

The risks factors for developing malignancy ($p<0.05$) include male gender, non-Indian ethnicity, onset of RA at an older age, untreated RA and higher disease activity.

Conclusion:

The incidence of solid-organ malignancies was higher than hematological malignancies, unlike that in the literature. The overall risk of malignancy is higher in RA patients. Chronic inflammation from RA is associated with increased risk of malignancy.

Table 1

Crude Rates (CR) and Age standardize rates (ASR) of specific cancer types among the general population and rheumatoid arthritis cohort

Gender	Maligancy	Singapore general population (2009-2013)				1106 RA patients (2001-2013)				
	Cancer Types	Observed cancer cases	CR	ASR	95% CI for ASR	total RA	Observed cancer cases	Cancer %	CR	ASR
Male	All cancers	28520	305.2	229.3	(226.5, 232)	177	20	100	1194.10	310.30
	Lung	4318	46.2	34	(33, 35)		8	40	477.64	148.63
	Lymphoid neoplasms	1890	20.2	16.7	(15.9, 17.5)		3	15	179.11	38.91
	Stomach	1414	15.1	11.1	(10.5, 11.7)		3	15	179.11	36.35
	Kidney & other urinary	1035	11.1	8.1	(7.6, 8.6)		2	10	119.41	29.45
	Colo-rectum	4935	52.8	38.7	(37.6, 39.8)		1	5	59.7	15
	Prostate	3456	37	28.1	(27.1, 29)		1	5	59.7	10.01
	Nasopharynx	1122	12	8.4	(7.9, 8.9)		1	5	59.7	19.44
Female	All cancers	30237	314.6	213.8	(213.8, 216.3)	928	61	100	665.00	232.52
	Colo-rectum	3996	41.6	26.3	(25.5, 27.1)		11	18.03	119.92	32.83
	Female Breast	8867	92.2	63.4	(62.1, 64.8)		10	16.39	109.02	46.68
	Lymphoid neoplasms	1323	13.8	10.8	(10.2, 11.5)		7	11.47	76.31	31.59
	Lung	2294	23.9	15	(14.4, 15.6)		6	9.84	65.41	27.46
	Skin, including Melanoma	1321	13.7	8.4	(7.9, 8.8)		5	8.2	54.51	15.82
	Cervix uteri	952	9.9	6.8	(6.4, 7.3)		5	8.2	54.51	21.76
	Stomach	1089	11.3	6.9	(6.5, 7.3)		3	4.92	32.7	7.7
	Corpus uteri	1922	20	13.8	(13.2, 14.4)		2	3.28	21.8	6.45
	Pancreatic						2	3.28	21.8	8
	Thyroid	1076	11.2	8.4	(7.8, 8.9)		2	3.28	21.8	8.01
	Ovary, etc.	1646	17.1	12.5	(11.8, 13.1)		1	1.64	1.64	2.78

Note: Both the ASR for Singapore general population and our RA cohort were standardized to Segi's world population age structure. CR; ASR: Per 100,000 person-year

Table 2

Demographics, disease characteristics and treatment history of patients without malignancy and those who develop malignancy					
		Total No. of Patients n=1106 (%)	**No. of Patients without maligancy n=1025 (%)**	**No. of Patients with maligancy after 1st study entry n=81 (%)**	**Univariate test p-value (t-test or chi2)**
Demographics					
Age at RA onset (yrs)	mean (SD)	45.03 (13.40)	44.58 (13.20)	50.77 (14.59)	0.0001
Age at RA diagnosis (yrs)	mean (SD)	47.31 (13.69)	46.74 (13.55)	54.43 (13.52)	<0.0001
Duration of RA onset to RA diagnosis (mths)	mean (SD)	27.34 (66.63)	26.02 (64.86)	43.96 (84.61)	0.0196
Gender	Male	177 (16.02)	157 (15.33)	20 (24.69)	0.0390
Ethnicity	Chinese	849 (76.83)	780 (76.17)	69 (85.19)	0.1350
	Malay	96 (8.69)	91 (8.89)	5 (6.17)	
	Indian	129 (11.67)	125 (12.21)	4 (4.94)	
	Others	31 (2.81)	28 (2.73)	3 (3.70)	
Chinese	Non-Chinese	256 (23.17)	244 (23.83)	12 (14.81)	0.0750
	Chinese	849 (76.83)	780 (76.17)	69 (85.19)	
Indian	Non-Indian	976 (88.33)	899 (87.79)	77 (95.06)	0.0480
	Indian	129 (11.67)	125 (12.21)	4 (4.94)	
Education	<= primary	489(44.99)	448(44.53)	41(50.62)	0.2980
	>=secondary	598(55.01)	558(55.47)	40(49.38)	
Smoking	Ever	150 (13.56)	134 (13.07)	16 (19.75)	0.0930
Disease characteristics					
Rheumatoid Factor	Positive	797 (77.15)	744 (77.66)	53 (70.67)	0.1980
Anti-CCP	Positive	548 (74.36)	513 (74.56)	35 (71.43)	0.6140
Radiographic Erosion	Positive	648 (58.7)	592 (57.87)	56 (69.14)	0.0600
ESR at 1st study visit	mean (SD)	37.58 (27.06)	36.98 (26.60)	45.15 (31.54)	0.0102
CRP at 1st study visit	mean (SD)	20.23 (23.21)	19.11 (22.24)	33.56 (30.59)	0.0248
No. of Tender Joints at 1st study visit	mean (SD)	1.84 (3.80)	1.78 (3.69)	2.54 (4.94)	0.0817
No. of Swollen Joints at 1st study visit	mean (SD)	2.34 (3.59)	2.26 (3.45)	3.37 (4.90)	0.0072
No. of deformity joints at 1st study visit	mean (SD)	2.30 (4.07)	2.32 (4.14)	2.09 (3.18)	0.6166
DAS28 at 1st study visit	mean (SD)	3.35 (1.41)	3.33 (1.39)	3.61 (1.57)	0.0894
Treatment history					
Duration of RA onset to 1st DMARD usage (mths)	mean (SD)	40.64 (65.34)	39.43 (61.78)	55.88 (99.04)	0.0292
No. of DMARDs used at lst study visit	Mean (SD)	2.02 (1.29)	2.03 (1.28)	1.88 (1.32)	0.3057
Methotrexate	Ever	802 (72.51)	745 (72.68)	57 (70.37)	0.6980
Sulfasalazine	Ever	671 (60.67)	620 (60.49)	51 (62.96)	0.7240
Hydroxychloroquine	Ever	459 (41.50)	433 (42.24)	26 (32.10)	0.0800
Leflunomide	Ever	47 (4.25)	44 (4.29)	3 (3.70)	1.0000
Gold	Ever	91 (8.23)	84 (8.20)	7 (8.64)	0.8340
Penicillamine	Ever	106 (9.58)	99 (9.66)	7 (8.64)	1.0000
Ciclosporin A	Ever	17 (1.54)	15 (1.46)	2 (2.47)	0.3570
Biologics	Ever	6 (0.54)	6 (0.59)	0 (0)	1.0000

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arthritis-patients-from-singapore

Abstract Number: 1515

Accounting for Rheumatoid Arthritis in the Determination of 10 Year Cardiovascular Risk

Rupal Chavda and **Rochella A. Ostrowski**, Rheumatology, Loyola University Medical Center, Maywood, IL
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Background/Purpose:

Patients with rheumatoid arthritis (RA) carry a higher risk for cardiovascular disease (CVD) independent of traditional risk factors. In this study, we set out to determine the proportion of patients in our practice who receive cholesterol screening, and we evaluated the effects of the EULAR (European League Against Rheumatism) risk multiplication factor[1] on the number of RA patients identified as having a high or moderate 10 year risk for CVD.

Methods:

A chart review was performed for adult RA patients evaluated as return visits in the division of Rheumatology at our institution from June 1, 2012 to June 1, 2013. Clinical information was reviewed for CVD or CVD risk equivalents (cerebrovascular accident, peripheral artery disease, diabetes mellitus). The Framingham 10 year risk for CVD was calculated for patients who did not have CVD or CVD risk equivalents. A risk multiplier of 1.5 recommended by the EULAR for patients with 2 risk factors (disease duration > 10 years, seropositivity, or severe extra-articular manifestations) was applied. We evaluated the proportion of patients who received cholesterol screening and the proportion of patients taking statin therapy as indicated by the 10 year risk, for CVD, with and without the EULAR risk multiplication factor.

Results:

Of 520 patients who met inclusion criteria, 364 (70% , 95%CI 66.0-73.9%) received cholesterol screening. The proportion of patients with ≥2 CVD risk factors who had high or moderate risk (>20% or 10-20% 10 year risk respectively) increased from 12.5% to 20% when the EULAR risk multiplication factor was applied (Table 1). Amongst patients with any number of risk factors, the proportion of patients with high or moderate risk increased from 10.3% to 14.6% (Table 2). Of 16 patients with ≥2 risk factors who were not at target for low density lipoprotein (LDL) levels, 11 were not receiving statin therapy. In the larger patient cohort, 31 patients were not at LDL goal, and 23 of these were not on statin therapy.

Conclusion:

Given the increased risk for CVD in RA patients, methods to increase the rate of cholesterol screening should be explored. Additionally, the EULAR multiplication factor serves as a valuable tool when determining the 10 year risk for CVD in RA patients who otherwise may not be identified as requiring lipid lowering therapy.

References:

1. Peters MJL et al. EULAR evidence-based recommendations for cardiovascular risk management in patients with rheumatoid arthritis and other forms of inflammatory arthritis. Ann Rheum Dis 2010;69:325-31.

Distribution of 10-year cardiovascular risk in patients with ≥2 risk factors

10 Year Risk	Patients, n (%)	
	Without EULAR Multiplier	With EULAR Multiplier
High Risk >20%	4 (3.3%)	8 (6.7%)
	3 on statin, 2 not at goal	5 on statin, 3 not at goal
	1 not on statin, 1 not at goal	3 not on statin, 3 not at goal
Moderate Risk 10-20% risk	11 (9.2%)	16 (13.3%)
	5 on statin, 1 not at goal	9 on statin, 2 not at goal
	6 not on statin, 4 not at goal	7 not on statin, 5 not at goal
Low Risk <10% risk	105 (87.5%)	96 (80%)
	41 on statin, 3 not at goal	35 on statin, 2 not at goal
	64 not on statin, 5 not at goal	61 not on statin, 2 not at goal
Total	120	120

Table 1. Risk distribution in patients with ≥2 risk factors for cardiovascular disease.

10 year cardiovascular risk in patients without cardiovascular disease

	Without EULAR Multiplier	With EULAR Multiplier
High Risk >20%	5 (1.8%)	13 (4.6%)
	3 on statin, 2 not at goal	6 on statin, 4 not at goal
	2 not on statin, 2 not at goal	7 not on statin, 6 not at goal
Moderate Risk 10-20%	24 (8.5%)	28 (10.0%)
	9 on statin, 2 not at goal	13 on statin, 2 not at goal
	15 not on statin, 9 not at goal	18 not on statin, 9 not at goal
Low Risk <10%	252 (89.7%)	240 (85.4%)
	72 on statins, 2 not at goal	65 on statin, 2 not at goal
	179 not on statin, 11 not at goal	174 not on statin, 8 not at goal
Total	281	281

Table 2. Risk distribution in patients without coronary artery disease

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Disclosure: R. Chavda, None; **R. A. Ostrowski**, None.

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Abstract Number: 1516

Quality Improvement in Elderly Patients with Rheumatoid Arthritis: Pharmacotherapy and Identification of Cognitive Dysfunction

Brett Smith[1] and Kenneth S. O'Rourke[2], [1]Section on Rheumatology and Immunology, Wake Forest School of Medicine, Winston-Salem, NC, [2]Section on Rheumatology and Immunology, Wake Forest University School of Medicine, Winston-Salem, NC

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Background/Purpose: Cognitive impairment (CI) casts a significant burden on individuals, caretakers and the US health care system with an estimated prevalence between 10-20%. While CI is seen in a portion of the general population, it has also been identified in systemic lupus erythematosus, primary Sjogren's syndrome, antiphospholipid syndrome and rheumatoid arthritis (RA). However, no study has specifically evaluated the prevalence of CI in adults with RA over the age of 65. Our goal was to assess the prevalence of CI in a cohort of elderly patients with RA, and to pilot an educational intervention in those affected.

Methods: A cross sectional, survey based study was conducted at a single tertiary center, outpatient rheumatology clinic. Inclusion criteria were >65 years of age and a history of RA by 1987 criteria. Exclusion criteria included overlap syndromes. Thirty patients were consecutively enrolled and underwent our novel rheumatology-specific screening tool, the Rheumatology Mini-Cog (RMC). Those who failed were administered the Mini-cog. Those passing the Mini-cog were presumed not to have CI and administered an educational intervention using the Teach Back method. Those failing the Mini-cog were presumed to have CI and participated in an educational intervention with a family member or friend.

Results: Thirty patients were recruited during routine office visits. The average age was 72.2 years, 83% were Caucasian and 70% were female. Eight of 30 patients (26.7%) were found to have CI. Of those with CI, there was a higher prevalence of erosive disease (57.1% vs 83.3%, p=0.36), longer disease duration (10.2 vs 19.5 years, p=0.01), higher RAPID-3 scores (9.16 vs 12.98, p=0.18), use of multiple DMARDs (22.7% vs 75%, p=0.04) and anti-TNF usage (13.6% vs 50%, p=0.06). There was no difference in frequency of diabetes, hypertension, depression or anti-depressant usage between groups.

Conclusion: Our study suggests the prevalence of CI in RA patients is significantly higher than the general population and may benefit from a one-time screening. The prevalence of CI was also correlated with disease duration and more aggressive disease, suggesting RA is an independent risk factor. While this is the first study to identify CI in older adults with RA, further studies would be warranted to assess the use of validated instruments and potential interventions, if CI is found.

TABLE 1. Main study results			
	No CI	**CI**	**P-values**
	22	8	
Age, yrs (mean)	65-80 (71.7)	69-81 (74.3)	0.15
Ethnicity (%) Caucasian African American	_ 18 (81.8) 4 (18.2)	_ 7 (87.5) 1 (12.5)	1.00
Gender: n (%) Male Female	_ 7 (31.9) 15 (68.1)	_ 2 (25.0) 6 (75.0)	0.39
Diagnosis (years)	10.2 (2-20)	19.5 (1-43)	0.01
Seropositive (%)	15/16 (93.7)	4/5 (80)	0.42
Erosive disease (%)	13/22 (57.1)	6/7 (83.3)	0.36
RA Medications (%)	Statistically significant Multiple agents – 5 (22.7) Not significant Anti-TNF – 3 (13.6) Biologics - 6 Prednisone – 1 Methotrexate – 14 Sulfasalazine – 2 leflunomide – 3 Hydroxychloroquine – 3 NSAID (no DMARD) – 1 tofacitinib – 1 None – 2	Statistically significant Multiple agents – 6 (75) Not significant Anti-TNF – 4 (50) Biologics - 5 Prednisone – 1 Methotrexate – 7 Sulfasalazine – 1 leflunomide – 1 Hydroxychloroquine – 2 NSAID (no DMARD) – 0 tofacitinib – 0 None -0	_ 0.04 _ 0.06 0.10 _ 0.37
MD-HAQ	1.51 (0-5.7)	2.92 (0.3-7.7)	0.10
RAPID-3	9.16 (0-23.5)	12.98 (0.3-23.5)	0.18
PHQ8 median	6 (0-16)	4 (0-20)	0.92
CNS insult history	No history – 22/22	No history 8/8	
Lives with partner or spouse	11/22	4/7	1.00
Diabetes Mellitus (%)	5 (22.7)	0 (0)	0.29
Hypertension (%)	17 (77.2)	3 (37.5)	0.07
SSRI/SNRI use (%)	4 (18.1)	1 (12.5)	1.00

CI: Cognitive Impairment; MD-HAQ: Multidimensional Health Assessment Questionnaire, 0-10; RAPID-3: 0-30 (remission <3, low disease activity (DA) 3.1-6, moderate DA 6.1-12, high DA >12); PHQ8: Patient Health Questionnaire, 0-24 (>10 consistent with major depression)

TABLE 2. RMC and Mini-Cog results			
	No CI	**CI**	**P-value**
RMC	Medications pass – 15/22 Laboratory pass – 4/22	Medications pass – 2/8 Laboratory pass – 0/8	0.04 0.26
Mini-Cog	Word recall (1/3) – 3 (2/3) – 5 (3/3) – 10 Passed CDT - 18/18	Word recall (0/3) – 2 (1/3) – 3 (2/3) – 3 Passed CDT – 0/8	

CDT: Clock Draw Test

Disclosure: B. Smith, None; **K. S. O'Rourke**, None.

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Abstract Number: 1518

Relationship Between Estimated Sodium and Potassium Intake with Blood Pressure and Inflammatory Markers in Patients with Rheumatoid Arthritis

Cecilia P. Chung[1], Michelle J. Ormseth[2], Annette M. Oeser[3], Joseph F. Solus[4], Chimalum Okafor[5], Jens Titze[5], Yahua Zhang[5] and C. Michael Stein[6], [1]Medicine, Div of Rheumatology & Immunology, Vanderbilt University, Nashville, TN, [2]Department of Medicine, Division of Rheumatology, Vanderbilt University, Nashville, TN, [3]Vanderbilt University, Nashville, TN, [4]Clinical Pharmacology, Vanderbilt University, Nashville, TN, [5]Medicine, Vanderbilt University, Nashville, TN, [6]Div of Clinical Pharmacology, Vanderbilt University, Nashville, TN

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Background/Purpose: Hypertension is highly prevalent in patients with rheumatoid arthritis (RA). High sodium and low potassium intake are both modifiable determinants of blood pressure in the general population and can be estimated by measuring urinary sodium and potassium excretion. Moreover, a high sodium:potassium ratio is associated with increased risk of high blood pressure. However, little is known about the relationship between sodium and potassium intake and blood pressure in patients with RA. Thus, we examined the hypothesis that sodium and potassium excretion is related to blood pressure and markers of inflammation in patients with RA.

Methods: We studied 166 patients with RA and 92 control subjects frequency-matched for age, sex, and race. First morning urine samples were collected and the concentrations of urine sodium and potassium were measured by flame photometry and 24 hour sodium and potassium excretion were estimated with the Kawasaki formula, a validated method that incorporates age, sex, height, weight, and urine creatinine. Blood pressure was the average of two resting measurements. In patients with RA, sedimentation rate and concentrations of vascular cell adhesion molecule-1, C-reactive protein, interleukin-6 and tumor necrosis factor were measured. Fisher's exact and Wilcoxon's tests were used to compare categorical and continuous variables, respectively. The associations between systolic (SBP), diastolic blood pressures (DBP), and inflammatory markers with estimated 24 hour urinary sodium, potassium, and sodium:potassium intake ratio were tested using Spearman correlations. For the blood pressure analyses, linear regressions were modeled to adjust for age, sex, and race.

Results: Patients with RA and control subjects had a similar mean age (54.2±11.9 vs. 53.2±11.6, p=0.43), were predominantly female (69% vs. 63%, p=0.41) and Caucasian (89% vs. 85%, p=0.44). Patients with RA had higher rates of hypertension (54% vs. 39%, p = 0.03). The estimated 24 hour sodium [median (interquartile range) of 5.1 (3.9-6.6) and 4.9 (4.0-6.5) g/day, respectively, p=0.90] and potassium [2.5 (2.1-3.2) and 2.7 (2.2-3.8) g/day, p=0.08] intake were similar in patients with RA and control subjects. The urinary sodium:potassium ratio was higher in patients with RA than in controls [2.0 (1.6-2.4) and 1.7 (1.5-2.1), p=0.02] but was not associated with blood pressure in either group. Lower potassium (g/day) intake was associated with DBP in patients with RA [β coefficient (95% CI) =-1.79**,** p=0.04], but there was no significant association between the estimated sodium or potassium intake or their ratio with markers of inflammation (all p>0.05).

Conclusion: Patients with RA had significantly lower estimated sodium:potassium intake ratio than control subjects. Higher 24 hour potassium intake was significantly associated with lower DBP in patients with RA. Further studies are needed to evaluate the impact of diets with low sodium and high potassium content on blood pressure in patients with RA.

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Abstract Number: 1519

Pleuropulmonary Manifestations in Rheumatoid Arthritis Patients

Suzan Attar[1] and Omar Amoudi[2], [1]Internal Medicine, MBBCH. FRCPC. ABIM, Jeddah, Saudi Arabia, [2]Internal Medicine, FRCPC, Jeddah, Saudi Arabia

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Background/Purpose: Pulmonary involvement in rheumatoid arthritis (RA) patients is associated with high morbidity and mortality. Nevertheless, limited data are available regarding such lung complications in the Middle East, especially in the Kingdome of Saudi Arabia. The objective of the current study were to determine the prevalence of pleuropulmonary manifestations and to identify the risk factors predicting lung involvement.

Methods: This was a retrospective study involving 419 RA patients diagnosed at a tertiary center over a 12.5-year period. RA was diagnosed on the 2010 American College of Rheumatology (ACR) criteria. The frequency of pulmonary manifestations were recorded based on combined results from the chest X-rays, pulmonary function tests, and high resolution computed tomography (HRCT) scan on the chest.

Results: The overall frequency of lung involvement in RA was 25.8%. Pneumonia and bronchiectasis were the most common abnormalities (36% and 35% respectively). HRCT scan was more sensitive in detecting of pleuropulmonary abnormalities. . The presence of comorbid illness (OR=3.19, 95% CI: 2.02–5.1), male gender (OR=2.4, 95% CI: 1.3–4.24), and the presence of extra-articular manifestations (OR=2.35, 95% CI: 0.4–4.01) were significantly predicting lung involvement .

Conclusion: Pneumonia and bronchiactasis were the most common abnormalities seen in RA patients in Saudi Arabia. This finding were comparable with other studies.. The presence of comorbidity , male gender and extra-articular manifestation were statistically associated with lung involvement .

Table 1: Demographic and clinical characteristics of 419 RA patients

Variable	RA patients with pulmonary (n=108)	RA patients without pulmonary (n=311)	*P*-value
Age, years ± SD	52.97 ± 15	43.21 ± 15.43	**0.001***†
Gender, n (%)			
Male	23 (21.3)	32 (10.3)	**0.004***†
Female	85 (78.7)	279 (89.7)	
Disease duration, years ± SD	4.67 ± 6.1	3.1 ± 3.8	**0.002**†
ExRA, n (%)	29 (27)	42 (13.5)	**0.001**‡*
DAS28, mean ± SD	3.74 ± 1.27	3.89 ± 1.41	0.323†
Comorbid illness, n (%)	53 (49)	72 (23)	**0.001**‡*
Death, n (%)	16 (15)	8 (2.6)	**0.001***†
Smoking, n (%)			0.9*
Active	12	30	
Non-smoker	90	263	
Ex-smoker	11	14	
Medication, n (%)			
Methotrexate	75	180	0.86‡
Leflunomide	19	36	0.63†
Sulfasalazine	27	26	**0.001**‡
Biologics	33	58	0.27*
ESR, mean ± SD	45.4 ± 26.3	33.4 ± 21.8	**0.001***†
High, n (%)	86 (80)	220 (71)	**0.049**‡
CRP, mean ± SD	33.2 ± 53	16.9 ± 31	**0.001**‡†
High, n (%)	86 (80)	233 (75)	0.36*
RF, mean ± SD	287 ± 921	107 ± 435	**0.007**‡†
Positive, n (%)	63 (59)	136 (44)	**0.01***†
Anti-CCP, mean ± SD	205 ± 249	273 ± 314	**0.007**‡†
Positive, n (%)	85 (79)	227 (73)	0.25*

Legend: RA, rheumatoid arthritis; ExRA, extra-articular manifestations of RA; SD, standard deviation; DAS28, Disease Activity Score in 28 Joints; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; RF, rheumatoid factor; CCP, cyclic citrullinated peptide. *Signifiant positive association: $P<0.05$. Test of significance via †t-test or *chi-square test.

Table 2: Final clinical diagnoses in RA patients with lung involvement (n=108) based on clinical, chest X-ray, HRCT, and PFT findings*

Final Clinical Diagnosis	Patients (n=108)	Pulmonary involvement (% of 100)
Pneumonia	39	36
Bronchiectasis	38	35
Lung fibrosis	25	23
Pleural disease	16	14.8
Tuberculosis	13	12
MTX-induced lung disease	9	8.2
Rheumatoid Nodule	9	8.2
Collapse	8	7.4
BOOP	5	4.6
Pulmonary embolism	4	3.7
Small airway disease	3	2.7
Vasculitis	2	1.8
DAH	1	0.9
Caplan's syndrome	0	0

Legend: HRCT, high-resolution computed tomography; PFT, pulmonary function tests; RA, rheumatoid arthritis; MTX, methotrexate, BOOP, bronchiolitis obliterans organizing pneumonia; DAH, diffuse alveolar hemorrhage. *Some patients present multiple features

Table 3: Risk factors associated with pulmonary manifestation in 108 RA patients

Predictor	RA patients with pulmonary n (%)	X^2	*P*-value	OR	95% CI
Clinical:					
Sex, male	23 (21.3)	8.5	**0.004***	**2.4**	(1.3-4.24)
ExRA	29 (16.9)	10.1	**0.001***	**2.35**	(1.4-4.01)
Comorbidities	53 (49)	25.73	**0.001***	**3.19**	(2.02-5.1)
Biochemical:					
ESR-high	86 (80)	3.22	**0.049***	**1.61**	(0.95-2.74)
CRP-high	86 (80)	0.98	0.36	1.31	(0.77-2.23)
RF$^+$	63 (59)	6.8	**0.01***	**1.8**	(1.16-2.81)
Anti-CCP$^+$	85 (79)	1.36	0.25	1.36	(0.8-2.3)

Legend: RA, rheumatoid arthritis; X^2, chi-square; OR, odds ratio; CI, confidence interval; ExRA, extra-articular manifestations of RA; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; RF, rheumatoid factor; CCP, cyclic citrullinated peptide.
*Significant positive association: $P<0.05$.

Disclosure: **S. Attar**, None; **O. Amoudi**, None.

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Abstract Number: 1520

Safety, Clinical and Immunologic Effectiveness of the Live Zoster Vaccine Administered to Patients Receiving Anti-TNF Biologics

Jeffrey R. Curtis[1,2], Anita Turner[3], Corretta Thomas[4], Stacey Cofield[4], Randall Parks[5], Jennifer H. Ku[6], Ilhem Messaoudi- Powers[7], Keith Wanzeck[1] and Kevin L. Winthrop[8], [1]University of Alabama at Birmingham, Birmingham, AL, [2]Rheumatology & Immunology, University of Alabama-Birmingham, Birmingham, AL, [3]Clinical Immunology and Rheumatology, University of Alabama at Birmingham, Birmingham, AL, [4]School of Public Health, University of Alabama at Birmingham, Birmingham, AL, [5]Rheumatology, University of Alabama at Birmingham, Birmingham, AL, [6]Casey Eye Institute, Oregon Health & Science Univ, Portland, OR, [7]Oregon Health and Sciences University, Portland, OR, [8]Oregon Health & Science University, Portland, OR
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Background/Purpose:

The live herpes zoster vaccine (ZV) has been shown to be safe and effective in large randomized controlled trials of older adults. It is currently contraindicated in participants receiving immunomodulatory therapies such as biologic agents due to theoretical concerns regarding safety.

Methods:

VERVE is a 2-site, pilot study (n=125 participants) preparatory to a large NIH-funded pragmatic randomized controlled trial (RCT) of 1,000 participants

receiving anti-TNF therapy. Participants must be age >= 50 years, receiving any FDA-approved anti-TNF therapy for rheumatoid arthritis (RA), psoriatic arthritis (PsA) or other spondyloarthritis. Participants were randomized to ZV or blinded placebo. The primary outcome was immunogenicity at 6 weeks; secondary outcomes included clinical safety, tolerability, and long-term clinical effectiveness. For the pilot study, participants must also not have received glucocorticoid therapy within the past month. **Results** of this ongoing trial have not yet been unblinded. Therefore only baseline characteristics at the time of this abstract were available, presented as mean(SD) or %, as applicable.

Results:

A total of 95 participants have been screened for VERVE as of June 2015. Of these, 19 have been randomized (20.0%); 3(3.2%) tested negative on screening varicella ELISA testing and were considered screen failures; 73 (76.8%) have been enrolled and are awaiting randomization. Characteristics of the 19 randomized participants included age 60(7) years, 68.4% women, 73.7% with RA, 15.8% PsA. The most commonly used concomitant DMARD therapies were methotrexate (85.7%) and hydroxychloroquine (7.1%). Concomitant biologics included adalimumab (47.1%), etanercept (23.5%), Infliximab (17.6%), and golimumab (11.8%). The majority of participants had moderate disease activity (42.1%), with mean CDAI of 13.7(10.6). Among the 19 randomized who received ZV or placebo, there were no clinically significant serious adverse events attributable to the vaccine in the 40(16) days of follow-up (5.7 weeks; range 2.3, 9.0).

Conclusion:

Preliminary results from VERVE have shown no immediate safety-related issues when given to patients with autoimmune diseases being actively treated with anti-TNF biologic agents. Ongoing results for the entirety of the pilot study are expected by Nov. 2015 to further characterize the immunogenicity and effectiveness of the vaccine in abti-TNF users.

Disclosure: J. R. Curtis, Roche/Genentech, UCB, Janssen, CORRONA, Amgen, Pfizer, BMS, Crescendo, AbbVie, 2,Roche/Genentech, UCB, Janssen, CORRONA, Amgen, Pfizer, BMS, Crescendo, AbbVie, 5; **A. Turner**, None; **C. Thomas**, None; **S. Cofield**, None; **R. Parks**, None; **J. H. Ku**, None; **I. Messaoudi- Powers**, None; **K. Wanzeck**, None; **K. L. Winthrop**, BMS, 2,AbbVie, BMS, UCB, Amgen, 5.

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Abstract Number: 1521

Screening for Urinary Tract Infection in Rheumatoid Arthritis Patients Treated with TNF-Inhibitors in the Daily Clinic

Renata Baronaite Hansen[1], Anne Brun Hesselvig[2], Rolf Magnus Arpi[2], Eva Kristin Jonassen[1], Gunhild Bukh[1] and Ole Rintek Madsen[1], [1]Department of Rheumatology/C, Department of Rheumatology/C, Copenhagen University Hospital Gentofte, Hellerup, Denmark, [2]Department of Clinical Microbiology, Department of Clinical Microbiology, Copenhagen University Hospital Herlev, Herlev, Denmark

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Background/Purpose: Patients with rheumatoid arthritis (RA) treated with biologic agents are at increased risk of infection. Therefore, screening for urinary tract infection (UTI) with urine dipsticks (UD) is often performed as part of monitoring in the daily clinic regardless of UTI symptoms. We examined the prevalence of bacteriuria detected by UD and urine culture (UC), and the value of UD compared to UC in TNFi-treated RA patients. Secondary aims were to assess the reproducibility of UD and the association between UTI symptoms and results of UD and UC.

Methods: Urine samples from 126 adult RA patients treated with TNFi for ³ 6 months were collected according to standard guidelines and tested twice by use of an automated UD test (Clinitek) (one patient had only one UD performed), followed by quantitative UC. Positive UD test was defined as presence of leucocyte esterase and/or nitrite. UC with more than 100,000 CFU/mL was considered positive. True and false positive and negative rates (TPR, FPR, TNR and FNR) and positive and negative predictive values (PPV and NPV) were calculated. Cross-tabulations and X^2-tests were used to analyze the results.

Results: Patient characteristics are shown in Table 1 and urine test results in Table 2 and 3. Only one patient (0.8%) had UTI symptoms (UD negative). 4.8% (n = 6) of the patients had a positive UC. None of these had UTI symptoms and only 50% (n = 3) were UD positive (dipstick 1, 2 or both). In the patients as a whole (n = 126), UD was positive in 23% of the cases but only 10.3% (PPV) of these had a positive UC. The NPV for UD was 96.9% versus 95.2% for UTI symptoms. Duplicate UD results agreed (positive or negative) in 97.6% of the cases indicating high reproducibility.

Conclusion: Less than 5% of RA patients treated with TNFi had a positive UC, none of these had UTI symptoms and UD detected only half of the cases. The PPV for UD was only 10%. The NPV for UD was high, reflecting the low prevalence of positive UC in the study population. The results question the value of general UTI screening with UD and/or UC in the daily clinic.

Table 1. Basic characteristics of 126 RA patients.

Male:female ratio	1:3
Age at diagnosis (yrs), mean/SD (range)	44/14.13 (11.1-76.8)
Time since diagnosis (yrs), mean/SD (range)	15.1/10.7 (1.4-43.9)
Length of treatment with TNFi (yrs), mean/SD (range)	4.5/3.4 (0.1-12.9)
Positive RF and/or anti-CCP, n /%	84/67 (unknown in 7)
Erosive disease, n /%	69/55
Concomitant DMARDs, n /%	102/81
DAS28-CRP, mean/SD (range)	2.64/0.97 (1.2-6.5)
HAQ-DI, mean/SD (range)	0.78/0.65 (0-2.88)

Table 2. Urine dipstick (UD) compared with urine culture (UC).

	UD pos	**UD neg**	***Totals***
UC pos	3	3	6
UC neg	26	94	120
Totals	29	97	126
PPV=10.3; NPV=96.9; TPR=50; TNR=78.3; FPR =21.6; FNR=50.0 [all in %]; X^2=2.6, p= 0.11			

Table 3. Urinary tract infection (UTI) symptoms compared

with urine culture (UC).

	+UTI symp.	**- UTI symp.**	***Totals***
UC pos	0	6	6
UC neg	1	119	120
Totals	1	125	126
PPV= 0; NPV=95.2; TPR=0; TNR=99.2; FPR=0.8; FNR=100 [all in %]; X^2 =0.05, p=0.82			

Disclosure: R. Baronaite Hansen, None; **A. Brun Hesselvig**, None; **R. M. Arpi**, None; **E. K. Jonassen**, None; **G. Bukh**, None; **O. Rintek Madsen**, None.

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Abstract Number: 1522

Correlation of Oxidized Low Density Lipoprotein Levels with Carotid Intima Media Thickness in Rheumatoid Arthritis Patients

GHAN SHYAM PANGTEY[1], SANJAY PARMAR[1], RITU SINGH[2] and RAMA ANAND[3], [1]DEPARTMENT OF MEDICINE, LADY HARDINGE MEDICAL COLLEGE, New Delhi, India, [2]BIOCHEMISTRY, LADY HARDINGE MEDICAL COLLEGE, New Delhi, India, [3]DEAPRTMENT OF RADIOLOGY, LADY HARDINGE MEDICAL COLLEGE, DELHI, India

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Background/Purpose:

Rheumatoid Arthritis (RA) patients are more prone to atherosclerosis. Oxidation of Low-density lipoprotein (LDL) is an important event in the development of atherosclerosis, especially of coronary and carotid arteries. We hypothesized that due to increased systemic inflammatory response in RA patients there will be higher subclinical/ clinical morphologic evidence of atherosclerosis in carotid arteries, leading to increased carotid intima media thickness (IMT). Our primary objective was to correlate serum Oxidized LDL level with Carotid IMT in RA patients; secondary objective was to correlate oxidized LDL

with disease activity by DAS 28.

Methods:

This descriptive observational case control study recruited 30 RA patients (1987 ACR criteria) without any comorbidities (diabetes mellitus, hypothyroidism, morbid obesity, dyslipidemia, chronic kidney disease, chronic liver disease, or known atherosclerotic disease) and 30 age and sex matched healthy controls; active smokers and non consenting participants were excluded. After history, examination and routine laboratory investigations, oxidized LDL levels were obtained by ELISA method. Carotid IMT was measured by Doppler ultrasonography (Philips HDI5000): Common carotid IMT (CCIMT), carotid bulb IMT (CBIMT), total carotid IMT (TCIMT), and internal carotid IMT (ICIMT) were measured by trainned radiologist. Means were compared using unpaired "t" test; correlation was measured using Pearson correlation method. SPSS version 19 was used for statistical analysis, and $p<0.05$ was considered significant.

Results:

Mean age of cases and controls was 43.13±13.32 and 42.87±15.03 years respectively; 86.67% (26/30) of all cases were females. DAS 28 score was found to be high among 27 cases in a range of severe disease activity (>5.1), while in 3 cases it was found that disease activity was in moderate range (3.2-5.1). Values of CCIMT, CBIMT, and TCIMT were significantly higher in RA patients ($p<0.05$); ICIMT values was not significantly different from controls. Mean oxidized LDL level was significantly higher in RA patients (9.03±6.12 microgram/ml vs 3.01±2.67 microgram/ml; $P<0.0001$). Pearson correlation test failed to show any correlation between oxidized LDL values and CCIMT, CBIMT, TCIMT, and ICIMT values in both cases and controls (Table 1). Oxidized LDL level was not significantly associated with disease activity (DAS 28) in RA patients.

Table 1:Correlation of oxidized LDL and CIMT in cases

	Ox-LDL	CCIMT	CBIMT	ICIMT	TCIMT
OX-LDLPearson correlation	1	-.115	-.277	-.139	-.203
Sig(2tailed)		.544	.138	.465	.281
CCIMT Pearson correlation	-.115	1	.113	.485	.881
Sig(2tailed)	.544		.551	.007	.000
CBIMT Pearson correlation	-.277	.113	1	.484	.516
Sig(2tailed)	.138	.551		.007	.004
ICIMT Pearson correlation	-.139	.485	.484	1	.775
Sig(2tailed)	.465	.007	.007		.000
TCIMT Pearson correlation	-.203	.881	.516	.775	1
Sig(2tailed)	.281	.000	.004	.000	

Conclusion:

On comparision with the general population, oxidized LDL values as well as carotid IMT values were markedly higher in RA patients, but the correlation was statistically non signifcant. Oxidized LDL values were also not statistically correlated with disease activity (DAS 28). Oxidized LDL can be used as an inflammatory marker in RA patients. This is the first study in RA patient from India and there is need for larger similar studies after these encouraging results.

Disclosure: G. S. PANGTEY, None; **S. PARMAR**, None; **R. SINGH**, None; **R. ANAND**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/correlation-of-oxidized-low-density-lipoprotein-levels-with-carotid-intima-media-thickness-in-rheumatoid-arthritis-patients

Abstract Number: 1523

Ischemia Modified Albumin Levels in Rheumatoid Arthritis

Ali Ugur Uslu[1], **Adem Kucuk**[2], Sevket Balta[3], Sevket Arslan[4], Levent Tekin[5], Sami Kucuksen[6], Aysun Toker[7] and Mehmet Kayrak[8], [1]Internal Medicine, Eskisehir Military Hospital, Eskisehir, Turkey, [2]Necmettin Erbakan U Meram T F, Necmettin Erbakan U Meram T F, Konya, Turkey, [3]Cardiology, Eskisehir Military Hospital, Eskisehir, Turkey, [4]Allergy and Clinical Immunology, Necmettin Erbakan University, Konya, Turkey, [5]Physical Medicine and Rehabilitation, Beyhekim State Hospital, Konya, Turkey, [6]MD, kONYA, Turkey, [7]Biochemistry, Necmettin Erbakan University, Konya, Turkey, [8]Necmettin Erbakan University, Division of Cardiology, Konya, Turkey

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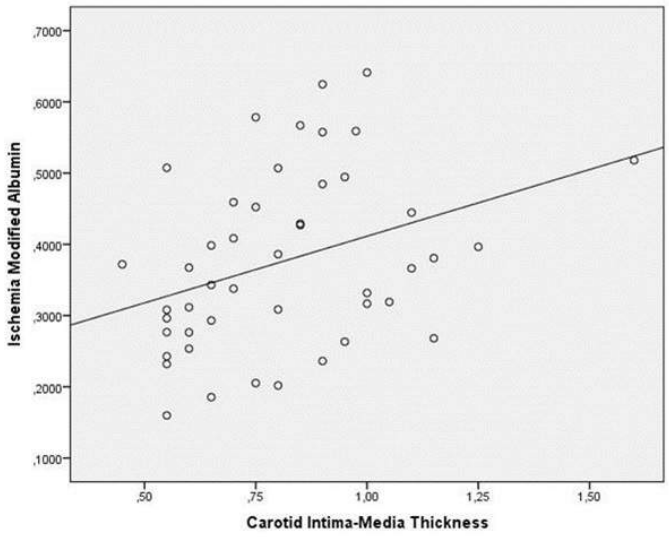
Background/Purpose: Cardiovascular diseases, among which atherosclerotic heart disease, are known to be one of the most important mortality and morbidity causes in patients with Rheumatoid Arthritis (RA). Ischemia modified albumin (IMA) is a potential marker that can be used to assess atherosclerosis-related myocardial ischemia. Another frequently used marker for the assessment of atherosclerotic lesions is the carotid intima media thickness (CIMT). To evaluate role that IMA has on atherosclerosis development and its clinical usability in patients with RA, by assessing the values of IMA and CIMT.

Methods: Our prospective study was conducted between June 2012 and March 2013 at the rheumatology department of Meram Medical School. 52 RA patients, diagnosed according to the criteria of the 1987 American College of Rheumatology, and an age- and sex-matched control group of 46 healthy subjects were included in this study.

Results: No significant difference was detected between the groups with respect to age, sex and body mass index. Baseline laboratory characteristics of patients and controls. In the patient's group the IMA and CIMT values were found to be 0.37±0.12 ABSU and 0.80±0.22 mm respectively while in the control group were 0.31±0.11 ABSU and 0.51±0.18 mm respectively. The IMA and CIMT values were significantly higher in the patient's group ($p=0.022$ and $p<0.0001$ respectively). A positive correlation was found between IMA, CIMT and DAS-28 ($p=0.016$ and $p=0.002$ respectively) (Figure 1).

Conclusion: Since the values of IMA were higher in the patient's group compared to control and because of its correlation with CIMT, we suggest the usage of IMA as an early marker of atherosclerosis in RA patients.

Figure 1. Correlation between IMA and CIMT



Disclosure: A. U. Uslu, None; **A. Kucuk**, None; **S. Balta**, None; **S. Arslan**, None; **L. Tekin**, None; **S. Kucuksen**, None; **A. Toker**, None; **M. Kayrak**, None.

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Abstract Number: 1524

Evaluation of Changes in Cardiovascular Risk Factors Among Patients with RA Prescribed Biologic Dmards

E Alemao[1], T Simon[2], KK Gandhi[1], H Kawabata[2] and Jeffrey R. Curtis[3], [1]Bristol-Myers Squibb, Princeton, NJ, [2]Bristol-Myers Squibb, Hopewell, NJ, [3]University of Alabama at Birmingham, Birmingham, AL

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Background/Purpose: Studies have reported that TNF-inhibitors (TNF-Is) are associated with a reduced risk of cardiovascular (CV) events,[1] but data on their effects on traditional CV risk factors in clinical practice are limited. The objective of this analysis was to evaluate mean changes from baseline (CFB) in CV risk factors of blood pressure (BP), lipids, hemoglobin A1c (A1c) and CRP among adult RA patients (pts) prescribed first bDMARDs. A secondary objective was to compare mean CFB in CV risk factors in pts prescribed abatacept (ABA) vs TNF-Is and other non-TNF-Is (excluding ABA). **Methods:** A retrospective analysis was conducted using GE Centricity® data, a nationally representative electronic database of >17 million de-identified medical records. Inclusion criteria were: ≥1 RA diagnosis code (January 2000–February 2014), aged ≥18 yrs at diagnosis, received a prescription for a bDMARD (index bDMARD), no bDMARD prescription during baseline (12 months prior to index bDMARD), ≥1 CV risk factor measured during the baseline period and 1 during follow-up, and receiving index bDMARD during 12-month follow-up. Lab values closest to the 12-month interval in a +/- 6-month window were used to calculate CFB. CFB in CV risk factors were described using mean, variance and SEs. Regression analyses were conducted for CFB in CV risk factors as dependent variables, and baseline covariates of demographics, co-morbidities, treatments to manage CV risk factors and RA treatments as independent variables. Sensitivity analyses were conducted to assess changes in CV risk factors among pts who had treatment changes for BP, lipids and diabetes. **Results:** 17,960 RA pts were included in the analysis. Mean (SD) age: 53.8 (13.5) yrs; 75.6% female; 6.5% had a CV event during baseline. Mean (SE; p-value) CFB were: systolic BP –0.50 mm Hg (0.165; 0.002); diastolic BP –0.28 mm Hg (0.103; 0.006); low-density lipoprotein (LDL) –2.42

mg/dL (0.81; 0.003); high-density lipoprotein (HDL) 0.23 mg/dL (0.27; 0.402); total cholesterol (TC) –1.87 mg/dL (0.83; 0.024); triglycerides –0.23 mg/dL (1.36; 0.864); A1c 0.01% (0.04; 0.767); CRP –0.61 mg/dl (0.099; <0.0001). Most (69%) pts did not have treatment for CV risk factors at baseline or follow-up; within this untreated subgroup, the CFB in CV risk factors were only statistically significant for HDL and CRP. Beta coefficients of the regression analysis for CFB in CV risk factors between pts prescribed ABA vs TNF-Is and ABA vs non-TNF-Is are shown in the Table; none were significant at an alpha level of 0.05.

Conclusion:

Though we observed that CV risk factors of BP, lipids (LDL-cholesterol and TC) and CRP levels were significantly reduced in RA pts prescribed bDMARDs, these reductions (except CRP) are likely driven by treatment for CV risk factors. There were no differences in changes in CV risk factor levels between pts prescribed abatacept and those prescribed TNF-Is or other non-TNF-Is.

1. Solomon DH, et al. *Am J Med* 2013;**126**:730.e9-730.e17.

Table. Comparison of CV risk factor changes between ABA vs TNF-Is and ABA vs non-TNF-Is (excluding ABA)

	*Non-TNF-Is (excluding ABA) vs ABA	p-value comparing non-TNF-Is vs ABA	*TNF-Is vs ABA	p-value comparing TNF-Is vs ABA
Change in diastolic BP (mm Hg)	(n=858) 0.2313	0.7663	(n=11,217) 0.0068	0.9890
Change in systolic BP (mm Hg)	(n=859) –0.8450	0.4968	(n=11,224) –0.7392	0.3507
LDL-cholesterol (mg/dL)	(n=135) –4.9075	0.3579	(n=1382) –1.9861	0.5859
HDL-cholesterol (mg/dL)	(n=162) 0.5214	0.7770	(n=1706) –1.1205	0.3495
Total cholesterol (mg/dL)	(n=151) –0.8647	0.8806	(n=1696) –2.2164	0.5535
Triglyceride (mg/dL)	(n=161) –6.2453	0.4969	(n=1714) 1.6441	0.7855
A1c (%)	(n=83) –0.3282	0.1997	(n=771) –0.1519	0.3590
CRP	(n=246) –0.2444	0.7572	(n=3585) –0.3862	0.4403

*Regression coefficients, ABA is the reference group. A1c=hemoglobin A1c; ABA=abatacept; BP=blood pressure; CV=cardiovascular; HDL=high-density lipoprotein; LDL=low-density lipoprotein.

Disclosure: E. Alemao, Bristol-Myers Squibb, 3,Bristol-Myers Squibb, 1; **T. Simon**, Bristol-Myers Squibb, 3; **K. Gandhi**, Bristol-Myers Squibb, 1,Bristol-Myers Squibb, 3; **H. Kawabata**, Bristol-Myers Squibb, 1,Bristol-Myers Squibb, 3; **J. R. Curtis**, Roche/Genentech, UCB, Janssen, CORRONA, Amgen, Pfizer, BMS, Crescendo, AbbVie, 2,Roche/Genentech, UCB, Janssen, CORRONA, Amgen, Pfizer, BMS, Crescendo, AbbVie, 5.

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Abstract Number: 1525

Detection of Previous Tuberculosis Infections in Japanese Rheumatoid Arthritis Patients: Comparison of Two Interferon-G Releasing Assays and the Impact of CD4-Positive Lymphocytes

Shogo Banno[1], Shiho Iwagaitsu[2], Taio Naniwa[3], Hironobu Nobata[4], Hirokazu Imai[4], Shinya Tamechika[2], Shinji Maeda[2] and Akio Niimi[2], [1]Rheumatology and Nephrology, Aichi Medical University School of Medicine, Aichi-prefecture, Japan, [2]Allergy, Respiratory Medicine and Immunology, Nagoya City University Graduate School of Medical Science, Nagoya City, Japan, [3]Allergy, Respiratory Medicine and Immunology, Nagoya City University Graduate School of Medical Science, Nagoya city, Japan, [4]Rheumatology and Nephrology, Aichi Medical University School of Medicine, Nagakute City, Japan
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Session Time: 9:00AM-11:00AM

Background/Purpose: We aimed to evaluate the performance of QFT-GIT and T-SPOT.TB assays to predict the risk of latent tuberculosis infection (LTBI) in Japanese rheumatoid arthritis (RA) patients, measured simultaneously total and CD4-positive lymphocytes. When total or CD4-positive lymphocytes are suspected to be low due to aggressive treatment of RA, it remains unclear whether interferon-γ release assays (IGRAs) can be used reliably without increasing indeterminate results, and are affected by peripheral lymphocyte and CD4-positive cell counts

Methods: Because of no gold standard for LTBI, we compared with or without previous pulmonary tuberculosis infection as an alternative diagnosis using chest CT. We defined a history of TB infection (past TB infection group) as chest CT findings with old pulmonary TB infection. As a comparable control (non-TB infection group), we included a group of patients without prior contact with active TB, or old TB infection on chest CT. Sixty-eight patients treated with MTX and/or biologics were divided into two groups: 33 with and 35 without a past TB infection. MTX dose was 9.2 mg in those with a past TB infection and 11.0 mg in those without. Biologics was received 41% in the past TB and 57% in non-TB infection group. Mean total and CD4-positive lymphocyte in the past TB infection group decreased to 1,091/μL and 491/μL, respectively.

Results: The sensitivity and specificity of QFT-GIT for discriminating past TB infection were 21.2% and 100%, respectively. With a lower cutoff of 0.1 IU/mL (gray zone), the sensitivity and specificity of QFT-GIT were 30.3% and 96.9%, respectively. This gray zone of QFT-GIT requires further investigation to estimate the risk of TB. Positive T-SPOT.TB (SFC ≥6) were found in 21.9% in the past TB infection group, and 15.6% had SFC ≥8. With the positive cutoff (SCF ≥6) of T-SPOT.TB, the sensitivity and specificity were 21.9% and 100%. In the past TB infection group, 5 patients had positive QFT-GIT (≥0.35 IU/mL) and T-SPOT.TB (≥6 spots). The results for 4 patients with past TB were negative with T-SPOT.TB, but of these 4 patients, 3 in positive and 1 in the gray zone for QFT-GIT. The overall agreement of two IGRAs was high. Results were indeterminate in 4 (5.9%) of 68 patients, due to 3 patients decrease positive control of QFT-GIT and 1 increased negative control of T-SPOT.TB. QFT-GIT yielded results in 43% with low lymphocyte (<1000/μL) and 47% with low CD4-positive lymphocyte (<500/μL). In both IGRAs, PHA mitogen responses were not different between those treated with or without biologics. The positive rates of QFT-GIT and T-SPOT.TB decreased upon stimulation with TB antigens according to total and CD4-positive lymphocyte counts: this effect was more notable in QFT-GIT than T-SPOT.TB. When total lymphocytes (<1,000/μL) and CD4-positive lymphocytes (<500/μL) were low, the positive rates of QFT-GIT and T-SPOT.TB were low. Even where total and CD4-positive lymphocyte counts were low, the positive rate of QFT-GIT was increased when the gray zone range was included.

Conclusion: Two IGRAs had high specificities, but may falsely identify past TB infection owing to low sensitivities. Despite low total and CD4-positive lymphocyte counts, IGRAs could be utilized without high indeterminate rates.

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Abstract Number: 1526

Employment and Quality of Life Among Patients with Rheumatoid Arhtritis in Four Latin-American Countries

Ricardo Xavier[1,2], Fernando Chalem[3], Javier Duhau[4], Jorge Morales[5,6], Cesar Ramos-Remus[7], Jose Fernando Molina[8], Eugenia Carnide[9] and Annette Perez-Gilbe[10], [1]Hospital de Clínicas de Porto Alegre, Porto Alegre, Brazil, [2]RUA ATILIO BILIBIO, 120 CASA 9, Universidade Federal Do Rio Grande Do Sul, Porto Alegre, Brazil, [3]Fundación Instituto de Reumatología Fernando Chalem, Bogota, Colombia, [4]Centro de Investigaciones en Enfermedades Reumáticas (CIER), Buenos Aires, Argentina, [5]Imagenology X ray, Hospital de Especialidades Centro Medico La Raza IMSS, Mexico, Mexico, [6]Rheumatology, Hospital Aranda de la Parra, Leon, Mexico, [7]Unidad de Investigacion en Enf. Cronico-Degenerativas, Guadalajara, Mexico, [8]Reumalab, Medellín, Colombia, [9]Abbvie Inc, São Paulo, Brazil, [10]Abbvie Inc, San Juan
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Background/Purpose: Rheumatoid Arthritis impacts negatively on quality of life and work productivity. There are virtually no data on the employment status and burden of disease in RA patients from Latin-America (LA). To assess the burden of RA on work productivity and health related quality of life in LA patients.

Methods: Consecutive RA patients attending 20 rheumatology outpatient clinics distributed in Argentina, Brazil, Colombia and Mexico were included and completed the following standard questionnaires: Workplace Activity Limitations Scale (WALS), Work Productivity and Activity Impairment (WPAI), Work Limitations Questionnaire (WLQ), EuroQol (EQ-5D) and Short Form 36 Health Survey (SF-36). Sociodemographic data were also collected.

Results: The study included 309 patients, 90% female, mean age of 43 years (SD 9) and disease duration of 8 years (SD 8). At least 40% of patients reported some difficulty in all workplace activities (WALS), especially "crouching, bending, kneeling or working in awkward positions" (83%) and "lifting, carrying or moving objects" (80%). WPAI showed employment rate of 58%, and mean work time lost in a week of 4.3hs (SD 15.8). For WLQ, physical job demands were affected in 42% of patients followed by time demands in 34%. Mean self-evaluated health status using EQ-5D visual analogue scale (where 0=worst and 100=best health status) was 69 (SD 20), ranging from 63 (SD 22) in Brazil to 75 (SD 21) in Mexico. EQ-5D dimension mostly impaired was pain and discomfort with only 20.3% reporting have no problems in that dimension, while 72% reported have no problems with self-care. SF-36 physical and mental component scores for the total sample were 39 (SD 9.8) and 45(SD 11.4), respectively. Lower values were observed for the physical component in Brazil (34) and the mental component in Argentina and Colombia (44). The table below summarizes these results for each country analyzed.

Conclusion: RA affects both work performance and quality of life in a substantial proportion of patients. Although similar trends were shown among countries, Brazilian patients reported to be more affected in most of evaluated aspects.

Table 1

Results	Argentina(N=78)	Brazil (N=77)	Colombia (N=76)	Mexico (N=78)	Total (N=290)
WPAI Employed %	73	40	61	54	58
WLQ Physical demands %	38	50	36	44	42
WLQ Time demands %	25	44	32	33	34
EQ-VAS mean (SD)	72 (17)	63 (22)	67 (20)	75 (21)	69 (20)
EQ-5D Pain and discomfort dimension %	NP 28 SP 67 EP 5	NP 10 SP 83 EP 7	NP 19 SP 70 EP 11	NP 24 SP 71 EP 5	NP 20 SP 73 EP 7
EQ-5D Self-care dimension %	NP 79 SP 21 EP -	NP 62 SP 38 EP -	NP 72 SP 27 EP 1	NP 74 SP 26 EP -	NP 72 SP 28 EP -
SF-36 PCS mean (SD)	42 (9.7)	34 (9.6)	39 (9.1)	41 (10.7)	39 (9.8)
SF-36 MCS mean (SD)	44 (11.9)	47 (12.5)	44 (9.8)	47 (11.3)	45 (11.4)

SD: Standard deviation; NP: No problem; SP: Some problems; EP: Extreme problems
PCS: Physical component score; MCS: Mental component score

Disclosure: R. Xavier, AstraZeneca, 5,Hospira, 5,Janssen Pharmaceutica Product, L.P., 5,Pfizer Inc, 5,AbbVie, 8,AstraZeneca, 8,Janssen Pharmaceutica Product, L.P., 8,Pfizer Inc, 8,Roche Pharmaceuticals, 8; **F. Chalem**, Abbvie, 5; **J. Duhau**, Abbvie, 2; **J. Morales**, Abbvie, Amgen, Lilly, Merck, Novartis, Pfizer, Roche, Sanofi and Servier, 5; **C. Ramos-Remus**, None; **J. F. Molina**, Abbvie, 2; **E. Carnide**, Abbvie, 3; **A. Perez-Gilbe**, Abbvie, 3.

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Abstract Number: 1527

Serum Inflammation Identifies Increased Risk of Frailty in Rheumatoid Arthritis

James S. Andrews[1], Elizabeth R. Wahl[2], Gabriela Schmajuk[3], Edward H. Yelin[4] and Patricia P. Katz[5], [1]Rheumatology, University of California San Francisco, San Francisco, CA, [2]Medicine/Rheumatology, San Francisco Veterans Affairs Medical Center, San Francisco, CA, [3]San Francisco VA Medical Center, University of California, San Francisco, San Francisco, CA, [4]University of California, San Francisco, San Francisco, CA, [5]Rheumatology, UCSF, SF, CA

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Background/Purpose: Frailty has been defined as "an excess vulnerability to stressors, with reduced ability to maintain or regain homeostasis after a destabilizing event" [1]. Frailty is closely related to body composition and physical functioning, and is associated with increased risk of poor health outcomes including death. Serum inflammation is associated with differences in body composition and physical functioning in the general population and individuals with chronic disease. The ability of serum markers of inflammation to identify increased frailty among individuals with rheumatoid arthritis (RA) is unknown. This study tests whether serum erythrocyte sedimentation rate (ESR) and C-Reactive Protein (CRP) are associated with increased risk of frailty among men and women with RA.

Methods: Participants were individuals in a longitudinal cohort with physician-documented RA. All measures were collected during an in-person research visit. ESR and high sensitivity CRP were assessed from blood samples using standard clinical assays. Individuals with 3 or more of the following physical deficits were classified as frail[1]: 1) body mass index $\leq$ 18.5, 2) low grip strength (adjusted for sex and BMI, measured by handheld dynamometer), 3) severe fatigue (measured by the Fatigue Severity Inventory), 4) slow 4-meter walking speed (adjusted for sex and height), 5) low physical activity (measured by the International Physical Activity Questionnaire). Individuals with 1 or 2 deficits were classified as "pre-frail", and those with no deficits as "robust." [1] Multinomial logistic regression analyses controlling for age, sex, smoking status, RA disease duration, prednisone use, tumor necrosis factor inhibitor use, appendicular lean mass, and pain modeled the effects of ESR and CRP on severity of frailty.

Results: Of the 141 participants, 60% were female; mean age was 58 (±11) years, duration of RA was 19 (±11) years, ESR was 19 (±19) mm/h, and hsCRP was 5 (± 8) mg/L. Sixteen participants (11%) were frail, 86 (61%) pre-frail, 22 (16%) robust, and 17 (12%) were missing grip strength data. In adjusted models, higher ESR was associated with significantly increased risk of frailty (Table 1). Similar trends were observed between CRP and risk of frailty, but did not reach statistical significance in adjusted models.

Conclusion: Frailty and pre-frailty were common in our cohort of individuals with RA, with a greater prevalence than that of geriatric populations. Serum levels of ESR were associated with approximately twice the risk of being frail or pre-frail compared to being robust. CRP demonstrated similar effects on

risk of frailty, though trends did not reach statistical significance. These findings underscore the high burden of frailty among individuals with RA, and they may suggest a clinical role for serum ESR and CRP in identifying individuals with RA at greatest risk of frailty.

[1]Fried J Am Geriatr Soc 2001;56:M146

Table 1: Multinomial Logistic Regression Relative Risk Ratios (95% CIs) for the Effect of Serum Sedimentation Rate and C-Reactive Protein on Risk of Frailty Category among Individuals with RA

	ESR		CRP	
	Unadjusted	Adjusted[#]	Unadjusted	Adjusted[#]
Frail	1.69	2.56*	1.49	1.96+
	(0.94, 3.07)	(1.16, 5.65)	(0.88, 2.52)	(0.96, 4.03)
Pre-Frail	1.43	1.92*	1.26	1.66+
	(0.95, 2.15)	(1.05, 3.48)	(0.85, 1.86)	(0.94, 2.94)
Robust	Reference	Reference	Reference	Reference

[#]Model is adjusted for age, sex, smoking status, disease duration, prednisone use, tumor necrosis factor inhibitor use, appendicular lean mass, and pain due to rheumatoid arthritis.

Frail= 3 or more physical deficits, Pre-frail= 1-2 physical deficits, Robust= 0 physical deficits (Fried LP et al., J Gerontol A Biol Sci Med Sci, 2001; 56:M146)

*p<0.05, +p<0.1

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Abstract Number: 1528

Predictors of Employment, Work Productivity Loss, Activity Impairment, and Regaining Employment in Latinos with Rheumatoid Arthritis in the United States

George A. Karpouzas[1], Taylor Draper[2], Elizabeth Hernandez[3], Rosalinda Moran[3] and Sarah Ormseth[3], [1]Harbor UCLA Med Ctr, Torrance, CA, [2]Cousins Center for Psychoneuroimmunology, University of California, Los Angeles, Los Angeles, CA, [3]Rheumatology, Harbor-UCLA Medical Center, Torrance, CA

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Background/Purpose: Patients with Rheumatoid arthritis (RA) experience declining functional ability, quality of life, employment and work productivity. Such outcomes have been described in homogeneous, mostly Caucasian cohorts. Our objective was to characterize baseline determinants of employment, absenteeism, presenteeism, work productivity loss (WPL), and activity impairment (AI) in Latinos with RA in the US. We further explored longitudinal predictors of both maintenance of employment, as well as of regaining employment over time.

Methods: We assessed 303 Latinos with RA and regular follow up in a single center between 2011 and 2014. Evaluator outcomes- including global disease activity (EGA), swollen and tender joints, sedimentation rate (ESR)- and patient reported outcomes such as global activity (PGA), disability (Health Assessment Questionnaire, HAQ-DI), pain, fatigue, and depression (Patient Health Questionnaire, PHQ9) were recorded at baseline and follow-up visits, at a median of 2 years. A Work Productivity and Activity Impairment (WPAI) questionnaire was completed at both times. Linear and logistic regression models evaluated predictors of outcomes of interest at baseline. Cox regression models assessed survival of employment, regaining employment, and their determinants longitudinally.

Results: At baseline, 77 (25%) patients were employed; they were younger, had lower ESR, prednisone use and numbers of concurrent synthetic disease modifying agents-DMARDs (all <0.05). They also had lower PGA, disability, pain, fatigue, and activity impairment (all <0.05). Higher HAQ-DI, DMARD numbers, and pain negatively associated with employment (table 1). Fatigue and HAQ-DI strongly predicted presenteeism and WPL in those employed, while pain and PGA additionally predicted AI in all. Those remaining employed (68%) had lower depression scores; employment survival was further predicted by decrease in tender joints, fatigue, and EGA. Those gaining employment (11%) were significantly younger, with lower baseline HAQ-DI and greater changes in HAQ-DI (all, p<0.05).

Conclusion: Few Latinos with RA are gainfully employed. HAQ-DI is a durable predictor of baseline employment, work productivity loss and activity impairment; its change- in those unemployed- further determines who regains employment. Patient-reported outcomes such as fatigue, pain, and PGA

significantly and differentially contribute to several aspects of work productivity and activity impairment.

Table 1: Independent, multivariate contributors to Employment, Absenteeism, Presenteeism, Work Productivity Loss and Activity Impairment in Latinos with RA in the US

	Employment		Absenteeism		Presenteeism		Work Productivity Loss		Activity Impairment	
Univariate Factors	OR (95% CI)	p	B (95% CI)	p	B (95% CI)	p	B (95% CI)	p	B (95% CI)	p
Age	0.98 (0.95-1.01)	0.2	-0.04 (-0.07,-0.008)	*0.02*	-	-	-	-	-	-
SJC	1.13 (1.05-1.21)	*0.001*	-	-	0.11 (-1.46-1.67)	0.89	-0.26 (-2.02-1.50)	0.77	-1.08 (-1.05-0.89)	0.87
n-DMARD	0.67 (0.49-0.92)	*0.01*	-	-	-	-	-	-	-	-
Fibromyalgia	0.50 (0.16-1.57)	0.24	1.52 (0.21-2.83)	*0.02*	-	-	5.31 (-16.36-27.0)	0.63	2.98 (-3.44-9.40)	0.36
HAQ-DI	0.49 (0.29-0.83)	*0.008*	-0.22 (-0.75-0.32)	0.42	9.48 (1.47-17.52)	*0.02*	9.61 (0.85-18.38)	*0.03*	11.93 (8.39-15.47)	*0.000*
Pain	0.55 (0.31-0.98)	*0.04*	-0.56 (-1.15-0.03)	0.06	-7.22 (-15.76-1.32)	0.1	-6.21 (-15.3-2.9)	0.18	6.20 (2.0-10.4)	*0.004*
PGDA	1.07 (0.89-1.30)	0.46	0.19 (-0.007-0.38)	0.06	2.02 (-0.61-4.65)	0.13	2.07 (-0.93-5.06)	0.17	1.84 (0.46-3.21)	*0.009*
Fatigue	1.99 (0.85-1.16)	0.94	0.10 (-0.09-0.28)	0.3	4.34 (1.78-6.91)	*0.001*	4.94 (2.16-7.71)	*0.001*	1.08 (-0.05-2.21)	0.06

Disclosure: G. A. Karpouzas, None; **T. Draper**, None; **E. Hernandez**, None; **R. Moran**, None; **S. Ormseth**, None.

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Abstract Number: 1529

Trabecular Bone Score in Early Rheumatoid Arthritis

Eulalia Armengol[1], Helena Borrell Paños[1], Joan Miquel Nolla[1], Javier Narváez[2] and Carmen Gomez Vaquero[1], [1]Department of Rheumatology, Hospital Universitario de Bellvitge, Barcelona, Spain, [2]Rheumatology, Hospital Universitario de Bellvitge, Barcelona, Spain
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Background/Purpose:

Rheumatoid Arthritis (RA) is associated with low bone mass and increased risk of fragility fractures that are related to patient characteristics, treatments and disease activity.

Trabecular Bone Score (TBS) is a new gray-level texture measurement derived from lumbar spine DXA images, independent of bone mineral density (BMD).

In early RA patients, to quantify TBS and its determinants.

Methods:

From an early RA unit, we selected all the patients who had been prospectively followed from the disease onset according to a predefined protocol, based on a tight control strategy, and had at least a bone densitometry available to calculate TBS. Four patients were excluded because of a body mass index (BMI) greater than 35 kg/m^2, since TBS is not reliable in those cases. The study variables were: 1) Demographics: age, sex, body mass index (BMI); 2) RA history: duration, RF, ACPA; 3) Disease activity: DAS28 and CRP; 4) Disability: HAQ; 5) RA treatment; 6) Spine and proximal femur BMD; and 7) TBS.

Results:

We included 170 patients (116 female) with a mean age of 54 ± 14 years and a BMI of 27 ± 4.5 kg/m^2. Sixty-seven percent of the patients had RF+ and 60% had ACPA + (mean title: 330 ± 524 U/L). At diagnosis, mean DAS28 was 5.77 ± 1.31; CRP was 26 ± 39.3 mg/L; and HAQ, 1.500 ± 0.654.

Mean BMD in lumbar spine was 0.967 ± 0.162 g/cm^2; in femoral neck, 0.779 ± 0.218 g/cm^2; and in total femur was 0.952 ± 0.143 g/cm^2. Forty-nine percent of the patients had a normal BMD, 34% had osteopenia and 17% had osteoporosis, according to WHO diagnostic classification. Mean TBS was 1.345 ± 0.123. Fifty-two percent of the patients had normal bone microarchitecture, 35% had partially degraded microarchitecture and 13% had degraded microarchitecture. Ten-year probability of having a major osteoporotic fracture, calculated by combining TBS and WHO categories according to data of Hans D *et al** and expressed according to the system of the Canadian Association of Radiologists and Osteoporosis Canada (CAROC), was low (< 10%) in 78% of the patients, medium (10-20%) in 16% and high (>20%) in 6%.

In the multivariate analysis, TBS correlated with age (r: -0.50), BMI (r: -0.50), CRP (r: -0.15) and BMD at lumbar spine (r: 0.34). These variables accounted for 51% of the variability of TBS (Regression line: TBS: 1.583 - (0.003 x age) - (0.013 x BMI) + (0.273 x LS BMD)). TBS did not correlate with other study variables.

Conclusion:

Almost half of early RA patients have a deterioration of bone microarchitecture assessed by TBS. In these patients, TBS is very dependent on age, BMI and BMD at lumbar spine. Other disease variables are not related to TBS.

*Hans D. J Bone Miner Res 2011; 26: 2762-9.

Disclosure: E. Armengol, None; **H. Borrell Paños**, None; **J. M. Nolla**, None; **J. Narváez**, None; **C. Gomez Vaquero**, None.

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Abstract Number: 1530

Neutrophil Function and Survival Unaffected in Healthy Subjects Following Single Administration of Tocilizumab

Laurence Lok[1], Jatinder Juss[1], Neda Farahi[1], Chrystalla Loutsios[1], Chandra Solanki[2], Adrien Michael Peters[3], Sophie Dimonaco[4], Francis Donaldson[4], Benjamin Porter-Brown[4] and Edwin Chilvers[1], [1]Department of Medicine, University of Cambridge School of Clinical Medicine, Cambridge, United Kingdom, [2]Department of Nuclear Medicine, Cambridge University Hospitals, Cambridge, United Kingdom, [3]Division of Clinical and Laboratory Investigation, Brighton and Sussex Medical School, Brighton, United Kingdom, [4]Roche Products Ltd., Welwyn Garden City, United Kingdom
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Background/Purpose: Decreases in circulating neutrophil counts have been observed in adults with rheumatoid arthritis (RA) and children with systemic or polyarticular juvenile idiopathic arthritis treated with the interleukin-6 (IL-6) receptor-α antagonist tocilizumab (TCZ). However, no temporal relationship with risk for infection has been demonstrated to date, and the mechanism of neutrophil count decrease associated with TCZ is unclear. Previous research in RA patients showed that TCZ had no effect on neutrophil function or survival when assessed 4 and 12 weeks after TCZ initiation[1]; however, the effects of TCZ on neutrophil function and survival at the neutrophil nadir (day 4 [D4] after TCZ administration) have not been assessed.

Methods: Healthy male subjects age 18-65 years received a single intravenous dose (blinded to subjects only) of TCZ 8 mg/kg or placebo (PBO) on day 0 (D0). Neutrophil function and survival were assessed ex vivo in isolated polymorphonuclear leukocytes (PMNs) on D0 predose and on D4. Neutrophil apoptosis, phagocytosis, production of reactive oxygen species (ROS), morphology, and surface markers (adhesion molecules CD11b, CD62L, and CD162; CD16) were assessed.

Results: TCZ was administered to 12 subjects and PBO to 6 subjects. Neutrophil count decreased with TCZ but not with PBO. No subjects experienced a drop in their neutrophil count $<1\times10^9$/L. TCZ-treated subjects were divided into 2 groups: PMN high (subjects with ≤50% reduction in D4 neutrophil count relative to baseline, n=5) and PMN low (subjects with >50% reduction in D4 neutrophil count relative to baseline, n=7). Mean neutrophil counts at D4 as percentages of D0 levels were 102% in the PBO group, 72% in the PMN-high group, and 45% in the PMN-low group. The functional capacity of neutrophils was unaffected by the administration of TCZ, as demonstrated by intact respiratory burst activity and intact phagocytosis of heat-killed *S. pneumoniae* at D4 (Table). Survival of neutrophils after 20 hours of culture was unaffected in the TCZ-treated subjects, with apoptosis rates showing no differences between PBO and TCZ groups either under control conditions or in the presence of the prosurvival factors granulocyte macrophage–colony-stimulating factor and tumor necrosis factor-α (Table). Surface markers and neutrophil shape change were also similar among the PBO, PMN-low, and PMN-high groups at D4 in both control and stimulated PMNs (Table). No serious adverse events were reported.

Table. Function and Survival of Neutrophils 4 Days After TCZ Administration

	PBO (n = 6)		PMN High (n = 5)		PMN Low (n = 7)	
	Day 0	Day 4	Day 0	Day 4	Day 0	Day 4
ROS generation, RLU absolute						
Unprimed PMN	47,271 (17,823)	30,561 (7,279)	35,636 (7,621)	30,083 (5,757)	26,067 (5,600)	23,301 (4,250)
TNF-α-primed PMN	129,736 (21,453)	111,300 (18,035)	145,072 (19,468)	99,815 (20,268)	90,139 (20,491)	72,328 (11,499)
ROS generation, RLU fold change						
Unprimed PMN	1 (0)	1 (0)	1 (0)	1 (0)	1 (0)	1 (0)
TNF-α-primed PMN	3.7 (0.6)	4.2 (0.8)	4.6 (1.0)	3.3 (0.5)	3.4 (0.5)	3.1 (0.3)
Phagocytosis						
eFluor670 median fluorescence	2,164 (350)	2,849 (565)	1,548 (106)	2,526 (293)	2,463 (393)	3,273 (422)
% phagocytosis	63.7 (4.1)	68.0 (3.6)	59.9 (2.0)	67.3 (2.3)	63.5 (3.4)	72.8 (2.7)
Apoptosis						
Morphology (% apoptotic cells)						
Untreated	68.3 (3.5)	62.3 (2.9)	66.9 (2.4)	65.1 (2.7)	60.6 (2.7)	54.7 (3.0)
GM-CSF	24.5 (4.4)	23.6 (3.6)	26.8 (4.4)	19.4 (1.4)	27.8 (5.4)	16.0 (1.9)
TNF-α	46.5 (4.0)	44.3 (1.2)	40.3 (2.6)	43.1 (5.3)	42.4 (4.2)	38.0 (1.6)
Flow cytometry (% annexin V+ cells)						
Untreated	74.0 (3.4)	68.7 (2.6)	73.2 (2.5)	65.2 (4.1)	70.4 (1.5)	63.3 (4.0)
GM-CSF	38.1 (4.6)	33.9 (3.8)	38.2 (5.9)	25.6 (3.0)	35.2 (4.5)	26.6 (3.5)
TNF-α	53.8 (4.1)	51.2 (1.3)	47.7 (2.2)	50.4 (3.2)	47.5 (2.9)	50.4 (4.1)
Neutrophil surface markers						
CD11b-BV421						
0 min	12,490 (1,729)	12,633 (2,062)	16,358 (2,642)	15,751 (2,043)	13,996 (1,494)	17,764 (1,910)
30 min fMLP	31,542 (3,452)	39,629 (2,699)	43,286 (5,204)	44,481 (5,049)	34,280 (2,747)	41,339 (2,723)
CD16-FITC						
0 min	15,587 (719)	15,822 (741)	16,867 (2,520)	16,872 (1,874)	14,122 (1,508)	15,901 (1,476)
30 min fMLP	15,022 (1,800)	17,145 (884)	18,144 (3,521)	18,229 (2,613)	13,522 (2,531)	14,707 (2,205)
CD62L-APC						
0 min	791 (162)	563 (37)	772 (129)	650 (201)	514 (99)	767 (65)
30 min fMLP	−5 (6)	6 (3)	10 (15)	5 (9)	4 (7)	9 (12)
CD162-PE						
0 min	3,379 (633)	3,393 (454)	3,988 (861)	3,253 (895)	4,109 (583)	3,849 (314)
30 min fMLP	1,581 (320)	1,571 (219)	2,027 (519)	1,568 (472)	1,966 (275)	1,733 (154)
Shape change						
Flow cytometry (forward scatter)						
0 min	76,428 (2,936)	78,041 (3,057)	77,004 (4,258)	76,645 (5,619)	76,059 (2,059)	80,849 (2,700)
30 min fMLP	142,111 (10,028)	140,222 (8,414)	133,800 (11,462)	132,133 (10,219)	129,667 (5,188)	131,191 (5,034)
Flow cytometry (% FSC-high cells)						
0 min	7.5 (1.0)	10.9 (1.7)	11.7 (4.1)	11.5 (2.1)	12.3 (1.7)	14.2 (2.6)
30 min fMLP	74.0 (5.0)	74.6 (4.5)	73.3 (5.6)	72.8 (4.9)	70.7 (3.4)	69.4 (3.1)
Morphology (% shape change)						
0 min	8.1 (0.7)	9.4 (1.3)	11.5 (3.4)	8.6 (0.4)	9.5 (1.4)	9.6 (1.2)
30 min fMLP	66.3 (4.0)	68.5 (2.4)	64.8 (3.0)	69.2 (3.4)	67.0 (3.7)	66.1 (2.3)

FSC, forward scatter; FITC, fluorescein isothiocyanate; fMLP, *N*-formyl-methionyl-leucyl-phenylalanine; GM-CSF, granulocyte macrophage–colony-stimulating factor; HRP, horseradish peroxidase; PI, propidium iodide; PMN, polymorphonuclear leukocytes; RLU, relative light unit; ROS, reactive oxygen species; TNF-α, tumor necrosis factor-α. Data are means (SE). ROS generation was measured by peak fMLP-stimulated HRP-luminol chemiluminescence. Bacterial phagocytosis was measured by fluorescence of eFluor670-labelled, heat-killed *S. pneumoniae* by flow cytometry. Apoptosis was measured by flow cytometry using annexin V-FITC/PI staining and by assessment of microscopic morphology. Neutrophil surface markers were measured by flow cytometry in control and fMLP-stimulated PMNs. Shape change in control and fMLP-stimulated PMNs was measured by flow cytometry, as median FSC and as percentage shape change, and by microscopic morphology.

Conclusion: IL-6 blockade with TCZ resulted in reduced counts of circulating neutrophils. However, the functional capacity and survival of neutrophils at the D4 nadir were unaffected by TCZ treatment; this may support why, to date, no temporal associations between decreased circulating neutrophil counts and increased risk for infection have been observed.

Reference

1. Wright HL et al. *Rheumatology*. 2014; 53:1321-31.

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The Changing Face of Septic Arthritis Complicating Rheumatoid Arthritis in the Era of

Biotherapies. Retrospective Single-Center Study over 35 Years

Jean-Jacques Dubost[1], Bruno Pereira[2], Anne Tournadre[3], Zuzana Tatar[1], Marion Couderc[1] and Martin Soubrier[1], [1]Rheumatology department CHU Clermont-Ferrand, Clermont-Ferrand, France, [2]Biostatistics unit (DRCI), CHU Clermont-Ferrand, Clermont-Ferrand, France, [3]Rheumatology, UNH-UMR 1019 INRA University of Auvergne and Rheumatology department CHU Clermont-Ferrand, Clermont-Ferrand, France
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Background/Purpose: Rheumatoid arthritis (RA) is a risk factor for septic arthritis (SA), and anti-TNF therapy doubles the risk of SA. The purpose of this study was to see whether the frequency and features of SA complicating RA have changed over the last 35 years.

Methods: This retrospective single-center study included the full register of all patients hospitalized at the rheumatology department of Clermont-Ferrand—CHU between 1979 and 2013 for septic arthritis bacteriologically documented by synovial fluid and/or blood culture samples. The periods 1979–2002 (period before biotherapies) and 2003–2013 (last decade in the era of biotherapies) were compared.

Results: Between 1979 and 2013, 64/514 (12.5%) SA presented with a RA—21/153 (13.7%) in the 2003–2013 period and 43/361 (11.9%) in the 1979–2002 period. Over the past decade, median age of SA–RA patients increased (61 *vs* 68 years; $p<0.02$) and predominant gender became males (52% *vs* 40%). The features of the RA remained unchanged: history (18 years (8–29) *vs* 16 (8–25)), rheumatoid factor (95% *vs* 87%), and corticosteroids (91% *vs* 81%) at the same mean dose (10 mg/d). 71% in the period before biotherapies and 63% in the last decade received a DMARD. Over the last decade 24% (*vs* 0; $p<0.003$) of patients received a biologic DMARD: etanercept (n=2), adalimumab (n=1), rituximab (n=1), tocilizumab (n=1). Proportion of polyarticular infection had decreased (9.5% *vs* 37%; $p<0.02$), down to the same level as SA-non-RA cases (8%). Proportion of *S. aureus* infections had stabilized (62% *vs* 74%) in SA-RA patients but was higher than SA-non-RA (47% and 53%). MRSA infections became more frequent in SA-RA (31% *vs* 6%; $p<0.05$) in contrast to SA-non-RA cases (8% *vs* 16%; ns). Gram-negative bacilli infections have tended to become more frequent (19% *vs* 5%; $p=0.08$). Blood cultures less often tested positive (29% *vs* 47%; ns). Mortality rates has fallen slightly (5% *vs* 9%; ns), in contrast to SA-non-RA cases (7% *vs* 6%; ns).

Conclusion: This study brings reassuring findings—in the era of biotherapies, the frequency of septic arthritis complicating rheumatoid arthritis has stabilized, and the most severe septic polyarticular forms are on the decline.

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Abstract Number: 1532

Occurrence of Valvular Heart Disease in Rheumatoid Arthritis: A Population Based Study

Tamanna Khullar[1], John P. Bois[1], Cynthia S. Crowson[2], Megan L. Krause[3] and Rekha Mankad[1], [1]Cardiovascular Diseases, Mayo Clinic, Rochester, MN, [2]Health Sciences Research, Mayo Clinic, Rochester, MN, [3]Rheumatology, Mayo Clinic, Rochester, MN
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Background/Purpose: Patients with rheumatoid arthritis (RA) are known to have an increased risk of cardiovascular disease, particularly atherosclerosis and heart failure. However, little is known about the occurrence of valvular heart disease (VHD) in RA. The purpose of our study was to investigate the occurrence of VHD among patients with RA compared to the general population.

Methods: A population based inception cohort of residents of a geographically well-defined area with adult onset RA who met 1987 ACR criteria in 1998-2007 and a comparison cohort of age and sex matched non-RA subjects from the same population base were assembled and followed until death, migration or the present. Echocardiograms were reviewed to determine the occurrence of VHD as defined by the 2014 ACC/AHA guidelines. Cumulative incidence of VHD adjusted for the competing risk of death was estimated.

Results: The study included 379 patients with RA and 379 non-RA subjects (mean age 55.1 [SD 15.2] years, 69% women in both cohorts). Among these cohort of patients, 117 patients with RA and 89 non-RA subjects had at least 1 echocardiogram performed after incidence/index date. The prevalence of VHD was similar in the RA and non-RA cohorts at RA incidence/index date(2% versus 3%; $P=0.82$). The cumulative incidence (± SE) of any valve disease during follow up was higher among patients with RA compared to non-RA subjects(26% ± 2.5% versus 16.9% ± 2.1% at 10 years; $P=0.013$). The

difference persisted after adjustment for age, sex, and calendar year of RA incidence/index date (hazard ratio[HR]:1.49; 95%CI: 1.11,1.99). Among all valve diseases, the cumulative incidence of any grade of mitral regurgitation (MR) (24.6% ± 2.4% versus 15.6% ± 2.0% at 10 years; p=0.015) and tricuspid regurgitation (TR) (23.1% ± 2.4% versus 16.3% ± 2.1%; p=0.045) were significantly higher in patients with RA compared to non-RA subjects. The cumulative incidence of at least moderate MR (4.3% ± 1.2% versus 3.0% ± 0.9%; p=0.95) and at least moderate TR (6.6% ± 1.5% versus 3.7% ± 1.1%; p=0.23) were not significantly different between RA and non-RA. Risk factors for valve disease occurrence in patients with RA included age (HR 2.08 per 10 year increase; 95% CI: 1.79, 2.42), atrial fibrillation (HR 2.67: 95%CI: 1.63, 4.37), stroke (HR 2.45; 95%CI: 1.41, 4.26), coronary heart disease (HR: 2.25; 95%CI: 1.45, 3.49). Joint erosions were associated with reduced risk of valvular disease (HR 0.67, 95% CI 0.45, 0.99). Rheumatoid nodules, joint surgery, elevated ESR in first year of diagnosis, DMARDs, and biologics were not associated with risk of valve disease. Risk factors for at least moderate valve disease included atrial fibrillation and stroke as well as severe extra-articular manifestations (HR 4.22; 95%CI: 1.64, 10.86).

Conclusion: Although VHD has not been considered to be a major cardiac manifestation of RA, our current study has revealed a higher than anticipated incidence of asymptomatic valvular involvement. MR and TR incidence is more common than any other valve diseases.

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Abstract Number: 1533

Age Related Disability in Daily Life Should be Considered in Older Than Sixty-Five-Year-Old Rheumatoid Arthritis Patient

Ichiro Yoshii[1] and Tatsumi Chijiwa[2], [1]Department of Orthopaedic Surgery, Yoshii Hospital, Shimanto, Japan, [2]Rheumatology, Kochi Memorial Hospital, Kochi, Japan

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Background/Purpose:

In treating rheumatoid arthritis (RA), patient's activity in daily life (ADL) is extremely important factor, because RA is chronic inflammatory disease that leads discomfort or disability in ADL in natural. In RA treatment, patient is usually interviewed and evaluated. Health assessment questionnaire (HAQ) is common index for ADL. In general, HAQ is thought to be influenced by disease activity and structural damage, thus it consists of activity related HAQ (ACT-HAQ) and damage related HAQ (DAM-HAQ). It is widely accepted in rheumatologist. However, HAQ often results in unexpected. It is more frequently seen in elderly patient, that even joint deformity is minimum and disease activity is well controlled. We have been thinking that HAQ is not only with ACT-HAQ and DAM-HAQ, but other factors have affected on HAQ. Aging is candidate for HAQ influencing factor. We have evaluated effect of aging on HAQ.

Methods:

579 RA patients had been treated more than 1 year in our clinic. In these, 257 patients who have been treated consecutively for more than three years had been recruited for analysis in this study. These patients have been consulted in one to three months interval, and have been evaluated their disease activity as twenty-eight joints disease activity score with C-reactive protein (DAS28-CRP), daily activity as HAQ disability index (HAQ-DI), and radiographic evaluation with Sharp/van der Heijde score (SHS) from X-ray pictures of bilateral hands and feet have been taken at first, and mostly one year period. HAQ-DI, DAS28-CRP, SHS, and age at first (@BL), and average value of these indices in follow up (@F) were calculated for every patient, and relationship between HAQ-DI@F, and each of other indices had been evaluated statistically with single regression analysis. Then relationship between HAQ-DI@F and every other index had evaluated with multiple regression analysis.

In additional, patients were classified according to Age@F, whether less than sixty-five (G-Y) or not (G-O). HAQ-DI@F, DAS28-CRP@F, and SHS@F of the two groups were compared statistically with ANOVA. Relationship between age and HAQ@F were statistically evaluated with linear regression analysis for each age group.

Results:

All indices but DAS28-CRP@BL demonstrated significant positive relationship with HAQ-DI@F ($p < 0.0001$) in single regression analysis, and for multiple regression analysis, every index has demonstrated significant positive relationship between HAQ-DI@F.

In ANOVA study, G-O demonstrated significantly higher HAQ-DI in both @BL and @F ($p < 0.0001$), although no significant difference have demonstrated for other indices. Age@F demonstrated significant positive correlation with HAQ@F in G-O ($p < 0.0001$), although in G-Y there have shown no significant correlation.

Conclusion:

These results suggested that HAQ-DI is not consisted only with ACT-HAQ and DAM-HAQ. HAQ@BL has extremely strong influence on HAQ-DI

thereafter, and at the same time, age is also very important factor that determines HAQ-DI. For the reason, elderly patients tend to diminish HAQ-DI reduction by disease activity control. In treating RA, we need to consider patient's age to make optimal results for treatment.

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Abstract Number: 1534

Temporal Trends and Outcomes of Acute Myocardial Infarction in Rheumatoid Arthritis Hospitalizations

Narender Annapureddy[1], Achint Patel[2], Rabi Yacoub[3], Krishna Pakanati[4], Shiv Agarwal[5], Priya Simoes[6], Shaan Patel[3], Sunil Kamat[7], Alexandre Benjo[8] and Girish Nadkarni[9], [1]Rheumatology and Immunology, Vanderbilt University, Nashville, TN, [2]Public Health, Icahn School of Medicine at Mount Sinai, New York, NY, [3]Icahn School of Medicine at Mount Sinai, New York, NY, [4]Gateway Medical Center, Clarksville, TN, [5]Cardiology, University of Arkansas Medical Sciences, Little Rock, AR, [6]Internal Medicine, St.Lukes Roosevelt Hospital Center at Mount Sinai, New York, NY, [7]Critical Care, Kokilaben Dhirubhai Ambani Hospital and Medical Research Institute, Mumbai, India, [8]Ochsner Clinic Foundation, New Orleans, NY, [9]Nephrology, Icahn School of Medicine at Mount Sinai, New York, NY

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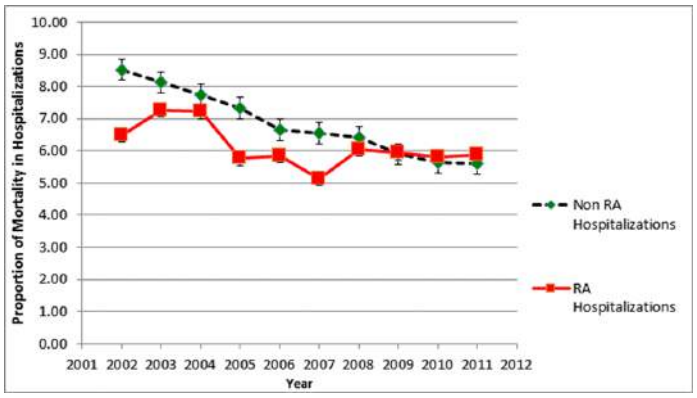
Background/Purpose: Rheumatoid arthritis (RA) is associated with increased risk of cardiac mortality. With better treatment modalities, some studies suggest that infarction (AMI) mortality in RA has decreased. We aimed to evaluate temporal trends of incidence and mortality of RA in AMI hospitalizations in a nationally representative sample.

Methods: We reviewed Nationwide Inpatient Sample (NIS) data over 10 year period from 2002-2011 for adult AMI hospitalizations as a primary diagnosis with RA as secondary diagnosis using validated ICD9-CM codes. We calculated unadjusted proportions of mortality yearly and used survey logistic regression to calculate adjusted odds ratios (aOR) for hospital mortality and adverse discharge and after stratifying for age (≤50 vs. >50).

Results: We identified a total of 6588743 AMI hospitalizations from 2002-2011 of which 77040 (1.16%) had a diagnosis for RA. The proportion of patients with RA in AMI hospitalizations increased from 0.96% in 2002 to 1.44% in 2011. RA hospitalizations were older (70.4 vs. 67.7 years; p<0.01); more female (62.7% vs. 40%; p<0.01); with a higher proportion of whites (82.3% vs. 77.7%; p<0.01) and a higher Charlson comorbidity index (2 vs. 1.5; p<0.01). The unadjusted mortality rates in RA hospitalizations yearly were similar to hospitalizations without RA. (Figure 1) After adjusting for age, gender, race, Charlson comorbidity index, hospital level characteristics, cardiac procedures, RA hospitalizations had lower odds-ratio for hospital mortality (aOR=0.76; 95% CI= 0.70-0.83; p<0.01) compared to non-RA hospitalizations. However, in hospitalizations ≤50 years, there was no significant difference in the adjusted odds of hospital mortality (aOR=0.68; 95% CI 0.38-1.21; p=0.19) or adverse discharge (adjusted aOR=1.03; 95% CI 0.84-1.28; p=0.73)

Conclusion: The odds of hospital mortality in RA hospitalizations with AMI are lower than non-RA hospitalizations. This is likely related to better disease recognition and risk modification in RA patients. However, the mortality in RA hospitalizations younger than 50 years was similar to non-RA hospitalizations, suggesting an unmet need for better disease and comorbidity management in younger RA patients.

Figure 1. Proportion of Mortality in AMI Hospitalizations Stratified by Rheumatoid Arthritis Status



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The Clinical Impact of Overweight in Rheumatoid Arthritis Patients: Comparison Between Korean and Other Countries within the Comora Study

Kichul Shin[1], Eun Young Ahn[2], Hyun Mi Kwon[2], In Ah Choi[3], Yeonsoo Baik[4] and Yeong Wook Song[2], [1]Division of Rheumatology, Department of Internal Medicine, Seoul Metropolitan Government-Seoul National University Boramae Medical Center, Seoul, South Korea, [2]Division of Rheumatology, Department of Internal Medicine, Seoul National University Hospital, Seoul, South Korea, [3]Division of Rheumatology, Department of internal medicine, Chungbook National University Hospital, Cheongju-si, South Korea, [4]Division of Rheumatology, Department of internal medicine, SMG-SNU Boramae Medical Center, Seoul, South Korea

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Background/Purpose: Obesity has recently been spotlighted as an important comorbidity in rheumatoid arthritis (RA); not only associated with disease severity but also its development. Despite that the long-term impact of obesity in RA should be studied in longitudinal studies, our aim was to investigate what clinical aspects of obese Korean RA patients would differ from those with normal body mass index (BMI) in a cross-sectional study.

Methods: COMORA is an international (17 countries), cross-sectional study investigating demographics, disease characteristics, and comorbidities (cardiovascular, infections, cancer, gastrointestinal, pulmonary, osteoporosis and psychiatric disorders) in RA patients. The Korean delegation consisting of 11 centers nationwide provided clinical data of total 1050 RA patients. We divided the RA patients into 2 groups (table); those with normal BMI (n= 834) versus (vs.) BMI equal to, or higher than 25 (abnormal BMI, n= 216).

Results: Demographic and medication data between normal vs. abnormal BMI were mostly comparable, but not for age (55.4 vs. 58.5, p= 0.0005) and education level (lower in the abnormal BMI group, p= 0.0072). Additional parameters were compared adjusting age, gender, disease duration, and education level. Disease activity at survey was similar between the 2 groups. Modified HAQ scores were significantly higher in patients with abnormal BMI (p= 0.028), and prevalence of hypertension, dyslipidemia were much higher in the abnormal BMI group, as expected. Additionally, data from the other 16 countries (COMORA-EK) was compared with Korean patients (COMORA-K). Interestingly, abnormal BMI patients in COMORA-EK showed higher disease activity (swollen, tender joint counts, DAS28-ESR, DAS28-CRP), which was not appreciated in COMORA-K.

Conclusion: These data demonstrate that overweight RA patients have worse functional status in general, yet abnormal BMI does not seem to affect disease activity in Korean patients to the degree observed in COMORA-EK.

Table. Selected clinical parameters from COMORA-K and -EK

Parameters	COMORA-K				COMORA-EK			
	Normal BMI (n= 834)	Abnormal BMI (n= 216)	p-value	p-value*	Normal BMI (n= 1710)	Abnormal BMI (n= 1810)	p-value	p-value*
Body mass index	21.4 ± 2.1	27.5 ± 2.4	< 0.001		22.0 ± 2.1	30.2 ± 4.7	< 0.001	
Age, years	55.4 ± 12.4	58.4 ± 11.1	0.0005		56.2 ± 14.3	56.4 ± 12.0	0.6018	
Gender (female %)	83	82	0.6026		82	80	0.0882	
Disease duration	7.0 ± 6.3	6.6 ± 6.2	0.4796		10.1 ± 9.2	9.6 ± 8.6	0.0811	
Seropositivity, %	88	86	0.7686		83	80	0.3733	
DAS28-ESR	3.51 ± 1.45	3.61 ± 1.41	0.3681	0.5496	3.61 ± 1.53	3.92 ± 1.52	< 0.001	**0.0019**
DAS28-CRP	2.72 ± 1.28	2.69 ± 1.20	0.8276	0.5807	3.31 ± 1.62	3.58 ± 1.65	< 0.001	**0.0299**
Modified HAQ	0.35 ± 0.50	0.46 ± 0.55	0.005	**0.0282**	0.49 ± 0.57	0.55 ± 0.57	0.0012	**0.0004**
EQ-5D-3L	0.76 ± 0.14	0.73 ± 0.16	0.0165	0.1073	0.75 ± 0.15	0.73 ± 0.15	< 0.001	**< 0.001**

Values are mean ± S.D.

BMI, body mass index; DAS, disease activity score; ESR, erythrocyte sedimentation rate; CRP, c-reactive protein; HAQ, health assessment questionnaire

*Adjusted by age, gender, disease duration, and education level

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Abstract Number: 1536

Sensorineural Hearing Impairment and Subclinical Atherosclerosis in Rheumatoid Arthritis Patients without Traditional Cardiovascular Risk Factors

Hector Macias Reyes[1], **Sergio Duran-Barragan**[2,3], Cynthia Cardenas Contreras[4], Cesar Chavez Martin[4], Eduardo Gomez[2], Rosa Navarro Hernandez[2], Jorge Aguilar Arreola[2,5], Paul Perez-Cruz[2,5], Carlos Yanowsky Gonzalez[2] and Monica Vazquez-Del Mercado[2,5], [1]1. Hospital Civil Fray Antonio Alcalde, Guadalajara, Mexico, [2]Centro Universitario de Ciencias de la Salud, Universidad de Guadalajara, Instituto de Investigación en Reumatología y del Sistema Musculoesquelético, Guadalajara, Mexico, [3]Clinica de Investigación en Reumatología y Obesidad, Guadalajara, Mexico, [4]Hospital Civil Fray Antonio Alcalde, Guadalajara, Mexico, [5]Servicio de Reumatología, División de Medicina Interna, Hospital Civil Dr. Juan I. Menchaca, Guadalajara, Mexico
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Background/Purpose: Rheumatoid arthritis (RA) is characterized by inflammation of the synovial membrane of the diarthrodial joints which include arthrodesis of the middle ear, (incudomalleolar and incudostapedial joints) causing conductive hearing impairment (CHI). Extra-articular involvement may also affect the auditory system targeting the inner ear causing sensorineural hearing impairment (SNHI). The majority of the risk factors for SNHI reported in the literature are related to the cardiovascular system, as the inner ear may be vulnerable to circulatory alterations affecting the labyrinthine artery; however the physiopathology of hearing impairment in RA remains unclear. We decided to evaluate, in a cohort of RA patients without known cardiovascular risk factors, the association of hearing impairment and subclinical atherosclerosis.

Methods: RA patients (according to the ACR classification criteria) with no known traditional cardiovascular risk factors were included. Routine clinical and laboratory assessments for RA patients were included. Pure tone air (125 – 8000 Hz) and bone conduction (250 – 6000 Hz) thresholds were obtained, tympanograms were classified according to Jerger and impedance audiometry was done. SNHI was defined if the average thresholds for at least one of low-, mid-, or high-frequency ranges were ≥25 decibels (dB) hearing level in one or both ears. Carotid Intima-Media Thickness (cIMT) was assessed. Two segments from the common carotid artery (CCA), one from the carotid bifurcation (BF) and two from the internal carotid artery (ICA) were evaluated. Patients were classified according to the cIMT with a cut-off point of 0.6mm.

Results: Forty-one RA patients were included into the study, 39 (95.1%) were female. Mean (SD) age and disease duration were 46.46 (10.20) and 7.05 (7.37) years respectively. Twelve patients (29.2%) had normal audition, 29 (70.8%) had hearing impairment; of them, 28 (68.3%) had SNHI [22 (53.6%) bilateral, 24 (58.5%) left and 26 (63.4%) right], three patients (7.3%) had right CHI and one (2.4%) had left CHI. No significant differences were found between disease activity, rheumatoid factor and anti-CCP among SNHL and normal hearing RA groups. Patients with SNHI had thicker levels of cIMT in the media segment of carotid common artery vs patient with normal hearing (right ear 0.21±0.29 vs 0.02±0.10 mm, $p = 0.007$; left ear 0.20±0.30 vs 0.06±0.18 mm, $p = 0.075$) (Table 1)

Table 1. Type of audition according to the cIMT

	Rigth ear			Left ear		
cIMT (right and left, respectively, mm)	Normal n = 15	SNHI n = 26	*p*	Normal n = 17	SNHI n = 24	*p*
Proximal CCA	0.43 ± 0.29	0.46 ± 0.29	0.740	0.41 ± 0.28	0.50 ± 0.32	0.370
Media CCA	0.02 ± 0.10	0.21 ± 0.29	**0.007**	0.06 ± 0.18	0.20 ± 0.30	0.075
Distal CCA	0.44 ± 0.42	0.61 ± 0.45	0.244	0.45 ± 0.31	0.57 ± 0.39	0.341
Bulb	0.48 ± 0.36	0.51 ± 0.34	0.784	0.54 ± 0.44	0.50 ± 0.41	0.754
Proximal ICA	0.44 ± 0.30	0.46 ± 0.28	0.791	0.49 ± 0.36	0.40 ± 0.30	0.420
Distal ICA	0.34 ± 0.30	0.40 ± 0.38	0.562	0.35 ± 0.34	0.39 ± 0.29	0.704

cIMT, carotid intima media thickness; SNHI, sensorineural hearing impairment; CCA, carotid common artery; variables are expressed as mean ± standard deviation. Statistical significance: $p \leq 0.05$

Conclusion: Thickening of the carotid Intima-Media was associated with SNHI in RA patients. Unknown cardiovascular risk factors may contribute to accelerated atherosclerosis and hearing impairment in RA patients. Further studies are needed to elucidate this association.

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Abstract Number: 1537

Effect of TNF-Alpha Blockade on Body Composition in Inflammatory Rheumatic Disease: Systematic Review with Meta-Analysis

sarah marouen[1], Thomas Barnetche[2], Bernard Combe[3], Jacques Morel[4] and Claire I. Daien[4], [1]Rhumatology Department, Lapeyronie Hospital and Montpellier University, Montpellier, France, [2]Rheumatology Department, Pellegrin University Hospital, BORDEAUX, France, [3]Rheumatology, Hopital Lapeyronie, Montpellier, France, [4]Department of rheumatology, Lapeyronie Hospital and Montpellier University, Montpellier, France
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Background/Purpose:

Patients with chronic inflammatory rheumatic disease have elevated circulating concentrations of TNF-alpha and other pro-inflammatory cytokines that can modify body composition. Metabolic changes are involved in the onset of cardiovascular disease events. We aimed to evaluate the body composition of patients with Rheumatoid Arthritis (RA) or Spondyloarthritis (SpA) and to assess the effect of TNF-alpha inhibitors (TNFi) on body composition, using systematic review with meta-analysis.

Methods:

PubMed, Cochrane Library, and congress abstracts databases were searched for articles published up to February 2015. Search terms were ("body fat distribution" OR "fat mass" OR "lean mass" OR "body mass component" OR "body composition" OR "body fat distribution") AND ("rheumatoid arthritis" OR "spondylarthritis" OR "psoriatic arthritis" OR "spondylitis" OR "ankylosing spondylitis"). We restricted the search to adult subjects and body composition using by Dual Energy X-Ray Absorptiometry (DEXA). TNFi effects on body composition were assessed at 6, 12 and 24 months in a systematic review. A meta-analysis comparing DEXA body composition in patients with RA or SpA versus healthy controls was performed using Revman program with an inverse variance model. Heterogeneity was evaluated with Cochran's Q-test and I^2value P-values less than 0.05 were considered as significant.

Results:

Among the 208 articles reviewed, 16 studies met the inclusion criteria. In RA patients, a significant increase in fat mass (+ 1.85 kg, p = 0.02, n= 328, I^2= 0%), adiposity (+ 1.7 %, p < 0.00001, n= 219, I^2= 0%) and android mass (+ 3.53 kg, p < 0.00001, n= 309, I^2= 74%) and a significant decrease in lean mass (- 3.03 kg, p = 0.01, n= 308, I^2= 70%), were observed. In SpA patients, a significant but modest increase in fat mass (+ 0.69 kg, p = 0.03, n= 143, I^2= 0%) and a significant decrease in lean mass (-3.74 kg, p = 0.03, n= 143, I^2= 28%) was observed. TNFi did not modify body composition at 6 and 12 months, whereas at 24 months TNFi were associated with fat mass increase in RA patients (+ 2.32 kg, p = 0.04, I^2= 32%) and SpA patients (+1.64 kg, p<0.00001, I^2= 0%) and lean mass increase in RA patients (+0.49 kg, p=0.003, I^2= 0%) and in SpA patients (+0.9 kg, p<0.0001, I^2= 0%).

Conclusion:

Only RA patients have a significant increase of fat mass, that could be related to frequent steroids usage by contrast with SpA. Both RA and SpA patients have a significant decrease of lean mass probably explained by chronic inflammation since it was restored 2 years after initiation of TNFi. Increase of fat mass after TNFi may be explained by an increase in ghrelin.

Disclosure: S. marouen, None; **T. Barnetche**, None; **B. Combe**, None; **J. Morel**, None; **C. I. Daien**, None.

Abstract Number: 1538

Clinical Analysis of 30 Rheumatoid Arthritis Patients Complicated with Malignant Lymphoma, Especially Methotrexate-Related Lymphoproliferative Disorder

Takuma Tsuzuki Wada[1], Yuji Akiyama[1] and Toshihide Mimura[2], [1]Department of Rheumatology & Applied Immunology, Faculty of Medicine, Saitama

Medical University, Iruma, Japan, [2]Department of Rheumatology and Applied Immunology, Faculty of Medicine, Saitama Medical University, Saitama, Japan
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Background/Purpose: Recently, methotrexate (MTX) has been considered as the anchor drug in the treatment of rheumatoid arthritis (RA). However, it has been reported that MTX occasionally induced lymphoproliferative disorder (LPD) most of which is malignant lymphoma (ML), especially in Japan. MTX-LPD is one of the "other iatrogenic immunodeficiency-associated lymphoproliferative disorders (OIIA-LPD)" in the WHO classification. A line of evidence suggests that Epstein-Barr virus (EBV) infection may be involved in the pathogenesis of MTX-LPD, however, precise mechanism and the risk factor of MTX-LPD have not been known yet. Although some of MTX-LPD naturally improves by discontinuing MTX, other may need the chemotherapy for fatal ML. Taken together with the several reports showing that RA itself increases the risk of ML, this problem needs to be solved. Thus, we investigated clinical courses of 30 RA patients complicated with ML in our hospital.

Methods: We analyzed clinical characteristics and course of 30 RA patients complicated with ML retrospectively and compared their laboratory data with those from 1260 RA patients without ML in our department.

Results: Characteristics of the thirty patients (23 female); age 62.5±10.0 years, disease duration 9.2±0.6 years. Twenty-one were diagnosed as MTX-LPD. Three patients with MTX-LPD were naturally improved by discontinuing MTX, however, 2 of those patients were relapsed. Twelve patients among 15 patients with MTX-LPD on chemotherapy have continued to be complete remission. One patient died after chemotherapy. The dose of MTX was under 8mg/week in 13 among 15 patients and duration of MTX was under 5 years in 11 among 15 patients. The histological type of MTX-LPD was diffuse large B-cell lymphoma (DLBCL) in 16 patients. The most first-symptom is palpable tumors in 15 (50%) patients. Serum CRP was elevated 2 months before ML onset and LDH was elevated at the time of ML onset. The numbers of lymphocytes, hemoglobin and IgG were significantly lower and those of LDH, CRP and ESR were significantly higher compared with non-ML RA patients.

Conclusion: We clarified clinical characteristics of RA patients complicated with ML. From our study, the summarized clinical characteristics of MTX-LPD were as follows; age of onset; from 50 to 70 years old, MTX-duration; within 5 years when start to receive MTX, histology; DLBCL, and first symptom; palpable tumor. MTX-LPD developed in RApatients in spite of low dose MTX and relapsed patients exist after cessation of MTX. The levels of CRP rather than LDH might be elevated earlier before diagnosis of ML. Furthermore, low lymphocytes and IgG might be the risk factors of ML, including MTX-LPD.

Disclosure: T. T. Wada, None; **Y. Akiyama**, None; **T. Mimura**, None.

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Abstract Number: 1539

Control of Modifiable Cardiovascular Risk Factors in Rheumatoid Arthritis Patients Compared to Traditional High-Risk Cardiovascular Disease Patients

Brian LaMoreaux[1], Alexa Meara[2] and Wael N. Jarjour[3], [1]Rheumatology, The Ohio State University, Columbus, OH, [2]Internal Medicine/Rheumatology, The Ohio State University, Columbus, OH, [3]Department of Internal Medicine, Division of Immunology and Rheumatology, The Ohio State University Medical Center, Columbus, OH
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Background/Purpose: Rheumatoid arthritis (RA) is a chronic systemic inflammatory autoimmune disease affecting one percent of the population. The main cause of mortality among RA patients is cardiovascular disease (CVD), which occurs on average 10 years earlier than in the general population. Even when traditional risk factors such as hypertension, tobacco use, diabetes, and dyslipidemia are accounted for, there is still an elevated CVD risk associated with having RA that may be partly due to systemic inflammation from RA. Many rheumatologists routinely recommended that primary care providers (PCPs) follow the established guidelines for high risk cardiovascular patients in terms of modifiable CVD risk factors when treating RA patients. In this study we are comparing modifiable risk factor control in RA patients to high risk CVD patients.

Methods: Retrospective data was collected from the year 2013 in rheumatology, internal medicine, family medicine, and cardiovascular medicine clinics. ICD-9 codes were defined for patient selection: 1) RA without other CVD codes as the RA group, and 2) the CVD group which included one or more of myocardial infarction, diabetes, peripheral vascular disease, and coronary atherosclerotic disease without an RA code. Demographics including age and sex

as well as modifiable CVD risk factors including systolic and diastolic blood pressure (BP), body mass index (BMI), smoking status, and lipid panel including total cholesterol, high-density lipoproteins (HDL), low-density lipoproteins (LDL), and triglycerides (TG) were collected. RA patients were then compared to high risk CVD patients in terms of these modifiable risk factors.

Results: The CVD group was on average older, smoked more, and had an equal gender ratio. BMI was lower in the RA group (**Table 1**). Systolic BP was similar in the two groups, though diastolic BP was slightly higher in the RA patients (**Table 1**). As expected, many RA patients had missing cholesterol data presumably because they received screening studies through their primary care provider outside of the university system. However, in the RA patient subgroup with available lipid data, analyses showed that RA patients had significantly higher mean total cholesterol, HDL, and LDL, while CVD patients had higher triglycerides (**Table 1**).

Conclusion: Despite an emerging body of evidence that RA patients should be treated as high risk CVD patients in terms of modifiable CVD risk factors, RA patients in our study had reasonable BP control but did not meet most lipid goals. Opportunities for improvement are numerous, starting with patient and provider education and increasing the frequency of PCP visits. Our future studies will examine the same cohort longitudinally and evaluate the rate of cardiovascular events. We also plan to study PCP attitudes towards RA patients and CVD risk, as well as on CVD risk factor control.

TABLE 1: Modifiable CVD Risk Factors

Category	Rheumatoid Arthritis Patients: Mean (SD)	High-Risk CVD Patients: Mean(SD)	Estimated Difference Ratio (95% Confidence Interval)	p-value
Age	56.7 (13.1)	59.5 (13.5)	-2.81 (-3.53, -2.09)	<0.001
BMI	29.7 (7.5)	33.5 (8.5)	0.89 (0.88, 0.90)	<0.001
Systolic BP	127.2 (17.2)	126.8 (15.8)	1.00 (1, 1.01)	0.491
Diastolic BP	77.2 (9.7)	75.2 (10.2)	1.03 (1.02, 10.4)	<0.001
Total Cholesterol	181.9 (38.1)	167.8 (41.8)	1.09 (1.06, 1.13)	<0.001
HDL	52.5 (14.4)	44.9 (12.7)	1.17 (1.13, 1.21)	<0.001
LDL	105.7 (32)	92.1 (34.4)	1.17 (1.12, 1.24)	<0.001
TG	122.6 (73.6)	153.1 (93)	0.82 (0.76, 0.88)	<0.001

Disclosure: B. LaMoreaux, None; **A. Meara**, None; **W. N. Jarjour**, None.

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Abstract Number: 1540

Cardiovascular Risk Management in Rheumatoid Arthritis Patients

Calin Popa[1], Elke.E.A. Arts[1], Inger L. Meek[1], Frank H.J. van den Hoogen[2] and Jaap Fransen[1], [1]Rheumatology, Radboud University Nijmegen Medical Centre, Nijmegen, Netherlands, [2]Rheumatology, Sint Maartenskliniek, Nijmegen, Netherlands
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Background/Purpose: Rheumatoid arthritis (RA) patients have been previously shown to have a higher cardiovascular (CV) burden as compared to the general population. The CV risk in RA seems still underestimated. We present here the results of a 1.5 year experience of our Department with the CV risk management in RA patients.

Methods: RA patients have been consecutively screened on lipid profile and blood pressure. Other CV risk factors have been also recorded (smoking, CV history, family history of premature atherosclerotic events, weight –BMI, renal function, glucose). Patients fulfilled either the 1987 ACR criteria or the revised ACR-EULAR criteria for the diagnosis of RA. They were visiting the outpatient clinic for their regular controls. The SCORE index has been used to determine their 10-year risk to develop CV event/ death by CV event.

Results: In total, 342 RA patients have been consecutively screened. Among them 181 patients have been tested in primary prevention setting and were further analyzed (Table 1). Forty patients (22%) had hypertension. Thirty-three patients (18%) should have been treated with statins according to their 10-years CV risk as calculated using the algorithms for the general population. This percentage almost tripled (52%) if CBO recommendations for RA patients have been applied. Finally, 17% of the studied group had a high CV risk according to SCORE index for the general population, increasing to 21% according to SCORE-EULAR and to 49% when CBO guidelines recommendations for RA patients have been applied (Table 2).

Conclusion: There is a relative high percentage of RA patients in need for primary prevention measures, yet the use of SCORE-CBO might easily overestimate/exaggerate the risk. Screening for CV risk factors early in the course of disease should be integrated in the standards protocols for RA

management. Applying the “treat to target” strategy together with primary prevention measures might drastically reduce CV burden in RA in the near future.

	Primary prevention (N=181)
Age (years)	56 ± 14
Gender (M:F)	70:111
Disease duration (years)	10 ± 8
Rheumatoid factor (% positive)	73 (%)
BMI (kg/m²)	25 ± 4
Total cholesterol (mmol/l)	5.41 ± 1.03
HDL (mmol/l)	1.38 ± 0.34
TC:HDL	4.11 ± 1.14
Systolic blood pressure (mmHg)	127 ± 16
Diastolic blood pressure (mmHg)	76 ± 10
Smokers (%)	23 (%)

Table 1. Main characteristics of the RA group in which the screening has been applied in the primary prevention setting (mean ± SD); BMI = body mass index; HDL = high-density lipoprotein; TC = total cholesterol;

	SCORE	SCORE-EULAR	SCORE-CBO
Low risk (<10%)	124	113	57
Intermediate risk (10-19)	25	29	36
High risk (>20%)	32	39	88

Table 2. Distribution of CV risk among the 181 RA patients. SCORE-EULAR = SCORE index according to EULAR recommendations (x 1.5 when two of the following factors have been present: rheumatoid factor, disease duration> 10 years, extra-articular manifestations); EULAR-CBO = SCORE according to 2011 CBO guidelines (adding 15 years to current age)

Disclosure: C. Popa, None; **E. E. A. Arts**, None; **I. L. Meek**, None; **F. H. J. van den Hoogen**, None; **J. Fransen**, None.

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Abstract Number: 1541

Subgroups of Established Rheumatoid Arthritis Patients Can be Characterized By Patient and Physician Assessment Discrepancy, Anxiety and Depression and Presence of Depression Might be Associated with Slower Response to Treatment

Yong Gil Hwang[1], Juan (June) Feng[2], Heather Eng[2], Jason Lyons[2], Anthony Fabio[3] and Larry W. Moreland[4], [1]Department of Medicine, University of Pittsburgh, Pittsburgh, PA, [2]Epidemiology Data Center, University of Pittsburgh, Graduate School of Public Health, Pittsburgh, PA, [3]Department Of Epidemiology, Graduate School of Public Health, University of Pittsburgh, Pittsburgh, PA, [4]Rheumatology & Clinical Immunology, University of Pittsburgh, Pittsburgh, PA

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Background/Purpose: Rheumatoid arthritis (RA) is a heterogeneous inflammatory disease with various signs and symptoms. Previous studies have shown that RA patients can be sub-grouped based on inflammation, pain, and mental health, but it cannot be readily implemented without extra burden in daily practice. We identified subgroups of RA patients using the American College of Rheumatology (ACR) core data set measures and Multi-Dimensional Health Assessment Questionnaire (MDHAQ) and investigated the clinical significance of the subgroups.

Methods: RA subjects enrolled in the University of Pittsburgh Rheumatoid Arthritis Comparative Effectiveness Registry (RACER) with moderate to high disease activity by Clinical Disease Activity Index (CDAI > 10) were included. Based on previous work, ACR core set measures and sleep, anxiety; depression questions in MDHAQ at the initial visit were included as clustering variables. Remission or mild disease activity (CDAI ≤ 10) was considered as low disease activity (LDA). Time to achieve LDA was calculated for each cluster identified. We used a hierarchical clustering procedure with the Ward method. To examine differences between clusters, we used the Kruskal-Wallis test comparing the factors between each of the clusters.

Results: For the 175 subjects analyzed, subject age was 57.5 ± 13.4 (Mean±SD) years with disease duration of 13.7 ± 13.5 years. Five clusters were identified but the majority of subjects were grouped into cluster 1 (reference cluster). (Table.1) Qualitative comparison showed that 5 clusters can be

grouped into 2 categories (Physical Global Assessment [PhGA] - Patient Global Assessment [PtGA] concordant group [Cluster 1, 2, 3] and PhGA-PtGA discordant group [cluster 3, 4]). Furthermore, they were different in anxiety and depression level. Although cluster 2 and 3 had similar disease activity, cluster 2 had higher anxiety and cluster 3 had higher depression. Similarly, cluster 4 had higher anxiety and cluster 5 had higher depression. Clusters having higher depression (cluster 3 in comparison with cluster 1 and 2, cluster 5 in comparison with cluster 4) had longer time to achieve low disease activity when compared with other similar clusters (Table.2).

Conclusion: This study suggests that discrepancy between patient and physician global assessment, severity of anxiety and depression can be useful to identify and distinguish subgroups of RA patients. Severity of depression may be associated with longer time to achieve low disease activity. Given very small numbers in other clusters except the reference cluster, further analyses will be necessary to confirm these findings.

Table 1. Clinical characteristics of the patients, used as variables to define the clusters

Characteristics Mean (Min-Max)	Cluster 1 (n=134)	Cluster 2 (n=14)	Cluster 3 (n=16)	Cluster 4 (n=4)	Cluster 5 (n=2)	P[1]
Total Swollen	8.00(0.00-26.00)	7.50(2.00-26.00)	7.50(1.00-13.00)	5.50(2.00-8.00)	9.50(4.00-15.00)	0.90544
Total Tender	8.51(1.00-28.00)	7.71(1.00-19.00)	6.88(1.00-16.00)	8.00(5.00-12.00)	5.00(4.00-6.00)	0.85361
Physician Global Health	4.76(0.00-10.00)	4.89(2.00-8.50)	4.63(1.00-10.00)	4.13(3.00-6.00)	5.50(5.00-6.00)	0.84530
Patient Global Health	5.87(0.00-10.00)	5.75(2.50-9.00)	5.63(3.00-8.50)	6.13(5.00-8.50)	7.25(6.00-8.50)	0.81949
HAQ	3.02(0.00-7.70)	3.52(0.00-7.70)	2.33(0.30-6.30)	4.03(1.7-6.70)	2.50(1.70-3.30)	0.32824
Patient Pain VAS	6.37(0.50-10.00)	6.39(2.50-10.00)	6.66(3.00-10.00)	7.50(6.50-8.50)	8.75(8.50-9.00)	0.44445
CRP mg/dL	0.64(0.02-3.54)	0.45(0.03-1.29)	0.69(0.05-2.00)	0.71(0.05-1.45)	0.23(0.14-0.33)	0.60441
R3 Sleep	1.26(0.00-3.00)	1.36(0.00-2.00)	0.94(0.00-3.00)	1.00(0.00-2.00)	1.50(1.00-2.00)	0.46614
R3 Anxiety	0.72(0.00-3.00)[234]	1.50(1.00-3.00)[68]	0.25(0.00-1.00)[9]	2.00(2.00-2.00)[11]	0.00(0.00-0.00)	0.00000
R3 Depression	0.72(0.00-3.00)[35]	0.50(0.00-2.00)[68]	1.25(1.00-2.00)[910]	0.00(0.00-0.00)[11]	2.00(2.00-2.00)	0.00033

[1] P values are p value Kruskal-Wallis Test for overall difference. [2] Cluster 1 significantly different from cluster 2($p \leq 0.05$) [3] Cluster 1 significantly different from cluster 3($p \leq 0.05$) [4] Cluster 1 significantly different from cluster 4($p \leq 0.05$) [5] Cluster 1 significantly different from cluster 5($p \leq 0.05$) [6] Cluster 2 significantly different from cluster 3($p \leq 0.05$) [7] Cluster 2 significantly different from cluster 4($p \leq 0.05$)

[8] Cluster 2 significantly different from cluster 5($p \leq 0.05$) [9] Cluster 3 significantly different from cluster 4($p \leq 0.05$) [10] Cluster 3 significantly different from cluster 5($p \leq 0.05$) [11] Cluster 4 significantly different from cluster 5($p \leq 0.05$)

Table.2 Time to achieve low disease activity (remission or mild disease activity by Clinical Disease Activity Index) for each cluster

	Patients numbers	% of patients achieved Low disease activity	Mean time to achieve low disease activity
Cluster . *	5	17.39	68.25
Cluster 1	134	100	242.4
Cluster 2	14	100	263.2
Cluster 3	16	100	293.6
Cluster 4	4	100	86.8
Cluster 5	2	100	357.5

(*Among 175 subjects, 170 were qualified for cluster analysis)

Disclosure: Y. G. Hwang, None; **J. Feng**, None; **H. Eng**, None; **J. Lyons**, None; **A. Fabio**, None; **L. W. Moreland**, None.

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Abstract Number: 1542

Arterial Vascular Events in Hispanics from Puerto Rico with Rheumatoid Arthritis

Ariana González-Meléndez[1], Ruth Fred-Jimenez[2], Mariangelí Arroyo-Ávila[2], Leyda Díaz-Correa[2], Naydi Pérez-Ríos[3], Noelia Rodríguez-Pérez[2], Grissel Ríos[2] and Luis M. Vilá[2], [1]School of Medicine, Ponce Health Sciences University, Ponce, PR, [2]Department of Medicine, Division of Rheumatology, University of Puerto Rico Medical Sciences Campus, San Juan, PR, [3]Puerto Rico Clinical and Translational Research Consortium, University of Puerto

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Background/Purpose: Arterial vascular events have a great impact in the morbidity and mortality of rheumatoid arthritis (RA). Traditional and nontraditional risk factors for arterial vascular events vary widely among different ethnic groups. Few studies have been conducted in Hispanics from the United States. Thus, we determined the factors associated with the occurrence of arterial vascular events in a cohort of Hispanics from Puerto Rico with RA.

Methods: RA patients (per American College of Rheumatology classification criteria) of Puerto Rican ethnicity (self and four grandparents) were studied to determine the demographic features, health-related behaviors, clinical manifestations, disease activity (per disease activity score 28 [DAS28]), comorbid conditions, functional status (per Health Assessment Questionnaire [HAQ]), and pharmacologic profile associated with arterial vascular events. An arterial vascular event was defined as the occurrence of myocardial infarction, angina pectoris, vascular procedure for coronary artery disease, stroke, or peripheral artery disease. Patient characteristics were analyzed by bivariable (chi-square and Student's t tests) and multivariable (logistic regression) analyses.

Results: In total, 405 RA patients were studied. The mean (standard deviation [SD]) age was 56.1 (13.9) years and the mean (SD) disease duration was 15.0 (50.7) years; 87.2% were woman. Forty-three patients (10.6%) had at least one incident arterial vascular event. In the bivariable analyses, patients with arterial vascular events were more likely to be male (23.3% vs. 11.6%, p= 0.031) and older (63.0 [11.1] vs. 55.2 [14.0] years, p<0.001) and to have more extra-articular manifestations (69.8% vs. 48.9%, p=0.010), disease activity (DAS28 score, 4.21 [1.81] vs. 3.61 [1.45], p=0.044), functional disability (HAQ score, 1.40 [0.89] vs. 1.09 [0.78], p=0.017), arterial hypertension (83.7% vs. 51.7%, p<0.001), diabetes mellitus (25.6% vs. 13.8%, p=0.041), dyslipidemia (81.0% vs. 45.3%, p<0.001) and peripheral venous disease (11.6% vs. 3.9%, p=0.040) than those without arterial vascular events. No differences were found for disease duration, smoking, exercise, body mass index, joint deformities, erosive disease, and exposure to nonsteroidal anti-inflammatory drugs, corticosteroids, disease modifying anti-rheumatic drugs and biologic agents. In the multivariable analysis adjusted for gender and age, extra-articular manifestations (OR=2.08, 95% CI 1.03-4.20), functional status (OR=2.52, 95% CI 1.24-5.11), arterial hypertension (OR= 3.43, 95% CI 1.40-8.41), dyslipidemia (OR= 4.48, 95% CI 2.00-10.04) and peripheral venous disease (OR=2.93, 95% CI .96-8.97) retained significance.

Conclusion: This is the first study examining the prevalence and correlates of arterial vascular events in Hispanics from Puerto Rico with RA. Patients with extra-articular manifestations and greater disability as well as those with traditional risk factors for cardiovascular disease were at higher risk. Awareness of these factors may lead to more effective management strategies of patients at risk for arterial vascular events.

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Abstract Number: 1543

Traditional Risk Score Underestimates the Cardiovascular Risk in Rheumatoid Arthritis Patients

Tomas Cazenave[1], Natalia Zamora[1], Gustavo Citera[1,2] and Marcos G. Rosemffet[1], [1]Rheumatology, Instituto de Rehabilitación Psicofísica, Buenos Aires, Argentina, [2]Rheumatology, Instituto de Rehabilitacion Psicofisica, Buenos Aires, Argentina
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Background/Purpose: An increased incidence of cardiovascular (CV) mortality has been reported in patients with rheumatoid arthritis (RA). Adequate stratification of the CV risk is an issue of major importance in these patients. ***Objective:***To compare the CV risk estimated by a traditional score with carotid ultrasound (US) assessment in RA patients.

Methods: A cross-sectional study including RA patients without history of CV events was designed. Data collected included clinical and demographic characteristics. All patients were evaluated for traditional CV risk factors. CV risk was stratified according to Framingham Score. Carotid US was performed to assess the presence of subclinical atherosclerosis. The presence of cIMT >0.90 mm and/or carotid plaques (US Carotid Atherosclerosis=UCA) were considered a marker of CV high risk. The association between clinical characteristics and US findings was assessed using univariate and multivariate analysis. ROC curves were developed to estimate cut-off values.

Results: We included 60 patients with RA. Mean age was 54.2±12.3 years, and 78% were female. Mean disease duration was 13±9 years, and mean DAS28 was 3.8±1.17. All patients were receiving DMARDs, 36% biologic treatment and 58% oral steroids (mean dose: 6.22±2.3). Eleven patients (18%)

had hypertension, 16 (26,7%) dyslipidemia and 28 (46%) were exposed to tobacco (pack/year mean:10.8±7.4). The Framingham median score was 6.05 (IQR:3.4-10.2); 45 (75%), 10 (16.7%) and 5 (8.3%) patients were classified as low, moderate and high CV risk, respectively. US assessment detected UCA (plaque and/or cIMT >0.90) in 33 (55%) patients, plaques in 30 (50%), and cIMT >0.90 in 18 (30%). The UCA frequencies observed in the different Framingham categories were: Low: 20/45 (44.4%), Moderate: 8/10 (80%), High: 5/5 (100%). In the univariated analysis the presence of UCA was more frequent in older patients (p<0.0001) and with longer disease duration (p=0.057). After adjusting for multiple confounders age was the only variable that remained associated with UCA. In the ROC analysis the optimal cutoff value for age, that predicts UCA presence was 53.5 years with a sensitivity and specificity of 84.8% and 81.5%, respectively (AUC: 0.89).The UCA prevalence was 84.8% (n = 28) in patients with age ≥53.5 years, compared to only 15.2% (n = 5) in those with age <53.5 years.

Conclusion: More than a half of patients classified in low-moderate risk according to Framingham score presented subclinical atherosclerosis in carotid US assessment. A large majority of patients older than 53.5 years showed high-risk carotid involvement, which may require intensive CV risk management.

Disclosure: T. Cazenave, None; **N. Zamora**, None; **G. Citera**, None; **M. G. Rosemffet**, None.

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Abstract Number: 1544

Resiliency As a Predictor of Depressive Symptoms in Patients with Rheumatoid Arthritis

Matt Woo[1], Nadil Zeiadin[1], Hayley Yurgan[2], Dean Tripp[3] and Mala Joneja[1], [1]Medicine, Queen's University, Kingston, ON, Canada, [2]Psychology, Queen's University, Kingston, ON, Canada, [3]Psychology, Anaesthesiology, Urology, Queen's University, Kingston, ON, Canada
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SESSION INFORMATION
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Session Type: ACR Poster Session B
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Background/Purpose: Rheumatoid arthritis is a chronic, systemic, autoimmune disease affecting 0.5 – 1% of the adult population that leads to a progressive decline in functional status[1]. Psychological distress, including depression, is common among patients with rheumatoid arthritis and a predictor of functional outcome[2]. Resiliency, the presence of effective coping and adaptation when faced with loss, hardship or adversity has been shown to be a protective factor in chronic disease, including autoimmune disorders such as SLE[3]. In this study, we aimed to assess predictors of depressive symptoms in patients with rheumatoid arthritis.

Methods: Twenty-one patients with a diagnosis of rheumatoid arthritis from a single center in Kingston, Ontario were evaluated with a demographics questionnaire, a 9-item self-reported depression scale (Patient Health Questionnaire 9, PHQ-9), a 4-item resilience scale (Brief Resilience Coping Scale, BRCS), as well as a physician administered measure of objective disease activity (DAS-28). Multiple regression analysis was conducted to assess predictors of depressive symptoms.

Results: The sample had low to moderate disease activity ($M = 3.10$, $SD = 1.56$). The mean PHQ-9 score was 4.09 ($SD = 4.03$) and the mean resilience score was 13.86 ($SD = 4.07$). Disease activity ($\beta = .38$) and resilience ($\beta = -.47$) were significant predictors of depressive symptoms, $R^2 = .73$, adjusted $R^2 = .64$, $F(5, 15) = 8.20$, $p < .01$. Disease activity is a positive predictor and resiliency is a negative predictor of depressive symptoms.

Conclusion: Resilience had the greatest regression weight, implicating resilience as an important target for psychological intervention. Assessment of resilience in patients with rheumatoid arthritis may allow for the identification of patients at risk for psychosocial distress and allow for the implementation of targeted therapies to improve functional status.

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Disclosure: M. Woo, None; **N. Zeiadin**, None; **H. Yurgan**, None; **D. Tripp**, None; **M. Joneja**, None.

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Abstract Number: 1545

Comparison of Statin Eligibility According to the Adult Treatment Panel III, ACC/AHA Blood Cholesterol Guideline and Presence of Carotid Plaque By Ultrasound in Hispanics with Rheumatoid Arthritis

Alberto Cardenas-de La Garza[1], Raymundo Vera-Pineda[2], Dionicio A. Galarza-Delgado[1], Jose Ramon Azpiri-Lopez[3], Iris J. Colunga-Pedraza[1], Jesus Zacarias Villarreal-Pérez[4], Griselda Serna-Peña[5] and Mario Alberto Garza-Elizondo[1], [1]Rheumatology, Hospital Universitario, UANL., Monterrey, Mexico, [2]Cardiology., Hospital Universitario, UANL., Monterrey, Mexico, [3]Cardiology, Hospital Universitario, UANL., Monterrey, Mexico, [4]Endocrinology, Hospital Universitario, UANL., Monterrey, Mexico, [5]Internal Medicine, Hospital Universitario, UANL., Monterrey, Mexico

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Background/Purpose:

Atherosclerotic cardiovascular disease (ASCVD) is the number one cause of death in rheumatoid arthritis (RA) patients. RA itself is an independent risk factor for ASCVD comparable to that of diabetes. Lipid-lowering therapy with statins is one of the most effective drug treatments for primary and secondary ASCVD prevention. The American College of Cardiology/American Heart Association (ACC/AHA) 2013 guidelines on the treatment of blood cholesterol and the Adult Treatment Panel-III (ATP-III) guidelines differ between their strategies for initiating statins in primary prevention. Carotid ultrasound is a non-invasive tool useful for the detection of subclinical atherosclerosis. Presence of carotid plaque (CP) is an indication of lipid-lowering therapy with statins. The objective of the present study is to compare statin treatment recommendation according to ACC/AHA 2013 guidelines, ATP-III guidelines and CP by carotid ultrasound.

Methods:

An observational, cross-sectional study was designed based on a cohort of RA statin-naïve, 40 to 75 year old, Hispanics that attended a referral center. All fulfilled the 1987 ACR and the 2010 ACR/EULAR classification criteria for RA. Exclusion criteria included overlap syndromes, previous ASCVD (myocardial infarction, stroke and peripheral arterial disease), dyslipidemia, pregnancy, and statin use at baseline. CP was evaluated with B-mode ultrasound and defined as focal thickening at least 50% greater than that of the surrounding wall or carotid intima media-thickness ≥1.2 mm. Multiplication of the scales by 1.5 was performed when applicable according to EULAR cardiovascular risk 2008 recommendations.

Results:

A total of 62 patients were included in the analysis. The patients' characteristics are shown in Table 1. The mean age was 56.4 ±9.74 years. Women accounted for 55 (88.7%). Mean disease duration in years was 11.46 ±9.73. Statin therapy was recommended by ATP-III guidelines in 8 (12.9%) cases and by ACC/AHA 2013 guidelines in 23 (37.1%) cases. CP by carotid US was identified in 28 (45.2%) patients. McNemar's test revealed statistical difference in statin therapy recommendation between CP and ATP-III guidelines ($p \leq 0.001$), and ACC/AHA and ATP-III guidelines ($p \leq 0.001$). No difference was noted between CP and ACC/AHA guidelines ($p = 0.332$).

Conclusion:

In this Hispanic cohort of RA patients, statin treatment recommendation varies among CP and ATP-III guidelines, and ACC/AHA and ATP-III guidelines. No difference was found between CP and ACC/AHA 2013 guidelines. The recent ACC/AHA guidelines may offer better risk assessment for early detection of cardiovascular risk in RA but further prospective studies are needed to evaluate it.

Patients' characteristics	
Age (years); mean ± SD	56.40 ± 9.74
Women; n (%)	55 (88.7)
Disease duration (years); mean ± SD	11.46 ± 9.73
Diabetes; n (%)	6 (9.7)
Anti-hypertensive treatment; n (%)	22 (35.5)
Family history of coronary heart disease; n (%)	6 (9.7)
Active smoking; n (%)	16 (25.8)
Positive rheumatoid factor or anti-cyclic citrullinated peptide; n (%)	45 (72.6)
Body mass index; mean ± SD	28.63 ± 5.57
Systolic blood pressure (mmHg); median (Q1-Q3)	120 (116.75-135.25)
Diastolic blood pressure (mmHg); mean ± SD	78.65 ± 13.89
Remission by DAS28 ESR; n (%)	33 (53.2)
LDL cholesterol (mg/dl); mean ± SD	105.41 ± 26.47
HDL cholesterol (mg/dl); mean ± SD	55.17 ± 9.74
Framingham lipids 10-year risk calculator; median (Q1-Q3)	7.86 (4.70-14.06)
ACC/AHA 2013 10-year ASCVD risk Pooled Cohort Equation; median (Q1-Q3)	4.00 (1.60-12.91)
Treatment recommended by ATP-III guidelines; n (%)	8 (12.9)
Treatment recommended by ACC/AHA 2013 guidelines; n (%)	23 (37.1)
Carotid plaque; n (%)	28 (45.2)

Disclosure: A. Cardenas-de La Garza, None; **R. Vera-Pineda**, None; **D. A. Galarza-Delgado**, None; **J. R. Azpiri-Lopez**, None; **I. J. Colunga-Pedraza**, None; **J. Z. Villarreal-Pérez**, None; **G. Serna-Peña**, None; **M. A. Garza-Elizondo**, None.

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Abstract Number: 1546

What Is the Impact of Smoking on the Risk of Rheumatoid Arthritis Progression: A Systematic Review of the Risk Factor Paradox

Sharan K. Rai[1], Natalie McCormick[2], Uyen Sa D.T. Nguyen[3], Yuqing Zhang[4], Jeffrey A. Sparks[5], Elizabeth W. Karlson[6] and Hyon K. Choi[7],
[1]Experimental Medicine, University of British Columbia, Vancouver, BC, Canada, [2]Pharmaceutical Sciences, University of British Columbia, Vancouver, BC, Canada, [3]Orthopedics and Physical Rehabilitation, University of Massachusetts Medical School, Worcester, MA, [4]Clinical Epidemiology and Training Unit, Boston University School of Medicine, Boston, MA, [5]Division of Rheumatology, Immunology, and Allergy, Brigham & Women's Hospital, Boston, MA, [6]Rheumatology, Brigham & Women's Hospital, Boston, MA, [7]Rheumatology, Allergy and Immunology, Massachusetts General Hospital, Harvard Medical School, Boston, MA

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Background/Purpose: Rheumatoid arthritis (RA) is a chronic inflammatory disease that leads to progressive joint deformity, destruction, and disability. While smoking is recognized as a strong environmental risk factor for the development of RA, the relationship between smoking and the progression of RA has often been reported to be inconsistent or paradoxical ("the risk factor paradox"). To summarize the relevant data to date, we conducted a systematic review of the literature on the impact of smoking on the risk of RA progression.

Methods: We conducted a mapped search of MEDLINE and EMBASE databases for articles published from database inception to June 2015. Additional articles were retrieved by a hand-search of relevant bibliographies. Our search strategy used a combination of mapped subject headings (i.e., MeSH and Emtree terms) and keywords for unindexed concepts relating to the themes of RA progression and smoking/tobacco use. Full-text articles meeting the following criteria were included in the systematic review: 1) RA patient population; 2) outcome of a change in RA status (e.g., radiologic progression, functional status, or disease severity); 3) original research article; and 4) English language. Studies were excluded if they reported the impact of smoking on the risk of incident RA. Non-human studies, reviews, and case reports/series were additionally excluded.

Results: We identified 685 unique citations with our search strategy. Of these, 28 studies met all inclusion criteria and were included in the systematic review. The main outcomes reported included radiographic progression (e.g., Larsen or Sharp/van der Heijde score) (n=14 studies), disease activity (e.g., DAS) (n=13), treatment response (n=6), functional status and disability (e.g., HAQ) (n=7), achievement of remission (n=2), and total joint replacement (n=1). Overall, smoking did not have a significant impact on RA outcomes and progression, and in some studies (n=4) smoking actually conferred a protective impact **(see Table)**. Only two of 14 studies on radiographic progression reported a hazardous effect, and the impact of smoking on functional status was non-significant in all studies identified. Additionally, there was no significant association between smoking status and achievement of remission.

Conclusion: While smoking is a well-established risk factor for incident RA, findings from the majority of studies identified in this systematic review suggest that it does not confer the same impact on disease progression. Although biological explanations for these counterintuitive results may exist, an enticing methodologic explanation is a type of selection bias known as index event bias. Appropriate methods to correct for this bias should be explored to determine the true impact of smoking on the risk of RA progression.

Table. Summary of Reported Associations between Smoking and RA Progression

Outcome	Protective or Null Association	Hazardous Association
Radiologic progression (n=14)	12	2*
Disease activity (n=13)	11	2
Treatment response (n=6)	5	1
Functional status/disability (n=7)	7	0
Remission (n=2)	2	0
Total joint replacement (n=1)	1	0

*One was based on a cross-sectional analysis of a cohort study

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Disclosure: **S. K. Rai**, None; **N. McCormick**, None; **U. S. D. T. Nguyen**, None; **Y. Zhang**, None; **J. A. Sparks**, None; **E. W. Karlson**, None; **H. K. Choi**, None.

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Abstract Number: 1547

Implementing an Electronic Medical Recorded-Based Clinical Decision Support Tool Did Not Improve Cardiovascular Risk Screening in Rheumatoid Arthritis Patients

Anand Kumthekar[1], Michail Alevizos[2], Nicole Jordan[3] and **Anna R. Broder**[4], [1]Medicine, Albert Einstein College of Medicine/Jacobi Medical Center, Bronx, NY, [2]Medicine, Albert Einstien College of Medicine/Jacobi Medical Center, Bronx, NY, [3]Montefiore Medical Center, New York, NY, [4]Rheumatology-Forchheimer 701N, Albert Einstein College of Medicine/Montefiore Medical Center, Bronx, NY

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Background/Purpose: Cardiovascular disease (CVD) is the leading cause of death among individuals with rheumatoid arthritis (RA). The 2010 EULAR guidelines recommend annual CV risk assessment for all RA patients in accordance with national guidelines[1]. However, CVD risks are not being assessed frequently and systematically in RA patients. We implemented an Electronic Medical Record (EMR)-based clinical decision support intervention at a large tertiary care center and assessed the effects of this intervention on lipid screening among RA patients by treating rheumatologists.

Methods: We developed a self-populated form that was incorporated into each EMR rheumatology visit and contained the following information (Image): 1) dates of the latest assessment of CVD risks (body mass index (BMI), blood pressure, smoking, lipid screening); 2) the latest values for all of the above CVD risks; 3) Framingham risk score calculator. To evaluate the impact of this EMR-based intervention, lipid screening rates among adult RA patients

were compared pre and post implementing this EMR tool. LDL levels were compared for patients seen, pre-intervention, 1/1/2012-6/30/2012 (2012), and post-intervention, 1/1/2014-6/30/2014 (2014). RA patients were identified using a previously validated algorithm requiring two or more visits with the ICD9 code *714.0 (Rheumatoid arthritis),* and at least one prescription for a disease modifying anti-rheumatic medication[2]. The first visit within the study period was defined as the index visit. Wilcoxon-Mann-Whitney tests were used to compare continuous variables, and Pearson's Chi-square tests (or Fisher's exact test when appropriate) were used to compare categorical variables.

Results: 131 and 111 RA patients seen in outpatient rheumatology clinics by rheumatologists in 2012 and 2014, respectively. Sex, race, and ethnicity were similar: 35% vs. 29% were Black, 60% and 64% were Hispanic, 12% and 9% were men. There were no age differences: mean (SD) 58(14) years old in 2012, and 59 (14) years old in 2014. BMI was also similar: mean (SD) 30(7) kg/m^2 in 2012, and 30(6) kg/m^2 in 2014. Lipid screening frequency in the subsequent 6 months was 32% in 2012 and 23% in 2014 (p=0.12). Median (SD) LDL was 96 (30) mg/dl in 2012, and 109 (36) mg/dl in 2014 (p=0.09)

Conclusion: Implementing an EMR based decision support tool did not improve rates of screening for lipid abnormalities among RA patients. Lipid screening rates remained low. Further studies are needed to identify and address barriers to CVD screening in RA among rheumatologists and primary care providers.

References:

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2. Kim SY, et al. Arthritis Res Ther. 2011 Feb 23;13(1):R32)

Image: Decision support tool to aid rheumatologists with cardiovascular screening

Disclosure: A. Kumthekar, None; **M. Alevizos**, None; **N. Jordan**, None; **A. R. Broder**, Pfizer Inc, 2.

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Abstract Number: 1548

Comparison of 5 Cardiovascular Risk Calculators in a Hispanic Rheumatoid Arthritis Cohort

Alberto Cardenas-de La Garza[1], Raymundo Vera-Pineda[2], Dionicio A. Galarza-Delgado[1], Jose Ramon Azpiri-Lopez[3], Iris J. Colunga-Pedraza[1], Griselda Serna-Peña[4] and Mario Alberto Garza-Elizondo[1], [1]Rheumatology, Hospital Universitario, UANL., Monterrey, Mexico, [2]Cardiology., Hospital Universitario, UANL., Monterrey, Mexico, [3]Cardiology, Hospital Universitario, UANL., Monterrey, Mexico, [4]Internal Medicine, Hospital Universitario, UANL., Monterrey, Mexico

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Background/Purpose:

Atherosclerotic cardiovascular disease (ASCVD) is the leading cause of death in RA. Management and stratification of ASCVD in RA patients is still a matter of debate. Performance of cardiovascular risk calculators, including Framingham Risk Scores (FRS) BMI and Lipids, Reynolds Risk Scale (RRS) and QRISK2 have shown poor results in RA. The recent ACC/AHA 2013 risk calculator (OMNIBUS) has not been compared against the other scales in RA patients.

Methods:

An observational, cross-sectional, prospective study was designed. Patients with RA that fulfilled ACR/EULAR 2010 classification criteria and attended a reference center were included. Cardiovascular risk was calculated by 5 different scales using the official online calculators. Patients with prior ASCVD, overlap syndromes, out of the predefined age range (40-75 years old) or with missing data were excluded.

Sample size was calculated to determine a 5% difference between scales. Friedman test was used to identify difference between the calculators considering a $p<0.05$ as statistically significant. To determine differences between each algorithm, Wilcoxon signed-rank tests were used and considered significant when $p<0.005$ due to repeated measurement analysis.

Results:

A total of 93 patients were included. Mean age was 56.8±8.8 years old and mean disease duration of 12.84±8.3 years. Women accounted for 86 (92.6%). The population's demographical data is shown in Table 1. Friedman test determined a significant difference between the scales ($p<0.001$). Wilcoxon signed-rank test results are shown in Table 2. RRS estimation was significantly lower than any other calculator ($p<0.001$). FRS BMI gave higher values than the other algorithms ($p<0.001$). OMNIBUS risk was lower than FRS Lipids and QRISK2 ($p<0.001$). There was no difference between QRISK2 and FRS Lipids ($p=0.964$). OMNIBUS gave higher values than RRS ($p<0.001$).

Conclusion:

In our cohort of Hispanics with RA, FRS BMI provided higher risk values than any other scale. There was no difference between FRS Lipids and QRISK2 estimations. OMNIBUS stratified patients lower than FRS Lipids and QRISK2. Prospective information is needed to determine if FRS BMI could represent the best option in RA.

Table 1. Demographical characteristics	
Age (yo), mean ± SD	56.8 (8.824)
Feminine, n (%)	86(92.5)
Family history of ASCVD, n (%)	11 (11.8)
Current smoking, n (%)	9 (9.7)
Dyslipidemia, n (%)	28 (30.1)
Type 2 Diabetes Mellitus, n (%)	12 (12.9)
Currently on antihypertensive drugs, n (%)	32 (34.4)
Extra articular manifestations, n (%)	3 (3.2%)
Disease duration (yo), mean ± SD	12.84 (8.32)
BMI, mean ± SD	27.71 (4.70)
Systolic BP (mmHg), mean ± SD	121.07 (13.77)
DAS 28-CRP, mean ± SD	3.492 (1.378)
Total cholesterol (mg/dl), mean ± SD	186.44 (30.26)
HDL cholesterol (mg/dl), mean ± SD	55.62 (17.03)
LDL cholesterol (mg/dl), mean ± SD	100.85 (26.22)
TC : HDL ratio, mean ± SD	3.60 (1.06)
hs-CRP (mg/dl), median (p25-p75)	.96 (.635-1.395)
Omnibus (%), median (p25-p75)	2.8 (1.2-6.2)
Framingham lipids (%), median (p25-p75)	6 (3.3-9.25)
Framingham BMI (%), median (p25-p75)	7.9 (4.4-11.95)
QRISK2 (%), median (p25-p75)	6.2 (2.6-12.35)
Reynolds Risk (%), median (p25-p75)	2 (1-3.5)

Table 2. Wilcoxon signed test results					
Scale Median (p25-p75)	OMNIBUS 2.8 (1.2-6.2)	FRS Lipids 6 (3.3-9.25)	FRS BMI 7.9 (4.4-11.95)	QRISK2 6.2 (2.6-12.35)	RRS 2 (1-3.5)
OMNIBUS 2.8 (1.2-6.2)		$p<.001$	$p<.001$	$p<.001$	$p<.001$
FRS Lipids 6 (3.3-9.25)	$p<.001$		$p<.001$	$p<.964$	$p<.001$
FRS BMI	$p<.001$	$p<.001$		$p<.001$	$p<.001$

Disclosure: A. Cardenas-de La Garza, None; **R. Vera-Pineda**, None; **D. A. Galarza-Delgado**, None; **J. R. Azpiri-Lopez**, None; **I. J. Colunga-Pedraza**, None; **G. Serna-Peña**, None; **M. A. Garza-Elizondo**, None.

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Abstract Number: 1549

7.9 (4.4-11.95)					
QRISK2 6.2 (2.6-12.35)	*p*<.001	*p*<.964	*p*<.001		*p*<.001
RRS 2 (1-3.5)	*p*<.001	*p*<.001	*p*<.001	*p*<.001	

Prevalence of Co-Morbidities and Evaluation of Their Monitoring in Korean Patients with RA: Comparison with the Results of an International, Cross-Sectional Study (COMORA)

In Ah Choi[1], Sung-Hwan Park[2], Hoon-Suk Cha[3], Won Park[4], Hyun Ah Kim[5], Dae-Hyun Yoo[6], Han Joo Baek[7], SeungGeun Lee[8], Yoon Jong Lee[9], Yong Bum Park[10], Seung-Cheol Shim[11], Ihsane Hmamouchi[12] and Yeong Wook Song[13], [1]Rheumatology, Division of Rheumatology, Department of Internal Medicine, Seoul National University Hospital, Seoul, South Korea, [2]Division of Rheumatology, Department of Internal Medicine, Seoul St. Mary's Hospital, Seoul, South Korea, [3]Division of Rheumatology, Department of Internal Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea, [4]Division of Rheumatology, Department of Internal Medicine, Inha University Hospital, Incheon, South Korea, [5]Division of Rheumatology, Department of Internal Medicine, Hallym University Sacred Heart Hospital, Anyang, South Korea, [6]Division of Rheumatology, Department of Internal Medicine, Hanyang University Hospital for Rheumatic Diseases, Seoul, South Korea, [7]Rheumatology, Gachon University Gil Medical Center, Incheon, South Korea, [8]Division of Rheumatology, Department of Internal Medicine, Pusan Nationl University Hospital, Busan, South Korea, [9]Division of rheumatology Seoul National University Bundang Hospital, Seongnam, South Korea, [10]Division of Rheumatology, Department of Internal Medicine, Yoesei University Severance Hospital, Seoul, South Korea, [11]Division of Rheumatology, Department of Internal Medicine, Eulji University Hospital, Daejeon, South Korea, [12]El Ayachi Hospital, Rabat, Morocco, [13]Division of Rheumatology, Department of Internal Medicine, Seoul National University Hospital, Seoul, South Korea

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Background/Purpose: Rheumatoid Arthritis (RA) patients are at increased risk of developing co-morbid conditions. We designed this study to evaluate the prevalence of comorbidities and their monitoring in Korean RA patients compared with the patients from other countries.

Methods: We analyzed the demographics, disease characteristics, comorbidities and their monitoring states of 1050 RA patients from 11 Korean centers and compared with those of 3520 patients from 16 other countries using COMORA database.

Results:

The prevalence of obese patients was significantly lower and married patients was higher in Korean patients (p<0.0001, both). Disease duration was shorter, uses of prednisolone and NSAIDs were more frequent and the use of biologics was lower in Korean patients (p<0.0001, all). The prevalence of cardiovascular (CV) event was not significantly different between two groups. The prevalence of basocellular skin cancer was significantly lower in Korean patients (p<0.0001).

The proportion of current smoker, patients who have a family history of CV disease, hyperlipidemia and patients with Framingham score >20% were significantly lower, although the prevalence of diabetes was higher in Korean patients (p<0.0001, all).

Annual evaluation of CV risk was less frequently performed in Korean (p=0.0011) although the use of antiplatelet agent was more frequent (p=0.0004). Prostatic and skin cancer monitoring were less frequently performed (p<0.0001) but lung and breast cancer monitoring were more frequently performed (p=0.048 and p<0.0001). Vitamin D supplement was less frequently used (p<0.0001).

When we analyzed the association of GI disease with medication, the risk of GI ulcer was increase with prednisolone (Odds ratio 1.68, 95% CI 1.34-2.09) and NSAIDs (odds ratio 1.44, 95% CI 1.16-1.79) in patients from other countries. The usage of NSAID was protective for the development of colon cancer in RA patients of Korea (odds ratio 0.09, 95% CI 0.01-0.86) and other countries (odds ratio 0.3, 95% CI 0.12-0.75). The usage of biologic agents increased the risk of lymphoma in countries other than Korea (odds ratio 19.08, 95% CI 2.51-145.27).

Conclusion: There are differences in the prevalence of co-morbidities and monitoring states of the risk factors between patients in Korea and the other countries. The prevalence of CV morbidity was similar between two groups although the prevalence of CV risk factors is significantly low in Korean, suggesting more attention to yearly CV risk monitoring is needed. The usage of NSAID was protective for the development of colon cancer in RA patients of Korea and other countries.

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Abstract Number: 1550

Flares of Disease Activity As Risk Factor for the Occurrence of Myocardial Infarction in Patients with Rheumatoid Arthritis

Esmee Bakker[1], Pauline Geuijen[2], Beata Radovits[1], Delia Popa-Diaconu[1], Calin Popa[1], Elke Arts[1], Alfons A. den Broeder[3] and **Jaap Fransen**[1], [1]Rheumatology, Radboud University Medical Centre, Nijmegen, Netherlands, [2]Rheumatology, Radboud University Medical Center, Nijmegen, Netherlands, [3]Rheumatology, Sint Maartenskliniek, Nijmegen, Netherlands
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Background/Purpose: Rheumatoid arthritis (RA) patients have an increased risk of cardiovascular diseases (CVD). The underlying mechanism is partly explained by the inflammation process in both RA and atherosclerosis. Atherosclerosis is an important risk factor for the occurrence of premature coronary heart disease, like myocardial infarction (MI) (1). A higher average level of disease activity in RA patients might cause MI, however this hypothesis was not confirmed (2). Probably, flares are more important than the average level of disease activity as risk factor for CVD in RA. Therefore, the objective was to determine whether the annual flare rate is associated with the occurrence of MI in RA patients.

Methods: We used case-control data from a large Dutch prospective RA cohort, which started in 1985. Medical files of RA patients were used to determine the occurrence of MI events. Patients were defined as cases at the moment they experienced a MI event. Randomly chosen RA controls were matched on disease duration; the time between RA diagnosis and MI event or censoring. Flares were defined as an increase in DAS28>1.2 or >0.6 if DAS28≥3.2. The annual flare rate was calculated as the number of flares divided by disease duration. Other important characteristics of RA and risk factors for CVD were determined at baseline or during follow-up. Characteristics of cases and controls were compared by t-tests or non-parametric Mann-Whitney U. Logistic regression was performed to determine the crude association between the annual flare rate and occurrence of MI. Confounding variables were taken into account using multivariate logistic regression.

Results: The study population consisted of 41 cases and 181 matched controls. Cases were older and more frequently male while also risk factors for CVD were raised in cases, like: significantly higher BMI, total cholesterol, triglyceride, LDL, atherogenic index, incidence of hypertension and, a significantly lower HDL, compared to controls. Other characteristics like smoking status, disease duration, average DAS28, C-reactive protein levels, rheumatoid factor positivity, prevalence of diabetes mellitus, and medication use did not differ significantly between cases and controls. The crude OR of the annual flare rate and the occurrence of MI was 0.78 (95% CI: 0.48; 1.25). The OR adjusted for age, LDL, male gender, cholesterol, hypertension, and HDL was 0.97 (95% CI: 0.58; 1.68).

Conclusion: No significant association was found between annual flare rate and the occurrence of MI in RA patients. This implies that the presence of flares in disease activity does not contribute to the increased CVD risk in RA patients, in contrast to expectations.

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Abstract Number: 1551

Rheumatoid Vasculitis: A Decline in the XXI Century

Anne Riveros Frutos, Melania Martínez-Morillo, Samantha Rodriguez-Muguruza, Juana Sanint, Agueda Prior, Jeronima Cañellas, Susana Holgado, Maria Lourdes Mateo, Xavier Tena and Alejandro Olivé, Rheumatology, Hospital Universitari Germans Trias i Pujol, Barcelona, Spain
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Background/Purpose: Rheumatoid vasculitis is an extra articular manifestation of rheumatoid arthritis (RA), that occurs during the course of long standing disease. It is associated with a poor prognosis

Objectives: To describe the clinical characteristics, incidence, treatment, and outcome of patients diagnosed with rheumatoid vasculitis (RV) at a Rheumatology service of a University hospital during the last 30 years

Methods: Retrospective study (1984-2014). Location: University hospital. Referral area: 850.000 inhabitants. Medical records of patients with diagnosis of RA were reviewed, from the Rheumatology service data base. Inclusion criteria: patients with RV with histopathological confirmation of vasculitis or high suspicion based on clinical or radiological (arteriography) findings (according to Scott and Bacon criteria)

Results: A total of 18 patients were included: 6 (33.3%) females and 12 (66.7%) males, mean age of 10.13 ± 66.5 (49-83 years). The clinical characteristics of patients are listed in Table 1. The most common clinical presentation was skin involvement with palpable purpura and digital ulcers. Other common manifestations were multineuritis and systemic involvement. Heart, eyes, or pulmonary involvements secondary to RV were absent. Laboratory tests at diagnosis of RV, showed an increased of acute phase reactants and anemia. All patients had a positive rheumatoid factor, citrullinated antibodies were determined only in five (27.8%) cases, being positive in all of them.Histological confirmation was possible in 8 (44.4%) cases, in the other 10 (55.6%) cases the diagnosis was made with clinical or radiological findings. Most patients were treated with pulse steroids associated with other immunosuppressive drugs. Seven (38.9%) patients died. Three of them (16.7%) secondary to vasculitis, and 4 (22.2%) of other causes. The incidence of rheumatoid vasculitis has decreased considerably in the last decade. Just 4 cases were diagnosed during the last 10 years

Clinical characteristics		N (%) OR mean (range)
Comorbidities	HTA	9 (50%)
	Diabetes Mellitus	2 (11,1%)
	Smoker	9 (50%)
	Peripheral vascular disease	3 (16.7%)
Characteristics of RA	Disease duration (years)	5,8 ± 5,6 (1-17)
	Rheumatoid nodules	8 (44,4%)
	Radiographic erosions	11 (61,1%)
	Pulmonary involvement	3 (16,7%)
	Renal involvement	1 (5,6%)
Clinical presentation	Cutaneous vasculitis	12 (66,7%)
	Multineuritis	12 (66,7%)
	Mesenteric vasculitis	2 (11,1%)
	Systemic involvement	8 (44,4%)
	Renal involvement	1 (5,6%)
Laboratory	Leukocytosis (>$10x10^{9)}$	9 (50%)
	Anemia (Hb<12g/dl)	9 (50%)
	Thrombocytosis	2 (11,1%)
	ESR	70,76± 28,46 mm3
	C-reactive protein	50,27±56,77 mg/dl
	FR positive	18 (100%)
	ACPA positive	5 (100%)
	ANA positive	4 (22,2%)
	ANCA positive	4 (22,2%)
	Cryoglobulins positives	2 (11,1%)
	Hypocomplementemia	4 (22,2%)
AR treatment previous to the RV	NSAIDs	17 (94,4%)
	Glucocorticoids	16 (88,9%)
	Metotrexate	12 (66,7%)
	Antimalarial	9 (50%)
	D-penicillamine	4 (22,2%)
	Leflunomide	5 (27,8%)
	Gold salts	3 (16,7%)
Treatment of RV	Glucocorticoids	16 (88,9%)
	Cyclophosphamide	10 (55,6%)
	Gammaglobulin	1 (5,6%)
	Azathioprine	1 (5,6%)
	Rituximab	1 (5,6%)
Evolution	Improvement	10 (55,6%)
	Worsening	6 (33,4%)
	Unknown	2 (11,1%)
Recurrence		5 (27,8%)
Death		3 (16,7%)

Conclusion: RV is a rare complication of RA. Cutaneous and neurological involvement is more common. It is more frequent in male smokers with seropositive and nodular RA. Histological diagnosis is difficult. Currently the incidence is decreasing, however mortality is still high

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Illness Perceptions in Rheumatoid Arthritis: A Comparison of Canadian and Nigerian Patients

Susan J. Bartlett[1], Olufemi Adelowo[2], Maria Celia Bazan Bardales[3] and **Ines Colmegna**[4], [1]Medicine , Divisions of Clinical Epidemiology, Rheumatology, Respirology, McGill University, Montreal, QC, Canada, [2]Rheumatology, Arthrimed Specialist Clinic, Lagos, Nigeria, [3]Rheumatology, McGill University, Montreal, QC, Canada, [4]McGill University, Montreal, QC, Canada

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Background/Purpose: Illness perceptions (IP) are the beliefs and expectations that an individual has about medical conditions. IP cluster around five coherent themes and provide a framework for patients to make sense of their symptoms, assess health risk, and direct action and coping. Positive IPs have been associated with higher adherence, better disease outcomes and wellbeing in several chronic diseases while addressing negative or incorrect perceptions has been shown to improve disease outcomes. We explored IP of Canadian and Nigerian RA patients.

Methods: Consecutive RA patients at two academic centers (Montreal and Lagos) completed the Illness Perception Questionnaire–Revised from 2013-14. Sociodemographic (age, sex, and education) and disease characteristics (duration, treatment, CDAI, HAQ) were obtained and compared with t-tests and chi-square, Spearman correlations were calculated between IPQ-R scales and CDAI levels and t-tests and ANOVA were used to compare IPQ scores between countries and across disease activity levels.

Results: 83 Canadian and 30 Nigerian patients completed the survey. While there were no significant differences in the age, sex and education or use of biologics between groups, African participants reported shorter disease duration and had higher CDAI and patient global scores (Table 1). In Canadians, Timeline-Cyclic, Consequences, and Treatment Control were associated with CDAI (rho's=.28 to -.40; p<.05) whereas in Nigerians, Emotional Representations were moderately associated with CDAI (rho=.40; p<.05)(Table 2). Scores on Timeline – Chronic and Illness Coherence were significantly (p<.05) higher in Canadians whereas Treatment Control scores were significantly higher in Nigerians. Beliefs about causes of RA were similar in patients from both countries, although 'chance' or 'other factors' were cited by Nigerians.

Conclusion: Canadians were more likely to view their arthritis symptoms as coherent and chronic whereas Nigerians were more likely to view their RA as controllable through treatments but resulting in greater emotional distress. Understanding illness perceptions, beliefs about aetiology, and expectations about controllability may offer new insight into patient behaviors (e.g., adherence to treatment) that impact long-term outcomes.

Table 1. Characteristics of Participants in Canada and Nigeria

Characteristic	**Canada**	**Nigeria**	**Sig**
N	83	30	
Age (yrs)			.583
18-29	6 (7%)	2 (7%)	
30-49	34 (45%)	16 (53%)	
50-69	31 (37%)	10 (33%)	
70+	12 (14%)	2 (7%)	
Female (%)	66 (80%)	24 (83%)	.705
Education (yrs)	15 (4)	16 (5)	.607
RA duration (yr)			.018
< 1	13 (16%)	13 (43%)	
1-5	32 (39%)	6 (20%)	
5-10	18 (22%)	5 (17%)	
10+	20 (24%)	6 (20%)	
Biologics (ever)	23 (28%)	4 (14%0	.117
HAQ	.55 (.64)	N/A	
Tender (28)	3.5 (4.5)	6.5 (7.4)	.013
Swollen (28)	2.3 (3.7)	3.9 (5.8)	.086
Patient Global	2.7 (2.4)	3.8 (2.3)	.027
CDAI	10.4 (10.2)	17.4 (13.9)	.005
Remission	22 (27%)	1 (3%)	.017
Low	29 (35%)	11 (38%)	
Moderate	22 (27%)	8 (28%)	
High	10 (14%)	9 (31%)	
Values are mean ± SD unless otherwise indicated			

Table 2. Association of IPQ Scales with CDAI and mean scores by disease activity level.

IPQ-R Subscale (range)	CDAI (rho)		All		Remission		Low		Moderate		High	
	CAN	NIG	CAN	NIG	CAN N=22	NIG N=1	CAN N=29	NIG N=11	CAN N=22	NIG N=11	CAN N=10	NIG N=9
Identity	.08	.59	5 (2)	7 (3)	5 (3)	---	5 (3)	5 (1)	6 (2)	4 (1)	6 (2)	9 (3)
Timeline Chronic (6-30)	.17	-.21	23 (5)	14 (6)*	22 (6)	18	22 (6)	14 (7)	24 (4)	15 (5)	23 (5)	12 (7)
- Cyclical (4-20)	**.38**	-.02	13 (3)	12 (4)	**12 (4)^{a}**	16	**13 (4)^{a,b}**	11 (4)	**14 (3)^{b}**	12 (4)	**15 (2) ^{b,c}**	12 (3)
Consequences (6-30)	**.28**	**.38**	20 (5)	21 (5)	**18 (5)^{a}**	19	**19 (5)^{a}**	18 (5)	**20 (4)^{a,b}**	23 (3)	**23 (4)^{b}**	23 (5)
Control – Treatment (5-25)	**-.40**	.06	19 (3)	21 (3)*	**20 (3)^{a}**	14	**18 (3)^{b}**	21 (4)	**18 (3)^{b}**	20 (2)	**18 (2)^{b}**	22 (3)
-- Personal (6-30)	-.13	.20	22 (4)	22 (6)	23 (4)	18	21 (3)	21 (5)	21 (4)	23 (4)	22 (4)	21 (8)
Understanding of RA (5-25)	-.09	-.17	18 (4)	16 (5)*	18 (5)	11	18 (4)	18 (5)	18 (4)	15 (4)	16 (4)	15 (6)
Emotional Response (6-30)	.15	**.40**	17 (6)	19 (7)†	15 (6)	**7**	17 (5)	**16 (6)^{a}**	16 (6)	**20 (7)^{a,b}**	18 (6)	**22 (5)^{b}**

*p<.05; †p=.07. Different superscripts indicate significant different groups using Duncan's tests.

Table 3. Participant rankings of top three causes of RA by country.

	Canada	Nigeria
Risk Factors (genetics, diet, aging, smoking, previous medical care)	40 (48%)	12 (40%)
Altered Immunity (germs/virus, pollution, changes in immunity)	17 (21%)	6 (20%)
Psychological Factors (stress, negative emotions, overwork	14 (17%)	5 (17%)
Don't Know	9 (11%)	2 (7%)
Accident / chance	3 (4%)	2 (7%)
Other (spiritual, cold, drug reaction)	--	3 (10%)
chi square .091		

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Abstract Number: 1553

Effect of Drug Therapy on Net Cholesterol Efflux Capacity of HDL-Enriched Serum in Rheumatoid Arthritis

Michelle J. Ormseth[1], S. Louis Bridges Jr.[2], Jeffrey R. Curtis[3], Joseph F. Solus[4], Patricia Yancey[5], MacRae F. Linton[6], Sean Davies[6], L Jackson Roberts II[7], Kasey C. Vickers[6], Valentina Kon[6], Sergio Fazio[8], C Michael Stein[6] and TETRAD Investigators, [1]Department of Medicine, Division of Rheumatology, Vanderbilt University, Nashville, TN, [2]Clinical Immunology and Rheumatology, University of Alabama at Birmingham, Birmingham, AL, [3]University of Alabama at Birmingham, Birmingham, AL, [4]Clinical Pharmacology, Vanderbilt University, Nashville, TN, [5]Medicine, Vanderbilt University, Nashville, TN, [6]Vanderbilt University, Nashville, TN, [7]Pharmacology, Vanderbilt University, Nashville, TN, [8]Oregon Health and Science University, Portland, OR
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Background/Purpose: Patients with rheumatoid arthritis (RA) have increased coronary heart disease risk. Some RA therapies may modify this risk, but underlying mechanisms are unclear. The cholesterol efflux capacity of HDL (the ability of HDL to remove cholesterol from lipid-laden macrophages) is associated with reduced coronary heart disease risk in non-RA populations. Inflammation can impair the function of HDL. We hypothesized that better control of inflammation with methotrexate, adalimumab and tocilizumab would increase the net cholesterol efflux capacity of HDL-enriched serum in patients with RA.

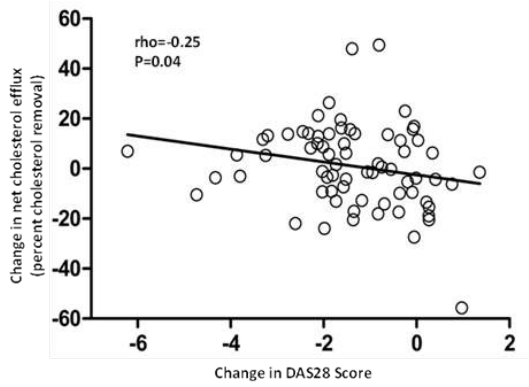
Methods: A longitudinal multi-center study (Treatment Efficacy and Toxicity in Rheumatoid Arthritis Database and Repository or TETRAD) obtained clinical information and serum samples from 70 patients with RA before and 6 months after starting a new therapy for RA. RA disease activity was measured by DAS28. The study included patients starting methotrexate (n=23), adalimumab (n=22), and tocilizumab (n=25). Net cholesterol efflux capacity of HDL-enriched serum was measured on paired serum samples using THP-1 macrophages and a fluorometric assay for cholesterol measurement. Wilcoxon signed rank tests were used to compare paired continuous data.

Results: DAS28 score decreased significantly in all three groups after treatment (P<0.001). Net cholesterol efflux capacity (mean± SD) was not significantly changed after 6 months of new therapy (baseline, 36.9% units ± 17.3 vs. 6 months, 38.0% units ± 16.9, P=0.58) (Table). Change in cholesterol efflux capacity was modestly associated with change in DAS28 (rho=-0.25, P=0.04) (Figure). Among patients with baseline impaired net cholesterol efflux capacity (efflux capacity below mean), tocilizumab resulted in modest, significant improvement in net cholesterol efflux (baseline, 21.9% units ± 14.7 vs. 6 months, 31.1% units ± 12.8, P=0.02), but this was not observed with methotrexate or adalimumab users or among those with normal baseline efflux capacity (all P>0.05).

Conclusion: The net cholesterol efflux capacity of HDL did not change significantly after 6 months of new RA therapy but was weakly associated with change in disease activity. Among patients with impaired net cholesterol efflux capacity at baseline, there was a modest improvement after treatment with tocilizumab, but not with methotrexate or adalimumab. Further studies are needed to define the relationship between cholesterol efflux capacity and coronary heart disease risk in patients with RA.

Table: Net cholesterol efflux capacity before and after DMARD or biologic therapy

	Baseline	6 Months	Absolute Change	P value
All patients				
All drugs (N=70)	36.9% ± 17.3	38.0% ± 16.9	1.1% ± 16.6	0.58
Methotrexate (N=23)	41.2% ±13.9	38.0% ± 17.5	-3.3% ± 20.2	0.38
Adalimumab (N=22)	36.1% ±16.8	38.5% ± 18.2	2.3% ± 14.6	0.44
Tocilizumab (N=25)	33.7% ± 20.1	37.6% ± 15.8	3.9% ± 14.2	0.23
Patients with impaired baseline net cholesterol efflux				
All drugs (N=37)	24.1% ±11.3	31.0% ±12.4	6.8% ±15.7	0.02
Methotrexate (N=10)	28.8% ± 9.5	34.0% ± 12.6	5.1% ± 19.7	0.80
Adalimumab (N=12)	22.9% ± 6.6	28.0% ± 14.5	5.1% ± 14.4	0.27
Tocilizumab (N=15)	21.9% ± 14.7	31.3% ± 12.8	9.4% ± 14.4	0.02



Abstract Number: 1554

Severe Pneumonia after a 13-Prevalent Pneumonoccal Conjugate Vaccine (Prevena 13) Among Patients with Rheumatoid Arthritis

Sung Hae Chang[1] and Seong-Su Nah[2], [1]internal medicine, seoul national university, seoul, South Korea, [2]Soonchunhyang clinical medical research center, Department of Soonchunhyang clinical medical research center, Choenan, South Korea

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Background/Purpose: Disease modifying anti-rheumatic drugs (DMARDs) including methotrexate (MTX) and biologics were ported to attenuate response to a previous 23-prevalent pneumococcal polysaccharide vaccine. Recently, a 13-prevalent pneumococcal conjugate vaccine (PCV13) for adults became easily available but clinical outcome has never been evaluated. Here, we investigated clinical outcomes and associated factors of severe pneumonia after PCV13 administration.

Methods: : We searched patients who received 13-prevalent pneumonoccal vaccine rheumatologic clinic of Cheonan Soonchunhyang university hospital. Severe pneumonia defined as pneumonia requiring in-hospital treatment. We investigated history of severe pneumonia and underlying lung disease including interstitial lung disease (ILD), asthma, chronic obstructive pulmonary disease (COPD) and pneumoconiosis. A total cumulative dose of glucocorticoid and history administration of biologics or DMARDs after PCV13 injection was also investigated. The Chi-Square or Fisher's exact test and Mann-Whiteney test was used assessing association between above mentioned factors and severe pneumonia as appropriate.

Results:

Among a total of 123 patients, female was 82.1 % (101/123) and the mean (standard deviation, SD) follow-up duration was 22.2 (8.0) weeks. The mean (SD) age were age 54.7 ± 14.2 equal or 34 of 123 patients (27.6%) were more than 65 year-old. Thirteen patients had underlying lung disease: ILD= 4, asthma or COPD = 7, bronchiectasis = 6 and pneumoconiosis = 1. One- hundred-four (84.6%), 97 (78.9%), 40 (32.5) and 38 (30.9%) patients were experienced MTX, hydroxycholoroquine, sulfasalazine, and leflunomide respectively. Numbers of patients who had history of biologics use during follow-up duration were as follows: adalimumab 31 (35.2%), etanercept 7 (5.7%), infliximab 10 (8.1%), golimumab 4 (3.3%), tocilizumab 6 (4.9%), and abatacept 5 (4.1%). The mean (SD) of cumulative glucocorticoid dose was 2875.6 (2475.8) of prednisolone. After PCV13, 5.7% (7/123) of patients had severe pneumonia requiring in-hospital treatment during a mean of 22.2 weeks of follow-up. The presence of underlying lung disease ($p = 1.1 \times 10^{-4}$ by Fisher's exact test) and a total cumulative glucocorticoid dose ($p = 0.014$ by Mann-Whitney test) was associated with development of severe pneumonia but age (≥ 65 year-old) or other medication including DMARDs and biologics was not.

Conclusion:

After PCV13 administration, development of severe pneumonia was associated with underlying lung conditions and cumulative glucocorticoid dose but not with age or biologics use.

Disclosure: S. H. Chang, None; **S. S. Nah**, None.

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Abstract Number: 1555

Geography and the Influence of Comorbidity on the Prevalence of Depression in Patients with Rheumatoid Arthritis,a Study Across Seventeen Countries

Raluca Dumitru[1], Elizabeth M.A. Hensor[2], Ihsane Hmamouchi[3], Paul Emery[2], Maxime Dougados[4] and Maya H. Buch[5], [1]University of Leeds, Leeds Institute of Molecular Medicine and LMBRU, Leeds, United Kingdom, [2]Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds, Leeds, United Kingdom, [3]El Ayachi Hospital, Rabat, Morocco, [4]Service de Rhumatologie B, GHU Cochin, F-75014 France, PARIS, France, [5]Division of Rheumatic and Musculoskeletal Disease, University of Leeds, Leeds Institute of Molecular Medicine and LMBRU, Leeds, United Kingdom

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Background/Purpose: Comorbidities represent a major challenge for patients with rheumatoid arthritis. Depression is one of the most common comorbidities with prevalence up to 38%. Disease activity measures and comorbidities show inconsistent association with depression. There is limited data assessing the prevalence of depression and its association with clinical characteristics in a large cohort, among different countries.

Objectives: Our study aimed to assess the prevalence of depression diagnosis and patient-reported anxiety or depression and their association with 28-disease activity score (DAS28) and comorbidity among 17 different countries, using the COMORA dataset[1] ('Prevalence of Comorbidities in Rheumatoid Arthritis and evaluation of their monitoring: results of an international, cross-sectional study').

Methods: Demographics, clinical characteristics, treatment and comorbidities were recorded for each patient. Multilevel binary logistic regression models were constructed for depression diagnosis (DD) and for patient-reported anxiety or depression (PRAD). An initial null model tested for inter-country differences in prevalence. Unadjusted models were then built for each independent variable (DAS28 and comorbidity). Models were then adjusted for age and sex.

Results: 3674 patients from 17 countries were included [mean (SD) age 56 (13) years; DAS28 3.72 (1.5)]. 30% were diagnosed with at least one comorbidity, 15% with a depression diagnosis and 38% reported anxiety or depression. Moving from a lower to a higher risk country increased the odds of DD and PRAD by a median of 2.5 and 1.76 fold respectively. In unadjusted models, DAS28 and comorbidity count were positively associated with the measures of depression. Adjusting for age and sex, the association between DAS28 and odds of DD showed borderline-significant variation between countries (p=0.053); in the 'average' country there was no association, but the higher a country's mean DAS28, the greater the increase in the odds of DD for each unit of DAS28. The number of comorbidities was positively associated with the odds of DD and the association did not vary between countries. DAS28 and comorbidity count were positively associated with the odds of PRAD and neither of these associations differed significantly by country.

Conclusion: This study confirms that RA patients have a high prevalence of depression and that this varies between countries. Comorbidity is associated with prevalence of depression whilst the association with DAS28 is more variable. These data suggest that country level factors and additional comorbidity play particularly important roles for depression.

References: 1 Dougados M, Ann Rheum Dis, 2014.

Table 1: Logistic regression models of depression diagnosis and patient-reported anxiety or depression.

Outcome	Depression diagnosis	Anxiety or depression
Null model:		
Intercept (95% CI)	-1.89 (-2.32, -1.46)	-0.59 (-0.86, -0.32)
Intercept variance (95% CI)	0.74 (0.34, 1.59)	0.29 (0.14, 0.61)
Intercept LR test: Chi-sq, p	205.0, p<0.001	204.8, p<0.001
Median odds ratio (95% CrI)	2.47 (1.82, 3.74)	1.76 (1.46, 2.28)
Unadjusted models:		
DAS28-ESR (95% CI), p	0.11 (0.04, 0.17), p=0.002	0.40 (0.35, 0.45), p<0.001
Comorbidity (95% CI), p	0.25 (0.12, 0.38), p<0.001	0.24 (0.14, 0.35), p<0.001
Adjusted model:		
Age (95% CI), p	-0.01 (-0.09, 0.07), p=0.806	0.02 (-0.04, 0.08), p=0.486
Female (95% CI), p	0.69 (0.40, 0.98), p<0.001	0.53 (0.33, 0.73), p<0.001
Comorbidity (95% CI), p	0.26 (0.12, 0.40), p<0.001	0.21 (0.10, 0.33), p<0.001
DAS28-ESR (95% CI), p	0.04 (-0.06, 0.14), p=0.409	0.38 (0.33, 0.44), p<0.001
Comorbidity LR test: Chi-sq, p	1.53, p=0.464	0.23, p=0.891
DAS28-ESR LR test: Chi-sq, p	5.88, p=0.053	5.27, p=0.072
DAS28-ESR slope variance (95% CI)	0.01 (0.00, 0.07)	n/a
DAS28-ESR I-S covariance (95% CI)	0.08 (-0.02, 0.18)	n/a
DAS28-ESR I-S correlation	0.78	n/a
Values presented are logits (log-odds) unless otherwise stated. Chi-sq Chi-square; CI Confidence Interval; CrI Credible Interval; I-S Intercept-Slope; LR likelihood ratio		

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Abstract Number: 1556

The Medication Information-Seeking Behaviors of Rheumatoid Arthritis Patients Who Are Prescribed a New DMARD

Delesha Carpenter[1], Lorie Geryk[2], Courtney Arrindell[3], Beth Jonas[4] and Susan J. Blalock[5], [1]Division of Pharmaceutical Outcomes and Policy, University of North Carolina Eshelman School of Pharmacy, Asheville, NC, [2]Division of Pharmaceutical Outcomes and Policy, University of North Carolina Eshelman School of Pharmacy, Chapel Hill, NC, [3]University of North Carolina at Chapel Hill, Chapel Hill, NC, [4]Thurston Arthritis Research Ct, UNC-Chapel Hill, Chapel Hill, NC, [5]School of Pharmacy, UNC at Chapel Hill, Chapel Hill, NC

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Background/Purpose:

We present preliminary longitudinal data about the information-seeking behaviors and medication experiences of RA patients who are prescribed a new DMARD.

Methods: We recruited a convenience sample of 32 adult English-speaking RA patients who were prescribed a new self-administered DMARD from one rheumatology clinic in a southeastern state. At the office visit during which the new DMARD was prescribed, patients reported demographic characteristics and satisfaction with DMARD information provided by their rheumatologist (alpha=0.89). Patients then used a 1-week medication diary to document their experiences with side effects. Patients also completed a 1-week and 1-month follow-up telephone interview during which they reported their use of 15 DMARD information sources, whether their DMARD prescription had been filled, and their medication adherence (8-item Morisky Medication Adherence Scale). We calculated descriptive statistics to describe the sources of DMARD information that patients consulted most often. We examined bivariate associations to determine correlates of DMARD information-seeking and ran a linear regression to examine whether information-seeking predicted DMARD adherence at 1-month follow-up. The regression controlled for patient age, gender, race, reading level, disease duration, and whether DMARD side effects had been experienced (yes/no).

Results: Participants were primarily women (91%) and white (70%). The mean age and disease duration were 48.3 (SD=14.1) and 9.4 years (SD=9.4), respectively. Only 3 (10%) of patients were not satisfied with the DMARD information provided by their rheumatologist. Within 1 week of their office visit, 88% of patients had sought DMARD information; most commonly from brochures/pamphlets (57%), medication package inserts (55%), and the Internet (47%). Patients who experienced side effects sought more information ($t_{(26)}$ =2.27, $p<0.05$) and older patients sought less information ($r=-0.42$, $p<0.05$). Between 1-week and 1-month follow-up, 73% of patients sought additional DMARD information. At 1-month follow-up, 10 patients still had not filled their DMARD prescription, primarily due to lack of insurance approval or cost. Patients who sought greater amounts of information were less adherent (beta=-0.78, $p<0.001$).

Conclusion: Most RA patients seek information about their DMARDS. Information-seeking is influenced by demographic characteristics and their experience with side effects. Patients who sought more information were less adherent.

Disclosure: D. Carpenter, None; **L. Geryk**, None; **C. Arrindell**, None; **B. Jonas**, None; **S. J. Blalock**, None.

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Abstract Number: 1557

The Impact of Hindfoot Deformity on Disability of Korean Patients with Rheumatoid Arthritis

Hye-Jin Jeong[1], Il Woong Sohn[1], Seung Lee[1], Seung Taek Song[1], Soo-Kyung Cho[2] and Yoon-Kyoung Sung[2], [1]Hanyang University Hospital for Rheumatic Diseases, Seoul, South Korea, [2]Department of Rheumatology, Hanyang University Hospital for Rheumatic Diseases, Seoul, South Korea
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Background/Purpose: Rheumatoid arthritis (RA) commonly involves the hindfoot, but this part is frequently overlooked when caring for patients with multiple joints pain and deformity. For example, disease activity score (DAS)-28 is most widely used assessment tool of disease activity, but the joints in the feet including hind foot are not included in the 28 joint count. Functional disability has been identified as a core outcome measure in RA and it is affected by various factors. However, until now, there have been few studies performed to assess the impact of hindfoot deformity on the functional disability of RA patients. This study aims to evaluate the impact of hindfoot deformities on the functional disability of RA patients.

Methods: In this cross-sectional study, we evaluated about foot deformities using AP and lateral views of simple radiography. The deformities of feet were divided into three parts: the hindfoot, midfoot, and forefoot deformity. We compared the clinical features including HAQ score of RA patients according to the presence of hindfoot deformity, and then performed univariate and multivariable logistic analyses to find the impact of hindfoot deformities on functional disability.

Results: A total of 120 patients (113 females, 7 males) with a mean age of 46.9 years were included in this study. The prevalences of hindfoot, midfoot and forefoot deformities were 33 (27.5%), 41 (34.2%) and 49 (40.8%), respectively. Patients who had hindfoot deformity showed longer disease duration, higher disease activity, higher functional disability, and commonly prescribed with biologic DMARDs comopared with patients without hindfoot deformity. In the univariate analysis, hindfoot deformity showed 4.2 fold increased risk of higher functional disability group (HAQ score $\geq$ 0.5 as a median). After adjusting age, disease duration, disease activity, biologic DMARD use, and other feet deformities, hindfoot deformity showed high odds ratio (OR) but not statistically significant (OR 2.6, 95% CI 0.77-8.57).

Conclusion: The hindfoot deformities might be associated with functional disability of RA patients. Further study with large sample size will be helpful to identify the impact of hindfoot deformity on the functional disability of RA patients.

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Abstract Number: 1558

Serum Cathepsin S and Cystatin C Relation with Carotid Subclinical Atheromatosis in Rheumatoid Arthritis Patients

Beatriz Tejera Segura[1], De Vera-González AM[2], Raquel López-Mejías[3], Miguel A. Gonzalez-Gay[4] and Ivan Ferraz-Amaro[1], [1]Division of Rheumatology, University Hospital of Canary Islands, Tenerife, Spain, [2]Central Laboratory Division, University Hospital of Canary Islands, Tenerife, Spain, [3]Rheumatology, Hospital Universitario Marqués de Valdecilla. IFIMAV, Santander, Spain, [4]Reumatologia, Hospital Universitario Marqués de Valdecilla, IDIVAL, University of Cantabria, Santander, Spain

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Background/Purpose: Rheumatoid arthritis (RA) is a chronic inflammatory disease associated with increased cardiovascular risks. Cathepsin S, a cysteine protease implicated in intracellular and extracellular proteolysis, and its endogenous inhibitor cystatin C has been both associated with increased cardiovascular mortality in general population.

Objective. To assess if serum cathepsin S and cystatin C, two novel markers of cardiovascular disease risk are associated with subclinical carotid atherosclerosis in RA patients.

Methods: Serum cystatin C and cathepsin S levels, ultrasound carotid intima-media thickness (cIMT) and carotid plaques were assessed in a cross-sectional study involving 178 RA patients.Multivariate regression analysis was assessed to study the relationship between cathepsin S and cystatin C serum levels and cardiovascular risk factors and disease related data.

Results: Mean cIMT was 0.670 ± 0.143 mm, and 66 patients (37%) had carotid plaques in the carotid ultrasound assessment. Both cystatin C and cathepsin S were significantly associated with hypertension, diabetes and dyslipidemia. Cathepsin S was inversely related with male gender whereas cystatin was strongly associated with age. Regarding RA related data; cathepsin S was associated with disease duration and cystatin C was positively related with higher levels of ESR. Neither positive rheumatoid factor nor prednisone use were associated with cystatin C or cathepsin S. A trend for lower levels of cystatin C was observed in patients undergoing anti-TNF-alpha therapy (*log* beta coef. -0.20 (-0.44-0.04), p=0.09). An association between disease activity scores with higher levels of cystatin C, but not with cathepsin S, was found. Cystatin C levels were associated with cIMT in the subgroup of patients included in the higher quartile of cIMT (OR 1.31, 95%CI [1.00-1.72], p=0.04) after adjusting for traditional cardiovascular risk factors, age and sex. An association between serum cystatin C levels and carotid plaques was also found in the univariate analysis (OR 1.37, 95%CI [1.06-1.76], p=0.02). However, this significant association was lost after adjusting for traditional cardiovascular risk factors and age. Cathepsin S was not associated with cIMT or carotid plaques.

Conclusion: High cystatin C serum levels identify a subgroup of RA patients with a high risk of subclinical atherosclerotic disease.

Disclosure: B. Tejera Segura, None; **D. V. G. AM**, None; **R. López-Mejías**, None; **M. A. Gonzalez-Gay**, None; **I. Ferraz-Amaro**, None.

Abstract Number: 1559

Clinical Characteristics and Medication Use Among Arab Patients with Rheumatoid Arthritis in Some Arab States

Karim Bayoumy[1], Soha Roger Dargham[1], Wessam Elhaq[1], Samar Al Emadi[2], Mohammed Hammoudeh[2], Basel Masri[3], Hussein Halabi[4], Humeira Badsha[5], Imad Uthman[6], Salah Mahdy[2], Robert Plenge[7], Richa Saxena[7], Marianthi Kapiri[1] and Thurayya Arayssi[8], [1]Weill Cornell Medical College in Qatar, Doha, Qatar, [2]Medicine, Hamad Medical Corporation, Doha, Qatar, [3]Jordan Hospital, Amman, Jordan, [4]Medicine, King Faisal Specialist Hospital and research center, Jeddah, Saudi Arabia, [5]Al Biraa Arthritis and Bone Clinic, Dubai, United Arab Emirates, [6]Internal Medicine, American University of Beirut, Beirut, Lebanon, [7]The Broad Institute of MIT and Harvard, Program of Medical and Population Genetics, Cambridge, MA, [8]Internal Medicine, Weill Cornell Medical College in Qatar, Doha, Qatar

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Background/Purpose:

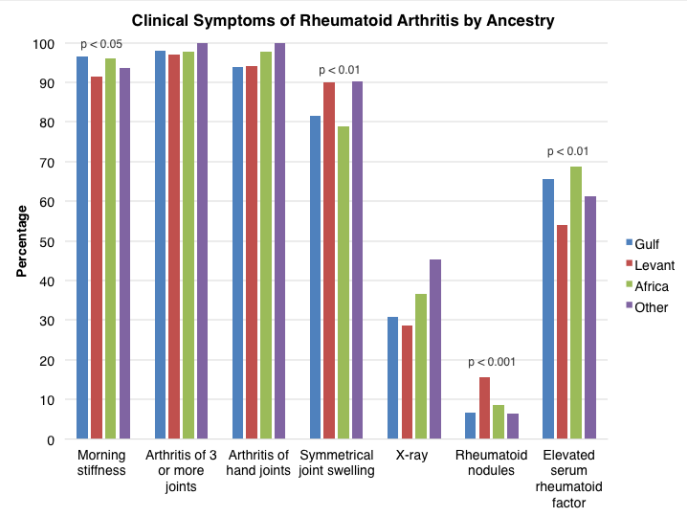
Data on the clinical and genetic characteristics of Arab patients with Rheumatoid Arthritis (RA) is limited. Our aim is to report on the clinical manifestations of the first 844 patients recruited into "The Genetics of Rheumatoid Arthritis in some Arab States (GRASS) study".

Methods:

GRASS is a multicenter case-control study that aims to study the clinical and genetic characteristics of patients of Arab ancestry. Subjects were recruited from 5 centers in Jordan, Kingdom of Saudi Arabia (KSA), Lebanon, Qatar and the United Arab Emirates (UAE). To be eligible for enrollment, subjects had to be 1) of Arab ancestry by self-report, 2) be > 18 years of age. Cases had to be diagnosed as per the 1987 ACR RA criteria. Controls were eligible if they did not have RA or autoimmune disease. Ancestry, demographic, lifestyle, clinical and treatment data was collected via an on-line questionnaire by interviewing the subjects and retrieving information form the medical records. Ancestry was classified into 3 categories as Gulf, Levant or North Africa, when 3 or more grandparents were from the same region. Subjects, which did not fall under those categories for ancestry, were classified as "Other". Data were analyzed using Pearson Chi Square and Fisher's Exact tests.

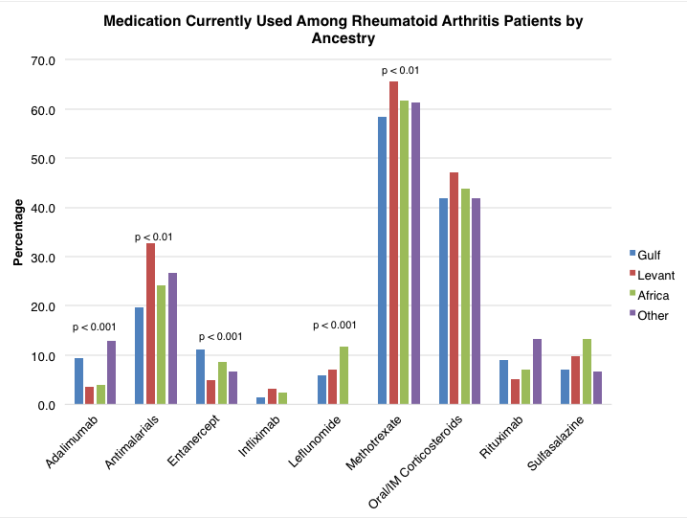
Results:

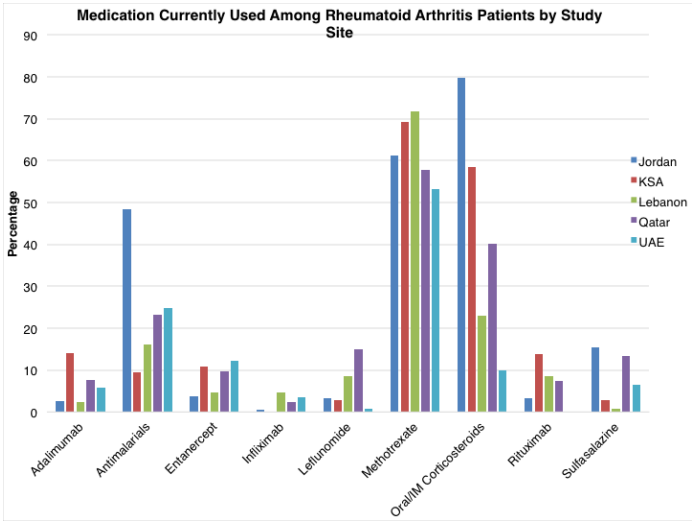
A total of 844 cases, 718 (85.1%) women and 126 men (14.9%) (F/M: 6/1), were enrolled from June 2012 to April 2015. The most common age range of diagnosis for both genders was 30-49(not significant when stratified by study site or ancestry, p>0.05).



The rates of CCP positive, RF positive, CCP/RF positive and seronegative cases differed based on ancestry (p<0.01, excludes the UAE). CCP/RF positive cases were the most common for all ancestries, with The Gulf (174,62.4%) and North Africa (63,62.4%) showing an equal rate of CCP/RF positive cases followed by "Other" (14, 50.0%) and the Levant (48.3). The Levant (77, 26.2%) and "Other" (7, 25.0%) showed a higher rate of seronegative cases than the Gulf (38, 13.6%) and North Africa (15, 14.9%).

Medication use:





Conclusion:

The clinical characteristics of RA and its medical management differ between Arabs of different ancestries found in the Arab region. These differences must be further explored in the context of genetic factors and the influence of GDP on medication use.

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Abstract Number: 1560

The Effect of Anti Estrogen Therapy (AET) on Rheumatoid Arthritis

Bassam Alhaddad[1], Amrita Kaur Bath[2], Bassem Zraik[3], Mohamed Alalwani[4] and Stanley P Ballou[1], [1]Rheumatology, Case Western Reserve University, MetroHealth Medical Center, Cleveland, OH, [2]Internal medicine, Fairview Hospital- Cleveland Cinic, Cleveland, OH, [3]Internal Medicine, Fairview Hospital- Cleveland Clinic, cleveland, OH, [4]Hospital Medicine, Cleveland Clinic, Cleveland, OH

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Background/Purpose: The well-known positive effect of pregnancy on improving Rheumatoid Arthritis (RA) disease activity suggests that hormonal changes may play a role in disease pathogenesis and raises a concern that anti-estrogen therapy (AET) including Aromatase Inhibitors [AI] and selective estrogen receptor modulators [**SERMs**] may have an adverse effect on RA. AI can cause musculoskeletal symptoms including AI induced arthritis. Recent observations by our group suggest an increased incidence of RA among patients using either AI or SERMs (1). We intended to examine the effect of AET on disease activity in patients with established RA.

Methods: We searched the electronic medical records in 2 medical centers for patients with the diagnoses of both breast cancer and RA. Of 435 charts reviewed, we identified 40 who had validated RA diagnosis, used SERMs or AI for breast cancer and had appropriate rheumatology evaluation. Data collected included age, BMI, smoking, RA disease duration, clinical status, serology and medication use. The primary outcome measure was worsening of disease within 6 months of AET initiation compared to the most recent evaluation prior to AET, using 2 visits before and 2 after AET. Worsening was defined as an increase in swollen & tender joint count, patient and/or physician global assessment, or documented flare/worsening by rheumatologist assessment, including the need to discontinue AET or modify RA therapy. Worsening could not be attributed to changes or discontinuation of RA therapy. We also reviewed patients who developed RA following initiation of AET.

Results: Thirty eight patients were analyzed. Mean age was 59 years and median duration of RA prior to cancer diagnosis was 8.2 years. AETs used included tamoxifen (6), anastrazole (23) and other AI (9). RA clinical status prior to AET initiation was classified as complete remission (25%), stable (55%) and active (20%), 76.7% were seropositive. Seven patients developed new onset seropositive RA with a mean of 12 months (1-24 months) following initiation of AI (5 patients) and tamoxifen (2). RA worsened in 18 out of 31 patients (58%) after initiating AET, primarily after AI (16/18 patients). On comparing patients who worsened to those who did not (table 1), worsening group was significantly more likely to be younger and seropositive, while age and BMI did not differ between groups. Eighty three percent of patients who were not on DMARDs or biologics worsened while the patients who were maintained on biologics did not.

Table 1: Comparison of Patients with and without RA worsening

Factor	Total (N=31)	Worsening Yes (N=18)	Worsening No (N=13)	p-value
Disease status				0.61[d]
. Remission	8(25.8)	6(33.3)	2(15.4)	
. Stable/Mild	17(54.8)	9(50.0)	8(61.5)	
. Active	6(19.4)	3(16.7)	3(23.1)	
smoking				0.48[d]
• **yes**	10(32.3)	5(27.8)	5(38.5)	
• **No**	21(67.7)	13(72.2)	8(61.5)	
seropositive				***0.025[d]***
. Yes	23(76.7)	16(94.1)	7(53.8)	
. No	7(23.3)	1(5.9)	6(46.2)	
chemotherapy				0.40[d]
. Yes	7(24.1)	3(17.6)	4(33.3)	
. No	22(75.9)	14(82.4)	8(66.7)	
No RA meds or prednisone only				***0.023[c]***
. RA Meds	19(61.3)	8(44.4)	11(84.6)	
. Prednisone or None	12(38.7)	10(55.6)	2(15.4)	
DMARD				0.47[c]
. No DMARD	19(61.3)	12(66.7)	7(53.8)	
. DMARD	12(38.7)	6(33.3)	6(46.2)	
On biologics				***0.023[d]***
. No Biologics	27(87.1)	18(100.0)	9(69.2)	
. Biologics	4(12.9)	0(0.0)	4(30.8)	
Patient Age(Years)	59.2±17.0	54.7±19.0	65.3±11.7	0.085[a]
Disease duration(Years)	7.1±8.5	7.6±10.2	6.3±4.9	0.71[a]
BMI	29.6±8.6	28.0±7.1	31.8±10.3	0.23[a]

Values presented as Mean ± SD, Median [P25, P75], Median (min, max) or N (column %).

p-values: a=ANOVA, b=Kruskal-Wallis test, c=Pearson's chi-square test, d=Fisher's Exact test.

Conclusion: Our study includes the largest reported number of new onset RA cases following the initiation of AET, Our data suggest that use of AET may worsen RA in patients with established disease, especially in those who are not on DMARDs or biologic therapy.

References: 1-Chen JY, Ballou SP. The Effect of Antiestrogen Agents on Risk of Autoimmune Disorders in Patients with Breast Cancer. J Rheumatol. 2014 Oct 1

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Abstract Number: 1561

The Effect of TNF Blockers on Bone Mineral Density in Rheumatoid Arthritis Patients Receiving Bisphosphonate

Doo-Ho Lim[1], Seokchan Hong[2], Soo Min Ahn[2], Byeongzu Ghang[3], Wook Jang Seo[4], Yong-Gil Kim[1], Chang-Keun Lee[1] and Bin Yoo[1], [1]Division of Rheumatology, Department of Internal Medicine, Department of Rheumatology, University of Ulsan College of Medicine, Asan Medical Center, Seoul, South Korea, [2]Division of Rheumatology, Department of Internal Medicine, University of Ulsan College of Medicine, Asan Medical Center, Seoul, South Korea, [3]Division of Rheumatology, Department of Internal Medicine, Univerisy of Ulsan College of Medicine, Asan Medical Center, Seoul, South Korea, [4]Internal Medicine, Seoul Veterans Hospital, Seoul, South Korea

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Background/Purpose:

Osteoporosis is more frequently observed in patients with rheumatoid arthritis (RA) than in general population. Bisphosphonate (BP), which suppresses bone resorption by inhibiting osteoclast activation, has been most commonly used for treatment of osteoporosis. Previous studies demonstrated that anti-TNF therapy has a beneficial effect on bone loss possibly through anti-inflammatory effects as well as its inhibitory effects on osteoclast activation. However, there have been few studies assessing the role of TNF blocker for osteoporosis in RA patients under concomitant treatment with BP. Therefore, we performed a retrospective longitudinal study to investigate the changes in bone loss in RA patients received BP with or without TNF blockers.

Methods:

The study cohort consisted of 107 RA patients who were diagnosed with osteoporosis and treated with BP, at a tertiary referral center from Jan. 2005 to Dec. 2013. The areal bone mineral density (BMD) (g/cm^2) of the lumbar spine, femur neck, trochanter and total femur was measured by dual-energy X-ray absorptiometry. Follow-up BMD was obtained at 1.22 ± 0.36 years after initial acquisition of BMD. The rate of change in the BMD was expressed as the annualized percentage change of BMD between initial measurement and subsequent measurement.

Results:

Among RA patients receiving BP with (n = 19) and without TNF blockers (n = 88), 19 (100.0 %) and 80 (90.9 %) were women, respectively. The mean ages at initial BMD for these subjects were 67.4 ± 10.3 years (range, 46 - 84 years) and 66.1 ± 8.3 years (range, 43 - 83 years), respectively (P = 0.569). There was no significant difference in baseline clinical characteristics including laboratory data, baseline BMD and dose of corticosteroid between the two groups. With BP Treatment, follow-up BMD was significantly increased at the area of lumbar spine in RA patients regardless of concomitant use of TNF blockers. Further, there were no statistical significant differences in annualized BMD changes between RA patients receiving BP with or without TNF blockers, although there was a numerical difference in the BMD changes between the two groups (Table 1).

Conclusion:

In RA patients with osteoporosis receiving BP, there was a no significant additional effect of TNF blockers for bone loss. Therefore, administration of BP is still important in treatment of osteoporosis in patients with RA, even in those who were taking TNF blockers.

Table 1. Comparison of mean annualized changes of BMD between patients with and without TNF-blockers

Annualized BMD changes (%/yr)	With TNF blockers (n = 19)	Without TNF blockers (n = 88)	p value
Lumbar spine	4.11 ± 7.2	2.61 ± 7.9	0.450
Neck of femur	2.61 ± 8.5	0.63 ± 7.9	0.328
Trochanter	3.45 ± 17.4	-0.53 ± 9.8	0.173
Total of femur	2.54 ± 10.2	-0.30 ± 5.9	0.103

BMD; Bone Mineral Density

Disclosure: D. H. Lim, None; **S. Hong**, None; **S. M. Ahn**, None; **B. Ghang**, None; **W. J. Seo**, None; **Y. G. Kim**, None; **C. K. Lee**, None; **B. Yoo**, None.

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Abstract Number: 1562

Clinical Correlates, Outcomes and Predictors of Episcleritis and Scleritis Associated with Rheumatoid Arthritis

Cristian Caimmi[1], Wendy M. Smith[2], Cynthia S. Crowson[3], Eric L. Matteson[4] and Ashima Makol[5], [1]Unit of Rheumatology, Department of Medicine,, University of Verona, Verona, Italy, [2]Department of Ophthalmology, Mayo Clinic, Rochester, MN, [3]Division of Rheumatology and Department of Health Sciences Research, Mayo Clinic, Rochester, MN, [4]Division of Rheumatology, Department of Internal Medicine and Department of Health Sciences Research, Mayo Clinic, Rochester, MN, [5]Division of Rheumatology, Department of Internal Medicine, Mayo Clinic, Rochester, MN

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Background/Purpose: Inflammatory ocular disease (IOD) has traditionally been regarded as a severe extra-articular manifestation of rheumatoid arthritis (RA) with high mortality. This study aims to evaluate episcleritis (EP) and scleritis (SC) among a recent large single-institution cohort of patients with RA to determine clinical correlates, outcomes and risk factors.

Methods: A retrospective review was performed to assemble a cohort of patients with EP and SC among RA patients evaluated between 1/1/1996-12/31/2013. All cases met the 1987 ACR criteria for RA. Cases were compared to age- and sex-matched comparators with RA without IOD to identify risk factors. Chi-square and rank sum tests were used to compare characteristics between groups. Kaplan-Meier methods were used to analyze outcomes.

Results: We identified 56 patients (75% female, 92% white, mean age 60 y) with IOD (23 EP, 33 SC). Median follow up was 6.6 y (IQR 4.6 – 13.1) for EP and 3.1 y (IQR 1.3-5.9) for SC. One third had bilateral eye involvement (74 eyes). Majority had seropositive, erosive RA with a median duration of 10.8 y (IQR 3.9-22.2). Although clinical presentation was similar, with conjunctival injection noted in majority, eye pain and headache were more common with SC. Markers of inflammation were elevated in 7/15 SC and 6/15 EP.

EP was primarily treated with topical therapy but SC required systemic therapy (Table) and immunosuppressive agents. SC patients experienced greater loss of visual acuity during disease course (mean 0.3 vs 0.1 logMAR, p = 0.002). At 1 year, the cumulative incidence (CI) of resolution was 65% for EP vs 30% for SC (HR 0.61, p = 0.11) and CI of a new episode of IOD was 10% for EP vs 31% for SC (HR 2.71, p=0.14).

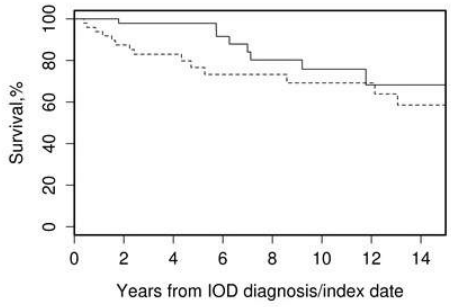
The 56 patients with IOD were compared to 54 age, sex and disease duration matched subjects with RA but without IOD (median disease duration 10.8 y vs. 9.9 y, p = 0.54; median follow up 5.9 y (IQR 2.7-10.4) for IOD patients and 4.3 y (IQR 1.7-10.9) for comparators). Cases had a higher prevalence of severe extra-articular manifestation (ExRA) (Malmo criteria) (25% vs 4%, p = 0.002) and dry eye syndrome (43% vs 19%, p = 0.007). Ten year survival was 76% for IOD vs 69% for non-IOD subjects (HR 0.49: 95% CI: 0.21-1.16, p = 0.10). Patients with SC had a somewhat higher mortality than EP (HR 3.96, 95%CI 0.79-19.75, p=0.094). The incidence of cardiovascular events in 5-years follow up was similar among cases and non-IOD subjects (13% vs 12%, p = 0.933), while new ExRA were more frequent in cases (41% vs 8%, p = 0.006).

Conclusion: Severe ExRA and dry eye syndrome are associated with increased risk of developing SC and EP in patients with RA. SC and EP further predispose to developing additional ExRA, increasing the burden of disease. In contrast to older literature, survival among IOD patients is now at least as good as in those without IOD, perhaps due to modern RA treatment strategies or secular disease trends.

		Episcleritis (n= 23)	Scleritis (n= 33)	p-value
Age, years*		53.5 (47.8-66.2)	65.3 (51.6-70.8)	0.11
Disease duration, years*		8.7 (3.9-13.7)	14.6 (3.9-22.8)	0.30
Female		20 (87%)	22 (67%)	0.071
Treatment	Topical drugs	21 (91%)	23 (70%)	0.053
	Oral NSAIDs	5 (22%)	3 (10%)	0.24
	Systemic glucocorticoids	2 (9%)	23 (72%)	**<0.001**
	Cyclophosphamide	0 (0%)	8 (25%)	**0.009**
	Methotrexate	0 (0%)	10 (30%)	**0.004**
	Other DMARDs	2 (9%)	6 (18%)	0.32
	Anti-TNF	0 (0%)	9 (27%)	**0.006**
	Rituximab	0 (0%)	1 (3%)	0.40

*Median (interquartile range)

Survival in patients with RA and scleritis /episcleritis (solid line) and RA subjects without inflammatory ocular disease (IOD; dashed line).



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Abstract Number: 1563

Dyslipidemia and Hyperglycemia, Two Cardiometabolic Parameters, Independently Predict Poor Outcome in Early Rheumatoid Arthritis: Results from Espoir Cohort

Claire I. Daien[1], Jeremie Sellam[2], Nathalie Rincheval[3], Bruno Fautrel[4], Alain Saraux[5], Francis Berenbaum[6], Jacques Morel[1], Jean-Pierre Daures[7] and

Bernard Combe[8], [1]Department of rheumatology, Lapeyronie Hospital and Montpellier University, Montpellier, France, [2]Department of Rheumatology, Assistance Publique – Hôpitaux de Paris, Saint-Antoine Hospital, Paris, France, [3]Biostatistic, EA 2415, Epidemiology unit, Montpellier, France, [4]Rheumatology, AP-HP Pitié-Salpêtrière Hospital / Pierre and Marie Curie University Paris 6 GRC-08 (EEMOIS), Paris, France, [5]Rheumatology Department, CHU de la Cavale Blanche, Brest Cedex, France, [6]Rheumatology and Paris VI University, Saint-Antoine Hospital, Paris, France, [7]Biostatistic, EA 2415 Epidemiology unit, Montpellier, France, [8]Rheumatology, Hopital Lapeyronie, Montpellier, France
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Background/Purpose: Previous studies showed that obesity in patients with rheumatoid arthritis (RA) is associated with higher disease activity. Beyond obesity, cardiometabolic disturbances may impact the prognosis of RA. We aimed to evaluate the impact of cardio-metabolic clustering (CMC) and of its components at the time of RA diagnosis on disease activity and radiographic progression through the 3 first years of evolution.

Methods: 494 patients from the French early arthritis cohort ESPOIR, fulfilling the ACR/EULAR 2010 criteria and with data available for CMC assessment, were included. CMC was defined as ≥ 2 abnormalities among low levels of HDL cholesterol, elevated levels of triglycerides, blood pressure ≥130/85 mmHg, elevated glycemia and insulin-resistance (Wildman RP et al. Arch Intern Med. 2008;168(15):1617-1624.). Patients were split into 4 categories: non-obese with or without (w/o) CMC and obese patients (BMI≥30 kg/m²) w/o CMC. Baseline characteristics were compared using Chi² and Kruskal Wallis tests. The evolution of DAS28-ESR and total Sharp score at 6 months, 1, 2 and 3 years was compared between the different groups using univariate and multivariate mixed models. Multivariate mixed models including CMC components were used to assess parameters associated with outcomes. Multivariate models including obesity, age, gender, rheumatoid factor or ACPA positivity, CRP (for DAS28 model) and DAS28 (for total Sharp model) were used to assess independent associations between HDL, glycemia and RA outcomes.

Results: 192 and 229 non-obese patients respectively with and without CMC and 55 and 18 obese patients respectively with and without CMC were included. At baseline, age, gender, rheumatoid factor positivity and DAS28 were significantly different between the 4 groups. In univariate mixed models, DAS28 and HAQ evolution during the 3 first years were significantly different between the 4 groups ($p<0.001$), with higher values in obese patients and in patients with CMC. CMC was associated with higher DAS28 and HAQ through the 3 years in non-obese patients ($p=0.003$ and $p<0.001$), but not in obese patients. CMC was also associated with a higher total Sharp score only in non-obese patients ($p=0.02$). In a multivariate model, the only components of CMC associated with outcomes were HDL cholesterol level and glycemia. Low HDL cholesterol level at baseline was an independent predictor of DAS28 during the 3 first years after multiple adjustment ($p=0.003$). Similarly, hyperglycemia at baseline was associated with a higher total Sharp score ($p=0.035$).

Conclusion: In early RA, low HDL cholesterol level and hyperglycemia are independently associated with subsequent higher DAS28 and more severe radiographic progression, respectively. Beyond cardiovascular complications, systematic screening of the CMC in RA patients will help to delineate more accurately disease prognosis.

Disclosure: C. I. Daien, Roche Pharmaceuticals, 5,Bristol-Myers Squibb, 5,UCB, 5; **J. Sellam**, None; **N. Rincheval**, None; **B. Fautrel**, None; **A. Saraux**, None; **F. Berenbaum**, None; **J. Morel**, None; **J. P. Daures**, None; **B. Combe**, None.

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Abstract Number: 1564

Initiation of Disease Modifying Therapies and Subsequent Weight Change in Rheumatoid Arthritis

Joshua Baker[1], Brian Sauer[2], Kaleb Michaud[3], Grant W. Cannon[4], Said Ibrahim[5], Liron Caplan[6], Lisa A. Davis[6], Amy C. Cannella[7] and Ted R. Mikuls[8], [1]Medicine/Rheumatology, University of Pennsylvania, Philadelphia, PA, [2]IDEAS Center and Division of Epidemiology, HSR&D SLC VA Medical Center and University of Utah, Salt Lake City, UT, [3]Rheumatology & Immunology, University of Nebraska Medical Center and National Data Base for Rheumatic Diseases, Omaha, NE, [4]Internal Medicine, Veterans Affairs Salt Lake City Health Care System, Salt Lake City, UT, [5]Medicine, University of Pennsylvania, Philadelphia, PA, [6]Div of Rheumatology, Univ of CO Denver School of Med, Aurora, CO, [7]Section of Rheumatology, University of Nebraska Med Ctr, Omaha, NE, [8]University of Nebraska Medical Center, Omaha, NE
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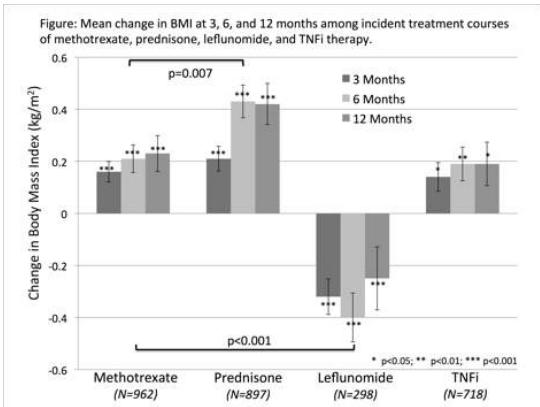
Background/Purpose: Low body mass index (BMI) predicts adverse outcomes in rheumatoid arthritis (RA), in part due to weight loss among patients with severe disease and comorbid illness. Weight loss is a strong predictor of adverse long-term outcomes including death. We examined how common therapies

influence short-term changes in BMI in a large database of patients with RA.

Methods: We used 3 administrative VA database sources: the Corporate Data Warehouse (CDW), the Decision Support System (DSS) National Pharmacy Extract, and the Pharmacy Benefits Management (PBM) database. Among patients with at least one diagnosis code for RA, algorithms integrated sources to define unique dispensing episodes of methotrexate, prednisone, leflunomide, and Tumor Necrosis Factor inhibitors (TNFi). The closest values for CRP and BMI within 30 days of the treatment start date were used as baseline values. CRP and BMI values 90, 180, and 365 days from the treatment start date (+/- 30 days) were recorded. Important weight loss was defined as a decrease in BMI of more than 1 kg/m^2. Regression models evaluated changes in BMI at 6-months among treatments compared to methotrexate adjusting for potential confounders such as demographics, seropositivity, CRP, 6-month change in CRP, disease duration, current smoking, and comorbid conditions, including the Rheumatology Disease Comorbidity Index (RDCI). Matched weighting on propensity was utilized adjust for confounding by indication. Sensitivity analyses considered dual use of other RA therapies.

Results: There were 45,264 unique incident treatment courses in 31,175 patients with available BMI data. There were differences in patient characteristics between those receiving different treatments. Prednisone-treated patients had more weight gain, while those receiving leflunomide had substantially greater weight loss ($p<0.001$) (Figure). In multivariable models there was more weight loss among leflunomide users compared to methotrexate [β: -0.40 (-0.45, -0.35) $p<0.001$] and more weight gain among prednisone users [β: 0.072 (0.042, 0.10) $p<0.001$] while no differences were observed with TNFi. There was a greater risk of weight loss for leflunomide after adjustment [OR 1.73 (1.55, 1.79) $p<0.001$]. Associations between therapies and weight change were not attenuated with propensity-adjustment or in sensitivity analyses. Predictors of weight loss included older age, greater CRP, no improvement in CRP, greater BMI, current smoking, disease duration, RDCI, lung disease, and malignancy. Weight loss was associated with drug discontinuation at 6 months and death at 3 years.

Conclusion: Patients initiating leflunomide are marginally (75%) more likely to lose a clinically significant amount of weight compared to those who start other therapies after adjusting for confounding factors. Prednisone use is independently associated with modest weight gain.



Disclosure: J. Baker, None; **B. Sauer**, None; **K. Michaud**, None; **G. W. Cannon**, Amgen, 2; **S. Ibrahim**, None; **L. Caplan**, None; **L. A. Davis**, None; **A. C. Cannella**, None; **T. R. Mikuls**, None.

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Abstract Number: 1565

High Disease Activity over Time and Persistent Inflammation Are Associated with Increased Risk of Cardiovascular Disease in Patients with Early Rheumatoid Arthritis

Emil Rydell[1,2], Christina Book[1,2], Jan-Åke Nilsson[1,2], Minna Willim[1,2], Lennart T.H. Jacobsson[1,3] and **Carl Turesson**[1,4], [1]Rheumatology, Department of Clinical Sciences, Malmö, Lund University, Malmö, Sweden, [2]Department of Rheumatology, Skåne University Hospital, Malmö, Sweden, [3]Department of Rheumatology and Inflammation Research, Sahlgrenska Academy at Gothenburg University, Gothenburg, Sweden, [4]Lund University, Rheumatology, Dept. of Clinical Sciences,, Malmö, Sweden

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Background/Purpose:

Rheumatoid arthritis (RA) is associated with an increased rate of cardiovascular (CV) disease. Systemic inflammation has been implicated as a key factor behind CV comorbidity in RA. The objective of this study was to investigate the impact of disease activity and inflammation over the first two years on the risk of subsequent CV events in patients with early RA.

Methods:

An inception cohort of patients with early RA (symptom duration <12 months), recruited in 1995-2005 from a defined area, was investigated. Patients were followed according to a structured program, with follow-up visit at 6, 12 and 24 months after inclusion. The clinical examinations were performed by the same rheumatologist. Those included in the study were managed according to usual care, with no pre-specified protocol for anti-rheumatic treatment or CV prevention. Patients with a 24-month visit in 1998 or later were included in the present analysis. Data on CV events (hospitalization or out-patient visit due to coronary artery disease, cerebrovascular disease or peripheral artery disease) during the period 1998-2011, based on diagnostic codes, were retrieved from a regional health care register. Traditional CV risk factors were investigated in a structured review of the medical records. Cox regression models were used to assess associations between the area under the curve (AUC) for disease activity parameters over the first two years, and CV events occurring later during the disease course. Furthermore, the impact of disease activity parameters at the 2-year follow-up were assessed in separate models. Since the assay for CRP was modified to a high-sensitivity analysis during the study period, the AUC for CRP could not be calculated. CRP was therefore modelled as a dichotomized variable (above vs. below the 75th percentile at 2 years).

Results:

A total of 207 patients with early RA (70 % women, mean age 62 years) were followed from the 24-month visit to the first CV event, migration from the region, death or Dec 31, 2011. CV events occurred in 54 patients during the follow-up. A high disease activity over the first two years (defined as AUC for DAS28 above the median) was associated with a significantly increased risk of CV events (age-sex adjusted hazard ratio (HR) 2.03; 95 % confidence interval (CI) 1.15-3.60). In separate analyses, it was demonstrated that patients with CRP at two years within the highest quartile (>11 mg/l) had a significantly higher risk of CV events compared to those with lower CRP values (age-sex adjusted HR 1.82; 95 % CI 1.04-3.17). Results were similar in models adjusted for smoking, hypertension and diabetes in addition to age and sex (multivariate adjusted HRs for DAS28-AUC above the median: 2.05 (95% CI 1.13-3.73); for CRP>11 mg/l: 1.90 (95% CI 1.06-3.42)).

Conclusion:

A high disease activity during the first two years after RA diagnosis and a high CRP at the two-year follow-up were both associated with a doubled risk of CV events. These findings suggest that patients with persistently active RA are at particularly increased risk, and highlight the importance of disease control for CV prevention in patients with early RA.

Disclosure: E. Rydell, None; **C. Book**, None; **J. Nilsson**, None; **M. Willim**, None; **L. T. H. Jacobsson**, None; **C. Turesson**, None.

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Abstract Number: 1566

The Impact of Severe Extra-Articular Manifestations and Patient Reported Outcome Measures on Cardiovascular Disease in Rheumatoid Arthritis

Lisa Theander[1], Jan-Åke Nilsson[1], Minna Willim[1,2], Britt-Marie Nyhäll-Wåhlin[1,3], Lennart T.H. Jacobsson[1,4] and **Carl Turesson**[1,5], [1]Rheumatology, Department of Clinical Sciences, Malmö, Lund University, Malmö, Sweden, [2]Department of Rheumatology, Skåne University Hospital, Malmö, Sweden, [3]Department of Rheumatology, Falun Hospital, Falun, Sweden, [4]Department of Rheumatology and Inflammation Research, Sahlgrenska Academy at Gothenburg University, Gothenburg, Sweden, [5]Lund University, Rheumatology, Dept. of Clinical Sciences,, Malmö, Sweden
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Background/Purpose: Rheumatoid arthritis (RA) is associated with increased risk of cardiovascular disease (CVD). Disease severity, including extra-articular rheumatoid arthritis (ExRA) manifestations, has previously been demonstrated to be a major risk factor for CVD. With improved treatment possibilities, it is important to assess potential changes in the effect of disease severity measures on development of CVD in patients with RA. The aim of this study was to investigate the impact of patient reported outcome measures (PROMs) and severe ExRA on the risk of CVD in a community based sample of patients with RA.

Methods:

A dynamic community based cohort of patients with RA (n=1977) was studied. Information on CVD events was obtained from a regional health care register. Clinical records were reviewed from January 1, 1998 to December 31, 2011, and cases with severe ExRA (i.e. pericarditis, pleuritis, vasculitis, interstitial lung disease, neuropathy, episcleritis/scleritis, Felty's syndrome and glomerulonephritis), classified according to predefined criteria, were identified. The impact of time dependent incident severe ExRA on CVD was examined in Cox regression models. Questionnaires including the Health Assessment Questionnaire (HAQ) and visual analogue scales (VAS) for current pain and global health were sent to the patients in 1997, 2002, 2005 and 2009. The impact of baseline PROMs, based on the first available questionnaire for each patient, on the risk of CVD was examined in Cox regression models.

Results:

There were 1436 (72.6%) women and 541 (27.6%) men in the study cohort. At the start of follow-up the mean age was 59.9 years and the median disease duration was 5.0 years. During the follow-up, 619 patients had at least one CVD event. There were 387 cases with coronary artery disease (CAD), 221 with cerebrovascular disease and 185 with peripheral artery disease (PAD). Seventy-two patients with a previous history of severe ExRA were excluded. Incident severe ExRA (n=121) did not predict CVD overall [age and sex adjusted HR 0.99; 95% CI 0.70-1.39], CAD, cerebrovascular disease or PAD. In a sensitivity analysis, episcleritis and pleuritis (n=34), which may be regarded as milder ExRA manifestations, were excluded. Severe ExRA was still not associated with a significantly increased risk of CVD (age-sex adjusted HR 1.21; 95 % CI 0.85-1.71), although there was a borderline association with PAD (age-sex adjusted HR 1.68; 0.99-2.84). Greater disability, measured by HAQ at baseline, was predictive of CVD [age and sex adjusted HR (per SD) 1.13, 95% CI 1.03-1.25]. There was a positive association between HAQ and CAD as well as PAD, but not with cerebrovascular disease. Similar patterns were seen in models including VAS for current pain and global health, which were both predictive of CVD overall, CAD and PAD, but not of cerebrovascular events.

Conclusion: Severe ExRA did not predict cardiovascular disease in this cohort of patients with RA. Potential explanations for this discrepancy from previous studies include differences in case selection and improved management of ExRA over time. Disease severity, measured by PROMs, predicted the occurrence of CVD, with the exception of cerebrovascular disease.

Disclosure: L. Theander, None; **J. Nilsson**, None; **M. Willim**, None; **B. M. Nyhäll-Wåhlin**, None; **L. T. H. Jacobsson**, None; **C. Turesson**, None.

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Abstract Number: 1567

Occurrence of Serious Infection in Patients with Rheumatoid Arthritis Treated with Biologics and Denosumab Observed in a Clinical Setting

Matthew Wong-Pack[1], Rod Rodjanapiches[1], Arthur Lau[1,2,3], George Ioannidis[1,3], Sally Wade[4], Leslie Spangler[4], Celia JF Lin[4], Patrick Roy-Gayos[1], William G Bensen[1,3], Robert Bensen[3] and Jonathan D Adachi[1,3], [1]McMaster University, Hamilton, ON, Canada, [2]Division of Rheumatology, McMaster University, Hamilton, ON, Canada, [3]St Joseph's Healthcare Hamilton, Hamilton, ON, Canada, [4]Amgen Inc., Thousand Oaks, CA

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Background/Purpose: Previous studies combining immunosuppressive biologics have shown an increased risk of infections. Few studies have examined the risk of infection with concurrent use of the anti-osteoporosis agent, denosumab (DMAb), a human monoclonal antibody, and an immunosuppressive biologic used to treat rheumatoid arthritis (RA). In this study we examined the occurrence of serious and opportunistic infections in two RA populations: patients treated concurrently with DMAb and an immunosuppressive biologic, and patients treated with only an immunosuppressive biologic.

Methods: We reviewed a select group of RA patients from two rheumatology practices in Hamilton, Ontario, Canada, between the study period of July 01, 2010 and July 31, 2014. Patients were included if they were ≥ 18 years of age with RA, registered in the treatment center ≥ 3 months before and after the index date, and received ≥ 1 injection/infusion or filled a prescription for an immunosuppressive biologic therapy for RA. Patients were excluded if they had HIV or AIDS, were receiving cancer treatment or immunosuppressive therapies for conditions other than RA, or were living in a nursing home. We examined two RA patient groups: those who had used DMAb and an immunosuppressive biologic concomitantly in the study period (concurrent group) and those who had used an immunosuppressive biologic alone in the study period (biologic-alone group). The concurrent group was assigned an index date derived from their initial DMAb injection. A frequency-matching technique utilizing the index date of the concurrent group was used to select the index date of the biologic-alone group. Serious infection was defined as resulting in hospitalization or an ER visit with use of IV antibiotics, associated with the primary diagnosis of infection. Instances of serious or opportunistic infections were recorded. The observational period for infections was between the index date and July 31, 2014 or loss to follow-up, whichever came first. As this was not a comparative study, each group was analyzed separately.

Results: A total of 218 patients met eligibility criteria for the study (N = 109 concurrent group; N = 109 biologic-alone group). Descriptive statistics for both groups are provided in Table 1. Three events of serious infection occurred in three patients in the concurrent group (three cases of pneumonia resulting in hospitalization), and three events of serious infection occurred in three patients in the biologic-alone group (two cases of pneumonia and one upper respiratory tract infection, all resulting in hospitalization). In both groups, all patients recovered and there were no instances of opportunistic infections or death.

Conclusion: RA patients may require treatment for bone loss due to intrinsic disease, steroid use, and advancing age. This study demonstrates a low occurrence of serious infections in biologically-treated RA patients, including patients with concurrent DMAb use.

Table 1: Participant Characteristics* of the Concurrent (Denosumab + Biologic) Group and Biologic-alone Group

Characteristic	Concurrent Group N = 109	Biologic-alone Group N = 109
Women, % (n)	86.2 (94)	85.3 (93)
Patient age, years	66.4 (10.8)	58.1 (10.8)
Average follow-up time, years	2.5 (1.2)	2.4 (1.2)
Body mass index, kg/m^2	27.2 (5.4)	31.3 (11.1)
History of fracture, % (n)	8.3 (9)	7.3 (8)
T-score ≤ −2.5 at the spine or hip, % (n)	45.9 (50)	15.6 (17)
Chronic kidney disease, % (n)	0.9 (1)	0.9 (1)
Chronic obstructive pulmonary disease, % (n)	3.7 (4)	7.3 (8)
Cardiovascular disease, % (n)	6.4 (7)	12.8 (14)
Diabetes, % (n)	7.3 (8)	7.3 (8)
Liver disease, % (n)	0.9 (1)	0.0 (0)
Smoking status, number of patients,% (n)		
Past	26.6 (29)	22.9 (25)
Current	11.9 (13)	19.3 (21)
Never	60.6 (66)	53.2 (58)
Status unknown	0.9 (1)	4.6 (5)
Systemic glucocorticoid usage, % (n)	46.8 (51)	41.3 (45)
C-reactive protein, mg/L	4.6 (6.7)	3.4 (4.5)
Erythrocyte sedimentation rate, mm/h	18.6 (16.7)	17.5 (14.7)

*Data recorded within ± 6 months of the index date.
Data are means (standard deviation) unless otherwise noted.

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Abstract Number: 1568

Cardiac Morphology and Function in Patients with Acute Coronary Syndrome Complicated with Rheumatoid Arthritis

Li-Li Pan[1] and Tian Wang[2], [1]Rheumatology and Immunology, Beijing Anzhen Hospital affiliated to Capital Medical University, Beijing, China, [2]1. Department of Rheumatology and Immunology,, Beijing An Zhen Hospital, Capital Medical University, Beijing Institute of Heart, Lung, and Blood Vessel Diseases, Beijing, China

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Session Title: Rheumatoid Arthritis - Clinical Aspects Poster II

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Session Time: 9:00AM-11:00AM

Background/Purpose: Cardiovascular diseases are important contributors to the excess of overall morbidity and mortality in patients with rheumatoid arthritis (RA). The aim of this study is to investigate the effects of RA on cardiac remodeling in patients with acute coronary syndrome (ACS)

Methods: Sixty-one patients with ACS complicated with RA and 55 age- and sex-matched patients with ACS having no RA (controls) were enrolled; General parameters and cardiovascular risk factors were compared in 2 groups. Echocardiogram measurements were used to determine the changes of cardiac morphology and function.

Results: Mean value of BMI in patients of ACS+RA group (27.50±3.53) was significantly higher than that of the controls (24.84±2.36) (P<0.05). No difference was observed in the levels of serum TG, TC and LDL-C, but HDL levels were significantly lower in ACS+RA patients (0.91±0.20 mmol/L) than that in controls(1.10±0.23mmol/L) (P<0.05). Serum HCY (17.27±4.71 mmol/L) ,CRP levels(9.84±5.50 mg/L) and ESR (28.35±15.87 mm/1h) were significantly higher in patients in the ACS+RA group than controls (13.16±4.23 mmol/L,P<0.05), (4.21±3.25 mg/L, P<0.01), (9.33±3.88 mm/1h, P<0.01) respectively. The BNP levels in patients of ACS+RA group (386.31±225.88 pg/ml) was significantly higher than the control group (258.43±136.97 pg/ml),(P<0.05). Rate of left ventricular (LV)hypertrophy (50.8%), and LV diastolic dysfunction (E/A<1) (96.7%) were significantly higher in the ACS+RA group(29.1%, *P*<0.05), (61.6%),(*P*<0.01). While the LV ejection fraction % were significantly lower (54.86±12.12% Vs 63.83±5.61%), (*P*<0.05). Incidence of tricuspid regurgitation (45.9%) and pulmonary valve regurgitation (9.8%) were significantly higher in ACS patients complicated with RA than that in control (12.7%, *P*<0.01) (0%*P*<0.05). Comparison of aortic and mitral regurgitation between the two groups had no statistical significance.

Conclusion: with ACS complicated with RA are more likely to be afflicted with left ventricular remodeling, reduction of systolic and diastolic functions, and cardiac valve impairment.

Disclosure: L. L. Pan, None; **T. Wang**, None.

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Abstract Number: 1569

Rituximab Efficacy in the Treatment of Diffuse Interstitial Lung Disease Associated with Rheumatoid Arthritis

Javier Narváez[1], Milagros Ricse[2], Juan José Alegre[3], Gloria Albert Espi[3], Carmen Gomez Vaquero[4], Helena Borrell Paños[2], Eulalia Armengol[2], Joan Miquel Nolla[2], Susana Herrera[5] and Maria Molina[6], [1]Rheumatology, Hospital Universitario de Bellvitge, Barcelona, Spain, [2]Department of Rheumatology, Hospital Universitario de Bellvitge, Barcelona, Spain, [3]Rheumatology Department, Hospital Universitario Doctor Peset, Valencia, Spain, [4]Department of Rheumatology, Hospital Universitario Bellvitge, Barcelona, Spain, [5]Deparment of Pneumology, Hospital Universitario Dr Peset, Valencia, Spain, [6]Department of Pneumology, Hospital Universitario de Bellvitge, Barcelona, Spain

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SESSION INFORMATION

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Background/Purpose: To investigate the efficacy and safety of rituximab (RTX) in the the management of progressive rheumatoid arthritis related interstitial lung disease (RA-ILD).

Methods: An open observational study was performed in patients with progressive RA-ILD (evidence of clinical and functional decline) and inadequate articular response (DAS28 > 3.2) despite treatment with glucocorticoids and synthetic DMARDs.

The following main efficacy variables were evaluated at the end of follow-up: *1)* the improvement of joint counts measured by DAS28-ESR and *2)* the evolution of pulmonary function tests (PFT) according to definitions from the American Thoracic Society, including *a) improvement:* if an increase in FVC ≥ 10% or DLCO ≥ 15% is observed; *b) stabilization:* if changes in FVC are less than 10% or 15% in DLCO; and *c) worsening:* if FVC decreases ≥ 10% or DLCO ≥ 15%.

Results: Thus far, 13 patients have been included (seven women) with a mean age (± SD) of 53 ± 13 years (range, 35-74). All patients were ACPA positive.

The time of evolution (median) was 24 months (range, 8-168) for RA and seven months (range 1-16) for RA-ILD. Regarding tissue specificity, 10 (77%) cases corresponded to NSIP and three to UIP.

Once RA-ILD was diagnosed, patients with NSIP received prednisone treatment at a dose of 0.75-1 mg/kg, whereas patients with UIP were treated with prednisone at a dose of 10-15 mg/day and N-acetylcysteine at a dose of 1800 mg/day. In addition, methotrexate was substituted for leflunomide in eight patients, azathioprine in three, and salazopyrin in two.

At the start of RTX treatment (dose: 1 g on days 1 and 15, repeating the cycle after six months depending on the response), the mean DAS28 value was 5.5 ± 1.1, baseline FCV (%) was 75 ± 15, and baseline DLCO (%) was 55.5 ± 21.

At the end of an 11-month (median, range 6-111) follow-up period, the mean DAS28-ESR score decreased to 3 ± 1.3 (% improvement: -45.45%; range, -62 to -24%). In seven patients (54%), remission of the joint disease (DAS28 < 2.6) was achieved, and in six patients, there was low activity (DAS28 ≤ 3.2). The evolution of PFT values is shown in the following table:

	FVC	**DLCO**	**Postreatment high resolution computed tomography (HRCT)** **(N=8)**
Improvement	5	1	1
Stabilization	8	11	7
Worsening	0	1	0

Considering the total sample, FCV improvement (FCV after treatment: 87 ± 18; 16% improvement) and DLCO stabilization (DLCO after treatment: 59.3 ± 22; 6.8% improvement) were achieved. The number of RTX cycles administered (mean ± SD) was 3.25 ±1.5 (range, 1-6).

The frequency of adverse effects was low, occurring in only one patient (8%) who developed pulmonary aspergillosis at five months of treatment, forcing a temporary suspension of treatment.

Conclusion: In our experience, RTX is a relatively safe and effective drug for the treatment of patients with active symptomatic RA-ILD and an insufficient articular response despite treatment with glucocorticoids and synthetic DMARDs. In this subgroup of patients RTX administration achieved remission/low activity of clinical joints and, at a minimum, PFT were stabilized.

Abstract Number: 1570

End Stage Renal Disease (ESRD) in Patients with Rheumatoid Arthritis

Sunita Paudyal[1], Monique Bethel[2], Frances Yang[1], Alyce Oliver[1], Michael Skelton[1], Christopher Rice[1], Brian Le[3], Shilpa Brown[1], Stanley Nahman[1] and Laura Carbone[4], [1]Georgia Regents University, Augusta, GA, [2]Internal Medicine, Georgia Regents University, Augusta, GA, [3]Medicine, Georgia Regents University, Augusta, GA, [4]Rheumatology, Georgia Regents University, Augusta, GA
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Background/Purpose:

Substantial progress has been made in the treatment of rheumatoid arthritis (RA) and life expectancy has increased. As the population of patients with RA continues to age, they may be more likely to suffer from diseases of aging, including ESRD. However, the characteristics of patients with RA and ESRD, treatment patterns for RA in the setting of ESRD and the impact of RA on mortality in ESRD have not been previously been examined. The purpose of this study was to determine the prevalence of ESRD and reasons for dialysis in RA, treatment modalities for RA in the setting of ESRD and five year cardiovascular mortality in patients with RA and ESRD compared to those with ESRD without RA.

Methods:

Retrospective cohort study of adult ESRD patients with RA without HIV in the United States Renal Data System (USRDS) beginning in calendar year 2011. Medicare Part D beneficiary data was used to determine filled prescriptions for medications that might be used to treat RA including corticosteroids, DMARDs and biologics. Cox proportional hazard models were estimated to determine five year cardiovascular-related mortality in patients with RA compared to all others with ESRD without RA.

Results:

There were 28,589 patients with RA and ESRD in 2011. Based on population estimates of the frequency of RA in adults in the United States, approximately 2% of adult patients with RA have ESRD. Patients with ESRD and RA are more likely to be female, to have hypertension, diabetes, atrial fibrillation and cardiovascular events ($p<0.01$ for all) than those with ESRD without RA. Hypertensive renal disease (30%) and type II diabetes (25%) are the most common causes of ESRD in RA; amyloidosis, vasculitis and analgesic nephropathy are uncommon, accounting for less than 5% of all cases. More than half of ESRD patients with RA had a filled prescription for a medication for RA treatment; most commonly prednisone (42% of all prescriptions). Ten percent of all filled prescriptions were for hydroxychloroquine; 2.63% for leflunomide and 1.39% for sulfasalazine. Biologics were a rare class of filled prescription therapies (etanercept 1.59%;adalimumab 1.07%; golimumab, infliximab, anakinra and abatacept each comprised <1% of total filled prescriptions in this population). After adjustment for covariates, compared to patients without RA with ESRD, five year cardiovascular mortality in patients with RA and ESRD was significantly increased (HR 1.42 (95%CI 1.38-1.47).

Conclusion:

ESRD is infrequent in patients with RA but has a significant impact on cardiovascular mortality. Similar to the general ESRD population, hypertension and diabetes mellitus are the most common causes of dialysis. Prednisone and hydroxychloroquine are the most frequent prescriptions filled that could be used to treat RA; use of biologics appears uncommon in this population. Further prospective studies of the impact of ESRD on outcomes in RA and optimal treatments for RA in the setting of ESRD are needed.

Disclosure: S. Paudyal, None; **M. Bethel**, None; **F. Yang**, None; **A. Oliver**, None; **M. Skelton**, None; **C. Rice**, None; **B. Le**, None; **S. Brown**, None; **S. Nahman**, None; **L. Carbone**, None.

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Abstract Number: 1571

How Substantive Is Heart Rate Variability As a Predictor of Anti-TNF Treatment Outcome for Inflammatory Arthritis?

Andrew Holman[1] and Edmund Ng[2], [1]Inmedix, Normandy Park, WA, [2]Statistical Thinking, Seattle, WA
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Background/Purpose:

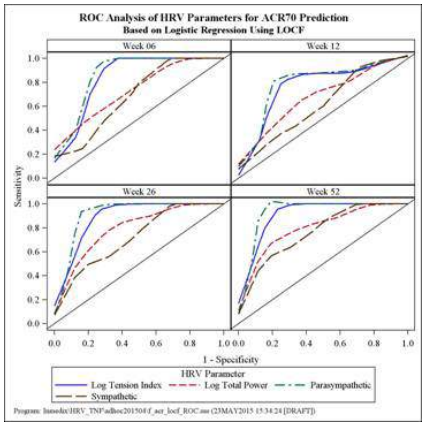
As rheumatologists search for new targets to improve immunosuppressive outcomes, the autonomic nervous system (ANS) as a co-factor in autoimmune disease expression has gained interest. At ACR 2014, heart rate variability (HRV), an accepted assessment of ANS state, was described as a biomarker in SLE. At ACR 2008, HRV predicted biologic treatment outcome for inflammatory arthritis in a 52-week, double-blind, prospective study[1]. But, how worthy is HRV as a metric with pathophysiologic and even therapeutic impact?

Methods:

An in depth, *post hoc* analysis of the clinical study that established proprietary HRV (Omegawave Ltd, Espoo, Finland) as a predictor of biologic treatment outcome for inflammatory arthritis was conducted.[1] To further evaluate the performance of HRV measures in predicting ACR outcomes, receiver operating characteristic (ROC) analysis have been carried out. Area under the ROC curve (AUC) was calculated and the ROC curve was plotted for each of the HRV measures. Youden index was used to find the optimal cutoff at which the sensitivity and specificity were maximized. Relative risk (RR) of the ACR response at the optimal cutoff was also calculated.

Results:

Thirty-three patients (25 rheumatoid and 8 psoriatic arthritis by ACR criteria) were included in the analysis.[1] All HRV measures (parasympathetic, sympathetic, tension index, total power) achieved better prediction with increasing duration of anti-TNF therapy as measured by the AUC. The HRV measures provided moderate to high AUC values at week 26 and week 52 for ACR20/50/70 (range: 0.631 to 0.926). ROC AUC (95% CI) was most optimal for parasympathetic and log tension index to predict ACR70 response at 52 weeks at 0.926 (0.834, 1.000) and 0.918 (0.824, 1.000), respectively. At the optimal cutoff, sensitivity and specificity for the parasympathetic HRV measure to predict ACR70 at 52 weeks were 100% and 88.5%, respectively, and for the tension index, 100.0% and 84.6%, respectively. RR for all HRV measures at optimal cutoffs for ACR20/50/70 at 26 and 52 weeks ranged from 2.23 to infinity (all p-values < 0.05). Patients with parasympathetic > the optimal cutoff (0.17) were 16 times (RR 95% CI: 2.22 to 115.14) more likely to achieve ACR70 at 52 weeks than patients with parasympathetic ≤ the optimal cutoff (p-value < 0.001).



Conclusion:

Expanded statistical analyses of the referenced study further supports HRV as substantively impactful of prediction of anti-TNF biologic treatment outcome of inflammatory arthritis. These findings may encourage study in other diseases, with non-anti-TNF immunosuppressive regimens; expand elucidation of ANS immunomodulatory mechanisms that impact autoimmune disease expression and treatment response; and target the ANS as a prolific source of new therapeutics able to enhance immunosuppressive regimens.

1. *Autonomic Neurosci Basic Clinical 2008;143:58-67.*

Disclosure: A. Holman, Inmedix, 4; **E. Ng**, Inmedix, 5.

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Abstract Number: 1572

Plasma Apolipoprotein B48 Levels in Patients with Rheumatoid Arthritis: Evaluating Novel Cardiovascular Risk Factors

Deborah van Breukelen-van der Stoep[1], Derkjen van Zeben[1], Marijke de Vries[2], Boudewijn Klop[2], Noelle van der Meulen[2], Gert Jan van de Geijn[3],

Hans Janssen[3], Pedro Valdivielso[4], José Rioja[4], José Ramirez-Bollero[4], Mieke Hazes[5], Erwin Birnie[6,7] and Manuel Castro Cabezas[8], [1]Department of Rheumatology, Sint Franciscus Gasthuis, Rotterdam, Netherlands, [2]Department of Internal Medicine, Sint Franciscus Gasthuis, Rotterdam, Netherlands, [3]Department of Clinical Chemistry, Sint Franciscus Gasthuis, Rotterdam, Netherlands, [4]Department of Internal Medicine and Dermatology, Hospital Virgen de la Victoria, Malaga, Spain, [5]Department of Rheumatology, Erasmus Medical Centre Rotterdam, Rotterdam, Netherlands, [6]Statistics and Education, Sint Franciscus Gasthuis, Rotterdam, Netherlands, [7]Insitute of Health Policy and Management, Erasmus University, Rotterdam, Netherlands, [8]Department of Internal Medicine, Sint Francicscus Gasthuis, Rotterdam, Netherlands
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Background/Purpose: Chylomicrons, with apolipoprotein (apo) B48 as a structural protein, induce leukocyte and complement activation and contribute to atherosclerosis. ApoB48 is higher in conditions associated with a higher degree of systemic inflammation and apoB48 helps to identify patients at increased cardiovascular risk. There are no data available on apoB48 levels in rheumatoid arthritis (RA) in relation to atherosclerosis. Since classical risk factors do not predict the cardiovascular risk well in RA, search for novel markers of risk is relevant. The objective of this study was to investigate the levels of apoB48 in RA patients compared to patients with coronary artery disease (CAD) and its association with metabolic and other lipid parameters, carotid intima media thickness (cIMT) and the estimated cardiovascular risk.

Methods: RA patients, without the presence of clinical cardiovascular disease or diabetes mellitus and participating in the FRANCIS study, were included. Also subjects with CAD (CAD+) and without RA were included. Blood samples were collected after an overnight fast and a complete lipid profile, including total plasma apoB and apoB48 (ELISA) were measured. cIMT was measured using ultrasound.

Results: 328 Patients with RA and 56 CAD+ patients were included. RA patients were younger (53±11 vs. 68±11 yrs; P<0.001), more often female (68% vs. 34%; P<0.001) and had lower remnant cholesterol (remnant-C) concentrations (0.52±0.26 vs. 0.75±34 mmol/l; P<0.001) and triglycerides (1.25±0.88 vs. 1.83±1.12 mmol/l; P<0.001) compared to CAD+ patients. Median apoB48 was significantly higher in RA patients compared to CAD+ patients (8.6 [IQR 5.2-12.5] vs. 7.1 [IQR 4.9-10.4] mg/L; P=0.026). In RA apoB48 correlated positively with triglycerides (r=0.616; P<0.001), remnant-C (r=0.479; P<0.001), LDL-cholesterol (r=0.123; P=0.03) and the cardiovascular risk score according to the SCORE model (r=0,141; P=0.011). No significant correlation between apoB48 and cIMT (r=0.103; P=0.07), BMI (r=0.014; P=0.81), systolic blood pressure (r=0.095; P=0.09), glucose (r=0.106; p=0.06)and RA DAS28 (-0.32; P=0.58) was found.

Conclusion: In RA apoB48 is associated with an increased cardiovascular risk score and may contribute to the increased atherogenesis of RA. Since apoB48 in RA was higher compared to CAD+ patients, despite lower triglycerides and remnant-C, chylomicron remnant clearance may be impaired in RA.

Abstract Number: 1573

Plasma Pentraxin 3 Concentration Is Associated with Progression of Radiographic Joint Damage but Not with Carotid Atherosclerosis in Female Patients with Rheumatoid Arthritis: Results from a 3-Year Prospective Study

Yu Asanuma[1], Yuki Shimada[2], Yoshimi Aizaki[1], Kazuhiro Yokota[1], Noritsune Kouzu[3], Yoshitake Takebayashi[4], Hisashi Noma[4], Shinichi Kawai[5] and Toshihide Mimura[2], [1]Department of Rheumatology and Applied Immunology, Faculty of Medicine, Saitama Medical University, Saitama, Japan, [2]Saitama Medical University, Saitama, Japan, [3]Kouzu Orthopaedic Clinic, Chiba, Japan, [4]The Institute of Statistical Mathematics, Tokyo, Japan, [5]Div of Rheum/dept of Int Med, Toho Uni Sch of Med, Tokyo, Japan
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Background/Purpose:

Pentraxin 3 (PTX3) plays an important role in inflammation, immunity, and atherosclerosis. Plasma PTX3 level is recognized as a marker that responds to local inflammation. PTX3 stimulates osteoclastogenesis by increasing osteoblast RANKL production in vitro. PTX3 is strongly expressed in human

atherosclerotic plaque, and plasma PTX3 concentration increases in patients with atherosclerotic cardiovascular disease such as unstable angina pectoris and myocardial infarction. Rheumatoid arthritis (RA) is a chronic inflammatory disorder, which is known to develop joint damage and atherosclerosis. We examined the hypotheses that the PTX3 concentrations are elevated in patients with RA and are associated with 3-year progression of joint destruction and subclinical atherosclerosis.

Methods: Plasma PTX3 concentrations were measured in 72 female patients with RA and 80 healthy control. The patients were also evaluated with respect to their clinical characteristics, joint damage, atherosclerosis and medications. Radiographs of the hands and feet were evaluated using the van der Heijde modified Sharp scoring method at baseline and at 3 years in patients with RA. We also performed carotid ultrasonography to measure subclinical atherosclerosis at the two time points in RA patients. Among female patients with RA, we investigated whether plasma PTX3 levels were associated with the progression of joint destruction and carotid intima media thickness (IMT), a surrogate marker of atherosclerosis during 3 years of follow-up.

Results:

Plasma PTX3 levels were significantly higher in female patients with RA (4.05±2.91 ng/mL) compared to healthy females (1.61±1.05 ng/mL) (Wilcoxon's rank sum test: P<0.001). Follow-up imaging of articular radiographs and carotid ultrasonography were not obtained from 10 and 8 patients, respectively. Progression of joint damage was observed in 72.6% out of 62 patients during 3 years. Incident plaque was observed in 45% patients (40 out of 64) without baseline plaque. IMT progression was detected in 34 (53%) out of 64 patients. By multivariate analysis using multiple linear regression model for the RA patients, baseline plasma PTX3 levels were significantly associated with total Sharp score (P=0.004), erosion score (P=0.002) and joint space narrowing score (P=0.031) after 3 years follow-up with adjustment for baseline score of joint damage, age, BMI, rheumatoid factor, DAS28-ESR4, postmenopausal, use of biologics. Besides, PTX3 did not predict 3-year carotid artery IMT progression nor incident plaque in RA.

Conclusion: Female patients with RA have increased concentrations of PTX3 compared with control subjects. PTX3 was significantly associated with radiographic progression of joint damage but not with carotid atherosclerosis in RA.

Disclosure: Y. Asanuma, None; **Y. Shimada**, None; **Y. Aizaki**, None; **K. Yokota**, None; **N. Kouzu**, None; **Y. Takebayashi**, None; **H. Noma**, None; **S. Kawai**, None; **T. Mimura**, None.

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Abstract Number: 1574

Associations of Serum Anti-Malondialdehyde-Acetaldehyde (MAA) Antibodies with Cardiovascular and Respiratory Mortality in Men with Rheumatoid Arthritis

Bryant R. England[1], Geoffrey M. Thiele[2], Michael J. Duryee[3], Lynell Klassen[4], Jeremy Sokolove[5], William H. Robinson[6], Daniel Anderson[7], Harlan Sayles[7], Kaleb Michaud[8], Liron Caplan[9], Lisa A. Davis[9], Grant W. Cannon[10], Brian Sauer[11], E. Blair Solow[12], Andreas Reimold[13], Gail S. Kerr[14], Pascale Schwab[15], Joshua F. Baker[16] and Ted R. Mikuls[17], [1]Division of Rheumatology, Department of Internal Medicine, University of Nebraska Medical Center, Omaha, NE, [2]Research Services 151, Omaha VA Medical Center, Omaha, NE, [3]Internal Medicine Division of Rheumatology, University of Nebraska Medical Center, Omaha, NE, [4]Dept of Internal Medicine, Univ of Nebraska Med Ctr, Omaha, NE, [5]Division of Immunology and Rheumatology, Stanford University Medical Center, Mountain View, CA, [6]Division of Immunology and Rheumatology, Stanford University School of Medicine, Stanford, CA, [7]University of Nebraska Medical Center, Omaha, NE, [8]Rheumatology & Immunology, University of Nebraska Medical Center and National Data Base for Rheumatic Diseases, Omaha, NE, [9]Div of Rheumatology, Univ of CO Denver School of Med, Aurora, CO, [10]Division of Rheumatology, Salt Lake City VA Medical Center and University of Utah, Salt Lake City, UT, [11]Salt Lake City VA Medical Center and University of Utah, Salt Lake City, UT, [12]Rheumatology, UT Southwestern Medical Center, Dallas, TX, [13]Rheumatology, VAMC, University of Texas Southwestern Medical Center, Dallas, TX, [14]VAMC, Georgetown University, Washington, DC, [15]Div Arth & Rheum Dis, Oregon Health & Sci Univ OP09, Portland, OR, [16]Rheumatology, University of Pennsylvania, Philadelphia, PA, [17]Medicine, University of Nebraska Medical Center, Omaha, NE

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Background/Purpose: Mortality from cardiovascular (CV) and respiratory causes is increased in rheumatoid arthritis (RA). Predictive serologic biomarkers of these events are lacking. Previously, we have shown anti-malondialdehyde-acetaldehyde (MAA) antibodies to be associated with disease severity in RA. Anti-MAA antibodies also predict coronary artery disease in the general population and are a marker of smoking and alcohol exposure in the lung. The potential of anti-MAA antibodies as biomarkers of CV and respiratory mortality in RA was assessed in conjunction with serum cytokines / chemokines (CK) and anti-citrullinated protein antibodies (ACPA).

Methods: Male participants in the Veterans Affairs RA registry were followed from enrollment until death or December 2013. Using banked serum from enrollment, anti-MAA antibodies were measured with ELISA, CKs were measured using a bead-based multiplex assay, and ACPAs were measured using multiplex antigen array. CK and ACPA scores were calculated from individual CKs and ACPAs. Vital status and cause of death were determined through the National Death Index. Associations with cause-specific mortality were examined using multivariable competing-risks regression adjusting for age, race, smoking status, body mass index, comorbidity, visit frequency, nodules, RF concentration, enrollment DAS-28, baseline DMARDs and prednisone use.

Biomarkers were analyzed as log transformed continuous variables and ordinal categorical variables by quartile.

Results: There were 1,552 patients included with 321 all-cause, 100 CV, and 50 respiratory deaths occurring over 5,940 patient-years of follow-up. Patients were older (mean 65 ± 10 years), had established disease (median 8.6 years), were seropositive for RF (81%) or anti-CCP antibody (79%), and had frequent smoking history (83% current or former). Associations with cause-specific mortality are shown in Table 1. IgA and IgM anti-MAA antibodies were associated with respiratory mortality. There was a trend towards an association between both respiratory and CV mortality with increasing IgA anti-MAA antibody quartiles. An inverse association of ACPA score with respiratory mortality was observed, though this did not reach statistical significance.

Table 1. Associations of Serum Anti-MAA Antibodies, Cytokines, and ACPAs with CV and Respiratory Mortality in RA.

	All-Cause	Cardiovascular	Respiratory
	Hazard Ratio (95% Confidence Interval) P trend Across Quartiles		
IgA anti-MAA	**1.13 (1.02-1.24) P = 0.019** **P trend < 0.001**	1.01 (0.78-1.32) P = 0.92 P trend = 0.062	**1.20 (1.02-1.42) P = 0.029** P trend = 0.055
IgM anti-MAA	1.05 (0.95-1.15) P = 0.36 P trend = 0.31	1.00 (0.85-1.19) P = 0.97 P trend = 0.46	**1.18 (1.00-1.38) P = 0.05** P trend = 0.43
IgG anti-MAA	0.98 (0.95-1.02) P = 0.33 P trend = 0.51	0.95 (0.71-1.25) P = 0.70 P trend = 0.61	0.93 (0.76-1.15) P = 0.52 P trend = 0.50
Cytokine score	**1.21 (1.08-1.36) P = 0.001** **P trend = 0.012**	1.05 (0.91-1.21) P = 0.49 P trend = 0.96	1.00 (0.67-1.48) P = 0.99 P trend = 0.51
ACPA score	0.98 (0.90-1.06) P = 0.59 P trend = 0.57	0.97 (0.89-1.05) P = 0.38 P trend = 0.48	0.87 (0.75-1.01) P = 0.06 P trend = 0.14
Abbreviations: MAA, malondialdehyde-acetaldehyde; ACPA, anti-citrullinated protein antibody.			

Conclusion: Serum IgA and IgM anti-MAA antibodies predict respiratory mortality in RA independent of disease activity and smoking status, showing promise as a potential biomarker. Further studies are needed to identify the MAA modified peptides driving these antibody responses and to investigate if the observed association is more closely related to smoking-related lung disease (i.e. COPD) or RA-related lung disease (i.e. ILD).

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Abstract Number: 1575

Serum Vascular Cell Adhesion Molecule-1 (VCAM-1) Levels Are Associated with Vascular Dysfunction and Increased Cardiovascular Risk in an Animal Model and Patients with Rheumatoid Arthritis

Ruth Davies[1], Daniela Iacono[2], Lauren A. Jordan[1], Jessica O Williams[1], Charlotte Rawlings[1], Derek Lang[3], Anwen S. Williams[1] and Ernest H. Choy[1], [1]Cardiff University, Institute of Infection and Immunity, Tenovus Building, University Hospital of Wales, Cardiff, United Kingdom, [2]Department of Clinical and Experimental Medicine. Rheumatology Section. Second University of Naples, Naples, Italy, [3]Institute of Molecular and Experimental Medicine, Cardiff University School of Medicine, Cardiff, United Kingdom

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SESSION INFORMATION

Session Date: Monday, November 9, 2015

Session Title: Rheumatoid Arthritis - Clinical Aspects Poster II

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose:

Mortality is increased in Rheumatoid arthritis (RA) patients mainly due to cardiovascular (CV) disease; however the biologic mechanisms are unknown. Increased CV risk in RA is attributed to both traditional risk factors and systemic inflammation. CV risk scores, even after modification as recommended by EULAR, underestimate risk in RA and thus there is a need to develop a better means of risk stratification. Murine collagen induced arthritis (mCIA) is associated with vascular dysfunction, characterised by reduced vascular constriction to 5-hydroxytryptamine (5-HT). This study was undertaken to characterise the relationship between VCAM-1, which is induced in proatherosclerotic conditions in the general population, and vascular dysfunction in mCIA and CV risk in RA patients.

Methods:

mCIA was induced in DBA/1 mice. Severity of arthritis was assessed by arthritis index score. Constriction responses to 5-HT were used to assess vascular function in isolated sections of thoracic aorta. Serum VCAM-1 was measured with ELISA.

Serum VCAM-1, IL-6, ESR and CRP were measured with ELISA in RA patients (182 patients, F:M 4:1, mean age 60 years (range 21-89), mean disease duration 11.4 ± 11 years). CV risk was calculated using the Framingham risk calculator and the QRISK2 algorithm. The latter includes RA as an independent CV risk factor.

Results:

In mCIA VCAM-1 levels (mean 1500ug/mL, range 929-2528) correlated with arthritis index score (r=0.43, p=0.03) and negatively correlated with maximal aortic contraction (r =-0.35, p<0.05) (Figure1).

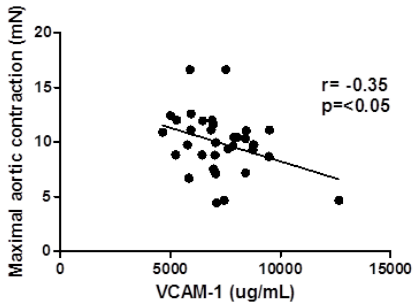

Figure 1. VCAM-1 is negatively correlated with maximal aortic contraction in mCIA in DBA-1 mice

In patients with RA, VCAM-1 was significantly higher in those with a Framingham CV risk score >10% over 10 years (1200ng/mL ± 547) compared to those with <10% risk (937ng/mL ± 570, p=0.02). Similarly the respective VCAM-1 levels using the QRISK2 were 1179ng/mL ± 583 versus 949ng/mL ± 564, p<0.05. VCAM-1 was positively correlated with IL-6 levels (R=0.24, p= 0.008), DAS28 (r=0.25, p= 0.03) and age (r=0.26, p= 0.002). There was no statistically significant correlation between VCAM-1 level and disease duration, statin use, BMI, cholesterol, systolic BP, gender or smoking.

One of the major differences between QRISK2 and Framingham is inclusion of RA as an independent risk factor in the former. QRISK2 and Framingham CV risk scores were correlated moderately (r=0.7, p<0.0001). Multivariate analysis using backward stepwise multiple regression, found that VCAM-1 (p=0.002) was a statistically significant independent predictor of QRISK2 score when added to Framingham and increased R^2 from 0.6 to 0.62.

Conclusion:

VCAM-1 levels correlate not only with disease activity and vascular dysfunction in mCIA but also disease activity and CV risk in RA. VCAM-1 is a potential biomarker for CV disease in RA warrants further investigation.

Disclosure: R. Davies, None; **D. Iacono**, None; **L. A. Jordan**, None; **J. O. Williams**, None; **C. Rawlings**, None; **D. Lang**, None; **A. S. Williams**, None; **E. H. Choy**, Abbott Allergan, Amgen, AZ, BMS, BI, Chelsea, Chugai, Daiichi Sankyo, Eli Lilly, Ferring, GSK, Hospita, ISIS, Jazz, Janssen, MedImmune, Merrimack, MSD, Napp, Novimmune, Novartis, Pierre Fabre, Pfizer, Regeneron, Roche, Sanofi-Aventis, Schering Plough, Ton, 5.

with-vascular-dysfunction-and-increased-cardiovascular-risk-in-an-animal-model-and-patients-with-rheumatoid-arthritis

Abstract Number: 1576

Effect of Conventional Synthetic and Biological Disease Modifying Anti-Rheumatic Drugs on the Immunogenicity of Hepatitis B Vaccine in Patients with Rheumatoid Arthritis

Samanan Intongkam[1], Rattapol Pakchotanon[2], Sumapa Chaiamnuay[2], Paijit Asavatanabodee[2] and Pongthorn Narongroeknawin[2], [1]Internal medicine, Rheumatic Disease Unit, Department of Internal Medicine, Phramongkutklao Hospital and Phramongkutklao College of Medicine, Bangkok, Thailand, [2]Rheumatic Disease Unit, Department of Internal Medicine, Phramongkutklao Hospital and Phramongkutklao College of Medicine, Bangkok, Thailand

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Background/Purpose:

Immunogenicity of pneumococcal and influenza vaccine in patients with rheumatoid arthritis (RA) have been assessed in many studies. However, the humoral immune response of hepatitis B vaccination in RA patients is not clearly known. This study aims to assess the humoral immune response of hepatitis B vaccination in RA patients receiving conventional synthetic and biological disease modifying anti-rheumatic drugs (csDMARDs and bDMARDs).

Methods:

Forty-five patients with RA (study group), 33 patients received only csDMARDs and 12 patients received both csDMARDs and bDMARDs, and 9 healthy age- and sex-matched subjects (control group) were enrolled in this prospective open-label single-center study. All patients had negative results for hepatitis B surface antigen, hepatitis B core antibody, and hepatitis B surface antibody (anti-HBs) on screening. All subjects received 20 µg of recombinant hepatitis B vaccine (Euvax B®) at weeks 0, 4, and 24. Blood samples were collected 8 weeks after receipt of the third vaccine dose to test for anti-HBs. The responder and high responder were defined as anti-HBs levels of ≥ 10 mIU/ml and ≥ 100 mIU/ml, respectively. Treatment related adverse events reported by patients or observed by physician were collected at every visit. The study was approved by the ethic committee and institutional review board.

Results:

Eight weeks after vaccination, the number of responder significantly lower in study group than control group (64% vs 100%, $p = 0.04$) (Table). In the study group, older age and rituximab use were significantly associated with hepatitis B vaccine non-response ($p = 0.04$ and $p = 0.02$, respectively), while disease duration, disease activity, comorbidities, and the use of prednisolone, methotrexate, etanercept, or infliximab were not associated with hepatitis B vaccine non-response. In subgroup analyses, RA patients receiving csDMARDs tended to has lower number of responder compared with control group (70% vs 100%, $p = 0.09$). However, the number of high responder was significantly lower in patients receiving csDMARDs compared with control group (52% vs 100%, $p = 0.01$). In RA patients receiving bDMARDs, the number of responder and high responder were significantly lower compared with control group (50% vs 100%, $p = 0.02$, 42% vs 100%, $p = 0.01$). No serious adverse event was observed, but one patient (2%) experienced flare of arthritis.

Conclusion:

In RA patients receiving csDMARDs and bDMARDs, older age and rituximab use associated with impaired humoral immune response to hepatitis B vaccine. Further studies are required to confirm these findings in larger numbers of subjects.

Table Proportions of responders and high responders in rheumatoid arthritis patients receiving conventional synthetic and biological disease modifying anti-rheumatic drugs compared with healthy subjects

	Healthy subjects	All RA patients	RA receiving csDMARDs	RA receiving bDMARDs
	(n = 9)	**(n = 45)**	**(n = 33)**	**(n = 12)**
Responder (anti-HBs ≥ 10 mIU/ml), %	100%	64% ($p = 0.04$)	70% ($p = 0.09$)	50% ($p = 0.02$)
High responder (anti-HBs ≥ 100 mIU/ml), %	100%	49% ($p = 0.01$)	52% ($p = 0.01$)	42% ($p = 0.01$)

Disclosure: S. Intongkam, None; **R. Pakchotanon**, None; **S. Chaiamnuay**, None; **P. Asavatanabodee**, None; **P. Narongroeknawin**, None.

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Abstract Number: 1577

Periodontal Evaluation Is Associated with Increased Likelihood of Achieving Low Disease Activity in Rheumatoid Arthritis with Methotrexate

Melanie Rohr[1], James R. O'Dell[1], Abhijeet Danve[2], Harlan Sayles[1], Geoffrey M. Thiele[3], Jeffrey Payne[4] and Ted R. Mikuls[5], [1]University of Nebraska Medical Center, Omaha, NE, [2]Rheumatology, University of Nebraska Medical Center, Omaha, NE, [3]Research Services 151, Omaha VA Medical Center, Omaha, NE, [4]College of Dentistry, University of Nebraska Medical Center, Lincoln, NE, [5]Medicine, University of Nebraska Medical Center, Omaha, NE
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Background/Purpose: Rheumatoid arthritis (RA) outcomes have improved substantially due to the development of new drug therapies, but also due to emphasis on early aggressive MTX therapy. Although MTX monotherapy is highly effective in approximately one-third of patients, a majority require additional treatment to achieve optimal disease control. Despite growing evidence suggesting a link between periodontitis (PD) and RA pathogenesis there are limited investigations examining whether PD impacts treatment response. This study explores the relationship between PD, smoking, and treatment response to MTX in early RA.

Methods: This is a 16-week, open-label prospective study of RA patients with active disease defined as ≥ 4 swollen and tender joints. Patients completed a questionnaire at enrollment that included items detailing their history of PD: 1. Have you been told you have periodontal disease? 2. Have you required deep cleaning or scaling? 3. Have you been seen by a periodontist? At the initial visit, patients were started on MTX 15 mg weekly. Repeat evaluation at 8 weeks was performed; if patients were not in remission as defined by a DAS28- ESR < 2.6, MTX was increased to 20 mg weekly for the remainder of the study. The primary outcome of this analysis was achievement of low disease activity, defined as a DAS-28 < 3.2 at week 16. For this pilot study, associations of patient factors with treatment response were examined using unadjusted-logistic regression.

Results: Eighty-five RA patients have completed the study and were included in this analysis; 89% were Caucasian and 75% were women. After 16 weeks, 43 (51%) patients achieved a DAS-28 < 3.2. Factors associated with better MTX response included male gender (OR 4.4; 95% CI 1.4-13.8) and prior evaluation by a periodontist (OR 4.0; 95% CI 1.3-13.4) (Table). There was no association of MTX treatment response with other factors examined including age, disease duration, and known PD risk factors including smoking or diabetes. There was no association of "known PD" or "a requirement of deep cleaning" with treatment response.

Conclusion: Results of this pilot study suggest a potential correlation between periodontal disease evaluation and RA treatment response with those reporting prior care from a periodontist being more than 4-times as likely to achieve low disease activity with MTX use. These preliminary findings suggest that PD treatment could be an important component in a comprehensive approach to treating early RA with MTX. Further information is required to confirm these results in a larger patient population and to evaluate if the timing of PD treatment or whether specific oral pathogens or other factors that may be affected by periodontal disease alter MTX response.

Baseline Patient Characteristics and Associations with Achieving Low Disease Activity (n = 90)

Characteristic	DAS-28 < 3.2 Mean (SD) or number (%) (N=43)	DAS-28 ≥ 3.2 Mean (SD) or number (%) (N=42)	OR (95% CI)	P-value
Demographics and Disease Duration				
Mean age, years	58 (14)	36 (18)	1.1 (1.0-1.1)	0.28
Male gender	16 (37%)	5 (12%)	4.4 (1.4-13.8)	**0.01**
Caucasian	39 (95%)	34(83%)	3.7 (0.7-19.7)	0.12
Disease duration, months	20 (43)	19 (29)	1.0 (0.9-1.0)	0.94
Self-reported PD				
Seen by a periodontist	14 (34%)	5 (12%)	4.0 (1.3-13.4)	**0.02**
Known periodontal disease	5 (12%)	8 (19%)	0.5 (0.1-1.6)	0.22
Required deep cleaning	7 (16%)	7 (17%)	1.0 (0.3-3.1)	0.94
PD risk factors				
Smoking				
Never	17 (40%)	19 (45%)	Referent	----
Current Smoker	9 (21%)	9 (21%)	1.0 (0.3-3.2)	0.97
Former Smoker	17 (40%)	14 (33%)	1.4 (0.5-3.8)	1.40
Diabetes mellitus	4 (9%)	7 (17%)	0.5 (0.1-2.0)	0.36

Disclosure: M. Rohr, None; **J. R. O'Dell**, None; **A. Danve**, None; **H. Sayles**, None; **G. M. Thiele**, None; **J. Payne**, None; **T. R. Mikuls**, None.

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Abstract Number: 1578

Serum Rheumatoid Factor and Anti-Cyclic Citrullinated Peptide Antibody Are Associated with Subclinical Interstitial Lung Disease in the Multi-Ethnic Study of Atherosclerosis: A Population-Based Study

Elana J. Bernstein[1], R. Graham Barr[2], John H.M. Austin[3], Steven M. Kawut[4], Ganesh Raghu[5], Jessica L. Sell[6], Eric A. Hoffman[7], John D. Newell Jr.[8],

Jubal R. Watts Jr.[9], P. Hrudaya Nath[10], Sushil K. Sonavane[9], Joan M. Bathon[1], Darcy S. Majka[11] and David J. Lederer[2], [1]Rheumatology, Columbia University College of Physicians & Surgeons, New York, NY, [2]Medicine, Columbia University College of Physicians & Surgeons, New York, NY, [3]Radiology, Columbia University College of Physicians & Surgeons, New York, NY, [4]Division of Pulmonary, Allergy, and Critical Care, University of Pennsylvania, Philadelphia, PA, [5]University of Washington, Seattle, WA, [6]Columbia University College of Physicians & Surgeons, New York, NY, [7]University of Iowa, Iowa City, IA, [8]Radiology, University of Iowa, Iowa City, IA, [9]Radiology, University of Alabama at Birmingham, Birmingham, AL, [10]University of Alabama at Birmingham, Birmingham, AL, [11]Division of Rheumatology, Northwestern University, Chicago, IL
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Background/Purpose: Approximately 30% of adults diagnosed with interstitial lung disease (ILD) have an underlying established autoimmune disease. Based on the strong links between autoimmunity and ILD, we performed the current study to determine whether serum rheumatoid factor (RF) IgM and IgA and anti-cyclic citrullinated peptide antibody (anti-CCP) were associated with subclinical ILD in a population-based cohort.

Methods: MESA is a multi-center, prospective cohort study of 6814 men and women aged 45-84 when recruited in 2000-2002 (exam 1) from 6 US sites. RF and anti-CCP were measured via ELISA at exam 1. Cardiac CT scans were performed at exam 1. Participants returned for 4 subsequent exams, the most recent in 2010-2012. High attenuation areas (HAAs) were assessed on exam 1 cardiac CTs and defined as the volume of lung with a CT attenuation value between -600 and -250 Hounsfield units. 2430 full lung CT scans performed from 2010-2012 were each visually inspected by 1 expert radiologist for the presence or absence of ILD and the following interstitial lung abnormalities (ILAs) affecting >5% of any lung zone in a non-dependent fashion: ground glass abnormalities, reticular abnormalities, diffuse centrilobular nodularity, nonemphysematous cysts, honeycombing, and traction bronchiectasis. RF IgM and IgA and anti-CCP were modeled as the independent continuous variables of interest in linear or Poisson regression models, with HAA and ILA as the dependent variables, adjusting for demographics, anthropometrics, site, smoking, and CT parameters.

Results: RF was measured and HAA quantified in 6736 participants at exam 1; anti-CCP was measured in 6728. Median age was 62 (IQR 53-70). 53% were female, 39% white, 27% African American, 12% Chinese American, and 22% Hispanic. 14% were current smokers; 45% were never smokers. In fully adjusted models, HAA increased by 0.49% per doubling of RF IgM (95% CI 0.11 to 0.86%, p-value = 0.01) and by 0.94% per doubling of RF IgA (95% CI 0.49 to 1.39%, p-value < 0.001). In fully adjusted models, the prevalence of ILA increased by 10% per log unit change in RF IgM (PR 1.10, 95% CI 0.997 to 1.22, p-value = 0.057) and by 17% per log unit change in RF IgA (PR 1.17, 95% CI 1.04 to 1.30, p-value = 0.006). There was no significant association between anti-CCP and HAA or ILA. Among ever smokers, in fully adjusted models, the prevalence of ILA increased by 21% per each natural log unit increase of RF IgM (PR 1.21, 95% CI 1.07 to 1.36), by 21% per each natural log unit increase of RF IgA (PR 1.21, 95% CI 1.08 to 1.36), and by 19% per each log unit increase of anti-CCP (PR 1.19, 95% CI 1.03 to 1.37). Among never smokers, there was no statistically significant association between RF IgM, RF IgA, or anti-CCP and the prevalence of ILA.

Conclusion: In this large population-based multi-ethnic study, we found significant associations between serum levels of RF IgM and RF IgA and subclinical ILD. Moreover, smoking modified the associations of RF and anti-CCP with subclinical ILD. Our findings suggest that RA-related autoimmunity may contribute to the development of ILD in a community-based population sample.

Disclosure: E. J. Bernstein, None; **R. G. Barr**, None; **J. H. M. Austin**, None; **S. M. Kawut**, None; **G. Raghu**, None; **J. L. Sell**, None; **E. A. Hoffman**, VIDA Diagnostics, Inc., 1,VIDA Diagnostics, Inc., 9; **J. D. Newell Jr.**, VIDA Diagnostics, Inc., 1,VIDA Diagnostics, Inc., 5,VIDA Diagnostics, Inc., 9,GSK, 5; **J. R. Watts Jr.**, IPF Rally Educational Advisory Board, 6,IPF Rally Educational Advisory Board, 9; **P. H. Nath**, None; **S. K. Sonavane**, None; **J. M. Bathon**, None; **D. S. Majka**, None; **D. J. Lederer**, None.

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Abstract Number: 1579

Association of Myocardial Abnormalities with N-Terminal Pro-Brain Natriuretic Peptide and Disease Activity in Rheumatoid Arthritis without Cardiac Symptoms, Assessed By Cardiac Magnetic Resonance Imaging

Hitomi Kobayashi[1], Yasuyuki Kobayashi[2], Isamu Yokoe[3], Natsumi Ikumi[4,5], Hirotake Inomata[6], Atsuma Nishiwaki[6], Noboru Kitamura[1], Kaita Sugiyama[6], Hidetake Shiraiwa[6], Masataka Nozaki[6], Yosuke Nagasawa[6], Yoshihiro Matsukawa[5] and Masami Takei[1], [1]Division of Hematology and Rheumatology, Nihon University School of Medicine, Tokyo, Japan, [2]Advanced Biomedical Imaging Informatics, St.Marianna University School of Medicine, Kawasaki, Japan, [3]Rheumatology, Itabashi Chuo Medical Center, Tokyo, Japan, [4]Nihon University School of Medicine, Shinjuku, Japan, [5]Division of Heamatology and Rheumatology, Nihon University School of Medicine, Tokyo, Japan, [6]Nihon University School of Medicine, Tokyo, Japan
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Background/Purpose: Rheumatoid arthritis (RA) is a multi-organ inflammatory disorder associated with high cardiovascular morbidity and mortality. Cardiac involvements are typically clinically silent, only manifesting as heart failure after an extended subclinical phase. Myocardial abnormalities may arise from a number of distinct processes, including myocardial inflammation and/or myocardial fibrosis, any of which may be active in RA. We aimed to assess cardiac involvements using a cardiac magnetic resonance imaging (CMR) approach and to determine its association with disease characteristics and N-terminal pro-brain natriuretic peptide (NT-proBNP) level in RA patients without cardiac symptoms.

Methods: Consecutive RA patients without cardiac symptoms were enrolled. RA patients with no history and/or clinical findings of systemic and pulmonary hypertension, coronary artery disease, valvular heart disease, atrial fibrillation, diabetes mellitus, and dyslipidemia underwent CMR. RA patients received conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) or biologic DMARDs (bDMARDs). Late gadolinium enhancement (LGE) was obtained for the assessment of myocardial fibrosis. Using Black-Blood T2-weighted image (T2-WI), myocardial inflammation could be assessed. We evaluated the prevalence of CMR abnormalities, and investigated possible associations of CMR abnormalities with RA disease characteristics, and NT-proBNP level.

Results: Sixty patients (mean age, 55.2 ± 1.3 years; 85% female) were enrolled. Thirty RA patients received csDMARDs [25, methotrexate (MTX) (8.7±2.1mg); 5, other drugs)] and 30 RA patients received bDMARDs [15, infliximab 3 mg/kg; 15, tocilizumab 8 mg/kg plus methotrexate (8.6±1.4 mg)]. Twenty RA patients (33%) demonstrated myocardial abnormalities. High intensity on T2-WI was seen in seven RA patients (11%). LGE was found in 19 RA patients (32%), six of whom also demonstrated high intensity on T2-WI. Simplified Disease Activity Index (SDAI) scores were significantly higher in LGE-positive compared to LGE-negative (p=0.011). LGE was significantly associated with high NT-proBNP and SDAI (p=0.005, p=0.018, respectively). The use of bDMARDs was significantly associated with LGE-negative findings (p=0.0017). Other RA characteristics such as disease duration, autoantibody status, and cardiovascular risk factors were not significantly associated with myocardial abnormalities. After adjusting for confounding by age, RA duration, rheumatoid factor and bDMARDs, the association of LGE with SDAI remained significant (p=0.023), in which the SDAI scores were, on average, 10.9 units higher in LGE-positive than in LGE-negative. Receiver operating characteristic analysis showed NT-proBNP reliably detected myocardial abnormalities (area under the curve 0.856; 95% confidence interval, 0.833–0.904).

Conclusion: Subclinical myocardial abnormalities are common in RA patients without cardiac symptoms, associated with SDAI and NT-proBNP level. NT-proBNP level reliably detected the presence of cardiac involvements appeares to be useful markers to risk stratify RA patients.

Disclosure: H. Kobayashi, None; **Y. Kobayashi**, None; **I. Yokoe**, None; **N. Ikumi**, None; **H. Inomata**, None; **A. Nishiwaki**, None; **N. Kitamura**, None; **K. Sugiyama**, None; **H. Shiraiwa**, None; **M. Nozaki**, None; **Y. Nagasawa**, None; **Y. Matsukawa**, None; **M. Takei**, None.

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Abstract Number: 1580

Abnormal High Density Lipoproteins in Synovial Fluid from Patients with Rheumatoid Arthritis Compared to Patients with Non-Inflammatory Arthritis

Christina Charles-Schoeman[1], Yuen Yin Lee[2], Ani Shahbazian[1], David Meriwether[3], Peter Kim[2] and Srinivasa T. Reddy[4], [1]Medicine-Rheumatology, University of California Los Angeles, Los Angeles, CA, [2]Medicine- Rheumatology, University of California Los Angeles, Los Angeles, CA, [3]Medicine-Cardiology, University of California Los Angeles, Los Angeles, CA, [4]Medicine-Cardiology, University of California Los Angeles, Los Angeles, CA
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Background/Purpose: High levels of rheumatoid arthritis (RA) disease activity have been associated with abnormal function of circulating high density lipoproteins (HDL) and increased cardiovascular risk. Oxidative modifications to the HDL particle by enzymes such as myeloperoxidase (MPO) occur in atherosclerotic plaques of non-RA patients and adversely affect HDL function. In the current work, we evaluated the oxidant environment and anti-oxidant function of HDL in synovial fluid (SF) from RA patients compared to patients with non-inflammatory arthritis (NIA).

Methods: HDL was isolated from synovial fluid of 10 RA patients and 11 NIA patients by dextran bead precipitation. HDL's anti-oxidant function was measured by a cell free assay as described previously (*A&R* 2009; 60(10): 2870-9). MPO and paraoxonase 1 (PON1) activity (using both paraoxonase and arylesterase assays), were measured in SF by previously published assays with minor modifications (*ARD* 2012 Jul;71(7):1157-62, *A&R* 2012; 64(6):1828-37). Oxidation products of arachidonic acid and linoleic acid including 5 hydroxyeicosatetraenoic acid (HETE), 12-HETE, 15-HETE, 9-hydroxyoctadecadienoic acid (HODE) and 13-HODE were measured in synovial fluid by mass spectrometry as described previously with minor modifications (*Drug Metab Lett.* 2010; 4(3): 139-48). Total and HDL cholesterol (HDL-C) levels in SF were determined by standard methods.

Results: HDL in SF from RA patients had significantly worse anti-inflammatory, anti-oxidant function as measured by a higher mean HDL inflammatory index (HII) compared to SF HDL from patients with NIA (see table). RA SF had significantly higher MPO activity and higher levels of 15-HETE which were most strongly correlated with SF macrophage cell counts (r values= 0.7 and 0.6 respectively, p values <0.05) and showed trends for correlations with the HII (r = 0.5 and 0.3 respectively, p values =0.2). Higher levels of total cholesterol, HDL-C, and PON1 activity were noted in RA SF compared to NIA SF (see table).

Conclusion: HDL is increased in RA SF and is pro-inflammatory and pro-oxidant compared to HDL from NIA SF. These findings suggest a potential mechanism by which circulating HDL in active RA patients lose their protective capacity by exposure to the pro-oxidant joint milieu, linking high RA disease activity to abnormal HDL function, and potentially increased CV risk.

Group	HII	Age (yrs)	F (%)	SF total WBC Ct.	SF Neut. Ct.	SF Mac. Ct.	MPO activity (ng/ml)	HDL-C (mg/dL)	TC (mg/dL)	PON activity (U/ml)	Aryl activity (U/ml)	5HETE (ng/ml SF)	12HETE (ng/ml SF)	15HETE(ng/ml SF)	9HODE (ng/ml SF)	13HODE (ng/ml SF)
RA SF	2.1 ± 1.9*	55± 13	60	15409 ± 6153*	11840±7000*	2074±1490*	74 ± 48*	18 ± 10	59 ± 17*	412 ± 150*	93± 43*	0.44± 0.33	0.12± 0.07	0.37± 0.07*	1.31± 1.70	4.15± 4.20
NIA SF	0.5 ± 0.1	69 ± 19	55	617 ± 496	120 ± 177	247 ± 135	0.9 ± 0.6	12 ± 7	26 ± 17	122± 129	27± 10	0.57± 0.68	0.12± 0.05	0.26± 0.11	0.63± 0.36	2.02± 1.20

HII=HDL Inflammatory Index; F = Female; WBC = White blood cell; Ct = count; Neut = neutrophil; Mac = macrophage; TC = total cholesterol; Aryl = Arylesterase. *p value < 0.05 compared to NIA.

Disclosure: C. Charles-Schoeman, None; **Y. Y. Lee**, None; **A. Shahbazian**, None; **D. Meriwether**, None; **P. Kim**, None; **S. T. Reddy**, None.

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Abstract Number: 1581

Cardiac Involvement in Patients with Amyloid a Amyloidosis Due to Rheumatoid Arthritis

Daisuke Kobayashi[1], Satoshi Ito[1], Yoko Wada[2], Akira Murasawa[1], Ichiei Narita[2] and Kiyoshi Nakazono[1], [1]Niigata Rheumatic Center, Shibata, Japan, [2]Department of Clinical Nephrology and Rheumatology, Niigata University Graduate School of Medical and Dental Sciences, Niigata, Japan
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Background/Purpose:

Rheumatoid arthritis (RA) is one of the major causes of amyloid A (AA) amyloidosis, the major organs affected being the kidneys and gastrointestinal (GI) tract. Although cardiac amyloidosis is the principal cause of death in patients with amyloid L (AL) amyloidosis, significant cardiac involvement in AA amyloidosis is thought to be rare. On the other hand, the survival rate of hemodialysis patients with AA amyloidosis associated with RA has been shown to be low, and our previous study revealed that cardiac failure accounted for more than half of the mortality in these patients. Here we attempted to clarify the nature of cardiac involvement in patients with RA-associated AA amyloidosis and its clinical significance.

Methods:

Forty-seven RA patients (7 males, 40 females) with AA amyloidosis who were followed up at our hospital and Niigata University Hospital between 2001 and 2014 were enrolled. All of the patients fulfilled the 2010 ACR/EULAR classification criteria for RA, had undergone biposy of the GI tract (n=41), myocardium (n=2), kidney (n=2), or abdominal fat (n=2), and had been confirmed to have reactive AA amyloidosis by histopathological examination. The patients' background data and echocardiographic features were analyzed retrospectively. Data indicated are median values [range].

Results:

The median age of the 47 patients was 68 [48-89] years, the mean period between RA onset and echocardiographic examination was 25 [2-43] years, and

the mean period between the onset of AA amyloidosis and echocardiographic examination was 1723 [0-7682] days. Echocardiography showed that the median left ventricular (LV) posterior wall thickness was 10.9 [6.0-16.6] mm, with an interventricular septal thickness of 11.0 [5.5-17.0] mm, and an ejection fraction (EF) of 70.0% [32.3-85.4%]. Twenty-seven patients with a LV wall thickness of >11.0 mm were assigned to a LV hypertrophy (LVH+) group, and their clinical features were compared to the remainder (LVH- group; n=20). The Mann-Whitney U test demonstrated no significant differences between the LVH+ and LVH- groups at the baseline in terms of patient age (68 [48-89] years vs. 68 [50-86] years; p=0.829), duration of RA (27[4-41] years vs. 23[2-43] years; p=0.59), and DAS28(3)-CRP (2.73[1.15-5.36] vs. 3.23 [1.42-6.87]; p=0.09). Patients in the LVH+ group had a higher systolic blood pressure (137.4 [116-170] vs. 128.1 [116-170] mmHg in the normal group, p=0.024), a lower echocardiogram EF (68.1% [32.3-85.0%] vs 72.5% [59.6-79.3%]; p=0.03), and a lower estimated glomerular filtration rate (eGFR) (38.7 [13.0-98.8] ml/min/1.73 m^2 vs. 62.8 [19.2-126.4] ml/min/1.73 m^2; p=0.003). Fatalities in the LVH group (n=27) vs. normal group (n=20) were 13 vs. 1 at three years. Log rank test revealed that an older age (>65 years; p=0.073), lower eGFR (<40 ml/min/1.73 m^2; p=0.027), and LVH+ (p=0.002) were associated with higher mortality at 3 years after echocardiography. The Cox hazard regression model indicated LVH+ as an independent risk factor (hazard ratio = 12.4; 95% CI 1.62 – 94.8; p = 0.016).

Conclusion:

Thickening of the LV wall is a notable cardiac feature of patients with AA amyloidosis and is strongly suspected to contribute to a poor prognosis.

Disclosure: D. Kobayashi, None; **S. Ito**, None; **Y. Wada**, None; **A. Murasawa**, None; **I. Narita**, None; **K. Nakazono**, None.

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Abstract Number: 1582

Joint Damage Associated with Loss of Body Mass in Rheumatoid Arthritis

Jose Felix Restrepo[1], Inmaculada del Rincon[2], Daniel Battafarano[3] and Agustin Escalante[4], [1]Rheumatology, University of Texas Health Science Center at San Antonio, San Antonio, TX, [2]Medicine, University of Texas Health Science Center at San Antonio, San Antonio, TX, [3]Rheumatology, San Antonio Military Medical Center, JBSA - Ft Sam Houston, TX, [4]Dept. of Medicine-Rheumatology, University of Texas Health Science Center at San Antonio, San Antonio, TX

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Background/Purpose:

Body mass index (BMI) is a predictor of long-term outcome in rheumatoid arthritis and has been associated with joint damage. Our objective was to examine the association between changes in body mass and joint damage in a cohort of rheumatoid arthritis patients.

Methods:

From 1996 to 2009, we recruited 1328 consecutive patients who met the 1987 criteria for RA from private and public rheumatology practices in San Antonio, Texas. All patients participated in a comprehensive baseline evaluation of their clinical and psychosocial characteristics conducted by a physician and trained research assistants and yearly follow up evaluations in which we assessed clinical and laboratory features.

We included the following variables in the analysis: age of RA onset, duration of RA, sex, ethnicity, DAS28 ESR, smoking and current use of steroids. Joint damage was measured using a radiograph of the hands, scored according to Sharp technique. Body mass was measured using the height and weight, expressed as Kg/M^2.

Statistical Analysis:

We used cross-sectional time- series, generalized estimating equation regression models including all follow up visits to estimate independent associations between variables and body mass change over time.

Results:

We studied 1328 patients (347 male, 981 female) who participated in 3609 evaluations during a period of 8338 person- years. During this time body mass was lost at a rate of 0 .26 Kg/M2 per 5 years ($p<0.0001$). The body mass of patients in the lowest joint damage tertile remained stable, with a rate of change of -0.011 Kg/M2 per 5-years. By comparison, patients in the highest damage quartile lost body mass at a rate of 0.29 Kg/M^2 per 5 years ($p<.0001$). Other variables independently associated with lower BMI were age of RA onset, smoking, and non-Hispanic White ethnicity. Current use of steroids and the DAS28ESR were not associated with changes in BMI or the risk of weight loss independent of other factors. When we divided the sample into tertiles according with the sharp score, the association with body mass displayed a dose-response pattern, with higher sharp scores associated with lower body mass (Table 1).

Table 1. Rate of body mass loss according to the sharp score

Sharp Score	Rate of body mas loss (Kg/M^2) per 5 year(95% CI)	p-value
0 - 23	-0.011 (-0.17, 0.20)	Ref
24 - 85	-0.23 (-0.39, -0.069)	**<0.005**
86 - 471	-0.29 (-0.44, -0.14)	**<0.0001**

Conclusion:

Joint damage was associated with loss of body mass in this RA cohort, with the greatest loss observed among patients with the most severe joint damage. Active smoking, age of onset of RA, duration of RA and white ethnicity were also associated with greater loss of body mass over time. This provides evidence of the systemic effects of joint inflammation.

Disclosure: J. F. Restrepo, None; **I. del Rincon**, None; **D. Battafarano**, None; **A. Escalante**, None.

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Abstract Number: 1583

Identifying Risk Factors for Progression of Rheumatoid Arthritis-Associated Interstitial Lung Disease

Yashaar Chaichian[1], Dina Bassiri[2], Imre Noth[3], Mary Strek[3], Tammy Utset[1] and Rekha Vij[3], [1]Medicine, Section of Rheumatology, University of Chicago Medical Center, Chicago, IL, [2]Statistical & Applied Research, ACT, Inc., Iowa City, IA, [3]Medicine, Section of Pulmonary/Critical Care, University of Chicago Medical Center, Chicago, IL

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Session Time: 9:00AM-11:00AM

Background/Purpose:

Interstitial lung disease (ILD) is recognized as a frequent extra-articular manifestation of rheumatoid arthritis (RA) associated with significant morbidity and mortality. Nevertheless, risk factors predicting progression of pulmonary disease in RA-ILD are poorly understood. Specifically, no studies to date have examined whether race/ethnicity or cyclic citrullinated peptide (CCP) antibodies are associated with a progressive disease course. In addition, the frequency of parallel lung and joint activity in patients with RA-ILD is unknown. We assessed the aforementioned clinical factors, along with others, for their association with progressive RA-ILD. We secondarily examined how often pulmonary activity parallels RA joint activity.

Methods:

We performed a retrospective observational study of 47 adults with RA-ILD who met ACR 1987 classification criteria for RA and had typical interstitial abnormalities on chest CT not due to other causes. Progressive RA-ILD was defined as a decrease in forced vital capacity of >10% predicted or diffusing capacity for carbon monoxide of >15% predicted on a minimum of two successive pulmonary function tests (PFTs) ≥8 weeks apart. Parallel ILD and joint activity required concordant worsening in PFTs and evidence of joint disease flare over a three month period. Fisher's exact test and logistic regression were used to compare categorical variables of interest, while an unpaired t-test and logistic regression were used for continuous variables.

Results:

Thirty six patients (77%) had progressive RA-ILD; 11 patients (23%) had stable RA-ILD. On bivariate analysis, high-titer rheumatoid factor (RF) was significantly associated with progressive RA-ILD (p=0.0394). There was also a trend toward association in African Americans (p=0.0912), as well as in patients with high-titer CCP antibodies (p=0.0973) and history of tobacco abuse (p=0.0933). Multivariate analysis using regular logistic regression with overall model fit of p <0.05 suggested statistically significant association with high-titer RF (p=0.0378), and a trend toward association with ILD progression in African Americans (p=0.0514) and in those with a smoking history (p=0.0820). Exact logistic regression, however, revealed only a trend toward association between presence of high-titer RF and progressive RA-ILD (p=0.0936). Twenty eight patients had serial rheumatology assessments coinciding with PFTs: 9 patients (32%) had parallel ILD and joint activity. None of the factors associated with RA-ILD disease progression were significantly associated with parallel or non-parallel ILD and joint activity.

Conclusion:

RA-ILD patients with high-titer RF in particular, as well as those who are African American or have a history of tobacco abuse may be at higher risk for progressive lung disease and warrant close monitoring. In contrast, multivariate analysis suggests that high-titer CCP antibodies do not appear to be associated with disease progression. As most RA-ILD patients did not have parallel ILD and joint activity, different factors may contribute to pulmonary and articular disease flares.

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Abstract Number: 1584

Metabolic Syndrome Is Associated with Disease Activity in Patients with Rheumatoid Arthritis: A Prospective Cohort Study

Pongchirat Tantayakom[1], Ajchara Koolvisoot[1], Emvalee Arromdee[1], Praveena Chiowchanwisawakit[1], Chayawee Muangchan[1] and **Wanruchada Katchamart**[2], [1]Division of Rheumatology, Department of Medicine, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand, [2]Medicine, Division of Rheumatology, Department of Medicine, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand
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Background/Purpose: Rheumatoid arthritis (RA) is a chronic systemic inflammatory disease involving articular and extra-articular systems, including cardiovascular (CVS), respiratory, as well as hematologic systems, etc. Among extra-articular manifestations, CVS disease is a leading cause of morbidity and mortality in the recent years. Patients with RA also have increased risk of metabolic syndrome (MS), compared to general population**.** Chronic systemic inflammation from both RA and MS could promote endothelial dysfunction and atherosclerotic plaques development leading to increase in CVS risk. Our objective was to investigate the association between MS and disease activity in patients with RA.

Methods: Siriraj Rheumatoid Arthritis registry is a prospective cohort study establishing since May 2011. A total of 267 patients who had complete data in February 2015 were included in these analyses. All clinical and laboratory data related to disease activity, functional status, and parameters of MS according to the 2001 National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) were collected. For cumulative disease activity, time-adjusted mean (TAM) of disease activity score (DAS) 28 was calculated. The TAM of DAS28 is the area under a curve (AUC) of DAS28 plotted against time, divided by the total length of time from first to last measurement. Univariate and backward stepwise multivariate analyses were performed to identify factors associated with MS.

Results: Most (88%) were female with the mean age ± standard deviation of 59 ± 11.1 years old. MS was found in 43 patients (16%). High blood pressure was the most prevalent components of MS in both RA with MS and non-MS. Patients with MS had a significantly lower proportion of patients with remission (time adjusted mean of disease activity score 28 or DAS28 < 2.6) than those with non-MS (2.3% vs. 16.5%, p = 0.02). Multiple logistic regression analysis identified 4 independent factors associated with MS including age [odds ratio (OR) 1.01, 95% confidence interval (CI) (0.98 to 1.05)], body mass index [OR 1.2, 95% CI 1.1 to 1.3], educational level ≤ 12 years [OR 5.92, 95% CI 1.47 to 23.83], and disease remission [OR 0.11, 95% CI 0.01 to 0.93]. This model correctly predicted 84% of cases.

Conclusion: Disease activity of RA, body mass index, and educational level are associated with metabolic syndrome in patients with RA

Table Odds ratios for the presence of metabolic syndrome in patients with rheumatoid arthritis

	Univariate analysis			Multivariate analysis		
	OR	**95% CI**	**P value**	**OR**	**95% CI**	**P value**
Age	1.02	0.99-1.06	0.14	1.01	0.98-1.05	0.44
Body mass index	1.17	1.09-1.25	< 0.001	1.20	1.1-1.3	< 0.001
Education level ≤ 12 years	3.8	1.3-11.1	0.02	5.92	1.47-23.83	0.01
Rituximab use	9.69	2.22-42.25	0.002	17.44	2.91-104.67	0.002
TAM of DAS28 < 2.6	0.12	0.16-0.90	0.04	0.11	0.01-0.93	0.04

CI = confidence intervals; OR = odds ratio; TAM = time-adjusted mean; DAS 28= disease activity score28

Disclosure: P. Tantayakom, None; **A. Koolvisoot**, None; **E. Arromdee**, None; **P. Chiowchanwisawakit**, None; **C. Muangchan**, None; **W. Katchamart**, None.

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Abstract Number: 1585

Vaccination Uptake in Patients with Rheumatoid Arthritis Treated with Disease-Modifying Anti-Rheumatic Drug Therapy: A Retrospective Cohort Study Using UK Primary Care Electronic Medical Records

Ruth Costello[1], Kevin L. Winthrop[2], Stephen R Pye[1] and William G Dixon[3], [1]Arthritis Research UK Centre for Epidemiology, The University of Manchester, Manchester, United Kingdom, [2]Oregon Health and Science University, Portland, OR, [3]Manchester Academic Health Sciences Centre, Arthritis Research UK Centre for Epidemiology, The University of Manchester, Manchester, United Kingdom

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Background/Purpose: The guidelines for the management of rheumatoid arthritis (RA) recommend an annual influenza vaccine and a pneumonia vaccination (EULAR, 2011), prior to starting disease-modifying anti-rheumatic drug (DMARD) therapy. It is not clear how well these guidelines are adhered to in the UK. This study aimed to measure the extent to which patients with RA are vaccinated in the UK, and to determine the timing of the vaccinations in relation to starting DMARD therapy.

Methods: This was a retrospective cohort study using data from the Clinical Practice Research Datalink (CPRD). An inception cohort of adult patients, diagnosed with RA and prescribed DMARD therapy during follow-up (1st January 2000 – 31st December 2013) were identified. Vaccination status was considered as follows: 1) Influenza: The influenza season was estimated to start on 1st September each year and all patients were considered unvaccinated at this point. Patients were considered vaccinated if they received an influenza vaccine between 1st September and 31st August the following year. 2) Pneumonia: Following vaccination patients were considered vaccinated for the rest of follow-up. For both influenza and pneumonia vaccines, descriptive statistics show i) the proportion having at least one vaccination, ii) the observed and expected use and iii) the proportion of first vaccinations occurring prior to DMARD therapy initiation. Patients were stratified by age 65 at the start of follow-up, given differences in vaccination guidelines for the general population.

Results: There were 17877 patients with RA identified who were treated with DMARD therapy during follow-up (median follow-up 5.1 years).

Age below 65 years (N=11391): 8309 (73%) patients had received at least one influenza vaccination, of whom 3021 (36%) were vaccinated prior to starting DMARD therapy. Of those expected to have up to 5 vaccinations, 20% - 30% received all expected vaccinations. There were 4960 (44%) patients who had received at least one pneumonia vaccination, of whom 1269 (26%) were vaccinated prior to starting DMARD therapy.

Age 65 years and over (N=6486): 5858 (90%) patients received at least one influenza vaccination, of whom 4590 (78%) were vaccinated prior to starting DMARD therapy. Of those expected to have up to 5 vaccinations, 55%-75% received all expected vaccinations. There were 4026 (62%) patients who received at least one pneumonia vaccination, of whom 2498 (62%) received a vaccination prior to starting DMARD therapy (Table 1).

Conclusion: One in five patients received no influenza vaccine and 1 in 2 patients received no pneumonia vaccine over 5 years of follow-up. Of those vaccinated, only half of patients were vaccinated prior to initiating DMARD therapy. In a five year period, only 1 in 3 patients received regular annual influenza vaccines. There remains significant scope to improve the uptake of vaccinations in patients with RA.

Table 1: Influenza and pneumonia vaccination uptake, and the timing of vaccinations in relation to starting DMARD therapy (N=17,877).

		Influenza vaccination *N (%) unless otherwise specified*			**Pneumonia vaccination** *N (%) unless otherwise specified*		
		<65 years	**≥65 years**	**Total**	**<65 years**	**≥65 years**	**Total**
Ever had a vaccination[1]	Yes	8309 (72.9)	5858 (90.3)	14167 (79.2)	4960 (43.5)	4026 (62.1)	8986 (50.3)
	No	3082 (27.1)	628 (9.7)	3710 (20.8)	6431 (56.5)	2460 (37.9)	8891 (49.7)
Vaccinated when DMARDs initiated[2]	Yes	3021 (36.4)	4590 (78.4)	7611 (53.7)	1269 (25.6)	2498 (62.0)	3767 (41.9)
	No	5288 (63.6)	1268 (21.7)	6556 (46.3)	3691 (74.4)	1528 (38.0)	5219 (58.1)
Number of vaccinations received vs number expected (received/expected)[1] *For influenza vaccination those who were expected to have 5 vaccinations or less included only (N=7691)*	0/1	146 (69.5)	35 (25.2)	181 (51.9)	6431 (56.5)	2460 (37.9)	8891 (49.7)
	1/1	64 (30.5)	104 (74.8)	168 (48.1)	4743 (41.6)	3809 (58.7)	8552 (47.8)
	2+/1	-	-	-	217 (1.9)	217 (3.4)	434 (2.5)
	0/2	499 (47.6)	121 (16.0)	620 (34.4)			
	1/2	274 (26.1)	139 (18.4)	413 (22.9)	-	-	-
	2/2	275 (26.2)	496 (65.6)	771 (42.7)			
	0/3	420 (36.1)	101 (12.3)	521 (26.3)			
	1/3	205 (17.6)	67 (8.1)	272 (13.7)			
	2/3	260 (22.4)	172 (20.9)	432 (21.7)	-	-	-
	3/3	277 (23.8)	483 (58.7)	760 (38.3)			
	0/4	330 (30.5)	64 (8.8)	394 (21.8)			
	1/4	141 (13.0)	31 (4.3)	172 (9.5)			
	2/4	134 (12.4)	52 (7.1)	186 (10.3)			
	3/4	259 (24.0)	159 (21.8)	418 (23.1)	-	-	-
	4/4	217 (20.1)	423 (58.0)	640 (35.4)			
	0/5	307 (29.0)	66 (9.6)	373 (21.4)			
	1/5	123 (11.6)	22 (3.2)	145 (8.3)			
	2/5	99 (9.4)	23 (3.4)	122 (7.0)			
	3/5	128 (12.1)	54 (7.9)	182 (10.4)			
	4/5	182 (17.2)	143 (20.9)	325 (18.7)	-	-	-
	5/5	220 (20.8)	376 (55.0)	596 (34.2)			

[1] Whole cohort (N=17877) [2] Those who ever received a vaccination only.

Disclosure: R. Costello, None; **K. L. Winthrop**, BMS, 2,AbbVie, BMS, UCB, Amgen, 5; **S. R. Pye**, None; **W. G. Dixon**, None.

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Abstract Number: 1586

Weight Loss in Obese Rheumatoid Arthritis (RA) Patients Improves Disease Activity without Modifying RA Treatment

Elisa Gremese[1], Maria Rita Gigante[1], Barbara Tolusso[1], Anna Laura Fedele[1], Silvia Canestri[1], Barbara Aquilanti[2], Clara Di Mario[1], Luca Petricca[1], Stefano Alivernini[1] and Gianfranco Ferraccioli[1], [1]Division of Rheumatology, Institute of Rheumatology, Catholic University of the Sacred Heart, Rome, Italy, [2]Dietology Service, Association Columbus, Catholic University of the Sacred Heart, Rome, Italy
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Background/Purpose: Obesity is recognized as a systemic, low-grade inflammatory state and the adipose tissue as an endocrine organ releasing pro-inflammatory cytokines. On the other hand, obesity is one of the potentially preventable risk factors for rheumatoid arthritis (RA) being associated with RA onset, disease severity and poor response to therapy (1,2). The aim was to evaluate whether in obese RA patients with a low-moderate disease activity, a weight loss obtained with a controlled nutritional intervention may lead to an improvement of disease activity and to reduce the need of increasing therapeutic regimens, without modifying RA treatment during the study period.

Methods: 63 consecutive obese RA patients (BMI>30 Kg/m2), not in disease remission and with a low-moderate disease activity (1.6<DAS<3.7), in stable therapy with conventional DMARDs (cDMARDs) and/or biological DMARDs (bDMARDs) for at least 12 weeks, were enrolled. All patients underwent a scheduled dietetic regimen under a Nutritionist guide, aimed at a weight loss >5% of the baseline weight at the 6thmonths (T6) of follow-up, maintaining unchanged the RA therapy. Patients were evaluated by the Rheumatologist and the Nutritionist every 2 months and at each visit clinical and laboratory data and the ACR/EULAR core data set was registered. Disease activity was evaluated by the Disease Activity Score on 44 joints (DAS) and the Simplified Disease Activity Index (SDAI).

Results: Of the 63 RA patients reaching the 6thmonth FU (82.8% female, age 56.5±12.5 years, disease duration 8.1±8.1 years, 66.9% seropositive, baseline DAS 2.8±0.7, baseline BMI 35.3±4.3), 35 (55.5%) were under cDMARDs-only therapy and 28 (44.5%) under bDMARDs therapy+/- cDMARDs.

At T6, the mean reduction of body weight was 6.7±4.7 Kg (7.3±6.0% of baseline body weight, p<0.01 vs T0) and that of DAS was 0.8±1.0 (DAS T6: 2.0±0.7, p<0.01 vs DAS T0).

Dividing patients according to the percentage of weight loss at T6, the 40 (63.5%) RA patients reaching a weight reduction >5% of the baseline body weight obtained higher rates of DAS remission than patients with a weight reduction <5% (DAS remission at T6: 35.0% vs 9.1%, respectively, p=0.03), as well as of SDAI remission (34.2% vs 4.8%, p=0.01).

The difference was even more significant considering a weight reduction >10%, with a DAS remission at T6 of 55.6% in RA patients reaching >10% of weight reduction with respect to 13.6% in patients not reaching this outcome (p<0.01), and a SDAI remission at T6 of 62.5% and 9.3%, respectively (p<0.01). Results were similar between patients under cDMARDs-only and bDMARDs treatment.

Conclusion: A weight loss obtained with a controlled diet in obese still active RA patients can allow to obtain a better disease control without changing the treatment of RA, and in particular a weight loss >10% permits to reach disease remission in a significant percentage of patients, therefore reducing the need of an increase/modification of therapy. The effects of weight loss based on a nutritional intervention, and so applicable at the population level, on the RA disease course appears to be crucial in terms of potential clinical and pharmacoeconomics perspectives.

References:

1. Crowson CS, Arthritis Care Res 2013

2. Gremese E, Arthritis Care Res 2012

Disclosure: E. Gremese, None; **M. R. Gigante**, None; **B. Tolusso**, None; **A. L. Fedele**, None; **S. Canestri**, None; **B. Aquilanti**, None; **C. Di Mario**, None; **L. Petricca**, None; **S. Alivernini**, None; **G. Ferraccioli**, None.

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Abstract Number: 1587

Deriving a Comorbidity Index Form the Meddra Classification: Performance of Rheumatic Disease Comorbidity Index, Charlson-Deyo Index and Functional Comorbidity Index Among Patients with RA in NOR-DMARD Cohort

Polina Putrik[1], Sofia Ramiro[2], Elisabeth Lie[3], Andras Keszei[4], Tore K. Kvien[5], Till Uhlig[6] and Annelies Boonen[7], [1]Department of Internal Medicine, Division of Rheumatology, Maastricht University Medical Center, Maastricht, Netherlands, [2]Rheumatology, Leiden University Medical Center, Leiden, Netherlands, [3]Dept. of Rheumatology, Diakonhjemmet Hospital, Oslo, Norway, [4]Epidemiology, Maastricht University, Maastricht, Netherlands, [5]Dept of Rheumatology, Diakonhjemmet Hospital, Oslo, Norway, [6]Diakonhjemmet Hospital, Oslo, Norway, [7]Maastricht University Medical Center, Maastricht, Netherlands

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Background/Purpose:

Comorbidities have an important impact on outcomes in chronic diseases. A new and simple to compute index, the Rheumatic Disease Comorbidity Index (RDCI), has recently been proposed in addition to existing indices. Evidence on its performance in relation to functional status and health-related quality of life compared to other known indices is scarce.

Medical Dictionary for Regulatory Activities (MedDRA) is a clinically validated international medical terminology dictionary used by regulatory authorities and by researchers to code comorbidities and adverse events. However, no simple algorithm is as yet available to convert MedDRA classification into existing comorbidity indices.

Objective of this study was o develop algorithms to calculate the RDCI, Charlson-Deyo index (CDI) and Functional comorbidity index (FCI) from MedDRA, and to test in patients with RA how MedDRA-derived indices predict function (HAQ) and health-related quality of life (based on SF-36).

Methods:

First, two researchers coded the conditions listed in MedDRA classification into the categories of each index. Next, using data from patients with RA from the Norwegian NOR-DMARD study (2000-2012), we tested predictive values of the RDCI, CDI, and FCI for physical function (HAQ) and Physical and Mental Component Summary measures (PCS and MCS) from SF-36. Outcomes (HAQ, MCS and PCS) were modeled at baseline and over time. Two models were constructed for each outcome: a bare model (age and gender) and a clinical model (including also DAS28). Generalised estimating equations (GEE) (outcome over time) and linear regression models (outcome at baseline) were fitted and model fit measures (the quasi likelihood under the independence model criterion (QIC) for GEE and R-square for linear regression) were compared. We examined which of the three indices provided the best model fit to draw conclusions about the comparative performance of the indices: the lower the QIC or the higher the R-square, the better the model fit.

Results:

Data from 4,080 patients were analysed (28.4% male, mean age 56 yrs, mean DAS28 at baseline 4.9). RDCI (mean 0.6, range 0-6) and FCI (mean 0.40, range 0-6) performed comparably well in predicting the three outcomes considered. CDI (mean 0.24, range 0-7) performed worst on all outcomes HAQ, SF-36 PCS and MCS. Of note, the comorbidities had almost no influence on SF-36 MCS (Table).

Table. Comparison of model fit statistics (QIC and R-square values) between models with RDCI, CDI and FCI (independent variables, separate models) and HAQ and physical and mental components of the SF-36 as an outcome

	QIC model fit for generalized mixed models*					
	Bare (Age+Gender)			Clinical (Age+Gender+DAS28)		
Outcome	RDCI	CDI	FCI	RDCI	CDI	FCI
HAQ	6412.30	6461.20	6393.20	4082.80	4103.90	4068.50
PCS	2924367.70	2965552.40	2925563.40	1730682.70	1752722.20	1731299.80
MCS	3051232.70	3060469.10	3042722.20	2515911.80	2520164.00	2510062.10
	R2 model fit for linear regressions*					
	Bare (Age+Gender)			Clinical (Age+Gender+DAS28)		
Outcome	RDCI	CDI	FCI	RDCI	CDI	FCI
HAQ	3.23%	2.57%	3.50%	28.30%	27.95%	28.47%
PCS	5.15%	3.90%	5.36%	23.78%	22.94%	23.92%
MCS	0.96%	0.79%	1.00%	3.15%	3.04%	3.18%

*n=3842-4006

best model fit | worst model fit

Conclusion:

We have shown that the MedDRA classification, which is widely used in registries and clinical trials can be used to compute currently used comorbidity indices. The new RDCI performed comparably well with FCI on HAQ and the SF-36 (both physical and mental components). CDI performed worst on all outcomes explored, but it needs to be reminded the CDI was developed to predict mortality and not functioning.

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Abstract Number: 1588

Increased Fracture Risk in Patients with Early Rheumatoid Arthritis: A Prospective General Population-Matched Cohort Study

Britt-Marie Nyhäll-Wåhlin[1], Sofia Ajeganova[2], Ingemar F Petersson[3] and Maria LE Andersson[4], [1]Department of Rheumatology, Falun Hospital, Falun, Sweden, [2]Rheumatology unit, Department of Medicine,, Karolinska Institutet at Karolinska University Hospital Huddinge, Stockholm, Sweden, [3]Lund University, Department of Orthopedics, Clinical Sciences Lund, Lund, Sweden, [4]R&D Centre Spenshult, Halmstad, Halmstad, Sweden
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Background/Purpose:

Fragility fractures represent one of the serious extra-articular manifestations of rheumatoid arthritis (RA). The aim of this study was to investigate whether fracture incidence differs between patients with early RA and the general population.

Methods:

The patients were recruited from the BARFOT (Better Anti-Rheumatic FarmacO Therapy) cohort, which is a Swedish multicentre observational study of patients with early RA (disease duration ≤ 12 months at inclusion). All patients fulfilled the 1987 American College of Rheumatology classification criteria and were included between 1992 and 2006. Each patient was matched by sex, age and residential area (at the date of inclusion into the BARFOT) with 4 population controls. Controls without diagnosed RA were randomly selected from the general population using data from the Swedish Central Statistics Office. Incidental fractures were identified through the Swedish Inpatients Register, the Swedish Outpatients Register and the Swedish Cause of Death Register until December 2013. In this study, fractures of wrist, upper arm and hip were considered, as these locations of fractures are supposed to be typical for fragility fractures and can be accurately defined through the registries. The first fracture and total number of all fragility fractures throughout the study period were considered. Fracture incidence rates were calculated and Kaplan-Meier analysis was used to compare the time to the first fracture and rate of fracture occurrence among RA patients and in matched population controls. Analysis were performed for the total study population and also stratified by inclusion period; 1992-1999 and 2000-2006.

Results:

During a mean (SD) follow-up period of 14 (3.9) years 617 of 2751 (22.4%) patients with RA and 1898 of 11004 (17.2%) of controls experienced a fracture ($p < 0.001$). Compared with controls, patients with RA had an increased risk of fractures in upper arm, OR (95% CI) 1.43 (1.12-1.83); $p=0.005$, hip, OR 1.45 (1.23-1.72); $p<0.001$, and other fractures, OR 2.72 (1.57-3.28); $p<0.001$), but not in wrist, OR 1.04 (0.85-1.26); $p=0.714$. Except for wrist fractures, the number of fractures/1000 person-years was significantly increased in RA-patients (upper arm 2.9 vs. 1.9; hip 6.7 vs. 4.8; other 2.5 vs. 1.4). In total population and in the groups stratified by inclusion periods, the mean times to the first fracture in upper arm, hip and fragility fractures of other locations were shorter in patients than in controls.

Conclusion:

In this study we observed an increased risk of fragility fractures in patients with early RA compared with matched population controls. Further studies are needed to explain the increased fracture risk in patients with RA.

Disclosure: B. M. Nyhäll-Wåhlin, None; **S. Ajeganova**, None; **I. F. Petersson**, None; **M. L. Andersson**, None.

Abstract Number: 1589

Impact of Osteoarthritis of the Hand on Disease Activity Scores and Health Status in Patients with Rheumatoid Arthritis

Hector Fabricio Espinosa Ortega[1], Cesar Alejandro Arce Salinas[2] and Emmanuel Ruiz Medrano[3], [1]Rheumatology, Hospital Central Sur Alta Especialidad Pemex, Mexico City, Mexico, [2]Rheumatology, Hospital Central Sur de Alta Especialidad Pemex, Mexico, Mexico, [3]Hospital Central Sur de Alta Especialidad Pemex, Mexico, Mexico
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Background/Purpose:

Rheumatoid arthritis (RA) is a polyarticular autoimmune inflammatory disease characterized for pain, joint edema and functional limitation. Some items in evaluation could be affected by other medical conditions. Hand osteoarthritis can coexist with RA but its effect is unknown. The aim of our study was to describe the impact of hand osteoarthritis on rheumatoid arthritis pain, disease activity and health status.

Methods:

We performed a descriptive and transversal study comparing patients with RA with and without hand osteoarthritis. A total of 41 patients per group were calculated to find a difference of 20mm in visual analogue scale (VAS) of pain. Demographic characteristics were registered as well as disease characteristics, treatment, disease activity, patient and physician global assessment, function disability (HAQ-DI score) and quality of life; quality of sleep, depression and anxiety diagnosis were also analyzed.

Results:

We included 83 patient; 42 RA patients with hand OA and 41 without; demographic characteristics were similar but patients with OA were older than controls (63,5 ± 11,6 vs 55,7 ± 10,8; p=0.002). Comorbities were more prevalent among patients with osteoarthritis. (Table 1). Characteristics of the disease (RA) were similar among the groups (Table 2); there were no differences on treatment strategies (methotrexate monotherapy, steroids and biologic use); although NSAID use was more frequent among patients with hand osteoarthritis (92.6% vs 78.5%) it was not significant. Depression and anxiety prevalence were similar but self-reported quality of sleep was poorer in patients with OA. Patients with OA reported more intensity of pain, resulted in worse global assessment (patient and physician reported), higher activity (DAS 28, SDAI and CDAI), showed more disability but interestingly, reported similar quality of life scores (Table 3). Patients without hand OA were more probable to achieve remission compared with patients with this condition [OR 4,09 (IC 95% 1,2 - 13,46)].

Conclusion:

Although it might be regarded as a benign condition, osteoarthritis of the hand exerts a great impact over patients with rheumatoid arthritis, affecting the possibility of achieving response to treatment.

Table 1 . Demographic characteristics	RA plus OA	RA without OA	p
Age, years (mean, SD)	63,5 ± 11,6	55,7 ± 10,8	0.002
Female gender (%)	95	90	NS
Weight, mean (SD)	64,4 ± 12,2	64,5 ± 10,1	NS
Heigh, mean (SD)	1,58 ± 0,07	1,56 ± 0,06	NS
BMI, mean (SD)	26,4±4,3	25,5±3,8	NS
Smoking habit, %	11,9	14,6	NS
Diabetes, %	26,1	7,3	0,03
Hypertension, %	47,6	21,9	0,01
Menopause, %	85,7	63,4	0,01

BMI= Body mass index

Table 3. Outcomes	RA plus OA	RA without OA	p
Pain VAS (mean, SD)	57,7 ± 30,1	36,6 ± 31,3	0.002
Patient global assessment VAS (mean, SD)	50,6 ± 30,3	31 ± 27,5	0.003
Physician global assessment VAS (mean SD)	26,4 ± 19	16,4 ± 13,6	0.008
DAS 28 -ESR mean, SD	3,88 ± 1,04	3,17 ± 1,01	0.002
Remission (%)	7,1	29,2	0,01
SDAI (mean, SD).	14,45 ± 10,1	8,67 ± 6,44	0.003
Remission (%)	11,9	31,7	0.02
CDAI (mean, SD).	11,4 ± 7,9	6,66 ± 5,94	0.003
Remission (%)	9,5	34,1	0.006
HAQ-DI (mean, SD)	1,16 ± 0,73	0,79 ± 0,81	0.036
RAQoL mean, SD	11,3 ± 7,7	10,6 ± 9,2	NS

VAS = visual analgue scale; DAS= Disease Avtivity Score; SDAI= Simplified Disease Activity Index; CDAI= Clinical Disease Activity Index; HAQ-DI= Health Assessment Questionnaire Disabilitiy Index; RAQoL= Rheumatoid Arthritis Quality of Life

Table 2. Disease characteristics	RA plus OA	RA without OA	p
RA duration, years (mean, SD)	15,9±11,6	14,9 ± 11,5	NS
Rheumatoid factor, positivity (%)	82,9	73,8	NS
ACPA, positivity (%)	36,5	40,4	NS
ESR, mm/hr (mean, SD)	30,1±16	33,1±21,9	NS
CRP, mg/dL (mean, SD)	2,83±5,83	1,85±2,56	NS
DMARD use	**	**	
Methotrexate monotherapy (%)	21,42	21,95	NS
Biologic agents use (%)	14,6	14,2	NS
Steroid use (%)	36,5	33,3	NS
NSAID use (%)	92,6	78,5	NS
Depresion (%)	14,2	14,3	NS
Anxiety (%)	4,76	4,87	NS
Poor sleep quality (%)	66,6	46,3	0.05

RA= rheumatoid arthritis; ACPA= anti cyclic peptide antibodies; ESR= eritrosedimentation rate; CRP= C reactive protein; DMARD; disease modifying antirheumatic drug; NSAID= non steroid antiinflmmatory drug

Disclosure: H. F. Espinosa Ortega, None; **C. A. Arce Salinas**, None; **E. Ruiz Medrano**, None.

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Rheumatoid Arthritis-Related Interstitial Lung Disease (RA-ILD): Methotrexate and the Extension of Lung Disease Are Associated to Prognosis

Jorge Rojas-Serrano[1], Denisse Herrera-Bringas[2], Renzo Perez-Dorame[3], Mayra Mejia[2] and Heidegger Mateos-Toledo[4], [1]Interstitial Lung Diseases Unit, Instituto Nacional de Enfermedades Respiratorias, Mexico City, Mexico, [2]Interstitial Lung Diseases Unit, Insituto Nacional de Enfermedades Respiratorias, Mexico, Mexico, [3]Intertitial Lung Disease Unit, Instituto Nacional de Enfermedades Respiratorias, Mexico, Mexico, [4]Interstitial Lung Diseases Unit, Instituto Nacional de Enfermedades Respiratorias, Mexico, Mexico

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Background/Purpose:

Interstitial lung disease (ILD) is a severe rheumatoid arthritis manifestation with a median survival of 2.6 years. Worst survival has been associated to usual interstitial pneumonia (UIP)-like patterns in high-resolution lung CT (HRCT) scans. To date, no formal recommendations to treat RA-ILD exist. Moreover, the use of methotrexate in RA-ILD is controversial. Our aim was to evaluate prognostic factors in a RA-ILD cohort, including extension of lung disease and methotrexate with their association to survival.

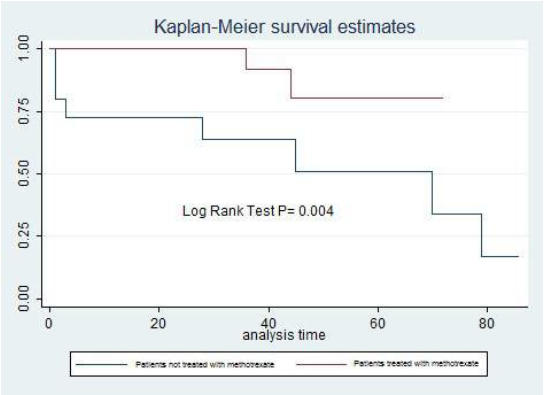
Methods:

RA patients (ACR 87 or ACR/EULAR 2010 criteria) with ILD were included. At the baseline, pulmonary function tests were realized and a high-resolution chest tomography was obtained. A radiologist evaluated the ILD tomographic pattern and the extension of lung disease with the Kazerooni index for lung inflammation and fibrosis. The survival function was estimated and Cox regression was used to evaluate factors associated to prognosis.

Results:

68 patients were included, mostly females (85%) with a median age of 58 years old, (IQR: 53-66). UIP tomographic pattern was present in 18 patients (27%), non-specific interstitial pneumonia (NSIP) pattern in 20 (29.85%), nevertheless, there was considerable overlapping of tomographic patters with mixed pattern (combination of two ILD tomographic patterns) in 25 of the patients (37%). There was no difference in survival according to the HRCT pattern of the patients. Variables associated to mortality were the extension of lung fibrosis according to the Kazerooni index (HR: 2.53, 95% CI: 1.16 – 5.51, p = 0.02) and the extension of lung inflammation (ground glass Kazerooni score) (HR: 4.03, 95% CI: 1.56- 10.39, p = 0.004). Treatment with methotrexate was associated to survival (figure) (HR: 0.13, 95% CI: 0.02 – 0.64, p =0.012). A multivariable Cox regression analysis including methotrexate treatment, extension of lung inflammation and extension of lung disease is shown in table.

Variable	HR	95% CI	P
Methotrexate treatment during follow up	0.16	0.02 – 0.99	0.049
Kazerooni ground glass score (lung inflammation)	4.24	1.53 – 11.72	0.005
Kazerooni fibrosis score (lung fibrosis)	1.84	0.65 – 5.2	0.25



Conclusion:

Methotrexate treatment during follow up was associated with survival. The extension of lung disease and not the tomographic pattern is associated to mortality.

Disclosure: J. Rojas-Serrano, None; **D. Herrera-Bringas**, None; **R. Perez-Dorame**, None; **M. Mejia**, None; **H. Mateos-Toledo**, None.

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Abstract Number: 1591

A Low Adiponectin Level in Rheumatoid Arthritis Is Associated with Coronary Artery Disease

Jon Roger Eidet[1], Ida G. Fostad[2], Kelly J. Shields[3], Torstein Lyberg[1], Tor Paaske Utheim[1], Anita Kåss[4], Knut Mikkelsen[5], Terje Veel[6], Kjell Saatvedt[7], Morten Wang Fagerland[8], Matthew Liang[9] and Ivana Hollan[5], [1]Department of Medical Biochemistry, Oslo University Hospital, Oslo, Norway, [2]Department of Oral Biology, Faculty of Dentistry, University of Oslo, Oslo, Norway, [3]Medicine, Lupus Center of Excellence / Allegheny Health Network, Pittsburgh, PA, [4]Rheumatology, Betanien Hospital, Skien, Norway, [5]Lillehammer Hospital for Rheumatic Diseases, Lillehammer, Norway, [6]Department of Cardiac Surgery, Feiring Heart Clinic, Feiring, Norway, [7]Department of Cardiothoracic Surgery, Oslo University Hospital, Oslo, Norway, [8]Department of Biostatistics, Oslo University Hospital, Oslo, Norway, [9]Department of Rheumatology, Brigham and Women' s Hospital, Boston, Boston, MA
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Background/Purpose: Adipokines exert pleiotropic actions, including immunoregulatory and matrix degrading effects. There is evidence of adipokine involvement in the pathogenesis of cardiovascular (CV) disease as well as inflammatory rheumatic disease (IRD). It is well known, in the general population, that increased circulating leptin is associated with CV risk while adiponectin has a cardioprotective effect. Altered circulating adiponectin and leptin levels may contribute to the accelerated atherosclerosis in IRD. The aim of this study was to compare plasma levels of leptin and adiponectin in coronary artery disease (CAD) patients with and without rheumatoid arthritis (RA), patients with RA without CAD and healthy controls (HC).

Methods: Leptin and adiponectin were measured in plasma by ELISA in four groups of patients from the Feiring Heart Biopsy Study: 1) RA patients referred to coronary artery bypass grafting (CABG) (CAD+RA group, n=22); 2) Patients without RA, referred to CABG (CAD non-RA group, n=52); 3) RA patients without CAD (RA non-CAD group, n=17); and 4) HC (n=29).

Results: Adiponectin was significantly lower in CAD+RA than in RA without CAD (Figure 1A). The mean leptin was significantly lower in HC than in CAD non-RA, CAD+RA and RA without CAD (Figure 1B). Leptin/adiponectin-ratio was significantly lower in HC than in CAD non-RA and CAD+RA (Figure 1C). In linear regression analyses, CAD was related to lower adiponectin levels, and this relationship was independent of age, sex, RA, triglycerides, HDL and ESR (Table 1). CAD was associated with higher leptin and leptin/adiponectin-ratio, and these associations were independent of age, sex and RA (Table 2 and 3). There were no significant associations between adiponectin, leptin or leptin/adiponectin-ratio and RA disease activity score 28 (DAS28).

Image/graph:

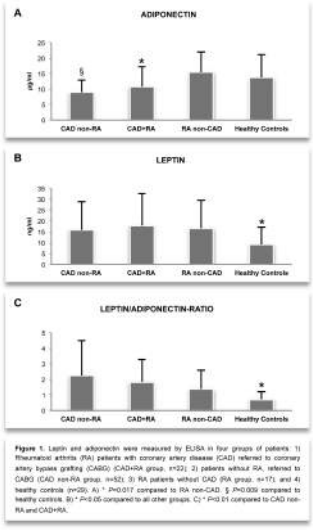

Table 1. Clinical Predictors of Adiponectin Level

	Model I			Model II		
	β	95% CI	P	β	95% CI	P
CAD	-0.424	-0.282, -0.126	<0.001	-0.237	-0.209, -0.022	0.018
RA	0.061	-0.050, 0.111	0.258	0.076	-0.045, 0.125	0.355
Age	0.300	0.003, 0.010	<0.001	0.276	0.002, 0.010	0.002
Female	0.434	0.138, 0.274	<0.001	0.369	0.103, 0.254	<0.001
Triglycerides	-	-	-	-0.053	-0.081, 0.043	0.545
HDL	-	-	-	0.323	0.063, 0.281	0.002
ESR	-	-	-	-0.018	-0.003, 0.002	0.539

CI = confidence interval; CAD = coronary artery disease; RA = rheumatoid arthritis; HDL = high density lipoprotein; ESR = erythrocyte sedimentation rate

Table 2. Clinical Predictors of Leptin Level

	β	95% CI	P
CAD	0.223	0.041, 0.326	0.012
RA	0.080	-0.051, 0.108	0.297
Age	0.091	-0.003, 0.010	0.266
Female	0.526	0.300, 0.551	<0.001

CI = confidence interval; CAD = coronary artery disease; RA = rheumatoid arthritis

Table 3. Clinical Predictors of Leptin/adiponectin-ratio

	β	95% CI	P
CAD	0.424	0.210, 0.562	<0.001
RA	0.033	-0.129, 0.182	0.700
Age	-0.080	-0.011, 0.005	0.410
Female	0.239	0.096, 0.370	0.007

CI = confidence interval; CAD = coronary artery disease; RA = rheumatoid arthritis

Figure 1. Leptin and adiponectin were measured by ELISA in four groups of patients: 1) Rheumatoid arthritis (RA) patients with coronary artery disease (CAD) referred to coronary artery bypass grafting (CABG) (CAD+RA group, n=22); 2) patients without RA, referred to CABG (CAD non-RA group, n=52); 3) RA patients without CAD (RA group, n=17); and 4) healthy controls (n=29). A) * P=0.017 compared to RA non-CAD. § P=0.009 compared to healthy controls. B) * P<0.05 compared to all other groups. C) * P=0.01 compared to CAD non-RA and CAD+RA.

Conclusion: CAD was related to higher circulating levels of leptin and leptin/adiponectin ratio, but to lower circulating levels of adiponectin. The

relationship between adiponectin and CAD was independent of age, sex, triglycerides, HDL and ESR. As previously described for non-RA patients, increased circulating adiponectin may also provide a cardioprotective effect in RA patients.

Disclosure: J. R. Eidet, None; **I. G. Fostad**, None; **K. J. Shields**, None; **T. Lyberg**, None; **T. P. Utheim**, None; **A. Kåss**, None; **K. Mikkelsen**, None; **T. Veel**, None; **K. Saatvedt**, None; **M. W. Fagerland**, None; **M. Liang**, None; **I. Hollan**, None.

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Abstract Number: 1592

Sex Differences in Cardiovascular Risk Factors and Event Rates in Patients with Rheumatoid Arthritis – Data from 13 Rheumatology Centers

Silvia Rollefstad[1], Eirik Ikdahl[1], Cynthia S. Crowson[2], Sherine Gabriel[3], George D. Kitas[4], Piet L van Riel[5], Anne Grete Semb[6] and ATACC-RA, [1]Preventive Cardio-Rheuma Clinic, Department of Rheumatology, Diakonhjemmet Hospital, Oslo, Norway, [2]Health Sciences Research, Mayo Clinic, Rochester, MN, [3]Division of Rheumatology; Department of Health Sciences Research, Mayo Clinic, Rochester, MN, [4]The Dudley Group of Hospitals NHS Foundation Trust, Dudley, United Kingdom, [5]Scientific Institute for Quality of Healthcare, Radboud University Medical Center, Nijmegen, Netherlands, [6]Diakonhjemmet Hospital, Oslo, Norway

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Background/Purpose: Patients with rheumatoid arthritis (RA) have an excess risk of cardiovascular disease (CVD). There is a clear female to male preponderance of RA. In the general population it is well documented that females have their CVD diagnosed at a later stage compared to males. We therefore evaluated if CVD risk prediction and CVD event rates differed between females and males with RA, and if adjustments for traditional and RA specific risk factors were of importance regarding sex differences in CVD event rates.

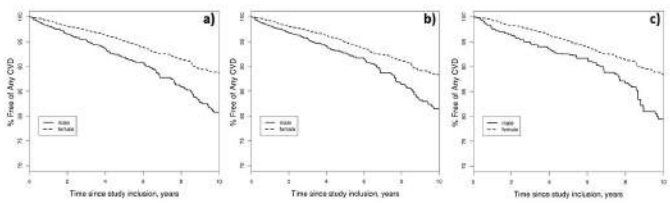
Methods: RA cohorts from 13 rheumatology centers were compared. Data on CVD risk factors and RA characteristics were collected at baseline for each cohort; CVD outcomes (myocardial infarction, angina, revascularization, CVD death, stroke and peripheral vascular disease) were collected using standardized definitions. Standardized incidence ratios (SIR) (observed/expected CVD event) were calculated with respect to sex using the following risk calculators FRS, SCORE, ACC/AHA and QRISK II. The CVD-free survival between the sexes was compared using adjusted Kaplan-Meier plots.

Results: 5638 patients with RA and no prior CVD were included (mean age: 55.3 [SD: 14.0] years, 76% female). During a mean follow-up of 5.8 (SD: 4.4) years, 437 patients developed CVD events. Male patients had a significantly higher burden of traditional CVD risk factors, including increased blood pressure, higher total cholesterol and were more frequently smokers ($p<0.001$ for all). Female RA patients used more anti-rheumatic medication, both synthetic and biologic disease modifying anti-rheumatic drugs ($p<0.001$). Erythrocyte sedimentation rate was higher in females, while C-reactive protein (CRP) levels were highest in males ($p<0.001$ for both). SIRs (95% CI) using the various CVD risk calculators were for females and males: FRS: 1.02 (0.80, 1.31) and 0.86 (0.67, 1.12) ($p=0.19$), SCORE: 0.34 (0.17, 0.67) and 0.25 (0.11, 0.58) ($p=0.98$), ACC/AHA: 0.72 (0.50, 1.04) and 0.56 (0.36, 0.88) ($p=0.74$) and QRISKII 0.61 (0.47, 0.79) and 0.52 (0.35, 0.79) ($p=0.42$). The 10 year CVD-free survival differed significantly between the sexes, both when adjusting for a) age, b) age and CVD risk factors and c) age, CVD risk factors and RA disease characteristics (Females [mean %±SD] 88.3±0.3, males 79.4±0.4), $p<0.001$ for all (Figure 1).

Conclusion:

In a large international cohort of patients with RA, there was no sex difference in the ability of the various risk calculators to predict CVD. However, the FRS seems to predict CVD risk more accurately compared to the other risk calculators in both sexes. CVD-free survival was significantly higher in females, even after adjustments for both traditional and RA specific risk factors.

Figure 1. Kaplan Meier plots for CVD-free survival by sex in patients with rheumatoid arthritis



Disclosure: S. Rollefstad, None; **E. Ikdahl**, None; **C. S. Crowson**, None; **S. Gabriel**, None; **G. D. Kitas**, None; **P. L. van Riel**, None; **A. G. Semb**, None.

Abstract Number: 1593

Telomere Length and Cardiovascular Risk in Rheumatoid Arthritis

Michelle J. Ormseth[1], Joseph F. Solus[2], Annette M. Oeser[3], Aihua Bian[4], Tebeb Gebretsadik[4], Ayumi Shintani[5], Paolo Raggi[6] and C Michael Stein[5], [1]Department of Medicine, Division of Rheumatology, Vanderbilt University, Nashville, TN, [2]Clinical Pharmacology, Vanderbilt University, Nashville, TN, [3]Medicine, Vanderbilt University, Nashville, TN, [4]Biostatistics, Vanderbilt University, Nashville, TN, [5]Vanderbilt University, Nashville, TN, [6]Emory University, Atlanta, GA

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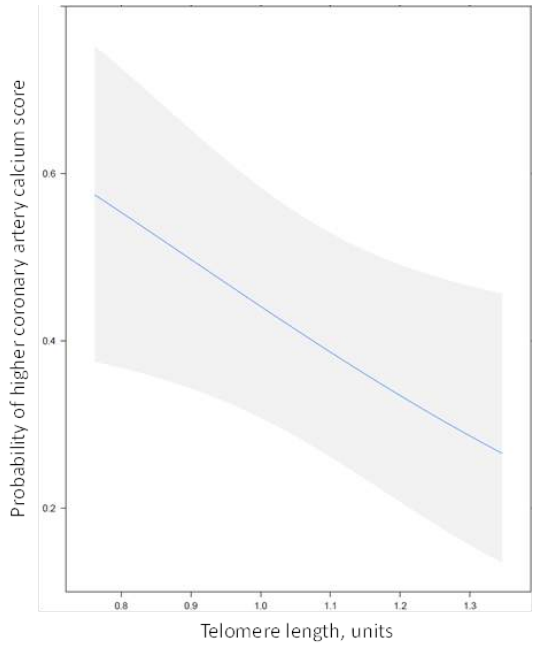
Background/Purpose: Telomeres protect against DNA damage and shorten with each cell division; their length may be a marker of cardiovascular and overall biological aging. Patients with rheumatoid arthritis (RA) have accelerated cardiovascular disease resulting in early mortality. The relationship between telomere length and atherosclerosis in RA is not known. We examined the hypothesis that reduced telomere length is associated with increased coronary atherosclerosis in RA.

Methods: We performed a cross-sectional study in 145 patients with RA and 87 control subjects frequency matched for age, race and sex. Coronary artery calcium score, a measure of coronary atherosclerosis, was determined by non-contrast cardiac computed tomography. Telomere length was measured from DNA extracted from whole blood, using real-time quantitative polymerase chain reaction and expressed as the ratio of telomeric repeats to a single-copy gene (T/S ratio). The associations between telomere length and coronary artery calcium score and disease activity (DAS28) were assessed with Spearman correlation, proportional odds logistic regression, and linear regression adjusting for age, race and sex in patients with RA.

Results: Telomere length was significantly inversely correlated with age in patients with RA (rho=-0.37, P<0.001) and control subjects (rho=-0.39, P=0.001). Among patients with RA, for every interquartile range (IQR) decrease in telomere length (T/S ratio), the odds of higher coronary artery calcium score increased by 38% (95% CI: 4, 60%), after adjusting for age, race and sex (P adjusted= 0.03) (Figure). Telomere length was not associated with DAS28 (P adjusted= 0.17). Telomere length was not significantly different in patients with RA (median [IQR]: 1.02 units [0.9, 1.11 units]) compared to control subjects (1.05 units [0.95, 1.17 units]; P= 0.10).

Conclusion: Telomere length is inversely associated with coronary artery calcium score independent of age, race and sex in patients with RA.



Abstract Number: 1594

No Association of Anti-Citrullinated Peptide Antibodies with Coronary Artery Calcification in Two Rheumatoid Arthritis Cohorts without Clinical Cardiovascular Disease

Laura Geraldino-Pardilla[1], Jon T. Giles[2], Jeremy Sokolove[3], Afshin Zartoshti[4], WH Robinson[5] and Joan M. Bathon[6], [1]Division of Rheumatology, Columbia University College of Physicians & Surgeons, New York, NY, [2]Division of Rheumatology, Columbia University, College of Physicians & Surgeons, New York, NY, [3]Medicine, VA Palo Alto HealthCare System and Stanford University, Palo Alto, CA, [4]Rheumatology, Columbia University Medical Center, NY, NY, [5]Medicine, Division of Immunology and Rheumatology, Stanford University School of Medicine, Stanford, CA, [6]Rheumatology, Columbia University College of Physicians & Surgeons, New York, NY

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SESSION INFORMATION

Session Date: Monday, November 9, 2015

Session Title: Rheumatoid Arthritis - Clinical Aspects Poster II

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: Citrullinated proteins have been found in atherosclerotic plaques. However, contradictory results currently exist regarding the association of anti-citrullinated peptide antibodies (ACPAs) with coronary artery disease in RA patients. Our objective was to test this association in two different cohorts of RA patients without known cardiovascular disease (CVD).

Methods: One-hundred and ninety-five patients underwent cardiac multi-detector row computed tomography for coronary artery calcium (CAC) measurement and concurrent serum testing of a panel of 17 specific ACPAs using a custom Bio-Plex bead array. With a high ACPA level defined as ≥ 75th percentile, the association of each ACPA and CAC was tested. A second independent validation cohort of 75 RA patients without CVD was investigated assessing the association of CAC with an expanded panel of 30 ACPAs. CVD risk factors and RA characteristics were adjusted for.

Results: In cohort 1, the mean age was 59 ±9, with 51% of the patients being females, 85% self-identified as white, 65% were RF or anti-CCP positive, and had a median disease duration of 9years (4-17). In cohort 2, the mean age was 54±13, predominantly females (85%), only 37% were white, 79% were RF or anti-CCP positive, and had a median disease duration of 7years (3-17). In both studies, the DAS28 CRP score was in the moderate range, and about 40% were hypertensive. Cohort 2 study subjects were more likely to have diabetes (13% vs. 7%), and fewer were smokers (7% vs. 12%). In cohort 1, no association between ACPA reactivity and CAC was found. In cohort 2, high levels of ACPAs targeting citrullinated vimentin and the citrullinated vimentin58-77 were associated with higher levels of CAC (p=0.05 and p=0.04, respectively) in univariable linear regression models. However, when adjusted for potential confounders, this association lost statistical significance (p=0.11 and p=0.12, respectively) (Figure 1).

Conclusion: Higher levels of the ACPAs tested in our panel were not significantly associated with CAC in two cohorts of RA patients without known CVD. However, it is conceivable that other as yet unidentified citrullinated vascular proteins could be targets for APCAs.

Figure 1. Association of Anti-Citrullinated Vimentin with Coronary Artery Calcium Score.

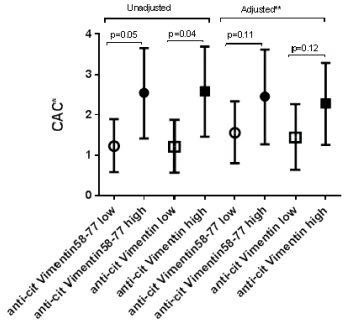

Figure 1. Mean and 95% C.I. values of the log transformed coronary artery calcium (CAC)+1* per category of ACPA reactivity against citrullinated vimenin58-77 and citrullinated vimentin (dichotomized at the 75th percentile). **Adjusted analyses accounts for age, RA disease duration, hypertension, diabetes and TNF-inhibitor use.

Disclosure: L. Geraldino-Pardilla, None; **J. T. Giles**, None; **J. Sokolove**, None; **A. Zartoshti**, None; **W. Robinson**, None; **J. M. Bathon**, None.

Abstract Number: 1595

Impaired Coronary Flow Reserve in Rheumatoid Arthritis: A Robust Indicator of Cardiac Structure Associated with Systemic Inflammation and Rheumatoid Arthritis Treatments

Isabelle Amigues[1], Jon T. Giles[1], Sabahat Bokhari[2], Afshin Zartoshti[3], Richard Weinberg[2], Cesare Russo[4] and Joan Bathon[3], [1]Division of Rheumatology, Columbia University, College of Physicians & Surgeons, New York, NY, [2]Cardiology, Columbia University Medical Center, NY, NY, [3]Rheumatology, Columbia University Medical Center, NY, NY, [4]Division of Cardiology, Columbia University, College of Physicians & Surgeons, New York, NY
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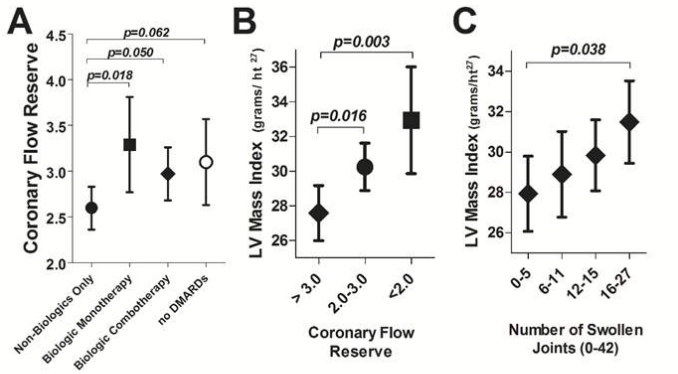
Background/Purpose: Myocardial microvascular dysfunction may precede or coexist with coronary atherosclerosis and heart failure, two conditions over-represented in RA. Coronary flow reserve (CFR) offers an indirect index of myocardial microvascular function. We investigated indicators of CFR and its association with cardiac structure and function in RA.

Methods: RA patients without known cardiovascular disease underwent ^{13}N-ammonia cardiac positron emission tomography (PET) vasodilator myocardial perfusion imaging to evaluate myocardial ischemia and CFR. Global myocardial blood flow (MBF) was quantified at rest and during peak hyperemia with CFR=peak stress MBF/rest MBF, Participants also underwent 3-D echocardiography to assess left ventricular (LV) mass, volumes, and systolic and diastolic function. Mass and volume measures were indexed to height. Generalized linear models were used to explore the associations of patient characteristics with CFR, and measures of LV structure and function.

Results: A total of 76 RA patients [mean age=54 yrs; 80% Female; 43% and 36% non-Hispanic White and Hispanic, respectively; Median RA duration=7.1 yrs; 70% RF or anti-CCP positive; mean DAS28=3.6; 39% treated with biologics] were analyzed. Mean ± SD CFR was 2.9 ± 0.8, and 12% had a CFR<2.0 (an established abnormal threshold). After adjustment, male sex, IL-6, and non-biologic DMARD use were significantly and inversely associated with CFR, while biologic use was associated positively. On average, CFR was lower by 0.18 units for every log unit higher IL-6 (p=0.022). Adjusting for sex and IL-6, RA patients treated with only non-biologics had significantly lower CFR compared with those treated with any biologics or no DMARDs (Fig 1.a). Associations were maintained after adjusting for coronary macrovascular disease [i.e. coronary artery calcification (CAC)]. CFR was not associated with diabetes, smoking, prednisone use, or lipids in adjusted models. Adjusting for relevant demographic and CVD risk factors, CFR<2.0 was associated with a 5.4 unit higher LV mass index (p=0.003; Fig 1.b), the equivalent of 60 mm Hg higher systolic blood pressure (SBP). In the same model, each swollen joint, on average, was associated with a 0.16 unit higher LV mass index (p=0.038), equivalent to almost 2 mm Hg higher SBP, per joint (Fig 1.c). Lower CFR was also significantly associated with higher LV end-diastolic and systolic volumes, but there was no significant association with ejection fraction or measures of diastolic dysfunction.

Conclusion: Higher IL-6 and non-treatment with biologics were among the strongest indicators of lower CFR, which, along with higher swollen joint counts, was associated with higher LV mass. These data suggest that articular and systemic inflammation may contribute to the microvascular and myocardial structural changes in RA that are known to precede heart failure.



Means and 95% confidence intervals are depicted. Panel A is adjusted for age and IL-6, which were the only other relevant covariates retained in multivariable modeling. Panels B and C are adjusted for age, systolic blood pressure, rheumatoid factor, swollen joint count, myocardial flourodeoxyglucose uptake, and coronary flow reserve.

Disclosure: I. Amigues, None; **J. T. Giles**, None; **S. Bokhari**, None; **A. Zartoshti**, None; **R. Weinberg**, None; **C. Russo**, None; **J. Bathon**, None.

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Abstract Number: 1596

Diagnosis of Carotid Plaque By 4 Cardiovascular Risk Scores in Rheumatoid Arthritis

Raymundo Vera-Pineda[1], Alberto Cardenas-de La Garza[2], Dionicio A. Galarza-Delgado[2], Jose Ramon Azpiri-Lopez[3], Iris J. Colunga-Pedraza[2], Judith Garcia-Colunga[4], Guillermo Elizondo[4], Mario Alberto Garza-Elizondo[2], Jesus Zacarias Villarreal-Pérez[5] and Griselda Serna-Peña[6], [1]Cardiology., Hospital Universitario, UANL., Monterrey, Mexico, [2]Rheumatology, Hospital Universitario, UANL., Monterrey, Mexico, [3]Cardiology, Hospital Universitario, UANL., Monterrey, Mexico, [4]Radiology, Hospital Universitario, UANL., Monterrey, Mexico, [5]Endocrinology, Hospital Universitario, UANL., Monterrey, Mexico, [6]Internal Medicine, Hospital Universitario, UANL., Monterrey, Mexico
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Session Time: 9:00AM-11:00AM

Background/Purpose:

The leading cause of death in RA is atherosclerotic cardiovascular disease (ASCVD). Traditional risk factors do not explain the increased cardiovascular risk (CVR), which appears to be linked to inflammatory pathways. Several CVR calculators have been developed for the general population. The most widely used are the Framingham Lipids (FRS Lipids), Framingham BMI (FRS BMI), ACC/AHA 2013 cardiovascular risk calculator (OMNIBUS) and QRISK2 calculator. FRS has shown to underestimate and QRISK2 to overestimate CVR. Carotid artery evaluation by ultrasound is a useful tool for the detection of subclinical atherosclerosis. Carotid plaque (CP) presence significantly increases the risk of ASCVD, mainly stroke and myocardial infarction.

Methods:

A cross-sectional study was designed. Patients with RA were prospectively and consecutively recruited. All fulfilled the ACR/EULAR 2010 classification criteria. Presence of prior ASCVD, overlap syndromes and patients younger than 40 or older than 75 were excluded. A certified radiologist performed the carotid ultrasound. CP was defined as focal thickening of at least 50% greater than that of the surrounding wall or carotid intima media-thickness ≥ 1.2 mm. CVR by 4 different algorithms was calculated online in the official sites. Diagnostic performance was calculated using receiver operating characteristics (ROC curves). Area under the curve (AUC) values greater than .5 with $p<0.05$ were considered statistically significant.

Results:

A total of 97 patients were included. The demographical characteristics are shown in table 1. CP was present in 40 patients (41.2%). Patients with CP were categorized as low-risk by FRS Lipids in 60%, QRISK2 IN 50%, OMNIBUS in 50% and FRS BMI in 42.5% of cases. ROC curves showed poor AUC values, with no significant difference between them ($p>0.05$). The best cut-off point for OMNIBUS was 2.05%, 5% for FRS Lipids, 4.95% for FRS BMI and a 2.9% for QRISK2 (Table2).

Conclusion:

CVR calculators are poor diagnostic tools for CP detection. There is no difference between the ROC curves for the different CVR algorithms in RA. Most of the patients with CP are stratified as low-risk patients by current algorithms.

Table 2. ROC curves and Diagnostic performances

CVR Scale	AUC ± Standard error	P value	Suggested Cut-off value	Sensitivity	Specificity	Negative predictive value
OMNIBUS	.690 ± .053	.001	2.05%	.900	.473	.871
FRS Lipids	.681 ± .054	.002	5%	.900	.386	.846
FRS BMI	.671 ± .055	.004	4.95%	.900	.350	.833
QRISK2	.677 ± .054	.003	2.9%	.900	.350	.833

Table 1. Demographical characteristics	
Feminine, n (%)	88 (90.7)
Age (yo), mean ± SD	56.3 ± 9.6
Duration of disease (yo), mean ± SD	12.78 ± 8.2
Currently smoking, n (%)	25 (25.8)
Family history of MI, n (%)	9 (9.3)
Dyslipidemia, n (%)	26(26.8)
Type 2 diabetes mellitus, n (%)	14 (14.4)
On antihypertensive drugs, n (%)	36 (37.1)
Total cholesterol (mg/dl),	187.59 ±

Disclosure: R. Vera-Pineda, None; **A. Cardenas-de La Garza**, None; **D. A. Galarza-Delgado**, None; **J. R. Azpiri-Lopez**, None; **I. J. Colunga-Pedraza**, None; **J. Garcia-Colunga**, None; **G. Elizondo**, None; **M. A. Garza-Elizondo**, None; **J. Z. Villarreal-Pérez**, None; **G. Serna-Peña**, None.

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Abstract Number: 1597

Variability in Health Assessment Questionnaire Based on Type of

mean ± SD	33.6
HDL cholesterol (mg/dl), mean ± SD	55.75 ± 15.6
LDL cholesterol (mg/dl), mean ± SD	101.2 ± 29.4
ESR, mean ± SD	26.49 ± 13.9
BMI, mean ± SD	28.12 ± 4.96
Systolic BP (mmHg), mean ± SD	124.7 ± 14.3
OMNIBUS, median (p25-p75)	3.8 (1.6-7.05)
FRS Lipids, median (p25-p75)	7.1 (4.6-10.6)
FRS BMI, median (p25-p75)	9.4 (4.95-14.7)
QRISK2, median (p25-p75)	7 (2.9-13.3)
CIMT, median (p25-p75)	.08 (.07-.09)

Health Insurance Coverage and Rheumatology Practice

Jacqueline Stewart[1], Regan Arendse[2], Boulos Haraoui[3], Michael Starr[4], Denis Choquette[5], Michelle Teo[6], Dalton Sholter[7], Emmanouil Rampakakis[8], Eliofotisti Psaradellis[9], Brendan Osborne[10], Karina Maslova[11], Cathy Tkaczyk[10], Francois Nantel[12] and Allen J Lehman[11], [1]Penticton Regional Hospital, Penticton, BC, Canada, [2]University of Saskatchewan, Saskatoon, SK, Canada, [3]Institut de Rhumatologie de Montréal and University of Montreal, Montreal, QC, Canada, [4]Rheumatology, McGill University, Montreal, QC, Canada, [5]Rheumatology Department, Institut de Rhumatologie de Montréal and University of Montreal, Montreal, QC, Canada, [6]Rheumatology, Penticton Regional Hospital, Penticton, BC, Canada, [7]Rheumatology Associates, Edmonton, AB, Canada, [8]JSS Medical Research, St-Laurent, QC, Canada, [9]JSS Medical Research, Montreal, QC, Canada, [10]Medical Affairs, Janssen Inc., Toronto, ON, Canada, [11]Janssen Inc., Toronto, ON, Canada, [12]19 Green belt Dr, Janssen Inc., Toronto, ON, Canada

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Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose : Previous studies in rheumatoid arthritis (RA) have shown that patient socioeconomic status (SES) impacts patient prognosis. We hypothesized that public vs. private healthcare coverage would be a surrogate of low SES. The aim of this analysis was to assess the association between patient health insurance coverage and disease parameters with emphasis on functional activity in RA patients initiating treatment with anti-TNF agents in Canadian routine clinical practice.

Methods : BioTRAC is an ongoing, prospective registry of patients initiating treatment for RA, ankylosing spondylitis, or psoriatic arthritis with infliximab (IFX) or golimumab (GLM). Eligible people for this analysis included RA patients treated with IFX who were enrolled since 2002 or with GLM enrolled since 2010. Independent predictors of HAQ were identified using generalized linear models.

Results: A total of 1144 patients were included of whom 598 (52.3%) had public insurance. Patients with public insurance were older (59.7 vs. 51.8 years; P<0.001), had longer disease duration (9.3 vs. 7.5 years; P=0.029), and were more likely to be from British Columbia (81.2% vs. 18.8%) and Manitoba (68.8% vs. 31.3%) but less likely to be from the Maritimes (30.6% vs. 69.4%) (P<0.001). With respect to disease activity, patients with public insurance had higher CDAI (37.3 vs. 30.3; P<0.001), DAS28 (6.0 vs. 5.2; P<0.001), swollen joint count (11.0 vs. 8.5; P<0.001), tender joint count (12.8 vs. 10.3; P<0.001), patient global (62.1 vs. 55.5; P<0.001), and HAQ (1.74 vs. 1.36; P<0.001).

Multivariate analysis adjusting for age (P=0.028), gender (P<0.001), anti-TNF agent (P=0.227), and CDAI (P<0.001) showed that private insurance type was a significant independent predictor of lower HAQ (1.28 vs. 1.52; P<0.001). Furthermore, rheumatology practice was also identified as a significant predictor of HAQ (P=0.027; Figure 1).

Conclusion: The results of this analysis suggest that, upon adjusting for patient demographics and disease activity, significant variation exists in the HAQ score based on the type of health insurance coverage and the rheumatology practice which may reflect differences inherent to the patient SES or to the manner of administration of the HAQ instrument.

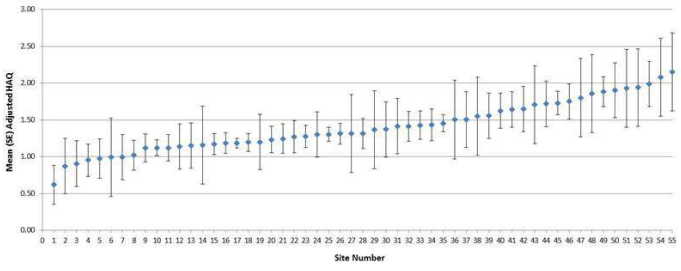

Figure 1. Mean (SD) Adjusted HAQ by Participating Site

Disclosure: J. Stewart, Janssen Inc., 5; **R. Arendse**, Janssen Inc., 5; **B. Haraoui**, Janssen Inc.,, 5; **M. Starr**, Janssen Inc, 5; **D. Choquette**, Janssen Inc., 5,AbbVie, 5,Amgen, 5,Celgene, 5,BMS, 5,Pfizer Inc, 5; **M. Teo**, Janssen Inc., 5; **D. Sholter**, Janssen Inc., 5; **E. Rampakakis**, JSS Medical Research, a Contract Research Organization, 3; **E. Psaradellis**, JSS Medical Research, 3; **B. Osborne**, Janssen Inc., 3; **K. Maslova**, Janssen Inc., 3; **C. Tkaczyk**, Janssen Inc., 3; **F. Nantel**, Janssen Inc., 3; **A. J. Lehman**, Janssen Inc., 3.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/variability-in-health-assessment-questionnaire-based-on-type-of-health-insurance-coverage-and-rheumatology-practice

Abstract Number: 1598

Obesity and the Risk for Development of Rheumatoid Arthritis – Results from a Population-Based Nested Case-Control Study

Lotta Ljung[1,2] and Solbritt Rantapää-Dahlqvist[3], [1]Department of Medicine, Solna, Clinical epidemiology unit, Karolinska Institutet, Stockholm, Sweden, [2]Department for Public Health and Clinical Medicine/Rheumatology, Umeå University, Umeå, Sweden, [3]Department for Public Health and Clinical Medicine/ Rheumatology, Umeå University, Umeå, Sweden

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Session Time: 9:00AM-11:00AM

Background/Purpose:

Studies on obesity and the risk for development of rheumatoid arthritis (RA) have shown diverse results. In this study we evaluated the association between obesity and subsequent risk for development of RA.

Methods:

In The Västerbotten Interventional Program (VIP) or/and The WHO project Multinational MONItoring of Trends and Determinants of CArdiovascular Disease (MONICA) 1985-2013 individuals with RA (according to the ACR/ARA 1987 Classification criteria, with year of onset of symptoms 1989-2013) were identified (cases, n=557), and data from the latest visit antedating onset of RA symptoms were retrieved. From the same population-based, prospective cohorts 1671 controls, matched for age, sex, cohort, inclusion year, cohort and area of inhabitance (rural/urban) were randomly selected. Prospectively collected data on body mass index (BMI; weight/lenght^2), smoking habits, and educational level was used in calculations of odds ratio; OR (95% confidence interval) in conditional logistical regression assessing associations between obesity and the risk for development of RA. Missing variables were handled by multiple imputation (smoking 2.2%, BMI 0.6%, and education 1.6%).

Results:

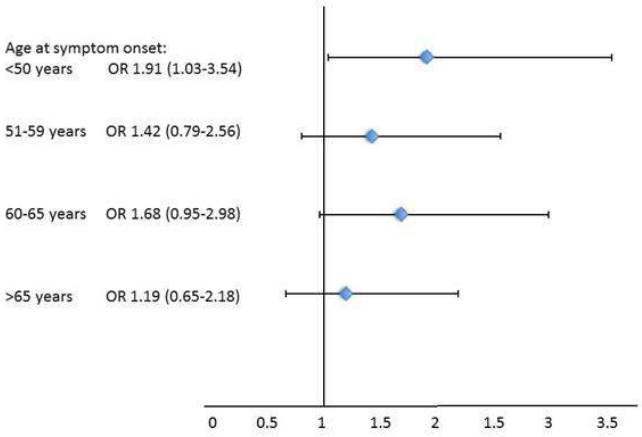
The cases (mean age at RA symptom onset 58 SD 11 years, 68% women) had been included in the cohorts (MONICA n=50, VIP n=507) at a mean of 6.2 SD 4.7 years before the onset of symptoms of RA. Obesity (BMI≥30) was associated with an increased risk for RA development, OR 1.5 (1.1-2.0), compared to those with normal weight (BMI 18.5-25). The association was observed in both sexes (Table 1). Stratifying the patients on age at onset of symptoms of RA the association between obesity and the risk of RA was only observed in the quartile with disease debut at 50 years of age, or earlier, OR for obesity vs. normal weight 1.9 (1.03-3.5) (Figure 1).

Table 1. Conditional logistic regression models with case-controls sets matched for age, sex, area of inhabitance, cohort and year of visit in the cohort, assessing odds ratios for the risk for development of RA associated with categories based on body mass index

		Cases (n=557)	Controls (n=1,671)	OR1 (95% CI)	OR2 (95% CI)
All	Under- or normal weight	228 (41%)	778 (47%)	Reference	Reference
	Overweight	229 (41%)	655 (40%)	1.21 (0.97–1.50)	1.23 (0.98–1.55)
	Obese	97 (18%)	227 (14%)	1.47 (1.11–1.95)	1.49 (1.11–1.99)
Men	Under- or normal weight	58 (33%)	200 (38%)	Reference	Reference
	Overweight	89 (50%)	264 (50%)	1.17 (0.80–1.73)	1.26 (0.83–1.90)
	Obese	31 (17%)	67 (13%)	1.64 (0.96–2.78)	1.78 (1.01–3.12)
Women	Under- or normal weight	170 (45%)	578 (51%)	Reference	Reference
	Overweight	140 (37%)	391 (35%)	1.23 (0.95–1.60)	1.24 (0.95–1.62)
	Obese	66 (18%)	160 (14%)	1.41 (1.01–1.97)	1.42 (1.01–2.01)

OR1 = Unadjusted model. OR2 = Model adjusted for smoking and educational level.

Figure 1. Odds ratios for the association between obesity and risk of development of RA in subgroups based on age at onset of symptoms of RA.



Conclusion:

Obesity was associated with a moderately increased risk for subsequent development of RA. The association was observed in both men and women, but mainly in patients with early onset of RA.

Disclosure: L. Ljung, None; **S. Rantapää-Dahlqvist**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/obesity-and-the-risk-for-development-of-rheumatoid-arthritis-results-from-a-population-based-nested-case-control-study

Abstract Number: 1599

Clinical Characteristics of Interstitial Lung Disease (ILD) in Rheumatoid Arthritis (RA) Patients in High Resolutional CT (HRCT) and Titer of Anti Citrullinated Peptide Antibodies (anti-CCP2)

Masaomi Yamasaki, Rheumatology, Shin-Yokohama Arthritis and Rheumatology Clinic, Yokohama, Japan
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Background/Purpose:

To investigate clinical characteristics of interstitial lung disease (ILD) in rheumatoid arthritis (RA) patients. And to analyze whether high resolutional CT (HRCT) and anti citrullinated peptide antibodies (anti-CCP2) can predict the outcome of ILD in RA.

Methods:

405 patients with RA were treated at our hospital and followed up at least one year as newly onset RA. All patients were performed chest radiological examinations at the initial presentation. The HRCT findings which include (1) ground glass opacity, (2) air-space consolidation, linear opacity including (3) septal line and (4) non-septal line, (5) honeycomb lung, (6) traction bronchiectasis, (7)pleural irregularity, and (8)pleural effusion were scored as the CT scoring system. The extent of involvement of each abnormality was assessed independently for each of the three zones of each lung. The HRCT extent score was represented the sum of the score of each lung. HRCT parameters which include the extension score and the clinical features which include anti-CCP2 at the initial presentation were retrospectively analyzed.

Results:

189 out of 405 patients had abnormal chest radiological findings which included bronchiectasis, bronchitis and ILD (46.7%). 93 (28 male (40.0%), 67 female (22.7%)) out of 405 patients showed ILD at initial presentation (23.0%). 6 out of 93 patients had shortness of breath and showed a rapidly progressive ILD (6.5%). In HRCT findings, ILD in these 6 cases were widely spread at the initial presentation. The rest of 87 patients showed no progression of ILD and asymptomatic (=subclinical ILD). However there were no difference in the HRCT findings which include nonseptal linear attenuation, ground-glass attenuation and air space consolidation between rapidly progressive ILD group and asymptomatic group, rapidly progressive ILD group showed more higher degree in honeycombing (p=0.00018) and extensive ILD (p=0.0068). Higher anti-CCP2 titers were found in higher extensive score of ILD (p=0.0214). Prognosis of the rapidly progressive ILD was variable. The rapidly progressive ILD are treated with immunosuppressive agent

which include high dose steroid, cyclophosphamide, azathioprine, cyclosporineA (CsA) and Mycophenolate Mofetil(MMF) for ILD. 2 patients treated with CsA , one with MMF and one with tacrolimus showed improving of ILD on HRCT. But in other 2 patients were resistant to these immunosuppressive agents.

Conclusion:

HRCT findings focused on the extension score at the initial presentation is a useful predictor of the outcome of ILD in RA. Anti-CCP2 is one of the related factor of the extension score. This study suggests that RA patients with preexisting honeycombing lung and extensive ILD must be aware of rapidly progressive ILD which need immunosuppressant.

Disclosure: M. Yamasaki, None;

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/clinical-characteristics-of-interstitial-lung-disease-ild-in-rheumatoid-arthritis-ra-patients-in-high-resolutional-ct-hrct-and-titer-of-anti-citrullinated-peptide-antibodies-anti-ccp2

Abstract Number: 1600

Pulmonary Manifestations in Early Rheumatoid Arthritis: A 6 Month Follow up Study

Gudrun Reynisdottir[1], Helga Olsen[2], Johan Grunewald[2], Magnus Skold[2], Anders Eklund[3] and **Anca I Catrina**[4], [1]Rheumatology Unit, Department of Medicine, Karolinska University Hospital and Karolinska Institutet, Stockholm, Sweden, [2]Department of Medicine, Division of Respiratory Medicine, Karolinska University Hospital, Karolinska Institute, Stockholm, Sweden, [3]Division of Respiratory Medicine, Karolinska University Hospital, Karolinska Institute, Stockholm, Sweden, [4]Unit of Rheumatology, Department of Medicine Solna, Karolinska University Hospital, Karolinska Institutet, Stockholm, Sweden
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Background/Purpose:

Pulmonary manifestations are common in rheumatoid arthritis (RA). However, limited information is available concerning the early development of such manifestations in newly diagnosed patients. In this study we present the six months follow up data of a previously published study, documenting the pulmonary response to standard disease modifying anti rheumatic drug (DMARD) treatment in patients with early RA.

Methods:

A total of 143 patients with newly diagnosed RA were recruited via the Early Arthritis Clinic (Karolinska University Hospital in Stockholm, Sweden). Patient characteristics were recorded at baseline, and high resolution computed tomography (HRCT) and spirometry were performed at inclusion and after six months of treatment.

Results: HRCT at baseline demonstrated parenchymal abnormalities in 54% of patients and/or airway changes in 66% of patients. Pulmonary fibrosis was evident in twelve patients. At 6 months follow up, no obvious changes were observed with the exception of radiographic progression of pulmonary fibrosis in one third of patients (four of 12 patients). Furthermore, an additional three patients developed new radiographic changes suggestive of early interstitial lung disease. Spirometry was abnormal in 62% of patients at inclusion, with a reduced DLco and/or airways obstruction being the most common findings (occurring in 52% and 32%, respectively). At follow up, the forced expiratory volume in one second (FEV1) had decreased by a mean of 70 ml in all patients. The reduction was numerically larger in current smokers compared to never smokers (150 ml versus 30 ml), but was independent of antibody status.

Conclusion:

RA patients frequently exhibit pulmonary HRCT changes and signs of airway inflammation, already at the early stages of the disease, not obviously related to methotrexate treatment and smoking. Pre-clinical interstitial lung disease (ILD) is prevalent and may be progressive.

Disclosure: G. Reynisdottir, None; **H. Olsen**, None; **J. Grunewald**, None; **M. Skold**, None; **A. Eklund**, None; **A. I. Catrina**, None.

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Abstract Number: 1601

Evaluation of Glucose Metabolism in Rheumatic Patients: A Case Control Study

Mattia Bellan[1], Simone Bor[2], Roberta Pedrazzoli[3], Daniele Sola[2], Antonello Gibbin[2], Giulia Guaschino[2], Alessandro Gualerzi[2], Serena Favretto[2], Mirta

Menegatti[2], Gian Piero Carnevale Schianca[3], Mario Pirisi[2] and Pier Paolo Sainaghi[3], [1]Department of Translational Medicine, Università del Piemonte Orientale UPO, Novara, Italy, [2]Università del Piemonte Orientale UPO, Novara, Italy, [3]Division of Internal Medicine, Immuno-rheumatology Unit, "Maggiore della Carità" Hospital, Novara, Italy
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Background/Purpose:

Whether glucose metabolism is abnormal in patients affected by inflammatory arthritis is controversial. In the present study, we aimed to evaluate glucose metabolism in a cohort of rheumatic patients with respect to matched controls.

Methods:

We prospectively recruited patients affected by inflammatory arthritis followed-up at our Immunorheumatology Unit. We selected two sex-age and BMI matched controls from a cohort of patients who underwent an Oral Glucose Tolerance Test (OGTT) in our Metabolic Unit. Rheumatologic diagnosis were based on ACR/EULAR 2010 classification criteria for Rheumatoid Arthritis (RA), CASPAR criteria for Psoriatic Arthritis (PsA) and ASAS Criteria for Spondyloarthritis (SpA).

Results:

The study population includes 97 cases (F=68, 70.1%) affected by RA (N=53, 54.6%), PsA, (N=35, 36.1%) or other SpA, (N=9, 9.3%) and 194 matched controls. Cases and controls were similar with regard to age, BMI, waist circumference (WC) and rate of arterial hypertension. We could not detect any difference between case and controls in glucose and insulin plasma concentration neither at baseline nor after OGTT. HOMA was similar in the two groups as well as Glycated haemoglobin (HbA1C).

In the group of cases C-Reactive Protein (CRP) was directly related to: plasma glucose at baseline (G0; p=0.0005); plasma glucose after OGTT (G120; p=0.0002); insulin plasma concentration after OGTT (I120'; p=0.006); HbA1C (p=0.02). Erythrocyte sedimentation rate (ESR) was directly related to: G0 (p=0.02); G120; p=0.002; HbA1C (p=0.03).

We then focused our attention on RA patients. According to DAS28-ESR, 33 patients were in remission, while 18 showed a residual disease activity. CRP was still correlated to G0, G120 and HbA1C even in patients with a DAS28<2.6; anyway in a multivariate regression model the only independent predictor of all these variables was BMI. In fact patients with a pathological BMI had also a significantly higher CRP (0.33 [0.15-0.60]) than people with a normal BMI (0.16 [0.06-0.43]); p=0.04. In patients with residual disease activity DAS28 was linked to I0 (p=0.034, as well as ESR (p=0.004); ESR was also directly related to HOMA (p=0.002). in multivariate regression model ESR was a predictor of HOMA (p=0.003), as well as BMI and WC, independently by cumulative steroid dose.

Conclusion:

In patients with rheumatic disease, glucose metabolism is not different from general population if remission has been achieved. However, among patients with residual activity ESR is a strong predictor of insulin resistance, suggesting that the inflammatory state induced by the rheumatic condition may represent a factor in the development of an altered glucose metabolism.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/evaluation-of-glucose-metabolism-in-rheumatic-patients-a-case-control-study

Abstract Number: 1602

Beta Cells Function and Insulin Resistance during Tocilizumab Treatment in Non-Diabetic RA Patients: Results from a Single-Center Study

Gorica Ristic[1], Vesna Subota[2], Petar Ristic[3], Dejana Stanisavljevic[4], Arsen Ristic[5], Branislava Glisic[1], Milan Petronijevic[1] and Dusan Stefanovic[1], [1]Department of Rheumatology and Clinical Immunology, Military Medical Academy, Belgrade, Serbia, [2]Institute of Medical Biochemistry, Military Medical Academy, Belgrade, Serbia, [3]Department of Endocrinology, Military Medical Academy, Belgrade, Serbia, [4]Institute of Medical Statistics, Belgrade University School of Medicine, Belgrade, Serbia, [5]Department of Cardiology, Clinical Center of Serbia & Belgrade University School of Medicine, Belgrade, Serbia
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Background/Purpose: Insulin resistance (IR) is increased and β-cell function impaired in rheumatoid arthritis (RA). The aim of this study was to evaluate whether treatment with tocilizumab (TCZ) results in attenuation of IR and improvement of β-cell function.

Methods: The study population included 31 RA pts, (mean age 53.5±11.1 yrs, RA duration 7.1±6.5 yrs, all on disease modifying antirheumatic drugs, 77.4% on steroids (8.0±2.9 mg)), without diabetes, cardiovascular diseases, and previous treatment with biologic drugs. Disease activity was assessed using mDAS28-SE and mHAQ. Insulin resistance was calculated using the updated-computer Homeostasis Model Assessment (HOMA2-IR), with an algorithm to determine insulin sensitivity (%S) and β cell function (%B) from fasting plasma glucose and specific insulin, or C peptide concentrations. We used C peptide to calculate β cell function, as a marker of secretion, and proinsulin as indicator of β cell dysfunction. Serum specific insulin was measured by a sensitive ELISA and the values were logarithmically transformed (coefficient of variation 42-55%). Association between baseline HOMA2-IR, demographics, disease-related factors, and inflammation markers (SE, hsCRP IL-6) was evaluated using linear regression. Changes in HOMA2-IR, HOMA2%-B, HOMA2%-IS and proinsulin concentration during TCZ therapy were assessed using a general linear method.

Results: Baseline logHOMA2-IR was associated with body mass index, triglycerides concentration and mHAQ (β-coefficients [95% CI]: 2.64 [0.003,0.023; p=0.013], 2.79 [0.074, 0.500;p=0.010], and 2.082 [0.005, 0.572;p=0.046], respectively) but not with DAS28-SE, RF or anti CCP positivity, IL-6 level, ESR, CRP, or steroids. After 12 weeks of TCZ treatment, HOMA-IR was reduced and HOMA2%-IS was improved but did not change after 24 weeks of treatment although parameters of disease activity (DAS28-SE, mHAQ), and inflammation markers (ESR value) continued to decrease. Improvement of %IS did not follow better β cell function assessed by HOMA2%-B. Importantly, proinsulin concentration was significantly reduced after 12 weeks of TCZ, without changes further on (Table 1).

Conclusion: These data support hypothesis that inflammation and disease activity could not fully elucidate the presence of IR and β cell dysfunction in RA pts and that β cell dysfunction is at least in part independent of IR.

Table 1. Changes in disease activity, inflammation markers, HOMA2-IR, HOMA2%-B, HOMA2%-IS and proinsulin concentration after 12 and 24 weeks of TCZ therapy in 31 RA pts without diabetes and cardiovascular diseases.

CLINICAL AND LABORATORY PARAMETERS	3 months of TCZ 0 vs. 3 months	6 months of TCZ 3 vs. 6 months	6 months of TCZ 0 vs. 6 months
DAS 28-SE	362.28***	18.93***	439.87***
mHAQ	94.48***	6.20*	138.84***
logESR (mm/h)	119.7***	5.10*	164.9***
logIL-6	31.3***	0.56	22.8***
logHOMA2-IR	4.30*	0.20	2.34
logHOMA2%-IS	4.81*	0.07	2.43
logC pep (pmol/L)	5.76*	0.93	1.95
logHOMA2%-B	1.08	0.09	1.55
logProinsulin	12.68***	0.031	9.51**

*p<0.05; **p<0.01; ***p≤0.001, determined by a General Linear Model

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Disclosure: G. Ristic, None; **V. Subota**, None; **P. Ristic**, None; **D. Stanisavljevic**, None; **A. Ristic**, None; **B. Glisic**, None; **M. Petronijevic**, None; **D. Stefanovic**, None.

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Abstract Number: 1603

Safety of Biologic and Non-Biologic Disease-Modifying Antirheumatic Drug (DMARD) Therapy in Veterans with Rheumatoid Arthritis and Chronic Hepatitis C Infection

Jeffrey R. Curtis[1,2], Mary Jane Burton[3], Shou Yang[1], Lang Chen[1], Ted R. Mikuls[4], Jasvinder A. Singh[2], Kevin L. Winthrop[5] and John Baddley[2,6], [1]University of Alabama at Birmingham, Birmingham, AL, [2]Birmingham VAMC, Birmingham, AL, [3]Jackson VAMC, Jackson, MS, [4]University of Nebraska Medical Center, Omaha, NE, [5]Oregon Health and Science University, Portland, OR, [6]Medicine, University of Alabama at Birmingham, Birmingham, AL
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Background/Purpose: Among patients with rheumatoid arthritis and hepatitis C virus (HCV) infection, the impact of biologic and nonbiologic DMARD therapy on hepatotoxicity has received limited study.

Methods: Using 1997-2011 national data from the US Veteran's Health Administration, we identified a cohort of 38,433 rheumatologist-diagnosed RA patients. Eligible patients had HCV infection (defined by detectable HCV RNA) and subsequently initiated a new biologic (infliximab, adalimumab, etanercept; rituximab) or nonbiologic (hydroxychloroquine, sulfasalazine, methotrexate, leflunomide) DMARD that they had never been on previously. Patients were required to have a baseline ALT <66 IU/mL and quantifiable HCV RNA within 90 days prior to starting biologic/DMARD therapy (defined as "index date") as well as ALT and HCV RNA measurement within 1 year after index date. Patients with HIV and hematologic malignancy were excluded. Patients could contribute more than one treatment episode provided they switched to a new biologic/DMARD they had not previously used, or switched to a previously used biologic/DMARD they had not used in the past year. The primary outcome of interest was hepatotoxicity, defined as ALT elevation ≥100 IU/L (corresponding to 3x ULN for women and 2.5x ULN for men) or increase in HCV RNA by one log, and was examined within the first year of biologic/DMARD use. Current exposure was defined as-treated based on day supply (injection biologics) or usual dosing intervals (infused biologics*).***Results*** were reported as the cumulative incidence of patients achieving pre-defined hepatotoxicity at 3, 6 and 12-months post-biologic exposure.

Results:

RA patients with HCV (n=748) were identified and contributed 1097 biologic/DMARD treatment episodes. Mean age was 59.8 years and 77.3% were male. Nearly half of biologic users (47.4%) were also prescribed methotrexate and/or leflunomide. Overall, ALT elevations were uncommon, with 37 hepatotoxicity events (ALT ≥100 IU/L or HCV RNA increase by one log) occurring within 12 months (3.4%). Treatment episodes with biologics demonstrated increased frequency of hepatotoxicity (ALT ≥100 IU/L or HCV RNA increase by one log) than nonbiologics (4.8% vs 2.3%, p=0.028). Most hepatotoxicity events occurred within 6 months of DMARD initiation (29/37, 78%).

Table: Cumulative hepatotoxicity events among RA patients with HCV within 12 months of initiating biologic/nonbiologic DMARDs

		Cumulative Hepatotoxicity Events		
Drug	Number exposed	3-months	6-months	12-months
ADA	180	3(1.7%)	7(3.9%)	8(4.4%)
ETA	179	4(2.2%)	7(3.9%)	10 (5.6%)
INF	48	0(0%)	2(4.2%)	2(4.2%)
RIT	28	1(3.6%)	1(3.6%)	1 (3.6%)
ABA	22	0(0%)	1(4.6%)	1(4.6%)
LEF	91	1(1.1%)	2(2.2%)	2(2.2%)
MTX	156	0(0%)	4(2.6%)	6(3.9%)
HCQ	272	2(0.7%)	2(0.7%%)	4(1.5%)
SSZ	121	3(2.5%)	3(2.5%)	3(2.5%)
Total	1097	14(1.3%)	29(2.6%)	37(3.4%)

ADA=adalimumab; ETA=etanercept; INF=infliximab; RIT=rituximab, ABA=abatacept;

LEF=leflunomide; MTX=methotrexate; SSZ-HCQ=sulfasalazine/hydroxychloroquine

Conclusion: In US Veterans with HCV and RA receiving biologic and nonbiologic DMARDs, the frequency of treatment-related hepatotoxicity (ALT ≥100 IU/L) was low, with a higher frequency observed in treatment episodes with current biologic use. The majority of hepatotoxicity events occurred within 6 months after biologic/DMARD initiation.

Disclosure: J. R. Curtis, Roche/Genentech, UCB, Janssen, CORRONA, Amgen, Pfizer, BMS, Crescendo, AbbVie, 2,Roche/Genentech, UCB, Janssen, CORRONA, Amgen, Pfizer, BMS, Crescendo, AbbVie, 5; **M. J. Burton**, None; **S. Yang**, None; **L. Chen**, None; **T. R. Mikuls**, None; **J. A. Singh**, None; **K. L. Winthrop**, BMS, 2,AbbVie, BMS, UCB, Amgen, 5; **J. Baddley**, Pfizer, Astellas, Merck, 5,BMS, 2.

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Abstract Number: 1604

Cardiovascular Disease in a Large Incident Cohort of Early Inflammatory Arthritis

Lillian Barra[1], Janet E. Pope[2], Carol Hitchon[3], Gilles Boire[4], Daming Lin[5], J Carter Thorne[6], Diane Tin[7], Edward C. Keystone[8], Boulos Haraoui[9], VP Bykerk[6] and CATCH, [1]Medicine, Division of Rheumatology, Western University, London, ON, Canada, [2]University of Western Ontario, London, ON, Canada, [3]University of Manitoba, Winnipeg, MB, Canada, [4]Department of Medicine/Division of Rheumatology, Université de Sherbrooke, Sherbrooke, QC, Canada, [5]Rheumatology, Mount Sinai Hospital, University of Toronto, Toronto, ON, Canada, [6]University of Toronto, Toronto, ON, Canada, [7]The Arthritis Program, Southlake Regional Health Centre, Newmarket, ON, Canada, [8]Mount Sinai Hospital, University of Toronto, Toronto, ON, Canada, [9]Institut de Rhumatologie de Montréal and University of Montreal, Montreal, QC, Canada

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Cardiovascular Disease in a Large Incident Cohort of Early Inflammatory Arthritis

Background/Purpose: Rheumatoid Arthritis (RA) is associated with an increased risk of cardiovascular disease (CVD). The aim of this study is to determine the incidence and predictors of CVD in Early Inflammatory Arthritis (EIA) from the Canadian early arthritis cohort (CATCH).

Methods: CATCH is a multicentre, prospective inception cohort of patients with EIA. Cardiovascular disease (CVD) was defined as an acute coronary syndrome, percutaneous or surgical intervention for coronary artery disease, stroke, transient ischemic attack, peripheral vascular disease requiring surgical intervention or death secondary to CVD. Pre-existing diagnoses of CVD, risk factors and medications for CVD were collected at baseline by physician. Incident CVD events and cardiac medications after study enrollment were self-reported by patients. Stepwise logistic regression was used to identify predictors for CVD.

Results: 2652 patients were enrolled in the study with a mean follow-up of 3.4 (SD 2.1) years. At baseline, 180 (7%) had pre-existing CVD. During the course of follow-up there were 62 new CVD events in 57 subjects. There were a total of 6 deaths (1 secondary to CVD). The incidence rate of CVD for years 1, 2, 3, 4 and 5 of the study, respectively were: 2.3, 4.4, 15.4, 10.4, 10.8 per 1000 person-years. Patients with new CVD events were older, more likely male and have higher rates of traditional CVD risk factors (Table 1). Arthritis-related factors were not significantly associated with the risk of CVD. Independent predictors of CVD were male gender (OR 1.8 (95% CI: 1.0-3.0), dyslipidemia (OR 1.8 (95% CI: 1.1-3.2)), hypertension (OR 2.7 (95% CI: 1.6-4.6)) and the use of non-steroidal anti-inflammatories (NSAIDs) (OR 3.2 (95% CI: 1.8-5.6). Less than 25% of subjects with a CVD diagnosis reported taking aspirin or cholesterol-lowering drugs during the follow-up period.

Conclusion: The rate of CVD events in patients with EIA was higher later in the disease course. CVD appears to be under-treated and is independently associated with traditional CVD risk factors and the use of NSAIDs.

Table 1: Baseline characteristics of EIA patients with a new CVD event versus those that did not have a new CVD event

	New CVD	No New CVD	p-value
N	57	2595	
Age, mean years (SD)	61.2 (13.6)	53.3 (14.8)	<0.0001
Female	31 (54)	1874 (72)	0.0037
Symptom Duration, days mean (SD)	234.8 (129.0)	184.7 (115.9)	<0.0001
Ever Smoker[a]	41 (72)	1441 (56)	0.0136
RA criteria[b]	52 (93)	2218 (86)	0.1314
Seropositive[c]	29 (76)	1150 (67)	0.2307
DAS28, mean (SD)	4.87 (1.50)	4.66 (1.45)	0.3017
HAQ, mean (SD)	0.86 (0.67)	0.88 (0.69)	0.8130
Erosions[d]	15 (31)	480 (23)	0.2375
CRP, mean (SD) (mg/L)	14.8 (17.9)	13.9 (17.9)	0.7004
ESR, mean (SD)	26.5 (22.8)	26.4 (22.7)	0.9820
Diabetes	9 (16)	210 (8)	0.037
Hypertension	31 (54)	703 (27)	<0.0001
Dyslipidemia	19 (33)	426 (16)	0.0007
DMARDs	50 (88)	2128 (82)	0.2800
Methotrexate	39 (68)	1712 (65)	0.5458
Biologics	3 (5)	52 (2)	0.1192
Corticosteroids	32 (56)	1271 (49)	0.2674
NSAID	14 (25)	234 (9)	<0.0001

[a]Defined as past or present smoker

[b]Meets ACR 1987 RA criteria or ACR/EULAR 2010 RA criteria

[c]N=1752 with available data on antibodies; seropositive defined as Rheumatoid Factor or Anti-Citrullinated Peptide Antibody positive

[d]N= 2103 with available data on presence of erosions on plain radiographs

EIA= Early Inflammatory Arthritis, DAS28= Disease Activity Score 28, HAQ= Health Assessment Questionnaire Score, ESR= Erythrocyte Sedimentation Rate, CRP= C-Reactive Protein, , ACR=American College of Rheumatology, RA= Rheumatoid Arthritis, EULAR= European League Against Rheumatism, DMARDs= Disease Modifying Anti-Rheumatic Drugs, NSAID= Non-Steroidal Anti-Inflammatories

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Abstract Number: 1605

Enhanced Oxidant Signaling in Inflammatory Macrophages in Rheumatoid Arthritis (RA) and in Coronary Artery Disease (CAD)

Tsuyoshi Shirai[1], Benedikt Schaefgen[1], Barbara Wallis[1], Eric L. Matteson[2], Themistocles L. Assimes[3], David G. Harrison[4], Jorg Goronzy[5] and Cornelia M. Weyand[6], [1]Medicine: Immunology and Rheumatology, Stanford University School of Medicine, Stanford, CA, [2]Rheumatology, Mayo Clinic, Rochester, MN, [3]Stanford University School of Medicine, Stanford, CA, [4]Clinical Pharmacology, Vanderbilt University School of Medicine, Nashville, TN, [5]Medicine/Division of Immunology & Rheumatology, Stanford University School of Medicine, Stanford, CA, [6]Medicine, Stanford University School of Medicine, Stanford, CA

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Background/Purpose: RA patients have a 2-fold increased risk of developing coronary artery disease (CAD) regardless of traditional risk factors. Atherosclerosis, the underlying process in CAD, is a chronic maladaptive inflammatory response, and macrophages play a critical role in its progression through cytokine and chemokine secretion, production of tissue-injurious enzymes and amplification of adaptive immune responses. Here, we have examined macrophages in RA and CAD, with the goal to identify disease-specific and shared molecular pathways swaying such myeloid cells towards pathogenic inflammation.

Methods: Patients with RA who fulfilled 2010 ACR/EULAR RA Classification Criteria, CAD patients with a history of at least one myocardial infarction (>3 months post event), and healthy controls were enrolled. Monocytes isolated from peripheral blood were differentiated into macrophages with macrophage colony stimulating factor. To recapitulate an inflammatory tissue environment, macrophages were stimulated with IFN-γ and lipopolysaccharide. Gene expression profiles were analyzed by quantitative RT-PCR. Intracellular cytokines were measured by flow cytometry. Intracellular reactive oxygen species (ROS) were quantified using CellROX. The oxidant superoxide was scavenged using the superoxide dismutase mimetic, Tempol.

Results: Compared to healthy macrophages, RA and CAD macrophages shared the enhanced expression of the oxidative stress response gene, NAD(P)H:quinone oxidoreductase 1 (NQO1). Measurements with redox-sensitive probes confirmed an oversupply of reactive oxidant species. Also, RA and CAD macrophages were programmed to produce higher levels of the chemokine CCL18, which promotes T cell recruitment and is highly expressed in the atherosclerotic plaque. Scavenging of ROS with Tempol suppressed CCL18 production, implicating oxidant species in regulating the chemokine secretion profile. Depriving macrophages of glucose had profound implications on both ROS production and the gene expression pattern. Specifically, reducing glycolytic flux by treatment with 2-deoxy-glucose restored the expression of the negative regulators Krüppel-like factor (KLF)2 and KLF4, which inhibit inflammatory effector functions.

Conclusion: Enhanced glucose metabolism acts as an upstream regulator of inflammatory macrophage functions. ROS, produced in excess by glucose-addicted macrophages, influence the chemokine production pattern, specifically CCL18, a predominant chemokine in atherosclerotic plaque. Patients with RA and CAD share common features in macrophage differentiation towards hyperinflammtory effector cells. Such macrophages may contribute to the acceleration of CAD in RA patients.

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Abstract Number: 1606

Telomere Damage in Rheumatoid Arthritis

Yinyin Li[1], Jihang Ju[1], Thomas M. Bush[2], Mark C. Genovese[3], Jorg Goronzy[1] and Cornelia M. Weyand[4], [1]Medicine: Immunology and Rheumatology, Stanford University School of Medicine, Stanford, CA, [2]Medicine/Rheumatology, Santa Clara Valley Medical Center, San Jose, CA, [3]Division of

Rheumatology, Stanford University Medical Center, Palo Alto, CA, [4]Medicine, Stanford University School of Medicine, Stanford, CA
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Session Time: 9:00AM-11:00AM

Background/Purpose: Production of anti-CCP autoantibodies, the hallmark of rheumatoid arthritis (RA), is dependent on T cell help, positioning T cells into a pinnacle position in the breakdown of self-tolerance. Such RA T cells have features of premature senescence and age-inappropriately erode their telomeric sequences. It has been speculated that senescence and telomere erosion result from increased proliferative pressure, but the underlying mechanism is not understood. To explore why RA T cells lose telomeric sequences, we have analyzed the structure and function of telomere-residing proteins in CD4 T cells, focusing on DNA repair molecules involved in telomeric maintenance.

Methods: Naïve $CD4^+CD45RA^+$ T cells were purified from anti-CCP^+ RA patients and age-matched controls and stimulated by T cell receptor triggering. The length and structural intactness of the telomeric cap of individual telomeres was examined by fluorescence-in-situ-hybridization in metaphase nuclei. DNA repair molecules were mapped to the telomere by multicolor confocal microscopy, utilizing the shelterin protein TRF2 as a telomere-specific marker. To investigate the function of individual DNA damage proteins in telomere protection, we employed siRNA knockdown technology.

Results: Metaphase nuclei from RA T cells consistently had structurally damaged telomeres. Almost 70% of nuclei had structural abnormalities, including telomere fragility products, end apposition, telomere fusion and signal free ends ($p=0.001$ compared to age-matched controls). Confocal analysis demonstrated that the protein complexes recruited to duplicating telomeres were significantly different in RA and control T cells, with RA telomeres lacking the MRN complex ($p=0.002$). Knockdown of the MRN component MRE11 in healthy T cells promptly produced telomeric damage, quantified by the telomeric localization of the damage-sensing protein 53BP1 ($p=0.0001$). Also, forced MRE11 loss rapidly induced T cell senescence, as demonstrated by the induction of the cyclin-dependent kinase inhibitor 2A ($p=0.01$) and the cell surface marker CD57 ($p=0.04$).

Conclusion: Telomeres in RA T cells are not only shortened, but are structurally damaged. The protein complex surrounding RA telomeres lacks the repair molecule MRE11, and knockdown of MRE11 in healthy T cells promptly reproduces the telomere damage phenotype of RA T cells. MRE11 loss is mechanistically linked to T cell senescence. Telomeric erosion and premature senescence in RA T cells results from insufficiencies in the DNA repair machinery.

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Abstract Number: 1607

Rheumatoid Factor Is Associated with the Distribution of Hand Joint Destruction in a Dose-Dependent Manner

Chikashi Terao[1], Noriyuki Yamakawa[2], Koichiro Yano[3], I.M. Markusse[4], Katsunori Ikari[3], Shinji Yoshida[3], Moritoshi Furu[5], Motomu Hashimoto[5], Hiromu Ito[5], Takao Fujii[6], Koichiro Ohmura[7], Kosaku Murakami[7], Meiko Takahashi[2], Masahide Hamaguchi[8], Yasuharu Tabara[2], Atsuo Taniguchi[3], Shigeki Momohara[3], Soumya Raychaudhuri[9], Cornelia F. Allaart[10], Hisashi Yamanaka[11], Tsuneyo Mimori[12] and Fumihiko Matsuda[13], [1]Departments of Genetics and Rheumatology, Brigham and Women's Hospital, Boston, MA, [2]Kyoto University Graduate School of Medicine, Kyoto, Japan, [3]Institute of Rheumatology, Tokyo Women's Medical University, Tokyo, Japan, [4]LUMC, Leiden, Netherlands, [5]Department of the Control for Rheumatic Diseases, Department of the Control for Rheumatic Diseases, Graduate School of Medicine, Kyoto University, Kyoto, Japan, [6]Dept of Rheum/Clinical Immun, Kyoto University Graduate School of Medicine, Kyoto, Japan, [7]Dept of Rheum & Clinical Immun, Kyoto Univ Grad School of Med, Kyoto, Japan, [8]Kyoto Prefectural University of Medicine, Graduate School of Medical Science, Kyoto, Japan, [9]Arthritis Research UK Centre for Genetics and Genomics, Centre for Musculoskeletal Research, Manchester Academic Health Science Centre, The University of Manchester, Manchester, United Kingdom, [10]Rheumatology, LUMC, Leiden, Netherlands, [11]Tokyo Women's Medical University, Tokyo, Japan, [12]Dept of Rheum & Clinical Immun, Kyoto Univ Grad Schl of Med, Kyoto, Japan, [13]Genomic Center, Kyoto University Graduate School of Medicine, Kyoto, Japan
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Background/Purpose: Rheumatoid arthritis (RA) is a chronic disease leading to joint destruction. Although many studies have addressed correlates associated with the speed of joint destruction, less attention has been paid to the distribution of joint destruction in RA. Here, we divided hand bone destruction into fingers and non-fingers in patients with RA and analyzed which factor is associated with finger joint destruction.

Methods: We recruited a total of 1,215 Japanese subjects with RA as two different sets. We assessed the degree of joint destruction by total sharp score (TSS). TSS of fingers and non-fingers were used as a dependent variable and a covariate, respectively. Age, sex, disease duration, smoking, C-reactive protein, RA treatment, positivity and levels of anti-citrullinated peptide antibody (ACPA) and rheumatoid factor (RF) were used as candidates of correlates. We assessed overall effect in meta-analysis. We further tested findings in Japanese subjects for their associations in 157 Dutch RA patients in the BeSt study in which treatment regimens were strictly specified. The association was also analyzed between finger TSS and HLA-DRB1 alleles or genetic risk scores based on haplotypes of amino acid residues associated with RA susceptibility. We also extended the analyses to TSS in the foot joints.

Results: Unsurprisingly, disease duration was associated with finger TSS ($p \leq 0.00037$). RF positivity and levels showed significant associations with finger TSS after adjusting for covariates ($p=0.0022$ and 8.1×10^{-7}, respectively). These associations were true to time-averaged finger TSS. We observed association between RF positivity and finger TSS in the BeSt study ($p=0.049$). We did not find associations between finger TSS and positivity or levels of ACPA. ACPA(-)RF(+) subjects were found to explain the difference between RF and ACPA. No associations of HLA-DRB1 alleles or genetic risk scores were observed. RF positivity and levels also showed a significant association with foot TSS or combination of foot and finger TSS.

Conclusion: RF positivity and levels are associated with finger joint destruction independently from non-finger joint destruction and covariates. Our findings might suggest different mechanisms between joint destruction of finger and non-finger joints in RA.

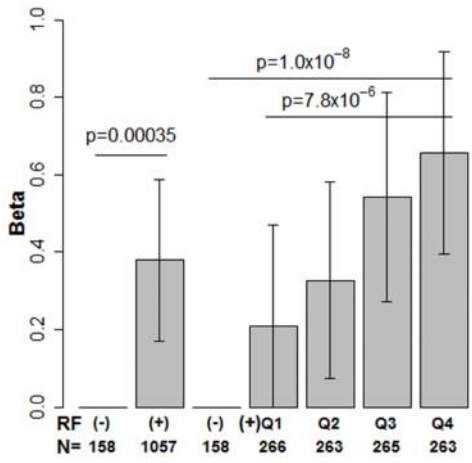

Figure. Associations between finger TSS and positivity or levels of rheumatoid factor.

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Abstract Number: 1608

Protective Role of the Vitamin D Receptor Apai (rs7975232) Polymorphism Against Subclinical Atherosclerosis in Patients with Rheumatoid Arthritis from Northern Spain

Raquel López-Mejías[1], Fernanda Genre[1], Sara Remuzgo-Martínez[1], Gema Robledo[2], Begoña Ubilla[1], Veronica Mijares[1], Javier Llorca[3], Montserrat Robustillo-Villarino[4], Alfonso Corrales[1], Carlos González-Juanatey[5], Jose A. Miranda-Filloy[6], Trinitario Pina[7], Ricardo Blanco[7], Esther Vicente[8], Juan José Alegre[9], Cesar Magro[10], Enrique Raya[11], Beatriz Tejera[12], Marco A Ramírez Huaranga[13], Ivan Ferraz-Amaro[12], Santos Castañeda[14], Javier Martín[2] and Miguel A. Gonzalez-Gay[1,15], [1]Epidemiology, Genetics and Atherosclerosis Research Group on Systemic Inflammatory Diseases, Rheumatology Division, IDIVAL, Santander, Spain, [2]Institute of Parasitology and Biomedicine López-Neyra, IPBLN-CSIC, Granada, Spain, [3]Department of Epidemiology and Computational Biology, School of Medicine, University of Cantabria, and CIBER Epidemiología y Salud Pública (CIBERESP), IDIVAL, Santander, Spain, [4]Rheumatology Department, Hospital Universitario Doctor Peset, Valencia, Spain, [5]Cardiology Division, Hospital Lucus Augusti, Lugo, Spain, [6]Rheumatology Division, Hospital Lucus Augusti, Lugo, Spain, [7]Rheumatology, Hospital Universitario Marqués de Valdecilla. IDIVAL, Santander, Spain, [8]Rheumatology Department, Hospital Universitario la Princesa, IIS-Princesa, Madrid, Spain, [9]Rheumatology, Rheumatology Department, Hospital Universitario Doctor Peset, Valencia, Spain, [10]Rheumatology Department, Hospital Clínico San Cecilio, Granada, Spain, [11]Rheumatology, Hospital Clínico San Cecilio, Granada, Spain, [12]Rheumatology Division, Hospital Universitario de Canarias, Santa Cruz de Tenerife, Spain, [13]Rheumatology Department, Hospital General Universitario de Ciudad Real, Ciudad Real, Spain, [14]Rheumatology, H.U. La Princesa, Madrid, Spain, [15]Cardiovascular Pathophysiology and Genomics Research Unit, School of Physiology, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa

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Background/Purpose: Several *vitamin D receptor* (*VDR)* polymorphisms have been associated with cardiovascular (CV) and autoimmune diseases. Carotid plaques are surrogate markers of severe atherosclerotic disease. Rheumatoid arthritis (RA) is a chronic inflammatory autoimmune disease associated with an increased risk of CV death, mainly due to a process of accelerated atherogenesis. Patients with RA have increased frequency of carotid plaques when compared with the general population. The aim of the present study was to determine the potential association of TaqI (rs731236), ApaI (rs7975232), BsmI (rs1544410) and FokI (rs2228570) *VDR* polymorphisms with carotid plaques in patients with RA.

Methods: A total of 591 RA patients from Northern Spain who met the 1987 American College of Rheumatology (ACR) and the 2010 ACR/European League Against Rheumatism criteria for RA were genotyped for rs731236, rs7975232, rs1544410 and rs2228570 *VDR* polymorphisms by TaqMan genotyping assays. In addition, the presence of carotid plaques was evaluated in these patients by carotid ultrasound technology.

Results: RA patients carrying *VDR* rs7975232 CC genotype had a decreased risk of carotid plaques, after adjustment for sex, age and traditional CV risk factors (p=0.014, OR=0.46, 95% CI: [0.24-0.85]). This effect was also found in patients who carried the mutant *VDR* rs7975232 C allele, after adjustment for potential confounder factors (p=0.018, OR=0.70, 95% CI: [0.52-0.94]). Although no association between rs731236, rs1544410 and rs2228570 *VDR* polymorphisms and presence of carotid plaques was observed, RA patients who carried the GATG haplotype (which harbors the A allele of rs7975232) had an increased risk of carotid plaques, after adjustment for sex, age and traditional CV risk factors (p=0.003, OR=2.20, 95% CI: [1.30-3.73]).

Conclusion: Our results show a protective effect of the *VDR* rs7975232 allele C on the risk of severe atherosclerosis in patients with RA.

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Abstract Number: 1609

Lack of Association Between ZHX2, Lepr, Gckr and ASCL1 and Carotid Intima-Media Thickness, Carotid Plaques and Cardiovascular Disease in Patients with Rheumatoid Arthritis

Raquel López-Mejías[1], Fernanda Genre[1], Sara Remuzgo-Martínez[1], Montserrat Robustillo-Villarino[2], Alfonso Corrales[1], Javier Llorca[3], Carlos González-Juanatey[4], Begoña Ubilla[1], Jose A. Miranda-Filloy[5], Veronica Mijares[1], Trinitario Pina[6], Ricardo Blanco[6], Juan José Alegre[2], Marco A Ramírez Huaranga[7], Maria D Mínguez Sánchez[7], Carmen Gomez Vaquero[8], Luis Rodriguez Rodriguez[9], Benjamin Fernandez Gutierrez[9], Alejandro Balsa[10], Dora Pascual-Salcedo[10], Francisco Lopez Longo[11], Patricia E. Carreira[12], Cesar Magro[13], Enrique Raya[14], Beatriz Tejera[15], Ivan Ferraz-Amaro[15], Esther Vicente[16], Isidoro González-Alvaro[16], Santos Castañeda[17], Javier Martín[18] and Miguel A. Gonzalez-Gay[1,19], [1]Epidemiology, Genetics and Atherosclerosis Research Group on Systemic Inflammatory Diseases, Rheumatology Division, IDIVAL, Santander, Spain, [2]Rheumatology Department, Hospital Universitario Doctor Peset, Valencia, Spain, [3]Department of Epidemiology and Computational Biology, School of Medicine, University of Cantabria, and CIBER Epidemiología y Salud Pública (CIBERESP), IDIVAL, Santander, Spain, [4]Cardiology Division, Hospital Lucus Augusti, Lugo, Spain, [5]Rheumatology Division, Hospital Lucus Augusti, Lugo, Spain, [6]Rheumatology, Hospital Universitario Marqués de Valdecilla. IDIVAL, Santander, Spain, [7]Rheumatology Department, Hospital General Universitario de Ciudad Real, Ciudad Real, Spain, [8]Department of Rheumatology, Hospital Universitario de Bellvitge, Barcelona, Spain, [9]Department of Rheumatology, Hospital Clínico San Carlos, Madrid, Spain, [10]Department of Rheumatology, Hospital La Paz, Madrid, Spain, [11]Department of Rheumatology, Hospital General Universitario Gregorio Marañón, Madrid, Spain, [12]Department of Rheumatology, Hospital Universitario 12 de Octubre, Madrid, Spain, [13]Rheumatology Department, Hospital Clínico San Cecilio, Granada, Spain, [14]Rheumatology, Hospital Clínico San Cecilio, Granada, Spain, [15]Rheumatology Division, Hospital Universitario de Canarias, Santa Cruz de Tenerife, Spain, [16]Rheumatology Department, Hospital Universitario la Princesa, IIS-Princesa, Madrid, Spain, [17]Rheumatology, H.U. La Princesa, Madrid, Spain, [18]Institute of Parasitology and Biomedicine López-Neyra, IPBLN-CSIC, Granada, Spain, [19]Cardiovascular Pathophysiology and Genomics Research Unit, School of Physiology, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa
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Background/Purpose: Rheumatoid arthritis (RA) is a polygenic disease associated with accelerated atherosclerosis and increased cardiovascular (CV) mortality. Recent studies have identified the *ZHX2* rs11781551 polymorphism as the most relevant genetic variant associated with carotid intima-media thickness (cIMT) values and *LEPR* rs4420065, *GCKR* rs1260326 and *ASCL1* rs10745954 as polymorphisms related to C-reactive protein levels in non-rheumatic Caucasians individuals. Accordingly, we evaluated the potential relationship between these 4 polymorphisms and subclinical atherosclerosis (assessed by cIMT and presence/absence of carotid plaques) and CV disease in RA.

Methods: 2,298 Spanish RA patients were genotyped for these 4 polymorphisms by TaqMan assays. Subclinical atherosclerosis was evaluated in 907 of these patients by carotid ultrasound.

Results: No statistically significant differences were found when each polymorphism was assessed according to cIMT values and presence/absence of carotid plaques in RA after adjustment the results for potential confounders. Moreover, no significant differences were obtained when RA patients were stratified according to the presence/absence of CV disease after adjustment for potential confounders.

Conclusion: Our results do not confirm an association between *ZHX2* rs11781551, *LEPR r*s4420065*, GCKR* rs1260326 and *ASCL1* rs10745954 and subclinical atherosclerosis and CV disease in RA.

This study was supported by European Union FEDER funds and “Fondo de Investigación Sanitaria” (grants PI06/0024, PS09/00748 and PI12/00060) (Spain). This work was also partially supported by RETICS Programs RD12/0009 (RIER) from “Instituto de Salud Carlos III” (ISCIII) (Spain), and in part by grants from the European IMI BTCure Program. FG and BU are supported by funds from the RETICS Program (RIER) (RD12/0009/0013). RLM is a recipient of a Sara Borrell postdoctoral fellowship from the “Instituto de Salud Carlos III” at the Spanish Ministry of Health (Spain) (CD12/00425).

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Abstract Number: 1610

DNA Methylation Changes Observed in Rheumatoid Arthritis Joint Tissue Are Detectable in CD4+ Naive T Cells from Peripheral Blood

Calliope Holingue[1], Brooke Rhead[1], Michael Cole[1], Xiaorong Shao[1], Hong L. Quach[1], Diana Quach[1], Elizabeth Sinclair[2], Jonathan D. Graf[3], Thomas M. Link[4], Ruby Harrison[5], Vladimir Chernitskiy[6], Wei Wang[7], Gary S. Firestein[8], Lisa F. Barcellos[1] and Lindsey A. Criswell[5], [1]Genetic Epidemiology and Genomics Laboratory, University of California, Berkeley, Berkeley, CA, [2]Division of Laboratory Medicine, University of California, San Francisco, San Francisco, CA, [3]Div Of Rheumatology, Division of Rheumatology, UCSF, San Francisco, CA, [4]Musculoskeletal Quantitative Imaging Research Group, Department of Radiology and Biomedical Imaging, University of California, San Francisco, San Francisco, CA, [5]Rosalind Russell / Ephraim P. Engleman Rheumatology Research Center, University of California, San Francisco, San Francisco, CA, [6]Rheumatology, University of California, San Francisco, San Francisco, CA, [7]Chemistry and Biochemistry, University of California, San Diego, La Jolla, CA, [8]Division of Rheumatology, Allergy and Immunology, University of California, San Diego, La Jolla, CA

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Session Time: 9:00AM-11:00AM

Background/Purpose:

Aberrant DNA methylation patterns have previously been associated with rheumatoid arthritis (RA) [MIM 180300]. Our study aimed to determine whether differentially methylated CpGs in synovium-derived fibroblast-like synoviocytes (FLS) of RA patients were also differentially methylated in peripheral blood samples.

Methods:

DNA methylation was measured by generating 371 genome-wide DNA methylation profiles for 63 RA cases (all satisfied the ACR classification criteria, 57 were seropositive), and 31 controls using Illumina HumanMethylation450 (450k) BeadChips. Cells from peripheral blood were FACS-sorted and CD14+ monocytes, CD19+ B cells, CD4+ memory T cells, and CD4+ naive T cells were assayed for each individual. One-tailed Wilcoxon rank sum tests were used to analyze case-control differences in the FLS candidates within these four cell types. Receiver operating characteristic (ROC) curve analysis was employed to test the predictive power of a hypermethylation score based on the differentially methylated sites we observed.

Results:

Of the 5,532 hypermethylated FLS candidates, 1,056 (19%) were hypermethylated in CD4+ naive T cells of our RA cases compared to controls (FDR $q<0.05$). No other CpG candidates achieved significance in the other cell types. A hypermethylation score was calculated based on these results and had an area under the curve (AUC) of 0.73 when predicting RA case status. This hypermethylation score was compared to having the HLA-DRB1 shared epitope (SE) (yes/no) and a continuous genetic risk score consisting of 43 non-HLA SNPs (Yarwood 2013 and Eyre 2012). The SE model had an AUC of 0.66 (0.56-0.77), and the genetic risk score had an AUC of 0.51 (0.38-0.63). A combined model of shared epitope, GRS and the methylation score had an AUC of 0.78, which was the best predictive model. Both methylation score and SE remained significant ($p<0.05$) when included in a multivariable logistic model of methylation score, SE and genetic risk score, with RA case-status as the outcome. Although the methylation score had a greater AUC than the SE (0.73 versus 0.66), the SE had a larger odds ratio in the multivariable logistic regression model (5.31 versus 1.06).

Conclusion:

Our results suggest that measurement of DNA methylation in CD4+ naive T cells of peripheral blood may have diagnostic or prognostic value and represents one of the first steps towards precision medicine in RA.

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Abstract Number: 1611

Gene Expression Profiling Reflects Increased Expression of Coronary Artery Disease Associated Genes in a Case-Control Matched Study of Patient with Rheumatoid Arthritis

Erica Peart[1], **Kim Huffman**[2], William E. Kraus[3], Phil Beineke[4], Jim Wingrove[4] and Steve Rosenberg[4], [1]Rheumatology, Duke University Medical Center, Durham, NC, [2]Durham Veterans Affairs Medical Center, Durham, NC, [3]Duke Pepper Center, Durham, NC, [4]CardioDx, Redwood City, CA

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Session Time: 9:00AM-11:00AM

Background/Purpose:

Peripheral blood gene expression profiling has been used to identify gene signatures which reflect a variety of pathologic conditions. The CorusCAD¨ test is a peripheral blood gene expression test incorporating age, sex, and gene expression into an algorithm which assesses obstructive CAD (coronary artery disease) likelihood in non-diabetic patients without inflammatory diseases. Our objective was to evaluate the validity of the CorusCAD¨ expression profile with CAD in persons with rheumatoid arthritis (RA), a chronic inflammatory condition.

Methods:

Twenty RA-non RA, case-control matched pairs of individuals with a range of known CAD were identified in a large cardiac catheterization cohort, CATHGEN. Rheumatoid arthritis patients were identified using ICD9 codes, and diagnosis was confirmed by chart review. Controls, without RA, were matched by sex, age, race, number of diseased coronary vessels, and BMI. Persons with type 2 diabetes were excluded. Gene expression levels of 23 CAD-associated genes composing the CorusCAD¨ score were used to determine the age, sex, gene expression scores (ASGES). ASGES were compared in RA and controls using a matched pair analytic approach (paired t-test).

Results:

In persons with RA, the range of CorusCAD¨ ASGES scores was similar for those with and without RA. Independent of CAD, persons with RA had higher Corus ASGES scores than matched controls ($P<0.04$). Specifically, RA contributed to a 10% increase in CorusCAD¨ ASGES when controlling for CAD using the matched design. RA was associated with higher expression levels for 6 of the 23 genes ($P<0.05$ for all, not adjusted for multiple comparisons): S100 calcium binding protein A12; interleukin-18 receptor accessory protein; caspase 5; S100 calcium binding protein A8; aquaporin 9; and cluster of differentiation (CD)79b. All except aquaporin 9 are associated with higher expression in CAD.

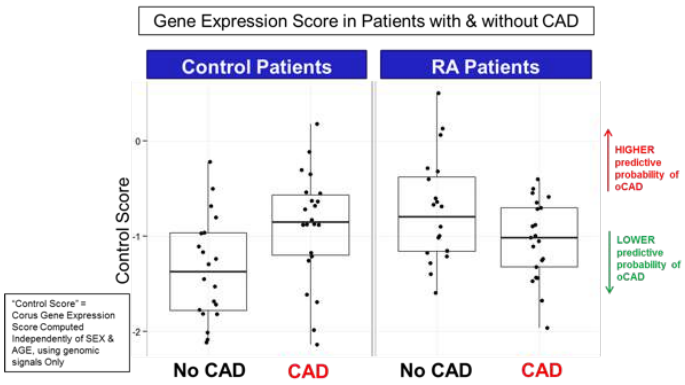

Figure 1. Corus gene expression scores (GES) are higher in RA patients compared to matched controls. GES was not able to differentiate oCAD in RA patients. (Figure contains results from the original 40 pairs, and not the selected subset with RA confirmed by chart review. However, the inability to distinguish oCAD remained when using only the confirmed RA subset.) oCAD = obstructive coronary artery disease

Conclusion:

Across a range of known coronary disease severity, RA is associated with increased expression of CAD-associated genes; among these are two genes associated with neutrophil activation, S100A8 and S100A12. Both are associated with RA disease activity in published studies. Further work on the mechanism and consequences of gene activation for these genes is indicated.

Disclosure: E. Peart, None; **K. Huffman**, None; **W. E. Kraus**, None; **P. Beineke**, CardioDx, 1,CardioDx, 3; **J. Wingrove**, CardioDx, 1,CardioDx, 3; **S. Rosenberg**, CardioDx, 1,CardioDx, 5.

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Abstract Number: 1612

Association of Single Nucleotide Polymorphisms of PADI4 and HLA-DRB1 Alleles with Susceptibility to Rheumatoid Arthritis-Related Lung Diseases

Seung-Cheol Shim[1], In-Seol Yoo[2], Su-Jin Yoo[1], Young Kim[1], Jinhyun Kim[3] and Seong-Wook Kang[2], [1]Rheumatology, Chungnam National University School of Medicine, Daejeon, South Korea, [2]Department of Internal Medicine, Chungnam National University School of Medicine, Daejeon, South Korea, [3]Internal medicine, Chungnam National University School of Medicine, Daejeon, South Korea

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Background/Purpose:

Lung diseases (LD) are common extra-articular manifestations in rheumatoid arthritis (RA). Recent studies have shown the association of RA-LD with anti-citrullinated protein antibodies. The peptidylarginine deiminase (PADI) mediates post-translational deimination of peptidylarginine to a non-standard amino acid peptidylcitrulline.

The aim of the present study was to investigate whether the single nucleotide polymorphisms (SNPs) of *PADI4* are associated with RA-LD.

Methods:

Blood samples and clinical data were collected from 116 consecutive RA patients who satisfied the 1987 American College of Rheumatology classification criteria. RA-LD was diagnosed using high-resolution computed tomography of the chest and a pulmonary function test. All of the patients were genotyped for SNPs of *PADI4* and HLA-DRB1 alleles. The independent *t*-test or Mann-Whitney test for continuous variables, the chi-square test or Fisher's exact test for categorical variables, and multivariate logistic regression analysis to assess genetic susceptibility to RA-LD were performed.

Results:

Of the 103 RA patients, 8 (7.8%) had interstitial lung disease (ILD) and 33 (32.0%) had small airway disease (AD). High titers of ACPA (≥80 U/mL; p=0.022) and RF (≥ULN×3; p=0.008) were significantly associated with susceptibility to RA-LD. The minor allele homozygote of padi4_92 was susceptible to RA-large AD (OR = 3.11 , 95% CI = 1.29-7.48). The recessive genotypes of padi4_89 (OR = 3.69, 95% CI = 1.14-11.95) and padi4_104 (OR = 3.47, 95% CI = 1.10-11.00) were susceptible to large AD. HLA-DRB1 *0405 was protective against the development of RA-AD (OR = 0.32, 95% CI = 0.11-0.98). The combination of any HLA-DRB1 *04 alleles except the *0405 and padi4_92 GG+ presented a synergistic effect on the development of

RA-large AD (OR = 17.73, 95% CI = 2.22-141.63).

Conclusion:

This study demonstrates the association of SNPs of *PADI4*and HLA-DRB1 alleles with susceptibility to RA-LD.

Table 1. Association of the SNPs of *PADI4*with the development of each pattern of lung diseases.

SNP	Allele	RA-no LD (n = 16)	RA-ILD (n = 8)	OR (95% CI)	RA-Large AD (n = 63)	OR (95% CI)	RA-Small AD (n = 6)	OR (95% CI)	RA- CombinedAD (n = 23)	OR (95% CI)
padi4_89										
	A	0.625	0.500	1	0.476	1	0.667	1	0.609	1
	G	0.375	0.500	0.71 (0.05-10.21)	0.524	1.85 (0.82-4.18)	0.333	0.68 (0.16-2.91)	0.391	0.84 (0.29-2.41)
padi4_92										
	C	0.375	0.375	1	0.151	**1**	0.500	1	0.348	1
	G	0.625	0.625	0.32 (0.03-3.42)	0.849	**3.11 (1.29-7.48)**	0.500	0.53 (0.13-2.13)	0.652	1.04 (0.36-3.00)
padi4_104										
	C	0.656	0.562	1	0.587	1	0.833	1	0.630	1
	T	0.344	0.438	0.13 (0.004-4.17)	0.413	1.27 (0.56-2.90)	0.167	0.30 (0.05-1.75)	0.370	0.90 (0.31-2.62)

Table 2. Association of genotypes of *PADI4*with the development of each pattern of lung diseases.

SNP	Genotype	RA-no LD (n = 16)	RA-ILD (n = 8)	OR (95% CI)	RA-Large AD (n = 63)	OR (95% CI)	RA-Small AD (n = 6)	OR (95% CI)	RA-CombinedAD (n = 23)	OR (95% CI)
padi4_89										
	AA	8 (50.0)	3 (37.5)	1	13 (20.6)	**1**	3 (50.0)	1	8 (34.8)	1
	AG+GG	8 (50.0)	5 (62.5)	0.74 (0.07-7.85)	50 (79.4)	**3.69 (1.14-11.95)**	3 (50.0)	0.75 (0.10-5.60)	15 (62.5)	1.57 (0.36-6.79)
	AG	5 (31.3)	2 (25.0)	1	34 (54.0)	1	2 (33.3)	1	12 (52.2)	1
	AA+GG	11 (68.8)	6 (75.0)	1.02 (0.11-9.51)	29 ((46.0)	0.41 (0.12-1.33)	4 (66.7)	1.00 (0.13-7.77)	11 (47.8)	0.32 (0.07-1.52)
	AA+AG	13 (81.2)	6 (75.0)	1	47 (74.6)	1	5 (83.3)	1	20 (87.0)	1
	GG	3 (18.8)	2 (25.0)	0.71 (0.05-10.21)	16 (25.4)	1.56 (0.38-6.41)	1 (16.7)	0.64 (0.05-8.54)	3 (13.0)	0.26 (0.03-2.16)
padi4_92										
	CC	4 (25.0)	3 (37.5)	1	7 (11.1)	1	2 (33.3)	1	8 (34.8)	1
	CG+GG	12 (75.0)	5 (62.5)	8.85 (0.64-123.30)	56 (88.9)	2.31 (0.58-9.21)	4 (66.7)	0.65 (0.08-5.29)	15 (65.2)	0.65 (0.13-3.17)
	CG	4 (25.0)	0 (0.0)	1	5 (7.9)	1	2 (33.3)	1	0 (0.0)	1
	CC+GG	12 (75.0)	8 (100.0)	7.09 (0.11-455.14)	58 (92.1)	4.37 (0.95-20.15)	4 (66.7)	0.50 (0.06-4.47)	23 (100.0)	0.06 (0.001-2.37)
	CC+CG	8 (50.0)	3 (37.5)	1	12 (19.0)	**1**	4 (66.7)	1	8 (34.8)	1
	GG	8 (50.0)	5 (62.5)	0.32 (0.03-3.42)	51 (81.0)	**4.07 (1.25-13.30)**	2 (33.3)	0.39 (0.05-3.11)	15 (65.2)	1.57 (0.36-6.79)
padi4_104										
	CC	9 (56.2)	3 (37.5)	1	17 (27.0)	**1**	4 (66.7)	1	9 (39.1)	1
	CT+TT	7 (43.8)	5 (62.5)	0.55 (0.06-5.11)	46 (73.0)	**3.47 (1.10-11.00)**	2 (33.3)	0.57 (0.08-4.34)	14 (60.9)	2.01 (0.46-8.76)
	CT	3 (18.8)	3 (37.5)	1	39 (61.9)	**1**	2 (33.3)	1	11 (47.8)	**1**
	CC+TT	13 (81.3)	5 (62.5)	0.36 (0.04-3.65)	24 (38.1)	**0.13 (0.03-0.51)**	4 (66.7)	0.38 (0.04-3.54)	12 (52.2)	**0.10 (0.01-0.95)**
	CC+CT	12 (75.0)	5 (62.5)	1	57 90.5)	1	6 (100.0)	1	20 (87.0)	1
	TT	4 (25.0)	3 (37.5)	0.13 (0.004-4.17)	6 (9.5)	0.23 (0.05-1.05)	0 (0.0)	0.06 (0.001-6.60)	3 (13.0)	0.23 (0.04-1.52)

Table 3. Combined effects of HLA-DRB1 *0405 allele and padi4_92 genotype on the development of each pattern of lung diseases.

	RA-no LD (n = 16)	RA-ILD (n = 8)	OR (95% CI)	RA-Large AD (n = 63) missing = 1	OR (95% CI)	RA-Small AD (n = 6)	OR (95% CI)	RA-Combined AD (n = 23)	OR (95% CI)	RA-AD (n = 92) missing = 1	OR (95% CI)	RA-LD (n = 100) missing = 1	OR (95% CI)
*0405+/padi4_92GG-	4 (25.0)	2 (25.0)	1	3 (4.8)	1	1 (16.7)	1	1 (4.3)	1	5 (5.5)	1	7 (7.1)	1
*0405+/padi4_92GG+	6 (37.5)	1 (12.5)	0.25 (0.01-4.69)	19 (30.6)	3.95 (0.68-23.01)	0 (0.0)	0.18 (0.004-7.75)	7 (30.4)	2.99 (0.21-42.94)	26 (28.6)	3.31 (0.65-16.81)	27 (27.3)	2.61 (0.55-12.39)
*0405-/padi4_92GG-	4 (25.0)	1 (12.5)	0.91 (0.04-21.33)	9 (14.5)	2.63 (0.38-17.98)	3 (50.0)	2.56 (0.22-29.47)	7 (30.4)	5.14 (3.41-77.67)	19 (20.9)	3.37 (0.60-19.12)	20 (20.2)	2.78 (0.52-14.78)
*0405-/padi4_92GG+	2 (12.5)	4 (50.0)	0.44 (0.02-10.44)	31 (50.0)	**17.73 (2.22-141.63)**	2 (33.3)	2.59 (0.17-38.75)	8 (34.8)	**11.45 (0.64-205.69)**	41 (45.1)	**15.76 (2.20-112.96)**	45 (45.5)	**12.32 (1.81-83.98)**

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Abstract Number: 1613

Expression of the Genes Facilitating Methotrexate Action within Rheumatoid Subcutaneous Nodules

Emma Houlder[1], Melanie Millier[2], John Highton[3], Lisa K. Stamp[4] and **Paul Hessian**[2], [1]Medicine, University of Otago, Dunedin, New Zealand, [2]Department of Medicine, University of Otago, Dunedin, New Zealand, [3]Dept of Medicine, University of Otago, Dunedin, New Zealand, [4]Medicine, University of Otago, Christchurch, Christchurch, New Zealand

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Background/Purpose: Methotrexate (MTX) is the most frequently used DMARD in the treatment of rheumatoid arthritis (RA). There are known links between the use of MTX and accelerated development of rheumatoid nodules in RA, although the mechanisms are unclear. Little is known of the potential for an anti-folate mode of action by MTX within nodule tissue. Previous studies indicate that adenosine release and genetic factors may be important to nodule development. However, the potential for these mechanisms to operate within nodules is unknown. The objective of this study was to determine whether MTX affects the expression of genes encoding adenosine receptors, MTX transporters and metabolising enzymes within subcutaneous rheumatoid nodules.

Methods: Subcutaneous nodule tissues (n=23) were obtained following elective surgery from 21 patients with RA, including 16 nodules from 15 patients receiving MTX and 7 nodules from 6 patients without MTX therapy. Plasma levels for 15 cytokines were measured in paired bloods from 12 patients using Bio-Plex Pro human Th17 assays (BioRad). Quantitative real-time PCR assays (Applied Biosystems) were used to determine the expression of SLC19A1, ABCB1, ABCC1, ABCG2, GGH, FPGS, MTR, MTRR and TYMS, ADORs A1, A2A, A2B, and A3 genes within each nodule. Differences in normalised gene expression between groups was determined by Mann Whitney U tests and Spearman correlations between gene expression used to establish gene connectivity.

Results: All genes examined were expressed in all 23 nodule tissues. Amongst all genes, only the expression of MTR, encoding 5-methyltetrahydrofolate-homocysteine methyl transferase, was affected by MTX therapy, with reduced MTR expression in nodules from patients on MTX therapy, compared to those not receiving MTX (1.682ng vs 3.625ng respectively; p=0.023). The potential for gene co-regulation and connectivity was determined based on gene expression correlations. Greatest connectivity was established for TYMS, where expression significantly correlated, positively with GGH and FPGS and negatively with ADORA1, ABCG2 and MTR expression. MTX therapy impacted on this connectivity maintaining especially the TYMS with MTR and ADDORA1 negative correlations. Finally we found no evidence for an effect from interleukin (IL)-23, IL-6, TNFalpha or IFNgamma in plasma on gene expression within nodules.

Conclusion: The genes responsible for MTX transport, metabolism and mode of action are expressed in subcutaneous rheumatoid nodules. Amongst the genes investigated, MTX therapy impacts only on MTR gene expression, which is significantly reduced in nodules by MTX therapy. Plasma levels of key cytokines driving RA have no impact on nodule gene expression. Our data demonstrate the potential for MTX to exert its anti-inflammatory effects witin

nodules; that MTX influences connectivity between gene expresion in nodules; and suggest that, through MTR expression, DNA methylation might be an underlying mechanism important to the formation of this extraarticular inflammatory lesion.

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Abstract Number: 1614

The Impact of High Risk Susceptible Gene LILRA3 on Joint Inflammation in Rheumatoid Arthritis

Mengru Liu[1], Yan Du[2], Jing Zhang[1], Fanlei Hu[1], Li Zheng[3], Yingni Li[3], Jianping Guo[1] and Z. Li[1], [1]Department of Rheumatology and Immunology, Peking University People's Hospital, Beijing, China, [2]Department of Rheumatology and Immunology, The Second Affiliated Hospital, School of Medicine, Zhejiang University, Zhejiang, China, [3]Peking University People's Hospital, Beijing, China
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Background/Purpose: Leukocyte immunoglobulin-like receptor A3 (LILRA3) is a putatively secreted protein belongs to the leukocyte immunoglobulin-like receptor (LILR) family. Based on our research that LILRA3 is a novel genetic risk for rheumatoid arthritis (RA) in Chinese Han population , we undertake this study to investigate the role of LILRA3 on synovium inflammation in RA patients.

Methods: i) The expression of LILRA3 in serum and synovial fluid from patients with RA ,OA, and health controls were measured by using ELISA. ii) Fibroblast-like synoviocytes (FLSs) from RA patients were stimulated with different concentration of recombinant LILRA3 protein in the presence or absence of tumour necrosis factor (TNF)-α and interleukin (IL)-1β. iii) FLSs from patients with RA were transfected with LILRA3 plasmid or control vector and 24 hours later were treated with TNF-α and IL-1β co-culture. The expression of inflammatory mediators, including IL-6,IL-8, MMP-1and MMP-3 was measured by q-PCR array and ELISA. MARKinse signaling pathway activation levels were detected by Western Blotting method. One-way analysis of variance was used to detect the differences between the group means.

Results: Compared with health controls, the expression of LILRA3 in RA and OA serum was high and LILRA3 was specifically express in synovial fluid with RA patients. We demonstrated that LILRA3 can promote the secretion of inflammatory factors independently or synergy with TNF-α and IL-1β both in vitro and in a transfect system. Furthermore, we proved that LILRA3 can promoted synovium inflammation through the activation of the signaling pathways, particularly the ERK and JNK pathways.

Conclusion:

Our data demonstrate that LILRA3 is a potent new pro-inflammatory factor in RA. LILRA3 can aggravates synovium inflammation through MARKinse signaling pathway. These findings may give us some clues for the study on the pathogenesis of RA.

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Abstract Number: 1615

Lack of Replication of the Association Between Anti-Citrullinated Fibrinogen and Subclinical Atherosclerosis in Patients with Rheumatoid Arthritis

Ariana Montes[1], Alfonso Corrales[2], Manuel Calaza[3], Raquel López-Mejías[4], José Antonio Parra[5], Miguel Angel Gonzalez-Gay[6] and **Antonio Gonzalez**[7], [1]Laboratorio Investigacion 10 and Rheumatology Unit, Instituto Investigacion Sanitaria- Hospital Clinico Universitario de Santiago, Santiago de Compostela, Spain, [2]Hospital Universitario Marqués de Valdecilla. IDIVAL. Santander. Spain, Santander, Spain, [3]Laboratorio Investigacion 10 and Rheumatology Unit. Instituto Investigacion Sanitaria.Hospital Clinico Universitario de Santiago, Santiago de Compostela, Spain, [4]Epidemiology, Genetics and Atherosclerosis Research Group on Systemic Inflammatory Diseases, Rheumatology Division, IDIVAL, Santander, Spain, [5]Radiology Division, Hospital Universitario Marqués de Valdecilla, Santander, Spain, [6]Rheumatology, Hospital Universitario Marqués de Valdecilla. IDIVAL, Santander, Spain, [7]Instituto Investigacion Sanitaria-Hospital Clinico Universitario de Santiago, Santiago de Compostela, Spain
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Background/Purpose:

A recent study has suggested that the excess cardiovascular (CV) risk observed in patients with rheumatoid arthritis (RA) could be partially explained by immune-complexes of antibodies against citrullinated proteins that locally promote and perpetuate inflammation and progression of atherosclerotic plaques (1). Our aim has been to replicate one of the observations supporting this hypothesis: association between anti-citrullinated fibrinogen (citFib) and subclinical atherosclerosis.

Methods:

Three surrogate markers of atherosclerosis were assessed in 124 patients with RA, with no previous history of CV events: carotid intima-media thickness (cIMT) and carotid plaques assessed by carotid ultrasonography (US), and coronary artery calcification score (CACS) performed by multi-detector computed tomography (MDCT) scan. We analyzed the relationship of these three markers of subclinical atherosclerosis with the presence and levels of autoantibodies, including anti-citFib, anti-CCP2 and RF.

Results:

CV risk based on gender, age, cholesterol, systolic blood pressure and smoking status was low or moderate for most patients, and only 17 patients showed ≥ 5 % risk of fatal events in 10 years according with classical risk factors. In contrast, most patients (81.4 %) showed at least one sign of subclinical aterosclerosis: carotid plaques were present in 69.4 % of the patients, moderate to high CACS in 21.0 %, and cIMT > 0.9 mm in 15.6 %. None of these surrogate markers of atherosclerosis showed a significant association with anti-citFib antibodies (either against the whole protein present in 33.9 % of the patients, or against an immunodominant peptide present in 23.4 %) or with anti-CCP2 (60.7 %) or RF (58.1 %) in this series of patients with RA. In addition, no significant association was observed when the patients were analyzed according to sex, seropositive status RA or combined atherosclerosis surrogate markers.

Conclusion:

Our results do not support a relationship between anti-citFib antibodies and subclinical atherosclerosis in RA questioning the claim that these antibodies have a role in the increased risk of CV disease observed in patients with RA.

1. Sokolove J, *et al. Arthritis Rheum.* 2013;65:1719-24.

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Abstract Number: 1616

Identification of Genes Regulating TRAIL-Induced Apoptosis in Rheumatoid Arthritis Fibroblasts-like Synoviocytes (RA FLS)

Rachel Audo[1,2], Bernard Combe[3,4], Michael Hahne[5] and **Jacques Morel**[6], [1]Rheumatology, Teaching Hospital of Lapeyronie, Montpellier, France, [2]IGMM, CNRS UMR5535, Montpellier, Montpellier, France, [3]Department of Rheumatology, Lapeyronie Hospital, Montpellier, France, [4]Montpellier University, Montpellier, France, [5]IGMM-CNRS UMR5535, Montpellier, France, [6]Department of rheumatology, Lapeyronie Hospital and Montpellier University, Montpellier, France

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Background/Purpose:

We previously described that sensitivity to TRAIL-induced apoptosis varied in rheumatoid arthritis (RA) fibroblasts-like-synoviocytes (FLS) from one patient to another, and was inversly correlated with disease severity. Therefore, we screened for genes differentially expressed in RA FLS sensitive and resistant to TRAIL induced apoptosis.

Methods:

The sensitivity of RAFLS was defined based on the percentage of TRAIL-induced apoptosis: 0-10% for resistant RAFLS (RAFLS-R) and above 25% for sensitive RAFLS (RAFLS-S). We performed transcriptomic comparison using microarray to compare sensitive (n=6) and resistant RAFLS (n=6). Differential expression was validated using quantitative PCR (q-RTPCR) and we examined the implication of identified candidates in the regulation of apoptosis using siRNA .

Results:

Microarray analysis revealed 10 functional genes differentially expressed according to TRAIL sensitivity. These factors are implicated in different functions, such as the respiratory chain (ND3), the transport of lipids (OSBP2, PLTP), the regulation of signalling linked to extracellular factors (SULF2, GALNT1, SIAE) or the regulation of gene expression (TET2 and LARP6). We confirmed differential expression for GALNT1 ($p<0.05$) and LARP6 ($p<0.05$) by q-RTPCR, with an overexpression of LARP6 in RAFLS-R and of GALNT1 in RAFLS-S, while SULF2 also tended to be overexpressed in RAFLS-S ($p=0.1$). LARP6 protein was also significantly overexpressed in RAFLS-R (n=6) compared to RAFLS-S (n=7) ($p<0.05$). Using siRNA extinction, we demonstrated the implication of GALNT1, SULF2 and LARP6 in the control of TRAIL induced responses since the siRNA which target GALNT-1, SULF-2 significantly decreased ($p<0.05$, n=7) while siRNA targeting LARP6 significantly increased TRAIL-induced apoptosis of RAFLS ($p<0.01$, n=10).

DISCUSSION: Concurring with the demonstration of the importance of glycosylation in the regulation of TRAIL sensitivity in cancer cells line , we demonstrated that GALNT1 and SULF2 are factors participating in TRAIL-induced apoptosis in FLS. We also did the first demonstration that LARP6 participate to the resistance against TRAIL-induced apoptosis.

Conclusion: To conclude, we described several new potential targets controlling TRAIL induced cell death in RAFLS. These results are of particular interest since GALNT1 and LARP6 have been implicated in the regulation of cell death or in cancer and may represent interesting targets to induce apoptosis of RAFLS.

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Abstract Number: 1617

Evidence for Citrullinated Inhibitor of DNA Binding 1 (Id1) As a Novel Autoantigen Candidate in Rheumatoid Arthritis

Ray A. Ohara[1], Gautam Edhayan[1], W. Alexander Stinson[2], Phillip L. Campbell[1], Henriette A. Remmer[3], M. Asif Amin[1], David A. Fox[1] and Jeffrey H. Ruth[1], [1]Internal Medicine, Division of Rheumatology, University of Michigan Medical Center, Ann Arbor, MI, [2]Division of Rheumatology, University of Michigan Medical Center, Ann Arbor, MI, [3]Biomedical Research Core Facilities, Proteomics & Peptide Synthesis Core, University of Michigan Medical School, Ann Arbor, MI

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Background/Purpose: Inhibitor of DNA-binding 1 (Id1) is a nuclear transcription factor actively transcribed in endothelial progenitor cells and in cells that exhibit hyperproliferative responses such as synovial fibroblasts. Previously, we identified Id1 as an angiogenic factor expressed in rheumatoid arthritis (RA) synovial tissues (STs) and upregulated in RA synovial fluids (SFs). Although it is a relatively small protein of approximately 16 kDA, Id1 contains 10 modifiable arginines. As a variety of citrullinated proteins is known to bind to anti-citrullinated protein antibodies (ACPAs), we investigated citrullinated Id1 (citId1) as a potential autoantigen in RA.

Methods: RA SFs were immunodepleted of Id1 and measured by ELISA using anti-modified citrulline (AMC) antibody for total citrullinated antigens pre and post Id1 depletion. Id1 was also immunoprecipitated from homogenized RA STs and analyzed by Western blot (WB) using anti-human Id1 or AMC antibodies. CitId1 was prepared *in vitro* from recombinant human (rh) Id1 by incubation with rh peptidyl arginine deiminase 4 (PAD4); noncitrullinated Id1 (noncitId1) was prepared identically without rhPAD4. To confirm the citrullination sites, citId1 and noncitId1 were analyzed using liquid chromatography-tandem mass spectrometry (LC-MS/MS). To test the presence of ACPAs to citId1, normal (NL) and RA patient peripheral blood (PB) sera immunodepleted of rheumatoid factor (RF) were analyzed using immunodot blot (IDB). CitId1 and noncitId1 were dotted onto nitrocellulose membranes, blocked, and incubated in the patient sera. Bovine serum albumin (BSA) and citBSA were used as antigen controls; anti-human Id1 antibody and rh IgG were used as sera controls. Epithelial-derived neutrophil-activating peptide-78 (ENA-78/CXCL5) and citENA-78/CXCL5 were similarly tested for autoantigenicity.

Results: ELISA analysis of RA SFs showed that the levels of total citrullinated antigens were significantly reduced upon immunodepletion of Id1. WB analysis of immunoprecipitated Id1 from homogenized RA STs showed that a significant portion of the total Id1 was in the modified form. LC-MS/MS analysis provided 97% sequence coverage for citId1, identifying 9 of the 10 total arginines, and 77% sequence coverage for noncitId1, identifying 7 arginines. Of the 9 identified arginines in citId1, citrullination sites were localized specifically at R33, R44, R52, R75, R87, and R121. Of the 7 identified

arginines in noncitId1, R87 was identified to be citrullinated, showing that at least one arginine is natively citrullinated in Id1. IDB analysis of mouse anti-human Id1 antibody (previously used in immunodepletion and immunoprecipitation) showed positive signals from both citId1 and noncitId1, suggesting that this binding epitope was not modified by citrullination. IDB analysis of the patient sera showed robust signals for citId1, and weak but significant signals for citENA-78/CXCL5, from multiple RA patient PB sera, displaying a four-fold increase in average reactivity for citId1 as compared to NL patient PB sera.

Conclusion: We show for the first time the presence of ACPAs with specificity to citId1 in RA patient PB sera, and propose citId1 as a novel autoantigen candidate in RA.

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Abstract Number: 1618

The Protective Effect of HLA-DRB1*13 Alleles during Specific Phases in the Development of ACPA-Positive RA

J. van Heemst[1], A.H. Hensvold[2], X. Jiang[2], H. van Steenbergen[1], L. Klareskog[2], T. W. J. Huizinga[1], A.H.M. van der Helm- van Mil[1], A.I. Catrina[2], René E. M. Toes[1], K. Lundberg[2] and **Diane van der Woude**[1], [1]Leiden University Medical Center, Leiden, Netherlands, [2]Karolinska Institute, Stockholm, Sweden
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Background/Purpose: HLA-DRB1*13 alleles are associated with protection from anti-citrullinated protein antibody (ACPA-)positive rheumatoid arthritis (RA). It is however unknown at which phase of disease development (seroconversion, ACPA maturation, disease onset or outcome) these alleles are most important. We therefore examined the effect of HLA-DRB1*13 on: ACPA-presence (:systemic autoimmunity associated with RA) in individuals with and without RA, on ACPA characteristics and on clinical outcome measures.

Methods: The effect of HLA-DRB1*13 on ACPA-presence in subjects with or without RA was assessed in the Swedish twin registry (n=10748). ACPA characteristics were studied in ACPA-positive RA patients from the Swedish Epidemiological Investigation of RA (EIRA, n=1224) and the Dutch Leiden Early Arthritis Clinic (EAC, n=441). Disease activity at inclusion and disease outcome (DMARD-free sustained remission and radiographic progression) was assessed in RA patients from the EAC.

Results: HLA-DRB1*13 is associated with protection from ACPA-positive RA (prevalence 16% versus 28% in ACPA-negative RA), but not with significant protection from ACPA in individuals without RA (prevalence: 22%, p-value 0.09). HLA-DRB1*13 is associated with lower ACPA-levels (EIRA: 447 U/ml versus 691 U/ml, p-value: 0,0002) and decreased citrullinated epitope recognition (EIRA: $p< 0.0001$). No association between HLA-DRB1*13 and disease activity or outcome was found.

Conclusion: These data indicate that HLA-DRB1*13 mainly affects the onset of ACPA-positive RA in ACPA-positive non-RA individuals. In RA, HLA-DRB1*13 influences ACPA characteristics, but not the disease course. This implies that therapeutic strategies aimed at emulating the HLA-DBR1*13 protective effect may be most effective in ACPA-positive healthy individuals at risk for RA.

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Abstract Number: 1619

Genetic Influences of Susceptibility to Rheumatoid Arthritis in African Americans

Vincent A. Laufer[1], Richard J. Reynolds[2], Maria I. Danila[3], Hemant K. Tiwari[4], Amit Patki[4], Carl D. Langefeld[5], Devin Absher[6], Donna K. Arnett[7] and S. Louis Bridges Jr.[8], [1]Division of Clinical Rheumatology and Immunology, University of Alabama at Birmingham, Birmingham, AL, [2]Medicine, University of Alabama at Birmingham, Birmingham, AL, [3]AL, [4]Biostatistics, University of Alabama at Birmingham, Birmingham, AL, [5]Biostatistical Sciences, Wake Forest School of Medicine, Winston-Salem, NC, [6]Hudson Alpha Institute for Biotechnology, Huntsville, AL, [7]University of Alabama at Birmingham, Birmingham, AL, [8]Clinical Immunology and Rheumatology, University of Alabama at Birmingham, Birmingham, AL
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Background/Purpose: Trans-ethnic analyses have found similarities and differences in genetic influences on RA susceptibility among Caucasians and Asians, making both validation and novel gene association studies important in the less well studied African-American (AA) population.

Methods: 535 ACPA-positive AA RA cases and 1,506 AA controls were genotyped using Illumina Omni 1M and 1S arrays. Associated and suggestive loci were defined as variants within 100kB on either side of lead SNPs identified by Okada et al [Nature 506:376 (2014)] with a p-value of $<10^{-8}$, or $< 10^{-5}$, respectively. In addition to traditional association analyses, we used the novel technique, Probabilistic Identification of Causal SNPs (PICS) [Farh et al. Nature 518:337 (2015)], to identify candidate causal SNPs. We used a binomial test to assess whether SNPs with association p-values (using two thresholds: $p<0.01$ and $p<0.001$) in AA RA were enriched for PICS identified in 21 autoimmune diseases as provided by Farh et al.

Results: The association of HLA-DRB1 and PRKCQ was confirmed through the chip data, as was the absence of association of PTPN22, with RA in AA. We found a peak of association at 5p15.31 with the most strongly associated SNP being rs13169313 ($p = 4.87*10^{-8}$, OR=1.44, nearest gene, MTRR). Initial analysis of this locus seems to implicate ancestral African haplotypes, not Caucasian haplotypes. Figure 1 shows a LocusZoom plot of this region. There was significant enrichment of association of autoimmune disease PICS SNPs among SNPs associated with RA at p-value < 0.01 ($p=1.55*10^{-11}$) and at p-value < 0.001 ($p=5.9*10^{-5}$, binomial test).

Conclusion: This analysis confirms gene and variant-level associations of HLA-DRB1 and PRKCQ with RA in AA and shows association with 5p15.31. The marked enrichment of PICS SNPs with low association p-values in our cohort suggests pleiotropy between autoimmune diseases and susceptibility to RA in AA.

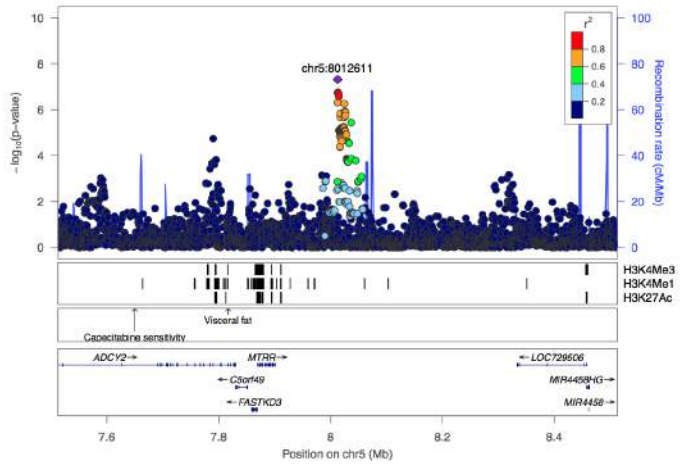

Figure 1 – LocusZoom plot of this region. Here, colored dots refer to linkage to the lead SNP assuming West African LD patterns. The correlation between association p-values and LD to the lead SNP is substantially weaker if European LD is assumed.

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Abstract Number: 1620

DNA Methylation Profiling of Rheumatoid Arthritis Peripheral Blood Identifies Hypermethylation of TRIM69 Promoter Region in CD4+ T Cells Associated with Disease Activity

Amanda Mok[1], Brooke Rhead[1], Calliope Holingue[1], Xiaorong Shao[1], Diana Quach[1], Hong L. Quach[1], Elizabeth Sinclair[2], Jonathan D. Graf[3], Thomas M. Link[4], Ruby Harrison[3], Vladimir Chernitskiy[3], Wei Wang[5], Gary S. Firestein[6], Lisa F. Barcellos[1] and Lindsey A. Criswell[3], [1]Genetic Epidemiology and Genomics Laboratory, University of California, Berkeley, Berkeley, CA, [2]Division of Laboratory Medicine, University of California, San Francisco, San Francisco, CA, [3]Rosalind Russell / Ephraim P. Engleman Rheumatology Research Center, University of California, San Francisco, San Francisco, CA, [4]Department of Radiology and Biomedical Imaging, Musculoskeletal Quantitative Imaging Research, UCSF, San Francisco, CA, [5]Chemistry and Biochemistry, University of California, San Diego, La Jolla, CA, [6]Division of Rheumatology, Allergy and Immunology, University of California, San Diego, La Jolla, CA

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Background/Purpose: Epigenetic modifications have been previously associated with rheumatoid arthritis (RA [MIM 180300]). This study aimed to determine whether differential DNA methylation in peripheral blood samples is associated with disease activity among RA patients.

Methods: Peripheral blood samples were taken from 59 RA patients in the University of California, San Francisco RA cohort (all satisfied ACR classification criteria; 53 were seropositive; 41 had evidence of erosive disease). Cells were FACS-sorted into 4 immune cell subsets (CD14+ monocytes, CD19+ B cells, CD4+ memory T cells, CD4+ naïve T cells) per individual, and 233 epigenome-wide DNA methylation profiles were generated using Illumina HumanMethylation450 BeadChips. Patients were also evaluated with the Clinical Disease Activity Index (CDAI) and divided into 2 categories based on cutoffs recommended by the American College of Rheumatology: remission (CDAI<2.8, n=14), and active disease (CDAI≥2.8, n=45). One-tailed Wilcoxon rank sum tests were used to evaluate methylation differences between the two patient categories for candidate CpG sites previously found to be differentially methylated in fibroblast-like synoviocytes derived from RA patients compared to osteoarthritis patients or normal controls.

Results: Of the 13,938 candidate loci, 1 CpG (cg05439368, upstream of *TRIM69*) was significantly hypermethylated and 1 CpG (cg07135032, in *LMX1A*) was significantly hypomethylated in CD4+ memory T cells (FDR q<0.05). No other CpG candidates achieved significance in the other cell types. CpGs within 1500 bp of *TRIM69* were subsequently evaluated, and a block of 6 CpGs (including cg05439368) in the promoter region of *TRIM69* was hypermethylated (p<0.05) in both the CD4+ memory and CD4+ naïve T cell subsets, suggesting that dysregulation of *TRIM69* expression in CD4+ T cells may be associated with RA disease activity. *TRIM69* has been reported to directly interact with a number of toll-like receptors (TLRs), a family of proteins involved in the innate immune response to microbial agents.

Conclusion: Our results identify a potential biological mechanism underlying disease activity in RA cases. This study is the first to report methylation differences associated with RA CDAI scores.

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Abstract Number: 1621

Genetic Contributions to Radiographic Damage in African Americans with Rheumatoid Arthritis on a Panel of Autoimmune Disease Markers

Vincent A. Laufer[1], Richard J. Reynolds[2], Peter K. Gregersen[3], S. Louis Bridges Jr.[4], Maria I. Danila[5] and CLEAR Investigators, [1]Division of Clinical Rheumatology and Immunology, University of Alabama at Birmingham, Birmingham, AL, [2]Medicine, University of Alabama at Birmingham, Birmingham, AL, [3]Robert S. Boas Center for Genomics and Human Genetics, Feinstein Institute for Med Res, Manhasset, NY, [4]Clinical Immunology and Rheumatology, University of Alabama at Birmingham, Birmingham, AL, [5]AL
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Background/Purpose: Rheumatoid arthritis (RA) is a complex autoimmune condition affecting 0.5-1% of populations worldwide and having a significant heritable component. A major endophenotype within RA is erosive joint damage, which is associated with autoantibodies and is manifested by bony erosions and joint space narrowing. In this study we seek to uncover influences on RA severity using the Immunochip custom array in order to both validate established loci of RA severity and discover novel contributing loci.

Methods: Genotyping was performed on the Immunochip custom array, which was designed for the interrogation of autoimmune phenotypes. In addition, hand and foot radiographs from 548 African American RA patients were available for this study. The total radiographic score ranged from 0 to 140, and we separated these patients into two groups, those having an erosion score of 0 (n=235) and those having an erosion score greater than 0 (n=313). After standard quality control measures for genotype missingness, Hardy-Weinberg equilibrium, etc., logistic regression was carried out while controlling for disease duration, proportion of European admixture, sex, Body Mass Index (BMI), smoking status, DMARD or Biologic use, and number of HLA-DRB1 risk alleles as covariates. We also fitted zero-inflated negative binomial models using total radiographic score as count data. We defined statistical significance at $p=3.1*10^{-6}$based on an Neff of 16,154 calculated using Plink.

Results: rs1466576 reached Immunochip-wide statistical significance (OR=2.19, $p = 1.81*10^{-6}$, nearest gene, *PCBD1*). *CTLA4* also showed suggestive evidence of association with radiographic severity, and the lead SNP was rs73055463, OR=0.39, $p=1.47*10^{-5}$) in CTLA4, an established risk locus in rheumatoid arthritis. Finally, rs506746 (in NALCN, near ITGBL1) was associated with RA severity ($p=9.93*10^{-7}$) using zero-inflated negative binomial

model).

Conclusion: This is the first study to evaluate the genetic contribution to radiographic severity in African Americans with RA. Using the Immunochip we found that PCBD1, NALCN/ITGBL1, and CTLA4 are associated with radiographic severity in African Americans with RA. These findings, while preliminary, may help extend knowledge of the genetic basis of radiographic damage in RA among African Americans, an understudied population in RA research.

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Abstract Number: 1622

Genome-Wide Association Analysis and Whole Genome Sequencing Identify Variants Associated with Radiographic Severity of Rheumatoid Arthritis in African Americans

Vincent A. Laufer[1], Richard J. Reynolds[2], Maria I. Danila[3], R. Curtis Hendrickson[4], Elliot J. Lefkowitz[5], Devin Absher[6], Robert P. Kimberly[7] and S. Louis Bridges Jr.[8], [1]Division of Clinical Rheumatology and Immunology, University of Alabama at Birmingham, Birmingham, AL, [2]Medicine, University of Alabama at Birmingham, Birmingham, AL, [3]AL, [4]University of Alabama at Birmingham, Birmingham, AL, [5]Microbiology, University of Alabama at Birmingham, Birmingham, AL, [6]Hudson Alpha Institute for Biotechnology, Huntsville, AL, [7]Medicine, Clinical Immun & Rheumatology, University of Alabama at Birmingham, Birmingham, AL, [8]Clinical Immunology and Rheumatology, University of Alabama at Birmingham, Birmingham, AL
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Background/Purpose: Joint damage manifested by bony erosions and joint space narrowing is a major contributor to the morbidity and mortality of RA. Reports in Caucasians (EA) indicate that as much as 58% of radiographic severity of RA may be heritable, but little is known about the heritability of this phenotype, especially in African Americans (AA).

Methods: 175 AA RA patients with longstanding ACPA-positive RA that never progressed to radiographic damage, and 264 autoantibody-positive AA RA patients with radiographic joint damage were genotyped using Illumina Omni 1M and 1S arrays. Whole genome sequence (WGS) data (Complete Genomics) was obtained on a subset of 62 autoantibody-positive AA RA patients (31 with radiographic damage, 31 without damage). DMARD/biologic use, disease duration, sex, smoking status, and the top 10 principal components were included as covariates. We sought variants associated with radiographic damage using a genome-wide significance threshold of $p < 10\text{-}8$. Using our WGS data, we analyzed 126 loci for association with damage: 101 loci associated with susceptibility in EA and 25 loci previously reported to be associated with radiographic severity of RA among EA. We conducted covariate-controlled gene based testing ($\alpha = 4*10\text{-}4$) on these loci using SKAT-O and then conducted immune cell enhancer burden tests ($\alpha = 1.6*10\text{-}5$) in these regions.

Results: We did not detect any associations of SNP variants with damage at a genome wide level of significance with Illumina 1M/1S data; the most strongly associated variant with radiographic damage was rs4743949 (chr9:92722181, $p = 5.76*10\text{-}7$, OR= 0.60) located in an enhancer region nearest mir4290, a non-coding RNA, and about 800kB 5' of Syk. Gene burden testing of WGS data revealed loci having an enrichment of variants that have previously associated with radiographic severity of RA. 3 of the 25 gene burden tests showed evidence of association; these were ILF3 ($1.31*10\text{-}4$, gene based burden test), ATG5 ($7.27*10\text{-}7$, T-cell enhancer region), and CXCR5 ($p=1.28*10\text{-}5$, B-cell enhancer region). We did not detect association of radiographic severity with the HLA-DRB1 locus in either single variant or burden testing.

Conclusion: Consistent with recent reports, variation in enhancer regions, many of which are T-cell enhancers, were associated with damage. For example, the enhancer region of ATG5, a gene important for T and B cell lymphocyte development and required for appropriate processing of antigens for presentation by MHC class II, was significantly associated. The HLA region was not found to be associated with RA severity in this study, possibly because the whole cohort is ACPA positive. Appropriate parsing of NGS data may elucidate associated loci that are missed using array-based GWA studies.

Disclosure: V. A. Laufer, None; **R. J. Reynolds**, K01 NIH Research Grant, 2; **M. I. Danila**, None; **R. C. Hendrickson**, None; **E. J. Lefkowitz**, None; **D. Absher**, None; **R. P. Kimberly**, None; **S. L. Bridges Jr.**, None.

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Abstract Number: 1623

Genome-Wide Association Study of DNA Methylation in Th1 and Th17 Cells in Rheumatoid Arthritis

Katharina Stutzer[1], Fausto Pirronello[1], Simone Wahl[2], Hendrik Schulze-Koops[1], Alla Skapenko[1] and Jan Leipe[3], [1]Division of Rheumatology and Clinical Immunology, University of Munich, Munich, Germany, [2]Research Unit of Molecular Epidemiology, Helmholtz Zentrum München, Munich, Germany, [3]Division of Rheumatology and Clinical Immunology, Med. Klinik und Poliklinik IV, University of Munich, Munich, Germany
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Background/Purpose: Rheumatoid arthritis (RA) is a common autoimmune disease characterized by systemic inflammation. Although the understanding of the pathogenesis is incomplete, there is substantial evidence that an increased Th17 cell response plays an important role in the disease onset. Further attempts to understand the RA pathogenesis recently raised interest in elucidating cell specific epigenetic modifications. In the current study we investigated genome-wide DNA methylation patterns in Th1 and Th17 cells from RA patients.

Methods: Early treatment-naive RA patients (n=6) were included into the study. For control gender- and age-matched healthy controls (n=6, HC) were analyzed. CD4 memory T cells were separated from the peripheral blood using magnetic beads. After overnight stimulation with anti-CD3/CD28 sorting of Th1 and Th17 cells was performed by FACS based on cytokine secretion assay for IL-17 and IFNγ. Subsequently, DNA was isolated, bisulfite-converted and amplified. Epigenome-wide association analysis was performed using the Infinium HumanMethylation 450 Bead Chip Kit assessing more than 480,000 CpG positions. Data were normalized using an algorithm in R software and further analyzed based on an established pipeline.

Results: Comparative analysis of methylation status of Th17 cells from RA patients and HC revealed 853 differentially methylated CpGs located mostly in transcription factor encoding genes such as NFATC1 and TBX2 or in genes for cytokines/cytokine receptors such as LTB and IL4R. Comparison of methylation status of Th1 cells from RA patients and HC identified 1209 differentially methylated CpGs. Interestingly, the most prominent differences were found in several Th17-characteristic genes such as CCL20, IL17R, and IL1R or in LTBD1 and NFATC2 genes. Analysis of Th1 and Th17 cell methylation regardless of whether from RA patients or HC yielded 664 differentially methylated CpGs. Remarkably, methylation differences were found in transcription factor encoding genes such as RUNX3 and TBX21, and in chemokine and cytokine genes such as IL17A, CCL1, CCL20, CXCL14, CXCR5 and XCL2.

Conclusion: Thus, the identified differences were primarily localized in genes encoding cytokines/ chemokines or transcription factors indicating that transcriptional programs leading to different soluble mediator profile might contribute to Th17 prone autoimmune reaction in RA. These data might therefore identify epigenetic patterns associated with the unrestricted Th17 response in RA and might delineate an epigenetic mechanism contributing to disease pathogenesis.

Abstract Number: 1624

Epigenetic Profiling of CD14+ and CD16+ Monocyte Subtypes in Rheumatoid Arthritis. Alterations Related to Cardiovascular Disease and Endothelial Dysfunction

Nuria Barbarroja[1,2], Patricia Ruiz-Limon[1], Carlos Perez-Sanchez[1], Yolanda Jiménez Gómez[1], MariCarmen Abalos-Aguilera[1], Pedro Segui[3], Pilar Font[1], Ángeles Aguirre Zamorano[1], Jerusalem Calvo-Gutierrez[1], Rafaela Ortega[1], M. Carmen Castro Villegas[1], Eduardo Collantes-Estévez[1], Alejandro Escudero-Contreras[1] and Chary Lopez-Pedrera[1], [1]IMIBIC-Reina Sofia University Hospital, Rheumatology Unit, Cordoba, Spain, [2]Rheumatology Unit, IMIBIC-Reina Sofia University Hospital, Cordoba, Spain, [3]IMIBIC-Reina Sofia University Hospital, Radiology Unit, Cordoba, Spain
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Background/Purpose: Monocytes play a key role in the pathogenesis of the cardiovascular disease (CVD). Three monocyte subsets have been described based on their CD14 and CD16 profile, with different actions in the vascular pathology. The distribution of these monocytes subsets and their epigenetic profile associated with CVD in rheumatoid arthritis (RA) remain unravelled. **Objectives:** 1) to functionally characterize the monocytes subsets in RA patients and analyze their role in the endothelial dysfunction, altered oxidative status and proinflammatory/prothrombotic profile associated to RA. 2) to evaluate the role of anti-CCPs

Methods:

Thirty RA patients and 15 healthy donors were included. Endothelial function was measured through post occlusive hyperaemia using Laser-Doppler. Carotid intima media thickness (CIMT) was used as atherosclerosis marker. The monocyte subsets were characterized by flow cytometry and isolated by

immuno-magnetic selection. Proinflammatory cytokines, peroxides levels and cellular activation markers were analyzed. NanoString nCounter miRNA Expression Array was used to profile 800 microRNAs in isolated CD14+ and CD16+ monocytes. PCR array gene expression was used to analyze the expression of 84 genes related to atherosclerosis. In vitro treatment of T lymphocytes with supernatants of CD14+ or CD16+ precultured cells with or without IgG anti-CCPs was performed.

Results:

CD16+ monocytes were significantly extended in RA patients. These subsets had increased protein and gene expression of proinflammatory cytokines, markers of atherosclerosis and peroxide levels. Isolated CD14+ healthy monocytes treated with IgG anti-CCPs showed increased CD16 and decreased CD14 gene expression after 48 h. Supernatant from CD16+ monocytes treated with IgGs anti-CCPs induced a significant increased expression of inflammatory molecules in T lymphocytes compared to CD14+ or untreated CD16+ supernatants or IgG anti-CCPs directly added to lymphocytes. miRNA expression profiling showed that 38 miRNAs were significantly altered (³2 fold) in CD14+ RA monocytes compared to CD16+ RA monocytes. Functional classification of those miRNAs showed a preponderance of targets mRNAs involved in the pathological process of RA such as inflammatory state, immune response and CVD. .

RA patients had impaired endothelial function, with a reduced perfusion value after ischemia. Increased CD16+ monocytes and reduced CD14+ cells percentage were associated with a pathologic CIMT. Clinical parameters strongly correlated with endothelial dysfunction, decreased percentage of CD14+ monocytes and increased number of CD16+ subsets.

Conclusion:

1) RA patients exhibit an increased number of CD16+ monocytes, which display a specific atherogenic and inflammatory pattern directly associated to the autoimmune profile, the progression of the disease and the altered microvascular function. This atherogenic profile might be associated with an altered epigenetic pattern, and seems to be modulated, at least partially, by anti-CCPs. That data suggest that CD16+ subpopulation might play a key role in the CVD pathogenesis associated with RA.

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Abstract Number: 1625

Role of Macrophages in the Cardiovascular Disease Associated to Rheumatoid Arthritis: Effects of ANTI-CCPS in the Phenotypic Switching and the Insulin Signalling

Patricia Ruiz-Limon, Yolanda Jiménez Gómez, Carlos Perez-Sanchez, MariCarmen Abalos-Aguilera, M.Ángeles Aguirre Zamorano, Jerusalem Calvo-Gutierrez, Rafaela Ortega, Eduardo Collantes-Estévez, Alejandro Escudero-Contreras, Chary Lopez-Pedrera and Nuria Barbarroja, IMIBIC-Reina Sofia University Hospital, Rheumatology Unit, Cordoba, Spain

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Background/Purpose:

Macrophages play a key role in the pathogenesis of the rheumatoid arthritis (RA). Under certain stimulus conditions these cells are able to switch their phenotypes to M1 or M2 states, which are characterized by different inflammatory and tissue repair properties. Thus, M1 macrophages are predominantly recruited in inflammatory states and associated with tisular damage. An imbalance in the M1/M2 proportion has been reported in the synovium of RA patients. The molecular mechanisms undertaken this phenotypic switching in RA are not completely defined. In addition, the role of anti-CCPs antibodies in the switch of macrophage polarization has not been studied yet.

Objectives: To analyze the role of anti-CCPs in the polarization state, inflammatory process and the insulin signalling of macrophages

Methods:

M0 macrophages were differentiated from the monocytic cell line THP-1 and primary healthy monocytes. These macrophages were treated with different concentrations of IgGs isolated from healthy donors or RA patients having high levels of anti-CCPs and non-rheumatoid factor for 96 hours. Cells were collected every 24 hours of treatment. In order to analyze the response to insulin, the macrophages were treated with insulin (100 nM) for 10, 20 and 30 min before collecting the cells. The characterization of the polarization states M1 and M2 was performed through flow cytometry and the mRNA expression levels of M1 markers (HLA-DR, iNOS, IL1b, TNFa e IL-23) and M2 (CD206, Arg e IL-10). Moreover, the JNK expression and phosphorylation was analyzed. Finally, the response to insulin was studied through the mRNA expression of AKT and IRS-1 and the protein expression and phosphorylation of

AKT (a key molecule mediating insulin signalling).

Results:

Flow cytometry studies showed that macrophages treated with IgGs anti-CCPs had higher protein expression of M1 markers such as HLA-DR and iNOS and reduced expression of CD206, M2 marker, compared with macrophages treated with IgGs isolated from healthy donors. In addition, IgGs anti-CCPs increased the mRNA expression levels of TNFa, IL1b and IL-23, molecules associated to M1 state, and reduced expression of IL-10, mainly expressed by M2 macrophages. After treatment with IgGs anti-CCPs, macrophages showed significantly lower AKT phosphorylation induced by insulin compared to the macrophages treated with normal IgGs. Moreover, anti-CCPs reduced the expression of AKT and IRS-1. This reduction was accompanied with an increase in the JNK phosphorylation, main molecule initiating the process of inflammation. These effects were significant after 24 hours treatment with 100 ug/ml doses of anti-CCPs.

Conclusion:

1) Anti-CCPs antibodies act as inductors of M1 polarization state, promoting an imbalance of M1/M2 proportion which has been associated with a chronic inflammatory profile and joint damage in RA. 2) These antibodies also produce a defect in the insulin signalling of macrophages, by reducing the response to insulin, suggesting its possible implication in the insulin resistance and the development of the metabolic syndrome related to RA.

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Abstract Number: 1626

The Association of HLA-DRB1 Alleles and Amino Acid Residues with Radiographic Severity in African Americans with Seropositive Rheumatoid Arthritis

Richard J. Reynolds[1], Maria I. Danila[2], Vincent A. Laufer[3], Krishnan Raman[1], S. Louis Bridges Jr.[4] and CLEAR Investigators, [1]Medicine, University of Alabama at Birmingham, Birmingham, AL, [2]AL, [3]Division of Clinical Rheumatology and Immunology, University of Alabama at Birmingham, Birmingham, AL, [4]Clinical Immunology and Rheumatology, University of Alabama at Birmingham, Birmingham, AL

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SESSION INFORMATION

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Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose:

Val and Leu at *HLA-DRB1* position 11 have been reported to be associated with radiographic progression in Caucasians with RA, independent of shared epitope status but not independent of ACPA status. In this study we examined the role of Val at position 11 in radiographic severity of RA in African Americans.

Methods:

DNA samples were directly sequenced for *HLA-DRB1* and then aligned to call four digit resolution genotypes from seropositive (either RF or ACPA positive) RA patients from the Consortium for the Longitudinal Evaluation of African Americans with Rheumatoid Arthritis (CLEAR) Registry. Radiographic severity was defined as total Sharp/van der Heijde scores of hands/feet at study entry (mean (SD) disease duration 7.7 (9.4) years). Base models of van der Heijde modified total Sharp scores (N = 527) were fit using a negative binomial regression conditional on the covariates, sex, disease duration, BMI, local European ancestry at *HLA-DRB1* (estimated using HAPMIX), and smoking. A second series of models were fit that included the covariates of the base model plus the presence of amino acid residues at 29 selected positions from 9 through 86. A third model was fit that included the base model's covariates plus the presence of 21 four digit alleles with appreciable frequency in the patient sample. Significance tests were performed by log likelihood ratio tests of the full and base models.

Results:

From the base model, disease duration (P < 2.0E-16) was positively associated, and local ancestry was negatively associated (P = 0.032) with radiographic severity. Four digit alleles were significantly associated with radiographic severity (χ^2 = 41, DF = 21, P = 0.0056), but substitutions of residues at amino acid positions were not, after multiple testing correction. Val 11 was not associated with radiographic severity (P value = 0.55), but the study was well-powered (0.85) to detect the OR previously reported in Caucasians (1.75). *HLA-DRB1* *04:01, *09:01, *13:03, and *16:02 were significantly associated with radiographic severity in this study.

Conclusion:

In African Americans with seropositive RA, *HLA-DRB1* alleles, but not Val 11, are associated with radiographic severity. Local European ancestry was negatively associated with radiographic damage, but did not modify the associations of the alleles with radiographic severity (χ^2 = 27, DF=21, P = 0.17). These findings have implications on the mechanisms of radiographic damage in RA.

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Abstract Number: 1627

HIF-1alpha Knockdown Down-Regulates Glycolytic Metabolism and Induces Rheumatoid Synovial Fibroblast Cell Death

Manuel J. Del Rey[1], Alicia Usategui[1], Álvaro Valín[1], María Sánchez-Aragó[2], José M. Cuezva[2], Carmen M. García-Herrero[1], María Galindo[1], Juan D. Cañete[3], Francisco J. Blanco[4], Gabriel Criado[1] and Jose L. Pablos[1], [1]Servicio de Reumatología, Instituto de Investigación Hospital 12 de Octubre (i+12), Madrid, Spain, [2]Departamento de Biología Molecular, Centro de Biología Molecular Severo Ochoa, Centro de Investigación Biomédica en Red de Enfermedades Raras (CIBERER), Instituto de Investigación Hospital 12 de Octubre, Universidad Autónoma de Madrid, Madrid, Spain, [3]Unitat d'Artritis, Servei de Reumatologia, Hospital Clínic de Barcelona and Institut d'Investigacions Biomèdiques August Pí i Sunyer, Barcelona, Spain, [4]Laboratorio de Investigación Osteoarticular y del Envejecimiento, Instituto de Investigación Biomédica de A Coruña, INIBIC, A Coruña, Spain
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Background/Purpose: Intense synovial fibroblast (SF) hyperplasia contributes to the chronic inflammation and osteoarticular destruction that characterizes rheumatoid arthritis (RA)**.** Hypoxia-inducible factor 1α (HIF-1α) plays a pivotal role in the metabolic adaptation of SF in hypoxic inflamed joints. The purpose of this study was to analyze the impact of HIF-1α knockdown on metabolic regulation and cell survival of rheumatoid arthritis SF (RASF).

Methods: HIF-1α was silenced using lentiviral vectors or siRNA duplexes transfer strategies. Cell viability upon HIF-1α silencing was analyzed by Alamar Blue assay in SF lines from RA, osteoarthritic or healthy synovium and LC5 lung fibroblasts. To analyze the effect of HIF-1α silencing on RASF *in vivo*, RASF were engrafted into an air pouch in NOD *scid gamma* (NSG) mice and siRNA duplexes (siHIF-1α or control, 9 mice per group) were administered locally. After 11 days mice were sacrificed, pouch membranes dissected and analyzed by immunoperoxidase labeling to quantify the number of human nuclei per pouch wall area. Proteomic analysis was performed in silenced HIF-1α RASF by iTRAQ labelling, and expression of identified glycolytic enzymes as GAPDH, TPI1 and ENO1 was confirmed by western blot. Energy metabolism was analyzed in silenced RASF and LC5 cells by measuring oxygen consumption rate (OCR) with a XF24 Extracellular Flux Analyzer (Seahorse Bioscience, Billerica, MA, USA), and lactate production by Lactate colorimetric assay kit II (Biovision, Milpitas, CA, USA).

Results: HIF-1α silencing induced cell death in cultured SF regardless of their origen but not in LC5 cells. The number of RASF engrafted into the air pouch was significantly reduced in HIF-1α compared to control siRNA injected mice (205±174 vs 393±237 nuclei/mm^2, p=0.04 Mann-Whitney U-test). iTRAQ analysis identified 321 proteins in HIF-1α silenced and control RASF, down-regulated proteins included several glycolytic enzymes but only GAPDH expression was significantly decreased in siHIF-1α transduced compared to non-silenced RASF (ratio GAPDH/β-actin 0.54±0.28 vs 0.85±0.18, p=0.004 Wilcoxon test). The oligomycin sensitive respiratory rate (OSR) as indicator of oxidative phosphorylation was significantly reduced in RASF compared to LC5 (14.1±3.5 vs 62.2±8.8 pmol O_2/min/5000 cells, p<0.0001 Mann-Whitney U-test). Lactate production was significantly higher in RASF compared to LC5 (26.6±12.6 vs 12.2±1.9 nmol/mg/hour, p=0.003 Mann-Whitney U-test), and was reduced by HIF-1α silencing. Treatment of RASF with the GAPDH inhibitor 3-bromopyruvate (3BrP) also induced cell death in cultured RASF.

Conclusion: Our data show that RASF metabolism is mainly glycolytic and demonstrate that the regulatory role of HIF-1α in the glycolytic metabolism is critical for SF survival. In addition, local targeting of HIF-1α may provide a feasible strategy to reduce the pathogenic contribution of SF to chronic arthritis.

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Abstract Number: 1628

A Novel Histone Deacetylase 6 Inhibitor, CKD-H059 Inhibits the Inflammatory Response in Rheumatoid Arthritis

Yu Jin Jang[1], Bo Ram Oh[2], Hyojin Lim[3], Daekwon Bae[3], Nina Ha[3], Young il Choi[4], Jin Kyun Park[5], Eun Young Lee[5], Eun Bong Lee[5] and Yeong Wook Song[5,6], [1]Department of Molecular Medicine and Biopharmaceutical Sciences, BK 21 plus Graduate School of Convergence Science and Technology, and College of Medicine or College of Parmarcy, Seoul National University, Seoul, South Korea, [2]Department of Molecular Medicine and Biopharmaceutical Sciences, Graduate School of Convergence Science and Technology, and College of Medicine, Seoul National University, Seoul, South Korea, [3]Department of Pharmacology and Toxicology, CKD Research Institute, CKD Pharmaceutical Company, Seoul, South Korea, [4]315-20 dongbaekjukjeon-daero, giheung-gu, Pharmacology lab, Hyo-Jong Research Laboratories, CKD Pharmaceutical Company, Yongin-si, South Korea, [5]Division of Rheumatology, Department of Internal Medicine, Seoul National University, Seoul, South Korea, [6]Department of Molecular Medicine and Biopharmaceutical Sciences, Graduate School of Convergence Science and Technology and College of Medicine Seoul National University, Seoul, South Korea
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Background/Purpose: Epigenetic changes including histone modification play an important role in development of rheumatoid arthritis (RA). Histone deacetylase inhibitor (HDACi) increases transcription of numerous genes by rendering chromatin state more accessible for transcription factor and RNA-polymerase, leading to anti-proliferative and anti-inflammatory effects. In addition, direct change in acetylation state of cellular proteins may alter cellular function.

This study was aimed to investigate the effects of CKD-H059, a novel HDAC-6 inhibitor, on regulatory T (Treg) cells and fibroblast-like-synoviocytes (FLS) of RA patients in vitro and on development of arthritis in vivo.

Methods: Regulatory T cells (iTreg) were induced from naïve CD4+ T cells of RA patients. CSFE labeled effector T cells (Teff) from healthy subjects were co-cultured with iTreg in the increasing concentrations of CKD-H059 and Teff proliferation was analyzed by flow cytometry. After 24 hour activation with IL-1β in the increasing concentrations of CKD-H059, proliferation and IL-6 production of RA-FLS were assessed. Cytoplasmic acetylation of α-tubulin in the activated RA-FLS was visualized by confocal microscopy. Adjuvant-induced arthritis (AIA) was induced in mice that were treated with oral CKD-H059 (3, 10, 30, 50, 100 mg/kg) and the severity of arthritis was assessed on 9, 13, and 16 days.

Results: In the presence of CKD-H059, iTreg efficiently inhibited the proliferation of Teff in a dose dependent manner. CKD-H059 induced acetylation of α-tubulin in cytoskeleton with subsequent cell morphology change (i.e. from long spindle form into round flat cells) and inhibited cell proliferation and production of pro-inflammatory cytokine IL-6. In AIA mice, oral CKD-H059 was able to prevent the development of clinical arthritis in a dose-dependent manner.

Conclusion: The novel HDAC6 inhibitor CKD-H059 inhibits the inflammatory response in T cells and FLS of RA in vitro and ameliorates arthritis severity in vivo. Therefore, CKD-H059 might offer a novel treatment option for RA.

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Abstract Number: 1629

Non-Interventional Clinical Study Investigating the Use of Golimumab in Patients with Rheumatoid Arthritis, Psoriatic Arthritis, and Ankylosing Spondylitis in Germany – 3rd Interim Analysis

Matthias H. Thomas[1], Klaus Krüger[2], Pee Aries[3], Martin Bohl-Buehler[4], Jan Brandt-Juergens[5], Verena Rickert[6] and Siegfried Wassenberg[7], [1]Medical Affairs, MSD Sharp & Dohme GmbH, Bünde, Germany, [2]Praxiszentrum St. Bonifatius, München, Germany, [3]Rheumatologie im Struenseehaus, Hamburg, Germany, [4]Friedrich-Ebert-Str. 35, Rheumahaus, Potsdam, Germany, [5]Praxis Brandt-Juergens/Karberg, Berlin, Germany, [6]Medical Affairs, MSD Sharp&Dohme GmbH, Haar, Germany, [7]Fachkrankenhaus, Ratingen, Germany
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Background/Purpose:

Golimumab (GOL) has shown its efficacy and safety in various randomized clinical trials with accurately selected patients. Data from daily clinical practice in Germany are still lacking.

To gather data from German patients with a known moderate to severe inflammatory rheumatic disease (RA, PsA, AS) treated with GOL sc in daily clinical practice. The aim of this non-interventional, prospective, multicenter study was to show the safety, effectiveness, socio- and health economic parameters, and quality of life reported by patients in a real-life setting.

Methods:

1,598 patients with RA, AS or PsA at 168 German study sites were enrolled in GO-NICE. The study explored days of sick leave, ability to work, hospitalizations, data of quality of life and clinical effectiveness by DAS28, PsARC and BASDAI as well as safety of GOL 50 mg sc therapy. This 3rd interim analysis evaluates all patients treated for at least 12 months or more until 31st March 2014.

Results:

A total of 1,218 patients met the criteria for the 3rd interim analysis.

RA (n=401, 33%): The mean age was 54.9 years, 26.9% were male. The DAS28 was initially at 5.0 and dropped within 24 months to 3.0. After 3 months of therapy, 35.8% of patients were in remission (DAS28 <2.6), after 24 months 42.4%. 46.1% of the RA patients worked full or part-time at baseline (BL).

PsA (n=408, 33.6%): The mean age was 50.4 yrs, 46.3% were male. 159 patients had a nail involvement (39%), 86 dactylitis (21.1%) and 57 enthesitis (14%). 52.3% of PsA-patients had a good response (mod. PsARC) after 3 months with increase to 67.8% at 24 month. 55.0% of PsA-patients worked fully or part-time al BL.

AS (n=407, 33.5%): The mean age was 42.9 years, 67.1% were male. The most common extra-articular manifestations were iritis (16%), enthesitis (13.8%), CED (6.1%) and dactylitis (3.9%). The mean BASDAI score (1-10) decreased from 5.1 (month 0) to 2.3 (24 months). 69.9% of AS patients were employed fully or part-time at BL.

Days of absenteeism from work dropped in RA patients from 16.0 to 8.2 (-48.8%) in PsA from 10.0 to 3.2 (-68.0%) and AS from 14.4 to 4.1 days (-71.7%) within the past six months. The disease impact on quality of work within past 6 months, determined by 0 (no impact) to 10 (very severe impact) decreased within the 24 months treatment from 5.0 to 2.4 (RA-) from 4.7 to 2.2 (PsA-) and from 4.0 to 2.2 (AS-patients). The proportion of patients who required hospitalization decreased from 11.4% to 1.2%, physiotherapy from 24.4% to 10.7%, and massage treatment from 11.3% to 3.4% within the first year of treatment. An improvement of the quality of life (EQ-5D-3L) was seen in all three patient groups in all five domains after 6 months and was maintained over the time.

After 24 months, 80% of the rheumatologists rated the treatment course of as "successful", 10-15% as" partially successful", and less than 5% as "unsuccessful".

The safety profile of GOL was consistent with that observed in other studies of GOL.

Conclusion:

GOL sc once monthly is an effective treatment in patients with RA, PsA and AS in a real-life setting in Germany. It shows remarkable improvements in health economic and patient-reported quality of life parameters. No new safety signals were detected.

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Abstract Number: 1630

Progressive Destruction of Large Joints in Patients with Rheumatoid Arthritis Treated with Biologic Agents

Arata Nakajima[1], Masato Sonobe[2] and Koichi Nakagawa[2], [1]Orthopaedics, Toho University Sakura Medical Center, Sakura, Japan, [2]Toho University Sakura Medical Center, Sakura, Japan

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Background/Purpose: Many clinical trials have revealed that biologic agents inhibit destruction of small joints, however, there have been a few reports demonstrating their inhibitory effects on destruction of large joins. In this study, we investigated progressive destruction of large joints in patients with

rheumatoid arthritis (RA) treated with biologic agents and determined risk factor(s) associated with progressive destruction.

Methods: We assessed a total of 273 large joints in upper and lower extremities including the shoulder, elbow, hip, knee and ankle of 67 patients. Prior to the treatment with biologic agents, X-rays for tender and/or swollen large joints in individuals were taken, and the follow-up X-rays were taken at least once between 11 and 36 months (mean 18.6) after the initial examinations. At the time of follow-up, progressive destruction was defined when at least one of the following changes was detected: 1) progressive Larsen grade (LG), 2) increase in bone erosion and/or appearance of new bone erosion, and 3) progressive joint space narrowing.

Results: Progressive destruction was seen in 14 patients (20.9%) and 17 joints (7.2%). To determine factors associated with the progressive destruction, we first performed a univariate analysis regarding variables including height, body weight, age, disease duration, CRP, DAS28, stage, LG, MTX dose, PSL dose, and X-ray intervals between the initial and the follow-up time. As shown in Table 1, LG alone was statistically significant (P<0.01). Next, the variables with a P value of <0.1 in the univariate analysis, which included LG, stage and CRP, were subject to a multivariate logistic regression analysis. As a result, LG alone was extracted as a risk factor associated with progressive destruction (odds ratio: 2.28, 95%CI: 1.19-4.36). The cutoff value of LG that discriminated progression from non-progression by the ROC curve was determined to be 2.5 (sensitivity: 0.529, specificity: 0.805), suggesting that progressive destruction of large joints is expected to be increased when LG is 3 or higher (Figure 1).

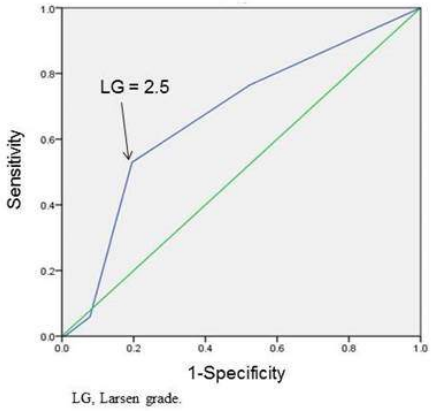
Conclusion: These results suggest that progressive destruction of large joints cannot be stopped completely even under the tight control using biologic agents. Furthermore, results of the ROC curve indicate that the bone damage of large joints should not be advanced to LG-3. Since the risk factor(s) of progressive destruction are associated with the extent of individual joint damage but not with patients' disease characteristics, regular X-ray examinations for large joints are indispensable.

Table 1. Univariate analyses for the disease characteristics of patients with progression and non-progression in destruction of large joints.

Variables	Progression (N=17)	Non-progression (N=256)	P
Height (cm)	152.3±7.0	154.8±6.0	0.165
Body weight (kg)	53.7±9.5	52.7±9.9	0.696
Age (y)	62.9±11.1	60.9±12.8	0.770
Disease duration (y)	15.1±13.6	11.8±11.2	0.305
CRP	4.51±4.89	2.87±3.52	0.079
DAS28-ESR	4.91±1.09	4.71±1.31	0.716
Stage (Steinbrocker's classification)			0.093*
I, II	3/17 (17.6%)	93/256 (36.3%)	
III, IV	14/17 (82.4%)	163/256 (63.7%)	
Larsen grade			0.005*
I	4/17 (23.5%)	122/256 (47.7%)	
II	4/17 (23.5%)	84/256 (32.8%)	
III, IV, V	9/17 (52.9%)	50/256 (19.5%)	
X-ray follow-up periods (m)	19.7±7.1	18.0±5.6	0.367
MTX dose (mg/week)	5.9±4.0	6.3±3.6	1.000
PSL dose (mg/day)	5.5±4.8	3.8±3.8	0.142

*P value was calculated by the chi-square test.

Figure 1. The ROC curve discriminating progression from non-progression in destruction of large joints.



LG, Larsen grade.

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Abstract Number: 1631

Adverse Events to Biologic Agents in Elderly Patients with Rheumatoid Arthritis: Cohort with 13 Years of Follow-up

Zulema Rosales[1,2], Leticia Leon[1], Alejandro Gomez-Gomez[2], Lucía Arietti[2], Esperanza Pato Cour[2], José Luis Fernández Rueda[1], Juan A Jover[2] and Lydia Abasolo[1], [1]Instituto de Investigación Sanitaria San Carlos (IdISSC), Madrid, Spain, [2]Rheumatology, Hospital Clínico San Carlos, Madrid, Spain
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Background/Purpose: After more than a decade using biological agents (BA), is widely known their efficacy in the treatment of Rheumatoid Arthritis (RA) and their relationship with Adverse Drug reaction (ADR). We know that drugs metabolism changes with age and, thus, the AE but we have no concrete information about AE with BA in these patients in real life. The purpose of our study was to describe the incidence and characteristics of moderate and severe ADR to BA in a cohort of elderly patients with RA.

Methods: Observational longitudinal study from 1999 to 2013 was conducted. RA patients followed in outpatient clinic at Hospital Clinico San Carlos, which started BA treatment after 65 years of age, were included. Primary outcome: discontinuation due to an ADR (moderate: suspension of the drug regardless of the impact; severe: suspension and hospitalization or death) related to BA (Etanercept (ETN); Infliximab (INF); Adalimumab (ADA); Rituximab (RTX); and other BA [Golimumab, Certolizumab, Abatacept and Tozilizumab]). Co variables: sociodemographic, clinical and therapy. Incidence rates of discontinuation due to ADR (IR) per 100 patient-years were estimated using survival techniques with their respective 95% confidence interval [95% CI]. Comparison between BA ADR discontinuation rates and other associated factors were run by Cox regression models.

Results: We included 286 courses of BA therapy in 146 patients (604 patient-years). Of these, 78% were women with a mean age at diagnosis of 66.5 ± 7 years and a median time to the start of the first BA of 6 ± 4 years. ADA (27.3%), followed by INF (22.4%), ETN (21.3%), and RTX (19.2%) were the most frequently used. Treatment was suspended due to ADRs in 111 cases (IR: 18.3 [15.2 -22.1]), 56% of them were severe (IR: 10.3 [8-13.2), with 16 deaths during the study period (IR: 2.6 [1.6-4.2]. The retention rate for discontinuation due to ADR was 71%, 50%, 35% and 20% for the first, third, fifth and tenth year. The most frequent cause for ADR was infection (50.5%; IR: 9.3 [7.1-12]). The crude IR of discontinuation was lower for ETN (IR for all ADRs: 14.5 [9-23.3]; IR for severe: 5.1 [2.3-11.4]) compared to TNF- antagonists and RTX. In the multivariate analysis for all ADRs after adjusting by calendar time, age and sex: a) for all ADRs: INF was the BA with the highest risk of ADR development, compared to ETN. No other BAs comparisons achieved statistical signification. Concomitant triple therapy with DMARDs, corticoids, functional loss, and specific comorbidities were other independent factors found; b) for severe ADRs: INF achieved the highest risk of ADR development, compared to ETN, ADA and RTX. ETN also had lower risk compared to RTX. Age of the patient, concomitant corticoids, and specific comorbidities were also associated.

Conclusion: After 5 years of treatment, two thirds of the patients over 65 years have discontinuated BA due to ADRs, mainly related to infections. 18.4 % and 10.3% patient * year discontinued BAs due to all ADR and severe ADRs respectively. The mortality rate in our study was 2.7%. We have found differences in discontinuation rates among BA due to ADRs, being Infliximab the BA with the highest risk. We have also found other clinical factors that modify their survival due to ADRs.

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Abstract Number: 1632

Do RA Susceptibility Loci Predict Response to Methotrexate As First DMARD in Early RA?

Thomas Frisell[1], Saedis Saevarsdottir[2,3] and Johan Askling[1,4], [1]Clinical Epidemiology Unit, Department of Medicine, Karolinska Institutet, Stockholm, Sweden, [2]Rheumatology Unit, Karolinska University Hospital, Karolinska Institutet, Stockholm, Sweden, [3]Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden, [4]Rheumatology Unit, Karolinska University Hospital, Stockholm, Sweden
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Background/Purpose: Improved means to predict which RA patients will respond to methotrexate monotherapy, the preferred first line therapy in early RA, would allow patients to more quickly receive effective treatment, possibly preventing irreversible joint damage. Among the more than 100 risk loci so far identified as risk factors for RA, many tag genes in pathways targeted by current therapies and/or that are involved in general inflammatory response. Thus, it would not be unexpected if alleles influencing RA risk also have an effect on RA treatment response.

Methods: We linked recent onset RA patients from the EIRA study (genotyped with the Illumina Immunochip array) to prospectively recorded data on

treatment and clinical characteristics in the nationwide Swedish Rheumatology register (SRQ). The cohort was defined as those who started methotrexate monotherapy as first DMARD treatment 2000-2012 (n=1390), and had at least one return visit with recorded DAS28 within 2-8 months after treatment start (92%, N=1278).Based on previous meta-GWAS data on risk factors for RA development, we identified 76 risk loci tagged by SNPs on the Immunochip (R^2>0.6), and calculated a risk score by weighting alleles by their published log-odds, standardizing the sum against an RA-free population. The association of RA risk score, individual SNPs, and the shared epitope alleles, with DAS28-based EULAR response at the evaluation visit closest to 3 months after initiation, was estimated using logistic regression models.

Results: With respect to RA risk, the genetic risk score was a stronger predictor of onset of ACPA+ than ACPA- RA (odds ratio per stdev increase: 2.2 vs 1.2). With respect to response to methotrexate, the number of SNPs associated to EULAR response in individual analyses was not higher than expected by chance (3/76 SNPs had p<0.05 in ACPA+, 2/76 in ACPA-), and there was no association of the genetic risk score to methotrexate response in RA overall, nor in ACPA+ (Table). Higher genetic risk score was, however, associated with borderline significantly better response to methotrexate in ACPA- RA (odds ratio [95%CI]: 1.27 [1.01-1.60]).

Conclusion: We found no association between identified RA susceptibility loci and response to methotrexate monotherapy in RA overall nor in the ACPA-positive subgroup. The borderline increased EULAR response with higher genetic risk score among ACPA- RA patients may reflect individuals within this subset with a “correct” diagnosis of RA, and hence more likely to respond to this therapy.

Table. Odds ratios and 95% confidence intervals for Good/Moderate vs No EULAR response after 3 months of methotrexate monotherapy in 1278 early RA patients

	Overall RA	ACPA+	ACPA-
Risc score as linear cov	1.02 (0.91-1.15)	0.97 (0.83-1.13)	1.27 (1.01-1.60)
1st Quartile (lowest)	Ref	Ref	Ref
2nd Quartile	1.17 (0.73-1.89)	1.03 (0.50-2.14)	1.35 (0.70-2.61)
3rd Quartile	1.37 (0.87-2.16)	1.26 (0.64-2.49)	1.83 (0.89-3.77)
4th Quartile	1.19 (0.79-1.79)	1.10 (0.59-2.06)	1.74 (0.90-3.34)
Nr of SE alleles	0.93 (0.77-1.13)	0.99 (0.76-1.29)	0.95 (0.65-1.39)

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Abstract Number: 1633

Long-Term Radiographic and Patient-Reported Outcomes Based on Clinical Disease Activity Index Responses with Tofacitinib at 6 Months

Vibeke Strand[1], Arthur Kavanaugh[2], Alan J. Kivitz[3], Désirée van der Heijde[4], Elaine Hoffmann[5], Ermeg Akylbekova[6], Arif Soonasra[7], Mark Snyder[7], Koshika Soma[5], Eustratios Bananis[7] and Josef S. Smolen[8], [1]Biopharmaceutical Consultant, Portola Valley, CA, [2]University of California, San Diego School of Medicine, LaJolla, CA, [3]Altoona Center for Clinical Research, Duncansville, PA, [4]Rheumatology, Leiden University Medical Center, Leiden, Netherlands, [5]Pfizer Inc, Groton, CT, [6]Quintiles, Atlanta, GA, [7]Pfizer Inc, Collegeville, PA, [8]Medical University of Vienna, Vienna, Austria
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Background/Purpose: Tofacitinib is an oral Janus kinase inhibitor for the treatment of RA. This analysis assessed if patients achieving Clinical Disease Activity Index (CDAI) remission (REM) or low disease activity (LDA) at Month 6 had less radiographic progression and improved patient-reported outcomes (PROs) at Month 24 and compared results between tofacitinib and MTX.

Methods: ORAL Start (NCT01039688) and ORAL Scan (NCT00847613) were Phase 3 randomized, controlled trials (RCTs) in MTX therapeutically-naïve and MTX-inadequate response (IR) patients with RA, respectively, who received tofacitinib 5 or 10 mg twice daily (BID) monotherapy vs MTX monotherapy or tofacitinib 5 or 10 mg BID + MTX vs placebo + MTX, respectively. This was an observed analysis of patients with radiographs at Months 6, 12, and 24, excluding placebo-treated patients in ORAL Scan. Patients were assigned to subpopulations according to CDAI responses at Month 6: REM (CDAI ≤2.8); LDA (CDAI >2.8 to ≤10); or incomplete-responders (CDAI >10). Outcomes included the proportion of patients with no radiographic progression (change in modified Total Sharp Score [mTSS] ≤0) and/or HAQ-Disability Index (HAQ-DI) <0.5 (defined as normative) at Month 24, and mean changes from baseline in mTSS and HAQ-DI.

Results: In ORAL Start, 250, 269, and 98 patients received tofacitinib 5 mg BID, tofacitinib 10 mg BID, and MTX, respectively. In ORAL Scan, 193 and 201 patients received tofacitinib 5 and 10 mg BID, respectively. Baseline demographics were generally similar between subpopulations within each RCT; however, incomplete-responders generally had higher baseline disease activity. In both ORAL Start and Scan, patients in REM or LDA with tofacitinib at Month 6 were more likely to be non-progressors and achieve normative HAQ-DI scores at Month 24 (Table). Tofacitinib-treated patients in REM at Month

6 generally had better HAQ-DI scores at Month 24 than LDA patients. In ORAL Start at Month 6, a higher proportion of tofacitinib- than MTX-treated patients were in REM or LDA (Table). CDAI incomplete-responders receiving tofacitinib had improved HAQ-DI scores and less radiographic progression compared with MTX. Overall, more patients receiving tofacitinib than MTX in REM or LDA were non-progressors and achieved HAQ-DI scores <0.5.

Conclusion: More MTX-naïve or MTX-IR tofacitinib-treated patients achieving CDAI REM or LDA at Month 6 were radiographic non-progressors with normative HAQ-DI scores at Month 24, compared to CDAI incomplete-responders. In ORAL Start, more tofacitinib than MTX-treated MTX-naïve patients achieved CDAI REM or LDA at Month 6 with better PROs and radiographic outcomes at Month 24.

Table. Radiographic progression and PROs at Month 24 in responders and inadequate responders at Month 6

Parameter	ORAL Start									ORAL Scan					
	CDAI remitters at Month 6 (CDAI ≤2.8)			CDAI LDA at Month 6 (CDAI >2.8 to ≤10)			CDAI incomplete-responders at Month 6 (CDAI >10)			CDAI remitters at Month 6 (CDAI ≤2.8)		CDAI LDA at Month 6 (CDAI >2.8 to ≤10)		CDAI incomplete-responders at Month 6 (CDAI >10)	
	Tofacitinib		MTX	Tofacitinib		MTX	Tofacitinib		MTX	Tofacitinib		Tofacitinib		Tofacitinib	
	5 mg BID	10 mg BID		5 mg BID	10 mg BID		5 mg BID	10 mg BID		5 mg BID	10 mg BID	5 mg BID	10 mg BID	5 mg BID	10 mg BID
N (%)	33 (13.2)	54 (20.1)	10 (10.2)	89 (35.6)	117 (43.5)	25 (25.5)	128 (51.2)	98 (36.4)	63 (64.3)	20 (10.4)	33 (16.4)	71 (36.8)	74 (30.8)	102 (52.8)	94 (40.8)
Radiographic non-progression (mTSS ≤0) at Month 24, % (95% CI)	72.7 (54.5, 86.7)	79.6 (66.5, 89.4)	60.0 (26.2, 87.8)	69.7 (59.0, 79.0)	72.7 (63.6, 80.5)	72.0 (50.6, 87.9)	68.8 (60.0, 76.7)	66.3 (56.1, 75.6)	42.9 (30.5, 56.0)	95.0 (75.1, 99.9)	78.8 (61.1, 91.0)	69.0 (56.9, 79.5)	75.7 (64.3, 84.9)	67.7 (57.7, 76.6)	64.9 (54.4, 74.5)
mTSS change from baseline at Month 24, mean (95% CI)	0.2 (-0.0, 0.4)	0.1 (-0.1, 0.3)	0.3 (-0.4, 1.1)	0.5 (0.1, 1.0)	0.4 (-0.1, 0.8)	0.5 (-0.1, 1.0)	0.7 (0.2, 1.3)	0.1 (-0.7, 0.8)	2.0 (1.0, 3.0)	-0.8 (-1.5, 0.0)	0.1 (-0.1, 0.3)	0.5 (0.1, 0.9)	-0.3 (-0.5, 0.0)	0.8 (0.3, 1.2)	0.6 (0.2, 1.1)
HAQ-DI <0.5 status at Month 24, % (95% CI)	78.8 (61.1, 91.0)	87.0 (75.1, 94.6)	70.0 (34.8, 93.3)	64.0 (55.2, 74.0)	62.4 (53.0, 71.2)	52.0 (31.3, 72.2)	37.5 (29.1, 46.5)	36.7 (27.2, 47.1)	28.6 (17.9, 41.4)	70.0 (45.7, 88.1)	54.6 (36.4, 71.9)	43.7 (31.9, 56.0)	66.2 (54.5, 76.6)	18.6 (11.6, 27.6)	29.8 (20.8, 40.1)
HAQ-DI change from baseline at Month 24, mean (95% CI)	-1.0 (-1.2, -0.7)	-1.3 (-1.5, -1.1)	-1.1 (-1.8, -0.4)	-1.1 (-1.3, -0.8)	-1.1 (-1.3, -1.0)	-0.8 (-1.1, -0.5)	-0.8 (-1.0, -0.7)	-0.9 (-1.0, -0.7)	-0.7 (-0.9, -0.6)	-0.7 (-1.0, -0.5)	-1.0 (-1.2, -0.8)	-0.6 (-0.8, -0.5)	-0.7 (-0.9, -0.6)	-0.4 (-0.5, -0.3)	-0.5 (-0.7, -0.4)

BID, twice daily; CDAI, Clinical Disease Activity Index; CI, confidence interval; HAQ-DI, health assessment questionnaire-disability-index; LDA, low disease activity; MTX, methotrexate; mTSS, modified Total Sharp Score; PROs, patient-reported outcomes

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Abstract Number: 1634

The Effects of Glucocorticoids on the Efficacy of Tofacitinib As Monotherapy and in Combination Therapy with Nonbiologic Dmards: An Analysis of Data from Six Phase 3 Studies

Roy Fleischmann[1], Christina Charles-Schoeman[2], Gerd Burmester[3], Cristiano Zerbini[4], Peter Nash[5], Kenneth Kwok[6], Koshika Soma[7], Alan Mendelsohn[8] and Eustratios Bananis[8], [1]Metroplex Clinical Research Center, Dallas, TX, [2]University of California, Los Angeles, CA, [3]Department of Rheumatology and Clinical Immunology, Charité - Universitätsmedizin Berlin, Berlin, Germany, [4]Centro Paulista de Investigação Clinica, São Paulo, Brazil, [5]Nambour Hospital, Sunshine Coast and Department of Medicine, University of Queensland, Queensland, Australia, [6]Pfizer Inc, New York, NY, [7]Pfizer Inc, Groton, CT, [8]Pfizer Inc, Collegeville, PA

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Background/Purpose: Tofacitinib is an oral Janus kinase inhibitor for the treatment of RA. Patients with RA often receive concomitant treatment with glucocorticoids (GCs) to control inflammatory symptoms. Therefore, the objective of this analysis was to determine whether the presence or absence of oral GCs has an effect on the efficacy of tofacitinib as monotherapy or in combination with nonbiologic DMARDs, within the RA program.

Methods: Tofacitinib efficacy data were analyzed from six Phase 3 (P3) studies. Data were pooled from four P3 studies in which patients with inadequate response (IR) to MTX, biologic/nonbiologic DMARDs, or TNF inhibitors (TNFi) received tofacitinib in combination with MTX or other nonbiologic DMARDs. Data from two P3 tofacitinib monotherapy studies, ORAL Solo (in DMARD-IR patients) and ORAL Start (in MTX-naïve patients), were analyzed separately. In the P3 tofacitinib clinical program, patients receiving GCs (≤10 mg/day of prednisone or equivalent) prior to enrollment were required to remain on a stable dose throughout the study. The following efficacy endpoints were assessed for patients receiving tofacitinib 5 or 10 mg twice daily, placebo +/- DMARDs or +/- MTX (comparator arms), +/- concomitant GCs: ACR response criteria (ACR20, ACR50, ACR70), Clinical Disease Activity Index (CDAI), disease activity score in 28 joints using the ESR (DAS28-4 [ESR]), and HAQ-disability index (HAQ-DI).

Results: In total, 3200 tofacitinib-treated patients were included in this analysis. 279 (57%) and 354 (46%) tofacitinib-treated patients in the P3 monotherapy studies ORAL Solo and ORAL Start were using concomitant GCs, respectively, as were 1129 (58%) tofacitinib-treated patients in the pooled P3 combination studies. Within each study, baseline demography and disease characteristics were similar regardless of concomitant GC use. The efficacy of

tofacitinib, placebo +/- DMARDs or MTX, +/- concomitant GCs at 3 months is presented in the Table. Tofacitinib-treated patients had significantly greater treatment responses compared with the comparator arms for almost all efficacy endpoints. Similar responses were observed with tofacitinib regardless of concomitant GC use.

Conclusion: Tofacitinib was more effective than placebo +/- DMARDs or MTX as monotherapy and combination therapy. As expected, the efficacy of tofacitinib was similar in patients receiving and not receiving concomitant GCs as these patients had active disease in spite of their background GCs. A randomized clinical trial in GC-naïve patients with RA is needed to determine the effect of the addition of GCs on the efficacy of tofacitinib.

Table: Efficacy of tofacitinib as monotherapy or combination therapy with or without GCs at 3 months

	ORAL Solo (DMARD-IR[a])			ORAL Start (MTX-naïve)			Pooled data from four Phase 3 studies of tofacitinib in combination with DMARDs[b] (DMARD-IR[a])		
	Placebo (+/- GCs) (N=70/52)	Tofacitinib 5 mg BID (+/- GCs) (N=139/104)	Tofacitinib 10 mg BID (+/- GCs) (N=140/105)	MTX (+/- GCs) (N=87/99)	Tofacitinib 5 mg BID (+/- GCs) (N=181/192)	Tofacitinib 10 mg BID (+/- GCs) (N=173/224)	Placebo + DMARDs (+/- GCs) (N=322/237)	Tofacitinib 5 mg BID (+/- GCs) (N=579/394)	Tofacitinib 10 mg BID (+/- GCs) (N=550/419)
ACR20 (%)	29/24	58*/63*	61*/72*	48/56	71*/69*	75*/80*	29/22	54*/57*	60*/63*
ACR50 (%)	13/12	32*/30*	36*/38*	17/23	38*/42*	46*/53*	9/7	28*/30*	32*/33*
ACR70 (%)	6/6	17*/14	19*/22*	4/7	20*/20*	24*/29*	2/2	10*/11*	15*/15*
CDAI ≤ 10 (LDA) (%)	10/14	28*/32*	30*/38*	15/21	36*/40*	42*/50*	11/8	28*/30*	32*/36*
CDAI ≤ 2.8 (remission) (%)	3/0	6/5*	9/8*	2/4	8*/10	9*/13*	0/1	5*/6*	5*/8*
HAQ-DI improvement ≤ 0.22 (%)	43/40	59*/63*	70*/65*	63/71	78*/76	83*/82*	47/42	63*/64*	70*/68*
HAQ-DI improvement ≤ 0.5 (%)	24/28	47*/45*	54*/43	42/47	65*/62*	73*/71*	27/20	44*/44*	53*/51*
Mean change from baseline in HAQ (LS mean)	-0.2/-0.1	-0.5*/-0.5*	-0.6*/-0.5*	-0.5/-0.5	-0.7*/-0.8*	-0.8*/-0.9*	-0.2/-0.2	-0.4*/-0.5*	-0.5*/-0.5*
Mean change from baseline in DAS28-4 (ESR) (LS mean)	-1.1/-1.1	-1.9*/-2.0*	-2.0*/-2.3*	-1.5/-1.6	-2.3*/-2.5*	-2.5*/-2.7*	-0.8/-0.7	-1.8*/-1.8*	-2.0*/-2.0*
Mean change from baseline in CDAI (LS mean)	-11.5/-12.7	-20.5*/-21.9*	-22.1*/-25.0*	-16.3/-18.1	-22.8*/-24.7*	-24.5*/-26.1*	-9.8/-8.7	-17.8*/-18.2*	-19.8*/-19.9*

[a]Patients with an IR to DMARDs.

bORAL Scan, ORAL Step, ORAL Sync and ORAL Standard.

*Significant difference from the comparator arm: the 95% CI for the difference from the comparator arm does not cross 0.

N, number of patients randomized and treated; denominators for each outcome at Month 3 are different depending upon the number of patients with evaluable outcomes.

ACR, American College of Rheumatology response criteria; BID, twice daily; CDAI, Clinical Disease Activity Index; CI, confidence interval; DAS28-4, disease activity score in 28 joints; DMARDs, nonbiologic disease-modifying antirheumatic drug; ESR, erythrocyte sedimentation rate; GC, glucocorticoid; HAQ-DI, health assessment questionnaire-disability index; IR, inadequate response; LS, least squares; MTX, methotrexate

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Abstract Number: 1635

Development of New Bioassay System Measuring Inhibitory Strength of IL-6/STAT3 Signal Under Tocilizumab Treatment in Rheumatoid Arthritis Patients

Shuntaro Saito[1], Katsuya Suzuki[1], Kunihiro Yamaoka[1] and Tsutomu Takeuchi[2], [1]Division of Rheumatology, Department of Internal Medicine, Keio University School of Medicine, Tokyo, Japan, [2]Keio University School of Medicine, Tokyo, Japan

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Background/Purpose: Tocilizumab (TCZ) is a IL-6 receptor blockade, administered intravenously every 4 weeks and efficiently inhibits IL-6/STAT3 signaling pathway. We have previously reported the usefulness of adjusting the dosing interval based on the disease activity of rheumatoid arthritis (RA). We herein hypothesized that strength of IL-6/STAT3 signaling could differ in each patient. Accurate measurement strategy of inhibitory strength of IL-6/STAT3 signal in RA patients who administered TCZ, has not been currently established. So, we assessed IL-6 induced phosphorylated-STAT3 (pSTAT3) in RA patients treated with TCZ and achieved low disease activity.

Methods: Whole blood was collected from RA patients in low disease activity (LDA; CDAI <=□10) treated with intravenous TCZ (8mg/kg) every 3 weeks (3w group; n=10), 4 weeks (4w group; n=10), 5 weeks (5w group; n=10) or with methotrexate (mean dose: 9.0 mg/week, range: 4-14 mg/week) (control group, n=10). Recombinant human (rh) IL-6 (0, 0.1, 1, 10, 100 ng/ml) was exogenously added to whole blood and proportion of pSTAT3 positive CD4+ T cells (% in CD4+ T cell) was measured by Phosflow cytometric analysis (BD, USA). Serum IL-6 and soluble IL-6 receptor (sIL-6R) were measured by ELISA, expression of membrane IL-6R (mIL-6R, CD126) and gp130 (CD130) on CD4+T cell were analyzed by flow cytometry.

Results: Proportion of pSTAT3 positive CD4+ T cells increased in a dose dependent manner of exogenous rhIL-6 in each treatment group. Although, all patients were in LDA, %pSTAT3 was significantly increased in control group (mean: 58.6%) from the lowest concentration (0.1 ng/ml) of rhIL-6 compared to TCZ treated patients (mean: 0.0%, 0.0%, 12.2% in 3w, 4w, 5w group respectively). %pSTAT3 showed significant increase from low concentration (1 ng/ml) of rhIL-6 in 5w group (mean: 27.4%), while 4w group showed complete inhibition of pSTAT3 (mean: 0.0%). On the other hand, stimulation with 10, 100 ng/ml of rhIL-6 resulted in significantly suppressed pSTAT3 in 3w group (mean: 0.0%, 3.1%) compared to 4w group (mean: 5.6%, 29.2%). Serum IL-6 level was significantly higher in TCZ group than control group, and 3w and 4w group exhibited significantly higher IL-6 level compared to 5w group. Although sIL-6R concentration and mIL-6R expression were upregulated in TCZ group compared to control group, no significant difference were observed among 3w, 4w, 5w group. Meanwhile, gp130 level expression did not differ among each treatment group.

Conclusion: Our study demonstrated that IL-6 stimulated-pSTAT3 detection assay is a useful method to assess the inhibitory strength of IL-6/STAT3 signaling in RA patients treated with TCZ. Our results also suggested that further alteration of dosing interval of TCZ could be possible in certain RA patients, with our new method. Measurement of pSTAT3 in RA patients treated with TCZ could be a promising strategy to optimize treatment.

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Clinical Benefit of 1-Year Certolizumab Pegol Treatment in MTX-Naïve, Early Rheumatoid Arthritis Patients Is Maintained after Discontinuation up to 1 Year

Tatsuya Atsumi[1], Kazuhiko Yamamoto[2], Tsutomu Takeuchi[3], Hisashi Yamanaka[4], Naoki Ishiguro[5], Yoshiya Tanaka[6], Katsumi Eguchi[7], Akira Watanabe[8], Hideki Origasa[9], Toshiharu Shoji[10], Osamu Togo[11], Toshiyuki Okada[12], Désirée van der Heijde[13], Nobuyuki Miyasaka[14] and Takao Koike[15], [1]Division of Rheumatology, Endocrinology and Nephrology, Hokkaido University Graduate School of Medicine, Sapporo, Japan, [2]Department of Allergy and Rheumatology, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan, [3]Keio University School of Medicine, Tokyo, Japan, [4]Tokyo Women's Medical University, Tokyo, Japan, [5]Department of Orthopedic Suregery, Nagoya University Hospital, Nagoya, Japan, [6]The First Department of Internal Medicine, University of Occupational and Environmental Health, Kitakyushu, Japan, [7]Department of Immunology and Rheumatology, Nagasaki University, Nagasaki, Japan, [8]Tohoku University, Sendai, Japan, [9]Division of Biostatistics and Clinical Epidemiology, University of Toyama School of Medicine, Toyama, Toyama, Japan, [10]Department of Clinical Research and Development, Otsuka Pharmaceutical Co., Ltd, Shinagawa-ku, Tokyo, Japan, [11]Biometrics Group, UCB Pharma, Tokyo, Japan, [12]Astellas Pharma Inc., Japan, Tokyo, Japan, [13]University Hospital, Maastricht, Netherlands, [14]Tokyo Medical and Dental University, Tokyo, Japan, [15]Medicine II, Hokkaido University Graduate School of Medicine, Sapporo, Japan
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Background/Purpose: Efficacy and safety of certolizumab pegol (CZP) treatment in combination with optimized-dose MTX in Japanese MTX-naïve early rheumatoid arthritis (RA) patients (pts) with poor prognostic factors has previously been reported.[1] Here we report 2-year data from the C-OPERA study, investigating maintenance of clinical effect after discontinuing CZP treatment in an observational post-treatment period while continuing MTX treatment.

Methods: MTX-naïve pts with early RA (defined as ≤12 months from onset of persistent symptoms) fulfilling the 2010 ACR/EULAR classification criteria and poor prognostic factors were eligible to enter C-OPERA; a multicenter, double-blind (DB), randomized study (NCT01451203). Pts were randomized to CZP+MTX (n=159) or placebo (PBO)+MTX (n=157) with oral MTX escalated up to 16 mg by Week (Wk) 8 (optimized dose), if tolerated. After completing 52-wk DB period, CZP (n=108) or PBO (n=71) was discontinued and pts continued with MTX monotherapy up to Wk104 in 52-wk post CZP-treatment period. Pts who were in DAS(ESR) ≥3.2 for two consecutive visits (4 wks) or longer after Wk24 could receive rescue treatment with CZP and

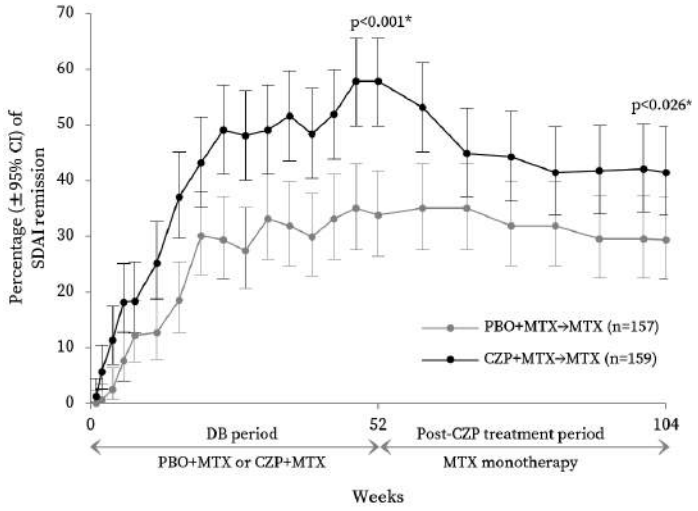
were excluded from the post-CZP treatment period. Full analysis set (FAS) population was analyzed. Last observation carried forward (LOCF) imputation was used for missing data for clinical remission, whereas linear extrapolation was employed to estimate mTSS in patients who withdrew before Wk104.

Results: In CZP+MTX→MTX group, SDAI remission rate was decreased over the initial 16 weeks from 57.9% to 44.9% after CZP discontinuation. However, the rate remained stable thereafter, with higher rate of SDAI remission compared with PBO+MTX→MTX up to Wk104 (41.5% vs 29.3%; p=0.026 [Figure A]). Similar trend was observed in DAS28(ESR) and Boolean remission. Pts retreated with CZP due to flare after CZP discontinuation (n=28) showed rapid clinical improvement after CZP retreatment. The CZP+MTX→MTX group showed significantly less radiographic progression at Wk104 (mean change from baseline (CFB) in mTSS: 0.66±5.38 vs 3.01±9.66; p=0.001 [Figure B]) with higher non-radiographic progression rate (CFB in mTSS≤0.5) (84.2% vs 67.5%; p<0.001). Incidence of overall adverse events was similar between groups, with no new or unexpected safety signals.

Conclusion: The clinical benefit of initial 1-year CZP treatment in MTX-naïve early RA patients was still observed after discontinuing CZP for an additional 1 year while continuing optimized MTX monotherapy.

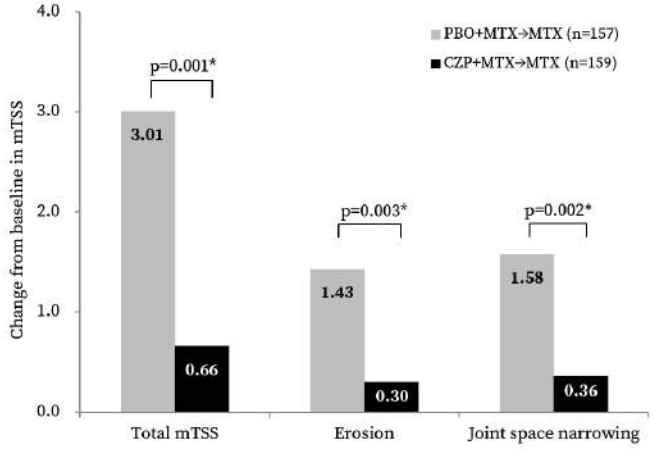
Reference: 1. Atsumi T. Ann Rheum Dis 2014;73(S2):484

Figure A: SDAI remission over time



FAS, LOCF; *Fisher's exact test, CZP+MTX vs PBO+MTX

Figure B: Radiographic progression at Week 104



FAS, Linear extrapolation; *ANCOVA on the ranks

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Quintiles, MSD, Asahi Kasei, 5; **K. Eguchi**, UCB Pharma, 5; **A. Watanabe**, Daiichi-Sankyo, Kyorin, Shionogi, Taisho, Dainippon-Sumitomo, Taiho, Toyama Chemical, Meiji Seika, 2,MSD, GSK, Shionogi, Daiichi-Sankyo, Taisho-Toyama, Dainippon-Sumitomo, Mitsubishi-Tanabe, Pfizer, 8; **H. Origasa**, UCB Pharma, Astellas, 5; **T. Shoji**, UCB Pharma, 3; **O. Togo**, UCB Pharma, 3; **T. Okada**, Astellas, 3; **D. van der Heijde**, Abbvie, Amgen, AstraZeneca, Augurex, Bristol-Myers Squibb, Boehringer Ingelheim, Celgene, Centocor, Chugai, Covagen, Daiichi, Eli-Lilly, Galapagos, GlaxoSmithKline, Janssen, Merck, Novo-Nordisk, Otsuka, Pfizer, Roche, Sanofi-Aventis, UCB Pharma, Vertex, 5,Abbvie, Amgen, AstraZeneca, Augurex, Bristol-Myers Squibb, Boehringer Ingelheim, Celgene, Centocor, Chugai, Covagen, Daiichi, Eli-Lilly, Galapagos, GlaxoSmithKline, Janssen, Merck, Novo-Nordisk, Otsuka, Pfizer, Roche, Sanofi-Aventis, UCB Pharma, Vertex, 2; **N. Miyasaka**, Pfizer, Takeda, Mitsubishi-Tanabe, Chugai, Abbott, Eisai and Astellas, 2; **T. Koike**, Abbvie, Astellas, BMS, Chugai, Daiichi-Sankyo, Eisai, Mitsubishi-Tanabe, Pfizer, Santen, Taisho-Toyama, Takeda, Teijin, UCB. Speakers bureau: UCB Pharma, Pfizer, Chugai, Abbott, Mitsubishi-Tanabe, Takeda, Eisai, Santen, Astellas, Taisho-Toyama, BMS, Teiji, 5.

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Abstract Number: 1637

TNFi Combination Therapy, Switching and Persistence Patterns By Longitudinal Disease Activity Strata in Patients with Rheumatoid Arthritis

Leslie Harrold[1,2], George W. Reed[1,2], Natalie Boytsov[3], Carol L. Gaich[3], Marc Mason[4], Xiang Zhang[3], Cynthia J. Larmore[3], Sabrina Deveikis[4] and Andre B. Araujo[3], [1]University of Massachusetts Medical School, Worcester, MA, [2]Corrona, LLC, Southborough, MA, [3]Eli Lilly and Company, Indianapolis, IN, [4]Corrona, LLC., Southborough, MA

First publication: September 29, 2015

SESSION INFORMATION

Session Date: Monday, November 9, 2015

Session Title: Rheumatoid Arthritis - Small Molecules, Biologics and Gene Therapy Poster II

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: The purpose of this study was to describe the treatment patterns in biologic naïve initiators of TNF-inhibitors (TNFi) based on their disease activity over a 1-year follow-up period from a national cohort of patients with rheumatoid arthritis (RA).

Methods: Using data from the Corrona registry, biologic naïve RA patients were identified between 1/1/2006 and 8/31/2013 who had initiated their first TNFi (the index date) after any prior use of ≥1 conventional disease modifying anti-rheumatic drug (cDMARD). The patients were categorized into disease activity strata defined by the lowest level of disease activity reached using the Clinical Disease Activity Index (CDAI) across all visits reported while on TNFi therapy in Corrona during the 1 year follow-up period including the index date. The mutually exclusive strata are as follows: sustained remission - attained remission (CDAI ≤2.8) on at least 2 consecutive visits; remission - attained remission on at least one visit; sustained LDA - remission was never attained on any visits, but reached low disease activity (LDA; 2.8< CDAI ≤10) on at least 2 consecutive visits; LDA - attained LDA; and moderate/high disease activity (MDA/HDA) (CDAI>10) - never achieved remission or LDA on any visit. Patients were compared on demographics, RA disease characteristics, and treatment patterns. Comparisons across these disease activity strata were performed with one-way ANOVA for continuous variables and chi-square test for categorical variables.

Results: There were 1931 RA patients who met inclusion criteria of whom 15% achieved sustained remission (n=286), 22% remission (n=426), 14% sustained LDA (n=271), 23% LDA (n=436) and 27% MDA/HDA (n=512). The groups differed in terms of demographics (Table 1). Those with higher levels of disease activity (MDA/HDA) were older at disease onset, had higher baseline levels of disease activity and greater functional impairment based on the modified Health Assessment Questionnaire (mHAQ). There were significant differences between the groups in terms of combination therapy (Table 1). Higher disease activity was associated with less use of methotrexate (MTX) based combination therapy (e.g, more use of TNFi monotherapy or combination therapy with a non- MTX cDMARD). Switching to another TNFi occurred in 14% of the population, 6.5 to 8.4 months after initiation, on average. At the study conclusion, 331 (17%) had discontinued TNFi therapy with 99% switching to a non-TNFi biologic. Those with higher levels of disease activity switched more frequently to both another TNFi or to a non-TNFi biologic.

Conclusion: Majority of patients (63%) did not achieve remission or sustained remission. Those in the lower disease activity strata were more likely to have been prescribed a TNFi with MTX as compared to MTX monotherapy or in combination with a non-MTX cDMARD, while those with higher disease activity were more likely to have been switched to another biologic.

Table 1 Baseline characteristics and treatment patterns over 1 year follow-up.

	Overall Population n=1931	Sustained Remission n=286	Remission n=426	Sustained LDA n=271	LDA n=436	MDA/HDA n=512	p*
Sex Female, %	n=1909 74.6%	n=282 68.1%	n=421 73.6%	n=267 77.5%	n=432 74.3%	n=507 77.7%	p=0.0350
Race White Caucasian Non-White	n=1931 86.9% 13.1%	n=286 89.9% 10.1%	n=426 88.5% 11.5%	n=271 87.5% 12.5%	n=436 84.6% 15.4%	n=512 85.6% 14.4%	Race: p=0.0230[a]
Ethnicity Hispanic/Latino	n=1931 5.6%	n=286 6.3%	n=426 4.9%	n=271 5.5%	n=436 5.1%	n=512 6.5%	Ethnicity: p=0.8180
Age in years Mean (SD)	n=1906 56.2 (12.4)	n=282 59.0 (12.7)	n=420 55.5 (12.7)	n=267 55.5 (11.8)	n=432 57.7 (12.8)	n=505 57.6 (11.5)	p<0.0001
RA Age of onset in years Mean (SD)	n=1902 49.9 (13.1)	n=281 47.3 (13.5)	n=418 49.6 (13.3)	n=266 50.1 (12.5)	n=432 50.6 (13.5)	n=505 50.9 (12.6)	p=0.0031
Rheumatoid Arthritis Factor Positivity (RF+)[2], %	n=1173 71.7%	n=183 78.1%	n=269 74.4%	n=168 69.1%	n=253 71.5%	n=300 67.0%	p=0.0740
Comorbidities History of Diabetes, %	n=1931 7.6%	n=286 4.6%	n=426 4.9%	n=271 7.4%	n=436 10.6%	n=512 9.2%	p=0.0040
Baseline CDAI Mean (SD)	n=1931 18.5 (14.5)	n=286 12.2 (13.3)	n=426 13.0 (13.5)	n=271 17.9 (12.1)	n=436 16.7 (12.5)	n=512 28.5 (13.4)	p<0.0001
Baseline mHAQ *(range: 0 to 3)* Mean (SD)	n=1927 0.4 (0.5)	n=286 0.2 (0.3)	n=425 0.3 (0.4)	n=271 0.4 (0.4)	n=434 0.4 (0.4)	n=511 0.7 (0.5)	p<0.0001
Mean TNFi drugs used, SD	1.15 (0.37)	1.07 (0.28)	1.08 (0.28)	1.13 (0.33)	1.19 (0.40)	1.22 (0.46)	p<0.0001
Total TNFi drugs used, n Monotherapy[4], % TNFi with (non-MTX) cDMARDs[5], % TNFi with MTX[5], %	n_{Total}=2213 14.4% 24.6% 61.0%	n_{Total}=306 11.4% 20.9% 67.6%	n_{Total}=461 15.8% 21.5% 62.7%	n_{Total}=305 11.1% 23.6% 65.2%	n_{Total}=517 14.9% 25.9% 59.2%	n_{Total}=624 16.0% 28.2% 55.8%	p=0.0115
Proportion switching to another biologic —Proportion switching to TNFi —Proportion switching to non-TNFi biologic	13.8% 17.1%	6.3% 0%	8.0% 11.3%	12.5% 0%	18.1% 22.0%	19.9% 36.5%	p=0.0310 p<0.0001
Mean length of time in months to first switch to another TNFi (conditional on switching to another TNFi), *mean (SD)*	7.7 (3.3)	6.6 (3.9)	6.5 (3.4)	7.7 (3.3)	8.4 (3.1)	7.8 (3.1)	p=0.0310

* Significance testing is performed with one-way ANOVA for continuous variables, and chi-square tests of association for categorical variables.
[a] This p value is not representative of the collapsed categories but with separate race categories.
[2] RF and CCP testing is not required on all Corrona RA patients; therefore, these counts are available only on a reduced set of RA patients.
[3] Treatment patterns are defined at first use (initiation) of each TNF.

Disclosure: L. Harrold, Corrona LLC, 3,Pfizer, AstraZeneca, 2,Genentech., 5; **G. W. Reed**, Corrona, LLC, 3,Corrona, LLC, 1; **N. Boytsov**, Eli Lilly and Company, 1,Eli Lilly and Company, 3; **C. L. Gaich**, Eli Lilly and Company, 3; **M. Mason**, Corrona, LLC, 3; **X. Zhang**, Eli Lilly and Company, 3; **C. J. Larmore**, Eli Lilly and Company, 1,Eli Lilly and Company, 3; **S. Deveikis**, Corrona LLC, 3; **A. B. Araujo**, Eli Lilly and Company, 1,Eli Lilly and Company, 3.

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Abstract Number: 1638

Early Response As a Predictor of Long-Term Remission in DMARD-Naïve Patients with Severe, Active and Progressive Rheumatoid Arthritis Treated with Certolizumab Pegol in Combination with Methotrexate

Michael Weinblatt[1], Clifton Bingham[2], Gerd Burmester[3], VP Bykerk[4], Daniel E. Furst[5], Xavier Mariette[6], Désirée van der Heijde[7], Daljit Tatla[8], Catherine Arendt[9], Irina Mountian[10], Brenda VanLunen[11] and Paul Emery[12], [1]Rheumatology Immunology & Allergy, Brigham and Women's Hospital, Boston, MA, [2]Johns Hopkins University, Baltimore, MD, [3]Department of Rheumatology and Clinical Immunology, Charité - Universitätsmedizin Berlin, Berlin, Germany, [4]Hospital for Special Surgery, New York, NY, [5]Medicine, University of California, Los Angeles, David Geffen School of Medicine, Los Angeles, CA, [6]Université Paris-Sud, AP-HP, Hôpitaux Universitaires Paris-Sud, Paris, France, [7]University Hospital, Maastricht, Netherlands, [8]8010 Arco Corporate Dr, UCB Pharma, Raleigh, NC, [9]Global Medical Affairs, UCB Pharma, Brussels, Belgium, [10]UCB Pharma, Brussels, Belgium, [11]UCB Pharma, Raleigh, NC, [12]Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds, Leeds, United Kingdom
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Session Type: ACR Poster Session B
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Background/Purpose:

In established rheumatoid arthritis (RA), a lack of response to treatment with certolizumab pegol (CZP) at early timepoints is associated with a low probability of achieving future target responses.[1] The phase 3 C-EARLY study (NCT01519791) assessed efficacy and safety of CZP in inducing and maintaining a sustained clinical response and inhibiting radiographic damage in DMARD-naïve patients (pts) with active, severe, progressive RA with poor prognostic factors in comparison to MTX alone. Here, we examine the association between response to CZP+MTX in this pt population at an early visit (improvement/lack of improvement from baseline [BL] in DAS28[ESR] at Week [Wk] 12) and remission at Wk52.

Methods:

This multicenter, double-blind, randomized study enrolled pts who were DMARD-naïve with active, severe, progressive RA (<1 year since diagnosis at BL, fulfilling 2010 ACR/EULAR criteria: ≥4 swollen and ≥4 tender joints; DAS28[ESR]≥3.2; CRP≥10 mg/L and/or ESR≥ 28 mm/hr, rheumatoid factor/ACPA positive). 879 pts were randomized 3:1 to CZP (400 mg at Wks 0, 2 and 4, then 200 mg every 2 wks to Wk52+MTX; n=660) or PBO+MTX Q2W (n=219).

MTX was initiated at 10 mg/wk and increased to 25 mg/wk by Wk8, maximum tolerated dose per patient (optimized dose) was maintained to Wk52. Predictability analyses consisted of positive predictive value (PPV; probability of achieving Wk52 remission after achieving a Wk12 response) and negative predictive value (NPV; probability of failing to achieve Wk52 remission after failing to achieve a Wk12 response). Remission was defined as DAS28(ESR)<2.6; Wk12 responses analyzed were change from BL in DAS28(ESR) ≥0.6 and ≥1.2. Observed data were utilized for Wk12 responses; missing Wk52 values were imputed using non-responder imputation.

Results:

At Wk52, 42.6% CZP+MTX pts vs 26.8% PBO+MTX pts achieved remission (DAS28[ESR] <2.6) (Table A). NPV of early responses was high (Table B): CZP+MTX-treated pts who did not achieve DAS28(ESR) improvements from BL ≥0.6 or ≥1.2 points at Wk12 had a high probability of not being in remission at Wk52; 92% and 93% respectively. Pts who did achieve an improvement from BL in DAS28(ESR) of ≥0.6 and ≥1.2 at Wk12 had 45% and 49% chance of Wk52 remission (Table B), respectively.

Conclusion:

DMARD-naïve pts with active, severe and progressive RA who failed to achieve DAS28(ESR) improvements at Wk12 after treatment with CZP+MTX were unlikely to be in remission at Wk52. These findings in DMARD-naïve pts are consistent with earlier reports in pts with established disease.

References:

1. van der Heijde D. J Rheumatol 2012; 39:1326-33

Table A: Patients achieving remission (DAS28[ESR]<2.6) by visit following CZP+MTX treatment (NRI)

	DAS28(ESR)<2.6 (NRI)	
	PBO+MTX (n=213)	CZP+MTX (n=655)
	n (%)	n (%)
Visit		
Week 12	26 (12.2)	124 (18.9)
Week 24	28 (13.1)	171 (26.1)
Week 52	57 (26.8)	279 (42.6)

Table B: Positive and negative predictive values of early clinical responses with CZP+MTX treatment (NRI)

Week 12 DAS28(ESR) reduction from baseline (observed case)	Week 52 remission (NRI) (DAS28[ESR]<2.6)
	PPV
≥0.6 (n=608)	0.45
≥1.2 (n=558)	0.49
	NPV
<0.6 (n=36)	0.92
<1.2 (n=86)	0.93

NPV: negative predictive value; PPV: positive predictive value.

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Abstract Number: 1639

Clinical Outcomes for Rheumatoid Arthritis Patients Receiving Tofacitinib Monotherapy in the Open-Label Long-Term Extension over 6 Years

Roy Fleischmann[1], Yusuf Yazici[2], Jürgen Wollenhaupt[3], Lisy Wang[4], Anna Maniccia[5], Kenneth Kwok[4], Liza Takiya[5] and Ronald van Vollenhoven[6], [1]Rheumatology, Metroplex Clinical Research Center, Dallas, TX, [2]New York University Hospital for Joint Diseases, New York, NY, [3]Teaching Hospital of the University of Hamburg, Schoen-Klinik Hamburg-Eilbek, Hamburg, Germany, [4]Pfizer Inc, Groton, CT, [5]Pfizer Inc, New York, NY, [6]The Karolinska Institute, Stockholm, Sweden

First publication: September 29, 2015

SESSION INFORMATION

Session Date: Monday, November 9, 2015

Session Title: Rheumatoid Arthritis - Small Molecules, Biologics and Gene Therapy Poster II

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: Treatment options delivering sustained efficacy when given as monotherapy in RA are limited.[1] Tofacitinib is an oral Janus kinase inhibitor for the treatment of RA. Tofacitinib monotherapy demonstrated efficacy in adult patients (pts) with RA in two index studies (ORAL Solo[2] and Start[3]). Open-label, long-term extension (LTE) studies enrolled pts to evaluate safety and efficacy of tofacitinib monotherapy and combination therapy. Here we present data up to Month (Mo) 84 for safety and Mo 60 for efficacy for pts who stayed on tofacitinib monotherapy in LTE studies.

Methods: Data were pooled from two tofacitinib LTE studies (NCT00413699 [ongoing; database unlocked as of Apr 2014 data cut-off] and NCT00661661). Pts from Phase (P) 1/2/3 tofacitinib index studies received tofacitinib 5 or 10 mg twice daily (BID) as monotherapy or with background csDMARD in LTE. For tofacitinib and permitted concomitant RA medications, dose adjustments were allowed for inadequate efficacy or safety reasons. In this analysis, pts were assigned to tofacitinib 5 or 10 mg BID groups based on average total daily dose in LTE (<15 mg/day or ≥15 mg/day, respectively). Monotherapy was defined as those pts who received tofacitinib without other DMARDs (except antimalarials) throughout the LTE. Baseline (BL) values were those of the index studies for pts enrolling in LTE within 14 days of index study; for all others, BL was start of LTE. Safety was evaluated up to Mo 84 and efficacy to Mo 60 due to limited sample size.

Results: 1808 pts initiated LTE on tofacitinib monotherapy; 1638 (91%) stayed on monotherapy throughout LTE (504 on 5 mg BID; 1134 on 10 mg BID). For pts staying on monotherapy, mean (max) treatment duration was 1157 (2522) and 788 (2104) days for 5 and 10 mg, respectively. Efficacy responses for tofacitinib monotherapy were stable up to Mo 60 (Table 1). In 5 and 10 mg groups, 68% and 88% of pts, respectively, stayed on initial dose throughout LTE. Proportion of pts staying on steroids decreased from 56% to 39% and 41% to 23%, respectively, from baseline to Mo 60. Rates of discontinuation due to lack of efficacy and adverse events (AE), and of serious infection and malignancies (excluding non-melanoma skin cancer) were low (Table 2).

Conclusion: In this analysis of pts receiving tofacitinib monotherapy in LTE studies, over 90% of pts stayed on monotherapy, most did not have tofacitinib dose adjustments or add a DMARD, and efficacy was sustained over 60 months, with low rates of discontinuations due to lack of efficacy or AEs.

References: 1. Smolen JS et al. Ann Rheum Dis 2014; 73: 492-509; 2. Fleischmann R et al. N Engl J Med 2012; 367: 495-507; 3. Lee EB et al. N Engl J Med 2014; 370: 2377-2386.

Table 1: Efficacy responses over time in patients receiving tofacitinib monotherapy

	Tofacitinib 5 mg BID				Tofacitinib 10 mg BID			
	ACR20, % (N)	ACR50, % (N)	Change from baseline in DAS28-4(ESR) score, mean (N)	Change from baseline in HAQ-DI score, mean (N)	ACR20, % (N)	ACR50, % (N)	Change from baseline in DAS28-4(ESR) score, mean (N)	Change from baseline in HAQ-DI score, mean (N)
Month 3	81.0 (483)	58.6 (483)	-2.7 (473)	-0.64 (477)	80.1 (1087)	59.8 (1087)	-2.9 (1067)	-0.75 (1078)
Month 6	79.8 (470)	58.1 (470)	-2.7 (455)	-0.63 (461)	79.5 (1060)	60.5 (1060)	-2.9 (1043)	-0.74 (1050)
Month 9	84.2 (450)	61.8 (450)	-2.8 (442)	-0.65 (443)	79.5 (1024)	59.4 (1024)	-2.9 (1008)	-0.75 (1011)
Month 12	82.8 (436)	62.6 (436)	-2.8 (431)	-0.66 (428)	81.9 (986)	61.4 (986)	-3.0 (964)	-0.75 (978)
Month 24	86.9 (365)	69.0 (365)	-2.9 (359)	-0.67 (359)	76.8 (529)	58.4 (529)	-2.9 (517)	-0.67 (522)
Month 36	87.9 (331)	66.8 (331)	-2.9 (326)	-0.64 (324)	78.8 (392)	57.9 (392)	-3.0 (385)	-0.65 (390)
Month 48	87.7 (187)	67.4 (187)	-3.1 (180)	-0.67 (183)	78.0 (141)	52.5 (141)	-3.0 (137)	-0.65 (140)
Month 60	87.8 (115)	69.6 (115)	-3.0 (115)	-0.64 (113)	66.7 (24)	25.0 (24)	-2.5 (24)	-0.54 (24)

ACR, American College of Rheumatology response; BID, twice daily; DAS28, disease activity score; HAQ-DI, Health Assessment Questionnaire-Disability Index; N, number of evaluable patients

Table 2: Summary of discontinuations, serious infections, and malignancies (excluding NMSC) in patients receiving tofacitinib monotherapy up to data cut-off		
	Tofacitinib 5 mg BID N=504	**Tofacitinib 10 mg BID N=1134**
Tofacitinib exposure, patient-years	1612	2476
Discontinuations, n (%)	217 (43.1)	323 (28.5)
Due to lack of efficacy	16 (3.2)	16 (1.4)
Due to AEs	108 (21.4)	152 (13.4)
IR (95% CI) of discontinuations due to AEs	7.1 (5.8, 8.5)	6.2 (5.2, 7.2)
IR (95% CI) of serious infection	2.9 (2.2, 3.9)	2.4 (1.9, 3.1)
IR (95% CI) of malignancies (excluding NMSC)	1.0 (0.6, 1.6)	0.7 (0.4, 1.1)
AE, adverse event; BID, twice daily; CI, confidence interval; IR, incidence rate (patients with events per 100 patient-years); NMSC, non-melanoma skin cancer		

Disclosure: R. Fleischmann, Pfizer Inc, 2,Pfizer Inc, 5; **Y. Yazici**, BMS, Celgene, Genentech, 2,BMS, Celgene, Genentech, 5; **J. Wollenhaupt**, Roche, Chugai Pharma, Pfizer Inc, Abbott, and UCB, 5,Roche, Chugai Pharma, Pfizer Inc, Abbott, and UCB, 8; **L. Wang**, Pfizer Inc, 3,Pfizer Inc, 1; **A. Maniccia**, Pfizer Inc, 1,Pfizer Inc, 3; **K. Kwok**, Pfizer Inc, 1,Pfizer Inc, 3; **L. Takiya**, Pfizer Inc, 1,Pfizer Inc, 3; **R. van Vollenhoven**, Pfizer Inc, 2,Pfizer Inc, 5.

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Abstract Number: 1640

Effect of Methotrexate Dose on the Efficacy of Tofacitinib: Treatment Outcomes from a Phase 3 Clinical Trial of Patients with Rheumatoid Arthritis

Roy Fleischmann[1], Philip J. Mease[2], Sergio Schwartzman[3], Lie-Ju Hwang[4], Aditya Patel[5], Koshika Soma[4], Carol A. Connell[6], Liza Takiya[4] and Eustratios Bananis[7], [1]Rheumatology, Metroplex Clinical Research Center, Dallas, TX, [2]Rheumatology Research, Swedish Medical Center, Seattle, WA, [3]Hospital for Special Surgery, New York, NY, [4]Pfizer Inc, New York, NY, [5]Inventiv Health Inc, South Plainfield, NJ, [6]Pfizer Inc, Groton, CT, [7]Pfizer Inc, Collegeville, PA

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Session Title: Rheumatoid Arthritis - Small Molecules, Biologics and Gene Therapy Poster II

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Background/Purpose: Tofacitinib is an oral Janus kinase inhibitor for the treatment of rheumatoid arthritis (RA). ORAL Scan was a 2-year, randomized, Phase 3, clinical trial that evaluated tofacitinib therapy with background methotrexate (MTX) in patients (pts) with RA and an inadequate response (IR) to MTX.[1] In this analysis, the effect of MTX dose on tofacitinib efficacy in pts from ORAL Scan was studied.

Methods: In ORAL Scan, MTX-IR pts with RA were randomized 4:4:1:1 to tofacitinib 5 mg twice daily (BID), tofacitinib 10 mg BID, or placebo with advancement to 5 mg BID or to 10 mg BID at Month 3 or Month 6, in combination with background MTX. MTX dose was stable throughout the study and was categorized as Low (≤12.5 mg/week), Medium (>12.5 to <17.5 mg/week), or High (≥17.5 mg/week). Endpoints evaluated at Month 6 included ACR response rates, proportion of pts achieving low disease activity measured by Clinical Disease Activity Index (CDAI ≤10), CDAI defined remission rate (CDAI ≤2.8), proportion of pts achieving an improvement ≥0.5 in Health Assessment Questionnaire-Disability Index (HAQ-DI), and least squares mean change from baseline in HAQ-DI, Disease Activity Score (DAS28-4[ESR]), and CDAI. Binary variables were evaluated with non-responder imputation, and continuous variables were analyzed using a longitudinal model. Regression analyses were conducted to evaluate efficacy responses by MTX dose group and other covariates.

Results: 797 pts were randomized and treated (tofacitinib 5 mg BID, n=321; tofacitinib 10 mg BID, n=316; placebo, n=160). 242 pts were included in the Low MTX (9 mg mean) dose group, 333 in the Medium MTX (15 mg mean) dose group, and 222 in the High MTX (21 mg mean) dose group. Baseline demographics and disease characteristics were similar across MTX dose groups, though weight, BMI, glucocorticoid (GC) use, and CDAI were higher in the High MTX dose group. At Month 6, greater efficacy was seen with tofacitinib compared to placebo for all endpoints across the 3 MTX dose groups (Table). Efficacy for placebo-treated pts was generally numerically greater in the Medium and High MTX dose groups than in the Low MTX dose group. Efficacy with tofacitinib appeared similar regardless of MTX dose group. Regression analyses demonstrated a lack of effect of BMI, GC use and MTX dose groups on efficacy assessments.

Conclusion: In this post-hoc analysis, clinical efficacy of tofacitinib at Month 6 was greater than placebo, and appeared similar regardless of MTX dose, as in these pts, tofacitinib was added to patients that had an inadequate response to MTX. Higher MTX doses did not appear to result in additional efficacy to tofacitinib than lower doses. A randomized clinical trial is needed in which different doses of MTX are added to tofacitinib in MTX-naïve pts in order to examine the effect of MTX dose on tofacitinib efficacy.

Reference: 1. van der Heijde D et al. Arthritis Rheum 2013; 65: 559-570.

Table: Efficacy responses at Month 6 by MTX dose group and treatment group for patients in ORAL Scan

	Low MTX (≤12.5 mg/week; category mean = 9 mg/week)			Medium MTX (>12.5 to <17.5 mg/week; category mean = 15 mg/week)			High MTX (≥17.5 mg/week; category mean = 21 mg/week)		
	N=242			N=333			N=222		
	Placebo	Tofacitinib 5 mg BID	Tofacitinib 10 mg BID	Placebo	Tofacitinib 5 mg BID	Tofacitinib 10 mg BID	Placebo	Tofacitinib 5 mg BID	Tofacitinib 10 mg BID
	N=47	N=102	N=93	N=73	N=131	N=129	N=40	N=88	N=94
ACR20, %	22.2	54.0*	62.2*	27.5	48.0*	62.4*	25.0	53.6*	60.6*
ACR50, %	6.7	35.0*	44.4*	7.3	31.2*	42.4*	12.5	31.0*	44.7*
ACR70, %	0.0	17.0*	24.4*	2.9	15.2*	21.6*	0.0	10.7*	21.3*
CDAI ≤10, %	8.9	42.0*	52.2*	13.0	32.0*	41.1*	12.5	35.7*	39.4*
CDAI ≤2.8, %	2.2	9.0	13.3*	1.5	8.8*	13.7*	0.0	9.5*	16.0*
HAQ-DI change ≥0.5, %	8.9	32.0*	45.6*	14.5	36.0*	47.6*	7.5	36.1*	50.0*
LS mean CFB in HAQ-DI	-0.01	-0.46*	-0.57*	-0.25	-0.56*	-0.62*	-0.28	-0.45	-0.68*
LS mean CFB in DAS28-4 (ESR)	-1.00	-2.15*	-2.48*	-1.33	-2.28*	-2.39*	-2.07	-2.14	-2.67*
LS mean CFB in CDAI	-13.0	-21.4*	-22.7*	-16.3	-22.6*	-23.3*	-20.12	-23.3	-25.8*

*p<0.05 vs placebo

Data for binary endpoints are full analysis set with non-responder imputation; data for continuous endpoints are full analysis set, longitudinal model. Non-responder imputation was applied to patients who discontinued, and to patients who, at Month 3, had not achieved a 20% improvement in tender and swollen joint counts regardless of treatment assignment.

ACR, American College of Rheumatology response; BID, twice daily; CDAI, Clinical Disease Activity Index; CFB, change from baseline; DAS28, Disease Activity Score; ESR, erythrocyte sedimentation rate; HAQ-DI, Health Assessment Questionnaire-Disability Index; LS, least squares; MTX, methotrexate

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Abstract Number: 1641

B Cell Depletion with Rituximab in Patients with Rheumatoid Arthritis: Multiplex Bead Array Reveals Kinetics of IgG and IgA Autoantibodies to Citrullinated Antigens

Geraldine Cambridge[1], Lauren J. Lahey[2], Maria J. Leandro[1], William H. Robinson[3] and Jeremy Sokolove[4], [1]Rheumatology, University College London, London, United Kingdom, [2]Medicine, VA Palo Alto HealthCare System and Stanford University, Palo Alto, CA, [3]VA Palo Alto Health Care System and Stanford University, Palo Alto, CA, [4]Medicine, VA Palo Alto Health Care System and Stanford University, Palo Alto, CA

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Background/Purpose:

Seropositivity for rheumatoid factors and anti-citrullinated (Cit) protein antibodies (ACPA) are the strongest predictor for clinical response to rituximab (RTX) in rheumatoid arthritis (RA). ACPAs are routinely detected using cyclic Cit peptides (CCP). However, the wide variety of non-cross reactive epitopes recognized by ACPA may explain why fluctuations in anti-CCP antibodies are not a reliable measure of response to therapies. We therefore investigated the kinetics of individual IgG- and IgA-ACPA in relation to clinical improvement (during B cell depletion) and recurrence of symptoms following RTX using multiplex antigen array.

Methods:

16 patients with active RA (DAS28 ≥ 5.1; median duration 20 years) undergoing initial cycles of RTX were included. All achieved B cell depletion in the peripheral blood (<5 cells/µl) and clinically responded (ΔDAS28≥1.2) within 5 months (median=3). Follow-up to re-treatment or relapse was 4-13 months. IgG and IgA antibodies binding to a custom, bead-based, antigen array comprising CCP and 29 RA-associated Cit-antigens and 22 corresponding native antigens, based on those in inflamed synovium, was assessed using mean fluorescence intensity (MFI). To compensate for number of binding sites per antigen, MFI were Z-normalized in serial studies, with Z score >1 'positive'. Spearman's Rank, T-tests used for data analysis.

Results:

Pre-RTX, IgG- and IgA-binding (MFI) to Cit antigens were strongly correlated (R^2=0.75; p<0.0001) but MFI of IgA-Cit were approximately 10 fold lower. Mean % change in ACPA from baseline to clinical improvement (during depletion phase), was significantly greater for IgA-Cit (-43%) than IgG-Cit (-21%) (p=0.003), largely due to 24% (16/65) of IgG-Cit antibodies, but only 3/47 IgA-Cit, showing a transient increase following RTX. Amongst IgG- and IgA-Cit antibodies that fell following RTX, some increased prior to relapse (n=28 and 27 respectively) whereas others continued to fall (n=21 and 17). In those rising to relapse after an initial fall, 13/21 different Cit antigens recognized by IgG also bound IgA. Although putative 'new' specificities (baseline Z score ≤1; relapse Z score >1) were recognized by 9 IgG- and 10 IgA-Cit, most (7 IgG; 6 IgA) were detectable at low levels before RTX. Cit-fibrinogen derived targets were consistently detected in all different ACPA patterns post-RTX, but no particular specificities were identified.

Conclusion:

After RTX, ACPA showed a variety of profiles, presumably due to the ability of RTX to deplete or modify the function of different parent B cell clones. Some IgG-Cit (rarely IgA-Cit) rose after RTX, despite peripheral B cell depletion, suggesting that IgG-B cells were more resistant, or that the half-lives of IgG or IgA plasma cells vary. Location within protective niches in tissues may also aid survival. Expansion of pre-existing memory B cells appeared to accompany disease resumption after RTX with levels of many autoantibody specificities present pre-RTX rising with B cell reconstitution or impending relapse. Dissection of the ACPA response using multiplex bead array revealed diverse kinetics of ACPA-committed B cells which could be exploited for more efficient B cell directed therapies.

Disclosure: G. Cambridge, None; **L. J. Lahey**, None; **M. J. Leandro**, None; **W. H. Robinson**, Atreca, Inc, 5,Atreca, Inc, 4; **J. Sokolove**, None.

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Abstract Number: 1642

A Systematic Review and Network Meta-Analysis on the Efficacy of Tumor Necrosis Factor Inhibitor-Methotrexate Combination Therapy Versus Triple Therapy in Methotrexate Inadequate Responders with Rheumatoid Arthritis

Roy Fleischmann[1], Janet E. Pope[2], Vanita Tongbram[3], Derek Tang[4], James Chung[5], David Collier[5], Shilpa Urs[3], Kerigo Ndirangu[3], George A. Wells[6] and Ronald F. van Vollenhoven[7], [1]Rheumatology, Metroplex Clinical Research Center, Dallas, TX, [2]University of Western Ontario, London, ON, Canada, [3]ICON Plc., Morristown, NJ, [4]Amgen, Inc., Thousand Oaks, CA, [5]Amgen Inc., Thousand Oaks, CA, [6]Cardiovascular Research Reference Centre, University of Ottawa Heart Institute, Ottawa, ON, Canada, [7]Department of Medicine, Unit for Clinical Therapy Research, Inflammatory Diseases (ClinTRID), The Karolinska Institute, Stockholm, Sweden

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Background/Purpose: Previously published rheumatoid arthritis (RA) trials in which TNFi-MTX and triple therapy (MTX + hydroxychloroquine + sulfasalazine) were included as treatment arms in MTX inadequate responder (MTX-IR) patients did not convincingly demonstrate superiority for TNFi-MTX. This could be due to trials being underpowered to detect true differences.[1,2]The objective of this study was to estimate the efficacy and radiographic benefits of TNFi-MTX vs. triple therapy in MTX-IRs by conducting a systematic review and network meta-analysis. This is an important, clinically relevant question in MTX-IRs.

Methods: Medline, EMBASE, and the Cochrane Library were searched for randomized controlled trials that used either TNFi-MTX or triple therapy as one of the treatment arms in MTX-IRs with RA. The primary endpoint for this analysis was ACR70 at 6 months. Other endpoints included ACR20, ACR50, DAS28 LDA, DAS28 remission, EULAR good response, and no radiographic progression; and changes in DAS28 score, joint erosion, joint space narrowing, and various versions of Sharp scores from baseline. Endpoints were analyzed at 3 months, 6 months, 1 year, and 2 years from baseline when feasible. Data from direct and indirect comparisons between TNFi-MTX and triple therapy were pooled and quantitatively analyzed using fixed and random effects Bayesian models (FEM and REM) in WinBUGS version 1.4.3. Relative treatment effects were generated as odds ratio [OR] (OR>1 indicated a benefit towards triple therapy) for dichotomous endpoints and mean differences (D<0 indicated a benefit towards triple therapy) for continuous endpoints.

Results: A total of 39 studies met the study eligibility criteria, corresponding to 12,749 randomized patients. MTX-IRs were significantly less likely to achieve ACR70 with triple therapy than with TNFi-MTX at 6 months in both fixed effects models (FEM) (OR=0.35, 95% Credible Interval [CrI]: 0.19,

0.64) and random effects models (REM) (OR=0.36, 95% CrI: 0.16, 0.80). All endpoints except for DAS28 score change from baseline showed a statistically significant benefit of TNFi-MTX relative to triple therapy in FEM but not REM at some point within the 2 years of evaluation from baseline. Across the 27 analyzable endpoint-time scenarios evaluated, 26 numerically favored TNFi-MTX in both FEM and REM.

Conclusion: In this network meta-analysis of MTX-IR patients, triple therapy had a 65% significantly lower odds than TNFi-MTX in achieving an ACR70 at 6 months. The benefits of TNFi-MTX over triple therapy were shown across clinical and radiographic endpoints in the MTX-IR population, supporting the use of biological therapy in this setting.

References: 1. O'Dell JR, Mikuls TR, Taylor TH, et al. N Engl J Med 2013;369:307–18.

2. van Vollenhoven RF, Ernestam S, Geborek P, et al. Lancet 2009;374:459–66.

Table. Relative treatment effects concerning efficacy and radiographic endpoints in the MTX non-responder population

Endpoints	3 months		6 months		1 year		2 years	
	Fixed	Random	Fixed	Random	Fixed	Random	Fixed	Random
ACR70	1.27 (0.42, 4.10)	1.30 (0.17, 10.1)	0.35 (0.19, 0.64)[d]*	0.36 (0.16, 0.80)[d]*	0.55 (0.22, 1.31)	0.56 (0.13, 2.27)	0.82 (0.41, 1.63)	0.81 (<0.01, 428.2)
EULAR good response	0.94 (0.54, 1.63)	0.94 (<0.01-148.7)	0.61 (0.35, 1.07)	0.62 (<0.01, 353.3)	0.51 (0.29, 0.86)*	0.50 (<0.01, 249.2)	NA	NA
ACR50	0.55 (0.27, 1.08)	0.55 (0.18-1.61)	0.61 (0.41, 0.90)*	0.60 (0.13, 2.83)	0.51 (0.27, 0.96)*	0.50 (0.07, 3.61)	0.65 (0.37, 1.14)	0.65 (<0.01, 347.7)
ACR20	0.90 (0.52, 1.57)	0.90 (0.33, 2.50)	0.80 (0.57, 1.15)	0.75 (0.22, 2.52)	0.54 (0.32, 0.91)*	0.54 (0.08, 3.46)	0.75 (0.44, 1.24)	0.75 (<0.01, 405.1)
DAS28-ESR/CRP LDA	NA	NA	0.62 (0.38, <1.00)*	0.62 (<0.01, 90.0)	NA	NA	NA	NA
DAS28-ESR/CRP remission	NA	NA	0.52 (0.28, 0.95)*	0.52 (0.10, 2.56)	NA	NA	NA	NA
DDAS28-ESR/CRP	NA	NA	0.27 (-0.02, 0.56)	0.27 (-1.10, 1.65)	NA	NA	NA	NA
No radiographic progression	NA	NA	NA	NA	NA	NA	NA	NA
DmTSS	NA	NA	0.42 (-0.22, 1.06)	0.42 (-1.37, 2.18)	2.09 (-0.09, 4.26)	2.08 (-4.79, 8.90)	3.23 (0.39, 6.10)*	3.22 (-3.50, 10.0)
DJoint erosion	NA	NA	0.26 (-0.04, 0.56)	0.26 (-1.60, 2.17)	0.90 (-0.16, 1.98)	0.92 (-5.50, 7.33)	1.53 (0.05, 2.96)*	1.54 (-4.90, 7.96)
DJoint space narrowing	NA	NA	0.16 (-0.27, 0.59)	0.16 (-0.48, 0.81)	1.29 (0.04, 2.53)*	1.25 (-4.35, 6.86)	1.66 (>-0.01, 3.34)	1.66 (-4.82, 8.10)

[a]data presented as odds ratio (OR) (95% CI) or as mean (95% CI) from either a fixed effects or random effects model

[b]data presented as mean (95% CI) for all endpoints measuring mean change (D) from baseline

[c]OR<1 and mean>0 indicates a benefit towards the TNFi-MTX group (vs. triple therapy)

[d]pre-specified primary endpoint

*p<0.05

Disclosure: R. Fleischmann, Amgen Inc., 2,Amgen Inc., 5; **J. E. Pope**, Amgen Inc., 2,Amgen Inc., 5; **V. Tongbram**, Amgen Inc., 5; **D. Tang**, Amgen Inc., 3,Amgen Inc., 1; **J. Chung**, Amgen Inc., 1,Amgen Inc., 3; **D. Collier**, Amgen Inc., 1,Amgen Inc., 3; **S. Urs**, Amgen Inc., 5; **K. Ndirangu**, Amgen Inc., 5; **G. A. Wells**, Amgen Inc., 5; **R. F. van Vollenhoven**, AbbVie, Amgen, BMS, GSK, Pfizer, Roche, UCB, 2,AbbVie, Biotest, BMS, Celgene, Crescendo, GSK, Janssen, Lilly, Merck, Novartis, Pfizer, Roche, UCB, Vertex, 5.

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Abstract Number: 1643

Modified-Release Formulation of Tofacitinib: Evaluation of Pharmacokinetics Compared with Immediate-Release Tofacitinib and Impact of Food

Manisha Lamba[1], Rong Wang[1], Tracey Fletcher[2], Christine Alvey[1], Joseph Kushner[1] and Thomas Stock[2], [1]Pfizer Inc, Groton, CT, [2]Pfizer Inc, Collegeville, PA

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Background/Purpose: Tofacitinib is an oral Janus kinase inhibitor for the treatment of RA. A modified-release (MR) formulation has been designed to enable once daily (QD) dosing and achieve a comparable clinical profile to the approved 5 mg twice daily (BID) immediate-release formulation (IR). Two key clinical pharmacology studies have been conducted to evaluate pharmacokinetic (PK) performance of the MR formulation.

Methods: Two randomized, open-label, cross-over, Phase 1 studies were conducted in healthy volunteers (HV). HV were randomly assigned 1:1 to one of two treatment sequences in each study. In study A (Pfizer study A3921212), HV were given tofacitinib MR 11 mg QD or tofacitinib IR 5 mg BID under both single- and multiple-dose conditions to assess relative bioavailability (BA) of the MR formulation compared with the IR formulation. Duration of multiple-dose phase was 5 days. In study B (NCT0208475, Pfizer study A3921180) tofacitinib MR 11 mg single dose was given under fed and fasted conditions to

evaluate the impact of a high-fat meal on BA. HV were aged 18-55 years, with body mass index 17.5 30.5 kg/m^2, total body weight >50 kg, and no evidence of active or latent tuberculosis infection.

Results: In study A (N=24), MR and IR achieved maximum plasma concentration (C_{max}) at 4 hours and 0.5 hours post-dose, respectively; mean terminal half-life ($t_{1/2}$) was 5.9 and 3.2 hours, respectively. Area under the plasma-concentration time profile (AUC) and C_{max} after both single- and multiple-dose administrations were equivalent between MR and IR (Table 1); minimum plasma concentration was 29% lower for the MR formulation. In study B (N=24), maximum plasma concentrations were achieved 1 hour later in the presence of food. Mean $t_{1/2}$ was 4.4 and 5.5 hours, under fed and fasted conditions, respectively. AUC was essentially the same under fed and fasted conditions (Table 2). C_{max} increased by 27% under fed conditions (Table 2), and peak concentrations were achieved 1 hour later in the presence of food. Tofacitinib MR, under fasted and fed conditions, was well tolerated in both studies. Most reported adverse events (AEs) were mild and related to study treatment; AEs were similar in frequency and type for tofacitinib MR and IR.

Conclusion: The tofacitinib MR formulation given QD has equivalent AUC and C_{max} to the IR formulation given BID; C_{min} for MR is ~29% lower. Food does not impact the BA of tofacitinib from the MR formulation. Tofacitinib was well tolerated in both studies.

Table 1. Statistical comparison of tofacitinib PK parameters for tofacitinib MR 11 mg QD and tofacitinib IR 5 mg BID treatments during single- and multiple-dose phases (study A)

	Adjusted geometric means			
Parameter (units)	**Tofacitinib MR 11 mg QD (Test)**	**Tofacitinib IR 5 mg q12 (Reference)**	**Ratio (Test/Reference) of adjusted geometric means[a]**	**90% CI for ratio[a]**
Single-dose phase				
AUC_{inf}, ng·hr/mL	253.2	243.7	103.92	98.81, 109.28
C_{max}, ng/mL	35.98	39.22	91.75	83.27, 101.09
	Adjusted geometric means			
	Tofacitinib MR 11 mg QD (Test)	**Tofacitinib IR 5 mg BID (Reference)**	**Ratio (Test/Reference) of adjusted geometric means[a]**	**90% CI for ratio[a]**
Multiple-dose phase (steady-state)				
AUC_{24}, ng·hr/mL	268.5	263.4	101.94	97.79, 106.27
C_{max}, ng/mL	38.19	40.89	93.41	84.14, 103.69
C_{min}, ng/mL	1.044	1.478	70.64	59.01, 84.56

[a]The ratios (and 90% CIs) are expressed as percentages

AUC, area under the curve; AUC_{inf}, AUC from time zero to infinite time; AUC_{24}, AUC for time 0 to 24 hours; BID, twice daily; CI, confidence interval; C_{max}, maximal plasma concentration; C_{min}, minimum plasma concentration; IR, immediate-release; MR, modified-release; PK, pharmacokinetic; QD, once daily; q12, every 12 hours

Table 2. Statistical comparison of tofacitinib PK parameters following single doses of tofacitinib MR 11 mg under fasted and fed conditions (study B)

	Adjusted geometric means		**Ratio (Test/Reference) of adjusted geometric means[a]**	
Parameter (units)	**Tofacitinib MR 11 mg Fed (Test)**	**Tofacitinib MR 11 mg Fasted (Reference)**		**90% CI for ratio[a]**
AUC_{inf} (ng·hr/mL)	268.6	265.6	101.11	96.94, 105.46
C_{max} (ng/mL)	47.09	37.02	127.21	116.57, 138.83

[a]The ratios (and 90% CIs) are expressed as percentages

AUC, area under the plasma concentration-time profile; AUC_{inf}, AUC from time zero extrapolated to infinite time; CI, confidence interval; C_{max}, maximum plasma concentration; MR, modified release; PK, pharmacokinetic

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Disclosure: M. Lamba, Pfizer Inc, 1,Pfizer Inc, 3; **R. Wang**, Pfizer Inc, 1,Pfizer Inc, 3; **T. Fletcher**, Pfizer Inc, 1,Pfizer Inc, 3; **C. Alvey**, Pfizer Inc, 1,Pfizer Inc, 3; **J. Kushner**, Pfizer Inc, 1,Joseph Kushner, 3; **T. Stock**, Pfizer Inc, 1,Pfizer Inc, 3.

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Abstract Number: 1644

Routine Assessment of Patient Index Data 3 (RAPID3)-Defined Remission Is As Stringent As ACR/EULAR Boolean-Defined Remission in a Clinical Trial of Patients with Early Rheumatoid Arthritis Treated with Abatacept

Yusuf Yazici[1], KK Gandhi[2], E Alemao[2] and Daniel E. Furst[3], [1]NYU Hospital for Joint Diseases, New York, NY, [2]Bristol-Myers Squibb, Princeton, NJ,

[3]Medicine, University of California, Los Angeles, David Geffen School of Medicine, Los Angeles, CA
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Background/Purpose: Routine Assessment of Patient Index Data 3 (RAPID3) comprises the three patient-reported ACR RA Core Data Set measures: function (HAQ-DI), pain and patient global estimate of status (10-cm visual analog scale). These can be scored in <10 seconds, making RAPID3 suitable for use in routine clinical practice where it provides quantitative data to supplement qualitative assessments. Significant correlations between RAPID3 scores and DAS28 (CRP) and CDAI have been reported previously.[1,2] In this analysis, we examined time to first RAPID3 remission compared with time to first remission, as defined by other disease activity measures (DAS28 [CRP], CDAI, SDAI, Boolean). **Methods:** We performed *post hoc* analyses of data from AVERT, a Phase IIIb, randomized, active-controlled trial of 24 months, with a 12-month, double-blind treatment period, in which patients were randomized 1:1:1 to subcutaneous abatacept (ABA) + MTX, ABA monotherapy or MTX alone.[3] RAPID3 scores were calculated at baseline and 3-monthly intervals thereafter, up to 12 months. Definitions of remission were RAPID3 ≤3 (scale of 0–30), DAS28 (CRP) <2.6, CDAI ≤2.8, SDAI ≤3.3 and Boolean: TJC28 ≤1, SJC28 ≤1, patient global assessment of disease activity (0–10 cm) ≤1 and high-sensitivity CRP ≤1 mg/dL. Proportions of patients in RAPID3, DAS28 (CRP), CDAI, SDAI and ACR/EULAR Boolean remission at each time point were calculated. Proportions at 3, 6, 9 and 12 months were compared using cross-tabulation analysis. Agreement between RAPID3 disease activity states and those of other measures were assessed using kappa statistics. Time to first RAPID3 remission was compared with time to first remission, as defined by other disease activity measures (DAS28, CDAI, SDAI, Boolean) using Kaplan–Meier plots. **Results:** Among the total AVERT population, the percentages of patients in remission according to each measure at Month 12 were: RAPID3, 29.3%; Boolean, 28.8%; SDAI, 32.2%; CDAI, 33.6%; and DAS28 (CRP), 50.1%. For each treatment arm, good agreement was observed between RAPID3 and Boolean, SDAI and CDAI remission at Month 12 (0.45–0.67); these kappa correlations were higher than those with DAS28 (CRP) (0.19–0.48). The patterns of time to RAPID3 remission were most similar to Boolean and show that ABA + MTX and ABA monotherapy lead to a faster onset of remission than MTX alone (Figure).

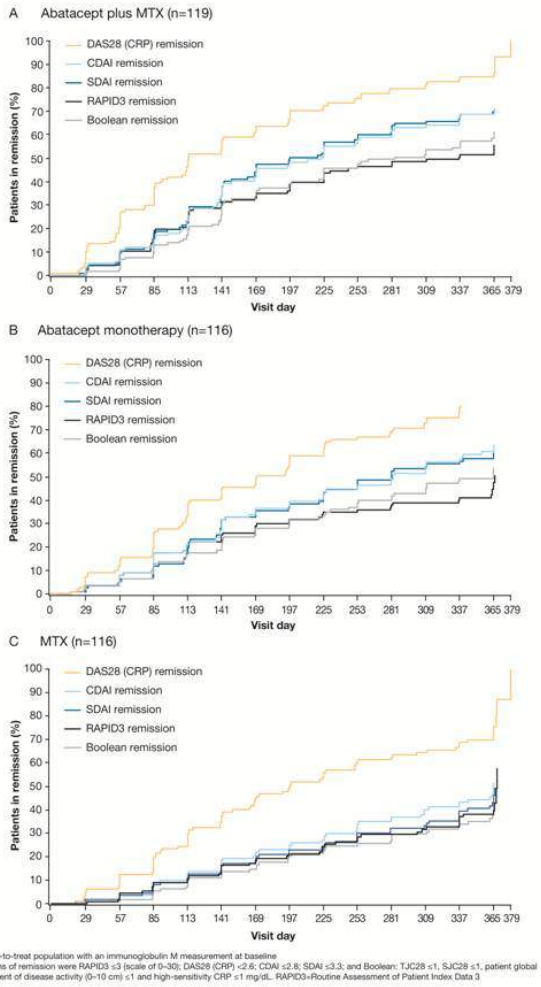
Conclusion: RAPID3-defined remission may be as stringent as ACR/EULAR Boolean-defined remission and agrees well with SDAI and CDAI remission criteria. RAPID3 may be used in clinical trials in addition to routine clinical care in early RA. In agreement with other remission criteria, abatacept results in a high rate of RAPID3-defined remission in early RA, with a faster time to remission than MTX.

1. Pincus T, et al. *J Rheumatol* 2011;**38**:2565–71.

2. Pincus T, et al. *J Rheumatol* 2008;**35**:2136–47.

3. Emery P, et al. *Ann Rheum Dis* 2015;**74**:19–26.

Figure. Kaplan–Meier Plot of Time to First Remission by Disease Activity Measures in Each Treatment Arm



Intention-to-treat population with an immunoglobulin M measurement at baseline
Definitions of remission were RAPID3 ≤3 (scale of 0–30); DAS28 (CRP) <2.6; CDAI ≤2.8; SDAI ≤3.3; and Boolean: TJC28 ≤1, SJC28 ≤1, patient global assessment of disease activity (0–10 cm) ≤1 and high-sensitivity CRP ≤1 mg/dL. RAPID3=Routine Assessment of Patient Index Data 3

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Abstract Number: 1645

Tofacitinib, an Oral Janus Kinase Inhibitor, in the Treatment of Rheumatoid Arthritis: Safety and Clinical and Radiographic Efficacy in Open-Label, Long-Term Extension Studies over 7 Years

Jürgen Wollenhaupt[1], Joel Silverfield[2], Eun Bong Lee[3], Ketti Terry[4], Kenneth Kwok[5], Irina Lazariciu[6], Chudy Nduaka[7], Carol A. Connell[4], Ryan DeMasi[5] and Lisy Wang[4], [1]Schoen-Klinik Hamburg-Eilbek Teaching Hospital of the University of Hamburg, Hamburg, Germany, [2]Healthpoint Medical Group, Tampa, FL, [3]Seoul National University, Seoul, South Korea, [4]Pfizer Inc, Groton, CT, [5]Pfizer Inc, New York, NY, [6]Quintiles, Saint-Laurent, QC, Canada, [7]Pfizer Inc, Collegeville, PA
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Background/Purpose: Tofacitinib is an oral Janus kinase inhibitor for the treatment of rheumatoid arthritis (RA). We report tofacitinib safety, tolerability, and clinical response over 84 months (mo), and radiographic data over 12 mo, in long-term extension (LTE) studies.

Methods: Data were pooled from two open-label studies (NCT00413699 [ongoing; database unlocked at March 2015 data-cut] and NCT00661661 [completed]) of patients (pts) with RA who completed randomized Phase (P)1, P2, or P3 tofacitinib studies. Pts received tofacitinib 5 or 10 mg BID as monotherapy or with background DMARDs; data from both doses ±background DMARDs were pooled. Baseline (BL) was that of P1/P2/P3 studies for pts enrolling ≤14 days after last dose, and start of LTE study for all other pts. For radiographic data, BL was last P1/P2/P3 study value. Primary endpoints: AEs and laboratory safety. Confirmed data are reported for decreased hemoglobin (Hgb), neutrophil and lymphocyte counts, and increases >50% from BL in creatinine. Secondary endpoints: ACR responses, DAS28-4(ESR), HAQ DI, and modified total Sharp score (mTSS). Safety data were included over 96 mo and efficacy data up to Mo 84 (n≤30 post-Mo 84).

Results: 4,867 pts were treated (mean [max] duration: 1,107 [2,895] days). BL data were from index studies for 90.9% of pts. Total tofacitinib exposure was 14,926 pt-years (py); 79.2% of pts maintained initial dose. In total, 2,132 pts (43.8%) discontinued (AEs: 1,051 [21.6%]; insufficient clinical response: 153 [3.1%]). Most common AE classes: infections and infestations (67.6%), musculoskeletal/connective tissue disorders (37.3%), and GI disorders (32.4%). Most common AEs: nasopharyngitis (18.1%), upper respiratory tract infection (16.2%), bronchitis (11.7%), and urinary tract infection (11.5%). Serious AEs occurred in 26.8% of pts (incidence rate [IR] 9.7/100 py [95% CI 9.2, 10.2]), and serious infection events (SIEs) in 8.4% of pts (IR 2.8/100 py [95% CI 2.5, 3.0]). Malignancies excluding NMSC were reported in 3.0% of pts (IR 1.0/100 py [95% CI 0.8, 1.1]). IRs for SIEs and malignancies through Mo 96 did not increase vs reported data through Mo 84.[1] Decreased Hgb (>30% decrease from BL/Hgb <8 g/dL) occurred in 6.8% of pts. Increased aminotransferases (>3 × ULN) occurred in 5.4% (ALT) and 3.1% (AST) of pts. Moderate to severe neutropenia (absolute neutrophil count [ANC] 0.5–1.5 × $10^3/mm^3$) was noted in 1.5% of pts; there were no confirmed cases of ANC <0.5 × $10^3/mm^3$. Confirmed absolute lymphocyte counts <0.5 × $10^3/mm^3$ occurred in 1.3% of pts. Increases >50% from BL in creatinine were seen in 2.4% of pts. ACR20, ACR50, and ACR70 response rates were sustained from Mo 1 (73.8%, 49.8%, and 29.3%) to Mo 84 (79.4%, 66.7%, and 46.0%). Mean DAS28 4(ESR) was 6.29 at BL, 3.74 at Mo 1, and 3.20 at Mo 84. Mean HAQ-DI score was 1.42 at BL, 0.81 at Mo 1, and 0.78 at Mo 84. Radiographic data were available for 1,099 pts. Mean mTSS was 24.0 at BL (last index value), 25.1 at Mo 6, and 24.3 at Mo 12. Mean change from BL in mTSS was 0.3 at Mo 6 and 0.2 at Mo 12.

Conclusion: Consistent safety and sustained efficacy over 84 mo was seen in pts with RA receiving tofacitinib 5 or 10 mg BID in LTE studies. Changes in mTSS were minimal at Mo 12 in LTE studies.

Reference: 1. Wollenhaupt J et al. *Arthritis Rheum* 2014; 66: S375.

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Abstract Number: 1646

Which Factors Influence the Prescription of Tocilizumab Alone or in Combination with Dmards in Rheumatoid Arthritis Patients in a Real Life Setting? the ACT-Solo Study: An Analysis of Efficacy and Safety at 12 Months

Jacques Tebib[1], Isabelle Idier[2], Mathieu Coudert[3], David Pau[4], Jean-Francis Maillefert[5] and Rene-Marc Flipo[6], [1]Rheumatology, Hospices Civils de Lyon, Centre Hospitalier Lyon-Sud, Pierre-Bénite, France, [2]Chugai Pharma, La Defense, France, [3]Statistics, Experis IT, Nanterre, France, [4]Statistics, Roche, Boulogne-Billancourt, France, [5]Rheumatology, University Hospital, Dijon, France, [6]Rheumatology, University Hospital, Lille, France
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Background/Purpose: Baseline factors influencing the use of tocilizumab (TCZ) in monotherapy (Mono) instead of combination with DMARDs (Combo) in real-life practice in RA patients (pts) as described previously in the ACT-Solo study were: no MTX over the past 2 years, past-history of severe infection, age ≥ 65 years and an increased DAS28[1]. Drug retention rate, efficacy and tolerance of TCZ at M12 with a focus on Mono and Combo are described here.

Methods: Prospective, multicenter, longitudinal, non-interventional 12-month study in RA pts requiring TCZ according to their physician. *Treatment:* TCZ as prescribed in real life. *Primary endpoint*[1]: Baseline factors influencing the use of TCZ in Mono or Combo. *Secondary endpoints*: drug retention rate, premature withdrawals, safety and efficacy. *Data collected*: pts characteristics at baseline and after TCZ initiation, monthly disease activity components, RA treatments. *Statistical analysis*: Efficacy population was pts fulfilling inclusion and non-inclusion criteria and with ≥1 TCZ infusion. Safety population was all pts with ≥1 TCZ infusion.

Results: 608 pts were recruited of whom 603 were analysed for safety and 577 (Total) for other endpoints. At baseline: mean age 57±13 years, 454 (79%) females, at least 1 co-morbidity: 409 (71%), mean RA duration: 11±9 years, RF or ACPA positive: 478 (86%), erosive disease: 435 (77 %), mean DAS28:

5.2±1.3. Past RA treatments included DMARDs + biologics in 75%, only DMARDs in 24%. MTX was previously prescribed in 95% of pts and in 71% within the last 2 years. TCZ Mono was initiated in 228 (40%) pts and TCZ Combo in 349 (60%) pts of whom 80% received MTX (mean 16±5mg/w). Steroids (GCs) were used in 386 (67%) pts (mean 10±7mg/d). 337 pts completed M12 visit. 194 pts withdrew for: AE 53 pts, inefficacy 88, patiens wish 12, lost to follow-up 23, other 18. At M12, drug retention rate was 69% in Total, 67% in Mono, 71% in Combo. Mean number of TCZ infusions was 9.4±4.1; mean time between infusions was 31.8 ±12.6 days. 29% of the pts experienced at least 1 discontinuation, 25% and 33% in Mono and Combo groups respectively. DMARD was added in 20 Mono and definitely stopped in 25 Combo pts. 170 (50%) pts remained on GCs, 66 (51%) in Mono group and 104 (50%) in Combo group. At M12, mean DAS28 in Total, Mono and Combo were 2.4±1.3, 2.4±1.3 and 2.3±1.2 respectively. DAS28 remission was 35% in Total, 35% and 36% in Mono and Combo respectively (p=0.83). Using propensity score, no effect of Mono was observed on drug retention HR= 1.194 [0.852,1.673], p=0.30 ; DAS remission OR= 1.111 [0.773,1.597], p=0.57; or GCs use OR= 0.880 [0.558,1.387], p=0.58 at M12. No new safety signal was reported. 325 (54%) patients had at least one AE, 74 (12%) had at least one serious AE with no differences between Mono and Combo.

Conclusion: At 12 months, drug retention rate was 69% in pts receiving TCZ in real life. In Total group mean DAS28 decreased from 5.2±1.3 to 2.35±1.26. No new safety signal occurred. Propensity scores showed no differences between Mono and Combo for drug retention, DAS remission or use of steroids. Safety was comparable in both groups.

This study was conducted thanks to an unrestricted grant from Roche Chugai France.

Ref.: 1. Maillefert et al. ACT SOLO EULAR 2014 SCIE-1154

Disclosure: J. Tebib, None; **I. Idier**, Chugai Employee, 3; **M. Coudert**, Roche Employee, 3; **D. Pau**, Roche Employee, 3; **J. F. Maillefert**, None; **R. M. Flipo**, Consultant for Roche and Chugai France, 5.

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Abstract Number: 1647

A Randomized, Clinical Trial to Assess the Relative Efficacy and Tolerability of Two Doses of Etoricoxib in Patients with Rheumatoid Arthritis

Kara Bickham[1], Désirée van der Heijde[2], Narinder Rawal[3], Joachim Sieper[4], Boyd Scott[5], Nancy Frontera[1], Sandhya Shah[1], Paul Stryszak[1], Dimitris Papanicolaou[1], Zoran Popmihajlov[1] and Paul Peloso[1], [1]Merck & Co., Inc., Kenilworth, NJ, [2]University Hospital, Maastricht, Netherlands, [3]Orebro University Hospital, Orebro, Sweden, [4]Rheumatology, Charite - Campus Benjamin Franklin, Berlin, Germany, [5]Merck Sharp & Dohme Corp., Whitehouse Station, NJ

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Background/Purpose:

Etoricoxib, a selective cyclooxygenase-2 (COX-2) inhibitor, provides symptom modification in RA patients. Previous dose-ranging studies in RA demonstrated the clinical efficacy of etoricoxib 90 mg vs placebo (PBO). In these studies, etoricoxib 60 mg demonstrated some clinically meaningful treatment effects, therefore the current study further evaluated the efficacy of etoricoxib 60 mg and 90 mg in RA.

Methods:

This was a 2-part, double-blind, PBO controlled study in RA. Part I (6 weeks) assessed the efficacy of etoricoxib 60 mg and 90 mg vs PBO. Part II (6 weeks) evaluated whether subjects with inadequate pain relief on etoricoxib 60 mg in Part I benefitted from increasing to etoricoxib 90 mg in Part II. Patients were ≥18 years of age, with a diagnosis of RA ≥6 months prior to screening and prior clinical response to NSAIDs. Patients were required to have a disease flare after NSAID washout prior to randomization. Eligible patients were randomized to one of four treatment groups: PBO in Part I; etoricoxib 60 mg in Part I & II; etoricoxib 60 mg in Part I followed by 90 mg in Part II; or etoricoxib 90 mg in Part I in a 2:7:7:8 ratio, respectively. Primary endpoints were Disease Activity Score evaluating 28 joints and C reactive protein level (DAS28-CRP) index and Patient Global Assessment of Pain (PGAP) score (0-100 mm VAS) after 6 weeks of treatment in Part I. Safety and tolerability measures included independent adjudication of all thrombotic cardiovascular and serious upper GI AEs.

Results:

In total, 1404 patients were randomized; 83.5% were female; the mean age was 53.8 years, 75.4% were Caucasian, 1228 patients completed Part I and 713 patients continued to Part II. Both 60 mg and 90 mg etoricoxib were superior to PBO for the treatment of RA on both primary efficacy endpoints: change from baseline DAS28-CRP score (Table 1A) and change from baseline PGAP score (Table 1B). For DAS28-CRP, there was no significant treatment difference between etoricoxib 90 mg and 60 mg (Table 1A). Etoricoxib 90 mg demonstrated a small, but statistically significant decrease in baseline PGAP score as compared to 60 mg (Table 1B). In Part II, inadequate pain responders did not experience a significant decrease in PGAP score after increasing the etoricoxib dose from 60 mg to 90 mg compared to inadequate pain responders who stayed on 60 mg (Table 1C). In both etoricoxib 90 mg and 60 mg groups, the incidence of SAEs and drug-related AEs were similar between the two treatment groups.

Conclusion:

Both etoricoxib 90 mg and 60 mg are superior to PBO in relieving the symptoms of RA. Etoricoxib 90 mg vs 60 mg resulted in a statistically significant, though small, improvement in PGAP score, but not DAS28-CRP. Dose escalation from 60 mg to 90 mg in pain inadequate responders did not significantly improve efficacy. Both etoricoxib 90 mg and 60 mg were well tolerated and no new safety signals were identified.

A:Part I: DAS 28-CRP index time-weighted average change from baseline over 6 weeks

Treatment	N	LS Mean change†	Between etoricoxib and placebo		Between etoricoxib doses	
			Difference in LS mean† change† (95% CI)	p-value†	Difference in LS mean† change† (95% CI)	p-value†
Placebo	103	-1.10				
Etoricoxib 60 mg	732	-1.39	-0.29 (-0.49, -0.09)	0.004		
Etoricoxib 90 mg	426	-1.37	-0.27 (-0.48, -0.06)	0.034	0.02 (-0.10, 0.14)	0.730

B: Part I Patient Global Assessment of Pain (VAS) time weighted average change from baseline over 6 weeks

Treatment	N	LS Mean change†	Between etoricoxib and placebo		Between etoricoxib doses	
			Difference in LS mean† change† (95% CI)	p-value†	Difference in LS mean† change† (95% CI)	p-value†
Placebo	108	-20.26				
Etoricoxib 60 mg	751	-28.25	-7.99 (-11.85, -4.13)	<0.001		
Etoricoxib 90 mg	430	-30.96	-10.70 (-14.74, -6.66)	<0.001	-2.71 (-4.98, -0.45)	0.019

C: Part II: Average Change from Week 6 at Weeks 10 and 12 in Patient Global Assessment of Pain (VAS) Among Pain Inadequate Responders From Part I (Modified Intention-to-Treat Population)

Treatment	N	LS Mean (95% CI)	Difference in LS Mean (80% CI)	p-Value†
Etoricoxib 60 mg/60 mg	188	-11.96 (-14.96, -8.97)		
Etoricoxib 90 mg/90 mg	187	-10.35 (-13.32, -7.39)	1.61 (-0.49, 3.71)	0.327

†The LS means and p-values were derived from the analysis of covariance model with terms for treatment, biologics use, and baseline value as a covariate. Comparisons to placebo were based on Tukey-Ciminera-Heyse trend test with a step-down procedure

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Abstract Number: 1648

The Balance of Foxp3/Ror-Gammat Expression Is Altered By Tocilizumab and By Abatacept in Patients with Rheumatoid Arthritis

Yoshifumi Tada[1], Syuichi Koarada[2], Nobuyuki Ono[2], Akihito Maruyama[2], Satoko Tashiro[2], Yukiko Tokuda[2], Yukihide Ono[2], Yoshinobu Nakao[2] and Akihide Ohta[3], [1]Department of Internal Medicine, Division of Rheumatology, Saga University, Saga, Japan, [2]Rheumatology, Saga University, Saga, Japan, [3]Department of Adult and Gerontological Nursing, Saga University School of Medicine, Saga, Japan

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Background/Purpose: It has been shown that the balance between Th17 cells and regulatory T (Treg) cells plays an important role for the development of autoimmune diseases including rheumatoid arthritis (RA). Th17 cells secrete IL-17 and generally promote autoimmunity, whereas Treg cells interact with a various cells and regulate autoimmunity and inflammation. Recent studies showed that the treatment with abatacept (ABT) or tocilizumab (TCZ) affected the population of Th17 cells and Treg cells in patients with RA. Although not unanimously approved, several reports showed that Treg cells are decreased by ABT and increased by TCZ, and that Th17 cells are decreased by TCZ. To further investigate the effect of ABT and TCZ on the skewing of T cells, we analyzed the expression of master regulators of helper T cell lineages, in patients with RA treated with ABT or TCZ.

Methods: Ten patients treated with ABT and 9 patients treated with TCZ were enrolled. All patients met the 2010 ACR/EULAR classification criteria. Total RNA was extracted from peripheral blood cells at baseline, and after 12 weeks and 24 weeks of therapy. The expression levels of T-bet, GATA3, Foxp3 and Ror-γt were measured by real-time PCR using Light Cycler 480. Because of different T cell counts in each sample, relative expression levels were expressed as the ratios of two genes (T-bet/GATA3, Foxp3/GATA3, Foxp3/T-bet, Foxp3/Ror-γt, Ror-γt/T-bet, Ror-γt/GATA3). And the changes in these ratios (the ratios at baseline were defined as 1.00) were determined. This study was approved by the local ethics committee, and written informed consent was obtained from all patients.

Results: In patients treated with ABT, the mean DAS28CRP was 3.92 before treatment, and 5 patients achieved remission or low disease activity, whereas in patients treated with TCZ, the mean CDAI was 14.7 before treatment, and 8 patients achieved remission. The Foxp3/Ror-γt ratio was decreased after ABT therapy (0.67 ± 0.16 (0.33 to 0.91) at 24 weeks, p=0.0034), but was increased after TCZ therapy (2.00 ± 1.03 (0.63 to 3.47) at 24 weeks, p=0.0035).

In addition, the Ror-γt/GATA3 ratio was decreased after TCZ therapy (0.78 ± 0.39 (0.29 to 1.70) at 24 weeks, p=0.0029). Except for these, no significant skewing was observed. No significant relationships between clinical response to the treatment and the changes in the ratios were detected.

Conclusion: The treatment with TCZ or ABT differently affected the balance of Foxp3/Ror-γt expression in the peripheral blood of patients with RA.

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Abstract Number: 1649

Long-Term Safety and Efficacy of Olokizumab in Patients with Moderate-to-Severe Rheumatoid Arthritis Who Have Previously Failed Anti-TNF Treatment

Mark C. Genovese[1], Roy Fleischmann[2], Yoshiya Tanaka[3], Daniel E. Furst[4], Hisashi Yamanaka[5], Rajesh Joshi[6], Wei Zhu[7], Jing Shao[8], Hideki Mashimo[8] and Tsutomu Takeuchi[9], [1]Division of Rheumatology, Stanford University Medical Center, Palo Alto, CA, [2]Metroplex Clinical Research Center, University of Texas Southwestern Medical Center, Department of Medicine, Dallas, TX, [3]The First Department of Internal Medicine, University of Occupational and Environmental Health, Kitakyushu, Japan, [4]Medicine, University of California, Los Angeles, David Geffen School of Medicine, Los Angeles, CA, [5]Institute of Rheumatology, Tokyo Women's Medical University, Tokyo, Japan, [6]Quintiles Inc., Mumbai, India, [7]UCB Pharma, Raleigh, NC, [8]UCB Pharma, Tokyo, Japan, [9]Keio University School of Medicine, Tokyo, Japan

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Background/Purpose:

Olokizumab (OKZ) is a humanized anti-interleukin-6 monoclonal antibody in development for moderate-to-severe rheumatoid arthritis (RA) treatment. OKZ efficacy and safety were assessed in the 12-week (wk) randomized controlled trials (RCTs) RA0056 (NCT01242488) and RA0083 (NCT01463059), which enrolled Western and Asian RA patients respectively, who had failed previous anti-TNF therapy. OKZ significantly reduced disease activity vs placebo (PBO).[1] Here we report results from the open-label extension (OLE) studies of these RCTs, RA0057 (NCT01296711) and RA0089 (NCT01533714).

Methods:

In the RCTs, RA pts on MTX who had failed anti-TNF therapy were recruited from Belgium, the US and the UK (RA0056), and Japan, Korea and Taiwan (RA0083). Pts received PBO, subcutaneous (sc) OKZ 60/120/240 mg every 2 weeks (Q2W) or 4 weeks (Q4W) (240 mg Q2W in RA0056 only), or (in RA0056 only) intravenous tocilizumab (TCZ) 8 mg/kg Q2W. Completers were eligible for the OLEs, in which all pts received sc OKZ 120 mg Q2W + MTX (RA0057: 12.5–25.0 mg/wk to Wk 12, after which dose could be reduced; RA0089: 6-16 mg/wk in Japan, 7.5-20 mg/wk in Korea and Taiwan). Pts with ongoing serious adverse events (SAEs) were excluded.

The primary objective of both studies was to assess long-term safety of OKZ; secondary objectives were to assess long-term efficacy by change from OLE baseline (BL) in Disease Activity Score 28 C-reactive protein (DAS28[CRP]) (4-variable). RA0057 was planned to run for 5 years, RA0089 to marketing application approval. Both OLEs were prematurely terminated when the drug was partnered: data are available to Wk90 in RA0057 and Wk89 in RA0089. Pts receiving ≥6 months' OL treatment are considered completers. Data are reported for the full analysis set (all pts who received ≥1 dose of OKZ with ≥1 efficacy measurement in the OLE).

Results:

198 pts completed RA0056; 190 (114 OKZ, 40 PBO, 36 TCZ) enrolled in RA0057. 105 pts completed RA0083; 103 (79 OKZ, 24 PBO) enrolled in RA0089. 67 (35.3%) pts completed RA0057 (median [min–max] exposure: 51 [0–98] wks); 82 (79.6%) pts completed RA0089 (median [min–max] exposure: 40 [0–76] wks) (Table).

Treatment-emergent (TE) AEs occurred in 180 (94.7%) and 91 (88.3%) pts in RA0057 and RA0089 respectively; TEAEs and serious TEAEs are summarized in the Table.

Efficacy measures continued to improve in the OLEs, most notably, as expected, in PBO pts switching to OKZ. Disease activity in each treatment group was as follows: Wk48 mean DAS28[CRP] change from BL in RA0057: PBO: -1.76, OKZ:-0.60, TCZ: -0.43; in RA0089: PBO: -1.70, OKZ:-0.68. Data past Wk48 were not interpreted due to low pt numbers.

Conclusion:

OKZ was well-tolerated, with an expected safety profile for this class of agent. Reductions in disease activity were sustained to Wk48. These results support the development of OKZ for the treatment of moderate-to-severe RA in Western and Asian pts.

References:

1. Genovese M. Ann Rheum Dis 2014;73(9):1607–14

Table: Patient disposition and adverse events in the RA0057 and RA0089 studies

	RA0057 (N=190)		RA0089 (N=103)	
	Patients n (%) [a]	Events	Patients n (%) [a]	Events
Patient disposition				
Patients enrolled	190 (100.0)	-	103 (100.0)	-
Patients randomized	190 (100.0)	-	102 (99.0)	
Completed study [b]	67 (35.3)	-	82 (79.6)	-
Prematurely withdrawn	123 (64.7)	-	21 (20.4)	-
AE	32 (16.8)	-	8 (7.8)	-
Lack of efficacy	13 (6.8)	-	1 (1.0)	-
Protocol violation	2 (1.1)	-	0	-
Lost to follow-up	10 (5.3)	-	0	-
Consent withdrawn (not due to adverse event)	14 (7.4)	-	3 (2.9)	-
Other (including study termination)	52 (27.4)	-	9 (8.7)	-
OKZ exposure				
<12 months	95 (50.0)	-	82 (79.6)	-
≥12 months and <18 months	59 (31.1)	-	21 (20.4)	-
≥18 months and <24 months	36 (19.0)	-	0	-
MedDRA System Organ Class Preferred Term				
TEAEs [c]	180 (94.7)	1642	91 (88.3)	646
Infections and infestations	130 (68.4)	361	67 (65.0)	156
Urinary tract infection	28 (14.7)	64	4 (3.9)	4
Upper respiratory tract infection	36 (18.9)	48	9 (8.7)	17
Bronchitis	21 (11.1)	25	4 (3.9)	5
Sinusitis	19 (10.0)	21	1 (1.0)	1
Nasopharyngitis	18 (9.5)	26	34 (33.0)	47
Musculoskeletal and connective tissue disorders	91 (47.9)	200	21 (20.4)	27
Arthralgia	22 (11.6)	36	2 (1.9)	2
Back pain	23 (12.1)	24	2 (1.9)	2
Rheumatoid arthritis	21 (11.1)	24	0	0
Gastrointestinal disorders	68 (35.8)	124	46 (44.7)	85
Diarrhoea	19 (10.0)	21	7 (6.8)	8
Stomatitis	2 (1.1)	2	13 (12.6)	23
Gastric Perforation	1 (0.5)	1	0	0
General disorders and administration site conditions	65 (34.2)	195	19 (18.4)	74
Injection site reaction	21 (11.1)	30	3 (2.9)	5
Respiratory, thoracic, and mediastinal disorders	60 (31.6)	109	24 (23.3)	33
Cough	25 (13.2)	33	9 (8.7)	13
Serious TEAEs	50 (26.3)	82	14 (13.6)	20
Infections and infestations	19 (10.0)	24	7 (6.8)	7
Neoplasms benign, malignant and unspecified [d]	6 (3.2)	8	1 (1.0)	1
TEAEs leading to discontinuation of OKZ	33 (17.4)	33	7 (6.7)	7
Deaths [e]	2 (1.1)	2	0	0

[a] All percentages are based on number of subjects enrolled [b] Both studies were prematurely terminated for further drug development, unrelated to safety or efficacy; [c] TEAEs occurring in ≥10% of pts in the safety set in either OLE by preferred term, and those considered of special interest, are listed; [d] including cysts and polyps; [e] One death due to road traffic accident (deemed unrelated to study drug), one death in a pt with multiple comorbidities after discontinuation of study drug, due to necrotizing fasciitis, acute renal failure, multi-system organ failure and sepsis. Necrotizing fasciitis and sepsis were deemed related to study drug; acute renal failure and multi-system organ failure were deemed unrelated to study drug.
TEAE: Treatment emergent adverse event.

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Abstract Number: 1650

Tocilizumab Monotherapy in Early Rheumatoid Arthritis: Data from Two Phase 3 Randomized Controlled Trials

Gerd Burmester[1], Attila Pethö-Schramm[2], Caroline Keane[3] and Graeme Jones[4], [1]Department of Rheumatology and Clinical Immunology, Charité - Universitätsmedizin Berlin, Berlin, Germany, [2]F. Hoffmann-La Roche, Basel, Switzerland, [3]Roche Products Ltd., Welwyn Garden City, United Kingdom, [4]Menzies Institute for Medical Research, University of Tasmania, Hobart, Australia

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Background/Purpose: Disease remission is the current treatment goal for patients (pts) with early RA (eRA). Initiation of an anti-TNF agent ± methotrexate (MTX) is recommended for pts with severe eRA of poor prognosis.[1] Data from 2 phase 3 clinical trials, FUNCTION[2] and AMBITION,[3] have shown the efficacy of tocilizumab (TCZ) in eRA pts, and TCZ was recently approved in the Europe Union for the treatment of severe, active, progressive RA in MTX-naive pts.[4] Data from the 2 phase 3 trials on TCZ and MTX as monotherapy in eRA pts are presented.

Methods: In FUNCTION, MTX-naive pts with active RA of ≤2 years' duration received intravenous (IV) TCZ 8 mg/kg (TCZ8) + oral MTX, IV TCZ8 monotherapy, IV TCZ 4 mg/kg + oral MTX, or oral MTX monotherapy. In AMBITION, pts with moderate to severe RA who were MTX naive or had not received MTX for ≥6 months received IV TCZ8 or oral MTX as monotherapy. Twenty-four-week data are included from FUNCTION pts who received TCZ8 or MTX monotherapy and from AMBITION pts with RA of ≤2 years' duration (exploratory subanalysis). Key efficacy end points are remission rates based on Disease Activity Score using 28 joints (DAS28-erythrocyte sedimentation rate [ESR] <2.6), American College of Rheumatology (ACR) response, and physical function assessed by Health Assessment Questionnaire–Disability Index (HAQ-DI) at week 24.

Results: Included were 241 AMBITION pts (mean RA duration, 0.7 years) and 579 FUNCTION pts (mean RA duration, 0.4-0.5 years). Baseline characteristics were similar across pt groups analyzed except that all FUNCTION pts were MTX naive and had low previous rates of DMARD use, whereas 89.2% of the AMBITION eRA subpopulation were MTX naive and had greater previous rates of DMARD use (Table 1). Across both studies, greater proportions of pts receiving TCZ8 than receiving MTX achieved DAS28-ESR remission (Table 2). The difference between arms was statistically significant in FUNCTION, and the weighted difference in response for TCZ8 compared with MTX was 22.4% in AMBITION, which is similar to the corresponding value in FUNCTION (Table 2). In both studies, ACR response rates were similar or numerically greater with TCZ8 than with MTX, and change from baseline in HAQ-DI score was numerically higher with TCZ8 than with MTX (Table 2). Safety of TCZ8 in the eRA population in FUNCTION and AMBITION was consistent with the known safety profile of TCZ.

Table 1. Baseline Characteristics (ITT population)

	FUNCTION		AMBITION Early RA Subpopulation[a]	
	MTX n = 287	TCZ8 n = 292	MTX n = 125	TCZ8 N = 116
Age, years, mean (SD)	49.6 (13.0)	49.9 (13.2)	49.3 (13.2)	48.1 (14.8)
Female, n (%)	229 (80)	219 (75)	94 (75)	89 (77)
MTX naive, n (%)	287 (100)	292 (100)	110 (88)	105 (91)
Previous DMARDs, n, mean (SD)[b]	0.2 (0.4)	0.3 (0.5)	0.4 (0.8)	0.4 (0.7)
DAS28-ESR, mean (SD)	6.6 (1.0)	6.7 (1.0)	6.8 (0.9)	6.6 (1.0)
HAQ-DI, mean (SD)	1.48 (0.66)[c]	1.58 (0.67)[d]	1.5 (0.64)[e]	1.5 (0.67)
RF+, n (%)	254 (89)	262 (90)[f]	87 (70)	80 (69)
CRP, mg/dL, mean (SD)	2.31 (2.67)	2.48 (3.19)	3.62 (4.07)	3.27 (3.56)
Oral CS use, n (%)	109 (38)	118 (40)	53 (42)	52 (45)

ITT, intent-to-treat.
[a]Exploratory subanalysis in patients in AMBITION who had RA for ≤2 years at baseline. [b]Includes tumor necrosis factor inhibitors for AMBITION pts. [c]n = 284. [d]n = 289. [e]n = 124. [f]n = 291.

Table 2. Efficacy at Week 24 (ITT population)

	FUNCTION		AMBITION Early RA Subpopulation[a]	
	MTX n = 287	TCZ8 n = 292	MTX n = 125	TCZ8 N = 116
DAS28-ESR remission (<2.6), n (%) [95% CI]	43 (15.0) [10.9, 19.1]	113 (38.7)[c] [33.1, 44.3]	20 (16.0) [9.6, 22.4]	43 (37.1) [28.3, 45.9]
Weighted difference vs MTX (95% CI)	23.9 (17.0, 30.9)		22.4 (10.0, 34.7)	
ACR20, n (%)[b]	187 (65.2)	205 (70.2)	75 (60.0)	85 (73.3)
Weighted difference vs MTX (95% CI)	0.05 (–0.02, 0.13)		0.16 (0.03, 0.28)	
ACR50, n (%)[b]	124 (43.2)	139 (47.6)	51 (40.8)	62 (53.4)
Weighted difference vs MTX (95% CI)	0.05 (–0.03, 0.13)		0.16 (0.03, 0.28)	
ACR70, n (%)[b]	73 (25.4)	88 (30.1)	24 (19.2)	41 (35.3)
Weighted difference vs MTX (95% CI)	0.05 (–0.02, 0.12)		0.16 (0.04, 0.29)	
HAQ-DI mean change from baseline	–0.61 n = 246	–0.65 n = 265	–0.73 n = 110	–0.88 n = 104
Weighted difference vs MTX (95% CI)	–0.04 (–0.14, 0.06)		–0.15 (–0.30, 0.00)	
HAQ-DI categorical change ≥0.3, n/N (%)	148/214 (69.2)	170/230 (73.9)	79/110 (71.8)	79/104 (76.0)

ITT, intent-to-treat.
[a]Exploratory subanalysis in patients in AMBITION who had RA for ≤2 years at baseline.
[b]Patients who withdrew were classified as nonresponders.
[c]$p < 0.0001$.

Conclusion: These findings demonstrate the efficacy of IV TCZ8 as monotherapy in phase 3 clinical trials in pts with eRA who are primarily MTX naive. In these pts, TCZ8 had a safety profile consistent with that reported in patients with more advanced disease.

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Abstract Number: 1651

Comparison of Oral Glucocorticoid (OGC)-Sparing Effects in Tocilizumab and Other Biologic Dmards Using Multilevel Models in an Administrative Health Care Claims Database

Brandon Arnieri[1], Khaled Sarsour[1], David Oliveri[1], Attila Pethö-Schramm[2], Avani Shah[1] and George Quartey[1], [1]Genentech, South San Francisco, CA, [2]F. Hoffmann-La Roche, Basel, Switzerland

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Background/Purpose : The current treatment paradigm in rheumatoid arthritis (RA) is to attempt to decrease, when clinically feasible, concomitant use of OGCs after their use as part of the initial therapeutic approach. This study examined OGC-sparing effects of tocilizumab (TCZ) and RA biologics used second-line (BDM2) in RA patients (pts) treated with combination therapies and monotherapies.

Methods: This was a retrospective cohort study performed using the Truven MarketScan administrative claims database. RA pts were identified as those with an RA diagnosis (ICD-9-CM: 714.xx excluding 714.3x) followed by confirmatory RA diagnosis in 7-365 days or confirmatory DMARD procedure or prescription any time after the initial RA diagnosis. Pts had to be ≥18 y at the time of RA index date and continuously enrolled around the RA index date. Pts were then split into 2 treatment groups: TCZ treated and BDM2 treated, not including TCZ. Cohort demographic characteristics and treatment history were analyzed. OGC use and dosing were investigated during several time frames with respect to index therapy initiation. OGC doses were calculated using a prednisone-equivalent dose for each medication. A multilevel random coefficient model was used to test for statistically significant OGC-sparing effects of TCZ compared with BDM2 over time while adjusting for baseline OGC use, comorbidities, and demographics.

Results: The analysis population comprised 10,402 pts (2604 in TCZ initiator cohort, 8209 in BDM2 comparator cohort). Mean age at RA diagnosis was similar between the cohorts (51.0 vs 51.2 y). More women were observed in the TCZ cohort (81.2% vs 77.1%). Mean baseline Charlson Comorbidity Index (CCI) scores and individual comorbidities were higher in the TCZ cohort (2.6 vs 2.3). Mean baseline cumulative OGC dose was higher for TCZ than BDM2 (1988 mg vs 1616 mg). In multivariate results, there was a significant reduction in OGC use in both cohorts over time (b=0.177 mg/d; $p<0.000$). There was a significant time × cohort interaction such that the TCZ cohort had an additional reduction of 0.167 mg/d ($p<0.0001$). In the TCZ cohort, mean OGC dose decreased over time from 4.6 mg/d in months 1-3 to 1.2 mg/d in months 27-30, a 74% reduction. In the BDM2 cohort, mean OGC use decreased from 3.3 mg/d to 1.4 mg/d, a 58% reduction in the same period. Factors significantly associated with greater OGC use over time included baseline comorbidities as measured by the CCI (b=0.85, $p<0.0001$), female sex (b=0.99, $p<0.000$), and baseline OGC dose (b=0.78 mg/d, $p<0.0001$). Similar results were observed when we restricted the analysis to pts on monotherapy though the sample size was smaller.

Conclusion: In this large cohort of RA pts, initiators of TCZ had greater mean starting and cumulative baseline OGC doses and higher mean CCIs than initiators of other RA biologics previously treated with bDMARDs, implying that historically they might have been more difficult to treat. We found statistically significant OGC-sparing effects in RA pts treated with TCZ and BDM2. TCZ use was associated with significantly quicker and relatively more pronounced taper of OGC than BDM2. The clinical implications of such OGC-sparing effects warrant further investigation.

Disclosure: B. Arnieri, F. Hoffmann-La Roche, 1,F. Hoffmann-La Roche, 3; **K. Sarsour**, Roche, 1,Roche, 3; **D. Oliveri**, Genentech, 3; **A. Pethö-Schramm**, F. Hoffmann-La Roche, 3,F. Hoffmann-La Roche, 1; **A. Shah**, Roche, 3; **G. Quartey**, Roche, 1,Genentech, 3.

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Abstract Number: 1652

A HPLC-SRM-MS Based Method for the Detection of Adherence to Low-Dose Oral Methotrexate

James Bluett[1], Thierry Wendling[2], Kayode Ogungbenro[2], Isabel Riba-Garcia[3], Richard Unwin[3], Suzanne M. Verstappen[4] and Anne Barton[5,6], [1]Arthritis Research UK Centre for Genetics and Genomics, The University of Manchester, Manchester, United Kingdom, [2]Centre for Applied Pharmacokinetic Research, Manchester Pharmacy School, The University of Manchester, Manchester, United Kingdom, [3]Centre for Advanced Discovery and Experimental Therapeutics (CADET), Central Manchester University Hospitals NHS Foundation Trust, Manchester Academic Health Sciences Centre, Manchester, United Kingdom, [4]Arthritis Research UK Centre for Epidemiology, The University of Manchester, Manchester, United Kingdom, [5]Arthritis Research UK Centre for Genetics and Genomics, University of Manchester, Manchester, United Kingdom, [6]NIHR Manchester Musculoskeletal Biomedical Research Unit, Central Manchester Foundation Trust and University of Manchester, Manchester Academy of Health Sciences, Manchester, United Kingdom

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Background/Purpose:

Whilst methotrexate (MTX) is the first-line treatment of rheumatoid arthritis (RA), response is not universal. Rates of adherence reported in the literature range from 59% to 107% and non-adherence is associated with poor treatment response. There is no gold standard measurement of adherence and currently no biochemical test of MTX levels in blood samples is available to objectively assess adherence. The aim, therefore, was i) to develop a liquid chromatography-selected reaction monitoring mass spectrometry (HPLC-SRM-MS) method to measure the concentrations of both MTX and its major metabolite 7-OH-MTX in plasma; ii) to apply the assay to a cohort of patients with RA undergoing MTX therapy and iii) to develop a population pharmacokinetic model to explore the relationship of MTX ingestion with ability to detect the analytes over time.

Methods:

A HPLC-SRM-MS method to detect MTX and 7-OH-MTX was developed according to the European Medicines Agency guidelines. RA patients (n=20) using oral MTX were admitted for 24 hours and on 2 subsequent days within 7 days of MTX administration. Nine blood samples were taken during the study period to measure MTX and 7-OH-MTX levels in plasma. All samples were analysed in triplicate, and the data were used to develop a population pharmacokinetic model. Effects of covariates (body weight and serum creatinine levels) on the model parameters were tested. Finally, simulations were performed to predict the proportion of patients with detectable concentrations of both MTX and 7-OH-MTX over time.

Results:

Twenty RA patients (65% female) completed the study with median (IQR) age of 66 (56-70) years, serum creatinine 72 (68-79) umol/l and weight 77 (68-84) kg. MTX dose ranged from 7.5 to 25mg. The lower limit of quantification for MTX and 7-OH-MTX was 0.5 and 0.75nM respectively. The model that best described the plasma concentration-time data was a two-compartment model with a first-order absorption process for MTX, and one linked compartment for 7-OH-MTX. Bodyweight was included as a covariate. The effect of serum creatinine levels on the systemic clearance of MTX was negligible. Inter-subject variability could be estimated for all parameters and appeared to be highest for the absorption parameter. The simulations suggest that after administration of 15 mg of MTX, approximately 70% of patients will have detectable MTX plasma concentrations 144 hours (6 days) post-dose (figure 1) but that the optimal time for testing would be within 60 hours (10% undetectable).

Conclusion:

A HPLC-SRM-MS assay to measure MTX and 7-OH-MTX levels in patients on low dose MTX has been developed. A population pharmacokinetic model of plasma MTX and 7-OH-MTX levels can be used as a qualitative tool to evaluate patients' adherence to treatment.

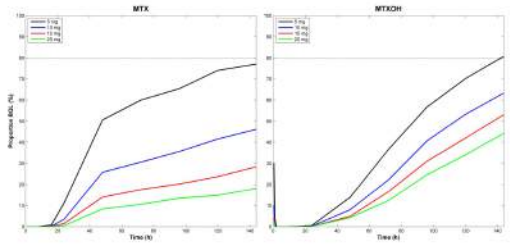

Figure 1. Simulated (n=1000) expected proportion of subjects with undetectable MTX/7-OH-MTX levels over time after administration of different oral MTX doses.

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Abstract Number: 1653

Trends over Time in Achievement of Low Disease Activity Among Biologic Initiators with Rheumatoid Arthritis

Leslie Harrold[1,2], J. Lynn Palmer[3], Jeffrey R. Curtis[4], Jeffrey D. Greenberg[2,5] and Joel M. Kremer[6], [1]University of Massachusetts Medical School, Worcester, MA, [2]Corrona, LLC, Southborough, MA, [3]Corrona Research Foundation, Albany, NY, [4]University of Alabama at Birmingham, Birmingham, AL, [5]NYU School of Medicine, New York, NY, [6]Albany Medical College and The Center for Rheumatology, Albany, NY

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Background/Purpose: There is a growing emphasis on treating patients to a target level of low disease activity (LDA) or remission to order to improve outcomes associated with rheumatoid arthritis (RA). Our objective was to examine trends in the achievement of LDA over the past decade among RA patients initiating their first biologic agent.

Methods: Using the Corrona registry, we identified new initiators of biologic therapy in distinct periods of calendar time over the last decade (2002-2004, 2005-2007, 2008-2010, 2011-2013) with moderate or high disease activity at the time of the initiation based on the Clinical Disease Activity Index (CDAI >10), and a follow-up CDAI measured at 1 year (+/- 3 months). The primary outcome was achievement of LDA (CDAI ≤ 10) at 12 months with the secondary outcome being change in CDAI. Trends over time between the groups were examined using Chi square tests or Kruskal Wallis test as appropriate. Multivariable linear and logistic regression models were performed to model the association between time period and the outcome of interest.

Results: We identified 2,597 biologic initiators who met inclusion criteria (2002-2004: 238; 2005-2007: 569; 2008-2010: 640; 2011-2013: 1150). The majority of patients were female (70-78%) with a mean age of 57-58. Patients in the later time periods were more often nonwhite (Groups 1-4: 15% vs. 14% vs. 20% vs. 19%; p=0.02), had a greater body mass index (Groups 1-4: 27.7 vs. 28.8 vs. 27.8 vs. 29.2, p=0.0005), fewer years of RA disease duration (Groups 1-4: 7 vs. 5 vs. 3 vs. 3, p<0.0001), and less concomitant prednisone use (Groups 1-4: 40% vs. 33% vs. 33% vs. 30%, p=0.03). Unadjusted rates of LDA increased over time with 44% in 2002-2004 to 51% in 2011-2013 (Table 1). Adjustment for baseline disease characteristics revealed an increased likelihood of LDA in the later time periods (2008-2010 and 2011-2013). The unadjusted mean improvement in CDAI ranged from 12.2 to 13.6, which exceeds the minimally clinically important difference. There was a greater reduction in CDAI over the successive time periods, although not significant. In the adjusted models, those treated in 2008-2010 had a greater decrease in CDAI as compared to those treated in 2002-2004.

Conclusion: Using the U.S. Corrona registry, the proportion of RA patients achieving LDA when initiating a biologic in moderate or high disease activity has increased over time. Since 2005 treatment with biologics has resulted in >50% of patients reaching LDA by 12 months. Additional investigation is needed to understand the factors contributing to the trend in improved disease control, such as availability of new therapeutic agents, more treatment accelerations by providers and greater acceptance of medications by patients, in order to inform efforts to further increase the proportion of patients who achieve LDA.

Table 1.

	Year Category				
	2002-2004	2005-2007	2008-2010	2011-2013	P value for trend
Total N=2597	238	569	640	1150	
Primary Outcomes: Achievement of LDA N (%)					
Unadjusted N (%)	105 (44%)	292 (51%)	371 (58%)	590 (51%)	0.0016
Adjusted* OR (95% CI)	1	1.49 (0.99,2.25)	2.08 (1.38,3.15)	1.72 (1.15,2.56)	
Secondary outcomes: Mean change in CDAI					
Unadjusted, mean change in CDAI (std dev)	-12.2 (14.8)	-13.2 (13.7)	-13.4 (14.8)	-13.6 (14.3)	0.57
Adjusted** B coeff (p value)	Ref	-1.24 (p=0.13)	-2.13 (p=0.05)	-1.95 (p=0.17)	

*adjusted for age, gender, body mass index, disease duration, baseline CDAI, patient pain, functional status and insurance (what about concomitant nbDMARDs including MTX? Baseline glucocorticoids?)
** adjusted for age, gender, body mass index, disease duration, baseline CDAI, patient pain, work status

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Disclosure: L. Harrold, Corrona, LLC, 3,Genentech., 5,Pfizer, AstraZeneca, 2; **J. L. Palmer**, None; **J. R. Curtis**, Roche, Genentech, UCB Pharma, Janssen,

CORRONA, Amgen, Pfizer, BMS, Crescendo, AbbVie, 2,Roche, Genentech, UCB Pharma, Janssen, CORRONA, Amgen, Pfizer, BMS, Crescendo, AbbVie, 5; **J. D. Greenberg**, Corrona, LLC., 3,Corrona, LLC., 1,AstraZeneca, Pfizer, Celgene, Novartis, 5; **J. M. Kremer**, Corrona, LLC, 3,Corrona, LLC., 1,AbbVie, Amgen, BMS, Genentech, Lilly, Pfizer, 5.

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Abstract Number: 1654

A Systematic Review and Network Meta-Analysis on the Efficacy of Tumor Necrosis Factor Inhibitor-Methotrexate Combination Therapy Versus Triple Therapy in Methotrexate-Naïve Patients with Rheumatoid Arthritis

Roy Fleischmann[1], Janet E. Pope[2], Vanita Tongbram[3], Derek Tang[4], James Chung[5], David Collier[5], Shilpa Urs[3], Kerigo Ndirangu[3], George A. Wells[6] and Ronald F. van Vollenhoven[7], [1]University of Texas Southwestern Medical Center, Dallas, TX, [2]University of Western Ontario, London, ON, Canada, [3]ICON Plc., Morristown, NJ, [4]Amgen, Inc., Thousand Oaks, CA, [5]Amgen Inc., Thousand Oaks, CA, [6]Cardiovascular Research Reference Centre, University of Ottawa Heart Institute, Ottawa, ON, Canada, [7]Department of Medicine, Unit for Clinical Therapy Research, Inflammatory Diseases (ClinTRID), The Karolinska Institute, Stockholm, Sweden

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Background/Purpose: Several published randomized head-to-head trials in rheumatoid arthritis (RA) have compared TNFi-MTX with triple therapy (MTX + hydroxychloroquine + sulfasalazine) in MTX-naive patients (MTX-Ns) where most were designed as non-inferiority studies.[1]Pooled analyses of multiple trials through network meta-analysis may improve the precision of point estimates and allow more accurate interpretation of results with more power to determine between-groups differences. Thus, the objective of this study was to estimate the efficacy and radiographic benefits of TNFi-MTX vs. triple therapy in MTX-Ns by conducting a systematic review and network meta-analysis.

Methods: Medline, EMBASE, and the Cochrane Library were searched for randomized controlled trials that used either TNFi-MTX or triple therapy as one of the treatment arms in MTX-Ns with RA. The primary endpoint for this analysis was ACR70 at 6 months. Other endpoints included ACR20, ACR50, DAS28 LDA, DAS28 remission, EULAR good response, and no radiographic progression; and changes in DAS28, joint erosion, joint space narrowing, and various versions of Sharp scores from baseline. Endpoints were analyzed at 3 months, 6 months, 1 year, and 2 years from baseline when feasible. Data from direct and indirect comparisons between TNFi-MTX and triple therapy were pooled and quantitatively analyzed using fixed and random effects Bayesian models (FEM and REM) in WinBUGS version 1.4.3. Relative treatment effects were generated as odds ratio [OR] (OR>1 indicated a benefit towards triple therapy) for dichotomous endpoints and mean differences (D<0 indicated a benefit towards triple therapy) for continuous endpoints.

Results: A total of 21 studies met the study eligibility criteria, corresponding to 8,118 randomized patients. MTX-Ns were not statistically different in achieving ACR70 with triple therapy than with TNFi-MTX at 6 months in both the FEM (OR=0.76, 95% credible interval [CrI]: 0.36, 1.50) and REM (OR=0.77, 95% CrI: 0.31, 1.76). The following endpoints showed a statistically significant benefit in FEM but not REM: ACR70 at two years (FEM: OR=0.44, 95%CrI: 0.22, 0.82; REM: OR=0.43, 95% CrI: 0.14, 1.28), and proportion with no radiographic progression (FEM: =0.48, 95%CrI: 0.25, 0.90; REM: OR=0.47, 95%CrI: 0.15, 1.41). Across the 15 analyzable endpoint-time scenarios evaluated, 11 numerically favored TNFi-MTX in both FEM and REM.

Conclusion: In this network meta-analysis of MTX-N patients, most endpoints numerically favored TNFi-MTX but with no statistically significant differences between triple therapy and TNFi-MTX. At the group level the two treatment strategies appear similar.

References: 1. Moreland LW, O'Dell JR, Paulus HE, et al. Arthritis Rheum 2012;64:2824–35.

Table. Relative treatment effects concerning efficacy and radiographic endpoints in the MTX naïve population[a-c]

Endpoints	3 months		6 months		1 year		2 years	
	Fixed	Random	Fixed	Random	Fixed	Random	Fixed	Random
ACR70	NA	NA	0.76[d] (0.36, 1.50)	0.77[d] (0.31, 1.76)	NA	NA	0.44 (0.22, 0.82)*	0.43 (0.14, 1.28)
ACR50	NA	NA	0.92 (0.60, 1.40)	0.92 (0.52, 1.58)	NA	NA	0.79 (0.48, 1.31)	0.76 (0.15, 4.05)
ACR20	NA	NA	1.03 (0.70, 1.52)	1.02 (0.56, 1.77)	NA	NA	0.82 (0.53, 1.25)	0.82 (0.16, 3.99)
DAS28 LDA	NA	NA	NA	NA	NA	NA	NA	NA
DAS28 remission	NA	NA	NA	NA	NA	NA	1.12 (0.73, 1.73)	1.10 (0.50, 2.52)
DDAS28	0.14 (-0.10,	0.18 (-0.61,	0.09 (-0.15,	0.07 (-1.00,	-0.10 (-0.37,	-0.10 (-0.82,	-0.10 (-0.45,	-0.11 (-5.35,

	0.37)	0.98)	0.33)	1.10)	0.17)	0.62)	0.26)	4.91)
No radiographic progression	NA	NA	NA	NA	NA	NA	0.48 (0.25, 0.90)*	0.47 (0.15, 1.41)
DmTSS	NA	NA	NA	NA	NA	NA	1.40 (-2.23, 4.97)	1.42 (-5.58, 8.35)
DJoint erosion	NA	NA	NA	NA	NA	NA	0.30 (-1.10, 1.70)	0.31 (-4.82, 5.41)
DJoint space narrowing	NA	NA	NA	NA	NA	NA	0.79 (-1.72, 3.27)	0.82 (-4.36, 6.01)

[a]data presented as odds ratio (OR) (95% CI) or as mean (95% CI) from either a fixed effects or random effects model

[b]data presented as mean (95% CI) for all endpoints measuring mean change (D) from baseline

[c]OR<1 and mean>0 indicates a benefit towards the TNFi-MTX group (vs. triple therapy)

[d]pre-specified primary endpoint

*p<0.05

Disclosure: R. Fleischmann, Amgen Inc., 2,Amgen Inc., 5; **J. E. Pope**, Amgen Inc., 2,Amgen Inc., 5; **V. Tongbram**, Amgen Inc., 5; **D. Tang**, Amgen Inc., 3,Amgen Inc., 1; **J. Chung**, Amgen Inc., 1,Amgen Inc., 3; **D. Collier**, Amgen Inc., 1,Amgen Inc., 3; **S. Urs**, Amgen Inc., 5; **K. Ndirangu**, Amgen Inc., 5; **G. A. Wells**, Amgen Inc., 5; **R. F. van Vollenhoven**, AbbVie, Amgen, BMS, GSK, Pfizer, Roche, UCB, 2,AbbVie, Biotest, BMS, Celgene, Crescendo, GSK, Janssen, Lilly, Merck, Novartis, Pfizer, Roche, UCB, Vertex, 5.

Abstract Number: 1655

Effectiveness of Monotherapy in Rheumatoid Arthritis (RA) Patients Initiating a Tumor Necrosis Factor Inhibitor (TNFi) Vs a Non-TNFi in a Large US Commercial and Medicare Advantage Plan

Benjamin Chastek[1], Jeffrey R. Curtis[2], Laura K. Becker[3], George J. Joseph[4] and **Chieh-I Chen**[5], [1]Optum Insight, Eden Prairie, MN, [2]University of Alabama at Birmingham, Birmingham, AL, [3]Optum, Eden Prairie, MN, [4]Global Health Economics & Outcomes Research (HEOR), Sanofi, Bridgewater, NJ, [5]Regeneron Pharmaceuticals, Inc., Tarrytown, NY

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Background/Purpose: Monotherapy accounts for approximately 30% of biologic disease-modifying anti-rheumatic drug (DMARD) use in RA (Emery P et al. Ann Rheum Dis 2013;72:1897-904). A validated algorithm can assess effectiveness of these drugs from claims data (Curtis JR et al. Arthritis Res Ther. 2011;13:R155). The objective of this study was to apply the algorithm to evaluate effectiveness of monotherapy in patients initiating TNFi and non-TNFi biologics.

Methods: Optum claims data (January 2009-February 2014) were analyzed. The index date was the date of the first claim for a biologic DMARD or tofacitinib after the patient was enrolled for ≥6 months. Inclusion criteria were age ≥18 years at index, RA diagnosis (ICD-9-CM 714.0x) pre-index or the first 30 days post-index, and monotherapy (no conventional DMARD for 120 days post-index). Key exclusion criteria were a previous claim for the index drug during the pre-index period, use of a biologic for a non-RA indication (eg, psoriasis), or <12 months of continuous enrollment with medical and pharmacy benefits after the index date ("post-index period"). Consistent with the validated algorithm, RA was considered effectively treated if the patient met all 6 criteria post-index: (1) high adherence (infusions per labeling or medication possession ratio ≥80% for other medications); (2) no increase in biologic dose; (3) no biologic switch; (4) no new non-biologic DMARD; (5) no new/increased oral glucocorticoid; and (6) <2 glucocorticoid injections >90 days after the index date.

Results: New monotherapy was initiated in 2,147 RA patients: IV TNFi (n=246), IV non-TNFi (n=266), SC TNFi (n=1,595), SC non-TNFi (n=36), or tofacitinib (n=4). Mean age was 52.9 years (SD, 13.4), 77.0% were female, and 81.0% were commercially insured. Achievement of all 6 effectiveness criteria was not different between new non-TNFi monotherapy and new TNFi monotherapy (20.9% vs 20.8%, p=0.947); patients initiating TNFi monotherapy were more likely to increase their index biologic dose (Table). Patients initiating IV non-TNFi monotherapy were more likely to achieve all 6 effectiveness criteria (21.4% vs 10.6%, p<0.001); patients initiating IV TNFi monotherapy were more likely to have high adherence and more likely to increase their biologic dose (Table). Small sample sizes for SC non TNFi or tofacitinib limited interpretation of their effectiveness.

Conclusion: Application of the claims-based algorithm considered non-TNFi monotherapy initiation to have similar (all non-TNFi) or better (IV non-TNFi) effectiveness compared with TNFi monotherapy initiation in RA.

Table. Achievement of claims-based RA effectiveness algorithm criteria, TNFi vs non-TNFi				
Algorithm Criterion	Total		Intravenous	
	TNFi (n=1841)	Non-TNFi (n=306)	TNFi (n=246)	Non-TNFi (n=266)
High adherence	31.7%	30.4%	43.9%	30.5%*
No increase in biologic dose	91.0%	97.1%*	52.9%	96.6%*
No new non-biologic DMARD	87.5%	86.9%	88.6%	86.8%
No biologic switch	82.1%	81.7%	84.6%	83.5%
No new/increased oral glucocorticoid	85.5%	84.3%	87.8%	85.0%
<2 intra-articular injections	92.7%	92.2%	91.5%	92.5%
Effective (met all 6 criteria)	20.8%	20.9%	10.6%	21.4%*
*p < 0.001 for TNFi vs non-TNFi. DMARD = disease-modifying anti-rheumatic drug; TNFi = tumor necrosis factor inhibitor.				

Jonathan Latham of PharmaScribe, LLC provided medical writing assistance.

Disclosure: B. Chastek, Optum, 3; **J. R. Curtis**, Roche, Genentech, UCB Pharma, Janssen, CORRONA, Amgen, Pfizer, BMS, Crescendo, AbbVie, 2,Roche, Genentech, UCB Pharma, Janssen, CORRONA, Amgen, Pfizer, BMS, Crescendo, AbbVie, 5; **L. K. Becker**, Optum, 3; **G. J. Joseph**, Sanofi-Aventis Pharmaceutical, 1,Amgen, 1,Pfizer Inc, 1,Sanofi-Aventis Pharmaceutical, 3; **C. I. Chen**, Regeneron Pharmaceuticals, Inc., 1,Regeneron Pharmaceuticals, Inc., 3.

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Abstract Number: 1656

Repeated CD4+ T-Cell Depletion in Patients with Rheumatoid Arthritis over Multiple Cycles of Rituximab Treatment

Matthieu Lavielle[1], Denis Mulleman[1], Hsueh Cheng Sung[2], Clément Bahuaud[2], Philippe Goupille[1], Hervé Watier[3] and Gilles Thibault[3], [1]Service de Rhumatologie, CHRU de Tours, Université François-Rabelais de Tours, CNRS 7292, Tours, France, [2]Université François-Rabelais de Tours, CNRS 7292, Tours, France, [3]Laboratoire d'Immunologie, CHRU de Tours, Université François-Rabelais de Tours, CNRS 7292, Tours, France

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Background/Purpose: CD4+ T-cell depletion after a first cycle of rituximab (RTX) in patients with rheumatoid arthritis (RA) was previously reported by our group (Mélet J et al. Arthritis Rheum 2013). This effect was not observed in non-responders. The aim of the study was to describe CD4+ T-cell changes over multiple, repeated cycles of RTX (two infusions of 1000 mg each, 2 weeks apart) and their potential relationship with disease activity.

Methods: Patients who started RTX for treatment of RA in our centre between July 2007 and July 2013 were included and studied retrospectively until November 2014. Disease activity was assessed by disease activity score on 28 joints (DAS28) and peripheral blood CD4+ T-cell counts were measured by flow cytometry. In each cycle, pre-treatment, post-treatment and re-treatment CD4+ T-cell counts were compared using Wilcoxon's matched-pairs signed rank test.

Results: In each cycle, the mean CD4+ T-cell count was systematically above the normal range prior to the first and second infusions. The improved clinical response observed with the repeated RTX treatment was associated with normalisation of the mean CD4+ T-cell count in each cycle, this effect being slightly additive. Post-RTX CD4+ T-cell counts were sometimes below 300/mm^3. B-cell counts usually remained low when patients were re-treated. Conversely, RTX-induced CD4+ T-cell depletion was temporary and was followed by an almost complete recovery of the pre-treatment count. Additionally, all of the non-responders to cycle 1 demonstrated only a small decrease or even an increase in CD4+ T-cells in this first cycle; of the non-responders to cycle 1 who were subsequently re-treated, those who had high depletion (i.e.>33%) in the second cycle were more likely to be responders than others (11 of 11 versus 11 of 21). Interestingly, 80 % of these patients became responders and had greater CD4+ depletion in cycle 2 than in cycle 1.

Conclusion: Repeated post-treatment CD4+ T-cell depletion occur over successive cycles of RTX in RA patients. These results suggest that CD4+ T-cell variations induced by RTX are more closely related to changes in disease activity than B-cell variations. Monitoring circulating CD4+ T-cells might be helpful for clinicians when assessing disease activity and also for consequent evaluation of treatment efficacy or for the determination of re-treatment intervals in RTX-treated RA patients.

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Abstract Number: 1657

Evaluation of Bone and Joint Proteins for Prognostic Association with Radiographic Progression and Disease Activity in Methotrexate Inadequate Responder Rheumatoid Arthritis Patients in a Sarilumab Phase 3 Study

Anita Boyapati[1], Jérôme Msihid[2], Jennifer D Hamilton[1], Cem Gabay[3], Neil Graham[1] and Stefano Fiore[4], [1]Regeneron Pharmaceuticals, Inc., Tarrytown, NY, [2]Sanofi R&D, France, Chilly-Mazarin, NJ, France, [3]Rheumatology, Geneva University Hospital, Geneva, Switzerland, [4]Sanofi, Bridgewater, NJ
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Background/Purpose: In patients with early RA, autoantibodies, elevated MMP-3, and acute phase proteins are prognostic biomarkers of joint damage and disease activity. However, the ability to identify patients most likely to have progressive disease is limited in those with established RA.

The MOBILITY study (NCT01061736) included MTX inadequate responder (MTX-IR) RA patients. Two doses of sarilumab (SAR) studied (200 mg every 2 wks [q2w] and 150 mg q2w) + MTX significantly reduced radiographic joint damage compared with placebo (Pbo) + MTX, including modified total Sharp score (mTSS), erosion score (ES), and joint space narrowing (JSN). Mean change from baseline in mTSS at wk 52 was 0.90 and 0.25 for SAR 150 mg and 200 mg + MTX, respectively, and 2.78 for Pbo + MTX (P<0.0001 vs Pbo). The most common treatment-emergent adverse events with SAR included infections, neutropenia, injection site reactions, and increased transaminases. SAR 200 mg + MTX also significantly decreased levels of bone erosion and joint inflammation markers such as receptor-activated NFκB ligand (RANKL), MMP-3, and MMP-cleaved fragments of collagen types 1 and 3 (C1M and C3M) relative to Pbo + MTX.[1] The objective of this study was to evaluate the prognostic utility of proteins involved in bone resorption and joint inflammation in patients treated with Pbo + MTX from the MOBILITY study.

Methods: Serum markers were measured at baseline and posttreatment in patients receiving Pbo + MTX (n=128) or subcutaneous SAR 200 mg q2w + MTX (n=131). For baseline analysis, both treatment groups were included; for posttreatment analysis, only Pbo + MTX patients were analyzed. Spearman ranked correlations (rho) were calculated between baseline markers and baseline radiographic scores (x-ray) or DAS28-CRP for both treatment groups. Correlations between baseline biomarkers and change from baseline in x-ray scores at wk 52 or DAS28-CRP at wk 24 were calculated for the Pbo + MTX group. No adjustment for multiplicity was performed.

Results: Correlations were observed between baseline MMP-3 levels and baseline x-ray scores as well as wk 52 change from baseline in mTSS and ES (Table). Baseline C1M was associated with wk 52 JSN progression. Baseline C1M and C3M correlated with baseline DAS28-CRP (rho = 0.36 and 0.199, respectively; P<0.01). No significant correlations were identified between baseline levels of RANKL, osteoprotegerin, OC, or CTX-1 with baseline clinical scores.

	Clinical parameter	Spearman rho
Baseline MMP-3	Baseline mTSS	0.206*
	Baseline JSN	0.206*
All patients (N=258)[a]	Baseline ES	0.198†
	Baseline DAS28-CRP	0.213*
Baseline MMP-3	Dwk 52 mTSS	0.193†
	Dwk 52 JSN	0.111NS
Pbo + MTX (n=128)	Dwk 52 ES	0.180†
	Dwk 24 DAS28-CRP	-0.117NS

ES, erosion score; JSN, joint space narrowing; mTSS, modified total Sharp score; NS, not significant.

Rho = Spearman ranked correlation; unadjusted P values. *P<0.001. †P<0.05. NS= P>0.05. [a]For 1 patient, baseline MMP-3 value was missing.

Conclusion: Analysis of markers described in the literature as prognostic of structural damage and disease activity in MTX-IR patients showed correlation in MOBILITY patients. These data suggest that multivariate analysis of markers may be necessary to identify increased risk of joint destruction and elevated disease activity in patients with established RA.

1. Boyapati et al. Presented at: ACR; November 14-19, 2014; Boston, MA.

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Abstract Number: 1658

Rheumatoid Factor Status Affects the Efficacy of First Biological Treatment in RA

Yoshikazu Ogawa[1], Nobunori Takahashi[2], Koji Funahashi[2], Shuji Asai[3], Toki Takemoto[3], Tatsuo Watanabe[3], Nobuyuki Asai[2], Naoki Ishiguro[4] and Toshihisa Kojima[2], [1]orthopedic surgery, Nagoya University Hospital, Nagoya, Japan, [2]Department of Orthopedic Surgery, Nagoya University Hospital, Nagoya, Japan, [3]Nagoya University Hospital, Nagoya, Japan, [4]Department of Orthopedic Suregery, Nagoya University Hospital, Nagoya, Japan
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Background/Purpose:

Rheumatoid factor (RF) is considered an important factor in diagnosing rheumatoid arthritis (RA). The association between the treatment efficacy of biological agents and RF status (negative or positive) is unclear; therefore, in the present study, we elucidated whether pretreatment RF examination outcomes affect the efficacy of first biological treatment in RA.

Methods:

The records of relevant patients with RA were derived from Tsurumai Biologics Communication Registry (TBCR) where the department of Nagoya University and 20 affiliated hospitals in Japan are enrolled. The relevant data of a total of 707 patients with RA who met the 2010 ACR–EULAR classification criteria for RA were recorded with regard to both pre- and post-biological treatment DAS28ESR; the RF status was divided into negative (0–15 U/ml) or positive (>15 U/ml). RF-negative patients (n = 118) and RF-positive patients (n = 589) were compared with regard to the effect of the RF status on biological treatment. Only bio-naïve patients were included in this study, and those who received second or latter biological treatment were excluded. We analyzed the relevant data using the analysis of covariance method (ANCOVA), with pretreatment DAS28ESR as the covariate.

Results:

The demographic characteristics of each group at baseline are presented in Table 1. Pretreatment DAS28ESR was significantly associated with DAS28ESR improvement, with a higher pretreatment DAS28ESR corresponding to larger DAS28ESR improvement ($p < 0.01$; Figure 1). Pretreatment DAS28ESR was 5.07 in RF-negative patients and 5.34 in RF-positive patients, with DAS28ESR improvement of 2.25 and 2.09, respectively. Compensating each DAS28ESR according to pretreatment value using ANCOVA, DAS28ESR improvement was 2.40 in RF-negative patients and 2.06 in RF-positive patients, respectively, and the difference was significant ($p < 0.05$; Table 2).

Conclusion:

The RF status significantly affected DAS28ESR improvement in the first biological treatment. Additionally, the efficacy of the first biological treatment in RF-positive patients was inferior to that in RF-negative patients with RA.

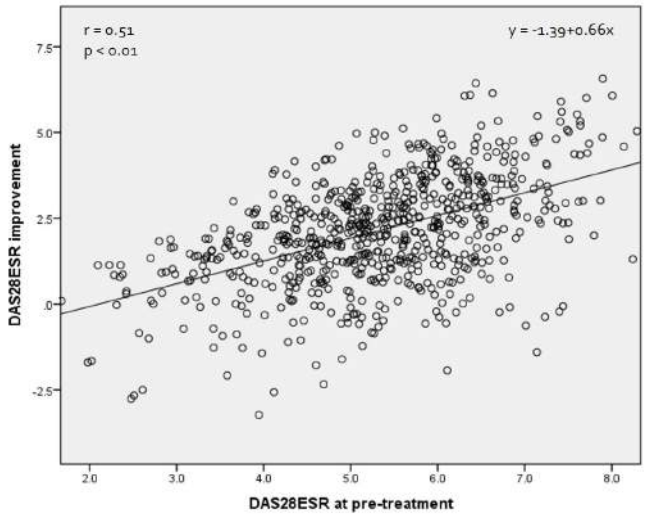

Figure 1. Relationship between pretreatment DAS28ESR and DAS28ESR improvement

Table 1. Baseline characteristics of RF-negative and RF-positive patients

	RF negative (n = 118)	RF positive (n = 589)	p
Age, Mean ± SD years	56.9 ± 15.3	60.2 ± 13.9	<0.05
Sex, % female	88.9	80.6	<0.05
Disease duration, Mean ± SD years	8.0 ± 8.3	9.6 ± 9.7	0.12
Stage, I/II/III/IV , %	28.8/37.8/23.7/29.7	14.7/22.8/29.9/32.5	<0.05
Class, I/II/III/IV, %	28.8/50.0/21.2/0	23.8/49.2/25.6/1.4	0.15
Methotrexate, %	88.3	79.3	<0.05
Methotrexate dose (mg/week), Mean ± SD mg	7.7 ± 2.1	7.9 ± 2.6	0.46
Oral steroids, %	54.2	63.1	0.18
Dose of oral steroids (prednisone equivalent mg/day), Mean ± SD mg	4.8 ± 2.7	4.7 ± 2.1	0.7
Biological agents, %			0.27
Abatacept	6.8	9.0	
Adalimumab	12.7	15.8	
Certolizumab Pegol	1.7	3.2	
Etanercept	31.4	30.2	
Golimumab	5.9	7.5	
Infliximab	28.8	25.9	
Tocilizumab	12.7	9.4	

Table 2. DAS28ESR improvement in each group and pairwise comparisons

Dependent Variable: DAS28ESR improvement

	Estimates				Pairwise Comparisons				
RF status	Mean	Std. Error	95% Confidence Interval		Mean Difference	Std. Error	Sig.b	95% Confidence Interval for Differenceb	
			Lower Limit	Upper Limit				Lower Limit	Upper Limit
negative	2.403a	0.126	2.155	2.65	.344*	0.138	0.01	0.073	0.616
positive	2.058a	0.056	1.948	2.169	−.344*	0.138	0.01	−0.616	−0.073

a Covariates appearing in the model are evaluated at the following values: Pretreatment DAS28ESR = 5.295310609727918.
b Adjustment for multiple comparisons: Least Significant Difference (equivalent to no adjustments).
* The mean difference is significant at the .05 level.

Disclosure: Y. Ogawa, None; **N. Takahashi**, None; **K. Funahashi**, None; **S. Asai**, None; **T. Takemoto**, None; **T. Watanabe**, None; **N. Asai**, None; **N. Ishiguro**, None; **T. Kojima**, None.

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Abstract Number: 1659

Lack of Effect of Reduced Folic Acid Supplementation on Disease Activity in RA

Lisa K. Stamp[1], Jill Drake[2], John L. O'Donnell[3], Christopher Frampton[4] and Peter T. Chapman[5], [1]Medicine, University of Otago, Christchurch, Christchurch, New Zealand, [2]Rheumatology, Immunology and Allergy, Christchurch Hospital, Christchurch, New Zealand, [3]Immunology, Canterbury Health Laboratories, Christchurch, New Zealand, [4]University of Otago, Christchurch, Christchurch, New Zealand, [5]Rheumatology, Christchurch Hospital, Christchurch, New Zealand

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Background/Purpose: It is recommended that all patients receiving MTX also receive at least 5mg/week of folic acid in an effort to reduce occurrence of MTX associated adverse effects. Previous research has suggested that supplemental folic acid has no detrimental effects on control of RA. However, we have shown that patients with higher red blood cell (RBC) folate have more active RA compared to those with lower RBC folate concentrations. The aim of this study was to determine whether reducing the amount of supplemental folic acid patients receive improves disease control in RA patients receiving MTX

Methods: A randomized double blind controlled trial of the effect of reducing folic acid supplementation was undertaken in patients with RA as defined by ARA 1987 criteria. Patients were on MTX for at least 3 months at a stable dose for at least one month. All patients had active disease as defined by DAS28≥3.2 or required a change in therapy as determined by the treating clinician. Patients were randomized to receive supplemental folic acid 5mg/week (high dose or 0.8mg/week low dose. Patients were seen at weeks 4, 8, 16 and 24. Disease activity, full blood count, liver function tests, RBC folate and RBC methotrexate polyglutamates (MTXPGs) were collected at each visit along with reports of adverse events.

Results: Forty patients were recruited. Demographics are outlined in the table. The mean (SD) change in RBC folate between baseline and 24 weeks was +87.9 (57.4) nmol/l in the high dose group and -113.3 (65.7) nmol/l in the low dose group ($p<0.05$). There was no significant difference in the change in DAS28CRP between the high and low dose groups at 24 weeks (-0.14 (SEM 0.30) vs -0.31 (0.37) respectively ($p=0.72$)). One patient in the high dose group and one in the low dose group had a transient reduction in neutrophils (1.7 and $1.5x10^9$/l respectively). Three patients in the low dose and one in the higher dose group had an increase in ALT (all <1.5x upper limit normal). One patient in the low dose group had an increase in AST (<1.5x upper limit normal).

There was no relationship between change in RBC folate and change in DAS28 irrespective of randomisation ($r=0.05$, $p=0.80$). There was no significant association between change in RBC folate and change in RBC MTX polyglutamate concentrations ($p>0.05$ for all).

Conclusion: We have shown that a reduction in RBC folate resulting from a reduction in oral supplemental folic acid was not associated with a change in RA disease activity and there was no change in RBC methotrexate polyglutamate concentrations or adverse effects. The relatively low DAS28 at entry may have made it difficult for a difference to be observed.

Demographics	High dose	Low dose

	(n=22)	(n=18)
Age mean (range) years	61.9 (41.5-82.5)	57.2 (38.2-76.1)
Female n (%)	15 (68%)	13 (72%)
NZ European n (%)	19 (86.4%)	18 (100%)
Duration of RA mean (range) years	9.8 (0.5-40)	9.5 (1-40)
RF n (%)	16/21 (76%)	14 (78%)
CCP n (%)	17/21 (81%)	12/17 (71%)
Radiographic erosions n (%)	15 (68%)	13 (72%)
Nodules n (%)	3 (13.7%)	2 (11%)
Smoker n (%)	7 (31.8%)	3 (17%)
MTX dose mg/wk median (range)	20 (2.5 -20)	20 (15-20)
NSAID	9 (41%)	6 (33%)
Any other DMARD	8 (36%)	13 (72%)
Prednisone	6 (27%)	9 (50%)
Prednisone dose mg/d mean (range)	6.7 (5-10)	4.8 (1-9)
DAS28 CRP baseline mean (range)	3.5 (2.4 - 5.9)	3.8 (2.6-5.8)

Table: Demographics

Disclosure: L. K. Stamp, None; **J. Drake**, None; **J. L. O'Donnell**, None; **C. Frampton**, None; **P. T. Chapman**, None.

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Abstract Number: 1660

Two-Year Prospective Study of Patients with Rheumatic Disease on Dose Reduction of Biological Therapy

M. Victoria Hernández[1], Jose Inciarte-Mundo[2], Sonia Cabrera-Villalba[3], Virginia Ruiz-Esquide[4], Julio Ramirez[2], Andrea Cuervo[4], Juan D. Cañete[4,5] and Raimon Sanmarti[2], [1]Arthritis Unit, Rheumatology, Hospital Clinic, Barcelona, Spain, [2]Arthritis Unit. Rheumatology, Hospital Clínic of Barcelona, Barcelona, Spain, [3]Rheumatology Department, Hospital Clinic i Provincial, Barcelona, Spain, [4]Arthritis Unit. Rheumatology, Hospital Clínic, Barcelona, Spain, [5]Hospital Clinic, Barcelona, Arthritis Unit, Rheumatology Department, Barcelona, Spain

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Background/Purpose: Dose reduction of biological therapy in patients with chronic arthritis (CA) with good clinical response is a common pattern in clinical practice. However, most published studies are based on cross-sectional data in small groups of patients. We analyse the evolution of CA patients receiving low doses of biologics and the predictive factors associated with maintaining reduced doses of biological therapy

Methods: Prospective, observational study that analysed the evolution of 153 patients treated with standard or reduced doses of biologics with a two-year follow up. Variables analysed: age, sex, diagnosis, disease duration, previous treatment (sDMARD, bDMARD), current bDMARD and dosage, duration of biological treatment. In patients on reduced doses: concomitant therapy (sDMARD, steroids), ESR and CRP were collected. In rheumatoid arthritis (RA) patients, autoantibody status, erosions, and DAS-28 score were analysed. A logistic regression model was used to identify factors associated with maintaining the reduced dose after 2 years. The confidence interval of the area under the ROC curve was estimated by bootstrap technique to internally validate the predictive capacity of the model

Results: 153 patients were included between June and November 2011: 82 RA, 29 ankylosing spondylitis (AS), 20 psoriatic arthritis (PsA) and 22 with other diagnoses: 70 patients (45.7%) were on reduced doses of biologics. This cohort was followed prospectively for 2 years until November 2013. Of the 153 patients initially included, 142 remained on biologics after 2 years and 11 discontinued (6 on lower doses and 5 on standard doses: 3 due to adverse events (malignancies), 2 to pregnancies, 2 to prolonged remission, 1 to death and 3 lost to follow-up). After 2 years of follow-up, 56 patients remained on low-dose biological therapy (39.4%) and 8 (5.6%) required an increase in the dose to the standard regimen. By contrast, 19 patients receiving the standard dose were on reduced doses at 2 years. 75 (52.8%) patients were on a reduced dose after 2 years follow up. In patients (37 RA, 13 PsA) in whom DAS-28 was analysed (mean ± SD), 17.9% (8 AR, 2 PsA) had low disease activity (2.8 ± 0.2) and 71.4% (29 AR 11, PsA) were in remission (1.9 ± 0.5). Univariate analysis showed that patients who remained on a reduced dose after 2 years had less use of concomitant steroids in 2011 [9% vs 45% ($p < 0.0001$)] and lower ESR [8 ± 6 vs 2.9 ± 1.5 ($p < 0.0001$)], CRP [0.1 ± 0.2 vs 0.3 ± 1.1 ($p < 0.0001$)], and DAS-28 [2.3 ± 0.3 vs 2.9 ± 1.5 ($p < 0.0001$)] in 2011. Multivariate analysis showed that lower use of concomitant steroids in 2011 in all patients [adjusted odds ratio (AOR) = 0.15, 95% CI 0.05 to 0.52, p = 0.0026] was independently associated with the maintenance of reduced doses. In RA patients, a lower DAS-28 in 2011 was also a predictor of maintaining reduced doses [AOR = 0.24, 95% CI 0.10 to 0.59, p= 0.0018]. The area under the ROC curve was 85.5% [95% (74.2% -91.5%]

Conclusion: In our cohort, 87.5% of patients receiving reduced doses in 2011 remained on them after 2 years of follow up. Factors associated with the maintenance of a clinical response with reduced biological doses in the multivariate model were lower previous use of steroids and a lower DAS-28 score

Disclosure: M. V. Hernández, None; **J. Inciarte-Mundo**, None; **S. Cabrera-Villalba**, None; **V. Ruiz-Esquide**, None; **J. Ramirez**, None; **A. Cuervo**, None; **J. D. Cañete**, None; **R. Sanmarti**, None.

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Abstract Number: 1661

Translational Data and Phase 1 Study Results of a New Monoclonal Antibody Targeting Toll like Receptor 4 (TLR4) Developed for Rheumatoid Arthritis (RA) Treatment with a Potential for Personalized Medicine

Emmanuel Monnet[1], Limin Shang[1], Geneviève Lapeyre[1], Kathy De Graaf[2], Eric Hatterer[1], Gaelle Wambiekele[1], Walter Ferlin[1], Philippe Jacqmin[3], Cem Gabay[4], Jeremy Sokolove[5], Simon Jones[6], Ernest H. Choy[7], Iain B. McInnes[8], Marie Kosco-Vilbois[1] and Cristina De Min[1], [1]NovImmune S.A., Geneva, Switzerland, [2]Novimmune S.A., Geneva, Switzerland, [3]SGS Exprimo, Mechelen, Belgium, [4]Rheumatology, Geneva University Hospital, Geneva, Switzerland, [5]Medicine, VA Palo Alto Health Care System and Stanford University, Palo Alto, CA, [6]Cardiff Institute of Infection & Immunity, Cardiff, United Kingdom, [7]Cardiff University, Institute of Infection and Immunity, Tenovus Building, University Hospital of Wales, Cardiff, United Kingdom, [8]Institute of Infection, Immunity and Inflammation, College of Medicine, Veterinary Medicine and Life Sciences, University of Glasgow, Glasgow, United Kingdom

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Background/Purpose: Innate immunity is implicated in RA pathogenesis and is likely mediated via TLR pathways, with anti-citrullinated protein antibodies (ACPA) serving as key triggers**.** NI-0101 is the first monoclonal antibody (mAb) that blocks TLR4 signaling independently of ligand type (i.e., exogenous/endogenous) and concentration. The objectives of the study were 1) To investigate NI-0101 ability to block TLR4-mediated inflammatory cytokine production induced by endogenous TLR4 ligands using RA patient samples; 2) To evaluate the effect of TLR4 blockade on arthritis progression in RA mouse model; 3) To determine preliminary tolerability, safety, pharmacokinetic (PK)/pharmacodynamic (PD) profiles after single administrations of different NI-0101 doses to Healthy Volunteers (HV).

Methods: Monocytes obtained from HV or RA patients were stimulated with citrullinated protein immune complexes (cP-IC) or synovial fluids (SF) of RA patients in the presence and absence of NI-0101. The correlation of TLR4 blockade with level of endogenous TLR4 ligands in paired SF and serum was assessed. In parallel, the anti-mouse TLR4 surrogate mAb, 5E3, was tested in a collagen induced arthritis (CIA) murine model of RA. Finally, a PK/PD guided single ascending dose Phase 1 study was conducted in 73 HV, in the presence of *in vivo* and *ex vivo* challenges with the TLR4 ligand, lipopolysaccharide (LPS).

Results: *In vitro*, NI-0101 efficiently blocked monocyte TLR4 activation by cP-IC and SF from sub-populations of RA patients. This inhibition correlated with the presence of anti-citrullinated protein antibodies and citrullinated fibrinogen immune complexes in the SF and matching sera (Figure 1A). Administration of 5E3 inhibited arthritis progression in the CIA mouse model (Figure 1B). NI-0101 was administered up to a single dose of 15 mg/kg in the Phase 1 study in HV and showed no safety concerns. The predictable PK profile was biphasic, similar to other therapeutic IgG targeting cell surface receptors. NI-0101 administration inhibited *ex vivo* and *in vivo* LPS-induced cytokine release (complete inhibition from a dose of 1 mg/kg) (Figure 1C), as well as prevented CRP increase and occurrence of flu-like symptoms following LPS administration to HV. NI-0101 PK/PD profiles allowed, through modeling and simulation of multiple administration of NI-0101, to identify an appropriate dose range to be tested in Phase 2 trials.

Conclusion: NI-0101 blocks TLR4 activation induced by TLR4 ligands (cP-IC) present in SF and serum in a subgroup of RA patients and *in vivo* LPS challenges in HV. NI-0101 safety and PK/PD profiles in HV allow initiation of Phase 2 development. Taken together, these data strongly support the potential of TLR4 as a valid therapeutic target in RA, and provide an opportunity to evaluate specific endogenous TLR4 ligands as biomarkers of NI-0101 treatment response in Phase 2 trials.

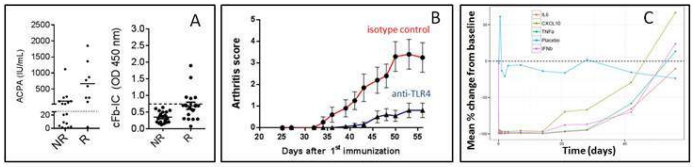

Figure 1: TLR4 blockade by NI-0101 (anti-human mAb) or 5E3 (anti-mouse mAb) correlates, *in vitro*, with serum ACPA levels and immune complexes (A), prevents disease progression in mice (B) and inhibits cytokine release induced by LPS in HV (C). A: Correlation of *in vitro* RA monocyte response to NI-0101 (measured by IL-6 inhibition after RASF stimulation; NR: no response (absence of inhibition), R: response (inhibition)) with ACPA levels in serum matching SF samples and with cFb-IC in RASF samples. B: Arthritis score in CIA mouse model in presence of isotype control or 5E3. C: Mean percentage change from baseline of cytokine levels induced by LPS after administration of a single dose of 1 mg/kg of NI-0101 in HV; line designated 'placebo': IL-6 data of the placebo group.

Disclosure: E. Monnet, Novimmune, 3; **L. Shang**, Novimmune, 3; **G. Lapeyre**, Novimmune, 3; **K. De Graaf**, Novimmune, 3; **E. Hatterer**, Novimmune, 3; **G. Wambiekele**, Novimmune, 3; **W. Ferlin**, Novimmune, 3; **P. Jacqmin**, Novimmune, 5; **C. Gabay**, Novimmune, 5; **J. Sokolove**, Novimmune, 5; **S. Jones**, Novimmune, 5; **E. H. Choy**, Novimmune, 5; **I. B. McInnes**, Novimmune, 5; **M. Kosco-Vilbois**, Novimmune, 3; **C. De Min**, Novimmune, 3.

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Abstract Number: 1662

Treat to Target of Remission Is Effective but Not All Patients Are Always in Remission

Laura M.M. Steunebrink[1], Peter M. ten Klooster[2], Harald E. Vonkeman[3], G.A. Versteeg[1], Arie E. van der Bijl[4] and Mart A.F.J. van de Laar[1], [1]Rheumatology, Medisch Spectrum Twente - Arthritis Center Twente, Enschede, Netherlands, [2]Psychology, Health & Technology, University of Twente, Enschede, Netherlands, [3]Ariensplein 1, Medisch Spectrum Twente - Arthritis Center Twente, Enschede, Netherlands, [4]Isala Klinieken, Zwolle, Netherlands
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Background/Purpose: Presently the goals of rheumatoid arthritis (RA) therapy are to control symptoms, to prevent joint damage and disability. Attaining long-term clinical remission or at least low disease activity (LDA) is mandatory to reach these goals. Treat-to-target (T2T) protocols have been shown to be feasible and superior to non-protocolled care in treating early RA patients in daily clinical practice. However, not all patients may equally benefit from these treatment protocols. Not reaching remission or loss of remission results in periods of moderate to high disease activity in which signs and symptoms impair the health status of patients. Moreover, longer periods of moderate to high disease activity probably affect long term outcome. The objective of the present study was to identify the proportion of RA patients not receiving optimal long-term clinical benefit from T2T therapy.

Methods: Data were used from patients with early RA included in the DREAM remission induction cohort between January 2006 till June 2010. Patients were treated according to a step-up strategy aiming at remission, which consisted of methotrexate, followed by the addition of sulfasalazine and subsequently exchange of sulfasalazine with a TNFi in case of persistent disease activity. Patients were evaluated at the outpatient clinic at baseline and every 3 months thereafter. ESR-DAS28 was used to assess if patients were in LDA (DAS28 ≤3.2) or remission (DAS28 <2.6) at every visit. T2T therapy is considered not fully effective in case the patient's disease activity is moderate to high over a period of ≥ 6 months.

Results: Five-year follow-up data were available from 229 patients (63.3% female, mean age 57.7 years). Between 1 and 5 years after disease onset and start of T2T treatment, the mean DAS28 scores over time remained stable and below the cutoff for remission (Figure). In this period however, 67 (29.3%) patients experienced at least one episode of ≥ 6 months with low, moderate or high disease activity (DAS28> 2,6). Moreover, 34 (14.8%) patients experienced at least one episode of ≥ 6 months with moderate or high disease activity (DAS28> 3,2).

Conclusion: At the population level, T2T therapy in early RA results in stable low disease activity. However, even in this very well managed population, a relevant proportion of patients is not always in remission. This suggests an unmet need that deserves additional study to further improve RA management.

Abstract Number: 1663

Influence of Age and Renal Impairment on Pharmacokinetics of Filgotinib (GLPG0634), a Selective JAK1 Inhibitor

Namour Florence[1], Liesbeth Fagard[2], Annegret Van der Aa[2], Sandy Goss[3], Pille Harrison[2] and Chantal Tasset[2], [1]Galapagos SASU, Romainville, France, [2]Galapagos NV, Mechelen, Belgium, [3]Abbvie, Chicago, IL
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Background/Purpose: Filgotinib is an oral, selective Janus kinase 1 (JAK1) inhibitor combining clinical efficacy and a rapid onset of action with a good safety profile in patients with rheumatoid arthritis (RA). While people of any age can be affected by RA, the disease is common in the elderly. Age-related processes may have an impact on drug metabolism and pharmacokinetics (PK), among others from an age-related decline in enzymes activity and glomerular filtration rate (GFR). Given that metabolism followed by renal excretion is the main routes of elimination for filgotinib and its active metabolite, the impact of age as well as renal impairment on PK and safety of filgotinib was studied./Assess the PK, tolerability and safety of filgotinib in elderly subjects and in subjects with various degrees of renal impairment.

Methods: The effect of age on filgotinib PK was assessed in a single-center Phase 1 study with two groups (N=10 per group) of healthy elderly subjects (65-74 years and ≥75 years) and one group of younger healthy subjects (40-50 years). In a second single-center Phase 1 study, subjects with mild (GFR: 60-89 mL/min/1.73m²; n=6), moderate (GFR: 30-59 mL/min/1.73m²; n=6) and severe (GFR: 15-29 mL/min/1.73m²; n=3) renal impairment and one group with normal renal function (GFR: ≥ 90 mL/min/1.73m²; n=9) were included to investigate the effect of renal impairment on filgotinib PK. In both studies, male and female subjects received once daily 100 mg filgotinib orally for 10 days. The PK of filgotinib and its main metabolite were evaluated. Standard safety assessments were performed throughout the studies.

Results: At steady state, filgotinib plasma exposure was moderately increased (1.4-fold) in the oldest subjects (≥75y) compared to younger subjects. Neither the apparent terminal elimination half-life nor the amounts of filgotinib excreted unchanged in urine were impacted by the age. An exposure increase was also observed for its main metabolite, suggesting no impact of age on filgotinib' drug metabolism. Renal clearance of filgotinib and its main active metabolite decreased with the degree of renal impairment leading to 1.5- and 2.7-fold increase in exposure in subjects with severe renal impairment, respectively. Filgotinib was generally safe and well tolerated in elderly and in subjects with renal impairment. There were no deaths or serious adverse events reported. Most of the treatment emergent adverse advents (TEAEs) were mild. Safety profiles in elderly and in subjects with renal impairment were similar to young heathy subjects.

Conclusion: Higher age and mild to moderate impairment of renal function has a limited impact on the PK of filgotinib. In severe renal impairment, the exposure to filgotinib's active metabolite is elevated, consistent with its renal elimination pathway. This was not associated with safety signals in these Phase 1 studies.

Disclosure: N. Florence, GALAPAGOS, 3; **L. Fagard**, GALAPAGOS, 3; **A. Van der Aa**, Galapagos, 3; **S. Goss**, AbbVie, 3; **P. Harrison**, Galapagos, 3; **C. Tasset**, Galapagos, 3.

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Abstract Number: 1664

Switch from Tocilizumab + Methotrexate to Tocilizumab Monotherapy. Maintenance of Response in Patients with Rheumatoid Arthritis at Low Disease Activity.

Jose L. Pablos[1], Navarro Sarabia F[2], Francisco J. Blanco[3], Jose Andres Roman Ivorra[4], Alberto Alonso[5], Emilio Martin-Mola[6] and Miguel Cantalejo-Moreira[7], [1]Servicio de Reumatología, Hospital 12 de Octubre, Madrid, Spain, [2]Rheumatologist Service, Hospital. Virgen Macarena, Sevilla, Spain, [3]Cartilage Biology Group. Rheumatology Division, INIBIC-Hospital Universitario A Coruña, A Coruña, Spain, [4]Rheumatology, H.U. P. La Fe, Valencia, Spain, [5]H Cruces, Baracaldo, Spain, [6]H La Paz, Madrid, Spain, [7]Rheumatology Unit, Hospital de Fuenlabrada, Fuenlabrada, Spain
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Session Time: 9:00AM-11:00AM

Background/Purpose:

Tocilizumab (TCZ) represents an efficacious alternative for patients with rheumatoid arthritis (RA) with an inadequate clinical response to biological or non-biological disease-modifying anrirheumatic drugs (DMARDs). Previous data support the use of TCZ in monotherapy but there are limited data on its efficacy compared to TCZ + MTX (methotrexate).

Methods:

The study was designed as a phase III, randomized, double-blind, parallel-group (1:1), multicentre clinical trial. During the first part of the study all patients with active RA and previous inadequate response to MTX were treated with combined TCZ 8 mg/Kg i.v. every 4 weeks + oral MTX for 16 weeks and then all which showed a low activity (DAS28 ≤ 3.2) were randomized (1:1) to either TCZ + MTX or TCZ + placebo with a follow-up of 28 weeks. Secondary endpoints included clinical response after 28 weeks, improvement of general status and quality of life. Safety assessment was also assessed and included adverse events, serious adverse events, and change in laboratory parameters. Sample size was calculated in 79 patients per group in order to detect a minimum disease activity score (DAS28) clinically relevant difference of 0.5 (standard deviation 1.1) with 80% power and two-sided 5% alpha level. Statistical analysis was performed with SAS v9.2, and included analysis of covariance for the primary endpoint (with week 16 DAS28 as a covariate), and descriptive parameters for secondary endpoints, with an intention to treat approach. Safety cumulative incidences were estimated using Kaplan-Meier methods. (ClinicalTrials.gov Identifier: NCT01399697.)

Results:

The first part of the study included 263 RA patients with previous inadequate response to MTX (DAS28 5.6 ± 1.2). Of those, 165 patients showed low disease activity (LDA) at 16 weeks (DAS ≤ 3.2) and were randomized to TCZ + MTX (n=83) or TCZ + placebo (n=82). DAS28 from week 16 to week 28 did not change significantly in both groups (from 1.77 to 1.87 with TCZ + MTX, and from 1.96 to 1.98 with TCZ + placebo, ANOVA, p=0.89). Remission rates (DAS28<2.6) at week 28 were similar in both groups TCZ + MTX and TCZ monotherapy (82.3% and 75.9% respectively, p=0.33), and similar to those at week 16 in both groups (84.0% and 72.0% respectively). No statistically significant differences were observed in any of the secondary variables. The incidence of adverse events after week 16 was similar in both groups. Hypertransaminasemia was the most frequently adverse event reported in both groups (9.6% and 4.9%, respectively)

Conclusion:

Switching from TCZ + MTX to TCZ monotherapy in patients with LDA is not followed by any clinical change, either in the efficacy or the safety profiles. Therefore, the TCZ monotherapy could be an efficacious and safe alternative for those patients not suitable to receive MTX in combination.

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Abstract Number: 1665

Treatment Patterns in Rheumatoid Arthritis after Methotrexate: Data from a Rheumatoid Arthritis Cohort

Janet E. Pope[1], Mohammad Movahedi[2,3], Angela Cesta[2], Xiuying Li[2], Sandra Couto[2], Emmanouil Rampakakis[3], John S. Sampalis[3,4], Claire Bombardier[2,5,6] and OBRI Investigators, [1]University of Western Ontario, London, ON, Canada, [2]Toronto General Hospital Research Institute, University Health Network, Toronto, ON, Canada, [3]JSS Medical Research, St-Laurent, QC, Canada, [4]McGill University, Montreal, QC, Canada, [5]University of Toronto, Department of Medicine (DOM) and Institute of Health Policy Management, and Evaluation (IHPME), Toronto, ON, Canada, [6]Division of Rheumatology, Mount Sinai Hospital, Toronto, ON, Canada

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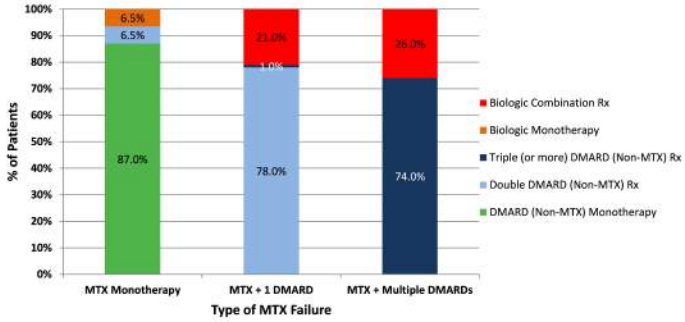
Background/Purpose:

Guidelines support the use of combination conventional synthetic Disease-Modifying Antirheumatic Drugs (csDMARDs), switching csDMARDs and/or use of biologic DMARDs (bDMARDs) treatment in active rheumatoid arthritis (RA) after use of methotrexate (MTX).

The purpose of this study was to determine treatment practices after use of MTX in patients with RA who were on either monotherapy or combination csDMARDs in a large observational cohort (OBRI) in order to determine contemporary practice where use of bDMARDs from government coverage is restricted to active RA (+RF and/or +ACPA) or erosions, SJC≥5 with MTX failure, combination failure (triple csDMARDs: MTX + hydroxychloroquine + sulfasalazine) or use of leflunomide. **Methods:** Patients enrolled in the Ontario Best Practices Research Initiative (OBRI) with documented MTX failure defined as discontinuation due to side effect, primary / secondary failure, or patient / physician decision were included. Demographics and disease parameters at MTX failure were compared between monotherapy failures, double therapy (Rx) failures, and triple Rx failures. **Results:** A total of 313 patients with MTX failure were included with a mean (SD) age of 58.8 (13.2) years and disease duration of 6.7 (8.2) years. Of these, 102 (32.6%) were on MTX monotherapy, 156 (49.8%) were on double (MTX +1 csDMARD) Rx, and 55 (17.6%) were on triple or more (MTX + multiple csDMARDs) Rx, respectively, at the time of MTX failure. At the time of MTX failure disease duration was significantly higher in patients failing monotherapy and double Rx as compared to triple Rx (7.5 vs. 6.8 vs. 4.5 years, respectively; P=0.003). Figure 1 shows the disposition of patients who transitioned to csDMARD monotherapy, csDMARD combination Rx or bDMARDs treatment. Patients receiving monotherapy were more apt to have switches to other monotherapy whereas those on combination Rx received more combination csDMARDs and bDMARDs combination Rx. **Conclusion:** There are inherent differences in the selection of subsequent treatment regimen between patients failing MTX monotherapy vs. MTX combination therapy. Overall, the results of the current analysis suggest the use of a sequential treatment intensification strategy in routine clinical practice in Ontario. **Figure 1: Treatment Profile after MTX Failure by Type of MTX Failure**



Disclosure: J. E. Pope, Abbott,Amgen, Pfizer, Roche, Janssen, BMS, UCB, 5; **M. Movahedi**, JSS Medical Research, a Contract Research Organization, 3; **A. Cesta**, None; **X. Li**, None; **S. Couto**, None; **E. Rampakakis**, JSS Medical Research, a Contract Research Organization, 3; **J. S. Sampalis**, JSS Medical Research, a contract research organization, 3; **C. Bombardier**, Abbvie, Amgen, Bristol Myers Squibb, Hospira, Janssen, Roche, Pfizer, UCB, 2.

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Abstract Number: 1666

Mitochondrial Haplogroups in Patients with Rheumatoid Arthritis with Respect to Biological Treatment

Pernille Hurup Duhn[1], Jacob Sode[2,3,4], Christian Hagen[5], Michael Christiansen[5,6] and Henning Locht[4], [1]Department of Rheumatology, Frederiksberg Hospital, University of Copenhagen, Copenhagen, Denmark, [2]Institute of Regional Health Research, University of Southern Denmark, Odense, Denmark, [3]Department of Autoimmunology and Biomarkers, Statens Serum Institut, Copenhagen, Denmark, [4]Department of Rheumatology, Frederiksberg Hospital, Frederiksberg, Denmark, [5]Department of Congenital Disorders, Statens Serum Institut, Copenhagen, Copenhagen, Denmark, [6]Department of Biomedical Sciences, Faculty of Health and Life Science, University of Copenhagen, Copenhagen, Denmark

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Background/Purpose:

Throughout evolution mutations in mitochondrial DNA (mtDNA) have accumulated sequentially subdividing the human population into different haplogroups classificed from A-Z. Specific mtDNA haplogroups have been associated with the development of several conditions such as Alzheimer and Parkinsons diseases. RA is a chronic auto-inflammatory disorder in which the pathogenesis is not fully understood. We analyzed the distribution of mtDNA haplogroups in a cohort of patients with RA defined by disease activity, presence of rheumatoid factor, and biological or conventional treatment.

We compared the distribution of mtDNA haplogroups in the RA-cohort with two historical control groups from the background population.

Methods:

Two-hundred nineteen consecutive patients with RA had mtDNA, isolated, sequenced and haplogroups were identified from blood samples. Patients were diagnosed according to the American College of Rheumatology (ACR)/European league against Rheumatism (EULAR) criteria. Demographic and clinical data (rheumatoid factor status, erosions, disease activity score 28-joints (DAS-28), biological/synthetic anti-rheumatic treatments were retrieved from the Danish nationwide database (DANBIO). Logistic regression analyses were performed to test for associations.

Results:

One-hundred eighty-four patients were eligible for analysis (29 were excluded due to rare non-European haplogroups, 6 had unknown haplogroups). Haplogroup frequencies were as follows: H (n= 88, 47.8%), U (n= 37, 20.1%), T (n= 22, 12.0%), J (n= 16, 8.7%), K (n= 11, 5.9%), HV (n= 6, 3.3%) and V (n= 4, 2.2%). In the overall RA-cohort the distribution of individual haplotypes was identical to the background population. None of the haplogroups were significantly associated with gender, anti-CCP, IgM RF or DAS-28. Macrohaplogroup HV was associated with administration of biological treatment (OR = 2.13; 95% Confidence Interval (CI): 1.13 - 4.07; p = 0.020). However, we found a trend towards fewer erosions in patients with haplogroup HV (OR = 0.54, 95% CI: 0.29 - 1.00, p = 0.051).

Conclusion:

The distribution of mtDNA haplogroups in the RA-cohort did not differ from the background population. However, there was a significant overrepresentation of individuals with haplogroup HV (OR 2.13) among patients undergoing biological treatment. When patients were grouped according to presence of radiographic erosion there was a trend pointing in the opposite direction. Erosive patients were less likely to belong to haplogroup HV (OR 0.54). When subjects were stratified according to DAS-28 level there were no significant associations with a certain haplogroup. We have shown that in a randomly selected cohort of patients with RA the HV mtDNA haplogroup may be overrepresented in a subgroup of patients, but no clear association with respect to diseases severity was observed.

Disclosure: P. H. Duhn, None; **J. Sode**, None; **C. Hagen**, None; **M. Christiansen**, None; **H. Locht**, None.

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Abstract Number: 1667

Clinical Parameters and B Cell Subsets As Biomarkers of Response to Tocilizumab in Rheumatoid Arthritis

Anna Laura Fedele, Barbara Tolusso, Elisa Gremese, Silvia Canestri, Clara Di Mario, Marcin Nowik and Gianfranco Ferraccioli, Division of Rheumatology, Institute of Rheumatology, Catholic University of the Sacred Heart, Rome, Italy

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Background/Purpose: Tocilizumab (TCZ) is an effective treatment for Rheumatoid Arthritis (RA) and it is a modifier of B cell subsets in vivo, inducing changes in the distribution of B-cell subpopulations[1-3]. Our purpose was to define whether the combination of clinical parameters and B cell subset analysis at baseline could help to identify the best responders to TCZ, and to examine whether changes after 3 months could predict the occurrence of response to therapy over time.

Methods: 63 RA patients not responder to previous cDMARDs and/or bDMARDS were studied, of which: A) 17 (27.0%) with an early RA (ERA), treated according to a tight control strategy and B) 46 (73.0%) with a long-standing disease (LSRA). All patients were treated with TCZ at a dose of 8 mg/Kg every 4 weeks. At baseline, and every 3 months, demographic and immunological data and the ACR/EULAR core data set were recorded. At each visit, clinical improvement and remission were evaluated according to ACR/EULAR criteria[4]. At baseline and every 3 months peripheral blood samples were collected and analyzed by flow-cytometry for the distribution of circulating B-cell subsets using IgD-CD27 classification[5].

Results: In the whole RA cohort, 16.4% and 17.6% of patients treated with TCZ, reached the ACR/EULAR remission (SDAI≤3.3) at 6th and 12thmonths of follow-up (FU), respectively.

The percentage of ACR/EULAR remission after 3, 6 and 12 months of TCZ therapy was higher in male patients compared to female subjects ($p<0.05$), in ERA compared to LSRA patients ($p<0.05$), and in subjects with baseline moderate disease activity (SDAI≤26) compared to patients with a high disease activity ($p<0.05$). Moreover, a lower percentage of RA patients already treated with bDMARDS reached remission over time compared to cDMARDs treated subjects ($p<0.05$). Autoantibody seropositivity or BMI did not influence the outcome over time.

A decrease of the percentage of post-switched (IgD-CD27+; *p=0.001*) and double negative (IgD-CD27-; *p=0.004*) memory B cells occurred after 12 months of treatment with TCZ, together with an increase of the percentage of naïve (IgD+CD27-; *p=0.05*) B cells.

A higher percentage of reduction of double negative memory B cells at 3 months of TCZ treatment was observed in RA patients reaching remission (SDAI≤3.3) at 6 months compared to patients not achieving this target (*p=0.02*).

At the multivariate analysis, a disease duration less than 12 months [OR (95%CI): 24.1 (1.7-341.8)], a moderate disease activity (SDAI≤26) at baseline [OR (95%CI): 18.5 (1.4-250)] and a higher reduction of double negative B cells at 3 months of FU [OR (95%CI): 1.05 (1.001-1.1)] arose as significant independent predictors of ACR/EULAR remission (SDAI≤3.3) at 6thmonth of TCZ treatment.

Conclusion: In our cohort of TCZ-treated RA patients, being male, having a disease duration less than 12 months and a moderate disease activity at baseline represent the best clinical matrix to predict remission at 6 months. Furthermore, a significant reduction of DN memory B cells at the 3th month of FU has emerged as an early biomarker of remission at the 6thmonth of treatment.

References:

1. Roll P et al. Arthritis Rheum 2011

2. Muhammad K et al. Ann Rheum Dis 2011

3. Mahmood Z et al. Arth Res Ther 2015

4. Felson DT et al. Arthritis Rheum 2011

Disclosure: A. L. Fedele, None; **B. Tolusso**, None; **E. Gremese**, None; **S. Canestri**, None; **C. Di Mario**, None; **M. Nowik**, None; **G. Ferraccioli**, None.

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Abstract Number: 1668

Patterns of Relapse in the Rheumatoid Arthritis Cohort Treated with Rituximab at University College London

Elena Becerra, Geraldine Cambridge, Inmaculada de la Torre and Maria J. Leandro, Centre for Rheumatology, Department of Medicine, University College London, London, United Kingdom
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Patterns of relapse in the Rheumatoid Arthritis cohort treated with Rituximab at University College London

Background/Purpose: Two patterns of relapse were defined in the first studies of Rituximab (RTX) therapy in patients with Rheumatoid Arthritis (RA): either occurring coincident with B-cell return (concordant relapse – C-R) or 'delayed' occurring months after B-cell return (discordant relapse - D-R), with around 50% of patients belonging to each subgroup in the first 24 patients studied. Later clinical observations showed a greater frequency of C-R pattern. Our study analyzed the current frequency of patients showing a concordant/discordant pattern of relapse after their first cycle of RTX.

Methods: Retrospective observational study of the RA cohort treated with RTX at University College Hospital, selecting patients with a good response to the 1st cycle of RTX and analyzing the pattern of relapse after that cycle. All patients fulfilled the 1987 revised ACR criteria and had severe disease activity (DAS28 > 5.1). Data were collected on demographics, previous and concomitant therapy, months to repopulation and months to relapse. B cell depletion was confirmed by CD19 determination of <5/microl of the total lymphocyte population. B cell repopulation was considered when B cells were again detectable in peripheral blood (CD19 count >5/microl of the total lymphocyte population). Patients with a poor response to the therapy, or treated with a second cycle because of persistent disease activity were taken out of the analysis.

Results: 271 patients have received RTX at our unit between 1998 and 2012. Total patient-years follow up was 886.05 and total number of cycles administered was 910. We selected 168 patients with a good response after 1 cycle of RTX and followed up at least until their first relapse, which occurred 4 to 67 months after the first cycle. Mean time to repopulation was 7.3 months (range 3-20 months) and mean time to relapse was 10.4 months (range 3-67 months). Patients were then divided in two patterns of relapse, that is C-R if relapse occurred less than 3 months after repopulation was first documented, and D-R if it occurred more than 3 months after such repopulation. Seventy % (118 patients) were C-R, with a mean time to repopulation of 7.1 months (range 4-20 months) and a mean time to relapse of 7.7 months (range 4-20 months); Thirty % (50 patients) were D-R, with a mean time to repopulation of 7.8 months (range 3-20 months) and a mean time to relapse of 17.4 months (range 6-67 months).

Conclusion: there are two clear patterns of relapse after repopulation in patients with RA treated with RTX, with a higher frequency of concordant patients. In one third of the patients a discordant pattern of relapse has been identified. The decision of when to retreat RA patients with RTX should be made for each patient individually, taking into account the patterns of relapse described. This will possibly decrease the risk of adverse events and reduce costs for each therapy.

Characteristics	n = 168 patients
Mean age (range)	56 years (range 18-85)
Female no (%)	132 (78%)
Mean years of disease (range)	15 years (range 1-56)
Rheumatoid factor-positive, no (%)	154 (91 %)
Anti-CCP positive, no (%)	137 (81 %)
Previous methotrexate/ other DMARDS, no (%)	157 (93 %) / 153 (91 %)
Mean no (range) previous DMARDs (including methotrexate)	3 (0-6)
Previous TNF inhibitor, no (%); mean no (range)	110 (65 %); 1,24 (0-3)
Concomitant oral steroids, no (%)	47 (28 %)
Concomitant methotrexate/ other DMARDS, no(%)	71 (42 %) / 42 (25 %)
Concomitant cyclophosphamide no (%)	25 (15 %)

Disclosure: E. Becerra, None; **G. Cambridge**, None; **I. de la Torre**, Eli Lilly and Company, 3; **M. J. Leandro**, Genentech and Biogen IDEC Inc., 5,Roche Pharmaceuticals, 5.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/patterns-of-relapse-in-the-rheumatoid-arthritis-cohort-treated-with-rituximab-at-university-college-london

Abstract Number: 1669

Serum Survivin Predicts Responses to Treatment in Active Rheumatoid Arthritis

Adrian Levitsky[1], Malin C. Erlandsson[2], Ronald F. van Vollenhoven[1] and Maria I. Bokarewa[2], [1]Department of Medicine, Unit for Clinical Therapy Research, Inflammatory Diseases (ClinTRID), The Karolinska Institute, Stockholm, Sweden, [2]Rheumatology and Inflammation Research, University of Gothenburg, Gothenburg, Sweden

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Background/Purpose:

Survivin is an oncological biomarker. In rheumatoid arthritis (RA), elevated serum *survivin* is common and has been used to predict disease onset and progressive joint damage. We investigated the predictive capacity of *survivin* for response to various antirheumatic treatments in patients with early RA.

Methods:

Survivin levels in serum were measured using ELISA in 302 patients enrolled in the Swedish pharmacotherapy (SWEFOT) trial at baseline and at 3, 12, and 24 months of follow-up. *Survivin* levels >0.45 ng/mL were considered positive. After methotrexate (MTX) monotherapy for 3 months, responders (DAS28≤3.2) remained on MTX, while non-responders were randomized to triple therapy (MTX+sulfasalazine+hydroxychloroquine) or anti-TNF (MTX+infliximab). The core-set outcomes (i.e. DAS28, HAQ, pain & global VAS) were evaluated at 3, 12, and 24 months in relation to *survivin* status.

Results:

Over one-third of all patients (n=114) were *survivin*-positive at baseline. S*urvivin*-positive ever-smokers (51/71 vs. 64/112, OR 1.91 [95% CI 1.01-3.62], p=0.045) and *survivin*-negative patients who converted to positive over 24 months (13/161 vs. 2/100, OR 4.30 [0.95, 19.49], p=0.037) responded seldom to MTX.

At 3 months, *survivin*-positive patients among MTX responders who converted to negative (n=11) had greater reductions in DAS28, HAQ and global VAS vs. those who remained positive (n=28). A delay in improvement from functional disability was shown among the patients who remained positive, as the HAQ value was already higher despite MTX response. At 12 months, *survivin*-positive MTX responders who continued monotherapy had a higher risk of disease re-activation compared to *survivin*-negative patients (12/36 vs. 7/52, OR 3.21 [1.12-9.24], p=0.032) and deteriorated in HAQ over 24 months.

Among *survivin*-positive patients on triple therapy, converting to negative (n=19) was associated with a lower DAS28 at 12 months (2.34 vs. 4.12, p=0.046) and a higher frequency of low disease activity (DAS≤3.2, 86% vs. 37%, p=0.056) at 24 months vs. converting to positive (n=7). Lower pain (p=0.048) and global VAS (p=0.015) at 12 months was also found compared to the same subgroup, which was not observed among anti-TNF – where no differences in core-set outcomes were observed between the *survivin* groups. The patients on triple therapy who converted to negative attained a lower DAS28 at 12 months compared to those on anti-TNF (2.34 vs. 3.43, p=0.045). *Survivin*-positive patients on anti-TNF had a higher risk to have active disease at 24 months compared to those on triple therapy (DAS28>3.2, 16/29 vs. 9/32, OR 3.15 [1.09-9.10], p=0.037; DAS28, 3.50 vs. 2.37, p=0.020).

Conclusion:

S*urvivin*-positive patients who initially respond to MTX monotherapy have worse long-term outcomes than *survivin*-negative patients, and conversion from positive to negative is associated with a good response to conventional disease-modifying antirheumatic drugs. For *survivin*-positive patients with early RA who fail MTX, triple therapy is associated with a better likelihood for response than anti-TNF therapy.

Disclosure: A. Levitsky, None; **M. C. Erlandsson**, None; **R. F. van Vollenhoven**, AbbVie, BMS, GSK, Pfizer, Roche, UCB, 2,AbbVie, Biotest, BMS, Crescendo, GSK, Janssen, Lilly, Merck, Pfizer, Roche, UCB, Vertex, 5; **M. I. Bokarewa**, None.

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Abstract Number: 1670

Rapidity of Therapeutic Response of Biologics Compared to Methotrexate Monotherapy in Early RA: A Network Meta-Analysis

Raveendhara R. Bannuru, Mikala Osani, Anbuselvan Dharmarajan, Elizaveta Vaysbrot and Timothy E. McAlindon, Rheumatology, Tufts Medical Center, Boston, MA

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Background/Purpose: Rapidity of onset of therapeutic efficacy may be critically important in the management of early RA and may reduce long-term impact of the disease. Traditional DMARDs have slow onset, potentially losing an opportunity to mitigate damage. Information on the trajectory of response to biologics relative to DMARDs in early RA could be important in making treatment decisions and influencing payer decisions. We therefore performed a network meta-analysis comparing biologics and tofacitinib to MTX in early RA, specifically evaluating treatment responses at early time points.

Methods: Medline, EMBASE, Web of Science, and Cochrane Database were searched from inception through June 1, 2015. We included all randomized controlled trials involving early RA patients that reported extractable data for disease activity score (DAS) remission, and ACR50, and compared a biologic/tofacitinib with/without MTX to MTX. Odds ratios were calculated for all DAS remission and ACR 50 outcomes reported at the following time points: 2, 4, 8, 12, 16, and 24 weeks. Network meta-analysis was performed using a Bayesian hierarchical random effects model for mixed multiple treatment comparisons.

Results: We included 18 studies involving 8658 patients with early RA. The mean age of the patients ranged from 48 to 55 years, and the mean disease

duration ranged from 2 to 43 months. 83% were biologic naïve and 78% were MTX naïve (Table 1). Biologic + MTX combination therapy worked more quickly than MTX achieving better ACR50 and DAS remission rates even at week 2 (Table 2). Although the therapeutic trajectories converge over time, they remain significantly different for up to 6 months. Tofacitinib monotherapy emerged as the best treatment option at almost all the time points with odds ratios for DAS remission compared to MTX monotherapy ranging from 18.97 (95% Credible interval 1.68, 354.32) at 4 weeks to 3.42 (1.64, 8.26) at 24 weeks, and ACR50 ranging from 7.53 (1.35, 44.96) at 4 weeks to 3.54 (1.65, 7.85) at 24 weeks.

Conclusion: Biologics combined with MTX, or tofacitinib alone, both result in faster onset of efficacy than MTX alone for early RA. Onset of efficacy is evident as early as 2 weeks, with superiority over MTX that persists for as long as six months. Our findings suggest that early introduction of biologics could produce rapid and sustained suppression of inflammatory disease, preserving function and reducing joint damage. Consideration should be given to whether the health economics favor introduction of biologics/tofacitinib earlier in the treatment pathway.

Table 1: Study and Patient Characteristics

Author, Year	Comparison - Dose & N	Treatment 1 - Dose & N	Treatment 2 - Dose & N	Mean age (years)	Female (%)	RA Duration (months)	Treatment experience	Baseline DAS28 score
Westhovens, 2009	MTX+ iv Placebo 253	iv Abatacept, 10 mg/kg once every other week for 4 weeks, then every month+ MTX 256	NA	50	78	6.5	MTX and biologic naïve. 2.7-4% of patients were taking DMARDs at baseline.	MTX/Pbo: 6.2 ABT/MTX: 6.3
Schiff, 2014	sc Adalimumab, 40 mg every other wk+ MTX 328	sc Abatacept, 125 mg once/wk+ MTX 318	NA	51	82	21.6	Biologic naïve DMARD-IR	ADA/MTX: 5.5 ABT/MTX: 5.5
Soubrier, 2009	MTX 32	sc Adalimumab, 40 mg every other wk+ MTX 33	NA	48	80	4.4 (median)	MTX and biologic naïve. Other treatment not described.	MTX: 6.15 ADA/MTX: 6.31
Detert, 2013	sc MTX+ sc Placebo 85	sc Adalimumab, 40 mg every other wk+ SC MTX 87	NA	50	69	1.7	DMARD and biologic naïve	MTX/Pbo: 6.3 ADA/MTX: 6.2
Heimans, 2013	MTX+HCQ+ SSZ 83	sc Adalimumab, 40 mg every other wk+ MTX 78	NA	50	76	3.1	DMARD and biologic naïve. Pretreated with MTX and GCs before randomization.	MTX/HCQ/ SSZ: 3.6 ADA/MTX: 3.6
Hørslev-Petersen, 2014	MTX+ sc Placebo 91	sc Adalimumab, 40 mg every other wk+ MTX 89	NA	55	66	3.1	DMARD and biologic naïve	MTX/Pbo: 5.6 (median) ADA/MTX: 5.5 (median)
Keystone, 2014	MTX+ sc Placebo 257	sc Adalimumab, 40 mg every other wk+ MTX 268	sc Adalimumab, 40 mg every other wk+ oral Placebo 274	52	74	8.8	MTX and biologic naïve. Other DMARDs: 30%	MTX/Pbo: 6.3 ADA/MTX: 6.3 ADA/Pbo: 6.4
		sc Adalimumab, 40 mg					MTX and biologic naïve.	

Smolen, 2014	MTX+ sc Placebo 112	sc Adalimumab, 40 mg every other wk+ MTX 207	NA	49	71	3.9	One or more DMARDs: 8.8-12.7%	MTX/Pbo: 5.5 ADA/MTX: 5.8
Takeuchi, 2014	MTX+ sc Placebo 163	sc Adalimumab, 40 mg every other wk+ MTX 170	NA	54	81	3.6	MTX and biologic naïve. 1 DMARD: 34-43% 2 DMARDs: 10-11%	MTX/Pbo: 6.6 ADA/MTX: 6.6
Bathon, 2000	MTX+ sc Placebo 217	sc Etanercept, 25 mg twice/wk+ oral Placebo 207	NA	50	75	12	MTX and biologic naïve. One or more DMARDs: 39-46%	ND
Emery, 2008	MTX+ sc Placebo 263	sc Etanercept, 50 mg once/wk+ MTX 265	NA	51	73	9.0	MTX and biologic naïve. One or more DMARDs: 18-24%	MTX/Pbo: 6.5 ETN/MTX: 6.5
Nam, 2014	MTX+ sc Placebo 55	sc Etanercept, 50 mg once/wk+ MTX 55	NA	48	76	8 (median)	DMARD and biologic naïve	MTX/Pbo: 4.17 ETN/MTX: 4.1
Emery, 2009	MTX+ sc Placebo 160	sc Golimumab, 50 or 100 mg once/mo+ MTX 318	sc Golimumab 100 mg once/mo+ oral Placebo 159	50	83	42.6	Biologic naïve One or more DMARDs: 50.3-58.5%	MTX/Pbo: 6.2 GOL/MTX: 6.3 GOL/Pbo: 6.3
Smolen, 2009	MTX+ iv Placebo 298	iv Infliximab, 3 mg/kg or 6 mg/kg once at baseline, then wk 2 and 6, then at 8 wk intervals for 46 wks+ MTX 751	NA	50	71	10.4	MTX and biologic naïve; 68-71% of patients were naïve to all DMARDs at baseline.	MTX/Pbo: 6.69 IFX/MTX: 6.67
Tak, 2011	MTX+ iv Placebo 250	iv Rituximab, 2 infusions 500 mg or 1000 mg on day 1 and day 15+ MTX	NA	48	81	4.8 (median)	MTX and biologic naïve; 69-72% of patients were naïve to all DMARDs at baseline	MTX/Pbo: 7.1 RTX/Pbo: 7
Maini, 2006	MTX+ iv Placebo 49	iv Tocilizumab, 4 mg/kg or 8 mg/kg once every 4 wk+ MTX 101	iv Tocilizumab, 4 mg/kg or 8 mg/kg once every 4 wk+ oral Placebo 99	50	79	9.8	MTX-IR. Other treatment not described.	MTX/Pbo: 6.75 TCZ/MTX: 6.41 TCZ/Pbo: 6.49
Burmester, 2013	MTX+ iv Placebo 287	iv Tocilizumab, 4 mg/kg or 8 mg/kg once every 4 wk+ MTX 578	Iv Tocilizumab, 8 mg/kg once every 4 wk+ oral Placebo 292	ND	ND	4.8 - 6	MTX naïve. Other treatment not described. MTX naïve.	6.6 - 6.7 MTX/Pbo:

Lee, 2014	MTX+ oral Placebo 186	Oral Tofacitinib, 10 mg twice/day+ oral Placebo 397	NA	50	79	36.8	One or more DMARDs: 39%. Biologic experience not described.	6.6 TOF/Pbo: 6.5

N= Number of Patients; ND= No data available; NA= Not applicable; RA= Rheumatoid Arthritis; sc= Subcutaneous; iv= Intravenous; wk= weeks; mo=months; DMARD-IR= Incomplete response to one or more disease modifying anti-rheumatic drug; Pbo= Placebo; MTX/HCQ/SSZ= Triple DMARD therapy with Methotrexate, Hydroxychloroquine, and Sulphasalazine; GC= Glucocorticoid

Table 2: Estimates of Odds Ratios for comparative efficacy of biologic and Methotrexate therapy in early RA patients within six months of treatment initiation

ACR50

Treatment		Week 2	Week 4	Week 8	Week 12	Week 16	Week 24
MTX	N	745	1091	1091	1380	793	1720
	OR	*REF*	*REF*	*REF*	*REF*	*REF*	*REF*
Abatacept +MTX	N	574	574	574	574	574	574
	OR	3.62 (0.49, 20.09)	2.44 (0.63, 9.17)	**2.75 (1.11, 7.00)**	**2.26 (1.35, 4.36)**	1.97 (0.66, 6.14)	**2.06 (1.09, 3.56)**
Adalimumab +MTX	N	705	705	705	1006	498	1060
	OR	**7.21 (1.62, 29.59)**	**3.99 (1.41, 11.95)**	**3.28 (1.60, 7.25)**	**2.61 (1.86, 4.13)**	2.45 (0.86, 7.52)	**2.17 (1.43, 3.12)**
Adalimumab	N	0	0	0	274	0	274
	OR	----------	----------	----------	1.23 (0.63, 2.61)	----------	0.82 (0.41, 1.64)
Etanercept	N	207	207	207	207	207	207
	OR	**21.59 (1.59, 766.48)**	**9.14 (1.57, 61.17)**	2.36 (0.71, 8.05)	1.21 (0.58, 2.98)	1.50 (0.38, 5.68)	1.46 (0.68, 3.33)
Golimumab +MTX	N	0	318	318	318	318	318
	OR	----------	2.45 (0.44, 14.08)	1.63 (0.47, 5.34)	1.80 (0.85, 4.47)	1.19 (0.29, 4.81)	1.48 (0.66, 3.31)
Golimumab	N	0	159	159	159	159	159
	OR	----------	3.53 (0.62, 20.91)	1.38 (0.40, 4.48)	1.77 (0.74, 3.72)	0.89 (0.22, 3.46)	1.15 (0.51, 2.68)
Rituximab +MTX	N	0	499	499	499	499	499
	OR	----------	1.24 (0.21, 6.83)	1.70 (0.54, 5.68)	1.54 (0.77, 3.43)	1.85 (0.48, 7.11)	1.69 (0.75, 3.59)
Tocilizumab +MTX	N	0	0	0	0	99	578
	OR	----------	----------	----------	----------	1.98 (0.46, 8.83)	1.57 (0.73, 3.31)
Tocilizumab	N	0	0	0	0	106	292
	OR	----------	----------	----------	----------	1.28 (0.30, 5.36)	1.21 (0.55, 2.57)
Tofacitinib	N	0	397	397	397	0	397
	OR	----------	**7.53 (1.35, 44.96)**	**4.75 (1.46, 15.62)**	**4.14 (1.76, 8.83)**	----------	**3.54 (1.65, 7.85)**

DAS Remission

Treatment		Week 2	Week 4	Week 8	Week 12	Week 16	Week 24
MTX	N	683	1209	1239	1466	1319	2161
	OR	*REF*	*REF*	*REF*	*REF*	*REF*	*REF*
Abatacept +MTX	N	256	256	256	256	256	256
	OR	1.10 (0.01, 119.06)	6.23 (0.72, 71.30)	3.15 (0.25, 39.76)	2.15 (0.54, 9.16)	1.79 (0.22, 14.74)	**2.25 (1.10, 4.61)**
Adalimumab +MTX	N	207	296	383	564	87	821
	OR	3.67 (0.23,	2.42 (0.64, 9.23)	3.10 (0.76,	**2.31 (1.06, 5.12)**	2.17 (0.27,	**2.21 (1.55, 3.06)**

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Abstract Number: 1671

Discovery of PRN1008, a Novel, Reversible Covalent BTK Inhibitor in Clinical Development for Rheumatoid Arthritis

Ronald J. Hill[1], Patrick Smith[2], Janakan Krishnarajah[3], J. Michael Bradshaw[1], Mohammad Masjedizadeh[1], Angelina Bisconte[1], Dane Karr[1], Timothy D. Owens[1], Ken Brameld[1], Jens Oliver Funk[1], David M. Goldstein[1], Philip A. Nunn[1] and Steven G. Gourlay[1], [1]Principia Biopharma, South San Francisco, CA, [2]d3 Medicine, Parsippany, NJ, [3]Linear Research Pty Ltd, Perth, Australia

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SESSION INFORMATION

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Session Title: Rheumatoid Arthritis - Small Molecules, Biologics and Gene Therapy Poster II

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: There is strong pre-clinical validation for Bruton's Tyrosine Kinase (BTK) as a therapeutic target for autoimmune diseases based on multiple animal models. Principia discovered a potent, selective inhibitor of BTK that forms a reversible covalent bond to a cysteine residue (Cys481) which results in prolonged residence time. We characterized the potency, selectivity and durability of target binding of PRN1008 in addition to testing its efficacy in an animal model of arthritis. Furthermore the safety, tolerability and PK/PD profile of PRN1008 was tested in a phase 1 clinical trial to assess its potential as a treatment for RA.

Methods: PRN1008 was tested for potency, durability and selectivity in biochemical and cell-based functional assays. The in vivo efficacy of PRN1008 was tested in a rat model of collagen-induced arthritis

		64.54)	(0.04, 9.23)	13.96)	**(1.06, 5.12)**	17.65)	**(1.33, 5.06)**
Adalimumab	N	0	0	0	274	0	274
	OR	------	------	------	1.01 (0.28, 3.58)	------	0.71 (0.37, 1.32)
Etanercept +MTX	N	320	320	265	320	320	320
	OR	**8.24 (1.28, 83.38)**	**8.58 (2.21, 36.43)**	7.67 (0.65, 104.32)	**3.13 (1.08, 8.38)**	3.19 (0.39, 26.16)	**2.28 (1.33, 3.88)**
Golimumab +MTX	N	0	0	0	0	0	318
	OR	------	------	------	------	------	1.54 (0.78, 3.13)
Golimumab	N	0	0	0	0	0	159
	OR	------	------	------	------	------	0.85 (0.39, 1.78)
Infliximab +MTX	N	0	0	0	0	751	0
	OR	------	------	------	------	2.07 (0.25, 16.82)	------
MTX/HCQ/SSZ	N	0	0	0	0	83	0
	OR	------	------	------	------	2.31 (0.13, 47.63)	------
Rituximab +MTX	N	0	499	499	499	499	499
	OR	------	9.61 (0.97, 346.41)	2.86 (0.23, 40.10)	2.73 (0.66, 12.10)	2.31 (0.26, 19.10)	1.36 (0.68, 2.84)
Tocilizumab +MTX	N	0	0	0	0	99	578
	OR	------	------	------	------	6.17 (0.64, 64.34)	**3.62 (1.84, 7.06)**
Tocilizumab	N	0	0	0	0	106	292
	OR	------	------	------	------	2.45 (0.25, 27.93)	**3.67 (1.82, 7.09)**
Tofactinib	N	0	397	397	397	0	397
	OR	------	**18.97 (1.68, 354.32)**	5.08 (0.39, 67.21)	**4.06 (1.02, 17.79)**	------	**3.42 (1.64, 8.26)**

Statistically significant odds ratios are presented in bold text. “REF”: MTX is the reference group. OR=odds ratio, ORs >1 favor the treatments over the reference group; N=number of patients randomized to a treatment group at that specific time point; DAS= Disease activity score

rheumatoid arthritis.

was tested in a rat model of collagen-induced arthritis (CIA). The first-in-human study consisted of two randomized, double-blind, placebo-controlled parts: Part A, 5 SAD cohorts (50-1200 mg) and Part B, 4 MAD cohorts with 10 days treatment (300mg and 600mg QD, 300mg and 450mg BID). Safety was assessed clinically and by ECG, vital sign and laboratory measurements. PRN1008 pharmacodynamic coverage was assessed by BTK occupancy; Pharmacokinetic/pharmacodynamic analysis was performed to characterize the relationship between BTK occupancy and PRN1008 PK.

Results: PRN1008 is very potent against BTK (IC50 = 1.3 ± 0.5 nM) and highly selective when tested against a broad panel of kinases. Cysteine targeting by PRN1008 results in a slow off-rate demonstrated by retention of 79 ± 2% of binding to BTK in PBMC 18 hours after washout in vitro. The covalent cysteine binding was completely reversible after denaturation of the target. Human B cell proliferation and activation (CD69 expression) were inhibited by PRN1008 with IC50 of 5 ± 2.4 nM and 123 ± 38 nM, respectively. Dose dependent efficacy in rat CIA was observed at trough BTK occupancies of 16 ± 3.6% to 79 ± 4.2%. PRN1008 was safe and well-tolerated in both parts of the human study without changes in vital signs, ECG or laboratory measurements. In humans dosed with PRN1008, BTK maximal occupancy was 90 ± 6% (mean ± SD) and 93 ± 2% at four hours on day 1 and day 10, respectively. BTK maximal occupancy at trough (12 or 24 hours) on day 10 ranged from 59 ± 11 to 80 ± 6%, when plasma PRN1008 was essentially cleared, demonstrating an extended PD effect. PK/PD analyses revealed that maximum occupancy was exposure-dependent; the rate of occupancy loss tended to be faster in subjects who did not achieve > 90% occupancy at 4h. Intersubject variability in occupancy was very low, particularly in subjects whose plasma exposures resulted in >90% occupancy at 4 hrs.

Conclusion: PRN1008 is a potent, selective and reversible covalent inhibitor of BTK with extended PD effects in vivo. PRN1008 was safe and well tolerated after single and 10 day dosing in humans. Dosing to achieve > 90% occupancy after a dose results in consistent and prolonged target occupancy. BTK target coverage with a daily dose of ≥300mg reached therapeutic levels based on translational studies in a rat model of arthritis. These data support continued development of PRN1008 as a therapeutic agent for rheumatoid arthritis.

Disclosure: R. J. Hill, Principia Biopharma, 1; **P. Smith**, Principia Biopharma, 5; **J. Krishnarajah**, Principia Biopharma, 2; **J. M. Bradshaw**, Principia Biopharma, 3; **M. Masjedizadeh**, Principia Biopharma, 1; **A. Bisconte**, Principia Biopharma, 3; **D. Karr**, Principia Biopharma, 3; **T. D. Owens**, Principia Biopharma, 1; **K. Brameld**, Principia Biopharma, 1; **J. O. Funk**, Principia Biopharma, 1; **D. M. Goldstein**, Principia Biopharma, 1; **P. A. Nunn**, Principia Biopharma, 3; **S. G. Gourlay**, Principia Biopharma, 1.

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Abstract Number: 1672

One-Year Safety of Sirukumab Monotherapy: Results from a Randomized, Double-Blind, Parallel-Group, Multicenter Study in Japanese Subjects with Moderate to Severe Rheumatoid Arthritis

Tsutomu Takeuchi[1], Hisashi Yamanaka[2], Masayoshi Harigai[3], Ryo Tamamura[4], Yuchi Kato[4], Yoshifumi Ukyo[4], Toshikazu Nakano[4], Takayuki Ota[4], Benjamin Hsu[5] and Yoshiya Tanaka[6], [1]Keio University School of Medicine, Tokyo, Japan, [2]Dept. of Rheumatology, Tokyo Women's Medical University,

Tokyo, Japan, [3]Dept of Pharmacovigilance, Tokyo Medical and Dental University, Tokyo, Japan, [4]Janssen Pharmaceutical K.K., Tokyo, Japan, [5]Janssen Research & Development, LLC, Spring House, PA, [6]The First Dept. of Internal Medicine, University of Occupational & Environmental Health, Kitakyusyu, Japan

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SESSION INFORMATION

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Session Title: Rheumatoid Arthritis - Small Molecules, Biologics and Gene Therapy Poster II

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose:

Interleukin-6 (IL-6) is a pleiotropic cytokine known for its proinflammatory functions. In rheumatoid arthritis (RA), increased concentrations of IL-6 may stimulate leukocyte recruitment to the joint and promote osteoclast maturation and activation, contributing to joint damage. Sirukumab is a human anti-IL-6 monoclonal antibody under development for RA treatment. This study was sponsored by Janssen in collaboration with GSK.

Methods:

The primary objective of this study was to assess the safety of sirukumab monotherapy in Japanese subjects with moderate to severe RA. The study consisted of a 52-week double-blind treatment phase and a 16-week post-treatment phase. In total, 122 subjects were randomized 1:1 to sirukumab 50mg every 4 weeks (q4) or sirukumab 100mg every 2 weeks (q2). No disease-modifying anti-rheumatic drugs (DMARDs) were permitted until Week 24.

Results:

Of the 122 subjects randomized in the 50mg q4 group and the 100mg q2 group, respectively: 77.0% and 70.5% were female; mean weights were 55.0 and 56.8 kg; mean disease durations were 7.60 and 7.95 years; and 14 and 10 subjects had experienced treatment with previous biologics (Table 1).

Safety: In 122 treated subjects, 56 subjects in the 50mg q4 group and 58 subjects in the 100mg q2 group experienced at least 1 adverse event (AE); there was no marked difference between the 2 groups. In addition, 9 subjects in the 50mg q4 group and 5 subjects in the 100mg q2 group discontinued the study agent due to AEs; 23 subjects in the 50mg q4 group and 24 subjects in the 100mg q2 group experienced injection site reactions, and 1 subject discontinued due to it. There were no deaths, major adverse cardiac events, or serious gastrointestinal perforations. Serious AEs (SAEs) were observed in 4 subjects in the 50mg q4 group and 5 subjects in the 100mg q2 group (Table 2). SAEs of “osteomyelitis”, “borderline serous tumor of ovary”, and “acute sinusitis” were mild or moderate, and considered reasonably related to the study drug.

Efficacy: At Week 24, the proportions of ACR20/50/70 responses were 73.8/49.2/24.6% in the 50mg q4 group and 82.0/63.9/36.1% in the 100mg q2 group. ACR responses were generally maintained through Week 52.

Conclusion:

Sirukumab 50mg q4 and 100mg q2 monotherapy dose regimens for 52 weeks were well tolerated in Japanese RA patients. The proportions of AEs in both groups were similar and there were no dose-dependent safety issues. The proportions of ACR 20/50/70 responses at Week 24 in the 100mg q2 group were numerically higher than those in the 50mg q4 group; however, the number of subjects was too limited to make conclusions about dose response.

Table 1: Demographics and Baseline Characteristics

	Sirukumab, 50mg q4	Sirukumab, 100mg q2
Randomized, n	61	61
Female, n (%)	47 (77.0%)	43 (70.5%)
Age, mean years (SD)	55.4 (10.7)	54.7 (12.2)
Weight, mean kg (SD)	55.0 (12.2)	56.8 (9.7)
Disease duration, mean years (SD)	7.60 (8.19)	7.95 (6.47)
DAS 28 (CRP) score, mean (SD)	5.6 (0.8)	5.8 (1.1)
Subjects treated with previous biologics, n (%)	14 (23.0%)	10 (16.4%)

Table 2: Summary of Treatment-emergent Adverse Events Through Week 52

	Sirukumab, 50mg q4	Sirukumab, 100mg q2
Treated, n	61	61
Any AEs, n (%)	56 (91.8%)	58 (95.1%)
Discontinuation due to AEs	9 (14.8%)	5 (8.2%)
Injection-site reaction AEs	23 (37.7%)	24 (39.3%)
SAEs, n (%)	4 (6.6%)	5 (8.2%)
SAEs reasonably related to study drug	1 (1.6%)	2 (3.3%)
Serious treatment-emergent infections	1 (1.6%)	2 (3.3%)
Malignancies, n (%)	0	1 (1.6%)

Tanabe Pharma Co., Pfizer Japan Inc., Santen Pharmaceutical Co. Ltd., Takeda Pharmaceutical Co. Ltd., Teijin Pharma Ltd., AbbVie GK, A, 2,AstraZeneca K.K., Eli Lily Japan K.K., Novartis Pharma K.K., Mitsubishi Tanabe Pharma Co., Asahi Kasei Medical K.K., AbbVie GK, Daiichi Sankyo Co. Ltd., Bristol-Myers K.K., Nipponkayaku Co. Ltd., 5,AbbVie GK, Bristol-Myers K.K., Chugai Pharmaceutical Co. Ltd., Eisai Co. Ltd., Janssen Pharmaceutical K.K., Mitsubishi Tanabe Pharma Co., Pfizer Japan Inc., Takeda Pharmaceutical Co. Ltd., Astellas Pharma, Daiichi Sankyo Co. Ltd., Celtrion, Nipponkayaku C, 8; **H. Yamanaka**, Abbott Immunology Pharmaceuticals, 2,AbbVie, 2,Asahikasei, 2,Astellas, 2,AstraZeneca, 2,Bristol-Myers Squibb, 2,Chugai, 2,Daiichi Sankyo, 2,Eisai, 2,GlaxoSmithKline, 2,Janssen Pharmaceutica Product, L.P., 2,Mitsubishi Tanabe, 2,MSD, 2,Nippon Kayaku, 2,Pfizer Inc, 2,Santen, 2,Taishotoyama, 2,Takeda, 2,Teijin, 2,Abbott Immunology Pharmaceuticals, 5,AbbVie, 5,Astellas, 5,AstraZeneca, 5,Bristol-Myers Squibb, 5,Chugai, 5,Daiichi Sankyo, 5,Eisai, 5,Mitsubishi Tanabe, 5,Nippon Kayaku, 5,Pfizer Inc, 5,Takeda, 5,Teijin, 5,Abbott Immunology Pharmaceuticals, 8,AbbVie, 8,Astellas, 8,Bristol-Myers Squibb, 8,Chugai, 8,Eisai, 8,Mitsubishi Tanabe, 8,Pfizer Inc, 8,Takeda, 8,Teijin, 8; **M. Harigai**, AbbVie Japan, Astellas Pharma, Bristol Myers Squibb, Chugai Pharmaceutical, Eisai, Mitsubishi Tanabe Pharma, Ono Pharmaceutical, Santen Pharmaceutical, Takeda Pharmaceutical, UCB Japan, Teijin Pharma, 2,AbbVie Japan, Janssen Pharma, Chugai Pharmaceutical, Teijin Pharma, Eli Lilly Japan, Zenyaku Kogyo, 5; **R. Tamamura**, Janssen Pharmaceutical K.K., 3; **Y. Kato**, Janssen Pharmaceutical K.K., 3; **Y. Ukyo**, Janssen Japan, 3; **T. Nakano**, Janssen Pharmaceutical K.K., 3; **T. Ota**, Janssen Pharmaceutical, 3; **B. Hsu**, Johnson & Johnson, 1,Johnson & Johnson, 3; **Y. Tanaka**, AbbVie, Daiichi-Sankyo, Chugai, Takeda, Mitsubishi-Tanabe, Bristol-Myers, Astellas, Eisai, Janssen, Pfizer, Asahi-kasei, Eli Lilly, GlaxoSmithKline, UCB, Teijin, MSD, Santen, 5,Mitsubishi-Tanabe, Takeda, Chugai, Astellas, Eisai, Taisho-Toyama, Kyowa-Kirin, AbbVie, Bristol-Myers, 2.

Abstract Number: 1673

The Transcription Factor Nuclear Protein Transcriptional Regulator 1 May Contribute to Increased Risk of Cardiovascular Disease in Patients with Rheumatoid Arthritis

Ida G. Fostad[1], Jon Roger Eidet[2], Torstein Lyberg[2], Ole K. Olstad[2], Tor Paaske Utheim[1,2], Knut Mikkelsen[3], Allan Wiik[4] and Ivana Hollan[3], [1]Department of Oral Biology, Faculty of Dentistry, University of Oslo, Oslo, Norway, [2]Department of Medical Biochemistry, Oslo University Hospital, Oslo, Norway, [3]Lillehammer Hospital for Rheumatic Diseases, Lillehammer, Norway, [4]Clinical Biochem/Immunology, Statens Serum Institute, Copenhagen S, Denmark
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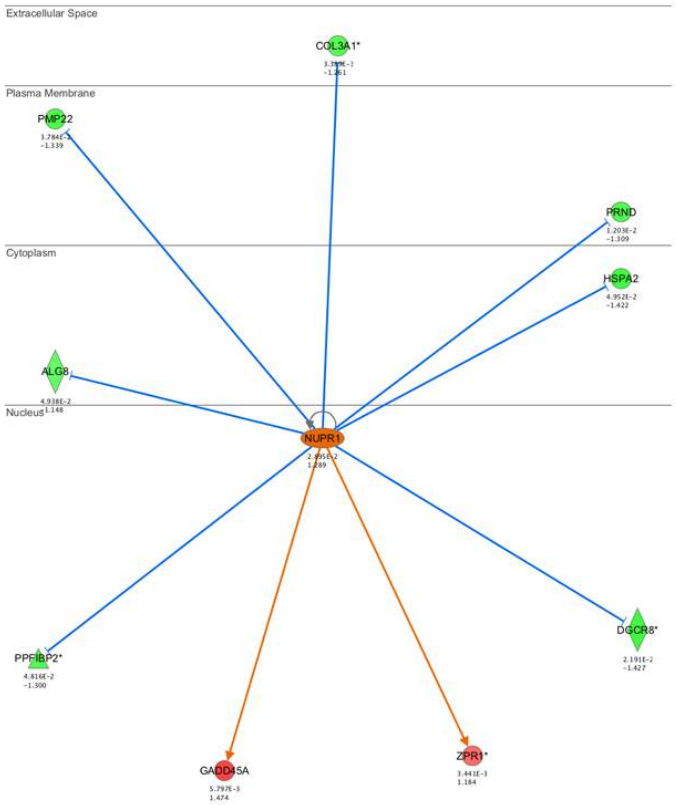
Session Type: ACR Poster Session B
Session Time: 9:00AM-11:00AM

Background/Purpose: The cause of accelerated atherosclerosis in rheumatoid arthritis (RA) is still unclear and appears to be multifactorial. Besides the traditional risk factors, also RA-specific risk factors play a role. Notably, vascular inflammation in the vascular adventitia may be a crucial factor. Elucidating the pathomechanism of cardiovascular (CV) disease in RA is essential in order to provide optimal CV prevention and treatment. Examination of vascular specimens may provide important clues for such an endeavor. The purpose of the study was to compare the gene expression profile in the aortic adventitia in coronary artery disease (CAD) patients with and without RA.

Methods: Total RNA was isolated from biopsies of the adventitia of the ascending aorta removed during coronary artery bypass grafting in patients with (n=8) and without (n=8) RA. The gene expression profile was determined using Affymetrix microarray. The CEL files were imported into the Partek Genomics Suite software, and differentially expressed genes were identified by one-way ANOVA (p<0.05; FC>1.1).

Results: Non-supervised hierarchical clustering analyses showed that the gene expression profiles clustered into two groups. A total of 15586 transcripts were identified, of which 201 were differentially expressed between the groups (p<0.05). Upstream analysis demonstrated activation of the stress-induced nuclear protein transcriptional regulator 1 (NUPR1) in RA patients (z-score: 3.0). Nine target molecules of NUPR1 were identified, including the endothelial dysfunction-related growth arrest and DNA-damage-inducible alpha (GADD45A), which was up-regulated in RA patients (p=0.006; FC=1.474) (Figure 1).



Conclusion: NUPR1 is a known key player in the cellular stress response. Our results indicate that the increased CV risk in RA might be related to activation of NUPR1, with downstream activation of GADD45A, which in turn promotes endothelial dysfunction. Interestingly, NUPR1 has also been linked to heart failure, and GADD45A to immune senescence, autoimmunity and inflammation, and to endothelial dysfunction. In theory, factors of the NUPR1 pathway might be a target for novel therapy.

Disclosure: I. G. Fostad, None; **J. R. Eidet**, None; **T. Lyberg**, None; **O. K. Olstad**, None; **T. P. Utheim**, None; **K. Mikkelsen**, None; **A. Wiik**, None; **I. Hollan**, None.

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Abstract Number: 1674

Predictive Factors of Persistence in Therapy with Abatacept in Patients with Rheumatoid Arthritis

Silvia Piantoni[1], Enrico Colombo[1], Angela Tincani[1], Paolo Airò[2] and Mirko Scarsi[3], [1]Rheumatology and Clinical Immunology Unit, Spedali Civili and University of Brescia, Brescia, Italy, [2]Rheumatology and Clinical immunology Unit, Spedali Civili of Brescia, Brescia, Italy, [3]Internal Medicine Unit, Esine Vallecamonica Hospital, ASL Vallecamonica-Sebino, Esine, Italy

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Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose:

The prediction of a stable treatment for rheumatoid arthritis (RA) is one of the targets of clinical research in rheumatology. However, only few biomarkers were successfully described as predictors of retention in therapy with biological agents. The aim of this paper was to investigate whether T-cell characterization might be used as predictor of abatacept (ABA) treatment continuation.

Methods:

Data are expressed as median (10^{th}-90^{th}percentile), if not otherwise specified. Seventy-one consecutive RA patients treated with ABA were prospectively

followed (female: 80%; age: 54 (40-71) years; disease duration: 7 (1-19) years; rheumatoid factor positivity: 81%; anti-cyclic citrullinated peptide (ACPA) positivity: 83%; DAS-28 (CRP): 5.1 (3.9-6.5); number of previous disease-modifying antirheumatic drugs: 3 (1-5); numbers of previous biological treatments: 2 (0-3), ABA as first line biological treatment: n=17).

T-cell characterization was performed by multi-color flow-cytometry (Navios, Beckman-Coulter).

Results:

At the end of our investigation, 28 patients discontinued ABA after 8 (4-16) months (18 for inefficacy; 5 for adverse events; 5 for other reasons) and 43 patients were still in therapy after 31 (13-62) months. In patients that maintained the treatment we observed: a lower proportion of smokers (25.6% vs 51.9%; p=0.03); a not significant lower proportion of ACPA positivity (76% vs 89.5%; p=0.13); a higher proportion of CD8+ terminally differentiated effector memory (TDEM) T-cells at baseline (38.7 (20.7-55.9) vs 22.0 (7.8-39.2) % of CD8+ T-cells; p=0.002). Other demographic, clinical and laboratory parameters were not different. Logistic multivariate analysis showed that only the proportion of CD8+TDEM T-cells was an independent predictive factor of high retention rate (OR (95% IC)=6.2 (1.2 to 30.8), p=0.026).

The ROC analysis showed a significant performance of this biomarker for prediction of persistence in therapy (using a cut-off of 30.6%: AUC: 0.760+0.07; p=0.002). patients with a high proportion of CD8+TDEM had a higher probability of continuing the treatment for a longer period of time (Mantel-Cox test: p<0.01). The positive and the negative predictive value of this test for treatment continuation were 83.3% and 65.0% respectively.

Conclusion:

T-cell characterization for identification of TDEM CD8+ T-cells might be a useful test to predict persistence in therapy with ABA. It can be speculated that a high TDEM CD8+ T cell percentage might be a marker of previous repeated T-cell activation, identifying a subset of patients in which the CD28 costimulation blockade with ABA may be particularly efficacious.

Disclosure: S. Piantoni, None; **E. Colombo**, None; **A. Tincani**, None; **P. Airò**, None; **M. Scarsi**, None.

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Abstract Number: 1675

Efficacy and Safety of Switched CT-P10 from Innovator Rituximab Compared to Those of Maintained CT-P10 in Patients with Rheumatoid Arthritis up to 56 Weeks

Dae-Hyun Yoo[1], Won Park[2], Chang-Hee Suh[3], Seung-Cheol Shim[4], Fidencio Cons Molina[5], Slawomir Jeka[6], Jan Brzezicki[7], Francisco G. Medina-Rodriguez[8], Pawel Hrycaj[9], Piotr Wiland[10], Eun Young Lee[11], Pavel Shesternya[12], Volodymyr Kovalenko[13], Leysan Myasoutova[14], Marina Stanislav[15], Sebastiao Radominski[16], Mie Jin Lim[17], Jung-Yoon Choe[18], Sung Young Lee[19] and Sang Joon Lee[20], [1]Department of Rheumatology, Hanyang University Hospital for Rheumatic Diseases, Seoul, South Korea, [2]Division of Rheumatology, Department of Internal Medicine, Inha University Hospital, Incheon, South Korea, [3]Department of Rheumatology, Ajou University Hospital, Suwon, South Korea, [4]Department of Internal Medicine, Chungnam National University Hospital, Daejeon, South Korea, [5]Centro de Investigacion en Artritis y Osteoporosis, Mexicali, Mexico, [6]University Hospital Nr 2 Dr. Jan Biziel, Collegium Medicum in Bydgoszcz, Nicolaus Copernicus University in Torun, Clinic of Rheumatology and Connective Tissue Diseases, Bydgoszcz, Poland, [7]Wojewodzki Szpital Zespolony w Elablagu, Elblag, Poland, [8]Rheumatology, LaSalle University, Mexico City, Mexico, [9]Department of Rheumatology and Clinical Immunology, Poznan University of Medical Sciences, Poznan, Poland, [10]Department of Rheumatology, Medical University of Wroclaw, Wroclaw, Poland, [11]Division of Rheumatology, Department of Internal Medicine, Seoul National University College of Medicine, Seoul, South Korea, [12]Rheumatology Department, Krasnoyarsk State Medical University, Krasnoyarsk, Russia, [13]Section of Non-coronarogenic Myocardial Diseases and Clinical Rheumatology, National Scientific Center, Kiev, Ukraine, [14]City Reumatology Center, Research Medical Complex Vashe Zdorovie, Kazan, Russia, [15]Research Rheumatology Institute n. a. V.A. Nassonova, Moscow, Russia, [16]CETI-Centro de estudos em Terapias Inovadoras, Universidade Federal do Parana, Curitiba, Brazil, [17]Division of Rheumatology, Departments of Internal Medicine, Inha University Hospital, Incheion, South Korea, [18]Internal Medicine, Catholic University of Daegu, School of Medicine, Daegu, South Korea, [19]Clinical Planning Department, CELLTRION, Inc., Incheon, South Korea, [20]CELLTRION, Inc., Incheon, South Korea

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SESSION INFORMATION

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Session Time: 9:00AM-11:00AM

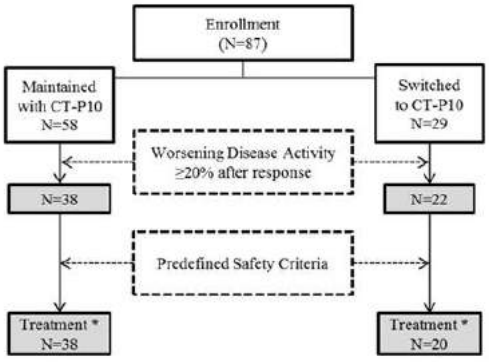
Background/Purpose: Pharmacokinetic (PK) equivalence and similarity of clinical efficacy, safety and immunogenicity up to week 24 were demonstrated between CT-P10, a biosimilar candidate for innovator rituximab (RTX), and RTX groups in patients with rheumatoid arthritis (RA) [1].

The objective of this open-label study was to confirm efficacy and safety of switched CT P10 from RTX in RA patients (NCT01873443).

Methods : A total of 87 patients, who completed up to 72 weeks of the phase I randomized controlled trial (NCT01534884), entered into the open-label extension study for maximum of 56 weeks: 58 and 29 patients were recruited from CT-P10 and RTX groups, respectively, in the controlled study. Thirty

eight (65.5%) and 20 (69.0%) patients in each group received CT-P10 treatment according to DAS28 and the predefined safety criteria during this open-label study (Figure 1). Among 29 patients who did not receive CT-P10 treatment during the study, disease activity was well controlled until the end of study in 20 and 7 patients from the CT P10 and RTX groups, respectively. Two patients in RTX group did not receive CT-P10 treatment due to safety reason. Efficacy and safety assessments were monitored throughout the study.

Figure 1 Patient Disposition



* Last course of treatment was allowed until week 80 of entire study period (controlled study + open-label study)
Note: Number of patients who omitted an additional course of treatment due to stable disease activity/ safety: CT-P10, 20/0; RTX, 7/2

Results : The DAS28-CRP and ESR improvement at Week 24 after the last CT-P10 infusion were similar in the 2 treatment groups; -2.2 for both groups in DAS28-CRP (p=0.9474) and -2.7 for maintained CT-P10 group and -2.4 for switched CT-P10 group in DAS28-ESR (p=0.5687).

The proportion of patients experienced at least one adverse event (AE) or serious AE was comparable between maintained and switched CT-P10 groups. Infusion related reactions were reported in 1 patient in each treatment group (Table 1).

No deaths, malignancy or AEs leading to permanent study drug discontinuation were reported during the study.

Table 1 Efficacy by DAS28 Changes

	Maintained CT-P10 Group	Switched CT-P10 Group
DAS28-CRP, Mean ± SD (n)		
Baseline	5.9 ± 0.90 (38)	5.8 ± 0.72 (18)
Changes at Week 24 after 1st Course	-2.2 ±1.15 (33)	-2.2 ± 1.16 (16)
DAS28-ESR, Mean ± SD (n)		
Baseline	6.8 ±0.83 (38)	6.5 ±0.80 (18)
Changes at Week 24 after 1st Course	-2.7 ±1.17 (34)	-2.4 ±1.33 (16)

RTX, innovator rituximab; DAS28, disease activity score in 28 joints; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; SD, standard deviation

Table 2 Safety Summary

	Maintained CT-P10 Group N=38	Switched CT-P10 Group N=20	Total N=58
Number of Patients (%) with at Least One			
AE	9 (23.7)	4 (20.0)	13 (22.4)
Serious AE	1 (2.6)	1 (5.0)	2 (3.4)
Infusion-related reaction	1 (2.6)	1 (5.0)	2 (3.4)
Infection	3 (7.9)	2 (10.0)	5 (8.6)
Malignancy	0	0	0
Discontinuation due to AEs	0	0	0

RTX, innovator rituximab; AE, adverse events

Conclusion : Switched CT-P10 from RTX demonstrated comparable efficacy and safety profiles compared to those of maintained CT-P10. Maintained CT-P10 was also well tolerated and effective up to 2 years in RA patients.

Reference

[1] Yoo DH, et al. Arthritis Rheum 2013; 65 (Suppl 10): S736

Disclosure: D. H. Yoo, CELLTRION, Inc., 5; **W. Park**, CELLTRION, Inc., 5; **C. H. Suh**, CELLTRION, Inc., 5; **S. C. Shim**, CELLTRION, Inc., 5; **F. Cons Molina**, CELLTRION, Inc., 2; **S. Jeka**, CELLTRION, Inc., 2; **J. Brzezicki**, CELLTRION, Inc., 2; **F. G. Medina-Rodriguez**, CELLTRION, Inc., 2; **P. Hrycaj**, CELLTRION, Inc., 2; **P. Wiland**, CELLTRION, Inc., 2; **E. Y. Lee**, CELLTRION, Inc., 2; **P. Shesternya**, CELLTRION, Inc., 2; **V. Kovalenko**, CELLTRION, Inc., 2; **L. Myasoutova**, CELLTRION, Inc., 2; **M. Stanislav**, CELLTRION, Inc., 2; **S. Radominski**, CELLTRION, Inc., 2; **M. J. Lim**, CELLTRION, Inc., 2; **J. Y. Choe**, CELLTRION, Inc., 2; **S. Y. Lee**, CELLTRION, Inc., 3; **S. J. Lee**, CELLTRION, Inc., 3.

Abstract Number: 1676

Systematic Review and Network Meta-Analysis of Combination Treatments in Disease Modifying Anti-Rheumatic Drug Experienced Patients with Severe Rheumatoid Arthritis: Analysis of American College of Rheumatology Criteria Scores 20, 50, and 70: An Update

Michelle E. Orme[1], Charles Hawes[2] and Stephen A. Mitchell[3], [1]ICERA consulting UK, Swindon, United Kingdom, [2]Pfizer UK, Surrey, United Kingdom, [3]Abacus International UK, Bicester, United Kingdom

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Background/Purpose: Biologic disease-modifying anti-rheumatic drugs (DMARDs) in combination with conventional DMARDs provide patients with severe rheumatoid arthritis (RA) and an inadequate response to conventional DMARDs with treatment options. A previously published systematic review/network meta-analysis (NMA)[1] comparing the relative efficacy of biologic DMARDS was updated to take account of new clinical evidence for current and recently licensed treatments with alternative modes of administration, i.e. subcutaneous (SC) versus intravenous (IV).

Methods: The systematic review undertaken in April 2011 was updated in November 2014. Literature searches were conducted in MEDLINE, EMBASE and the Cochrane Library, in addition to hand searches of conference proceedings and reference lists. A Bayesian NMA, which estimates the relative effectiveness of treatments whilst preserving the randomized comparisons within each trial, was conducted in WinBUGS using a random-effects logit-link model fitted to the binomial trial data namely the count of patients reaching American College of Rheumatology (ACR) scores 20/50/70 at follow-up.

Results: In addition to the 13,647 citations originally identified[1], 7,328 citations were identified in the update, of which 18,337 were excluded after screening the title/abstract. After reviewing 2,638 full-text papers, 43 studies enrolling over 15,000 patients and reporting ACR outcomes between 12 and 30 weeks were identified for inclusion in the meta-analysis. The following nine biologic DMARDs/ conventional DMARD combinations were included in the evidence network: abatacept IV (5 randomized controlled trials (RCTs), n=1,484); abatacept SC (3 RCTs, n=1,113); adalimumab (8 RCTs, n=1,112); certolizumab pegol (4 RCTs, n=802); etanercept (8 RCTs, n=881); golimumab (4 RCTs, n=345); infliximab (7 RCTs, n=1,122); tocilizumab IV (8 RCTs, n=2,545); tocilizumab SC (1 RCT, n=631).

The table below presents the NMA results for ACR20/50/70 outcomes for combination treatments of interest.

TABLE		
Treatment	**Median OR vs. cDMARD (95% CrI)**	**% patients achieving ACR20/50/70 (95% CrI)**
ACR20		
Conventional DMARD	-	28.5% (25.0%, 32.4%)
Abatacept 10mg/kg/4 weeks IV + cDMARD	3.11 (2.06, 4.62)*	55.4% (44.2%, 65.7%)
Abatacept 125mg/week SC + cDMARD	3.50 (2.04, 6.23)*	58.3% (44.1%, 71.7%)
Adalimumab 40mg/2 weeks + cDMARD	3.22 (2.30, 4.53)*	56.3% (46.8%, 65.5%)
Certolizumab pegol 200mg/2 weeks + cDMARD	9.23 (5.78, 14.69)*	78.6% (69.2%, 85.9%)
Etanercept 2x25mg/week + cDMARD	9.39 (5.02, 17.98)*	79.0% (66.1%, 88.0%)
Golimumab 50mg/4 weeks + cDMARD	3.79 (2.35, 6.04)*	60.2% (47.7%, 71.4%)
Infliximab 3mg/kg/8 weeks + cDMARD	3.18 (2.23, 4.50)*	56.0% (46.2%, 65.3%)
Tocilizumab 162mg/week SC + cDMARD	4.18 (1.98, 9.22)*	62.5% (43.8%, 79.0%)
Tocilizumab 8mg/kg/4 weeks IV + cDMARD	4.63 (3.31, 6.64)*	64.9% (55.9%, 73.4%)
ACR50		
Conventional DMARD	-	12.6% (10.3%, 15.2%)
Abatacept 10mg/kg/4 weeks IV + cDMARD	3.58 (2.23, 5.90)*	33.9% (23.3%, 47.0%)
Abatacept 125mg/week SC + cDMARD	3.86 (2.06, 7.37)*	35.7% (22.2%, 52.4%)
Adalimumab 40mg/2 weeks + cDMARD	3.71 (2.49, 5.57)*	34.8% (25.3%, 45.9%)
Certolizumab pegol 200mg/2 weeks + cDMARD	6.86 (3.97, 12.03)*	49.7% (35.3%, 64.3%)
Etanercept 2x25mg/week + cDMARD	11.24 (4.96, 26.87)*	61.7% (40.9%, 79.9%)
Golimumab 50mg/4 weeks + cDMARD	4.63 (2.41, 9.24)*	40.0% (24.9%, 57.8%)
Infliximab 3mg/kg/8 weeks + cDMARD	3.68 (2.42, 5.74)*	34.6% (24.8%, 46.4%)
Tocilizumab 162mg/week SC + cDMARD	5.27 (2.09, 13.43)*	43.0% (22.7%, 66.4%)
Tocilizumab 8mg/kg/4 weeks IV + cDMARD	5.47 (3.58, 8.50)*	44.1% (32.7%, 56.3%)
ACR70		
Conventional DMARD	-	4.2% (3.1%, 5.7%)
Abatacept 10mg/kg/4 weeks IV+ cDMARD	3.65 (2.34, 6.13)*	13.8% (8.5%, 22.7%)
Abatacept 125mg/week SC + cDMARD	4.08 (2.36, 7.75)*	15.2% (8.7%, 26.7%)
Adalimumab 40mg/2 weeks + cDMARD	4.39 (2.84, 6.97)*	16.1% (10.1%, 25.2%)
Certolizumab pegol 200mg/2 weeks + cDMARD	13.66 (6.68, 33.64)*	37.4% (21.5%, 60.8%)
Etanercept 2x25mg/week + cDMARD	19.66 (5.31, 139.3)*	46.3% (18.2%, 86.3%)
Golimumab 50mg/4 weeks + cDMARD	5.51 (2.60, 12.65)*	19.5% (9.6%, 37.3%)
Infliximab 3mg/kg/8 weeks + cDMARD	3.63 (2.359, 5.88)*	13.7% (8.5%, 22.1%)
Tocilizumab 162mg/week SC + cDMARD	6.24 (2.63, 14.29)*	21.5% (9.9%, 39.8%)
Tocilizumab 8mg/kg/4 weeks IV + cDMARD	7.28 (4.53, 11.73)*	24.2% (15.2%, 36.4%)
Abbreviations: CrI, credible interval (Bayesian equivalent of a confidence interval); IV, intravenous; OR, odds ratio; SC, subcutaneous; *significant		

difference based on the 95% CrI

Conclusion: Based on the meta-analysis of the studies that met the inclusion criteria for this review, all biologic DMARDs in combination with conventional DMARDs were significantly more effective than conventional DMARDs alone in improving ACR 20/50/70 outcomes in patients with severe RA and an inadequate response to conventional DMARDs.

Etanercept in combination with conventional DMARDs was the most effective biologic DMARD combination in terms of ACR 20/50/70 response.

References: Orme ME et al. Systematic review and network meta-analysis of combination and monotherapy treatments in disease-modifying antirheumatic drug-experienced patients with rheumatoid arthritis: analysis of American College of Rheumatology criteria scores 20, 50, and 70. Biologics. 2012 (6): 429-64.

Disclosure: M. E. Orme, ICERA consulting, 5; **C. Hawes**, Pfizer Ltd, 3; **S. A. Mitchell**, Abacus International, 5.

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Abstract Number: 1677

Disease-Regulated Expression of Anti-Inflammatory Interleukin-10 for the Treatment of Rheumatoid Arthritis

Mathijs G.A. Broeren[1], Miranda B. Bennink[1], Onno J. Arntz[2], Wim van den Berg[2] and Fons A.J. van de Loo[2], [1]Experimental Rheumatology, Radboud university medical center, Nijmegen, The Netherlands, Nijmegen, Netherlands, [2]Experimental Rheumatology, Radboud university medical center, Nijmegen, Netherlands

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Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: The current treatment for patients with rheumatoid arthritis (RA) consists of biological drugs, often in combination with methotrexate. However, some patients fail to respond to biological therapy in one or multiple joints. We are therefore aiming to develop a gene therapy for local treatment of affected joints. By using disease-inducible promoters to drive expression, the joints will only produce biological drugs during a disease flare.

Methods: Microarrays on joint tissue of 20 RA patients and 7 patients without joint disease were analyzed to find genes that are upregulated in the joint during active disease.

The promoter of the *CXCL10* gene was isolated from human cDNA and cloned into a lentiviral vector containing the firefly luciferase reporter gene. THP-1 cells were transduced with the lentiviral constructs and stimulated for 6 hours with pro-inflammatory stimuli, 64 RA patient sera and 63 control sera to determine the inducibility of the promoters. The luciferase reporter gene was replaced by IL-10 and the expression of recombinant IL-10 was measured under control of the *CXCL10*promoter. The production of TNFα, IL-1β, IL-8 and MCP-1 by lipopolysaccharide (LPS) stimulated synovial cells were measured by multiplex ELISA assay.

Results: The microarrays showed a 10-fold upregulation of *CXCL10*, an interferon inducible gene known to be expressed by many cell types. Primary cells obtained from patient synovium were transduced with the *CXCL10*-luciferase reporter vector and stimulated with pro-inflammatory lipopolysaccharide (LPS) or with TNFα. This resulted in a 3.3- and 2.3-fold upregulation of the luciferase signal respectively. The *CXCL10* promoter was also activated by serum from RA patients and could significantly distinguish between RA serum and healthy donor serum (P=0.017). The *CXCL10* promoter in THP-1 monocytes showed a 33.7-fold upregulation after 8h stimulation with TNFα. The promoter activity declined after 96h, but was re-inducible by a second TNFα-stimulation. This shows the temporal responsiveness of the *CXCL10*promoter to inflammatory signals and the vigilant state under basal conditions. For therapeutic testing, the luciferase reporter gene was replaced by the anti-inflammatory Interleukin-10 (IL-10) gene. RA synovial cells transduced with the CXCL10-IL10 lentivirus produced significantly less pro-inflammatory cytokines (TNFα, IL-1β, IL-8 and MCP-1) after LPS stimulation compared to control virus. This was observed in multiple patients. These results show the functionality of the CXCL10-IL10 lentivirus in the desired synovial target cells.

Conclusion: Our CXCL10 regulated IL-10 gene construct shows good responsiveness to inflammatory stimuli and inhibits inflammatory cytokine production by RA synovial cells. CXCL10-regulated IL10 overexpression can thus provide inflammation-inducible local gene therapy suitable for joints with persistent RA that are refractory to treatment.

Disclosure: M. G. A. Broeren, None; **M. B. Bennink**, None; **O. J. Arntz**, None; **W. van den Berg**, None; **F. A. J. van de Loo**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/disease-regulated-expression-of-anti-inflammatory-interleukin-10-for-the-treatment-of-rheumatoid-arthritis

Abstract Number: 1678

Does the Level of Disease Control Achieved with Biologics Influence Overall Costs for Health Care and Work Loss in RA?

Jonas K Eriksson[1], Martin Neovius[2], Johan Askling[3] and ARTIS study group, [1]Clinical Epidemiology Unit, Dept of Medicine, Karolinska Institutet, Stockholm, Sweden, [2]Clinical Epidemiology Unit, Karolinska Institutet, Stockholm, Sweden, [3]Rheumatology Unit, Rheumatology Unit, Karolinska University Hospital, Stockholm, Sweden

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SESSION INFORMATION

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Session Time: 9:00AM-11:00AM

Background/Purpose:

Numerous studies have modeled whether biologic drugs are good value for money in the treatment of RA, in terms of reducing health care use and work loss to a higher extent than when using alternative therapeutic options. However, whereas several studies have estimated costs in RA and in relation to therapies, few studies have investigated cost trajectories in relation to the clinical response to such therapies. The aim of this study was therefore to estimate the societal monthly costs related to work loss, health care use, and prescription drug use over 2 years in relation to the level of disease activity control achieved after start of biologic therapy.

Methods:

RA patients ≥18y with a treatment period of ≥3 months with a first ever biologic drug between 2006 through 2010 were identified from the Swedish Rheumatology Quality Register (including the Swedish Biologics Register ARTIS). Based on start DAS28 and the lowest registered DAS28 during visits 3 to 12 months after biologic start, patients were categorized as EULAR good, moderate and no responders.

Data on work loss, health care use, drug use, and mortality were retrieved from nationwide registers. Patients were followed from 12 months before the DAS28 evaluation until first of 24 months of follow-up, death, emigration, or Dec 31, 2012. As a general population benchmark we used five sex-, age-, and county-matched comparators per RA patient.

Results:

A total of 3788 patients with RA who started their first biologic therapy in 2006 through 2010 were identified (mean age, 56.7y; 75% women; mean disease duration, 10.2y). Of these, 1950 (51%) patients achieved and were categorized as EULAR good response (55.1y; 72%; 10.0y), 1208 (32%) achieved moderate response (59.0y; 79%; 10.6y), and 630 (17%) patients never reached any EULAR response (57.2y; 77%; 10.1y).

The mean monthly cost at 24 months after DAS28 evaluation was lower in working age patients with good response (n=1249) compared to patients with moderate or no response (n=1052; $2837 vs $3799; adjusted mean difference [95% CI], -$242 [-503; -$15]; **Figure**). The lower monthly cost in patients with good response was mainly driven by reduced work loss costs.

In patients ≥65y, the mean monthly health care cost was similar across the response groups.

Conclusion:

Working age RA patients who achieve a good level of disease control during the year after start of biologic therapy have lower monthly costs as compared to patients with moderate or no response. However, the monthly cost in those who achieved good disease control was still around 3 times higher compared to the general population 2 years after biologic therapy initiation.

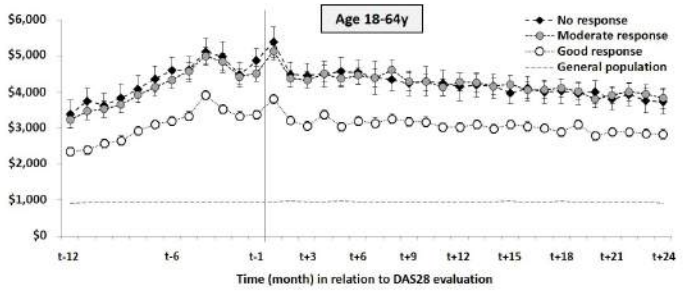

Figure Trajectories of costs for hospital care, drugs and lost work days, stratified by EULAR good, moderate and no response in working age patients with RA and their matched general population comparators

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Disclosure: J. K. Eriksson, None; **M. Neovius**, None; **J. Askling**, AstraZeneca, Pfizer, UCB, Roche, Merck, BMS, Abbvie., 9.

Abstract Number: 1679

Vicm Is a Novel Biomarker of Macrophage Activity Evaluated in a Phase IIb Clinical Trial of Mavrilimumab

Anne C. Bay-Jensen[1], Xiang Guo[2], Joachim Høg Mortensen[1], Morten Asser Karsdal[1] and Wendy White[2], [1]Biomarkers and Research, Nordic Bioscience, Herlev, Denmark, [2]Translational Sciences, MedImmune, LLC, Gaithersburg, MD
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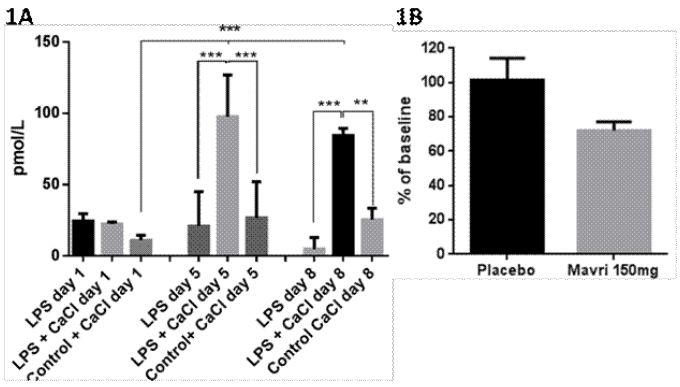
Background/Purpose: Rheumatoid arthritis (RA) is an autoimmune disease driven by chronic inflammation, upheld by sustained recruitment and infiltration of leucocytes, especially macrophages. Mavrilimumab is a fully human monoclonal antibody targeting the granulocyte-macrophage colony-stimulating factor receptor-α. Mavrilimumab suppresses the effect of granulocytes and monocytes/macrophages, in RA. Serologic biomarkers can also be used to assess efficacy. The serum neo-epitope biomarker, citrullinated and MMP-degraded vimentin (VICM), is a marker of inflammation. We investigated whether the biomarker VICM is biomarker of activated macrophages, and whether mavrilimumab modulates serum concentrations of VICM in RA patients.

Methods: *In- vitro* experiments were carried out on peripheral mononuclear cells (PBMCs). Isolated monocytes were differentiated by incubating with M-CSF for 5 days prior to any treatment, and were cultured as a monolayer on plastic. Cells were treated either with lipopolysaccharide (LPS), LPS + calcium chloride (CaCl), or only CaCl as control. Treatment of LPS was 100ng/ml, and CaCl was 0.22µg/mL. Conditioned medium were collected at Days 1, 5, and 8, and stored for ELISA analysis. The *in-vitro* studies was repeated 4 times and analyzed by Kruskal-Wallis analysis. Serum samples were from the Phase IIb RCT (NCT01706926) of RA patients (n=140) receiving either placebo or 150-mg every-other-week dosages of mavri, in combination with methotrexate, for 169 days. VICM was measured at Days 0 and 169. Spearman's correlations were carried out to investigate the association between disease activity (DAS28 and mTSS) and serum concentrations of VICM, and changes in VICM concentrations after mavrilimumab treatment compared to placebo.

Results: The *in-vitro* data indicated that the release of VICM was significantly greater in supernatants from activated macrophages (LPS+CaCl treated) at Days 5 and 8 ($p<0.01$), compared with controls (Fig. 1A), indicating that VICM is a biomarker of activated macrophages. Mavrilimumab significantly inhibited VICM serum concentrations (30%) in patients receiving 150 mg every other week compared with placebo at Day 169 ($p<0.05$) (Fig. 1B), as well as suppressed the presence of CD14 positives cells by approximately 12%. In addition, VICM correlated significantly with DAS28 ($r=0.13$, $p<0.05$), mTSS ($r=0.15$, $p<0.01$) and CRP ($r=0.26$, $p<0.01$) at baseline. Patients with mTSS>23.5 had significantly elevated VICM serum concentrations compared with patients with mTSS<23.5 at baseline ($p<0.01$).

Conclusion: The data indicate that VICM is biomarker of activated macrophages by revealing i) the direct release of VICM from activated macrophages *in vitro,* and ii) a significant suppression upon treatment with the mavrilimumab. These data support further development of mavrilimumab and other drugs targeting macrophages in RA.



Disclosure: A. C. Bay-Jensen, Nordic Bioscience Diagnostic, 1,Nordic Bioscience Diagnostic, 3; **X. Guo**, AstraZeneca, 1,MedImmune, 3; **J. H. Mortensen**, Nordic Bioscience, 3; **M. A. Karsdal**, Nordic Bioscience Diagnostic, 1,Nordic Bioscience Diagnostic, 3; **W. White**, AstraZeneca, 1,MedImmune, 3.

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Abstract Number: 1680

Selective JAK1 Inhibition with Filgotinib (GLPG0634) Decreases Plasma Markers of

Inflammation and Joint Damage in Patients with Rheumatoid Arthritis

René Galien[1], Annegret Van der Aa[2], Roland Blanque[1], Sophie Darquenne[1], Pille Harrison[2] and Chantal Tasset[2], [1]Galapagos SASU, Romainville, France, [2]Galapagos NV, Mechelen, Belgium

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Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose:

Among the 4 Janus kinase (JAK) family members, JAK1 often has a dominant role in the intracellular signaling for cytokines involved in auto-immune and inflammatory diseases, such as rheumatoid arthritis (RA). We therefore hypothesized that inhibiting JAK1 only would provide an efficacious treatment for RA, and may avoid potential side effects associated with inhibition of other JAKs. Filgotinib (GLPG0634) displays a strong selectivity for inhibition of JAK1 over JAK2, JAK3 and TYK2. In phase 2a clinical trials, filgotinib rapidly improved signs and symptoms of RA with good tolerability and safety. The data reported here present the changes in serum pharmacodynamic markers observed in RA patients after 4 weeks of treatment with filgotinib.

Methods:

RA patients (n=91) with insufficient response to MTX were randomized to receive placebo or 30, 75, 150, or 300 mg filgotinib once-daily orally for 4 weeks as add-on to MTX in a double-blind phase 2a study. Blood was sampled pre-dose and on the last day of treatment. Concentrations of the biomarkers chitinase-3 L1 (CHI3L1)/YKL-40 and SAA were quantified using an ELISA assay from R&D Systems. All other biomarker concentrations were evaluated at Myriad RBM Inc. using the InflammationMAP© assay. For each parameter, data are reported in percentage relative to the baseline value of each individual.

Results:

After 4 weeks of treatment with filgotinib, levels of the acute phase proteins CRP and haptoglobin dose-dependently decreased in RA patients. IL-18 and SAA, two markers of inflammation, and sTNFR2 whose expression is increased in RA patients, also displayed a significant decrease. The plasma concentration of ICAM-1 and VCAM-1, both known to play a major role in the adhesion and recruitment of leukocytes, was also decreased. The concentration of the metalloprotease MMP3, involved in tissue remodelling and induced in inflammation, decreased following treatment with 150 and 300 mg QD. Both CHI3L1 and VEGF, whose expressions are controlled by JAK1-activating gp130 receptors and STAT transcription factors, were decreased at all doses of filgotinib.

TREATMENT	CRP	Haptoglobin	IL-18	SAA	sTNFR2	ICAM-1	VCAM-1	MMP3	CHI3L1	VEGF
PLACEBO	94 +/- 15	101 +/- 15	1034 +/- 4	88 +/- 14	94 +/- 4	97 +/- 6	99 +/- 3	92 +/- 10	120 +/- 5	138 +/- 23
75 mg	72 +/- 13	91 +/- 7	96 +/- 5	86 +/- 20	111 +/- 10	97 +/- 3	110 +/- 6	116 +/- 20	76 +/- 9 ***	106 +/-5
150 mg	38 +/- 10 **	71 +/- 9	83 +/- 6 *	43 +/- 10	80 +/- 6 **	87 +/- 6	85 +/- 3 **	66 +/- 10	74 +/- 8 **	111 +/-6
300mg	22 +/- 5 ***	50 +/- 6 **	82 +/- 3 **	38 +/- 8 *	79 +/- 4 *	79 +/- 3 *	89 +/- 2	54 +/- 6 *	56 +/-8 ***	97 +/- 8 *

Percent change from baseline in biomarkers after 4 weeks of filgotinib treatment (Mean +/- SEM - Kruskal – Wallis + Dunn's post hoc tests *: $p<0.05$; **: $p<0.01$; ***: $p<0.001$, compared to baseline)

Conclusion:

Within 4 weeks of treatment with the JAK1-selective inhibitor filgotinib in RA patients, plasma markers of inflammation and joint damage significantly decreased. Markers linked to JAK1-dependent signalling were also significantly impacted. Overall, together with the previously reported clinical efficacy of filgotinib, these results support that inhibition of JAK1 is sufficient to correct inflammation in RA patients, and may offer a treatment strategy that avoids side effects associated with inhibition of other JAKs.

Disclosure: R. Galien, Galapagos SASU, 3,AbbVie, 2; **A. Van der Aa**, Galapagos NV, 3,AbbVie, 2; **R. Blanque**, Galapagos SASU, 3,AbbVie, 2; **S. Darquenne**, Galapagos SASU, 3,AbbVie, 2; **P. Harrison**, Galapagos NV, 3,AbbVie, 2; **C. Tasset**, Galapagos NV, 3,AbbVie, 2.

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Abstract Number: 1681

4-Week Treatment of Rheumatoid Arthritis Patients with the JAK1-Selective Inhibitor Filgotinib (GLPG0634) Changes Lipid Profile with a Preferential Increase in HDL

René Galien[1], Pille Harrison[2], Reginald Brys[2], Annegret Van der Aa[2], Gerben van 't Klooster[2] and Chantal Tasset[2], [1]Galapagos SASU, Romainville,

France, [2]Galapagos NV, Mechelen, Belgium
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Background/Purpose:

Patients with active rheumatoid arthritis (RA) present low levels of lipids - total cholesterol (TC), low density lipoprotein-cholesterol (LDL-c), high density lipoprotein-cholesterol (HDL-c) and triglycerides (TG) - and yet are at a higher risk of cardiovascular disease. RA therapies may modulate lipid levels, presumably because of their anti-inflammatory effects, but some treatments preferentially increase LDL-c, thereby worsening the atherogenic index. We previously reported that 4-week treatment with the JAK1 selective inhibitor filgotinib (GLPG0634), showed a different profile with little effect on LDL-c and a dose-dependent increase in HDL-c. The current study further characterizes the lipid profile of RA patients after filgotinib treatment.

Methods:

RA patients (n=91) with insufficient response to MTX were randomized to receive placebo or 30, 75, 150 or 300 mg filgotinib once-daily orally for 4 weeks as add-on to MTX in a double-blind phase 2a study. Blood was sampled pre-dose and on the last day of treatment. Plasma PCSK9, ApoC-II, ApoC-III, SAA, and CETP concentrations were measured using ELISA kits. Plasma CETP and LCAT activities were determined using a commercial assay from Roar Biomedical. Plasma cholesterol (total and non-HDL-cholesterol), HDL-c, TG, ApoA-I and ApoB were measured using assays available from Diasys. CETP expression in white blood cells (WBC) was measured using qPCR.

Results:

HDL-c increased after treatment with 75, 150 and 300 mg of filgotinib, whereas TC and non-HDL-c increased in plasma only with 300mg dose, compared to baseline.

TREATMENT	TC	non-HDL-c	HDL-c	TC/HDL-c
PLACEBO	110 +/- 7	110 +/- 8	116 +/- 10	98 +/- 5
30 mg	126 +/- 16	131 +/- 20	107 +/- 5	119 +/- 14
75 mg	105 +/- 5	103 +/- 7	114 +/- 4 ***	93 +/- 4
150 mg	99 +/- 5	96 +/- 5	111 +/- 5 *	90 +/- 4 **
300mg	119 +/- 3 ***	113 +/- 3 ***	146 +/- 7 ***	85 +/- 5 ***

Percent change from baseline in biomarkers after 4 weeks of filgotinib treatment (Mean +/- SEM – T-test *: p<0.05; **: p<0.01; ***: p<0.001, compared to baseline)

TC/HDL-c ratio (atherogenic index) decreased after 4 weeks of filgotinib treatment . Plasma concentrations of ApoA-I, ApoB, ApoC-II and ApoC-III also indicated a preferential increase in HDL-c over LDL-c, with an increase in ApoA-I, ApoC-II and ApoC-III and no change in ApoB concentrations, resulting in a decrease in ApoB/ApoA-I ratio. CETP gene expression in circulating WBC as well as protein concentration and enzyme activity in plasma decreased after treatment. LCAT activity and paraoxonase-1 (PON-1) levels increased with filgotinib treatment. There was no change in plasma concentration of PCSK9.

Conclusion:

These early data show that 4 weeks of treatment with filgotinib changed the lipid profile in RA patients, with a preferential increase in HDL-c. As a consequence, the atherogenic index in RA patients improved with doses of 150 and 300 mg once daily. This correlated with changes in HDL-c proteins and enzymes involved in HDL-c homeostasis such as ApoA-1, PON-1, LCAT and CETP, but not in those linked to LDL-c (ApoB, PCSK9). Further longer-term studies are needed to confirm these findings and their cardiovascular relevance.

Disclosure: R. Galien, Galapagos SASU, 3,AbbVie, 2; **P. Harrison**, Galapagos NV, 3,AbbVie, 2; **R. Brys**, Galapagos NV, 3,AbbVie, 2; **A. Van der Aa**, Galapagos NV, 3,AbbVie, 2; **G. van 't Klooster**, Galapagos NV, 3,Abboie, 2; **C. Tasset**, Galapagos NV, 3,AbbVie, 2.

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Abstract Number: 1682

Suppression of Chronic Arthritis By a Novel Nuclear Factor of Activated T-Cell 5 (NFAT5) Inhibitor

Wan-Uk Kim[1], Eun-Jin Han[2], Chong-Hyeon Yoon[3], Ki-Jo Kim[4], Seung-Ah Yoo[5], Bong Ki Hong[5] and Saseong Lee[5], [1]Internal Medicine, Seoul St. Mary's Hospital, The Catholic University of Korea, Seoul, South Korea, [2]Institute of Bone & Joint Disease, The Catholic University of Korea, Seoul, South Korea, [3]Division of Rheumatology, Department of Internal Medicine, College of Medicine, The Catholic University of Korea, Seoul, South Korea, [4]St. Mary's

Hospital, Seoul, South Korea, [5]Institute of Bone and Joint Diseases, The Catholic University of Korea, Seoul, South Korea
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Background/Purpose: We reported that nuclear factor of activated T-cells 5 (NFAT5), originally identified as an osmo-protective transcription factor, has a critical role in the pathogenesis of rheumatoid arthritis (RA). In the present study, we investigated to discover a small molecule to specifically inhibit pro-inflammatory activity of NFAT5.

Methods: We screened small molecules (>150,000) to effectively suppress biosynthesis of nitric oxide (NO), a sensitive end-product of NFAT5 in RAW 264.7 macrophages using high-throughput drug screening. Fluorescence-activated cell sorting (FACS) analysis was performed to confirm a direct NFAT5 inhibitory activity of the candidate chemicals using RAW 264.7 macrophages transfected stably with a novel NFAT5-specific GFP reporter under lipopolysaccharide (LPS) stimulation. Expression of NFAT5 and its target genes was confirmed by quantitative RT-PCR, western blot, ELSIA, and NO assay. *In vivo*effect was tested in adjuvant-induced arthritis (AIA) and collagen-induced arthritis (CIA) mice models.

Results: NFAT5 regulated the production of NO and IL-6 by RAW 264.7 macrophages under LPS stimulation. Among the screened small molecules, filtered were 198 candidate chemicals that strongly inhibited the NO production (IC50 < 1 μM). After testing direct NFAT5 inhibitory activity and *in vitro* cytotoxicity, KRN2 and its oral derivative with high serum stability (KRN5) were finally selected. These compounds did not affect NFAT1-4, NF-κB, p38 MAP kinase and CREB activity, excluding the potential off-target effect of the candidate molecules. We further found out the inhibitory mechanism of KRN2 in regulating NF-κB binding capacity on the NF-κB binding site in the promoter region of NFAT5. Interestingly, these compounds inhibited LPS-induced IL-6, TNF-α, GM-CSF, iNOS, nitric oxide production in RAW 264.7 macrophages, while they did not affect *AR* and *SMIT*mRNA expression involved in osmo-protection and cellular homeostasis. Effectively, KRN2 and KRN5 alleviated disease severity of arthritis and oral administration of KRN5 successfully prevented the development of arthritis in experimental mice models.

Conclusion: We identified selective inhibitors of NFAT5 (KRN2 and KRN5) that potently inhibited the production of pro-inflammatory mediators in macrophages and effectively suppressed the development of experimental arthritis. These compounds could be a good candidate for treating the chronic inflammatory arthritis.

Disclosure: W. U. Kim, Korea Healthcare Technology R&D Project, National Research Foundation of Korea (NRF) funded by the Ministry of Education, 2; **E. J. Han**, None; **C. H. Yoon**, None; **K. J. Kim**, None; **S. A. Yoo**, None; **B. K. Hong**, None; **S. Lee**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/suppression-of-chronic-arthritis-by-a-novel-nuclear-factor-of-activated-t-cell-5-nfat5-inhibitor

Abstract Number: 1683

Epithelial Changes in Response to Tocilizumab Combined with Methotrexate in Rheumatoid Arthritis: Evaluated on Circulating Fragments of Type IV Collagen

Natasja Stæhr Gudman[1], Inger Byrjalsen[2], Kishwar Musa[3], Stephanie Nina Kehlet[3], Morten Asser Karsdal[4] and Anne C. Bay-Jensen[4], [1]Nordic Bioscience A/S, Herlev, Denmark, [2]Research & Development, Nordic Bioscience, Herlev, Denmark, [3]Laboratory, Nordic Bioscience, Herlev, Denmark, [4]Biomarkers and Research, Nordic Bioscience, Herlev, Denmark
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Session Time: 9:00AM-11:00AM

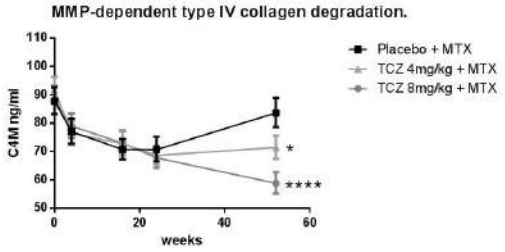
Background/Purpose: It is well documented that epithelium turnover is markedly increased in the affected joints of rheumatoid arthritis (RA). This causes disruption of the well organized supramolecular architectures of the basal lamina composed of a network of collagen IV and other components such as laminins, nidogens or perlecan. The aim of this study was to 1) investigate the circulating levels of MMP-degraded collagen type IV fragments in RA and 2) if TCZ may reduce the epithelial turnover of the RA pathogenesis.

Methods: The LITHE biomarker study (n =682) was a phase III double-blind, placebo (PBO)-controlled, parallel group study of 4- and 8-mg/kg TCZ in combination with methotrexate (MTX). The biomarker C4M, a competitive ELISA assay evaluating fragments of type IV collagen, was tested in serum from baseline and week 4, 16, 24, and 52. A dose-dependent effect was investigated and the differences between groups were evaluated by Mann-Whitney test. Early response was evaluated at week 16 as 7-20% improvement in swollen/tender joint counts; and ACR50 was evaluated at week 52.

Results: All of the 3 patient groups experienced a decrease of C4M from baseline to week 16 of roughly 20%. At this point there were no significant differences between the C4M levels of the placebo group compared to treatment groups. This level seemed to be stabile from week 16-24 for all of the 3

groups. Interestingly, from week 24-52 C4M in the placebo group significantly increased ($p<0.0001$) from a geometric mean of 70.7ng/ml to 83.6ng/ml. The C4M level of the patient group receiving TCZ 4mg/kg was steady with a geometric mean of 68.6 at week 24 and 71.4 at week 52. Patients in the TCZ 8mg/kg had a significant decrease ($p=0.0017$) from a geometric mean of 67.8 to 58.8 from week 24-52.There was a significant difference in C4M level between placebo and treatment groups at week 52 ($p<0.05$).

Conclusion: The differences of C4M between the 3 treatment groups at week 52, indicate a dose-dependent reduction of epithelial degradation as an effect of treatment over time. Furthermore, the decrease of C4M from baseline to week 16 in all of the 3 treatment groups, suggests that MTX has an additional effect on top of that of TCZ.



Evaluation of biomarker levels at baseline, week 4, 16, 24 and 52. Differences between Placebo and TCZ 4mg/kg or TCZ 8mg/kg were evaluated by mean of Mann-Whitney tests. *$p<0.05$, ** $p<0.01$, ***$p<0.001$, ****$p<0.0001$. *Error bars are illustrated as geometric mean + 95% CI.*

Disclosure: N. S. Gudman, Nordic Bioscience Diagnostic, 3; **I. Byrjalsen**, Nordic Bioscience Diagnostic, 3; **K. Musa**, Nordic Bioscience Diagnostic, 3; **S. N. Kehlet**, Nordic Bioscience, Laboratory, 3; **M. A. Karsdal**, Nordic Bioscience Diagnostic, 1,Nordic Bioscience Diagnostic, 3; **A. C. Bay-Jensen**, Nordic Bioscience Diagnostic, 1,Nordic Bioscience Diagnostic, 3.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/epithelial-changes-in-response-to-tocilizumab-combined-with-methotrexate-in-rheumatoid-arthritis-evaluated-on-circulating-fragments-of-type-iv-collagen

Abstract Number: 1684

Malignancies in Patients with Incident Psoriatic Arthritis 1970-2008 in Relation to a Comparator Cohort: A Population-Based Case-Control Study

Katelynn Wilton[1,2], Brittny T. Major[3], Cynthia Crowson[3] and Eric L. Matteson[4], [1]Medical Scientist Training Program, Mayo Clinic, Rochester, MN, [2]Medical Scientist Training Program, Mayo Clinic Rochester, Rochester, MN, [3]Biostatistics, Mayo Clinic, Rochester, MN, [4]Rheumatology, Mayo Clinic, Rochester, MN

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Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose:

In psoriatic arthritis (PsA), misdirected inflammation and therapeutic use of immunosuppressants causes global immune compromise. Similar immunocompromised states, as in rheumatoid arthritis and psoriasis patients, have resulted in an increased risk of malignancy. The aim of our study was to compare the development of malignancy in patients with PsA to comparators without PsA.

Methods:

A geographically well-defined population based cohort of 217 patients diagnosed with PsA was identified by individual medical record review. Cases were classified according to the ClASsification Criteria for Psoriatic ARthritis (CASPAR) criteria. Medical records of 217 PsA cases and a comparison cohort of 271 age and sex matched subjects from the same source population were evaluated retrospectively for cancer occurrence. Patients in both cohorts were followed until death, migration from the geographic area or 12/31/2014. Malignancy information was retrieved from the institutional Cancer Registry data to determine prevalence of most major malignancy types. Information concerning non-melanoma skin cancer incidence was collected manually. Cumulative incidence of malignancy adjusted for competing risk of death was used for malignancy incidence analysis. Cohort comparisons were performed using Gray's test.

Results:

The PsA and non-PsA cohorts (mean age at incidence/index date: 44.0 [SD: 14.2] years; 60% male in both cohorts) were followed on average 15.3 (SD 9.4) and 15.9 (SD 8.6) years, respectively. Prior to PsA incidence/index date, 8 patients with PsA and 15 non-PsA subjects had malignancies ($p=0.20$). During

follow-up, a total of 28 malignancies were detected in the patients with PsA (cumulative incidence at 10 years after PsA incidence: 9.3% [SE 2.2%}), and 41 malignancies were diagnosed in the comparator subjects, representing no statistical difference in malignancy incidence (cumulative incidence at 10 years after index date: 9.4% [SE 2.2%], p=0.21). The relative risk of most individual malignancies was not statistically increased in the PsA cohort compared to the non-PsA cohort. There were more non-melanoma skin cancers in the PsA cohort (n=23 compared to 14 in the comparator cohort) although the difference did not reaching statistical significance (p= 0.09).

Conclusion:

The risk of cancer in this population based cohort of patients with PsA is not increased compared to the general population. This finding is consistent with several other studies employing other methodologies. There were numerically more non-melanoma skin cancers in the PsA cohort, which may be related to the generally increased risk of these cancers seen in psoriasis. We suggest that patients with PsA should be routinely screened for occurrence of these skin cancers.

Disclosure: K. Wilton, None; **B. T. Major**, None; **C. Crowson**, None; **E. L. Matteson**, Novartis/Sanofi/Centocor-Jansen/Celgene/Amgen/Roche/Genentech/Mesoblast/Pfizer, 2.

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Abstract Number: 1685

Metabolic Syndrome in Patients with Psoriatic Arthritis Is Associated to Peripheral Disease Activity

Camilla De Gaspari[1,2], Julio C. B. Moraes[3,4], Percival D Sampaio-Barros[5,6], Celio R. Gonçalves[7], Carla G.S. Saad[8] and Cláudia Goldenstein-Schainberg[9], [1]Rheumatology Division, University of Sao Paulo, São Paulo, Brazil, [2]Rheumatology, Universidade de São Paulo, São Paulo, Brazil, [3]Rheumatology, Faculdade de Medicina Universidade de São Paulo, São Paulo, Brazil, [4]Rheumatology Division, Faculdade de Medicina da Universidade de São Paulo., Jundiai, Brazil, [5]Rheumatology Division, Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil, [6]Faculdade de Medicina da Universidade de São Paulo, Rheumatology Division, Brazil, Sao Paulo, Brazil, [7]Reumatologia, Faculdade de Medicina da Universidade de São Paulo, Sao Paulo, Brazil, [8]Rheumatology Division, Rheumatology Division, Faculdade de Medicina da USP, São Paulo, Brazil, [9]Clínica Médica, Faculdade de Medicina da Universidade de São Paulo, Sao Paulo, Brazil

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Session Time: 9:00AM-11:00AM

Background/Purpose: Psoriatic arthritis (PsA) is present in about 30% of cutaneous psoriasis (PsO) patients. Both PsO and PsA are frequently associated to comorbidities that have important implications in the global approach of the psoriatic disease. In PsO, metabolic syndrome (MetS) is associated with disease severity and in PsA the relationship with MetS is likely linked to the underlying chronic inflammatory process. Although MetS is common in PsA, there are no data regarding its prevalence and association with disease activity in brazilian patients. Therefore our objectives were to evaluate the prevalence of MetS, associated comorbidities and correlate findings with some parameters of disease activity in a cohort of Brazilian patients with PsA from a single tertiary center.

Methods: One hundred and one PsA patients regularly followed-up at our outpatient rheumatology clinic during the period of October 2013 to April 2014 were evaluated. All patients were assessed for obesity by measurement of body mass index, functional impairment by HAQ, physical activity practice and the presence of comorbidities including arterial hypertension, diabetes, dyslipidemia, MetS and non-alcoholic fatty liver disease (NAFLD) by abdominal ultrasound. The NCEP-ACT III criteria were used to identify subjects with MetS while DAS 28, BASDAI and ASDAS to evaluate PsA disease activity. Student's t-test, Chi-square and Fisher's exact tests were performed for statistical analyses and P values ≤ 0.05 were considered significant.

Results: Gender proportion was similar with 49 males (48.5%) and 52 females (51.5%), mean age = 54.8+-13yrs (range 26-85yrs) and mean disease duration = 14.4+-8.1yrs (range 04-44yrs). Only 25% PsA patients had normal weight and 75% were overweight. The majority were sedentary (74%), in one third of them (28%) due to joint pain though not associated to worse HAQ score (p=0.7). Half patients (50/101=49.5%) had MetS, with comparable frequencies in both genders and regardless of types of cutaneous PsO involvement. Overall prevalence of arterial hypertension was 49%, dyslipidemia 58%, diabetes 22%, obesity 31% and NAFLD 62%, significantly higher in patients with MetS in comparison to those without MetS (76%vs.23%; 68%vs.27%; 40%vs.4%; 52%vs.9%; 83%vs.22% respectively) (p=0.001). Interestingly, the prevalence of MetS was lower in axial PsA subjects compared to those without axial manifestation (28%vs.49%, p=0.03), and no difference was observed among other PsA subtypes (p>0.05). Further analysis of patients with vs. without MetS revealed that those with MetS used less non-steroidal anti-inflammatory drugs (NSAIDs) (52%vs.74%, p= 0.019), less leflunomide (6%vs.20%, p=0.041) and had higher DAS 28 scores (3.1vs.2.8, p=0.025). Mean HAQ scores were for patients with and without MetS [(0.8 (0.5-2.3) vs. 1(0-3)p=0.4]

Conclusion: The considerable prevalence of MetS in patients with PsA associated to peripheral joint disease activity strengthens a common inflammatory pathway for both conditions. Early disease management including specific therapy allied to lifestyle changes and weight loss, not only to reduce comorbidities, but also to improve disease control, is mandatory.

Disclosure: C. De Gaspari, None; **J. C. B. Moraes**, None; **P. D. Sampaio-Barros**, None; **C. R. Gonçalves**, None; **C. G. S. Saad**, None; **C. Goldenstein-Schainberg**, None.

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Abstract Number: 1686

Body Mass Index Is Associated with Hip Arthritis in Patients with Ankylosing Spondylitis

Hyemin Jeong[1], Jiwon Hwang[2], Young Hee Eun[1], Eun-Jung Park[3], Ji-Min Oh[4], Hyungjin Kim[5], Joong Kyong Ahn[6], Jaejoon Lee[1], Chan Hong Jeon[7], Eun-mi Koh[8] and Hoon-Suk Cha[9], [1]Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea, [2]Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, Seoul, South Korea, [3]Department of Medicine, Jeju National University Hospital, Jeju University School of Medicine, Jeju, South Korea, [4]Anyang SAM Hospital, Anyang, South Korea, [5]Department of medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea, [6]Department of Medicine, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, Seoul, South Korea, [7]Department of Internal Medicine, Soonchunhyang University College of Medicine, Bucheon, South Korea, [8]Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea, [9]Division of Rheumatology, Department of Internal Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea

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Session Title: Spondylarthropathies and Psoriatic Arthritis - Comorbidities and Treatment Poster II

Session Type: ACR Poster Session B

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Background/Purpose:

To evaluate the clinical courses and associated factors of hip arthritis in patients with ankylosing spondylitis (AS).

Methods:

In this retrospective analysis, we evaluated 488 AS patients at a single tertiary hospital. Among the patients with hip arthritis in AS, radiographic hip arthritis was assessed using the Bath Ankylosing Spondylitis Radiology Hip Index (BASRI-h), and the average of the hip joint space width (interbone distance) at three distinct sites between the acetabulum and femoral head was recorded at baseline and the last visit at the outpatient clinic.

Results:

Among 488 patients with AS, 60 (12.3%) patients had hip arthritis. Body mass index (BMI) and erythrocyte sedimentation rate (ESR) were associated with hip involvement (OR 1.11, 95% CI 1.03 to 1.20, p = 0.005 and OR 1.01, 95% CI 1.00 to 1.02, p = 0.004, respectively). Long disease duration and advanced axial disease were associated with severe hip involvement (3≥BASRI-h) at baseline. BASRI-h and interbone distance did not change significantly in patients with hip involvement during the follow-up period of 81.4 ± 35.7 months. Five patients had hip joint replacement surgery during follow-up period. The BMI and initial BASRI-h were associated with joint replacement surgery (OR 1.29, 95% CI 1.01 to 1.65, p = 0.044 and OR 4.90, 95% CI 1.05 to 22.78, p = 0.043, respectively).

Conclusion:

Most of the patients with hip arthritis in AS showed no significant radiographic progression during the follow-up period. BMI was associated with hip arthritis in patients with AS.

Disclosure: H. Jeong, None; **J. Hwang**, None; **Y. H. Eun**, None; **E. J. Park**, None; **J. M. Oh**, None; **H. Kim**, None; **J. K. Ahn**, None; **J. Lee**, None; **C. H. Jeon**, None; **E. M. Koh**, None; **H. S. Cha**, None.

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Abstract Number: 1687

Increased Carotid Intima-Media Thickness in Psoriatic Arthritis Patients Compared with Systemic Lupus Erythematosus Patients and Healthy Controls

Handan Yarkan[1], Aslıgul Dunya[2], Pinar Cetin[1], Gercek Can[1], Nurullah Akkoc[3] and **Fatos Onen**[1], [1]Rheumatology, Dokuz Eylul University Faculty of Medicine, Izmir, Turkey, [2]Dokuz Eylul University Faculty of Medicine, Izmir, Turkey, [3]Department of Rheumatology, Dokuz Eylul University, Faculty of Medicine, Izmir, Turkey

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Background/Purpose: The aim of this study was to investigate carotid intima-media thickness (IMT) in patients with psoriatic arthritis (PsA) and compare it with those in patients with systemic lupus erythematosus (SLE) and healthy controls (HC).

Patients and Methods: Non-diabetic patients with PsA and age and body mass index (BMI) matched patients with SLE were included. Bilateral carotid IMTs were evaluated by using B-mode ultrasonography in PsA patients and compared with those in controls.

Results: There were 42 PsA patients (30 female, 12 male; mean age: 45.36 ± 8.9 years) who fulfilled CASPAR criteria and 38 patients (37 female, 1 male; 41.2± 13.0 years) who fulfilled the 1982 revised ACR criteria for SLE. Thirthy healthy hospital workers (27 female, 3 male; mean age 41.2 ± 6.8 years) were recruited as HC. The frequency of hiperlipidemia was found to be significantly higher in patients with PsA than SLE patients and HC ($p<0.001$) but hypertension was more common in SLE patients ($p=0.002$). The averaged carotid IMT was found to be higher in PsA patients in comparison with the SLE patients and HC ($p<0.001$).

Conclusion: This study showed that carotid IMT measurements were higher in PsA patients than SLE patients and HC.

Table 1. B-mode ultrasonography results in the study subjects

	Averaged CCA IMT (mm)	Right CCA IMT (mm)	Left CCA IMT (mm)
PsA patients (n:42)	0.76 ± 0.15*	0.72 ± 0.12*	0.79 ± 0.18*
SLE patients (n:38)	0.58 ± 0.11	0.56 ± 0.12	0.60 ± 0.12
Healthy controls (n:30)	0.57 ± 0.12	0.55 ± 0.12	0.59 ± 0.15

Data are mean ± SD (*$p<0.001$ for PsA patients vs SLE patients and healthy controls). CCA: common carotid artery

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Disclosure: H. Yarkan, None; **A. Dunya**, None; **P. Cetin**, None; **G. Can**, None; **N. Akkoc**, None; **F. Onen**, None.

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Abstract Number: 1688

Trends in Hospitalizations and Charges for Ankylosing Spondylitis, 1993-2012

Na Lu[1], Hyon Choi[2] and **Maureen Dubreuil**[3,4], [1]Boston University School of Medicine, Boston, MA, [2]Massachussetts General Hospital/Harvard Medical School, Boston, MA, [3]Rheumatology, Boston VA HealthCare System, Boston, MA, [4]Rheumatology, Boston University School of Medicine, Boston, MA

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Background/Purpose: In the last two decades, tumor necrosis factor alpha (TNFα) inhibitors have been approved for use, and recommended as part of clinical treatment guidelines for people with ankylosing spondylitis (AS) who fail non-steroidal anti-inflammatory drugs and physiotherapy. Contemporary data on US hospitalization rates, costs and length of stay in the TNFα era have not been examined. We sought to determine rates of hospitalization, length of stay and hospitalization costs for patients with AS over the past two decades.

Methods: Using the Nationwide Inpatient Sample (NIS), we evaluated trends in hospitalizations for AS between 1993 and 2012. We describe rates of hospitalization and hospital charges among US residents hospitalized with a principal diagnosis of AS using ICD-9 codes from the NIS. Analyses were performed using NIS sampling weights to obtain US national estimates.

Results: Rates of hospitalization for AS as a principal diagnosis decreased from 0.4/100,000 to 0.2/100,000 over the study period, and mean length of stay also decreased from 8.9 days to 5.7 days (**Table** and **Figure**). However, mean hospitalization charges increased from $40,855 to $94,047, after adjustment for inflation to 2012 US dollars using the Consumer Price Index. The numbers of in-hospital deaths were too low for meaningful comparisons over time.

Conclusion: Rates of hospitalizations for AS and mean length of stay has decreased in AS, providing a benchmark for the perceived improvement in AS care, which may be related to use of biologics. However, hospitalization charges for AS have more than doubled from 1993 to 2012. The reasons for the drastic increase in hospitalization charges warrant further investigation.

Table. Hospitalization rates, mean length of stay and mean hospitalization charges for US residents hospitalized with a principal diagnosis of ankylosing spondylitis between 1993 and 2013 in the Nationwide Inpatient Sample.

	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012
Total discharges (N)	912	959	1,005	887	804	723	773	765	685	679	680	739	780	608	567	610	590	594	583	480
Rate of discharges[+]	0.4	0.4	0.4	0.3	0.3	0.3	0.3	0.3	0.2	0.2	0.2	0.3	0.3	0.2	0.2	0.2	0.2	0.2	0.2	0.2
Length of stay, days (mean)	8.9	8.0	9.0	8.1	7.3	6.3	6.3	5.6	6.8	5.4	5.8	7.9	6.6	5.6	6.1	5.8	5.2	5.5	5.2	5.7
Charges, $ (mean), unadj.	19,831	19,701	26,247	22,423	24,681	24,422	27,937	25,954	26,779	29,782	30,536	47,206	54,455	44,878	65,053	64,912	61,228	75,879	87,102	94,047
Charges, $ (mean), adj to 2012 US$	40,856	38,741	49,390	40,771	43.652	41.856	54.637	41.292	40.730	43.268	42.646	63.163	76.051	55.387	76.889	73.980	67.636	81.053	90.294	94.047
In-hospital deaths	18 (2.0%)	16 (1.7%)	23 (2.3%)	22 (2.5%)	17 (2.1%)	*	19 (2.5%)	*	*	*	*	14 (2.0%)	*	*	14 (2.4%)	*	*	*	10 (1.8%)	*

[+]Per 100,000 persons; *Numbers under 10 are not reported in NIS

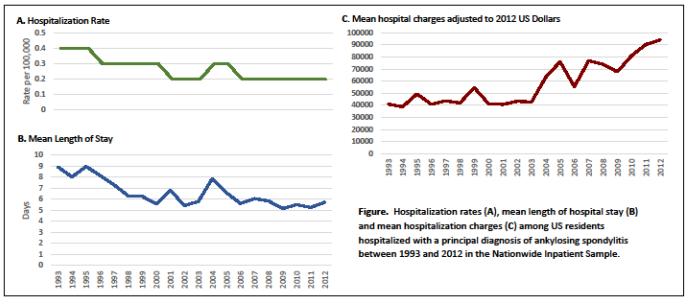

Figure. Hospitalization rates (A), mean length of hospital stay (B) and mean hospitalization charges (C) among US residents hospitalized with a principal diagnosis of ankylosing spondylitis between 1993 and 2012 in the Nationwide Inpatient Sample.

Disclosure: N. Lu, None; **H. Choi**, Takeda Pharmaceuticals International, Inc., 5,Astra-Zeneca Pharmaceuticals, 5,Astra-Zeneca Pharmaceuticals, 9; **M. Dubreuil**, None.

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Abstract Number: 1689

Cross Sectional Study Investigating the Effect of the Presence of Fibromyalgia on Common Clinical Disease Activity Indices in Patients with Psoriatic Arthritis

Shay Brikman[1], **Victoria Furer**[2], Yonatan Wolman[3], Sara Borok Lev-Ran[4], Ari Polachek[5], Ofir Elalouf[2], Amir Sharabi[6], Ilana Kaufman[1], Daphna Paran[5] and Ori Elkayam[6], [1]Tel Aviv Sourasky Medical Center, Tel Aviv, Israel, [2]Rheumatology, Tel-Aviv Medical Center, Sackler Faculty of Medicine, Tel-Aviv University, Tel-Aviv, Israel, [3]Medicine B, Tel Aviv Sourasky Medical Center, The Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel, [4]Tel Aviv Sourasky Medical Center, Tel AViv, Israel, [5]Rheumatology, Tel Aviv Sourasky Medical Center and the Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel, [6]Tel Aviv Sourasky Medical Center, The Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel
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Background/Purpose:

To study the effect of the presence of fibromyalgia (FMS) on common clinical disease activity indices in patients with psoriatic arthritis (PsA).

Methods:

Seventy –three consecutive outpatients with PsA (mean age 51.7 years old;

42 females, 57.5 %) were enrolled in a prospective cross-sectional study.

Patients were evaluated for the presence of fibromyalgia according to the ACR criteria. In parallel, they all underwent a clinical evaluation of diseases activity as well as application of patient reported outcomes questionnaires including HAQ, BASDAI, and DLQI. Disease activity was evaluated using the Composite Psoriatic Disease Activity Index (CPDAI), Minimal Disease Activity (MDA) and Disease Activity index for Psoriatic Arthritis (DAPSA) scores.

Results:

The overall prevalence of FMS was 17.8% (13 patients), with a significant higher prevalence of female gender (12 patients, 92.3%, P = 0.005). CPDAI and DAPSA scores were significantly higher in patients with PsA and FMS (9.23 ± 1.92; 27.53 ± 19.23) than in patients with PsA alone (4.25 ± 3.14; 12.82 ± 12.71; P < 0.001; P = 0.003). None of the patients with FMS complied with the criteria of MDA, whereas twenty-six PsA-only patients complied with it (43.3%, P = 0.003). HAQ, BASDAI and LEI scores were significantly worse in patients with PsA and associated FMS (Table 1).

Conclusion:

FMS is related to worse scores on the CPDAI, DAPSA, MDA, HAQ, BASDAI and LEI in patients with PsA. The presence of FMS distorts our clinical understanding of the abovementioned indices, thus, it should be taken into consideration in the treatment algorithm in order to avoid unnecessary upgrading of treatment.

Table 1.

Indices	PsA (n = 60)	PsA and FMS (n = 13, 17.8%)	Pv
CPDAI ± SD	4.25 ± 3.14	9.23 ± 1.92	< 0.001
DAPSA ± SD	12.82 ± 12.7	27.53 ± 19.23	0.003
MDA (%)	26 (43.3%)	0	0.003
HAQ median	0.25 (0-1)	1.75 (1.07-2.37)	<0.001
BASDAI±SD	2.87± 2.35	7.18±1.73	<0.001
LEI median	0 (0-1)	3 (2-4)	<0.001
PASI	2.1 (0-1)	3 (2-4)	0.22

Disclosure: S. Brikman, None; **V. Furer**, None; **Y. Wolman**, None; **S. Borok Lev-Ran**, None; **A. Polachek**, None; **O. Elalouf**, None; **A. Sharabi**, None; **I. Kaufman**, None; **D. Paran**, None; **O. Elkayam**, None.

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Abstract Number: 1690

Fibromyalgia in Spondyloarthritis: Impact on Disease Activity Assessment

Jean Wach, Marie-Claude Letroublon and **Jacques G Tebib**, Rheumatology, Hospices Civils de Lyon, Centre Hospitalier Lyon-Sud, Pierre-Bénite, France
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Background/Purpose:

Spondyloarthritis (SpA) is the second most frequent inflammatory rheumatic disease, which main manifestations are spinal pain and peripheral arthritis or enthesitis. Fibromyalgia (FM), a diffuse painful syndrome that may be associated with SpA, shares a number of common symptoms such as pain, fatigue and sleep disturbance. Still, its influence on SpA disease activity assessment, mainly dependant on patient-based outcome measures, has been poorly studied.

Methods:

This monocentric cross-sectional study included consecutive patients with SpA (according to the Assessment of SpondyloArthritis international Society (ASAS) classification criteria) from one of the authors clinics (JGT) between March 2010 and May 2011. FM was diagnosed according to the 1990 ACR

classification criteria. A controlled population of FM without SpA was included. Patients characteristics, BASDAI, ASDAS-CRP, BASFI, BASMI, SF-36 were compared.

Results:

The study included 103 SpA patients (table 1). Eighteen patients (17.5%) presented a concomitant FM, including 12 out of 81 axial SpA (14.8%) and 6 out of 22 peripheral SpA (27.3%). Demographics were not different except for sex, with a female predominance in FM group (66.7% VS 29.4%; p=0.0056), more important in peripheral forms (100% VS 43.7%; p=0.0461). In the whole population, BASDAI was higher in FM patients, whereas ASDAS-CRP was not significantly different (table 2). Still, median ASDAS-CRP corresponded to high disease activity in SpA-FM patients compared to moderate activity in non-FM patients. In the axial SpA subgroup, there was no difference in the functional index BASFI (median (IQR): axial SpA-FM (n=10) 1.4 (2.7); axial SpA without FM (n=65) 0.9 (2.5); p=0.2921) and in the metrological index BASMI (median (IQR): axial SpA-FM (n=12) 1.5 (1.8); axial SpA without FM (n=64) 1.5 (3.8); p=0.3526). Number of painful joints was higher in SpA-FM patients (n=102; median (IQR): 2.8 (4.5) VS 0 (1); p<0.0001) while number of swelling joints was not. Quality of life assessed by SF-36 was not different between non-FM (n=82) and FM patients (n=15), except for the health concept "physical health" which was lower in SpA-FM patients (median (IQR): 70 (45) VS 85 (25); p=0.0156). Comparison of the 18 SpA-FM with 18 FM control patients showed no difference in demographic characteristics, BASDAI or ASDAS-CRP.

Conclusion:

FM is frequently associated with SpA, especially in peripheral forms. Disease activity measured by BASDAI and to a lesser extent ASDAS-CRP may be overestimated in SpA-FM patients and then could lead to inappropriate treatment escalation.

Table 1. Population characteristics.

	SpA (n=85)	SpA FM (n=18)	p*
Demographics			
Age, years	41.9 (20.8)	46.4 (22.9)	0.3550
Women	25 (29.4%)	12 (66.7%)	**0.0056**
BMI, kg/m^2	25.6 (5.7)	25.4 (4.6)	0.8758
Marital status	55 (64.7%)	13 (72.2%)	0.5970
Children (n=91)	56 (75.7%)	13 (76.5%)	1
Urban location	51 (60.0%)	11 (61.1%)	1
Worker (n=102)	58 (68.2%)	11 (64.7%)	0.7820
SpA profile			
Disease duration, years (n=102)	10.5 (13.8)	9.5 (10.8)	0.7819
Axial SpA (ASAS)	69 (81.2%)	12 (66.7%)	0.2073
- Radiographic (n=78)	50 (75.6%)	5 (41.7%)	**0.0341**
Peripheral manifestations	45 (52.9%)	12 (66.7%)	0.3117
- Arthritis	39 (45.9%)	9 (50.0%)	0.7990
- Enthesitis	9 (10.6%)	4 (22.2%)	0.2352
- Dactylitis	6 (7.1%)	2 (11.1%)	0.6263
Psoriasis	29 (34.1%)	4 (22.2%)	0.4119
IBD	3 (3.5%)	1 (5.6%)	0.5420
Uveitis	17 (20.0%)	1 (5.5%)	0.1864
HLA B27 (n=98)	53 (65.4%)	13 (76.5%)	0.5703

SpA: spondyloarthritis; FM: fibromyalgia; SI: sacroiliitis; IBD: inflammatory bowel disease.
Data presented in median (IQR) or number (percent) as appropriate.
*:p<0.05% considered significant.

Table 2. Comparison of BASDAI and ASDAS-CRP according to fibromyalgia status between spondyloarthritis patients.

	SpA (n=85)	SpA FM (n=18)	p*	aSpA (n=69)	aSpA FM (n=12)	p**	pSpA (n=16)	pSpA FM (n=6)	p***
BASDAI	2.2 (3.1)	4.2 (4.2)	**0.0068**	2.2 (3.2)	3.2 (5.4)	0.1587	2.2 (2.5)	4.7 (3.0)	**0.0064**
BASDAI 1	2.5 (4)	4.8 (5.4)	0.0861	2.5 (4.8)	3.5 (6.3)	0.7139	2 (4.5)	5.5 (4.5)	**0.0105**
BASDAI 2	2.5 (5)	5.5 (4.8)	**0.0137**	2.5 (5)	5.3 (6)	0.1534	2 (2.5)	5.5 (4.1)	**0.0131**
BASDAI 3	1 (3.5)	3.8 (5)	**0.0018**	0.5 (2.5)	3.3 (5.9)	**0.0333**	2.8 (3.8)	5.5 (3.1)	**0.0199**
BASDAI 4	1 (3.3)	4.8 (4.4)	**0.0019**	0.5 (2.5)	3.3 (5.3)	**0.0427**	2.3 (3.9)	5 (2.5)	**0.0313**
BASDAI 5	2 (4.5)	3.8 (4.1)	0.1450	2.5 (4.5)	2.5 (4.9)	0.5428	1.8 (2.5)	4 (2.6)	**0.0459**
BASDAI 6	1 (2.5)	2 (1.9)	0.9683	1 (2.5)	2.3 (2.6)	0.8500	1.8 (2.2)	1.5 (3)	0.7922
ASDAS-CRP	2 (1.3)	2.7 (2)	0.1264	2 (1.3)	2.5 (2.3)	0.5148	2 (1.2)	2.7 (1.2)	0.1307
PGA	2.5 (4)	3.8 (4.4)	0.2146	2 (4.3)	3.6 (5.1)	0.3403	2.8 (3.3)	4.3 (3)	0.415
CRP (mg/l)	4 (7)	3,5 (8,8)	0,8646	4 (7,5)	2 (8)	0,5612	4 (7)	7,5 (11)	0,5213

SpA: spondyloarthritis; aSpA: axial SpA; pSpA: peripheral SpA; FM: fibromyalgia, PGA: patient's global assessment.
Data presented in median (IQR).
*,**,*** Mann-Whitney t-test; p<0.05% considered significant.

Disclosure: J. Wach, None; **M. C. Letroublon**, None; **J. G. Tebib**, None.

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Abstract Number: 1691

The Presence of Fibromialgia May Influence the Clinimetric Evaluation of Patients with Ankylosing Spondylitis, but Has No Impact on Disease Activity Assessment

Emilio Buschiazzo[1], Natalia Zamora[2], Fernando Andres Sommerfleck[3], Romina Rojas Tessel[4], Mariana Benegas[5], Pablo Arturi[6,7], Maria Elena Crespo[4], Emilce Schneeberger[8] and Gustavo Citera[2], [1]Rheumatology, Hospital Sr Del Milagro, Salta, Argentina, [2]Rheumatology, Instituto de Rehabilitación Psicofísica, Buenos Aires, Argentina, [3]Rheumatologia, Instituto de Rehabilitación Psicofísica, Buenos Aires, Argentina, [4]Hospital Sr Del Milagro, Salta, Argentina, [5]Sanatorio Mitre, Buenos Aires, Argentina, [6]Rheumatology, Instituto de Rehabilitacion Psicofisica and Fundacion Reumatologica Argentina, Buenos Aires, Argentina, [7]Rheumatology, Hospital Italiano de La Plata, La Plata, Argentina, [8]Instituto de Rehabilitación Psicofísica, Buenos Aires,

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Background/Purpose:

Fibromyalgia (FM) can be present concomitantly in patients with Ankylosing Spondylitis (AS). It may overestimate the evaluation of disease activity, resulting in more intensive treatment. The Objective of this study was to evaluate the influence of the concomitant presence of FM in the evaluation of patients with AS.

Methods:

Consecutive patients with AS (1984 New York criteria), were included. The presence of concomitant FM was assessed by both 1990 and 2010 ACR criteria. Data regarding sociodemographic characteristics (age, sex), disease duration, treatment, disease activity (BASDAI, ASDAS-ESR, SASDAS, global patient VAS), funcional capacity (BASFI), quality of life (ASQoL), enthesitis (MASES), tender and swollen 44/46 joint count, CRP and ESR, Fibromyalgia Impact Questionnaire (FIQ) was assessed. Categorical data was expressed in frequency and percentage and compared by chi2 or Fisher exact test, continuous data was expressed as median and interquartile range (IQR), and compared by Mann-Whitney-U-Test or Student's T-Test. Multivariate analysis was performed taking activity indexes as dependent variables, adjusting for confounders. A $p < 0.05$ value was considered as significant.

Results:

50 patients were included, 44 (88%) male, median age 40 years (IQR 31-52), disease duration 9.1 years (IQR 2-20), 40 (80%) were treated with NSAIDs, 21 (42%) with TNF alpha blockers. Median BASDAI, ASDAS-ESR and SASDAS were 5.2 (IQR 1.8-6.9), 2.4 (IQR 1.7-3.6) and 19.4 (IQR 6.9-29.1) respectively. FM was present in 12 patients (24%), 7 (14%) and 6 (12%) fulfilled 2010 and 1990 criteria respectively, leaving only one patient overlapping both criteria. In the univariate analysis patients with FM had significantly higher values of disease activity scores, BASFI, ASQoL, FIQ, MASES, tender joints, patient's VAS, number of fibrositic points, but similar ESR, CPR and swollen joint count. All the patients with FM were at the high or very high activity groups according to ASDAS-ESR / SASDAS. In the multivariate analysis, the presence of FM remained significantly associated with higher MASES and poorer ASQoL, but had lost influence in disease activity indexes (BASDAI, ASDAS-ESR nor SADAS).

Conclusion:

In our cohort of patients with AS enthesis evaluation by MASES and quality of life were significantly influenced by the presence of FM, but it had no impact on disease activity assessment. In the evaluation of the enthesis it should be taken in account the coexistence of FM and AS in order to use more specific tools to evaluate them.

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Abstract Number: 1692

Serious Infections in Psoriasis Patients with Psoriatic Arthritis in the Psoriasis Longitudinal Assessment and Registry Study

Christopher T. Ritchlin[1], Alice B. Gottlieb[2], Alan Menter[3], Philip J. Mease[4], Sunil Kalia[5], Francisco Kerdel[6], Shelly Kafka[7], G James Morgan[7], Wayne Langholff[8], Steve Fakharzadeh[7] and Kavitha Goyal[7], [1]Allergy, Immunology and Rheumatololgy Division, University of Rochester Medical Center, Rochester, NY, [2]Tufts Medical Center and Tufts University School of Medicine, Boston, MA, [3]Baylor University Medical Center, Dallsa, TX, [4]Swedish Medical Center and University of Washington School of Medicine, Seattle, WA, [5]University of British Columbia, Vancouver, BC, Canada, [6]University of Miami, Miami, FL, [7]Janssen Scientific Affairs, LLC, Horsham, PA, [8]Janssen Research & Development, LLC, Spring House, PA
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Background/Purpose: To describe the rates of serious infections in psoriasis patients with psoriatic arthritis(PsA) from PSOLAR.

Methods: PSOLAR is an international, disease-based, observational study in which patients eligible for, or receiving conventional systemic and biologic agents for the treatment of psoriasis are followed prospectively. The characteristics and cumulative incidence rates of serious infections, occurring within 91 days of biologic administration, for patients who reported PsA,including a subset with PsA confirmed by a joint-specialist are summarized. Cohorts were defined as and attribution was based on treatment exposure in the following order (regardless of sequence and duration): (1) ustekinumab(UST) (2) other sponsor biologic (primarily infliximab[IFX]) (3) non-sponsor biologic (primarily adalimumab/etanercept[ADA/ETN]), and (4) non-biologic therapies(NB) (including immunodulators [eg MTX, cyclosporine], phototherapy, and topical therapy). Exposure to any therapy higher in the order precluded inclusion in the lower cohorts. Multivariate analyses using Cox hazard regression were used to identify predictors of time to first serious infection (using exposure within 91 days for biologics [compared to no biologic use] and for immunomodulators [compared to no immunomodulator use]).

Results: As of Aug 23, 2014, PSOLAR was fully enrolled with 12093 patients (40388 total patient-years [PY] of follow-up).Number of patients with reported PsA was overall 4316: 1489 UST, 776 IFX, 1680 ADA/ETN, 371 NB; of these patients, 1719 had confirmed PsA (664 UST, 356 IFX, 576 ADA/ETN, 123 NB). Baseline demographics and medical history were generally balanced across cohorts and were comparable to confirmed PsA subset; however, in overall PsA sub-group, more patients in NB cohort were >=65yrs of age(UST 9.9%, IFX 13.9%, ADA/ETN 12.5% , NB 25.6%)and had a medical history of cancer (UST 3.3%, IFX 3.5%, ADA/ETN 3.9%, NB 8.4%).In the overall PsA subgroup (15 029 PY of follow-up), rates of serious infections per 100 PY were: UST 1.12, IFX 3.36, ADA/ETN 2.49, and NB 2.20. Among the confirmed PsA subset, rates per 100 PY were: UST 1.06, IFX 2.83, ADA/ETN 2.58, NB 1.63. In the overall PsA sub-group, increasing age, male gender, current/prior smoking, history of significant infection, diabetes, and use of biologics (other than UST as a combined group) were associated with increased risk for serious infection; no increased risk was observed with UST and immunomodulators. In patients with confirmed PsA, diabetes, history of significant infection, more severe skin psoriasis, and use of biologics other than UST (as a combined group) were significantly associated with increased infection risk; UST and immunomodulators were not associated. Inherent bias with respect to observational data may apply. Variability in size and clinical features was noted among treatment groups.Incidence rates are not adjusted for differences. Individual biologics beyond UST were not evaluated individually in statistical analyses.

Conclusion: Results suggest a higher risk of serious infections with biologics (as a combined group), other than UST, in comparison with no biologic usage; increased risk was not observed with UST or immunomodulators.

Disclosure: C. T. Ritchlin, Janssen Scientific Affairs, LLC, 2; **A. B. Gottlieb**, Janssen Scientific Affairs, LLC, 2; **A. Menter**, Janssen Scientific Affairs, LLC, 2; **P. J. Mease**, Janssen Scientific Affairs, LLC, 2; **S. Kalia**, Janssen Scientific Affairs, LLC, 2; **F. Kerdel**, Janssen Scientfic Affairs, LLC, 2; **S. Kafka**, Janssen Scientific Affairs, LLC, 3; **G. J. Morgan**, Janssen Scientfic Affairs, LLC, 3; **W. Langholff**, Janssen R & D, LLC, 3; **S. Fakharzadeh**, Janssen Scientific Affairs, LLC, 3; **K. Goyal**, Janssen Scientfic Affairs, LLC, 3.

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Abstract Number: 1693

High Prevalence of Cardiac Disease in Patients with Ankylosing Spondylitis

Sjoerd C. Heslinga[1], Thelma C. Konings[2], Otto Kamp[2], Mike J.L. Peters[3], Yvo M. Smulders[3], Irene E. Van der Horst - Bruinsma[1] and Mike T. Nurmohamed[1], [1]Rheumatology, Reade, Amsterdam Rheumatology and immunology Center, Amsterdam, Netherlands, [2]Cardiology, VU University Medical Center, Amsterdam, Netherlands, [3]Internal Medicine, VU University Medical Center, Amsterdam, Netherlands

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Background/Purpose:

Ankylosing spondylitis (AS) is associated with increased risk of concomitant cardiac disease, such as valvular regurgitation, conduction disturbances and decreased ventricular function (1). However, contemporary data are not available. Therefore, we investigated the prevalence of cardiac manifestations in AS patients between 50 and 75 years old.

Methods:

We performed a cross sectional study in randomly selected AS patients between 50 and 75 years old. Patients were screened for cardiac disease using standard transthoracic echocardiography (TTE) that included two-dimensional, three-dimensional and M-mode echocardiography, spectral Doppler, color Doppler and tissue Doppler imaging. Systolic left ventricular (LV) dysfunction was defined as an ejection fraction <50%. Diastolic LV dysfunction (DD) was graded into three categories: mild (grade I), pseudonormal (grade II) and restrictive (grade III). Valvular parameters and aortic diameters were evaluated according to the current echocardiographic guidelines.

Results:

One-hundred-ten AS patients (27 females, 25%) with a mean age of 60±7 years and a mean disease duration of 21±12 years were included. 24 patients (22%) had a history of CV disease, including stroke (n=2), myocardial infarction (n=4), rhythm disorders (n=8), other (n=4) or a combination (n=6).

Seven patients (6%) had systolic LV dysfunction. Of 107 patients diastolic LV function could be determined: 32% had DD grade I, 19% DD grade II and 0% DD grade III.

In patients without a history of CV disease, a new cardiac abnormality was found on TTE in 20 (18%) which required treatment or follow-up by a cardiologist: ventricular dysfunction (n=3), aortic (root) dilatation (n=10), valvular regurgitation (n=5), rhythm disorders (n=1), or a combination (n=1).

Conclusion:

In patients with a long duration of AS without a history of cardiac disease or symptoms, there is a high prevalence of cardiac manifestations, with high prevalences of LV dysfunction, valvular disease and aortic (root) dilatation. This high prevalence might ultimately translate into increased CV morbidity and mortality. The potential clinical impact and effect on CV mortality remains to be determined.

References:

1) Nurmohamed MT, van der Horst-Bruinsma I, Maksymowych WP. Cardiovascular and cerebrovascular diseases in ankylosing spondylitis: current insights. Curr Rheumatol Rep 2012 Oct;14(5):415-21.

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Disclosure: S. C. Heslinga, None; **T. C. Konings**, None; **O. Kamp**, None; **M. J. L. Peters**, None; **Y. M. Smulders**, None; **I. E. Van der Horst - Bruinsma**, None; **M. T. Nurmohamed**, None.

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Abstract Number: 1694

All-Cause Mortality and Malignancies in Psoriasis Patients with Psoriatic Arthritis in the Psoriasis Longitudinal Assessment and Registry Study

Philip J. Mease[1], Alice B. Gottlieb[2], Alan Menter[3], Christopher T. Ritchlin[4], Sunil Kalia[5], Francisco Kerdel[6], Shelly Kafka[7], James Morgan[7], Wayne Langholff[8], Steve Fakharzadeh[7] and Kavitha Goyal[7], [1]Swedish Medical Center and University of Washington School of Medicine, Seattle, WA, [2]Tufts Medical Center and Tufts University School of Medicine, Boston, MA, [3]Baylor Research Institute, Dallas, TX, [4]Allergy, Immunology and Rheumatololgy Division, University of Rochester Medical Center, Rochester, NY, [5]University of British Columbia, Vancouver, BC, Canada, [6]University of Miami, Miami, FL, [7]Janssen Scientific Affairs, LLC, Horsham, PA, [8]Janssen Research & Development, LLC, Spring House, PA
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Background/Purpose: Describe characteristics and incidence rates of all-cause mortality and malignancies (excluding NMSC) in psoriasis pts with psoriatic arthritis (PsA) from PSOLAR.

Methods: PSOLAR is an international, disease-based, observational study in which pts eligible for, or receiving conventional systemic and biologic agents for psoriasis are followed prospectively. Characteristics and safety for pts who reported PsA, including a narrower subset with PsA confirmed by a joint-specialist,are summarized. Cohorts were defined as and attribution was based on treatment exposure prior to/during registry, in the following order (regardless of sequence and duration): (1)ustekinumab(UST) (2)other sponsor biologic(primarily infliximab[IFX]) (3)non-sponsor biologic(primarily adalimumab/etanercept [ADA/ETN]), and (4)non-biologic therapies(NB) (including immunomodulators [eg.MTX, CsA], phototherapy, and topical therapy). Exposure to any therapy higher in the order precluded inclusion in the lower cohorts. Multivariate analyses using Cox hazard regression were used to identify predictors of time to first malignancy and mortality [compared to no biologic use] and for immunomodulators [compared to no immunomodulator use].

Results: As of Aug 23, 2014,PSOLAR is fully enrolled with 12093 pts (40388 total pt-years [PY] of follow-up). Number of pts with reported PsA overall was 4316: 1489 UST, 776 IFX, 1680 ADA/ETN, 371 NB; of these pts, 1719 had confirmed PsA (664 UST, 356 IFX, 576 ADA/ETN, 123 NB). Baseline demographics and medical history were generally balanced across cohorts; however, in overall PsA sub-group, more pts in the NB cohort were >=65yrs of age (UST 9.9%, IFX 13.9%, ADA/ETN 12.5%, NB 25.6%) and had a medical history of cancer (UST 3.3%, IFX 3.5%, ADA/ETN 3.9%, NB 8.4%). In the overall PsA subgroup, cumulative incidence rates per 100PY for all-cause mortality were UST 0.28, IFX 0.30, ADA/ETN 0.52, NB 0.70; age, obesity, history of cardiovascular disease(CVD), history of diabetes and smoking were predictors of time to mortality. Cumulative incidence rates per 100PY for malignancy were UST 0.57, IFX 0.67, ADA/ETN 0.64, and NB 1.01; age and history of malignancy were predictors of time to first malignancy. Biologic and immunomodulator use were not predictors for mortality or malignancy. Among the confirmed PsA subset, cumulative incidence rates per 100PY for all-cause mortality UST 0.21, IFX 0.36, ADA/ETN 0.38, NB 0.25 and for malignancy UST 0.52, IFX 0.54, ADA/ETN 1.02, NB 1.25. Inherent bias with observational data may apply. Variability in size and clinical features was noted among groups. Incidence rates are not adjusted for differences(adjustment for key factors are included in statistical analyses). Small numbers of pts in the confirmed PsA subset precluded assessment of risk factors.

Conclusion: Unadjusted rates of all-cause mortality and malignancies for biologics were generally comparable among both PsA subsets. Advanced age, history of malignancy were predictors of time to first malignancy and age, obesity, CVD history, diabetes history and smoking were predictors for time to mortality based on overall PsA subset; biologics and immunomodulators were not predictors for mortality or malignancy.

Disclosure: P. J. Mease, Janssen Scientific Affairs, LLC, 2; **A. B. Gottlieb**, Amgen, 2,AbbVie, 2,Celgene, 2,Coronado, 2,Eli Lilly, 2,Janssen, 2,Levia, 2,Merck, 2,Pfizer, 2,AbbVie, 5,Actelion, 5,Akros, 5,Amgen, 5,Astellas, 5,Bristol-Myers Squibb, 5,Canfite, 5,Catabasis, 5,Celgene, 5,Coronado, 5,CSL Behring Biotherapies for Life, 5,Dermipsor, 5,Eli Lilly, 5,GlaxoSmithKline, 5,Incyte, 5,Janssen, 5,Karyopharm, 5,Novartis, 5,Novo Nordisk, 5,Pfizer, 5,Sanofi Aventix, 5,UCB Pharma, 5,Vertex, 5,Xenoport, 5; **A. Menter**, Boehringer Ingelheim, 2,Boehringer Ingelheim, 5; **C. T. Ritchlin**, Janssen Scientific Affairs, LLC, 2; **S. Kalia**, Janssen Scientific Affairs, LLC, 2; **F. Kerdel**, Janssen Scientfic Affairs, LLC, 2; **S. Kafka**, Janssen Scientific Affairs, LLC, 3; **J. Morgan**, Janssen Scientfic Affairs, LLC, 3; **W. Langholff**, Janssen R & D, LLC, 3; **S. Fakharzadeh**, Janssen Scientific Affairs, LLC, 3; **K. Goyal**, Janssen Scientfic Affairs, LLC, 3.

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Abstract Number: 1695

Fatigue May be Independently Active at a Certain Part of Spondyloarthritis Patients: Hur-BIO Real Life Results

Umut Kalyoncu[1], Abdulsamet Erden[1], Levent Kilic[1], Emrah Seyhoglu[2], Denizcan Güven[2], Burak Yasin Aktas[2], Yusuf Ziya Sener[2], Omer Karadag[1], Sule Apras Bilgen[1], Ali Akdogan[1], Sedat Kiraz[1] and **Ihsan Ertenli**[1], [1]Rheumatology, Hacettepe University Faculty of Medicine, Ankara, Turkey, [2]Internal Medicine, Hacettepe University Faculty of Medicine, Ankara, Turkey

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Background/Purpose: Fatigue is one of the essential patient reported outcome almost all inflammatory rheumatic diseases. However, fatigue may be affected from multidimensional factors such as psychological (i.e. depression), physiologic (i.e. anemia) or both. In the clinical practice, active fatigue state may be proceed during remission according to other measures. Objective of this study was to assess frequency of active fatigue level at spondyloarthritis patients during ASAS partial remission.

Methods: Hacettepe University Rheumatology Biologic Registry (HUR-BIO) is a single center biological registry since 2005. HUR-BIO includes 933 ankylosing spondylitis (AS) and 143 axial spondyloarthritis (AxSpA) patients under anti-TNF drugs. After September 2012, we regularly collected outcome measures such as Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), BASDAI 2, 5 and 6. questions, Bath Ankylosing Spondylitis Functional Index (BASFI), CRP, 100mm visual analog scales (VAS) for patient global assessment (PtGA), fatigue and pain every 6 months. Assessment of SpondyloArthritis International Society (ASAS) partial remission was defined as less than 20/100 mm of BASFI, back pain, morning stiffness and PtGA. Active fatigue level was defined as more than 40/100 mm.

Results: Overall, 716 patients (602 AS and 114 AxSpA) were assessed between September 2012 and January 2015 and 452 (63.1%) of patients were male. Mean age was 40.3±11.3 years old, mean disease duration was 8.9±7.1 years and mean symptom duration was 13.2±8.8 years. Initial biological drugs were etanercept 249 (34.8%), infliximab 208 (29.1%), adalimumab 197 (27.5%) and golimumab 62 (8.6%). Fatigue assessed at 1762 times from 716 patients over time. Active fatigue level detected at 663 of those 1762 (37.6%) visits. During this period, ASAS partial remission was detected 489 of 1697 assessment (28.8%). Active fatigue level found 30 of those 489 (6.1%) patients who were ASAS partial remission.

Conclusion: In the routine practice, active fatigue level present at about 38% of spondyloarthritis patients despite biological treatment. Almost six percent of patients with ASAS partial remission were still active fatigue levels. Unfortunately, we did not evaluate possible causes of fatigue other than rheumatic diseases. Comprehensive psychologic and physiologic evaluation should be performed in these certain part of spondyloarthritis patients. Physicians should be keep in mind that fatigue may be continue otherwise clinical remission.

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Score Classification Underestimates the Real Cardiovascular Risk in Psoriatic Arthritis Patients

Maria Paz Martínez-Vidal[1], Cristina Fernández-Carballido[2], Francisca Sivera[3], Raquel Martín-Doménech[1], Nieves Martínez-Alberola[1] and Alejandro San Martin[4], [1]Rheumatology, Hospital General Universitario Elda, ELDA, Spain, [2]Rheumatology, Hospital General Universitario de Elda, Elda (Alicante), Spain, [3]Reumatología, Hospital General Universitario de Elda, Alicante, Spain, [4]Rheumatology, Univesity General Hospital, ELDA, Spain

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Background/Purpose: SCORE tables underestimate the Cardiovascular Risk (CVR) for patients with Rheumatoid Arthritis (RA) and EULAR recommends multiplying by 1.5 the CVR obtained from them in RA patients. A concern exists that CVR in Psoriatic Arthritis (PsA) might be underestimated. Several studies show that the carotid intima-media thickness (CIMT) and the presence of cholesterol plaques (CP) detected with Ultrasound (US) are significantly associated with CVR. Our objectives were to assess the CVR profile in PsA patients using the SCORE/European recommendations and to study the presence of subclinical CV disease by US techniques. **Methods:** Ongoing transversal descriptive study of PsA patients from a Rheumatology Unit. Variables: Age, gender, psoriasis and PsA duration, PsA type and therapy; classic CVR factors (BMI, hypertension, dyslipidaemia, smoking, diabetes); prevalent personal and familiar CV events (coronary, cerebrovascular and thromboembolic events, sudden death). The probability of fatal atherosclerotic CV events over a 10 year period was calculated (Spanish SCORE chart/European recommendations). Then all patients underwent bilateral US carotid study (GE LOGIQ S7 Expert US Equipment). The common CIMT (average and maximum) measured in both common carotids using an automatized lecture of the distal intima-media wall in a surface of 1.39 cm or 300 points, 1 cm caudal to the carotid bulb. Plaques defined according to the Mannheim consensus. Statistical analysis: Descriptive, univariate (t-Test and Chi2) and multivariate analyses (ANOVA) were performed. **Results:** 72 PsA patients were included: mean age 57±11.2 years (53% male). 3 patients had a prevalent CV event. Clinical characteristics summarized in Table 1. Risk levels before/after the US study summarized in table 2. In the US study, 25 patients had pathological IMT thickness or atheroma plaques (35.21%), The final CVR was upgraded due to the US in 23 patients (31.9%). Patients with peripheral PsA had significantly higher CIMT than the other forms of PsA (p=0.03). None of the other variables were associated with CIMT nor with the presence of plaques. A positive association between HBP and CIMT was found (p=0.001, CI 95% -0.19,-0.05) on multivariate analyses. The 3 patients with CV events had significantly higher CIMT (p=0.08, CI 95%= -0.31, -0.09) and all had plaques (p=0.04). **Conclusion:** In this sample, a substantial proportion of patients with PsA are at a very high risk of a fatal CV event. The SCORE/European classification seems to underestimate the CV risk, as 31.9% of the patients were upgraded to a higher risk after the US study.

Table 1.

		Absolute values (n)	
DISEASE TYPE	Axial	28	38.9%
	Only axial	3	4.2%
	Peripheral	69	95.8%
	Only peripheral	44	61.1%
	Psoriasis duration (months)	222.61	SD 163.51
	PsA duration (months)	132.89	SD 121.11
TREATMENT	NSAID only	5	6.9%
	DMARDs	40	55.6%
	Biological therapies	26	36.1%
	Others (cyclosporine)	1	1.4%
CARDIOVASCULAR EVENTS	Personal	3	4.2%
	Familiar	29	40.3%
CLASSICAL CVR FACTORS	DM	13	18.1%
	Hypertension	22	30.6%
	Dyslipidaemia	13	18.1%
	Tobacco	12	16.7%
		Mean	SD
CLINICAL PARAMETERS	BMI	29.7	5.1
	Cholesterol mg/dl (total)	186	31.8
	LDL-Cholesterol mg/dl	107	29.1
	HDL-Cholesterol mg/dl	55.5	20.1
US PARAMETERS (n=71)	Right CIMT (average/maximum) mm	0.57/0.68	0.14/0.17
	Left CIMT (average/maximum) mm	0.63/.075	0.18/0.20
	Presence of plaques (any)	25	35.2%
	Upgrade	23	31.9%

Table 2.

	RISK LEVEL			
	Low	**Intermediate**	**High**	**Very high**
SCORE/European recommendations	**0**	**46 (64.8%)**	**21 (29.6%)**	**4 (5.6%)**
Carotid US study	**0**	**28 (39.4%)**	**16 (22.5%)**	**27 (38.1%)**

Disclosure: M. P. Martínez-Vidal, None; **C. Fernández-Carballido**, None; **F. Sivera**, None; **R. Martín-Doménech**, None; **N. Martínez-Alberola**, None; **A. San Martin**, None.

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Abstract Number: 1697

Obstructive Sleep Apnea and Fatigue in Inflammatory Arthritis Patients Taking TNF-Inhibitors

Brian Breviu[1], Tawnie Braaten[1], Daniel Clegg[2] and Jessica Walsh[3], [1]Department of Internal Medicine, Salt Lake City Veteran Affairs and University of Utah Medical Centers, Salt Lake City, UT, [2]Rheumatology, Salt Lake City Veteran Affairs and University of Utah Medical Centers, Salt Lake City, UT, [3]Rheumatology, Salt Lake City Veterans Affairs, Salt Lake City, UT

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Background/Purpose: Fatigue improves with TNF-inhibition (TNF-i) in people with inflammatory arthritis (IA), but the mechanistic relationships between TNF-i and fatigue are not well understood. Since Obstructive Sleep Apnea (OSA) is a common cause of fatigue in IA patients and TNF-i alters inflammatory pathways that contribute to both IA and OSA, we hypothesized that TNF-i would improve fatigue by altering OSA. Our aim was to explore the relationship between TNF-i, OSA, and fatigue in IA patients.

Methods: Consecutive rheumatology clinic patients who anticipated starting a TNF-inhibitor for IA were screened for OSA with the STOP-Bang questionnaire. Participants with positive screens completed questionnaires and a 2-night ApneaLink home sleep study, before TNF-i and again 2 to 3 weeks after their first dose. Sleep studies were analyzed by both an automated ApneaLink scoring system and a sleep specialist. OSA parameters and fatigue were compared before and after initiation of TNF-i, with adjustment for change in arthritis severity (patient global assessment of arthritis). OSA was assessed with the Apnea Hypopnea Index (AHI) and percent time below 90% oxygen saturation (%time<90%). Fatigue was measured with the Functional Severity Scale (FSS) and Functional Outcome of Sleep Questionnaire (FOSQ).

Results: Eighteen participants completed the pre- and post-TNF-i sleep studies and questionnaires. The mean age was 54 years and 72% were male (Table 1). TNF-i was not associated with improvements in AHI or %time<90%, after adjustment for change in arthritis severity (Table 2). There were non-significant improvements in fatigue.

Conclusion: OSA parameters did not improve within 2-3 weeks of initiating TNF-i, suggesting that fatigue improvements were not driven by OSA changes. The limitations of this proof of concept study include the small sample size and the short time of TNF-i. Additional research is required to understand how TNF-i influences fatigue in IA patients.

Table 1: Baseline demographics and disease characteristics

Variables	Number or Mean (% or SD)
Male	13 (72.2)
Age	54.4 ± 14.5
Body Mass Index	30.6 ± 7.1
Inflammatory Arthritis Subtype	
Axial spondyloarthritis	4 (22.2)
Psoriatic Arthritis	10 (55.6)
Rheumatoid Arthritis	3 (16.7)
Enteropathic Arthritis	1 (5.6)
Alcohol Use	4 (22.2)
Sleep Medication Use*	6 (33.3)
TNF-inhibitor	
Etanercept	4 (22.2)
Adalimumab	10 (55.6)
Infliximab	4 (22.2)

*Sleep medications included trazodone, zolpidem, melatonin, alprazolam

Table 2: Obstructive sleep apnea parameters & fatigue before & after initiation of TNF-inhibition

	Before TNF-i (Mean ± SD)	2-3 weeks after TNF-i (Mean ± SD)	Unadjusted p value	Adjusted p value*
AHI	12.5 ± 8.5	13.1 ± 10.3	0.18	0.97
% time<90%	29.5 ± 30.2	35.4 ± 36.3	0.22	0.18
FSS**	43.1 ± 15.6	41.3 ± 13.5	0.40	0.08
FOSQ***	11.4± 3.8	11.8 ± 3.5	0.79	0.09

*Adjusted for change in patient global assessment of arthritis severity

**FSS= Fatigue Severity Scale: Higher values represent increased fatigue

***FOSQ = Functional Outcome of Sleep Questionnaire: Higher values represent decreased fatigue

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High Prevalence of Traditional Cardiovascular Risk Factors in an Ankylosing Spondylitis Cohort

Gillian Fitzgerald[1], Dara J Lundon[2], Phil Gallagher[3], Claire Sheehy[4], Catherine Sullivan[5], Carmel Silke[6], Frances Stafford[7], Killian O Rourke[8], Muhammad Haroon[9], Ronan Mullan[10], Oliver FitzGerald[11] and Finbar (Barry) O'Shea[12], [1]Rheumatology, St James's Hospital, Dublin 8, Ireland, [2]School of Medicine, University College Dublin, Dublin, Ireland, [3]Rheumatology, St. Vincent's University Hospital, Dublin, Ireland, [4]University Hospital Waterford, Waterford, Ireland, [5]Rheumatology, UCHG Ireland, Galway, Ireland, [6]Rheumatology, Sligo University Hospital, Sligo, Ireland, [7]Rheumatology, Blackrock Clinic, Co Dublin, Ireland, [8]Rheumatology, Midlands Regional Hospital, Tullamore, Co Offaly, Ireland, [9]Rheumatology, Kerry General Hospital, Co Kerry, Ireland, [10]Department of Rheumatology, Tallaght Hospital, TCD, Dublin 24, Ireland, [11]St Vincent's University Hospital, Centre for Arthritis and Rheumatic Diseases, Dublin Academic Medical Centre, St Vincent's University Hospital, Dublin 4, Dublin 4, Ireland, [12]Rheumatology Dept, St James's Hospital, Dublin, Ireland

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Background/Purpose:

Patients with Ankylosing Spondylitis (AS) have previously been considered an otherwise healthy patient population. However, emerging evidence suggests AS is an independent risk factor for developing cardiovascular (CV) disease. Due to the predominantly young age of AS patients, screening for other traditional CV risk factors is often not performed. The AS Registry of Ireland (ASRI) was established in 2013. The objectives of ASRI are to provide descriptive epidemiological data on the AS population in Ireland and to establish a registry for potential future studies of genetics, aetiology and therapeutics. The purpose of this study was to evaluate the prevalence of traditional CV risk factors in a well characterised AS patient cohort.

Methods:

A standardised detailed clinical assessment is performed on each patient and entered in a web-based database. Disease activity is assessed by Bath AS Disease Activity Index (BASDAI), function by the Bath AS Functional Index (BASFI) and Health Assessment Questionnaire (HAQ) and quality of life by AS Quality of Life (ASQoL). Structured interviews provide patient-reported data, which include the presence of traditional CV risk factors, other comorbidities and employment status. Statistical analysis is performed using SPSS.

Results:

As of June 2015, 340 patients are enrolled in ASRI: 79.7% males, mean age 47.6 (SD 12.6). The mean disease duration is 21.6 years (SD 12), with an average delay to diagnosis of 8.9 years (SD 8.5). Mean BASDAI is 3.9 (SD 2.4), BASFI 3.8 (SD 2.6), HAQ 0.56 (SD 0.52) and ASQoL 6.27 (SD 5.4). 46.5% of the cohort is engaged in full-time employment. 44.2% of those who are unemployed or in part-time employment only, cite AS as the causative reason. Co-morbidities are listed in table 1, the most prevalent being hypertension (25.9%), hyperlipidaemia (20.9%), smoking (current smoker 27.4%; ex-smoker 32.1%) and depression (13.5%). Patients are significantly more likely to have a higher BASDAI if they are a smoker ($p<0.05$) or have depression ($P<0.001$), with a trend towards higher disease activity in those with hypertension ($p=0.06$). Higher BASFI scores are associated with hypertension, osteoporosis, diabetes and hyperlipidaemia ($p<0.05$). Peptic ulcer disease is associated with a trend towards higher BASDAI ($p=0.09$) and BASFI ($p=0.05$).

Conclusion:

Despite their relatively young age, there is a high prevalence of traditional CV risk factors in this patient cohort, in particular hypertension, hyperlipidaemia and smoking. The presence of co-morbidities is associated with higher disease activity and functional impairment in this patient cohort. With increasing focus on AS as an independent risk factor for CV disease, quality improvement initiatives are needed to improve the recognition of traditional CV risk factors among AS patients.

Table 1: Prevalence of comorbidities

Co-morbidity	Prevalence (%)
Ex-smoker	32.1
Current smoker	27.4
Hypertension	25.9
Hyperlipidaemia	20.9
Peptic ulcer disease	9.1
Osteoporosis	7.4
Diabetes mellitus	5.6
Ischaemic heart disease	3.2
Cancer	3.2
Cerebrovascular disease	1.8

Abstract Number: 1699

Obesity and Pediatric Psoriatic Arthritis

Cynthia Manos[1], Timothy Brandon[2], Rui Xiao[3], Jon M. Burnham[4] and Pamela F. Weiss[1], [1]Rheumatology, Children's Hospital of Philadelphia, Philadelphia, PA, [2]Pediatrics, Children's Hospital of Philadelphia, Philadelphia, PA, [3]Department of Pediatrics, Division of Biostatistics, Children's Hospital of Philadelphia, Philadelphia, PA, [4]Pediatric Rheumatology, Children's Hospital of Philadelphia, Philadelphia, PA
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Background/Purpose: Studies in adults have shown a significant association between obesity and psoriatic arthritis. The association of obesity with pediatric psoriatic arthritis is unknown. We aimed to evaluate the prevalence of obesity in a pediatric psoriatic arthritis cohort.

Methods: We conducted a retrospective cross-sectional study of children with psoriatic arthritis evaluated at a single center between 6/2010 and 9/2014. The cohort consisted of children with an ICD-9-CM code of 696.0 "Psoriatic arthritis" given at diagnosis or a subsequent follow-up visit. Age- and sex-specific Z-scores for weight, height, and body mass index (BMI) were calculated based on the 2000 CDC Growth data. Overweight or obese was defined as a BMI greater than or equal to the 85th and 95thpercentile, respectively. Differences in clinical and demographic characteristics who were overweight and not overweight were assessed using Wilcoxon rank sum test, t-test or chi-squared test, as appropriate. The association of age, sex, active joint count, and presence of psoriasis with being overweight was tested using univariate logistic regression. The reference population consisted of 909 healthy participants recruited from general pediatric clinics in the surrounding community for multiple studies done by the Nutrition and Growth laboratory at our institution.

Results: During the study period 48 children with psoriatic arthritis were evaluated. 34 (71%) were female and 17 (35.4%) had a first-degree relative with psoriasis. 29 (60.4%) and 19 (39.6%) of children had psoriasis or dactylitis at diagnosis, respectively. 3 (6.3%) and 5 (10.4%) of the children with psoriatic arthritis were overweight or obese, respectively. Mean BMI z-scores for children with psoriatic arthritis and the reference group were 0.40 (SD 0.96) and 0.36 (SD 1.01), respectively. In comparison to the reference population the proportion of children with psoriatic arthritis who were overweight was not statistically different (0.30 versus 0.17; p=0.06). Comparison of demographics and clinical features between those children with psoriatic arthritis who were overweight and not overweight are shown in the Table. In univariate logistic regression, female sex was associated with significantly decreased odds of being overweight (Odds ratio: 0.17, 95% CI: 0.03 to 0.87). Age, disease duration, psoriasis, dactylitis, and active joint count at diagnosis were not significantly associated with being overweight.

Conclusion: 17% of our psoriatic arthritis cohort was overweight or obese. Female sex was associated with decreased odds of being overweight. The lack of association of obesity with pediatric psoriatic arthritis may be secondary to our limited sample size or may be reflective of true differences in pediatric and adult disease.

Table. Comparison of demographic and clinical features of children who were not overweight and those who were overweight or obese

	All N= 48	**Overweight or obese N= 8**	**Not-overweight N= 40**	**p-value**
Age in years, mean (SD)	12.2 (4.8)	12.2 (5.1)	12.0 (3.2)	0.92
Female sex, N (%)	34 (71)	3 (0.38)	31 (0.78)	**0.02**
Disease duration in years, mean (SD)	5.0 (4.2)	1.8 (3.1)	3.7 (3.9)	0.20
Psoriasis, N (%)	29 (60.4)	4 (50.0)	25 (62.5)	0.44
Dactylitis, N (%)	19 (39.6)	4 (50)	15 (37.5)	0.51
Active joint count^, median (IQR)	3 (1-7)	2.5 (1-4)	3 (1-7.5)	0.54

Legend ^active joint count at diagnosis

Disclosure: C. Manos, None; **T. Brandon**, None; **R. Xiao**, None; **J. M. Burnham**, None; **P. F. Weiss**, None.

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Abstract Number: 1700

Subclinical Atherosclerosis in Ankylosing Spondylitis. Does It Really Exist and Which Are the Effects of Treatments? a Systematic Review

Clément Prati[1], Céline Demougeot[2], Xavier Guillot[2] and Daniel Wendling[3], [1]Service de Rhumatologie, CHRU J Minjoz, Besançon, France, [2]EA 4267 FDE, FHU INCREASE, Université de Bourgogne Franche-Comté, Besançon, France, [3]Université de Franche-Comté, Besançon, France
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Background/Purpose:

Accelerated atherosclerosis and increased cardiovascular morbidity and mortality have been associated with ankylosing spondylitis (AS). Noninvasive angiological methods have been developped to evaluate endothelial and vascular dysfunction which is correlated with future development of atherosclerosis. The objectives were to determinate the presence or not of a subclinical vascular dysfunction in AS and if treatments could have an effect on it. A systematic review was done.

Methods:

Studies evaluating subclinical atherosclerosis and vascular function in AS were identified using Pubmed, (Ovid, EMBASE). Search terms included "ankylosing spondylitis" AND (endothelial OR vascular OR intima media thickness (IMT) OR Flow mediated dilatation (FMD) OR pulse wave velocity (PWV) OR atherosclerosis). This identified 353 results after limiting to French and English. The final selection identified 29 articles.

Results:

Overall, 1529 AS patients were included representing 38 studies: 8 studies about endothelial function, 198 AS patients and 130 healthy control (HC); 20 studies about carotid IMT, 900 AS and 644 HC; 10 studies about arterial rigidity, 431 AS and 285 HC. In cross-sectional studies, 4/6 indicated endothelial dysfunction in AS versus HC, 9/18 indicated increased cIMT and 3/5 increased arterial rigidity. About ED, 3 open label studies noted positive effect of TNFα blockers and spironolactone on FMD and rosuvastatin improved FMD in a placebo controlled study after 24 weeks. TNFα blockers seems not to improve neither cIMT (2 studies) nor arterial rigidity (5 studies). Exercise alone has improved arterial rigidity in 15 patients after 12 weeks.

Conclusion:

Whereas early and accelerated atherosclerosis is patent in AS, presence of subclinical atherosclerotic lesions is controversial in the literature especially concerning cIMT and arterial stiffness. This is reinforced by the lack of TNF blockers efficacy. Conversely it seems that endothelial dysfunction is present and reversible after treatment with TNF blockers, statin and spironolactone. These results are consistent to treat AS patients with early effective treatment to prevent the risk of CV morbidity and mortality.

Disclosure: C. Prati, None; **C. Demougeot**, None; **X. Guillot**, None; **D. Wendling**, None.

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Abstract Number: 1701

Long Term Outcome of Total Hip Replacement in Patients with Ankylosing Spondylitis

Ana Lizarraga[1], Natalia Zamora[1], Graciela Betancur[1], Luis Alejandro Cayetti[2], Emilce Schneeberger[2], Maria Celeste Orozco[3], Fernando Andres Sommerfleck[4] and Gustavo Citera[3], [1]Reumatologia, Instituto de Rehabilitación Psicofísica, Buenos Aires, Argentina, [2]Instituto de Rehabilitación Psicofísica, Buenos Aires, Argentina, [3]Rheumatology, Instituto de Rehabilitación Psicofísica, Buenos Aires, Argentina, [4]Rheumatologia, Instituto de Rehabilitación Psicofísica, Buenos Aires, Argentina

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Background/Purpose: Total hip replacement (THR) surgery is a reliable therapeutic intervention for patients with severe hip involvement. The aim of our study was to determine the long term outcome and associated risk factors of THR in patients with Ankylosing Spondylitis (AS).

Methods: Patients ≥ 18 years with AxSpA diagnosis according to ASAS or NY criteria of ESPAXIA cohort were included. Demographic data, disease duration, comorbidities and current treatment were collected. Pain, patient global assessment (VAS), disease activity (BASDAI), functional capacity (BASFI), enthesitis (MASES), axial mobility (BASMI) and radiological damage (mSASSS) were assessed. THR data included: date of each total hip arthroplasty (right, left), surgery complications and revision. Actual hip pain by VAS and Steimbroker functional class (FC I-IV). Patients were asked to determine the level of pain previous to the surgery (VAS). Hips functional capacity was evaluated by Merle d´Aubigné and Postel method. Pelvis x rays were taken to determine: presence of periprosthesic osteolysis of the femoral and acetabular components, fracture, luxation and heterotopic ossification (HO) according to Brooker´s classification. Statistical analysis: T test, Mann Whitney, $Chi^2$and Fisher test. Multiple logistic regression analysis to explore risk factors associated to THR.

Results: 190 patients were evaluated and 25 (13,15%) underwent THR. 16 patients were included in the analysis (2 died and 7 lost follow-up). Nine (56,2%) had bilateral THR. Fifteen (93,8%) were male, median age of 45 years (IQR 35-44), median disease duration 28,5 years (IQR 18-35,2). 11 (68,8%) were *HLA-B27*positive . The median time of THR's evolution was 12,5 years (IQR 8.7-16.7). 25 prosthesis were evaluated (14 right y 11 left). 48% were cemented and 54% were non cemented. 3 (12%) prosthesis had surgery complications, 3 (12%) had revision surgery. A relief of pain was observed after THR surgery median pain (VAS) previous surgery 10 cm (IQR 9.7-10) vs 0 cm (IQR 0-1.2). There was also improvement after the surgery in FC: 6 (24%) class II, 16 (64%) class III y 3 (12%) class IV and at the moment of evaluation 15 (60%) class II y 10 (40%) class III. Merle d`Aubigné and Postel method median value 15,2 (IQR 13,5-17). We evaluated 22 THR x rays. 11 (50%) prosthesis had acetabular osteolysis, 3 (13,6%) subluxation and 1 peri-prosthesis fracture. 15/17 hips (88,2 %) had femoral osteolysis. 15 had heterotopic ossification, (4 grade I, 4 II, 6 III y 1 IV). THR was associated with longer disease duration (27,1 ± 10,6 vs 19,6 ± 13,4 years, p= 0,03), younger age at the beginning of symptoms (17,4 ±7,6 vs 26,2 ±11,9 years, p= 0,0001), minor MASES (0,6 ±1,2 vs 1,6 ±2,3 p= 0,007) and more frequency of biologic treatment (50% vs 23,6%, p=0,03). In the multivariate analysis, the only variable independently associated with THR was younger age at the beginning of symptoms [β 0,91 (IC95% 0,85-0,97) p=0,001].

Conclusion: A substantial relief in pain and improvement of functional capacity were seen in AS patients who underwent THR . Younger age at disease onset was the only predictor associated to THR.

Disclosure: A. Lizarraga, None; **N. Zamora**, None; **G. Betancur**, None; **L. A. Cayetti**, None; **E. Schneeberger**, None; **M. C. Orozco**, None; **F. A. Sommerfleck**, None; **G. Citera**, None.

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Abstract Number: 1702

Osteoporosis in Psoriatic Arthritis

Ali Aldei[1], Shelly Chandran[2], Suzanne Li[2], Vinod Chandran[3] and Dafna Gladman[3], [1]Medicine, University of Toronto, Toronto Western Hospital, Toronto, ON, Canada, [2]University of Toronto, Toronto Western Hospital, Toronto, ON, Canada, [3]Rheumatology, University of Toronto, Toronto Western Hospital, Toronto, ON, Canada

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Session Time: 9:00AM-11:00AM

Background/Purpose: Psoriatic Arthritis (PsA) is an inflammatory arthritis affecting peripheral and axial joints in patients with psoriasis. The disease process in PsA comprises of complex bone involvement. A preliminary review of studies evaluating Osteoporosis in PsA provides inconsistent and conflicting results. The aim of this this study was to analyze Bone Mineral Density (BMD) in patients with (PsA), as well as to investigate its possible associations with measures of disease activity and functional capacity.

Methods: Consecutive Patients from PsA Clinic underwent BMD scan of spine L1-L4 and left Femoral Neck using Hologic Discovery A – 84248 model between March and May of 2015. BMD was expressed as g/cm2, Z-score and T-score. The percentage of patients with T-score ≤ -2.5 SD (WHO osteoporosis definition) and with Z-score ≤ -1.0 SD was calculated. Disease activity measures included: tender, swollen and damaged joint counts, patient and physician global assessment, presence of enthesitis, nail involvement and Psoriasis Area Severity Index (PASI) score. Laboratory tests included inflammatory markers ESR and CRP. Health Assessment Questionnaire (HAQ) and Short Form 36 Health Survey were used to assess functional status. Patients' clinical, laboratory and radiological data were extracted from PsA program computer database. Statistical analysis included descriptive statistics, linear regression models and logistic regression models controlling for age.

Results: Total of 61 patients [38 males (mean age 56.57 ± 10.19 years) and 23 females (mean age 53.95 ± 10.76)] years were studied. According to WHO definition, spinal osteoporosis was found in 3% of patients and femoral neck osteoporosis in 5% of patients. Spinal osteopenia was found in 28% of patients and femoral neck osteopenia in 39%.

Disease activity measures of the recruited patients [mean (SD) or proportion] at the time of BMD assessment included: tender joint count 3.8 (7.7), swollen joint count 0.7 (1.7), clinically damaged joint count 9.1 (12.3), patient global 2.6 (0.9), physician global 1.8 (0.7), presence of enthesitis 7 (12%), nail involvement 10 (16%), ESR 14.8 (10.8), CRP 5.2 (3.3), HAQ 0.5 (0.4), Short Form -36 PCS 39.5 (10.4) and Short Form-36 MCS 50.1(12.5).

None of the clinical or laboratory features were associated with bone density either using linear regression with bone density in g/cm^{2}measured by the BMD as outcome, or with logistic regression using low versus normal bone density as outcome.

Conclusion: In our cohort of PsA patients, prevalence of osteoporosis was not increased. BMD was not associated with disease activity or functional status.

Disclosure: A. Aldei, None; **S. Chandran**, None; **S. Li**, None; **V. Chandran**, None; **D. Gladman**, None.

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Abstract Number: 1703

Obesity Is Related with Active State in Psoriatic Arthritis and Rheumatoid Arthritis but Not Ankylosing Spondylitis at Real Life Biological Cohort

Umut Kalyoncu, Levent Kilic, Abdulsamet Erden, Alper Sari, Berkan Armagan, Omer Karadag, Ali Akdogan, Sule Apras Bilgen and Ihsan Ertenli, Rheumatology, Hacettepe University Faculty of Medicine, Ankara, Turkey

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Background/Purpose: Adipose tissue and adipokines are linked to inflammation. The relationship of obesity to rheumatologic disease activity is complex and recent studies demonstrate a connection (1-3). Our objective was to assess association of disease activity with obesity in rheumatoid arthritis (RA), ankylosing spondylitis (AS) and psoriatic arthritis (PsA) in a single center biological registry.

Methods: Hacettepe University Rheumatology Biological database is a single center registry, including 1015 RA, 814 AS and 203 PsA patients on biologics. Collected data include demographics, 28 tender/swollen joint counts, 100mm visual analog scale (VAS) for patient global assessment (PtGA), fatigue, pain, ESR, CRP, health assessment questionnaire (HAQ), Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Bath Ankylosing Spondylitis Functional Index (BASFI), PsAID-12 and DAS-28. BMI was recorded before anti-TNF treatments. BMI≥30 was defined as obesity. We used the following cut-offs to dichotomize groups: DAS28>3.2, BASDAI>4, BASFI>4, PSAID>4, HAQ>0.5, SJC≥1, TJC≥1, for PtGA/BASDAI/BASFI/Fatigue/Pain>40 mm, ESR and CRP>ULN.

Results: There were 655 RA (79.1%F), 624 AS (33.5% F) and 161 PsA (65.8%F), patients. Mean(SD) age was 52.8 (12.5) 41.8 (11.4) and 44.8 (11.8) years. Mean(SD) disease duration was 11.5 (8.0), 10.1(7.5) and 10.3(7.3) years. In RA, AS and PsA mean(SD) BMI was 29.1 (5.9), 27.2 (5.4), 28.7 (6.1); and %BMI>30 were 40.2, 24.5 and 37.3. Disease activity groups by BMI categories are shown in Table.

Conclusion: In these cross sectional view, obese RA (DAS-28, all PROs, acute phase reactants) and PsA (BASDAI, PsAID, pain) patients had more active state, however obesity did not influence on activity of AS patients. Functional impairment of obese patients may be related mechanical effect of weight rather than disease activity. For each disease, different influence of BMI on disease activities need to assess at other biological registries.

References:

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Table. Disease activity and patient reported measures by BMI categories

Measures	Diagnosis	BMI≥30	BMI<30	p-value
DAS-28 > 3.2	RA	135/247 (54.6)	159/365(43.6)	**0.007**
	AS	NA	NA	NA
n (%)	PsA	24/46 (52.2)	33/82 (40.2)	0.19
BASDAI > 4	RA	NA	NA	NA
	AS	46/152 (30.3)	126/429 (29.4)	0.41
n (%)	PsA	38/60 (63.3)	35/99 (35.3)	**0.001**
BASFI>4	RA	NA	NA	NA
	AS	53/151 (35.1)	108/467 (23.1)	**0.004**
n (%)	PsA	28/60 (46.7)	26/99 (26.3)	**0.008**
PsAID>4	RA	NA	NA	NA
	AS	NA	NA	NA
n (%)	PsA	40/60 (66.7)	44/101 (43.6)	**0.005**
HAQ > 0.5	RA	155/253 (61.3)	166/371 (44.7)	**<0.001**
	AS	NA	NA	NA
n (%)	PsA	32/60 (53.3)	40/100 (40.0)	0.10
SJC ≥ 1	RA	116/252 (46.0)	150/372 (40.3)	0.16
	AS	3/136 (2.2)	13/415 (3.1)	0.58
n (%)	PsA	13/48 (27.1)	25/88 (28.4)	0.87
TJC ≥ 1	RA	165/252 (65.5)	216/372 (58.1)	0.062
	AS	9/137 (6.6)	23/415 (5.5)	0.65
n (%)	PsA	21/48 (43.7)	35/88 (39.8)	0.65
PtGA > 40 mm	RA	146/255 (57.2)	177/382 (46.3)	**0.007**
	AS	52/153 (33.9)	155/471 (32.9)	0.81
n (%)	PsA	35/60 (58.3)	44/100 (44.0)	0.079
Pain > 40 mm	RA	152/256 (59.3)	182/383 (47.5)	**0.003**
	AS	50/150 (33.3)	165/463 (21.6)	0.61
n (%)	PsA	38/59 (64.4)	47/99 (47.5)	**0.039**
Fatigue > 40 mm	RA	156/256 (60.9)	186/283 (65.7)	**0.002**
	AS	56/150 (37.3)	157/463 (33.9)	0.44
n (%)	PsA	38/59 (64.4)	49/99 (49.5)	0.068
CRP > ULN	RA	113/248 (45.6)	124/359 (34.5)	**0.006**
	AS	65/143 (45.5)	160/438 (36.5)	0.057
n (%)	PsA	23/56 (41.1)	37/91 (40.6)	0.96
ESR > ULN	RA	122/255 (47.8)	115/371 (30.9)	**<0.001**
	AS	38/148 (25.7)	101/455 (22.2)	0.38
n (%)	PsA	22/56 (39.3)	28/92 (30.4)	0.27

Disclosure: U. Kalyoncu, None; **L. Kilic**, None; **A. Erden**, None; **A. Sari**, None; **B. Armagan**, None; **O. Karadag**, None; **A. Akdogan**, None; **S. Apras Bilgen**, None; **I. Ertenli**, None.

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Abstract Number: 1704

Prevalence of Obesity and Metabolic Syndrome in Patients with Axial Spondyloarthritis

Graciela Betancur[1], Maria Celeste Orozco[2], Emilce Schneeberger[2], Ana Lizarraga[1], Natalia Zamora[2], Fernando Andres Sommerfleck[3] and Gustavo Citera[2], [1]Reumatologia, Instituto de Rehabilitación Psicofísica, Buenos Aires, Argentina, [2]Rheumatology, Instituto de Rehabilitación Psicofísica, Buenos Aires, Argentina, [3]Rheumatologia, Instituto de Rehabilitación Psicofísica, Buenos Aires, Argentina

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Background/Purpose: Estimate the prevalence of Obesity (O) and Metabolic Syndrome (MS) in AxSpA and evaluate its association with sociodemographic and clinical variables.

Methods: We included patients ≥18 yrs diagnosed with AxSpA (ASAS criteria and/or NY criteria) belonging to ESPAXIA cohort. Socio-demographic data (age, sex, occupation, education), disease characteristics (disease duration, extra-articular manifestations, comorbidities, current treatment) and cardiovascular risk factors (smoking, hypertension, diabetes, dyslipidemia and sedentary) were collected. Physical examination was performed: height (cm), weight (Kg), abdominal circumference (cm), blood pressure (average of two measures), swollen joint count (44), enthesitis (MASES index). BMI was calculated. Patients were classified according to WHO in Normal: BMI 18.5-24.9; Overweight: BMI ≥25; and Obesity: BMI ≥30 (grade I: BMI 30-34.9, II: BMI 35-39.9 and III: BMI ≥40). The MS was evaluated according to NCEP ATP III and ALAD (Latin American Diabetes Association). Radiographs of cervical spine, lumbar spine and sacroiliac joints were evaluated by a blinded observer using mSASSS index (ICC ≥ 0.90). Glucose, lipid analysis, ESR and CRP were tested. All patients completed self-reported questionnaires BASDI, BASFI and ASQoL. *Statistical analysis:* Univariate and multivariate analysis were performed to evaluate association of MS and O with socio-demographic and clinical variables.

Results: 187 patients were included, 74.2% were male with median age of 45 yrs and median disease duration of 18.5 yrs. Median weight was 77.5 kg, median height 169 cm and median BMI was 26.67 (23.7-29.44). 33.7% had normal BMI, 42.8% overweight and 23.5% obesity (65% grade I, 20.5% grade II, 13.6% grade III). Obese patients had longer disease duration (24.5 ± 14.55 vs 16.8 ± 12.8 yrs, p=0.01), were older (51.7±13 7 vs 41.3±13.8 yrs, p=0.001), had worse functional capacity (BASFI 4.9±2.8 vs 3.5±2.5 p=0.02) and poorer quality of life (ASQoL 8.3±4.7 vs 3.5±2.5 p=0.02) compared to patients with normal BMI. In multivariate analysis adjusting for age and disease duration only male sex was associated with obesity. 117 patients had complete data to evaluate MS. 73.5% were male, with median disease duration of 19.5 yrs. 28 patients met criteria of MS by ATP III and 27 by ALAD. Patients with MS were older (55.7±9.6 vs 43.1±12 yrs, p=0.0001), had longer disease duration (24.6 ± 10.3 vs 18.5 ± 12.2 yrs, p = 0.01), higher frequency of cardiovascular complications (60.7% vs 34.8% p=0.02), hepatobiliary diseases (39.3% vs 19.1% p=0.04) and alcohol consumption (21.4% vs 5.6%, p=0.02). They also had higher radiological damage (mSASSS 42.9 ± 2.8 vs 23.1 ± 25.7 p=0.02), which remained significant after adjusting for disease duration. The presence of MS did not have influence on other disease variables.

Conclusion: 23.5% of our AxSpA patients were obese and 23% fullfilled MS criteria. Obesity was higher in men and those patients with MS had higher radiological damage.

Disclosure: G. Betancur, None; **M. C. Orozco**, None; **E. Schneeberger**, None; **A. Lizarraga**, None; **N. Zamora**, None; **F. A. Sommerfleck**, None; **G. Citera**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/prevalence-of-obesity-and-metabolic-syndrome-in-patients-with-axial-spondyloarthritis

Abstract Number: 1705

Acute Anterior Uveitis in Ankylosing Spondylitis: Association with Inflammatory Bowel Disease and Psoriasis Independent of HLA-B27

Ahmed Omar[1], Tristan Boyd[2], Ismail Sari[1], Arane Thavaneswaran[3], Renise Ayearst[1], Robert D Inman[4] and Nigil Haroon[1], [1]Rheumatology, Toronto Western Hospital, University of Toronto, Toronto, ON, Canada, [2]Rheumatology, University of California San Diego, La Jolla, CA, [3]Rheumatology, University of Toronto, Toronto Western Hospital, Toronto, ON, Canada, [4]Immunlogy and Institute of Medical Science, Toronto Western Hospital, University of Toronto, Toronto, ON, Canada

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Background/Purpose: Acute anterior uveitis (AAU) is the most common extra-articular manifestation in patients with ankylosing spondylitis (AS), developing in 20-30% of these patients during the course of their disease.

Our aim was to study the characteristics and risk factors associated with AAU in our cohort of AS patients.

Methods: From our longitudinal observational cohort, 716 patients with AS (meeting modified New York Criteria) and at least 2 years follow up were included and who were followed from January 2006 to November 2013. Patients with (AAU+) and without (AAU-) uveitis were compared. Uveitis flare rates were calculated per year. T-test, Chi-squared tests and logistic regression were used where appropriate.

Results: Of the 716 patients, 225 (31.4%) had a reported diagnosis of AAU at their baseline clinic visit. Patients with AAU+ were older compared to the AAU- group (mean age of 42.6 vs 37.9 years; p< 0.001). AAU started after the onset of back pain in the majority of patients with only 10.5% of patients reporting onset of AAU before onset of AS related back pain. Patients with AAU had higher HLA-B27 (B27) prevalence (91.8% vs 82.1%, p<0.05). In the multivariate analysis (MVA), AAU was independently associated with age, B27, psoriasis, IBD and elevated CRP. B27 (OR=2.66 [95% CI=1.44-4.9]), psoriasis (OR=2.36 [95% CI=1.41-3.97]) and IBD (OR=2.25 [95% CI=1.27-4]) are the strongest independent predictors of AAU. Within the AS/IBD group (n=86), 43% of these patients had a history of AAU, of which 81% were B27 positive.

In patients with AAU , there was a trend towards more peripheral arthritis and enthesitis. The BASMI score was higher in patients with AAU (3.3 vs 2.7, P<0.05), however there was no association found on MVA. There was no significant difference found between the two groups in terms of BASDAI score,

hypertension, diabetes, previous history of myocardial infarctions and smoking history.

There was no difference found between NSAID use at baseline (66.1% vs. 66.5%, p=0.90). Patients with AAU were more frequently treated with DMARDs (26% vs. 16.5%, p<0.01). Sulfasalazine was used more frequently in the AAU+ group (14.2% vs. 7.9%, p<0.01). Use of biologics was similar at baseline (22.2% vs. 18.4%, p=0.23).

Conclusion: In our cohort of AS patients, an increased frequency of HLA-B27 was seen in AAU+ AS. AAU+ AS is associated with psoriasis and IBD. The psoriasis and IBD association is independent of HLA-B27, suggesting an interaction of other genetic as well as environmental factors. At baseline DMARD use was associated with AAU, likely reflecting the association with peripheral joint disease.

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Abstract Number: 1706

Prevalence and Factors Associated with Non-Traumatic Vertebral Fractures in Psoriatic Arthritis

Shelly Chandran[1], Sindhu R. Johnson[2], Angela Cheung[3], David Salonen[4] and Dafna Gladman[5], [1]University of Toronto, Toronto Western Hospital, Toronto, ON, Canada, [2]Dept of Rheumatology, Toronto Western and Mt. Sinai Hospitals, University of Toronto, Toronto, ON, Canada, [3]Department of Medicine, University of Toronto, Toronto, ON, Canada, [4]Department of Medical Imaging, University Health Network, Toronto, ON, Canada, [5]Rheumatology, University of Toronto, Toronto Western Hospital, Toronto, ON, Canada

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Background/Purpose: The prevalence of osteoporotic vertebral fractures (VF) in psoriatic arthritis (PsA) is not known. We aim to determine the prevalence and factors associated with non-traumatic radiographic VF in patients with PsA.

Methods: The most recent digital plain radiographs of the thoracic and lumbar spine as well as demographic, clinical, laboratory and imaging information on a large cohort of patients diagnosed with PsA, satisfying CASPAR classification criteria, were retrieved from a database. Fractures were diagnosed by quantitative morphometric assessment (QMA) on lateral spinal radiographs of lumbar and thoracic spine (T6-L4) that was previously demonstrated to have high inter- and intra-assessor reliability. Covariates including demographic features, measures of disease activity, body mass index and pharmacologic treatment, particularly OP-causing treatments like corticosteroids and methotrexate were investigated as factors associated with VF in PsA using descriptive statistics and logistic regression.

Results:

Data on 450 patients [191 (42%) females, mean age at the time of x-ray 54.4 ±13.6 years, mean PsA duration 18±11.9 years] were retrieved from the database. Only 24 (5.3%) patients (1 fracture-13, 2 fractures-9, >2 fractures-2) were diagnosed with VF. Univariate logistic regression analyses revealed that age (OR 1.08, 95% CI [1.04, 1.12], p value <0.0001), duration of psoriasis (OR 1.03, 95% CI [1.004, 1.062], p=0.027), PsA duration (OR 1.05, 95% CI [1.02, 1.09], p=0.002) and therapy with bisphosphonates (OR 4.92, 95% CI [1.29, 18.76], p=0.02) were associated with increased odds of the presence of VF, whereas race, sex, menopausal status, smoking, BMI, damaged joint count, presence of DISH, axial disease, enthesitis, dactylitis, time-averaged ESR, therapy with topical or systemic corticosteroids, NSAIDs, and methotrexate, HAQ and SF36 physical and mental component summary scores were not. Therapy with biologic agents showed a trend towards less odds of the presence of VF (OR 0.42, 95% CI [0.17, 1.02] p=0.056). Multivariate logistic regression analysis with backward elimination with age, sex, psoriasis and PsA duration, and therapy with bisphosphonates and biologics in the model revealed that only age (OR 1.08, 95% CI [1.04,1.12], P<0.0001) was independently associated with VF in PsA.

Conclusion: Prevalence of VF is low in PsA. PsA related variables are not associated with the presence of VF in patients with PsA.

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Abstract Number: 1707

Comorbidity Burden and Medication Use Among Patients with Psoriatic Arthritis in the US

Joseph F. Merola[1], Simeng Han[2], Jipan Xie[2], Huaying Song[2], Vivian Herrera[3], Jin Wei[2], Eric Q. Wu[2] and Jacqueline B. Palmer[3], [1]Brigham and Women's Hospital, Boston, MA, [2]Analysis Group, Inc., Boston, MA, [3]Novartis Pharmaceuticals Corporation, East Hanover, NJ
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Background/Purpose:

Psoriatic arthritis (PsA) is a chronic inflammatory disease that is associated with various comorbidities. This study aimed to assess the comorbidity burden and medication use among PsA patients as compared to matched controls who did not have PsA or psoriasis (PsO).

Methods:

Adults (18-64 years) with ≥2 claims for PsA diagnosis (ICD-9-CM: 696.0) that are ≥30 days apart were selected from the Truven Health MarketScan claims database (07/2009-06/2014) and constituted the case group. The index date was a randomly selected calendar date after the first claim for PsA. Cases were required to have ≥ 12 months continuous eligibility after the index date (the study period). Controls free of PsA and PsO (ICD-9-CM code: 696.0 and 696.1) in the entire claims history were assigned the same index date and study period as the matched cases. All selected patients were further required to have ≥12 months before the index date (washout period), which was used to confirm that controls were free of PsA and PsO. Cases and controls were matched 1:1 on age as of the index date, gender, and geographic region. Patient demographics as of the index date, comorbidities (including both PsA-associated and non-PsA-associated comorbidities), and medication use during the study period were compared between cases and controls. Wilcoxon signed rank tests were used to compare continuous variables and McNemar's tests were used to compare binary variables. Bonferroni correction was used to adjust for multiple comparisons.

Results:

A total of 35,061 matched pairs were included in this study with a mean age of 49.11±10.20 years and 47.27% were male. In general, PsA patients had significant higher rates of non-PsA-associated comorbidities compared to the controls, most notably, chronic pulmonary disease (22.70% vs. 14.50%, p<0.0001), liver disease [excluding fatty liver] (12.78% vs. 5.48%, p<0.0001) and co-prevalent rheumatic disease (6.25% vs. 0.98%, p<0.0001). PsA patients also had higher rates of PsA-associated comorbidities, notably, psychiatric diseases including anxiety (17.34% vs. 12.04%) and depression (21.71% vs. 13.14%), inflammatory eye disease including uveitis (2.41% vs. 0.64%) and scleritis (0.89% vs. 0.27%), inflammatory bowel disease [Crohn's disease or ulcerative colitis] (2.70% vs. 1.08%), celiac disease (0.75% vs. 0.30%) and gout (6.93% vs. 2.88%) (all p<0.0001). PsA patients had significantly higher rates of all-cause medication use (96.64%) and larger number of unique medications filled (12.04) than controls (78.95% and 5.59 respectively). Significant differences were also seen in the mean number of unique medications filled between PsA patients and controls for non-PsA-related medications (9.74 vs. 5.20), antidepressants (0.58 vs. 0.31), antidiabetics (0.28 vs. 0.18) and cardiovascular agents (1.53 vs. 1.05) (all p<0.0001).

Conclusion:

PsA patients had a significantly higher comorbidity burden compared to matched subjects without PsA or PsO. PsA patients also incurred significantly more medication use overall and related to these comorbid conditions. This study represents a unique look at the comorbidity burden and prevalence among a large US PsA population.

Disclosure: J. F. Merola, Novartis Pharmaceuticals Corporation, 5,Biogen Idec, 2,Biogen Idec, 5,Biogen Idec, 9,Abbvie, 5,Abbvie, 8,Abbvie, 9,Amgen, 5,Amgen, 9,Eli Lilly and Company, 5,Pfizer Inc, 9,Janssen Pharmaceutica Product, L.P., 5; **S. Han**, Analysis Group, Inc., 3; **J. Xie**, Analysis Group, Inc., 3; **H. Song**, Analysis Group, Inc., 3; **V. Herrera**, Novartis Pharmaceuticals Corporation, 3,Novartis Pharmaceuticals Corporation, 1; **J. Wei**, Analysis Group, Inc., 3; **E. Q. Wu**, Analysis Group, Inc., 3; **J. B. Palmer**, Novartis Pharmaceuticals Corporation, 3.

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Abstract Number: 1708

Predictors of Depression Severity in Ankylosing Spondylitis

Mark Hwang[1], MinJae Lee[2], Michael M. Ward[3], Lianne S. Gensler[4], Matthew A. Brown[5], Shervin Assassi[6], Laura A. Diekman[7], Mohammad H. Rahbar[8], Michael H. Weisman[9] and John D. Reveille[10], [1]Internal Medicine, University of Texas Health Science Center at Houston, Houston, TX, [2]Biostatistics/Epidemiology/Research Design (BERD) Core | Center for Clinical and Translational Sciences, University of Texas Health Science Center at Houston, Houston, TX, [3]NIH/NIAMS, Bethesda, MD, [4]Medicine/Rheumatology, University of California, San Francisco, San Francisco, CA, [5]The University of Queensland Diamantina Institute, Brisbane, Australia, [6]Rheumatology, University of Texas Medical School at Houston, Houston, TX, [7]Rheumatology, University of Texas Medical School, Houston, TX, [8]The University of Texas Health Science Center at Houston, Houston, TX, [9]Rheumatology, Cedars-Sinai Medical Center, Los Angeles, CA, [10]Rheumatology, University of Texas Health Science Center at Houston, Houston, TX
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Background/Purpose:

Depression is a known comorbidity of ankylosing spondylitis (AS) with over one-third of AS patients affected and increased depression-rate ratio compared to the general population. Predictors of depression in AS have not been comprehensively reported. The purpose of this study is to examine the baseline demographic and clinical predictors of depression in addition to depression severity over time in AS. The baseline predictors of depression in AS were also studied over time on depression severity.

Methods:

Using the Center for Epidemiological Studies Depression (CES-D) Scale for depression severity, 622 patients who met modified New York criteria for AS and were followed at least two years were studied from the Prospective Study of Outcomes in Ankylosing Spondylitis cohort. Univariable/multivariable longitudinal analyses using mixed effect negative binomial regression models were conducted to assess the clinical/demographic features associated with CES-D score accounting for correlation of repeated CES-D measures over time.

Results:

The cohort was 73% male and 81% of patients were white, having a mean age 42.4 years (SD= 13.8). The mean disease duration at baseline was 17.5 years (SD±13.1). The median CES-D score at baseline was 9 (IQR= [5, 17]). In the univariable longitudinal model, independent factors positively associated with a higher CES-D score included: smoking , have multiple comorbidities, Hispanic ethnicity, greater reported pain, disease activity (by the Bath Ankylosing Spondylitis Disease Activity Index), functional impairment (by the Bath Ankylosing Spondylitis Functional Index), elevated CRP, NSAID use, DMARD use, anti-depressants use, narcotic use, and self-reported depression. Inversely associated factors included: marital status (married), exercise and TNF –α inhibitor use. Baseline radiographic severity did not have any statistically associations with CES-D scores. In multivariable analysis (Table 1), positive correlations with current smoking, functional impairment, disease activity, greater pain perception, usage of DMARDS and narcotic pain analgesics and self-reported depression. Inverse associations were found with being married, exercising > 120 minutes per week, and, curiously, greater baseline radiographic severity (as measured by the Bath Ankylosing Spondylitis Radiographic Index).

Conclusion:

This study identifies demographic and clinical factors that predict longitudinal depression severity and demonstrates potentially modifiable targets to treat depression in AS patients.

Table 1. Multivariable Associations of Selected Variables on Longitudinal CES-D Score

Variable	Rate Ratio (95% CI)	P Value
Male	1.02 (0.9,1.16)	0.717
Married	0.86 (0.77,0.96)	0.006
Age ≥40	1.11 (0.99,1.25)	0.083
working pay	0.98 (0.87,1.09)	0.669
Exercise ≥120min/week	0.91 (0.86,0.97)	0.003
currently smoking	1.25 (1.08,1.45)	0.003
BASFI ≥40	1.16 (1.07,1.25)	0.0003
BASDAI ≥40	1.35 (1.27,1.44)	<0.0001
BASRI baseline≥6	0.83 (0.73,0.94)	0.0034
depression	1.38 (1.19,1.6)	<.0001
pain scale ≥50	1.21 (1.13,1.3)	<.0001
Patient Global Assessment of Disease Activity≥23	1.5 (1.34,1.69)	<.0001
CRP abnormal	1.00 (0.94,1.07)	0.891
anti-depressant use	1.09 (0.97,1.22)	0.130
NSAID use	1.01 (0.95,1.07)	0.801
DMARD use	1.14 (1.04,1.25)	0.005
Narcotics use	1.17 (1.07,1.28)	0.0004
Hypnotics use	1.11 (0.94,1.31)	0.230
TNF –α inhibitor use	1.00 (0.93,1.08)	0.9636

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Subclinical Atherosclerosis in Patients with Psoriatic Arthritis and the Role of Vitamin D

Montserrat Robustillo-Villarino[1], Cristina Vergara-Dangond[1], Gloria Albert Espi[1], Marcos Cerqueira[2], Desamparados Ybañez García[1], Elia Valls[1],

Elvira Vicens-Bernabeu[1], Juan José Alegre[1] and Àngels Martínez-Ferrer[1], [1]Rheumatology Department, Hospital Universitario Doctor Peset, Valencia, Spain, [2]Hospital de Ponte de Lima, ULSAM, Department of Rheumatology,Hospital de Ponte de Lima, ULSAM, Ponte de Lima, Portugal
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Background/Purpose: Psoriatic arthritis (PsA) is associated with increased cardiovascular risk (CV)[i]. Several studies associate low levels of 25-hydroxivitamin D (25OHD) with a greater prevalence of CV risk[ii]. Carotid ultrasound is a useful method to detect subclinical CV disease[iii]. To estimate CV risk and contrast it to presence of subclinical atherosclerosis in patients with PsA. To determine the relation between 25OHD deficit and presence of subclinical vascular damage.

Methods: Cross-sectional study included patients with PsA and peripheral joint affection of over one year evolution meeting CASPAR criteria. Demographic (sex, age, IMT), clinical (classic CV risk factors, previous CV incidents) and analytical data (liver and kidney function, calcium, phosphorus, 25OHD and PTH, total cholesterol and HDL) were recorded. CV risk was estimated with SCORE stratification table for low risk countries such as Spain. Ultrasound study was performed with Esaote MyLab xv70, 7-12 mHz linear transducer. An automated program assessed the IMT through radiofrequency (Quality intima media thickness in real time [QIMT]). Measurements were taken at the bilateral common carotid artery, and presence of atheroma plaque in the extra-cranial carotid artery was recorded following the Manheim consensus. Statistical analysis done with SPSS 17.0 program.

Results: 90 patients comprised the study, 24 of which were excluded due to high CV risk (prior CV event, glomerular filtration rate <60mg/dL, and/or Type I or II diabetes with target organ injury). Mean age was 53±11 years and most patients were women (58%), 30% were smokers, 29% were obese (mean BMI: 27±5). Mean DAS28 was 2.3±0.8 and mean HAQ was 0.5±0.7. Mean 25OHD levels were 27.56±12.8ng/dl, and PTH 54±23pg/ml. 61% of patients had vitamin D insufficiency (<30ng/ml) and 30.3% deficiency (<20ng/ml). 42%(28) of patients had low CVR estimated by SCORE (0), 49%(32) medium risk (SCORE ≥1 y<5), and 1.5% (1) high or very high risk (SCORE≥5). Mean IMT was 0.71±0.14mm and 9% exhibited IMT>0,9mm. Atheroma plaque was found in 34%. 34% of patients exhibited a pathological ultrasound (plaque and/or pathological IMT). We didn't observe any association between DAS28 or HAQ and pathologic findings in carotid evaluation. Based on these results, 25% of patients with Low and 45% of patients with Medium SCORE should be reclassified as High Risk.

RISK LEVEL	IMT > 0,9mm	Presence of atheroma plaque	Pathological ultrasound
LOW	2/28 (7.1%)	7/28 (25%)	7/28 (25%)
MEDIUM	5/32 (15.6%)	14/31 (45.2%)	14/31 (45.2%)
HIGH or VERY HIGH	0/0 (0%)	0/1 (0%)	0/1 (0%)

No association was observed between 25OHD levels or densitometric findings and DAS28, HAQ, presence of atheroma plaque or IMT.

Conclusion: We proved that SCORE underestimated CV risk in patients with PsA and that carotid ultrasound allows to re-stratify such risk. Patients with atheroma plaque or pathological IMT do not show lower levels of 25OHD than those without these vascular changes.

[i] Horreau C, et al. J Eur Acad Dermatol Venereol. 2013 Aug;27 Suppl3:12-29.

[ii]Amer M, et al. Am J Med. 2013 Jun;126:509-14.

[iii] Perk J, et al. Atherosclerosis. 2012 Jul;223:1-68.

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Abstract Number: 1710

Enthesitis in Psoriatic Arthritis: Incidence, Prevalence and Characteristics

Ari Polachek[1], Suzanne Li[2], Vinod Chandran[1] and Dafna Gladman[1], [1]Rheumatology, University of Toronto, Toronto Western Hospital, Toronto, ON, Canada, [2]University of Toronto, Toronto Western Hospital, Toronto, ON, Canada
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Background/Purpose:

Enthesitis reflects inflammation at the insertion of tendons and ligaments into bone and is a well-known component of psoriatic arthritis (PsA). It is part of the stem requirements of the CASPAR (Classification Criteria for Psoriatic Arthritis) criteria. However, little is known about the characteristics of enthesitis in patients with PsA.

The aim of this study was to evaluate the incidence, prevalence, and characteristics of enthesitis in patients with PsA.

Methods:

The study population included patients with PsA who were followed at 6 month interval according to a standard protocol from January 2008 to December 2014. Enthesitis was defined as the presence of at least one painful entheseal site of the 18 entheseal insertion locations of the SPARCC (Spondyloarthritis Research Consortium of Canada) enthesitis index. Descriptive statistics are provided. Incidence calculated per patient-year of follow-up.

Results:

Of 803 patients who were evaluated during this period 281 had enthesitis on at least one visit, with a prevalence of 35%. 192 patients developed enthesitis during the course of follow-up, with an annual incidence of 0.9%. Among the 281 patients with enthesitis the mean (SD) age at enthesitis diagnosis was 49 years (± 12.7) and PsA duration was 11.4 years (± 11.3). At the time of enthesitis the BMI was 30 (± 6.4), mean number of actively inflamed joints was 9.5 (±11.1) and 52 (19%) patients had dactylitis. The mean psoriasis area severity index (PASI) score was 4 (±5.7) and the mean modified nail psoriasis severity index (mNAPSI) score was 6.1 (± 9.9). 31 (11%) patients had a diagnosis of concomitant osteoarthritis, 33 (12%) diabetes mellitus and 42 (15%) fibromyalgia. 81 (31%) patients had elevated ESR, 115 (41%) patients had elevated CRP and 14% were positive for HLA-B*27. The X-ray evaluation revealed plantar spurs in 143 (53%) patients, Achilles spurs in 99 (37%) and sacroiliitis in 116 (42%). The treatment at diagnosis included NSAIDS in 205 (73%) patients, DMARDS in 154 (55%) and biologics drugs in 95 (34%).

Most of the patients had 1 or 2 (110 and 99 patients, respectively) tender entheseal sites. The 3 most common tender entheseal sites were: Achilles tendons, plantar fascia and, lateral epicondyles (24.2%, 20.8% and 17.2%, respectively).

Conclusion:

Clinical enthesitis is common, occurring in 35% of PsA patients. Usually it appears in only 1 or a few sites simultaneously and the most symptomatic locations are Achilles tendons, plantar fascia and lateral epicondyles.

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Abstract Number: 1711

Enthesitis in Psoriatic Arthritis – Disease Association and Risk Factors

Ari Polachek[1], Suzanne Li[2], Vinod Chandran[1] and Dafna Gladman[1], [1]Rheumatology, University of Toronto, Toronto Western Hospital, Toronto, ON, Canada, [2]University of Toronto, Toronto Western Hospital, Toronto, ON, Canada
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Background/Purpose:

Psoriatic arthritis (PsA) is a heterogeneous disease presenting with musculoskeletal and extra-articular manifestation. Enthesitis is a well-known component of PsA. However, little is known about the disease association and risk factors of clinical enthesitis in patients with PsA.

Aim: To evaluate the disease association and risk factors of clinical enthesitis in patients with PsA.

Methods:

The study population included patients with PsA who were followed at 6 months interval according to a standard protocol from January 2008 to December 2014. Enthesitis was defined as the presence of at least one painful entheseal site of the 18 entheseal insertion locations of the SPARCC (Spondyloarthritis Research Consortium of Canada) enthesitis index. Logistic regression was used to analyze baseline characteristics associated with enthesitis and a Cox regression analysis was used to identify predictors for the development of enthesitis in those without enthesitis at baseline.

Results:

Of 803 patients who were seen during this period 281 (35%) had clinical enthesitis on at least one visit, while 522 (65%) did not. The enthesitis group was

significantly younger at baseline and was younger at psoriasis diagnosis. The mean active joint count as well as the presence of tenosynovitis were significantly higher in the enthesitis group. The damaged joint count and the mean Steinbrocker score were significantly lower in the enthesitis group. Fibromyalgia was more prevalent in the enthesitis group. Quality of life and function were significantly poorer in the enthesitis group. The enthesitis group used significantly more NSAIDS. Multivariate logistic regression analysis showed that the following variables were independently associated with the presence of enthesitis: younger age (OR 0.98, p=0.03), higher mean active joints (OR 1.06, p<0.0001), less damaged joints (OR 0.97, p=0.01), presence of tenosynovitis (OR 2.75, p=0.0008) and NSAIDS use (OR 1.6, p=0.01). 128 (16%) patients were diagnosed with new clinical enthesitis during follow-up. Predictive factors for development of enthesitis are shown in the table 1.

able 1: Multivariate cox regression analysis risk factors for enthesitis in PsA patients

Variable	Hazard Ratio	Lower C.I	Higher C.I	P-value
Age at baseline	**0.98**	**0.97**	**0.99**	**0.007**
Age at psoriasis diagnosis	0.99	0.98	1.004	0.2
Gender	1.01	0.8	1.3	0.92
BMI	1.02	0.99	1.04	0.1
Active joint count	**1.02**	**1.007**	**1.03**	**0.003**
Presence of tenosynovitis	**2.1**	**1.45**	**3.01**	**<0.0001**
Damaged joint counts	**0.97**	**0.95**	**0.99**	**0.003**
Steinbrocker score	0.99	0.98	1.02	0.9
PASI	1.009	0.99	1.03	0.4
Presence of nail lesions	1.09	0.82	1.44	0.5
Presence of sacroiliitis	1.06	0.8	1.4	0.7
Presence of fibromyalgia	1.2	0.82	1.8	0.3
HAQ	**1.5**	**1.2**	**1.8**	**0.0009**
NSAIDS use	1.3	0.96	1.74	0.08

Conclusion: PsA patients with enthesitis are younger, have higher active joint counts, more tenosynovitis, less damage and worse quality of life. The same variables are predictive of developing enthesitis during the course of PsA.

Disclosure: A. Polachek, None; **S. Li**, None; **V. Chandran**, None; **D. Gladman**, None.

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Abstract Number: 1712

Development of a Novel SI Joint CT Score for Diagnosis of Axial Spondylitis

Jonathan Chan[1,2], Ismail Sari[3,4], David Salonen[5], Robert D Inman[6] and Nigil Haroon[7], [1]Rheumatology, Spondylitis program, Toronto Western Hospital, University of Toronto, Toronto, ON, Canada, [2]Rheumatology, University of British Columbia, Vancouver, BC, Canada, [3]Rheumatology, Toronto Western Hospital, University of Toronto, Toronto, ON, Canada, [4]Rheumatology, Dokuz Eylul University School Of Medicine, Department Of Internal Medicine, Division Of Rheumatology, Izmir, Turkey, [5]Department of Medical Imaging, University Health Network, Toronto, ON, Canada, [6]Immunlogy and Institute of Medical Science, Toronto Western Hospital, University of Toronto, Toronto, ON, Canada, [7]Rheumatology, Toronto Western Hospital, Toronto, ON, Canada
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Background/Purpose: The diagnosis of ankylosing spondylitis (AS) is based on pelvic radiographs plagued by poor sensitivity, specificity, and reproducibility. Many AS patients, particularly those with inflammatory bowel disease (IBD), may have CT scans performed for other clinical indications and sacroiliitis may be incidentally noted. Though the modified New York (mNY) criteria have never been validated in CT imaging, previous studies have used a radiologist's adaptation of the criteria as a gold standard for diagnosing sacroiliitis.

Our objective is to develop a validated scoring system for sacroiliitis on CT that can ground future studies in prevalence and pathogenesis.

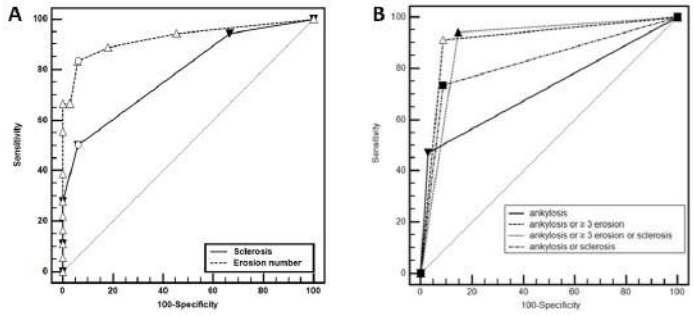
Methods: Patients from the Toronto AS clinic meeting mNY criteria for AS who had CT scans of the abdomen/pelvis were matched to controls by age and gender. Control patients had their charts reviewed to ensure they had no history of spondylitis, colitis, uveitis, or psoriasis. A training exercise involving 10 CT scans (5 AS and 5 controls) was conducted to identify candidate features and to optimize reliability. A derivation cohort of 24 CT scans (12 AS and 12 controls) was used to test these features. Finally, 2 blinded readers performed a validation study on 68 CT scans (34 AS and 34 controls).

SI joints were divided into left and right as well as iliac and sacral segments for a total for 4 segments. The maximum number of erosions seen on a single slice was counted for each segment. The sum of these values gave a total erosion score. Sclerosis was only measured on the slice with the longest synovial length. Inter- and intra-observer values, sensitivity, specificity, and likelihood ratios (LR) were calculated for variables that correlated with AS. Combinations of variables were trialed to maximize sensitivity and specificity.

Results: Features with the highest +LR included ankylosis, number of erosions, iliac sclerosis >0.5cm, and sacral sclerosis >0.3cm. Inter-reader reliability for these variables were 1.0 for ankylosis, 0.99 for number of iliac erosions, 0.99 for number of sacral erosions, 0.58 for iliac sclerosis, and 0.39 for sacral sclerosis. Fig 1A demonstrates the ROC curves for the total erosion number as well as the increasing depth of sclerosis. A total erosion number of ≥3 erosions was found to have the highest sensitivity and specificity for AS. Fig 1B demonstrates the ROC curves for combinations of ankylosis, sclerosis, and erosions for diagnosing AS. Sclerosis was defined as either >0.5cm of iliac or >0.3cm of sacral sclerosis >1cm in length. The presence of >1cm of ankylosis or ≥3 total erosions resulted in a sensitivity of 91% and specificity of 91%. The addition of >0.5cm of iliac sclerosis or >0.3cm of sacral sclerosis marginally increased the sensitivity to 94% but decreased specificity to 86%.

Conclusion: It is proposed that the presence of ankylosis >1cm or ≥3 total erosions has the greatest diagnostic utility for AS.

Fig 1



Disclosure: J. Chan, None; **I. Sari**, None; **D. Salonen**, None; **R. D. Inman**, None; **N. Haroon**, None.

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Abstract Number: 1713

Fat Metaplasia on Sacroiliac Joint Magnetic Resonance Imaging at Baseline Is Associated with Spinal Radiographic Progression in Patients with Axial Spondyloarthritis

Kwi Young Kang[1], In Je Kim[2], Yeon Sik Hong[3], Sung-Hwan Park[4] and Ji Hyeon Ju[5], [1]#505, Banpo-dong, Seocho-gu, Division of Rheumatology, Department of Internal Medicine, Catholic University of Korea, Seoul, South Korea, [2]Division of Rheumatology, Department of Internal Medicine, Ewha Womans University School of Medicine, Seoul, South Korea, [3]catholic University of Korea, Incheon, South Korea, [4]Kangnam St Mary's Hospital, Seoul, South Korea, [5]Division of Rheumatology, Department of Internal Medicine, College of Medicine, The Catholic University of Korea, Seoul, South Korea
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Background/Purpose: To study the relationship between inflammatory and structural lesions in the sacroiliac joints (SIJs) on MRI and spinal progression observed on conventional radiographs in patients with axial spondyloarthritis (axSpA).

Methods: One hundred and ten patients who fulfilled the ASAS axSpA criteria were enrolled. All underwent SIJ MRI at baseline and lumbar spine radiographs at baseline and after 2 years. Inflammatory and structural lesions on SIJ MRI were scored using the SPondyloArthritis Research Consortium of Canada (SPARCC) method. Spinal radiographs were scored using the Stoke AS Spinal Score (SASSS). Multivariate logistic regression analysis was performed to identify predictors of spinal progression.

Results: Among the 110 patients, 25 (23%) showed significant radiographic progression (change of SASSS≥2) over 2 years. There was no change in the SASSS over 2 years according to the type of inflammatory lesion. Patients with fat metaplasia or ankyloses on baseline MRI showed a significantly higher SASSS at 2 years than those without ($p<0.001$). According to univariate logistic regression analysis, age at diagnosis, HLA-B27 positivity, the presence of fat metaplasia, erosion, and ankyloses on SIJ MRI, increased baseline CRP levels, and the presence of syndesmophytes at baseline were associated with spinal progression over 2 years. Multivariate analysis identified syndesmophytes and severe fat metaplasia on baseline SIJ MRI as predictive of spinal radiographic progression (OR, 7.92 and 8.25, respectively).

Conclusion: Inflammatory lesions in the SIJs on baseline MRI were not associated with spinal radiographic progression. However, fat metaplasia at baseline was significantly associated with spinal progression after 2 years.

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Abstract Number: 1714

Young Patients with Back Pain and Maximally 1 Spa Feature: Is It Useful to Test HLA-B27 or Image the Sacroiliac Joints?

Pauline Bakker[1], Zineb Ez-Zaitouni[2], Miranda van Lunteren[2], Manouk de Hooge[3], Rosaline van den Berg[4], Inger Jorid Berg[5], Robert B. M. Landewé[6], Maikel van Oosterhout[7], Roberta Ramonda[8], Monique Reijnierse[9], Floris van Gaalen[1] and Désirée van der Heijde[10], [1]Rheumatology, Leiden University Medical Center, Leiden, Netherlands, [2]Leiden University Medical Centre, Leiden, Netherlands, [3]Department of Rheumatology, Leiden University Medical Centre, Leiden, Netherlands, [4]Leiden University Medical Center, Leiden, Netherlands, [5]Department of Rheumatology, Diakonhjemmet Hospital, Oslo, Norway, [6]Rheumatology, University Hospital Maastricht, Maastricht, Netherlands, [7]Rheumatology, GHZ Hospital, Gouda, Netherlands, [8]Cattedra, Voc Rheumatology, University of Padua, Padova, Italy, [9]Radiology, Leiden University Medical Center, Leiden, Netherlands, [10]University Hospital, Maastricht, Netherlands

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Background/Purpose: Axial SpondyloArthritis (axSpA) is a heterogeneous disease. The likelihood of diagnosis varies depending upon the specific findings that are present. However, it is debated whether additional examinations (i.e. HLA-B27 testing and imaging of the sacro-iliac joints (SIJ)) should be performed in patients with a low suspicion of axSpA: i.e. negative findings on medical history, physical examination, CRP/ESR measurement. By this study we aim to investigate if HLA-B27 testing and imaging of the SIJ is useful in young patients with back pain and maximally 1 SpA feature.

Methods: The SPACE cohort includes patients with chronic back pain (≥3 months ≤2 years, onset <45 years) recruited from 6 participating centres across Europe. All patients underwent full diagnostic work-up: MRI and x-rays SIJ, HLA-B27 testing and assessment of all other SpA-features. Patients were classified according to the ASAS axSpA-criteria.

Results: In this analysis, 133 patients from 4 participating centres were included. Of the 38/133 (28.6%) patients with 0 SpA-features; 4/38 (10.5%) were classified according to the ASAS-axSpA criteria after additional investigations (imaging arm only: 2MRI+/mNY+, 1MRI+/mNY-, 1MRI-/mNY+). Of the 95/133 (71.4%) patients with 1 SpA-feature; 22/95 (23.2%) patients fulfilled the ASAS-axSpA criteria (imaging arm only: 3MRI+/mNY+, 15MRI+/mNY-, 4MRI-/mNY+). Those patients presented the following features: 7 IBP, 5 IBD, 4 positive family history for SpA, 3 good response to NSAIDs, 2 raised CRP/ESR, 1 enthesitis.

Conclusion: In patients with CBP and 0 or 1 SpA-feature after medical history, physical examination and CRP/ESR measurement, subsequent HLA-B27 testing and imaging led to fulfilment of the axSpA-criteria in 11% and 23% respectively. Therefore in these patients, the disease cannot be ruled out without additional imaging and/or HLA-B27 testing.

Table 1: classification and diagnosis of patients with 0 and 1 SpA-feature after HLA-B27 and SIJ-imaging

No. of SpA-features	HLA B27 status	Imaging status	ASAS axSpa YES	Rheum Spa YES	ASAS axSpA NO	Rheum SpA NO
0	B27 +	MRI+mNY+	2	2	-	
		MRI+mNY-	1	1	-	
		MRI-mNY+	1		-	1
		MRI-mNY-	-	2	3	1
	B27 -	MRI+mNY+	-		-	
		MRI+mNY-	-	2	5	2*
		MRI-mNY+	-		-	
		MRI-mNY-	-		26	26
1	B27 +	MRI+mNY+	2		-	1*
		MRI+mNY-	4	3	-	1
		MRI-mNY+	1		-	*
		MRI-mNY-	-	2	15	12*
	B27 -	MRI+mNY+	1	1		
		MRI+mNY-	11	8		3
		MRI-mNY+	3	2		1
		MRI-mNY-	-	1	58	57
Total			26	24	107	105

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Abstract Number: 1715

Sensivity and Specificity of Clinical Criteria to Identify Patients in Ultrasound Remission in Psoriatic Arthritis

Brigitte Michelsen[1], Andreas P Diamantopoulos[2], Hilde Berner Hammer[3], Arthur Kavanaugh[4] and Glenn Haugeberg[1,5,6], [1]Rheumatology, Hospital of Southern Norway Trust, Kristiansand, Norway, [2]Haugesund Rheumatism Hospital, Haugesund, Norway, [3]Rheumatology, Diakonhjemmet Hospital, Oslo, Norway, [4]University of California, San Diego School of Medicine, LaJolla, CA, [5]Rheumatology, The Norwegian University of Science and Technology, Trondheim, Norway, [6]Rheumatology, Martina Hansens Hospital, Gjettum, Norway

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Background/Purpose: To date, although several have been proposed, there are no validated remission criteria in psoriatic arthritis (PsA). Validated criteria for minimal disease activity (MDA) in PsA have been established. This study aimed to compare sensivity and specificity of different potential remission criteria to identify patients in remission as defined by musculoskeletal ultrasound (US).

Methods: In this cross sectional study PsA patients were consecutively recruited from an outpatient clinic. All the patients fulfilled the CASPAR criteria for PsA. The following potential remission criteria were assessed: **(1)** Disease Activity Index for Psoriatic Arthritis (DAPSA) ≤3.3, **(2)** Composite Psoriasis Disease Activity Index (CPDAI) <2, **(3)** Psoriatic ArthritiS Disease Activity Score (PASDAS) <2.4 **(4)** Boolean's definition of remission modified for PsA, meeting all of the following criteria: 68 tender joints (TJC68) ≤1, 66 swollen joints (SJC66)≤1, Maastricht Ankylosing Spondylitis Enthesitis Score (MASES) ≤1, dactylitis count ≤1, evaluator's global assessment (EGA) ≤1 (0-10 scale), patient's global assessment (PGA) ≤1 (0-10 scale), C-reactive protein ≤1mg/dl **(5)** MDA, meeting 5 of the 7 following criteria: TJC68 ≤1, SJC66 ≤1, Psoriasis Area Severity Index (PASI) ≤1, patient's pain ≤15 (0-100 scale), PGA ≤20 (0-100 scale), Modified Health Assessment Questionnaire (MHAQ) ≤0.5 and MASES ≤1. US evaluation was performed on 68 joints, 15 tendons and 29 entheses if clinical findings indicating inflammation. Mandatory US evaluation was performed on 34 joints, 15 tendons and 10 entheses. US remission was defined as power Doppler (PD) score=0 in all joints, entheses and tendons. Chi-Square test or Fishers exact test (as appropriate) was used to calculate proportions. The odds ratio (OR) within the 95% confidence interval was calculated using the 2 x 2 table. A value of p<0,05 was accepted as statistically significant.

Results: A total of 141 PsA patients were included. Mean (SD) age was 52,4 (10,2) years, mean disease duration 9,5 (6,6) years and 72% were females. Median (range) TJC68 was 6 (0-55), SJC66 0 (0-6), MASES 2 (0-13). Mean (SD) EGA was 14,8 (12,3), PGA 36,3 (24,4), DAPSA 18,3 (14,1), CPDAI 6,2 (2,7) and PASDAS 3,1 (0,4). Overall, US remission was achieved by 70 (49,6%) patients. Sensivity and specificity of clinical criteria to identify patients in US remission are displayed in the table.

	Sensivity (%)	Specificity (%)	OR (95% CI)	p
MDA (n=32)	30.0	84.3	2.3 (1.0-5.2)	**0.048**
DAPSA≤3.3 (n=14)	15.7	95.8	4.2 (1.1-15.9)	**0.025**
CPDAI>2 (n=12)	13.0	95.7	3.4 (0.9-13.0)	0.066
PASDAS<2.4 (n=11)	8.6	93.0	1.2 (0.4-4.3)	0.748
Boolean's for PsA (n=8)	10.0	98.6	7.8 (0.9-65.0)	**0.033**

Conclusion: MDA, DAPSA and Boolean's PsA remission criteria had some utility as regards identifying PsA patients in US remission. Off note, while the specificity of these criteria was good, the sensivity was quite poor.

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Abstract Number: 1716

Prevalence of Joint Symptoms and Frequency of Joint Exams for Patients with Plaque Psoriasis without Confirmed Psoriatic Arthritis: A US Analysis

Tatiana Makhinova[1], Robert Wood[2], **Derek Tang**[3], James Piercy[2], Steve Lobosco[4], Bradley S. Stolshek[5] and David J. Harrison[5], [1]College of Pharmacy, University of Texas at Austin, Austin, TX, [2]Adelphi Real World, Macclesfield, United Kingdom, [3]Amgen, Inc., Thousand Oaks, CA, [4]Adelphi Real World Ltd., Macclesfield, United Kingdom, [5]Amgen Inc., Thousand Oaks, CA
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Background/Purpose: Due to the high prevalence of PsA among patients with PsO,[1] rheumatologists and dermatologists should recognize early signs and symptoms of joint involvement among patients with PsO without diagnosed PsA.[2,3]This analysis sought to evaluate the prevalence of joint symptoms and frequency of joint exams for patients with plaque PsO without PsA in the US.

Methods: This analysis was based on US data from the Adelphi 2011 and 2013 Psoriasis Disease Specific Programme, a cross-sectional survey of 91 dermatologists and their patients with PsO. Patients with suspected or confirmed PsA were excluded from the analysis. Joint symptoms were reported separately from both patients and physicians. Joint exams were reported by physicians and included tender joint count, swollen joint count, rheumatoid factor, immunoglobin A and immunoglobin M tests. Clinical and health-related quality of life (HRQoL) parameters were compared between 2 groups: patients with physician-reported joint symptoms without joint exams, and patients without physician-reported joint symptoms or who had a joint exam. Similar comparisons were made using patient rather than physician-reported joint symptoms. T-tests or Mann-Whitney U tests for numerical variables and chi-square tests or Fisher's exact tests for categorical variables were applied.

Results: A total of 1,002 patients were included in the analysis (mean age 45.7±15.7 [SD], 54.8% male). Overall, only 4.3% received joint exams. Physician-reported joint symptoms were less frequent than patient-reported joint symptoms (8.5% vs. 25.4%). Among those with physician-reported and patient-reported joint symptoms, 79.0% and 90.7% of patients did not receive a joint exam, respectively. Only 6.7% of the entire sample had physician-reported symptoms but no joint exams, while 22.9% had patient-reported symptoms but no joint exams. Compared with patients without physician-reported joint symptoms or who had a joint exam, patients with physician-reported joint symptoms but no joint exams had significantly poorer EuroQoL-5D (3L) (EQ-5D) utility scores (0.83 vs. 0.91), greater activity impairment (21.4% vs. 14.9%) as measured by the Work Productivity and Activity Impairment questionnaire (WPAI), and more severe psoriasis (Body Surface Area: 14.1% vs. 9.7%) (all $p<0.05$). Compared with patients who did not self-report symptoms or who had a joint exam, patients who self-reported symptoms but had no joints exams had significantly poorer EQ-5D utility scores (0.87 vs. 0.91) and greater activity impairment (19.3% vs. 14.0%) as measured by the WPAI (both $p<0.05$).

Conclusion: In the US, over three quarters of PsO patients without a diagnosis of PsA did not receive a joint exam when the patient or patients' physician reported joint symptoms. Early diagnostic actions such as referral to a rheumatologist or joint exams could increase recognition of PsA, leading to earlier diagnosis and appropriate treatment.

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3. Mease P et al. J Am Acad Dermatol 2013;69(5):729-35.

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Abstract Number: 1717

Factors Associated with the Decision of the Rheumatologist to Order Sacro-Iliac Joints Magnetic Resonance Imaging (SI-MRI) or Order HLA-B27 Testing in Patients with Spondyloarthritis in Clinical Practice

Wilson Bautista-Molano[1,2], Robert Landewé[3], Cesar Serna[4], Rafael R. Valle[5] and Désirée van der Heijde[6], [1]Department of Rheumatology, Leiden University Medical Center, Leiden, The Netherlands, Leiden, Netherlands, [2]Department of Rheumatology, Faculty of Medicine HMC/UMNG, Bogota, Colombia, Bogotá, Colombia, [3]Department of Rheumatology, Amsterdam Rheumatology Center, Amsterdam, The Netherlands, Amsterdam, Netherlands, [4]Statistics and Mathematics Department, Universidad Central, Bogotá, Colombia, Bogotá, Colombia, [5]Rheumatology/Immunology, Department of Rheumatology, Faculty of Medicine HMC/UMNG, Bogota, Colombia, Bogota, Colombia, [6]Dept. of Rheumatology, Leiden University Medical Center, Leiden, Netherlands
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Background/Purpose: Magnetic resonance imaging of sacroiliac joints (MRI-SI) and HLA-B27 testing are important tools in the diagnosis of spondyloarthritis (SpA). The aim of the study was to evaluate the patient´s characteristics associated with the clinical decision to request MRI-SI and/or HLA-B27 in daily practice

Methods: A cohort of patients referred to a specialised rheumatology outpatient clinic in a national referral centre was used. Data related to age, gender, number of initial symptom at presentation (arthritis and/or enthesitis and/or back pain and/or buttock pain), disease duration, infection history, past and currently present SpA features (chronic back pain, inflammatory back pain (IBP), asymmetric oligoarthritis, enthesitis (heel pain), dactylitis, buttock pain, uveitis, psoriasis and inflammatory bowel disease) were collected from the clinical record. BASDAI and ASDAS were calculated. Patients with the clinical diagnosis of SpA according to the rheumatologist were included. Information on MRI-SI and HLA-B27 was available only for those patients for whom the rheumatologists decided to order these tests. Characteristics associated with ordering MRI-SI or HLA-B27 separately were identified with univariable analyses. Variables with a p-value <0.05 and data available over 80% of cases were entered in the (backward) multivariable analysis. Colinearity and interactions were checked and relevant interactions were excluded A multivariable logistic regression analysis was used to evaluate factors related with the decision to perform MRI-SI and/or HLA-B27 and odds ratios (95% CI) were calculated

Results: In total, 581 patients with SpA were included, 72% were men, with a mean age of 34.6±12.1 years, age at symptom onset of 28,0±10.3 years and disease duration of 7.3±9.7 years. Disease activity was calculated separately for axial and peripheral SpA and was rather high for both: BASDAI: 5.4 (2.4) and ASDAS-ESR: 3 (0.9). For axial SpA ASDAS-CRP was 2.6 (0.8) and for peripheral SpA was 2.3 (0.9). Of these patients, 24% (n=137) had MRI-SI and 77% (n=441) had HLA-B27 testing ordered. Predictive factors for ordering a MRI-SI were IBP (OR=1.81), enthesitis (OR=1.57) and the number of initial symptoms at presentation (OR=1.27). Predictive factors of HLA-B27 testing were the number of initial symptoms at presentation (OR=1.45) and uveitis (OR=3.19) Table1

Conclusion: IBP, enthesitis, and the number of symptoms at presentation were independently associated with ordering an MRI-SI. The number of symptoms at presentation and to some extent uveitis were associated with the request of HLA-B27. This study provides insight in characteristics that prompt rheumatologists to order complementary imaging or HLA-B27 testing in the diagnostic work-up of patients with SpA

Table 1. Association of SpA disease characteristics that independently prompt to ordering MRI-SI and HLA-B27. Results from a multivariable logistic regression model.

	MRI-SI ordered		**HLA-B27 ordered**	
Explanatory variables	OR (95% CI)	p Value	OR (95% CI)	p Value
Male gender	0.79 (0.50-1.22)	0.28	0.85 (0.53-1.36)	0.50
Number of symptoms at presentation (0-4)	1.27 (1.10-1.47)	**≤0.001**	1.45 (1.24-1.71)	**≤0.001**
Disease duration	0.90 (0.57-1.41)	0.66	1.26 (0.77-2.04)	0.34
Chronic back pain	1.57 (0.72-3.23)	0.26	0.96 (0.53-1.73)	0.90
Inflammatory back pain	1.81 (1.13-2.90)	**0.01**	1.14 (0.70-1.85)	0.58
Arthritis	0.85 (0.54-1.33)	0.48	1.15 (0.70-1.89)	0.55
Enthesitis	1.57 (1.00-2.49)	**0.04**	0.89 (0.58-1.38)	0.62

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Abstract Number: 1718

Entheseal Abnormalities and Nail Involvement at the Distal Interphalangeal Joints on Ultrasound Examination in Patients with Psoriasis and Psoriatic Arthritis. Could the Nail-Enthesitis Theory be Supported?

M Laura Acosta-Felquer[1], Erika Catay[2], Leandro Ferreyra-Garrot[3], Santiago Ruta[1], David A. Navarta[4], Javier Rosa[5], Ricardo Galimberti[6], Maria L. Galimberti[6], Ricardo Garcia-Monaco[7] and Enrique R. Soriano[8], [1]Rheumatology Unit, Internal Medicine Service, Hospital Italiano de Buenos Aires, Buenos Aires, Argentina, [2]Rheumatology Unit, Internal Medicine Service, Hospital Italiano de Buenos Aires, Instituto Universitario Hospital Italiano de Buenos Aires, and Fundacion PM Catoggio,, Buenos Aires, Argentina, [3]Rheumatology Section, Internal Medicine Service, Hospital Italiano de Buenos Aires, Instituto Universitario Hospital Italiano de Buenos Aires, and Fundacion PM Catoggio, Internal Medicine, Argentina, Buenos Aires, Argentina, [4]Internal Medicine, Rheumatology Unit, Internal Medicine Service, Hospital Italiano de Buenos Aires, Buenos Aires, Argentina, [5]Rheumatology, Hospital Italiano de

Buenos Aires, Buenos Aires, Argentina, [6]Dermatology Service, Hospital Italiano de Buenos Aires, Buenos Aires, Argentina, [7]Radiology and Imagenology Department, Hospital italiano de Buenos Aires, Buenos Aires, Argentina, [8]Internal Medicine, Hospital Italiano de Buenos Aires, Buenos Aires, Argentina
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Background/Purpose:

It has been shown that nail involvement in psoriasis is associated with systemic enthesopathy. The association of enthesopathy and nail disease at distal interphalangeal (DIP) joints in psoriasis (PsO) and psoriatic arthritis (PsA) has not been studied until now. Our purpose was to analyze the association of nail involvement and extensor tendon enthesopathy at DIP level in patients with PsO and PsA.

Methods:

Consecutive patients with PsO or PsA were included. Patients with DIP osteoarthrtitis were excluded. Patients were seen by trained rheumatologists and dermatologists, for diagnosis and the Psoriasis Area and Severity Index (PASI), and the modify Nail Psoriasis Severity Index (mNAPSI) were calculated. Ultrasound (US) examinations included the second to fourth extensor tendon insertions at DIP joints bilaterally. The Outcome Measures in Rheumatoid Arthritis (OMERACT) definition of enthesopathy was adopted. Prevalence with 95% confidence intervals of enthesopathy was calculated for PsO and PsA with and without nail involvement and compared. The relationship between nail involvement and enthesopathy was also analyzed at fingers level.

Results:

One hundred and ten patients were included (table 1). US showed extensor tendon enthesopathy (ETE) in at least one DIP joint in 9 patients with PsO (17%; 95% CI: 8-29 %) and in 18 with PsA (32 %; 95%CI: 20-46%) (p=0.059). Among patients with PsO, 20% (95%CI: 7-41%) and 14% (95% CI:4-32%) of those with and without clinical nail involvement showed ETE on US examination, respectively (p=0.542). Among PsA patients, the prevalence of ETE was 30% (95% CI: 15-49%) for patients with clinical nail involvement and 35 % (95% CI: 17-56%) for those without nail involvement, respectively (p=0.712). On logistic regression analysis, the diagnosis of PsA (OR: 3.3; 95% CI: 1.1-9.8; p=0.032), but not nail involvement (OR: 1.1 (95% CI: 0.42-3); p=0.824 was associated with ETE, while the use of DMARDs was protective (OR: 0.33; 95% CI: 0.11-0.99; p=0.0481). Table 2 shows the relationship between ETE and clinical nail involvement at fingers level.

Table 1. Patients' characteristics

Features	PsO (n= 54)	PsA (n=56)
Females, n (%)	26 (53)	28 (46)
Mean disease duration, yrs (SD)	10.4 (8)	4.9 (6)
Nail involvement, n (%)	25 (46.3)	30 (54)
Mean PASI (SD)	4.3 (5)	3.4 (5.4)
Mean mNAPSI (SD)	6.7 (10.4)	9.3 (12.4)
Treated with DMARDs, n (%)	14 (26)	39 (70)
Treated with TNFi, n (%)	3 (6)	12 (21)

Table 2. Association between extensor tendon enthesopathy and nail involvment at fingers level

	Psoriasis Patients (n=54)		Psoriatic Arthritis Patients (n=56)		All Patients (n=110)	
	Nails with clinical involvement (n= 93)	Normal nails (n=339)	Nails with clinical involvement (n=143)	Normal nails (n=305)	Nails with clinical involvement (n=236)	Normal Nails (n=644)
Number of fingers with Extensor tendon enthesopathy (%)	57 (61)	57 (17)	86 (60)	67 (22)	143 (60)	124 (19)
OR (95% CI)	7.8 (4.6-13.4)	p<0.0001	5.4 (3.4-8.4)	p<0.0001	6.5 (4.6-9.1)	P<0.0001

Conclusion: Extensor tendon enthesopathy at DIP joints was more frequent in PsA than in PsO. No association was found between nail involvement and extensor tendon enthesopathy at patients' level. There was a significant increased prevalence of extensor tendon enthesopathy in fingers with involved nails both in PsO and PsA. These features might support the nail-entheseal pathogenesis theory at DIP level.

Disclosure: M. L. Acosta-Felquer, None; **E. Catay**, None; **L. Ferreyra-Garrot**, None; **S. Ruta**, None; **D. A. Navarta**, None; **J. Rosa**, None; **R. Galimberti**, None; **M. L. Galimberti**, None; **R. Garcia-Monaco**, None; **E. R. Soriano**, Abbvie; Janssen; UCB; Roche; Bristol Myers Squibb, 2,Abbvie; UCB; Janssen; Roche; Bristol Myers Squibb; Pfizer; Novartis, 8.

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Abstract Number: 1719

Can Structural Progression on MRI of Sacroiliac Joints in Patients with Spondyloarthritis be Reliably Detected and What Type of Calibration Is Necessary to Achieve This?

Walter Maksymowych[1], Susanne Juhl Pedersen[2], Victoria Navarro-Compán[3], Stephanie Wichuk[1], Josefina Marin[4], Manouk de Hooge[5], Robert G Lambert[6], Désirée van der Heijde[5] and Rosaline van den Berg[5], [1]Medicine, Medicine, University of Alberta, Edmonton, AB, Canada, [2]Copenhagen Center for Arthritis Research, Glostrup Hospital, University of Copenhagen, Copenhagen, Denmark, [3]Rheumatology, University Hospital La Paz, Madrid, Spain, [4]Rheumatology Unit, Internal Medicine Service, Hospital Italiano de Buenos Aires, Buenos Aires, Argentina, [5]Leiden University Medical Center, Leiden, Netherlands, [6]Radiology, Radiology, University of Alberta, Edmonton, AB, Canada

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Background/Purpose: There is growing interest in the management of early axial spondyloarthritis and intervention with disease-modifying agents while disease is still confined to the sacroiliac joints (SIJ). Assessment of structural lesions of the SIJ on MRI may be a helpful tool to monitor disease progression but requires evidence that change in such lesions can be reliably detected and the type of calibration necessary to achieve this. We aimed to assess reliability of detection of structural lesions in the SIJ on MRI and the impact of calibration using either a standardized web-based training module or a set of DICOM-based reference MRI scans.

Methods: In this international multicenter study, 5 readers without exposure to the application of scoring methods specifically for structural lesions in the SIJ reviewed either a web-based training module (n=3) that included standardized definitions for and examples of erosion, fat metaplasia, backfill, and ankylosis, or a set of DICOM-based reference MRI scans (n=2). Both calibration methods included instructions for the scoring of lesions according to the Spondyloarthritis Research Consortium of Canada SIJ Structural Score (SSS) on 5 consecutive semi-coronal slices through the SIJ using a binary method based on presence/absence of the lesion in SIJ quadrants (erosion, fat metaplasia (range 0-40)) or SIJ halves (backfill, ankylosis range (0-20)). Baseline and 2-year T1-weighted (T1W) scans from 30 patients with axial SpA blinded to patient characteristics, short-tau inversion recovery (STIR) scan, and time point, were scored and data entered directly online using a web-based schematic of the SIJ. Interobserver reliability for status and change scores was calculated by intra-class correlation coefficient (ICC) and comparisons made with pre-specified expert readers (n=3).

Results: Mean (SD) reduction in SSS erosion score was significantly greater for expert readers (-1.62 (4.05)) and for DICOM-trained readers (-1.40 (3.42)) than for web-based module trained readers (-0.47 (1.56)). Mean (SD) increase in SSS backfill score was significantly greater for expert readers (0.82 (3.87)) than for web-based module trained readers (-0.07 (1.67)). ICC differed between groups mainly for 2-year change in erosion and backfill. Although reliability was superior for DICOM-trained readers, substantial reliability with expert readers was attainable following training with the web-based module (Table).

Conclusion: Structural lesions in the SIJ on MRI are often heterogeneous in appearance and their evolution may not be reliably detected without the more rigorous approach to calibration using DICOM scans.

Table. Interobserver ICC

Calibration Method and Reader		Erosion		Fat metaplasia		Backfill		Ankylosis	
		Status	Change	Status	Change	Status	Change	Status	Change
Web-based Module*	R1	0.06	-0.11	0.48	0.43	0.10	0.12	0.87	0.37
	R2	0.74	0.27	0.62	0.61	0.80	0.36	0.97	0.38
	R3	0.71	0.62	0.36	0.66	0.83	0.54	0.98	0.50
DICOM-based*	R1	0.56	0.68	0.91	0.71	0.51	0.66	0.96	0.88
	R2	0.53	0.51	0.77	0.77	0.68	0.47	0.98	0.94
Expert readers		0.71	0.66	0.60	0.71	0.81	0.76	0.97	0.64

*ICC for each reader based on comparison with mean score of 3 expert readers

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Disclosure: W. Maksymowych, None; **S. J. Pedersen**, None; **V. Navarro-Compán**, None; **S. Wichuk**, None; **J. Marin**, None; **M. de Hooge**, None; **R. G. Lambert**, None; **D. van der Heijde**, None; **R. van den Berg**, None.

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Abstract Number: 1720

Quantitative Assessment of Bone Marrow Fat Using Magnetic Resonance Imaging in Patients with Spondyloarthropathy

Bon San Koo[1], Yoonah Song[2], Kyung-Bin Joo[3], Seunghun Lee[2] and Tae-Hwan Kim[4], [1]Division of Rheumatology, Department of Internal Medicine, Konkuk University College of Medicine, Chungju, South Korea, [2]Department of Radiology, Hanyang University College of Medicine, Seoul Hospital, Seoul, South Korea, [3]Department of Radiology, Department of Radiology, Hanynag University Hospital for Rheumatic Diseases, Seoul, South Korea, [4]Department of Rheumatology, Hanyang University Hospital for Rheumatic Diseases, Seoul, South Korea

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Background/Purpose: Fat metaplasia in the bone marrow is an indicator of disease progression in spondyloarthropathy (SpA). This study aimed to evaluate the bone marrow fat content in patients with SpA using advanced magnetic resonance imaging (MRI) techniques to measure the proton density fat-fraction and identify fat-fraction changes according to disease progression.

Methods: A total of 129 patients with SpA who underwent a pelvis MRI at Hanyang University Hospital for Rheumatic Diseases from September 2014 to March 2015 were retrospectively evaluated. Quantitative fatty infiltration was assessed on the fat-signal fraction maps using the Dixon technique. Fat fractions were quantified after measuring the signal intensity within the region of interest (ROI) over the periarticular bone marrow where there was no contamination from the bony cortex or joint spaces. The ROIs were drawn at each of two sites of the right and left ilium. MRI was used to examine the fat fraction at inflammatory regions (inflammatory fat) and noninflammatory regions (noninflammatory fat) in the bone marrow. Clinical characteristics and the correlation between the sacroiliac (SI) joint grades and fat fractions were evaluated.

Results: Patients had a mean age of 32.2 ± 11.6 years, and 84 were male (65%). Mean symptom duration was 4.2 ± 6.0 years, and 84 out of 116 patients (72.4%) had tested positive for HLA-B27. Mean right and left SI joint grades on the radiograph were 1.7 ± 1.3 and 1.8 ± 1.3, respectively. Mean fractions of inflammatory fat were 82.6% ± 9.8% and 82.0% ± 11.1% (right) and 82.4% ± 10.2% and 82.2% ± 10.3% (left), while the mean fractions of noninflammatory fat were 51.1% ± 9.6% and 53.2% ± 9.6% (right) and 52.8% ± 9.5 % and 53.4% ± 11.0% (left). A significant correlation was found between right and left inflammatory fat fractions and right ($p = 0.003$ and $p = 0.005$) and left ($p = 0.000$ and $p = 0.000$) SI joint grades on the radiographs, respectively (Spearman correlation analysis), although no correlation was found between the total noninflammatory fat fraction and each SI joint grade on the radiographs (Figure 1). A significant correlation was also found between inflammatory fat fractions and modified Stoke Ankylosing Spondylitis Spinal Score.

Conclusion: The inflammatory fat fraction of the bone marrow increased in SpA patients who showed severe radiographic SI joint changes. Quantitative MRI assessment of the fat fraction may represent another useful imaging technique to evaluate the progression of SpA.

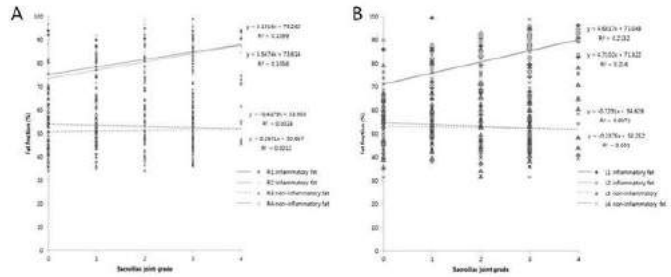

Figure 1. Correlation between sacroiliac joint grade and fat fraction of the bone marrow in the ilium. (A) Right sacroilium. (B) Left sacroilium.

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Abstract Number: 1721

Factors Predictive of Radiographic Progression in Ankylosing Spondylitis

Ismail Sari[1], Jonathan Chan[2], Ahmed Omar[1], Mohamed Bedaiwi[1], Renise Ayearst[1], Robert D Inman[3] and Nigil Haroon[1], [1]Rheumatology, Toronto Western Hospital, University of Toronto, Toronto, ON, Canada, [2]Rheumatology, Spondylitis program, Toronto Western Hospital, University of Toronto, Toronto, ON, Canada, [3]Immunlogy and Institute of Medical Science, Toronto Western Hospital, University of Toronto, Toronto, ON, Canada

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Background/Purpose: Ankylosing spondylitis (AS) is a chronic inflammatory disease that primarily affects the axial skeleton. New bone formation resulting in syndesmophytes can lead to spinal ankylosis and associated disability and poor functional outcomes. Conventional X-rays represent the gold-standard for the assessment of the radiographic damage. In this study, we evaluated a cohort of AS patients to identify factors associated with radiographic progression.

Methods: AS patients (satisfying the modified New York criteria) who had a full set of baseline and follow-up x-rays at a minimum interval of 2 years were included in the study. Two readers scored the X-rays independently. In discordant cases, radiographs were evaluated by an arbitrator. Radiographic damage was assessed by the modified Stoke Ankylosing Spondylitis Spinal Score (mSASSS). Progression was defined as ≥2 mSASSS change between two time points. Clinical variables at baseline were derived from the database and included disease duration, B27 status, demographics, smoking, BASDAI, BASFI, BASMI, SF-36-PCS, -MCS, and ASQoL.

Results: There were 288 patients with a total of 822 x-rays. The mean age and disease duration were 38.7±13.6 and 15.9±10.8 years respectively. 77.1% of the patients were male and 78% were B27 positive. The mean interval between first and last x ray (ΔTime) was 55.9±23.8 months. Total mSASSS change (ΔTotal) was 2.84±6.03 for the cohort overall. The mean mSASSS change/year (ΔYear) was 0.67±1.3 unit. 47.9% of the total patients had damage at baseline as defined as an mSASSS score ≥2. The reliability between the observers regarding lumbar, cervical and total mSASSS scores were 0.97, 0.94 and 0.94 respectively. Overall, 40.6% of the patients progressed during the period of observation. Comparison of progressors *vs*non-progressors revealed that age, disease duration, smoking history, baseline radiological damage and baseline BASMI were significantly higher in the patients who progressed ($p<0.005$). Logistic regression analysis showed that smoking and baseline radiological damage independently predicted the radiographic progression with an odds ratio of 2.8 and 22.8 respectively. In addition to baseline mSASSS, degree of sacroiliitis at baseline was associated with radiographic progression.

Conclusion: AS Patients who are smokers and have baseline changes in SI joints or spine are more likely to demonstrate radiographic progression.

Table 1: Comparison of progressors *vs* non-progressors

	Non-Progressors (n=171)	***Progressors (n=117)***	***P value***
Age, years	34.8±13.5	44.4±11.8	<0.0001
Sex, Male, %	73.7	82.1	0.11
Disease duration, years	13.9±9.9	19.1±11.3	<0.0001
B27, %	79.5	75.9	0.47
ΔTime, months	52.5±20	57±25.4	0.11
ΔTotal	-0.02±0.5	7±7.7	<0.0001
ΔYear	0±0.13	1.64±1.6	<0.0001
Right SIJ score	2.77±0.9	3.3±0.9	<0.0001
Left SIJ score	2.77±0.9	3.2±0.9	<0.0001
Hip involvement, %	9.3	10.7	0.67
Baseline damage, %	28.1	76.9	<0.0001
CRP (mg/L)	12.8±22.1	13.2±18.4	0.88
BASDAI	4.5±2.48	4.5±2.45	0.86
BASMI	1.8±1.9	3.6±2.2	<0.0001
SF-PCS	37.9±11.3	37±10.7	0.37
SF-MCS	47.1±11.5	46.1±11.9	0.96
ASQoL	6.9±5.9	7.8±5.8	0.36
Smoking,%	36.1	49.6	0.03
Arthritis, %	72.9	70.9	0.8
Uveitis, %	30.6	40.2	0.1
Psoriasis, %	18.8	19.7	0.88
IBD, %	14.1	17.1	0.51

Results are given as mean±SD

Disclosure: I. Sari, None; **J. Chan**, None; **A. Omar**, None; **M. Bedaiwi**, None; **R. Ayearst**, None; **R. D. Inman**, None; **N. Haroon**, None.

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Abstract Number: 1722

What Is the Clinical Utility of MR Imaging in the Management of Nr-Axspa Patients?

Ismail Sari[1], Ahmed Omar[1], Jonathan Chan[2], Mohamed Bedaiwi[1], Renise Ayearst[1], Nigil Haroon[1] and Robert D Inman[3], [1]Rheumatology, Toronto Western Hospital, University of Toronto, Toronto, ON, Canada, [2]Rheumatology, Spondylitis program, Toronto Western Hospital, University of Toronto, Toronto, ON, Canada, [3]Immunlogy and Institute of Medical Science, Toronto Western Hospital, University of Toronto, Toronto, ON, Canada

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Background/Purpose: The ASAS classification criteria have provided new insights in the classification of axial spondyloarthropathy (axSpA). MR imaging (MRI) is an intrinsic component of the imaging arm of the classification criteria for non-radiographic (nr)-axSpA. The scheme classifies these patients by the imaging arm if the MRI is positive or by the clinical arm if such MRI evidence is lacking. The current algorithm does not address the clinical utility of MRI in patients who meet the clinical criteria, in which B27 is mandatory. The main aim of our study was to compare clinical features and outcomes of nr-axSpA patients stratified into MRI-Pos, MRI-Neg, and MRI-ND (not done) subsets. The study provided the opportunity to define clinical commonalities and differences between these three subsets, and to address the added value of MRI in the management of nr-axSpA.

Methods: Patients who met the criteria for nr-axSpA by the imaging arm or the clinical arm were included. Patients who met the NY criteria for AS were excluded. X-rays and MRIs were scored by two rheumatologists, blinded to clinical diagnosis. Discordant results were settled by a third reader. Patients classified as nr-axSpA were further stratified into the imaging or clinical arms. The clinical arm was further stratified into MRI-Neg and MRI-ND groups. Clinical characteristics were then obtained for each group from the clinical database.

Results: There were 107 patients fulfilling ASAS criteria for nr-axSpA. The median age of the patients was 35.2 (18-64) years, 51.4% were male and 85% were B27+. There were 37 patients in the imaging arm and 70 patients in the clinical arm. The intraclass correlation coefficient of the readers for right and left SIJ were 0.75 and 0.73 respectively. The kappa value of the readers for MR classification was 0.74. Age, sex distribution and disease duration were similar between the three groups (Table 1). Extra-articular features, acute phase reactants, BASDAI and BASMI were also comparable between the three groups. There were 45 (42.1%) patients who were treated with TNF inhibitors. Subgroup analysis of the patients who received TNFi treatment showed that biological treatment utilization, biologic switch frequencies, and rates of biologic non-response were similar between the three groups.

Conclusion: The clinical profiles of nr-axSpA patients with and without MRI confirmation are comparable, including response to biologic therapy. This suggests that there is a degree of homogeneity in the nr-axSpA cohort when patients are classified on clinical grounds alone. Including B27 as a mandatory inclusion criterion likely underlies this homogeneity, and does so to a greater extent than imaging studies.

Table 1: Clinical and demographical characteristics of the groups

	MR(+), n=37	Clinical arm MR(-) n=38	Clinical arm MR ND n=32	p
Age (years)	33.9 (18-56)	40.4 (18-64)	37.5 (18-63)	0.42
Disease duration (years)	4 (1.5-28)	11 (1-34)	7 (1-38)	0.15
Sex (M %)	54.1	47.4	53.1	0.82
B27 (%)	56.8	100	100	<0.0001
Smoking (%)	40	29	29.6	0.59
BASFI	2.7 (0-10)	1.9 (0-8)	2.3 (0-7.8)	0.6
BASDAI	4.5 (0.6-9.8)	3 (0-9.2)	3.8 (0-9.2)	0.81
BASMI	2 (0-5)	1 (0-5)	1 (0-2)	0.19
ESR	6.5 (1-122)	5 (1-52)	6.5 (1-63)	0.81
CRP	3 (0-135)	3 (0-38)	3 (0-28)	0.62
Biologic ever (%)	43.2	47.4	34.4	0.54
Biologic switch ever (%)	43.8	44.4	36.4	0.9
Biologic switch, LOE, %	85.7	71.4	75	0.8
NSAIDs, continuous use (%)	86.4	79.2	71.4	0.48
Arthritis (%)	48.6	47.4	59.4	0.56
Uveitis, %	16.2	28.9	34.4	0.21
Psoriasis, %	13.5	18.4	12.5	0.75
Dactilytis, %	8.1	2.7	6.3	0.59
IBD, %	8.1	2.6	3.1	0.47
Enthesitis, %	33.3	32.1	25	0.76
Family history, %	5.7	22.2	45.2	0.001
Subgroup analysis of the patients receiving TNFi treatment				
	Mr+, n=16	**Mr-, n=18**	**Mr (ND), n=11**	**p value**
Current TNF, %	68.8	55.6	90.9	0.14
Switch ever, %	43.8	44.4	36.4	0.9
Switch, LOE, %	85.7	71.4	75	0.8
Number of switch	2 (1-4)	2 (1-4)	1.5 (1-4)	0.87
ΔBASDAI	-1.5 (-7.8-3.2)	-2.6 (-6.6-3.4)	-3.6 (-4.8-3.8)	0.69
ΔCRP	0 (-23-0)	0 (-10-1)	-2 (-32-0)	0.13

Continous data are presented with median with minimum-maximum values

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Abstract Number: 1723

Prevalence of Sacroiliitis in Inflammatory Bowel Disease Using a Standardized CT Scoring System

Jonathan Chan[1], Ismail Sari[2], David Salonen[3], Mark S. Silverberg[4], Nigil Haroon[2] and Robert D Inman[5], [1]Rheumatology, Spondylitis program, Toronto Western Hospital, University of Toronto, Toronto, ON, Canada, [2]Rheumatology, Toronto Western Hospital, University of Toronto, Toronto, ON, Canada, [3]Department of Medical Imaging, University Health Network, Toronto, ON, Canada, [4]Zane Cohen Centre for Digestive Diseases, Mount Sinai Hospital IBD Group,, Zane Cohen Centre for Digestive Diseases, Mount Sinai Hospital, Toronto, ON, Canada, [5]Immunlogy and Institute of Medical Science, Toronto Western Hospital, University of Toronto, Toronto, ON, Canada

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Background/Purpose: Previous studies assessing the prevalence of sacroiliitis in patients with inflammatory bowel disease (IBD) using CT scans have relied on the general impression of a radiologist. These estimates have ranged between 30-45%; however, only a small proportion of these patients were symptomatic and only patients who had symptoms suggestive of spondylitis had an increased frequency of HLA-B27. To date, the prevalence of sacroiliitis in IBD patients using a standardized CT scoring system is not known.

Our aim is to determine the prevalence of sacroiliitis in patients with IBD using a validated standardized CT scoring system and to compare this prevalence to that in a non-IBD control population.

Methods:

Patients with IBD were recruited from one gastroenterology clinic and control patients were recruited from a urology clinic. The chart of each control patient was reviewed to ensure there was no history of back pain, spondylitis, psoriasis, colitis, or uveitis. Two blinded readers scored the CT scans using two diagnostic models: **Model 1:** ankylosis or ≥3 erosions; **Model 2:**ankylosis, ≥3 erosions, ≥0.5cm of iliac sclerosis, or ≥0.3cm of sacral sclerosis. These models have been developed and validated in our previous study to have a sensitivity of 91% and 94% and a specificity of 91% and 86% respectively. We also noted the presence of lumbar spine syndesmophytes and whether the reporting radiologist had noted sacroiliitis in their reporting.

Results:

The percent of patients who fulfilled the various models for sacroilitis are presented in Table 1.

Table 1: Prevalence of sacroiliitis according to each model

	Model 1	Model 2
Control (n=108)	5.6%	13%
Crohn's disease (n=233)	15%	17.2%
Ulcerative colitis (n=83)	16.9%	21.7%

There was no significant difference in prevalence of sacroiliitis between patients with CD and UC with a Chi^2test= 0.725. There was a significant difference in the number of erosions between control and IBD patients but no difference in rate of ankylosis or sclerosis.

Amongst the 49 CT scan positive patients, radiologist comments were reported on 39 images and sacroiliitis was noted in 16 cases. Only 5 of these 49 patients had been referred to the spondylitis clinic. Amongst the 267 CT scan negative patients, radiologist comments were reported on 184 images and 5 definite and 4 possible cases of sacroiliitis were noted.

Conclusion: Using a standardized CT scoring system, the prevalence of sacroiliitis in IBD patients is 16% with no difference between CD and UC patients. This indicates a 3-fold increase in prevalence over non-IBD controls. Despite a growing awareness of the high prevalence of sacroiliitis in patients with IBD, a significant proportion of patients have never been referred to a rheumatologist. Finally, there may be a small proportion of asymptomatic patients who have changes in their sacroiliac joints suggestive of sacroiliitis, though this is of uncertain clinical significance.

Disclosure: J. Chan, None; **I. Sari**, None; **D. Salonen**, None; **M. S. Silverberg**, None; **N. Haroon**, None; **R. D. Inman**, None.

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Abstract Number: 1724

Abdominal X-Rays Can Reliably Detect the Majority of CT Positive Sacroiliitis in an IBD Cohort

Jonathan Chan[1], Ismail Sari[2], Ahmed Omar[2], Mark S. Silverberg[3], David Salonen[4], Robert D Inman[5] and Nigil Haroon[2], [1]Rheumatology, Spondylitis program, Toronto Western Hospital, University of Toronto, Toronto, ON, Canada, [2]Rheumatology, Toronto Western Hospital, University of Toronto, Toronto, ON, Canada, [3]Zane Cohen Centre for Digestive Diseases, Mount Sinai Hospital IBD Group,, Zane Cohen Centre for Digestive Diseases, Mount Sinai Hospital, Toronto, ON, Canada, [4]Department of Medical Imaging, University Health Network, Toronto, ON, Canada, [5]Immunlogy and Institute of Medical Science, Toronto Western Hospital, University of Toronto, Toronto, ON, Canada

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Background/Purpose: There is a well-documented association between inflammatory bowel disease (IBD) and ankylosing spondylitis (AS). The hallmark feature of AS is the presence of sacroiliitis that has traditionally been diagnosed using an AP view of the pelvis on X-ray. Many IBD patients receive supine and erect abdominal X-rays in the management of their bowel disease and it is not known whether these films can be used in the diagnosis of AS.

Many experts agree that CT scan is a superior imaging modality for the diagnosis of sacroiliitis though until recently there was no definition of what constituted a positive CT. Recently we have described a standardized scoring system for the diagnosis of sacroiliitis which is anchored in the modified New

York criteria (mNY). To date, there has not been a study assessing the diagnostic utility of abdominal X-rays for the diagnosis of spondyloarthritis in IBD patients.

We aim to compare the reproducibility and test characteristics of abdominal X-rays in detecting CT-positive sacroiliitis in a IBD cohort.

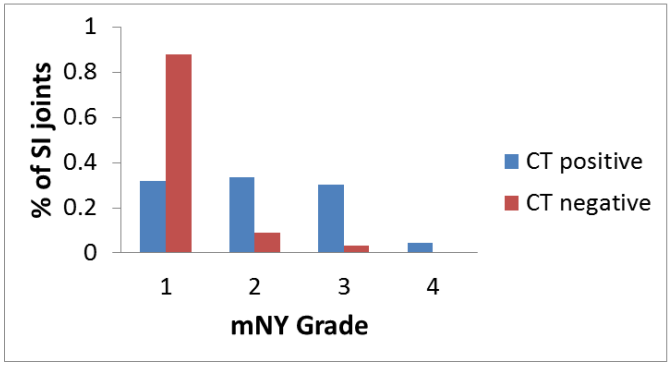
Methods: In a previous study, we identified IBD patients who had a CT scan of their abdomen/pelvis from one IBD clinic. CT scans were read by 2 blinded readers and 49 patients were identified as having sacroiliitis according to a recently validated scoring system. Of these 49 patients, 33 were found to have abdominal X-rays done within 1 year of their CT scan.

The 33 patients included in the study were matched by age, gender, and IBD subtype to control IBD patients (n=33). X-rays were randomized and read by two experienced blinded readers according to modified New York grade. Discordant results were settled by a third reader. Patients were classified as having diagnostic or non-diagnostic SI joints and inter-reader reliability as well as the prevalence of specific features of sacroiliitis was determined.

Results: The median age for IBD patients was 35 years (range 17-75) and 64% were male. Within the CT positive group, 21/33 (64%) were scored as having diagnostic X-rays according to mNY grading system. Amongst the CT-negative control group, X-rays identified sacroiliitis in 3/33 (9%) patients. Inter-reader reliability for diagnosis of sacroiliitis using X-rays was good (κ=0.659) which was similar to that found with CT scan (κ=0.697). Cramér's V correlation between the two imaging modalities revealed an r=0.647. Chi squared test was used to compare the two nominal variables and showed a p value <0.0001. Fig 1 shows the distribution of SI joint grade according to CT scan result.

Conclusion: Abdominal X-ray and CT scan have a similar inter-reader reproducibility for the diagnosis of sacroiliitis. Abdominal X-ray is able to detect the majority of patients with CT-positive sacroiliitis; however, 36% of CT-positive patients would not have been identified. These results need to be further correlated with clinical context to confirm a diagnosis of spondyloarthritis.

Fig 1: Distribution of SI joint grade according to CT scan results



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Reliable Evaluation of Structural Lesions of the Sacroiliac Joints on MRI in Patients with Axial Spondyloarthritis That Is Comparable to Evaluation of Inflammation Despite Minimal Calibration

Rosaline van den Berg[1], Susanne Juhl Pedersen[2], Victoria Navarro-Compán[3], Stephanie Wichuk[4], Manouk de Hooge[5], Robert G Lambert[6], Désirée van der Heijde[5] and Walter Maksymowych[7], [1]Leiden University Medical Center, Leiden, Netherlands, [2]Copenhagen Center for Arthritis Research, Glostrup Hospital, University of Copenhagen, Copenhagen, Denmark, [3]Rheumatology, University Hospital La Paz, Madrid, Spain, [4]Medicine, Medicine, University of Alberta, Edmonton, AB, Canada, [5]Rheumatology, Leiden University Medical Center, Leiden, Netherlands, [6]Radiology, Radiology, University of Alberta, Edmonton, AB, Canada, [7]Medicine/Rheumatic Dis Unit, Medicine, University of Alberta, Edmonton, AB, Canada

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Background/Purpose: There is growing recognition of the importance of structural lesions of the sacroiliac joints (SIJ) on MRI to the diagnostic evaluation of axial spondyloarthritis (axSpA) but it is unclear to what degree current definitions for such lesions and methods for evaluation of the SIJ allow reliable assessment between different centers and readers. We aimed to assess reliability of evaluation of structural SIJ lesions on MRI without conducting

calibration exercises between readers at two centers, readers at one center being internally calibrated and having extensive experience in evaluation of structural lesions in the SIJ.

Methods: All readers simultaneously evaluated T1-weighted and short tau inversion recovery (STIR) scans from 9 patients with non-specific back pain and 23 with axial SpA from 2 centers (Leiden=12, Edmonton=20). All readers were internally calibrated, and readers in one center have extensive experience in evaluation of structural lesions in the SIJ. Scans were read blinded to patient characteristics, diagnosis, and scan origin, and data entered directly online using a web-based schematic of the SIJ. Bone marrow edema (BME) and structural lesions (erosion, fat metaplasia, sclerosis, ankylosis) were scored on consecutive semi-coronal slices through the SIJ using a binary method based on presence/absence of the lesion in SIJ quadrants except for ankylosis, which was assessed according to SIJ halves. Slices were selected according to the methodology used in the Spondyloarthritis Research Consortium of Canada (SPARCC) MRI SIJ inflammation scoring method. Interobserver reliability was calculated by intra-class correlation coefficient (ICC) and comparisons made with pre-specified expert readers.

Results: Mean (SD) scores for BME, erosion, fat metaplasia, sclerosis, and ankylosis were 5.3 (7.1), 6.1 (5.5), 6.5 (7.5), 2.5 (3.4), 0.3 (1.2) with significantly higher scores being recorded for BME, erosion, and fat metaplasia by expert readers. Mean (range) for sensitivity/specificity for expert clinician diagnosis of SpA was 0.85 (0.75-0.91)/0.88 (0.79-1.00), sensitivity of expert readers being higher (0.90 vs 0.81) though specificity was lower (0.85 vs 0.92). Interobserver reliability for structural lesions was comparable between groups of readers and approached the reliability of BME for erosion, and fat metaplasia (Table). Reliability for sclerosis and ankylosis varied although few cases demonstrated significant involvement with these lesions.

Conclusion: The presence and extent of erosion and fat metaplasia can be reliably assessed by simultaneous evaluation of T1W and STIR scans even without calibration between readers and seems promising for diagnostic evaluation. Evaluation of ankylosis and sclerosis, on the other hand, requires further study in cohorts that have more cases with these lesions.

Table. ICC [95% confidence intervals]

MRI Feature	Leiden Scans (n=12)		Edmonton Scans (n=20)		All scans (n=32)
	Expert Readers (n=2)	Inexperienced Readers (n=3)	Expert Readers (n=2)	Inexperienced Readers (n=3)	All Readers
BME	0.90 (0.63-0.97)	0.81 (0.58-0.93)	0.86 (0.67-0.94)	0.74 (0.54-0.88)	0.77 (0.65-0.87)
Erosion	0.43 (0.10-0.79)	0.62 (0.27-0.86)	0.80 (0.56-0.92)	0.68 (0.42-0.85)	0.60 (0.44-0.78)
Fat metaplasia	0.84 (0.33-0.96)	0.81 (0.57-0.94)	0.65 (0.33-0.96)	0.59 (0.34-0.79)	0.65 (0.50-0.79)
Sclerosis	0.69 (0.25-0.90)	0.64 (0.32-0.87)	0.45 (0.00-0.74)	0.09 (-0.07-0.35)	0.62 (0.41-0.77)
Ankylosis	0.60 (0.09-0.86)	0.92 (0.80-0.97)	0.00(-0.41-0.43)	0.24 (-0.01-0.54)	0.64 (0.50-0.78)

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Abstract Number: 1726

Reliability of Radiographic Assessment of Psoriatic Arthritis Mutilans

Dennis Wong[1], Ker-Ai Lee[2], Richard J. Cook[3], Dafna Gladman[4], Lihi Eder[4] and Vinod Chandran[4], [1]University of Toronto, Toronto Western Hospital, Toronto, ON, Canada, [2]Department of Statistics and Actuarial Science, University of Waterloo, Waterloo, ON, Canada, [3]Statistics and Actuarial Science, University of Waterloo, Waterloo, ON, Canada, [4]Rheumatology, University of Toronto, Toronto Western Hospital, Toronto, ON, Canada
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Background/Purpose: Psoriatic arthritis mutilans (PsAM) is the most severe form of Psoriatic arthritis (PsA). Research on PsAM has been hampered by the lack of an accepted disease definition and a consensus on radiographic assessment. We recently performed a systematic review of the literature and conducted a survey of members of the Group for Research and Assessment of Psoriasis and PsA (GRAPPA) to identify radiographic features associated with PsAM. Based on the results of these studies, joint erosion of the entire articular surfaces on both sides of the joint, bone resorption leading to bone shortening, pencil-in-cup deformity, ankylosis, and subluxation were deemed to be PsAM manifestations. Thus, the aim of this study was to determine the reliability of assessing PsAM features on plain radiographs.

Methods: The radiographs of 35 PsA patients who have one of the five features in at least one joint of the hands or feet were retrieved and duplicated to generate 70 sets of images. Three rheumatologists, blinded to diagnosis, independently evaluated the radiographs for the five PsAM features in random order. A total of 42 joints, including wrists, all joints of the hand, all metatarsophalangeal joints and the interphalangeal joints of the first toes, were evaluated for each set of images. Inter- and Intra-observer reliability of the five features (joint erosion of the entire articular surfaces on both sides, bone resorption, pencil-in-cup change, ankylosis, and subluxation) in each joint were determined using the kappa statistic with standard errors calculated to accommodate an association between joints within patients.

Results: Moderate inter-rater agreement was observed for radiographic assessment of PsAM when the five PsAM features were considered as separate categories (kappa 0.63). The kappa improved to 0.83 when the PsAM features were grouped together as one category, indicating excellent inter-rater reliability in identifying severe joint damage. However, the specific agreement for each of the five PsAM features ranged from poor to moderate. Specifically, the assessment of joint erosion involving entire articular surfaces on both sides of the joint and bone resorption showed a kappa of 0.22 and 0.17, respectively whereas pencil-in-cup change, ankylosis and subluxation showed a kappa of 0.59, 0.76 and 0.52, respectively. Intra-rater reliability is excellent with an overall kappa ranging from 0.81 - 0.83. Based on these results, a revised evaluation protocol, where subluxation was removed and bone resorption and joint erosion were combined into one category as severe osteolysis, was applied to the analysis. The assessment of severe osteolysis showed an improved kappa of 0.54, and the kappa for overall inter-rater agreement in PsAM assessment increased to 0.72 with the revised protocol.

Conclusion: These results indicate that there is moderate agreement in radiographic assessment of severe joint damage associated with PsAM. However, the agreement for specific features such as severe joint erosion and bone resorption was poor. The new definitions of the PsAM features and the revised evaluation protocol showed promising result in improving the feature-specific and overall agreement in radiographic assessment of PsAM.

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MRI Vertebral Corner Inflammation Followed By Fat Deposition Is the Strongest Contributor to the Development of New Bone at the Same Vertebral Corner: A Multi-Level Longitudinal Analysis in Patients with Ankylosing Spondylitis

Pedro Machado[1], Xenofon Baraliakos[2], Désirée van der Heijde[3], Juergen Braun[2] and Robert Landewé[4], [1]Rheumatology, Leiden University Medical Center, Leiden, Netherlands, [2]Rheumazentrum Ruhrgebiet, Herne, Germany, [3]Dept. of Rheumatology, Leiden University Medical Center, Leiden, Netherlands, [4]Division of Clinical Immunology and Rheumatology, Academic Medical Center / University of Amsterdam, Amsterdam, Netherlands
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Background/Purpose: Syndesmophyte formation in ankylosing spondylitis (AS) is still insufficiently understood. Previous studies have suggested an association between MRI vertebral corner inflammation (VCI) and vertebral corner fat deposition (VCFD) and the subsequent development of radiographic syndesmophytes (SYN). Our aim was to investigate the relationship between MRI inflammation and fat deposition at a VE and the development of a SYN at the same VE.

Methods: A random 80% sample of the ASSERT database was used for this analysis. ASSERT was a 24-week (wk) RCT comparing infliximab monotherapy and placebo in patients with active AS, with an open extension until 102wks with all patients on infliximab. Spinal MRIs (T1-weighted and STIR images) at baseline, 24wks and 102wks were assessed by 2 readers independently who scored each VE for the presence or absence of VCI and VCFD. Spinal X-rays (baseline and 102wks) were scored by 2 different readers independently using the mSASSS. Data were analysed at the VE level in the 24 VEs assessed by the mSASSS (anterior VEs of the cervical and lumbar spine), using a multi-level approach to adjust for within-patient correlation and MRI reader (GEE for binomial outcomes). Particular emphasis was on a sequence analysis, which aimed at the specific sequence VCI→VCFD→SYN. The following variables were considered potential covariates and adjusted for when appropriate: treatment, gender, presence of SYN/ankylosis at baseline (patient level), HLA-B27, baseline- and time-averaged BASDAI/ASDAS/CRP, age, BMI and disease duration. Readers were unaware of the patient's identity, their treatment, the scores of the other imaging modality, and the true time-order of the images (fully unbiased scores).

Results: After excluding VEs with SYN or ankylosis at baseline and non-evaluable VEs, data from 3079 to 3363 MRI and X-ray paired case-definitions, belonging to up to 177 patients, were analysed. The presence of VCI (adjusted (ad)OR=1.98-1.93) as well as the presence of VCFD (adOR=1.59-2.32) at any time point (TP) was significantly associated with the development of a new SYN. The strength of the association increased by combining VCI and VCFD, both when analysing VEs with VCI and VCFD present across any of the three TP (simultaneously or not) (adOR=2.29-2.73) and also when analysing

only newly developed VCFD preceded by inflammation in the same VE at a previous TP (adOR=2.45-3.01) (sequence analysis, VCI→VCFD→SYN). The complete absence of both VCI and VCFD across the three TP was protective for the development of a new SYN (aOR= 0.45-0.62) (Table). However, a large proportion of SYN developed in VEs without MRI inflammation or fat degeneration at any of the three TP (42-66%, depending on the combination of MRI- and X-ray reader).

Conclusion: Both VCI and VCFD contribute to the development of a new SYN in AS, especially if VCI precedes VCFD. But this typical sequence only partially explains the development of new SYN in AS.

Table. Multivariable GEE results (adjOR; 95% CI) for the outcome SYN formation according to X-ray reader 1 (R1) or/and reader 2 (R1)					
Variables	**SYN formation according to R1 or R2**				
VCI at any TP	1.98 (1.49, 2.62)	-	-	-	-
VCFD at any TP	-	2.32 (1.85, 2.91)	-	-	-
New VCFD preceded by VCI	-	-	2.45 (1.66, 3.60)	-	-
Sequential or simultaneous presence of VCI and VCFD across the 3 TP	-	-	-	2.73 (2.00, 3.74)	-
Absence of VCI or VCFD across the 3 TP	-	-	-	-	0.45 (0.36, 0.56)
Treatment (infliximab)	1.03 (0.75, 1.41)	1.09 (0.80, 1.49)	1.02 (0.74, 1.40)	1.05 (0.77, 1.44)	1.04 (0.76, 1.44)
Gender (male)	3.30 (1.94, 5.60)	3.02 (1.79, 5.10)	3.39 (2.01, 5.74)	3.36 (1.98, 5.70)	3.00 (1.77, 5.08)
SYN/ankylosis at baseline	2.91 (2.00, 4.25)	2.82 (1.92, 4.13)	2.95 (2.02, 4.29)	2.89 (1.98, 4.21)	2.81 (1.91, 4.11)
Variables	**SYN formation according to R1 and R2**				
VCI at any TP	1.93 (1.22, 3.05)				
VCFD at any TP	-	1.60 (1.10, 2.33)			
New VCFD preceded by VCI	-	-	3.01 (1.76, 5.13)		
Sequential or simultaneous presence of VCI and VCFD across the 3 TP	-	-		2.29 (1.37, 3.83)	
Absence of VCI or VCFD across the 3 TP	-	-			0.62 (0.43, 0.89)
Treatment (infliximab)	1.29 (0.68, 2.44)	1.26 (0.66, 2.39)	1.28 (0.67, 2.43)	1.32 (0.70, 2.50)	1.30 (0.68, 2.49)
Gender (male)	2.50 (0.83, 7.51)	2.36 (0.80, 6.97)	2.48 (0.85, 7.26)	2.47 (0.83, 7.33)	2.29 (0.77, 6.77)
SYN/ankylosis at baseline	4.11 (1.56,	4.22 (1.58,	4.19 (1.60,	4.14 (1.58,	4.18 (1.56,

	10.8)	11.2)	11.0)	10.9)	11.2)

Disclosure: P. Machado, None; **X. Baraliakos**, None; **D. van der Heijde**, None; **J. Braun**, None; **R. Landewé**, None.

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Abstract Number: 1728

Diffusion Weighted Imaging Is a Sensitive and Specific MRI Protocol for the Diagnosis and Assessment of Disease Severity in Ankylosing Spondylitis

Linda A. Bradbury[1], Kelly A. Hollis[2], Benoit Gautier[2], Sateesh Shankaranarayana[3], Philip Robinson[4], Nivene Saad[3], Kim-Anh Lê Cao[2] and **Matthew A. Brown**[1], [1]The University of Queensland Diamantina Institute, Brisbane, Australia, [2]University of Queensland Diamantina Institute, Brisbane, Australia, [3]Princess Alexandra Hospital, Brisbane, Australia, [4]Human Genetics Group, University of Queensland Diamantina Insititute, Brisbane, Australia
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Background/Purpose: Diffusion weighted imaging (DWI) is an MRI protocol which assesses the random Brownian motion of water molecules in the tissue imaged; this motion is restricted in inflamed tissue. Previous studies have suggested that this approach may have diagnostic potential in AS. We sought to test the diagnostic capacity of DWI, and to assess its potential an objective measure of treatment response to TNF-inhibition, in AS.

Methods: Three cohorts were studied: 1. 18 AS patients with BASDAI>4 and ESR>25 and/or CRP>10 meeting the modified New York Criteria for AS; 2. 20 cases with non-radiographic axial SpA as defined by the ASAS criteria, and 3. 20 non-AS patients with chronic low back pain >3 months duration aged >18 years but <45 years. Group 1 patients were studied immediately prior to and following 14 weeks of treatment with adalimumab 40mg s/c fortnightly. All Group 2 patients met the imaging arm of the ASAS criteria and 13 also met the clinical criteria. Ten Group 3 patients met the ASAS clinical criteria, but none met the imaging criteria, and all were assessed as having non-inflammatory back disease clinically. Patients were assessed by DWI (right and left iliac ADC measures corrected for sacral background measure), BASDAI, BASFI, BASMI, ASDAS-CRP, CRP and ESR. Patients on corticosteroids were excluded, and NSAID and analgesic medications were kept stable during the follow-up study of Group 1 patients.

Results: At baseline BASDAI, BASFI, BASMI, ASDAS-CRP, CRP and ESR levels were increased in Group 1 patients, but similar between Group 2 and 3 patients (CRP levels were increased in Group 2 vs 3 patients). Post treatment Group 1 patients had lower BASDAI, BASFI, ASDAS-CRP, and similar BASMI, CRP and ESR levels, compared with either Group 2 or 3 patients. ROC curve analysis showed that none of these measures individually discriminated between Group 1 and 2 patients vs non-inflammatory controls (AUC values 51-74%). In contrast DWI ADC values showed good discriminatory performance (AUC 86%, $P<10^{-5}$, sensitivity 88%, specificity 81%). The AUC for G2 vs G3 was similarly high (90%, $P<10^{-5}$, sensitivity 90%, specificity 85%). DWI ADC scores correlated poorly with other disease activity measures (correlation coefficients -0.27 to +0.36, overall dataset). Comparing patients pre and post adalimumab treatment, BASDAI, BASFI, ASDAS-CRP, ASDAS-ESR, CRP and ESR had high discriminatory performance (AUC 99%, 81%, 99%, 97%, 95% and 88% respectively). DWI ADC values were significantly lower post adalimumab treatment (0.45±0.433 pre, 0.154±0.23 post, P=0.022), but had only modest discriminating capacity (AUC 64%).

Conclusion: DWI imaging is informative for diagnosis of AS and non-radiographic axial spondyloarthritis, but has only moderate utility in assessment of disease activity or treatment response.

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Abstract Number: 1729

Predictors and Clinical Factors Associated with Change in Spinal Inflammation Assessed on MRI over 2 Years: Data from Tasmanian Ankylosing Spondylitis Study

Hussain Ijaz Khan[1], Louisa Chou[2], Patricia Lewis[3], Anitra Wilson[3], Janet Millner[4] and Jane Zochling[3], [1]Musculoskeletal Unit, Menzies Institute of Medical Research, Hobart, Australia, [2]Menzies Institute of Medical Research, University of Tasmania, Hobart, 7000, Australia, [3]Menzies Institute of Medical Research, Hobart, Australia, [4]Physiotherapy, Royal Hobart Hospital, Hobart, Australia
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Background/Purpose:

Ankylosing Spondylitis (AS) is debilitating disease affecting the axial skeleton which is often difficult to diagnose in early stages. Magnetic Resonance Imaging (MRI) is a valuable tool in detecting early inflammatory lesions of the spine and monitoring treatment effects. The longitudinal relationship between changes in MRI inflammation and measures of clinical disease activity remains uncertain. The aim of this study was to describe the predictors of change in spinal inflammation and the association with change in clinical outcomes.

Methods:

129 participants [mean age (years) 41 (17-72); 64 % male] were studied at baseline and 2 years. MRI of the spine and sacroiliac (SI) joints were performed at the baseline and follow-up visits. Images were scored, using the Spondyloarthritis Research Consortium of Canada (SPARCC) 6–discovertebral unit (6-DVU) and SPARCC method for the SI joints. Radiographs were used to assess structural damage at the cervical/lumbar spine and SI joints. Disease activity was assessed using ESR measurements, Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and Bath AS disease activity index or by the AS disease activity score (ASDAS). Functional limitations and disability were assessed using the Bath Ankylosing Spondylitis Functional Index (BASFI) and the Health Assessment Questionnaire (HAQ) respectively.

Results:

Table 1 describes the characteristics of the participants split by the mean spinal MRI score at the baseline visit. A higher spinal MRI score was significantly associated with older age, male gender, higher BMI, higher BASMI, BASDAI and BASFI scores, and a more advanced disease at the SI joint.

Only higher mean BASDAI ($p=0.025$) and HAQ ($p=0.024$) scores significantly predicted an increase in spinal MRI scores over 2 years (data not shown).

Table 2 describes the association between change in spinal MRI score and change in clinical outcomes over 2 years. Increases in BASDAI, BASFI and ASDAS scores, but not BASMI, were independently associated with an increase in the severity of the spinal MRI scores.

Conclusion:

In summary, only high BASDAI and HAQ scores predicted an increase in MRI spinal inflammation over 2 years. Increase in MRI spinal inflammation in turn, was independently associated with worsening clinical outcomes such as BASDAI, BASFI and ASDAS. These results suggest that MRI spinal inflammation mirrors clinical outcomes over 2 years.

Table 1: Baseline characteristics of participants split by mean spine MRI score*			
	Mean total spine score <9.9 (n=69)	Mean total spine Score ≥ 9.9 (n=60)	P-Value
Age (years)	**37.1(13.7)**	**44.1(12.9)**	**0.006**
Males (%)	**52**	**80**	**0.001**
BMI	**25.4(3.2)**	**27.2(4.9)**	**0.033**
BASMI score (mean)	**2.1(1.5)**	**2.6(1.5)**	**0.034**
BASDAI score (mean)	**3.6(2.3)**	**4.5(2.3)**	**0.033**
BASFI score (mean)	**2.9(2.4)**	**3.3(2.7)**	**0.032**
HAQ score (mean)	5.6	5.8	0.838
Total SI joint MRI score (mean)	12.3(13.5)	18.9(20.6)	0.070
Total SI joint radiographic score (mean)	**3.0(2.6)**	**4.5(2.5)**	**0.001**
Total cervical spine radiographic score (mean)	3.6(6.5)	6.5(10.1)	0.104
Total lumbar spine radiographic score (mean)	3.0(7.7)	4.4(9.5)	0.402
*Mean (SD) except for percentages. P-values determined by t-test or x2 test (where appropriate)			

Table 2: Association between change in spine MRI score and change in clinical outcomes			
	Change in spine MRI score		
	Unadjusted β (95%CI)	Adjusted[a] β (95%CI)	Adjusted[b] β (95%CI)
Change in BASMI	**+0.99 (+0.06, +1.91)**	+1.02 (-0.01, +2.05)	+1.31 (-0.44, +3.08)
Change in BASDAI	**+0.59 (+0.26, +0.92)**	**+0.69 (+0.32, +1.06)**	**+0.89 (+0.31, +1.49)**
Change in BASFI	**+0.77 (+0.26, +1.28)**	**+0.73 (+0.16, +1.30)**	**+0.94 (+0.29, +1.71)**
Change in ASDAS^	**+1.21 (+0.07, +2.16)**	**+1.22 (+0.08, +2.10)**	**+1.54 (+0.22, +2.87)**
[a] adjusted for age, sex and bmi [b]adjusted for age, sex, bmi, duration of disease, ESR, NSAID treatment and anti-TNF treatment ^ASDAS score calculated using ESR			

Disclosure: H. I. Khan, None; **L. Chou**, None; **P. Lewis**, None; **A. Wilson**, None; **J. Millner**, None; **J. Zochling**, None.

Abstract Number: 1730

Good Control of Inflammation Counterbalances a Negative Impact of Radiographic Spinal Progression on Functional Status and Spinal Mobility in Patients with Ankylosing Spondylitis Treated with TNF Inhibitors

Denis Poddubnyy[1], Aleksandra Fedorova[1], Joachim Listing[2], Hildrun Haibel[1], Xenofon Baraliakos[3], Jürgen Braun[3] and Joachim Sieper[1], [1]Charité Universitätsmedizin Berlin, Berlin, Germany, [2]German Rheumatism Research Centre, Berlin, Germany, [3]Rheumazentrum Ruhrgebiet, Herne, Germany
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Background/Purpose:

Impaired function and spinal mobility in patients with ankylosing spondylitis (AS) can be caused by both spinal inflammation and new bone formation. Anti-TNF therapy has been shown to reduce inflammation but the influence on radiographic progression is less clear. The aim of the study was to investigate the impact of long-term (up to 10 years) anti-TNF therapy on function and spinal mobility in relation to radiographic progression in the spine in patients with AS.

Methods:

Altogether 60 patients with AS from two long-term trials with TNF blockers (43 on infliximab and 17 on etanercept) were included in this analysis based on availability of spinal x-rays performed at baseline and at least at one following time-point (year 2, 4, 6, 8, 10) during the follow-up. Spinal radiographs (cervical and lumbar spine lateral views) were scored according to the modified Stoke Ankylosing Spondylitis Spine Score (mSASSS) system by two readers (DP and AF) not blinded for the time point. The functional status was assessed by means of the Bath Ankylosing Spondylitis Functional Index (BASFI), spinal mobility – by the Bath Ankylosing Spondylitis Metrology Index (BASMI, 0-10), and clinical disease activity - by the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI).

Results:

Patients treated with infliximab and etanercept had similar baseline characteristics with regards of age, gender, HLA-B27 status, symptom duration, disease activity and baseline structural damage that allowed pooling of the data. After the BASFI, BASMI, and BASDAI had initially improved significantly in response to anti-TNF therapy these two outcome parameters remained remarkably stable at low levels over 10 years in those patients who remained on the drug over time despite the observed mean increase of the mSASSS by 6 points. The cumulative probability plots (figure) demonstrate no increase of BASFI and BASMI with increasing mSASSS. In the multivariate analysis, there was no association between mSASSS change and BASFI change, while there was some impact of the mSASSS change on BASMI change over time (table). BASDAI demonstrated a strong association with functional status and, to a lesser extent, with spinal mobility.

Conclusion:

Functional status in patients with advanced AS remained stable during long-term anti-TNF therapy despite radiographic progression. Under these conditions, the BASFI course correlated strongly with BASDAI but not with the mSASSS. This might indicate that a good control of inflammation is able to overweight the negative effect of structural damage in the spine on the functional status in AS.

Figure: Cumulative probability plots of BASFI (A) and BASMI (B) changes from baseline in relation to radiographic spinal progression over 10 years of follow up

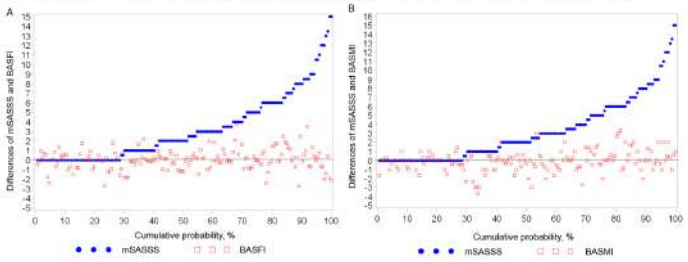

Table: Impact of radiographic spinal progression and disease activity on functional status and spinal mobility in AS under long-term anti-TNF treatment

	BASFI change from baseline (week 12)		BASMI change from baseline (week 12)	
	ß (95% CI)	p	ß (95% CI)	p
mSASSS change from baseline	0.0 (-0.04 to 0.03)	0.95	0.05 (0.01 to 0.09)	0.020
BASDAI	0.50 (0.39 to 0.61)	<0.001	0.11 (0.00 to 0.22)	0.055

ß – regression coefficients from the generalised linear mixed model analysis

Disclosure: D. Poddubnyy, AbbVie, MSD, Pfizer, UCB, 5; **A. Fedorova**, None; **J. Listing**, AbbVie, Celltrion, Hospira, MSD, Pfizer, UCB, 2,Pfizer, 5; **H. Haibel**, AbbVie, MSD, Pfizer, 5; **X. Baraliakos**, AbbVie, MSD, Pfizer, UCB, 5; **J. Braun**, AbbVie, MSD, Pfizer, UCB, 5,AbbVie, MSD, Pfizer, 2; **J. Sieper**, AbbVie, MSD, Pfizer, UCB, 5,AbbVie, MSD, Pfizer, 2.

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Abstract Number: 1731

Radiographic Damage of Facet Joints and Vertebral Bodies in the Cervical Spine in Patients with Ankylosing Spondylitis Treated with TNF Inhibitors

Fiona Maas[1], Suzanne Arends[1], Elisabeth Brouwer[1], Eveline van der Veer[2], Hendrika Bootsma[1], Rizwana Chaudhry[1], Monique Efde[3], Freke Wink[3] and Anneke Spoorenberg[1], [1]Rheumatology and Clinical Immunology, University Medical Center Groningen, University of Groningen, Groningen, Netherlands, [2]Laboratory Medicine, University Medical Center Groningen, University of Groningen, Groningen, Netherlands, [3]Rheumatology, Medical Center Leeuwarden, Leeuwarden, Netherlands

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Background/Purpose: In ankylosing spondylitis (AS), syndesmophyte formation and ankylosis of the vertebral bodies are characteristic radiographic changes that are evaluated during follow-up. However, the facet joints are also involved in the disease process. Our aim was to investigate the prevalence and incidence of radiographic facet joint involvement in comparison to damage of vertebral bodies in the cervical spine of AS patients treated with TNF-α inhibitors. Second, to explore the association of facet joint involvement with patient characteristics and clinical outcome.

Methods: Consecutive patients from the Groningen Leeuwarden AS (GLAS) cohort who started treatment with TNF-α inhibitors because of active disease were included. Available lateral radiographs of the cervical spine at baseline and after 4 years of follow-up were scored by two trained and independent readers blinded to patient characteristics and time sequence. Facet joints of C2-C3 up to C6-C7 were scored according to the method of de Vlam *et al.* (0: normal, 1: joint space narrowing or erosion, 2: partial blurring or ankylosis, 3: complete blurring or ankylosis). Definite damage and progression of facet joints was defined as the presence and development of partial/complete blurring or ankylosis (score ≥2) in ≥1 facet joint, respectively. The modified Stoke AS Spine Score (mSASSS) was used to assess radiographic damage of the vertebral bodies. Definite damage and progression was defined as the presence and development of ≥1 (bridging) syndesmophyte, respectively.

Results: Of 108 included patients, 76% were male, mean age was 43±11 years, median symptom duration 17 years (range 1-50), 84% were HLA-B27 positive, mean BASDAI was 5.9±1.7, and mean ASDAS 3.8±0.8.

At baseline, 28 (26%) patients had definite damage of facet joints with on average 3 facet joints involved. Fifty-nine (55%) patients had definite damage of vertebral bodies. Damage of facet joints exclusively occurred in 5 (5%) patients. Patients with damage of facet joints were more frequently male, older, had longer symptom duration, more frequently a history of psoriasis, larger occiput-to-wall distance, and higher mSASSS of the cervical spine (all $p<0.05$).

After 4 years of follow-up, 13 (12%) patients showed definite progression of facet joints and 28 (26%) showed definite progression of vertebral bodies. Progression of facet joints without progression of vertebral bodies was seen in 8 (7%) patients.

Conclusion: In this observational cohort of AS patients with active disease, 26% had radiographic damage of facet joints whereas 55% had damage of vertebral bodies. Damage of facet joints was associated with male gender and more advanced disease. During 4 years of TNF-α blocking therapy, 12% showed definite progression of facet joints. More than half of these patients did not show progression of vertebral bodies.

Disclosure: F. Maas, None; **S. Arends**, Pfizer Inc, 2,Abbvie, 2; **E. Brouwer**, Abbvie, 2,Pfizer Inc, 2; **E. van der Veer**, None; **H. Bootsma**, Roche Pharmaceuticals, 2,Bristol-Myers Squibb, 2; **R. Chaudhry**, None; **M. Efde**, None; **F. Wink**, Abbvie, 5; **A. Spoorenberg**, Abbvie, 2,Pfizer Inc, 2,Abbvie,

5,Pfizer Inc, 5,UCB, 5.

Abstract Number: 1732

Slow Spinal Radiographic Progression in Patients with Ankylosing Spondylitis Treated with TNF Inhibitors

Fiona Maas[1], Suzanne Arends[1], Ivette Essers[2], Elisabeth Brouwer[1], Eveline van der Veer[3], Freke Wink[4], Monique Efde[4], Hendrika Bootsma[1] and **Anneke Spoorenberg**[1], [1]Rheumatology and Clinical Immunology, University Medical Center Groningen, University of Groningen, Groningen, Netherlands, [2]Rheumatology, Maastricht University Medical Center, Maastricht, Netherlands, [3]Laboratory Medicine, University Medical Center Groningen, University of Groningen, Groningen, Netherlands, [4]Rheumatology, Medical Center Leeuwarden, Leeuwarden, Netherlands

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Background/Purpose: Assessing radiographic progression in ankylosing spondylitis (AS) is challenging. The results regarding the effect of tumor necrosis factor-alpha (TNF-α) blocking therapy on spinal radiographic progression are difficult to interpret due to methodological limitations. Our aim was to evaluate spinal radiographic progression over 2 to 8 years of follow-up in a large cohort of AS patients treated with TNF-α inhibitors.

Methods: Consecutive patients from the Groningen Leeuwarden AS (GLAS) cohort who started treatment with TNF-α inhibitors because of active disease were included. Available lateral cervical and lumbar radiographs at baseline and after at least one follow-up visit at 2, 4, 6, or 8 years were scored in chronological time order by two trained and independent readers using the modified Stoke AS Spine Score (mSASSS). Descriptive statistics for 0-2, 0-4, 0-6, 0-8 years and generalized estimating equations (GEE) for complete cases over 8 years were used to evaluate spinal radiographic progression.

Results: In total, 193 GLAS patients were included; 69% were male, mean age was 42 ± 11 years, median symptom duration was 15 years (range 1-53), 78% were HLA-B27 positive, and median baseline mSASSS was 2.5 (range 0-68).

The mean spinal radiographic progression ranged from 1.7 ± 2.8 over the first 2 years to 7.0 ± 5.3 over 8 years of follow-up (Table 1). GEE analysis of complete cases over 8 years (n=19) revealed that the logarithmic time model had the best fit for the data. This model showed a deflection in mSASSS over time; the estimated progression rate was 2.3, 1.4, 1.0 and 0.8 during 0-2, 2-4, 4-6, and 6-8 years, respectively.

Conclusion: This observational study showed overall slow spinal radiographic progression in AS patients treated with TNF-α inhibitors. In a limited number of patients, complete case analysis indicated a deflection in spinal radiographic progression during 8 years of follow-up.

Table 1. Spinal radiographic progression in AS patients who started treatment with TNF-α inhibitors.

	N	Mean ± SD	Median (range)
All included patients			
Baseline mSASSS	193	9.9 ± 15.5	2.5 (0.0-67.8)
mSASSS progression 0-2yr	168	1.7 ± 2.8	0.0 (0.0-15.0)
mSASSS progression 0-4yr	135	3.4 ± 4.6	1.7 (0.0-19.8)
mSASSS progression 0-6 yr	83	4.4 ± 5.1	2.5 (0.0-22.8)
mSASSS progression 0-8yr	41	7.0 ± 6.3	6.2 (0.0-22.0)
Complete cases over 8 years			
Baseline mSASSS	19	10.0 ± 12.9	5.4 (0.0-47.5)
mSASSS progression 0-2yr	19	2.2 ± 2.7	1.0 (0.0-7.0)
mSASSS progression 2-4yr	19	1.6 ± 2.1	0.5 (0.0-7.0)
mSASSS progression 4-6yr	19	0.9 ± 1.3	0.0 (0.0-4.7)
mSASSS progression 6-8yr	19	0.9 ± 1.4	0.0 (0.0-4.7)

Abbvie, 5; **M. Efde**, None; **H. Bootsma**, Roche Pharmaceuticals, 2,Bristol-Myers Squibb, 2; **A. Spoorenberg**, Abbvie, 2,Pfizer Inc, 2,Abbvie, 5,Pfizer Inc, 5,UCB, 5.

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Abstract Number: 1733

A Close Correlation Between Radiologic Progression Severity and Trabecular Bone Loss in Male Patients with Ankylosing Spondylitis

Ki-Jo Kim[1,2], In-Woon Baek[3], Chong-Hyeun Yoon[4,5], Wan-Uk Kim[6] and Chul-Soo Cho[3], [1]Internal Medicine, St. Vincent's Hospital, The Catholic University of Korea, Suwon, South Korea, [2]St. Mary's Hospital, Seoul, South Korea, [3]Internal Medicine, Yeouido St. Mary's Hospital, The Catholic University of Korea, Seoul, South Korea, [4]Division of Rheumatology, Department of Internal Medicine, College of Medicine, The Catholic University of Korea, Seoul, South Korea, [5]Internal Medicine, Uijeongbu St. Mary's Hospital, The Catholic University of Korea, Uijeongbu, South Korea, [6]Internal Medicine, Seoul St. Mary's Hospital, The Catholic University of Korea, Seoul, South Korea
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Background/Purpose: Ankylosing spondylitis (AS) is a chronic, progressive disease characterized by inflammation of entheses. Inflammation is associated with cortical new bone formation leading to progressive ankylosis of the spine and sacroiliac joints but also with trabecular bone loss leading to osteoporosis. The aim of this study is to investigate the association of spinal radiologic progression with bone mineral density in male AS patients.

Methods: Clinical and radiographic data were collected in 116 male AS patients. Spinal radiographs were scored using the modified Stoke AS Spinal Score (mSASSS) and spinal bone mineral density (BMD) of anteroposterior (AP) and lateral (Lat) views was measured by dual-energy x-ray absorptiometry (DEXA).

Results: Seventy three (62.9%) patients had syndesmophyte(s) at their lumbar spine (L-spine) and 45 patients (38.8%) were treated by tumor necrosis factor (TNF) inhibitors. mSASSS and BMD were significantly higher in patients with syndesmophyte(s) (All $P < 0.05$). For the 2nd and 3rd lumbar vertebra, BMD of AP view was significantly higher in vertebrae with syndesmophyte(s) ($P = 0.001$) while BMD of Lat view was decreased and did not differ between those with and without syndesmophyte(s). Moreover, L-spine mSASSS was positively correlated with BMD of AP view ($\gamma = 0.239$, $P = 0.010$) while negatively correlated with BMD of Lat view ($\gamma = -0.209$, $P = 0.025$). These correlations were significant when adjusted for age, HLA-B27, smoking, treatment drugs (NSAIDs, TNF inhibitors, statins and bisphosphonate), body mass index and C-reactive protein.

Conclusion: Trabecular BMD was decreased and correlated with severity of radiologic progression in L-spine of male AS patients, suggesting a parallel progression between cortical bone formation and trabecular bone loss.

Disclosure: K. J. Kim, None; **I. W. Baek**, None; **C. H. Yoon**, None; **W. U. Kim**, None; **C. S. Cho**, None.

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Abstract Number: 1734

Computer Aided Syndesmophyte Measurement on Spinal Radiographs in Axial Spondyloarthritis Patients

F. de Bruin[1], Rosaline van den Berg[1], M. Reijnierse[2], D. van der Heijde[3,4] and B.C. Stoel[2], [1]Leiden University Medical Center, Leiden, Netherlands, [2]Radiology, Leiden University Medical Center, Leiden, Netherlands, [3]Department of Rheumatology, Leiden University Medical Center, Leiden, Netherlands, [4]Rheumatology, Diakonhjemmet Hospital, Oslo, Norway
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Background/Purpose:

Quantifying syndesmophyte (Synd) length and angle in axial spondyloarthritis (axSpA) patients (pts) can be a helpful tool in monitoring disease progression. Objective was to evaluate in-house-developed software that aids in quantifying Synds length and angle on radiographs, to test its inter and intrareader reliability and to assess progression over time.

Methods:

The cervical and lumbar spine radiographs at baseline and follow up (24 months) of 18 axSpA pts were analysed twice using the software tool, by two independent readers, blinded for time sequence and the results of the other reader. The software establishes the vertebral body (VB) contours based on signal contrast and anatomical landmarks (figure 1). The length and angle of Synds is based on the distance between the maximum extending point and the 'native' VB corner (figure 2). Length was measured in mm and sum scores were calculated per pt by adding up all Synds. Pts were also analysed using the mSASSS. Inter- and intrareader reliability were analysed using Bland Altman (B&A) plots. Reliability of progression was evaluated using smallest detectable change (SDC) analysis.

Results:

In total, each reader analysed 1728 vertebral corners (VC) of 72 images. B&A plots for intra and interreader variability showed a large variability in length of Synds in both the individual VCs and for the total sum of the patients (figure 3). When analysing change score over time within one patient, SDC showed that almost all progression fell within the SDC (SDC= 12.9 and 20.4 mm) (for reading 1: 11/18 patients (61%) and reading 2: 15/18 (83%)), while those patients did show 'real progression' as measured with the mSASSS.

Conclusion:

Computer aided measurement of Synds on radiographs was not feasible. The restrictions associated with radiographs (overprojection, patient position dependent variability) and the size of the lesions of interest were not compatible. Overall, semi-automatic detection did not have added value to existing manual tools.

Figure 1

Figure 2

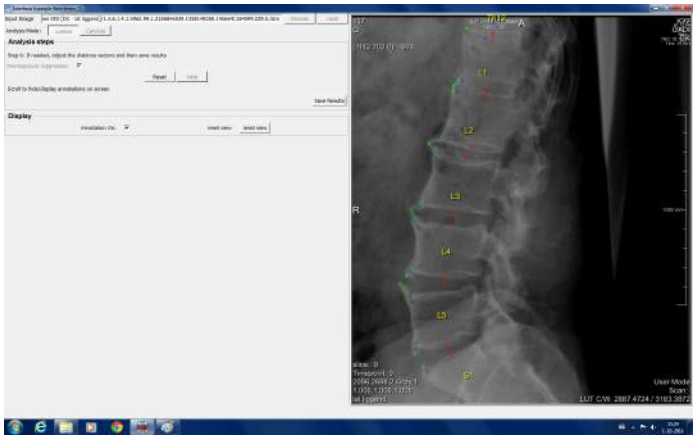

Figure 3

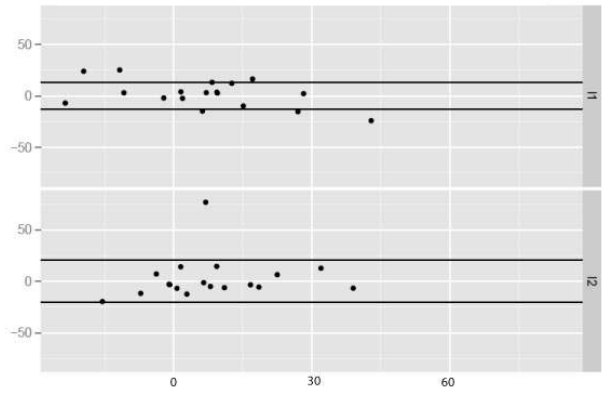

Figure 1.
I1 = Reading 1, I2 = Reading 2. Length in mm.
X-axis: Mean progression of Observer 1 and Observer 2.
Y-axis: Difference between the progression of Observer 1 and Observer 2.
Black horizontal lines indicate the Smallest Detectable Change, in I1 SDC = 12.9 and in I2 SDC = 20.4

Disclosure: F. de Bruin, None; **R. van den Berg**, None; **M. Reijnierse**, None; **D. van der Heijde**, None; **B. C. Stoel**, None.

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Abstract Number: 1735

Imaging and Clinical Factors Associated with Subchondral Sacroiliac Fatty Marrow in Axial Spondyloarthritis

Kavi Devulapalli[1], Xenofon Baraliakos[2], Daria Motamedi[1] and Lianne S. Gensler[3], [1]Radiology, UCSF, SAN FRANCISCO, CA, [2]Rheumazentrum Ruhrgebiet, Herne, Germany, [3]Medicine/Rheumatology, University of California, San Francisco, San Francisco, CA
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Background/Purpose:

Magnetic resonance imaging (MR) plays an important role in the evaluation of inflammatory and structural changes in axial spondyloarthritis (axSpA) patients. Prior research suggests subchondral fatty marrow is an imaging precursor to ankylosis. The ability to predict new bone formation in patients with axSpA may have treatment implications. The goal of the current study is to evaluate imaging and clinical factors associated with subchondral sacroiliac joint (SIJ) fatty marrow.

Methods:

A retrospective analysis of 91 AxSpA patients who underwent a lumbar spine or pelvis MR with axial and coronal T1 in addition to fluid sensitive sequences was performed. Images were reviewed by a radiologist and evaluated for findings of both active and structural disease in addition to disease distribution. Bone marrow edema was quantified using the Spondyloarthritis Research Consortium of Canada (SPARCC) quadrant based approach method. Clinical variables including gender, age, race, disease duration and classification, current or prior Tumor Necrosis Factor alpha inhibitor (TNFi) therapy, HLA-B27 status, history of uveitis, inflammatory bowel disease and psoriasis were collected. Univariable analyses with c2 and Student's t-Test were performed on dichotomous and continuous variables. Multivariable logistic regression was performed after adjusting for gender and disease duration.

Results:

Of the 91 patients, 76 (83.5%) demonstrated sacroiliac (SI) joint abnormalities on MR with 90.8% of these demonstrating bilateral and 56.6% demonstrating symmetric changes. Distribution of abnormalities included bone marrow edema in 56.7% with a SPARCC score of 7.30 ± 11.53, erosions in 44.7%, fatty marrow in 52.3% and ankylosis in 19.7% of patients. Covariates independently associated with fatty marrow change included disease duration ≥10 years (OR 3.5, 95% CI [1.05-11.9], p=0.04), psoriasis (OR 29.1, 95% CI [1.34-633.5], p=0.032) and symmetric sacroiliitis (OR 4.36, 95% CI [1.30-14.59], p=0.02). There was no association with TNFi therapy (Table 1).

Conclusion:

Our data demonstrates fatty marrow replacement is associated with longer disease duration (≥10 years) and the presence of psoriasis in addition to the imaging finding of symmetric disease distribution. Additional studies are warranted to explore the role of psoriasis in the development of chronic sacroiliitis and ankylosis.

Table 1. Multivariable analysis after adjustment for gender and disease duration

	Odds Ratio	95% Confidence Interval	p-value
Gender	2.24	0.64 - 7.79	0.20
Disease Duration (≥10 years)	**3.54**	**1.05 - 11.87**	**0.04**
Psoriasis	**29.1**	**1.34 - 633.52**	**0.03**
Erosions	0.38	0.12 - 1.23	0.11
Symmetric disease distribution	**4.36**	**1.30 - 14.59**	**0.02**
Bilateral disease distribution	4.25	0.31 - 58.25	0.28

Disclosure: K. Devulapalli, None; **X. Baraliakos**, None; **D. Motamedi**, None; **L. S. Gensler**, None.

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Abstract Number: 1736

Is There Evidence to Support Replacing Conventional AP Pelvis Radiographs with Dedicated Sacroiliac Joint Views for the Diagnosis of Sacroiliitis?

Ahmed Omar[1], Ismail Sari[1], Mohamed Bedaiwi[1], Nigil Haroon[1] and Robert D Inman[2], [1]Rheumatology, Toronto Western Hospital, University of Toronto, Toronto, ON, Canada, [2]Immunlogy and Institute of Medical Science, Toronto Western Hospital, University of Toronto, Toronto, ON, Canada
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Background/Purpose: Despite the development of advanced imaging modalities such as MRI and CT, conventional radiography remains the cornerstone for the diagnosis and classification of Ankylosing Spondylitis (AS). Ease of access and cost may be contributory continued use of X-rays. The AP pelvis radiograph has long been the established standard for the screening and grading of sacroiliitis, despite its well-documented poor reproducibility. There is a lack of recent research that compares the standard AP pelvis (APPx) view with dedicated sacroiliac views. To the best of our knowledge, no previous studies compared AP pelvis vs the angled frontal “Ferguson” view (SIJx), a modality that has been advocated anecdotally by many clinicians. Our aim was to compare the APPx view with the dedicated SIJx view in order to clarify if one modality has a clear advantage for diagnosis and grading of sacroiliitis.

Methods: 103 patients who had simultaneous APPX and SIJx modalities on the same date with an established diagnosis of Axial spondyloarthritis (SpA), either through the modified NY criteria or through the 2009 ASAS criteria were randomly selected from the axial SpA registry. One independent coordinator randomized the sequence of these patients and prepared the x rays to be read on two separate computer terminals with all patient identifiers removed. Two rheumatologist independently reviewed both the SIJx and the APPx and scored the graphs according the modified NY criteria. Intra-reader and inter-reader agreements were obtained for both the APPx and SIJx evaluations by using the Cohen-weighted kappa statistic and the intraclass correlation coefficient (ICC). Mean SIJ scores were also calculated.

Results: A total of 206 radiographs were read (103 for each modality). Intra-observer reliability of the observers showed similar agreements with regards to right and left SIJ evaluation (Table 1) which was also reflected in the kappa for diagnosis of AS (fulfilling NY criteria) between the observers. The inter-rater agreement showed similar values between the imaging modalities. This agreement was also replicated when separately evaluating SIJ’s with score grading of 0 to 2. The SIJ dedicated view did not significantly influence the diagnosis and there was no statistically significant change for the overall population as outlined on Table 1. The average SIJ scores obtained from each observer showed similar values for both modalities.

Conclusion: There was agreement between dedicated SIJ and the AP pelvis x-ray reads. Either modality can be employed to evaluate the sacroiliac joints for sacroiliitis with the dedicated SIJ imaging showing no clear superiority over the standard AP Pelvis view.

Table 1: Comparison of agreement between the two methods of SIJ scoring				
Intra-observer reliability			**Observer 1**	
Observer 2				
Right SIJ		0.46 (0.29-0.59)	0.64 (0.5-0.74)	
Left SIJ		0.69 (0.58-0.78)	0.64 (0.51-0.74)	
Diagnostic*		0.53	0.48	
Inter-observer reliability				
	SIJ view		**Pelvis view**	
Right SIJ	0.72 (0.6-0.8)		0.58 (0.44-0.7)	
Left SIJ	0.66 (0.54-0.76)		0.68 (0.56-0.72)	
Diagnostic*	0.49		0.31	
Right SIJ 012*	0.32		0.42	
Left SIJ 012*	0.41		0.53	
Diagnostic change from baseline AP pelvis vs SIJ view				
	Observer1		**Observer2**	
Non radigraphic axial SpA (nrSpA) to AS (%)	5.8		9.9	
AS to nrSpA (%)	4.9		10.7	
Mean SIJ Grade (from grade 1 to 4)				
	SIJ View		**AP Pelvis**	
	Right	Left	Right	Left
Observer 1	2.6±0.91	2.8±0.77	2.7±0.85	2.8±0.78
Observer 2	2.2±1.1	2.4±0.94	2.3±1.1	2.3±1.1
Reproducibility of the methods and reliability of observers were evaluated by means of the single measures intraclass correlation coefficient (ICC) values and *kappa statistics where appropriate. Continous data is presented with mean±SD				

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Abstract Number: 1737

Increased Osteoclast Precursors with an Elevated DC-STAMP Expression May Identify Psoriasis Patients at Risk for Psoriatic Arthritis

Yahui Grace Chiu[1], Sutha Shanmugarajah[2], Dongge Li[3], Megan Freiburger[4], Sharon Moorehead[5], Dafna Gladman[6] and Christopher T. Ritchlin[7], [1]Allergy, Immunology, and Rheumatology, University of Rochester, Rochester, NY, [2]Toronto Western Hospital, Toronto, ON, Canada, [3]Allergy, Immunology and Rheumatology, University of Rochester, Rochester, NY, [4]Biology, University of Rochester, Rochester, NY, [5]Allergy, Immunology & Rheumatology, University of Rochester, Rochester, NY, [6]Allergy, Immunology & Rheumatology, Toronto Western Hospital, Toronto, ON, Canada, [7]Allergy, Immunology and Rheumatololgy Division, University of Rochester Medical Center, Rochester, NY

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Background/Purpose:

Approximately 25% of psoriasis (Ps) patients develop into psoriatic arthritis (PsA) within 10 years. This Ps-to-PsA transition paradigm provides a unique opportunity to recognize preclinical symptoms to prevent further joint destruction by early intervention. Early identification of Ps patients prone to develop PsA, however, has been challenging due to diverse Ps clinical features, limited understanding of the molecular events, and the absence of reliable biomarkers. To fill up these gaps, we focused our studies on DC-STAMP (Dendritic Cell-Specific Transmembrane Protein), a 7-pass transmembrane protein essential for osteoclast (OC) differentiation. We previously demonstrated an elevated frequency of DC-STAMP+ osteoclast precursors (OCP) in PsA patients, suggesting DC-STAMP may serve as a surrogate to monitor DC-STAMP+ OCPs in human blood. To further validate DC-STAMP as a potential biomarker in psoriatic disease diagnosis, herein, we evaluated the circulating OCP frequency, DC-STAMP+ cell frequency, DC-STAMP expression level in healthy control (HC), Ps, and PsA patients.

Methods:

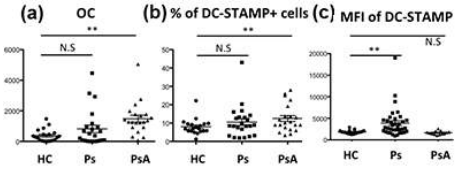
21 PsA, 36 Ps and 20 HC were recruited for this study from the International Psoriatic Arthritis Research Team (IPART) registry. We set up a standard operating procedure (SOP) by collecting blood from 20 HC one week apart. DAS28/DAS44, ESR, CRP, PASI score and disease duration years were collected. The numbers of OCP were assessed by in vitro culture, and the frequency of circulating DC-STAMP+ cells and DC-STAMP expression level (by

mean fluorescence intensity (MFI)) were determined by flow cytometry analysis.

Results:

The disease duration years & PASI score for Ps and PsA were 24.1 ± 14.6 vs. 15.2 ± 7.8 and 6.5 ± 8.2 vs. 4,6 ± 2.4, respectively. The reliability and reproducibility of our SOP for cell isolation, staining, and flow analysis were confirmed by HC blood that were collected one week apart from the same subject. The results of DC-STAMP+ cell frequency and DC-STAMP expression level were summarized by 3 dot-plots shown below.

**: significant; N.S.: not significant; y-axis: cell events or frequency.



Conclusion:

The frequency of OCP (dotplot (a)) and DC-STAMP+ cells (dotplot (b)) were significantly higher in PsA patients than HC. In contrast, the expression level of DC-STAMP as represented by the MFI was significantly higher in Ps than HC (dotplot (c)). These data collectively suggested that the frequency of OCP & DC-STAMP+ cells are good biomarkers of PsA, whereas the DC-STAMP expression level serves better as the Ps biomarker. Our studies also established the ranges of OCP, DC-STAMP+ cell frequency, and DC-STAMP expression level for the cohorts of HC, Ps and PsA. Intriguingly, a subset of Ps patients showed an elevated frequency of DC-STAMP+ cells and an increased DC-STAMP expression level (outliers in dotplots (b) & (c) for Ps). These Ps patients will be followed longitudinally to determine if these markers can predict future PsA onset.

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Abstract Number: 1738

Assessing the Validity of the Multi-Biomarker Disease Activity Assay in Patients with Psoriatic Arthritis

Tristan Boyd[1], Doquyen H. Huynh[1], P. Scott Eastman[2], Ferhan Qureshi[3], Eric H. Sasso[4], Rebecca J. Bolce[4], Joshua Hillman[5], David L. Boyle[6] and Arthur Kavanaugh[7], [1]Rheumatology, University of California San Diego, La Jolla, CA, [2]Crescendo Bioscience, South San Francisco, CA, [3]Crescendo Bioscience, Inc., South San Francisco, CA, [4]Crescendo Bioscience Inc., South San Francisco, CA, [5]Div of Rheum, UCSD School of Medicine, La Jolla, CA, [6]Division of Rheumatology, Allergy and Immunology, University of California, San Diego, La Jolla, CA, [7]University of California, San Diego School of Medicine, LaJolla, CA

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Background/Purpose:

Considerable heterogeneity across clinical domains of psoriatic arthritis (PsA) can make assessment of disease activity challenging. As a result, there has been interest in developing biomarkers to assess disease activity. In rheumatoid arthritis (RA), a multi-biomarker disease activity (MBDA) assay, a weighted composite of 12 serum protein biomarkers, has been shown to correlate with disease activity.[1] Our objective was to investigate if the MBDA score and its biomarker panel correlated with disease activity across different domains of PsA.

Methods:

A cross-sectional sample of 30 adult patients with PsA fulfilling the CASPAR criteria[2] was recruited from UCSD Arthritis Clinics. Clinical data and serum samples were collected and serum was analyzed for MBDA score and its individual components[3], as well as intracellular adhesion molecule 1 (ICAM-1), interleukin 6 receptor (IL-6R), and macrophage-derived cytokine (MDC).

Results:

The table shows patient characteristics:

Table. Patient Characteristics (N=30)

Gender (male), N (%)	15 (50.0)
Age (years), mean ± SE	49.5 ± 11.2
Psoriatic arthritis duration (years), mean ± SE	7.9 ± 8.9
Psoriasis duration (years), mean ± SE	14.7 ± 13.6
Skin psoriasis, N (%)	23 (76.7)
Skin BSA (%), mean ± SE	9.0 ± 23.0
Enthesitis, N (%)	8 (26.7)
Dactylitis, N (%)	2 (6.7)
Nail psoriasis, N (%)	15 (50.0)
Tender joint count 28 joints, mean ± SE	2.9 ± 4.4
Swollen joint count 28 joints, mean ± SE	2.7 ± 3.4
Physician global (VAS 0-10 cm), mean ± SE	3.3 ± 2.8
Patient global (VAS 0-10 cm), mean ± SE	4.4 ± 3.3
HAQ score, mean ± SE	0.7 ± 0.7
CDAI, mean ± SE	13.2 ± 11.5
DAS28, mean ± SE	2.68 ± 1.75
DAS28-CRP, mean ± SE	2.61 ± 1.25
Current biologics, N (%)	15 (50.0)
Current DMARDs, N (%)	14 (46.7)
Current NSAIDs, N (%)	12 (40.0)
Current topical therapy, N (%)	10 (33.3)

Abbreviations: BSA, body surface area; VAS, visual analogue scale; HAQ, health assessment questionnaire; CDAI, clinical disease activity index; DAS, disease activity score; DMARDs, disease modifying antirheumatic drugs; NSAIDs, nonsteroidal anti-inflammatory drugs.

The average MBDA score was 39.6, which would be consistent with a moderate disease activity score in RA patients.[1] In our PsA cohort, the MBDA score was most strongly correlated with physician global assessment (Pearson correlation coefficient, r=0.57), DAS28 (r=0.53), and skin BSA (r=0.50). Correlations were poorer with CDAI (r=0.35), SJC28 (r=0.35), patient global assessment (r=-0.08), HAQ score (r=0.15), and pain score (r=0.12). Analysis of individual biomarkers showed strong correlations, in many cases stronger than the composite MBDA score: e.g., serum amyloid A (SAA), tumor necrosis factor receptor superfamily member 1A (TNF-RI), MDC, and leptin with skin BSA (r=0.85, 0.84, 0.75, 0.72, respectively); leptin and ICAM-1 with DAS28 score (r=0.62 and 0.52); and SAA and vascular cell adhesion molecule 1 (VCAM-1) with physician global assessment (r=0.67 and 0.61).

Conclusion:

These data suggest the MBDA score can correlate with facets of disease activity in PsA. However, individual biomarkers were frequently found to correlate, often more strongly, with different domains of disease activity raising the possibility that specific composite scores could be created for each PsA domain. Whether these serum biomarkers are modulated by therapy and associated with clinical response warrants further study.

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1. Curtis JR, et al. *Arthritis Care Res* 2012; 64: 1794-1803

2. Taylor W, et al. *Arthritis Rheum* 2006; 54: 2665-2673

3. Eastman PS, et al. *J Pharm Biomed Anal* 2012; 70: 415-24

Disclosure: T. Boyd, None; **D. H. Huynh**, None; **P. S. Eastman**, Crescendo Bioscience, 3; **F. Qureshi**, Crescendo Bioscience, 3; **E. H. Sasso**, Crescendo Bioscience, 3; **R. J. Bolce**, Crescendo Bioscience, 3; **J. Hillman**, None; **D. L. Boyle**, None; **A. Kavanaugh**, None.

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Abstract Number: 1739

The Ratio of Glycated Hemoglobin A1c (HbA1c) to Glycated Albumin (GA) Is Correlated with Ankylosing Spondylitis Disease Activity Score (ASDAS) in Non-Diabetic Patients with Ankylosing Spondylitis

Se-Jin Byun[1], Jason Jungsik Song[2], Yong-Beom Park[1], Soo-Kon Lee[1] and Sang-Won Lee[1], [1]Department of Internal Medicine, Yonsei University College of Medicine, Seoul, South Korea, [2]Division of Rheumatology, Department of Internal Medicine, Yonsei University College of Medicine, Seoul, South Korea
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Background/Purpose: With the growing awareness of disease course of ankylosing spondylitis (AS) and recent development of novel treatments which might be the most effective for early stage of disease, there is an unmet need for markers that can assess disease activity more simply in those individuals at the highest risk for a bad outcome. Bath ankylosing spondylitis disease activity index (BASDAI) has been the most widely used clinical disease activity

measure in AS. However, the BASDAI has no consideration for laboratory inflammatory markers. Furthermore, an elevated ESR or CRP is present in only about 40-50% of patients with active AS. Glycated albumin (GA) was initially viewed as an adjunct to glycated hemoglobin (HbA1c), but it has recently been reported that chronic inflammation is positively correlated with HbA1c level, whereas it is negatively associated with GA. We evaluated the availability of the ratio of HbA1c and GA as an adjunctive marker to the Ankylosing Spondylitis Disease Activity Score (ASDAS) already proposed.

Methods: A total of 58 non-diabetic AS patients who met the modified New York classification criteria were included. ESR, CRP, ASDAS-ESR, ASDAS-CRP, BASDAI, and patient's global assessment (BASG) were assessed.

Results: The median [interquartile range, IQR] HbA1c/GA ratio was 0.42 [0.40, 0.44]. The medians [IQR] of A1C, GA. ESR, CRP, ASDAS-ESR, and ASDAS-CRP level were respectively 5.5 [5.3, 5.6] %, 13.1 [12.4, 13.8] %, 17.5 [6.0, 32.5] mm/hr, 1.5 [0.7, 6.4] mg/l, 2.44 [1.38, 3.03], and 1.92 [1.22, 2.59] in the patients with AS. HbA1c significantly correlated with ASDAS-ESR, ASDAS-CRP, BASDAI and BASG ($r = 0.328$, $p < 0.05$; $r = 0.356$, $p < 0.05$; $r = 0.326$, $p < 0.05$; $r = 0.440$, $p < 0.01$, respectively). GA showed a weak negative association with ESR, CRP and ASDAS score, but there was no significant difference statistically. There were significant correlations between the ratio of HbA1c/GA and disease activity based on ASDAS in AS patients (for ASDAS-ESR, $r = 0.367$, $p < 0.05$; for ASDAS-CRP, $r = 0.462$, $p < 0.01$; for ESR, $r = 0.417$, $p < 0.01$; for CRP, $r = 0.356$, $p < 0.05$).

Conclusion: In patients with AS, HbA1c/GA ratio correlate with disease activity, and consequently combination of these parameters may serve as a better marker of disease severity.

Table Correlation between HbA1c/GA ratio, HbA1c, GA. ESR, CRP, ASDAS-ESR, and ASDAS-CRP in 58 patients with AS

	ESR	CRP	ASDAS-ESR	ASDAS-CRP	BASDAI	BASG
HbA1c/GA	**0.417***	0.356#	0.367#	**0.462***	0.293	0.162
HbA1c	0.257	0.249	0.328#	0.356#	0.326#	**0.440***
GA	-0.281	-0.233	-0.219	-0.105	-0.084	0.073
ESR			**0.624***	**0.423***	0.222	0.089
CRP	**0.421***		0.342#	**0.597***	0.102	0.030

HbA1c, glycated hemoglobin A1c; GA, glycated albumin; ASDAS, Ankylosing Spondylitis Disease Activity Score; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASG, Bath Ankylosing Spondylitis Patient Global Score

r is determined by Spearman's rank correlation test

Bold characters indicate a statistically significant difference with a *p*-value < 0.05, *and r values* ≥ 0.4

Statistical significance $p < 0.05$

* Statistical significance $p < 0.01$

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Abstract Number: 1740

Anti-Cyclic Citrullinated Peptide Antibodies and Inflammatory Bowel Disease

Jaita Mukherjee[1], Maria Mouyis[1], Kavina Shah[1], Mohammad Mahdi Saeidinejad[1], Ayesha Akbar[2] and Shahir Hamdulay[1], [1]Rheumatology, Northwick Park Hospital, Middlesex, United Kingdom, [2]Gastroenterology, Northwick Park Hospital, Middlesex, United Kingdom
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Background/Purpose:

Enteropathic arthropathy refers to the pattern of inflammatory arthritis seen in association with gastrointestinal pathology. Arthritis in the presence of inflammatory bowel disease can occur in patients with Ulcerative Colitis and Crohn's disease. Typically, patients may present with an asymmetrical pauciarticular pattern of joint disease in conjunction with flares of bowel disease. Anti-cyclic citrullinated (Anti-CCP) antibodies are highly specific in patients with rheumatoid arthritis and its presence is often used as a diagnostic marker, but an association with inflammatory bowel disease remains unclear. We explore the prevalence of Anti-CCP and rheumatoid factor (RF) antibodies in patients with enteropathic arthritis.

Methods:

A retrospective analysis was performed using data collected from consecutive patients with enteropathic arthritis attending general rheumatology clinic.

Baseline demographic data, history and duration of bowel disease, treatment, pattern of inflammatory arthritis, and Anti-CCP and RF titres were recorded. Anti-CCP antibodies were detected using a commercially available fluorescence enzyme immunoassay (Phadia). The same data set were also recorded for consecutive patients with inflammatory bowel disease in the absence of arthritis.

Results:

Full demographic data and characteristics were obtained from 31 patients with enteropathic arthritis and 30 patients without arthritis. In the study population 55% had a diagnosis of Crohn's disease (n=17) and 45% had Ulcerative Colitis (n=14). 26% patients had axial involvement only, 48% presented with peripheral joint disease only (n=15), 26% had evidence of both peripheral and axial disease. Of the patients with peripheral joint involvement, 22% patients were found to be positive for Anti-CCP antibodies (n=5) with small joint involvement and no evidence of erosive disease on radiological assessment. Table 1 demonstrates demographic data in patients with enteropathic arthritis.

The prevalence of Anti-CCP and rheumatoid factor antibodies in the control group was 0.

	Peripheral (n=15)	Axial (n=8)	Peripheral and Axial (n=8)
Mean Age (years)	47.6	40.125	43.75
Range (years)	30-70	27-54	27-71
Male:Female	7:8	7:1	3:5
Ulcerative Colitis	10	5	2
Crohn's Disease	5	3	6
Anti-CCP positive	5	0	0
Rheumatoid Factor positive	3	0	1

Conclusion:

Our results suggest that Anti-CCP antibodies may also be present in patients with enteropathic arthritis who have a small joint peripheral arthritis in the absence of axial disease. These patients may initially be incorrectly diagnosed with rheumatoid arthritis, rather than articular manifestations of their underlying bowel disease, as the pattern of joint involvement is similar. Further investigation with larger numbers is required to explore the association between inflammatory bowel disease and Anti-CCP antibodies.

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Abstract Number: 1741

Abdominal Fat Mass Assessment in Recent Onset Spondyloarthritis: Data from the DESIR Cohort

Hélène Che[1], Adrien Etcheto[2], Camille Souffir[3], Sami Kolta[4], Pascal Richette[5], Anna Molto[6], Maxime Dougados[2], Christian Roux[4] and Karine Briot[4], [1]Cochin Hospital, Paris Descartes University, Paris, France, [2]Université Paris René Descartes and Hôpital Cochin, Paris, France, [3]Service de rhumatologie, Hopital Cochin, Paris, France, [4]Rheumatology B Department, Hôpital Cochin, Paris, France, [5]Université Paris Diderot, UFR médicale, Paris, France; APHP Hôpital Lariboisière, Fédération de Rhumatologie and Inserm U1132, Hôpital Lariboisière, Paris, France, [6]Hopital Cochin, Paris Descartes University, Paris, France

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Background/Purpose:

Studies have shown a strong prevalence of cardiovascular events among patients with spondyloarthritis (SpA). Recent studies indicate that visceral adipose tissue (VAT) is highly associated with insulin resistance and cardiovascular events. Dual energy X-ray absorptiometry (DXA) is a validated technique able to accurately determine cross-sectionally the mass of discret fat deposits.

The objectives of our study were to assess the 2-year changes in abdominal fat mass in patients with early inflammatory back pain suggestive of SpA, in the DESIR cohort and to identify the variables significantly associated with these changes.

Methods:

Among the 708 patients of the DESIR cohort (inflammatory back pain of less than 3 years duration suggestive of axial SpA), 265 had BMD measurements at baseline and after 2 years of follow-up, and 129 had body composition and abdominal adiposity measurements. Alongside the evaluation of clinical and paraclinical features associated with early SpA and increased cardiovascular risk, DXA was performed to evaluate body composition and abdominal adipose tissue (subcutaneous adipose tissue (SAT) and VAT). We assessed changes in abdominal fat mass (VAT, SAT) over 2 years. Then, we assessed the variables associated with abdominal fat mass changes using linear regressions. Afterwards, we compared the abdominal fat mass changes in patients treated with TNF-blockers or free of TNF-blockers. Finally, we tested the role of inflammation (defined by a CRP >6mg/L or presence of MRI inflammatory signals at the spine or sacro-iliac joint level) in the 2-year abdominal fat mass changes.

Results:

A total of 129 patients of the DESIR cohort (71 men (55.0%), mean age of 33.0 (±8.6) years old) with a mean disease duration of 17.9 (±10.7) months, were included. Their mean body mass index was 23.7 (±3.5) kg/m^2 and the prevalence of obesity (BMI>30 kg/m²) was 6.2%. We did not find any significant changes of SAT over 2 years; VAT tended to increase over 2 years from baseline of 7.3% (±28%) (p= 0.054). 2-year VAT changes was significantly associated with the presence of the baseline ASAS criteria fulfillment (p=0.015), hypercholesterolemia at baseline (p=0.007), hypertriglyceridemia at baseline (p=0.0026) and 2-year changes in BMI (p<0.01).

Thirty nine (30.2%) patients received anti-TNF treatment during the 2 years follow-up period. The SAT changes were not significantly different between patients with and without anti-TNF (+2.9%, p=0.323). However, VAT tended to increase from baseline in the anti-TNF group (+5.2%, p=0.053).

Presence or absence of inflammation had no significant impact on 2-year abdominal fat mass changes (p=0.358 for VAT and p=0.508 for SAT).

Conclusion:

To our knowledge, this study is the first one assessing the abdominal adiposity changes in early inflammatory back pain suggestive of SpA. VAT tended to increase over a 2 years follow-up period, especially in patients receiving anti-TNF. Further studies with larger samples are necessary to confirm or not these results and to evaluate their clinical relevance.

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Abstract Number: 1742

Fingerprint Biomarkers of Type I and III Collagen in Axial Spondyloarthropathy (axSpA) and Psoriatic Arthritis (PsA). Association with Disease Activity and Diagnostic Capacity

Natasja Stæhr Gudman[1], Anne Friesgaard Christensen[2], Grith Lykke Sørensen[3], Anne C. Bay-Jensen[4], Anne Sofie Siebuhr[5], Morten Asser Karsdal[6], Heidi Lausten Munk[7], Leif Ejstrup[8], Anne Gitte Loft[9] and Peter Junker[10], [1]Nordic Bioscience A/S, Herlev, Denmark, [2]Rheumatology, Odense University Hospital, Odense, Denmark, [3]Cardiovascular and Renal Research, Institute of Molecular Medicin, University of Southern Denmark, Odense, Denmark, [4]Biomarkers and Research, Rheumatology, Nordic Bioscience, Herlev, Denmark, [5]Biomarkers and Research, Nordic Bioscience, Herlev, Denmark, [6]Research & Development, Nordic Bioscience, Herlev, Denmark, [7]Department of Rheumatology, Odense University Hospital, Odense, Denmark, [8]Odense University Hosp, SDR Blvd, Odense, Denmark, [9]Department of Rheumatology, Vejle Hospital, Vejle, Denmark, [10]University of Southern Denmark, Odense, Denmark

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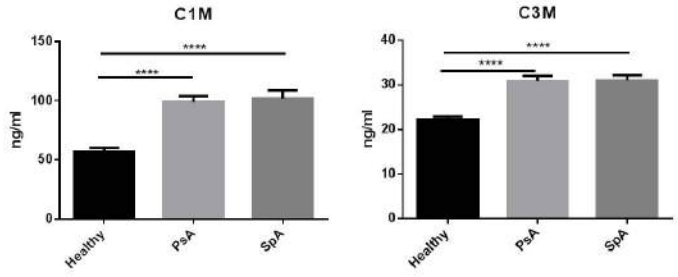
Background/Purpose: AxSpA and PsA are core members of the spondyloarthritis complex. One cardinal characteristic shared by these two conditions is increased remodeling of bone and soft connective tissue in and around peripheral joints, axial skeleton and entheseal insertions leading to synovitis, enthesitis and ankylosis in advanced disease. Studies using seromarkers which reflect extracellular matrix constituent metabolism may provide insight into the activity and dynamics of connective remodeling and thereby pave the way for improved diagnostics and management. The aims of this investigation were to study C1M and C3M, which reflect the turnover of collagen I and III, in order to assess their utility as diagnostic and disease activity markers.

Methods: Ninety-nine patients with PsA, 110 with axSpA and 120 healthy control subjects were included. Demographic and clinical disease measures were recorded.C1M and C3M were quantified using in house competitive ELISAs. Biomarker results are presented as median with 95% CI. Mann Whitney test was applied for inter-group comparisons and correlations were studied using Spearmans test. Receiver operator characteristics (ROC) curve analysis was carried out to evaluate the diagnostic potential of the biomarkers.

Results: C1M and C3M were significantly increased in both axSpA and PsA as compared with healthy controls (Figure). Thus, in axSPA C1M and C3M amounted to 77.6 (71.3-84.6)ng/ml and 27.7 (26.2-29.7)ng/ml respectively, in PsA to 85.6 (78.2-96.2)ng/ml and 28.7 (26.7-31.0)ng/ml versus controls 48.3(43.3-53.2) and 20.9 (20.0-21.7) respectively. C1M and C3M levels did not differ significantly between axSpA and PsA. Serum levels of C1M and C3M were not affected by treatment, or smoking status, but SpA HLA-B27+ patients had significantly higher levels of both C1M (p=0.001) and C3M (p=0.006) compared to HLAB-27- SpA patients. C1M was significantly correlated with DAS28 (PsA: r=0.22, p=0.028, SpA: r=0.40, p<0.0001) and ASDAS (PsA: r=0.29, p=0.003, SpA:r=0.35, r=0.0002). Also C3M was significantly correlated with DAS28 (PsA: r=0.22, p=0.025, SpA: r=0.74, p<0.0001) and ASDAS (PsA: r=0.32, p=0.0013, SpA: r=0.216, p=0.026). C1M and C3M were highly correlated (p>0.0001 in all groups) but they did not correlate with demographics including age, BMI or gender. Segregation between healthy and diseased based on C1M levels resulted in an AUC of 0.83 for PsA (0.76-0.86) and 0.79 (0.73-0.84) for SpA. C3M could also segregate between healthy and diseased with an AUC of 0.77 (0.71-0.82) for PsA and 0.78 (0.72-0.83) for SpA.

Conclusion: These findings indicate that soft connective tissue remodeling is equally increased in axSpA and PsA reflecting disease activity and that collagen type I and III turnover are mediated by closely coupled mechanisms. ROC curve analyses suggest that both C1M and C3M may be useful for diagnostic purposes in axSpA and PsA.



Evaluation of C1M and C3M in Healthy, SpA and PsA. Mann-Whitney tests were used for intergroup comparison, *p<0.05, ** p<0.01, ***p<0.001, ****p<0.0001

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Abstract Number: 1743

Gender Differences in Ankylosing Spondylitis: Men Derive Greater Benefit from Tumor Necrosis Factor Alpha Inhibitors

Jennifer Mandal[1], Michael M. Ward[2], Michael Weisman[3], Jillian Simard[4], Matthew A. Brown[5], MinJae Lee[6], Mohammad H. Rahbar[7], John D. Reveille[8] and Lianne S. Gensler[9], [1]Medicine, University of California San Francisco, San Francisco, CA, [2]NIH/NIAMS, Bethesda, MD, [3]Cedars-Sinai Medical Center, Los Angeles, CA, [4]University of California San Francisco, San Francisco, CA, [5]The University of Queensland Diamantina Institute, Brisbane, Australia, [6]Biostatistics/Epidemiology/Research Design (BERD) Core | Center for Clinical and Translational Sciences, University of Texas Health Science Center at Houston, Houston, TX, [7]The University of Texas Health Science Center at Houston, Houston, TX, [8]Rheumatology, University of Texas Health Science Center at Houston, Houston, TX, [9]Medicine/Rheumatology, University of California, San Francisco, San Francisco, CA
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Background/Purpose:

Ankylosing spondylitis (AS) manifests differently in men and women. Women with AS have less severe radiographic disease, yet tend to report more severe symptoms. Little is known about the relationship between gender and disease activity in response to tumor necrosis factor alpha inhibitors (TNFi) in AS. The objective of this study was to explore the longitudinal relationship between gender, TNFi use, and disease activity among patients with AS.

Methods:

In this prospective multicenter cohort study, 659 participants meeting the modified New York criteria were recruited from 2003-2015 and followed every 6 months. Data collection included: demographics, medication history at each visit, comorbidities, depression scales, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and disease activity, measured by the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI). Univariable logistic regression models were performed to identify potential confounders associated with both gender and BASDAI, and these were incorporated into a

longitudinal multivariable mixed effect Poisson regression model using BASDAI as the dependent variable (Table 1). Possible interaction effects were also evaluated while developing the final model.

Results:

Participants were 73.3% men and 79.1% white, with mean age at enrollment of 42.9 ±13.9 years. In the multivariable analysis, gender significantly modified the effect of TNFi on disease activity, measured by BASDAI (p-value for interaction=0.048). TNFi use was associated with better BASDAI scores in both men and women, however men derived a greater reduction in disease activity from TNFi use compared to women (Rate Ratio = 0.79, 95% CI= 0.73-0.85, p <0.0001 for men, and RR= 0.89, 95% CI= 0.81-0.97, p= 0.0059 for women; Figure 1). There was no significant interaction between gender and other pharmacologic agents, including nonsteroidal anti-inflammatory drugs (NSAIDs) and opiates.

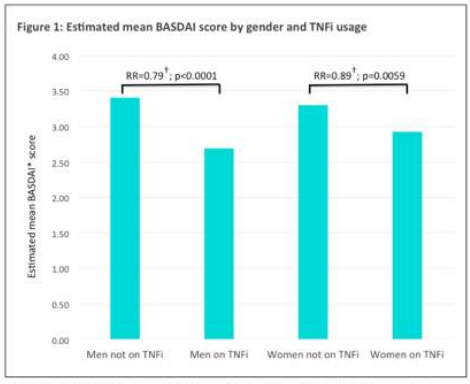
Conclusion:

Although men and women with AS both respond to TNFi treatment, men tend to derive greater benefit than women. Gender had a significant modifying effect on the relationship between TNFi use and disease activity. This effect modification, which was not present with NSAIDs or opiates, may suggest an underlying biological mechanism. It is also possible that the specific symptoms reported by men on the BASDAI are more likely to be mediated by TNF compared to the symptoms reported by women.

Table 1.
Factors associated with longitudinal BASDAI score from mixed effect multivariable Poisson regression model

	Rate Ratio (95% CI)	P
Gender-TNFi interaction		***0.048***
TNFi use vs No use		
Female	**0.89 (0.81-0.97)**	**0.0059**
Male	**0.79 (0.73-0.85)**	**<0.0001**
Married	0.93 (0.88-0.99)	0.0167
Education past high school	0.95 (0.88-1.04)	0.2624
White race	1.04 (0.95-1.13)	0.4269
Age ≥40	1.05 (0.97-1.13)	0.1952
Narcotic use at baseline	1.13 (1.06-1.21)	0.0004
NSAID use at baseline	0.96 (0.90-1.03)	0.2326
Elevated CRP at baseline	0.93 (0.87-0.99)	0.0188
mSASSS ≥4 at baseline	1.05 (0.98-1.12)	0.1949
BASFI ≥40 at baseline	1.13 (1.04-1.22)	0.0022
CES-D ≥8 at baseline	1.09 (1.004-1.17)	0.0386
≥1 comorbidity	1.10 (1.02-1.18)	0.0114
Ever smoker	1.03 (0.97-1.09)	0.3499
History of peripheral joint involvement	1.01 (0.95-1.08)	0.6815

BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; TNFi = tumor necrosis factor alpha inhibitor; CRP = C-reactive protein; BASFI = Bath Ankylosing Spondylitis Functional Index; mSASSS = modified Stokes Ankylosing Spondylitis Spine Score; NSAID = non-steroidal anti-inflammatory drug; CES-D = Center for Epidemiologic Study Depression Scale



*BASDAI = Bath Ankylosing Spondylitis Disease Activity Index, a 1-10 scale. Higher scores indicate worse disease activity.
†Gender-TNFi interaction: p=0.048

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Abstract Number: 1744

Free DKK-1 Serum Levels Are Unchanged in Spondyloarthritis Patients Treated By Etanercept

Corinne Miceli-Richard[1], Bernard Combe[2], Francis Berenbaum[3], Thierry Schaeverbeke[4], Maria Dilleen[5], Nandan Koppiker[6], Isabelle Logeart[7], Arnaud Dubanchet[7] and Maxime Dougados[8], [1]Rheumatology, Cochin Hospital, Paris Descartes University, Paris, France, [2]Rheumatology, Hopital Lapeyronie, Montpellier, France, [3]Rheumatology and Paris VI University, Saint-Antoine Hospital, Paris, France, [4]Rheumatology, CHU Bordeaux, Bordeaux, France, [5]Pfizer GIPB, Sandwich, United Kingdom, [6]Pfizer PGRD, Sandwich, United Kingdom, [7]Pfizer, Paris, France, [8]Paris-Descartes University, Paris, France
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Background/Purpose:

DKK-1 and SOST are two inhibitory proteins of the Wnt signaling pathway that lead to decreased bone formation by osteoblasts and osteocytes, respectively. Functional DKK-1 serum levels have been reported to be decreased and dysfunctional in spondyloarthritis (1,2) and a preliminary study involving a limited number of SpA patients suggested that functional DKK-1 serum levels might also decrease under anti-TNF treatment (2). Due to the limited number of patients included in this latest study and the lack of data assessing free DKK-1 and SOST in SpA, a post-hoc examination of the SPARSE study was designed to assess free DKK-1 and SOST serum levels at Baseline and 24 weeks after etanercept or placebo treatment in patients from the SPARSE study.

Methods:

In the SPARSE study, patients were randomized to receive either etanercept (N=42) or placebo (n=48) in case of active AxSpA disease (defined by mini BASDAI ≥ 4) despite optimal NSAIDs intake. Free DKK-1 and SOST serum levels were measured in 90 patients from the SPARSE study at Baseline and at Week 8 (w8). DKK-1 and SOST serum levels were assessed by the use of a classic sandwich ELISA test (Biomedica, Vienna) and results were provided in pmol/L. Changes in DKK-1 and SOST serum levels were adjusted for disease activity, CRP levels, NSAIDs intake, X-ray status and treatment groups.

Results:

LS Mean (SE) serum DKK-1 at Baseline was not significantly different between treatment groups (ETN: 36.2 +/- 1.97; PBO: 37.1 +/- 1.84; p=0.72). At Baseline, DKK-1 was not associated with any patient or disease characteristics: ASDAS-CRP (r=0.096; 95% CI [-0.122, 0.305]); CRP (r=0.002; 95% CI [-0.210, 0.214]); X-ray status (LS Mean (SE): negative 37.4 (+/-2.38) versus positive 36.3 (+/- 1.77); p=0.71). There were no significant differences between treatment groups in the change from Baseline to w8 in the DKK-1 serum levels (p=0.91). We also considered patients with (N=67) or w/o NSAIDs intake (n=19) within the week preceding w8 serum level assessment and found no significant difference (p=0.99). We further assessed DKK-1 serum levels at Baseline according to their Baseline CRP (<6mg/L; ≥6mg/L), X-ray status (Positive; Negative), or NSAIDs intake (Yes; No) within the week preceding w8, and found no significant differences. These analyses were repeated for SOST serum levels at Baseline and with the exception of patients with Negative X-ray status at Baseline having significantly lower values than those patients with Positive X-ray status (p=0.047), no significant differences were observed in terms of the Baseline disease characteristics; Similarly there were no differences between treatment groups in the change from Baseline to w8 for SOST serum levels.

Conclusion:

This post-hoc examination of patients randomized in the SPARSE study suggest that etanercept does not significantly change DKK-1 or SOST serum levels within the 8 first weeks of treatment. Disease activity, CRP, NSAIDs intake and X-ray status were not significantly associated with DKK-1 serum levels. These results should be considered in the context of previous studies suggesting that DKK-1 was dysfunctional in SpA patients (2).

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Abstract Number: 1745

Predictors of Sustained Remission on Anti-TNF in an Observational Cohort of Patients with Ankylosing Spondylitis: The Role of MRI Parameters of Inflammation and Structural Damage

Susanne Juhl Pedersen[1], Stephanie Wichuk[2], Praveena Chiowchanwisawakit[3], Zheng Zhao[4], Sasha Bernatsky[5], Robert GW Lambert[6], Barbara Conner-Spady[7], Don Spady[8] and Walter Maksymowych[9], [1]Copenhagen Center for Arthritis Research, Glostrup Hospital, University of Copenhagen, Copenhagen, Denmark, [2]Department of Medicine, Medicine, University of Alberta, Edmonton, AB, Canada, [3]Rheumatology, Medicine, Siriraj Hospital, Mahidol University, Bangkok, Thailand, [4]Rheumatology, Chinese PLA General Hospital, Beijing, China, [5]Rheum/Clin. Epid., McGill MUHC/RVH, Montreal, QC, Canada, [6]Department of Radiology & Diagnostic Imaging, Radiology, University of Alberta, Edmonton, AB, Canada, [7]Medicine, Medicine, University of Alberta, Edmonton, AB, Canada, [8]Medicine, University of Alberta, Edmonton, AB, Canada, [9]Medicine/Rheumatic Dis Unit, Medicine, University of Alberta, Edmonton, AB, Canada

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Background/Purpose: Sustained clinical remission is one of the key benchmarks for treatment of AS over the long term. We aimed to determine the factors predictive of sustained clinical remission on anti-tumor necrosis factor alpha (anti-TNFα) therapy and the role of MRI parameters of inflammation and structural damage at baseline and after treatment.

Methods: In the FOllow-up Research Cohort in AS (FORCAST), AS patients from Northern Alberta attending community and academic practices are assessed for clinical and laboratory outcomes every 6 months, radiography at baseline and 2 years, MRI at baseline, at 3-6 months for patients starting anti-TNFα, and annually. MRI inflammation was assessed using Spondyloarthritis Research Consortium of Canada (SPARCC) Sacroiliac Joint (SIJ) and 23-DVU Spine scores while structural change was assessed independently using the SPARCC SIJ Structural Scores (SSS) for fat metaplasia, erosion, backfill, ankylosis and the Fat Ankylosing Spondylitis Spine Score (FASSS) score for fat metaplasia. Sustained clinical remission was defined as ASDAS<1.3 at two consecutive 6-monthly visits. We used univariate and multivariate logistic regression to assess patient demographics, smoking, B27, NSAID utilization, and baseline CRP, ASDAS, mSASSS, SPARCC scores, SSS, and FASSS scores, adjusted for duration of follow up. We also assessed attainment post-treatment of CRP<6mg/L, ASDAS<1.3, and SPARCC MRI remission (SIJ <2 and spine <3) as predictors of future remission.

Results: We assessed 316 patients on anti-TNF therapy of mean (SD) age 41.2 (12.3) years, 78% males, mean (SD) symptom duration 18.7 (11.1) years, and mean (SD) duration of follow up of 1704 (961.4) days, of whom 144 had MRI evaluation. 98 (31.0%) achieved sustained ASDAS remission after mean (SD) follow up of 848.3 (682.4) days. In univariate analyses, patients attaining ASDAS remission were younger (p<0.0001), had shorter disease duration (p<0.0001), lower baseline ASDAS (p=0.01), were not current smokers (p=0.01), had definite SIJ erosion (p=0.01) but low spinal fat metaplasia (FASSS<5) (p=0.01) and SIJ ankylosis scores (p=0.01), and post-treatment scores indicating SPARCC MRI remission of inflammation (p=0.02), and normalised CRP (p=0.01). In multivariate analyses adjusted for duration of follow up, age, current smoking, baseline ASDAS, and normalized CRP were the strongest clinical predictors. The best models (in terms of *R-squared values)* included age, sex, ASDAS, current smoker, duration of follow up, and an MRI structural parameter (SSS erosion or ankylosis).

Conclusion: Current smoking is negatively associated with attainment of sustained remission to anti-TNF. Sustained remission is more likely in patients attaining normalised CRP, in the presence of definite SIJ erosion, and in the absence of SIJ ankylosis.

	Adjusted R^2	Significant independent variables	OR [95%CI]	P value
Basic Model (age, sex, ASDAS, current smoker, duration of follow up)	0.12	age	0.95 [0.92-0.98]	<0.0001
		Baseline ASDAS	0.65 [0.47-0.90]	0.009
		Current smoking	0.33 [0.14-0.80]	0.014
Basic Model plus post-treatment CRP<6	0.17	Post-treatment CRP<6	10.30 [1.28-82.62]	0.028
Basic model plus SSS erosion ³2	0.38	Baseline ASDAS	0.34 [0.14-0.84]	0.019
		SSS erosion ³2	8.86 [1.57-50.0]	0.013
Basic model plus SSS ankylosis	0.39	Baseline ASDAS	0.34 [0.13-0.92]	0.033
		SSS ankylosis	0.86 [0.76-0.98]	0.019

Disclosure: S. J. Pedersen, None; **S. Wichuk**, None; **P. Chiowchanwisawakit**, None; **Z. Zhao**, None; **S. Bernatsky**, None; **R. G. Lambert**, None; **B. Conner-Spady**, None; **D. Spady**, None; **W. Maksymowych**, Abbvie, 5,Amgen, 5,Eli Lilly and Company, 5,Boehringer Ingelheim, 5,Janssen Pharmaceutica Product, L.P., 5,Pfizer Inc, 5,UCB, 5,Abbvie, 2.

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Abstract Number: 1746

Patient's Ability of Coping Is Influencing the Correlation Between Clinical and Ultrasonographic Evidence of Disease Activity in Psoriatic Arthritis

Brigitte Michelsen[1], Andreas P Diamantopoulos[1,2], Hilde Berner Hammer[3], Dag Magnar Soldal[4], Arthur Kavanaugh[5] and Glenn Haugeberg[1,6,7], [1]Rheumatology, Hospital of Southern Norway Trust, Kristiansand, Norway, [2]Rheumatology, Haugesund Hospital for Rheumatic Diseases, Haugesund, Norway, [3]Rheumatology, Diakonhjemmet Hospital, Oslo, Norway, [4]Rheumatology, Hospital of Southern Norway, Kristiansand, Norway, [5]University of California, San Diego School of Medicine, LaJolla, CA, [6]Rheumatology, Martina Hansens Hospital, Gjettum, Norway, [7]Rheumatology, The Norwegian University of Science and Technology, Trondheim, Norway

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Background/Purpose: Coping may be defined as the set of adaptive processes a patient uses to live well with aspects of disease such as pain. Coping may represent an ability to help manage symptoms in patients with arthritides. This study aimed to explore the influence of patient's ability to cope on patient reported outcome measures (PROs) and composite clinical scores in psoriatic arthritis (PsA), and to determine whether differential ability to cope influences the association between clinical and ultrasonographic (US) findings in PsA.

Methods: In this cross sectional study 141 PsA patients were consecutively recruited from an out-patient clinic. They all fulfilled the CASPAR criteria for PsA. 66 swollen/68 tender joint count (SJC/TJC), PROs and composite scores were registered. US evaluation of 34 joints and additionally joints found to be swollen/tender by 66/68 joint count, 15 tendons, 10 entheses and additionally entheses found to be tender by clinical examination of 19 other entheses was performed. Patients reported their level of coping on a visual analogue scale (VAS, range 0-100 mm, 100 mm worst coping). Gray scale (GS) and power Doppler (PD) sum scores of joints, entheses and tendons were assessed. Correlation analyses were performed by Spearman's rank correlation test (non-parametric distribution of the data). To explore the relation between patient's ability of coping, clinical factors and composite scores we used multiple regression analyses.

Results: We found that coping was strongly correlated ($p<0.001$) to joint pain ($r=0.67$), patient global assessment (PGA) ($r=0.73$) and TJC68 ($r=0.42$). When separating into good (116 patients) and poor (24 patients) ability of coping (defined as ≤50 and >50 mm on a VAS scale, respectively), we found that patients with poor ability of coping had no correlations between several PROs and composite scores, whereas patients with good ability of coping had weak to moderate correlations (table). Patients with poor ability of coping had on average higher Disease Activity Index for Psoriatic Arthritis (DAPSA) (20.0±2.5, $p<0.001$), Composite Psoriasis Disease Activity Index (CPDAI) (2.8±0.5, $p<0.001$), Psoriatic ArthritiS Disease Activity Score (PASDAS) (0.27±0.1, $p=0.006$) score, Disease Activity Score 28 (DAS28) (1.1±0.2, $p<0.001$) and Simple Disease Activity Index (SDAI) (10,7±1.3, $p<0.001$), model adjusted for age, gender and PD sum score.

	Good coping		Poor coping		Good coping		Poor coping	
	GS total	PD total	GS total	PD total	GS joints	PD joints	GS joints	PD joints
TJC 68	NS	NS	NS	NS	NS	NS	NS	NS
SJC 66	0,18*	0,31**	NS	NS	0,27**	0,46***	NS	NS
PGA	NS	0,19*	NS	NS	NS	NS	NS	NS
DAPSA	NS	0,23*	NS	NS	NS	0,23*	NS	NS
DAS28	0,23*	0,27**	NS	NS	NS	0,33***	NS	NS
SDAI	0,23*	0,26**	NS	NS	NS	0,30**	NS	NS

Spearman's rank correlation test, *p<0.05, **p<0.01, ***p<0.001

Conclusion: Patient's ability of coping is influencing PROs in PsA. US evaluation of disease activity is correlated to clinical findings for patients with good ability of coping, but not for patients with poor ability of coping.

Disclosure: B. Michelsen, None; **A. P. Diamantopoulos**, None; **H. B. Hammer**, None; **D. M. Soldal**, None; **A. Kavanaugh**, None; **G. Haugeberg**, Pfizer Norway, 2.

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Abstract Number: 1747

Predictors of Survival on Anti-TNF in an Observational Cohort of Patients with Ankylosing Spondylitis: The Role of MRI Parameters of Inflammation and Structural Damage

Walter Maksymowych[1], Zheng Zhao[2], Stephanie Wichuk[1], Praveena Chiowchanwisawakit[3], Robert G Lambert[4], Sasha Bernatsky[5], Barbara Conner-Spady[1], Donald Spady[1] and Susanne Juhl Pedersen[6], [1]Medicine, Medicine, University of Alberta, Edmonton, AB, Canada, [2]Rheumatology, Chinese PLA General Hospital, Beijing, China, [3]Rheumatology, Medicine, Siriraj Hospital, Mahidol University, Bangkok, Thailand, [4]Radiology, Radiology, University of Alberta, Edmonton, AB, Canada, [5]Rheum/Clin. Epid., McGill MUHC/RVH, Montreal, QC, Canada, [6]Copenhagen Center for Arthritis Research, Glostrup Hospital, University of Copenhagen, Copenhagen, Denmark

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Background/Purpose: There has been no data reported evaluating MRI parameters of inflammation and structural damage. We aimed to identify factors influencing survival on anti-TNF therapy in real world practice specifically focusing on the role of MRI parameters of inflammation and structural damage.

Methods: In the FOllow-up Research Cohort in AS (FORCAST), AS patients from Northern Alberta attending community and academic practices are assessed for clinical and laboratory outcomes every 6 months, radiography at baseline and 2 years, MRI at baseline, at 3-6 months for patients starting anti-tumor necrosis factor alpha (anti-TNFα), and annually. MRI inflammation was assessed using Spondyloarthritis Research Consortium of Canada (SPARCC) Sacroiliac Joint (SIJ) and Spine scores while structural change was assessed independently using the SPARCC SIJ Structural Score (SSS) for fat metaplasia, erosion, backfill, ankylosis and the Fat AS Spine Score (FASSS) for fat metaplasia in the spine. MRI scans were scored independently by 2 readers and adjudicated by a third reader according to pre-specified rules. We used Kaplan–Meier plots, log rank tests and univariate and multivariate Cox regression

analyses to assess the effects of patient demographics, smoking, B27, NSAID utilization, and baseline CRP, ASDAS, mSASSS, SPARCC scores, SSS and FASSS scores on drug survival. We also assessed early attainment post-treatment of CRP<6mg/L, ASDAS<1.3, and SPARCC remission (SIJ <2, Spine <3) as predictors of anti-TNF survival.

Results: We recruited 480 patients on anti-TNF, mean (SD) age 41.0 (12.7) years, 74.4% males, mean (SD) symptom duration 18.4 (11.6) years, mean (SD) survival on first anti-TNF 1228.1 (1036.9) days. The number discontinuing first-time anti-TNF prescription was 126 (26.3%) after mean (SD) follow up of 814.8 days from first prescription date, of which 28% was for lack of efficacy (LOE), and 17% for adverse events. There were 45 primary and 82 secondary failures. 125 patients had MRI at baseline and 100 had at least one follow up MRI. Univariate analysis showed that male sex (HR 0.56, p=0.002), baseline CRP (HR 0.99, p=0.03) and early post-treatment attainment of ASDAS<1.3 (HR 0.57, p=0.02), and CRP<6mg/L (HR 0.56, p=0.02) were significant predictors of drug survival. Early attainment of SPARCC SIJ remission was the best MRI predictor of drug survival (HR 0.58, p=0.14). In multivariate analysis of clinical predictors, SPARCC SIJ < 2 (adjusted OR=2.2[1.02-4.74]; p=0.043) was a significant predictor.

Conclusion: From an extensive array of patient demographic and disease severity variables, attainment of normalized CRP or low disease activity state within first year of starting an anti-TNF was most strongly associated with survival on treatment. Early remission of MRI inflammation may also be a factor but this requires further study with larger sample size.

Table. Multivariable Cox Regression

Variable	Hazard Ratio	P value	95% CI
Age	0.82	0.47	0.48-1.41
Gender	1.01	0.29	0.99-1.03
Baseline CRP	0.99	0.035	0.98-1.00
CRP<6 post-treatment*	0.46	0.008	0.26-0.82
ASDAS<1.3 post-treatment*	0.54	0.027	0.32-0.93

*Within first year of treatment

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Abstract Number: 1748

Degenerative Changes at the Lumbar Spine in Patients with Axial Spondyloarthritis and Non-Specific Mechanical Low Back Pain: A Magnetic Resonance Imaging Study

Serkan Senol[1], Gamze Kilic[2], Sevgi Baspinar[2], Erkan Kilic[3] and **Salih Ozgocmen**[4], [1]Division of Neuroradiology, Erciyes University, Faculty of Medicine, Radiology, Kayseri, Turkey, [2]Dept. PRM, Erciyes University, Faculty of Medicine,Division of Rheumatology, Kayseri, Turkey, [3]Dept PRM, Erciyes University, Faculty of Medicine,Division of Rheumatology, Kayseri, Turkey, [4]Dept.PRM, Erciyes University, Faculty of Medicine,Division of Rheumatology, Kayseri, Turkey

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Background/Purpose: Magnetic resonance imaging (MRI) has become an invaluable tool for early diagnosis of axial spondyloarthritis (axSpA) and several MRI-based studies have identified SpA-related inflammatory or structural findings in the spine. However, the exact frequency of degenerative changes (DCs) at the spine in pts with axSpA as a potential cause of low back pain (LBP) is not completely clarified. Therefore, the aim of this study was to document DCs on lumbar MRI in pts with axSpA and non-specific mechanical (mLBP).

Methods: Pts with chronic LBP were consecutively recruited from our out-patient clinic. All of the pts were assessed for ASAS classification criteria for axSpA and all underwent lumbar spinal MRI. Patients with a history of spinal surgery or injections were excluded. A qualified reader (unaware of the clinical diagnosis and variables) scored anonymized sagittal and axial T1 and T2-weighted MR scans of the lumbar spine. Degree of disc degeneration (DD) (Pfirrmann 5 point scale, class ≤2 considered normal), endplate changes (Modic 3 point scale) and presence of annular rupture, disc bulging, protrusion or extrusion at each spinal level from L1-L2 to L5-S1 were assessed. Patients without definite sacroiliitis on pelvic X-ray were defined as nr-axSpA, and patients with definite sacroiliitis on pelvic X-ray according to modified New York criteria were defined as AS (pelvic X-rays were scored upon consensus of three readers).

Results: Two hundred sixty-seven pts with axSpA (123 nr-axSpA, 144 AS) and 105 pts with mLBP were included (age 18 to 60). Pts with nr-axSpA were

younger (35.43+8.72, years) than pts with AS and mLBP (38.78+7.99, p=0.0008; 41.37+10.77 years, p<0.0001, respectively). Pts with AS had longer symptom duration (11.33+6.93, years) than pts with nr-axSpA and mLBP (6.74, p<0.0001 and 6.13, p<0.0001, respectively). The prevalence of lumbar herniated nucleus pulposus (protrusion or extrusion at any level) in nr-axSpA was higher than pts with AS. In the multivariate logistic regression analysis (adjusted for confounding variables), the presence of MCs (OR, 6.76; 95% CI; 2.09-21.83, p=0.001), LHNP (protrusion or extrusion) (OR , 3.67; 95% CI; 1.57-8. 26, p=0.028), as well as advance age (>50 years) (OR, 33.54; 95% CI; 3.83-293.97 p=0.001) were factors associated with the risk of DD in axSpA. BASMI and BASFI scores were higher and Schober test was more restricted in patients with axSpA who had coexisting DD.

Conclusion: Prevalence of DCs is higher in pts with mLBP than pts with axSpA. However substantial proportion of pts with axSpA had DD at the lumbar spine which increased with age. Spinal DCs might be an alternative explanation for complaints and might interfere with diagnostic decision making in pts with axSpA.

Table 1. The crude percentages of degenerative changes at the lumbar spine

	axSpA (n=267)	**mLBP (n=105)**	**p**
	N(%)	N(%)	
DD-L1-L2	117(43.8)	63(60.0)	0.005
DD-L2-L3	119(42.3)	64(61.0)	0.004
DD-L3-L4	125(46.8)	71(67.6)	<0.0001
DD-L4-L5	144(53.9)	71(67.6)	0.016
DD-L5-S1	144(53.9)	71(67.6)	0.016
DD-any level	163(61.0)	74(70.5)	0.089
LHNP-L1-L2 (bulg./ prot./ extr.)	12(4.5)/3(1.1)/0(0)	12(11.4)/1(1.0)/0(0)	0.014/ 1.0 /NA
LHNP-L2-L3 (bulg./ prot./ extr.)	22(8.2)/3(1.1)/0(0)	18(17.1)/2(1.9)/0(0)	0.013/ 0.624/ NA
LHNP-L3-L4 (bulg./ prot./ extr.)	44(16.5)/8(3.0)/2(0.7)	33(31.4)/11(10.5)/0(0.0)	0.0014/ 0.003/ 1.0
LHNP-L4-L5 (bulg./ prot./ extr.)	89(33.3)/41(15.4)/1(0.4)	40(38.1)/32(30.5)/3(2.9)	0.385/0.0009 /0.070
LHNP-L5-S1 (bulg./ prot./ extr.)	86(32.2)/53(19.8)/3(1.1)	30(28.6)/47(44.8)/5(4.8)	0.495/0.0001 / 0.043
LHNP-any level protrusion or extrusion	80(30.0)	65(61.9)	<0.0001
Annuler Fissur/rupture-any level	81(30.3)	51(48.6)	0.001
Modic change Type 1 any level	16(6.0)	6(5.7)	0.918
Modic change Type 2 any level	57(21.3)	16(15.2)	0.182
Modic change Type 3 any level	1(0)	0(0)	1.000
Modic changes-any level	69(25.8)	20(19.0)	0.167

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Abstract Number: 1749

Clinical Characteristics of Axial Spondyloarthritis Patients Progressing from Non-Diagnostic to Diagnostic Radiographic Sacroiliitis

Ismail Sari[1], Jonathan Chan[2], Ahmed Omar[1], Mohamed Bedaiwi[1], Nigil Haroon[1] and Robert D Inman[3], [1]Rheumatology, Toronto Western Hospital, University of Toronto, Toronto, ON, Canada, [2]Rheumatology, Spondylitis program, Toronto Western Hospital, University of Toronto, Toronto, ON, Canada, [3]Immunlogy and Institute of Medical Science, Toronto Western Hospital, University of Toronto, Toronto, ON, Canada

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Background/Purpose: Ankylosing spondylitis (AS) is a chronic inflammatory disease that mainly affects the axial skeleton in which the diagnosis includes diagnostic X-ray changes in the sacroiliac joints. The spectrum of axial spondyloarthritis (axSpA) ranges from non-radiographic (nr) axSpA to AS. Variable rates of progression from nrAxSpA to AS have been reported. However, factors predictive of this progression are poorly defined. In this study, we aimed to identify the characteristics of patients who progressed from nrAxSpA to AS according to modified New York criteria (mNYc).

Methods: In our registry, there were 44 nraxSpA patients according to the ASAS definition who had serial follow-up pelvic X-rays. Two independent readers scored the first and last available pelvic radiographs for each patient and identified the patients who progressed to AS. Discordant results were settled by a third reader. Spinal radiographic damage was assessed by the modified Stoke AS Spinal Score (mSASSS). Baseline information regarding symptom duration, B27 status, biological drug usage, clinical variables, smoking, BASDAI, ESR and CRP were then obtained from the database.

Results:

Characteristics of progressors: Over a median period of 52.5 (25-126) months, 9 (20.5%) out of 44 patients progressed from non-radiographic stage to AS at a rate of 4.7%/year.The median transition time was 47 (23-89) months. There were 8 (88.9%) men and 1 (11.1%)woman. The median age at diagnosis was 22.3 (18-63) years. The median disease duration was 5 (1-19) years. HLA-B27 was positive in 7 (77.8%) patients. Smoking history was positive in 5 (55.6%) patients. The frequency of arthritis, uveitis, enthesitis, dactylitis and family history of AS were 6 (66.7%), 3 (33.3%), 5 (55.6%), 1 (11.1%) and 2 (22.2%) respectively. There were 6 (66.7%) patients who had been treated with TNF-inhibitors (TNFi). **Comparison of progressors vs.**

non-progressors: There were 35 patients who did not progress to AS. The median follow-up of these patients were 33 (24-89) months. Comparison of both groups showed that follow-up duration, disease duration, HLA-B27 status, smoking, extra-articular features, family history, baseline BASDAI, and TNFi treatment were not different between the groups. On the other hand, progressors showed significantly higher baseline CRP, higher frequency of male sex and lower age at onset compared to the non-progressors (Table-1).

Conclusion: Male sex, younger age at onset and higher baseline CRP are factors predictive of progression from nr-axSpA to AS.

Table 1: Comparison of baseline profiles of nr-axSpA progressors *vs* non-progressors.

	Patients progressed to AS (n=9)	Patients without progression (n=35)	P value
Age, yr	22.2 (18-63)	35.3 (18-57)	0.03
Sex (male), %	88.9	51.4	0.04
Disease duration, yr	5 (1-19)	9 (1-24)	0.32
Duration of follow-up, months	52.5 (25-126)	33 (24-89)	0.1
HLA-B27, %	77.8	82.9	0.66
Peripheral arthritis, %	66.7	77.1	0.67
Uveitis, %	33.3	20	0.4
Enthesitis, %	55.6	47.1	0.72
Family history of AS, %	22.2	26.5	1
Dactylitis, %	11.1	5.7	0.51
Smoking, %	55.6	26.5	0.12
Biological use, %	66.7	74.3	0.69
BASDAI	3 (0-7.2)	2.9 (0-8.9)	0.87
CRP (mg/L)	9 (3-124)	3 (3-35)	0.03

* Data is presented with median (minimum-maximum) values

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Abstract Number: 1750

Identification of Autoantibody-Inducing CD4 T Cell (aiCD4 T cell) That Causes Systemic Lupus Erythematosus (SLE) As DOCK8+ CD4 T Cell: Proof of Concept of Self-Organized Criticality Theory

Shunichi Shiozawa[1], Yumi Miyazaki[2], Kazuko Shiozawa[3] and Ken Tsumiyama[2], [1]Department of Medicine, Rheumatic Diseases Unit, Kyushu University Beppu Hospital, Beppu, Japan, [2]Medicine, Rheumatic Diseases Unit, Kyushu University Beppu Hospital, Beppu, Japan, [3]Rheumatic Diseases Center, Konan Kakogawa Hospital, Kakogawa, Japan

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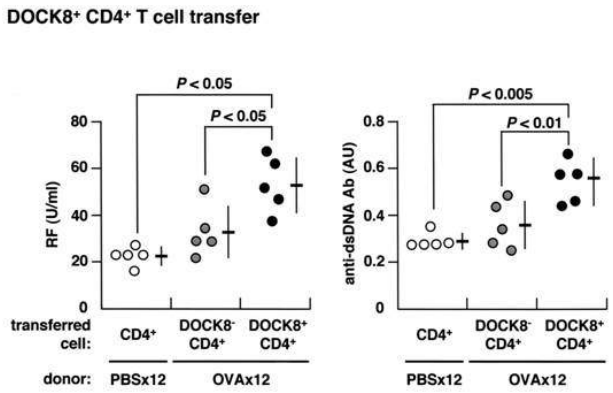
Background/Purpose: We have shown that repeated immunization with antigen causes systemic autoimmunity in mice otherwise not prone to spontaneous autoimmune diseases. Overstimulation of CD4 T cells led to the development of autoantibody-inducing CD4 T (*ai*CD4 T) cell which had undergone *de novo* T cell receptor (TCR) revision. These cells originated predominantly from thymus-passed lymphocytes at the periphery. These *ai*CD4 T cells were capable of inducing a variety of autoantibodies and stimulating CD8 T cells, driving them to become antigen-specific cytotoxic T lymphocytes (CTL). These CTLs could be further matured thru antigen cross-presentation, after which they caused tissue injury identical to that observed in SLE. Thus, systemic autoimmunity appears to be the inevitable consequence of over-stimulating the host's immune system by repeated immunization with antigen to levels that surpass system's self-organized criticality. We have thus proposed the 'eSelf-organized criticality theory' of autoimmunity (Tsumiyama K et al. PLoS ONE 4(12): e8382, 2009), explaining the cause of SLE. Here we identify the *ai*CD4 T cell responsible for inducing SLE as the DOCK8+ CD4 T cell subset.

Methods: BALB/c mice were immunized 12x with OVA. Isolated CD4 subsets were adoptively transferred into naïve recipients, and *ai*CD4 T cells were screened by analysis of the autoantibodies generated in the sera of recipient mice. Membrane fractions of the CD4 T cell subsets responsible for inducing the disease were isolated and examined by mass spectrometry, and candidate proteins specifically expressed in the $CD45RB^{lo}CD122^{lo}$ CD4 T cell fraction were identified by antibody staining. The CD4 T subset expressing the candidate protein of interest was confirmed to be the *ai*CD4 T cell subset by cell transfer into naïve recipients.

Results: Thru fractionation of CD4 T cell subsets and microarray analyses, we found that *ai*CD4 T cells belonged to CD45RB^{lo}CD122^{lo}PD1^{+} CD4 subset. We then isolated membrane and cytoplasmic fractions of these cells and analyzed their proteins by mass spectrometry, and found that among several candidate proteins, DOCK8 was specifically expressed in the membrane fraction of this subset. Adoptive transfer of DOCK8+ CD4 cells from mice immunized 12x with OVA caused an increase in both RF and anti-dsDNA antibody production in the naïve recipients.

Conclusion: The *ai*CD4 T cell subset that induces SLE is identified as DOCK8+ CD4 T cells.



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Abstract Number: 1751

Modulation of IRF4 Function Promotes Expansion of Effector Tregs in Lupus

Alessandra B. Pernis[1], Uma Chandrasekaran[2], Woelsung Yi[2], Sanjay Gupta[3], Chien-Huan Weng[4], Eugenia Giannopoulou[2], Yurii Chinenov[5], Govind Bhagat[6], Rolf Jessberger[7] and Casey Weaver[8], [1]Autoimmunity & Inflammation, Hospital for Special Surgery, New York, NY, [2]Hospital for Special Surgery, New York, NY, [3]Autoimmunity & Inflammation Research Program, Hospital for Special Surgery, New York, NY, [4]Weill Cornell Medical College, New York, NY, [5]Arthritis & Tissue Degeneration Program, Hospital for Special Surgery, New York, NY, [6]Department of Pathology & Cell Biology, Columbia University, New York, NY, [7]Dresden University of Technology, Dresden, Dresden, Germany, [8]University of Alabama, Birmingham, AL
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Background/Purpose: Acquisition of an effector phenotype is critical for Treg function in chronic inflammatory settings such as those encountered in autoimmune diseases like lupus. Although IRF4 is an essential controller of effector Tregs, the mechanisms orchestrating its function in these cells are largely unknown. In non-Tregs, IRF4 function can be modulated by interaction with DEF6 and its homologue SWAP-70. Mice lacking DEF6 and SWAP-70 (DKO mice) develop a lupus-like syndrome but display normal survival. The purpose of this study was to test the hypothesis that DEF6 and SWAP-70 restrain IRF4 activity in Tregs and that, in DKO mice, Tregs have an increased ability to become effector Tregs and thus blunt disease severity.

Methods: FACS analysis of DKO mice was employed to systematically evaluate Treg frequencies and effector Treg phenotypes during disease development. DKO mice were crossed to Blimp1-YFP-10BiT dual reporter mice to assess expression of the Blimp1-IL10 gene module in DKO Tregs. Selective deletion of IRF4 in the Treg compartment was achieved by crossing DKO mice with Foxp3-Cre IRF4$^{fl/fl}$ mice.

Results:

Unlike naïve T_H cells that express only DEF6, Tregs were found to express both DEF6 and SWAP-70. Analysis of DKO mice demonstrated that the concomitant absence of these two molecules leads to increased numbers of Tregs, which acquire an effector phenotype in a cell-intrinsic manner. In addition, DKO Tregs exhibit enhanced expression of the Blimp-1-IL-10 axis. Notably, DKO effector Tregs survive and expand as disease progresses. The expansion of DKO Tregs was associated with the upregulation of genes controlling autophagy and was found to be IRF4-dependent. Unlike the remarkable accumulation of most effector Tregs, DKO mice exhibited only a minimal expansion of T_{FR} cells resulting in an imbalanced T_{FH}/T_{FR} ratio over time.

Conclusion:

This work uncovers the existence of mechanisms that, by acting on IRF4, can fine-tune the function and survival of effector Tregs and maximize the fitness of effector Tregs in chronic inflammatory conditions. These studies suggest that, despite the presence of autoimmune features such as dysregulated humoral

responses, the existence of a powerful effector Treg compartment that successfully survives in an unfavorable inflammatory environment can effectively limit disease development. Such a scenario is highly relevant to human SLE whose clinical heterogeneity could be linked, at least in part, to the presence/absence of long-lived effector Tregs.

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Abstract Number: 1752

Characterization of Epitopes Identified with Cerebral Vasculature Injury

Melissa Butts[1], Jess Edison[1], Christopher Tracy[1], Brian Stout[1], Huazhen Chen[2] and Chantal Moratz[2], [1]Rheumatology, Walter Reed National Military Medical Center, Bethesda, MD, [2]Medicine, Uniformed Services University School of Health Sciences, Bethesda, MD
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Background/Purpose: There is an association between natural antibodies, such as anti-phospholipid antibodies, and vasculature injury in stroke and in SLE models of systemic ischemic damage. There is also a correlation between chronic inflammatory micro-environments and long term neuro-degeneration. Preliminary data in our mild traumatic brain injury model demonstrated the development of long term inflammation at the Blood Brain Barrier (BBB) and mild neurocognitive memory defects. The objective of this study is to determine if the chronic inflammatory microenvironment produced in the BBB in our model, was correlated with increasing preferential association between complement and natural antibodies to mediated vascular damage. We utilized a long-term longitudinal study to explore this relationship.

Methods: Multiple HIFU exposure was used to induce cerebral vascular injury. Briefly, the animals were anesthetized with 5% Isoflurane and the scalp region was cleared of fur using Nair. Animals assigned to the HIFU-exposure (3 exposures 24 hours apart) experienced a one-millisecond pulse while sham animals did not. Animals were harvested at a series of time points 2 hours to 30 days post injury. Immunocytochemistry and Immunofluorescence analysis of brain slices was performed to assess vascular integrity and injury.

Results: In the immune competent (C57Bl/6) strain HIFU injury resulted in the activation of the endothelium of the BBB, increased permeability of the BBB to low molecular weight molecules, and deposition of complement C3b, all of which support disruption of endothelial integrity. In longitudinal studies, a sustained neuro-inflammation was evident 30 days after injury and correlated with neuro-cognitive deficits. Initial data has demonstrated increased IgG deposition on the luminal surface of the BBB endothelium immediately after injury and at 30 days post injury. At the 30 day post injury time point there is an increased susceptibility to vascular injury as evidenced by Ferritin deposits within the Virchow-Robin space of the BBB structural unit, specifically in the hippocampus. At early time points, IgG was associated with complement at the BBB, but epitopes associated with natural antibodies were not dominant. By 30 days, there was a preferential association between natural antibodies and complement deposition. Specifically, anti-phospholipid type epitopes were detected.

Conclusion: Preliminary data suggest that anti-phospholipid type natural antibodies have a stronger association with vascular damage at the 30 day time point than other pathogenic type antibodies. We are currently assessing if the anti-phospholipid antibodies are co-localized with ferritin breaches of the BBB. Elucidating the mechanics of vascular injury which results in both sustained neuro-pathology and neuro-cognitive decline would provide insight into the emergence and progression in vascular associated neuro-degeneration. These finding may illuminate a mechanism in Neuropsychiatric Systemic Lupus Erythematous (NPSLE), although there is a correlation of NPSLE with some antibodies, a well-delineated mechanism of how antibody induced cerebral damage occurs has not been defined.

Disclosure: M. Butts, None; **J. Edison**, None; **C. Tracy**, None; **B. Stout**, None; **H. Chen**, None; **C. Moratz**, None.

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Abstract Number: 1753

Response Gene to Complement-32 Promotes Plasma Cell Differentiation and Enhances Lupus-like Chronic Graft Versus Host Disease

Vinh Nguyen[1], Alexandru Tatomir[2], Armugam Mekala[3], Horea Rus[4] and **Violeta Rus**[5], [1]Medicine, University of Maryland Schoole of Medicine, Baltimore, MD, [2]Neurology, University of Maryland School of Medicine, Baltimore, MD, [3]University of Maryland School of Medicine, Baltimore, MD, [4]Neurology, University of Maryland School of Medicine and Veteran Affairs Medical Center, Baltimore, MD, [5]Medicine, University of Maryland School of Medicine and Veteran Affairs Medical Center, Baltimore, MD

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Background/Purpose:

Response Gene to Complement (RGC)-32 is an intracellular protein initially discovered in rat oligodendrocytes in response to complement activation. It plays a role in cell growth and promotes cell cycle activation and Akt phosphorylation. RGC-32 is also a downstream target of TGF-β in fibroblasts and renal proximal tubular cells and plays a role in renal fibrogenesis. In the immune system RGC-32 is expressed by both T and B lymphocyte subsets. Our prior studies have indicated that RGC-32 promotes Th17 differentiation of mouse CD4 T cells and is highly expressed in human IL-17+ CD4 cells. Whether RGC-32 expression in B cells plays a role their activation, differentiation and development of autoimmunity is not known. To address this question we used WT and RGC-32 KO mice to determine whether lack of RGC-32 impairs B cell differentiation and activation and/or alters autoimmune parameters in the Bm12-into-B6 chronic graft versus host disease (cGVHD) model of lupus.

Methods:

Purified B cells from WT or RGC-32 KO mice were cultured with lps, anti-CD40mAb, IL-21 and IL-6, IL-4 or TGFβ and RGC-32 mRNA and protein expression was determined by flow cytometry and RT-PCR. TLR-dependent and T-dependent B cell differentiation to plasma cells (PC) was induced with lps and with CD40mAb plus IL-4, respectively. The number of $CD138^{hi}B220^{lo}$ PC was determined 3 days later. Bm12-into-B6 cGVHD was induced by i.p. injection of $100x10^6$Bm12 splenocytes into WT or RGC-32 KO recipients. B cell parameters of cGVHD including host B cell number and activation, anti-dsDNA Ab production, GC B cell number and proliferation, PC number in spleen and bone marrow (BM), expression of transcription factors IRF4 and Blimp1 were assessed at 2 and 4 weeks by flow cytometry, RT-PCR, ELISA and ELISPOT.

Results:

RGC-32 mRNA was expressed at baseline in B cells and was upregulated by lps, anti-CD40mAb, IL-21 and IL-6. RGC-32KO B cells failed to differentiate normally to PC in vitro as demonstrated by a 2 fold reduction in PC numbers generated after lps and anti-CD40mAb+IL-4 stimulation and impaired upregulation of Prdm1 and IRF4 mRNA. In vivo, mRNA expression of RGC-32 was significantly upregulated in spleen cells from cGVHD mice compared to uninjected WT B6 mice. RGC-32 upregulation was detected in both $B220^+$ B cells and $B220^+$ PNA^+ germinal center (GC) cells. Induction of cGVHD in RGC-32KO hosts resulted in an attenuated autoimmune phenotype as demonstrated by: 1) decreased production of anti-dsDNA autoAb. 2) decreased number and proliferation of GC B cells. 3) decreased number of IgG anti-dsDNA secreting PC in BM and 4) decreased IRF4 and Prdm1 mRNA expression.

Conclusion:

These results suggest that expression of RGC-32 in B cells is critical for optimal GC proliferation, PC differentiation and autoantibody production in a murine model of lupus. These data support the idea that RGC-32 blockade has the potential to attenuate autoimmune parameters of cGVHD and possibly reverse abnormalities in the T and B cell pathways that contribute to lupus pathogenesis. These observations provide a compelling rationale for further investigating the therapeutic potential of RGC-32 blockade in murine and human lupus.

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Abstract Number: 1754

BANK1 Controls the Development of SLE By Modulating TLR7 Signaling and Type I IFN-Induced Translation Initiation Pathway in B Cells

Ying-Yu Wu[1], Ramesh Kumar[2], Harini Bagavant[1] and **Marta E. Alarcon Riquelme**[3], [1]Arthritis and Clinical Immunology, Oklahoma Medical Research Foundation, Oklahoma City, OK, [2]Oklahoma Medical Research Foundation, Oklahoma Cty, OK, [3]Arthritis & Clinical Immunology, Oklahoma Medical Research Foundation, Center for Genomics and Oncological Research Pfizer-University of Granada-Junta de Andalucia, Oklahoma City, OK

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Background/Purpose: BANK1 is a susceptibility gene for SLE, and we have shown that stimulation of TLR9 agonist leads to a reduction in the activation of the translation initiation pathway. Here we investigated the effects of the adaptor *Bank1* in TLR7 signaling using the B6.*Sle1.yaa*mouse, a lupus model that develops disease through exacerbated TLR7 expression.

Methods: Crosses of B6.*Sle1.yaa* with *Bank1*-/-mice were produced and studied for the development of disease and signaling following TLR7 and IFNa stimulation.

Results: Bank1 deficiency maintained several B and myeloid cell phenotypes close to normal wild-type levels. Most striking was the reduction in total serum IgG antibodies, but not of IgM, and reduced serum levels of autoantibodies, IL-6 and BAFF, features accompanied by reduced mortality. Purified B cells from *Bank1* deficient mice had strongly reduced *IFNb*, *Irf7*, *Aicda* and *Stat1* gene expression following TLR7 agonist stimulation. Furthermore, phosphorylation of the transcription factor STAT1 was impaired as was the nuclear translocation of IRF7, a key molecule in TLR7 signaling. As the optimal function of B cells depends on type I interferon, we investigated if *Bank1*deficiency had effects on the IFNAR signaling pathway. We demonstrate that BANK1 controls activation of the eIF4E translation initiation pathway induced by type I IFN, hence controlling interferon-inducible genes.

Conclusion: Our results show that BANK1 controls TLR7 and IFNAR signaling in B cells, modulating transcription and translation initiation events, respectively, and contributing to autoimmune disease development.

Disclosure: Y. Y. Wu, None; **R. Kumar**, None; **H. Bagavant**, None; **M. E. Alarcon Riquelme**, None.

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Abstract Number: 1755

The Lymphotoxin/Megakaryoblastic Leukemia 1/Actin Axis As a Master Regulator of TLR Signaling in Lupus

John D. Mountz[1], Jun Li[2], Jennie Hamilton[3], PingAr Yang[4], Qi Wu[5], Bao Luo[6], Yanna Ding[3], Hao Li[6], David Crossman[7], Erik Malarkey[8], Yong Zhou[2], Yang-Xin Fu[9] and Hui-Chen Hsu[5], [1]Department of Medicine, Clinical Immunology & Rheumatology, University of Alabama at Birmingham and Birmingham VA Medical center, Birmingham, AL, [2]Medicine, University of Alabama at Birmingham, Birmingham, AL, [3]University of Alabama at Birmingham, Birmingham, AL, [4]Department of Medicine, Clinical Immunology & Rheumatology, University of Alabama at Birmingham, Birmingham, AL, [5]Department of Medicine, University of Alabama at Birmingham, Birmingham, AL, [6]Division of Clinical Immunology and Rheumatology, Department of Medicine, University of Alabama at Birmingham, Birmingham, AL, [7]Genetics, University of Alabama at Birmingham, Birmingham, AL, [8]Cell, Development, and Integrated Biology, University of Alabama at Birmingham, Birmingham, AL, [9]Department of Pathology, The University of Chicago, Chicago, IL
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Background/Purpose: Marginal zone macrophages (MZMs) of the spleen are essential for rapid and tolerogenic clearance of apoptotic cells (ACs). MZMs are decreased in two mouse models of lupus and in SLE subject spleens. Absence of lymphotoxin beta receptor (LTβR) signaling in the MZMs in lupus BXD2 mice leads to a defect in megakaryoblastic leukemia 1 (MKL1)/actin polymerization. The purpose of this study was to determine the mechanism underlying the development of inflammatory AC phagocytic MZMs.

Methods: Stimulation of LTβR signaling was carried out *in vitro* with an agonistic anti-LTβR and blocked *in vivo* with a soluble LTβR-Fc. MZMs were analyzed and sorted by flow cytometry. Gene expression analysis was carried out by RT-PCR. Time-lapse imaging was carried out on a Nikon A1R two-photon microscope. ACs were induced by dexamethasone and labeled with DAPI. Actin polymerization was determined using a GFP LifeAct adenovirus transfection of macrophages (Mϕs).

Results: Two-photon live cell imaging revealed defects in actin polymerization and slower cytoplasmic encapsulation of ACs at the surface of Mϕ from BXD2 and B6-*Mkl1*$^{-/-}$ mice. Ingestion of ACs occurred after prolonged membrane interaction (>5 min) with ACs. In contrast, stimulation of BXD2 Mϕ with an agonistic anti-LTβR resulted in strong actin polymerization. These Mϕs exhibited robust proactive degradation of ACs characterized by cytoplasm/actin protrusions, phagocytic cup formation, and digestion of ACs. *In vivo* LTβR signaling blockade of MZMs after administration of LTβR-Fc resulted in an increase in *Il6* and a decrease in *Il10*. There was also a 4-6 fold increase in the expression of serine proteases, normally found in azurophilic granules, including neutrophil elastase (*Elane*), Protenase-3, and Cathepsin G, in MZMs of BXD2 compared to B6 mice. Increases in ELANE activity were observed in BXD2 MZMs following AC phagocytosis or after addition of RNPs but were suppressed by anti-LTβR. Gene analysis shows that there was down-regulation of the intracellular inhibitor of TLR signaling, TRIM30α, in MZMs of BXD2, B6-*Mkl1*$^{-/-}$ or LTβ$^{f/f}$xCD19.Cre mice, compared to that in B6 MZMs. Down-regulation of TRIM30α in MZMs of BXD2 and B6-*Mkl1*$^{-/-}$ was further verified by confocal imaging analysis.

Conclusion: The results show that decreased LTβR signaling in MZMs results in enhanced immunogenic response to ACs via: (1) a defect in actin polymerization and defective AC phagolysosomes formation; (2) a decreased repression of serine proteases that can bind to DNA or RNA protein complexes in the endolysosome to promote inflammatory degradation of ACs that can stimulate TLRs; and (3) a decrease in TRIM30α which is a key inhibitor of downstream TLR signaling from endolysosomes and Mϕ. Since MZMs are essential for tolerogenic uptake of ACs, the work here pinpoints specific cellular mechanistic and molecular defects and suggest novel interventions that may reverse the immunogenic uptake of ACs.

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The Oxidative Burst Mediates Anti-Inflammatory Clearance of Dead Cells in a Mouse Model of SLE and Inflammatory Arthritis

Jonas Hahn[1], Deborah Kienhöfer[1], Luis Munoz[1], Martin Herrmann[2], Gerhard Krönke[3], Rikard Holmdahl[4], Georg Schett[5] and **Markus Hoffmann**[1], [1]Medicine III, Rheumatology and Immunology, University of Erlangen-Nuremberg, Erlangen, Germany, [2]Medicine III, Rheumatology and Immunology, University of Erlangen-Nuremberg, Osterreich, Germany, [3]Internal Medicine 3, University of Erlangen-Nuremberg, Erlangen, Germany, [4]Department of Medical Biochemistry and Biophysics, Karolinska Institutet, Stockholm, Sweden, [5]Department of Internal Medicine 3 and Institute for Clinical Immunology, University of Erlangen-Nuremberg, Erlangen, Germany

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Background/Purpose:

The production of reactive oxygen species (ROS) via the oxidative burst has recently been implicated in regulation of inflammation and protection from arthritis, multiple sclerosis, and psoriasis. The aim of this project was to elucidate the impact of the oxidative burst on lupus-like autoimmunity.

Methods:

The clinical course of pristane-induced lupus (PIL) was compared between WT and ROS-deficient (Ncf1**) mice by analysis of serological markers and organ involvement. *Ex vivo*phagocytosis assays and flow cytometry were employed to analyze uptake and degradation of cell debris. Formation of neutrophil extracellular traps (NETs) was monitored in blood and peritonea. Involvement of the antioxidative response was investigated by qPCR and ChIP.

Results:

Ncf1** mice developed strongly elevated levels of typical lupus-autoantibodies, e.g., anti-dsDNA, anti-histone and anti-Sm/RNP, arthritis, and glomerulonephritis resulting in earlier death. The enhanced inflammation also gives rise to higher serum levels of pro-inflammatory cytokines. Mice with a specific ROS-deficiency in neutrophil granulocytes exhibited an intermediate phenotype. We observed a preferential uptake of dead cell material but not of inert latex beads into inflammatory monocytes and granulocytes, and a dramatically reduced ability to forms NETs in Ncf1** mice. A similar phagocytosis phenotype was observed in patients with SLE. Immunoglobulin G-coating of latex beads significantly enhanced their uptake. Genes related to the antioxidative response dependent on the transcription factor NRF2 were strongly downregulated in Ncf1** mice.

Conclusion:

Our results show that autoimmunity occurring in the ROS-deficient Ncf1** mouse gives rise to exacerbated Rupus. Aberrant phagocytosis in ROS-deficient animals caused by spontaneously occurring autoantibodies to surface molecules of dead cells and a defective regulatory antioxidative response contribute to this phenotype.

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Abstract Number: 1757

Absence of Estrogen Receptor Alpha Is Protective Against Nephrotoxic Serum-Induced Nephritis

Chelsea Corradetti[1], Neelakshi Jog[2], Michael Madaio[3] and **Roberto Caricchio**[4], [1]Temple University, Philadelphia, PA, [2]Rheumatology, Oklahoma Medical Research Foundation, Oklahoma City, OK, [3]Medicine, Medical College of Georgia, Augusta, GA, [4]Medicine, Rheumatology, Temple University, Philadelphia, PA

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Background/Purpose:

Glomerulonephritis (GN) is one of the most serious manifestations of systemic lupus erythematous (SLE). Lupus GN is characterized by severe inflammation and necrosis and it accounts for most morbidity and mortality. Although SLE occurs more often in women, both sexes develop GN and in males often develops earlier and is more severe. There is sex bias in SLE and estrogens may play an important role in GN susceptibility and progression. Interestingly, estrogen receptor alpha (ER-α) in the renal tissue is highly expressed and the renal specific estrogen-induced gene activation is second only to that of reproductive organs. Therefore, we investigated the impact of estrogens on the development of nephritis in both males and female mice by using an inducible model of immune-mediated nephropathy.

Methods: We first investigated the functional status of the immune system in the ER-α KO mice by immunizing them with standard foreign antigen (OVA). We then used the nephrotoxic serum induced nephritis (NTN) model to induce GN in the ER-α KO mice. ER-α WT littermates were used as control. Progression of renal disease was monitored by blood urea nitrogen and body weight. Renal damage was also assessed by histology. Nephrotoxic serum binding and immune complex deposition were determined by immunofluorescence. Quantitative real-time PCR was also performed to measure expression of TNF-α, IL-6, and MCP-1 in the kidneys of KO and WT mice.

Results:

We found that the ER-α KO and WT mice produced similar levels of anti-OVA antibodies upon OVA antigen immunization (p=n.s.). These results suggest that the lack of ER-α does not grossly impair the immune response. We also found that the lack of ER-α protects from NTN as the KO mice have significantly less kidney disease than the WT ($p<0.05$). The most striking differences were less glomerular cellular proliferation and fibrosis. Both sexes were protected albeit the males to a lesser extent. Importantly the NTN model was fully functional in the ER-α KO, as both strains of mice had similar levels of immune complex deposition within the glomeruli; both ER-α KO and WT mice increased the expression of pro-inflammatory cytokines such as TNF-α and IL-6 suggesting that the immune and inflammatory response were similar but that the differences in cellular damage were responsible for the renal protection.

Conclusion: Our results demonstrate that the lack of ER-α allows appropriate immune response but nevertheless protects from NTN, a model of lupus GN. Moreover, our results demonstrate that the protection is secondary to a reduced cellular damage rather than an impairment of the immune system. Interestingly, estrogens influenced the renal outcome also in males albeit to a lesser degree. Based on these results we conclude that estrogens not only play a role in predisposing to SLE but also are important in regulating the cell damage during GN.

Disclosure: C. Corradetti, None; **N. Jog**, None; **M. Madaio**, None; **R. Caricchio**, None.

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Alterations in Nuclear Structure Promote Lupus Autoimmunity in a Mouse Model

Namrata Singh[1], Duncan Johnstone[2], Kayla Martin[3], Italo Tempera[4], Mariana J. Kaplan[5] and Michael Denny[6], [1]Internal Medicine, University of Iowa, Iowa City, IA, [2]Nephrology, Internal Medicine, Temple University School of Medicine, Philadelphia, PA, [3]Microbiology and Immunology, Temple University, Philadelphia, PA, [4]Micorbiology/Immunology, Fels Institute for Cancer Research, Philadelphia, PA, [5]Systemic Autoimmunity Branch, National Institute of Arthritis and Musculoskeletal and Skin Diseases, National Institutes of Health, Bethesda, MD, [6]Internal Medicine, Temple University School of Medicine, Philadelphia, PA
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Background/Purpose: SLE is regarded as a failure of the immune system to maintain tolerance to self-antigens. Despite steady advances defining the importance of inflammatory mediators in the progression and severity of the disease, the underlying mechanisms driving the development of autoimmunity remain unresolved. SLE is characterized by the presence of autoantibodies recognizing components of the cell nucleus. While the contribution of immune system dysfunction to the loss of immunological tolerance is an area of intense investigation, the potential role for alterations in the structure of the nucleus itself has not been considered. The nucleus is stabilized by a network of proteins called lamins, with B-type lamins anchored by associations with Lamin B receptor (Lbr). Lbr spans the inner nuclear membrane and associates with heterochromatin to maintain its distribution at the nuclear membrane margins. Impaired expression of Lbr causes autosomal dominant disruptions in nuclear structure that include the Pelger-Huet Anomaly. In mice, *Lbr* is within lupus susceptibility intervals identified on chromosome 1. Given the role of Lbr in stabilizing nuclear structure and its ability to bind chromatin, we hypothesized

that an autosomal dominant disruption in *Lbr*, would contribute to the development of anti-nuclear autoimmunity when expressed in a lupus-prone genetic background.

Methods: To introduce an autosomal dominant disruption in *Lbr* into a lupus-prone genetic background, c57Bl/6 mice harboring a spontaneous mutation within a splice junction in *Lbr* (B6.Lbr$^{ic/+}$) were crossed with the lupus-prone mouse strain New Zealand White (NZW). The development of autoantibodies and kidney damage was assessed in the (NZW×B6.Lbr^{ic})F_1 offspring.

Results:

Female (NZW×B6.Lbr^{ic})F_1 mice developed splenomegaly and glomerulonephritis with immune complex deposition, perivascular cellular infiltrates, and kidney damage. Titers of anti-chromatin antibodies of the IgG2 subclasses exceeded those of aged female MRL-Fas^{lpr} mice, and autoantibodies recognizing the A-type lamina and histone H3 with covalent modifications associated with gene activation were present. Anti-neutrophil antibodies developed, but the autoreactivity was not directed against myeloperoxidase or proteinase 3, rather it was attributable to anti-calreticulin of the IgM subclass.

Conclusion:

Alterations in nuclear structure contribute to lupus autoimmunity when expressed in a lupus-prone genetic background. Thus, environmental factors that disrupt nuclear architecture, such as viral infection or chemical exposure, may also promote lupus autoimmunity in genetically-predisposed individuals, suggesting a fundamental contribution for cell biology in the development of SLE.

Disclosure: N. Singh, None; **D. Johnstone**, None; **K. Martin**, None; **I. Tempera**, None; **M. J. Kaplan**, None; **M. Denny**, None.

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Abstract Number: 1759

Activation of T-Follicular Helper Cells and B Cells in Ultraviolet Light-Induced Murine Model of Systemic Lupus Erythematosus

Misha Zarbafian[1], Mehran Ghoreishi[2] and Jan Dutz[2], [1]Medicine, University of British Columbia Vancouver Fraser Medical Program, Vancouver, BC, Canada, [2]University of British Columbia Department of Dermatology and Skin Science, Vancouver, BC, Canada
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Background/Purpose: Non-obese diabetic (NOD) mice repeatedly exposed to ultraviolet (UV) light and Toll-like receptor-7 (TLR7) agonist cream (imiquimod) develop lupus-like disease, modeling a possible cutaneous trigger for systemic lupus erythematosus (SLE) in genetically predisposed individuals. T-follicular helper (TFH) cells are known to support B cell maturation in germinal centers, leading to auto-antibody production in the context of SLE. Increased frequency of circulating TFH cells in the peripheral blood of human SLE patients has been associated with more severe disease, characterized by more lupus-associated auto-antibodies and end-organ manifestations. High-mobility group protein B1 (HMGB1) is a pro-inflammatory cytokine, which facilitates auto-antibody production in SLE both locally and systemically. HMGB1 release from the cell nucleus in skin occurs early in sun-induced lesions, and correlates with the progression of SLE disease. We sought to characterize TFH cells and B cells in skin-draining lymph nodes of NOD mice treated with UV and topical imiquimod cream (TLR7 agonist).

Methods: NOD and Balb/C mice received weekly UVB radiation (5000 J/m^2) and 25 µg of topical imiquimod cream. Skin-draining lymph nodes were analyzed by flow cytometry after four treatments to determine the activation status and number of TFH cells and B cells. Serum was collected to measure inflammatory cytokines such as TNFa, IL-6, and IFNg. Extra-nuclear expression of HMGB1 was evaluated in skin samples from both strains after four treatments.

Results: There was expansion of both TFH and B cells, as well as increased expression of the B cell activation marker CD40 in skin-draining lymph nodes of NOD mice following combined UV and imiquimod therapy, in contrast to Balb/C mice. Extra-nuclear expression of HMGB1 was greater in NOD mice, whereas expression in Balb/C mice was largely limited to the nucleus.

Conclusion: Skin-draining lymph node TFH cell expansion is an early event after UV and TLR7 agonist therapy and is correlated with auto-antibody production. HMGB1 redistribution in the skin also correlates with auto-antibody production. Quantification of circulating TFH cells and local HMGB1 expression may serve as markers for predicting SLE onset in genetically predisposed individuals.

Disclosure: M. Zarbafian, None; **M. Ghoreishi**, None; **J. Dutz**, None.

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Abstract Number: 1760

PD-1 Signaling Interferes with OX40 to Alter the Suppressive Function and Proliferation of CD4+ Regulatory T Cells in Lupus Mice

Maida Wong[1] and Bevra H. Hahn[2,3], [1]Division of Rheumatology, Department of Medicine, David Geffen School of Medicine, University of California Los Angeles, Los Angeles, CA, [2]Medicine, UCLA David Geffen School of Medicine, Division of Rheumatology, Los Angeles, CA, [3]Rheumatology, Professor Emeritus, Department of Medicine/Rheumatology, David Geffen School of Medicine UCLA, Los Angeles, CA

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Background/Purpose: In systemic lupus erythematosus (SLE), the dysregulated production of autoantibodies is a consequence of disrupted T cell homeostasis. Programmed death-1 (PD1), a negative regulatory signal in T cells, limits certain T-cell mediated immune responses. Increased PD1 expression on T cells inhibits cell activation and proliferation, and its blockade reinstates immune cell function. Our laboratory has shown that attenuated, but not absent PD1 signaling enables T_{reg} to survive, and suppress helper T cells (T_h) and B cells. These suppressors are designated $PD1^{lo}T_{reg}$. Our gene array data have shown that attenuated PD1 expression in T_{reg} down-regulates several members of the TNF receptor family (TNRF). It has been reported that OX40, a member of the TNRF superfamily, is known to be up-regulated in immune cells from patients with autoimmune diseases. We therefore hypothesize that one mechanism by which PD1 sustains T_{reg} proliferation and suppressive function is by reducing OX40 expression on T_{reg}.

Methods: We treated lupus-prone BWF_1 mice with a neutralizing Ab against PD1 or control isotype-matched IgG intraperitoneally. T_{reg} from the spleens were isolated and cocultured with unmanipulated $CD4^+CD25^-$ T_h and B cells. Expression of OX40 and PD1 on T_{reg} was measured by flow cytometry. The ability of T_{reg} to regulate T_h was assessed by measuring the ratio of T_{reg}: T_h after coculture, with the phenotypes defined as: T_{reg} ($Foxp3^+CD4^+CD25^+CD127^-$), T_{h1} ($CD4^+CD25^-IFN\gamma^+$), T_{h2} ($CD4^+CD25^-IL4^+$), T_{h17} ($CD4^+CD25^-IL17a^+$). Cytokine production of T_{reg} and T_h was measured in the culture media by ELISA. Next, we treated T_{reg} with an agonistic OX40 Ab *in vitro*, and set up the colculture experiments and deterrmine cell proliferation and cytokine production as described above.

Results: OX40 expression was lower in $PD1^{lo}T_{reg}$ from anti-PD1-treated mice when compared to $PD1^{hi}T_{reg}$ from controls. In particular, all $Foxp3^+PD1^{lo}T_{reg}$ have either low or no OX40 expression. T_h was predominantly T_{h2} over T_{h1} and T_{h17} in the coculture with $PD1^{lo}T_{reg}$, with decreased expression of IFN-g and IL-17 in the culture media. When $PD1^{lo}T_{reg}$ were treated with agonistic OX40, their suppressive function was attenuated, but not completely abrogated. Although Foxp3 expression in $PD1^{lo}T_{reg}$ was not significantly diminished, there was decreased production of TGFβ . In the coculture, activation of OX40 was associated with increased proliferation of T_{h1}. However, treating $PD1^-T_{reg}$ with antagonistic OX40 could not restore the suppressivity in T_{reg}.

Conclusion: Effective induction of T_{reg} is associated with low expression of PD1, which permits the cells to survive and perform a cell suppressive function. Attentuated PD-1 expression in T_{reg} reduced OX40 expression on T_{reg}, which helped restore the suppressive capacity and proliferation of T_{reg}. The suppressive function induced by low PD1 expression is influenced by, but not dependent on, low OX40 expression. PD1 and OX40 signaling most likely crosstalk to regulate the suppressive capacity and survival of T_{reg} to achieve peripheral tolerance in SLE but are not the only pathways involved.

Disclosure: M. Wong, None; **B. H. Hahn**, Merck, Exxagen, Biogen Idec, Bristol Myers Squibb, 5.

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Abstract Number: 1762

Reciprocal Roles of Intestinal Microbiota in the Pathogenesis of Organ-Specific Autoimmune Diseases in a Lymphopenia-Induced Autoimmunity Mouse Model

Toshiki Eri[1], Kimito Kawahata[2], Ei Bannai[1], Takeyuki Kanzaki[3], Lisa Akahira[1], Kazuya Michishita[1] and Kazuhiko Yamamoto[1], [1]Department of Allergy and Rheumatology, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan, [2]Department of Rheumatology, Graduate School of Medical and Dental Sciences, Tokyo Medical and Dental University (TMDU), Tokyo, Japan, [3]Internal Medicine, Yamanashi Prefectural Central Hospital, Yamanashi, Japan

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Background/Purpose: Past studies reported lymphopenia mouse transfer model which transfer $CD4^+CD25^-$ cells from wild-type BALB/c mouse into athymic nude BALB/c mice produce lupus-like systemic autoantibodies and develop multiple organ-specific autoimmune diseases. Previously, we reported that transferred T cells undergo homeostatic proliferation and differentiate into follicular helper T cells under the presence of intestinal microbiota, which promote germinal center formation and autoantibody production within 4 weeks. Next, we would like to investigate the roles of intestinal microbiota in the pathogenesis of long-term organ-specific autoimmunity in this mouse model.

Methods: $CD4^+CD25^-$ cells taken from spleen of wild-type BALB/c mouse were adoptively injected into nude BALB/c mice. Some recipient mice were orally administrated broad-spectrum antibiotics including ciprofloxacin, imipenem, metronidazole and vancomycin in drinking water. Immunofluorescence, and ELISA were performed to detect ANAs and anti-parietal cell antibodies. Histopathological investigation was performed 5 month after the transfer.

Results: T cell-transferred nude mice developed gastritis, colitis, sialoadenitis and oophoritis at high rates in 5 months. Combination of above 4 antibiotics decreased the incidence of gastritis, colitis and oophoritis, but exacerbated sialoadenitis. Single vancomycin administration inhibited the colitis and exacerbated the others.

Conclusion: Depletion or alteration of intestinal microbiota can ameliorate or exacerbate organ-specific autoimmunity in a lymphopenia-induced autoimmunity mouse model. This result should be noted when we search for the novel microbiological therapeutic approach to autoimmune diseases. Further investigation is needed to detect specific microorganisms involved in the inflammation of each organ.

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Abstract Number: 1763

Neutrophil Netosis Formation during the UVB Induced-Skin Inflammation

Ming-Lin Liu[1,2], Meena Sharma[1,3], Shwetapadma Sahu[4,5] and Victoria Werth[4,6], [1]Department of Dermatology, University of Pennsylvania, Philadelphia, PA, [2]Department of Dermatology,, Philadelphia V.A. Medical Center, Philadelphia, PA, [3]Department of Dermatology, Philadelphia V.A. Medical Center, Philadelphia, PA, [4]Dermatology, University of Pennsylvania, Philadelphia, PA, [5]Philadelphia V.A. Medical Center, Philadelphia, PA, [6]Dermatology, Philadelphia V.A. Medical Center, Philadelphia, PA
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Background/Purpose:

Excessive exposure to sunlight, particularly ultraviolet B (UVB), induces autoimmune skin inflammation and other skin diseases. Although UVB mainly causes damage to the epidermis, photodamage is followed by inflammatory responses, which can be highly detrimental. Skin inflammation in turn can further exacerbate photodamage and, if recurring or long-lasting, can induce pathogenic alterations. Previous studies from ours and other groups showed that the immediate response in the skin to UVB exposure is to induce the release of TNFα and other inflammatory cytokines from keratinocytes in the epidermis. Neutrophils are the most common circulating leukocyte. Similar to other injury or acute inflammation, neutrophils are also the earliest immune cells recruited to the site of photodamage in response to UVB exposure, followed by the monocyte/macrophages and T lymphocytes. However, little is known about the role of neutrophils in UVB-induced skin inflammation, and previous photobiology studies have mainly focused on the role of other cell types on UVB-induced detrimental effects in skin. Neutrophil NETosis, a novel type of neutrophil cell death, releases neutrophil extracellular traps (NETs) that have been shown to be important in autoimmune inflammation. Given that the induction of TNFα and infiltration of neutrophils both appear within hours after UVB exposure, and neutrophils are unable to become NETotic in TNFα KO mice, we sought to determine whether UVB exposure can induce neutrophil NETosis in vivo.

Methods:

Human primary neutrophils were treated without or with TNFα to study the in vitro effects of TNFα on neutrophil NETosis. To explore the effects of UVB exposure on neutrophil NETosis in vivo during the skin inflammatory responses, we exposed C57/BL6 wild-type and *MRL/lpr* lupus prone mice to UVB according to our published protocol with minor modification.

Results:

In the in vitro study, we found the increased neutrophil NETosis when we treated human primary neutrophils with TNFα, a proinflammatory cytokine that can be induced in UVB-exposed mice. In the in vivo study, our preliminary experiments showed that UVB exposure (250 mJ/cm^2/day for 5 consecutive days) of female wild-type mice significantly induces skin inflammation with infiltration of inflammatory cells, and many of the infiltrated neutrophils become

NETotic in the inflamed skin of the UVB exposed WT mice as compared to sham WT mice without UVB exposure. Similarly, we found that UVB exposure (100 mJ/cm^2/day for 10 consecutive days) can also induce neutrophil NETosis in UVB-irradiated *MRL/lpr* lupus-prone mice

Conclusion:

Our studies indicate that UVB exposure of mice can induce skin inflammation with increased neutrophil NETosis, possibly through the induction of the proinflammatory cytokine, TNFα. Neutrophil NETosis may be involved in UVB-induced skin inflammation.

Disclosure: M. L. Liu, None; **M. Sharma**, None; **S. Sahu**, None; **V. Werth**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/neutrophil-netosis-formation-during-the-uvb-induced-skin-inflammation

Abstract Number: 1764

Type 1 Interferon in the Skin Stimulated By Ultraviolet B Light Generates Immune Suppression Mediated By Idoleamine 2,3-Dioxygenase 1

Clayton Sontheimer[1] and Keith B. Elkon[2], [1]Pediatric Rheumatology, University of Washington, Seattle, WA, [2]Division of Rheumatology, University of Washington, Seattle, WA

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SESSION INFORMATION

Session Date: Monday, November 9, 2015

Session Title: Systemic Lupus Erythematosus - Animal Models Poster I

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose:

Photosensitivity is a common symptom in patients with systemic lupus erythematosus (SLE) and lupus skin lesions show local Type 1 Interferon (IFN-I) profiles similar to that seen in the blood. The pathogenic effect of ultraviolet light (UV) in SLE stands in contrast to the immunosuppressive effects of UV in the normal host, and UV light is used to treat various skin diseases such as psoriasis. Differences in the mechanisms linking UV light to immune suppression versus inflammation and cutaneous flares of lupus are not well understood. Here, we asked whether, and under what conditions, repetitive UVB-exposure induces IFN-I and examined what its biological effects were in the skin in the normal host.

Methods:

Shaved C57BL/6 (B6) and IFNAR KO (B6 background) mice were irradiated with narrowband UVB at 100 mJ/cm^2/day for 5 consecutive days. To inhibit idoleamine 2,3-dioxygenase 1 (IDO1) *in vivo*,1-Methyl-d-tryptophan (1-MT) was added to drinking water (2 mg/mL) and fed to mice *ad libitum*beginning 3 days prior to irradiation until experiment end. Serial punch biopsies (6 mm) were obtained at 3, 24, and 72 hrs following UVB exposure. Skin immune cell populations were analyzed by flow cytometry using CD45, CD11b, Ly6C, Ly6G, MHC II, CD64, and CD3. Skin samples were examined for mRNA expression by QPCR of pro-inflammatory cytokines and Interferon Stimulated Genes (ISG), and skin samples were analyzed histologically by H&E and for IDO1 expression by immunofluorescence

Results:

Repeated UVB exposure in normal wild-type B6 mice induced a modest IFN-I skin response with bimodal peaks at 3 and 72 hrs when compared to mice receiving a single UVB dose and non-irradiated control mice. Surprisingly, UVB-irradiated IFNAR KO mice that were unable to respond to IFN-I, had increased levels of pro-inflammatory cytokines such as TNF and IL-6 at 3 and 24 hr time points and had increased levels of inflammation by pathology scores. These findings suggest a protective role for IFN-I. Since IDO1 is an ISG and a potent suppressor of inflammation, we examined IDO1 expression following UVB. Significantly, UVB induced expression of IDO1 in the skin in B6 but not IFNAR KO mice. Consistent with this finding, inhibition of IDO1 by 1-MT treatment in B6 mice caused increased cellular infiltration, worsened histologic appearance, and increased pro-inflammatory cytokines similar to that seen in IFNAR KO mice. Infiltrating dendritic cells in IDO1-inhibited mice had decreased IL-10 levels compared to B6 mice. IDO1 inhibition in IFNAR KO mice did not alter UVB-induced inflammation consistent with IFN-I and IDO1 being in the same pathway.

Conclusion:

In the normal host, repeated doses of UVB induces an IFN-I response in the skin that attenuates pro-inflammatory signals and limits cellular recruitment. Immunosuppression is at least in part mediated though expression and activity of IDO1. This establishes a unique role for IFN-induced IDO1 in promoting the protective effects of UVB in healthy individuals. Loss of this pathway may contribute to the enhanced UVB response as observed in lupus photosensitivity.

Disclosure: C. Sontheimer, None; **K. B. Elkon**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/type-1-interferon-in-the-skin-stimulated-by-ultraviolet-b-light-generates-immune-suppression-mediated-by-idoleamine-23-dioxygenase-1

Abstract Number: 1765

MiR155 Deficient Mice Show Reduced Disease Severity in Pristane-Induced Lupus

Harald Leiss[1], Wilhelm Salzberger[2], Barbara Schwarzecker[3], Irina Gessl[1], Nicolas Kozakowski[4], Stephan Blüml[5], Antonia Puchner[1], Birgit Niederreiter[6], Carl-Walter Steiner[2], Josef S. Smolen[7] and Georg H. Stummvoll[2], [1]Department of Rheumatology, Medical University of Vienna, Vienna, Austria, [2]Rheumatology, Medical University of Vienna, Vienna, Austria, [3]Department of Internal Medicine III, Division of Rheumatology, Medical University of Vienna, Vienna, Austria, [4]Department of Pathology, Medical University of Vienna, Vienna, Austria, [5]Division of Rheumatology, Medical University of Vienna, Vienna, Austria, [6]Rheumatology, Internal Medicine III, Medical University of Vienna, Vienna, Austria, [7]Division of Rheumatology, Department of Internal Medicine III, Medical University of Vienna, Vienna, Austria

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Background/Purpose:

MicroRNAs (miRs) are an important class of regulators of gene expression that are associated with a variety of biological functions. Deregulation of endogenous miR155 was observed in many autoimmune conditions, including SLE. We herein examine the role of miR155 in the development of systemic manifestations in murine pristane induced lupus by evaluating the severity of organ involvement and assessing serum antibody-levels and T helper cell homeostasis.

Methods:

MiR155-deficient (miR155-PIL) and C57/Bl6 (WT-PIL) mice were injected i.p. with 0.5ml of pristane or PBS as control (WT-PBS). In order to observe the effects of miR155 deficiency in fully developed SLE, we analyzed the mice 8 months after induction.

A blinded specialist appraised histological features of GN using the composite kidney biopsy score (KBS). Histological features of pneumonitis were quantified by an image analysis system: Lungs were scored for the severity of perivascular inflammation by analyzing the numbers of affected vessels and the area of the inflammatory infiltrate. In order to assess the composition of these infiltrates, specimens were stained with B220 (B), CD3 (T), Neu7/4 (neutrophils) and F4/80 (macrophages) and analyzed by cell-identification algorithms for nuclear segmentation (HistoQuest®).

Anti-dsDNA, anti-histone and anti-chromatin antibodies (abs) were measured by ELISA.

Lymphocytes were isolated from spleens and analyzed separately for each mouse by standard FACS procedures. For analysis of the Th1, 2 or 17 subsets, respectively, cells were re-stimulated *in vivo*with anti-CD3 and anti-CD28abs.

Results:

Lungs were affected in both pristane-treated groups, but not in controls. MiR155-PIL had reduced lupus severity as indicated by significantly decreased perivascular inflammatory area with B cells being the most prominent inflammatory cell type in the HistoQuest analysis. Without showing clinical abnormalities WT-PIL had a more severe renal involvement in the kidney biopsy score than miR-PIL. Corresponding with reduced severity in organ involvement, miR155-PIL had lower serum levels of anti-dsDNA, anti-histone and anti-chromatin-abs, decreased frequencies of $CD4^+$ cells (14.24 ± 0.7587 vs. 18.04 ± 1.075, p=0.01) and slightly lower frequencies of activated $CD4^+CD25^+Foxp3^-$ cells (1.539 ± 0.1279 vs. 1.838 ± 0.2259, p=ns.). Interestingly, also frequencies of $CD4^+CD25^+Foxp3^+$ regulatory T cells were lower in Mir155-PIL (1.689 ± 0.1388 vs. 2.375 ± 0.2320, p=0.03). Upon restimulation, $CD4^+$cells showed a more pronounced Th2 and Th17 response in WT-PIL, but no significant differences in Th1 phenotype.

Conclusion:

MiR155 deficiency in PIL mice did not prevent the development of disease, but was associated with less severe lung and kidney involvement, lower serum auto-abs levels and lower Th17 and Th2 frequencies when analyzed in fully established PIL after 8 months. Thus, antagonisation of miR155 might be a beneficial future approach in treating SLE.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/mir155-deficient-mice-show-reduced-disease-severity-in-pristane-induced-lupus

Abstract Number: 1766

HPV Vaccination of Nzbxw/F1 Mice

Maria Teresa Arango[1], Lucija Tomljenovic[2], Miri Blank[1] and **Yehuda Shoenfeld**[3], [1]Sheba Medical Center, Zabludowicz Center for Autoimmune Diseases, affiliated to Sackler Faculty of Medicine, Tel-Aviv University, Ramat Gan, Israel, [2]University of British Columbia, Neural Dynamics Research Group, Department of Ophthalmology and Visual Sciences, Vancouver, BC, Canada, [3]Sheba Medical Center, Zabludowicz Center for Autoimmune Diseases, affiliated to affiliated to Sackler Faculty of Medicine, Tel-Aviv University, Ramat Gan, Israel
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Background/Purpose:

Human-papilloma virus vaccine (HPVv) is currently used worldwide. Still this vaccine has been linked to a variety of neurological and autoimmune manifestations. For instance, case series have document adverse events related to the vaccination in systemic lupus erythematosus (SLE). Moreover, the HPVv contains aluminum hydroxide as adjuvant which has been also associated with neurological adverse events. Therefore, our goal was to evaluate the effects of immunization with HPVv or Alum in SLE prone mice.

Methods:

Three groups of NZB/W F_1 mice were vaccinated with HPVv (Gardasil), Aluminum hydroxide (Alum) or the vehicle at 6 weeks of age. The mice received three injections equivalent to the human dose. Mice were followed for lupus and behavior parameters, including anti-dsDNA antibodies titers, urine protein levels, immunoglobulin deposited in the kidney mesangium, behavioral and neurocognitive functions (i.e. novel object recognition, staircase, Y-maze, rotarod and the forced swimming tests).

Results:

Mice immunized with HPVv had higher titers of anti-dsDNA antibodies earlier as well as accelerated proteinuria between the age of 20 to 24 weeks ($p<0.05$) compared with vehicle and alum groups. Similarly, we observed a trend in long and short term memory deficiency following immunization with HPVv. Interestingly, the mice did not show any motor involvement as in the roatorod all the animals had good performance; however in the FST mice immunized with HPVv were immobile for a longer time in comparison to Alum and vehicle which indicates depressive like behavior.

Conclusion:

We demonstrated that immunization with the HPVv accelerates the onset of renal disease in lupus mice. Likewise, we showed that vaccine together with its adjuvant can affect behavioral and neurocognitive functions in particular accelerating the appearance of depressive like behavior.

Disclosure: M. T. Arango, None; **L. Tomljenovic**, None; **M. Blank**, None; **Y. Shoenfeld**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/hpv-vaccination-of-nzbxwf1-mice

Abstract Number: 1767

Noninvasive Assessment of Macrophage Activation in Experimental Glomerulonephritis Using Optical Imaging with Near-Infrared Light Serves As a Surrogate of Disease Activity

Sebastian Braehler[1], Dongyue Huang[2], Matthew Cheung[2], Walter Akers[3] and **Alfred Kim**[2], [1]Pathology & Immunology, Washington University School of Medicine, Saint Louis, MO, [2]Rheumatology, Washington University School of Medicine, Saint Louis, MO, [3]Mallinckrodt Institute of Radiology, Washington University School of Medicine, Saint Louis, MO
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Background/Purpose: Glomerulonephritis (GN) represents a major cause of morbidity & mortality. The standard for diagnosing GN is through renal biopsy, but this is not performed uniformly across many centers. There is an unmet need to identify a noninvasive approach for recognizing GN. Recent advances in deep tissue imaging using probes detected by nearinfrared (NIR) wavelengths have enabled the noninvasive probing of biologic activity. Macrophage infiltration of the kidney is observed in early GN and once activated, express the cysteine protease cathepsin B. Thus, renal macrophage activation can be assessed using an NIR probe that becomes fluorescent upon cleavage by cathepsin B. We tested the ability of using NIR optical imaging to assess renal macrophage activation as a noninvasive marker for early-stage GN.

Methods: GN was induced in 129 mice by nephrotoxic serum (NTS) delivered intravenously (IV). Proteinuria was assessed using albumin ELISA &

chromogenic creatinine assay. H&E and PAS stained slides of mouse kidneys were observed using light microscopy. Presence of renal macrophages was confirmed using FACS. NIR optical imaging of anesthetized mice was performed following IV administration of a cleavable sensor for cathepsin B & fluorescence intensity of kidney regions quantified.

Results: In mice with uninflamed kidneys, we confirmed the paucity of renal macrophages. Accordingly, there was minimal renal fluorescence signal as determined by fluorescent molecular imaging of cathepsin B activity. 3 days post-NTS administration, we observed a massive influx of macrophages into the kidney, along with nephrotic range proteinuria. This correlated with a significant increase in renal fluorescence intensity signal in NTS mice compared to control mice.

Conclusion: Induction of GN by NTS caused significant macrophage infiltration, which was detected noninvasively by a cathepsin B-activatable probe and NIR optical imaging. These data establish the proof-of-principle that NIR optical imaging may represent a translatable approach to establishing early stages of GN.

Disclosure: S. Braehler, None; **D. Huang**, None; **M. Cheung**, None; **W. Akers**, None; **A. Kim**, Kypha, Inc., 2,Amgen, Janssen, Pfizer, 5.

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Abstract Number: 1768

Improved Tissue Clearing and 2-Photon Imaging of Mouse Kidneys Reveals Immune Cell Architecture in Nephrotoxic Nephritis

Matthew Cheung, Dongyue Huang and **Alfred Kim**, Rheumatology, Washington University School of Medicine, Saint Louis, MO
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Background/Purpose: Tissue clearing approaches such as CLARITY renders tissue transparent, and in combination with two-photon microscopy, enables microscopic visualization deep internal structures within unaltered organs. These cutting edge approaches have drastically improved the understanding of cellular circuits in the brain. However, application of this approach has only recently been described for the kidney. Here, we clear mouse kidneys to better understand the immune cell architecture following induction of nephrotoxic nephritis (NTN) using a modified lipid removal approach that also worked for human kidney fragments.

Methods: 129 mice were injected intravenously with nephrotoxic serum to induce NTN. Mice were perfused with an acrylamide monomer solution to form the basis of the hydrogel. Lipid removal was accomplished using 8% sodium dodecyl sulfate (SDS). An aminoalcohol solution was used to quench light absorbing heme in red blood cells trapped within the tissue. Cleared mouse kidneys were stained with antibodies specific for B cells, T cells, macrophages, and dendritic cells (DCs). Human kidney fragments were incubated in acrylamide monomer solution, then cleared as mentioned above. Cleared tissue was imaged using two-photon microscopy.

Results: Compared to previously published protocols, perfusion of acrylamide monomers into mice significantly accelerated the tissue clearing process. Enhanced tissue clearing was observed when we incubated kidneys in aminoalcohols. We observed vast networks of lymphocytes, macrophages, and DCs in cleared NTN kidneys compared to control kidneys. Human kidneys also were cleared using this approach, and we noted DC networks in healthy donor controls.

Conclusion: We identified a new protocol that enhanced and accelerated tissue clearing in mouse and human kidneys. Using this approach, we found elaborate networks of lymphocytes and monocyte-derived cells in NTN mouse kidneys. We also observed DC networks in healthy human kidney donor fragments. These data demonstrate the utility of tissue clearing in evaluating cellular architecture in mouse and human kidneys.

Disclosure: M. Cheung, None; **D. Huang**, None; **A. Kim**, Kypha, Inc., 2,Amgen, Janssen, Pfizer, 5.

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Abstract Number: 1769

Role of Topical Administration of Peptidylarginine Deiminase Inhibitors in Murine Lupus

Erica Moore[1], Huw Lewis[2], Carolyne K. Smith[1], Venkataraman Subramaniam[3], Victoria Hoffmann[4], Paul Thompson[5] and Mariana J. Kaplan[1], [1]Systemic Autoimmunity Branch, National Institute of Arthritis and Musculoskeletal and Skin Diseases, National Institutes of Health, Bethesda, MD, [2]Immuno Inflammation, GSK, Stevenage, United Kingdom, [3]University of Massachusetts, Boston, MA, [4]ORS, National Institutes of Health, Bethesda, MD, [5]University of Massachusetts, Worcester, MA

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Background/Purpose: Peptidylarginine deiminases (PADs), specifically PAD4, have recently been implicated in the pathogenesis of systemic lupus erythematosus (SLE) through their role in citrullinating histones in myeloid cells and promoting neutrophil extracellular trap (NET) formation. Systemic administration of the pan-PAD inhibitors Cl-amidine and BB-Cl-amidine were previously shown to abrogate lupus manifestations and vascular damage in various murine models of SLE, including improvements in skin disease in the MRL/*lpr* model. Whether topical administration of PAD inhibitors can modulate skin involvement in murine lupus once disease is clinically apparent, without promoting other systemic effects, remains to be determined.

Methods: MRL/lpr mice received topical administration of either vehicle, the pan-PAD irreversible inhibitor Cl-amidine or the PAD4-specific reversible inhibitor GSK484 twice daily at 20 mg/kg, upon the development of skin rash. Only affected skin areas were treated. Mice were euthanized at 17 weeks of age. Autoantibodies were quantified by ELISA. Urinary albumin:creatinine ratios were calculated. Cell subsets in the spleen were quantified by flow cytometry and bone marrow NETosis was measured by fluorescent microscopy.

Results: Upon development of facial alopecia, treament with topical Cl-amidine and GSK484 induced an initial improvement in the area and severity of the lesions compared to the vehicle-treated mice. However, the skin effects observed in the GSK484-treated mice were transient, whereas the Cl-amidine treated mice continued improving to the point that no facial alopecia could be detected at euthanasia. By histology, no mice treated with Cl-amidine developed ulcers, while 25% of GSK484 and vehicle-treated mice did. Otherwise, preliminary histology analysis showed that skin inflammatory scoring was not statistically different between groups. Further, total body, spleen or lymph node weight did not differ among the 3 groups. Skin topical treatment did not modify bone marrow NETosis or circulating autoantibodies. Analysis of splenic immune cell subsets revealed that Cl-amidine-treated mice displayed significant decreases in CD4+ T cells and significant increases in neutrophils.There were no significant differences between GSK484 and vehicle-treated mice in any systemic features.Topical administration was well tolerated by mice.

Conclusion: Topical administration of pan-PAD inhibitors may modulate skin disease in lupus animal models. Future studies should further assess the role of topical PAD inhibition in SLE. This study supports a putative role for PAD inhibition as a therapeutic approach in this disease.

Disclosure: E. Moore, None; **H. Lewis**, GSK, 3; **C. K. Smith**, None; **V. Subramaniam**, None; **V. Hoffmann**, None; **P. Thompson**, Padlock Therapeutics, 9; **M. J. Kaplan**, Padlock, 9.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/role-of-topical-administration-of-peptidylarginine-deiminase-inhibitors-in-murine-lupus

Abstract Number: 1770

A New Perspective in Extracorporeal Immunotherapy of Systemic Lupus Erythematosus: Dnase I-Based Blood Perfusion Experiment Using Rat Model

Ekaterina Simakova, Andrey Trofimenko, Ilya Gontar and Irina Zborovskaya, Research Institute of Clinical and Experimental Rheumatology, Volgograd, Russia

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Session Time: 9:00AM-11:00AM

Background/Purpose: DNA, nucleosomes, and other deoxyribonucleoproteins (DNP) are currently believed to be the key autoantigens in SLE. However, these extracellular DNP itself appear to be just a cellular debris without any essential function. This paradox could open up a potential for degradation of the autoantigen and anti-dsDNA-containing ICs. We were to evaluate efficacy and safety of experimental in vivo blood perfusion through DNase I-containing magnetic beads under preliminary short-term examination using rat model of SLE-like alterations of DNP elimination.

Methods: In the experiments we used 20 female Wistar rats (50-54 weeks), randomized in 2 groups. Precalculated group size was 10 rats for each group. All the experimental protocols fulfilled the Declaration of Helsinki of the World Medical Association. The SLE-like disorders of DNP elimination were simulated by method of N. Jiang et al (2003) which was followed by intravenous injection of anti-dsDNA. Magnetic beads were synthesized using the emulsion polymerization technique. In the experimental group after preliminary heparinization blood was perfused through mini column with DNase I-containing magnetic beads (0.2 ml). Beads for the placebo group didn't contain any active substance. Titers of IgG deposited in rat kidneys (IgG_f) were measured by direct immunofluorescence on kidney cryoslices, serum circulating immune complexes (CIC) by polyethylene glycol precipitation assay, and plasma DNA by fluorimetry with PicoGreen. serum anti-dsDNA, CBC, total plasma protein, plasma creatinine, ALT, and AST were determined using conventional methods. All these measurements except IgG_fwere performed before and after perfusion.

Results: There were no significant differences between experimental and placebo groups in the initial marker means. We revealed distinct differences

between the experimental and placebo control groups in DNA ($p<0.001$) and CIC concentrations ($p<0.001$) after the perfusion. Geometric mean of IgG_f titer was significantly higher in placebo perfusion group comparing to perfusion through DNase I-containing beads ($p=0.002$). After the perfusion serum creatinine, being initially increased, demonstrated significant lowering in the experimental group comparing to placebo ($p<0.001$). Other markers didn't reveal any significant changes in both groups.

Conclusion: We have demonstrated clear efficacy of the extracorporeal perfusion in vivo for preventing kidney damage by diminishing of circulating DNA and CIC. As we speculated, the modeling protocol simulates not only glomerular deposition of DNA-containing immune complexes, but also induced filtration disorder. Lowering of DNA and DNA-containing immune complexes by the perfusion could diminish the extent of kidney damage. There was no blood cell destruction or hepatotoxicity during our experiment.

Disclosure: E. Simakova, None; **A. Trofimenko**, None; **I. Gontar**, None; **I. Zborovskaya**, None.

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Abstract Number: 1771

Blockade of Immune Complex-Mediated Glomerulonephritis By Highly Selective Inhibition of Bruton's Tyrosine Kinase

Samantha Chalmers[1], Jessica Doerner[2], Todd Bosanac[3], Sara Khalil[3], Dustin Smith[3], Christian Harcken[3], Janice Dimock[3], Evan Der[2], Leal Herlitz[4], Deborah Webb[3], Elise Seccareccia[3], Jay Fine[3], Elliott Klein[3], Meera Ramanujam[3] and Chaim Putterman[5], [1]Microbiology and Immunology, Albert Einstein College of Medicine, Bronx, NY, [2]Albert Einstein College of Medicine, Bronx, NY, [3]Boehringer Ingelheim Pharmaceuticals Inc., Ridgefield, CT, [4]Cleveland Clinic, Cleveland, OH, [5]Division of Rheumatology, Albert Einstein College of Medicine, Bronx, NY

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Background/Purpose:

Renal disease with loss of organ function results in significant morbidity and mortality in SLE. In the kidneys of affected patients, autoantibody-containing immune complexes (ICs) trigger pathological changes via activation of complement cascades and Fc receptors on resident and infiltrating cells. Bruton's tyrosine kinase (BTK) is a tyrosine kinase important for B cell development, Fc receptor signaling, and macrophage polarization. In this study, we explore the role of BTK in the pathogenesis of nephritis in an inducible model of lupus nephritis (LN).

Methods:

We investigated the effects of a novel, highly selective and potent (mouse whole blood CD69 IC_{50}= 13±2 nM) BTK inhibitor, BI-BTK-1 (Boehringer Ingelheim), in female 129 sv/J mice (10 weeks of age) injected with nephrotoxic serum (NTS), an experimental model which closely mimics LN. Mice pre-immunized with rabbit IgG (Day 0) were administered NTS containing rabbit anti-mouse glomerular antibodies (Day 5), inducing a severe IC-mediated crescentic glomerulonephritis. Mice were treated once daily with vehicle alone or BI-BTK-1 (0.3-10 mg/kg, n=16/group), beginning on Day 4. In addition, mice that did not receive the NTS transfer were used as healthy controls.

Results:

NTS-challenged mice treated with BI-BTK-1 exhibited a statistically significant, dose responsive protection from kidney disease compared to control treated mice, despite equal levels of glomerular IgG deposition and mouse anti-rabbit IgG in all experimental groups. Compared to control treated mice, NTS-challenged mice treated with 10 mg/kg BI-BTK-1 had significantly less proteinuria (1220 mg/dl vs 10 mg/dl, respectively, $p<0.0005$), serum creatinine (0.74 mg/dl vs 0.48 mg/dl, respectively, $p<0.03$), and BUN (82 mg/dl vs 25 mg/dl, respectively, $p<0.03$) (Day 11). Histology assessment confirmed marked renal protection in the BI-BTK-1 treatment groups, as evidenced by significantly less immune deposition ($p<0.0001$), endocapillary proliferation ($p<0.0001$), glomerular crescent formation ($p<0.0001$), interstitial inflammation ($p<0.002$), and tubular casts/dilatation ($p<0.0001$). Flow cytometry analysis showed decreased recruitment of inflammatory monocytes from the splenic reservoir in BI-BTK-1 treated mice. Furthermore, serum profiling and kidney gene expression analyses revealed that BTK inhibition was associated with a significant decrease in the levels of key LN-relevant inflammatory cytokines and chemokines (e.g. MIP-1a, MCP-1 and CSF-1).

Conclusion:

Our results suggest an important role for BTK activation in myeloid cells in the pathogenesis of immune complex-mediated nephritis. Studies to examine the effect of treatment initiation after the development of nephritis are now in progress. Taken together with previously published studies, these findings further strengthen the rationale for selective BTK inhibition as a promising approach to the treatment of LN.

Disclosure: S. Chalmers, None; **J. Doerner**, None; **T. Bosanac**, Boehringer Ingelheim, 3; **S. Khalil**, Boehringer Ingelheim, 3; **D. Smith**, Boehringer Ingelheim, 3; **C. Harcken**, Boehringer Ingelheim, 3; **J. Dimock**, Boehringer Ingelheim, 3; **E. Der**, None; **L. Herlitz**, None; **D. Webb**, Boehringer Ingelheim, 3; **E. Seccareccia**, Boehringer Ingelheim, 3; **J. Fine**, Boehringer Ingelheim, 3; **E. Klein**, Boehringer Ingelheim, 3; **M. Ramanujam**, Boehringer Ingelheim, 3;

Abstract Number: 1772

Anti-Pentraxin 3 Antibodies Ameliorate Disease Manifestations and Lupus-like Nephritis in New Zealand Black/New Zealand White F1 Mice

Mariele Gatto[1], Nicola Bassi[1], Anna Ghirardello[1], Roberto Luisetto[1], Silvano Bettio[1], Luca Iaccarino[1], Leonardo Punzi[2] and Andrea Doria[2], [1]Department of Medicine-DIMED, University of Padova, Padova, Italy, [2]Department of Medicine - DIMED, University of Padova, Padova, Italy

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Session Time: 9:00AM-11:00AM

Background/Purpose: Pentraxin 3 (PTX3) is an acute-phase protein released by different cell types including renal epithelial cells and immune-competent cells. PTX3 is able to either dampen or fuel inflammation through binding of apoptotic cells and complement fragment 1 (C1q).

Anti-dsDNA and anti-C1q antibodies are associated with lupus glomerulonephritis (LGN). By contrast, we have recently demonstrated a negative association between anti-PTX3 antibodies and LGN and a direct correlation between PTX3 renal staining and proteinuria in SLE patients.

Hereby we aim at exploring effects of anti-PTX3 antibodies in a murine model of SLE, focusing on lupus-like nephritis.

Methods: Thirty New Zealand Black/White (NZB/NZW F1) mice were split into 3 groups of 10 mice each and intraperitoneally injected with 100 µg of PTX3 in 100 µl of alum and 100 µl of phosphate buffer saline (PBS) (group 1), 100 µl of alum and 100 µl of PBS (group 2) or 200 µl of PBS (group 3), 3 times 3 weeks apart from the 11^{th} week of age, until natural death.

We analyzed titers and time of occurrence of anti-PTX3, anti-dsDNA and anti-C1q antibodies by monthly blood sampling since week 11. Antibody serum levels were evaluated by standardized home-made ELISA and expressed as the median (min-max) of the mean optical density of the double of every serum.

Proteinuria was weekly examined by multireactive strips (Siemens). Survival and proteinuria-free survival (<300 mg/dl) were evaluated according to Kaplan-Meier method.

Kidneys, lungs, liver and spleen were harvested at death for histological analysis. Expression of collagen (Coll)-IV and TGF-β mRNA was evaluated on kidney specimens by spectrophotometric analysis.

IBM SPSS Statistics 22 for Windows software (IBM SPSS Inc., USA) was used for statistical analysis.

The study was approved by the National Institutional Animal Care and Use Committee.

Results: Serum autoantibody and proteinuria levels are reported in Table 1. Only group 1 mice developed anti-PTX3 antibodies. Anti-dsDNA and anti-C1q antibodies appeared significantly later and at lower titer in group 1 vs. group 2 and 3 ($p<0.0001$). Group 1 mice lived significantly longer than control mice ($p=0.03$) and had proteinuria significantly delayed and reduced ($p<0.05$, weeks 22 to 28).

Coll-IV and TGF-β mRNA were found less frequently in kidneys from group 1 mice vs. group 2 and 3 (TGF-β, group 1 vs. group 2, $p =0.028$; group 1 vs. group 3 $p=0.042$; Coll-IV group 1 vs. group 2, $p=0.018$; group 1 vs. group 3, $p= 0.029$). No significant difference was found in group 2 vs. group 3.

Harvested organs displayed inflammatory lesions in all mice, albeit milder lesions in group 1. Seven out of 10 mice of group 2 and all mice of group 3 had mesangial hyperplasia and renal perivascular lymphoplasmocitosis, not found in group 1.

Conclusion: Anti-PTX3 antibodies seem to attenuate and delay lupus-like manifestations including LGN in NZB/NZW F1 mice

Table 1. Comparison of circulating autoantibodies levels and proteinuria levels between Group 1, Group 2 and Group 3, expressed as median (min-max).

	Group 1	Group 2	Group 3	Group 1 vs. Group 2 p	Group 2 vs. Group 3 p
PTX3					
W11	0.014 (0.006-0.067)	0.021 (0.002-0.049)	0.037 (0.008-0.067)	n.s.	n.s.
W14	1.029 (0.408-1.990)	0.061 (0.039-0.168)	0.030 (0.017-0.061)	<0.0001	n.s.
W17	1.794 (1.624-2.982)	0.094 (0.044-0.160)	0.022 (0.003-0.106)	<0.0001	n.s.
W22	2.201 (1.265-2.591)	0.039 (0.015-0.149)	0.028 (0.005-0.129)	<0.0001	n.s.
W28	0.451 (0.121-2.036)	0.049 (0.015-0.138)	0.023 (0.150-0.189)	<0.0001	n.s.
W35	0.300 (0.010-0.915)	0.047 (0.039-0.082)	0.023 (0.019-0.073)	n.s.	n.s.
Anti-C1q					
W11	0.114 (0.105-0.189)	0.183 (0.103-0.216)	0.100 (0.073-0.145)	n.s.	n.s.
W14	0.165 (0.133-0.197)	0.228 (0.184-0.297)	0.193 (0.119-0.281)	0.002	n.s.
W17	0.207 (0.149-0.360)	0.315 (0.190-0.397)	0.333 (0.261-0.383)	0.015	n.s.
W22	0.368 (0.237-0.484)	0.494 (0.422-0.951)	0.553 (0.398-0.751)	0.002	n.s.
W28	0.609 (0.543-0.967)	0.701 (0.528-1.214)	0.845 (0.568-1.259)	n.s.	n.s.
W35	0.853 (0.688-1.314)	1.222 (0.795-1.862)	1.427 (1.357-1.498)	n.s.	n.s.
Anti-dsDNA					
W11	0.033 (0.020-0.061)	0.082 (0.014-0.129)	0.092 (0.003-0.142)	n.s.	n.s.
W14	0.043 (0.022-0.130)	0.135 (0.105-0.196)	0.157 (0.071-0.203)	<0.0001	n.s.
W17	0.100 (0.050-0.131)	0.224 (0.202-0.263)	0.265 (0.191-0.498)	<0.0001	n.s.
W22	0.168 (0.113-0.216)	0.328 (0.304-0.359)	0.355 (0.305-0.489)	<0.0001	n.s.
W28	0.252 (0.126-0.564)	0.434 (0.364-0.824)	0.464 (0.427-0.967)	0.028	n.s.
W35	0.326 (0.216-0.534)	0.549 (0.537-0.581)	0.593 (0.561-0.626)	0.016	n.s.
Proteinuria					
W19	0 (0-0)	0 (0-15)	0 (0-15)	n.s.	n.s.
W22	15 (15-30)	30 (0-30)	30 (15-30)	n.s.	n.s.
W26	15 (15-30)	30 (15-100)	30 (30-30)	0.008	n.s.
W28	30 (15-100)	200 (30-2000)	300 (100-2000)	0.002	n.s.
W30	100 (30-100)	300 (100-2000)	300 (100-2000)	<0.0001	n.s.
W33	100 (30-300)	300 (300-2000)	300 (300-2000)	0.0002	n.s.
W35	300 (100-2000)	2000 (300-2000)	2000 (300-2000)	n.s.	n.s.

PTX3: long pentraxin 3; anti-PTX3: antibodies against long pentraxin 3; n.s.: not significant; anti-C1q: antibodies against complement fragment 1; anti-dsDNA: antibodies against double stranded DNA.

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Abstract Number: 1773

Pan JAK Inhibitor Tofacitinib Ameliorate Autoimmunity and Nephritis in Lupus Prone Mice Via Inhibition of Interferon Signaling Pathway

Keigo Ikeda[1,2], Kunihiro Hayakawa[2], Maki Fujishiro[3], Mikiko Kawasaki[3], Takuya Hirai[2,4], Shinji Morimoto[2,4], Yoshinari Takasaki[5] and Iwao Sekigawa[3,4], [1]Department of Internal Medicine and Rheumatology, Juntendo University Urayasu Hospital, Tomioka, Urayasu, Chiba, Japan, [2]Institute for Environmental and Gender Specific Medicine, Juntendo University Graduate School of Medicine, Chiba, Japan, [3]Institute for Environment and Gender Specific Medicine, Juntendo University Graduate School of Medicine, Chiba, Japan, [4]Department of Internal Medicine and Rheumatology, Juntendo University Urayasu Hospital, Chiba, Japan, [5]Department of Internal Medicine and Rheumatology, Juntendo University School of Medicine, Tokyo, Japan
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Background/Purpose: We previously reported that Janus kinase/signal transducer and activator of transcription (JAK/STAT) pathway-mediated regulation of interferon (IFN) regulatory factor (IRF)-related genes may have an important role in the disease activity of systemic lupus erythematosus (SLE) through analyzing the difference of gene expression in peripheral blood CD3+ T cells obtained from active and inactive phases of SLE patients. Recently pan JAK inhibitor tofacitinib (TOFA) were developed and successfully applied to patients with rheumatoid arthritis. Therefore, the application possibility of TOFA was investigated for the new therapeutic strategy of SLE.

Methods: Monotherapy with TOFA or dual therapy with TOFA and 0.5mg/kg dexamethasone (DEXA) had been administered to two-lupus model mice with different genetic background, MRL/lpr for ten weeks and (NZB/NZW) F1 for eleven weeks, respectively. We evaluated and analyzed the disease, pathological and immunological condition of these mice. In addition, the gene expression obtained from SLE mouse CD4+ and patients CD3+ T cells were analyzed by DNA microarray and real-time PCR.

Results: Anti-DNA antibody titers and proteinuria were decreased in any TOFA administered groups. Both glomerular and interstitial nephritis were ameliorated in pathological kidney image analysis. Deposition of immunoglobulin and complements in the kidney were also significantly diminished. In CD4+ T cell analysis, $CD44^{low}CD62L^{high}$ naïve cells increased and $CD44^{high}CD62L^{low}$effector/memory cells significantly decreased in TOFA administered groups. Dual therapy with DEXA showed tendency to indicate stronger inhibitory effect comparing with monotherapy through any analysis. After TOFA administration, the gene expression of IFN induced protein with tetratricopeptide repeats 3 (IFIT3) that is related with IFN signaling pathway and contribute to anti-viral mechanism was significantly suppressed in both CD4+ from lupus prone mice and CD3+ T cells from SLE patients.

Conclusion: Both TOFA monotherapy and dual therapy with DEXA could suppress nephritis and modify immunological function in SLE mice with different genetic background. IFN signaling pathway was supposed to be important for the functional mechanism of TOFA to improve the disease condition. TOFA may contribute to the development of a new therapeutic strategy for SLE.

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Abstract Number: 1774

Bone Marrow Derived Dendritic Cells Modified By Lentiviral-Mediated RelB shRNA Possess Tolerogenic Phenotype and Functions on Lupus Splenic Lymphocytes

Haijing Wu, Yi Lo, Albert Chan and **Mo Yin Mok**, Department of Medicine, University of Hong Kong, Hong Kong, Hong Kong
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Background/Purpose:

Systemic lupus erythematosus (SLE) is an autoimmune disease that is characterized by high morbidity and mortality and remains challenging in treatment. Dendritic cells (DCs) have been shown to participate in the initiation and perpetuation of lupus pathogenesis. DCs that can induce tolerogenicity appear as potential cell-based therapy in this condition. In this study, we examined the *in vitro* tolerogenic properties of bone-marrow derived DCs (BMDCs) in the murine lupus setting.

Methods:

We used lentiviral transduction of RelB-silencing shRNA to modify expression of RelB, a key transcription factor regulating DC maturation, in BMDCs from MRL/MpJ mice. Tolerogenic properties of RelB-modified DCs were compared to scrambled control (SC)-modified DCs.

Results:

RelB expression was found to be significantly reduced in RelB-modified DCs derived from MRL/MpJ mice, wild type of the same genetic background as MRL/lpr lupus-prone mice. These MRL/MpJ RelB-modified DCs displayed semi-mature phenotype with expression of lower levels of co-stimulatory molecules compared to SC-modified DCs. RelB-modified DCs were found to be low producer of IL-12p70, can induce hyporesponsiveness of splenic T cells from MRL/MpJ and lupus-prone MRL/lpr mice. Furthermore, they downregulated IFN-γ expression and induced IL-10 producing T cells in MRL/MpJ splenocytes, and attenuated IFN-γ and IL-17 expression in MRL/lpr splenic CD4+ lymphocytes. Splenocytes primed by RelB-modified DCs demonstrated antigen-specific suppressive effect on allogeneic splenocytes.

Conclusion:

RelB-silencing in DCs generates DCs of tolerogenic properties with immunomodulatory function and appears as potential option of cell-targeted therapy.

Disclosure: H. Wu, None; **Y. Lo**, None; **A. Chan**, None; **M. Y. Mok**, None.

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Abstract Number: 1775

Fn14 Deficiency Protects Lupus-Prone Mice from Cutaneous Lesions Induced By Ultraviolet B (UVB) Irradiation

Jessica Doerner[1], Adam Friedman[2], Linda Burkly[3] and **Chaim Putterman**[4], [1]Albert Einstein College of Medicine, Bronx, NY, [2]Department of Dermatology, George Washington School of Medicine and Health Sciences, Washington, DC, [3]Biogen Idec, Cambridge, MA, [4]The Division of Rheumatology, Albert Einstein College of Medicine, Bronx, NY

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Background/Purpose: Sunlight, via ultraviolet B (UVB) irradiation, is a well-recognized trigger of cutaneous lupus erythematosus (CLE) skin lesions. TNF-like weak inducer of apoptosis (TWEAK), a TNF superfamily member (TNFRSF12), is a soluble cytokine that binds to its sole known signaling receptor, Fn14 (TNFRSF12A). TWEAK and Fn14 are upregulated following tissue inflammation and/or injury, and this signaling pathway is important in critical biologic processes including angiogenesis, cell survival, and local inflammation. Both TWEAK/Fn14 and UVB promote apoptosis and induce the production of proinflammatory cytokines; we wanted to investigate the potential synergism between these two pathways in lupus-associated skin disease by investigating the effects of UVB on lupus-prone mice with or without Fn14.

Methods: To evaluate a possible role for UVB in the pathogenesis of CLE, we exposed female lupus-prone MRL/lpr Fn14 wild type (WT) (n=14) and knockout (KO) mice (n=15) at 14-15 weeks of age to UVB irradiation (2 doses of 50 mJ/cm^2 each, 24 hours apart), and evaluated the severity of skin lesions 24 hours after the last dose. Histology was scored using a numerical system, and skin sections were stained and scored for infiltrating macrophages using IBA-1 immunofluorescence. Additionally, snap-frozen skin was analyzed by RT-PCR for inflammatory cytokine expression.

Results: MRL/lpr Fn14 WT mice developed significantly more severe skin involvement following exposure to UVB when compared to strain, age, and gender matched Fn14 KO mice (mean skin score: MRL/lpr Fn14 WT=3.8±0.4, MRL/lpr Fn14 KO=2.5±0.3, p-value=0.01). Histologically, MRL/lpr Fn14 WT mice had significantly more apoptotic keratinocytes and basement membrane degeneration. MRL/lpr Fn14 WT mice also had increased dermal infiltration by macrophages following UVB (MRL/lpr Fn14 WT=5.1±0.3, MRL/lpr Fn14 KO=3.3±0.3, p-value=0.0002). RT-PCR revealed higher levels of skin expression of CXCL10 (MRL/lpr Fn14 WT=5.5±1.0, MRL/lpr Fn14 KO=2.3±1.0 p-value=0.06) and RANTES (MRL/lpr Fn14 WT=6.8±1.3, MRL/lpr Fn14 KO=1.2±0.3, p-value=0.004) in MRL/lpr Fn14 WT as compared to MRL/lpr Fn14 KO mice.

Conclusion: UVB-induced skin inflammation is significantly attenuated in Fn14 deficient MRL/lpr lupus-prone mice. Our data suggests a novel role for the TWEAK/Fn14 signaling pathway in the induction of cutaneous lupus lesions following exposure to UVB irradiation.

Disclosure: J. Doerner, None; **A. Friedman**, None; **L. Burkly**, Biogen Idec, 3; **C. Putterman**, Biogen Idec, 2.

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Abstract Number: 1776

Significantly Reduced Lymphadenopathy, Salivary Gland Infiltrates and Proteinuria in MRL-Lpr/Lpr Mice Treated with Ultrasoluble Curcumin/Turmeric: Increased Survival with Curcumin

Treatment

Biji T Kurien[1,2,3], Valerie M Harris[1,4], Syed MS Quadri[1,4], Patricia Coutinho-de Souza[1], Joshua Cavett[5,6], Amanda Moyer[4], Bilal Ittiq[7], Angela Metcalf[6], Husayn Ramji[8], Dat Truong[8], Kristi A. Koelsch[4,9,10], Mike Centola[11], Adam Payne[12], D. Danda[13] and **R. Hal Scofield**[1,14], [1]Oklahoma Medical Research Foundation, Oklahoma City, OK, [2]U.S. Department of Veterans Affairs Medical Center, Oklahoma City, OK, [3]College of Medicine, University of Oklahoma Health Sciences Center, Oklahoma City, OK, [4]University of Oklahoma Health Sciences Center, Oklahoma City, OK, [5]Allergy and Immunology, Oklahoma Medical Research Foundation, Oklahoma City, OK, [6]Medicine, University of Oklahoma Health Sciences Center, Oklahoma City, OK, [7]University of Oklahoma Health Sciences Center, Oklahoma, OK, [8]University of Oklahoma, Oklahoma City, OK, [9]Arthritis and Clinical Immunology, Oklahoma Medical Research Foundation, Okalahoma City, OK, [10]Department Veterans Affairs Medical Center, Oklahoma City, OK, [11]Haus Bioceuticals, Oklahoma City, OK, [12]Arthritis and Immunology, Oklahoma Medical Research Foun, Oklahoma City, OK, [13]Christian Medical College, Vellore, India, [14]US Department of Veterans Affairs Medical Center, Oklahoma City, OK

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Background/Purpose:

Commercial curcumin (CU), derived from food spice turmeric, has been widely studied as a potential therapeutic for a variety of oncological and inflammatory conditions. Commercial CU has been found to be safe in very high doses in clinical trials. Turmeric (TU) has been shown to ameliorate human refractory lupus nephritis. Lack of solubility and bioavailability has hindered CU's therapeutic efficacy in human diseases. Previous studies have used CU solubilized in organic solvents or as CU powder supplemented in animal feed. We have solubilized CU with heat/pressure in water, obtaining up to 36-fold increase in solubility. We hypothesized that this ultrasoluble CU, as well as ultrasoluble TU will ameliorate systemic lupus erythematosus (SLE) and Sjogren's Syndrome (SS)-like disease in MRL-*lpr/lpr*mice, a well-studied animal model for both SLE and SS.

Methods:

Eighteen female MRL-MpJ (6-week old) and 18 female MRL-*lpr/lpr* (6-week) mice were used. Female MRL-*lpr* mice develop SLE-like disease at the 10^{th} week and die at an average age of 17 weeks. MRL-MpJ mice, used as control, develop SLE-like disease around 47 weeks and typically die at 73 weeks). Six mice of each strain received autoclaved water (*lpr*-water or MpJ-water group), water with ultrasoluble CU (*lpr*-CU or MpJ-CU group) or water with ultrasoluble TU (*lpr*-TU or MpJ-TU group) in water bottle.

Results:

By 14 weeks of age, 4/6 *lpr*-water group developed severe SLE-like disease with lymphadenopathy (in 5/6 mice), urinary cell casts and proteinuria. *lpr*-CU and *lpr*-TU mice had significantly reduced proteinuria, lymphadenopathy and no urinary cell casts. Sera (1:80 dilution, bleed 3) from 6/6 *lpr*-water group were positive for ANA, weakly positive in *lpr*-CU and negative in *lpr*-TU mice. Anti-dsDNA was positive by week 8 in *lpr*-water and *lpr*-CU, but not in *lpr*-TU mice. Significant levels of anti-RNP and anti-Sm autoantibodies developed by 8th week in *lpr*-water group, but not in *lpr*-CU and *lpr*-TU groups (these groups developed antibodies only by 10^{th} week). *lpr*-CU group had a 20% survival advantage over *lpr*-water group. However, *lpr*-TU group lived an average of 16 days shorter than *lpr*-water group due to complications unrelated to SLE-like illness. CU or TU treatment inhibited lymphadenopathy significantly compared to water treated mice (p=0.03 and p=0.02 respectively). Average lymph node weights were 248±1147, 99±330 and 49±67.49 mg respectively for *lpr*-water, *lpr*-CU and *lpr*-TU groups. TUNEL assay showed that lymphocytes in lymph nodes of TU and CU treated mice underwent apoptosis. Salivary gland histopathology studies show significantly reduced cellular infiltration in *lpr*-CU and *lpr*-TU groups, compared to *lpr*-water group, while there was a trend towards reduced kidney damage in *lpr*-CU and *lpr*-TU groups. Severe tail skin lesions occurred in *lpr*-water group (2 mice) and not in the *lpr*-CU and *lpr*-TU groups (week 24). Surprisingly, as seen with MRL-*lpr* mice, MpJ-water group developed autoantibodies by 8^{th} bleed (but at levels lower than *lpr*-water group). MpJ-CU and MpJ-TU groups did not develop autoantibodies at this time, as observed in *lpr*-CU and *lpr*-TU mice.

Conclusion:

Ultrasoluble CU/TU could prove useful as a therapeutic intervention in SLE and SS.

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Abstract Number: 1777

Lymphocyte Depletion, Recovery and Efficacy in NZBWF1 Lupus Mice Following Continuous or Intermittent Dosing Regimen of Venetoclax (ABT-199), a Potent and Selective BCL-2 Inhibitor

Li Chun Wang[1], Stuart Perper[1], Kimberly Black[1], Regina Mario[1], Candace Graff[2,3], Dawna Hartman[3], Andrew Souers[4], Steven Elmore[4] and Lisa Olson[1,3], [1]Immunology, AbbVie Inc, AbbVie Bioresearch Center, Worcester, MA, [2]DMPK, AbbVie Inc, AbbVie Bioresearch Center, Worcester, MA, [3]AbbVie Inc, AbbVie Bioresearch Center, Worcester, MA, [4]AbbVie Inc., North Chicago, IL
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Background/Purpose:

Proteins in the BCL-2 family are key regulators of apoptosis, or programmed cell death. We report here that continuous daily treatment with 30mpk venetoclax (ABT-199), a selective BCL-2 inhibitor, produces a sustained lymphocyte depletion in peripheral blood that correlates with reduced disease severity in NZBWF1 lupus mice. The time course for lymphocyte depletion, recovery and efficacy following multiple dosing regimen was investigated.

Methods:

For lymphocyte recovery studies, C57BL6 mice were treated with a single 30 mpk dose of venetoclax or once daily 30 mpk dose for 7 days. Changes in lymphocytes in peripheral blood were assessed weekly by a Celldyn 3700 blood analyzer. For efficacy studies, venetoclax was administered once daily to NZBWF1 lupus mice by one of three dosing schedules: (1) continuous dosing for 28 weeks (30 mpk); (2) dosing on day 1 of a 7 day cycle for 28 cycles (100mpk); or (3) intermittent dosing on days 1-7 of a 28-day cycle for 7 cycles (30 or 100 mpk). Proteinuria and survival data are presented as Kaplan-Meyer survival curves. B and T cells in peripheral blood were analyzed by flow cytometry.

Results:

While a single 30 mpk dose of venetoclax leads to significant lymphocyte depletion within 24 hours followed by recovery to baseline by day 7, 7 days of continuous dosing is followed by lymphocyte recovery by day 28. Weekly proteinuria and survival endpoints reveal comparable efficacy between the intermittent dosing cycles at 100 mpk dose of venetoclax and continuous dosing at 30 mpk of venetoclax. Numbers of B and T cells from the first two intermittent cycles showed trends toward partial or complete recovery by day 28 versus sustained depletions in animals with continuous dosing.

Conclusion:

We have identified an intermittent dosing schedule for venetoclax that conveys compelling efficacy in NZBWF1 lupus mice without persistent lymphocyte depletion. This dosing regimen may translate into a more favorable benefit-risk profile and hence has been incorporated into a phase 1 trial in SLE patients.

Disclosure: L. C. Wang, AbbVie, 1; **S. Perper**, None; **K. Black**, AbbVie, 1; **R. Mario**, AbbVie, 1; **C. Graff**, AbbVie, 1; **D. Hartman**, AbbVie, 1; **A. Souers**, AbbVie, 1; **S. Elmore**, AbbVie, 1; **L. Olson**, AbbVie, 1.

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Abstract Number: 1778

Disease Progression Is Altered By Moderate Exercise and Social Stress in a Murine Model of Lupus Nephritis

Jeffrey Hampton[1], Nicholas A. Young[2], Sudha Agarwal[3], Saba Aqel[3], Kendra Jones[3], Lai-Chu Wu[2,4], Nicole Powell[5], John Sheridan[5], Michael Bruss[3] and Wael N. Jarjour[2], [1]Immunology and Rheumatoloty, The Ohio State University Wexner Medical Center, Columbus, OH, [2]Immunology and Rheumatology, The Ohio State University Wexner Medical Center, Columbus, OH, [3]Rheumatology and Immunology, The Ohio State University Wexner Medical Center, Columbus, OH, [4]Biological Chemistry and Pharmacology, The Ohio State University College of Medicine, Columbus, OH, [5]Institute for Behavioral Medicine Research, The Ohio State University Wexner Medical Center, Columbus, OH
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Background/Purpose: Chronic inflammation is pathognomonic of autoimmune diseases and contributes to organ damage. Our group has previously shown that moderate daily exercise reduces systemic inflammation in an acute inflammatory mouse model. It has also been shown that social stress results in systemic inflammation. NZM2410 mice develop severe nephritis with an auto-antibody profile similar to that of Systemic Lupus Erythematosus (SLE). We investigated the effects of stress and exercise on chronic inflammatory changes in lupus nephritis.

Methods: All experimental and control studies were carried out using NZM2410 after approval by the IACUC. Mice in the exercise cohort were walked on a treadmill daily at a pace of 8 m/min beginning at 18 weeks. Stress was induced in a separate cohort daily over 6 consecutive days by placing an aggressor male in a cage with a pre-existing social hierarchy. To track disease progression, serum was collected weekly for blood urea nitrogen (BUN) level analysis and weights were documented. Early removal criteria was defined as a BUN level exceeding 50 mg/dL and/or a 20% decrease in weight from baseline. Exercise mice were compared to a non-exercise control group and stress mice were compared to randomly selected, age matched controls upon meeting early removal criteria. Tissues were collected in formalin, paraffin embedded and stained for analysis. Histopathological scoring of coded specimens was performed by a board licensed veterinarian.

Results: At 34 weeks, the entire non-exercise cohort met early removal, whereas 50% of the exercise group survived until 39 weeks and pixel intensity of F4/80 + infiltration was significantly lower in the exercise mice group. In contrast, compared to age matched controls, the mice that underwent social stress showed a significant increase in F4/80 + infiltrate which corresponded to significantly more kidney damage as observed during histopathological analysis.

Conclusion: Exercise and social stress have opposite effects on the NZM2410 chronic inflammatory model of SLE and have significant effects on experimental outcomes. Our data suggest that stress reduction and moderate daily exercise may have positive effects on the clinical course of patients with chronic inflammation associated with systemic autoimmune diseases and should be explored as therapeutic intervention.

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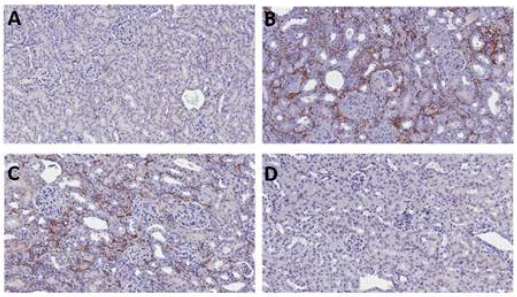

F4/80 positive staining of kidney sections from control (A), stress (B), non-exercise (C) and exercise mice (D). Stress induced greater infiltration of F4/80 positive cells compared to age matched controls, while exercise reduced the amount of F4/80 positive staining compared to non-exercise mice. Images taken at 20x magnification.

Disclosure: J. Hampton, None; **N. A. Young**, None; **S. Agarwal**, None; **S. Aqel**, None; **K. Jones**, None; **L. C. Wu**, None; **N. Powell**, None; **J. Sheridan**, None; **M. Bruss**, None; **W. N. Jarjour**, None.

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Abstract Number: 1779

Characterization of Anti-Nuclear Antibody (ANA) Signatures in Murine Models of Lupus Using Genalyte Maverick Technology

Jacqueline Loud[1], Stuart Perper[2], Rachel Twomey[2] and Stephen Clarke[2], [1]Immunology Pharmacology, AbbVie Inc, AbbVie Bioresearch Center, Worcester, MA, [2]Immunology Pharmacology, Abbvie Bioresearch Center Inc., Worcester, MA

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SESSION INFORMATION

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Session Title: Systemic Lupus Erythematosus - Animal Models Poster II

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Session Time: 9:00AM-11:00AM

Background/Purpose: Systemic lupus erythematosus (SLE) and lupus nephritis (LN) are autoimmune diseases characterized by circulating antibodies to nuclear self-antigens, including reactivities to double-stranded DNA, RNP and Sm. Preclinical mouse models exist that mimic aspects of human SLE/LN disease, and are used to study pathogenic mechanisms as well as to test responses to anti-inflammatory treatments. In clinical samples, autoantibody reactivity to nuclear antigens is heterogeneous, with individual patients exhibiting unique anti-nuclear antibody (ANA) signatures. We postulated that each distinct mouse model of lupus may also exhibit its own ANA signature, and that by identifying ANA reactivity profiles in preclinical lupus models, robust preclinical biomarker strategies and hypotheses for links with particular aspects of human disease may be devised.

Methods: A Genalyte Maverick instrument was used to assess IgG reactivity to 13 clinically-relevant nuclear antigens including: SS-A 60, SS-A 52, SS-B, Sm, Sm/RNP, Scl-70, Jo-1, nucleosome, PCNA, Ku, Centromere A & B, Ribosomal P and dsDNA in a simultaneous manner. Analysis was performed on frozen plasma samples archived from several murine lupus models, including spontaneous NZBW-F1, IFNα-accelerated NZBW-F1, and spontaneous MRL-*lpr*. In some samples, both Maverick technology and in-house ELISA assays were used to assess ANA to dsDNA and Sm/RNP for cross-methodology validation.

Results: Maverick analysis of nuclear antigen reactivities showed that each murine model had a distinct ANA signature. Spontaneous NZBW-F1 mice developed strong reactivity to dsDNA, with a lesser anti-RNP component. However, when NZBW-F1 disease was accelerated via injection of a non-replicative IFNα-inducing adenovirus, ANA reactivity was stronger to RNP nuclear antigen, with a lesser anti-dsDNA component. Both male and female MRL-*lpr* mice showed strong, age-dependent increases in multiple ANAs including reactivity to dsDNA, RNP, Sm, and nucleosome. Maverick assessment of ANA reactivities to dsDNA and Sm/RNP significantly correlated to titers generated by in-house ELISAs. Additional Maverick assessments of ANA from IFNα-accelerated NZBW-F1 mice treated prophylactically with mycophenolate mofetil (Cellcept), showed Cellcept significantly prevented anti-RNP autoantibody production, but only a trend was seen for decreases in anti-dsDNA autoantibody production.

Conclusion: These results show that each murine lupus model may exhibit its own unique ANA signature, and that Genalyte Maverick technology is a quick and useful methodology for identifying this signature via simultaneous assessment of several ANA from a single plasma sample. Furthermore, understanding ANA reactivity profiles in each model may help guide better preclinical biomarker design and will have impact on interpreting efficacy of anti-inflammatory treatments.

Disclosure: J. Loud, Abbvie Bioresearch Center Inc., 3; **S. Perper**, Abbvie Bioresearch Center Inc., 3; **R. Twomey**, Abbvie Bioresearch Center Inc., 3; **S. Clarke**, Abbvie Bioresearch Center Inc., 3.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/characterization-of-anti-nuclear-antibody-ana-signatures-in-murine-models-of-lupus-using-genalyte-maverick-technology

Abstract Number: 1780

Oxidative Stress Protects Against Nephritis Induced By Chronic Graft Versus Host Disease

Zachary Oaks[1], Adam Bartos[2], Miguel Beckford[3], Mark Haas[4] and Andras Perl[5], [1]Medicine, SUNY Upstate, Syracuse, NY, [2]Medicine, SUNY, Syracuse, NY, [3]SUNY Upstate, Syracuse, NY, [4]Cedars-Sinai Medical Center, Los Angeles, CA, [5]Department of Medicine, SUNY Upstate Medical University, Syracuse, NY

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Background/Purpose: Systemic lupus erythematosus (SLE) is characterized by glutathione depletion and oxidative stress in T cells which lead to abnormal lineage development and dysfunction. In turn, treatment with N-acetylcysteine (NAC), which is an amino acid precursor of glutathione, reversed T cell dysfunction, reduced anti-DNA production, and disease activity in a double-blind randomized placebo-controlled clinical trial of SLE patients. Nephritis in Chronic graft versus host disease (cGvHD) has been used as a mouse model of lupus. However, NAC worsened GvHD in a recent clinical trial. Given the nuanced role of oxidative stress in the immune system, we examined the impact of transaldolase (TAL) deficiency, which causes glutathione depletion, and its reversal by NAC on cGVHD.

Methods: Age and gender matched C57BL/6 wild-type (TAL+/+) and TAL-deficient (TAL-/-) mice were fed with drinking water without (TAL+/+ n=18; TAL-/- n=17) or with 10 g/L NAC (TAL+/+ n=8; TAL-/- n=5). 10^8 MHC-mismatched bm12 splenocytes were injected intraperitoneally. Urine and serum were collected at baseline and every 4 weeks until study completion at 23 weeks. Anti-nuclear antibodies (ANA) and proteinuria were measured and expressed relative to day 0, preceding injection of bm12 cells, and standardized at 1.0 for each mouse. CD3, CD19, CD4, CD8, FoxP3, CD25, Helios, mTOR, and glutathione were measured by flow cytometry of splenocytes. Severity of glomerulonephritis was blindly scored by an experienced renal pathologist. Statistical analysis was done by t-tests or ANOVA using GraphPad 5.0 software; with $p<0.05$ considered significant.

Results: Proteinuria was significantly increased in TAL+/+ mice (5.19 ±3.12) relative to TAL-/- mice (0.86 ±0.06; $p<0.01$) at 23-weeks. NAC further increased proteinuria in TAL+/+ mice (10.91 ± 3.45; $p<0.05$) but not in TAL-/- mice. By 12 weeks, TAL+/+ mice on normal water (1.81 ±0.22 ; $p=0.02$) or NAC (7.54 ±3.25; $p=0.01$) as well as TAL-/- mice on NAC had significantly increased ANA production relative to baseline (4.07 ± 0.22; $p=0.009$). In contrast, TAL-/- mice on normal water showed no increase in ANA during the study. Kidney pathology revealed reduced glomerulosclerosis in TAL-/- mice (0.3125 ± 0.1197) relative to TAL+/+ mice (0.7778 ± 0.1726; $p=0.04$). GSH levels were reduced in both T and B cells of TAL-/- mice, while NAC treatment enhanced GSH in both cell types of TAL+/+ and TAL-/- mice. Flow cytometry revealed an expansion of CD8 T cells in TAL-/- mice on normal water (21.6 ±1.3%) relative to TAL+/+ mice on normal (15.2 ±1.0%; $p=0.0003$) and NAC-containing water (14.4 ± 2.0%; $p=0.009$). $CD4^+FoxP3^+Helios^+$ Tregs were depleted from 10.7% in TAL+/+ mice to 5.1% in TAL-/- mice ($p=0.001$). NAC expanded Tregs both in TAL+/+ and TAL-/- mice. B cells were depleted in TAL-/- mice on normal water (48.2 ± 1.9%) relative to all other groups (TAL+/+ mice on normal water: 58.3 ± 1.6%, $p=0.0003$; TAL+/+ mice on NAC: 60.6 ± 3.0%, $p=0.003$; TAL-/- mice on NAC: 60.7 ± 4.4%, $p=0.045$).

Conclusion: Oxidative stress and Treg depletion protect against ANA production and nephritis via the expansion of CD8 T cells and contraction of B cells in cGvHD.

Disclosure: Z. Oaks, None; **A. Bartos**, None; **M. Beckford**, None; **M. Haas**, None; **A. Perl**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/oxidative-stress-protects-against-nephritis-induced-by-chronic-graft-versus-host-disease

Abstract Number: 1781

Comparative Efficacy and Safety of Tacrolimus, Mycophenolate Mofetil, and Cyclophosphamide As Induction Therapy for Lupus Nephritis: A Bayesian Network Meta-Analysis of Randomized Controlled Trials

Young Ho Lee and Gwan Gyu Song, Rheumatology, Korea University Medical Center, Seoul, South Korea
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Session Type: ACR Poster Session B
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Background/Purpose: Cyclophosphamide (CYC) regimens improved renal outcomes, and have long been considered the gold standard for inducing renal remission and preventing renal flares in proliferative glomerulonephritis (WHO class III and IV). However, their benefits are outweighed by the significant drug-related adverse effects, such as an increased risk of serious infections and ovarian toxicity. Thus, other immunosuppressive drugs have been used for induction treatment of lupus nephritis, such as mycophenolate mofetil (MMF), and tacrolimus. However, evidence from a small number randomized controlled trials (RCT) comparing the relative efficacy and safety of tacrolimus or MMF with CYC, as induction agents in lupus nephritis, has been inconclusive, mainly because of their small sample sizes. This study aimed to assess the relative efficacy and safety of tacrolimus, MMF, and CYC as induction therapy for lupus nephritis.

Methods: RCTs examining the efficacy and safety of tacrolimus, MMF, and CYC for induction therapy in patients with lupus nephritis were included. We performed a Bayesian random-effects network meta-analysis to combine direct and indirect evidence from the RCTs.

Results: Nine RCTs including 972 patients met the inclusion criteria. There pairwise comparisons were performed, including 11 direct comparisons. Tacrolimus showed a significantly higher overall response rate (complete remission plus partial remission) than CYC (OR 2.35, 95% credible interval (CrI) 1.03–5.45), and was more efficacious than MMF (OR 1.60, 95% CrI 0.70–3.57). MMF was superior to CYC in terms of overall response (OR 1.45, 95% CrI 0.96–2.42). Ranking probability based on the surface under the cumulative ranking curve (SUCRA) indicated that tacrolimus had the highest probability of being the best treatment for achieving the overall response (SUCRA = 0.9321), followed by MMF (SUCRA = 0.5385), and CYC (SUCRA = 0.0294). In terms of safety, tacrolimus showed the highest probability of decreasing the risk of serious infections (SUCRA = 0.9253), followed by MMF (SUCRA = 0.4027), and CYC (SUCRA = 0.1720).

Conclusion: Tacrolimus was the most efficacious induction treatment for patients with lupus nephritis, and had the highest probability of decreasing the risk of serious infections. Higher remission rates combined with a more favorable safety profile suggest that MMF is superior to CYC as induction treatment in these patients.

Disclosure: Y. H. Lee, None; **G. G. Song**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/comparative-efficacy-and-safety-of-tacrolimus-mycophenolate-mofetil-and-cyclophosphamide-as-induction-therapy-for-lupus-nephritis-a-bayesian-network-meta-analysis-of-randomized-controlled-trials

Abstract Number: 1782

a Double-Blind, Randomized, Parallel-Group Study of Hydroxychloroquine on Cutaneous Lupus Erythematosus in Japan

Naoto Yokogawa[1], Toshiya Takahashi[2], Toshiaki Sato[3] and Naohisa Yokota[4], [1]on behalf of Japanese Hydroxychloroquine Study Group, Japan, Japan, [2]Sanofi K.K., Tokyo, Japan, [3]Sanofi.KK, Tokyo, Japan, [4]Sanofi KK, Tokyo, Japan
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Background/Purpose:

In Japan hydroxychloroquine (HCQ) is still unavailable due to the banning of chloroquine in 1974 following allegations that it caused severe retinopathy. Therefore, a multicenter, double-blind, randomized, parallel-group trial was conducted to develop HCQ on cutaneous lupus erythematosus (CLE) in Japan (NCT01551069).

Methods:

Japanese CLE patients (age≥18) with or without SLE were included. Patients with Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI) activity score <4, and fluctuations of CLASI ≥20% in the screening period, administration of prednisolone >15mg/day, and pain VAS or fatigue VAS of 0 in SLE patients were excluded. The study spanned 55 weeks and fell into three phases: the first was the double-blind (HCQ or placebo in a 3:1 ratio for 16 weeks), the second was the single-blind (using HCQ for 36 weeks), and the third was the follow-up phase lasting 3 weeks. This was a baseline-controlled study and placebo was used as a reference. Primary endpoint was a change in CLASI activity score from baseline to 16 weeks. A change in CLASI activity score during the single-blind period was also measured. As secondary endpoints, Skindex29, 7-point scale global assessment (GA) of skin by patient, 5-point scale central photo evaluation, were assessed at Week 16 and, based on them 7-point scale GA of skin was scored by investigator. In SLE cases, the VAS assessment of pain and fatigue, RAPID 3 (Routine assessment of patient index data 3), and focused BILAG index were assessed at Week 16. Safety was assessed up to 55 weeks.

Results:

103 patients were randomized and 72 in HCQ group, 24 in placebo group were analyzed for efficacy. The CLASI score at Week 16 showed significant improvement in both groups (HCQ group: -4.6±6.4, p<0.0001; placebo group: -3.2±4.5, p=0.002). The placebo group experienced further improvement lasting to Week 52 after switching to HCQ, showing a change of -3.3±4.6 compared with -2.1±3.3 for the HCQ group. Skindex29 improved significantly from baseline to 16 weeks in the HCQ group. The percentage of "≥slightly improved" by GA of skin by patient, "≥improved" by central photo evaluation, and "≥improved" by GA of skin by investigator, were 72.9%, 59.4%, and 51.4% in the HCQ group and 47.8%, 30.4%, and 8.7% in the placebo group, respectively. In 56 SLE patients, pain VAS, fatigue VAS, and RAPID3 improved significantly from baseline to 16 weeks in the HCQ group. Active musculoskeletal system (A-C) defined by BILAG improved to be one letter down in 42.1% of the HCQ group at Week 16. Drug eruption, Stevens-Johnson syndrome, hepatic dysfunction, and cellulitis were noted as serious treatment-emergent adverse events related to HCQ treatment. No retinopathy occurred.

Conclusion:

The first clinical trial of HCQ on CLE confirmed the benefits and tolerability of HCQ.

Funding:

Sanofi KK

Japanese Hydroxychloroquine Study Group: Yokogawa N (Tokyo Metropolitan Tama Medical Center, Rheumatology), Furukawa F (Wakayama Medical University, Dermatology), Eto H (St. Luke's International Hospital, Dermatology), Tanikawa A (Keio University School of Medicine, Dermatology), Ikeda T (Wakayama Medical University, Dermatology), Yamamoto K (The University of Tokyo, Allergy and Rheumatology)

Disclosure: N. Yokogawa, None; **T. Takahashi**, Sanofi KK, 3; **T. Sato**, Sanofi KK, 3; **N. Yokota**, Sanofi KK, 3.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/a-double-blind-randomized-parallel-group-study-of-hydroxychloroquine-on-cutaneous-lupus-erythematosus-in-japan

Abstract Number: 1783

Dietary Fish Oil Supplementation Raises Serum Essential Fatty Acid Concentrations in Patients with Systemic Lupus Erythematosus and Correlates with Improvements in Inflammation and Pain

Cristina Arriens[1], Carlos Rodriguez-Navas[2], David R. Karp[1], Jeffrey McDonald[2] and Chandra Mohan[3], [1]Internal Medicine - Rheumatic Diseases, University of Texas Southwestern Medical Center, Dallas, TX, [2]Molecular Genetics, University of Texas Southwestern Medical Center, Dallas, TX, [3]Biomedical Engineering, University of Houston, Houston, TX

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Background/Purpose: A comprehensive metabolomic screen comparing sera from patients with systemic lupus erythematosus (SLE) to healthy controls (HC) indicated a relative deficiency in omega-3 fatty acids. A randomized clinical trial of fish oil supplements in patients with SLE was undertaken. This study noted improvements in the fish oil treatment group when compared to a parallel placebo group in quality of life, global disease activity, erythrocyte sedimentation rate (ESR), and the cytokines Interleukin (IL)-12 and IL-13. A follow-up study was performed to verify that serum lipid profiles were impacted by oral fish oil supplementation and to correlate alterations of serum omega-3 fatty acid levels with the clinical improvements noted in the trial.

Methods: Fifty SLE patients were recruited, 25 supplemented with fish oil (FO) and 25 with olive oil placebo. At baseline and after 6 months of FO supplementation, Short Form-36 (SF-36), SLE Disease Activity Index (SLEDAI), Physician Global Assessment (PGA), and serum free fatty acid (FFA)

profiles were completed. Demographic information and clinical laboratory data were collected from the electronic medical record. Liquid-liquid extraction was performed to isolate the FFA from all available serum samples. Quantification of FFA levels was determined by gas chromatography/ mass spectrometry. Data analysis utilized non-parametric statistical testing, Mann-Whitney to compare groups and Spearman for correlation.

Results: Eighteen fish oil and fourteen placebo patients completed the study. Baseline FFA levels and demographics did not differ significantly between the two groups. Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) levels (ng/ul) were converted to percent of total FFA for normalization. The median change in EPA level in the fish oil group was 0.037 [IQR 0.0013– 0.039] compared to -0.0084 [-0.035 – 0.029] in the placebo group, yielding a significant difference between groups (p=0.022). The median change in DHA level in the fish oil group was 0.10 [-0.21 – 1.16] compared to -0.022 [-0.075 – 0.023] in the placebo group, also significant (p=0.013). The change in EPA and DHA levels were compared to change in SF-36 parameters, ESR, SLEDAI, IL-13, and IL-12. Increase in EPA correlated with improvement of SF-36 Pain (r=0.48, p=0.0053) and reduction of ESR level (r=-0.41, p=0.021). Increase in DHA level correlated with reduction of ESR level (r=-0.30, p=0.099) and increase in IL-13 level (r=0.30, p=0.099).

Conclusion: A placebo-controlled clinical trial of fish oil supplements in SLE patients verified the ability to change important serum omega-3 fatty acid levels by dietary intervention. Serum from both treatment and placebo patients completing the trial had comparable fatty acid profiles at baseline, and achieved a significant increase in EPA, DHA, and PUFA levels with oral supplementation of fish oil. Patients with SLE may potentially have reduced EPA and DHA levels due to dietary intake and/or increased metabolism. Oral supplementation can overcome this deficit. Additionally, benefits noted in quality of life, specifically pain, and inflammation may be partially explained by the increases in DHA and EPA levels.

Disclosure: C. Arriens, None; **C. Rodriguez-Navas**, None; **D. R. Karp**, None; **J. McDonald**, None; **C. Mohan**, None.

Abstract Number: 1784

Treatment with Belimumab in SLE Does Not Impair Antibody Response to 13-Valent Pneumococcal Conjugate Vaccine

Johanna Nagel[1], Tore Saxne[2], Pierre Geborek[3], Anders A. Bengtsson[4], Søren Jacobsen[5], Charlotte Sværke Jørgensen[6], Andreas Jönsen[7] and **Meliha C. Kapetanovic**[3], [1]Department of Clinical Sciences, Lund, Section of Rheumatology, Lund University and Skåne University Hospital, Lund, Sweden, Lund, Sweden, [2]Dept of Clinical Sciences, Lund, Section of Rheumatology, Lund University, Lund, Sweden, [3]Department of Clinical Sciences Lund, Section of Rheumatology Lund University and Skåne University Hospital, Lund, Sweden, [4]Rheumatology, Inst of Clinical sciences, Lund, Sweden, [5]Center for Rheumatology and Spine Diseases, Rigshospitalet - Glostrup, University of Copenhagen, Denmark, Glostrup, Denmark, [6]Department of Microbiological Diagnostics & Virology, Statens Serum Institut, Copenhagen, Denmark, [7]Department of Rheumatology, Lund University Hospital, Lund, Sweden
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Background/Purpose: To explore the impact of SLE disease and belimumab given in addition to standard of care therapy on antibody response after vaccination with PCV13 in SLE patients and healthy controls.

Methods: In total, 47 SLE patients (mean age 50.8 years; 94% female; mean disease duration 16.1 years; mean SLEDAI 1.9) and 21 healthy controls (mean age 43.6 years, 86% female) were immunised with a single dose of PCV13. Of these, 11 patients were treated with belimumab in addition to traditional DMARDs (hydroxychloroquine, HCQ; azathioprine, AZA, o or prednisolone). Mean (range) belimumab treatment duration was 9 (2-31) months. Remaining 36 patients received the following treatments: no DMARD (n=7); HCQ (n=10), HCQ+AZA (n=10), AZA or DMARDs other than HCQ (n=9). In total, 31of 47 (66%) of SLE patients had concomitant prednisolone (mean dose 51mg/week; range 17,5-140 mg/week). The quantification of serotype specific IgG levels to 12 pneumococcal capsular polysaccharides (1, 3, 4, 5, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F) was performed in serum samples taken immediately before and 4-6 weeks after vaccination using multiplex fluorescent microsphere immunoassay (Luminex). Geometric mean levels (GML) and differences between post- and prevaccination antibody levels (fold increase) were calculated from log transformed pre- and postvaccination antibody levels and then compared using paired T-test. General linear model for repeated measurements was used to determine the impact of SLE diagnosis and different treatments on antibody response for all 12 serotypes tested with adjustment for age. Concomitant prednisolone, AZA/other DMARD or HCL were included separately in the analysis as covariates.

Results: Postvaccination antibody levels to 12 serotypes increased significantly in both SLE patients and controls (p between <0.001 and 0.005). Compared to controls patients with SLE as a group showed significantly lower post-vaccination antibody levels and lower fold increase in antibody levels after vaccination (p=0.004 and p=0.009, respectively; adjusted for age and sex). Higher age was associated with lower antibody levels after vaccination (p<0.001) among SLE patients but not controls. When each treatment group was compared to controls including adjustment for age and sex, SLE on belimumab and SLE on HCQ were not different compared to controls, whereas SLE without DMARD, SLE patients on AZA+HCQ, and SLE on AZA or DMARDs other than HCQ had significantly lower fold increase in antibody levels after vaccination (p=0.007, p=0.004 and 0.047, respectively). When different SLE treatments were compared to each other, including adjustment for age, sex, concomitant prednisolone and concomitant DMARDs, the differences were not significant.

Conclusion: Compared to controls, SLE patients had in general lower antibody levels following vaccination with 13-valent pneumococcal conjugate

vaccine. However, belimumab given in addition to traditional DMARDs or prednisolone did not further impair antibody response. Only higher age was significantly associated with lower post-vaccination antibody levels among SLE patients.

Clinical trial registration: NCT02240888

Disclosure: J. Nagel, None; **T. Saxne**, None; **P. Geborek**, None; **A. A. Bengtsson**, None; **S. Jacobsen**, None; **C. Sværke Jørgensen**, None; **A. Jönsen**, None; **M. C. Kapetanovic**, None.

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Abstract Number: 1785

Clinical Characteristics and Relative Factors of Infections in Southern Chinese Patients with Systemic Lupus Erythematosus

Zhongping Zhan, Dongying Chen, Qian Qiu and Liuqin Liang, Department of Rheumatology, The First Affiliated Hospital of Sun Yat-sen University, Guangzhou, China

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Background/Purpose: To determine the clinical characteristics and to identify relative factors of infection in patients with Systemic Lupus Erythematosus, to provide a data for making the diagnosis and preventable scheme of infection.

Methods: A retrospective review of the medical records of 3827 patients hospitalized with Systemic Lupus Erythematosus admitted in our center from January 2008 to June 2013 were performed.1290 cases were defined as infection group(IG) and 1278 of the other were defined as non-infection group(NIG).The data were analyzed with the statistics software SPSS19.0. Relative factors of infection in patients with SLE were identified with multifactor logistic regress analysis.

Results:

1. 1290 patients (33.7%) suffered at least one infection.The incidence of patients that suffered from 2 infections was 13.41% (173/1290) and the incidence was 1.70 %(22/1290) that suffered from 3. The incidence of nosocomial infection was 22.6 %(341/1507).

2. According to Systemic lupus erythematosus disease activity index, there are 331 stable cases, mild activity for 315 cases (24.4%), moderate activity for 306 cases (23.7%), and severe activity of 338 cases (26.2%). There are 497 cases (38.5%) with multiple system damage and 747 cases (57.91%) with single system damage;

3. the most common infection focus the respiratory tract (66.5%, including upper respiratory tract (28.1%) and lung (38.4%)), digestive tact (7.2%), Skin (7.0%), bloodstream (3.6%).

4. the most common identified pathogenic organism was gram negative bacteria (61.3%). Most of them were Escherichia coli; gram positive bacterial (22.6%). Most of them were Streptococcus pneumonia and Staphylococcus aureus; the fungi (16.2%). Most of them were Candidaalbieans.

5. Multi-factor analysis showed that the risk factors of infection in Patients with SLE included: Age, SLE damage involving the system number, SLEDAI scores, prednisone dosage of average daily, neutral grain percentage (NEUT %), platelet count (PLT), serum creatinine (Scr), total bilirubin (TIBL), blood sedimentation (ESR), c-reactive protein (CRP), immunoglobulin G (IgG), procalcitonin (PCT).

Conclusion: SLE has an increased risk for infection. The rate of of nosocomial infection is high. The respiratory tract was the most affected localization and the bacterial infection was the most common. Opportunistic pathogens and resistant bacteria were frequently seen.The older the patient was, the more system damage involved, the higher the SLEDAI score, or the more prednisone dosage was taken, the risker the patient got infection. It suggest that the patient got an infection when the proportion of neutrophils (NEUT %), platelet count (PLT), serum creatinine (Scr), total bilirubin (TIBL), aspertate aminotransferase (AST), blood sedimentation (ESR), c-reactive protein (CRP), calcitonin (PCT) went up , immunoglobulin G (IgG) went down.

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Abstract Number: 1786

Improvements in Health-Related Quality of Life and Fatigue Following Administration of an IL-6

Monoclonal Antibody (PF-04236921) in an Enriched Population of Subjects with Active SLE

Vibeke Strand[1], Annette Diehl[2], Jared Christensen[2], Joseph Wajdula[2], Sudhakar Sridharan[3] and Paul J Healey[2], [1]Biopharmaceutical Consultant, Portola Valley, CA, [2]Pfizer Inc, New York City, NY, [3]PPD Inc, Rockville, MA

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Background/Purpose: The 10 mg dose of PF-04236921 showed evidence of efficacy in a phase 2 randomized controlled trial (RCT) in SLE.[1,2] Here patient-reported outcomes (PROs) from this trial are presented.

Methods: Subjects with active SLE (SLEDAI-2K ≥6; BILAG A in ≥1 organ system or B in ≥2 organ systems) received PF-04236921 10, 50, or 200 mg, or placebo, SC every 8 weeks; the 200 mg dose was prematurely discontinued due to safety findings. The primary endpoint was the SLE Responder Index-4 (SRI-4) at Week 24. Secondary endpoints included Short Form-36 (SF-36), Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue, and European Quality of Life (EQ-5D) visual analog scale (VAS). These PROs were analyzed by least squares (LS) mean changes from baseline at Week 24, without imputation. An enriched population of subjects with one or more indicators of high baseline disease activity (SLEDAI-2K ≥10, detectable anti-dsDNA levels, prednisone >7.5 mg/day, and/or low complement) was defined for a post-hoc analysis.

Results: Baseline SF-36 physical (PCS) and mental component summary (MCS), and domain scores were lower than age- and gender-matched US norms and other RCTs in SLE,[3] indicating that subjects enrolled in this trial were more impacted by their disease. In the enriched population, statistically significant improvements in SF-36 PCS scores were reported with 10 mg versus placebo, and physical functioning, bodily pain, general health and vitality domain scores approached statistical significance; all of which exceeded minimum clinically important differences (MCID; Table 1). Numerical improvements in FACIT-Fatigue and EQ-5D VAS with 10 mg exceeded MCID in both total and enriched populations. Improvements reported with 50 mg differed from placebo, but statistical significance was not achieved in either population (Table 1).

Conclusion: These results demonstrate statistically significant and clinically important improvements in SF-36 PCS scores for the 10 mg dose in the enriched population, supported by changes >MCID in 4 of 8 SF-36 domains, FACIT-Fatigue, and EQ-5D VAS. These results are consistent with the primary efficacy data and indicate greater benefit following treatment with PF-04236921 10 mg in the enriched population.

ClinicalTrials.gov identifier, NCT01405196

1. Wallace D et al. ACR Annual Meeting 2014

2. Smolen J et al. EULAR Annual Meeting 2015

3. Strand V et al. Ann Rheum Dis 2014;73:838-844

Table 1. Summary of Health-related Quality of Life Outcomes in the Total and Enriched Populations at Week 24, According to Treatment with Placebo, PF-04236921 10 mg, or PF-04236921 50 mg.

	Total Population			Enriched Population		
	Placebo (n=45)	10 mg (n=43)	50 mg (n=46)	Placebo (n=33)	10 mg (n=28)	50 mg (n=37)
SF-36 PCS						
Mean score at baseline (SD)	34.64 (10.2)	34.01 (8.0)	34.47 (8.4)	33.68 (10.1)	33.58 (7.9)	34.85 (8.4)
LS mean change from baseline (SE)*	3.08 (1.2)	6.04 (1.2)	5.67 (1.2)	2.80 (1.4)	7.60 (1.5)	5.07 (1.3)
p value versus placebo		0.092	0.129		**0.020**	0.232
SF-36 MCS						
Mean score at baseline (SD)	39.94 (9.7)	39.50 (11.9)	42.36 (9.7)	38.55(10.0)	41.08 (10.9)	41.91 (10.1)
LS mean change from baseline (SE)*	2.95 (1.4)	2.94 (1.4)	2.21 (1.4)	2.04 (1.6)	2.69 (1.7)	1.56 (1.5)
p value versus placebo		0.997	0.706		0.779	0.827
SF-36 Physical Functioning						
Mean score at baseline (SD)	51.44 (27.8)	48.56 (25.2)	51.28 (24.3)	48.03 (28.0)	46.33 (26.5)	51.05 (24.1)
LS mean change from baseline (SE)*	4.99 (3.4)	10.96 (3.5)	12.48 (3.4)	4.62 (4.0)	15.09 (4.4)	12.44 (3.8)
p value versus placebo		0.231	0.124		0.080	0.158
SF-36 Role Physical						
Mean score at baseline (SD)	43.77 (26.8)	38.49 (24.8)	47.09 (21.7)	41.12 (26.2)	39.81 (22.8)	48.21 (21.5)
LS mean change from baseline (SE)*	10.91 (3.4)	15.29 (3.5)	16.05 (3.3)	8.44 (3.9)	14.63 (4.3)	13.83 (3.7)
p value versus placebo		0.368	0.278		0.285	0.321
SF-36 Bodily Pain						
Mean score at baseline (SD)	39.47 (22.5)	37.78 (20.3)	39.94 (20.8)	37.39 (22.3)	38.13 (21.6)	41.13 (21.9)
LS mean change from baseline (SE)*	7.92 (3.2)	13.38 (3.3)	13.94 (3.2)	6.43 (3.9)	17.79 (4.2)	11.56 (3.7)
p value versus placebo		0.245	0.189		0.051	0.338
SF-36 General Health						
Mean score at baseline (SD)	34.42 (18.7)	34.62 (19.0)	33.94 (11.9)	31.82 (18.1)	36.13 (18.9)	33.87 (12.4)
LS mean change from baseline (SE)*	7.35 (2.5)	12.53 (2.6)	5.14 (2.5)	6.80 (2.7)	14.13 (3.0)	4.59 (2.6)
p value versus placebo		0.153	0.532		0.072	0.555
SF-36 Vitality						
Mean score at baseline (SD)	35.02 (22.1)	38.91 (21.4)	41.25 (17.8)	34.30 (20.9)	41.69 (21.4)	41.31 (17.7)
LS mean change from baseline (SE)*	6.86 (3.0)	10.30 (3.1)	7.44 (3.0)	3.45 (3.5)	12.05 (3.8)	4.19 (3.3)
p value versus placebo		0.432	0.893		0.101	0.879
SF-36 Social Functioning						
Mean score at baseline (SD)	51.67 (25.2)	54.44 (24.5)	57.71 (22.1)	46.97 (26.3)	54.58 (24.7)	57.57 (22.8)
LS mean change from baseline (SE)*	7.62 (3.5)	6.78 (3.5)	9.58 (3.4)	5.80 (4.1)	10.02 (4.5)	9.54 (3.9)
p value versus placebo		0.865	0.687		0.493	0.516
SF-36 Role Emotional						
Mean score at baseline (SD)	61.29 (24.6)	56.48 (30.0)	61.17 (27.1)	59.85 (25.7)	57.50 (28.6)	60.97 (26.6)
LS mean change from baseline (SE)*	6.49 (3.4)	6.65 (3.5)	10.80 (3.3)	3.62 (3.7)	5.89 (4.1)	8.98 (3.6)
p value versus placebo		0.974	0.363		0.685	0.302
SF-36 Mental Health						
Mean score at baseline (SD)	57.67 (18.7)	55.00 (20.6)	63.19 (16.2)	53.94 (19.0)	58.17 (21.1)	62.37 (16.5)
LS mean change from baseline (SE)*	5.25 (2.5)	6.96 (2.6)	2.70 (2.5)	4.20 (3.0)	6.78 (3.3)	2.75 (2.9)
p value versus placebo		0.636	0.475		0.563	0.731
FACIT-Fatigue						
Mean score at baseline (SD)	25.96 (11.8)	25.91 (11.4)	29.38 (10.3)	24.61 (11.8)	27.03 (11.4)	28.37 (10.0)
LS mean change from baseline (SE)*	2.82 (1.5)	4.43 (1.6)	3.47 (1.5)	1.16 (1.8)	5.28 (2.0)	3.68 (1.8)
p value versus placebo		0.460	0.763		0.137	0.329
EQ-5D VAS						
Mean score at baseline (SD)	56.69 (22.9)	55.20 (21.5)	57.60 (18.5)	52.45 (23.2)	56.00 (20.8)	56.79 (18.9)
LS mean change from baseline (SE)*	5.99 (2.8)	10.30 (2.8)	6.18 (2.7)	2.30 (3.2)	11.47 (3.5)	6.10 (3.0)
p value versus placebo		0.281	0.961		0.058	0.393

*Shading indicates that the change was greater than the MCID (SF-36 PCS and MCS, >2.5 change from baseline; SF-36 domain scores, >5 change from baseline; FACIT-Fatigue >4, change from baseline; EQ-5D, >10 change from baseline)
EQ-5D, European Quality of Life 5 Dimensions; FACIT, Functional Assessment of Chronic Illness Therapy; MCID, minimum clinically important difference; MCS, mental component score; PCS, physical component score, SD, standard deviation; SE, standard error; SF-36, Short Form-36; VAS, visual analog scale

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Abstract Number: 1787

Innate Immunity, Arterial Inflammation and Vascular Stiffness in Patients with Systemic Lupus Erythematosus

Monica Purmalek[1], Simantini Sakhardande[1], Yenealem Temesgen-Oyelakin[2], Alice Fike[3], Taufiq Salahuddin[4], Balaji Natarajan[4], Zerai Manna[2], Elizabeth Joyal[2], Sarfaraz Hasni[2], Nehal N. Mehta[4] and Mariana J. Kaplan[1], [1]Systemic Autoimmunity Branch, National Institute of Arthritis and Musculoskeletal and Skin Diseases, National Institutes of Health, Bethesda, MD, [2]National Institute of Arthritis and Musculoskeletal and Skin Diseases, National Institutes of Health, Bethesda, MD, [3]Office of the Clinical Director, National Institute of Arthritis and Musculoskeletal and Skin Diseases, National Institutes of Health, Bethesda, MD, [4]NHLBI, National Institutes of Health, Bethesda, MD
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Background/Purpose: Patients with systemic lupus erythematosus (SLE) show a striking increase in risk of atherosclerotic cardiovascular disease (CVD) not explained by Framingham risk, compared to age and gender matched controls. Immune dysregulation and innate immune responses associated to aberrant neutrophils (low density granulocytes, LDGs) and neutrophil extracellular traps (NETs) may play key roles in conferring enhanced CV risk, driving vascular damage and, potentially, atherosclerosis. Whether neutrophils are associated to and predict vascular inflammation and eventually clinical vascular events remains to be determined.

Methods: SLE patients fulfilling ACR classification criteria were compared to age and gender-matched controls. Clinical and demographic characteristics were recorded at each visit. Individuals underwent assessment of a) vascular function of various arterial territories (peripheral arterial tonometry of the

microvasculature (Endopat) and arterial compliance by cardio-ankle vascular index (CAVI)); b) aortic inflammation by FDG-PET/CT; c) anatomical assessment of plaque by coronary CT angiogram. Circulating LDGs were quantified by flow cytometry and NET products in plasma were quantified by ELISA.

Results:

Lupus (n=20) and healthy controls (n=15) did not differ in age, gender, ethnicity, tobacco use, Framingham score, or insulin resistance. Median disease duration was 20.5 years (IQR 9.3-54 years) and SLEDAI was 2+4.8. Arterial stiffness, assessed by CAVI and by Endopat augmentation index (AI), was increased in SLE (CAVI: 7.24[5.6-9.3]) vs. controls (6.53[5.1-8.3]; p = 0.03; AI: 25.7[0.05-78.9]) vs. controls (6.81[-17.4-55.4], p = 0.003). SLE patients displayed enhanced arterial inflammation by FDG-PET/CT (target:background ratio (TBR; SLE 1.67(1.4-2.3) vs. controls 1.52(1.4-1.7), p=0.05). Differences in control and SLE persisted in multivariate regression analysis adjusting for age and gender (TBR and Endopat), and Framingham risk score and BMI (CAVI and Endopat).Use of antimalarials or steroids was negatively associated with arterial stiffness (r=-0.44, p=0.05 and r=-0.51, p=0.02, respectively). LDGs, and plasma NET products were elevated in SLE and associated with enhanced arterial inflammation (TBR) and noncalcified plaque burden

Conclusion: Individuals with SLE demonstrate increased arterial stiffness and prominent arterial inflammation suggestive of enhanced risk for unstable plaque. Dysregulation in neutrophil function and NETosis occurs in vivo in SLE in association with arterial inflammation and vascular dysfunction. These observations indicate that neutrophils may be important drivers of vascular damage in SLE.

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Abstract Number: 1788

Lipoprotein Subfractions and Cardiovascular Disease in Systemic Lupus Erythematosus

Simantini Sakhardande[1], Monica Purmalek[1], Maureen Sampson[2], Yenealem Temesgen-Oyelakim[3], Alice Fike[4], Taufiq Salahuddin[5], Balaji Natarajan[5], Zerai Manna[6], Elizabeth Joyal[6], Marcus Chen[5], Sarfaraz Hasni[6], Nehal N. Mehta[5,7], Alan Remaley[5] and Mariana J. Kaplan[1], [1]Systemic Autoimmunity Branch, National Institute of Arthritis and Musculoskeletal and Skin Diseases, National Institutes of Health, Bethesda, MD, [2]CC/NIH, Bethesda, MD, [3]Office of the Clinical Director,National Institute of Arthritis and Musculoskeletal and Skin Diseases, National Institutes of Health, Bethesda, MD, [4]Office of the Clinical Director, National Institute of Arthritis and Musculoskeletal and Skin Diseases, National Institutes of Health, Bethesda, MD, [5]NHLBI, National Institutes of Health, Bethesda, MD, [6]National Institute of Arthritis and Musculoskeletal and Skin Diseases, National Institutes of Health, Bethesda, MD, [7]National Heart Lung Blood Institute, Cardiovascular and Pulmonary Division, NHLBI, National Institutes of Health, Bethesda, MD
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Background/Purpose: Risk of atherosclerotic cardiovascular disease (CVD) is significantly enhanced in systemic lupus erythematosus (SLE) compared to age and gender matched controls. While this risk is not explained by the Framingham equation, lipoprotein abnormalities in phenotype and function have been detected in SLE. Recent studies in the general population suggest that CV risk may be more closely related to atherogenic lipoprotein particle numbers than LDL cholesterol. However, this association in SLE remains incompletely characterized. To this effect, associations between lipoprotein particle subfractions and disease activity, vascular dysfunction, and arterial inflammation in SLE and healthy controls were assessed.

Methods: SLE (n=20) and age and gender matched controls (n=15) underwent vascular function and anatomical assessments measuring peripheral arterial tonometry of the microvasculature (Endopat), arterial stiffness by cardio-ankle vascular index (CAVI), aortic inflammation by FDG-PET/CT, and quantification of plaque by coronary CT angiogram (CTA). Particle concentrations of lipoprotein subfractions and particle sizes were measured by nuclear magnetic resonance spectroscopy (LipoScience).

Results: Lupus and control individuals did not differ in age, gender, tobacco use, standard lipid profile, BMI, or Framingham score. Total HDL, medium HDL, and intermediate–density lipoprotein (IDL) particle counts were significantly decreased in SLE (p=0.02, 0.015, 0.018, respectively) while VLDL and small VLDL particle counts were increased (p=0.048 and 0.035, respectively). In SLE, arterial stiffness assessed by CAVI correlated positively with total HDL particle count (r=0.489, p=0.03) and negatively with large VLDL particle count (r=-0.553, p=0.01). Arterial inflammation, assessed by target:background ratio in FDG-PET/CT, significantly correlated with medium VLDL particle count (r=0.51, p=0.05), while noncalcified burden of the right coronary artery negatively correlated with large+medium VLDL particle counts (r=-0.57, p=0.05). There was a significant difference (p=0.023) in small HDL particle count (p=0.023) between SLE patients on prednisone (median=11.4 [IQR: 7.3-15.1]) and not on prednisone (median=19.9 [IQR: 13.8-21.8]). Furthermore, there was a negative correlation between SLEDAI and total HDL particle count in SLE (r=-0.454, p=0.044).

Conclusion: Individuals with SLE demonstrate significant differences in lipoprotein particle size and composition that associate with markers of vascular risk. The role medications play in these abnormalities remains to be determined. Longitudinal analysis will assess whether abnormalities in lipoprotein composition predict progression of CVD in SLE and determine the utility of following changes in lipoprotein subfractions as therapeutic targets.

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Abstract Number: 1789

Infections Observed in Rituximab Treated Patients with Refractory Systemic Lupus Erythematosus (SLE): Results from a National Multicentre Register

Eoghan M. McCarthy[1,2], Emily Sutton[3], David A. Isenberg[4], Anisur Rahman[4], Benjamin Rhodes[5], Peter Hewins[6], Neil J McHugh[7], Ben Parker[8], Bridget Griffiths[9], Peter Lanyon[10], Edward M. Vital[11], Lee-Suan Teh[12], Mohammed Akil[13], Hazem Youssef[14], David P. D'Cruz[15], Munther Khamashta[16], Nicola Erb[17], David Jayne[18], Christopher J. Edwards[19], Athiveer Prabu[20], Michael Batley[21], Nagui Gendi[22], Bhaskar Dasgupta[23,24], Richard J. Stratton[25], Chee-Seng Yee[26], Asad Zoma[27], Caroline Gordon[28], Antoni Chan[29], Steven Young Min[30], Shirish Dubey[31], Jon King[32], Denise De Lord[33], Edmond O'Riordan[34], Rachel Jeffery[35], Waji Hassan[36], Marian Regan[37] and Ian N. Bruce[38], [1]NIHR Manchester Musculoskeletal Biomedical Research Unit, Central Manchester University Hospital NHS Foundation Trust, Manchester, United Kingdom, [2]The University of Manchester, Centre for Musculoskeletal Research, Institute of Inflammation and Repair, Manchester Academic Health Science Centre, Mmanchester, United Kingdom, [3]University of Manchester, Manchester Academic Health Science Centre, Arthritis Research UK Centre for Epidemiology, Manchester, United Kingdom, [4]Centre for Rheumatology Research, University College London, London, England, [5]Rheumatology, Queen Elizabeth Hospital, Birmingham, United Kingdom, [6]Queen Elizabeth Hospital, Birmingham, United Kingdom, [7]Rheumatology, Bath Institute of Rheumatic Diseases, Royal National Hospital for Rheumatic Diseases, Bath, United Kingdom, [8]Stopford Building, Arthritis Research UK Centre for Epidemiology, Centre for Musculoskeletal Research, Institute of Inflammation and Repair, Manchester Academic Health Science Centre, The University of Manchester, Manchester, United Kingdom, [9]Rheumatology, Freeman Hospital, Newcastle Upon Tyne, United Kingdom, [10]Nottingham University Hospitals NHS Trust, Nottingham, United Kingdom, [11]Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds, Leeds, United Kingdom, [12]Department of Rheumatology, Royal Blackburn Hospital, Blackburn, United Kingdom, [13]Sheffield Center Rheumatic Dis, Sheffield South Yorkshire, United Kingdom, [14]Department of Rheumatology, NHS Grampian, Aberdeen, United Kingdom, [15]Louise Coote Lupus Unit, Guy's and St Thomas' Hospital, London, United Kingdom, [16]Louise Coote Lupus Unit, St Thomas' Hospital, London, United Kingdom, [17]Department of Rheumatology, The Dudley Group NHS Foundation Trust, Dudley, United Kingdom, [18]Medicine, Addenbrooke's Hospital, Cambridge, United Kingdom, [19]University Hospital Southampton, Southampton, United Kingdom, [20]Worcester Royal Hospital, Worcester, Worcester, United Kingdom, [21]Rheumatology, Maidstone and Tunbridge Wells Hospital, Kent, United Kingdom, [22]Rheumatology, Basildon & Thurroch University Hospitals NHS Trust, Basildon, Essex, United Kingdom, [23]Southend University Hospital, Southend, United Kingdom, [24]Rheumatology, Southend University Hospital, Essex, United Kingdom, [25]Centre for Rheumatology and Connective Tissue Disease, University College London, London, United Kingdom, [26]Department of Rheumatology, Doncaster and Bassetlaw Hospitals NHS Foundation Trust, Doncaster, United Kingdom, [27]Rheumatology, Hairmyres Hospital, East Kilbride, United Kingdom, [28]Rheumatology Research Group, School of Immunity and Infection, College of Medical and Dental Sciences, University of Birmingham, Birmingham, United Kingdom, [29]Rheumatology, Royal Berkshire NHS Foundation Trust, Reading, United Kingdom, [30]Rheumatology, Queen Alexandra Hospital, Portsmouth, United Kingdom, [31]Rheumatology, University Hospitals Coventry and Warwickshire, Coventry, United Kingdom, [32]Rheumatology, Derriford Hospital, Plymouth, United Kingdom, [33]Rheumatology, Queen Elizabeth the Queen Mother Hospital, East Kent, United Kingdom, [34]Renal Medicine, Salford Royal Foundation Trust, Manchester, United Kingdom, [35]Rheumatology, Northampton General Hospital, Northampton, United Kingdom, [36]Rheumatology, University Hospitals of Leicester, Leicester, United Kingdom, [37]Rheumatology, Royal Derby Hospital, Derby, United Kingdom, [38]Central Manchester University Hospital NHS Foundation Trust and Manchester Academic Health Science Centre, NIHR Manchester Musculoskeletal Biomedical Research Unit, Manchester, United Kingdom

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Background/Purpose:

SLE is associated with a significantly increased risk of infection. Both disease activity and the medications required to control disease are contributory factors. Rituximab is used in the treatment of SLE patients refractory to standard immunosuppressive therapy. The objective of this analysis is to describe the frequency and pattern of infections associated with Rituximab use in this cohort of SLE patients.

Methods:

Patients with SLE (≥ 4 ACR 1997 criteria) on Rituximab enrolled in the BILAG-BR, a UK, multicentre, prospective study of safety and efficacy of biologics in SLE were analysed. Infection related events were coded using Medra software. Serious infections (SI) were defined as any infection resulting in treatment with iv antibiotics, hospitalisation, disability or death. For the purposes of the study, infections occurring within 9 months of Rituximab were deemed to be therapy related.

Results:

In the period May 2010-March 2015, 208 Rituximab treated patients were followed for a median (IQR) of 1 (0.5-2) yrs. There were 204 infectious episodes observed in 77 (37%) patients, 173 (85%) of which occurred within the 9 month period of interest. 50 patients suffered multiple infections. There were 25 (14%) serious infections in 20 (10%) patients within the 9 month window. The overall and serious infection rates/100 patient years follow up were 57.9 and 8.3 respectively.

The frequency of all infections and SI's are described in Table 1.The most frequent opportunistic infections reported were Candida (n=8 in 7 patients) and Herpes zoster (shingles) (n=6 in 6 patients).

The highest rate of infections occurred in the first 3 months following treatment with Rituximab: 102 (59%) which declined over time, with 57 (33%) infections occurring between 3 - 6 months and 14 (8%) between 6 – 9 months. A similar trend was noted for SI's with 14 (56%) occurring within 3 months, 8 (32%) at 3-6 months and 3 (12%) at 6-9 months.

There was a higher number and proportion of non-respiratory infections within the first 3 months post-rituximab (non-respiratory infections: < 3 months = 55/102 (54%) vs 3–9 months = 27/71 (38%), OR 1.9 (95% C.I. 1.03-3.5, p = 0.04). There were no significant differences in individual SI's across the time points, although the proportion of non-respiratory SIs was also higher in the first 3 months post-rituximab [8/14 (58%) vs 4/11 (36%)].

No infection related deaths were reported.

Conclusion:

An increased number of infections were observed in the first 3 months post-rituximab therapy with a higher proportion of these early infections being non-respiratory in nature. This could be explained by the period of maximum B cell depletion, the effect of concomitant glucocorticoids or the effect of disease activity before maximum efficacy of rituximab. Physicians and patients should have increased vigilance for infection, particularly in the early months following rituximab therapy.

Table 1. Infection rates in Rituximab treated patients.

	All infections (% all infections)	Serious Infections (% total SI)
Total	173	25
Respiratory	91 (53)	14 (52)
Urinary	30 (17)	3 (11)
Opportunistic	15 (9)	1 (4)
Skin	10 (6)	0 (0)
GI	7 (4)	4 (15)
Other	20 (12)	3 (19)

Disclosure: E. M. McCarthy, None; **E. Sutton**, None; **D. A. Isenberg**, Bristol-Myers Squibb, 2; **A. Rahman**, Bristol-Myers Squibb, 2; **B. Rhodes**, None; **P. Hewins**, None; **N. J. McHugh**, None; **B. Parker**, None; **B. Griffiths**, None; **P. Lanyon**, None; **E. M. Vital**, None; **L. S. Teh**, None; **M. Akil**, None; **H. Youssef**, None; **D. P. D'Cruz**, GlaxoSmithKline, 2,UCB, 8,Eli Lilly and Company, 5; **M. Khamashta**, Bristol-Myers Squibb, 2; **N. Erb**, None; **D. Jayne**, None; **C. J. Edwards**, Abbvie, Pfizer, Lilly, Celtrion, Mundipharma, Samsung, Anthera, UCB, Celgene, Roche, Bristol-Myers Squibb, Janssen, 8; **A. Prabu**, None; **M. Batley**, None; **N. Gendi**, None; **B. Dasgupta**, GSK, Servier,UCB, 5; **R. J. Stratton**, None; **C. S. Yee**, None; **A. Zoma**, Bristol-Myers Squibb, 2; **C. Gordon**, UCB, 2,UCB,, 5,Merck Pharmaceuticals, 5,Paraxel, 5,Eli Lilly and Company, 8; **A. Chan**, None; **S. Young Min**, None; **S. Dubey**, None; **J. King**, None; **D. De Lord**, None; **E. O'Riordan**, None; **R. Jeffery**, None; **W. Hassan**, None; **M. Regan**, Roche Pharmaceuticals, 8,Chugai, 8; **I. N. Bruce**, Bristol-Myers Squibb, 2,GSK, 8,Roche Pharmaceuticals, 5.

Abstract Number: 1790

Mycophenolate Mofetil Suppresses Humoral Response to Pneumococcal Vaccine in Patients with Systemic Lupus Erythematosus and Other Autoimmune Diseases

Mark Tratenberg[1,2], Julia Ash[1], Kirk Sperber[1], Amy Wasserman[3] and Slavica Bobic[1], [1]Rheumatology, New York Medical College, Valhalla, NY, [2]Medicine-Rheumatology, New York Medical College, Valhalla, NY, [3]New York Medical College, Valhalla, NY

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Background/Purpose: To determine the efficacy of pneumococcal polysaccharide vaccine (PPV-23) in patients on mycophenolate mofetil (MMF) therapy and compare efficacy to other DMARDS.

Methods: In a pilot study, we evaluated 20 patients immunized with PPV-23. The MMF study group included 10 patients (8 SLE, 1 uveitis and 1 dermatomyositis). The control group also included 10 patients (4 RA, 3 SLE, 1 PsA, 1 uveitis) treated with methotrexate, hydroxychloroquine or etanercept. Both groups were similar regarding average age, (put in ages of both groups) gender (put in % female of the both groups) and prednisone use (put in % prednisone use of both groups). Serum samples for 14 pneumococcal serotypes were collected pre-immunization and eight weeks post-immunization. Serum IgG titers were analyzed using ELISA. We calculated the stimulation index (SI) of 14 serotypes by dividing the post-immunization titer by the pre-immunization titer to determine vaccination efficacy. Based on the American Academy of Allergy, Asthma and Immunology (AAAAI) definition of protective titers, the primary endpoints of the study were either a ≥ 2-fold, > 3-fold or > 4-fold increase in post-immunization antibody titers and ≥ 1.3ug/ml antibody concentration in at least 70% of the 14 pneumococcal serotypes.

Results: Humoral responses to PPV23 in patients treated with MMF were significantly lower compared to the control group. Suppressed antibody responses were observed in the MMF group as defined by a lack of 4-fold ($p = 0.0001$), 3-fold ($p = 0.001$), and 2-fold ($p = 0.0163$) increase in the SI vs the control group. Twenty percent of patients receiving MMF (n=3) and fifty percent of patients (n=8) in the control group had a ≥ 2-fold increase in post-immunization antibody titers to 10 of the 14 serotypes. Forty percent of patients in the MMF group had protective antibody levels (> 1.3 ug/ml) as compared to sixty percent on other DMARDS (8.29 + 2.79 vs 9.22 + 4.84, $p = 0.51$). Statistical significant differences were also observed in serotypes 51 and 4 ($p = 0.05$ and $p = 0.025$ respectively) between MMF and the control group.

Conclusion: To our knowledge, this is the first investigation of the efficacy of pneumococcal polysaccharide vaccine (PPV-23) in patients taking MMF for SLE and other autoimmune diseases. In this pilot study, humoral responses following pneumococcal vaccination in patients receiving MMF were suppressed and lower than in patients on other DMARDS. The recommendation for pneumococcal immunization prior to MMF initiation is therefore supported.

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Abstract Number: 1791

Does Renin-Angiotensin System Blockade Protect Lupus Nephritis Patients from Atherosclerotic Cardiovascular Events? a Case-Control Study

Konstantinos Tselios[1], Dafna Gladman[2], Jiandong Su[2] and Murray Urowitz[2,3], [1]Medicine, University of Toronto, Toronto Western Hospital, Toronto, ON, Canada, [2]Rheumatology, University of Toronto, Toronto Western Hospital, Toronto, ON, Canada, [3]Rheumatology, U of Toronto, Toronto Western Hospital, Toronto, ON, Canada

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Background/Purpose: Angiotensin converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) are currently used as an adjuvant treatment in lupus nephritis (LN) patients for the optimal control of proteinuria. However, it is not known if these agents have an atheroprotective effect, similar to that described in other at-risk populations. The aim of this study was to assess their atheroprotective role in LN.

Methods: Using the electronic database of the longitudinal observation cohort study of the University of Toronto Lupus Clinic, we identified 144 patients (123 females, mean age at disease onset 34±12.1 years, mean follow up time 14.9±8.6 years) with LN (diagnosis according to 1997 ACR criteria) who were treated with ACEIs/ARBs for, at least, 5 years for proteinuria. The control group comprised of 301 LN patients (262 females, mean age at disease onset 34.1±13.2, mean follow up time 13.4±7.9 years) who did not receive ACEIs/ARBs treatment. All patients were followed for the occurrence of atherosclerotic cardiovascular events (CVEs), consisting of transient ischemic attack and stroke, angina, myocardial infarction (MI), percutaneous transluminal coronary angioplasty (PTCA), coronary artery bypass graft (CABG), congestive heart failure and pacemaker insertion as well as peripheral vascular disease. Patients with pre-existing CVEs were excluded. Statistical software SAS (version 9.3) was used for analysis; $p<0.05$ was considered significant.

Results: There were no significant differences in the cumulative occurrence of CVEs between the two groups [14/144, 9.7% for treated vs 26/301, 8.6% for untreated patients, $p=0.708$]; however, hard events (stroke, MI, CABG, PTCA) were less frequent in treated patients [6/144, 4.17% vs 16/301, 5.32%]. Details on the type of CVEs in the two groups are presented in the table.

	TIA	Stroke	Angina	MI	PTCA	CABG	CHF	Pacemaker	PVD
Treated (n=144)	0	1	8	3	1	1	2	0	1
Non-treated (n=301)	1	6	6	5	2	3	1	2	1

TIA: transient ischemic attack, CHF: congestive heart failure, PVD: peripheral vascular disease

Patients treated with ACEIs/ARBs were more frequently hypertensive [100% vs 52.8%, $p<0.001$] and diabetic [10.4% vs 4.7%, $p=0.021$] whereas the

controls had more frequently hypercholesterolemia [27.9% vs 18.1%, p=0.024] and elevated triglycerides [14% vs 4.9%, p=0.004]; other parameters did not differ significantly. Regression analysis (Weibull parametric model) failed to confirm ACEIs/ARBs non-use as an important predictor of future CVEs. The only significant predictors in both groups were age at LN diagnosis and cumulative corticosteroid dose.

Conclusion: Our data do not support the hypothesis that ACEIs/ARBs may be protective against atherosclerotic CVEs in LN patients. In this cohort, only age at LN diagnosis and cumulative prednisone dose were important predictors for these outcomes.

Disclosure: K. Tselios, None; **D. Gladman**, None; **J. Su**, None; **M. Urowitz**, None.

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Abstract Number: 1792

Optimal Monitoring for Coronary Heart Disease Risk in Systemic Lupus Erythematosus Patients: a Systematic Review

Konstantinos Tselios[1], Barry J. Sheane[2], Dafna Gladman[3] and Murray Urowitz[3,4], [1]Medicine, University of Toronto, Toronto Western Hospital, Toronto, ON, Canada, [2]Rheumatology, St James Hospital, Dublin, Ireland, [3]Rheumatology, University of Toronto, Toronto Western Hospital, Toronto, ON, Canada, [4]Rheumatology, U of Toronto, Toronto Western Hospital, Toronto, ON, Canada

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Background/Purpose: Premature coronary heart disease (CHD) represents a significant cause of morbidity and mortality in systemic lupus erythematosus (SLE). Several studies have been conducted to identify traditional and disease-related factors that have an impact on the atherosclerotic process, as well as methods to quantify the atherosclerotic burden in subclinical stages. Aim of this systematic review was to identify the minimum investigations to optimally monitor the risk of atherosclerotic CHD in SLE in routine practice.

Methods: An English-restricted systematic literature review was performed, using PRISMA guidelines, through Ovid Medline, Embase and the Cochrane Central databases from inception until the third week of May 2014. Specific search-terms included, among others, “systemic lupus erythematosus”, “atherosclerosis”, “coronary artery disease”, “myocardial ischemia”, “acute coronary syndrome”, “myocardial infarction”, “angina pectoris”. Two independent reviewers assessed all articles (5178 in total); upon disagreement, final decision was reached through discussion with a third reviewer. We finally identified 101 eligible articles, 23 with cardiovascular events (CVEs) and 78 with measures of subclinical atherosclerosis as end-points. The Newcastle-Ottawa scale for observational studies was used for quality assessment (all included studies had ≥6 stars).

Results: Both traditional and disease-specific risk factors were identified with independent predictive ability for clinical CHD. The most consistent traditional factors were age (particularly 48 years or in post-menopausal state), male gender, arterial hypertension, dyslipidemia and smoking. SLE factors most commonly associated with clinical CHD were overall disease activity, cumulative damage, disease duration, antiphospholipid antibodies, high sensitivity C-reactive protein and renal disease. Corticosteroids were linked to increased atherosclerotic risk; anti-malarials were shown to be protective. In regard to imaging techniques, only carotid ultrasonography for the assessment of intima-media thickness and plaque area were shown to independently predict future CVEs in lupus patients. Relative risks for CVEs for each identified risk factor are shown in the table.

Parameter						
	Age	Male gender	Hypertension	Dyslipidemia	Smoking	
RR	1.04-5.1	1.56-6.2	1.05-3.5	TC: 3.9-6.9 TG: 1.15-8	2.2-3.7	
	Disease activity	Cumulative damage	Disease duration	Renal disease	aPL	hs-CRP
RR	1.05-1.2	1.3-4.1	1.1-4.5	1.2-6.8	1.74-5.8	1.6-3.4
	IMT	TPA				
RR	2.02	4.26-9.55				

RR: relative risk, TC: total cholesterol, TG: triglycerides, aPL: antiphospholipid antibodies, IMT: intima-media thickness (carotid artery), TPA: total plaque area (carotid artery)

Conclusion: Premature CHD in lupus patients is multifactorial; modifiable traditional risk factors should be monitored initially and at frequent intervals to ensure prompt management. Disease specific factors play a key role in the atherogenetic process and should also be evaluated on a regular basis. Carotid ultrasonography holds promise in predicting cardiovascular events in SLE and should be performed in selected high-risk patients.

Disclosure: K. Tselios, None; **B. J. Sheane**, None; **D. Gladman**, None; **M. Urowitz**, None.

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Abstract Number: 1793

Is There a Relationship Between Antimalarial Treatment and Elevated Muscle Enzymes in Systemic Lupus Erythematosus

Konstantinos Tselios[1], Dafna Gladman[2], Jiandong Su[2] and Murray Urowitz[2,3], [1]Medicine, University of Toronto, Toronto Western Hospital, Toronto, ON, Canada, [2]Rheumatology, University of Toronto, Toronto Western Hospital, Toronto, ON, Canada, [3]Rheumatology, U of Toronto, Toronto Western Hospital, Toronto, ON, Canada

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Background/Purpose: Elevated muscle enzymes in the course of systemic lupus erythematosus (SLE) usually represent active myositis or drug-related toxicity. Lipid-lowering agents and, less frequently, antimalarials (chloroquine, CQ and hydroxychloroquine, HCQ) have been implicated. Aim of this observational cohort study was to delineate the possible role of antimalarials in inducing myotoxicity.

Methods: Patients with SLE have been followed prospectively s according to a standard protocol at 2-6 month interval. From this cohort we identified 325 patients who had elevated muscle enzymes, defined as abnormal creatine phosphokinase (CPK) measurements in at least two consecutive visits. Fifty-four patients on statins/fibrates and/or myositis were excluded. The final cohort of 271 patients (cases) were compared to 1453 patients who never had elevated CPK levels during their follow-up (controls) with regard to epidemiological variables and antimalarial treatment. Statistical software SAS (version 9.3) was used for analysis; $p<0.05$ was considered significant.

Results: Cases and controls did not differ with regard to gender, age at disease diagnosis and disease duration. Controls were characterised by higher disease activity and cumulative damage. Black patients were more commonly had elevated CPK levels (57/271, 21% vs. 143/1453, 9.8%, $p<0.001$). Antimalarial use was more frequent in cases (216/271, 79.7% vs 821/1453, 56.5%, $p<0.001$). Total frequency of elevated CPK in antimalarial users was 216/1322, 16.3%. Duration of antimalarial use was longer in patients with elevated CPK levels (4.33±4.96 years vs. 3.84±5.47 years, $p<0.001$). Cox multiple regression analysis showed antimalarials to be strong predictors for CPK elevation [HR=8.6 (CI=5.7-13) for CQ, $p<0.001$ and HR=7.4 (CI=5.2-10.4) for HCQ, $p<0.001$]. The cumulative CQ dose before the first abnormal CPK measurement was 148±324g in 2.0±4.4 years; for HCQ that was 307±426g in 2.6±3.6 years. In all patients CPK levels did not exceed 2-4x the upper limit of normal regardless of the duration of therapy. Over 7.3±5.6 years of follow-up, 18 patients (8.3%) developed clinical myopathy with proximal muscle weakness of the lower limbs. Of 203/216 patients who had more than 2 subsequent clinic visits after the second visit with elevated CPK and continued taking antimalarials, 101 (49.8%) patients had persistent enzyme elevation, 30 (14.8%) had intermittent elevation whereas in 72 (35.4%) CPK normalised immediately or shortly after that visit. Of note, one patient developed HCQ-induced cardiomyopathy after 13 years and a cumulative dose of 1623g.

Conclusion: Chronic antimalarial use is a risk factor for muscle enzyme elevation in SLE patients. In the vast majority of patients, CPK elevation remains a biochemical abnormality as it evolves to clinical myopathy in less than 10%; however, it persists in almost two thirds of the patients with continuous antimalarial treatment. Further studies are needed to assess abnormal CPK value in predicting serious outcomes, such as cardiomyopathy.

Disclosure: K. Tselios, None; **D. Gladman**, None; **J. Su**, None; **M. Urowitz**, None.

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Abstract Number: 1794

Unexplained Decline in Rates of Cardiovascular Events in a Large Cohort of SLE Patients

Michelle Petri[1] and Laurence S Magder[2], [1]Johns Hopkins University School of Medicine, Baltimore, MD, [2]University of Maryland School of Medicine, Baltimore, MD

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Background/Purpose: We have observed a decline in rates of cardiovascular events in systemic lupus erythamatosus (SLE) pateints in our clinic. In this work presented below, we have quantified the decline in rates and assessed the degree to which the decline could be explained by changes in medication use (greater use of hydroxychoroquine, reduced use of corticosteroids), tighter control of cardiovascular risk factors, or demographic changes in our clinic.

Methods: This analysis is based on retrospective data from the Hopkins Lupus Cohort experience since 1993. A cardiovascular event (CVE) was defined as the occurrence of a stroke, myocardial infarction (MI), coronary procedure, incident angina, or claudication. The analysis was performed based on a data set with one record per patient-month of participation in the Hopkins Lupus Cohort. Each record contained data regarding the patient's clinical history up until that time, the most recently measured levels of disease activity, medications taken at that time, and whether a CVE occurred during that month. Using this file, rates of CVE per person-year of follow-up were calculated for subgroups of follow-up defined by date, medication, disease activity, and demographics. Multivariable models were fit using pooled logistic regression.

Results: Table 1 shows the rates of CVE at different periods of time. The rate of events dropped by approximately 50% after 2010. Table 2 shows the rates of events by calendar time in strata defined by potentially explanatory variables. The reduction in CVE rates after 2010 was observed in all strata defined by corticosteroid or hydroxychloroquine use, systolic blood pressure, and lupus disease activity. Based on a multivariable model, the reduced rates of CVE after 2010 persisted after adjusting simultaneously for age, race, sex, recent systolic blood pressure and serum cholesterol, history of diabetes, smoking, recent SLE disease activity, corticosteroid dose and hydroxychloroquine use (Odds ratio comparing 2010-2014 to previous years: 0.53, 95% confidence interval 0.32, 0.88, p-value=0.015)

Table 1: Rate of cardiovascular events during cohort participation by year

Calendar Year	Number of Events	Person-years of Follow-up	Rate per 1000 person-yrs
1993-1998	20	2,009	10.0
1999-2004	50	3,742	13.4
2005-2009	51	3,951	12.9
2010+	25	4,108	6.1

Table 2. Rates of cardiovascular events by period in strata defined by potentially confounding or explanatory variables.

Stratifying Variable	1993-2009			2010-2014		
	Events	Person-Years	Rate per 1000 person-yrs	Events	Person-years	Rate per 1000 person-yrs
Recent Prednisone use	43	4278	10.1	10	2043	4.9
None	28	2364	11.8	7	829	9.1
1-9	24	1262	19.0	2	260	7.7
10-19	21	571	36.8	2	96	20.9
20+						
Recent Plaquenil use	49	2981	16.4	6	614	9.8
No	67	5493	12.2	18	3285	5.5
Yes						
Most Recent SBP	28	3560	7.9	6	1755	3.4
<120	27	1918	14.1	8	807	9.9
120-129	20	1434	13.9	2	641	3.1
130-139	23	1276	18.0	5	500	10.0
140-159	11	302	36.5	3	120	25.1
160+						
Most Recent SLEDAI	33	3558	9.3	8	1656	4.8
0	24	2192	10.9	5	1147	4.4
1-2	27	1561	17.3	3	566	5.3
3-4	26	1197	21.7	8	454	16.4
5+						

Conclusion: The reduced rate of cardiovascular events could not be explained by demographics, medications, cardiovascular risk factors, or lupus-specific variables. Further work is needed to explain the drop in rates. Identifying the reason for the drop in rates could have important implications for CVE prevention among SLE patients.

Disclosure: M. Petri, None; **L. S. Magder**, None.

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Abstract Number: 1795

Long-Term Safety and Efficacy of Tacrolimus for Lupus Nephritis Patients in Real World Setting -Results from 5 Year Interim Analysis of Post Marketing Surveillance of 1376 Patients in Japan-

Tsutomu Takeuchi[1] and Naoko Wakasugi[2], [1]Division of Rheumatology, Department of Internal Medicine, Keio University School of Medicine, Tokyo, Japan, [2]Astellas Pharma Inc., Tokyo, Japan

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Background/Purpose:

Tacrolimus (Tac) is an immunosuppressive macrolide that blocks T cell activation by specifically inhibiting calcineurin. Some randomized controlled studies have shown that TAC is an effective for induction and maintenance treatment for lupus nephritis (LN). However, there are few reports of the long term outcome of TAC for LN patients in the large real clinical setting.To assess the long-term safety and efficacy of TAC for LN patients in the real clinical setting, post-marketing surveillance was conducted (NCT01410747).

Methods:

All the patients TAC administered for LN were registered between 2007 and 2010, and the registered patients will be followed for 10 years, the safety and efficacy were evaluated at the 28 week and each year. The primary efficacy endpoint is renal failure, and secondary endpoints are urine protein creatinine ratio, serum creatinine (estimated glomerular filtration rate (eGFR)), serum component C3, anti-ds DNA and steroid dosage.

Results:

This interim analysis included all the registered 1376 patients from 292 medical sites, and the median follow up period is 1827.0 days (5 years), including 215 patients with biopsy-proven Class IV and 159 patients with Class V. The most common serious adverse drug events (ADRs) were infections, in which herpes zoster, cellulitis and diabetes mellitus, at incidence rates of 1.0%, 0.9% and 0.8%, respectively. The TAC continuation rate was 83.5% at 1 year and 71.3% at 3 years, and 62.9% at 5 years. There was a significant decrease in urine protein creatinine ratio from the 4 weeks later after TAC treatment, also the serum component C3 and anti-ds DNA antibodies were improved from the 4 weeks later and the eGFR was maintained for 5 years in both Class IV and Class V.

Conclusion:

These results show the long term safety and efficacy of TAC for LN maintenance treatment in the real clinical setting.

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Abstract Number: 1796

Progression of Atherosclerosis Might be Prevented By Decrease of Serum Resistin Level after Glucocorticoid Therapy in Patients with Systemic Autoimmune Disease

Shotaro Masuoka, Nahoko Tanaka, Natsuko Kusunoki, Tatsuhiro Yamamoto, Kaichi Kaneko, Sei Muraoka, Makoto Kaburaki, Kotaro Shikano, Natsuki Fujio, Hiroshi Sato, Mai Kawazoe, Emiko Shindo, Soichi Yamada, Kenji Takagi, Toshihiro Nanki and Shinichi Kawai, Division of Rheumatology, Department of Internal Medicine, School of Medicine, Faculty of Medicine, Toho University, Tokyo, Japan

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Background/Purpose: Development of atherosclerosis is accelerated in patients with systemic autoimmune diseases. However, underlying mechanisms of accelerated atherosclerosis remains unknown, and the impact of pharmacotherapies such as glucocorticoid on atherosclerosis is still controversial in these patients. Adipose tissue synthesizes and releases physiologically active molecules that are known as adipokines. It have recently been implicated that they are important regulators of several processes including inflammation and they may also play a role in atherosclerosis. We then prospectively investigated the association of adipokines and glucocorticoid therapy with progression of premature atherosclerosis in patients with systemic autoimmune diseases.

Methods: Thirty-eight patients (27 women, mean age of 49.3 ± 15.2 years old) with systemic autoimmune diseases, including systemic lupus erythematosus (n=16) , polymyositis/dermatomyositis (n=14), vasculitis syndrome (n=6) and adult onset Still's disease (n=2) were enrolled in this study. All subjects had active disease and started glucocorticoid therapy (prednisolone at 30 mg or more daily). Patients who had previously taken glucocorticoid or other immunosuppressive drugs were excluded. The carotid arteries were examined by ultrasonography to detect premature atherosclerosis at initiating glucocorticoid therapy and after a follow-up of mean 3 years. Serum levels of 3 adipokines [resistin, leptin, and high molecular weight (HMW)-adiponectin] were measured with respective enzyme-linked immunosorbent assay kit.

Results: Twenty-three of the 38 patients (60.5%) had carotid artery plaques at baseline. Among those without plaque at baseline, 2 patients (5.3%) showed new plaques after follow-up periods. Intima-media thickness (IMT) was significantly increased from median 0.675 (IQR 0.500-0.813) mm at baseline to 0.725 (0.588-0.725) mm at follow-up ($p = 0.04$). Serum resistin levels decreased [from 7.3 (3.7-16.8) to 6.1 (2.9-8.8), $p = 0.013$], while serum leptin [from 2.6 (1.9-10.1) to 24.6 (12.4-54.7), $p < 0.001$] and HMW-adiponectin levels [from 8.3 (3.7-11.8) to 12.4 (7.0-17.8), $p < 0.001$] increased after glucocorticoid therapy. In multivariate analysis, average yearly change in IMT over follow-up periods was positively associated with male sex, diabetes mellitus, and yearly change in serum resistin levels. In contrast, average yearly change in IMT in this analysis was negatively associated with cumulative prednisolone exposure.

Conclusion: This study showed that premature atherosclerosis was detected at high incidence in patients with systemic autoimmune diseases before glucocorticoid therapy. Overall, these patients had an increased IMT during the follow-up periods, which was positively associated with yearly change of resistin. However, increased IMT was negatively associated with prednisolone therapy. Our findings suggest that glucocorticoid may prevent accelerated atherosclerosis, partly through regulating the balance in concentrations of adipokines such as resistin which might be associated with atherosclerotic progression in systemic autoimmune diseases.

Disclosure: S. Masuoka, None; **N. Tanaka**, None; **N. Kusunoki**, None; **T. Yamamoto**, None; **K. Kaneko**, None; **S. Muraoka**, None; **M. Kaburaki**, None; **K. Shikano**, None; **N. Fujio**, None; **H. Sato**, None; **M. Kawazoe**, None; **E. Shindo**, None; **S. Yamada**, None; **K. Takagi**, None; **T. Nanki**, None; **S. Kawai**, None.

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Abstract Number: 1797

Insulin Resistance Is Not Associated with Increased Risk of Subclinical Atheromatosis in Patients with Systemic Lupus Erythematosus from Northern Spain

Leyre Riancho-Zarrabeitia[1], Alfonso Corrales[2], Nuria Vegas-Revenga[1], Lucía Dominguez-Casas[1], Javier Rueda-Gotor[2], Montserrat Santos-Gómez[1], Maria T. García-Unzueta[3], Ricardo Blanco[1] and Miguel Angel Gonzalez-Gay[1], [1]Rheumatology, Hospital Universitario Marqués de Valdecilla. IDIVAL, Santander, Spain, [2]rheumatology, Hospital Universitario Marqués de Valdecilla. IDIVAL, Santander, Spain, [3]Biochemistry, Hospital Universitario Marqués de Valdecilla. IDIVAL, Santander, Spain

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SESSION INFORMATION

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Background/Purpose: Metabolic syndrome is a recently defined clustering of cardiovascular risk (CV) factors associated with insulin resistance (IR) and an increased risk of CV disease. Systemic lupus erythematosus (SLE) patients have an increased prevalence of IR which may contribute to the development accelerated atherosclerosis in these patients. In this study we aimed to establish if IR is associated with increased risk of subclinical atherosclerosis in SL.

Methods: Seventy-two Northern Spanish women with SLE and 72 age and sex matched controls were studied. Traditional CV risk factors were recorded according to a standardized protocol. Carotid ultrasonography was done by a MyLab 70 scanner (Esaote; Genoa, Italy), equipped with 7–12 MHz linear transducer and the automated software guided technique radiofrequency—Quality Intima Media Thickness in real-time (QIMT, Esaote, Maastricht, Holland) to determine carotid intima-media thickness (cIMT) and plaques, according to the Mannheim Carotid Intima-Media Thickness Consensus. IR was evaluated using the homeostasis model assessment (HOMA-IR) and quantitative insulin-sensitivity check index (QUICKI).

Results:

There were no statistically significant differences in the frequency of smoking, hypertension, dyslipidemia, diabetes mellitus, body mass index, or personal and family history of CV events between SLE patients and controls. Nevertheless, cIMT was significantly higher in SLE patients than in controls (0.654 ± 0.128 mm versus 0.588

±0.097 mm, p= 0.001). This difference remained statistically significant after adjustment for age and body mass index. Moreover, the frequency of carotid plaques was also increased in SLE patients (47% versus 27% in controls; p=0.023), being bilateral in 22% of patients and 13% of controls. The statistically significant difference persisted after adjusting for traditional CV risk factors. However, no correlation between HOMA-IR or QUICKI and cIMT was observed in SLE patients (r=0.06 and 0.034, respectively). Although SLE patients with plaques had higher levels of HOMA-IR (1.45± 1.01) and lower levels of QUICKI (0.35± 0.06) than those without plaques (1.15±0.65 and 0.36± 0.04, respectively), no statistically significant differences were observed.

Conclusion: The increased frequency of subclinical atherosclerosis observed in Northern Spanish SLE patients is not associated with metabolic syndrome features including IR.

Disclosure: L. Riancho-Zarrabeitia, None; **A. Corrales**, None; **N. Vegas-Revenga**, None; **L. Dominguez-Casas**, None; **J. Rueda-Gotor**, None; **M. Santos-Gómez**, None; **M. T. García-Unzueta**, None; **R. Blanco**, None; **M. A. Gonzalez-Gay**, None.

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Abstract Number: 1798

Progression of Noncalcified and Calcified Coronary Plaque (by CT Angiography) in SLE

Michelle Petri[1], Armin Zadeh[1], Adnan Kiani[1] and Laurence S Magder[2], [1]Johns Hopkins University School of Medicine, Baltimore, MD, [2]University of Maryland School of Medicine, Baltimore, MD

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Background/Purpose: Accelerated atherosclerosis leading to premature coronary artery disease remains the major cause of late death in SLE. Coronary artery calcium (CAC) is a late phase of atherosclerosis. Noncalcified coronary plaque (NCP) represents an early inflammatory plaque more likely to rupture.

Methods: To determine rates of CAC and NCP progression and identify risk factors for progression, CT angiography was performed at baseline and after several years of follow-up in 38 SLE patients; 36 scans allowed repeat assessment of NCP and 35 for CAC. Duration between assessments was 2-3 years (13%), 3-4 years (53%), 4-7 years (21%) and >7 years (13%). Of the patients, 37% were below 45 years; 76% female; 74% Caucasian and 18% African-American. CAC was quantified by the Agatston score and classified as none, low (1-99) or high (100+). NCP was quantified based on a score that we have previously described and classified as none, low (<0.5) or high (0.5+). SLE disease activity was quantified using the SELENA-SLEDAI and Physician Global Assessment (PGA) indices. To assess the association between quantitative clinical variables and changes in NCP adjusting for time we fit linear regression models.

Results: Tables 1 and 2 show the follow-up classifications for CAC and NCP, respectively, by baseline classification.

Table 1: Number (%) with CAC at follow-up by baseline level

		Follow-up		
		None	Low	High
Baseline	None	23 (96%)	1 (4%)	0 (0%)
	Low	1 (20%)	3 (60%)	1 (20%)
	High	0 (0%)	0 (0%)	6 (100%)

Table 2: Number (%) with NCP at follow-up by baseline level

		Follow-up		
		Low	Medium	High
Baseline	Low	4 (33%)	3 (25%)	5 (42%)
	Medium	1 (6%)	13 (72%)	4 (22%)
	HIgh	0 (0%)	4 (67%)	2 (18%)

For CAC, the pre-post scores agreed qualitatively for 32/35 (91%), while for NCP, the pre-post scores agree qualitatively for 19/36 (53%). Twelve (33%) had an increase in NCP while 5 had a decrease. Change in NCP was positively associated with time between assessments (estimated mean change score of 0.09 per year, p=0.038). Table 3 shows the association between various exposures experienced between the assessments and mean change in NCP score.

Table 3. Mean change in NCP score by various clinical variables, adjusted for time between assessments.		
Clinical Variable	Mean Change*	P-value
SLEDAI at the time of follow-up assessment	0.01 (per 1 unit change)	0.82
PGA at the time of follow-up assessment	-0.16 (per 1 unit change)	0.28
Mean SLEDAI	-0.02 (per 1 unit change)	0.63
Mean PGA	-0.19 (per 1 unit change)	0.20
Mean Systolic Blood Pressure	-0.08 (per 10 mmHg change)	0.19
Mean Total Serum Cholesterol	-0.08 (per 25 mm/dl change	0.26
History of Smoking	-0.12	0.49
Current Smoking	-0.33	0.17
Mean Lupus Anticoagulant (dRVVT)	0.01 (per second)	0.61
Proportion of time with Low C3	0.06 (per 0.5 difference)	0.66
Proportion of time with Low C4	-0.01 (per 0.5 difference)	0.95
Proportion of time with positive anti-dsDNA	0.11 (per 0.5 difference	0.33
Mean Daily Prednisone Dose	-0.19 (per 10 mg/d difference)	0.38
Proportion of time on Plaquenil	-0.07 (per 0.5 difference)	0.71
*Means and proportions calculated over the interval between the two plaque assessments.		

Conclusion: Calcified coronary plaque levels were relatively stable over a period of 2-7 years. Noncalcified coronary plaque levels were more variable and more likely to increase over time. Those with longer duration of follow-up tended to have increases in noncalcified plaque. Traditional cardiovascular risk factors and SLE-related measures did not predict increases in noncalcified coronary plaque. Noncalcified coronary plaque, the plaque most likely to rupture and lead to a cardiovascular event, is likely to increase over time regardless of traditional cardiovascular risk factors and SLE clinical and serologic activity.

Disclosure: M. Petri, None; **A. Zadeh**, None; **A. Kiani**, None; **L. S. Magder**, None.

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Abstract Number: 1799

IgG Levels Correlate Inversely with Proteinuria Among Participants in the Abatacept and Cyclophosphamide Combination Therapy for Lupus Nephritis Trial, but Hypogammaglobulinemia Was Not Associated with an Increased Risk of Serious Infection

Sara G. Murray[1], Noha Lim[2], Michael Stahly[2], Dawn Smilek[3] and David Wofsy[4], [1]Medicine, University of California, San Francisco, San Francisco, CA, [2]Immune Tolerance Network, Bethesda, MD, [3]Immune Tolerance Network, San Francisco, CA, [4]University of California, San Francisco, San Francisco, CA
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Background/Purpose: Hypogammaglobulinemia has been associated with serious infectious adverse events (SIAE) and may occur during immunosuppressive therapy for lupus nephritis (LN). It is possible that proteinuria contributes to low Ig levels, but this relationship has not been explored. We analyzed data from the Abatacept and Cyclophosphamide Combination Therapy for Lupus Nephritis (ACCESS) trial to evaluate the relationship between proteinuria and IgG levels in patients undergoing treatment for LN with the Euro-Lupus Nephritis (ELN) regimen.

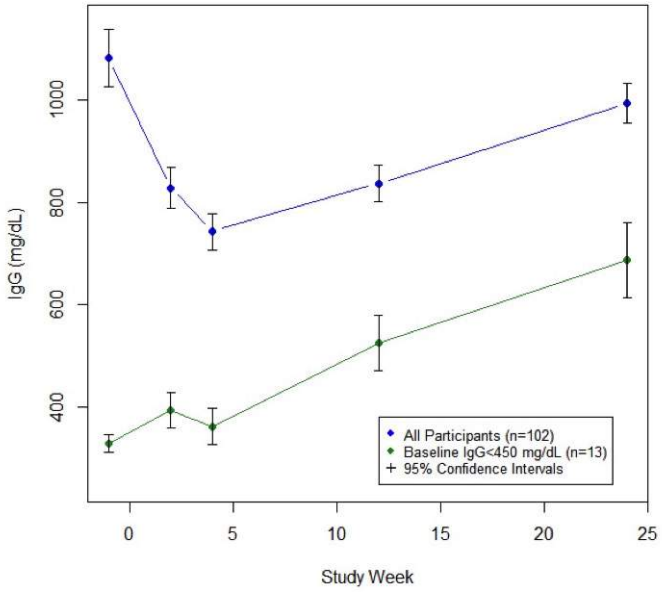
Methods: The ACCESS trial compared abatacept to placebo in LN patients undergoing ELN treatment with cyclophosphamide followed by azathioprine. Shortly after the trial began, the protocol was amended to include quantitative Ig measurements at baseline and weeks 2, 4, 12, and 24 in all subsequent participants (n=102). For the purpose of this analysis, hypogammaglobulinemia was defined by an IgG level <450 mg/dL based on previous studies indicating that this level of IgG is associated with an increased infection risk in people with hereditary immunodeficiency. Urine protein-to-creatinine ratio (UPCR) was calculated using 24-hour urine collections. SIAE were included if they were grade 3 or higher or were associated with hospitalization. Fisher's exact test was used to evaluate categorical relationships, and correlation and linear regression were used to assess continuous relationships between

measurements.

Results: Linear regression analysis showed an inverse correlation between proteinuria and IgG levels (r=-0.42, p<0.0001). At baseline, 24% of participants with UPCR ≥3 had IgG<450 mg/dL, compared with 5% of participants with UPCR <3 (p=0.013). Eleven participants experienced SIAE during treatment. None of the SIAE occurred among the 13 participants with low baseline IgG, compared to 11/89 participants with IgG ≥450 at baseline (0% vs. 12%). Overall, 31 participants had transiently low IgG (<450 mg/dL) at some time during treatment, whereas 71 participants never experienced low IgG. SIAE occurred in 3/31 (10%) participants who had low IgG at some point vs. 8/71 (11%) participants who never had low IgG. Mean IgG levels were lowest approximately 4 weeks following initiation of therapy and then rose (see Figure), so that only 1/78 participants who reached the primary study endpoint at week 24 had IgG <450 mg/dL at that point. Results in the abatacept and placebo subsets were similar.

Conclusion: Our results demonstrate an inverse relationship between proteinuria and low IgG levels in LN. However, low IgG was not associated with an increased risk of SIAE in the ACCESS trial, even among participants with IgG <450 mg/dL. Moreover, among participants who completed 24 weeks of ELN treatment, hypogammaglobulinemia corrected in all but one subject. These findings suggest that low IgG levels should not be a contraindication to immunosuppressive treatment of active LN.

Figure. IgG levels following treatment with the Euro-Lupus Nephritis regimen in the ACCESS trial, in all participants and the subset of participants with baseline IgG<450 mg/dL.



Disclosure: S. G. Murray, None; **N. Lim**, None; **M. Stahly**, None; **D. Smilek**, None; **D. Wofsy**, Genentech and Biogen IDEC Inc., 5,Anthera Pharmaceuticals, 5,GlaxoSmithKline, 5,Aurinia, 5.

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Abstract Number: 1800

A Novel Anti-CD28 Domain Antibody Antagonist Shows a Favorable Pharmacokinetic, Pharmacodynamic and Safety Profile

R Shi[1], M Honczarenko[1], S Zhang[2], CA Fleener[3], J Mora[1], S Lee[1], X Liu[1], DE Shevell[1], Z Yang[1], H Wang[1] and B Murthy[1], [1]Bristol-Myers Squibb, Princeton, NJ, [2]GlaxoSmithKline, King of Prussia, PA, [3]Pfizer Inc, Groton, CT

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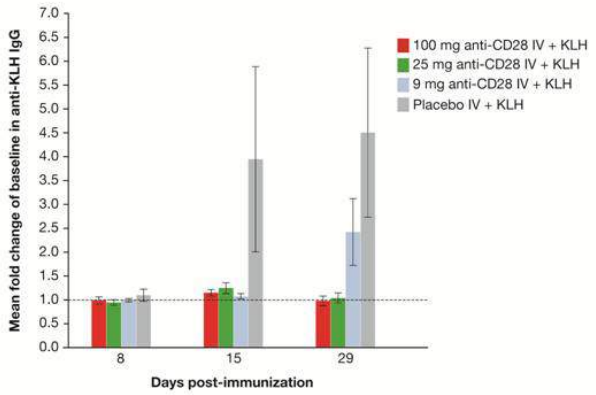
Background/Purpose: Antagonism of the CD28 costimulation receptor is thought to block T-cell activation, making this a promising target for the treatment of many autoimmune diseases, including systemic lupus erythematosus. Given the cytokine storm seen with the CD28 agonist TGN1412,1 it is important to cautiously characterize the clinical profile of agents targeting CD28. Furthermore, evaluating target engagement and immunosuppression is critical to establishing proof of mechanism before testing in patients. Here, we report the pharmacokinetics (PK), pharmacodynamics (PD) and safety profile of a novel anti-CD28 domain antibody (dAb) from 2 Phase I studies in healthy subjects. **Methods:** Minimal anticipated biological effect level (MABEL) approach was used to select a 0.01 mg starting dose in the single ascending dose (SAD) study. In this double-blind first-in-human study, 9 subjects/panel were randomized

to 9 IV (0.01–100 mg), 3 SC (9–50 mg) or placebo panels. Subsequently, a keyhole limpet hemocyanin (KLH) challenge was performed in 16 subjects/panel, who received 1 of 3 IV doses (9–100 mg) or placebo. In a double-blind multiple ascending dose (MAD) study, subjects received 1 of 3 active SC treatments (6.25 mg 2x/month, 12.5 mg weekly or 37.5 mg weekly) or placebo. PK, PD and safety were assessed. **Results:** A total of 180 subjects were treated and 169 completed the SAD/MAD studies. The PK of anti-CD28 was linear after IV infusion and SC administration, such that C_{max} and $AUC_{(INF)}$ increased dose proportionally. Bioavailability after SC administration was estimated at 68.2%. The half-life was comparable for both administration routes (5–7 days). High levels (≥80%) of receptor occupancy were maintained for ≥2 weeks at doses of ≥9 mg (IV and SC) in SAD and throughout the dosing interval in MAD. Single IV doses of ≥9 mg anti-CD28 inhibited antibody production against KLH for 2 weeks, demonstrating immunosuppressive activity (Figure). No significant serum cytokine changes nor any clinically relevant changes in T/B/natural killer cell numbers were observed in SAD or MAD. There was a low incidence of detectable anti-drug antibodies (≤16.7% in each dose group); no immunogenicity responses were persistent, with no impact on drug clearance nor correlation to AEs. The most commonly reported AEs were headache (SAD) and infections (MAD), which were study drug-related but did not show dose dependency.

Conclusion: The PK of SC anti-CD28 is favorable, with high bioavailability and the ability to maintain serum concentrations over a 2-week dosing interval. Following IV and SC administration, anti-CD28 was safe at all doses studied, without evidence of cytokine release. Anti-CD28 saturates the target receptor resulting in KLH response inhibition. The observed immunosuppressive activity indicates that anti-CD28 has potential to show clinical activity in the treatment of autoimmune disease.

1. Suntharalingam G, et al. *N Engl J Med* 2006;**355**:1018–28.

Figure. Anti-CD28 suppression on KLH-induced IgG response at 8 days, 15 days and 29 days after single IV dose administration in healthy subjects



Disclosure: R. Shi, Bristol-Myers Squibb, 3,Bristol-Myers Squibb, 1; **M. Honczarenko**, Bristol-Myers Squibb, 3,Bristol-Myers Squibb, 1; **S. Zhang**, Bristol-Myers Squibb, 1; **C. Fleener**, Bristol-Myers Squibb, 1; **J. Mora**, Bristol-Myers Squibb, 3,Bristol-Myers Squibb, 1; **S. Lee**, Bristol-Myers Squibb, 3,Bristol-Myers Squibb, 1; **X. Liu**, Bristol-Myers Squibb, 3,Bristol-Myers Squibb, 1; **D. Shevell**, Bristol-Myers Squibb, 3,Bristol-Myers Squibb, 1,Mercher and Co Inc., 1; **Z. Yang**, Bristol-Myers Squibb, 3,Bristol-Myers Squibb, 1; **H. Wang**, Bristol-Myers Squibb, 3; **B. Murthy**, Bristol-Myers Squibb, 3,Bristol-Myers Squibb, 1,Johnson & Johnson, 1.

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Abstract Number: 1801

Hydroxychloroquine Retinopathy: Application of the 2011 Screening Guidelines in an Academic Practice

Syed Mahmood Shah, Michelle Petri and Hendrik Scholl, Johns Hopkins University School of Medicine, Baltimore, MD
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Background/Purpose: The risk of end-stage retinopathy (bull's eye maculopathy) from hydroxychloroquine (HCQ) is low (0.65%, Wolfe and Marmor, 2010). With recent advances in retinal structure and function testing, early changes on optical coherence tomography (OCT), fundus autoflourescence (FAF), multifocal electroretinography (mfERG), and microperimetry (MP) are being used to detect early signs of hydroxychloroquine retinopathy. Risk of retinopathy as defined by combinations of these tests ranges from 7.5-12% in those on HCQ for at least 5 years or longer. The American Academy of Ophthalmology (AAO) revised its guidelines in 2011 advocating the use of OCT, FAF and mfERG as ancillary tests to ophthalmic exam and visual fields.

Methods: Ophthalmic exam, OCT, FAF, mfERG and MP by experienced retina specialists were performed in 72 eyes of 36 consecutive SLE patients meeting SLICC criteria and on hydroxychloroquine.

Results: Eleven of 72 eyes (15%) had abnormal OCT findings with 2 eyes (2%) deemed possibly related to HCQ, 26 eyes had abnormal mfERG (36%) with 3 eyes (4%) deemed possibly related to HCQ, 19 eyes had abnormal MP (26%) and 10 abnormal FAF (13%). No patient showed changes in all 4 tests suggestive of HCQ retinopathy.

Conclusion: Our series demonstrates that, in the absence of baseline pre-HCQ data for the AAO recommended ancillary tests, it may be difficult to interpret changes seen on these tests. Most of the screenings are done by regular ophthalmologists who may lack the equipment and experience with specialized testing such as mfERG, FAF and OCT. Nonspecific abnormalities are common with these tests, which need careful interpretation by retina specialists. We recommend repeat testing in those with abnormal tests and additional testing in patients in whom all four modalities were not used to determine early toxicity. We do not recommend discontinuing hydroxychloroquine based on nonspecific abnormalities alone and/or abnormalities that are not supported by the respective other modalities.

Disclosure: S. M. Shah, None; **M. Petri**, None; **H. Scholl**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/hydroxychloroquine-retinopathy-application-of-the-2011-screening-guidelines-in-an-academic-practice

Abstract Number: 1802

Hydroxychloroquine Level Variants and Predictors in a Connective Tissue Disease Population

Ann Biehl[1], Maryam Ghaderi-Yeganeh[2], Zerai Manna[3], Abhijit Dasgupta[4], Mariana J. Kaplan[5] and Sarfaraz Hasni[3], [1]Department of Pharmacy, National Institutes of Health Clinical Center, Bethesda, MD, [2]National Institutes of Arthritis, Musculoskeletal and Skin Diseases, National Institutes of Health, Bethesda, MD, [3]National Institute of Arthritis and Musculoskeletal and Skin Diseases, National Institutes of Health, Bethesda, MD, [4]National Institutes of Arthritis, Musculoskeletal and Skin Diseases,, National Institutes of Health, Bethesda, MD, [5]Systemic Autoimmunity Branch, National Institute of Arthritis and Musculoskeletal and Skin Diseases, National Institutes of Health, Bethesda, MD

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Background/Purpose: Hydroxychloroquine (HCQ) dose adjustment in patients with impaired renal function has been suggested to prevent toxicity. However, evidence to support this practice is scant. Recently, focus has shifted to applying principles of therapeutic drug monitoring to HCQ to assess the potential for toxicity. We measured HCQ blood levels in connective tissue disease (CTD) patients with normal versus impaired renal function (GFR < 60 ml/min) to assess the impact of renal impairment on HCQ clearance. We also examined the impact of other patient-specific variables on HCQ levels, including age, concomitant medications, body mass index (BMI), ethnicity, HCQ duration, and disease activity level.

Methods: CTD patients on HCQ at a steady state dose of up to 6.5 mg/kg daily meeting ACR Criteria for Systemic Lupus Erythematosus or Rheumatoid Arthritis were eligible. Patients were excluded if they were i) deemed noncompliant through interview, prescription history review or with a resultant whole blood [HCQ] < 200 ng/ml; ii) on hemodialysis; iii) diagnosed with concomitant underlying liver disease; iv) pregnant; v) morbidly obese (BMI > 40); or vi) hypoalbuminemic (<2 g/dl). Whole blood random HCQ levels were quantified using high-performance liquid chromatography assay. Univariate analyses were performed on additional variables to evaluate other possible confounders on HCQ levels. SLE disease activity was calculated using SELENA-SLEDAI score at the time of HCQ level.

Results: There were no statistically significant differences in HCQ levels between the impaired renal function cohort (n = 11, GFR range 21-59 ml/min; mean [HCQ] 1052.7 ng/ml +/- 653.2) and patients with GFR > 60 ml/min (n = 25, range 62-120 ml/min; mean [HCQ] 1010.4 ng/ml +/- 491.5; p = 0.7310). There was no significant association between age, concomitant use of proton-pump inhibitors or prednisone, ethnicity, body mass index, duration of HCQ therapy or SLEDAI score and HCQ level.

Table-1 Comparing HCQ Level by GFR and other variables

Variables	Number of subjects	HCQ Level Mean ± STD	P-value**
GFR			0.7310
GFR≤ 60	n=11	1052.7±653.2	
GFR> 60	n=25	1010.4±491.5	
Age (Years)			0.1253
Age(20-50)	n =23	893.5±396.7	
Age (51-80)	n =13	1253.1±679.5	
PPI use			0.1622
No	n =26	963.8±560.3	
Yes	n =9	1142.2±472.1	
Ethnicity			0.3524
African American	n =9	1078.9±348.0	
Asian	n =8	840±269.8	
Caucasian	n =9	893.3±595.3	
Hispanic	n =10	1237±734.8	
Prednisone use			0.8084
No	n =7	1215.7±885.0	
Yes	n =26	962.7±431.2	
BMI			0.1012
Normal	n = 12	1155.83 ± 578.7	
Overweight	n = 10	728.0 ± 246.0	
Obese	n = 11	1013.6 ± 381.5	
Duration of HCQ therapy			0.6219
0-5 years	n = 11	945.5 ± 655.6	
6-10 years	n = 15	1084.0 ± 565.6	
> 11 years	n = 6	1036.7 ± 398.2	
SLEDAI			
Score (≤4)	n =26	1043.9 ± 463.6	0.4047
Score (>4)	n =8	782.5 ± 363.6	

P Value (*) were obtained using Wilcoxon-Mann-Whitney test and Kruskal-Wallis Test

Conclusion: There is wide inter-patient variability in HCQ blood levels. The influence of impaired renal function on HCQ metabolism and toxicity has yet to be fully elucidated. While recent literature indicates a statistically significant difference in HCQ levels for SLE patients with impaired renal function compared with a large cohort with normal renal function, a clinically significant difference in levels between patient populations was not illustrated. Our smaller study demonstrates the profound variability in levels and associated challenges that must be adjudicated before HCQ level monitoring can have wide clinical applicability. While there is growing interest in utilizing HCQ levels to guide therapy and prevent toxicity, additional studies in larger renal impairment patient populations are required.

Disclosure: A. Biehl, None; **M. Ghaderi-Yeganeh**, None; **Z. Manna**, None; **A. Dasgupta**, None; **M. J. Kaplan**, None; **S. Hasni**, None.

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Abstract Number: 1803

Serum Adipocyte Fatty Acid-Binding Protein Level Is Elevated in Patients with Systemic Lupus Erythematosus (SLE) but Not Associated with Biophysical Markers of Cardiovascular Disease

Anselm Mak[1,2], Herbert Schwarz[3], Nien Yee Kow[2], Sen Hee Tay[4] and Lieng Hsi Ling[2,5], [1]National University Health System, Singapore, Singapore, [2]Medicine, National University of Singapore, Singapore, Singapore, [3]Physiology, National Unversity of Singapore, Singapore, Singapore, [4]National University of Singapore, Singapore, Singapore, [5]National Unversity Heart Centre Singapore, National Unversity Health System, Singapore, Singapore

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Background/Purpose: Adipocyte fatty acid-binding protein (aFABP) is an intracellular lipid-binding protein expressed in adipocytes and macrophages, particularly in inflammatory conditions. Recently, high circulating serum aFABP levels have been shown to predict the development of metabolic syndrome, atherosclerosis and ischaemic stroke. Being an inflammatory disease, circulating aFABP level is expected to be raised in patients with SLE. However, a recent study failed to demonstrate higher aFABP levels in SLE patients than in healthy controls (HC), likely due to the lack of power of the study and optimally matched HC. Here, we aimed to address if serum aFABP level is indeed higher in SLE patients by comparing a larger number of SLE patients with HC stringently matched for age, sex and BMI. In addition, potential associations between serum aFABP levels and clinical and disease-related factors, as well as biophysical markers of cardiovascular (CVS) disease were explored in SLE patients.

Methods: Adult patients who fulfilled the 2012 SLICC classification criteria for SLE and HC matched for age, gender and BMI were recruited. Subjects with a history of hypertension, diabetes mellitus, renal impairment, CVS and cerebrovascular diseases, and those who were on statins were excluded. Clinical parameters including daily prednisolone dose, SLEDAI, SLICC/DI, and serum C3, C4, anti-dsDNA, total cholesterol (TC) and HDL-c levels were obtained. Serum aFABP levels were determined by ELISA. Endothelial function, arterial stiffness and carotid atherosclerosis were assessed by brachial artery flow-mediated dilation (FMD), pulse-wave velocity (PWV) and carotid intima-media thickness (cIMT) respectively using the Prosound Alpha-10 ultrasound system. Relationships between serum aFABP levels and disease-related factors, FMD, PWV and cIMT were explored by bivariate correlations.

Results:

Seventy one SLE patients and 71 matched HC (6 men in each group) were studied. The mean±SD age (year), BMI and atherogenic index (TC/HDL-c) of SLE patients and HC were 39.21±13.4 and 40.37±12.9, 22.06±4.3 and 22.86±4.2 and 3.09±1.6 and 3.22±1.4 (p=0.611) respectively. In SLE patients, the mean ±SD daily prednisolone dose, SLEDAI and SLICC/DI were 13.43±14.4mg, 6.52±5.4 and 0.17±0.4 respectively. SLE patients had significantly lower FMD than HC (3.82±2.9% vs 4.76±3.0%, p=0.027). PWV and cIMT did not differ between both groups (p=0.739 and p=0.762, respectively). Serum aFABP was significantly higher in SLE patients than that in HC (14.82±3.3ng/ml vs. 13.69±4.6ng/ml, p<0.001). However, no association between serum aFABP levels and serum C3, C4 and anti-dsDNA levels, SLEDAI, SLICC/DI, BMI, atherogenic index, daily prednisolone dose, FMD, PWV and cIMT was found in the SLE group. In HC, no association was noted between serum aFABP levels and BMI, FMD, PWV, cIMT and atherogenic index.

Conclusion:

While we confirmed that SLE patients had significantly higher aFABP levels and lower FMD than age, sex-, and BMI-matched HC, no association between aFABP and various biophysical markers of CVS disease was found. Prospective studies addressing the CVS impact of aFABP in SLE by evaluating adjusted mean aFABP levels over time and CVS events in SLE patients are warranted.

Abstract Number: 1804

Association of the Metabolic Syndrome (MetS) with Vascular Complications, End Stage Renal Failure (ESRF) and Mortality in Patients with Systemic Lupus Erythematosus (SLE): A Cohort Analysis

Chi Chiu Mok[1], Kar Li Chan[1], Sau Mei Tse[1] and Ling Yin Ho[2], [1]Medicine, Tuen Mun Hospital, Hong Kong, Hong Kong, [2]Dept of Medicine, Tuen Mun Hospital, Hong Kong SAR, Hong Kong

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Background/Purpose:

To study the association between the metabolic syndrome (MetS) and vascular events, end stage renal failure (ESRF) and mortality in patients with SLE

Methods:

Patients who fulfilled ≥4 1997 ACR criteria for SLE and were followed in the rheumatology clinics of Tuen Mun Hospital, Hong Kong were studied. Inclusion criteria were those who had clinical and laboratory assessment for the presence of the MetS within 5 years of the latest date of follow-up or death.

The MetS was defined by the updated joint consensus criteria, using the Asian criteria for central obesity, when >=3 of the following components were present: (1) Increased waist circumference to ³ 90cm in men or ³ 80cm in women; (2) Elevated blood pressure to ≥130/85mmHg or requiring drug therapy; (3) Elevated serum triglyceride level to ≥1.7mmol/L; (4) Reduced serum high density lipoprotein (HDL)-cholesterol to ≤1.0mmol/L in men and ≤1.3mmol/L in women; and (5) Elevated fasting glucose level to ³5.6mmol/L. Data on vascular complications (cerebrovascular, cardiovascular, peripheral vascular disease) and the occurrence of ESRF were retrieved from our cohort database. The association of the MetS with various vascular events, ESRF and mortality was studied by logistic regression models with adjustment for age, sex and the follow-up time since the onset of SLE.

Results:

660 SLE patients were studied (93% women; age 45.4±14 years). The mean follow-up time of the patients since the onset of SLE was 12.2±7.8 years. 143 SLE patients were excluded (younger age and shorter disease duration; but no difference in the frequency of SLE manifestations compared with the included patients). The mean body mass index (BMI) of the patients studied was 22.4±4.0kg/m^2 (13% >27kg/m^2). 97 (15%) of the studied patients qualified the MetS (28% fulfilling waist; 19% fulfilling blood pressure; 27% fulfilling triglyceride; 32% fulfilling HDL and 10% fulfilling glucose criteria). There were a total of 88 arterial vascular events in 77 (11.7%) patients. The most common arterial events were stroke / transient ischemic attack (57%), followed by acute coronary syndrome / angina (27%), peripheral vascular disease (PVD) (12.5%) and arterial thrombosis at other sites (4.5%). 24 (3.6%) patients in our SLE cohort developed ESRF. Separate logistic regression models revealed that the MetS was associated with any arterial events (odds ratio [OR] 2.84[1.62-5.00]; p<0.001), coronary events (OR 3.41[1.40-8.30]; p=0.007; PVD and other arterial events (OR 6.09[1.84-20.1]; p=0.003), adjusted for age, sex and follow-up time. The MetS, however, was not significantly associated with cerebrovascular events (OR 2.00[0.98-4.06]; p=0.06). The presence of the MetS was associated with mortality (OR 2.27[1.20-4.28]; p=0.01) and the occurrence of ESRF (OR 5.67[2.30-14.0]; p<0.001).

Conclusion:

The MetS, which is a constellation of vascular risk factors, was significantly associated with coronary and peripheral arterial events in patients with SLE. Moreover, the presence of the MetS within 5 years of latest follow-up was associated with mortality and the occurrence of ESRF.

Disclosure: C. C. Mok, None; **K. L. Chan**, None; **S. M. Tse**, None; **L. Y. Ho**, None.

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Abstract Number: 1805

Functional and Mechanistic Characterization of Anifrolumab, a Fully Human, Anti-IFNAR1 Monoclonal Antibody for the Treatment of Systemic Lupus Erythematosus

Jeffrey Riggs[1], Brian Naiman[2], Jing Zhang[1], Yan Xu[1], Inna Vainshtein[3], Carl Hay[1], Kevin Schifferli[1], Pina Cardarelli[4], Meina Liang[5], Lorin Roskos[6], Jane Connor[7], Roland Kolbeck[8], Anthony Coyle[9] and Michael Fung[1], [1]MedImmune LLC, Gaithersburg, MD, [2]Research, MedImmune LLC, Gaithersburg, MD, [3]MedImmune LLC, Hayward, CA, [4]Medarex, Sunnyvale, CA, [5]PKPD&Bioanalysis, MedImmune LLC, Hayward, CA, [6]MedImmune LLC, Mountain View, CA, [7]Respiratory, Inflammation and Autoimmunity (RIA), MedImmune LLC, Gaithersburg, MD, [8]Department of Respiratory, Inflammation and Autoimmunity, MedImmune LLC, Gaithersburg, MD, [9]Centers for Therapeutic Innovation, Pfizer, Inc. (formerly MedImmune LLC, Gaithersburg, MD, USA), Cambridge, MA

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Background/Purpose: Increased type I interferon (IFN) activities are associated with the pathogenesis of systemic lupus erythematosus (SLE). Anifrolumab, a fully human, IgG_1 κ monoclonal antibody in clinical development for the treatment of SLE, targets the type-I IFN receptor subunit 1 and blocks type-I IFN signaling. We present its functional properties and mechanism of action.

Methods: Using a 293H ISRE-luciferase reporter assay, we tested the potency of anifrolumab against different subtypes of recombinant human type-I IFNs (including α, β, and ω) and sera from SLE patients. The neutralizing activity of anifrolumab against IFN-mediated STAT1-phosphorylation induced by recombinant human IFN-α2 and CpG-induced plasmacytoid dendritic cell (pDC) culture supernatant was examined in human peripheral blood mononuclear cells (PBMCs) via western blotting and immune flow cytometry detection. Anifrolumab's mechanism of action was determined by studying the binding and internalization of antibody/receptor complex using THP-1 monocytic cells. We further studied the protective effects of a surrogate mouse anti-mouse IFNAR1 (5A3) monoclonal antibody in a murine NZB/W F1 lupus model induced by overexpressing mouse IFN-α through an adenoviral vector.

Results: Anifrolumab binds to human IFNAR1 with high affinity and high specificity. It inhibits the activities of recombinant human type-I IFNs (including 12 subtypes of α, β, and ω) at an average IC_{50} of 0.55±1.8 nM in 293H cell-based assays. It also inhibits natural type I IFNs from the sera of SLE patients by more than 99%, and, in selected patients, inhibits type-I IFN activity with an average IC_{50} of 0.5 nM. Blocking IFNAR1 by anifrolumab led to complete suppression of phosphorylation of STAT1 in human PBMCs stimulated by either recombinant human IFN-α or CpG-stimulated human pDC-derived culture supernatants containing natural type I IFNs. Binding of the antibody to IFNAR1-expressing THP-1 cells induced rapid and complete internalization in 1 to 2 hours. Blocking IFNAR1 by surrogate monoclonal antibody 5A3 protected ADV-IFN-α–accelerated lupus mice from developing proteinuria and renal injury. It also decreased anti-dsDNA autoantibody titers.

Conclusion: Anifrolumab effectively blocks the activity of different subtypes of type-I IFNs, including those from the sera of SLE patients. It induces rapid IFNAR1 internalization on target cells, thus inhibiting receptor signaling induced by type-I IFNs. The data from the mouse lupus study further support that blocking IFNAR1 by anifrolumab could have therapeutic benefits in SLE patients with high type-I IFN activities.

Disclosure: J. Riggs, AstraZeneca/MedImmune, 3,AstraZeneca, 1; **B. Naiman**, AstraZeneca/MedImmune, 3,AstraZeneca/MedImmune, 1; **J. Zhang**, AstraZeneca/MedImmune, 3,AstraZeneca/MedImmune, 1; **Y. Xu**, AstraZeneca/MedImmune, 3,AstraZeneca, 1; **I. Vainshtein**, AstraZeneca/MedImmune, 3,AstraZeneca/MedImmune, 1; **C. Hay**, AstraZeneca/MedImmune, 3,AstraZeneca/MedImmune, 1; **K. Schifferli**, AstraZeneca/MedImmune, 3,AstraZeneca/MedImmune, 1; **P. Cardarelli**, Medarex, 3; **M. Liang**, AstraZeneca/MedImmune, 3,AstraZeneca/MedImmune, 1; **L. Roskos**, AstraZeneca/MedImmune, 3,AstraZeneca/MedImmune, 1; **J. Connor**, AstraZeneca/MedImmune, 3,AstraZeneca/MedImmune, 1; **R. Kolbeck**, AstraZeneca/MedImmune, 3,AstraZeneca/MedImmune, 1; **A. Coyle**, AstraZeneca/MedImmune, 3,AstraZeneca/MedImmune, 1; **M. Fung**, AstraZeneca/MedImmune, 3,AstraZeneca/MedImmune, 1.

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Abstract Number: 1806

Hydroxychloroquine Serum Levels and Flares of Systemic Lupus Erythematosus: A Longitudinal Cohort Analysis

Chi Chiu Mok[1], Hannah Penn[2], Sau Mei Tse[1], Loralie Langman[2], Kar Li Chan[1] and Paul Jannetto[3], [1]Medicine, Tuen Mun Hospital, Hong Kong, Hong Kong, [2]Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, MN, [3]Director, Toxicology and Drug Monitoring Laboratory, Mayo Clinic, Rochester, MN

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Background/Purpose: To study the relationship between the serum hydroxychloroquine (HCQ) concentration and flares of systemic lupus erythematosus (SLE) in a longitudinal cohort of Chinese patients.

Methods:

Patients who fulfilled ≥4 of the ACR criteria for SLE and had been treated with HCQ for >6 months were recruited in November 2011. Patients had been prescribed HCQ at dosages of 200 mg/300 mg/400 mg/day at the discretion of physicians. Blood was assayed for the levels of HCQ by an in-house technique using the tandem mass spectrometry (SPE-MS/MS). Patients were stratified according to the HCQ levels; group 1 (<10 ng/ml, total non-compliance); group 2 (10-500 ng/ml, sub-therapeutic); and group 3 (≥500 ng/ml, therapeutic); and were followed longitudinally for serial assessment of disease activity (SELENA-SLEDAI) and the occurrence of mild/moderate or severe SLE flares (SELENA flare instrument). Comparison was made among these groups in the baseline and mean summated SLEDAI over time (AUC), and the annual incidence of mild/moderate and severe flares by the non-parametric Kruskal Wallis test. Bivariate correlation of two covariates was performed by Spearman's rank correlation.

Results:

276 SLE patients were studied (94% women; age 41.0±13.8 years; SLE duration 8.7±6.6 years). HCQ was used for the treatment of mucocutaneous or musculoskeletal manifestations, or both, in 93% of patients. The proportion of patients with HCQ levels of <10, 10-500, ≥500 ng/ml was 11%, 77% and 12%, respectively. The HCQ levels correlated significantly with the prescribed daily dosage (Rho 0.44; p<0.001), which was also correlated with the baseline SLEDAI score (Rho 0.30; p<0.001), indicating higher doses were used for more active SLE manifestations. After a follow-up of 32.5±5.5 months, 153 mild flares and 91 severe flares developed in our patients. The mean summated SLEDAI score over time was: 2.3±2.2 (group 1); 2.6±1.9 (group 2); and 3.5±2.5 (group 3), respectively (p=0.06). The annual incidence of mild/moderate and severe flares was: 0.21±0.32 and 0.14±0.42 (group 1); 0.19±0.33 and 0.12±0.29 (group 2); and 0.32±0.57 and 0.19±0.57 (group 3), respectively (p=NS in all). In patients with clinical and serological remission (SLEDAI=0) (N=73), therapeutic HCQ levels (>500ng/ml) were associated with lower summated mean SLEDAI over time (0.07±0.15) and no occurrence of disease flares (mild/moderate/severe) as compared to the other groups, although the differences were not statistically significant.

Conclusion:

"Sub-therapeutic" serum HCQ levels were frequent in our SLE patients, which was probably contributed by the low dosage prescribed for maintenance treatment in many patients with quiescent disease, as well as non-compliance. Patients with higher HCQ levels tended to have a higher disease activity over time and more frequent flares, indicating they had more refractory manifestations that required higher doses of HCQ for treatment. In patients with clinical and serological remission, therapeutic levels of HCQ were associated with lower disease activity over time and incidence of disease flares. HCQ drug level monitoring may play a role in identifying non-compliance to enhance the long-term efficacy of HCQ.

Disclosure: C. C. Mok, None; **H. Penn**, None; **S. M. Tse**, None; **L. Langman**, None; **K. L. Chan**, None; **P. Jannetto**, None.

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Abstract Number: 1807

Estimated Sodium and Potassium Intake Are Associated with Blood Pressure in Patients with Systemic Lupus Erythematosus

April Barnado, Annette M. Oeser, Yahua Zhang, Jens Titze, C. Michael Stein and Cecilia P. Chung, Medicine, Vanderbilt University, Nashville, TN
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Background/Purpose: The prevalence of hypertension is increased in patients with systemic lupus erythematosus (SLE). Sodium (Na^+) and potassium (K^+) intake are modifiable determinants of blood pressure in the general population and can be estimated by measuring urinary Na^+ and K^+. Higher Na^+ and lower K^+ intake, as well as a higher Na^+: K^+ ratio, are associated with elevated blood pressure. However, the contribution of Na^+ and K^+ intake to hypertension in SLE is not known. We hypothesized that urinary excretion of Na^+ and K^+, as an estimate of intake, are related to blood pressure in SLE.
Methods: We studied 178 patients with SLE and 86 control subjects frequency-matched for age, sex, and race. First morning urine specimens were collected and urine Na^+ and K^+ concentrations measured by flame photometry. The Kawasaki formula, a validated method that incorporates age, sex, height, weight, and urinary creatinine, was used to estimate 24 hour urine Na^+ and K^+ excretion. Blood pressure was the average of two resting measurements. Fisher's exact and Mann-Whitney U tests were used to compare categorical and continuous variables, respectively. The associations between systolic (SBP) and diastolic blood pressures (DBP) with estimated 24 hour urinary Na^+, K^+, and Na^+ : K^+ ratio were tested using Spearman correlation and then modeled using linear regression adjusting for age, sex, and race. Two-sided p values < 0.05 were significant.

Results: Descriptive variables including demographics, blood pressure, and urinary values for SLE patients and controls are shown in Table 1. The estimated 24 hour urinary Na^+ excretion was similar in SLE patients vs. controls, but the estimated 24 hour urinary K^+ excretion was significantly lower in SLE patients compared to controls. The urinary Na^+: K^+ ratio was higher in SLE patients than in controls, and this difference remained significant when subjects taking anti-hypertensive drugs, including diuretics, were excluded. In SLE patients, higher urinary Na^+: K^+ ratio was significantly associated with higher SBP [β coefficient (95% CI) =4.01 (0.57-7.46), p=0.023] and DBP [β coefficient=4.41 (1.71-7.11), p=0.002] after adjustment for age, sex, and race. In controls, there was no significant association with estimated 24 hour urinary Na^+, K^+, and Na^+: K^+ ratio and SBP and DBP. **Conclusion:** SLE patients had significantly lower estimated 24 hour urinary K^+ and higher estimated 24 hour urinary Na^+: K^+ ratio than control subjects. The estimated 24 hour urinary Na^+: K^+ ratio was significantly associated with SBP and DBP in SLE patients but not in controls. Our studies suggest that diets with low Na^+ and high K^+ content may reduce the risk of hypertension in SLE patients.

Table 1. Demographics of SLE cases and controls.

Characteristics	SLE (n = 178)	Controls (n = 86)	P value*
Mean age (years ± standard deviation)	40.9 ± 12	41.2 ± 12	0.76
Female sex (%)	88%	86%	0.70
Race/ethnicity (%) Caucasian Non-Caucasian	68% 32%	72% 28%	0.67
Hypertension (%)	44%	19%	< 0.001
Anti-hypertensive use (%)	36%	12%	< 0.001
Mean systolic blood pressure (mm Hg)	120 ± 17_	118 ± 14	0.63
Mean diastolic blood pressure (mm Hg)	73 ± 13	71 ± 10	0.21
Estimated 24 hour urinary sodium (gm)	4.2 ± 1.8	4.5 ± 2.1	0.54
Estimated 24 hour urinary potassium (gm)	2.0 ± 0.7	2.4 ± 0.9	< 0.001
Estimated 24 hour urinary sodium to potassium ratio	2.2 ± 0.7	1.9 ± 0.6	0.001

*Wilcoxon rank-sum and Fisher's exact test for continuous and dichotomous variables, respectively.

pressure-in-patients-with-systemic-lupus-erythematosus

Abstract Number: 1808

Exercise Is Associated with Improved Cardiometabolic Risk Factors in Patients with SLE

Michelle J. Ormseth[1], Annette M. Oeser[2] and C Michael Stein[3], [1]Department of Medicine, Division of Rheumatology, Vanderbilt University, Nashville, TN, [2]Medicine, Vanderbilt University, Nashville, TN, [3]Vanderbilt University, Nashville, TN
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Background/Purpose: Patients with systemic lupus erythematosus (SLE) have an increased prevalence of insulin resistance and the metabolic syndrome. Exercise has been shown to improve insulin resistance and components of the metabolic syndrome in the general population. However, few studies have evaluated the effects of exercise on the metabolic health of patients with SLE.

Methods: We performed a cross sectional study of 165 patients with SLE and recorded the amount of dedicated exercise performed outside of daily activities as metabolic equivalents in minutes per week (METs). We measured clinical variables, fasting insulin and glucose, and calculated the homeostasis model assessment (HOMA) as a measure of insulin resistance. Metabolic syndrome was defined by the National Cholesterol Education Program Adult Treatment Panel III definition. Current MET expenditure was categorized into quartiles and we used these to determine the relationship between exercise and the metabolic syndrome and its individual components using binary logistic regression and multivariable regression analyses adjusting for age, race and sex.

Results: Patients with SLE (n=165) had a median [IQR] age of 41 years [30-48], 89.1% were female, median BMI was 27.5 kg/m^2[23.6-32.74], and 29% had metabolic syndrome. Median disease duration was 7 years [3-12] and SLEDAI was 4 [0-6]. The median exercise expenditure was 200 MET min/week [0-591.75]. With each quartile increase in METs, resting heart rate decreased by 2.3 beats per minute (95% CI, 0.7-4.0 beats per minute) (P=0.006). The odds of having metabolic syndrome was decreased by 25.9% (0.8-44.6%) for each quartile increase in METs (P=0.044). Each increasing quartile of exercise was associated with a 12.3% (0.2-22.9%) decrease in HOMA (P=0.045), 8.9 mg/dl (0.5-17.3 mg/dl) decrease in triglycerides (P=0.037), and 2.5 mg/dl (0.7-4.3 mg/dl) increase in HDL (P=0.006), but no significant change in the presence of hypertension (P=0.10), fasting glucose level (P=0.14), or BMI (P=0.11). There was a non-significant trend toward decreased waist circumference with increasing exercise (P=0.06).

Conclusion: Some cardiometabolic benefits are associated with the amount of exercise performed in patients with SLE, particularly decreased odds of having metabolic syndrome and improvement in insulin resistance, and triglyceride and HDL levels. Future interventional studies to determine if exercise can prevent or reverse the metabolic syndrome and its associated adverse cardiometabolic risk factors in patients with SLE patients will be of interest.

Disclosure: M. J. Ormseth, None; **A. M. Oeser**, None; **C. M. Stein**, None.

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Abstract Number: 1809

Real Life Implementation of Lupus Nephritis Randomized Controlled Trials

Angela Pakozdi[1], Ravindra Rajakariar[2], Muhammad Magdi Yaqoob[2] and Dev Pyne[1], [1]Rheumatology, Barts Health NHS Trust, London, United Kingdom, [2]Renal Medicine, Barts Health NHS Trust, London, United Kingdom
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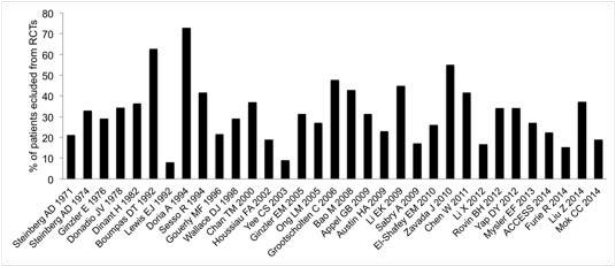
Background/Purpose: Randomized controlled trials (RCTs) are the gold standard for assessing treatment efficacy. However, due to their often strict design, generalization of research results to real populations may be problematic. Our objective was to estimate the proportion of our lupus nephritis (LN) patients who would have been ineligible to participate in RCTs, as an indicator of how well LN RCT findings could be transferred to our clinical practice.

Methods: A systematic literature search until May 2015 was performed using PubMed, Medline, EMBASE and Cochrane databases to identify full text English publications reporting RCTs on LN. We focused on trial inclusion and exclusion criteria related to lupus. The criteria were classified into 3 broad categories: (1) severe disease (low GFR, high serum creatinine); (2) mild disease (low level proteinuria, serum albumin, relatively preserved GFR) and (3)

prohibited immunosuppressive drugs used at time of LN onset. LN patients with biopsy proven proliferative (class III, IV) or membranous (class V) LN, diagnosed 1995-2013, were identified from our database; their baseline characteristics were compared with each RCT's entry criteria for eligibility.

Results: We identified 137 patients with a biopsy proven diagnosis of active LN, with mean age of 33.6 years (± 11.5 SD) at LN onset. 85.4% (n=117) were female, 50% were Black, 34% were Asian and 16% were White Caucasian. 81% had proliferative (n=111, 30% class III, 51% class IV, with or without membranous component), whilst 19% had pure membranous LN (n=26). Baseline clinical activity showed mean proteinuria of 5.5 g/24hr (± 5.1 SD), serum albumin of 27.3 g/L (± 7.4 SD), and serum creatinine of 159 µmol/L (± 166 SD). Whilst 33% (n=45) had a normal GFR (>90 ml/min/1.73m^2), 18% had a GFR <30 ml/min/1.73m^2. 33 RCTs were selected from the databases, of which only 4 published the number of patients screened, and only two disclosed the factors leading to non-randomization. Overall, on average, 32% of our LN patients were not eligible to enter the RCTs (range 8-73%) (Figure). 26 RCTs (79%) excluded patients with category 1 (severe disease) which would have rejected up to 61% of our patients from trial inclusion; 20 RCTs (63%) excluded patients with category 2 (mild disease) which would have omitted up to 44% of our cohort, and 22 trials (67%) excluded patients with category 3 (prior use of selected immunosuppressive drugs) resulting in ineligibility of up to 16% of our cohort.

Conclusion: Nearly 1/3 of our newly diagnosed active LN population would have been excluded from RCTs by design, due to factors directly related to their renal disease. Clinicians should be aware that trial samples may not adequately reflect their LN population and therefore research results may not be generalizable to all LN patients in clinical practice. Our study highlights the need for more pragmatic trials designed for those with milder or more severe LN.



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Abstract Number: 1810

A Five-Year Follow-up of Microvascular Dysfunction and Coronary Artery Disease in SLE: Results from a Community-Based Lupus Cohort

Vaneet K. Sandhu[1], Mariko L. Ishimori[1], Janet Wei[2], Louise Thomson[2], Daniel Berman[2], Jay Schapira[2], Noel Bairey Merz[2], Daniel Wallace[3] and Michael Weisman[3], [1]Rheumatology, Cedars-Sinai Medical Center, Los Angeles, CA, [2]Cardiology, Cedars-Sinai Medical Center, Los Angeles, CA, [3]Cedars-Sinai Medical Center, Los Angeles, CA

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Background/Purpose:

To investigate serial changes in the prevalence of coronary microvascular dysfunction and coronary artery disease (CAD) by cardiac imaging in a cohort of SLE patients with chest pain.

Methods:

Twenty female SLE patients with chest pain (CP) underwent stress cardiac MRI (CMR) and coronary CT angiography (CCTA) at baseline with follow-up imaging at 5-years in addition to history of major cardiac or vascular events, CAD risk factors, SLE activity, hormones and medications.

1.5T CMR was performed with gadolinium stress and rest 1st-pass perfusion and delayed enhancement. Analysis was conducted semi-quantitatively by myocardial perfusion reserve index (MPRI) and by visual 5-point segmental scoring. Patients also underwent 64-slice CCTA. Images were analyzed for coronary artery calcium score, plaque type, location, and stenosis. In the absence of obstructive CAD, patients with abnormal myocardial perfusion or MPRI <1.84 are suspected to have coronary microvascular dysfunction.

Results:

Of 17 subjects re-enrolled for follow-up, 15 (mean age 47, BMI 26) underwent follow-up imaging: 14 underwent both stress CMR and CCTA and 1 had CCTA alone. Seven of 15 subjects had abnormal imaging at follow-up (Table 1): 4 abnormal CMR with no CAD, 2 normal CMR with nonobstructive CAD, and 1 abnormal CMR with ischemic scar and obstructive CAD. Framingham risk score and Reynold's risk score were </= 1% in all patients, yet 11 (73%) reported CP in the 4 weeks preceding initial study visit. Five of 15 patients (33%) were hyperlipidemic, 10 (67%) menopausal, 2 (13%) diabetic, 5 (33%) smokers, and 7 (47%) with current corticosteroid use. The average SLEDAI in patients that underwent follow-up imaging was 3.6.

In our follow-up cohort, we note a 36% prevalence of abnormal CMR and 20% abnormal CCTA (1 obstructive, 2 nonobstructive CAD). Of 8 subjects with baseline abnormal CMR, half had continued CP and similar or worse CMR on follow-up. Mean MPRI at 5-year follow-up was 2.19 versus 2.04 (p=0.28) at

baseline in the subepicardium and 1.85 versus 1.86 (p=0.70) in the subendocardium. Using Wilcoxon signed-rank test, results were not significantly different between baseline and follow-up MPRI.

Conclusion:

Some patients demonstrate reversible hypoperfusion and others progress to worsening subendocardial disease in the absence of obstructive CAD, suggesting coronary microvascular dysfunction and challenging the theory of SLE-related accelerated CAD. Those with abnormal CCTA at follow-up were >/= 55 years of age, suggesting age-related, not accelerated, increase in coronary atherosclerosis. Abnormal CMR did not correlate with abnormal CCTA. While duration of follow-up was short, no major cardiac events were reported, and macrovascular CAD progression is no more than the general population. Microvascular disease progression and potential cardiac risk-stratifying interventions merit additional studies.

Table 1: Subjects with abnormal imaging

Subject	Age	Baseline perfusion defect (%) on CMR	Follow-up Perfusion defect (%) on CMR	Baseline CCTA: plaque (yes/no)	Follow-up CCTA: new plaque (yes/no)	Elevated CRP	Obesity (BMI>/=30)	HLD	Menopausal	Diabetes	Depression	Current steroid therapy	Current HRT	Smoking history
2	34	None	9%	No	No	Yes	Yes	No	No	Yes	Yes	Yes	No	Yes
3	56	None	None		Yes	Yes	No	Yes	Yes	No	No	No	Yes	Yes
4	52	38%	11%	No	No	Yes	Yes	No	No	Yes	Yes	Yes	No	Yes
5	57	28%	12.5%*	Yes	Yes	No	No	No	Yes	No	Yes	Yes	Yes	Yes
6	59	14%	10%	No	No	No	No	No	Yes	No	Yes	No	Yes	No
11	65	9%	None	Yes	Yes	No	No	Yes	Yes	No	No	No	No	No
12	58	16%	19%	No	No	Yes	Yes	Yes	Yes	No	Yes	No	No	No

BMI: body mass index (kg/m^2), HLD: hyperlipidemia, defined by total cholesterol >200mg/dL, HRT: hormone-replacement therapy

* Small subendocardial infarction with significant stenosis

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Abstract Number: 1811

Depression and Progression of Subclinical Cardiovascular Disease in Systemic Lupus Erythematosus

April Jorge[1], Apinya Lertratanakul[2], Julia (Jungwha) Lee[3], William Pearce[1], David McPherson[4], Trina Thompson[5], Emma Barinas-Mitchell[6] and Rosalind Ramsey-Goldman[1], [1]Northwestern University Feinberg School of Medicine, Chicago, IL, [2]Northwestern University, Chicago, IL, [3]Department of Preventive Medicine, Biostatistics Collaboration Center, Northwestern University Feinberg School of Medicine, Chicago, IL, [4]University of Texas Health Science Center, Houston, TX, [5]Saint Francis University, Ebensburg, PA, [6]University of Pittsburgh, Pittsburgh, PA

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Background/Purpose: Women with SLE have an increased incidence of premature cardiovascular disease (CVD). Depression is also common among SLE patients. A relationship between depression and increased inflammation leading to CVD has been proposed. The aim of this study was to evaluate the relationship between depression and the progression of subclinical CVD in women with SLE.

Methods: In a prospective case-control study, the Study of Lupus Vascular and Bone Long-term Endpoints (SOLVABLE), there were 185 women with SLE meeting ACR revised classification criteria and 186 controls. Participants were evaluated at baseline and 5 years, including demographic data, laboratory studies, CVD risk factors, depression screening with the Center for Epidemiologic Studies Depression Scale (CES-D) questionnaire, ultrasound evaluations of carotid artery intima-media thickness (IMT) and carotid plaque, and assessment of SLE disease activity and damage for the SLE cases. Depression was defined as CES-D score > or = 16. Plaque progression was defined by an increase in number of plaques over 5 years. IMT progression was defined as increase in IMT over 5 years. HTN was defined as systolic blood pressure (BP) >140mmHg, diastolic BP >90mmHg, or taking anti-hypertensive medication. Descriptive statistics were calculated for baseline variables. Logistic regression was used to evaluate the association between baseline

depression and the progression of carotid plaque. Linear regression was used for baseline depression and progression of IMT.

Results: A total of 149 participants with SLE and 126 controls completed follow-up over 5 years. The SLE group was younger (48.6 years vs. 52.2, p=0.003) and had more hypertension (HTN) (57.7% vs. 31.8%, p<.0001), diabetes (9.4% vs. 0.8%, p=0.01) and aspirin use (20.8% vs. 7.1%, p=0.001). There were no significant differences between the groups regarding race/ethnicity, BMI, total cholesterol/high density lipoprotein (HDL) ratio, or statin use. The SLE group had a higher rate of depression, 40% compared with 15% in the control group (p <0.001). The average SLE disease duration was 12 years (SD 8.6 years), and baseline SLEDAI 2000 and ACR/SLICC scores were 4.0 (SD 3.6) and 1.6 (SD 1.8), respectively. In Table 1, in both the unadjusted and adjusted models, the presence of baseline depression correlated with increased progression of IMT in the SLE group, but not in the control group. There was no association between depression and carotid plaque in either group.

Conclusion: Women with SLE have higher rates of depression than healthy peers. SLE patients with depression have an increased risk of developing subclinical CVD, as measured by IMT, a more sensitive measure of atheroma burden, but not by carotid plaque. The data suggest that depression, a potentially modifiable risk factor, may contribute to the increased risk of subclinical CVD in women with SLE.

Table 1. Progression of Carotid Plaque and IMT at 5 Years

		Carotid Plaque	Carotid IMT		
		Odds Ratio (95% CI)	Depressed IMT mean change from baseline to 5 years (mm)	Not Depressed IMT mean change from baseline to 5 years (mm)	p-value
SLE Cases	Unadjusted	1.43 (0.68, 3.03)	0.06	0.03	0.02
	Adjusted for Age, BMI, Total Cholesterol/HDL ratio, HTN	1.03 (0.45, 2.40)	0.06	0.03	0.03
Controls	Unadjusted	0.042 (0.05, 3.27)	0.02	0.03	0.8
	Adjusted for Age, BMI, Total Cholesterol/HDL ratio, HTN	0.31 (0.04, 2.66)	0.02	0.03	0.9

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Abstract Number: 1812

The First Randomized Control Trial to Evaluate the Effectiveness of Bortezomib for Refractory Systemic Lupus Erythematosus

Tomonori Ishii[1], Yoshiya Tanaka[2], Atsushi Kawakami[3], Kazuyoshi Saito[2], Kunihiro Ichinose[4], Yuko Shirota[5], Hiroshi Fujii[5], Yoko Fujita[6], Yukiko Kamogawa[5], Tomoaki Machiyama[5], Kanae Akita[5] and Hideo Harigae[5], [1]Department of Clinical Trial Implementation, Tohoku University Hospital, Clinical Research, Innovation and Education Center, Sendai, Japan, [2]The First Department of Internal Medicine, University of Occupational and Environmental Health, Kitakyushu, Japan, [3]Department of Immunology and Rheumatology, Nagasaki University, Nagasaki, Japan, [4]Department of Immunology and Rheumatology, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan, [5]Department of Hematology and Rheumatology, Tohoku University Graduate School of Medicine, Sendai, Japan, [6]Department of Hematolgy and Rheumatolgy, Tohoku University Graduate School of Medicine, Sendai, Japan

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Background/Purpose:

Systemic lupus erythematosus (SLE) is a disease characterized by production and deposition of anti-dsDNA antibody. In recent years, treatment methods targeting antibody-producing B cell line have been reported as new approaches to SLE treatment. Bortezomib is a proteasome inhibitor targeting plasma cells, and is widely used in the treatment of plasma cell tumors. Here, we evaluated the efficacy and safety of bortezomib versus placebo for the treatment of SLE cases in which disease activity could not be controlled by conventional combined use of immunosuppresssants and steroids.

Methods:

Fourteen patients in whom the dose of predonine could not be reduced to ≤10 mg/day despite the concomitant immunosuppressive therapy and moderate disease activity persisted (SLEDAI, ≥6 points; positive for anti-dsDNA antibody) were randomized by using the anti-dsDNA antibody as a randomization factor. Bortezomib, 1.3 mg/m^2, or placebo was administered twice weekly, 8 times in total to patients. Endpoints were changes in anti-dsDNA antibody titer at Week 24 and SLE responder index (SRI).

Results:

Among the 14 patients, 8 and 6 patients were assigned to the bortezomib group and the placebo group, respectively; however, 4 of the 8 patients in the bortezomib group and 2 of the 6 patients in the placebo group discontinued the trial. The reason for discontinuation was inability to continue the trial due to adverse reactions in all of the 4 patients in the bortezomib group, and insufficient effects in both of the 2 patients in the placebo group. In the bortezomib group, only one patient could complete the treatment as planned, while 7 others failed to complete the minimum protocol treatment because of adverse reactions. Four patients each in the bortezomib and placebo groups, who could complete the trial, were included in the following analysis.

The percent change of the anti-dsDNA antibody titer at treatment 24, which was defined as the primary endpoint, was 4.24% in the bortezomib group and -1.96% in the placebo group, which did not support the efficacy of bortezomib. However, when LOCF analysis was used by including the patients who discontinued the treatment, -11.34% and 23.88% were obtained as reference values in the bortezomib and placebo groups, respectively, suggesting that the patients who needed to discontinue the trial because of adverse reactions might have responded well to bortezomib. On the other hand, the SRI at Week 12 was 75% in the bortezomib group and 40% in the placebo group. Although the difference did not reach statistical significance, these results appear to be promising in terms of the efficacy of bortezomib.

Conclusion:

Since bortezomib therapy for SLE is associated with many adverse reactions, it is necessary to select indications carefully and to establish the protocol aiming at the prevention of adverse reactions. On the other hand, we observed improvement of clinical findings such as skin symptoms, regardless of the anti-dsDNA antibody titer, in a patient in the bortezomib group. In fact, SRI tended to be high in the bortezomib group. These findings suggest that bortezomib may be effective in treating various symptoms of SLE though the mechanism other than inhibition of anti-dsDNA antibody production.

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Abstract Number: 1813

Novel Mechanism of Action of Anti-Malarial Drugs in the Inhibition of Type I Interferon Production

Jie An[1], Joshua Woodward[2], Mark Minie[3], YuFeng Peng[4], Tomikazu Sasaki[5] and Keith B. Elkon[6], [1]Division of Rheumatology, Department of Medicine & Immunology, University of Washington, Seattle, WA, [2]Department of Microbiology, University of Washington, Seattle, WA, [3]Department of Bioengineering, University of Washington, Seattle, WA, [4]Rheumatology, University of Washington, Seattle, WA, [5]Department of Chemistry, University of Washington, Seattle, WA, [6]Department of Medicine & Immunology, University of Washington, Seattle, WA
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Background/Purpose: Anti-malarial drugs (AMD) such as Hydroxychloroquine (HCQ) and Quinacrine (QC) are effective in the treatment of skin rash and arthritis in systemic lupus erythematosus (SLE). AMD have multiple modes of action, but precisely which mechanism(s) are responsible for their beneficial action is uncertain. Type I interferon, (IFN-I) is strongly implicated in the pathogenesis of SLE as well as rare monogenic 'interferonopathies' such as Aicardi-Goutieres Syndrome (AGS). Recently, a new DNA activated IFN-I pathway, cyclic GMP-AMP (cGAMP) synthase (cGAS), was discovered and linked to AGS. To identify potential inhibitors of the DNA-cGAS interaction, we performed *in silico* screening of chemical and drug libraries.

Methods: *In silico* structure-based drug screening were provided by the CANDO docking algorithm. Predictions made by CANDO were confirmed by Autodock Vina and analyzed via PyMOL. cGAS activity/cGAMP production was analyzed by Thin Layer Chromatography (TLC). DNA-binding to cGAS in the presence or absence of AMD was determined by Electrophoretic Mobility Shift Assay (EMSA). Following DNA cell transfections, cytokines were quantified by qPCR, ELISA or an ISRE-luciferase reporter assay.

Results: *In silico* screening of chemical and drug libraries identified several antimalarial drugs (AMD) including HCQ, QC, Chloroquine (CQ), Primaquine (PQ) and 9-amino-6-chloro-2-methoxyacridine (ACMA), which could potentially inhibit cGAS activity by interacting with the cGAS/DNA dimer complex. These AMD inhibited cGAS activity/cGAMP production in a dose dependent manner. Interestingly, the *in silico* predicted binding affinities of these AMD correlated well with their potency (QC>ACMA>HCQ>CQ>PQ) to inhibit cGAS activity, validating the prediction of our computational analysis. EMSA revealed that AMD disrupted the double stranded DNA-cGAS complex in a dose dependent manner, indicating that AMD blocked dsDNA/cGAS binding. These AMD also inhibited IFN-I expression in THP1 cells transfected with dsDNA and in 293T cells transfected with cGAS/STING plasmids validating that cGAS is a target of AMD. Based on these results and *in silico* modeling, we synthesized several new AMD. One of these compounds, X6, had excellent water solubility and cell penetration. Fluorescence microscopy revealed that X6 localized to the cytosol and had a lower toxicity profile compared to QC. *In vitro* and cell based studies, revealed that X6 was a more potent inhibitor of IFN-I production following dsDNA transfection into reporter cells than HCQ. X6 was also more potent than HCQ in the inhibition of IFN-a production following CpGA stimulation of PBMC.

Conclusion: Our studies identify the cytosolic DNA sensor, cGAS, as a target of AMD activity, which provide a novel mechanism of action of these AMD. This observation together with decades of experience of AMD in human diseases, suggest that this widely used family of drugs with a strong safety profile could be repurposed to target interferonopathies and possibly other autoimmune disorders related to cGAS over-activity.

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Abstract Number: 1814

Efficacy of Isoniazid Chemoprophylaxis in Lupus Nephritis Patients

Jin Young Moon, Hyun Mi Kwon, Eun Young Ahn, Jin Kyun Park, Yeong Wook Song and Eun Bong Lee, Division of Rheumatology, Department of Internal Medicine, Seoul National University Hospital, Seoul, South Korea

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Background/Purpose: Treatment of lupus nephritis requires aggressive immunosuppressive drugs which includes high dose glucocorticoids. Immunosuppressive treatment is a risk factor for opportunistic infections such as mycobacterium tuberculosis (Tbc). However, the efficacy of isoniazid (INH) chemoprophylaxis has not been evaluated in lupus nephritis patients.

The aim of this study was to investigate the preventive effect of INH chemoprophylaxis on incidence of Tbc infection in patients with lupus nephritis on immunosuppressive treatment.

Methods: In this retrospective cohort study, 332 patients with lupus nephritis were enrolled, who received glucocorticoids and immunosuppressive treatment at Seoul National University Hospital between 2004 and 2015. Information on baseline clinical characteristics and treatment were obtained from electronic medical record review. Incidence rates of Tbc were compared between patients who took INH prophylaxis (prophylaxis group) and those who did not (non-prophylaxis group), using log-rank test. Then, incidence rates of Tbc were investigated in subgroups of patients; those who received prednisolone >= 60 mg/day and high dose glucocorticoid pulse therapy.

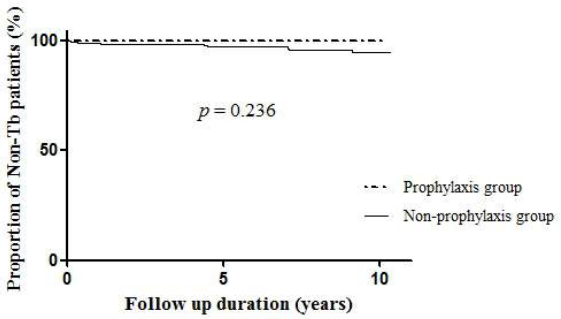
Results: A total of 332 patients with lupus nephritis were identified during the study period. The mean age was 35.3 ± 14.8 years and 266 (80.1%) were female. Among 332 patients, sixty-nine (20.8%) patients received INH prophylaxis and 263 (79.2%) patients did not. No case of Tbc developed in 69 patients of INH prophylaxis group while 9 cases of Tbc developed in 263 patients of non-prophylaxis group (0.0/100 person-years (PY) vs 0.53/100 PYs, p=0.236, by log-rank test). INH prophylaxis was effective neither in high dose (>= 60 mg/day or its equivalents) prednisolone group (0.00/100 PYs vs 0.58/100 PYs, p=0.288, by log-rank test), nor in patients who received glucocorticoid pulse therapy (0.00/100 PYs vs 0.69/100 PYs, p=0.161, by log-rank test). No patient died of Tbc infection.

Conclusion: In this retrospective review, INH chemoprophylaxis did not lead to statistically significant prevention of Tbc in lupus nephritis patients.

Table 1. Isoniazid chemoprophylaxis in patients with lupus nephritis

	Prophylaxis (n = 69)	Non-prophylaxis (n = 263)	*p*-value
Age, mean ± SD years	37.78±13.47	34.60±15.07	0.092
Female sex (%)	55 (79.7)	211 (80.2)	0.924
Follow up duration, mean ± SD years	3.74±2.59	6.48±3.65	<0.001
Prednisolone >= 60 mg/day (%)	45 (65.2)	74 (28.1)	<0.001
Steroid cumulative dose, mean ± SD mg	27556.78±16875.22	21967.13±15196.75	0.014
Steroid pulse (%)	62 (89.9)	150 (57.0)	<0.001
Rituximab (%)	0 (0)	6 (2.3)	0.214
Mycophenolate mofetil (%)	16 (23.2)	144 (54.8)	<0.001
Tacrolimus (%)	23 (33.3)	57 (21.7)	0.057
Cyclophosphamide (%)	47 (68.1)	111 (42.2)	<0.001
Mycobacterium tuberculosis IR, /100 person-years	0	0.53	0.496

Figure 1. Mycobacterium Tbc occurrence rate in all lupus nephritis patients



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Abstract Number: 1815

Hydroxychloroquine Blood Levels in Systemic Lupus Erythematosus: Clarifying Dosing Controversies and Improving Adherence

Laura Durcan[1], William Clarke[2], Laurence S Magder[3] and Michelle Petri[1], [1]Rheumatology, Johns Hopkins University Hospital, Baltimore, MD, [2]Department of Pathology, Clinical Chemistry., Johns Hopkins University Hospital, Baltimore, MD, [3]Epidemiology and Preventive Medicine, University of MD, Baltimore, MD

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Background/Purpose:

Hydroxychloroquine is at the cornerstone of systemic lupus erythematosus (SLE) management. It is used for both its effect on disease activity and long-term benefits. Poor medication adherence in SLE predicts bad outcomes. One way to assess adherence is to measure blood levels. Conflicting data exist regarding hydroxychloroquine blood levels and disease activity. There is also dosing controversy; rheumatologists recommend weight-based, while ophthalmologists advocate height-based ‘ideal body weight’ dosing. This work was undertaken, in a large lupus cohort, using sequential hydroxychloroquine blood levels to clarify these issues.

Methods:

Patients with SLE in a longitudinal cohort were prescribed hydroxychloroquine not to exceed 6.5mg/kg (max 400mg/day). In hemodialysis, the dose was 200mg after each session, in renal insufficiency it was 200mg daily. Levels were measured at each visit with a therapeutic range of 500-2000 ng/ml. Those with a sub-therapeutic level were informed and counselled on the importance of adherence. Vitamin D levels were measured and patients were prescribed 50,000 units per week if their level was below 40ng/ml. Patients were divided according to baseline blood hydroxychloroquine level. To assess the impact of measurement and counseling on adherence, we compared the proportion of patients with a level of 500ng/ml or higher based on how many prior assessments the patient had.

Results:

The proportion of patients with hydroxychloroquine levels in the therapeutic range differed significantly by age, gender and vitamin D level. There was a trend toward lower levels with renal failure. Blood levels were similar regardless of height, BMI and ideal body weight. Comparing those with undetectable, sub-therapeutic and therapeutic levels, disease activity decreased (SLEDAI 2.92, 2.36 and 2.20)(P=0.04, for trend). There was a correlation between blood levels of vitamin D and hydroxychloroquine levels which increased in parallel (correlation coefficient 0.12, $p<0.0022$). At first measurement, 56% had therapeutic hydroxychloroquine blood levels and by the third measurement this increased to 80% ($p =<0.0001$).

Conclusion:

There was a trend towards higher disease activity with lower hydroxychloroquine levels. We show that weight-based dosing (max 400mg daily) is appropriate and that height does not appear to influence levels. Measurement, counseling and repeated testing can significantly increase adherences rates.

Table 1. Number (%) with Various Levels of Hydroxychloroquine at the first Hydroxychloroquine Assessment by Patient Characteristics.

Characteristics	HCQ <15 ng/ml	HCQ 15–500 ng/ml	HCQ 500-2000 ng/ml	HCQ ≥2000 ng/ml	P value
All (n=686)	88 (13%)	216 (31%)	366 (53%)	16 (2%)	
Gender					0.050
Female (n=633)	84 (13%)	206 (33%)	329 (52%)	15 (2%)	
Male (n=53)	4 (8%)	10 (19%)	38 (71%)	1 (2%)	
Ethnicity					0.41
Caucasian (n=333)	37 (11%)	104 (31%)	182 (55%)	10 (3%)	
African-American (n=287)	43 (15%)	86 (30%)	154 (54%)	4 (1%)	
Other (n=66)	8 (12%)	26 (39%)	30 (45%)	2 (3%)	
Age					0.0018
≤30 yrs (n=89)	10 (11%)	18 (20%)	59 (66%)	2 (2%)	
30-44 yrs (n=244)	28 (11%)	98 (40%)	114 (47%)	4 (2%)	
45-59 yrs (n=230)	36 (16%)	75 (33%)	114 (49%)	6 (3%)	
60 + yrs (n=123)	14 (11%)	25 (20%)	80 (65%)	4 (3%)	
Education					0.12
Less than HS (n=51)	5 (10%)	18 (35%)	25 (49%)	3 (6%)	
High school (n=160)	30 (19%)	49 (31%)	78 (49%)	3 (2%)	
Some college (n=465)	52 (11%)	144 (31%)	259 (56%)	10 (2%)	
Family income					0.54
≤$30,000 (n=195)	29 (15%)	59 (30%)	103 (53%)	4 (2%)	
$30,000-$60,000(n=160)	26 (16%)	47 (29%)	84 (53%)	3 (2%)	
Over $60,000 (n=316)	32 (10%)	105 (33%)	170 (54%)	9 (3%)	
BMI					0.26
<20 (n=66)	9 (14%)	20 (30%)	34 (52%)	3 (5%)	
20-24.99 (n=203)	25 (12%)	57 (28%)	114 (56%)	7 (3%)	
25-25.99 (n=185)	30 (16%)	55 (30%)	97 (52%)	3 (2%)	
30+ (n=215)	19 (9%)	79 (37%)	114 (53%)	3 (1%)	
SLEDAI					0.38
0 (n=267)	27 (10%)	83 (31%)	150 (52%)	7 (3%)	
1-3 (n=217)	32 (15%)	71 (33%)	112 (52%)	2 (1%)	
4+ (n=202)	29 (14%)	62 (31%)	104 (51%)	7 (3%)	
PGA					0.37
0 (n=193)	15 (8%)	59 (31%)	114 (59%)	5 (3%)	
>0 to 0.99 (n=301)	42 (14%)	98 (33%)	157 (52%)	4 (1%)	
1.00 to 1.49 (n=80)	14 (18%)	23 (29%)	40 (50%)	3 (4%)	
1.50-1.99 (n=56)	6 (11%)	19 (34%)	29 (52%)	2 (4%)	
2.00+ (n=48)	9	16	21	2	

2.0+ (n=48)	(19%)	(33%)	(44%)	(4%)	
Vitamin D					0.011
< 40 ng/ml (n=359)	55 (15%)	125 (35%)	170 (47%)	9 (3%)	
40+ ng/ml (n=321)	33 (10%)	89 (28%)	192 (60%)	7 (2%)	
Creatinine (mg/ml)					0.029
<1.4 (n=618)	76 (12%)	195 (32%)	334 (54%)	13 (2%)	
1.4-4.9 (n=15)	5 (33%)	4 (27%)	6 (40%)	0 (0%)	
5.0 + (n=6)	1 (17%)	3 (50%)	1 (17%)	1 (17%)	
Height (inches)					0.31
<60 (n=20)	5 (25%)	3 (15%)	11 (55%)	1 (5%)	
60-62.5 (n=221)	22 (10%)	78 (35%)	113 (51%)	8 (4%)	
63-67.9 (n=320)	44 (14%)	97 (30%)	174 (54%)	5 (2%)	
68+ (n=113)	15 (13%)	33 (29%)	63 (56%)	2 (2%)	
Ideal Body Weight					0.82
Less than (n=95)	14 (15%)	28 (29%)	50 (53%)	3 (3%)	
Greater than (n=574)	69 (12%)	183 (32%)	309 (54%)	13 (2%)	

HCQ= hydroxychloroquine, BMI=body mass index, SLEDAI= Systemic Lupus Erythematosus Disease Activity Index, PGA= Physician Global Assessment.

Disclosure: L. Durcan, None; **W. Clarke**, None; **L. S. Magder**, None; **M. Petri**, None.

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Abstract Number: 1816

Long-Term Outcome of Tacrolimus Therapy As a Maintenance Strategy in Patients with Lupus Nephritis

Yun Jung Choi[1], Won-Seok Lee[2], Myong-Joo Hong[3], Chang-Hoon Lee[4], Myeung Su Lee[5], Young Sun Suh[6], Sang-Il Lee[7] and Wan-Hee Yoo[8], [1]Division of Rheumatology, Department of Internal Medicine, Chonbuk National University Medical School and Research Institute of Clinical Medicine of Chonbuk National University Hospital-Chonbuk National University, JeonJu, South Korea, [2]Division of Rheumatology, Department of Internal Medicine, Chonbuk National University Medical School and Research Institute of Clinical Medicine of Chonbuk National University Hospital-Chonbuk National University, jeonju, South Korea, [3]Internal Medicine, Presbyterian Medical center, Jeonju, South Korea, [4]Department of Internal Medicine, School of Medicine, Wonkwang University, Iksan, Chonbuk, South Korea, [5]Internal Medicine, School of Medicine, Wonkwang University, Iksan, Chonbuk, South Korea, [6]Division of Rheumatology, Department of Internal Medicine, School of Medicine, The Catholic University of Korea, Seoul St. Mary's Hospital, Seoul, South Korea, [7]Division of Rheumatology, Department of Internal Medicine, Gyeongsang National University School of Medicine, Jinju, South Korea, [8]Division of Rhuematology, Department of Internal Medicine, Chonbuk National University Medical School and Research Institute of Clinical Medicine of Chonbuk National University Hospital-Chonbuk National University, Jeonju, South Korea

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Background/Purpose: Lupus nephritis(LN) is one of the significant cause of mortality in patients with systemic lupus erythematosus. Tacrolimus, a calcineurin inhibitor widely used in prevention of organ transplant rejections, has been recently applied to the treatment of LN due to its immunosuppressive effects. However, there are few reports regarding the long-term effects of tacrolimus as a maintenance treatment of LN. We aimed to investigate long-term outcomes and tolerability of tacrolimus after being switched from azathioprine or mycophenolate mofetil (MMF) due to intolerability.

Methods: The records of 27 LN patients who received tacrolimus treatment for 39.2month(S.D 1.2) were reviewed retrospectively. Tacrolimus was used as a maintenance therapy alternative to azathioprine (n = 13) or MMF (n = 16) after treatment with high-dose glucocorticoids and cyclophosphamide or MMF in all patients.

Results: After induction therapy with high-dose glucocorticoids and cyclophosphamide or MMF, proteinuria (3.4 ± 3.34 to 1.56 ± 1.78 g/24 hr), GFR (81.83 ± 28.1 to 119.34 ± 32.64 mL/min/1.73m^2), serum C3 (51.64 ± 20.21 to 73.34 ± 19.0mg/dL), C4 (8.54 ± 6.04 to 13.8 ± 6.98 mg/dL) and anti-dsDNA antibody (92.45 ± 74.54 to 72.78 ± 68.67 IU/mL) improved. These improvements were maintained by tacrolimus therapy 39 months after changing from MMF or azathioprine(proteinuria, 0.22 ± 0.19g/24 hr; GFR, 110.06 ± 36.84 mL/min/1.73m^2; serum C3, 77.27± 15.85 mg/dL; C4, 14.88 ± 6.33mg/dL; and anti-dsDNA antibody, 48.87 ± 55.01 IU/mL). One patient developed end-stage renal failure, and the1-, 2- and 3-year renal survival rates were 100%, 96%, and 96%, respectively. Two patients (7.4%) had infections that required hospitalization (urinary tract infection or herpes zoster) and four patients had hair loss. One death occurred because of biliary cancer.

Conclusion: In our study, the efficacy and tolerability of tacrolimus in treating LN as a maintenance therapy was favorable with minor complications. Further detailed investigations to confirm its long term efficacy and safety will be needed for identifying its role as a long-term maintenance agent.

Disclosure: Y. J. Choi, None; **W. S. Lee**, None; **M. J. Hong**, None; **C. H. Lee**, None; **M. S. Lee**, None; **Y. S. Suh**, None; **S. I. Lee**, None; **W. H. Yoo**, None.

Abstract Number: 1817

Myocardial Tissue Characterization with Native Myocardial T1 Mapping in SLE Patients with Chest Pain

Jaime Shaw[1], Mariko L. Ishimori[2], Vaneet K. Sandhu[2], Behzad Sharif[3], Louise Thomson[4], Debiao Li[1], Jay Schapira[4], Daniel Wallace[3], Noel Bairey Merz[4], Michael Weisman[3] and Daniel Berman[4], [1]Biomedical Imaging Research Institute, Cedars-Sinai Medical Center, Los Angeles, CA, [2]Rheumatology, Cedars-Sinai Medical Center, Los Angeles, CA, [3]Cedars-Sinai Medical Center, Los Angeles, CA, [4]Cardiology, Cedars-Sinai Medical Center, Los Angeles, CA

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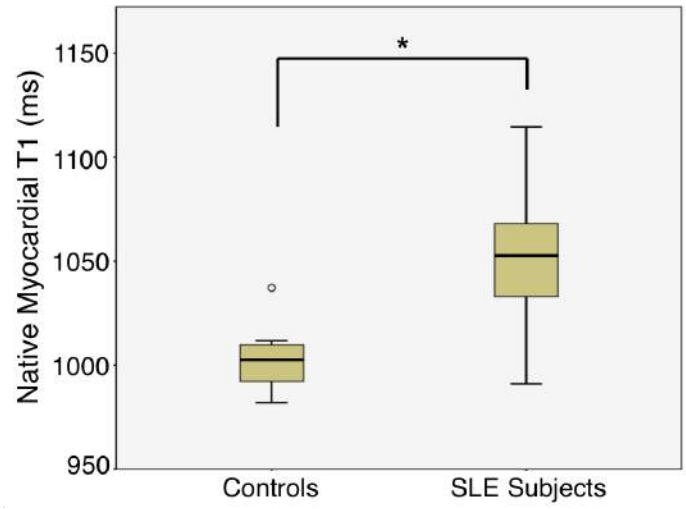
Background/Purpose: SLE patients often exhibit signs and symptoms of cardiac ischemia with an overall increased prevalence of coronary artery disease (CAD), microvascular dysfunction and myocarditis in this population. Potentially, these processes may be associated with subclinical changes in myocardial tissue. Elevated native myocardial T1, a cardiac magnetic resonance imaging (CMRI) measure of myocardial fibrosis, has previously been shown in asymptomatic SLE patients, implying subclinical myocardial disease. We assessed the hypothesis that native myocardial T1 would be abnormally elevated in SLE subjects with chest pain.

Methods: We evaluated 13 women with SLE, chest pain but no obstructive coronary disease and 7 matched normal controls using native T1 mapping at 1.5T (Siemens Avanto) CMRI with a 5(3)3 MOLLI sequence in a single mid-ventricular slice. Healthy controls had a normal exercise stress test and no history of cardiovascular disease.

Results: The healthy control group (n=7) and SLE group (n=13) were well matched in age (47.9±9.2 vs 46.4±11, p=0.773) and BMI (24.8±2.6 vs 26.0±7.6, p=0.710). Eight SLE subjects had current or past corticosteroid use and 7 had current or past use of a cytotoxic agent. Average SLE duration was 19.5 years. Native myocardial T1 values were increased in the women with SLE and chest pain compared to reference control women (1049.4±34.3 vs 1003.8±18.9 milliseconds, p=0.005). No significant relationship was shown between native myocardial T1 and age, BMI, disease duration, or SLEDAI. However, native myocardial T1 positively correlated with corticosteroid use (r=0.507, p=0.077) as well as the use of cytotoxic agents (r=0.495, p=0.086).

Conclusion: Among women with SLE, chest pain, and no obstructive coronary disease, native myocardial T1 measured by CMR is consistent with diffuse fibrosis compared to controls.



Disclosure: J. Shaw, None; **M. L. Ishimori**, None; **V. K. Sandhu**, None; **B. Sharif**, None; **L. Thomson**, None; **D. Li**, None; **J. Schapira**, None; **D. Wallace**, None; **N. Bairey Merz**, None; **M. Weisman**, None; **D. Berman**, None.

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Abstract Number: 1818

Cyclophosphamide and Cumulative Steroid Dose Associated with Higher Risk of Infections in Patients with Lupus Nephritis

Shubhasree Dutta Choudhury[1], Ann Biehl[2], Maryam Ghaderi-yeganeh[3], Zerai Manna[4] and Sarfaraz Hasni[4], [1]National Institute of Arthritis, Musculoskeletal and Skin Diseases2, National Institutes of Health, Bethesda, MD, [2]Department of Pharmacy, National Institutes of Health Clinical Center, Bethesda, MD, [3]National Institutes of Health Clinical Center Department of Pharmacy, National Institutes of Health, Bethesa, MD, [4]National Institute of Arthritis and Musculoskeletal and Skin Diseases, National Institutes of Health, Bethesda, MD

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Background/Purpose:

Immune dysregulation associated with SLE leads to a substantially high background risk of infection. This risk of infection further increases with the use of immunosuppressive drugs like cyclophosphamide. Our objective was to determine the incidence and types of infections (especially pneumocystis jirovecii (PCJ)) in SLE patients treated with cyclophosphamide, and to identify relative contribution of other variables like patient demographics, steroid dose, other immunosuppressive agents, baseline white blood cell(WBC) count and absolute neutrophil count(ANC) to the risk of infection.

Methods:

We did retrospective chart review of SLE patients presented to our institute over the last 10 years, who have received at least 6 doses of monthly cyclophosphamide infusions(induction phase) and were followed up for 6 months post-induction(maintenance phase) for lupus nephritis. The timings and types of infection, cumulative steroid dose, and maintenance phase immunosuppressive regimen were recorded. Statistical analyses were done using SAS software(SAS Institute, Cary, NC).

Results:

Majority (90.5%) of the 31 patients with complete records were female. Mean age was 31.4 years (15- 50 years), 50% Hispanic, 23.8% African American, 11.9% Asian and 14.3% were Caucasian. None of our patients were on routine prophylaxis for infections including PCJ.

There were 42 episodes of infection in 31 patients. Different types of infection were UTI, URI, line sepsis, bacterial pneumonia, PCJ mucocutaneous infections (fungal/ viral/ bacterial) and viral gastroenteritis.

Incidence of infection was significantly higher among Hispanic patients (p value 0.0425).

As expected, the rate of infection was found to be significantly higher during the induction phase (65.9%) compared to the maintenance phase (34.1%) (p

value=0.0041).

Cumulative steroid dose during the induction phase was associated with significantly higher rates of infection (Table 1).

Incidence of infection during maintenance phase tends to be higher in patients on quarterly cyclophosphamide infusion compared to those on daily oral azathioprine or mycophenoalte mofetial.

We did not find any association between baseline WBC count or ANC and risk of infection.

Conclusion:

In our cohort of SLE patients we found higher infection rates among Hispanics.

Patients with higher cumulative steroid dose during monthly cyclophosphamide infusions are at the highest risk of infection. Surprisingly only one episode of PCJ was found in our cohort despite absence of routine prophylaxis.

Maintenance treatment with quarterly cyclophosphamide was associated with higher rates of infection as compared to azathioprine or mycophenolate.

Our study limitations include retrospective review, modest numbers and short duration of follow-up. Larger prospective studies with long-term follow-up are needed to confirm our results.

Table-1 Comparing steroids on incidence of infection using time dependent multivariate analysis patients treated with Cyclophosphamide

Type of Infection	Number of Events	Cumulative Steroids Mean ± STD	*P* value
UTI			0.0342**
Infection	*n=7*	13773.6 ± 7076.4	
No Infection	*n=35*	11432.1 ± 5433.6	
Pos. Blood Cx			0.0522
Infection	*n=2*	9010.8 ± 4967.4	
No Infection	*n=40*	12021.9 ± 5795.6	
Bacterial PNA			0.0369**
Infection	*n=2*	17566.7 ± 11030.9	
No Infection	*n=40*	11546.7 ± 5417.2	
Pneumocystis carinii PNA			0.0241**
Infection	*n=1*	23305.0 ± 0.0	
No Infection	*n=41*	11554.2 ± 5484.9	
Mucocutaneous Fungal Infection			0.0742
Infection	*n=3*	8418.3 ± 2392.4	
No Infection	*n=39*	12054.8 ± 5822.8	
URI			0.0501
Infection	*n=13*	13649.2 ± 7371.2	
No Infection	*n=29*	11039.2 ± 4749.2	
Mucocutaneous Bacterial Infection			0.0264**
Infection	*n=1*	18360.0 ± 0.0	
No Infection	*n=41*	11678.9 ± 5710.9	
Mucocutaneous Viral Infection			0.0248**
Infection	*n=8*	15292.3 ± 5935.1	
No Infection	*n=34*	10949.1 ± 5419.5	
Viral Gastroenteritis			0.0206**
Infection	*n=3*	17584.4 ± 7008.6	
No Infection	*n=35*	11373.1 ± 5457.4	

P Value (*) was obtained using Cox hazard proportional time to event model

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Abstract Number: 1819

Comparison of Electrocardiographic ST-T Changes and QTc Duration in Patients with Systemic Lupus Erythematosus and Rheumatoid Arthritis

Laura Geraldino-Pardilla[1], Yevgeniya Gartshteyn[2], Jon T. Giles[3], Thania Perez[4], Anca D. Askanase[5] and Joan M. Bathon[6], [1]Division of Rheumatology,

Columbia University College of Physicians & Surgeons, New York, NY, [2]Medicine, Columbia University, College of Physicians & Surgeons, New York, NY, [3]Division of Rheumatology, Columbia University, College of Physicians & Surgeons, New York, NY, [4]Columbia University, College of Physicians & Surgeons, New York, NY, [5]Department of Medicine Rhemuatology, Colombia University, New York, NY, [6]Rheumatology, Columbia University College of Physicians & Surgeons, New York, NY

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Background/Purpose: Cardiovascular disease (CVD) is a leading cause of death in systemic lupus erythematosus (SLE) and in rheumatoid arthritis (RA). Longer corrected QT segments (QTc) and a high prevalence of repolarization abnormalities have been recently described in the electrocardiograms (EKG) of SLE patients. In addition, both QTc prolongation and ST-T changes have been associated with increased cardiovascular mortality in the general population. Our objective was to evaluate QTc duration and ST-T changes in a tertiary lupus center and compare it with a cohort of RA patients without CVD.

Methods: Fifty SLE patients meeting ACR classification criteria were cross-sectionally evaluated and compared with 139 RA patients without known CVD. Demographics, disease characteristics, disease activity, and comorbidities were ascertained. Linear and logistic regression models were used to assess the associations with QTc duration and ST-T changes, adjusting for CVD risk factors.

Results: SLE patients (38 ±14 years old, 92% females, 73% Hispanic) had a median disease duration of 8 years and median SLEDAI-2K of 6. Forty-four percent had a history of lupus nephritis, 62% were on antimalarials, and 52% and 30% were SSA and SSB antibody positive, respectively. RA patients (59 ± 8 years old, 61% females, 87% white) had a median disease duration of 8 years, a mean DAS28-CRP of 3.6, 68% were anti-CCP antibody positive, and 48% were on biologics. SLE patients were more likely to be smokers (24% vs. 9%), and 7 (14%) had known CVD. There was no difference in the prevalence of hypertension, diabetes, aspirin or statin use between the two groups (Table 1). The prevalence of ST-T changes was higher in SLE vs. RA (58% vs. 15%, respectively; p<0.0001) representing an 8-fold higher odds. After adjusting for age, smoking, CVD, and aspirin use, the difference remained statistically significant (OR=8.5; p=0.0003). The QTc duration was significantly longer in SLE vs. RA patients in the univariable and in the adjusted analyses (435 vs. 418 ms, p=<0.0001; and 438 vs. 423 ms, p=0.0007, respectively) (Figure 1). Similar results were seen when limiting the analysis to only those without CVD. In SLE patients no specific disease characteristics were associated with these EKG changes. In the RA group, biologics were protective for the occurrence of ST-T changes.

Conclusion: More frequent ST-T changes and a longer QTc duration were seen in SLE when compared to RA patients. Longitudinal studies to evaluate the progression of these EKG changes and their risk for life-threatening arrhythmias and cardiovascular death in these patients are needed.

Table 1. Patient Characteristics.

	RA (n=139)	SLE (n=50)	p value
Demographics			
Age (years)	59 ± 8	38 ± 14	<0.0001
Female	85 (61%)	46(92%)	<0.0001
White	121 (87%)	0	<0.0001
Hispanic	1 (1%)	33 (73%)	<0.0001
Clinical Features			
Disease duration (years)	8 (4-16)	8 (3-13)	0.57
SLEDAI-2K	-	6 (2-12)	-
DAS28-CRP	3.6 ± 1.0	-	-
Moderate to severe disease activity*	86 (62%)	25 (50%)	0.14
Lupus nephritis	-	22 (44%)	-
Antimalarials	-	31 (32%)	-
Mycophenolate mofetil current	-	(42%)	-
Azathioprine current	-	5 (10%)	-
Non-biologic DMARD current	117 (85%)	-	-
Biologic current	66 (48%)	-	-
Corticosteroids current	50 (36%)	26 (52%)	0.05
Auto-Antibodies			
dsDNA	-	45 (90%)	-
SSA	-	26 (52%)	-
SSB	-	15 (30%)	-
RF> 40 units	85 (61%)	-	-
CCP > 60 units	94 (68%)	-	-
Cardiovascular risk factors/disease			
Hypertension	56 (40%)	20 (40%)	0.97
Diabetes	10 (7%)	2 (4%)	0.43
Current smoking	13 (9%)	12 (24%)	0.009
History of CVD	0	7 (14%)	<0.0001
Aspirin use	44 (32%)	12 (24%)	0.31
Lipid lowering medication use	23 (16%)	8 (16%)	0.97

Table 1. Characteristics are expressed as n (%), as the mean ± SD, or as the median (interquartile range). *Based on a SLEDAI-2K>6, and a DAS28-CRP ≥3.2 for the SLE and RA patients, respectively.

Figure 1. Prevalence of ST-T changes and QTc duration in systemic lupus erythematosus vs. rheumatoid arthritis patients.

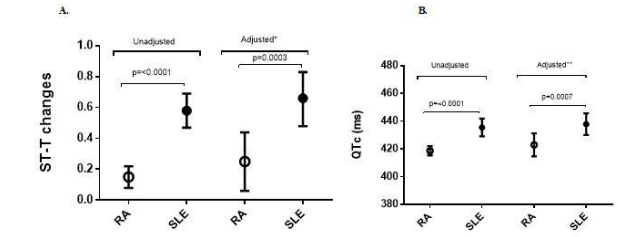

Figure 1. A. Prevalence of ST-T changes in systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA) patients. In the unadjusted model: OR=7.8 (3.7-16.1). In the adjusted model: OR=8.5 (2.6-27.4). *Adjusted analysis accounts for age, cardiovascular disease, current smoking, and aspirin use. **B.** QTc mean and 95% CI in RA and SLE patients. **Adjusted for age and history of cardiovascular disease.

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Abstract Number: 1820

Prevalence and Risk-Factors for Asymptomatic Coronary-Artery Calcifications in Young Patients with Systemic Lupus Erythematosus

Juanita Romero-Diaz[1], Rocio Moran-Contla[2], Eric Kimura-Hayama[3], Sergio Criales-Vera[3], Carlos Núñez-Álvarez[2], Roberto Ivan Acosta-Hernandez[4], Mario César Ocampo-Torres[5] and Jorge Sánchez-Guerrero[6], [1]Immunology and Rheumatology, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico city, Mexico, [2]Instituto Nacional de Cs Medicas y Nutricion Salvador Zubiran, Mexico city, Mexico, [3]Radiology Department, Instituto Nacional de Cardiologia, Mexico City, Mexico, [4]Society for Worldwide Med Exchange, North Bay Village, FL, [5]Immunology and Rheumatology, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico, [6]Rheumatology, Mount Sinai Hospital and University Health Network, Toronto Canada, Toronto, ON, Canada

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Background/Purpose:

Premature atherosclerosis is a major cause of morbidity and mortality in females with systemic lupus erythematosus (SLE), but little is known about the frequency, extent, and risk-factors of coronary-artery calcifications (CAC) in young patients with SLE.

Methods:

We studied 223 SLE patients (95 males and 128 females) attending our outpatient clinic and 193 healthy subjects (100 males, 93 females) w/o preexisting coronary heart disease, matched by age and race. Patients and controls had a standardized assessment of demographic characteristics and traditional cardiovascular risk factors. In addition, lupus patients had an evaluation of lupus characteristics, medications, and laboratory tests including immunological, extended lipid profile, homocystein, and hsCRP. All patients and healthy controls were screened for coronary-artery calcifications using a 64-slice Multidetector Computed Tomography and the extent of calcification was measured by means of the Agatson score.

Results:

Mean (SD) age of lupus patients and controls was 32.9 (9.4) and 33.5 (9.8) years, respectively. Coronary-calcifications were detected in 25 patients (11%) and 7 (4%) controls (OR 3.35, 95% CI 1.36-9.38, p=0.004). Median calcium score in patients was 15.9 (0.2-576.8), and 7.7 (1.1-140.2) in controls. Calcifications in lupus patients and controls were detected since age 32 and 41 years, respectively. In two patients, calcifications were detected within 3 years of diagnosis. The multivariate analysis showed that age (OR 1.13, 95% CI 1.08 – 1.18), smoking (OR 3.50 95% CI 1.32 – 9.27), male gender (OR 2.62 95% CI 1.04 – 6.57), and SLE diagnosis (OR 4.41 95% CI 1.64 – 11.85) were associated with CAC in the whole population.

Among the lupus patients, those with calcifications were older (42.1 + 8.6 vs 31.8 + 8.9 years, P<0.001), males (68% vs 39%, P=0.006), waist (91.4 + 14.2 vs 85.6 + 12.7 cm, P=0.02), current smoking (32% vs 10%, P=0.006), hypertension (48% vs 28%, P=0.04), homocysteine levels (17.1 + 14.8 vs 11.7 + 6.4, P=0.009), Framingham risk score [5(1-25) vs 1(1-13), P<0.001], MetS (44% vs 15% , P=0.001]. Lupus duration was longer (11.1 + 8.9 vs 5.8 + 4.3 years, P=0.006), and cumulative dose of prednisone higher [61.7(0.24-454.2) vs 49.9(8.5-106.5) grams, P=0.001] in comparison to patients with no calcifications. No difference was observed in lupus manifestations, clinical activity during the course of the disease, autoantibodies, and use of anti-malarials and aspirin. Logistic regression adjusting by disease duration showed an independent association of age (OR 1.12, 95% CI 1.05-1.16, p= P<0.001), smoking (OR 3.69,

95% CI 1.04-13.1, p=0.04) and cumulative dose of prednisone (OR 1.03, 95% CI 1.005-1.06, p=0.02) with calcifications.

Conclusion:

Asymptomatic coronary-artery calcifications are more common, extensive, and present at younger age in SLE patients than in the controls. Their association, principally to traditional risk-factors than lupus characteristics, raise the possibility of modifying their burden.

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Abstract Number: 1821

Leptin, Adiponectin, and Resistin As Serum Markers of Fatigue in Systemic Lupus Erythematosus: A Pilot Study

Mary Mahieu[1], Grace Ahn[2], Joan S. Chmiel[3], Dorothy D. Dunlop[4], Irene Helenowski[3], Pamela Semanik[5], Jing Song[4], Rowland W. Chang[3] and Rosalind Ramsey-Goldman[6], [1]Rheumatology, Northwestern University Feinberg School of Medicine, Chicago, IL, [2]Rheumatology, Falls Medical Specialists, Baltimore, MD, [3]Preventive Medicine, Northwestern University Feinberg School of Medicine, Chicago, IL, [4]Institute for Healthcare Studies, Northwestern University Feinberg School of Medicine, Chicago, IL, [5]Nursing, Rush University College of Nursing, Chicago, IL, [6]Northwestern University Feinberg School of Medicine, Chicago, IL

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Background/Purpose: Fatigue, a common symptom in systemic lupus erythematosus (SLE) patients, is ameliorated by physical activity. Adiposity and adipokines may be associated with patient-reported fatigue. We describe associations between adipokines (leptin, adiponectin, and resistin) and fatigue, physical activity, and SLE disease activity.

Methods: We examined adipokines, self-reported fatigue, and objective physical activity in 129 patients meeting ACR revised criteria for definite SLE from the Activity in Lupus to Energize and Renew (ALTER) study. Body mass index (BMI), disease activity (Safety of Estrogens in Systemic Lupus Erythematosus National Assessment – Systemic Lupus Erythematosus Disease Activity Index [SELENA-SLEDAI]), and disease damage (Systemic Lupus International Collaborating Clinics Damage Index [SDI]) were measured. Fatigue was assessed by the Fatigue Severity Scale (FSS). A triaxial accelerometer was worn for 7 days, and physical activity was estimated by total accelerometer vector magnitude (VM) counts. Six patients with <4 valid days of accelerometer wear were excluded from physical activity analyses. Leptin, adiponectin, and resistin were measured in stored serum with a Luminex bead-based assay. Adipokine data were logarithmically transformed for inclusion in linear regression models describing relationships between FSS and adipokines. Spearman correlation coefficients assessed associations between adipokines, physical activity, and SELENA-SLEDAI.

Results: Participants were female (94%), Caucasian (53%), and mean age 45.5 years (SD 10.9). BMI was 28.1 kg/m^2 (8.2). SELENA-SLEDAI was 2.4 (2.8) and SDI was 1.7 (2.2). FSS score was 4.4 (1.6), consistent with clinically relevant fatigue. Mean adipokine levels were: leptin 44.2 ng/ml (47.6), adiponectin 13.5 µg/ml (10.8) and resistin 1.9 ng/ml (1.5). No significant associations were found between adipokines and FSS in any of the regression models (Table 1). BMI ≥ 30 kg/m^2 (obesity) was associated with FSS in adjusted models (p <0.05, data not shown). Weak correlations between leptin, adiponectin, and physical activity, and between adiponectin and SELENA-SLEDAI score, were not significant after adjusting for BMI (Table 2).

Conclusion: No relationships were found between adipokines and fatigue in SLE patients. This study demonstrates that adipokines are correlated with physical activity (leptin and adiponectin) and SLE disease activity (adiponectin), but most of these associations can be explained by BMI.

Table 1. Linear regression model results for FSS (dependent variable) and each adipokine measure (predictor variable, natural log scale)					
	Adjustment Variables	Regression coefficient	Leptin	Adiponectin	Resistin
Model 1	Unadjusted	β	0.25	-0.11	0.36
		95% CI	-0.05, 0.54	-0.53, 0.32	-0.08, 0.81
Model 2	BMI, age, sex, race/ethnicity	β	-0.12	0.08	0.32
		95% CI	-0.59, 0.35	-0.39, 0.55	-0.12, 0.76
Model 3	Model 2 plus SELENA-SLEDAI	β	-0.17	0.02	0.26
		95% CI	-0.65, 0.30	-0.46, 0.50	-0.19, 0.72
Model 4	Model 2 plus total accelerometer VM counts and wear time (n=123)	β	-0.14	0.26	0.24
		95% CI	-0.61, 0.32	-0.21, 0.72	-0.21, 0.70

CI = confidence interval

Table 2. Spearman correlations for adipokines, physical activity, and SLE disease activity					
	Adjustment Variables	Correlation coefficient	Leptin	Adiponectin	Resistin
Total accelerometer VM counts (n=123)	Accelerometer wear time	r	-0.25	0.20	-0.07
		95% CI	-0.41, -0.08	0.02, 0.36	-0.25, 0.10
	Accelerometer wear time plus BMI	r	-0.06	0.11	-0.04
		95% CI	-0.24, 0.12	-0.08, 0.28	-0.22, 0.14
SELENA-SLEDAI (n=129)	Unadjusted	r	0.02	0.18	0.08
		95% CI	-0.15, 0.19	0.01, 0.34	-0.09, 0.25
	BMI	r	0.16	0.15	0.09
		95% CI	-0.02, 0.32	-0.02, 0.32	-0.08, 0.26

Bolded r-values (95% CI) indicate statistical significance.

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Abstract Number: 1822

Pharmacokinetics of the Selective B-Cell Lymphoma-2 (Bcl-2) Inhibitor, ABT-199, in Female Subjects with Systemic Lupus Erythromatosus

Mukul Minocha[1], Shekman Wong[2], Jiewei Zeng[2], Peng Lu[3], Jeroen Medema[2] and **Ahmed Othman**[4], [1]Clinical Pharmacology and Pharmacometrics, AbbVie, North Chicago, IL, [2]AbbVie Inc., North Chicago, IL, [3]AbbVie Inc., Worcester, MA, [4]AbbVie, North Chicago, IL

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Background/Purpose: Selective Inhibition of Bcl-2 pathway may offer clinical efficacy in Systemic Lupus Erythromatosus (SLE) by restoring apoptosis in autoreactive cells, which may lead to immune response resolution. ABT-199 is an orally bioavailable, selective Bcl-2 inhibitor currently under evaluation for treatment of SLE and several oncology indications. This work characterized the pharmacokinetics of ABT-199 in female subjects with SLE following single and multiple dosing

Methods: Single escalating oral doses (10, 30, 90, 180, 300, 500 mg or matching placebo, total 48 subjects) and multiple escalating oral doses (30, 60, 120, 240, 400, 600 mg or matching placebo, total 50 subjects) of ABT-199 were evaluated. The multiple dose evaluation consisted of two cycles each including once daily dosing under non-fasting conditions for 7 days followed by a 21 day washout period. Both evaluations followed randomized, double-blind, placebo-controlled designs (3:1 active: placebo). Serial blood samples were collected for characterization of ABT-199 pharmacokinetics.

Results: ABT-199 followed bi-exponential disposition with peak plasma concentrations observed within 4 to 8 hours post dose. Steady-state exposures were achieved within 4 days of dosing. ABT-199 exposure did not deviate significantly from dose proportionality over the evaluated dose range and the median steady-state accumulation ratio was 1.1 to 1.5. ABT-199 terminal elimination half-life ranged from 7 to 17 hours and the effective half-life, calculated based on C_{max} to C_{trough} ratio at steady state, was 9 to 11 hours. The fraction of ABT-199 dose eliminated unchanged in urine was negligible

Conclusion: ABT-199 displayed favorable pharmacokinetic profile in female subjects with SLE that warrants further clinical evaluations

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Disclosure: M. Minocha, AbbVie, 1,AbbVie, 3; **S. Wong**, AbbVie, 3; **J. Zeng**, AbbVie, 1,AbbVie, 3; **P. Lu**, AbbVie, 1,AbbVie, 3; **J. Medema**, AbbVie, 1,AbbVie, 3; **A. Othman**, AbbVie, 1,AbbVie, 3.

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Abstract Number: 1823

Visceral Adiposity in Premenopausal Lupus Patients: Correlation with Systemic Inflammation

Luciana Seguro[1], Valéria Caparbo[2], Eloisa Bonfá[1] and Rosa M R Pereira[3], [1]Rheumatology Division, Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil, [2]Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil, [3]Rheumatology, Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil

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Background/Purpose:

SLE is associated with high prevalence of metabolic syndrome and obesity, which can be related to the high risk of cardiovascular events in this group of patients. Visceral adipose tissue (VAT) correlates more accurately with cardiovascular risk factors than other measures of adiposity. The aim of this study was to evaluate VAT in premenopausal SLE patients compared to controls.

Methods:

The study included 63 premenopausal SLE patients and 186 age-matched healthy women. Demographic, anthropometric, disease and treatment parameters were evaluated. Visceral adipose tissue (VAT) parameters were measured by Hologic dual X-ray absorptiometry (DXA) scanner equipped with APEX 4.0 software.

Results:

SLE patients had mean disease duration of 5.25 ± 3.8 years, mean SLEDAI activity score of 4.35 ± 5.13, mean SLICC damage index of 0.70 ± 0.80, mean current prednisone dose of 11.60 ± 12.10 mg/day and cumulative glucocorticoid dose of 5.27 ± 5.57 g. SLE patients and controls had similar age (31.14 ± 6.87 vs. 30.68 ± 7.70 years, p=0.673), weight (66.87 ± 13.60 vs. 64.84 ± 14.22 kg, p=0.324), height (1.60 ± 0.06 vs. 1.61 ± 0.06 m, p=0.290) and body mass index (25.98 ± 5.05 vs. 24.91 ± 4.94 kg/m^2, p=0.145). SLE patients and controls had similar fat mass (23.31 ± 8.79 vs. 21.92 ± 8.64 kg, p=0.273), fat percentage (33.84 ± 6.45 vs. 33.05 ± 5.98 %, p=0.376) and fat mass/height² (9.09 ± 3.4 vs. 8.65 ± 3.83 kg/m^2, p=1.413). SLE patients had higher values of VAT parameters than controls, namely VAT mass (362.16 ± 196.12 vs. 303.36 ± 187.19 g, p=0.034), VAT volume (391.55 ± 212.07 vs. 329.14 ± 203.57, p=0.038) and VAT area (75.12 ± 40.69 vs. 63.16 ±39.09, p=0.039). SLE patients had higher trunk/legs fat percentage ratio (0.84 ± 0.22 vs. 0.76 ± 0.19, p=0.003) and trunk/limb fat mass ratio (0.84 ± 0.22 vs. 0.76 ± 0.19, p=0.008) than controls. In SLE patients, VAT area correlated with CRP levels (R=0.30, p=0.018) but not with age (p=0.079), disease duration (0.912), SLEDAI disease activity score (p=0.068), SLICC damage index (p=0.054), cumulative glucocorticoid dose (p=0.141) or hydroxychloroquine use (p=0.851).

Conclusion:

This study provides original evidence that SLE is associated with altered adiposity distribution and increased visceral adipose tissue. The observed correlation with CRP levels, independent of disease activity, suggests the role of visceral fat as an additional risk factor for cardiovascular events in SLE patients. Longitudinal studies are necessary to confirm the long-term effect of VAT in cardiovascular events in SLE.

Disclosure: L. Seguro, None; **V. Caparbo**, None; **E. Bonfá**, None, 2; **R. M. R. Pereira**, None, 2.

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Abstract Number: 1824

Tripterygium Wilfordii for the Treatment of Systemic Lupus Systematosus: Meta-Analysis of Randomized Controlled Trials

Yixia Ye[1], Bo Chen[2], Robert A. Kalish[3] and Chenchen Wang[4], [1]Rheumatology, Tufts Medical Center, Boston, MA, [2]Orthopaedics and Traumatology, Shuguang Hospital affiliated to Shanghai University of T.C.M., Shanghai, China, [3]Medicine, Tufts Medical Center, Boston, MA, [4]Rheumatology, Tufts Medical Center, Bosotn, MA

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Background/Purpose: Tripterygium Wilfordii (TPW), a Chinese herbal medication, has been widely used in China for various chronic inflammatory and autoimmune diseases, including systemic lupus erythematosus (SLE). Although the immunologic mechanism is poorly understood, studies have shown that TPW inhibits T cell activation, cytokine gene transcription in T cells and T cell expression of interleukin-2. To better inform clinical practice, we systematically analyze randomized controlled trials (RCTs) on the use of TPW in the treatment of SLE.

Methods: We performed a comprehensive search of three Chinese databases, two English academic database and reference lists of published articles through April 2015. We included only RCTs, in which TPW was used for the treatment of adult patients with SLE. The effect of TPW on clinical signs, symptoms and laboratory tests of SLE was measured. The effectiveness rate was determined as the percentage of number of patients with complete and partial response divided by the total number of patients in the study. We also performed random-effect meta-analysis using the number of patients who improved with treatment in the experimental and control groups when appropriate.

Results: We identified 31 potentially relevant studies. Eight RCTs with a total of 431 subjects met eligibility criteria. **Table 1** summarizes the trials evaluating the effect of TPW on the improvement of clinical signs, symptoms and laboratory tests in patients with SLE. All studies were published in China between 1989 and 2014. Studied subjects received TPW (variable dose on different formulation) alone or with steroids (mainly prednisone 0.5-1 mg/kg/day) in experimental group (Leflunamide 10mg bid in one group), compared with prednisone alone in control group (MTX 10mg weekly in one group). Duration of treatments ranged from 0.5 to 6 months. Comparing with a variety of controls, six of the eight studies have shown a statistically significant improvement in clinical signs and symptoms, including rash, arthritis/arthralgia, photosensitivity, fever, pleuritis, cerebritis and hair loss. Improvements of sedimentary rate, C-reactive protein, dsDNA, Complete Blood Count, proteinuria, hematuria, anti-Smith Antibody, complements and renal function were also noted. Meta-analysis showed an increase of clinical effective rate of 33% in experimental patients compared with controls (Risk Ratio (RR)=1.20; 95%CI: 1.06-1.37; p=0.006; **Figure 1**), suggesting that TPW improves the clinical signs, symptoms, abnormal laboratories associated with SLE. No serious adverse events were reported.

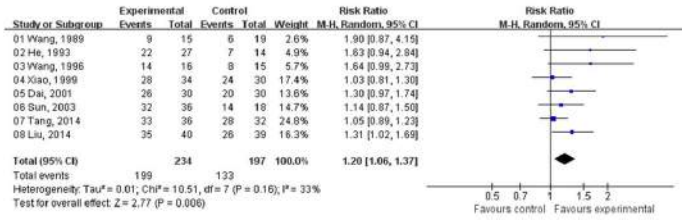
Conclusion: Evidence suggests that TPW may be a safe and effective treatment that provides a glimmer of hope in the treatment of SLE. However, standard criteria of improvement were not used, making it difficult to compare the results between different studies. Further rigorously designed and well-controlled RCTs of efficacy of TPW in SLE are warranted.

Table 1. 8 RCTs of *Tripterygium Wilfordii* for SLE treatment

Author Year	Type lupus	N (F:M)	age (mean)	Treatment	control	Duration (month)	outcome measures	P value results
1) Wang 1989	SLE/DLE	42 (18:5)	31.4	TPW 10g tid	prednisone 30-60mg daily	0.5 - 21	effecive: 60% vs 31.6% ineffective: 26.7% vs 63.2% worsen:: 13.3% vs 5.3%	p>0.10 86.7% vs 94.7%
2) He 1993	SLE	41 (39:2)	31.2	TPW 12-15g/day prednisone 1mg/kg/day	prednisone * 1mg/kg/day	18 - 24	effecive: 81.5% vs 50% ineffective: 18.5% vs 50%	p<0.05, 81.5% vs 50%
3) Wang 1996	SLE	31 (29:2)	37	TPW, 10g/day; Chinese herbs prednisone, 40-50mg/day	prednisone 40-50mg daily	1	effecive: 38% vs 27% partial: 50% vs 27% ineffective: 6% vs 33% worsen/death: 6% vs 13%	p<0.05, 87.5% vs 53.3%
4) Xiao 1999	SLE	64 (no data)	29.7	TPW 20mg tid prednisone 30-60mg daily	prednisone 30-60mg daily	No data	effecive: 35.3% vs 13.3% partial: 47% vs 66.7% ineffective: 8.8% vs 16.7% worsen/death: 8.8% vs 3.3%	p<0.05, 35.3% vs 13.3%
5) Dai 2001	SLE	60 (43:17)	21-65	TPW 2-4 pills tid	prednisone 10mg tid	3	effecive: 46.7% vs 36.7% partial: 40% vs 30% ineffective: 13.3% vs 33.3%	p<0.01, 87% vs 67%
6) Sun 2003	SLE	54 (47:7)	33.7	TPW 30-60mg tid	prednisone 20-40mg daily	1.5 - 2	effecive: 50% vs 33.3% partial: 38.9% vs 44.4% ineffective: 11.1% vs 22.2%	p<0.01, 94.4% vs 77.8%
7) Tang 2014	SLE	68 (30:38)	35	TPW1.5mg/kg tid Leflunomide 10mg bid	prednisone 1mg/kg/day taper to 12.5mg/day	1.5 - 2	effecive: 38.9% vs 43.8% partial: 52.8% vs 43.8% ineffective: 8.3% vs 12.5%	p>0.05, 91.67% vs 87.5%
8) Liu 2014	SLE	79 (71:8)	18-70	TPW 20mg tid prednisone 0.5mg/kg/day	prednisone 0.5mg/kg/day MTX 10mg weekly	6	effecive:52.5% vs 46.2% partial: 35% vs 20.5% ineffective: 12.5% vs 33.3%	p<0.01, 87.5% vs 66.7%

1.The diagnostic criteria: 1). Group 1-6: 1982 revised criteria for classification of SLE by ACR; 2). Group 8: 1997 update of 1982 revised criteria; 3). Group 7: 2011 revised criteria for classification of SLE by Chinese college of medicine.
2: outcome measures: 1). effective: clinical symptoms and laboratory tests significantly improved/normalized; 2). partial effective: clinical symptoms and laboratory tests partially improved; 3). ineffective: no changes in the clinical symptoms and laboratory tests;
4). worse/dead: clinical symptoms and laboratory tests worsen/ study subject died.
3. results: the effective rate (%) was determined as the percentage of number of study subjects with effective and partial effective outcome divided by the total number of study subjects, except group 4 which used the number of study subjects with effective outcome divided by total number of study subjects.
*cyclophosphamide2 was added in the control group for the patients who did not respond to steroids.

Figure 1. The effectiveness of *Tripterygium Wilfordii* for SLE



Disclosure: Y. Ye, National Center for Complementary and Integrative Health, 2; **B. Chen**, National Center for Complementary and Integrative Health, 2; **R. A. Kalish**, National Center for Complementary and Integrative Health, 2; **C. Wang**, National Center for Complementary and Integrative Health, 2.

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Abstract Number: 1825

Osteoprotegerin Is Associated with Lupus and with Coronary Artery Calcification

Indu Poornima[1], Kelly J. Shields[2], Susan Manzi[3], Rosalind Ramsey-Goldman[4], Carrie Richardson[5], Lewis Kuller[6], George Kondos[7], James Carr[5], Craig Langman[5], Heather Price[5], Daniel Edmundowicz[8] and Rachel Mackey[9], [1]Division of Cardiology, Allegheny Health Network, Pittsburgh, PA, [2]Rheumatology, Allegheny Singer Research Institute, Pittsburgh, PA, [3]Rheumatology, Allegheny Health Network, Pittsburgh, PA, [4]Northwestern University Feinberg School of Medicine, Chicago, IL, [5]Northwestern University, Evanston, IL, [6]Epidemiology, University of Pittsburgh, Pittsburgh, PA, [7]University of Illinois in Chicago, Chicago, IL, [8]Cardiology, Temple University School of Medicine, Philadelphia, PA, [9]Department of Epidemiology, University of Pittsburgh, Pittsburgh, PA

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Background/Purpose: In the general population, we and others have reported that higher osteoprotegerin (OPG), a protein involved in bone remodeling, is associated with higher levels of coronary artery calcification (CAC). Higher levels of OPG have been reported in SLE associated bone fractures and nephritis. We have previously reported higher CAC in women with systemic lupus erythematosus (SLE) vs. healthy controls (HC) in two SLE case-control studies, HEARTS and SOLVABLE but the association of OPG with CAC in SLE is unknown. Therefore we hypothesized that in HEARTS and SOLVABLE, higher serum OPG would be associated with the higher levels of CAC seen in SLE.

Methods: Levels of OPG were assayed by ELISA in frozen samples of plasma (HEARTS) and serum (SOLVABLE). CAC was measured by CT in both

studies and ordinal logistic regression models were used to estimate adjusted ORs for being in a higher CAC category (0, 1-10, 11-100 and >100) vs. the next lower category.

Results:

Combining HEARTS (n cases /controls=125/124, age and race-matched) and SOLVABLE (n cases/controls= 185/184, age and race-matched), mean age (for cases, controls) was 46, 48 years, % postmenopausal (45, 40%), % African-American (AA) (23, 22%), %current smoking (11, 10%) and %ever smoking (37, 44%). The distribution of CAC among the 620 women was CAC=0: n=397 (218 HC and 179 SLE), CAC=1-10: n=109 (52 HC, 57 SLE), CAC 11-100: n=64 (29 HC, 35 SLE) and CAC>=100: n= 43(9 HC, 34 SLE.) In both studies, OPG was higher for SLE vs. HC, AA vs. white, and post- vs. premenopause ($p<0.05$). Among the entire group, OPG was higher with higher CAC category, with OR (95%CI) = 1.35(1.14, 1.59) per SD OPG and 2.21(1.32, 3.71) for the 4th vs. 1stquartile of OPG (Q4 vs. Q1). Based on the racial differences noted in OPG levels, subgroup analyses were conducted by race and case-control status, showing a consistent positive association for white HC and SLE and AA HC. However, among AA SLE cases (n=67), there was no association of OPG with higher CAC (OR=1.0, p=0.9). Therefore all subsequent analyses excluded AA SLE cases in models adjusted for study, race, LDL-C and smoking. Higher OPG was significantly associated with higher CAC category for SLE cases, OR (95%CI) for Q4 vs. Q1= 2.80 (1.25-6.30) and for HC: 2.40 (1.03, 5.58), in separate models. Among the entire group (HC+SLE), the OR for Q4 vs Q1 OPG in predicting higher CAC was 2.78 (1.57, 4.94), and with adjustment for SLE, was 2.72 (1.53, 4.84). For SLE vs. HC, the OR for higher CAC was 2.20 (1.47, 3.29), and 2.14 (1.43, 3.22) when adjusted for OPG (quartiles). Results were similar in sensitivity analyses restricted to HEARTS only, or white women only, or white post-menopausal women only.

Conclusion:

In 2 SLE case-control studies, higher OPG was associated both with SLE and with higher CAC among cases and controls, except for AA SLE cases. The association of SLE with higher CAC was only slightly attenuated by concurrent levels of OPG. Longitudinal studies in larger samples are warranted to clarify the role of OPG in the increased CAC noted in SLE, and potential differences by race.

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Abstract Number: 1826

Small LDL-P Increases with Increased Disease Activity in SLE

Laura Durcan[1], Deborah Winegar[2], Margery Connelly[2], James Otvos[2], Laurence S Magder[3] and Michelle Petri[1], [1]Rheumatology, Johns Hopkins University Hospital, Baltimore, MD, [2]LabCorp, Raleigh, NC, [3]Epidemiology and Preventive Medicine, University of MD, Baltimore, MD

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Background/Purpose:

Systemic lupus erythematosus (SLE) associates with accelerated atherosclerotic cardiovascular (CV) disease which is not fully explained by traditional CV risk factors. Disease activity, prednisone treatment and immunologic abnormalities are thought to contribute. Dyslipidemia is common in SLE patients, who have mild elevations in triglycerides (TG) and sometimes low HDL cholesterol levels. Recent evidence suggests that low density lipoprotein particle number (LDL-P) is a better marker of cardiovascular risk than LDL cholesterol levels. Lipoprotein subclass analyses have shown that SLE patients have larger VLDL particles and lower levels of large HDL particles compared to control subjects, but little is known about how these markers change with disease activity. We evaluated SLE patients during high disease activity and compared this to no or low disease activity to determine how lipoproteins change with active SLE.

Methods:

Patients were identified as part of a longitudinal lupus cohort. At each visit, plasma samples were collected. Global disease activity was measured using the SLEDAI. Patients were included who had at least one visit with SLEDAI of 4+ (high disease activity) and one visit with SLEDAI<3 (low disease activity). Plasma was analyzed for lipoprotein particle concentrations using nuclear magnetic resonance spectroscopy (NMR). The NMR spectrum also contains a signal termed GlycA derived from the carbohydrate chains of circulating acute phase glycoproteins that is a marker of systemic inflammation. Lipoprotein particle and GlycA levels were compared between high activity and no or low disease activity visits using t-tests. Further analysis compared consecutive visits to see whether changes in lipoprotein parameters were associated with a flare.

Results:

Thirty-three patients met inclusion criteria (97% female, age range 19-76, 48% Caucasian and 48% African American). The mean number of visits per person with high Vs. low disease activity were 2.1 and 2.4 respectively. The total LDL particle number (LDL-P) and small LDL-P levels were higher with disease activity as was VLDL size (Table 1). GlycA levels were unchanged with active disease but were higher than those described for healthy

populations.

Conclusion:

Although the lipoprotein profiles of SLE patients have been previously described, alterations in these profiles with disease activity have not been investigated. Here we demonstrate, for the first time in adult SLE, adverse changes in novel lipid parameters with disease activity. Thus, we can now demonstrate one potential mechanism by which SLE disease activity influences atherosclerosis. GlycA was unchanged with disease activity, but higher than reported controls, which may make it useful in stratification of CV risk in SLE.

Table 1. Mean Person-specific differences in marker level between visits with and without disease activity.

Marker	Mean (SD) during visits with SLEDAI 4+	Mean (SD) during visits with SLEDAI <=3	Mean (SD) Difference	P-value
Total VLDL & Chylomicrons	50.5 (28.0)	53.1 (21.2)	-2.6 (30.1)	0.63
Large VLDL particles	3.3 (2.2)	3.0 (1.9)	0.3 (1.5)	0.30
Medium VLDL particles	13.3 (8.7)	12.3 (8.6)	1.0 (7.3)	0.44
Small VLDL particles	33.9 (23.0)	37.8 (18.9)	-3.8 (26.5)	0.41
Total LDL particles	1047.8 (317.7)	976.6 (309.8)	71.2 (145.9)	0.0085
IDL particles	223.9 (81.4)	239.4 (103.4)	-15.4 (89.1)	0.33
Large LDL particles	369.2 (276.9)	365.7 (221.1)	3.4 (175.7)	0.91
Small LDL particle	454.7 (266.4)	371.5 (229.5)	83.2 (156.5)	0.0045
Total HDL particles	31.2 (9.2)	31.7 (7.2)	-0.5 (5.8)	0.60
Large HDL particles	9.0 (4.3)	9.7 (4.5)	-0.7 (2.7)	0.15
Medium HDL particles	10.1 (5.0)	11.2 (4.1)	-1.0 (5.1)	0.26
Small HDL particles	12.1 (6.2)	10.9 (5.6)	1.2 (5.6)	0.23
VLDL size	48.3 (6.1)	46.2 (6.4)	2.1 (6.4)	0.075
LDL size	21.1 (0.8)	21.2 (0.6)	-0.1 (0.7)	0.42
HDL size	9.8 (0.6)	9.8 (0.6)	-0.02 (0.3)	0.71
Triglycerides	109.5 (35.4)	108.3 (32.1)	1.2 (27.2)	0.79
HDL-C	56.5 (20.4)	59.0 (18.4)	-2.5 (10.8)	0.20
Insulin resistance score	35.3 (19.9)	31.7 (19.5)	3.6 (13.6)	0.14
GlycA	486.2 (81.6)	469.7 (82.4)	16.5 (82.4)	0.26

Disclosure: L. Durcan, None; **D. Winegar**, LabCorp/Liposcience, 3; **M. Connelly**, LabCorp/LipoScience, 3; **J. Otvos**, None; **L. S. Magder**, None; **M. Petri**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/small-ldl-p-increases-with-increased-disease-activity-in-sle

Abstract Number: 1827

Plasma Myeloperoxidase Levels Are Inversely Associated with Carotid Plaque in SLE

Maureen A. McMahon[1,2], Jennifer M. Grossman[3,4,5], Lori Sahakian[6,7], Elaine Lourenco[8], John FitzGerald[9,10], Christina Charles-Schoeman[3], Alan Gorn[3,10], Michael Weisman[11], Daniel J Wallace[12,13], Bevra H. Hahn[3,14] and Brian Skaggs[3], [1]Div of Rheumatology, UCLA David Geffen School of Medicine, Division of Rheumatology, Los Angeles, CA, [2]Division of Rheumatology, UCLA David Geffen School of Medicine, Los Angeles, CA, [3]Medicine, UCLA David Geffen School of Medicine, Division of Rheumatology, Los Angeles, CA, [4]Div of Rheumatology, UCLA David Geffen School of

Medicine, Los Angeles, CA, [5]Rheumatology, UCLA, Los Angeles, CA, [6]Division of Rheumatology, Department of Medicine, UCLA David Geffen School of Medicine, Division of Rheumatology, Los Angeles, CA, [7]Division of Rheumatology, Department of Medicine,, UCLA David Geffen School of Medicine, Los Angeles, CA, [8]UCLA David Geffen School of Medicine, Division of Rheumatology, Los Angeles, CA, [9]Rheumatology, UCLA David Geffen School of Medicine, Division of Rheumatology, Los Angeles, CA, [10]Rheumatology, UCLA David Geffen School of Medicine, Los Angeles, CA, [11]Rheumatology, Cedars-Sinai Medical Center, West Hollywood, CA, [12]Division of Rheumatology, Cedars-Sinai Medical Center/David Geffen School of Medicine at UCLA, Los Angeles, CA, [13]Cedars-Sinai Medical Center, West Hollywood, CA, [14]Rheumatology, Professor Emeritus, Department of Medicine/Rheumatology, David Geffen School of Medicine UCLA, Los Angeles, CA
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Background/Purpose:

: Women with SLE have increased risk of atherosclerosis (ATH) that is not adequately explained by traditional risk factors. We previously discovered that a high risk score on a panel of traditional and novel biomarkers, the PREDICTS score, confers 28-fold increased odds for the presence of any current, progressive, or acquired carotid plaque, both in patients with SLE and in control subjects, and is significantly associated with higher rates of IMT progression. The biomarkers included in the panel are sTWEAK (≥373 pg/mL), pro-inflammatory HDL (piHDL), age≥48, homocysteine ≥ 12 mmol/L, leptin ≥34 ng/dL, and DMII. It is unknown, however, whether other biomarkers of oxidative stress predict future progression of ATH in SLE.

Myeloperoxidase (MPO) is an enzyme and heme protein that catalyzes the formation of several reactive oxygen species, and has been linked to inflammation and ATH in the general population. Furthermore, MPO is present in NETs, and has been implicated in the generation of piHDL. To determine whether plasma MPO levels might predict future development of subclinical ATH and whether piHDL might mediate this effect, we measured baseline plasma MPO levels and the progression piHDL function and of plaque using carotid ultrasound in a cohort of SLE patients.

Methods:

Female SLE subjects not taking statins at baseline were studied. B-mode and Doppler scanning of carotid arteries was performed at baseline and at 24-36 months. Plasma MPO levels were measured in the baseline blood samples using ELISA (R&D Biosystems).

Results:

Repeat carotid ultrasounds and MPO measurements were completed on 202 women with SLE. The mean age of the SLE group was 43.7 ± 12.5 years. Plaque progression (defined as new or increased plaque) was seen in 42 subjects (21%). Mean baseline plasma MPO levels were significantly lower in SLE patients with plaque progression compared to those without: 17.8 ± 15.2 pg/mL in patients with plaque progression vs. 38.2 ± 60.9 pg/mL in SLE without ($p<0.001$) However, there was no significant difference in baseline MPO levels among subjects with plaque presence at baseline. Baseline MPO levels were inversely correlated with pro-inflammatory HDL function at follow-up ($r=-0.33$, $p<0.001$), but no correlation between MPO levels and presence of pro-inflammatory HDL was observed at baseline. Using logistic regression to control for traditional cardiac risk factors and the PREDICTS risk profile, the variables still significantly associated with plaque progression in SLE included high PREDICTS (OR 27.0 $p<0.001$), MPO levels in the lowest half (OR 4.2, $p=0.005$), and non-Caucasian ethnicity (OR 4.5, $p=0.003$).

Conclusion:

Plasma MPO levels are significantly and independently inversely associated with plaque progression on carotid ultrasound in patients with SLE. Lower baseline MPO levels are also significantly associated with future formation of inflammatory piHDL, suggesting that this could be one mechanism to explain the association.

Disclosure: M. A. McMahon, None; **J. M. Grossman**, NIH, 2; **L. Sahakian**, None; **E. Lourenco**, None; **J. FitzGerald**, None; **C. Charles-Schoeman**, Pfizer Inc, 2,Pfizer Inc, 5; **A. Gorn**, None; **M. Weisman**, None; **D. J. Wallace**, None; **B. H. Hahn**, Merck, Exxagen, Biogen Idec, Bristol Myers Squibb, 5; **B. Skaggs**, None.

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Abstract Number: 1828

Target Modulation of a Type I Interferon Gene Signature and Pharmacokinetics of Anifrolumab in a Phase IIb Study of Patients with Moderate to Severe Systemic Lupus Erythematosus

Philip Brohawn[1], Lingning Santiago[2], Chris Morehouse[1], Brandon Higgs[1], Gabor Illei[1] and Koustubh Ranade[1], [1]MedImmune, Gaithersburg, MD, [2]MedImmune, Mountain View, CA
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Background/Purpose: Anifrolumab is a fully human IgG1 monoclonal antibody directed against subunit 1 of the type I interferon receptor (IFNAR1). Anifrolumab blocks the binding of type IIFN and inhibits the biologic activity of all type I IFNs. The PD and PK effects of anifrolumab were assessed through analysis of the blood of adult patients with moderate to severe SLE enrolled in a Phase IIb study (MI-CP1013).

Methods: Adult patients who satisfied ACR classification criteria for SLE were enrolled in a Phase IIb randomized controlled trial and received anifrolumab 300 or 1,000 mg intravenously every 4 weeks, or placebo, in addition to standard of care. Blood specimens were collected for PK and PD assessments at selected time points from pre-dosage to 422 days after initial administration. Transcript profiling was conducted through real-time quantitative reverse transcription–polymerase chain reaction (qRT–PCR) on a 21-gene type I IFN-inducible gene signature (IFNGS). Neutralization scores were calculated throughout the dosing schedule for each available time point (Days 29 to 365), based on patients' Day-1 baseline expression IFNGS values. Percentage neutralization scores for each dosage arm were summarized (median) for all available time points. Serum anifrolumab concentrations were measured using a validated electrochemiluminescence assay.

Results: A total of 215 of 305 patients (70.5%) were positive at baseline for the IFNGS. Expression of IFNGS in whole blood decreased following anifrolumab administration for all dosages in patients positive for the IFNGS at baseline. In the 300-mg every-4-week dosage arm, a median signature neutralization range (85.2–89.7%) was observed between Day 29 and 365. Maximum median neutralization (89.7%) was observed at Day 169. In the 1,000-mg every-4- week dosage arm, a median signature neutralization range (86.8–91.9%) was observed between Day 29 and 365. Maximum median neutralization (91.9%) was observed at Day 365, although comparable median neutralization was observed earlier, at Day 141 (91.7%). Negligible IFNGS modulation was noted for the placebo arm at each time point assessed. For all patients who received anifrolumab, near maximum median signature neutralization was observed at the first time point assessed (Day 29). As a result of target-mediated clearance, PK exposure of anifrolumab was more than dose-proportional between the 300 and 1,000 mg doses. On Day 169, mean±SD C_{trough}increased more than dose proportionally from 18.8±10.9 to 115±62.9 µg/mL, when the dosage was increased from 300 mg to 1,000 mg every 4 weeks. There were no obvious differences in PK in the study between patients who were IFNGS-positive vs. IFNGS-negative.

Conclusion: Anifrolumab demonstrated expected mechanism of action in SLE. Target engagement of anifrolumab was confirmed with near maximum and sustained inhibition of the IFNGS. These data support the selection of 300 mg every 4 weeks as the dosage for study in Phase III pivotal trials.

Disclosure: P. Brohawn, AstraZeneca, 1; **L. Santiago**, MedImmune, 3,AstraZeneca, Pfizer, Theravance, 1; **C. Morehouse**, MedImmune, 1,MedImmune, 3; **B. Higgs**, AstraZeneca, 1,MedImmune, 3; **G. Illei**, AstraZeneca, 1,MedImmune, 3; **K. Ranade**, AstraZeneca, 1,MedImmune/AstraZeneca, 3.

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Abstract Number: 1829

Heart Rate Variability Is Associated with SLE Flare and with TNF- and IFN-Mediated Signaling

Aikaterini Thanou[1], Stavros Stavrakis[2], John Dyer[2], Stan Kamp[3], Melissa E. Munroe[1], David Albert[4], Judith A. James[5] and Joan T. Merrill[3], [1]Arthritis and Clinical Immunology, Oklahoma Medical Research Foundation, Oklahoma City, OK, [2]Heart Rhythm Institute, University of Oklahoma Health Sciences Center, Oklahoma City, OK, [3]Clinical Pharmacology, Oklahoma Medical Research Foundation, Oklahoma City, OK, [4]AliveCor, Inc., San Francisco, CA, [5]Arthritis and Clinical Immunology, University of Oklahoma Health Sciences Center and Oklahoma Medical Research Foundation, Oklahoma City, OK
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Background/Purpose: Decreased heart rate variability (HRV), associated with adverse outcomes in cardiovascular diseases, is frequently seen in patients with SLE. The LF/HF ratio, a HRV measure, reflects sympathovagal balance. We examined associations of HRV with SLE activity and cytokine expression.

Methods: 53 SLE patients were evaluated at 2 visits (total 106 visits) with BILAG, SLEDAI, PGA and SFI (SELENA Flare Index). Caffeine, tobacco and medications were recorded. HRV (RMSSD, pNN50, HF, LF/HF ratio) was measured using a 5-minute ECG. Plasma cytokines were assessed by ELISA or a multiplex immunoassay.

Results: Baseline HRV was inversely related to disease activity and flare (table). Changes in HRV between visits were inversely related to changes in SLEDAI and PGA. Hydroxychloroquine dose was associated with increased HRV. Age, caffeine, tobacco and other medications had no impact. Plasma TNFRII and MIG inversely correlated with baseline HRV, and similar trends were observed for BLyS, IL-1α, IFNα and IP-10. Using multivariate linear regression model with backward elimination, TNFRII was an independent predictor of baseline HRV after adjusting for hydroxychloroquine dose and plasma BLyS, IL-1α and IFNα. In a similar model, MIG impact remained significant adjusting for the same variables. Furthermore, changes in the LF/HF ratio between visits were associated with changes in TNFRII (p=0.048) and MIG (p=0.029).

Conclusion: Impaired HRV, particularly the LF/HF ratio, is associated with lupus disease activity, acute flare state, and several cytokines related to TNF

and IFN pathways. The strongest association was with TNFRII and MIG, confirming and expanding previous immune connections to vagal signaling.

p values		Univariate linear regression Dependent variables at baseline				Multivariate linear regression Dependent variables at baseline			
		RMSSD	pNN50	HF	LF/HF	RMSSD	pNN50	HF	LF/HF
	BILAG	0.259	**0.019**	**0.02**	**0.024**				
	SLEDAI	0.683	0.312	0.488	**0.073**				
	PGA	0.651	**0.014**	0.154	**0.062**				
	Flare (SFI)	0.456	0.329	**0.047**	**0.008**	**ns**	**ns**	**ns**	**ns**
Independent variables at Baseline	**BLyS**	0.778	0.29	0.115	**0.071**	**ns**	**ns**	**ns**	**ns**
	IL-17A	0.689	0.132	0.174	0.988				
	TNFα	0.361	0.533	0.354	0.903				
	TNFRII	**<0.001**	**0.01**	**0.039**	**0.024**	**<0.001**	**0.01**	**0.039**	**0.024**
	IL-1α	0.089	**0.099**	0.254	0.485	**ns**	**ns**	**ns**	**ns**
	IFNα	0.420	**0.076**	0.272	0.124	**ns**	**ns**	**ns**	**ns**
	MIG	**0.007**	**0.015**	**0.018**	**0.026**	**0.007**	**0.015**	**0.018**	**0.026**
	IP-10	0.202	**0.088**	0.122	0.189				

Disclosure: **A. Thanou**, None; **S. Stavrakis**, None; **J. Dyer**, None; **S. Kamp**, None; **M. E. Munroe**, None; **D. Albert**, AliveCor, Inc.., 3; **J. A. James**, None; **J. T. Merrill**, None.

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Abstract Number: 1830

Periodontal Disease in Lupus Erythematosus and Cardiovascular Risk Factors

Maria Cecilia Goizueta[1], Luciana Gonzalez Lucero[1], Maria Constanza Bertolaccini[2], Ramiro Maldonado[1], Raul Sueldo[1], Raul Nicolas Martinez[1], María Silvia Yacuzzi[1], Maximiliano Machado Escobar[1], Mirta Santana[1], Jose Rodriguez Skegro[1], Eugenia fatima del Valle Reynoso[1], Patricia Morales[1], Liliana Galindo[1], Veronica Bellomio[1] and Eleonora Lucero[1], [1]Hospital Angel Cruz Padilla, Tucumán, Argentina, [2]Rheumatology, Hospital Angel Cruz Padilla, Tucumán, Argentina

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Background/Purpose: The aim of this study was to determine the prevalence of periodontal disease (POD) in patients with Systemic Lupus Erythematosus (SLE) and its relationship with cardiovascular risk factors.

Methods: Cross-sectional study. POD was determined in patients diagnosed with SLE (ACR criteria 1982/1997) between the months of May to December 2014, through dental evaluation using the Loe and Sillness index with measurement of bags and plaque on all four sides of each tooth in both jaws. We evaluate: Demographic data: age at diagnosis and time of evolution, use and dose glucocorticoids in the last six months, SELENA-SLEDAI, laboratory variables: erythrocyte sedimentation rate (ESR mm), ultrasensitive PCR (hsCRP mg/l), cholesterol (mg/dl), triglycerides (mg/dl) HDL (mg/dL) and LDL (mg/dl). Cardiovascular variables: presence of metabolic syndrome (ATP III criteria), Body Mass Index (BMI), CVD risk as hsCRP value (Low <1 intermediate 1-3 and high> 3 mg/lt). Presence of Diabetes Mellitus (WHO criteria DBT- 1999), Arterial Hypertension (JNC VIII recommendations), hypercholesterolemia (cholesterol ≥ 200mg / dl) and smoking. Doppler ultrasound of neck vessels was performed using ultrasound with measurement of Intimate Media combined thickness (IMT) of common carotid artery, carotid bulb, and internal carotid and number of plaques. Dental variables: presence of POD according to severity and extent. Statistical analysis: descriptive statistics; for categorical variables: Chi 2 test, Fisher exact test; T test for continuous variables.

Results: Of 123 patients evaluated, 33 were excluded due to dentures in both jaws, 2 for pregnancy, 3 for drug use affecting the dental evaluation and 4 by the presence of other diseases. Finally, 81 patients were included, 91.4% (n = 74) women, mean age of 34.2 ± 11.9 years and mean age at diagnosis of SLE of 25.2 ± 8.1 years, duration of disease 104.8 ± 94.9 months and median SELENA SLEDAI of 2 (0-22). They were treated with GC in the last six months 64.2% (n = 52), 22.2% (n = 18) with doses > 0.5 mg /kg/day. The prevalence of periodontal disease was 48.1% (95%CI 37.3 - 59); 17.3% (n = 14) with mild to moderate type of both arches, 11.1% (n = 9) of an arcade and 12.3% (n = 10) with chronic marginal gingivitis. Of 81 patients, 21% (n = 17) met criteria for diagnosis of MS, 38.3% (n = 31) overweight and 14.8% (n = 12) obese; 29.6% (n = 24) had hypercholesterolemia, 2 were diabetics and three smokers. The mean hsCRP was 8.8 ± 12.9. CVD risk messured by hsCRP was higher at 46.9% (n = 38), intermediate in 24.7% (n = 20) and low in 28.4% (n = 23). Doppler ultrasound of neck vessels was performed in 58 patients with a mean of 0.5 ± 0.7mm MICS. No patient had atherosclerotic plaques. Statistically significant association between the presence of periodontal disease and use of corticosteroids in the last 6 months was found (p = 0.05) but none between POD and MS, DBT, hypercholesterolemia, hsCRP, BMI or SLEDAI (p = NS) in this population.

Conclusion: The prevalence of periodontal disease was 48.8%. There was no association between POD and cardiovascular risk.

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Abstract Number: 1831

Initial Risk Factor Profile and Long-Term Cardiovascular Outcome in Women with Systemic Lupus Erythematosus

Konstantinos Tselios[1], Dafna Gladman[2], Jiandong Su[2], Olga Ace[3], Arthy Sabapathy[3], Anne MacKinnon[3] and Murray Urowitz[4,5], [1]Medicine, University of Toronto, Toronto Western Hospital, Toronto, ON, Canada, [2]Rheumatology, University of Toronto, Toronto Western Hospital, Toronto, ON, Canada, [3]University of Toronto, Toronto Western Hospital, Toronto, ON, Canada, [4]University of Toronto, Toronto, ON, Canada, [5]Rheumatology, U of Toronto, Toronto Western Hospital, Toronto, ON, Canada

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Background/Purpose: We previously reported the influence of traditional and disease-related risk factors on the development of cardiovascular disease (CVD) in patients with systemic lupus erythematosus (SLE) followed for 7 years. The aim of this study was to further investigate their impact on clinical CVD in SLE patients and controls after 15 years of follow-up.

Methods: Two hundred and fifty women with SLE and no prior history of CVD (age 44.5±12 years, disease duration 13.7±9.7 years) and 250 age-matched healthy women (age 44.1±14 years) were recruited between 1998 and 2000. Recorded risk factors at baseline included arterial hypertension, diabetes mellitus, dyslipidemia (total cholesterol, triglycerides, HDL, LDL, VLDL), smoking, family history of premature CVD and body mass index. Patients and controls were prospectively followed for 14±4.1 and 15.9±1.9 years respectively for the development of cardiovascular events (CVEs). CVEs included angina pectoris, myocardial infarction (MI, fatal and non-fatal) transient ischemic attack (TIA), stroke (fatal and non-fatal), and were recorded at clinic visit for patients and by interview and chart review for controls. Statistical software SAS (version 9.3) was used for analysis; $p<0.05$ was considered significant.

Results: Initial risk factor profile revealed a higher prevalence of arterial hypertension (83/250, 33.2% vs 32/250, 12.8%, $p<0.001$) and diabetes mellitus (12/250, 4.8% vs 2/250, 0.8%, $p=0.007$) in patients' group. The frequency of other variables did not differ significantly. Follow-up data, after 15 years, were available for 211 patients and 137 controls. There were 32 deaths in SLE patients and 7 in controls. CVEs occurred in 32/179 patients (17.9%) and 8/130 controls (6.2%), Table 1. Angina and MI were more common in SLE than controls (17/211, 12.8% vs. 9/137, 6.5%, $p=0.005$). There were no statistically significant differences for TIA and stroke.

	Angina	MI (non-fatal)	MI (fatal)	TIA	Stroke (non-fatal)	Stroke (fatal)
SLE (n=211) N (%)	17 (8.1%)	10 (4.7%)	6 (2.8%)	4 (1.9%)	5 (2.4%)	2 (0.9%)
Controls (n=137)	4 (2.9%)	5 (3.6%)	0 (0%)	2 (1.5%)	1 (0.7%)	0 (0%)

Multivariate Cox-regression analysis demonstrated SLE [HR=2.89, 95% CI 1.22-6.81], family history [HR=2.25, 95% CI 1.13-4.45], triglycerides [HR=1.45, 95 CI 1.03-2.02], 10-year Framingham score [HR=1.12, 95% CI 1.05-1.19] and serum creatinine [HR=1.01 95% CI (1.0-1.02)] to be important predictors for CVEs. Patients with SLE with CVEs compared to those without were older (47.6±9.6 vs. 41.5±10.6 years, $p=0.003$), had higher serum creatinine (94.7±59.4 vs. 75.4±23.2 µmol/L, $p=0.003$) and, more frequently, hypertension (43.8% vs. 24.5%, $p=0.028$), hypercholesterolemia (46.9% vs. 27.9%, $p=0.036$) and family history of CVD (56.3% vs. 34%, $p=0.019$).

Conclusion: SLE patients have a 3-fold increased risk for clinical CVD as compared to healthy controls in the long term. Coronary heart disease was significantly more frequent than cerebrovascular disease. SLE itself, as well as traditional risk factors, are important predictors for CVEs.

Disclosure: K. Tselios, None; **D. Gladman**, None; **J. Su**, None; **O. Ace**, None; **A. Sabapathy**, None; **A. MacKinnon**, None; **M. Urowitz**, None.

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Abstract Number: 1832

Recurrence-Rate of Thrombotic Events in SLE Patients Negative for Antiphospholipid Antibodies

Mohammed Attar[1], Jiandong Su[2], Stacey E. Morrison[3], Samar Alharbi[4], Khawla Al-Ghanim[5], Dafna Gladman[2], Murray Urowitz[6,7] and Jorge Sánchez-Guerrero[8], [1]Rheumatology, Toronto Western Hospital, Toronto, ON, Canada, [2]Rheumatology, University of Toronto, Toronto Western Hospital, Toronto, ON, Canada, [3]Div Rheumatology Rm MP-10-304, Toronto Western Hospital, Toronto, ON, Canada, [4]Rheumatology, University Health Network, Toronto, ON, Canada, [5]Rheumatology, TWH, Toronto, ON, Canada, [6]University of Toronto, Toronto, ON, Canada, [7]Rheumatology, U of Toronto, Toronto Western Hospital, Toronto, ON, Canada, [8]Rheumatology, Mount Sinai Hospital and University Health Network, Toronto Canada, Toronto, ON, Canada
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Background/Purpose: Thrombotic events (TE) are common in patients with SLE. Antiphospholipid antibodies (aPL) are a risk factor for incident and recurrent TE; therefore these patients receive long term anticoagulation for secondary prophylaxis. SLE patients with negative aPL antibodies are also at increased risk of TE; however, the recurrence rate, type of TE, factors associated, and the optimal duration of anticoagulation is unknown. In the general population, the recurrence-rate of thrombosis at 5 years is 12.4%. The objective of this study is to determine the recurrence-rate of TE, type, and risk-factors associated in SLE patients negative for aPL antibodies according to the Sapporo Criteria.

Methods: The study was conducted within a prospective cohort. We identified patients with negative aPL (aCL and LA), who developed incident arterial (ATE) or venous thrombosis (VTE) during follow-up in the cohort, after 1990 when the aPL antibodies tests became widely available, and enrolled into the cohort within 5 years of SLE diagnosis. The demographic (age, ethnicity), clinical (disease duration, ACR criteria, SLE manifestations), autoantibodies (anti-dsDNA, anti-ENA, C_3, C_4), disease activity (SLEDAI-2K), disease damage (SDI) and treatment (prednisone, immunosuppressants, antimalarials, low-dose aspirin), type of TE (ATE, VTE), and traditional TE risk-factors (smoking, cholesterol levels, hypertension) were assessed. Main outcomes were the recurrence rate of TE, type, and variables associated.

Results: Forty SLE patients with negative aPL antibodies and incident TE were identified; they developed 14 ATE, and 29 VTE (3 patients had both ATE and VTE). Nine (22.5%) patients developed a second TE during 207.31 patient-years (py) of follow-up; recurrence-rate 4.3 TE per 100 py. The first event in seven patients was VTE, one ATE, and one both VTE/ATE. Eight recurrent events were VTE, and only one ATE; the concordance of vascular bed involved between both TE was total. Most (78%) recurrent events developed within 15 months after the first TE. Although non-statistically significant, patients with recurrent TE were female (100% vs. 81%), had younger age (25.8 ± 9.9 vs. 34.2 ± 14.9 yrs.), were predominantly of African ancestry (50% vs 16%), and had shorter SLE duration at first TE (1.7 ± 1.5 vs. 4.8 ± 4.9 years) in comparison to patients with no recurrence. No differences in other clinical manifestations, activity, damage or treatment were observed. The prevalence of traditional thrombotic risk-factors was also similar between groups.

Conclusion: The recurrence-rate of TE is elevated among SLE patients with negative aPL antibodies, particularly VTE. Most recurrent TE happened within 15 months from the first TE and were seen in young female patients, with short disease duration and predominantly in those with African ancestry. If these results are confirmed in larger studies, they should be useful to better stratify recurrence risk and define the length of anticoagulation in this SLE subpopulation.

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Abstract Number: 1833

Musculoskeletal Complications of Systemic Lupus Erythematosus: Risk Factors for and Prevalence of Avascular Necrosis and Osteoporosis

Maeve Gamble[1] and Janet E. Pope[2], [1]Medicine, University of Western Ontario, London, ON, Canada, [2]University of Western Ontario, London, ON, Canada
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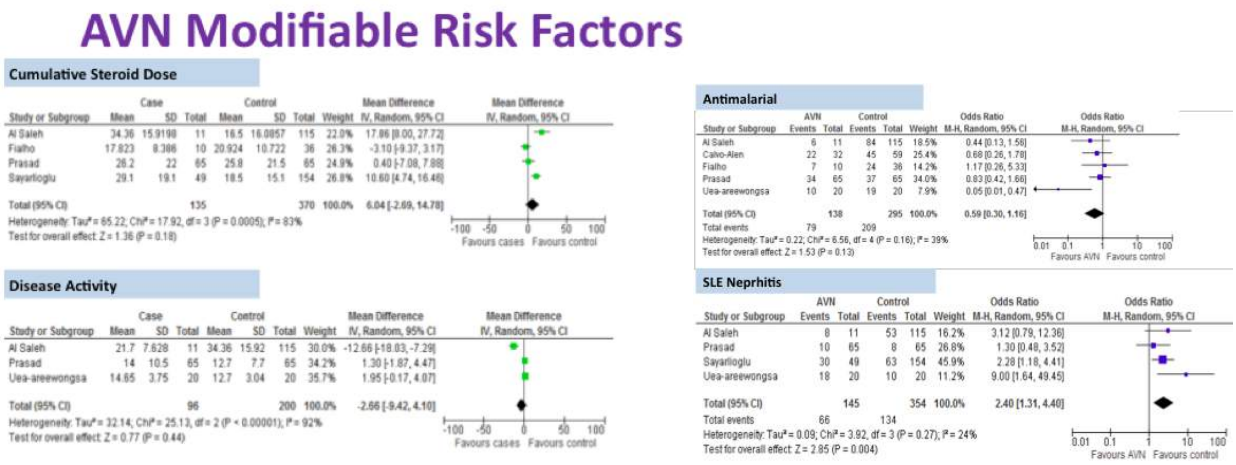
Background/Purpose: Osteoporosis (OP) and avascular necrosis (AVN) are well-recognized musculoskeletal complications of systemic lupus erythematosus (SLE) and cause morbidity. Steroid therapy and the underlying disease process are major contributors to these complications and the degree to which each influences the development of OP and AVN is unclear. Precise rates of AVN and OP are are far higher than the general population. The aim of this study was to identify the prevalence of OP and AVN and modifiable risk factors associated with their development in SLE.

Methods:

A comprehensive review of published articles and unpublished abstracts was conducted using the PubMed, EMBASE, and Cochrane databases. All articles relating to risk factors for AVN and OP in SLE were included. Exclusion criteria were: pediatric OP, publication with 44 or fewer SLE patients, and studies using the same patient population.

Results: Ten articles pertaining to AVN and 13 with OP were included. The prevalence of OP was 12% (range 5%-23%) and osteopenia 38% (9%-50%). Age, cumulative steroid dose, SLE damage, and low BMI were frequently reported risk factors. Other risks in some studies included: white or non-African Caribbean ethnicity, limited physical activity, premature ovarian failure, decreased vitamin D, decreased osteocalcin, low C4, positive anti-Smith antibody, and negative anti-Ro antibody. The cumulative dose of glucocorticosteroids was not significantly related to AVN. There was no difference in disease activity in patients who did and did not develop AVN (p=0.7). SLE renal involvement had more AVN (OR 2.4, 95% CI 1.5,3.8). Other risks in some studies were: cytotoxic drugs (cyclophosphamide and mycophenolate mofetil), serositis, Raynaud's, vasculitis, and seropositivty including anti-Smith and antiphospholip Abs. Antimalarial drugs were not significantly protective for AVN. Figures show some associations with AVN in SLE.

Conclusion: Several risk factors for OP and AVN were identified. Steroids were associated with OP. Renal involvement and vasculitis are associated with AVN.



Disclosure: M. Gamble, None; **J. E. Pope**, None.

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Abstract Number: 1834

Total Hip Arthroplasty Outcomes: A 17 Year Experience in a Single-Center: Is Systemic Lupus Erythematosus a Real Risk Factor for Adverse Outcomes?

Marco González-Contreras[1], Javier Merayo-Chalico[1], Rigoberto Ortíz-Hernández[2], Diana Gómez-Martín[2] and Jorge Alcocer-Varela[2], [1]Immunology and Rheumatology, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico, [2]Department of Immunology and Rheumatology, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico

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SESSION INFORMATION

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Session Type: ACR Poster Session B

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Background/Purpose: In patients with systemic lupus erythematosus (SLE), persistent joint activity and treatment with glucocorticoids are associated with musculoskeletal complications, including hip osteonecrosis. About 30% of these patients develop disability and become candidates for surgical treatment. The frequency of total hip arthroplasty (THA) in these patients has increased progressively. The aim of this study was to evaluate postoperative outcomes and potential risk factors for complications after THA in SLE patients in comparison to other inflammatory and non-inflammatory diseases.

Methods: We performed a retrospective cohort study at a tertiary care center in Mexico City between 1995 and 2013. All patients with SLE (ACR criteria ≥4), who underwent THA were included (n=58). They were compared with a group of patients with rheumatoid arthritis (RA) and other group with

osteoarthritis (OA), matched by gender and date of surgery. All surgeries were performed by the same surgical team. The main outcome was frequency of any postoperative complication during follow-up. The assessed complications were: transfusion requirement, hematoma, thrombosis, infections, aseptic loosening and prosthesis dislocation.

Results: We included 174 patients that underwent THA during the study period. The surgical indication was avascular necrosis in most patients with SLE and RA (98%). Univariate analysis revealed that patients with SLE were younger (p<0.001), and had a longer hospitalization (p=0.001), as well as more transfusional requirements (p=0.004). Other variables are shown in Table 1. Global complications in THA in patients with SLE were more prevalent than in the other groups (36% vs 9%, p<0.001). Most of these events occurred during the postoperative hospitalization. After multivariate analysis, risk factors for THA complications were: SLE (HR 2.8, 95%CI 1.2-6.8; p=0.018) and low postoperative hemoglobin (HR 0.77, 95%CI 0.73-0.83; p<0.001). There was a trend towards a higher risk of complications in patients with history of glucocorticoid treatment (p=0.055). Long-term complications after THA were not different among groups.

Conclusion: To our knowledge, this is the largest single-center study regarding the clinical outcomes after THA in SLE patients. Our data suggest that SLE is an independent risk factor for adverse postoperative outcomes, mainly immediate complications. Particular emphasis should be made on attaining optimal postoperative hemoglobin levels after THA in SLE patients. Our data suggest that even though SLE is associated with increased risk of immediate complications, the long term outcome is good enough to offer surgical treatment, such as THA, that will eventually improve quality of life.

Table 1 Baseline demographic, clinical and laboratory characteristics in patients with total hip arthroplasty

Variables (mean±SEM)	*Total hip arthroplasty in SLE (n=58)*	*Total hip arthroplasty in RA/OA (n=116)*
Age, [years]	**34.4 ± 1.05**	55.1 ± 1.47
SLEDAI, [points]	1.31 ± 0.32	N/A
Preoperative glucocorticoid dose [mg/day]	**2.1 ± 0.49**	0.3 ± 0.12
Cumulative glucocorticoid dose [mg/year]	**755.1 ± 160.49**	125.8 ± 47.26
Postoperative hemoglobin [gr/dL]	**9.0 ± 0.23**	9.6 ± 0.12
Transoperative transfusion requirements (%)	**19/58 (32.7)**	8/156 (6.8)
Hospitalization length, [days]	**11.3 ± 0.86**	8.2 ± 0.13
Global complications (%) • Immediate (same hospitalization period as the surgical event) • Mediate • Late (≥30 days after hospital discharge)	**21/58 (36.2)** **17/58 (29.3)** 0 4/58 (6.8)	11/116 (9.4) 10/116 (8.6) 0 1 (0.68)

Values in bold are statistical significant (p <0.05)

Disclosure: M. González-Contreras, None; **J. Merayo-Chalico**, None; **R. Ortíz-Hernández**, None; **D. Gómez-Martín**, None; **J. Alcocer-Varela**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/total-hip-arthroplasty-outcomes-a-17-year-experience-in-a-single-center-is-systemic-lupus-erythematosus-a-real-risk-factor-for-adverse-outcomes

Abstract Number: 1835

Systemic Lupus Erythematosus Does Not Increase Risk of Adverse Events in the First 6 Months after Total Knee Replacement

Arielle Fein[1], Caroline Figgie[1], Taylor Dodds[2], Joshua Wright-Chisem[3], Michael Parks[4], Lisa Mandl[5], Edwin Su[6], Jane E. Salmon[5,7], David J. Mayman[4], Yuo-Yu Lee[8], Mark P. Figgie[2] and Susan M. Goodman[7], [1]Research, Hospital for Special Surgery, New York, NY, [2]Orthopaedics, Hospital for Special Surgery, New York, NY, [3]University of Illinois at Chicago College of Medicine, Chicago, IL, [4]Orthopedics, Hospital for Special Surgery, New York, NY, [5]Hospital for Special Surgery, New York, NY, [6]Orthopedic Surgery, Hospital for Special Surgery, New York, NY, [7]Rheumatology, Hospital for Special Surgery, New York, NY, [8]Epidemiology and Biostatistics, Hospital for Special Surgery, New York, NY

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Background/Purpose: More Systemic Lupus Erythematosus (SLE) patients are undergoing total knee arthroplasty (TKA) with equivalent benefits to osteoarthritis (OA) patients. While post-surgical adverse events (AEs) are increased after total hip arthroplasty, whether a similar increase occurs after

TKA is unknown. This study compares 6-month AEs in SLE and OA.

Methods: Patients enrolled in institutional arthroplasty and lupus registries who underwent TKA between 2007 and 2014 were eligible for this retrospective case-control study. SLE patients were identified by ICD-9 code 710.0 and confirmed by chart review. OA controls were matched 2:1 with SLE cases on age, sex, year, and procedure. TKA for fractures were excluded. 6-month AEs were collected through chart review and a self-report questionnaire. Baseline characteristics were compared and regression analysis was performed to determine independent predictors of AE.

Results: 52 SLE TKA were matched to 104 OA. There were no differences in mean age and sex (See Table 1). There was no difference in the percentage of SLE vs. OA patients with complete 26-week follow-up (SLE 82.7% vs. OA 79.6%; p-value=0.65). 38.4% of SLE patients had ≥1 Charlson-Deyo comorbidity vs. 17.3% of OA (p-value<0.001; SLE not counted as a comorbidity). Pre- and perioperative "stress-dose" steroid use were increased in SLE (28.8% vs. 1.9%, p-value<0.001; 30.8% vs. 2.9%, p-value=0.01). Patients who received stress-dose steroids did not experience more AEs (37.5% of SLE on steroids had AEs vs. 38.9% SLE no steroids vs. 27.9% OA; p-value=0.40). SLE patients did not experience more major (SLE 25.0% vs. OA 19.2%; p-value=0.41), minor (SLE 15.4% vs. OA 10.6%; p-value=0.39), or total (SLE 38.5% vs. OA 27.9%; p-value=0.18) AEs. In a multiple logistic regression analysis controlling for comorbidities, SLE was not an independent risk factor for AEs (OR 1.61, 95% CI 0.74-3.50). Comorbidities were also not significantly associated with AEs when controlling for diagnosis (OR 1.05, 95% CI 0.46-2.39).

Conclusion: Despite increased comorbidities and steroid use, AEs are not increased in SLE patients after TKA and SLE is not an independent risk factor for AEs. Stress-dose steroid use does not increase risk of AEs. These important findings should guide recommendations for TKA in SLE patients.

Table 1: Patient Characteristics

	SLE (n = 52)	OA (n = 104)	P value
Age (SD)	57.9 (14.7)	58.8 (11.6)	0.72
Female, n (%)	51 (98.1%)	102 (98.1%)	0.99
BMI (SD)	30.2 (8.3)	32.4 (8.2)	0.12
Unilateral, n (%)	22 (42.3%)	50 (48.1%)	0.87
Charlson-Deyo Comorbidity, n (%)*			**0.001**
0 comorbidities	24 (46.2%)	86 (82.7%)	
1-2 comorbidities	19 (36.5%)	17 (16.3%)	
3+ comorbidities	1 (1.9%)	1 (1.0%)	
Diabetes, n (%)	10 (19.2%)	13 (12.5%)	0.26
Anesthesia Type, n (%)			
Neuraxial	27 (51.9%)	60 (57.7%)	0.49
General	2 (3.8%)	1 (1.0%)	0.26
Regional	0	1 (1.0%)	0.99
Adjunct Block	25 (48.1%)	40 (38.5%)	0.25
Length of Stay (SD)	5.4 (1.5)	5.0 (1.0)	0.06
Operative time (SD)	84.4 (23.6)	87.6 (23.8)	0.46
Coumadin as DVT Prophylaxis, n (%)	49 (94.2%)	88 (84.6%)	0.07
Pre-Operative Corticosteroid Use, n (%)	15 (28.8%)	2 (1.9%)	**<.0001**
Perioperative "Stress-Dose" Steroid Use, n (%)	16 (30.8%)	3 (2.9%)	**0.01**
Discharged to Inpatient Rehab, n (%)	26 (50.0%)	44 (42.3%)	0.09
Weeks of Follow-Up (SD)	23.2 (6.4)	22.8 (6.8)	0.72
Complete 6 Months (26 weeks) of Follow-Up, n (%)	43 (82.7%)	82 (79.6%)	0.65

*SLE excluded in comorbidity count; Comorbidity scores were missing in 15.4% of SLE patients.

Continuous variables were compared between groups using two-sample Student t-test. Categorical variables were compared between groups using Chi-square or Fisher exact test, as appropriate. Fisher exact test was used when 50% of the cells have expected count less than 5.

Table 2: Adverse Events			
	SLE (n = 52)	OA (n = 104)	P value
Major Events			
Acute Renal Insufficiency	0 (0%)	0 (0%)	N/A
Arrhythmia	3 (5.8%)	4 (3.8%)	0.69
Deep Vein Thrombosis	0 (0%)	0 (0%)	N/A
Falls	1 (1.9%)	3 (2.9%)	0.99
Post-Operative Fracture	0 (0%)	1 (1.0%)	0.99
Dislocation	0 (0%)	0 (0%)	N/A
Manipulation	2 (3.8%)	9 (8.7%)	0.34
Additional Surgery (excluding manipulation)	7 (13.5%)	6 (5.8%)	0.13
Any Major Event	13 (25.0%)	20 (19.2%)	0.41
Minor Events			
Superficial Surgical Site Infection	3 (5.8%)	1 (1.0%)	0.11
Excessive Surgical Site Drainage	2 (3.8%)	4 (3.8%)	0.56
Surgical Site Ecchymosis	1 (1.9%)	3 (2.9%)	0.99
Surgical Site Erythema	4 (7.7%)	4 (3.8%)	0.44
Spinal Headache	0 (0%)	1 (1.0%)	0.99
Delayed Wound Healing	1 (1.9%)	1 (1.0%)	0.99
Any Minor Event	8 (15.4%)	11 (10.6%)	0.39
Categorical variables were compared between groups using Chi-square or Fisher exact test, as appropriate. Fisher exact test was used when 50% of the cells have expected count less than 5.			

Table 3: Adverse Events and Stress-Dose Steroid Use				
	SLE Steroid (n = 16)	SLE No Steroid (n = 36)	OA (n = 104)	P-Value
Any AE, n (%)	6 (37.5%)	14 (38.9%)	29 (27.9%)	0.40
Any Major AE, n (%)	4 (25.0%)	9 (25.0%)	20 (19.2%)	0.71
Number of AEs Experienced, n (%)				0.37
0	10 (62.5%)	22 (61.1%)	75 (72.1%)	
1	5 (31.3%)	10 (27.8%)	21 (20.2%)	
2	0 (0%)	4 (11.1%)	5 (4.8%)	
3	0 (0%)	0 (0%)	2 (1.9%)	
4	1 (6.3%)	0 (0%)	1 (1.0%)	
Categorical variables were compared between groups using Chi-square or Fisher exact test, as appropriate. Fisher exact test was used when 50% of the cells have expected count less than 5.				

Disclosure: **A. Fein**, None; **C. Figgie**, None; **T. Dodds**, None; **J. Wright-Chisem**, None; **M. Parks**, Zimmer, Inc, 5,Orthopeadic Research and Education Foundation, 6,American Academy of Orthopaedic Surgery Orthopaedic Learning Center, 6,New York State Society of Orthopaedic Surgeons, 6; **L. Mandl**, Up To Date, 7,Annals of Internal Medicine, 9; **E. Su**, None; **J. E. Salmon**, None; **D. J. Mayman**, None; **Y. Y. Lee**, None; **M. P. Figgie**, None; **S. M. Goodman**, None.

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Abstract Number: 1836

Standardized Incidence Ratio (SIR), Time Trend and Risk Factors of Avascular Bone Necrosis (AVN) in Patients with Systemic Lupus Erythematosus (SLE)

Sau Mei Tse[1], Chi Chiu Mok[1], Kar Li Chan[1] and Ling Yin Ho[2], [1]Medicine, Tuen Mun Hospital, Hong Kong, Hong Kong, [2]Dept of Medicine, Tuen Mun Hospital, Hong Kong SAR, Hong Kong
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Background/Purpose: To study the standardized incidence ratio (SIR), time trend and risk factors of AVN in patients with SLE.

Methods:

The records of all patients who fulfilled >=4 ACR criteria for SLE between 1999 and 2014 were reviewed. Patients who developed AVN at any sites ever since the diagnosis of SLE were identified. SLE controls who did not have AVN were randomly selected from our cohort database in a 4:1 (control/case) ratio, matched for age, sex and SLE duration. The SIR of AVN in SLE and its time trend was calculated by data retrieved from our hospital clinical information registry and the Census data from our Government. Risk factors for AVN in SLE were studied by multivariate logistic regression. A propensity score derived from a separate logistic regression model for the probability of use of high-dose prednisolone (>0.8mg/kg/day) therapy according to the prevalence of different SLE manifestations was used for adjustment.

Results:

55 patients with symptomatic AVN were identified (87% women; age 33.4±12.4 years; SLE duration 61.2±62.2 months) and were matched with 220 control SLE patients without AVN. The point prevalence of AVN in our SLE cohort (N=743) was 7.4%. All the patients with AVN had been treated with glucocorticoids (GCs). Compared to controls, AVN patients had used a longer duration of steroid (51.4±61.2 vs 45.6±46.8 months; p=0.45) and a significantly higher cumulative doses of prednisolone (16.5±14.6 vs 10.7±11.3 grams; p=0.003). The SDI damage score was also significantly higher in AVN patients than controls (3.5±1.8 vs 0.4±0.9; p<0.001). A total of 104 sites of AVN were diagnosed in 55 patients (69% >=2 sites; 12.7% >=3 sites; 5.4% >=4 sites and 1.8% >=5 sites). The hip was the most commonly affected region (82%), followed by the femoral condyle (9%) and the humeral head (5%). Bilateral involvement was present in 67% cases. Surgical treatment (core decompression, vascularized bone graft or joint replacement) was performed in 41% of patients. The age and sex stratified SIRs of AVN in our SLE patients was 131 (86.6-199; p<0.001) in the period 1995-2004 and 56.0 (34.3-91.4; p<0.001) in the period 2005-2014. In both decades, the age stratified SIR was highest in the youngest age group (<19 years of age). Logistic regression revealed the following factors independently associated with AVN, adjusted by the propensity score for high-dose prednisolone: preceding septic arthritis of the involved joint (odds ratio [OR] 15.4[1.3-181.2]; p=0.03), Cushingoid body habitus (OR 2.3[1.0-5.1]; p=0.043), LDL-cholesterol level (OR 1.4[1.0-2.0];p=0.041), maximum daily dose of prednisolone (mg/kg) (OR 6.0[1.2-30.7];p=0.031) and cumulative dose of prednisolone in the first 6 months of treatment of a SLE flare (OR 1.4[1.0-1.8];p=0.047).

Conclusion:

AVN is prevalent in SLE patients, particularly in younger patients. The use of GCs remains the strongest independent factor associated with AVN. Cushingoid body habitus, serum LDL-cholesterol level and preceding septic arthritis of the involved joints are independently associated with AVN. There is a trend of reduction in the SIR of AVN in our SLE patients over the past 2 decades, which is probably attributed by the more judicious use of GCs and the early administration of GC-sparing agents.

Disclosure: S. M. Tse, None; **C. C. Mok**, None; **K. L. Chan**, None; **L. Y. Ho**, None.

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Abstract Number: 1837

Predictability of Musculoskeletal Flares and Hand Deformities in Systemic Lupus Erythematosus By High Resolution Ultrasound : 5-Year Clinical and Imaging Prospective Follow-up Study

Matteo Piga[1], Alessandra Gabba[1], Mattia Congia[1], Fabiana Figus[1], Alberto Floris[1,2], Alberto Cauli[1] and Alessandro Mathieu[1], [1]University of Cagliari, Cagliari, Italy, [2]University of Oxford, Oxford, United Kingdom
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Background/Purpose:

SLE patients develop non-deforming non-erosive (NDNE) arthritis in 70-80%, but 5-15% of cases progresses into Jaccoud's arthropathy (JA) a non-erosive

deforming arthritis. This study was aimed to investigate risk factors for development of JA in SLE patients with a focus on the progression and predictive values of synovitis, tenosynovitis and erosions detected by high-resolution ultrasound (US).

Methods:

Ninety-four consecutive patients diagnosed with SLE and NDNE musculoskeletal involvement were recruited in a 5-year prospective follow-up study. Sixty healthy subject served as controls.

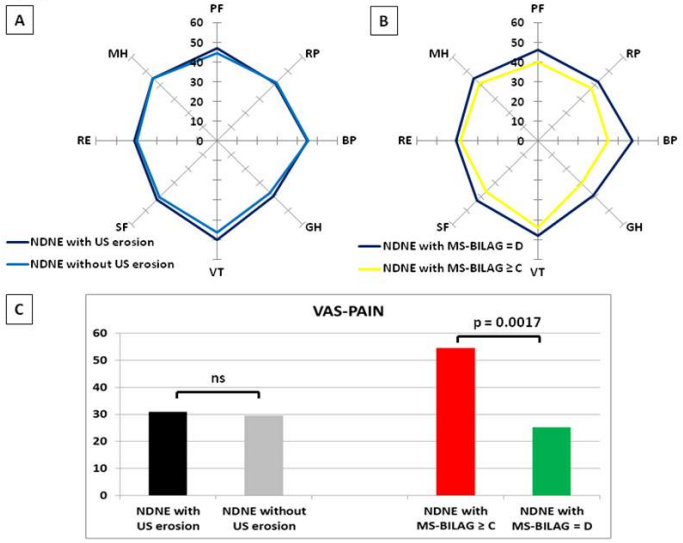
Every 6 months, or more frequently according to clinical needs, each patients underwent physical examination and a large panel of laboratory investigations. The occurrence of musculoskeletal flares was evaluated using the musculoskeletal item of BILAG2004 index. X-ray and US examination were performed at baseline and at the end of study. Patient reported outcomes (PROs) by means of SF36v2, HAQ and VAS-Pain were assessed.

Clinical, serological and US findings were used as covariates to identify risk factors for development of hand deformities (according to Spronk PE, et al. Ann Rheum Dis 1992;51:358-61). Stepwise Cox proportional hazard and logistic regression models were fitted with covariates with $p<0.1$ to predict outcomes; $p<0.05$ was considered significant. Odds ratio (OR) with 95% confidence interval (95% CI) was calculated.

Results:

Eighty patients (mean age 45.5±13.2 years; disease duration 10.7±7.1 years) completed the 5-year follow-up. Hand deformities developed in 5 (6.2%) patients with a JA estimated incidence rate of 1.25 per 100 patient-year. Longer disease duration (p=0.010; OR 1.3 95%CI 1.1-1.5) and MS flares during follow-up (p=0.017 ; OR 7.0 95%CI 1.4-35.5) independently conferred an increased risk for development of JA. Over 860 clinical assessments, 13 musculoskeletal flares (3 “A” severe and 10 “B” moderate) in 10 (12.5%) patients were recorded. US evidence of synovial proliferation with power-Doppler signal in joints or tendons (p=0.005; RR 6.7 95%CI 1.8 – 22.6) was the only independent risk factor for musculoskeletal flare. New US erosions were detected in 13 (19.7%) patients but none of them had erosions on X-ray. Active musculoskeletal involvement was responsible of worse PROs than detection of US erosions (Figure 1).

Figure 1. How each component of the SF36v2 (A and B) and VAS-Pain (C) vary in SLE patients suffering with NDNE according to the presence of US erosions and active MS symptoms classified as MS-BILAG ≥ C.



Conclusion:

Development of JA was more likely in patients with musculoskeletal flares and longer disease duration. US abnormalities identify a subset of SLE patients with more aggressive musculoskeletal involvement, higher risk for flares and, therefore, at risk for development of JA and deterioration of PROs.

Disclosure: M. Piga, None; **A. Gabba**, None; **M. Congia**, None; **F. Figus**, None; **A. Floris**, None; **A. Cauli**, None; **A. Mathieu**, None.

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Abstract Number: 1838

Joint Ultrasonography May be Useful to Assess Disease Activity in Systemic Lupus Erythematosus (SLE) Patients: A Prospective Multicenter Study

Carine Salliot[1], Emmanuelle Dernis Labous[2], Aleth Perdriger[3], Jean David Albert[4], Amelie Denis[5], Saloua Mammou[6], Isabelle Griffoul[7], Benoit Le Goff[8], Sandrine Jousse-Joulin[9], Christophe Richez[10], Nicolas Poursac[10], Mohamed Hamidou[11], Virginie Martaille[12], Antoine Valery[13] and Emilie Ducourau[14], [1]Rheumatology, CHR Orleans, Orléans, France, [2]Réseau Hôpital et Ville en Rhumatologie (RHEVER) Network, Paris, France, [3]Service de Rhumatologie, CHU de Rennes, Rennes, France, [4]Rheumatology Unit, Rennes, France, [5]Rheumatology, CH Le Mans, Le Mans, France, [6]Rheumatology, CHU Tours, Tours,

France, [7]Rheumatology, CHU TOURS, Tours, France, [8]Rheumatology, Nantes University Hospital, Nantes, France, [9]Rheumatology, CHu La cavle Blanche, Brest, France, [10]Rheumatology, CHU Bordeaux, Bordeaux, France, [11]Internal Medicine Department, Nantes University Hospital, Nantes, France, [12]Rheumatology, CHR Orléans, Orleans, France, [13]Statistics, CHR Orleans, Orleans, France, [14]Rheumatology, CHR Orleans, Orleans, France
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Background/Purpose: Arthritis is a current manifestation of SLE and participates to the SLEDAI composite score calculation (0 to 105). Ultrasonography (US) is a validated and sensitive tool for joint assessment. Published studies showed US joint abnormalities in SLE patients with or without joint pain. Nevertheless, US evaluations were not standardized and no study compared clinical and US assessments. Our objectives were 1) to describe US joint abnormalities in SLE population, 2) to compare clinical and US standardized joint assessments, 3) to estimate the reliability of clinical swollen joint count (C-SJC) and SLEDAI (C-SLEDAI) score *versus* US-SJC and US-SLEDAI.

Methods:

In an observational prospective multicenter study, we recruited consecutive SLE patients (with or without joint involvement). All fulfilled SLICC classification criteria. Evaluation included a clinical standardized joint assessment (on 40 joints), a B-mode and power Doppler (PD) US examination of the same joints, hands X-Rays, biological parameters and ongoing treatments. US was blinded to clinical assessment and performed the same day in accordance of the OMERACT guidelines. Clinical and US joint assessments included wrists, MCP, IPP, elbows, shoulders, knees, ankles and MTP. Twenty six tendons were evaluated by US (wrist extensors, finger flectors and tendons of the ankles). A joint was considered as having synovitis if the grading was ≥1 through B-mode. Reliability between clinic and B-mode US was calculated at patient level using the intraclass correlation coefficient (ICC [95% Confidence Interval]).

Results:

141 SLE patients were recruited in 7 French hospitals. 88.6% were women, mean age was 45.3±14.8 years. SLE duration was 11.7±9.7 years. 58.1%, 72.3% and 20.5% were receiving corticosteroids, hydroxychloroquine and methotrexate respectively. Mean CRP was 6.7±11.6 mg/l and ESR was 19.4 ±19.3mm, 90.6% had increased antinuclear antibody and 46% had increased anti-DNA. Sixty one patients (43.6%) had inflammatory joint pain but 124 (88%) had at least one US abnormality (effusion, synovial hypertrophy, tenosynovitis with or without PD signal). Among the 5,640 joints and 3,666 tendons assessed, 442 effusions (7.8%), 549 synovial hypertrophy (9.7%) and 117 tenosynovitis (3.2%) were detected. 170 joints (3%) had PD signal. Synovitis were mainly detected on the wrists (46.4%), MCP2 (19.8%), MTP1 (26.2%) and MTP2 (18.4%). Tenosynovitis were seen on finger flectors (31%) and extensor carpi ulnaris (10%). Mean US-SJC was significantly higher than C-SJC: 3.5±5.3 *versus* 1.5±3.6. SJC reliability was poor (ICC 0.33 [95%CI 0.16-0.48] between clinical and US assessments. Among 92 patients with a C-SJC equal to 0, 64% (59/92) had at least 1 US synovitis. Mean US-SLEDAI was significantly higher than C-SLEDAI: 4.8±3.4 versus 2.9±3.5. SLEDAI reliability was mild (ICC 0.68 [95%CI 0.27-0.84]) between clinical and US assessments. Nevertheless, US-SLEDAI score was higher than C-SLEDAI in 51% of patients by detecting asymptomatic synovitis.

Conclusion: Joints and tendons US may be useful to assess joint involvement in SLE patients and SLEDAI score calculation.

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Abstract Number: 1839

Safety and Immunogenicity of Quadrivalent Human Papilloma Virus (qHPV) Vaccine (Gardasil®) in Systemic Lupus Erythematous (SLE), Phase I Trial Completion

J. Patricia Dhar[1,2], Lynnette Essenmacher[3], Renee Dhar[4], Ardella Magee[5], Joel Ager[6] and Robert Sokol[7], [1]Internal Medicine, Wayne State University, Detroit, MI, [2]Internal Medicine, Central Michigan University College of Medicine, Saginaw, MI, [3]Wayne State University School of Medicine, Detroit, MI, [4]CMED medical student, Central Michigan University College of Medicine, Mt. Pleasant, MI, [5]Clinical and Translational Research Center, Wayne State University, Detroit, MI, [6]Family Medicine, Wayne State University School of Medicine, Detroit, MI, [7]Department of Obstetrics & Gynecology, Wayne State University School of Medicine, Detroit, MI
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Background/Purpose:

Women with SLE are at increased risk for HPV-related cervical disease. The qHPV vaccine immunizes and is protective against HPV types that cause the majority of cervical cancer (types 16 &18) and genital warts (types 6 &11).This study evaluated the safety and immunogenicity of qHPV vaccine in SLE.

Methods:

In this trial**,** 34 women ages 19-50 years (yrs.) with a history of mild to moderate SLE by ACR criteria & minimally active or inactive SLE received qHPV vaccine at the standard dosing schedule (0, 2 months, 6 months). This study was approved by the Human Investigation Committee at Wayne State University & the U.S. Food and Drug Administration. Patients were excluded if they had active disease (SELENA-SLEDAI >2), history of severe disease, deep venous thrombosis, on >400 mg/day of hydroxychloroquine, on >15 mg/day of prednisone, or had active infections. Patients were monitored for adverse events (AE), SLE flare, generation of thrombogenic antibodies and thrombosis. Antibody (Ab) levels to HPV 6,11,16 &18 were evaluated pre-vaccine administration and one month after the 3rd vaccine shot. Ab levels were measured by HPV competitive Luminex Immunoassay. Analysis of rise in Geometric Mean Titers (GMTs) was performed using paired t-tests and of seropositivity status (y/n) using McNemar's test.

Results:

The women in the study: African-American (79%), mean age 38.1 yrs., mean age at diagnosis of SLE at 28.6 yrs., 32.4% had a history of smoking, 91% had 4 or more sexual partners, 50% had a history of sexually transmitted diseases, and only 27.3% used condoms on a regular basis. History of abnormal pap smears occurred in 52.9% {range: ASCUS (atypical glandular cells of undetermined significance) to CIN 3 (cervical intraepithelial neoplasia grade 3)}. Vaccine site reactions (VSRs) occurred in 59%, all mild, most common reaction being pain (VSRs in normal women=83.9% for Gardasil® vs. 75.4% for controls). For the non-vaccine site AEs (nvAE), 97% experienced at least one nvAE; there were 487 nvAEs reported from 33 patients and 90% of these were mild. There were 9 serious AEs, none related to vaccine or SLE and all resolved. The most common nvAEs reported were musculoskeletal (n=106) followed by nervous system (n=98, mostly headaches), gastrointestinal (n=49), general disorders (n=45) and dermatologic (n=45). None of the nvAEs were related to vaccine or SLE. No patient experienced any flare of SLE, thrombosis, or generation of thrombogenic antibodies.

Positive HPV Ab titers were seen in 21-53% of the women at baseline for all HPV types (52.9% for HPV 6, 20.6% for HPV 11, 44.1% for HPV 16 & 20.6% for HPV 18), indicating previous exposure to the HPV types in the vaccine. Highly immunogenic responses were seen in all patients. There was a statistically significant rise in mean (GMTs) post vaccine series completion for both HPV naive and HPV exposed women for all 4 HPV types, with a seroconversion rate of 100% in HPV naïve women.

Conclusion:

Preliminary data from our study shows that qHPV vaccine is generally safe, well tolerated, and highly immunogenic in women with SLE. These results suggest that the qHPV vaccine may be of benefit in women with SLE who are at increased risk for HPV-related cervical disease.

Disclosure: J. P. Dhar, None; **L. Essenmacher**, None; **R. Dhar**, None; **A. Magee**, None; **J. Ager**, None; **R. Sokol**, None.

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Abstract Number: 1840

How Good a Job Are We Rheumatologists Doing in Screening for Hepatitis B and C before Immuno-Suppressive/s Initiation in SLE?

Chandrahasa Annem[1], Joel A. Block[2] and Meenakshi Jolly[3], [1]RHEUMATOLOGY, RUSH UNIVERSITY, CHICAGO, IL, [2]Rush University Medical Center, Chicago, IL, [3]Department of Medicine, Section of Rheumatology, Rush University Medical Center, Chicago, IL
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Background/Purpose: Hepatitis B & C viral infections are widely prevalent and the potential of immunosuppressive medications (ISM) to exacerbate an underlying viral infection is well reported. Established guidelines are poorly defined regarding Hepatitis B and C screening prior to initiation of ISM, and may result in (a) physician practice variations, (b) missed opportunities for optimal health care and outcomes, and (c) complicate management plans for patients in need of ISM. We sought to better understand existing practices for viral hepatitis screening, and study the prevalence and correlates of Hepatitis B and C screening among Systemic Lupus Erythematosus (SLE) patients on ISM.

Methods: We conducted a retrospective chart review of 100 SLE patients receiving ISM and being followed in outpatient rheumatology clinics. Data collected included demographics, total number, name and current dose of ISMs being currently used, and if testing (and results) for Hepatitis B and C was

ordered prior to ISM initiation. ISM use was defined as current use of any ISM including corticosteroids (CS). Significant ISM use was defined as current use of prednisone > 7.5 mg/day along with an ISM other than hydroxychloroquine. Descriptive statistics were obtained. Chi square test were used to compare discrete variables, while t tests were used to compare continuous variables. Mann –Whitney test was used when data was not normally distributed. P value < 0.05 was considered significant on two tailed tests.

Results: 86% were women and the mean (SD) age was 27.9 ± 4 years. Forty one percent of patients were taking one ISM, 41% were on two and 19% were on three ISMs'. Nearly half of the patients were on CS with a median dose of 5 mg/day. Hepatitis B & C screening tests were performed in 34% and 33% patients respectively. All the patients tested for Hepatitis B Surface Antigen (HBS Ag) were negative. Of those tested, 12/29 had Hepatitis B Surface Antibody (HBS Ab), 2/29 Hepatitis B core Antibody (HBc Ab) & 1/33 had Hepatitis C antibody (HCV Ab). Screening tests were offered more frequently to younger patients, those on more than one ISM, those on CS and those on significant ISM. Among those on significant ISM, 47% were screened for HBS Ag, as compared to 22% of patients not on significant ISM (p=0.007). Likewise, 47% on significant ISM were screened for HCV Ab as compared to 20% not on significant ISM (p=0.004).

Conclusion: Less than 40% of those on ISM received Hepatitis B & C screening in SLE. Less than half of SLE patients that were tested prior to ISM showed immunity against Hepatitis B virus. Nearly 7% of SLE patients tested for Hepatitis B before ISM, showed chronic Hepatitis B, while 3% of SLE patients tested positive for Hepatitis C virus before ISM. These results indicate opportunities to improve screening and detect Hepatitis B/C in SLE patients on ISM. Education of physicians treating patients at higher risk and harmonization of various recommendations on Hepatitis B and C screening is indicated.

Table 1: Descriptives and Correlates of Hepatitis B and C Screening Tests in SLE			
Age (Mean (SD)) years	27.9 (4.9)		
Gender (%) Women	86		
Ethnicity			
White	29		
African American	38		
Hispanic	19		
Other	24		
No of ISM used			
1 ISM	40		
2 ISM	41		
3 ISM	19		
Specific ISM used			
Corticosteroids (CS)	58		
Median (IQR) corticosteroid dose (mg/day)	5 (20)		
Hydroxycholoroquine (HCQ)	76		
Methotrexate	9		
Azathioprine	10		
Mycophenolate- Mofetil	18		
Rituximab	2		
Hepatitis B and C status	**Screened**	**Positive**	
Hepatitis B Surface Antigen (HBSAg)	34	0	
Hepatitis B Surface Antibody	27	12	
Hepatitis B core antibody	28	2	
Hepatitis C Antibody (HCVAb)	33	1	
Correlates for Screening	**Screened**	**Not Screened**	**P value**
Age (Mean (SD)) years			
Hepatitis B Surface Ag screen	25.6(4.1)	29.1 (5.0)	<0.001
Hepatitis C Ab screen	25.5(4.2)	29.1(4.9)	<0.001
Number of ISM			
Hepatitis B Surface Ag screen	2.00(0.69)	1.68(0.74)	0.04
Hepatitis C Ab screen	1.97(0.68)	1.70(0.75)	0.08
Median (IQR) Dose of CS in HBSAg (mg/day)	10 (20)	2.5 (20)	0.04
Median (IQR) Dose of CS in HCVAb (mg/day)	10 (30)	5(20)	0.03
Use of Corticosteroids	**Odds Ratio**	**P-value**	
Hepatitis B Surface Ag screen	2.8(CI 1.1-6.8)	0.02	
Hepatitis C Ab screen	2.6(CI 1.0-6.4)	0.04	
Significant ISM			
Hepatitis B Surface Ag screen	3.2 (CI 1.3-7.7)	0.007	
Hepatitis C Ab screen	3.6(CI 1.5-8.8)	0.004	
ISM: Immunosuppressive medication			
CS: Corticosteroids, Significant ISM: Prednisone >7.5 mg/day & ISM other than HCQ			

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Abstract Number: 1841

Meningitis in Systemic Lupus Erythematosus Patients: Epidemiologic Profile of Listeria Monocytogenes Infection. a Single-Center Study

Ana Barrera-Vargas[1], Javier Merayo-Chalico[2], Armelle Pérez Cortés Villalobos[3], Alfredo Ponce de León[3], Jorge Alcocer-Varela[1] and Diana Gómez-Martín[1], [1]Department of Immunology and Rheumatology, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico, [2]Immunology and Rheumatology, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico, [3]Department of Infectology and Microbiology, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico

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Background/Purpose: Infections are an important cause of morbidity and mortality in systemic lupus erythematosus (SLE) patients. These patients are more prone to develop infections, both because of intrinsic immune system abnormalities associated with the disease and immunosuppressive therapy. *Listeria monocytogenes* is a foodborne pathogen that may cause invasive disease, including bacteremia and meningitis, in immunocompromised patients. The aim of this study was to address characteristics and risk factors associated with meningitis by *L. monocytogenes* and to compare them with meningitis caused by other bacteria in SLE patients.

Methods: We performed a retrospective cohort study in a tertiary care center in Mexico City between 2000 and 2015. SLE patients who had a cerebrospinal fluid (CSF) culture positive for *L. monocytogenes* or other gram-positive bacteria were included. All patients fulfilled at least 4 ACR criteria for SLE. We also analyzed patients without SLE with a positive CSF culture for *L. monocytogenes*. Patients with a clinical diagnosis of meningitis but without a positive CSF culture were excluded. Demographic, clinical and serologic features both 3 months before and at the infection were recorded.

Results: Fourteen patients had a positive CSF culture for *L. monocytogenes* during the study period, and 9 of them (64%) had SLE. Among all SLE patients with meningitis proven by a positive CSF culture (n=22), infection with *L. monocytogenes* represented 41%. Group B *streptococcus* and *S. pneumoniae* were the second most common pathogens, each accounting for 14%.

There was no difference in SLEDAI score, complement and anti-dsDNA levels 3 months prior to the infection between both SLE groups. Prednisone and azathioprine dose 3 months before the infection were higher in patients with *L. monocytogenes* meningitis (p=0.025 and 0.043, respectively).

At the time of the infection, there was no difference in complement and antidsDNA levels; SLEDAI and SDI scores; prednisone, immunosuppressive and antimalarial drug dose; and CSF findings between both groups. Most SLE patients with *L. monocytogenes* received ampicillin (89%) during the first 24 hours after admission. SLE patients with *L. monocytogenes* had shorter stays in an intensive care unit (p=0.034) and lower mortality at 6 months (11 *vs* 54%, p=0.04) than those with meningitis by other bacteria. There was also a trend for lower mortality in patients with *L. monocytogenes* meningitis and SLE compared to those without SLE (11 vs 60%, p=0.052).

Conclusion: This is the largest, single-center study regarding *L. monocytogenes* meningitis in SLE patients. *L. monocytogenes* was a common cause for meningitis in our cohort, and SLE patients seemed especially susceptible to this pathogen. Other immunosupressed patients (HIV, transplant recipients, chemotherapy, other rheumatologic diseases) are routinely treated at our institution and the incidence in those patients was clearly lower. Whether a specific immunologic defect predisposes SLE patients to *L. monocytogenes* remains to be determined. On the other hand, mortality and days in an intensive care unit were lower in SLE patients with *L. monocytogenes*, which could be related to the prompt initiation of appropriate antibiotic therapy.

Disclosure: A. Barrera-Vargas, None; **J. Merayo-Chalico**, None; **A. Pérez Cortés Villalobos**, None; **A. Ponce de León**, None; **J. Alcocer-Varela**, None; **D. Gómez-Martín**, None.

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Abstract Number: 1842

Systemic Lupus Erythematosus and Chikungunya Fever: Interactions during the 2014 Outbreak in Martinique

Bastien Bigeard[1], Katlyne Polomat[2], Emilie Javelle[3], Serge ARFI[2], Lauren Brunier-Agot[4], Florence MOINET[2], Fatiha Najioullah[5], Elodie Curlier[6], Andre Cabié[7], Michel DeBandt[1], Georges Jean Baptiste[2] and **Christophe Deligny**[2], [1]internal medicine and rheumatology, Zobda Quitman Hospital, Fort de France, Martinique, [2]Rheumatology and Internal Medicine, Zobda Quitman Hospital, Fort de France, Martinique, [3]Tropical and Infectious Diseases, Laveran Military Teaching Hospital, Marseille, France, [4]Internal medicine and rheumatology, Zobda Quitman Hospital, Fort de France, Martinique, [5]virology, Zobda Quitman Hospital, Fort de France, Martinique, [6]infectiology, dermatology and internal medicine, CHU de Guadeloupe, Pointe à Pitre, Guadeloupe, [7]infectious disease, Zobda Quitman Hospital, Fort de France, Martinique

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Background/Purpose: There is no data in the literature about chikungunya fever (chik) and SLE. Martinique (French West Indies) experienced for the first time an outbreak of chik during the year 2014 that was an opportunity to study the relation between SLE and this viral infection.

Methods: The main objective was to describe the evolution of Chik patients with SLE. We also searched to know (1) if chik could modify SLE disease activity, (2) the role of SLE treatments, particularly immunosuppressive drugs, during the Chik episode. We perform a retrospective, monocentric, systematic evaluation of all SLE patients (fulfilling 1997 ACR criteria) followed in the internal medicine and rheumatology unit of the University hospital, between january 2014 and may 2015, assessing (1) SLE activity, (2) the presence of signs compatible with a chik episode. A systematic viral serology was prescribed with their usual biological follow up for all patients. Chik severity was considered if an encephalopathy, myocarditis, hepatitis, or multiorgan failure was present.

Results:

167 patients were screened for chik by serology, and we had a result for 110 in may 2015. 56 were included with a positive serology for chik (female: 53; male: 3). Their basic parameters were: mean age at serology (46.5 years, range: 23-81), time since SLE diagnosis to chik episode (12.9 years), renal involvement (42.8%), treatment by immunosuppressant drugs (33.9%), hydroxychloroquine or chloroquine (86.8%), prednisone (64.8%), rituximab (n=3). Clinical signs compatible with a Chik episode were found in 82.6% of the patients with a positive serology. Four patients (7%), all younger than 55 years and one treated by mycophénolate, exhibit severe signs of chik including encephalopathy (n=4) associated with bullous cutaneous lesions (n=3), kidney involvement (n=2). One of these 4 patients who was not immunosuppressed, died in a context of systemic capillary leak syndrome and multiorgan failure. Six of 56 positive patients (10.7%) experienced a lupus flare, all after a symptomatic chik fever: 5/6 were on prednisone, 5/6 hydroxychloroquine and 3/6 (50%) immunosuppressive drugs.

Conclusion: SLE can lead to severe Chik infection and should be considered as a group at risk. Chik fever can probably induce SLE flare. Immunosuppressive drugs seem not influence the clinical picture of chik.

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Abstract Number: 1843

Bloodstream Infections in Systemic Lupus Erythematosus Patients Are Associated with Severe Lupus Flares

José Jiram Torres Ruiz[1], Ana Barrera-Vargas[2], Rigoberto Ortíz-Hernández[2], Jorge Alcocer-Varela[2] and Diana Gómez-Martín[2], [1]Department of Immunology and Rheumatology, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico, Mexico, [2]Department of Immunology and Rheumatology, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico

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Background/Purpose: Infections are an important cause of mortality and morbidity in systemic lupus erythematosus (SLE) patients. Bloodstream infections (BI), which are especially severe and relatively common in these patients, are associated with a high mortality rate, both during the infectious episode and during follow-up. Whereas there is evidence that bacterial infections can trigger autoimmunity, the relationship between BI and severe lupus flares has not been fully addressed. The aim of this study was to assess whether BI are a risk factor for severe lupus flare.

Methods: We performed a retrospective cohort study comparing 107 SLE patients with an episode of BI and 107 hospitalized or ambulatory SLE patients without BI. All subjects satisfied the ACR classification criteria and none of them had severe lupus flare at baseline. Time zero was considered as: a) The episode of BI in the first group b) Hospitalization for another cause, or the medical assessment prior to the last follow-up visit as an ambulatory patient in the non-BI group. Patients were followed for three months. The primary outcome was severe lupus flare according to SELENA-SLEDAI criteria. Differences between groups were assessed by Student's t test. Cox proportional hazards model was used to estimate the relative risk of severe flare, along with 95% confidence interval.

Results: Thirty patients (14%) developed the primary outcome (severe flare) during follow-up; 25 (83.3%) of them had an episode of BI in the previous three months, compared with 5 (16.6%) without a history of BI ($p<0.001$). A high percentage of patients with severe lupus flare had a SLEDAI score >12 (36.6%). Among these flares, severe thrombocytopenia (33.3%) and renal flare (43.3%) were the most frequent. There was no difference in prednisone, cyclophosphamide and mycophenolate mofetil dose between patients who presented severe lupus flare and those who did not. Nevertheless, the basal SLEDAI, C3, C4, anti-dsDNA and azathioprine dose were significantly higher in the former group. After multivariate analysis, the presence of BI (HR 6.24, 95% CI 1.405-27.725, p=0.016), low C4 levels (HR 3.2, 95% CI 1.272-8.078, p=0.014) and lymphopenia <1000 cells/ml (HR 5.02, 95% CI 1.137-22.23, p=0.033) remained independently associated with severe lupus flare.

Interestingly, while only 10.3% of BI episodes were caused by *S. pneumoniae*, 54.5% of patients infected by that microorganism developed a severe SLE flare. Noteworthy, infection by *S. pneumoniae* remained as an independent risk factor for lupus flare in the BI group (HR 2.75, 95% CI 1.406-5.403, p=0.019).

Conclusion: SLE patients with BI have an increased risk for severe disease flare. Also, lymphopenia and low C4 were significant predictors in our cohort. Among patients with BI, when *S. pneumoniae* was the causing agent, the risk of severe SLE flare augmented significantly. High mortality associated with BI

in SLE patients may not only be related to the infection *per se*, but also to the development of severe disease activity. Patients with an episode of BI, and specifically those who fulfill the other aforementioned characteristics, should be followed up closely in order to detect and treat flares in a timely manner.

Disclosure: J. J. Torres Ruiz, None; **A. Barrera-Vargas**, None; **R. Ortíz-Hernández**, None; **J. Alcocer-Varela**, None; **D. Gómez-Martín**, None.

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Abstract Number: 1844

Risk Factors for Complicated Pneumonia in Systemic Lupus Erythematosus (SLE)

Gabriela García-Guevara[1], Ricardo Ríos-Corzo[2], Juan Ávila-Vázquez[3], John Hernández-Flores[4], Eduardo Carrillo-Maravilla[5], Juan Jakez-Ocampo[6], Hilda Fragoso-Loyo[7], Luis Llorente[8] and **Yemil Atisha-Fregoso**[9], [1]Vasco de Quiroga #15, Tlalpan, Belisario Domínguez Sección XVI, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico, Mexico, [2]Escuela de Medicina, Instituto Tecnológico y de Estudios Superiores de Monterrey, Monterrey, Mexico, [3]Escuela Nacional de Medicina, Instituto Tecnológico y de Estudios Superiores de Monterrey, Mexico, Mexico, [4]Escuela de Medicina, Benemérita Universidad Autónoma de Puebla, Puebla, Mexico, [5]Medicina Interna, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico, Mexico, [6]Immunology and Rheumatology, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, México, Mexico, [7]Vasco de Quiroga 15 Col Seccio, INNCMSZ-Departamento de Inmunología y Reumato, Mexico, Mexico, [8]Immunology and Rheumatology, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico, [9]Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubiran, Mexico City, Mexico

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Background/Purpose:

Pneumonia, remains as a main cause of mortality in patients with SLE. In patients without autoimmune disease, scores as Pneumonia Severity Index (PSI) and CURB-65 can identify patients at low risk of complications. These indexes has not been validated in patients with SLE.

The aim of this study was to stablish the rate of complications of patients with SLE and pneumonia, identify specific risk factors associated with bad prognosis in these patients and describe the clinical behavior of PSI and CURB-65 to identify patients at low risk of complications.

Methods:

We retrospectively reviewed medical records of patients with SLE (ACR criteria) and pneumonia who attended the emergency room in a single tertiary care center, (January 2010 - March 2015). We collected laboratory and clinical data: demographics, treatment, risk factors commonly associated with poor outcome in pneumonia, and disease activity (SLEDAI-2K). Patients were followed for 30 days after discharge. A composite negative outcome were defined as need of mechanical ventilation (MV), septic shock or death during follow up.

Statistics. Initially we conducted a univariate analysis, using Student T, Mann-Whitney U, Chi squared or Fisher's exact test as appropriate. Thereafter we conducted a multivariate analysis (logistic regression) with all variables with a p value ≤ 0.10.

Results:

We included 163 patients (121 women, 74%), who presented 194 episodes of pneumonia. At evaluation the mean ± SD age was 34.6 ± 12.4 years. Time since diagnosis of SLE 7.1 ± 8.2 years. SLEDAI 2K was 8 ± 5.6.

Duration of hospitalization was 10.7 ± 7.2 days. Fifty seven (29%) patients had the composite outcome: 13 (7%) septic shock, 50 (26%) needed MV and 12 (6%) patients died.

Variables who reach clinical significance in the univariate analysis were: body mass index (BMI) (higher risk for patients with BMI lower than 19), chronic kidney disease, congestive heart failure, use of methotrexate and use of tacrolimus. Clinical variables with significant association were respiratory rate (RR), heart rate (HR), body temperature, oxygen saturation (detected by pulse oximetry), leukopenia, confusion, changes in pH and procalcitonin levels.

In the multivariate analysis remain significant: low BMI (beta exponential 4.02, 95% CI 1.4 – 11.6, p=0.010), RR (beta exp 1.08, 95% CI 1.02 – 1.15, p=0.006), HR (beta exp 1.04, 95% CI 1.02 – 1.06, p=0.001), body temperature (beta exp 0.46, 95% CI 0.28 – 0.75, p=0.002) and arterial pH (beta exp 0.001, 95% CI 0.00001 – 0.079, p=0.002).

Twenty nine patients (14.9%) had zero points in CURB65 (low risk), 4 of them (13.8%) had an adverse outcome. A score of zero in CURB65 had a sensitivity of 93% and specificity of 18% for identifying patients without complications. Sixty patients were classified as Class I in PSI, 7 of them had a negative outcome. Class I in PSI had a sensitivity of 88% and specificity of 39% for identifying patients without complications.

Conclusion:

In this study none SLE associated variable was significant associated with bad prognosis in patients with SLE and pneumonia. PSI and CURB65 are in general accurate but misclassified about 10% of patients as low risk, so clinical judgement must complement these tools.

Disclosure: G. García-Guevara, None; **R. Ríos-Corzo**, None; **J. Ávila-Vázquez**, None; **J. Hernández-Flores**, None; **E. Carrillo-Maravilla**, None; **J. Jakez-Ocampo**, None; **H. Fragoso-Loyo**, None; **L. Llorente**, None; **Y. Atisha-Fregoso**, None.

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Abstract Number: 1845

HMGB1 Early Marker in Lupus Nephritis

Aisha Badawy[1], **Randa Salam**[2], Hanan Fouad[3], Amira Bassam[4] and Sahar Lashen[5], [1]Internal medicine cairo university, professor of internal medicine and rheumatology, cairo, Egypt, [2]Internal medicine cairo university, Assistant professor internal medicine, cairo, Egypt, [3]medical biochemistry cairo university, Professor of medical biochemistry, cairo, Egypt, [4]pathology Cairo university, Lecturer of Pathology Cairo university, cairo, Egypt, [5]Internal medicine, assistant lecturer of internal medicine cairo university, cairo, Egypt

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Session Date: Monday, November 9, 2015

Session Title: Systemic Lupus Erythematosus - Human Etiology and Pathogenesis Poster II

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose:

Systemic Lupus Erythematosis is a systemic autoimmune disease characterised by involvement of multiple organ systems Lupus nephritis (LN) is a severe and frequent manifestation of systemic lupus erythematosis (SLE). Its pathogenesis has not been fully elucidated but immune complexes are considered to contribute to the inflammatory pathology in LN.

The aim of the study to assess the potential role of HMGB1 (high-mobility group box proteins) in SLE and whether urinary and serum levels of HMGB1 reflect renal inflammation and correlate with disease activity,

Methods:

In **a** Case control study 61 Systemic lupus patients fulfilling the classification criteria for the diagnosis of SLE (divided in 4 groups)selected from Internal Medicine Department, Kasr Al-Aini Hospital, Cairo University after ethical committee approval and getting written informed consent from each patient.

Group 1: 21 patients with lupus nephritis ,**Group 2:** 21 patients with lupus activity without nephritis .**Group 3:** 19 patients without activity as estimated by SLEDAI < 4 ,**Group 4:**included 13 healthy volunteers age and sex matched.

Participants were subjected to: Detailed medical history., Complete physical examination. disease activity scoring using SLEDAI.

Laboratory investigations: Complete blood count. ,Kidney function tests , Urine analysis,ESR,ANA,,Anti dsDNA. ,C3, C4 levels. plasma and urinary levels of HMGB1 assessed by ELISA

Study of HMGB1 in renal biopsy from 21 patients with active lupus nephritis The activity index (AI) and chronicity index (CI) were calculated for each specimen with maximum scores of 24 for the AI and 12 for the CI.

Cellular distribution of HMGB1 was determined in the kidney by counting one hundred nuclei (glomerular, tubular, and stromal) in three bright field pictures and scoring both HMGB1-positive (brown) and HMGB1-negative (blue) nuclei

Results:

Plasma and urinary HMGB1 were in lupus with activity however significantly elevated in patients with active LN compared to patients without active nephritis($p<0.037$). and control($p<0.001$).Plasma and urinary HMGB1 and renal tissue levels HMGB1 levels correlated with SLEDAI differentiating SLE without nephritis from SLE with nephritis using ROC curve a higher sensitivity and specificity of HMGB1 in lupus nephritis compared with other groups 95.1% and 100% respectively Similarly, renal tissue of active LN patients showed strong expression of HMGB1 at cytoplasmic and extracellular sites suggesting active release of HMGB1

Conclusion:

The present study demonstrates increase in plasma, urine, renal tissue HMGB1 levels in SLE patients, in particular in those with active LN. Increase in HMGB1 levels correlated to SLE activity index (SLEDAI). Thus we suggest that HMGB1 may play an important role in renal pathology in SLE patients and HMGB1 blocking may be of future interest in development new treatment strategies for lupus nephritis

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Disclosure: A. Badawy, None; **R. Salam**, None; **H. Fouad**, None; **A. Bassam**, None; **S. Lashen**, None.

Abstract Number: 1846

IGFBP-2 As a Novel Biomarker for Disease Activity and Renal Pathology in Lupus Nephritis

Huihua Ding[1], Chandra Mohan[1] and Tianfu Wu[2], [1]Biomedical Engineering, University of Houston, Houston, TX, [2]Department of Biomedical Engineering, University of Houston, Houston, TX

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Background/Purpose:

Lupus nephritis (LN) is one of the most serious manifestations of systemic lupus erythematosus. Invasive renal biopsy remains the golden standard for the diagnosis and management of LN. The objective of this study is to validate serum IGFBP-2 as a novel biomarker of LN and to examine if it could reflect renal pathology in LN patients.

Methods:

Serum samples from 85 biopsy-proven lupus nephritis patients, 18 chromic kidney disease (CKD) controls and 20 healthy controls were used for ELISA testing of IGFBP-2 levels.

Results:

Compared to CKD patients of origins other than lupus or healthy controls, serum IGFBP-2 levels were significantly elevated in LN patients. Serum IGFBP-2 levels were able to discriminate LN patients from healthy controls with an Area Under the Curve (AUC) of 0.97 [95% CI: 0.93 to 1.00; $P < 0.0001$] and CKD disease controls (AUC: 0.65 [95% CI: 0.52 to 0.78; $P = 0.043$]). In addition, serum IGFBP-2 could serve as a potential indicator of both SLEDAI (active vs. inactive: 448.1 ± 51.9 ng/ml vs. 263.7 ± 41.7 ng/ml; $P = 0.009$) and rSLEADAI in LN patients (active vs. inactive: 429.1 ± 44.5 ng/ml vs. 213.3 ± 49.1 ng/ml; $P = 0.007$). Correlation analysis showed a significant correlation between serum IGFBP-2 levels and SLEDAI score ($r = 0.379$, $P < 0.0001$, $n = 85$) as well as rSLEDAI score ($r = 0.409$, $P < 0.0001$, $n = 85$). Serum IGFBP-2 levels also correlated well with serum creatinine levels ($r = 0.658$, $P < 0.001$, $n = 85$), urine protein-to-creatinine levels ($r = 0.397$, $P < 0.001$, $n = 85$), and eGFR levels ($r = -0.680$, $P < 0.001$, $n = 85$). More importantly, in 19 concurrent patients' samples, serum IGFBP-2 correlate with the chronicity index of concurrent renal pathology ($r = 0.576$, $P = 0.01$).

Conclusion:

Serum IGFBP-2 appears to be a promising biomarker for lupus nephritis, reflective of disease activity and chronicity changes in renal pathology.

Disclosure: H. Ding, None; **C. Mohan**, None; **T. Wu**, None.

Abstract Number: 1847

Serum Ferritin and Insulin-like Growth Factor-Binding Protein 2 As Biomarkers of Clinical and Histopathological Treatment Response in Lupus Nephritis

Ioannis Parodis[1], Huihua Ding[2], Agneta Zickert[1], Chandra Mohan[2] and Iva Gunnarsson[1], [1]Department of Medicine, Rheumatology Unit, Karolinska Institutet, Stockholm, Sweden, [2]Biomedical Engineering, University of Houston, Houston, TX

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Background/Purpose: Lupus nephritis (LN) is a severe manifestation of Systemic Lupus Erythematosus (SLE). Renal biopsy is gold standard for evaluation of renal activity and damage in LN. Evaluation of new biomarkers for non-invasive assessment of renal pathology is warranted. Ferritin is considered an acute phase protein and studies have reported elevated serum concentrations in patients with active SLE, as compared to patients with inactive disease, and

also correlations with LN. Insulin-like Growth Factor-Binding Protein 2 (IGFBP2) has been found to be a robust diagnostic and prognostic biomarker in malignancies. In animal models, IGFBP2 expression was increased in anti-glomerular basement membrane (anti-GBM) glomerulonephritis and MRL/lpr lupus mice. The role of these molecules in LN has yet to be clarified.

Methods: Serum levels of Ferritin and IGFBP2 were assessed by ELISA (Raybiotech Inc. and R&D Systems, respectively) in 64 patients with biopsy-ascertained active LN before and after completion of induction treatment. Follow-up renal biopsies were performed after a mean time of 8.1 months. Reduced proteinuria by ≥50%, normal or improved estimated Glomerular Filtration Rate (eGFR) by ≥25%, and inactive urinary sediment signified clinical responders (CR). Improvement of Activity Index in the follow-up biopsies by ≥50% signified histopathological responders (HR). Long-term renal outcome after a mean time of 10.9 years was determined by the last eGFR.

Results: Serum Ferritin and IGFBP2 levels declined following induction therapy for LN in both CR and HR ($p<0.001$). In clinical non-responders (CNR), IGFBP2 levels remained unchanged ($p=0.438$) while Ferritin levels declined ($p=0.030$). In histopathological non-responders (HNR), both Ferritin ($p=0.056$) and IGFBP2 ($p=0.158$) levels remained stable.

In patients with proliferative LN (PLN; n=52), Ferritin and IGFBP2 levels declined following therapy in both CR and HR ($p<0.001$). Ferritin and IGFB2 levels declined in CNR ($p<0.05$). In HNR, IGFBP2 levels remained stable ($p=0.086$) while Ferritin levels declined ($p=0.011$).

In patients with membranous LN (MLN; n=12), Ferritin and IGFBP2 levels declined in CR ($p<0.05$), but not in CNR. Ferritin levels declined in HR ($p=0.046$), but not in HNR while IGFBP2 levels remained stable in both HR and HNR.

Follow-up IGFBP2 levels were higher in CNR compared to CR ($p=0.004$). There was no correlation between Ferritin or IGFBP2 concentrations and long-term renal outcome. We noted a correlation between IGFBP2 levels and Chronicity Index at follow-up ($p=0.009$, $r=0.324$).

Conclusion: The decreases in Ferritin and IGFBP2 levels following induction therapy suggest an association of these molecules with renal disease activity. The data also suggest higher follow-up IGFBP2 levels as a biomarker of unfavorable treatment outcome in LN and point to IGFBP2 being a candidate biomarker of histopathological outcome following induction treatment for PLN. Moreover, our results indicate an important role and a potential utilization of both Ferritin and IGFBP2 as biomarkers of treatment response in MLN. The correlation between Chronicity Index and IGFBP2 levels at follow-up suggests IGFBP2 as a biomarker of renal damage in LN patients after induction therapy.

Disclosure: I. Parodis, None; **H. Ding**, None; **A. Zickert**, None; **C. Mohan**, None; **I. Gunnarsson**, None.

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Abstract Number: 1848

Increased Expression of Bruton Tyrosine Kinase in Patients with Lupus Nephritis and Its Clinic Significance

Wei Kong, Wei Deng, Xuebing Feng, Genhong Yao, Weiwei Chen, Xiaojun Tang, Yue Sun, Saisai Huang, Zhuoya Zhang, Bingyu Shi and **Lingyun Sun**, Department of Rheumatology and Immunology, The Affiliated Drum Tower Hospital of Nanjing University Medical School, Nanjing, China

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Session Time: 9:00AM-11:00AM

Background/Purpose: Systemic lupus erythematosus (SLE) is an autoimmune disease manifested by multiorgan impairment including glomerulonephritis, cutaneous lesions and arthritis. B cells participate in the onset of SLE. As a downstream signaling molecule of B-cell receptor (BCR) signaling pathway, Bruton tyrosine kinase (Btk) is involved in the development, activation and survival of B cells. It is reported that transgenic mice overexpressing Btk specifically in B cells could produce antinuclear antibody and develop a lupus-like symptoms. The aim of our study was to identify the specific role of Btk in lupus nephritis.

Methods: The percentages of Btk positive $CD19^+$ B cells from 28 SLE patients and 28 healthy donors were examined by flow cytometry. The correlation between the percentages of Btk positive $CD19^+$ B cells and some lupus related clinical indicators were analyzed. Immunohistochemistry was used to detect the Btk expression in kidney biopsies from 8 lupus nephritis (LN) patients and 8 controls. The levels of Btk expression in glomerulus were detected by image-pro plus analysis, and represented by mean optical density (MOD).

Results: The frequency of Btk^+CD19^+ B cells from SLE patients is up-regulated compared with the healthy controls (3.89 ± 0.31 vs 2.61 ± 0.21, $p<0.01$), significantly correlating with the SLE activity (SLEDAI) ($r=0.53$), levels of serum anti-dsDNA antibody ($r=0.41$), levels of serum C3 ($r=-0.41$), and the amount of 24 hours urine protein ($r=0.59$). We also found that the frequency of Btk^+CD19^+ B cells in the patients with lupus nephritis was significantly higher compared with the patients without lupus nephritis (4.71 ± 0.481 vs 3.19 ± 0.30, $p<0.05$). The levels of Btk expression in glomerulus were markedly increased in LN patients compared with controls (0.04 ± 0.01 vs 0.01 ± 0.00, $p<0.001$).

Conclusion: Btk expression is significantly increased in LN, which may be a promising therapeutic target for the molecular therapy of SLE.

Disclosure: W. Kong, None; **W. Deng**, None; **X. Feng**, None; **G. Yao**, None; **W. Chen**, None; **X. Tang**, None; **Y. Sun**, None; **S. Huang**, None; **Z. Zhang**, None; **B. Shi**, None; **L. Sun**, None.

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Abstract Number: 1849

Serum Axl and Tumor Necrosis Factor Receptor II Portend Long-Term Renal Outcome in Lupus Nephritis

Ioannis Parodis[1], Huihua Ding[2], Agneta Zickert[1], Chandra Mohan[2] and Iva Gunnarsson[1], [1]Department of Medicine, Rheumatology Unit, Karolinska Institutet, Stockholm, Sweden, [2]Biomedical Engineering, University of Houston, Houston, TX
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Background/Purpose: Lupus nephritis (LN) is a severe manifestation of Systemic Lupus Erythematosus (SLE). Renal biopsy is gold standard for evaluation of renal activity and damage. New non-invasive biomarkers are warranted. Axl belongs to the Thyro3-Axl-Mer receptor tyrosine kinase subfamily and is mainly expressed on antigen presenting cells. Tumor Necrosis Factor Receptors (TNFRs) are involved in the pathogenesis of SLE. In previous reports, levels of the soluble forms of Axl and TNFRII were elevated in SLE patients, and Axl levels correlated with disease activity. The role of these molecules in LN remains to be clarified.

Methods: Serum levels of Axl and TNFRII were assessed by ELISA (R&D Systems) in 64 patients with biopsy-ascertained active LN before and after induction treatment. Follow-up renal biopsies were performed after a mean time of 8.1 months. Reduced proteinuria by ≥50%, normal or improved estimated Glomerular Filtration Rate (eGFR) by ≥25%, and inactive urinary sediment signified clinical responders (CR). Improvement of Activity Index (AI) in the follow-up renal biopsies by ≥50% signified histopathological responders (HR). Long-term renal outcome after a mean time of 10.9 years was determined by the last eGFR.

Results: Serum levels of Axl and TNFRII declined following induction therapy for LN in both CR and HR ($p<0.005$). In clinical non-responders (CNR), Axl levels remained unchanged while TNFRII levels declined ($p=0.049$). In histopathological non-responders (HNR), Axl levels remained stable while TNFRII levels declined ($p=0.008$).

In patients with proliferative LN (PLN; n=52), Axl and TNFRII levels declined in both CR and HR ($p<0.005$). Axl levels remained stable in CNR and HNR while TNFRII levels declined ($p<0.05$).

In patients with membranous LN (MLN; n=12), Axl and TNFRII levels declined in CR ($p<0.05$), but not in CNR. TNFRII levels declined in HR ($p=0.046$), but not in HNR, while Axl levels remained stable both in HR and HNR.

Baseline Axl and both baseline and follow-up TNFRII levels correlated inversely with the last eGFR ($p=0.014$, $r=-0.307$; $p=0.021$, $r=-0.290$; $p=0.043$, $r=-0.256$, respectively). Baseline TNFRII levels correlated with AI in baseline biopsies ($p=0.026$, $r=0.279$) and both baseline and follow-up Chronicity Index (CI) scores ($p=0.012$, $r=0.313$ and $p=0.003$, $r=0.373$, respectively). TNFRII levels correlated with CI at follow-up ($p<0.001$, $r=0.535$). Both baseline and follow-up Axl levels correlated with follow-up CI scores ($p=0.022$, $r=0.289$ and $p=0.037$, $r=0.264$, respectively).

Conclusion: Our data suggest Axl as a candidate biomarker of renal activity and treatment response in PLN and TNFRII as a candidate biomarker of renal activity and response in MLN. Higher baseline Axl and TNFRII levels were associated with unfavorable long-term renal outcome, supporting a role of these molecules in more severe renal disease and a more unfavorable prognosis. Moreover, our data suggest Axl as a candidate biomarker of renal damage in LN patients after induction therapy and TNFRII as a biomarker of both renal activity and damage in LN.

Disclosure: I. Parodis, None; **H. Ding**, None; **A. Zickert**, None; **C. Mohan**, None; **I. Gunnarsson**, None.

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Abstract Number: 1850

Increased Levels of Immunoglobulin Binding Protein 1 Are Associated with Disease Activity Including Renal Damage in Patients with Systemic Lupus Erythematosus

Eun-Ju Lee[1,2], Seokchan Hong[3], Doo-Ho Lim[1], Yong-Gil Kim[1], Chang-Keun Lee[1] and Bin Yoo[1], [1]Division of Rheumatology, Department of Internal Medicine, Department of Rheumatology, University of Ulsan College of Medicine, Asan Medical Center, Seoul, South Korea, [2]Asan Institute for Life Science, Asan Medical Center, Seoul, South Korea, [3]Department of Rheumatology, University of Ulsan College of Medicine, Asan Medical Center, Seoul,

South Korea
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Background/Purpose: Systemic lupus erythematous (SLE) is a multisystem autoimmune inflammatory disease. Lupus nephritis (LN) is one of the most serious complications in patients with SLE. Immunoglobulin binding protein 1 (IGBP1) originally was discovered as a phosphoprotein associated with the immunoglobulin receptor in B cells. This protein interacts with the catalytic subunit of protein phosphatase PP2A (PP2A), highly conserved serine/threonine phosphatase, and regulates differentiation, proliferation, and apoptosis of B cells. It has been reported that expression and activity of its catalytic subunit (PP2Ac) is increased in T cells from patients with SLE. However, the study of IGBP1 in patients with SLE has not been examined. The objective of the present study was to determine IGBP1 levels in SLE patients and identify any correlations between IGBP1 levels with other clinical variables and especially, renal pathology in patients with LN.

Methods: The levels of IGBP1 were measured in plasma and urine of SLE patients with (n=40) or without (n=30) LN, and healthy subjects (n=18). Correlation analyses between IGBP1 levels and the diseases-related variables including c-reactive protein (CRP), erythrocyte sedimentation rate (ESR), anti-double-stranded DNA antibody (anti-dsDNA), and SLE Disease Activity Index (SLEDAI) were examined. In addition, to evaluate if IGBP1 can differentiate LN disease severity, we performed IGBP1 levels regarding classes of kidney biopsy samples and correlation analyses of plasma IGBP1 levels with activity index score or chronicity index score in renal biopsy samples.

Results: Plasma levels of IGBP1 in SLE patients were significantly higher in SLE patients with (8.48 ng/ml) or without (9.69 ng/ml) LN than in healthy individuals (4.90 ng/ml). Among the diseases-related variables, SLEDAI scores were significantly correlated with the levels of IGBP1 in plasma (p= 0.0429) and urine (p= 0.0011). Interestingly, LN patients with Class III and IV had higher IGBP1 levels compared to those of II and V groups. Further, plasma IGBP1 levels had a significant positive association with chronicity index score (p= 0.0072).

Conclusion: This study demonstrates that the levels of plasma and urinary IGBP1 were significantly higher in SLE patients and were correlated with disease activity and chronicity index score of renal pathology. Therefore, IGBP1 might be a valuable tool for determining high disease activity in SLE patients and more severe kidney damage in LN patients.

Disclosure: E. J. Lee, None; **S. Hong**, None; **D. H. Lim**, None; **Y. G. Kim**, None; **C. K. Lee**, None; **B. Yoo**, None.

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Abstract Number: 1851

Antibody Against Ribonuclease-H Is a Novel Autoantibody Specifically Recognized in Systemic Lupus Erhythematosus

Kazuhisa Nozawa[1], Kentaro Doe[2], Kaori Hiruma[3], Yusuke Yamada[4] and Yoshinari Takasaki[5], [1]2-1-1 Hongo Bunkyo-ku, Juntendo University, Tokyo, Japan, [2]2-1-1 Hongo, Bunkyo-Ku, Juntendo University School of Medicine, Tokyo, Japan, [3]Rheumatology, Juntendo University School of Medicine, Tokyo, Japan, [4]Department of Rheumatology, Juntendo University School of Medicine, Tokyo, Japan, [5]Department of Internal Medicine and Rheumatology, Juntendo University School of Medicine, Tokyo, Japan
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Background/Purpose:

Proliferating cell nuclear antigen (PCNA) is known to be an autoantigen specifically recognized in patients with SLE. PCNA constitutes PCNA-complex along with several PCNA-binding proteins in vivo. We have consecutively published that autoantibodies to PCNA-binding proteins are easily produced in SLE patients as well as autoantibody to PCNA itself. Furthermore, we have recently published the novel serum autoantibody to chromatine assembly factor-1(CAF-1), which belongs to the PCNA-binding proteins, might be an useful biomarker for neuropsychiatric (NP) SLE. Ribonuclease-H (RNase-H) also belongs to the PCNA-binding proteins and functions as a regulating factor for cell division in coordination with other PCNA-binding proteins such as CAF-1. Therefore, we assume that RNase-H will be a candidate of autoantigen specifically recognized in SLE and investigated the clinical association of anti-RNase-H antibody with SLE patients.

Methods:

Patients sera consisting of SLE (n=57), PM/DM (n=40), SSc (n=39), SS (n=28), MCTD (n=28), RA (n=29), and normal healthy controls (NHCs) (n=73)

were collected from serum bank of Juntendo University Hospital with their informed consent. Immunoreactivity against both RNase-H and CAF-1 recombinant antigens was evaluated by ELISA and was further confirmed by immunoblotting. The cut-off value designating a positive reaction in ELISA was defined as the mean value of NHCs +3 standard deviations.

Results:

Serum anti-RNase-H antibody was observed in 33% of SLE patients. The anti-RNase-H antibody was not recognized in both all control diseases and NHCs. Moreover, the coexistence of anti-RNase-H antibody and anti-U1 RNP antibody revealed high incidence of NPSLE. Moreover, titer of anti-RNase-H antibody was strongly correlated with titer of anti-CAF-1 antibody in regression analysis.

Conclusion:

In the present study, we identified anti-RNase-H antibody as a novel autoantibody specifically recognized in SLE. Measurement of anti-RNase-H antibody can be used for the diagnosis of SLE. Moreover, it might be a useful biomarker for NPSLE when anti-U1 RNP antibody coexists. The strong correlation in titer of anti-RNase-H and CAF-1 antibodies suggested that a breakdown of immune tolerance against component proteins of PCNA-complex lead to elicit autoimmune response to the other components of PCNA-binding proteins. This phenomenon is considered as epitope spreading which plays important role for the autoantibody production in SLE.

Disclosure: K. Nozawa, None; **K. Doe**, None; **K. Hiruma**, None; **Y. Yamada**, None; **Y. Takasaki**, None.

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Abstract Number: 1852

Association of Antibodies to the NR1 Subunit of N-Methyl-D-Aspartate Receptors with Neuropsychiatric Systemic Lupus Erythematosus

Eisuke Ogawa[1], Tatsuo Nagai[2], Yuko Sakuma[3], Yoshiyuki Arinuma[4] and Shunsei Hirohata[4], [1]Int Med/Rheumatol & Infec Dis, Kitasato University School of Medicine, Sagamihara, Japan, [2]Department of Rheumatology and Infectious Diseases, Kitasato University School of Medicine, Sagamihara, Japan, [3]Department of Rheumatology and Infectious Diseases, Kitasato University School of Medicine, Kanagawa, Japan, [4]Rheumatology and Infectious Diseases, Kitasato University School of Medicine, Kanagawa, Japan

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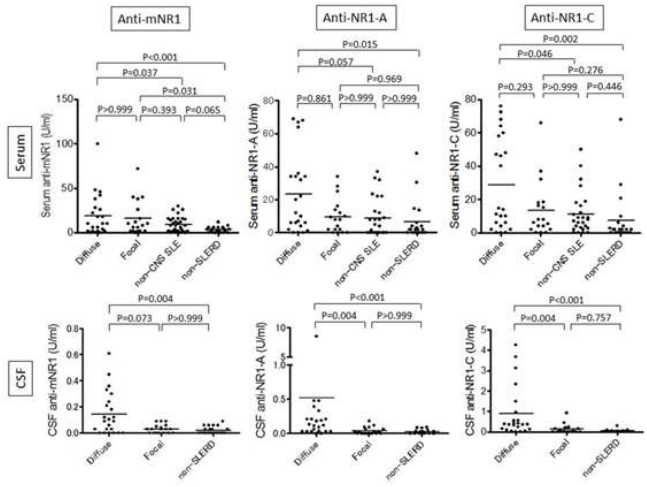
Background/Purpose: To explore the roles of autoantibodies to N-methyl-D-aspartate (NMDA) receptor NR1 subunit in the pathogenesis of neuropsychiatric systemic lupus erythematosus (NPSLE).

Methods: Paired serum and CSF specimens were obtained from 41 patients with NPSLE (22 with diffuse psychiatric/neuropsychological syndromes [diffuse NPSLE] and 19 with neurologic syndromes or polyneuropathy [focal NPSLE]), 21 patients with various rheumatic diseases other than SLE (non-SLERD). Sera were also obtained from 27 SLE patients without neuropsychiatric manifestations (non-CNS SLE). Antibodies to murine NR1 (mNR1) or to 4 different preparations of synthetic 25-amino-acid (AA) peptides of human NR1 were measured by ELISA.

Results: Serum anti-mNR1 levels were significantly higher in NPSLE than in non-SLERD. Sera from NPSLE patients bound efficiently to the AA residues 19-44 from the N-terminus of NR1 (NR1-A) or 57-81 (NR1-C), but not to the AA residues 37-62 (NR1-B) or 75-100 (NR1-D). Accordingly, serum anti-NR1-A and anti-NR1-C were also elevated in NPSLE compared with non-SLERD, although there was no difference between diffuse NPSLE and focal NPSLE. By contrast, CSF anti-NR1-A as well as CSF anti-NR1-C levels were significantly elevated in diffuse NPSLE compared with focal NPSLE or with non-SLERD. Finally, both anti-NR1-A and anti-NR1-C bound to the surface of SK-N-MC cells.

Conclusion: These results demonstrate that autoantibodies to NMDA receptor NR1, especially to the AA residues 19-44 and the AA residues 57-81 from the N-terminus are expressed in NPSLE. Moreover, the data also indicate that anti-NR1-A and anti-NR1-C play a pivotal role in the pathogenesis of diffuse NPSLE.



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Abstract Number: 1853

Binding of a Novel IgG3 VH4-34 Monoclonal Antibody to ssRNA in SLE

Asiya Chida[1], Kevin Cashman[1], Scott Jenks[2], Louise Hartson[1], Youliang Wang[1], Quan-Zhen Li Li[3,4], Chandra Mohan[5] and Ignacio Sanz[6,7], [1]Medicine, Emory University, Atlanta, GA, [2]Rheumatology, Emory University School of Medicine, Atlanta, GA, [3]Immunology, University of Texas Southwestern Medical Center, Dallas, TX, [4]Department of Immunology and Microarray Core Facility, University of Texas Southwestern Medical Center, Dallas, TX, [5]Biomedical Engineering, University of Houston, Houston, TX, [6]Rheumatology, Emory University, Atlanta, GA, [7]Medicine/Rheumatology, Emory University, Atlanta, GA

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Background/Purpose: IgG antibodies expressing the idiotope for the 9G4 idiotype, the framework-1 hydrophobic patch (HP) of VH4-34, are expanded in SLE and provide a unique model to understand the participation of different autoantigens in the regulation of this disease. In particular the antibodies to single stranded RNA (ssRNA) have been implicated in viral infections in SLE. Here, we sought to understand the contribution of VH4-34 antibodies that bind to ssRNA in the pathogenesis of SLE.

Methods:

A panel of 9G4 + monoclonal antibodies (mabs) was generated from IgD+ CD27- naïve B cells and IgD-CD27+ memory B cells of SLE patients. A total of 30 monoclonal antibodies, (20 native antibodies and corresponding HP altered mutants) were tested for anti-ssRNA binding by ELISA. Two representative antibodies with strong ssRNA reactivity were also tested against a proteome auantigen microarray and by immunofluorescence.

Results:

Out of the 30 mabs with diverse antigenic binding patterns, 2 derived from SLE memory B cells (22%) had strong autoreactivity with ssRNA. These antibodies also bound other Ags including: apoptotic and B cell binding, dsDNA, chromatin, Ribosomal P, and were also positive for ssRNA. These two antibodies were of the IgG3 subclass and were clonally related with a single amino acid difference within the CDR2, and identical CDR3 regions of the heavy chain. Further, the corresponding 9G4- HP mutant of these two abs showed binding to ssRNA albeit with decreased intensity.

Conclusion:

Our preliminary results suggest that the anti-RNA response may be abundant in SLE memory B cells and mediated by expanded clones with a predominance of IgG3 antibodies. 9G4 mutagenesis experiments indicate that, while the HP may influence binding is not determinant of this type of autoreactivity. These findings are consistent with the lack of ssRNA binding of naïve antibodies and suggests that such autoreactivity is dependent on the conventional antigen binding site and may require somatic hypermutation. Larger studies will be required to understand the structural basis, generation and selection of ssRNA antibodies in SLE. Such studies will shed light into the role of exogenous and endogenous RNA antibodies to SLE autoreactivity.

This work was supported in part by the following grants from National Institute of Health (NIH): NIH-NIAID: 5R37AI049660-12; NIH-NIAID ACE U19:

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Abstract Number: 1854

Identification and Characterization of microRNAs Related to the Pathogenesis of Cardiovascular Disease in Patients with Antiphospholipid Syndrome and Systemic Lupus Erythematosus. Role of Specific Autoantibodies

Chary Lopez-Pedrera[1], Maria Ángeles Aguirre Zamorano[1], Patricia Ruiz-Limon[1], Nuria Barbarroja[1], Yolanda Jiménez Gómez[1], Eduardo Collantes-Estevez[1], Mª Jose Cuadrado[2], Rocio Gonzalez-Conejero[3], Constantino Martinez[3] and Carlos Perez-Sanchez[1], [1]IMIBIC-Reina Sofia University Hospital, Rheumatology Unit, Cordoba, Spain, [2]Lupus Research Unit, The Rayne Institute, St Thomas' Hospital, London, United Kingdom, [3]Regional Centre for Blood Donation, University of Murcia, Murcia, Spain

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Background/Purpose:

1) To identify and characterize miRNAs related to the pathogenesis of CVD in antiphospholipid syndrome (APS) and systemic lupus erythematosus (SLE) patients; 2) To evaluate the effect of specific autoantibodies in the regulation of miRNAs related to the pro-atherothrombotic status in both disorders.

Methods:

In silico searching allowed the identification of a number of miRNAs involved in the regulation of atherothrombosis. Six miRNAs (miR-124a, -125a, -125b, -146a, -155, and -222) were selected and quantified by RT-PCR in leukocytes from 20 APS and 43 SLE patients, and 28 healthy donors. Pro-inflammatory and prothrombotic proteins and oxidative stress markers were evaluated by flow cytometry. Proteins related to the biogenesis of miRNAs were quantified by RT-PCR and Western Blot. The clinical cardiovascular disease (CVD) profile was further recorded in APS and SLE patients.

Monocytes and neutrophils isolated from healthy donors were treated with anticardiolipin IgG isotype (ACA-IgG) and anti-dsDNA antibodies purified from APS and SLE patients' serum, respectively, or with IgG from healthy donors (IgG -NHS). Levels of selected miRNAs and their target molecules were determined. Expression of proteins involved in miRNAs biogenesis (Drosha, Dicer, Ago-1, Ago-2 and 2, and Xpo-5) were further analyzed. Transfections were performed with precursors of the miRNAs found altered, to identify key target proteins in both pathologies.

Results:

The expression levels of the selected miRNAs in neutrophils were significantly lower in APS and SLE than in the control group. Accordingly, gene and protein expression levels of molecules related to miRNA biogenesis were reduced in neutrophils from APS and SLE. In monocytes, miR124a and -125a were low in APS and SLE patients, while miR-146a and miR-155 appeared elevated. Correlation studies showed, in both pathologies, that the altered expression of all selected miRNAs correlated with the disease activity index, and parameters related to autoimmunity, thrombosis, inflammation and oxidative stress. Association studies showed that the occurrence of thrombotic events and the presence of a pathological increase of carotid intima media thickness were also linked to the altered levels of the measured miRNAs. The expression levels of all miRNAs were significantly reduced in neutrophils treated with ACA-IgG and anti-dsDNA compared to those treated with IgG-NHS. Both autoantibodies also decreased the expression of proteins related to miRNA biogenesis in these cells. In monocytes, treatment with ACA-IgG and anti-dsDNA significantly reduced the levels of miR-124a and miR-125b, as well as increased miR-146a and miR-155 expression. Monocyte transfections with pre-miR-124a and miR-125a, either separately or simultaneously, caused a drop in the expression of target molecules related to the atherothrombotic process in APS and SLE.

Conclusion: 1. Specific miRNAs might act as potential biomarkers of atherothrombosis in APS and SLE patients. 2. Some autoantibodies regulate this atherothrombotic status, at least partially, through epigenetic mechanisms such as modulation of miRNAs. Supported by CTS-7940, PI12/01511, SER.

Disclosure: **C. Lopez-Pedrera**, None; **M. Aguirre Zamorano**, None; **P. Ruiz-Limon**, None; **N. Barbarroja**, None; **Y. Jiménez Gómez**, None; **E. Collantes-Estevez**, None; **M. J. Cuadrado**, None; **R. Gonzalez-Conejero**, None; **C. Martinez**, None; **C. Perez-Sanchez**, None.

Abstract Number: 1855

Systemic Lupus Erythematosus Exosomes Contain Distinct RNA Transcripts That Differentiate

Disease Activity and Modulate Cellular Function

Samantha Slight-Webb[1], Krista M. Bean[1], Nicolas Dominguez[1], Mikhail G. Dozmorov[2], Judith A. James[3] and Joel M. Guthridge[1], [1]Arthritis and Clinical Immunology, Oklahoma Medical Research Foundation, Oklahoma City, OK, [2]Arthritis and Clincial Immunology Research Program, Oklahoma Medical Research Foundation, Oklahoma City, OK, [3]Arthritis & Clinical Immunology Research Program, Oklahoma Medical Research Foundation, Oklahoma City, OK

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Background/Purpose: Systemic lupus erythematosus (SLE) is a complex autoimmune disease involving multiple organ systems and periods of waxing and waning disease activity. The lack of well-defined disease biomarkers to predict disease flares hinders therapeutic optimization. Exosomes are secreted intraluminal vesicles involved in cell-cell communication and can be sampled from patients using minimally invasive methods. By identifying the role of exosomes in driving SLE disease activity, early biomarkers of flare and disease specific pathways can be identified.

Methods: Exosomes were isolated from plasma of healthy controls (n=10) and SLE patients with either elevated disease activity (SLEDAI≥6; n=5; SLE-hi) or low disease activity (SLEDAI≤4; n=7; SLE-lo) using Exoquick Isolation Reagent (SBI). Total RNA from plasma exosomes were extracted and purified using SBI's Seramir Kit and libraries were constructed using a modified Illumina adapter method and sequenced on an Illumina MiSeq v3 instrument. Cleaned sequences were filtered and sequences with lengths ≥18 nt were aligned using Bowtie 2 against the human genome reference sequences. Hairpin and mature miRNA sequence hits were identified using BLAST in MiRBase. BLAST searches for transkingdom RNAs with known associations in SLE were also performed. Differentially expressed genes were determined using DESeq2 R package. Characterization of exosome size and quantity was determined by electron microscopy and EXOCET Assay (SBI), respectively. Further, isolated exosomes from SLE-hi and SLE-lo disease activity patients and healthy controls were co-cultured with healthy control PBMCS for 48 hours and cellular activation and cytokine production of PBMCs was measured by flow cytometry and ELISA.

Results: SLE-hi patient exosomes had an increased median size (mdn 115.5nm) compared to SLE-lo patients (mdn 103.0nm) ($p<0.0001$), however, the abundance of exosomes did not differ between SLE disease activity or healthy controls (mdn $1.4x10^{12}$/ml). Exosome RNA libraries from SLE-hi patients had significantly more raw and clean RNA reads compared to healthy controls ($p<0.0082$) and SLE-lo patients ($p<0.05$). Further, SLE patients had 77 differentially expressed transcripts compared to healthy controls and 28 differentially expressed transcripts between high and low SLE disease activity ($p<0.05$) including Y RNAs and those associated with Epstein-Barr virus, transcriptional and post-transcriptional regulation, cytokinesis and apoptosis. Interestingly, when exosomes from SLE patients were incubated with healthy control PBMCs, SLE exosomes activated more CD4+ T cells ($p=0.0196$) and monocytes ($p=0.0294$). Further, PBMCs treated with SLE-hi exosomes produced greater amounts of IL-6 ($p<0.05$), but significantly reduced amounts of IL-10 ($p<0.005$) compared to PBMCs treated with exosomes from SLE-lo patients.

Conclusion: Our findings suggest that exosomes from active SLE patients have distinct characteristics and components that contribute to immune cell activation, inflammatory cytokine production, and impaired regulatory cytokine production which may contribute to lupus disease pathogenesis and activity.

Disclosure: S. Slight-Webb, None; **K. M. Bean**, None; **N. Dominguez**, None; **M. G. Dozmorov**, None; **J. A. James**, None; **J. M. Guthridge**, None.

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Abstract Number: 1856

Exosomes from Patients with Active Systemic Lupus Erythematosus Induce a Strong Inflammatory Response

Joo Youn Lee[1], Jin Kyun Park[1,2], Eun Young Lee[3], Eun Bong Lee[3] and Yeong Wook Song[1,2], [1]Department of Molecular Medicine and Biopharmaceutical Sciences, Graduate School of Convergence Science and Technology and College of Medicine Seoul National University, Seoul, South Korea, [2]Division of Rheumatology, Department of Internal Medicine, Seoul National University, Seoul, South Korea, [3]Division of Rheumatology, Department of Internal Medicine, Seoul National University Hospital, Seoul, South Korea

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Background/Purpose: Exosomes are 60–150 nm membrane vesicles that are secreted by various cells into surrounding body fluids including blood and urine. As vehicles for intercellular communication, they are involved in immune cell activation. To date, the role of exosomes in pathogenesis of systemic

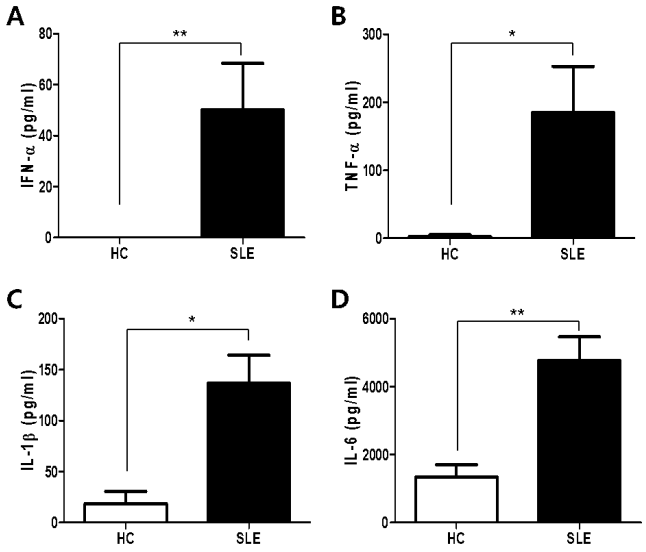
lupus erythematosus (SLE) hasve not been fully elucidated. This study was aimed to investigate as to whether exosome formation is increased and whether they effectively contribute to proinflammatory cytokine response in patients with SLE.

Methods: Serum samples from SLE patients, rheumatoid arthritis (RA) patients and healthy controls were obtained at Seoul National University Hospital. Exosomes were isolated from sera using ExoQuick and quantified using EXOCET. Healthy peripheral blood mononuclear cells (PBMCs) were stimulated with exosomes from SLE patients, RA patients or healthy controls. After 24 hours, production of interferon (IFN)-a, interleukin (IL)-1b, IL-6, and tumor necrosis factor (TNF)-a were measured using ELISA. Correlation between SLE disease activity index (SLEDAI) and exosome levels was assessed by Spearman correlation.

Results: The purified exosomes were 60-150nm in size and had a membrane bilayer on electron microscopy. Exosomes from SLE induced healthy PBMCs to produce high levels of IFN-a, IL-1b, IL-6, and TNF-a, whereas exosomes derived from RA patients or healthy controls did not (Figure 1). Exosome-depleted SLE serum and SLE exosomes that were mechanically disrupted fail to elicit any significant proinflammatory cytokine production. The serum levels of exosomes were significantly higher in SLE patients than healthy controls ($21.13x10^7 \pm 3.711 x10^7$ *vs*. $110.4 x10^7 \pm 20.62 x10^7$, p=0.037) and their levels correlated with SLEDAI in patients with SLE (r=0.3663, p=0.0371).

Conclusion: These data suggest that exosomes are generated and they contribute to proinflammatory response in patients with SLE. Exosomes might serve as a novel biomarker of disease activity. Treatment targeting exosome might offer a new therapeutic option.

Figure 1. Production of proinflammatory cytokines IFN-a (A), TNF-a(B), IL-1b (C), and IL-6 (D) by the healthy PBMCs after stimulation with exosomes from HC or SLE patients. Data are presented as the mean±SEM. * $p<0.05$; ** $p<0.01$



Disclosure: J. Y. Lee, None; **J. K. Park**, None; **E. Y. Lee**, None; **E. B. Lee**, None; **Y. W. Song**, None.

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Abstract Number: 1857

Identification of the Long Noncoding RNA NEAT1 As a Novel Inflammatory Regulator Acting through MAPK Pathway in Human Lupus

Yuanjia Tang[1], Feifei Zhang[2], Bo Qu[3] and Nan Shen[4], [1]Shanghai Institute of Rheumatology, Renji Hospital,Shanghai JiaoTong University School of Medicine, Shanghai, China, [2]Institute of Health Sciences, Shanghai Institutes for Biological Sciences (SIBS), Chinese Academy of Sciences (CAS) & Shanghai Jiao Tong University School of Medicine (SJTUSM), Shanghai, China, Shanghai, China, [3]Shanghai Institute of Rheumatology,Renji Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China, [4]The Center for Autoimmune Genomics and Etiology (CAGE),Cincinnati Children's Hospital Medical Center,Cincinnati, Ohio, United States of America, Cincinnati, OH

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Background/Purpose: Long noncoding RNAs (lncRNAs) have recently been identified to be tightly linked to diverse human diseases. This study was

undertaken to investigate the contribution of the lncRNA NEAT1 which was identified to be involved in innate immune response to the pathogenesis of Systemic Lupus Erythematosus (SLE)

Methods: RT-PCR was used to compare NEAT1 expression between SLE patients and controls. Stimulation and transfection in THP-1 cells were conducted to determine the biologic function of NEAT1. Microarray and Western Blotting were performed to investigate in which pathway NEAT1 was involved. Correlation between NEAT1 expression and the disease activity of SLE patients was evaluated.

Results: NEAT1 expression was abnormally increased in the peripheral blood mononuclear cells (PBMCs) of SLE patients. We sorted the main three subsets of PBMCs (T cells, B cells, Monocytes), then compared the NEAT1 expression between SLE patients and healthy donors in these cell subsets in details and respectively. It was showed NEAT1 dominantly expressed in monocytes and was significantly up-regulated in monocytes of SLE patients compared with normal controls. Additionally, NEAT1 expression was induced by LPS via p38 activation in THP-1, the monocytic cell lines. We wondered whether or not NEAT1 would be involved in regulation of LPS-triggered induction of numerous inflammatory factors and found silencing NEAT1 significantly reduced the expression of a group of chemokines and cytokines, including IL-6, CXCL10, etc., which were induced by LPS continuously and in late stages. Furthermore, it was identified that NEAT1 selectively regulates LPS continuously-induced and late-response genes mainly through affecting the activation of the late MAPK pathway, especially the activation of JNK and ERK. Importantly, it was observed that in SLE patients, the overexpressed NEAT1 level correlates positively with the disease activity and NEAT1-regulated cytokines and chemokines.These indicate NEAT1 may be a potential contributor to the pathogenesis of lupus patients.

Conclusion: NEAT1 regulates a subset of LPS-induced inflammatory factors through affecting the activation of MAPK signaling pathway. The increased NEAT1 expression may be a potential contributor to the elevated production of a number of cytokines and chemokines in SLE patients. Our findings suggest lncRNA contributes to the pathogenesis of lupus and provides potential novel target for therapeutic intervention.

Disclosure: Y. Tang, None; **F. Zhang**, None; **B. Qu**, None; **N. Shen**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/identification-of-the-long-noncoding-rna-neat1-as-a-novel-inflammatory-regulator-acting-through-mapk-pathway-in-human-lupus

Abstract Number: 1858

Serum Tartrate Resistant Acid Phosphatase (TRAP) Levels Are Decreased and Associated with Anti-Maa Antibodies in Systemic Lupus Erythematosus (SLE) Patients

Kathleen Borghoff[1], Andy Hollins[2], Michael J. Duryee[1], Ted R. Mikuls[2], Zhixin Zhang[3], Kaihong Su[4], Michelene Hearth-Holmes[5] and Geoffrey M. Thiele[6], [1]Internal Medicine Division of Rheumatology, University of Nebraska Medical Center, Omaha, NE, [2]University of Nebraska Medical Center, Omaha, NE, [3]Department of Pathology and Microbiology, University of Nebraska Medical Center, Omaha, NE, [4]Pathology and Microbiology, University of Nebraska Medical Center, Omaha, NE, [5]Division of Rheumatology, University of Nebraska College of Medicine and VA Nebraska Western Iowa Health Care System, Omaha, NE, [6]Omaha VA Medical Center and University of Nebraska Medical Center, Omaha, NE

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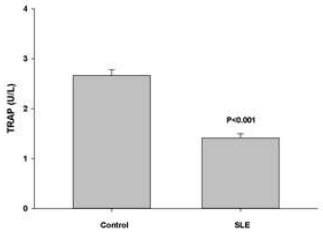
Background/Purpose: Previous studies have shown that patients with systemic lupus erythematosus (SLE) are prone to systemic osteoporosis, bone loss and fracture. Paradoxically, previous studies have shown that inflammation in these patients causes the inhibition of ostoclastogenesis. Recently, serum antibodies to Malondialdehyde-Acetaldehyde (MAA) antibodies have be found in SLE patients. However, their role in disease process has not be determined. Therefore, it was the purpose of this study to explore the role of bone markers in SLE and their interaction with antibodies to MAA modified proteins.

Methods: Eighty-eight SLE patients, all satisfying ACR classification criteria, and 92 controls were examined. Serum antibody levels were measured by enzyme-linked immunosorbent assay (ELISA) for levels of IgG, IgA, and IgM anti-MAA antibodies specific to the MAA epitope, TRAP and BAP. Pearson correlation coefficients were used to examine associations of bone markers with MAA antibodies.

Results: Bone markers were assessed and revealed a decrease in TRAP levels in the SLE cohort (1.41 U/L) as compared to the controls (2.67 U/L) ($P<0.001$) (Figure 1). BAP levels remained unchanged between the two groups. Bone markers were compared to serum IgA, IgG, and IgM anti-MAA levels and showed associations with IgM anti-MAA levels and TRAP ($R=0.273$, $P<0.01$). There were no associations with BAP demonstrated in the study.

Conclusion: These data show that patients with SLE have significantly lower TRAP levels as compared to controls. This decrease could be related to the inhibition of osteoclastogenesis shown in other studies. In addition, TRAP concentrations were associated with anti-MAA IgM levels consistent with the increased inflammatory burden that characterizes SLE. These data may be useful in helping predict disease status in patients with SLE. More work needs to be done to determine other bone markers and their role in SLE.



Disclosure: **K. Borghoff**, None; **A. Hollins**, None; **M. J. Duryee**, None; **T. R. Mikuls**, None; **Z. Zhang**, None; **K. Su**, None; **M. Hearth-Holmes**, None; **G. M. Thiele**, None.

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Abstract Number: 1859

Anti-Interferon Autoantibodies in Systemic Lupus Erythematosus Are Biologically Active and Have Distinct Functions

Sarthak Gupta[1,2], Ioanna P. Tatouli[3], Lindsey B. Rosen[1], Sarfaraz Hasni[2], Illias Alevizos[4], Zerai G. Manna[2], Juan Rivera[2], Chao Jiang[2,5], Richard M. Siegel[6], Steven M. Holland[1], Haralampos M. Moutsopoulos[3] and Sarah K. Browne[1,7], [1]Laboratory of Clinical Infectious Diseases, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD, [2]National Institute of Arthritis and Musculoskeletal and Skin Diseases, National Institutes of Health, Bethesda, MD, [3]Department of Pathophysiology, School of Medicine, National University of Athens, Athens, Greece, [4]National Institute of Dental and Craniofacial Research, National Institutes of Health, Bethesda, MD, [5]National Center for Complementary and Alternative Medicine, National Institutes of Health, Bethesda, MD, [6]NIAMS, Immunoregulation Section, Autoimmunity Branch, Bethesda, MD, [7]Office of Vaccines Research and Review, Center for Biologics Evaluation and Research, US Food and Drug Administration, Silver Spring, MD

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Background/Purpose:

Anticytokine autoantibodies are pathogenic in many hematologic, pulmonary and infectious diseases. However, a systematic investigation of their presence and significance in autoimmune diseases is lacking.

Methods:

Serum samples from patients with systemic lupus erythematosus (SLE) (n=199), primary Sjšgren's syndrome (SS) (n=150) and rheumatoid arthritis (RA) (n=149) were compared to healthy controls (n=200) for autoantibodies against 24 cytokines using a multiplex bead-based assay. All patients fulfilled ACR classification criteria for their respective diseases. Any anticytokine autoantibody concentration above two standard deviations of the mean of healthy controls for the same target was classified as positive. Biological activity was evaluated by the ability of sera to block cytokine-induced signal transduction or protein expression. RNA sequencing was performed on whole blood in a subset of controls and SLE patients.

Results:

SLE and SS patients had a disproportionate presence of autoantibodies against interferons (IFNs) as well as the IFN-responsive chemokine IFN-inducible-protein-10 (IP-10) (Table. 1). Autoantibodies against type I IFN, IL-12 and IL-22 were neutralizing. In SLE, anti-IFN-γ autoantibodies tracked with increased disease activity, anti-double-stranded-DNA antibodies, and elevated expression of IFN-α/β-inducible genes (Table 2 and Figure 1). Conversely, SLE patients with blocking anti-IFN-α autoantibodies normalized their type I IFN gene signature. Autoantibodies were observed against macrophage-colony stimulating factor, IL-4, IL-7, IL-17 and IL-22, which had not been previously identified in the context of rheumatologic disease. Novel anti-type III IFN (λ2, λ3) and anti-IP-10 autoantibodies were detected.

Conclusion:

Anticytokine autoantibodies are a common feature of autoimmune diseases and extend to more cytokines than previously appreciated. Patterns of anticytokine autoantibodies appeared to be specific to each disease. In particular, anti-IFN autoantibodies were overrepresented in SLE and SS. Autoantibodies against type I and type II IFNs in SLE are biologically active and appear to have distinct functional roles, suggesting a contribution to disease pathogenesis that may alter both expression and the course of clinical disease.

Table 1: Distribution of Anticytokine Autoantibodies in Rheumatologic Diseases.

	SLE (199) N (%)	SS (150) N (%)	RA (149) N (%)
Total Positive	76 (38%)	63 (42%)	30 (20%)
Anti-G-CSF	1 (0.5%)	6 (4%)	0 (0%)
Anti-GM-CSF	6 (3%)	9 (6%)	3 (2%)
Anti-M-CSF	6 (3%)	6 (4%)	1 (0.7%)
Anti-TNF	3 (1.5%)	3 (2%)	2 (1.3%)**
Anti-LTα	4 (2%)	9 (6%)	2 (1.3%)**
Anti-IFNα	**12 (6%)***	**5 (3.3%)***	1 (0.7%)
Anti-IFNβ	**10 (5%)***	**7 (4.7%)***	3 (2%)
Anti-IFNω	**7 (3.5%)***	**8 (5.3%)***	1 (0.7%)
Anti-IFNγ	14 (7%)	14 (9.3%)	1 (0.7%)
Anti-IFNλ1	9 (4.5%)	6 (4%)	5 (3.4%)
Anti-IFNλ2	3 (1.5%)	2 (1.3%)	2 (1.3%)
Anti-IFNλ3	4 (2%)	4 (2.7%)	4 (2.7%)
Anti-IL-1α	7 (3.5%)	9 (6%)	8 (5.4%)
Anti-IL-4	13 (6.5%)	7 (4.7%)	2 (1.3%)
Anti-IL-6	6 (3%)	6 (4%)	2 (1.3%)
Anti-IL-7	7 (3.5%)	2 (1.3%)	2 (1.3%)
Anti-IL-10	6 (3%)	4 (2.7%)	2 (1.3%)
Anti-IL-12	**10 (5%)***	**9 (6%)***	10 (6.7%)
Anti-IL-15	5 (2.5%)	4 (2.7%)	1 (0.7%)
Anti-IL-17A	2 (1%)	5 (3.3%)	0 (0%)
Anti-IL-17F	7 (3.5%)	4 (2.7%)	3 (2%)
Anti-IL-18	5 (2.5%)	4 (2.7%)	1 (0.7%)
Anti-IL-22	9 (4.5%)	**6 (4%)***	1 (0.7%)
Anti-IP-10	17 (8.5%)	15 (10%)	1 (0.7%)

* Blocking autoantibodies detected
** Patients who received anti-TNF biologics were analyzed as anti-TNF or anti-LTα negative
G-CSF: granulocyte-colony stimulating factor; GM-CSF: granulocyte monocyte-colony stimulating factor; M-CSF: macrophage-colony stimulating factor; TNF: tumor necrosis factor; LTα: lymphotoxin-α; IFN: interferon; IL: interleukin; IP-10: interferon-inducible-protein-10

Table 2: Association Between Disease Activity Indices and Presence of Anti-interferon Autoantibodies in SLE Patients

	Any anti-interferon aab negative (n=148)	Any anti-interferon aab positive (n=43)	p-value#
SLEDAI Score, median (range)	0 (0-33)	2 (0-18)	0.0075*
Low complements (C3, C4), n (%)	35 (23.8)	19 (44.2)	0.0092*
Increased anti-dsDNA, n (%)	41 (27.7)	25 (58.1)	0.0002*

	Any anti-interferon-α aab negative (n=179)	Any anti-interferon-α aab positive (n=12)	p-value#
SLEDAI Score, median (range)	1 (0-33)	2 (0-4)	0.8334
Low complements (C3, C4), n (%)	29 (29.2)	2 (16.7)	0.5142
Increased anti-dsDNA, n (%)	35 (33.0)	7 (41.7)	0.0736

	Any anti-interferon-β aab negative (n=181)	Any anti-interferon-β aab positive (n=10)	p-value#
SLEDAI Score, median (range)	1 (0-33)	2.5 (0-8)	0.1597
Low complements (C3, C4), n (%)	49 (27.2)	5 (50.0)	0.1201
Increased anti-dsDNA, n (%)	60 (33.3)	6 (60.0)	0.0967

	Any anti-interferon-ω aab negative (n=184)	Any anti-interferon-ω aab positive (n=7)	p-value#
SLEDAI Score, median (range)	1.5 (0-33)	2 (0-4)	0.4868
Low complements (C3, C4), n (%)	53 (28.8)	1 (14.3)	0.6752
Increased anti-dsDNA, n (%)	62 (33.7)	4 (57.1)	0.2370

	Anti-interferon-γ aab negative (n=177)	Anti-interferon-γ aab positive (n=14)	p-value#
SLEDAI Score, median (range)	1 (0-33)	4 (0-18)	0.0022*
Low complements (C3, C4), n (%)	47 (26.7)	7 (50)	0.0629
Increased anti-dsDNA, n (%)	55 (31.1)	11 (78.6)	0.0003*

 # p-values calculated using Wilcoxon-Mann-Whitney test or Fisher's exact test
SLEDAI: Systemic Lupus Erythematosus Disease Activity Index
anti-dsDNA: anti-double-stranded-DNA
aab: autoantibody
Low complements was defined as C3<80 mg/dl or C4<15 mg/dl and high anti-dsDNA antibody defined as >30 IU/mL.

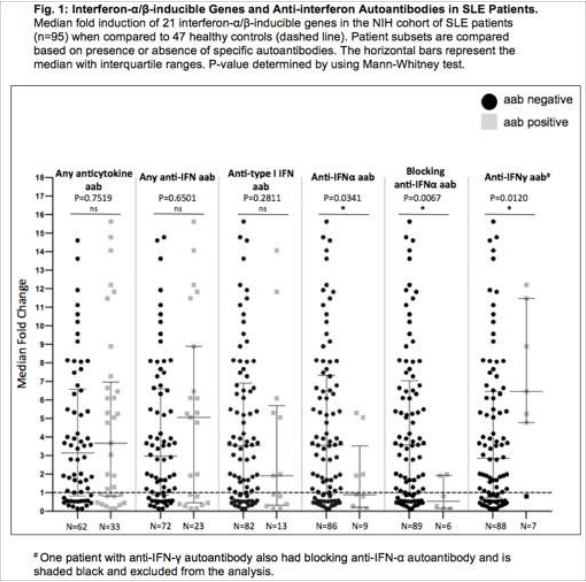

Fig. 1: Interferon-α/β-inducible Genes and Anti-interferon Autoantibodies in SLE Patients. Median fold induction of 21 interferon-α/β-inducible genes in the NIH cohort of SLE patients (n=95) when compared to 47 healthy controls (dashed line). Patient subsets are compared based on presence or absence of specific autoantibodies. The horizontal bars represent the median with interquartile ranges. P-value determined by using Mann-Whitney test.

One patient with anti-IFN-γ autoantibody also had blocking anti-IFN-α autoantibody and is shaded black and excluded from the analysis.

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Abstract Number: 1860

Autoantibodies Utilizing the Immunoglobulin Heavy Chain Variable Region Gene 4-34 (VH4-34) Exhibit Autoreactivity Towards, and Potential Competition with Galectins within Systemic Lupus Erythematosus (SLE)

Kevin Cashman[1], Asiya Chida[2] and Ignacio Sanz[2], [1]Department of Medicine- Division of Rheumatology, Emory University, Atlanta, GA, [2]Medicine, Emory University, Atlanta, GA

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Background/Purpose:

Systemic lupus erythematosus (SLE) is an autoimmune disorder characterized by the propagation of autoreactive B cell populations leading to the production of pathogenic antibodies directed towards self antigens such as: nuclear antigens, cytokines, and dsDNA. However, this autoreactive B cell expansion within SLE patients is not uniform suggesting specific antigen selection, and skews the antibody repertoire. One such expansion is in antibodies encoded by the VH4-34 gene. This antibody family has been shown to enrich for binding to autoantigens such as dsDNA, and can be uniquely examined due to the expression of the idiotope specific for the 9G4 idiotypic antibody. 9G4+ antibodies are unique in that the VH region expresses a hydrophobic patch (HP)(which acts as the 9G4 idiotope) within the framework 1 region of the heavy chain, which allows for antigen binding independent of the CDR3. This HP is what dictates binding to erythrocytes through interactions with N-acteyllactosamine glycans. Additionally, a secreted glycan binding protein family, the galectins, is also increased within SLE patients and has been shown to bind to many of the same antigenic targets as 9G4+ antibodies. Interestingly, SLE patients exhibit autoantibodies (autoAbs) against galectins, strongly suggesting an importance for galectin autoreactivity and a possible interaction between VH4-34 autoAbs and galectins. The purpose of this study is to understand this role between VH4-34 encoded Ig and galectin binding and/or competition in context of the pathogenesis of SLE.

Methods:

ELISA was utilized to assess total IgG and 9G4-specific anti-galectin autoAb levels of varying galectin family members within the sera of 16 SLE patients and healthy controls (HC). Single-cell sorts of 9G4+ IgG B cell populations followed by monoclonal antibody (mAb) expression and site directed mutagenesis (SDM) of the VH4-34 HP generated pairs of antibodies that could be independently tested for galectin binding either dependent or independent of the HP.

Results:

The VH4-34 gene segment encoded a significant portion of the total galectin-3 autoAbs directed against recombinant human galectins (50% of SLE patients were anti-Galectin-3 positive). Galectin-1 and galecin-9 autoAb titers showed no such relationship however there was 9G4 autoreactivity in 6.25% and 18.75% of SLE patients respectively, and no 9G4+ anti-galectin reactivity within the HC group. There was no correlation of anti-galectin autoAbs and SLEDAI. Two mAb derived from a pool of 20 (6.67%) 9G4+ mAbs and their SDM mutants tested, were cross-reactive between both galectin-1 and galectin-9. This interaction was also determined to be a result of the CDR3 and not the HP.

Conclusion:

These data determine a novel antigen specific interaction between 9G4+ Ig and certain galectins. Understanding how these interactions interfere with galectin biology will be useful in determining the physiologic cost of this relationship within SLE. The derivation of anti-galectin 9G4+ mAb, which binds through the CDR3, suggests galectins to be potent autoantigens. *Work supported by NIH-NIAID 5R37AI049660-12*

Disclosure: K. Cashman, None; **A. Chida**, None; **I. Sanz**, None.

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Abstract Number: 1861

Anti-Ds-DNA Antibodies Regulate Atherothrombosis in Systemic Lupus Erythematosus through the Induction of Netosis and the Prothrombotic and Proinflammatory Activities of Monocytes

Carlos Perez-Sanchez[1], M.Ángeles Aguirre Zamorano[1], María Galindo[2], Patricia Ruiz-Limon[1], Nuria Barbarroja[1], Yolanda Jiménez Gómez[1], Pedro Segui[3], Eduardo Collantes-Estevez[1], Mª Jose Cuadrado[4] and Chary Lopez-Pedrera[1], [1]IMIBIC-Reina Sofia University Hospital, Rheumatology Unit, Cordoba, Spain, [2]Department of Rheumatology. Hospital Universitario 12 de Octubre, Madrid, Spain, [3]IMIBIC-Reina Sofia University Hospital, Radiology Unit, Cordoba, Spain, [4]Lupus Research Unit, St Thomas Hospital, London, United Kingdom
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Background/Purpose: Atherothrombosis in systemic lupus erythematosus (SLE) has been related to the combined effects of autoimmune elements and cells of the immune system, where monocytes play an essential role. Different monocyte subsets with distinct patho-physiological actions have been described in cardiovascular disease (CVD). Netosis suffered by neutrophils in SLE might further contribute to the development of inflammatory and thrombotic processes. Aim: 1. To analyse in vivo the involvement of different leukocyte subsets and netosis in the development of CVD in SLE patients. 2. To evaluate in vitro the role of anti-dsDNA antibodies in these processes.

Methods: The study was conducted in 23 SLE patients and 10 healthy donors. Endothelial function was assessed by measuring the post-occlusive hyperaemia using Laser-Doppler. Monocyte subsets (MON1: CD14+/CD16-, MON2: CD14+/CD16+; MON3: CD14dim/CD16+) were characterized by flow cytometry. Classical (CD14+) and non-classical (MON2/MON3, CD16+) monocytes were purified using immuno-magnetic selection. Various markers of oxidative stress, inflammatory cytokines and prothrombotic mediators were quantified. In purified neutrophils, levels of oxidative stress and elastase were analyzed, as well as the percentage of netosis after labeling with Sytox. Purified neutrophils and monocytes from healthy donors were treated in vitro with anti-dsDNA antibodies isolated from the serum of SLE patients, and markers of inflammation, thrombosis, oxidative stress and NETosis were evaluated.

Results: SLE patients showed impaired micro-vascular endothelial function (reduction of hyperaemia post occlusion area) and increased plasma levels of pro-inflammatory proteins (IL6, IL8, MCP-1 and PCR). Percentage of MON2 was found increased and associated to the disease status. Moreover, this monocyte subset showed an increase in TF, IKK and TNFα expression, and a decrease in intracellular glutathione (GSH) in relation to MON1. Increases in neutrophil elastase levels and the percentage of cells suffering netosis were also identified. Neutrophils further displayed altered mitochondrial membrane potential and a decrease in GSH. The increased percentage of MON2 and molecules related to inflammation and thrombosis, endothelial dysfunction, oxidative status and netosis were associated with the occurrence of thrombotic events, as well as with the presence of anti-dsDNA antibodies. In vitro treatment of monocytes and neutrophils with anti-dsDNA antibodies promoted an increase in the production of NETosis and peroxides, and a number of proinflammatory and prothrombotic molecules.

Conclusion: 1. In SLE patients, the CD16 + monocyte subtype –present in higher proportion than in healthy donors- is associated with disease activity, thrombosis development and endothelial dysfunction. 2. Positivity for anti-dsDNA antibodies is linked to an increase of atherothrombotic markers in SLE patients. 3. Anti-dsDNA antibodies, in vitro, promote NETosis and modulate the expression of various molecules related to inflammation and thrombosis. Together, that data suggest the involvement of such autoantibodies on atherothrombosis development in SLE.

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erythematosus-through-the-induction-of-netosis-and-the-prothrombotic-and-proinflammatory-activities-of-monocytes

Abstract Number: 1862

Identification of Homogeneous Systemic Lupus Erythematosus (SLE) Patient Groups Using Clustered Autoantibody Reactivities

Petra Budde[1], Hans-Dieter Zucht[1], Daniel Chamrad[1], Anna Telaar[1], Johannes Schulte-Pelkum[1], Stefan Vordenbäumen[2], Peter Schulz-Knappe[1] and Matthias Schneider[3], [1]Protagen AG, Dortmund, Germany, [2]Department of Rheumatology, Univ. Duesseldorf, Düsseldorf, Germany, [3]Rheumatology, Heinrich-Heine-University, Duesseldorf, Germany

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Background/Purpose: In SLE, early diagnosis, differentiation to other autoimmune diseases and prognostic stratification are still great challenges. Hence, SLE represents an enormous challenge for the clinical development of effective therapies.Detecting a broad set of SLE-associated autoantibodies might help to investigate the number, co-prevalence and similarities of autoantibody reactivities in SLE patients. Here, we describe the development of a multiplexed autoantibody assay, which enables the comprehensive analysis of 87 autoantibodies in SLE patients

Methods: A Luminex bead-based autoantibody assay was designed by combining traditional with novel antigens. Autoantibodies were selected to be used for the a) diagnosis and b) differential diagnosis of SLE; have previously been linked to c) disease activity, and d) specific organ involvement; e) react with proteins encoded by interferon type I response genes; and f) may have utility for patient subgrouping. Autoantibody reactivity against these antigens was tested in over 700 SLE, healthy control (n=1000), and autoimmune disease samples (n=500).

Results: Based on the individual marker pattern, patients either belong to clusters defined by characteristic markers, or are phenotypically more overlapping with other autoimmune diseases. The analysis of the autoantibody reactivity yields at least four different reactivity groups (G1-G4) including patients: G1: with a higher disease activity score, broad and homogeneous autoantibody reactivity; G2: with broad, but heterogeneous autoantibody reactivity; G3) who have few autoantibodies and G4) with unusual autoantibody pattern.

Conclusion: The multiplexed analysis of autoantibodies in SLE enables defining an autoantibody reactivity score and SLE patient clusters. This might support the stratification of SLE patients into more homogenous subgroups in clinical studies thereby increasing the probability of successful drug development.

Disclosure: P. Budde, Protagen AG, 3; **H. D. Zucht**, Protagen AG, 3; **D. Chamrad**, Protagen AG, 3; **A. Telaar**, Protagen AG, 3; **J. Schulte-Pelkum**, Protagen AG, 3; **S. Vordenbäumen**, None; **P. Schulz-Knappe**, Protagen AG, 3; **M. Schneider**, None.

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Abstract Number: 1863

Epigenetic Changes in SLE Implicate Enhancers As a Force in Pathologic Cell Behavior

Lihua Shi[1], Li Song[1], Zhe Zhang[2], Michelle Petri[3] and **Kathleen E. Sullivan**[4], [1]Immunology ARC 1216, The Children's Hospital of Philadelphia, Philadelphia, PA, [2]Bioinformatics, Children's Hospital of Philadelphia, Bioinformatics, Philadelphia, PA, [3]Rheumatology, Johns Hopkins University Hospital, Baltimore, MD, [4]Allergy Immunology, The Children's Hospital of Philadelphia, Philadelphia, PA

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Background/Purpose: We previously identified novel non-coding RNAs that were markedly overexpressed in SLE patient monocytes. Among all classes of RNAs, these non-coding RNAs were by far the most highly over-expressed in SLE. We hypothesized that these novel RNAs represented regulatory RNAs. The purpose of this study was to determine whether the non-coding RNAs mapped to enhancers that regulated gene activity.

Methods: We used transfection of over-expression vectors and knockdown of non-coding RNAs to test their function. ChIP assays for H3K27ac, as a mark of active enhancers, and H3K4me3, as mark for promoter activity were performed. qRT-PCR was used to investigate the putative enhancers and to define

functionality.

Results: Over-expression of noncoding RNAs in control monocytes could be induced by LPS in a p38-dependent manner. We examined two clusters of non-coding RNAs in more detail at the IL-1 and the ADAM28 loci. At both loci, LPS treatment was associated with significant induction of H3K27ac at the site of the non-coding RNA, supporting a role in enhancer activation and defining these specific non-coding RNAs as enhancer RNAs. Acquisition of H3K27ac at the enhancer site was concordant with induction of the non-coding RNA and preceded changes in H3K4me3 at the promoter. LPS induced not only the enhancer RNA but also induced expression of the adjacent mRNA. To investigate the role of the p38 pathway, we examined AP-1, a downstream regulator of p38 activity. We tested for loading onto the enhancer and promoter regions by ChIP assay for c-jun, one of common group of proteins incorporated into the dimer of AP-1. Both at the IL1 and ADAM28 loci, c-jun was loaded onto the enhancer without increased loading at the promoter at early time points. Therefore, LPS induced c-jun loading onto the enhancer with concordant changes in enhancer RNA and acquisition of H3K27ac at the enhancer suggesting that this pathway activated the enhancers. To investigate the function of the enhancer RNAs specifically, we manipulated the amount of expression. Knockdown of one enhancer RNA within the IL1 cluster, led to diminished levels of multiple enhancer RNAs at that locus and diminished expression of IL1. Therefore, the enhancer RNA performs a critical function for gene expression.

Conclusion: These data define a set of disease-specific enhancers that appear to be dysregulated in SLE. Impressive over-expression of these enhancer RNAs suggests that the regulatory network is highly dysregulated in SLE. Enhancers have not been previously examined in SLE and identification of novel disease-specific enhancers is of critical importance in considering new epigenetically-directed therapeutics. This study identifies a specific pathway that activates these normally latent enhancer RNAs in SLE.

Disclosure: L. Shi, None; **L. Song**, None; **Z. Zhang**, None; **M. Petri**, None; **K. E. Sullivan**, Baxter, 2,Immune Deficiency Foundation, 5,Janssen Pharmaceutica Product, L.P., 5.

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Abstract Number: 1864

H3K4me3 Peak Shape Dictates Transcription and Regulates Differential Expression in SLE

Kathleen E. Sullivan[1], Lihua Shi[2], Li Song[3], Michelle Petri[4] and Zhe Zhang[5], [1]Allergy Immunology, The Children's Hospital of Philadelphia, Philadelphia, PA, [2]Immunology ARC 1216, The Children's Hospital of Philadelphia, Philadelphia, PA, [3]Allergy Immunology, Children's Hospital of Philadelphia, Philadelphia, PA, [4]Rheumatology, Johns Hopkins University Hospital, Baltimore, MD, [5]Bioinformatics, Children's Hospital of Philadelphia, Bioinformatics, Philadelphia, PA

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Background/Purpose: H3K4me3 is a post-translational modification of histone H3 associated typically with gene activation. We had previously characterized changes in H3K4me3 associated with SLE in monocytes and found that many genes had higher peaks of H3K4me3 in SLE. In the current study, we further analyzed these changes to better define the transcription factors impacting these changes.

Methods: Eight female controls and six female SLE monocyte samples were utilized for analysis. The SLE patients had low to moderate disease activity and were not on high level immune suppression. Using ChIP-seq data from these samples, we analyzed changes in breadth and shape of the H4K4me3 peaks in SLE and then correlated these changes with paired RNA-seq data. H3K4me3 peaks were classified as Narrow, Extended Upstream, Extended Downstream and Extended Symmetric patterns.

Results: We found that there was a strong association between the H3K4me3 breadth and likelihood of differential expression. Genes with narrow H3K4me3 were less likely to have increased expression in SLE while those with extended H3K4me3 downstream of their TSSs were more likely to have increased expression in SLE. We then looked at the change of H3K4me3 breadth in SLE. H3K4me3 peak shape was mostly stable in primary monocytes. Among 907 sites that switched patterns from control to SLE, none of them switched between narrow sites and any of the three broad sites. The most common switch was 131 sites that switched from Extended Symmetric to Extended Downstream. We previously reported that H3K4me3 increases in SLE were associated with increased expression of corresponding genes in SLE patients. To address the impact of location of H3K4me3, we analyzed changes in shape of H3K4me3 peaks in SLE with changes in transcript levels. Expression change was very sensitive to H3K4me3 change at the downstream regions. From 1% to 10%, every one percent increase of H3K4me3 at the immediate downstream region lead to a 1.5% increase in gene expression on average. Of the genes having significantly increased expression in SLE, 78.8% also had increased H3K4me3 at the downstream regions, while the percentages were 55.0% and 47.1% for TSSs and upstream regions, respectively. Indeed, the average H3K4me3 change of these genes peaked (~8%) at approximately 700bp downstream of their TSSs.

Conclusion: This study provides refinement in our understanding of the epigenetic changes associated with SLE. The change may occur adjacent to transcription factor binding where a histone modification enzyme has been recruited. Efforts to identify such transcription factors have typically focused on upstream peaks, whereas our data supports a focus on the downstream peaks. This finding may facilitate identification of epigenetic therapeutics.

Disclosure: K. E. Sullivan, Baxter, 2,Immune Deficiency Foundation, 5,Janssen Pharmaceutica Product, L.P., 5; **L. Shi**, None; **L. Song**, None; **M. Petri**, None; **Z. Zhang**, None.

Abstract Number: 1865

Association Between Changes in Expression of Gene Signatures and Disease Activity Among Patients with Systemic Lupus Erythematosus

Michelle Petri[1], Wei Fu[2], Ann Ranger[3], Norm Allaire[4], Patrick Cullen[4] and Laurence S Magder[5], [1]Johns Hopkins University School of Medicine, Baltimore, MD, [2]Rheumatology, Johns Hopkins University School of Medicine, Baltimore, MD, [3]Biogen Inc., Cambridge, MA, [4]Biogen Idec Inc., Cambridge, MA, [5]University of Maryland School of Medicine, Baltimore, MD

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Background/Purpose: In recent work, we showed that a single measurement of several gene signatures in whole blood was associated with levels of disease activity at that time and in the next year. In this study, we assessed the stability of these gene signatures over time, and whether changes in expression coincide with changes in disease activity.

Methods: Blood was collected at clinic visits from 298 members of a well-characterized SLE cohort (SPARE). 82 patients contributed one visit, 194 patients contributed 2 visits, 22 patients contributed 3 or more visits. The interval between visits was approximately 28 to 135 days. Levels of the BAFF gene transcript, plasma cell signature, Interferon (IFN)-α signature and the Low Density Granulocytes (LDG)-associated Neutrophil gene signature were assessed in PAXgene-preserved peripheral blood by global microarray and qPCR. For multi-gene signatures, the geometric mean was calculated. The stability of repeated measures of gene expression was quantified using intra-class correlation coefficients (ICC). To provide a frame of reference we also computed the ICC for systolic blood pressure and weight. SLE disease activity was measured using the Physicians Global Assessment (PGA) and the SELENA-SLEDAI index and its components.The associations between changes in gene expression and changes in disease activity between two visits from the same person were assessed using linear regression models.

Results: Table 1 shows the intraclass correlation coefficients for repeated measures of the gene signatures and also, to provide reference values, for systolic blood pressure and weight. It can be seen that the gene expression markers show more within-person stability than systolic blood pressure. The IFN-α signature exhibited the most stability. Table 2 shows the association between changes in gene signature markers and changes in disease activity indices, adjusting for change in prednisone dose. Few strong associations were observed. A one standard deviation (SD) increase in expression of the plasma cell signature was associated with a 0.57 increase in SLEDAI values.

Table 1: Within-patient Intraclass Correlation Coefficients (ICC) for Four Gene Expression Signatures, Systolic Blood Pressure, and Weight.

Variables	IFN-α	BAFF	LDG	Plasma Cell	Systolic Blood Pressure	Weight
ICC	0.84	0.61	0.79	0.61	0.53	0.99

Table 2: Estimated Expected Change in Disease Activity Index for a One Standard Deviation Increase in Each Gene Marker.

Boimarker	Disease Activity Index									
	PGA		SLEDAI		SLEDAI MS		SLEDAI SKIN		SLEDAI Renal	
	Change	P-value	Change	P-value	Change	P-value	Change	P-value	Change	P-value
IFN-α	0.06	0.34	0.09	0.77	0.07	0.54	-0.11	0.29	0.11	0.56
BAFF	0.03	0.38	0.11	0.57	0.03	0.67	-0.12	0.07	0.14	0.24
LDG	-0.14	0.05	-0.18	0.6	-0.13	0.32	-0.01	0.93	0.08	0.71
PC	0.06	0.19	0.57	0.01	0.14	0.05	0.12	0.08	0.2	0.11

Conclusion: The gene signatures that we studied are relatively stable within patients over time. Although previous work has shown them related to disease activity, within a patient there was not a strong association between changes in gene expression and changes in disease activity. This suggests that these gene signatures may not be dynamic indicators of disease activity under current standard of care therapy, but more likely to be indicators of subsets of patients with different underlying disease processes.

Abstract Number: 1866

Fall in Dicer1 Gene Expression Flags Abnormal Lymphocyte Activation in Lupus

Olga Sanchez-Pernaute[1], Fredeswinda Romero[2], Maria Perez-Ferro[1], Cristina Serrano[3], María J Martinez-Becerra[4], F Javier de la Hera[5] and Rosario Haro[6], [1]Section for Autoimmune Diseases, Rheumatology, Jiménez Díaz Foundation University Hospital, Madrid, Spain, [2]Section for Autoimmune Diseases. Rheumatology., Jiménez Díaz Foundation University Hospital, Madrid, Spain, [3]Section for Autoimmune Diseases. Immunology, Jiménez Díaz Foundation University Hospital, Madrid, Spain, [4]Immunology, Jiménez Díaz Foundation University Hospital, Madrid, Spain, [5]Section for Autoimmune Diseases, Internal Medicine, Jiménez Díaz Foundation University Hospital, Madrid, Spain, [6]Section for Autoimmune Diseases. Dermatology, Jiménez Díaz Foundation University Hospital, Madrid, Spain

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Background/Purpose: The integrity of the microRNA machinery is required for the normal reactivity of the immune system both during differentiation and upon antigen engagement. Dicer1 is a pivotal molecule of the microRNA biogenesis. Suppression of Dicer1 in lymphoid progenitors from mice render cells auto-reactive. In this study we have looked into Dicer1 gene expression in relationship with the activation of mononuclear cell subsets in patients with lupus.

Methods: The study was conducted in 36 patients with lupus (34 women) fulfilling ACR classification criteria, of which 21 were considered to have active disease. Circulating monocytes, T cells and B cells were sorted with magnetic beads, and gene expression analysis was carried out using Sybr green based qPCR techniques after RNA isolation and retro-transcription. Statistics were run with SPSS using non-parametric methods.

Results: Levels of Dicer1 in monocytes and in T cells were found to drop in association to c'4 decrease (p 0.09, p 0.03). Lower expression levels of Dicer1 were found in monocytes from patients with anti phospholipid antibodies (p 0.09), while in T cells the fall of Dicer1 levels was associated to lower platelet counts (p 0.002). Patients with positive antiDNA antibodies at the time of the study showed lower levels of Dicer1 in B lymphocytes (p 0.02). There was an inverse association between levels of Dicer1 in B cells and SLEDAI scores (p 0.04), C-reactive protein (p 0.03), and proteinuria (p 0.09). In addition to these activity features, we analysed the relationship between suppression of Dicer1 and mechanisms of cell growth. Globally, the down-regulation of Dicer1 gene expression was associated to an enhancement of miR181a, a master miRNA involved in positive selection of immune cells, in each of the mononuclear cell subpopulations. On the other hand, there was an inverse relationship between Dicer1 levels in monocytes and circulating NK cells (p 0.02).

Conclusion: Overall, the relative suppression of Dicer1 gene expression in patients with lupus identified a subgroup of patients with activation of the complement classical pathway and enhanced lymphocyte survival. Particularly in B cells, the drop of Dicer1 appeared to be a marker of activity and nephritis. Together, our data suggest that a deregulation of the microRNA system contributes to the abnormal activation of immune cells in lupus. In addition, measuring Dicer1 expression could be of interest as a biomarker of distinct subgroups of patients.

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Abstract Number: 1867

Functional Androgen Receptor Variants Associated with Greater Damage in Systemic Lupus Erythematosus

Yun Deng[1], Jennifer M. Grossman[1,2], Qiong Fu[1], William J. Martin[1], Judith A. James[3], Joan T. Merrill[4], Diane L. Kamen[5], Gary S. Gilkeson[5], Susan A. Boackle[6], Chaim Putterman[7], Jane E. Salmon[8], Vasileios C. Kyttaris[9], George C. Tsokos[9], Matthew Quirk[10], Seema Kamble[1], Melissa Barcelona[1], Erika Magdangal[10], Lori Sahakian[11], Seung Yoon Lee[1], Tracy Y. Lin[1], Weiling Chen[1], Jennifer M.P. Woo[12], Ornella J. Rullo[12], Deborah K. McCurdy[12], Bevra H. Hahn[13,14], Maureen A. McMahon[11], Sang-Cheol Bae[15] and Betty P. Tsao[1], [1]Division of Rheumatology, Department of Medicine, David Geffen School of Medicine University of California Los Angeles, Los Angeles, CA, [2]Rheumatology, UCLA, Los Angeles, CA, [3]Arthritis and Clinical Immunology, University of Oklahoma Health Sciences Center and Oklahoma Medical Research Foundation, Oklahoma City, OK, [4]Clinical Pharmacology Research Program, Oklahoma Medical Research Foundation, Oklahoma City, OK, [5]Department of Medicine, Division of Rheumatology, Medical University of South Carolina, Charleston, SC, [6]Division of Rheumatology, University of Colorado School of Medicine, Aurora, CO, [7]Division of Rheumatology, Albert Einstein College of Medicine, New York, NY, [8]Division of Rheumatology, Hospital for Special Surgery, Weill Cornell Medical College, New York, NY, [9]Division

of Rheumatology, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, [10]Division of Rheumatology, Department of Medicine,, David Geffen School of Medicine University of California Los Angeles, Los Angeles, CA, [11]Division of Rheumatology, Department of Medicine, UCLA David Geffen School of Medicine, Division of Rheumatology, Los Angeles, CA, [12]Pediatric Rheumatology, Mattel Children's Hospital, University of California Los Angeles, Los Angeles, CA, [13]Medicine, UCLA David Geffen School of Medicine, Division of Rheumatology, Los Angeles, CA, [14]Rheumatology, Professor Emeritus, Department of Medicine/Rheumatology, David Geffen School of Medicine UCLA, Los Angeles, CA, [15]Rheumatology, Hanyang University Hospital for Rheumatic Diseases, Seoul, South Korea

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SESSION INFORMATION

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Background/Purpose :

Organ damage predicts physical disability and mortality of SLE. Given that men with SLE tend to develop accelerated damage, we selected an X-linked androgen receptor (AR) variant, the short CAG repeat encoding ≤17 copies of polyglutamine that confers enhanced receptor-mediated transcriptional activity associated with more maleness, to test for association with damage in 1,703 (213 male and 1,490 female) SLE patients recruited at multiple centers with mean (±SD) disease duration of 10 (±7.9) years.

Methods:

Association of damage assessed by the SLICC/ACR Damage Index (SDI) with clinical features (gender, ethnicity, age at diagnosis, disease duration and cumulative exposure to glucocorticoids) and/or CAG repeat length (genotyped by PCR) were analyzed using univariate and multivariate regression tests.

Results:

Risk factors identified by univariate analysis associated with greater damage (defined as SDI≥2) were male gender, longer disease duration, higher cumulative prednisone usage and African American (AA) ancestry compared to European American (EA); Asian ancestry protected against damage. Except male gender, all other factors were confirmed in the multivariate model of greater damage: longer disease duration (OR [95%CI] =2.08 [1.72-2.51], *P*=5.0E-14), higher cumulative prednisone usage (1.49 [1.28-1.75], *P*=6.8E-07), AA ancestry (1.99 [1.44-2.74], *P*=2.5E-05), and Asian ancestry (0.32 [0.23-0.44], *P*=1.6E-11). After adjusting for these covariates, the short CAG repeat (≤17) was associated with greater damage in AA (OR_{adj}=1.84 [1.12-3.02], P_{adj}=0.015) and EA patients (OR_{adj}=1.66 [1.03-2.66], P_{adj}=0.037) (Table 1). This genetic association remained statistically significant in AA women and there was a trend toward significance in EA women. Compared to EA/AA patients, fewer proportions of Asians had damage and short CAG repeat and Hispanics (HS) had smaller sample size, contributing to no genetic association. Renal damage defined by SDI (observed in 12.7% patients) was associated with male gender (OR=1.76 [1.18-2.62], *P*=0.006), younger age at diagnosis (OR=1.65 [1.08-2.50], *P*=0.02), longer disease duration (OR=1.50 [1.16-1.96], *P*=0.002), higher prednisone usage (OR=1.60 [1.29-2.00], *P*=3.0E-05), AA (OR=5.09 [3.09-8.37], *P*=1.5E-10) and HS (OR=2.83 [1.54-5.20], *P*=0.001) ancestries. The short CAG repeat was associated with renal damage in AA patients only (OR_{adj}=1.91 [1.04-3.51], P_{adj}=0.038).

Conclusion:

In addition to confirming previously reported risk factors for damage accrual in SLE, we identified short CAG repeats with an enhanced AR transactivation activity to be associated with greater damage in EA and female AA SLE patients and renal damage in AA patients. Our data supports genetic contribution, including a role of X-linked androgen receptor-mediated activity, to organ damage in SLE of multiple ancestries.

Table 1. Association of higher transactivating AR variant(1) with greater damage in African- and European-American SLE patients

Ethnicity	N* (%SDI≥2)	% CAG ≤17 in SDI≥2 vs. SDI<2	OR (95%CI)	P	Adjusted* OR (95%CI)	P
African American	328 (52.7)	75.7 vs. 60.6	2.02 (1.26-3.25)	0.0042	**1.84 (1.12-3.02)**	***0.015***
European American	393 (39.4)	35.5 vs. 25.2	1.63 (1.05-2.54)	0.032	**1.66 (1.03-2.66)**	***0.037***
Asian	840 (23.7)	22.6 vs. 20.0	1.17 (0.80-1.72)	0.42	1.18 (0.79-1.75)	0.42
Hispanics	142 (40.8)	20.7 vs. 17.9	1.20 (0.51-2.80)	0.67	1.00 (0.40-2.49)	0.99

For each female subject, the mean number of CAG repeats is calculated from the average of both alleles (maternal and paternal).
(1): Ding D, et al. Effect of a short CAG (glutamine) repeat on human androgen receptor function. Prostate. 2004;58(1):23-32.
*N: Number of SLE patients.
*Adjusted for disease duration and cumulative prednisone usage. Disease duration was defined as: 0=≤5 yrs, 1=6-20 yrs, 2=>20 yrs; cumulative prednisone usage was defined as: 0=0-10 grams, 1=10-20 grams, 2=>20 grams.

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Abstract Number: 1868

BLK Pathway-Associated rs13277113 GA Genotype Is More Frequent in Systemic Lupus Erythematosus Patients and Associated with Low Gene Expression and Increased Flares

Omer Nuri Pamuk[1], Hakan Gurkan[2], Mehmet Ali Balci[1], Hilmi Tozkir[3], Julide Duymaz[2], Gülce Sari[2], Metin Yazar[2] and Gulsum Pamuk[4], [1]Department of Rheumatology, Trakya University Medical Faculty, Edirne, Turkey, [2]Trakya University Medical Faculty, EDIRNE, Turkey, [3]Genetics, Trakya University Medical Faculty, EDIRNE, Turkey, [4]Hematology, Trakya University Medical Faculty, Edirne, Turkey
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Background/Purpose: It was reported that genetic variations in B cell signal transduction were associated with susceptibility to SLE. However, these studies were limited in number and were performed in only certain populations. In our study, we aimed to evaluate the relationship between some important genetic variations and expressions of these genes in our SLE population. We also determined their association with clinical parameters.

Methods: 84 SLE patients (79F, 5M, mean age: 37.6) and 105 healthy controls (98F, 7M, mean age: 38.2) were included into the study. SLEDAI scores and flares according to SELENA-SLEDAI were also recorded. Genomic DNA and cDNA were obtained from peripheral venous blood. BLK (rs13277113 and rs2736340), LYN (rs7829816 and rs6983130), SYK (rs2613310), CD247 (rs704853) polymorphisms, gene expressions of SRC-B family kinases (BLK, HCK, LCK ve LYN) and SYK kinases (SYK, ZAP70) which are important in B-cell signal transduction and were found to be important in whole genome analyses in various races were studied by Real-time PCR in the Genetics Department.

Results:

The heterozygous genotypic pattern (GA) for rs13277113 polymorphism was more frequent in patients with SLE when compared to controls (48.8% vs. 31.4%, p=0.015). Other genotype variants were similar in SLE patients and controls. In SLE group, the heterozygous genotype (GA) for rs13277113 was significantly less frequent in initially active SLE patients (41.2% vs. 73.3%) and more frequent in anti-Ribosomal-P positive (14.6% vs. 0%) SLE patients (p values for both=0.01).AA genotype for rs2613310 was significantly more frequent in patients with thrombocytopenia (16.9% vs. none, p=0.048), in patients with positive anti-dsDNA (59.3% vs. 32%, p=0.01), and those with anti-nucleosome antibodies (23.7% vs. 4%, p=0.004). SLE flares according to SELENA-SLEDAI flare index was significantly more frequent in GA (rs13277113) (70% vs. 37%) and CT (rs 2736340) genotypes (66.7% vs. 35.2%) than in other genotypes (p values, 0.004 and 0.006). In the group which had flares according to SELENA flare index, the average delta CT value for BLK gene expression tended to be higher than in the group without flares (12.2±2.6 vs. 10.8±1.6, p=0.08). Quantitative relative expression of Syk gene, as calculated by delta-delta-CT method, showed significant difference between the average delta CT value for SLE patients and controls (7.5±1.2 vs. 7.8±1, p=0.02). The relative expression of mRNA for Syk gene to β2 microglobulin was increased by 1.22 fold in patients with SLE as compared to controls.The statistically significant intergenotypic variation in the delta-CT values was found in patients with GG and GA genotypes for rs13277113 (BLK) (10.8±2.1 vs 11.7±2.2, p=0.019). GA genotype showed higher delta-CT value representing lower gene expression at mRNA level. AA genotype groups was very small.

Conclusion: We observed more frequent heterozygous GA genotypic pattern (rs13277113) in our SLE patients compared to controls; and it was associated with BLK expression and disease flare. In spite of the fact that Syk genotype was not increased in SLE patients, Syk expression was seen to be more frequent.

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Abstract Number: 1869

Association of CLEC16A with SLE in a Large Multi-Ancestry Cohort and Implication in B-Cell Receptor Signaling

Isaac TW Harley[1,2,3], Samuel Vaughn[4], Adrienne H. Williams[5], Julie T. Ziegler[6], Mary Comeau[7], Miranda Marion[8], Stuart Glenn[9], Adam Adler[10], Kenneth M. Kaufman[11], Sang-Cheol Bae[12], Carl D. Langefeld[13], Jennifer Kelly[14], Patrick M. Gaffney[15], R. Hal Scofield[16], Michelle Petri[17], Jeffrey C. Edberg[18], Joel M. Guthridge[15], Susan A. Boackle[19], Barry Freedman[20], Diane L. Kamen[21], Elizabeth E. Brown on behalf of PROFILE[22], Gary S. Gilkeson[23], John D. Reveille[24], Joan T. Merrill[25], Marta E. Alarcón-Riquelme[26], Timothy Vyse[27], Lindsey A. Criswell[28], Rosalind Ramsey-Goldman[29], Juan-Manuel Anaya[30], Betty P. Tsao[31], Judith A. James[32], Graciela S. Alarcón[33], Anne M. Stevens[34], Kathy Moser Sivils[15], Robert P. Kimberly[35], Luis M. Vilá[36], Chaim O. Jacob[37], Bahram Namjou[38], Leah C. Kottyan[39], Timothy B. Niewold[40] and John B. Harley[11,41], [1]Division of Internal Medicine, University of Colorado, Aurora, CO, [2]Immunobiology Graduate Program and Medical Scientist Training Program, University of Cincinnati College of Medicine, Cincinnati, OH, [3]Center for Autoimmune Genomics and Etiology, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, [4]Division of Rheumatology and The Center for Autoimmune Genomics and Etiology, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, [5]Dept of Med, Div of Rheum, NYU School of Medicine, New York, NY, [6]Biostatistical Sciences and Center for Public Health Genomics, Wake Forest University Health

Sciences, Winston-Salem, NC, [7]Wake Forest University Health Sciences, Winston-Salem, NC, [8]Department of Biostatistical Sciences, Wake Forest University Health Sciences, Wake Forest, NC, [9]Arthritis and Clinical Immunology Research Program, Oklahoma Medical Research Foundation, Oklahoma City, OK, [10]Arthritis and Clinical Immunology Research Program, Oklahoma Medical Research Foundation, Oklahoma City,, OK, [11]US Department of Veterans Affairs Medical Center, Cincinnati, OH, [12]Hanyang University Hospital for Rheumatic Diseases, Seoul, South Korea, [13]Wake Forest University, Wake Forest, NC, [14]Oklahoma Medical Research Foundation, Oklahoma City, OK, [15]Arthritis and Clinical Immunology, Oklahoma Medical Research Foundation, Oklahoma City, OK, [16]Department of Pathology, University of Oklahoma Health Sciences Center, Oklahoma City, OK, [17]Rheumatology, Johns Hopkins University Hospital, Baltimore, MD, [18]Medicine/Rheumatology, University of Alabama at Birmingham, Birmingham, AL, [19]Division of Rheumatology, University of Colorado School of Medicine, Aurora, CO, [20]Department of Internal Medicine, Wake Forest University Health Sciences, Wake Forest, NC, [21]Medicine, Medical University of South Carolina, Charleston, SC, [22]University of Alabama at Birmingham, Birmingham, AL, [23]Department of Rheumatology, Medical University of South Carolina, Charleston, SC, [24]Rheumatology, University of Texas Health Science Center at Houston, Houston, TX, [25]Clinical Pharmacology, Oklahoma Medical Research Foundation, Oklahoma City, OK, [26]Oklahoma Medical Research Foundation and Centro de Genómica e Investigación Oncológica Pfizer-Universidad de Granada-Junta de Andalucía (GENYO), Granada, Spain, Oklahoma City, OK, [27]Division of Genetics and Molecular Medicine and Division of Immunology, Infection and Inflammatory Disease, King's College London, London, United Kingdom, [28]Rosalind Russell / Ephraim P. Engleman Rheumatology Research Center, University of California, San Francisco, San Francisco, CA, [29]Northwestern University Feinberg School of Medicine, Chicago, IL, [30]Cell Biol and Immunogenetics, CIB-Rosario University, Medellin, Colombia, [31]Medicine/Rheumatology, Division of Rheumatology, UCLA, Los Angeles, CA, [32]Arthritis and Clinical Immunology, University of Oklahoma Health Sciences Center and Oklahoma Medical Research Foundation, Oklahoma City, OK, [33]U of Alabama, Birmingham, AL, [34]Seattle Children's Res Inst, Seattle Children's Hospital, Seattle, WA, [35]Medicine, Clinical Immun & Rheumatology, University of Alabama at Birmingham, Birmingham, AL, [36]Department of Medicine, Division of Rheumatology, University of Puerto Rico Medical Sciences Campus, San Juan, PR, [37]Medicine/Div of Rheumatology, USC School of Medicine, Los Angeles, CA, [38]Oklahoma Medical Research Foundation, Edmond, OK, [39]3333 Burnet Ave., Ml 15012, Cincinnati, OH, [40]Division of Rheumatology and Department of Immunology, Mayo Clinic, Rochester, MN, [41]Center for Autoimmune Genomics and Etiology (CAGE), Cincinnati Children's Hospital Medical Center, Cincinnati, OH

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Background/Purpose: Immune-mediated diseases appear to share a common genetic basis. Here we describe genetic association of single nucleotide polymorphisms (SNPs) within *CLEC16A* with SLE in a large multi-ancestry cohort of SLE cases and controls. In immune-mediated diseases where this locus has been implicated, it appears to have complex genetic architecture with multiple independent association signals and multiple plausible candidate genes. Few studies to date have focused on the function of human *CLEC16A*. However, recent studies defining the role of the *Drosophila* ortholog of *CLEC16A*, *Ema*, suggest several plausible mechanisms through which variation at this gene might plausibly influence autoimmunity and SLE risk. Here, we also undertake evaluation of one such hypothesis, that variation in *CLEC16A* modulates B-cell receptor (BCR) signaling and thus autoimmunity.

Methods: First, we genotyped a panel of previously reported immune mediated disease susceptibility loci in a large collection of SLE case-matched control samples as part of the collaborative Large Lupus Association Study 2 (LLAS2). As part of the panel, we tested SNPs in *CLEC16A* for genetic association with SLE. After adjusting for admixture using a panel of ancestry informative markers, filtering for SNP missingness, departure from Hardy-Weinberg equilibrium and minor allele frequency, SNPs were tested for association using an additive genetic model. Association testing was carried out in each AIM-defined ancestry subgroup and meta-analysis of the population specific results was also performed. All SLE patients met the 1997 ACR criteria for classification of SLE. In addition, B cells from control subjects were incubated with anti-BCR for 30 min at 4°C, then placed at 37°C as indicated. Cross-linked surface remnant BCR was detected with fluorescent-tag secondary antibody and co-localization with labelled *CLEC16A* was then calculated.

Results: We found evidence for association at previously defined autoimmune susceptibility loci was stronger than expected by chance. In addition to this, a SNP in CLEC16A was associated in each AIM-defined ancestry subgroup (European, African, Asian and Native American/Hispanic Ancestry groups) with the same allele in the same direction. ($P_{meta} < 4.96*10^{-7}$, Phet = 0.6874, N = 15751). We find that while CLEC16A co-localizes with the BCR following BCR internalization. This occurs in the endosomal compartment, where the *Drosophila* ortholog of *CLEC16A*, *Ema*, also operates.

Conclusion: Taken together, our data confirm the association of this locus with SLE in multiple ancestry groups and suggest a role for human *CLEC16A* in BCR signaling in the endosome, where its *Drosophila* ortholog, *Ema* has been shown to operate.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/association-of-clec16a-with-sle-in-a-large-multi-ancestry-cohort-and-implication-in-b-cell-receptor-signaling

Abstract Number: 1870

A Lupus-Associated Variant in Purine Nucleoside Phosphorylase (PNP) Causes Cell Cycle Abnormalities

Yogita Ghodke-Puranik[1], Jessica M. Dorschner[1], Danielle Vsetecka[1], Shreyasee Amin[2], Ashima Makol[3], Floranne C. Ernste[2], Thomas Osborn[2], Kevin Moder[2], Vaidehi Chowdhary[4], Mark A. Jensen[5] and **Timothy B. Niewold**[1], [1]Division of Rheumatology and Department of Immunology, Mayo Clinic, Rochester, MN, [2]Division of Rheumatology, Mayo Clinic, Rochester, MN, [3]Division of Rheumatology, Department of Internal Medicine, Mayo Clinic, Rochester, MN, [4]Rheumatology, Mayo Clinic, Rochester, MN, [5]Divsion of Rheumatology and Department of Immunology, Mayo Clinic, Rochester, MN
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Background/Purpose: Systemic lupus erythematosus (SLE) is a multi-system, autoimmune disease characterized by autoantibodies to nucleic acids and nucleosomal proteins. The type I interferon pathway is dysregulated in SLE and IFN-α levels are high in patients. We performed a genome-wide association study and found a missense SNP (C297T:gly51ser) in the *PNP* gene that associates with high IFN levels in SLE (rs1049564; $P=1.24 \times 10^{-7}$). PNP is a key enzyme of purine metabolism. PNP deficiency leads to dysregulated deoxynucleotide levels, a block in DNA synthesis, and defective immunity. Previously, the rs1049564 SNP was thought not to impact PNP function. To show a functional link between rs1049564 and SLE, we performed in vitro experiments using HAPMAP cell lines and patient leukocyte samples with and without the PNP variant.

Methods: To determine if the rs1049564 variant alters PNP function, we exposed 6 HAPMAP cell lines (2 homozygous (CC), 2 heterozygous, and 2 homozygous (TT)) to a dose curve of deoxyguanosine (dGuo; nucleotide precursor and a substrate for PNP). One day later cells were analyzed for cell cycle phase using Click-iT plus EdU chemistry combined with FxCycle violet stain and flow cytometry. Various pharmacological agents were tested for their ability to reverse the cell cycle block caused by the PNP variant. A similar approach was used to study PNP function in SLE patient samples with and without the rs1049564 variant. Colorimetric enzyme and ELISA assays were used to measure the functional activity of the different PNP isoforms.

Results: We find that the rs1049564 variant causes increased S phase block and cell death in lymphoblastoid cells. Cell lines homozygous for rs1049564 (TT) had 2 fold increases in S phase block compared to cell lines without the PNP variant (CC). The cell cycle block caused by the PNP variant could be reversed pharmacologically and similar findings were observed in SLE patient cells.

Conclusion: These results suggest that the rs1049564 *PNP* polymorphism is a loss of function variant that leads to altered PNP function and subsequent S-phase block in select cell subsets within the lymphocyte compartment. This may lead to increased frequencies of circulating apoptotic lymphocytes, and higher type I IFN levels in human SLE. These findings have pharmacogenomic implications, as the S-phase block can be rescued in our in vitro experiments, suggesting a potential for personalized therapeutics.

Disclosure: Y. Ghodke-Puranik, None; **J. M. Dorschner**, None; **D. Vsetecka**, None; **S. Amin**, None; **A. Makol**, None; **F. C. Ernste**, None; **T. Osborn**, None; **K. Moder**, None; **V. Chowdhary**, None; **M. A. Jensen**, None; **T. B. Niewold**, None.

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Abstract Number: 1871

Familial Aggregation of Rheumatoid Arthritis, Sjögren's Syndrome, and Systemic Sclerosis Were Detected in Systemic Lupus Erythematous Families

Rufei Lu[1], Hua Chen[1], Krista Bean[1], Teresa Aberle[1], Joel Guthridge[1] and Judith James[1,2], [1]Arthritis & Clinical Immunology, Oklahoma Medical Research Foundation, Oklahoma City, OK, [2]Medicine & Pathology, Univ. of Oklahoma, Okla, OK
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Background/Purpose: Many systemic autoimmune diseases share heritable and non-heritable risks, as well as some clinical manifestations. A recent meta-analysis based upon genome-wide genetic studies contrasting and comparing a number of major autoimmune diseases revealed expected and unexpected heritable correlations among different diseases and highlighted the exceptional genetic complexity of human autoimmune diseases even without evaluating the similarities and dissimilarity in clinical prevalence and manifestations. Here, we surveyed systemic lupus erythematosus (SLE) patients and their family members from lupus family registry and repository (LFRR), as well as unrelated unaffected healthy individuals (HC) in attempt to provide valuable insights into the effects of heritable and non-heritable factors on pathogenesis of many of these autoimmune diseases.

Methods:

To assess the concurrency of SLE, rheumatoid arthritis (RA), hypothyroidism, Type I diabetes, systemic sclerosis (SSc), and Sjogren's syndrome (SS) in this collection by surveying 3203 African Americans(AA), 4950 European Americans (EA), and 741 Hispanics (HIS). ACR >= 4 was used to identify SLE patients as well as the family members of the SLE patients. Self-reported RA was further verified by anti-CCP^+, anti-RF^+, and DMARD usage. Self-reported Sjogrens was confirmed by anti-Ro and/or anti-La. Self-reported hypothyroidism was verified by usage of exogenous thyroid hormones. Self-reported Type I diabetes was further confirmed by usage of Insulin. Proportionality, chi-square, and mixed regression tests were used to analyze prevalence differences of concurrent autoimmune diseases, as well as to detect gender effects among different populations.

Results:

In EA, SLE patients were more likely to also meet RA criteria [p<0.01; OR (95% CI), 108.03 (26.45 – 441.19)], SS (p<0.01; 120.18, 16.67 – 866.69), SSc (p<0.01; 36.05, 4.95 – 262.56), and Hypothyroidism compared to HC. Family members of EA SLE patients were also more likely to have RA (p<0.05; 5.55, 1.33 – 23.06), SS (p=0.07; 6.40, 0.86 – 47.47), as well as hypothyroidism compared to HC. However, there was no enrichment of Type I Diabetes in EA family member of SLE patients. AA SLE patients were also more likely to concurrently meet criteria for RA (p<0.01; 142.61, 30.53 – 666.23), SS (p<0.01; 27.62, 5.79 – 131.82), or SSc (p<0.01; 7.19, 2.21 – 23.42) compared to AA healthy controls. Additionally, AA family members of SLE patients were more likely to meet RA criteria (p=0.07; 3.93, 0.88 – 17.66) compared to AA healthy control population. Finally, in the HIS population, SLE patients were more likely to also meet criteria for SS (p<0.01; 29.46, 3.97 – 218.26). No enrichment of assessed autoimmune diseases were noted in HIS family members of SLE patients. The prevalence of majority autoimmune diseases observed in this study is comparable to published works.

Conclusion: In conclusion, genetically similar autoimmune diseases such as RA, SLE, SS, and SSc had higher concurrent prevalence in SLE patients and their family members compared to more genetically distant autoimmune disease like Type I Diabetes and hypothyroidism.

Disclosure: R. Lu, None; **H. Chen**, None; **K. Bean**, None; **T. Aberle**, None; **J. Guthridge**, None; **J. James**, None.

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Abstract Number: 1872

Symptomatic and Electrodiagnostic Features of Peripheral Neuropathy in Scleroderma

Julie J. Paik[1], Andrew Mammen[2], Fredrick M. Wigley[3], Ami A. Shah[4], Laura K. Hummers[5] and Michael Polydefkis[6], [1]Rheumatology, Johns Hopkins University, Baltimore, MD, [2]Center Tower Ste 5300, Johns Hopkins University School of Medicine, Baltimore, MD, [3]Rheum Div/Mason F Lord, Johns Hopkins University School of Medicine, Baltimore, MD, [4]Rheumatology, Johns Hopkins University School of Medicine, Baltimore, MD, [5]Johns Hopkins University School of Medicine, Baltimore, MD, [6]Neurology, Johns Hopkins University, Baltimore, MD
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Title: Symptomatic and electrodiagnostic features of peripheral neuropathy in scleroderma

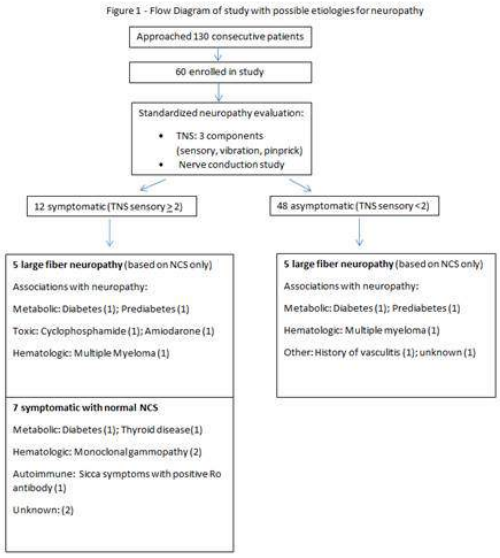
Background/Purpose: Peripheral neuropathy in scleroderma has been poorly characterized and the prevalence is unknown. The purpose of this study was to determine the prevalence of peripheral neuropathy in scleroderma.

Methods: The prevalence of length dependent peripheral neuropathy was rigorously assessed using signs and symptoms of neuropathy derived from a previously validated Total Neuropathy Score (TNS), and standardized nerve conduction study (NCS). Criteria for enrollment was an established diagnosis of scleroderma based upon the 1980 American College of Rheumatology (ACR) criteria for scleroderma, possessing at least 3 of 5 features of the CREST syndrome, or having all 3 of the following features: Raynaud's phenomenon, nail fold capillary changes and a scleroderma-specific antibody. Enrolled subjects underwent a uniform evaluation (TNS) that consisted of neuropathy symptom assessment by questionnaire, physical examination using objective measurement tools (graduated Rydel-Seiffer 64 Hz tuning fork and NeuroPen), and a standardized nerve conduction protocol. Those who were symptomatic or had NCS evidence of peripheral neuropathy underwent laboratory evaluation for secondary causes of neuropathy. We defined the presence of neuropathy to be those who either were screen positive on the TNS and/or electrophysiologic evidence of neuropathy. Statistical analyses were performed using the statistical software (STATA, release 12.1; StateCorp, College Station, Texas). Fischer's exact test was used to analyze differences in dichotomous variables. Differences between means were examined using the Student's t test for continuous variables.

Results: 130 subjects were approached for participation and 60 enrolled. Of the 60 subjects, 50 (83.3%) were female, 37(61.7%) were of the limited cutaneous subtype and 23 (38.3%) were the diffuse subtype of scleroderma. The mean age was 55 ± 11.1 years and mean disease duration was 15.3 ± 10.1 years. 17/60 (28%) had evidence of a peripheral neuropathy as defined by the presence of neuropathic symptoms on the TNS and/or electrophysiologic evidence of neuropathy. Subjects with neuropathy were more likely to be male (60% vs. 40%, p=0.02), African-American (41% vs. 4.6%, p=0.001), have diabetes (17.7% vs 0%, p=0.02), have limited cutaneous scleroderma (82.3% vs. 53.5%, p=0.04), and have RNP antibodies (23.5% vs 0%, p=0.009) than those without neuropathy. A potential non-scleroderma etiology for the peripheral neuropathy was defined in 82.3% (14/17) of subjects with neuropathy.

Conclusion: While symptoms or objective evidence of peripheral neuropathy is common among patients with scleroderma, the cause is usually explained by

co-morbid non-scleroderma related causes.



Disclosure: J. J. Paik, None; **A. Mammen**, None; **F. M. Wigley**, None; **A. A. Shah**, None; **L. K. Hummers**, None; **M. Polydefkis**, None.

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Abstract Number: 1873

Inter and Intrarater Reliability of the Modified Rodnan Skin Score in Early Diffuse Systemic Sclerosis

Jessica K. Gordon[1], Veronica J. Berrocal[2], Shervin Assassi[3], Elana J. Bernstein[4], Robyn T. Domsic[5], Faye N. Hant[6], Monique E. Hinchcliff[7], Elena Schiopu[8], Virginia D. Steen[9], Tracy M. Frech[10] and Dinesh Khanna[11], [1]Rheumatology, Hospital for Special Surgery, New York, NY, [2]Div of Rheumatology, University of Michigan, Ann Arbor, MI, [3]Rheumatology, University of Texas Medical School at Houston, Houston, TX, [4]Rheumatology, Columbia University College of Physicians & Surgeons, New York, NY, [5]Medicine - Rheumatology, University of Pittsburgh, Pittsburgh, PA, [6]Dept of Medicine, Medical University of South Carolina, Charleston, SC, [7]Division of Rheumatology, Division of Rheumatology, Northwestern University, Feinberg School of Medicine, Chicago, IL, [8]University of Michigan, Ann Arbor, MI, [9]Rheumatology, Georgetown University Medical Center, Washington, DC, [10]Div of Rheumatology, University of Utah, Salt Lake City, UT, [11]Division of Rheumatology, University of Michigan, Ann Arbor, MI
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Session Time: 9:00AM-11:00AM

Background/Purpose:

The Modified Rodnan Skin Score (MRSS) is a semiquantitative assessment of skin thickness which is a commonly used outcome measure in Systemic Sclerosis (SSc) clinical trials. The MRSS has been shown to be reproducible among different observers and within the same observer over time as determined by inter and intraobserver means and standard deviations (SD). The objective of this study was to determine the inter and intrarater reliability of the MRSS in patients with early diffuse cutaneous (dc) SSc in the Prospective Registry of Early Systemic Sclerosis (PRESS) Cohort.

Methods:

A cross-sectional study was conducted over one day. Seven patients meeting ACR/EULAR criteria for SSc, with the diffuse subtype, and from the PRESS Cohort were examined by 10 rheumatologists. Prior to the exercise, the rheumatologists were trained in the MRSS examination as part of an investigator meeting for the Abatacept in Systemic Sclerosis Trial (ASSET.) The MRSS was performed by 10 examiners at 2 separate times on 5 patients. Patients underwent diagnostic testing between examinations, and so significant time elapsed between assessments, decreasing the possibility of recall bias. Data collection sheets were collected by a research coordinator immediately following each examination, and the investigators did not discuss their examinations with each other in order to avoid bias. For the continuous variable MRSS we computed the inter and intrarater reliability by fitting a linear mixed model to

the examiners' ratings with random effects for patient, rater, and patient by rater. For inter/intrarater reliability, the following values represent the following degrees of agreement: <0 – poor; 0-0.2 – slight; 0.21- 0.4 – fair; 0.41- 0.6 – moderate; 0.61-0.8 – substantial; and 0.81-1.0 – almost perfect agreement.

Results:

The mean age of the patients was 41.6 ± 19.8 years and the mean disease duration from the first non-Raynaud's symptom was 2.7 ± 0.8 years. Three patients were female and 4 male.

The interrater reliability for the MRSS was 0.81, and the intrarater reliability for the MRSS was 0.94. The interobserver mean for the MRSS was 14.67 and the within patient standard deviation was 4.04. The intraobserver mean for the MRSS was 15.04 and the within patient standard deviation was 2.30.

Conclusion:

We found the MRSS to have inter and intra-rater reliability of 0.81 and 0.94, respectively, suggesting almost perfect agreement among this group of investigators examining patients with early dcSSc. The within patient standard deviation was 4.04 in our study which is comparable to previously published figures of 4.6.[1] The intra observer patient standard deviation was 2.30 which is also similar to the previously published figure of 2.45. Our study confirms the reliability of MRSS in the study of patients with dcSSc. In-person training for MRSS should be considered before starting a multicenter randomized controlled trial.

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[1] Clements, PJ, et al. J Rheumatol 1995;22:1281-5

Disclosure: J. K. Gordon, Bayer, 5; **V. J. Berrocal**, None; **S. Assassi**, Biogen Idec, 5,Boehringer Ingelheim, 5; **E. J. Bernstein**, None; **R. T. Domsic**, Biogen-Idec, 5,Bayer, 5; **F. N. Hant**, None; **M. E. Hinchcliff**, None; **E. Schiopu**, None; **V. D. Steen**, None; **T. M. Frech**, None; **D. Khanna**, Bristol-Myers Squibb, 2,EMD Serono, 2,Genentech and Biogen IDEC Inc., 2,Bayer, 5,Biogen Idec, 5,Cytori, 5,EMD Serono, 5,Forward, 5,Genentech and Biogen IDEC Inc., 5,Gilead, 5,Lycera, 5,Seattle Genetics, 5.

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Abstract Number: 1874

Impact of Socioeconomic Status on Survival in Connective Tissue Disease Associated and Idiopathic Pulmonary Arterial Hypertension

Helen Jin[1], John T. Granton[2], John Thenganatt[3], Jakov Moric[3], Ambika Gupta[1], Amie T. Kron[1], Cathy Chau[1] and Sindhu R. Johnson[1], [1]Toronto Scleroderma Program, Toronto Western Hospital, Mount Sinai Hospital, University of Toronto, University Health Network Pulmonary Hypertension Programme, Toronto, ON, Canada, [2]Medicine, Univeristiy Health Network Pulmonary Hypertension Programme, Toronto General Hospital and University of Toronto, Toronto, ON, Canada, [3]Univeristiy Health Network Pulmonary Hypertension Programme, Toronto General Hospital and University of Toronto, Toronto, ON, Canada

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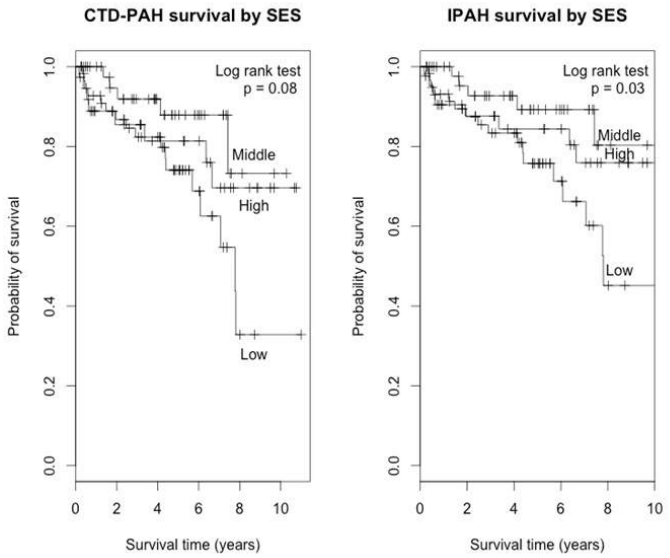
Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: Poorer health outcomes for persons with chronic diseases have been reported in association with lower socioeconomic status (SES). No such evaluation exists for patients with connective tissue disease associated pulmonary arterial hypertension (CTD-PAH). We evaluated the impact of SES on survival of patients with CTD-PAH and idiopathic PAH (IPAH).

Methods: A retrospective cohort study of patients attending the University Health Network Pulmonary Hypertension Programme and the Toronto Scleroderma Program was conducted. Using postal codes and census information for median household income, SES (low, middle, high) was assigned to each individual. Kaplan Meier curves were used to compare survival in different SES groups.

Results: 600 patients (n=445 CTD, n=155 IPAH) were identified. There were 209 deaths (n=177 CTD, n=32 IPAH). CTD-PAH patients stratified by SES had 5-year survival of 81.4% (95%CI 68.7%, 96.3%) for high SES, 87.9% (95%CI 77.2%, 100%) for middle SES and 74.1% (95%CI 62.2%, 88.3%) for low SES. IPAH patients stratified by SES had 5-year survival of 84.4% (95%CI 73.5%, 96.9%) for high SES, 89.2% (95%CI 79.7%, 100%) for middle SES and 75.7% (95%CI 64.4%, 89.0%) for low SES. IPAH patients with low SES had worse survival (log rank test p=0.03), and CTD-PAH patients had similar findings that bordered on statistical significance (log rank test p=0.08).



Conclusion: Socioeconomic inequalities appear to impact survival. Further research is required to understand the underlying basis for these findings including differences in disease severity, proximity to a hospital and effect of moving from one SES region to another.

Disclosure: H. Jin, None; **J. T. Granton**, Actelion, Bayer and GSK, 5,Bayer, Actelion, Pfizer, 9,Actelion and Bayer, 9,Actelion Pharmaceuticals US, 9,IKARIA, 9; **J. Thenganatt**, Pfizer Inc, Bayer, Actelion, 9; **J. Moric**, Actelion Pharmaceuticals US, Intermune, 9; **A. Gupta**, None; **A. T. Kron**, None; **C. Chau**, None; **S. R. Johnson**, None.

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Abstract Number: 1875

Deep Vein Thrombosis and Pulmonary Embolism in Systemic Sclerois

Nabil Hakami[1,2] and Sindhu R. Johnson[3], [1]Rheumatology, Toronto Scleroderma Program,Toronto Western Hospital, Mount Sinai Hospital,, Toronto, ON, Canada, [2]King Fahad Central Hospital, Riyad, Saudi Arabia, [3]Toronto Scleroderma Program, Toronto Western Hospital, Mount Sinai Hospital, University of Toronto, University Health Network Pulmonary Hypertension Programme, Toronto, ON, Canada

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Session Time: 9:00AM-11:00AM

Background/Purpose: In systemic sclerosis (SSc) vasculopathy causes frequent episodes of reperfusion injury and free radical mediated endothelial dysfunction, which may influence the onset of local thrombotic complications. Venous thromboembolism (VTE) is a vascular phenomenon that includes deep vein thrombosis (DVT) and pulmonary embolism (PE). The objectives of this study are to evaluate the prevalence of DVT and PE in SSc and evaluate risk factors for the development of PE or DVT in SSc patients.

Methods: We conducted a retrospective cohort study of patients who fulfilled the ACR–EULAR classification criteria for SSc attending the Toronto Scleroderma Program (Toronto Western Hospital, Mount Sinai Hospital, Toronto General Hospital) between 1970 - 2015. DVT was defined as the presence of thrombus on doppler ultrasound of either upper or lower extremity. PE was defined as the presence of thrombus on CT angiogram of the thorax.

Results: 927 SSc patients were included (761 females, 166 males). There were 31 (1.6%) VTE events, which is 10 times more frequent than would be expected in the general population. The prevalence of DVT was 16/927 (1.7%) and PE was 19/927 (2.1%). Anticardiolipin antibody was present in 1 patient with PE. Lupus anticoagulant was not present in any of the patients with VTE events. Patients with ILD more frequently experienced DVT (RR 2.85 95%CI (1.08, 7.54) but not PE (RR 1.82 (95%CI 0.89, 3.70). There was no significant difference in the occurrence of DVT or PE between SSc subtype (relative risk (RR) 0.95 (95%CI 0.46, 1.97), RR1.1 (95%CI 0.62, 2.04)), or presence of cancer (RR 2.48, (95%CI 0.81, 7.5), RR 0.87 (95%CI 0.20, 3.73), respectively.

Conclusion: Although uncommon, DVT and PE appear to occur more frequently in SSc. DVT occurs more frequently in SSc-ILD patients. VTE do not appear to be related to a hypercoagulable state.

Disclosure: N. Hakami, None; **S. R. Johnson**, None.

Abstract Number: 1876

Caveolin 1 Gene Variants May Effect Disease Progression in Systemic Sclerosis Related Interstitial Lung Disease

Sule Yavuz[1], Elena Lopez-Isac[2], Ahmet Mesut Onat[3], Neslihan Yilmaz[4], Levent Kilic[5], Ali Akdogan[5] and Javier Martín[6], [1]Rheumatology, Istanbul Bilim University, Faculty of Medicine,Department of Rheumatology, Istanbul, Turkey, [2]Institute of Parasitology and Biomedicine López-Neyra, IPBLN-CSIC, Granada, Spain, [3]Rheumatology, Gaziantep University School of Medicine, Gaziantep, Turkey, [4]Istanbul Bilim University, Faculty of Medicine, Rheumatology Department, Istanbul, Turkey, [5]Hacettepe University Vasculitis Center (HUVAC), Ankara, Turkey, [6]Instituto de Parasitología y Biomedicina López- Neyra, IPBLN-CSIC, PTS-Granada, Granada, Spain

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Session Time: 9:00AM-11:00AM

Background/Purpose:

To determine possible association of Cav-1 genetic variants: rs926198, rs959173 and rs9920 with SSc and/or SSc-related ILD progression.

Methods:

Three Cav-1 single nucleotide polymorphisms (SNPs) (rs 926198, rs 959173 and rs 9920) were genotyped in a total of 630 Turkish individuals (410 SSc patients and 220 healthy subjects). Genotyping was performed using TaqMan 5' allele discrimination predesigned assays from *Applied Biosystems*, Foster City, CA, USA) in a LightCycler® 480 Real-Time PCR System (*Roche Applied Science,* Mannheim, Germany). Genotyping call rate was > 98% for all the genotyped SNPs. Serum and sputum samples were collected from 54 SSc-ILD patients at 0, 6, and 12 months. Quantitative CT images were taken at 0,12 months. The possible association of Cav-1 gene SNPs and ILD progression in one-year follow up was determined.

Results:

A total of 402 SSc patients were recruited to the study (Mean age: 48.9 (12-78) and F:M; 390:20). The clinical characteristics of patients were as follows: Limited cutaneous SSc vs diffuse cutaneous SSc were 60.4% (n=243) vs 39.6 %(n=159), respectively. Interstitial lung disease was observed in 58.6% of patients (n=222). Anti-topoisomerase I antibodies (ATA) were found in 42.6% of patients (n=176). No significant association was observed between any CAV1 SNP and ATA. Genotype analysis and minor allele frequencies of the Cav-1 rs926198, rs959173 and rs 9920 SNP in patients with SSc and controls were shown in table 1. Among SSc-ILD patients who carried the rs959173 C minor allele displayed significantly higher CAV-1 in serum and lesser progression in ILD than in those carrying TT genotype (0.364±0.118 vs 0.247±072, $p<0.001$)

Conclusion:

Our results suggest that Cav1 rs959173 C allele may have a protective role in SSc-ILD progressions. Although a clear association of Cav 1 genetic variants and SSc was not determined in the Turkish patients with SSc, similar trends were observed with the previously published Italian cohort by Manetti M[1].

Table 1.

SNP	Subgroup	TT	TC	CC	MAF(%)	P value
rs926198T/C	Controls (n:217)	87 (40.1%)	98 (45.2%)	32 (14.7%)	37.3	NS
	SSc (n:402)	162(40.3%)	173 (43%)	67(16.7%)	38.1	NS
	lCSc (n:243)	97(39.9%)	110(45.2%)	36(14.9%)	37.4	NS
	dCSc (n:159)	62(38.9%)	73(42.1%)	24 (15%)	38.0	NS
rs959173T/C	Controls (n:217)	149(68.7%)	63 (29%)	5 (2.3%)	16.8	NS
	SSc (n:400)	284 (71%)	104(26%)	10 (2.5%)	15.5	NS
	lCSc (n:243)	170(69.9%)	67(27.6%)	6 (2.46%)	16.3	NS
	dCSc (n:157)	111(70%)	42 (26.8%)	4 (2.5%)	15.9	NS
Rs9920T/C	Controls (n:217)	192(88.6%)	25 (11.5%)	0	5.8	NS
	SSc (n:402)	342 (85.1%)	54 (13.4%)	6(1.5%)	8.2	NS
	lCSc (n:243)	194(79.8%)	46(18.4%)	3(1.2%)	10.7	P<0.01
	dCSc (n:159)	134(84.3%)	22(13.8%)	3(1.9%)	8.8	NS

Disclosure: S. Yavuz, None; **E. Lopez-Isac**, None; **A. M. Onat**, None; **N. Yilmaz**, None; **L. Kilic**, None; **A. Akdogan**, None; **J. Martín**, None.

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Abstract Number: 1877

Prevalence and Risk Factors for Left Ventricular Diastolic Dysfunction in Scleroderma

Srikanth Vemulapalli[1] and Vivien Hsu[2], [1]Graduate School of Biomedical Sciences, Rutgers University, New Brunswick, NJ, [2]Medicine, Rutgers University, New Brunswick, NJ

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Session Time: 9:00AM-11:00AM

Background/Purpose: Left ventricular diastolic dysfunction (LVDD) is more common in systemic sclerosis (SSc) compared to the general population (1). Focal myocardial ischemia and fibrosis are thought to be important in its pathogenesis (2). LVDD leading to heart failure is associated with increased mortality. Risk factors in SSc are not known, although advanced SSc lung complications may be more common (3).

Methods: We collected clinical information from a cohort of SSc (4) outpatients seen consecutively in our Scleroderma Program. LVDD was confirmed by the last echocardiogram (Tissue Doppler) report. Interstitial lung disease (ILD) confirmed by high resolution chest CT (HRCT) and pulmonary hypertension (PH) diagnosed by right heart catheterization. Univariate and multivariate regression analyses were conducted to determine common factors associated with LVDD.

Results: Table 1 shows analysis of 300 patients; 133(44%) had LVDD. Univariate analysis found patient's advanced age, disease duration (from onset of Raynaud's phenomenon), Anti-centromere antibody, presence of SSc lung complications, systemic hypertension, smoking, valvular heart disease, chronic kidney and thyroid diseases were commonly associated with LVDD. However, using multivariable regression analysis, advanced age was the most significant factor associated with LVDD, followed by systemic hypertension, and SSc lung complications.

Conclusion: LVDD was common in our SSc cohort with a prevalence of 44%. Advanced age, systemic hypertension, and the presence of ILD or PH were

independent risk factors for LVDD. LVDD should be considered in any SSc patient with dyspnea. Further research to find more effective treatment for LVDD is needed to improve outcomes in this patient population.

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3. Hinchcliff, M et al: ***Clin Exp Rheumatol.*** 2012; 30(2 Suppl 71): p. S30-7.
4. Hoogen F et al: ***Arthritis Rheum.*** 2013; 65 (11):2737-47 and ***Ann Rheum. Dis.*** 2013; 72(11): 1747-55,

Table 1: Clinical characteristics in SSc patients with and without LVDD.

Characteristic	Absent LVDD (N=167)	Present LVDD (N=133)	p-Value
Age, yrs (Mean+SD)	53 + 13	66 + 10	<0.001*
Female, n(%)	141(84)	116(87)	0.5
BMI: Normal, n(%)	75(45)	55(41)	0.8
Underweight	14(8)	9(7)	
Overweight	52(31)	42(33)	
Obese	28(18)	27(20)	
Race: Caucasian, n(%)	105(63)	94(71)	0 .3
Hispanic	19(11)	8(6)	
African American	22(13)	12(9)	
Asian	10(6)	8(6)	
Native American	11(7)	11(8)	
Type of Scleroderma:	63(38)	42(32)	0.05
Diffuse,n(%)	54(32)	61(46)	
Limited	50(30)	30(22)	
Overlap			
Disease Duration(years) (Mean+SD)	12 + 8	18 + 12	<0.001*
Years of Raynaud (Mean+SD)	12 + 9	18 + 13	<0.001*
mRSS (Mean+SD)	12 + 10	9 + 9	0.05
	61(37)	51(38)	0.3
NailfoldCapillaroscopy: N/(%)	86(51)	57(43)	
Normal			
Abnormal			
Autoantibodies:	147(86)	118(84)	0.9
ANA, n(%)	28(17)	15(11)	0.16
Anti-nucleolar	38(22)	44(33)	0.04*
Anti-centromere	48(29)	29(22)	0.2
Anti-Scl70	13(8)	10(8)	0.9
Anti-RNA pol 3	21(13)	14(11)	0.6
Anti-RNP antibody	5(2)	1(1)	0.2
Anti-PMScl			
Pulmonary fibrosis	81 (49)	48 (36)	0.03
Absent n(%)	86 (51)	85 (64)	<0.001
Present n(%)	18 (11)	36 (27)	

Pulmonary Hypertension n(%)			
Systemic Hypertension n(%)	39(23)	64(48)	0.001
Valvular heart disease n(%)	27(16)	38(29)	0.01

Table 2: Multivariate Regression Analysis for clinical characteristics associated with LVDD

	b*	**p-value**	**Crude OR (95% CI)**	**Adjusted OR (95% CI)**	**P -value**
Age	0.308113	**0.000003**	1.60 (1.50-1.70)	1.39 (1.26 – 1.52)	<0.001
Disease Duration	0.146509	0.192798			
Duration of Raynaud (yrs)	-0.052186	0.635159			
Systemic Hypertension	0.150522	**0.00853**	.30 (1.16-1.46)	1.16 (1.04-1.30)	<0.01
Smoking history	0.088763	0.099324			
Thyroid disease	-0.038341	0.501586			
Valvular heart disease	0.052880	0.339044			
Renal disease	0.053526	0.325202			
Pulmonary fibrosis	0.120043	**0.03971**	1.13 (1.01-1.27)	1.13 (1.01-1.26)	< 0.04
Pulmonary hypertension	0.133191	**0.01769**	1.23 (1.10 – 1.38)	1.16 (1.02 – 1.27)	<0.02
Anti-Centromere	0.086025	0.162729			

Disclosure: S. Vemulapalli, None; **V. Hsu**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/prevalence-and-risk-factors-for-left-ventricular-diastolic-dysfunction-in-scleroderma

Abstract Number: 1878

Diagnostic Performance of the 2013 ACR/EULAR Classification Criteria for Systemic Sclerosis: Results from a Brazilian Validation Cohort

Farley Carvalho[1], Cintia Camargo[2], Bruna Fernandez[1] and **Cristiane Kayser**[2], [1]Universidade Federal de São Paulo, São Paulo, Brazil, [2]Rheumatology Division, Universidade Federal de São Paulo, São Paulo, Brazil

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Session Time: 9:00AM-11:00AM

Background/Purpose: New classification criteria for systemic sclerosis (SSc) were proposed by the ACR/EULAR in 2013, due to the low sensitivity of the 1980 ACR classification criteria for patients with early and limited SSc. This study aimed to evaluate the diagnostic performance of the new ACR/EULAR classification criteria for SSc in clinical practice including patients with early SSc.

Methods: Data from 178 patients with SSc, including 122 patients with established SSc (according to the 1980 ACR criteria) and 56 with early SSc (according to the LeRoy and Medsger 2001 criteria) were consecutively collected from September 2014 to May 2015 from a tertiary outpatient clinic. Data from 141 control patients with systemic lupus erythematosus, dermato/polymyositis, mixed connective tissue disease, undifferentiated connective tissue disease, Sjögren's Syndrome, and primary Raynaud's phenomenon were also collected. The sensitivity and specificity of the old and the new ACR/EULAR criteria were determined in several subgroups of patients with early SSc. The diagnostic performance of each item of the new criteria was also evaluated.

The performance of the new ACR/EULAR criteria in discriminating SSc patients from controls was also evaluated by means of the Receiver Operating Characteristic (ROC) curve analysis. The best cut-off was determined based on the Youden's index criteria.

Results: The new classification criteria showed a sensitivity of 77.6% and a specificity of 98.5% among the 178 patients with established and early SSc, and had a significantly higher sensitivity compared to the 1980 ACR criteria ($p<0.001$) (Table 1). Sixteen of 56 (28.5%) patients who were classified as patients with early SSc, were newly classified as SSc by the 2013 ACR/EULAR criteria. Sensitivity and specificity showed an excellent performance when only early SSc patients with both abnormal nailfold capillaroscopy and positive SSc-related antibodies were included (sensitivity of 90.0% and specificity of 98.5%) (Table 1). For this sample, the new classification criteria presented high accuracy in diagnosing SSc, with an area under the ROC curve (AUC) of 0.996 (95%CI 0.99-1.00; $p<0.001$). The best cut-off was a score of ≥8 (sensitivity of 96.1% and specificity of 97.9%). Abnormal nailfold capillaroscopy and sclerodactily were the individual items with the best performance (sensitivity of 93.3% and 78.2%; specificity of 83.6% and 100%, respectively).

Table 1.Sensitivity and specificity of the 1980 ACR criteria and the 2013 ACR/EULAR criteria in different subsets of patients

	ACR 1980		ACR/EULAR 2013	
	Sensitivity (95% CI)	**Specificity (95% CI)**	**Sensitivity (95% CI)**	**Specificity (95% CI)**
SSc patients (established and early SSc) (n=178)	68% (0.60- 0.74)	100% (0.97- 1.00)	77.6% (0.71-0.83)	98.5% (0.94-0.99)
Established SSc and early SSc with abnormal nailfold capillaroscopy and positive SSc-related antibodies (n=152)	80% (0.73-0.85)	100% (0.97-1.00)	90% (0.85-0.94)	98.5% (0.94-0.99)
Early SSc (n=56)	0% (0-0.06)	100% (0.97-1.00)	28.5% (0.18-0.41)	98.5% (0.94-0.99)
Early SSc subsets				
Raynaud's phenomenon plus abnormal nailfold capillaroscopy and positive SSc-related antibodies (n=13)	-	-	53% (0.29-0.76)	98.5% (0.94-0.99)
Raynaud's phenomenon plus abnormal nailfold capillaroscopy and negative SSc-related antibodies (n=31)	-	-	22% (0.11-0.39))	98.5% (0.94-0.99)
Raynaud's phenomenon plus normal nailfold capillaroscopy and positive SSc-related antibodies (n=12)	-	-	16% (0.04-0.44)	98.5% (0.94-0.99)

Conclusion: The 2013 ACR/EULAR classification criteria for SSc presented higher sensitivity than the 1980 ACR criteria particularly among patients with early SSc. The cut-off of ≥ 8 for total score showed an excellent sensitivity with no loss of the specificity for the classification of patients with SSc in this cohort of patients, and may allow early intervention among patients with early disease.

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Abstract Number: 1879

Immunosuppressive "Routine" Treatment of SSc Patients with Limited Cutaneous Involvement and Interstitial Lung Disease

Dörte Huscher[1], Sabine Adler[2], Elise Siegert[3], Giuseppina Abignano[4], Yannick Allanore[5], Jerome Avouac[6], Kerstin Becker[7], Laszlo Czirjak[8,9], Francesco Del Galdo[10], Christopher P. Denton[11], Oliver Distler[12], Ivan Foeldvari[13], Beata Garay-Toth[14], Serena Guiducci[15], Veronika K. Jaeger[16], Veronika Lóránd[9], Marco Matucci-Cerinic[17], Britta Maurer[18], Ulf Müller-Ladner[19], Svetlana I. Nihtyanova[20], Ingo H. Tarner[21], Gabriele Valentini[22], Serena Vettori[23], Ulrich A. Walker[24] and Gabriela Riemekasten[25], [1]Charité-University Hospital and German Rheumatism Research Centre, Berlin, Germany, [2]Rheumatology, Immunology, Allergology, University Hospital Bern, Bern, Switzerland, [3]Rheumatology and Clinical Immunology, Charité – University Hospital, Berlin, Berlin, Germany, [4]Clinical and Experimental Medicine, Second University of Naples, Napoli, Italy, [5]Department of Rheumatology A, Paris Descartes University, Cochin Hospital, Paris, France, [6]Paris Descartes University, Rheumatology A department, Cochin Hospital, Paris, France, [7]Rheumatology and Clinical Immunology, Charité University Hospital, Berlin, Germany, [8]Rheumatology, Pecs, Hungary, [9]Rheumatology and Immunology Medical School, University of Pécs, Pécs, Hungary, [10]Scleroderma Group, Leeds Institute of Molecular Medicine, Leeds, United Kingdom, [11]Rheumatology and Connective Tissue Diseases, University College London, London, United Kingdom, [12]Department of Rheumatology, Research of Systemic Autoimmune Diseases, University Hospital Zurich, Zurich, Switzerland, [13]Hamburger Zentrum für Kinder-und Jugendrheumatologie, Hamburg, Germany, [14]FESCA, Budapest, Hungary, [15]Rheumatology, University of Florence, Florence, Italy, [16]Department of Rheumatology, University Hospital

Basel, Basel, Switzerland, [17]Dept of Medicine/Div of Rheum, University of Florence, Firenze, Italy, [18]r, University Hospital Zurich, Zurich, Switzerland, [19]Internal Medicine and Rheumatology, Justus-Liebig-University of Giessen, Kerckhoff-Klinik, Bad Nauheim, Germany, [20]Rheumatology, UCL Division of Medicine, London, United Kingdom, [21]Rheumatology and Clinical Immunology, Justus-Liebig-University of Giessen, Kerckhoff-Klinik, Bad Nauheim, Germany, [22]Internal and Experimental Medicine, Rheumatology Unit, Second University of Naples, Naples, Italy, [23]Department of Internal and Experimental Medicine, Rheumatology Unit, Second University of Naples, Naples, Italy, [24]Rheumatology, Systemic Sclerosis, Basel, Switzerland, [25]Clinic of Rheumatology, University of Luebeck, Lübeck, Germany
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Background/Purpose:

Interstitial lung disease (ILD) represents one of the most frequent causes of death in systemic sclerosis (SSc) patients. Yet, there are no approved drugs for treatment of SSc-ILD. At present, data on immunosuppressive therapy in patients with ILD and limited cutaneous (lc) involvement are missing.

Methods:

The European Scleroderma Trials and Research (EUSTAR) database was established in 2004 to annually collect data on specialized care of patients with SSc. Data from patients with lc SSc and ILD, where immunosuppressive therapy can be assumed to be mainly intended to treat ILD, were analyzed to describe current use of immunosuppressants and to recognize patterns of treatment choices.

Results:

Out of a cohort of 12,536 SSc patients, we identified 1,814 adult patients fulfilling the 1980 ACR or the 2013 ACR-EULAR criteria, with lc involvement and signs of ILD (either on chest X-ray or high resolution computed tomography) with at least one valid report on immunosuppressive treatment.

Mean age was 58.7±13.1 years, with 88.9% females and a mean SSc disease duration of 10.2±8.6 years. Mean mRSS was 6.1±4.7.

Compared to the 1,119 (62%) patients who had at least one episode of immunosuppressive therapy the 695 (38%) patients without use of immunosuppressants ever were on average 5 years older, had a 2.4 years longer median disease duration, higher DLCO (single breath) and FVC values and consequently less often a pulmonary restrictive defect.

The immunosuppressants most frequently used were prednisolone (pred; 52.6%), azathioprine (aza; 13.9%), cyclophosphamide (cyc; 13.8%), methotrexate (mtx; 11.7%), and mycophenolate mofetil (mmf; 11.0%); all others were prescribed in less than 2%. With regard to highest treatment intensity ever received, 31.6% of the patients got monotherapies and 26.3% combinations of two drugs, while triple therapy was comparably rare with 3.6%. Overall, immunosuppressive treatment was less frequent than in diffuse cutaneous type (82%), this was true for mmf or cyc monotherapy and any combination therapies.

When comparing patient characteristics at the treatment start of the most frequent regimens, differences compared to the “never IS” group and between treatment arms become apparent with regard to age, NYHA class, Scl70 antibodies, mRSS, ground glass opacification, lung function parameters and the proportion with pulmonary restrictive defect (table 1).

Table 1: Patient characteristics in the never IS group and at start of most frequent treatment regimens which are sorted by descending FVC; significant differences (p<0.05) compared to the never IS group are marked with a *.

	never IS (n=695)	MTX (n=47)	Pred (n=350)	MMF (n=49)	AZA (n=66)	Pred+ MTX (n=80)	Pred+ MMF (n=71)	Pred+ AZA (n=104)	CYC (n=32)	Pred+ CYC (n=68)
	%	%	%	%	%	%	%	%	%	%
Male gender	9.8	*0	8.3	16.3	13.6	6.3	14.1	16.3	12.5	7.4
NYHA class III+IV	13.5	9.3	*19.0	23.9	6.3	11.1	19.7	17.3	*39.3	*26.5
SCL70+	22.9	*44.7	*32.7	*51.3	*38.6	*35.8	*46.0	*41.3	*43.5	*45.9
Ground glass opacification	26.2	31.0	25.8	*50.0	39.0	35.7	*57.4	*38.4	*55.6	*51.9
Pulmonary restrictive defect	29.8	31.0	33.8	39.5	*44.8	35.5	*43.6	*40.7	*56.5	*46.9
	mean	mean	mean	mean	mean	mean	mean	mean	mean	mean
Age (years)	61.9	*58.6	61.0	*56.1	*56.6	*58.5	*54.6	*56.2	*58.1	*54.2
Disease duration (years)	11.7	10.7	*13.2	13.1	12.2	12.0	12.2	12.5	8.8	10.2
mRSS	6.1	5.2	*4.6	*4.5	*4.3	*4.8	*4.1	*4.8	6.9	*4.9
DLCO/SB (%pred.)	68.0	65.9	*60.9	*58.8	*61.8	*62.3	*55.4	*60.1	*46.5	*51.4
FVC (%pred.)	97.4	98.0	*91.6	*91.5	*90.3	*89.3	*88.2	*84.0	*83.3	*82.1
FEV1 (%pred.)	92.6	94.2	90.0	90.7	87.6	90.9	88.3	*85.6	*80.5	*87.6
TLC (%pred.)	91.4	92.9	*84.7	*80.0	*81.9	86.2	*81.6	*77.7	*76.4	*74.7

mRSS= modified Rodnan skin score; DLCO/SB= single breath diffusing capacity for monoxide; FVC= forced vital capacity; FEV1= forced expiratory volume in 1 second, TLC= total lung capacity

Conclusion:

“Everyday” use of immunosuppressants is frequent in SSc-ILD patients with lc involvement, showing a wide variety of single and combined immunosuppressive therapies with distinct patient patterns between treatment regimens. However, prospective studies are still necessary to define indications and outcomes. The EU-funded international FP7 DeSScipher research project was initiated to achieve this goal, comprising 5 prospective observational trials addressing the most frequent medical problems in SSc patients.

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Abstract Number: 1880

Circulating Microparticle Populations May Differentiate Between Connective Tissue Diseases.

Eoghan M. McCarthy[1,2], Daniel Moreno-Martinez[3], Fiona Wilkinson[4], Neil J McHugh[5,6], Ian N. Bruce[7,8], Yvonne Alexander[3], John D. Pauling[6,9] and Ben Parker[7,8], [1]The University of Manchester, Centre for Musculoskeletal Research, Institute of Inflammation and Repair, Manchester Academic Health Science Centre, Mmanchester, United Kingdom, [2]NIHR Manchester Musculoskeletal Biomedical Research Unit, Central Manchester University Hospital NHS Foundation Trust, Manchester, United Kingdom, [3]Healthcare Science Research Institute, Manchester Metropolitan University, Manchester, United Kingdom, [4]School of Healthcare Science, Manchester Metropolitan University, Manchester, United Kingdom, [5]Rheumatology, Bath Institute of Rheumatic Diseases, Royal National Hospital for Rheumatic Diseases, Bath, United Kingdom, [6]Department of Pharmacy and Pharmacology, University of Bath, Bath, United Kingdom, [7]Central Manchester University Hospital NHS Foundation Trust and Manchester Academic Health Science Centre, NIHR Manchester Musculoskeletal Biomedical Research Unit, Manchester, United Kingdom, [8]Stopford Building, Arthritis Research UK Centre for Epidemiology, Centre for Musculoskeletal Research, Institute of Inflammation and Repair, Manchester Academic Health Science Centre, The University of Manchester, Manchester, United Kingdom, [9]Upper Borough Walls, Royal National Hospital for Rheumatic Disease, Bath, United Kingdom

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Background/Purpose:

Microparticles (MPs) are membrane-bound vesicles derived from vascular and intravascular cells such as endothelial cells (EMPs) and platelets (PMPs). Circulating MPs levels are altered in autoimmune rheumatic diseases (AIRDs) and may act as a diagnostic and prognostic biomarker, but their precise functional role remains to be elucidated. We investigated EMP and PMP numbers across a spectrum of AIRDs with the aim of comparing the levels of, and relationship between, EMPs and PMPs.

Methods:

Patients with Systemic Lupus Erythematosus (SLE) (n=24), Systemic Sclerosis (SSc) (n=24), Primary Raynauds Phenomenon(RP) (n=17) and “other CTD” (n=15) (Primary Sjogrens Syndrome, UCTD or MCTD) as well as 15 healthy controls were recruited. Plasma levels of EMPs (AnnexinV+/CD31+/CD42b-) and PMPs (AnnexinV+/CD31+/CD42b+ or AnnexinV+/CD31-/CD42b+) were quantified using flow cytometry.

Results:

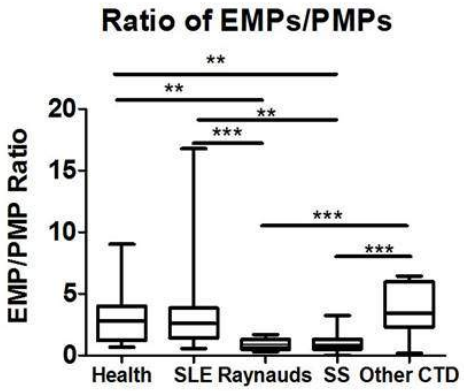
Patients with SLE had significantly higher EMPs compared with healthy controls and SSc patients [(SLE vs health 293,889/ml vs 132,171/ml, $p = 0.03$), (SLE vs SSc 293,889/ml vs 161,271/ml, $p = 0.04$)]. In contrast significantly higher PMP levels were noted in SSc and primary RP when compared to healthy controls and patients in the other CTD cohort [(SSc vs health 186,348/ml vs 41,085/ml, $p < 0.001$), (SSc vs other CTD 186,348/ml vs 58,178/ml, $p < 0.001$)]. No significant difference was observed in PMP levels between SLE patients and those with SSc/RP.

A modest correlation was noted between EMP and PMP levels in health (Spearman $r = 0.6$, $p = 0.017$). This relationship appeared stronger in SLE (Spearman $r = 0.72$, $p < 0.0001$) and other CTD patients (Spearman $r = 0.75$, $p < 0.0001$). The association between EMPs and PMPs was notably less strong in SSc (Spearman $r = 0.45$, $p = 0.014$) and RP (Spearman $r = 0.37$, $p= 0.15$). A significantly lower EMP/PMP ratio was seen in SSc/RP patients in comparison to both healthy controls and SLE/other CTD patients (Figure 1). Improved disease control, following alteration in immunosuppressive therapy, was associated with a reduction in EMP and PMP numbers in SLE, a result that was significant for PMPs (75,969/ml vs 32,171/ml, $p = 0.02$). In contrast, the addition of Asasantin in SSc/primary RP patients did not affect MP levels at follow up.

Conclusion:

MP populations differ across the spectrum of AIRDS, with high PMPs seen in SSc/RP and high EMPs observed in SLE. The ratio of EMPs/PMPs appears to distinguish between SLE/other CTD and SSc/primary RP, suggesting differential production of MPs according to the vascular pathology and bed involved. Improved disease control reduces PMP levels in SLE, but antiplatelet agents do not materially affect MP numbers in SSc/RP. MPs may therefore act as diagnostic and prognostic biomarkers in AIRDs.

Figure 1. The ratio of EMPs/PMPs in SLE, primary Raynauds, Systemic Sclerosis and other CTD patients.



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Abstract Number: 1881

Is the Presence of Esophageal Dilation a Poor Prognostic Factor in Dilated Interstitial Lung Disease Associated with Systemic Sclerosis?

Javier Narváez[1], Sergi Heredia[2], Helena Borrell Paños[2], Eulalia Armengol[2], Eugenia De Lama[3] and Jose Antonio Narvaez[3], [1]Rheumatology, Hospital Universitario de Bellvitge, Barcelona, Spain, [2]Department of Rheumatology, Hospital Universitario de Bellvitge, Barcelona, Spain, [3]Department of Radiology. Hospital Universitario de Bellvitge, Barcelona, Spain

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Background/Purpose: Several studies have shown that gastroesophageal reflux disease (GERD) is a risk factor in the progression of idiopathic pulmonary fibrosis. In systemic sclerosis (SSc), esophageal involvement is common; however, it does not generate symptoms in 50% of patients. Therefore, the presence of esophageal dilation and GERD may be a poor prognostic factor in patients with systemic sclerosis and diffuse interstitial lung disease (ILD-SSc) as a result of recurrent episodes of micro-aspiration. Our objective was to analyze whether the presence of esophageal dilation is a poor prognostic factor in ILD-SSc.

Methods: Thirty-one patients with SSc (ACR/EULAR 2013 criteria) and secondary symptomatic ILD, as confirmed by thoracic HRCT, were studied. HRCT images performed at the time of ILD diagnosis were reviewed with particular attention to: *a)*the presence of dilation in the lower two-thirds of the esophagus and b) the extent of ground glass areas and fibrotic changes (honeycombing areas, thickening of the interlobular septa and traction bronchiectasis with architectural distortion). The extent of HRCT lung abnormalities were scored in 3 categories: 1 = involvement of < 25% of total pulmonary parenchyma, 2 = 25-30%, and 3 = > 50%.

Results: Esophageal dilation was detected in the HRCT of 15 (48%) patients. The main clinical characteristics of the patients and the results from the comparative study between groups are shown in the following table:

	Esophageal dilation in the HRCT N= 15	No esophageal dilation in the HRCT N=16	*p*
Age (mean±SD), yrs	54 ± 16	63 ± 15	0.120
SSc Types	Limited :5 Diffuse: 9 SSc sine escleroderma 1	Limited: 12 Difuse: 2 SSc sine escleroderma:2	0.022
SSc disease duration (median ±SD), months	102 ± 143	112 ± 95	0.812
ILD type	NSIP: 12 UIP: 3	NSIP:12 UIP:4	0.095
ILD disease duration (median ±SD), months	35 ± 27	70 ± 44	0.014
Baseline HRCT			
Ground glass areas	Score 1: 6 Score 2: 6 Score 3: 0	Score 1: 10 Score 2: 1 Score 3: 0	0.033
Fibrotic changes	Score 1: 2 Score 2: 4 Score 3: 0	Score 1: 4 Score 2: 0 Score 3: 0	0.035
Baseline PFT			
FVC% (mean ± SD)	83.9 ± 22.1	103.4 ± 19.5	0.015
TLC%	87.9 ± 25.7	110.7 ± 33.9	0.116
DLCO%	57.4 ± 17.9	71.3 ± 24.3	0.095
PFT at the end of the follow-up period			
FVC%	79 ± 20.8	98.3 ± 26	0.031
TLC%	79 ±19.2	98.5 ± 26.8	0.067
DLCO%	48.8 ±15.7	62.2 ±18.3	0.046
Treatment with CYC and/or rituximab	10 (67%)	5 (31%)	0.049
Treatment with proton pump inhibitors	14 (93%)	11 (69%)	0.172

At the time of ILD-SSc diagnosis, patients with esophageal dilation showed a greater extent of *ground glass* areas ($P = 0.033$) and fibrotic changes ($P = 0.035$) in the HRCT. A relatively common finding in these patients was an asymmetry in injury severity with greater involvement in one of the two lungs. In addition, patients with esophageal dilation showed greater deterioration of lung function parameters, although the differences were only statistically significant for baseline ($P = 0.015$) and final ($P = 0.031$) FVC measurements and for the final DLCO measurement ($P= 0.046$). These patients also received more frequent treatment with CYC or rituximab.

Conclusion: The presence of esophageal dilation appears to be a poor prognostic factor in ILD-SSc, which relates to a greater extent of HRCT lung abnormalities and further deterioration in baseline pulmonary function tests (PFT)

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Abstract Number: 1882

The Predictive Value of Pulmonary Function Tests to Diagnose Interstitial Lung Disease in Adults with Early Diffuse Cutaneous Systemic Sclerosis

Elana J. Bernstein[1], Veronica J. Berrocal[2], Virginia D. Steen[3], Victoria K. Shanmugam[4,5], Ami A. Shah[6], Monique E. Hinchcliff[7], Faye N. Hant[8], Jessica K. Gordon[9], Tracy M. Frech[10], Robyn T. Domsic[11], Shervin Assassi[12] and Dinesh Khanna[13], [1]Rheumatology, Columbia University College of Physicians & Surgeons, New York, NY, [2]Div of Rheumatology, University of Michigan, Ann Arbor, MI, [3]Rheumatology, Georgetown University Medical Center, Washington, DC, [4]Division of Rheumatology, The George Washington University, Washington, DC, [5]Director, Division of Rheumatology, The George Washington University, Washington, DC, [6]Rheumatology, Johns Hopkins University School of Medicine, Baltimore, MD, [7]Rheumatology, Northwestern University, Chicago, IL, [8]Dept of Medicine, Medical University of South Carolina, Charleston, SC, [9]Rheumatology, Hospital for Special Surgery, New York, NY, [10]Div of Rheumatology, University of Utah, Salt Lake City, UT, [11]Medicine - Rheumatology, University of Pittsburgh, Pittsburgh, PA, [12]Rheumatology, University of Texas Medical School at Houston, Houston, TX, [13]Division of Rheumatology, University of Michigan, Ann Arbor, MI

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Background/Purpose: Interstitial lung disease (ILD) is the leading cause of death in patients with systemic sclerosis (SSc). Patients with diffuse cutaneous systemic sclerosis (dcSSc) have an increased risk of the development of ILD. High resolution computed tomography of the chest (HRCT) is the radiographic gold standard for the diagnosis of ILD. Pulmonary function testing (PFT) is a common screening method for ILD. However, some SSc patients with entirely normal PFTs have ILD evident on their HRCTs. Our aim was to assess the performance characteristics of PFTs for the diagnosis of ILD in patients with early dcSSc, using HRCT as the reference standard.

Methods: Subjects were enrolled in the Prospective Registry of Early Systemic Sclerosis (PRESS), a multicenter, prospective registry of adults with early dcSSc (disease duration < 2 years from first non-Raynaud's symptom), between April 2012 and June 2015. Subjects were included in this study if they had baseline PFTs. The presence or absence of ILD on HRCT was determined by chest radiologists at each center. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of forced vital capacity (FVC), total lung capacity (TLC), and diffusion capacity for carbon monoxide (DLCO) for the diagnosis of ILD were calculated. A cut-off point of <80 %predicted was defined as abnormal for each PFT parameter.

Results: The mean age of the 91 subjects with baseline measurements of FVC was 52 years (± 15.3); 68% were female and 74% were white. 54% of the 50 subjects who underwent HRCT had radiographic evidence of ILD (Table 1). DLCO had a higher sensitivity for the diagnosis of ILD than either FVC or TLC alone (Table 2). The combination of FVC and DLCO had a higher sensitivity for the diagnosis of ILD than DLCO alone. However, all PFT parameters (either alone or in combination) had only moderate specificity.

Conclusion: Although the combination of FVC and DLCO had excellent sensitivity for the diagnosis of ILD in early dcSSc, this combination only had moderate specificity for the diagnosis of ILD. Given the increased risk of ILD in patients with dcSSc, it may be reasonable to order an HRCT for all patients newly diagnosed with dcSSc, regardless of PFT results. Future work is needed to develop the optimal screening algorithm for ILD in patients with dcSSc.

Table 1: Baseline Characteristics of Subjects	
	N = 91
Age, mean ± SD	52.0 ± 15.3
Female sex, n (%)	62 (68.1)
Race	
Black, n (%)	10 (15.3)
White, n (%)	71 (73.7)
ANA positive, n (%)	58/68 (85.3)
Anti-Scl-70 positive, n (%)	22/67 (32.8)
Anti-RNA polymerase III positive, n (%)	34/56 (60.7)
FVC %predicted, mean ± SD	79.9 ± 21.2
TLC %predicted, mean ± SD	84.4 ± 23.8 n = 61
DLCO %predicted, mean ± SD	70.1 ± 25.5 n = 86
ILD on HRCT, n (%)	27/50 (54.0)

Table 2: Performance Characteristics of PFTs with HRCT for the Diagnosis of ILD					
Test	**N**	**Sensitivity**	**Specificity**	**PPV**	**NPV**
FVC < 80 %predicted	45	56.0%	55.0%	60.9%	50.0%
TLC < 80 %predicted	34	52.9%	70.6%	64.3%	60.0%
DLCO < 80 %predicted	42	86.4%	60.0%	70.4%	80.0%
FVC & DLCO < 80 %predicted	42	90.9%	45.0%	64.5%	81.8%
FVC & DLCO & TLC < 80 %predicted	34	88.2%	47.1%	62.5%	80.0%

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Abstract Number: 1883

Association of Myocardial Abnormalities with Disease Characteristic and Brain Natriuretic Peptide (BNP) in Systemic Sclerosis without Cardiac Symptoms As Assessed Using Cardiac Magnetic Resonance Imaging; A Prospective Multi Center Study

Kaita Sugiyama[1], Hitomi Kobayashi[2], Yasuyuki Kobayashi[3], Yosuke Nagasawa[1], Natsumi Ikumi[4], Takamasa Nozaki[5], Hirotake Inomata[1], Hidetaka Shiraiwa[6], Hiromi Karasawa[6], Noboru Kitamura[7], Mitsuhiro Iwata[5], Yoshihiro Matsukawa[6] and Masami Takei[5], [1]Nihon University School of Medicine, Tokyo, Japan, [2]Hematology and Rheumatology, Nihon University School of Medicine, Tokyo, Japan, [3]Advanced Biomedical Imaging Informatics, St.Marianna University School of Medicine, Kawasaki, Japan, [4]Nihon University School of Medicine, Shinjuku, Japan, [5]Division of Hematology and Rheumatology, Nihon University School of Medicine, Tokyo, Japan, [6]Division of Heamatology and Rheumatology, Nihon University School of Medicine, Tokyo, Japan, [7]NIhon University School of Medicine, Tokyo, Japan
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Background/Purpose: In the majority of SSc patients, however, cardiac involvement often remains subclinical. Primary myocardial abnomalities are characterized by fibrosis. Cardiovascular magnetic resonance (CMR) can non-invasively detect subclinical myocardial inflammation and fibrosis. Brain natriuretic peptide (BNP) has become important cardiac biomarkers. We evaluated the association of myocardial abnormalities and LV geometry ,assessed by CMR, with disease characteristic and BNP in SSc patients without cardiac symptoms.

Methods: Patients were recruited from3 hospitals in Tokyo. This study compared consecutive female SSc patients without cardiac symptoms and healthy female controls with no history or clinical findings of systemic and pulmonary hypertension by echocardiography, coronary artery disease, valvular heart disease, atrial fibrillation, diabetes mellitus, and dyslipidemia. All underwent contrast or non-contrast CMR on a 3.0-T scanner. LV function was measured using ejection fraction (EF), end-systolic volume (ESV), end-diastolic volume (EDV), stroke volume (SV), and cardiac output (CO). LV hypertrophy was measured by absolute LV mass (LVM) and LVM index (LVMI) determined by LVM/body surface area. LGE was obtained to assess myocardial fibrosis. Myocardial inflammation was assessed by black- blood T2WI. Serum BNP concentrations were measured simultaneously.

Results: There were 50 SSc patients with a mean age of 55.1 ± 7.7 years; 25 had diffuse type and 25 had limited type. There were 20 healthy controls with a mean age of 56.9 ± 3.1 years. There were no significant differences in terms of age, gender, and cardiovascular risk factors. Compared with the control, SSc patients had a significantly higher EDV with tendency towards a high LVMI. There was no difference in EF between control and patients of SSc . LGE (+) was detected in 27 of 50 (54%) SSc patients. T2WI was observed in 13 of 50 (26%) patients of SSc. There were no differences in LGE and T2WI between the diffuse and limited type. The mean of BNP level in SSc group was significantly higher than that of the control group ($P = 0.02$). The mean of BNP level in SSc patients with LGE (+) was significantly higher than that of SSc patients without LGE ($P < 0.001$). BNP level in SSc patients was significantly correlated with LVMI ($P < 0.001$) but not correlated with EF. Eccentric hypertrophy was observed in 55% of LGE (+) patients. LGE (+) was correlated with anti Scl-70 antibody ($P=0.004$). Receiver operating characteristic analysis showed BNP reliably detected myocardial abnormalities (area under the curve 0.896; 95% confidence interval, 0.873–0.924). Considering patients with SSc with normal echocardiography, and using a 18.0 pg/ml cut-off concentration, sensitivity and specificity were 91% and 70% in the detection of overall cardiac involvement.

Conclusion: Cardiac involvement is common in SSc even in the absence of cardiac symptoms, and includes myocardial inflammation as well as myocardial fibrosis. Our data suggest that SSc-specific autoimmunity against Scl-70 mediates these changes. BNP level may be useful in future in the study of treatments aimed at preventing or reducing adverse myocardial processes in SSc.

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Sensitivity to Change of Nailfold Videocapillaroscopy and Relationship with Disease Progression

Jerome Avouac[1], Elide Toniolo[2], Gemma Lepri[3], Charlotte Hurabielle[4], Anaïs Vallet[5] and Yannick Allanore[6], [1]Rheumatology A department and INSERM U1016, Paris Descartes University, Cochin Hospital, Paris, France, [2]Rheumatology Unit. Hospital de la Santa Creu i Sant Pau, Barcelona, Spain, [3]Department of Internal Medicine, Rheumatology Section, Transition Clinic, University of Florence, Italy, Florence, Italy, [4]Rheumatology A department, paris Descartes University, Cochin Hospital, Paris, France, [5]Rheumatology A department, Paris Descartes University, Cochin Hospital, Paris, France, [6]Paris Descartes University, Rheumatology A department, Cochin Hospital, And Eular Scleroderma Trials And Research (EUSTAR) Board, Paris, France
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Background/Purpose: Nailfold videocapillaroscopy (NVC) is a simple, non-invasive and inexpensive imaging technique that allows a detailed assessment of skin microcirculation. Although NVC has face and content validity for the detection of microvascular damages related to systemic sclerosis (SSc), its sensitivity to change has not been assessed in detail. Our aim was to determine in a prospective cohort the merit of NVC to detect meaningful changes over time and whether these changes are associated with disease progression.

Methods: A prospective cohort of 140 SSc patients was recruited over a 12-month period and was followed up on an annual basis for 3 years. NVC was performed at inclusion and repeated once a year by four investigators (ET, GL, CH and AV) according to a standardized procedure. NVC pictures were analysed by one investigator (JA) and classified as early, active and late patterns. Organ progression was defined according to validated definitions. The worsening of the Medsger severity scale (from category 1-2 to category 3-4) was considered as a marker of disease progression.

Results: The mean ± standard deviation (SD) age of the 140 patients (111 women) was 56±11 year old and the mean ± SD disease duration was 9±8 years at baseline. 55 patients had the diffuse cutaneous subset. At least 3 annual NVC evaluations were available for each patient. A change of NVC pattern was observed in 29 SSc patients (21%) during the follow-up period.

A progression from a normal or early NVC pattern to an active NVC pattern was detected in 15 patients (10%). Patients who progressed to the active NVC pattern were more likely to have shorter disease duration (6±7 years vs. 11±9 years, p=0.03). Progression was independent of age, gender, cutaneous subset, past or current digital ulcers (DU), and use of vasodilators at baseline. Patients who progressed to the active NVC pattern were significantly less at risk to develop ischemic DU during follow-up (hazard ratio, HR: 0.78, 95% Confidence Interval, CI 0.17-0.95).

A progression to a late NVC pattern was observed in 14 patients (10%). Patients with the diffuse cutaneous subset and with precapillary PAH at baseline were more likely to progress to a late NVC pattern (HR: 2.39, 95% CI 1.03-7.10 and HR: 13.30, 95% CI 2.46-71.99, respectively). Progression to the late pattern was independent of age, sex, disease duration, past or current DU, and use of vasodilators at baseline. Progression to a late NVC pattern was associated with the occurrence of new ischemic DU (HR: 4.51, 95% CI 1.68-12.14), lung vascular progression (HR: 5.12 95% CI 1.23-21.27), progression of skin fibrosis (HR: 3.70, 95% CI 1.14-11.94) and worsening of Medsger disease severity scale (HR: 4.47, 95% CI 1.63-12.26).

Conclusion: Change of the NVC pattern was observed in 20% of patient with SSc during a follow-up of 3 years. NVC has the ability to detect meaningful changes over time associated with markers of disease progression. Our results support the use of NVC for the routine follow-up of SSc patients in order to improve their risk stratification. NVC might be used in the future to select high-risk patients and change to a late NVC pattern might be regarded as potential surrogate marker for disease severity.

Disclosure: J. Avouac, None; **E. Toniolo**, None; **G. Lepri**, None; **C. Hurabielle**, None; **A. Vallet**, None; **Y. Allanore**, None.

Abstract Number: 1885

Identification and Clinical Correlations of Rare Autoantibodies in Systemic Sclerosis and Poly/Dermatomyositis Patients

Angela Ceribelli[1,2], Natasa Isailovic[3], Maria De Santis[4], Elena Generali[1], Marco Massarotti[5], Minoru Satoh[6] and Carlo Selmi[7,8], [1]Internal Medicine- Unit of Rheumatology and Clinical Immunology, Humanitas Clinical and Research Center, Rozzano (MI), Italy, [2]BIOMETRA, University of Milan, Milan, Italy, [3]Internal Medicine; Unit of Rheumatology and Clinical Immunology, Humanitas Clinical and Research Center, Rozzano (MI), Italy, [4]Internal Medicine, Unit of Rheumatology and Clinical Immunology, Humanitas Clinical and Research Center, Rozzano (MI), Italy, [5]Internal Medicine- Unit of Rheumatology and Clinical Immunology, Humanitas Clinical and Research Center, Rozzano (Milan), Italy, [6]Department of Clinical Nursing, School of Health Sciences, University of Occupational and Environmental Health, Kitakyushu, Japan, [7]Internal Medicine- Unit of Rheumatology and Clinical Immunology, Humanitas Clinical and Research Center, Rozzano, Italy, [8]BIOMETRA Department, University of Milan, Milan, Italy
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Background/Purpose: Systemic Sclerosis (SSc), Polymyositis (PM) and Dermatomyositis (DM) are characterized by the presence of serum autoantibodies (autoAbs) which are central in the diagnosis, predicting organ involvement, follow-up and therapy. However, patients can be negative for commercially available autoantibody tests such as anti-centromere (ACA), -topo I and RNA polymerase III in SSc and -Jo-1 in PM. Our aim is to apply immunoprecipitation (IP) to SSc and PM/DM patients to identify new and rare autoantibodies, to study their clinical association.

Methods: We investigated sera from consecutive patients with SSc (n=28, out of a total of 98 SSc patients attending our Unit in 2014-2015), PM (n=15) and DM (n=9) by protein-IP of ^{35}S-methionine-labeled K562 cell extract followed by SDS-PAGE and autoradiography. Statistical analysis was performed by Prism (GraphPad Software 4.0) by Fisher exact test and statistical significance at $p< 0.05$.

Results: 28 SSc sera were tested by IP to identify rare autoAbs (see Table). A common set of several proteins of 140/40-25kD that needs further characterization for antigen identification was observed in 8 SSc cases. It is significantly associated with ACA positivity (50%, 8/16 ACA vs 0/12 others; p=0.008), and these patients have severe Raynaud's with digital ulcers requiring IV prostacyclin (75%, 6/8 vs 7/54 ACA+, 13%; p=0.0006), with

esophageal involvement in 4 cases. In 15 PM patients, one each of anti-TIF1 gamma/alpha, -PL-7 and -PL-12 were identified by IP. In 9 DM cases, IP identified 2 anti-Ro/SSA, 2 anti-Mi-2 and 1 anti-TIF1 gamma/alpha: this case had juvenile DM with Hodgkin's lymphoma 3 years before the onset of DM symptoms.

Autoantibody	Disease	Sex	ANA	Disease manifestations	Cancer
Anti-Ku (n=1)	Limited SSc	Female	Speckled	Digital ulcers	No
Anti-replication protein A (n=1)	Diffuse SSc	Female	ACA+ speckled	Alveolitis, GI tract disease, fasciitis and digital ulcers	No
Anti-NOR90 (n=1)	Limited SSc	Male	Speckled+ nucleolar	Pulmonary fibrosis and pulmonary arterial hypertension	Yes
Anti-Ago2/Su (n=1) with anti-topo I	Diffuse SSc	Female	Homogeneous+ nucleolar	Alveolitis and digital ulcers	No
Anti-140/40-25k (n=8)	Limited SSc	Female	ACA	Digital ulcers (n=6), esophageal involvement (n=4)	No
Anti-TIF1 gamma/alpha (n=2)	DM (n=1) PM (n=1)	Female Male	Speckled	High CPK at onset, no organ involved in both cases	Yes in DM
Anti-Mi-2 (n=2)	DM	Female	Speckled	Skin and muscle disease, no organ involvement	Yes in 1 case
Anti-PL-7 (n=1)	PM	Female	Cytoplasmic	Anti-synthetase syndrome	No
Anti-PL-12 (n=1)	PM	Female	Nucleolar	Anti-synthetase syndrome	No

Conclusion: Protein and RNA-IP can be used to identify rare and unknown autoantibodies in systemic autoimmune rheumatic diseases such as SSc and PM/DM and may identify new biomarkers for rare diseases.

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Myocardial Fibrosis Detected By Magnetic Resonance Imaging Is a Predictor of Heart Failure in Systemic Sclerosis (SSc) Patients

Tatiana Sofia Rodriguez-Reyna[1], Martha Morelos-Guzmán[2], Pamela Mercado Velazquez[3], Pablo Henrandez-Reyes[4], Karla Montero-Duarte[5], Cynthia Martinez-Reyes[6], Carlos Reyes-Utrera[6] and Carlos Nunez Alvarez[3], [1]Immunology and Rheumatology, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico, [2]Radiology, Instituto Nacional de Ciencias Medicas y Nutricion Salvador Zubiran, Mexico City, Mexico, [3]Immunology and Rheumatology, Instituto Nacional de Ciencias Medicas y Nutricion Salvador Zubiran, Mexico, Mexico, [4]Department of Cardiology, Instituto Nacional de Ciencias Medicas y Nutricion Salvador Zubiran, Mexico City, Mexico, [5]Department of Imaging and Radiology, Instituto Nacional de Ciencias Medicas y Nutricion Salvador Zubiran, Mexico City, Mexico, [6]Immunology and Rheumatology, Instituto Nacional de Ciencias Medicas y Nutricion Salvador Zubiran, Mexico City, Mexico

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Background/Purpose: In previous studies we showed that prevalence of myocardial fibrosis in SSc patients is 45% and is associated to diffuse disease (dcSSc) and lower left ventricle ejection fraction (LVEF); microvascular damage was also very frequent (79%). Our aim was to identify baseline characteristics associated to the development of cardiovascular outcomes (heart failure, coronary artery disease, arrhythmias, vasculopathy, and death) in SSc patients with previously documented myocardial fibrosis and microvascular damage.

Patients and **Methods:** We included 62 SSc patients who participated in the study of prevalence of myocardial fibrosis (2008-2010) and in our local SSc cohort. We performed baseline clinical evaluation, cardiac MRI, coronary angiotomography, transthoracic echocardiogram, and yearly clinical and

cardiovascular evaluation that included Medsger's severity scale items, electrocardiogram, echocardiogram, chest X ray or HRCT and spirometry; we registered presence and severity of internal organ involvement and cardiovascular outcomes. Ordinal variables were analyzed using Chi square test and Fisher test when appropriate, numeric variables were compared using Student's t test or Mann Whitney U when appropriate, logistic regression was used to perform multivariable analysis.

Results: We obtained follow-up information from 61 patients (29 dcSSc, 32 lcSSc), mean follow up was 43.5 months. Univariate analysis showed that elevated basal ultrasensitive CRP was associated to higher overall mortality at the end of follow-up (p=0.003, OR=22, 95% CI 2.3-209), and microvascular damage at baseline was associated to recurrent digital tip ischemic ulcers (p=0.05). Multivariable analysis showed that: myocardial fibrosis, particularly in the middle LV segments was associated to the development of heart failure (p=0.04, OR 8.9, 95%CI 1.07-76); lower LVEF was associated to the development of coronary artery disease (p=0.02, OR 0.66, 95%CI 0.47-0.9); finally, insertion point fibrosis (p=0.01, OR 11.1, 95%CI 2.5-55.5) and elevated ultrasensitive CRP (p=0.04, OR 5.2, 95%CI 1.82-25.6) were associated to recurrent digital tip ulcers.

Conclusion: This study shows that elevated ultrasensitive CRP, the presence of myocardial fibrosis and microvascular damage are predictors of cardiovascular outcomes in SSc patients. Patients with myocardial fibrosis experience progressive decline in LVEF when compared to those without fibrosis. Future studies should focus on therapeutic strategies for this group of patients.

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Deficiency in Micronutrients Is a Frequent Burden in Patients with Systemic Sclerosis

Jasmin Laeubli[1], **Rucsandra Dobrota**[1], Britta Maurer[1], Suzana Jordan[2], Benjamin Misselwitz[3], Mark Fox[3] and Oliver Distler[1], [1]Division of Rheumatology, University Hospital Zurich, Zurich, Switzerland, [2]Department of Rheumatology, University Hospital Zurich, Zurich, Switzerland, [3]Division of Gastroenterology, University Hospital Zurich, Zurich, Switzerland

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Background/Purpose: Micronutrients are essential dietary factors involved in many metabolic processes, including oxidative stress, collagen synthesis and wound healing, which are key aspects of the pathogenesis of systemic sclerosis (SSc). Considering the frequent gastrointestinal involvement and impaired nutritional status (1,2), we hypothesized that the micronutrients could be profoundly affected in SSc patients.

Methods: Patients with SSc were prospectively included between 2009 and 2014. Clinical assessment, data recording and quality controls were done according to EUSTAR standards. In addition, the UCLA SCTC-GIT 2.0 questionnaire was applied. The following micronutrients were measured: zinc, selenium, prealbumin, holotranscobalamin, folic acid. Patients with a specific micronutrient deficiency or with deficiency in at least one micronutrient ("any deficiency") were compared to patients with a normal micronutrient pattern. The two-sided Fisher's exact test, the t-test and the Mann-Whitney were used, as appropriate. Multivariable logistic regression was applied to identify predictors of a deficiency in micronutrients in SSc patients.

Results: Nearly half (43.7%) of the 176 SSc patients included had a deficiency in at least one of the measured micronutrients. The most frequent deficit was in selenium (21.9%), followed by folic acid (16.6%) and prealbumin (15.0%). Even more, 19.3% of patients had multiple micronutrient deficiencies. There was a significant association between low levels of selenium and zinc, prealbumin and zinc and folic acid and zinc. Patients with a lower body mass index (BMI) had lower zinc levels, and those with low prealbumin had more stomach symptoms. The strongest ($p<0.01$) clinical parameters associated with any deficiency in micronutrients were lower hemoglobin ($p<0.001$), higher modified Rodnan skin score (p=0.007) and proximal skin thickening (p=0.009), as shown in Table 1. Proximal skin thickening, low hemoglobin and a low BMI were confirmed in the multivariable model as independent predictors of a deficit in micronutrients in patients with SSc.

Conclusion: Our study reveals that micronutrient deficiencies are a frequent burden in SSc patients and correlate with clinical aspects of the disease. Moreover, often more than one micronutrient is affected. In our cohort, patients with proximal skin fibrosis and lower BMI were more likely to show a deficiency in micronutrients, suggesting that screening for micronutrient status should be prioritized in these patients.

References:

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Table 1. Correlations between disease characteristics and any micronutrient deficiency

Disease characteristics (frequencies)	% of patients with **disease characteristic**	% of patients with **disease characteristic**	**Fisher's exact test, two-sided p value**

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	present when **there is any micronutrient deficiency**	**present** when **micronutrients are normal**	
Skin thickening of the fingers of both hands extending proximal to the MCP joints	61% (36/59)	37.6% (29/77)	p = 0.009
Pitting scars on fingertips	47.4% (27/57)	29.8% (23/77)	p = 0.047
ACR-criteria for systemic sclerosis fulfilled	78.2% (61/78)	60% (57/95)	p = 0.014
CK-elevation	6.5% (5/77)	19.8% (19/96)	p = 0.014
Disease characteristics (mean +/- SD)	Patients with **any deficiency**	patients with **no deficiencies**	**Double t -test**
BMI	23.5 +/- 4.1	24.77 +/- 4	p = 0.048
Disease characteristics (median(quartile1,3))	Patients with **any deficiency**	patients with **no deficiencies**	**Mann-Whitney U**
Modified Rodnan Skin Score	6 (2, 11.25)	3 (0, 8)	p = 0.007
Erythrocyte sedimentation rate	18 (8, 30)	10 (6, 22.5)	p = 0.027
HB (g/dl)	12.4 (11.4, 13.5)	13.6 (12.7, 14.325)	p<0.001

ACR, American College of Rheumatology; BMI, Body-Mass-Index; CK, creatine kinase; HB, Hemoglobin; MCP, metacarpophalangeal joint.

Normal serum levels of the micronutrients: zinc: 9 – 21µmol/l, selenium: 0.8 – 1.1µmol/l, prealbumin: 200 – 400mg/l, folic acid: > 4 µg/l, holotranscobalamin: > 35pmol/l. Measurement techniques: zinc - flame atomic absorption spectrometry (F-AAS); selenium - graphite furnace atomic absorption spectrometry (GF-AAS); prealbumin - immunonephelometry; holotranscobalamin - chemiluminescence microparticle immunoassay (CMIA); folic acid - chemiluminescence immunoassay.

Pfizer, Pharmacyclics, Ergonex, BMS, Sanofi-Aventis, United BioSource Corporation, Roche/Genentech, Medac, Biovitrium, Boehringer Ingelheim Pharma, Novartis, 4D Science, Active Biotec, Bayer-Schering, Sinoxa, Serodapharm, EpiPharm, Biogen, Inven, 5,Actelion, Pfizer, Pharmacyclics, Ergonex, BMS, Sanofi-Aventis, United BioSource Corporation, Roche/Genentech, Medac, Biovitrium, Boehringer Ingelheim Pharma, Novartis, 4D Science, Active Biotec, Bayer-Schering, Sinoxa, Serodapharm, EpiPharm, Biogen, Inven, 2.

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Abstract Number: 1888

There Is a Need for New Systemic Sclerosis Subset Criteria: A Content Analytic Approach

Sindhu Johnson[1], Medha Soowamber[2], Jaap Fransen[3], Dinesh Khanna[4], Frank H.J. van den Hoogen[5], Murray Baron[6], Marco Matucci Cerinic[7], Christopher P. Denton[8], Thomas A. Medsger Jr.[9], Patricia E. Carreira[10], Gabriela Riemekasten[11], Jorg HW. Distler[12], Armando Gabrielli[13], Virginia D. Steen[14], Lorinda Chung[15], Richard Silver[16], John Varga[17], Ulf Müller-Ladner[18], Madelon C. Vonk[19], Ulrich A. Walker[20], Frank Wollheim[21], Ariane L. Herrick[22], Daniel E. Furst[23], Lazlo Czirjak[24], Otylia Kowal-Bielecka[25], Francesco Del Galdo[26], Maurizio Cutolo[27], Nicolas Hunzelmann[28], Charles Murray[29], Ivan Foeldvari[30], Luc Mouthon[31], Nemanja Damjanov[32], Bashar Kahaleh[33], Tracy M. Frech[34], Shervin Assassi[35], Lesley Ann Saketkoo[36] and Janet E. Pope[37], [1]Toronto Scleroderma Program, Toronto Western Hospital, Mount Sinai Hospital, University of Toronto, University Health Network Pulmonary Hypertension Programme, Toronto, ON, Canada, [2]Rheumatology, University of Toronto/ Toronto Western Hospital, Toronto, ON, Canada, [3]Rheumatology, Radboud University Medical Centre, Nijmegen, Netherlands, [4]Medicine, University of Michigan, Ann Arbor, MI, [5]Rheumatology, Sint Maartenskliniek, Nijmegen, Netherlands, [6]Pavillion A, Rm 216, Jewish General Hospital, Montreal, QC, Canada, [7]Department of BioMedicine, Division of Rheumatology, Transition Unit, University of Florence, Firenze, Italy, [8]Centre for Rheumatology, Royal Free Hospital, London, United Kingdom, [9]Medicine/Rheumatology, Univ of Pittsburgh, Pittsburgh, PA, [10]Department of Rheumatology, Hospital Universitario 12 de Octubre, Madrid, Spain, [11]Rheumatology, Human medicine, BERLIN, Germany, [12]Department of Internal Medicine 3, University of Erlangen-Nuremberg, Erlangen, Germany, [13]Clinica Medica, Università Politecnica delle Marche, Ancona, Italy, [14]Rheumatology, Georgetown University Medical Center, Washington, DC, [15]Division of Immunology and Rheumatology, Stanford University School of Medicine, Stanford, CA, [16]Div Rheumatology & Immunology, Medical University of South Carolina, Charleston, SC, [17]Medicine, Northwestern University Feinberg School of Medicine, Chicago, IL, [18]Rheumatology, Internal Medicine, Bad Nauheim, Germany, [19]Rheumatology, Rheumatology, Nijmegen, Netherlands, [20]Rheumatology, Systemic Sclerosis, Basel, Switzerland, [21]Rheumatology, Lund University Hospital, Lund, Sweden, [22]Centre for Musculoskeletal Research, University of Manchester, Manchester Academic Health Science Centre, Manchester, United Kingdom, [23]Medicine, University of California, Los Angeles, David Geffen School of Medicine, Los Angeles, CA, [24]University of Pécs Medical Center, Pécs, Hungary, [25]Department of Rheumatology and Internal Medicine, Medical University of Bialystok, Bialystok, Poland, [26]University of Leeds, Leeds, United Kingdom, [27]Research Laboratory and Academic Division of Clinical Rheumatology, Department of Internal Medicine, University of Genova, Genova, Italy, [28]Department of Dermatology, University of Cologne, Cologne, Germany, [29]Department of Gastroenterology, Royal Free Hospital, London, United Kingdom, [30]Rheumatology, Hamburg, Germany, [31]Department of Internal Medicine, Department of Internal Medicine, Cochin Hospital, Referent Center for Necrotizing Vasculitis and Systemic Sclerosis, Paris-Descartes University, AP-HP, Paris, France, [32]Resavska 69, Institute of Rheumatology, Belgrade, Serbia, [33]Medicine/Rheumatology, The University of Toledo, Toledo, OH, [34]Div of Rheumatology, University of Utah Medical Ctr, Salt Lake City, UT, [35]Rheumatology, University of Texas Medical School at Houston, Houston, TX, [36]Tulane University Lung Center, New Orleans Scleroderma and Sarcoidosis Patient Care and Research Center, New Orleans, LA, [37]University of Western Ontario, London, ON, Canada

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Background/Purpose: Systemic sclerosis (SSc) is a family of diseases unified by the presence of immune activation, vasculopathy and fibrosis. The

concept of SSc subsets cannot be easily measured but is considered to be real. To evaluate the purpose, strengths and limitations of the limited/diffuse subset criteria, and identify areas requiring improvement.

Methods: We conducted a content analytic study consisting of semi-structured interviews with 30 SSc experts. The interview transcripts underwent an iterative process with text deconstructed to single thought units until a saturated conceptual framework with coding was achieved and respondent occurrence tabulated. This was followed by serial cross-referential analyses establishing a set of pervasive complex thought clusters.

Results: Of the 30 experts, 26 (87%) were male, 19 (63%) were from Europe and 11 (37%) were from North America. The experts had seen SSc patients for a mean 23 (SD 10.7) years, and saw a mean of 122 (SD 185) new SSc patients annually. Three thematic clusters were noted regarding the utility of subsetting: to facilitate research and communication, to inform management, and to inform prognosis (prediction of internal organ involvement, survival). The strength of the limited/diffuse system was its ease of use, however 10% stated this system has 'little or no value.' Limitations of the diffuse/limited classification were the risk of misclassification, predictions/generalizations did not always hold true, and that the elbow or knee threshold is arbitrary. 87% use more than 2 subsets including: SSc sine scleroderma, overlap conditions, antibody determined subsets, subsetting based on speed of progression, and age of onset (juvenile, elderly). Considerations for the next phase of criteria development include incorporation of rate of change and hierarchal clustering (limited/diffuse, then by antibodies).

Conclusion: We interviewed international SSc experts and synthesized their views on subset criteria. These results can inform our efforts to develop revised criteria to guide research, prognostication and management.

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Abstract Number: 1889

Exhaled Nitric Oxide in Systemic Sclerosis Lung Disease

Natalie K. Kozij[1], John T. Granton[2], Philip E. Silkoff[3], John Thenganatt[4], Shobha Chakravorty[4] and Sindhu R. Johnson[5], [1]Department of Medicine, University Health Network Pulmonary Hypertension Programme, Toronto General Hospital, University of Toronto, Toronto, Ontario, Canada., Toronto, ON, Canada, [2]Medicine, Univeristiy Health Network Pulmonary Hypertension Programme, Toronto General Hospital and University of Toronto, Toronto, ON, Canada, [3]Medicine, Temple University, Philadelphia, PA, [4]Respirology, University Health Network Pulmonary Hypertension Programme, Toronto, ON, Canada, [5]Toronto Scleroderma Program, Division of Rheumatology, Toronto Western Hospital, Mount Sinai Hospital, Institue of Health Policy, Management and Evaluation, University of Toronto, Toronto, ON, Canada

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Background/Purpose: We evaluated the ability of alveolar and conducting airway nitric oxide (NO) to discriminate between systemic sclerosis (SSc) with and without lung involvement, idiopathic PAH (IPAH), and healthy subjects.

Methods: Consecutive patients in the University Health Network Pulmonary Hypertension Program and Toronto Scleroderma Program were screened. Exhaled nitric oxide was measured at 50, 100, 150, 200 and 250 mL/s using chemiluminescent detection. Alveolar and conducting airway NO were partitioned using a two-compartment model of axial diffusion (CMAD) and the trumpet model of axial diffusion (TMAD).

Results: 60 subjects were recruited: SSc (n=18), SSc-PAH (n=7), SSc-ILD (n=4), SSc-PAH and ILD (n=6), SLE-PAH (n=6), IPAH (n=9) and healthy controls (n=10). Using the CMAD model, healthy subjects had lower median (IQR) alveolar NO than all PAH patients (2.0 ppb (1.5,2.5) versus 3.14 ppb (2.3,4.0), p=0.008). SSc-ILD patients had significantly lower median conducting airway NO compared to controls (1009.5 versus 1342.1 ml*ppb/s, p=0.04). SSc-PAH patients had increased conducting airway NO that inversely correlated with DLCO (Pearson's r -0.88 (95%CI -0.99, -0.26). Median serum BNP values were higher in SSc-PAH patients than SSc patients without pulmonary involvement (358.8 versus 11.6 pg/ml, p=0.01).

Conclusion: Compartmental exhaled NO measurements vary depending on the type of pulmonary pathology present in individuals with SSc, supporting discriminative validity in SSc lung disease.

Disclosure: **N. K. Kozij**, None; **J. T. Granton**, Actelion Pharmaceuticals US, Bayer and GSK, 5,Bayer, Actelion, Pfizer, 9,Actelion and Bayer, 9,Actelion Pharmaceuticals US, 9,IKARIA, 9; **P. E. Silkoff**, None; **J. Thenganatt**, Pfizer Inc, Actelion, and Bayer, 9; **S. Chakravorty**, None; **S. R. Johnson**, None.

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Subclinical Biventricular Systolic Function Is Impaired in Patients with Systemic Sclerosis with Real Time 3-D Echpcardiography: 1 Year Follow-up Study

Sule Yavuz[1], Taylan Sahin[2], Selen Yurdakul[2], Neslihan Yilmaz[3] and Saide Ertekin[4], [1]Rheumatology, Istanbul Bilim University, Faculty of Medicine,Department of Rheumatology, Istanbul, Turkey, [2]Cardiology, Istanbul Bilim University Dept of Cardiology, Istanbul, Turkey, [3]Istanbul Bilim University, Faculty of Medicine, Rheumatology Department, Istanbul, Turkey, [4]Cardiology, Istanbul Bilim University, Dept of Cardiology, Istanbul, Turkey
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Background/Purpose:

Silent myocardial involvement is associated with poor prognosis in patients with systemic sclerosis (SSc). Here, we aimed to evaluate subclinical left ventricular (LV) and right ventricular (RV) systolic dysfunction in SSc patients without any cardiovascular disease, by using both strain imaging method, “speckle tracking” (STE) and real time 3-D Echocardiography.

Methods:

Fifty-five SSc patients were screened, 7 patients were excluded because of ischemic heart disease. 25 age and sex-matched healthy controls (HC), without any cardiac disease and with preserved LV-EF were studied as controls. Conventional echocardiography, STE-based strain imaging and real time 3-D echocardiography (Bothell, WA,USA) were performed to assess biventricular deformation analyse. Association with anti-Scl 70 was sought in patients with SSc.

Results:

In SSc patients (Female/Male: 44/4) the mean age was 47.7 years. Anti Scl-70 seropositivity was 22 (45.8%). Left ventricular conventional echocardiographic measurements (LV end diastolic diameter, LV end systolic diameter and LV EF) were similar between SSc and HC (table1). Both LV and RV longitudinal peak systolic strain/ strain rate were significantly impaired in SSc, demonstrating subclinical LV and RV systolic dysfunction ($p \leq 0.001$). LVESV was significantly increased in SSc (44.3±7.3 vs 37.8±2.4; SSc vs HC, $p < 0.001$)

Systolic PAB was negatively correlated with both LV and RV longitudinal peak systolic strain/strain rate (LV: r=-0.552 and r= -0.637, respectively, $p<0.001$ and RV: r=-0.547 and r=-0.638, respectively, p=0.001). Anti Scl -70 positive patients had impaired LV longitudinal peak systolic strain and strain rate values, compared to the others, however the difference did not reach statistical significance (13.01±1.26 % to 13.04±1.90 %, p=0.96 for strain; 0.30±0.06 1/s to 0.31±0.15 1/s, p=0.79 for strain rate). There was a trend for decreasing left ventricular strain and increasing LEVSV in 1 year analysis of SSc patients but it did not reach statistical significance.

Conclusion:

SSc is associated with myocardial systolic dysfunction. Both deformation analysis by STE-based strain imaging and end systolic left ventricular volume analysis by real time 3-D echocardiography are promising modalities that allow us for non-invasive, comprehensive analysis of early deterioration in biventricular systolic function in patients with SSc.

Table1. Speckle tracking echocardiography (STE) and real time 3-D echocardiography results of SSc patiens and healthy controls.

	SSc n=48	**HC n=25**	**p value**
LV longitudinal peak systolic strain (%)	13.3± 0.82	20.35±3.05	0.0001
LV strain rate (1/s)	0.91±0.21	1.70±0.47	0.0001
RV longitudinal peak systolic strain (%)	11.68±1.61	14.63±2.35	0.001
RV strain rate (1/s)	0.31±0.01	2.73±0.4	0.0001
LVEDV (ml)	104.6±16.2	106±17.5	0.63
LVESV (ml)	44.3±7.3	37.8±2.4	0.0001

Values were presented as mean ±SD. LV; left ventricul, RV; right ventricul, LVEDV;left ventricular end diastolic volume,LVESV; left ventricular end systolic volume

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Abstract Number: 1891

Parameters That Predict Worsening of Skin Thickness in Patients with Early Diffuse Cutaneous Systemic Sclerosis

Masataka Kuwana[1], Minoru Hasegawa[2], Yucihiro Shirai[1], Osamu Ishikawa[3], Hirahito Endo[4], Fumihide Ogawa[5], Daisuke Goto[6], Shinichi Sato[7], Hironobu Ihn[8], Yasushi Kawaguchi[9] and Kazuhiko Takehara[10], [1]Department of Allergy and Rheumatology, Nippon Medical School Graduate School of Medicine, Tokyo, Japan, [2]Dermatology, Faculty of Medical Sciences, University of Fukui, Fukui, Japan, [3]Department of Dermatology, Gunma University Graduate School of Medicine, Gunma, Japan, [4]Department of Rheumatology, Jusendo General Hospital, Koriyama, Japan, [5]Department of Dermatology, Nagasaki University Graduate School of Biomedical Science, Nagasaki, Japan, [6]Division of Clinical Immunology, Doctoral Program in Clinical Sciences, University of Tsukuba, Graduate School of Comprehensive Human Sciences, Tsukuba, Japan, [7]Dermatology, University of Tokyo Graduate School of Medicine, Tokyo, Japan, [8]Department of Dermatology and Plastic Surgery, Faculty of Life Sciences, Kumamoto University, Kumamoto, Japan, [9]Institute of Rheumatology, Tokyo Women's Medical University, Tokyo, Japan, [10]Dermatology, Kanazawa University Graduate School of Medical Science, Kanazawa City, Japan

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Background/Purpose: Skin thickness is a hallmark of systemic sclerosis (SSc), and its progression is associated with poor prognosis. The modified Rodnan total skin thickness score (MRSS) is widely used for evaluating extent and severity of skin thickness. Serial changes of MRSS during the disease course are highly heterogeneous among patients with diffuse cutaneous SSc (dcSSc): some show worsening of the score, but others experience regression. This study was aimed to identify parameters that predict worsening of MRSS in patients with early dcSSc using a multicenter prospective cohort conducted by the Scleroderma Study Conference of Japan.

Methods: A total of 171 patients with early dcSSc were selected from the prospective cohort database based on fulfillment of 1980 American College of Rheumatology preliminary criteria, dcSSc, MRSS ≥7 at entry, disease duration <60 months at entry, and valid data for MRSS at one year. Worsening of skin thickness was defined as increase in MRSS ≥3 points and ≥25% from baseline to one year. In univariate analysis, patients who experienced progression of skin thickness were compared with non-progressors, and selected predictive markers were included in multivariate logistic regression analysis.

Results: Only 23 patients (13.5%) experienced worsening of MRSS at one year. In progressors, MRSS increased at one year from 14.4 ± 6.5 to 21.4 ± 7.2 ($P < 0.0001$), and still maintained a high score over 5 years (20.6 ± 9.0 and 16.8 ± 8.7 at 3 and 5 years, respectively). In contrast, non-progressors showed continuous decrease of MRSS in the following 5 years (21.5 ± 8.9 at baseline, 13.0 ± 7.0 at one year, 11.2 ± 7.6 at 3 years, and 9.0 ± 6.4 at 5 years). Univariate analyses identified short disease duration ($P = 0.002$), negative anti-RNA polymerase III ($P = 0.03$), low baseline MRSS ($P = 0.0003$), tendon friction rubs ($P = 0.02$), absence of nailfold bleeding ($P = 0.001$), joint synovitis ($P = 0.01$), high KL-6 ($P = 0.005$), and high erythrocyte sedimentation rate (ESR) ($P= 0.0001$) as predictors for worsening of MRSS at one year. There was no difference in use of immunosuppressant or corticosteroids between progressors and non-progressors. In the multivariate analysis, disease duration (odds ratio 0.93 [0.87-0.99]), baseline MRSS (0.85 [0.77-0.95]), nailfold bleeding (0.25 [0.07-0.85]), and ESR (1.04 [1.01-1.08]) were selected as independent parameters associated with subsequent progression of the disease. Assessment of the best predictive model revealed that patients with disease duration ≤20 months, baseline MRSS ≤20, and ESR ≥21 mm/hour had the high risk of worsening of MRSS within one year, at sensitivity of 57% and specificity of 91% (odds ratio 13.5 [5.0-36.8]).

Conclusion: This study successfully identified dcSSc patients at the high risk of subsequent worsening of skin thickness. This information is useful in selecting patients who require intensive treatment with potential disease-modifying agents and in improving clinical trial design by enrichment for eligible progressors.

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Impact of Cardiac Magnetic Resonance Imaging with T1 Mapping and Multi-b Value Diffusion-Weighted Sequences in Systemic Sclerosis for the Assessment of Myocardial Microscopic Fibrosis and Perfusion

Benjamin Terrier[1], Hervé Gouya[2], Alice Berezne[1], Alexis Regent[3], Pascal Cohen[1], Loïc Guillevin[4], Claire Le Jeunne[5], Paul Legmann[2], Olivier Vignaux[6] and Luc Mouthon[7], [1]Internal Medicine, National Referral Center for Rare Systemic Autoimmune Diseases, Hôpital Cochin, Paris, France, [2]AP-HP Cochin Hospital, Department of Radiology B, Paris, France, [3]Service de médecine interne, Hôpital Cochin, Paris, France, [4]Internal Medicine, Hopital Cochin, Paris, France, [5]Department of Internal Medicine, Hotel-Dieu Hospital, AP-HP, Paris, Paris, France, [6]Radiology, Cochin University Hospital, Paris, France, [7]Department of Internal Medicine, Department of Internal Medicine, Cochin Hospital, Referent Center for Necrotizing Vasculitis and Systemic Sclerosis, Paris-Descartes University, AP-HP, Paris, France
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Background/Purpose: Systemic sclerosis (SSc) is a complex disease associating vasculopathy, cutaneous and visceral fibrosis, and autoimmunity. Myocardial microscopic fibrosis may occur and potentially lead to impaired myocardial contraction or cardiac conduction. Cardiac magnetic resonance imaging (CMRI) is now widely used for the non-invasive characterization of myocardium. The aim of this study is to evaluate the impact of CMRI with T1 mapping and multi-b value diffusion-weighted sequences in SSc for the assessment of myocardial fibrosis and perfusion.

Methods: We conducted a single-center prospective study of consecutive patients with SSc. CMRI with T1 mapping and multi-b value diffusion-weighted sequences were performed in all patients. T1 mapping sequences assess collagen myocardial infiltration, defining microscopic fibrosis. Multi-b value diffusion-weighted sequences assess tissue perfusion by measuring F coefficient.

Results: Forty patients, 35 women and 5 men, mean age 54.7 ± 14.6 years, were included. Patients had: diffuse cutaneous forms in 19 cases, limited cutaneous forms in 16 cases, and limited forms in 5 cases. Median modified Rodnan skin score was 6 (0-38) and median time from disease diagnosis to CMRI was 77 months (1-302).

Myocardial microscopic fibrosis, defined on T1 mapping sequences by a value greater than 1250 ms, was found in 21 (53%) SSc patients. Conversely, it was found in none of 20 healthy controls (12 males and 8 females, mean age 28 years).

Demographic characteristics were similar between SSc patients with and without myocardial microscopic fibrosis on CMRI. However, SSc patients with myocardial microscopic fibrosis had more frequent diffuse cutaneous form (67% vs. 26%, P=0.01), higher modified Rodnan skin score (11 vs. 2, P = 0.036) and more frequent infiltrative lung disease (48% vs. 16%, P=0.046). Patients with early diffuse cutaneous form (less than 4 years of evolution) had myocardial microscopic fibrosis in 86%. Patients with anti-RNA polymerase III antibody, anti-Scl70 or anti-fibrillarin antibodies, associated with diffuse cutaneous forms had myocardial microscopic fibrosis in 83%. Conversely, patients with anti-centromere antibodies had a myocardial microscopic fibrosis in 46%.

Analysis of F coefficient in multi-b value diffusion-weighted sequences revealed a perfusion defect (defined by a factor F <0.5) in 25% of SSc patients. All of these patients (100%) had a myocardial microscopic fibrosis, while only 37% of patients without perfusion defect had myocardial microscopic fibrosis (P=0.0005).

Finally, in patients with myocardial microscopic fibrosis, the use of arterial vasodilators was associated with improved tissue perfusion with an F coefficient >0.5 in 67% compared to 29% in patients not receiving arterial vasodilators.

Conclusion: This study investigates for the first time CMRI with T1 mapping and multi-b value diffusion-weighted sequences in SSc. Myocardial microscopic fibrosis is observed in half of the patients, especially in those with diffuse cutaneous forms. Microscopic fibrosis was strongly associated with myocardial perfusion defect, with a beneficial effect of arterial vasodilators on myocardial perfusion.

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Abstract Number: 1893

Relationship Between Vitamin D Levels and Disease Activity in Patients with Systemic Sclerosis

Julia Romero[1], Amalia Schiel[2], Mariana Landa[2], María Luisa Díaz[3], María Eugenia Lara[1], Mariano Rivero[4], Marina Khoury[5], Mirtha Alonso[2] and Juan Carlos Barreira[1], [1]Rheumatology Service, British Hospital, Buenos Aires, Argentina, [2]Central Laboratory, British Hospital, Buenos Aires, Argentina, [3]Nuclear Medicine, British Hospital, Buenos Aires, Argentina, [4]Rheumatolgy Service, British Hospital, Buenos Aires, Argentina, [5]Teaching and Research, British Hospital, Buenos Aires, Argentina
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Background/Purpose: Low Vitamin D (VD) levels have been observed in several autoimmune diseases, including systemic sclerosis (SSc). Some studies have shown the importance of VD in SSc, but its significance has not yet been determined. We aim to evaluate differences in serum levels of VD in SSc patients compared to a control group, and to correlate such levels with disease activity, clinical and laboratory features.

Methods: We included patients diagnosed with SSc according to ACR 1980 criteria and subtypes according to Le Roy, who consecutively attended the Rheumatology Service in spring and summer during 2 years. Patients with overlapping syndromes, diseases or drugs that interfered with VD serum level 6 months prior to study entry were excluded. A control group of 58 blood donors without autoimmune disease and negative autoantibodies was matched by sex and age. Determination of $25(OH)D_3$ was performed through radioimmunoassay-chemiluminescence assay. Levels between 20 and 29.9ng/ml were classified as VD insufficiency while concentrations lower than 20ng/ml as deficiency. For the SSc group, demographic and clinical data were collected, and mRSS (modified Rodnan Skin Score), scleroderma health assessment questionnaire (S-HAQ), EUSTAR Disease Activity Score and Medsger Severity Score were performed. Statistical Analysis: Numerical variables were compared by Student's t test or Mann-Whitney test and categorical variables by x^2 test. A value of $p<0.05$ was considered significant.

Results: The SSc group included 58 patients; median age of 57 years. The mean value of VD was 19.9±8.7ng/ml in the SSc group, and 29.6±8.6ng/ml in the control group ($P<0.001$). A total of 29 patients (50%) in the SSc group had deficiency, 20 (34.5%) had insufficiency and 9 (15.5%) presented normal levels. In the control group, 6 (10.3%) presented deficiency, 27 (46.6%) insufficiency and 25 (43.1%) normal VD levels. SSc group patients presented a statistically significant higher frequency of deficiency ($p\leq0.001$) but not of insufficiency ($p=0.607$). Out of the 22 patients (38%) with diffuse SSc, 17 (77%) presented deficiency, 4 (18%) insufficiency and 1 (5%) normal VD levels. Among the 36 patients (62%) with limited disease, 12 (33%) had deficiency, 16 (44%) insufficiency and 8 (23%) normal levels. The group of diffuse SSc presented a significantly higher frequency of hypovitaminosis D (VD<30ng/ml)($p=0.005$). Patients with suboptimal levels showed higher Rodnan Score, S-HAQ, EUSTAR Disease Activity Score (all with $p\leq0.001$) and Medsger Score ($p=0.002$) and late SD pattern ($p=0.049$). All presented normal calcemia, calciuria and parathormone. A subgroup of 16 patients (28%) received low doses of steroids (prednisone or equivalent ≤10mg/d) with no significant difference in VD level compared to those who did not receive it.

Conclusion: Hypovitaminosis D was found in more than 80% of SSc patients with a significant difference compared to healthy controls. They presented more frequently the diffuse form, higher cutaneous involvement, more severe and active disease and higher levels of disability.

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Abstract Number: 1894

Calcium Channel Blockers Are More Effective in the Treatment of Primary Raynaud's Phenomenon Compared to Secondary: A Meta-Analyis

Janet E. Pope[1], Fadumo Rirash[2], Paul Tingey[3], Sarah Harding[4], Lara J. Maxwell[5], Peter Tugwell[6], Jordi Pardo[7], Elizabeth Ghogomu[8] and George A. Wells[9], [1]University of Western Ontario, London, ON, Canada, [2]Medicine/Rheumatology, University of Western Ontario, London, ON, Canada, [3]Faculty of Medicine, University of Queensland, Brisbane, Australia, [4]ERLanger, ERLanger, KY, [5]Centre for Global Health, Institute of Population Health, University of Ottawa, Ottawa, ON, Canada, [6]Center For Global Health, Institute of Population Hlth, Ottawa, ON, Canada, [7]University of Ottawa, Ottawa, ON, Canada, [8]University of Ottawa, Cochrane Musculoskeletal Group, Ottawa, ON, Canada, [9]Cardiovascular Research Reference Centre, University of Ottawa Heart Institute, Ottawa, ON, Canada
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Background/Purpose: To assess the benefits and harms of calcium channel blockers (CCBs) versus placebo for the treatment of Raynaud's phenomenon (RP) comparing primary to secondary RP associated with connective tissue disease (CTD), especially systemic sclerosis (SSc).

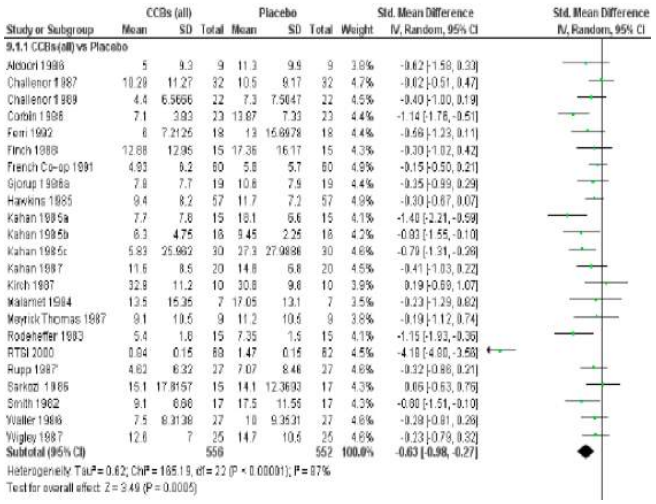
Methods: The Cochrane library, MEDLINE, EMBASE and Clinicaltrials.gov were searched up to June 2014 for randomized controlled trials (RCTs) examining RP. Outcomes of interest were: Frequency, Duration and Severity of RP attacks, Pain, Patient global, Withdrawals and Serious adverse events. Fixed effects models were used to calculate mean differences (MD) or standardized mean differences (SMD) for continuous outcomes and risk ratios for dichotomous outcomes. Heterogeneity was determined and significant if $I^2>50\%$. Subgroup analyses by: disease type (primary or secondary), CCB dosage (low, medium or high) and CCB drug were performed.

Results: Of the 2337 articles, 939 participants from 36 RCTs investigating the effect of CCBs vs. placebo were included. The majority were crossover RCTs with low to moderate quality using low dose CCBs. CCBs were more effective in reducing the frequency of attacks (22 RCTs, N=978, MD -2.62, 95%CI -3.38,-1.88, $p<0.00001$, Figure) and the severity of attacks (17 trials, N=792, MD -0.73 95%CI -0.99, -0.47, $p<0.00001$).No significant differences in duration, pain or withdrawals between CCBs and placebo occurred. Patient global was only reported in one study. CCBs reduced the frequency and

severity of attacks irrespective of dosage, particularly for primary RP. CCBs reduced frequency of attacks/week in primary RP by 3.9 vs. 0.5 in secondary RP. Similar results were seen in severity of attacks for low dose vs. medium dose CCBs and primary vs. secondary RP. Low dose CCBs reduced the frequency of attacks by 3.3 per week vs. medium dose at 5.6. Crossover studies may have had carryover effects.

Conclusion: Primary RP is more responsive to CCBs than secondary from CTD especially SSc.

CCBs vs. placebo for frequency of attacks



Disclosure: J. E. Pope, None; **F. Rirash**, None; **P. Tingey**, None; **S. Harding**, None; **L. J. Maxwell**, None; **P. Tugwell**, None; **J. Pardo**, None; **E. Ghogomu**, None; **G. A. Wells**, None.

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Abstract Number: 1895

Correlation of Scleroderma Interstitial Lung Disease with Gastroesophageal Reflux

Brady Bulian[1], W Leroy Griffing[2] and Michael Crowell[3], [1]Internal Medicine, Mayo Clinic Arizona, Scottsdale, AZ, [2]Rheumatology, Mayo Clinic Arizona, Scottsdale, AZ, [3]Gastroenterology, Mayo Clinic Arizona, Scottsdale, AZ

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Background/Purpose: Systemic sclerosis (SSc) is a connective tissue disease involving the skin and visceral organs, most commonly the gastrointestinal tract and lungs. Interstitial lung disease (ILD) is present in up to 75% of cases and is the leading cause of mortality in SSc. Recent studies have shown a correlation between gastroesophageal reflux (GER) and SSc-ILD, however, doubt remains regarding the extent to which GER affects ILD. In this study we compared GER, esophageal dysmotility and lower esophageal sphincter (LES) tone in those with and without ILD, hypothesizing that the presence and extent of esophageal involvement would correlate with presence and extent of ILD.

Methods: A retrospective review identified thirty-nine patient cases of SSc that met diagnostic criteria as set by the American College of Rheumatology. Data were collected from high-resolution computed tomography (HRCT), pulmonary function testing (PFT), esophageal pH-Impedance testing (pH-I) and high-resolution esophageal manometry (HREM) to assess GER, esophageal dysmotility and lower esophageal sphincter tone in those with and without ILD. Significant GER was defined as DeMeester score > 14.72 on pH-I and Goh criteria[3] were used to stage ILD as limited or extensive.

Results: The ILD and non-ILD groups were similar in regards to sex, age, disease duration or modified Rodnan skin score. Patients with ILD had higher rates of significant GER at 75% vs. 33% of controls ($p = 0.01$). The ILD group also had higher rates of absent peristalsis at 100% vs. 59% ($p = 0.009$) and hypotensive LES at 92% vs. 70% ($p = 0.13$). In subgroup analysis of those with extensive ILD vs. limited ILD, 83% vs. 50% had significant GER ($p = 0.19$). These results are listed below in Table 1.

Table 1. Demographics and data of ILD (N=12) vs. non-ILD (N=27) groups and Extensive ILD[3] (N=6) vs. Limited ILD[3] groups (N=6). (mean ± SD)

Demographics	**ILD**	**Non-ILD**	
Age (years)	56.71 ± 11.95	58.50 ±12.72	*p* = 0.67
Sex (male)	17% (2 of 12)	11% (3 of 27)	*p* = 0.62
SSc duration[1] (years)	10.07 ± 8.89	5.58 ± 4.25	*p* = 0.11
MRSS	14.15 ± 12.81	21.00 ± 12.04	*p* = 0.14
Data			
Significant GER[2]	75 % (8 of 12)	33% (9 of 27)	*p* = 0.01
Average DeMeester	43.35 ± 38.92	29.66 ± 56.47	*p* = 0.45
Absent peristalsis	100% (12 of 12)	59% (16 of 27)	*p* = 0.009
Hypotensive LES	92% (11 of 12)	70% (19 of 27)	*p* = 0.13
	Extensive ILD[3]	**Limited ILD[3]**	
Significant GER[2]	83% (5 of 6)	50% (3 of 6)	*p* = 0.19
Average DeMeester	49.83 ± 43.74	36.87 ± 36.31	*p* = 0.59

Abbreviations: ILD = Interstitial lung disease**. SSc** = Systemic sclerosis. **MRSS** = Modified Rodnan Skin Score. **GER** = Gastroesophageal reflux. **LES** = Lower esophageal sphincter. **1:** Defined by first onset of non-Raynaud's phenomenon SSc feature. **2:** Determined as DeMeester score greater than 14.72 on pH-Impedance testing. **3:** As outlined by Goh N.S., et al. Interstitial lung disease in systemic sclerosis: a simple staging system. AJRCCM. 177, 1248-1254 (2008).

Conclusion: We report a statistically significant positive correlation between SSc-ILD and the presence of significant GER or esophageal dysmotility, with a trend toward extensive ILD in those with more severe GER. These findings support the notion that GER likely contributes to the development and progression of SSc-ILD, and that aggressive medical or surgical treatment of GER is warranted to decrease the morbidity and mortality associated with ILD.

Disclosure: B. Bulian, None; **W. L. Griffing**, None; **M. Crowell**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/correlation-of-scleroderma-interstitial-lung-disease-with-gastroesophageal-reflux

Abstract Number: 1896

Early Signs, Symptoms and Auto-Antibodies to Predict Diffuse Cutaneous or Limited Cutaneous Systemic Sclerosis at First Presentation

WMT van den Hombergh[1], HKA Knaapen-Hans[1], Patricia E. Carreira[2,3], FHJ van den Hoogen[1], Jaap Fransen[1] and MC Vonk[1], [1]Rheumatology, Radboud University Medical Centre, Nijmegen, Netherlands, [2]Rheumatology, Hospital Universitario 12 de Octubre, Madrid, Spain, [3]Rheumatology Unit, Hospital 12 de Octubre, Hospital 12 de Octubre, Madrid, Spain

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SESSION INFORMATION

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Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

ABSTRACT

Background/Purpose:

Diffuse cutaneous systemic sclerosis (dcSSc) is associated with a poorer prognosis compared to limited cutaneous SSc (lcSSc), due to earlier and more

severe organ involvement (1). Early recognition of dcSSc patients is advantageous to apply timely screening or treatment. Possibly, differences between dcSSc and dcSSc in the early course of disease may be useful for early differentiation of subtypes. To determine whether the timing of both Raynaud's phenomenon (RP) and the first non-Raynaud (non-RP) symptom and the type of the first non-RP symptom, combined with disease specific auto-antibodies are predictive for the development of dcSSc or lcSSc.

Methods: The Nijmegen Systemic Sclerosis cohort consists of prospectively followed SSc patients. Demographic s, data about RP and the first non-RP symptom, and disease specific auto-antibodies were collected at first presentation, patients were followed up at least 1 year after diagnosis to confirm subtype of SSc. Univariate and multivariate logistic regression was used for predictive modeling. Performance was analyzed using discrimination and calibration, in an external cohort of 445 SSc patients from Madrid.

Results: A total of 553 SSc patients were included, 176 (31%) was classified as dcSSc. Time between RP and the first non-RP symptom differed between dcSSc and lcSSc (0.0 vs. 0.4 years; p<0.001). Puffy fingers (37%) and scleroderma (22%) were the most common first non-RP symptoms. The final prediction model had an area under the ROC curve of 0.79 (95% CI 0.75-0.83), a sensitivity of 87% and a specificity of 61%. External validation of this model showed a sensitivity of 78% (95% CI 0.74-0.83) and a specificity of 65%. A simple scoring method was created, with a cut point indicative for dcSSc.

Table 1. Prediction models

	Model 1		Model 2		Model 3		Score
	B	*p-value*	*B*	*p-value*	*B*	*p-value*	*value*
Male	0.9	<0.001			0.4	0.049	0.5
Time RP to non-RP < 3 months	0.9	<0.001			0.7	0.001	1.0
Scleroderma	0.7	0.001			0.6	0.014	1.0
ACA			-2.7	<0.001	-2.4	<0.001	-2.5
ATA			0.8	<0.001	0.7	0.004	1.0
Anti-RNP			-1.1	0.018	-1.1	0.023	-1.5
Constant	-1.8	<0.001	-0.54	<0.001	-1.2	<0.001	

Timing first non-Raynaud: the first non-Raynaud symptom occured less than three months after RP. Scleroderma: scleroderma skin changes of fingers, hands or face. ACA anti-centromere antibodies; ATA anti-topoisomerase-1 antibodies; anti-RNP anti-ribonucleoprotein-1 antibodies. *B* regression coefficient. Score value: rounded B coefficients

Conclusion: This study presents a simple scoring method to improve recognition of patients prone to development of dcSSc. The easy accessible items in the model will help clinicians to recognize patients prone to dcSSc, who are expected to have a poorer prognosis.

1. Steen VD, Medsger TA, Jr. Severe organ involvement in systemic sclerosis with diffuse scleroderma. Arthritis Rheum. 2000;43(11):2437-44.

Disclosure: W. van den Hombergh, None; **H. Knaapen-Hans**, None; **P. E. Carreira**, None; **F. van den Hoogen**, None; **J. Fransen**, None; **M. Vonk**, None.

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Abstract Number: 1897

Fragmented Qrs Patterns Do Not Correlate with the Degree of Lung and Skin Involvement in Patients with Systemic Sclerosis

Didem Uzunaslan[1], Caner Saygin[1], Mehmet Kostek[2], Mehmet Ozdemir[2], Tufan Torun[2], Servet Altay[3] and **Gulen Hatemi**[4], [1]Cleveland Clinic, Cleveland, OH, [2]Istanbul University, Cerrahpasa Faculty of Medicine, Istanbul, Turkey, [3]Edirne Community Hospital, Edirne, Turkey, [4]Rheumatology, Istanbul University, Cerrahpasa Medical School, Istanbul, Turkey

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Background/Purpose: Cardiac involvement is a common subclinical feature of systemic sclerosis (SSc) and results from the widespread fibrosis observed during disease course. Fragmented QRS (fQRS) patterns are seen in myocardial interstitial fibrosis which is also the characteristic feature of SSc. The aim of this study is to evaluate the frequency of fQRS patterns in SSc patients and investigate its association with other clinical findings by using healthy and diseased controls.

Methods: 63 SSc patients who attended our outpatient clinic for their routine controls, who did not have cardiac symptoms and fulfilled 2013 ACR/EULAR classification criteria were enrolled in the study. Standard 12-lead EKG, pulmonary function tests, and echocardiography were performed in all participants. Fragmented QRS was described as the presence of an additional R wave or R or S wave bridging, or the presence of QRS fragmentation on two consecutive

derivations. Nailfold capillaroscopy and Rodnan skin scores were assessed by an experienced rheumatologist. Serologic and demographic data were obtained from patient records. We also enrolled 87 RA patients and 100 healthy controls as diseased and healthy controls, respectively.

Results: The frequency of QRS fragmentation was similar between SSc and RA patients (χ^2:4.994, p=0.105, df:2), and significantly higher than healthy controls (χ^2:4.382, p=0.036, df:1) (Table). Among 12 SSc patients with fQRS (19%), 5 had notched S waves, 5 had notched R waves, and 3 had rSr pattern. SSc patients had significantly higher rates of QT dispersion when compared to RA and healthy controls (p=0.006). Both SSc and RA patients had significantly higher P dispersion durations than healthy controls (p<0.0001). In univariate analysis, SSc patients with fQRS had longer disease duration, higher Rodnan skin scores, and pulmonary artery pressures, lower forced vital capacity and diffusion capacity, and higher rates of abnormal nailfold capillary patterns. In multivariate analysis, none of these parameters predicted the presence of fQRS.

Conclusion: The frequency of fQRS patterns was higher in our SSc and RA patients. However, this increase in fQRS frequency did not correlate with more severe disease involvement. Longitudinal studies are required to determine whether these fQRS patterns predict early myocardial fibrosis in SSc.

Table.

	SSc (n=63)	**RA (n=87)**	**Healthy Controls (n=100)**	P value
Age (years±SD)	47.3 ± 12.01	52.6 ± 13.1	45.97 ± 10.39	<0.0001
Disease duration (years)	8.22 ± 7.96	9.90 ±10.01		0.272
fQRS	19.0% (12/63)	11.49% (10/87)	8% (8/100)	0.105
QT dispersion	0.035 ± 0.015	0.029 ± 0.016	0.028 ± 0.011	0.006
P dispersion	0.024 ± 0.011	0.024 ± 0.016	0.017 ± 0.009	<0.0001

Disclosure: D. Uzunaslan, None; **C. Saygin**, None; **M. Kostek**, None; **M. Ozdemir**, None; **T. Torun**, None; **S. Altay**, None; **G. Hatemi**, None.

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Abstract Number: 1898

Are There Risk Factors for Calcinosis in Scleroderma?

Sneha Pai[1] and Vivien Hsu[2], [1]Rheumatology, Robert Wood Johnson Medical School Hospital, New Brunswick, NJ, [2]Medicine, Rutgers University, New Brunswick, NJ

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Background/Purpose: Calcinosis is the deposition of calcium hydroxyapatite in the soft tissues in patients with scleroderma spectrum disorders (SSc). Risk factors are unknown and there is no effective medical treatment.

Methods: In this IRB-approved study, we compared clinical characteristics of SSc (1) patients with (SSc-calcinosis) and without calcinosis (SSc-control) seen consecutively in the outpatient Rutgers-RWJ Scleroderma Program. Our analysis included demographic and SSc clinical characteristics, comorbidities (osteoporosis, hypertension, diabetes and thyroid disease), autoantibodies (ANA, Scleroderma and Anti-Centromere) and imaging results. Univariate and multivariate regression analyses were conducted to determine common factors associated with calcinosis.

Results: There were 215 SSc patients enrolled, 65 SSc-calcinosis (81.5% were females) and 150 SSc-controls (77% were females). SSc-calcinosis patients were older (p=0.026) with significantly longer disease duration (20 ± 10.5 years vs 12 ± 8 years, p<0.0001). Twenty nine (45%) SSc-calcinosis patients had diffuse scleroderma and 15 (23%) also had overlap with other rheumatic diseases (2, 3). In the univariate analysis (see Table 1), Caucasian females with limited SSc, advanced age, longer disease duration, presence of osteoporosis and the Anti-centromere antibody were all statistically significant. In the multivariate analysis, SSc-calcinosis patients had significantly less ischemic digital ulcer history, but , longer disease duration and osteoporosis (adjusted for age) remained independently associated with calcinosis.

Conclusion: Calcinosis is common in both limited and diffuse SSc. Those with longer disease duration and osteoporosis may be at higher risk to develop calcinosis. Larger studies are needed to confirm these observations.

References:

1. Hoogen FVD et al. *Ann Rheum Dis*, 2013; 72:1747-1755 and *Arthritis Rheum*, 2013; 65(11):2737-57.
2. Aletaha D et al. *Arthritis Rheum*, 2010; 62:2569–2581.
3. Mastagia FL et al. *Rheum Dis.Clin. North Am*, 2002; 28(4): 723-41.

Table 1: Analyses of clinical characteristics associated with and without SSc-calcinosis

	Univariate Analysis			Multivariate Analysis		
	p-value	**OR**	**95% CI**	**p-value**	**OR**	**95% CI**
Age (years)	0.0257			0.0693		
Sex	0.01	3.44	1.27 – 9.25	0.8490	0.8346	0.12 – 5.36
Disease onset (from Raynaud onset)	**<0.0001**			**0.0024**		
Disease onset (from non-Raynaud symptoms)	**<0.0001**			**0.0274**		
Race (Caucasian vs. other)	0.0164			0.1625		0.098 – 1.47
Diagnosis of limited SSc	0.0292	0.514	0.281 – 0.93	0.1553	2.895	0.668 – 12.53
Myopathy	0.030	0.34	0.127 – 0.93	0.7066	0.6961	0.105 – 4.59
Pulmonary fibrosis	0.0499	0.54	0.299 – 1.00			
Ischemic digital ulcer history	<0.0001	0.1906	0.092 – 0.39	0.0001	0.0522	0.012 – 0.22
Acro-osteolysis	0.0565	2.124	0.970 – 4.64			
Osteoporosis	**0.0001**	**3.2387**	**1.760 – 5.95**	**0.0122**	**5.2018**	**1.432 – 18.88**
Anti-nuclear Antibody (ANA)	0.0263	0.4013	0.176 – 0.91	0.0740	0.2108	0.038 – 1.162
Scleroderma Antibody (Scl70)	0.3424	0.72	0.365 – 1.42			
Anti-centromere Antibody	0.0469	2.020	1.002 – 4.06	0.8406	1.199	0.203 – 7.083

Disclosure: S. Pai, None; **V. Hsu**, None.

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Abstract Number: 1899

Aortic Stenosis Is Increased in Systemic Sclerosis Patients with Pulmonary Arterial Hypertension Compared to Other Forms of Pulmonary Arterial Hypertension

María Martín López[1], Otto Martin Olivas Vergara[2], Mario Rodríguez[3], Carmen D Merino[4], Carmen Jiménez[5,6], Estibaliz Loza[7], Pilar Escribano[5,6], Loreto Carmona[8] and Patricia E. Carreira[2], [1]RHEUMATOLOGY, Hospital Universitario 12 de Octubre, Madrid, Spain, [2]Rheumatology, Hospital Universitario 12 de Octubre, Madrid, Spain, [3]Hospital Universitario 12 de Octubre, Madrid, Spain, [4]Fundación Hospital de Alcorcón, Madrid, Spain, [5]Cardiology Department, Hospital Universitario 12 de Octubre, Madrid, Spain, [6]Multidisciplinary Pulmonary Hypertension Unit. Hospital Universitario 12 de Octubre, Madrid, Spain, [7]Research Unit. Sociedad Española de Reumatología, Madrid, Spain, [8]Instituto de Salud Musculoesquelética, Madrid, Spain
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Background/Purpose: Degenerative aortic stenosis (DAS) is the most common form of valvular heart disease associated with advancing age. DAS pathophysiology has not been clearly elucidated, but biomechanical factors, inflammation and atherosclerosis are believed to have an essential role in its development. In the last years we have detected an increased frequency of DAS in systemic sclerosis (SSc) patients, especially in those with pulmonary arterial hypertension (PAH), not found in other forms of PAH.

Objective: To analyze the prevalence and risk factors for DAS in SSc-PAH, compared to patients with other forms of PAH.

Methods: All patients with systemic sclerosis (SSc) followed in the Rheumatology Department between Jan 1990 and May 2015 were included in a prospective data base containing demographic and clinical data. Patients with PAH confirmed by right heart catheterization (RHC) older than 60 y were selected. As a control group, primary or thromboembolic PAH (IPAH/CTEPH) patients older than 60 were selected from the hospital PH registry. Presence of DAS was defined by transthoracic echocardiography, following current guidelines recommendations. Demographic data, cardiovascular risk factors (smoking, systemic arterial hypertension (HPT), dyslipemia, diabetes mellitus, obesity) and time of follow-up from PAH diagnosis were compared between groups. Descriptive statistics, univariate and multivariate logistic regression analysis were performed.

Results: Thirty three SSc-HAP (30w,3m, 71±6 y) and 85 IPAH/CTEPH (50w,35m, 77±6 y) were included. SSc-HAP patients were younger than IPAH/CTEPH (p<.0001), more frequently women (p=.001), less smokers (p=.04), and had more HTP (p<.0001). Time of follow-up from PAH diagnosis was shorter in SSc patients (4±4y vs 6±4y, p=.02). DAS was present in 6/24 SSc-HAP and in 1/75 IPAH/CTEPH (p=.001). Univariate analysis, showed association of DAS with SSc (p=.004) and HTP (p=.003). Multivariate analysis adjusted by age, sex and cardiovascular risk factors showed SSc as the only independent factor associated with DAS (p=.003) in our group.

Conclusion: Prevalence of degenerative aortic stenosis (DAS) is increased in SSc-PAH, compared with other forms of PAH, and this association is independent of age, sex and cardiovascular risk factors. Our results suggest than inflammation present in SSc-PAH and not in other forms of PAH could be a factor involved in the development of DAS in our patients.

Disclosure: M. Martín López, None; **O. M. Olivas Vergara**, None; **M. Rodríguez**, None; **C. D. Merino**, None; **C. Jiménez**, None; **E. Loza**, None; **P. Escribano**, None; **L. Carmona**, None; **P. E. Carreira**, None.

Abstract Number: 1900

Performance of the Detect Protocol for Pulmonary Arterial Detection in Systemic Sclerosis Patients in Clinical Practice

Otto Martin Olivas Vergara[1], Beatriz E. Joven[1], Belen Diaz Anton[2], Carmen Jiménez[2], Maria Martin Lopez[3], Pilar Escribano[2] and Patricia E. Carreira[1,2], [1]Rheumatology, Hospital Universitario 12 de Octubre, Madrid, Spain, [2]Multidisciplinary Pulmonary Hypertension Unit. Hospital Universitario 12 de Octubre, Madrid, Spain, [3]RHEUMATOLOGY, Hospital Universitario 12 de Octubre, Madrid, Spain

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Background/Purpose: To analyze the usefulness of the DETECT protocol (1) for the prediction of pulmonary hypertension (PH) and pulmonary arterial hypertension (PAH) in routine clinical practice in a systemic sclerosis (SSc) clinic.

Methods: All patients with SSc seen in the Rheumatology Department with a right heart catheterization (RHC) performed between Jan 1998 and May 2015 and with an echocardiography available within 3 months of the RHC were included. The two steps DETECT score was retrospectively obtained. Receiver Operating Characteristic (ROC) curve and area under the curve (AUC) were calculated for the ability of DETECT score to identify PH and PAH patients. Associations of clinical and RHC data, DETECT score, and disparity between PH and PAH diagnosis and DETECT score, were analysed.

Results: The study included 61patients (82% women, 75% limited cutaneous (lc) SSc, 57±15 y). Mean disease duration from first non-Raynaud symptom was 11±10 years. Pulmonary hypertension (PH) was confirmed by RHC in 50 (82%) patients, of those 38 (62%) had PAH. Other causes of PH were pulmonary fibrosis in 10 patients, with associated myocardiopathy in 3. Other 2 patients had non SSc associated valvulopathy. ROC curve showed an elevated discriminatory capacity of the DETECT score for prediction of PH and PAH, with AUC of 0.930 and 0.867 respectively. Disparity between PH in RHC and DETECT score was present in 10 patients. Only one patient, with severe hypertrophic cardiomyopathy and secondary PH had a negative DETECT score. The other 9 patients, 6 with cardiopathy (3 valvulopathy, 3 SSc related cardiomyopathy) had a positive DETECT score but did not present PH in RHC. Other 11 patients presented PH of other causes (1 non SSc valvulopathy, 9 PF, 4 also with SSc cardiomyopathy) Disparity between PH in RHC and DETECT score was more frequent in the presence of any cardiopathy (p<.002), absence of right axis deviation (p<.011) and higher tricuspid jet velocity (TJV)(p<.0001). Disparity between PAH diagnosis and DETECT score was more frequent in males (p=.011), with dcSSc (p=.031), PF (p<.0001) or cardiopathy (p<.0001), higher TJV (p<. 001), lower FVC (p<.001), higher uric acid (p=.007) and less frequent in the absence of right axis deviation (p=.0026) and in ACA+ patients (p=.003). The results were similar when only the 33 patients who would have been included in the DETECT study (disease duration higher than 3 years and DLCO lower than 60%) were analyzed. When the 28 patients who would not have been included in the DETECT study (less than 3 years of disease duration or DLCO higher than 60%), only the presence of dcSSc (p=.013) or cardiomyopathy (p=.013) were associated with disparity between PH in RHC and DETECT score.

Conclusion: The DETECT algorithm performs very well in a routine clinical setting for early detection of PAH and also of PH or other causes in SSc patients. Our results suggest that the algorithm would not perform as well in patients with any type of cardiopathy.

(1) Coghlan JG, Denton CP et al. Evidence-based detection of pulmonary arterial hypertension in systemic sclerosis: the DETECT study. ARD 2014;73:1340-9

Disclosure: O. M. Olivas Vergara, None; **B. E. Joven**, None; **B. Diaz Anton**, None; **C. Jiménez**, None; **M. Martin Lopez**, None; **P. Escribano**, None; **P. E. Carreira**, None.

Abstract Number: 1901

Association of Serum Adipokines Adipsin, Adiponectin, and Leptin/Adiponectin Ratio with Systemic Sclerosis

Benjamin Korman[1], Roberta Goncalves Marangoni[1], Monique E. Hinchcliff[2], Sanjiv Shah[3], Mary A. Carns[4], Rosalind Ramsey-Goldman[5] and John Varga[6], [1]Division of Rheumatology, Northwestern University, Chicago, IL, [2]Division of Rheumatology, Division of Rheumatology, Northwestern University, Feinberg School of Medicine, Chicago, IL, [3]Northwestern University, Chicago, IL, [4]Rheumatology, Northwestern University, Chicago, IL, [5]Northwestern University Feinberg School of Medicine, Chicago, IL, [6]Division of Rheumatology, Northwestern University, Feinberg School of Medicine, Chicago, IL

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Background/Purpose: Patients with systemic sclerosis (SSc) display reductions in adipose tissue, particularly intradermal adipose tissue. There are currently no well-validated serum biomarkers in SSc, and adipokines represent an attractive biomarker because of their roles in inflammation, vascular function, and fibrosis. Previous studies have shown an association between circulating levels of the adipokine adiponectin and SSc, particularly in patients with diffuse cutaneous involvement (dcSSc). This study sought to determine if adipokine profiles were associated with dcSSc and measures of SSc organ involvement.

Methods: 82 dcSSc patients and 35 healthy controls were included in the study. All dcSSc patients underwent standard laboratory assessment, pulmonary function tests, and the modified Rodnan skin score (MRSS) within 6 months of the serum collection. 54 patients also had research quantitated echocardiograms within 6 months of serum collection. Serum leptin, adiponectin, and adipsin levels were measured by luminex assays in all patients and controls. Mann-Whitney U test and Kruskall-Wallis tests were used in binary between-group comparisons and testing of inter-group variability.

Results: Distributions of age, sex, and BMI in dcSSc patients and healthy controls were not different although a higher proportion of patients than controls were female (77% vs 58%, p=0.002). Among patients, the mean disease duration was 3.6 years, 29% were Scl70 antibody positive, 44% were RNA polymerase III antibody positive, the mean MRSS was 18.5, the mean predicted forced vital capacity (FVC) was 75%, the mean echo-measured pulmonary artery systolic pressure was 33 mmHg, and 17% had diastolic dysfunction.

Adiponectin (4.3 vs 5.8 µg/ml, p=0.04) and adipsin (7.1 vs 9.0 pg/ml, p=0.001) levels in dcSSc patients were significantly lower than controls. Low levels of adiponectin and adipsin were associated with decreased FVC (p=0.001, and p=0.02, respectively). Patients also had an increased leptin/adiponectin ratio compared to controls (0.31 vs 0.26, p=0.004) and this ratio was associated with diastolic dysfunction (p=0.04) and left ventricular ejection fraction (p=0.05). Leptin was not associated with disease, but among patients, there was an association between higher leptin levels and BMI (p=0.01) and diastolic dysfunction (p=0.01). None of the adipokine levels were significantly associated with antibody status, disease duration, MRSS, or pulmonary artery pressure.

Conclusion: This study affirms the association of decreased adiponectin with dcSSc and finds new associations between decreased serum adipsin and an increased leptin/adiponectin ratio with dcSSc. Adipokine profiles may be useful in assessing risk and monitoring cardiac and pulmonary manifestations of SSc.

Abstract Number: 1902

Systemic Sclerosis and Lung Cancer Risk: Data from the Canadian Scleroderma Research Group

Lama Sakr[1], Elie Younanian[2], **Marie Hudson**[3], Mianbo Wang[4], Murray Baron[5] and Sasha Bernatsky[6], [1]Division of Pulmonary Diseases, Jewish General Hospital, Montreal, QC, Canada, [2]Division of Pulmonary Diseases, McGill University, Montreal, QC, Canada, [3]McGill University, Jewish General Hospital, Montreal, QC, Canada, [4]Lady Davis Institute for Medical Research, Montreal, QC, Canada, [5]Jewish General Hospital, Lady Davis Institute and McGill University, Montreal, QC, Canada, [6]Divisions of Rheumatology and Clinical Epidemiology, McGill University Health Centre, Montreal, QC, Canada

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Background/Purpose:

The literature supports an increased incidence of certain malignancies in patients with systemic sclerosis (SSc), including lung cancers. Predictors of lung cancer in SSc remain uncertain. We aim to identify potential independent predictors of lung cancer risk in SSc.

Methods:

Our analyses were based on data from the Canadian Scleroderma Research Group (CSRG) registry, an open cohort of 1560 patients with SSc, who were enrolled from 2004 and followed for a maximum of 11 years. Lung cancer cases occuring at any time after the baseline CSRG visit were identified based on physician reports at each annual follow-up visit. Time to lung cancer diagnosis was calculated from the onset of the first non-Raynaud symptoms, with left censoring to account for time between onset of first non-Raynauds symptoms and cohort entry. Demographic, clinical and serological characteristics of patients with and without lung cancer were compared. Cox proportional hazards models were used to estimate adjusted hazard ratios (HRs) with 95% confidence intervals (CIs), with the outcome of lung cancer adjusted for sex, age, race/ethnicity and the number of pack-years smoked.

Results:

Over the 5487.32 total person-years of follow-up, a total of 18 SSc patients were diagnosed with lung cancer (0.33 cancers per 100 person-years). Nine patients (9/27) were excluded from the cox analysis because of diagnosis of cancer prior to cohort entry. Patients with lung cancer were older at cohort entry (60.6 ± 11.4 standard deviation, SD vs. 55.5 ± 12.3 SD years), and more likely to have a past or current smoking history (88.9 vs. 59.1%), a higher prevalence of interstitial lung disease (65.4% vs. 30.2%), lower FVC (87% vs. 91.6% predicted) and more severe gas exchange abnormalities (DLCO 52.3% vs. 72.7% predicted). Male sex (HR, 3.13; 95% CI, 1.06-9.09), the presence of intersititial lung disease at cohort entry (HR, 2.96; 95% CI, 1.10-7.96) and smoking (HR, 6.17; 95% CI, 1.29- 29.50) were independently associated with an increased risk of lung cancer, after adjusting for age and race/ethnicity.

Conclusion:

Smoking history is an important predictor of lung cancer in SSc. Male sex and ILD are also associated with an increased risk of lung cancer in SSc, independent of smoking history.

Abstract Number: 1903

Assessment of Subclinical Atherosclerosis in Patients with Systemic Sclerosis: Results from a Multicentric Cohort

Codrina Ancuta[1,2], Codruta Belibou[3], Cristina Pomirleanu[1,4], Carina Mihai[5], Ioan Ancuta[5], Patricia E. Carreira[6], Jose Luis Rosales Alexander[7], Juan José Alegre[8], Valeria Riccieri[9], Maria J. Salvador[10] and Rodica Chirieac[4], [1]Rheumatology, Gr.T.Popa University of Medicine and Pharmacy, Iasi, Romania, [2]Rheumatology 2, Clinical Rehablitation Hospital, Iasi, Romania, [3]Research Department, Clinical Rehabilitation Hospital, Iasi, Romania, [4]Rheumatology 2, Clinical Rehabilitation Hospital, Iasi, Romania, [5]Department of Internal Medicine and Rheumatology, Dr.I.Cantacuzino Hospital, Carol Davila University of Medicine and Pharmacy, Bucharest, Romania, [6]Multidisciplinary Pulmonary Hypertension Unit. Hospital Universitario 12 de Octubre, Madrid, Spain, [7]Rheumatology, Hospiten Health Network, Tenerife, Spain, [8]Rheumatology Department, Hospital Universitario Doctor Peset, Valencia, Spain, [9]Cattedra di Reumatologia, Dip Clinica e Terapia Medica, Sapienza Università di Roma, Roma, Italy, [10]Rheumatology, Centro Hospitalar e Universitário de Coimbra - Hospitais da Universidade de Coimbra, EPE, Coimbra, Portugal
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Background/Purpose: Although numerous studies have reported different findings on subclinical and definite atherosclerosis (AS) in autoimmune rheumatic diseases, data in systemic sclerosis (SSc) are still challenging. The main objectives of our study were to assess surrogate biomarkers of subclinical AS as measured by carotid ultrasound and to evaluate potential relation with different cardiovascular risk factor in different settings of SSc.

Methods: We conducted a cross-sectional prospective study in 6 European EUSTAR (European Scleroderma Trials and Research) centers on 301 consecutive SSs patients enrolled in the SSAS (Early Accelerated Atherosclerosis in Systemic Sclerosis) cohort (88.3% women, 71.4% limited skin involvement SSc). Traditional (smoking, hypertension, diabetes, abnormal lipid pattern, familial history of cardiovascular disease) and non-traditional cardio-vascular risk factors (disease activity and severity, hsCRP, immune profile, glucocorticoids, synthetic immunosuppressives) as well as surrogate biomarkers for subclinical AS (carotid scanning measuring common carotid arteries intima-media thickness, cIMT, and plaques in common, internal and

external carotid) were collected in all patients as a single point data. Subgroup analysis based on skin extent and serology profile was further performed using SPSS.

Results: We reported an average of 0.65±0.14 mm (0.43-1.20) for cIMT, with a slight tendency of higher values in diffuse cutaneous (dc) SSc subgroup as compared with limited cutaneous (lc) SSc with no statistically significance ($p>0.05$). In addition we identified several statistically significant correlations between cIMT and age, systolic blood pressure, abnormal lipid profile (cholesterol, total chol/HDL-col, triglycerides), disease duration, activity and severity (EUSTAR score, MEDSGER severity scale) ($p<0.05$), maintained in subgroup analysis. However, no significant relation with the glucocorticoid and immunosuppressive intake was demonstrated. At least one carotid plaque causing no or non-significant stenosis was observed in up to one third of cases, particularly in dcSSc, with age, smoking and hypertension independently associated with AS plaques, as well as the cumulative steroid dose ($p<0.05$). Although subgroup analysis suggested a higher values for AS parameters and risk factors in dcSSc as well as anti-SCL and ACA-positive patients, data were not statistically significant ($p>0.05$). Actual results confirm interim analysis data.

Conclusion: SSc is associated with an increased risk of developing subclinical AS, although early AS is not a hallmark of the disease. Age, dyslipidemia and hypertension as well as disease duration, activity and severity are listed as potential risk factors for AS particularly in dcSSc subtype.

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Abstract Number: 1904

Development of the Mawdsley Calcinosis Questionnaire (MCQ) Version 1 – a Patient-Reported Outcome Measure (PROM) for Systemic Sclerosis Related Calcinosis (SSc-Ca)

Lesley Ann Saketkoo[1], Kim Fligelstone[2], Evan Busman[3], Angela Christensen[4], Sophia Cenac[5], Samara Khalique[6], Andrew Aubin[7], Veronika K. Jaeger[8], Anne Mawdsley[9], Jessica K. Gordon[10], Randi Kaufman[11], Murray Baron[12], Virginia D. Steen[13] and Tracy M. Frech[14], [1]Tulane University Lung Center, New Orleans Scleroderma and Sarcoidosis Patient Care and Research Center, New Orleans, LA, [2]Royal Free Hospital, Scleroderma Unit and Scleroderma Society, London, United Kingdom, [3]Atlanta Scleroderma Support Group, Atlanta, GA, [4]Tulane University School of Medicine, New Orleans, LA, [5]Louisiana State University Health Science Center, New Orleans, LA, [6]Louisiana State University Health Sciences Center, New Orleans, LA, [7]Louisiana State University School of Medicine, New Orleans, LA, [8]Department of Rheumatology, University Hospital Basel, Basel, Switzerland, [9]Raynaud's & Scleroderma - Care and Support UK, Cheshire, United Kingdom, [10]Rheumatology, Hospital for Special Surgery, New York, NY, [11]Lousiana State University Health Sciences Center - School of Public Health, New Orleans, LA, [12]Jewish General Hospital, Lady Davis Institute and McGill University, Montreal, QC, Canada, [13]Rheumatology, Georgetown University Medical Center, Washington, DC, [14]Div of Rheumatology, University of Utah, Salt Lake City, UT

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Background/Purpose: SSc-Ca is a poorly understood vascular complication of SSc that usually related to extreme constant pain and infection/amputation risk for persons living with SSc-Ca (PLWSC). No recognized treatment exists for SSc-Ca. There are no standardized measures of therapeutic responsiveness to assess potential medication impact on SSc-Ca. **Results** here reflect the next phases of PROM development.

Methods: Qualitative analysis from 31 PLWSC interviews revealed insight into self-management, quality of life, mental/physical function and natural history of SSc-Ca. Seventy-eight concepts were collectively reported by participants. Of these, 21 items related to any sphere of function or body structure were extracted by iterative analyses. Patient Research Partners (PRP) experienced in SSc research and questionnaires, assisted in formulating potential question stems. Nine PLWSC assisted in field-testing (FT) in face to face interviews and by quantitative response to potential PROM items using a 0-5 Likert rating ‘usefulness' of potential PROM item in indicating improvement/ worsening of SSc-Ca – ‘not applicable to me' was an option. Selection of preferred vocabulary, time reference, context and response scale (RS) format, length, verbiage and images were examined with all participants.

Results: Four PROM domains resulted: Quantity/Frequency (4 items), Pain/Sensation (5), Physical Function (4) and Psychological Impact (6). The MCQ pre-test version is indexed in table 1. Two of 4 quantity items were rated ≥4 by >80%, for which scoring are yet to be determined, quantile scales are considered. For scalable items, there was 100% selection of a 0-10 scale over various formats 0-5, 0-7, 0-9 scales, >90% selected Likert response over VAS, a reflective time reference of ‘2 weeks', and a reflective severity reference of ‘what is the worst degree' with 100% selection for single or brief word descriptors to cap scales i.e. ‘none' to ‘worst possible'. Thirteen of the 17 scaled items were rated ≥4 by >80% of participants and 100% 4 items. Two scaled questions pertaining strictly to Raynauds and digital ulcers may be incorporated as ‘stabilisation' questions scored separately for comparative reference. Only the 2 participants experiencing foot calcinosis rated the ‘walking' item highly; causing consideration for a test question combining upper and extremity physical function in order to create a uniformly weighted instrument.

Table 1. Items, domains, *=rating with >80% participants rating item with ≥4 (very to extremely useful)

Item	Domain	Items rating >4*	Scale
Geographical location	Reference only	*	None, report only
Hemisphere/season	Reference only	*	None, report only
Month	Reference only	*	None, report only
Number of calcinosis lesions (open or closed)	Quantity/Frequency	*	Undetermined
Number of calcinosis lesions you FEEL that you have	Quantity/Frequency	-	Undetermined
Number of digital ulcers	Quantity/Frequency	*	Undetermined/ comparative
Number of digital ulcers you think related to calcinosis	Quantity/Frequency	_	Undetermined
Stem to below items is: 'In the past TWO WEEKS, what is the worst degree that...'			
Raynaud's interfered with daily activities?	Reference	*	0-10 for comparative reference
Digital ulcers interfered with daily activities?	Reference	*	0-10 for comparative reference
Experienced pain from calcinosis?	Pain/Sensation	*	0-10 for scoring
You felt any areas of calcinosis getting tighter or having more pressure?	Pain/Sensation	*100%	0-10 for scoring
You felt any areas of calcinosis GROWING under your skin?	Pain/Sensation	*	0-10 for scoring
Your felt any areas of your calcinosis THROBBING?	Pain/Sensation	*	0-10 for scoring
Your calcinosis has been TENDER to TOUCH?	Pain/Sensation	*100%	0-10 for scoring
You felt the need to PROTECT areas of your calcinosis?	Psychological Impact	*100%	0-10 for scoring
You have been FEARFUL or WORRIED that any of the calcinosis areas are infected?	Psychological Impact	*	0-10 for scoring
You have been worried that a calcinoisis wound might not heal?	Psychological Impact	*100%	0-10 for scoring
Your calcinosis interfered with ability to care for self	Physical Function	*	0-10 for scoring
Your calcinosis interfered with your ability to use your hands?	Physical Function	*	0-10 for scoring
Your calcinosis interfered with walking?	Physical Function	(25%)	0-10 for scoring
Your calcinosis interfered with your ability to work (paid or unpaid)	Physical Function	*	0-10 for scoring
Your calcinosis made you feel down, depressed or hopeless?	Psychological Impact	-	0-10 for scoring
Your calcinosis interfered with your ability to enjoy and 'be there' for your friends and family?	Psychological Impact	-	0-10 for scoring
Your calcinosis interfered with your ability to enjoy recreational activities (hobbies, sports, etc)?	Psychological Impact	-	0-10 for scoring

Conclusion: This is the first known SSc-Ca PROM developed according to FDA Guidance. These items will undergo test/re-test validation with subsequent multi-centre prospective assessment of the surviving MCQ items beginning in July 2015. The MCQ is named in honor of Anne*Mawdsley*- an original research team member, founder of the Raynauds & Scleroderma Association UK, and a PLWSC who raised over £10 million for SSc research, education and advocacy in her lifetime.

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Abstract Number: 1905

Stimulators of Soluble Guanylate Cyclase (sGC) Inhibit Experimental Skin Fibrosis of Different Aetiologies

Peter Sandner[1,2], Clara Dees[3], Joerg H. W. Distler[3], Christian Beyer[3], Alfiya Distler[3], Yun Zhang[4], Katrin Palumbo-Zerr[4], Georg A. Schett[5], Alina Soare[3,6], Oliver Distler[7] and Emanuel Haasbach[8], [1]Bayer Health Care, Global Drug Discovery, Bayer Pharma AG, Wuppertal, Germany, [2]Institute of Pharmacology, Hannover Medical School, Hannover, Germany, [3]Department of Internal Medicine 3, University of Erlangen-Nuremberg, Erlangen, Germany, [4]Department of Internal Medicine 3 and Institute for Clinical Immunology, University of Erlangen-Nuremberg, Erlangen, Germany, [5]Department of Medicine 3, University of Erlangen-Nuremberg, Erlangen, Germany, [6]Carol Davila University of Medicine and Pharmacy, Internal Medicine and Rheumatology, Cantacuzino Hospital, Bucharest, Romania, [7]Research of Systemic Autoimmune Diseases, Center of Experimental Rheumatology, University Hospital Zurich, Zurich, Switzerland, [8]Bayer HealthCare, Bayer Pharma AG, Wuppertal, Germany
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Session Time: 9:00AM-11:00AM

Background/Purpose:

Systemic sclerosis (SSc) is characterised by fibrosis and vascular alterations, both of which account for the high morbidity and mortality of SSc. Although several therapies are in clinical use for the treatment of vascular manifestations, no targeted therapies are yet approved for the treatment of fibrosis.

Stimulators of the soluble guanylate cyclase (sGC) have recently been shown to inhibit transforming growth factor-β signaling. Here, we aimed to demonstrate that Riociguat, the drug candidate for clinical trials in systemic sclerosis (SSc), is effective in experimental fibrosis and to compare its efficacy

to that of phosphodiesterase V inhibitors that also increase the intracellular levels of cyclic guanosine monophosphate (cGMP).

Methods:

The antifibrotic effects of Riociguat and Sildenafil were compared in the tight-skin 1 model, in bleomycin-induced fibrosis and in a model of sclerodermatous chronic graft-versus-host-disease (cGvHD). Doses of 0.1 – 3 mg/kg twice a day for Riociguat and of 3 – 10 mg/kg twice a day for Sildenafil were used. In addition to the antifibrotic effects, the effects on cardiovascular parameters were measured in conscious mice implanted with telemetry devices.

Results:

Riociguat dose-dependently reduced skin thickening, myofibroblast differentiation and accumulation of collagen with potent antifibrotic effects at 1 and 3 mg/kg. Riociguat also ameliorated fibrosis of the gastrointestinal tract in the cGvHD model. The antifibrotic effects were associated with reduced phosphorylation of extracellular signal-regulated kinases and effects on cardiovascular parameters. Sildenafil at doses of 3 and 10 mg/kg exerted mild antifibrotic effects that were significantly less pronounced compared with 1 and 3 mg/kg Riociguat.

Conclusion:

These data demonstrated potent antifibrotic effects of Riociguat on experimental skin and organ fibrosis. These findings suggest a role for Riociguat for the treatment of fibrotic diseases, especially for the treatment of SSc. A phase II study with Riociguat in patients with diffuse cutaneous systemic sclerosis (dcSSc) is ongoing.

Disclosure: P. Sandner, Bayer Pharma AG, 3; **C. Dees**, None; **J. H. W. Distler**, consultancy relationships and/or has received research funding from Actelion, Active Biotech, Array Biopharma, Bayer Pharma AG, Boehringer Ingelheim, Celgene, GlaxoSmithKline, JB Therapeutics, Karo Bio, Novartis, Sanofi-Aventis, SigmaTau, UCB Pharma and i, 2; **C. Beyer**, None; **A. Distler**, None; **Y. Zhang**, None; **K. Palumbo-Zerr**, None; **G. A. Schett**, None; **A. Soare**, None; **O. Distler**, Consultancy relationships and/or has received research funding from Actelion, Pfizer, Ergonex, BMS, Sanofi-Aventis, United BioSource Corporation, Medac, Biovitrium, Boehringer Ingelheim, Bayer Pharma AG, Novartis, 4D Science and Active Biotech in the area, 2; **E. Haasbach**, Bayer Pharma AG, 3.

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Abstract Number: 1906

Stimulators of Soluble Guanylate Cyclase (sGC) Improve Wound Healing in the Tsk-1 Mouse Skin Fibrosis Mode

Peter Sandner[1,2], Christian Beyer[3], Joerg H. W. Distler[3] and Emanuel Haasbach[1], [1]Bayer HealthCare, Bayer Pharma AG, Wuppertal, Germany, [2]Institute of Pharmacology, Hannover Medical School, Hannover, Germany, [3]Department of Internal Medicine 3, University of Erlangen-Nuremberg, Erlangen, Germany

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Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose:

Systemic sclerosis (SSc) is a multisystem disorder characterized by thickening of the skin and distinctive involvement of multiple internal organs. In addition to skin fibrosis, SSc causes alterations of the microvasculature and severe peripheral vasculopathies, including perivascular fibrosis, Raynaud´s phenomena and the formation of digital ulcers (DU). Many drugs, proposed to have anti-fibrotic effects, inhibit wound healing and might thus further complicate the healing of ischemic ulcers in SSc.

Soluble guanylate cyclase (sGC) stimulators like Riociguat inhibit the release of collagen in fibrosis models, and improve acral perfusion due to their vasodilatory effects. Therefore we hypothesize that the vasodilatory effects of Riociguat may balance its inhibitory effects on collagen release in wound healing and may thus not negatively affect wound healing in SSc patients. The aim of these studies was to characterize the effects of the sGC stimulators BAY 63-2521 (Riociguat) and BAY 41-2272 on wound healing in the tsk-1 mouse skin fibrosis model.

Methods:

The tight-skin (tsk-1) mouse model of SSc was used to evaluate the effects of the sGC stimulators BAY 63-2521 (Riociguat) and BAY 41-2272 on wound closure in mice with skin fibrosis. During anesthesia, WT mice and tsk-1 mice were bilaterally punched, establishing a defined round wound with 4 mm in diameter. WT mice and tsk-1 mice were treated with either placebo, BAY 63-2521 or BAY 41-2272 and efficacy was measured by reduction of wound area, 3 days after punching.

Results:

In WT mice a reduction in wound size by 68% ± 2% was found after 3 days. Compared to WT mice, wound closure was significantly attenuated in tsk-1 mice with a reduction in wound size of only 52% ± 2 %. Treatment with the sGC stimulator BAY 63-2521 (Riociguat) had no influence on wound healing in WT mice. In tsk-1 mice both sGC stimulators caused a dose-dependent and significant improvement of wound healing. Wound sizes were reduced by 59% ± 4%, 65% ± 3% ($p < 0.05$) and 70% ± 2% ($p < 0.0001$) with 0.3, 1 or 3 mg/kg BAY 63-2521, respectively. And tsk-1 mice treated with 1 or 3 mg/kg BAY 41-2272 showed a reduction of 64% ± 3% and 73% ± 2% ($p < 0.0005$).

Conclusion:

These data imply that the sGC stimulators BAY 63-2521 (Riociguat) and BAY 41-2272 could become a efficacious treatment option for SSc-related vasculopathies, especially for prevention and healing of DU.

Disclosure: P. Sandner, Bayer Pharma AG, 3; **C. Beyer**, None; **J. H. W. Distler**, consultancy relationships and/or has received research funding from Actelion, Active Biotech, Array Biopharma, Bayer Pharma AG, Boehringer Ingelheim, Celgene, GlaxoSmithKline, JB Therapeutics, Karo Bio, Novartis, Sanofi-Aventis, SigmaTau, UCB Pharma and i, 2; **E. Haasbach**, Bayer Pharma AG, 3.

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Abstract Number: 1907

Inhibition of Phosphodiesterase 4 (PDE4) Reduces Dermal Fibrosis By Interfering with the Release of Pro-Fibrotic Cytokines from M2-Macrophages

Christiane Maier, Christian Beyer, Jeorg HW Distler and Georg Schett, Department of Internal Medicine 3 and Institute for Clinical Immunology, University of Erlangen-Nuremberg, Erlangen, Germany

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Session Time: 9:00AM-11:00AM

Background/Purpose:

PDE4 catalyses the breakdown of the second messengers cAMP and cGMP to modulate intracellular effects. PDE4 is mainly expressed in inflammatory cells, and its inhibition leads to reduced inflammatory cell activity. In this study, we examined the role of PDE4 inhibition in skin fibrosis and evaluated its potential as an anti-fibrotic target in systemic sclerosis (SSc).

Methods:

We studied the anti-fibrotic effects of the PDE4-specific inhibitor rolipram in the models of bleomycin-induced skin fibrosis and sclerodermatous chronic graft versus host disease (sclGvHD), reflecting local and systemic inflammatory fibrotic disease. To better understand the anti-fibrotic activity of PDE4 blockade, we treated fibroblasts and macrophages obtained from healthy individuals and patients suffering from diffuse cutaneous SSc with rolipram and investigated its effects on fibrosis relevant cytokines.

Results:

PDE4 inhibition had potent dose-dependent anti-fibrotic effects in bleomycin-induced skin fibrosis and sclGvHD. In bleomycin-induced skin fibrosis, the treatment with the higher dosis (5 mg/kg once daily) of rolipram reduced skin thickness by 36% ($p < 0.001$), hydroxyproline content by 42% ($p = 0.004$) and the number of α-SMA-positive myofibroblasts by 24% ($p < 0.001$). The anti-fibrotic activity of PDE4 inhibition was also prominent in sclGvHD in which we observed reductions of skin thickness by 95% ($p = 0.002$) and of activated myofibroblasts by 24% ($p = 0.002$). The hydroxyproline content showed an almost significant decrease upon PDE4 inhibition. In line with the mode of action of PDE4 blockade, we observed reduced leukocytes counts in bleomycin-induced skin fibrosis (by 37%; $p = 0,012$) and in sclGvHD (by 78%; $p = 0.005$).

Consistent with our in vivo findings and the fact that PDE4 is mainly expressed in inflammatory cells, we showed that fibroblasts were not the direct targets of the anti-fibrotic effects of PDE4 blockage. By contrast, PDE4 inhibition decreased the release of pro-fibrotic cytokines IL-6 and 13, TGF-β1 and β2, and fibronectin-1 from activated M2 macrophages obtained from healthy volunteers and SSc patients, resulting in reduced fibroblast activation and collagen release.

Conclusion:

PDE4 inhibition reduces the release of pro-fibrotic cytokines from M2 macrophages, which leads to decreased fibroblast activation and collagen release. Importantly, rolipram is a lead compound of the PDE4 inhibitor apremilast, which is approved for the treatment of psoriatic arthritis. Therefore, our preclinical findings might prompt the use of PDE4 inhibitors in clinical studies with patients suffering from SSc, in particular those with inflammation-driven fibrosis.

Disclosure: C. Maier, None; **C. Beyer**, None; **J. H. Distler**, None; **G. Schett**, None.

Abstract Number: 1908

Macitentan Responsiveness Supports the Validity of a Murine Model of Pulmonary Hypertension in Scleroderma Associated with Altered Tgfbeta/BMPR2 Signalling

Emma C. Derrett-Smith[1], Vincent Sobanski[2], Adrian Gilbane[2], Sarah Trinder[3], Yasmina Bauer[4], Berengère Renault[4], Marc Iglarz[4], David Abraham[5], Alan M. Holmes[6] and Christopher P. Denton[7], [1]Centre for Rheumatology and Connective Tissue Diseases,, UCL Division of Medicine, London, United Kingdom, [2]UCL Division of Medicine, London, United Kingdom, [3]Centre for Rheumatology and Connective Tissue Disease, UCL Division of Medicine, London, United Kingdom, [4]Actelion Pharmaceuticals Ltd., Allschwil, Switzerland, [5]Centre for Rheumatology and Connective Tissue Disease, University College London, London, United Kingdom, [6]Centre for Rheumatology and Connective Tissue Diseases, UCL Division of Medicine, London, United Kingdom, [7]Rheumatology and Connective Tissue Diseases, University College London, London, United Kingdom

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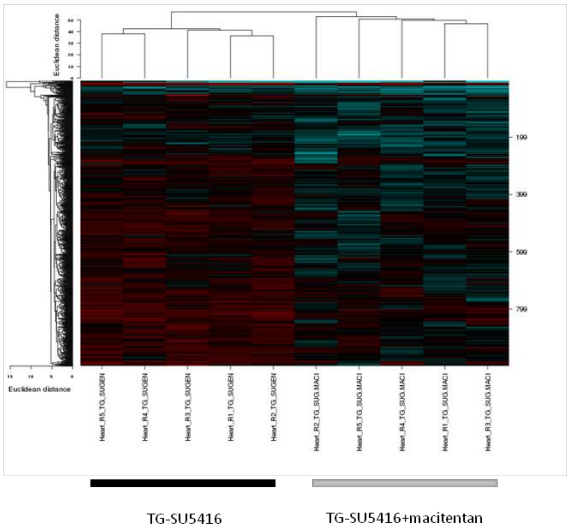
Background/Purpose: Pulmonary arterial hypertension (PAH) is an important complication of systemic sclerosis (SSc) that occurs in around 10% of cases. We have previously shown that an imbalance between TGFbeta and BMPRII signalling in the transgenic mouse strain TβRIIΔk-fib contributes to the development of PH following pulmonary endothelial injury. In this study, we have both prevented and treated PH in this mouse strain using macitentan, an endothelin receptor antagonist licensed to treat PAH in connective tissue disease.

Methods: SU5416 was administered to all TβRIIΔk-fib transgenic (TG) mice and littermate wildtype (WT) animals to induce endothelial injury with subsequent endoluminal proliferation and PH in transgenic mice only. Mice were treated daily with either macitentan or vehicle alone (n=8 each group) from either 2 days before or 8 days following SU5416 administration to assess prevention or treatment respectively. The development of PH in each group was assessed by histology and immunohistochemistry of vessel architecture, *in vivo* haemodynamic studies and RV mass index measurements following 3 weeks of treatment. Microarray analysis of right ventricular tissue was performed.

Results: : All TG mice developed a perivascular inflammatory infiltrate and smooth muscle layer hypertrophy after SU5416 administration. RV mass index was elevated in TG animals receiving vehicle compared to other groups. In particular co-administration of macitentan to TG animals treated with SU5416 resulted in normal RV mass (TG vehicle 0.29±0.007, TG macitentan at day -2 0.24±0.007, $p<0.05$). The increase in RV systolic pressure in TG animals treated with SU5416 was abrogated by macitentan (TG vehicle 28.8±3.2, TG+macitentan at day -2 22.0±2.9, TG+macitentan at day +8, 24.4±1.8, $p<0.05$) without any significant change in systemic arterial blood pressure. Explanted TG lung fibroblasts showed an increase in TGFbeta signalling and downregulation of BMPRII compared with WT littermates following macitentan treatment. Pulmonary arteriolar occlusion occurred in 21% of vessels in TG mice treated with vehicle with no occlusion in any other vessels. Gene expression analysis of whole right ventricle showed alterations in key genes known to be associated with cardiac muscle remodelling and failure. Figure 1 shows the cluster analysis of TG mice treated with SU5416 compared with those also treated with macitentan.

Conclusion: Macitentan prevents and treats the development of histological and haemodynamic PH in this mouse model of SSc. The pivotal role for perturbed endothelin activity in a model that replicates the imbalance in TGFbeta and BMPRII signalling seen in PAH-SSc lung is shown. It underpins the value of this model as a platform for experimental therapeutic studies.

Figure 1: Heatmap of genes downregulated by macitentan in right ventricles of SU5416 treated mice



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View Abstract and Citation Information Online - http://acrabstracts.org/abstract/macitentan-responsiveness-supports-the-validity-of-a-murine-model-of-pulmonary-hypertension-in-scleroderma-associated-with-altered-tgfbetabmpr2-signalling

Abstract Number: 1909

Nailfold Capillaroscopic Assessment and Vascular Biomarkers in Systemic Sclerosis: Low CD40L Levels in Patients with Late Scleroderma Patterns

Yasemin Yalcinkaya[1], Suzan Cinar[2], Sevil Kamali[3], Ozlem Pehlivan[4], Lale Ocal[1], Gunnur Deniz[2] and Murat Inanc[3], [1]Istanbul Medical Faculty, Department of Internal Medicine, Division of Rheumatology, Istanbul University, Istanbul, Turkey, [2]Department of Immunology, Istanbul University, Institute of Experimental Medicine (DETAE), Istanbul, Turkey, [3]Department of Internal Medicine, Division of Rheumatology, Istanbul University, Istanbul Faculty of Medicine, Istanbul, Turkey, [4]Istanbul Faculty of Medicine, Department of Internal Medicine, Division of Rheumatology, Istanbul University, Istanbul, Turkey
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Background/Purpose: To determine the relationship between vascular biomarkers reflecting the vascular injury and neoangiogenesis with nailfold capillaroscopic changes in systemic sclerosis (SSc).

Methods: Seventy-two SSc patients (66 female) fulfilling Leroy and Medsger classification criteria were evaluated, including clinical findings, nailfold videocapillaroscopy (NVC) was performed qualitatively (early, active and late scleroderma patterns) in all patients (Cutolo M, et al. J Rheumatol 2000). Serum samples of patients were collected for flow-cytometric analysis of CD40L, tPA, MCP-1, sE-selectin, IL-8, IL-6, VEGF, sP-selectin, TGF-β1 and VCAM levels (Bender MedSystems, Vienna, Austria) at the same time with NVC. **Results** were compared with Pearson chi-square / Fischer's, Mann Withney U ve Kruskal Wallis tests.

Results: The mean age of the patients was 44.9 and disease duration from the appearance of Raynaud's and non-Raynaud symptoms were 5.8±5.9 and 3.2±2.4 years. Of the patients 23 (%32) had diffuse and 49 (%68) limited cutaneous involvement, 15(%21) were anti-centromere(+) and 34(%47) were anti-Scl70(+).

When we compared with healthy subjects; tPA (p=0.02), MCP-1 (p=0.001), sE-selectin (p=0.008) and TGF-β1(p=0.001) levels were significantly higher, sP-selectin (p=0.011) ve IL-8(p=0.001) levels were lower in SSc patients (table-1)(figure-1). SSc patients grouped according to NVC patterns as 'early'(n=10), 'active'(n=37) and 'late'(n=25). Between groups according to NVC patterns, only sCD40L(pg/ml) levels were significantly lower in the 'late' group (p=0.043), higher in patients with limitted cutaneus involvement (p=0.01) and smoking history (n=32,%44) (p=0.033). The other markers were similar between NVC groups.

Table-1: Vascular Biomarkers in Healthy Controls, Systemic Sclerosis and NVC patterns

Biomarker Levels (mean ±SD)	Healthy Controls (n=20)	Systemic Sclerosis (n=72)	NVC Early (n=10)	NVC Active (n=37)	NVC Late (n=25)
sCD40L (pg/ml)	**24620±13051**	**27847±33315**	**27584±14694**	**34656±42750**	**17877±16911¶**
tPA (pg/ml)	2415±1279*	4036±6961	3173±1364	4835±9577	3199±1742
MCP-1 (pg/ml)	907±300**	1302±550	1096±433	1372±636	1282±437
sE-selectin (ng/ml)	205±78**	269±106	212±69	283±110	272±107
IL-8 (pg/ml)	49±73**	22±80	7±14	22±82	30±93
IL-6 (pg/ml)	0	0.6±2.8	17.9	13.3	9.3/2.8
VEGF (pg/ml)	704±363	776±591	996±904	745±570	733±464
sP-selectin (ng/ml)	364±137*	287±86	316±83	292±98	267±62
TGF-β1 (pg/ml)	2421±4785**	8277±8592	12115±9511	8128±9140	6964±7155
VCAM (pg/ml)	3231±1435	3945±1754	3951±1062	4091±1771	3727±1973

**p<0.05, **p<0.01 When healthy controls and sytemic sclerosis patients were compared with Mann-Whitney tests, ¶ p<0.05 When early, active and late NVC patterns in systemis sclerosis patients were compared with Kruskal-Wallis test*

Conclusion: There was lower sCD40L serum levels in patients with late NVC patterns, although the levels were similar to healthy controls in patients with early, active NVC patterns. CD40L may be a key molecule in the early/active phase of vascular involvement. Higher concentrations of sCD40L in patients with limited cutaneous disease and smoking history might be related to its role in vascular pathology. NVC is a useful method for investigating the vascular pathogenesis in SSc.

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Abstract Number: 1910

Increased Circulating CD204/CD206 Double Positive Monocyte/Macrophages in Systemic Sclerosis Patients with "Early" Capillaroscopic Pattern of Microvascular Damage

Stefano Soldano[1], Paola Contini[2], Paola Montagna[1], Renata Brizzolara[1], Amelia Chiara Trombetta[3], Barbara Ruaro[3], Alberto Sulli[3], Sabrina Paolino[3], Carmen Pizzorni[3], Bruno Seriolo[1], Marco A. Cimmino[3] and **Maurizio Cutolo**[3], [1]Research Laboratory and Academic Division of Clinical Rheumatology, Department of Internal Medicine, University of Genova, Genoa, Italy, Genoa, Italy, [2]Division of Clinical Immunology, Department of Internal Medicine, University of Genova, Genoa, Italy, Genoa, Italy, [3]Research Laboratory and Academic Division of Clinical Rheumatology, Department of Internal Medicine, IRCCS A.O.U. San Martino-IST, University of Genova, Genoa, Italy, Genoa, Italy

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Background/Purpose: Immune-inflammatory cells participate together with endothelial cells and myofibroblasts in the tissue damage that characterizes fibrotic diseases, including systemic sclerosis (SSc) (1). Among immune cells, alternative activated macrophages (M2) are implicated in the pathogenesis of fibrosis through the production of profibrotic molecules (i.e. fibronectin and TGFβ), as observed in lung fibrosis and cancer (1). M2 are characterized by an increased expression of specific markers, such as CD206 (mannose receptor1) and scavenger receptors (CD204 and CD163) and we investigated their presence in the peripheral blood (PB) of SSc patients (pts) (1). Furthermore, since endothelin-1 (ET-1) has been shown to promote the fibrotic process in SSc, we tested possible *in vitro* effects of ET-1 in inducing the transition of cultured human macrophages into the M2 phenotype (2).

Methods: Twenty-six randomized female SSc pts (65±10 years), who fulfilled the new EULAR/ACR criteria (3), and ten healthy subjects (HS, 62±10 years) were enrolled into the study after EC approval and Informed Consent signed. Nailfold videocapillaroscopy (NVC) was performed to define the pattern of mycroangiopathy (4). PB from SSc pts and HS was analysed by flow cytometry investigating cells positive for CD204, CD206 and CD14 (monocyte/macrophage marker). Cultured human monocyte cells (THP1, $1x10^6$ cells/ml) were activated to macrophages with phorbol myristate acetate (25ng/ml) and then either untreated or treated with ET-1 (100mM) or IL4 (10ng/ml, as inducer of M2) for 72 hrs in growth medium at 5% of fetal bovine serum. Gene and protein expressions of CD204, CD206 and CD163 were investigated by qRT-PCR and immunocytochemistry. Statistical analysis was performed by Mann-Whitney non-parametric test.

Results: SSc pts showed a significant increased percentage of circulating $CD204^+/CD206^+$cells compared to HS ($p<0.05$). NVC analysis identified 13 SSc pts with an "early" pattern and 13 SSc pts with an "active/late" pattern of microangiopathy. Of note, the percentage of $CD204^+/CD206^+$cells was significantly increased exclusively in those SSc pts who showed an "early" pattern ($p<0.05$ vs. HS). The qRT-PCR showed that ET-1 induced a significant increase in the gene expression of CD204, CD206 and CD163 in cultured macrophages ($p<0.05$ vs. untreated cells for all M2 markers). In addition, immunocytochemistry showed that ET-1 further increased the protein expression of CD204 and induced the *de novo* synthesis of CD206 vs. untreated cells. These effects on gene and protein expressions of M2 markers were similar to those induced by treatment with IL4.

Conclusion: Increased percentage of cells with M2 phenotype seems evident in the PB of SSc pts and significantly in those characterized by an "early" NVC pattern of mycroangiopathy. The ability of ET-1 to induce the expression of M2 markers in human macrophages might suggest its possible action in driving the polarization of macrophages into a M2 phenotype.

References: 1 Wynn TA et al. Nat Med 2012;18:1028-40. 2 Cutolo M et al. J Rheumatol 2015;42:456-63. 3 van der Hoogen F et al. Arthrit Rheum 2013;65:2737-47. 4 Sulli A et al J Rheumatol 2009;36:1235-9.

Disclosure: S. Soldano, None; **P. Contini**, None; **P. Montagna**, None; **R. Brizzolara**, None; **A. C. Trombetta**, None; **B. Ruaro**, None; **A. Sulli**, None; **S. Paolino**, None; **C. Pizzorni**, None; **B. Seriolo**, None; **M. A. Cimmino**, None; **M. Cutolo**, None.

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Abstract Number: 1911

Monocyte Chemoattractant Protein-1 (MCP-1, CCL2) Is a Potential Local Marker of Renal Involvement in Scleroderma

Edward Stern[1,2], Cassandra Hong[2], Voon H. Ong[2], Aine Burns[1], Robert Unwin[3] and Christopher P. Denton[4], [1]Nephrology, Royal Free Hospital, London, United Kingdom, [2]Rheumatology, UCL Division of Medicine, London, United Kingdom, [3]Nephrology, UCL Division of Medicine, London, United Kingdom, [4]Rheumatology and Connective Tissue Diseases, University College London, London, United Kingdom

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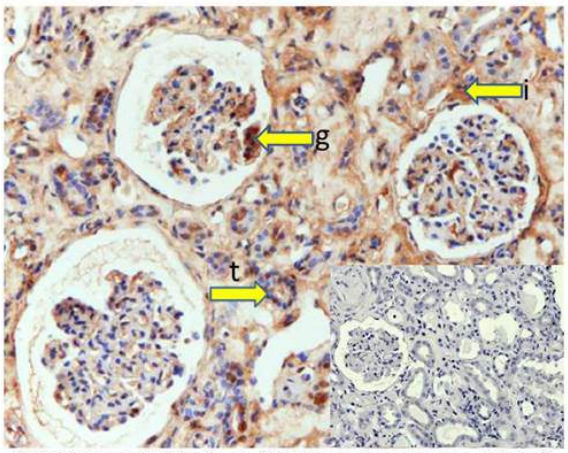
Background/Purpose: Renal disease in scleroderma (SSc), including scleroderma renal crisis (SRC), remains a major clinical challenge. Previous studies showed up to 50% of SSc patients have renal involvement. We sought to gain insight into the pathogenesis of SSc kidney disease by examining markers of disease in serum, urine and renal biopsy specimens.

Methods: We collected urine and serum from 80 SSc patients, with or without renal involvement, for comparison with patients with kidney disease of other causes (n=10) and healthy controls (n=12). We performed multiplex analysis of candidate markers of disease activity or severity in SSc and renal injury: MCP-1, MCP-3, IL-6, IL-18, TNFalpha, and VEGF. In a further experiment we examined biopsies of patients with SRC using immunostaining for MCP-1.

Results: 40 SSC patients were in the subgroup with renal involvement ("SSc-CKD") defined by eGFR, urinalysis or a history of SRC. Serum MCP-1 was increased in SSc compared with controls, with SSc-CKD significantly lower than SSc without renal involvement. Mean serum MCP-1 was 132 pg/ml (95% CI 105-162) for SSc with normal renal function compared with 65 pg/ml in SSc-CKD (49-81, $p<0.001$ for this comparison). MCP-1 was not increased in renal disease of other causes (mean 47 pg/ml, 23-85) compared with controls (mean 53 pg/ml, 25-85, $p=0.848$). Conversely, urine MCP-1:creatinine ratio was higher in SSc-CKD (mean 64, 32-111) than in SSc with normal renal function (mean 23, 18-28, $p=0.046$). 20 SRC cases confirmed on histology were stained with IgG antibodies for MCP-1 (see figure). Expression was highest in the tubules, interstitium and vasculature. The number of typical "onion skin" arterial lesions seen was positively correlated with the level of MCP-1 expression in the vasculature overall ($p=0.048$).



MCP-1 immunostaining in an SRC biopsy demonstrates uptake in glomeruli (g), tubules (t) and interstitium (i).
Inset shows MCP-1 IgG control.

Conclusion: This is the first study to measure MCP-1 in the urine of SSc patients. Elevated urine MCP-1 in SSc with renal involvement was corroborated by immunohistochemistry demonstrating marked expression of the chemokine in the kidneys of affected patients. The identification of urine MCP-1 as a marker for local expression in the kidney may help define organ-specific effects of this chemokine, which has previously been reported to be increased in serum in association with pulmonary complications. Our findings support further investigation of urine concentrations of MCP-1 as a marker or mediator of renal disease in SSc.

Disclosure: E. Stern, None; **C. Hong**, None; **V. H. Ong**, None; **A. Burns**, None; **R. Unwin**, AstraZeneca, 5; **C. P. Denton**, GlaxoSmithKline, 2,Actelion Pharmaceuticals US, 5,GlaxoSmithKline, 5,Serono, 5,Inventiva, 5,CSL Behring, 2,Bayer, 5.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/monocyte-chemoattractant-protein-1-mcp-1-ccl2-is-a-potential-local-marker-of-renal-involvement-in-scleroderma

Abstract Number: 1912

Glycyrrhizin Ameliorates Fibrosis, Vasculopathy, and Immune Abnormalities in Animal Models of Systemic Sclerosis

Takashi Yamashita[1], Yoshihide Asano[2], Takashi Taniguchi[1], Ryosuke Saigusa[3], Kouki Nakamura[1], Syunnsuke Miura[2], Tetsuo Toyama[1], Takehiro Takahashi[1], Yohei Ichimura[1], Ayumi Yoshizaki[1], Maria Trojanowska[4] and Shinichi Sato[1], [1]Dermatology, University of Tokyo Graduate School of Medicine, Tokyo, Japan, [2]University of Tokyo Graduate School of Medicine, Tokyo, Japan, [3]7-3-1 Hongo, Bunkyo-ku, University of Tokyo Graduate School of Medicine, Tokyo, Japan, [4]Arthritis Center, Boston University, Arthritis Center, Boston, MA
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Background/Purpose: Systemic sclerosis (SSc) is a multisystem autoimmune disease characterized by vasculopathy and fibrosis of the skin and various internal organs. Glycyrrhizin, a triterpenoid saponin glycoside from the roots of licorice, is a clinically approved for the treatment of chronic hepatic diseases and itching dermatitis and has also been used for Kampo in the Orient from ancient times. Importantly, glycyrrhizin has been shown to modulate the pathological processes of fibrosis, inflammation, and vasculopathy in some experimental disease models. Based on these backgrounds, we investigated the effect of glycyrrhizin on the three cardinal pathological features of SSc, including tissue fibrosis, inflammation, and vasculopathy, utilizing bleomycin (BLM)-treated mice recapitulating the fibrotic and inflammatory aspects of SSc and endothelial cell-specific *Fli1* knockout (*Fli1*ECKO) mice mimicking SSc vasculopathy.

Methods: Wild type C57BL/6 mice were subcutaneously injected with BLM or phosphate buffered saline (PBS) for the indicated period of time together with daily intraperitoneal injection of glycyrrhizin (30mg/kg) or PBS. mRNA and/or protein levels of target molecules were determined by quantitative reverse transcription-PCR, immunostaining, and/or immunoblotting in the skin samples and cultivated cells. Th1/Th2/Th17 polarization of immune response and macrophages polarization were evaluated by flow cytometry. Vascular permeability was evaluated by Evans blue dye injection in *Fli1*ECKO mice.

Results: Glycyrrhizin significantly ameliorated dermal thickness and collagen contents and decreased the number of myofibroblasts in BLM-treated mice. Consistent with these findings, glycyrrhizin significantly suppressed mRNA levels of the *Col1a1*, *Col1a2*, and *Col3a1* genes, while not those of the *Ctgf* and *Tgfb* genes in the lesional skin of BLM-treated mice. Since mRNA levels of the *Thbs1* gene, encoding thrombospondin 1 which activates latent form of TGF-B, were significantly reduced under the same condition, glycyrrhizin is likely to prevent the development of BLM-induced dermal fibrosis at least partially

by blocking autocrine TGF-B signaling in dermal fibroblasts. As for the expression profiles of cytokines and chemokines, the reduction of IL-4 and IL-6 was noted in the lesional skin of BLM-treated mice administered glycyrrhizin. Consistently, glycyrrhizin attenuated the BLM-dependent induction of Th2 cells in draining lymph nodes and spleen, partially contributing to the prevention of BLM-induced dermal fibrosis. Relevant to this finding, the expression levels of M2 macrophage markers were decreased by glycyrrhizin in the lesional skin of BLM-treated mice. With respect to the pathological vascular aspects, glycyrrhizin prevented the BLM-dependent induction of endothelial-to-mesenchymal transition, also associated with the reduction of dermal fibrosis by this agent, and improved the leaky vascular phenotype of *Fli1*ECKO mice.

Conclusion: Glycyrrhizin has potential preventive and/or therapeutic effects on the pathological dermal fibrosis and vasculopathy similar to SSc by acting on fibroblasts, endothelial cells, and immune cells.

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Abstract Number: 1913

Lysyl Oxidase Induces Fibrosis Via Upregulation of IL-6 and Serves As a Biomarker to Monitor Response to Therapy

Tetsuya Nishimoto[1], Takahisa Takihara[2], Logan Mlakar[3] and Carol Feghali-Bostwick[3], [1]Department of Medicine, Medical University of South Carolina, Charleston, SC, [2]Tokai University School of Medicine, Kanagawa, Japan, [3]Medical University of South Carolina, Charleston, SC
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Background/Purpose: Lysyl oxidase (LOX) is a copper-dependent amine oxidase whose primary function is the covalent crosslinking of collagens in the extracellular matrix (ECM). Fibrosis is one of the important causes of morbidity and mortality in fibroproliferative disorders such as Systemic sclerosis (SSc). It was recently reported that LOX levels are increased in sera of SSc patients and associated with dermal fibrosis. In this study, we investigated the role of LOX in the pathophysiology of SSc.

Methods: LOX expression was examined in lung fibroblasts from 9 healthy controls (HC), 21 SSc patients, and 10 idiopathic pulmonary fibrosis (IPF) patients by real-time PCR. LOX was detected in HC and SSc lung tissues by immunohistochemistry. *In vivo*, LOX levels were quantified in lungs and sera of mice treated with bleomycin in combination with an endostatin-derived peptide that ameliorates fibrosis. LOX mRNA and activity levels were measured *in vivo* in lung tissues and serum samples using real-time PCR, ELISA and activity assay, respectively. *In vitro*, LOX mRNA levels and activity were measured in primary normal human lung fibroblasts treated with TGF-β and endostatin-derived peptide. To examine the effect of LOX, primary lung fibroblasts and lung tissues were treated with recombinant LOX with or without the inhibitor, β-aminopropionitrile (BAPN), and the expression levels of ECM (collagen and fibronectin) and pro-fibrotic factors (IL-6 and TGF-β) were measured by real-time PCR, ELISA, immunoblotting, and hydroxyproline assay.

Results: : LOX mRNA and protein levels were significantly increased in lung fibroblasts of SSc patients compared to HC and IPF patients. Interestingly, the highest levels of LOX were detected in SSc patients with pulmonary fibrosis. *In vivo*, bleomycin significantly induced LOX mRNA expression in lung tissues. Further, bleomycin increased LOX protein and activity levels in the circulation, suggesting that circulating LOX protein and activity levels paralleled levels in lung tissues. Amelioration of bleomycin-induced pulmonary fibrosis by endostatin peptide reduced LOX expression and activity. *In vitro*, TGF-β induced collagen and fibronectin production, LOX expression and activity. Endostatin peptide abrogated these effects. Recombinant LOX induced collagen and fibronectin production *in vitro* in lung fibroblasts and *ex vivo* in human lung tissues maintained in organ culture. The inhibition of LOX catalytic activity by BAPN failed to abrogate LOX-induced ECM production. LOX increased the production of IL-6 but not TGF-β *in vitro* and *ex vivo*.

Conclusion: LOX expression and activity correlated with fibrosis *ex vivo*, *in vitro*, and *in vivo*. LOX induced ECM production *in vitro* and *ex vivo* via upregulation of IL-6. Therefore, measuring LOX levels and activity serves as a novel biomarker for fibroproliferative disorders and for monitoring response to therapy, and LOX likely plays a direct pathogenic role in SSc independently of its crosslinking function.

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Abstract Number: 1914

Oncostatin M As a Potential Molecular Target in Systemic Sclerosis

Maria Feeney[1], Farhat Syed[2], Korsa Khan[3], Xu Shiwen[4], Katherine Sully[5], Sarah Trinder[6], Paul Wilson[7], David Abraham[6,8], Alan M. Holmes[6] and Christopher P. Denton[9], [1]Biopharm Research, GlaxoSmithKline, Stevenage, United Kingdom, [2]Immuno-Inflammation, GlaxoSmithKline, Stevenage, United Kingdom, [3]Centre For Rheumatology and Connective Tissue Diseases, UCL Medical School, London, United Kingdom, [4]UCL Medical School, London, United Kingdom, [5]Biopharm Translational Medicine, GlaxoSmithKline, Stevenage, United Kingdom, [6]Centre for Rheumatology and Connective Tissue Diseases, UCL Medical School, London, United Kingdom, [7]Quantitative Sciences, GlaxoSmithKline, Stevenage, United Kingdom, [8]Centre for Rheumatology and Connective Tissue Disease, University College London, London, United Kingdom, [9]Rheumatology and Connective Tissue Diseases, UCL Medical School, London, United Kingdom

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Background/Purpose: Oncostatin M (OSM) is a pleiotropic member of the gp130/ IL-6 cytokine family, produced by a variety of immune cells, including macrophages, neutrophils and activated T cells. OSM signals through two receptors; gp130/ LIF low affinity receptor (LIFR) and gp130/ OSM high affinity receptor (OSMR); activating JAK/STAT, ERK1/2 and p38 MAPK pathways. The rationale for the role of OSM in Systemic Sclerosis (SSc) lies in that key disease components, i.e. inflammation, vascular dysregulation and fibrosis, complement the biological activities of the target.

Methods: Serum OSM levels were measured by custom OSM ELISA in 63 diffuse cutaneous (Dc) SSc and 18 age-matched healthy donors (HD). Transcriptomics data derived from published DcSSc skin biopsies were mined for OSM and known OSM-regulated genes. The presence of OSM, OSMR, and phospho(p)STAT3 in skin biopsies from HD (n=12), involved limited cutaneous (Lc)SSc (n=12), and involved and uninvolved DcSSc (n=13) patients was assessed by immunohistochemistry (IHC). Primary dermal fibroblasts isolated from HD or DcSSc skin were incubated with OSM at 2, 20 or 200ng/ml and cell associated collagen type I (Col-1), and connective tissue growth factor (CTGF) assessed by Western blot analysis at 24hrs and 72hrs.

Results: Serum OSM levels were significantly (P=0.004) increased in DcSSc patients compared with HDs (Table 1). OSM and OSM-regulated genes, including S100A9 and VCAM-1, were upregulated in the DcSSc skin. IHC analysis confirmed OSM, OSMR and pSTAT3 expression in skin biopsies from SSc patients and HDs, with a similar expression pattern in both. SSc skin biopsies exhibited significantly higher inflammatory cell infiltrates compared to HDs, and were strongly positive for OSM, OSMR and pSTAT3. Uninvolved DcSSc skin had significantly more OSM positive immune cell infiltrates and increased pSTAT3 expression than HDs, but not compared to involved DcSSc skin. Involved DcSSc skin exhibited significantly more pSTAT3 positive fibroblasts compared to HDs ($p<0.01$). The number of pSTAT3 positive immune cell infiltrates was further significantly enhanced in involved compared to uninvolved tissue. Increased numbers of positive OSM and pSTAT3 fibroblasts were present in involved versus uninvolved skin. OSM induced CTGF after 24hrs in 4/5 DcSSc dermal fibroblast cell lines tested. No induction above baseline was observed in the two HD dermal fibroblast cell lines. Following 72hrs stimulation, OSM increased Col-I in 5/7 HD fibroblast lines and 4/7 in the DcSSc fibroblast lines.

Conclusion: DcSSc patients have increased OSM serum levels and upregulated OSM and OSM-related genes in skin biopsies. In addition, OSM, OSMR and pSTAT3 are increased in DcSSc skin and dermal fibroblasts from these patients produce Col-I and CTGF in response to OSM. These data support targeted approaches to modulating OSM for the treatment of SSc.

Table 1: OSM levels in SSc serum

Serum OSM Levels	Numbers	Median (pg/ml)	Range
Healthy Donors	18	15	9.77-60pg/ml
DcSSc	63	26	9.77-4849pg/ml

Disclosure: M. Feeney, GSK, 3; **F. Syed**, GSK, 3; **K. Khan**, None; **X. Shiwen**, None; **K. Sully**, GSK, 3; **S. Trinder**, None; **P. Wilson**, GSK, 3; **D. Abraham**, None; **A. M. Holmes**, None; **C. P. Denton**, GlaxoSmithKline, 2,Actelion Pharmaceuticals US, 5,GlaxoSmithKline, 5,Serono, 5,Inventiva, 5,CSL Behring, 2,Bayer, 5.

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Abstract Number: 1915

Pathogenetic Overlap Between Localised and Systemic Scleroderma: A Study of Nodular and Keloidal Morphea Occurring in Systemic Sclerosis

Emma C. Derrett-Smith[1], Nataliya Gak[2], Svetlana I. Nihtyanova[3], Voon H. Ong[3], Victoria Swale[2], Cate Orteu[2] and Christopher P. Denton[4], [1]Centre for Rheumatology and Connective Tissue Diseases,, UCL Division of Medicine, London, United Kingdom, [2]Royal Free London NHS Foundation Trust, London, United Kingdom, [3]Rheumatology, UCL Division of Medicine, London, United Kingdom, [4]Rheumatology and Connective Tissue Diseases, University College London, London, United Kingdom

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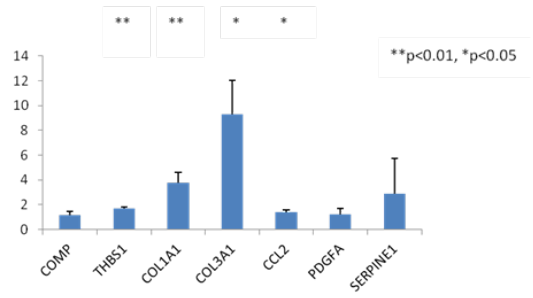
Background/Purpose: Localised scleroderma can occur in overlap with systemic sclerosis (SSc); nodular and keloidal morphea are rare subtypes but can be disfiguring and challenging to treat. Published literature suggests that keloid scarring and SSc skin share TGFbeta regulated gene expression alterations and that nodular and keloidal morphea represent a spectrum of keloid formation in SSc. This study aims to determine the pathological differences between these conditions and addresses the hypothesis that bone marrow derived fibroblast progenitors (fibrocytes) link them.

Methods: We examined a clinical database of 2200 patients with SSc defined by ACR/EULAR classification criteria to identify patients with a clinical or pathological diagnosis of localised scleroderma. The demographics, clinical features and laboratory parameters of those with nodular or keloidal morphea were examined in detail. We identified structural and biochemical differences by examining paired skin biopsies from these lesions and standard forearm biopsy site in SSc (n=6). Skin biopsies from patients with both early and established diffuse cutaneous SSc were used as controls.

Results: 49 patients (2.2%) had both localised scleroderma and SSc. Data from this group were broadly comparable to the SSc cohort, excepting a higher prevalence in females (female:male ratio 11:1). Three subtypes of localised scleroderma were prevalent: plaque morphea (67%); linear morphea (8.0%) and nodular or keloidal morphea (25%). Plaque and linear morphea patients had predominantly limited cutaneous SSc (88% and 75% respectively) while the majority of nodular/keloidal morphea patients had diffuse cutaneous SSc (92%, $p<0.001$). There were no clear serological associations. Keloid nodules were localised on the upper chest rather than areas of high SSc skin disease activity. Examination of histology in 5 of 12 patients with nodular/keloidal morphea identified acute inflammatory infiltrates, mucin deposition and altered distribution of collagen compared to SSc skin biopsies. Expression analysis of TGFbeta regulated genes identified multiple significant differences in expression within morphea lesions and at other sites in the same patients (figure 1). A significant increase in CCl2 expression may be associated with fibrocyte recruitment.

Conclusion: This is the largest analysis of localised scleroderma in SSc. There are associations of subtypes of localised scleroderma with subsets of SSc which are not related to serology. Paired examination of histological samples and gene expression of nodular or keloidal SSc skin identifies increased TGFbeta downstream activity compared with other biopsy sites suggesting that this mediator may be a key driver of localised scleroderma in SSc.

Figure 1: Gene expression in keloidal/nodular scleroderma compared with forearm biopsy in same patient



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Abstract Number: 1916

Validation of Novel Biomarker Candidates for Systemic Sclerosis

Johannes Schulte-Pelkum[1], Petra Budde[1], Hans-Dieter Zucht[1], Daniel Wirtz[1], Peter Schulz-Knappe[1], Oliver Distler[2], Suzana Jordan[3], Nicolas Hunzelmann[4], Matthias Schneider[5] and Britta Maurer[2], [1]Protagen AG, Dortmund, Germany, [2]Division of Rheumatology, University Hospital Zurich, Zurich, Switzerland, [3]Department of Rheumatology, University Hospital Zurich, Zurich, Switzerland, [4]Department of Dermatology, University of Cologne, Cologne, Germany, [5]Rheumatology, Heinrich-Heine-University, Duesseldorf, Germany
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Background/Purpose:

Systemic sclerosis (SSc) is a systemic autoimmune disease that manifests as progressive fibrosis of the skin and internal organs. SSc is associated with the presence of several autoantibodies (aab) to intracellular targets, with the three most important SSc-specific being anti-centromere antibodies, anti-Scl70 antibodies and anti-RNA polymerase III antibodies, which occur in over 50% of SSc patients. Autoantibody specificities are strongly associated with pattern of organ involvement and disease outcome, making autoantibodies an essential tool in the clinical management of SSc. This highlights the need for additional specific and sensitive diagnostic and prognostic biomarkers in SSc. We have recently conducted high-content autoantibody profiling studies of SSc, systemic autoimmune diseases (AID), and healthy controls and found novel SSc-associated autoantibodies. These novel SSc-associated autoantibody biomarker candidates and their diagnostic value were evaluated by testing samples derived from 2 different SSc cohorts from the University Hospital Düsseldorf and the University Hospital Zurich.

Methods:

Three novel identified biomarker candidates, namely Lysine (K)-specific demethylase 6B (*KDM6B*), Protein Phosphatase Inhibitor 2 (PPP1R2) and Bicaudal Drosophila Homolog 2 (BICD2) were developed into research ELISA Kits using highly purified recombinant antigen and evaluated. Autoantibody specificities were analyzed using an independent and well characterized cohort consisting with sera of patients suffering from SSc (n=198), myositis (n=20), RA (n=20), SLE (n=40) and healthy blood donors (n=132). Assay threshold levels were calculated using a receiver operation characteristic analysis and set for specificities of 90% (KDM6B) and 95% for PPP1R2 and BICD2, respectively.

Results:

Using the respective cut off for the ELISA tests we were able to find autoantibody reactivity against BICD2 in 34 of 198 (17.2 %) of SSc patients and 11 of 212 (5.1%) of control samples, against PPP1R2 in 21 of 198 (10.6%) SSc and 11 of 212 controls (5.1%) and against KDM6B in 25 of 198 (12.6%) SSc patients and 21 of 212 controls (9.9%), respectively. Positive results of anti-BICD2 and anti-PPP1R2 aab co-migrated with anti-Centromere aab, but were also found in anti-Centromere and anti-Scl 70 negative samples. Interestingly, both anti- BICD2 and anti-PPP1R2 aab were found in SSc samples tested negative for anti-RNA Polymerase III auto-reactivity. Epitope mapping of KDM6B revealed reactivity against multiple epitopes of which reactivity against an EBNA-2 like polyproline-stretch in the sequence of the protein was strongest and could be blocked by polyproline. Interestingly, this reactivity occurred also in other AID samples.

Conclusion:

In this study we were able to confirm the diagnostic value and high specificity of the newly discovered autoantigens using ELISA. While PPP1R2 and BICD2 were found to be elevated in patients suffering from SSc, we found that autoantibodies against KDM6B are at least in part generated through a homology to EBNA-2 and could thus be a key target the suspected link between EBNA infection and autoimmune connective tissue diseases.

Disclosure: J. Schulte-Pelkum, Protagen AG, 3; **P. Budde**, Protagen AG, 3; **H. D. Zucht**, Protagen AG, 3; **D. Wirtz**, Protagen AG, 3; **P. Schulz-Knappe**, Protagen AG, 3; **O. Distler**, Consultancy relationships and/or has received research funding from Actelion, Pfizer, Ergonex, BMS, Sanofi-Aventis, United BioSource Corporation, Medac, Biovitrium, Boehringer Ingelheim, Bayer Pharma AG, Novartis, 4D Science and Active Biotech in the area, 2; **S. Jordan**, None; **N. Hunzelmann**, None; **M. Schneider**, None; **B. Maurer**, None.

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Developing and Validating a Serum Biomarker for the Extent of Skin Disease in Patients with Diffuse Cutaneous Systemic Sclerosis

Lisa Rice[1], Julio Mantero[2], Giuseppina Stifano[1], Jessica Ziemek[3], Robyn T. Domsic[4] and Robert Lafyatis[1], [1]Boston University School of Medicine, Boston, MA, [2]Rheumatology, Boston University School of Medicine, Boston, MA, [3]Rheumatology/Arthritis Center, Boston University School of Medicine, Boston, MA, [4]Medicine - Rheumatology, University of Pittsburgh, Pittsburgh, PA

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Background/Purpose: In this study we aimed to both agonistically investigate alterations in the serum proteome of patients with diffuse cutaneous systemic sclerosis (dcSSc), as well as to identify differentially expressed proteins that correlate with disease severity cross-sectionally and longitudinally. Our goal was to identify a combination of serum proteins that would provide a biological measure of the extent of skin disease and thus have the potential to be used as a pharmacodynamic (PD) biomarker.

Methods: Sera from a cohort of dcSSc patients (n=12) were analyzed by SOMAscan aptamer technology (1129 proteins) for differences in protein levels compared to healthy control sera (n=4), and for correlation of protein levels with the modified Rodnan skin score (MRSS). In a separate cohort of patients, ELISAs were used to validate these proteins in cross-sectional samples (n=31) and in longitudinal samples (n=17). Mixed models were used to define a potential model for a PD biomarker composed of multiple proteins. This longitudinal model was then validated in an independent cohort (n=20). Baseline demographics for each of the four groups are included below.

Results: Forty-three analytes were identified as both differentially regulated in dcSSc patients compared to healthy controls, as well as correlated with MRSS (FDR<0.01). Ten proteins were tested for validation in a separate, larger cohort. Eight out of the ten proteins tested successfully validated as

different from healthy controls and retained moderate cross-sectional correlations with the MRSS. These eight analytes were next examined for longitudinal change. The combination of two analytes (IL1R4 and Spondin-1) was used in a mixed model to best describe longitudinal change, and this model was successfully validated in an independent cohort.

Conclusion: In this study we have discovered that two novel proteins, not previously associated with SSc, are upregulated in patients and correlate with the extent of skin disease both cross-sectionally and longitudinally. Further, we have developed a PD biomarker based on levels of these proteins and show that this biomarker can be applied to assess changes in skin disease in dSSc patients over time, applicable to clinic or clinical trial settings.

Baseline Demographics	Somalogic (n=12)	Cross Sectional (n=31)	Longitudinal 1 (n=17)	Longitudinal 2 (n=20)
Age (year)				
Mean (sd)	50.9 (9.3)	49.2 (12.5)	48.7 (12.23)	54.7 (9.4)
Median (Range)	50 (37-70)	48 (21-71)	48 (27-71)	53 (34-71)
Sex				
Percent Female (n)	75% (9)	70% (22)	82% (14)	55% (11)
Percent Male (n)	25% (3)	29% (9)	17% (3)	45% (9)
Modified Rodnan Skin Score				
Mean (sd)	30.4 (6.8)	20.4 (10.9)	17.4 (11.5)	22.5 (12.0)
Median (Range)	30 (21-42)	19 (3-45)	14 (2-45)	22 (2-48)
Disease duration (months)				
Mean (sd)	12 (5.5)	18.6 (17.9)	24.8 (20.7)	17.3 (12.7)
Median (Range)	12 (1-19)	13 (2-82)	16 (2-81)	13 (2-57)

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Abstract Number: 1918

Pharmacologic Targeting of Mitochondrial Dysfunction in Systemic Sclerosis: Enhanced SIRT3 Signaling

Kaname Akamata[1], Mitra Bhattacharyya[1], Mahesh Gupta[2], Jack Arbiser[3], David Kamp[4], Jun Wei[1] and John Varga[1], [1]Division of Rheumatology, Northwestern University, Feinberg School of Medicine, Chicago, IL, [2]University of Chicago, Departments of Surgery, Chicago, IL, [3]Department of Dermatology, Emory University School of Medicine Winship Cancer Institute Atlanta Veterans Administration Health Center, Atlanta, GA, [4]Department of Medicine, Division of Pulmonary & Critical Care Medicine, Jesse Brown VA Medical Center and Northwestern University Feinberg School of Medicine, Chicago, IL

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Background/Purpose: Recent evidences suggest that cytosolic and mitochondrial reactive oxygen species (ROS), play pivotal roles in modulating TGF-β-induced profibrotic responses and are implicated in pathogenesis of systemic sclerosis (SSc). The NAD^+dependent deacetylase SIRT3 is a key regulator of mitochondrial ROS production. Honokiol activates cellular expression and activity of SIRT3. Here we investigated the anti-fibrotic potential of Honokiol and its synthetic analogues.

Methods: The expression of SIRT3 in fibroblasts was inquired in publicly-available microarray datasets and validated by real-time qPCR and Western analysis. The effects of SIRT3 activators on TGF-b-induced profibrotic responses were examined in neonatal foreskin fibroblasts, adult healthy and SSc dermal fibroblasts and normal human lung fibroblasts.

Results: Analysis of published microarray datasets revealed that TGF-β significantly suppresses SIRT3 mRNA expression in both healthy and SSc dermal fibroblasts. These results were validated by qPCR and Western analysis. Honokiol and its analogues stimulated SIRT3 expression and activation and

abrogated TGF-b-induced collagen, a-smooth muscle actin and fibronectin EDA expression in neonatal foreskin fibroblasts and adult normal human lung fibroblasts. These results were confirmed by real-time qPCR, Western analysis and immunofluorescence. Moreover, ectopic expression of SIRT3 in normal fibroblasts dose-dependently abrogated TGF-β-induced collagen synthesis and myofibroblast differentiation. The inhibitory effects of honokiol analogues were diminished in SIRT3-null mouse embryonic fibroblasts.

Conclusion: Our results provide evidence that mitochondrial ROS play a role in fibroblast activation, and SIRT3 is a novel target for anti-fibrotic therapy. Pharmacological modulation of the SIRT3 expression or activity might have a therapeutic potential in SSc.

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Genetic Deletion of Toll-like Receptor 4 (Tlr4) Abrogates TGF-β1-Induced Endothelial-to-Mesenchymal Transition (EndoMT) in Murine Pulmonary Endothelial Cells

Peter J. Wermuth[1] and Sergio A. Jimenez[2], [1]Jefferson Institute of Molecular Medicine, Division of Connective Tissue Diseases and Scleroderma Center, Thomas Jefferson University, Philadelphia, PA, [2]Jefferson Institute of Molecular Medicine, Division of Connective Tissue Diseases and Scleroderma Center,Thomas Jefferson University, Philadelphia, PA

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Background/Purpose:

Systemic sclerosis (SSc) is a systemic autoimmune disease of unknown etiology whose pathogenesis involves the regulation of a diverse range of molecular pathways. The clinical and pathologic manifestations of SSc arise from fibroproliferative vascular lesions; excessive and progressive synthesis and deposition of collagen and other extracellular matrix (ECM) macromolecules in the skin and various internal organs; and activation of innate and adaptive immunity. Several recent studies indicate a pivotal role for Toll-like receptor (TLR) signaling in the pathogenesis of several autoimmune diseases including SSc. Endothelial-to-mesenchymal transition (EndoMT) may play a role in generating activated myofibroblasts responsible for the uncontrolled ECM production in many fibrotic diseases, including SSc. Thus, the purpose of these studies was to compare the ability of TGF-β1 and the Tlr4 inducer lipopolysaccharide (LPS) to induce EndoMT in endothelial cells (EC) isolated from C57BL6/J or Tlr4 knockout (KO) mice.

Methods: Lung EC were isolated from three C57Bl/6J control and three TLR4 KO mice by enzymatic dissociation and were immumopurified employing sequential immunomagnetic selection with anti-CD31 and anti-CD102 antibodies followed by *in vitro* culture and treatment with either TGF-β1, LPS or TGF- β1 plus LPS. EndoMT was assessed by monitoring EC morphological changes and loss of EC molecular markers. Type I, type III and type IV collagens, α-SMA, fibronectin, and various mesenchymal cell- or EC-specific gene expression was assessed by semi-quantitative RT-PCR in triplicate for three replicates per cell line.

Results: Treatment of lung ECs isolated from C57BL6/J control mice with TGF-β1 induced the expected loss of EC morphology causing them to assume a more spindle fibroblast-like appearance. Remarkably, LPS alone caused similar morphologic EC changes. Both agents caused downregulation of the expression of EC-specific genes and concomitant upregulation of mesenchymal-specific genes, including Col1a1, Col3a1, fibronectin 1 (Fn1) and the Fn-Eda splice variant. In contrast, the EndoMT-associated changes in gene expression induced by TGF-β1 or LPS were completely abrogated in EC from Tlr4 KO mice compared to EC from C57BL6/J control or Tlr4 KO mice and their morphology was unaffected by treatment.

Conclusion: Signaling through Tlr4 can mediate EndoMT in murine lung EC since LPS treatment induces morphologic and gene expression changes associated with the EndoMT process. Further, Tlr4 signaling is required for TGF-β1 EndoMT in murine lung EC since genetic deletion of the Tlr4 gene results in the loss of TGF-β1-mediated EndoMT as shown by the rentention of characteristic EC morphology and failure to downregulate EC-specific genes or upregulate mesenchymal-specific genes. Thus, one mechanism by which Tlr4 signaling can assume a pathogenetic role in SSc-associated pulmonary fibrosis and other fibrotic diseases is by inducing the transdifferentiation of EC to profibrotic activated myofibroblasts. Thus, Tlr4 signaling inhibition in EC could represent an important and novel strategy to ameliorate the fibroproliferative process responsible for fibrotic diseases.

Disclosure: P. J. Wermuth, None; **S. A. Jimenez**, None.

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Differential Production of Th17-Related Cytokines By Toll like Receptor (TLR)-Ligands-

Stimulated Monocyte-Derived Dendritic Cells (Mo-DCs) from Systemic Sclerosis (SSc) Patients; Relevance of IL-22 and IL-33 According to Disease Subtype and Stage

Tatiana Sofia Rodriguez-Reyna[1], Adrián Caballero[1], Luís Jiménez-Álvarez[2], Gustavo Ramirez[2], José Eduardo Márquez García[2], Alfredo Cruz Lagunas[3], Guadualupe Lima[4], Janette Furuzawa-Carballeda[5], Luis Llorente[1] and Joaquin Zuniga[6], [1]Immunology and Rheumatology, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico, [2]Immunology, Instituto Nacional de Enfermedades Respiratorias, Mexico City, Mexico, [3]Immunology, Instituto Nacional de Enfermedades Respiratorias, Mexico, Mexico, [4]Immunology and Rheumatology, Instituto Nacional de Ciencias Medicas y Nutricion, Mexico City, Mexico, [5]Immunology and Rheumatology, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico city, Mexico, [6]Immunology, Instituo Nacional de Enfermedades Respiratorias Ismael Cosio Villegas, Mexico, Mexico
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Background/Purpose: Systemic sclerosis (SSc) patients exhibit alterations in innate and acquired cellular responses including an enhanced inflammatory response to toll like receptor (TLR) agonists that lead to increased production of Th1, Th2 and Th17-associated cytokines and may be associated to disease progression and phenotype. Pathogenic mechanisms of these alterations are not fully understood. The aim of this study was to determine the effect of TLR3, TLR4 and TLR9 stimulation of monocyte derived dendritic cells (Mo-DCs) in the production of Th17-related molecules in SSc patients.

Methods: We included 16 SSc patients (4 early limited cutaneous lcSSc, 4 late lcSSc, 4, early diffuse cutaneous dcSSc and 4 late dcSSc patients) and 5 non-related healthy controls. We isolated peripheral blood mononuclear cells (PBMCs) from 55 ml of venous blood. Mo-DCs were differentiated using a commercially available and validated medium containing GM-CSF and IL-4 from ex vivo purified CD14+ monocytes from ex-vivo purified CD14+ monocytes, stimulated with TLR agonists (LPS/TLR4, poly:IC/TLR3, CpG/TLR9) and co-cultured with PBMCs. Cytokine levels in supernatants were measured after 96 h, by Luminex. Differences were evaluated by Mann-Whitney U test.

Results: All SSc patients were females (mean age 48+/-14.4 years). We found significantly higher levels ($p<0.05$) of IL-6, IL-10, IL-17F, IL-22, IL-23, IL-31, IL-1b and IFN-g in LPS/TLR4-stimulated Mo-DCs-PBMC co-culture supernatants from lcSSc patients when compared to those from dcSSc patients. In contrast, Mo-DCs-PBMC co-cultures from dcSSc patients produced higher levels of IL-33 with and without TLR agonist stimulation than lcSSc patients' co-cultures. When SSc patients were categorized as early and late SSc we found that LPS/TLR4-stimulated Mo-DCs-PBMC co-cultures from early SSc patients produced higher amounts of IL-6, IL-10, IL-17F, IL-22, IFN-g and TNF-a when compared to those from late SSc patients. Interestingly, IL-33 secretion was increased with or without stimulation with TLR agonists ($p<0.05$) in Mo-DCs-PBMC co-cultures from late SSc in comparison with those from early SSc patients.

Conclusion: Mo-DCs stimulation with TLR4 ligand potently induces cytokines involved with the pro-inflammatory Th17 phenotype. TLR4-stimulated Mo-DCs from lcSSc patients produce higher amounts of Th17 (IL-6, IL-22 and IL-23) and Th1 cytokines. Early SSc patients exhibit enhanced Th17 responses. Mo-DCs from dcSSc and late SSc patients exhibit enhanced production of IL-33. Our findings suggest that functional variations in the production of Th17 cytokines by Mo-DCs are associated with different SSc clinical subsets and phases

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Abstract Number: 1921

Role of TLRs in the Abnormal Secretion of CXCL-4 By Plasmacytoid Dendritic Cells of Patients with Systemic Sclerosis

Marie-Dominique Ah Kioon[1], Eliza Pelrine[2], Robert F. Spiera[3], Jessica K. Gordon[3] and Franck J. Barrat[1], [1]Autoimmunity and Inflammation Program, Hospital for Special Surgery, New York, NY, [2]Hospital for Special Surgery, New York, NY, [3]Rheumatology, Hospital for Special Surgery, New York, NY
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Background/Purpose:

Systemic Sclerosis (SSc) is an autoimmune disorder of the connective tissue due to excessive extracellular matrix deposition, leading to fibrosis of the skin and lung. The disease is characterized by the presence of elevated levels of IFN-regulated genes implicating plasmacytoid dendritic cells (PDC) and recently, it was shown that CXCL4 levels correlated with lung and skin fibrosis making this chemokine an interesting biomarker and highlighting the role of PDC in the disease pathogenesis (van Bon et al. NEJM, 2014). Our aim is to better understand what is controlling the activation of PDC in SSc patients.

Methods:

Blood was obtained from 33 SSc patients, 9 classified as early diffuse (edSSc), 15 as late diffuse SSc (ldSSc) and 9 limited (lSSc) and from 13 healthy volunteers (HV). PBMC were isolated and PDC purified either using BDCA4 magnetic beads (Miltenyi) or by cell sorting and purity was routinely >96%. The percentage of immune cells in total PBMC was analyzed by flow cytometry. Gene expression was analyzed in PBMC and PDC by Q-PCR. PDC were cultured for 24h and IFNa and CXCL4 secretion analyzed by ELISA.

Results:

First, we observed that the percentage of PDC and CD8+ T cells were significantly decreased in SSc PBMC as compared to HV (0.25%±0.02 vs 0.51% ±0.09; p=0.003 and 13%±0.8 vs 20%±0.9; p<0.001 respectively) while the percentage of monocytes and CD4+ T cells were significantly increased (24% ±1.9 vs 13.8%±2.4; p=0.002 and 42%±2.7 vs 33.2%±2.8; p=0.03 respectively). No difference was observed for B cell in SSc PBMC as compared to HV (6.1±0.9 vs 7.9±1.0; NS). As assessed by qPCR, we observed increased level of IFN-regulated genes in SSc patients, as genes such as ISG54, MxB or IP10 were significantly upregulated as compared to HV (in relative Ct to the housekeeping gene Ubiquitin: 641±85 vs 262±69; p=0.02, 421±35 vs 245±39; p=0.03 and 96±12 vs 52±8.5; p=0.005 respectively). Interestingly, this increase was observed in all the patients irrespective of subtypes. We also observed that purified PDC from SSc patients spontaneously secreted CXCL-4 (17,111±1,855 vs 6,903±662 pg/ml; p=0.001). We also noted a disruption in the expression pattern of TLRs in PDC which was confirmed by functional assay using specific agonists or inhibitors of the TLR pathway.

Conclusion:

Taken altogether our data suggests a role of PDC in the pathogenesis of SSc by the involvement of the TLR pathway. This could explain the abnormal activation state of these cells in patients as suggested by the presence of high IFN responses and the migration of PDC to the sites of inflammation such as the skin and lung of the patients.

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Abstract Number: 1922

Peripheral B Lymphocytes Secrete Both Interleukin 6 and Transforming Growth Factor-Beta and Potentiate Fibroblast Activation in Systemic Sclerosis

Nicolas Dumoitier[1,2,3,4], Sebastien Lofek[2,3,5], Alexis Regent[6], Jonathan London[7], Benjamin Chaigne[1,2,3,8], Benjamin Terrier[2,7,9,10], Nadine Varin-Blank[4,11] and **Luc Mouthon**[1,2,4,6], [1]Infection, Immunité, Inflammation, Institut Cochin, INSERM U1016, Paris, France, [2]CNRS, UMR8104, Paris, France, [3]Université Paris Descartes, Paris, France, [4]Labex Inflamex, Université Sorbonne Paris Cité, Paris, France, [5]Infection,Immunité, Inflammation, Institut Cochin, INSERM U1016, Paris, France, [6]Internal Medicine, National Referral Center for Rare Systemic Autoimmune Diseases, Hôpital Cochin, Paris, France, [7]Internal Medecine, National Referral Center for Rare Systemic Autoimmune Diseases, Hôpital Cochin, Paris, France, [8]Internal Medecine, National Referral Center for Rare Systemic Autoimmune Diseases, Hôpital Cochinl, Paris, France, [9]Infection, Immunité, Inflammation, Institut Cochin INSERM U1016, Paris, France, [10]Université Paris Descartes, paris, France, [11]UFR SMBH, INSERM, UMR978, Bobigny, France
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Background/Purpose: Systemic sclerosis (SSc) is a rare connective tissue disease characterized by fibroblasts activation, increased extra-cellular matrix synthesis associated with autoimmunity. However, the potential role of B lymphocytes in the pathophysiology of SSc is still poorly defined.

Methods: Phenotyping of peripheral blood B cell subpopulations, activating and inhibitory receptor expressions, Interleukin 6 (IL-6) and transforming growth factor-beta (TGF-β) productions were characterized by flow cytometry and multiplex assay. Fibroblasts proliferation rate and collagen production upon incubation with supernatants of B cell isolated from patients or healthy controls were assessed using XTT, BrdU, Ki67 immunofluorescence staining and collagen assay, respectively.

Results:

Eighty patients (including 18 males) with SSc fulfilling the ACR/EULAR criteria, (22 with diffuse SSc, dSSc and 58 with limited cutaneous SSc, lSSc), and 21 healthy controls (HC) were studied. The proportion of IgD^{-} $CD27^{+}$ B cells was significantly lower for SSc patients (Mean±SD 19.33%±11.85) as for HC (25.91%±11.25) (p=0.041). Increased proportions of B cells expressing CD69 (8.29%±7.77 vs 2.36%±2.29 p=0.0017) and CD95 (47.02%±19.82 vs 28.93%±11.21 (p=0.0004)) were found in both lSSc and dSSc. Compared to HC and lSSc, B lymphocytes from dSSc patients also presented with higher

proportions of cells positive for CD5 (24.12%±7.93 for dSSc vs 14.09%±6.58 for lSSc (p=0.0296) and 14.21%±5.34 for HC), CD86 (39.89%±22.11 for dSSc vs 17.72%±13.98 for lSSc (p=0.0007) and 11.68%±11.09 for HC), IL-6R (33.64%±23.12 for dSSc vs 17.91%±13.62 for lSSc (p<0.0001) and 12.08±8.68 for HC) and IL-21R (32.55%±20.19 for dSSc vs 5.76%±4.40 for lSSc (p<0.0001) and 5.93%±3.29 for HC). Intracellular flow cytometry identified a significantly increased proportion of IL-6 (24.53%±6.69 vs 13.23%±4.71 (p<0.0001)) and TGF-β (18.38%±10.22 vs 6.31%±3.62 (p<0.0001)) positive B lymphocytes in patients with SSc as compared to HC. Using multiplex assay, increased production of IL-6 (314.3 pg/ml±317.8 vs 6.10pg/ml±2.58 (p=0.0007)) and TGF-β (1020pg/ml±569 vs 163.8pg/ml±98.69 (p=0.0011)) altogether with reduced production of IL-10 (8.67pg/ml±6.22 vs 333.1pg/ml ±123.7 (p=0.0008)) were detected upon stimulation of B lymphocytes isolated from SSc patients compared to HC. Fibroblast proliferation and collagen production were also significantly increased in the presence of B cell supernatant from SSc patients as compared to HC.

Conclusion: We characterized a differential activation of peripheral B cells of patients exhibiting dSSc with an upregulation of CD5, CD86, IL-6R and IL-21R compare to lSSc patients and HC. B lymphocytes of SSc patients also expressed more CD69 and CD95 compare to HC. Peripheral B lymphocytes secreted both interleukin 6 and transforming growth factor-beta, and activated fibroblasts in patients with SSc.

Disclosure: N. Dumoitier, None; **S. Lofek**, None; **A. Regent**, None; **J. London**, None; **B. Chaigne**, None; **B. Terrier**, Roche Pharmaceuticals, 5; **N. Varin-Blank**, None; **L. Mouthon**, Roche Pharmaceuticals, 5.

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Abstract Number: 1923

The Role of Inflammatory Myeloid Cell Compartment in Myocardial Fibrogenesis and Remodelling in Systemic Sclerosis

Veronika Haunerdinger[1], Przemyslaw Blyszczuk[2], Elena Pachera[1], Rucsandra Dobrota[3], Britta Maurer[1], Ulrich Grabmaier[4], Karl Sotlar[5], Oliver Distler[1] and **Gabriela Kania**[1], [1]Research of Systemic Autoimmune Diseases, Division of Rheumatology, University Hospital Zurich, 8952 Schlieren, Switzerland, [2]Cardioimmunology, Center of Molecular Cardiology, University of Zurich, 8952 Schlieren, Switzerland, [3]Division of Rheumatology, University Hospital Zurich, Zurich, Switzerland, [4]Medical Clinic und Polyclinic I, Campus Großhadern, Maximilians University Munich, 81377 Munich, Germany, [5]Institute of Pathology, Ludwig Maximilians University Munich, 81377 Munich, Germany

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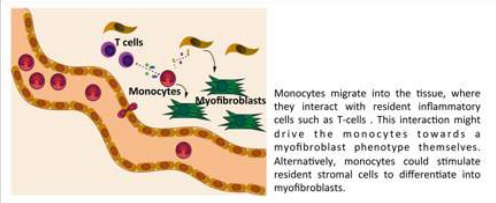
Background/Purpose: During the last years, there was a shift in systemic sclerosis (SSc)-related causes of death, indicating cardiac involvement and inflammatory dilated cardiomyopathy (iDCM) as one of the major cause of death in these patients. Insight from iDCM models revealed that bone marrow derived cells serve as a main source of pathological myofibroblasts. Nevertheless, despite the high unmet clinical need, so far little is known about the etiology of iDCM and the mechanisms leading to heart dysfunction in SSc patients. We hypothesized that the inflammatory myeloid cell compartment might be involved in post-inflammatory cellular remodelling in SSc patients.

Methods: $CD14^+$ monocytes, isolated from peripheral blood of SSc patients and healthy subjects, were differentiated towards a myofibroblast phenotype by 7-day stimulation with TGF-β1/IL-1β/IL-4/IL-10/IL-13 with or without inhibitors of TGF-β receptor I, Smad2/3 or canonical Wnt signalling. We established a co-culture system allowing co-culture of monocytes with human fibroblasts or activated human T cells in order to analyse the role of direct and indirect cell-to-cell-interaction on differentiation potentials. Moreover, an endomyocardial biopsy from a SSc patient, who underwent heart transplantation, was screened with immunohistochemistry.

Results: $CD14^+$ monocytes up-regulated myofibroblast markers (αSMA, fibronectin, collagen I), the transcription factor Fra-2 and different Wnts in cytokine-enriched monoculture. In direct co-cultures: a) with fibroblasts (in the presence of TGF-β1, n=7) or b) with T cells stimulated with IL-2/IL-7/IL-15/IL-21 (activation of common γ-chain receptor, n=3), or c) with CD3/CD28 activated T-cells (activation of T cell receptor, n=2) monocytes differentiated towards a myofibroblast phenotype. Interestingly, activation of the common γ-chain receptor in T cells up-regulated mostly αSMA gene expression, while activation of T cell receptor up-regulated αSMA, fibronectin and collagen I gene expression in the fibroblasts. Inhibition of TGF-β receptor I or the canonical Smad2/3-dependent pathway, and inactivation of extracellular Wnt or TCF/β-catenin-mediated transcription significantly abrogated the myofibroblast differentiation of $CD14^+$ monocytes. Moreover, human myocardium of a SSc patient with iDCM revealed the presence of $CD14^+/Fra\text{-}2^+$ monocyte-derived fibroblast-like cells in the fibrotic myocardium.

Conclusion: We showed here that TGF-β/Wnt/Fra-2 signalling axis mediates the differentiation of circulating monocytes towards a myofibroblast phenotype. Therefore, these cells might be considered as a potential cellular source for pathological myofibroblasts in SSc.



Disclosure: V. Haunerdinger, None; **P. Blyszczuk**, None; **E. Pachera**, None; **R. Dobrota**, Pfizer Inc, 2; **B. Maurer**, None; **U. Grabmaier**, None; **K. Sotlar**, None; **O. Distler**, Consultancy relationships and/or has received research funding from Actelion, Pfizer, Ergonex, BMS, Sanofi-Aventis, United BioSource Corporation, Medac, Biovitrium, Boehringer Ingelheim, Bayer Pharma AG, Novartis, 4D Science and Active Biotech in the area, 2; **G. Kania**, None.

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Abstract Number: 1924

Increased Stat1 and Stat 1 Phosphorylation in Patients with Systemic Sclerosis (SSc)

Martyna Skwarek, Julia Fantana, Babett Heschel, **Martin Aringer** and Christoph Kittel, Medicine III, University Medical Center and Faculty of Medicine at the TU Dresden, Dresden, Germany

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Background/Purpose: To analyze Stat1 and phosphorylated Stat1, the interleukin-6 (IL-6) receptor-Stat3 axis, and membrane bound tumor necrosis factor (mTNF) and TNF receptors 1 and 2 (CD120a and CD120b), in patients with SSc.

Methods: We prepared PBMC of 30 patients with SSc and 42 healthy individuals (HC). CRP, ESR, modified Rodnan skin score (mRSS) and the EULAR activity score were recorded. For determining the percentages of CD120a, CD120b, CD126 and CD130 positive cells, PBMC were directly stained with PE-labelled or control antibodies. Ex vivo and after 15 minutes of incubation with or without recombinant human interferon-γ (IFN γ) or interleukin-6 (IL-6), PBMC were fixed with formaldehyde (2%), permeabilized with methanol (80%), and stained with PE-labelled control antibodies or antibodies to Stat1 or phosphorylated Stat1 (pStat1) or pStat3, respectively. Stained cells were immediately analyzed on a Becton Dickinson FACSCalibur fluorocytometer, independently gating for lymphocytes and monocytes. As a semiquantitative measure of (p)Stat contents, mean fluorescence intensity (mfi) was used. Data were expressed as mean±SD.

Results: Both chains of the IL-6 receptor, CD126 and CD130, were expressed on decreased percentages of SSc lymphocytes (50.2±18.1% vs. 60.0±7.9%, p=0.0086, and 52.6±15.1% vs. 59.6±9.5%, p=0.0212, respectively). This translated into a diminished increase of pStat3 in SSc lymphocytes upon IL-6 stimulation (Δmfi 17.2±12.1 vs. 20.5±9.3, p=0.03, and 35.8±17.1 vs. 54.1±25.0, p=0.0129, respectively). In contrast, the increase in pStat1 upon IFNγ stimulation was more pronounced in SSc lymphocytes (Δmfi 10.5±11.2 vs. 4.8±3.7, p=0.0035), albeit their increased Stat1 contents (mfi 51.2±27.4 vs. 16.7±9.1, p < 0.0001) suggested ongoing activity of the IFN system in SSc. While the percentages of IL-6R positive monocytes were not significantly different from those of HC, their IL-6 induced increase in pStat3 was nevertheless decreased (Δmfi 35.8±17.1 vs. 54.1±25.0, p=0.0129), and their IFNγ induced increase in pStat1 showed a trend towards being higher than normal (Δmfi 60.9±53.3 vs. 44.9±24.9, p=0.32). The percentage of mTNF positive lymphocytes was slightly decreased (2.3±0.8% vs. 3.2±1.8%, p = 0.0357), while mTNF monocytes were increased (68.1±30.0% vs. 24.3±24.4%, p<0.0001). CD120b was increased on both SSc lymphocytes (67.2±18.6 vs. 58.4±11.9, p=0.0017) and monocytes (93.4±9.0% vs. 75.4±19.9%, p < 0,001), whereas CD120a was increased on SSc monocytes (31.3±21.5% vs. 13.6±9.7%, p = 0.001) only.

Conclusion: Our results suggest upregulation of the IFN-Stat1 and the IL-6-Stat3 axis in SSc, with a shift towards increased Stat1 phosphorylation. In addition, increased TNF and TNF receptors were found on SSc monocytes.

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Abstract Number: 1925

Interleukin-35 Is Upregulated in Systemic Sclerosis and Its Serum Levels Are Increased in Early Disease

Michal Tomcík[1], Pawel Zerr[2], Katrin Palumbo-Zerr[2], Hana Storkanova[1], Hana Hulejova[3], Maja Spiritovic[4], Ondrej Kodet[5], Jiri Stork[5], Radim Becvar[1], Jiri Vencovsky[1], Karel Pavelka[6], Maria Filkova[7], Jorg HW Distler[2] and Ladislav Senolt[8], [1]Institute of Rheumatology, Department of Rheumatology, 1st Faculty of Medicine, Charles University, Prague, Czech Republic, [2]Department of Internal Medicine 3 and Institute for Clinical Immunology, University of Erlangen-Nuremberg, Erlangen, Germany, [3]Institute of Rheumatology and Department of Rheumatology, Prague, Czech Republic, [4]Faculty of Physical Education and Sport, Charles University, Prague, Czech Republic, [5]Department of Dermatology and Venereology, First Faculty of Medicine, Charles University, Prague, Czech Republic, [6]Charles University, Prague, Czech Republic, [7]Institute of Rheumatology and Department of Rheumatology, 1st Faculty of Medicine, Charles University, Prague, Czech Republic, [8]Institute of Rheumatology and Department of Rheumatology, 1st Faculty of Medicine, Charles University, Prague, Czech Republic, Prague, Czech Republic
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Background/Purpose: Interleukin-35 (IL-35) is the most recent addition to the IL-12 family, which also comprises IL-12, IL-23 and IL-27. IL-35 consists of two chains, p35/IL-12a and EBI3/IL-27b, and exerts immunomodulatory activities in experimental and human autoimmune inflammatory conditions. Its potential role has been proposed in the pathogenesis of rheumatoid arthritis, sarcoidosis and systemic lupus erythematosus. However, its role in systemic sclerosis (SSc) has not been studied to date. The aim of this study was to assess IL-35 expression in the skin, dermal fibroblasts and circulation of SSc patients and characterize its potential association with SSc-related features.

Methods: Expression of IL-35 in the skin and dermal fibroblasts was quantified by qPCR, immunohistochemistry and immunofluorescence. Serum levels of IL-35 were analyzed by high sensitivity ELISA (Life Sciences, Hubei, PRC), and routine laboratory parameters such as CRP (by turbidimetry), ANA (by immunofluorescence) and autoantibodies of the ENA complex (by immunoblot) were measured in 40 SSc patients who met the EULAR/ACR 2013 criteria for SSc. Serum IL-35 was also determined in 40 healthy volunteers matched by age and sex.

Results: IL-35 chains EBI3 and p35 were overexpressed in the fibrotic skin of patients with SSc compared to that of healthy controls on both mRNA ($p<0.05$, $p<0.05$) and protein level ($p<0.001$, $p<0.001$). In fibrotic SSc skin, in contrast to non-fibrotic healthy skin, prominent staining for both IL-35 subunits was detected in dermal fibroblasts, myofibroblasts and perivascular inflammatory cells. Overexpression of IL-35 persisted in cultured dermal fibroblasts from SSc patients which maintained an increased mRNA ($p<0.05$, $p<0.05$) and protein level of both IL-35 subunits and released increased levels of IL-35 into supernatants ($p<0.05$) compared to healthy dermal fibroblasts. Stimulation with the main pro-fibrotic cytokine, TGF-β, increased the mRNA ($p<0.05$, $p<0.05$) and protein levels of both IL-35 chains, and enhanced the release of IL-35 into the supernatants ($p<0.05$), as well. Incubation with recombinant IL-35 induced an activated phenotype in resting fibroblasts (increased the expression of α-smooth muscle actin and stress fibers) and enhanced the release of collagen in a dose-dependent manner. IL-35 serum levels were increased in patients with SSc compared to healthy controls (median(IQR): 83.9 (45.1–146.1) vs. 36.2 (17.2–49.4) pg/ml, $p<0.0001$). Furthermore, serum IL-35 negatively correlated with disease duration ($p<0.01$, $r=-0.434$), and was increased in patients with early SSc pattern on capillaroscopy assessment compared to those with active and late SSc patterns ($p<0.05$, $p<0.05$). No correlations of serum IL-35 with other SSc-related features were observed.

Conclusion:

The present study demonstrates an overexpression of IL-35 in the skin, dermal fibroblasts and serum of SSc patients. TGF-β induces IL-35, which in turn activates resting fibroblasts and enhances the release of collagen thereby contributing to aberrant TGF-β signaling in SSc. Elevated serum IL-35 is associated with early, inflammatory stages of SSc.

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Abstract Number: 1926

Wnt5a Activates Wnt/PCP-Signaling to Promote Fibroblast Activation and Fibrosis

Chih-Wei Chen[1], Neng-Yu Lin[1], Yun Zhang[1], Jingang Huang[1], Katrin Palumbo-Zerr[1], Alexandra Schambony[2], Christian Beyer[1], Georg Schett[1] and Jeorg HW Distler[1], [1]Department of Internal Medicine 3 and Institute for Clinical Immunology, University of Erlangen-Nuremberg, Erlangen, Germany, [2]Department of Biology, Development Biology, University of Erlangen-Nuremberg, Erlangen, Germany
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Background/Purpose: While canonical Wnt/beta-catenin signaling has been identified as a core pathway of fibrosis in SSc, non-canonical Wnt signaling pathways have not yet been analyzed. A subset of Wnt proteins can activate non-canonical Wnt pathways that are independent of beta-catenin by binding to different cell surface receptors to modulate cellular functions such as proliferation and differentiation.

In this study we aimed to characterize the role of Wnt5a in fibrotic diseases.

Methods: The expression of non-canonical Wnt ligands was analyzed by qPCR, IF and Western blot in patients with SSc, IPF and healthy controls as well as in experimental fibrosis. The effect of fibroblast-specific (col1a2; CreER) as ubiquitous (ubiquitin; CreER) knockout of Wnt5a was evaluated in bleomycin-induced fibrosis and in experimental cGvHD. Wnt5a-induced signaling was analyzed in vitro and in vivo using small molecule inhibitors, siRNA mediated knockdown, Western blots and reporter assays.

Results: The mRNA and protein levels of Wnt5a, but not other non-canonical Wnt ligands, were increased in skin and lungs of patients with SSc and IPF as compared to healthy volunteers. Wnt5a was also upregulated in murine models of fibrosis. Co-staining with cell-type specific markers identified fibroblasts as a major cellular source of Wnt5a in fibrotic diseases. Wnt5a induced myofibroblast differentiation and collagen release *in vitro* and induced pulmonary and dermal fibrosis *in vivo*. In contrast, inducible fibroblast-specific knockout of Wnt5a ameliorated bleomycin-induced fibrosis and experimental cGvHD. The effects of fibroblast-specific knockout were comparable to those in mice with inducible ubiquitous knockout. The pro-fibrotic effects of Wnt5a were independent of Wnt/beta-catenin and Wnt/Calcium signaling, but were mediated by Wnt/PCP signaling with phosphorylation of JNK and cJun. Consistently, pharmacologic or genetic inactivation of JNK or cJun abrogated the pro-fibrotic effects of Wnt5a *in vitro* and *in vivo*. The stimulatory effects of Wnt5a on fibroblasts were biphasic. Western Blots and SBE-reporter assays demonstrated that, at early timepoints, Wnt5a activated JNK, which cross-phosphorylated Smad3 to stimulate the expression of TGFbeta/Smad-dependent genes. This early effect was completely blocked by inactivation of JNK. At later timepoints, Wnt5a induced the expression of TGFbeta to upregulated pro-fibrotic genes. In contrast to the early effects, the delayed effects of Wnt5a were blocked by neutralization of TGFbeta or by TGFbetaRI inhibition.

Conclusion: We characterize Wnt5a as a novel mediator of fibroblast activation in fibrotic diseases. Wnt5a is upregulated in SSc and IPF and induces fibroblast activation and tissue fibrosis. The pro-fibrotic effects of Wnt5a are independent of canonical Wnt signaling and are mediated by JNK-induced activation of Smad3 at early time points and transcriptional upregulation of TGFbeta at later time points.

Disclosure: C. W. Chen, None; **N. Y. Lin**, None; **Y. Zhang**, None; **J. Huang**, None; **K. Palumbo-Zerr**, None; **A. Schambony**, None; **C. Beyer**, None; **G. Schett**, None; **J. H. Distler**, None.

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Abstract Number: 1927

Salinomycin Induces Potent Suppression of TGF-β1-Mediated Expression of Profibrotic Genes in Cultured Dermal Fibroblasts from Normal Donors and from Donors with Systemic Sclerosis (SSc): A Novel Anti-Fibrotic Treatment for Tissue Fibrosis in SSc

Peter J. Wermuth[1] and Sergio A. Jimenez[2], [1]Jefferson Institute of Molecular Medicine, Division of Connective Tissue Diseases and Scleroderma Center, Thomas Jefferson University, Philadelphia, PA, [2]Jefferson Institute of Molecular Medicine, Division of Connective Tissue Diseases and Scleroderma Center,Thomas Jefferson University, Philadelphia, PA
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Background/Purpose: Activated myofibroblasts are the primary mediators of the excessive synthesis and deposition of collagens and other extracellular matrix (ECM) macromolecules during the pathogenesis of fibrotic diseases including Systemic Sclerosis (SSc). TGF-β signaling plays a pivotal role in the differentiation and activation of myofibrolasts. Salinomycin, a polyether ionophore antibiotic isolated from *Streptomyces albus* has been shown to cause a selective inhibition of cancer stem cells. Recently, salinomycin has been reported to possess potent anti-myofibroblast properties, specifically targeting TGF-β-mediated myofibroblast activation and to inhibit TGF-β-induced collagen production, cell proliferation, contraction and migration in cultured primary normal human fibroblasts. The purpose of these studies was to perform a dose-response analysis of the effect of salinomycin on the expression of profibrotic genes in cultured dermal fibroblasts isolated from normal donors and donors with SSc to evaluate whether the reported inhibition of the

profibrotic consequences of TGF-β signaling will produce an effect on dermal fibroblasts isolated from SSc donors.

Methods: Normal and SSc dermal fibroblasts were cultured in the presence of 100, 250 or 500 nM salinomycin alone or in combination with 10 ng/mL TGF-β1. After 72 hours, total RNA was isolated and the effects of salinomycin on the expression of profibrotic genes were assess by semiquantitative RT-PCR in triplicate on three replicates per normal and SSc cell line. Levels of ECM proteins in culture media and levels of α-SMA in cell lysates were evaluated by Western blot.

Results: Treatment of both cultured normal and SSc dermal fibroblasts with salinomycin induced a potent concentration-dependent decrease in the expression of several genes associated with fibrosis, including type I and type III collagens (COL1A1 and COL3A1), fibronectin 1 (FN1) and the FN-EDA splice variant as well as decreased expression of the myofibroblast marker α-SMA. A similar effect was observed in TGF-β-treated normal and SSc fibroblasts. Remarkably, treatment of SSc fibroblasts with salinomycin caused a potent downregulation of the elevated levels of profibrotic gene transcripts in these cells.

Conclusion: The observed effects of salinomycin on cultured dermal fibroblasts from normal and SSc donors are consistent with its reported ability to suppress TGF-β-mediated myofibroblast differentiation and activation. Intriguingly, the ability of salinomycin to greatly reduce expression of COL1A1, COL3A1, FN1, FN-EDA and α-SMA was also seen in non-TGF-β treated cells from SSc donors, thus strongly supporting the concept that salinomycin may represent a potent and novel antifibrotic agent for the treatment of SSc.

Disclosure: P. J. Wermuth, None; **S. A. Jimenez**, None.

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Abstract Number: 1928

Isolation and Initial Characterization of Dermal Vascular Smooth Muscle Cells in Systemic Sclerosis

Shadia Nada[1], Farouk Abu Alhana[2], Yongqing Wang[2], **Nezam Altorok**[3] and Bashar Kahaleh[4], [1]Internal Medicine, Divison of Rheumatology, The University of Toledo, Toledo, OH, [2]The University of Toledo, Toledo, OH, [3]Internal Medicine, Division of Rheumatology, The University of Toledo, Toledo, OH, [4]Medicine/Rheumatology, The University of Toledo, Toledo, OH

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Background/Purpose: Nearly all patients with Systemic sclerosis (SSc) suffer from vascular dysfunction as illustrated by the uniform presence of Raynaud's phenomena. The role of vascular smooth muscle cells (VSMCs) in the development of vascular dysfunction is still unknown. In this study, we isolated VSMCs from skin biopsy, and we examined their functional phenotype.

Methods: We obtained 4 mm punch-skin-biopsy from 3 patients with diffuse cutaneous SSc and 3 matched healthy controls. Skin specimens were treated with a mixture of proteases, then after digestion we plated cells in culture media and harvested the primary cell culture after 10 days. VSMCs were isolated by magnetic microbeads using cell surface markers. First, we depleted total cells from CD31+ cells, followed by positive selection for CD146 + cells. To confirm the identity of this cell population (CD31- CD146+), we performed immunoflorocytometry staining for smooth muscle myosin heavy chain 11 (MYH11), Desmin and NG2. We investigated cell proliferation by using Bromodeoxyuridine (BrdU) assay, and cell viability in normal culture conditions as well as low serum conditions using MTT assay.

Results: Out of the total cells obtained from primary cell culture, 15% were CD31- CD146 + (VSMCs). The majority of cells in this population stained for smooth muscle MYH11 (89.1%), in addition to Desmin and NG2, while the CD31+ and the fibroblast cell populations did not. This staining pattern differentiates VSMCs from pericytes. Next, we evaluated cell proliferation using BrdU, and we demonstrated uptake of BrdU by 19% of the control-VSMCs compared to 34% of SSc-VSMCs (P= 0.0031). The MTT assay showed increase cell proliferation of SSc-VSMCs compared to control-VSMCs (0.44 and 0.25, respectively. P= 7.38E-08). Under serum starvation conditions, SSc-VSMCs exhibited more proliferation capacity than control-VSMCs (0.30 and 0.21, respectively. P= 5.73E-13). Also, we performed immunoflorocytometry staining for B-catenin and we demonstrate a cytoplasmic to nuclear translocation of B-catenin in SSc-VSMCs but not in control-VSMCs. This finding may imply potential involvement of B-catenin in the induction of VSMCs activation in SSc.

Conclusion: This is the first report of the successful isolation and initial characterization of SSc-VSMCs. We believe that increased proliferation of SSc-VSMCs in association with resistance to apoptosis may greatly impact the vascular lesion in SSc. Further studies are warranted to fully understand the trigger and maintenance of the abnormal SSc-VSMCs phenotype.

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Abstract Number: 1929

Somatic Mutations in Clonally Expanded Cytotoxic Lymphocytes in Patients with Newly Diagnosed Rheumatoid Arthritis

Paula Savola[1], Tiina Kelkka[1], Hanna Rajala[1], Antti Kuuliala[2], Krista Kuuliala[2], Samuli Eldfors[3], Pekka Ellonen[3], Sonja Lagstrom[3], Rajiv Kumar Khajuria[1], Taina Jaatinen[4], Riitta Koivuniemi[5], Heikki Repo[2], Janna Saarela[3], Kimmo Porkka[1], Marjatta Leirisalo-Repo[6] and Satu Mustjoki[1], [1]Department of Hematology, Hematology Research Unit Helsinki, University of Helsinki, Comprehensive Cancer Center, Helsinki University Hospital, Helsinki, Finland, [2]Department of Bacteriology and Immunology, Haartman Institute, University of Helsinki, Helsinki, Finland, [3]Institute for Molecular Medicine Finland (FIMM), University of Helsinki, Helsinki, Finland, [4]Clinical Laboratory, Finnish Red Cross Blood Service, Helsinki, Finland, [5]Department of Medicine, Division of Rheumatology, University of Helsinki and Helsinki University Hospital, Helsinki, Finland, [6]Rheumatology, University of Helsinki and Helsinki University Hospital, Helsinki, Finland

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Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: In rheumatoid arthritis (RA), the mechanisms initiating immune dysregulation leading to joint damage are incompletely understood. Previous studies show that large CD8+ T cell lymphocyte clones occur commonly in RA. We hypothesized that in some RA patients, lymphocytes may have acquired somatic mutations resulting in clonal expansions and abnormal immune reactivity.

Methods: We used flow cytometry and deep T-cell receptor sequencing to assess T-cell clonality in a cohort of 82 newly diagnosed RA patients. These patients fulfilled the ACR/EULAR 2010 criteria for RA. Further, acquired genetic changes either in sorted CD8+ or CD4+ T cells were investigated with a next-generation sequencing panel consisting of 986 known immunoregulatory genes. Mutations discovered with this panel were validated and screened from other patients with the deep Amplicon sequencing method.

Results: Significant (>10%) clonal CD8+ T-cell expansions were present in 51% (34/67) of RA patient peripheral blood samples. In two out of 15 patients (13%) sequenced with the next-generation immunogene panel, somatic, high-confidence missense mutations were discovered. Patient 1 had mutations in *PADI4* (peptidyl arginine deiminase, type IV), *PROM1* (prominin 1) and *C5* (complement component 5) genes, and patient 2 in *IRF1* (interferon regulatory factor 1), *SLAMF6* (SLAM family member 6) and *SEC14L3* (SEC14-like 3 (S. cerevisiae)) genes. These mutations were restricted to the expanded CD8+ T-cell clones and they persisted during immunosuppressive therapy. Functionally, mutated *PADI4* led to decreased expression and enzymatic activity of the PADI4, whereas mutated *IRF1* resulted in increased *STAT1* expression. However, no recurrent mutations in these genes were found in other patients.

Conclusion: Clonal CD8+ T-cell expansions were observed in a significant proportion of RA patients, and in two patients expanded CD8+ T-cell clones harbored acquired somatic mutations in genes (*PADI4* and *IRF1*) known to be causally relevant for the pathogenesis of RA. The mutations in these two genes changed the protein function. Further studies utilizing unbiased sequencing assays are needed to validate the role of somatic mutations as inducers of T-cell activation and autoimmunity in RA.

Disclosure: P. Savola, None; **T. Kelkka**, None; **H. Rajala**, None; **A. Kuuliala**, None; **K. Kuuliala**, None; **S. Eldfors**, None; **P. Ellonen**, None; **S. Lagstrom**, None; **R. K. Khajuria**, None; **T. Jaatinen**, None; **R. Koivuniemi**, None; **H. Repo**, None; **J. Saarela**, Roche Pharmaceuticals, 5; **K. Porkka**, Pfizer Inc, 9,Bristol-Myers Squibb, 9,Novartis Pharmaceutical Corporation, 9; **M. Leirisalo-Repo**, None; **S. Mustjoki**, Pfizer Inc, 9,Novartis Pharmaceutical Corporation, 9,Bristol-Myers Squibb, 9.

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Abstract Number: 1930

Identification of a Broadly Immunogenic Prevotella Copri T Cell Epitope in Patients with Rheumatoid Arthritis

Annalisa Pianta[1], Elise E. Drouin[1], Sheila Arvikar[2], Klemen Strle[1], Jameson T. Crowley[1], Qi Wang[3], Catherine E. Costello[3] and Allen C. Steere[4], [1]Center for Immunology and Inflammatory Diseases, Massachusetts General Hospital, Harvard Medical School, Boston, MA, [2]Division of Rheumatology, Allergy & Immunology, Massachusetts General Hospital, Harvard Medical School, Boston, MA, [3]Center for Biomedical Mass Spectrometry, Boston University School of Medicine, Boston, MA, [4]Center for Immunolgy and Inflammatory Diseases, Massachusetts General Hospital, Harvard Medical School, Boston, MA

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Background/Purpose:

Specific microorganisms in the gut microbiome may have a pathogenic role in rheumatoid arthritis (RA). Recently, Scher et al. showed that *Prevotella copri*, an intestinal microbe, was over-expanded in stool samples from patients with new-onset RA (NORA). This organism has a sequence for a peptidylarginine deiminase-like (PAD-like) enzyme, which may lead to citrullinated neoepitopes and anti-citrullinated protein antibodies (ACPA). However, little is known about immune responses to *P. copri*, and its role in RA pathogenesis is not yet clear.

Methods:

To address these issues, we used an innovative approach that combines discovery-based proteomics and translational research. Accordingly, we identified microbial and self HLA-DR-presented peptides (T cell epitopes) in patients' synovial tissue, joint fluid or peripheral blood (PB), using tandem mass spectrometry. The identified peptides were synthesized and tested for T cell reactivity with the matching patient's PBMC by IFN-g ELISpot assay. Immunoreactive peptides or source proteins were then tested for T and B cell responses using cells and sera from our cohort of DMARD-naive NORA patients and controls. All RA patients met the 2010 ACR/EULAR criteria for RA.

Results:

From the HLA-DR-presented peptides isolated from the PB of one RA patient (HLA-DRB1*0401/0101), we identified an immunogenic T cell epitope derived from bacterial signal sequence of a 27-kDa protein of *P. copri* (*Pc*-p27), implying that this organism or components of it were present in this patient's circulating phagocytic cells. When testing was done in additional patients, 17 of 40 (42%) NORA patients had T cell reactivity with this single epitope of *Pc*-p27. In addition, 10 of 78 NORA patients (13%) had IgG antibodies to *Pc*-p27; 8 of 78 patients (10%) had IgA antibodies to this protein, but only 1 patient had both IgG and IgA antibody responses. In contrast, no patients with other forms of arthritis or healthy control subjects had T or B cell responses to this protein. IgA antibody responses to *Pc*-p27 correlated with higher serum IL-23 levels (suggestive of Th17 responses) and more frequent ACPA, whereas IgG antibody responses to the protein correlated with lower IL-23 levels and less frequent ACPA, suggesting that patients may have advantageous (IgG) or disadvantageous (IgA) responses to this *P. copri* protein. Moreover, Th1 responses to the identified epitope of *Pc*-p27, as determined by IFN-g secretion, were usually concordant with IgG antibody responses to the protein, but no patients with IgA antibody responses to *Pc*-p27 had this Th1 response.

Conclusion:

The identification of a single T cell epitope in an individual patient provided a bridge to the discovery of a broadly immunogenic *P. copri* protein. There appears to be dichotomous immune responses to this protein. We postulate that Th1 responses and IgG antibodies to *Pc*-p27 more effectively control the expansion or systemic spread of the organism. In contrast, IgA antibodies to *Pc*-p27, which are associated with higher IL-23 levels (suggestive of Th17 responses) and greater frequency of ACPA, may be less effective in controlling the organism and may enhance the development of autoimmune responses.

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Abstract Number: 1931

PLCe1 Mediates Cellular Adhesion Downstream of SDF-1 in T Cells

Adam Mor[1] and Marianne Strazza[2], [1]Rheumatology and Pathology, NYU Langone Medical Center, New York, NY, [2]NYU, New York, NY
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Background/Purpose:

The presentation of chemokines by endothelial cells results in chemoattraction of leukocytes that express the correlative chemokine receptors. In this way, chemokines direct leukocyte trafficking throughout the body. Upon receptor binding, arrested leukocytes, here T cells, firmly adhere to the endothelium and subsequently crawl along the blood vessel wall in search of an area permissive to cellular passage or transmigration. As a result, chemokine induced T cell adhesion is both rapid and polarized. This is in contrast to antigen receptor mediated T cell adhesion, which is characterized by slow kinetics and operates under different physical forces.

Methods:

Thus, the goal of this work was to identify the unique signaling pathways regulating T cell adhesion downstream of chemokine receptors.

Results:

We have shown that SDF-1α induced Rap1 activation is transient in comparison to the sustained Rap1 activation observed following stimulation of the T cell receptor. Using an inhibitory RNA screen we have identified that the guanine nucleotide exchange factor mediating SDF-1α-Rap1 activation is PLCε1. Further studies show that knockdown of PLCε1 in T cells interferes with SDF-1α induced Rap1 activation and firm adhesion, as observed through adhesion studies performed under sheer flow. Through the analysis of morphological changes following stimulation, we show that PLCε1 is also necessary for migration. Structure-function analysis of PLCε1 uncovers the contribution of different domains to its guanine exchange activity.

Conclusion:

In conclusion, we uncover a novel signaling pathway where SDF-1α induces T cell adhesion through activation of PLCε1. While T cell trafficking plays an important role in healthy immune surveillance, inflammatory responses, and autoimmune diseases, chemokine induced signaling cascades are currently understood in only the broadest sense.

Disclosure: A. Mor, None; **M. Strazza**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/plce1-mediates-cellular-adhesion-downstream-of-sdf-1-in-t-cells

Abstract Number: 1932

IL-17A-Low CCR6+ Th Cell Populations of Patients with Rheumatoid Arthritis Are Pathogenic, Multidrug Resistant and Associated with DMARD and Glucocorticoid Treatment Response

Jan Piet van Hamburg[1], Sandra M.J. Paulissen[2], Nadine Davelaar[1], Mieke Hazes[3] and Erik Lubberts[1], [1]Rheumatology and Immunology, Erasmus MC, University Medical Center Rotterdam, Rotterdam, Netherlands, [2]Room Nb-84, Erasmus MC, University Medical Center Rotterdam, Rotterdam, Netherlands, [3]Rheumatology, Erasmus MC, University Medical Center Rotterdam, Rotterdam, Netherlands

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Background/Purpose: CCR6+ T-helper (Th) cells and their pro-inflammatory cytokines including IL-17A are implicated in the pathogenesis of rheumatoid arthritis (RA). However, within the CCR6+ Th population various subpopulations are present and the clinical relevance of each subpopulation in RA is unclear. Therefore, we characterized CCR6+ Th subpopulations with regard to pathogenic potential and treatment outcome in RA.

Methods: Within total CCR6+ Th cells from patients with RA, CCR4+CXCR3- (Th17), CCR4-CXCR3+ (Th17.1), CCR4/CXCR3 double-positive (DP) and double-negative (DN) cells were distinguished and/or sorted by flow cytometry. These subpopulations were: analyzed for Th17/Th1-associated factors; co-cultured with RA-derived synovial fibroblasts (RASF); related to disease-modifying antirheumatic drugs (DMARDs) and glucocorticoid (GC) therapy response; analyzed regarding the expression of multidrug transporters MDR1 and MRP1 and drug efflux potential.

Results: All CCR6+ Th subpopulations expressed the Th17 associated transcription factor, RORC+ and were present in RA peripheral blood and synovial fluid. Despite differential IL-17A, IL-17F, IFNγ and TBX21 expression, all CCR6+ Th subpopulations, including IL-17A low-producing Th17.1, DP and DN cells, showed pathogenic activity in the induction of IL-1β, IL-6, IL-8, COX-2 and MMP-3 expression by RASF. MDR1 expression levels and MDR1 efflux activity were significantly higher in Th17.1 and DN cells, in comparison to the other CCR6+ Th subpopulations and Th1 cells. In contrast, MRP1 expression and efflux activity was present in all CCR6+ Th subpopulations and increased upon DMARD/GC therapy. Moreover, the lack of response of DMARD/GC therapy was accompanied with increased drug efflux potential by CCR6+ Th cell populations.

Conclusion: Despite distinct differences in Th17/Th1 characteristics, including IL-17A production, all CCR6+ Th subpopulations of patients with RA display pathogenic activity. Future treatment strategies towards CCR6+ Th cells in RA may therefore focus on targets shared by all subpopulations. Furthermore, personalized treatment strategies may be improved by using drug efflux potential of CCR6+ Th cells to monitor DMARD/GC therapy response.

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Abstract Number: 1933

Rheumatoid Arthritis Patient T Cells Recognize Neutrophil Extracellular Traps

Dana E. Orange[1,2,3], Nathalie Blachere[1], Salina Parveen[1], John Fak[1], Mayu Frank[1] and Robert Darnell[3,4,5], [1]The Rockefeller University, New York, NY,

[2]Rheumatology, Hospital for Special Surgery, New York, NY, [3]The New York Genome Center, New York, NY, [4]Laboratory of Molecular Neuro-Oncology, The Rockefeller University, New York, NY, [5]Howard Hughes Medical Institute, New York, NY
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Background/Purpose:

The majority of patients with rheumatoid arthritis (RA) harbor anti-citrullinated peptide antibodies, which are correlated with more severe disease. Tetramer based assays have demonstrated that RA patient T cells that recognize citrullinated antigen are more likely to be activated effectors that produce inflammatory cytokines such as IFNg, and less likely to be T regulatory cells. Measurement of citrullinated autoantigen T cell responses could be clinically useful to help predict prognosis or treatment response in patients with RA. A T cell assay that is not restricted to certain MHC II alleles would enable testing of large numbers of RA patients. Since NETing neutrophils externalize targets of RA autoantibodies, we hypothesized that neutrophil NETS could be a source of naturally processed citrullinated antigen to elicit RA patient T cell responses in vitro.

Methods:

All-Trans Retinoic Acid (ATRA) was used to differentiate HL60 cells. Growth rate, nuclear morphology, cell surface CD11b expression, and PAD2, PAD4 and MPO mRNA expression were measured. Differentiated cells were exposed to UV irradiation, PMA and ionomycin and cell death by necrosis, apoptosis and NETosis were compared by immunohistochemistry as well as FACS staining with TOPRO and Annexin V. Citrullination of cells undergoing different types of cell death was compared by western blot. ACPA+ RA and matched control PBMC derived DC were fed granulocytes that had died by various mechanisms and used to probe immediate ex vivo T cell responses using the 40 hour IFNg ELISPOT assay and 18 hour FACS based assays for early activation markers such as CD69 and CD25.

Results:

ATRA treatment of HL60 cells causes them to differentiate into neutrophil like cells as measured by growth curves, CD11b expression and upregulation of PAD2 and PAD4, enzymes that cause citrullination. When treated with UV, ATRA differentiated cells die by apoptosis, while ionomycin and PMA induce NETosis. RA patient but not control T cells produced IFNg and upregulated CD69 and CD25 in response to ionomycin treated ATRA HL60 NET lysate but not ionomycin HL60 (PAD2 and PAD4 low expressing) control lysate.

Conclusion:

RA patients may harbor an expanded population of memory T cells, which recognize NET derived antigen.

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Abstract Number: 1934

Autophagy Pathway As a Target of Therapeutic P140 Peptide Used in Lupus

Maud Wilhelm[1], Fengjuan Wang[2], Nicolas Schall[2], Michael Faludi[3], Jean Francois Kleinmann[4], Emil P. Nashi[5], Thierry Martin[6], Jean Sibilia[7], Jean-Louis Pasquali[8], Daniel Wallace[9] and **Sylviane Muller**[10], [1]Immunopathologie & Chimie Thérapeutique, CNRS, Strasbourg, France, [2]CNRS, Strasbourg, France, [3]761 Graham, McGill University, Mont-Royal, QC, Canada, [4]Rheumatology, Strasbourg University Hospital, Strasbourg, France, [5]Rheumatology, McGill University Health Centre, Montreal, QC, Canada, [6]Cnrs UPR9021, IBMC, Strasbourg, France, [7]Department of Rheumatology, Strasbourg University Hospital, Strasbourg, France, [8]Strasbourg University, Hospital, CNRS UPR 3572, Strasbourg, France, [9]Cedars-Sinai/UCLA, Los Angeles, CA, [10]CNRS Institut de Biologie Moléculaire et Cellulaire, Strasbourg, France
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SESSION INFORMATION
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Background/Purpose: P140 is a 21-mer peptide (sequence 131-151, phosphorylated at position 140) that is derived from the spliceosomal protein U1-70K. In a multicenter, randomized, placebo-controlled phase IIb study, P140/Lupuzor™ had no adverse safety signals and met its primary efficacy end points in

lupus patients[1]. These results confirm data generated in MRL/lpr lupus-prone mice in which the preclinical studies were performed. We found previously that P140 reduces autophagic flux in MRL/lpr B cells[2] and that macroautophagy (the best characterized type of autophagy) is abnormally enhanced in T lymphocytes from lupus mice and patients[3]. More recently, we discovered that in MRL/lpr mice, P140 more precisely targets a selective form of autophagy, chaperone-mediated autophagy. We deciphered the successive steps of P140 action leading *in fine* to a decay of endogenous antigen processing and loading to MHCII molecules and as a consequence, to a lower activation of autoreactive T cells[4]. Here, the mechanism of action of P140 was further studied in peripheral cells from normal and lupus individuals.

Methods: Studies were performed *ex vivo* on B cells from normal donors and lupus patients. A scrambled peptide was used as control. Immunocytochemical analyses were applied to identify the way of P140 enters into B cells. The effect of P140 on MHCII molecules stability was studied using western immunoblotting (WB) and FACS analyses. FACS studies were used to evaluate the effect of P140 on the B cells differentiation into plasmablasts and plasma cells and on BCR signaling amplitude. Microscopy and WB analyses were performed to study the effect of P140 on autophagy.

Results: P140 that is not immunogenic in lupus patients[5] showed no direct effect on BCR signaling in normal B cells (mature, transitional, IgG/IgM memory). As in MRL/lpr mice, P140 enters human B cells via a clathrin-dependent endo-lysosomal pathway and induces a decrease of MHCII expression. Higher the SLEDAI score of patients was, higher the P140 effect was measurable. P140 did not induce apoptosis of B cells from healthy or lupus patients. The autophagic flux was affected in P140-treated B cells.

Conclusion: Our findings provide strong arguments to conclude that the mechanism of action of P140 peptide is similar in MRL/lpr mice and lupus patients. These results shed light on mechanisms by which P140/Lupuzor modulates lupus disease in humans affected by this disorder.

Refs: [1]Zimmer et al. *ARD* 2013; [2]Page et al. *ARD* 2011; [3]Gros et al. *Autophagy* 2012; [4]Macri et al. *Autophagy* 2015; [5]Schall & Muller *Lupus* 2015.

Disclosure: M. Wilhelm, None; **F. Wang**, None; **N. Schall**, ImmuPharma, 3; **M. Faludi**, None; **J. F. Kleinmann**, None; **E. P. Nashi**, None; **T. Martin**, None; **J. Sibilia**, None; **J. L. Pasquali**, None; **D. Wallace**, None; **S. Muller**, ImmuPharma, 5.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/autophagy-pathway-as-a-target-of-therapeutic-p140-peptide-used-in-lupus

Abstract Number: 1935

Regulation of T Follicular Helper Cells in Systemic Lupus Erythematosus By E3 Ubiquitin Ligase Cbl-b

William Willis[1], Yun Xiao[2], Nicholas A. Young[1], Wael N. Jarjour[1] and Jian Zhang[2], [1]Immunology and Rheumatology, The Ohio State University Wexner Medical Center, Columbus, OH, [2]Microbial Infection and Immunity, The Ohio State University Wexner Medical Center, Columbus, OH
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Background/Purpose: Activation of polyclonal $CD4^+$ T cells and B cells is a hallmark of human and murine **lupus**, which suggests a global defect in the maintenance of T and B cell tolerance. Recent studies unveil a central role of T follicular helper (Tfh) cells that is critical in providing help to B cells in the overproduction of pathogenic auto-antibodies and tissue damage in lupus. However, how Tfh cells are deregulated in lupus in mice and humans is currently unknown. The E3 ubiquitin ligase Cbl-b plays a crucial role in T cell activation, tolerance induction, and Th2 cell differentiation. Cbl-b polymorphisms are linked to human lupus, and furthermore, Cbl-b expression has been shown to be reduced in human lupus T cells. However, the role of Cbl-b in lupus pathogenesis is still poorly defined. In this study, we test the hypothesis that Cbl-b targets Bcl6, the master transcriptional regulator for Tfh cell development, for ubiquitination and degradation in mice.

Methods: We introduced Cbl-b deficiency or a point mutation within RING finger domain of Cbl-b, into *lpr* mice (carrying a mutation in *Fas* gene) on a C57BL/6 background (B6-*lpr.Cblb-/-* and B6-*lpr.CblbC373A*, respectively). To test the feasibility of silencing *Cblb* in human T cells, peripheral $CD4^+$ T cells isolated from peripheral blood mononuclear cells (PBMC) of healthy human donors were transfected with siRNA targeting Cbl-b using liposomal or nucleofection-based methods.

Results: B6-*lpr.Cblb-/-* and B6-*lpr.CblbC373A* mice displayed an exacerbated and severe lupus-like syndrome. This was associated with expanded Tfh cells, GC B cells, and plasma cells in the lymph nodes and spleens and heightened anti-dsDNA titers in the sera. At molecular level, Cbl-b bound to Bcl-6 upon Tfh differentiation condition in a Bcl-6 tyrosine-phosphorylation dependent manner. Furthermore, Bcl-6 ubiquitination and degradation was abrogated in T cells lacking Cbl-b. Consistent with this data, Tfh from SLE patients express lower levels of Cbl-b compared to those from healthy donors.

Conclusion: Our results suggest that that Cbl-b may be the E3 ubiquitin ligase that targets Bcl-6 for degradation. Because both B6-*lpr* and human lupus T cells express significantly less Cbl-b, deregulated Cbl-b expression in human and murine lupus may be a driver of heightened Tfh and GC B cells causing overproduction of pathogenic auto-antibodies.

Disclosure: W. Willis, None; **Y. Xiao**, None; **N. A. Young**, None; **W. N. Jarjour**, None; **J. Zhang**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/regulation-of-t-follicular-helper-cells-in-systemic-lupus-erythematosus-by-e3-ubiquitin-ligase-cbl-b

Abstract Number: 1936

STAT3-Regulated Gene Expression in Circulating CD4+ T Cells Discriminates RA Patients Independently of Clinical Parameters in Early Arthritis: A Validation Study

Arthur G Pratt[1], Amy E. Anderson[1], Dennis W Lendrem[2], Andrew Skelton[2], Jonathan Massey[3], Nisha Nair[3], Julie Diboll[2], Ben Hargreaves[2], Philip M Brown[2], Anne Barton[4,5] and John D Isaacs[2], [1]Institute of Cellular Medicine (Musculoskeletal Research Group), National Institute for Health Research Newcastle Biomedical Research Centre based at Newcastle Hospitals Foundation Trust and Newcastle University, Newcastle upon Tyne, United Kingdom, [2]Institute of Cellular Medicine (Musculoskeletal Research Group), NIHR Newcastle Biomedical Research Centre, Newcastle Hospitals Foundation Trust and Newcastle University, Newcastle upon Tyne, United Kingdom, [3]NIHR Manchester Musculoskeletal Biomedical Research Unit, Manchester Academy of Health Sciences, Manchester, United Kingdom, [4]NIHR Manchester Musculoskeletal Biomedical Research Unit, Manchester Academic Health Science Centre, Manchester, United Kingdom, [5]Arthritis Research UK Centre for Genetics and Genomics, University of Manchester, Manchester, United Kingdom
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Background/Purpose:

A previously described transcriptional signature present in circulating CD4+ T cells of early rheumatoid arthritis (RA) patients implicated STAT3 signalling as an early pathophysiological event[1]. We sought to validate this finding through independent replication and microarray meta-analysis.

Methods:

Microarray technology was used to measure gene expression in highly purified peripheral blood CD4+ T cells from treatment-naïve RA patients and disease controls recruited from an early arthritis clinic. Analysis focussed on 12 transcripts identified during the previous study, and concurrent STAT3 pathway activation was determined in the same cells by flow cytometry. A meta-analysis analysis of previous and current gene expression findings employed multivariate and receiver operator characteristic curve analysis.

Results:

In the independent cohort of 161 patients, normalised expression of 11 of the 12 original signature genes differed significantly between RA patients and controls. Differential regulation was most pronounced for the STAT3 target genes PIM1, BCL3 and SOCS3 (>1.3-fold difference; $p<0.004$), each of whose expression correlated strongly with paired intracellular phospho-STAT3, and these 3 genes' expression accounted for the majority of the signature's ability to segregate diagnoses by hierarchical clustering (Figure 1A). The ability of the same 3 genes, or pairs thereof, to segregate RA patients from disease controls was confirmed in the meta-analysis of 279 patients (E.g. Figure 1B). Moreover, both the 12 gene and the 3 gene signatures added independent discriminatory value to a consideration of clinical parameters including age, swollen/tender joint counts and acute phase response with respect to diagnosis (Figure 1C).

Conclusion:

The STAT3 mediated dysregulation of BCL3, SOCS3 and PIM1 in circulating CD4+ T cells is confirmed as an independent early event in RA pathogenesis. The mechanistic and functional implications of this observation are being investigated.

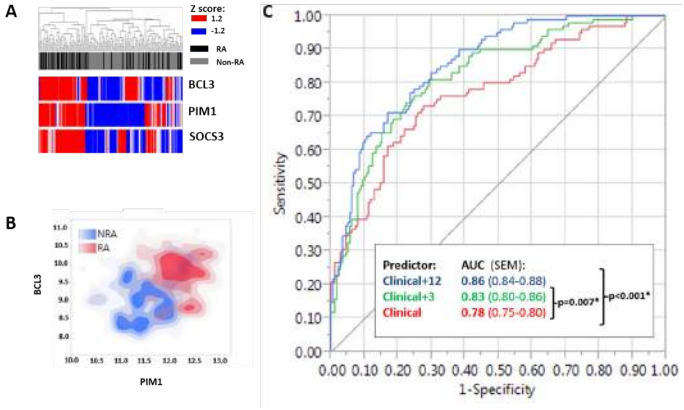

Figure 1. A. Hierarchical clustering based on 3 genes' expression in T cells discriminates early RA patients from disease controls. **B** Non-parametric density plot depicting utility of BCL3 and PIM1 alone in discriminating RA patients. **C**. Adding either a 3 gene or 12 gene CD4+ T cell "signature" to a predictive model based on clinical parameters alone significantly enhanced discrimination of RA from non-RA.

1. Pratt AG et al. 2012; Annals of the Rheumatic Diseases

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Abstract Number: 1937

Dalazatide (ShK-186), a First-in-Class Blocker of Kv1.3 Potassium Channel on Effector Memory T Cells: Safety, Tolerability and Proof of Concept of Immunomodulation in Patients with Active Plaque Psoriasis

Ernesto J. Munoz-Elias[1], David Peckham[1], Kayla Norton[1], Judilyn Duculan[2], Inna Cueto[2], Xuan Li[3], James Qin[4], Kurt Lustig[5], Eric Tarcha[1], Jared Odegard[4], James G. Krueger[2] and Shawn P. Iadonato[1], [1]Kineta Inc, Seattle, WA, [2]Rockefeller University, New York, NY, [3]Rockefeller University, New York, WA, [4]Benaroya Research Institute at Virginia Mason, Seattle, WA, [5]Kineta Inc., Seattle, WA

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Session Title: T cell Biology and Targets in Autoimmune Disease Poster I

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Session Time: 9:00AM-11:00AM

Background/Purpose: Effector memory T cells of both CD4 and CD8 lineages are key drivers of autoimmunity and are pathogenic in several autoimmune diseases including psoriasis, atopic dermatitis, lupus nephritis, and inflammatory bowel disease among others by both human clinical and animal experimental data. Kv1.3 is a potassium channel required for sustained intracellular calcium influx, proliferation and activation of effector memory T cells. Dalazatide (ShK-186) is a potent, highly specific, first-in-class peptide blocker of Kv1.3 and effector memory T cells. Here we report on the safety, tolerability, pharmacodynamics and immunomodulating proof-of-concept data for dalazatide from a phase Ib study in patients with active plaque psoriasis.

Methods: A double blind trial was conducted in patients with active mild to moderate plaque psoriasis. Cohorts received either 30 mcg (n=10), 60 mcg (n=10 or placebo (n=4) twice weekly subcutaneous injections for 4 weeks with 4 weeks of follow up. Skin lesion biopsies were collected at baseline and at week 4 post treatment for gene expression and immunohistological analyses. Plasma, serum and peripheral blood mononuclear cells were collected at baseline and at several times during the study. Target lesions were evaluated at baseline and at day 32.

Results: The treatment was well tolerated with all subjects completing the study and reporting only mild adverse events. 50% of subjects in 60 mcg group achieved clinical improvement in target lesion. Improvements were observed as early as day 15 and for up to 4 weeks following last dose (day 57, end-of-study). Ongoing improvement continued during follow-up period in some subjects. 90% of subjects in 60 mcg group had reduction in PASI score.

Conclusion: These results demonstrate that twice weekly subcutaneous dosing of Kv1.3 blocker dalazatide is safe and well tolerated in psoriasis patients. Improvement in clinical disease endpoints provides proof-of-concept data for the immunomodulating mechanism of action of dalazatide in a prototypical T cell mediated autoimmune disease

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Disclosure: E. J. Munoz-Elias, Kineta Inc, 3; **D. Peckham**, Kineta Inc, 3; **K. Norton**, Kineta Inc, 3; **J. Duculan**, None; **I. Cueto**, None; **X. Li**, None; **J. Qin**, None; **K. Lustig**, Kineta Inc, 3; **E. Tarcha**, Kineta Inc, 3; **J. Odegard**, None; **J. G. Krueger**, None; **S. P. Iadonato**, Kineta Inc, 3.

Abstract Number: 1938

Engaging PD-1 Resuscitates Synovial Treg Cells and Dampens the Joint Infiltrating T Cells in Rheumatoid Arthritis

Dipendra Kumar Mitra[1] and Kaustav Chowdhury[2], [1]Transplant Immunology & Immunogenetics, All India Institute of Medical Sciences, Delhi, India, [2]TRANSPLANT IMMUNOLOGY AND IMMUNOGENETICS, ALL INDIA INSTITUTE OF MEDICAL SCIENCES, New Delhi, India
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Background/Purpose:

Enrichment of regulatory T cells (Treg) has been reported in the synovial fluid (SF) of RA patients, although they fail to alleviate the joint inflammation. These cells utilize programed death receptor-1 (PD-1) mediated pathway to dampen the effector T cell response. We hypothesized that deficit in the PD-1 pathway may be responsible for functional incapacitation of locally accumulated Treg cells in RA patients. To understand the cause of the failure of locally enriched Treg cells in controlling synovial inflammation, we investigated the role of PD-1 in modulating the function of the infiltrating T cells. Here, we demonstrate that lack of PD-L1 on synovial machorphages ($CD14^+$ cells) incapacitates the Treg cells and engaging PD-L1 can functionally resuscitate the Treg cells and dampens the inflammatory T cells.

Methods:

We isolated mononuclear cells from peripheral blood (PBL) and synovial fluid (SF) 25 active RA patients. Surface expression of PD-1 and its ligand (PD-L1) were seen on Treg cells and macrophages ($CD14^+$) by the use of flowcytometry. Anti inflammatory cytokine IL-10, TGF-β in Treg ($CD4^+FoxP3^+$) and proinflammatory cytokines IFN-γ, IL-17A, TNF-α in effector T cells ($CD4^+$) were measured with FACS based intracellular staining after treatment with PD-L1 Fusion chimeric protein (PD-L1 Fc) in presence of TCR engagement.

Results: Our result shows that synovial Treg cells are compromised in their IL-10, TGF-β production in-spite of local enrichment of $PD\text{-}1^+$ Treg ($CD4^+FOXP3^+$) cells. Engaging PD-1 with PD-L1 Fc, IL-10 & TGF-β production by Treg cells. Interestingly, this was accompanied by simultaneous decrease in the frequency of synovial $IFN\text{-}\gamma^+$, $TNF\text{-}\alpha^+$, $IL\text{-}17A^+$ effector T cells and their proliferation. Moreover, blocking IL-10, TGF-β with specific antibody in similar condition(s) failed to suppress the infiltrating T cells of synovial fluid. This suggests, that deficit of PD-1 mediated suppressive pathway incapacitates the locally accumulated Treg cells.

Conclusion:

Our results indicate that deficit of PD-1 mediated suppressive pathway incapacitates the locally accumulated Treg cells and engaging PD-1 may restore the suppressive function of synovial Treg cells via IL-10, TGF-β production. Rejuvenating synovial Treg cells may be used to ameliorate the joint inflammation in rheumatoid arthritis.

Disclosure: D. K. Mitra, None; **K. Chowdhury**, None.

Abstract Number: 1939

Anti-GM-CSF Treatment Promotes Synovial Monocyte-Derived Dendritic Cells and Increases Th17 Cells during Experimental Arthritis

Debbie M. Roeleveld[1], Peter M. van der Kraan[1], Wim B. van den Berg[1], Ian P. Wicks[2] and Marije I. Koenders[1], [1]Experimental Rheumatology, Radboud university medical center, Nijmegen, Netherlands, [2]Inflammation Division, Walter and Eliza Hall Institute of Medical Research, Parkville, Australia
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Background/Purpose: Monocyte-derived dendritic cells (MoDCs) differentiate from monocytes under inflammatory conditions like RA, and are very potent in presenting antigen to T cells. GM-CSF-responsive MoDCs have been shown to promote Th17 cell differentiation during experimental autoimmune encephalomyelitis (EAE). Since the pathogenicity of Th17 cells in EAE has been associated with the production of both IL-17 and GM-CSF, this introduces an interesting feedback-loop within the suggested MoDC-Th17 pathway. In this study, we aimed to further elucidate this GM-CSF/Th17 pathway by determining the contribution of GM-CSF-producing cells in driving synovial MoDC levels and promoting Th17 differentiation during experimental arthritis. In addition, we analyzed the GM-CSF expression by CD4+ T cells under Th17 differentiation conditions to further unravel the interaction between these two cytokines.

Methods: Arthritis was elicited in C57Bl/6 mice by intra-articular injections of methylated BSA in combination with subcutaneous injection of IL-1β. To investigate the *in vivo* role of GM-CSF in synovial MoDC and Th17 development, the mice were treated with anti-GM-CSF or control antibodies on day 0, 2, and 4 after arthritis induction. Synovial MoDC and Th17 levels were determined 7 days after arthritis onset. To elucidate which GM-CSF-producing cellular compartment is mainly responsible for synovial MoDC and Th17 development, bone marrow (BM) chimeras were created by transferring BM of GM-CSF knockout mice to irradiated wild-type mice or vice versa, and MoDC and Th17 levels were determined by FACS on synovial tissue 7 days after arthritis induction. In addition, GM-CSF expression by Th17 cells was studied *ex vivo* using naïve murine CD4+ T cells differentiated under various culturing conditions, and both Th17 differentiation efficacy and GM-CSF levels were assessed.

Results: Unexpectedly, inhibiting the GM-CSF pathway during murine experimental arthritis using neutralizing antibodies increased MoDC levels in the arthritic synovium. Interestingly, the percentage of synovial Th17 cells was also increased by this anti-GM-CSF treatment, suggesting a negative feedback of GM-CSF on Th17 development. Our study using bone marrow chimera mice showed that particularly mice deficient for BM-derived GM-CSF had increased levels of synovial MoDCs as well as Th17 cells, confirming the antagonistic regulation of MoDCs and Th17 cells by GM-CSF. Finally, our *ex vivo* studies showed that, while Th17 cells did not produce much GM-CSF, differentiation of naïve T cells under conditions suboptimal for Th17 development resulted in increased levels of GM-CSF, indicating deviating differentiation conditions and antagonistic regulation of IL-17 and GM-CSF by CD4+ T cells.

Conclusion: Our experiments are the first to demonstrate increased levels of synovial MoDCs and Th17 cells after anti-GM-CSF treatment, confirming a loop between GM-CSF and differentiation of MoDCs and Th17 cells. However, contradictory to what has been shown in EAE, GM-CSF was shown to have a negative impact on this loop. This negative regulation between GM-CSF and Th17 cells provides further rationale for a combination blocking strategy of IL-17 and GM-CSF in the treatment of RA.

Disclosure: D. M. Roeleveld, None; **P. M. van der Kraan**, None; **W. B. van den Berg**, None; **I. P. Wicks**, None; **M. I. Koenders**, None.

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A Circulating Reservoir of Pathogenic-like CD4+ T Cells Shares a Genetic and Phenotypic Signature with the Inflamed Synovial Micro-Environment

Roberto Spreafico[1,2], **Maura Rossetti**[1,2], Jorg van Loosdregt[1], Carol A. Wallace[3], Margherita Massa[4], Silvia Magni-Manzoni[5], Marco Gattorno[6], Alberto Martini[7], Daniel Lovell[8,9] and Salvatore Albani[2,10], [1]Sanford-Burnham Medical Research Institute, La Jolla, CA, [2]SingHealth Translational Immunology and Inflammation Centre, Singapore Health Services Pte Ltd, Singapore, Singapore, [3]Seattle Children's Hospital and Research Institute, Seattle, WA, [4]Lab Biotecnologie, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy, [5]Pediatric Rheumatology, IRCCS Ospedale Pediatrico Bambino Gesù, Rome, Italy, [6]Instituto Giannina Gaslini and University of Genova, Genova, Italy, [7]Istituto G. Gaslini, Universita' di Genova, Genova, Italy, [8]Cincinnati Children's Hospital Medical Center, Cincinnati, OH, [9]Rheumatology, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, [10]Duke-National University of Singapore Graduate Medical School, Singapore, Singapore

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Background/Purpose: Systemic immunological processes are profoundly shaped by the micro-environments where antigen recognition occurs. Identifying molecular signatures distinctive of such processes is pivotal to understand pathogenic immune responses and manipulate them for therapeutic purposes. Unfortunately, direct investigation of peripheral tissues, enriched in pathogenic T cells, is often impossible or imposingly invasive in humans. Conversely, blood is easily accessible, but pathogenic signatures are diluted systemically as a result of the strict compartmentalisation of immune responses. In this work, we aimed at defining immune mediators shared between the bloodstream and the synovial micro-environment, and relevant for disease activity in autoimmune arthritis.

Methods: CD4+ T cells from blood and synovium of patients with juvenile idiopathic arthritis (JIA) were immunophenotyped by flow cytometry. The TCR repertoire of a circulating subset showing similarity with the synovium was analysed through next-generation sequencing to confirm enrichment in synovial clonotypes. Finally, clinical relevance was established by monitoring this subset in the blood of patients with JIA and rheumatoid arthritis (RA).

Results: A small subset of circulating CD4+ T cells replicated the phenotypic signature of lymphocytes infiltrating the inflamed synovium. These circulating pathogenic-like lymphocytes (CPLs) were enriched in synovial clonotypes and exhibited strong production of pro-inflammatory cytokines. Importantly, CPLs were expanded in JIA patients not responding to therapy, and also correlated with disease activity in patients with RA.

Conclusion: CPLs provide an accessible reservoir of pathogenic cells recirculating into the bloodstream and correlating with disease activity, to be exploited for diagnostic and research purposes.

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View Abstract and Citation Information Online - http://acrabstracts.org/abstract/a-circulating-reservoir-of-pathogenic-like-cd4-t-cells-shares-a-genetic-and-phenotypic-signature-with-the-inflamed-synovial-micro-environment

Abstract Number: 1941

Senescent T-Cells Expedite RANKL-Dependent Bone Loss in Rheumatoid Arthritis

Johannes Fessler[1], Rusmir Husic[2], Elisabeth Lerchbaum[3], Verena Schwetz[3], Claudia Stiegler[3], Barbara Obermayer-Pietsch[3], Winfried B. Graninger[4] and Christian Dejaco[5], [1]Rheumatology and Immunology, Medical University Graz, Graz, Austria, [2]Rheumatology, Medical University Graz, Graz, Austria, [3]Division of Endocrinology and Metabolism, Medical University Graz, Graz, Austria, [4]Internal Medicine/Rheumatology, Medical University Graz, Graz, Austria, [5]Department of Rheumatology and Immunology, Medical University Graz, Graz, Austria
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Background/Purpose:

To study the influence of senescent $CD28^-$T-cells on systemic osteoporosis in rheumatoid arthritis (RA) and patients with primary osteoporosis.

Methods:

Prospective, cross-sectional study on 104 patients with RA (mean age 62.2 [±SD 12.6], 76% female, SDAI 13.5 [±10.2]) and 111 non-RA controls (mean age 60.7 [±11.3], 84.7% female). Bone mineral density (BMD) was determined by DEXA. PBMCs were retrieved at the same day of BMD measurement and were stained with anti-RANKL, CD3, CD4, CD8, CD45RA, CD45RO and/or CD28 mAbs to measure surface and intracellular expression of RANKL on T-cells and to determine the prevalence of T-cell subsets by flow cytometry. The capacity of T-cell subsets to induce osteoclastogenesis was assessed via TRAP staining in the presence of monocytes and M-CSF (25ng/ml) *in vitro*.

Results:

A reduced BMD as determined by DEXA was found in 58.1% of RA patients (14% with osteoporosis, 44.1% with osteopenia) and 56.1% of non-RA controls (38.8% with osteoporosis, 17.3% with osteopenia). RA patients with reduced BMD had higher prevalences of circulating $CD4^+CD28^-$ (3.2% [0.1–41.2] vs. 0.7% [0.1–33.9], p=0.048). In non-RA controls we observed the same effect (3.5% [0.1–30.4] vs. 1.3% [0.1–34], p=0.032).

Surface RANKL expression was higher on $CD4^+CD28^-$ T-cells (3.1% [0-57.9]) compared to naïve $CD4^+CD28^+CD45RA^+$ (1.5 [0-45.3], p<0.001) and memory $CD4^+CD28^+CD45RO^+$ (1.9 [0-38], p=0.006) T-cells. Moreover, surface RANKL expression was higher in RA patients than non-RA controls in all T-cell subsets (all p<0.05). After stimulation with anti-CD3 antibody, RANKL production was higher in $CD4^+CD28^-$ T-cells (intracellular RANKL MFI: 870.2 [±205.9]) compared to naïve $CD4^+CD28^+CD45RA^+$ (713 [±182.3], p=0.001) T-cells, whereas RANKL levels were similar in $CD4^+CD28^-$ T-cells and memory $CD4^+CD28^+CD45RO^+$ (862.2 [±289.7], p=0.207) T-cells. Similar results were obtained after stimulation with PHA or ConA.

The *in vitro* ability of T-cell subsets to induce osteoclastogenesis was higher in senescent $CD28^-$ T-cells compared to their $CD28^+$ counterparts as indicated by TRAP-staining ((27.5 [±15.8] TRAP positive cells vs. 20.5 [±7.9], p=0.128).

Conclusion:

Senescent $CD28^-$ T-cells are linked with the occurrence of systemic bone loss. Increased expression of RANKL on $CD4^+CD28^-$ T-cells compared to other T-cell subsets may result in higher direct stimulation of osteoclastogenesis by this subset.

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Abstract Number: 1942

B Cell Depletion By Rituximab in Lymphocyte Subpopulations from Peripheral Blood in Patients with Rheumatoid Arthritis

Leticia Merino-Meléndez[1], Jorge López-López[2], Irene Llorente[1], Santos Castañeda[3], Federico Herrera[2], Teresa Velasco[4], Lorena Vega[5], Francisco Rodriguez[5], Jose María Alvaro-Gracia[3], Rosario Garcia-Vicuña[6], Cecilia Muñoz-Calleja[2] and Isidoro Gonzalez-Alvaro[7], [1]Rheumatology, H.U. La Princesa, Madrid, Spain, [2]Immunology, Hospital Universitario de La Princesa, Madrid, Spain, [3]Hospital Universitario de La Princesa. IIS La Princesa, Madrid, Spain, [4]Rheumatology, H.U La Princesa, Madrid, Spain, [5]H.U. La Princesa, Madrid, Spain, [6]Rheumatology, Hospital Universitario de La Princesa. IIS La Princesa, Madrid, Spain, [7]Hospital Univ. de La Princesa, IIS Princesa, Madrid, Spain
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Background/Purpose: Rheumatoid arthritis (RA) is a chronic disease that leads to inflammation of the joints and other tissues. Rituximab (Rtx) is a therapeutic monoclonal antibody directed against CD20 that induces an important depletion of B cells. Although little is known about how it modifies the homeostasis of lymphoid subpopulations, it has been successfully used in RA.

The objective of this study was to know whether Rtx modifies the ratio of the different lymphocyte subpopulations from peripheral blood in RA patients.

Methods: We studied 62 RA patients that underwent treatment with Rtx because of active RA and failure to at least one previous anti-rheumatic drug. The patients were divided into those naïve for Rtx treatment (RtxN n=21) and those who had received at least one previous cycle of treatment with Rtx (RtxS n=41). Peripheral blood samples for lymphoid subpopulation analysis were obtained at different times in both RtxN and RtxS patients: before the first infusion of Rtx (baseline) and at 3, 6 and 8 months after it (T3, T6 and T8 respectively).

We studied different combinations of molecules that allowed us to calculate the percentage of T cell subpopulations, including memory and naïve T cells, effector and central memory T cells, follicular T helper cells and regulatory T cells. In the case of B cells, we analyzed memory and naïve B cells, Marginal Zone B cells, follicular B cells and plasmablasts B cells, at each visit. Differences between groups were analyzed by ANOVA test.

Results: At baseline, there was a significant difference in the percentage of a considerable number of B cell subsets. In particular, we observed an important decrease in memory B cells and an increase in follicular B cells. We also detected an increase in CD38+CD24+CD10+ B cells in RtxS.

Regarding T cell subpopulations, we only observed a significant decrease in Th17 cells and in follicular T helper cells in RtxS.

During the follow up period, the differences in T cells observed at baseline became much smaller presumably because of the effects of Rtx. At T3 only CD4 + T cells and memory T cells, defined by the absence of CD62L, were significantly lower in RtxS.

At T6, we observed an increase in the CD8+CCR6- CXCR6- subpopulation in RtxS.

At T8, as some patients had already repopulated B cell subsets, we found differences in B cells, and we detected a decrease in the CD38- B cell population. Taking into account the T cell population, we noted an increase in total T cells in RtxS with a significant decrease in effector-memory T cells.

Conclusion: Depletion of B cells through Rtx treatment leads to a profound change in the subpopulations of peripheral blood B cells, due to repopulation, and also of T cells. This suggests that mature B cells play a relevant role in the homeostasis of T cells.

Acknowledgements: L. Merino and J. López have contributed equally to this work.

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Abstract Number: 1943

Potent and Selective Tyk2 Inhibitors Block Th1- and Th17- Mediated Immune Responses and Reduce Disease Progression in Rodent Models of Delayed-Type Hypersensitivity and Psoriasis

Wenyan Miao[1], Craig Masse[1], Jeremy Greenwood[2], Rosana Kapeller[1] and William Westlin[1], [1]Nimbus Therapeutics, Cambridge, MA, [2]Schrodinger Inc., New York, NY
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Background/Purpose: Tyk2 is a member of the JAK family kinases and is a key mediator of IL-12, IL-23, and type I interferon signaling. These cytokines have been implicated in the pathogenesis of multiple inflammatory and autoimmune diseases such as lupus, psoriasis and inflammatory bowel diseases. Supported by compelling data from human genetic association studies, Tyk2 inhibition is an attractive therapeutic strategy for these diseases.

Methods: One of the challenges of developing selective Tyk2 inhibitors is the high sequence homology of the active site among the members of the JAK family kinases. We utilized cutting edge proprietary structure-based drug design tools to identify highly potent and selective inhibitors of Tyk2. These inhibitors were characterized for their potency and selectivity in the enzyme and cell-based assays, and in mouse models of delayed type hypersensitivity and psoriasis.

Results: We have identified Tyk2 inhibitors with up to 720-, 540-, and 210-fold selectivity against JAK1, JAK2, and JAK3 respectively, with potent cellular activity and excellent cellular selectivity against other JAK family kinases in human peripheral blood mononuclear cells. NDI-031301 is a Tyk2 inhibitor with a Ki of 0.5 nM that is 107-, 85-, and 15-fold selective against JAK1, JAK2, and JAK3 respectively. It blocks IL-12 induced phospho-STAT4 and GM-CSF induced phospho-STAT5 in human PBMCs with $IC_{50}$of 0.1 μM and 2.6 μM, respectively. NDI-031301 has excellent selectivity against a panel of 364 kinases, showing less than 70% inhibition at 300 nM against all but 16 of the kinases tested. It also showed less than 50% inhibition up to 30 μM against human CYP enzymes and hERG channel. In addition, NDI-031301 has an attractive PK profile with good oral bioavailability in rodents and dogs. Studies with humans carrying inactive forms of Tyk2 and mice deficient in Tyk2 revealed a role in Th1 and Th17 polarization. We investigated the in vivo activity and mechanism of action of Nimbus Tyk2 inhibitors in a methylated-BSA induced mouse delayed type hypersensitivity model. At 100 mg/kg dose, orally administered NDI-031301 reduced paw swelling and paw weight, as well as Th1 (IFNγ) and Th17 (IL-17A and IL-22) cytokines in the inflamed paws by more than 50%. It also dramatically reduced Th1 cells in the draining lymph nodes and suppressed over 85% of in vitro antigen-induced IFNγ response in the draining lymph node cells. In an IL-23-induced mouse psoriasis model, NDI-031301 dose-dependently reduced skin inflammation with up to 76% inhibition of ear swelling at 100 mg/kg, highlighting the role of Tyk2 inhibition in Th17 pathogenesis. Finally, NDI-031301 was highly efficacious in an imiquimod-induced mouse psoriasis model, showing dose-dependent reduction of psoriasis score, spleen weight, and improved skin histology. 30 mg/kg of NDI-031301 treatment blocked disease progression and 100 mg/kg treatment reversed the disease.

Conclusion: Utilizing unique and innovative structure-based drug design technologies, we rapidly designed highly potent and selective Tyk2 inhibitors for use as potential therapeutics in inflammatory disorders involving Th1, Th17, and type I interferon pathogenesis.

Disclosure: W. Miao, Nimbus Therapeutics, 3; **C. Masse**, Nimbus Therapeutics, 3; **J. Greenwood**, Schrondinger Inc., 3; **R. Kapeller**, Nimbus Therapeutics, 3; **W. Westlin**, Nimbus Therapeutics, 3.

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Abstract Number: 1944

Dalazatide Modulates CD4+ Effector Memory T-Cell Activity of Patients with Granulomatosis with Polyangiitis in Vitro

Lucas L. Lintermans[1], Ernesto J. Muñoz-Elías[2], Minke G. Huitema[1], Elisabeth Brouwer[1], Abraham Rutgers[1], Coen A. Stegeman[3], Peter Heeringa[4] and Wayel H. Abdulahad[1], [1]Rheumatology and Clinical Immunology, University Medical Center Groningen, University of Groningen, Groningen, Netherlands, [2]Translational Immunology & Preclinical Development, Kineta, Inc., Seattle, WA, [3]Nephrology, University Medical Center Groningen, University of Groningen, Groningen, Netherlands, [4]Pathology and Medical Biology, University Medical Center Groningen, University of Groningen, Groningen, Netherlands
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Session Time: 9:00AM-11:00AM

Background/Purpose: There is substantial evidence that $CD4^+$ effector memory T (T_{EM}) cells play a crucial role in the pathogenesis of Granulomatosis with polyangiitis (GPA). The activation of $CD4^+$ T_{EM}-cells is uniquely dependent on the voltage-gated potassium Kv1.3 channel. Blocking Kv1.3 channels with the exquisitely specific, highly potent peptide inhibitor dalazatide (formerly ShK-186) has been shown to ameliorate autoimmune disease in animal

models of multiple sclerosis and rheumatoid arthritis. Therefore, selective targeting of pathogenic $CD4^+$ T_{EM}-cells is a very promising selective treatment for GPA patients. The aim of this study is to modulate $CD4^+$ T_{EM}-cell activity via Kv1.3 blockade using a specific peptide inhibitor dalazatide in peripheral blood of GPA patients *in vitro*.

Methods: Peripheral blood of remission GPA patients (R-GPA; *n=24*) and age- and sex-matched healthy controls (HCs; *n=15*) was stimulated *in vitro* with PMA/Ca-Ionomycin in the presence and absence of the Kv1.3 blocker, dalazatide. After stimulation cells were fixed, permeabilized and stained for surface markers (CD3, CD8, CD45RO and CCR7), and intracellular cytokines (IL-4, IL-17, IL-21, IFNγ and TNFα). Relative frequencies of pro-inflammatory cytokine expression were assessed within total $CD4^+$ T-cells and $CD4^+$ T-cell subsets using flow cytometry. Unstimulated samples were used as a guide to delineate positive and negative populations for the cytokine production.

Results: The percentage of $CD4^+$ T_{EM} cells was significantly increased in R-GPA patients compared to HCs. The intracellular cytokine production in total $CD4^+$ T-cells after stimulation was significantly increased in R-GPA patients compared to HCs. Dalazatide suppressed the intracellular cytokine production in total $CD4^+$ T-cells of GPA patients, in a dose dependent manner, to levels observed in stimulated total $CD4^+$ T-cells of HCs. Similar assays performed in sorted $CD4^+$ T-cell subsets revealed that dalazatide predominantly inhibited cytokine production in $CD4^+$ T_{EM}-cells, whereas cytokine production by naïve- and central memory $CD4^+$ T-cells was unaffected. production.

Conclusion: The selective Kv1.3 blocker, dalazatide modulates $CD4^+$ T-cell activity in GPA patients *in vitro*. Importantly, dalazatide was able to normalize the pro-inflammatory cytokine production in $CD4^+$ T cells from GPA patients. Furthermore, the effect of dalazatide predominantly affects $CD4^+$ T_{EM}-cells by reducing intracellular cytokine production while sparing other $CD4^+$ T-cell subsets. These data indicate that dalazatide may hold therapeutic promise in the treatment of GPA by selectively targeting $CD4^+$ T_{EM}-cells. duction by naïve- and central memory $CD4^+$ T-cells was unaffected. production.

Disclosure: L. L. Lintermans, None; **E. J. Muñoz-Elías**, Kineta, Inc., 3; **M. G. Huitema**, None; **E. Brouwer**, Abbvie, 2,Pfizer Inc, 2; **A. Rutgers**, None; **C. A. Stegeman**, None; **P. Heeringa**, None; **W. H. Abdulahad**, None.

Abstract Number: 1945

microRNA-30a Promotes the Inflammatory Response of Rheumatoid Arthritis By Regulating Th1 Cell Differentiation

Jing Zhang[1], HUA YE[2], Jianping Guo[1], Yan Du[3], Mengru Liu[1] and Zhanguo Li[4], [1]Department of Rheumatology and Immunology, Peking University People's Hospital, Beijing, China, [2]No.11 XIZHIMENG SOUTH STREET,, Peking University People's Hospital, Beijing, China, [3]Department of Rheumatology and Immunology, The Second Affiliated Hospital, School of Medicine, Zhejiang University, Zhejiang, China, [4]Peking University People's Hospital, Beijing, China

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SESSION INFORMATION

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Session Title: T cell Biology and Targets in Autoimmune Disease Poster I

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: In our previous study, the transcriptome profiles of $CD4^+$T cells from 13 active RA cases and 9 healthy controls were accessed by microarrays. a total of 1496 differential genes were identified. To investigate whether these significant differential genes were regulated by miRNAs, further studies were carried out for the new regulating effect of miRNAs in $CD4^+$T cell, the results not only benefit to understanding the pathogenesis of RA, but also explore a new strategy for immunotherapy of RA.

Methods: Peripheral blood $CD4^+$T cells isolated from RA patients and healthy individuals were performed by microarray analysis. The selected candidate genes and miRNA were validated by quantitative real-time PCR (qPCR). Dual luciferase reporter assay system and western blot were used to validate the direct function of miR-30a and SOCS3. In order to determine whether miR-30a affects IL-6 or IFN-r-mediated JAK-STAT pathway by targeting SOCS3. We transfected a synthetic miR-30a mimic or its inhibitor in Jurcat cells, Western Blot was used to detect the SOCS3 and STAT3 protein level after stimulated by IL-6 or IFN-r. To investigate the potential differentiation effect of miR-30a, we over-expressed miR-30a in naïve T cell, and T cell subsets were tested by Flow cytometry. To further show that miR-30a plays a significant role in RA pathogenesis, we constructed CIA models, the synthesis miR-30a antagomir or NC antagomir were injected by tail vein respectively. After injection for 70 days, H&E staining and micro-computed tomography (micro-CT) confirmed that the inflammatory infiltration and bone erosion was reduced in the group of miR-30a antagomir CIA mice compared to the control group.

Results: MiR-30a expression increased in RA patients compared to controls, and it markedly repressed the reporter activity of the 3'untranslated regions (UTRs) of SOCS3, mutation of the 3' UTRs of the repressed gene confirmed that SOCS3 was the target of miR-30a. Consistent with the reporter assays, the expressions of endogenous SOCS3 protein were decreased in 293T cells by over-expression of miR-30a mimic. Over expression of miR-30a increased the phosphorylation level of STAT3, which may be regulated by the IL-6/IFN-r-mediated JAK-STAT activation pathway. Th1 subsets was remarkable higher in naïve T cells transfected by miR-30a mimic, which suggested that miR-30a may promote the differentiation of $CD4^+$T cells, but had no effect in the proliferation. In our animal experiment, the clinical core of CIA mice were lower in the miR-30a antagomir mice (micro-CT) confirmed that inflammatory

infiltration and bone erosion were relieved in the miR-30a antagomir mice.

Conclusion: Over expression of miR-30a in CD4+T cell inhibited the protein level of SOCS3 and promoted the differentiation of Th1 cell, which may be regulated by the IL-6/IFN-r-mediated JAK-STAT pathway. The results also provide evidence that down-regulating expression of miR-30a in CIA mice decreased the arthritis score, as well as reduce the degree of bone erosion and cell invasion.

Disclosure: J. Zhang, None; **H. YE**, None; **J. Guo**, None; **Y. Du**, None; **M. Liu**, None; **Z. Li**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/microrna-30a-promotes-the-inflammatory-response-of-rheumatoid-arthritis-by-regulating-th1-cell-differentiation

Abstract Number: 1946

A Novel HLA-DRB1*10:01 Restricted T Cell Epitope from Citrullinated Type II Collagen Relevant for Rheumatoid Arthritis

Karine Chemin[1], Sabrina Pollastro[2], Eddie James[3], Changrong Ge[4], Inka Albrecht[5], Jessica Herrath[6], Christina Gerstner[7], Thais Rizzi[2], Karolina Tandre[8], Lars Rönnblom[8], Anca I Catrina[9], Rikard Holmdahl[10], L. Klareskog[11], Niek De Vries[12] and Vivianne Malmström[11], [1]Medicine, Rheumatology Unit, Department of Medicine, Solna, Karolinska Institutet, Stockholm, Sweden, [2]Department of Clinical Immunology and Rheumatology, Amsterdam, Netherlands, [3]Benaroya Research Institute at Virginia Mason, Seattle, WA, [4]Department of Medical Biochemistry and Biophysics, Medical Inflammation Research, Karolinska Institute, Stockholm, Sweden, [5]Rheumatology Unit, Department of Medicine, Solna, Karolinska Institutet, Stockholm, Sweden, [6]Department of Medicine,, Rheumatology Unit, Department of Medicine, Solna, Karolinska Institutet, Stockholm, Sweden, [7]Department of Medicine, Rheumatology Unit, Karolinska University Hospital, Solna, Stockholm, Sweden, [8]Section of Rheumatology, Department of Medical Sciences, Uppsala University, Uppsala, Sweden, [9]Unit of Rheumatology, Department of Medicine Solna, Karolinska University Hospital, Karolinska Institutet, Stockholm, Sweden, [10]Department of Medical Biochemistry and Biophysics, Karolinska Institutet, Stockholm, Sweden, [11]Rheumatology Unit, Department of Medicine, Karolinska Institutet, Stockholm, Sweden, [12]Dept. of Clinical Immunology & Rheumatology, Amsterdam Rheumatology and immunology Center, Academic Medical Center/University of Amsterdam, Amsterdam, Netherlands

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Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose:

Antibodies against citrullinated collagen type II (Cit-CII) are common in sera and synovial fluids of Rheumatoid Arthritis (RA) patients, whereas the known CII T-cell epitope is not dependent on citrullination. This study aimed to identify Cit-CII restricted T-cell epitopes relevant to RA and to functionally characterize Cit-CII specific CD4+ T cells with regard to immune function and TCR Vbeta signatures.

Methods: PBMCs from HLA-DRB1*10:01 positive RA patients and healthy donors were stimulated with candidate peptides in vitro. CD154 up-regulation was utilized as a marker of antigen-specific activation. One citrullinated peptide, Cit-CII(311-325) was able to activate CD4+ T cells and was selected for further analysis. Cytokine production measurement by Luminex technology and anti-DR blocking experiments were conducted. Direct binding assays using HLA-DRB1*10:01 and *04:01 monomers were performed. Antigen-specific T cells were CD154-enriched and their T-Cell Receptor (TCR) Vbeta chain was sequenced with high-throughput sequencing.

Results:

A new citrullinated CII peptide was identified based on its ability to activate CD4+ T cells from HLA-DRB1*10:01individuals. When stimulated in vitro, Cit-CII autoreactive T cells produced pro-inflammatory cytokines. Cit-CII(311-325) binds with low affinity to HLA-DRB1*10:01 but not to HLA-DRB1*0401 while the native version was unable to bind either of them. Finally, Highly Expanded Clones (HECs) were identified in the TCR Vbeta repertoire of Cit-CII(311-325) stimulated PBMCs.

Conclusion:

These results illustrate the ability of the citrullination process to create T-cell epitopes from CII, a cartilage-restricted protein relevant to RA pathogenesis. The exclusive binding of Cit-CII(311-325) to HLA*DRB1*10:01 suggests that citrulline T-cell autoimmunity might vary between individuals carrying different RA-associated HLA-DR molecules.

Disclosure: K. Chemin, None; **S. Pollastro**, None; **E. James**, None; **C. Ge**, None; **I. Albrecht**, None; **J. Herrath**, None; **C. Gerstner**, None; **T. Rizzi**, None; **K. Tandre**, None; **L. Rönnblom**, None; **A. I. Catrina**, None; **R. Holmdahl**, None; **L. Klareskog**, None; **N. De Vries**, None; **V. Malmström**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/a-novel-hla-drb11001-restricted-t-cell-epitope-from-citrullinated-type-ii-collagen-relevant-for-rheumatoid-arthritis

Abstract Number: 1947

Hypermethylation of Treg-Specific Demethylated Regions in the Ikaros Transcription Factor Family Members, Helios and Eos, in Rheumatoid Arthritis Tregs

Alla Skapenko[1], Viktoria Soentgerath[1], Sonja Haupt[2], Jan Leipe[1] and Hendrik Schulze-Koops[1], [1]Division of Rheumatology and Clinical Immunology, University of Munich, Munich, Germany, [2]Division of Rheumatology and Clinical Immunology, Med.Klinik und Poliklinik IV, University of Munich, Munich, Germany

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Session Title: T cell Biology and Targets in Autoimmune Disease Poster I

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: Foxp3 is the signature transcription factor of regulatory T cells (Tregs) and facilitates many of the characteristic functions of Tregs. Members of the Ikaros family of transcription factors have been implicated in controlling the phenotype of Tregs, in part by interacting with Foxp3. Ikaros family zinc finger 4 (IKZF4, Eos) mediates Foxp3-dependent gene silencing and is required to maintain the phenotype of Foxp3-positive Tregs, whereas IKFZ2 (Helios) is involved in the suppression of IL2 gene transcription and upregulation of Foxp3. An important regulation level of tissue-specific geneexpression is DNA methylation. In particular, Treg-specific gene expression is controlled by DNA methylation within characteristic clusters, Treg-specific demethylation regions.

Methods: To analyze the DNA methylation status of Treg-specific demethylated regions (TSDR) of Foxp3, Helios and Eos in T cells from patients with rheumatoid arthritis (RA) and to compare the level of methylation to that in T cells from healthy controls.

Results: All analyzed regions were completely methylated in effector T cells from RA patients and controls. In contrast, considerable degrees of demethylation were detected in the regions of interest in CD25+CD127- T cells, in line with the hypothesis of an important regulatory mechanism facilitating Treg-specific gene expression. No differences were detected between Tregs from RA patients and controls with regard to the level of methylation within the TSDR of FoxP3. Importantly, the methylation rate of the CNS CpG island in the Helios gene was significantly higher in Tregs from RA patients than in those from controls (55% vs. 40%, $p<0.05$). Similarly, the CpGs within exon 6 of the Helios gene were demethylated to a significantly different level between RA patients and controls (50% vs. 40% methylation, respectively; $p<0.05$). Finally, in the CNS CpG island of the Eos gene, the methylation level in Tregs from RA patients was also significantly higher as compared to healthy control Tregs (68% vs. 53%, $p<0.01$).

Conclusion: The data are consistent with the hypothesis of Treg specific expression of Helios and Eos regulated by DNA methylation within Treg-specific demethylation regions. Furthermore, the data suggest that impaired function Tregs in RA might be related to an altered expression of Helios and Eos as a consequence of increased DNA methylation. This mechanism might provide a molecular epigenetic insight into the pathogenesis of autoimmune diseases.

Disclosure: A. Skapenko, None; **V. Soentgerath**, None; **S. Haupt**, None; **J. Leipe**, None; **H. Schulze-Koops**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/hypermethylation-of-treg-specific-demethylated-regions-in-the-ikaros-transcription-factor-family-members-helios-and-eos-in-rheumatoid-arthritis-tregs

Abstract Number: 1948

Early Rheumatoid Arthritis Patients Have Higher Fractions of Circulating Th2 Cells, Th17 Cells and Regulatory T Cells, Similar Fractions of Follicular Helper T Cells, and Lower Fractions of Th17/Th1 Cells and Th1 Cells Compared to Healthy Controls

Jayesh Pandya, Magnus Hallström, Kerstin Andersson, Inger Nordström, Anna-Carin Lundell and **Anna Rudin**, Dept of Rheumatology and Inflammation Research, The Sahlgrenska Academy at University of Gothenburg, Gothenburg, Sweden

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SESSION INFORMATION

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Session Title: T cell Biology and Targets in Autoimmune Disease Poster I

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: A comprehensive analysis of the circulating T cell subtype pattern, including T helper 1 (Th1) cells, Th2 cells, Th17 cells, Th1/Th17 cells, T follicular helper (Tfh) cells, T follicular regulatory (Tfr) cells and T regulatory (Treg) cells in early untreated early RA compared to healthy controls has previously not been published.

Methods: Twenty-six patients with early RA satisfying the ACR 2010 criteria who had not received any DMARDS or prednisolone donated blood together with 18 sex and age matched healthy controls. Peripheral blood mononuclear cells were stained and analyzed by flow cytometry for combinations of

chemokine receptors CCR4, CCR6 and CXCR3 to define Th1, Th2, Th17 and Th1/Th17 cells. Follicular T helper cells were defined using the expression of CXCR5 but lack of FOXP3, while follicular regulatory T cells were defined as expressing both CXCR5 and FOXP3. Regulatory T-cells were defined as expressing either CD25 and low CD127 or FOXP3. Analysis of mRNA expression for the respective transcription factors were performed on flow cytometry sorted cells and cytokine production from the cultured sorted T cells was analyzed to confirm that the chemokine receptor expression correctly defined the T cell subtypes. In addition, CTLA-4 was analyzed on both conventional and regulatory CD4+ T-cells. The disease activity of the patients was measured DAS28 and CDAI. The data was analyzed using multivariate factor analyses followed by univariate analyses.

Results: Multivariate discriminant analysis including all T cell subtypes showed that the best discriminators for early RA were the proportions of Th2 and Th17 cells that were found in higher proportions in early RA than in healthy controls and the Th1/Th17 cells that were found in lower fractions in early RA than in controls. Regulatory T cells were found in higher proportions in early RA than in controls, while the proportions of circulating follicular helper T cells did not differ between the groups. Principal component analysis of the T cells subtypes in the patients showed that Th2 cells clustered with the Th17 cells, Th1/Th17 cells clustered with the Th1 cells and Tfh cells clustered with the Tfreg cells, whereas Tregs and Th0 cells were positioned separately. Strong negative correlations were obtained between Th17 cells and the Th1 cells. The clinical inflammatory activity in untreated early RA was unrelated to any of the proportions of the circulating T cells subtypes except for the proportions of the CTLA-4 positive T cells that were positively related to higher clinical activity.

Conclusion: We found a dominance of circulating Th2 cells together with Th17 cells in early RA and the former should attract more attention in relation to pathogenesis of early stages of the disease. Knowledge on what T cell subtypes dominate in the circulation in early rheumatoid arthritis may also guide us in developing new targeted treatments for this group.

Disclosure: J. Pandya, None; **M. Hallström**, None; **K. Andersson**, None; **I. Nordström**, None; **A. C. Lundell**, None; **A. Rudin**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/early-rheumatoid-arthritis-patients-have-higher-fractions-of-circulating-th2-cells-th17-cells-and-regulatory-t-cells-similar-fractions-of-follicular-helper-t-cells-and-lower-fractions-of-th17

Abstract Number: 1949

Generation and Immunophenotyping of Citrullin-Specific T Cell Lines from Peripheral Blood and Synovial Fluid of ACPA+ RA Patients

Muhammad Sohel Mia[1], Christina Gerstner[1], Daniel Ramsköld[1], Jessica Herrath[2], Anatoly Dubnovitsky[1,3], Marline Marline[4], Annika van Vollenhoven[1], Qiaolin Deng[4], Adnane Achour[3] and Vivianne Malmström[5], [1]Department of Medicine, Rheumatology Unit, Karolinska University Hospital, Solna, Stockholm, Sweden, [2]Department of Medicine,, Rheumatology Unit, Department of Medicine, Solna, Karolinska Institutet, Stockholm, Sweden, [3]Department of Medicine, Science for Life Laboraories, Karolinska Institute, Stockholm, Sweden, [4]Cell and Molecular Biology Department, Ludwig Institute for Cancer Research, Karolinska Institute, Solna, Stockholm, Sweden, [5]Rheumatology Unit, Department of Medicine, Karolinska Institutet, Stockholm, Sweden
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SESSION INFORMATION
Session Date: Monday, November 9, 2015
Session Title: T cell Biology and Targets in Autoimmune Disease Poster I
Session Type: ACR Poster Session B
Session Time: 9:00AM-11:00AM

Background/Purpose: Citrulline autoimmunity is a characteristic of ACPA^{+} Rheumatoid Arthritis (RA). Many autoantigens have been implicated even within patients of the same HLA such as HLA-DR*0401. By HLA-tetramer technology, autoreactive T cells can be captured and studied, but ACPA status cannot predict which T cell specificity will be most abundant. The present study aimed to evaluate the functional and transcriptional character of citrullin-specific T cells from RA synovial fluid and peripheral blood.

Methods: Peripheral blood mononuclear (PBMC) and synovial fluid mononuclear cells (SFMC) were isolated HLA-DR*04:01+ subjects. A pool of HLA DRB1*0401 class II tetramers (Tmr) were used to isolate autoreactive CD4+ T cells recognizing validated T cell epitopes from citrullinated alpha-enolase and vimentin T cell lines were generated following polyclonal stimuli and expansion and their specificity determined by stimulating with the same set of peptides used in the tetramers. Proliferation and cytokine profiling was measured by thymidine incorporation and cytokine bead array respectively. Smart-seq-2 RNA seq methods were used to perform transcriptomical analyses.

Results: By the tetramer pool technology we can reproducibly capture and grow autoreactive T cells even from synovial fluid and from modest cell numbers. Approximately half of the Tmr positive cell lines from both SFMC (42%) and PBMC (47%) were positive upon rechallenge. Citrulline reactivity was confirmed by both proliferation and cytokine output. We also demonstrate proof of principle of single cells transcriptomics (n=24) from RA synovial fluid with identification of approx 3000 genes per cell.

Conclusion: We demonstrated that citrulline specific T cell lines could be generated from both peripheral blood and synovial fluid. By this method we can capture autoreactive T cells even from modest number of cells without knowing the dominant T cell subset. This will enable identification of autoreactive T cell receptors (TCR) and down stream studies of e.g. T cell – APC interaction.

Disclosure: M. S. Mia, None; **C. Gerstner**, None; **D. Ramsköld**, None; **J. Herrath**, None; **A. Dubnovitsky**, None; **M. Marline**, None; **A. van Vollenhoven**, None; **Q. Deng**, None; **A. Achour**, None; **V. Malmström**, No commercial Interest, 2.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/generation-and-immunophenotyping-of-citrullin-specific-t-cell-lines-

from-peripheral-blood-and-synovial-fluid-of-acpa-ra-patients

Abstract Number: 1950

Methylation-Dependent Interference of Two Promoters for the Treg-Specific Protein, Garp, Contributes to Altered Treg Function in Rheumatoid Arthritis

Viktoria Soentgerath[1], Sonja Haupt[2], Jan Leipe[3], Hendrik Schulze-Koops[1] and Alla Skapenko[1], [1]Division of Rheumatology and Clinical Immunology, University of Munich, Munich, Germany, [2]Division of Rheumatology and Clinical Immunology, Med.Klinik und Poliklinik IV, University of Munich, Munich, Germany, [3]Division of Rheumatology, University of Munich, Munich, Germany
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SESSION INFORMATION
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Session Title: T cell Biology and Targets in Autoimmune Disease Poster I
Session Type: ACR Poster Session B
Session Time: 9:00AM-11:00AM

Background/Purpose: Recently, genome-wide studies identified several Treg-specific genes containing hypomethylated regions that are critical for their expression, so called Treg-specific demethylated regions (TSDR). For example, stable expression of the master transcription factor of Tregs, Foxp3, and expression of the Treg-specific surface receptor, GARP, are regulated by epigenetic modifications of intragenic TSDRs. We hypothesized that impaired Treg function in patients with autoimmune diseases, such as rheumatoid arthritis (RA), might be caused by changes in DNA methylation of Treg-signature gene loci.

Methods: In the current study, we investigated the methylation status of the TSDRs of the *FOXP3* and *GARP*genes in RA patients. CD25+ CD127- CD4 Tregs and CD25- CD4 T cells were isolated from the peripheral blood of therapy-naive RA patients as well as of age- and sex-matched healthy volunteers using magnetic cell sorting. Genomic DNA was isolated and processed by bisulfite conversion. The TSDRs were amplified by PCR using primers specific for bisulfite converted DNA. The PCR products were cloned and subsequently sequenced to compare the CpG methylation level and pattern between healthy individuals and RA patients.

Results: No differences in *FOXP3* TSDR methylation were found between Tregs from RA patients and controls. In marked contrast, the TSDRs in the intragenic promoter and in the first intron of *GARP* were surprisingly demethylated to a greater extent in Tregs from RA patients than in Tregs from healthy controls. The higher degree of the demethylation of the *GARP* gene locus in RA was coincident with lower *GARP* mRNA expression upon Treg activation and with higher disease activity. As expected, decreased methylation and decreased *GARP* mRNA expression were reflected by diminished GARP protein expression at the cell surface. In depth molecular analysis revealed that *GARP* expression in Tregs is tightly regulated by two alternative promoters. Binding of the transcriptional machinery to the demethylated intragenic promoter and the intronic TSDR acts like a roadblock resulting in Treg-specific attenuation of *GARP* transcription.

Conclusion: These data indicate that altered methylation in Treg-specific genes, such as *GARP*, in RA might facilitate impaired Treg function and, thus, contribute to disease pathogenesis.

Disclosure: V. Soentgerath, None; **S. Haupt**, None; **J. Leipe**, None; **H. Schulze-Koops**, None; **A. Skapenko**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/methylation-dependent-interference-of-two-promoters-for-the-treg-specific-protein-garp-contributes-to-altered-treg-function-in-rheumatoid-arthritis

Abstract Number: 1951

The Incidence Rate of Giant Cell Arteritis in Slovenia

Natasa Potocnik[1], Alojzija Hocevar[1], Ziga Rotar[1], Joze Pizem[2], Marko Hawlina[3], Ana Fakin[3] and Matija Tomšič[1], [1]Department of Rheumatology, University Medical Centre Ljubljana, Ljubljana, Slovenia, [2]Institute of Pathology, University of Ljubljana, Faculty of Medicine, Ljubljana, Slovenia, [3]Department of Ophthalmology, University Medical Centre Ljubljana, Ljubljana, Slovenia
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SESSION INFORMATION
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Session Title: Vasculitis Poster II
Session Type: ACR Poster Session B
Session Time: 9:00AM-11:00AM

Background/Purpose:

Giant cell arteritis (GCA) is the most common systemic vasculitis in adults aged 50 years or above. Annual incidence rates vary widely from 6.9–76.6 per

10^5 of adults in this age group, depending on the region.[1] Our aim was to determine the incidence rate of GCA in our population.

Methods: We prospectively collected incident cases of GCA from January 1st 2011 to December 31st 2014 at our department of rheumatology which is a part of an integrated secondary/tertiary university teaching hospital that is the only referral center serving a region representing approximately a quarter of the national adult population. Additionally, newly diagnosed cases of GCA between January 1st 2009 and December 31st 2010 were retrospectively identified by searching the electronic patient records for ICD-10 codes M31.5 and M31.6 at our department. The retrospective approach and search strategy was also applied on electronic medical records at the departments of infectious diseases and ophthalmology between January 1st 2009 and December 31st 2014. To further reduce possibility of underreporting, the attached medical faculty's Institute of Pathology provided a list of all temporal artery biopsies examined during the observation period which were then cross-referenced with the hospital's electronic medical records. Annual incidence rate for GCA was then calculated.

Results:

During the six year observation period we identified 137 new cases of GCA (68% female; mean (IQR) age 75.9 (11.1) years) from a well-defined adult white Caucasian population of 235,596 inhabitants aged 50 or above. The temporal artery biopsy was consistent with GCA, negative or not performed in 80.2 %, 19.8 %, and 8.0 % of cases, respectively. Thus, the average six years annual incidence of GCA in our population is 9.7 (95 % CI 8.1–15.5), the highest was in 2010 (11.7 (95% CI 7.7-17.1)), and the lowest in 2013 (7.5 (95% CI 4.4-11.8)) per 10^5 adults aged 50 or above.

Conclusion:

The average annual incidence rate of 9.7 per 10^5 adults aged 50 or above makes GCA the most common systemic vasculitis in our population.

Reference:

1. Gonzalez-Gay MA, Vazquez-Rodriguez TR, Lopez-Diaz MJ et al. Epidemiology of Giant Cell Arteritis and Polymyalgia Rheumatica. Arthritis Rheum 2009;61:1454-61.

Disclosure: **N. Potocnik**, None; **A. Hocevar**, None; **Z. Rotar**, None; **J. Pizem**, None; **M. Hawlina**, None; **A. Fakin**, None; **M. Tomšič**, None.

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Abstract Number: 1952

Lack of Association of a 6.7 Kbp Deletion of LILRA3 with Giant Cell Arteritis

Ana Márquez[1], Tamara Fernández-Aranguren[2], Maria C. Cid[3], José Hernández-Rodríguez[3], Roser Solans[4], Marc Ramentol[4], Santos Castañeda[5], Jose A. Miranda-Filloy[6], Inmaculada C. Morado[7], Javier Narváez[8], Eugenio De Miguel[9], Bernardo Sopeña[10], Jordi Monfort[11], Maria Jesus Garcia-Villanueva[12], Norberto Ortego-Centeno[13], Torsten Witte[14], Miguel Angel Gonzalez-Gay[15], Javier Martín[2] and Spanish GCA Group, [1]Instituto de Parasitología y Biomedicina López-Neyra, IPBLN-CSIC, PTS-Granada and Systemic Autoimmune Diseases Unit, Hospital Clínico San Cecilio, Granada, Spain, [2]Instituto de Parasitología y Biomedicina López- Neyra, IPBLN-CSIC, PTS-Granada, Granada, Spain, [3]Vasculitis Research Unit, Department of Autoimmune Diseases, Hospital Clínic University of Barcelona, Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Barcelona, Spain, [4]Autoimmune Systemic Diseases Unit, Department of Internal Medicine, Hospital Vall d'Hebron, Autonomous University of Barcelona, Barcelona, Spain, [5]Hospital Universitario de La Princesa. IIS La Princesa, Madrid, Spain, [6]Department of Rheumatology, Hospital Xeral-Calde, Lugo, Spain, [7]Department of Rheumatology, Hospital Clínico San Carlos, Madrid, Spain, [8]Rheumatology Department, Hospital Universitari de Bellvitge, L'Hospitalet de Llobregat, Spain, [9]Department of Rheumatology, Hospital Universitario La Paz, Madrid, Spain, [10]Department of Internal Medicine, Complejo Hospitalario Universitario de Vigo, Vigo, Spain, [11]Department of Rheumatology, Grup de recerca cel•lular en inflamació i cartílag. IMIM (Institut de Recerca Hospital del Mar), Barcelona, Spain, [12]Department of Rheumatology, Hospital Ramón y Cajal, Madrid, Spain, [13]Systemic Autoimmune Diseases Unit, Hospital Clínico San Cecilio, Granada, Spain, [14]Hannover Medical School, Hanover, Germany, [15]Department of Rheumatology, Hospital Universitario Marqués de Valdecilla, IDIVAL, Santander, Spain

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Background/Purpose: Leukocyte immunoglobulin-like receptor A3 (*LILRA3A*) encodes a member of a family of immunoreceptors which is predominantly expressed on antigen presenting cells, acting as a soluble receptor for class I major histocompatibility complex (MHC) antigens. Recently published studies have implicated a 6.7 kb genetic deletion of *LILRA3*, comprising the first seven exons of the gene, in the genetic predisposition to rheumatoid arthritis, multiple sclerosis, and Sjögren's syndrome. Given the proposed role of *LILRA3A* in autoimmunity, we aimed to assess whether this deletion represents a novel genetic risk factor for GCA and its main clinical subgroups.

Methods: A total of 969 biopsy-proven GCA patients and 1593 healthy controls of Spanish Caucasian origin were included in the study. The *LILRA3* deletion was genotyped by polymerase chain reaction using specific primers for detecting presence or absence of the complete gene.

Results: No statistically significant differences were found when allele and genotype distributions were compared between GCA patients and controls (allelic p-value= 0.924, OR=1.01, CI 95%=0.87-1.17). Likewise, the subphenotype analysis considering the main clinical complications of the disease (rheumatic polymyalgia, visual manifestations, jaw claudication and stroke) yield similar negative results.

Conclusion: Our data suggest that the *LILRA3* deletion do not play a significant role in GCA susceptibility or severity.

Disclosure: A. Márquez, None; **T. Fernández-Aranguren**, None; **M. C. Cid**, None; **J. Hernández-Rodríguez**, None; **R. Solans**, None; **M. Ramentol**, None; **S. Castañeda**, None; **J. A. Miranda-Filloy**, None; **I. C. Morado**, None; **J. Narváez**, None; **E. De Miguel**, None; **B. Sopeña**, None; **J. Monfort**, None; **M. J. Garcia-Villanueva**, None; **N. Ortego-Centeno**, None; **T. Witte**, None; **M. A. Gonzalez-Gay**, None; **J. Martín**, None.

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Abstract Number: 1953

Identification of Genetic Factors Associated with Clinical Manifestations of Giant Cell Arteritis through a Stratified Large-Scale Analysis

Ana Márquez[1], Francisco David Carmona[2], Maria C. Cid[3], José Hernández-Rodríguez[3], Roser Solans[4], Marc Ramentol[4], Santos Castañeda[5], Jose A. Miranda-Filloy[6], Inmaculada C. Morado[7], Javier Narváez[8], Eugenio De Miguel[9], Bernardo Sopeña[10], Jordi Monfort[11], Maria Jesus Garcia-Villanueva[12], Norberto Ortego-Centeno[13], Miguel Angel Gonzalez-Gay[14], Javier Martín[15] and Spanish GCA Group, [1]Instituto de Parasitología y Biomedicina López-Neyra, IPBLN-CSIC, PTS-Granada and Systemic Autoimmune Diseases Unit, Hospital Clínico San Cecilio, Granada, Spain, [2]Instituto de Parasitología y Biomedicina López-Neyra, IPBLN-CSIC, PTS-Granada, Granada, Spain, [3]Vasculitis Research Unit, Department of Autoimmune Diseases, Hospital Clínic University of Barcelona, Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Barcelona, Spain, [4]Autoimmune Systemic Diseases Unit, Department of Internal Medicine, Hospital Vall d'Hebron, Autonomous University of Barcelona, Barcelona, Spain, [5]Department of Rheumatology, Hospital de la Princesa, IIS-Princesa, Madrid, Spain, [6]Department of Rheumatology, Hospital Xeral-Calde, Lugo, Spain, [7]Department of Rheumatology, Hospital Clínico San Carlos, Madrid, Spain, [8]Rheumatology, Hospital Universitario de Bellvitge, Barcelona, Spain, [9]Department of Rheumatology, Hospital Universitario La Paz, Madrid, Spain, [10]Department of Internal Medicine, Complejo Hospitalario Universitario de Vigo, Vigo, Spain, [11]Department of Rheumatology, Grup de recerca cel•lular en inflamació i cartílag. IMIM (Institut de Recerca Hospital del Mar), Barcelona, Spain, [12]Department of Rheumatology, Hospital Ramón y Cajal, Madrid, Spain, [13]Systemic Autoimmune Diseases Unit, Hospital Clínico San Cecilio, Granada, Spain, [14]Rheumatology, Hospital Universitario Marqués de Valdecilla. IDIVAL, Santander, Spain, [15]Instituto de Parasitología y Biomedicina López- Neyra, IPBLN-CSIC, PTS-Granada, Granada, Spain

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Background/Purpose: Giant cell arteritis (GCA) is a large-vessel vasculitis that primarily affects the aorta and external carotid arteries and their branches, leading to ischemic manifestations such as headaches or jaw claudication. Visual loss, commonly secondary to anterior ischemic optic neuropathy, represents the most severe complication. Polymyalgia rheumatica (PMR), characterised by aching and morning stiffness in the neck, shoulder and pelvic girdle, is present in up to 50% of patients. Less often, neurological symptoms, such as transient ischemic attacks and strokes, have been identified in GCA patients. The aim of the present study was to perform a stratified analysis of a published Immunochip to identify genetic factors contributing to the main clinical manifestations of GCA.

Methods: Data from an Immunochip performed on 763 Spanish GCA patients were stratified according to the presence/absence of PMR, jaw claudication, visual manifestations (transient visual loss including amaurosis fugax, permanent visual loss, or diplopia) and stroke. Allele frequencies were compared between the different subgroups of GCA patients and 1,517 unaffected controls, and between patients with and without the considered phenotypes. Logistic regression analyses adjusted by the 3 first principal components and sex were performed using an additive model.

Results: After genotyping and quality control, 132,117 genetic variants were analyzed in GCA patients showing PMR (n=318), jaw claudication (n=331), visual manifestations (n=228) or stroke (n=43). Several *loci* showed suggestive associations with the different clinical manifestations, specifically *MAFB* (a transcription factor involved in the monocyte-macrophage differentiation) was associated with jaw claudication ($p=2.31x10^{-6}$, OR=1.57), *KIR2DL1/KIR2DL4* (transmembrane glycoproteins playing an important role in the immune response regulation) appeared to be involved in PMR ($p=5.26x10^{-6}$, OR=1.69), *ADAMTSL3* (implicated in angiogenesis and up regulated in astrocytes from the optic nerve in patients with glaucoma) showed an association with the development of visual manifestations ($p=9.57x10^{-6}$, OR=1.69), and *SULT6B1* (a sulfotransferase which catalyzes the sulfonation of xenobiotics, hormones and neurotransmitters) was implicated in GCA-associated stroke ($p=1.67x10^{-5}$, OR=2.68). In all cases, the analysis of GCA patients accordingly with the presence/absence of each clinical condition also reached statistical significance (p=0.025, $p=3.89x10^{-3}$, $p=4.94x10^{-3}$ and $p=8.96x10^{-6}$, respectively).

Conclusion: Using a stratified large-scale analysis, we have identified four novel *loci* potentially involved in the development of the main clinical complications occurring in GCA patients.

Disclosure: A. Márquez, None; **F. D. Carmona**, None; **M. C. Cid**, None; **J. Hernández-Rodríguez**, None; **R. Solans**, None; **M. Ramentol**, None; **S. Castañeda**, None; **J. A. Miranda-Filloy**, None; **I. C. Morado**, None; **J. Narváez**, None; **E. De Miguel**, None; **B. Sopeña**, None; **J. Monfort**, None; **M. J. Garcia-Villanueva**, None; **N. Ortego-Centeno**, None; **M. A. Gonzalez-Gay**, None; **J. Martín**, None.

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Abstract Number: 1954

How Can We Use Ultrasound in the Diagnosis and Management of Patients with Giant Cell Arteritis?

Cristina Ponte[1,2], Sophie Vaggers[1], Jan Sznajd[1], Lorraine O'Neill[1], Jennifer Piper[3], Jessica Gunn[1], Kulveer Mankia[1] and Raashid Luqmani[1], [1]Nuffield Department of Orthopaedics Rheumatology and Musculoskeletal Sciences, University of Oxford, Oxford, United Kingdom, [2]Rheumatology and Metabolic Bone Diseases Department, Rheumatology Research Unit - IMM, Lisbon Academic Medical Centre, Lisbon, Portugal, [3]Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences, University of Oxford, Oxford, United Kingdom
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Background/Purpose:

Giant cell arteritis (GCA), the most common primary vasculitis, can cause irreversible blindness in 20-30% of untreated cases, but glucocorticoid therapy leads to significant toxicity in > 80% of patients. Ultrasound has proven to be effective in diagnosing GCA and has shown advantages in monitoring disease activity. We reviewed data on all patients referred to a single university hospital between August 2014 and March 2015 who were seen in a “fast-track” service established to diagnose and evaluate suspected GCA or a suspected flare. All patients underwent rapid evaluation by a combination of ultrasound (of the temporal and axillary arteries) and standard clinical assessment to reduce the risk of misdiagnosis or instituting unnecessary treatment.

Methods:

We performed a retrospective analysis and comparison of the ultrasound findings with the clinical features, temporal artery biopsy (TAB) results and decision to treat patients with suspected or established GCA. The ultrasound scan was considered positive when we identified the presence of a dark halo around the temporal artery wall or a homogeneous hypoechoic wall thickness > 1.5 mm in the axillary arteries.

Results:

We performed 137 scans in 118 patients (67% females, mean [SD] age 71 ± 11 years). In 89 cases, patients were referred for suspected GCA: 60% were already on high-doses of steroids (mean of 12 ± 10 days); 78% had headache; 62% high inflammatory markers; 43% abnormal vascular examination (e.g. diminished/absent pulse or bruits); 34% scalp tenderness; 33% polymyalgia rheumatica; 25% jaw claudication and 25% visual symptoms. In 32 cases the scan was positive: 9 also had a TAB (4 positive) and all were treated as GCA. In 50 cases the scan was negative: 20 also had a TAB (1 positive) and 5 were treated as GCA. In 7 cases the scan was inconclusive requiring further investigations (e.g. TAB). Patients with a positive scan had a mean CRP of 51.8 ± 50.8 g/dl and a mean ESR of 42.4 ± 40.1 mm/hour; patients with a negative scan had a mean CRP of 14.9 ± 21.9 g/dl and a mean ESR of 26.8 ± 23.5 mm/hour (p=0.003 and p=0.245, respectively). We scanned 48 patients with an established diagnosis of GCA to assess for flare or monitor disease activity: 25 had a positive scan (18 increased medication; 7 were follow-ups with improvement from baseline) and 23 had a negative scan (allowing a safer taper or withdrawal of glucocorticoids). Patients with a positive scan had a mean CRP of 10.7 ± 10.3 g/dl and a mean ESR of 21.4 ± 18.0 mm/hour; patients with a negative scan had a mean CRP of 3.9 ± 4.3 g/dl and a mean ESR of 24.1 ± 17.4 mm/hour (p=0.025 and p=0.663, respectively).

Conclusion:

The combination of rapid clinical evaluation and ultrasound were key elements in diagnosis and monitoring of GCA, allowing more flexible use of glucocorticoid dose regimens and reducing the number of TABs required. The only patient with a negative scan but a positive TAB had already received 20 days of glucocorticoids, suggesting that delay in investigation after starting therapy could affect the results of the scan.

Disclosure: C. Ponte, None; **S. Vaggers**, None; **J. Sznajd**, None; **L. O'Neill**, None; **J. Piper**, None; **J. Gunn**, None; **K. Mankia**, None; **R. Luqmani**, GSK, 5,Chemocentryx, 5,Roche Pharmaceuticals, 5.

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Abstract Number: 1955

The Performance of Colour-Doppler Sonography of Temporal Arteries in Patients Suspect of

Having Giant Cell Arteritis in Daily Clinical Practice

Alojzija Hocevar, Rok Ješe, Ziga Rotar and Matija Tomšič, Department of Rheumatology, University Medical Centre Ljubljana, Ljubljana, Slovenia
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Background/Purpose:

The Colour-Doppler Sonography of temporal arteries (CDS-TA) has recently gained momentum as a potential non-invasive tool for diagnosing GCA. Our aim was to evaluate the diagnostic value of CDS-TA in suspected GCA cases in daily clinical practice.

Methods: Subjects with suspected GCA underwent CDS-TA prior to temporal artery biopsy (TAB). CDS-TA was performed on a Philips IU22 using a 5–17.5 MHz linear probe. TA were assessed in longitudinal and transversal planes. The "halo sign" (dark hypo echoic circumferential wall thickening), stenosis or occlusion were considered a positive finding. In addition to CDS-TA, clinical examination, extensive laboratory work-up, and TAB were performed. Diagnosis was established in accordance with the American College of Rheumatology (ACR) criteria.

Results: From 1.9.2011 to 31.5.2015 (45 months) 139 subjects with suspected GCA were identified. GCA was diagnosed in 96/139 (69.1%). The remaining 43/139 (30.9%) who were not diagnosed with GCA served as controls. CDS-TA was performed in 138/139 subjects (95/96 GCA patients and in 43/43 controls). The "halo sign" was observed in 74 (77.9%) of GCA patients and in none of the controls. The "halo sign" was unilateral in 28/74 (37.8%) and bilateral in 46/74 of GCA patients. Stenoses were found in 41/95 (43.1%) of GCA patients and in 2/43 (4.7%) controls. TA occlusion was demonstrated in 13/95 (13.7%) of GCA patients and in none of the controls. In our population the CDS-TA had an estimated diagnostic sensitivity of 77.9% and specificity of 95.4% with diagnosis based on the ACR criteria serving as a gold standard. A positive CDS-TA had 97.4% positive and 66.1% negative predictive value for GCA. The TAB for the same group had a diagnostic sensitivity of 80.0% and specificity of 90.3%; and a 95.5% positive and a 63.6% negative predictive value. There was an 80% matching of CDS-TA and TAB (Table 1).

Suspected GCA	positive CDS-TA	negative CDS-TA	CDS-TA not performed	Total
Positive TAB	54	4	1	59
Inconclusive TAB	4	4	0	8
Negative TAB	10	34	0	44
TAB not done	8	20	0	28
Total	76	62	1	

Table 1. Crossmatching of CDS-TA and TAB in suspected GCA

Conclusion:

The diagnostic value of CDS-TA for diagnosing GCA is comparable, if not superior to TAB. In case of characteristic sonographic changes, CDS-TA may obviate the need for TAB.

Disclosure: A. Hocevar, None; **R. Ješe**, None; **Z. Rotar**, None; **M. Tomšič**, None.

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Abstract Number: 1956

Risk of Cerebrovascular Accident in Patients with Polymyalgia Rheumatica: A Systematic Review and Meta-Analysis

Patompong Ungprasert[1], Narat Srivali[2] and Wonngarm Kittanamongkolchai[3], [1]Rheumatology, Mayo Clinic, Rochester, MN, [2]Pulmonary and Critical Care Medicine, Mayo Clinic, Rochester, MN, [3]Nephrology and hypertension, Mayo Clinic, Rochester, MN
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Risk of Cerebrovascular Accident in Patients with Polymyalgia Rheumatica: A Systematic Review and Meta-analysis

Background/Purpose: Several chronic inflammatory disorders, such as rheumatoid arthritis and systemic lupus erythematosus, have been shown to increase risk of cerebrovascular accident (CVA). However, the data on polymyalgia rheumatica (PMR), another common chronic inflammatory disease in older adults, are limited. Thus, to further investigate this association, we conducted a systematic review and meta-analysis of observational studies that compared the risk of CVA in patients with PMR versus participants without it.

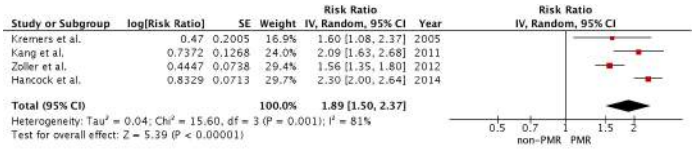
Methods: Two investigators independently searched published studies indexed in MEDLINE, EMBASE and the Cochrane database from inception to April 2015 using the terms "polymyalgia rheumatica" and "PMR" combined with the terms for cerebrovascular disease. A manual search of references of selected

articles was also performed. The inclusion criteria were as follows: (1) cohort or case-control study evaluating the association between PMR and CVA (2) odds ratio (OR), relative risk (RR) or hazard ratio (HR) or standardized incidence ratio (SIR) with 95% confidence interval (CI) were provided. Study eligibility was independently determined by the two investigators. The quality of included studies was, again, independently assessed by the two investigators using Newcastle-Ottawa scale.

RevMan 5.3 software was used for the data analysis. Point estimates and standard errors were extracted from individual studies and were combined by the generic inverse variance method of DerSimonian and Laird. Given the high likelihood of between study variance, we used a random-effect model rather than a fixed-effect model. Statistical heterogeneity was assessed using the Cochran's Q test.

Results: Out of 346 potentially relevant articles, four studies (three retrospective cohort studies and one case-control study) were identified and included in our data analysis. The pooled risk ratio of CVA in patients with PMR was 1.89 (95% CI, 1.50 to 2.37). The statistical heterogeneity of this meta-analysis was high with an I^2 of 81%.

Conclusion: Our study demonstrated a significantly elevated CVA risk among patients with PMR.



Disclosure: P. Ungprasert, None; **N. Srivali**, None; **W. Kittanamongkolchai**, None.

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Abstract Number: 1957

Colour-Doppler Ultrasonography of Epiaortic Arteries in Patients with Giant Cell Arteritis

Alojzija Hocevar, Rok Ješe, Ziga Rotar and Matija Tomšič, Department of Rheumatology, University Medical Centre Ljubljana, Ljubljana, Slovenia
First publication: September 29, 2015

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Background/Purpose:

Giant cell arteritis (GCA) is the most common systemic vasculitis in patients over 50 years of age. Large vessel disease outside temporal arteries is increasingly being recognised. Our aim was to evaluate the involvement of large epiaortic arteries in patients with GCA using Colour Doppler Ultrasonography (CDS) in daily clinical practice.

Methods:

CDS of epiaortic arteries was performed using a 5–17.5 MHz linear probe in patients with newly diagnosed GCA prior to or up to 2 days after starting glucocorticoids. Carotid, vertebral, subclavian, axillary as well as occipital, facial and thyroid arteries were assessed in longitudinal and transversal planes. The “halo sign” (i.e. a hypoechoic circumferential wall thickening, was considered a positive finding.

Results:

From September 1, 2011 to May 31, 2015 CDS of epiaortic arteries was performed in 87 GCA patients. In 33/87 patients (37.9%) involvement of examined arteries was found. (Table 1).A single artery region was affected in 13 patients (39.4%), and 20 patients had more than one vascular region affected.

The group of patients with large artery involvement had significantly longer disease duration (p= 0.009), were more commonly females (p=0.003), had less commonly positive CDS of temporal arteries (p=0,023) and had a higher risk for severe visual disturbances (50% vs. 9.1% permanent visual loss, relative risk 5.5 (95%CI 1.2-25.8)), than those without large vessel involvement. Clinical characteristics of both groups are presented in Table 2.

Arteries	GCA cases with vasculitic changes (%)

Table 1. Large artery disease in GCA patients, assessed by DCS

Table 2. Clinical characteristics of GCA patients with or without large artery disease

Carotid arteries	12.6%
Vertebral arteries	11.5%
Subclavian arteries	17.2%
Axillary arteries	17.2%
Thyroid artereis	3.4%
Occipital arteries	17.8%
Facial arteries	17.8%

Characteristics	GCA with large vessel disease (33)	GCA without large vessel disease (54)
gender (F:M ratio)	10	1.6
age (yrs; median, IQR)	72.1 (66.3; 78.6)	74.9 (68.7; 78.8)
disease duration (days, median, IQR)	60 (30; 101)	29 (14; 60)
general symptoms (%)	84.2%	70.4%
PMR symptoms (%)	15.2%	20.4%
new headache (%)	66.7%	77.8%
jaw claudication (%)	39.4%	42.6%
visual disturbances (%)	18.2%	40.7%
permanent visual loss (% of visual dist.)	50%	9.1%
dry cough (%)	24.2%	16.7%
ESR (mm/h; median , IQR)	89 (59; 109)	81 (58; 101)
CRP (mg/l; median, IQR)	82 (51; 122)	63 (32; 124)
positive TA biopsy (%)	78.3%	85.4%
positive TA CDS (%)	66.7%	88.9%

Conclusion:

Epiaortic large artery involvement was demonstrated in more than 1/3 of our GCA cases. CDS of epiaortic arteries in addition to CDS of temporal arteries increases the diagnostic yield in GCA.

Disclosure: A. Hocevar, None; **R. Ješe**, None; **Z. Rotar**, None; **M. Tomšič**, None.

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Abstract Number: 1958

Diagnostic Value of Ultrasonography-Derived Signs in Giant Cell Arteritis: Literature Review and Meta-Analysis

Fanny BUSQUET[1], Léa Rouxel[2], Thomas Barnetche[3] and Thierry Schaeverbeke[4], [1]intern of hospital, BORDEAUX, France, [2]intern of hospital, Bordeaux, France, [3]PHD, bordeaux, France, [4]department head, Bordeaux, France
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Background/Purpose:

Giant Cell Arteritis (GCA) is the most common form of systemic inflammatory vasculitis in elderly people, with prevalence still increasing, and for which there is no consensual diagnostic method. Indeed the relevance of temporal artery wall edema is still a matter of debate, despite two previous meta-analyses by Karassa *et al.* in 2005 and Arida *et al.* in 2010. We re-evaluated the diagnostic value of the ultrasonography-derived signs of the temporal artery for GCA diagnosis.

Methods:

We selected prospective studies concerning patients with suspected GCA published up to February 2015 in the Pubmed, Cochrane library and Embase databases. Studies using ultrasound biomicroscopy were excluded.

Diagnostic performances were determined for the following ultrasonographic signs: halo (unilateral or bilateral), blood flow abnormalities (stenosis and/or occlusions) and unilateral halo associated with BFA. The gold standard used was either the American College of Rheumatology (ACR) 1990 criteria or temporal artery biopsy. Weighed sensitivity and specificity for each sign were assessed, as well as statistical heterogeneity. P-values less than 0.05 were considered as significant.

Results:

We included 16 studies involving 964 patients suspected of GCA. Among these patients, 448 patients were diagnosed by ACR criteria (41% of which were ACR+) and 764 by temporal biopsy (48% of which showed temporal arteritis).

Ultrasound was performed in all patients. The halo sign was found in 29% of cases among which 76% had a positive biopsy. Among patients ACR+, the unilateral halo sign had an overall sensitivity of 68.2% (95% CI 0.58-0.79) and specificity of 93.2% (95 % CI 0.88-0.99). The same sign did not improve when associated to BFA: overall sensitivity of 64.2% (95% CI 0.17-1.17) and specificity of 93.4% (95% CI 0.85-1). The bilateral halo sign among ACR+ patients had an overall sensitivity of 58.2% (95% CI 0.19-0.97). The latter's specificity was about 100% (95% CI 0.92-1) but was only estimated in one study. Among patients with a positive biopsy, the unilateral halo sign had an overall sensitivity of 82.4% (95% CI 0.77-0.88) and specificity of 86.8% (95% CI 0.82-0.92) with the same absence of improvement as in the previous group when associated to BFA. The bilateral halo sign achieved an overall sensitivity of 51.7% (95% CI 0.42-0.62) and specificity of 82.4%(95% CI 0.57-1). It is to be noticed that between-study heterogeneity was very significant for all these calculations ($I2 > 40\%$). A positive biopsy was found in 58 patients among the 439 without the halo sign (13% of false-negative). 80.7% of ACR+ patients had a positive biopsy and 19.3% had a normal biopsy.

Conclusion:

Among all ultrasonography-derived signs, the unilateral halo sign may be sufficient in GCA diagnosis. However, this meta-analysis did not confirm the infallibility of these signs, in particular in case of an absence of ultrasonographic signs. This last situation should be explored in further studies.

Disclosure: F. BUSQUET, None; **L. Rouxel**, None; **T. Barnetche**, None; **T. Schaeverbeke**, None.

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Abstract Number: 1959

Color Doppler Ultrasonography Appears to Perform Better Than Magnetic Resonance Angiography in the Diagnostics of Patients with Systemic Large Vessel Vasculitis

Andreas P Diamantopoulos[1,2], Julia Geiger[3], Frode Lohne[4], Geirmund Myklebust[5] and Wolfgang A. Schmidt[6], [1]Rheumatology, Hospital of Southern Norway Trust, Kristiansand, Norway, [2]Rheumatology, Haugesund Hospital for Rheumatic Diseases, Haugesund, Norway, [3]Department of Radiology, University Children's Hospital, Zurich, Switzerland, [4]Radiology, Hospital of Southern Norway Trust, Kristiansand, Norway, [5]Rheumatology, Hospital of Southern Norway, Kristiansand, Norway, [6]Medical Center for Rheumatology and Clinical Immunology Berlin-Buch, Immanuel Krankenhaus Berlin, Berlin, Germany

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Session Time: 9:00AM-11:00AM

Background/Purpose:

Color Doppler ultrasound (CDUS) and Magnetic resonance angiography (MRA) has been extensively used in the diagnostics of large vessel vasculitis (LVV) [giant cell arteritis (GCA) and Takayasu arteritis (TA)]. No studies exist, which compare the diagnostic accuracy of CDUS and MRA of LVV in the supra-aortic large vessels. The aim of this study is to perform a head-to-head comparison between CDUS and MRA of temporal arteries and supra-aortic large vessels in a group of LVV patients.

Methods:

MUSES (Magnetic resonance angiography vs Ultrasonography in Systemic large vEssel vasculitis, Clinical Trials.gov NCT02042092), is a prospective cross-sectional study. Patients diagnosed with LVV by ultrasound, MRA, Computed Tomography Angiography or Positron Emission Tomography, were identified and included in MUSES at the Department of Rheumatology, in Kristiansand between January 2014 and January 2015. One ultrasonographer experienced in the use of vascular ultrasound (APD) examined and recruited the LVV patients. MRA imaging was performed within one week after the ultrasound evaluation and one radiologist evaluated the MRA images locally (FL). The common temporal, carotid, subclavian, vertebral, axillary arteries and the thoracic aorta were evaluated. Films and images of CDUS and MRA examinations were recorded. The recorded data has been surveyed by two external experts, one on vascular ultrasound (WAS) and one on MR imaging (JG). Both experts were blinded to clinical and laboratory data and were unaware of distribution and size of the vasculitis lesions. The experts applied a dichotomous score (vasculitis: yes/no) in every evaluated vessel. The identification of vasculitis in any vessel represented an independent result.

Results:

Twenty-seven patients were recruited [(12 males, 15 females, median age 69 years (IQR 62-76)]. Twenty-five patients were diagnosed with GCA and 2 with TA. Eight patients had new onset LVV and 19 had long lasting disease (median disease duration 2 years, IQR 0-5). Median time between CDUS and MRA examination was 2 days (IRQ 1-4). Median CRP was 8 mg/l (IQR 3-24) and ESR 24 mm/hr. (IQR 9-53). In two patients, no vasculitis changes were observed in any vessel, either on CDUS or MRA. In the remaining 25 patients, CDUS revealed vasculitis in all patients, while MRA was positive in 20 patients. The temporal artery and the supra-aortic vessels in which CDUS, MRA or both modalities revealed vasculitis changes are presented in table 1.

Conclusion:

It seems that CDUS is more sensitive to detect vasculitis changes in large vessels. Further, CDUS revealed vasculitis in more patients than MRA. Thus, we recommend CDUS as a first line evaluation in all patients suspected to have LVV.

Table 1.

	CDUS vasculitis only	MRA vasculitis only	Vasculitis in both modalities
Left common temporal	2	1	10
Left parietal temporal	6	1	8
Left frontal temporal	2	3	7
Right common temporal	3	6	7
Right parietal temporal	2	5	8
Right frontal temporal	2	7	8
Left carotid	13	1	1
Right carotid	12	0	4
Left subclavian	10	1	5
Right subclavian	5	1	3
Left vertebral	3	0	0
Right vertebral	2	0	0
Left axillary	11	0	3
Right axillary	15	1	4
Thoracic aorta	2	0	0

Disclosure: A. P. Diamantopoulos, None; **J. Geiger**, None; **F. Lohne**, None; **G. Myklebust**, None; **W. A. Schmidt**, GlaxoSmithKline, 5,Roche Pharmaceuticals, 5,Roche Pharmaceuticals, 8.

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Abstract Number: 1960

a Structured and Extensive Training Program on Vascular Ultrasound, Results in an Excellent Agreement Between Ultrasound and Temporal Artery Biopsy in the Diagnosis of Giant Cell Arteritis

Stavros Chrysidis[1], Ulrich Fredberg[2], Uffe Møller Døhn[3], Tove Lorenzen[4], Lene Terslev[5], Knud Larsen[6] and **Andreas P Diamantopoulos**[7], [1]Department of Rheumatology, Hospital of Southwest Denmark, Esbjerg, Denmark, [2]Department of Internal Medicine, Diagnostic Centre Region Hospital Silkeborg Denmark, Silkeborg, Denmark, [3]Center for Rheumatology and Spine Diseases, Copenhagen Center for Arthritis Research (COPECARE), Center for Rheumatology and Spine Diseases, Rigshospitalet - Glostrup, University of Copenhagen, Glostrup, Denmark, [4]Diagnostic Centre, Region Hospital Silkeborg, Silkeborg, Denmark, [5]Copenhagen University Hospital at Glostrup, Copenhagen, Denmark, [6]otolaryngology, Southwest hospital, Esbjerg, Denmark, [7]Rheumatology, Haugesund Hospital for Rheumatic Diseases, Haugesund, Norway
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Background/Purpose: There is an increased use of vascular ultrasound (US) for diagnosing giant cell arteritis (GCA). Consequently, extensive and structured training of ultrasonographers performing vascular ultrasound is required in order to ensure standardization of examination technique and machine settings to obtain reliable results**.** The primary aim of this study was to evaluate the results of a standardized training program for ultrasonographers in the diagnosis of temporal artery (TA) vasculitis in GCA.

Methods: Rheumatologists with long-standing experience in musculoskeletal US were extensively trained in the use of vascular US by a specific program. Initially participation in the International Workshop on US in Large Vessel Vasculitis and Polymyalgia Rheumatica in Kristiansand, Norway (5 hours theoretical and 10 hours supervised hands-on education) followed by a two day workshop in Denmark (6 hours of supervised hands-on trainings and 1 hour of image evaluation)with additional training and standardization of scanning technique and optimization of settings . Immediately after this training program a US study on patients suspected for GCA was initiated. Patients were examined with high-end US equipment with high resolution transducers, optimized vascular settings and standardized examination technique. After the US examination of TA, a temporal artery biopsy (TAB) was performed. Pictures and film clips of all three TA branches in two planes were recorded and evaluated by the performing sonographer and by a blinded expert. Detailed feedback on the

US technique was given to the performing sonographer by the external expert.

US was considered positive in the presence of the halo sign (hypoechoic arterial wall swelling) and/or the presence of a positive compression-sign (arterial wall remaining visible upon compression with US transducer).

Results: During 12 months, 37 patients from three Danish Rheumatologic Departments (Esbjerg, Glostrup, Silkeborg) suspected to have GCA were recruited. In 20 patients with a positive TAB for GCA, US was positive in all patients according to both the performing sonographer and the blinded external expert.

In 15 patients with negative TAB, neither the performing sonographer, nor the external reader found signs of vasculitis. In one patient with a negative TAB, US showed vasculitis (both readers) and in one the local sonographer's finding of US vasculitis was rejected by the blinded expert.

In total, 222 branches of TA were scanned and vasculitis changes were observed in 82 branches (expert) and in 80 branches (performing sonographer). The inter-observer agreement between the performing sonographer and the blinded expert was excellent in all three centres/departments (Cohens kappa-coefficient: Esbjerg k=0.88, Glostrup k=0.90 and Silkeborg k=0.82).

Conclusion: Following an intense structured training program on vascular ultrasound using high quality equipment, we were able to obtain an excellent agreement between US of TA and subsequent TAB in patients suspected for GCA. Furthermore, an excellent interobserver agreement between the performing sonographers and the blinded expert reader were seen. This training set-up could be useful in the implementation of US for diagnosing GCA .

Disclosure: S. Chrysidis, None; **U. Fredberg**, None; **U. M. Døhn**, None; **T. Lorenzen**, None; **L. Terslev**, None; **K. Larsen**, None; **A. P. Diamantopoulos**, None.

Abstract Number: 1961

Interobserver Agreement on Ultrasonographic and Magnetic Resonance Angiography Findings in Patients with Large Vessel Vasculitis

Andreas P Diamantopoulos[1,2], Julia Geiger[3], Frode Lohne[4], Geirmund Myklebust[5] and Wolfgang A. Schmidt[6], [1]Rheumatology, Haugesund Hospital for Rheumatic Diseases, Haugesund, Norway, [2]Rheumatology, Hospital of Southern Norway Trust, Kristiansand, Norway, [3]Department of Radiology, University Children's Hospital, Zurich, Switzerland, [4]Radiology, Hospital of Southern Norway Trust, Kristiansand, Norway, [5]Rheumatology, Hospital of Southern Norway, Kristiansand, Norway, [6]Medical Center for Rheumatology and Clinical Immunology Berlin-Buch, Immanuel Krankenhaus Berlin, Berlin, Germany

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Background/Purpose: Ultrasound and Magnetic resonance angiography (MRA) yields a high sensitivity and specificity regarding the diagnosis of cranial giant cell arteritis (GCA). Ultrasound and MRA can also depict extracranial large vessel vasculitis (LVV) in both GCA and Takayasu arteritis (TA) patients. Until now, no studies have examined the interobserver agreement of the ultrasonographic and MRA findings in LVV patients. Hence, the aim of this study was to examine the interobserver agreement of the ultrasound and MRA examination of temporal arteries and large vessels in LVV patients.

Methods: This study is a part of the MUSES project (Magnetic resonance angiography vs ultrasonography in Systemic large vessel vasculitis), a prospective cross-sectional study. Patients who were diagnosed with LVV by ultrasound, MRA or CTA were identified and included in the study at the Department of Rheumatology, Hospital of Southern Norway Trust in Kristiansand from January 2014 to January 2015. One ultrasonographer experienced in vascular ultrasound (APD) examined and recruited the LVV patients. MRA imaging was performed within one week after the ultrasound evaluation and one radiologist evaluated the MRA images locally (FL). The common temporal, temporal parietal branch, temporal frontal branch , carotid , subclavian , vertebral , axillary arteries, and thoracic aorta were scanned in all patients. Cranial arteries were assessed in T1-weighted high-resolution transverse slices post contrast, and the aorta and supraaortic arteries based on coronal MRA images. Films and images of both ultrasound and MRA evaluation of every artery were recorded, and two experts; one for vascular ultrasound (WAS) and one for MRA (JG) surveyed the data. Both experts were blinded to clinical and laboratory data. To calculate the inter-observer agreement between ultrasonographers (WAS, APD) and radiologists (FL, JG) the Cohen's kappa test has been used.

Results: Twenty-seven patients were included in this study [(12 males, 15 females, median age 69 years (IQR 62-76)]. Twenty-five patients were diagnosed with GCA and 2 with TA. Eight patients had new onset LVV and 19 had long lasting disease (median disease duration 2 years, IQR 0-5). Median CRP was 8 mg/l (IQR 3-24) and ESR 24 mm/hr. (IQR 9-53). None of the patients had affection of the vertebral artery and thoracic aorta on MRA.

The inter-observer agreement for the various arteries for both ultrasound and MRA are reported in table 1.

Conclusion: Ultrasonographic findings of temporal, aorta and supraaortic arteries in patients with LVV appears to be highly detectable and can be recorded in films for further evaluation. The low interobserver reliability in MRA could be partly explained by the sequences used for vascular imaging.

Table. 1

	Kappa values	
	Reliability Ultrasound (WAS, APD)	**Reliability MRA (FL, JG)**
Common temporal	**0.96**	**0.35**
Parietal branch	**0.85**	**0.29**
Frontal branch	**0.78**	**0.46**
Carotid arteries	**0.54**	**0.32**
Subclavian arteries	**0.78**	**0.20**
Vertebral arteries	**0.89**	**(-)**
Axillary arteries	**0.96**	**0.32**
Thoracic aorta	**1.00**	**(-)**

Disclosure: A. P. Diamantopoulos, None; **J. Geiger**, None; **F. Lohne**, None; **G. Myklebust**, None; **W. A. Schmidt**, GlaxoSmithKline, 5,Roche Pharmaceuticals, 5,Roche Pharmaceuticals, 8.

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Abstract Number: 1962

Inter-Rater Analysis of Ultrasound and Histological Findings in Patients with Suspected Giant Cell Arteritis

Raashid Luqmani[1], Ellen Lee[2], Surjeet Singh[3], Michael Gillett[2], Wolfgang A. Schmidt[4], Mike Bradburn[2], Bhaskar Dasgupta[5], Andreas P Diamantopoulos[6], Wulf Forrester-Barker[7], William Hamilton[8], Shauna Masters[9], Brendan McDonald[10], Eugene McNally[7], Colin T. Pease[11], Jennifer Piper[7], John Salmon[12], Allan Wailoo[2], Konrad Wolfe[13], Andrew Hutchings[14] and TABUL Sonographers Group and TABUL Pathologists Group, [1]Nuffield Department of Orthopaedics Rheumatology and Musculoskeletal Sciences, University of Oxford, Oxford, United Kingdom, [2]School of Health and Related Research, University of Sheffield, Sheffield, United Kingdom, [3]1Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences, University of Oxford, Oxford, United Kingdom, [4]Medical Center for Rheumatology and Clinical Immunology Berlin-Buch, Immanuel Krankenhaus Berlin, Berlin, Germany, [5]Rheumatology, Southend University Hospital, Essex, United Kingdom, [6]Department of Rheumatology, Hospital of Southern Norway Trust, Kristiansand, Norway, [7]Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences, University of Oxford, Oxford, United Kingdom, [8]Primary Care, University of Exeter, Exeter, United Kingdom, [9]Nuffield Department of Orthopaedics Rheumatology and Musculoskeletal Science, University of Oxford, Oxford, United Kingdom, [10]Department of Neuropathology and Ocular Pathology, Oxford University Hospitals NHS Trust, Oxford, United Kingdom, [11]Rheumatology, Leeds Teaching Hospitals NHS Trust, Leeds, United Kingdom, [12]Ophthalmology, Oxford University Hospitals NHS Trust, Oxford, United Kingdom, [13]Department of Pathology, Southend University Hospital, Essex, United Kingdom, [14]Health Services Research Unit, London School of Hygiene and Tropical Medicine, London, United Kingdom

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SESSION INFORMATION

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Background/Purpose:

Ultrasound is emerging as an alternative test to performing a temporal artery biopsy in the diagnosis of giant cell arteritis (GCA). Little is known of the variability in interpretation of these tests by sonographers and pathologists. We undertook an inter-observer analysis to assess agreement between sonographers in interpreting ultrasound videos, and between pathologists for biopsy images, in patients with suspected GCA.

Methods:

We developed a web exercise with 30 cases randomly sampled from patients with suspected GCA recruited to a large multicentre study comparing ultrasound with biopsy for the diagnosis of GCA. We used 5 practice cases, followed by the 30 unique cases and 6 interspersed repeats, showing ultrasound videos of both temporal arteries and high quality scanned images of biopsies. Trained sonographers and pathologists from the study were asked to assess the compatibility of the videos and images with a diagnosis of GCA and indicate how confident they were of the diagnosis. Inter-observer agreement between sonographers and between pathologists was evaluated using two-way random effects analysis of variance to estimate the intra-class correlation coefficient (ICC) for agreement. Intra-observer reproducibility was evaluated using kappa statistics for the 6 repeated cases.

Results:

All 12 sonographers agreed unanimously on 10/30 cases; 4 as GCA and 6 as not GCA. In 5 cases at least 3 sonographers differed from the majority. All 14 pathologists agreed unanimously on 11 cases; 6 as GCA and 5 as not GCA. In 5 cases at least 3 differed from the majority and in 1 case the pathologists were evenly divided between GCA and not GCA. Overall agreement was similar between the two groups: the ICC for sonographers 0.61 (95% CI 0.48, 0.75) and for pathologists 0.62 (95% CI 0.49, 0.76). After allowing for confidence in the interpretation of the videos and images, inter-observer agreement between sonographers (ICC 0.58, 95% CI 0.44, 0.72) was lower than between pathologists (ICC 0.72, 95% CI 0.60, 0.83). Evidence of giant cells was indicated by the original reporting pathologist in 8/30 cases; in 6/8, the pathologists unanimously judged the biopsy images to be consistent with GCA. For intra-observer reproducibility of the repeated cases the sonographers (raw agreement 86%, kappa 0.69) performed less well than the pathologists (raw agreement 92%, kappa 0.83).

Conclusion:

We have shown that the level of agreement between sonographers is similar to that between pathologists for assessing the compatibility of videos or images with a diagnosis of GCA. Pathologists performed better after allowing for certainty in interpretation and for intra-observer reproducibility. However, the level of agreement was not as high as might be expected and suggests scope for improved training for interpreting temporal artery ultrasound and further investigation of how histological abnormalities other than giant cells are interpreted by pathologists. Interpreting results to support or overturn a diagnosis of suspected GCA should be undertaken in the light of these findings.

Disclosure: R. Luqmani, GSK, 5,Chemocentryx, 5,Roche Pharmaceuticals, 5; **E. Lee**, None; **S. Singh**, None; **M. Gillett**, None; **W. A. Schmidt**, GlaxoSmithKline, 5,Roche Pharmaceuticals, 5,Roche Pharmaceuticals, 8; **M. Bradburn**, None; **B. Dasgupta**, GSK, Servier,UCB, 5; **A. P. Diamantopoulos**, None; **W. Forrester-Barker**, None; **W. Hamilton**, None; **S. Masters**, None; **B. McDonald**, None; **E. McNally**, None; **C. T. Pease**, None; **J. Piper**, None; **J. Salmon**, None; **A. Wailoo**, None; **K. Wolfe**, None; **A. Hutchings**, None.

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Abstract Number: 1963

Specialty of Provider Referring for Temporal Artery Biopsy Affects the Likelihood of Giant Cell Arteritis (GCA) Diagnosis

Lindsay Lally[1] and Robert F. Spiera[2], [1]Rheumatology, Hospital for Special Surgery, New York, NY, [2]Rheumatology, HSS, New York, NY
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Background/Purpose: Presenting signs/symptoms of GCA can be nonspecific and patients can initially present to a spectrum of clinical specialties. While temporal artery biopsy (TAB) is recommended for confirming a GCA diagnosis, many patients without GCA are referred for TAB and started on high-dose steroids while awaiting the procedure, which can result in toxicity. Several studies have evaluated clinical predictors of positive TAB among patients with suspected GCA but none have evaluated if the specialty of the provider referring for TAB affects the likelihood of a patient ultimately being diagnosed with GCA.

Methods: All TAB performed at a tertiary care center over 5 years were identified. Medical records were reviewed; those without adequate clinical information were excluded. Whether a patient was referred for TAB by a rheumatologist, internist, ophthalmologist, or neurologist was noted. Subjects were categorized according to 1990 ACR criteria and TAB status as having GCA or no GCA: those with GCA and negative TAB met ³3 ACR criteria and were treated as GCA for at least 6mths based on reviewing chart following TAB.

Results: Of 188 subjects analyzed, 52 (27.7%) ultimately were recognized as having GCA. 23 (12.2%) had positive TAB and clinical GCA, and 29 (15.4%) had negative TAB but were clinically diagnosed as GCA. There were a similar number of referrals from each of the 4 specialties. Rheumatologists were responsible for referring 28/52 (53.8%) of cases ultimately diagnosed as GCA for TAB. Compared to all other specialties, rheumatologists had the highest odds of referring a case ultimately deemed to have GCA for TAB. Patients referred by rheumatologists had 5.43 (95% CI: 2.70, 10.99) times the odds of having GCA compared to patients referred by internists, ophthalmologists, or neurologists ($p < 0.001$). Rheumatologists were also more likely to have referred a patient with a positive TAB than other specialists OR 3.41 (95% CI 1.40-8.33) p=0.007. Using rheumatologists as the reference group, patients referred by internists, neurologists or ophthalmologists all had a lower odds of being diagnosed with GCA (Table 1) Adjusting for presenting symptoms (PMR, vision loss, headache) that may cause referral bias, patients referred for TAB by rheumatologists remained more likely than those referred by other specialists to have GCA, OR 5.49(95% CI 2.60-11.63), p<0.001.

Conclusion: In this cohort, patients referred for TAB by rheumatologists had a significantly higher likelihood of having GCA or positive TAB compared to those referred by all other specialties. These data may support more wide-spread implementation of fast-track pathways, where feasible, which would permit a rheumatologic evaluation for all patients with suspected GCA prior to TAB.

Table 1: Odds of GCA Diagnosis By Referring Specialty

	Total Referrals for TAB (%)	GCA cases, (%)	Odds ratio (95% CI)*	P-value

*Odds of having GCA compared to patients referred by rheumatologists

Specialty	TAB, n(%)	n(%)	(95% CI)*	Value
Rheumatology	52 (27.7)	28 (53.8)		
Internal Medicine	47 (25.0)	15 (28.8)	0.40 (0.18-0.91)	0.029
Neurology	53 (28.2)	5 (9.6)	0.09 (0.03-0.26)	<0.001
Ophthalmology	36 (19.1)	4 (7.7)	0.11 (0.03-0.35)	<0.001

Disclosure: L. Lally, None; **R. F. Spiera**, None.

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Abstract Number: 1964

Biomarkers in Temporal Artery Biopsies and Sera of Patients with Giant Cell Arteritis

Katja Lakota[1], Tadeja Kuret[2], Polona Žigon[1], Ziga Rotar[1], Matija Tomsic[1], Saša Čučnik[1,2], Snezna Sodin Semrl[1,3] and Alojzija Hocevar[1], [1]Department of Rheumatology, University Medical Centre Ljubljana, Ljubljana, Slovenia, [2]Faculty of Pharmacy, University of Ljubljana, Ljubljana, Slovenia, [3]Faculty of Mathematics, Natural Science and Information Technology, University of Primorska, Koper, Slovenia

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Background/Purpose: Giant cell arteritis (GCA) is a large- and medium- vessel arteritis characterized by a range of histological patterns of vascular wall injury. The temporal artery biopsy (TAB), although invasive, is still the gold standard for diagnosis. Markers in sera and tissues of the arteries associated with the pathology of GCA might serve as an aid in diagnosing and understanding GCA pathogenesis. Our aim was to determine mRNA levels of selected cytokines, chemokines, acute phase proteins, adhesion molecules and matrix metalloproteinases (MMPs) as well as their inhibitors in TAB specimens of patients with GCA as compared to patients without GCA. We also aimed to determine sera concentrations of 21 selected proteins in patients and healthy blood donors.

Methods: Biopsies of temporal arteries were obtained from subjects suspected to have GCA. In GCA cases, TAB was performed before the introduction of glucocorticoids. Specimens were processed in the TissueLyser (Qiagen) and RNA was isolated (miRCURY, Exiqon). QPCR was used to determine the mRNA expression levels of selected proteins in TABs of GCA (n=6, 5 females, mean age 67) and nonGCA patients (n=6, 4 females, mean age 75). Concentrations of sera proteins were measured by Luminex using custom prepared Premixed kit (R&D Systems, Abingdon) in GCA (n=93, 66 female, mean age 73), nonGCA patients (n=29, 13 females, mean age 72) and blood donors (n=8, 1 female, mean age 44).

Results: Ferritin, MMP9, TIMP1, TIMP2, VCAM and MARCO showed increased mRNA expression in TAB specimens of GCA patients compared to nonGCA patients (Table 1), while mRNA levels of IL-12, IL-8, ApoA1 and MMP2 were decreased. Levels of CRP, SAA, IL-6 and haptoglobin were significantly increased in sera of GCA compared to the nonGCA group (Table 2). MMP9 and MMP2 protein levels had a divergent trend of change, specifically MMP9 was increased in sera of GCA patients as compared to nonGCA, while MMP2 was decreased. Interestingly, CHI3L1, IFNg, IL-10, IL-8, TNFα, VCAM1 sera levels were significantly elevated in GCA patients versus blood donors.

Conclusion: MMP/TIMP ratios in TABs and acute phase protein levels of SAA, CRP, haptoglobin, as well as IL-6 in sera significantly distinguish between nonGCA and GCA patients.

Table 1: Expression of mRNA in TAB specimens of GCA vs. nonGCA patients

		Cytokines			Chemokine	Acute phase proteins		Matrix Metalloproteinases and their Inhibitors						Adhesion molecules		Macrophage receptor
		Th1		Th17				MMPs			inhibitors		ratio			
Patients		IL-12	TNFα	IL-6	IL-8	ferritin	Apo A1	MMP2	MMP9	MMP12	TIMP1	TIMP2	MMP2/ TIMP2	MMP9/ TIMP1	VCAM	ICAM	MARCO
non GCA patients	1	1.35	1.50	1.47	1.33	0.55	1.29	1.30	0.95	0.48	0.10	0.46	2.85	9.85	0.35	1.49	0.70
	2	1.00	0.70	1.16	1.06	1.50	1.09	1.12	0.55	0.78	0.51	1.10	1.02	1.07	1.39	0.88	1.00
	3	1.17	1.22	1.24	1.22	0.20	1.47	1.83	0.49	0.53	0.03	0.21	8.88	14.11	0.06	1.32	0.46
	4	1.71	1.10	1.51	1.61	0.32	1.73	2.67	1.10	0.57	0.06	0.27	9.78	19.20	0.13	1.91	0.66
	5	1.84	1.65	1.69	1.83	0.37	1.60	3.10	0.61	0.66	0.06	0.25	12.51	11.00	0.11	2.34	0.50
	6	2.55	3.04	2.54	2.54	0.43	2.32	3.84	1.74	1.07	0.07	0.16	23.47	23.62	0.10	2.31	0.97
Median		**1.53**	1.36	1.49	**1.47**	**0.40**	**1.54**	**2.25**	**0.78**	0.62	**0.07**	**0.26**	**9.33**	**12.56**	**0.12**	1.70	**0.68**
GCA patients	7	2.21	1.66	2.03	1.99	2.07	1.32	1.77	1.24	0.72	0.39	1.51	1.18	3.19	0.56	1.65	2.26
	8	1.18	2.44	1.55	1.17	0.83	0.79	0.73	1.07	0.47	0.71	0.65	1.13	1.51	4.11	1.74	1.16
	9	0.52	1.11	0.71	0.70	1.45	0.46	0.64	1.22	0.65	0.59	0.86	0.75	2.06	1.52	0.88	1.97
	10	0.57	0.36	0.55	0.68	0.51	0.57	1.49	0.43	0.21	0.18	0.52	2.88	2.38	2.17	0.48	0.28
	11	1.00	1.00	1.00	1.00	1	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
	12	2.17	2.55	2.17	2.02	0.46	2.00	1.85	0.78	0.86	0.37	0.63	2.95	2.13	0.72	2.71	1.08
Median		**1.09**	1.38	1.27	**1.08**	**0.91**	**0.90**	**1.25**	**1.04**	0.69	**0.49**	**0.75**	**1.15**	**2.09**	**1.26**	1.33	**1.12**

Table 2: Concentration of selected proteins in GCA patients as compared to nonGCA and blood donors

	Analyte median (IQR)			Mann Whitney test (p values)	
	Blood donors (n=8)	nonGCA patients (n=6)	GCA patients (n=42)	Blood donors vs. GCA patients	nonGCA patients vs. GCA patients
CD62L	698.7 (641.3-770.2)	797.4 (788.4-814.9)	757.5 (696.2-825.7)	0.229	0.165
CHI3L1	10.3 (7.7-15.2)	42.7 (29.7-106.3)	78.7 (28.5-118.6)	**<0.0001**	0.732
ICAM1	399.0 (178.1-670.4)	533.0 (324.5-801.5)	332.9 (163.2-774.2)	0.832	0.366
IFN γ	0	0 (0-0.1)	0.1 (0.0-0.5)	**0.026**	0.258
IL-10	1.4 (0.7-3.6)	4.1 (2.9-4.7)	3.8 (2.9-5.8)	**0.039**	0.614
IL-12	0 (0-27.9)	0 (03.5)	0 (0-3.5)	0.525	0.842
IL-22	9.7 (1.1-19.3)	0 (0-1.7)	4.3 (0-14.2)	0.290	0.244
IL-33	0.4 (0-0.9)	2.1 (0.8-2.5)	0.8 (0.0-1.6)	0.237	0.311
IL-4	0 (0-1.8)	0	0 (0-10.8)	0.268	0.143
IL-8	7.8 (6.7-16.6)	635.3 (243.2-925.2)	444.8 (74.6-1253.6)	**<0.0001**	0.827
MMP 2	71.2 (67.6-75.2)	77.5 (67.5-79.5)	74.3 (64.5-79.3)	0.643	0.513
MMP9	17.0 (9.4-28.5)	60.9 (36.6-94.5)	87.9 (46.2-104.7)	**<0.0001**	0.585
TNF α	0	3.2 (0.4-6.5)	3.6 (0.6-12.8)	**0.001**	0.616
VCAM1	608.4 (58.3-794.6)	1084.4 (1005.4-1774.1)	862.2 (741.6-1144.6)	**0.032**	0.350
	/	nonGCA patients (n=29)	GCA patients (n=93)	/	nonGCA patients vs. GCA patients
SAA		24.8 (3.4-173.0)	205.0 (70.2-469.0)		**0.001**
IL6		7.0 (1.0-15.3)	23.0 (7.0-42.0)		**0.001**
CRP		14.5 (5.0-48.0)	66.5 (36.0-123.5)		**<0.0001**
Feritin	/	271 (141.5-542.5)	315 (156.0-488.5)	/	0.921
Fibrinogen		6.9 (5.1-8.1)	7.6 (6.4-8.5)		0.155
PCT		0.1 (0-0.1)	0.1 (0-0.1)		0.901
Haptoglobin		3.1 (4.6-4.2)	5.0 (3.4-6.1)		**<0.0001**

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View Abstract and Citation Information Online - http://acrabstracts.org/abstract/biomarkers-in-temporal-artery-biopsies-and-sera-of-patients-with-giant-cell-arteritis

Abstract Number: 1965

T Cell Activation, Proliferation and Differentiation Markers Lack Diagnostic Accuracy for Detecting Active GCA and PMR

Kornelis S.M. van der Geest[1], Wayel H. Abdulahad[2], Qi Wang[2], Mirjam Roffel[2], Gerda Horst[2], Abraham Rutgers[2], Annemieke M.H. Boots[2] and **Elisabeth Brouwer**[2], [1]Dept. of Rheumatology and Clinical Immunology, University Medical Center Groningen, University of Groningen, Groningen, Netherlands, [2]Rheumatology and Clinical Immunology, University Medical Center Groningen, University of Groningen, Groningen, Netherlands

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Session Title: Vasculitis Poster II

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: The most important biomarker in GCA and PMR patients is increased erythrocytes sedimentation rate (ESR) and/ or increased serum level of C-reactive protein (CRP). However, ample evidence indicates that the ESR and CRP are not increased at diagnosis in a subset of patients [1, 2]. Furthermore, recent data indicate that the ability of these inflammatory markers to detect active disease during tapering of corticosteroid may be compromised [3]. SinceT cell play a critical role in the development of both diseases [4], we set out to investigate cellular makers of T cell activation, proliferation and differentiation for their ability to detect active disease in patients with GCA and PMR.

Methods: CD4 counts, CD8 counts and absolute numbers of CD4 and CD8 T cell differentiation subsets were determined by flow cytometry in peripheral blood of 28 newly-diagnosed, untreated GCA/PMR patients, 16 corticosteroid treated GCA/PMR patients in remission and 25 healthy controls. Expression of the activation marker HLA-DR and proliferation marker Ki-67 determined. Receiver operating characteristic (ROC) analysis with area under the curve (AUC) and Spearman's correlation coefficients were performed.

Results: CD4 T cell counts were decreased in newly-diagnosed GCA and PMR patients. Central memory CD4 T cells were decreased in GCA patients only, and terminally differentiated CD4 T cells in PMR patients only. In GCA patients, CD4 T cells showed increased percentages of HLA-DR+ and Ki-67+ cells. No modulations were observed in the CD8 T cell compartment of GCA and PMR patients. Eleven CD4 T cell parameters provided only moderate discrimination between newly-diagnosed GCA/PMR patients and healthy controls, as indicated by AUC's of 0.7-0.8. Of these markers only the percentage of Ki-67+ terminally differentiated CD4 T cells in GCA patient normalized during remission, and correlated weakly with the ESR and CRP.

Conclusion: Although the CD4 T cell compartment was modulated in GCA and PMR patients, cellular markers of CD4 T cell activation, proliferation and differentiation are not useful for detecting active GCA and PMR.

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Disclosure: K. S. M. van der Geest, None; **W. H. Abdulahad**, None; **Q. Wang**, None; **M. Roffel**, None; **G. Horst**, None; **A. Rutgers**, None; **A. M. H. Boots**, None; **E. Brouwer**, Abbvie, 2,Pfizer Inc, 2.

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Abstract Number: 1966

Active PMR and GCA Is Associated with Changes in Monocyte Subset Composition

Qi Wang[1], Kornelis S.M. van der Geest[2], Wayel H. Abdulahad[1], Johanna Westra[3], Annemieke M.H. Boots[1] and **Elisabeth Brouwer**[1], [1]Rheumatology and Clinical Immunology, University Medical Center Groningen, University of Groningen, Groningen, Netherlands, [2]Hanzeplein 1, Hpc: Aa21, University Medical Center Groningen, University of Groningen, Groningen, Netherlands, [3]Rheumatology and Clinical Immunology, University of Groningen, University Medical Center Groningen, Groningen, Netherlands

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Background/Purpose: Giant cell arteritis (GCA) and polymyalgia rheumatica (PMR) are two closely related syndromes affecting older people. Proinflammatory cytokine IL-6 is found increased in both GCA/PMR patients and in the aged healthy population[1]. Pro-inflammatory monocytes, identified by CD16 and CD14 expression, increase with age and are potent producers of IL-6[2]. Importantly, monocyte-derived macrophages have been identified in the inflamed arteries of GCA and contribute to the immunopathology of GCA[3]. Yet, peripheral monocyte subsets are less well studied in GCA and PMR patients. In the current study, we assessed the distribution of different monocyte subsets in newly diagnosed GCA and PMR patients before and after glucocorticoid (GC) treatment.

Methods: Peripheral blood samples of 16 newly-diagnosed GCA patients, 17 newly-diagnosed PMR patients and 16 age-matched, healthy controls (HCs) were studied. In a prospective, longitudinal study design, samples were obtained from 12 GCA and 10 PMR patients who were in remission after 12 weeks of treatment with GCs. Absolute numbers of total monocytes and classical($CD14^{bright}CD16^{-}$), intermediate($CD14^{bright}CD16^{dim}$) and non-classical($CD14^{dim}CD16^{bright}$) monocytes were determined by truecount and flow cytometry.

Results: Total numbers of circulating monocytes were increased in newly-diagnosed PMR patients but not in GCA patients when compared to age-matched HCs. Following 12 weeks of GC treatment, monocyte numbers normalized in PMR patients. When analysing absolute numbers of classical, intermediate and non-classical monocytes, we found the classical monocytes increased in PMR. No significant changes were noted in GCA. GC treatment in GCA tended to decrease numbers of non-classical monocytes ($p=0.091$).

When analysing relative changes in monocyte composition, the increase in classical monocytes in PMR was mirrored by a relative decrease of non-classical monocytes while proportions of intermediate type monocytes were unchanged. Interestingly, although we did not detect significant changes in absolute numbers, a similar decrease of non-classical monocytes was observed in newly diagnosed GCA patients. Moreover, GC treatment of GCA led to a further relative decrease of non-classical monocytes only.

Conclusion: We are the first to show that peripheral monocyte numbers are modulated during active PMR but not GCA. Treatment with GCs normalised monocyte numbers in PMR. Active disease in both PMR and GCA led to changes in monocyte composition showing decreases of non-classical monocytes. Different dynamics of monocyte subset distribution in PMR and GCA may help to unravel disease pathogenesis. Additional studies on different subsets of monocytes in GCA and PMR are ongoing.

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Disclosure: Q. Wang, None; **K. S. M. van der Geest**, None; **W. H. Abdulahad**, None; **J. Westra**, None; **A. M. H. Boots**, None; **E. Brouwer**, Abbvie, 2,Pfizer Inc, 2.

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composition

Abstract Number: 1967

Deregulation of Interleukin-22 Pathway in Giant Cell Arteritis

Stefania Croci[1], Alessandro Zerbini[1], Francesco Muratore[2], Lucia Belloni[3], Francesco Ciccia[4], Luigi Boiardi[2], Elena Simonazzi[3], Alberto Cavazza[5], Luca Cimino[6], Antonio Moramarco[6], Aroldo Rizzo[7], Maria Parmeggiani[8] and Carlo Salvarani[9,10], [1]Clinical Immunology, Allergy and Advanced Biotechnologies Unit,, Arcispedale S Maria Nuova-IRCCS, Reggio Emilia, Italy, [2]Rheumatology Service, Arcispedale S Maria Nuova, IRCCS, Reggio Emilia, Italy, [3]Clinical Immunology, Allergy and Advanced Biotechnologies Unit, Arcispedale S Maria Nuova-IRCCS, Reggio Emilia, Italy, [4]Rheumatology Unit, University of Palermo, Palermo, Italy, [5]Pathology Unit, Arcispedale S Maria Nuova-IRCCS, Reggio Emilia, Italy, [6]Ophthalmology Unit, Arcispedale S Maria Nuova-IRCCS, Reggio Emilia, Italy, [7]Pathology Unit, Azienda Ospedaliera Ospedali Riuniti Villa Sofia-Cervello, Palermo, Italy, [8]. Clinical Immunology, Allergy and Advanced Biotechnologies Unit, Arcispedale S Maria Nuova-IRCCS, Reggio Emilia, Italy, [9]Rheumatology, Arcispedale S.Maria Nuova, Reggio Emilia, Italy, [10]Rheumatology, Arcispedale S Maria Nuova-IRCCS, Reggio Emilia, Italy
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Background/Purpose: Interleukin-22 (IL-22) is produced by immune cells but acts only on non-hematopoietic cells, particularly at the barrier interface. We thus hypothesized that IL-22 pathway might be deregulated in giant cell arteritis (GCA), an inflammatory vasculitis affecting large and medium-sized arteries.

Methods: 22 patients subjected to temporal artery biopsy (TAB) at the Arcispedale Santa Maria Nuova-IRCCS (Reggio Emilia, Italy) for a suspicion of GCA were included in the study. They were divided in two groups after histological analysis: GCA patients with TABs showing a transmural immune infiltrate (n=15) and patients with non-inflamed TABs who received a different diagnosis (n=7). Healthy subjects were also included for the analyzes in peripheral blood (n=10). Expression of IL-22 and IL-22 receptor chain 1 (IL-22R1) were determined in TABs by immunohistochemistry. Levels of IL-22 in peripheral blood mononuclear cells (PBMCs) were investigated by real-time PCR and in plasma by ELISA.

Results: IL-22 and IL-22R1 were more expressed in inflamed TABs compared to normal TABs. IL-22 was mainly expressed by granulomas and cells of the media layer. IL-22R1 was mainly expressed by endothelial cells facing the arterial lumen. Expression of IL-22 mRNA was higher in PBMCs from GCA patients compared to healthy subjects. Similarly, GCA patients had an higher concentration of IL-22 in plasma. Levels of IL-22 in plasma positively correlated with IL-22 gene expression in PBMCs and with serum C-reactive protein. Ongoing studies with flow cytometry will allow to determine if Th22 lymphocytes are also deregulated in GCA patients.

Conclusion: Increased production of IL-22 might be involved in GCA pathogenesis.

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Abstract Number: 1968

Distinct Distribution Patterns of Large Vessel Vasculitis Assessed with 18f-FDG PET/CT: Evidence from Principal Component and Cluster Analyses

Alessandra Soriano[1], Giulia Pazzola[1], Pierluigi Boiardi[1], Francesco Muratore[1], Pierluigi Macchioni[1], Raffaella Aldigeri[2], Massimiliano Casali[3], Annibale Versari[3] and Carlo Salvarani[1,4], [1]Rheumatology Unit, Internal Medicine Department, Arcispedale Santa Maria Nuova - IRCCS, Reggio Emilia, Italy, [2]Department of Clinical and Experimental Medicine, University of Parma, Parma, Italy, [3]Nuclear Medicine Unit, Arcispedale Santa Maria Nuova - IRCCS, Reggio Emilia, Italy, [4]Rheumatology Unit, Internal Medicine Department, Arcispedale Santa Maria Nuova - IRCCS, and University of Modena and Reggio Emilia, Reggio Emilia, Italy
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Background/Purpose:

The performance of ^{18}F-FDG PET/CT in the diagnosis and assessment of disease activity of LVV has not been fully established. The interpretation of data from ^{18}F-FDG PET/CT studies on LVV is difficult mainly due to (1) the scarcity of studies; (2) the heterogeneity of the LVV populations examined in each study; (3) the variety in the qualitative and semi-quantitative methods for imaging analyses. In the absence of gold standard parameters for the assessment of LVV arterial inflammation *via* ^{18}F-FDG PET/CT, there is a great need to develop analytical methodologies useful to properly exploit the information derived from such studies.

Latent class analysis has recently been used to investigate alternative ways to classify LVV in few angiographic and MRI studies, on the basis of distribution patterns of arterial lesions. Other classical techniques - such as principal component analysis (PCA) and cluster analysis (CA) - have not yet been applied to investigate the distribution patterns of LVV, assessed by ^{18}F-FDG PET/CT.

The aim of our study was to investigate whether PCA and CA are useful methods in identifying distinct distribution patterns of LVV, according to the specific diagnostic entity examined (giant cell arteritis, GCA; Takayasu's arteritis, TA).

Methods:

A total of 135 ^{18}F-FDG PET/CT studies performed for extra-cranial evaluation of LVV have been retrospectively examined by a nuclear physician blinded to clinical data. Maximum standardized uptake values (SUVmax) in 14 vascular districts including aortic segments (ascending aorta thoracic aorta, aortic arch, descending thoracic aorta and abdominal aorta) and the main tributaries (carotid, subclavian, axillary, iliac and femoral arteries; each bilaterally) have been measured and then transformed into *Z*-scores. Identification of distribution patterns of vascular involvement has been performed using PCA and agglomerative hierarchical CA (*SPSS Statistics*, version 22nd).

Results:

PCA and CA performed on the entire population of LVV subjects identified 3 groups of vascular districts with similar trends in terms of standardized SUVmax: (1) epiaortic arteries; (2) aortic arch and ascending aorta; (3) descending and abdominal aorta, together with iliac and femoral arteries. The same aggregation pattern has been observed in the PCA and CA performed on the GCA group, but not on the TA group, where a component including the entire aortic district (thoracic and abdominal aorta) was identified.

Conclusion:

PCA and cluster analysis approach revealed a subtle skewing in terms of distribution patterns of arterial involvement between the two main variants of LVV, assessed by ^{18}F-FDG PET/CT SUVmax values. The influence of atherosclerosis and immunosenescence on the different trends in the aorta districts of TA and GCA needs to be further elucidated.

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Disclosure: A. Soriano, None; **G. Pazzola**, None; **P. Boiardi**, None; **F. Muratore**, None; **P. Macchioni**, None; **R. Aldigeri**, None; **M. Casali**, None; **A. Versari**, None; **C. Salvarani**, None.

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Abstract Number: 1969

Can We Predict the Relapse of Giant Cell Arteritis?

Alojzija Hocevar, Rok Ješe, Ziga Rotar, Sonja Praprotnik, Matija Tomšič and Saša Čučnik, Department of Rheumatology, University Medical Centre Ljubljana, Ljubljana, Slovenia
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Background/Purpose:

Relapses during glucocorticoid (GC) tapering are frequent in giant cell arteritis (GCA). Anemia at the time of GCA diagnosis was a predictor of flare in a recent study.[1] We aimed to determine the markers of relapsing GCA.

Methods:

At a single secondary/tertiary rheumatology center we prospectively followed patients diagnosed with GCA between 01.09.2011 and 30.09.2014. Follow up visits with predetermined clinical and laboratory tests were performed 12, 24, 48, 96 and 144-weeks after diagnosis. Patients who completed follow up visits at 6 months or later were included in the analysis. Patients were treated in line with the EULAR recommendations.[2] In short, patients with uncomplicated GCA with initial oral methylprednisolone (MP) 32-48 mg qd, while those with ischemic complications or large vessel disease first received MP 250 mg on 3 consecutive days intravenously. MP tapering was started 2-4 weeks after treatment initiation slowly to 4 mg qd which was continued for at least 1.5 years. In patients who relapsed during the MP tapering unscheduled visits were arranged and treatment was adjusted.

Results:

During the observation period 74 (71.6% female) new GCA cases were identified, with a median (IQR) age 73.3 (67.3-77.2) years and symptom duration 30 (14-77) days. One patient died of cancer during the initial diagnostic work-up, 1 refused the treatment and 2 were lost to follow up. The remaining 70 (94.6%) patients were followed for a median (IQR) 102 (51–126) weeks. Throughout the observation period GCA relapsed in 32/70 (45.7%) patients. One patient suffered visual loss at relapse. One patient had two relapses, others one episode. Median (IQR) time to relapse was 24.8 (13.5–44.0) weeks. Median (IQR) prednisolone equivalent dose of MP at relapse was 6.0 (4.0-12.0) mg. Treatment adjustments in patients who relapsed included a temporary increase of MP dose (32/32), and add-on therapy with leflunomide 20 mg qd (18/32) or weekly methotrexate (2/32). Baseline characteristics of patients who relapsed and those who did not are presented in Table 1. At baseline, the patients who relapsed had a significantly higher erythrocyte sedimentation rate (p=0.024), C-reactive protein (p=0.007), as well as the serum amyloid A (p=0.002), haptoglobin (p=0.002), and fibrinogen (p=0.031) levels than those who did not. Disease duration before treatment introduction, large vessel disease, GC dosing scheme and anemia were not a predictor of the GCA relapses.

Characteristic	**Relapsed (32)**	**Nonrelapsed (38)**	**p value**
Median age (IQR) [years]	73.2 (65.7–77.0)	73.2(68.6–75.7)	0.596
% female	68.8	71.1	1.0
Median (IQR) disease duration [days]	30 (12–101)	30 (14–60)	0.855
% general symptoms	68.8	73.7	0.791
% PMR	15.6	21.1	0.759
% headache	65.6	78.9	0.283
% jaw claudication	31.3	39.5	0.617
% visual symptoms	31.3	36.8	0.801
% dry cough	25.0	13.2	0.232
% clinically changed TA	59.4	60.5	1.0
% LVV	38.7	31.3	0.603
% smoking history	43.8	36.8	0.628
IV pulse MP (250 mg)	43.8	42.1	1.0
Median (IQR) MP dose [mg/kg BW]	0.7 (0.6-0.8)	0.7(0.6-0.8)	0.675
Median (IQR) ESR [mm/h]	94 (71–107)	70 (52–90)	**0.024**
Median (IQR) CRP [mg/l]	90 (67–124)	52 (32–70)	**0.007**
Median (IQR) hemoglobin [g/l]	117 (103–124)	119 (108–130)	0.142
Median (IQR) platelets [x 10^9/l]	364 (305–440)	346 (286–430)	0.419
Median (IQR) albumin [mg/l]	31 (30-34)	34 (29–37)	0.106
Median (IQR) SAA [mg/l]	299 (178–738)	115 (40–270)	**0.002**
Median (IQR) ferritin [mcg/l]	366 (192–633)	210 (124–476)	0.149
Median (IQR) fibrinogen [g/l]	8.3 (7.9–8.6)	7.1 (6.1–8.4)	**0.031**
Median (IQR) haptoglobin [g/l]	5.7 (5.2–6.8)	3.7 (3.0–5.1)	**0.002**
Median (IQR) IL-6 [ng/l]	30.0 (8.0-80.8)	19.0 (6.3-36.3)	0.157

Legend: PMR p*olymyalgia rheumatica*; TA temporal arteries; LVV large vessel vasculitis (US or PET/CT); ESR erythrocyte sedimentation rate; CRP C-reactive protein; SAA serum amyloid A; IL-6 interleukin 6; BW body weight; IV pulse MP intravenous methyl-prednisolone pulse 250 mg qd on 3 consecutive days

In our cohort higher markers of systemic inflammation at baseline predicts the GCA relapse during the glucocorticoid taper.**Conclusion:**

References:

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Abstract Number: 1970

Incidence and Predictors of Thoracic Aortic Damage in Biopsy-Proven Giant Cell Arteritis: A Single-Institution Cohort Study

Matthew J. Koster[1], Cristian Labarca[2], Cynthia S. Crowson[3], Eric L. Matteson[1] and Kenneth J. Warrington[1], [1]Rheumatology, Mayo Clinic, Rochester, MN, [2]Rheumatology, Clinica Alemana Universidad del Desarrollo, Santiago, Chile, [3]Health Sciences Research, Mayo Clinic, Rochester, MN
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Background/Purpose: Patients with giant cell arteritis (GCA) are at an increased risk for aortic structural damage; however, the timing and predisposing characteristics for development of aortic aneurysm is poorly understood. The aim of this study was to evaluate the incidence and predictors of thoracic aortic aneurysm in a large single-institution cohort of patients with biopsy-proven GCA.

Methods: A retrospective review was performed to identify all patients with biopsy-proven GCA from 1998 through 2013. Demographic, clinical, laboratory, radiographic, and treatment data at baseline and subsequent followup visits were collected. Kaplan-Meier methods were used to estimate cumulative incidence and Cox models were used to examine potential predictors of development of aneurysm/dilatation of the thoracic aorta.

Results: The cohort included 286 patients with biopsy-proven GCA (213 females and 73 males, mean [±SD] age 75 [±7.6] years) with a mean (±SD) follow up of 6 (±3.9) years.

130 patients had 280 imaging studies (41% magnetic resonance angiography [MRA], 55% computed tomographic angiography [CTA] and 4% conventional angiography). The median time from diagnosis to first imaging study was 0.2 [interquartile range (IQR) 0.0, 2.7] years. Of the 130 patients, 48% underwent follow up imaging studies.

At the first imaging study, 14 (11%) patients had evidence of aneurysm or dilatation of the thoracic aorta and 28 (22%) patients had thoracic aorta thickening. Excluding prevalent cases, the cumulative incidence (±SE) for aneurysm/dilatation of the thoracic aorta during followup was 0% at both 1-yr and 2-yrs but increased to 9% (±0.4) at 5-years. Among all patients with GCA evaluated with vascular imaging, thoracic aortic aneurysm/dilatation was detected in 11% (±3) at 1-yr, 11% (±3) at 2-yrs, and 15% (±3) at 5-yrs.

Patient baseline demographics, cardiovascular risk, clinical presentation, laboratory values, and initial treatment were assessed to predict incidence of thoracic aortic damage. Baseline thickening of the thoracic aorta was not a risk factor for subsequent aneurysm/dilatation (p=0.99). Neither the presence of relapse (p=0.99) nor the number of relapses (p=0.65) were associated with development of thoracic aortic damage [HR (95% CI): 0.88 (0.50, 1.54); p=0.65]. Furthermore, there was no difference in initial prednisone dose between patients who did and did not develop aortic damage. The sole predictor for development of thoracic aortic aneurysm/dilatation was a history of smoking [HR (95% CI) 28.1: (1.59, 495.71); p=0.023].

Conclusion: In our cohort, thoracic aortic aneurysm/dilatation was seen in 11% of patients at baseline evaluation and increased to 15% at 5-yrs after diagnosis. Former smokers were at a 28-fold increased risk for developing thoracic aortic damage. Surveillance for aortic damage should be pursued in all patients with GCA, particularly those with a smoking history. Prospective investigations into screening methods and optimal frequency are warranted

Disclosure: M. J. Koster, None; **C. Labarca**, None; **C. S. Crowson**, None; **E. L. Matteson**, Novartis/Sanofi/Centocor-Jansen/Celgene/Amgen/Roche/Genentech/Mesoblast/Pfizer, 2; **K. J. Warrington**, None.

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Abstract Number: 1971

Healthcare Utilization and Direct Medical Costs of Giant Cell Arteritis

Matthew J. Koster[1], Sara J. Achenbach[2], Cynthia S. Crowson[2], Eric L. Matteson[1], Hilal Maradit Kremers[2] and Kenneth J. Warrington[1], [1]Rheumatology, Mayo Clinic, Rochester, MN, [2]Department of Health Sciences Research, Mayo Clinic, Rochester, MN
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SESSION INFORMATION
Session Date: Monday, November 9, 2015

Session Title: Vasculitis Poster II
Session Type: ACR Poster Session B
Session Time: 9:00AM-11:00AM

Title: Healthcare Utilization and Direct Medical Costs of Giant Cell Arteritis

Background/Purpose: Giant cell arteritis (GCA) is the most common systemic vasculitis in patients aged ≥ 50 years. Few studies have evaluated the economic impact of this condition and have been limited to inpatient-only data sources. Although the majority of healthcare for patients with GCA is provided as an outpatient, utilization and costs from this healthcare sector is largely unknown.

Methods: This study utilized a retrospective, population-based cohort of patients diagnosed with GCA, as defined by 1990 ACR criteria, in 1982-2009 and a reference cohort of patients without GCA matched on age, sex, and calendar year from the same population. Standardized cost data (inflation-adjusted to 2014 dollars) for 1987-2014 and outpatient utilization data for 1995-2014 were obtained from the Mayo Clinic Cost Data Warehouse and analyzed from one year before and up to five years after the GCA diagnosis/index date. Utilization and costs were compared between GCA and non-GCA cohorts using signed rank two-tailed paired analyses.

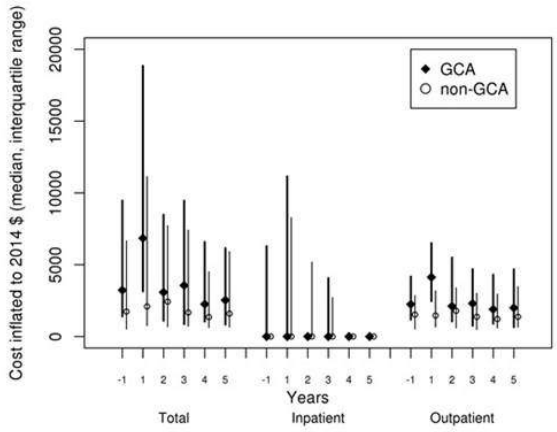
Results: The GCA cohort consisted of 147 patients (118 female, 29 male) with a mean (±SD) age of 77.2 (±8.2). The non-GCA cohort comprised 147 patients with a mean (±SD) age of 76.9 (±8.5) years.

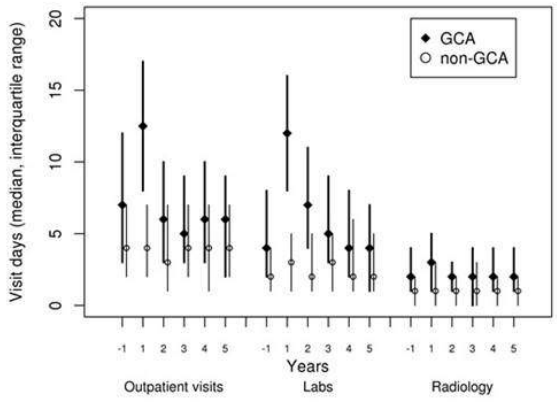
During the year preceding diagnosis, excess healthcare cost related to GCA was only significantly increased in the month immediately preceding GCA diagnosis [mean (±SD) excess cost $1127 (±5154)]. Following diagnosis, significant annual excess outpatient cost was observed for patients with GCA in each of the first four years [mean excess cost (±SD): 0-1 yrs $1307 (±15581), p<0.001; 1-2yrs $908 (±5917), p=0.009; 2-3 yrs $1324 (±4648), p=0.007; 3-4 yrs $609 (±4596), p=0.04] but was similar between GCA and non-GCA subjects in the 5th year. There were no significant differences in inpatient costs between GCA and non-GCA subjects.

Patients with GCA had higher utilization of laboratory visit days annually for each of the first 3 years following diagnosis, as well as increased outpatient physician visits and combined radiology for years 0-1, 1-2, and 3-4 years (see figure). Ophthalmologic procedures/surgery were increased for years 0-1, 1-2, and 4-5. Emergency medicine visits, musculoskeletal and cardiovascular procedures/surgery were similar between GCA and non-GCA groups throughout the study period.

Conclusion: Direct medical costs were increased in the month preceding and outpatient costs were increased in the first 4 years following GCA diagnosis and then return to levels similar to non-GCA subjects. A higher utilization of outpatient physician, laboratory and radiology visits, as well as ophthalmologic procedures among these patients accounts for the observed increased cost of care.

Figure. Costs (upper panel) and utilization of health care resources (lower panel) in patients with GCA and non-GCA subjects by year of followup from one year prior to 5 years after GCA diagnosis/index date





Disclosure: M. J. Koster, None; **S. J. Achenbach**, None; **C. S. Crowson**, None; **E. L. Matteson**, Novartis/Sanofi/Centocor-Jansen/Celgene/Amgen/Roche/Genentech/Mesoblast/Pfizer, 2; **H. Maradit Kremers**, None; **K. J. Warrington**, None.

Abstract Number: 1972

Cardiovascular and Cerebrovascular Disease and Social Deprivation in Patients with Giant Cell Arteritis

Joanna Robson[1], Amit Kiran[2], Andrew Hutchings[3], Joseph Maskell[4], Nigel K Arden[5], Willie Hamilton[6], Bhaskar Dasgupta[7,8] and Raashid Luqmani[9], [1]Nuffield Department of Orthopaedics Rheumatology and Musculoskeletal Sciences, University of Oxford, University of Oxford, Oxford, United Kingdom, [2]Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Science, University of Oxford, Oxford, United Kingdom, [3]Department of Health Services Research and Policy, London School of Hygiene and Tropical Medicine, London, United Kingdom, [4]Faculty of Medicine, University of Southampton, Southampton, United Kingdom, [5]Oxford NIHR Musculoskeletal Biomedical Research Unit, University of Oxford, Oxford, United Kingdom, [6]Primary Care, University of Exeter, Exeter, United Kingdom, [7]Southend University Hospital, Southend, United Kingdom, [8]Rheumatology, Southend University Hospital, Essex, United Kingdom, [9]Nuffield Department of Orthopaedics Rheumatology and Musculoskeletal Sciences, University of Oxford, Oxford, United Kingdom

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Session Time: 9:00AM-11:00AM

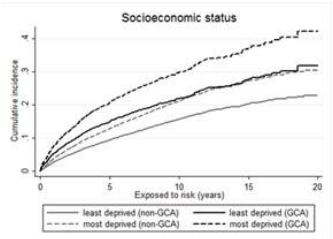
Background/Purpose: Giant cell arteritis (GCA) is the most common form of vasculitis in the UK, with an incidence of 2.2 cases per 10,000 person-years. Cerebrovascular and cardiovascular disease may be increased in patients with GCA but risk factors are not confirmed. Social deprivation may be associated with visual ischaemic complications in GCA. This study evaluated the risk of cerebrovascular and cardiovascular disease in patients with GCA compared with matched controls, and identified predictors of these outcomes.

Methods: A UK General Practice Research Database (GPRD) from 1991 to 2001 was used for a parallel cohort study of 5,827 patients with GCA and 37,090 controls, matched on age, gender and location (GP practice).A multivariable competing risk model (non-cardiovascular related death as the competing risk) determined the relative risk (subhazard ratio, SHR) between non-GCA and GCA patients for each of the following outcomes "cerebrovascular disease", "cardiovascular disease" or "cardiovascular or cerebrovascular disease" (three analyses). The model adjusted for smoking history, history of hypertension, prior use of anti-hypertensives, history of diabetes or prior use of diabetic medications, history of hyperlipidaemia, prior use of lipid- lowering medications) and Index of Multiple Deprivation (IMD) quintiles. The model was then run on each cohort separately to identify predictors of cerebrovascular and cardiovascular disease (age and gender were now included).

Results: Comparing the GCA cohort with the non-GCA cohort, the SHR (95% CI) for cerebrovascular disease (1.45 [1.31-1.60]), cardiovascular disease (1.49 [1.37-1.62]) and for cerebrovascular or cardiovascular disease (1.47 [1.37-1.57]) were increased. In the GCA cohort only, predictors of the composite outcome of "cardiovascular or cerebrovascular disease" included increasing age (1.98 (1.62-2.42), $p<0.001$ for patients >80 compared with those <65 years); male gender (1.20 (1.05-1.38), $p<0.001$) and those in the most deprived IMD quintile compared with the least deprived (1.34 (1.01-1.78), $p<0.05$). A history of hypertension was predictive of cardiovascular disease within the GCA cohort (1.53 (1.14-2.05), $p<0.01$) but no other significant associations were seen between the other conventional cardiovascular risk factors and either cardiovascular or cerebrovascular disease as either separate or composite outcomes.

Conclusion: Patients with GCA are fifty percent more likely to have cerebrovascular disease or cardiovascular disease than age, gender and location matched controls. This effect is independent of conventional cardiovascular risk factors but may be associated with higher levels of social deprivation.

Figure 1. Cumulative incidence of cerebrovascular and cardiovascular disease by level of social deprivation in patients with and without giant cell arteritis



Disclosure: J. Robson, None; **A. Kiran**, None; **A. Hutchings**, None; **J. Maskell**, None; **N. K. Arden**, None; **W. Hamilton**, None; **B. Dasgupta**, GSK, Servier,UCB, 5; **R. Luqmani**, GSK, 5,Chemocentryx, 5,Roche Pharmaceuticals, 5.

Abstract Number: 1973

Giant Cell Arteritis and Risk of Cerebrovascular Accident: A Systematic Review and Meta-Analysis

Patompong Ungprasert[1], Narat Srivali[2] and Wonngarm Kittanamongkolchai[3], [1]Rheumatology, Mayo Clinic, Rochester, MN, [2]Pulmonary and Critical Care Medicine, Mayo Clinic, Rochester, MN, [3]Nephrology and hypertension, Mayo Clinic, Rochester, MN

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Giant Cell Arteritis and Risk of Cerebrovascular Accident: A Systematic Review and Meta-analysis

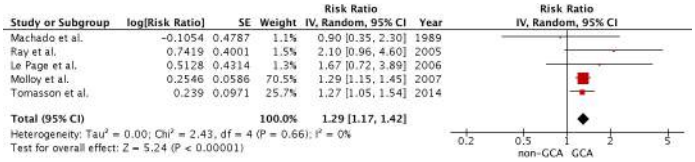
Background/Purpose: Several chronic inflammatory disorders, such as systemic lupus erythematosus and psoriatic arthritis, have been linked to an increased risk of cerebrovascular accident (CVA). However, the data on giant cell arteritis (GCA), one of the most common systemic vasculitides in older adults, are unclear as epidemiologic studies yielded inconsistent results. Thus, to further investigate this association, we conducted a systematic review and meta-analysis of observational studies that compared the risk of CVA in patients with GCA versus participants without it.

Methods: Two investigators independently searched published studies indexed in MEDLINE, EMBASE and the Cochrane database from inception to April 2015 using the terms "giant cell arteritis" and "temporal arteritis" combined with the terms for cerebrovascular accident. A manual search of references of selected articles was also performed. The inclusion criteria were as follows: (1) cohort or case-control study evaluating the association between GCA and CVA (2) odds ratio (OR), relative risk (RR) or hazard ratio (HR) or standardized incidence ratio (SIR) with 95% confidence interval (CI) were provided. Study eligibility was independently determined by the two investigators. Newcastle-Ottawa scale was used to assess the quality of the included studies.

Point estimates and standard errors were extracted from individual studies and were combined by the generic inverse variance method of DerSimonian and Laird. In light of the high likelihood of between study variance, we used a random-effect model rather than a fixed-effect model. Statistical heterogeneity was assessed using the Cochran's Q test. This statistical analysis was performed using RevMan 5.3 software.

Results: Out of 713 potentially relevant articles, five studies (three retrospective cohort studies, one prospective study and one case-control study) were identified and included in our data analysis. The pooled risk ratio of CVA in patients with GCA was 1.29 (95% CI, 1.17 to 1.42). The statistical heterogeneity of this meta-analysis was insignificant with an I^2 of 0%.

Conclusion: Our study demonstrated a significantly increased CVA risk among patients with GCA with 29% excess risk compared with general population.



Disclosure: P. Ungprasert, None; **N. Srivali**, None; **W. Kittanamongkolchai**, None.

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Abstract Number: 1974

Do Patients with Giant Cell Arteritis Meet the 2011 United Kingdom Department of Health Guidance on Physical Activity?

Joanna Robson[1], Karolina Lada[2], Anne Miller[3], Wilby Williamson[1], Julia Newton[2] and Raashid Luqmani[4], [1]Rheumatology, University of Oxford, Oxford, United Kingdom, [2]University of Oxford, Oxford, United Kingdom, [3]Nuffield Orthopaedic Center, Oxford., Oxford, United Kingdom, [4]Nuffield Department of Orthopaedics Rheumatology and Musculoskeletal Sciences, University of Oxford, Oxford, United Kingdom

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Background/Purpose: Physical inactivity is the fourth leading risk factor for global mortality accounting for 6% of deaths. Patients with giant cell arteritis (GCA) are at increased risk of cardiovascular disease and psychological stress due to GCA and its treatment (typically high dose glucocorticoids), which may be helped by introducing or maintaining regular physical activity (PA). According to the 2011 United Kingdom Department of Health guidance on physical activity for all adults, including those with a chronic disease, adults should be exercising every day and adults should perform moderate physical activity totaling ≥2.5 hours per week or perform vigorous physical activity totaling ≥75 minutes per week. We hypothesise that patients are not meeting these guidelines.

Methods: We collected information on demographics and presenting features from hospital records of recently diagnosed patients with GCA. We carried out a postal survey including: the Standardised International Physical Activity Questionnaire (IPAQ) and a questionnaire to identify any barriers to participation in PA and to ask about any advice given to patients regarding PA (from healthcare professionals, family and friends). We compared patient participation in exercise with the 2011 guidelines on physical activity.

Results: The response rate was 51/102. Responding participants had a mean age (SD) of 73.6 years (7.3) and 33 [64.7%] were female. The median time from diagnosis of GCA was 17.5 months [interquartile range (IQR) 11-28 months], median CRP before steroids was 30 mg/l [IQR 10-87]. Presenting features included headache (74.5%), polymyalgia rheumatica (51.0%), transient visual loss (21.6%), permanent visual loss (5.9%) and stroke (3.9%). Twenty two (43.1%) patients reported walking for >10 minutes per day, 7 (13.7%) reported moderate PA and 1 (2.0%) reported vigorous daily PA. Eleven (21.6%) performed ≥2.5 hours/week of moderate PA including 1 patient reporting ≥75 minutes of vigorous PA per week. Reasons for limiting their physical activity included: muscle weakness (53%), stiffness (49%), fatigue (37%) and pain (37%). 23.5% had concerns about the safety of exercise. Patients recalled being given advice about physical activity by general practitioners (33.3%), rheumatologists (37.2%), family or friends (45.1% and physiotherapists (23.5%). **Conclusion:** Physical activity has the potential to improve musculoskeletal, cardiovascular and mental health problems in patients with GCA receiving high dose glucocorticoids, but only 21.6 % of patients met national UK guidance on total duration of physical activity. Only 33.3 % patients received exercise advice from their GP and 37.2% from their rheumatologist. Further work is needed to explore the safety and benefits of physical activity in GCA.

Reasons given by patients for limiting physical activity (PA) since diagnosis of giant cell arteritis (GCA), frequency (%)

	Strongly agree	Agree	Disagree	Strongly disagree	Missing
Fatigue	15 (29.4)	19 (37.2)	10 (19.6)	5 (9.8)	2(3.9)
Pain	8 (15.7)	18 (35.3)	17 (33.3)	6 (11.8)	2(3.9)
Muscle weakness	12 (23.5)	27 (52.9)	10 (19.6)	1 (2.0)	1 (2.0)
Stiffness	5 (9.8)	24 (47.1)	16 (31.4)	4 (7.8)	2 (3.9)
Concerns about safety	2 (3.9)	10 (19.6)	25 (49.0)	11 (21.6)	3 (5.9)

Disclosure: J. Robson, None; **K. Lada**, None; **A. Miller**, None; **W. Williamson**, None; **J. Newton**, None; **R. Luqmani**, GSK, 5,Chemocentryx, 5,Roche Pharmaceuticals, 5.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/do-patients-with-giant-cell-arteritis-meet-the-2011-united-kingdom-department-of-health-guidance-on-physical-activity

Abstract Number: 1975

Risk of Mortality of Patients with Giant Cell Arteritis: A Systematic Review and Meta-Analysis

Catherine Hill[1], Rachel Black[2], Johannes Nossent[3], Carlee Ruediger[4], Jem Ninan[5] and Susan Lester[6], [1]Rheumatology Unit, The Queen Elizabeth Hospital, Woodville, Australia, [2]Medicine, University of Adelaide, Adelaide, Australia, [3]Medicine, University of Western Australia, WA, Australia, [4]Rheumatology, The Queen Elizabeth Hospital, Woodville, Australia, [5]Rheumatology, Modbury Hospital, Modbury, Australia, [6]Rheumatology, Basil Hetzel Institute, QEH, Woodville South, Australia

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Background/Purpose: Previous studies of mortality associated with GCA have shown conflicting results.We conducted a systematic review and meta-analysis of observational studies to compare the mortality risk in patients with GCA compared to the general population.

Methods: We searched for published studies indexed in MEDLINE and EMBASE and the Cochrane database from inception to June 18, 2015 using the terms “giant cell arteritis” and “temporal arteritis” combined with the terms for death, mortality and survival. A manual search of references of retrieved articles was also performed.

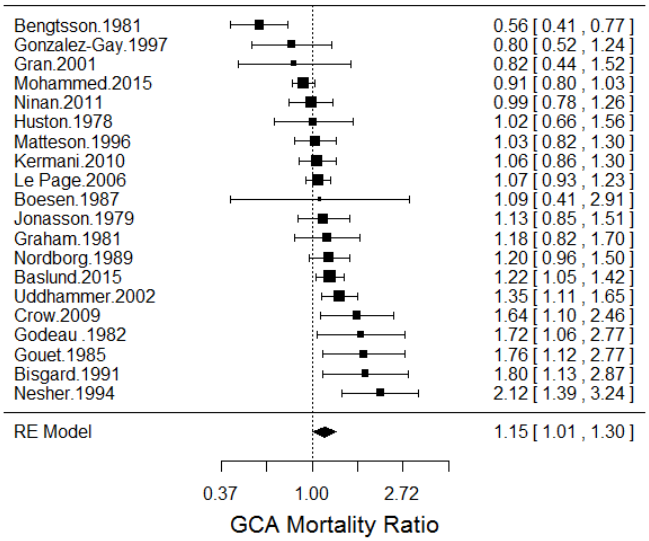
The inclusion criteria were (1) observational studies of biopsy-proven GCA published as original studies to evaluate the association between GCA and mortality (2) comparison of mortality of patients to general population. No language limitation was imposed. Studies published only in abstract form were excluded.

Study eligibility was independently determined by the two investigators. Differing decisions were resolved by consensus with a third reviewer. The quality of each study was independently assessed by the two investigators using Newcastle-Ottawa scale.

Studies were included in the meta-analysis, if numerical data was extractable from the published paper. This included studies in which the standardised mortality ratio (SMR), relative risk (RR's), hazard ratio (HRs) were provided. If data was only presented in graph form, then the graphs were digitized and the HR estimated from a cumulative complementary log-log regression model. The R library metaphor was used to perform a random effects, inverse variance weighted meta-analysis.

Results: Out of 435 potentially relevant articles, 60 full papers were reviewed and subsequently 23 studies were included. This included 21 studies published in English, one in Norwegian and one in French, with publication dates from 1971-2015. There were 5092 cases of GCA (range 19-1787). The majority of studies were from Nordic countries (n=10), North America (5), France (3), UK (2), Spain (1), Israel (1) and Australia (1). Usable data was obtained from 20/23 studies. The combined SMR for GCA mortality indicated a small increase in mortality with GCA: SMR 1.15, 95% CI 1.01, 1.30), p = 0.035. There was evidence of heterogeneity between studies (I^2 = 77%).

Conclusion: This meta-analysis demonstrated that there is an increased mortality associated with GCA, compared to the general population. However, this increase is small, although statistically significant.



Disclosure: C. Hill, None; **R. Black**, None; **J. Nossent**, None; **C. Ruediger**, None; **J. Ninan**, None; **S. Lester**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/risk-of-mortality-of-patients-with-giant-cell-arteritis-a-systematic-review-and-meta-analysis

Abstract Number: 1976

Corticosteroid Therapy in Giant Cell Arteritis, Predictors for Long-Term Remission

Luigi Boiardi[1], Giovanna Restuccia[2], Pierluigi Macchioni[1], Francesco Muratore[1], Alberto Cavazza[3], Luca Cimino[4], Raffaella Aldigeri[5], Mariagazia Catanoso[6], Nicolò Pipitone[6] and Carlo Salvarani[7], [1]Rheumatology Service, Arcispedale S Maria Nuova, IRCCS, Reggio Emilia, Italy, [2]Rheumatology Service, Arcispedale S Maria Nuova-IRCCS, 42100, Italy, [3]Pathology Unit, Arcispedale S Maria Nuova-IRCCS, Reggio Emilia, Italy, [4]Ophthalmology Unit, Arcispedale S Maria Nuova-IRCCS, Reggio Emilia, Italy, [5]Department of Clinical and Experimental Medicine, University of Parma, Parma, Italy, [6]Rheumatology Service, Arcispedale S Maria Nuova-IRCCS, Reggio Emilia, Italy, [7]Rheumatology Unit, Internal Medicine Department, Arcispedale Santa Maria Nuova - IRCCS, Reggio Emilia, Italy

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Background/Purpose:

The aim of our study was to determine the frequency and the predictors of long-lasting remission in a cohort of consecutive patients with biopsy-proven GCA.

Methods:

We recruited all patients with a diagnosis of biopsy-proven GCA performed at our Center between 1986 through 2007. Only patients with a follow-up period longer than 6 months were included in the study. A pathologist with expertise in vasculitis reviewed all temporal artery biopsies (TABs). Demographic, clinical and laboratory data at presentation and at each follow-up visit were retrospectively collected. Long-lasting remission was recorded as the date of permanent discontinuation of treatment without recurrence of symptoms and elevation of inflammatory markers for at least 1 year.Logistic regression was used to calculate the predictors for long-lasting remission.

Results:

182 patients had a diagnosis of biopsy-proven GCA in the study period. 156 patients had a follow-up of at least 6 months and represented our study population. The median of follow-up period for the 156 patients included was 80 (range 49-125) months. The median initial dosage of prednisone was 50 mg/day. The median duration required to achieve a maintenance dose of prednisone less than 5 mg/day was 8.5 months (range 7.0-12.0). The median duration required to achieve a permanent steroid discontinuation was 21 months (range 12.5-36) in our cohort. 58 patients (37%) were able to discontinue treatment at least 1 year before the end of follow-up without ever having flares. At the time of the last follow-up visit 72 patients (46%) were still taking glucocorticoids. Predictive variables for long-lasting remission were age less 70 years (0.030) and male gender (p=0.030).

Conclusion:

37% of patients of our cohort were able to remain in persistent treatment-free remission (no flare during the entire follow-up period). Predictive variables for long lasting remission were age less 70 years and male gender.

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Abstract Number: 1977

Long-Term Survival of Methotrexate in Giant Cell Arteritis Patients in Clinical Practice

Dalifer Freites Núñez[1], Zulema Rosales[1,2], Lucía Arietti[1], Leticia Leon[2], Inmaculada Morado[1], Benjamín Fernández-Gutiérrez[3], Luis Rodriguez-Rodriguez[2], Juan A Jover[1] and Lydia Abasolo[2], [1]Rheumatology, Hospital Clínico San Carlos, Madrid, Spain, [2]Instituto de Investigación Sanitaria San Carlos (IdISSC), Madrid, Spain, [3]Department of Rheumatology, Hospital Clínico San Carlos, Madrid, Spain
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Background/Purpose: It has is been demonstrated the safety and efficacy of Methotrexate (MTX) in the treatment of Giant Cell Arteritis (GCA) in clinical trials, but it is important to know the long-term survival of the drug in real life conditions. The purpose of our study was to analyze, in clinical practice conditions, the long-term survival of MTX in patients with GCA. Factors associated to its discontinuation rate were also investigated.

Methods: This is an observational longitudinal study with a maximum follow-up of 20 years. We included GCA patients treated with MTX and followed in outpatient clinic at Hospital Clínico San Carlos, in Madrid from January 1991 until September 2014. Primary outcome: discontinuation of MTX due to: a) adverse drug reaction (ADR), (classified as moderate when the drug was suspended regardless of the impact, and severe when ADR required hospitalization or death); b) inefficacy; c) improvement or remission; and d) patient decision. Covariables analized were: sociodemographic, clinicals and therapy. Incidence rates of MTX discontinuation (IR) per 100 patient-years with their respective 95% confidence interval [95% CI] were estimated using survival techniques. Associated factors to discontinuation were run by Cox regression models.

Results: Eighty two patients with 96 courses of MTX therapy (168.3 patient-years) were included. They were mostly women (75.6%), the mean age at diagnosis was 76.7±7.3 years. The IR of MTX discontinuation was estimated in 38.6 [30.2-49.2]. The IR due to ADR was 21.3[15.4-29.6] most of them infections and not severe (IR if severe ADR: 6.6 [1.6-7.9]). The IR of discontinuation due to improvement was 11.9 [7, 7-18.42] and the IR due to inefficacy was 1.8 [0.6-5.5]. In the multivariate analysis for risk of discontinuation due to inefficacy, the number of relapses was associated to higher risk to discontinuation whereas elevated ESR and higher average doses of corticosteroids had less risk of discontinuation. In the final model for discontinuation due to ADRs, age at diagnosis, male, visual disturbances, cardiovascular and general symptoms at diagnosis had higher risk of discontinuation. However, treatment with MTX at diagnosis had a lower risk of suspension for ADRs. The independent factors that influenced the suspension due to improvement were

fewer recurrences during the follow-up and the younger the age at onset of disease.

Conclusion: MTX treatment for GCA, seems safe and effective in clinical practice. A low incidence of serious adverse events, a low incidence of discontinuation due to inefficacy and a high incidence of discontinuation due to improvement or remission were observed. We have also found several sociodemographic and clinical factors that can modify its survival.

Disclosure: D. Freites Núñez, None; **Z. Rosales**, None; **L. Arietti**, None; **L. Leon**, None; **I. Morado**, None; **B. Fernández-Gutiérrez**, None; **L. Rodriguez-Rodriguez**, None; **J. A. Jover**, None; **L. Abasolo**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/long-term-survival-of-methotrexate-in-giant-cell-arteritis-patients-in-clinical-practice

Abstract Number: 1978

Tocilizumab in Refractory Large Vessel Vasculitis with Aorta Involvement. Study on 10 Patients Evaluated By Positron Emission Tomoghraphy

Carlotta Nannini[1], Stelvio Sestini[2], Laura Niccoli[3], **Emanuele Cassarà**[4], Olga Kaloudi[5] and Fabrizio Cantini[6], [1]Rheumatology, Prato Hospital, Prato, Italy, [2]Radiology Department, Prato, Italy, [3]Prato Hospital, Prato, Italy, [4]Rheumatology, Hospital of Prato, Prato, Italy, [5]PRato, Prato Hospital, Prato, Italy, [6]Prato, Prato, Italy

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Background/Purpose: Large vessel vasculitis (LVV) with aorta involvement are often refractory to common immunosuppressive therapy. Due to the pathogenic role of IL-6 in, we prospectively treated 10 patients with anti-IL6 receptor monoclonal antibody, tocilizumab (TCZ). Efficacy was assessed by clinical and laboratory parameters and by ^{18}F-fluorodeoxyglucose positron emission tomography ([^{18}F]FDG-PET).

Methods: 10 (9 women/1 men) patients with LVV diagnosed by [^{18}F]FDG-PET imaging who were treated with intravenous TCZ at the dose of 8 mg/Kg/monthly. Prednisone (PDN) at stable dose of 10 mg/day or less was allowed and, based on clinical response, the drug was interrupted thereafter. At baseline and after 6 months of therapy, patients underwent [^{18}F]FDG-PET imaging evaluation. Severity of large vessel inflammation was evaluated by using the standardized uptake value (SUV) of [^{18}F]FDG accumulation and the SUVmax normalized for liver [^{18}F]FDG uptake. Anova test was used for comparison between groups. C-Reactive protein (CRP) and erythrocyte sedimentation rate (ESR) were measured. Pain visual analogue scale (VAS) was evaluated before and after treatment and correlated with percentage of SUVmax variation trough linear regression. SPSS was used for statistical analysis.

Results:

The mean age±SD was 59± 15 years. The underlying conditions were: Takayasu arteritis (n=4 cases), giant cell arteritis (GCA) (n=4), and aortitis (n=2). TCZ was the first biologic drugs used in 5 cases (2 aortitis and 3 GCA). In the remaining cases anti-TNF infliximab was prescribed before TCZ (infliximab at the dose of 5 mg/kg/iv/8 weeks/iv).

After 6 months of TCZ [^{18}F]FDG-PET was repeated, at that time all patients experienced clinical improvement with a reduction of erythrocyte sedimentation rate (ESR) from 55 ± 27SD 1st h to 14±14SD 1sth and C-reactive protein from 5±4 SD mg/dl to 0.2±0.1SDmg/dl.

VAS pain improved form 9.03 ± 0.7 SD cm to 2.35± 1.15 SD cm

Before TCZ , 44% of patients had fever and 22% Polymialgia rheumatica who disappeared after 3 months of treatment.

SUVmax before TCZ was 2.83 ± 0.33 SD after TCZ was 2.08± 0,28 with p value= 0,0001. SUV max normalized for liver before TCZ was 1,24± 0.24 after TCZ was 0.87± 0.18 with p value=0,001.

The greatest percentage of SUVmax variation was correlated with the greatest percentage of VAS pain improvement with a statistical significant correlation of 0.0001. PDN interruption was possible in all patients after two infusions of TCZ.

Conclusion: TCZ appears to be effective in patients with large vessel vasculitis refractory to corticosteroids or to anti-TNF drugs. The well- known diagnostic value of [^{18}F]FDG-PET is enriched by the quantitative evaluation of vessel inflammation that is fundamental for the treatment follow-up.

Disclosure: C. Nannini, None; **S. Sestini**, None; **L. Niccoli**, None; **E. Cassarà**, None; **O. Kaloudi**, None; **F. Cantini**, None.

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Abstract Number: 1979

Baseline Data on Patients Enrolled in a Randomized, Double-Blind Trial of Tocilizumab in Giant Cell Arteritis

Katie Tuckwell[1], Neil Collinson[1], Micki Klearman[2], Sophie Dimonaco[1], John H. Stone[3] and on behalf of the GiACTA Investigators, [1]Roche Products Ltd., Welwyn Garden City, United Kingdom, [2]Genentech, South San Francisco, CA, [3]Massachusetts General Hospital Rheumatology Unit, Harvard Medical School, Boston, MA

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SESSION INFORMATION

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Session Title: Vasculitis Poster II

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: GiACTA, a randomized, double-blind, placebo-controlled trial of the interleukin-6 receptor alpha inhibitor tocilizumab (TCZ) in patients (pts) with giant cell arteritis (GCA), is the largest trial conducted in GCA to date (NCT01791153) and the first trial in any disease to use a variable-dose, blinded corticosteroid (CS) taper. The hypothesis is that TCZ is effective at achieving sustained, CS-free remission in pts with GCA. For this analysis, 241 of 251 pts had been enrolled. We report baseline characteristics and compare features of pts with newly diagnosed vs relapsing disease.

Methods: The 4 major inclusion criteria are age ≥50 y, historical ESR ≥50 mm/h or CRP ≥2.45 mg/dL, unequivocal cranial GCA or polymyalgia rheumatica (PMR) symptoms, and positive temporal artery biopsy (TAB) or imaging study (positron emission tomography, computed tomography angiography, or magnetic resonance angiography) showing large-vessel vasculitis. There are 4 arms: TCZ 162 mg subcutaneous (SC) QW + 6-mo prednisone taper; TCZ 162 mg SC Q2W + 6-mo prednisone taper; 6-mo prednisone taper only; 12-mo prednisone taper only. Initial prednisone dose (20-60 mg/d) is at investigator discretion. The taper is blinded at doses <20 mg/d. Data are from a live study database.

Results: Of the enrolled pts, 119 (49%) have newly diagnosed GCA and 122 (51%) have relapsing GCA; mean ages are 68 y (range, 52-84) and 70 y (range, 52-85), respectively; 76% are women, and 75% of all pts have met the ACR 1990 criteria for GCA in addition to the GiACTA inclusion criteria. At diagnosis, 61% of newly diagnosed and 57% of relapsing pts had PMR symptoms, 75% and 78% had cranial symptoms, and 20% and 17% had PMR symptoms only. At diagnosis, 57% of newly diagnosed and 59% of relapsing pts had positive TAB; 47% and 41% had positive imaging results. More than one-third of pts had negative TAB results or no TAB performed but positive imaging results. Baseline comorbidities in newly diagnosed and relapsing pts include hypertension (50% and 59%), osteoporosis (12% and 19%), and diabetes (13% and 15%). Mean [SD] baseline BMI is higher in relapsing vs newly diagnosed pts (men, 28.8 [6.1] vs 25.8 [4.2]; women, 26.2 [4.8] vs 24.7 [3.9]). Mean [SD] baseline prednisone dose for newly diagnosed GCA pts was 39.8 mg [13.2] vs 29.8 mg [11.8] for relapsing pts; 18% of newly diagnosed and 5% of relapsing pts entered the study on 60 mg/d prednisone, whereas 8% of newly diagnosed and 39% of relapsing pts entered the study at 20 mg/d.

Conclusion: Demographics of the GiACTA population reflect the epidemiologic profile of GCA (*Arthritis Care Res*. 2015;67:390). Many pts were enrolled based on large-vessel imaging rather than TAB, reflecting the increased use of imaging to diagnose large-vessel vasculitis since development of the 1990 ACR criteria for GCA. The higher baseline prednisone dose in newly diagnosed pts reflects concern about preventing acute damage (eg, vision loss) in that subpopulation; the lower starting dose received by relapsing pts may indicate early detection of relapse and the need to limit toxicity in this CS-exposed subpopulation. Relapsing pts have more comorbidities, likely due to long-term CS treatment for GCA.

Disclosure: K. Tuckwell, Roche Products Ltd., 3; **N. Collinson**, Roche Products Ltd., 3; **M. Klearman**, Roche, 1,Genentech, 3; **S. Dimonaco**, Roche Products Ltd., 3; **J. H. Stone**, Roche, Genentech, 2,Genentech, 5.

Abstract Number: 1980

Tocilizumab in Giant Cell Arteritis: A Multicentre Open-Label Study in France

Alexis Regent[1], Serge Redeker[2], Alban Deroux[3], Pierre Kieffer[4], Kim Heang Ly[5], Maxime Dougados[6], Claire Larroche[7], Loïc Guillevin[1], Laurence Bouillet[8], Olivier Espitia[9], Nathalie Costedoat-Chalumeau[10], Martin Soubrier[11], Benoit Brihaye[12], François Lifermann[13], Guillaume Lefèvre[14], Xavier Puéchal[1], Luc Mouthon[1], Eric Toussirot[15] and GFEV and CRI, [1]Internal Medicine, National Referral Center for Rare Systemic Autoimmune Diseases, Hôpital Cochin, Paris, France, [2]43 rue de l'isle, Ch Abbeville, Abbeville, France, [3]Internal Medicine, CHU Grenoble, Grenoble, France, [4]Hopital Emile Muller, Mulhouse Cedex 1, France, [5]CHU de Limoges, Service de médecine interne, Limoges, France, [6]Medicine Faculty, Paris-Descartes University, Paris, UPRES-EA 4058, Cochin Hospital, Rheumatology B, Paris, France, [7]Internal Medicine, Paris, France, [8]CHU, Grenoble, France, [9]Internal Medicine, Nantes University Hospital, Nantes, France, [10]Internal Medicine Department, Cochin Hospital, "René-Descartes Paris V" University, Paris, France, [11]Rheumatology department CHU Clermont-Ferrand, Clermont-Ferrand, France, [12]Service de médecine interne et médecine polyvalente, Saint Quentin, France, [13]CH Dax, Dax, France, [14]Service de médecine interne, Centre National de Référence de la Sclérodermie Systémique, Hôpital Claude Huriez, CHRU Lille, Lille, France, [15]Service de Rhumatologie, CHU J Minjoz, Besancon, France

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Background/Purpose:

To report the French experience on the efficacy and safety of tocilizumab (TCZ) in patients with giant cell arteritis (GCA) and outcome after treatment withdrawal.

Methods:

A retrospective multicenter study included patients treated with TCZ for their GCA. Treatment efficacy was evaluated at a clinical and biological level. Side effects and outcome after treatment withdrawal were also recorded.

Results:

Thirty-four patients (27 women and 7 males) aged 70.5±8.2 (mean±SD) were included. Diagnosis of GCA was based on the ACR criteria (30 patients) and/or on imaging abnormalities suggestive of GCA (8 patients). Treatment included glucocorticoids in all patients and another immunosuppressant before TCZ introduction in 20/34 patients (59%). TCZ (8 mg/kg monthly) was prescribed after a mean disease duration of 18 months (0-107) and patients were treated for a mean of 6.4±4.5 months. It was effective in all but 6 patients who still had mild symptoms while CRP was reduced from 40.4±45.6 mg/L to 1.5±1.8 mg/L ($p<0.0001$) and glucocorticoids were tapered from 26.3±13.8 to 10.3±8.3 ($p<0,0001$). One patient died from septic shock and TCZ was stopped in 3 patients for severe adverse events (tuberculous pericarditis, liver cytolysis and neutropenia). Among the 23 patients who stopped treatment (planned medical decision in 2O cases, side effects in 3 cases) eight patients experienced relapses occurring after a mean of 3.5±1.3 months and TCZ was started again in 5 of them.

Conclusion:

Under TCZ therapy, patients with GCA have a rapid and sustained improvement. However, side effects were noticeable and should be kept in mind in these patients. Questions remain regarding the suspensive nature of this treatment and this should be specifically addressed in future studies.

Disclosure: A. Regent, None; **S. Redeker**, None; **A. Deroux**, None; **P. Kieffer**, None; **K. H. Ly**, None; **M. Dougados**, None; **C. Larroche**, None; **L. Guillevin**, None; **L. Bouillet**, None; **O. Espitia**, None; **N. Costedoat-Chalumeau**, None; **M. Soubrier**, None; **B. Brihaye**, None; **F. Lifermann**, None; **G. Lefèvre**, None; **X. Puéchal**, None; **L. Mouthon**, None; **E. Toussirot**, None.

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Abstract Number: 1981

Increased Extracellular Water Measured By Bioimpedance Analysis in Polymyalgia Rheumatica Patients – Sign of Volume Overload

Florian Günther[1,2], Boris P. Ehrenstein[2], Martin Fleck[1] and Rainer Straub[1], [1]Department of Internal Medicine I, University of Regensburg, 93042 Regensburg, Germany, [2]Department of Rheumatology/Clinical Immunology, Asklepios Medical Center, 93077 Bad Abbach, Germany
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Background/Purpose: Water retention is a typical feature of acute inflammatory episodes, chiefly implemented by the sympathetic nervous system (SNS) and the hypothalamic-pituitary-adrenal (HPA) axis. This is an important compensatory mechanism counteracting expected water loss, for example due to sweating. Both SNS and HPA axis are activated in polymyalgia rheumatica (PMR). As retention mechanisms may similarly apply in this disease, we hypothesized increased water retention in PMR.

Methods: Using bioimpedance analysis body composition was investigated in 56 healthy controls and 28 treatment-naive PMR patients. PMR patients were matched to healthy controls for age and weight. All PMR patients satisfied the 2012 EULAR/ACR classification criteria for PMR (including musculoskeletal ultrasound). 28 PMR patients were tested before and after 10 days of glucocorticoid based therapy (CRP and ESR markedly decreased). Correlations of extracellular water, systolic and diastolic blood pressure with parameters of inflammation were investigated in PMR patients as well as in healthy controls.

Results: Fat mass (fat free mass) was higher (lower) in PMR patients than controls, indicating sarcopenia and cachectic obesity in PMR patients (mean ± SD: 38.6 ± 6.7 versus 24.1 ± 5.4% of body weight, $p < 0.001$; 61.3 ± 6.7 versus 75.9 ± 5.4%, $p < 0.001$). Extracellular water (ECW) was markedly higher in PMR patients than controls (mean ± SD: 49.5 ± 6.2% versus 37.8 ± 2.6% of total body water, $p < 0.001$, Figure 1). Systolic and diastolic blood pressure were higher in PMR patients compared to controls, even before glucocorticoid treatment was initiated (mean ± SD: 146.9 ± 18.3 mmHg versus 119.3 ± 5.4

mmHg, p < 0.001; 84.4 ± 12.8 mmHg versus 78.0 ± 1.6 mmHg, p < 0.001). Extracellular water levels did not change in PMR patients upon 10 days of intensified treatment.

Conclusion: This study demonstrated increased extracellular water as sign of fluid overload in patients with PMR. These results indicate that volume changes are imprinted as long-lasting mechanisms as water distribution is not affected by short-term anti-inflammatory therapy.

Disclosure: F. Günther, None; **B. P. Ehrenstein**, None; **M. Fleck**, None; **R. Straub**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/increased-extracellular-water-measured-by-bioimpedance-analysis-in-polymyalgia-rheumatica-patients-sign-of-volume-overload

Abstract Number: 1982

Sonographic Scoring of the Synovial Components in the Shoulder Revealed That Shoulder Synovitis in PMR Patients Is Milder Than That in Elderly-Onset RA Patients with PMR-like Onset

Takeshi Suzuki, Division of Allergy and Rheumatology, Japanese Red Cross Medical Center, Tokyo, Japan; Division of Rheumatology, Mitsui Memorial Hosipital, Tokyo, Japan

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Background/Purpose: Through the clinical experience, we noted that there seems to be differences not in the kind or the frequency but in the severity of synovial inflammation between polymyalgia rheumatica (PMR) and elderly-onset rheumatoid arthritis with PMR-like onset (polymyalgic-EORA). We compared the severity of the shoulder syonvitis between PMR and polymyalgic-EORA using semi-quantitative US scoring of the synovial components, and also explored the application of the scoring system to the differential diagnosis between the two diseases.

Methods: We analyzed consecutive records of 15 PMR patients and 15 polymyalgic-EORA patients. All of them were examined by US before treatment-start. The severity of tenosynovitis of the long-head of the biceps (LHB), bursitis of shoulder including subdeltoid, subacrominal and subcoracoid bursitis, and joint synovitis of grenohumeral joint (GHJ) were subjectively scored for grey-scale (GS) and power Doppler (PD) on a four-point scale: 0 = absent, 1 = mild, 2 = moderate or 3 = severe. Sum of the scores of one shoulder was defined as "shoulder synovitis score (SSS)", and sum of the scores of both shoulders was defined as "patient-shoulder synovitis score (PSSS)". The correlation between PSSS and serum markers was assessed. Indices contributing to discriminating between the two diseases were explored.

Results: There was a tendency that synovitis in each synovial component in the shoulder in PMR was milder than that in polymyalgic-EORA, while there was no difference in the frequencies of synovitis (Table). There were statistically significant differences in the PD-grade of LHB, GS-grade of LHB, bursitis and GHJ. There was also a significant difference in GS-score of bursitis (0.40 ± 0.62 vs 1.2 ± 1.2, p=0.003), PD-score of bursitis (0.37 ± 0.72 vs 1.0 ± 1.2, p=0.015) and SSS (4.0 ± 2.2 vs 6.2 ± 4.6, p=0.023) (mean ± SD, PMR vs polymyalgic-EORA). PSSS in PMR tended to be lower than that in polymyalgic-EORA (7.7 ± 3.8 vs 12.3 ± 8.6, p=0.072).

PSSS were positively correlated with serum MMP3 (|R|=0.707, p< 0.0001). Both PSSS (|R|=0.602, p= 0.0175) and MMP3 (|R|=0.463, p= 0.095) were positively correlated with serum CRP in polymyalgic-EORA but not in PMR. The ratio of PSSS to CRP (mg/dL) (PSSS/CRP) was significantly lower in PMR than in polymyalgic-EORA (1.35 ± 1.63 vs 5.55 ± 4.46, p=0.003). The ratio of MMP3 (ng/mL) x10^4 to CRP (MMP3/CRP) was significantly lower in PMR than in polymyalgic-EORA (32.2 ± 35.9 vs 101 ± 87.1, p=0.006). These two ratios may be useful for discriminating between the two diseases, because ROC analysis for PSSS/CRP and MMP3/CRP demonstrated areas under the curve of 0.902 and 0.852, respectively.

Conclusion: Semi-quantitative US scoring of the synovial components in the shoulder revealed that shoulder synovitis in PMR is milder than that in EORA patients with PMR-like onset. The application of the scoring system may be useful for discriminating between the two diseases.

Diagnosis	PMR n=30					EORA n=30				
Score	0	1	2	3	1~3	0	1	2	3	1~3
LHB GS (%)	6.7	60.0[a]	26.7	6.7	93.3	23.3	30.0[a]	26.7	20.0	76.7
LHB PD (%)	10.0	50.0[a]	36.7	3.3[a]	90.0	26.7	23.3[a]	23.3	26.7[a]	73.3
Bursa GS (%)	66.7	26.7	6.7	0.0[b]	33.3	43.3	16.7	16.7	23.3[b]	56.7
Bursa PD (%)	73.3	20.0	3.3	3.3	26.7	50.0	16.7	16.7	16.7	50.0
GHJ GS (%)	70.0	26.7[a]	3.3	0.0	30.0	73.3	3.3[a]	16.7	6.7	26.7
GHJ PD (%)	83.3	13.3	3.3	0.0	16.7	73.3	16.7	0.0	10.0	26.7

a, $p<0.05$; b, $p<0.01$

Disclosure: T. Suzuki, None;

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Abstract Number: 1983

Interspinous Bursitis Evaluation By Ultrasound Is Very Useful for Diagnosis of Polymyalgia Rheumatica

Kensuke Kume[1], Kanzo Amano[2], Susumu Yamada[1], Toshikatsu Kanazawa[3], Hiroshi Komori[1], Kazuhiko Hatta[4] and Noriko Kuwaba[5], [1]Rheumatology, Hiroshima Clinic, Hiroshima, Japan, [2]rheumatology., hiroshima clinic, Hiroshima, Japan, [3]rheumatology, hiroshima clinic, hiroshima, Japan, [4]Rheumatology, Hatta Clinic, Kure, Japan, [5]Medical Research, Sanki Clinical Link, Hiroshima, Japan
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Background/Purpose: Polymyalgia rheumatica (PMR) is a common inflammatory disease of the elderly, and 2012 provisional classification criteria were suggested, however it is provisional and not meant for diagnosis purpose[1)]. Ultrasound(US), MRI and other modalities were often detected interspinous bursitis in patients with PMR[2)]. To develop 2012 provisional classification criteria, adding interspinous bursitis evaluation by US.

Methods: This is a prospective cohort study. Candidate criteria were evaluated 117 patients with new onset untreated PMR, and 128 patiens non-PMR comparison subjects with conditions mimicking PMR. We compared the sensitivity and specificity of 2012 provisional classification criteria with 2012 provisional classification criteria, adding interspinous bursitis evaluation by US. US evaluation was checked cervical and lumbar spine, and if at least one interspinous bursitis was detected, it was calculated 1 point. Total score(interspinous bursitis evaluation by US score plus 2012 provisional classification criteria with US score) was 5 or more, it is categorised as PMR.

Results: 2012 provisional classification criteria scoring system had 68% sensitivity and 79% specificity. Adding interspinous bursitis by US had significantly increased sensitivity to 86 %($p<0.05$), and not significantly decreased specificity to 76 %($p=0.47$) Surprisingly, PMR patients without cervical or lumbar pain had interspinous bursitis with high prevalence. (74%) No correlation was found between interspinous bursitis by US and spontaneous or provoked pain. ($r=0.12$, $P=0.45$)

Conclusion: Interspinous bursitis by US is very sensitive in patients with PMR. Interspinous bursitis by US should be added classification criteria for PMR. If patients were suspected of PMR, interspinous bursitis by US should be performed with or without cervical or lumbar pain.

References)

1)Dasgupta B, et al. 2012 Provisional classification criteria for polymyalgia rheumatica: a European League Against Rheumatism/American College of Rheumatology collaborative initiative.Ann Rheum Dis. 2012 Apr;71(4):484-92. doi: 10.1136/annrheumdis-2011-200329.

2)Camellino D, et al. Interspinous bursitis is common in polymyalgia rheumatica, but is not associated with spinal pain.Arthritis Res Ther. 2014 Dec 1;16(6):492. [Epub ahead of print]

Disclosure: K. Kume, None; **K. Amano**, None; **S. Yamada**, None; **T. Kanazawa**, None; **H. Komori**, None; **K. Hatta**, None; **N. Kuwaba**, None.

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Abstract Number: 1984

Incidence and Intensity of 18fdg Uptake on Whole Body PET/CT in Patients with Polymyalgia Rheumatica

Claire Owen[1,2], Aurora Poon[3,4], Sze Ting Lee[2,3,4], Christine McMenamin[1], Kunthi Pathmaraj[3], Andrew Scott[2,3,4] and Russell Buchanan[1,2], [1]Rheumatology, Austin Health, Heidelberg VIC, Australia, [2]Medicine, University of Melbourne, Parkville VIC, Australia, [3]Department of Molecular Imaging and Therapy, Austin Health, Heidelberg VIC, Australia, [4]Olivia Newton-John Cancer Research Institute, Heidelberg VIC, Australia
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Incidence and Intensity of ^{18}FDG Uptake on Whole Body PET/CT in Patients with Polymyalgia Rheumatica

C.E. Owen[1,2], A.M.T. Poon[2,3], S.T. Lee[2,3,4], K. Pathmakaj[3], C. McMenamin[1], A.M. Scott[2,3,4], R.R.C. Buchanan[1,2]

[1]Department of Rheumatology, Austin Health, Heidelberg VIC [2]Department of Medicine, University of Melbourne, Parkville VIC [3]Department of Molecular Imaging and Therapy, Austin Health, Heidelberg VIC [4]Olivia Newton-John Cancer Research Institute, Heidelberg VIC

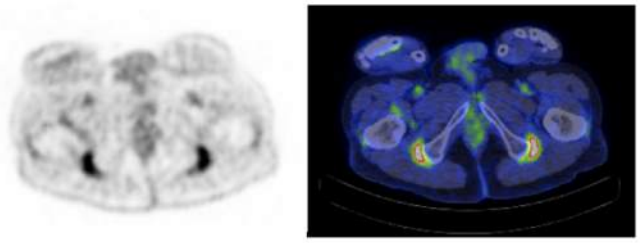
Background/Purpose: To characterise the incidence and intensity of ^{18}Fluorodeoxyglucose (^{18}FDG) uptake on whole body PET/CT in untreated patients with newly diagnosed Polymyalgia Rheumatica (PMR).

Methods: Patients with newly diagnosed PMR according to the 2012 EULAR/ACR Classification Criteria[1] were prospectively recruited. A whole body scan from skull vertex to toes (including dedicated hand views) was performed at baseline using a Phillips TF PET/CT machine in all untreated patients. A range of demographic, clinical and laboratory data were collected. Images were reviewed with Medview software by an experienced Nuclear Medicine Physician. Both qualitative and semi-quantitative (standardised uptake value maximum [SUV_{max}]) analysis of joint and vascular ^{18}FDG uptake were performed. Statistical analyses were undertaken using Stata 13.0 (Statcorp, College Station, TX, USA).

Results: Thirteen patients with PMR were recruited. Mean age was 68.47 years, there was a slight male predominance (53.85%) and all were Caucasian. All patients reported bilateral shoulder pain at presentation, but hip symptoms were less common (69.23%). Disease activity was high (mean PMR-AS 80.29) and the median HAQ-DI score was 2.125. In addition to involvement of the shoulder capsule (11/13, 84.62%), hip capsule (11/13, 84.62%), trochanteric bursae (12/13, 92.31%) and interspinous bursae (10/13, 76.92%), a high incidence of ^{18}FDG uptake at the ischial tuberosities (12/13, 92.31%) and knee capsule (9/13, 69.23%) was seen. Involvement of the palmar aspect of the hands/wrists and feet was also observed in 5/13 (38.46%) and 2/13 (15.38%) cases respectively. With respect to SUV_{max} at sites of ^{18}FDG uptake, the highest mean result occurred at the ischial tuberosities (4.38) followed by the shoulder capsule (3.94), interspinous bursae (3.62) and knee capsule (3.48).

Conclusion: Patients with newly diagnosed, untreated PMR exhibit most intense ^{18}FDG uptake at the ischial tuberosities on whole body PET/CT. Frequent involvement of peripheral joints, especially the knee capsule, is also observed.

Figure 1: Intense ^{18}FDG uptake at the ischial tuberosities in a patient with newly diagnosed, untreated PMR.



1. Dasgupta B et al. (2012). Provisional classification criteria for polymyalgia rheumatica: a EULAR/ACR collaborative initiative. Arthritis & Rheumatism. 2012;64(4):943-54.

Disclosure: C. Owen, None; **A. Poon**, None; **S. T. Lee**, None; **C. McMenamin**, None; **K. Pathmaraj**, None; **A. Scott**, None; **R. Buchanan**, None.

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Abstract Number: 1985

Abnormal B-Cell Distribution Is Improved By Tocilizumab Monotherapy in Patients with Polymyalgia Rheumatica

Guillermo Carvajal Alegria[1], Valerie Devauchelle[2], Yves Renaudineau[3], Alain Saraux[4], Jacques-Olivier Pers[5] and Divi Cornec[6], [1]Immunology, CHRU MORVAN, BREST, France, [2]Service de Rhumatologie, CHU Brest, Brest, France, [3]Immunology, Brest University Medical School Hospital, Brest, France, [4]Rheumatology Department, CHU de la Cavale Blanche, Brest Cedex, France, [5]EA2216/ERI29 UBO, Brest, France, [6]Department of rheumatology, Brest Occidentale University, Brest, France

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Background/Purpose:

Abnormalities in B-cell population distribution were recently reported in polymyalgia rheumatica (PMR) and giant cell arteritis, which improved with glucocorticoids. Our objective here was to analyze the subsets of lymphocytes in patients with PMR and to follow their evolution after tocilizumab treatment.

Methods*:*

The TENOR study was an open labelled prospective trial including patients with recent PMR fulfilling the Chuang criteria. The disease duration was less than 12 months, and patients had active disease and were glucocorticoids (GCs) free. Patients with suspected giant cell arteritis were excluded. Patients were treated with tocilizumab infusions (week 0, 4 and 8) without GCs (period 1) and then by low-dose GCs from week 12 to week 24 (period 2). All patients were in clinical remission at the end of period 1 (tocilizumab monotherapy). Peripheral blood lymphocyte profiling was performed by multicolor flow cytometry in 18 patients at week (W) 0 (before first tocilizumab infusion), W2, W12 and W24. They were compared to 16 sex and age-matched healthy controls.

Results*:*

At baseline, total lymphocyte (p=0.31), T cell (p=0.46), B cell (p=0.08) and NK cell (p=0.905) levels were similar between PMR patients and controls. Transitional B cells ($CD24^{high}$, $CD38^{high}$) and mature-naïve B cells ($CD24^{low}$, $CD38^{low}$) were lower in patients with PMR than in controls, 3±6 vs 6±6 per mm^3 (p=0.01) and 46±41 vs 92±53 per mm^3 (p=0.01), respectively. After tocilizumab, total lymphocyte count slightly increased (1739 ± 539/mm^3 at W0, 2030 ±591/mm^3 at W2, 2068 ±775/mm^3 at W12, and 2031 ± 584/mm^3 at W24, p<0.01). The absolute number of T cells and $CD8^+$ T cells rose between W0 and W24, from 1295 ±405/mm^3 to 1541 ±429/mm^3 (p=0.03) and from 357 ±215/mm^3 to 446 ±328/mm^3 (p=0.04) respectively, but proportions were unchanged. The absolute number and proportion of $CD4^+$ T cells and NK cells were unaffected by the treatment. In contrast, both absolute number and proportion of B cells increased between W0 and W12, respectively from 176±105/mm^3 to 260 ±192/mm^3 (p=0.004) and from 10.1% to 13.0% (p<0.001). Among B-cell subsets, these modifications were mainly attributable to the variations of the memory compartment. Unswitched (IgD+CD27+) and switched (IgD-CD27+) memory B-cell absolute number and proportions significantly increased after tocilizumab (p<0.001).

Conclusion:

The drastic clinical improvement following tocilizumab monotherapy in PMR patients is paralleled by an increase in peripheral blood memory B cells. These observations suggest that B cells are involved in disease pathophysiology, and that IL-6 blockade could restore B-cell homeostasis.

Disclosure: G. Carvajal Alegria, None; **V. Devauchelle**, None; **Y. Renaudineau**, None; **A. Saraux**, None; **J. O. Pers**, None; **D. Cornec**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/abnormal-b-cell-distribution-is-improved-by-tocilizumab-monotherapy-in-patients-with-polymyalgia-rheumatica

Abstract Number: 1986

Clinical Efficacy of Tocilizumab in Polymyalgia Rheumatica: An OPEN-Label Study.

Eric Toussirot[1], Antoine Martin[2], Martin Soubrier[3], serge redeker[4], Alexis Régent[5] and Le CRI[6], [1]Service de Rhumatologie, CHU J Minjoz, Besancon, France, [2]Rheumatology, Centre Hospitalier, St Brieuc, France, [3]Rheumatology department CHU Clermont-Ferrand, Clermont-Ferrand, France, [4]43 rue de l'isle, Ch Abbeville, Abbeville, France, [5]Paris Descartes University, UPRES-EA 4058, Paris, France, [6]Rheumatology, CHU, Strasbourg, France

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SESSION INFORMATION

Session Date: Monday, November 9, 2015
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Background/Purpose: polymyalgia rheumatic (PMR) is a chronic inflammatory disorder of unknown etiology that affects elderly people. Glucocorticoids (GC) are still the mainstay of therapy for PMR. Despite this treatment, the disease may relapse or GC dosage cannot be tapered or alternatively, some patients are GC-refractory. Methotrexate (MTX) may be helpful in these cases, but this medication gave contradictory results. Anti TNFa are not effective in PMR. Although the pathogenesis of PMR is unknown, overproduction of proinflammatory cytokines can contribute to its development. It has recently been suggested that IL-6 is probably involved in PMR and giant cell arteritis (GCA). Tocilizumab (TCZ), an anti- IL-6 receptor antibody, gave promising results in single cases of GCA or in open-label studies. **Results** on the clinical efficacy of TCZ in pure or isolated PMR are limited.

Objectives: to report our experience (efficacy and safety) of TCZ in the treatment of patients with isolated PMR who had an inadequate response to GC and/or to other conventional therapies.

Methods: a call for observations of all case of patient with PMR who received TCZ was sent to the members of the French specialist network "Club Rhumatismes & Inflammation" (CRI) (rheumatologist and internal medicine). Patients must satisfied the Healey criteria for PMR and had isolated or predominant PMR clinical features.

Results: 7 cases were declared during a 12 months period. Patients included were 4 men and 3 women, mean age 73.4 ± 7.9 years, disease duration 2.3 ± 1.6 years, mean duration of GC treatment before starting TCZ: 16.1 ± 9.2 months. Clinical features were PMR symptoms for all and only one patient had proved associated GCA but without related clinical manifestations. All the patients were GC refractory requiring a daily dosage of prednisone ranging from 10 to 20 mg. Beside GC and before TCZ administration, patients had received MTX (6 cases), leflunomide (1 case) or a TNFa blocking agent (2 cases). TCZ was given as a monthly infusion (8 mg/kg). The mean number of infusions given were 6.4(range: 3-17). All the patients responded to the treatment with an improvement of the PMR-AS score (score before and after TCZ: 32.3 and 7.8, respectively), and CRP levels (CRP before and after TCZ: 56.9 and 4.6 mg/L). GC dosage was tapered from 15- 20 mg to 2.5-5 mg (5 cases) or stopped (2 cases). Clinical and laboratory improvement were obtained within the first 3 months after the onset of TCZ. The safety was excellent without any adverse event.

Conclusion: As previously reported in GCA, TCZ seems very effective in PMR patients who were unable to taper GC, with a prompt response and a GC-sparing effect. This biological agent may be adequately evaluated in a randomized controlled trial in order to determine its place in the treatment of PMR.

Disclosure: E. Toussirot, None; **A. Martin**, None; **M. Soubrier**, None; **S. redeker**, None; **A. Régent**, None; **L. CRI**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/clinical-efficacy-of-tocilizumab-in-polymyalgia-rheumatica-an-open-label-study

Abstract Number: 1987

Dramatic Efficacy of Tocilizumab As First Line Therapy in Patients with Recent Polymyalgia Rheumatica (PMR): Results of the First Longitudinal Prospective Study

Valerie Devauchelle[1], Alain Saraux[2], Jean-Marie Berthelot[3], Divi Cornec[4], Yves Renaudineau[5], Sandrine Jousse-Joulin[1], Thierry Marhadour[6], Solene Querellou[7], Florent Garrigues[8], Michel De Bandt[9] and Maelenn Gouillou[10], [1]Rheumatology, Brest university medical school, EA 2216, UBO and CHU de la Cavale Blanche,, Brest, France, [2]Rheumatology Department, CHU de la Cavale Blanche, Brest Cedex, France, [3]Rheumatology, University Hospital, Nantes, France, [4]Department of rheumatology, Brest Occidentale University, Brest, France, [5]Immunology, Brest University Medical School Hospital, Brest, France, [6]CHU La Cavale Blanche, Brest, France, [7]Nuclear Medicine Department, Morvan University Hospital, Brest, France, [8]Radiology department, Cavale Blanche Hospital and Brest Occidentale University, Brest, France, [9]Rheumatology department, CHU Fort de France, Fort de France, France, [10]Clinical Investigation Centre (CIC) 1412, CHU Cavale Blanche- Institut National de la Santé et de la Recherche Médicale (INSERM), Brest, France
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Background/Purpose: Glucocorticoids (GCs) are the cornerstone treatment of polymyalgia rheumatica (PMR) but induce several adverse events.

Methods:

Objectives: To evaluate efficacy and safety of tocilizumab as first line therapy in PMR.

Design: Prospective open label study (ClinicalTrials.gov: NCT01713842).

Setting: 2 university hospitals in France.

Patients: 20 glucocorticoids (GCs) naives patients with recent PMR fulfilling the Chuang criteria, with a disease duration of less than 12 months and an active disease ((PMR-AS)> 10) were included. Patients with suspected giant cell arteritis were excluded.

Intervention: All patients received tocilizumab infusions (week 0, 4 and 8) without GCs (period 1) and then oral GCs from week 12 to week 24 according to the PMR-AS at week 12 (patients with PMR-AS£10 were treated by 0.15mg/kg whereas those with PMR-AS>10 received 0.30 mg/kg). The primary endpoint was the response to tocilizumab based on PMR-AS£ 10 at week 12. Secondary endpoints were the PMR-AS response at weeks 2,4,8,12,16, 20 and 24 and the GCs sparing effect.

Results:

At inclusion, median PMR-AS was 36.6 (IQR: 30.4-43.8). At week 12, all patients reached the primary end point and were included in the low dose corticosteroid group. Median PMR-AS at week 12 and 24 were respectively 4.5 (IQR: 3.2-6.8) p< 0.001 and 0.95 (IQR: 0.4-2) p<0.001. No treatment rescue was necessary. Improvement was moderate by ultrasound, MRI and TEP-CT. The infusions of tocilizumab induced a GCs sparing effect of 70.2%. The sensitivity analysis based on a determined dosage of GC of 15mg/day without taking account of the patient's weight found similar results. Most frequent adverse events were transient neutropenia and leucopenia reported in 3 and 5 patients. One patient received only one infusion of tocilizumab due to adverse event.Limitations**:**Infusions were done every 4 weeks and not every 2 weeks as in systemic disease. This could explain a slower response than supposed with GCs.

Conclusion:

Monotherapy with Tocilizumab has a major efficacy in recent PMR and allows a sparing corticosteroid effect.

Disclosure: V. Devauchelle, None; **A. Saraux**, None; **J. M. Berthelot**, None; **D. Cornec**, None; **Y. Renaudineau**, None; **S. Jousse-Joulin**, None; **T. Marhadour**, None; **S. Querellou**, None; **F. Garrigues**, None; **M. De Bandt**, None; **M. Gouillou**, None.

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Abstract Number: 1988

Efficacy and Safety of Mizoribine for Polymyalgia Rheumatica: Analysis of 47 Cases

Ryo Rokutanda[1], Chisun Min[2], Yuko Kataoka[1], Tokutaro Tsuda[1], Shunya Kaneshita[1], Ken-ichi Yamaguchi[3], Koji Takasugi[4], Masei Suda[1], Akira Takeda[3], Yukio Matsui[1,3], Mitsumasa Kishimoto[1] and Masato Okada[1], [1]Immuno-Rheumatology Center, St. Luke's International Hospital, Tokyo, Japan, [2]Division of Allergy and Rheumatology, St. Luke's International Hospital, Tokyo, Japan, [3]Allergy and Rheumatology, St. Luke's International Hospital, Tokyo, Japan, [4]Imuno-Rheumatology Center, St. Luke's International Hospital, Tokyo, Japan
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Background/Purpose: Polymyalgia rheumatic (PMR) is an inflammatory rheumatic disease characterized by aching and morning stiffness of body, which is seen almost exclusively in adults over the age of 50. Glucocorticoid has been mainstay of the treatment, and methotrexate is generally recommended in patients resistant to initial steroid therapy. However, since several studies have shown greater toxicity of methotrexate in elderly patients, searching for less toxic immunosuppressive agent is warranted. Mizoribine (MZR) is an immunosuppressive agent which inhibits lymphocyte proliferation via inhibitory effect on the synthesis of inosine monophosphate dehydrogenase. While its efficacy and well tolerability for rheumatoid arthritis, systemic lupus erythematosus, autoimmune nephritis and suppression of rejection in renal transplantation is well established, few studies have examined the use of MZR for PMR.

Methods: We extracted all the patients who were given MZR for treatment of PMR during the period of July 2009 to June 2014. Retrospective medical charts review were performed to check the patients' background, duration and drug survival rate of MZR use, and reasons for discontinuation. Serum inflammatory markers and dose of corticosteroids at the time of last follow-up were compared those at the time of MZR initiation.

Results: Forty-seven PMR patients (16 male and 31 female, mean aged 73.5±7.9 year old) were treated by MZR during the study period. Mean disease duration at the time of MZR initiation and mean duration of MZR use are 415±61 days and 423±345 days, respectively. Twelve patients had discontinued MZR, and the reasons of discontinuation are as follows: remission (4 paitents), ineffectiveness (4patients), and adverse reaction (4 patients). The dose of PSL at the time of last follow-up was significantly lower than the PSL dose at the time of MZR initiation.

Conclusion: Mizroribine shows efficacy and well-tolerability in patients with polymyalgia rheumatica.

Disclosure: R. Rokutanda, None; **C. Min**, None; **Y. Kataoka**, None; **T. Tsuda**, None; **S. Kaneshita**, None; **K. I. Yamaguchi**, None; **K. Takasugi**, None; **M. Suda**, None; **A. Takeda**, None; **Y. Matsui**, None; **M. Kishimoto**, None; **M. Okada**, None.

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Abstract Number: 1989

Treatment of Refractory Non-Infectious Aortitis: Tocilizumab Compared to Antitnf Alfa Agents. Multicenter Study of 44 Patients

Montserrat Santos-Gómez[1], Javier Loricera[1], Ricardo Blanco[1], Jose L. Hernández[2], Santos Castañeda[3], Norberto Ortego-Centeno[4], M. Enriqueta Peiró[1], Paz Collado[5], Sheila Melchor[6], Antonio Mera[7], Eva Pérez-Pampin[8], Esteban Rubio Romero[9], Jaime Calvo-Alen[10], Elena Aurrecoechea[11], Iñigo Rúa-Figueroa[12], Mauricio Minguez[13], Gabriel Herrero-Beaumont[14], Beatriz Bravo[15], José Rosas[16], Javier Narváez[17], Javier Calvo[18], Rafael Ariza-Ariza[19], Mercedes Freire[20], Pablo Lluch Mesquida[21], Cristina Mata[22], Eva Galindez-Agirregoikoa[23], Juan María Blanco Madrigal[23], Amalia Sánchez[24], José Salvatierra[25], Vanesa Calvo-Río[1], Carmen Gonzalez-Vela[26], Natalia Palmou[1], Leyre Riancho-Zarrabeitia[1] and Miguel Angel Gonzalez-Gay[1], [1]Rheumatology, Hospital Universitario Marqués de Valdecilla. IDIVAL, Santander, Spain, [2]Internal Medicine, Hospital Universitario Marqués de Valdecilla. IDIVAL, Santander, Spain, [3]Rheumatology, Hospital Universitario de la Princesa, Madrid, Spain, [4]Systemic Autoimmune Diseases Unit, Hospital Universitario San Cecilio, Granada, Spain, [5]Rheumatology, Pediatric Rheumatology Unit, Hospital Universitario Severo Ochoa, Madrid, Spain, [6]Rheumatology, Hospital Universitario 12 de Octubre, Madrid, Spain, [7]Hospital Universitario de Santiago de Compostela, La Coruña, Spain, [8]Rheumatology, Hospital Universitario de Santiago de Compostela, La coruña, Spain, [9]Rheumatology Department,, Hospital Universitario Virgen del Rocío, Sevilla, Spain, [10]Rheumatology Division, Hospital de Sierrallana, Torrelavega, Spain, [11]Rheumatology, Hospital de Sierrallana, Torrelavega, Spain, [12]Rheumatology, Hospital Universitario Dr. Negrin, Las Palmas de Gran Canarias, Spain, [13]Department of Rheumatology, Hospital Universitario San Juan, Alicante, Spain, [14]Department of Osteoarticular Pathology, Hospital Universitario Fundación Jiménez Díaz, Madrid, Spain, [15]Pediatric rheumatology, Hospital Virgen de las Nieves, Granada, Spain, [16]Rheumatology, Hospital Marina Baixa, Villajoyosa, Spain, [17]Rheumatology, Hospital Universitario de Bellvitge, Barcelona, Spain, [18]Rheumatology, Hospital General Consorcio de Valencia, Valencia, Spain, [19]Rheumatology, Hospital Universitario Virgen de la Macarena, Sevilla, Spain, [20]Rheumatology, Complejo Hospitalario Universitario de A Coruña, La Coruna, Spain, [21]Hospital Mateu Orfila, Mahón (Menorca), Spain, [22]Rheumatology, Hospital de Sierrallana, Laredo, Spain, [23]Rheumatology, Hospital Universitario de Basurto, Bilbao, Spain, [24]Hospital Lucus Augusti, Lugo, Spain, [25]Hospital Universitario de San Cecilio, Granada, Spain, [26]Pathology, Hospital Universitario Marqués de Valdecilla. IDIVAL, Santander, Spain

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Background/Purpose:

Aortitis is often refractory to conventional immunosuppressive (IS) therapy. The use of biological therapy, such as tocilizumab (TCZ) and anti-TNFα agents have been reported.

Our aim was to compare the efficacy of TCZ with anti-TNFα therapy in patients with aortitis.

Methods:

Retrospective multicenter study of patients with aortitis refractory to traditional IS agents.

Results:

We studied 44 patients (36 W/8 M; 51±19 years); 25 with TCZ and 19 with anti-TNFα agents (IFX=14, ADA=3, and ETN=2). Baseline features of patients on TCZ compared to the anti-TNFα group (always in this order) showed a) mean age: 58±20 vs 42±13 years (p=0.003), b) women: 84% vs 79%, (p=0.97), c) underlying conditions: Takayasu arteritis, 8 vs 11 cases (p=0.08); giant cell arteritis, 15 vs 2 (p=0.0025); relapsing polychondritis, 1 vs 1 (p=0.59); ulcerative colitis, 0 vs 1 (p=0.88); Crohn's disease, 0 vs 1 (p=0.88); Behçet's disease, 0 vs 1 (p=0.88); sarcoidosis, 0 vs 1 (p=0.88); psoriatic arthritis, 0 vs 1 (p=0.88); and idiopathic aortitis, 1 vs 0 (p=0.88) d) mean of previous traditional IS agents (1.1 vs 1.7, p=0.069) and biological therapies (0.3 vs 0.1, p=0.23). After 3 months of treatment, most patients in both groups had experienced a clinical and acute phase reactants improvement, as well as a reduction of the corticosteroid dose. This favourable response was maintained over time (Table). The improvement observed by imaging techniques was similar in both groups. After a median follow-up of 12 [9-17] vs 16 [12-36] months (p=0.014), TCZ was withdrawn due to severe neutropenia (n=1); recurrent pneumonia (n=1); cytomegalovirus infection (n=1) and systemic lupus erythematosus (n=1). Other adverse effects were thrombocytopenia (n=1) and infusional hypotension (n=1). One patient died due to a stroke in the setting of an infective endocarditis, and another one discontinued TCZ because of inefficacy. In the anti-TNFα group, 3 patients on IFX discontinued due to inefficacy (n=1), recurrent pneumonia (n=1) and severe infusional reaction (n=1).

Conclusion:

Biological therapy appears effective and relatively safe in patients with aortitis refractory to traditional IS drugs. In this series, TCZ seems to be slightly more effective than anti-TNFα agents.

TABLE

	TCZ (n= 25)	anti-TNFα (n= 19)	p
Partial clinical improvement N; %#			
At 3 months	22; 88% (25)	10; 55% (18)	0.09
At 6 months	18; 90% (20)	11; 69% (16)	0.022
At 12 months	15; 100%) (15)	15; (94%) (16)	0.97
CRP, median [IQR]			
At onset	2.8 [0.8-5.4] (24)	1.5 [0.1-2.6] (15)	-
At 3 months	0.1 [0.1-0.6] (23)	0.1 [0.1-0.5] (12)	0.65
At 6 months	0.1 [0.1-0.5] (19)	0.3 [0.1-0.9] (12)	0.52
At 12 months	0.1 [0.1-0.5] (15)	0.2 [0.1-0.6] (11)	0.87
ESR, median [IQR]			
At onset	43 [16-72] (23)	37.5 [30-56] (14)	-
At 3 months	7 [2-11] (21)	17.5 [9-25] (14)	0.22
At 6 months	4 [2-7] (15)	16 [9-20] (13)	0.020
At 12 months	6 [2-11] (11)	16 [11-18] (13)	0.027
Improvement by imaging (between 3-6 months)	11; 73% (15)	10; 77% (13)	0.18
Prednisone dose, median [IQR]			
At onset	25 [10-50] (24)	20 [5-50] (17)	-
At 3 months	10 [7.5-20] (25)	12.5 [5-20] (15)	0.28
At 6 months	5 [2.5-10] (19)	10 [5-10] (16)	0.043
At 12 months	2.5 [0-5] (15)	7.5 [5-10] (16)	0.003

Improvement in at least one clinical manifestation.

In brackets, the number of patients with available data.

For CRP, ESR and prednisone daily requirement, "p" refers to the percentage of improvement at 3, 6 and 12 months compared to baseline (TCZ vs. anti-TNF)

Disclosure: M. Santos-Gómez, None; **J. Loricera**, None; **R. Blanco**, None; **J. L. Hernández**, None; **S. Castañeda**, None; **N. Ortego-Centeno**, None; **M. E. Peiró**, None; **P. Collado**, None; **S. Melchor**, None; **A. Mera**, None; **E. Pérez-Pampin**, None; **E. Rubio Romero**, None; **J. Calvo-Alen**, None; **E. Aurrecoechea**, None; **I. Rúa-Figueroa**, None; **M. Minguez**, None; **G. Herrero-Beaumont**, None; **B. Bravo**, None; **J. Rosas**, None; **J. Narváez**, None; **J. Calvo**, None; **R. Ariza-Ariza**, None; **M. Freire**, None; **P. Lluch Mesquida**, None; **C. Mata**, None; **E. Galindez-Agirregoikoa**, None; **J. M. Blanco Madrigal**, None; **A. Sánchez**, None; **J. Salvatierra**, None; **V. Calvo-Río**, None; **C. Gonzalez-Vela**, None; **N. Palmou**, None; **L. Riancho-Zarrabeitia**, None; **M. A. Gonzalez-Gay**, None.

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Abstract Number: 1990

Corticosteroid Use in Idiopathic Aortitis: A Systematic Review

Nancy Maltez[1] and Nataliya Milman[2], [1]Internal Medicine, University of Ottawa, Ottawa, ON, Canada, [2]Division of Rheumatology, University of Ottawa, Ottawa, ON, Canada

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Background/Purpose:

Idiopathic aortitis (IA) is a poorly defined entity with no specific pathological or clinical criteria for its classification or diagnosis, except for the presence of aortic inflammation and absence of clinical features of another systemic condition. Most of the present knowledge about IA comes from retrospective series of cases with pathologically identified aortitis. The objective of this systematic review was to clarify available data regarding outcomes in patients treated with corticosteroids and those without treatment.

Methods:

Data sources: Search strategy using terms “aortitis” and “idiopathic/isolated” identified published articles and abstracts using MEDLINE and EMBASE databases.

Study selection: Inclusion criteria required that cases of idiopathic aortitis be confirmed by pathology. Abstracts and case reports were excluded except for abstracts that complemented published manuscripts; reviews were used for triangulation. Authors were contacted for clarifications when required.

Data extraction: Data were extracted independently by two reviewers. Our primary goal was to compare outcomes between patients treated with corticosteroids and untreated patients. The primary outcomes included: development of new vascular lesions, clinical complications, delayed diagnosis of other rheumatological diseases and vascular death. Secondary outcomes included preoperative symptoms, ESR/CRP levels and presence of branch vessel disease.

Results:

Search yielded 262 records of which 10 fulfilled inclusion criteria. The majority of studies were retrospective. Even the few studies that reported on treatment status described very few events of interest: Miller *et al* described no new vascular lesions in two treated patients versus one lesion in 19 untreated patients while Clifford *et al* reported 2 new vascular lesions in 11 treated and 27 in 54 untreated patients. Wang *et al* reported one new vascular lesion (new aortic aneurysm) in the treated group and none in the untreated patients. Two studies described the need for re-operation, reported in two treated and none of the untreated patients in each of the studies. Finally, Liang *et al* reported 4 deaths (of unspecified cause) among untreated patients and none in the treated group.

Conclusion:

Few studies report clinical outcomes in patients diagnosed with idiopathic aortitis treated with corticosteroids. Consequently, there exists a lack of data to guide therapy and long term management of these individuals. The retrospective nature and small cohorts from which data is extracted make it difficult to draw conclusions. Future studies are required to better understand outcomes.

Disclosure: N. Maltez, None; **N. Milman**, None.

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Abstract Number: 1991

Large Vessel Involvement By IgG4-Related Disease

Cory Perugino[1], Zachary Wallace[1] and John H. Stone[2], [1]Rheumatology, Massachusetts General Hospital, Boston, MA, [2]Massachusetts General Hospital Rheumatology Unit, Harvard Medical School, Boston, MA

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Background/Purpose:

IgG4-related disease (IgG4-RD) is a systemic fibro-inflammatory condition of uncertain etiology. Reports have described inflammatory aortitis and peri-aortitis in the setting of retroperitoneal fibrosis (RPF) but have not adequately distinguished between these two manifestations. The frequency, radiologic features, and response of vascular complications to B cell depletion remain poorly-defined. We describe the clinical features, radiology findings, and treatment response in a large cohort of patients with IgG4-RD affecting the large vessels.

Methods:

All patients had biopsy-proven IgG4-RD. Clinical records of all patients diagnosed with IgG4-RD in our Center were reviewed. All radiologic studies were reviewed independently by two vascular radiologists. We distinguished between primary large blood-vessel inflammation and secondary vascular involvement, defined as disease related to the effects of adjacent inflammation (e.g., peri-aortitis associated with retroperitoneal fibrosis).

Results:

Of the 160 IgG4-RD patients in this cohort, 36 (22.5%) had large-vessel involvement. The mean age of the patients with large-vessel manifestations of IgG4-RD was 54.6 years. Twenty-seven (75%) were male and nine (25%) were female. Fifteen patients (42%) had primary involvement of their vasculature by IgG4-RD (IgG4-related vasculitis). Inflammatory aortic aneurysms (IAA), which affected eleven patients - 7% of the cohort overall - were observed in the abdominal aorta in seven cases, the thoracic aorta in seven, and both the thoracic and abdominal aorta in three. IAA of either the thoracic or abdominal aorta or both comprised the most common manifestation of IgG4-related vasculitis. Three patients had aortic dissection or contained perforation. Peri-aortitis in the setting of RPF accounted for 25 of 27 cases (93%) of secondary vascular involvement by IgG4-RD. Six patients demonstrated evidence of both primary and secondary blood vessel involvement. Twenty-two of the 36 patients with vascular disease were treated with rituximab and 62.5% showed stabilized or improved radiologic findings following treatment.

Conclusion:

IgG4-RD is a unique, distinctive and treatable cause of large-vessel vasculopathy, comprising both primary vasculitis and secondary vascular involvement. The most common manifestation of IgG4-related vasculitis is inflammatory aortic aneurysm. Peri-aortitis with sparing of the aortic wall is the most common secondary vascular manifestation.

Disclosure: C. Perugino, None; **Z. Wallace**, None; **J. H. Stone**, Roche, Genentech, 2,Genentech, 5.

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Abstract Number: 1992

Plasma Endothelin-1 Parallels the Vasoconstriction Phase in Reversible Cerebral Vasoconstriction Syndrome

Seby John[1], Leonard H. Calabrese[2], Juan J. Maya[3], Alex Massiello[4], Ken Uchino[1], Serpil Erzurum[5], Allison Janocha[5] and Rula A Hajj-Ali[6], [1]Cerebrovascular Center, Cleveland Clinic Foundation, Cleveland, OH, [2]Rheumatic & Immunologic Dis, Cleveland Clinic Foundation, Cleveland, OH, [3]Internal Medicine, Cleveland Clinic, Cleveland, OH, [4]Rheumatology, Cleveland Clinic, Cleveland, OH, [5]Cleveland Clinic, Cleveland, OH, [6]Rheumatic and Immunologic Dis, Cleveland Clinic, Cleveland, OH

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Plasma Endothelin-1 parallels the vasoconstriction phase in Reversible Cerebral Vasoconstriction Syndrome

Background/Purpose: Cerebral vasoconstriction is thought to be the underlying pathogenetic mechanism of Reversible Cerebral Vasoconstriction Syndromes (RCVS). However, mediators of the syndrome at molecular levels have not been elucidated. We previously reported that Endothelin-1 (E-1), a potent vasoconstrictor, is increased during the acute vasoconstrictive (ictal) phase in RCVS as compared to matched controls. Herein, we report on the levels of E-1 in the resolution phase of RCVS as compared to the ictal phase.

Methods: 14 paired samples from 7 patients were identified from the Cleveland Clinic prospective RCVS registry, who had blood samples collected during the ictal and resolution phases of RCVS symptoms. Further, E-1 levels were measured from 7 healthy controls of similar race and gender, who were then matched to the RCVS patients using a one-to-one Greedy matching algorithm based on age. Plasma E-1 levels were measured using Quantikine Endothelin-1 enzyme-linked immunosorbent assay kit (from R& D Systems) according to the user manual. Average E-1 levels at the ictal phase of RCVS were compared to the average E-1 levels during the resolution phase and matched healthy patients using mixed effects modeling to account for matched group clustering.

Results: The RCVS and control groups were well matched with respect to age and sex (table 1). During RCVS ictal phase, average plasma E-1 level (pg/ml) was significantly higher compared to resolution phase E-1 levels (2.063 ± 0.593 vs. 1.483 ± 0.278, $p = 0.037$). There was no difference between E-1 levels of RCVS at the resolution phase and healthy matched controls (1.483 ± 0.278 vs. 1.171 ± 0.278, $p = 0.312$). Two RCVS patients (RCVS 4 and 6) did not have complete radiologic resolution of vasoconstriction at follow-up testing. When excluding these 2 patients, the difference between the average E-1 levels during RCVS ictal phase and resolution phase was significantly higher (2.317 ± 0.487 vs. 1.377 ± 0.223, $p = 0.004$), while average E-1 levels at the resolution phase remained not significantly different compared to healthy matched controls (1.377 ± 0.223 vs. 1.115 ± 0.319, $p=0.262$).

Conclusion: Plasma Endothelin-1 (E-1) levels decrease to normal levels during the resolution phase of RCVS. This is more apparent in patients with complete resolution of radiological cerebral vasoconstriction, compared to those with persistent radiological vasoconstriction. These results suggest a major role of E-1 in the pathogenesis of RCVS.

Table 1

RCVS Patient	Age	Sex	RCVS Ictal Phase E-1 level (pg/ml)	RCVS Resolution Phase E-1 level (pg/ml)	Control Patient	Age	Sex	E-1 level (pg/ml)
RCVS 1	55	F	2.709	1.559	Control 1	56	F	1.238
RCVS 2	53	F	2.845	1.2	Control 2	50	F	0.794
RCVS 3	67	F	1.91	1.078	Control 3	66	F	0.783
RCVS 4	32	M	1.3	1.562	Control 4	35	M	1.294
RCVS 5	56	F	1.728	1.562	Control 5	56	F	1.238
RCVS 6	46	F	1.556	1.933	Control 6	45	F	1.328
RCVS 7	40	M	2.396	1.488	Control 7	42	M	1.522
Mean	50	F 5(71%)	2.063	1.483		50	F 5(71%)	1.171
STDev	12		0.593	0.278		10		0.278

Disclosure: S. John, None; **L. H. Calabrese**, None; **J. J. Maya**, None; **A. Massiello**, None; **K. Uchino**, None; **S. Erzurum**, None; **A. Janocha**, None; **R. A. Hajj-Ali**, None.

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Abstract Number: 1993

Imaging Findings of Cerebral Amyloid Angiopathy, Abeta-Related Angiitis (ABRA) and Cerebral Amyloid Angiopathy-Related Inflammation: A Single Institution 25 Year Experience

Carlo Salvarani[1], Jonathan M Morris[2], Caterina Giannini[2], Teresa J. H. Christianson[3], Robert D. Brown Jr.[4] and Gene G. Hunder[5], [1]Rheumatology, Arcispedale S Maria Nuova-IRCCS, Reggio Emilia, Italy, [2]Mayo Clinic, Rochester, MN, [3]Division of Biomedical Statistics & Informatics, Mayo Clinic, Rochester, MN, [4]Department of Neurology, Mayo Clinic, Rochester, MN, [5]Dept Internal Med/Rheum, Mayo Clinic, Rochester, MN
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Background/Purpose: To investigate the role of imaging in differentiating cerebral amyloid angiopathy (CAA) with and without inflammation.

Methods: We studied 54 patients seen over 25 years with pathological evidence of CAA with or without vascular inflammation and with available neuroimaging at the time of diagnosis. All pathological specimens were reviewed by one neuropathologist to evaluate the presence and distribution of inflammation associated with amyloid. All available neuroimaging findings were reviewed by a neuroradiologist. Clinical data were recorded

Results: Radiologic findings at diagnosis were available in 27 patients with CAA without inflammation, 22 with Aβ-related angiitis (ABRA) and 5 with CAA-related inflammation (CAA-RI). On MRI, leptomeningeal disease alone or with infiltrative white matter was significantly more frequent at presentation in patients with ABRA or CAA-RI compared to those with CAA (8 of 27, 29.6% vs 1 of 27, 3.7%, p = 0.02; and 11 of 27, 40.7% vs 1 of 27, 3.7%, p = 0.002, respectively), while lobar hemorrhage was more frequent in patients with CAA (17 of 27, 62.3% vs 2 of 27, 7.4%, p = 0.0001). Overall, leptomeningeal involvement at presentation was present in 70.4% (19 of 27) of patients with ABRA or CAA-RI and in only 7.4% (2 of 27) of patients with CAA (p = 0.0001). The sensitivity and specificity of leptomeningeal enhancement to identify patients with ABRA or CAA-RI were 70% and 93% respectively, while the positive likelihood ratio (LR) was 9.5. The sensitivity and specificity of intracerebral hemorrhage to identify patients with CAA were 63% and 93% respectively, while the positive LR was 8.5. Prior microhemorrhages at the grey white junction on GRE and/or SWI sequences were more frequently observed in patients with ABRA or CAA-RI compared to those with CAA (19 of 27, 70.4% vs 10 of 27, 37%, p = 0.03).

Conclusion: Leptomeningeal enhancement and lobar hemorrhage at presentation may enable differentiation between CAA with and without inflammation. SWI or GRE image aid in determining the correct diagnosis of ABRA or CAA-RI and aid in the decision regarding treatment.

Disclosure: C. Salvarani, None; **J. M. Morris**, None; **C. Giannini**, None; **T. J. H. Christianson**, None; **R. D. Brown Jr.**, None; **G. G. Hunder**, None.

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Abstract Number: 1994

Electronic Patient Reported Outcome Measures in Systemic Lupus Erythematosus : A Potential Disease Modifying Impact on the Management of Disease Activity Flares and Damage Accrual

Yasser M. El Miedany[1], Sami Bahlas[2], Maha El Gaafary[3], Sally Youssef[4] and Ihab Ahmed[5], [1]Rheumatology, Darent Valley Hospital, Dartford, United Kingdom, [2]Medicine, King Abdulaziz University, Jeddah, Saudi Arabia, [3]Community, Environmental and Occupational Medicine, Ain Shams University, Abbassia, Egypt, [4]Rheumatology and Rehabilitation Departmennt, Ain Shams University, Cairo, Egypt, [5]Medicine, Cairo University, Cairo, Egypt
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Background/Purpose:

Patient reported outcomes measures (PROMs) are changing the landscape in rheumatology care. Electronic PROMs (ePROMs) is a new patient-centric model of collaboration that fully engages patients in the decision making and governance to optimize controlling their disease activity and its management.

Objectives. To assess the value of ePROMs in the assessment and management of SLE disease activity flares observed over a 24-month period; its association with adherence to therapy as well as organ damage adjusted for potential confounding factors.

Methods:

A randomized, controlled crossover study carried out over 24-month duration. 147 SLE patients meeting the revised ACR criteria were enrolled. Disease activity was assessed using the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) whereas organ damage was scored using the SLICC/ACR Damage Index (SDI). In the first 12-month, the patients were assessed once every 3-months. Prior to their assessment in the clinic, each patient completed a PROMs questionnaire (paper format) [1]. Flare was defined as an increase ≥4 points in the SLEDAI between two clinic visits. At 12-months, the patients were randomized into a cohort of 73 patients who continued their care in the same style and 74 patients who completed an online ePROMs questionnaire on monthly basis for another 12-month period. The patients were given an appointment in an SLE hot clinic should their SLEDAI shows an increase of more than three points, management was adjusted accordingly. Otherwise every patient was seen every 3-months. The data captured were then retrospectively analysed at the end of the 24-month study period to determine the association between the number of flares and damage accrual. Adherence to therapy was also assessed at the end of the study.

Results:

At the end of the first year of the study, the mean of SLEDAI and SDI were 8.72 (6.1) and 1.9 (2.2) respectively. At the end of the second year the mean SLEDAI and SDI in the ePROMs cohort was 3.1 (2.6) and 1.2 (1.3) respectively, whereas in the control group the SDI an SLEDAI mean was 7.63 (6.7) and 1.8 (2.3) respectively ($p< 0.01$). Adjusting for possible confounding variables, the number of flares, regardless of their severity, was associated with damage accrual (OR 2.03, 95% CI 1.34 to 2.83, $p<0.001$). Adherence to therapy was significantly ($p<0.1$) higher in the ePROMs group whereas stopping DMARDs for intolerability was significantly ($p<0.01$) higher in the control group at 24-months of treatment.

Conclusion:

ePROMs has a potential disease modifying effect as it facilitated close monitoring of disease activity with an option of management escalation whenever indicated. Disease activity as measured by SLEDAI over a 24-month observation period predicted the risk of subsequent organ damage independently of other known risk factors.

Reference:

1. El Miedany Y et al. Ann Rheum Dis 2013; 72(Suppl3):484

Disclosure: Y. M. El Miedany, None; **S. Bahlas**, None; **M. El Gaafary**, None; **S. Youssef**, None; **I. Ahmed**, None.

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Abstract Number: 1995

Does the Risk of Serious Infections Among Elderly RA Patients Differ By Age of Disease Onset?

Sofia Pedro[1], Ted R. Mikuls[2] and Kaleb Michaud[3], [1]National Data Bank for Rheumatic Diseases, Wichita, KS, [2]University of Nebraska Medical Center, Omaha, NE, [3]Internal Medicine, University of Nebraska Medical Center, Omaha, NE
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Background/Purpose: Elderly-onset RA (EORA) patients (age of onset>60) are less likely to be treated with biologics even when accounting for disease activity compared to young-onset RA (YORA) patients (age<60) at the same age. We hypothesize that this difference is related to an increased risk of serious infections in EORA vs. YORA patients**.**

Methods: Participants with RA were followed biannually from 1998 through 2014 in a large US longitudinal study. Each EORA patient was matched to 3 YORA patients based on age, sex, and calendar year of study entry, which required all patients to have age>60. Serious infections were defined as those requiring hospitalization, intravenous antibiotics, or led to death within a year after the patient's last observation. Infections were validated from hospitalization, physician, and death records. Survival analysis methods (Cox regression, time to first infection using time-varying covariates and Andersen-Gill multiple failures model) were applied. Confounders included ethnicity, comorbidity index, HAQ, pain, education, prednisone use, urban vs. rural home, previous serious infection, and prior number of DMARDs. DMARD treatments were grouped using the following hierarchical classification: monotherapy MTX (reference), none, non-cytotoxic DMARD, cytotoxic DMARD, TNF, and non-TNF biologic. A risk window of 3 months was considered for all DMARDs except rituximab within the non-TNF group had 12 months.

Results: A total of 1,865 EORA patients were matched with 5,595 YORA patients. In both groups, 25% were male and 91% white and a median age between 65-70. EORA and YORA patients had 4.4 (4.2) and 20.9 (12.6) years of RA duration, respectively. Self-reported prior infections were 4.1% and 7.1% for EORA and YORA patients, respectively (P<0.01). There were 1,198 serious infections, 207 (11.0%) in EORA and 998 (17.8%) in YORA patients. Figure presents incident rates (first and multiple) by age group. Adjusted for other confounders, the HR of EORA vs. YORA was 0.84 (0.64-1.11) for first infection and 1.03 (0.86-1.23) for multiple. Prednisone, cytotoxic DMARDs, and no DMARD treatment were associated with an increased risk of serious infections as well as worse HAQ or pain, prior infections, and comorbidities (Table). Sensitivity analysis stratified patients by decade of age and no differences were found.

Conclusion: We found no increased risk of serious infections in EORA vs. YORA patients. Our results support providing similar treatment for EORA patients as done for elderly YORA patients

Figure. Serious infection incidence rates by decade of age.

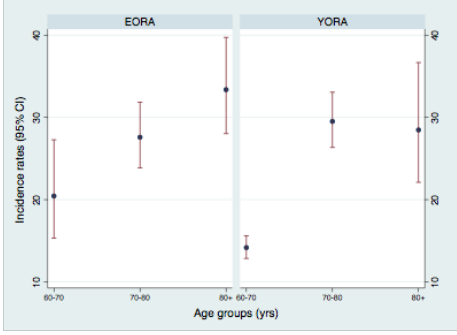

Table. Cox regression for time to first infection and multiple infections.

	Time to first infection		Time to multiple infections	
	Haz. Ratio	95% CI	Haz. Ratio	95% CI
EORA (vs. YORA)	0.84	(0.64 - 1.11)	1.03	(0.86 - 1.23)
DMARD treatment (Hierar.)	ref. monotherapy MTX			
None	1.24	(0.98 - 1.56)	1.24	(1.06 - 1.47)
Non-cytotoxic DMARD*¤	0.72	(0.56 - 0.93)	0.82	(0.69 - 0.98)
Cytotoxic DMARD	1.04	(0.78 - 1.39)	1.14	(0.93 - 1.40)
TNF biologic	0.91	(0.72 - 1.15)	0.96	(0.81 - 1.13)
Non-TNF biologic*¤	0.43	(0.25 - 0.75)	0.48	(0.33 - 0.69)
Prednisone*¤	2.19	(1.88 - 2.54)	2.08	(1.87 - 2.31)
Male*¤	1.37	(1.16 - 1.62)	1.42	(1.26 - 1.60)
Age*¤	1.36	(1.09 - 1.69)	1.23	(1.07 - 1.40)
Age-squared*¤	1.00	(1.00 - 1.00)	1.00	(1.00 - 1.00)
RA Duration (log yrs)	0.97	(0.84 - 1.11)	1.07	(0.97 - 1.19)
Caucasion*¤	1.77	(1.25 - 2.50)	1.80	(1.38 - 2.34)
HAQ (0-3)*¤	1.43	(1.27 - 1.61)	1.47	(1.35 - 1.59)
Pain (0-10)*¤	1.05	(1.02 - 1.08)	1.04	(1.01 - 1.06)
Education (yrs)¤	0.98	(0.95 - 1.01)	0.97	(0.95 - 0.99)
Cormorbidity index (0-9)*¤	1.18	(1.13 - 1.24)	1.19	(1.15 - 1.23)
# of prior DMARDs (log)*¤	1.14	(1.03 - 1.25)	1.10	(1.04 - 1.18)
# of prior biologics (log)	1.04	(0.92 - 1.19)	1.05	(0.97 - 1.15)
Urban (vs. rural)*¤	1.17	(1.00 - 1.36)	1.13	(1.01 - 1.26)
Prior infection¤	1.23	(0.96 - 1.57)	1.49	(1.27 - 1.75)

*P<0.01 for time to first infection; ¤P<0.01 for time to multiple infections

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Disclosure: S. Pedro, None; **T. R. Mikuls**, None; **K. Michaud**, None.

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Abstract Number: 1996

Complement Activation Predicts Adverse Pregnancy Outcome in Patients with SLE and/or aPL Antibodies

Jane E. Salmon[1,2], Mimi Kim[3], Marta Guerra[4], Elianna Kaplowitz[1], Carl Laskin[5], Michelle Petri[6], Ware D. Branch[7,8], Michael Lockshin[9], Lisa R. Sammaritano[2], Joan T. Merrill[10], Mary D. Stephenson[11], Munther Khamashta[12], Alan M. Peaceman[13], Anne Lynch[14] and Jill P. Buyon[15], [1]Hospital for Special Surgery, New York, NY, [2]Rheumatology, Hospital for Special Surgery, New York, NY, [3]Biostatistics and Research Design Resource, Albert Einstein Coll Med, Bronx, NY, [4]Rheumatology 3rd Fl Rsrch, Hospital for Special Surgery, New York, NY, [5]Medicine, Rheumatology and Obstetrics and Gynecology, University of Toronto and LifeQuest Centre for Reproductive Medicine, Toronto, ON, Canada, [6]Johns Hopkins University School of Medicine, Baltimore, MD, [7]University of Utah, Salt Lake City, UT, [8]Intermountain Healthcare, Salt Lake City, UT, [9]Barbara Volcker Center for Women & Rheumatic Disease, Hospital for Special Surgery, New York, NY, [10]Clinical Pharmacology, Oklahoma Medical Research Foundation, Oklahoma City, OK,

[11]University of Illinois College of Medicine, Chicago, IL, [12]Graham Hughes Lupus Research Laboratory, The Rayne Institute, St Thomas' Hospital, London, United Kingdom, [13]Northwestern University Feinberg School of Medicine, Chicago, IL, [14]Colorado School of Public Health, Aurora, CO, [15]NYU School of Medicine, New York, NY

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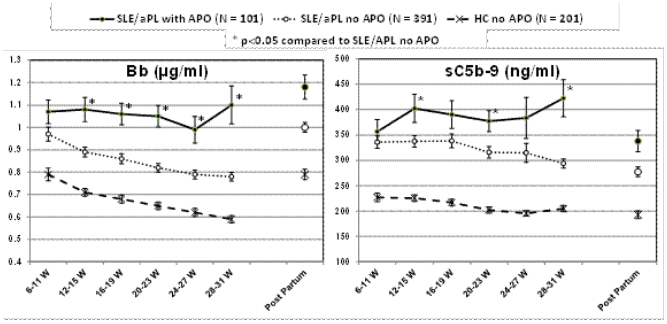
Background/Purpose: Women with SLE and/or aPL antibodies (SLE/APL) are at increased risk for adverse pregnancy outcomes (APO) yet identification of those destined for complications remains challenging. Murine studies implicate complement activation as an essential and causative factor in fetal loss and growth restriction. Activation of the alternative complement pathway, demonstrated by increased levels of the factor B fragment Bb, occurs in non-autoimmune patients with preeclampsia. Activation of all complement pathways leads to production of terminal complex C5b-9. We hypothesized that Bb and soluble C5b-9 (sC5b-9) would be elevated in the circulation starting early in the pregnancy of patients destined for APOs.

Methods: The PROMISSE Study (**P**redictors of p**R**egnancy **O**utcome: Bio**M**arkers **I**n antiphospholipid antibody **S**yndrome and **S**ystemic **L**upus **E**rythematosus) enrolled pregnant women with ≥4 ACR SLE criteria and/or aPL antibodies and healthy pregnant controls (HC). Subjects were evaluated and blood collected monthly beginning at <12 wks gestation. Exclusion criteria were multi-fetal pregnancy, prednisone >20mg/d, proteinuria >1gm/24hr, and creatinine >1.2 mg/dL. APOs were: fetal death, neonatal death, preterm delivery <36 wks because of preeclampsia or placental insufficiency, and/or growth restriction <5th %ile. Complement split products were measured on serial blood samples in 492 SLE/APL patients and in 201 HC. Levels of Bb and sC5b-9 (by MicroVue™ Bb Plus and SC5b-9 Plus EIA Kits) were compared at each time point using analysis of variance followed by pairwise comparisons with the Bonferroni method. Rates of change in complement activation products through 27 wks of pregnancy were estimated and compared using linear mixed effects models.

Results: APO occurred in 20.5% of SLE/APL pregnancies. Compared to SLE/APL patients with no APO, Bb and sC5b-9 were significantly higher as early as 12-15 wks in those destined for pregnancy complications and remained significantly elevated through 31 wks. Bb and sC5b-9 were significantly higher, starting as early as 12 wks, in SLE/APL patients regardless of outcome, compared to HCs. In all three groups, there was a decrease in Bb as pregnancy progressed, but the rate of decrease was significantly smaller in patients with APO compared to SLE/APL without APO and HC. Because complement activation often precedes and accompanies SLE flares, it is of note that in patients without flares, increased Bb still predicted poor outcomes.

Conclusion: In pregnant SLE/APL patients, increased Bb and sC5b-9 is detectable early in pregnancy and is strongly associated with APO. Our findings support the concept that activation of complement, particularly the alternative pathway, contributes to APO. In addition to identifying those destined for APO, they provide a rationale for blockade of complement to prevent APOs in high risk SLE/APL patients.



Disclosure: J. E. Salmon, None; **M. Kim**, None; **M. Guerra**, None; **E. Kaplowitz**, None; **C. Laskin**, None; **M. Petri**, None; **W. D. Branch**, None; **M. Lockshin**, None; **L. R. Sammaritano**, None; **J. T. Merrill**, Bristol-Myers Squibb, 2; **M. D. Stephenson**, None; **M. Khamashta**, None; **A. M. Peaceman**, None; **A. Lynch**, None; **J. P. Buyon**, None.

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Abstract Number: 1997

Underuse of Methotrexate (MTX) in the Treatment of Rheumatoid Arthritis (RA) in the United States (US): Results of a Comprehensive Pharmaceutical Claims Analysis

James R. O'Dell[1], Melanie Rohr[1], Stanley B. Cohen[2], J Carter Thorne[3] and Ted R. Mikuls[1], [1]University of Nebraska Medical Center, Omaha, NE, [2]Metroplex Clinical Research Center, Dallas, TX, [3]Southlake Regional Health Centre, Newmarket, ON, Canada

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Background/Purpose:

MTX is the anchor DMARD for RA treatment, but there is limited information about its appropriate use in clinical practice. This claims analysis was aimed at gaining insight into how MTX is employed for RA treatment in the US.

Methods: The analysis used Symphony Health Solutions' anonymized patient-level claims data which captures ~274 million US patients. The analysis included RA patients identified by ICD-9 codes 714.0 and 714.30 who initiated treatment with oral MTX in 2009 and were followed to 2014. Information obtained included: demographic characteristics, switches from oral to subcutaneous (SC) MTX and/or biologics (with or without concomitant MTX), timing of treatment changes, and oral MTX or SC MTX dosing at the times of switches/additions or end of follow-up. Independent t-tests were used to assess significance of differences among treatment paths.

Results: The study included 35,640 patients (Table). Of these, 15,599 (43.8%) continued on oral MTX alone (Group 1), through the end of the follow-up period and 17,528 (49.2%) added or switched to a biologic agent (Group 2). The median time to adding a biologic in Group 2 was 170 days and 41.5% of the patients added a biologic within 90 days of initiating oral MTX. In addition, only 7% of patients switched from oral to SC MTX (Group 3) after a median of 534 days of oral therapy; 14.0% of these patients switched within the first 90 days of oral MTX treatment. Overall, 71% of patients who switched from oral to SC MTX remained on this treatment for approximately 3 years and those who added a biologic did so after a median of 289 days. Median time for progression to a biologic was significantly longer (823 days; time on oral + time on SC) for patients who received SC MTX vs those who received only oral drug (170 days) (P<0.0001).

Oral MTX Initiation 2009		**Duration of Oral MTX Prior to Biologic (days)**	**Oral MTX Dose Prior to Biologic (mg/week)**	**SC MTX Dose Prior to Biologic (mg/week)**	**Duration of SC MTX Prior to Biologic (days)**	**MTX Dose at Last Follow-up 2014 (mg/week)**
N=35,640	n (%)	Mean ± SD Median				
Group 1: Remained on only oral MTX through 2014	15,599 (43.8%)	NA	NA	NA	NA	15 ± 5 15
Group 2: Biologic initiated during follow-up period	17,528 (49.2%)	478 ± 580 170	15 ± 5 15	NA	NA	NA
Group 3: Switched from oral to SC MTX and remained on this treatment or had biologic added	2,513 (7.0%)	729 ± 623[1] 534	17 ± 5[1] 15	21 ± 5[2] 20	457 ± 456[2] 289	21 ± 5[3] 20

1. P<0.0001 vs Group 2

2. For 711 patients who switched to a biologic

3. For 1,802 patients who remained on SC MTX until the end of follow-up

Conclusion:

In the US, MTX is frequently under-dosed, given for an inadequate length of time, and rarely switched to SC before the initiation of biologic therapy. More than 40% of RA patients who initiate treatment with oral MTX switched to or had a biologic added within 90 days after a median dose of only 15 mg/week. Switching to SC MTX prevents the need for or significantly extends time to a biologic. More appropriate optimization of MTX could lead to better control of RA and would be expected to produce significant cost savings.

Disclosure: J. R. O'Dell, Medac Pharma, Inc, 5,Antares, 5,Abbvie, 5,Eli Lilly and Company, 5,Pfizer Inc, 5; **M. Rohr**, None; **S. B. Cohen**, Amgen, 2,Bristol-Myers Squibb, 2,Abbvie, 2,UCB, 2,Janssen Pharmaceutica Product, L.P., 2,Pfizer Inc, 2,Roche Pharmaceuticals, 2,Amgen, 5,Bristol-Myers Squibb, 5,Pfizer Inc, 5,Medac Pharma Inc, 5; **J. C. Thorne**, Abbvie, 5,Amgen, 5,AstraZeneca, 5,Bristol-Myers Squibb, 5,Celgene, 5,Centocor, Inc., 5,Genzyme Corporation, 5,Hospira, 5,Pfizer Inc, 5,Roche Pharmaceuticals, 5,Genzyme Corporation, 8,Medac Pharma Inc, 8,Antares, 8,Abbvie, 2,Amgen, 2,AstraZeneca, 2,Celgene, 2,Eli Lilly and Company, 2,Novartis Pharmaceutical Corporation, 2,Pfizer Inc, 2; **T. R. Mikuls**, Roche Pharmaceuticals, 2,Pfizer Inc, 5.

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Abstract Number: 1998

A National Electronic Health Record-Enabled Registry in Rheumatology: The ACR's Rheumatology Informatics System for Effectiveness (RISE)

Jinoos Yazdany[1], Rachel Myslinski[2], Melissa Francisco[3], Nick Bansback[4], Megan E. B. Clowse[5], Deborah Collier[6], Karen Law[7], Katherine Liao[8], Kaleb Michaud[9], Esi Morgan-DeWitt[10], Jim Oates[11], Catalina Orozco[12], Andreas Reimold[13], Julia F Simard[14] and Salahuddin Kazi[15], [1]University of California, San Francisco, San Francisco, CA, [2]Governance & Ethics Specialist, Amer College of Rheumatology, Atlanta, GA, [3]Practice, Advocacy & Quality, American College of Rheumatology, Atlanta, GA, [4]Population and Public Health, The University of British Columbia, Vancouver, BC, Canada, [5]Clinical Rheumatologist, Duke University Medical Center, Durham, NC, [6]Rheumatology, Allergy, and Immunology, Massachusetts General Hospital, Harvard Medical School, Boston, MA, [7]Emory University School of Medicine, Atlanta, GA, [8]Division of Rheumatology, Immunology, and Allergy, Brigham & Women's Hospital, Boston, MA, [9]Rheumatology & Immunology, University of Nebraska Medical Center and National Data Bank, Omaha, NE, [10]Pediatric rheumatology, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, [11]Medicine, Medical University of South Carolina, Charleston, SC, [12]Arthritis Consultation Ctr, Dallas, TX, [13]Rheumatology, VAMC, University of Texas Southwestern Medical Center, Dallas, TX, [14]Division of Epidemiology, Health Research and Policy Department, and Division of Immunology & Rheumatology, Department of Medicine, Stanford School of Medicine, Stanford, CA, [15]Internal Medicine/Rheumatology, UT Southwestern Medical Center, Dallas, TX
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SESSION INFORMATION
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Session Time: 11:00AM-12:30PM

Title: A National Electronic Health Record-Enabled Registry in Rheumatology: The ACR's Rheumatology Informatics System for Effectiveness (RISE)

Background/Purpose: In 2014, the ACR launched the Rheumatology Informatics System for Effectiveness (RISE), a national electronic health record (EHR)-enabled registry. RISE passively collects data from EHRs of participating practices, provides advanced quality measurement and data analytic capacities, and can be used to fulfill national quality reporting requirements. Here we detail the characteristics of practices participating in RISE, patient characteristics and performance on several nationally endorsed quality measures.

Methods: RISE has achieved certification as a Centers for Medicare and Medicaid Services (CMS) Qualified Clinical Data Registry (QCDR), allowing collection of data on quality of care without individual patient informed consent. Participating practices enter a Data Use Agreement with the ACR, after which local data are mapped, validated and uploaded regularly to the central registry. Practices can access an analytics dashboard that allows review of up-to-date information on quality measures by provider and practice as well as national benchmarks. RISE currently includes data on numerous quality measures regarding rheumatoid arthritis (RA), drug safety, osteoporosis prevention and treatment, low back pain, and preventive health care (e.g. smoking, blood pressure management). We analyzed data between April 1, 2014 and March 31, 2015 to characterize initial practices and patients captured in RISE. We also calculated performance on several RA quality measures recently endorsed by the National Quality Forum (DMARD use, disease activity measurement, functional status measurement).

Results: During the dates examined, RISE included data on 184,858 patients, including 49,205 with RA (Table). Two hundred five clinicians across 39 sites contributed data to RISE; 72% of clinicians were in a group practice, 25% were solo practitioners and 4% were part of a larger health system. Characteristics of patients in RISE are summarized in the Table. For the subset of patients with RA, 50.7% of patients had a disease activity score recorded, 53.2% had a functional status score recorded, and 82.1% were taking a DMARD, as defined by national quality measures.

Conclusion: The ACR has launched a national EHR-enabled registry that aims to provide critical infrastructure for improving quality of care in rheumatology, to fulfill national performance reporting requirements, and to serve as a unique data source to generate new knowledge regarding rheumatic disease. Data validation and mapping is ongoing and RISE will be available to both the research and clinical community to use to advance rheumatology.

Table 1. Baseline characteristics of patients in the ACR's RISE national registry.

Characteristic	Total N (N = Distinct Patient)
Age at last encounter, mean (SD)	59 (± 16.1)
Sex	
Female, n (%)	138,748 (75.1%)
Male, n (%)	46,106 (24.9%)
Missing, n (%)	4 (0.002%)
Race, n (%)	
White	114,252 (61.8%)
Black	14,765 (8.0%)
Asian	2,816 (1.5%)
American Indian/Alaskan Native	2,989 (1.6%)
Native Hawaiian/Pacific Islander	84 (0.05%)
Other	19,703 (10.7%)
Missing	29,260 (15.8%)
Insurance/Payer type (at last encounter), n (%)	
Medicare	72,731 (39.3%)
Medicaid	6,584 (3.6%)
Commercial	12,7159 (68.8%)
Other	14,975 (8.1%)
Missing	25,200 (13.6%)
Selected Diagnoses (ICD9 code at last encounter), n (%)	
Rheumatoid arthritis (ICD 9 714.0, 714.1, 714.2, 714.3 714.81)	49,205 (26.6%)
Knee osteoarthritis (ICD9 715.16, 719.46)	33,824 (19.3%)
Sjogren's syndrome (ICD9 370.4, 710.2, 730.2)	11,762 (6.4%)
Systemic lupus erythematous (ICD9 710.0,695.4)	11,720(6.3%)
Gout (ICD9 274.xx, 984.9)	7,160 (4.1%)
Spondyloarthropathy (ICD9 720.xx, 696.0))	4,306 (2.3%)
Systemic sclerosis (ICD9 710.1)	2,062 (1.1%)
Vasculitis (ICD9 446.0, 446.1, 446.2, 446.4, 446.5, 446.7, 686.1, 287.0	1805(0.98%)
Sarcoidosis (ICD9 135)	1169 (0.6%)
Smoking, n (%) (last encounter)	
Never	107,578 (61.21%)
Current	18,394 (10.47%)
Former	34,608 (19.69%)
Missing	11,613 (6.61%)
Blood pressure, mmHg, mean (SD) (last encounter)	
Systolic	125.28 (±15.92)
Diastolic	75.18 (±9.68)
Diastolic>90 OR Systolic> 140	24,916 (14.18%)

Disclosure: J. Yazdany, None; **R. Myslinski**, None; **M. Francisco**, None; **N. Bansback**, None; **M. E. B. Clowse**, UCB Pharma, 5; **D. Collier**, None; **K. Law**, None; **K. Liao**, None; **K. Michaud**, None; **E. Morgan-DeWitt**, None; **J. Oates**, None; **C. Orozco**, None; **A. Reimold**, None; **J. F. Simard**, None; **S. Kazi**, None.

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Abstract Number: 1999

Improvement in Mortality in RA Compared to the General Population – Closing the Mortality Gap

Diane Lacaille[1,2], Eric C. Sayre[3] and Michal Abrahamowicz[4], [1]Rheumatology, University of British Columbia, Vancouver, BC, Canada, [2]Rheumatology, Arthritis Research Canada, Richmond, BC, Canada, [3]Arthritis Research Canada, Richmond, BC, Canada, [4]Division of Clinical Epidemiology, McGill University, Montreal, QC, Canada

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Background/Purpose: Increased mortality in RA is believed to be a consequence of inflammation. With improved treatment, mortality would be expected to decrease over time. The objective of our study was to compare mortality risk in RA vs. general population controls across RA incident cohorts of earlier vs. later RA onset.

Methods: We conducted a retrospective cohort study of a population based cohort of all incident RA cases in BC with matched general population controls, using administrative health data. RA cases were selected if they had ≥2 MD visits > 2 mos apart for RA in 01/1996-12/2006, with no prior RA visit since 1990. Cases were excluded if they had ≥2 subsequent MD visits for another inflammatory arthritis; if they saw a rheumatologist and the RA diagnosis was never confirmed; or if there were no subsequent RA visits over a F/U >5 yrs. General population controls were randomly selected, matched 1:1 on birth yr, gender and calendar yr of inclusion. Cohorts were divided into earlier (RA onset 1996-2000) and later (2001-2006) cohorts. Data were obtained on all physician visits and vital statistics data including cause of death from death certificates, until Dec 2010.

Person-years (PY) of F/U were calculated from index date to end of F/U, last health care use, or death. Cases and controls were right censored at 5 yrs of F/U to ensure equal F/U time when comparing mortality rates between earlier and later incident cohorts. Sensitivity analyses including all years of F/U yielded similar results. All cause and cause-specific mortality rates and 95% CI were calculated for RA cohorts and controls, along with mortality rate ratios. In addition, we obtained hazard ratios (HRs) for mortality in RA vs. controls via exponential regression models adjusting for age, testing differences between incident cohorts via an interaction term.

Results: The sample included 24,914 RA cases and controls (66.5% female; mean [SD] age 57.3 [17.4] years) contributing 112,431 and 113,100 PY of follow-up, resp., with 2747 and 2123 deaths observed in RA and controls, yielding all-cause mortality rates of 24.43 and 18.77 per 1000 PY in RA and controls, resp., with a mortality rate ratio of 1.30 (95%CI: 1.23;1.38). Mortality risk in RA vs. controls differed across incident cohorts. Mortality was significantly increased in RA vs. controls in earlier, but not later, incident cohorts, for all-cause as well as cause-specific mortality (Table 1). In the age-adjusted exponential mortality models, a significant interaction between RA (vs. controls) and incident cohort (early vs. late) was found ($p<0.001$) for all-cause, CVD and cancer, but not infection ($p=0.31$).

Conclusion: In our population-based incident RA cohort, the risk of mortality compared to the general population has improved over time. The mortality gap between RA and the general population present in people with RA onset on or before 2000 was no longer present in people with RA onset after 2000.

Table 1: Mortality Risk in RA compared to general population controls				
	Mortality rate RA (per 1000 PY)	**Mortality rate controls (pre 1000 PY)**	**Mortality rate ratio (95% CI) RA vs. controls**	**Adj. Hazard Ratio (95% CI) RA vs. controls**
Entire cohort,	24.43	18.77	1.30 (1.23; 1.38)	1.24 (1.17; 1.31)
all cause mortality	8.49	6.53	1.30 (1.18; 1.43)	1.23 (1.12; 1.36)
mortality from CVD	1.45	0.86	1.69 (1.31; 2.20)	1.61 (1.25; 2.07)
mortality from infection	6.48	5.42	1.20 (1.07; 1.33)	1.14 (1.02; 1.27)
mortality from cancer				
All cause mortality:	32.68	19.90	1.64 (1.52; 1.78)	1.55 (1.43; 1.68)
Incident cohort 1996-2000	18.29	17.88	1.02 (0.94; 1.11)	0.98 (0.90; 1.06)
Incident cohort 2001-2006				
Mortality from CVD	12.30	7.40	1.66 (1.46; 1.90)	1.58 (1.38; 1.80)
Incident cohort 1996-2000	5.66	5.85	0.97 (0.83; 1.12)	0.92 (0.80; 1.06)
Incident cohort 2001-2006				
Mortality from infections	1.88	0.96	1.95 (1.36; 2.83)	1.83 (1.29; 2.60)
Incident cohort 1996-2000	1.13	0.78	1.46 (1.00; 2.14)	1.41 (0.98; 2.03)
Incident cohort 2001-2006				
Mortality from cancer	8.61	5.55	1.55 (1.33; 1.81)	1.46 (1.26; 1.70)
Incident cohort 1996-2000	4.90	5.32	0.92 (0.79; 1.08)	0.89 (0.76; 1.04)
Incident cohort 2001-2006				
Abbreviations: CI= Confidence Intervals; CVD cardiovascular diseases				

Disclosure: D. Lacaille, None; **E. C. Sayre**, None; **M. Abrahamowicz**, None.

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Abstract Number: 2000

Immune Response Against Â Î²2GPI Drives Th1 Inflammation in Atherosclerotic Plaques of Patients with Primary Antiphospholipid Syndrome

Pier Luigi Meroni[1,2], Marisa Benagiano[3], Maria Gerosa[4], Jacopo Romagnoli[5], Michael Mahler[6], Maria Orietta Borghi[7,8], Alessia Grassi[9], Chiara Della Bella[3], Giacomo Emmi[3], Amedeo Amedei[3,10], Elena Silvestri[3], Lorenzo Emmi[11], Domenico Prisco[9,10] and Mario Milco D'Elios[3,10], [1]Clinical Sciences and Community Heath, Department of Clinical Sciences and Community Health, University of Milan, Milan, Italy, [2]Laboratory of Immuno-rheumatology, Laboratory of Immuno-rheumatology, IRCCS Istituto Auxologico Italiano, Cusano Milanino, Italy, [3]Department of Experimental and Clinical Medicine, Department of Experimental and Clinical Medicine, University of Florence, Florence, Italy, [4]Division of Rheumatology, Department of Clinical Sciences and Community Health, Ospedale Gaetano Pini, University of Milan, Milano, Italy, [5]Department of Surgery, Department of Surgery, Catholic University of

Rome, Rome, Italy, [6]Inova Diagnostics, San Diego, CA, [7]Department of Clinical Sciences and Community Health, Department of Clinical Sciences and Community Health, University of Milan, Milan, Italy, [8]Laboratory of Immuno-rheumatology, IRCCS Istituto Auxologico Italiano, Milan, Italy, [9]Department of Experimental and Clinical Medicine,, Department of Experimental and Clinical Medicine, University of Florence, Florence, Italy, [10]Internal Interdisciplinary Medicine Center for Autoimmune Systemic Diseases, Lupus Clinic, Internal Interdisciplinary Medicine Center for Autoimmune Systemic Diseases, Lupus Clinic, AOU Careggi, Florence, Italy, [11]Internal Interdisciplinary Medicine Center for Autoimmune Systemic Diseases, Lupus Clinic,, Internal Interdisciplinary Medicine Center for Autoimmune Systemic Diseases, Lupus Clinic, AOU Careggi, Florence, Italy
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SESSION INFORMATION

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Session Title: Antiphospholipid Syndrome: Recent findings
Session Type: ACR Concurrent Abstract Session
Session Time: 2:30PM-4:00PM

Background/Purpose:

Antiphospholipid syndrome (APS) is characterized by the presence of arterial and venous thrombosis, and by recurrent abortions, in patients with persistent presence of autoantibodies against phospholipid-binding proteins (aPL), such as β2-Glycoprotein I (β2GPI). Arterial thrombosis has been also related to accelerated atherosclerosis in experimental models, however contrasting findings have been reported in clinical studies of patients with primary APS regarding an increased number of plaques or an abnormal arterial wall thickness. In spite of that, aPL predicts adverse arterial outcomes (Hollan et al Autoimmun Rev 12:1004;2013). Aim of the study was to investigate the role of the anti-β2GPI immune response in atherosclerotic lesions.

Methods:

We investigated the cytokine production induced by β2GPI, and its domains (DI, DII, DIII, DIV, DV) in activated T cells that infiltrate *in vivo* atherosclerotic lesions of patients with primary APS atherothrombosis. We also examined the helper function of β2GPI-specific T cells for monocyte matrix metalloproteinase (MMP)-9 and tissue factor (TF) production, as well as their cytolytic potential and their helper function for antibody production.

Results:

We report that APS patients with atherothrombosis harbor *in vivo* activated $CD4^+$ T cells that recognize β2GPI in atherothrombotic lesions. We characterized the submolecular specificity of plaque infiltrating T cells and found that the majority of them recognize their epitopes within the DI domain. β2GPI and its domains induce T cell proliferation and expression of IFN-g in plaque-derived T cell clones. β2GPI-specific T cells display helper function for monocyte MMP-9 and TF production, and promote antibody production in autologous B cells. Moreover, plaque-derived β2GPI-specific $CD4^+$ T lymphocytes express both perforin-mediated and Fas-FasLigand mediated cytotoxicity.

Conclusion:

β2GPI, and especially DI domain, drive a local Th1 inflammatory response, with subsequent plaque instability which eventually favors atherothrombosis. This finding may explain the association between aPL and arterial thrombosis in spite of the lack of the evidence for surrogate markers of atherosclerosis - such as number of plaques and increased arterial wall thickness - in primary APS patients with high prevalence of arterial events.

Abstract Number: 2001

Reduction of HLA Class II Expression and Beta-2-Glycoprotein I Presentation By Fluvastatin in Vitro and in Vivo: Possible Mechanism of Statin-Induced-Deprocoagulation in the Antiphospholipid Syndrome

Toshiyuki Watanabe[1,2], Kenji Oku[1], Olga Amengual[1], Ryo Hisada[1], Kazumasa Ohmura[1], Haruki Shida[1], Yuka Shimizu[1], Masaru Kato[1], Toshiyuki Bohgaki[1], Tetsuya Horita[1], Shinsuke Yasuda[1], Akihiro Ishizu[3], Hisashi Arase[4] and Tatsuya Atsumi[1], [1]Division of Rheumatology, Endocrinology and Nephrology, Hokkaido University Graduate School of Medicine, Sapporo, Japan, [2]3rd Department of Internal medicine, Hokkaido P.W.F.A.C Obihiro-Kosei General Hospital, Obihiro, Japan, [3]Faculty of Health Sciences, Hokkaido University, Sapporo, Japan, [4]Laboratory of Immunochemistry, WPI Immunology Frontier Research Center, Osaka University, Suita, Japan
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Session Title: Antiphospholipid Syndrome: Recent findings
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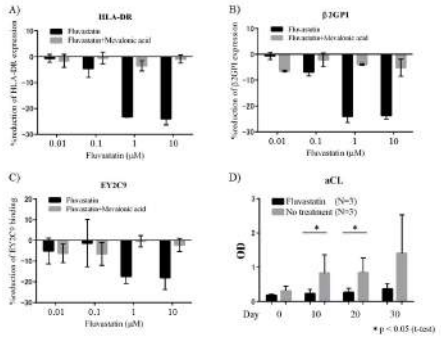
Session Time: 2:30PM-4:00PM

Background/Purpose: Human leukocyte antigen (HLA)-DRB1*07:01 is one of the susceptibility alleles for antiphospholipid syndrome (APS). Recently we have reported that beta-2-glycoprotein I (b2GPI) /HLA class II complex is targeted by anti-b2GPI antibody. The 3-hydroxy-3-methyl-glutaryl-CoA reductase inhibitors (statins) reduce procoagulant cell activation by anti-b2GPI antibody, thus having potential benefit for patients with APS, although the mechanisms have not been clarified. The aim of this study was to identify the mechanisms involved in the reduction of anti-b2GPI antibody induced procoagulant activity by statins.

Methods: b2GPI was co-transfected into immortalized human umbilical vein endothelial cell (HUEhT-1) and human monocytic cell line (THP-1), together with HLA-DRA*01:01/DRB1*07:01 (HLA-DR7) or HLA-DRA*01:01/DRB1*08:01 (HLA-DR8). Fluvastatin was added to cells in the presence or absence of mevalonic acid. The expression of HLA-DR and b2GPI on the cell surfaces was assessed by flowcytometry (FCM). The binding ability of human monoclonal anti-b2GPI antibody (EY2C9) to these cells was analyzed by FCM. In an *in vivo* study using env-pX rats, as a spontaneous rat model of APS, fluvastatin (200 mg/day) was administered orally for 30 days. The titer of anti-cardiolipin/b2GPI complex (aCL) was sequentially determined every 10 days.

Results: Both the expression of b2GPI and binding of EY2C9 were more highly observed on the surface of HUEhT-1 and THP-1 co-transfected with HLA-DR7 than HLA-DR8. The expression of b2GPI was not detected on the surface of cells transfected with b2GPI alone. In HUEhT-1 co-transfected with b2GPI and HLA-DR7, the addition of fluvastatin suppressed the expression of HLA-DR, as well as the expression of b2GPI presented on HLA-DR (Figure 1A and 1B). This inhibitory effect was reduced by mevalonic acid. In addition, the EY2C9 binding to HUEhT-1 was reduced by fluvastatin (Figure 1C). Similar results were obtained in THP-1 transfected with b2GPI and HLA-DR7. In the rat model experiment, the administration of fluvastatin to env-pX significantly reduced the titer of aCL (Figure 1D)

Conclusion: Fluvastatin inhibited the expression of b2GPI/HLA class II complex, leading to down regulation of anti-b2GPI antibody binding. The aCL titer in env-pX rats was reduced by fluvastatin as well. The inhibition of the pathogenic autoantigen presentation through the reduction of HLA-DR expression might be one of the mechanisms involved in the deprocoagulating effects of statins.



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Abstract Number: 2002

Dnase Treatment Protects Against DVT Formation in a Mouse Model of Antiphospholipid Syndrome

He Meng[1], Srilakshmi Yalavarthi[2], Levi F. Mazza[3], Megan A. Elfline[1], Catherine E. Luke[1], Peter K. Henke[1] and **Jason S. Knight**[2], [1]University of Michigan, Ann Arbor, MI, [2]Division of Rheumatology, University of Michigan, Ann Arbor, MI, [3]Department of Internal Medicine, Division of Rheumatology, University of Michigan, Ann Arbor, MI

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Session Date: Monday, November 9, 2015

Session Title: Antiphospholipid Syndrome: Recent findings

Session Type: ACR Concurrent Abstract Session

Session Time: 2:30PM-4:00PM

Background/Purpose: Antiphospholipid antibodies, especially those targeting beta-2-glycoprotein I (β_2GPI), have been shown to amplify thrombosis in mice. However, most published models have relied on endothelial injury, induced by either laser or pinch injury. Here, we have characterized a model of deep vein thrombosis (DVT) in which flow through the inferior vena cava (IVC) is restricted without causing complete occlusion, and in which the endothelium is not specifically damaged. This model results in a thrombus that recapitulates the histologic characteristics of human DVT.

Methods: Total IgG fractions were prepared from either healthy volunteers or two different primary antiphospholipid syndrome (APS) patients, both with high-titer anti-β_2GPI IgG. C57BL/6 wild-type mice were treated with two doses (500 µg each) of either control or APS IgG by intraperitoneal injection, 48 hours apart. Around the time of the second treatment, a laparotomy was performed, and a ligature was fastened around the IVC over a blunted 30-gauge needle (which served as a spacer). After removal of the spacer, the abdomen was closed, and the mouse was allowed to recover. The resulting stenosis causes an 80-90% reduction in IVC blood flow. Some mice were additionally treated with infusion of DNase (Pulmozyme/dornase alfa) immediately after surgery. DVT formation was assessed at 6 and 48 hours after surgery.

Results: APS IgG injection resulted in circulating anti-β_2GPI IgG levels of 10-20 SGU (standard IgG units), in contrast to control IgG, which gave undetectable levels. Importantly, mice treated with APS IgG were significantly more likely to form IVC thrombi than mice treated with control IgG. At 6 hours, 40% of control mice formed thrombi, as compared to >90% of APS mice. At 48 hours, these numbers were 50-60% for control mice, and >90% for APS mice. By both histology and western blotting, the thrombi were rich in citrullinated histone H3 (cit-H3; a marker of neutrophil extracellular traps/NETs), There was also a significant increase in circulating cell-free DNA in the APS mice, as compared to controls, at the 6-hour time point. Treatment with DNase was highly effective in preventing thrombus formation at 6 hours, reducing the percentage of clots in APS mice from >90% to ~33%. Further supporting a mechanistic role for NETs, anti-β_2GPI IgG promoted NET release from C57BL/6 neutrophils *in vitro*. Of note, a spontaneous model of APS (NZW x BXSB F_1) was also associated with >90% DVT formation following IVC stenosis; neutrophil characterization and treatment experiments are underway in these mice.

Conclusion: IgG isolated from APS patients increase the frequency of thrombus formation in a model of DVT that recapitulates the histology of human thrombi. This increase can be abrogated by treatment with DNase, suggesting a role for extracellular DNA in thrombus formation. Further, cit-H3 was abundant in non-nuclease-treated thrombi. Overall, these data point to a role for NETs as perpetuators, and possibly initiators, of the prothrombotic phenotype in APS. This line of investigation has the potential to suggest new, non-anticoagulant approaches for the treatment of APS.

Disclosure: H. Meng, None; **S. Yalavarthi**, None; **L. F. Mazza**, None; **M. A. Elfline**, None; **C. E. Luke**, None; **P. K. Henke**, None; **J. S. Knight**, None.

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Abstract Number: 2003

Primary Antiphospholipid Syndrome Is Characterized By Endothelial Progenitor Dysfunction and a Type I Interferon Signature

Robert C. Grenn[1], Srilakshmi Yalavarthi[2], Paula L. Bockenstedt[3] and Jason S. Knight[2], [1]University of Michigan, Ann Arbor, MI, [2]Division of Rheumatology, University of Michigan, Ann Arbor, MI, [3]Department of Internal Medicine, Division of Hematology/Oncology, University of Michigan, Ann Arbor, MI

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SESSION INFORMATION

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Session Title: Antiphospholipid Syndrome: Recent findings

Session Type: ACR Concurrent Abstract Session

Session Time: 2:30PM-4:00PM

Background/Purpose: Patients with primary antiphospholipid syndrome (APS) are at risk for endothelial dysfunction and accelerated atherosclerosis. In systemic lupus erythematosus (SLE), there is a well-established defect in the function of circulating endothelial progenitors, which leads to an accrual of endothelial damage over time. This defect has been at least partially attributed to elevated levels of type I interferons (IFNs). Whether these pathways are important in primary APS is unknown.

Methods: Peripheral blood mononuclear cells (PBMCs) were isolated from patients with primary APS (n=20-30, depending on the specific experiment) or healthy volunteers. The function of circulating endothelial progenitors was measured by culturing PBMCs under pro-angiogenic conditions and then quantifying their differentiation into mature endothelial cells (ECs). APS EC differentiation was tested with freshly-isolated PBMCs from primary APS patients, as well as with control PBMCs cultured in the presence of APS sera. Using quantitative PCR, the expression of three type I IFN-responsive genes was assessed in PBMCs: *PRKR*, *IFIT1*, and *IF144*. Expression levels were compared to age- and gender-matched healthy volunteers, and also to patients with SLE (n=15). The direct role of antiphospholipid antibodies in promoting endothelial progenitor dysfunction was characterized by injecting purified IgG fractions from APS patients and controls into mice.

Results: Primary APS was associated with a defect in endothelial progenitor function. When cultured under pro-angiogenic conditions, APS PBMCs produced fewer mature ECs than controls. Similarly, treatment of control PBMCs with APS sera impaired differentiation into ECs (as compared to heterologous control sera), implicating circulating factors in the defect. Interestingly, injection of purified IgG from "triple-positive" APS patients into mice impaired the function of murine endothelial progenitors, arguing that the antiphospholipid antibodies themselves can set the phenotype in motion. PBMCs from patients with primary APS have upregulated expression of the type I IFN-responsive genes *PRKR*, *IFIT1*, and *IF144*, as compared to healthy controls. The IFN signature of primary APS was similar to that seen in SLE patients, and was most robust in the anti-β_2GPI IgG-positive subpopulation of APS patients.

Conclusion: We describe, for the first time to our knowledge, a type I IFN signature in the PBMC fraction of patients with primary APS. Paralleling this finding, circulating endothelial progenitors appear to be dysfunctional in primary APS. Whether the endothelial progenitor defect is attributable to elevated type I IFN synthesis, or possibly direct toxicity from antiphospholipid antibodies, is currently under investigation. This work has the potential to suggest

novel approaches to preventing vascular damage in APS patients, such as anti-IFN drugs.

Disclosure: R. C. Grenn, None; **S. Yalavarthi**, None; **P. L. Bockenstedt**, None; **J. S. Knight**, None.

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Abstract Number: 2004

Procoagulant Property of a Novel Patient-Derived Autoimmune IgG Type Monoclonal Anticardiolipin Antibody That Binds to Beta 2 Glycoprotein Domain I but Not to Total Beta 2 Glycoprotein I Molecule

Kenji Oku[1], Yusaku Kanetsuka[1], Olga Amengual[1], Hiroyuki Nakamura[1], Kazumasa Oomura[1], Toshiyuki Bohgaki[2], Tetsuya Horita[1], Shinsuke Yasuda[1], Bas deLaat[3] and Tatsuya Atsumi[1], [1]Division of Rheumatology, Endocrinology and Nephrology, Hokkaido University Graduate School of Medicine, Sapporo, Japan, [2]Medicine II, Hokkaido University Graduate School of Medicine, Sapporo, Japan, [3]Department of Biochemistry, Cardiovascular research Institute Maastricht, Maastricht University, Maastricht, Netherlands
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Background/Purpose: Anti-cardiolipin/β_2 glycoprotein I (aCL/β_2GPI) antibodies are representative antiphospholipid antibodies(aPLs) that target the complex of cardiolipin (or anionic molecules) and β_2GPI. However, aCL is often regarded as an autoantibody with relatively lower specificity and the significance of its detection may considered to have secondary role to detection of aβ_2GPI. Recently, the antibodies to β_2GPI domain I (aβ_2GPI DI) are reported as more specific to the manifestations of antiphospholipid syndrome (APS). In this study, the immunological and functional diversity of aCL/β_2GPI was examined in newly established monoclonal autoimmune aCL derived from a patient with APS.

Methods: B cells from 40 APS patients were immortalized with EBV infection to clone aCL antibody-producing cells using limiting dilution and sorting techniques. A stable cell line containing an IgG-type monoclonal antibody (EV35102) was established by introducing genes in the IgG variable region into CHO-K1 cells. The presence of a homologous antigen of EV35102 was examined by ELISA. The anticoagulation function of EV35102 was evaluated in monocytes from healthy persons using quantification of induced tissue factor (TF) mRNA by real-time PCR after treatment of the cells with EV35102. The activation of intra-cellular signal protein was analyzed with the antibody array kit (Pathscan^{TM} : Cell Signaling Technology, USA). Regarding the result of ELISA tests for the monoclonal antibodies, the cohort of 182 APS patients (with and without systemic lupus erythematosus(SLE) and 141 patients with connective tissue diseases were analyzed of their aPL profiles. Five clotting assays for testing lupus anticoagulant and 7 enzyme-linked immunosorbent assays(IgG/IgM aCL, IgG/IgM aβ_2GPI and aβ_2GPI D1) were performed.

Results: EV35102 bound to cardiolipin only in the presence of β_2GPI, thus behaving as a typical β_2GPI-dependent aCL. However, EV35102 did not recognize total β_2GPI molecule in any conditions (negative for aβ_2GPI). Surprisingly EV35102 bound to domain I of β_2GPI (positive for aDI). EV35102 significantly induced monocyte TF mRNA expression compared with the IgG control (9.23+/-2.79 vs. 2.18+/-0.32, $p<0.05$). The p38 Mitogen-activated protein kinase(MAPK) significantly and specifically phosphorylated in the monocytes stimulated with EV35102 compared with the IgG control (OD value : 2.92+/-0.31 vs 1.23 +/-0.51 , $p<0.05$). Anti CL antibody positive with negative aβ_2GPI IgG was found in 5/141 in non-APS control and 20/182 in APS. Among 20 APS patients with aCL IgG positive and aβ_2GPI negative, 4/20 were aβ_2GPI DI positive. None of the non-APS with aCL positive, ab2GPI negative showed ab2GPI D1 positive.

Conclusion: EV35102 represented a new subset of aCL/β_2GPI in patients with APS; its epitope would locate on domain I of β_2GPI, but the antibodies are undetectable by anti-(total) β_2GPI assay. EV35102 had procoagulant property thus this subset of aCL/β_2GPI is possible to be pathogenic. The diversity in aCL/β_2GPI should be recognised and aCL assay is still useful for screening this subset.

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Abstract Number: 2005

Circulating Mirnas As Potential Disease Biomarkers in Antiphospholipid Syndrome Patients

Carlos Perez-Sanchez[1], Mihaela Diana Ivanoiu[1], Maria Ángeles Aguirre Zamorano[1], Patricia Ruiz-Limon[1], Nuria Barbarroja[1], Yolanda Jiménez Gómez[1],

Maria Carmen Abalos-Aguilera[1], Rocio Gonzalez-Conejero[2], Constantino Martinez[2], Eduardo Collantes-Estevez[1], Mª Jose Cuadrado[3] and Chary Lopez-Pedrera[1], [1]IMIBIC-Reina Sofia University Hospital, Rheumatology Unit, Cordoba, Spain, [2]Regional Centre for Blood Donation, University of Murcia, Murcia, Spain, [3]Lupus Research Unit, The Rayne Institute, St Thomas' Hospital, London, United Kingdom
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Background/Purpose: Epigenetic anomalies are emerging as striking pathogenic features of autoimmune disorders. MicroRNAs (miRNAs) are small non-coding RNAs with a key role in regulatory networks that might represent a novel class of disease biomarkers. Yet, the contribution of circulating miRNAs to the pathogenesis of antiphospholipid syndrome (APS) and their potential role as biomarkers of this disease are still unknown. Purpose: To determine the circulating miRNA signature of APS and to identify potential circulating microRNAs that might represent non-invasive biomarkers of the disease.

Methods: Total RNAs were isolated from plasma of 10 APS patients and 10 healthy controls, cDNA transcribed and pooled, and human plasma miRNA polymerase chain reaction (PCR) arrays were performed. Then, selected miRNAs were analyzed in a validation cohort consisting of 72 APS patients and 38 healthy donors. To evaluate their patho-physiological relevance, a functional analysis was conducted by using the Ingenuity Pathway Analysis (IPA) software. Association and correlation studies with clinical and serological variables were also performed.

Results: miRNA-PCR-Array showed that 22 circulating microRNAs were differentially expressed in APS patients in relation to the control group (fold change≥2). IPA analysis indicated that a high number of these microRNAs had targets mainly involved in processes related to cardiovascular disease (40%, including arteriosclerosis, hypertension, and coronary artery disease) inflammatory response (50%), and reproductive system disease (45%, i.e endometriosis and preeclampsia). Validation analysis by RT-PCR showed that the levels of three microRNAs (miR-19b, miR-20a and miR-296) were significantly increased in plasma of APS patients. These miRNAs have been further demonstrated to be specifically involved in preeclampsia (miR-296), inflammation and thrombosis (miR-19b and -20a) in other autoimmune and inflammatory disorders. Receiver operating characteristics (ROC) curve analysis showed that the ratio of combination for the three miRNAs could discriminate APS patients from healthy donors with a 70% of sensitivity and specificity and an area under curve (AUC) close to 1 (0,72), thus pointing at these microRNAs as potential diagnostic biomarkers of APS. Analysis of interrelation with clinical variables showed that the expression levels of miR-296 were associated with the occurrence of recurrent thrombosis, while the expression levels of miR-20a were most specifically linked to episodes of arterial thrombosis, and further correlated with the erythrocyte sedimentation rate.

Conclusion: We have identified a set of serum miRNAs as potential APS biomarkers, primarily involved in key clinical features of this autoimmune condition.

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View Abstract and Citation Information Online - http://acrabstracts.org/abstract/circulating-mirnas-as-potential-disease-biomarkers-in-antiphospholipid-syndrome-patients

Abstract Number: 2006

Effect Size of the Anti-Aggrecanase-2 Monoclonal Antibody CRB0017 in Rodent Models of Osteoarthritis

Gianfranco Caselli[1], Riccardo Chiusaroli[2], Michela Visintin[3], Marco Lanza[2], Flora Ferrari[2], Dario Tremolada[2], Beatrice Barbetta[2], Giampaolo Giacovelli[2], Albino Bonazzi[2] and Lucio Claudio Rovati[2], [1]Pharmacology & Toxicology, Rottapharm Biotech Srl, Monza, Italy, [2]Rottapharm Biotech Srl, Monza, Italy, [3]Rottapharm Biotech Srl, Trieste, Italy
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Background/Purpose : There is huge interest in the family of “A Disintegrin And Metalloproteinase with ThromboSpondin motifs” (ADAMTS) proteinases, especially aggrecanase-2 (ADAMTS-5), as therapeutic targets in osteoarthritis (OA). CRB0017 is a chimeric murine/human IgG4 monoclonal antibody that specifically recognizes the spacer domain of human ADAMTS-5 and binds it with nanomolar affinity. CRB0017 is under preclinical development as a potential disease modifying osteoarthritis drug (DMOAD).

We previously published a brief report (Chiusaroli, *Osteoarthritis Cartilage*, 2013) showing the efficacy of intra-articular (i.a.) CRB0017 in a model of

spontaneous OA, the STR/ort mouse. In this study we replicated the experiment in the STR/ort mouse and evaluated the activity of CRB0017 in two surgical models of OA in rodents: the Destabilization of Medial Meniscus (DMM) in mice; and the Medial Meniscal Tear (MMT) in rats. Moreover, all data collected were combined in a meta-analysis to estimate the overall effect size of CRB0017 in rodent models of OA.

Methods : Because it is hard to standardize different batches during early phases of a monoclonal antibody development, all experiments were done at the maximum feasible dose (MFD), as determined by the concentration achieved in each batch and by the maximum feasible volume for i.a. injection in rats and mice.

Male STR/ort mice were recruited at 5 months of age, randomized, and treated i.a. in each knee with CRB0017 or vehicle (4µl/knee). Four different experiments were conducted in the STR/ort mouse (MFDs: Exp1 12 µg/knee, n=34 evaluable joints; Exp2 11.2 µg/knee, n=28-29; Exp3 72 µg/knee n=33-38; Exp4 20 µg/knee, n=21-18). Treatment was repeated after 6 weeks (in Exp 4, 3 monthly administrations), and mice were killed 3 months after recruitment.

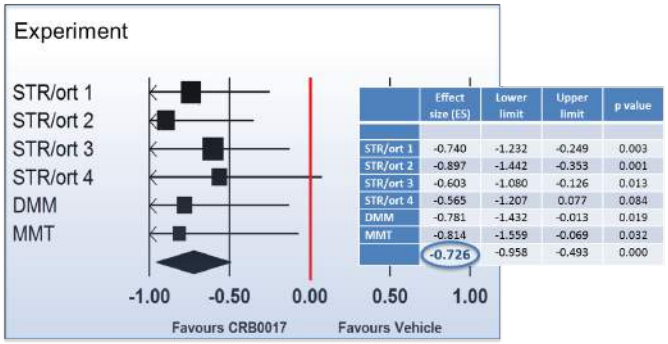
DMM was performed in C57BL/6J mice (10 weeks old at surgery; CRB0017 i.a. injection [MFD 72 µg in 4 µL] 1 week after surgery; injection repeated after 1 and 2 months; sacrifice at 3 months, n=19-20).

MMT was performed in Lewis rats (9 weeks old at surgery; CRB0017 i.a. injection [MFD 71 µg/knee in 15 µL] 1 week after surgery; sacrifice 3 weeks after treatment, n=15).

At sacrifice, the femorotibial joints were explanted and processed for histology. Scoring procedure was carried out in a blind fashion according to both Mankin's (not shown) and OARSI methods. For quantitative outcome data, Cohen's *d* effect size was used in the meta-analysis of OA models.

Results : CRB0017 markedly reduced the histological damage in spontaneous and surgical models of OA in mice and rats, which is consistent with a disease modifying activity. Pooled data (OARSI score) showed a highly significant overall effect size of 0.726 (Cohen's *d*; see figure).

Figure – Effect size on OARSI score, Cohen's *d*



	Effect size (ES)	Lower limit	Upper limit	p value
STR/ort 1	-0.740	-1.232	-0.249	0.003
STR/ort 2	-0.897	-1.442	-0.353	0.001
STR/ort 3	-0.603	-1.080	-0.126	0.013
STR/ort 4	-0.565	-1.207	0.077	0.084
DMM	-0.781	-1.432	-0.013	0.019
MMT	-0.814	-1.559	-0.069	0.032
	-0.726	-0.958	-0.493	0.000

Effect size (ES) is the best, single indicator of the quantitative efficacy of an intervention vs. the comparator (e.g. placebo/vehicle)

- ES = [(mean change active) – (mean change placebo)]/pooled standard deviation
- ES (absolute value)<0.20 = not clinically relevant; ES>0.20 = small (common clinical outcome for therapeutic interventions in OA); ES>0.50 = moderate; ES>0.80 = large

Conclusion : Aggregate data from clinically relevant models of spontaneous or surgical OA in rodents clearly show the potential of CRB0017 as a DMOAD. The product is slated to enter Phase I in early 2016.

Disclosure: G. Caselli, Rottapharm Biotech Srl, 3; **R. Chiusaroli**, Rottapharm Biotech Srl, 3; **M. Visintin**, Rottapharm Biotech Srl, 3; **M. Lanza**, Rottapharm Biotech Srl, 3; **F. Ferrari**, Rottapharm Biotech Srl, 3; **D. Tremolada**, Rottapharm Biotech Srl, 3; **B. Barbetta**, Rottapharm Biotech Srl, 3; **G. Giacovelli**, Rottapharm Biotech Srl, 3; **A. Bonazzi**, Rottapharm Biotech Srl, 3; **L. C. Rovati**, Rottapharm Biotech Srl, 3.

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Abstract Number: 2007

Discovery of an Intra-Articular Injection Small Molecule Inhibitor of the Wnt Pathway (SM04690) As a Potential Disease Modifying Treatment for Knee Osteoarthritis

Charlene Barroga, Yong Hu, Vishal Deshmukh and John Hood, Samumed, San Diego, CA

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Session Date: Monday, November 9, 2015

Session Title: Biology and Pathology of Bone and Joint: Ostearthritis Pathogenesis

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Session Time: 2:30PM-4:00PM

Background/Purpose:

Wnt has a key role in the formation of bone, cartilage and synovium. Increased Wnt signaling may contribute to initiation and progression of osteoarthritis (OA) by inducing cartilage degradation and reducing its thickness.[1] Polymorphisms in Wnt signaling genes are associated with increased susceptibility to OA.[2] SM04690, a novel, small molecule inhibitor of the Wnt pathway was evaluated in preclinical studies to determine its potential to treat OA.

Methods:

SM04690's capacity to inhibit the Wnt pathway was determined via a cellular screen using a luciferase reporter driven by a Wnt-responsive promoter. SM04690's ability to induce chondrogenesis was established using differentiation of primary human mesenchymal stem cells (hMSC) to chondrocytes, as determined by Safranin-O staining and upregulation of chondrogenic genes. Pharmacokinetics were evaluated by intra-articular (IA) injection in Sprague Dawley rats and Beagle dogs, followed by evaluation of compound concentration in joints and plasma. *In vivo* activity was evaluated in the anterior cruciate ligament transection (ACLT) combined with medial meniscal tear model in rats, in which SM04690 or vehicle control was injected into the IA space of the damaged knee (N=8-12/group), followed by histological evaluation using blinded Osteoarthritis Research Society International (OARSI) scoring [0-24].[3]

Results:

In vitro, SM04690 inhibited Wnt pathway activation with EC_{50}≈3 nM. Consistent with Wnt's role in chondrogenesis, SM04690 induced hMSCs to differentiate to chondrocytes with EC_{50}≈30 nM as measured by staining and expression of chondrogenic markers: SOX9, collagen2A, aggrecan and TIMP1. *In vivo*, a single IA injection of SM04690 into knees of Sprague Dawley rats or Beagle dogs resulted in a joint concentration above target EC_{50} with a residence time of 60-90 days. No compound was detectable in plasma immediately after IA injection or 30–180 days post-injection. In ACLT model, one injection of SM04690 2 weeks post-injury improved cartilage health in a dose-dependent manner relative to vehicle, with no observable toxicity. Histology in ACLT model shows marked cartilage degradation in vehicle (**Figure 1B**), while SM04690 showed cartilage thickness similar (**1C**) to normal (**1A**) non-ACLT knee. At optimal IA dose of 0.3 ug/knee in rats, OARSI scores decreased significantly from 4.7 to 2.5, P=0.006 (**Figure 2**).

Conclusion:

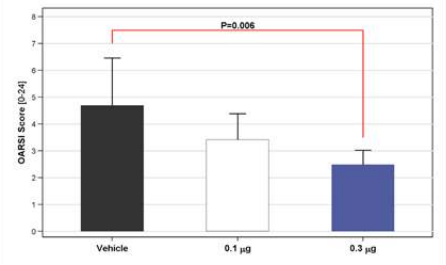
SM04690 was shown to inhibit the Wnt pathway, induce chondrogenesis and improve cartilage health in rat models of OA after a single IA injection. SM04690 was maintained in joint space for up to 90 days with no detectable SM04690 in plasma, consistent with a low potential for systemic toxicity. These data suggest that locally injected SM04690 may have potential as a disease modifying therapy for OA.

References:

1. Gelse *Osteoarthr Cartil* 2012; 20(2):162-71
2. Wu *Curr Pharm Des* 2012; 18:3293
3. Bendele *J Musculoskeletal Neuronal Interact* 2001; 1:363

Figure 1. Exemplary histologic images of A) Normal Rat Knee, B) Vehicle ACLT Knee and C) SM04690-treated ACLT Knee with cartilage staining

Figure 2. Average OARSI Score upon Histology by SM04690 Treatment Groups



Disclosure: C. Barroga, Samumed, 3; **Y. Hu**, Samumed, 3; **V. Deshmukh**, Samumed, 3; **J. Hood**, Samumed, 3.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/discovery-of-an-intra-articular-injection-small-molecule-inhibitor-of-the-wnt-pathway-sm04690-as-a-potential-disease-modifying-treatment-for-knee-osteoarthritis

Abstract Number: 2008

WISP1 Aggravates Osteoarthritis By Modulation of TGF-β Signaling and Positive Regulation of Canonical Wnt Signaling

Martijn H. van den Bosch[1], Arjen Blom[1], Azusa Maeda[2], Tina Kilts[2], Wim van den Berg[1], Floris Lafeber[3], Peter van Lent[1], Marian Young[2] and Peter van der Kraan[1], [1]Experimental Rheumatology, Radboud university medical center, Nijmegen, Netherlands, [2]NIDCR/NIH, Bethesda, MD, [3]Rheumatology and

Clinical Immunology, University Medical Center Utrecht, Utrecht, Netherlands
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Background/Purpose: Many osteoarthritis (OA) patients show synovial activation, which is suggested to be involved in joint destruction. Previously, we found synovial overexpression of Wnt ligands in experimental OA models. In addition, we found increased expression of WISP1, a downstream protein of canonical Wnt signaling, in both synovium and cartilage. In this study we investigated the role of WISP1 in experimental OA models in WISP1 KO mice and determined if WISP1 was involved in progression of early human OA.

Methods: Pathway analysis of microarray data from the synovium of a collagenase-induced OA (CIOA) and destabilization of the medial meniscus (DMM) model was performed using DAVID bioinformatics software. Microarray analysis was performed on synovial tissue of patients with early complaints of knee or hip pain, enrolled in the CHECK study. Expression data was correlated with progression between baseline and the five-year follow-up measurement. Progression was defined as decreased joint space width of at least 1 mm and progression of osteophyte formation of at least 4x in size. CIOA, DMM and anterior cruciate ligament transection (ACLT) experimental OA models were induced in WT and WISP1 knockout mice. Joint pathology was assessed by histology. Human OA synovium was obtained after joint replacement surgery and stimulated with WISP1. Smad phosphorylation and β-catenin accumulation were determined using immunohistochemistry.

Results: Pathway analysis showed enrichment of Wnt signaling in both the CIOA and DMM at various time points. In addition, microarray analysis of synovial tissue from patients in the CHECK study showed that WISP1 expression was correlated with the progression of OA between baseline and the five-year follow-up measurement. To further pinpoint the role of WISP1 in the etiopathology of OA, we induced experimental OA in WT and WISP1 KO mice. We found significantly decreased cartilage damage in the knee joints of WISP1 KO mice in three models of experimental OA. Synovium of WISP1 KO mice showed reduced expression of MMPs, which is in line with our finding that stimulation of human OA synovium with WISP1 increased the MMP expression. TGF-β signaling via Smad 2/3 is crucial for maintaining cartilage homeostasis, while signaling via Smad 1/5/8 is associated with chondrocyte hypertrophy. To determine if WISP1 affects TGF-β signaling, we stained WT and WISP1 depleted joints for phosphorylated Smad 2/3 and found increased pSmad 2/3 in the WISP1 KO mice. In addition, recent data showed that WISP1 could regulate the accumulation of β-catenin, and positively control canonical Wnt signaling, further aggravating the OA pathology. Staining for β-catenin indeed showed that WISP1 depleted joints have decreased levels of β-catenin accumulation in the cartilage.

Conclusion: Overexpression of WISP1 in the joint may play an important role in OA pathology via modulation of TGF-β signaling and positive feedback on canonical Wnt signaling. Targeting upstream Wnt signaling likely causes undesired side effects, as the pathway is extremely complex and involved in many processes. Specific downregulation of WISP1 may more specifically target pathological events that take place during OA without interfering with normal processes.

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View Abstract and Citation Information Online - http://acrabstracts.org/abstract/wisp1-aggravates-osteoarthritis-by-modulation-of-tgf-signaling-and-positive-regulation-of-canonical-wnt-signaling

Abstract Number: 2009

CC-Chemokine Receptor 7 (CCR7) Deficiency Reduces Early Structural and Functional Features of Disease in a Murine Model of Osteoarthritis

Nisha Sambamurthy[1,2], Vu Nguyen[1,2], Patrick Diviney[3], Justin Gan[4], Charles Bush-Joseph[5], Susanna Chubinskaya[6], Anne-Marie Malfait[7], George Dodge[2,3] and Carla R. Scanzello[8,9], [1]Medicine / Rheumatology, University of Pennsylvania, Philadelphia, PA, [2]Research, Philadelphia VA Medical Center, Philadelphia, PA, [3]Orthopedics, University of Pennsylvania, Philadelphia, PA, [4]Rheumatology, Rush University Medical Center, Chicago, IL, [5]Orthopedics, Rush University Medical Center, Chicago, IL, [6]Biochemistry, Rush University Medical Center, Chicago, IL, [7]Rush University Medeical Center, Chicago, IL, [8]Rheumatology, University of Pennsylvania, Philadelphia, PA, [9]Rheumatology, University of Pennsylvania Perelman School of Medicine & Philadelphia VA Medical Center, Philadelphia, PA
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Background/Purpose: Synovial expression of CCR7 has been associated with inflammation and severity of symptoms in patients with meniscal tears and early osteoarthritis (OA). This receptor plays a role in trafficking of leukocytes and aids in the development of chronic inflammation. The current aim was to determine if CCR7 plays a mechanistic role in development of OA-related structural and functional manifestations after destabilization of the medial

meniscus (DMM) in a murine model of knee OA.

Methods: To confirm expression of CCR7 in humans, knee synovial tissues from 15 patients with meniscal tears, and 9 asymptomatic organ donors were collected through IRB-approved biorepositories. Immunoperoxidase staining for CCR7 was evaluated by automated image analysis. To investigate effects of CCR7 deficiency *in vivo*, genetically modified mice lacking expression of CCR7 ($CCR7^{-/-}$) and C57BL/6 congenic controls were obtained from Jackson Laboratory. Male mice were subjected to DMM surgery at 10-12 weeks of age. Six weeks after surgery, groups of 5 mice were sacrificed and knee joints evaluated by histopathology for cartilage degeneration and osteophyte size using standard methods. Synovial lining hyperplasia was scored on a scale of 0-3 with 0 = one cell layer thick, 1= 2-3 cell layers, 2 = 4-5 cell layers, and 3 = >6 cell layers thick. Changes in spontaneous climbing activity were measured longitudinally (up to 16 weeks) after DMM surgery in the two strains, using the LABORAS®laboratory animal behavior analysis system (Metris B.V., Hoofdorp, The Netherlands).

Results: Synovial CCR7 staining was significantly higher in patients with meniscal tears (Mean % area +/- SEM = 12.26 +/- 2.4) compared to asymptomatic donors (3.55 +/- 2.7, p=0.01). Six-weeks after DMM surgery, $CCR7^{-/-}$ mice exhibited reduced cartilage degeneration (Mean +/- SEM = 1.60+/-0.81) and osteophyte size (0.80+/-0.20) compared to their C57BL/6 controls (cartilage = 5.20+/-1.06, osteophyte = 1.40+/-0.24, p<0.0001). Slight increases in synovial hyperplasia in response to DMM surgery occurred in both strains of mice (p=ns). C57BL/6 mice decreased their climbing activity post-operatively starting at 4 weeks, and decreases were maximal at 8 weeks post-DMM surgery (46.87% lower than pre-DMM, p=0.012). In contrast, at 4 weeks post-DMM $CCR7^{-/-}$ mice maintained pre-operative climbing activity and climbing was significantly increased by 8 weeks post-DMM (25.64% higher than pre-DMM, p = 0.001). At 8 weeks, time spent climbing was lower in C57BL/6 DMM mice compared to sham (p=0.0145) and naïve (p =0.00205) controls, while $CCR7^{-/-}$ mice showed no significant differences between DMM-operated, sham and naïve control groups

Conclusion: In the DMM model of OA, $CCR7^{-/-}$ mice showed reduced cartilage degeneration and osteophyte size at 6 weeks post-surgery and improved function (measured by climbing activity) by 8 weeks post-surgery in contrast to their C57BL/6 counterparts. Based on these results, CCR7 may be a potential target for therapy with both structure- and symptom- modifying effects in OA. Future studies will investigate the use of targeted treatments aimed at the blockade of CCR7 and its ligands in this model.

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View Abstract and Citation Information Online - http://acrabstracts.org/abstract/cc-chemokine-receptor-7-ccr7-deficiency-reduces-early-structural-and-functional-features-of-disease-in-a-murine-model-of-osteoarthritis

Abstract Number: 2010

Adenosine A2A Receptor, but Not A2B Receptor, Deletion Leads to Development of Osteoarthritis (OA) in Mice and Administration of a Liposomal Suspension of Adenosine Prevents/Treats Osteoarthritis in Rats

CARMEN CORCIULO[1], MATIN Lendhey[2], AUSTIN RAMME[2], Tuere Wilder[3], ORAN KENNEDY[2] and Bruce Cronstein[4], [1]Medicine, NYU-School of Medicine, New York, NY, [2]Department of Orthopaedic Surgery, NYU-School of Medicine, New York, NY, [3]Dept of Med, Div of Rheum, NYU School of Medicine, New York, NY, [4]Medicine, Division of Rheumatology, NYU School of Medicine, NEW YORK, NY
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Background/Purpose: Adenosine, acting at its receptors, regulates chondrocyte function and inflammation, two components of OA. Mice lacking adenosine A2A receptors (A2AR) have increasing difficulty walking as they age. We report here that A2ARKO mice have changes consistent with OA in their knees and treatment with a liposomal adenosine (lipado) suspension abrogates development of OA in a rat anterior cruciate ligament (ACL) injury model of OA.

Methods: Knee joints of WT and A2ARKO mice (n=5/group) were studied by micro-computed (μCT) analysis and immunohistochemistry. Locomotor activity in mice was measured with open-field and rotarod tests. Primary articular chondrocytes from neonatal WT or A2ARKO mice were studied for altered expression of OA markers. OA was induced in rats by mechanical rupture of ACL. Rats (n=3/group) were treated with intra-articular injection of 100μl of saline, a liposomal formulation containing adenosine (10 mg/Kg) or empty liposomes (lipo) and weight and knee swelling of the rats were monitored. Rat legs were harvested after 56 days to evaluate the joints and plasma cytokine levels were quantitated in rats, WT and A2ARKO mice.

Results: A2ARKO mice did not move as far as WT mice (A2ARKO=664±123 cm vs WT=1404±128 cm, p<0.001); nor did they move as fast (A2ARKO=1.11±0.21 cm/sec vs WT=2.34±0.21 cm/sec, p<0.001) and fell more quickly from the rotarod apparatus (A2ARKO=86±11sec vs WT=145±22 sec, p<0.05). A2ARKO mice had progressive joint damage consistent with OA (e.g. OARSI score at 16 weeks for A2ARKO=3.7±0.6 *vs* WT=1.5±0.2, p<0.01). In contrast, knee joints of 19wk old A2BRKO mice did not differ from WT. Chondrocytes isolated from neonatal A2ARKO mice, but not WT, spontaneously expressed and secreted collagen X, fibronectin, osteopontin and MMP-13. Rats treated with intra-articular lipado were significantly less swollen (difference between uninjured and injured knee was 2.32±0.07mm for saline group, 2.35±0.36mm for lipo-treated and 0.93±0.12mm for lipado-treated, p<0.01, 1-way ANOVA). Macroscopic evaluation of joints showed near-normal appearing cartilage in lipado-treated rats but pitting and loss of cartilage in saline or lipo-treated rats. There was a marked reduction of subchondral bone changes in μCTs of lipado-treated mice as well and plasma

levels of IL-1b, IL-6, IFNg, IL-5, TNFa and RANTES were significantly lower in rats treated with lipado.

Conclusion: These findings suggest that the presence and tonic activation of A2AR in the joint are important for maintaining joint homeostasis. Moreover these results suggest that adenosine receptors may be a novel target for treatment of OA.

Disclosure: C. CORCIULO, None; **M. Lendhey**, None; **A. RAMME**, None; **T. Wilder**, None; **O. KENNEDY**, None; **B. Cronstein**, Bristol-Myers Squibb, 5,Novartis Pharmaceutical Corporation, 5,Canfite Pharma, 5,Revive Therapeutics, 5,Regeneron, 5,Gismo Therapeutics, 5,Antares Pharmaceuticals, 5,Canfite Pharma, 1,Gilead Pharmaceuticals, 2,AstraZeneca, 2,Takeda, 2,Celgene, 2.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/adenosine-a2a-receptor-but-not-a2b-receptor-deletion-leads-to-development-of-osteoarthritis-oa-in-mice-and-administration-of-a-liposomal-suspension-of-adenosine-preventstreats-osteoarthritis-in-r

Abstract Number: 2011

Disruption of the Molecular Clock in Mesenchymal Cells Causes an Osteoarthritis-like Disease in Mice

Joerg Ermann and Antonios Aliprantis, Rheumatology, Immunology and Allergy, Brigham and Women's Hospital, Harvard Medical School, Boston, MA
First publication: September 29, 2015

SESSION INFORMATION
Session Date: Monday, November 9, 2015
Session Title: Biology and Pathology of Bone and Joint: Osteoarthritis Pathogenesis
Session Type: ACR Concurrent Abstract Session
Session Time: 2:30PM-4:00PM

Background/Purpose: Tissue-intrinsic circadian molecular clocks control many physiological processes. The function of these clocks in cells of the musculoskeletal system and their contribution to disease is poorly understood however. Here, we investigated the peripheral joint phenotype in mice genetically deficient for the core circadian molecular clock regulator Brain and muscle Arntl-like 1 (*Bmal1*).

Methods: We generated mice with conditional deletion of *Bmal1* in mesenchymal cells of the limbs by crossing *Bmal1*$^{fl/fl}$ and *Prx1-cre* mice. Forepaws and hindfeet of *Bmal1*$^{fl/fl}$ and *Bmal1*$^{fl/fl}$*.Prx1-cre* mice were analyzed by histology and micro-computed tomography at 4, 8, and 12 weeks of age. Germline *Bmal*$^{-/-}$ mice were analyzed in parallel. Gene expression in the Achilles tendon was analyzed by real-time qPCR.

Results: As previously described in *Bmal1*$^{-/-}$ germline knockout mice, *Bmal1*$^{fl/fl}$*.Prx1-cre* mice develop spontaneous Achilles tendon ossification. In addition, both *Bmal1*$^{-/-}$ and *Bmal1*$^{fl/fl}$*.Prx1-cre* mice develop an osteoproliferative arthropathy in their forepaws, most prominently affecting the metacarpophalangeal and proximal interphalangeal joints, with radiographic similarity to the osteophytes seen in human hand osteoarthritis. Both the Achilles tendon and forepaw phenotypes are 100% penetrant by 8 weeks of age. Gene expression analysis of mRNA isolated from the Achilles tendon of *Bmal1*$^{fl/fl}$*.Prx1-cre* mice demonstrated (1) a marked reduction in *Bmal1* expression and (2) loss of the cyclic expression pattern of core clock genes (*Clock*, *Nr1d1*), indicating deregulation of the circadian molecular clock. Longitudinal gene expression analysis revealed up-regulation of genes involved in bone formation (*Alpl*, *Ocn*, *Osx*) in the Achilles tendon. Furthermore, we found induction of canonical target genes of Hedgehog signaling (*Ptch1*, *Gli1*) but not of Bone morphogenetic protein (BPM) or Wnt signaling pathways.

Conclusion: Mice with either global or mesenchymal cell-specific deletion of *Bmal1* develop Achilles tendon ossification and a forepaw arthropathy with marked radiographic similarity to hand osteoarthritis. Disruption of circadian rhythms in peripheral tissues, such as tendons and joints, may contribute to degenerative conditions of the musculoskeletal system.

Disclosure: J. Ermann, None; **A. Aliprantis**, Nutech Medical, 5.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/disruption-of-the-molecular-clock-in-mesenchymal-cells-causes-an-osteoarthritis-like-disease-in-mice

Abstract Number: 2012

TNF Confers Pathogenic Memory in Synovial Fibroblasts Via Chromatin Remodeling, NF-Kb-Dependent Transcription and MAPK-Mediated mRNA Stabilization

Konstantinos Loupasakis[1], Christopher Sohn[2], Lionel B. Ivashkiv[3] and George D. Kalliolias[2], [1]Rheumatology, Hospital for Special Surgery Weill Cornell Medical College, New York, NY, [2]Hospital for Special Surgery, New York, NY, [3]Arthritis and Tissue Degeneration Program and the David Z. Rosensweig Genomics Research Center, Hospital for Special Surgery, New York, NY
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SESSION INFORMATION

Session Date: Monday, November 9, 2015
Session Title: Cytokines, Mediators, Cell-cell Adhesion, Cell Trafficking and Angiogenesis II
Session Type: ACR Concurrent Abstract Session
Session Time: 2:30PM-4:00PM

Background/Purpose: We investigated mechanisms driving pathogenic behavior of synovial fibroblasts (FLS) in rheumatoid arthritis (RA).

Methods: FLS from RA patients (1987 classification criteria) were extracted. Expression of 249 inflammation-related genes was measured by nanoString technology. Active transcription was evaluated by primary transcripts. Chromatin accessibility was assessed by FAIRE assay. mRNA decay rates, after blocking transcription with actinomycin D (ActD), were calculated in a semi-log plot. The role of NF-kB and MAPKs was tested with inhibitors iIKK, SB202190, SP600125, U0126.

Results: Using strict criteria (expression level >100 at 72h of TNF-stimulation and >3-fold induction compared to control), a cluster of 34 genes displayed sustained induction (2 independent experiments) (Figure 1A). 18/34 genes retained high mRNA expression levels despite removal (washing) and blockade (infliximab) of TNFa (Figure 1B-C). In unwashed conditions, active transcription at TNF 72h was variably present depending on the gene. High levels of active transcription were maintained in genes such as IL6, IL8, CXCL1, CXCL2, CXCL3, CXCL6 and TNFAIP3, even after removal of TNF (Figure 1D and not shown). Continuous transcription was NF-kB dependent (Figure 1E). Sustained IL6 promoter chromatin remodeling was retained for days post-wash (Figure 1F and not shown). Highly expressed genes, such as CCL5 and MMP3, displayed minimal ongoing transcription (Figure 1D and not shown). Prolonged (4-8h) inhibition of transcription with ActD at TNF 72h (Figure 2A) significantly decreased TNFAIP3 mRNA (Figure 2B). Expression of other genes, such as IL6, IL8, CXCL1, CXCL3, CXCL6, CCL5 and MMP3, was minimally affected by ActD (Figure 2B and not shown), suggesting increased mRNA stability. Decay rates of mRNA for a group of TNF-inducible genes, such as IL6 and CXCL1, gradually decreased with time (Figure 2C), indicating TNF-inducible mRNA stabilization effect, which was MAPK-dependent (Figure 2D). Decay rates of mRNA of other genes were not dynamically regulated by TNF, and were either persistently stable (e.g CCL5) or unstable (e.g TNFAIP3) (Figure 2C).

Conclusion: We have identified a sustained inflammation-related gene expression program in TNF-stimulated RA FLS. Within this program there are different classes of genes based on the relative contribution of transcription and mRNA stability (Figure 2E). TNF drives MAPK-dependent stabilization of certain transcripts and persistent chromatin remodeling in genes such as IL6, indicating TNF-induced memory effect in FLS.

Figure 1

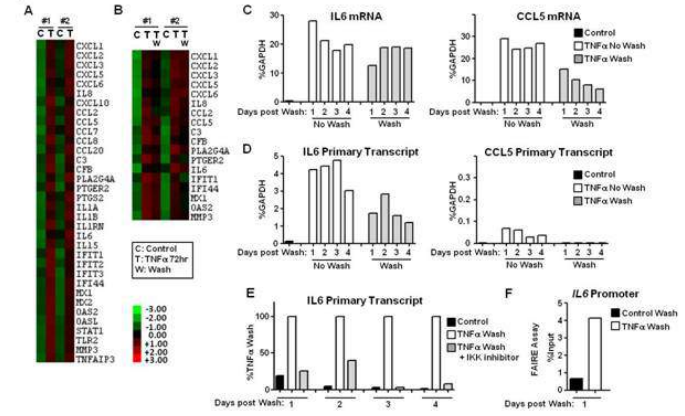
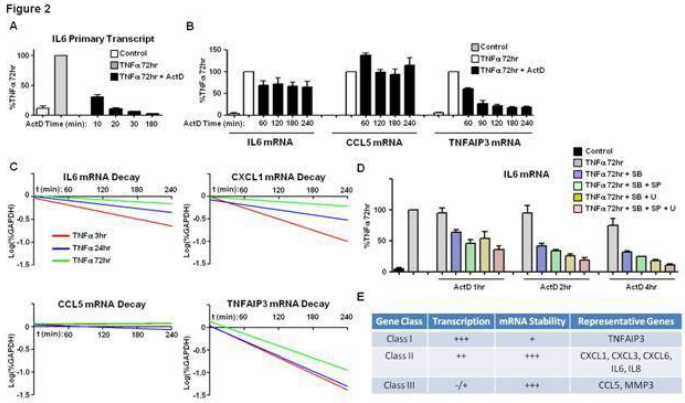


Figure 2



Disclosure: K. Loupasakis, None; **C. Sohn**, None; **L. B. Ivashkiv**, None; **G. D. Kalliolias**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/tnf-confers-pathogenic-memory-in-synovial-fibroblasts-via-chromatin-remodeling-nf-kb-dependent-transcription-and-mapk-mediated-mrna-stabilization

Abstract Number: 2013

TIARP Attenuates Autoantibody-Mediated Arthritis Via the Suppression of Neutrophil

Infiltration into the Joint

Asuka Inoue[1], Isao Matsumoto[1], Yuki Tanaka[2], Naoto Umeda[1], Hoshimi Kawaguchi[1], Hiroshi Ebe[1], Yoshihiro Matsumoto[3] and Takayuki Sumida[1], [1]Department of Internal Medicine, Faculty of Medicine, University of Tsukuba, Tsukuba, Japan, [2]Department of Internal Medicine, University of Tsukuba, Tsukuba, Japan, [3]Product Research Department, Chugai Pharmaceutical Co., Ltd., Gotemba, Japan
First publication: September 29, 2015

SESSION INFORMATION
Session Date: Monday, November 9, 2015
Session Title: Cytokines, Mediators, Cell-cell Adhesion, Cell Trafficking and Angiogenesis II
Session Type: ACR Concurrent Abstract Session
Session Time: 2:30PM-4:00PM

Background/Purpose:

TIARP (TNFα-induced adipose-related protein) is dominantly expressed in macrophages (Mφ), neutrophils (PMN) and fibroblast-like synoviocytes (FLS). Recently, we found that TIARP functions as a negative regulator in autoimmune arthritis through the suppression of IL-6 production, NF-κB, STAT3 signaling in Mφ, although the molecular mechanism of TIARP-expressing cells in arthritis remains uncertain. The purpose of this study is to elucidate the functional role of TIARP in the pathogenesis of arthritis, especially focusing on PMN and FLS.

Methods:

(1) K/BxN serum-transferred arthritis was induced to TIARP$^{-/-}$or WT, then the ankle thickness was monitored. Mice were also treated with intravenous administration of anti-Gr1 Ab (for the depletion of PMN) or control Ab every other day after the induction of arthritis. (2) RNAs were extracted from TIARP$^{-/-}$or WT PMN, subsequently compared by Gene chip. (3) The expression of CXCR1 and CXCR2 on PMN was analyzed, and the chemoattractant activity of TIARP$^{-/-}$ or WT PMN was tested by trans-well chemotaxis assays. (4) Using TIARP$^{-/-}$or WT FLS, the expression of IL-6, TNFα and CXCL2 after TNFα stimulation were compared. (5) To verify the effect of CXCL2, we performed the chemotaxis assay of PMN by applying to the lower chamber with anti-CXCL2 Ab. (6) The production of IL-17, TNFa and IL-6 from PMN stimulated by immune-complex (IC) were measured by ELISA. (7) Anti-IL-6R Ab was administrated every other day after the induction of serum transferred arthritis.

Results:

(1) The severity of arthritis in TIARP$^{-/-}$ mice was markedly exacerbated, and the recruitment of PMN into the joint was significantly enhanced. TIARP$^{-/-}$mice treated with anti-Gr1 Ab showed significantly reduced cellular infiltrate into the joint, and reduced synovial thickening. (2) Gene ontology analysis of up-regulated genes in TIARP$^{-/-}$PMN demonstrated the enrichment of genes involved in chemotaxis. (3) The expression of CXCR1/2 was significantly higher in TIARP$^{-/-}$ PMN, and the recruitment capacity was enhanced. (4) The expressions of IL-6 and CXCL2 in TIARP$^{-/-}$ FLS were significantly higher than in WT, whereas RANKL, MMP3 and MMP9 were not different. (5) The numbers of migrated PMN were significantly decreased by the addition of anti-CXCL2 Ab. (6) The production of IL-17, TNFa and IL-6 were comparable between WT and TIARP$^{-/-}$PMN. (7) Serum-transferred arthritis in TIARP$^{-/-}$ mice was attenuated by the blockade of IL-6R signaling, and recruitment of PMN into the joint of TIARP$^{-/-}$mice was suppressed.

Conclusion:

TIARP might down-regulate the production of CXCL2 from FLS and the expression of CXCR1/2 in PMN, resulting in the protective ability of neutrophil migration in arthritic joints, probably via the inhibition of IL-6 signaling.

Abstract Number: 2014

Deficiency of IL-27 Exacerbate Sjögren's Syndrome through Inhibiting Differentiation of Type 1 Regulatory T Cells

Genhong Yao[1], Bingyu Shi[1], Jingjing Qi[1], Ying Wang[1], Weiwei Chen[1], Xiaojun Tang[1], Dandan Wang[2], Xuebing Feng[1] and Lingyun Sun[1], [1]Department of Rheumatology and Immunology, The Affiliated Drum Tower Hospital of Nanjing University Medical School, Nanjing, China, [2]Department of Rheumatology and immunology, The Affiliated Drum Tower Hospital of Nanjing University Medical School, Nanjing, China

First publication: September 29, 2015

SESSION INFORMATION

Session Date: Monday, November 9, 2015

Session Title: Cytokines, Mediators, Cell-cell Adhesion, Cell Trafficking and Angiogenesis II

Session Type: ACR Concurrent Abstract Session

Session Time: 2:30PM-4:00PM

Background/Purpose: Sjögren's Syndrome (SS) is a systemic autoimmune disease characterized by chronic inflammation involving the exocrine glands, particularly the salivary and lacrimal glands. The pathogenesis of SS is complicated with many respects remaining elusive. IL-27, a member of IL-12 cytokine family, has the pro- and anti-inflammatory properties during immune responses. IL-27 can induce the differentiation of type 1 regulatory T (Tr1) cells from human naive CD4+ T cells. Recent studies have shown that IL-27 was involved in anti-inflammatory functions in SS. However, the underlying mechanism of IL-27 in SS is still unknown. In the present study, Tr1 cells were studied in IL-27 knock-out and wild-type SS models and patients for the purpose to explore the specific mechanism of IL-27 in SS.

Methods: IL-27 mRNA expression in PBMC of SS patients was detected by real-time PCR. Serum IL-10 of SS patients and model animals was determined by ELISA. Infiltrated IL-10+ cells in labial gland of SS patients were assessed by immunohistochemistry. Tr1 cells in human peripheral blood and mice spleen were measured by flow cytometry.

Results: IL-27 mRNA expression was decreased in SS patients. The level of IL-27 mRNA in patients with glandular infiltration was higher than those with extraglandular manifestation (Fig 1).

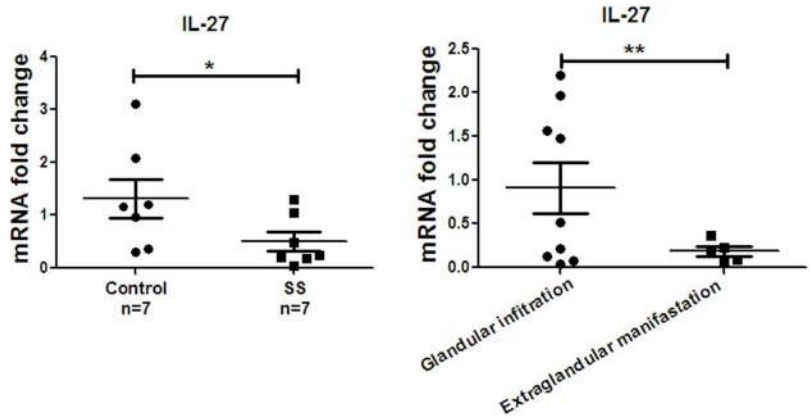


Figure 1

In SS patients, infiltrated IL-10+ cells in labial gland were significantly decreased (Fig 2 A and B). Serum IL-10 was significantly decreased in SS patients than healthy controls (Fig 2C). Compared with control, the frequency of Tr1 cells in peripheral blood of SS patients significantly reduced (Fig 2D).

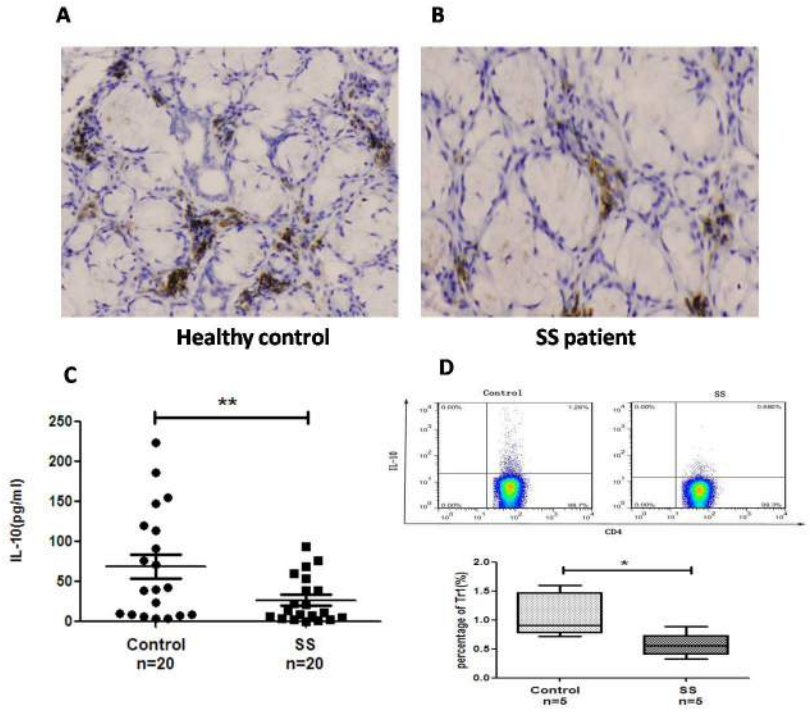


Figure 2

IL-27 deficient NOD (Non-Obese Diabetic) mice displayed more severe SS-like autoimmune disorders than NOD mice. The saliva flow rate was decreased and the submandibular gland weight/body weight index increased (Fig 3A and B). The percentage of CD4+IL-10+ Tr1 cells in splenocytes was significantly lower than NOD mice (Fig 3C). The serum IL-10 also decreased significantly (Fig 3D).

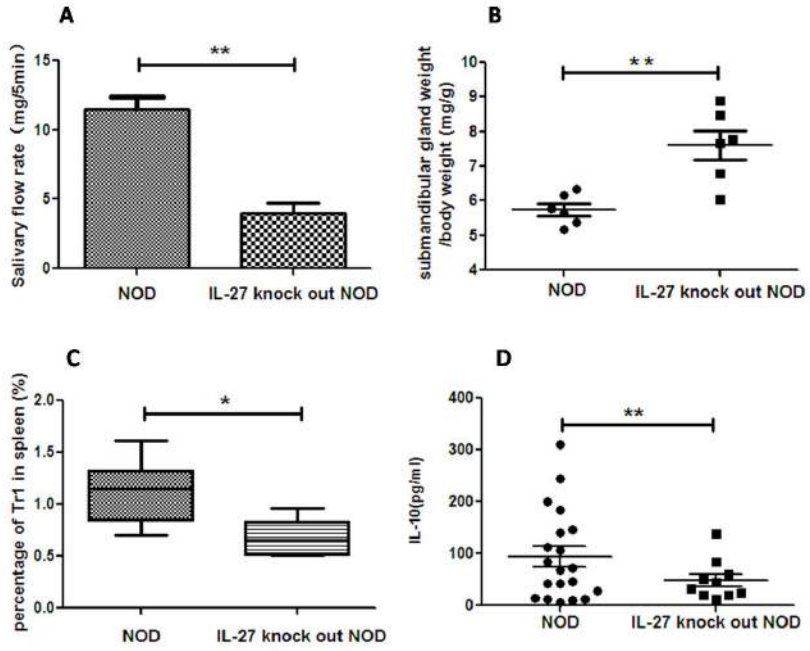


Figure 3

Conclusion: In general, these findings indicated that IL-27 deficiency deteriorated the disease symptoms of SS through loss of inducing Tr1 cells differentiation. Our data suggested that IL-27 and IL-27-induced Tr1 cells played an important role in the pathogenesis of SS.

Disclosure: **G. Yao**, None; **B. Shi**, None; **J. Qi**, None; **Y. Wang**, None; **W. Chen**, None; **X. Tang**, None; **D. Wang**, None; **X. Feng**, None; **L. Sun**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/deficiency-of-il-27-exacerbate-sjogrens-syndrome-through-inhibiting-differentiation-of-type-1-regulatory-t-cells

Abstract Number: 2015

Targeting Non-Canonical NF-Kappa B Signaling Inhibits Angiogenesis in a Novel 3D Model of Rheumatoid Arthritis Synovial Angiogenesis

Chrissta X. Maracle[1], Paulina Kucharzewska[2], Boy Helder[1], Arjan W. Griffioen[3], Henric K. Olsson[2] and Sander W. Tas[4], [1]Clinical Immunology and Rheumatology, Amsterdam Rheumatology and immunology Center | Academic Medical Center, Amsterdam, Netherlands, [2]Astra Zeneca, Mölndal, Sweden, [3]Medical Oncology, VU University Medical Center, Amsterdam, Netherlands, [4]Clinical Immunology and Rheumatology, Amsterdam Rheumatology and immunology Center | Academic Medical Center/University of Amsterdam, Amsterdam, Netherlands

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SESSION INFORMATION

Session Date: Monday, November 9, 2015

Session Title: Cytokines, Mediators, Cell-cell Adhesion, Cell Trafficking and Angiogenesis II

Session Type: ACR Concurrent Abstract Session

Session Time: 2:30PM-4:00PM

Background/Purpose:

Pathological angiogenesis is a crucial part of disease progression in rheumatoid arthritis (RA) and is often considered the switch from acute to chronic inflammation. It is a complex process mediated by several different cell types in the inflamed synovium. However, many of the *in vitro*models of angiogenesis focus solely on endothelial cells (EC), even though RA fibroblast-like synoviocytes (FLS) and immune cells also contribute to angiogenesis. Hence, a system that includes RA FLS as well as RA synovial fluid (SF) containing immune cell products such as cytokines, chemokines and growth factors, would be more representative of synovial angiogenesis. We have recently demonstrated that the non-canonical NF-kB pathway, with its main regulatory enzyme NF-kB inducing kinase (NIK), plays an important role in synovial angiogenesis. Therefore, we set out to investigate whether inhibition of this pathway may hold therapeutic potential in mitigating pathological angiogenesis associated with RA.

Objective:

Generate a representative 3D *in vitro*model of RA synovial angiogenesis and screen the effects of targeting the non-canonical NF-κB pathway using siRNA or small molecule pharmacological inhibitors.

Methods:

Human primary EC were co-cultured with RA FLS after pre-incubation with cell tracker dyes and incubated overnight to form spheroids. Subsequently, spheroids were plated in collagen gel and stimulated with 10% RA SF, growth factors (GF) or well-known activators of non-canonical NF-kB signaling (lymphotoxin beta (LT) or LIGHT). To establish NIK dependency, EC were pre-transfected with NIK-targeting siRNA before incorporation into spheroids. Furthermore, several pharmacological inhibitors were screened for their ability to block sprout formation. Spheroids were imaged by confocal microscopy and quantified using Leica QWin Plus software.

Results:

We established a robust 3D model of angiogenesis containing both EC and RA FLS. LT, LIGHT, RA SF and GF stimulations led to significant increases in sprout formation as compared to basal conditions ($p<0.05$). The LT and LIGHT induced sprout formation proved to be NIK dependent as spheroids containing EC transfected with NIK targeting siRNA had significant reductions in vessel formation as compared to the non-targeting controls ($p<0.05$). Sprouting promoted by GF and RA SF was

significantly blocked by the angiogenesis inhibitor Anginex ($p<0.05$). Finally, targeting of the non-canonical pathway using a small molecule pharmacological NIK inhibitor significantly reduced sprout formation caused by LT and LIGHT, and importantly also RA SF-induced sprout formation ($p<0.05$).

Conclusion:

We developed a novel 3D model that incorporates essential elements of synovial inflammation, namely EC, RA FLS and RA SF, which proves to be an effective tool for studying synovial angiogenesis. Using this system, we have further demonstrated a role for the non-canonical NF-kB pathway, and its central regulator NIK, in neovascularization associated with RA. Moreover, we have shown that the 3D model is useful for testing small molecule inhibitors of angiogenesis and found that targeting non-canonical NF-kB signaling is an effective method to block pathological angiogenesis.

Disclosure: C. X. Maracle, None; **P. Kucharzewska**, None; **B. Helder**, None; **A. W. Griffioen**, None; **H. K. Olsson**, None; **S. W. Tas**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/targeting-non-canonical-nf-kappa-b-signaling-inhibits-angiogenesis-in-a-novel-3d-model-of-rheumatoid-arthritis-synovial-angiogenesis

Abstract Number: 2016

Functional Tertiary Lymphoid Structures within the Kidneys of Lupus Prone Mice Resembles Lymph Nodes in Gene Expression Profiling Analysis and Are Detected By in Vivo Imaging

Premasany Kanapathippillai, Sayed Esmaeil Dorraji and **Kristin A Fenton**, RNA and Molecular Pathology, UIT, The Artic University of Norway, Tromso, Norway

First publication: September 29, 2015

SESSION INFORMATION

Session Date: Monday, November 9, 2015

Session Title: Cytokines, Mediators, Cell-cell Adhesion, Cell Trafficking and Angiogenesis II

Session Type: ACR Concurrent Abstract Session

Session Time: 2:30PM-4:00PM

Background/Purpose:

The formation of tertiary lymphoid structures (TLS) are known to occur during the development of several diseases, including systemic lupus erythematosus (SLE), but in why and how they are formed is largely unknown and thus under intense investigation. We have recently discovered immune aggregates within the kidney of lupus prone mice resembling TLS. By using gene and protein expression analysis in combination with cell specific analysis and in vivo imaging, we wanted to investigate the formation of TLS in a longitudinal study of murine lupus nephritis.

Methods:

By using immunohistochemistry and immunofluorescent analysis on kidney section from 85 (NZBXNZW)F1 (NZB/W) lupus prone mice and 20 BALB/c control mice the presence of infiltrating immune cells and the formation of highly organized TLS were analyzed. RNA was isolated from: total kidneys; macro dissected TLS from kidneys; and renal lymph nodes (LN) of NZB/W mice at three different disease stages; young (n=5, only total kidney and LN), proven anti-dsDNA ab positive for 4-5 weeks (n=5), and proteinuric (n=5). RNA samples were prepared for sequencing using the Qiagen Allprep total RNA kit (total kidney) or by Trizol extraction (TLS and LN). Sequencing of total kidney mRNA was performed using the Illumina HiSeq 2500. mRNA from TLS and LN was sequenced using the IonTorrent PGM. Differential expression analysis were performed using the edgeR package. To detect the formation of TLS in vivo we performed a pilot study using positron emission tomography (PET) by tail vein injection of the positron-emitting isotope 18-F-fluro-2-deoxy-D-glucose (FDG) combined with computed tomography (CT) for anatomical localization.

Results:

T cells and NK cells were the first cells to infiltrate the kidneys and the detection observed as early as 10 weeks old and before the mice start to produce anti-dsDNA abs. Gene expression profiling of total kidneys demonstrated an increase in genes involved in T cell activation, NK cell mediated cytotoxicity, B cell activation and inflammation mediated by chemokines and cytokines among others. Upregulation of genes specific for LN indicating a functional TLS within the kidneys of lupus prone mice. Comparing the gene expression profile in TLS and LN from anti-dsDNA ab positive mice confirmed this, but demonstrated a slightly different gene expression in TLS compared to LN from the same mice. In vivo imaging of renal uptake of FDG revealed a promising retention of FDG in kidneys of young NZB/W mice with anti-dsDNA ab production compared to ab negative NZB/W mice and control BALB/c mice. The FDG uptake increased further in NZB/W mice with detectable TLS and in proteinuric mice.

Conclusion:

The induction of anti-dsDNA antibodies, formation and deposition of immune complexes, and the formation and expansion of TLS in lupus nephritis, may promote progression into an end stage kidney disease in SLE. Understanding the mechanisms of the disease pathology is important for the development of new diagnostic approaches and treatment strategies. In vivo imaging detecting TLS can be useful for early diagnosis and individualized treatment of SLE patients with lupus nephritis.

Disclosure: P. Kanapathippillai, None; **S. E. Dorraji**, None; **K. A. Fenton**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/functional-tertiary-lymphoid-structures-within-the-kidneys-of-lupus-prone-mice-resembles-lymph-nodes-in-gene-expression-profiling-analysis-and-are-detected-by-in-vivo-imaging

Abstract Number: 2017

DNA Methylation Governs the Ability of Apoptotic Cells to Suppress Inflammatory Arthritis Via Reciprocal Regulation of IL-6 and TGF-Beta

Clare Notley[1], Christine Jordan[2], Jenny McGovern[2], Mark Brown[2] and **Michael R. Ehrenstein**[3], [1]Rheumatology, UCL, London, United Kingdom, [2]UCL, London, United Kingdom, [3]Medicine, University College London, London, United Kingdom

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SESSION INFORMATION

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Session Title: Cytokines, Mediators, Cell-cell Adhesion, Cell Trafficking and Angiogenesis II

Session Type: ACR Concurrent Abstract Session

Session Time: 2:30PM-4:00PM

Background/Purpose: Apoptotic cells (AC) have potent anti-inflammatory effects. Injection of apoptotic dendritic cells into mice suppresses the severity of antigen-induced arthritis through increased TGFβ production by resident dendritic cells. However, we have shown that AC that have been previously activated with LPS stimulate a spike in IL-6 production in vivo which inhibits TGFβ and abolishes their immunoregulatory capacity. We set out to define the intrinsic properties of AC that govern their immunomodulatory properties.

Methods: Antigen induced arthritis was used to test the effects of AC in vivo. Peripheral blood samples were obtained from patients with rheumatoid arthritis (all fulfilling ACR criteria) and healthy controls. DNA methylation from human and murine AC was assayed by ELISA and HPLC. We modulated the methylation of AC DNA to determine its role in governing the balance between pro- and anti-inflammatory cytokine production. For some experiments DNA isolated from AC were loaded into liposomes to analyse their properties in vivo. All results refer to murine studies except where specified.

Results: DNA from activated AC was significantly demethylated compared to resting AC. Demethylation of DNA using 5-azacytidine prior to apoptosis induction abrogated the protective effect of resting AC upon inflammatory arthritis. DNA from resting and activated AC loaded into liposomes had identical effects in vivo as the AC cells themselves. Remethylation of the DNA isolated from activated AC using CpG methylase and loaded into liposomes restored their ability to suppress inflammatory arthritis. Suppression of disease was associated with the production of TGFβ, and reversal of suppression with significantly increased IL-6. Apoptotic CD4+ T cells from patients with rheumatoid arthritis were significantly demethylated compared to healthy controls and led to significantly increased production of IL-6 when cultured with healthy macrophages compared to

healthy AC which induced increased TGFβ production.

Conclusion: Our results reveal that DNA methylation acts as the molecular switch that controls the TGFβ dependent regulatory properties of AC. Activated apoptotic cells by virtue of their hypomethylated DNA induce the production of IL-6, which suppresses TGFβ and promotes a pro-inflammatory milieu. Manipulation of activated AC DNA can restore their protective properties offering novel therapeutic approaches for inflammatory arthritis and other autoimmune rheumatic diseases.

Disclosure: C. Notley, None; **C. Jordan**, None; **J. McGovern**, None; **M. Brown**, None; **M. R. Ehrenstein**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/dna-methylation-governs-the-ability-of-apoptotic-cells-to-suppress-inflammatory-arthritis-via-reciprocal-regulation-of-il-6-and-tgf-beta

Abstract Number: 2018

Sodium Chloride Consumption, Together with Smoking, Is Associated with ACPA Positivity

Xia Jiang[1], Björn Sundström[2], Lars Alfredsson[3], Lars Klareskog[4], Solbritt Rantapaa-Dahlqvist[5] and Camilla Bengtsson[6], [1]Karolinska Institutet, Stockholm, Sweden, [2]2. Department of Public Health and Clinical Medicine, Rheumatology, Umeå University, Umeå, Sweden, [3]Unit of Cardiovascular Epidemiology, Institute of Enviornmental Medicine, Karolinska Institutet, Karolinska Institutet, Stockholm, Sweden, [4]Rheumatology Unit, Karolinska University Hospital, Stockholm, Sweden, [5]Department of Public Health and Clinical Medicine/ Rheumatology, Umeå University, Umeå, Sweden, [6]The Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden

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SESSION INFORMATION

Session Date: Monday, November 9, 2015

Session Title: Epidemiology and Public Health II: RA and Lifestyle Factors

Session Type: ACR Concurrent Abstract Session

Session Time: 2:30PM-4:00PM

Background/Purpose:

Increased salt concentration enhances the production of T_H17 cells, which are highly proinflammatory and are pivotal in rheumatoid arthritis (RA) pathogenesis.[1, 2] A population-based study has identified an increased RA risk among smokers who also consume a high amount of sodium, as well as a significant additive interaction between smoking and high sodium intake for the development of ACPA-positive RA.[3] Based on these results, we aimed at investigating the role of salt consumption, together with smoking, with regard to the development of ACPA-positivity.

Methods:

The analysis involved 1294 newly diagnosed cases recruited from the EIRA project during 2009-2011. Smoking status (categorized as never/ever smoking), smoking intensity (cut-off at 20 pack-years) and other lifestyle related factors were reported through self-administrated questionnaires at baseline. Sodium consumption was calculated using an algorithm based on data from food questionnaire and was categorized as low, median and high intake. We calculated the odds ratio (OR) and 95% confidence intervals (95%CI) associated with combinations of smoking and salt regarding the development of ACPA positivity in a case-only analysis.

Results:

We identified an increased risk of belonging to the ACPA-positive RA subset among ever smokers (OR=1.4, 95%CI: 0.9-2.1) and heavy smokers (OR=2.6, 95%CI: 1.6-4.1) who had a medium to high sodium intake compared with never smokers with low intake. We further observed a dose response effect between pack-years of smoking and sodium intake with regard to ACPA-positivity (light or never smokers/median sodium intake: 1.0 (0.7-1.4); light or never smokers/high sodium intake: 0.9 (0.6-1.3); heavy smokers/low sodium intake: 1.4 (0.8-2.4); heavy smokers/median sodium intake: 2.1 (1.2-3.7); heavy smokers/high sodium

intake: 3.2 (1.7-6.0); p-trend <0.0001).

Conclusion: We observed an increased risk of ACPA-positivity among high sodium intake (heavy) smokers, compared with never smokers with low sodium intake, as well as a dose response effect of sodium intake among heavy smokers.

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2. Wu C, Yosef N, Thalhamer T, et al. Induction of pathogenic TH17 cells by inducible salt-sensing kinase SGK1. Nature 2013;**496**:513-517.

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Disclosure: X. Jiang, None; **B. Sundström**, None; **L. Alfredsson**, None; **L. Klareskog**, None; **S. Rantapaa-Dahlqvist**, None; **C. Bengtsson**, None.

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Abstract Number: 2019

Serum Biomarkers of Inflammatory Arthritis in First Degree Relatives of Patients with Rheumatoid Arthritis and Their Association with Lifestyle Risk Factors

Jamie C Sergeant and RA-MAP Consortium, NIHR Manchester Musculoskeletal Biomedical Research Unit, Central Manchester University Hospitals NHS Foundation Trust, Manchester, United Kingdom, Arthritis Research UK Centre for Epidemiology, Centre for Musculoskeletal Research, Manchester Academic Health Science Centre, University of Manchester, Manchester, United Kingdom

First publication: September 29, 2015

SESSION INFORMATION

Session Date: Monday, November 9, 2015

Session Title: Epidemiology and Public Health II: RA and Lifestyle Factors

Session Type: ACR Concurrent Abstract Session

Session Time: 2:30PM-4:00PM

Background/Purpose:

Rheumatoid factor (RF), anti-cyclic citrullinated peptide antibodies (anti-CCP) and C-reactive protein (CRP) are known serum biomarkers of inflammatory arthritis (IA) and have potential predictive value in high risk groups. We measured RF, anti-CCP and CRP levels in the PRe-clinical EValuation of Novel Targets in RA (PREVeNT RA) study, a register of first degree relatives (FDRs) of patients with rheumatoid arthritis (RA), and assessed their associations with known lifestyle risk factors for IA. The aim of PREVeNT RA is to study FDRs of RA patients to identify risk factors for developing RA and so help inform the development of interventions for preventing RA.

Methods:

FDRs of patients with established RA are being recruited from across the UK. FDRs are free of IA and >30 years old at time of recruitment. Following informed consent, participants complete an online questionnaire to ascertain lifestyle factors potentially associated with risk of RA and provide a blood sample for central storage and analysis. For this study, we measured RF (normal ≤20 IU/ml), anti-CCP (normal ≤7 U/ml) and high sensitivity (hs) CRP (normal ≤5 mg/l) on FDRs recruited up to April 2015. Associations between these biomarkers and current smoking status, alcohol intake (units/week), body mass index (BMI, kg/m^2 – derived from self-reported height and weight) and self-reported diabetes were assessed with Fisher's exact or Mann-Whitney tests, then adjusted for age and sex with multiple logistic or linear regression.

Results:

Complete data were available for 469 participants. Baseline characteristics are shown in Table 1 and overlap in biomarker status is shown in Figure 1. Associations between biomarkers and lifestyle risk factors are shown in Table 2. On average, RF positive participants drank 5.49 (95% CI (1.92, 9.06)) more units of alcohol a week and those with elevated CRP had a 3.78 kg/m^2 (95% CI (2.64, 4.92)) higher BMI.

Conclusion:

In this FDR cohort lifestyle factors associated with future onset of IA were also associated with biomarkers of serological risk and low-grade inflammation. These initial results suggest that early targeting of 'at risk' lifestyle factors may, at a population level, reduce future risk of RA onset.

Table 1: Baseline Characteristics

Characteristic	All (n=469)
Female	358 (76.3%)
Age (years)	51 (41, 62)
Current smoker	29 (6.2%)
Alcohol intake (units/week)	5 (1, 10)
BMI (kg/m^2)	25.2 (22.4, 28.7)
Obese (BMI≥30)	91 (19.4%)
Self-reported diabetes	16 (3.4%)
RF (IU/ml)	8.3 (6.6, 10.3)
RF positive (> 20 IU/ml)	26 (5.5%)
Anti-CCP (U/ml)	0.8 (0.5, 1.0)
Anti-CCP positive (> 7 U/ml)	7 (1.5%)
hsCRP (mg/l)	1.4 (0.7, 3.2)
hsCRP elevated (> 5 mg/l)	88 (18.8%)

Values are number (%) or median (inter-quartile range)

Figure 1: Venn diagram of serum biomarker status (n=469)

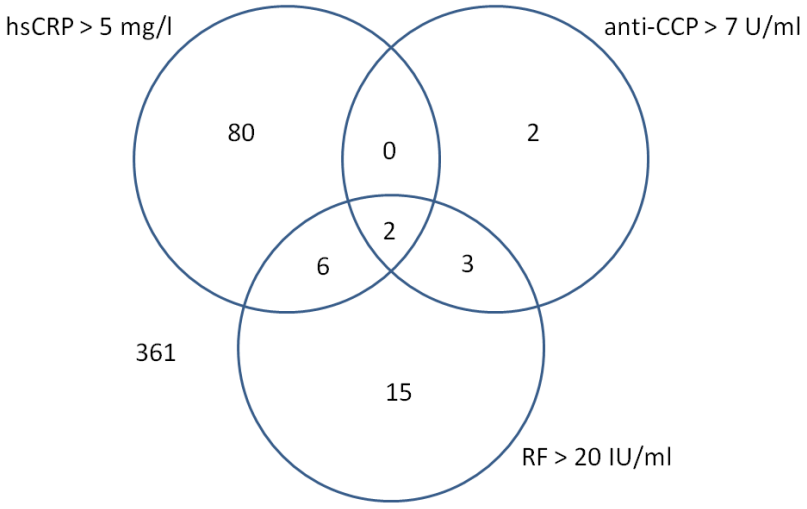

Table 2: Associations between serum biomarkers and lifestyle risk factors (n=469)

Outcome	Predictor					
	RF positive		Anti-CCP positive		hsCRP elevated	
	Test *p*	Regression adj. OR or β	Test *p*	Regression adj. OR or β	Test *p*	Regression adj. OR or β
Current smoking (OR)	0.07	2.93 (0.93, 9.22)	1.00	NA	0.81	1.10 (0.43, 2.82)
Alcohol intake (β)	**0.03**	**5.49 (1.92, 9.06)**	0.69	2.06 (-4.74, 8.85)	0.51	0.09 (-2.04, 2.22)
BMI (β)	0.48	-0.19 (-2.21, 1.82)	0.72	-0.88 (-4.67, 2.92)	**<0.001**	**3.78 (2.64, 4.92)**
Diabetes (OR)	0.61	1.05 (0.13, 8.37)	1.00	NA	0.09	2.82 (0.96, 8.27)

Test: Fisher's exact (current smoking, diabetes) or Mann-Whitney (alcohol intake, BMI) test between outcome and predictor.
Regression: age and sex adjusted logistic regression odds ratio (OR) (current smoking, diabetes) or age and sex adjusted linear regression coefficient (β) (alcohol intake, BMI), with 95% confidence interval.
NAs: perfect prediction in logistic regression (due to small number of anti-CCP positive individuals)

Disclosure: J. C. Sergeant, None;

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Abstract Number: 2020

Elevated BMI and ACPA Together Increase RA Risk and Independently Accelerate Time to RA

Sara K. Tedeschi[1], Jing Cui[2], Elizabeth V. Arkema[3], Jeffrey A. Sparks[1], Elizabeth W. Karlson[1] and Karen H. Costenbader[1,4], [1]Rheumatology, Brigham & Women's Hospital, Boston, MA, [2]Division of Rheumatology, Immunology, and Allergy, Brigham & Women's Hospital, Boston, MA, [3]Karolinska Institutet, Stockholm, Sweden, [4]Rheumatology, Immunology & Allergy, Brigham & Women's Hospital, Boston, MA

First publication: September 29, 2015

SESSION INFORMATION

Session Date: Monday, November 9, 2015

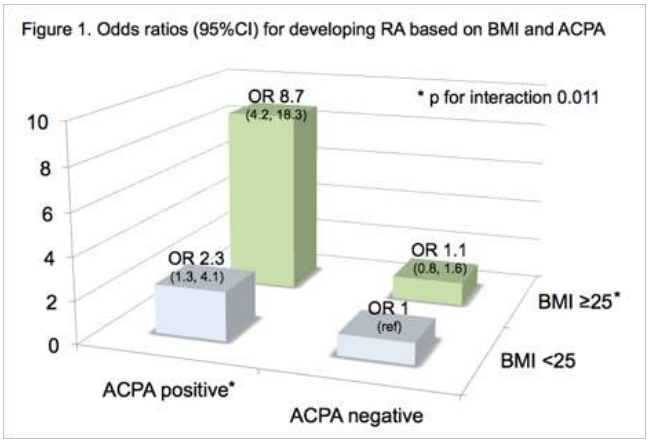
Session Title: Epidemiology and Public Health II: RA and Lifestyle Factors

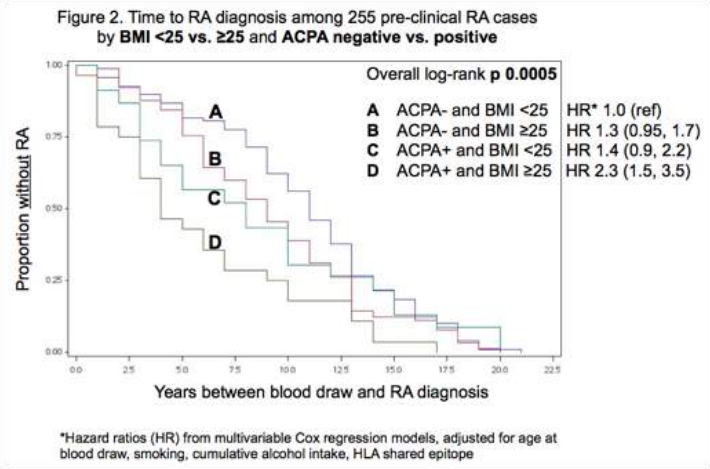
Session Type: ACR Concurrent Abstract Session

Session Time: 2:30PM-4:00PM

<>**Background/Purpose:** Obesity and anti-citrullinated peptide antibodies (ACPA) are risk factors for RA. We investigated whether body mass index (BMI) and ACPA interact in determining RA risk and time to RA. <> <>**Methods:** We conducted a nested case-control study within the Nurses' Health Studies (NHS and NHSII). Self-reported incident RA was confirmed by medical record review for ACR criteria. A blood sample was collected (1989-90 for NHS, 1996-99 for NHSII) prior to diagnosis among pre-RA cases and on a similar date for controls matched on age, menopausal status and hormone use. Seven types of novel ACPA were measured by multiplex bead-based assay (W. Robinson lab, Stanford). For each ACPA, a value ³3 SD above the mean in controls was considered positive. Exposures from biennial questionnaires before blood draw included age, BMI, smoking, and alcohol intake. In the primary analysis, conditional logistic regression models adjusting for covariates provided OR (95% CI) for developing RA, for ACPA (³1 ACPA+), BMI, and a multiplicative interaction of ACPA and BMI (<25 vs. ³25 kg/m^2). In a secondary case-only analysis, multivariable-adjusted Cox regression models provided HR (95% CI) for time to RA. Kaplan-Meier curves and log-rank tests compared time to RA for subgroups of pre-RA cases stratified by ACPA and BMI. <> <>**Results:** Among 255 pre-RA cases and 778 matched controls, mean age was 51.4 (±8.0) years and mean BMI 25.2 (±4.5)

kg/m^2; 98% were White and 11.4% were ACPA+. In multivariable conditional logistic regression, there was a significant interaction between ACPA+ and BMI ³25 for RA risk (p 0.011) (Fig. 1) Among pre-RA cases, mean time to RA was 8.9 (± 5.3) years after blood draw. Time to RA was shortest among those with BMI ³25 and ACPA+ (5.3 ± 4.8 years) and longest in those with BMI<25 and ACPA- (10.5 ± 5.0 years) (log rank p 0.0002). In multivariable Cox models, women with BMI ³25 and ACPA+ had the highest risk for RA (HR 2.3, 95%CI 1.5, 3.5) (Fig. 2). <> <>**Conclusion:** Among women who later developed RA and matched controls, elevated BMI and ACPA+ interacted to increase RA risk, suggesting that these factors are synergistic. Time to RA was shortest in pre-RA cases with both elevated BMI and ACPA+. Obesity may accelerate onset of RA in particular among those who are already ACPA+. The biological mechanism behind our findings warrants further investigation.





Disclosure: S. K. Tedeschi, None; **J. Cui**, None; **E. V. Arkema**, None; **J. A. Sparks**, None; **E. W. Karlson**, None; **K. H. Costenbader**, Arthritis Care and Research, 5,International Journal of Clinical Practice, 5.

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Abstract Number: 2021

Omega-3 Fatty Acids Are Associated with a Lower Prevalence of Autoantibody Positivity in HLA-DR Shared Epitope Positive Subjects Who Are at Increased Risk for Future RA

Ryan W. Gan[1], M. Kristen Demoruelle[2], Kevin D. Deane[3], Michael H. Weisman[4], Jane H. Buckner[5], Peter K. Gregersen[6], Ted R. Mikuls[7], James R. O'Dell[7], Richard M. Keating[8], Tasha Fingerlin[9], Gary O. Zerbe[10], Michael J. Clare-Salzler[11], V. Michael Holers[12] and Jill M. Norris[13], [1]Colorado School of Public Health, University of Colorado Denver, Aurora, CO, [2]Rheumatology, University of Colorado School of Medicine, Aurora, CO, [3]Division of Rheumatology, U Colo Denver, Aurora, CO,

[4]Rheumatology, Cedars-Sinai Medical Center, Los Angeles, CA, [5]Benaroya Research Institute at Virginia Mason, Seattle, WA, [6]Feinstein Insititute for Medical Research, Manhasset, NY, [7]University of Nebraska Medical Center, Omaha, NE, [8]Division of Rheumatology, Scripps Health, La Jolla, CA, [9]National Jewish Health, Denver, CO, [10]Biostatistics and Informatics, Colorado School of Public Health / University of Colorado Anschutz Medical Campus, Aurora, CO, [11]Experimental Pathology, University of Florida, College of Medicine, Gainesville, FL, [12]Rheumatology Division, Univ of Colorado School of Med, Aurora, CO, [13]University of Colorado Denver, Aurora, CO
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SESSION INFORMATION

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Session Type: ACR Concurrent Abstract Session
Session Time: 2:30PM-4:00PM

Background/Purpose: Studies of fish intake suggest that omega-3 fatty acids (n-3 FAs) could be protective against the development of RA. Previously, we found n-3 FAs were inversely associated with anti-CCP2 positivity in subjects without RA, but at risk for future RA (Gan 2015). In this present study, we investigated whether n-3 FAs were also associated with RF positivity, and if the associations between n-3 FA and these autoantibodies (Abs) differed by HLA shared epitope (SE) positivity, in subjects at risk for future RA.

Methods: The Studies of the Etiology of RA (SERA) cohort includes subjects who are RA-free by 1987 ACR criteria, but who are at increased risk for future RA, based on family history of RA. To examine the association between n-3 FA and Ab positivity, we utilized two approaches: 1) a nested case-control study to determine the association between RF and anti-CCP2 positivity and percent of n-3 FA in erythrocyte membranes (RBC n-3 FA%); 2) a cross-sectional study of the baseline visit of the larger SERA cohort, in which we determined the association between n-3 FA supplement use and RF and anti-CCP2 positivity. We assessed the role of SE as an effect modifier using an interaction term in logistic regression models. As significant n-3 FA*SE interactions were detected for RF, results were stratified by SE status for both RF and anti-CCP2 for comparison.

Results: In the nested case-control study, increases in several RBC n-3 FA%s were associated with a lower prevalence of RF and anti-CCP positivity in SE positive subjects but not SE negative subjects (Table 1). In the larger SERA cohort baseline analyses, n-3 FA supplement use was associated with a lower prevalence of RF positivity in SE positive subjects, but not SE negative subjects; similar trends were seen with anti-CCP2 positivity (Table 2).

Conclusion: We demonstrate that n-3 FAs are inversely associated with RF positivity in SE positive subjects with a familial risk of RA. In combination with our prior work that found n-3 FAs are inversely associated with anti-CCP2 positivity, these data suggests a potential protective effect of n-3 FAs against broader RA-related autoimmunity. Furthermore, the protective effect of n-3 FAs on RA-related autoimmunity may be most pronounced in SE positive subjects. Our findings could be explained by the ability of n-3 FAs to change the conformation of membrane MHC class II molecules and alter antigen presentation and Ab generation (Hughes 1996, Rockett 2015), or other adaptive immune mechanisms yet to be identified. This needs further investigation, as it could lead to the use of n-3 FAs in the prevention of RA.

Table 1: Nested case-control study associations between increasing RBC n-3 FA% and the outcomes of anti-CCP2 and RF by shared epitope status (27 RF positive subjects, 40 anti-CCP2 positive subjects, and 69 antibody negative subjects).

	RF						
	SE Positive			**SE Negative**			
	(n=11 RF pos.)			**(n=16 RF pos.)**			
RBC n-3 FA%		**95%**			**95%**		
	OR*	**CI**	**p**	**OR***	**CI**	**p**	**p_{inter}**
Total n-3 FA	**0.27**	**0.10-0.79**	**0.02**	**0.94**	**0.49-1.78**	**0.84**	**0.04**
ALA(18:3n-3)	1.02	0.54-1.93	0.94	1.21	0.59-2.48	0.60	0.73
EPA(20:5n-3)	0.43	0.10-1.82	0.25	0.98	0.55-1.75	0.95	0.28
DPA(22:5n-3)	**0.39**	**0.17-0.89**	**0.03**	0.74	0.35-1.56	0.42	0.26
DHA(22:6n-3)	**0.34**	**0.13-0.91**	**0.03**	1.02	0.52-1.98	0.96	0.06
EPA+DHA	**0.31**	**0.10-0.91**	**0.03**	0.99	0.53-1.87	0.98	0.06
	Anti-CCP2						
	SE Positive			**SE Negative**			
	(n=24 Anti-CCP2 pos.)			**(n=16 Anti-CCP2 pos.)**			
RBC n-3 FA%		**95%**			**95%**		
	OR*	**CI**	**p**	**OR***	**CI**	**p**	**p_{inter}**
Total n-3 FA	**0.42**	**0.20-0.89**	**0.03**	0.74	0.39-1.40	0.35	0.24
ALA(18:3n-3)	0.90	0.24-1.50	0.68	0.68	0.27-1.71	0.41	0.60
EPA(20:5n-3)	**0.27**	**0.09-0.83**	**0.02**	0.61	0.32-1.17	0.14	0.20
DPA(22:5n-3)	0.84	0.47-1.52	0.56	0.92	0.46-1.83	0.80	0.85
DHA(22:6n-3)	**0.47**	**0.24-0.92**	**0.03**	0.79	0.42-1.51	0.48	0.25
EPA+DHA	**0.40**	**0.18-0.85**	**0.02**	0.73	0.39-1.37	0.33	0.20

*Adjusted for age at visit, sex, race, site, current smoker, and income. The odds ratios reported are for a standard deviation (SD) difference in n-3 FA %. SDs: Total n-3 FA = 1.8; ALA = 0.3; EPA = 0.6; DPA = 2.2; DHA = 3.5; EPA+DHA = 4.1.

p-value for interaction, testing a difference in the effect of n-3 FA % in RBCs between SE positive and negative stratums.

Table 2: Cross-sectional study associations between self-reported n-3 FA supplement use and the outcomes of RF (n=115 subjects) and anti-CCP2 (n=44 subjects) positivity at baseline by SE status in 2,331 subjects at baseline.

	RF						
	SE Positive (n=60 RF pos.)			SE Negative (n=55 RF pos.)			
n-3 FA Supplement	**OR***	**95% CI**	**p**	**OR***	**95% CI**	**p**	**p_{inter}**
Yes vs. No	0.35	0.15-0.82	0.02	1.21	0.64-2.28	0.56	0.02

	Anti-CCP2						
	SE Positive (n=27 Anti-CCP2 pos.)			SE Negative (n=17 Anti-CCP2 pos.)			
n-3 FA Supplement	**OR***	**95% CI**	**p**	**OR***	**95% CI**	**p**	**p_{inter}**
Yes vs. No	0.28	0.07-1.20	0.09	1.11	0.35-3.49	0.83	0.14

*Model includes interaction term between n-3 FA supplement use and SE, adjusted for age, sex, race, site, current smoking, and other supplement use. The RF outcome model excluded the 44 anti-CCP2 positive subjects from the analysis. The anti-CCP2 outcome model excluded the 115 RF positive subjects from the analysis.

p-value for interaction, testing a difference in the effect of n-3 FA supplement use between SE positive and negative stratums.

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Abstract Number: 2022

Adherence to the Dietary Guidelines for Americans and Risk of Developing Rheumatoid Arthritis in Young and Middle-Aged Women

Yang Hu[1], Jeffrey A. Sparks[2], Karen H. Costenbader[3], Frank Hu[4], Elizabeth W. Karlson[5] and **Bing Lu**[5], [1]Nutrition, Harvard School of Public Health, Boston, MA, [2]Division of Rheumatology, Immunology, and Allergy, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, [3]Rheumatology, Immunology and Allergy, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, [4]Harvard School of Public Health, Boston, MA, [5]Division of Rheumatology, Immunology and Allergy, Brigham and Women's Hospital, Harvard Medical School, Boston, MA

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SESSION INFORMATION

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Session Title: Epidemiology and Public Health II: RA and Lifestyle Factors

Session Type: ACR Concurrent Abstract Session

Session Time: 2:30PM-4:00PM

Background/Purpose: Little is known about the effect of adherence to the Dietary Guidelines for Americans on risk of developing rheumatoid arthritis (RA). The Alternative Healthy Eating Index 2010 (AHEI-2010) measures how well Americans' diets conform to these guidelines. We aimed to evaluate the association between AHEI-2010 and risk of RA in young and middle-aged women using Nurses' Health Study II (NHS II), a large prospective cohort study.

Methods: The NHS II was initiated in 1989 and comprised 116,430 female registered nurses, aged 25–42 years. RA cases were initially self-reported then confirmed by a connective tissue disease screening questionnaire and medical record review according to the 1987 ACR criteria. Seropositive RA was defined as positive rheumatoid factor or anti-citrullinated peptide antibody and

was determined by chart review or laboratory measurement.Dietary data were obtained from validated food frequency questionnaires at baseline and approximately every 4 years during follow-up. The AHEI-2010 was derived based on foods and nutrients that have been consistently associated with lower risk of chronic diseases in clinical and epidemiologic investigations. Each of the 11 components including vegetables, fruits, whole grains, nuts and legumes, sugar-sweetened beverages, red /processed meat, trans-fat % of energy, long-chain omega-3 fats, polyunsaturated fat, sodium and alcohol has a minimum score of 0 and a maximum score of 10 according to the dietary guidelines and daily intakes. AHEI-2010 ranges from 0 to 110. Time-varying Cox regression models were used to explore the association between cumulative averaged AHEI-2010 and risk of RA after adjusting for potential confounding factors.

Results: During the 1,751,803person-years of follow-up from 1991 to 2011 in NHS II, 347 RA cases (215 seropositive, 132 seronegative) were identified. In the multivariable adjusted model, we found greater adherence to AHEI-2010 was associated with reduced risk of RA. Women in the highest quartile of AHEI-2010 had 33% (HR=0.67, 95% confidence interval 0.49-0.91) reduced risk compared to the women in the lowest quartile (p-trend 0.006) (Table). After additional adjustmentfor BMI, the results were consistent.Further stratified analyses demonstrated that the association of AHEI-2010 with RA risk was stronger in seronegative RA than in seropositive RA.

Conclusion: Data from this large prospective cohort study suggest that better adherence to the Dietary Guidelines for Americans is associated with reduced risk of developing RA in young and middle-aged women. Our results suggest that diet may be particularly important for risk of seronegative RA and further research is warranted to confirm these findings.

Table. Hazard ratios (95% CI) for incident RA according to cumulative AHEI-2010 in Nurses' Health Study II (NHS II, 1991-2010)[1]

	AHEI-2010 quartiles				*P*-trend[2]
	Q1	Q2	Q3	Q4	
All RA					
Case/person-years	100/437,225	90/438,122	80/438,142	77/438,314	
Age adjusted model	1.00	0.85(0.64,1.13)	0.74(0.55,0.99)	0.69(0.51,0.93)	0.010
Multivariable-model[3]	1.00	0.85(0.64,1.13)	0.73(0.54,0.98)	0.67(0.49,0.91)	0.006
Multivariable-model[4]	1.00	0.85(0.64,1.14)	0.75(0.56,1.01)	0.72(0.53,0.98)	0.026
Sero-positive RA					
Case/person-years	62/436,775	51/437,712	51/437,780	51/438,009	
Age adjusted model	1.00	0.79(0.54,1.14)	0.78(0.53,1.12)	0.76(0.52,1.10)	0.164
Multivariable-model[3]	1.00	0.78(0.54,1.13)	0.75(0.52,1.10)	0.72(0.50,1.06)	0.102
Multivariable-model[4]	1.00	0.79(0.55,1.15)	0.79(0.54,1.14)	0.80(0.54,1.17)	0.254
Sero-negative RA					
Case/person-years	38/436,452	39/437,429	29/437,494	26/437,712	
Age adjusted model	1.00	0.95(0.61,1.48)	0.69(0.42,1.11)	0.59(0.35,0.97)	0.017
Multivariable-model[3]	1.00	0.95(0.61,1.49)	0.69(0.42,1.12)	0.59(0.35,0.97)	0.019
Multivariable-model[4]	1.00	0.95(0.61,1.49)	0.70(0.43,1.14)	0.61(0.37,1.02)	0.032

[1]Hazard ratios were calculated by using time-varying Cox proportional hazards models.

[2]p-trend was derived from tests of linear trend across categories of AHEI scores by treating the median value of each category as a continuous variable.

[3] Adjusted for age, smoking (pack-years), total calorie intake. Additional adjustment for census tract median family income, alcohol use and physical activity did not change the statistical significance.

[4]Additional adjustment for BMI (kg/m^2; <25, 25–29.9, or ≥30).

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Abstract Number: 2023

Breastfeeding, Oral Contraceptive and the Risk of Rheumatoid Arthritis: Results from the Swedish Epidemiological Investigation of RA Study

Cecilia Orellana[1], Lars Klareskog[2], Lars Alfredsson[3,4] and Camilla Bengtsson[1], [1]Karolinska Institutet, Institute of Environmental Medicine, Stockholm, Sweden, [2]Department of Medicine, Karolinska University Hospital, Stockholm, Sweden, [3]Karolinska Institute, Institute of Environmental Medicine, Stockholm, Sweden, [4]Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden

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SESSION INFORMATION

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Session Title: Epidemiology and Public Health II: RA and Lifestyle Factors

Session Type: ACR Concurrent Abstract Session

Session Time: 2:30PM-4:00PM

Background/Purpose: Breastfeeding (BF) has been associated with both a decreased and an increased risk of developing rheumatoid arthritis (RA). Regarding oral contraceptive (OC) use and the risk of RA a few studies have shown a negative association but the majority of reports have been unable to demonstrate an association. To the best of our knowledge no previous study has investigated the impact of BF and OC use on the two subgroups of RA, characterized by presence/absence of antibodies to citrullinated peptides (ACPA). Our aim was to study the association between BF history and OC use and the risk of ACPA-positive/-negative RA among women.

Methods: Data from the Epidemiological Investigation of RA (EIRA), a population-based case-control study, comprising women aged 18-75+ living in Sweden, between 1996 and 2013 was analyzed (2637 cases and 4244 controls). For BF, data was available between 2006 and 2013 (884 cases and 1947 controls, parous women). An extensive questionnaire was answered by the participants, including questions regarding duration of BF for each delivered child, OC use and potential confounders (education, smoking, BMI, alcohol consumption, postmenopausal hormone therapy, and reproductive factors). Total BF history among parous women was calculated as the sum of the duration of BF for each delivered child and categorized as 0-6, 7-12 and ≥13 months. Current use of OCs was defined as those who were currently using OCs during the index-year and started at least one year before symptoms debut. Past users were defined as those who used OCs in the past and had stopped at least the year before the index-year. Ever users were defined as current and past users while never users correspond to women who had never used OCs before the index-year. We calculated odds ratios (ORs) with 95% confidence intervals (CI) of developing ACPA-positive/-negative RA, by means of unconditional logistic regression, adjusting for age, residential area and pack-years.

Results: A longer history of BF was associated with a reduced risk of developing RA (OR=0.76, 95% CI 0.62-0.93 and OR=0.91, 95% CI 0.74-1.12 for breastfeeding ≥13 months and 7-12 months respectively, compared with up to 6 months). The trend was significant for ACPA+ RA (*p-value* 0.0088), but not for ACPA- RA (*p-value* 0.2833). These estimates were attenuated when we adjusted for pack-years. Ever users of OC had a decreased risk of developing RA compared with never users (OR=0.88, 95% CI 0.79-0.98), mainly due to a decreased risk among past OC users (OR=0.88, 95% CI 0.80-0.98). The association was significant for ACPA+ but not for ACPA- RA. A longer duration of ever OC use (≥8 years) was significantly associated with a decreased risk of RA overall (OR=0.83, 95% CI 0.73-0.94) and ACPA+ RA (OR=0.82, 95% CI 0.71-0.95), while a borderline association was found for ACPA- RA (OR=0.83, 95% CI 0.69-1.01).

Conclusion: Both BF and OC use were associated with a reduced risk of developing RA, especially for ACPA+ RA. Our study contributes to the knowledge of environmental risk factors and its different impact on the subgroups of RA.

Disclosure: C. Orellana, None; **L. Klareskog**, None; **L. Alfredsson**, None; **C. Bengtsson**, None.

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Abstract Number: 2024

Replacing Radiographic Sacroiliitis By Structural Lesions on MRI of the Sacroiliac Joints in Two Early Axial Spa Cohorts: What Is the Impact on the

Classification of Patients According to the ASAS Axial Spa Criteria?

Pauline Bakker[1], Rosaline van den Berg[2], Manouk de Hooge[3], Zineb Ez-Zaitouni[4], Miranda van Lunteren[4], Karen M. Fagerli[5], Roberta Ramonda[6], Robert B. M. Landewé[7], Maikel van Oosterhout[8], Monique Reijnierse[9], Floris van Gaalen[1], Pascal Claudepierre[10], Daniel Wendling[11], Maxime Dougados[12] and Désirée van der Heijde[13], [1]Rheumatology, Leiden University Medical Center, Leiden, Netherlands, [2]Leiden University Medical Center, Leiden, Netherlands, [3]Department of Rheumatology, Leiden University Medical Centre, Leiden, Netherlands, [4]Leiden University Medical Centre, Leiden, Netherlands, [5]Rheumatology, Diakonhjemmet Hospital, Oslo, Norway, [6]Cattedra, Voc Rheumatology, University of Padua, Padova, Italy, [7]Rheumatology, University Hospital Maastricht, Maastricht, Netherlands, [8]Rheumatology, GHZ Hospital, Gouda, Netherlands, [9]Radiology, Leiden University Medical Center, Leiden, Netherlands, [10]Hôpital Henri Mondor, Créteil, France, [11]Université de Franche-Comté, Besançon, France, [12]Paris-Descartes University, Paris, France, [13]Department of Rheumatology, Leiden University Medical Center, Leiden, the Netherlands, Leiden, Netherlands

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Session Type: ACR Concurrent Abstract Session

Session Time: 2:30PM-4:00PM

Background/Purpose: Conventional radiography of the sacroiliac joints (X-SI) is the most commonly used imaging technique to detect structural lesions in axial SpondyloArthritis (axSpA). However, a reliable detection of radiographic sacroiliitis is challenging and might result in misclassification. Next to inflammatory lesions, structural lesions are visible on MRI. We aim to investigate the impact of replacement of X-SI by structural lesions on MRI on the ASAS axSpA classification of patients.

Methods: Patients in the SPondyloArthritis Caught Early (SPACE) cohort (chronic back pain: ≥3 mths, ≤2 yrs, onset <45 yrs) and DEvenir des Spondylarthropathies Indifférenciées Récentes (DESIR) cohort (aged 18-50 with inflammatory back pain (IBP): ≥3 mths, <3 yrs) with (suspicion of) axSpA underwent baseline MRI-SI and X-SI. Three well-calibrated readers, blinded for patient characteristics, read the images. MRI-SI (inflammatory lesions according to ASAS definition) and X-SI (modified New York criteria (mNY)) were considered positive if 2/3 readers agreed. MRI T1-w images were assessed on the presence of structural lesions. Mean scores of 2/3 agreeing readers (ASAS definition) were used in SPACE; in DESIR there were only 2 readers for MRI-SI-s and results were analysed for each reader separately. Previously, we proposed cut-offs to define a positive MRI-SI based on structural lesions (MRI-SI-s) based on <5% presence among no-SpA patients in the SPACE cohort: ≥3 erosions, ≥3 fatty lesions, ≥5 fat lesions and/or erosions. In this analysis, patients were classified according to the ASAS axSpA criteria using MRI-SI-s instead of X-SI and changes were visualized.

Results: In total, 294 (SPACE) and 582 (DESIR) patients were included of which 103 (35.0%) and 418 (71.8%) patients were classified as having ASAS axSpA, respectively. Using the ≥5 fatty lesions and/or erosions cut-off, classification did not change in 275+3+8 (286) patients (97.3%) in SPACE, not in 478+66+23 (567) patients (97.4%) by reader 1 in DESIR and not in 469+43+54 (566) (97.3%) patients by reader 2 in DESIR (table). In SPACE, 5 patients (1.7%) would not be classified as axSpA while 3 patients (1.0%) would be additionally classified as axSpA if only MRI-SI-s was performed. In DESIR, 12 and 10 patients would not be classified axSpA and 3 and 6 patients would be additionally classified axSpA (reader 1 and 2, respectively). Very similar results were found for the presence of fatty lesions or erosions alone (both cut-off of >3).

Conclusion: Replacement of radiographs by assessment of structural lesions on MRI does not lead to a different ASAS axSpA classification in the large majority of patients. These data are promising, however are from two early axSpA cohorts and need to be confirmed in patients with established disease.

	DESIR reader 1	DESIR reader 2	SPACE mean 2/3 readers
Classification remained the same	478	469	275
mNY+ patients with MRI-SI-struct- but remained ASAS+	66	43	3
mNY- patients with MRI-SI-struct+ within ASAS+	23	54	8
ASAS- patients based on mNY- became ASAS+ based on MRI-SI- struct+	3	6	3
ASAS+ patients based on mNY+ became ASAS- based on MRI-SI- struct-	12	10	5
Total	**582**	**582**	**294**

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Abstract Number: 2025

Modification of Structural Lesions on Magnetic Resonance Imaging By Etanercept: A 12-Week Randomized Placebo-Controlled Trial

Walter Maksymowych[1], Stephanie Wichuk[2], Maxime Dougados[3], Heather Jones[4], Annette Szumski[5], Lisa Marshall[4], Jack F Bukowski[6] and Robert G Lambert[7], [1]Department of Medicine, University of Alberta, Edmonton, AB, Canada, [2]Rheumatology Research Lab, University of Alberta, Edmonton, AB, Canada, [3]Rheumatology Department, Hôpital Cochin, Paris, France, [4]Inflammation Global Medical Affairs, Pfizer, Collegeville, PA, [5]Department of Biostatistics, Pfizer, Collegeville, PA, [6]Clinical Affairs, Pfizer, Collegeville, PA, [7]Department of Radiology & Diagnostic Imaging, University of Alberta, Edmonton, AB, Canada
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Session Time: 2:30PM-4:00PM

Background/Purpose: Modification of structural lesions by anti-TNF therapy has not been demonstrated in a randomized placebo (PBO)-controlled trial. The Spondyloarthritis Research Consortium of Canada (SPARCC) sacroiliac joint (SIJ) score (SSS) assesses the degree of fat metaplasia (new tissue growth after resolution of inflammation), erosion, backfill (new tissue growth at erosion site), and ankylosis observed on MRI in the SIJ. This analysis evaluated the impact on these lesions at 12 wks in patients with non-radiographic axial SpA receiving PBO or etanercept (ETN) in the EMBARK study (ClinicalTrials.gov: NCT01258738).

Methods: Patients had axial SpA per Assessment of SpondyloArthritis international Society (ASAS) criteria without meeting modified NY radiographic criteria; BASDAI score ≥4; symptoms for >3 months and <5 yrs; and had failed ≥2 NSAIDs. Patients were randomized to double-blind ETN 50 mg/wk or PBO for 12 wks, then received open-label ETN. Structural lesions were

scored using the SPARCC SSS method on T1-weighted spin echo (T1WSE) MRI. Two readers independently scored baseline (BL) and 12-wk T1WSE MRI scans, blinded to patients, time point, and inflammation scores assessed by short tau inversion recovery MRI scans. Readers' mean scores were used.

Results: Mean (SD) age was 32 (7.8) yrs, 60.5% were male, duration of disease symptoms was 2.4 (1.8) yrs, 71.6% were human leukocyte antigen B27+, and 80.9% had sacroiliitis on MRI (modified intent-to-treat [mITT] population, N=215). MRI scans from 185 patients (ETN, n=88; PBO, n=97) with BL and 12-wk scans were reviewed. At BL, there were no significant differences in mean SPARCC SSS scores between ETN and PBO (table). From BL to 12 wks, change in mean SPARCC SSS score was significantly greater for ETN than PBO for erosion (-0.57 vs -0.08, respectively, p=0.009) and backfill (0.36 vs 0.06, p=0.021). This treatment difference is also presented in cumulative probability plots (figure).

Conclusion: Treatment with ETN was associated with significantly greater reduction in erosion and increase in backfill at 12 wks vs. PBO, consistent with a very early reparative response to anti-TNF therapy. The impact of this new data on disease progression in SpA should be studied further.

Table. SPARCC SSS scores at baseline, week 12, and change from baseline to week 12

		ETN N=88	PBO N=97	*P*-value* ETN vs PBO Δ BL to week 12
Erosion	Baseline	2.25 (0.33)	1.73 (0.32)	0.009
	Week 12	1.68 (0.25)	1.65 (0.30)	
	Δ BL to week 12	-0.57 (0.16)	-0.08 (0.10)	
Backfill	Baseline	0.76 (0.22)	0.64 (0.20)	0.021
	Week 12	1.13 (0.29)	0.70 (0.23)	
	Δ BL to week 12	0.36 (0.12)	0.06 (0.06)	
Fat Metaplasia	Baseline	0.50 (0.19)	0.27 (0.09)	ns
	Week 12	0.56 (0.22)	0.32 (0.10)	
	Δ BL to week 12	0.06 (0.07)	0.05 (0.05)	
Ankylosis	Baseline	0.15 (0.10)	0.13 (0.11)	ns
	Week 12	0.15 (0.11)	0.13 (0.11)	
	Δ BL to week 12	0.01 (0.01)	0.01 (0.01)	

Values are mean (standard error). Observed case analysis, mITT population.

*2-sample t-test.

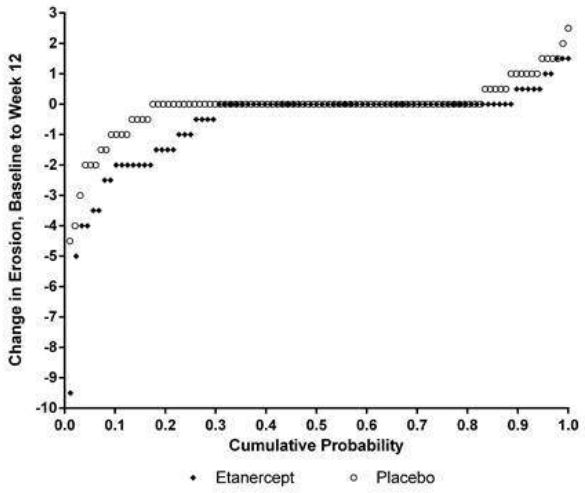
BL SPARCC SSS scores did not differ significantly between ETN and PBO.

Treatment differences in Δ BL to week 12 for erosion and backfill remained significant after adjusting for BL SPARCC SSS scores using analysis of covariance models.

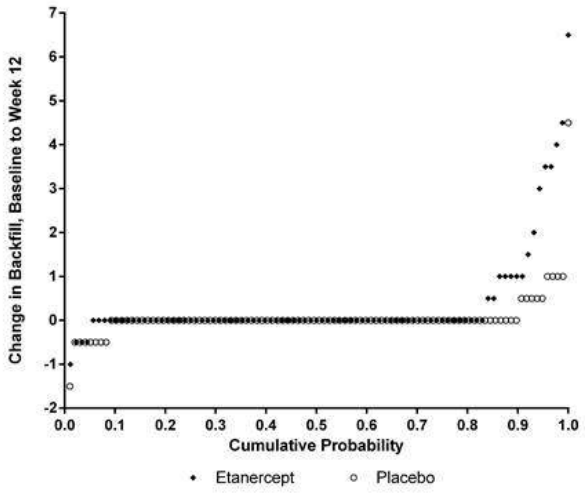
Δ, change; ns, non-significant.

Figure. Cumulative probability of change from baseline to week 12 in the etanercept and placebo groups for (A) erosion and (B) backfill.

A.



B.



Disclosure: W. Maksymowych, Abbvie, 5,Amgen, 5,Eli Lilly and Company, 5,Janssen Pharmaceutica Product, L.P., 5,Pfizer Inc, 5,UCB, 5,Abbvie, 2,Boehringer Ingelheim, 5; **S. Wichuk**, None; **M. Dougados**, Pfizer Inc, 5,UCB, 5,AbbVie, 5,Merck Pharmaceuticals, 5; **H. Jones**, Pfizer, Inc, 3,Pfizer, Inc, 1; **A. Szumski**, InVentiv Health, 3; **L. Marshall**, Pfizer Inc, 1,Pfizer Inc, 3; **J. F. Bukowski**, Pfizer Inc, 3; **R. G. Lambert**, None.

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Abstract Number: 2026

A Novel Technique for Quantifying Synovial Enhancement of Temporomandibular Joints from Mris of Patients with Juvenile Idiopathic Arthritis

Cory M. Resnick[1], **Pouya Vakilian**[2], Micheal Breen[3], David Zurakowski[4], Zachary S. Peacock[5] and Leonard B. Kaban[5], [1]Plastics and Oral Surgery, Boston Children's Hospital, boston, MA, [2]Harvard School of Dental Medicine, Boston, MA, [3]Radiology, Boston Children's Hospital, Boston, MA, [4]Departments of Anesthesia and Surgery, Boston Children's Hospital, Boston, MA, [5]Oral and Maxillofacial Surgery, Massachusetts General Hospital, Boston, MA

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Session Time: 2:30PM-4:00PM

Background/Purpose:

Juvenile Idiopathic Arthritis (JIA) commonly affects the temporomandibular joints (TMJ) and may cause growth disturbance, functional limitation and facial deformity. Early diagnosis and management may minimize these complications. History and clinical examination is of limited value in diagnosing TMJ arthritis. Magnetic resonance imaging with gadolinium is the most sensitive and specific diagnostic tool. Most centers provide only qualitative assessment of TMJ synovitis. The purpose of this study was to develop a technique to quantify synovial enhancement and to apply this to MRIs of TMJs affected by JIA and controls in order to establish a disease threshold, sensitivity and specificity for synovial enhancement.

Methods:

This is a case-control study of children (<16 years) who had MRIs with gadolinium that included the TMJs at Boston Children's Hospital or Massachusetts General Hospital from 2006-2015. Subjects were included in the 'JIA group' if they had a pre-existing diagnosis of JIA and had a subjective assessment of synovitis by the reading radiologist. The 'control group' included subjects without JIA who had an MRI for other reasons (e.g. hearing loss or visual disturbance). Coronal slices of a T1-weighted, gadolinium-enhanced MRI were used to assess the ratio of signal intensity of a $0.2mm^2$ region of interest (ROI) within the TM joint spaces to a $50mm^2$ ROI within the longus-capitus muscle, which controls for time after gadolinium infusion. Two raters carried out independent evaluations. A receiver operating characteristic (ROC) curve was created to determine the sensitivity and specificity of the ratios of enhancement **(Figure 1)**. Independent 2-sample *t* test (2-tailed) was performed for each group with unequal variance assumed. Statistical significance was set at $p<0.05$. Intra and inter-rater reliability was assessed using Intra-class Correlation Coefficient (ICC).

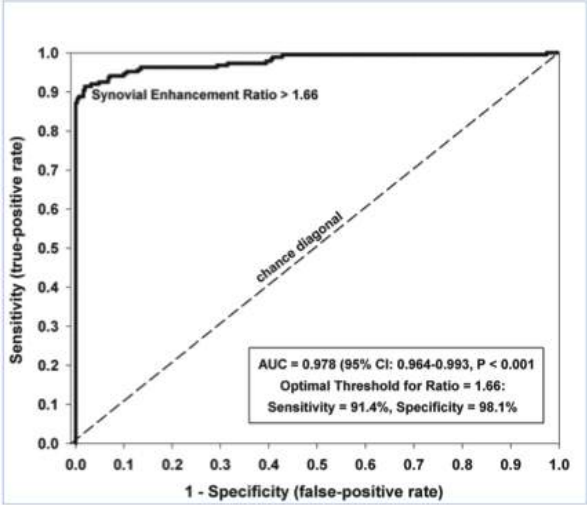
Results:

68 subjects (79% female, mean age 15.3 ± 2.5 yrs) with 112 MRIs with clear visualization of 187 TMJs were included in the JIA group. The control group consisted of 141 subjects (56% female, mean age 11.6 ± 3.5 yrs) with 159 MRIs with clear visualization of 311 TMJs. The mean signal intensity ratio in the JIA group was 3.03 ± 1.4 compared to 1.23 ± 0.16 in the control group ($p<0.001$). The resulting ICC was >0.8 indicating that raters had a high degree of agreement. The ROC analysis indicated a sensitivity of 91.4% and specificity of 98.1% in detecting synovitis with a signal intensity ratio cutoff of 1.66. The area under the curve was 0.978 (95% CI 0.964-0.993, $p<0.001$), and the maximum Youden J-index was 0.98.

Conclusion:

In conclusion, we present a reliable method to quantify TMJ synovial enhancement in MRIs with gadolinium that controls for time after contrast infusion. A signal intensity ratio of 1.66 discriminates TMJs affected by JIA from unaffected controls with a sensitivity of 91.4% and specificity of 98.1%.

Figure 1: Receiver operating characteristic curve showing the sensitivity and specificity of the ratios of enhancement.



Disclosure: C. M. Resnick, None; **P. Vakilian**, None; **M. Breen**, None; **D. Zurakowski**, None; **Z. S. Peacock**, None; **L. B. Kaban**, None.

Abstract Number: 2027

Development of a Dual Energy Computed Tomography Scoring System for Measurement of Urate Deposition in Gout

Sara Bayat[1], Opetaia Aati[2], Juergen Rech[1], Alexander Cavallaro[3], Michael Lell[3], Elizabeth Araujo[4], Christina Petsch[4], Lisa K. Stamp[5], Georg A. Schett[6], Bernhard Manger[1] and Nicola Dalbeth[2], [1]Department of Internal Medicine 3, Rheumatology & Immunology, University of Erlangen-Nuremberg, Erlangen, Germany, [2]Department of Medicine, University of Auckland, Auckland, New Zealand, [3]Department of Radiology, University of Erlangen-Nuremberg, Department of Radiology, Erlangen, Germany, [4]Medical Department 3, Rheumatology and Immunology, University of Erlangen-Nuremberg, Erlangen, Germany, [5]Medicine, University of Otago, Christchurch, Christchurch, New Zealand, [6]University of Erlangen-Nuremberg, Erlangen, Germany

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Development of a Dual Energy Computed Tomography Scoring System for Measurement of Urate Deposition in Gout

Background/Purpose: Dual energy computed tomography (DECT) can visualize urate crystal deposits in patients with gout and has a potential role as an outcome measure in gout studies. Although automated software is available for urate volume assessment, this method is time-consuming, due to the need to identify regions of interest and exclude areas of artefact. The aim of this study was to develop a semi-quantitative DECT scoring system for measurement of urate deposition in gout.

Methods: Following a structured review of images, a semi-quantitative DECT urate scoring method for foot/ankle scans was developed for testing. This method included four regions, each scored from 0-3, with a maximum total DECT urate score of 12. DECT scans from 224 patients (182 with gout, 42 without gout) were scored by two independent readers. Automated urate

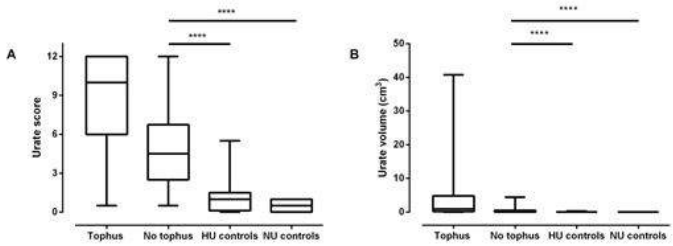
volumes were also measured. Paired scans from eight patients receiving pegloticase were analysed. A timing exercise was undertaken. The properties of the DECT urate score were analysed according to the Outcomes in Rheumatology Clinical Trials (OMERACT) filter.

Results: The inter-reader intraclass correlation coefficient (95%CI) for the DECT urate score was 0.98 (0.97-0.98). All scored regions contributed to the total DECT urate score. DECT urate scores and urate volumes were highly correlated (r=0.91, p<0.0001). Both DECT urate scores and urate volumes discriminated between gout and non-gout control participants, and between the tophaceous gout, non-tophaceous gout and control groups (Figure). Compared with urate volume, the DECT urate score had greater ability to discriminate between responders and non-responders to pegloticase therapy (p<0.001 for DECT urate score and >0.05 for urate volume). The mean (SD) time required for the DECT urate score was 121 (2) seconds and for urate volume was 240 (2) seconds ($p=2x10^{-31}$).

Conclusion: We have developed a novel semi-quantitative DECT scoring method for measurement of urate deposition. This method fulfils many aspects of the OMERACT filter.

Figure: Box and whisker plot showing discrimination between groups.

A. DECT urate scores and B. urate volumes for the following groups: tophaceous gout (tophus, n=89), non-tophaceous gout (no tophus, n=93), hyperuricaemic (HU) controls (n=28) and normouricaemic (NU) controls (n=14). Kruskall-Wallis p<0.0001 for both methods, ****Dunn's multiple comparisons test p<0.0001.



Disclosure: **S. Bayat**, None; **O. Aati**, None; **J. Rech**, None; **A. Cavallaro**, None; **M. Lell**, None; **E. Araujo**, None; **C. Petsch**, None; **L. K. Stamp**, None; **G. A. Schett**, None; **B. Manger**, None; **N. Dalbeth**, None.

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Abstract Number: 2028

Contribution of 18f-Fluoro-Dexoxyglucose Positron Emission Tomography for the Diagnosis of Polymyalgia Rheumatica: A Controlled Study

Maxime Sondag[1], Xavier Guillot[2], Frank Verhoeven[2], Clément Prati[3], Hatem Boulahdour[4] and **Daniel Wendling**[5], [1]Rheumatology, University Teaching Hospital, Besançon, France, [2]Service de Rhumatologie, CHRU J Minjoz, Besançon, France, [3]Service de Rhumatologie, CHU J Minjoz, Besancon, France, [4]Nuclear Medicine, University Teaching Hospital, Besançon, France, [5]Université de Franche-Comté, Besançon, France

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Background/Purpose:

Polymyalgia rheumatica (PMR) is a frequent inflammatory condition in elderly people. The place of imaging becomes important for positive and differential diagnosis like malignancy but there is no gold standard. We compared ^{18}f-Fluoro-Dexoxyglucose Positron Emission Tomography (FDG-PET/CT) findings in patients with PMR and controls without rheumatologic disease.

Methods:

Forty-six patients with a diagnosis of PMR, according to 2012 ACR/ EULAR criteria, who have had a FDG-PET/CT have been included. For comparison, fifty-tree patients who have had a FDG-PET/CT for initial staging or follow-up of neoplasm were included as controls. 17 sites where analyzed on PET: 2 shoulders, 2 acromio-clavicular and 2 sterno-clavicular joints, 2 greater trochanters, 2 hips, 2 ischial tuberosities, 2 iliopectinal bursitis, 2 pubic symphysis enthesis and only the interspinous space with the most FDG uptake. We used the semi-quantitative scoring system, by Goerres and al. to evaluate visually FDG uptake (0 to 3 compared to liver uptake) into these sites. We calculated the FDG uptake score corresponding to the mean of intensity over all sites, and the number of sites with significant uptake (FDG uptake 2 or 3) for each patient.

Results:

The two groups were comparable for the median patient age (68,9

for PMR vs. 68,1 years for controls). The characteristics of the patients of PMR group were 55% women, CRP 40,9mg/L, ESR 41,1mm, and an ACR/EULAR score without ultrasound of 4.78/6. Significant differences between the two groups were found for FDG uptake score and for number of sites with significant uptake (Table 1): 1.09 vs. 0.34, and 6.13 sites vs. 1.49 sites, p<0.0001.

With ROC curves analysis, we show that the presence of 3 or more sites with significant uptake is correlated with the diagnosis of PMR with 72% sensibility, 79% specificity [OR = 9.69]. For the FDG uptake score the cut off is 0.53 [Se 76%, Sp 79%; OR 12.1].

We found significant differences in all sites analyzed separately for FDG uptake score and number of sites with significant uptake compared to controls, particularly marked for shoulders, ischial tuberosities and interspinous bursitis (p<0.00001 for FDG uptake score).

Table 1.

	FDG uptake score (0 – 3)	Number of sites with significant uptake (0 – 17)
PMR group (N=46)	1.09 [%CI 1.06-1.11]	6.13 [%CI 4.99-7.26]
Control group (N=53)	0.34 [%CI 0.33-034]	1.49 [%CI 1.38-1.59]
p	p<0.0001	p<0.0001

Conclusion:

FDG-PET/CT for PMR diagnosis is useful: we found significant uptake in articular and peri-articular sites compared to controls particularly shoulders, ischial tuberosities and interspinous space. We propose the number of 3 sites with significant uptake and a FDG uptake score over 0.53 as cut-offs for the diagnosis of PMR.

Disclosure: M. Sondag, None; **X. Guillot**, None; **F. Verhoeven**, None; **C. Prati**, None; **H. Boulahdour**, None; **D. Wendling**, None.

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Abstract Number: 2029

Fever of Unknown Origin (FUO) and Inflammation of Unknown Origin (IUO): Is 18f-FDG-PET/CT a Useful First Line Diagnostic Strategy?

Verena Schönau[1], Kristin Vogel[2], Matthias Englbrecht[3], Bernhard Manger[3], Daniela Schmidt[4], Torsten Kuwert[4] and Georg Schett[2], [1]Department of Rheumatology and Immunology, University of Erlangen-Nuremberg, Erlangen, Germany, [2]Department of Internal Medicine 3 and Institute for Clinical Immunology, University of Erlangen-Nuremberg, Erlangen, Germany, [3]Department of Internal Medicine 3, Rheumatology & Immunology, University of Erlangen-Nuremberg, Erlangen, Germany, [4]Clinic of Nuclear Medicine, University of Erlangen-Nuremberg, Erlangen, Germany

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SESSION INFORMATION

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Session Title: Imaging of Rheumatic Diseases II: MRI, PET and CT

Session Type: ACR Concurrent Abstract Session

Session Time: 2:30PM-4:00PM

Background/Purpose:

FUO and IUO are rare but diagnostically challenging clinical problems. Because of the abundance of differential diagnoses, a generally accepted diagnostic guideline has not yet been established. Besides a thorough medical history, physical examination, and laboratory testing, imaging techniques are important tools in the diagnostic workup of FUO and IUO. In the last few years, ^{18}F-FDG-PET/CT has been found to be a suitable diagnostic tool for FUO/IUO, as it is able to detect inflammatory and malignant processes with a high spatial resolution.

Methods:

All patients presenting with FUO or IUO at the University Clinic of Erlangen between 2007 and 2014 were clinically documented and subjected to ^{18}F-FDG-PET/CT scanning with a Siemens Biograph™ TruePoint™ PET/CT. Images were evaluated by specialists at the Departments of Nuclear Medicine and Radiology of the University Clinic of Erlangen. Final diagnosis as documented in the patients´ electronic charts was recorded. ^{18}F-FDG-PET/CT scans were considered positive when a focal uptake of the tracer was detected additionally to the standard areas of physiological tracer uptake. ^{18}F-FDG-PET/CT results were compared to the final diagnosis and classified as helpful or non-helpful in establishing the final diagnosis. Multivariate logistic regression was used to identify clinical parameters that correlated with a helpful ^{18}F-FDG-PET/CT in patients with and without FUO as well as in patients with and without IUO.

Results:

Of the 236 patients enrolled 72 presented with FUO, 139 with IUO and 25 did not fulfill FUO or IUO criteria. 232 patients were included in the multivariate logistic regression model. Final diagnosis was established in 185 patients (78.4%, Table 1). In 123 (52.1% of all patients; 66.5% of diagnosed patients), the ^{18}F-FDG-PET/CT was helpful in finding the diagnosis. The chance was higher in patients without fever (OR=0.252; p=0.001), those aged >50 years (p=0.016; p=0.005, respectively) and those with a CRP level >30 mg/dl (p=0.007; p=0.003, respectively) .

Conclusion:

Our study shows that if the standard diagnostic tests (laboratory, chest x-ray and abdominal ultrasound) did not identify the cause of FUO/IUO, ^{18}F-FDG-PET/CT scanning should be applied in the early stage of the diagnostic process. An early use of a ^{18}F-FDG-PET/CT is especially helpful to establish a final diagnosis in patients with an elevated C-reactive protein and age over 50 years.

Category	N (%) FUO patients in category	N (%) IUO patients in category	N (%) non-FUO/IUO patients in category
Infection	11 (15.3%)	17 (12.2%)	0 (0%)
Malignancy	5 (6.9%)	11 (7.9%)	2 (8.0%)
Chronic inflammatory	35 (48.6%)	86 (61.9%)	10 (40.0%)
diseases	5 (6.9%)	29 (20.9%)	1 (4%)
1. Large vessel vasculitis	4 (5.6%)	25 (18%)	0 (0%)
2. Polymyalgia rheumatica	11 (15.3%)	0 (0%)	0 (0%)
3. Still's disease	1 (1.4%)	4 (2.9%)	4 (16%)
4. IgG4-related disease	14 (19.4%)	28 (20.1%)	5 (20%)
5. Others			
Miscellaneous	1 (1.4%)	2 (1.4%)	6 (24.0%)
No Diagnosis	20 (27.8%)	23 (16.5%)	7 (28.0%)
Total	72 (100%)	139 (100%)	25 (100%)

Disclosure: V. Schönau, None; **K. Vogel**, None; **M. Englbrecht**, None; **B. Manger**, None; **D. Schmidt**, None; **T. Kuwert**, None; **G. Schett**, None.

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Abstract Number: 2030

MRI Changes Associated with Neurological Compromise in Acute Pyogenic Vertebral Osteomyelitis: A Retrospective Study of 121 Patients

Géraldine Bart[1], Herve Redon[2], David Boutoille[3], Olivier Hamel[4], Yves Maugars[1] and Benoit Le Goff[1], [1]Rheumatology, Nantes University Hospital, Nantes, France, [2]Nouvelles cliniques nantaises, Nantes, France, [3]Infectious diseases, Nantes University Hospital, Nantes, France, [4]Neurosurgery, Nantes University Hospital, Nantes, France

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Background/Purpose:

Vertebral osteomyelitis is a rare but potentially severe disease: previous works have estimated that neurological complications occurred in up to 59% cases. However, these works were mainly surgical studies, so neurological complications might have been overestimated.

The aim of our study was to evaluate the frequency of neurological deficit (motor deficit: ASIA grade A to D and/or sphincter dysfunction) in a non-selected population of patients with pyogenic vertebral osteomyelitis and to find clinical and MRI signs associated with these complications.

Methods:

We reviewed medical charts of all patients with spondylodiscitis from 2007 to 2014 in a University Hospital and we included patients aged 18 years or older with infectious spondylodiscitis confirmed by MRI and with an identification of the causative agent or a good response to antibiotic therapy if all microbiological samples were sterile.

Results:

One hundred and twenty one patients were included. Mean age was 64.3 +/-15.6 years, mostly men (68.6%, n=83). Median duration of clinical signs before diagnosis on MRI was 21.5 days. Lombo-sacral spine was the most frequently affected (38%, n=46), followed by thoracic (23.1%, n=28), and cervical spine (19%, n=23). The 24 remaining patients (19.8%) had multifocal lesions. Overall, we found that 21.5% (n=26) of the patients had a neurological compromise and 14% (n=17) had surgical therapy for spinal or root nerve decompression. Neurological deficit was present at the time of admission for 14 patients and occurred during antibiotic course for 12 patients, on average 13 days after diagnosis (1-39 days). On MRI, 75.2% of patients (n=91) had an epidural inflammation 39.7% (n=48) had an epidural abscess. Clinical findings associated with motor deficit were: bacteriemiae (OR 3.36, p=0.04), acute onset of symptoms (<7 days) (OR 8.73, p=0.004). We found that several MRI patterns were associated with the presence of a neurological deficit: Cervical spine lesions (OR 3.36, p=0.011), dural compression (OR 5.22, p=0.0012), cerebro-spinal fluid interruption (OR 5.59 p<0,001), signal changes of the spinal cord (OR 6.82, p=0,006). Destruction of more than 50% of the sus-jacent vertebrae volume, kyphosis and erosions of the posterior column were also associated with higher risk of motor deficit: OR 8.45, p=0.017, OR 4.01, p=0.016 and OR 5.58, p=0.032, respectively. Finally, neither epidural phlegmon nor epidural abscesses, multifocal lesions, loss of disk height, nor roots nerve compression were associated with a higher risk of neurological deficit.

Conclusion:

Severe neurological deficit occurred in 1/5 of our patients. Patients with a cervical involvement, major vertebrae destruction and static troubles such as kyphosis, dural compression, cerebro-spinal fluid interruption and signal changes of the spinal cord on MRI were at risk of neurological deficit. In contrast, epidural abscesses or nerve roots compression were not significantly associated with such complications.

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Abstract Number: 2031

Tuberculosis in Patients Treated with Biological Drugs

Nadia Benzaquén[1], Maria Haye Salinas[2], Juan Pablo Pirola[3], Laura mariela Encinas[4], Francisco Caeiro[4], Alejandro J. Alvarellos[2], Maria Celina de la Vega Sr.[5], Gustavo Casado[6], Gimena Gomez Sr.[7], Gustavo Citera[8], Maria de los Angeles Gallardo[9], Ana Quinteros[10], Ida Elena Exeni[11], María Alejandra Medina[12], Pablo Astesana[13], Carolina Sanchez Andia[14], Graciela Gómez[15], Amelia Granel[16], Diana Dubinsky[17,18], Ana Capuccio[19,20], Alicia Eimon[7], R. Quintana[21], Bernardo Pons-Estel[22], Eduardo Mussano[23], Santiago Scarafia[24], Mercedes Argentina García[25], Mercedes De La Sota[26], Karin Kirmayr[27], Edson Javier Velozo[28], Sergio Paira[29], Ana M. Bertoli[30], Cesar Caprarulo[31], Santiago Aguero[32], Cristina Battagliotti[33], Sidney Soares de Souza[34,35], Emilia Cavillion[36], A. Perez Davila[37], J. C. Barreira[38], Maria Larroude[39,40], Francisco Tamaño[41], Alejandra Peluzzoni[42] and Veronica Saurit[4], [1]Reumatología, Hospital Privado Centro Médico de Córdoba, Córdoba, Argentina, [2]Rheumatology, Hospital Privado de Córdoba, Córdoba, Argentina, [3]Servicio de Reumatología, Hospital Privado Centro Médico de Córdoba, Córdoba, Argentina, [4]Reumatología, Hospital Privado de Córdoba, Córdoba, Argentina, [5]Hospital Argerich, Buenos Aires, Argentina, [6]Hospital Militar Central, Buenos Aires, Argentina, [7]CEMIC, Buenos Aires, Argentina, [8]Rheumatology, Consultorios Reumatológicos Pampa, Buenos Aires, Argentina, [9]Rheumatology Unit, Internal Medicine Service, Hospital Italiano de Buenos Aires, Instituto Universitario Hospital Italiano de Buenos Aires, and Fundacion PM Catoggio, Buenos Aires, Argentina, [10]Centro Integral De Reumatologia, Tucumán, Argentina, [11]BALCARCE 462 12F, SANATORIO PARQUE CORDOBA, CORDOBA, Argentina, [12]Hospital General de Agudos, Ciudad Autónoma de Buenos Aires, Argentina, [13]Internal Medicine, Unit of Rheumatology, Córdoba, Argentina, [14]Hospital Penna, CABA, Argentina, [15]Rheumatology, Instituto de Investigaciones Medicas Alfredo Lanari, Buenos Aires, Argentina, [16]CALLE 4 no 214, Hospital San Roque De Gonnet, Buenos

Aires, Argentina, [17]Hospital de Clinicas, CABA, Argentina, [18]Hospital de Clínicas, Jose de San Martin, Buenos Aires, Argentina, [19]Rheumatology, Hospital cesar Milstein, Buenos Aires, Argentina, [20]Hospital Cesar Milstein, CABA, Argentina, [21]Hospital Provincial, Rosario, Argentina, [22]Sanatorio Parque, Rosario, Argentina, [23]Córdoba, Servicio de Reumatología. Hospital Nacional de Clínicas. Facultad de Ciencias Médicas. Universidad Nacional de Córdoba, Córdoba, Argentina, [24]Rheumatology, Hospital Bernardino Rivadavia, Buenos Aires, Argentina, [25]Rheumatology Unit, HIGA San Martín, La Plata, Argentina, [26]Reumatología, Bahia Blanca, Argentina, [27]Centro Bariloche, Río Negro, Argentina, [28]Rheumatology, Sanatorio Adventista del Plata, Entre Rios, Argentina, [29]Hospital Jose Maria Cullen, Santa Fe, Argentina, [30]Reumatología, Clínica Universitaria Reina Fabiola, Córdoba, Argentina, [31]Reumatologia, French Hospital, Buenos Aires, Argentina, [32]Sanatorio Pasteur, Catamarca, Argentina, [33]Hospital de Niños Dr Orlando Alasia, Santa Fé, Argentina, [34]REUMAR, Buenos Aires, Argentina, [35]Ramallo 1851, Reumatología, Buenos Aires, Argentina, [36]Consultorio, Cordoba, Argentina, [37]Rheumatology, Hospital Manuel Rocca, Ciudad Autonoma de Buenos Aires, Argentina, [38]Rheumatology, Buenos Aires British Hospital, Buenos Aires, Argentina, [39]Tiempo, CABA, Argentina, [40]Consultorio, Buenos Aires, Argentina, [41]Reumatología, Atención Integral de Reumatología:, Capital Federal, Argentina, [42]Hospital Clínica José de San Martín, CABA, Argentina
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SESSION INFORMATION

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Session Time: 2:30PM-4:00PM

Background/Purpose:

Opportunistic infections are a major risk in with biological drugs therapy, being tuberculosis (TB) one of the most relevant.

Objectives: evaluate the frequency of the TB infections in patients from a national rheumatic disease database treated with biological drugs (BD)

Methods:

Patients included belong to BIOBADASAR, a database of rheumatic disease patients treated with BD in Argentina, created in 2010; this database includes patients diagnosed according with accepted criteria , treated with BD, and controls matched for diagnosis age and sex, not treated with BD.

Demographic, clinical and treatment characteristics were evaluated

The continuous variables are expressed as mean (M), average (m) and standard deviations (SD), inter Quartil range (IQR) or frequency as appropriate. An analysis of logistical regression was made to determine odds ratio (OR) and 95% confidence intervals (CI95%).

Results:

As of march 2015**,** 2928 patients were evaluated, 1709 (58.4%) had treatment with BD, and 1219 (41,6%) matched controls

Diagnoses were: Rheumatoid Arthritis (RA) 2315 (79.1%), Psoriatic Arthritis (PsA) 234 (8 %) and lupus 108 (3.7 %). Women (79.1 %), age 42.9±16.2.

BD include: anti TNF 1770, Abatacept 239, Rituximab 199, Tocilizumab 107, Tofacitinib 32, Belimumab 19, Ustekinumab 2, Anakinra 1; received more than one BD 355 (20.7%).

Of the 2928 patients, 13 (0.04%) had a TB diagnosed according to accepted criteria; 11(0.64%) were treated with BD, other 2 (0.16%) patients belonged to the non biologic treatment group; 12 (92,5%) of the TB patients had RA and 1 (7.7%) PsA

In 1701 patients (58.1%) PPD was performed, 119 (6,9 %) were positive > 5 mm, 93 (68.1%) treated with BD, one later developed TB

In 2100 patients, 71.7% chest x ray was performed with 31 (1.5%) showing pulmonary infiltrates, 25 (80.6%) treated with BD, none developed TB

Pulmonary TB was diagnosed in 11 (84.6%) patients. 2 (15.3%) had extra pulmonary disease; 12 patients (92.3 %) had full recovery one continues on therapy.

Time elapsed from onset of BD treatment until TB diagnosis was 12, RIQ 6-104 months.

Table 1: Tuberculosis risk according to treatment. Analysis of logistic regression

	p	OR	CI 95%
non-biological	0.13	Reference	Reference
Etanercept	0.25	3,72	0,68-20,38
Adalimumab	1.00	3,20	0,44-22,77
Abatacept	0.05	7,14	1,00-51,0
Infliximab	0.10	7,26	0,65-80,97
Tocilizumab	<0.01	15,65	2,17-12,60

Conclusion:

There was a low frequency of TB, with a significant difference in the biological drug treated group

Most the TB patients had pulmonary disease.

Most TB cases appeared after one year of therapy

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Abstract Number: 2032

Chaperonin Protein 14-3-3eta, Cyclic Citrullinated Peptide Antibody, and Rheumatoid Factor in the Differential Diagnosis of Chikungunya Arthritis Versus Rheumatoid Arthritis

Olga S. Zhukov[1], Rania W. Abolhosn[1], Jonnielyn G. Rivera[1], Mary Lape Nixon[2], Robert J. Lagier[3], Harry E. Prince[4], Hollis J. Batterman[4] and **Stanley J. Naides**[1], [1]Immunology, Quest Diagnostics Nichols Institute, San Juan Capistrano, CA, [2]Lab Sciences, Quest Diagnostics Focus Clinical Reference Laboratory, San Juan Capistrano, CA, [3]Research Support, Alameda, Quest Diagnostics Alameda, Alameda, CA, [4]Lab Services, Quest Diagnostics Focus Clinical Reference Laboratory, San Juan Capistrano, CA

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Session Time: 2:30PM-4:00PM

Background/Purpose: Chikungunya fever virus (CHIK) is emerging in the western hemisphere as a mosquito-borne, acute onset

arthritis. The majority of cases progress to persistent moderate to severe polyarthritis that clinically resembles rheumatoid arthritis (RA).[1] As the majority of CHIK arthritis patients reportedly lack rheumatoid factor (RF) and cyclic citrullinated peptide antibody (CCP), differential diagnosis includes seronegative RA.[2] Extracellular 14-3-3η, a chaperonin, is a novel biomarker for joint damage in rheumatoid arthritis (RA) and erosive psoriatic arthritis, with serum elevation occurring in early RA. We previously demonstrated that 21% of patients with early "seronegative" RA and 67% of patients with established "seronegative" RA are 14-3-3η-positive.[3]In order to determine the utility of RF, CCP, and 14-3-3η in the differential diagnosis of CHIK arthritis versus RA, we tested CHIK infected patient serum for 14-3-3η.

Methods: Serum samples were submitted for CHIK IgM and IgG serology. De-identified remnant samples positive for CHIK IgM were tested for 14-3-3η by a proprietary laboratory-developed sandwich ELISA. Rheumatoid factor (RF) isotypes and cyclic citrullinated peptide antibody (CCP) were determined by ELISA.

Results: Of 234 CHIK IgM-positive sera, 223 were also CHIK IgG-positive (95.3%, CI 91.7% to 97.6%). RF IgM was positive in 51 of the CHIK IgM-positive patients (21.8%, CI 16.7% to 27.6%), RF IgG in 7 (3.0%, CI 1.2% to 6.1%), and RF IgA in 10 (4.3%, CI 2.1% to 7.7%). CCP was positive in only 4 patients (1.7%, CI 0.5% to 4.3%). Two isotypes of RF were present in 7 patients, only one of which was CCP-positive. All 3 RF isotypes were present in 1 patient, but the patient was CCP-negative. At least one isotype of RF was positive in 59 patients (25.2%, CI 19.8% to 31.3%). 14-3-3η was positive in 25 patients (10.7%, CI 7.0% to 15.4%). Of those 25, RF was positive in only 6 (24.0%, CI 9.4% to 45.1%) and CCP was positive in only 2 (8.0%, CI 1.0% to 26.0%).

Conclusion: Nearly all patients were positive for CHIK IgG at the time of diagnosis based on a positive CHIK IgM. At least one RF isotype was present in 25.2% of patients. CCP was uncommon. 14-3-3η was present in only 10.7% in contrast to a 64% positivity rate in early RA patients.[4] Therefore, RF may not be helpful in differentiating early RA from CHIK arthritis. However, CCP and 14-3-3η occur less frequently in CHIK arthritis and when present may aid in the differential diagnosis of RA from CHIK arthritis.

References: 1. Arroyo-Avila, Vilá. *P R Health Sci J*. 34:71-77, 2015; 2. Miner et al. *Arth Rheum* 67:1214-20, 2015; 3. Naides, Marotta. *J Rheum*, in press; 4.. Maksymowych, et al. *J Rheum*. 41:2104-13, 2014.

Disclosure: O. S. Zhukov, Quest Diagnostics, 3; **R. W. Abolhosn**, Quest Diagnostics, 3; **J. G. Rivera**, Quest Diagnostics, 3; **M. Lape Nixon**, Quest Diagnostics, 3; **R. J. Lagier**, Quest Diagnostics, 3; **H. E. Prince**, Quest Diagnostics, 3; **H. J. Batterman**, Quest Diagnostics, 3; **S. J. Naides**, Quest Diagnostics, 3.

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Abstract Number: 2033

Clinical Manifestations Associated with Peripheral Joint Involvement in Patients with Acute Chikungunya Virus Infection

Mariangelí Arroyo-Ávila[1], Amanda Cabán[2], Marisela Irizarry-Pérez[3], Hilda Torres[3], Enid J. García[3], Héctor Gorbea[4] and Luis M. Vilá[1], [1]Department of Medicine, Division of Rheumatology, University of Puerto Rico Medical Sciences Campus, San Juan, PR, [2]Department of Medicine, University of Puerto Rico Medical Sciences Campus, San Juan, PR, [3]School of Medicine, Endowed Health Services Research Center, University of Puerto Rico Medical Sciences Campus, San Juan, PR, [4]Department of Medicine, Division of Infectious Diseases, University of Puerto Rico Medical Sciences Campus, San Juan, PR

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Background/Purpose: Chikungunya virus (CHIKV) infection causes an acute febrile illness usually accompanied by severe polyarthralgia and polyarthritis. Previous studies have shown that older age, female gender and some comorbid conditions are associated with chronic arthritis. However, the factors associated with acute arthralgia or arthritis are not well known. Thus, we studied the clinical manifestations associated with acute peripheral arthralgia/arthritis in a group of CHIKV patients from Puerto Rico.

Methods: As part of an acute febrile illness surveillance project, patients with fever or history of fever for ≤ 7 days evaluated at the emergency room of a community hospital in Puerto Rico were tested for several pathogens including CHIKV. All patients with positive CHIKV testing by either polymerase chain reaction or IgM enzyme-linked immunosorbent assays from June 2014 to September 2014 were studied. Demographic features, clinical manifestations, and comorbidities were determined. Patients with peripheral arthralgia and/or arthritis were compared to those without peripheral joint symptoms. To examine the differences between the study groups we used bivariable and multivariable analyses adjusting for confounding variables.

Results: In total, 172 patients with CHIKV infection were evaluated, of which 52.9% were female. The mean (standard deviation [SD]) age was 21.1 (± 19.3); 65.5% were ≤ 16 years of age, 25.7% were 17–54 years of age, and 8.8% were ≥ 55 years of age. Peripheral arthralgia/arthritis were seen in 156 (90.7%) patients, of whom 49 (31.4%) had signs of synovitis. In the bivariable analysis, patients with CHIKV arthralgias/arthritis were more likely to be older (21.3 [± 19.6] years vs. 8.2 [± 10.3] years, $p < 0.01$) and to have more myalgias (85.9% vs. 50.0%, $p < 0.01$), back pain (63.5% vs. 6.2%, $p < 0.01$), headaches (87.2% vs. 50.0%, $p < 0.01$), orbital pain (47.4% vs. 6.2%, $p < 0.01$), anorexia (71.8% vs. 37.5%, $p < 0.01$), nausea (62.8% vs. 18.8%, $p < 0.01$), and dizziness (48.1% vs. 12.5%, $p < 0.01$) than those without with peripheral joint involvement. No associations were found for gender, rash, pulmonary symptoms, cardiac manifestations, vomiting, diarrhea, abdominal pain, hematologic abnormalities, elevation of liver enzymes, renal manifestations, or comorbidities such as diabetes, hypertension, cardiac disease, asthma, chronic kidney disease and malignancy. The multivariable analysis is shown in the table.

Clinical manifestations associated with acute peripheral arthralgias/arthritis

Clinical features	OR (95% CI)	*p* value
Myalgias	4.65 (1.48 - 14.72)	<0.01
Back pain	16.77 (3.07 - 313.82)	<0.01
Headache	3.63 (1.06 – 12.53)	<0.05
Ocular pain	8.88 (1.65 – 165.19)	<0.05
Anorexia	5.68 (1.87 – 18.97)	<0.01
Nausea	6.88 (2.05 – 31.49)	<0.01
Dizziness	4.07 (0.98 – 27.69)	0.10

Conclusion: In this population of patients with acute CHIKV infection, peripheral joint involvement was associated with myalgias and back pain as well as non musculoskeletal manifestations such as headaches, ocular pain, anorexia and nausea. Clinicians should be aware that this constellation of symptoms is common in these patients.

Disclosure: **M. Arroyo-Ávila**, None; **A. Cabán**, None; **M. Irizarry-Pérez**, None; **H. Torres**, None; **E. J. García**, None; **H. Gorbea**, None; **L. M. Vilá**, None.

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Abstract Number: 2034

Nontuberculous Mycobacterial Diseases Do Not Cause Positive Autoantibody Testing, Results from a Tertiary Pulmonary Care Center

Barbara Goldstein[1], Jeffery J. Swigris[2], Shannon Kasperbauer[1], Pearlanne Zelarney[1] and JoAnn Zell[1], [1]Medicine, National Jewish Health, Denver, CO, [2]National Jewish Health, Denver, CO

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Session Title: Infection-related Rheumatic Disease

Session Type: ACR Concurrent Abstract Session

Session Time: 2:30PM-4:00PM

Background/Purpose: National Jewish Health (NJH) is a tertiary referral center for pulmonary and immunologic disease. The

infectious disease division at NJH specializes in the care of patients with chronic pulmonary infections, especially those with nontuberculous mycobacterial disease (NTM). The NTM patients have bronchiectasis and their sera are sent for autoantibodies to determine if there may be an underlying concomitant rheumatic disease predisposing to infection. It is well known that chronic infectious disease may increase the false positive rate of some immunologic tests. An example is a rheumatoid factor found in tuberculosis and/or hepatitis C. We chose to retrospectively analyze patients with NTM and autoantibodies to determine if these laboratory tests were more frequently positive in the absence of defined rheumatologic illness.

Methods: We queried our electronic medical record from February 2008 through May of 2015. We defined NTM cases as those with positive cultures at our institution or an appropriate ICD-9 code within the medical record. Patients with defined autoimmune disease (ICD- 9 codes with 710 or 714) and tuberculosis were excluded from our entire analysis. Antinuclear antibody (ANA), rheumatoid factor (RF), cyclic citrullinated peptide (CCP), SSA and SSB results were tabulated. We used a Chi-squared analysis to determine if these autoantibodies were more likely to return as positive in the NTM patients when compared with our overall patient population.

Results: During the study period, 3,721 cases of NTM were seen at NJH and 65% had at least one autoantibody resulted. RF, CCP and ANA testing were not more likely to return as positive in the setting of NTM. Furthermore, non-NTM cases within NJH were more likely to have a positive SSA or SSB antibody (OR 0.53, χ^2 19.1 with 1DF, p 0.0001 or OR 0.41, χ^2 10.0 with IDF, p 0.0015 see Table 1).

Conclusion: Patients with NTM were not more likely to have a positive ANA, RF, CCP as compared to the overall population. Additionally, the SSA and SSB were less likely to be positive in patients with NTM. This may indicate that NTM does not cause false positive results as is seen in diseases like tuberculosis. Therefore, in this setting, positive autoantibodies could indicate the presence of occult autoimmune disease.

Autoantibody	NTM+	NTM-	
RF+	822	3747	OR 1.01
RF-	1297	5971	
			χ^2 0.04 with 1DF
			p 0.84
CCP+	38	593	OR 1.32
CCP-	369	7576	
			χ^2 0.025 with 1DF
			p 0.12
ANA+	702	4478	OR 1.00
ANA-	1510	9602	
			χ^2 0.004 with 1DF
			p 0.95
SSA+	54	346	OR 0.53
SSA-	2001	6767	
			χ^2 19.1 with 1DF
			p 0.0001
SSB+	13	109	OR 0.41
SSB-	2040	6934	
			χ^2 10.0 with 1DF
			p 0.0015

Figure 1: 2 x 2 contingency tables representing individual patients and autoantibody results (excluding patients with defined autoimmune disease), odds ratios (OR), Chi-squared test (χ^2), and p values

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Abstract Number: 2035

Clinical Characteristics and Outcomes of Polyarticular Septic Arthritis

Sarah B. Lieber[1], Clara Zhu[2], Andrew Moore[3], Mary Louise Fowler[4], Robert H. Shmerling[5] and Ziv Paz[1], [1]Beth Israel Deaconess Medical Center, Boston, MA, [2]Medical School, Boston University School of Medicine, Boston, MA, [3]Medicine, Cambridge Health Alliance, Harvard Medical School, Cambridge, MA, [4]School of Medicine, Boston University School of Medicine, Boston, MA, [5]Medicine, Beth Israel Deaconess Medical Center, Boston, MA
First publication: September 29, 2015

SESSION INFORMATION
Session Date: Monday, November 9, 2015
Session Title: Infection-related Rheumatic Disease
Session Type: ACR Concurrent Abstract Session
Session Time: 2:30PM-4:00PM

Background/Purpose:

Polyarticular septic arthritis (polySA) is rare, but clinically important, with reported mortality rates approaching 30% even with appropriate therapy. Little is known regarding how patients with polySA differ from those with monoarticular septic arthritis (mSA). In addition, there is little known regarding outcomes of patients with polySA who have surgery compared with those who do not. We describe one of the largest cohorts of patients with culture-proven polySA with the aim of characterizing differences in clinical features and outcomes between those with polySA and mSA and between those with polySA treated conservatively or with surgery.

Methods:

We conducted a retrospective study of patients 18 years and older admitted to a single tertiary care center from 1998 to 2015 with culture-positive polySA. Only patients for whom synovial fluid cultures were available for each affected joint were included. Patients with polySA were stratified into operatively managed and conservatively managed groups and compared in aggregate to those with mSA. Microbial profiles, predisposing factors, sites of joint involvement, length of hospital stay (LOS), and 60-day readmission rates were determined.

Results:

Of 41 patients with polySA, 35 received surgical intervention. The most common organisms isolated from synovial fluid were methicillin-sensitive Staph aureus, group B Strep, and methicillin-resistant Staph aureus. The knee was most frequently involved (n = 27), followed by the shoulder (n = 12), wrist (n = 10), hip (n = 8) and elbow (n = 5). Patients with polySA managed surgically had a higher mean ESR ($p < 0.01$), CRP ($p = 0.02$), and synovial polymorphonuclear (PMN) leukocyte % ($p = 0.01$) and a longer mean LOS (18.1 vs. 4.7 days; $p = 0.04$), and a higher rate of discharge to a rehabilitation facility ($p < 0.01$) than their conservatively managed peers. Compared to those with mSA, patients with polySA were more likely to have rheumatoid arthritis ($p = 0.02$), malignancy ($p = 0.02$), or immunosuppression ($p = 0.05$) and had a higher mean peripheral white blood cell (WBC) count ($p < 0.01$), CRP ($p = 0.05$), and frequency of associated sepsis ($p = 0.01$). While rates of surgery were similar between the polySA and mSA groups, those with polySA required more repeat surgeries during the same admission ($p < 0.01$).

Conclusion:

In this large, retrospective cohort, patients with polySA were more medically complex and more likely to have systemic infection at presentation than those with mSA, but ultimately experienced similar outcomes, with the exception of requiring repeat surgery more often. Increased markers of systemic and synovial inflammation were found in patients with polySA managed surgically as compared to their conservatively managed peers. Future research should identify whether the observed differences between patients with polySA and mSA and between surgically or medically managed patients with polySA can be used to guide optimal management.

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polyarticular-septic-arthritis

Abstract Number: 2036

Infliximab Versus Adalimumab in Severe Uveitis: Multicenter Study from the French Uveitis Network

Hélène Vallet[1], Pascal Sève[2], Lucie Biard[3], Elodie Feurer[4], Sophie Rivière[5], Philip Bielfeld[6], Laurent Perard[7], Boris Bienvenu[8], Sébastien Abad[9], Aude Rigolet[10], Alban Deroux[11], Antoinette Perlat[12], Damien Sène[13], Isabelle Marie[14], Emmanuel Heron[15], Eric Hachulla[16], Olivier Fain[17], Gaëlle Clavel[18], Jean Sibilia[19], Nathalie Tieulié[20], Yoland Schoindre[21], Jean Baptiste Fraison[22], Guillaume Moulis[23], Thomas Papo[24], Gilles Blaison[25], Julie Gueudry[26], Olivier Lidove[27], Phuc LE Hoang[28], Catherine Chapelon[29], Mathieu Resche Regon[30], Patrice Cacoub[13], Bahram Bodaghi[28] and David Saadoun[31], [1]Internal medicine, DHU 2iB Internal Medicine Referal Center for Autoimmune diseases Pitie Hospital, Paris, France, [2]Internal medicine, CHU Lyon, Lyon, France, [3]Biostatistics, Saint-Louis Hospital, Paris, France, [4]Internal Medicine, Hôpital de la Croix Rousse, Lyon, France, [5]service de médecine interne A,, CHU de Montpellier, Montpellier Cedex 5, France, [6]CHU de Dijon, Dijon, France, [7]Hôpital Edouard Herriot, Lyon, France, [8]Internal Medicine, Hospital Caen, Caen, France, [9]Hôpital Avicenne, Bobigny, France, [10]Médecine Interne 1, Hôpital Pitié-Salpêtrière, Paris, France, [11]Internal Medicine, CHU Grenoble, Grenoble, France, [12]Internal medicine, CHU de Rennes, Rennes, France, [13]Department of Internal Medicine, Pitié-Salpêtrière Hospital, Paris, France, [14]Service de médecine interne, CHU de Rouen, Rouen, France., Rouen, France, [15]Internal medicine, Hôpital des XV-XX, Paris, France, [16]CHU Lille, Lille, France, [17]Internal Medicine, Hospital J. Verdier, Bondy, France, [18]Rheumatology, Fondation Rothschild, Paris, France, [19]Rheumatology, Hôpital de Hautepierre, Strasbourg, France, [20]CHU Nice, Nice, France, [21]Department de Internal Medicine and Clinical Immunology, Hôpital Pitié-Salpêtrière, AP-PH, UPMC, Paris, France, [22]Hôpital Jean Verdier, Bondy, France, [23]CHU Purpan, Toulouse, France, [24]CHU Bichat, Paris, France, [25]Internal Medicine, Hopital de Colmar, Colmar, France, [26]Ophtalmology, CHU de Rouen, Rouen, France, [27]Internal Medicine, Bichat-Claude Bernard Hospital, University Paris-7, Paris, France, [28]Ophtalmology, Assistance Publique-Hôpitaux de Paris, Hôpital Pitié Salpétrière, Paris, France, [29]Department of Internal Medicine 2. Referal center for SLE/APS, CHU Pitié-Salpêtrière, Paris, France, [30]biostatistics Saint Louis Hospital, paris, France, [31]Department of Internal Medicine and clinical Immunology. French National Reference Center for Autoimmune Diseases. DHU I2B (Inflammation, Immunotherapy and Biotherapy), UPMC, Paris VI, Hôpital Pitié Salpétrière, AP-HP, UPMC, Univ Paris 06, Paris, France

First publication: September 29, 2015

SESSION INFORMATION

Session Date: Monday, November 9, 2015
Session Title: Miscellaneous Rheumatic and Inflammatory Diseases Oral Session II
Session Type: ACR Concurrent Abstract Session
Session Time: 2:30PM-4:00PM

Background/Purpose:

Anti-tumour necrosis factor (TNF) molecules have become a valuable addition to the therapeutic armamentarium for patients with severe uveitis. However, direct comparison of safety and efficacy of infliximab (IFX) and adalimumab (ADA) is lacking.

In this French nationwide study, we analyzed the efficacy and safety of IFX and ADA in patients with severe uveitis.

Methods: 203 patients (31 [20-42] years with 57% of women) with severe uveitis treated with anti-TNF alpha (IFX 5mg/kg at week 0, 2, 6 and every 6 weeks or ADA 40mg/2 weeks) were included. Because of the non-randomized design, the comparison of the anti-TNF treatments was performed using a propensity score approach. The probability of receiving either IFX or ADA, conditionally on baseline characteristics, was computed using a logistic regression model. The comparison of efficacy between IFX and ADA was considered as the primary end-point. Ocular involvement response to treatment was evaluated according to the SUN Workgroup criteria.

Results: Uveitis was bilateral in 163 cases (80%). Main etiologies of uveitis included Behçet's disease (38%), juvenile

idiopathic arthritis (20%), spondylarthropathies (11%) and sarcoidosis (5%). The median duration of disease before starting anti-TNF treatment was 42 [15-104] months. Ninety six percent of patients achieved complete or partial response to anti-TNF alpha therapy. In univariate analysis, the factors associated with complete response of uveitis included Behçet's disease (OR=5.89 [1.65-21.0], p=0.006) and more than 5 uveitis flares before anti-TNFα treatment (OR: 2.37 [1.13-4.97], p=0.022). In contrast, previous immunosuppressive use was negatively associated with complete response to anti-TNFα (OR=0.25 [0.11-0.54]; p=0.0004). The complete response rate and the time to first improvement of uveitis were similar regardless the anti-TNFα (IFX or ADA) used (OR 0.88 [0.23-3.35]; p=0.85 and 0.93 [0.41-2.10] months; p=0.86, respectively) in a logistic regression model weighted by the inverse of propensity score. Side effects were reported for 28% of patients and 12% had serious adverse events. No significant difference was observed in terms of serious side effects between IFX and ADA (OR 0.25 [0.047-1.29]; p=0.097).

Conclusion: Overall efficacy and safety were equivalent between IFX and ADA in severe uveitis. Behçet's patients had a 4 times higher odds of complete response to anti-TNFα therapy.

Abstract Number: 2037

Rheumatic Manifestations May be the First Clinical Presentation of Arterial Calcification Due to CD73 Deficiency

Kam Newman[1], megha Sawhney[2], James D. Katz[3], richard siegel[4], alessandra brofferio[5] and Manfred Boehm[6], [1]national institutes of arthritis, musculoskeletal, and skin disease, National Institutes of Health, Bethesda, MD, [2]national institutes of health, Bethesda, MD, [3]Department of Medicine, Division of Rheumatology, The George Washington University, Washington, DC, [4]National Institute of Arthritis and Musculoskeletal and Skin Diseases, Bethesda, MD, [5]national institutes of health, Bethesda,, MD, [6]Laboratory of Cardiovascular Regenerative Medicine, National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, MD

First publication: September 29, 2015

SESSION INFORMATION

Session Date: Monday, November 9, 2015

Session Title: Miscellaneous Rheumatic and Inflammatory Diseases Oral Session II

Session Type: ACR Concurrent Abstract Session

Session Time: 2:30PM-4:00PM

Background/Purpose: ACDC is a hereditary ectopic mineralization syndrome caused by mutations in the NT5E gene that encodes CD73. CD73 is a membrane bound 5' ecto-nucleotidase that hydrolyzes 5'AMP into adenosine and inorganic phosphate. This autosomal recessive disease clinically manifests with extensive mineralization of arteries predominantly of the lower extremities. Claudication and arthralgia complaints are prominent among affected individuals. The anatomic distribution of some of the calcifications in ACDC could be due to a tissue-specific differential of adenosine receptor levels on different cell types, which could apply to not just vessels but the joint capsule as well. The focus of our study is to characterize the rheumatic manifestations of patients with ACDC.

Methods: Six individuals with genetically confirmed disease where assessed clinically, radiologically, immunologically and biochemically. Demographics and complete history and physicals were catalogued.

Results: Four out of 6 patients were female (Table 1). The mean age at onset of symptoms was 16.7 years. In 5 out of 6 individuals, the initial clinical presentation was arthralgia/arthritis and hence the first specialist seen was a rheumatologist. In the 6th instance, the initial presenting complaint was claudication hence culminating in evaluation by a vascular surgeon. The most

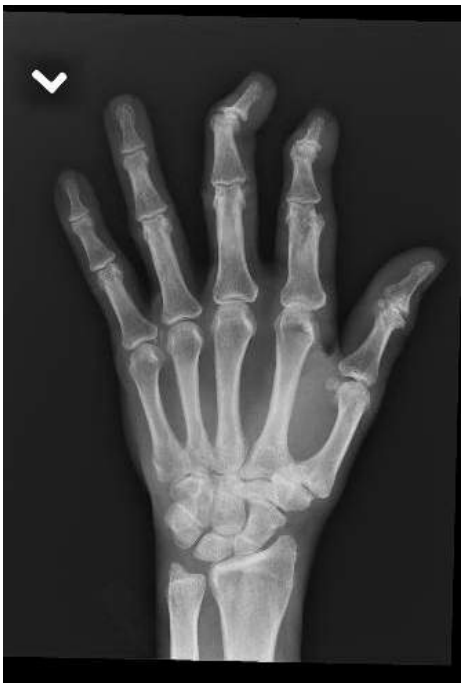
common pattern of arthritis was a symmetric, additive, small joint arthritis that in most cases was diagnosed as rheumatoid arthritis at initial presentation. The most common joints affected included PIPs and MCPs including reports of pain, stiffness, swelling and erythema. Episodic flares lasting up to ten days were reported by all subjects and these were responsive to either NSAIDs or short-term corticosteroids. Plain radiography demonstrates joint space loss, capsular calcification, heterotopic bone formation, homogeneous areas of soft tissue calcification and degenerative changes reminiscent of erosive osteoarthritis (image 1). Carpal erosions and meniscal calcifications were not a feature of the disease. All patients were ANA negative.

Conclusion: This is the first study to characterize the rheumatic manifestations of ACDC patients. A mixed degenerative-erosive radiological pattern is highlighted. Rheumatologists may be the first specialists to encounter these individuals and the presenting symptoms may be confused with rheumatoid arthritis.

Table 1. Clinical characteristics of the patients

Clinical Characteristic	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Age	55	60	50	59	57	49
Sex	F	F	F	M	M	F
Age at onset	18	16	16	17	17	16
Age of first joint involvement	18	16	16	16	17	35
Initial presentation	Arthralgia, arthritis	Arthralgia, arthritis	Arthralgia, arthritis	Arthralgia, arthritis	Arthralgia, arthritis	Intermittent claudication
Type of joint involvement	Polyarthralgia, stiffness, swelling, erythema	Polyarthralgia, stiffness, swelling, erythema	Polyarthralgia, stiffness, swelling, erythema	Polyarthralgia, stiffness, swelling, erythema	Polyarthralgia, stiffness, swelling, erythema	Polyarthralgia, stiffness, swelling, erythema
First specialist seen	PMD, sent to rheumatologist for RA	PMD, sent to rheumatologist for RA	PMD, sent to rheumatologist for RA	PMD, sent to rheumatologist for RA	PMD, sent to rheumatologist	PMD, sent to cardiovascular surgeon
Type of pain	Inflammatory	Inflammatory	Inflammatory	Inflammatory	Inflammatory	Inflammatory
Type of involved joints	Small	Small	Small	Medium	Small	Small
First involved joints	PIP	PIP, MCP	PIP, MCP, MTP	Right elbow	PIP, MCP	PIP, MCP, CMP
Symmetric	Y	Y	Y	Y	Y	Y
Additive arthritis	Y	Y	Y	Y	Y	Y
Flares	Y	Y	Y	Y	Y	Y
Duration of each flare	7-10 days	7-10 days	7-10 days	7-10 days	7-10 days	7-10 days
Response to NSAIDs	Aborts the flare	Aborts the flare	Aborts the flare	Aborts the flare	Aborts the flare	Aborts the flare
ANA	N	N	N	N	N	N
RF	N	N	N	N	N	N
Anti-CCP	N	N	N	N	N	N

Figure 1. Moderate degenerative changes of distal third DIP with subluxation and swan-neck deformity



View Abstract and Citation Information Online - http://acrabstracts.org/abstract/rheumatic-manifestations-may-be-the-first-clinical-presentation-of-arterial-calcification-due-to-cd73-deficiency

Abstract Number: 2038

Adalimumab in Patients with Active, Noninfectious Uveitis Using High-Dose Corticosteroids

Antoine P. Brezin[1], Phillippe Kestelyn[2], Joachim Van Calster[3], Glenn J. Jaffe[4], Jennifer E. Thorne[5], David Scales[6], Pablo Franco[7], Andrew D. Dick[8,9,10], Quan Dong Nguyen[11], Eric B. Suhler[12,13], Anne Camez[14], Alexandra P. Song[15], Martina Kron[14], Samir Tari[15], **James T. Rosenbaum**[16,17] and Arnd Heiligenhaus[18], [1]Université Paris Descartes, Hôpital Cochin, Paris, France, [2]Ghent University Hospital, Ghent, Belgium, [3]University Hospitals Leuven, Leuven, Belgium, [4]Duke University, Durham, NC, [5]Johns Hopkins Medical Institute, Baltimore, MD, [6]University of Texas Health Science Center, San Antonio, TX, [7]Organización Médica de Investigación (OMI), Buenos Aires, Argentina, [8]National Institute for Health Research (NIHR) Biomedical Research Centre at Moorfields Eye Hospital, London, United Kingdom, [9]University of Bristol, Bristol Eye Hospital, Bristol, United Kingdom, [10]University College London, Institute of Ophthalmology, London, United Kingdom, [11]Truhlsen Eye Institute, University of Nebraska Medical Center, Omaha, NE, [12]VA Portland Health Care System, Portland, OR, [13]Casey Eye Institute, Oregon Health & Science Univ, Portland, OR, [14]Abbvie Deutschland GmbH & Co KG, Ludwigshafen, Germany, [15]AbbVie Inc., North Chicago, IL, [16]Devers Eye Institute, Legacy Hospital system, Portland, OR, [17]Casey Eye Institute, Oregon Health & Science University, Portland, OR, [18]Department of Ophthalmology at St. Franziskus Hospital Muenster, University of Duisberg-Essen, Muenster, Germany

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SESSION INFORMATION

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Session Title: Miscellaneous Rheumatic and Inflammatory Diseases Oral Session II

Session Type: ACR Concurrent Abstract Session

Session Time: 2:30PM-4:00PM

Background/Purpose: Corticosteroids, currently the mainstay of uveitis treatment, are associated with adverse events and are not always fully effective. Multiple reports describe the use of biologics, including adalimumab (ADA), in the management of noninfectious uveitis, but there is a paucity of level 1 evidence to support efficacy of these drugs. This study assessed ADA efficacy and safety in patients with active, noninfectious uveitis despite the use of systemic corticosteroid therapy.

Methods: A total of 217 patients aged ≥18 years with active, noninfectious intermediate, posterior, or panuveitis (characterized by active, inflammatory chorioretinal or retinal vascular lesions; anterior chamber [AC] cell grade ≥2+; and/or vitreous haze [VH] grade ≥2+) despite ≥2 weeks of prednisone (10–60 mg/d) were randomized 1:1 to receive placebo or ADA (80 mg loading dose, 40 mg at week 1, followed by 40 mg every other week) for ≤80 weeks. All patients received a mandatory prednisone burst and taper schedule. Primary endpoint was time to treatment failure (TF) at or after Week 6 in ≥1 eye: new, active, inflammatory vascular lesions relative to baseline; worsening of BCVA by ≥15 letters; inability to achieve ≤0.5+ AC or VH grades at Week 6; 2-step increase in AC cell or VH grades after Week 6. Secondary endpoints included change in AC cell grade, VH grade, and logMAR BCVA; time to macular edema (ME); and percent change in central retinal thickness (CRT), all measured from best state achieved before Week 6 to final visit. Area under the curve (AUC) was calculated for AC cell, VH grade, and logMAR BCVA plotted against time.

Results: Patients receiving ADA were less likely to experience TF (HR=0.50; 95% CI, 0.36-0.70; P<0.001), with fewer associated TF causes. Median time to TF was 13 weeks for placebo and 24 weeks for ADA. Statistically significant differences in favor of ADA versus placebo for mean change from best state before Week 6 to the final visit were met for AC cell grade (P=0.011), VH grade (P<0.001), logMAR BCVA (P=0.003), and CRT (P=0.020). A statistically significant difference was not observed for time to OCT evidence of cystoid ME using the full analysis set. In a post-hoc analysis of ME (definition based on CRT, center point thickness 260-340 µm) performed on a subset of patients without macular hole or retinal detachment, ME risk was reduced by 67% in the ADA group versus placebo (HR=0.33; 95% CI, 0.12-0.90; P=0.023). Mean AUC values were significantly higher in the ADA group versus placebo, suggesting better and more durable control of AC cell (mean difference 34.3, 95%CI, 9.2-59.3; P=0.008), VH grade (35.4, 95%CI, 11.3-59.4; P=0.004), and improvement in logMAR BCVA (26.2, 95%CI, 7.0-45.3; P=0.008). Adverse event data were consistent with the safety profile across approved indications for ADA.

Conclusion: In patients with active, noninfectious intermediate, posterior, or panuveitis despite the use of corticosteroids, ADA significantly lowered the risk for recurrence of uveitic activity and BCVA loss. ADA also reduced the risk of developing ME in patients without preexisting macular pathology. The safety profile was consistent with the known safety profile across approved ADA indications.

Disclosure: A. P. Brezin, Abbvie, 5,AbbVie, 9; **P. Kestelyn**, None; **J. Van Calster**, MSD, 5,AbbVie, MSD, 9; **G. J. Jaffe**, Abbvie, 5; **J. E. Thorne**, AbbVie, Gilead, XOMA, 5,National Eye Institute and Allergan, Inc, 2; **D. Scales**, AbbVie, 9; **P. Franco**, None; **A. D. Dick**, Abbvie, 9; **Q. D. Nguyen**, AbbVie, Santen, XOMA, Bausch & Lomb, and chairs the Steering Committee for the VISUAL studies., 9; **E. B. Suhler**, AbbVie, 9,AbbVie and XOMA, 5,AbbVie, Bristol-Myers Squibb, EyeGate, Genentech, the National Eye Institute, Research to Prevent Blindness, and the Department of Veterans Affairs, 2; **A. Camez**, AbbVie, 1; **A. P. Song**, AbbVie, 1; **M. Kron**, AbbVie, 1; **S. Tari**, AbbVie, 1; **J. T. Rosenbaum**, AbbVie, UCB, XOMA, Santen, Novartis, Medimmune, Cavtherx, Portage, Topivert, Regeneron, Allergan, and Sanofi, 5,Alcon Research Institute, 2; **A. Heiligenhaus**, AbbVie, Pfizer, Novartis, and Deutsche Forschungsgemeinschaft, 2,AbbVie, Alimera Sciences, Allergan, Santen, and XOMA, 5.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/adalimumab-in-patients-with-active-noninfectious-uveitis-using-high-dose-corticosteroids

Abstract Number: 2039

Effect of Adalimumab on Visual Functioning (VFQ-25) in Visual-1 Trial Patients with Non-Anterior Non-Infectious Uveitis

John Sheppard[1], Avani D. Joshi[2], Manish Mittal[2], Keith Betts[3], Samir Tari[2], Yanjun Bao[2] and Andrew D Dick[4], [1]Virginia Eye Consultants and Eastern Virginia Medical School, Norfolk, VA, [2]AbbVie Inc., North Chicago, IL, [3]Analysis Group, Inc., Boston, MA, [4]University of Bristol, Bristol Eye Hospital, Bristol, United Kingdom

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SESSION INFORMATION

Session Date: Monday, November 9, 2015

Session Title: Miscellaneous Rheumatic and Inflammatory Diseases Oral Session II
Session Type: ACR Concurrent Abstract Session
Session Time: 2:30PM-4:00PM

Background/Purpose: To compare the effects of adalimumab and placebo on the National Eye Institute Visual Functioning Questionnaire 25 (VFQ-25) in subjects requiring high dose corticosteroids for active non-infectious intermediate-, posterior-, or pan-uveitis.

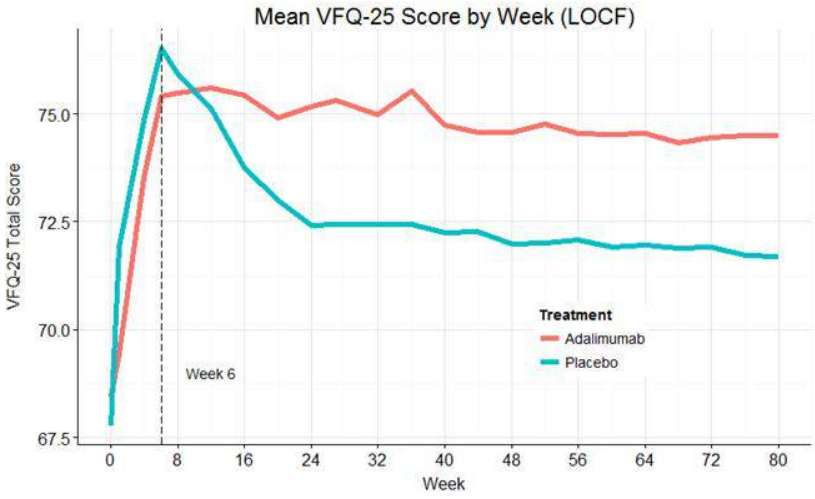
Methods: The VISUAL-1 clinical trial (NCT01148225) was a phase 3, randomized placebo-controlled study. It investigated the efficacy and safety of adalimumab (80 mg loading dose followed by 40 mg every other week) as maintenance therapy in subjects with active non-infectious intermediate-, posterior- or pan-uveitis. The VFQ-25 is a validated measure for assessing the impact of visual impairment from the patient's perspective. The VFQ-25 total score is calculated as the mean of 11 vision-related domains and scores range from 0 (worst vision functioning) to 100 (best vision functioning). The VFQ-25 was administered at every scheduled study visit of the 80 Week trial. As a ranked secondary outcome, the change in VFQ-25 from best state achieved prior to Week 6 to the final/early termination visit was compared between adalimumab and placebo using ANOVA. To investigate the temporal effects of adalimumab and placebo on VFQ-25 in a robust manner, a longitudinal GEE model (which incorporated all VFQ-25 measurements) was estimated.

Results: The VISUAL-1 clinical trial enrolled a total of 217 subjects (110 adalimumab, 107 placebo). The mean VFQ-25 total scores for adalimumab and placebo are similar through the tapering period but subsequently diverge and maintain separation through week 80 (**Figure 1**). The average change in VFQ-25 total score from best state achieved prior to Week 6 to the final / early termination visit was -5.50 for placebo and -1.30 for adalimumab. This corresponds to a statistically significant and clinically meaningful[1] increase of 4.20 (95% confidence interval [CI]: 1.02 – 7.38; P = 0.010) associated with adalimumab relative to placebo. The longitudinal model estimated a statistically significant treatment effect of adalimumab of 3.07 (95% CI: 2.09 – 4.06; P<0.001).

Conclusion: Treatment with adalimumab is associated with statistically significant improvements in visual functioning for subjects with active non-infectious non-anterior uveitis.

Reference: [1] Naik RK et al. *Qual Life Res.* 2013;22:2801–08.

Figure 1: Mean VFQ-25 Over Time



Disclosure: J. Sheppard, AbbVie, Alcon, Aldeyra, Allergan, Bausch & Lomb, EyeGate, 5; **A. D. Joshi**, AbbVie, 1,AbbVie, 3; **M. Mittal**, AbbVie, 1,AbbVie, 3; **K. Betts**, Analysis Group, and received payment from AbbVie to assist with research, 3; **S. Tari**,

AbbVie, 1,AbbVie, 3; **Y. Bao**, AbbVie, 1,AbbVie, 3; **A. D. Dick**, University of Bristol and in part supported by the National Institute for Health Research (NIHR) Biomedical Research Centre based at Moorfields Eye Hospital NHS Foundation Trust and University College London Institute of Ophthalmology, 3,AbbVie, Novartis, Q-Chips, 5.

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Abstract Number: 2040

T Follicular Helper like CD4+CXCR5+pd-1+ Cells and T Follicular Helper like Type 2 Cells Subsets Are Increased in IgG4-Related Disease Patients

Aurélie Grados[1], Mikael Ebbo[1], Christelle Piperoglou[2], Matthieu Groh[3], Alexis Regent[4], Maxime Samson[5], Benjamin Terrier[6], Nathalie Morel[7], Sylvain Audia[5], Francois Maurier[8], Julie Graveleau[9], Mohamed Hamidou[10], Amandine Forestier[11], Sylvain Palat[12], Emanuelle Bernit[1], Gilles Kaplanski[13], Frederique Retornaz[14], Bernard Bonotte[15], Catherine Farnarier[16], Jean-Robert Harle[17], Nathalie Costedoat-Chalumeau[7], Frederic Vely[18] and Nicolas Schleinitz[1], [1]Internal Medicine, Aix-Marseille Université, AP-HM, Marseille, France, [2]Immunology, CIML, AP-HM, Marseille, France, [3]National Referral Center for Rare Systemic Autoimmune Diseases, Hôpital Cochin, AP–HP, Université Paris Descartes, Paris, France, [4]Service de médecine interne, Hôpital Cochin, Paris, France, [5]Department of Internal Medicine and Clinical Immunology, Dijon University Hospital, Dijon, France, [6]Internal Medicine, National Referral Center for Rare Systemic Autoimmune Diseases, Hôpital Cochin, Paris, France, [7]Internal Medicine Department, Cochin Hospital, "René-Descartes Paris V" University, Paris, France, [8]Medecine Interne, Metz, France, [9]Medecine Interne Hotel Dieu Nantes, Nantes, France, [10]Internal Medicine Department, Nantes University Hospital, Nantes, France, [11]Internal Medicine, Groupe Hospitalier Mutualiste de Grenoble, Grenoble, France, [12]Service de Medecine Interne, CHU limoges, Limoges, France, [13]Internal Medicine hopital conception, Aix-Marseille Université, Marseille, France, [14]Conseil General 13 cellule recherche, Marseille, France, [15]Department of Internal medicine and Clinicla Immunology Dijon University Hospital, Dijon, France, [16]Laboratoire d'immunologie, Hopital de la Conception, Marseille, France, [17]Internal Medicine, Aix-Marseille Université, APHM, Marseille, France, [18]CIML, Laboratoire d'Immunologie Conception AP-HM, Aix-Marseille université, Marseille, France

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Background/Purpose:

IgG4 related disease (IgG4-RD) is associated with characteristic pathological changes including lymphoplasmocytic infiltration with abundant IgG4 positive plasma cells, storiform fibrosis and obliterative phlebitis. Recently an increase of plasmablasts in blood has been correlated with IgG4-RD activity. In IgG4-RD lesion tissues, germinal centers (GC) are often observed and could be source of plasmablasts. T follicular helper (Tfh) cells orchestrate antigen driven GC formation and B cell differentiation. Bona fide Tfh cells have been initially recognized in lymph nodes but a circulating counterpart characterized as Tfh like $CD4^+CXCR5^+PD\text{-}1^+$ cells has been reported. We analyzed the Tfh like cells and their subsets in blood of untreated IgG4-RD patients.

Methods:

Thirty patients with IgG4-RD were included prospectively in the study and compared to matched (age and gender) healthy controls (HC) and matched (age) primary Sjögren syndrome (pSS) patients. Patients fulfilled the 2011 comprehensive IgG4-RD diagnostic criteria and the 2002 American-European Consensus Group criteria for pSS. Peripheral blood mononuclear cells (PBMC) of patients and controls were analyzed by flow cytometry on a BD FACS Canto II. Tfh like cells were defined as $CD4^+CXCR5^+PD\text{-}1^+$. Subsets of Tfh were defined as Tfh2 $CCR6^-CXCR3^-$, Tfh-1 $CCR6^-CXCR3^+$ and Tfh-17 $CCR6^+CXCR3^-$.

The cytokine production by PBMC for IL-4, IL-10 and IL-17 was performed with the cytokine bead assay (CBA® kit, BD Biosciences). Statistical analysis was performed on PRISM software.

Results: The frequency and absolute numbers (AN) of $CD4^+CXCR5^+PD\text{-}1^+$Tfh like cells are increased in IgG4-RD when compared to HC ($p<0,001$) and pSS ($p<0,001$). In contrast the frequency ($p=0.1$) and AN ($p=0.2$) of $CD4^+CXCR5^+$ is not different from HC. Tfh-1 were decreased in IgG4-RD when compared to HC ($p=0.0005$) and pSS ($p=0.002$). Tfh-17 frequency only differed between IgG4-RD and pSS ($p=0.04$), increased in pSS. Tfh-2 were significantly increased in IgG4-RD when compred to HC ($p<0.0001$) and pSS ($p=0.01$). Tfh-2 values correlated with IgG4 serum levels ($p=0.03$) and IL-4 production by CBA assay ($p=0.01$) but not with IgG4-RD responder index ($p=0.4$) and plasmablasts numbers ($p=0.1$).

Conclusion: IgG4-related disease is associated with increased levels of T Follicular helper like $CD4^+CXCR5^+PD\text{-}1^+$ cells in blood. The increase of Tfh like cells is mainly related to an increase of the Tfh2 $CCR6^-CXCR3^-$ subset. These finding suggests that T follicular helper 2 cells, characterized by their ability to produce Th2 cytokines, play a role in IgG4-RD pathogenesis.

Abstract Number: 2041

Baseline Clinical and Laboratory Features of IgG4-Related Disease: Retrospective Japanese Multicenter Study of 333 Cases

Kazunori Yamada[1], Motohisa Yamamoto[2], Takako Saeki[3], Ichiro Mizushima[4], Shoko Matsui[5], Hiroki Takahashi[6], Mitsuhiro Kawano[7] and Shigeyuki Kawa[8], [1]Division of Rheumatology,, Kanazawa University Hospital, Kanazawa, Japan, [2]First Department of Internal Medicine, Sapporo Medical University School of Medicine, Sapporo, Japan, [3]Department of Internal Medicine, Nagaoka Red Cross Hospital, Nagaoka, Japan, [4]Kanazawa University Hospital, Kanazawa, Japan, [5]Health Administration Center, University of Toyama, Toyama, Japan, [6]epartment of Gastroenterology, Rheumatology and Clinical Immunology, Sapporo Medical University School of Medicine, Sapporo, Japan, [7]Division of Rheumatology, Kanazawa University Graduate School of Medicine, Kanazawa, Japan, [8]Center for Health, Safety and Environmental Management, Shinshu University, Matsumoto, Japan

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Background/Purpose: IgG4-related disease (IgG4-RD) is a widely recognized systemic inflammatory disorder. However, owing to its extremely diverse clinical picture, each clinician encounters a clinically distinct patient (pt) population depending on his/her specialty, and it is difficult to avoid institutional bias in a single center. This prompted us to conduct a relatively large-scale multicenter study with well-experienced physicians of IgG4-RD including rheumatologists, gastroenterologists, pulmonologists and nephrologists. The purpose of this study is to clarify the baseline clinical and laboratory features of IgG4-RD using a relatively large-scale cohort of 333 IgG4-RD pts.

Methods: Between 2001 and 2014, we retrospectively evaluated 333 pts with IgG4-RD in five institutions. The diagnosis of IgG4-RD was made based on the comprehensive diagnostic criteria or criteria of each organ. We analyzed the serum levels of IgG, IgG4, C3, C4, CH50 and CRP, the affected organs, the target organs for biopsy and treatment. We also determined the

prevalence of diabetes mellitus (DM) and malignancy.

Results: Two hundred and four pts were male, and 129 were female (male 61.3%). The mean age was 63.8 years (range 25-91). At diagnosis, mean serum IgG and IgG4 were 2404 mg/dL and 755 mg/dL respectively. Serum IgG4 was elevated in 317 of 332 (95.5%). Hypocomplementemia was seen in 137 of 327 (41.9%), with pts with kidney lesion showing an especially high frequency (59.5% vs. 36.3%, p<0.001). Serum level of CRP was less than 1.0 mg/dL in 90.2%. Mean number of organs involved was 3.2 (range 1-11); salivary gland (SG) was the most frequently involved organ (72.3%), followed by lacrimal gland (LG), pancreas, retroperitoneum (RP)/periaorta, kidney, and lung. Single organ involvement excluding lymph nodes was seen in 63 of 333 (18.9%), with the most frequently affected organs being SG followed by LG. RP/periaorta, lung and kidney were more frequently affected in males than in females, whereas LG and SG were more frequently affected in females than in males. Biopsy was performed in 270 of 333 (81.1%), with SG 45.1%, lung 16.7%, pancreas 15.3%, kidney 15.2%. Corticosteroid therapy was administered to 248 of 313 (79.2%), and the mean initial dose of prednisolone was 30.5 mg/day. The prevalence of DM was significantly higher in those with than without AIP (47.0% vs. 30.0%, p=0.005). The prevalence of malignancy was 16.8%.

Conclusion: The present study clarified the organs most frequently affected by IgG4-RD by a retrospective multicenter study. In addition, we reconfirmed the high frequency of hypocomplementemia in pts with kidney lesion. Moreover, in more than 95% of pts, serum elevated IgG4 levels were useful for the diagnosis of IgG4-RD.

Disclosure: K. Yamada, None; **M. Yamamoto**, None; **T. Saeki**, None; **I. Mizushima**, None; **S. Matsui**, None; **H. Takahashi**, None; **M. Kawano**, None; **S. Kawa**, None.

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Abstract Number: 2042

Pancreatitis Subtypes Survey in 852 Childhood-Onset Systemic Lupus Erythematosus Patients: A Multicenter Cohort

Victor L Marques[1], Natali W. Gormezano[1], Eloisa Bonfá[2], Nadia E Aikawa[3], Maria Teresa Terreri[4,5], Rosa M R Pereira[6], Claudia Saad-Magalhães[7], Andressa Guariento[8], Simone Appenzeller[9], Virgínia Ferriani[10], Cássia M. Barbosa[11], Valéria C. Ramos[12], Simone Lotufo[13] and Clovis A Silva[3], [1]Pediatric Rheumatology Unit, Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil, [2]Division of Rheumatology, Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil, [3]Pediatric Rheumatology, Faculdade de Medicina da Universidade de São Paulo, Sao Paulo, Brazil, [4]Pediatrics, Universidade Federal de São Paulo / UNIFESP, Sao Paulo, Brazil, [5]Pediatrics, Universidade Federal de Sao Paulo, São Paulo, Brazil, [6]Rheumatology, Faculdade de Medicina da USP, São Paulo, Brazil, [7]Brazil, Brazil, Brazil, [8]Pediatric Rheumatology Unit, Irmandade da Santa Casa de Misericórdia de São Paulo, São Paulo, Brazil, [9]Division of Rheumatology, Faculty of Medical Science, State University of Campinas, São Paulo, Brazil, [10]Department of Pediatrics School of Medicine of Ribeirão Preto, University of São Paulo (USP-RP), Ribeirão Preto, Brazil, [11]Pediatric Rheumatology Unit, Hospital Infantil Darcy Vargas, São Paulo, Brazil, [12]Pediatric Rheumatology Unit, Pontifical Catholic University of Sorocaba, São Paulo, Brazil, [13]Pediatric Rheumatology Unit, Hospital Municipal Infantil Menino Jesus, São Paulo, Brazil

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Background/Purpose: Pancreatitis is uncommon and a life-threatening SLE manifestation in childhood-onset systemic lupus erythematosus (c-SLE) and it has been restricted to case reports or case series. Recently the International Study Group of Pediatric Pancreatitis (INSPPIRE) proposed definitions to standardize pancreatitis in children. However, studies using these new definitions in a large population of c-SLE patients were not performed. Therefore, the objective of the study was to systematically classify pancreatitis in c-SLE according to INSPPIRE and determine the overall prevalence, clinical features, laboratory and

outcome of the first episode.

Methods: A retrospective multicenter study was performed in 852 cSLE patients from 10 Pediatric Rheumatology services of São Paulo state, Brazil. An investigator meeting was held to define the protocol, to harmonize clinical parameters definition, disease activity and damage tools scoring and outcome parameters. Demographic data, clinical, laboratorial, disease activity (SLEDAI-2K), cumulative damage (SLICC/ACR-DI), treatment and outcome were also evaluated.

Results: Pancreatitis was diagnosed in 22/852 (2.6%) cSLE patients. They were classified as: 20 (91%) acute pancreatitis, 2 (9%) acute recurrent pancreatitis and none had chronic pancreatitis. None of them had gallstone, traumatic pancreatitis or reported alcohol and tobacco use. The first pancreatitis episode was identified at disease onset in 6 (27%) cSLE patients. The comparison of patients with pancreatitis (first episode) and without this complication revealed higher median of SLEDAI-2K [21(0-41) vs. 2(0-45), $p<0.0001$]. The frequencies of fever (70% vs. 6%,$p<0.0001$), weight loss (50% vs. 3%,$p<0.0001$), hepatomegaly (36% vs. 2%,$p<0.0001$), splenomegaly (18% vs. 1%,$p<0.0001$), serositis (45% vs. 2%,$p<0.0001$), nephritis (75% vs. 20%,$p<0.0001$), arterial hypertension (59% vs. 12%,$p<0.0001$), acute renal failure (38% vs. 3%,$p<0.0001$), macrophage activation syndrome (36% vs. 0.5%, $p<0.0001$) and death (32% vs. 7%,$p=0.001$) were also higher in patients with pancreatitis. Frequencies of current methylprednisolone pulse ($p<0.0001$) and the median of current prednisone dose [55(15-60) vs. 11(1-90) mg/day, $p<0.0001$] were significantly higher in patients with pancreatitis, however no differences were observed of prednisone cumulative dose, intravenous methylprednisolone cumulative dose and total glucocorticoid cumulative dose in both groups ($p>0.05$). Of note, the two patients with acute recurrent pancreatitis had two episodes, with pain-free interval of 1 and 4 years.

Conclusion: This was the first study phenotyping pancreatitis according to INSPPIRE standardized definitions evidencing that this complication in c-SLE is predominantly an acute subtype with rare recurrence or progression to chronic damage. We also identified an association with current glucocorticoid use, disease activity and severity.

Disclosure: V. L. Marques, None; **N. W. Gormezano**, None; **E. Bonfá**, None, 2; **N. E. Aikawa**, None; **M. T. Terreri**, None; **R. M. R. Pereira**, None, 2; **C. Saad-Magalhães**, None; **A. Guariento**, None; **S. Appenzeller**, None; **V. Ferriani**, None; **C. M. Barbosa**, None; **V. C. Ramos**, None; **S. Lotufo**, None; **C. A. Silva**, None, 2.

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Abstract Number: 2043

Cell-Bound Complement Activation Products Have High Sensitivity and Specificity in Childhood-Onset Systemic Lupus Erythematosus and Juvenile Idiopathic Arthritis

Anca Askanase[1], Joyce Hui-Yuen[2], John Conklin[3], Derren Barken[4], Tyler O'Malley[5], Xiao Qing Li[6], Liza Mariel Bermudez[2], Andrew Eichenfield[7], Amy J. Starr[8], Lisa F. Imundo[9,10] and Thierry Dervieux[11], [1]Columbia University College of Physicians & Surgeons, New York, NY, [2]Pediatric Rheumatology, Columbia University Medical Center, New York, NY, [3]1261 Liberty Way Suite C, Exagen Diagnostics, Vista, CA, [4]Exagen Diagnostics, Inc., Vista, CA, [5]Research and Development, Exagen Diagnostics, Vista, CA, [6]Adult Rheumatology, Columbia University Medical Center, New York, NY, [7]Morgan Stanley Children's Hospital of NY-Presbyterian, Columbia University, New York, NY, [8]Columbia University Medical Center, New York, NY, [9]Assoociate Professor of Pediatrics in Medicine - Rheumatology, Columbia University Medical Center, New York, NY, [10]New York Presbyterian Hospitsl, Columbia University, New York, NY, [11]Research and Development, Exagen Diagnostics, Inc., Vista, CA
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Background/Purpose: Elevated levels of cell-bound complement activation products (C4d deposition on erythrocytes [EC4d]

and B lymphocytes [BC4d], CBCAPS) have been demonstrated to be sensitive and specific biomarkers in the differential diagnosis of adult systemic lupus erythematosus (SLE) and other rheumatic diseases. We sought to evaluate the usefulness of CBCAPS in the setting of childhood-onset SLE (cSLE).

Methods: This validation cohort included 28 patients with cSLE all diagnosed prior to their 19th birthdays, and 21 patients with juvenile idiopathic arthritis (JIA). All subjects fulfilled American College of Rheumatology SLE classification criteria. Venous blood was collected and shipped overnight to the reference clinical laboratory conducting the diagnostic testing for CBCAPS and autoimmune markers including antinuclear antibodies (ANA), anti-dsDNA antibodies and other cellular autoantibodies. The CBCAPS multi-analyte assay combining these markers in two consecutive tiers of analysis as currently approved by the Department of Health in the State of NY was calculated. Diagnostic test results were reported as positive (suggestive of SLE) or negative (suggestive of non-SLE). Test performances in this validation cohort were assessed using sensitivity, specificity, and positive and negative likelihood ratios (LR). All laboratory personnel were blinded to subject diagnosis during the pre-analytical, analytical and post-analytical phase of testing.

Results: The results of the cSLE and JIA patients are shown in the Table. Elevated CB-CAPS resulted in 28% higher sensitivity for cSLE than low complement, and higher specificity. After employing the two-tier analysis previously described, the CBCAPS multi-analyte assay yielded 81% sensitivity (22/27, one indeterminate test assessment) and a specificity of 84% (16/19, one indeterminate and one equivocal test assessment). Positive LR was 5.4 and negative LR was 0.2. Of note, the 5 cSLE patients presenting with a negative CBCAPS multi-analyte assay assessment were clinically in remission.

Conclusion: These pilot findings suggest that CBCAPS could provide useful markers for cSLE and differentiation from other autoimmune diseases.

Table: Patient demographics and results of CBCAPS assays

	SLE (n=28)	**JIA (n=21)**
Age	18±2	17±3
Female %	75%	77%
Duration of disease **Mean SLE disease activity index**	4.7±3.2 4.3±3.8 (range 0-16)	4.4±3.4
Low Complement	50% (14/28)	19% (4/21)
ANA **(indirect immunofluorescence)**	93% (26/28)	52% (11/21)
Anti-dsDNA **(confirmed Crithidia)**	54% (15/28)	5% (1/21)
Anti-Smith	18% (5/28)	0% (0/21)
EC4d>14 net mean fluorescence index (MFI) **EC4d>75 net MFI**	64% (18/28) 19% (4/21)	14% (3/21) 0% (0/21)
BC4d>60 net MFI **BC4d>200 net MFI**	63% (17/27) 14% (3/27)	4% (1/21) 0% (0/21)
Elevated CBCAPS **(EC4d>14 units MFI, or BC4d>60 units MFI)**	78% (21/27)	14% (3/21)

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Abstract Number: 2044

Axonal Dysfunction in Childhood-Onset Systemic Lupus Erythematosus. Association with Neuropsychiatric Manifestations and Disease Activity

Renan Frittoli[1], Mariana Postal[2], Karina Pelicari[2], Nailu Sinicato[3], Aline Tamires Lapa[4], Fernando Peres[1], Fernando Cendes[5], Roberto Marini Sr.[6], Gabriela Castellano[7], Leticia Rittner[8] and Simone Appenzeller[2], [1]State University of Campinas, Campinas, Brazil, [2]Medicine, State University of Campinas, Campinas, Brazil, [3]pEDIATRICS, State University of Campinas, Campinas, Brazil, [4]Rua Alexandre Fleming, Fcm09-Baraogeraldo, Campinas, Brazil, [5]Neurology, State University of Campinas, Campinas, Brazil, [6]Pediatric Rheumatology Unit, State University of Campinas, São Paulo, Brazil, [7]Medical Physics, State University of Campinas, Campinas, Brazil, [8]Electrical Engineering, State University of Campinas, Campinas, Brazil
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Background/Purpose: Involvement of the central nervous system is frequently observed in childhood-onset SLE patients (cSLE). Proton magnetic spectroscopy (1H-MRS) is an important non-invasive method of quantification of biological metabolites. Abnormalities in brain metabolites may predict future damage, such as lesions and atrophy in adults-onset SLE, however 1H-MRS have never been evaluated in cSLE. **Objective:** To determine the presence of axonal dysfunction in cSLE and to determine clinical, laboratory and treatment features associated with its occurrence. To associate axonal dysfunction with sera Th1 (IL-12, TNF-α, IFN-γ), Th2 (IL-6 and IL-10), Th17 (IL-17) cytokines levels and antiribosomal P protein antibodies (anti-P) and S100β.

Methods: We included 77 consecutive cSLE patients [median age 16 years (range 7-31)] from the Rheumatology outpatient unit (State University of Campinas) and 66 healthy controls [median age 18 years (8-32)]. We performed multi voxel 1H-MRS using point resolved spectroscopy sequence over the superior–posterior region of the corpus callosum (3T Phillips®scanner) and signals from N-acetylaspartate compounds (NAA), choline-based compounds (Cho); creatine containing compounds (Cr) and lactate (Lac) were measured and metabolites/Cr ratios were determined. A complete clinical, laboratory and neurological evaluation was performed in all subjects. Neurological manifestations were analyzed according to the ACR classification criteria. Mood and anxiety disorders were determined through Beck Depression and Beck Anxiety Inventory. SLE patients were further assessed for clinical and laboratory SLE manifestations, disease activity [SLE Disease Activity Index (SLEDAI)], damage [Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index (SDI)] and current and cumulative drug exposures. Th1 (IL-12, TNF-α, IFN-γ), Th2 (IL-6 and IL-10), Th17 (IL-17) cytokines levels, S100β levels and anti-P were measured by ELISA using commercial kits. Data were compared by non-parametric tests.

Results: NAA/Cr ratio (p=0.017) and Lac/Cr ratio (p=0.014) levels were significantly decreased and Cho/Cr ratio levels (p=0.038) were increased in cSLE patients when compared to healthy controls. We observed that Cho/Cr ratio was associated with symptoms of anxiety (p=0.02), cognitive decline (p=0.03), corticosteroid use (p=0.034) and correlated with IL-6 (r=0.568; p=0.002). NAA/Cr ratio was associated with disease activity (p=0.01) and correlated with IL-4 (r=0.375; p=0.024). Lac/Cr ratio was associated with symptoms of depression (p=0.016), presence of anti-P (p=0.04) and correlated with IFN-γ (r=0.611; p=0.004).

Conclusion: We observed significant axonal dysfunction in cSLE. Decreased NAA/Cr ratio was associated with disease activity and sera IL-4 levels and increased Cho/Cr ratio was associated with neuropsychiatric manifestations, cumulative dose of corticosteroids and IL-6, suggesting brain injury. Lac/Cr was associated with symptoms of depression, anti-P and IFN-γ. NAA, Cho and Lac may be useful as biomarkers in neuropsychiatric cSLE.

Disclosure: R. Frittoli, None; **M. Postal**, None; **K. Pelicari**, None; **N. Sinicato**, None; **A. T. Lapa**, None; **F. Peres**, None; **F. Cendes**, None; **R. Marini Sr.**, None; **G. Castellano**, None; **L. Rittner**, None; **S. Appenzeller**, None.

Abstract Number: 2045

Cross-Validation of the Pediatric Automated Neuropsychological Assessment Metrics-Cognitive Performance Scores in the Screening of Neurocognitive Impairment in Childhood-Onset Systemic Lupus Erythematosus

Jasmine Nguyen[1], Tricia Williams[2], Earl Silverman[3] and **Deborah M. Levy**[4], [1]Royal College of Surgeons in Ireland, Dublin, Ireland, [2]Psychology, Hospital for Sick Children, Toronto, ON, Canada, [3]Division of Rheumatology, Hospital for Sick Children and University of Toronto, Toronto, ON, Canada, [4]Rheumatology, The Hospital for Sick Children, Toronto, ON, Canada
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Background/Purpose: Neurocognitive impairment (NCI) is an important morbidity in childhood-onset systemic lupus erythematosus (cSLE); however, the gold standard formal neuropsychological assessment is difficult to access. Screening for NCI using computerized testing with the Pediatric Automated Neuropsychological Assessment Metrics (PedANAM) is a more feasible option. Four recently derived cognitive performance scores (CPS) use PedANAM raw data and differing statistical methods (weighted average, unweighted average, logistic regression and principal components analysis) to establish suggested cutoff values for patients requiring further evaluation. Our objectives were to examine external, concurrent, criterion and diagnostic validity of the PedANAM-CPS scores using a single-centre multiethnic cSLE cohort.

Methods: Patients were recruited within 18 months of cSLE onset, and all had a formal neuropsychological assessment battery and PedANAM testing on the same day. Validation of the PedANAM-CPS scores utilized sensitivity and specificity analyses in addition to other nonparametric statistical comparisons.

Results: 29 cSLE patients without premorbid NCI completed the study procedures. Median age at testing was 15.2 years, 83% were female. Six (21%) patients had NCI identified by formal testing. All four CPS scores were significantly different in patients with NCI, and predetermined cutoffs were reached only in patients with NCI (Table 1). Two of the 4 CPS scores (one using an unweighted average and the other a logistic regression model) had 100% sensitivity to detect NCI, while the CPS based on principal components analysis had the highest specificity (87%) for detecting NCI (Table 2). All four CPS scores were significantly correlated to 3 of the cognitive domains (visuoconstructive abilities, working memory and psychomotor speed), but not to attention and executive functioning as evaluated by formal neuropsychological testing.

Table 2: Sensitivity and Specificity of PedANAM-CPS for NCI

Table 1: PedANAM-CPS in NCI versus normal cognitive function

	Normal Cognitive Function (N=23)	Patients with NCI (N=6)	p-value
	(median, range)	(median, range)	
PedANAM-CPSmultiscore	3.79 (1.05 - 13.75)	7.37 (1.86 - 15.58)	0.04
PedANAM-CPS UWA*	0.45 (-2.47 - 0.86)	-0.75 (-1.20 - 0.04)	0.002
PedANAM-CPS Logit	-2.80 (-4.78 - 6.41)	-0.43 (-1.46 - 0.86)	0.003
PedANAM-CPS PCA*	1.17 (-8.14 - 2.45)	-2.33 (-3.11 - 0.53)	0.003
	Sensitivity (%, 95% CI)	Specificity (%, 95% CI)	
PedANAM-CPS multiscore	83.3 (43.7 - 97.0)	73.9 (53.5 - 87.5)	
PedANAM-CPS UWA*	100 (61.0 - 100)	73.9 (53.5 - 87.5)	
PedANAM-CPS Logit	100 (61.0 - 100)	56.5 (36.8 - 74.4)	
PedANAM-CPS PCA*	83.3 (43.7 - 97)	87.0 (67.9 - 95.5)	

*UWA = unweighted average; PCA = principal components analysis

Conclusion: The 4 PedANAM-CPS scores have high sensitivity and specificity for NCI in cSLE patients in our multiethnic cohort. The CPS scores are easily calculated by any clinician following administration of the PedANAM test battery, and can be used to discriminate cSLE patients who require referral for a formal neuropsychological assessment.

Disclosure: J. Nguyen, None; **T. Williams**, None; **E. Silverman**, None; **D. M. Levy**, None.

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Abstract Number: 2046

Long-Term Outcomes in Cardiac Neonatal Lupus and Associated Risk Factors for Morbidity

Amit Saxena[1], Peter M. Izmirly[1], Sara Sahl[1], Deborah Friedman[2] and Jill P. Buyon[3], [1]Medicine, Division of Rheumatology, New York University School of Medicine, New York, NY, [2]Pediatric Cardiology, New York Medical College, Valhalla, NY, [3]Department of Medicine, Division of Rheumatology, New York University School of Medicine, New York, NY
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Session Date: Monday, November 9, 2015
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Session Type: ACR Concurrent Abstract Session
Session Time: 2:30PM-4:00PM

Background/Purpose:

All women with anti-Ro antibodies face the risk of cardiac neonatal lupus (cardiac NL), which presents as congenital heart block (CHB) and/or cardiomyopathy in their offspring. While several groups report risk factors for short-term outcomes including mortality, follow up studies beyond infancy are scant. Such information is critical to family counseling as well as formulating strategies for management.

Methods:

Postnatal echocardiograms most distant to birth were evaluated in 178 children with cardiac NL enrolled in the Research Registry

for Neonatal Lupus (mean date of service 2/25/2012 ± 2.51 y). M-mode measurements were analyzed for abnormalities (z score > +2.0) of cardiac and aortic dimensions, as well as qualitative descriptions of abnormal ventricular function, chamber enlargement, and valvular dysfunction (at least moderate stenosis or regurgitation). Bivariate analyses of outcomes were performed with potential risk factors for morbidity including demographics, maternal medications during pregnancy, fetal heart rate at time of detection and lowest documented fetal rate, fetal echo dilated cardiomyopathy (DCM), endocardial fibroelastosis or hydrops, postnatal septal defects, permanent pacemaker (PPM) placement, age at PPM implantation and number of years with PPM.

Results:

Echo reports were available for 15 (8.4%) children age 0-1, 40 (22.5%) >1-5, 34 (19.1%) >5-10, 26 (14.6%) >10-15, 33 (18.5%) >15-20, and 30 (16.9%) >20. Left ventricular (LV) systolic function was qualitatively abnormal in 13.7% and low-normal in 9.1%. Abnormal LV function was more frequent in age groups 0-1 (26.7%) and >20 (26.7%) compared to others (p=0.004). In all ages, decreased LV function associated with lower fetal heart rate at detection of CHB (p=0.012) and nadir rate (p=0.002), as well as fetal DCM (p=0.035) and hydrops (p=0.048). Abnormal LV function also associated with need for PPM (p=0.029), younger age at PPM implantation (p=0.042), longer period of pacing (p=0.014), atrial septal defect (p=0.012) and black race (p=0.019). LV end diastolic dimension was enlarged in 21.5% by z score and 20.6% qualitatively. LV dilation associated with fetal DCM (p=0.04) and black race (p=0.028). The aortic root and/or ascending aorta were dilated in 27.8%, associated with a younger age (p=0.001) and lower fetal ventricular rate at detection (p=0.04). Valvular disease was present in 8.7%, associated with older age (p=0.001), fetal DCM (p=0.033), PPM (p=0.042) and longer period of pacing (p<0.001).

Conclusion:

The majority of cardiac NL children have normal heart size and function on follow up, however over 20% have abnormalities. Depressed LV function is more frequent in the first year of life, possibly due to the ongoing inflammatory insult from anti-Ro exposure in utero. Decreased function is more common again after age 20, which may be a result of long-term pacing. Known risk factors for mortality, including race and fetal factors (heart rate, DCM and hydrops) also predict long-term cardiac dysfunction. Aortic dilation is relatively common, but is noted less frequently in older individuals. Further studies are required to identify optimal pacing techniques and medical management to prevent complications of cardiac NL.

Disclosure: A. Saxena, None; **P. M. Izmirly**, None; **S. Sahl**, None; **D. Friedman**, None; **J. P. Buyon**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/long-term-outcomes-in-cardiac-neonatal-lupus-and-associated-risk-factors-for-morbidity

Abstract Number: 2047

A Randomised Double-Blind Placebo-Controlled Trial of Vitamin D Supplementation in Juvenile-Onset Systemic Lupus Erythematosus: Effects on Microarchitecture Measured By HR-pQCT

Glauce Lima[1], Juliane Paupitz[1], Nadia E Aikawa[2], Jackeline Couto Alvarenga[3], Eloisa Bonfá[1] and Rosa M R Pereira[4], [1]Rheumatology Division, Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil, [2]Rheumatology, Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil, [3]Division of Rheumatology, Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil, [4]Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil

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SESSION INFORMATION

Session Date: Monday, November 9, 2015

Session Title: Pediatric Rheumatology - Clinical and Therapeutic Aspects II: Pediatric Systemic Lupus Erythematosus

Session Type: ACR Concurrent Abstract Session

Session Time: 2:30PM-4:00PM

Background/Purpose: Vitamin D has an important effect in bone quality and vitamin D deficiency in Juvenile-onset Systemic Lupus Erythematosus patients (JoSLE) may be associated with lower spine and whole body bone mineral density. Besides,

vitamin D has an important immunomodulatory effect that justified its use in autoimmune disease including JoSLE. However, there are no trials that directly addressed the boosting of serum levels of 25-hydroxyvitamin D (25OHD) in bone microarchitecture in JoSLE. The aim of this study was to evaluate the effect of vitamin D supplementation on bone microarchitecture parameters in JoSLE.

Methods: This study was a randomized double-blind placebo-controlled 24-week trial conducted in the Rheumatology Outpatient Clinic, University of Sao Paulo. Forty JoSLE patients (according to ACR classification criteria) up to 25 years old were randomized (1:1) to receive oral cholecalciferol 50,000 IU/week (JoSLE-VitD)(n=22) or placebo (JoSLE-PL)(n=23). Before randomization a three months washout of vitamin D was performed for all patients. Medications remained stable throughout the study. Serum levels of 25OHD were measured using radioimmunoassay. Disease activity was assessed by the SLE Disease Activity Index (SLEDAI). Bone microarchitecture and volumetric bone density were analysed at baseline and after 24 weeks by HR-pQCT (High-resolution peripheral quantitative computed tomography) at tibia site.

Results: At baseline, groups were similar regarding, age, body mass index, organ involvement, glucocorticoid dose, use of immunosuppressive drugs, parameters of bone microarchitecture and volumetric density, SLEDAI and levels of 25OHD. The mean 25OHD serum levels at baseline were similar in JoSLE-VitD and JoSLE-PL groups (19.1 vs. 19.5 ng/ml, p=0.82), as well the mean serum levels of total calcium [9.4 (0.5) vs. 9.1 (0.5) mg/dl, p=0.11]. After 24 weeks, the mean level of 25OHD was higher in the JoSLE-VitD group [31.3 (8.6) vs. 16.5 (5.8) ng/ml, p<0.001] and also a higher decrease was observed in SLEDAI score in JoSLE-VitD [D(final – baseline) SLEDAI: -0.58 ± 2.39 vs. 1.25 ± 3.76, p=0.01)] compared to JoSLE-PL. No difference was observed regarding an improvement of any clinical parameter.

Concerning bone microarchiteture, an increase in trabecular number [DTb.N: 0.162 (0.24) *vs.* 0.028 (0.19) mm, p=0.024] and a decreased in trabecular separation [DTb.Sp: -0.045 (0.06) *vs*. 0.001 (0.04) mm, p=0.017] were observed in the JoSLE-VitD group compared to JoSLE-PL at tibia site. No differences were observed in other structural parameters [trabecular (Tb.Th) and cortical thickness (Ct.Th)] and volumetric bone mineral densities [trabecular (Tb.BMD) and cortical (Ct.BMD)] (p>0.05).

Conclusion: This study suggests that cholecalciferol supplementation for 24 weeks is effective in improving bone microarchitecture parameters in JoSLE patients. Therefore, a therapeutic intervention may be recommended for patients with 25OHD deficiency. (Clinical Trial Registry: NCT01892748).

Disclosure: G. Lima, None; **J. Paupitz**, None; **N. E. Aikawa**, None; **J. C. Alvarenga**, None; **E. Bonfá**, None, 2; **R. M. R. Pereira**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/a-randomised-double-blind-placebo-controlled-trial-of-vitamin-d-supplementation-in-juvenile-onset-systemic-lupus-erythematosus-effects-on-microarchitecture-measured-by-hr-pqct

Abstract Number: 2048

Hospitalization Trends of Rheumatoid Arthritis and Gout in the United States: A Crossroad

Sian Yik Lim[1], Na Lu[1], Mark Fisher[1], Amar Oza[1], Sharan K. Rai[2], Mariano E Menendez[1] and Hyon Choi[1], [1]Division of Rheumatology, Allergy and Immunology, Massachusetts General Hospital, Harvard Medical School, Boston, MA, [2]Experimental Medicine, University of British Columbia, Vancouver, BC, Canada

First publication: September 29, 2015

SESSION INFORMATION

Session Date: Monday, November 9, 2015

Session Title: Rheumatoid Arthritis - Clinical Aspects II: Infection, Malignancy and Other Comorbidites in RA

Session Type: ACR Concurrent Abstract Session

Session Time: 2:30PM-4:00PM

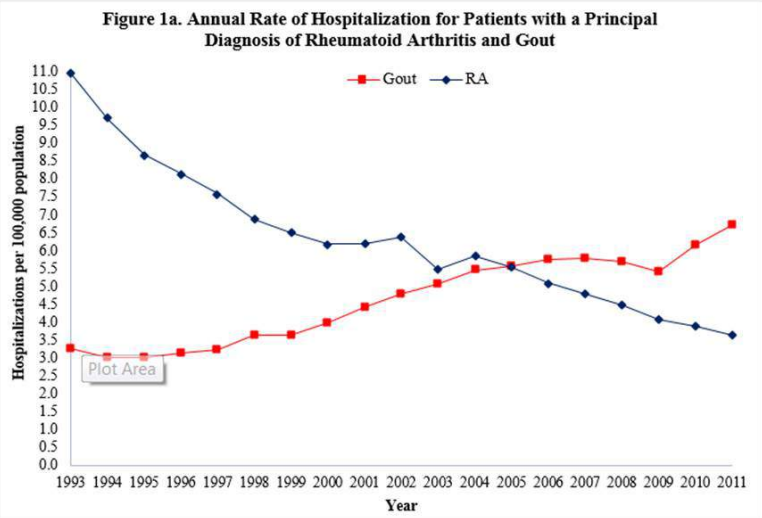
Background/Purpose: Rheumatoid arthritis (RA) and gout are the two most common inflammatory *arthritides in the US and beyond*. As hospitalization for these conditions are known to incur substantial resource use, hospitalization trends and associated costs could provide critical benchmarks to the field. Indeed, varying levels of perceived success in their care (including the

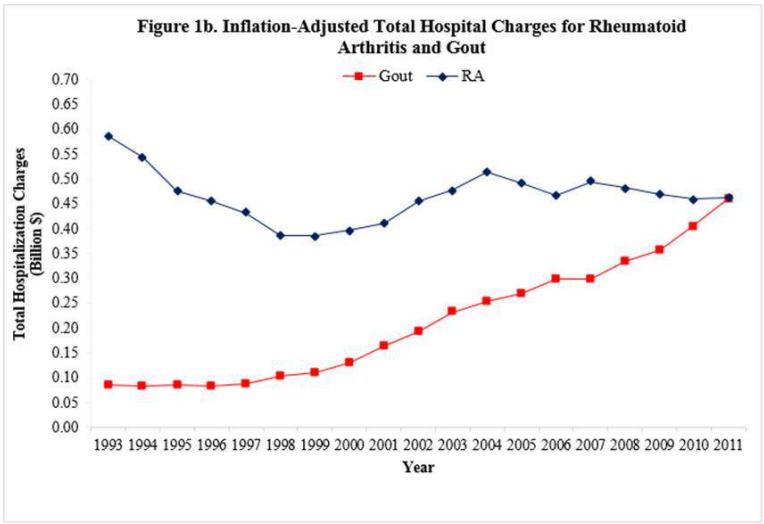
effects of new medications) and changing epidemiology (particularly for gout) may have made a substantial impact over the past several decades; however, no relevant data are available. To address this key knowledge gap, we evaluated hospitalization trends between 1993 and 2011 in the US.

Methods: We used the National Inpatient Sample (NIS), a database representative of hospitalizations in the US. We studied hospitalization trends of RA and gout (as the primary/principal discharge diagnosis using ICD-9-CM codes 714.0, 714.2, 714.30-714.33 and 274.0-274.9, respectively) from 1993 through 2011. We used total hospital charge trends as a proxy for total cost trends, as charge data were available for the entire study period. Additionally, we analyzed available cost data during the latest years (2006-2011), as well as the trend of the number of surgeries of total knee replacement, total hip replacement, and other major joint surgeries from 2002-2011, where these data were collected in the NIS.

Results: In 1993, admissions for RA were more than 3 times frequent than those for gout (**Figure 1a**). From 1993 to 2011, the admission rate for RA rapidly declined from 10.9 to 3.6 per 100,000 US adults, whereas that for gout steadily increased from 3.3 to 6.7 per 100,000 US adults, resulting in a reversal of hospitalization frequency between the two conditions in 2011. Inflation-adjusted total hospital charge trends for the two conditions reflected the hospitalization trends and became equal in 2011 ($0.46 billion USD) (**Figure 1b**). The available cost data over the last 6 years reflected the same trend, resulting in $0.13 billion USD for both conditions. Approximately 70% of RA admissions and 3% of gout admissions was associated with total joint replacement or other major joint surgeries from 2002-2011; the trend of the total number of such surgeries in the two conditions reflected overall hospitalization trends.

Conclusion: Our findings based on these nationally representative inpatient data indicate that primary hospitalization rates and the inpatient economic burden for RA have declined substantially over the past two decades, whereas those for gout has increased considerably. These strikingly contrasting trends provide a benchmark for the perceived improvement in RA care (likely related to the use of biologics), thereby preventing joint replacements; they also reflect suboptimal gout care in addition to its increasing prevalence. These data support the need to improve gout prevention and care.





Disclosure: **S. Y. Lim**, None; **N. Lu**, None; **M. Fisher**, None; **A. Oza**, None; **S. K. Rai**, None; **M. E. Menendez**, None; **H. Choi**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/hospitalization-trends-of-rheumatoid-arthritis-and-gout-in-the-united-states-a-crossroad

Abstract Number: 2049

Long Term Effectiveness of Herpes Zoster Vaccine Among Patients with Autoimmune and Inflammatory Diseases

Huifeng Yun[1], Fenglong Xie[2], John Baddley[3], Kevin L. Winthrop[4], Lang Chen[5] and Jeffrey R. Curtis[6], [1]Epidemiology, University of Alabama at Birmingham, Birmingham, AL, [2]Rheumatology & Immunology, University of Alabama at Birmingham, Birmingham, AL, [3]Medicine, University of Alabama at Birmingham, Birmingham, AL, [4]Oregon Health and Science University, Portland, OR, [5]University of Alabama at Bimingham, Birmingham, AL, [6]University of Alabama at Birmingham, Birmingham, AL
First publication: September 29, 2015

SESSION INFORMATION
Session Date: Monday, November 9, 2015
Session Title: Rheumatoid Arthritis - Clinical Aspects II: Infection, Malignancy and Other Comorbidites in RA

Session Type: ACR Concurrent Abstract Session
Session Time: 2:30PM-4:00PM

Background/Purpose:

The live herpes zoster (HZ) vaccine is effective in healthy older people to reduce the incidence and burden of HZ. Recent results from a long-term follow-up study of participants in the Shingles Prevention Study trial has shown that its protection attenuates by 10 years. The corresponding duration of protection afforded by vaccination for patients with autoimmune or inflammatory (AI) diseases is unclear.

Methods:

Using Medicare from 2006-2012 for patients with AI diseases, this retrospective cohort study identified HZ vaccinated patients who had no history of HZ before HZ vaccination, and had been continuously enrolled in Medicare Parts A, B and D during the 12 months prior to HZ vaccination (baseline) and throughout follow up. To control for confounding, patients without HZ vaccination were matched 2:1 to those with HZ vaccination on year of vaccination, age, gender, race, AI disease, biologic use, DMARDs and steroids. HZ cases were defined as the presence of an HZ diagnostic code plus concomitant anti-viral therapy. Follow up started one month after vaccination and ended at the earliest date of: HZ, death, loss of Medicare coverage or Dec 31, 2012. Matched patients were censored when vaccinated and then allowed to be included in the vaccination group. We calculated HZ incidence rates (IRs) yearly and used Poisson regression for repeated measures to calculate the adjusted risk ratio of HZ for each year using the first year as the reference.

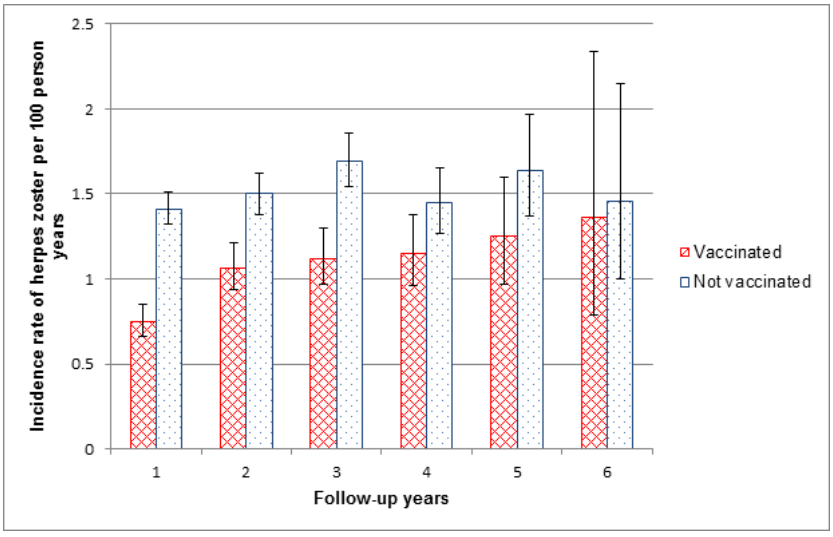
Results:

In the AI cohort, 46.5% had rheumatoid arthritis, 31.7% psoriasis, 4.5% psoriatic arthritis, 21.1% inflammatory bowel disease, and 1.4% ankylosing spondylitis. Of 43,369 HZ vaccinated patients and 86,738 matched unvaccinated patients, we identified 820 and 2,265 HZ events respectively. IRs among vaccinated increased from 0.75 per 100 person years in the 1st year post vaccination to 1.36 in the 6th year post (Figure). The HZ IRs among unvaccinated remained steady through the 6 years. After multivariable adjustment, vaccinated patients had significantly lower HZ risk compared to those not vaccinated in year 1 (RR 0.52, 95% CI 0.45-0.61), with waning protection over 5 years. By year 6, no significant protection against HZ was demonstrable (RR 0.92, CI: 0.45 – 1.86).

Conclusion:

HZ vaccine effectiveness decreased over time among patients with autoimmune and inflammatory diseases. Protection related to the live HZ vaccine appears to wane over 5 years, and re-vaccination might be considered at that time.

Figure: Incidence rate (IR) and 95% Confidence Interval for herpes zoster over time among patients who had HZ vaccination compared to the matched patients not vaccinated.



Disclosure: H. Yun, Amgen, 2; **F. Xie**, None; **J. Baddley**, Pfizer, Astellas, Merck, 5,BMS, 2; **K. L. Winthrop**, BMS, 2,AbbVie,

BMS, UCB, Amgen, 5; **L. Chen**, None; **J. R. Curtis**, Roche/Genentech, UCB, Janssen, CORRONA, Amgen, Pfizer, BMS, Crescendo, AbbVie, 2,Roche/Genentech, UCB, Janssen, CORRONA, Amgen, Pfizer, BMS, Crescendo, AbbVie, 5.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/long-term-effectiveness-of-herpes-zoster-vaccine-among-patients-with-autoimmune-and-inflammatory-diseases

Abstract Number: 2050

Herpes Zoster during the Tofacitinib Clinical Development Program for RA: Characterization of Herpes Zoster Incidence and Evaluation of Whether Herpes Zoster Predicts Subsequent Serious Infections or Malignancy

Kevin L. Winthrop[1], Yoshiya Tanaka[2], Kunihiro Yamaoka[3], Jeffrey R. Curtis[4], Chudy Nduaka[5], Haiyun Fan[5], Pinaki Biswas[6], Tomohiro Hirose[7], Sriram Krishnaswami[8], Hernan Valdez[6], Shigeyuki Toyoizumi[7], Koshika Soma[8] and Connie Chen[6], [1]Oregon Health & Science University, Portland, OR, [2]The First Department of Internal Medicine, University of Occupational and Environmental Health, Kitakyushu, Japan, [3]Keio University, Tokyo, Japan, [4]University of Alabama at Birmingham, Birmingham, AL, [5]Pfizer Inc, Collegeville, PA, [6]Pfizer Inc, New York, NY, [7]Pfizer Japan Inc, Tokyo, Japan, [8]Pfizer Inc, Groton, CT
First publication: September 29, 2015

SESSION INFORMATION
Session Date: Monday, November 9, 2015
Session Title: Rheumatoid Arthritis - Clinical Aspects II: Infection, Malignancy and Other Comorbidites in RA
Session Type: ACR Concurrent Abstract Session
Session Time: 2:30PM-4:00PM

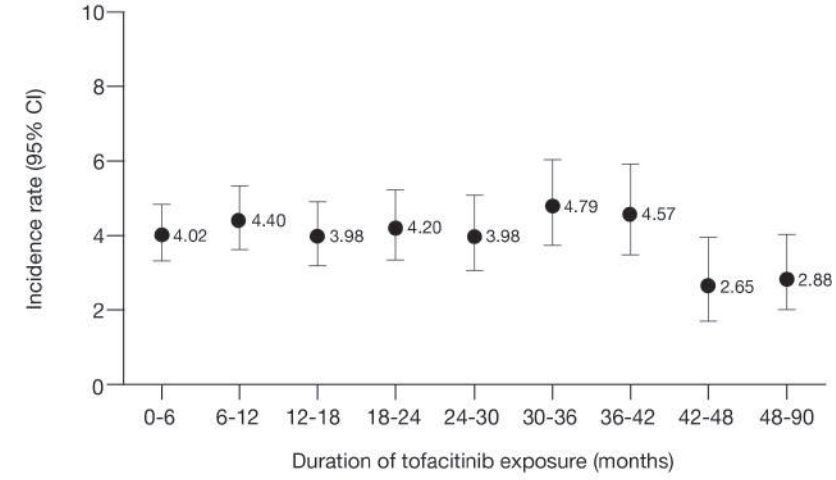
Background/Purpose: Tofacitinib is an oral Janus kinase inhibitor for the treatment of RA. The risk of herpes zoster (HZ) was elevated within the tofacitinib clinical development program, although it is unclear how HZ changed over time or whether HZ predicts the development of other events associated with immunosuppression, such as serious infection events (SIEs) or malignancy.

Methods: HZ cases were identified from Phase 1, 2, 3, and long-term extension (LTE) studies of the tofacitinib RA clinical development program (data cut-off April 2014; 1 LTE ongoing, database not locked). Crude incidence rates (IRs; patients with events per 100 patient-years, with 95% confidence intervals [CIs]) were calculated for HZ during discrete 6-month intervals of tofacitinib exposure. Characteristics of HZ events were summarized descriptively. We then evaluated whether HZ predicted subsequent SIE or malignancy (excluding non-melanoma skin cancer [NMSC]). Crude IRs for these outcomes were calculated among patients (pts) with/without prior HZ cases. For SIEs, Cox hazard models were used to evaluate the SIE risk difference between pts with and without prior HZ cases while controlling for other potential risk factors. This approach was not possible for malignancies due to the small number of events.

Results: There were 636 tofacitinib-associated HZ events in 6192 pts with 16,839 patient years of tofacitinib exposure. The overall IR (95% CI) for HZ was 4.04 (3.73, 4.37), with similar IRs across exposure durations (Fig 1). Among HZ cases, 84.3% (536) were female, median age 57 years, and 54.4% (346) were using corticosteroids at baseline. During tofacitinib exposure, 89.6% (570) of pts with HZ received anti-viral agents, and 7.4% (47) had a recurrence of HZ. Most HZ first events (93.9%) involved a single dermatome (95% resolved with treatment; 5% ongoing). None involved visceral dissemination or death. Post-herpetic neuralgia was infrequent (7.4%). Discontinuation due to a first HZ event occurred in 8.0% of cases. Among first non-serious HZ cases, 32 pts had a subsequent SIE (IR: 2.94 [2.01, 4.15]) and 9 pts had a subsequent malignancy (excluding NMSC; IR: 0.81 [0.37, 1.54]). In pts without HZ, IRs for SIEs (2.66 [2.40, 2.94]) and malignancy (0.94 [0.79, 1.12]) were similar. In the multivariable analysis (Fig 2), pts with HZ cases were no more likely to develop SIEs than pts without prior HZ (Hazard Ratio 0.77, p=0.172).

Conclusion: Within the RA clinical development program for tofacitinib, HZ incidence was stable over 90 months of exposure. Pts who developed HZ were no more likely to develop a subsequent SIE or malignancy as compared with those without HZ.

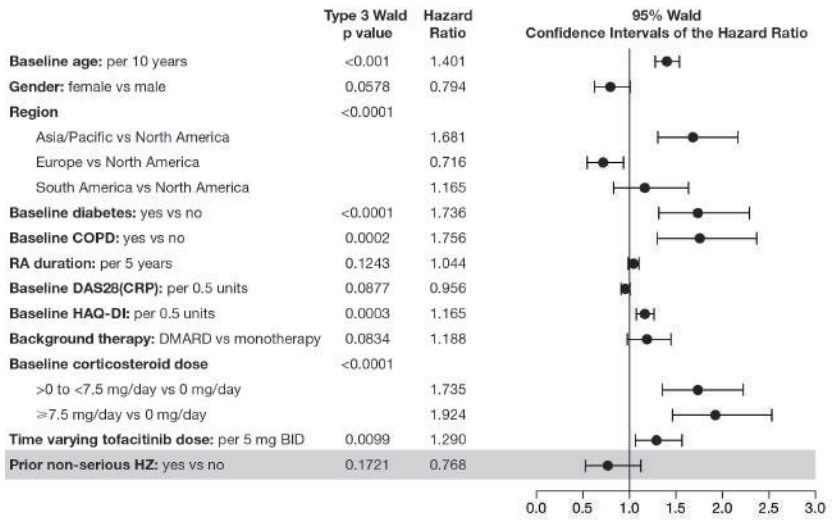
Figure 1. Incidence rates of first herpes zoster: all doses tofacitinib over discrete 6-month intervals



Patients	6192	5220	4651	4072	3666	3157	2845	2216	1573
Total pt-yrs	2810	2455	2155	1924	1672	1497	1260	910	1201
Patients with event	112	107	85	80	66	71	57	24	34

Data as of April 2014.
IRs are patients with events per 100 patient-years. Bars indicate 95% confidence limits.
CI, confidence interval; IR, incidence rate; pt-yrs, patient-years.

Figure 2. Risk factors for serious infection and subsequent risk of SIE post-non-serious herpes zoster from a Cox model analysis in Phase 1, Phase 2, Phase 3, and long-term extension studies



Only non-serious HZ cases were included. Follow-up data were not available for patients with serious HZ due to protocol requirement for discontinuation due to serious HZ.
Data as of April 2014.
Total patients analyzed = 5837
Number of patients with SIEs = 454
COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; DMARD, disease-modifying antirheumatic drug, DAS28, disease activity score in 28 joints; HAQ-DI, health assessment questionnaire-disability index; HZ, herpes zoster; SIEs, serious infection events

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Disclosure: K. L. Winthrop, Pfizer Inc, 2; **Y. Tanaka**, Abbvie, Chugai, Astellas, Takeda, Santen, Mitsubishi-Tanabe, Pfizer Inc, Janssen, Eisai, Daiichi-Sankyo, UCB, GlaxoSmithKline, and Bristol-Myers Squibb, 5,Abbvie, Chugai, Astellas, Takeda, Santen, Mitsubishi-Tanabe, Pfizer Inc, Janssen, Eisai, Daiichi-Sankyo, UCB, GlaxoSmithKline, and Bristol-Myers Squibb, 8,Abbvie, Chugai, Astellas, Takeda, Santen, Mitsubishi-Tanabe, Pfizer Inc, Janssen, Eisai, Daiichi-Sankyo, UCB, GlaxoSmithKline, and Bristol-Myers Squibb, 5,Mitsubishi-Tanabe, Chugai, MSD, Astellas, and Novartis, 2; **K. Yamaoka**, Pfizer Inc, 8,Pfizer Inc, 5; **J. R. Curtis**, Pfizer Inc, 2,Pfizer Inc, 5; **C. Nduaka**, Pfizer Inc, 1,Pfizer Inc, 3; **H. Fan**, Pfizer Inc, 1,Pfizer Inc, 3; **P. Biswas**, Pfizer Inc, 1,Pfizer Inc, 3; **T. Hirose**, Pfizer Japan Inc, 3; **S. Krishnaswami**, Pfizer Inc, 1,Pfizer Inc, 3; **H. Valdez**, Pfizer Inc, 1,Pfizer Inc, 3; **S. Toyoizumi**, Pfizer Japan Inc, 3; **K. Soma**, Pfizer Inc, 1,Pfizer Inc, 3; **C. Chen**, Pfizer Inc, 1,Pfizer Inc, 3.

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Abstract Number: 2051

Risk for Lower Intestinal Perforations in RA Patients Treated with Tocilizumab in Comparison to Treatment with TNF Inhibitors, Rituximab, Abatacept or Conventional Synthetic Dmards

Anja Strangfeld[1], Adrian Richter[2], Peter Herzer[3], Karin Rockwitz[4], Winfried Demary[5], Martin Aringer[6], Angela Zink[7] and Joachim Listing[8], [1]Epidemiology, German Rheumatism Research Center, Berlin, Germany, [2]German Rheumatism Research Center, Berlin, Germany, [3]Rheumatologist, Scientific Advisory Board, München, Germany, [4]Rheumatologic Practice, Goslar, Germany, [5]Rheumatologist, Hildesheim, Germany, [6]Rheumatology, Medicine III, University Clinical Center, Technical University Dresden, Dresden, Germany, [7]Epidemiologie, Deutsches Rheuma-Forschungszentrum, Berlin, Germany, [8]Epidemiology, DRFZ, Berlin, Germany

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Session Title: Rheumatoid Arthritis - Clinical Aspects II: Infection, Malignancy and Other Comorbidites in RA

Session Type: ACR Concurrent Abstract Session

Session Time: 2:30PM-4:00PM

Background/Purpose: Interleukin-6 has a direct protective effect on intestinal cells. Although several cases of lower intestinal perforations (LIP) were reported in clinical trials of tocilizumab (TCZ), the incidence in daily care remains unclear. The event rate is low in patients with rheumatoid arthritis (RA), and several factors may contribute to the risk for LIP. We aimed to examine the incidence of LIP in RA patients treated with biologic or conventional synthetic DMARDs (bDMARDs, csDMARDs).

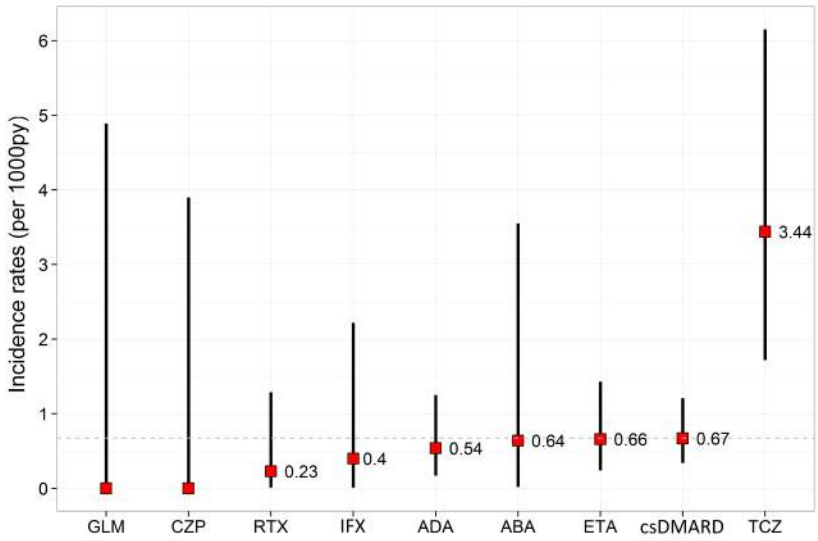
Methods: We used data from the German biologics register RABBIT with 13,600 RA patients included since 2001 at start of a csDMARD or bDMARD after at least one csDMARD failure. All serious gastrointestinal adverse events reported until 30th April 2015 which were possibly associated with perforations (including haemorrhages) were filtered (n=137) and validated with medical records or specific queries, blinded for treatment exposure. Only events with a definite (non-traumatic and non-iatrogenic) perforation of the lower intestinal tract were selected for the analysis. Treatment exposure was defined as treatment given in the last 3-months before the event. Due to low numbers of events multi-variable adjustment was not applied.

Results: In total, 35 LIPs (colon/sigma: 30, appendix: 4, terminal ileum: 1) were observed in 48,102 patient years (PY) - 16 of the patients died. In total, 27 of 35 patients with LIP had concomitant GCs, with a daily dose of ≥7,5mg in 12 patients. In the univariate analysis, current use of glucocorticoids (GC) and age were significantly associated with a higher risk of LIP (hazard ratio (HR) 1.25 per 5mg increase in GC dose [95%CI=1.2, 1.4], and HR 1.5 [1.3, 1.9] per 5 years increase in age).

11 LIP were observed in 1,765 patients treated with TCZ, corresponding to a five times higher incidence rate than in patients receiving csDMARDs only (IRR 5.1 (2.2, 11.8)). The incidence rate was also higher compared to patients treated with other bDMARDs (figure). The increased risk could not be explained by GC use and age of the TCZ treated patients which were similar to patients treated with other bDMARDs.

None of the patients with LIP had a history of diverticulitis known to the treating rheumatologist. Most often, diverticulitis was diagnosed simultaneously with LIP.

The incidence rates in anti-TNF treated patients in RABBIT were similar to those reported by others[1].



Conclusion: This 1st comparison of all bDMARDs available for the treatment of RA showed a significant risk of LIPs in patients treated with TCZ and confirms the signal detected in clinical trials. In none of the patients with LIP a history of diverticulitis was known, which may therefore not constitute sufficient information to support treatment decisions. To avoid additive effects on the risk of LIP concomitant GCs, should be tapered with initiation of TCZ treatment.

(1) Myasoedova E, et al. (2012). *J Rheumatol* 39(7):1355-1362.

Disclosure: A. Strangfeld, AbbVie, Celltrion, Hospira, Bristol-Myers Squibb, MSD Sharp&Dohme, Pfizer, Roche, and UCB., 2,BMS, Merck-Sharp & Dohme, Pfizer, Roche, Sanofi-Aventis, 9; **A. Richter**, None; **P. Herzer**, Abbvie, 9,Pfizer Inc, 9; **K. Rockwitz**, None; **W. Demary**, None; **M. Aringer**, Pfizer Inc, 9; **A. Zink**, AbbVie, Celltrion, Hospira, Bristol-Myers Squibb, MSD Sharp&Dohme, Pfizer, Roche, and UCB., 2,BMS, Merck-Sharp & Dohme, Pfizer, Roche, UCB., 9; **J. Listing**, AbbVie, Celltrion, Hospira, Bristol-Myers Squibb, MSD Sharp&Dohme, Pfizer, Roche, and UCB., 2,Pfizer Inc, 5.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/risk-for-lower-intestinal-perforations-in-ra-patients-treated-with-tocilizumab-in-comparison-to-treatment-with-tnf-inhibitors-rituximab-abatacept-or-conventional-synthetic-dmards

Abstract Number: 2052

Lymphoma in Patients with Rheumatoid Arthritis Treated with Biologic Drugs: Long-Term Follow-up of Risks and Lymphoma Subtypes

Karin Hellgren[1], Christer Sundström[2], Johan Askling[3], Eva Baecklund[4] and on behalf of the ARTIS study group, [1]Clinical Epidemiology Unit and Rheumatology Unit, Department of Medicine, Karolinska Institute at Karolinska University Hospital, Stockholm, Sweden, [2]Department of Genetics and Pathology, Uppsala University, Uppsala, Sweden, [3]Clinical Epidemiology Unit and Rheumatology Unit, Department of Medicine, Karolinska Institute, Stockholm, Sweden, [4]Rheumatology, Department of Medical Sciences, University Hospital, Uppsala, Sweden

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SESSION INFORMATION

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Session Title: Rheumatoid Arthritis - Clinical Aspects II: Infection, Malignancy and Other Comorbidites in RA

Session Type: ACR Concurrent Abstract Session

Session Time: 2:30PM-4:00PM

Background/Purpose: The long-term lymphoma risk in patients with rheumatoid arthritis (RA) treated with biologic disease modifying anti-rheumatic drugs (bDMARDs) remains a concern. The aim of this study was to extend assessments of overall and subtype-specific lymphoma risks with bDMARD therapy in RA.

Methods: By linking data from the nationwide Swedish Biologics (ARTIS), Patient, and Cancer Registers, we assembled a cohort of 13,240 RA patients starting a first bDMARD 1998-2012. As comparators we identified a national cohort of bio-naïve RA patients (n=46,568), and an age and gender matched general population referent cohort (n=458,846). Patients were followed until the first of lymphoma, emigration, death, end of study period (Dec 31, 2012) or start of bDMARD (for bio-naïve patients). We estimated hazard ratios (HR) using Cox models for lymphoma overall and for specific lymphoma subtypes according to ICD10-codes, adjusted for age, sex, calendar time, and selected co-morbidities. A histopathological review confirmed agreement between ICD-codes and the clinical subtype diagnosis in >80% of cases.

Results: We found 69 lymphomas during 75,661 person-years (py) in the bDMARD treated patients, 241 lymphomas (237,789 py) in the bio-naïve patients, and 1413 lymphomas (2,890,131 py) in the general population referent cohort. All of the bDMARD treated lymphoma patients were exposed to TNFi, 3 also to abatacept, 2 to anakinra and 2 to rituximab. Compared to the general population both bDMARD treated (HR=2.5; 95% CI 2.0-3.3) and bio-naïve patients (HR=2.2; 95% CI 1.9-2.5) were at increased risk for lymphoma. The lymphoma risk following start of a first TNFi (mean follow-up 5.9 years, maximum follow-up 15 years) or start of a first bDMARD were similar and not significantly increased compared to bio-naïve RA patients (HR bDMARD=1.2; 95% CI 0.9-1.6). There were no significant differences in HRs with age and calendar period at bDMARD start, time since treatment start or time on active bDMARD treatment in bDMARD treated vs. bio-naive RA. We noted a higher point estimate of lymphoma risk in men (HR=1.5) vs. women (HR=1.1); this difference was borderline significant (p=0.04).

There were no clear differences in lymphoma risks for different TNFi drugs (infliximab, etanercept, adalimumab). Due to few events, we abstained from assessing lymphoma risks for specific other bDMARDs.

Compared to the general population, bio-naive and bDMARD-treated RA patients were both at increased risks for most common lymphoma subtypes (Table).

Conclusion: Overall, the lymphoma risk in RA remains increased compared to the general population. TNFi-treatment with a mean follow-up for 5.9 years or overall bDMARD therapy does not substantially influence this risk. The distribution of lymphoma subtypes warrants further assessment.

Table Hazard Ratios for lymphoma overall and for specific lymphoma subtypes in patients with RA, treated with bDMARD (n=13,240) 1998-2012 and bio-naïve RA patients (n=46,568) versus general population comparator subjects (n=458,846) 2001-2012.

Lymphoma subtype[1]	N. lymphoma in bDMARD treated RA vs. general population	HR (95% CI)[6]	N. lymphoma in bio-naive RA vs. general population	HR (95% CI)[6]
All lymphoma	69/1413	2.5 (2.0-3.3)	241/1413	2.2 (1.9-2.5)
B-cell lymphoma	24/515	2.7 (1.7-4.1)	100/515	2.5 (2.0-3.1)
DLBCL[2]	18/371	2.9 (1.8-4.7)	80/371	2.8 (2.2-3.6)
Follicular lymphoma	9/203	2.1 (1.1-4.1)	29/203	1.8 (1.2-2.6)
CLL[3]	9/309	1.7 (0.9-3.3)	22/309	0.9 (0.6-1.4)
T/NK[4] cell lymphoma	7/69	6.0 (2.7-13.3)	9/69	1.4 (0.7-3.0)
Hodgkin lymphoma	7/55	4.7 (2.0-11.0)	13/55	2.7 (1.4-5.1)

[1]According to World Health Organization (WHO) classification, [2]DLBCL= Diffuse large B-cell lymphoma, [3]CLL= Chronic lymphocytic lymphoma [4] T/NK= T and natural killer cell, [6] Hazard ratios (HRs) with 95 % confidence interval adjusted for age, sex, and calendar time.

Disclosure: K. Hellgren, None; **C. Sundström**, None; **J. Askling**, AstraZeneca, Pfizer, UCB, Roche, Merck, BMS, Abbvie, 9; **E. Baecklund**, None.

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http://acrabstracts.org/abstract/lymphoma-in-patients-with-rheumatoid-arthritis-treated-with-biologic-drugs-long-term-follow-up-

of-risks-and-lymphoma-subtypes

Abstract Number: 2053

Adjustment of Skeletal Muscle Mass Estimates for the Extent of Adiposity Strengthens Relationships with Functional Outcomes in Rheumatoid Arthritis

Joshua Baker[1], Jon Giles[2], Mary Leonard[3], David Weber[4], Jin Long[5], Erik Jorgenson[6] and Patricia P. Katz[7],
[1]Medicine/Rheumatology, University of Pennsylvania, Philadelphia, PA, [2]Rheumatology, Columbia University Medical Center, NY, NY, [3]Stanford University, Palo Alto, CA, [4]Rochester University, Rochester, NY, [5]Children's Hospital of Philadelphia, Philadelphia, PA, [6]University of Pennsylvania, Philadelphia, PA, [7]Rheumatology, UCSF, SF, CA
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SESSION INFORMATION
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Session Title: Rheumatoid Arthritis - Clinical Aspects II: Infection, Malignancy and Other Comorbidites in RA
Session Type: ACR Concurrent Abstract Session
Session Time: 2:30PM-4:00PM

Background/Purpose: Skeletal muscle loss in rheumatoid arthritis (RA) has been described in association with poor physical functioning. Greater adiposity is simultaneously associated with both greater muscle mass and worse physical function and therefore is a potential confounder in the assessment of relationships between muscle and physical function. We aimed to determine if adjustment of muscle mass estimates for adiposity improves correlations with physical function in patients with RA.

Methods: Three large independent RA cohorts from academic institutions in the US were retrospectively analyzed in a cross-sectional design. Whole-body Dual-Energy Absorptiometry (DXA) measures of appendicular lean mass index (ALMI, kg/m^2) and fat mass index (FMI, kg/m^2) were converted to age, sex, and race-specific Z-Scores using NHANES reference ranges. Fat-adjusted ALMI Z-Scores (ie. standard deviations below average for that level of adiposity) were determined using a novel, comprehensive residual method to adjust for the normal age, sex, and race-specific associations between ALMI and FMI Z-Scores within NHANES. Associations between ALMI Z-Scores (standard and fat-adjusted) and physical functioning were assessed over the range of adiposity adjusting for age, sex, study, and disease activity measures, and assessing for interaction. Functional outcomes assessed included the Health Assessment Questionnaire (HAQ), Valued Life Activities assessment (VLA), and Short Physical Performance Battery (SPPB). Low lean for age was defined as an ALMI or fat-adjusted ALMI Z-Score of ≤ -1.

Results: A total of 415 patients were studied across the cohorts. The combined cohort had a mean ALMI Z-Score of -0.54, mean FMI Z-Score of -0.21, and mean fat-adjusted ALMI Z-Score of -0.53 (all $p<0.001$) suggesting significant muscle deficits compared with national reference ranges before and after adjustment for adiposity. Fat-adjusted ALMI Z-Scores demonstrated stronger associations with all three functional outcomes across all cohorts after adjustment for age and sex (Table). Associations were not attenuated with adjustment for CRP or pain scores. There was an independent association between FMI Z-Score and physical functioning outcomes with a stronger association seen among patients with greater FMI Z-Score (p for interaction <0.05). Fat-adjusted definitions of low lean mass for age more clearly identified those with functional impairment as measured by the HAQ, VLA or SPPB.

Conclusion: Fat-adjusted estimates of skeletal muscle mass deficits demonstrate stronger correlations with physical functioning in RA and thus represent a valid and potentially useful and important outcome measure. Fat mass also demonstrates independent associations with physical function. These observations have far-reaching implications for how we interpret, treat, and study body composition and its impact on physical functioning in RA.

Table 1: Age and sex-adjusted associations between unadjusted/fat-adjusted measures of appendicular lean mass with physical functioning (HAQ, VLA, SPPB) in combined cohort. Observations were similar across all 3 cohorts.

	HAQ (N=415)		Ln(VLA) (N=291)		Ln(SPPB) (N=356)	
	β (95% CI)	p	β (95% CI)	p	β (95% CI)	p
Standard ALMI Z	-0.081 (-0.14, -0.019)	0.01	-0.047 (-0.11, 0.013)	0.12	-0.0021 (-0.043, 0.047)	0.93
Fat-adj ALMI Z	-0.17 (-0.22, -0.12)	<0.001	-0.12 (-0.17, -0.076)	<0.001	0.071 (0.11, 0.036)	<0.001

Abbreviations: HAQ= Health Assessment Questionnaire; VLA= Valued Life Activities; SPPB= Short Physical Performance Battery; ALMI= Appendicular Lean Mass Index; OR= Odds Ratio; CI= Confidence Interval

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Disclosure: J. Baker, None; **J. Giles**, None; **M. Leonard**, None; **D. Weber**, None; **J. Long**, None; **E. Jorgenson**, None; **P. P. Katz**, None.

Abstract Number: 2054

Randomized, Double-Blind, Phase 3 Study of Efficacy and Safety of ABP 501 Compared with Adalimumab in Subjects with Moderate to Severe Rheumatoid Arthritis

Stanley B. Cohen[1], Mark C. Genovese[2], Ernest H. Choy[3], Fernando Perez-Ruiz[4], Jose L. Pablos[5], Nan Zhang[6] and Primal Kaur[7], [1]Metroplex Clinical Research Center, Dallas, TX, [2]Division of Rheumatology, Stanford University Medical Center, Palo Alto, CA, [3]Cardiff University, Institute of Infection and Immunity, Tenovus Building, University Hospital of Wales, Cardiff, United Kingdom, [4]Servicio de Reumatología, Vizcaya, Spain, [5]Instituto de Investigacion Hospital, Madrid, Spain, [6]Biosimilars, Amgen, Inc., Thousand Oaks, CA, [7]Amgen, Inc., Thousand Oaks, CA

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SESSION INFORMATION

Session Date: Monday, November 9, 2015

Session Title: Rheumatoid Arthritis-Small Molecules, Biologics and Gene Therapy III: Biosimilars

Session Type: ACR Concurrent Abstract Session

Session Time: 2:30PM-4:00PM

Background/Purpose:

ABP 501 is being developed as a biosimilar candidate to adalimumab (Humira®), a fully human recombinant monoclonal antibody. Evidence from analytical comparisons indicates that ABP 501 is highly similar to adalimumab. Pharmacokinetic equivalence between ABP 501 and adalimumab has been demonstrated in a phase I study. Here we present results from the Phase 3 study evaluating the efficacy, safety and immunogenicity in subjects with moderate to severe rheumatoid arthritis (RA) for the first adalimumab biosimilar candidate.

Methods:

This was a randomized, double-blind, active-controlled, equivalence study in adult subjects with moderate to severe RA who had an inadequate response to methotrexate. Subjects were randomized 1:1 to receive either ABP 501 (n=264) or adalimumab (n=262) 40 mg subcutaneously every 2 weeks until week 22 followed by safety follow-up to week 26. The primary endpoint was risk ratio (RR) of ACR20 at week 24; clinical equivalence was evaluated by comparing the 90% confidence interval (CI) of RR with an equivalence margin of 0.738–1.355 (1/0.738). Key secondary endpoints included ACR50 and ACR70, safety, and immunogenicity.

Results:

Baseline characteristics were well balanced between groups. At week 24, 74.6% of subjects (194/260) in the ABP 501 group and 72.4% (189/261) in the adalimumab group met the ACR20 response criteria; the RR of ACR20 was 1.039 with the 2-sided 90% CI of 0.954–1.133, which fell within the predefined equivalence margin of 0.738–1.355. At week 24, 49.2% of patients (120/244) in the ABP 501 group and 52.0% (131/252) in the adalimumab group met the ACR50 response criteria, and 26.0% of subjects (64/246) in the ABP 501 group and 22.9% (58/253) in the adalimumab group met the ACR70 response criteria. The incidence of treatment-emergent adverse events (TEAEs) was 50.0% for ABP 501 and 54.6% for adalimumab, and the incidence of any adverse event leading to discontinuation of the investigational product was 1.9% in for ABP 501 and 0.8% for adalimumab. The most frequently reported TEAEs were nasopharyngitis (ABP 501, 6.4%; adalimumab, 7.3%), headache (ABP 501, 4.5%; adalimumab, 4.2%), and arthralgia (ABP 501, 3.0%; adalimumab, 3.4%), cough (ABP 501: 2.7%; adalimumab: 3.1%) and upper respiratory tract infection (ABP 501: 1.5%; adalimumab: 3.8%). The incidence of serious TEAEs was 3.8% for ABP 501 and 5.0% for adalimumab; of note, 0.8% of patients in the ABP 501 group and 1.1% in the adalimumab group experienced serious infections. The incidence of binding antibodies was 38.3% in the ABP 501 group and 38.2% in the adalimumab group; incidence of neutralizing antibodies was 9.1% in the ABP 501 group and 11.1% in the adalimumab group.

Conclusion: Clinical equivalence between ABP 501 and adalimumab was demonstrated. The overall safety and immunogenicity of ABP 501 and adalimumab were similar.

Disclosure: S. B. Cohen, Amgen, Abbvie, BI, Pfizer, Sandoz, 5; **M. C. Genovese**, Amgen, 5; **E. H. Choy**, Abbott, Allergan, Amgen, AZ, BMS, BI, Chelsea, Chugai, DaiichiSankyo, EliLilly, Ferring, GSK, Hospita, ISIS, Jazz, Janssen, MedImmune, Merrimack, MSD, Napp, Novimmune, Novartis, PierreFabre, Pfizer, Regeneron, Roche, Sanofi-Aventis, ScheringPlough, UCB, T, 5; **F. Perez-Ruiz**, Amgen, 9; **J. L. Pablos**, None; **N. Zhang**, Amgen, 3; **P. Kaur**, Amgen, 3.

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Abstract Number: 2055

A Phase III, Randomized, Double-Blind Clinical Study Comparing SB4, an Etanercept Biosimilar, with Etanercept Reference Product (Enbrel®) in Patients with Moderate to Severe Rheumatoid Arthritis Despite Methotrexate Therapy (52-week Results)

Jiri Vencovsky[1], Anna Sylwestrzak[2], Piotr Leszczyñski[3], Wieslawa Porawska[4], Asta Baranauskaite[5], Vira Tseluyko[6], Vyacheslav Zhdan[7], Barbara Stasiuk[8], Roma Milasiene[9], Aaron Alejandro Barrera Rodriguez[10], Soo Yeon Cheong[11], Jeehoon Ghil[11] and **Paul Emery**[12], [1]Rheumatology, Institute of Rheumatology and Department of Rheumatology, 1st Faculty of Medicine, Charles University, Prague, Czech Republic, [2]NZOZ Medica Pro Familia Sp. z o.o., Warsaw, Poland, [3]Rheumatology and Rehabilitation, Poznan University of Medical Sciences, Poznan, Poland, [4]Poznanski Osrodek Medyczny NOVAMED, Poznan, Poland, [5]Lithuanian University of Health Sciences, Kaunas, Lithuania, [6]Internal Medicine and Rheumatology, Kharkiv Medical Academy of Postgraduate Education, Kharkiv, Ukraine, [7]M.V.Sklifosovskyi Poltava Regional Clinical Hospital, Poltava, Ukraine, [8]Medicome Sp. z o.o., Oswiecim, Poland, [9]Klaipeda University Hospital, Klaipeda, Lithuania, [10]Unidad de Atención Medica e Investigación en Salud (UNAMIS), Yucatán, Mexico, [11]Samsung Bioepis Co., Ltd., Incheon, South Korea, [12]Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds, Leeds, United Kingdom

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Session Title: Rheumatoid Arthritis-Small Molecules, Biologics and Gene Therapy III: Biosimilars

Session Type: ACR Concurrent Abstract Session

Session Time: 2:30PM-4:00PM

Background/Purpose: SB4 is a biologic agent developed as a biosimilar of the etanercept reference product (ETN). This study

was a randomized, double-blind, multicenter study and the equivalence of the primary endpoint (ACR20 at Week 24) was shown[1]. In this abstract, the results up to 52 weeks of the study comparing the long term efficacy, safety and immunogenicity, including radiographic progression, between SB4 and ETN are reported.

Methods: Patients with moderate to severe RA (according to the 1987 ACR criteria) despite MTX treatment were randomly assigned to receive weekly dose of 50 mg SB4 or ETN administered subcutaneously for 52 weeks. Efficacy, safety and immunogenicity outcomes were assessed up to Week 52 and radiographic damage was measured by the change in modified total sharp score (mTSS) from baseline to Week 52.

Results: A total of 596 patients with RA were randomized to either SB4 (N=299) or ETN (N=297) and 505 patients completed 52 weeks of treatment (SB4 N=259; ETN N=246). The ACR20 response rate at Week 52 was 80.8% vs. 81.5% in the per-protocol set (PPS) and 70.2% vs. 65.7% in the full analysis set (FAS) with non-responder analysis. The 95% confidence interval (CI) of the adjusted difference in ACR20 response rate was within [–15%, 15%] in both the PPS and FAS. The ACR50 and ACR70 response rates were also similar between SB4 and ETN (Table 1) and the mean change from baseline in mTSS was comparable between the two treatment groups (0.45 for SB4 and 0.74 for ETN).

The safety profile of SB4 was generally comparable to that of ETN (Table 2). Fewer injection site reactions were reported in the SB4 group compared to ETN and the incidence of anti-drug antibody was significantly lower in SB4 compared to ETN ($p<$ 0.001).

Conclusion: Efficacy including radiographic progression and safety were comparable between SB4 and ETN up to Week 52. The immunogenicity profile was lower in SB4 compared to ETN.

Table 1. ACR Response Rates at Week 52 in the Full Analysis Set*

ACR response	Treatment	Response rate	Adjusted difference rate**	95% CI
ACR20	SB4	70.2% (210/299)	4.48%	(–2.90%, 11.87%)
	ETN	65.7% (195/297)		
ACR50	SB4	47.8% (143/299)	5.48%	(–2.32%, 13.29%)
	ETN	42.1% (125/297)		
ACR70	SB4	30.4% (91/299)	5.90%	(–1.12%, 12.93%)
	ETN	24.6% (73/297)		

CI: confidence interval

*FAS follows the intention-to-treat (ITT) principle and includes all patients with at least 1 dose of the study drug. Patients without response at Week 52 were considered as non-responders.

**The difference rate was adjusted for baseline C-reactive protein and stratified by region.

Table 2. Safety and Immunogenicity Results

Patients with	SB4 (N=299) n	(%)	ETN (N=297) n	(%)
At least 1 TEAE	175	(58.5%)	179	(60.3%)
related	88	(29.4%)	109	(36.7%)
At least 1 SAE	18	(6.0%)	15	(5.1%)
related	2	(0.7%)	7	(2.4%)
Serious infection	1	(0.3%)	5	(1.7%)
Tuberculosis	0	(0.0%)	0	(0.0%)
Injection site reactions*	11	(3.7%)	52	(17.5%)
Malignancy	4	(1.3%)	1	(0.3%)
Death	2	(0.7%)	0	(0.0%)
At least 1 ADA positive test result up to Week 52	3	(1.0%)	39	(13.2%)

ADA: anti-drug antibody, SAE: serious adverse event, TEAE: treatment-emergent adverse event

*Numbers are based on high-level group term of administration site reactions.

Reference

1. Vencovsky J et al. EULAR 2015, FRI0128

Disclosure: J. Vencovsky, Samsung Bioepis, 5; **A. Sylwestrzak**, Samsung Bioepis, 2; **P. Leszczyñski**, Samsung Bioepis, Roche, MSD, Janssen, NovoNordisk, UCB, Novartis, GSK, BMS, 2,Roche, MSD, UCB, Pfizer, AbbVie, 5; **W. Porawska**, Samsung Bioepis, 2; **A. Baranauskaite**, Samsung Bioepis, 2; **V. Tseluyko**, Samsung Bioepis, 2; **V. Zhdan**, Samsung Bioepis, 2; **B. Stasiuk**, Samsung Bioepis, 2; **R. Milasiene**, Samsung Bioepis, 2; **A. A. Barrera Rodriguez**, Samsung Bioepis, 2; **S. Y. Cheong**, Samsung Bioepis, 3; **J. Ghil**, Samsung Bioepis, 3; **P. Emery**, Samsung Bioepis, AbbVie, Pfizer, Merck, UCB, BMS, Sandoz, 5.

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Abstract Number: 2056

A Randomized, Double-Blind, Phase III Study Comparing SB2, an Infliximab Biosimilar, to the Infliximab Reference Product (Remicade®) in Patients with Moderate to Severe Rheumatoid Arthritis Despite Methotrexate Therapy: 54-Week Results

Jung-Yoon Choe[1], Nenad Prodanovic[2], Jaroslaw Niebrzydowski[3], Ivan Staykov[4], Eva Dokoupilova[5], Asta Baranauskaite[6], Roman Yatsyshyn[7], Mevludin Mekic[8], Wieslawa Porawska[9], Hana Ciferska[10], Krystyna Jedrychowicz-Rosiak[11], Agnieszka Zielinska[12], Jasmine Choi[13], Young Hee Rho[13] and **Josef S. Smolen**[14], [1]Division of Rheumatology, Daegu Catholic University Medical Center, Daegu, South Korea, [2]Clinical Center Banja Luka, Banja Luka, Bosnia, [3]Medica Pro Familia, Gdynia, Poland, [4]MHAT "Dr. Ivan Seliminski", AD, Sliven, Bulgaria, [5]MEDICAL PLUS s.r.o, Uherske Hradiste, Czech Republic, [6]Lithuanian University of Health Sciences, Kaunas, Lithuania, [7]SHEI Ivano-Frankivsk NMU, Ivano-Frankivsk, Ukraine, [8]University Clinic Centre Sarajevo, Sarajevo, Bosnia, [9]Poznanski Osrodek Medyczny NOVAMED, Poznan, Poland, [10]Revmatologicky ustav, Praha 2, Czech Republic, [11]MCBK S.C., Grodzisk Mazowiecki, Poland, [12]Medica Pro Familia Sp. z o.o. Spolka Komandytowo-Akcyjna, Warszawa, Poland, [13]Samsung Bioepis Co., Ltd., Incheon, South Korea, [14]Medical University of Vienna, Vienna, Austria

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SESSION INFORMATION

Session Date: Monday, November 9, 2015
Session Title: Rheumatoid Arthritis-Small Molecules, Biologics and Gene Therapy III: Biosimilars
Session Type: ACR Concurrent Abstract Session
Session Time: 2:30PM-4:00PM

Background/Purpose: SB2 is developed as a biosimilar of the infliximab reference product (INF). 30-week efficacy and safety results from a randomized phase III study were recently presented[1]. The objective of this study is to compare the long-term efficacy, safety and immunogenicity between SB2 and INF, including progression of radiographic damage, up to 54 weeks.

Methods: This study is a randomized, double-blind phase III study. Patients with moderate to severe RA (1987 ACR criteria) despite methotrexate (MTX) were randomized in a 1:1 ratio to receive either SB2 or INF (3 mg/kg). Dose increments were allowed after week 30 up to 7.5 mg/kg. Dosing occurred at week 0, 2, 6 and then every 8 weeks until week 46. Efficacy, safety and immunogenicity outcomes were assessed up to week 54 at each visit. Radiographic damage was assessed by the change of modified total sharp score (mTSS) from baseline to week 54.

Results: A total of 584 patients were randomized to either SB2 (N=291) or INF (N=293) and 452 patients completed 54 weeks of treatment (SB2 N=227, INF N=225). The ACR20 response rate at week 54 in the full analysis set (FAS) was 50.7% in SB2 and 52.6% in INF (Figure 1). The ACR50 and ACR70 responses were also similar (32.1% vs. 29.7%; 18.3% vs. 17.7%, Figure 1). Other secondary efficacy parameters at week 54 such as DAS28 or EULAR response were similar between the two treatment groups. The change of mTSS was comparable between the two treatment groups (mean change: 0.38 in SB2 vs. 0.37 in INF; cumulative probability plot is shown in Figure 2). The safety profile of SB2 was generally comparable to that of INF (Table 1). The overall anti-drug antibody positivity up to week 54 was 62.4% in SB2 and 57.5% in INF (p-value = 0.270).

Conclusion: Up to 54 weeks, SB2 showed comparable long-term efficacy, safety and immunogenicity to those of INF and well tolerated. In particular, radiographic progression was comparable between SB2 and INF at 54 weeks.

Reference

1. Choe JY et al. EULAR 2015, SAT0152

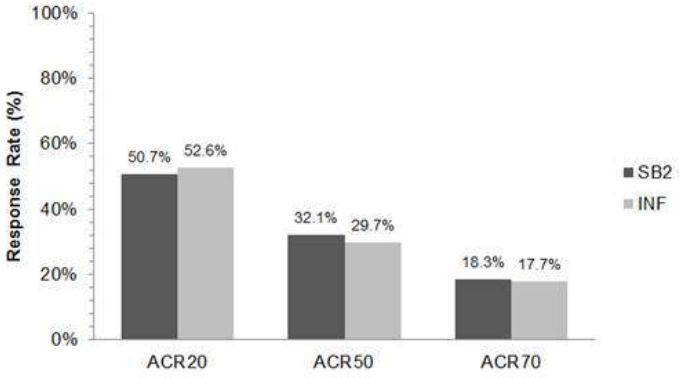

Figure 1. ACR20, 50, 70 Response Rates at Week 54 in the Full Analysis Set (FAS)*

*FAS follows the intention-to-treat (ITT) principle and includes all patients with at least 1 dose of the study drug. Patients without response at week 54 were considered as non-responders.

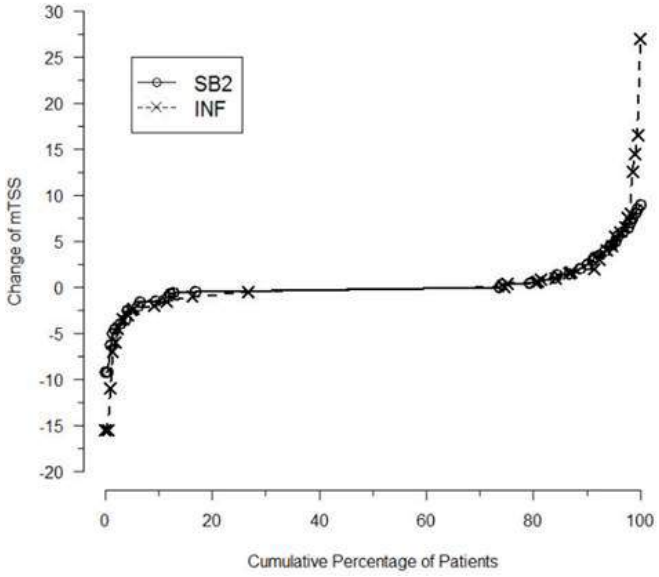

Figure 2. Cumulative Probability of Change in Modified Total Sharp Score (mTSS) from baseline at Week 54

Table 1. Safety Profile of the Study Population up to 54 weeks

Number of patients with	SB2 (N=290)*		INF (N=293)	
	n	%	n	%
At least 1 TEAE	179	61.7	191	65.2
At least 1 SAE	29	10.0	31	10.6
Total infections	85	29.3	110	37.5
Serious infections	9	3.1	6	2.0
Tuberculosis	1	0.3	1	0.3
Infusion-related reaction	17	5.9	15	5.1
Malignancy	2	0.7	0	0.0
Death	0	0	1	0.3

SAE: serious adverse event; TEAE: treatment-emergent adverse event.

*1 patient dropped out before receiving at least 1 dose of SB2.

Disclosure: J. Y. Choe, Samsung Bioepis, 2,Samsung Bioepis, 5; **N. Prodanovic**, Samsung Bioepis, 2; **J. Niebrzydowski**, Samsung Bioepis, 2; **I. Staykov**, Samsung Bioepis, 2; **E. Dokoupilova**, Samsung Bioepis, 2; **A. Baranauskaite**, Samsung Bioepis, AbbVie, 2; **R. Yatsyshyn**, Samsung Bioepis, 2; **M. Mekic**, Samsung Bioepis, 2; **W. Porawska**, Samsung Bioepis, 2; **H. Ciferska**, Samsung Bioepis, 2; **K. Jedrychowicz-Rosiak**, Samsung Bioepis, 2; **A. Zielinska**, Samsung Bioepis, 2; **J. Choi**, Samsung Bioepis, 3; **Y. H. Rho**, Samsung Bioepis, 3; **J. S. Smolen**, AbbVie, Jassen, MSD, Pfizer, Roche, UCB, 2,AbbVie, Amgen, AstraZeneca, Astro-Pharma, Celgene, GSK, Jassen, Lilly, Medimmune, MSD, Norvartis-Sandoz, Novo Nordisk, Pfizer, Roche, Samsung Bioepis, Sanofi, UCB, 5.

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Abstract Number: 2057

Antibodies to Infliximab in Remicade-Treated Rheumatic Patients Show Identical Reactivity Towards Biosimilars

Begoña Ruiz-Argüello[1], Ainara Maguregui[1], Ainhoa Ruiz del Agua[1], Dora Pascual-Salcedo[2], Ana Martínez[2], Teresa Jurado[3], Chamaida Plasencia[4], Alejandro Balsa[5], Francisca Llinares-Tello[6], José Rosas[7], Nerea Torres[1], Antonio Martínez[1] and **Daniel Nagore**[1], [1]R&D, Progenika-Grifols, Derio, Spain, [2]Immunology Unit, La Paz University Hospital-Immunology, Madrid, Spain, [3]Immunology, La Paz University Hospital-Idipaz, Madrid, Spain, [4]Rheumatology Unit, La Paz University Hospital-Rheumatology,

Madrid, Spain, [5]Rheumatology, La Paz University Hospital-Rheumatology Department, Madrid, Spain, [6]Clinical Analysis, Hospital Marina Baixa, Clinical Analysis, Villajoyosa, Spain, [7]Rheumatology, Hospital Marina Baixa, Villajoyosa, Spain
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SESSION INFORMATION
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Background/Purpose: Infliximab (IFX) is the most immunogenic of anti-TNFα drugs available to treat patients with rheumatic diseases. The recent approval of the first infliximab biosimilars in Europe has raised safety and efficacy concerns. Both Inflectra (IFT) and Remsima (RMS), contain exactly the same active molecule produced with the same manufacturing process, but branded differently. One of the main questions is whether patients treated with Remicade (RMC) can be effectively and safely switched to the biosimilar drug. The purpose of the study was to determine if antibodies to infliximab (ATI) in RMC-treated patients cross-react with the biosimilar.

Methods: A total of 256 samples from 256 patients with rheumatoid arthritis (RA) and Spondyloarthritis (SpA) under RMC were retrospectively selected for the study. Serum was collected immediately before the infusion (trough levels) and stored until the analysis. ATI trough levels were measured in parallel with three different bridging ELISA assays: a) Promonitor-ANTI-IFX CE marked kit (Progenika Biopharma SA, Spain) which uses RMC to crosslink patient anti-drug antibodies (ADA); b) the same assay but using RMS, and c) the same assay but using IFT. Briefly, bridging ELISA takes advantage of the two arms of immunoglobulins to crosslink precoated and HRP-conjugated IFX, used as a capture and detection reagent, respectively. The same cut-point (5 AU/mL), as recommended in the kit package insert, was used in the three assays. Spearman´s coefficient and percentages of agreement were used to study the correlation and association between each assay.

Results: In total, 131 samples out of 256 RMC-treated patient samples were tested positive with Promonitor-ANTI-IFX (51.2%, 131 patients). All were ATI-positive when either IFT or RMC bridging assays were used. Only one sample was positive to antibodies to the biosimilars and negative to antibodies against RMC (<5, 5.3 and 7.0 AU/mL of ATI for RMC, IFT and RMS, respectively), with very low ATI levels close to the cut-point, and attributed to experimental variability. Positive and Negative Percentage Agreements were 99.2%/100%, 99.2%/100% and 100%/100%, for RMC *vs.* IFT, RMC *vs.* RMS, and IFT *vs.* RMS, respectively. Spearman´s coefficients were determined to be 0.995, 0.996 and 0.998, for RMC *vs.* IFT, RMC *vs.* RMS, and IFT *vs.* RMS, respectively ($p<0.001$). This is the first study that demonstrates cross-immunogenicity between RMC and biosimilar molecules in patients with rheumatic diseases. Results are in agreement with previous data in patients with inflammatory bowel diseases.

Conclusion: ATI of RMC-treated patients cross-react with either IFT or RMS. Results suggest that the immune response is elicited by the same epitopes regardless of the molecule nature. ATI-positive patients treated with RMC should not be switched to a biosimilar treatment, since preexisting ATI will interact with the new drug, enhance clearance and potentially lead to loss of response and infusion-related reactions. Results also demonstrate that Promonitor-ANTI-IFX test can be used to monitor ATI in biosimilar-treated patients. This finding supports the utility for therapeutic drug monitoring before a switching strategy is considered.

Disclosure: B. Ruiz-Argüello, Progenika-Grifols, 3; **A. Maguregui**, Progenika-Grifols, 3; **A. Ruiz del Agua**, Progenika-Grifols, 3; **D. Pascual-Salcedo**, None; **A. Martínez**, None; **T. Jurado**, None; **C. Plasencia**, None; **A. Balsa**, None; **F. Llinares-Tello**, None; **J. Rosas**, None; **N. Torres**, Progenika-Grifols, 3; **A. Martínez**, Progenika-Grifols, 3; **D. Nagore**, Progenika-Grifols, 3.

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Abstract Number: 2058

Efficacy and Safety of Rituximab Biosimilar Candidate (CT-P10) and Innovator Rituximab in Patients with Rheumatoid Arthritis: Results from Phase I Randomized Controlled Trial over 72 Weeks

Dae-Hyun Yoo[1], Won Park[2], Chang-Hee Suh[3], Seung-Cheol Shim[4], Slawomir Jeka[5], Fidencio Cons Molina[6], Pawel Hrycaj[7], Wolfgang Spieler[8], Piotr Wiland[9], Jan Brzezicki[10], Eun Young Lee[11], Francisco G. Medina-Rodriguez[12], Pavel Shesternya[13], Sebastiao Radominski[14], Marina Stanislav[15], Volodymyr Kovalenko[16], Donghyuk Sheen[17], Leysan Myasoutova[18], Mie Jin Lim[19], Jung-Yoon Choe[20], Taek S. Kwon[21] and Sang Joon Lee[21], [1]Department of Rheumatology, Hanyang University Hospital for Rheumatic Diseases, Seoul, South Korea, [2]Division of Rheumatology, Department of Internal Medicine, Inha University Hospital, Incheon, South Korea, [3]Department of Rheumatology, Ajou University Hospital, Suwon, South Korea, [4]Department of Internal Medicine, Chungnam National University Hospital, Daejeon, South Korea, [5]University Hospital Nr 2 Dr. Jan Biziel, Collegium Medicum in Bydgoszcz, Nicolaus Copernicus University in Torun, Clinic of Rheumatology and Connective Tissue Diseases, Bydgoszcz, Poland, [6]Centro de Investigacion en Artritis y Osteoporosis, Mexicali, Mexico, [7]Department of Rheumatology and Clinical Immunology, Poznan University of Medical Sciences, Poznan, Poland, [8]Osteologie und Rheumatologie, ZeFOR GmbH Zentrum für Forschung, Zerbst, Germany, [9]Department of Rheumatology, Medical University of Wroclaw, Wroclaw, Poland, [10]Wojewodzki Szpital Zespolony w Elablagu, Elblag, Poland, [11]Division of Rheumatology, Department of Internal Medicine, Seoul National University College of Medicine, Seoul, South Korea, [12]Rheumatology, LaSalle University, Mexico City, Mexico, [13]Rheumatology Department, Krasnoyarsk State Medical University, Krasnoyarsk, Russia, [14]CETI-Centro de estudos em Terapias Inovadoras, Universidade Federal do Parana, Curitiba, Brazil, [15]Research Rheumatology Institute n. a. V.A. Nassonova, Moscow, Russia, [16]Section of Non-coronarogenic Myocardial Diseases and Clinical Rheumatology, National Scientific Center, Kiev, Ukraine, [17]Rheumatology, Eulji University Hospital, Daejeon, South Korea, [18]City Reumatology Center, Research Medical Complex Vashe Zdorovie, Kazan, Russia, [19]Division of Rheumatology, Departments of Internal Medicine, Inha University Hospital, Incheion, South Korea, [20]Internal Medicine, Catholic University of Daegu, School of Medicine, Daegu, South Korea, [21]CELLTRION, Inc., Incheon, South Korea
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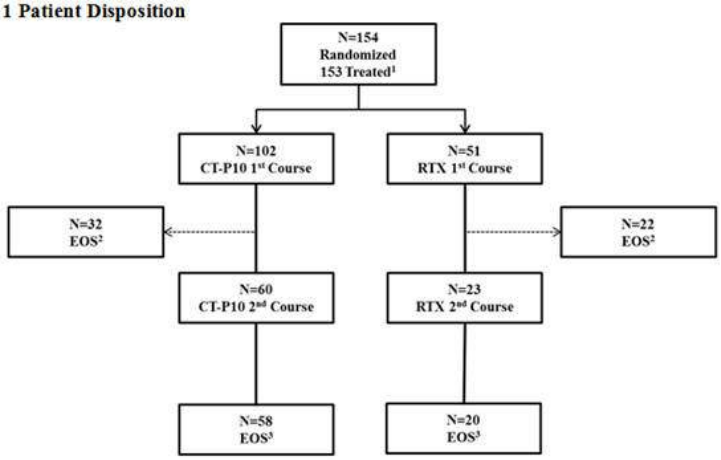
Background/Purpose: CT-P10 is a biosimilar candidate of innovator rituximab (RTX). PK profile and clinical data up to week 24 has been reported at ACR 2013[1]. Additional safety and efficacy were evaluated to confirm similarity between CT-P10 and RTX up to 72 weeks (NCT01534884).

Methods: Patients with active RA (1987 ACR criteria) and intolerant or unresponsive to anti TNF-a blocker were randomized 2:1 to receive 2 infusions (1,000 mg, IV each) of either CT-P10 or RTX, at a 2-week interval, in combination with methotrexate (MTX) and folic acid. The second course of treatment was initiated between weeks 24 ~ 48 based on disease activity and predefined safety criteria. The end of study visit for patients who did not receive the second course of treatment was conducted at week 48 (Figure 1). Efficacy was analyzed in per-protocol population.

Figure 1 Patient Disposition



Note: Patients received 2nd course depending on disease activity and predefined safety criteria from week 24 to week 48. Omitted 2nd course of treatment due to stable disease activity/safety/investigator decision/major deviation: CT-P10, 28/2/2/0; RTX, 19/0/2/1

[1] One patient did not receive a study drug due to difficulty to find the vein.

[2] Patients who did not receive 2nd course of treatment had the end of study visit at week 48.

[3] Patients who received both courses of treatment had the end of study visit at 24 weeks after the 2nd course of infusion.

Results: Of 154 patients randomized at baseline, 132 (85.7%) patients completed the study. The efficacy in terms of DAS28 changes and overall safety were comparable between CT-P10 and RTX treatment groups. The mean decreases from baseline in DAS28 at Week 24 after 1st and 2nd courses of treatment were similar between CT-P10 and RTX treatment groups (Table 1). The proportion of patients experienced at least one adverse event (AE), serious AE, infusion related reaction, infection, malignancy or lymphoma and discontinuation due to AE was similar between CT-P10 and RTX treatment groups (Table 2). Cervix carcinoma stage 0 was reported in a patient from RTX group, and no deaths were reported. B-cell kinetics between the CT P10 and RTX treatment groups were similar at all time points. The mean changes from baseline in IgM, IgG, and IgA were small, and there were no notable differences between the CT-P10 and RTX treatment groups.

Table 1 Efficacy of CT-P10 and Innovator Rituximab by DAS28 Changes

	CT-P10	RTX
DAS28-CRP, Mean ± SD (n)		
Baseline	6.0 ± 0.9 (100)	6.0 ± 0.8 (47)
Changes at Week 24 after 1st Course	−1.9 ± 1.2 (95)	−2.0 ± 1.5 (43)
Changes at Week 24 after 2nd Course	−2.4 ± 1.3 (58)	−2.0 ± 1.2 (20)
DAS28-ESR, Mean ± SD (n)		
Baseline	6.8 ± 0.8 (100)	6.7 ± 0.8 (47)
Changes at Week 24 after 1st Course	−2.1 ± 1.2 (95)	−2.1 ± 1.5 (43)
Changes at Week 24 after 2nd Course	−2.5 ± 1.3 (58)	−2.0 ± 1.2 (20)

RTX, innovator rituximab; DAS28, disease activity score in 28 joints; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; SD, standard deviation

Table 2 Safety Summary of CT-P10 and Innovator Rituximab

	CT-P10	RTX
	N=102	**N=51**
Number of Patients (%) with at Least One		
AE	73 (71.6)	43 (84.3)
Serious AE	14 (13.7)	7 (13.7)
Infusion-related reaction	20 (19.6)	10 (19.6)
Infection	39 (38.2)	21 (41.2)
Malignancy	0	1 (2.0)
Discontinuation due to AEs	6 (5.9)	4 (7.8)

RTX, innovator rituximab; AE, adverse events

Conclusion: CT-P10, a biosimilar candidate of RTX, showed highly similar efficacy and comparable safety profiles to RTX up to

72 weeks.

Reference

[1] Yoo DH, et al. Arthritis Rheum 2013; 65 (Suppl 10): S736

Disclosure: D. H. Yoo, CELLTRION, Inc., 5; **W. Park**, CELLTRION, Inc., 5; **C. H. Suh**, CELLTRION, Inc., 5; **S. C. Shim**, CELLTRION, Inc., 5; **S. Jeka**, CELLTRION, Inc., 2; **F. Cons Molina**, CELLTRION, Inc., 2; **P. Hrycaj**, CELLTRION, Inc., 2; **W. Spieler**, CELLTRION, Inc., 2; **P. Wiland**, CELLTRION, Inc., 2; **J. Brzezicki**, CELLTRION, Inc., 2; **E. Y. Lee**, CELLTRION, Inc., 2; **F. G. Medina-Rodriguez**, CELLTRION, Inc., 2; **P. Shesternya**, CELLTRION, Inc., 2; **S. Radominski**, CELLTRION, Inc., 2; **M. Stanislav**, CELLTRION, Inc., 2; **V. Kovalenko**, CELLTRION, Inc., 2; **D. Sheen**, CELLTRION, Inc., 2; **L. Myasoutova**, CELLTRION, Inc., 2; **M. J. Lim**, CELLTRION, Inc., 2; **J. Y. Choe**, CELLTRION, Inc., 2; **T. S. Kwon**, CELLTRION, Inc., 3; **S. J. Lee**, CELLTRION, Inc., 3.

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Abstract Number: 2059

Tumor Necrosis Factor Inhibitor Tapering Induced Radiographic Progression Is Driven By Weighted Mean Disease Activity over Time, Not Flaring or Lower TNFi Exposition

Alfons A. den Broeder[1], Chantal A.M. Bouman[1], Aatke van der Maas[2], Frank H.J. van den Hoogen[1], Noortje van Herwaarden[1] and R. Landewe[3], [1]Rheumatology, Sint Maartenskliniek, Nijmegen, Netherlands, [2]Hengstdal 3, Sint Maartenskliniek, Nijmegen, Netherlands, [3]Department of Internal Medicine, Division of Rheumatology, University Hospital Maastricht, Maastricht, Netherlands

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SESSION INFORMATION

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Session Title: Rheumatoid Arthritis-Small Molecules, Biologics and Gene Therapy III: Biosimilars

Session Type: ACR Concurrent Abstract Session

Session Time: 2:30PM-4:00PM

Background/Purpose:

DRESS, a randomized controlled strategy trial (RCT)[1] investigating disease activity guided tapering of etanercept and adalimumab compared to usual care in RA patients, indicated that minimal radiographic progression is more frequent in patients who attempted TNF inhibitor (TNFi) tapering. Possible explanations include higher mean disease activity, higher incidence of flaring, and/or lower TNFi use in the tapering group.

Methods:

Eighteen months data from the DRESS study were used. Change in Sharp van der Heijde (SvdH) score and percentage of patients with minimal progression (> 0.5 SvdH points) were used as outcomes. Mean time averaged disease activity (Disease Activity Score, DAS28CRP), occurrence and number of (major) flares per patient (flare definition DAS28CRP increase > 1.2, of > 0.6 and current DAS28CRP ≥3.2; major flare lasting > 12 weeks), and TNFi use (normalized percentage of the defined daily dose) during the study were used as independent variables. First, the independent contributions of the four disease activity measures were assessed by univariate and multivariate analyses. Thereafter, linear regression modeling was done with SvdH change as dependent variable, to assess the independent contribution of the disease activity measures and TNFi use, controlled for possible confounders including age, sex, BMI, smoking, baseline SvdH score, DAS28CRP, CRP, RF and ACPA status, and concomitant

sDMARDs.

Results:

All patients with 18 months data available (n=175) were included. Mean SvdH change was 0.75 and 0.15, and minimal radiographic progression was found in 39/121 (32%) and 9/59 (15%) patients in tapering and usual care group respectively (both $p<0.05$, number needed to harm [NNH]=6). Mean DAS28CRP and cumulative incidence of (major) flares were 2.3 (SD 0.5) and 2.1 (0.6) and 73% (12%) and 27% (10%) in tapering and usual care ($p<0.05$). Mean disease activity, but not incidence or number of (major) flares, was independently associated with radiographic progression. No confounding was present.

Conclusion:

The TNFi tapering strategy used in DRESS leads to higher risk for radiographic progression after 18 months than usual care. This is mainly caused by somewhat higher mean disease activity, but not so much by flaring after dose reduction attempts or lower TNFi use itself. Dose tapering of TNFi still seems a safe long-term approach, but long term disease activity should be kept on the lowest level possible using treat to target, and radiologic progression should be checked regularly.

Table 1: linear regression model

	Beta	P-value	95% Confidence interval
Mean DAS28CRP	0.51	0.005	0.15 to 0.86
% of defined daily dose of biological	-0.29	0.39	-0.96 to 0.38
constant	-0.4		

Disclosure: A. A. den Broeder, None; **C. A. M. Bouman**, None; **A. van der Maas**, None; **F. H. J. van den Hoogen**, None; **N. van Herwaarden**, None; **R. Landewe**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/tumor-necrosis-factor-inhibitor-tapering-induced-radiographic-progression-is-driven-by-weighted-mean-disease-activity-over-time-not-flaring-or-lower-tnfi-exposition

Abstract Number: 2060

Microscopic Bowel Inflammation in Spondyloarthritis As a Baseline Predictor of Anti-TNF Response

Heleen Cypers, Gaëlle Varkas, Filip van Den Bosch and Dirk Elewaut, Rheumatology, Ghent University Hospital, VIB, Ghent, Belgium

First publication: September 29, 2015

SESSION INFORMATION

Session Date: Monday, November 9, 2015

Session Title: Spondylarthropathies and Psoriatic Arthritis - Clinical Aspects and Treatment: Clinical Aspects

Session Type: ACR Concurrent Abstract Session

Session Time: 2:30PM-4:00PM

· **Background/Purpose:**

Microscopic bowel inflammation without associated gastro-intestinal symptoms is present in up to 50% of spondyloarthritis (SpA) patients. Two types of inflammation are distinguished based on histomorphology: an acute type resembling infectious enterocolitis, and a chronic type, resembling early Crohn's disease. Microscopic bowel inflammation in SpA was shown to be associated with a more severe disease phenotype, including more extensive bone marrow edema of the sacro-iliac joints, and an elevated risk of progression to ankylosing spondylitis or to full-blown Crohn's disease. Currently, it is unknown whether microscopic bowel inflammation affects response to therapy, particularly TNF inhibition.

Purpose: To assess the association between the presence of microscopic bowel inflammation, and initiation of and response to

anti-TNF therapy.

· **Methods:**

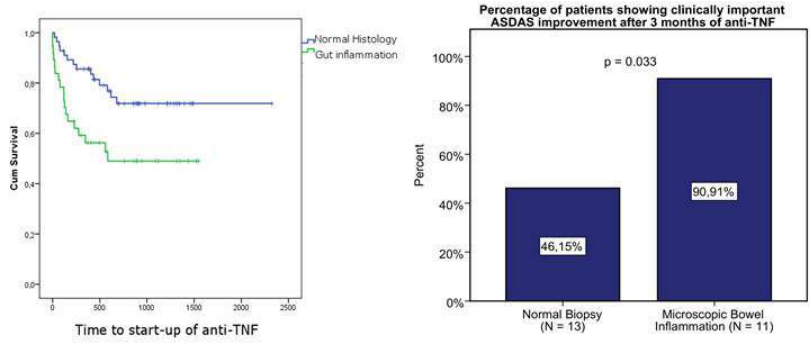
The Ghent Inflammatory Arthritis and spoNdylitis cohorT (GIANT) is a prospective observational cohort study, following patients with a new diagnosis of axial or peripheral SpA, classified according to the ASAS criteria. Patients underwent an ileocolonoscopy at baseline to assess the presence of microscopic bowel inflammation. For the assessment of response to anti-TNFα treatment ASDAS scores from the moment of anti-TNF initiation and after 3 months were compared. A clinically important improvement was defined as an ASDAS improvement of ≧ 1.1 as recommended by ASAS.

· **Results:**

Of the 93 patients assessed during this study period 39,8 % were started on anti-TNF. The presence or absence of gut inflammation was strongly linked to the rate at which anti-TNF therapy was started ($p<0.01$) (Fig 1 left). Response to anti-TNF was assessed in 24 axial spondyloarthritis patients, of which 46 % had microscopic bowel inflammation (N acute = 4; N chronic = 7). After 3 months of anti-TNF therapy 8 (33.3%) patients had no or slight (△< 1.1) ASDAS improvement, whereas 16 (66.7%) patients showed clinically important improvement. Ten out of 11 (90.9%) patients with microscopic bowel inflammation showed clinically important ASDAS improvement, whereas this was only the case for 6/13 (46.15%) patients with normal bowel histology ($p<0.05$) (Fig 1 right). The association between bowel inflammation and ASDAS response remained significant after correction for CRP using logistic regression analysis ($p = 0.041$; odds ratio 12.55 [1.115-141.269).

· **Conclusion:**

Mucosal inflammation in SpA is a risk factor for more extended and progressive disease resulting in a higher need for TNF inhibition. Most importantly, SpA patients with microscopic bowel inflammation at baseline responded better to anti-TNF therapy than those with normal bowel histology, and this association was independent of CRP. These findings underscore the relevance of gut inflammation in the clinical course of SpA.



Disclosure: H. Cypers, None; **G. Varkas**, None; **F. van Den Bosch**, AbbVie, Celgene, Janssen, Merck, Novartis, Pfizer, and UCB, 2,AbbVie, Celgene, Janssen, Merck, Novartis, Pfizer, and UCB, 8,AbbVie, Celgene, Janssen, Merck, Novartis, Pfizer, and UCB, 5; **D. Elewaut**, Abbott, 9.

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Abstract Number: 2061

Uncovering Crohn's Disease in Patients with Spondyloarthropathies Using Videocapsule Endoscopy

Uri Kopylov[1], Craig Watts[2], Michael Starr[3,4], Serge Dionne[5], Jamie Koenekoop[5] and **Ernest Seidman**[5], [1]Gastroenterolog, Research Institute of the McGill University Health Centre, Montreal, QC, Canada, [2]Department of Rheumatology, McGill University and Montreal General Hospital, Sainte-Anne-de-Bellevue, QC, Canada, [3]Rheumatology, McGill University, Montreal, QC, Canada, [4]Rheumatology, McGill University Health Centre, Montreal, QC, Canada, [5]Gastroenterology, Research Institute of the McGill University Health Centre, Montreal, QC, Canada

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Session Time: 2:30PM-4:00PM

Background/Purpose:

Inflammatory bowel disease (IBD) is clinically associated with spondylarthropathies (SpA) in 5-15% of cases. Protocol colonoscopic assessment demonstrated asymptomatic inflammation characteristic of Crohn's disease in up to 1/3 of SpA patients. Videocapsule endoscopy (VCE) is a superior diagnostic tool to detect small bowel (SB) mucosal pathology. However, it has been infrequently used to evaluate bowel inflammation in SpA. This study compared the accuracy of VCE to standard ileocolonoscopy (IC) for the detection of inflammatory bowel lesions in patients with SpA, and to describe the clinical and laboratory predictors of SB inflammation in this cohort.

Methods:

Prospective cross-sectional study, involving consenting patients > age 18 with an established diagnosis of SpA. Exclusion criteria included any NSAID use in the previous month or treatment with infliximab, adalimumab or certolizumab. All patients first were evaluated by VCE, followed by IC with biopsies. SB inflammation was quantified using the Lewis Score (LS). Significant inflammation was defined as LS ≥350. Screening tests evaluated included fecal calprotectin (FCP, Buhlmann Laboratories, Basel, Switzerland); levels ≥ 100 ug/g considered positive. A panel of serologic, inflammatory and genetic testing (IBD SGI Diagnostic™) was performed (Prometheus Labs, San Diego, CA). In a subgroup of patients, NOD2 mutations were assessed using a Sequenom array. **Results** were correlated with the presence of significant inflammation on VCE.

Results:

63 patients (54% female, mean age 42±13 years) were recruited; 2 patients refused IC and were disqualified. GI symptoms (chronic diarrhea/abdominal pain/weight loss) were present in 57%. FCP levels were elevated in 47% of patients. Significant SB inflammation was demonstrated by VCE in 25/61 (41%) of patients vs 8/61 (13.1%) by IC (p=0.036). All positive ileal and colonic biopsies were consistent with Crohn's disease. Elevated FCP levels significantly correlated with mucosal inflammation on VCE (r^2 =0.59, p=0.0001, sensitivity 70.6%, specificity 86.6%). Correlation was not observed with the presence of GI symptoms or an elevated CRP. There was no significant correlation between SGI and VCE (r^2 =0.1, p=0.4, sensitivity 26.3%, specificity 82.3%). None of the individual components of SGI was correlated with significant inflammation on VCE. The prevalence of NOD2 mutations was higher in patients with significant SB inflammation (27% vs 11%), however this difference did not reach statistical significance (p=0.22).

Conclusion:

Small bowel lesions consistent with Crohn's disease are more common in patients with SpA than generally acknowledged. VCE is superior to IC in detecting CD in patients with known SpA. Fecal calprotectin levels were significantly correlated with VCE results, while presence of GI symptoms, CRP and SGI results were poor predictors of small bowel inflammation in this patient cohort.

Disclosure: U. Kopylov, None; **C. Watts**, Abbott Immunology Pharmaceuticals, 5; **M. Starr**, Abbott Immunology Pharmaceuticals, 5,Abbott Immunology Pharmaceuticals, 8; **S. Dionne**, None; **J. Koenekoop**, None; **E. Seidman**, Abbott Immunology Pharmaceuticals, 5,Abbott Immunology Pharmaceuticals, 8,Prometheus Laboratories, 5.

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Abstract Number: 2062

How Reliable Is Self-Evaluation of Symptoms of Inflammatory Back Pain By Patients?

Denis Poddubnyy[1], Inge Spiller[1], Joachim Sieper[1] and Martin Rudwaleit[1,2], [1]Charité Universitätsmedizin Berlin, Berlin, Germany, [2]Klinikum Bielefeld, Bielefeld, Germany
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Background/Purpose:

Inflammatory back pain (IBP) is regarded as an important clinical parameter of axial spondyloarthritis (axSpA) and is often used in a diagnostic approach. Usually symptoms of inflammatory back pain are evaluated by a physician, however, self-evaluation of IBP symptoms by patients might be a useful approach for self-referral of patients and for time-saving. The aim of this study was to assess the reliability of self-evaluation of symptoms of IBP by patients as compared to an evaluation by a physician.

Methods:

A total of 405 consecutive patients referred to a rheumatologist because of chronic back pain starting at an age <45 years and in whom a diagnosis of axSpA was suspected were included in this multicentre study. A questionnaire containing 8 questions (yes/no) relevant for IBP parameters (duration >3 months, onset prior to 45 years of age, morning stiffness of 30 minutes or longer, insidious onset of back pain, improvement with exercise, improvement with rest, night awakening, alternating buttock pain) were answered by the patient. The same IBP questions were then evaluated by a rheumatologist blinded for presence or absence of other SpA-features and for the diagnosis, and finally by a second, unblinded rheumatologist who was responsible for the final diagnosis. The agreement among the patient and the 2 rheumatologists regarding the fulfilment of the Calin-, Berlin- and ASAS criteria were analysed.

Results:

A total of 180 patients (44.4%) were diagnosed with definite axSpA and in 225 patients (55.6%) SpA was excluded. The agreement on the fulfilment of different IBP criteria sets based on patient's self-assessment and on the judgement of two rheumatologists (blinded and unblinded) is presented in table. As reflected by the kappa-values, there was a moderate agreement on the fulfilment of IBP criteria between the patient and the blinded rheumatologist and fair to moderate between the patient and the unblinded (diagnosing) rheumatologist. The percentage agreement on the presence/absence of IBP was consistent and varied between 73% and 83%. Interestingly, nearly a similar level of agreement was observed between blinded and unblinded rheumatologists. The most consistent agreement results were obtained for the ASAS IBP criteria. Regarding single IBP items, there was a moderate agreement (kappa between 0.4 and 0.6) between patient's and rheumatologist's judgement for the majority of items with a trend for a better agreement between the patient and the blinded rheumatologist (as opposed to the unblinded one).

Conclusion:

The level of agreement between patient and rheumatologist regarding the assessment of IBP was acceptable. Patient's self-reporting of IBP might be used in daily clinical practice.

Table: Agreement on the fulfilment of various IBP criteria sets between patient (self-assessed) and rheumatologists.

		Patient	Blinded rheumatologist	Unblinded rheumatologist
Calin's criteria	**Patient**	-	0.52 (0.42-0.62) 83.2%	0.37 (0.26-0.48) 78.6%
	Blinded rheumatologist	0.52 (0.42-0.62) 83.2%	-	0.43 (0.32-0.53) 80.2%
	Unblinded rheumatologist	0.37 (0.26-0.48) 78.6%	0.43 (0.32-0.53) 80.2%	-
Berlin Criteria	**Patient**	-	0.49 (0.39-0.59) 82.7%	0.31 (0.21-0.41) 73.6%
	Blinded rheumatologist	0.49 (0.39-0.59) 82.7%	-	0.52 (0.43-0.61) 80.0%
	Unblinded rheumatologist	0.31 (0.21-0.41) 73.6%	0.52 (0.43-0.61) 80.0%	-
ASAS criteria	**Patient**	-	0.46 (0.37-0.56) 76.9%	0.42 (0.32-0.52) 76.6%
	Blinded rheumatologist	0.46 (0.37-0.56) 76.9%	-	0.46 (0.37-0.56) 77.3%
	Unblinded rheumatologist	0.42 (0.32-0.52) 76.6%	0.46 (0.37-0.56) 77.3%	-

Cohen's kappa with 95% CI and percent agreement are shown for 405 patients referred because of chronic back pain.

The blinded rheumatologist is unaware of other findings (laboratory, imaging, clinical) of the patient, the unblinded rheumatologist is the treating rheumatologist.

Disclosure: D. Poddubnyy, None; **I. Spiller**, None; **J. Sieper**, None; **M. Rudwaleit**, None.

Abstract Number: 2063

The Survival Impact of Statins in Psoriasis and Psoriatic Arthritis: A General Population-Based Cohort Study

Sian Yik Lim[1], Na Lu[2] and Hyon K. Choi[2], [1]Division of Rheumatology, Allergy and Immunology, Massachusetts General Hospital, Harvard Medical School, Boston, MA, [2]Rheumatology, Allergy and Immunology, Massachusetts General Hospital, Harvard Medical School, Boston, MA

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Session Title: Spondylarthropathies and Psoriatic Arthritis - Clinical Aspects and Treatment: Clinical Aspects

Session Type: ACR Concurrent Abstract Session

Session Time: 2:30PM-4:00PM

Background/Purpose:

Given their lipid-lowering and anti-inflammatory properties, statins may have dual cardioprotective and anti-rheumatic benefits in psoriasis or psoriatic arthritis. These effects may confer survival benefits in this particular patient population, at least similar to those observed in the JUPITER trial among otherwise healthy individuals with low LDL cholesterol but with elevated hsCRP

(i.e., a 20% reduction in overall mortality). However, no relevant data are available in the field. To address this knowledge gap, we evaluated the impact of statin initiation on the risk of mortality among patients with psoriasis or psoriatic arthritis in a general population context.

Methods:

We conducted an incident user cohort study with time-stratified propensity score matching in a United Kingdom general population database. We compared all-cause mortality between statin initiators and non-initiators among patients with a new diagnosis of psoriasis or psoriatic arthritis (n=36,228) between January 2000 and December 2012. To closely account for confounding by indication and potential calendar-time effects, we employed propensity score-matched cohorts of statin initiators and non-initiators within 1-year cohort accrual blocks. Propensity scores (i.e., the predicted probability of statin initiation) were estimated using 50 variables, including disease duration, demographics, socio-economic status, body mass index, lifestyle factors, comorbidities, medication use, and healthcare utilization. We used Cox proportional hazard models to calculate hazard ratios for mortality.

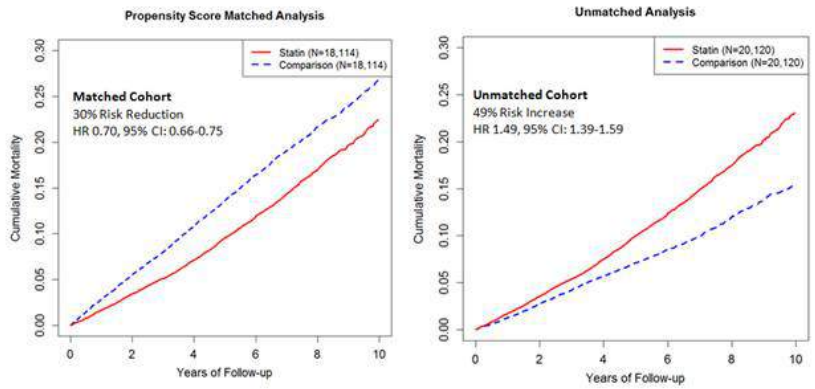
Results:

Of 18,114 statin initiators, 1831 died during the follow up period (mean=4.64 years), whereas among 18,114 matched non-initiators, 2374 died during the follow up period (mean=4.37 years). This corresponds to incidence rates of 21.8/1000 person-years (PY) and 29.9/1000 PY in the statin initiator and comparator groups, respectively. The baseline characteristics were well-balanced in the two groups. Statin initiation was associated with a 30% reduction in all-cause mortality (HR 0.70, 95% CI 0.66-0.75) (**Figure 1a**). When we compared the unmatched cohorts to examine the effectiveness of our propensity score matching, the statin initiators (n=20,120) actually showed a 49% higher risk of mortality (HR 1.49, 95% CI 1.39-1.59) than non-initiators (n=20,120 randomly selected, without propensity score matching) due to confounding by indication (**Figure 1b**).

Conclusion:

Findings from this general population study indicate that statin initiation is associated with a survival benefit among patients with psoriasis or psoriatic arthritis, and its magnitude appears larger than that shown in the JUPITER trial.

Figure 1. Time to death for the a) Propensity-Score Matched and b) Unmatched Cohorts



Disclosure: **S. Y. Lim**, None; **N. Lu**, None; **H. K. Choi**, None.

Abstract Number: 2064

Increase in IL-31 Serum Level in Recent Onset Spondyloarthritis – Data from the DESIR Cohort

Nicolas Rosine Jr.[1], Adrien Etcheto[2], Anna Moltó[3], Yassine Taoufik[4], Houria Chavez[4], Christian Roux[5], Karine Briot[5], Maxime Dougados[6] and Corinne Miceli[5], [1]Rheumatology Department, Hôpital Kremlin Bicêtre, Paris, France, [2]Rheumatology B, Rheumatology B Department, Paris-Descartes University, Cochin Hospital, Paris, France, [3]Paris Descartes University, Rheumatology Department, Cochin Hospital, AP-HP. INSERM (U1153): Clinical Epidemiology and Biostatistics, PRES Sorbonne Paris-Cité,, Paris, France, [4]Biologic Immunology, Hopital Bicetre, Université Paris Sud, AP-HP, Kremlin Bicetre, France, [5]Rheumatology B Department, Hôpital Cochin, Paris, France, [6]Rheumatology B Department,, Paris-Descartes University, APHP, Cochin Hospital, Paris, France

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Background/Purpose: IL-31 is a newly-described cytokine mainly produced by activated Th2 cells. IL-31 acts through IL31-RA and oncostatin heterodimeric receptors that activate STAT3 and STAT5. So far, IL31 has been mainly involved in airway hypersensitivity and atopic dermatitis. More recent data suggest its involvement in psoriasis and inflammatory bowel disease. We aimed to assess IL-31 serum levels in patients with recent onset axial spondyloarthritis (SpA).

Methods: The DESIR cohort is a prospective, multicenter French cohort of 708 patients with early inflammatory back pain (IBP) (duration >3 months and <3 years) suggestive of AxSpA (mean age 33.8 years; 53.8% women, 57% fulfilled the ASAS criteria). IL-31 and sCD40L were assessed using the multiplex and high sensitive 17-Plex ELISA (Bio-Plex Pro Human Cytokine 17-Plex Immunoassay, BioRad). Serum levels were assessed at baseline in 3 subgroups of patients: i. patients from the DESIR cohort fulfilling the ASAS criteria (ASAS + group, n=443); ii. IBP patients from the DESIR cohort not fulfilling the ASAS criteria (ASAS – group, n= 265); iii. Healthy controls age and sex-matched to a random sample of the DESIR cohort patients (control group, n=80).

Results: IL31 was significantly increased (p<0,001) in the ASAS+ group (median= 7.7 pg/ml ± 15.4, mean 12.6 pg/ml) and ASAS - group (median 6.3 pg/ml ± 16, mean = 11.3 pg/ml) compared to the control group (median=0.0±3.1, mean=1.1 pg/ml). IL31 was correlated with sCD40L(r=0.62; p<0.0001), with DKK-1 (r=0.27; p<0,001), and weakly with IFNg (r=0.12; p=0,016). Patients exhibiting a high level of IL31 had increased CRP (p=0.04), a mSASSS score <1: Yes 7.7 ± 10.7 versus No 13.02±15.07 (p=0.005), and a diagnosis of osteoporosis: Yes 14.1±16.7 versus No 10.7±13.6 (p=0.005). These results were confirmed in the multivariate analyses with a significant and independent association between IL31 and IFNg (p<0.0001), sCD40L (p<0.0001), DKK1 (p=0.02) serum levels, and osteoporosis (p=0.002).

Conclusion: IL31 serum levels are correlated with cytokines involved in a Th1 polarization. IL31 is also significantly correlated with the Wnt signaling inhibitory protein DKK-1 and associated with the osteoporotic phenotype of the patients. These preliminary results suggesting that IL31 might be involved in bone loss observed among SpA patients need to be confirmed in more severe forms of the disease.

Disclosure: N. Rosine Jr., None; **A. Etcheto**, None; **A. Moltó**, None; **Y. Taoufik**, None; **H. Chavez**, None; **C. Roux**, None; **K. Briot**, None; **M. Dougados**, None; **C. Miceli**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/increase-in-il-31-serum-level-in-recent-onset-spondyloarthritis-data-from-the-desir-cohort

Abstract Number: 2065

Verification of Novel Soluble Biomarkers That Differentiate Patients with Psoriatic Arthritis from Those with Psoriasis without Psoriatic Arthritis

Vinod Chandran[1], Daniela Cretu[2,3], Lisa Gao[4], Kun Liang[4], Antoninus Soosaipillai[3] and Eleftherios Diamandis[2,3,5], [1]Rheumatology, University of Toronto, Toronto Western Hospital, Toronto, ON, Canada, [2]Department of Laboratory Medicine and Pathobiology, University of Toronto, Toronto, ON, Canada, [3]Department of Pathology and Laboratory Medicine, Mount Sinai Hospital, Toronto, ON, Canada, [4]Department of Statistics and Actuarial Science, University of Waterloo, Waterloo, ON, Canada, [5]Department of Clinical Biochemistry, University Health Network, Toronto, ON, Canada
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Background/Purpose: There is a high prevalence of undiagnosed psoriatic arthritis (PsA) in psoriasis patients. Therefore identifying soluble biomarkers for PsA will help in screening psoriasis patients for appropriate referral to a rheumatologist. Our

purpose was to investigate whether serum levels of novel markers discovered by quantitative mass spectrometry (MS) of synovial fluid and skin biopsies, differentiate PsA patients from those with psoriasis without PsA (PsC).

Methods: Serum samples were obtained from 100 patients with PsA, 100 with PsC, and 100 healthy controls. Subjects were group matched for age and sex. No patient was undergoing treatment with biologics at the time of serum collection. Using enzyme-linked immunosorbent assays, four high-priority markers, previously discovered by quantitative MS of synovial fluid and skin biopsies, were analyzed in the serum: Mac-2-binding protein (M2BP), CD5-like protein (CD5L), Myeloperoxidase (MPO), and Integrin-β 5 (ITGB5), as well as previously established markers Matrix metalloproteinase-3 (MMP3) and C-reactive protein (CRP). Data were analyzed using logistic regression (LR), and receiver operating characteristic (ROC) curves were plotted.

Results: The 100 PsA patients (41 females, mean age 51 years) had mean psoriasis duration of 22.9 years, PsA duration of 14.6 years, swollen joint count 3.2, tender joint count 6, and PASI score of 4.7. The 100 PsC patients (45 females, mean age 50 years) had mean psoriasis duration of 20.3 years and PASI score of 4. The 100 controls (52 females) had a mean age of 35 years. Polychotomous LR (Table 1) showed that ITGB5, CRP and M2BP are markers that are significantly different between the three groups. The analyses also showed that CD5L, ITGB5, M2BP, MPO, MMP3 and CRP are independently associated with PsA, while CD5L, M2BP and MPO are independently associated with PsC. When comparing PsA to PsC, ITGB5, M2BP, and CRP were found to be independently associated with PsA (Table 2). ROC analysis (Figure 1) of this model showed an area under the ROC curve of 0.85 (95% CI [0.80, 0.90]).

Conclusion: CD5L, ITGB5, M2BP, MPO, MMP3 and CRP are soluble PsA markers. However, only ITGB5, M2BP and CRP, differentiate PsA from PsC.

Table 1. Polychotomous logistic regression analysis to identify biomarkers associated with PsA and PsC

		PsA		PsC	
Biomarkers	Homogeneity P-value[a]	OR[b] (95% CI)	P-value[c]	OR[b] (95% CI)	P-value[c]
CD5L, ng/mL	5.48E-01	1.67 (1.28, 2.17)	1.49E-04	1.57 (1.25, 1.97)	8.71E-05
ITGB5, ng/mL	1.18E-05	3.23 (1.98, 5.27)	2.88E-06	1.21 (0.89, 1.64)	2.14E-01
M2BP, ng/mL	1.97E-03	151.73 (19.64, 1172.19)	1.48E-06	9.19 (2.47, 34.25)	9.38E-04
MMP3, ng/mL	1.72E-01	1.79 (1.05, 3.06)	3.18E-02	1.39 (0.86, 2.26)	1.81E-01
MPO, ng/mL	5.33E-01	2.36 (1.50, 3.72)	1.97E-04	2.64 (1.75, 3.98)	3.27E-06
CRP, mg/L	1.40E-06	2.36 (1.67, 3.33)	9.93E-07	1.16 (0.91, 1.47)	2.28E-01

[a]Indicates whether the markers have significantly different effects when modeling PsA and PsC separately, and controlling for age, sex, and the other biomarkers listed.

[b]Odds ratio- indicates OR associated with a two-fold increase in the protein level

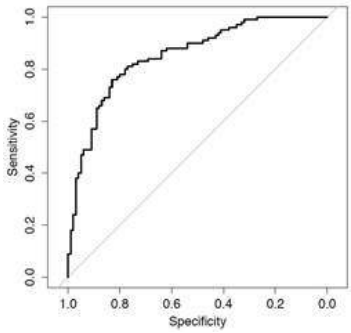
[c]Indicates the significance of difference between PsA or PsC, and controls.

Table 2. Logistic regression analysis comparing patients with PsA to PsC

	Univariate		Multivariate	
Biomarkers	OR[a] (95% CI)	P-value	OR[a] (95% CI)	P-value
CD5L, ng/mL	1.08 (0.92, 1.26)	3.63E-01	-	-
ITGB5, ng/mL	4.07 (2.44, 6.81)	8.36E-08	3.82 (2.18, 6.70)	3.05E-06
M2BP, ng/mL	29.72 (5.88, 150.09)	4.05E-05	32.32 (4.90, 213.32)	3.07E-04
MMP3, ng/mL	1.59 (1.21, 2.11)	1.00E-03	-	-
MPO, ng/mL	1.09 (0.83, 1.43)	5.40E-01	-	-
CRP, mg/mL	1.93 (1.50, 2.48)	2.55E-07	1.96 (1.46, 2.62)	5.84E-06

[a]Odds ratios associated with a two-fold increase in the protein level

Figure 1. ROC curve showing the AUC for the logistic regression model comparing PsA, to PsC patients.



Disclosure: V. Chandran, AbbVie, 2; **D. Cretu**, None; **L. Gao**, None; **K. Liang**, None; **A. Soosaipillai**, None; **E. Diamandis**, None.

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Abstract Number: 2066

Elevated Innate, Adaptive, and TNF-Superfamily Soluble Inflammatory Mediators Mark Impending Disease Flare, While Regulatory Mediators Distinguish Lack of Impending Disease Flare in African-American SLE Patients with Active Disease

Melissa E. Munroe[1], Evan G. Vista[2], Joan T. Merrill[3], Joel M. Guthridge[1], Virginia C. Roberts[1] and Judith A. James[4], [1]Arthritis and Clinical Immunology, Oklahoma Medical Research Foundation, Oklahoma City, OK, [2]Rheumatology and Clinical Immunology, University of Santo Tomas, Taguig City, Philippines, [3]Clinical Pharmacology, Oklahoma Medical Research Foundation, Oklahoma City, OK, [4]Arthritis and Clinical Immunology, University of Oklahoma Health Sciences Center and Oklahoma Medical Research Foundation, Oklahoma City, OK

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SESSION INFORMATION

Session Date: Monday, November 9, 2015

Session Title: Systemic Lupus Erythematosus - Clinical Aspects and Treatment III: Biomarkers

Session Type: ACR Concurrent Abstract Session
Session Time: 2:30PM-4:00PM

Background/Purpose: SLE is a multifaceted disease characterized by immune dysregulation and varied disease activity. Identifying mechanistic mediators of altered disease activity would help prevent damage and improve disease management. This study seeks to identify markers that correlate with disease activity and distinguish African American (AA) SLE patients with impending flare.

Methods: We evaluated changes in plasma soluble mediators preceding SELENA-SLEDAI defined flare in AA SLE patients who developed disease flare 6 or 12 weeks after baseline assessment compared to race, gender, and age (± 5 years)-matched SLE patients without impending flare (non-flare, NF) and healthy controls (n=13 in each group). In addition, mediators were assessed in 18 additional AA SLE patients with impending disease flare compared to a corresponding clinically stable period (self non-flare, SNF) from the same individual. Fifty-two soluble mediators, including innate, adaptive, and shed TNF-receptor superfamily members, were assessed; p-values were corrected for multiple comparisons (q-values). A combined soluble mediator score algorithm was calculated utilizing normalized (Flare vs NF or Flare vs SNF) soluble mediator levels for each patient at baseline (pre-flare) weighted by each patient's SELENA-SLEDAI score at time of disease flare.

Results: Patients with impending flare had significant ($q<0.01$) alterations in 32 soluble mediators at baseline preceding clinical flare by 6 to 12 weeks with significantly higher levels of pro-inflammatory mediators, including innate and adaptive cytokines. Baseline levels of regulatory cytokines, including IL-10 ($q=0.0045$) and TGF-β ($q=0.0004$), were higher in non-flare SLE patients, while pre-flare patients exhibited elevated levels of both innate and adaptive mediators, including IFN-α ($q=0.0008$), IFN-β ($q=0.0080$), IL-6 ($q=0.0004$), IL-12p70 ($q=0.0008$), IL-5 ($q=0.0004$), and IL-17A ($q=0.0004$). In addition, baseline levels of shed TNF-receptor superfamily members TNFRI ($q=0.0017$), TNFRII ($q=0.0394$), TRAIL ($q=0.0008$), FasL (0.0004), and CD40L ($q=0.0008$), but not BLyS ($q=0.5784$), were significantly greater in pre-flare patients compared to NF patients. These mediators were also significantly altered when comparing Flare and SNF samples from the same patient ($q<0.01$). The soluble mediator score was significantly higher in pre-flare SLE patients versus NF patients ($p<0.0001$) or SNF periods of stable disease ($p<0.0001$); every AA SLE patient followed longitudinally exhibited higher soluble mediator scores during their pre-flare period. No differences in the number or type of autoantibody specificities, nor differences in medication use, between pre-flare and NF or SNF SLE patients were noted.

Conclusion: Pro-inflammatory innate, adaptive, and TNF family mediators are elevated in pre-flare lupus patients, while elevated regulatory mediators were noted in AA SLE patients with stable disease. Alterations in the balance between inflammatory and regulatory mediators may help identify AA patients at risk of disease flare and help decipher SLE pathogenic mechanisms.

Disclosure: M. E. Munroe, None; **E. G. Vista**, None; **J. T. Merrill**, None; **J. M. Guthridge**, None; **V. C. Roberts**, None; **J. A. James**, None.

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Abstract Number: 2067

De-Convolution of Whole Blood Transcriptomic Data from a Phase IIb, Randomized, Double-Blind, Placebo-Controlled Trial of Abatacept in Systemic Lupus Erythematosus

S Bandyopadhyay[1], SE Connolly[1], O Jabado[1], S Kelly[1], M Maldonado[1], R Westhovens[2], P Nash[3], JT Merrill[4] and R Townsend[1], [1]Bristol-Myers Squibb, Princeton, NJ, [2]University Hospitals KU Leuven, Leuven, Belgium, [3]University of Queensland, Brisbane, Australia, [4]Oklahoma Medical Research Foundation, Oklahoma City, OK

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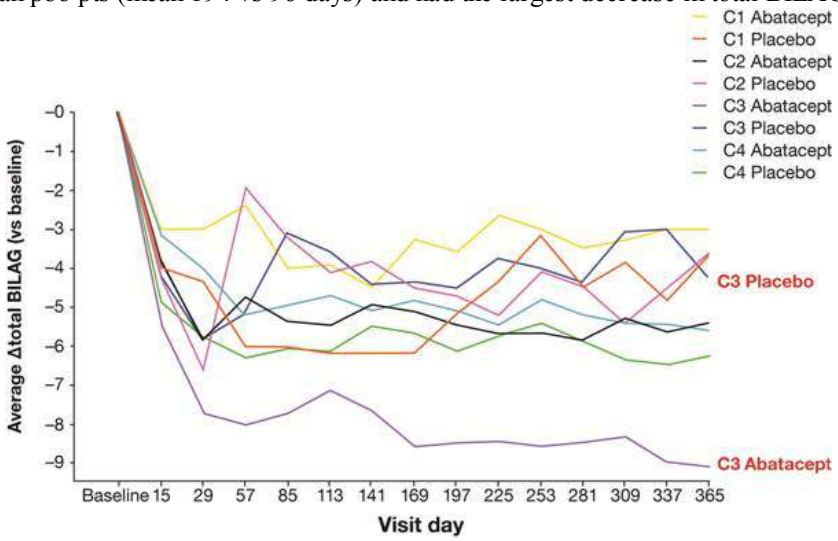
Session Type: ACR Concurrent Abstract Session
Session Time: 2:30PM-4:00PM

Background/Purpose: The Phase IIb IM101-042 trial was a randomized, double-blind, placebo-controlled trial of abatacept (ABA) in systemic lupus erythematosus patients (pts) with polyarthritis, discoid lesions or serositis. Pts were randomized 2:1 to receive ABA (monthly ~10 mg/kg; n=98) or placebo (pbo; n=46) following a month of high-dose corticosteroids, and with continuing background immunosuppression. To gain insights into responses to ABA in pathologic subsets of SLE, the current study applied a de-convolution algorithm to pts' baseline transcriptomic data from whole blood mRNA. **Methods:** Cell-specific marker genes that were identified for key immune cell types[1] were used in conjunction with a de-convolution algorithm[2] to identify cell proportions from whole blood transcriptomic data obtained by gene chip analysis of PAXgene mRNA in the 144 pt samples collected at trial baseline (before ABA or pbo) and 10 healthy volunteers. The de-convoluted pt-level data were used in an unsupervised analysis to generate consensus clustering for stratification. Pt clusters were then used to perform a *post hoc* analysis of clinical study results. **Results:** The primary study endpoints have been reported.[3] Higher levels of activated natural killer (NK) cells and neutrophils were seen in SLE pts vs healthy volunteers at baseline, while NK and T helper (Th) cells were lower in SLE pts than in healthy volunteers. At baseline, SLE pts were stratified by immune cell fractions into 4 major clusters characterized by a dominance of the listed cell type: C1, high Th cells; C2, high plasma cells (PCs); C3, high neutrophils, activated monocytes and activated dendritic cells; and C4, high B or NK cells. Median and average total British Isles Lupus Assessment Group (BILAG) scores at baseline were similar across all clusters and treatment arms. The C2 cluster (high PCs) contained most of the pts with high levels of anti-dsDNA. C1 cluster pts were the slowest to flare, regardless of treatment allocation (>170 days). In the C3 cluster, ABA-treated pts were slower to flare than pbo pts (mean 194 vs 96 days) and had the largest decrease in total BILAG score and greatest difference from pbo (Figure).



Conclusion: In a re-analysis of the Phase IIb abatacept trial in SLE, whole blood de-convolution identified 4 distinct peripheral blood mononuclear cell phenotypic clusters at baseline. These clusters demarcated distinct clinical characteristics and response to therapy. Whole blood de-convolution might provide insights into specific immune cell-driven disease pathogenesis and might improve patient stratification and enrich interpretation of trial data. 1. Abbas AR, et al. *Genes Immun* 2005;**6**:319–31. 2. Abbas AR, et al. *PLoS One* 2009;**4**:e6098. 3. Merrill JT, et al. *Arthritis Rheum* 2010;**62**:3077–87.

Disclosure: S. Bandyopadhyay, Bristol-Myers Squibb, 3,Bristol-Myers Squibb, 1; **S. Connolly**, Bristol-Myers Squibb, 1,Bristol-Myers Squibb, 3; **O. Jabado**, Bristol-Myers Squibb, 3,Bristol-Myers Squibb, 1; **S. Kelly**, Bristol-Myers Squibb, 3,Bristol-Myers Squibb, 1; **M. Maldonado**, Bristol-Myers Squibb, 1,Bristol-Myers Squibb, 3; **R. Westhovens**, Roche Pharmaceuticals, 2,Bristol-Myers Squibb, 8,Janssen, Galapagos, 5; **P. Nash**, Abbvie, Amgen, BMS< Janssen, Pfizer, Roche, Sanofi, Lily, MSD, Novartis, Celgene, UCB Newbridget, 2,Abbvie, Amgen, BMS< Janssen, Pfizer, Roche, Sanofi, Lily, MSD, Novartis, Celgene, UCB Newbridget, 5,Abbvie, Amgen, BMS< Janssen, Pfizer, Roche, Sanofi, Lily, MSD, Novartis, Celgene, UCB Newbridget, 8; **J. Merrill**, Bristol-Myers Squibb, GlaxoSmithKline, Xencor Macrogenics, 2,Bristol-Myers Squibb, GlaxoSmithKline, Mallinckrodt, MedImmune, Lilly, UCB, Takeda, Abbvie, Anthera, Neovacs, Receptos, Celgene, 5; **R. Townsend**, Bristol-Myers Squibb, 1,Bristol-Myers Squibb, 3.

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Abstract Number: 2068

Low Complement Is Associated with SLE Classification Criteria and Organ Damage

Laura Durcan[1], Wei Fu[2] and Michelle Petri[1], [1]Rheumatology, Johns Hopkins University Hospital, Baltimore, MD, [2]Rheumatology, Johns Hopkins University School of Medicine, Baltimore, MD

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Session Time: 2:30PM-4:00PM

Background/Purpose:

Low complements are included in the SLICC classification criteria for systemic lupus erythematosus (SLE) but are not considered in the ACR classification. As a result, the importance of low complement and its relationship to cumulative organ damage has not been systematically investigated. We evaluated the relationship between low complement, C3 and C4, SLICC criteria and organ damage in SLE.

Methods:

As part of a longitudinal lupus cohort, damage accrual and organ manifestations were evaluated quarterly. Damage was measured using SLICC/ACR Damage Index (SDI). C3 and C4 were measured as part of standard clinical care. Those with and without a history of low complement were compared and an odds ratio calculated and adjusted for ethnicity.

Results:

2399 patients were included in this analysis. 53% were Caucasian and 38% African American, the remainder had other ethnicity, mostly Asian. Low C4 was demonstrated in 47% and low C3 in 55%. The relationship between low complement and the SLICC Classification Criteria is outlined in Table 1. Low complement was more common in those with serositis, renal involvement, hematologic and neurologic criteria.

Addressing the SDI, both low C3 and low C4 associated significantly with stroke, pulmonary hypertension, valvular heart disease and all renal damage parameters. Avascular necrosis, hypertension and osteoporosis were also more common in those who had low complement. Significant relationships were demonstrated between low C4 in particular and seizures, scarring of the panniculum and mesenteric insufficiency while diminished C3 associated with pleural fibrosis and cardiomyopathy. These odds ratios remained significant when adjusted for ethnicity.

Conclusion:

Low complement associated strongly with the components of the SLICC criteria. There was also more damage accrual in those with low complement. This was particularly true in terms of renal outcome but also when considering those components of the damage index which associate with prednisone exposure. This points towards a more severe spectrum of disease in those with low complement and highlights the importance of these serological markers in the diagnosis and prediction of long-term outcomes in SLE. The relationship between low complement, stroke, valvular disease and pulmonary hypertension has not previously been described, but is fascinating given the concern for complement activation as part of antiphospholipid syndrome.

Table 1. The relationship between low C3 and C4 and the SLICC Classification Criteria.

SLICC CRITERIA		Low C3 OR (CI)	Low C4 OR (CI)
Malar rash		1.22 (1.04-1.43)	1.24 (1.06-1.46)
Discoid rash		1.36 (1.11-1.1.67)	1.12 (0.92-1.38)
Photosensitivity		0.8 (0.68-0.94)	0.92 (0.78-1.08)
Oral/Nasal Ulcers		0.74 (0.63-0.87)	0.86 (0.73-1.01)
Arthritis		1.05 (0.88-1.25)	1.31 (1.1-1.57)
Serositis	Pleurisy	1.47 (1.25-1.73)	1.44 (1.23-1.7)
	Pericarditis	1.78 (1.46-2.18)	1.69 (1.39-2.05)
Renal disorder		3.77 (3.14-4.48)	3.22 (2.72-3.81)
Neurologic	Seizures	1.51 (1.14-2.00)	1.54 (1.17-2.02)
	Acute confusional state	2.39 (1.52-3.77)	1.98 (1.31-3.01)
Hematologic	Hemolytic anemia	3.63 (2.61-5.04)	2.99 (2.23-4.01)
	Leukopenia	2.45 (2.08-2.89)	2.09 (1.77-2.46)
	Lymphopenia	2.13 (1.80-2.86)	2.13 (1.81-2.52)
	Thrombocytopenia	2.31 (1.87-2.86)	2.08 (1.70-2.55)
Immunologic	Anti-dsDNA	4.97 (4.16,5.94)	5.28 (4.39,6.35)
	Anti Sm	3.65 (2.89,4.61)	2.96 (2.39,3.66)
Anti-phospholipid	Anti-cardiolipin	1.76 (1.49-2.08)	1.84 (1.56-2.17)
	Anti- B2 Gly	1.97 (1.56-2.50)	1.81 (1.44-2.27)
	False positive RPR	2.24 (1.72,2.93)	2.97 (2.29,3.87)
	LAC	1.49 (1.23-1.79)	1.49 (1.24-1.79)
ANA		2.1 (1.34,3.3)	2.97 (1.78,4.94)

Table 2. SLE Damage index and relationship to low C3 and low C4.

SDI DAMAGE COMPONENT	C3 Odds Ratio (95%CI)	C4 Odds Ratio (95%CI)
Cataract	1.03 (0.83-1.28)	0.95 (0.78-1.82)
Retinal changes	1.24 (0.83-1.86)	0.81 (0.54-1.20)
Cognitive impairment	0.93 (0.60-1.27)	0.82 (0.59-1.27)
Seizure	1.22 (0.82-1.88)	1.53 (1.03-2.5)*
CVA	1.52 (1.12-2.07)*	1.50 (1.10-2.01)*
Cranial or Peripheral neuropathy	0.89 (0.68-1.18)	0.89 (0.67-1.18)
Transverse myelitis	2.89 (0.94-8.88)	1.30 (0.53-3.4)
GFR <50	3.70 (2.48-5.75)*	1.7 (1.21-2.50)*
Proteinuria	4.13 (2.20-5.57)*	1.92 (1.41-2.61)*
ESKD	3.51 (2.20-5.57)*	1.90 (1.25-2.7)*
Pulmonary hypertension	1.57 (1.05-2.33)*	1.32 (1.25-1.94)*
Pulmonary fibrosis	1.06 (0.78-1.46)	0.92 (0.67-1.26)
Shrinking lung	5.77 (0.79-46.7)	3.36 (0.66-16.38)
Pleural fibrosis	2.06 (1.20-3.54)*	1.45 (0.86-2.30)
Pulmonary infarction	2.74 (0.75-10.00)	1.24 (0.42-3.38)
Angina/CABG	0.79 (0.51-1.22)	0.72 (0.46-1.12)
Myocardial infarction	1.04 (0.69-1.55)	1.29 (0.84-1.98)
Cardiomyopathy	1.64 (1.05-2.57)*	1.29 (0.84-1.98)
Valvular heart disease	2.52 (1.45-4.47)*	1.81 (1.08-3.03)*
Pericarditis/pericardectomy	0.85 (0.46-1.59)	1.57 (0.59-2.91)
Claudication	1.17 (0.59-2.33)	1.39 (0.70-2.75)
Minor tissue loss	2.68 (0.87-8.25)	0.97 (0.57-2.91)
Significant tissue loss	1.64 (0.72-3.86)	1.29 (0.57-2.91)
DVT	1.34 ((0.86-2.07)	1.42 (0.92-2.18)
Lower GI surgery	0.76 (0.65-0.97)	0.89 (0.70-1.13)
Mesenteric insufficiency	1.64 (0.41-6.59)	8.80 (1.10-70.51)*
Chronic peritonitis	5.77 (0.70-47)	3.21 (0.66-16.37)
Upper GI surgery	1.15 (0.50-2.60)	1.09 (0.49-2.44)
Muscular atrophy/weakness	1.21 (0.73-2.00)	1.10 (0.94-1.84)
Arthritis	1.53 (1.08-2.17)	1.32 (0.94-1.84)
Osteoporosis	1.37 (1.07-1.77)*	1.33 (1.04-1.71)*
AVN	1.85 (1.40-2.43)*	1.49 (1.15-1.93)*
Osteomyelitis	1.23 (0.51-3.05)	1.10 (0.45-2.65)
Alopecia	1.20 (0.80-1.79)	1.12 (0.75-1.66)
Scarring of panniculum	1.66 (0.95-2.89)	1.70 (1.03-3.03)*
Skin ulceration	2.02 (0.93-4.42)	1.75 (0.84-3.63)
Premature gonadal failure	1.05 (0.72-1.53)	1.10 (0.75-1.60)
Diabetes	0.65 (0.48-0.87)	0.59 (0.43-0.81)

Malignancy	0.95 (0.73-1.24)	0.93 (0.72-1.21)
HTN	1.27 (1.07-1.51)*	1.21 (1.02-1.44)*

*=statistically significant.

Disclosure: L. Durcan, None; **W. Fu**, None; **M. Petri**, None.

Abstract Number: 2069

High Interferon Gene Signature Is Associated with Increased Disease Activity, Reduced Complement C3 and C4, and Increased Oral Corticosteroid Use in Systemic Lupus Erythematosus (SLE)

K Ranade, L Wang, P Brohawn, W Greth, J Drappa and G Illei, MedImmune, Gaithersburg, MD
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SESSION INFORMATION
Session Date: Monday, November 9, 2015
Session Title: Systemic Lupus Erythematosus - Clinical Aspects and Treatment III: Biomarkers
Session Type: ACR Concurrent Abstract Session
Session Time: 2:30PM-4:00PM

Background/Purpose: Increased expression of genes inducible by type 1 interferons has been observed in a subset of patients with systemic lupus erythematosus (SLE). Oral corticosteroids (OCS) are used to manage the signs and symptoms of SLE, with greater dosages needed for more severe disease. We explored associations between elevated expression of type I interferon–inducible genes in blood (IFN-high) and disease activity, complement C3 and C4 levels, autoantibodies to double-stranded DNA (dsDNA) or ribonucleoproteins (Sm, RNP), and use of OCS.

Methods: Baseline disease activity data (N=736) from two randomized controlled trials of sifalimumab (NCT01283139) and anifrolumab (NCT01438489), which enrolled patients with moderate to severe SLE (SLEDAI 2K≥6 and BILAG 1A or 2B and PGA≥1.0 on prednisone and/or immunosuppressants) were pooled. A new investigative-use only assay was used to determine IFN-high. Association between disease activity scores (SLEDAI-2K and CLASI <10 or ≥10), complement C3 or C4 (normal vs. low), autoantibodies to dsDNA, Sm, RNP (negative vs. positive), OCS dosage (< 10 or ≥10 mg/day), and IFN-high was assessed using chi-square tests.

Results: Pooled data from 736 patients were available for analysis. Mean age was 39.6±11.9. Ranges of SLEDAI and CLASI scores were 4–29 and 0–53, respectively, and 61% and 28% had SLEDAI 2K or CLASI scores ≥10. 57% received OCS ≥10 mg/day. 79% were IFN-high and had significantly greater odds of serological and clinical disease activity and of receiving ≥ 10 mg/day of OCS compared with patients who had low levels of type I IFN inducible gene expression in blood (IFN-low, Table).

Conclusion: Significant association of IFN-high with increased serological and clinical disease activity suggests that type I interferons are key drivers of disease in this cohort of patients with SLE. The association between IFN-high and greater OCS use is consistent with these patients having more severe disease.

Association of Baseline Type 1 Interferon (IFN)-Inducible Gene Expression Level in Whole Blood and Serological and Clinical Disease Activity and OCS Use in Patients Enrolled in Phase IIb Studies of Anifrolumab and Sifalimumab

Baseline measure	IFN-low N (%)	IFN-high N (%)	Odds ratio (95% CI) *p*-value
SLEDAI 2K			
<10	76 (48)	214 (37)	1.6 (1.12, 2.28)
≥10	81 (52)	365 (63)	*p*=0.009
CLASI			
<10	136 (87)	396 (68)	2.99 (1.83, 4.89)
≥10	21 (13)	183 (32)	*p*<0.001
Complement C3			
Normal	128 (82)	304 (53)	3.99 (2.58, 6.17)
Low	29 (19)	275 (48)	*p*<0.001
Complement C4			
Normal	146 (93)	401 (69)	5.89 (3.11, 11.15)
Low	11 (7)	178 (31)	*p*<0.001
Anti-dsDNA			
Negative	58 (42)	76 (15)	4.25 (2.8, 6.45)
Positive	79 (58)	440 (85)	*p*<0.001
Anti-Sm			
Negative	150 (96)	403 (70)	9.36 (4.3, 20.38)
Positive	7 (5)	176 (30)	*p*<0.001
Anti-RNP			
Negative	139 (92)	375 (66)	6.02 (3.26, 11.14)
Positive	12 (8)	195 (34)	*p*<0.001
Oral corticosteroid dosage			
<10 mg/day	81 (52)	232 (40)	1.59 (1.12, 2.27)
≥10 mg/day	76 (48)	347 (60)	*p*=0.01

Disclosure: K. Ranade, AstraZeneca, 1,MedImmune, 3; **L. Wang**, AstraZeneca, 1,MedImmune, 3; **P. Brohawn**, AstraZeneca, 1; **W. Greth**, MedImmune/AstraZeneca, 1; **J. Drappa**, MedImmune, 3; **G. Illei**, AstraZeneca, 1,MedImmune, 3.

Abstract Number: 2070

Urinary Biomarker Based "a-RAIL" Study in Adults with Lupus Nephritis

Gaurav Gulati[1], Khalid Abulaban[2], Jun Ying[3], Huijuan Song[4], Xiaolan Zhang[5], Qing Ma[6], Christopher Haffner[6], Kasha Wiley[7], Michael Bennett[8], Brad H. Rovin[4] and Hermine I. Brunner[9], [1]Division of Immunology, Allergy and Rheumatology, University of Cincinnati College of Medicine, Cincinnati, OH, [2]Pediatric Rheumatology, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, [3]University of Cincinnati, Cincinnati, OH, [4]Ohio State University Medical Center, Columbus, OH, [5]Ohio State University, Columbus, OH, [6]Cincinnati Children's Hospital and Medical Center, Cincinnati, OH, [7]Division of Rheumatology, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, [8]Division of Nephrology, Cincinnati Children`s Hospital Medical

Center, Cincinnati, OH, [9]Pediatric Rheumatology Collaborative Study Group, Cincinnati Children's Hospital Medical Center, Cincinnati, OH

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SESSION INFORMATION

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Session Title: Systemic Lupus Erythematosus - Clinical Aspects and Treatment III: Biomarkers

Session Type: ACR Concurrent Abstract Session

Session Time: 2:30PM-4:00PM

Background/Purpose:

The present study was aimed at developing an adult Renal Activity In Lupus (A-RAIL) algorithm for Lupus Nephritis (LN) activity assessment using urinary biomarkers (UBMs). A similar index for use in children with LN has been recently proposed.

Methods:

Adult Systemic Lupus Erythematosus (SLE) patients requiring a kidney biopsy as part of their standard care were enrolled. Patient demographics, SLE manifestations, laboratory parameters, renal activity/chronicity measures (R-SLEDAI, SDI-R) and a urine sample were collected at the time of biopsy. One expert read the biopsies in a blinded fashion to report National Institute of Health Activity and Chronicity indices (NIH-AI, NIH-CI). Patients were dichotomized as high activity or not based on the NIH-AI score of 10 as cut-off. UBMs measured included: kidney injury molecule 1, monocyte chemotactic protein 1, neutrophil gelatinase associated lipocalin, ceruloplasmin, adiponectin, hemopexin, alpha-1-acid glycoprotein, hepcidin, lipocalin-like prostaglandin synthase (L-PGDS), transferrin, vitamin D binding protein, transforming growth factor beta, endothelial protein C receptor, and liver type fatty acid-binding protein 1 using standardized ELISA-based assays (except L-PDGS and transferrin, measured by immune nephelometry). Urinary microalbumin and creatinine levels were measured to normalize for proteinuria in the analysis. Candidate RAIL predictors were firstly selected using univariate analyses, followed by stepwise selection in multiple logistic regression models. An A-RAIL algorithm was developed using the selected UBMs, and predictive accuracy calculated using the area under the Receiver Operating Characteristic (ROC) curve (AUC).

Results:

Of the 75 patients studied (age 32.4 ± 10.1 years), 78.7% were females. Caucasian and African American ethnicities were equally represented (46.7%). Mean NIH-AI and CI scores were 4.57 ± 4.11 and 3.23 ± 2.59 respectively. Renal activity was high in 11 (15%). No significant differences were noted for age, gender, ethnicity, or LN stage or laboratory parameters between the two activity groups, except lower C3 in high activity ($p = 0.029$). A-RAIL algorithm was studied using 10 significant UBMs and all analyses controlled for NIH-CI. The predictive accuracy of analysis was reported “outstanding” at the optimal score threshold ([AUC = 0.9 (95% CI 0.84 – 1.00]), and was similar when normalized for urinary creatinine or microalbumin [Table 1].

Conclusion:

The A-RAIL algorithm, termed “liquid biopsy for LN” by some, provides an accurate non-invasive assessment of LN activity. Its robustness and clinical usefulness is confirmed by use of various standards of normalization of proteinuria with LN. These results are very similar to the pediatric RAIL developed using six UBMs. This sets foundation for further studies assessing disease progression and response to therapy.

TABLE 1: Diagnostic Accuracy of A-RAIL Algorithm

Statistic	Adult RAIL Pathway Using 10 UBMs		
	Using Raw Data	Creatinine Adjusted	Microalbumin Adjusted
AUC (95% CI)	0.92 (0.84 - 1.00)	0.94 (0.88, 0.99)	0.90 (0.83, 0.98)
Sensitivity	90.9%	90.9%	90.9%
Specificity	83.6%	83.6%	78.7%
Positive Likelihood Ratio (LR+)	5.54	5.54	4.27
Negative Likelihood Ratio (LR-)	0.11	0.11	0.12
Logit cut	-1.86	-1.72	-1.83

Disclosure: G. Gulati, None; **K. Abulaban**, None; **J. Ying**, None; **H. Song**, None; **X. Zhang**, None; **Q. Ma**, None; **C. Haffner**, None; **K. Wiley**, None; **M. Bennett**, None; **B. H. Rovin**, Lilly, 5; **H. I. Brunner**, None.

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Abstract Number: 2071

Urinary Osteoprotegerin As Biomarker of Lupus Nephritis Disease Activity: Cross Sectional and Longitudinal Study

Ranjan Gupta[1], Amita Aggarwal[2], Sudhir sinha[3], Liza Rajasekhar[4], Akhilesh Yadav[1], Priyanka Gaur[1], Ramnath Misra[2] and Virsingh Negi[5], [1]Department of Clinical Immunology, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, India, [2]Clinical Immunology, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, India, [3]Department of Biochemistry, CSIR-central drug research institute, Lucknow, India, [4]Department of Rheumatology, Nizam Institute of Medical Sciences, Hyderabad, India, [5]Department of Clinical Immunology, JIPMER, Puducherry, India

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Session Time: 2:30PM-4:00PM

Background/Purpose:

Urinary biomarkers may help in identification, treatment and assessment of response to therapy in patients with lupus nephritis (LN). Osteoprotegerin (OPG) is produced by the kidney and may reflect the renal disease activity better than conventional markers. The data on its utility is sparse.

Methods:

Patients with SLE with active nephritis (AN), active disease without nephritis (active non-renal; ANR) and inactive disease (ID) were enrolled. Disease activity was assessed using renal SLEDAI (rSLEDAI) and SLEDAI. Patients with active nephritis were treated according to the ACR guidelines and followed up every 3 months for 1 year. Urine and serum samples were collected at baseline for all and every 3 months in patients of AN group. Urine samples from 24 healthy subjects (HC) and 20 patients each of rheumatoid arthritis (RA) and diabetic nephropathy (DM) served as controls. Serum (sOPG) and urinary OPG were measured using ELISA and urinary values were normalized for creatinine excretion. Variables are expressed as median (range) and non-parametric tests were used for statistical analysis.

Results:

A total of 121 SLE patients (females 113) were enrolled. At baseline, normalized urinary OPG (uOPG) was significantly higher in AN group as compared to ANR, ID, HC and DM (p-value <0.001 for all) but it was not different from RA. At baseline, uOPG correlated modestly with rSLEDAI (r=0.4, p-value <0.001) and SLEDAI (r=0.317, p-value <0.001) but not with sOPG levels. uOPG but not sOPG could differentiate between AN and ANR groups (Table 1).

Table 1. Baseline characteristics of SLE patients in the three categories

	Active Nephritis (AN)	Active Non-Renal (ANR)	Inactive Disease (ID)
Number	58	24	39
F:M	56:2	19:5	38:1
Median age (yrs)	27 (12 – 50)	28.5 (15 – 50)	28 (14 – 48)
rSLEDAI	8 (4 – 16)	0 (0)	0 (0)
SLEDAI	18 (6 – 28)	10 (5 – 20)	2 (0 – 4)
C3 (mg/dl)	48.5 (<16.9 – 125)	66.7 (17.3 – 163)	117 (34.2 – 194)
C4 (mg/dl)	7.8 (<5.6 – 55.7)	11.05 (<5.6 – 32.2)	24.15 (5.6 – 44.7)
Anti-ds DNA (IU/ml)	200 (24.7 – >300)	186.3 (<6.25 – >300)	51.35 (<6.25 – 200)
U_{Pr}/U_{Cr} ratio	3.3.7 (0.3 – 20.25)	0.37 (0.01 – 1.46)	0.11 (0 – 10.69)
Serum Creatinine (mg/dl)	0.9 (0.4 – 3.87)	0.82 (0.4 – 1.4)	0.8 (0.4 – 1.3)
Serum OPG (pg/ml)	1492.86 (624.09 – 4137.88)	1280.33 (116.16 – 2048.13)	1213.28 (368.37 – 1899.83)**
U_{OPG}/U_{Cr} (x 100 pg/mg)	12.29 (0 – 85.77)	2.36 (0 – 147.13)***	4.63 (0.07 – 42.53)***

p-value **= <0.01 and ***= <0.001 as compared to AN group

In the longitudinal study, uOPG decreased significantly at 3 and 6 months visits as compared to baseline (p-value <0.001) along with reduction in disease activity (Table 2). It showed an insignificant rise at 9 and 12 months. sOPG trends did not correlate with disease activity.

uOPG and not sOPG showed a rise before conventional markers in 2 patients who relapsed at 11 and 12 months respectively. Similarly, in 2 patients who developed chronic kidney disease, uOPG values remained persistently high throughout whereas sOPG did not.

Table 2. Change in different disease activity parameters, serum and normalized urinary OPG in the active nephritis group with treatment over 1 year

	Baseline	3 months	6 months	9 months	12 months
rSLEDAI	8 (4 – 16)	0 (0 – 12)	0 (0 – 4)	0 (0 – 4)	0 (0 – 8)
SLEDAI	18 (6 – 28)	2 (0 – 14)	2 (0 – 6)	2 (0 – 6)	2 (0 – 15)
C3 (mg/dl)	48.5 (16.9 – 125)	81.3 (7 – 161)	91.6 (47.1 – 174)	88.7 (33.4 – 168)	99.1 (35 – 165)
C4 (mg/dl)	7.8 (<5.6 – 55.7)	17.6 (<5.6 – 73.7)	19.6 (<5.6 – 61.1)	20.1 (<5.6 – 76.5)	19.2 (<5.6 – 58.4)
Anti-ds DNA (IU)	200 (24.7 – >300)	74.2 (8.4 – >300)	53.75 (<6.25 – 300)	72 (<6.5 – 300)	63.8 (<6.5 – 300)
U_{Pr}/U_{Cr} ratio	3.3.7 (0.3 – 20.25)	0.35 (0 – 13.55)	0.62 (0 – 3.98)	0.22 (0 – 6.98)	0.24 (0 – 6.25)
Serum Creatinine (mg/dl)	0.9 (0.4 – 3.87)	0.77 (0 – 4.12)	0.8 (056 – 1.7)	0.79 (0.4 – 1.3)	0.81 (0.4 – 1.3)
Serum OPG (pg/ml)	1492.86 (624.09 – 4137.88)	981.94 (591.57 – 1627.59)***	1219.74 (453.42 – 1916.27)**	826.79 (270.7 – 1872.65)***	1151.02 (0 – 1578.99)***
U_{OPG}/U_{Cr} (x 100 pg/mg)	12.29 (0 – 85.77)	4.66 (0.3 – 48.74)**	1.04 (0 – 15.98)***	3.25 (0 – 40.25)***	5.55 (0.06 – 67.71)***

p-value **= <0.01 and ***= <0.001 as compared to baseline values

Conclusion:

uOPG is derived from kidneys and among patients with active SLE, it helps differentiate between patients with and without LN. It shows modest correlation with disease activity and has a potential to predict poor response to therapy and relapse of LN.

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Abstract Number: 2072

Mitochondrial Reactive Oxygen Species Modulate Autoimmunity in Systemic Lupus Erythematosus

Luz P. Blanco[1], Christian Lood[2], Monica Purmalek[3], Suk See DeRavin[4], Carolyne K. Smith[3], Carmelo Carmona-Rivera[3], Harry Malech[4], Jeffrey Ledbetter[5], Keith B. Elkon[6] and Mariana J. Kaplan[1], [1]Systemic Autoimmunity Branch, National Institute of Arthritis and Musculoskeletal and Skin Diseases, National Institutes of Health, Bethesda, MD, [2]Internal Medicine, University of Washington, Seattle, WA, [3]Systemic Autoimmunity Branch, National Institute of Arthritis and Musculoskeletal and Skin Diseases, National Institutes of Health, Bethesda, MD, [4]NIAID/NIH, Bethesda, MD, [5]University of Washington, Seattle, WA, [6]Department of Medicine & Immunology, University of Washington, Seattle, WA

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Background/Purpose: Dysregulation in the formation of neutrophil extracellular traps (NETs) may contribute to modification and externalization of autoantigens and to organ damage in diverse autoimmune diseases including systemic lupus erythematosus (SLE). In SLE, a distinct subset of proinflammatory low-density granulocytes (LDGs) displays an exuberant capacity to form NETs in the absence of added stimulation. NETosis appears to require generation of reactive oxygen species (ROS). However, whether the process is strictly NADPH-oxidase dependent is unclear. Indeed, the role of other important sources of ROS like the mitochondria, in autoimmune NETosis, remains to be determined. This is particularly relevant as lack of a functional NADPH-oxidase, as seen in chronic granulomatous disease (CGD), is associated with enhanced predisposition to chronic inflammation and autoimmunity including SLE.

Methods: To clarify the contribution of mitochondrial ROS in the context of autoimmunity, mitochondrial activation and ROS were quantified in lupus LDGs by fluorescent microscopy and flow cytometry. Enrichment in oxidized mitochondrial DNA (ox-mitDNA) in isolated LDG NETs versus healthy control NETs was quantified with 8-Oxo-2'-deoxyguanosine antibodies and by calculating 16S/18S ratio by immunoprecipitation and qPCR. Various inhibitors of mitochondrial ROS and other sources of ROS were tested in lupus LDGs. Similar experiments were performed in neutrophils isolated from patients with CGD, to assess the role of NADPH-oxidase independent sources of ROS production. The type I IFN serum signature was quantified by assessing induction of IFN-inducible genes (ISGs) in THP1 cells. Circulating NET products were quantified by ELISA. Finally, the mitochondrial ROS inhibitor mitoTEMPO was administered systemically, continuously to lupus-prone female MRL/lpr mice for 7 weeks and, at euthanasia, lupus clinical phenotype, induction of ISGs, inflammatory cytokines and NETosis were quantified.

Results: Lupus LDGs displayed prominent enhancement of mitochondrial ROS synthesis when compared to healthy controls and lupus normal-density granulocytes. Lupus LDGs spontaneously formed NETs highly enriched in ox-mitDNA that significantly enhanced ISGs in monocytic cell lines. Emphasizing the role of mitochondria-derived ROS in autoimmune NETosis, CGD patients displayed an LDG population with exuberant spontaneous NET formation through enhanced mitochondrial ROS production and also had elevated type I IFN signature. There was a significant correlation between the development of autoimmunity in CGD patients and the serum type I IFN activity. Supporting the in vitro data, both lupus and CGD patients displayed evidence of enhanced in vivo NETosis. Importantly, lupus-prone mice that received mitoTEMPO displayed a significant decrease in proteinuria, autoantibodies, ISGs and proinflammatory cytokines, in association with hampered NETosis.

Conclusion: Mitochondrial ROS synthesis and ox-mitDNA appear to be key drivers of autoimmunity and proinflammatory responses in SLE and CGD and may represent novel therapeutic targets in these diseases.

Disclosure: L. P. Blanco, None; **C. Lood**, None; **M. Purmalek**, None; **S. S. DeRavin**, None; **C. K. Smith**, None; **C. Carmona-Rivera**, None; **H. Malech**, None; **J. Ledbetter**, None; **K. B. Elkon**, None; **M. J. Kaplan**, None.

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Abstract Number: 2073

Mitochondrial ROS Is a Novel Regulator of Sting-Mediated Type I IFN Production By Governing Extrusion of Oxidized Mitochondrial DNA upon Neutrophil Extracellular Trap Formation.

Christian Lood[1], Luz P. Blanco[2], Monica Purmalek[3], Carolyne K. Smith[3], Carmelo Carmona-Rivera[3], Jeffrey Ledbetter[4], Mariana J. Kaplan[2] and Keith B. Elkon[5], [1]Department of Medicine, Division of Rheumatology, University of Washington, Seattle, WA, [2]Systemic Autoimmunity Branch, National Institute of Arthritis and Musculoskeletal and Skin Diseases, National Institutes of Health, Bethesda, MD, [3]Systemic Autoimmunity Branch, National Institute of Arthritis and Musculoskeletal and Skin Diseases, National Institutes of Health, Bethesda, MD, [4]University of Washington, Seattle, WA, [5]Division of Rheumatology, University of Washington, Seattle, WA

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Background/Purpose: Neutrophil extracellular trap generation (NETosis) is a reactive oxygen species (ROS)-dependent cell death pathway implicated in autoimmune disorders such as systemic lupus erythematosus (SLE). However, since deficiencies in NADPH oxidase-mediated ROS production is associated with increased, rather than reduced, autoimmunity, this association has been challenged. Since mitochondria are major generators of ROS, we asked the following questions: i) is mitochondrial ROS required for NET formation? ii) what is the relative contribution and oxidative status of mitochondrial DNA in NETs? and iii) what are the immune stimulatory effects of mitochondrial products following RNP immune complex (IC) activation of neutrophils?

Methods: Mitochondrial ROS was quantified by the fluorescent dye MitoSOX. Diphenyleneiodonium (DPI), thenoyltrifluoroacetone (TTFA), rotenone and mitoTEMPO were used as ROS inhibitors. NET formation was quantified by fluorimetry and the extent of DNA oxidation determined using anti-8-oxo-2'-deoxyguanosine (8-OHdG) antibodies by ELISA or immunofluorescence (IF) microscopy. Immunoprecipitation and qPCR (16/18S ratio) were used to assess the origin and properties of NET DNA. To evaluate the inflammatory potential of mitochondrial DNA (mitDNA), oxidized or non-oxidized NET DNA was transfected into THP1 cells or injected into wild type or STING deficient mice.

Results: Following exposure of neutrophils to RNP IC, mitochondria became hypopolarized and translocated to the cell surface. The IC also stimulated mitochondria to produce ROS at levels similar to PMA stimulation. Mitochondrial ROS proved to be necessary for maximal NETosis since the selective inhibitors of mitochondrial ROS, TTFA and MitoTEMPO reduced NETosis by ~50% ($p<0.0001$, $n=8$). Furthermore, mitochondrial ROS stimulated by IC caused oxidation of DNA and IF revealed that DNA oxidation occurred predominantly in mitochondrial, rather than chromosomal, DNA. Using a dual immunoprecipitation and qPCR technique, we observed that the oxidized NET DNA displayed a high 16S/18S ratio, demonstrating that it was markedly enriched in mitDNA as compared to non-oxidized NET DNA ($p<0.01$, $n=9$). The oxidation of mitDNA was almost completely reversed in the presence of TTFA ($p<0.01$). When the inflammatory properties of oxidized mitDNA and non-oxidized DNA were compared *in vitro*, oxidized DNA was much more potent in inducing IL-6 and type I IFNs ($p<0.001$). Significantly, when oxidized mitDNA was injected into wild type and STING deficient mice, we observed that the oxidized mitDNA stimulated type I IFNs through a pathway that required the DNA sensor, STING ($p<0.001$).

Conclusion: Mitochondria play an important, previously unappreciated role in immune-mediated NETosis. Not only do they contribute to ROS that promotes NETosis but, also, oxidized mitDNA generated during NETosis has potent inflammatory properties *in vitro* and *in vivo* - including stimulation of type I IFN responses mediated through the STING pathway. We suggest that mitochondrial ROS and release of oxidized mitDNA may be instrumental in initiating or perpetuating autoimmunity and type I IFN signature seen in SLE patients.

Disclosure: C. Lood, None; **L. P. Blanco**, None; **M. Purmalek**, None; **C. K. Smith**, None; **C. Carmona-Rivera**, None; **J. Ledbetter**, None; **M. J. Kaplan**, None; **K. B. Elkon**, None.

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Abstract Number: 2074

Dominant Chilblain Lupus Due to an Activating Mutation of Sting – Suppression of Constitutive Type I Interferon Activation By JAK Inhibition

Christoph Fiehn[1], Nadja König[2], Christine Wolf[2], Mathias Lesche[3], Andreas Dahl[3], Claudia Guenther[4], Hanns-Martin Lorenz[5] and Min Ae Lee-Kirsch[2], [1]ACURA Centre for Rheumatic Diseases, Baden-Baden, Germany, [2]Department of Pediatrics, Medizinische Fakultät Carl Gustav Carus, Technische Universität Dresden, Dresden, Germany, [3]Department of Dermatology, Medizinische Fakultät Carl Gustav Carus, Technische Universität Dresden, Dresden, Germany, [4]Biotechnology Center, Technische Universität Dresden, Dresden, Germany, [5]Department of Internal Medicine 5, Division of Rheumatology, University of Heidelberg, Heidelberg, Germany

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Background/Purpose: Familial chilblain lupus is a monogenic form of cutaneous lupus erythematosus caused by mutations in the nucleases TREX1 or SAMHD1. The adapter molecule stimulator of interferon genes (STING) mediates DNA-induced activation of type I interferon (IFN) through binding of its ligand cyclic GMP-AMP (cGAMP). De novo STING mutations cause STING-associated vasculopathy with onset in infancy (SAVI), an autoinflammatory syndrome with vascular, cutaneous and pulmonary manifestations.

Methods: Clinical and genetic characterization of a large non-consanguineous family with chilblain lupus. Identification of the disease gene by exome sequencing. Analysis of skin histology. Functional testing of transfected wild type and mutant STING-cDNA on type I IFN activation. Evaluation of the response to short-term treatment with the JAK inhibitor tofacitimib on the transcriptional signature of IFN-induced genes in blood cells by quantitative RT-PCR.

Results: Five members of the family spanning four generations suffered from chilblain lupus since early childhood. Cold-induced inflammatory chilblain lesions were located at acral locations including fingers, toes, nose, ears, elbows and shins. Lesions presented as bluish-red infiltrations and led to mutilating necrotic ulcerations. In some patients, low-titred ANA and immune complexes were detectable; the skin histology was characterized by perivascular infiltrates and high MxA expression. Affected family members also exhibited increased expression of IFN-stimulated genes in blood. Mutations in TREX1 and SAMHD1 were excluded in the family. Exome sequencing identified a heterozygous STING mutation co-segregating with chilblain lupus. This previously unknown mutation affects a conserved amino acid residue located within the STING dimer interface and is predicted to be deleterious. Mutant STING-cDNA transfected into HEK cells led to phosphorylation of IRF3 and IFN-β production even in the absence of cGAMP stimulation. Treatment of two affected family members with the JAK inhibitor tofacitinib at 5 mg bid for 14 days led to a significant suppression of the transcriptional signature of IFN-induced genes in blood and to relief of symptoms of acral ischemia.

Conclusion: This is the first report of a family with dominant chilblain lupus due to an activating mutation of STING and expands the spectrum of type I interferonopathies. Suppression of chronically activated type I IFN signaling through inhibition of the JAK/STAT pathway with tofacitinib may represent a promising new therapeutic approach.

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Abstract Number: 2075

A Unique Naturally-Occurring Regulatory T Cell Subset Associated with Disease Activity in Patients with Systemic Lupus Erythematosus

Tetsuya Nishimoto[1], Yuka Okazaki[2], Hironari Hanaoka[1], Tsutomu Takeuchi[3] and Masataka Kuwana[2], [1]Division of Rheumatology, Department of Internal Medicine, Keio University School of Medicine, Tokyo, Japan, [2]Department of Allergy and Rheumatology, Nippon Medical School Graduate School of Medicine, Tokyo, Japan, [3]Keio University School of Medicine, Tokyo, Japan

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Background/Purpose: Foxp3 is a lineage-specifying transcription factor for $CD4^+$ regulatory T cells (Tregs), but recent studies have shown plasticity and heterogeneity within $CD4^+Foxp3^+$ cells, which include thymus-derived naturally-occurring Tregs (nTregs), peripherally-derived adaptive Tregs, and a subpopulation of activated effecter T cells. It has been reported that the number and function of $Foxp3^+$ Tregs are altered in patients with systemic lupus erythematosus (SLE), although data reported are somewhat conflicting. In this study, we examined phenotype and function of circulating $CD4^+Foxp3^+$ T cells in association with disease activity in SLE patients.

Methods: We enrolled 47 patients with SLE, 31 with organ-specific autoimmune diseases (15 multiple sclerosis and 16 primary immune thrombocytopenia), and 19 healthy subjects. Peripheral blood samples were obtained, and phenotype of $CD4^+Foxp3^+$ T cells was assessed using multi-color flow cytometry. Serial samples were evaluated in some SLE patients. Treg-specific demethylated region of the *Foxp3* gene (TSDR) was evaluated by methylation-specific polymerase-chain reaction using $CD4^+Foxp3^+$ T cells sorted by a flow cytometer. Immunoregulatory function of $CD4^+CD25^+$ T cells was examined by allogeneic mixed lymphocytes reaction. Finally, infiltration of IL-17-expressing $CD4^+Foxp3^+$ T cells was evaluated by immunohistochemistry of renal biopsy specimens obtained from 6 patients with active lupus nephritis (ISN/RPS-IV) and 5 with IgA nephropathy. Clinical information including SLE disease activity index (SLEDAI) at examination was retrospectively collected by review of clinical charts.

Results: $CD4^+Foxp3^+$ T cells were increased in circulation of SLE patients compared with organ-specific autoimmune disease controls or healthy subjects ($P < 0.01$ for all comparisons). Circulating $CD4^+Foxp3^+$ T cells were correlated positively with anti-double-strand DNA antibody levels or SLEDAI, and negatively with serum complement activity ($r > 0.52$, $P < 0.01$ for all correlations). Serial analysis in active SLE patients revealed reduction of $CD4^+Foxp3^+$ T cells after remission induction by immunosuppressive treatment. $CD4^+Foxp3^+$ T cells increased in peripheral blood of active SLE patients were nTregs, as determined by completely demethylated TSDR status. This SLE-specific nTreg subset represented unique phenotype; low expression of CD25, up-regulated expression of CD49d and CD127, expression of authentic Treg markers Helios and CD152, and expression of T helper 17 (Th17) markers CD161 and IL-17. The $CD4^+CD25^+$ T cells obtained from SLE patients exerted immunosuppressive ability comparable to those from healthy subjects. Finally, immunohistochemistry of renal specimens revealed that proportion of $Foxp3^+$ cells in infiltrating $CD4^+IL\text{-}17^+$ T cells was significantly increased in patients with active lupus nephritis than in those with IgA nephropathy (54% ± 10% versus 21% ± 9%, $P< 0.01$).

Conclusion: A unique nTreg subset acquiring both immunoregulatory and Th17 phenotypes is increased in circulation of active SLE patients, and may be involved in pathogenic process of SLE.

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Abstract Number: 2076

Development of Lupus Nephritis: Preclinical Evaluation of Patients Who Subsequently Develop Systemic Lupus Erythematosus Demonstrate Elevation of Select Soluble Mediators Prior to and at Disease Classification in Patients with Nephritis

Melissa E. Munroe[1], Jourdan R. Anderson[1], Julie M. Robertson[1], Timothy B. Niewold[2], George C. Tsokos[3], Michael P. Keith[4], Joan T. Merrill[5], Jill P. Buyon[6], John B. Harley[7] and Judith A. James[8], [1]Arthritis and Clinical Immunology, Oklahoma Medical Research Foundation, Oklahoma City, OK, [2]Division of Rheumatology and Department of Immunology, Mayo Clinic, Rochester, MN, [3]Division of Rheumatology, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, [4]Walter Reed National Military Medical Center, Bethesda, MD, [5]Clinical Pharmacology, Oklahoma Medical Research Foundation, Oklahoma City, OK, [6]Medicine, Division of Rheumatology, New York University School of Medicine, New York, NY, [7]Center for Autoimmune Genomics and Etiology (CAGE), Cincinnati Children's Hospital Medical Center, Cincinnati, OH, [8]Arthritis and Clinical Immunology, University of Oklahoma Health Sciences Center and Oklahoma Medical Research Foundation, Oklahoma

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Background/Purpose: SLE is a heterogeneous autoimmune disease marked by immune dysregulation and a spectrum of pathogenic autoantibodies. Why some patients have only moderate symptoms and others develop organ-threatening manifestations such as nephritis is unclear. We previously identified several cytokines that correlate with increased disease activity. This study evaluates the temporal expression of autoantibodies and cytokines during transition from preclinical lupus to SLE in patients who do or do not present with nephritis.

Methods: Sera from 83 SLE cases with serial specimens spanning from time points of no ACR criteria to SLE classification (average timespan= 4.7 years) were obtained from the Department of Defense Serum Repository (DODSR). Samples were tested for SLE-associated autoantibodies and 32 soluble inflammatory and regulatory mediators, including cytokines, chemokines, and soluble receptors, as well as serum interferon-α (IFN-α) activity by cell reporter assay (WISH). Demographic, clinical, medication data and ACR classification criteria were extracted from medical records.

Results: Thirty (36%) patients who transitioned to SLE met renal criteria within 5.2 (± 5.5) months of disease classification (range -5.2 to +12 months). Patients presenting with renal criteria were more likely to be male compared to patients without renal criteria ($p=0.016$). Cases who did not meet renal criteria were more likely to have a history of hydroxychloroquine use prior to SLE classification ($p<0.0001$). Although renal cases experienced earlier onset of autoantibody positivity compared to non-renal cases (mean -3.8 vs -2.6 years relative to SLE classification, $p=0.0442$), no differences in number or type of autoantibody specificity were detected, including anti-dsDNA. Of interest, cases meeting renal criteria exhibited elevated levels of a number of soluble mediators prior to developing nephritis and reaching SLE classification, including the adaptive mediators IL-4, IL-5, IL-12, and IFN-γ, the IFN-mediated chemokine, IP-10, as well as shed TNFRII (all $p<0.05$ compared to matched healthy controls), increasing again at the time of nephritis (all $p<0.02$ compared to pre-nephritis levels), along with the mediator SCF ($p<0.0001$). SCF, IL-5, IFN-γ, MCP-3, IP-10, and TNFRII were significantly increased at SLE classification in patients with renal criterion vs. non-renal patients (all $p<0.0001$). Nephritis occurred independently of BLyS and Type I IFN-α serum activity, as there was no difference in levels between renal and non-renal patients who transitioned to SLE.

Conclusion: The subset of severe onset SLE patients who develop early nephritis cannot be predicted by autoantibodies. However, these patients develop significantly altered levels of certain soluble inflammatory mediators as they move from pre-clinical to classified disease. Singular perturbations in immune mediated inflammatory processes, occurring long before clinical classification, may help identify individuals at high risk of renal involvement for early and continued monitoring and intervention.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/development-of-lupus-nephritis-preclinical-evaluation-of-patients-who-subsequently-develop-systemic-lupus-erythematosus-demonstrate-elevation-of-select-soluble-mediators-prior-to-and-at-disease-class

Abstract Number: 2077

Does Dysbiosis within the Intestinal Microbiome Contribute to SLE Pathogenesis?

Gregg J. Silverman[1], Lelise Getu[2], Haitao Niu[3], Hanane El Bannoudi[3], Adriana Heguy[4], Alexander Alekseyenko[5], Jill P. Buyon[6] and Doua Azzouz[3], [1]Dept of Medicine, NYU School of Medicine, New York, NY, [2]New York University School of Medicine, New York, NY, [3]Medicine, NYU School of Medicine, New York, NY, [4]Pathology, NYU School of Medicine, New York, NY, [5]Medicine, NYU SChool of Medicine, New York, NY, [6]Medicine, Division of Rheumatology, New York University

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Background/Purpose: Systemic lupus erythematosus (SLE) is the archetypic systemic autoimmune disease, caused by a combination of genetic and environmental factors. Animal models in other inflammatory and autoimmune diseases have provided ample evidence of a role for intestinal bacteria in development of the systemic immune responses and autoreactivity, and on the resolution of inflammation and tissue injury.

Methods: To characterize the intestinal microbiome from cross-sectional surveys of an urban SLE patient cohort, we performed community profiling of 16S bacterial rRNA genes using next generation sequencing of 83 stool samples from well-characterized SLE adult patients and 16 healthy controls. Fecal samples were also fractionated for endogenous IgA coated bacteria vs. non-coated bacteria in 28 SLE and all healthy controls.

Results: Based on principal coordinates analysis of genomic bacterial extracts, SLE samples were significantly different in microbial composition from the healthy subjects ($p<0.002$). SLE subjects also demonstrated significantly greater intragroup diversity, yet there was an overlap with the healthy subjects. In terms of the species diversity, as measured by Chao1 alpha diversity metric, SLE microbiomes exhibited less diversity than healthy subjects ($P<0.005$). Similar patterns were observed based on Shannon diversity ($P<0.01$). In SLE, these patterns were seen in both treated patients and in those not taking medications. At a Phylum level, SLE patients displayed a significant increase in Proteobacteria and decrease in Firmicutes compared to controls. In addition, SLE patients had increased representation of specific operational taxonomic units (OTUs). Interestingly the anaerobic species *Prevotella copri,* recently linked to new-onset RA, was expanded in a subset of SLE patients but not in healthy controls. Studies of sorted IgA-coated bacteria also identified differential representation of certain OTU in SLE, which did not appear to be treatment related.

Conclusion: These studies provide the first demonstration that clinical SLE disease is associated with microbiome imbalances, with decreases in taxonomic diversity and blooms of specific OTU, within the intestine. Studies of the intestinal bacteria coated with IgA highlighted that only microbes of certain genera and OTU are immunologically recognized by the lupus host. We speculate that these candidate pathobiont species may act as triggers for disease initiation and flares.

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Abstract Number: 2078

Reserve Capacity: Explaining the Link Between Socioeconomic Status and Depression/Anxiety Among Patients with Systemic Lupus Erythematosus

Desiree Azizoddin[1], Julia Ayeroff[2], Geraldine Zamora-Racaza[3], Taylor Draper[4], Sarah R. Ormseth[5], Michael H. Weisman[6], Lekeisha Sumner[7] and Perry M. Nicassio[8], [1]Cousins Center for Psychoneuroimmunology, University of California, Los Angeles, Los Angeles, CA, [2]Postbaccalaureate Premedical Program, University of Southern California, Los Angeles, CA, CA, [3]Division of Rheumatology, Cedars-Sinai Medical Center, Los Angeles, CA, [4]Psychology, Loma Linda University, Loma Linda, CA, [5]Cousins Center for PNI, University of California, Los Angeles, Los Angeles, CA, [6]Rheumatology, Cedars-Sinai Medical Center, Los Angeles, CA, [7]Department of Psychology,, Alliant University, Alhambra, CA, [8]Cousins Center for PNI, UCLA, LA, CA
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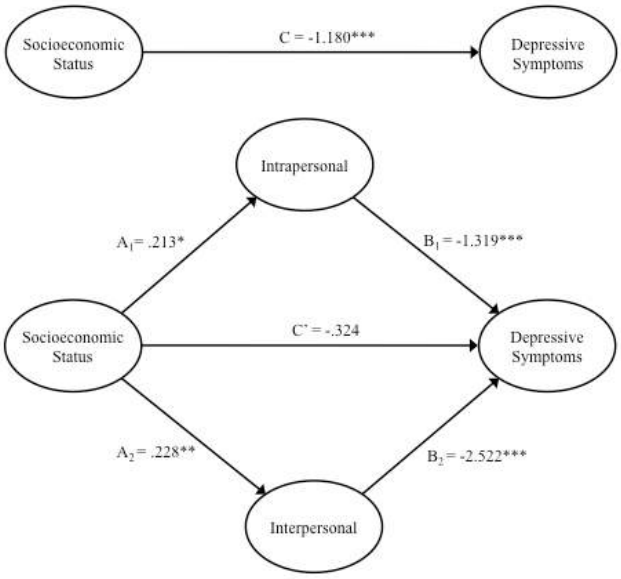
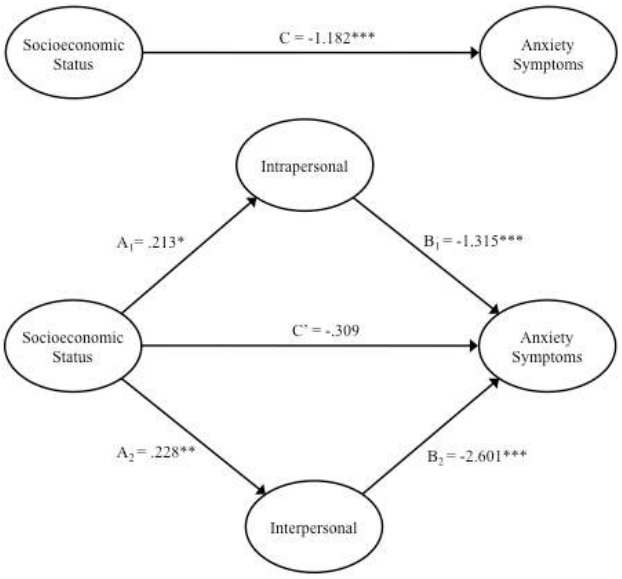
Background/Purpose: The purpose of this study was to assess the influence of socioeconomic status (SES) and measures of reserve capacity on depression and anxiety in patients with systemic lupus erythematosus (SLE). We examined whether reserve capacity/psychosocial variables explained the relationship between SES and levels of depression/anxiety in two separate meditation models. **Methods:** One hundred twenty-eight patients from Southern California with SLE completed self-report measures of demographic factors, disease activity (SLE Disease Activity Index), depression/anxiety (Hospital Anxiety and Depression Score), self-esteem (Rosenberg Self-Esteem Scale), social support (Social Provisions Scale), life orientation and optimism (Life Orientation Test – Revised), personal mastery (Personal Mastery Scale), and helplessness (Arthritis Helplessness Index). Two multiple meditational analyses were conducted utilizing an SPSS macro called "Indirect" (Preacher & Hayes, 2008), a program known to reduce complications with Type I Error and statistical power in multiple mediation models. **Results:** Results of confirmatory factors analyses revealed that social support variables made up an "interpersonal" latent factor; personal mastery, self-esteem, helplessness, and optimism variables made up an "intrapersonal" latent factors; and income, education, and perceived income made up an "SES" latent factor. Multiple mediation results revealed that, after controlling for disease activity and disease duration, features of reserve capacity including self-esteem, personal mastery, helplessness, optimism, and life orientation fully mediated the relationship between SES and depression/anxiety. After controlling for disease activity and disease duration, SES increased by one point and symptoms of depression decreased by .281 and .592 points through the mediating effects of interpersonal and intrapersonal reserve capacity, respectively. Additionally, as SES increased by one point, symptoms of anxiety decreased by .281 and .574 points through the mediating effects of interpersonal and intrapersonal reserve capacity, respectively. **Conclusion:** Results indicate that lower SES is indirectly associated with higher levels of depression and anxiety through the effects of lower psychosocial resilience resources. Providing interventions aimed at modifying reserve capacity variables, such as self-esteem, optimism, and sense of control may ultimately improve anxiety and depressive symptomatology in patients with SLE.





Disclosure: D. Azizoddin, None; **J. Ayeroff**, None; **G. Zamora-Racaza**, None; **T. Draper**, None; **S. R. Ormseth**, None; **M. H. Weisman**, None; **L. Sumner**, None; **P. M. Nicassio**, None.

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Abstract Number: 2079

Effectiveness of Renoprotective Approaches in Lupus Nephritis: More Than Just Immunosuppression

Maite Castro[1], Eduardo Ferreira Borba[1], Michelle Lopes[1], Sandra G. Pasoto[2], Eloisa Bonfá[1] and **Luciana Seguro**[2], [1]Rheumatology, Hospital das Clinicas, Faculdade de Medicina, University of São Paulo, São Paulo, Brazil, [2]Rheumatology Division, Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil

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Background/Purpose:

Hypertension and persistent proteinuria are risk factors for renal disease progression and are associated with high salt intake, poor adherence to medication and smoking. In systemic lupus erythematosus (SLE), proteinuria levels <0.8 g/day at 12 months is predictor of better long-term renal outcome. The aim of this study was to evaluate the effect of a multidisciplinary tight control renoprotective protocol (TCRP) in SLE patients with persistent proteinuria.

Methods:

All SLE patients (ACR criteria) followed at Lupus Outpatient Clinic were evaluated between September 2014 and May 2015. Twelve patients with persistent stable proteinuria >1g/24h (any time after 6-month induction and on regular maintenance therapy) were included in the TCRP (with a target of proteinuria <1g/24h and BP <130/80). The protocol consisted of visits every 2 weeks to assess: 1. Blood pressure (BP) control; 2. adherence to therapy; 3. dietary modifications. No change in immunosuppressive

drugs was allowed during the study period and glucocorticoid dose was lowered as indicated. Clinical, laboratory and treatment evaluation performed at baseline (T0) and after 3 months (T3) included: SLEDAI, 24h proteinuria, serum levels of creatinine, albumin, potassium, complement C3/C4, anti-dsDNA antibodies, change in glucocorticoid dose, renin angiotensin blockage intake.

Results:

Patients had mean age of 38.17 ± 7.85 years and disease duration of 9.75 ± 7.14 years. At nephritis presentation, three (25%) patients had creatinine >1mg/dL, 9 (75%) had positive anti-dsDNA and 8 (67%) had biopsy (5 membranous and 3 proliferative). Induction therapy consisted of mycophenolate (58%) and cyclophosphamide (42%), and maintenance therapy of mycophelonate (92%) and azathioprine (8%). The majority (75%) were under hydroxychloroquine. Renin angiotensin blockage was indicated in all patients as antiproteinuric and/or for BP control. At study entry (T0), 50% had BP > 130/80 mmHg. At least one dose optimization of these regimens and alternative agents were required in all patients during visits. At T3, 10 (83%) patients were using an angiotensin converting enzyme inhibitor, 7 (58%) an angiotensin receptor blocker and 5 (42%) of these patients were under combined therapy. Stable BP target was achieved by 10 (83%) patients at T3 with a significant reduction in diastolic BP ($p=0.029$). Of note, 24h proteinuria (2.06 ± 0.75 vs 0.94 ± 0.51 g/24h, $p<0.001$) reduced significantly, with a mean decline of 47.1 ± 19.2%. All patients had a decline in 24h proteinuria values and more than half (58%) of patients achieved proteinuria < 1g/24h at T3. Serum levels of creatinine (0.76 ± 0.18 vs 0.76 ± 0.18 mg/dL), albumin (3.94 ± 0.36 vs 3.99 ± 0.28 g/dL) as well as potassium, complement C3 and C4, frequency of anti-dsDNA and mean SLEDAI scores were similar at T0 and T3 ($p>0.05$). At T3, a decrease in mean prednisone dose was observed (10.63 ± 6.93 vs 5.83 ± 5.03 mg/day, $p=0.077$).

Conclusion:

This study suggests that a multidisciplinary tight control renoprotective protocol has a remarkable impact in reducing persistent proteinuria providing a brief window of opportunity for achieving the best predictor of long-term outcome in lupus nephritis.

Disclosure: M. Castro, None; **E. F. Borba**, None; **M. Lopes**, None; **S. G. Pasoto**, None; **E. Bonfá**, None, 2; **L. Seguro**, None.

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Abstract Number: 2080

Teaching Fellows in Lupus: Rheumatology Fellows Are Successful Educators in Improving Lupus Recognition By Frontline Healthcare Providers

Amy Caron[1], S. Sam Lim[2], Lexi Rene[3], Diane Gross[4], Maria Dall'Era[5], Rosalind Ramsey-Goldman[6] and Amanda Sammut[7], [1]Lupus Research Institute, New York City, NY, [2]Emory University School of Medicine, Atlanta, GA, [3]Rollins School of Public Health, Emory University, Atlanta, GA, [4]S.L.E. Lupus Foundation/Lupus Research Institute, New York, NY, [5]University of California San Francisco School of Medicine, San Francisco, CA, [6]Northwestern University Feinberg School of Medicine, Chicago, IL, [7]Columbia University Medical Center and Harlem Hospital Center, New York, NY
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Background/Purpose: The heterogeneity and non-specific features of lupus may delay diagnosis. This delay can lead to accrual of organ damage and an increased risk of death. Early detection by frontline providers (primary care and emergency room physicians, physician assistants, nurses, medical students) is critical to decrease the referral time for diagnosis and treatment. Average time devoted to lupus education in the first 2 years of medical school is 45 minutes and lupus education in years 3 and 4 is elective so frontline providers may not have the knowledge to recognize the disease. Given the shortage and high demand of rheumatologists, this project enlisted rheumatology fellows to deliver a standardized presentation.

Methods: Four cities were selected as pilot sites based on minority populations served, availability of rheumatology fellows, and local lupus experts. Fellows were trained to deliver standardized content developed material from the Lupus Initiative to provide a live presentation to frontline providers. Local lupus agencies assisted with outreach to schedule seminars. A voluntary, anonymous, paper-based pre/post assessment was used to evaluate changes in knowledge and confidence and to collect other qualitative data. A paired t-test was used to analyze the continuous variables and frequency tables were used for categorical variables.

Results: Preliminary data from 339 matched pre/post assessments were analyzed and scored on a 10 point scale. Total mean score increased 1.59 ($p<.0001$). Mean score improvement was greatest among nurses and physician assistants (3.09, 2.71 respectively; $p<.0001$) and providers in community health centers (3.00; $p<.0001$). 94% of participants gained confidence in knowing when to consider lupus based on patient history and exam and 93% in recognizing signs and symptoms. Over 90% were satisfied with the content, pace, and delivery of the seminar and 89% would attend another seminar led by a fellow. 100% of participating fellows noted the project as a positive experience.

Conclusion: Rheumatology fellows can effectively educate frontline providers about lupus recognition using a standardized presentation. Further dissemination and evaluation of this program is warranted.

Table 1. Comparison of Pre and Post Assessment Scores

Characteristics	N	Total Score Mean Diff (SD)	P-Value
Total Matched Assessments	**339**	**1.59 (1.65)**	**<0.0001**
Location			
Atlanta	96	1.18 (1.43)	<0.0001
Chicago	53	1.17 (1.49)	<0.0001
New York	149	1.87 (1.76)	<0.0001
San Francisco	41	2.10 (1.66)	<0.0001
Profession			
Doctors/ Residents	181	1.25 (1.48)	<0.0001
Physician Assistant/ Nurse Practitioner	17	2.71 (1.72)	<0.0001
Nurses	21	3.09 (1.61)	<0.0001
Medical Students	49	1.71 (1.54)	<0.0001
Place of Practice			
Emergency Room	46	1.15 (1.61)	<0.0001
Primary Care Office	41	1.88 (1.86)	<0.0001
Hospital	47	1.35 (1.30)	<0.0001
Community Health Center	16	3.00 (1.59)	<0.0001
Multiple Locations	71	1.59 (1.50)	<0.0001

Table 2. Confidence and Satisfaction

Confidence Change (Among respondents who were "Not Very" and "Not At All" Confident on Pre-assessment)	**N (%)**
Confidence knowing when to consider lupus based on patient history exam (N=140)	131 (93.6)
Confidence to recognize signs and symptoms of lupus (N=120)	111 (92.5)
Confidence to appropriately refer patients (N=90)	81 (90.0)
Satisfaction	**N (%)**
Very/Somewhat Satisfied with Content (N=288)	277 (96.2)
Very/Somewhat Satisfied with Pace (N=288)	269 (93.4)
Very/Somewhat Satisfied with Delivery of Content (N=288)	268 (93.1)
Highly Likely/Somewhat Likely to attend another seminar led by a Fellow (N=288)	255 (88.5)

Disclosure: A. Caron, None; **S. S. Lim**, None; **L. Rene**, None; **D. Gross**, None; **M. Dall'Era**, None; **R. Ramsey-Goldman**, None; **A. Sammut**, None.

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Abstract Number: 2081

The SLE Workshop: An Evaluation of a Long-Standing Hospital-Based Psychoeducational Program

Melissa T. Flores[1], Roberta Horton[1], Jillian A. Rose[1], Stephen A. Paget[2] and Michael Lockshin[3], [1]Social Work Programs, Hospital for Special Surgery, New York, NY, [2]Division of Rheumatology, Hospital for Special Surgery, New York, NY, [3]Barbara Volcker Center for Women & Rheumatic Disease, Hospital for Special Surgery, New York, NY

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Background/Purpose:

An evaluation was conducted of a monthly hospital-based psychoeducational support group, ongoing since 1985, for people with lupus. Each 2-hour session begins with a provider-led presentation on a lupus-related topic, followed by an evaluative survey and discussion.

Methods:

A 34-item survey with Likert scale and open-ended questions was mailed to 137 members. Items included user demographics, topic choices, satisfaction, impact and areas for improvement. Separate analyses on satisfaction and impact were conducted for core members (defined as attending ≥ 50% of prior year's sessions) and were also stratified by race/ethnicity. Chi-square and Fischer's exact tests were used to examine any differences.

Results:

53 surveys (39%) were returned. Most members (72%) were age 50+; 96% were female. 47% were white, 19% Asian, 14% Latino, 14% African American and 6% bi-racial. 80% had a Master's (51%) or Bachelor's (29%) degree. 50% had Medicare as their primary insurance with commercial insurance (36%) or Medicaid (14%); 28% had private insurance; 10% had Medicare only; average years since diagnosis was 16.

84% of all respondents were satisfied (64% strongly, 20% somewhat) overall; members of color reported ↑ overall satisfaction (88%) than whites (78%) with no significant difference. Members reported 95% satisfaction with the coordinator (69% strongly, 26% somewhat), 91% with speakers (62% strongly, 29% somewhat), 87% with topics (51% strongly, 36% somewhat) and 78% with discussions (52% strongly, 26% somewhat).

Whites reported ↑ satisfaction than members of color with speakers (100% vs. 84%) and the coordinator (100% vs. 91%), with no significant differences.

We assessed impact in 4 areas: knowledge, coping, self-management and social support. 86% agreed (61% strongly, 25% somewhat) their knowledge of lupus increased. 83% agreed (38% strongly, 45% somewhat) the groups helped them to cope. 82% agreed (34% strongly, 48% somewhat) they had ↑ ability to manage their lupus. 74% agreed (54% strongly, 20% somewhat) they had ↑ social support.

Members of color reported ↑ impact than whites for knowledge (88% vs. 71%), and whites reported ↑ ability to cope (88% vs. 80%); differences were not significant.

Core members responded to all measures of satisfaction and impact more highly than non-core members (i.e. 100% were satisfied overall).

Out of 25 topics, the 3 highest-rated were Medications, Arthritis/Joint Problems, and Environmental Triggers.

Responses to open-ended questions underscored the value of social support as well as self-management skills: “talking to others increased optimism,” “a health-saving resource,” and “more confident in talking with doctor.” Primary barriers to attendance were schedule conflicts, health and distance. Suggested improvements were ↑ time for speaker and discussion.

Conclusion:

Although limited by a small sample size, our results demonstrate the overall success of our program, the value it brings to our clients, and next steps for improving the program’s effectiveness. The differences in satisfaction and impact stratified by racial/ethnic groups and attendance rate were not found to be significant; we will continue to monitor and evaluate these identified trends.

Disclosure: M. T. Flores, None; **R. Horton**, None; **J. A. Rose**, None; **S. A. Paget**, MedScape, 8; **M. Lockshin**, None.

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Abstract Number: 2082

Evaluations of Social Support Are Associated with Well-Being Outcomes in Women with Systemic Lupus Erythematosus (SLE)

Stacey E. Morrison[1], Monique A.M. Gignac[2], Paul R. Fortin[3] and Dorcas Beaton[4], [1]Div Rheumatology Rm MP-10-304, Toronto Western Hospital, Toronto, ON, Canada, [2]Instititue for Work and Health, Toronto, ON, Canada, [3]Medicine, CHU de Québec - Université Laval, Québec, QC, Canada, [4]Mobility Program Clinical Research Unit, St Michael's Hospital, Toronto, ON, Canada
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Background/Purpose : Research on SLE and social support has often focused on the total amount of support provided. However, studies also report that some individuals feel under-supported whereas others feel too dependent on others. This study examined: 1) perceived support needs and support received for different domains (e.g., work, household activities) and types of support (instrumental, emotional and informational); 2) perceived concordant and discordant support; and 3) the relationship of support satisfaction with well-being (depression, life satisfaction, meaning of illness, illness intrusiveness) in women with SLE.

Methods : Women with SLE were recruited from the University of Toronto Lupus Cohort and completed a web or paper-based survey. Demographic (age, education), clinical (pain, fatigue, disease activity), and psychological perceptions (Center for Epidemiologic Studies Depression Scale (CES-D), life satisfaction, positive meaning of illness, illness intrusiveness) data were collected. Five domains of support were assessed (work/school, family, recreation, finance & household) along with 3 types of social support (instrumental, emotional & informational). Congruent and discordant support perceptions were created by examining needs and receipt for support, as well as support satisfaction. Separate analyses of variance (ANOVAs) examined differences in support and well-being within each domain and for each type of support.

Results : A total of 163 women with SLE, aged 50.7±16.1 years, with mean disease duration 21.9±13.7 years & mean disease activity ±3 months 2.4±2.6 on a 10-pt VAS responded. Participants reporting unsatisfactory support in at least one domain represented 47.8%, 43.1% & 53.9% of the sample for instrumental, emotional and informational support, respectively.

Although many women reported congruence between support needed and received, women often reported being under-supported in at least one domain of life. Few women reported being over-supported or dependent on others. In the work/school domain, depression and illness intrusiveness scores were significantly greater for those who viewed any type of social support as unsatisfactory compared to those receiving satisfactory support (all p-values < 0.01). Life satisfaction and meaning of illness scores were also significantly lower for those who reported dissatisfaction with their instrumental, emotional or informational support (all p-values < 0.001) in the work/education domain. Similar findings were found for other domains.

Conclusion: Previous research has often focused on the amount of support received. This research highlights that support needs vary and it is dissatisfaction with social support that often arises as a lack of congruence with support needed and received, not the amount of support, that is associated with well-being. These findings have implications for interventions. Further research, especially longitudinal studies, are needed to examine changes in support and well-being.

Disclosure: S. E. Morrison, None; **M. A. M. Gignac**, None; **P. R. Fortin**, GlaxoSmithKline, 5,Lilly, 5,AbbVie, 5; **D. Beaton**, None.

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Abstract Number: 2083

Predictors of Health Perceptions Among Women with Lupus

Patricia P. Katz[1], Eliza Chakravarty[2], Robert S. Katz[3] and Kaleb Michaud[4], [1]Medicine/Rheumatology, University of California San Francisco, San Francisco, CA, [2]Arthritis and Clinical Immunology, Oklahoma Medical Research Foundation, Oklahoma City, OK, [3]Rush University Medical Center, Chicago, IL, [4]Internal Medicine, University of Nebraska Medical Center, Omaha, NE
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Background/Purpose: Health perceptions, such as self-rated health, have been shown to predict multiple adverse health outcomes and to have a strong socioeconomic status (SES) gradient. Although SES-related health disparities have been found in lupus, previous studies have not examined the role of SES in health perceptions in lupus, independent of other health factors.

Methods: Data were from the National Data Bank for Rheumatic Diseases (NDB), for which participants complete questionnaires every 6 months. We included in analyses only women with lupus who responded to at least one questionnaire in 2014 (n = 481). Health perceptions were measured with 3 items: (1) health status numeric rating scale ranging from 0 (dead) to 100 (perfect health); (2) health satisfaction ("how satisfied are you with your health?"); responses ranged from very unsatisfied to very satisfied; and (3) overall health rating (excellent, good, fair, poor). The latter two items were dichotomized for analysis (satisfied or very satisfied vs. other; excellent or good vs. fair or poor). Potential predictors of health perceptions included SES (age, education, Medicaid or no health insurance vs other), lupus status (duration, disease activity measured with the Systemic Lupus Activity Questionnaire [SLAQ]), disease damage measured with the Brief Inventory of Lupus Damage [BILD]), and symptoms and other health factors (obesity, pain, physical function, fatigue, comorbidities, depressive symptoms, sleep, and smoking). Multiple linear and logistic regression analyses were conducted to identify independent predictors of health perceptions.

Results: Sample characteristics are shown in Table 1. In models including only age and SES variables, only low education was associated with health perceptions (Table 2). After adding lupus status, symptoms, and other health factors, SES variables were no longer associated with health perceptions. Four variables were consistently associated with each health rating: pain rating, physical function, disease activity, and smoking.

Conclusion: Health perceptions in lupus were primarily driven by health-related variables rather than SES. It is possible, however, that the effects of SES may be indirect; for example, smoking rates are higher among individuals with lower education. Additional study is needed to identify the ability of health perceptions s to predict health outcomes in lupus.

Table 1. Characteristics of sample			
SES variables			
Age, mean ± SD	57.9 ± 13.0	Education ≤ 12 years	22.1%
White	79.4%	Medicaid or no health insurance	13.5%
Lupus status			
Duration	21.0 ± 12.1	Disease damage (BILD)	3.3 ± 2.0
Disease activity (SLAQ)	11.0 ± 7.1		
Symptoms, other health factors			
Pain rating[1]	4.3 ± 3.0	Rheumatic Disease Comorbidity Index[5]	2.7 ± 1.8
Physical function[2]	38.4 ± 27.7	Obesity	33.6%
Fatigue[3]	5.2 ± 3.1	Depressive symptoms[6]	5.9 ± 5.4
Sleep[4]	4.4 ± 3.2	Smoking (current and past)	42.6%
Health perceptions			
Health status rating[7]	63.5 ± 20.9	Satisfied, very satisfied with health	44.8%
Excellent, good health	46.4%		

[1] Pain: 1-10 rating, higher rating = greater pain.

[2] Physical function: SF-36 Physical Function subscale, range 0 – 100, higher score = better function.

[3] Fatigue: 1-10 rating, higher rating = greater fatigue.

[4] Sleep: 0-10 rating of problematic sleep, higher rating = more sleep problems.

[5] Rheumatic Disease Comorbidity Index: Validated index that encompasses 11 comorbid illnesses (England BR, et al. *Arthritis Care Res*2015; 6: 865). Score ranges from 0-9.

[6] Depressive symptoms: from PHQ-8, higher score = more depressive symptoms.

[7] Rating of health state from 0 (dead) – 100 (perfect health)

Table 2. Regression results: Independent predictors of health perceptions*			
Significant associations	Health rating VAS§	Satisfied with health†	Excellent/good health†
Model 1: SES variables only			
Low education	-5.22 (0.10)	0.49 (0.30, 0.79)	0.52 (0.32, 0.87)
Model 2: SES + lupus status, symptoms, other health factors			
Low education		0.45 (0.19, 1.07)	
Pain rating	-1.32 (.02)	0.79 (0.67, 0.93)	0.82 (0.69, 0.99)
Physical function	0.23 (<.0001)	1.02 (1.01, 1.04)	1.05 (1.03, 1.07)
SLAQ	-0.44 (.04)	0.90 (0.83, 0.97)	0.89 (0.82, 0.97)
Smoking (current or former)	-3.84 (.07)	0.46 (0.23, 0.95)	0.29 (0.13, 0.65)
Comorbidity index			0.78 (0.61, 0.99)
BILD		1.22 (0.99, 1.51)	

* Table includes only predictors significant at $p \leq 0.10$.

§ Tabled values are beta (p-value) from multiple linear regression analysis

† Tabled values are odds ratio(95% confidence interval from multiple logistics regression analysis.

Disclosure: P. P. Katz, None; **E. Chakravarty**, None; **R. S. Katz**, None; **K. Michaud**, None.

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Abstract Number: 2084

Dendritic Cell-Specific Transmembrane Protein (DC-STAMP) Modulates Bone Resorption in Inflammatory Arthritis and Fracture Repair

Yahui Grace Chiu[1], Tzong-Ren Sheu[2], Jinbo Li[3], Dongge Li[4], Michael Thullen[2], Brendan Boyce[5], Christopher T. Ritchlin[6] and Javier Rangel-Moreno[7], [1]Allergy, Immunology, and Rheumatology, University of Rochester, Rochester, NY, [2]Center for Musculoskeletal Research, University of Rochester, Rochester, NY, [3]Pathology, University of Rochester, Rochester, NY, [4]Allergy, Immunology and Rheumatology, University of Rochester, Rochester, NY, [5]University of Rochester, Rochester, NY, [6]Allergy, Immunology and Rheumatololgy Division, University of Rochester Medical Center, Rochester, NY, [7]Allergy, Immunology & Rheumatology, University of Rochester, Rochester, NY

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Background/Purpose:

Osteoclasts (OC) direct pathologic bone resorption in osteoporosis and inflammatory arthritis. We previously demonstrated that DC-STAMP (Dendritic Cell-Specific Transmembrane protein), a 7-pass transmembrane protein, is not only essential for cell fusion during osteoclastogenesis but mice that lack this molecule also show impaired osteoblast (OB) differentiation. OC precursors arise from CD14+DC-STAMP+ cells in humans and the frequency of CD11b+DC-STAMP+ cells correlates with the extent of bone erosion in the TNF-Tg arthritis model. A rapid recruitment of DC-STAMP+ mononuclear cells to bone fracture sites and delayed bone healing in DC-STAMP knock-out (KO) mice suggested that DC-STAMP may also modulate fracture repair.

Methods:

(1) To investigate the interplay between DC-STAMP+ cells and OB, we examined the recruitment of DC-STAMP+ cells to the vicinity of OB using a mouse strain (collagen-I cre ROSA-rtta TRE-LacZ) whose OB lineage cells can be traced by the blue LacZ expression. OB differentiation was evaluated with the CFU-ALP and bone nodule formation assays. To examine the role of DC-STAMP+ cells in arthritis progression, we **(2)** introduced one copy of DC-STAMP knockout locus into the TNF+ mouse line and examined the effect of DC-STAMP KO on OB & OC differentiation and arthritis development; and **(3)** re-constituted lethally irradiated TNF-Tg mice with bone marrows (BM) from WT or DC-STAMP KO donors and compared arthritis progression between the two groups.

Results:

(1) Histology analysis: TRAP+DC-STAMP+ cells were recruited to the vicinity of LacZ+ OB at the bone fracture sites, whereas OB/OC co-localization was never detected on intact bones without fractures. (2) Genetic analysis: introduction of one DC-STAMP KO locus into the TNF+ background resulted in three phenotypes: (a) bone erosion was less severe; Bone Volume/Total volume (BV/TV: 18.2±5.7 & 12.0±3.1 in TNF+DC-STAMP+/- & TNF+DC-STAMP+/+) mice; (b) 6/15 mice showed asymmetric arthritis, suggesting an alleviated arthritis symptom; (c) OB differentiation was impaired (CFU-f units/well: 112±8 & 225±10 for TNF+DC-STAMP+/- & TNF+DC-STAMP+/+). (3) Bone marrow re-constitution: the expression level of DC-STAMP in the adoptively-transferred cells was up-regulated in the TNF+ background (the mean fluorescence intensity (MFI) in TNF+ and TNF- recipients were 1,205±82 & 723±98, respectively). TNF+ mice that received DC-STAMP+/+ donor cells developed severe arthritis approximately one week earlier than those receiving the DC-STAMP-/- donor cells (deformation scores: 8.0±2.5 & 5.0±3.2 for DC-STAMP+/+ & DC-STAMP-/- donors, respectively, at week-4 post-adoptive transfer).

Conclusion:

Aggregation of DC-STAMP+ cells around OB at fracture sites suggests that DC-STAMP is involved in OB:OC interactions. Arrested OB differentiation in DC-STAMP+/-TNF-Tg mice confirms our initial observations that DC-STAMP is required for adequate OB function. Moreover, DC-STAMP expression level increased in the presence of elevated *in vivo* TNFa concentration. Collectively, our data indicate that arthritis pathogenesis and bone repair can be modulated by the gene copy number and expression level of DC-STAMP.

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Abstract Number: 2085

DC-STAMP Regulates Osteoclastogenesis through the Ca2+ /NFATc1 Axis

Yahui Grace Chiu[1], Dongge Li[2], Yue-Xin Xu[3], Tzong-Ren Sheu[4], Minsoo Kim[5] and Christopher T. Ritchlin[6], [1]Allergy, Immunology, and Rheumatology, University of Rochester, Rochester, NY, [2]Allergy, Immunology and Rheumatology, University of Rochester, Rochester, NY, [3]Microbiology & Immunology, University of Rochester, Rochester, NY, [4]Center for Musculoskeletal Research, University of Rochester, Rochester, NY, [5]Microbiology and Immunology, University of Rochester, Rochester, NY, [6]Allergy, Immunology and Rheumatololgy Division, University of Rochester Medical Center, Rochester, NY
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Background/Purpose:

Osteoclasts (OC) are the only cell type known to erode bone. Many bone diseases including osteoporosis and arthritis are caused by excessive OC activity. The molecular mechanisms underlying cell-cell fusion, a key step in osteoclastogenesis (OCgenesis), are not well understood. Our studies focused on DC-STAMP (Dendritic Cell-Specific Transmembrane Protein), a 7-pass transmembrane protein which is expressed on the cell surface of OC precursors (OCPs) and is essential for OCgenesis. DC-STAMP knock-out (KO) mice form only mono-nucleated OC, and manifest mild osteopetrosis due to the absence of functional polykaryon OC. Previously, we identified an Immunoreceptor Tyrosine-based Inhibitory Motif (ITIM) on the cytoplasmic tail of DC-STAMP. By engineering a DC-STAMP:rhodopsin photactivatable chimeric molecule that can be activated by light, we demonstrated that the ITIM is a functional motif that alters intracellular Ca^{+2} flux, suggesting the potential role of DC-STAMP in signaling. Herein, we further examined the effect of ITIM deletion on bone erosion, cell mobility, and NFATc1 nuclear translocation.

Methods:

The wild-type (WT) and ITIM-deleted (TD) versions of DC-STAMP were tagged with GFP, and introduced into DC-STAMP-/- cells isolated from the DC-STAMP KO mice. DC-STAMP-/- cells which overexpress WT- or TD- DC-STAMP were tested for complementation to OC-forming deficiency by in vitro culture, bone erosion activity by bone wafer assay, cell surface distribution by confocal microscopy, and cell mobility by the scanning electron microscopy (SEM). The dynamic changes of NFATc1 protein after introduction of the WT DC-STAMP into DC-STAMP-/- cells were examined by Western blotting.

Results:

Deletion of the DC-STAMP ITIM was associated with decreased OCgenesis and altered downstream signaling as summarized by the following key observations. (1) Complementation: The OC-forming deficiency of DC-STAMP-/- cells was complemented when cells were infected with WT- but not TD- DC-STAMP; (2) Cell-cell fusion: Most of the TD-DC-STAMP-expressing cells were mononuclear, whereas a minority fused twice with 3 maximal nuclei per cell. As expected, TD cells showed smaller cell volumes than WT-DC-STAMP expressing cells due to the limited frequency of cell-cell fusion; (3) Bone erosion: TD-DC-STAMP-expressing cells showed decreased bone erosion activity as evidenced by smaller and shallower erosion pits (7.2 & 1.5 mm^2/pit area for WT & TD, respectively), which is associated with a reduced cell mobility revealed by SEM; (4) NFATc1 nuclear translocation: in contrast to WT-DC-STAMP, the NFATc1 proteins in TD-DC-STAMP-expressing cells failed to translocate to the nuclei.

Conclusion:

The ITIM on DC-STAMP is a functional motif that regulates OCgenesis through the Ca^{2+}/NFATc1 axis. Deletion of ITIM on DC-STAMP resulted in decreased bone erosion activity, impaired osteoclast mobility, and diminished nuclear translocation of NFATc1. This is the first demonstration that DC-STAMP regulates the translocation of NFATc1, a master transcription factor of OCgenesis. Targeted inhibition of the ITIM on DC-STAMP may prove an effective strategy to prevent pathologic bone in inflammatory and metabolic bone disorders.

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Abstract Number: 2086

Inhibition of Macrophage Inflammatory Protein 1-Alpha (CCL3) Significantly Reduced Bone Resorption in Vitro and the Development of Erosive Joint Pathology in Collagen-Induced Arthritis

Lauren A. Jordan[1], Ruth Davies[1], Alastair J. D. Robertson[2], Ann K. Harvey[1], Ernest H. Choy[1], Malin Erlandsson[3], Maria I. Bokarewa[4], Rachel J. Errington[1] and Anwen S. Williams[1], [1]Cardiff University, Institute of Infection and Immunity, Tenovus Building, University Hospital of Wales, Cardiff, United Kingdom, [2]William Harvey Hospital, Willesborough, Ashford, United Kingdom, [3]University of Goteborg, Goteborg, Sweden, [4]Guldhedsgatan 10, University of Goteborg, Goteborg, Sweden
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Background/Purpose:

The destruction of bone is a common feature of diseases like rheumatoid arthritis (RA) and multiple myeloma (MM). CCL3 is significantly elevated in the serum of patients with RA and MM; it is thought to contribute to leukocyte migration. A direct link between CCL3 and the development of osteoclast-dependent erosive bone pathology has not been evaluated previously. We studied CCL3's role in osteoclast (OC) differentiation from human macrophage precursor cells and its impact on bone resorption *in vitro* and *in vivo*.

Methods:

Human OC precursor cells ($CD14^{+ve}$ monocytes) from peripheral blood were seeded onto ivory disks and differentiated into OC using macrophage colony stimulating factor (M-CSF) and receptor activator of nuclear factor kappa-B ligand (RANKL) for 14 days alone or in combination with anti-CCL3 (8ng/mL) or osteoprotegerin (OPG; 8ng/mL). CCL3 was measured in culture supernatants by ELISA over the time-course. OC formation and resorption pits were visualised by tartrate-resistant acid phosphatase (TRAP) and toluidine blue staining respectively. Murine collagen-induced arthritis (CIA) was initiated after two intradermal immunizations of complete Freund's adjuvant and type (II) collagen (day 0 and day 21). Mice received intra-peritoneal injections (5mg/kg) of isotype control antibody (n=6) or anti-CCL3 (n=6) on day 21, 23, 25, 27, 28. Arthritis progression was measured daily to give a clinical score. Mice were culled on day 29. Bone erosion was observed in fixed forepaws and hind limbs by x-ray (12 joints per limb) and counted. OC counts, CCL3 concentration, percentage of the disk area resorbed, and number of eroded joints per mouse are reported as mean ± SEM. Statistical significance determined by 2-way ANOVA, Spearman's rank co-efficient or student's t-test as appropriate.

Results:

OC numbers per disk increased significantly over time (307 ± 81; $p \leq 0.01$ on day 14) with M-CSF and RANKL. A concomitant 5-fold increase in CCL3 levels (day 0 to 14) was observed ($p \leq 0.05$), which significantly correlated with OC number ($p \leq 0.01$, R= 0.32). Neutralisation of CCL3 led to a significant 3-fold reduction in OC differentiation (113 ± 41 OC/disk; $p \leq 0.05$) and were comparable to cultures supplemented with OPG. Anti-CCL3 treatment also significantly reduced the disk area resorbed (0.49 ± 0.13%; $p \leq 0.05$) compared to controls (1.54 ± 0.4%). OPG was more potent than anti-CCL3 in this regard (disk area resorbed = 0.04 ± 0.02%, $p \leq 0.05$ versus control). In CIA, anti-CCL3 had no significant effect on joint swelling, however, radiological progression of arthritis was substantially abated. The number of erosions in anti-CCL3 treated mice was halved (7 ± 2 ($p \leq 0.05$)) versus 15 ± 2 for isotype controls.

Conclusion:

For the first time we show the potent regulatory role of CCL3 in OC differentiation and OC-directed bone resorption in both *in vitro* and *in vivo* models. Our data unmasks the important function of CCL3 in the inflammatory milieu of a diseased joint and identifies this chemokine as target for further investigation as a marker for destructive bone disease associated with arthritis.

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Abstract Number: 2087

Defective Circadian Control in Mesenchymal Cells Reduces Adult Bone Mass

Julia F. Charles[1] and Joerg Ermann[2], [1]Rheumatology, Allergy and Immunology, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, [2]Rheumatology, Immunology and Allergy, Brigham and Women's Hospital, Harvard Medical School, Boston, MA

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Background/Purpose: Genetic disruption of the circadian molecular clock in mice is a powerful tool to dissect the role of circadian rhythms in health and disease. Several bone turnover markers show circadian variation in humans suggesting a function for the circadian molecular clock in bone physiology. In contrast to previous reports, we found that at 8 weeks of age (prior to the onset of heterotopic ossification) mice with germline deletion of the core circadian regulator *Bmal1* (Brain and muscle Arntl-like 1, $Bmal1^{-/-}$) have reduced trabecular and cortical bone compared with wildtype mice. Here, we ask whether the development of this phenotype can be mapped to disruption of the molecular clock in mesenchymal cells, osteoclasts, or both.

Methods: We generated mice with conditional deletion of *Bmal1* in mesenchymal cells of the limbs (*Prx1-cre*) or osteoclasts (*Ctk-cre*). We analyzed the bone phenotype of 8 week-old male mice comparing $Bmal1^{fl/fl}$.*Prx1-cre* mice with $Bmal1^{fl/fl}$ littermate controls, and $Bmal1^{fl/fl}$.*Ctk-cre* mice with $Bmal1^{fl/+}$.*Ctk-cre* littermate controls, respectively. Femurs were examined by micro-computed tomography and histology, and *in vitro*osteoclast and osteoblast differentiation assays were performed.

Results: Deletion of *Bmal1* in osteoclasts had no effect on *in vitro* osteoclast differentiation or resorptive function. Consistent with this, no differences in trabecular or cortical bone parameters were seen in $Bmal1^{fl/fl}$.*Ctk-cre* compared with $Bmal1^{fl/+}$.*Ctk-cre* controls. In contrast, we found a significant reduction of trabecular bone in $Bmal1^{fl/fl}$.*Prx1-cre* mice compared with controls (BV/TV 14.9% vs. 20.5% p=0.002; n=14) with corresponding significant changes in trabecular number, thickness, spacing and connectivity. Cortical parameters were also affected (C.Th. 0.15mm vs 0.17mm, p=0.008; n=14). *In vitro* assays failed to reveal an effect of mesenchymal *Bmal1* deletion on osteoclast formation or function. Differentiation of osteoblasts from $Bmal1^{fl/fl}$.*Prx1-cre* bone marrow stromal cells was also not significantly different from controls.

Conclusion: These results demonstrate that bone mass in mice is controlled by the cell-intrinsic circadian molecular clock in mesenchymal cells, whereas a functioning clock in osteoclasts appears dispensable for maintaining bone homeostasis.

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cells-reduces-adult-bone-mass

Abstract Number: 2088

Immature Dendritic Are Potent OC Precursors in RA and Are Targeted By RA-Specific Antibodies

Akilan Krishnamurthy[1], Vijay Joshua[2], Heidi Wähämaa[3], Vivianne Malmström[3], Khaled Amara[1], Jimmy Ytterberg[4] and **Anca I Catrina**[3], [1]Rheumatology Unit, Department of Medicine, Karolinska Institutet, Stockholm, Sweden, [2]Unit of Rheumatology, Department of Medicine Solna, Karolinska University Hospital, Karolinska Institutet, Stockholm, Sweden, [3]Rheumatology Unit, Department of Medicine, Karolinska Institute, Karolinska University Hospital, Stockholm, Sweden, [4]Rheumatology Unit, Department of Medicine, Solna, Karolinska Institutet, Stockholm, Sweden

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Background/Purpose:

Immature dendritic cells (iDC) have been shown to act as OC precursors and are important cell players in the pathogenesis of RA. We aimed to investigate the relationship between iDC derived osteoclastogenesis and specific immunity in RA.

Methods:

$CD14^+$ monocytes from PB of $ACPA^+$ RA patients and healthy individuals were first cultured in the presence of GM-CSF and IL-4 to generate iDC or in the presence of M-CSF to generate MΦ and then further differentiated to OC in the presence of RANKL and M-CSF. In parallel, cells were grown on osteoassay surfaces and bone resorption area was quantified by computer assisted image analysis. Mass spectrometry analysis was performed on different stages of differentiation of iDC and MΦ derived OC. ACPA positive and negative polyclonal IgGs were isolated from synovial fluid (SF, n=26) and peripheral blood (PB, n=38) samples of RA patients. Cytokines were measured by cytometric bead arrays in cultures supernatants. Immunohistochemistry (IHC) was used to stain the OCs with murinized monoclonal ACPAs derived from single SF derived B cells. The effect of IL-8 inhibition was tested in the OC cultures.

Results:

Principal component analysis confirmed distinct proteomic profiles during OC maturation from iDC and MΦ, respectively. Vimentin significantly increased during iDC-OC maturation, with citrullinated vimentin peptides detectable in matured OCs. Polyclonal ACPAs enhanced osteoclastogenesis and bone resorption from iDC (fold increase of 1.6±0.2 for OC number and 2.0±0.3 for bone resorption area). Similar effect was observed when the iDC were derived from ACPA+ RA patients (fold increase of 2.3±0.9 for OC number and 2.6±0.1 for bone resorption area). PB derived ACPAs were equally effective with SF ACPAs. Increased osteoclastogenesis was associated with significantly higher levels of IL-8 levels in cultures supernatants (fold increase of 2.4±0.5). Immunohistochemistry demonstrated presence of cit peptides in both iDC precursors and iDC-derived mature OCs suggesting that citrullination is important for iDC-OC differentiation and maturation (Figure 6B). PAD2 and PAD4 showed faint staining in CD14 monocytes with increased staining intensity in both iDC precursors and more mature OCs. The importance of citrullination and PAD enzymes for iDC transdifferentiation was confirmed by a dose-dependent inhibition of OC differentiation using PADi in the presence of RANKL and M-CSF. IL-8 was the main cytokine detected in the culture supernatants of iDC-derived cultures.

Conclusion:

iDC can effeiciently transdifferentiate in OC and are targeted by RA specific antibodies.

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Abstract Number: 2089

Netrin-1 and Its Receptors Unc5b and DCC May be Useful Targets for Preventing Multiple Myeloma Bone Lesions

Aranzazu Mediero[1], Tuere Wilder[2] and Bruce Cronstein[3], [1]Medicine, Divison of Translational Medicine, NYU School of Medicine, New York City, NY, [2]Dept of Med, Div of Rheum, NYU School of Medicine, New York, NY, [3]Medicine, Division of Rheumatology, NYU School of Medicine, NEW YORK, NY

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Background/Purpose: Multiple Myeloma is characterized by the uncontrolled proliferation of plasma cells. This type of malignancy is particularly trophic to bone where it induces osteoclastic destruction of bone. We have recently demonstrated that osteoclast differentiation is dependent upon the autocrine/paracrine expression of the laminin-like matrix protein and chemorepulsant netrin1 and binding of netrin1 to its cellular receptor unc5b. We therefore asked whether targeting netrin1 and its receptors unc5b and DCC could regulate myeloma spread in a murine model of myeloma.

Methods: 10^6 5TGM1-GFP myeloma cells (GFP expressing) were inoculated through the tail vein in 9 week old female C57Bl/KaLwRijHsd mice. Two weeks after inoculation animals were injected with monoclonal antibodies against Netrin-1, Unc5b and DCC weekly for 4 weeks (n=10 each). IVIS was performed for in vivo localization of myeloma bone lesions at the end of the experiment. Bone mineral density was measured by DEXA scanner and vertebrae and long bones were collected and prepared for microCT and histology analysis.

Results: IVIS imaging revealed a marked decrease in bone lesions in the anti-Netrin-1 and anti-Unc5b treated groups (n=6 and 9 mice respectively) when compared to control mice (n=6), whereas treatment results with anti-DCC antibody were more heterogeneous (n=7). There was an increase in total bone mineral density in anti-Unc5b and anti-DCC treated mice (0.63±0.09 g/cm^3 and 0.8±0.09 g/cm^3 respectively vs. 0.42v0.02 g/cm^3, $p<0.5$). microCT analysis revealed no changes in cortical bone parameters (Bone volume/total volume (BV/TV), bone volume (BV), total volume (TV) and Bone Mineral Density (BMD)) for any treatment group, but there was an increase in these parameters in Netrin-1 and Unc5b antibody-treated groups when trabecular bone was analyzed, consistent with the decrease in myeloma lesions (BV: 0.04±0.003 mm^3 and 0.08±0.01 mm^3 respectively vs. 0.02±0.003 mm^3, $p<0.05$; TV: 033±0.005 mm^3 and 0.36±0.01 mm^3 respectively vs. 0.26±0.002 mm^3, $p<0.05$; BV/TV: 2.87±0.3% and 0.08±0.01% respectively vs. 2.37±0.2, $p<0.05$; BMD: 0.64±0.009 g/cm^3 and 0.68±0.01 g/cm^3 respectively vs. 0.58±0.002 g/cm^3). There was also an increase in Trabecular thickness (Tb.Th), trabecular number (Tb.N.) and a decrease in trabecular separation (Tb.Sp.). TRAP staining revealed decreased osteoclasts in both anti-Netrin-1 and -Unc5b treated mice (7±1 and 6±1 cells/hpf respectively vs. 15±1 cells/hpf for control, $p<0.001$, n=5) but not for anti-DCC treated mice (13±1 cell/hpf vs. 15±1 cells/hpf for control, p=ns, n=5), and immunofluorescence analysis reveal a decrease in Cathepsin K positive cells that correlated with the decrease in TRAP-positive osteoclasts.

Conclusion: Anti-netrin-1 and -Unc5b treatment decreases osteoclast formation in a murine model of myeloma and decreases myeloma bone lesions. Targeting Netrin-1 or its receptor Unc5b may be a novel therapeutic approach for multiple myeloma.

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Abstract Number: 2090

Gender-Specific Pathways Linking Arthritis, Activity Limitation and Incident Heart Disease: A Causal Mediation Analysis of the Canadian Longitudinal National Population Health Survey

Orit Schieir[1], Sheilah. Hogg-Johnson[1,2], Richard H Glazier[3,4,5,6] and Elizabeth M. Badley[1,7], [1]Dalla Lana School of Public Health, University of Toronto, Toronto, ON, Canada, [2]Institute for Work and Health, Toronto, ON, Canada, [3]Family and Community Medicine, St. Michael's Hospital, Toronto, ON, Canada, [4]Centre for Research on Inner City Health, St. Michael's Hospital, Toronto, ON, Canada, [5]Family and Community Medicine, University of Toronto, Toronto, ON, Canada, [6]Institute for Clinical Evaluative Sciences, Toronto, ON, Canada, [7]Division of Health Care and Outcomes Research, Toronto Western Research Institute, University Health Network, Toronto, ON, Canada

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Background/Purpose: Arthritis and activity limitation are risk factors for cardiovascular (CVD) morbidity and mortality. As arthritis is a major cause of activity limitation, the objective of the present study was to estimate the extent to which increased heart disease risks in persons with arthritis are at least partially mediated through activity limitation pathways and potential variations by gender.

Methods: The longitudinal Canadian National Population Health Survey (NPHS) collected information on sociodemographic variables, self-reported physician-diagnosed chronic conditions, activity limitation, and lifestyle/health behaviors every 2 years from 1994/95 through 2010/11. Cause of death records for ischaemic heart disease and heart failure were confirmed against the Canadian Vital Statistics Database. Included variables were repeated measures of arthritis, activity limitation and heart disease lagged to ensure the proper temporal sequence, and the following baseline covariates: age, sex education, race, diabetes, high blood pressure, physical activity, BMI, smoking, alcohol consumption, use of pain medications and non-CVD comorbidity index. The analysis used a novel approach integrating recent advances in causal mediation with analyses of discrete event occurrence. Direct and indirect effects of arthritis on incident heart disease were obtained by combining estimates from a discrete-time survival model of heart disease regressed on arthritis and activity limitation controlling for all covariates measured at baseline with those from logistic regression of the mediator activity limitation regressed on arthritis and the same baseline covariates, stratified by gender.

Results: The sample included 11, 655 (5282 male, 6373 female) persons aged 18+ with no history of, or prevalent heart disease reported in the first 2 cycles of the NPHS (1994/5 and 1996/97). We identified 1442 incident heart disease events reported from 1998/99 to 2010/11. After adjusting for all covariates, arthritis and activity limitation were significantly associated with incident heart disease (arthritis OR (95% CI): 1.31 (1.10-1.56), activity limitation OR (95% CI) 1.61 (1.36-1.90)) in women, while only activity limitation was significant in men (arthritis OR (95% CI): 0.99 (0.81-1.20); activity limitation OR (95% CI): 1.59 (1.30-193)). Arthritis was significantly associated with activity limitation in both men (OR (95% CI): 3.25 (2.99-3.53)) and women (OR (95% CI): 2.85 (2.67-3.05)). Combining results from both regressions yielded significant direct (OR (95% CI): 1.31 (1.06-1.58)) and indirect effects (OR (95% CI): 1.09 (1.06-1.13)) of arthritis on heart disease with a proportion mediated by activity limitation of 28.5% in women. Only the indirect effect of activity limitation was significant in men (OR (95% CI): 1.09 (1.05-1.15)).

Conclusion: Findings from this longitudinal population based study help elucidate differences in the etiology of heart disease in men and women with arthritis, and have policy implications for arthritis prevention programs with priority for targeted interventions towards reducing disability in persons living with arthritis.

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Abstract Number: 2091

Influence of Increasing Physical Activity on Longitudinal Changes in Disability Status Among Inactive Older Adults

Jing Song[1], Abigail Gilbert[2], Rowland W. Chang[3], Christine Pellegrini[4], Linda S. Ehrlich-Jones[5], Julia (Jungwha) Lee[6], Daniel Pinto[7], Pamela Semanik[8], Leena Sharma[9], C. Kent Kwoh[10], Rebecca D. Jackson[11] and Dorothy D. Dunlop[12], [1]Institute for Healthcare Studies, Northwestern University, Chicago, IL, [2]Northwestern University Feinberg School of Medicine, Chicago, IL, [3]Dept Preventive Med, Northwestern Univ, Chicago, IL, [4]Department of Preventive Medicine, Northwestern University Feinberg School of Medicine, Chicago, IL, [5]Research CROR, Rehabilitation Institute Chicago, Chicago, IL, [6]Department of Preventive Medicine, Biostatistics Collaboration Center, Northwestern University Feinberg School of Medicine, Chicago, IL, [7]Department of Physical Therapy & Human Movement Sciences, Northwestern University, Chicago, IL, [8]College of Nursing, Rush University, Chicago, IL, [9]Rheumatology, Northwestern University Feinberg School of Medicine, Chicago, IL, [10]Rheumatology, University of Arizona, Tucson, AZ, [11]Ohio State University, Columbus, OH, [12]Inst Hlthcare Studies, Northwestern Univ, Chicago, IL
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Background/Purpose: An estimated 21% of disability attributed to arthritis is related to inactivity. This study analyzed data from the Osteoarthritis Initiative (OAI) to evaluate the influence of increasing physical activity on change in disability in previously inactive community-dwelling adults with or at greater risk to develop symptomatic radiographic knee osteoarthritis (OA).

Methods: Physical activity was measured by uniaxial accelerometers at baseline and 2 years. All study participants were inactive at baseline. Baseline inactivity was identified by the absence of a single 10-minute session of moderate or vigorous (MV) activity in a week. At 2 years of follow-up, inactive persons were further classified into three groups according to the Federal physical activity guidelines: those who (1) increased MV activity to meet guidelines (at least 150 minutes/week MV activity acquired in sessions ≥10min), (2) insufficiently increased MV activity (≥ 1 session/week but below guidelines) or (3) remained inactive. Disability domains of daily activity limitation (DAL) and frequency (DAF) assessed by Late-Life Disability Instrument were also ascertained at baseline and two years. Multiple linear regression evaluated the associations of changes in physical activity status with change in DAL and DAF adjusting for socioeconomic factors, health factors, and baseline DAL or DAF scores.

Results: The study included 545 adults with age range of 49-83 years; 64% had radiographic knee OA, 68% had WOMAC pain in at least one knee. At 2 years, 28% improved physical activity status. Compared to baseline, adults who remained inactive on average had worse DAL and DAF (mean change: -1.15 DAL, -0.46 DAF); people who became insufficiently active improved their DAL (mean change: 1.95 DAL, -0.41 DAF); those who met guidelines improved both their DAL and DAF (mean change: 10.31 DAL, 2.68 DAF). There was a significant graded relationship between increased physical activity and improved disability scores in both DAL (trend p-value <0.001) and DAF (trend p-value = 0.027) after adjusting for covariates.

Conclusion: These prospective data demonstrated increased physical activity was associated with reduced severity of disability over two years among previously inactive older adults. A significant graded relationship was found between improved physical activity status and decreased disability. While increasing physical activity to levels recommended by guidelines provided the most benefit, even increasing activity to below guideline levels was beneficial in reducing disability severity. These findings provide support for the encouragement of increasing activity to prevent worsening of disability.

Table. Late Life Disability Limitation and Frequency Average 2-year Changes from Baseline: Compared to those who remained inactive, those who moved from inactivity to more activity had significantly improved disability severity (positive average change)

			Year 2 Activity Status Among Baseline Inactive Adults			
			Remained Inactive	More Active		P value (trend)
				Insufficiently Active	Met Guidelines	
Disability domains of daily activity limitation (DAL)	Mean Change		-1.15	1.95	10.31	-
	Difference compared to Remained Inactive (95% CI)	Unadjusted	Reference	3.10 (0.78, 5.43)	11.46 (5.29, 17.63)	<.001
		Adjusted [a]	Reference	2.57 (0.30, 4.83)	10.15 (4.48, 15.81)	<.001
Disability domains of daily activity frequency (DAF)	Mean Change		-0.46	-0.41	2.68	-
	Difference compared to Remained Inactive (95% CI)	Unadjusted	Reference	0.05 (-0.74, 0.84)	3.14 (1.05, 5.23)	0.084
		Adjusted [a]	Reference	0.30 (-0.52, 1.12)	3.13 (1.07, 5.18)	0.027

[a] Adjusting factors: Socioeconomic factors (SES: age, live alone, gender, race, education, income), Health factors (comorbidity, high depressive symptoms, smoking, K/L grade, WOMAC pain, knee symptoms, knee injury, lower extremity pain), baseline DAL (DAF) score for models on change in DAL (DAF)

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Abstract Number: 2092

Knee Pain Burden Is Associated with Decreased Moderate to Vigorous Physical Activity: Data from the Osteoarthritis Initiative

Javad Razjouyan[1], Bijan Najafi[2], Erin Ashbeck[3], Dorothy D. Dunlop[4], Julia (Jungwha) Lee[5], Lynn Hamilton[3] and C. Kent Kwoh[6], [1]Consortium on Advanced Motion Performance (iCAMP), Department of Surgery, University of Arizona, Tucson, AZ, [2]Department of Surgery and Department of Biomedical Engineering, University of Arizona, Tucson, AZ, [3]Arthritis Center, University of Arizona, Tucson, AZ, [4]Institute for Healthcare Studies, Northwestern University Feinberg School of Medicine, Chicago, IL, [5]Department of Preventive Medicine, Biostatistics Collaboration Center, Northwestern University Feinberg School of Medicine, Chicago, IL, [6]Rheumatology, University of Arizona, Tucson, AZ

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Knee Pain Burden is Associated with Decreased Motor Performance: Data from the Osteoarthritis Initiative

Background/Purpose: The influence of knee pain perception on daily life motor performance in knee osteoarthritis (OA) patients has not been established. We examined the effect of knee pain on objectively measured cadence, a measure of motor performance in daily life, among community-dwelling adults with or at high risk for knee osteoarthritis.

Methods: Activity was objectively measured by accelerometer on 2,001 participants with or at risk of radiographic knee OA at the Osteoarthritis Initiative (OAI) 48-month clinic visit using ActiGraph GT1M uniaxial accelerometers (ActiGraph; Pensacola, FL). Participants were instructed to wear the sensor for seven consecutive days at least 10 hours per day. Analysis was restricted to those with at least four valid days of wear. Cadence is defined as the number of steps taken in a minute. The average maximum cadence/day was determined by identifying the maximum duration of moderate/vigorous activity (MVPA) and dividing the number of steps taken in the MVPA duration by MVPA minutes per day. These were then averaged over the number of valid days of wear. The Western Ontario and McMaster Universities Arthritis Index (WOMAC) was administered to assess the pain burden. Analysis of covariance was used to estimate sex-specific means (± standard error) of cadence across five categories of WOMAC pain (i.e., no pain and approximate quartiles of the non-zero pain score distribution), with adjustment for age, race, and body mass index.

Results: We included 1937 participants, 55% women, and with mean age of 65.1 (±9.1) years. Figure 1 shows a gradual decline in cadence with increasing WOMAC pain score. Mean cadence was significantly lower among men with WOMAC pain score >6 and significantly lower among women with WOMAC pain score >3, as compared to sex-specific means of participants with no pain.

Conclusion: Higher knee pain burden is associated with decreased motor performance in daily life as measured by cadence in both women and men. With the proliferation of accelerometers in smartphones, cadence may be an important outcome measure for interventions targeting pain in knee OA.

Average Maximum Daily Cadence (steps/minute)

WOMAC pain score (non-zero quartiles)	n	Men	p-value*	Women	p-value*
0	682	102.88± 1.67		100.81± 1.55	
1	285	102.02± 2.67	0.7845	101.73± 2.31	0.7375
2-3	392	104.20± 2.20	0.6329	97.23± 2.03	0.1607
4 to 6	310	100.14± 2.44	0.3557	92.21± 2.31	0.0021
>6	268	89.99± 2.83	<.0001	86.76± 2.39	<.0001

Mean ± standard error; means adjusted for age, race, and BMI
* Comparison of sex-specific mean with WOMAC pain score=0 group

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Abstract Number: 2093

Are General and Central Adiposity Associated with MRI-Assessed Structural Changes in the Knees of Older Adults?

Tomoko Fujii[1], Iva Miljkovic[1], Robert M. Boudreau[2], Ali Guermazi[3], Sara R. Piva[4], Elsa S. Strotmeyer[2], Laura Carbone[5], Tamara B. Harris[6], Elisa A. Marques[6], M Kyla Shea[7], Michael C. Nevitt[8], Anne B. Newman[2] and C Kent Kwoh[9], [1]University of Pittsburgh, Pittsburgh, PA, [2]Epidemiology, University of Pittsburgh, Pittsburgh, PA, [3]Department of Radiology, Boston University School of Medicine, Boston, MA, [4]Physical Therapy, University of Pittsburgh, Pittsburgh, PA, [5]Rheumatology, Georgia Regents University, Augusta, GA, [6]National Institute on Aging, Bethesda, MD, [7]Tuffs University, Boston, MA, [8]Epidemiology and Biostatistics, UCSF, San Francisco, CA, [9]University of Arizona, Tucson, AZ

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SESSION INFORMATION

Session Date: Monday, November 9, 2015

Session Title: Epidemiology and Public Health III: Risk Factors, Treatment and Outcomes of Gout and OA

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Background/Purpose:

Obesity is one of the few modifiable risk factors of knee osteoarthritis (OA). However, it is not established whether a mechanical or metabolic mechanism is more important for the development of knee OA. Central adiposity contributes more than peripheral adiposity to cardiometabolic diseases, while analogous associations with knee OA are not known. The aim of this study was to examine the associations of 1) total body fat mass and appendicular lean mass, 2) abdominal subcutaneous adipose tissue (SAT) and 3) visceral adipose tissue (VAT) with knee structural changes in community-dwelling older adults.

Methods:

A subsample (n=866, mean age 73.5±2.9, 525 women, 46% black) of the Health, Aging, Body Composition Study participants (n=3,075, mean age 73.6, 52% women, 42% black) was included in this analysis. Body composition was assessed at baseline using whole body DXA, and abdominal SAT area and VAT area (cm^2) were calculated from a single 10 mm thickness abdominal CT. Knee MRI images were obtained using a 1.5T system at the year 2 or year 3 visit and assessed using the Whole-Organ Magnetic Resonance Imaging Score (WORMS). The presence of any bone marrow lesion (BMLs, grade ≥1), cartilage damage (≥2), meniscus damage (≥1) and synovitis/effusion (≥1) was examined. The associations of body composition or adipose tissue measures with the knee outcomes were examined using logistic regression models stratified by sex. Total body fat mass and appendicular lean mass were entered in models simultaneously. VAT and SAT divided by body weight (cm^2/kg) were entered in separate models. In the final models, age, race, height, study site, education, history of knee injury, knee pain, smoking status, alcohol drinking, total physical activity, time spent watching TV and use of NSAIDs at baseline were adjusted. Correlation of knees within person was taken into account by generalized estimating equations.

Results:

In an analysis of 1,413 knees, higher appendicular lean mass was associated with higher odds of all knee MRI outcomes, but higher total body fat mass was associated only with lower odds of meniscus damage in men (Table 1). In women, higher appendicular lean mass was associated with BMLs and meniscus damage. Total body fat mass was also associated with BMLs, but the adjusted odds ratio was smaller than lean mass. Abdominal SAT or VAT were not significantly associated with any of the knee MRI outcomes in men. In women, higher abdominal SAT was associated with higher odds of BMLs, but no association was found for VAT.

Conclusion:

The stronger association between knee MRI outcomes and lean mass compared to total fat mass and the lack of the association with VAT suggest the importance of overall higher weight rather than total fat or central adiposity specifically for knee structural changes. This could indicate a mechanical rather than a metabolic pathway.

Table 1 Association between body composition and knee structural changes

Men

Outcomes	Total fat and appendicular lean			Abdominal SAT		VAT	
		aOR[1] [95% CI]	p-value	aOR[2] [95% CI]	p-value	aOR[2] [95% CI]	p-value
BMLs	Total fat	1.01 [0.97,1.04]	0.72	1.18 [0.88,1.58]	0.269	0.81 [0.59,1.10]	0.176
	Appendicular lean	1.15 [1.05,1.26]	0.003				
Cartilage damage	Total fat	0.98 [0.94,1.02]	0.36	1.19 [0.82,1.73]	0.357	0.69 [0.48,1.00]	0.05
	Appendicular lean	1.18 [1.04,1.33]	0.009				
Meniscus damage	Total fat	0.96 [0.93,0.99]	0.017	0.87 [0.66,1.14]	0.302	0.78 [0.57,1.07]	0.12
	Appendicular lean	1.17 [1.07,1.28]	0.001				
Synovitis/effusion	Total fat	0.98 [0.95,1.01]	0.191	0.94 [0.71,1.25]	0.672	0.75 [0.57,1.00]	0.051
	Appendicular lean	1.13 [1.03,1.23]	0.006				

Women

Outcomes	Total fat and appendicular lean			Abdominal SAT		VAT	
		aOR[1] [95% CI]	p-value	aOR[2] [95% CI]	p-value	aOR[2] [95% CI]	p-value
BMLs	Total fat	1.04 [1.01,1.07]	0.008	1.45 [1.23,1.70]	<.0001	1.07 [0.83,1.37]	0.62
	Appendicular lean	1.16 [1.05,1.28]	0.003				
Cartilage damage	Total fat	1.03 [0.99,1.06]	0.152	1.15 [0.95,1.40]	0.148	1.21 [0.85,1.71]	0.284
	Appendicular lean	1.13 [1.00,1.29]	0.058				
Meniscus damage	Total fat	1.01 [0.98,1.04]	0.409	1.04 [0.88,1.24]	0.608	1.07 [0.84,1.36]	0.609
	Appendicular lean	1.18 [1.07,1.29]	0.001				
Synovitis/effusion	Total fat	1.01 [0.98,1.04]	0.371	1.12 [0.95,1.31]	0.165	1.21 [0.94,1.56]	0.143
	Appendicular lean	1.10 [1.00,1.21]	0.059				

aOR adjusted odds ratio, CI confidence interval, SAT subcutaneous adipose tissue, VAT visceral adipose tissue
BML bone marrow lesion
[1]OR per 1 kg increase, [2]OR per 1 unit (cm^2/kg) increase
All odds ratios are adjusted for height, age, race, study site, education, knee injury, knee pain, smoking, alcohol intake, physical activity, time for TV watching and NSAIDs use.

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Abstract Number: 2094

Identification of Gout Flare Using an Administrative Claims Based Algorithm

Lindsey MacFarlane[1], Daniel H. Solomon[1] and Seoyoung C. Kim[2], [1]Rheumatology, Brigham and Women's Hospital, Boston, MA, [2]Division of Rheumatology; Division of Pharmacoepidemiology, Brigham and Women's Hospital, Boston, MA

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Background/Purpose:

Gout is a common inflammatory arthritis characterized by repeated acute flares. The ability to accurately identify gout flares is critical for comparative effectiveness studies of gout treatments. Prior studies use claims data to identify gout flares, however, these algorithms have not been validated. This study aimed to develop and validate a claims-based algorithm to identify gout flares.

Methods:

We identified patients receiving care at an academic medical center between 2006 and 2010 with a diagnosis of gout or hyperuricemia using an electronic medical record-Medicare claims linked dataset. We developed 3 algorithms to identify gout flares: 1) International Classification of Diseases, Ninth Revision (ICD-9) code for gout (274.X) and ≤ 1 dispensing for a gout-related medication including colchicine, nonsteroidal anti-inflammatory drugs, COX-2 selective inhibitors, and oral

glucocorticoids ≤ 7 days from the date of gout ICD-9 code. The algorithm was run for any gout-related medication and for the individual medication categories. 2) ICD-9 code for gout and a J code for injectable glucocorticoid or a current procedural terminology (CPT) code for arthrocentesis or joint injection ≤ 7 days from the date of gout ICD-9 visit code. 3) ICD-9 code for gout and a J code for injectable glucocorticoid or a CPT code for arthrocentesis or joint injection on the same day. Gout flares defined by the algorithms were confirmed through medical record review. Physician documentation of gout flare in the record was considered the gold standard. Positive predictive value (PPV) and 95 % confidence intervals (CI) of the algorithms were calculated. A set of 100 patients with a visit coded for gout but without any gout-related medication, arthrocentisis or injectable glucocorticoid claims was used to identify gout without flare and to calculate the negative predictive value (NPV).

Results:

503 flares were identified using the medication algorithm, and 290 were identified using the procedure ≤ 7 days algorithm. The mean age of the patients in the medication algorithm was 75 (±8) years, and 61% were male. The mean age for the procedure algorithm was 76 (±8) years and 68% were male. The PPV of medication claims ranged from 50-54%. The PPV of the procedure claims ≤ 7 days was 59%, the same day procedure claim was stronger with a PPV of 68% (Table). The NPV of the algorithm identifying gout without flare was 88% (95% CI 82, 94).

Table. Positive predictive value of algorithms

Algorithm	Records Identified	Confirmed Gout	Confirmed Flare	PPV of Flare Algorithm
	n	n	n	% (95% CI)
ICD-9 + medication claim for any gout related medications*	503	498	268	53.3 (48.9, 57.7)
ICD-9 + medication claim for colchicine	302	300	163	54.0 (48.4, 59.62)
ICD-9 + medication claim for NSAID/ COX-2 selective inhibitor	174	173	87	50.0 (42.6, 57.4)
ICD-9 + medication claim for glucocorticoids	270	266	145	53.7 (47.8, 59.7)
ICD-9 + CPT or J code within 7 days	290	287	172	59.3 (53.7, 65.0)
ICD-9 + CPT or J code on same day	196	194	134	68.4 (61.9, 74.9)

95% CI= 95% confidence interval; CI % (CI)ICD-9=International Classification of Diseases, 9thRevision; CPT= Current Procedural Terminology; PPV= Positive Predictive Value; NSAID=non steroidal anti-inflammatory; * gout-related medications include colchicine, NSAIDs, COX-2 selective inhibitor, and glucocorticoids

Conclusion:

Our results suggest that a claims-based algorithm utilizing a combination of diagnosis and procedure codes as well as medications may misclassify patients as having a gout flare and caution should be used in interpreting data using claims-based definition of flares. However, as the NPV was high, the claims-based algorithm may be useful to assess the absence of gout flare or to identify

a cohort of gout patients with low disease activity or disease remission.

Disclosure: L. MacFarlane, None; **D. H. Solomon**, Lilly, 2,Pfizer Inc, 2,AstraZeneca, 2,Amgen, 2,Corrona, 2,Genentech and Biogen IDEC Inc., 2; **S. C. Kim**, Pfizer Inc, 2,AstraZeneca, 2,Lilly, 2,Genentech and Biogen IDEC Inc., 2.

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Abstract Number: 2095

Dietary Patterns (DASH, Prudent, Western Diets) and the Risk of Gout in US Women – the Nurses Health Study

Jeewoong Choi[1], Na Lu[2], Yuqing Zhang[3], Sharan K. Rai[4], Gary C. Curhan[5] and **Hyon K. Choi**[2], [1]Massachusetts College of Pharmacy and Health Sciences, Boston, MA, [2]Rheumatology, Allergy and Immunology, Massachusetts General Hospital, Harvard Medical School, Boston, MA, [3]BUSM, Boston, MA, [4]Experimental Medicine, University of British Columbia, Vancouver, BC, Canada, [5]Renal Division, Brigham and Women's Hospital, Boston, MA

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Background/Purpose: There is a remarkable, rising disease burden of gout and associated cardiovascular-metabolic comorbidities (e.g., hypertension in 74% and obesity in 53% of cases in the US), underscoring an urgent need for holistic strategies to effectively address these conditions together. Individual dietary risk factors have been identified; however, a piecemeal approach focusing on certain specific dietary risk factors is often ineffective or impractical, and does not address comorbidities of gout. In contrast, a dietary pattern approach (e.g., the DASH or Western diet) reflects the way foods are consumed in reality, and can address the net health benefit and enhance applicability and sustainability in practice; however, data on dietary patterns and the risk of gout are scarce. We prospectively examined the relation between 3 major dietary patterns (the DASH, Prudent, and Western Diets) and the risk of gout in a large prospective study of US women.

Methods: We studied the risk of incident gout in 78,906 female participants using the American College of Rheumatology survey criteria for gout. Using dietary information obtained every 4 years over 22 years (1984-2006), we created a DASH dietary score based on its components, which emphasize fruits, vegetables, low-fat dairy foods, and reduced intake of saturated and total fat and sugar-sweetened beverages. We also identified two major dietary patterns (using factor analysis): “prudent” (characterized by higher consumption of vegetables, fruit, fish, poultry, and whole grains) and “western” (characterized by higher consumption of red meat, processed meat, fries, high-fat dairy products, refined grains, sweets, and desserts). We then calculated these pattern scores for each participant and prospectively examined the association between dietary pattern scores and the risk of gout, adjusting for potential confounders.

Results: During 22 years of follow-up, we documented 778 confirmed cases of incident gout. The DASH dietary pattern score was associated with a lower risk for gout (relative risk [RR] for extreme quintiles, 0.67 [CI, 0.53 to 0.84]; P <0.001 for trend). Similarly, the prudent dietary pattern score was associated with a modestly lower risk for gout (RR for extreme quintiles, 0.76 [CI, 0.60 to 0.97]; P = 0.04 for trend). In contrast, the western dietary pattern score was associated with an increased risk for gout (RR, 1.68 [CI, 1.28 to 2.21]; P <0.001 for trend).

Conclusion: The Western dietary pattern is associated with an increased risk of gout, which explains the rising burden of gout in Western countries. In contrast, the DASH diet and prudent dietary pattern are associated with a lower risk of gout. The DASH diet appears to offer an attractive additional nutritional approach for gout, as it also reduces blood pressure in hypertension (present in 74% of gout patients) and is also recommended to prevent CVD (a common comorbidity of gout).

Dietary pattern	Models	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5	P for trend
DASH Diet	No. of Cases	176	197	190	82	133	
	Person-years	316900	324130	371094	220054	357973	
	Age, BMI, Alcohol and calorie-adjusted	1 (reference)	0.98 (0.80,1.21)	0.82 (0.67,1.01)	0.61 (0.47,0.79)	0.67 (0.53,0.84)	<.0001
	Multivariate-adjusted	1 (reference)	0.97 (0.79,1.20)	0.82 (0.67,1.01)	0.60 (0.46,0.79)	0.67 (0.53,0.84)	<.0001
Prudent Pattern	No. of Cases	191	142	125	164	156	
	Person-years	367966	288488	255779	321864	356054	
	Age, BMI, Alcohol and calorie-adjusted	1 (reference)	0.91 (0.73,1.14)	0.86 (0.68,1.09)	0.90 (0.72,1.12)	0.80 (0.63,1.02)	0.09
	Multivariate-adjusted	1 (reference)	0.90 (0.72,1.12)	0.84 (0.66,1.06)	0.86 (0.69,1.08)	0.76 (0.60,0.97)	0.04
Western Pattern	No. of Cases	139	159	135	161	184	
	Person-years	345892	334228	317639	294488	297904	
	Age, BMI, Alcohol and calorie-adjusted	1 (reference)	1.14 (0.90,1.43)	1.04 (0.81,1.33)	1.39 (1.08,1.78)	1.71 (1.31,2.23)	<.0001
	Multivariate-adjusted	1 (reference)	1.13 (0.90,1.43)	1.03 (0.80,1.32)	1.37 (1.06,1.77)	1.68 (1.28,2.21)	0.0002

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Abstract Number: 2096

Immune Dysregulation in Patients with TRNT1 Deficiency

Angeliki Giannelou[1], Qing Zhou[2], Hong-Wei Sun[3], Dan Yang[4], Susan Moir[5], Jehad H. Edwan[3], Wanxia L. Tsai[3], Elisavet Serti[6], Monique Stoffels[2], Deborah L. Stone[7], Amanda K. Ombrello[7], Karyl Barron[5], Helen C. Su[5], Abdullah Al Sonbul[8], Sarita Joshi[9], Kimberly Risma[10], Lucie Sramkova[11], Martha M. Quezado[12], Katherine Calvo[13], Abu-Asab Mones[14], Gustavo Gutierrez-Cruz[3], Massimo G. Gadina[3], Markus Hafner[3], Ivona Aksentijevich[2,15] and Daniel Kastner[2], [1]National Human Genome Research Institute, National Institute of Arthritis and Musculoskeletal and Skin Diseases, National Institutes of Health, Bethesda, MD, [2]NIH/NHGRI, Metabolic, Cardiovascular, and Inflammatory Disease Genomics Branch, Bethesda, MD, [3]National Institute of Arthritis and Musculoskeletal and Skin Diseases, National Institutes of Health, Bethesda, MD, [4]National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, MD, [5]National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD, [6]Immunology Section, Liver Diseases Branch, NIDDK, NIH, Bethesda, MD, [7]National Human Genome Research Institute, National Institutes of Health, Bethesda, MD, [8]King Faisal Specialist Hospital & Research Center, Riyadh, Saudi Arabia, [9]Nationwide Children's Hospital, Columbus, OH, [10]Cincinnati Children's Hospital Medical Center, Cincinnati, OH, [11]Charles University 2nd Faculty of Medicine and UH Motol, Prague, Czech Republic, [12]Laboratory of Pathology/National Cancer Institute, National Institutes of Health, Bethesda, MD, [13]Department of Laboratory Medicine, National Institutes of Health, Bethesda, MD, [14]National Eye Institute, National Institutes of Health, Bethesda, MD, [15]Inflammatory Disease Section, National Human Genome Research Institute, Bethesda, MD

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Background/Purpose: Next generation sequencing has led to the discovery of new diseases and molecules regulating immune function. Hypomorphic mutations in the *TRNT1* gene cause a syndrome of sideroblastic anemia, immunodeficiency, periodic fevers and developmental delay, also known as SIFD. The TRNT1 enzyme catalyzes an essential step for tRNA maturation and protein synthesis, however, the underlying disease mechanisms are largely unknown. We aim to characterize the mechanisms of inflammation in this disease.

Methods: Whole exome sequencing or candidate gene screening was performed in two families, each with two affected siblings, and in three sporadic patients. Patient cells and tissue were used for deep RNA and tRNA sequencing, cytokine profiling, immunophenotyping through multicolor flow cytometry, H&E, immunohistochemistry and electron microscopy.

Results:

We identified seven patients with biallelic missense homozygous or compound heterozygous mutations in *TRNT1*. Four out of six mutations have not been reported. Three patients died of multiorgan failure. Two apparently unrelated patients shared the same genotype and had similar clinical presentation. Deep sequencing of tRNAs isolated from patients' fibroblasts showed a significant down-regulation of mature tRNAs when compared to healthy controls. RNA-sequencing of patients' whole blood revealed up-regulation of neutrophil-related genes. Consistent with these data, lesional biopsies from two patients' colon showed cryptitis with neutrophilic infiltration. Cultured patients' macrophages showed increased expression of proinflammatory cytokines IL-6, TNF-a, IL-1b, and accordingly, monocytes displayed increased phosphorylation of STAT3 ex vivo, possibly IL-6 induced, compared to monocytes isolated from healthy donors. Patients had variable degrees of B cell immunodeficiency with an increased population of immature B cells in the peripheral blood. Four patients had a bone marrow examination that revealed a markedly increased number of immature $CD10^{+}$ $CD20^{-}$B cells, and at the same time a decreased mature B cell population. Electron microscopy of BM smears showed evidence for abnormal morphology of blood vessels and endothelial cells, serum leakage and cellular debris in the stroma. Lymphocytes and monocytes displayed abnormal shape and degenerated mitochondria. Three patients have been on treatment with a TNF-a inhibitor that has shown promising results in attenuating the systemic inflammation and stabilizing the anemia.

Conclusion: Hypomorphic mutations in *TRNT1* are associated with a new, often severe, autoinflammatory disease manifesting a pleiotropic clinical phenotype. Given the essential function and ubiquitous expression of *TRNT1*, multiple cell types are affected. Myeloid cells, macrophages and neutrophils, might play an important role in mediating inflammation. Further studies may lead to the discovery of a new pathway regulating immune function.

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Abstract Number: 2097

HLA-B27 Expression Profoundly Shapes the Host-Microbiota Metabolome

Mark Asquith[1], Patrick Stauffer[2], Sean Davin[3], Stephen R. Planck[4], Phoebe Lin[5] and James T. Rosenbaum[6], [1]OHSU, Portland, OR, [2]Oregon Health & Science University, Portland, OR, [3]Oregon Health and Science University, Portland, OR, [4]Casey Eye Institute, Oregon Health & Science University, Portland, OR, [5]Casey Eye Institute, Oregon Health and Science University, Portland, OR, [6]Devers Eye Institute, Legacy Hospital system, Portland, OR

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Background/Purpose: The intestinal microbiota plays a pivotal role in both host fitness and disease. Increasing evidence implicates microbial metabolites in the modulation of host immunity in both the gut and the periphery. In this study we used the HLA-B27 transgenic rat model of spondylarthropathy (SpA) to test the hypothesis that HLA-B27, a key SpA risk allele, impacts the host-microbiota metabolome and this may contribute to B27-associated spondylarthropathy.

Methods: We used ultra performance liquid chromatography – tandem mass spectrometry (UPLC-MS/MS) to analyze the metabolic profiles of intestinal contents collected from Fischer HLA-B27/β2m rats and WT controls. Samples were collected at two time points, at 6 weeks of age and at 16 wks. These time points were chosen since they represent time points prior to and subsequent to the development of B27-associated inflammation. Intestinal dysbiosis in this study was analyzed using 16s rRNA sequencing and phyla/species-specific qRT-PCR primers.

For functional studies, microbial metabolities (short chain fatty acids) were administered *p.o.* in drinking water. Animals were treated for 10 weeks, with treatment beginning at 6 wks. The development of HLA-B27-associated inflammatory sequelae was analyzed longitudinally and at necropsy. Inflammatory cytokine expression was determined in intestinal tissue by RNA extraction and qRT-PCR.

Results: UPLC-MS/MS analysis detected the presence of 582 host and microbial metabolites. Changes in metabolites related to energetics, inflammation, redox homeostasis and the microbiome were observed at both time points examined. Microbial metabolites of amino acids and of dietary components were strongly impacted by HLA-B27 expression. Medium chain fatty acids (MCFAs) and short chain fatty acids (SCFAs) were globally dysregulated in HLA-B27+ animals. Moreover, 16s analysis of gut microbiota community structure revealed HLA-B27 expression was associated in a marked loss of SCFA-producing *Clostridial* spp. Strikingly, administration of SCFA propionate led to a significant attenuation of B27-dependent inflammation.

Conclusion: To our knowledge this is the first study to report that expression of SpA-susceptibility allele HLA-B27 profoundly impacts the host-microbiota metabolome. Of the many B27-dependent changes to both host and microbiota metabolic profiles, loss of medium and short chain fatty acids were amongst the most pronounced. SCFAs are a fermentation product of dietary fiber and HLA-B27 expression was associated with reduced colonization by multiple SCFA-producing bacteria. The successful attenuation of B27-dependent spondylarthropathy by targeting these microbial metabolites highlights the translational potential of metabolomic profiling of the intestinal microbiota. These data strongly support further studies of the host-microbiota metabolome in SpA patient populations.

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Abstract Number: 2098

Prioritizing Likely Causative Genes in Genome-Wide Association Studies (GWAS) Identified Risk Loci for Immune-Mediated Inflammatory Disorders Using Cell-Type Specific Expression Quantitative Loci (eQTL) Information

Elisa Docampo[1], Ming Fang[1], Julia Dmitrieva[1], Emilie Théâtre[1], Mahmoud Elansary[1], Rob Mariman[1], Ann-Stephan Gori[1], Myriam Mni[1], François Crins[2], Wouter Coppieters[2], Edouard Louis[3] and Michel Georges[1], [1]Unit of Animal Genomics, GIGA-R Université de Liège, Liège, Belgium, [2]GenoTranscriptomics platform, GIGA-R Université de Liège, Liège, Belgium, [3]Department of Gastroenterology, University Hospital CHU of Liège, Liège, Belgium

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<h1> **Background/Purpose:** </h1> Immune-mediated inflammatory disorders (IMIDs) share many genetic risk factors.

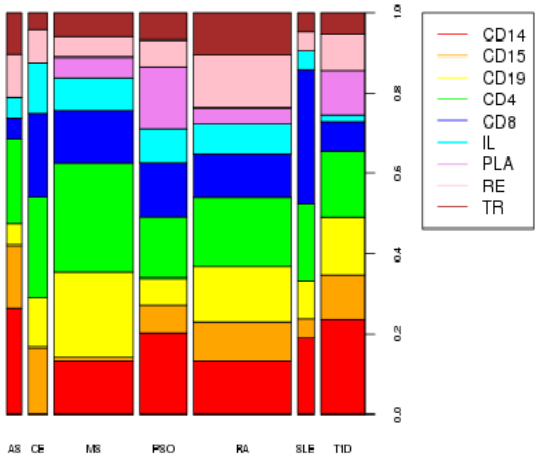
Pleiotropy may exist at different levels and most of the underlying mechanisms are still to be uncovered. GWAS have identified hundreds of risk loci for IMIDs but causative genes have been identified in only a handful of cases. Recent fine-mapping efforts indicate that only a minority of risk variants are coding. This suggests that most risk variants will be regulatory hence affecting disease risk via eQTL effects.

<h1> **Methods:** </h1> To aid in the identification of causative genes for IMIDs, we generated transcriptome information (HT12 arrays) for six blood cell types (CD4, CD8, CD19, CD14, CD15 and platelets) and intestinal biopsies at three anatomical locations (ileum, colon, rectum) for 350 healthy Caucasians. The same individuals were genotyped with SNP arrays interrogating > 700K variants, augmented by imputation from the 1KG project. To detect cis-eQTL we tested variants within 0.5 megabase windows centered on the tested probe. The nominal p-value of the best SNP within a cis-window was Sidak-corrected for the window-specific number of independent tests. The corresponding best, Sidak-corrected p-values for each probe were jointly used to estimate their respective false discovery rate. To identify likely causative genes in GWAS identified risk loci variants and also better understand pleiotropic effects, we (i) developed a method that quantifies the correlation between “disease association pattern” (DAP) and “eQTL association pattern” (EAP) and provides an empirical estimate of its significance, and (ii) evaluated the effect of fitting known risk variants as covariates in the eQTL analysis following Nica et al. (2010). We applied both approaches to celiac disease (CE) and rheumatoid arthritis (RA) and the second one to type one diabetes (T1D), multiple sclerosis (MS), systemic lupus erythematosus (SLE), ankylosing spondylitis (AS) and psoriasis (PSO).

<h1> **Results:** </h1> We detected > 16000 significant cis-eQTL, with a degree of sharing between cell types ranging from 38 to 90% highlighting the utility of our multi-tissue panel. GWAS variants were drivers of ciseQTL effects across the different tissues in 399 tests (23.6%), mostly in CD4 cells (Figure 1), and pinpointing 64 new gene-disease associations (3.7%). The number of shared loci and shared eQTL were highly correlated (rho=0.66).RA and SLE showed the highest degree of sharing.

<h1>**Conclusion:** </h1> We identified new potential candidate genes for IMIDs and characterized pleiotropic effects in terms of sign, magnitude and target tissue, through ciseQTL mapping in GWAS loci. These findings could shed a light on IMIDs pathogenesis and co-occurrence. Latest results will be presented.

Figure 1: Tissue Distribution of eQTLs driven by GWAS loci across IMIDs



Columns' width is proportional to the number of eQTLs.

Disclosure: E. Docampo, None; **M. Fang**, None; **J. Dmitrieva**, None; **E. Théâtre**, None; **M. Elansary**, None; **R. Mariman**, None; **A. S. Gori**, None; **M. Mni**, None; **F. Crins**, None; **W. Coppieters**, None; **E. Louis**, None; **M. Georges**, None.

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Abstract Number: 2099

Genome-Wide Association Study of Clinically-Defined Gout Identifies Multiple Risk Loci: A Clue for Future Companion Diagnostics of Gout

Hirotaka Matsuo[1], Ken Yamamoto[2], Hirofumi Nakaoka[3], Akiyoshi Nakayama[1], Masayuki Sakiyama[1], Atsushi Takahashi[4,5], Takahiro Nakamura[6], Yusuke Kawamura[1], Nobuyuki Hamajima[7], Ituro Inoue[8], Michiaki Kubo[4], Kimiyoshi Ichida[9], Hiroshi Ooyama[10], Toru Shimizu[11] and Nariyoshi Shinomiya[1], [1]Department of Integrative Physiology and Bio-Nano Medicine, National Defense Medical College, Tokorozawa, Japan, [2]Department of Medical Chemistry, Kurume University School of Medicine, Kurume, Japan, [3]Division of Human Genetics, Department of Integrated Genetics, National Institute of Genetics, Mishima, Japan, [4]Center for Integrative Medical Sciences, RIKEN, Yokohama, Japan, [5]Research Center, National Cerebral and Cardiovascular Center, Suita, Japan, [6]National Defense Medical College, Laboratory for Mathematics, Tokorozawa, Japan, [7]Department of Healthcare Administration, Nagoya University Graduate School of Medicine, Nagoya, Japan, [8]Department of Integrated Genetics, National Institute of Genetics, Mishima, Japan, [9]Department of Pathophysiology, Tokyo University of Pharmacy and Life Sciences, Hachioji, Japan, [10]Ryougoku East Gate Clinic, Tokyo, Japan, [11]Midorigaoka Hospital, Takatsuki, Japan
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Background/Purpose: Gout, caused by hyperuricaemia, is a multifactorial disease. Recently, genome-wide association studies (GWASs) of gout have been reported; however, they included self-reported gout cases. Therefore, the relationship between genetic variation and clinical subtypes of gout remains to be clarified. We hereby first performed a GWAS of clinically-defined gout cases only.

Methods: A GWAS was conducted with 945 clinically-defined gout cases and 1,213 controls in a Japanese male population. Additionally, a replication study of 1,048 clinically-defined cases and 1,334 controls was performed.

Results: We identified five susceptibility loci for gout at the genome-wide significance level ($p \quad 5.0 \times 10^{-8}$, which contained well-known urate transporter genes (*ABCG2* and *SLC2A9*) and additional genes reported to have relationships with metabolic pathways: rs1260326 ($p = 1.9 \times 10^{-12}$; OR = 1.36) of *GCKR* (a gene for glucose and lipid metabolism), rs2188380 ($p = 1.6 \times 10^{-23}$; OR = 1.75) of *MYL2-CUX2* (genes associated with cholesterol and diabetes mellitus), and rs4073582 ($p = 6.4 \times 10^{-9}$; OR = 1.66) of *CNIH-2* (a gene for regulation of glutamate signaling). The latter two are identified as novel loci for gout. Furthermore, we demonstrated that the identified SNPs were differentially associated with types of gout and clinical parameters underlying specific subtypes. The effect of the risk allele of each SNP on clinical parameters showed significant linear relationships with the ratio of the case-control ORs for two distinct types of gout ($r = 0.96$ [$p = 4.8 \times 10^{-4}$] for urate clearance and $r = 0.96$ [$p = 5.0 \times 10^{-4}$] for urinary urate excretion).

Conclusion: Our findings provide clues to better understand the pathogenesis of gout and will be useful to develop companion diagnostics of gout.

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Abstract Number: 2100

Hypomethylation in Enhancer and Promoter Regions of Interferon Regulated Genes in Multiple Tissues Is Associated with Primary Sjögren's Syndrome

Juliana Imgenberg-Kreuz[1], Johanna K Sandling[1,2], Jonas Carlsson Almlöf[1], Jessica Nordlund[1], Linnea Signér[2], Katrine B

Norheim[3], Roald Omdal[3], Majia-Leena Eloranta[2], Lars Rönnblom[2], Ann-Christine Syvänen[1] and Gunnel Nordmark[2], [1]Molecular Medicine and Science for Life Laboratory, Department of Medical Sciences, Uppsala University, Uppsala, Sweden, [2]Rheumatology and Science for Life Laboratory, Department of Medical Sciences, Uppsala University, Uppsala, Sweden, [3]Clinical Immunology Unit, Department of Internal Medicine, Stavanger University Hospital, Stavanger, Norway
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Background/Purpose:

Epigenetic modifications have emerged as important contributing factors in the pathogenesis of autoimmune diseases, including primary Sjögren's syndrome (pSS), and may act as a link between the environment and the genome. The aim of this study was to investigate DNA methylation in multiple tissues and its functional implications for pSS susceptibility.

Methods:

DNA prepared from whole blood samples (patients n=100, controls n=400), positively selected CD19+ B cells (patients n=24, controls n=47) and minor salivary gland biopsies (patients n=15, controls n=13) was analysed on the Illumina HumanMethylation 450k array, covering 485,000 CpG sites across the genome. Age and sex were included as covariates in the association model and a p-value of $<1x10^{-7}$ was considered significant (Bonferroni correction). Genomic coordinates of differentially methylated sites were tested for overlap with histone marks in publicly available data from reference B and T cells, and the association of genetic variants in known pSS risk loci with DNA methylation was investigated. In addition, gene expression was analysed by RNA-sequencing in CD19+ B cells from 16 patients and 24 controls.

Results:

We identified prominent hypomethylation in type I interferon regulated genes in whole blood, CD19+ B cells and minor salivary gland biopsies in patients with pSS. Enrichment for genomic overlap of these differentially methylated sites with histone marks of enhancer and promoter regions was observed. Analysis in whole blood from the controls showed that genetic variants located in or close to the pSS risk loci *DDX6-CXCR5*, *FAM167A-BLK*, *IL12A*, *IRF5-TNPO3*, *STAT4*, *TNIP1,* and within the HLA-region were associated with methylation levels at proximal CpG sites. In CD19+ B cells a correlation between hypomethylation and increased gene expression levels was identified for several interferon regulated genes with prominent hypomethylated sites overlapping enhancer regions, these genes included *MX1*, *IFI44L, IFITM1* and *RSAD2*.

Conclusion:

Our results further emphasize the role of DNA methylation in the pathogenesis of pSS. The importance of genes in the interferon system is highlighted, and the correlation with altered gene expression suggests a potential functional mechanism for differentially methylated CpG sites in pSS.

Abstract Number: 2101

HLA Associations in Mothers of Children with Cardiac Manifestations of Neonatal Lupus

Hannah C. Ainsworth[1], Carl D. Langefeld[1], Miranda C. Marion[2], Nathalie Costedoat-Chalumeau[3], Antonio Brucato[4], Jill P.

Buyon[5] and Robert M. Clancy[5], [1]Biostatistical Sciences, Wake Forest School of Medicine, Winston-Salem, NC, [2]Biostatistical Sciences and Center for Public Health Genomics, Wake Forest University Health Sciences, Winston-Salem, NC, [3]Internal Medicine Department, Cochin Hospital, "René-Descartes Paris V" University, Paris, France, [4]Internal Medicine, Hospital Papa Giovanni XXIII, Bergamo, Italy, [5]Medicine, Division of Rheumatology, New York University School of Medicine, New York, NY

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Background/Purpose: Cardiac manifestations of neonatal lupus, comprising atrioventricular conduction defects and cardiomyopathy, occur in fetuses exposed to anti-Ro/SSA antibodies, and carry substantial mortality. There is strong evidence of a genetic contribution to the risk (sibling recurrence risk ratio is ~3,000). Previously, in a case-control genome-wide association study, we reported that the 17 strongest associations were within the Human Leukocyte Antigen (HLA) region. Meisgen (2013) further underscored the potential importance of the HLA region when they observed two-digit classic HLA associations using family-based tests. Here, we report the first large-scale investigation of four-digit classic HLA associations in mothers with cardiac neonatal lupus (CNL) diagnosed children.

Methods: Parent-CNL-affected-offspring (n = 182) trios of European ancestry were genotyped using the Illumina Immunochip single nucleotide polymorphism (SNP) array and merged with 1073 non-lupus out-of-study controls (635 female). Admixture estimates were computed using ADMIXTURE. Classic four-digit HLA alleles in HLA-*A, -B, -C, -DPB1, -DQA1, -DQB1, and –DRB1* were imputed using high-quality SNPs and the software HIBAG. Analyses were computed on HLA alleles with a best guess allele count of at least 10 in cases or controls. Association analyses of CNL mothers vs non-lupus female controls were computed using logistic regression, adjusting for admixture. Transmission/disequilibrium tests (TDT) were computed using best guess HLA alleles to test for differential transmission to affected offspring.

Results: A total of 119 unique HLA alleles met quality control and allele frequency standards. Six HLA alleles met genome-wide significance: A*01:01(3.10, 1.47×10^{-12}), B*08:01(7.40, 2.56×10^{-24}), C*07:01(4.28, 1.27×10^{-17}), DQA1*05:01(8.22, 8.80×10^{-26}), DQB1*02:01(8.47, 6.03×10^{-26}), and DRB1*03:01(8.91, 1.03×10^{-26}) and four additional alleles met an HLA bonferoni threshold of 0.05/119=0.00042: DQA1*01:01(0.15,1.35×10^{-5}), DQA1*03:01(0.15, 1.00×10^{-4}), DQB1*05:01(0.21, 1.41×10^{-5}), and DRB1*01:01(0.11, 9.61×10^{-5}). To consider the joint effects across HLA genes, stepwise modeling was computed (Table).

	Allele Frequency		Single-allele	Stepwise	
HLA-allele	**Cases**	**Controls**	**P-value**	**OR (94% CI)**	**P-value**
B*08:01	0.382	0.121	2.56E-24	2.50 (1.41-4.45)	1.84E-03
DQB1*04:02	0.037	0.022	1.65E-01	6.32 (2.49-16.00)	1.02E-04
DQB1*06:02	0.189	0.132	3.60E-03	4.00 (2.57-6.23)	8.71E-10
DRB1*03:01	0.408	0.121	1.03E-26	7.98 (4.26-14.96)	8.94E-11
DRB1*11:01	0.061	0.046	2.42E-01	5.01 (2.17-11.60)	1.66E-04

None of the HLA alleles in the multilocus model exhibited differential transmission to offspring via a TDT ($p>0.15$). In addition, none of the 119 HLA alleles showed statistically significant evidence of differential transmission to the offspring after adjusting for multiple comparisons.

Conclusion: These analyses demonstrate the importance of the HLA region in mothers of CNL children. However, the four-digit classic HLA allele associations found in the mothers of CNL children were not differentially transmitted to the offspring. These results suggest that the maternal HLA profile contributes to an environment (e.g., anti-Ro antibodies) that increases the risk for CNL.

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Abstract Number: 2102

Higher Persistence and Adherence with Combination Therapy with Tumor Necrosis Factor Inhibitor+Methotrexate Combination Versus Triple Therapy in US Veterans with Rheumatoid Arthritis

Brian Sauer[1], Chia-Chen Teng[2], Jianwei Leng[3], Ted R. Mikuls[4], Jeffrey R. Curtis[5], Bradley S. Stolshek[6], Derek Tang[6] and Grant W. Cannon[7], [1]IDEAS Center and Division of Epidemiology, HSR&D SLC VA Medical Center and University of Utah, Salt Lake City, UT, [2]HSR&D SLC VA Medical Center and University of Utah, Salt Lake City, UT, [3]Internal Medicine Division of Epidemiology, HSR&D SLC VA Medical Center and University of Utah, Salt Lake City, UT, [4]University of Nebraska Medical Center, Omaha, NE, [5]University of Alabama at Birmingham, Birmingham, AL, [6]Amgen, Inc., Thousand Oaks, CA, [7]Division of Rheumatology, Salt Lake City VA Medical Center and University of Utah, Salt Lake City, UT

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Background/Purpose: Randomized controlled trials in RA have reported efficacy with both triple therapy (methotrexate [MTX] + hydroxychloroquine [HCQ] + sulfasalazine [SSZ]) and tumor necrosis factor inhibitor and MTX (TNFi-MTX) combinations. However, observational studies of clinical practice have been inconsistent when comparing persistence and adherence of these combinations. This analysis compared adjusted one-year persistence and adherence between triple and TNFi combination therapy in a real-world setting of US Veterans.

Methods: US veterans with RA initiating triple and TNFi combination therapy between Jan 1, 2006 and Dec 31, 2012 after 6-months of VA enrollment without prior triple or TNFi combination therapy were evaluated for 12-months. The index date the date that the last drug (index drug) of triple or TNFi combination was prescribed. To assure that the start of the index drug was intended as part of combination therapy, we required that all other drugs in the triple or TNFi combination have sequential dispensing within 90-days after initiation of index drug. A sensitivity analysis employed three different termination definitions of combination therapy: 1) Any drug in the combination drugs discontinued (i.e., gap $\geq$ 90 days); 2) New DMARD started, treatment reduced to monotherapy with non-biologic DMARD, or all DMARDs discontinued; 3) Same as #2 but switching within class (TNFi or other DMARDs) was allowed. To compare adherence, the Proportion of Days Covered (PDC)>80% was determined for each drug and the drugs in combination over the12 months. Propensity score matched weights were used to balance covariates when comparing risk ratios for each outcome among triple and combination therapy.

Results: A total of 3,204 TNFi-MTX and 1,160 triple therapy patients met the eligibility criteria (mean [SD] age at index 61 [11] vs. 62 [10], 16.0% vs. 9.0% female). After 12 months, persistence in the TNFi-MTX arm was significantly greater by all three approaches in both crude and propensity score weighted models (table1); favoring TNFi combination treatment. Twelve-month adherence to TNFi-MTX was approximately 41% higher than adherence to triple therapy [24% vs. 17%, RR: 1.41 (95%CI: 1.20,1.66)].

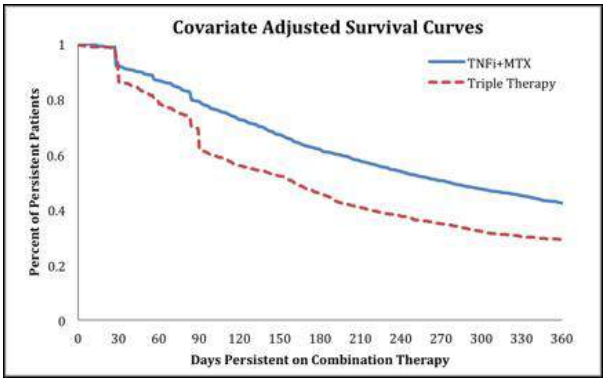

Table 1 Crude and Adjusted Estimates of Persistence

Outcomes	Crude Model				Matching Weights Adjusted Model			
	TNFi-MTX N=3,204	Triple Rx N=1,160	P Value	Relative Risk (95% CI)	TNFi-MTX	Triple Rx	P Value	Relative Risk (95% CI)
Definition 1	42.48%	29.22%	<0.001	1.45 (1.32-1.60)	42.31%	29.21%	<0.001	1.45 (1.29, 1.62)
Definition 2	55.09%	47.41%	<0.001	1.16 (1.09, 1.24)	53.67%	47.26%	0.0022	1.14 (1.05, 1.23)
Definition 3	60.46%	49.74%	<0.001	1.22 (1.14, 1.30)	59.16%	49.63%	<0.001	1.19 (1.10, 1.29)
Adherence Outcome	24.19%	17.33%	<0.001	1.4 (1.21, 1.61)	24.49%	17.34%	<0.001	1.41 (1.20, 1.66)

Conclusion: US Veterans initiating TNFi-MTX therapy consistently showed significantly greater persistence and adherence than those receiving triple therapy in clinical practice. Given differences between treatment strategies in terms of cost, tolerability, and patient preference, additional research focused on identifying factors that account for the observed differences in persistence and adherence will be important in informing RA management.

Disclosure: B. Sauer, Amgen, 2; **C. C. Teng**, Amgen, 2; **J. Leng**, Amgen, 2; **T. R. Mikuls**, Roche /Genetech, 2,Pfizer Inc, 5; **J. R. Curtis**, Roche, UCB Pharma, Janssen, CORRONA, Amgen, Pfizer, BMS, Crescendo,AbbVie, 2,Roche, UCB Pharma, Janssen, CORRONA, Amgen, Pfizer, BMS, Crescendo,AbbVie, 5; **B. S. Stolshek**, Amgen Inc., 3,Amgen Inc., 1; **D. Tang**, Amgen Inc., 3,Amgen Inc., 1; **G. W. Cannon**, Amgen, 2.

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Abstract Number: 2103

Temporal Trends in Drug Prescription, Utilization and Costs Among Rheumatoid Arthritis (RA) Patients Show Wide Regional Variation Despite Universal Drug Coverage

Mark Tatangelo[1], Michael Paterson[2], George A. Tomlinson[3], Nick Bansback[4], Jessica Widdifield[5], Tara Gomes[2] and Claire Bombardier[6], [1]University of Toronto, Toronto, ON, Canada, [2]Institute of Clinical Evaluative Sciences, Toronto, ON, Canada, [3]Medicine, Mount Sinai Hospital, Toronto, ON, Canada, [4]Centre for Health Evaluation and Outcome Sciences, Vancouver, BC, Canada, [5]University Health Network, Toronto, ON, Canada, [6]18 Strathearn Blvd, University of Toronto, Toronto, ON, Canada
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Background/Purpose: Monitoring of drug use and costs can: describe trends in expenditures over time, identify regional variations in access and indicate physicians' uptake of best-practice guidelines. Our aim was to describe drug use and costs of biologic (bDMARD) and conventional synthetic Disease Modifying Anti-Rheumatic drug (csDMARDs) in the context of single-payer universal drug coverage.

Methods: We performed a population-based analysis, identifying all RA patients (from 1995 to 2013) who were aged 65 years and older using a validated algorithm (1) (n=37,012). All patients received identical public drug coverage from a single public payer. Prescriptions were determined using the pharmacy claims database of the Ontario Drug Benefit Program. For each patient we recorded the annual number of prescriptions and costs for csDMARDs and bDMARDs and region of residence. Trends in annual drug use and costs were graphed by drug class and regional health authority.

Results: The total number of patients receiving RA medications tripled from 14,222 in 1995 to 37,012 in 2013. During that same time period csDMARD use and costs increased from $2.1M in 1995 to $8.5M in 2013(Fig 1.). When bDMARDs were introduced in 2001, 105 patients received bDMARDs (0.4%) increasing to 3226 patients (11%) in 2013. During that period the costs of bDMARDS increased from $0.78M to $54.6M (Fig 1.).

In 1995, per-patient drug costs in each regional health authority were an average of $500 per patient per year(Fig 2.). Since the introduction of bDMARDs in 2001, total cost and per-patient cost variation among regions has increased considerably, with drug expenditure in 2013 ranging from $1200 per patient per year to $2500 per patient per year(Fig 2.).

Conclusion: The number of patients with RA increased linearly over time from 1995 to 2013. The proportion of patients receiving csDMARDs grew at the same rate as the population of patients with RA. The introduction of bDMARDs was associated with an exponential rise of bDMARD use and cost over time driving the increase in total drug costs however the use of bDMARDs was lower than in the US where 27% of patients with a mean age of 70 received bDMARDs (2).

When analyzed by region, adoption of bDMARDs was associated with differential and widening variation in regional drug costs over time, indicating unequal use of bDMARD not explained by differences in reimbursement criteria. We hypothesize that regional access to rheumatology care and rheumatologist's varying propensity to prescribe bDMARDs are the primary drivers of inequitable utilization of bDMARDs.

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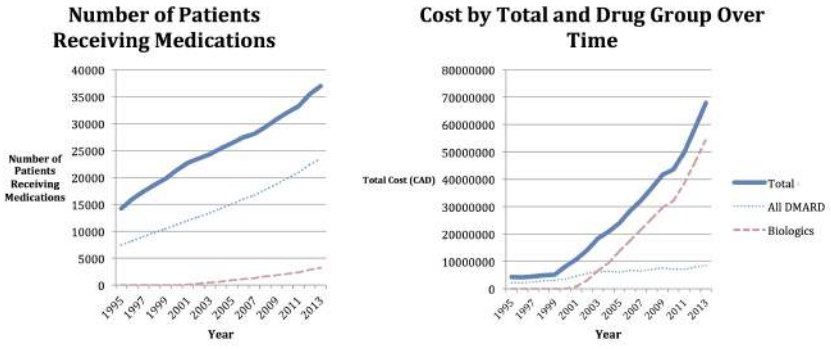

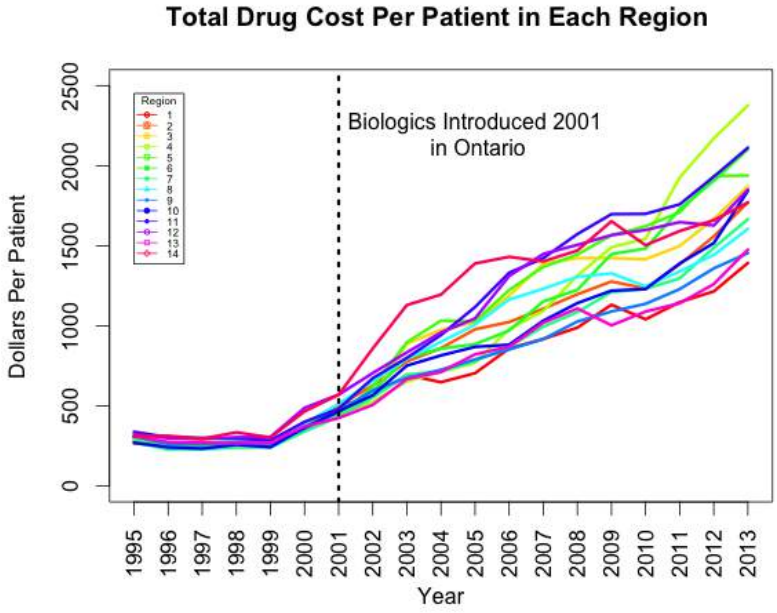

Disclosure: M. Tatangelo, None; **M. Paterson**, None; **G. A. Tomlinson**, None; **N. Bansback**, None; **J. Widdifield**, None; **T. Gomes**, None; **C. Bombardier**, None.

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Abstract Number: 2104

Influence on Treatment Decision Making of Providing Numerical Ranges of Side-Effect Risks

Nick Bansback[1,2], Mark Harrison[3], William G Dixon[4] and Paul Han[5], [1]Centre for Health Evaluation and Outcome Sciences, Vancouver, BC, Canada, [2]School of Population and Public Health, University of British Columbia, Vancouver, BC, Canada, [3]Centre for Health Evaluation and Outcomes Sciences, St Paul's Hospital, Vancouver, BC, Canada, [4]Manchester Academic Health Sciences Centre, Arthritis Research UK Centre for Epidemiology, The University of Manchester, Manchester, United Kingdom, [5]Center for Outcomes Research and Evaluation, Maine Medical Center, Portland, ME

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Background/Purpose: Doctors and patients make treatment decisions after weighing benefits and harms. For harms, while people prefer treatments with smaller risks, how they react to ambiguity—i.e., uncertainty arising from limitations in the reliability, credibility, or adequacy of risk information (often presented as a range of risks) – is less well understood. The objective of this study was to determine the relative importance of the magnitude of risk and ambiguity in the treatment decision-making context.

Methods: We invited members of an online panel to complete a survey which sought choices between two hypothetical rheumatoid arthritis treatments based on different levels of 4 attributes: probability of benefit (40%,55%,70%), probability (risk) of iatrogenic harm requiring treatment withdrawal (10%,20%,30%), ambiguity regarding risk of harm, expressed by risk estimate imprecision (none: point-estimate, low: range+/-5%, high: range+/-10%), and life expectancy (8,9,10 years). Each respondent

answered 10 pairwise Discrete Choice Experiment questions indicating strength of preference for each treatment, described using differing levels for each attribute as generated by a D-efficient experimental design. Conditional and mixed logit models were used to estimate coefficients for each attribute level and allow for estimation of marginal willingness to pay (WTP), in this case the duration of life they would be willing to give up to move between each of the attribute levels in the survey.

Results: Of 252 respondents, the mean age was 34 (range 20-67), 68% were male, and 52% had an education level of high school or less. Respondents placed greatest value on greater probability of benefit (WTP=1.34 years for 70% vs 40%, $p<0.001$), with lower but significant values for lower risk of harm (WTP=0.4 years for 10% vs 30%, $p<0.001$), and lower ambiguity (WTP=0.14 years, none vs high, $p<0.001$). Preliminary investigation of interactions suggested respondents were ambiguity-seeking when the risk of harm was low (10%), ambiguity-averse when the risk was high (30%), and ambiguity-neutral at the intermediate risk (20%). The degree of ambiguity aversion at high risk (30%) increased with the degree of imprecision in the risk estimate.

Conclusion: Current rheumatology patient information sources present harms of treatments by either providing point estimates (e.g. 3%, and ignore the ambiguity) or by providing ranges of risk estimates (e.g. 2-5%). This study suggests that providing ranges to communicate ambiguity make treatments more appealing when risks are small, but less appealing when risks are larger. While more research is needed to quantify differences in responses to ambiguity at other levels of risk, and for other outcomes, treatments, and disease states, this study highlights the implications of how risks are described, and the importance of developing strategies to communicate ambiguity in risk information.

Disclosure: N. Bansback, None; **M. Harrison**, None; **W. G. Dixon**, None; **P. Han**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/influence-on-treatment-decision-making-of-providing-numerical-ranges-of-side-effect-risks

Abstract Number: 2105

Drug Survival and Cost Effectiveness in Patients on Reduced Dose Anti-TNF: Results of a 4 Year Prospective Observational Study

John Stack[1], Claire-Louise Murphy[2], Clara Bannon[1], Eithne Murphy[1], Trevor Duffy[1] and Maurice Barry[1], [1]Rheumatology, Connolly Hospital Blanchardstown, Dublin, Ireland, [2]Rheumatology, Connolly Hospital Blanchardstow, Dublin, Ireland

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SESSION INFORMATION

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Session Time: 4:30PM-6:00PM

Background/Purpose:

Anti-TNF-α drugs are effective treatments for patients with inflammatory arthritis (IA). They are however expensive and their use carries a significant cost burden to the payer. Anti-TNF-α dose reduction in patients with stable disease in remission could lead to significant cost savings.

The aim of this prospective, non-blinded, non-randomised, observational study was to observe whether patients with IA (rheumatoid arthritis (RA), ankylosing spondylitis (AS) and psoriatic arthritis (PsA)) could successfully dose reduce anti-TNF-α over a 4 year period and to estimate the total cost savings associated with dose reduction.

Methods:

Anti-TNF-α dose reduction was offered to patients with IA who were in remission as defined by standardized disease activity indices (DAS-28 <2.6, BASDAI < 4). Patients on etanercept were reduced from 50mg weekly to 50mg fortnightly. Patients on adalimumab were reduced from 40mg fortnightly to 40mg monthly. Patients who agreed to dose reduction were invited to participate in the study which commenced in 2010. Patients were assessed for disease activity at 3, 6 , 12, 24, 36 and 48 months. Patients who remained in remission were encouraged to stay on the reduced dose anti-TNF-α. The primary end-point was the

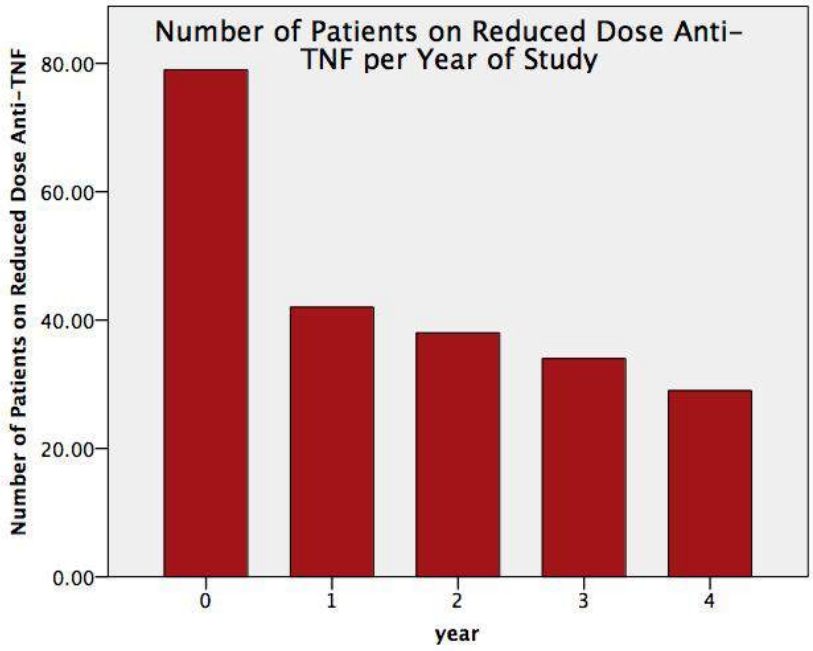
number of patients remaining on reduced dose anti-TNF-α at 4 years. Cost savings were estimated by deducting the actual total cost of anti-TNF-α used from the theoretical cost of using full dose anti-TNF-α had dose reduction not occurred.

Results:

79 patients with IA in remission were recruited. 57% had RA (n=45) ,13% PsA (n= 10) and 30% AS (n= 24). 57% (n=45) were on etanercept and 43% (n=34) were on adalimumab. The percentage of patients who remained on reduced dose anti-TNF-α at 4 years was 36% (n=29) (See figure 1). This resulted in net estimated savings to the exchequer of $1,373,761. The average cost saving per patient included in the study per year was $4346. A majority (53% n=37) of dose reduction failures occurred within the first year . Of the patients who successfully dose reduced at year 1 (n=42), a majority (69%, n=29) were able to maintain the dose reduction up to year 4. A greater percentage of AS patients (52 % n=12) were able to maintain dose reduction up to year 4 but this was not significant.

Conclusion:

Dose reduction of anti-TNF-α therapy in patients with IA in remission is feasible and can yield significant cost savings. Further studies could be designed to help define which patients are more likely to successfully dose reduce.



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Abstract Number: 2106

Intensification to Triple Therapy Non-Biologic Disease-Modifying Antirheumatic Drugs for Rheumatoid Arthritis in the United States from 2009 to 2014

Jeffrey A. Sparks[1], Alexis A. Krumme[2], Olga S. Matlin[3], Gregory Brill[2], William H. Shrank[3], Niteesh K. Choudhry[2] and Daniel H. Solomon[2,4], [1]Division of Rheumatology, Immunology, and Allergy, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, [2]Division of Pharmacoepidemiology and Pharmacoeconomics, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, [3]CVS Caremark, Woonsocket, RI, [4]Division of Rheumatology, Immunology and Allergy, Brigham and Women's Hospital, Harvard Medical School, Boston, MA

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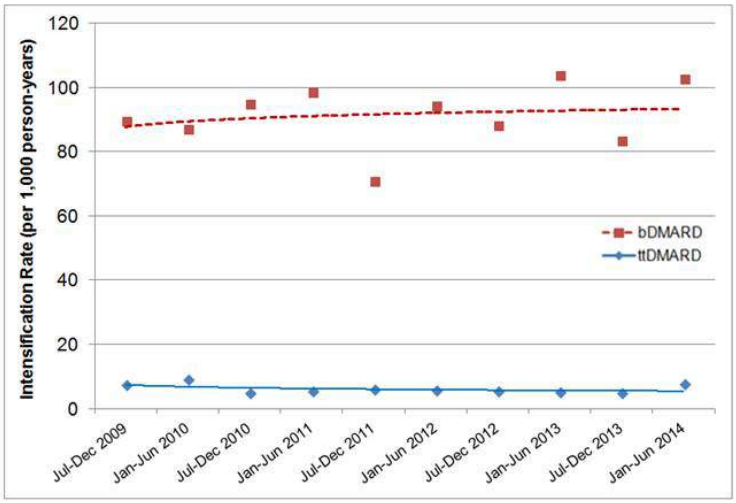
Background/Purpose: Several trials suggest that triple therapy with non-biologic disease-modifying antirheumatic drugs (ttDMARD) has similar efficacy compared to biologic DMARDs (bDMARD) for patients with RA. However, data on the use of ttDMARD in typical clinical practice and factors associated with intensification to ttDMARD have not been thoroughly examined. We evaluated progression to ttDMARD or bDMARD use after initial non-biologic DMARD (nbDMARD) prescription among patients with RA.

Methods: We used medical and prescription claims data from a large US commercial insurance program to evaluate ttDMARD use in RA between 1/1/2009 and 6/30/2014. Patients with a visit for RA and initial nbDMARD prescription were included after 180 days of continuous eligibility. ttDMARD use was defined as prescriptions for methotrexate, sulfasalazine, and hydroxychloroquine within 60 days. We calculated frequencies and rates for 6-month periods for the intensification to ttDMARD or bDMARD after initial nbDMARD prescription. We evaluated temporal, geographic, sociodemographic, clinical, and healthcare utilization factors as possible correlates of intensification to ttDMARD after initial nbDMARD using Cox regression models to estimate hazard ratios (HR), 95% confidence intervals (CI), adjusting for potential confounders.

Results: We analyzed 24,576 patients with initial nbDMARD prescription for RA during the study period. In this sample, 78% were female and mean age was 50.3 (SD 12.3) years. Methotrexate, sulfasalazine, or hydroxychloroquine were initially prescribed for 21,584 (88%) patients. During the entire 66-month study period, 2,739 (11.1%) intensified treatment to bDMARD compared to 181 (0.7%) who intensified to ttDMARD (see **Figure**). There was no increase in ttDMARD use over the study period. US geographic area was associated with intensification to ttDMARD: West (HR 1.82, 95% CI 1.14-2.88), South (HR 1.57, 95% CI 1.01-2.43), and Midwest (HR 1.78, 95% CI 0.99-3.20) compared to Northeast. Glucocorticoid use (HR 2.09, 95% CI 1.52-2.88) and nonsteroidal anti-inflammatory drug (NSAID) use (HR 1.62, 95% CI 1.19-2.21) prior to cohort entry date were significantly associated with subsequent ttDMARD intensification. Age, sex, year of entry into the cohort, median residence income, comorbidities, history of serious infection, rheumatologist appointment, and healthcare utilization factors were not associated with intensification to ttDMARD after initial nbDMARD prescription.

Conclusion: Despite reports during our study period suggesting equivalent efficacy of ttDMARD and bDMARD for RA, the use of ttDMARD after initial nbDMARD was infrequent and did not increase over time in this large nationwide study. Only 0.7% of RA patients were prescribed ttDMARD, despite 88% initially being prescribed methotrexate, sulfasalazine, or hydroxychloroquine. Further research investigating the use of ttDMARD for RA is warranted.

Figure. Intensification to triple therapy non-biologic DMARD or biologic DMARD use after initial non-biologic DMARD prescription for rheumatoid arthritis in a large US insurance claims database, 2009-2014.



Disclosure: J. A. Sparks, None; **A. A. Krumme**, None; **O. S. Matlin**, CVS Health, 1,CVS Health, 3; **G. Brill**, None; **W. H. Shrank**, CVS Caremark, 3; **N. K. Choudhry**, CVS Caremark, 2; **D. H. Solomon**, Amgen, Pfizer, Eli Lilly, the Consortium of Rheumatology Researchers of North America, 2,UpToDate, 7.

Abstract Number: 2107

Initiation of Combination Triple Therapy in Real World Clinical Practice Rarely Replicates the Protocols Used in Randomized Controlled Trials.

Grant W. Cannon[1], Chia-Chen Teng[2], Ted R. Mikuls[3], Jeffrey R. Curtis[4], Derek Tang[5], Bradley S. Stolshek[5] and Brian Sauer[6], [1]Division of Rheumatology, Salt Lake City VA Medical Center and University of Utah, Salt Lake City, UT, [2]HSR&D SLC VA Medical Center and University of Utah, Salt Lake City, UT, [3]Veteran Affairs Nebraska-Western Iowa Health Care System and University of Nebraska Medical Center, Omaha, NE, [4]University of Alabama at Birmingham, Birmingham, AL, [5]Amgen, Inc., Thousand Oaks, CA, [6]Salt Lake City VA Medical Center and University of Utah, Salt Lake City, UT

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Background/Purpose: Combination therapy with methotrexate (MTX), sulfasalazine (SUL), and hydroxychloroquine (HCQ) [triple therapy] is an effective treatment for rheumatoid arthritis (RA). Randomized controlled trials (RCTs) evaluating triple therapy have concomitantly added either SUL+HCQ to MTX or started all three drugs concurrently. Nevertheless, the frequency that providers actually initiate triple therapy in this manner is unknown. Understanding provider practices with the initiation of triple drug therapy is important as these practices might impact treatment effectiveness.

Objectives: To explore patterns of initiation of MTX, SUL and HCQ employed in patients who received triple therapy in real-world settings.

Methods: Using national Veterans Affairs (VA) databases, RA patients receiving triple therapy at any time between January 1, 2006 and December 31, 2012 were identified. Triple therapy was defined by evidence of any overlapping prescription of all three drugs within a 90-day period. Drug prescribing was considered concurrent (e.g. SUL+HCQ) if the initial prescriptions for the agents occurred within 30 days of each other, with subsequent prescription refills demonstrating intent to continue to prescribe all agents simultaneously. DMARD use in the six months prior to initiation of triple therapy was described herein to better understand treatment patterns leading to triple therapy.

Results: Triple therapy was prescribed in 1,160 patients. This cohort had a mean age of 62, was 91% male, 65% positive for RF and 59% positive for anti-CCP antibodies. Only 59 (5%) patients initiated all 3 drugs simultaneously; 171 (14%) had SUL and HCQ added concurrently to MTX (Table). There were 657 (57%) patients who were on MTX either alone or in combination with SUL or HCQ as a foundation to which other agent(s) were added. There were 666 (57%) patients who received drugs in a step-up fashion where the 3 drugs were added sequentially over time with more than 30 days between initiating each drug. In 38 (3%) patients, 2 drugs were added to either background HCQ or SUL. Triple therapy was started in 229 (19%) patients who were initially started on dual therapy then later escalated to triple therapy.

Sequence of drug therapy initiation (n=1,160)				
First drug(s)	Second drug(s)	Third drug	Number	Percent
Triple Drug Initiation Concordant with RCT Protocols (n=230 – 20%)				
HCQ+MTX+SUL			59	5.1%
MTX	SUL+HCQ		171	14.7%
Triple Drug Initiation Discordant with RCT Protocols (n=930 – 80%)				
MTX	HCQ	SUL	224	19.3%
MTX	SUL	HCQ	102	8.8%
MTX+HCQ	SUL		134	11.6%
MTX+SUL	HCQ		26	2.2%
HCQ+SUL	MTX		66	5.7%
HCQ	MTX	SUL	171	14.7%
HCQ	SUL	MTX	72	6.2%
HCQ	MTX+SUL		19	1.6%
SUL	MTX+HCQ		19	1.6%
SUL	MTX	HCQ	47	4.1%
SUL	HCQ	MTX	50	4.3%
TOTAL			1,160	

Conclusion: The spectrum of utilization patterns involved in initiation of individual drugs that comprise triple therapy is much wider in clinical practice than in RCTs. In contrast to initiation strategies evaluated in RCTs, only 20% of US Veterans initiating triple therapy either initiated all agents simultaneously or stepped up from MTX by concomitantly adding SUL/HCQ together. Rather, the additional drugs were commonly added in sequence rather than concurrently. Since clinical response and patient experience during sequential DMARD initiation may affect decisions to progress to triple therapy, RCT results describing the benefits of triple therapy may not generalize to clinical practice.

Disclosure: G. W. Cannon, Amgen, 2; **C. C. Teng**, Amgen, 2; **T. R. Mikuls**, Pfizer Inc, 5,Roche/Genetech, 2; **J. R. Curtis**, Roche, Genentech, UCB Pharma, Janssen, CORRONA, Amgen, Pfizer, BMS, Crescendo, AbbVie, 2,Roche, Genentech, UCB Pharma, Janssen, CORRONA, Amgen, Pfizer, BMS, Crescendo, AbbVie, 5; **D. Tang**, Amgen Inc., 3,Amgen Inc., 1; **B. S. Stolshek**, Amgen Inc., 3,Amgen Inc., 1; **B. Sauer**, Amgen, 2,Pfizer Inc, 5.

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Abstract Number: 2108

A Pragmatic Cluster-Randomized Controlled Trial of an Automated, Pharmacy-Based Intervention to Optimize Allopurinol Therapy in Gout

Ted R. Mikuls[1], T C Cheetham[2], Nazia Rashid[2], Gerald D. Levy[3], Artak Kerimian[4], KJ Low[2], Brian Coburn[5], David T. Redden[6], S. Louis Bridges Jr.[7], Kenneth G. Saag[6] and Jeffrey R. Curtis[7], [1]Medicine, University of Nebraska Medical Center, Omaha, NE, [2]Pharmacy Analytical Services, Kaiser Permanente Southern California, Downey, CA, [3]Rheumatology, Kaiser Permanente Southern California, Downey, CA, [4]Ambulatory Care Pharmacy, Kaiser Permanente Southern California, Downey, CA, [5]Internal Medicine - Rheumatology, University of Nebraska Medical Center, Omaha, NE, [6]University of Alabama at Birmingham, Birmingham, AL, [7]Clinical Immunology and Rheumatology, University of Alabama at Birmingham, Birmingham, AL
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Background/Purpose: Gout is a common form of inflammatory arthritis, often treated with allopurinol as a first-line urate lowering therapy. We have designed a large cluster-randomized study to examine the impact of a pharmacist-driven intervention as a means of optimizing allopurinol administration in gout. With enrollment and follow-up ongoing, completed efforts have focused on the development and implementation of the intervention and an interim assessment of its impact on allopurinol dose escalation and serum urate (sUA) testing.

Methods: An expert panel defined allopurinol treatment algorithms relevant for gout patients initiating therapy. The panel considered several allopurinol treatment decisions using the RAND/UCLA Appropriateness Method. Endorsed decisions were incorporated into an algorithm with pharmacist-led interventions that includes patient outreach designed around gradual allopurinol dose escalation with the goal of achieving and maintaining a sUA < 6.0 mg/dl. Ambulatory pharmacists conduct outreach primarily via telephone interactive voice recognition (IVR) system to assess adherence, facilitate sUA testing, provide education, and to adjust allopurinol dosing. Medical offices in the Kaiser Permanente Southern California health system were cluster randomized by geographic proximity (n = 103 clusters) to deliver either the pharmacist led intervention or usual care to patients receiving new allopurinol prescriptions. All participants received an introductory letter that included a gout information booklet and an opt-out option. The algorithm served as a guideline and the pharmacist was allowed to deviate from the guideline based on clinical circumstances.

Results: Two allopurinol treatment algorithms were developed, one for patients with CKD stage I/II and one for patients with CKD stage III/IV (stage V excluded); both incorporated a treat-to-target strategy of dose titration to achieve sUA ≤ 6.0 mg/dl. To date, 441 patients have enrolled in the intervention with 810 participants receiving usual care; 71 patients have opted out. Characteristics of gout patients enrolled between July 2014 and May 2015 are shown in addition to the number of allopurinol prescriptions dispensed, frequency of dose change, and sUA testing.

Conclusion: To address the typically suboptimal titration of allopurinol, we are conducting a large pragmatic cluster-randomized trial to examine a highly automated, exportable, pharmacist-driven intervention to optimize allopurinol treatment in gout. Deploying a treatment algorithm developed with expert input, approximately 1 of every 4 intervention patients has received allopurinol dose escalation, more than twice that observed in usual care. Novel elements of this intervention and its unique study design features will inform future gout care.

	INTERVENTION (N=441)	**CONTROL (N=810)**
Demographics		
Age, years, mean (SD)	58.3 (14.4)	57.9 (14.2)
Men, n (%)	357 (80.9%)	666 (82.2%)
Race / ethnicity, n (%)		
Caucasian	143 (32.4%)	243 (30.0%)
Other	298 (67.6%)	567 (70.0%)
Number of allopurinol prescriptions dispensed*		
One	48.1%	62.3%
Two	23.4%	21.1%
Three	19.3%	11.2%
Four or more	9.3%	5.3%
Allopurinol dose changes during observation		
Dose increased	26.5%	12.9%
Dose decreased	0.9%	0.3%
No dose change	72.6%	86.7%
Serum urate (SU) measurements		
Baseline SU measured	78.1%	78.2%
Follow-up SU measured	78.2%	43.8%

*Primarily dispensed as 100-day prescriptions

Disclosure: T. R. Mikuls, None; **T. C. Cheetham**, None; **N. Rashid**, None; **G. D. Levy**, None; **A. Kerimian**, None; **K. Low**, None; **B. Coburn**, None; **D. T. Redden**, None; **S. L. Bridges Jr.**, None; **K. G. Saag**, None; **J. R. Curtis**, Roche/Genentech, UCB, Janssen, CORRONA, Amgen, Pfizer, BMS, Crescendo, AbbVie, 2,Roche/Genentech, UCB, Janssen, CORRONA, Amgen, Pfizer, BMS, Crescendo, AbbVie, 5.

Abstract Number: 2109

Racial Disparities in the Risk of Hospitalized Severe Allopurinol Hypersensitivity Syndrome – a US Nationwide Study (2009-2011)

Na Lu[1], Sharan K. Rai[2], Jeewoong Choi[3] and Hyon K. Choi[1], [1]Rheumatology, Allergy and Immunology, Massachusetts General Hospital, Harvard Medical School, Boston, MA, [2]Experimental Medicine, University of British Columbia, Vancouver, BC, Canada, [3]Massachusetts College of Pharmacy and Health Sciences, Boston, MA

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Background/Purpose: Allopurinol is the leading choice of urate-lowering therapy for gout (>95% of treated cases); however, it is associated with the rare but potentially fatal allopurinol hypersensitivity syndrome (AHS) (i.e., Steven Johnson Syndrome [SJS] and Toxic Epidermal Necrolysis [TEN]). Beyond renal dosing to help reduce the risk of AHS, the recently discovered strong associations between HLA-B*5801 allele carriage and AHS led to the 2012 ACR recommendation to screen for this marker among high-risk Asians, but not Whites, given the higher allele frequency in Asians. This leaves several open questions: 1) are Asians at a higher risk of developing AHS than Whites, given the allele differences, and 2) what about other races? This obvious information can be immediately useful in clinical care and policy decisions. We examined this potential racial difference in the risk of hospitalized SJS and TEN using a nationwide inpatient dataset.

Methods: We used the National Inpatient Sample (NIS), a database representative of hospitalizations in the US from 2009-2011, where severe AHS (caused by uric acid metabolism drugs) patients were identified by a primary discharge diagnosis ICD-9-CM code for SJS (695.13) and TEN (695.14-15), followed by a secondary discharge diagnosis of an adverse effect caused by uric acid metabolism drugs in therapeutic use (E9447) or gout (274.x). In the context, severe AHS occurs almost exclusively related to allopurinol. We calculated race-specific hospitalization rate ratios for AHS using Whites as the reference; in-hospital mortality and length of stay were also compared. Analyses were performed using NIS sampling weights to obtain US national estimates.

Results: During 2009-2011 in the US, there were 608 patients admitted with SJS or TEN meeting our criteria. The mean age was 69 years and 47% were men. Of the 608, there was a substantial over-representation of Asians (23%) and Blacks (28%) as compared to Whites (32%) and Hispanics (5%), given their background population rates from the US census (5%, 13%, 78%, and 16%, respectively). The hospitalization rate ratios for AHS among Asians, Blacks, Hispanics, and Whites were 11.4, 5.2, 0.8, and 1.0 (referent). These ratios agreed with their *HLA-B*5801* frequencies in the US population (7.4%, 4%, 1%, and 1%, respectively). In-hospital mortality of the 608 was 13%. The mortality rate as well as the mean length of stay were higher among Asians than other races ($p=0.001$ and <0.001, respectively).

Conclusion: Our findings based on these nationally representative inpatient data indicate that race is a strong determinant of severe AHS risk: Asians (11x) > Blacks (5x) > Hispanics (1x) = Whites (1). Mortality and length of stay were worse among Asians. These data call for extra caution among Asians (and perhaps Blacks) when considering allopurinol, and support the ACR recommendation to screen for *HLA-B*5801* for high-risk Asians.

Table. Risk Estimates of Hospitalized Severe Allopurinol Hypersensitivity Syndrome by Race in the US (2009-2011)

	Age, Year (Mean ± SE)	Hospitalization Weighted N (%)	Hospitalization Rate per 100,000 persons	Hospitalization Rate Ratio	In-Hospital Death Weighted N (%)	Mean Length of Stay (SE)
RACE						
White	71 ± 2	197 (32)	0.027	1.00 (ref)	33 (17)	12.2 ± 2.1
Black	67 ± 2	171 (28)	0.141	5.2 (4.2 to 6.4)	*	9.4 ± 1.8
Hispanic	72 ± 2	31 (5)	0.020	0.8 (0.5 to 1.1)	*	6.2 ± 1.6
Asian	71 ± 2	143 (23)	0.310	11.4 (9.2 to 14.2)	29 (21)	18.5 ± 3.8
Other/Missing	65 ± 2	66 (11)	-	-	-	-
All	69 ± 1	608 (100)	0.066	-	76 (13)	12.7 ± 1.3

*Sample size smaller than the recommended to provide a nationally representative, robust estimate; - Not Applicable.

Abstract Number: 2110

Imaging and Safety Assessments Following Treatment with Febuxostat and Placebo for 2 Years in Subjects with Early Gout

Nicola Dalbeth[1], Kenneth G. Saag[2], William Palmer[3], Hyon Choi[3], Barbara Hunt[4], Patricia MacDonald[4], Ulrich Thienel[4] and Lhanoo Gunawardhana[4], [1]Department of Medicine, University of Auckland, Auckland, New Zealand, [2]Div Clinical Immun & Rheum, University of Alabama at Birmingham, Birmingham, AL, [3]Massachusetts General Hospital/Harvard Medical School, Boston, MA, [4]Takeda Pharmaceuticals International, Deerfield, IL

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Background/Purpose: No clinical trials had previously investigated the characteristics of joint damage in early gout or the benefit of instituting urate-lowering therapy (ULT) earlier in the course of the disease. The objectives of this study were to evaluate 1) the effect of febuxostat vs. placebo on joint damage after 2 years of treatment in subjects with early gout and 2) the safety of febuxostat.

Methods: Subjects with serum urate [sUA] ≥7.0 mg/dL received either febuxostat 40/80 mg or placebo for up to 2 years. Febuxostat was up titrated from 40 to 80 mg at the Month 1 visit if sUA ≥6.0 mg/dL at the Day 14 visit. Early gout was defined as having experienced ≤2 gout flares total, and only 1 flare during the previous 12 months. Joint damage was evaluated utilizing x-ray and magnetic resonance imaging (MRI). X-rays were assessed using a modified Sharp-van der Heijde (mSvdH) method validated in gout patients. MRI images were assessed using the rheumatoid arthritis MRI scoring (RAMRIS) system. For both X-ray and MRI assessments, the joint with the first gout flare was identified as the primary affected joint. Contrast-enhanced MRI images were used for scoring of synovitis. Safety assessments included adverse events (AEs), serious AEs and clinical laboratory measures.

Results: At baseline, mSvdH erosion score >0 in the primary affected joint was present in 9% of the placebo group and 14% of the febuxostat group. After 2 years of treatment, the placebo and febuxostat groups showed no differences in the changes from baseline in mSvdH erosion scores from the primary affected joint or from full hand and foot radiographs. At baseline, RAMRIS synovitis score >0 in the primary affected joint was present in 89% of the placebo group and 94% of the febuxostat group. There was a significant reduction in the RAMRIS synovitis score for the primary affected joint in the febuxostat group compared to the placebo group after 1 ($p=0.025$) and 2 ($p<0.001$) years of treatment. The RAMRIS erosion and bone edema scores showed no differences for the primary affected joint comparing febuxostat and placebo groups. The percentage of subjects with sUA levels <6.0 mg/dL was 62.8% and 5.7% after 2 years of treatment with febuxostat and placebo, respectively.

The most frequent treatment emergent adverse events (TEAE) and adjudicated major adverse cardiovascular events (MACE) are

summarized in Table 1.

Conclusion: This first clinical trial in early gout subjects demonstrated that treatment with febuxostat can achieve a significant reduction in synovitis compared to placebo. No measurable change in the affected joint erosion score was observed with and without ULT during the observation period. Febuxostat was generally well tolerated in this population of early gout subjects.

Table 1. Treatment Emergent Adverse Events (TEAE) and Major Adverse Cardiovascular Events (MACE)

	Placebo (n, %)	Febuxostat (n, %)
Total randomized	157	157
Subjects with any TEAE	115 (73.2)	115 (73.2)
Subjects with ≥1 treatment related TEAE	20 (12.7)	29 (18.5)
Most frequently reported TEAE (≥5% of subjects)[a]		
Musculoskeletal and connective tissue pain and discomfort	25 (15.9)	21 (13.4)
Joint related signs and symptoms	11 (7.0)	15 (9.6)
Liver function analyses	15 (9.6)	21 (13.4)
Skeletal and cardiac muscle analyses	11 (7.0)	9 (5.7)
Dermatitis and eczema	4 (2.5)	8 (5.1)
Headaches	11 (7.0)	5 (3.2)
Diarrhea (non-infective)	6 (3.8)	9 (5.7)
Edema	5 (3.2)	9 (5.7)
Upper respiratory tract infection	21 (13.4)	27 (17.2)
Upper respiratory tract signs and symptoms	1 (<1)	8 (5.1)
Subjects with MACE		
Cardiovascular Death	1 (<1%)	1 (<1%)
Nonfatal myocardial infarction	0	1 (<1%)
Nonfatal stroke	0	0
Unstable angina with urgent coronary revascularization	1 (<1%)	1 (<1%)

[a]Reported with Medical Dictionary for Regulatory Activities high level term.

Disclosure: N. Dalbeth, Takeda, 2,Teijin, 2,Menarini, 2,Pfizer Inc, 8,Ardea, 2,AstraZeneca, 2,Fonterra, 8; **K. G. Saag**, Ardea, AstraZeneca, Creala, Takeda, 2,Ardea, AstraZeneca, Creala, Takeda, 5; **W. Palmer**, None; **H. Choi**, Takeda, 5,AstraZeneca, 9; **B. Hunt**, Takeda, 3; **P. MacDonald**, Takeda, 3; **U. Thienel**, Takeda, 3; **L. Gunawardhana**, Takeda, 3.

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Abstract Number: 2111

A Study to Evaluate the Efficacy and Safety of Arhalofenate for Preventing Flares and Reducing Serum Uric Acid in Gout Patients

Alexandra Steinberg[1], Harinder Chera[1], Yun-Jung Choi[1], Robert Martin[1], Charles McWherter[1], Yunbin Zhang[2], **Pol Boudes**[1] and on behalf of the Arhalofenate Anti-Flare Therapy Study Group, [1]Cymabay Therapeutics, Newark, CA, [2]INC Research, Raleigh, NC

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SESSION INFORMATION

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Background/Purpose: Arhalofenate is a novel Urate-Lowering Anti-Flare Therapy (ULAFT) to treat gout. It lowers serum uric acid (sUA) by blocking URAT1, a tubular UA transporter, and reduces gout flares by blocking the local release of IL-1β. The study primary objective was to evaluate the anti-flare activity of arhalofenate in gout patients in the absence of background colchicine treatment.

Methods: This was a randomized, double-blind, placebo- and active-controlled phase 2b (NCT02063997) at 54 centers. Male or female gout subjects with a sUA ≥ 7.5 mg/dL and ≤ 12 mg/dL were enrolled. Subjects experienced at least three flares during the previous year and could not have been using Urate Lowering Therapy (ULT) and colchicine two weeks before screening. Subjects were randomized 1:2:2:2:2 to placebo, arhalofenate 600 mg or 800 mg, allopurinol 300 mg or allopurinol 300 mg combined with colchicine 0.6 mg. Randomization was stratified on sUA levels and presence of tophi. Dosing was once daily, orally for 12 weeks. Flares were recorded with an electronic diary. During study, flares were treated with non-steroidal or steroidal anti-inflammatory.

Results:

A total of 239 subjects were randomized and dosed, and constitute the efficacy (mITT) and safety population. The primary outcome of efficacy comparing flare rates between the arhalofenate 800 mg to allopurinol 300 mg groups was met with a 46% improvement (p = .0056). Additional key outcomes are presented in the table:

		Placebo	Arhalofenate 600 mg	Arhalofenate 800 mg	Allopurinol 300 mg	Allopurinol 300mg + 0.6 mg COL
	N	28	53	51	54	53
Flare rate		1.13	1.04	0.66[a]	1.24	0.40
Mean % change in sUA from baseline to	Week 8	+1	-14	-20	-30	-24
	Week 12	-1	-12[b]	-16[c]	-29	-25
Discontinued for safety		1	1	1	3	5
Serious Adverse Events (SAEs)		0	0	1	3	1

[a] 46% reduction vs. allopurinol 300 mg (p = .0056) and 41% reduction vs. placebo (p= .049)

[b] p = .0021 vs.placebo

[c] p = .0059 vs. placebo

There were no SAEs related to arhalofenate. There was one SAE of a kidney stone in a patient on allopurinol 300 mg. There were no meaningful differences in the number of patients reporting Treatment Emergent AEs (TEAEs). The most frequent TEAEs were increases in creatine phosphokinase (4.6%), upper respiratory tract infections (3.8%), hypertension and headache (both 3.3%) with no relevant differences between groups. No subjects on arhalofenate who developed an abnormal serum creatinine value that was more than 1.5 times above pre-treatment values.

Conclusion:

Arhalofenate at 800 mg significantly decreases gout flares when compared to allopurinol 300 mg. There was no statistical difference in flares between arhalofenate 800 mg and allopurinol 300 mg combined with colchicine. Arhalofenate 800 mg also significantly decreased flares when compared to placebo. These results indicate that Arhalofenate has intrinsic anti-inflammatory activities clinically associated with improvement in gout flares.

Arhalofenate sUA lowering activity, while significant compared to placebo, was lower than in the allopurinol 300 mg groups.

Arhalofenate was well tolerated and appeared safe.

Arhalofenate is currently in development for the treatment of gout as a combination therapy with ULT, both to lower serum uric acid and prevent flares.

Disclosure: A. Steinberg, Cymabay Therapeutics, 3,Cymabay Therapeutics, 1; **H. Chera**, Cymabay Therapeutics, 3,Cymabay Therapeutics, 1; **Y. J. Choi**, Cymabay Therapeutics, 3,Cymabay Therapeutics, 1; **R. Martin**, Cymabay Therapeutics, 3,Cymabay Therapeutics, 1; **C. McWherter**, Cymabay Therapeutics, 3,Cymabay Therapeutics, 1; **Y. Zhang**, Cymabay Therapeutics, 9; **P. Boudes**, Cymabay Therapeutics, 3,Cymabay Therapeutics, 1.

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Abstract Number: 2112

Analysis of Gout Subjects Receiving Lesinurad and Allopurinol Combination Therapy By Baseline Renal Function

Kenneth G. Saag[1], Thomas Bardin[2], Alexander So[3,4], Puja Khanna[5], Chris Storgard[6], Scott Baumgartner[7], Maple Fung[7], Nihar Bhakta[7], Scott Adler[8], Jeff Kopicko[7] and Michael A. Becker[9], [1]University of Alabama at Birmingham, Birmingham, AL, [2]Lariboisière Hospital, Paris, France, [3]Rheumatology, Centre Hospitalier Universitaire Vaudois, University of Lausanne, Lausanne, Switzerland, [4]CHU Vaudois, University of Lausanne, Lausanne, Switzerland, [5]Division of Rheumatology/Dept. of Internal Medicine, University of Michigan Medical Center, Ann Arbor, MI, [6]4939 Directors Place, Ardea Biosciences, Inc., San Diego, CA, [7]Ardea Biosciences, Inc., San Diego, CA, [8]AstraZeneca Pharmaceuticals, Wilmington, DE, [9]University of Chicago, Chicago, IL

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Background/Purpose: Two randomized, double-blind, placebo-controlled Phase III clinical trials showed that lesinurad (200 or 400 mg) when added to allopurinol (200-900 mg) significantly increased the proportion of gout patients achieving the serum uric acid (sUA) target of <6.0 mg/dL by Month 6, representing an approximate 2-fold increase with lesinurad 200 mg compared with allopurinol alone. Lesinurad was generally well tolerated, particularly at the 200 mg dose, where the safety profile was comparable to allopurinol alone, with the exception of a higher incidence in predominately reversible serum creatinine (sCr) elevations. As renal impairment and gout frequently coexist, the objective of the current pooled analysis was to explore efficacy and safety endpoints in gout patients based on baseline renal function.

Methods: Patient data were combined from 2 Phase III clinical studies examining the efficacy and safety of lesinurad, a selective uric acid reabsorption inhibitor (SURI), in combination with standard of care allopurinol (200-900 mg) (CLEAR 1 [NCT01510158], CLEAR 2 [NCT01493531]). In current analyses, patients were analyzed by baseline renal function using estimated creatinine clearance (eCrCl; Cockcroft-Gault formula using ideal body weight): <60, <90, and ≥90 mL/min.

Results: In total, 1208 patients were included in the analyses. Demographic characteristics, including age, gender, race, weight, and BMI, were broadly similar between patient groups stratified by baseline renal function. Efficacy, assessed by the proportions of patients with sUA <6.0 mg/dL at 6 and 12 months, was consistently greater (P<0.05) for both lesinurad doses (200 mg and 400 mg) than placebo in all groups assessed by baseline renal function (Table). There were no consistent differences in TEAE rates in patients based on baseline renal function (Table). sCr elevations occurred at higher rates in the lesinurad groups (particularly the 400 mg dose) versus placebo, without evident differences when analyzed by baseline renal function.

Conclusion: These combined analyses from 2 Phase III studies indicate that lesinurad in combination with allopurinol provides consistent, significant efficacy across all renal function groups. Safety findings were consistent between treatment groups across

all renal function categories.

Table: Efficacy and safety endpoints in CLEAR 1 and CLEAR 2 combined: stratification by baseline eCrCl <60, <90, and ≥90 mL/min

Baseline eCrCl	<60 mL/min			<90 mL/min			≥90 mL/min		
	PBO +XOI (n=80)	LESU200 mg +XOI (n=74)	LESU400 mg +XOI (n=70)	PBO +XOI (n=256)	LESU200 mg +XOI (n=241)	LESU400 mg +XOI (n=238)	PBO +XOI (n=149)	LESU200 mg +XOI (n=163)	LESU400 mg +XOI (n=161)
Efficacy endpoints (n, % patients)									
Proportion with sUA <6.0 mg/dL at Month 6 (LOCF)	26/77 (33.8)	44/74 (59.5)	46/69 (66.7)	83/249 (33.3)	149/235 (63.4)	161/236 (68.2)	31/145 (21.4)	96/159 (60.4)	112/159 (70.4)
Proportion with sUA <6.0 mg/dL at Month 12 (LOCF)	26/77 (33.8)	39/74 (52.7)	37/69 (53.6)	81/249 (32.5)	138/235 (58.7)	149/236 (63.1)	39/145 (26.9)	95/15 (59.7)	100/159 (62.9)
Safety endpoints (n, % patients)									
Any TEAE	58/80 (72.5)	63/74 (85.1)	57/70 (81.4)	182/256 (71.1)	178/241 (73.9)	191/238 (80.3)	102/149 (68.5)	120/163 (73.6)	125/161 (77.6)
sCr elevation ≥1.5x	2/80 (2.5)	5/74 (6.8)	9/70 (12.9)	3/256 (1.2)	15/241 (6.2)	40/238 (16.8)	6/149 (4.0)	9/163 (5.5)	22/161 (13.7)
Unresolved*cases of sCr elevation ≥1.5x as of last study visit	1	1	2	1	2	4	2	0	1
sCr elevation ≥2.0x	0/80 (0)	0/74 (0)	3/70 (4.3)	0/256 (0)	1/241 (0.4)	18/238 (7.6)	0/149 (0)	5/163 (3.1)	10/161 (6.2)
Unresolved* cases of sCr elevation ≥2.0x as of last study visit	0	0	0	0	0	3	0	0	1

*sCr resolution: sCr value returned to ≤1.2x baseline. LESU, lesinurad; PBO, placebo; LOCF, last observation carried forward.

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Abstract Number: 2113

Lesinurad, a Novel Selective Uric Acid Reabsorption Inhibitor, in Combination with Febuxostat, in Patients with Tophaceous Gout

Nicola Dalbeth[1], Graeme Jones[2], Robert Terkeltaub[3], Dinesh Khanna[4], Jeff Kopicko[5], Nihar Bhakta[5], Maple Fung[5], Chris Storgard[6], Scott Baumgartner[5] and Fernando Perez-Ruiz[7], [1]Department of Medicine, University of Auckland, Auckland, New Zealand, [2]Musculoskeletal Unit, Menzies Institute for Medical Research, University of Tasmania, Hobart, Australia, [3]Medicine-Rheumatology, University of California, San Diego, La Jolla, CA, [4]Div of Rheumatology, University of Michigan, Ann Arbor, MI, [5]Ardea Biosciences, Inc., San Diego, CA, [6]4939 Directors Place, Ardea Biosciences, Inc., San Diego, CA, [7]Servicio de Reumatologia, Hospital Universitario Cruces, Baracaldo, Spain
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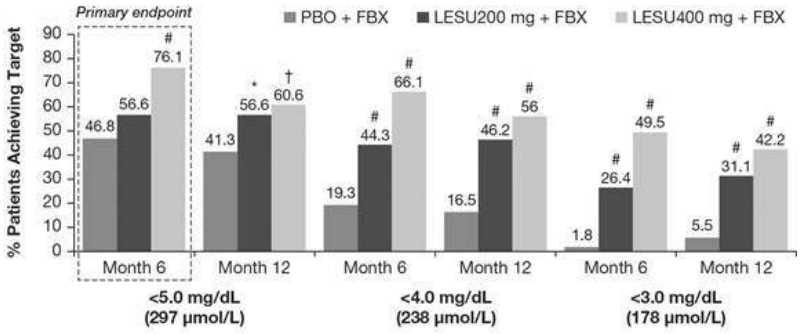
Background/Purpose: Lesinurad (LESU; RDEA594) is a selective uric acid reabsorption inhibitor (SURI) being investigated for the treatment of gout in combination with a xanthine oxidase inhibitor. The CRYSTAL study is a multinational, randomized, double-blind, placebo-controlled, Phase III clinical trial of LESU in combination with febuxostat (FBX) to determine efficacy and safety of combination therapy compared with FBX monotherapy in patients with tophaceous gout (NCT01510769).

Methods: Patients with gout, aged 18–85 yrs, with serum uric acid (sUA) ≥8 mg/dL (≥6 mg/dL on urate lowering therapy) and ≥1 tophus were given FBX 80 mg qd for 3 weeks before randomization to LESU (200 mg or 400 mg oral, qd) in combination with FBX or placebo (PBO) + FBX. Primary endpoint was proportion of patients with sUA <5.0 mg/dL by Month 6. Secondary endpoints included proportion of patients with complete resolution of ≥1 tophus and percent reduction in tophus area by Month 12. Safety assessments included adverse events and laboratory data.

Results: Patients (N=324) were white (79.9%) and male (95.4%) with mean±SD age of 54.1±11.0 yrs and 14.7±10.9 yrs since gout diagnosis. sUA was 8.7±1.6 mg/dL at screening and 5.3±1.6 mg/dL on FBX at randomization (28% with sUA ≥6 mg/dL). More patients achieved sUA levels <6, <5 (primary endpoint), <4, and <3 mg/dL with LESU+FBX (Figure). Percentage of patients with complete resolution of ≥1 tophus by Month 12 was 21.1%, 25.5%, and 30.3% for FBX+PBO, FBX+LESU200, and FBX+LESU400, respectively. Percent decrease in tophus area by Month 12 was 55.8% and 57.9% for FBX+LESU200 and FBX+LESU400, respectively, vs 31.3% for FBX + PBO (both nominal $P<0.05$). Safety data are reported in the Table. More serum creatinine (sCr) increases were observed with LESU+FBX; most resolved by last study visit (Table). Kidney stones were lower with LESU.

Conclusion: In patients with tophaceous gout, LESU (200 or 400 mg) in combination with FBX increased the proportion of patients achieving sUA <5 mg/dL at 6 months compared with FBX alone. LESU in combination with FBX resulted in greater tophus area resolution compared with FBX alone, as well as a dose-ordered numerical increase in the proportion of subjects having complete tophi resolution. LESU was generally well tolerated, except for higher incidence of predominately reversible sCr elevations. Combination therapy with LESU+FBX may represent a future treatment option for patients with tophaceous gout on FBX who warrant additional therapy.



Nonresponder imputation. *$P<0.05$; †$P<0.01$; ‡$P<0.0001$ vs PBO + FBX; no multiplicity adjustment.

	PBO + FBX N=109	LESU200 + FBX N=106	LESU400 + FBX N=109
Patients experiencing any TEAE	79 (72.5%)	87 (82.1%)	90 (82.6%)
Patients with serious TEAEs	10 (9.2%)	6 (5.7%)	9 (8.3%)
Patients with any renal-related AEs	6 (5.5%)	9 (8.5%)	11 (10.1%)
Patients with serious renal-related AEs	1 (0.9%)	0 (0%)	2 (1.8%)
Patients with kidney stones	4 (3.7%)	1 (0.9%)	2 (1.8%)
Patients with ≥2.0x increase in sCr	0 (0%)	3 (2.8%)	6 (5.5%)
Number (%) sCr elevations resolved by last study visit	–	2/3 (67%)	6/7 (86%)

Data are n (%).

Disclosure: **N. Dalbeth**, AstraZeneca, 2,Fonterra, 2,Novartis Pharmaceutical Corporation, 2,Savient, 8,Menarini, 8,Novartis Pharmaceutical Corporation, 8,Takeda, 8,AstraZeneca, 9,Fonterra, 9,Pfizer Inc, 9,Takeda, 9,Metabolex, 9; **G. Jones**, Abbvie, 2,Ardea BioSciences, 2,Novartis Pharmaceutical Corporation, 2,Auxilium, 2,Pfizer Inc, 9,Roche Pharmaceuticals, 9,Hospira, 9,Janssen Pharmaceutica Product, L.P., 9,UCB, 8,Roche Pharmaceuticals, 8,Janssen Pharmaceutica Product, L.P., 8,Abbvie, 8,Novartis Pharmaceutical Corporation, 8,Mundipharma, 8,Amgen, 8,Bristol-Myers Squibb, 8,Pfizer Inc, 8; **R. Terkeltaub**, ARDEA/AstraZeneca, Takeda, Revive, Relburn, UCB, 5; **D. Khanna**, AstraZeneca, 2,AstraZeneca, 5,Takeda, 5; **J. Kopicko**, Ardea Biosciences, 3; **N. Bhakta**, Ardea Biosciences, 3; **M. Fung**, Ardea Biosciences, 3; **C. Storgard**, Ardea Biosciences, 3; **S. Baumgartner**, Ardea Biosciences, 3; **F. Perez-Ruiz**, AstraZeneca, 8,Menarini, 5,AstraZeneca, 6,Menarini, 8,Cimabay, 6.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/lesinurad-a-novel-selective-uric-acid-reabsorption-inhibitor-in-combination-with-febuxostat-in-patients-with-tophaceous-gout

Abstract Number: 2114

Higher Total Knee Arthroplasty Revision Rates in Black Americans: A Systematic Literature Review and Meta-Analysis

Anne R. Bass[1], Kelly McHugh[1], Kara Fields[2,3], Rie Smethurst[4], Michael Parks[5] and Susan M. Goodman[1], [1]Rheumatology, Hospital for Special Surgery, New York, NY, [2]Medicine/Rheumatology, Hospital for Special Surgery, New York, NY, [3]Biostatistics, Hospital for Special Surgery, New York, NY, [4]Education - Academic Training, Hospital for Special Surgery, New York, NY, [5]Orthopedics, Hospital for Special Surgery, New York, NY

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Background/Purpose: Utilization of total knee arthroplasty (TKA) is lower among blacks than whites in the United States (U.S.), which may be due to blacks' perception of increased TKA risk. Approximately 4% of TKA require revision within five years. The purpose of this study was to determine whether U.S. blacks are at higher risk for TKA revision than U.S. whites.

Methods: A systematic review of English language articles, published during or after 2000, was performed on March 31, 2015 using Medline via PubMed, the Cochrane register and EMBASE. In addition, a hand search of unlisted journals that focus on

racial disparities was performed. Study inclusion criteria were (1) U.S. patient population, (2) TKA as the primary procedure; (3) follow up period at least 2 years; (4) reporting of revisions rates; (5) analysis of patient race as an independent predictor of revision. Two reviewers screened titles, abstracts and full text articles in a standardized manner. Meta-analysis was used to analyze the risk of revision TKA in blacks compared to whites.

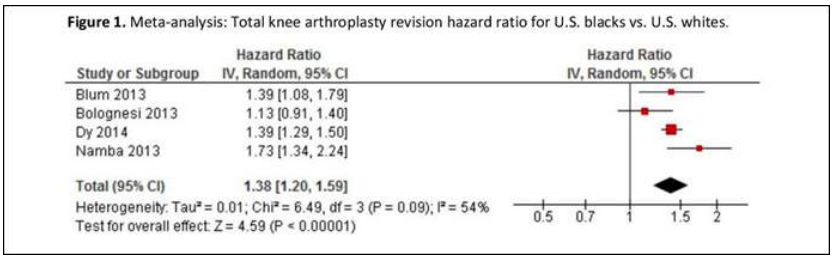
Results: 4286 studies were identified and screened by title, 106 by abstract and 24 by full text. Six studies met the inclusion criteria and were qualitatively reviewed (**Table 1**). Only 4 of the 6 studies could be meta-analyzed because of overlapping study populations in 3 of them. The meta-analysis represented 451,960 TKA patients, of whom 31,568 (7.0%) underwent revision surgery and 28,772 (6.3%) were black. The risk of revision TKA was significantly higher among U.S. blacks than U.S. whites (HR 1.38; 95% CI 1.20-1.59) (**Figure 1**). Analysis of the 3 studies with overlapping study populations demonstrated discordant results as a result of adjustment versus non-adjustment for insurance status (**Figure 2**).

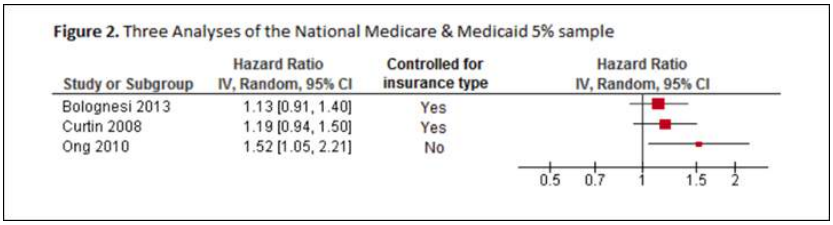
Conclusion: Blacks in the U.S. are at higher risk for revision TKA than whites, which may contribute to a perception of increased TKA risk among blacks. Socioeconomic status (as represented by insurance status) also contributes to revision risk and is an important confounder in analyses of race.

Table 1. Included studies and independent variables analyzed

Study	Database	Years	Follow up (yr)	Total N	White	Black	Revisions N	HR (CI)	P value	Age*	Sex*	LOS*	Comorbidity*	Insurance*	Hospital volume*	Hosp teaching status*	Urban or rural*	U.S region*
Blum ACR 2014	PA	2001-2007	5	17,385	16,436	949	1,183	1.39 (1.08-1.80)	0.01	√	√	√	√	√	√	√		
Bolognesi JBJS 2013	CMS	1999-2009	5	68,603	63,161	3,518	2,685	1.13 (0.92-1.39)	0.2398	√	√	√	√	√	√	√	√	√
Dy CORR 2014	NY CA	1997-2005	10	301,955	247,561	19,279	26,874	1.39 (1.29-1.49)	<0.001	√	√		√	√	√	√	√	√
Namba JA 2013	Kaiser	2001-2010	2.9	64,017	42,608	5,062	826	1.73 (1.3-2.25)	<0.001	√	√		√		√			
Curtin JA 2012	CMS	2001-2007	5	64,615	59,498	3,328	1,369	1.19 (0.94-1.5)	0.15	√	√		√	√			√	√
Ong CORR 2010	CMS	1997-2006	5	72,913	67,281	3,640	1,599	1.52 (1.05-2.21)	0.029	√	√		√					

ACR = Arthritis Care Research: JBJS = Journal of Bone and Joint Surgery American: CORR = Clinical Orthopedics and Related Research: JA = Journal of Arthroplasty: PA = Pennsylvania Health Care Cost Containment Council: CMS = Centers for Medicare & Medicaid Services (5% sample): NY CA = NY State Department of Health Statewide Planning and Research Cooperative System and CA Office of Statewide Health Planning and Development: Kaiser = Kaiser Permanente National Total Joint Replacement Registry.
*Included in multivariate regression analysis.





Disclosure: A. R. Bass, None; **K. McHugh**, None; **K. Fields**, None; **R. Smethurst**, None; **M. Parks**, Zimmer, Inc, 5,Orthopeadic Research and Education Foundation, 6,American Academy of Orthopaedic Surgery Orthopaedic Learning Center, 6,New York State Society of Orthopaedic Surgeons, 6; **S. M. Goodman**, None.

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Abstract Number: 2115

Intra-Operative Synovitis Predicts Worse Pain and Function 2 Years after Total Knee Arthroplasty for Osteoarthritis

Lisa Mandl[1], Shivi Duggal[2], Kelly McHugh[3], Xian Wu[4], Geoffrey H. Westrich[2], Thomas Sculco[2], John A. Carrino[5], Edward F. DiCarlo[6], Steven R. Goldring[1] and Charles Cornell[2], [1]Hospital for Special Surgery, New York, NY, [2]Orthopedics, Hospital for Special Surgery, New York, NY, [3]Rheumatology, Hospital for Special Surgery, New York, NY, [4]Biostatistics and Epidemiology, Weill Cornell Medical College, New York, NY, [5]Department of Radiology, Johns Hopkins University School of Medicine, Baltimore, MD, [6]Laboratory Medicine, Hospital for Special Surgery, New York, NY

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Intra-Operative Synovitis Predicts Worse Pain and Function 2 Years After Total Knee Arthroplasty for Osteoarthritis

Background/Purpose:

Total knee arthroplasty (TKA) is one of the most common elective orthopedic procedures in the US. However, up to 20% of patients have chronic post-operative pain. There is therefore an urgent need to identify modifiable risk factors to improve patients' outcomes. Inflammation is reversible, and has been associated with pain in knee osteoarthritis (KOA). However, whether inflammation is associated with chronic pain or other suboptimal outcomes after TKR is unknown. Therefore, this study investigated the association between pre-operative synovial inflammation and 2-year outcomes following TKA for KOA.

Methods:

We identified 33 KOA patients who underwent primary unilateral TKA and had chronic pain (WOMAC ≤60; 100 =best) at 2 years. Patients were matched 2:1 on surgeon and surgery date with TKA cases with little pain at 2 years, (WOMAC ≥70). All patients provided demographic and pre-and post-operative self-report data. Preoperative radiographs were graded by two blinded evaluators for alignment and Kellgren and Lawrence score. H+E slides of intra-operative synovial tissue were reviewed and graded for inflammation according to the validated Krenn Criteria. Prosthesis information, history of previous surgery to the index knee, post-operative steroid injection and manipulations were recorded from surgeons' and inpatient charts. Regression analyses were performed to evaluate whether pre-operative inflammation was an independent predictor of pain, function or stiffness 2 years after TKA.

Results:

Average age was 67 years, (±7.9), 65% were women and 91% were Caucasian. In a multivariate linear regression controlling for Krenn Score, post-operative steroid injection, age, MCS, PCS, pre-operative WOMAC pain and Euroqol, patients with greater inflammation (Krenn ≥3) had more pain at 2-years (WOMAC 65.01 vs. 76.14; p-value 0.03). Patients who had a steroid injection soon after TKA (based on surgeon's suspicion of tenosynovitis) were more likely to have worse 2 year WOMAC pain scores (60.3 vs. 80.9; p-value = 0.0495). Every 10 year increase in age was associated with a 6.6 unit increase in 2-year WOMAC pain score,(i.e. less pain.). Separate models showed a similar association between high Krenn score and worse 2-year function, (WOMAC Function 70.2 vs. 81.1; p-value 0.01), but no association between Krenn score and 2 year WOMAC stiffness. Neither radiographic findings nor implant type were associated with 2-year outcomes.

Conclusion:

Increased synovial inflammation at the time of surgery predicts worse WOMAC pain and function 2 years after TKA. This is a potentially modifiable risk factor which could be a target for future interventional trials.

TABLE 1 Baseline Demographics (n=99)	
	Average (Range) or %
Women (%)	65
Ethnicity (Caucasian)	90
Age (years)	67 (49-80)
BMI (kg/m^2)	31 (19.6-54.4)
American Society of Anesthesia Score	2 (1-3)
Kellgren & Lawrence Score	3.7 (2-4)
Varus (degrees)	2.6 (0-12)
KRENN Score	3.2 (1-6)
Procedure Time (minutes)	73 (51-114)
EUROQOL Score	0.68 (0.22-0.85)
MCS Score	55.4 (22.3-75.4)
PCS Score	32.3 (10.9-52.5)
Previous Surgery to Index Knee (%)	31
Posterior Stabilized (PSC) Knee Implanted (%)	78
Constrained Condylar Knee (CCK) Implanted (%)	13
WOMAC (pain)	55.5 (15-100)
WOMAC (function)	54.31 (11.8-89.1)
WOMAC (stiffness)	46.84 (0-100)
Post-operative Manipulation (%)	7
Post-operative Steroid Injection (%)	6
*WOMAC=Western Ontario and McMaster Universities Osteoarthritis Index; MCS/PCS=(mental/physical component scale) subscales of the SF-12 questionnaire, a generic measure of health and well-being scored 1-100 (100=best); EUROQOl=measure of current health status scored 0-1 (1=best)	

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Abstract Number: 2116

Advice to Remain Active While Awaiting Physiotherapy Is Associated with Superior Long-Term Outcome Among Patients with Distal Arm Pain – Results from a Randomised Controlled Trial

Gareth T Jones[1,2], Gary J. Macfarlane[1,2], Keith Palmer[3,4], David Coggon[3,4], Karen Walker-Bone[3,4], Kim Burton[5], Peter Heine[6], Candida McCabe[7,8], Paul McNamee[9] and Alex McConnachie[10], [1]Musculoskeletal Research Collaboration (Epidemiology Group), University of Aberdeen, Aberdeen, United Kingdom, [2]University of Aberdeen, Arthritis Research UK / MRC Centre for Musculoskeletal Health and Work, Aberdeen, United Kingdom, [3]MRC Lifecourse Epidemiology Unit, University of Southampton, Southampton, United Kingdom, [4]University of Southampton, Arthritis Research UK / MRC Centre for Musculoskeletal Health and Work, Southampton, United Kingdom, [5]Centre for Applied Psychological and Health Research, University of Huddersfield, Huddersfield, United Kingdom, [6]Warwick Clinical Trials Unit, University of Warwick, Coventry, United Kingdom, [7]Nursing and Midwifery, University of the West of England, Bristol, United Kingdom, [8]Royal United Hospital NHS Foundation Trust, Bath, United Kingdom, [9]Health Economics Research Unit, University of Aberdeen, Aberdeen, United Kingdom, [10]Robertson Centre for Biostatistics, University of Glasgow, Glasgow, United Kingdom
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Background/Purpose:

Pain in the distal upper limb (elbow, forearm, wrist or hand) is common, yet the best approach to management is unclear. While the etiological and prognostic factors are similar to other pain conditions, such as low back pain, management approaches differ greatly. Bed rest is no longer advocated for back pain, although patients with arm pain are often advised to rest and to avoid 'harmful' activities, while awaiting physiotherapy. This advice is without an evidence base.

We hypothesized a) that advice to remain active and maintain usual activities while awaiting physiotherapy, would be superior to advice to rest the arm; and b) that fast-track physiotherapy would be superior to normal (waiting list) physiotherapy.

Methods:

Multi-center randomized controlled trial (ISRCTN79085082). Patients with distal upper limb pain were identified from 14 out-patient physiotherapy departments across the UK. A telephone screening and pre-trial physical assessment confirmed eligibility and collected baseline information. Participants were randomized to either:

* Advice to remain active, or

* Advice to rest the arm

while awaiting physiotherapy, or

* Immediate physiotherapy,

using a mixed randomization/minimization algorithm to maintain treatment balance in terms of treatment center, gender, laterality (dominant, non-dominant, or bilateral problem), a broad categorization of diagnosis (elbow versus wrist/hand problem), and baseline arm function. Outcome was measured at 26 weeks using the modified DASH (Disabilities of the Arm, Shoulder and Hand) questionnaire which asks people to rate difficulty in performing eleven pre-specified activities over the past week, because

of pain in their distal upper limb. This was scored as 0 (no disability) versus >=1 (some disability). **Results** , from an intention-to-treat analysis, are presented as odds ratios (95% confidence intervals) for the probability of recovery.

Results:

539 patients were randomized evenly between the three groups (179, 182 and 178, respectively). Participants had a mean age of 49yrs (SD 13.6); 54.5% were female; and 87.6% were right handed. Approximately an equal number of patients reported pain in their elbow, wrist/hand, or both; and pain was most common in the dominant side (45.5%), or bilateral (24.7%). 435 participants (81%) provided follow-up data at 26 weeks.

32.1% of patients who received advice to rest were free of disability at 26 weeks, compared to 45.2% of those who received advice to remain active. Thus, advice to rest was associated with a decrease in the likelihood of recovery (odds ratio: 0.54; 95%CI: 0.32-0.90). There was no difference in recovery between those receiving immediate physiotherapy (35.8%) versus delayed (38.6%).

Conclusion:

We have shown, among patients referred to physiotherapy with distal upper limb pain, that advice to remain active is associated with a superior long-term outcome, compared with advice to rest the arm, but our results do not support the provision of 'fast-track' physiotherapy for such patients. These findings call into question current advice and provide evidence that the no-bed-rest management approaches now common in back pain perhaps have parallels in other regional musculoskeletal pain conditions.

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Abstract Number: 2117

Weight Predicts Back Pain in Young Adult Women, Independent of Physical Activity: Data from the Australian Longitudinal Study on Women's Health

Sharmayne Brady[1], Sultana Monira Hussain[2], Wendy Brown[3], Stephane Heritier[1], Baki Billah[1], Yuanyuan Wang[4], Helena Teede[5,6], Donna Urquhart[1] and Flavia Cicutinni[1], [1]Department of Epidemiology and Preventive Medicine, School of Public Health and Preventive Medicine, Monash University, Melbourne, Australia, [2]Department of Epidemiology and Preventive Medicine,, School of Public Health and Preventive Medicine, Monash University, Melbourne, Australia, [3]Faculty of Health and Behavioural Sciences, School of Human Movement Studies, University of Queensland, Brisbane, Australia, [4]Department of Epidemiology and Preventive Medicine, Monash University, Melbourne, Australia, [5]School of Public Health and Preventive Medicine, Department of Epidemiology and Preventive Medicine, Monash Centre for Health Research and Implementation, Monash University, Melbourne, Australia, [6]Diabetes and Endocrine Unit, Monash Health, Melbourne, Australia

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Background/Purpose:

Low back pain (LBP) causes enormous financial and disability burden worldwide, and therapeutic options have limited efficacy. This burden could be potentially reduced by gaining an understanding of the predictors of LBP in order to optimize preventive strategies. As having previous episodes of LBP are predictive of future recurrences, understanding the risk factors associated with

LBP in early adulthood are particularly important. There is evidence that women are more likely to suffer from LBP and utilise health care to a greater extent in comparison to men, and there is a paucity of data examining predictors of LBP, such as weight and physical activity, in young women. The aim of this study was to identify whether modifiable risk factors, weight and physical activity, were predictive of low back pain in young adult women.

Methods:

Participants took part in a large population-based cohort study, the Australian Longitudinal Study of Women's Health. Community dwelling women born between 1973 and 1978 were randomly selected from the national health insurance scheme database, which includes most permanent residents of Australia. Women were recruited nationally with intentional oversampling from rural and remote areas. Women completed questionnaires three-yearly between 2000 and 2012. In year 2000, 9,688 women completed the questionnaire and 83% completed follow up questionnaires 12 years later. Self-reported data on back pain, weight, height, age, education status, physical activity, and depression were collected at each of the five surveys.

Results:

In this cohort of women at baseline, median age was 24.6 years and 41% had self-reported back pain in the last 12 months. Women reporting back pain were more likely to seek help (38.2% vs. 3.4%, $p<0.001$) and be unemployed (19.7% vs. 15.7%, $p<0.001$) compared with those without back pain. Inadequate physical activity and depression were independent predictors of back pain over the following 12 years (both $p<0.001$), after adjusting for age, weight, height and education status. For every 5kg higher weight at baseline, there was a 5% (95% CI 1.04 - 1.06) increased risk of back pain over the next 12 years. Higher weight at each survey also predicted subsequent back pain risk three years later, with the adverse effects of weight being present at all levels of physical activity.

Conclusion:

Back pain is common in community-based young adult women. Higher weight, inadequate levels of physical activity and depression were all independent predictors of back pain over the following decade. Furthermore, the adverse effects of weight on back pain were not mitigated by physical activity. Our findings highlight the role of both weight gain and physical inactivity in back pain among young adult women and suggest potential opportunities for future prevention.

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Abstract Number: 2118

Prescription Medication Use in Community-Based US Adults with Chronic Low Back Pain: Nhanes 2009-2010

Anna Shmagel[1] and Robert Foley[2], [1]Rheumatic & Autoimmune Diseases, University of Minnesota Medical School, Minneapolis, MN, [2]Renal Diseases and Hypertension, University of Minnesota, Minneapolis, MN

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Background/Purpose: Chronic low back pain (cLBP) is a significant public health problem. Establishing treatment guidelines has been difficult due to heterogeneity of research data. Little is known about medication use for cLBP in the community.

Methods: We used data from the back pain survey, administered to a representative sample of US adults aged 20-69 (N = 5103)

during the 2009-2010 cycle of the National Health and Nutrition Examination Survey (NHANES). Participants who reported pain in the area between the lower posterior margin of the ribcage and the horizontal gluteal fold at the time of survey with a history of pain lasting almost every day for at least 3 months were classified as having cLBP (N = 700). Data on prescription medications was collected by a trained interviewer, verified with medication bottles when available, and recorded into an electronic database. We used Lexicon Plus® categories to search for the commonly prescribed medications for chronic pain: acetaminophen, NSAIDs, narcotic analgesics (including tramadol), other neurologics (gabapentin, pregabalin), topical analgesics, skeletal muscle relaxants, antidepressants, anxiolytics. Chi-square tests, analysis of variance and adjusted logistic regression models were used for comparisons.

Results: 68.6% of US adults with cLBP aged 20-69 were taking at least one prescription medication in the past 30 days. 18.8% were using narcotic analgesics, 9.9% acetaminophen (including in combination with narcotics), 9.7% NSAIDs, 8.5% muscle relaxants, 6.9% gabapentin or pregabalin. COX2 inhibitors and topical lidocaine preparations were rarely used, 0.5% each. The prevalence of antidepressant and anxiolytic use was 20.2% and 8.5% respectively. The median number of days on the current prescription was 1009 for antidepressants (IQR 316-1945), 750 for anxiolytics (IQR 162-1845), 702 for narcotics (IQR 314-1770), 682 for muscle relaxants (IQR 258-1688), 534 for gabapentin or pregabalin (IQR 224-1611), and 522 for NSAIDs (IQR 155-1924).

Conclusion: Despite recommendations to limit the use of narcotics in chronic pain and reports of increasing incidence of deaths due to narcotic overdose, narcotic analgesics along with antidepressants were the most prevalent prescription pain medications with extended duration of use in community-based US adults with chronic low back pain.

Disclosure: A. Shmagel, None; **R. Foley**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/prescription-medication-use-in-community-based-us-adults-with-chronic-low-back-pain-nhanes-2009-2010

Abstract Number: 2119

Findings and Therapeutic Impact of Magnetic Resonance Imaging (MRI) Studies for Patients with Lower Back Pain with Neurologic Symptoms. Are We Choosing Wisely?

Patrick Nguyen[1], Nathalie Carrier[2] and **Ariel Masetto**[3], [1]Internal Medicine, Université de Sherbrooke, Sherbrooke, QC, Canada, [2]Division of Rheumatology, Université de Sherbrooke, Sherbrooke, QC, Canada, [3]Rheumatology, Université de Sherbrooke, Sherbrooke, QC, Canada

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Background/Purpose: According to different guidelines, the presence of neurological symptoms in patients with lower back pain (LBP) is a validated indication for more complex imaging studies, including lumbar spine magnetic resonance imaging (MRI). This could help in confirming clinical diagnosis and eventually establishing a treatment plan. We aimed to study the findings and clinical impact of lumbar spine MRI indicated for patients with LBP complicated by neurologic symptoms in our center.

Methods: We retrospectively analyzed 436 consecutive lumbar spine MRI studies between 2010 and 2013.Our variables of interest were: age, source of the MRI request (general practitioners -GPs- or specialists), “positive” MRI findings (MRI confirming any kind of neurologic compression), correlation between described history and MRI findings, aetiology of neurological compression (osteoarthritis or discal degenerative disease) and finally, the clinical impact on treatment (considered positive for invasive treatment such as steroid injections or surgery versus negative for non-invasive treatment or clinical therapy).

Results: We selected 355 MRIs indicated for LBP with lower limb neurologic symptoms. Patients’ mean age was 52,3 ± 14,1

years, 44.9% female. Most MRI requests, 231(70%), came from GPs. The majority of described neurologic symptoms were sensitive 318 (89,3%). Contrary to our expectations, the rate of normal MRIs was significantly higher in MRIs indicated for motor than sensory symptoms: 15.8% vs 5.7%, respectively (p=0.032). We found normal MRI (with no neurological compressions) in 156 (43.9%) of patients. Among the 199 (56.1%) positive MRIs, there was a dissonance between history and MRI findings in 22 (11,1%) patients. Adding normal MRI studies (156) and MRI with neurologic compressions but without clinical concordance (22) : 178/355 (50,1%) of MRI were negative for clinical relevant neurologic compressions**.** The likelihood of asking for a positive MRI didn't differ between GPs and specialists (p=0,84). Only 87 patients (24,4%) had any invasive procedure, 46 (12,9%) had steroid injections and 41 (11,5%) had surgery. Patients whom MRI was prescribed by a specialist instead of a GP had a significantly higher rate of having an invasive procedure: 37.3% vs 18.6%, respectively (p<0.001).

Conclusion: In this retrospective cohort, half of MRI studies indicated for LBP with supposed neurologic symptoms were negative. In patients with positive MRIs, just one fourth had any kind of invasive procedure. Lumbar spine MRI studies are probably being overused in our center. We hypothesize potential misinterpretation of lower back pain with leg irradiation as true neurologic radicular symptoms. Moreover, even true radicular pain often resolves with non-invasive treatment. MRI studies should be reserved for refractory cases or those presenting major motor symptoms needing a more invasive treatment such as spinal injections or surgery.

Disclosure: P. Nguyen, None; **N. Carrier**, None; **A. Masetto**, None.

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Abstract Number: 2120

Alterations in Complement C3 and iC3b in SLE Pregnancies

Marta M. Guerra[1], Martin Schmidt[2], Elianna Kaplowitz[3], Vibeke Strand[4] and **Jane E. Salmon**[5], [1]Rheumatology 3rd Fl Rsrch, Hospital for Special Surgery, New York, NY, [2]Kypha, Inc., St. Louis, MO, [3]Hospital for Special Surgery, New York, NY, [4]Division of Immunology/Rheumatology, Stanford University School of Medicine, Portola Valley, CA, [5]Division of Rheumatology, Hospital for Special Surgery, Weill Cornell Medical College, New York, NY

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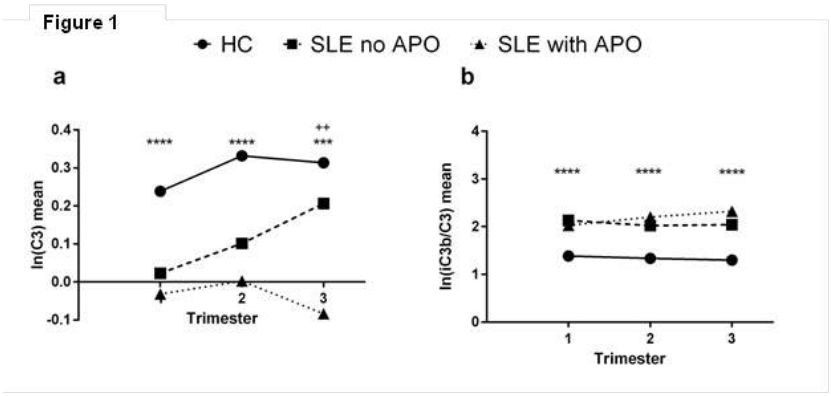
Background/Purpose: Pregnancy in patients with SLE is associated with increased risk of maternal and fetal complications. Studies in experimental models and humans suggest that complement activation contributes to fetal loss, preeclampsia and growth restriction. In a case control longitudinal study of pregnancy from PROMISSE (**P**redictors of p**R**egnancy **O**utcome: Bio**M**arkers **I**n antiphospholipid antibody **S**yndrome and **S**ystemic **L**upus **E**rythematosus), we investigated whether circulating levels of maternal complement C3 and its degradation product iC3b would vary during pregnancy and would be associated with adverse pregnancy outcomes (APO) in SLE patients.

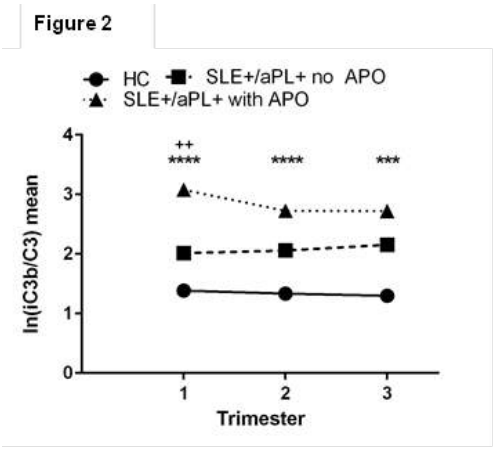
Methods: The PROMISSE Study enrolled pregnant women with ≥4 ACR SLE criteria and/or aPL antibodies and healthy pregnant controls (HC). Patients were considered aPL positive if aCL and/or antiβ2GP1 were ≥40 IU IgG or IgM and/or LA was positive in ≥2 determinations with at least once during pregnancy. Exclusion criteria were multi-fetal pregnancy, prednisone >20 mg/d, proteinuria >1 gm/24hr, and creatinine >1.2 mg/dL. APOs were defined as fetal death, neonatal death, preterm delivery <36 wks due to preeclampsia or placental insufficiency, and/or growth restriction <5th %ile. Fifty four SLE patients (18 with APO and 36 without) and 40 HCs were included in this study. C3 and iC3b were measured once per trimester in serial samples from maternal plasma using investigational lateral flow assays (Kypha, Inc. St. Louis, MO). Data were log transformed and analyzed (GraphPad Prism 6).

Results: Compared with HC, patients with SLE had lower C3, higher iC3b levels, and elevated iC3b/C3 ratios throughout pregnancy (Fig. 1, ****p<0.0001, p<0.001***, Tukey's post-hoc ++). Although neither C3 nor iC3b early in pregnancy predicted

APO (Fig. 1b), C3 levels were lower in the 3rd trimester in SLE with late APOs (n=13) compared with uncomplicated SLE and HC pregnancies (n=41) (Fig. 1b. ANOVA: F=9.213, P<0.001, Tukey's post-hoc). In the subset of aPL-positive SLE patients (n=13), elevated iC3b/C3 ratios were associated with APOs (n=5) (Fig. 2, ANOVA: F=19.48, ****p<0.0001, p<0.001***, Tukey's post-hoc ++).

Conclusion: During pregnancy, patients with SLE show evidence of complement activation and consumption. Lack of an increase in circulating C3 as pregnancy proceeds is associated with late APOs. If this is confirmed in larger populations accurate and rapid measurements of C3 and iC3b point of care assays may prove valuable in the management of SLE pregnancies.





Disclosure: M. M. Guerra, None; **M. Schmidt**, Kypha, Inc, 3; **E. Kaplowitz**, None; **V. Strand**, Kypha, Inc., 5; **J. E. Salmon**, None.

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Abstract Number: 2121

Placentas of Lupus Pregnancies Are Characterized By Marked Inflammatory Changes Despite Good Disease Control

Wendy Marder[1], Jason S. Knight[2], Mariana J. Kaplan[3], Emily C. Somers[4], Xu Zhang[4], Alexander A. O'Dell[5], Vasantha Padmanabhan[4] and Richard W. Lieberman[4], [1]Div of Rheumatology, University of Michigan, Ann Arbor, MI, [2]Division of Rheumatology, University of Michigan, Ann Arbor, MI, [3]National Institute of Arthritis and Musculoskeletal and Skin Diseases, National Institutes of Health, Bethesda, MD, [4]University of Michigan, Ann Arbor, MI, [5]Department of Internal Medicine, Division of Rheumatology, University of Michigan, Ann Arbor, MI

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Background/Purpose: Systemic lupus erythematosus (SLE) is associated with increased risk of adverse pregnancy outcomes (APO), including preeclampsia and intrauterine growth restriction. While significant placental pathology is expected in patients with preeclampsia, less is known about how lupus disease activity during pregnancy affects the placenta. Here, we describe a lupus population in which disease control was generally excellent during pregnancy, and in which only 30% of the pregnancies were complicated by preeclampsia. In addition to standard pathologic review, we also specifically quantified neutrophils and neutrophil extracellular traps (NETs) given their recognized association with preeclampsia in the general population, as well as endothelial damage in SLE.

Methods: Preeclampsia, SLE, and healthy placentas were scored for typical histologic features including inflammation, hemorrhage, and infarction. Neutrophils were quantified with the aid of immunohistochemical staining for the granular protein myeloperoxidase. NETs were identified by extracellular myeloperoxidase staining in the setting of decondensed nuclei. Nonparametric analysis was used to evaluate differences in netting and intact neutrophils between groups. Logistic regression was used to identify associations between histology and neutrophils.

Results: Placentas from 11 preeclampsia, 4 SLE+preeclampsia, 10 SLE pregnancies (no preeclampsia), and 10 healthy/control pregnancies were evaluated. Lupus disease activity during pregnancy was low in all but one patient. Surprisingly, as compared to controls, significantly more NETs were found infiltrating *not just*preeclampsia (p=0.0003) and SLE+preeclampsia (p=0.0345) placental intervillous spaces, but also all 10 of the SLE non-preeclampsia cases (p=0.0019). The ratio of NETs to total neutrophils was also increased in all three groups (p=0.0015, p=0.0345, p=0.0019, respectively, as compared to controls). The presence of NETs was further associated with striking histologic abnormalities including severe vasculitis with fibrinoid necrosis (p=0.02286), acute and chronic hemorrhage (p=0.02116), and laminar decidual necrosis (p=0.03458) in all groups. In summary, the placentas of clinically-stable SLE pregnancies were markedly inflamed and essentially indistinguishable from preeclampsia placentas.

Conclusion: Preeclampsia, SLE+preeclampsia, and clinically-stable SLE pregnancies were all associated with significantly higher numbers of intervillous NETs, and greater ratios of netting to total neutrophils as compared to controls. This was true not just for preeclampsia placentas, but also for placentas of lupus patients whose disease activity was low during pregnancy (and who did not have clinical preeclampsia). In summary, these data suggest lupus and preeclampsia pregnancies may share common pathogenesis that is elaborated in lupus despite clinically quiescent disease. Future studies of lupus pregnancies are required to elucidate mechanisms of this abnormal placentation, as it may have implications for both APOs and long-term outcomes of children born to mothers with SLE.

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Abstract Number: 2122

A Novel Severity Score Based on Cardiac Neonatal Lupus Manifestations Serves As a Predictor and Outcome Measure of Morbidity in Anti-Ro Exposed Fetuses

Amit Saxena[1], Peter M. Izmirly[1], Sung Won Han[2], Paraskevi Briassouli[1], Tania Rivera[3], Mark Halushka[4], Hua Zhong[5], Deborah Friedman[6], Robert Clancy[1] and Jill P. Buyon[1], [1]Medicine, Division of Rheumatology, New York University School of Medicine, New York, NY, [2]Department of Population Health, New York University School of Medicine, New York, NY, [3]Rheumatology, Scripps Memorial Hospital La Jolla, La Jolla, CA, [4]Division of Cardiovascular Pathology, John Hopkins Pathology, Baltmore, MD, [5]Population Health, New York University School of Medicine, New York, NY, [6]Pediatric Cardiology, New York Medical College, Valhalla, NY

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Background/Purpose: Women with anti-Ro face a spectrum of fetal consequences when pregnant, from complete wellbeing to death from cardiac neonatal lupus (cardiac NL). Transplacental passage of anti-Ro can result in transient bradycardia, first degree or advanced block, cardiomyopathy and/or death. A cardiac NL severity score was generated to identify demographic and clinical factors associated with morbidity, and serve as a predictor for long term outcomes.

Methods: The severity score (Table 1) was based on reported mortality risk factors, such as lower fetal heart rates (which

require earlier pacemaker) and extranodal disease. The score was calculated for anti-Ro positive pregnancies in the Research Registry for Neonatal Lupus. Pregnancies antedating affected children were excluded as anti-Ro could not be verified. The severity score was evaluated in univariate analysis with cord blood biomarkers related to inflammation/fibrosis: CRP (n=108), NT proBNP (n=118), Matrix Metalloproteinase 2 (MMP2) (n=63), and uPA/uPAR/plasminogen (n=49). Clinical correlates were evaluated in 779 pregnancies from 464 mothers, including race and maternal use of hydroxychloroquine (HCQ) and fluorinated steroids (FS). The score was also evaluated in relation to long term outcomes in affected children based on postnatal echocardiogram (n=150, mean age 11.7±9.3 y).

Results: Severity score positively associated with cord CRP (Regression coefficient (RC) 2.18, p=0.02), NT proBNP (RC 2.79, p=0.002), MMP2 (RC 1.01, p=0.01), uPA (RC 33.7, p<0.001), uPAR (RC 3.72, p<0.001) and plasminogen (RC 1.01, p=0.01). Mean score in fetuses exposed vs unexposed to HCQ was 2.8±6.9 vs 5.6±6.9 (p<0.001). Severity score was higher in black (7.9±8.4) vs other races (4.9±6.6) (p=0.017). Limiting the analysis to cardiac NL pregnancies, the score in HCQ exposed vs unexposed fetuses was 12.5±6.5 (n=17) vs 10.5±6.3 (n=328) (p=0.32). Histologic evaluation of an autopsy from a 19 week HCQ exposed fetus electively terminated with complete block did not reveal HCQ associated vacuolar changes in myocytes. Severity score was not different in cardiac NL cases exposed (10.9±6.2, n=181) and unexposed (10.1±6.2, n=162) to FS (p=0.26). The score was higher in those with abnormal ventricular function on long term evaluation (10.2±4.0 vs 7.7±3.7) (p=0.002).

Conclusion: This novel cardiac NL severity score can be utilized in pregnancy counseling both as an outcome measure associated with disease risk factors, and as a predictor of future morbidity. Cord blood biomarkers of inflammation/fibrosis positively associate with the score. HCQ use during anti-Ro exposed pregnancies associate with decreased severity score, consistent with its proposed role as a preventative measure. However in affected cases, HCQ and FS do not associate with severity. The association of severity score with long term ventricular function promotes its use for counseling and medical monitoring in cardiac NL cases.

Table 1: Severity Scores for Potential Outcomes in anti-SSA/Ro Exposed Fetuses

Unaffected	0
Sinus Bradycardia (transient)	1
1st Degree AV Block	2
Advanced AV Block, No PPM at 6 months	5
Advanced AV Block, PPM placed by 6 months	6
Advanced AV Block, PPM placed by 1 week	8
1 Extranodal Manifestation	14
>1 Extranodal Manifestation	16
Death	20

Advanced AV Block = 2nd or 3rd degree heart block; PPM = permanent pacemaker; Extranodal Manifestation = endocardial fibroelastosis, dilated cardiomyopathy or hydrops fetalis

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Abstract Number: 2123

Incidence and Prognosis of Neonatal and Late-Onset Dilated Cardiomyopathy Associated with Cardiac Neonatal Lupus

Kateri Levesque[1,2], Nathalie Morel[3], Alice Maltret[4], Gabriel Baron[5], Mohamed Hamidou[6], Pauline Orquevaux[7], Jean Charles Piette[8], Francois Barriere[9], Jérome Lebidois[4], Laurent Fermont[4], Olivier Fain[10], Arnaud Theulin[11], Francois Sassolas[12], Philippe Pézard[13], Gaëlle Guettrot-Imbert[14], Delphine Le Mercier[15], Sophie Georgin-Lavialle[16], Christophe Deligny[17], Eric Hachulla[18], Luc Mouthon[19], Philippe Ravaud[20], Elisabeth Villain[4], Damien Bonnet[21] and **Nathalie Costedoat-Chalumeau**[3], [1]Internal Medicine, CHU Ste-Justine, Montréal, QC, Canada, [2]Medicine Interne, Hopital Cochin, Paris, France, [3]Internal Medicine Department, Cochin Hospital, "René-Descartes Paris V" University, Paris, France, [4]Cardiology, Groupe Hospitalier Necker - Enfants Malades, Paris, France, [5]Hôpital Hôtel Dieu, Paris, France, [6]Internal Medicine Department, Nantes University Hospital, Nantes, France, [7]Hu Robert Debre, CHU Reims, Reims, France, [8]Internal Medicine Department, University Hospital "Pitié-Salpêtrière", "Pierre et Marie Curie Paris VI" University, Paris, France, [9]Pediatry, CHU Nantes, Nantes, France, [10]Internal Medicine, Hospital J. Verdier, Bondy, France, [11]Internal medicine, CHRU Strasbourg, Strasbourg, France, [12]Cardiology, CHU Lyon, Lyon, France, [13]Pediatric cardiologist, CHU Angers, Angers, France, [14]Internal Medicine, Hopital Saint-Antoine, Paris, France, [15]Obstetrics and gynecology, Hopital Necker, Paris, France, [16]Internal medicine, Hopital Tenon,

Paris, France, [17]Rhumatologie Et Médecine Interne, Centre hospitalier Universitaire de Fort de France, Fort de France, Martinique, [18]Service de Médecine Interne, Centre National de Référence des Maladies Systémiques Rares, Hôpital Claude Huriez, CHRU Lille, Lille, France, [19]Internal Medicine, National Referral Center for Rare Systemic Autoimmune Diseases, Hôpital Cochin, Paris, France, [20]Rheumatology, Paris, France, [21]Pediatric cardiologist, Hopital Necker, Paris, France
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Background/Purpose:

Dilated cardiomyopathy (DCM) is a well-known complication of cardiac neonatal lupus syndrome and is associated with a high mortality rate. Its risk factors are unclear.

Methods: We analyzed the occurrence of postnatal DCM (neonatal or of late-onset) among children with a high degree congenital heart block (CHB) included in the French registry of cardiac neonatal lupus (from 1976 to 2014). The presence of postnatal DCM was defined by left ventricular systolic dysfunction with left ventricle ejection fraction <45% requiring treatment or by death related to end-stage heart failure. All mothers were anti-SSA antibodies positive.

Results:

187 children with CHB were born alive. During a median follow-up of 7 years [birth to 36 years], 35 (18.8%, one missing data) had a DCM, and 22 (11.8%) died.

DCM could be categorized in 2 different subgroups: neonatal DCM (n=13, diagnosed before day 28 of life) or late-onset DCM (n=22, diagnosed at a median age of 15.2 months [3.6 months-22.8 years]). On univariate analysis, factors associated with neonatal DCM were maternal treatment with hydroxychloroquine, *in utero* cardiomegaly and DCM, and hydrops. By contrast, factors associated with late-onset DCM were non-European origin and significant *in utero* valvulopathy. In multivariate analysis, the only factor associated with neonatal DCM was *in utero* DCM (p=0.0001; HR 15.99 [95%CI: 3.93-65.01]), whereas the only factor associated with late-onset DCM was non-white race origin (p=0.0147; HR 3.65 [95%CI: 1.28-10.0]).

Twenty-two (11.8%) children died: 8 in the neonatal period and 14 after the first month of life and one child with DCM had a successful heart transplantation at 2.5 years of age. Neonatal deaths were always related to DCM and occurred during the first days of life despite intensive care and the placement of pacemaker in 2 out of 8 cases. The 14 later deaths occurred at a median time of 10 days after the diagnosis of DCM [0-58months]. Eleven (79%) of those deaths were the result of DCM.

The probability of survival at 10 years of age for a neonate with CHB was 87.1%: 23.1% in the presence of neonatal DCM, 53.9% for those who developed a late-onset DCM requiring treatment versus 98.6% in those without DCM. Prenatal fluorinated steroid (p=0.27; HR 1.65 [95%CI: 0.63-4.25]) did not prevent the development of late-onset DCM.

Conclusion:

The presence of in utero DCM carries a high risk of neonatal DCM. No classical risk factors were associated with late-onset DCM. The mortality associated with DCM (either neonatal or of late-onset) was high. Maternal treatment with fluorinated steroid did not prevent the development of late-onset DCM.

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Abstract Number: 2124

Racial Disparities in Lupus Pregnancy

Megan E. B. Clowse[1] and Chad Grotegut[2], [1]Rheumatology & Immunology, Duke University, Durham, NC, [2]Obstetrics & Gynecology, Duke University, Durham, NC

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Background/Purpose: Both lupus and pregnancy have significant racial disparities, with black women experiencing higher rates of complication compared to other race and ethnic groups. No large studies have focused on the impact of race/ethnicity on pregnancy outcomes among women with lupus.

Methods: Using the Nationwide Inpatient Sample (NIS) for years 2008-2010, pregnancy delivery discharges were identified and pregnancy outcomes were compared for women with lupus by maternal race/ethnicity. Women with lupus were identified using ICD-9 code 710.0. Adjusted odds ratios were calculated for various pregnancy outcomes comparing black or Hispanic women with lupus to white women with lupus.

Results: Between 2008 and 2010, there were 13,553 delivery discharges to women with lupus and 12,510,565 delivery discharges to women without lupus. Pregnant white women with lupus were, on average, 2 years older than pregnant black and Hispanic women with lupus (see Table). The cost for delivery among women with lupus was $2000-5000 higher for Hispanic and black women compared to white women. The rate of chronic hypertension was high in lupus pregnancies, but highest among black women (19.4%, OR 2.89) and Hispanic women (11.0%, OR 1.48) compared to white women (7.7%). Chronic renal failure was uncommon in pregnancy, but noted in 3.7% of black lupus pregnancies (OR 3.47). Thrombophilia, including antiphospholipid syndrome, was only noted in 4.9-6.7% of pregnancies and the rates were not different between white, black, and Hispanic lupus pregnancies.

The rate of pregnancy complication was high among lupus pregnancies. Over 40% of pregnancies to mothers of all races delivered via cesarean. Preterm labor occurred in 14-25% of pregnancies. Preeclampsia occurred in almost 20% of black and Hispanic pregnancies. After adjustment for predictors of pregnancy outcomes and racial differences in non-lupus pregnancy, black and Hispanic women with lupus had higher odds of acute renal failure, pneumonia, need for transfusion, preeclampsia, preterm labor and fetal growth restriction than white women with lupus.

Conclusion: Black and Hispanic women with lupus have disproportionately poor pregnancy outcomes compared to white women with lupus. These disparities are larger than expected in the general population. While this study is not designed to determine causation, we postulate that increased levels of lupus activity and damage among black and Hispanic women may be in part to blame. Additional sources of disparity may include differences in access to quality care and prescribed medications. This study suggests that identifying the key causes for these differences and targeting interventions to the women of greatest need is an essential next-step.

Table: The rates of medical and obstetric complications for white, black, and Hispanic women with lupus. The p-values are derived from multivariate logistic regression model that included variables that impact pregnancy outcome, including age, insurance status, thrombophilia, anemia, thrombocytopenia, drug use, alcohol use, tobacco use, chronic hypertension, chronic renal failure, diabetes, thyroid disorders, asthma, history of MI, multiple gestation, mode of delivery, and placenta previa.

	Systemic Lupus Erythematosus			p-value	p-value
	White n=5755	Black n=2762	Hispanic n=2088	Black vs. White	Hispanic vs. White
Maternal age, yrs	30.3 ± 12.5	28.3 ± 13.4	28.0 ± 13.6	p<0.0001	p<0.0001
Total charges, $	$12,289	$14,649	$17,453	p<0.0001	p<0.0001
Medical Complications in Pregnancy:					
Acute renal failure n (%)	16 (0.28%)	51 (1.8%)	49 (2.3%)	3.60 (1.91, 6.75) <0.0001	11.41 (6.05, 21.51) <0.0001
Pneumonia	15 (0.26%)	36 (1.3%)	28 (1.3%)	3.24 (1.76, 5.94) <0.0001	4.81 (2.60, 9.25) <0.0001
Transfusion	134 (2.3%)	151 (5.5%)	106 (5.1%)	1.30 (1.01, 1.68) <0.0001	1.52 (1.15, 2.02) <0.0001
Gestational diabetes	346 (6.0%)	75 (2.7%)	124 (5.9%)	0.42 (0.33, 0.55) <0.0001	1.05 (0.84, 1.30) 0.86
Obstetrical Complications:					
Preeclampsia, eclampia, gestational HTN	780 (13.5%)	525 (19.0%)	412 (19.7%)	1.16 (1.02, 1.32) <0.0001	1.44 (1.26, 1.65) <0.0001
Preterm labor	823 (14.3%)	682 (24.7%)	430 (20.6%)	1.59 (1.41, 1.79) <0.0001	1.51 (1.32, 1.73) <0.0001
Fetal growth restriction	317 (5.5%)	270 (9.8%)	182 (8.7%)	1.50 (1.26, 1.79) <0.0001	1.60 (1.32, 1.94) <0.0001

Disclosure: M. E. B. Clowse, None; **C. Grotegut**, None.

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Abstract Number: 2125

Rheumatic and Non-Rheumatic Autoimmune Diseases in SLE Offspring

Julie Couture[1], Sasha Bernatsky[2], Susan Scott[3], Christian A. Pineau[2] and Evelyne Vinet[2], [1]McGill University Health Centre, Montreal, QC, Canada, [2]Divisions of Rheumatology and Clinical Epidemiology, McGill University Health Centre, Montreal, QC, Canada, [3]Clinical Epidemiology, Research Institute of the McGill University Health Centre, Montreal, QC, Canada
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Background/Purpose: Autoimmune diseases (AID) have familial aggregation and frequently share a common genetic predisposition. Only few small uncontrolled studies have evaluated the risk of AID in SLE offspring, with inconsistent results. In a large population-based study, we aimed to determine if children born to mothers with SLE have an increased risk of rheumatic and non-rheumatic AID compared to children born to mothers without SLE.

Methods: The "Offspring of SLE mothers Registry (OSLER)" includes all women who had ≥1 hospitalization for delivery after SLE diagnosis, identified through Quebec's universal healthcare databases (1989-2009). OSLER also includes a randomly selected control group of women, matched at least 4: 1 for age and year of delivery, who did not have a diagnosis of SLE prior to or at the time of delivery. We identified children born live to SLE mothers and their matched controls, and ascertained rheumatic (i.e. juvenile idiopathic arthritis, SLE, systemic sclerosis, Sjögren's disease, inflammatory myositis, systemic vasculitis) and non-rheumatic (i.e. type 1 diabetes, inflammatory bowel disease, psoriasis, celiac disease, autoimmune thyroid disease, myasthenia gravis, multiple sclerosis) AID based on ≥1 hospitalization or ≥2 physician visits with a relevant diagnostic code, at least 2 months apart but within 24 months. The study interval spanned from birth to the first of the following: event of interest, age 18, death, or end of study. We performed multivariate analyses to adjust for maternal age, education, and ethnicity, as well as calendar year of birth and sex of the child.

Results: 509 women with SLE had 719 children, while 5824 matched controls had 8493 children. Mean follow-up was 9.1 (SD 5.8) years. Compared to controls, children born to mothers with SLE had similar records of rheumatic diagnoses [0.14% (95% CI 0.01, 0.90) vs 0.19% (95% CI 0.11, 0.32)]. However, there was a trend towards more non-rheumatic AID in offspring of mothers with SLE versus controls [1.11% (95% CI 0.52, 2.27) vs 0.48% (95% CI 0.35, 0.66)]. The most frequently observed non-rheumatic AID were Crohn's disease (0.56% in SLE offspring, versus 0.19% in control children) and type 1 diabetes (0.42% in SLE offspring, versus 0.22% in control children).

In multivariate analyses, children born to mother with SLE had a substantially increased risk of non-rheumatic AID compared to controls (OR 2.62, 95% CI 1.10, 6.24), while results were inconclusive for the risk of rheumatic AID (OR 0.78, 95% CI 0.10, 5.92).

Conclusion: Our novel data suggest that, compared to children from the general population, children born to women with SLE have an increased risk of non-rheumatic AID. Our effect estimate for the risk of rheumatic AID is inconclusive. Further study of these children, throughout late childhood, adolescence, and adulthood, would be additionally enlightening.

Disclosure: J. Couture, None; **S. Bernatsky**, None; **S. Scott**, None; **C. A. Pineau**, None; **E. Vinet**, None.

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Abstract Number: 2126

Trial of Atorvastatin for the Primary Prevention of Cardiovascular Events in Patients with Rheumatoid Arthritis

George D. Kitas[1], Peter Nightingale[2], Jane Armitage[3], Naveed Sattar[4], Jill Belch[5], Deborah P.M. Symmons[6] and TRACE RA Consortium, [1]Dudley Group NHS Foundation Trust, Dudley, and Arthritis Research Campaign Epidemiology Unit, University of Manchester, Manchester, United Kingdom, [2]Wolfson Computer Laboratory, University Hospitals Birmingham NHS Foundation Trust, Birmingham, United Kingdom, [3]Clinical Trial Service Unit and Epidemiology Unit, University of Oxford, Oxford, United Kingdom, [4]University of Glasgow, BHF Glasgow Cardiovascular Research Centre, Glasgow, United Kingdom, [5]Division of Cardiovascular and Diabetes Medicine, University of Dundee, Dundee, United Kingdom, [6]NIHR Manchester Musculoskeletal Biomedical Research Unit, Central Manchester University Hospitals NHS Foundation Trust, Manchester, United Kingdom
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Session Time: 4:30PM-6:00PM

Background/Purpose: Patients with rheumatoid arthritis (RA) are at increased risk for cardiovascular disease (CVD) compared to the general population, both due to classical and novel risk factors. It remains unclear whether primary prevention strategies for CVD are effective in high grade inflammatory conditions such as RA and there are no previous, CVD outcome statin trials in patients with RA. TRACE RA was designed to assess whether atorvastatin 40mg daily is superior to placebo for the primary prevention of CVD events in patients with RA.

Methods: Prospective, randomised, double-blind, placebo-controlled, UK multicentre trial in RA patients aged >50 years or RA duration >10 years; without known atherosclerotic disease, diabetes, myopathy; not taking statins. All patients were given lifestyle advice. Primary endpoint: a composite of CVD death, non-fatal myocardial infarction, cerebrovascular accident (excl. haemorrhagic stroke), transient ischaemic attack, revascularisation. Secondary endpoints included safety outcomes and lipid changes. The trial was designed to have 80% power at $p<0.05$ to detect a 32% risk reduction with atorvastatin based on 1.8% annual event rate, using intention to treat analysis. Cox regression stratified by centre, Fisher's exact test, Mann-Whitney test or Kendall's tau-b were used for analysis, as appropriate.

Results: Trial duration: August 2007-December 2012. 2986 patients from 102 centres were randomised and followed for a median of 2.53 years (IQR 1.94-3.50), providing 7,908 patient-years of follow-up. Atorvastatin and placebo groups did not differ at baseline for age, sex, weight, BMI, RA duration, activity, severity and seropositivity, blood pressure, lipid and glucose levels, family history of CVD or diabetes. Current smoking was higher in the atorvastatin group (18.4% vs 14.5%, $p=0.019$) and there were also significant differences in NSAID use, ethnicity and EQ5D. Reduction in LDL-c levels was significantly greater in the atorvastatin group compared to placebo (-1.07 vs - 0.14 mmol/l, $p<0.001$); the magnitude of LDL-c reduction reflected reported compliance. In the atorvastatin group 24 patients had a CVD event, compared to 36 in the placebo (hazard ratio 0.66, 95% confidence interval 0.39-1.11, $p=0.119$). After adjustment for baseline differences, compliance and non-study statin use, hazard ratio was 0.54 (0.30-0.99), $p=0.045$. Number and type of any reported adverse events were similar: 294(19.7%) in the atorvastatin and 292(19.5%) in the placebo group, $p=0.927$. Due to a lower (0.76% pa) than anticipated event rate, the trial was terminated early.

Conclusion: Treatment with Atorvastatin 40mg daily resulted in significantly greater reduction of LDL-c compared to placebo. The 34% (unadjusted) risk reduction for a major CVD event compared to placebo, although not statistically significant due to early termination of the trial, is in line with the Cholesterol Treatment Trialists' Collaboration meta-analysis of the effect of statins in other populations. Statin therapy was safe in patients with RA.

Disclosure: G. D. Kitas, None; **P. Nightingale**, None; **J. Armitage**, None; **N. Sattar**, AstraZeneca, Sanofi, Merck, Amgen, 5; **J. Belch**, None; **D. P. M. Symmons**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/trial-of-atorvastatin-for-the-primary-prevention-of-cardiovascular-events-in-patients-with-rheumatoid-arthritis

Abstract Number: 2127

Exploring the Lipid Paradox Theory in Rheumatoid Arthritis: Subclinical Coronary Atherosclerosis Is Higher Among Rheumatoid Arthritis Patients with the Lowest Circulating Low Density Lipoprotein Concentrations Compared with Controls

Jon T. Giles[1], Mary Chester M. Wasko[2], Cecilia P. Chung[3], Amy Kao[4], Sabahat Bokhari[5], Afshin Zartoshti[6], C. Michael Stein[7] and Joan M. Bathon[8,9], [1]Division of Rheumatology, Columbia University, College of Physicians & Surgeons, New York, NY, [2]West Penn Allegheny Health System, Temple University School of Medicine, Pittsburgh, PA, [3]Division of Rheumatology & Immunology, Vanderbilt University School of Medicine, Nashville, TN, [4]Biogen, Cambridge, MA, [5]Cardiology, Columbia University Medical Center, NY, NY, [6]Rheumatology, Columbia University Medical Center, NY, NY, [7]Div of Clinical Pharmacology, Vanderbilt University, Nashville, TN, [8]Medicine, Columbia University, College, New York, NY, [9]Rheumatology, Columbia University College of Physicians & Surgeons, New York, NY

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Background/Purpose: Several recent studies have identified RA patients with very low levels of circulating total and low density lipoprotein cholesterol (LDL-C) to be at particularly high risk for cardiovascular disease (CVD) events. However, it is unknown whether coronary atherosclerosis is higher than expected among those with low lipid levels.

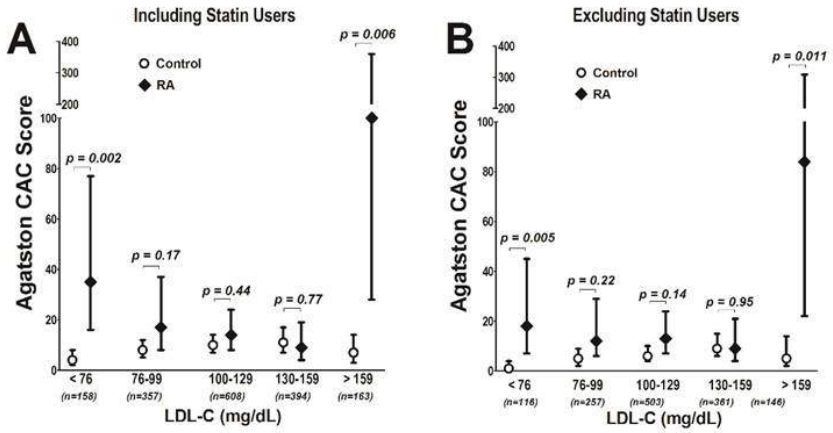
Methods: Data were pooled from 4 U.S. cohorts of RA patients and a compatible cohort of non-RA controls who all underwent similar assessments of serum lipids and coronary atherosclerosis [cardiac computed tomography scanning with coronary arterial calcium (CAC) calculated using the Agatston method]. Patients with prior known CVD were excluded. CAC scores according to strata of serum lipids were compared between the RA and control groups using multivariable (MV) linear regression, adjusting for pertinent confounders. The lowest stratum of LDL-C was defined at<76 mg/dL. Analyses were repeated excluding lipid lowering medication (LLM) users.

Results: A total of 629 RA patients and 1,073 non-RA controls were studied. Adjusting for unbalanced demographics, on average, the RA group had significantly lower BMI and waist circumference, higher systolic and diastolic blood pressures, more NSAID use and less use of aspirin. Smoking, diabetes, and HDL-C were similar between the groups. Mean total cholesterol did not differ for RA vs. control (193 vs 194 mg/dL, respectively; p=0.73); however, mean LDL-C was lower in the RA group (114 vs. 118 mg/dL; p=0.031). A higher proportion of RA patients had LDL-C<76 mg/dL (13 vs 8%; p=0.004), even when excluding LLM users (11 vs 7%; p=0.023). Adjusting for demographics, moderate/severe CAC (i.e. CAC≥100 units) was observed in 30% of the RA group compared with only 18% of controls (p<0.001).

In controls, the lowest average adjusted CAC scores were observed in those with a LDL-C<76 mg/dL. In contrast, average CAC scores were nearly 9-fold higher for RA patients in the same LDL stratum (p=0.002; Panel A). Absolute differences between the groups were diminished after excluding LLM users; however, RA patients with the lowest and highest LDL-C levels still had significantly higher CAC compared with controls. Similar relationships were observed for strata of total cholesterol. RA patients with LDL-C<76 mg/dL and not taking LLM were less likely to be RF positive and more likely to be prescribed hydroxychloroquine compared with those with higher LDL-C. They did not differ on disease duration, disease activity measures, or treatment with other DMARDs or prednisone.

Conclusion: These data suggest that RA patients with very low LDL-C may be candidates for heightened CVD screening and prevention

Figure. Adjusted* Coronary Arterial Calcium Scores According to RA Status and Strata of LDL-C



Graphs depict means and 95% confidence intervals for 629 RA patients and 1,073 non-RA controls (panel A), and 543 RA patients and 855 non-RA controls (panel B)
** Adjusted for Age, Gender, Race, Waist Circumference, Smoking, Diabetes, Hypertension, HDL-C, and Aspirin Use*

Disclosure: J. T. Giles, None; **M. C. M. Wasko**, None; **C. P. Chung**, None; **A. Kao**, Biogen, 1; **S. Bokhari**, None; **A. Zartoshti**, None; **C. M. Stein**, None; **J. M. Bathon**, None.

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Abstract Number: 2128

The Role of Insulin Resistance in the Development of Premature Atherosclerosis in Patients with Rheumatoid Arthritis

Gorica Ristic[1], Vesna Subota[2], Toplica Lepic[3], Dejana Stanisavljevic[4], Branislava Glisic[1], Milan Petronijevic[1], Arsen Ristic[5] and Dusan Stefanovic[1], [1]Department of Rheumatology and Clinical Immunology, Military Medical Academy, Belgrade, Serbia,

[2]Institute of Medical Biochemistry, Military Medical Academy, Belgrade, Serbia, [3]Department of Neurology, Military Medical Academy, Belgrade, Serbia, [4]Institute of Medical Statistics, Belgrade University School of Medicine, Belgrade, Serbia, [5]Department of Cardiology, Clinical Center of Serbia & Belgrade University School of Medicine, Belgrade, Serbia
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Session Time: 4:30PM-6:00PM

Background/Purpose: Accelerated atherosclerosis in rheumatoid arthritis (RA) is well established but the role of insulin resistance in RA pts without diabetes or metabolic syndrome remains to be determined. Therefore, the aim of our study was to investigate the prevalence of insulin resistance in RA pts with normal glycoregulation and its association with carotid intima-media thickness (IMT) and therapy exposure.

Methods: Our study population included 90 RA pts (age 52.4±9.9 yrs, 86.7% females, disease duration 9 yrs, range 4-13). We determined body mass index (BMI), waist circumference (WC), blood pressure, smoking habits, and disease activity score (mDAS28-SE). IMT was measured bilaterally, at common carotid (CCA), bifurcation (BF), and internal carotid arteries (CI). All pts were treated with disease modifying antirheumatic drugs, 65.6% were on steroids (<10 mg/day), and 27.8% were on biological therapy. IR was calculated using the updated-computer Homeostasis Model Assessment (HOMA2-IR), based on fasting plasma glucose and serum specific insulin concentrations (measured by ELISA). Insulin resistance was defined as HOMA2-IR>1.

Results: Insulin resistance was detected in 74.4% of pts with median value of 1.4 (range 1.0-2.3). Pts with insulin resistance compared to those without this condition had increased IMT (mm) at all levels of carotid arteries. CCA_{max}: 0.841±0.144 vs. 0.762±0.105 (p=0.018); CCA_{mean} 0.740±0.129 vs. 0.653±0.097, p=0.004; BF_{max}: 1.059±0.169 vs. 0.920±0.124, p=0.001; BF_{mean}: 0.908±0.141 vs. 0.782±0.126, p=0.000; CI_{max}: 0.678±0.085 vs. 0.620±0.121, p=0.014; CI_{mean}: 0.599±0.077 vs. 0.553±0.091, p=0.020. Both groups were comparable regarding RA duration and anti-inflammatory treatment including glycocorticoids. In multivariate logistic regression adjusted for age, BMI, WC, and triglycerides we found that statistical significance disappeared for CCA and CI but stil persisted for BF (e.g. for age BF_{max} β coef. 4.479, p=0.030; BF_{mean}: β coef. 6.516, p=0.017). In univariant regression analysis, we revealed predictive value of logHOMA2-IR for IMT BF_{max}: β coef. 0.253, p=0.001; BF_{mean}: β coef. 0.178, p= 0.006; CI_{max}: β coef 0.097 p=0.026; while for other levels statistical significance was borderline (for CI_{mean} and CCA_{mean}p=0.052, and for CCAmax p=0.064). On the other hand we found significant association of logHOMA2-IR with disease activity: DAS28 β coef 0.034, p=0.037.

Conclusion: RA pts with insulin resistance had significantly increased carotid IMT at all evaluated levels. Significant difference persisted for carotid BF even after adjustment for well known risk factors for atherosclerosis. Significant association of insulin resistance and disease activity may indicate the important role of RA itself in the interplay of IR and atherosclerosis.

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Abstract Number: 2129

Treatment-Naïve, Early Rheumatoid Arthritis Patients Demonstrate Abnormalities of Vascular and Myocardial Function on Cardiac MRI

Bara Erhayiem[1], Adam McDiarmid[1], Peter Swoboda[1], Ananth Kidambi[1], David Ripley[1], Tarique Musa[1], Laura Dobson[1], Pankaj Garg[1], Sarah Horton[2], Raluca Dumitru[3], Jacqueline Andrews[4], John Greenwood[5], Paul Emery[4,6], Sven Plein[1] and **Maya H. Buch**[2,7], [1]Leeds Institute of Cardiovascular And Metabolic Medicine, University of Leeds, Leeds, United Kingdom, [2]Leeds Institute of Rheumatic & Musculoskeletal Medicine, University of Leeds, Leeds, United Kingdom, [3]University of Leeds, Leeds

Institute of Molecular Medicine and LMBRU, Leeds, United Kingdom, [4]NIHR-Leeds Musculoskeletal Biomedical Research Unit and Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds, Leeds, United Kingdom, [5]Leeds Institute of Cardiovascular And Metabolic Medicinee, University of Leeds, Leeds, United Kingdom, [6]Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds, Leeds, United Kingdom, [7]NIHR - Leeds Musculoskeletal Biomedical Research Unit, Leeds, United Kingdom

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Session Type: ACR Concurrent Abstract Session

Session Time: 4:30PM-6:00PM

Treatment-na•ve, early rheumatoid arthritis patients demonstrate abnormalities of vascular and myocardial function on cardiac MRI

B Erhayiem, A McDiarmid, PP Swoboda, A Kidambi, DP Ripley, TA Musa, LE Dobson, P Garg, S Horton, R Dumitru, J Andrews, JP Greenwood, P Emery, S Plein, MH Buch

Background/Purpose:Cardiac studies of patients with rheumatoid arthritis (RA) have demonstrated abnormalities in left ventricular (LV) remodelling that is associated with development of heart failure and cardiovascular morbidity/mortality. No studies have evaluated changes in LV myocardial and vascular function in treatment-na•ve early RA (ERA). We evaluated whether patients with treatment-na•ve ERA demonstrate myocardial and vascular changes on cardiac MRI (CMR) compared with matched controls.

Methods: Eighty ERA patients (ACR/EULAR classification criteria) without CVD history underwent 3.0T CMR at a dedicated cardiology-CMR unit. Patient eligibility: symptoms for less than 1 year, DMARD treatment-na•ve, minimum disease activity score (DAS28) ³ 3.2. Thirty healthy controls were matched by age, sex and blood pressure. CMR protocol determined aortic distensibility (AD), LV dimensions, ventricular performance, strain analysis and extracellular volume (ECV; associated with diffuse myocardial fibrosis).

Results: Patients in ERA and control groups were of similar mean(SD) age [49.4(13.08) and 50(15) respectively, p=0.67] and systolic BP [123(16) and 120(13) respectively, p=0.43]. Median(IQR) ESR, CRP and mean(SD) DAS28 were 31(31)mm/hr, 8(23)mg/L and 5.6(1.5) respectively. 66(85%) and 59(76%) patients were ACPA and RF positive respectively. 17(21%) and 4913%) were current smokers in the ERA and control groups respectively.

Table 1 details CMR parameters. Aortic distensibility was significantly reduced in ERA patients compared to controls (median ±IQR, 3.3±2.15 $10^{-3}mmHg^{-1}$ versus 4.7±2.0 $10^{-3}mmHg^{-1}$, $p<0.001$). Other measures of arterial stiffness showed similar significant differences. Significant change in LV geometry was observed with lower LVmass index in the ERA group compared with controls. Significantly greater ECV and lower T1 were also recorded in the ERA group. Evidence for overt inflammation/fibrosis was seen in 6 patients with areas of focal non-ischaemic patterns of LGE.

Conclusion: This is a first CMR study on treatment-naive ERA patients that demonstrates abnormalities in vascular function, myocardial tissue composition and LV geometry; associated with poorer outcomes. These observations highlight presence of CV risk at the earliest stages of RA. Further investigation will determine the natural history including whether effective therapy can modulate these abnormalities.

Table 1: CMR findings between RA patients and controls. *Data presented as mean±SD unless otherwise stated. ECV=extra-cellular volume, EDV=End-diastolic volume, EF=Ejection fraction, LGE=Late-gadolinium enhancement, LV=Left ventricle*

Measurement	ERA n = 80	Control n = 30	p-value
Aortic distensibility, $10^{-3}mmHg^{-1}$	3.3± 1.5	4.7±2.0	**<0.001**
Aortic compliance	11.8±4.4	19.1±7.1	**<0.001**
Aortic strain	-0.17± -0.07	-0.25± -0.09	**<0.001**
Aortic stiffness index, μ	4.2±2.3	2.7±0.8	**<0.001**
LVEDV, ml	148±34	154±31	0.413
LVEF, %	60±5	62±5	0.126
LV Mass, g	82±23	95±19	**0.007**
LV Mass/LVEDV, g/ml	0.56±0.11	0.62±0.10	**0.005**
RVEDV, ml	159±42	178±42	**0.033**
RVEF, %	54±5	54±6	0.947
LGE, n (%)	6 (8)	1 (3)	0.671
Native T1, ms	1184±43	1202±35	**0.042**
ECV, %	27.3±3.8	25.1±2.7	**0.004**

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Abstract Number: 2130

Primary Prevention of Myocardial Infarction in Rheumatoid Arthritis Using Low-Dose Aspirin: A Case-Crossover Study

Josefina Durán Santa Cruz[1], Yuqing Zhang[2] and David T. Felson[3], [1]Department of Rheumatology, Pontificia Universidad Católica de Chile School of Medicine, Santiago, Chile, [2]Clinical Epidemiology and Training Unit, Boston University School of Medicine, Boston, MA, [3]Clinical Epidemiology Research and Training Unit, Boston University School of Medicine, Boston, MA
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Session Time: 4:30PM-6:00PM

Background/Purpose:

Subjects with rheumatoid arthritis (RA) are at a higher risk of developing cardiovascular (CV) disease which is the leading cause of death in subjects with RA. In the general population, there is unequivocal evidence supporting ASA as secondary prophylaxis for CV events, but its efficacy as primary prevention has been questioned. There is currently no consensus regarding use of ASA as primary prophylaxis and it is necessary to identify if its use is justified in particular risk profile groups. We performed a case-crossover study in RA subjects, to evaluate if a protective association exists between ASA use and myocardial infarction (MI).

Methods:

THIN, a population-based UK database, containing data provided from general practitioners was used. We included records

between 1/1/1995 and 9/30/2013. In the UK persons over age 60 get free ASA by prescription and 75% of use is by prescription. Subjects >60 years with RA, defined as one RA read code and one DMARD code within a year, constituted our study population. We excluded all subjects with history of MI, angina prior to study initiation or a coronary artery procedure (stent/coronary artery bypass graft) prior to the index date. To be included subjects had to have an incident MI/angina or a fatal MI. Each subject contributed two observations: a “case observation” and a “control observation”. For "case observations”, the index date was the MI/angina date. For "control observations”, the control date was 90 days prior to the index date. An individual was considered exposed if he/she used ASA within 7 days prior to the index date/control date. In addition, we examined effect of ASA use within 15 and zero days prior to the event. A conditional logistic regression was performed adjusting for drugs that are potential confounders (antiaggregants-anticoagulants, antihypertensives, NSAIDS, lipid-lowering drugs, glucocorticoids, nitrates). A sensitivity analysis was performed looking at males. As a secondary outcome we looked at MI and fatal MI.

Results:

We identified 705 RA patients who experienced incident MI/angina during the study period. The characteristics of the study subjects are described in Table 1. During the case period 192 subjects were exposed to ASA and during the control period 156 subjects were exposed, with 96 discordant exposure statuses within a subject in the two observation periods. There was no significant association between ASA use and CV events after adjusting for potential confounders (1.20 (0.73, 1.96)). When analysis was restricted to men, we again found no association was present (adjusted OR 1.12 (0.49, 2.52)). Findings were similar when considering MI as our outcome and when restricting exposure to 15 and zero days prior to the index date.

Conclusion:

This study suggests ASA is not effective in RA as primary prophylaxis.

Table 1. Study population characteristics.

Subjects (n)		705
Age (years, SD)		72.6 +- 7.2
Female		400 (56.7%)
Atrial Fibrillation		71 (10.1%)
Chronic Kidney Disease		103 (14.6%)
COPD		80 (11.3%)
Diabetes		114 (16.2%)
Dyslipidemia		79 (11.2%)
Hypertension		355 (50.4%)
Peripheral Vascular Disease		41 (5.8%)
Stroke		65 (9.2%)
AntiHypertensives		487 (69.1%)
Antiagregants/Anticoagulants		90 (12.8%)
Glucocorticoids		314 (44.5%)
Lipid-Lowering Drugs		215 (30.5%)
Nitrates		150 (21.3%)
NSAIDS		393 (55.7%)
Alcohol	non-drinker	168 (23.8%)
	ex-drinker	22 (3.1%)
	current drinker	438 (62.1%)
	missing	77 (10.9%)
BMI (continuous, kg/m^2)		27.0 +- 4.8
BMI (categorical)	underweight	27 (3.8%)
	normal	155 (22.0%)
	overweight	219 (31.1%)
	obese	125 (17.7%)
	missing	179 (25.4%)
GP visits		10 +- 13
Hospital visits		1 +- 1
RA Duration (years, SD)		6.4 +- 4.6
Smoking	non-smoker	284 (40.3%)

ex-smoker	253 (35.9%)
current smoker	138 (19.6%)
missing	30 (4.3%)

Disclosure: J. Durán Santa Cruz, None; **Y. Zhang**, None; **D. T. Felson**, None.

Abstract Number: 2131

Younger Age and Female Gender Are the Main Determinants of Underestimation of Cardiovascular Risk in Rheumatoid Arthritis Patients

Calin Popa[1,2], Alexander Rennings[3], Alfons A. den Broeder[4], Frank H.J. van den Hoogen[4], Inger L. Meek[1] and Jaap Fransen[1], [1]Rheumatology, Radboud University Nijmegen Medical Centre, Nijmegen, Netherlands, [2]Rheumatology, Bernhoven Hospital, Uden, Netherlands, [3]Internal Medicine, Radboud University Nijmegen Medical Centre, Nijmegen, Netherlands, [4]Rheumatology, Sint Maartenskliniek, Nijmegen, Netherlands

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Background/Purpose: Rheumatoid arthritis (RA) patients have an increased cardiovascular (CV) risk. Current algorithms generally underestimate the risk in these patients [1]. In a meta-analysis, we have recently shown that younger RA patients bare the highest excess risk as compared to age-matched counterparts from the general population [2]. *Objective:* To investigate whether gender and age are contributing to the misclassification of CV risk in RA patients, when current risk algorithms developed for the general population are used.

Methods: Prospectively collected data on cardiovascular risk factors and incident events from the Nijmegen inception cohort were analyzed, with up to 10 years follow-up [1]. Original as well as the EULAR modified (M_) SCORE algorithms were used to calculate the CV risk. Patients were stratified in deciles according to increasing risk and Hosmer-Lemeshow test was used to check concordance between observed and predicted risk, in subgroups based on gender and age.

Results: 863 prospectively followed RA patients were included in the analysis, 566 females and 297 males. During the first 10 years of follow-up 128 incident cardiovascular events had been recorded. In the whole group there was evidence of discrepancy between the predicted and observed CV risk (H-L test $p<0.003$) when the SCORE algorithm was applied. This mismatch was also present in the female subgroup (H-L test $p<0.001$), but it was less pronounced in males (H-L test $p=0.09$). Among the group of women who developed an event 40% had a predicted risk lower than 10% (corresponding to the low-risk group), whereas this was just 14 % in the RA males. When analyzing sub groups based on age, the H-L test p-values were: <55 years $p<0.001$, between 55 – 65 years $p=0.93$ and >65 years $p=0.96$. The discrepancy between observed and predicted CV events in the youngest RA patients consisted mainly of underestimation of the CV risk (5.3% predicted vs. 8.0% observed). Similar results were obtained when the M_SCORE was applied.

Conclusion: We report here in prospectively followed RA patients that CV risk is especially underestimated in women and younger patients. This suggests that modifying the weight for female gender and/or younger age in currently used CV risk algorithms might improve their predictive value in RA, contributing to better CV risk management in this group of patients.

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Disclosure: C. Popa, None; **A. Rennings**, None; **A. A. den Broeder**, None; **F. H. J. van den Hoogen**, None; **I. L. Meek**, None; **J. Fransen**, None.

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Abstract Number: 2132

Monocarboxylate Transporter 4, Associated with the Acidification of Synovial Fluid, Is a Novel Therapeutic Target for Inflammatory Arthritis

Wataru Fujii[1], Eishi Ashihara[2], Hidetake Nagahara[3], Yuji Kukida[1], Takahiro Seno[1,4], Aihiro Yamamoto[1], Masataka Kohno[1], Ryo Oda[5], Daigo Taniguchi[6], Hiroyoshi Fujiwara[5], Tsunao Kishida[7], Osam Mazda[7] and Yutaka Kawahito[1], [1]Inflammation and Immunology, Graduate School of Medical Science, Kyoto Prefectural University of Medicine, Kyoto, Japan, [2]Department of Clinical and Translational Physiology, Kyoto Pharmaceutical University, Kyoto, Japan, [3]Department of Inflammation and Immunology, Graduate School of Medical Science, Kyoto Prefectural University of Medicine, Kyoto, Japan, [4]Department of Rheumatic Diseases and Joint Function, Graduate School of Medical Science, Kyoto Prefectural University of Medicine, Kyoto, Japan, [5]Department of Orthopaedics, Graduate School of Medical Science, Kyoto Prefectural University of Medicine, kyoto, Japan, [6]Department of Orthopaedics, Graduate School of Medical Science, Kyoto Prefectural University of Medicine, Kyoto, Japan, [7]Department of Immunology, Graduate School of Medical Science, Kyoto Prefectural University of Medicine, Kyoto, Japan

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Background/Purpose: Synovial fluid pH is decreased in patients with rheumatoid arthritis (RA); however, the underlying mechanisms are unclear. Here, we examined the mechanism by which synovial fluid pH is regulated and explore the therapeutic strategy by manipulating this mechanism.

Methods: The pH and lactate concentration in synovial fluid from RA and osteoarthritis (OA) patients were determined. Cultured synovial fibroblasts (SFs) from the inflamed joints of patients with RA (RASFs) were examined for the expression of ion transporters that regulate intracellular and extracellular pH. The ion transporter up-regulated in RASF lines was then suppressed in RASFs by small interfering RNA (siRNA) and the effect of transfection on viability and proliferation was investigated. Finally, we examined the therapeutic effect of electro-transfer of *MCT4*-specific siRNA into the articular synovium of collagen-induced arthritis (CIA) mice.

Results: The synovial fluid from RA patients had significantly lower pH ($p < 0.01$) and higher lactate values ($p < 0.05$), respectively, than the synovial fluid from OA patients (Figure 1A). Synovial fluid pH correlated inversely with both the patient disease activity score (DAS)-28 CRP ($r = -0.51$, $p < 0.05$, Figure 1B) and synovial fluid lactate levels ($r = -0.71$, $p < 0.01$, Figure 1C). RASFs exhibited up-regulated transcription of monocarboxylate transporter (*MCT*) 4 mRNA. MCT4 exports intracellular lactate into the extracellular space. RASFs had significantly higher MCT4 protein levels than osteoarthritis synovial fibroblasts. Knockdown of *MCT4* induced RASF apoptosis (Figure 2), thereby inhibiting their proliferation. Moreover, electro-transfer of *MCT4*-specific siRNA into the articular synovium of CIA mice significantly reduced the severity of arthritis ($p < 0.05$, Figure 3).

Conclusion: RA activity correlated with decreased synovial fluid pH. This may be due to increased MCT4 expression in RASFs.

Silencing MCT4 induced apoptosis in RASFs and reduced the severity of CIA, suggesting that MCT4 is a potential therapeutic target for inflammatory arthritis.

Figure 1

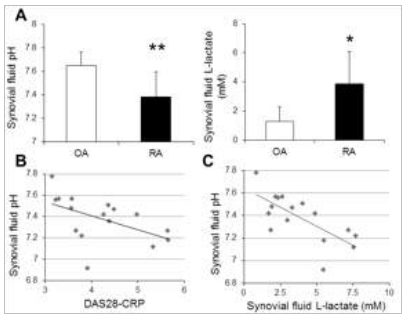


Figure 2

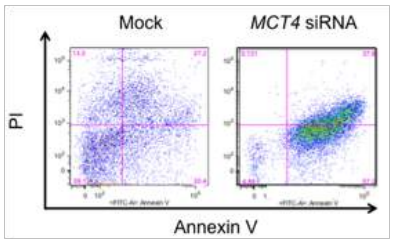
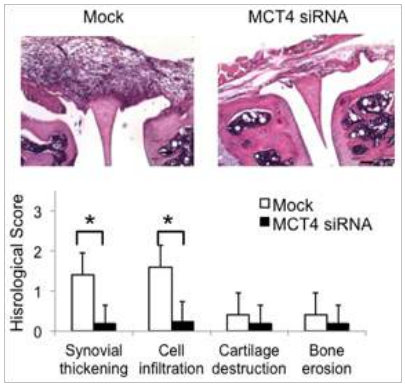


Figure 3



Disclosure: W. Fujii, None; **E. Ashihara**, None; **H. Nagahara**, None; **Y. Kukida**, None; **T. Seno**, None; **A. Yamamoto**, None; **M. Kohno**, None; **R. Oda**, None; **D. Taniguchi**, None; **H. Fujiwara**, None; **T. Kishida**, None; **O. Mazda**, None; **Y. Kawahito**, None.

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Abstract Number: 2133

Receptor Protein Tyrosine Phosphatase Alpha Enhances Rheumatoid Synovial Fibroblast Signaling and Promotes Arthritis in Mice

Stephanie M. Stanford[1], Mattias N. D. Svensson[1], Cristiano Sacchetti[1], Caila A. Pilo[1], Dennis J. Wu[1], William B. Kiosses[2], Annelie Hellvard[3], Brith Bergum[3], German R. Aleman Muench[1], Christian Elly[1], Yun-Cai Liu[1], Jeroen den Hertog[4,5], Ari Elson[6], Jan Sap[7], Piotr Mydel[3], David L. Boyle[8], Maripat Corr[8], Gary S. Firestein[8] and Nunzio Bottini[1], [1]Cellular Biology, La Jolla Institute for Allergy and Immunology, La Jolla, CA, [2]The Scripps Research Institute, La Jolla, CA, [3]Clinical Science, Broegelmann Research Laboratory, Bergen, Norway, [4]Hubrecht Institute-Koninklijke Nederlands Akademie van Wetenschappen

and University Medical Center Utrecht, Utrecht, Netherlands, [5]Institute of Biology Leiden, Leiden, Netherlands, [6]Department of Molecular Genetics, Weizmann Institute of Science, Rehovot, Israel, [7]Epigenetics and Cell Fate, Université Paris Diderot Sorbonne Paris Cité, Paris, France, [8]Division of Rheumatology, Allergy and Immunology, University of California at San Diego School of Medicine, La Jolla, CA
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Background/Purpose: Rheumatoid arthritis (RA) fibroblast-like synoviocytes (FLS) promote disease pathogenesis by aggressively invading the joint extracellular matrix. The focal adhesion kinase (FAK) signaling pathway is emerging as a contributor to the anomalous behavior of FLS in this disease. Because the receptor protein tyrosine phosphatase α (RPTPα), encoded by the *PTPRA* gene, is a key promoter of FAK signaling, we investigated whether RPTPα mediates FLS aggressiveness and joint damage.

Methods: Through RPTPα knockdown with cell-permeable morpholino antisense oligonucleotides, we assessed RA FLS gene expression in response to tumor necrosis factor (TNF) and interleukin 1β (IL-1β) by quantitative PCR, invasion in transwell assays in response to platelet-derived growth factor (PDGF), and activation of signaling pathways by Western blotting of FLS lysates. Arthritis development was examined in mice lacking *Ptpra* using the K/BxN passive serum transfer model. The contribution of radiosensitive and radioresistant cells to disease was evaluated by reciprocal bone-marrow transplantation. Pharmacological inhibition of RPTPα activity was achieved using a novel cell-permeable peptide.

Results: We found that RPTPα was enriched in the RA synovial lining and expressed in RA FLS. Upon RPTPα knockdown, PDGF-induced invasion of RA FLS was decreased by 49±8% ($p<0.0001$, Mann-Whitney test). RPTPα knockdown in RA FLS also decreased TNF-induced expression of C-X-C motif chemokine 10 (*CXCL10*) and matrix metalloproteinase 13 (*MMP13*) by >80% ($p<0.001$, Mann-Whitney test), and decreased IL-1β-induced production of *IL6*, *MMP3* and *MMP13* by ≥50% ($p<0.0001$, Mann-Whitney test). These phenotypes correlated with >3-fold increase in phosphorylation of SRC on inhibitory Y527 and decreased phosphorylation of FAK on stimulatory Y397. Treatment of RA FLS with inhibitors of SRC and FAK mimicked the effect of RPTPα knockdown. *Ptpra*-deficient mice were protected from arthritis development (58±3% decrease in area under the curve [AUC] of ankle swelling, $p<0.0001$, paired t-test), which we confirmed to be due to radioresistant cells. Importantly, pharmacological inhibition of RPTPα activity decreased TNF-induced expression of *CXCL10* in RA FLS by 65±16% and reduced arthritis in mice (32±1% decrease in AUC of ankle swelling, $p<0.05$, paired t-test).

Conclusion: These data suggest that RPTPα mediates pro-inflammatory and pro-invasive signaling in RA FLS by regulating phosphorylation of SRC and FAK. We also find that knockdown or pharmacological inhibition of RPTPα significantly ameliorates arthritis in an FLS-dependent model of RA, suggesting that inhibition of RPTPα could be a novel therapeutic strategy to target the aggressiveness of FLS in RA.

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Abstract Number: 2134

Metabolic Reprogramming in the Inflamed Joint Inhibits Pro-Inflammatory Mechanisms

Monika Biniecka[1], Mary Canavan[1], Chin Teck Ng[2], Wei Gao[1], Thomas Smith[3], Trudy McGarry[4], Douglas J. Veale[5] and Ursula

Fearon[4], [1]St. Vincent's University Hospital, Centre for Arthritis and Rheumatic Diseases, Dublin Academic Medical Centre, Dublin, Ireland, [2]Department of Medicine, Faculty of Medicine, University of Malaya, Kuala Lumpur, Malaysia, [3]Department of Endocrinology, St Vincent's University Hospital, Dublin, Ireland, [4]St. Vincent's University Hospital, Centre for Arthritis and Rheumatic Diseases, Dublin Academic Medical Centre, Dublin 4, Ireland, [5]St Vincent's University Hospital, Centre for Arthritis and Rheumatic Diseases, Dublin Academic Medical Centre, Dublin 4, Ireland

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Session Time: 4:30PM-6:00PM

Background/Purpose: To examine the relationship between synovial hypoxia, cellular bioenergetics and mitochondrial dysfunction with synovial inflammation.

Methods: Primary RASFC were cultured with 3% hypoxia, DMOG (stabilizes HIF1α) or lactic acid. Reactive oxygen species (ROS), mitochondrial membrane potential (MMP) and mitochondrial mass (MM) were quantified using fluorescent probes, RASFC invasion by Transwell Matrigel™ chambers, and VEGF, bFGF by ELISA. Alterations in the synovial mitochondrial genome were assessed by Random Mutation Capture assay. RASFC metabolism was assessed by the XF24 Flux analyser (Seahorse) which quantifies real-time aerobic and anaerobic bioenergetic profiles. To examine if altered metabolism is also observed *in vivo*, 44 patients with active inflammatory arthritis underwent arthroscopy, clinical assessment and synovial tissue oxygen (tpO_2) measurements. Synovial microscopic levels of glycolysis and oxidative phosphorylation (GAPDH, PKM2, GLUT1, ATP), inflammation (CD3, CD68) and angiogenesis (FactorVIII/αSMA) were quantified by immunohistology. A subgroup of patients underwent contiguous MRI and PET/CT imaging. Finally we examined the effect by blocking glycolysis using a small molecule, 3-(3-pyridinyl)-1-(4-pyridinyl)-2-propen-1-one (3PO) (which blocks PFKFB3) in RASFC, human microvascular endothelial cells (HMVEC) and RA synovial explant cultures. Migration, angiogenesis, HIF1α activation and pro-inflammatory mediators were assessed using specific functional assays, western blot and ELISA.

Results: In RASFC, hypoxia induced increased mitochondrial DNA mutations, MM, MMP, ROS and invasion but inhibited ATP indicating altered cellular energy metabolism (all $p<0.01$). Hypoxia increased the rate of glycolysis with concomitant attenuation of mitochondrial respiration ($p<0.01$), decreased basal and maximal respiration ($p<0.01$) with a simultaneous induction in glycolytic cell activity ($p<0.001$). Hypoxia inhibited RASFC glucose secretion ($p<0.05$) and increased lactate levels ($p<0.05$). Lactic acid in turn, induced RASFC invasion and secretion of bFGF and VEGF. Elevated RASFC glycolysis was concurrent with *in vivo* assessments, with synovial expression of GAPDH, PKM2 and GLUT1 significantly higher in patients with tpO2 levels *in vivo*<20mmHg (all $p<0.05$), in contrast to ATP which was significantly lower ($p<0.05$). Glycolytic marker expression also correlated with increased macroscopic/microscopic vascularity and synovitis (all $p<0.05$). PET/MRI hybrid images demonstrated close association between metabolic turnover and site of inflammation with tpO2 levels *in vivo*. Finally 3PO significantly inhibited RASFC migration, HIF1α activation, angiogenesis and secretion of IL-6, IL-8, MCP-1 and ICAM-1 (all $p<0.05$).

Conclusion: Hypoxia alters cellular bioenergetics by down-regulating mitochondrial respiration and promoting a switch to glycolysis in the inflamed joint. This may enable synovial cells to generate sufficient ATP to support enhanced synovial proliferation, angiogenesis and pannus formation. Blockade of glycolysis may represent a potential therapeutic strategy for RA and other autoimmune diseases.

Disclosure: M. Biniecka, None; **M. Canavan**, None; **C. T. Ng**, None; **W. Gao**, None; **T. Smith**, None; **T. McGarry**, None; **D. J. Veale**, None; **U. Fearon**, None.

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Abstract Number: 2135

miRNA-223 Delivery to Synovial Fibroblasts Via Monocyte-Derived Extracellular Vesicles Promotes Their Proliferation

Florian M.P. Meier[1], Derek S. Gilchrist[1], Derek Baxter[2], Diane Vaughan[1], Margaret Mullin[3], David W. McCarey[4], Pawel Herzyk[5], Julie Galbraith[5], Donna McIntyre[1], Russka Shumnalieva[6], Ulf Müller-Ladner[7], Iain B. McInnes[8] and Mariola Kurowska-Stolarska[1], [1]Institute of Infection, Immunity and Inflammation, College of Medical, Veterinary and Life Sciences, University of Glasgow, Glasgow, United Kingdom, [2]Department of Rheumatology, University Hospital Ayr, Ayr, United Kingdom, [3]School of Life Sciences, University of Glasgow, Glasgow, United Kingdom, [4]Glasgow Royal Infirmary, Glasgow, United Kingdom, [5]Polyomics Facility, Institute of Molecular Cell and Systems Biology, University of Glasgow, Glasgow, United Kingdom, [6]Department of Internal Medicine, Clinic of Rheumatology, Sofia, Bulgaria, [7]Internal Medicine and Rheumatology, Justus-Liebig-University of Giessen, Kerckhoff-Klinik, Bad Nauheim, Germany, [8]Institute of Infection, Immunity and Inflammation, College of Medicine, Veterinary Medicine and Life Sciences, University of Glasgow, Glasgow, United Kingdom
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Background/Purpose: Recently, it was shown that extracellular vesicles (EV) convey microRNAs (miR) from platelets to endothelial cells[1]and regulate recipient cell gene expression. Interaction of synovial monocyte (MC)/macrophages with synovial fibroblasts (SF) is a key step to the inflammatory process in rheumatoid arthritis (RA). We hypothesised that MC/macrophage regulate SF behavior by delivering specific microRNA via EVs.

Methods: Characterization of EVs from human $CD14^+$MCs and THP-1 cells was performed using scanning electron microscopy (SEM, n=3), nanosight trafficking analysis (NTA, n=3-7); and flow cytometry (n>4) with predefined sized beads for gating. smallRNA sequencing was performed on macrophages (n=4) and RASFs (n=4) as well as on macrophage-derived EVs (n=4). Macrophages were differentiated by culturing peripheral blood (PB) $CD14^+$MCs from RA patients with M-CSF and either stimulated with LPS or not. In addition, matched RA PB and synovial fluid $CD14^+$ (n=8), PB $CD14^+$ from RA DMARD responders (n=16), DMARD non-responders (n=22), Biologic resistant (n=41), and age-matched healthy controls (n=21) were isolated and used for validation. (Pre-)miR-223 expression and copy number was quantified in cells or tissues via TLDA, qPCR & in situ hybridisation with specific primers and probes. Targeted pathways were identified using prediction algorithms (TargetScanHuman6.2). Transfer of miR-223 from MCs to SFs was determined by fluorescence microscopy, direct cell co-culture and FACS, as well as transwell co-culture. RASF Proliferation assays and IL-6 ELISAs served as read-out.

Results: SEM & NTA revealed a mean size of EVs from MCs & THP-1 cells of about 250nm (range 50-800nm). EV production was induced in myeloid cells by LPS ($p<0.05$). SmallRNA sequencing revealed high levels of miR-223 in macrophages as opposed to a lack of its expression in RASF. miR-223 levels were significantly higher in PB $CD14^+$ cells of DMARD responders compared to DMARD non-responders and Biologic resistant RA patients ($p<0.05$ and $p<0.01$). miR-223 levels in $CD14^+$ cells showed significant positive correlations to CDAI and SDAI. miR-223 was downregulated in synovial fluid MCs compared to matched PB controls ($p< 0.01$) and its expression was down-regulated in MCs/macrophages upon LPS stimulation. In contrast, EVs derived from LPS stimulated THP-1 cells contained higher levels of miR-223 suggesting stimulation driven packing of miR-223 into EVs. If co-cultured with MCs for 3d, RASF acquire miR-223 expression, but not pre-miR-223 to a significant extent (n=6, $C_t$values <30) confirming transfer of mature miR-223 between cells. Prediction algorithms identified FBXW7, a ubiquitin ligase targeting cyclin E, as a candidate target for miR-223 in RASF. Co-culture of RASF with THP-1-derived EV increased RASF proliferation (n=3, $p<0.05$). miR-223 transfection (25nM & 50nM) itself led to an increase of RASF proliferation after 72 and 96h (n=6-8, $p<0.01$ for all).

Conclusion: miR-223 transfer from MCs/macrophages to SFs by EVs during initial or chronic phases of synovial inflammation could promote SF proliferation and represent a novel intercellular mechanism underlying the pathogenesis of rheumatoid arthritis.

[1]Laffont, B. *et al. Blood* (2013)

Abstract Number: 2136

Identification of Synovial Fibroblast Subsets That Define Pathology in Rheumatoid Arthritis

Fumitaka Mizoguchi[1], Kamil Slowikowski[2,3], Sook Kyung Chang[1], Deepak A. Rao[4], Hung Nguyen[1], Erika H. Noss[5], Brandon E. Earp[6], Philip E. Blazar[6], John Wright[6], Barry P. Simmons[6], Nir Hacohen[7,8,9], Peter A. Nigrovic[1,10], Soumya Raychaudhuri[2,3,11] and Michael B. Brenner[1], [1]Division of Rheumatology, Immunology, and Allergy, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, [2]Divisions of Rheumatology and Genetics, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, [3]Medical and Population Genetics Program, Broad Institute of MIT and Harvard, Cambridge, MA, [4]Rheumatology, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, [5]Divison of Rheumatology, Immunology, and Allergy, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, [6]Department of Orthopedic Surgery, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, [7]Broad Institute of MIT and Harvard, Cambridge, MA, [8]Massachusetts General Hospital, Charlestown, MA, [9]Harvard Medical School, Boston, MA, [10]Division of Immunology, Boston Children's Hospital, Boston, MA, [11]Arthritis Research UK Centre for Genetics and Genomics, Centre for Musculoskeletal Research, Manchester Academic Health Science Centre, The University of Manchester, Manchester, United Kingdom

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Background/Purpose: Synovial fibroblasts play crucial roles in the pathogenesis of rheumatoid arthritis (RA). They expand as part of the pannus, mediate degradation of cartilage, amplify inflammation, and contribute to osteoclastogenesis. Considering these diverse roles of synovial fibroblasts, we hypothesized that synovial fibroblasts may consist of several subsets with distinct functions, contrary to the common view of fibroblasts as a homogeneous population. Here we sought to identify fibroblast subsets and to characterize subpopulations important in the pathology of RA.

Methods: Synovial cells were isolated by enzymatic digestion from surgical specimens from osteoarthritis (OA) and RA patients. Flow cytometry was used to separate freshly isolated fibroblasts into subpopulations based on the expression of several mesenchymal cell markers. In our initial analysis, nine fibroblast subpopulations were collected by cell sorting and subjected to further analysis by Affymetrix GeneChip Human Gene 2.0 ST microarray. To validate results, we applied low-input RNA-sequencing and single cell RNA-sequencing to independent samples. The functions of these fibroblast subsets were examined by several in vitro assays including the response to TNF stimulation and co-culture with macrophages.

Results: Freshly isolated synovial fibroblasts were divided into several subpopulations based on the expression patterns of fibroblast markers including podoplanin, cadherin11, CD90, CD34, and CD146. The analysis of gene expression microarray data revealed 2,986 genes with significant (1% FDR) variation across fibroblast subpopulations. An independent sample of RA donors, from different joints than the original samples, and assayed via RNA-seq, showed consistent variation of these genes across fibroblast subpopulations. Pathways enriched with this variation included extracellular matrix disassembly (P=7.51e-11) and the TNF signaling pathway (P=1.96e-6). We defined distinct functional cell populations by population-specific expression of genes with well-studied functions. For example, CD34+, CD90+, cadherin11+ cells highly expressed IL-6, CCL2 and CXCL12. CD34-, CD90+, cadherin11+ cells highly expressed TNFSF11. CD34-, CD90- cells highly expressed IL-8, CXCL1, MMP-1 and MMP-3. Differential expression of several genes that mediate distinct fibroblast functions was confirmed at the protein level after culturing cells in the presence or absence of TNF. Functionally, CD34+, CD90+, cadherin11+ cells skewed macrophages into anti-inflammatory phenotype. CD34-, CD90+, cadherin11+ cells promoted osteoclastogenesis. In RA synovial tissue, the proportion of CD34-, CD90+, cadherin11+ cells was increased compared to that in OA.

Conclusion: 1) Synovial fibroblasts are composed of several subsets that are distinct in surface phenotype, transcriptional programs, and functional effects on other cell types. 2) The heterogeneity of fibroblasts and the selective expansion of particular subsets are relevant to understanding RA pathology.

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Abstract Number: 2137

Critical Role of Fibroblast-like Synoviocytes Glycolytic Metabolism in Rheumatoid Arthritis

Ricard Garcia-Carbonell[1], Ajit Divakaruni[1], Alessia Lodi[2], Ildefonso Vicente-Suarez[3], Hilde Cheroutre[4], Gerry Boss[1], Arindam Saha[1], Stefano Tiziani[5], Anne Murphy[6], Gary S. Firestein[7] and **Monica Guma**[6], [1]University of California, San Diego, La Jolla, CA, [2]nutritional Sciences, University of Texas at Austin, Austin, TX, [3]LIAI, La Jolla, CA, [4]Autoimmune Research, LIAI, La Jolla, CA, [5]Nutritional Sciences, University of Texas at Austin, Austin, TX, [6]Pharmacology, University of California, San Diego, La Jolla, CA, [7]Division of Rheumatology, Allergy and Immunology, University of California, San Diego, La Jolla, CA
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Background/Purpose: Glucose metabolism is altered not only in tumor cell growth but also in immune cells on activation. However, little is known about glucose metabolism in fibroblast-like synoviocytes (FLS). We recently showed that a glycolysis inhibitor suppressed the aggressive behavior of cultured RA FLS, including proliferation, cytokine secretion and cell migration. Here, we further evaluated changes in glucose metabolism in both RA synovium and RA FLS and its role in inflammation and joint damage.

Methods: The glucose metabolism profile of synovium was determined by ^{1}H-MRS. Analysis of FLS oxygen consumption/extracellular acidification was determined by Seahorse technology. Effect of inflammatory mediators on the glycolytic rate in FLS was determined by Seahorse after LPS and PDGF stimulation. Glucose metabolism related gene expression was determined by qPCR. The increase of glycolysis in a murine model was determined using IRDye®800CW 2-DG, a fluorescent optical imaging agent that assesses glucose uptake, and by FACS. For arthritis experiments, the glycolysis inhibitor bromopyruvate (BrPa; 5mg/kg) was injected daily i.p. at the peak of arthritis in two murine models, passive K/BxN model (from day 5) and collagen induced arthritis (from day 35).

Results: Compared to osteoarthritis (OA), RA FLS had a higher baseline glycolytic rate, a decreased mitochondrial respiration and increased extracellular acidification after LPS stimulation. Intracellular lactate was also higher in RA synovium and several metabolites related to glucose metabolism correlated with lactate levels, suggesting higher glucose metabolism in RA synovium samples. Glucose transporter 1 (GLUT1) expression correlated with FLS baseline functions and her expression increased after LPS and PDGF stimulation. In a mouse model of inflammatory arthritis, we observed an increase of glucose uptake in arthritic joints and an increase of glucose uptake and glycolytic gene expression in the CD45-PDPN+ stromal cell compartment. Glycolytic inhibition by BrPa administered in vivo significantly decreased arthritis severity in both animal models.

Conclusion: Targeting metabolic dysfunction offers a novel approach of understanding the mechanisms of disease and potential new treatments. Glycolytic inhibition may directly modulate synoviocyte-mediated inflammatory functions and could be an

effective treatment strategy for arthritis.

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Abstract Number: 2138

Safety and Efficacy Results of a Phase 2, Double-Blind, Placebo-Controlled Clinical Study of Duvelisib with Background Methotrexate (MTX) in Adults with Moderate-to-Severe Rheumatoid Arthritis (RA)

Richard Leff[1], Sunil Kumar[2], Natalia Nikulenkova[3], Igor Kaidashev[4], Kerstin Allen[5], Joi Dunbar[6], Howard Stern[7], Julian Adams[6] and Michael Weinblatt[8], [1]Clinical Research, Infinity Pharmaceuticals, Inc., Cambridge, MA, [2]Centre for Clinical Research and Effective Practice (CCRep), Auckland, New Zealand, [3]State Budgetary Healthcare Institution of Vladimir Region, Regional Clinical Hospital, Vladimir, Russia, [4]City Clinical Hospital #1 of Poltava City, Poltava, Ukraine, [5]Biostatistics, Infinity Pharmaceuticals, Inc., Cambridge, MA, [6]Infinity Pharmaceuticals, Inc., Cambridge, MA, [7]Translational Science, Infinity Pharmaceuticals, Inc., Cambridge, MA, [8]Division of Rheumatology, Immunology and Allergy, Brigham and Women's Hospital, Boston, MA

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Background/Purpose: Duvelisib is a potent, oral, dual inhibitor of phosphoinositide-3-kinase (PI3K)-δ,γ being developed for hematologic malignancies, and was also explored in early phase studies in inflammatory diseases. PI3K-δ,γ isoforms are necessary for adaptive and innate immunity and have significant, non-overlapping roles in immune cell signaling. **Results** from several preclinical arthritis models and the inhibition of basophil activation in a healthy subject study supported duvelisib dosing between 0.5 and 5 mg twice daily (BID) in this study. The objective of this phase 2 study was to determine the safety and efficacy of duvelisib at 0.5, 1, and 5 mg BID in adults with moderate-to-severe RA while receiving background MTX.

Methods: Adults with active RA (≥ 5 swollen and tender joints, and CRP > 7 mg/L [1.4 x ULN]) on stable background MTX were randomized to 12 weeks of double-blinded treatment with placebo or duvelisib (0.5, 1, or 5 mg BID). The primary endpoint was the proportion of subjects who achieve an ACR20 at Week 12. Immunophenotyping analysis of B- and T-cell subtypes and pharmacokinetics (PK) and safety were also assessed.

Results: Of 322 subjects enrolled, 274 completed 12 weeks of treatment. Most subjects were female (83.2%) and white (93.5%). Median age was 54.5 (21-71) years. Median time since diagnosis of RA was 78.2 (4.1-522) months; 73% of subjects had Class II RA. Mean duration of MTX prior to study entry was 54.7 (±52.1) months. The primary endpoint (ACR20 at Week 12) was not met for any of the doses of duvelisib tested in this study (Table). Although statistically significant improvements in some secondary endpoints were noted, there were no large, consistent or dose-related improvements over placebo. For example, the DAS28-CRP mean changes from baseline were greater with 0.5 and 5 mg BID than placebo after 12 weeks, but with small absolute differences (Table). Duvelisib appeared to be generally well tolerated: overall, the majority of adverse events (AEs) were Grade 1 or 2 and reversible. The most frequent AEs more common in duvelisib than placebo during treatment were anemia, elevated ALT/AST, lymphopenia, nausea, nasopharyngitis, and headache. Treatment discontinuations of 6 patients on duvelisib 5 mg BID and 1 placebo patient were required per protocol; these patients, with normal baseline ALT/AST, had reversible elevations > 3 x ULN, with no significant elevation in bilirubin. A statistically significant, but small increase from baseline in mean absolute counts of peripheral blood B-cells and T-cells (CD4+ and CD8+) at week 2 was observed at 5 mg BID.

Table: ACR20 and DAS28-CRP at Week 12

	Treatment Group (patients)			
	Placebo	**0.5 mg BID**	**1 mg BID**	**5 mg BID**
	(n=80)	**(n=81)**	**(n=80)**	**(n=81)**
ACR20, n (%)	37 (46.3%)	42 (51.9%)	36 (45.0%)	35 (43.2%)
DAS28-CRP, LS mean change from baseline (SE)	-1.28 (0.148)	-1.66 (0.147)	-1.36 (0.144)	-1.68 (0.161)

Conclusion: The findings from this study indicated that in subjects with RA on background MTX duvelisib administered at 0.5, 1, and 5 mg BID had no added benefit over placebo. No new safety signals associated with duvelisib therapy were identified.

Disclosure: R. Leff, Infinity Pharmaceuticals, Inc, 5; **S. Kumar**, None; **N. Nikulenkova**, None; **I. Kaidashev**, None; **K. Allen**, Infinity Pharmaceuticals, Inc, 3; **J. Dunbar**, Infinity Pharmaceutical, Inc, 3; **H. Stern**, Infinity Pharmaceuticals, Inc., 3; **J. Adams**, Infinity Pharmaceuticals, Inc., 3; **M. Weinblatt**, Infinity Pharmaceuticals, Inc., 5.

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Abstract Number: 2139

Results of a Phase 1b/2a Study of the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of XmAb®5871 in Patients with Rheumatoid Arthritis (RA)

Debra Zack[1], Maria Jaraczewska Baumann[2], Mariusz Korkosz[3], Gabriella Suljok[4], Petr Sramek[5], Bernadette Rojkovich[6], Stafan Daniluk[7], Janos Bartalos[8] and Paul Foster[1], [1]Xencor, Inc., San Diego, CA, [2]NZOZ Centrum Medyczne HCP, Poznan, Poland, [3]Malopolskie Centrum Medyczne, The University Hospital in Krakow, Krakow, Poland, [4]Drug Research Center Ltd., Baltonfüred, Hungary, [5]PRA CZ, Praha, Czech Republic, [6]Polyclinic of the Hospitaller Brothers of St John of God, Budapest, Hungary, [7]NZOZ Center of Osteoporosis and Osteoarticular Diseases, Bialystok, Poland, [8]PRA Hungary Ltd, Budapest, Hungary
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Background/Purpose:

XmAb®5871 is a humanized Fc engineered monoclonal antibody that binds to the B cell restricted surface antigen CD19 and has enhanced Fc binding to the inhibitory Fcγ receptor IIb (FcγRIIb). Co-ligation of CD19 and FcγRIIb by XmAb5871 has been demonstrated to reversibly down-regulate B cell activity. XmAb5871 is in development for the treatment of B cell mediated autoimmune disorders. The primary objective of this study was to determine the safety, tolerability, PK, PD and immunogenicity profile of XmAb5871 in patients with active RA on stable non-biologic DMARD therapy. A secondary objective (Part B) was to evaluate the effect of XmAb5871 on RA disease response at Day 85 as measured by changes in DAS28-CRP.

Methods:

This multi-center, randomized, placebo-controlled, double-blinded, clinical study was conducted in patients with active RA despite DMARD therapy. All patients fulfilled ACR criteria for RA. Patients received 6 IV infusions of XmAb5871 or placebo (Pbo) on an every 14 day schedule. In Part A, 30 RA patients were randomized to Pbo or XmAb5871 in 4 consecutive dose cohorts of 0.3, 1, 3, or 10 mg/kg. After completion of Part A, 27 patients with active disease were enrolled in an extension cohort, Part B, to receive either 10 mg/kg XmAb5871 or Pbo in a 2:1 ratio. Disease efficacy assessments occurred 2 weeks after the 6thinfusion on Day 85.

Results: A total of 57 patients were randomized; 40 patients received at least 1 dose of XmAb5871. Peripheral B cell count decreased ~40% from baseline after the 1st dose in all XmAb5871 cohorts and did not decrease further with subsequent doses. XmAb5871 was generally well tolerated, with 2 SAEs in the XmAb5871 group (infusion-related reaction, venous thrombosis). The most common treatment-related adverse events in the XmAb5871 group were nausea, vomiting or diarrhea that occurred only during the 1st infusion in 25% of patients. Two subjects experienced infusion reactions with hypotension (both at 10 mg/kg) and were discontinued. The nature and severity of these infusion reactions were consistent with those reported for other monoclonal antibody therapies. In Part B, 15 XmAb5871-treated and 8 Pbo-treated patients were evaluable for disease activity assessment at Day 85. More subjects treated with XmAb5871 (10 mg/kg) achieved DAS28-CRP low disease or remission at Day 85 than did the Pbo treated subjects. Similar trends were seen with other disease assessments. Median ACR Hybrid scores over time were consistently greater in XmAb5871-treated patients than in Pbo-treated patients.

	Part B		All		
	10.0 mg/kg XmAb5871	Placebo	All 10.0 mg/kg XmAb5871	All Placebo Part A and B	All XmAb5871 Part A and B
Day 85	N=15	N=8	N=21	N=15	N=36
ACR20	13 (86.7%)	5 (62.5%)	18 (85.7%)	7 (46.7%)	28 (77.8%)
ACR50	6 (40.0%)	1 (12.5%)	9 (42.9%)	2 (13.3%)	12 (33.3%)
ACR 70	3 (20.0%)	0 (0.0%)	3 (14.3%)	0 (0.0%)	5 (13.9%)
ACR Hybrid Score Mean (SD)	48.1(27.1)	24.2(35.5)	45.8(24.7)	22.3(29.8)	42.2(24.5)
ACR Hybrid Score Median	50.0	27.6	50.0	20.0	44.4
DAS28-CRP Disease Activity					
High	2 (13.3%)	2 (25.5%)	2 (9.5%)	3 (20.0%)	4 (11.1%)
Moderate	8 (53.3%)	6 (75.0%)	10 (47.6%)	11 (73.3%)	17 (47.2%)
Low	2 (13.3%)	0 (0.0%)	4 (19.0%)	0 (0.0%)	6 (16.7%)
Remission	3 (20.0%)	0 (0.0%)	5 (23.8%)	1 (6.7%)	9 (25.0%)
EULAR Response					
No	2 (13.3%)	2 (25.0%)	3 (14.3%)	7 (46.7%)	5 (13.9%)
Moderate	8 (53.3%)	6 (75.0%)	9 (42.9%)	7 (46.7%)	17 (47.2%)
Good	5 (33.3%)	0 (0.0%)	9 (42.9%)	1 (6.7%)	14 (38.9%)

Conclusion:

XmAb5871 administered over 12 weeks was found to be generally well tolerated. Although the trial was not powered to show a significant difference in efficacy results between XmAb5871 and Pbo, sufficient efficacy trends were seen to warrant continued clinical development of XmAb5871 in autoimmune diseases.

Disclosure: D. Zack, Xencor, Inc., 3,Xencor Inc., 1; **M. Jaraczewska Baumann**, None; **M. Korkosz**, None; **G. Suljok**, None; **P. Sramek**, None; **B. Rojkovich**, None; **S. Daniluk**, None; **J. Bartalos**, None; **P. Foster**, Xencor Inc., 3,Xencor Inc., 1.

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Abstract Number: 2140

Drug Specific Risk and Associated Factors for Vasculitis-like Events in Patients Exposed to Tumour Necrosis Factor-Î± Inhibitor Therapy: Results from the

British Society for Rheumatology Biologics Register for Rheumatoid Arthritis

Meghna Jani[1], William G Dixon[2], Lianne Kearsley-Fleet[3], Ian N. Bruce[4,5], Hector Chinoy[6,7], Anne Barton[6,8], Mark Lunt[9], Kath Watson[3], Deborah P.M. Symmons[1], Kimme L. Hyrich[3] and on behalf of the BSRBR-RA, [1]Centre for Musculoskeletal Research, University of Manchester, Arthritis Research UK Centre for Epidemiology, Manchester, United Kingdom, [2]Manchester Academic Health Sciences Centre, Arthritis Research UK Centre for Epidemiology, The University of Manchester, Manchester, United Kingdom, [3]Arthritis Research UK Centre for Epidemiology, The University of Manchester, Manchester, United Kingdom, [4]Stopford Building, Arthritis Research UK Centre for Epidemiology, Centre for Musculoskeletal Research, Institute of Inflammation and Repair, Manchester Academic Health Science Centre, The University of Manchester, Manchester, United Kingdom, [5]Central Manchester University Hospital NHS Foundation Trust and Manchester Academic Health Science Centre, NIHR Manchester Musculoskeletal Biomedical Research Unit, Manchester, United Kingdom, [6]Centre for Musculoskeletal Research, University of Manchester, Manchester, United Kingdom, [7]NIHR Manchester Musculoskeletal Biomedical Research Unit, Manchester Academy of Health Sciences, Manchester, United Kingdom, [8]NIHR Manchester Musculoskeletal Biomedical Research Unit, Central Manchester Foundation Trust and University of Manchester, Manchester Academy of Health Sciences, Manchester, United Kingdom, [9]Arthritis Research UK Centre for Epidemiology, Manchester, United Kingdom

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Session Time: 4:30PM-6:00PM

Background/Purpose:

The association between TNF inhibitors (TNFis) and vasculitis-like events, possibly secondary to induction of autoantibodies, has been well reported. However, the incidence, drug-specific differences and factors associated have been poorly characterised. The aims of this study were to (i) compare the drug specific risk of vasculitis-like events in TNFi treated RA patients to those receiving non-biologic (nb)DMARDs and (ii) assess factors associated with the event.

Methods:

The British Society for Rheumatology Biologics Register for RA (BSRBR-RA) is a prospective cohort study assessing the safety of biologics. This analysis included two cohorts recruited between 2001-2014: (i) patients starting first TNFi (adalimumab, etanercept, infliximab, certolizumab) (ii) biologic-naïve comparison cohort receiving nbDMARDs. To calculate drug-specific risk biologic-naïve patients at baseline on first TNFi only were included. Additional information from consultants was sought for events. Patients with baseline systemic vasculitis were excluded. The risk of an event was compared between the two cohorts using Cox proportional-hazard models, adjusted using deciles of propensity scores (PD). Events were attributed to TNFi therapy if they occurred within 90 days of being on drug. Follow-up was censored at first event, switching to another biologic, death, last returned clinical follow-up or 30/11/2014, whichever came first. A sensitivity analysis was performed excluding patients who had a possible secondary vasculitis cause (e.g. infection), on other medications associated with vasculitis-like events or known baseline nailfold vasculitis.

Results:

There were 94 incident cases: 14 in 3640 nbDMARD patients and 80 in 12,385 first TNFi-treated subjects, with 19,681 and 49,678 patient years of follow up generating crude incidence rates of 7/10,000 and 16/10,000 person years respectively (Table). After adjusting for PD, the hazard ratio of vasculitis-like events in patients on TNFi vs. nbDMARD was 1.03 (95% CI 0.51-2.09). Drug specific hazard ratios were highest in the etanercept and infliximab patients, however following adjustment was not significant (Table). Factors associated with lower rates included baseline MTX use (HR 0.8, 95% CI 0.74-0.88), SSZ (HR 0.58, 95% CI 0.51-0.66) or LEF (HR 0.66, 95% CI 0.54-0.77). Other variables associated with the outcome included male gender (HR 1.49, 95% CI 1.01-2.21), baseline DAS28 score (HR 1.42, 95% CI 1.20-1.68), disease duration (HR 1.02, 95% CI 1.01-1.04 per year), RF+ status (HR 1.79 (95% CI 1.16-2.75) and baseline HAQ (HR 1.63, 95% CI 1.18-2.26).

Table. Patient characteristics and risk of first vasculitis-like event on first drug

	nbDMARD (n=3640)	TNFi (n=12,385)	Infliximab (n=3,285)	Adalimumab (n=4,230)	Etanercept (n=4,306)	Certolizumab (n=564)
Age, mean (SD)	60 (12)	56 (12)	55 (12)	56 (12)	56 (12)	56 (12)
Follow up per subject, years: median (IQR)	6.0(3-8)	5.3 (2-8)	4.9 (2-9)	5.3 (2-7)	6.3 (3-9)	1.4 (1-2)
Main analysis: Risk of vasculitis-like events between nbDMARD and TNFi (all vasculitis events)						
Number of vasculitis-like events, n	14	80	26	17	37	0
Crude incidence rate of vasculitis-like events per 10, 000 person-years (95%-CI)	7 (4-12)	16 (13-20)	20 (14-30)	10 (6-16)	18 (13-25)	-
Unadjusted hazard ratio (95%-CI)	Referent	2.13 (1.21-3.77)*	2.66 (1.41-5.01)*	1.52 (0.78-2.96)	2.91 (1.60-5.29)*	-
Age- and gender adjusted hazard ratio (95%-CI)	Referent	2.33 (1.31-4.14)*	2.89 (1.50-5.49)*	1.64 (0.80-3.20)	3.27 (1.75-5.9)*	-
Propensity score adjusted hazard ratio (95%-CI) †	Referent	1.03 (0.51-2.09)	1.18 (0.54-2.56)	0.84 (0.39-1.77)	1.37 (0.64-2.79)	-
Sensitivity analysis (excluding events with possible secondary trigger)						
Number of vasculitis-like events, n (%)	13	67	22	16	29	0
Crude incidence rate of vasculitis-like events per 10, 000 person-years (95%-confidence interval)	6 (3-11)	13 (10-17)	18 (12-27)	10 (6-16)	14 (10-20)	-
- Unadjusted	Referent	1.93 (1.06-3.51)*	2.47 (1.26-4.82)*	1.56 (0.78-3.12)	2.31 (1.22-4.37)*	-

hazard ratio (95%-CI)						
- Age- and gender adjusted hazard ratio (95%-CI)	Referent	2.07 (1.13-3.78)*	2.64 (1.34-5.19)*	1.66 (0.83-3.34)	2.51 (1.31-4.78)*	-
- Propensity score adjusted hazard ratio (95%-CI) †	Referent	0.89 (0.42-1.86)	1.04 (0.46-2.36)	1.01 (0.46-2.19)	0.8 (0.37-1.77)	-

* $p<0.05$

† Fully adjusted model by propensity score consisting of age, gender, year of recruitment, DAS28, disease duration, rheumatoid factor, HAQ, steroid use, baseline DMARD use, smoking and comorbidities score

Conclusion:

In this large UK study, the absolute risk of vasculitis-like events in both groups was low. There were no significant differences in risk between TNFi agents after adjustment. Baseline use of MTX, SSZ and LEF were associated with lower rates.

Disclosure: M. Jani, Pfizer Inc, 8,Abbvie, UCB, 5; **W. G. Dixon**, None; **L. Kearsley-Fleet**, None; **I. N. Bruce**, Bristol-Myers Squibb, 2; **H. Chinoy**, Novartis, Janssen, Pfizer, UCB, Abbvie, Celgene, Servier, Roche, MSD, and aTyr, 5,Novartis, Janssen, Pfizer, UCB, Abbvie, Celgene, Servier, Roche, MSD, and aTyr, 2; **A. Barton**, Eli-Lilly, Pfizer, Abbvie, 2; **M. Lunt**, None; **K. Watson**, None; **D. P. M. Symmons**, None; **K. L. Hyrich**, None.

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Abstract Number: 2141

Risk of Cancer in Non-TNFi Biologics-Treated RA

Hjalmar Wadström[1], Johan Askling[2] and the ARTIS study group, [1]Clinical Epidemiology Unit, Department of Medicine, Karolinska Institute, Stockholm, Sweden, [2]Clinical Epidemiology Unit and Rheumatology Unit, Department of Medicine, Karolinska Institute, Stockholm, Sweden

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SESSION INFORMATION

Session Date: Monday, November 9, 2015

Session Title: Rheumatoid Arthritis-Small Molecules, Biologics and Gene Therapy IV: Safety of Targeted Therapies

Session Type: ACR Concurrent Abstract Session

Session Time: 4:30PM-6:00PM

Background/Purpose:

Immune incompetence may lower host surveillance against incipient tumours. Conversely, immune therapies have emerged as a promising therapeutic approach to cancer. Malignancies thus constitute an important aspect of the safety of biologics as used in Rheumatology, including agents targeting TNF, CD20, CTLA-4, and IL6. Previous reports concerning TNF inhibitors (TNFi) and risk of malignancies have mostly been reassuring. The risk of malignancies among RA patients treated with non-TNFi biologics is less well-known.

Methods:

Through linkages of Swedish national and population-based registers we assembled three cohorts of patients with RA initiating a first ever treatment of: 1) rituximab, 2) abatacept, 3) tocilizumab, 4) any TNFi, and 5) a cohort initiating a second TNFi. Also, 6) a biologics-naïve RA cohort was assembled, and 7) a general population comparator cohort, matched 1:10 on the biologics-naïve RA cohort. Through linkage with the Cancer Register information on cancer events were gathered. Outcomes were defined as first solid invasive malignancy, first hematologic malignancy, first invasive squamous cell skin cancer, and first solid or hematologic malignancy, all defined as first during follow-up. Patients were followed from treatment start until death, emigration, outcome or end of follow up. Crude incidences, as well as age and sex standardized incidences were calculated for outcomes from 2006 through 2012. Hazard ratios were calculated using Cox-regression, adjusted for age and sex.

Results:

Adjusted for age and sex, there were no statistically significant differences, for any of the outcomes, between initiators of non-TNFi biologics and initiators of a first or second TNFi, although small number of events precluded formal comparisons in some of the analyses.

Conclusion: The overall risk of malignancies among RA patients initiating rituximab, abatacept, or tocilizumab in clinical practice does not differ substantially from that of RA patients initiating a first or second TNF inhibitor, though risks for specific cancer sites or with longer latency cannot be excluded.

Table. Number of persons, events, crude incidence, standardized incidence, average follow-up time and hazard ratios for the different outcomes under study.

Outcome definition	Cohort	Number of persons at risk	Number of events	Crude incidence per 100,000 pys	Incidence rate standardized to the non-tnfi bio cohorts (by age and sex)	Mean follow-up, years	HR (adjusted for age and sex)
First invasive solid cancer	1 rituximab	2048	62	1028	1013	2.94	1.05 (0.82-1.34)
	2 abatacept	622	12	787	832	2.45	0.86 (0.49-1.51)
	3 tocilizumab	630	13	1186	1302	1.74	1.33 (0.77-2.30)
	4 First TNFi	7389	189	849	977	3.01	1.03 (0.89-1.18)
	5 Second TNFi	3120	71	858	986	2.65	1.05 (0.83-1.33)
	6 Biologics-naïve RA	43 523	2181	1212	1033	4.13	1.07 (1.02-1.12)
	7 General population	387 480	20172	1074	960	4.85	REF
First hematologic malignancy	1 rituximab	2048	5	82	84	2.98	1.08 (0.45-2.60)
	2 abatacept	622	4	260	258	2.47	NA
	3 tocilizumab	630	0	0	0	1.76	NA
	4 First TNFi	7389	21	93	99	3.05	1.51 (0.98-2.32)
	5 Second TNFi	3120	10	120	149	2.68	1.96 (1.05-3.65)
	6 Biologics-naïve RA	43 524	275	150	124	4.22	1.58 (1.39-1.80)
	7 General population	387 488	1694	88	74	4.95	REF
First invasive squamous cell skin cancer	1 rituximab	2048	9	147	135	2.98	2.23 (1.16-4.29)
	2 abatacept	622	2	130	180	2.48	NA
	3 tocilizumab	630	1	90	90	1.76	NA
	4 First TNFi	7389	25	111	145	3.05	2.36 (1.59-3.50)
	5 Second TNFi	3120	5	60	72	2.68	1.27 (0.53-3.05)
	6 Biologics-naïve RA	43526	330	180	116	4.22	1.67 (1.48-1.88)
	7 General	387 485	1819	95	73	4.95	REF

	population						
First invasive solid or hematologic cancer	1 rituximab	2048	66	1096	1086	2.94	1.04 (0.82-1.32)
	2 abatacept	622	16	1052	1096	2.45	1.07 (0.66-1.75)
	3 tocilizumab	630	13	1186	1309	1.74	1.25 (0.72-2.14)
	4 First TNFi	7389	208	936	1078	3.01	1.06 (0.92-1.21)
	5 Second TNFi	3120	81	981	1143	2.65	1.12 (0.90-1.39)
	6 Biologics-naïve RA	43521	2440	1360	1161	4.12	1.11 (1.06-1.16)
	7 General population	387 480	21735	1160	1037	4.84	REF

Disclosure: H. Wadström, None; **J. Askling**, AstraZeneca, Pfizer, UCB, Roche, Merck, BMS, Abbvie, 9.

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Abstract Number: 2142

Comparison of Interferon-γ Release Assay Versus Tuberculin Skin Test in the Golimumab UC and the Golimumab SC Rheumatology (RA, PsA, and AS) Clinical Study Programs

Elizabeth C. Hsia[1,2], Neil Schluger[3], John J. Cush[4], Eric L. Matteson[5], Stephen Xu[1], William Sandborn[6], Paul Rutgeerts[7] and Colleen Marano[1], [1]Janssen Research & Development, LLC, Spring House, PA, [2]University of Pennsylvania, Philadelphia, PA, [3]Columbia U College of Physicians & Surgeons, New York, NY, [4]Baylor Research Institute, Dallas, TX, [5]Division of Rheumatology, Department of Internal Medicine and Department of Health Sciences Research, Mayo Clinic, Rochester, MN, [6]Inflammatory Bowel Disease Center, Division of Gastroenterology, Department of Medicine, University of California San Diego, La Jolla, California, La Jolla, CA, [7]University Hospital Gasthuisberg, Leuven, Belgium

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Session Time: 4:30PM-6:00PM

Background/Purpose: Interferon-γ release assays (IGRAs) offer the possibility of an improved method to detect TB infections in pts with autoimmune disorders. Compare results of an IGRA vs standard TST as a screening tool for latent TB infection (LTBI) in the Golimumab [GLM] PURSUIT Ulcerative Colitis (UC) program versus GLM SC Rheumatology (RA, PsA, AS) program[1].

Methods: In both programs, pts were screened for LTBI using standard TST and IGRA to assess eligibility in the following studies: PURSUIT-SC and PURSUIT-IV; GO-BEFORE, GO-FORWARD, GO-AFTER, GO-REVEAL, and GO-RAISE, resp. Any pt with a newly identified positive finding for TB in whom there was no evidence of active TB was permitted to enter provided appropriate treatment for LTBI was initiated before or at the time of first dose of drug. TST was performed by the Mantoux method, using 5TUs of PPD standard or 2TU of PPD RT-23. TST was deemed positive for LTBI according to local country guidelines for an immunosuppressed host or, in the absence of local guidelines, according to an induration ≥5mm. The IGRA used to screen for LTBI was QuantiFERON-TB Gold In-Tube test. Overall IGRA and TST results were assessed. Prior BCG vaccination and con meds(ie corticosteroids and/or immunomodulators) on outcome was also assessed.

Results: In GLM PURSUIT, 1283 pts and in GLM Rheumatology 2282 pts had both IGRA and TST screening prior to GLM treatment. Both programs were global; differences were PURSUIT included S. Africa and the Rheum program included Asia. In the PURSUIT and Rheum programs, agreement between the TST and IGRA results, measured by the kappa coefficient, was 0.135 (95% CI, 0.050-0.220; p=0.028) and 0.22 (95% CI, 0.157-0.279; p=0.021), resp. Overall, in PURSUIT, 501(39.0%) of 1283 pts

had previously received BCG vaccine; among this vaccinated group, the rate of positivity for LTBI by TST was 10.4% vs 5.0% for IGRA positivity. In the Rheum program, 781 (34.2%) of 2282 pts had previously received BCG vaccine; within this vaccinated group, the rate of positivity for LTBI by TST was 15.2% vs 9.1% for IGRA positivity. PURSUIT pts who had not received the BCG vaccine, the rate of positivity by TST was 1.9% vs 2.8 % for IGRA positivity compared with 5.0% vs 5.8%, resp, in the Rheum program. When IGRA was repeated in PURSUIT pts whose results were initially indeterminate, the majority of pts(67.0%) were IGRA negative on repeat whereas the number of pts whose results were positive was 5.3%; IGRA remained indeterminate for 27.7%. Similar results were seen in the Rheum program (74% IGRA negative, 2.7% positive, and 23.2% remained indeterminate). Concomitant corticosteroid and/or immunomodulator use did not appear to have an impact on results.

Conclusion: Results of this comparison suggest IGRA provides greater specificity and possibly greater sensitivity than TST, and performs similarly in UC and Rheum populations.

Results from the GLM PURSUIT UC and GLM Rheumatology Programs		
Screening test results	PURSUIT UC	Rheumatology SC Program
IGRA/TST		
IGRA +	48/1283 (3.7%)	160/2282 (7.0%)
TST +	15/48 (31.3%)	59/160 (36.9%)
TST -	33/48 (68.8%)	101/160 (63.1%)
IGRA -	1201/1283 (93.6%)	2081/2282 (91.2%)
TST +	62/1201 (5.2%)	150/2081 (7.2%)
TST -	1139/1201 (94.8%)	1931/2081 (92.8%)
IGRA Indeterminate	34/1283 (2.7%)	41/2282 (1.8%)
TST +	2/34 (5.9%)	6/41 (14.6%)
TST -	32/34 (94.1%)	35/41 (85.4%)
Overall		
Positive by TST only	79/1283 (6.2%)	215/2282 (9.4%)
Positive by IGRA only	48/1283 (3.7%)	160/2282 (7.0%)
Positive by both TST and IGRA	15/1283 (1.2%)	59/2282 (2.6%)
Positive by either TST or IGRA	112/1283 (8.7%)	316/2282 (13.8%)

[1]Hsia EC et al. A & R Vol. 64, No 7, July 2012 pp 2068-2077

Disclosure: E. C. Hsia, Janssen R & D, LLC, 3; **N. Schluger**, Janssen R & D, LLC, 2; **J. J. Cush**, Janssen R & D, LLC, 2; **E. L. Matteson**, Janssen R & D, LLC, 2; **S. Xu**, Janssen R & D, LLC, 3; **W. Sandborn**, Janssen R & D, LLC, 2; **P. Rutgeerts**, Janssen R & D, LLC, 2; **C. Marano**, Janssen R & D, LLC, 3.

Abstract Number: 2143

A Safety Analysis of Tofacitinib 5mg Twice Daily Administered As Monotherapy or in Combination with Background Conventional Synthetic Dmards in a Phase 3 Rheumatoid Arthritis Population

Alan J Kivitz[1], Boulos Haraoui[2], Jeffrey Kaine[3], Vanessa Castellano[4], Eustratios Bananis[4], Carol A Connell[5], Elaine Hoffman[5] and Liza Takiya[6], [1]Altoona Center for Clinical Research, Duncansville, PA, [2]Institut de Rhumatologie de Montréal, Montréal, QC, Canada, [3]Sarasota Arthritis Research Center, Sarasota, FL, [4]Pfizer Inc, Collegeville, PA, [5]Pfizer Inc, Groton, CT, [6]Pfizer Inc, New York, NY

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Background/Purpose: Tofacitinib is an oral Janus kinase inhibitor for the treatment of rheumatoid arthritis (RA). In Phase 3 (P3) studies, tofacitinib demonstrated safety and efficacy at 5 and 10 mg BID when used as monotherapy or with conventional synthetic (cs) DMARDs (csDMARDs). Here, we examine the safety profile of tofacitinib 5 mg BID as monotherapy and combination therapy in the P3 RA program.

Methods: Safety data for tofacitinib were obtained from six double-blind P3 studies of 6–24 months duration and stratified by whether tofacitinib was administered as monotherapy (NCT00814307, ORAL Solo; NCT01039688, ORAL Start) or with csDMARDs (NCT00960440, ORAL Step; NCT00847613, ORAL Scan; NCT00856544, ORAL Sync; and NCT00853385, ORAL Standard). Patients (pts) in ORAL Start were methotrexate (MTX)-naïve while pts in all other studies had an inadequate response to cs or biologic DMARDs. Endpoints included: serious adverse events (SAEs), discontinuations due to adverse events (AEs), serious infection events (SIEs), opportunistic infections, herpes zoster (HZ), malignancies, major adverse cardiovascular events, gastrointestinal perforations, all-cause mortality, and laboratory safety data.

Results: Tofacitinib 5 mg BID was administered as monotherapy in 616 pts (243 from ORAL Solo and 373 from ORAL Start, mean age 51.1 years [yrs], mean RA duration 4.9 yrs, 49.8% received glucocorticoids [GC]) and combination therapy in 973 pts (mean age 53.4 yrs, mean RA duration 8.9 yrs, 57.8% received GC). Incidence rates (IRs) for SAEs, discontinuations due to AEs, SIEs and HZ were generally lower in pts receiving tofacitinib monotherapy vs combination therapy. A similar trend was observed when pts were stratified by GC use; however confidence intervals were wide and overlapping for some outcomes (Table 1). IRs for SIEs and HZ were greater for pts who received GC compared with those who did not irrespective of whether tofacitinib was given as monotherapy or in combination. Similar proportions of pts in the monotherapy and combination therapy groups had confirmed laboratory decreases in hemoglobin, neutrophil and lymphocyte counts, and increases in liver enzymes and serum creatinine (Table 2).

Conclusion: In this analysis, IRs for SAEs, discontinuations due to AEs, SIEs, and HZ were lower in the tofacitinib 5 mg BID monotherapy group vs the combination therapy group; however, IRs should be interpreted with caution as the data are from controlled studies of limited duration and MTX-naïve pts with shorter disease duration were included in the monotherapy group only.

Table 1. Incidence rates for safety events (Months 0–24)

Event/100 patient-years (95% CI) [patients with events]	**Tofacitinib 5 mg BID monotherapy** N=616 (728 patient-years)	**Tofacitinib 5 mg BID combination therapy** N=973 (1016 patient-years)
SAEs		
All patients	6.2 (4.6, 8.3) [44]	13.5 (11.3, 16.0) [130]
Patients with glucocorticoids	6.2 (3.9, 9.4) [22]*	16.2 (13.1, 19.9) [92]†
Patients without glucocorticoids	6.2 (3.9, 9.4) [22]‡	9.5 (6.7, 13.1) [38]§
Discontinuations due to AEs		
All patients	5.5 (4.1, 7.5) [40]	11.0 (9.1, 13.3) [111]
Patients with glucocorticoids	3.0 (1.5, 5.4) [11]*	12.4 (9.7, 15.5) [74]†
Patients without glucocorticoids	8.1 (5.4, 11.6) [29]‡	9.0 (6.4, 12.4) [37]§
Serious infection events		
All patients	1.7 (0.9, 2.9) [12]	3.6 (2.6, 4.9) [36]
Patients with glucocorticoids	2.5 (1.1, 4.7) [9]*	4.8 (3.2, 7.0) [29]†
Patients without glucocorticoids	0.8 (0.2, 2.4) [3]‡	1.7 (0.7, 3.5) [7]§
Herpes zoster		
All patients	2.0 (1.1, 3.3) [14]	4.4 (3.2, 5.9) [43]
Patients with glucocorticoids	3.4 (1.7, 5.9) [12]*	4.8 (3.2, 7.0) [28]†
Patients without glucocorticoids	0.6 (0.1, 2.0) [2]‡	3.7 (2.1, 6.1) [15]§
Opportunistic infections (excluding tuberculosis)	0	0.4 (0.1, 1.2) [3]¶
Tuberculosis	0	0
Malignancies (excluding NMSC)	0.4 (0.1, 1.3) [3]	0.8 (0.4, 1.6) [8]
NMSC	1.4 (0.7, 2.6) [10]	2.7 (1.9, 3.9) [27]
MACE	0.6 (0.2, 1.5) [4]	0.7 (0.3, 1.4) [7]
GI perforations	0	0
All-cause mortality††	0.1 (0.02, 1.0) [1]	0.7 (0.3, 1.4) [7]

*367 patient-years of exposure; n=320
†603 patient-years of exposure; n=579
‡361 patient-years of exposure; n=296
§412 patient-years of exposure; n=394
¶786 patient-years of exposure
††30-day rule – deaths occurring within 30 days of the last dose

AE, adverse event; BID, twice daily; CI, confidence interval; GI, gastrointestinal; MACE, major adverse cardiovascular event; NMSC, non-melanoma skin cancer; SAE, serious adverse event

Table 2. Confirmed laboratory safety data (Months 0–24)		
	Tofacitinib 5 mg BID monotherapy N=616	**Tofacitinib 5 mg BID combination therapy** N=973
Decreased hemoglobin, n (%)		
Decrease ≥1 g/dL to ≤2 g/dL	65 (10.6)	84 (8.6)
Decrease >2 g/dL to <3 g/dL or hemoglobin >7 g/dL, but <8 g/dL	11 (1.8)	12 (1.2)
Decrease of ≥3 g/dL or hemoglobin ≤7 g/dL	3 (0.5)	1 (0.1)
Neutropenia, n (%)		
1500–1999 cells/mm^3	17 (2.8)	31 (3.2)
500–1499 cells/mm^3	6 (1.0)	3 (0.3)
<500 cells/mm^3	0	0
Lymphopenia, n (%)		
1500–1999 cells/mm^3	211 (34.3)	277 (28.5)
500–1499 cells/mm^3	205 (33.3)	438 (45.0)
<500 cells/mm^3	1 (0.2)	1 (0.1)
Aminotransferases, n (%)		
AST ≥3 × ULN with normal baseline	1 (0.2)	3 (0.3)
ALT ≥3 × ULN with normal baseline	2 (0.4)	6 (0.7)
Serum creatinine, n (%)		
>50% increase from baseline	8 (1.3)	9 (0.9)
ALT, alanine aminotransferase; AST, aspartate aminotransferase; BID, twice daily; ULN, upper limit of normal		

Disclosure: **A. J. Kivitz**, Pfizer Inc, 8,Pfizer Inc, 5,Pfizer Inc, 2; **B. Haraoui**, Abbvie, Amgen, BMS, Janssen, Pfizer Inc, Roche and UCB., 2,Abbvie, Amgen, BMS, Janssen, Pfizer Inc, Roche and UCB., 9; **J. Kaine**, Pfizer Inc, BMS, 8; **V. Castellano**, Pfizer Inc, 1,Pfizer Inc, 3; **E. Bananis**, Pfizer Inc, 1,Pfizer Inc, 3; **C. A. Connell**, Pfizer Inc, 1,Pfizer Inc, 3; **E. Hoffman**, Pfizer Inc, 1,Pfizer Inc, 3; **L. Takiya**, Pfizer Inc, 1,Pfizer Inc, 3.

Abstract Number: 2144

Efficacy and Safety of Different Dose Regimens of a Selective IL-23p19 Inhibitor (BI 655066) Compared with Ustekinumab in Patients with Moderate-to-Severe Plaque Psoriasis with and without Psoriatic Arthritis

Kim Papp[1], Alan Menter[2], Howard Sofen[3], Stephen Tyring[4], Jean-Philippe Lacour[5], Beate Berner[6], Nathan Bennett[7], Stella Aslanyan[7], Mary Flack[7] and Paul Scholl[7], [1]Probity Clinical Research, Waterloo, ON, Canada, [2]Baylor Research Institute, Dallas, TX, [3]Dermatology Research Associates, Los Angeles, CA, [4]Center for Clinical Studies, Houston, TX, [5]Dermatology Department, Hôpital de L'Archet, Nice, France, [6]Boehringer Ingelheim Pharma GmbH & Co. KG, Biberach, Germany, [7]Boehringer Ingelheim Pharmaceuticals Inc., Ridgefield, CT

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Session Type: ACR Concurrent Abstract Session

Session Time: 4:30PM-6:00PM

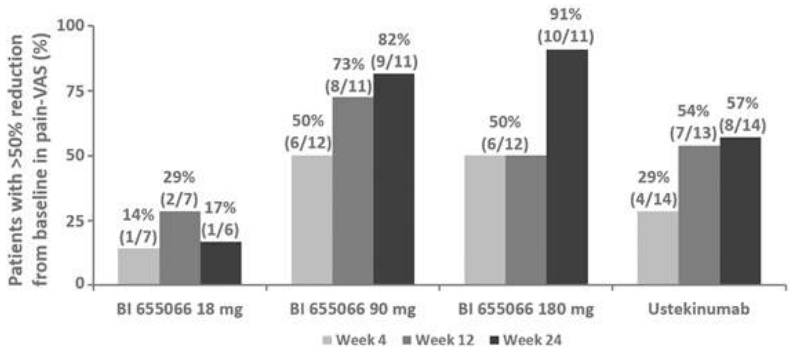
Background/Purpose: IL-23 is essential for the differentiation and maintenance of Th17 cells in psoriasis and psoriatic arthritis (PsA). We assessed the efficacy and safety of the humanized IgG1 monoclonal antibody BI 655066, which selectively inhibits IL-23p19, compared with ustekinumab, an IL-12/23 inhibitor, in patients with moderate-to-severe plaque psoriasis with and without concurrent PsA.

Methods: In this Phase 2 study (NCT02054481; 1311.02), 166 patients were randomly assigned (1:1:1:1 ratio) to receive subcutaneous injections of one of three dosage regimens of BI 655066 (18 mg single dose at Week 0; 90 or 180 mg at Weeks 0, 4, and 16), or ustekinumab (45 or 90 mg, based on weight, at Weeks 0, 4, and 16). Skin lesions were assessed using the Psoriasis Area and Severity Index (PASI) with the primary endpoint of PASI 90 (90% improvement in PASI score from baseline) at Week 12. Pain was assessed by visual analog scale (pain-VAS [0–100 mm]) at baseline (Week 0) and at Weeks 4, 12, and 24 in patients who had concurrent PsA. In this interim analysis, all patients had completed the Week 24 visit.

Results: The primary endpoint of PASI 90 response at Week 12 was achieved by 32.6% (14/43), 73.2% (30/41), and 81.0% (34/42) of BI 655066 patients in the 18, 90, and 180 mg groups, respectively, and 40.0% (16/40) of ustekinumab patients. A two-sided Cochran-Mantel-Haenszel test of PASI 90 response at Week 12 between the 18, 90, and 180 mg groups of BI 655066, and ustekinumab, gave p-values of 0.4337, 0.0013, and <0.0001, respectively. Among the 46 (27.7%) patients with PsA (either previously diagnosed by rheumatologist [n=13] or suspected by investigator [n=33]), median decreases from baseline in pain-VAS at Week 24 were 7.6%, 80.0%, and 86.5%, respectively, for the BI 655066 18, 90, and 180 mg dose groups, compared with 77.6% for ustekinumab. The criterion of >50% decrease in pain-VAS (defined post hoc) at Week 24 was achieved in 16.7% (1/6), 81.8% (9/11), and 90.9% (10/11) of patients in BI 655066 18, 90, and 180 mg dose groups, respectively, compared with 57.1% (8/14) for ustekinumab. In the BI 655066 90 and 180 mg dose arms the reductions in pain-VAS score were observed as early as 4 weeks, and were highest at 24 weeks (Figure 1). AEs were similar between treatment arms and there was no dose response relationship for any AE. Seven patients reported serious AEs (four in the 18 mg and two in the 90 mg BI 655066 arms and one in the ustekinumab arm); all were considered unrelated to study medication.

Conclusion: Selective blockade of IL-23p19 with BI 655066, in the 90 mg and 180 mg arms, were associated with PASI responses superior to ustekinumab in patients with moderate-to-severe plaque psoriasis. Treatment with BI 655066 or ustekinumab was associated with numeric improvement in pain-VAS in patients with diagnosed or suspected PsA. Further studies are needed to assess long-term efficacy and safety of BI 655066 in both psoriasis and PsA.

Figure 1. Reductions in pain-VAS score from baseline at Weeks 4, 12, and 24



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Abstract Number: 2145

Ixekizumab Improves Physical Function, Quality of Life, and Work Productivity in Biologic Disease-Modifying Antirheumatic Drug-Naive Patients with Active Psoriatic Arthritis

Alice B. Gottlieb[1], Philip J. Mease[2], Raquel S. Cuchacovich[3,4], Catherine L. Shuler[5], Chen-Yen Lin[5], Russel T. Burge[5], Suvajit Samanta[5], Chin H. Lee[5] and Dafna D. Gladman[6], [1]Dermatology, Tufts Medical Center, Boston, MA, [2]Department of Rheumatology, Swedish Medical Center and University of Washington, Seattle, WA, [3]School of Medicine, Rheumatology Division, Indiana University, Indianapolis, IN, [4]Bio Medicines Business Unit/Autoimmune Medical, Eli Lilly and Company, Indianapolis, IN, [5]Eli Lilly and Company, Indianapolis, IN, [6]Department of Medicine, Division of Rheumatology, University of Toronto, Toronto, ON, Canada

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SESSION INFORMATION

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Session Title: Spondylarthropathies and Psoriatic Arthritis - Clinical Aspects and Treatment:Treatment of PsA and SpA

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Session Time: 4:30PM-6:00PM

Background/Purpose: Psoriatic arthritis (PsA) is a chronic immune-mediated inflammatory disease associated with psoriasis, peripheral arthritis, enthesitis, dactylitis, and spondylitis. PsA has a significant negative impact on patients' quality of life, physical function, and work productivity. Ixekizumab is an IgG4 monoclonal antibody that binds with high affinity and specificity to the proinflammatory cytokine IL-17A, currently under investigation for the treatment of PsA.

Methods: In this phase 3 trial, 417 biologic disease-modifying antirheumatic drug (bDMARD)-naive patients with active PsA were randomized to receive up to 24 weeks of placebo (N=106); adalimumab 40 mg once every 2 weeks (Q2W; N=101) (active control); or ixekizumab 80 mg every 4 weeks (Q4W; N=107) or Q2W (N=103) following a 160 mg starting dose at Week 0. Patient Reported Outcomes (PROs) included, but were not limited to, Health Assessment Questionnaire – Disability Index (HAQ-DI), Short Form-36 Health Survey Physical Component Score (SF-36 PCS), European Quality of Life 5 Dimensions Visual Analog Scale (EQ-5D VAS), and Work Productivity and Activity Impairment-Specific Health Problem (WPAI-SHP), and were analyzed using the intent-to-treat population. Continuous PRO data were evaluated using a mixed-effects model for repeated measures. The model included data up to Week 24 for all patients except inadequate responders (IRs) for whom data after Week 16 were excluded. Categorical PRO data were compared using a logistic regression model; missing values were imputed with the non-responder imputation method, treating IRs as non-responders.

Results: Across treatment groups, baseline demographics and clinical characteristics were generally similar; population mean baseline scores for HAQ-DI, SF-36 PCS, and EQ-5D VAS were 1.17, 33.63, and 55.4, respectively, indicating reduced physical function and quality of life. Mean baseline scores for the individual components of the WPAI-SHP assessment were 8.6 for Absenteeism, 36.6 for Presenteeism, 38.9 for Work Productivity, and 47.0 for Activity Impairment. At Week 12, patients treated with either ixekizumab 80 mg Q4W or Q2W reported significantly greater improvements compared to placebo in HAQ-DI, SF-36, EQ-5D VAS, and WPAI-SHP (all components, except Absenteeism); improvements were maintained through Week 24 for all treatment groups (Table). Additionally at Weeks 12 and 24, the percentage of patients with a baseline HAQ-DI score ≥0.35 achieving minimally clinically important difference (MCID) for HAQ-DI (improvement from baseline in HAQ-DI ≥0.35) was significantly greater in both ixekizumab treatment arms compared to placebo (Table).

Conclusion: In bDMARD-naive patients with active PsA, ixekizumab significantly improved quality of life, physical function and work productivity.

Table. *PROs at Weeks 12 and 24 by treatment group.*

Change from Baseline (SE)	Placebo[a] (N=106)		Adalimumab 40 mg Q2W (N=101)		Ixekizumab 80 mg Q4W (N=107)		Ixekizumab 80 mg Q2W (N=103)	
	Week 12	Week 24	Week 12	Week 24	Week 12	Week 24	Week 12	Week 24
HAQ-DI[b]	-0.13 (0.05)	-0.18 (0.05)	-0.35 (0.05)**	-0.37 (0.05)*	-0.37 (0.05)**	-0.44 (0.05)**	-0.47 (0.05)**	-0.50 (0.05)**
SF-36 PCS[c]	2.27 (0.79)	2.94 (0.96)	5.71 (0.82)**	6.78 (0.90)*	5.76 (0.80)**	7.45 (0.89)**	7.64 (0.81)**	8.24 (0.90)**
EQ-5D VAS[c]	3.2 (2.0)	3.8 (2.4)	9.2 (2.1)*	10.3 (2.2)*	12.3 (2.0)**	11.9 (2.2)*	14.7 (2.1)**	13.1 (2.2)*
WPAI-SHP: Absenteeism[b]	-1.3 (1.6)	-0.2 (3.2)	-3.2 (1.6)	-0.5 (2.5)	-4.6 (1.5)	-5.5 (2.6)	-3.4 (1.6)	0.9 (2.8)
WPAI-SHP: Presenteeism[b]	-4.8 (2.9)	-6.8 (3.2)	-9.9 (2.9)	-13.2 (2.7)	-14.8 (2.8)*	-19.4 (2.6)**	-18.2 (3.0)**	-22.1 (2.8)**
WPAI-SHP: Work Productivity[b]	-5.4 (3.1)	-8.3 (3.5)	-11.7 (3.1)	-13.4 (3.0)	-15.2 (2.9)*	-20.6 (2.9)*	-19.0 (3.1)**	-20.7 (3.2)*
WPAI-SHP: Activity Impairment[b]	-5.8 (2.2)	-8.1 (2.5)	-11.5 (2.3)	-16.3 (2.3)*	-18.4 (2.3)**	-22.6 (2.3)**	-22.7 (2.3)**	-26.1 (2.3)**
n (%)	**Placebo (N=92)**		**Adalimumab 40 mg Q2W (N=89)**		**Ixekizumab 80 mg Q4W (N=100)**		**Ixekizumab 80 mg Q2W (N=90)**	
	Week 12	Week 24	Week 12	Week 24	Week 12	Week 24	Week 12	Week 24
HAQ-DI MCID[c]	27 (29.3)	24 (26.1)	44 (49.4)*	44 (49.4)**	49 (49.0)*	49 (49.0)**	58 (64.4)**	52 (57.8)**

*p<.05 vs. PBO; **p≤.001 vs. PBO

[a]The study was powered only for comparisons between ixekizumab and placebo or adalimumab and placebo.

[b]Decrease in score represents improvement. [c]Increase in score represents improvement. [c]MCID ≥0.35 improvement from baseline; only patients with a baseline HAQ-DI score ≥0.35 were included in the analysis.

EQ-5D VAS, European Quality of Life 5 Dimensions Visual Analog Scale; HAQ-DI, Health Assessment Questionnaire - Disability Index; MCID, Minimal Clinically Important Difference; SF-36 PCS, Short Form-36 Health Survey Physical Component Score; WPAI SHP, Work Productivity and Activity Impairment-Specific Health Problem.

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Company, 3; **D. D. Gladman**, AbbVie, 2,Amgen, 2,Celgene, 2,Janssen Pharmaceutica Product, L.P., 2,Novartis Pharmaceutical Corporation, 2,UCB Pharma, 2,AbbVie, 5,Amgen, 5,Bristol-Myers Squibb, 5,Celgene, 5,Eli Lilly and Company, 5,Novartis Pharmaceutical Corporation, 5,Pfizer Inc, 5,UCB Pharma, 5.

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Abstract Number: 2146

Secukinumab Provides Sustained Improvements in the Signs and Symptoms of Active Psoriatic Arthritis in Anti-TNF-Naive Patients and Those Previously Exposed to Anti-TNF Therapy: 52-Week Results from a Randomized, Double-Blind, Placebo-Controlled Phase 3 Trial with Subcutaneous Dosing

Arthur Kavanaugh[1], Iain B. McInnes[2], Philip J. Mease[3], Stephan Hall[4], Hector Chinoy[5], Alan J Kivitz[6], Manmath Patekar[7], Zailong Wang[8] and Shephard Mpofu[9], [1]University of California, San Diego School of Medicine, LaJolla, CA, [2]Immunology, Infection and Inflammation, University of Glasgow, Glasgow, United Kingdom, [3]Rheumatology Research, Swedish Medical Center, Seattle, WA, [4]Monash University, Melbourne, Australia, [5]University of Manchester, Manchester, United Kingdom, [6]Altoona Center for Clinical Research, Duncansville, PA, [7]Novartis Healthcare Pvt. Ltd., Hyderabad, India, [8]Novartis Pharmaceuticals Corporation, East Hanover, NJ, [9]Novartis Pharma AG, Basel, Switzerland
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Background/Purpose: There remains an unmet need for additional treatment options for patients (pts) with psoriatic arthritis (PsA) who have had an inadequate response to or intolerance of anti-tumor necrosis factor (anti-TNF) therapy. Secukinumab, a human anti–IL-17A monoclonal antibody, demonstrated significant efficacy in the randomized, double-blind, placebo (PBO)-controlled phase 3 FUTURE 2 study (NCT01752634).[1]Here, we present the 52-week (wk) efficacy and safety of secukinumab by anti-TNF history in pts enrolled in this study.

Methods: Pts were randomized to receive subcutaneous (s.c.) secukinumab 300 mg, 150 mg, or 75 mg, or placebo (PBO) at baseline, Wks 1, 2, 3, and 4, and then every 4 wks (q4wk) from Wk 8. At Wk 16, PBO-treated pts were re-randomized to receive secukinumab 300 mg or 150 mg s.c. q4wk from Wk 16 or 24, depending upon clinical response. Randomization was stratified by anti-TNF history: anti–TNF-naïve, or inadequate response/intolerance to not more than 3 anti-TNF agents (anti–TNF-IR). The primary endpoint was ACR20 response at Wk 24. Secondary endpoints were PASI 75/90, DAS28-CRP, SF-36 PCS, HAQ-DI, ACR 50, dactylitis, and enthesitis. ACR70 was an exploratory endpoint. Analyses used non-responder imputation (binary variables) and mixed-effect model repeated measures (continuous variables) through Wk 52. Analysis of primary and secondary endpoints stratified by anti-TNF history was pre-specified.

Results: Of the 397 pts enrolled in FUTURE 2, 65% were anti–TNF-naïve and 35% were anti–TNF-IR. At Wk 24, ACR 20/50/70 and PASI 75/90 responses were higher with secukinumab versus PBO in both anti–TNF-naïve and anti–TNF-IR pts (Table). Improvements with secukinumab versus PBO at Wk 24 were also observed for other secondary endpoints in both anti–TNF-naïve and anti–TNF-IR pts. Response rates were generally higher amongst anti–TNF-naïve pts versus anti–TNF-IR pts. The greatest improvements in the anti–TNF-IR group were generally observed with secukinumab 300 mg. Clinical responses to secukinumab were sustained or continued to improve through 52 wks of therapy in both anti–TNF-naïve and anti–TNF-IR pts (Table).

Conclusion: Secukinumab provided sustained improvements in the signs and symptoms of PsA in both anti–TNF-naïve and anti–TNF-IR pts.

Reference: 1. McInnes IB, et al. ACR/ARHP Annual Meeting, Boston, MA, USA. November 14-19, 2014. Oral Presentation L1.

Table: Efficacy of secukinumab at Wks 24 and 52

Responders (%)		FUTURE 2 Secukinumab 300 mg	FUTURE 2 Secukinumab 150 mg	FUTURE 2 Secukinumab 75 mg	PBO
Anti–TNF-IR[a]					
ACR20/50/70	N=	33	37	34	35
	Wk 24	45.5§/27.3‡/15.2‡	29.7/18.9/10.8	14.7/5.9/5.9	14.3/8.6/0.0
	Wk 52	54.5/27.3/18.2	37.8/21.6/13.5	35.3/17.6/8.8	-
PASI 75/90[b]	N=	11	22	17	12
	Wk 24	63.6‡/36.4	36.4/22.7	23.5/11.8	8.3/8.3
	Wk 52	63.6/45.5	50.0/40.9	41.2/23.5	-
Anti–TNF-naïve					
ACR20/50/70	N=	67	63	65	63
	Wk 24	58.2*/38.8*/22.4†	63.5*/44.4*/27.0*	36.9§/24.6§/6.2	15.9/6.3/1.6
	Wk 52	68.7/52.2/26.9	79.4/49.2/23.8	58.5/36.9/20.0	-
PASI 75/90[b]	N=	30	36	33	31
	Wk 24	63.3†/53.3†	55.6§/38.9§	30.3/12.1	19.4/9.7
	Wk 52	76.7/60.0	61.1/44.4	51.5/24.2	-

[a]Pts who had previously used up to 3 anti-TNF agents and had experienced an inadequate response or stopped treatment due to safety or tolerability reasons

[b]Pts who had psoriasis affecting ≥3% body surface area at baseline

Missing values were imputed as non-response (non-responder imputation)

*P<0.0001; †P<0.001; §P<0.01; ‡P<0.05 versus PBO

ACR, American College of Rheumatology response criteria; N, number of pts randomized; PASI, psoriasis area-and-severity index; PBO, placebo

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Disclosure: A. Kavanaugh, Novartis Pharmaceutical Corporation, 5; **I. B. McInnes**, Abbvie, Amgen, BMS, Celgene, Janssen, Lilly, Novartis, Pfizer, UCB, 5,Abbvie, Amgen, BMS, Celgene, Janssen, Lilly, Novartis, Pfizer, UCB, 2,Abbvie, Amgen, BMS, Celgene, Janssen, Lilly, Novartis, Pfizer, UCB, 9; **P. J. Mease**, Abbvie, Amgen, BMS, Celgene, Crescendo Bioscience, Genentech, Janssen, Lilly, Merck, Novartis, Pfizer, UCB, 2,Abbvie, Amgen, BMS, Celgene, Crescendo Bioscience, Genentech, Janssen, Lilly, Merck, Novartis, Pfizer, UCB, 5,Abbvie, Amgen, BMS, Celgene, Crescendo Bioscience, Genentech, Janssen, Lilly, Merck, Novartis, Pfizer, UCB, 9; **S. Hall**, None; **H. Chinoy**, Novartis, Janssen, Pfizer, UCB, Abbvie, Celgene, Servier, Roche, MSD, and aTyr, 5,Novartis, Janssen, Pfizer, UCB, Abbvie, Celgene, Servier, Roche, MSD, and aTyr, 2; **A. J. Kivitz**, Novartis Pharmaceutical Corporation, 5; **M. Patekar**, Novartis Pharmaceutical Corporation, 3; **Z. Wang**, Novartis Pharmaceutical Corporation, 3; **S. Mpofu**, Novartis Pharmaceutical Corporation, 3,Novartis Pharmaceutical Corporation, 1.

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Abstract Number: 2147

The Effect of Sulfasalazine and Methotrexate on the Immunogenicity of Infliximab and Adalimumab in Patients with Spondyloarthritis

Ana Martínez[1], Chamaida Plasencia-Rodriguez[2], Dora Pascual-Salcedo[3], Eva L. Kneepkens[4], Gertjan Wolbink[5], Alejandro Villalba[6], Teresa Jurado[1], Diana Peiteado[6], Laura Nuño[6], Andrea Jochems[1] and Alejandro Balsa[6], [1]Immunology Unit, La Paz University Hospital-IdiPaz, MADRID, Spain, [2]Rheumatology Department, La Paz University Hospital-Rheumatology Department, Madrid, Spain, [3]Immunology Unit, La Paz University Hospital-Immunology, Madrid, Spain, [4]Jan van Breemen Research Institute | Reade, Amsterdam, Netherlands, [5]Rheumatology, Jan van Breemen Research Institute | Reade, Amsterdam, Netherlands,

[6]Rheumatology, La Paz University Hospital-Rheumatology Department, Madrid, Spain
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SESSION INFORMATION

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Background/Purpose: Classic DMARDs are not routinely prescribed for axial spondyloarthritis (SpA). Recent studies have found that concomitant therapy with methotrexate (MTX) reduced immunogenicity of TNF inhibitors (TNFi). However the effect of sulfasalazine (SSZ) on the development of anti-drug antibodies (ADA) has not been properly studied. We investigated the effect of MTX or SSZ on ADA development in a cohort of SpA patients treated with Infliximab (Ifx) or Adalimumab (Ada).

Methods: SpA patients were enrolled from two prospective observational cohorts, Spain (n=122) and The Netherlands (n=85). Out of 208 SpA patients treated with Ifx or Ada we included 152 patients; 41(26.9%) with Ifx and 111(73%) with Ada, who had drug and ADA levels measured during the first year of TNFi therapy. Concomitant DMARD use was assessed at baseline.

Disease activity was measured at baseline, 6 months and 1 year by the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI). Low disease activity (LDA) was defined as BASDAI<4 with normal CRP and clinical improvement as ΔBASDAI>2. Serum drug levels were measured by ELISA and ADA levels were measured by ELISA(Spain) and ABT(The Netherlands) and samples were collected just before drug administration.

We performed the last observation carried forward analysis to include patients who dropped-out before one year.

Results: The demographic and clinical characteristics of the 152 SpA patients are shown in table1. ADA were detected in 26(17%) SpA patients: 5(19%) treated with Ifx and 21(81%) with Ada. Only 3 patients with ADA were treated with DMARS concomitantly, specifically with SSZ.

The majority of ADA appeared at 6 months: 17 (65%) patients and 9 (35%) developed ADA at 1 year. SpA patients treated with TNFi in monotherapy developed more frequently ADA than patients treated concomitantly with DMARDs: 23(26%) vs 3(4.7%), p=0.004. Patients treated with TNFi in combination with MTX or SSZ developed ADA less frequently than patients treated in monotherapy: 23(26%) vs 0(0%), p=0.02; 23(26%) vs 3(8%), p=0.03, respectively). However we did not find significant differences in ADA development when we compared SpA patients treated with MTX vs SSZ: 0(0%) vs 3(8%), p=0.54, respectively.

Most patients with ADA did not reach LDA during the first year of treatment: 9(38%) ADA positive patients vs 70(62%) ADA negative patients, p=0.04. ΔBASDAI was higher in ADA negative patients (Mdn, IQR): 2.2, 0.9-4 in ADA negative patients vs 1.1, 0.5-2.8 in ADA positive patients, p=0.03

Conclusion: In our cohorts of SpA patients treated with Ifx or Ada the concomitant use of DMARDs (MTX or SSZ) is associated with a lower development of ADA, which suggests a protective role of DMARDs to prevent immunogenicity and, hence, to prevent a secondary failure of the biological treatment.

Table 1: Clinical and demographic characteristics of patients grouped by presence of anti-drug antibodies (ADA).

Characteristics	**ADA- (n=126)**	**ADA+ (n=26)**	**p value**
Men, n (%)	75 (60%)	9 (35%)	ns
Age(years), mean (SD)	46.3±12.7	45.8±12.3	ns
HLA B27 positive, n (%)	91 (73%)	18 (75%)	ns
Disease duration (years), mean (SD)	10.7±9	11±10	ns
Biological treatment duration (years)	5.2±2.2	6±3	ns
Baseline BASDAI, mean (SD)	6.0±1.9	5.8±1.7	ns
Baseline ESR, mean (SD)	21.2±19	23.3±19.2	ns
Baseline CRP, mean (SD)	10.9±13.7	9.6±12	ns
Extraaxial manifestation (IBD,Psoriasis,Uveitis,Peripheral artritis)	60 (48%)	13 (50%)	ns
Concomitant treatment, n (%)			
Methotrexate (MTX)	15 (12%)	0 (0%)	0.004
Sulfasalazine (SZS)	33 (26%)	3 (12%)	
MTX + SZS	13 (10%)	0 (0%)	
TNF inhibitors monotherapy	65 (52%)	23 (88%)	

SD: standard deviation

ns: no significant; unpaired t test

Disclosure: A. Martínez, None; **C. Plasencia-Rodriguez**, None; **D. Pascual-Salcedo**, None; **E. L. Kneepkens**, Pfizer Inc, 2; **G. Wolbink**, Pfizer Inc, 2,Pfizer Inc, 5,Amgen, 5,AbbVie, 5,UCB, 5,BMS, 5; **A. Villalba**, None; **T. Jurado**, None; **D. Peiteado**, None; **L. Nuño**, None; **A. Jochems**, None; **A. Balsa**, None.

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Abstract Number: 2148

Secukinumab Provides Sustained Improvements in Psoriatic Arthritis: 2-Year Efficacy and Safety Results from a Phase 3 Randomized, Double-Blind, Placebo-Controlled Trial

Philip J. Mease[1], Iain B. McInnes[2], Bruce Kirkham[3], Arthur Kavanaugh[4], Proton Rahman[5], Désirée van der Heijde[6], Robert B.M. Landewé[7], P Nash[8], Luminita Pricop[9], Zailong Wang[10] and Shephard Mpofu[11], [1]Rheumatology Research, Swedish Medical Center, Seattle, WA, [2]Institute of Infection, Immunity and Inflammation, College of Medicine, Veterinary Medicine and Life Sciences, University of Glasgow, Glasgow, United Kingdom, [3]Guy's and St Thomas' NHS Foundation Trust, London, United Kingdom, [4]University of California, San Diego School of Medicine, LaJolla, CA, [5]Medicine, Memorial University, St John's, NF, Canada, [6]Rheumatology, Leiden University Medical Center, Leiden, Netherlands, [7]University of Amsterdam and Atrium Medical Center, Amsterdam, Netherlands, [8]Department of Medicine, University of Queensland, Brisbane, Australia, [9]Integrated Hospital

Care (IHC) Franchise, Novartis Pharmaceuticals Corporation, East Hanover, NJ, [10]Novartis Pharmaceuticals Corporation, East Hanover, NJ, [11]Novartis Pharma AG, Basel, Switzerland
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SESSION INFORMATION

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Background/Purpose: In the Phase 3, randomized, double-blind, placebo (PBO)-controlled, FUTURE 1 study (NCT01392326), the anti–interleukin-17A monoclonal antibody secukinumab provided rapid and significant improvements in key clinical domains of psoriatic arthritis (PsA), including signs and symptoms, joint structural damage, physical function and quality of life.[1] Here, we present the long-term efficacy and safety of secukinumab in patients (pts) enrolled in FUTURE 1 and treated for up to 104 weeks (wks).

Methods: A total of 606 adults with active PsA were randomized to receive secukinumab or PBO. Secukinumab pts received a 10 mg/kg i.v. loading dose at baseline (BL), Wks 2 and 4, and then either 150 mg s.c. (IV→150 mg) or 75 mg s.c. (IV→75 mg) every 4 wks from Wk 8. PBO was given on the same dosing schedule. At Wk 16, PBO-treated pts were re-randomized to receive secukinumab 150 or 75 mg s.c. from either Wk 16 or Wk 24, based on clinical response. Assessments of clinical efficacy at Wk 104 included: ACR 20/50/70; PASI 75/90; DAS28-CRP; SF-36 PCS; HAQ-DI; mTSS. Efficacy variables are presented from those pts originally randomized to secukinumab. Wk 104 data are as observed.

Results: 476 pts (78.5%) completed 104 wks of study (167 [82.7%] pts in the IV→150 mg group and 155 [76.7%] in the IV→75 mg group). At Wk 104, ACR 20/50/70 response rates were 73.9/46.4/28.1% with IV→150 mg and 68.8/35.5/22.5% with IV→75 mg (observed data). Sustained clinical improvements with secukinumab through Wk 104 were observed across several other clinically important domains of PsA (Table). Responses were sustained through Wk 104 in pts naïve to anti-TNF therapy and in those with an inadequate response or intolerance to these agents (anti-TNF-IR). ACR20 response rates (observed data) at Wk 104 in anti-TNF-naïve pts were 80.0% and 72.9% with IV→150 mg and IV→75 mg, respectively; corresponding rates in anti-TNF-IR pts were 55.3% and 54.8%. Between BL and Wk 104, 84.6% of x-ray completers in the IV→150 mg group and 83.9% in the IV→75 mg group, had no radiographic disease progression (≤0.5 change in mTSS). Over the entire study period (mean exposure to secukinumab of 627.1 days) the type, incidence and severity of AEs was consistent with that reported previously. Infections and infestations were the most common AE observed with secukinumab (67.9 per 100 pt-years). No cases of TB were reported. Malignant or unspecified tumors were reported at a rate of 0.3 per 100-pt years. Major adverse cardiac event rates with secukinumab were 0.7 per 100 pt-years. No suicides were recorded in secukinumab-treated patients.

Conclusion: Secukinumab provided sustained improvements in signs and symptoms and multiple clinical domains of active PsA in pts who completed 2 years of therapy. Secukinumab was well tolerated with a safety profile consistent with that previously reported.

Reference:

1. Mease P, et al. *Arthritis Rheumatol*. 2014;66:S423–4.

Table. Summary of Efficacy Results at Wk 104 (Observed Data)		
	Secukinumab IV → 150 mg	**Secukinumab IV → 75 mg**
ACR 20, n/N (%)	113/153 (73.9)	95/138 (68.8)
ACR 50, n/N (%)	71/153 (46.4)	49/138 (35.5)
ACR 70, n/N (%)	43/153 (28.1)	31/138 (22.5)
PASI 75, n/N (%)	68/82 (82.9)	59/84 (70.2)
PASI 90, n/N (%)	57/82 (69.5)	42/84 (50.0)
DAS28-CRP, mean change from BL	–1.78 (n = 151)	–1.80 (n = 138)
SF-36 PCS, mean change from BL	5.94 (n = 152)	5.31 (n = 143)
HAQ-DI, mean change from BL	–0.42 (n = 153)	–0.41 (n = 138)
ACR, American College of Rheumatology response criteria; BL, baseline; DAS28-CRP, Disease Activity Score 28 using C-reactive protein; HAQ-DI, Health Assessment Questionnaire Disability Index, i.v., intravenous; n, number of pts meeting criteria; N, total number of pts in the analysis; PASI, psoriasis area-and-severity index; pts, patients; s.c., subcutaneous; SF-36 PCS, Short Form 36 Physical Component Summary		

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Abstract Number: 2149

Dose Reduction Compared with Standard Dosing for Maintenance of Remission in Patients with Spondyloarthropathies and Clinical Remission with Anti-TNF: A Randomised Real-Life Trial

Jorge Gratacos-Masmitja[1], Caridad Pontes[2], Ferran Torres[3], Xavier Juanola[4], Antoni Vallano[5], TC Salman-Monte[6], Francisco J. Blanco[7], Agusti Sellas-Fernandez[8], Raimon Sanmarti[9], Gonzalo Calvo[10], Teresa Clavaguera[11], Raul Veroz Gonzalez[12], Juan

Carlos Torre Alonso[13], Jesus Sanz[14], Cristina Avendaño[15], Carlos Rodriguez-Lozano[16], Luis Francisco Linares[17], Ana Urruticoechea[18], Eduardo Collantes-Estévez[19], Rosa Morla Novell[20], Delia Reina[21], Eduardo Cuende[22], Pedro Zarco[23], Cruz Fernández- Espartero[24], Rosario Garcia-Vicuña[25], Carlos Alberto Montilla Morales[26], Eugenio De Miguel[27], Roser Vives[2] and Mireia Moreno[28], [1]Rheumatology, Hospital de Sabadell - Institut Universitari Parc Taulí, Sabadell, Spain, [2]Clinical Pharmacology, Hospital de Sabadell - Institut Universitari Parc Taulí, Sabadell, Spain, [3]Biostatistics and Data Management Platform, IDIBAPS - Hospital Clínic de Barcelona, Barcelona, Spain, [4]Rheumatology, Hospital Universitari de Bellvitge, Barcelona, Spain, [5]Hospital de Bellvitge, Barcelona, Spain, [6]Rheumatology, Hospital del Mar/Parc de Salut Mar, Barcelona, Spain, [7]Osteoarticular and Aging Research Lab. Proteomics Unit - Associated Node to ProteoRed, Rheumatology Division, Proteomics Group-ProteoRed/ISCIII, INIBIC-CHUAC, A Coruña, Spain, [8]Rheumatology, Hospital Universitario Valle Hebron, Barcelona, Spain, [9]Rheumatology Department, Hospital Clinic i Provincial, Barcelona, Spain, [10]Hospital Clínic de Barcelona, Barcelona, Spain, [11]CapiCAT group (Nailfold Capillaroscopy group from the Catalan Society for Rheumatology)., Catalonia, Spain, [12]Hospital de Mérida, Mérida, Spain, [13]Perez de la Sala 33, 3oA., H. Monte Naranco, Oviedo, Spain, [14]Rheumatology, Hospital Puerta de Hierro Majadahonda, Madrid, Spain, [15]Hospital Puerta de Hierro - Majadahonda, Madrid, Spain, [16]Hospital Ubniversitario Dr. Negrin, Las Palmas de Gran Canaria, Spain, [17]Rheumatology, Hospital Virgen de la Arrixaca, Murcia, Spain, [18]Hospital Can Misses, Ibiza, Spain, [19]IMIBIC-Reina Sofia University Hospital, Rheumatology Unit, Cordoba, Spain, [20]Rheumatology UNit., Hospital Sta Tecla, Tarragona, Spain, [21]Rheumatology, Hospital de Sant Joan Despí Moisès Broggi, Barcelona, Spain, [22]University Hospital Príncipe de Asturias, Immune System Diseases, Rheumatology department, Alcalá de Henares, Madrid, Spain, [23]H Fundación Alcorcón, Alcorcón, Spain, [24]Rheumatology, Hospital La Zarzuela, Madrid, Spain, [25]Rheumatology, Hospital Universitario de La Princesa. IIS La Princesa, Madrid, Spain, [26]Rheumatology, Hospital Universitario de Salamanca, Salamanca, Spain, [27]Rheumatology, University Hospital La Paz, Madrid, Spain, [28]Hospital de Sabadell - Institut Universitari Parc Taulí, Sabadell, Spain
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Background/Purpose: Tumour Necrosis Factor alpha inhibitors (TNFi) have proven to be effective in the treatment of with spondyloarthropaties. There is rationale to support that in patients who have achieved disease remission while on treatment with TNFi, a lower dose than that used to induce remission may suffice to maintain the disease inactive in the long term. Dose reduction schedules are empirically used in routine clinical practice, but up to now such practice is not based on evidence from clinical trials. With the hypothesis that reduced doses are non inferior to full doses in terms of maintenance of response and safety profile, and with the aim to generate evidence to guide clinical practice, a prospective, multicentre randomised open-label study with non-inferiority objective was jointly sponsored by the Spanish Societies of Clinical Pharmacology and Rheumatology.

Methods: A total of 126 patients with axial non-psoriatic spondyloarthritis that had been treated with TNFi for a minimum of 12 weeks and had achieved a sustained clinical remission (BASDI $\leq$ 2, no clinical arthritis or enthesitis and normal CRP) during additional 8 weeks or more were randomized (1:1) to continue with the full dose treatment (Control, C) or a reduced dose maintenance treatment according to a standardized protocol (Experimental, E) in 22 Spanish sites. The main study endpoint was the proportion of patients who after 1 year qualified for Acceptable Therapeutic Goal (ATG) (BASDAI, physician global assessment and patient and nocturnal axial pain VAS, all <4). The non-inferiority design assumed 87% of ATG in the control group and a lower limit for the 95%CI of the adjusted difference between treatments of 17% for the per protocol (PP) population. The proportion of patients with Ideal Therapeutic Goal (BASDAI, patient and physician global assessment, all < 2) was a key secondary endpoint. Other endpoints included ASAS Disease Activity Score, BASFI, and Quality of Life Questionnaire scores. Safety issues with special focus on infectious adverse events were also evaluated. Patients were visited every 8 weeks, following the recommendations of the Spanish Rheumatology Society. Patients were followed a minimum of 56 weeks or until treatment discontinuation. The study was registered with EudraCT: 2011-005871-18.

Results: Baseline characteristics are described in table 1. In the PP population 48 (82.8%) patients in the reduced arm and 47 (85.5%) patients in the full dose were on ATG at one year assessment, with adjusted difference (95%CI) of -2.5%(-16.6 to 11.7%), thus meeting the primary non inferiority study objective. The proportion of infectious events were 17.2% in E and 25.5% in C groups (NS).

Table 1. Study results

Baseline characteristics	*Control* *n=55*	*Experimental* *n=58*	*Total* *n=113*
Gender			
Male N (%)	48 (87.3%)	47 (81.0%)	95 (84.1%)
Age (years) (Mean (SD))	47.2 (13.6)	43.6 (12.4)	45.6 (13.0)
BMI (Mean (SD))	25.8 (3.4)	25.9 (3.8)	25.9 (3.6)
ASDAS-CRP (Median (P25,P75))	1.1 (0.8, 3.5)	1.0 (0.7, 1.9)	1.1 (0.7, 2.0)
BASDAI (Median (P25,P75))	1 (0.6, 1.7)	1 (0.2, 1.4)	1 (0.4, 1.6))
VAS nocturnal axial pain (Mean (SD))	0.84 (1.01)	1.02 (1.15)	0.93 (1.08)
Physician GA (Median (P25,P75))	1 (0.0, 2.0)	1 (0.0, 1.0)	1 (0.0, 1.0)
Patient GA (Median (P25,P75))	1 (0.0, 2.0)	1 (0.0, 1.0)	1 (0.0, 1.0)
TNFi treatment			
Adalimumab N (%)	22 (40.0%)	22 (37.9%)	44 (38.9%)
Etanercept N (%)	19 (34.5%)	19 (32.8%)	38 (33.6%)
Golimumab N (%)	4 (7.3%)	5 (8.6%)	9 (8.0%)
Infliximab N (%)	10 (18.2%)	12 (20.7%)	22 (19.5%)
NSAIDs Use N (%)	15 (27.3%)	13 (22.4%)	28 (24.8%)
Per protocol efficacy analysis	**Control** **N=55**	**Experimental** **N=58**	**Difference**
ATG 12 months (% [95%CI])	83.8% [64.8% to 102.7%]	81.3% [62.8% to 99.8%]	-2.5% [-16.6% to 11.7%]
ITG 12 months (% [95%CI])	83.7% [64.7% to 102.7%]	78.2% [59.7% to 96.8%]	-5.5% [-20.6% to 9.7%]
Intention to treat efficacy analysis	**Control** **N=60**	**Experimental** **N=60**	**Difference**
ATG 12 months (% [95%CI])	84.8% [66.2% to 103.3%]	80.1% [61.7% to 98.5%]	-4.7% [-18.6% to 9.3%]
ITG 12 months (% [95%CI])	84.7% [66.1% to 103.2%]	77.3% [59.0% to 95.7%]	-7.33% [-22.2% to 7.5%]
SD: Standard Deviation; BMI: Body Mass Index; ASDAS: AS Disease Activity Score; VAS: Visual Analogue Scale; GA: Global Assessment; ATG: Acceptable Therapeutic Goal; ITG: Ideal Therapeutic Goal			

Conclusion: This real-life study has shown that optimization of TNFi treatment is non inferior to full TNFi doses in maintaining Acceptable Therapeutic Goal after 1 year.

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Abstract Number: 2150

Treatment with Abatacept Prevents Experimental Dermal Fibrosis and Induces

Regression of Established Inflammation-Driven Fibrosis

Matthieu Ponsoye[1], Camelia Frantz[2], Nadira Ruzehaji[3], Muriel Elhai[4], Barbara Ruiz[1], Anne Cauvet[1], Yannick Allanore[5] and **Jerome Avouac**[4], [1]INSERM U1016, Paris Descartes University, Cochin Hospital, Paris, France, [2]Paris Descartes University, Rheumatology A department, Cochin Hospital, Paris, France, [3]INSERM U1016, Paris Descartes University, Paris, France, [4]Rheumatology A department and INSERM U1016, Paris Descartes University, Cochin Hospital, Paris, France, [5]Paris Descartes University, Rheumatology A department, Cochin Hospital, And Eular Scleroderma Trials And Research (EUSTAR) Board, Paris, France

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SESSION INFORMATION

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Session Title: Systemic Sclerosis, Fibrosing Syndromes and Raynaud's - Pathogenesis, Animal Models and Genetics I

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Background/Purpose: Early stages of systemic sclerosis (SSc) are characterized by inflammatory skin infiltrates mainly composed of activated T cells. Cytotoxic T-lymphocyte associated molecule-4 (CTLA-4) is a key regulator of T cell activation and preliminary data have suggested that it might contribute to SSc. Our aim was to investigate the efficacy of the CTLA-4-Ig abatacept, an inhibitor of T cell activation, in reducing skin fibrosis in complementary mouse models of SSc.

Methods: We first evaluated the antifibrotic properties of abatacept in the mouse model of bleomycin-induced dermal fibrosis. To assess whether abatacept might prevent the development of dermal fibrosis, mice received in parallel subcutaneous injections of bleomycin and intraperitoneal (i.p) injections of abatacept or purified human IgG1 at a dose of 100 mg every other day for three weeks. To assess whether abatacept might induce the regression of established dermal fibrosis, mice were challenged with bleomycin for 6 weeks and received i.p injections of 100 mg of abatacept or control IgG1 every other day during the last 3 weeks. Then, we investigated abatacept in the tight skin (Tsk-1) mice. Tsk-1 mice received i.p injections of 100 mg of abatacept or control IgG1 every other day for 5 weeks. Infiltrating T cells, B cells and monocytes were quantified in lesional skin by immunohistochemistry for CD3, CD22 and CD68. Inflammatory cytokines were measured in lesional skin by flow cytometry.

Results: Treatment with abatacept prevented the induction of bleomycin-induced dermal fibrosis: dermal thickness was significantly reduced by 48±5% in mice treated with abatacept compared to mice receiving the control IgG1 ($p=0.03$). Consistent with decreased dermal thickness, hydroxyproline content and myofibroblast counts were reduced upon treatment with abatacept by 63±4% ($p=0.02$) and 41±6% ($p=0.04$) respectively, compared to mice receiving the control antibody. In this model, treatment with abatacept led to decreased T cell, B cell and monocyte infiltration in the lesional skin. Upon bleomycin injections, skin IL-6 and IL-10 levels were significantly reduced upon abatacept treatment.

Abatacept also induced the regression of established bleomycin-induced dermal fibrosis: dermal thickness, hydroxyproline content and myofibroblast counts were reduced by 15±2% ($p<0.01$), 16±3% ($p<0.01$) and 33±5% ($p=0.01$) respectively, compared to mice receiving control antibody. Abatacept demonstrated no efficacy in Tsk-1 mice.

Conclusion: Using complementary mouse models of SSc, we demonstrate that abatacept can prevent and induce the regression of inflammation-driven experimental dermal fibrosis. Antifibrotic effects of abatacept are mediated in the bleomycin mouse model by the reduction of T cell, B cell and monocyte infiltration into lesional skin, and by the decreased of IL-6 and IL-10 skin levels. Translation to human disease is now required, and targeting early and inflammatory stages of SSc sounds the most appropriate. This strategy is currently under investigation in a phase-3 clinical trial assessing the efficacy of abatacept to improve skin involvement in patients with early diffuse SSc.

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Abstract Number: 2151

Inhibition of Myeloid-Associated Gene Expression in Skin Biopsy Samples of Systemic Sclerosis Patients Treated with Tocilizumab

Thierry Sornasse[1], Haiyin Chen[1], Lisa Rice[2], Giuseppina Stifano[2], Angelika Jahreis[1], Jeffrey Siegel[1] and Robert Lafyatis[2],
[1]Genentech, South San Francisco, CA, [2]Boston University School of Medicine, Boston, MA
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Background/Purpose: Systemic sclerosis (SSc) is a progressive, debilitating disease with limited treatment options. IL-6 has been implicated in disease pathogenesis. Tocilizumab (TCZ), an IL-6Rα inhibitor, was evaluated in the 2-year faSScinate study, a randomized, double-blind, placebo-controlled trial. At week 24 (primary end point), favorable trends in skin score for TCZ were detected though the primary skin score end point was not met. In addition, smaller declines in FVC were observed in the TCZ-treated patients.

Methods: Eighty-seven patients with active SSc were randomly assigned 1:1 to subcutaneous TCZ 162 mg or placebo (PBO) weekly for 48 weeks. The primary end point was mean change in modified Rodnan skin score from baseline at week 24. Gene expression analysis was performed on skin biopsy samples collected at baseline and week 24. First, genomewide expression analysis was conducted on all available biopsy samples and on biopsy samples of age- and sex-matched healthy volunteers (HVs) using custom Agilent 60-mer microarray (Epistem, Manchester, UK). Based on these data, 86 genes representing fibrosis, IFN, and myeloid pathways were selected for more quantitative gene expression analysis using nCounter technology (NanoString Technologies, Seattle, WA, USA). CCL18 serum levels were determined using an IMPACT-based immunoassay (Roche Diagnostics, Penzberg, Germany).

Results: Of the 86 genes selected for follow-up expression analysis, 75 were, on average, significantly overexpressed in SSc patients compared with HVs. Analysis of genes significantly downregulated after TCZ treatment and stable or increased with PBO identified a subset of 14 genes highly enriched for myeloid-associated genes, including genes associated with M2 macrophages (Table 1). All 14 genes were overexpressed in SSc patients compared with HVs. No effect of TCZ on the fibrosis and IFN pathways was detected. Serum levels of the M2 macrophage chemokine CCL18 revealed a rapid and sustained decrease from elevated levels in the TCZ group to close to levels in healthy controls but not in PBO controls.

Table 1. Relative Change in Expression Between Baseline and Week 24 in the TCZ and PBO Groups

Gene	ΔPBO, %	ΔTCZ, %	*p*	Gene	ΔPBO, %	ΔTCZ, %	*p*
*C1QB**	0.1	–42.3	0.0004	*IFI16*	–1.3	–16.2	0.0142
*CCL18**	–20.8	–58.3	0.0086	*MS4A4A**	–2.1	–30.9	0.0168
*CD14**	–3.2	–37.6	0.0002	*MSR1**	11.7	–29.9	0.0032
*CD163**	–4.7	–28.0	0.0410	*NNMT*	4.8	–27.1	0.0026
*FCGR1B**	20.4	–20.0	0.0007	*SOCS3*	3.4	–27.9	0.0157
*FCGR3B**	–3.6	–41.9	0.0018	*TLR7**	18.7	–21.5	0.0292
*FPR1**	22.4	–35.4	0.0040	*VSIG4**	0.2	–27.5	0.0248

p values were calculated using the fit least square model in JMP (SAS Institute Inc., Cary, NC, USA) of the change in expression levels between baseline and week 24 in the TCZ and PBO groups, corrected for baseline expression value.
*Myeloid-associated gene.

Conclusion: The effect of TCZ on myeloid-associated genes may reflect inhibition and/or depletion of skin-infiltrating macrophages. In addition, the effect of TCZ on CCL18 (RNA and protein), CD163, MS4A4A, and MSR1 suggests a specific inhibitory effect of TCZ on M2 macrophages, which are known to promote fibrosis and inflammation. These findings represent a potential novel mode of action for TCZ in SSc, which will be further investigated in the upcoming phase 3 study of TCZ in SSc.

Disclosure: T. Sornasse, Genentech, Inc., 1,Genentech, Inc., 3; **H. Chen**, Genentech, Inc., 1,Genentech, Inc., 3; **L. Rice**, None; **G. Stifano**, None; **A. Jahreis**, Genentech, Inc., 1,Genentech, Inc., 3; **J. Siegel**, Hoffmann-La Roche, Inc., 1,Genentech, Inc., 3; **R. Lafyatis**, Shire, Sanofi, Regeneron, Genentech, UCB, HGS, Precision Dermatology, Biogen, BMS, Inception, Stromedix, PRISM, Pfizer, 2,Shire, Sanofi, Regeneron, Roche/Genentech, Biogen, Lycera, Novartis, Celgene, BMS, Amira, Celdara, Celltex, Dart Therapeutics, ldera, Inception, lntermune, Medimmune, Precision Dermatology, Promedior, Zwitter, PRISM, UCB, Actelion, EMD Sereno, Akros, E, 5.

Abstract Number: 2152

Long Noncoding H19X Is a Key Mediator of Tgf-Beta Induced Pro-Fibrotic Effects in the Pathogenesis of Systemic Sclerosis and Other Fibrotic Diseases

Elena Pachera[1], Shervin Assassi[2], Gloria Salazar[2], Mojca Frank Bertoncelj[3], Rucsandra Dobrota[4], Matthias Brock[5], Serena Vettori[6], Claus Hellerbrand[7], Carol A. Feghali-Bostwick[8], Jeorg HW Distler[9], Gabriela Kania[10] and Oliver Distler[11], [1]Research of Systemic Autoimmune Diseases, Division of Rheumatology, University Hospital Zurich, Schileren, Switzerland, [2]Rheumatology, University of Texas Medical School at Houston, Houston, TX, [3]Center of Experimental Rheumatology, University Hospital Zurich, University Zurich, Zurich, Switzerland, [4]Division of Rheumatology, University Hospital Zurich, Zurich, Switzerland, [5]Department of Pulmonology, University Hospital Zurich, Schileren, Switzerland, [6]Department of Internal and Experimental Medicine, Rheumatology Unit, Second University of Naples, Naples, Italy, [7]Department of Internal Medicine I, University of Regensburg, Regensburg, Germany, [8]Medicine, University of Pittsburgh, Pittsburgh, PA, [9]Department of Internal Medicine 3 and Institute for Clinical Immunology, University of Erlangen-Nuremberg, Erlangen, Germany, [10]Research of Systemic Autoimmune Diseases, Division of Rheumatology, University Hospital Zurich, 8952 Schlieren, Switzerland, [11]Division of Rheumatology, University Hospital And Eular Scleroderma Trials And Research (EUSTAR) Board, Zurich, Switzerland
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Background/Purpose: Long noncoding RNAs (LncRNAs) are emerging as a novel class of noncoding transcripts involved in the regulation of gene expression. So far, for only few of them the function has been elucidated therefore their role in disease is poorly understood.

Methods: Here we aimed to identify candidate lncRNAs in systemic sclerosis (SSc) and investigate their function, particularly in relation to the TGFβ pathway and the development of the myofibroblast phenotype. RNA Sequencing Ilumina HiSeq2000 was performed in healthy control (HC) and SSc skin biopsies. Human skin fibroblasts were isolated from biopsies of SSc patients and HC; human pulmonary smooth muscle cells were purchased from Lonza. Cells were treated with 10 ng/ml TGFβ. TGFβR1 inhibitors (SD208 and SB431542) and siRNA against SMAD3 and SMAD4 were used to investigate TGFβ driven gene expression. LncRNA H19X was silenced in skin fibroblasts using locked nucleic acid antisense oligonucleotides (LNA GapmeRs), followed by qPCR analyses, immunofluorescence staining and Sircol assay. The expression of H19X was also measured in tissue samples of liver and lung fibrosis.

Results: RNA sequencing showed a significant upregulation of the lncRNA H19X in SSc versus HC skin biopsies. Importantly, the upregulation of H19X was not limited to SSc skin, but present also in the tissues from liver and lung fibrosis, indicating a broader role of H19X in fibrotic diseases. While there was no difference in the basal expression of H19X between SSc and HC cultured dermal fibroblasts, H19X was strongly and consistently induced by TGFβ. Induction of H19X by TGFβ was not limited to skin fibroblasts, but evident also in other cell types relevant for SSc, e.g. pulmonary vascular smooth muscle cells. Time curve analysis revealed that the upregulation of H19X by TGFβ was strongest after 6h reaching 12.8±0.7 induction; and dose curve analysis showed a steady increase of H19X over physiologically relevant TGFβ concentrations. These effects were TGFβR1 dependent as shown by the inhibition experiments with the chemical inhibitors SD208 and SB431542. Moreover, the upregulation of H19X by TGFβ was significantly impaired by silencing of SMAD3 and SMAD4, further pointing to a role of the canonical TGFβ pathway in H19X induction. Knockdown of H19X in skin fibroblasts led to a strong down-regulation of pro-fibrotic genes COL1A1, fibronectin and αSMA mRNAs. Immunofluorescence staining showed reduced αSMA and stress fibers formation in H19X silenced dermal fibroblasts indicating an involvement of H19X in the development of a myofibroblast phenotype. Furthermore, Sircol assay revealed a decrease of total collagen secretion upon H19X knockdown confirming the pro-fibrotic

effects of H19X.

Conclusion: This is the first study reporting changes in long-non coding RNAs in SSc and across fibrotic diseases. It opens new perspectives in studying the pathogenesis of fibrotic diseases by this novel class of regulatory, non-coding RNAs.

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Abstract Number: 2153

Nintedanib Ameliorates Fibrotic and Vascular Manifestations in Preclinical Models of Systemic Sclerosis

Jingang Huang[1], Christian Beyer[1], Yun Zhang[1], Katrin Palumbo-Zerr[2], Clara Dees[1], Oliver Distler[3], Georg A. Schett[4], Stefan Lutz Wollin[5] and Jorg HW. Distler[1], [1]Department of Internal Medicine 3 and Institute for Clinical Immunology, University of Erlangen-Nuremberg, Erlangen, Germany, [2]Department of Internal Medicine 3 and Institute for Clinical Immunology, Department of Internal Medicine 3 and Institute for Clinical Immunology, University of Erlangen-Nuremberg, Erlangen, Germany, [3]Department of Rheumatology, Research of Systemic Autoimmune Diseases, University Hospital Zurich, Zurich, Switzerland, [4]Institute for Clinical Immunology, Department of Internal Medicine 3 and Institute for Clinical Immunology, University of Erlangen-Nuremberg, Erlangen, Germany, [5]Boehringer-Ingelheim Pharma, Div. Research Germany, Bad Biberach, Germany
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Background/Purpose:

Nintedanib is a tyrosine kinase inhibitor that inhibits PDGF-, FGFR-, VEGFR-receptors and Src kinases. Nintedanib has recently been approved for the treatment of idiopathic pulmonary fibrosis (IPF). The aim of this study was to analyze the effects of nintedanib on fibrotic and vascular manifestations in preclinical models of systemic sclerosis (SSc) and to provide a scientific rationale for clinical trials in SSc.

Methods: The effects of nintedanib on migration, proliferation, myofibroblast differentiation and release of extracellular matrix were investigated by MTT- and scratch assays, stress fiber staining, qPCR and SirCol assays. The effects of nintedanib were evaluated in bleomycin-induced skin fibrosis, in murine sclerodermatous cGvHD, in Tsk-1 mice and in Fra2-tg mice.

Results:

Nintedanib reduced the PDGF- and TGFbeta-induced proliferation and migration more effectively than selective inhibition of PDGF-, VEGF or FGF-receptors. Nintedanib dose-dependently inhibited PDGF- and TGFbeta-induced myofibroblast differentiation and collagen release. In SSc fibroblasts, nintedanib also reduced the endogenous activation and decreased the collagen release even in the absence of exogenous stimulation. Nintedanib exerted potent anti-fibrotic effects in bleomycin-induced skin fibrosis, in experimental cGvHD, in Tsk-1 and in Fra2-tg mice with dose-dependent amelioration of dermal and pulmonary fibrosis. Of note, treatment with nintedanib also inhibited vascular manifestations in Fra2-tg mice. Nintedanib reduced proliferation of vascular smooth muscle cells and prevented thickening of the vessel walls and luminal occlusion of pulmonary arteries. Of note, treatment with nintedanib also inhibited apoptosis of dermal microvascular endothelial cells and blunted the

capillary rarefication in Fra2-tg mice.

Conclusion:

Nintedanib exerts potent anti-fibrotic effects in several complementary mouse models of SSc, but also ameliorates the histological features of PAH and of microangiopathy in Fra2-tg mice. The potent effects of nintedanib on fibrosis and vascular manifestations might have direct implications for the upcoming phase III clinical trial with nintedanib in SSc.

Disclosure: J. Huang, None; **C. Beyer**, None; **Y. Zhang**, None; **K. Palumbo-Zerr**, None; **C. Dees**, None; **O. Distler**, None; **G. A. Schett**, None; **S. L. Wollin**, employee of Boehringer-Ingelheim, 3; **J. H. Distler**, Research collaboration with Boehringer-Ingelheim, 9.

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Abstract Number: 2154

Inhibition of Gli Ameliorates the Pro-Fibrotic Effects of Transforming Growth Factor-Î² in Systemic Sclerosis

Ruifang Liang[1], Clara Dees[2], Katrin Palumbo-Zerr[3], Yun Zhang[3], Oliver Distler[4], Georg Schett[3] and Jeorg HW Distler[3], [1]Rheumatology and Internal Medicine 3, University of Erlangen-Nuremberg, Erlangen, Germany, [2]Department of Internal Medicine 3, University of Erlangen-Nuremberg, Erlangen, Germany, [3]Department of Internal Medicine 3 and Institute for Clinical Immunology, University of Erlangen-Nuremberg, Erlangen, Germany, [4]Division of Rheumatology, University Hospital And Eular Scleroderma Trials And Research (EUSTAR) Board, Zurich, Switzerland

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Background/Purpose: Hedgehog signaling plays a critical role in the pathogenesis of fibrosis in Systemic sclerosis (SSc). Besides canonical hedgehog signaling with Smoothened (Smo)-dependent activation of Gli transcription factors, Gli can be activated independently of classical hedgehog ligands and receptors (so-called non-canonical pathways). The aim of the present study was to evaluate the role of non-canonical hedgehog signaling in SSc and to test the efficacy of direct Gli-inhibitors that target simultaneously canonical and non-canonical hedgehog pathways.

Methods: The Gli-inhibitor GANT-61 was used to inhibit canonical as well as non-canonical hedgehog signaling, while the Smo-inhibitor vismodegib was used to selectively target canonical hedgehog signaling. In addition, Gli2 was selectively depleted in fibroblasts using the Cre LoxP system. The effects of pharmacologic or genetic of Gli2 on TGF-β signaling were analyzed in cultured fibroblasts, in bleomycin-induced pulmonary fibrosis and in mice with overexpression of a constitutively active TGF-b receptor I (TBRI).

Results: The expression of Gli2 was transcriptionally upregulated in fibroblasts and in murine tissues by TGF-β in a Smad-independent manner. Consistent with a novel role of Gli2 as a downstream mediator of TGF-β in fibroblasts, fibroblast-specific knockout of Gli2 reduced the stimulatory effects of TGF-β on fibroblasts and ameliorated TBR-induced skin fibrosis. The Gli2 inhibitor GANT-61 also prevented the stimulatory effects of TGF-β on fibroblasts *in vitro* and *in vivo*. Treatment with GANT-61 downregulated the levels of prototypical TGF-b targeted genes, reduced the collagen release and also blocked TGF-b-induced myofibroblast differentiation. In contrast, inhibition of canonical hedgehog signaling by vismodegib did not ameliorate TGF-β-induced fibroblast activation. Furthermore, GANT-61 ameliorated experimental fibrosis of the skin more efficiently than vismodegib. In the model of TBRI-induced fibrosis, mice treated with GANT-61 showed reduced dermal thickening, lower myofibroblast counts and decreased hydroxyproline content, whereas inhibition of canonical hedgehog signaling by vismodegib had no anti-fibrotic effect. GANT-61 also exerted potent anti-fibrotic effects in the model of bleomycin-induced pulmonary fibrosis and induced regression of pre-established fibrosis. In both models, GANT-61 did not only reduce levels of the hedgehog

target genes, but also the levels of the TGF-b target genes, thus confirming inhibition of TGF-b signaling upon targeting of Gli2.

Conclusion: We characterize Gli2 as a novel intracellular mediator of the pro-fibrotic effects of TGF-b. Pharmacologic inhibition of Gli2 targets canonical as well as non-canonical hedgehog signaling and ameliorates the pro-fibrotic effects of TGF-b . The potent anti-fibrotic effects of Gli2 inhibitors on cultured fibroblasts, dermal and pulmonary fibrosis and availability of direct Gli2 inhibitors for clinical use encourage additional studies to further explore the potential of Gli2 inhibitors for the treatment of fibrosis.

Disclosure: R. Liang, None; **C. Dees**, None; **K. Palumbo-Zerr**, None; **Y. Zhang**, None; **O. Distler**, None; **G. Schett**, None; **J. H. Distler**, None.

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Abstract Number: 2155

Inhibition of Sphingosine-1-Phosphate Signaling By AB22 As a Novel Strategy in the Treatment of Pulmonary Fibrosis Associated with Scleroderma

Ilia Atanelishvili[1], Yuichiro Shirai[2], Tanjina Akter[3], Erik Stolarzewicz[4], Rolf E Swenson[5], Richard Silver[6] and Galina S. Bogatkevich[7], [1]Division of Rheumatology & Immunology, Medical University of South Carolina,Charleston,USA, Charleston, SC, [2]Department of Allergy and Rheumatology, Nippon Medical School, Tokyo, Japan, Tokyo, Japan, [3]Medical University of South Carolina, charleston, SC, [4]Chem-Master International Inc, Stony Brook, NY, [5]Arroyo BioSciences, Silver Spring, MD, [6]Division of Rheumatology and Immunology, Medical University of South Carolina, Charleston, SC, [7]Division of Rheumatology & Immunology, Medical University of South Carolina, Charleston, SC

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Background/Purpose:

Activation of sphingosine-1-phosphate (S1P) signaling has been extensively documented in various fibrotic conditions including pulmonary fibrosis. The aim of this study was to provide a molecular basis for therapeutic intervention in lung fibrosis associated with scleroderma by inhibition of S1P using a novel S1P receptor 2 antagonist, AB22. AB22 has improved pharmacokinetics over other S1P receptor antagonists such as AB1 and JTE013.

Methods: AB22 and AB1 comparative efficacy was investigated in lung fibroblasts isolated from patients with scleroderma pulmonary fibrosis and in mice with bleomycin-induced pulmonary fibrosis. Lung injury was induced in 6-8 week old female C57BL/6 mice by a single intratracheal instillation of bleomycin. AB22 (Arroyo BioSciences, LLC, USA) was administrated once daily by gavage beginning on day 1 (early treatment, anti-inflammatory effect) or on day 8 (late treatment, anti-fibrotic effect) following bleomycin instillation. Two and three weeks after bleomycin instillation mice were euthanized, and broncho-alveolar lavage fluid (BALF) and lung tissue were investigated. Multiple sections from each lung were stained with hematoxylin and eosin (H&E) or with trichrome staining for collagen and other extracellular matrix proteins. For the area analysis of fibrotic changes, a quantitative fibrotic scale (Ashcroft scale) was used. Collagen, TGFβ, connective tissue growth factor (CTGF, CCN2), and α-smooth muscle actin (SMA) were studied by immunoblotting and immunofluorescent staining.

Results:

AB22 reduced collagen and CTGF in lung fibroblasts isolated from patients with scleroderma pulmonary fibrosis and in TGFβ-stimulated control fibroblasts to a higher extent as compared with AB1 and was selected for further testing in animal model of pulmonary fibrosis. Both early and late treatment with AB22 attenuated the development of bleomycin-induced pulmonary fibrosis, increased mouse survival, and decreased histological lung inflammation and fibrosis. AB22 significantly reduced

inflammatory cells and protein concentrations in BALF and diminished collagen, TGFβ, CTGF, and α-SMA expression in mice with bleomycin-induced lung fibrosis, whereas it had no effect on basal levels of these proteins.

Conclusion:

We conclude that inhibition of S1P receptor 2 using the oral antagonist AB22 restrains profibrotic events in lung fibroblasts and has marked anti-inflammatory and anti-fibrotic effects in a bleomycin model of lung injury. Inhibition of S1P signaling by AB22 may serve as a potential novel therapeutic avenue for the treatment of pulmonary fibrosis associated with scleroderma and other fibrosing diseases.

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Damage Assessment in Giant Cell Arteritis

Tanaz A. Kermani[1], Antoine G. Sreih[2], David Cuthbertson[3], Simon Carette[4], Gary S. Hoffman[5], Nader A. Khalidi[6], Curry L. Koening[7], Carol A. Langford[5], Carol A. McAlear[8], Paul A. Monach[9], Larry W. Moreland[10], Christian Pagnoux[4], Philip Seo[11], Kenneth J. Warrington[12], Steven R. Ytterberg[12] and Peter A. Merkel[13], [1]Rheumatology, University of California Los Angeles, Santa Monica, CA, [2]Department of Rheumatology, University of Pennsylvania, Philadelphia, PA, [3]Biostatistics and Informatics, Department of Pediatrics, University of South Florida, Tampa, FL, [4]Division of Rheumatology, Mount Sinai Hospital, University of Toronto, Toronto, ON, Canada, [5]Rheumatology, Cleveland Clinic, Cleveland, OH, [6]McMaster University, Hamilton, ON, Canada, [7]Rheumatology, University of Utah, Salt Lake City, UT, [8]Division of Rheumatology, University of Pennsylvania, Philadelphia, PA, [9]Rheumatology, Boston University School of Medicine, Boston, MA, [10]Rheumatology & Clinical Immunology, University of Pittsburgh, Pittsburgh, PA, [11]Division of Rheumatology, Johns Hopkins University, Baltimore, MD, [12]Rheumatology, Mayo Clinic, Rochester, MN, [13]Penn Vasculitis Center, Division of Rheumatology, University of Pennsylvania, Philadelphia, PA

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Background/Purpose: This study aimed to 1) catalogue damage in a longitudinal cohort of patients with giant cell arteritis (GCA) and 2) evaluate predictors of damage in GCA.

Methods: Patients with GCA enrolled in a prospective, multicenter, longitudinal study were included. Periodic assessment included a standardized protocol with the Vasculitis Damage Index (VDI) and the Large-Vessel Vasculitis Index of Damage (LVVID). Univariate analyses were used to evaluate predictors of any damage at last follow-up and accrual of new damage during follow-up.

Results: The study included 204 patients with GCA: 156 women (76%); mean age at diagnosis = 71.3±8.3 years; median (25^{th}, 75^{th} quartiles) time from diagnosis to entry in the cohort was 3.7 (1.0, 16.5) months. Mean (±SD) duration of follow-up for the cohort was 3.5 (±1.9) years.

At least 1 damage item was present on VDI in 54% of patients at baseline and 79% at last follow-up. For LVVID, at least 1 damage item was present in 60% at baseline and 82% at last follow-up. At least 1 damage item was recorded in 46/114 (40%) of patients diagnosed ≤180 days prior to study entry on VDI compared to 64/87 (74%) with disease duration >180 days ($p<0.0001$).

Similarly, 55/116 (47%) of patients diagnosed ≤180 days prior to study entry had at least 1 item by LVVID compared to 68/87 (78%) with disease duration >180 days (p<0.0001).

At last follow-up, at least 1 *new* item of damage was noted in 55% patients on VDI and 60% on LVVID. The median number of new damage items accrued was 1 (0-8) on VDI and 1 (0-8) on LVVID. The majority of the new damage items were cataracts (40%), hypertension (20%), osteoporosis (20%), new limb claudication/arterial occlusion/infarction (29%) and damage requiring vascular intervention (angioplasty, stent, bypass, 9%). Organ systems with damage at baseline and last follow-up are in the **Table.**

Only disease duration was associated with presence of any damage item at last follow-up (OR 1.22; 95% CI l 1.04, 1.44). Age at diagnosis, sex, any relapse, number of relapses, highest Birmingham Vasculitis Activity Score (BVAS) or highest Physician Global Assessment (PGA) were not associated with presence of damage.

Predictors of accrual of *new* damage were evaluated in 94 patients with newly-diagnosed GCA (enrolled within 90 days of GCA diagnosis) with mean (±SD) duration of follow-up 3.1 (±1.7) years. Age, sex, any relapse, number of relapses, highest BVAS, or highest PGA were not associated with new damage during follow-up.

Conclusion: Damage from vasculitis or its treatment is present in 40-50% of patients with GCA within 6 months of diagnosis, and, in >75% during follow-up. Most of the new damage accrued during follow-up is treatment-associated; however, significant disease-associated damage, especially from peripheral arterial manifestations also occurs. These results emphasize the cumulative burden of disease associated with GCA even after initial diagnosis and treatment.

Damage at baseline and last follow-up in patients with giant cell arteritis

Organ System	**VDI N=204**		**LVVID N=204**	
	Baseline N* (%)	Follow-up N* (%)	Baseline N* (%)	Follow-up N* (%)
Cardiac	21 (10)	44 (22)	33 (16)	51 (25)
Peripheral vascular**	58 (29)	66 (32)	53 (26)	66 (32)
Musculoskeletal	25 (12)	51 (25)	25 (12)	51 (25)
Ocular	45 (22)	89 (44)	54 (26)	92 (45)
Ear, Nose, and Throat	1 (0.5)	1 (0.5)	1 (0.5)	1 (0.5)
Gastrointestinal	1 (0.5)	2 (1)	0 (0)	1 (0.5)
Neuropsychiatric	4 (2)	8 (4)	5 (3)	6 (3)
Endocrine	8 (4)	10 (5)	11 (5)	9 (4)
Hematology/Oncology	0 (0)	8 (4)	0 (0)	7 (3)
Skin	1 (0.5)	1 (0.5)	4 (2)	7 (3)
Pulmonary	4 (2)	5 (3)	N/A	N/A
Renal	0 (0)	0 (0)	N/A	N/A
Other	7 (3)	15 (7)	27 (13)	44 (22)

VDI = Vasculitis Damage Index; LVVID = Large-Vessel Vasculitis Index of Damage

N* = number with ≥1 item captured in that category

** Peripheral vascular manifestations

NA = not applicable due to no items in this organ system appearing in LVVID

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Abstract Number: 2157

Relapse Characteristics and Glucocorticoid Use in Patients with Biopsy-Proven Giant Cell Arteritis

Matthew J. Koster[1], Cristian Labarca[2], Cynthia S. Crowson[3], Ashima Makol[1], Steven R. Ytterberg[4], Eric L. Matteson[1] and Kenneth J. Warrington[1], [1]Rheumatology, Mayo Clinic, Rochester, MN, [2]Rheumatology, Clinica Alemana Universidad del Desarrollo, Santiago, Chile, [3]Health Sciences Research, Mayo Clinic, Rochester, MN, [4]Rheumatology Division, Mayo Clinic, Rochester, MN

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Background/Purpose: Relapses in patients with giant cell arteritis (GCA) are common and often lead to higher cumulative use of glucocorticoids. This study aims to evaluate the relapse characteristics and glucocorticoid use among a large single-institution cohort of patients with biopsy-proven GCA.

Methods: A retrospective review was performed to identify all patients with biopsy-proven GCA from January 1998 to December 2013. Demographic, clinical, laboratory and treatment data at baseline and subsequent follow visits were collected. Relapse was defined as recurrence of clinical manifestations compatible with spectrum of GCA and/or increase in inflammatory markers (ESR/CRP), not otherwise explainable, which required reintroduction or increased dose of glucocorticoid therapy. Comparisons between relapse groups were performed using Chi-square and Kruskal-Wallis tests. Time to daily dose of <5 mg and 0 mg of prednisone as well as glucocorticoid-associated adverse events were assessed using Kaplan-Meier methods. Patients with initial oral prednisone dose of >40 mg and ≤40 mg were compared using Cox models.

Results: The cohort included 286 patients with biopsy-proven GCA (213 females and 73 males, mean [±SD] age 75.0 [±7.6] years) with a mean (±SD) followup of 6.0 (±3.9) years. During followup 213 patients (75%) had one or more relapses. In patients experiencing a relapse, 50% of relapses occurred during the first year, 68% during the first two years and 79% during the first five years of follow up. The median relapse rate observed was 0.4 [Interquartile range (IQR) 0.21, 0.64] relapses per year. We further evaluated patients in three groups; no relapse, low relapse rate (<0.5 relapses/yr), and high relapse rate (≥ 0.5 relapses/yr). A higher proportion of patients with hypertension (p=0.007), diabetes (p=0.04) and prior history of venous thrombosis (p=0.04) were present in the ≥0.5 relapse/yr group compared to the no relapse and <0.5 relapse/yr groups.

Twenty-two patients (8%) received pulse dose steroids at diagnosis. Of the remaining 264 patients, 155 (59%) initially received >40 mg and 109 (41%) ≤40 mg of daily oral prednisone. Comparing patients treated with an initial oral prednisone dose of >40mg/day with patients receiving ≤40mg/day, the mean (±SD) prednisone dose was higher at the following intervals: one year [7.4 (±2.3) g vs. 5.8 (±2.1) g; p<0.001], during the first two years [9.6 (±3.5) g vs. 7.7 (±2.7) g; p=0.01] and total follow up duration [10.0 (±4.9) g vs. 8.2 (±5.2) g; p=0.03]. Patients started on >40 mg/day reached <5 mg/day [HR 1.46 (1.09, 1.96); p=0.01] and 0 mg [HR 1.56 (1.09, 2.23); p=0.02] earlier than those started on ≤40 mg/day. Time to first relapse based on initial oral prednisone dose did not differ [HR 1.18 (0.88, 1.57); p=0.27].No difference in glucocorticoid-associated adverse events was seen between the two groups.

Conclusion: In our biopsy-proven GCA cohort, female sex, hypertension, diabetes and history of venous thrombosis were associated with increased risk of relapse. An initial prednisone dose of >40mg/day led to earlier steroid discontinuation without increase in glucocorticoid-associated adverse events.

Disclosure: M. J. Koster, None; **C. Labarca**, None; **C. S. Crowson**, None; **A. Makol**, None; **S. R. Ytterberg**, None; **E. L. Matteson**, Novartis/Sanofi/Centocor-Jansen/Celgene/Amgen/Roche/Genentech/Mesoblast/Pfizer, 2; **K. J. Warrington**, None.

Abstract Number: 2158

Mortality Associated with Giant Cell Arteritis from 1980 to 2011: An Analysis of the French National Death Certificate Database

Achille Aouba[1], Solange Gonzalez-Chiappe[2], Mireille Eb[3], Claire Delmas[1], Grégoire Rey[3], **Alfred Mahr**[2] and Boris Bienvenu[1], [1]Internal Medicine, Hospital Caen, Caen, France, [2]Internal Medicine, Hospital Saint-Louis, Paris, France, [3]Inserm-CépiDc, Hospital Bicêtre, Le Kremlin-Bicêtre, France

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Session Type: ACR Concurrent Abstract Session

Session Time: 4:30PM-6:00PM

Background/Purpose: Data from mostly small cohorts consistently suggest that a diagnosis of giant cell arteritis (GCA) does not substantially affect survival but GCA- and GCA treatment-related morbidity may result in specific patterns of causes of death. Large databases of death certificates allow for studying patterns of mortality associated with specific medical conditions and determining changes over time in the extent to which they contribute to mortality.

Methods: We obtained data from multiple-cause mortality files compiled by the French Epidemiological Center for the Medical Causes of Death (CépiDC) for 1980–2011. GCA cases were defined as decedents ≥55 years old with International Classification of Diseases (ICD) codes 446.5 (ICD-9) or M31.6 (ICD-10) listed as the underlying or contributory cause of death. We calculated annual death rates (using national census data as a denominator) and average ages at death for GCA and for the general French population; time trends were analyzed by linear regression. To investigate the relation between deaths associated with GCA due to other medical disorders, we calculated standardized mortality odds ratios (SMORs) for 16 conditions frequently listed as causes of death in the general population or with a known association with GCA morbidity or mortality. SMORs were computed from more detailed data from the death certificates from 2000 to 2011, in which GCA was listed as a contributory cause of death.

Results: Among the 14,927,440 death records compiled over the 32-year period for decedents ≥55 years old, 15,020 listed a diagnosis of GCA. Females accounted for 68% of GCA cases and 51% of general-population death records. GCA death rates increased from 1980 to 2000 (P<0.001) and decreased thereafter (P<0.001). Mean age at death for GCA patients was 83.6 years as compared with 79.6 years for the general population (≥55 years old); mean age at death from 1980 to 2011 increased by 6.4 years for patients with GCA (P<0.001) and by 3.2 years for the general population (P<0.001). From the analyses of 4,427 death certificates from 2000 to 2011, as compared with the general population (≥55 years old), GCA decedent certificates more often listed “arterial aneurysms/dissections” (SMOR: 2.42, 95% CI: 1.86–3.11), “hypertensive disease” (SMOR: 1.92, 95% CI: 1.64–2.23) or “infections (excluding pneumonia)” (SMOR: 1.77, 95% CI: 1.50–2.08) as the underlying cause of death but less often “malignant neoplasms (excluding blood cancers)” (SMOR: 0.46, 95% CI: 0.41–0.52).

Conclusion: The higher age at death with GCA as compared with the general population further supports that life expectancy is not decreased by GCA. The secular trends of increasing age at the time of death and the recent decline in GCA-associated death rates may reflect improved survival among GCA cases and/or a change in the epidemiological characteristics of GCA. Patients with GCA are at increased risk of dying from large-vessel disease and treatment-related co-morbidities, including cardiovascular disease and infection.

Disclosure: A. Aouba, None; **S. Gonzalez-Chiappe**, None; **M. Eb**, None; **C. Delmas**, None; **G. Rey**, None; **A. Mahr**, None; **B. Bienvenu**, None.

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Abstract Number: 2159

Second Temporal Artery Biopsies in Patients with Temporal Arteritis (TA)

John Fritzlen[1], Brian Younge[2], Cornelia M. Weyand[3], Gene G. Hunder[4], Jorg Goronzy[5], Kenneth J. Warrington[4] and Joseph Maleszewski[1], [1]Anatomical Pathology, Mayo Clinic, Rochester, MN, [2]Ophthalmology, Mayo Clinic, Rochester, MN, [3]Stanford, Stanford, CA, [4]Rheumatology, Mayo Clinic, Rochester, MN, [5]Emory University School of Medicine, Lowance Center for Human Immunology and Rheumatology, Atlanta, GA
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Background/Purpose: While many manifestations of TA improve quickly after starting glucocorticoid therapy, vascular inflammation appears to persist. To obtain more information about the duration of the histolopathologic changes after initiating glucocorticoids, we prospectively obtained second temporal artery biopsies in patients who had been treated for periods up to one year after first diagnostic biopsy. The study was approved by Mayo Clinic institutional IRB.

Methods: 231 patients were seen at the Mayo Clinical for suspected TA and had temporal artery biopsies (TAB) (2004-2010). In 89 (39%) TA was diagnosed. 40 of the 89 agreed to have a second TAB randomly assigned to 3, 6, 9, or 12 months after the first. The initial TAB was performed on the side clinically most suggestive of TA. The second was performed on the opposite side. Histories and physical exams were performed prior to the biopsies. After biopsy oral glucocorticoid therapy was given at a median initial dose of 60 mg/day (range 30-80/day) for one month and then reduced gradually by approximately 10% of the daily dose per 2 weeks as tolerated according to the patients' symptoms and findings. Histopathologic findings were retrospectively evaluated (in a blinded fashion) and documented by a cardiovascular pathologist (JJM).

Results: The cohort contained 28 women and the median age at diagnosis was 77 years (range 57-89). Manifestations at diagnosis were typical of TA and were similar among the four groups. Overall 26 had jaw claudication, 15 PMR, and 6 ischemic optic neuropathy (AION). Median hemoglobin for the 40 was 11.9 g/dl (range 9.3-14.1) and median ESR was 74 mm/hr (range 16-149). Second TAB still showed vasculitis in 7/10 at 3 mo., 9/12 at 6 mo, 4/9 at 9 mo, and 4/9 at 12 mo, at which time median prednisone doses were, respectively, 25.0 mg/d, 9 mg/d, 10 mg/d, and 4.5 mg/d. Overall those with a positive second TAB did not have a greater number of symptoms at diagnosis. However, all 6 pts with AION at diagnosis had vasculitis on second TAB (2 at 3 mo, 2 at 6 mo, 1 at 9 mo, and 1 at 12 mo. Of those with a positive second TAB at 3 mo, 2 had headaches, 1 jaw claudication, and 1 scalp tenderness. At 6 mo, 1 had headache and PMR, and at 9 and 12 mos, only 1 patient had headache. No patient developed any new manifestations of TA after therapy was started and no biopsy complications were observed. Giant cells were present on the initial biopsy in 22 of the 40 cases. Of those, 2 of 6 were still present at 3 mo, 6 of 8 were present at 6 mo, and none were found at 9 or 12 mos. Additionally, giant cells were found on three follow up biopsies that were not present on the first biopsy, 1 at 3 mo, 1 at 6 mo, 1 at 9 mo. Medial fibrosis was observed in 13 initial biopsies and 24 secondary biopsies with 6/10 at 3 mo, 9/12 at 6 mo, 5/9 at 9 mo, and 4/9 at 12 mo.

Conclusion: In a population of patients with TA treated with glucocorticoids, few reversible manifestations persisted after initiation of therapy, however, vasculitis continued in a diminishing number at 12 month follow-up. Medial fibrosis appears to correlate with chronicity of TA but is not always observed. Giant cells may persist up to 6 months after initial biopsy but are rarely seen after that point.

Disclosure: J. Fritzlen, None; **B. Younge**, None; **C. M. Weyand**, None; **G. G. Hunder**, None; **J. Goronzy**, None; **K. J. Warrington**, None; **J. Maleszewski**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/second-temporal-artery-biopsies-in-patients-with-temporal-arteritis-ta

Abstract Number: 2160

The Role of Ultrasound Compared to Biopsy of Temporal Arteries in the Diagnosis and Treatment of Giant Cell Arteritis: A Diagnostic Accuracy and Cost-Effectiveness Study

Raashid Luqmani[1], Ellen Lee[2], Surjeet Singh[3], Michael Gillett[2], Wolfgang A. Schmidt[4], Mike Bradburn[2], Bhaskar Dasgupta[5,6], Andreas P Diamantopoulos[7], Wulf Forrester-Barker[8], William Hamilton[9], Shauna Masters[10], Brendan McDonald[11], Eugene McNally[8], Colin T. Pease[12], Jennifer Piper[8], John Salmon[13], Allan Wailoo[2], Konrad Wolfe[14], Andrew Hutchings[15] and TABUL Study group, [1]Nuffield Department of Orthopaedics Rheumatology and Musculoskeletal Sciences, University of Oxford, Oxford, United Kingdom, [2]School of Health and Related Research, University of Sheffield, Sheffield, United Kingdom, [3]1Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences, University of Oxford, Oxford, United Kingdom, [4]Medical Center for Rheumatology and Clinical Immunology Berlin-Buch, Immanuel Krankenhaus Berlin, Berlin, Germany, [5]Rheumatology, Southend University Hospital, Essex, United Kingdom, [6]Southend University Hospital, Essex, United Kingdom, [7]Rheumatology, Hospital of Southern Norway Trust, Kristiansand, Norway, [8]Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences, University of Oxford, Oxford, United Kingdom, [9]Primary Care, University of Exeter, Exeter, United Kingdom, [10]Nuffield Department of Orthopaedics Rheumatology and Musculoskeletal Science, University of Oxford, Oxford, United Kingdom, [11]Department of Neuropathology and Ocular Pathology, Oxford University Hospitals NHS Trust, Oxford, United Kingdom, [12]Rheumatology, Leeds Teaching Hospitals NHS Trust, Leeds, United Kingdom, [13]Ophthalmology, Oxford University Hospitals NHS Trust, Oxford, United Kingdom, [14]Department of Pathology, Southend University Hospital, Essex, United Kingdom, [15]Health Services Research Unit, London School of Hygiene and Tropical Medicine, London, United Kingdom

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Background/Purpose:

Giant cell arteritis (GCA) is a relatively common form of primary systemic vasculitis which if untreated can lead to permanent sight loss. It is a medical emergency, requiring urgent treatment and investigation. We compared the value of ultrasound, as an alternative diagnostic test to temporal artery biopsy, which is typically negative in 10-30% of true cases. Our objective was to compare the effectiveness and cost effectiveness of ultrasound with biopsy in the diagnosis of patients with suspected GCA.

Methods:

We undertook a prospective multicentre cohort study of temporal artery biopsy compared to ultrasound of temporal and axillary arteries for diagnosis of newly suspected GCA. Sonographers received training and examined 10 healthy subjects and 1 patient with active GCA before participating in the study. We recruited patients referred to secondary care with suspected new onset of GCA. The main outcome measures were sensitivity, specificity and cost-effectiveness using a reference diagnosis derived from the final clinical diagnosis, American College of Rheumatology classification criteria for GCA and expert review. Cost-effectiveness analysis compared treatment costs, the impact of steroid toxicity in false-positives and the impact of GCA complications in false-negatives for the two tests and different testing strategies in combination with clinical judgement.

Results: We recruited 430 patients with suspected GCA from 20 centres between 2010 and 2013. We included 381 patients in the primary analysis (median age 71.1 years; 72% female) and 257 (67%) were given a reference diagnosis of GCA. The sensitivity of biopsy was 39% (95% CI 33-46%), significantly lower than previously published series and inferior to ultrasound (54%, 95% CI 48-60%); the specificity of biopsy was superior to ultrasound (100% vs 81%) compared to the gold standard defined by final diagnosis which included the results of the biopsy. Combining ultrasound with clinical judgement (sensitivity 93%, specificity 77%) was more cost-effective than biopsy with clinical judgement (sensitivity 91%, specificity 81%); incremental net monetary benefit was £493 (€546, US$703) per suspected case. A strategy of ultrasound for all suspected cases followed by biopsy in medium- and high-risk patients with a negative ultrasound was slightly more cost-effective (sensitivity 95%, specificity 77%, incremental net monetary benefit £498 [€552, US$710] per suspected case).

Conclusion:

We evaluated the role of ultrasound compared to biopsy as diagnostic tests in patients with suspected giant cell arteritis. We demonstrated that as primary investigation of suspected GCA, ultrasound can improve sensitivity but not specificity, when compared to biopsy. A diagnosis of GCA requires clinical assessment, based on the history and examination of the patient; a

combined strategy of scanning all patients followed by biopsy of scan negative cases provides an effective and cost effective method to evaluate patients with a medium to high index of suspicion of GCA.

Disclosure: R. Luqmani, GSK, 5,Chemocentryx, 5,Roche Pharmaceuticals, 5; **E. Lee**, None; **S. Singh**, None; **M. Gillett**, None; **W. A. Schmidt**, GlaxoSmithKline, 5,Roche Pharmaceuticals, 5,Roche Pharmaceuticals, 8; **M. Bradburn**, None; **B. Dasgupta**, GSK, Servier,UCB, 5; **A. P. Diamantopoulos**, None; **W. Forrester-Barker**, None; **W. Hamilton**, None; **S. Masters**, None; **B. McDonald**, None; **E. McNally**, None; **C. T. Pease**, None; **J. Piper**, None; **J. Salmon**, None; **A. Wailoo**, None; **K. Wolfe**, None; **A. Hutchings**, None.

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Abstract Number: 2161

Ustekinumab for the Treatment of Refractory Giant Cell Arteritis

Richard Conway[1,2], Lorraine O'Neill[3,4], Eileen O'Flynn[3], Geraldine M. McCarthy[5,6], Conor Murphy[7], Douglas J. Veale[8], Ursula Fearon[9] and Eamonn S. Molloy[10], [1]CARD Newman Research Fellow, University College Dublin, Dublin, Ireland, [2]Centre for Arthritis and Rheumatic Diseases, Dublin Academic Medical Centre, University College Dublin, Dublin, Ireland, [3]Rheumatology, Dublin Academic Medical Centre, St. Vincent's University Hospital, Dublin, Ireland, [4]Rheumatology, St. Vincent's University Hospital, Dublin 4, Ireland, [5]Rheumatology, Mater Misericordiae University Hospital, Dublin 7, Ireland, [6]University College Dublin, Dublin, Ireland, [7]Department of Ophthalmology, Royal Victoria Eye and Ear Hospital, Dublin, Ireland, [8]St Vincent's University Hospital, Centre for Arthritis and Rheumatic Diseases, Dublin Academic Medical Centre, Dublin 4, Ireland, [9]St. Vincent's University Hospital, Centre for Arthritis and Rheumatic Diseases, Dublin Academic Medical Centre, Dublin 4, Ireland, [10]St Vincent's University Hospital, Centre for Arthritis and Rheumatic Diseases, Dublin Academic Medical Centre, St Vincent's University Hospital, Dublin 4, Dublin 4, Ireland

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Background/Purpose:

Giant cell arteritis (GCA) requires treatment with high dose corticosteroids. Many patients require chronic steroid therapy with associated significant side effects. There is a lack of proven alternative therapies. Interleukin 12 (IL12) and interleukin 23 (IL23) drive Th1 and Th17 responses respectively which are central to the pathogenesis of GCA. The aim of this study was to evaluate the efficacy and safety of ustekinumab, an IL12/IL23 inhibitor in GCA.

Methods:

We performed a prospective open label study of ustekinumab in patients with refractory GCA. Ustekinumab was administered subcutaneously at a dose of 90mg at week 1 and week 4 followed by every 12 weeks. All patients met the 1990 ACR classification criteria for GCA. Patients underwent standardized clinical assessments. Disease activity was based on a combination of clinical assessment, acute phase reactants (ESR, CRP) and available imaging studies. Descriptive statistics were reported as median and interquartile range (IQR) or number (n) and percentages as appropriate, Wilcoxon Signed Rank test was used to compare between group differences. Statistical significance was set at $p<0.05$. All patients gave written informed consent and the study was approved by the ethics committee of St. Vincent's University Hospital.

Results:

12 patients commenced ustekinumab having failed to taper corticosteroid monotherapy and a median of 1 other immunosuppressive agent, with a median (IQR) of 3 (2, 5) prior relapses of GCA. 83% had experienced significant corticosteroid

side effects. Full demographic and clinical details are shown in Table 1. Median (IQR) duration of ustekinumab treatment at last follow-up was 8 (5, 11) months, 3 patients required an increase in dosing interval to 8-weekly. Median (IQR) steroid dose decreased significantly from 23mg (15, 33) to 5mg (3, 8) (p=0.003). No patient experienced a relapse of GCA during ustekinumab treatment. Efficacy outcomes are detailed in Table 2. 5 adverse events were recorded, 1 UTI, 1 LRTI, 1 hair loss, 1 parasthesia, and 1 dental abscess. 3 patients discontinued ustekinumab due to adverse events or personal preference, 2 subsequently had a relapse of GCA.

Conclusion:

Ustekinumab permitted a significant reduction in steroid dose and of other immunosuppressants in patients with refractory GCA. The efficacy of ustekinumab in GCA warrants further investigation in a randomized controlled trial.

Table 1: Baseline demographic and clinical details of included patients

Age, years, median (IQR)	68 (61, 73)
Female, n (%)	10 (83)
ACR criteria, n (%)	12 (100)
Biopsy positive, n (%)	7 (58)
Temporal artery ultrasound positive, n (%)	2 (17)
CT Angiogram positive, n (%)	3 (25)
Cranial-ischaemic complications, n (%)	2 (17%)
Vasculitis Damage Index, median (IQR)	2 (0, 2)
Disease duration, months, median (IQR)	30 (15, 39)
Failed steroid monotherapy, n (%)	12 (100)
Failed immunosuppressant, n (%)	11 (92)
Immunosuppressants failed, median (range)	1 (0, 3)
Failed methotrexate, n (%)	10 (83)
Duration methotrexate, months, median (IQR)	10 (5, 36)
Dose methotrexate, mg/week, median (IQR)	20 (15, 21)
Relapses, median (IQR)	3 (2, 5)
Clinical features at last relapse Cranial, n (%) PMR, n (%) Constitutional, n (%) Large vessel vasculitis, n (%)	7 (58) 5 (42) 6 (50) 4 (33)
Corticosteroid adverse events, n (%)	10 (83)

Table 2: Efficacy and safety outcomes

Outcome	At ustekinumab initiation	At last follow-up on ustekinumab	p-value
BVAS (median, IQR)	1 (0, 2)	0 (0, 0)	0.018
Prednisolone dose, mg, median (IQR)	23 (15, 33)	5 (3, 8)	0.003
ESR, mm/hr, median (IQR)	12 (2, 20)	18 (7, 30)	0.744
CRP mg/dL, median (IQR)	5 (2, 25)	16 (9, 36)	0.843
Physician assessed active GCA	12	1	-
Stopped corticosteroids, n (%)	-	3 (25)	-
Stopped other immunosuppressant, n (%)	-	8 (67)	-

Disclosure: R. Conway, None; **L. O'Neill**, None; **E. O'Flynn**, None; **G. M. McCarthy**, None; **C. Murphy**, None; **D. J. Veale**, None; **U. Fearon**, None; **E. S. Molloy**, None.

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Abstract Number: 2162

Associations Between Education and Health Status Among Hispanics with Self-Reported Arthritis and/or Joint Pain

Leigha Vilen[1], Rebecca J. Cleveland[2], Alfredo Rivadeneira[1], Mary Altpeter[3], Betsy Hackney[4], Victoria Sepulveda[2] and Leigh F. Callahan[4], [1]Thurston Arthritis Research Center, University of North Carolina at Chapel Hill, Chapel Hill, NC, [2]University of North Carolina at Chapel Hill, Chapel Hill, NC, [3]Institute on Aging, University of North Carolina at Chapel Hill, Chapel Hill, NC, [4]Thurston Arthritis Research Center, University of North Carolina, Chapel Hill, NC

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Background/Purpose: Understanding the associations between education and health status among Hispanics with arthritis and/or joint pain is crucial in adapting existing arthritis interventions for this minority population. Nationwide, 35.3% of Hispanics lack a high school diploma, (compared with 8.3% of non-Hispanic whites), indicating a need to assess the differences in health status among higher and lower educated Hispanics. The purpose of this study was to examine associations between education and health status in Hispanics with self-reported joint pain.

Methods: Adult Hispanic participants (n=285) were recruited from North Carolina clinics, churches, and a Mexican consulate for a 6 week pre-post evaluation of a self-directed walking program. Participants were recruited if they self-reported arthritis and/or joint pain and were physically inactive. Descriptive characteristics of the population include means and frequencies according to high school (HS) education level (<HS diploma or ≥HS diploma). Multi-level logistic regression models were used to explore associations between education and health status measures at baseline. All models were adjusted for gender, age, obesity, marital status and country of origin with study site adjusted for as a random effect.

Results: We found that 44% of participants had less than a high school education. These participants were significantly more likely to be born in Mexico (80.7%), be unmarried (14.4%), and speak only Spanish (95.0%) compared with more educated participants (Table 1). Participants lacking a high school diploma were also significantly more likely to have higher levels of fatigue (OR=1.68; 95% CI=1.01-2.80) and stiffness (OR=1.69; 95% CI=1.01-2.82), and poor general health (OR=3.11; 95% CI=1.78-5.42) (Table 2). Although failing to reach statistical significance in multivariable regression models, less educated participants also had a higher frequency of comorbidities, including heart disease, circulation problems, and diabetes. They were also more likely to have multiple chronic comorbid conditions

Conclusion: Compared to their more educated counterparts, Hispanics who self-reported arthritis and/or joint pain and were less educated had more severe joint symptoms and poorer general health. In addition, the lower educated group also showed higher rates of comorbidity and were more likely to have multiple comorbidities, which might account for some of the disparity in health status. These findings may help inform the selection and adaptation of arthritis interventions for Hispanics.

Table 1. Baseline characteristics of according to education

Baseline Characteristic	**Total Cohort**	**Education <HS**	**Education ≥HS**	**P-value[μ]**
No. of Subjects	285	126 (44.2%)	159 (55.8%)	
Demographic characteristics				
Age, mean (SD)	47.0 (11.1)	48.1 (17.5)	46.1 (14.7)	0.1445
Female, %	74.7	75.2	74.4	0.6289
Marital status				
Single, %	13.4	14.0	12.9	<.0001
Married, %	68.6	69.5	67.8	
Other, %	18.0	16.5	19.3	
BMI, mean (SD)	30.0 (6.23)	29.9 (8.56)	30.2 (8.91)	0.6607
Obesity, %	45.4	41.2	48.8	<.0001
Acculturation variables				
Born in Mexico, %	71.9	80.7	64.9	<.0001
Speak Spanish only, %	82.6	95.0	72.8	<.0001
Self-report Health Status				
Fatigue VAS (>=60), %	41.3	47.3	36.5	<.0001
Pain VAS (>=60), %	51.3	56.1	47.6	<.0001
Stiffness VAS (>=60), %	40.1	46.3	35.2	<.0001
ASE score (<=7), %	40.4	43.2	38.1	0.006
HAQ score (>=0.5), %	36.3	39.9	33.5	0.0004
RAI score (>=2), %	30.7	34.4	27.8	0.0001
General health (fair/poor), %	47.3	62.0	35.7	<.0001
Comorbidities				
Number comorbidities, mean (SD)	1.23 (1.55)	1.46 (2.63)	1.06 (1.88)	0.0371
High blood pressure, %	25.4	28.6	22.7	0.0004
Heart disease, %	5.0	5.9	4.3	0.0503
Circulation problems, %	23.7	29.2	19.4	<.0001
Stroke, %	1.8	1.6	1.9	0.5019
Diabetes, %	13.6	19.3	9.0	<.0001
Depression, %	17.9	20.5	15.9	0.0017

[μ]Chi-square p-value for categorical variables; T-test p-value for continuous variables

Table 2. Odds ratios (OR) and 95% confidence interval (CI) for the association between <HS education[μ] and health status measures at baseline

Health Status	**<HS Education[‡]**
Self-report Health Status	OR (95% CI)
Fatigue VAS (≥60)	1.62 (0.95-2.76)
Pain VAS (≥60)	1.68 (1.01-2.80)
Stiffness VAS (≥60)	1.69 (1.01-2.82)
ASE score (≤7)	1.45 (0.86-2.45)
HAQ score (≥0.5)	1.26 (0.73-2.18)
RAI score (≥2)	1.31 (0.76-2.28)
General health (fair/poor)	3.11 (1.78-5.42)
Comorbidities	
Number of comorbidities (≥2)	1.18 (0.67-2.06)
High blood pressure	1.08 (0.59-1.99)
Heart disease	1.46 (0.40-5.38)
Circulation problems	1.59 (0.87-2.92)
Stroke	1.19 (0.56-2.54)
Diabetes	1.74 (0.81-3.73)
Depression	1.37 (0.69-2.71)

[μ]Compared with education ≥HS; used with multiply imputed data for missing covariates and predictors

[‡]Adjusted for gender, age, obesity, marital status and country of origin; study site adjusted for as a random effect

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Disclosure: L. Vilen, None; **R. J. Cleveland**, None; **A. Rivadeneira**, None; **M. Altpeter**, None; **B. Hackney**, None; **V. Sepulveda**, None; **L. F. Callahan**, None.

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Abstract Number: 2163

Associations Between Sex Differences, Pain, Insomnia, and Depression in Older Adults with Osteoarthritis: A Cross-Sectional Study

Minhui Liu[1], Susan McCurry[1], Michael Vitiello[2], Basia Belza[1] and Michael Von Korff[3], [1]University of Washington School of Nursing, Seattle, WA, [2]Psychiatry and Behavioral Sciences, Biobehavioral Nursing and Health Systems, University of Washington School of Medicine, Seattle, WA, [3]Group Health Research Institute, Seattle, WA

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Background/Purpose:

Osteoarthritis (OA) is the most common form of arthritis and affects nearly 30 million Americans. Chronic pain is the major symptom in OA and patients often also live with other comorbidities, most notably insomnia and depression. Female sex has been shown to be an important risk factor for development of OA but few studies have examined its association with other comorbidities in persons with OA. The purpose of this study was to examine associations between sex and pain, insomnia and depression in older adults with OA. We hypothesized that the strength of any sex-related association would be increased with increasing numbers of comorbidities.

Methods:

8,057 participants aged 60+ with an electronic medical record OA diagnosis were mailed a screening questionnaire which asked about their pain, sleep disturbance, and depressive symptoms. Pain intensity, persistence, and interference were assessed by the Graded Chronic Pain Scale (GCPS). Insomnia severity was measured by the Insomnia Severity Index (ISI), and daytime dysfunction related to sleep was assessed by asking if participants had residual problems related to trouble sleeping, such as tiredness or poor concentration. Depression was measured by the Patient Health Questionnaire depression scale (PHQ-8). Cut points were determined based on upper tertiles of each comorbidity severity (GCPS $\geq$ 2, ISI $\geq$ 10, daytime dysfunction $\geq$ 4, and PHQ $\geq$ 6) to ensure equivalent comparisons. The Charlson Comorbidity Index was calculated from medical records of participants who had granted research access. Logistic regression analysis was conducted to examine the associations between sex and OA comorbidities.

Results:

3,321 participants completed the questionnaire. Overall, they were older (Mean = 72 yrs) and highly educated, with 81.6% completing at least community college. The majority were female (66.6%) and about 80% had one or more daytime problems related to trouble sleeping. The top four problems were trouble concentrating (13.8%), memory problems (13.7%), tiredness (12.5%), and upset stomach (11.3%). Females had a higher odds ratio of having pain and insomnia simultaneously than males (OR = 1.66, 95% CI = 1.37, 2.02), controlling for age, education, and comorbidity index. Similarly, females tended to have higher rates of pain with depression than males (OR = 1.63, 95% CI = 1.35, 1.99), and higher rates of comorbid insomnia and depression (OR = 1.57, 95% CI = 1.30, 1.88). As predicted, the association with sex appeared to be the strongest when considering the presence of the three comorbidities together (OR = 1.73, 95% CI = 1.40, 2.15), although the strength of association was similar. Females also had a higher odds ratio of daytime dysfunction related to sleep than males (OR = 1.59, 95% CI = 1.35, 1.87).

Conclusion:

Sex differences are associated with comorbid pain, insomnia, and depression in older adults with OA. Specifically, females are more likely to suffer these comorbid symptoms compared to males. In addition, the strength of this association increases with increasing comorbidity.

Disclosure: M. Liu, None; **S. McCurry**, None; **M. Vitiello**, None; **B. Belza**, None; **M. Von Korff**, None.

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Abstract Number: 2164

Burden of Symptomatic Knee Osteoarthritis in the United States: Impact of Race/Ethnicity, Age and Sex

Bhushan Deshpande[1], Jeffrey N. Katz[2], Daniel H. Solomon[2], Edward H. Yelin[3] and Elena Losina[2], [1]Orthopaedic and Arthritis Center for Outcomes Research, Brigham and Women's Hospital, Boston, MA, [2]Brigham and Women's Hospital and Harvard Medical School, Boston, MA, [3]University of California, San Francisco, San Francisco, CA

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Background/Purpose : Growing evidence suggests that the prevalence and incidence of knee OA is rising, partially due to increasing life expectancy and the growing obesity epidemic. The most commonly cited estimate of the burden of symptomatic knee OA in the US is 9.3 million individuals. This figure was derived using 2005 population estimates and is based on a prevalence estimate from a large cohort study of a predominantly white population from the 1980s. We sought to provide a contemporary estimate of the burden of knee OA in the US, taking into consideration racial/ethnic differences in obesity rates, age-

specific population size, and mortality rates. **Methods:** We used published prevalence rates of symptomatic knee OA derived from the National Health Interview Survey (2007-08) (NHIS), stratified by age, sex, race/ethnicity, and obesity status. We adjusted for self-reported OA diagnosis using positive predictive values of self-reported knee OA from the literature, and also derived the proportions of individuals with advanced (Kellgren-Lawrence grade 3 or 4), symptomatic knee OA using the validated Osteoarthritis Policy Model. We calculated the burden as the number of persons diagnosed with symptomatic knee OA by combining the stratified prevalence rates from NHIS with corresponding obesity rates from the National Health and Nutrition Examination Survey (2011-12) and population estimates from the Census Bureau (2012) among adults older than 25 years. **Results:** We estimated the overall prevalence of symptomatic knee OA as 15.6 million, with advanced knee OA comprising 8.9 million of those individuals (Table). Adults under 45 years old represented nearly 1.7 million cases of symptomatic knee OA and 0.7 million cases of advanced, symptomatic knee OA. The proportion of symptomatic knee OA cases classified as advanced among these younger persons was greater among males (36%–40%) than among females (28%–35%). Among individuals between 45 and 65 years of age, nearly 7 million have symptomatic knee OA, including 2 million racial/ethnic minorities. Prevalence was higher among females than males across all strata, and among women over 65 years of age, one in five were estimated to have symptomatic knee OA, with two-thirds of those having advanced disease. The prevalence of knee OA was greater among younger Hispanic and non-Hispanic Black women compared to non-Hispanic White women. **Conclusion:** Using contemporary national data on population size, obesity and OA prevalence, we estimated that 15.6 million persons in the US are living with symptomatic knee OA. This estimate is 68% higher than the prior estimate of 9.3 million. The majority of individuals with symptomatic knee OA are at an advanced stage of the disease. Policymakers should expect healthcare utilization for knee OA, particularly total knee replacement, to increase further in upcoming decades.

Table. Number of individuals (in thousands) with symptomatic and advanced (Kellgren-Lawrence grade 3 or 4), symptomatic knee osteoarthritis in the United States.

Age	Race/Ethnicity	Sex	Population	Symptomatic Knee OA Prevalence	Advanced, Symptomatic Knee OA Prevalence
25-44	Hispanic	Female	7,820	190 (2%)	60 (1%)
45-64			4,810	490 (10%)	260 (5%)
65+			1,800	350 (19%)	230 (13%)
25-44		Male	8,490	150 (2%)	60 (1%)
45-64			4,710	300 (6%)	160 (3%)
65+			1,350	190 (14%)	140 (10%)
25-44	Non-Hispanic Black	Female	5,690	170 (3%)	60 (1%)
45-64			5,250	560 (11%)	300 (6%)
65+			2,250	460 (20%)	310 (14%)
25-44		Male	5,170	90 (2%)	40 (1%)
45-64			4,530	311 (7%)	170 (4%)
65+			1,480	200 (14%)	140 (10%)
25-44	Non-Hispanic White	Female	24,460	550 (2%)	170 (1%)
45-64			29,820	2,730 (9%)	1,340 (4%)
65+			19,190	3,540 (18%)	2,330 (12%)
25-44		Male	24,820	430 (2%)	170 (0%)
45-64			28,950	2,060 (7%)	1,160 (1%)
65+			15,160	2,070 (14%)	1,440 (3%)
25-44	Non-Hispanic Other Race	Female	3,340	60 (2%)	20 (1%)
45-64			2,570	190 (7%)	80 (3%)
65+			1,090	180 (16%)	110 (10%)
25-44		Male	3,030	50 (2%)	20 (1%)
45-64			2,220	130 (6%)	60 (3%)
65+			840	110 (13%)	70 (9%)
Total			208,810	15,560 (7.5%)	8,900 (4.3%)

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Awareness and Reasons for Lack of Post-Fracture Osteoporosis Therapy: A Survey of Post-Menopausal Women

Denise Boudreau[1], Onchee Yu[1], Akhila Balasubramanian[2], Jane Grafton[1], Heidi Wirtz[3], Andreas Grauer[3], D. Barry Crittenden[3] and Delia Scholes[1], [1]Group Health Research Institute, Seattle, WA, [2]Center for Observational Research, Amgen, Inc., Thousand Oaks, CA, [3]Amgen Inc., Thousand Oaks, CA
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Background/Purpose: Osteoporotic fractures cause patient morbidity and increase risk for future fracture. Effective drug therapies for osteoporosis (OP) are available, yet only a minority of women receives osteoporosis pharmacotherapy (OP-Rx) post-fracture. Reasons for lack of post-fracture OP-Rx are not well understood. We undertook the first large scale survey of women with recent osteoporotic fractures to characterize their beliefs about OP and their physician interactions, and to understand the factors associated with lack of post-fracture OP-Rx.

Methods: A survey was mailed to 985 women, aged >55 years with an osteoporotic fracture in 2013-2014, who were enrollees of Group Health Cooperative, a large Northwest health plan. Receipt of OP-Rx in the 6 months post-fracture was determined from automated pharmacy data. The associations between factors of interest and non-receipt of post-fracture OP-Rx were assessed using age-adjusted modified Poisson regression with a robust sandwich estimator.

Results: 634 women returned the survey (73% response rate, excluding 119 ineligibles); mean age was 75 years (SD 11.1) and 77% were white. Primary fracture sites were distal forearm (31%), hip (27%), spine (14%), and humerus (18%). 84% of women did not receive OP-Rx within 6 months post fracture. Even among the 11% of women who were on OP-Rx prior to fracture, 40% did not continue therapy following the fracture. Only 20% of all respondents believed that OP-Rx reduces risk of fracture. Women who were not concerned about OP or future fractures, did not think OP caused their fracture, did not think OP-Rx was effective in reducing fractures, or did not believe a fracture put them at risk for future fracture were at increased risk for non-receipt of OP-Rx (Table). Similarly, women who did not discuss OP management or fracture prevention with their physicians, and whose primary source of information on OP was the media or family and friends rather than their medical providers were also at higher risk for not receiving OP-Rx.

Conclusion: The majority of women who suffered an OP fracture did not receive OP-Rx in the 6 months post-fracture. This study suggests that patient education about OP, the risk for future fracture after an initial fracture, and the potential benefits of therapy – through physician input or potentially other reliable sources – may help reverse the substantial under-treatment of women post-fracture.

Table. Association between patient perspectives and interactions with medical providers on non-receipt of osteoporosis pharmacotherapy (OP-Rx) within 6 months of osteoporotic fracture			
		Relative Risk[1]	**95% CI**
Patient self-reported perspectives and beliefs on osteoporosis and fracture			
Concerned about their future risk of fractures	Not at all vs. very/somewhat	1.13	1.05-1.21
Concerned about osteoporosis	Not at all vs. very/somewhat	1.21	1.14-1.28
Believe a fracture puts them at risk for future fractures	No vs. yes	1.17	1.09-1.25
Believe osteoporosis caused their fracture	No vs. yes	1.31	1.15-1.48
Believe OP-Rx reduces risk of fracture	No vs. yes	1.22	1.09-1.36
Believe harms of OP-Rx outweigh benefits	Yes vs. no	1.06	0.98-1.14
Interactions with medical providers on osteoporosis and fractures			
Primary source of information on osteoporosis	Media vs. medical provider Family/friends vs. medical provider	1.13 1.20	1.05-1.21 1.11-1.30
PCP aware of fracture	No vs. yes	1.08	1.00-1.17
Told had osteoporosis by provider	No vs. yes	1.25	1.16-1.36
Provider recommendation to prevent fractures and/or manage osteoporosis	OP-Rx Other (e.g. supplements, diet) No recommendation	(ref) 1.89 1.85	1.61-2.21 1.57-2.19
Contact with PCP post fracture	No vs. yes	1.03	0.92-1.15
Discussed preventing fractures	No vs. yes	1.13	1.04-1.24
Discussed managing osteoporosis	No vs. yes	1.38	1.23-1.54
Osteoporosis was among top 3 topics discussed at PCP visits	No vs. yes	1.34	1.21-1.49
Time spent with PCP	Not enough vs. enough	0.92	0.78-1.08

Abbreviations: OP-Rx –osteoporosis pharmacotherapy; PCP – primary care provider

[1] All risk estimates, except for age, are adjusted for age.

Disclosure: D. Boudreau, Amgen, 2; **O. Yu**, Amgen, 2; **A. Balasubramanian**, Amgen, 3,Amgen, 1; **J. Grafton**, Amgen, 2; **H. Wirtz**, Amgen, 1,Amgen, 3; **A. Grauer**, Amgen, 1,Amgen, 3; **D. B. Crittenden**, Amgen, 1,Amgen, 3; **D. Scholes**, Amgen, 2.

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Work Productivity in Newly Diagnosed, Untreated Rheumatoid Arthritis Patients

Siri Lillegraven[1], Nina P. Sundlisæter[1], Anna-Birgitte Aga[1], Inge C Olsen[1], Till Uhlig[2], Tore K. Kvien[1], Espen A. Haavardsholm[1] and The ARCTIC study group, [1]Dept. of Rheumatology, Diakonhjemmet Hospital, Oslo, Norway, [2]Diakonhjemmet Hospital, Oslo, Norway

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Background/Purpose:Rheumatoid arthritis (RA) is a known cause of work productivity loss. The goal within rheumatology today is to diagnose RA as soon as possible, to allow for early and aggressive treatment aiming for remission and sustained levels of daily activities. The objective of the current study was to assess work participation in an early, untreated RA cohort, and assess if work productivity differed across groups of patients according to disease activity.

Methods: Consecutive RA patients who fulfilled the 2010 ACR/EULAR classification criteria were recruited between October 2010 and April 2013. All patients had symptom duration <2 years from first swollen joint, and were disease modifying anti-rheumatic drug (DMARD) na•ve with indication for DMARD treatment at time of inclusion. The data collection included clinical examination, patient reported outcome measures (e.g. Work Productivity and Activity Impairment Questionnaire, WPAI) and laboratory assessment. We used data from WPAI and additional information on work participation to assess absenteeism (work time missed), presenteeism (impairment while at work) and overall work productivity loss (absenteeism plus presenteeism) due to RA. We then compared work participation across disease activity groups by Mann-Whitney U-test or chi-square test as appropriate.

Results: A total of 233 patients were included with median (25^{th} percentile, 75^{th} percentile) age 53.9 (41.7, 62.5) years, median disease duration from first swollen joint 5.7 (2.8, 10.2) months, 61.8 % female gender and 82.0% anti-citrullinated protein antibody (ACPA) positivity. 176 patients (75.5%) reported current employment (**Table**). Patients not reporting employment were retired (49.1%), on disability pension (19.3%) or unemployed for other reasons (31.6%). Although employed patients overall had limited absenteeism and moderate work productivity loss, patients with high disease activity had higher levels of absenteeism (median 71.4% vs 0.0%, p-value<0.001), presenteeism (40.0% vs. 10.0%, p-value < 0.01) and had impaired overall work productivity (85.7% vs. 50.0%, p-value <0.001) compared to patients in low disease activity (**Table**). There were no significant differences between groups with regards to age, gender, ACPA positivity and disease duration.

	All patients (n=233)	Low disease activity (n=33)	Moderate disease activity (n=103)	High disease activity (n=85)
Female %(n)	61.8 (144)	69.7 (23)	61.1 (63)	60.5 (52)
Age*	53.9 (41.7, 62.5)	52.2 (40.0, 62.7)	51.9 (40.4, 61.6)	55.3 (47.0, 62.9)
ACPA+ %(n)	82.0 (191)	84.9 (28)	87.4 (90)	75.3 (64)
Time since first swollen joint, months*	5.7 (2.8, 10.2)	7.2 (4.0, 9.9)	6.1 (3.4, 11)	4.2 (2.6, 9.6)
EQ-5D*	0.66 (0.23, 0.73)	0.73 (0.59, 0.80)	0.69 (0.52, 0.76)	0.52 (0.06, 0.66)
Currently employed %*	75.5 (176)	72.7 (24)	78.6 (81)	**70.1 (60)**
Absenteeism %*	0.0 (0.0, 100.0)	0.0 (0.0, 10.0)	0.0 (0.0, 50.0)	**71.4 (0.0, 100.0)¤**
Presenteeism %*	30.0 (10.0, 50.0)	10.0 (0.0, 40.0)	30.0 (10.0, 40.0)	**40.0 (20.0, 60.0)#**
Overall work impairment due to RA %*	50 (20.0, 100.0)	27.7 (0.0, 50.0)	40.0 (20.0, 70.0)	**85.7 (50.0, 100.0)¤**
# p-value <0.05 when compared to patients in low disease activity ¤ p-value<0.001 *Median (25th percentile, 75th percentile) Disease activity groups were defined according to disease activity score (DAS): low disease activity = DAS 1.6-2.4, moderate disease activity = DAS 2.4-3.7, high disease activity = DAS>3.7.				

Conclusion: Newly diagnosed DMARD-na•ve RA patients on average had low levels of absenteeism, but about half the patients had work impairment due to either absenteeism or presenteeism. Patients with high disease activity had higher levels of absenteeism, presenteeism and overall work impairment than patients with low disease activity. The data suggest that the 2010 ACR/EULAR classification criteria might capture RA patients with short symptom duration before significant loss of work productivity, but that even in this group many patients have already experienced work impairment due to their disease.

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Application of Combined Reporting of Benefit and Harm (OMERACT 3×3 methodology) to the Rheumatoid Arthritis Comparison of Active Therapies Trial

Maarten Boers[1,2], Sarah Leatherman[3], James R. O'Dell[4] and Jeffrey R. Curtis[5], [1]Rheumatology, Amsterdam Rheumatology and immunology Center, VU University medical center, Amsterdam, Netherlands, [2]Amsterdam Rheumatology and immunology Center, VU University Medical Center, Amsterdam, Netherlands, [3]MAVERIC CSPCC (151MAV), VA Boston Healthcare System, Boston, MA, [4]University of Nebraska Medical Center, Omaha, NE, [5]Birmingham VAMC, Birmingham, AL

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Background/Purpose:

The Outcome Measures in Rheumatology (OMERACT) Initiative has suggested an analysis of the occurrence of benefit and harm in trials simultaneously, at the individual patient level can enhance trial reports. We applied this method in a recent trial dataset.

Methods:

OMERACT suggests creating 3 levels of benefit and harm, and expressing each patient's outcome as a pair of values for benefit and harm. **Results** for the groups are summarized in 3x3 contingency tables. In addition, outcome of patients at the extremes can be labeled as 'unqualified success', resp. 'unmitigated failure'. The 48-week data of the recent 'RA Comparison of Active Therapies' (RACAT) study were re-analyzed according to this framework.

Three levels of harm were defined as 1) no adverse events (none), 2) at least one adverse event (AE), and 3) at least one serious adverse event or withdrawal from the trial due to an adverse event (SAE). The three levels of benefit were defined using both ACR and the EULAR response criteria. Under ACR criteria, the three levels of benefit were defined as 1) less than 20% improvement (none), 2) 20% or 50% improvement (moderate), and 3) 70% improvement or greater (good). Unqualified success was defined as achieving a good response without AE; unmitigated failure as no response with SAE. Chi-square tests assessed the association between benefit and harm, or exact tests where appropriate.

Results:

The trial compared addition of sulfasalazine and hydroxychloroquine or etanercept to methotrexate (MTX) in RA patients with inadequate response. Of the 353 randomized patients, 309 were followed to study completion at 48 weeks and were eligible for analysis. Of those, 226 (73%) experienced adverse events and 46 (15%) experienced serious adverse events.

Under the ACR criteria, 3% patients experienced an unqualified success, while 9% experienced an unmitigated failure. For the 154 patients randomized to triple therapy, the rates were 3 resp. 9% (Table); for the 155 MTX + etanercept the rates were 3 resp. 8% (Table).

Under EULAR criteria, 6% patients experienced an unqualified success while 4% experienced an unmitigated failure. For the triple therapy patients the rates were 4 resp 4%; for the MTX + etanercept patients the rates were 6 resp. 4%.

Benefit by both EULAR and ACR response distributions were significantly associated with the three levels of harm (p=0.008 and p=0.01, respectively): frequency of AE and SAE increased as response decreased. There we no significant differences in associations across treatment groups (p=0.83 and p=0.44 by EULAR and ACR criteria, respectively).

Conclusion:

This is the first study to suggest that in trials the occurrence of harm increases as benefit decreases.

Benefit – ACR Response (%)

Harm (%)	Triple Therapy (n=154) Good	Mod.	None		MTX+Etanercept (n=155) Good	Mod.	None	
None	3	4	3	10	3	8	3	14
AE	14	31	30	74	22	27	23	72
SAE	2	5	9	16	1	4	8	14
	19	40	42		26	39	34	

Disclosure: M. Boers, None; **S. Leatherman**, None; **J. R. O'Dell**, None; **J. R. Curtis**, None.

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The Smoking Paradox in the Development of Myocardial Infarction Among

Rheumatoid Arthritis Patients

Uyen Sa D.T. Nguyen[1], Yuqing Zhang[2], Na Lu[3], Jingbo Niu[4], David T. Felson[4], Michael P. Lavalley[5], Jeffrey A. Sparks[6], Shun-Chiao Chang[7], Elizabeth W. Karlson[8] and Hyon K. Choi[3], [1]Orthopedics and Physical Rehabilitation, University of Massachusetts Medical School, Worcester, MA, [2]Clinical Epidemilogy and Training Unit, Boston University School of Medicine, Boston, MA, [3]Rheumatology, Allergy and Immunology, Massachusetts General Hospital, Harvard Medical School, Boston, MA, [4]Clinical Epidemiology Research and Training Unit, Boston University School of Medicine, Boston, MA, [5]Biostatistics, Boston University, Boston, MA, [6]Division of Rheumatology, Immunology, and Allergy, Brigham & Women's Hospital, Boston, MA, [7]Division of Rheumatology, Immunology and Allergy, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, [8]Rheumatology, Brigham & Women's Hospital, Boston, MA

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Background/Purpose: Smoking is a strong risk factor for myocardial infarction (MI), but not among rheumatoid arthritis (RA) patients. These paradoxical findings may be due to index event bias (a type of selection bias) which arises from selecting a group of patients (e.g., RA) on the causal pathway (e.g., between smoking and MI); thus, true risk factors may appear spuriously null or protective. We sought to identify this paradox, and employ a sensitivity analysis to handle the unmeasured or uncontrolled factor (U) that could partly explain the paradox.

Methods: We used data from The Health Improvement Network (THIN), an electronic medical record database representative of the UK general population, from 1995-2015. We analyzed data from adults (≥ 20 years) free of RA and MI after at least 1 year of enrollment in the THIN database. Follow-up began with first recording of smoking status after the 1-year enrollment and ended at the time of MI, death, loss of follow-up, or the end of the study period, whichever came first. We assessed the effect of smoking on MI using Cox regression in the general population, and restricting on incident RA patients. We conducted a sensitivity analysis to correct for the bias from U, by varying the prevalence of U and its association with MI. Analyses were adjusted for baseline confounders.

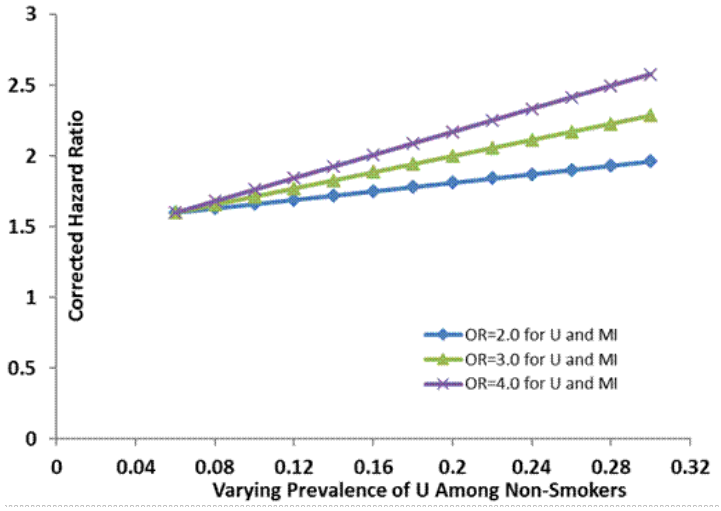
Results: Of ~3.7 million subjects (mean age 46 years; 55% women; 28% current-smokers and 19% ex-smokers), 16,061 developed incident RA of which 296 had incident MI. The adjusted hazard ratio (HR) for current smoking and MI among RA patients was 1.56 (95%CI: 1.15, 2.12), whereas the corresponding HR in the general population was 2.42 (95%CI: 2.37, 2.48) (**Table**). On the additive scale, the adjusted rate difference was 1.1 among RA patients, and 2.2 in the general population. For the biased HR of 1.6, the corrected HR estimate ranged from 1.60-2.57 when the prevalence of U was set to 6% among smokers, with the prevalence of U ranging from 20-30% in nonsmokers, and the association between U and MI ranging from 2.0-4.0 **(Figure)**.

Conclusion: We demonstrated that conditioning on RA can bias the association between smoking and MI toward the null, and provided a method to partly correct for this paradox. Since this bias could considerably mislead the conclusion about the contribution of modifiable risk factors to important clinical outcomes, investigators should consider appropriate design and analytic approaches to avoid such biases.

Table. Association between Smoking and MI in the General Population and Among RA Patients			
	Non-Smokers	**Ex-smokers**	**Current Smokers**
General Population	**N=1,999,923**	**N=725,400**	**N=1,046,288**
Number of MI	19,073	12,317	17,137
Total Follow-up Years	12,418,719	4,324,379	6,495,178
Rate (1/1000 person-yr)	1.54	2.85	2.64
Crude HR	*1.0*	*1.81 (1.77, 1.86)*	*1.71 (1.67, 1.75)*
Adjusted HR*	***1.0***	***1.24 (1.21, 1.28)***	***2.42 (2.37, 2.48)***
Among RA Patients	**N=7,520**	**N=3,588**	**N=4,953**
Number of MI	124	66	106
Total Follow-up Years	34,147	15,683	23,120
Rate (1/1000 person-yr)	3.63	4.21	4.58
Crude HR	*1.0*	*1.25 (0.91, 1.72)*	*1.32 (0.99, 1.74)*
Adjusted HR*	***1.0***	***1.03 (0.73, 1.44)***	***1.56 (1.15, 2.12)***
Adjusted for age, sex, baseline body mass index and alcohol intake			

Figure. Sensitivity Analysis of the Index Event Bias with a Biased HR of 1.6

(Assuming a 6% Prevalence of an Uncontrolled Factor (U) among Smokers)



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Low Education Is Associated with Mortality Among Individuals with Knee and/or Hip OA: The Johnston County Osteoarthritis Project

Rebecca J. Cleveland[1], Todd A. Schwartz[2], Jordan B. Renner[3], Joanne M. Jordan[4] and Leigh F. Callahan[4], [1]University of North Carolina at Chapel Hill, Chapel Hill, NC, [2]School of Nursing, University of North Carolina, Chapel Hill, NC, [3]Radiology, University of North Carolina, Chapel Hill, NC, [4]Thurston Arthritis Research Center, University of North Carolina, Chapel Hill, NC

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Background/Purpose: Low socioeconomic status (SES) is associated with an increased risk of death as well as knee and/or hip osteoarthritis (OA). SES and mortality has rarely been examined in individuals with OA. We therefore sought to explore whether SES at baseline was associated with death before follow-up assessments among those with knee and/or hip OA.

Methods: The association between SES and all-cause death over 25 years was explored in the Johnston County Osteoarthritis Project. We used baseline data from 1,333 individuals aged ≥45 who entered the cohort between 1990-1997 and who had known vital status at all three follow-up periods. Participants had radiographically confirmed knee and/or hip OA at baseline clinical assessment, defined as a Kellgren-Lawrence grade ≥2. Vital status was assessed at 3 follow up points (F1: 1999-2004; F2: 2006-2010, F3: 2013-2015), and deaths were identified through participant provided contacts and obituaries. SES measures at baseline included indicators for high school (HS) education (<HS diploma *vs.* ≥HS diploma), block group poverty (BGP) (≥20% *vs.* <20%), homeownership (own their home *vs.* not), and annual household income (<$30K *vs.* ≥$30K). Multilevel logistic regression models controlling for the primary sampling unit were used to estimate odds ratios (OR) and 95% confidence intervals (CI) for the association between individual SES measures at baseline and whether a death occurred separately for each follow-up point. All models were adjusted for baseline age, race, sex, cohort, education, BMI, use of an assistive walking device, history of smoking, stroke, diabetes, heart disease, high blood pressure and depression, plus additional adjustment for other SES measures.

Results: Mean age at baseline was 65.4 years, with 61.8% women and one-third African American. There were 49.0% with <HS education, 43.9% lived in areas with ≥20% BGP, 28.7% did not own their home and 82.6% had a household income <$30K. There were 234 deaths which had occurred before the F1 assessment (18.1%), 528 deaths before F2 (41.1%) and 680 deaths before F3 (52.9%). Those with <HS education had an increased odds of death that appeared to gain strength at subsequent follow up points (Table 1). By F3, those with <HS education had a 50% increased odds of death (OR=1.52; 95% CI=1.06-2.17). Although failing to reach statistical significance, we observed a similarly elevated OR for BGP ≥20% at each subsequent timepoint.

Conclusion: Among individuals with knee and/or hip OA, low education is associated with death, where odds of death seems to increase at subsequent follow-up periods. Results were independent of comorbidities and sociodemographic measures commonly linked to increased mortality, although lack of time-to-death and cause of death are limitations. Results suggest that those with low education may need more intensive guidance regarding self-management from clinicians.

Table 1. Adjusted odds ratios (95% CI)[¥] for death* at first, second and third follow-up according to SES measures assessed at baseline among those with knee and/or hip OA

	Follow-up 1		Follow-up 2		Follow-up 3	
	Deaths/Alive	OR (95% CI)	Deaths/Alive	OR (95% CI)	Deaths/Alive	OR (95% CI)
Education at baseline						
≥High School education	82/572	Ref.	200/454	Ref.	267/387	Ref.
<High School education[‡]	152/477	1.23 (0.86-1.77)	328/301	1.36 (1.02-1.83)	413/216	1.44 (1.08-1.94)
<High School education[µ]	152/477	1.14 (0.74-1.76)	328/301	1.44 (1.01-2.06)	413/216	1.52 (1.06-2.17)
20% BG Poverty at baseline						
Block Group Poverty<20%	118/551	Ref.	271/398	Ref.	347/322	Ref.
Block Group Poverty ≥20%[‡]	102/433	1.17 (0.80-1.70)	221/314	1.11 (0.81-1.51)	286/249	1.16 (0.85-1.58)
Block Group Poverty ≥20%[µ]	102/433	1.15 (0.77-1.73)	221/314	1.19 (0.84-1.69)	286/249	1.29 (0.91-1.83)
Homeownership at baseline						
Owns their home	149/795	Ref.	378/566	Ref.	487/457	Ref.
Doesn't own their home[‡]	86/256	1.59 (1.10-2.31)	152/190	1.12 (0.81-1.55)	196/146	1.25 (0.90-1.74)
Doesn't own their home[µ]	86/256	1.48 (0.97-2.26)	152/190	1.03 (0.71-1.51)	196/146	1.11 (0.75-1.65)
Household income at baseline						
Household income ≥$30k	21/160	Ref.	45/136	Ref.	64/117	Ref.
Household income <$30k[‡]	183/681	0.88 (0.49-1.59)	388/476	1.16 (0.72-1.86)	496/368	1.01 (0.64-1.60)
Household income <$30k[µ]	183/681	0.77 (0.41-1.45)	388/476	1.07 (0.64-1.78)	496/368	1.00 (0.61-1.62)

[¥]Controlling for primary sampling unit
*Compared to those known to be alive
[‡]Adjusted for age, race, sex, cohort, BMI, smoking, diabetes, heart disease, high blood pressure, stroke, depression, use of an assistive device at baseline
[µ]Additionally adjusted for other SES measures

Disclosure: R. J. Cleveland, None; **T. A. Schwartz**, None; **J. B. Renner**, None; **J. M. Jordan**, None; **L. F. Callahan**, None.

Abstract Number: 2170

Sleep Efficiency and Cardiovascular Risk Burden in Rheumatoid Arthritis

Samannaaz S. Khoja[1], Gustavo J. Almeida[2], Mary Chester M. Wasko[3] and Sara R. Piva[2], [1]Department of Physical Therapy, University of Pittsburgh, Pittsburgh, PA, [2]Physical Therapy, University of Pittsburgh, Pittsburgh, PA, [3]Lupus Center, Pittsburgh, PA

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Background/Purpose: Sleep is an important physiological process responsible for regulating several metabolic and hormonal processes; hence, poor sleep may negatively impact health. Reduced sleep duration and restless sleep (i.e., low sleep efficiency) has been related to a higher risk of cardiovascular disease (CVD) in the general population. Individuals with RA commonly report poor sleep quality, and also have greater CVD risk than their healthy counterparts. However, the relationship between sleep quality and CVD risk in RA is not clear. Thus, the aim of the study was to assess associations between objectively measured sleep quality (duration and efficiency) and CVD risk factors in RA.

Methods: This was a secondary, cross-sectional analysis of baseline data from two studies in persons diagnosed with RA based on the ACR classification criteria. Sleep duration and efficiency were measured using a multi-sensor activity monitor, the Sensewear Armband (Bodymedia, Pittsburgh), which has been validated against polysomnography as an accurate measure of sleep duration and efficiency. Sleep efficiency is expressed as a ratio of actual sleep time to lying down time. Subjects wore the monitor for 7 days and average daily sleep duration and efficiency were calculated. Cardiometabolic markers consisted of blood pressure, lipid profile, and insulin resistance measured by homeostatic model of assessment. Demographics, BMI, and disease severity using the DAS-28 were also obtained. Multiple linear regression models were used to determine the association between each cardiometabolic marker and sleep efficiency, and duration after adjusting for age, gender, cohort, BMI and DAS-28 scores.

Results: Complete data for data analysis was available in 89 subjects with RA, (90% female, 58 ± 9 years, BMI 29 ± 7 kg/m^2) who had mild functional limitations (HAQ score 0.8 ± 0.6), moderate disease activity (DAS-28 3.5 ± 1.2), and median RA duration of 15 years. Subjects spent 8.2 ± 1.5 hours lying down and 6.5 ± 1.4 hours in actual sleep, with a sleep efficiency of 80%. Adjusted models demonstrated that greater sleep efficiency significantly associated with lower low-density lipoproteins and higher high-density lipoproteins (p <. 05) (Table). In contrast, sleep duration was not associated with any cardiometabolic markers.

Conclusion: Poor sleep efficiency seems to be more indicative of non-favorable cardiometabolic markers in individuals with RA than sleep duration. Normal circadian rhythms are crucial for regulating several metabolic processes, including lipid metabolism. Hence, it stands to reason that poor sleep efficiency could directly influence certain cardiometabolic markers, independent of body size, and RA severity. Although the current study is limited due to its cross-sectional design, the findings indicate the need to further investigate the influence of sleep quality on CVD risk profile in RA.

TABLE. Associations between Sleep Duration and Efficiency, and Cardiometabolic Markers. Values represent standardized coefficients (β), R^2 change (R2Δ), and p-values from linear regression models.

	Sleep Efficiency			**Sleep Duration**		
Variables	β	$R^2\Delta$	P-value	β	$R^2\Delta$	P-value
Diastolic Blood Pressure, *mmHg*	-.09	.01	.40	.07	.01	.49
†Systolic Blood Pressure, *mmHg*	-.15	.02	.15	<.01	<.01	.99
†High Density Lipoprotein, *mg/dl*	**.19**	**.04**	**.03**	-.02	<.01	.81
†Low Density Lipoprotein, *mg/dl*	**-.22**	**.05**	**.04**	<-.01	<.01	.97
†Triglyceride level, *mg/dl*	-.07	.01	.49	-.11	.01	.33
†Insulin Resistance	-.09	.01	.34	-.02	<.01	.83

Models adjusted by age, gender, study cohort, BMI and DAS-28 scores

†Indicates that the dependent variable was log transformed to meet the assumptions for multiple linear regression.

Disclosure: S. S. Khoja, None; **G. J. Almeida**, None; **M. C. M. Wasko**, None; **S. R. Piva**, None.

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Abstract Number: 2171

A Comparison of Maternal Outcomes in Women with and without Juvenile Idiopathic Arthritis

Debbie Ehrmann Feldman[1], Sasha Bernatsky[2], Evelyne Vinet[3], Ciarán M. Duffy[4], Elizabeth Hazel[5], Garbis Meshefedjian[6], Marie-Pierre Sylvestre[7] and Anick Bérard[1], [1]Université de Montréal, Montréal, QC, Canada, [2]Rheum/Clin. Epid., McGill MUHC/RVH, Montreal, QC, Canada, [3]McGill University Health Centre, Montreal, QC, Canada, [4]Children's Hospital of Eastern Ontario and University of Ottawa, Ottawa, ON, Canada, [5]Rhematology, McGill University Health Centre, Montreal, QC, Canada, [6]Public Health Department of Montreal, Montreal, QC, Canada, [7]Université de Montréal, Montreal, QC, Canada

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Background/Purpose: Although there is a higher frequency of adverse maternal outcomes in mother with rheumatoid arthritis, little is known regarding mothers with juvenile idiopathic arthritis (JIA). Our objective was to determine whether women with a history of JIA have more adverse maternal outcomes than mothers who never had JIA.

Methods:

Our cohort study used data from physician billing and hospitalizations covering Québec, Canada. We identified all females with JIA with a first-time birth between 01/01/1983 and 12/31/2010, and assembled a control cohort of first-time mothers without JIA from the same administrative data, matching 4:1 for date of first birth, maternal age and area of residence. We compared maternal outcomes (hypertension, diabetes, preeclampsia/eclampsia) in the JIA versus non-JIA groups, using logistic regression. We adjusted for maternal education, and socioeconomic status (as measured by a geographic deprivation index).

Results:

Mean age at delivery was 24.7 years in the JIA group (n=1681) and 25.0 for the non-JIA group (n=6724). Mothers with JIA were more likely to have hypertension during pregnancy compared with those who did not have JIA (8.5% (95% confidence interval (CI) 7.3,9.9) vs 4.6%, 95% CI 4.2,5.2). The proportion in the JIA group with preeclampsia/eclampsia was 3.8% (95% CI 2.9,4.8)vs 2.8% (95% CI 2.4,3.2) in the non JIA group and the proportion with diabetes during pregnancy was 0.9% (95% CI 0.5,1.5) in the JIA group vs 0.6% in the non JIA group (95% CI 0.4,0.8). Among JIA mothers, 99% who had hypertension during pregnancy also had pre-pregnancy hypertension compared with 57% in the non JIA group. Similarly, 100% who had diabetes during pregnancy had pre-pregnancy diabetes in the JIA group vs. 63% in the non JIA group. In multivariate analyses, women with JIA were more likely to have hypertension during pregnancy (odds ratio (OR) 1.89, 95% confidence interval (CI) 1.55,2.28), but not preeclampsia/eclampsia (OR 1.06, 95% CI 0.80,1.42) compared to control women; the OR for diabetes during pregnancy (1.66, 95% CI 0.91,3.02) was inconclusive. Lower socioeconomic status was associated with all three adverse maternal outcomes in the entire group.

Conclusion:

Mothers with JIA were more likely to have hypertension during pregnancy compared to women without JIA. Further studies would be useful to assess the impact of medications and other factors (e.g. obesity) on maternal outcomes in JIA.

Disclosure: D. Ehrmann Feldman, None; **S. Bernatsky**, None; **E. Vinet**, None; **C. M. Duffy**, None; **E. Hazel**, None; **G. Meshefedjian**, None; **M. P. Sylvestre**, None; **A. Bérard**, None.

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Abstract Number: 2172

Distribution of Clinical Osteoarthritis and Associations to Health-Related Quality of Life in a Population-Based Osteoarthritis Cohort

Guro Økelsrud Lombnæs[1], **Karin Magnusson**[2] and Kåre Birger Hagen[1], [1]National Advisory Unit on Rehabilitation in Rheumatology, Department of Rheumatology, Diakonhjemmet Hospital, Oslo, Norway, [2]Department of Rheumatology, National Advisory Unit on Rehabilitation in Rheumatology, Diakonhjemmet Hospital, Oslo, Norway

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Background/Purpose:

Osteoarthritis (OA) is a major cause of musculoskeletal pain and disability, and is commonly reported to impair health-related quality of life (HRQoL). We aimed to examine the distribution of clinical OA in the hand-, knee-, and hip joints, and to investigate whether dimensions of HRQoL differ in mono-articular and poly-articular OA.

Methods:

Postal questionnaires regarding musculoskeletal pain, comorbidities and perceived HRQoL, assessed by the 36-item Short Form survey (SF-36), were sent to the general population (n=12.155, response rate 41.1%). Subsequently, those who self-reported OA in the hand-, hip- and/or knee joint(s) (n=1045) were invited to attend a clinical examination. 630 persons attended, of whom 547 participants free of inflammatory rheumatic disease were analyzed. Using the ACR-criteria for clinical OA, the participants were categorized into mono-articular OA (MOA, i.e. OA in one single joint site) or poly-articular OA (POA, i.e. OA in ≥ 2 joint sites) or no clinical OA (NOA). We performed crude and adjusted linear regression analyzes with the OA categories as the independent variable, using NOA as reference category, and the SF-36 eight dimensions as the dependent variable.

Results:

176 participants (32.2%) were categorized into the NOA group, 268 (49%) in the MOA group and 103 (18.8%) in the POA group (mean ± SD age 63.9 ± 8.8 years, 68% women). Clinical hand OA affected 75.5% of the OA population (Figure 1). Participants with POA had higher BMI (mean 29.4 ± 4.9) compared to participants with MOA (27.6 ± 4.7) (p = 0.003). Five out of eight SF-36 subcomponents were significantly poorer in the POA group compared to the NOA group (Figure 2), and remained significant in analyzes adjusted for age, gender, BMI, education and comorbidity: Social Functioning (B = -5.7, 95%CI = -11.2 to -0.1), Vitality (B = -6.7, 95% CI = -11.6 to -1.8), Pain (B = -7.5, 95% CI = -7.5 to -2.7), Physical Role (B = -15.1, 95% CI = -24.7 to -5.5) and Physical Functioning (B = -8.8, 95% CI = -13.6 to -4.0). There were no differences in any of the SF-36 subcomponents between the MOA and NOA groups.

Figure 1:

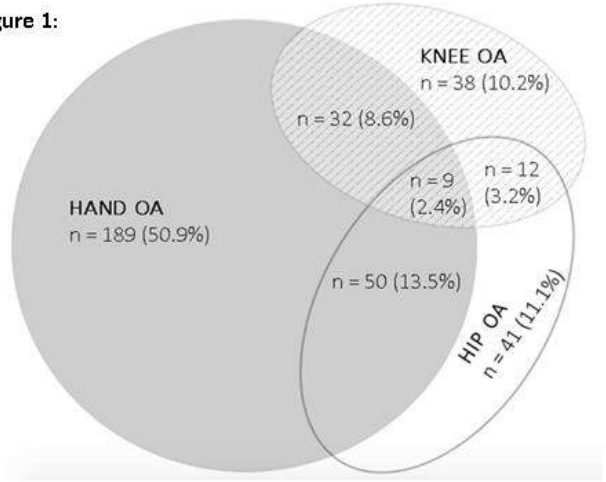
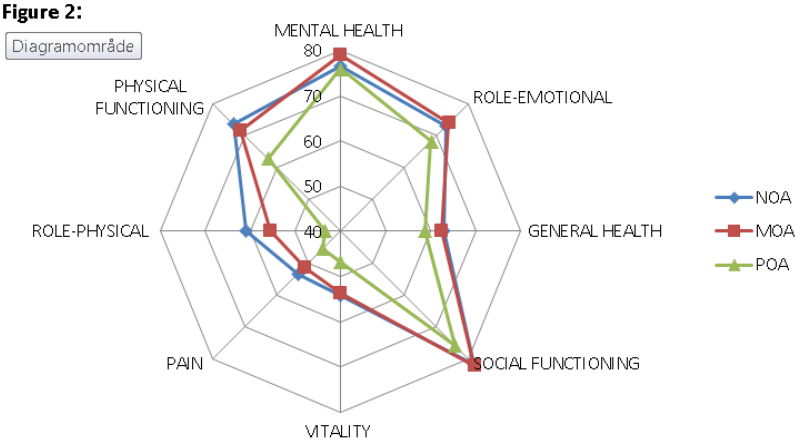


Figure 2:



Conclusion:

In a population-based cohort with self-reported OA, approximately one third got the OA diagnosis rejected according to the clinical ACR criteria. MOA, and specifically isolated hand OA without affection of the knees and hips, was the most common localization of clinical OA. POA was less prevalent, but was associated with diminished HRQoL dimensions in terms of poorer vitality, higher pain intensity as well as impaired physical- and social functioning compared to participants without clinical OA.

Disclosure: G. Økelsrud Lombnæs, None; **K. Magnusson**, None; **K. B. Hagen**, None.

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Abstract Number: 2173

Impact of Smoking on Patient-Reported Disease Status and Symptoms Among Women with Lupus

Patricia P. Katz[1], Eliza Chakravarty[2], Robert S. Katz[3] and Kaleb Michaud[4], [1]Medicine/Rheumatology, University of California San Francisco, San Francisco, CA, [2]Arthritis and Clinical Immunology, Oklahoma Medical Research Foundation, Oklahoma City, OK, [3]Rush University Medical Center, Chicago, IL, [4]Internal Medicine, University of Nebraska Medical Center, Omaha, NE

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Background/Purpose: Smoking appears to be associated both with an increased risk of rheumatoid arthritis and with more severe symptoms. The impact of smoking on patient-reported disease status and symptoms in lupus has not been reported.

Methods: Data were from the National Data Bank for Rheumatic Diseases (NDB), for which participants complete questionnaires every 6 months. Only women with lupus who responded to at least one of the two most recent completed questionnaires were included (n = 481). Self-reported lupus status was assessed with the Systemic Lupus Activity Questionnaire (SLAQ)[1], the Brief Inventory of Lupus Damage (BILD)[2], global assessment of health status (rating from 0 [doing very well] – 10 [doing very poorly]), and assessment of lupus activity (rating from 0 [not active] – 10 [very active]). Patient-reported symptoms were assessments of pain, fatigue, and sleep problems, each rated 0 – 10 with higher ratings reflecting worse symptoms, and depressive symptoms assessed with the PHQ-8. Bivariate and multivariate linear regression analyses estimated the relationship of current and former smoking on outcomes. Multivariate analyses controlled for age, low education, Medicaid or no health insurance, number of rheumatology visits, duration of lupus, obesity, Rheumatic Disease Comorbidity Index (RDCI)[3], and prednisone use.

Results: Mean age was 58 ± 13 years, 22% had education ≤ high school, and 15% had Medicaid or no health insurance. Mean disease duration was 21 ± 12 years, 34% were obese, and mean score on the RDCI was 2.7 ± 1.8. Means of each lupus status and symptom measure are shown in the Table. Six percent were current smokers, 31% were former smokers, and 63% had never smoked. In unadjusted analyses, current smokers had significantly worse scores than never smokers on all measures except the BILD (Table), and former smokers had worse scores on the SLAQ and ratings of lupus activity. After adjustment, the elevated scores of current smokers compared with never smokers remained for all measures except the BILD.

Conclusion: While current smoking was not common, it was associated with significantly worse patient assessments of lupus status and worse symptoms. Findings underscore the importance of assessing smoking and supporting smoking cessation efforts among women with lupus.

[1] Karlson EW, et al. *Lupus* 2003; 12:280.

[2] Yazdany J, et al. *Arthritis Care Res* 2011; 63:1170

[3] England BR, et al. *Arthritis Care Res* 2015; 6: 865

Table. Association of current and former smoking with patient-reported lupus status and symptoms				
	Overall mean ± SD	Smoking	Unadjusted*	Adjusted*
Global assessment of lupus (0 – 10 rating, higher score worse)	4.12 ± 2.57	Current	5.77 (.003)	5.55 (.004)
		Former	4.08 (.22)	3.98 (.35)
		Never	3.70 (ref)	3.75 (ref)
Lupus disease activity (Systemic Lupus Activity Questionnaire; SLAQ)	11.05 ± 7.14	Current	17.13 (.006)	16.89 (.004)
		Former	12.26 (.03)	11.80 (.17)
		Never	10.06 (ref)	10.25 (ref)
Lupus disease damage (Brief Inventory of Lupus Damage; BILD)	3.32 ± 2.08	Current	4.00 (.25)	3.79 (.21)
		Former	3.65 (.09)	3.38 (.69)
		Never	3.14 (ref)	3.27 (ref)
Lupus activity (0 – 100 rating, higher score worse)	30.04 ± 27.45	Current	52.50 (.009)	50.54 (.01)
		Former	35.92 (.02)	34.84 (.09)
		Never	26.74 (ref)	27.25 (ref)
Pain (0 – 10 rating, higher score worse)	4.30 ± 2.99	Current	6.04 (.01)	5.80 (.02)
		Former	4.13 (.51)	4.08 (.82)
		Never	3.90 (ref)	3.95 (ref)
Fatigue (0 – 10 rating, higher score worse)	5.15 ± 3.13	Current	6.85 (.03)	6.67 (.03)
		Former	4.95 (.95)	5.01 (.82)
		Never	4.93 (ref)	4.91 (ref)
Sleep problems (0 – 10 rating, higher score worse)	4.35 ± 3.21	Current	7.62 (<.0001)	7.38 (.0002)
		Former	4.35 (.49)	4.36 (.42)
		Never	4.08 (ref)	4.08 (ref)
Depressive symptoms (PHQ8)	5.92 ± 5.39	Current	11.12 (.003)	10.99 (.002)
		Former	6.54 (.12)	6.41 (.24)
		Never	5.38 (ref)	5.45 (ref)
* Unadjusted and adjusted means (p-values) calculated from linear regression analyses. Multivariate analyses controlled for age, duration of lupus, low education, Medicaid or no insurance, obesity, comorbidities, prednisone use, and number of rheumatologist visits, comparing current and former smokers to never smokers.				

Disclosure: P. P. Katz, None; **E. Chakravarty**, None; **R. S. Katz**, None; **K. Michaud**, None.

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Abstract Number: 2174

Neutrophils in Primary Antiphospholipid Syndrome Are Characterized By a Prominent Activated Phenotype and Uniquely Remodeled Chromatin Architecture

Patrick Coit, Srilakshmi Yalavarthi, Jason S. Knight and Amr H. Sawalha, Division of Rheumatology, University of Michigan, Ann Arbor, MI

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SESSION INFORMATION

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Session Title: Antiphospholipid Syndrome: Basic Science

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Antiphospholipid syndrome (APS) is a systemic autoimmune disease characterized by recurrent thrombotic events, pregnancy complications, and the presence of antiphospholipid antibodies. The pathogenesis of primary APS is incompletely understood. We aimed to investigate the role of neutrophils in primary APS.

Methods: We studied 19 patients with primary APS and 19 healthy controls matched for age, sex, and ethnicity. Neutrophils were extracted from peripheral blood samples using density gradient centrifugation followed by flow cytometry to confirm neutrophil purity. A comprehensive transcriptome analysis was performed using paired-end 100bp mRNA sequencing reads generated on an Illumina HiSeq 2000 instrument. A genome-wide DNA methylation analysis was performed using Infinium HumanMethylation450 BeadChip arrays. RNA sequencing data were normalized and analyzed following quality control assessment and filtering using EdgeR software package in the R programming environment. Differential gene expression between patients and controls was defined using a fold difference of >2 and a false discovery rate <0.01. DNA methylation analysis was performed using GenomeStudio (Illumina) and differentially methylated loci between patients and controls were identified using an absolute methylation difference of at least 10% and a P value <0.01 after correction for multiple testing. Bioinformatics analysis was performed using the Database for Annotation, Visualization, and Integrated Discovery (DAVID), and Ingenuity Pathway Analysis.

Results: RNA sequencing analysis identified 593 overexpressed and 769 underexpressed genes in neutrophils from primary APS patients compared to age, sex, and ethnicity matched healthy controls. Neutrophils in primary APS are characterized by a pro-inflammatory phenotype defined by prominent transcriptional overexpression of interferon-regulated genes such as IFIT1 (8-fold), IFIT3 (5-fold), IFI6 (5-fold), MX1 (5-fold), HERC5 (5-fold), IFIT2 (5-fold), and ISG15 (4-fold), among many others. Neutrophils from primary APS patients are also characterized by activation of the Toll-like receptor signaling pathway with overexpression of TLR4, TLR5, and TLR8 (2-3 folds). In addition, neutrophils from patients overexpressed several Fc-gamma receptors including FCGR1A, FCGR1B, FCGR2A, FCGR3A, and FCGR3B (2.5-3.5 folds). P-selectin glycoprotein ligand-1 (PSGL-1) and L-selectin (CD62L), which play an important role in neutrophil adhesion to the vessel wall and neutrophil degranulation, were both also overexpressed in primary APS neutrophils. DNA methylation analysis in neutrophils from primary APS suggests an epigenetic architecture that is unique and very distinct from lupus neutrophils. Indeed, DNA methylation profiles in a small number of specific CG sites are very sensitive and specific to stratify patients with primary APS versus lupus with an area under the ROC curve of ≥0.90.

Conclusion: Neutrophils in patients with primary APS are activated and likely play an important role in disease pathogenesis. Further, the DNA methylation signature in primary APS neutrophils suggests a unique epigenetic architecture that is distinctly dissimilar from lupus.

Disclosure: P. Coit, None; **S. Yalavarthi**, None; **J. S. Knight**, None; **A. H. Sawalha**, None.

Abstract Number: 2175

Comparative Study Between Coagucheck XS Versus Standard Laboratory Practice Protrombine Time for Monitoring Anticoagulant Therapy in Patients with Antiphospholipid Syndrome

Maria Ester Simeira Fonseca[1], Michelle Lopes[2], Christiane Pereira Gouvea[3] and Danieli Andrade[4], [1]Rheumatology, University of São Paulo, São Paulo, Brazil, [2]Rheumatology, Hospital das Clinicas, Faculdade de Medicina, University of São Paulo, São Paulo, Brazil, [3]Hematology, University of São Paulo, São Paulo, Brazil, [4]Autoimmunity & Inflammation, Hospital for Special Surgery, New York, NY

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Session Title: Antiphospholipid Syndrome: Basic Science

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Antiphospholipid Syndrome (APS) is an autoimmune disease characterized by antiphospholipid antibodies (aPL) associated with thrombosis and/or pregnancy morbidity. Although initially described in patients with systemic lupus erythematosus (SLE) it can occur in patients with no autoimmune disease. The standard treatment for thrombotic APS is anticoagulation with vitamin K antagonists. The prothrombin time (PT) and its corresponding INR (International English Normatized ratio) is the laboratory test used to target anticoagulation. Because inadequate anticoagulation therapy may be hazardous, a strict monitoring is needed. The CoaguCheck XS is a simple and prompt device that allows INR monitoring providing the result in seconds. Despite studies comparing CoaguCheck XS and PT analysis presented favorable correlation, there are scarce studies evaluating the use of CoaguCheck in APS patients. Purpose: Evaluate accuracy of CoaguCheck XS in APS patients, comparing it with standard method for plasma prothrombin time (PT). Furthermore, we analyzed other clinical and laboratorial features to check if they could interfere with CoaguCheck results.

Methods: This is a single center cross-sectional study with 94 APS patients from a rheumatology clinic tertiary hospital included from august 2014 to march 2015. All patients fulfilled APS Sydney´s criteria and all APS associated with SLE fulfilled ACR SLE criteria. The comparison of Coagucheck XS results versus standard laboratory practice for monitoring anticoagulant therapy was evaluated using the coefficient of determination (r) followed by the Bland-Altman test. Paired T test was also applied.

Results: The comparison between INR values from 94 patients measured with CoaguCheck XS and the standard PT resulted in a coefficient of correlation (r) of 0.95. The mean INR (S.D.) was 2.94 (1.41) with CoaguCheck XS and 2.43 (0.86) with standard PT. Dividing the INR values in into four ranges (INR < 2, INR 2-3, INR 3-4 and INR>4) we found that INR>4 group presented a poor correlation (r=0.64) compared to the other ranges ($p<0.05$). Although CoaguChek XS and standard PT are highly correlated, the INR values were not equal. In general CoacuCheck shows higher values than the standard PT test, with an average of 0.42 ± 0.54. Therefore we propose a simple linear regression model in order to predict the PT standard values using values obtained from CoaguChek. The model showed a R^2 of 87%, indicating a good quality of forecast, for INR<2.5. None of the clinical or laboratory variables evaluated interfered with CoaguCheck results. There was no difference in testing performance in primary APS and APS associated with SLE patients.

Conclusion: CoaguCheck XS is a simple and acceptable way of monitoring anticoagulation in APS patients presenting a good correlation with standard PT test if INR is <4. These results corfim previous reports from anticoagulated patients with no antiphospholipid syndrome.

Disclosure: M. E. Simeira Fonseca, None; **M. Lopes**, None; **C. Pereira Gouvea**, None; **D. Andrade**, None.

Abstract Number: 2176

The Ability of Recombinant Domain I of Beta-2-Glycoprotein I to Inhibit Lupus Anticoagulant Effect of IgG from Patients with APS Is Enhanced By Pegylation

Thomas McDonnell[1], Charis Pericleous[1], Ian Giles[1], Yiannis Ioannou[2] and Anisur Rahman[1], [1]Rayne Institute, Centre for Rheumatology Research, UCL Division of Medicine, London, United Kingdom, [2]Rayne Institute, Arthritis Research UK Centre for Adolescent Rheumatology, UCL Division of Medicine, London, United Kingdom

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SESSION INFORMATION

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Session Title: Antiphospholipid Syndrome: Basic Science

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose:

Antiphospholipid Syndrome (APS) is an autoimmune rheumatic disorder in which antiphospholipid antibodies (aPL) cause clinical events including vascular thrombosis (VT) and pregnancy morbidity (PM). In clinical practice aPL are detected by three tests, the anti-cardiolipin and anti-beta-2-glycoprotein I (beta2GPI) ELISAs and the lupus anticoagulant (LA) test. The LA test measures prolongation of clotting time caused by aPL present in the serum of patients. LA positivity is strongly associated with thrombosis and is the strongest predictor of PM in patients with APS. In testing potential efficacy of new therapeutic agents for APS it would therefore be very useful to be able to assay their ability to inhibit the LA effect of polyclonal IgG aPL in samples from patients. Here we describe a novel method for carrying out such tests and its application to testing PEGylated human recombinant domain I (DI) of beta2GPI. Recombinant DI has previously been shown to block binding and pro-thrombotic properties of purified IgG antibodies from patients with APS. PEGylation (chemical addition of polyethylene glycol) can increase half-life and reduce immunogenicity of small molecules, enhancing their potential for development as therapeutic agents.

Methods:

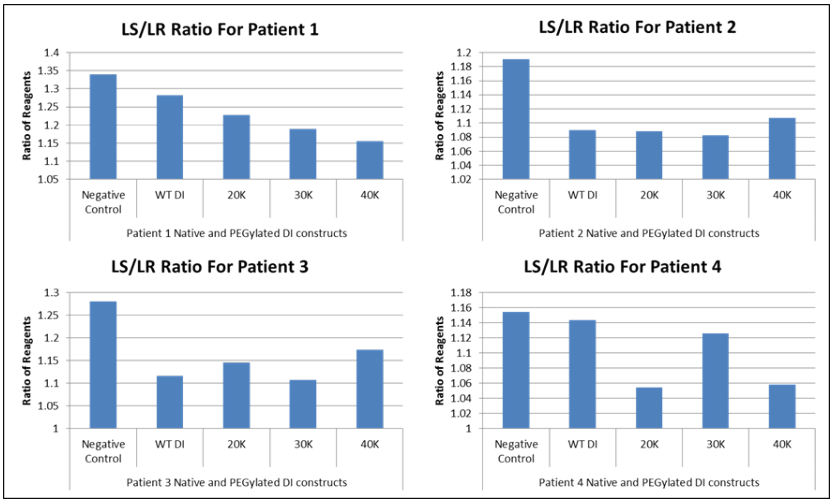
We used a Sysmex-CA coagulometer with a dRVVT Plus kit. The principle of the assay is that the sample to be tested is allowed to clot either in the presence or absence of a reagent containing excess phospholipid (two step test). aPL that cause an LA effect prolong clotting time in the LA sensitive test (LS) but not in the LA resistant test (LR) containing excess phospholipid. Thus the ratio of LS to LR clotting time is a measure of LA effect. We purified IgG from serum of patients with APS (n=4, all fulfilling Sydney criteria and known to be LA-positive) and added it to normal human plasma at a concentration of 500mcg/ml. These samples were then tested in the coagulometer assay either with or without pre-incubation with DI alone or DI PEGylated with three different sizes of PEG (20kDa, 30kDa and 40kDa).

Results:

The figure shows results for all four patients individually. In each case, purified IgG in the absence of inhibitor gave LS/LR ratio > 1.1, showing an LA effect. For all patients, addition of PEGylated DI reduced the LA effect on LS/LR ratio and the effect of PEGylated DI was greater than the effect of non-PEGylated DI in 3 out of 4 cases. This finding is particularly interesting because PEGylation generally reduces biological effects of small molecules. PEG alone has minimal effect.

Conclusion:

Using this assay, we demonstrated that it is possible to test ability of a putative therapeutic agent for APS to inhibit the LA effect. PEGylation of DI did not reduce its ability to inhibit the LA effect of IgG purified from patients with APS but actually increased inhibition. This finding may be beneficial in development of PEG-DI as a therapeutic.



Disclosure: **T. McDonnell**, PolyTherics, 9; **C. Pericleous**, PolyTherics, 9; **I. Giles**, PolyTherics, 9; **Y. Ioannou**, PolyTherics, 9; **A. Rahman**, PolyTherics, 9.

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Abstract Number: 2177

Pegylated Recombinant Domain I of Beta-2-Glycoprotein I, a Potential Therapeutic Agent for Antiphospholipid Syndrome, Fully Retains Its Ability to Inhibit Binding of IgG or IgA Antibodies from Patients with APS to Beta-2-Glycoprotein I in Vitro

Thomas McDonnell[1], Charis Pericleous[1], Yiannis Ioannou[2], Ian Giles[1] and Anisur Rahman[1], [1]Rayne Institute, Centre for Rheumatology Research, UCL Division of Medicine, London, United Kingdom, [2]Rayne Institute, Arthritis Research UK Centre for Adolescent Rheumatology, UCL Division of Medicine, London, United Kingdom

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Background/Purpose:

Antiphospholipid Syndrome (APS) is an autoimmune rheumatic disorder in which antiphospholipid antibodies (aPL) cause clinical events including vascular thrombosis (VT) and pregnancy morbidity (PM). The key antigen in APS is beta-2-glycoprotein I (beta2GPI), which consists of five domains. The N-terminal domain (DI) carries the main immunodominant epitope. We previously showed that recombinant human DI blocks binding of serum IgG from patients with APS (APS-IgG) to whole beta2GPI in ELISA and inhibits thrombosis induced by APS-IgG in a mouse model. A modified variant containing two point mutations (DI(D8S,D9G)) was a stronger inhibitor than wild-type DI. Small molecules such as DI require modification to make them viable as therapeutic agents. Chemical addition of polyethylene glycol (PEGylation) is one such modification , which increases half-life and reduces immunogenicity. Conversely, PEGylation can also reduce binding to ligands/receptors and biological activity. Larger PEG sizes may enhance half-life more but reduce activity more. Therefore, we investigated whether PEGylated DI of various sizes retain the ability to inhibit beta2GPI -binding of serum IgG and IgA from patients with APS.

Methods:

DI was expressed in E.Coli and PEGylated on its disulphide bonds. Three different PEGylated variants carrying 20kDa, 30 kDa and 40 kDa PEG were produced as well as non-PEGylated DI. Serum samples from four patients with APS, all fulfilling the Sydney classification criteria, were tested in an inhibition ELISA. This ELISA tests for binding of IgG or IgA to beta2GPI in the presence or absence of 100mcg/ml inhibitor. **Results** are expressed as the retained binding in presence of each inhibitor compared to binding with no inhibitor (defined as 100%).

Results:

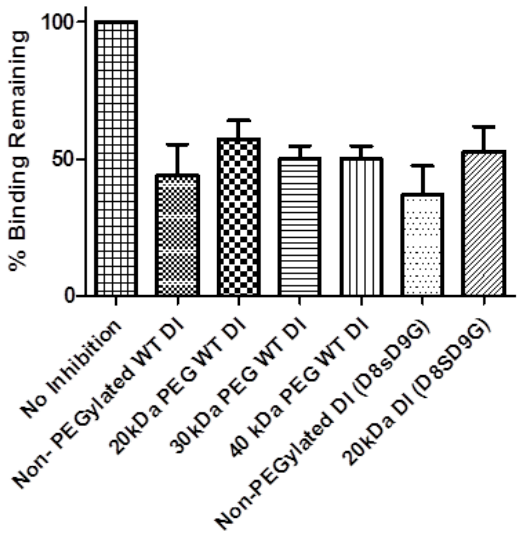
Figure 1 shows results for IgG. All PEGylated and non-PEGylated variants of DI significantly inhibit binding to beta2GPI by between 43-55% ($P<0.05$). Figure 2 shows results for IgA. All PEGylated and non-PEGylated variants of DI significantly inhibit binding to beta2GPI by between 40-55% ($P<0.005$). There were no significant differences between results for the different DI variants, showing that PEGylation does not alter inhibitory capacity of DI in this binding assay.

Similarly we showed that DI (D8S,D9G) carrying 20kDa PEG inhibits binding to beta2GPI of serum IgG ($P<0.01$) and IgA ($P<0.005$) from patients with APS. PEG alone shows <10% inhibition.

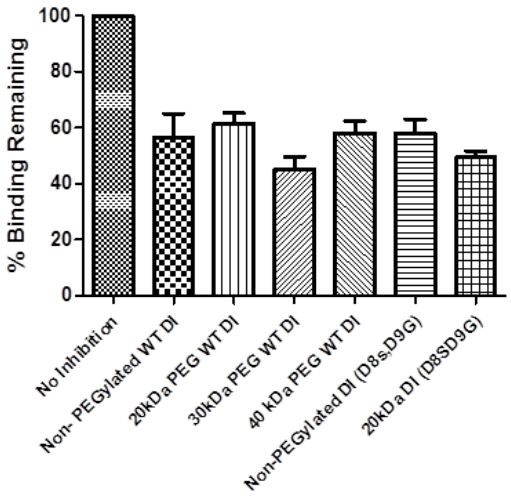
Conclusion:

PEGylation of DI and DI (D8S,D9G) allows retention of their ability to inhibit binding of both IgG and IgA from APS patients to beta2GPI, an important step in potential development as a therapeutic agent.

Inhibition of Serum IgG anti-B2GPI in the Presence of DI or DI (WT) PEG



Inhibition of Patient Serum Binding (IgA) to B2GPI in the Presence of DI and Variants



View Abstract and Citation Information Online - http://acrabstracts.org/abstract/pegylated-recombinant-domain-i-of-beta-2-glycoprotein-i-a-potential-therapeutic-agent-for-antiphospholipid-syndrome-fully-retains-its-ability-to-inhibit-binding-of-igg-or-iga-antibodies-from-patient

Abstract Number: 2178

Oxidation of beta2-Glycoprotein I (beta2-GPI) Associates with the Presence of Antibodies to Domain I of beta2-GPI in Patients with the Antiphospholipid Syndrome but Is Not Affected By the Antibodies in Vivo in a Rat Model

Maria Gabriella Raimondo[1,2], Charis Pericleous[3], Anna Radziszewska[4,5], Maria Orietta Borghi[6,7], Silvia S. Pierangeli[8], Pier Luigi Meroni[6,9], Ian Giles[3], Anisur Rahman[3] and Yiannis Ioannou[3,10], [1]Department of Clinical Sciences and Community Health, University of Milan, Milan, Italy, [2]Centre for Rheumatology Research, UCL Division of Medicine, University College London, London, United Kingdom, [3]Rayne Institute, Centre for Rheumatology Research, UCL Division of Medicine, London, United Kingdom, [4]The Rayne Institute, Arthritis Research UK Centre for Adolescent Rheumatology at University College London, Great Ormond Street Hospital and UCLH, University College London, London, United Kingdom, [5]The Rayne Institute, Centre for Rheumatology Research, UCL Division of Medicine, London, United Kingdom, [6]Department of Clinical Sciences and Community Health, Department of Clinical Sciences and Community Health, University of Milan, Milan, Italy, [7]Laboratory of Immuno-rheumatology, IRCCS Istituto Auxologico Italiano, Milan, Italy, [8]Rheumatology/Internal Medicine, University of Texas Medical Branch, Galveston, TX, [9]Immunorheumatology Research Laboratory, IRCCS Istituto Auxologico Italiano, Cusano Milanino (mi), Italy, [10]Rayne Institute, Arthritis Research UK Centre for Adolescent Rheumatology, UCL Division of Medicine, London, United Kingdom

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Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose:

β_2GPI represents the major antigenic target for antiphospholipid antibodies (aPL), the hallmark of antiphospholipid syndrome (APS). β_2GPI contains five homologous domains, with domain I (DI) being identified as the main antigenic epitope for pathogenic anti-β_2GPI. Antibodies targeting β_2GPI-DI (anti-DI) represent a key pathogenic sub-population of aPL, thus their detection may allow the identification of patients at highest clinical risk. It has been reported that β_2GPI *in vivo* exists in two interconvertible biochemical redox dependent configurations. The reduced form has a circular configuration maintained by interaction between the first and fifth domain thus potentially hiding the epitope on DI, whilst the oxidised protein has an open and linear shape in which the DI is exposed. It is known that the proportion of β_2GPI in the oxidised form is elevated in patients with APS. Thus, one hypothesis is that the oxidative state of β_2GPI might alter the exposure of neo-epitopes on DI thus providing an antigenic drive for anti-DI antibodies production. In this study we investigated the association between circulating oxidised form of β_2GPI and presence of anti-DI in APS patients.

Methods:

Serum samples from 44 patients who fulfilled the revised classification criteria for APS were tested (38 primary and 6 secondary APS). The samples were screened for IgG anti-DI, anti-β_2GPI and anti-cardiolipin (anti-CL). A sandwich ELISA for quantifying total β_2GPI levels within serum was performed for all samples. Biochemically reduced β_2GPI was detected via labelling free thiols within serum proteins with a biotinylated free-thiol binding reagent and then, via coating on a streptavidin plate, detecting

the presence of labelled β_2GPI with an anti-β_2GPI antibody, based on published methods. For the *in vivo* studies, male Sprague Dawley rats were injected intravenously with 1 mg of IgG purified pooled from 4 healthy individuals or 2 APS anti-DI positive patients (n=6 rats per IgG pool). Blood samples were collected 24-hour after IgG injection and assayed for reduced β_2GPI.

Results:

A negative correlation was found between the reduced proportion of β_2GPI and IgG anti-DI levels (Spearman r = -0.535, p = 0.0002). Furthermore, the proportion of reduced β_2GPI was lower in anti-DI positive than anti-DI negative APS patients (p = 0.0178). The relative amount of reduced β_2GPI was no different between patients who were positive or negative for anti-β_2GPI (p=0.757) or anti-CL (p=0.062). The reduced proportion of β_2GPI was no different within serum samples collected from healthy rats injected with purified anti-DI positive IgG from APS patients versus healthy controls (p=1.000).

Conclusion:

This study demonstrates that IgG anti-DI are strongly associated with the oxidative state of β_2GPI as compared to anti-CL and anti-β_2GPI antibodies. Furthermore, the *in vivo* injection of APS derived IgG did not affect the redox state of β_2GPI in the experimental rat-model employed. Though not proof, this study further supports the hypothesis that epitope exposure on DI of β_2GPI defined by the redox state of the protein might affect the antigenic drive of pathogenic anti-DI antibodies.

Disclosure: M. G. Raimondo, None; **C. Pericleous**, None; **A. Radziszewska**, None; **M. O. Borghi**, None; **S. S. Pierangeli**, None; **P. L. Meroni**, None; **I. Giles**, None; **A. Rahman**, None; **Y. Ioannou**, None.

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Abstract Number: 2179

Signaling By Mammalian Target of Rapamycin (mTORC) Highlight Pathological IgG and IgA in SLE Patients with Secondary APS

Robert Clancy[1], Sara Rasmussen[2], Janet Nwaukoni[1] and H. Michael Belmont[3], [1]Medicine, Division of Rheumatology, New York University School of Medicine, New York, NY, [2]Department of Medicine, Division of Rheumatology, New York University School of Medicine, New York, NY, [3]Hosp for Joint Disease, New York, NY

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Session Time: 9:00AM-11:00AM

Background/Purpose:

The spectrum of the vascular pathology affecting SLE patients with secondary antiphospholipid syndrome includes vasculopathy with endothelial cell hyperplasia as in APS nephropathy. Previous studies established a role for endothelial cell activation via the mammalian target of rapamycin (mTORC) but were limited to IgG fractions of primary APS patients. We extend this finding by studying SLE patients with secondary APS and demonstrate that this activity resides in both IgG and IgA fractions.

Methods:

Endothelial cell phenotypes were assessed using an immunofluorescent assay to report the mTORC biomarker, phospho-S6 ribosomal protein (S6RP) using the human microvascular cell line (serum starved HMEC1 with β2GP1 pretreatment) in the presence and absence of purified human IgG, IgGFab2, and IgA with or without LY294002, a mTORC inhibitor (5 min). We studied 8 SLE patients with secondary APS (mean age 46.8 ± .3, 89% female and 67% white), 4 disease controls that were either

SLE without APS or asymptomatic Ro+, and 3 controls. Purified IgG and IgA fractions were used as follows: SLE patients 4 IgG and IgA, 3 IgG and I IgA; 4 diseases controls 4 IgG and 2 IgA; and controls 2 IgG and 1 IgA. Immunofluorescence (IgG TRITC and Hoechst 33342) was reported using both intensity (1-3+) and a staining scale reflecting % positive cells (3 fields) with 1, <10%; 2, 10-30%; 3, 40-50%; and 4 >50%.

Results:

The phenotype of the endothelial cells which were co-incubated with the IgG fractions of 3 (of 8) patients were diffusely positive for phospho-S6RP (i.e. 3+ intensity, >3 on the scale of % positive cells), which was attenuated by co-incubation with LY294002 (1+, 1 % positive cells). Moreover, endothelial cells co-incubated with Fab2 subfraction retained the diffuse stain for phospho-6SRP. In addition, treatment of endothelial cells with IgA fractions from the same individuals resulted in an increase of phosphorylation of S6RP, suggesting the importance of both IgG and IgA APS isotypes. The patient with the greatest intensity and highest staining with both IgG and IgA fraction is triple and full house positive (eg positive for LAC as well as very high titer IgG, IgA and IgM ACA and β2GPI). For the total group of 8 SLE patients with APS antibodies however, there were no associations with APS titers and the ability to elicit the biomarker in HMEC1. The expression of phospho- S6RP by HMEC1 were within the ranges reported for no treatment (1+, <3 to report % positive cells) for IgG fractions isolated from disease controls, healthy controls, and IgG Fab2 from a disease control and a control IgA.

Conclusion:

These data support the novel finding that both IgG and IgA fractions from SLE patients with secondary APS activate endothelial cells via the mTORC pathway as demonstrated by S6RP phosphorylation.

Disclosure: R. Clancy, None; **S. Rasmussen**, None; **J. Nwaukoni**, None; **H. M. Belmont**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/signaling-by-mammalian-target-of-rapamycin-mtorc-highlight-pathological-igg-and-iga-in-sle-patients-with-secondary-aps

Abstract Number: 2180

Primary Antiphospholipid Syndrome Patients Display Increased Levels of Cell-Bound C4d in Comparison to SLE and Healthy Donors

Maria Gerosa[1,2], Paola Adele Lonati[3], Tania Ubiali[1], Martina Cornalba[1], Maria Orietta Borghi[1,4] and Pier Luigi Meroni[1,2,5], [1]Department of Clinical Sciences and Community Health, Department of Clinical Sciences and Community Health, University of Milan, Milan, Italy, [2]Division of Rheumatology, Division of Rheumatology, Istituto Ortopedico Gaetano Pini, Milan, Italy, [3]Laboratory of Immuno-rheumatology, Laboratory of Immuno-rheumatology, IRCCS Istituto Auxologico Italiano, Cusano Milanino, Jamaica, [4]Laboratory of Immuno-rheumatology, IRCCS Istituto Auxologico Italiano, Milan, Italy, [5]Laboratory of Immuno-rheumatology, Laboratory of Immuno-rheumatology, IRCCS Istituto Auxologico Italiano, Cusano Milanino, Italy

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SESSION INFORMATION

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Session Title: Antiphospholipid Syndrome: Basic Science

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose:

Systemic Lupus Erythematosus (SLE) patients display high levels of the cell-bound complement activation factor C4d deposits on erythrocytes, B lymphocytes and platelets. In particular, complement activation on platelets has been suggested to play a crucial role in the pathogenesis of thrombosis in SLE, especially in aPL positive patients. Several in vitro and in vivo studies have demonstrated an increased C4d deposition on platelets, that have been associated with stroke or other thrombotic complications in SLE.

Recently, the addition of purified anti-cardiolipin antibodies from Antiphospholipid antibody syndrome (APS) patients has been

demonstrated to increase C4d deposition on activated fixed platelets.

Thrombosis is an hallmark of APS and both platelets and complement have been suggested to be involved in the pathogenic pathways. However few data on complement activation and C4d deposition on platelets in Primary APS patients have been reported in the literature. Aim of the study was to evaluate C4d deposition on platelets, erythrocytes and B lymphocytes of Primary APS patients (PAPS) in comparison to aPL neg SLE patients and healthy donors (NHS).

Methods:

11 active SLE (SLEDAI 3-14) and 18 PAPS patients attending our Rheumatology Unit were consecutively enrolled. C4d deposition on platelets, erythrocytes and B lymphocytes was assessed by flow cytometry, using an anti-human C4d monoclonal antibody associated with specific lineage markers. **Results** were expressed as C4d positive cell percentage, mean and Standard Error Mean. Statistical analysis was performed by Mann Whitney test with significant limit $p<0.05$.

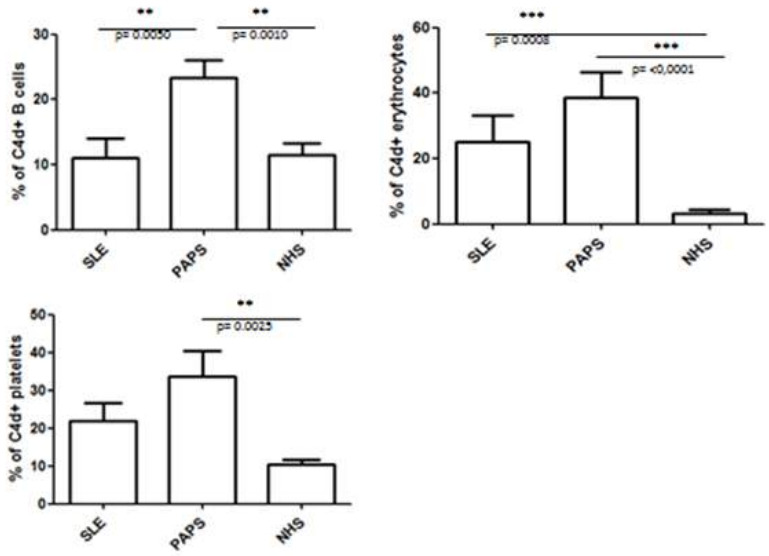
Results:

The proportion of C4d positive cells was higher in PAPS than SLE in all cell populations, with statistical significance for B cells ($p=0.005$) (fig 1). Comparing PAPS vs NHS, significant differences were detected for all cell types ($p<0.005$), while only erythrocytes C4d deposits were significantly higher in SLE patients than in NHS.

Conclusion:

we show for the first time that PAPS patients display higher levels of cell bound C4d in comparison to both NHS and SLE. These in vivo data suggest that: i) complement is activated in PAPS in spite of normal C3/C4 plasma levels: ii) increased complement activation on platelets may play a role in causing thrombocytopenia in PAPS. The increased C4d deposition on B lymphocytes deserves further investigation. As a whole our finding does suggest that cell-bound complement split products may represent a potential tool to characterize APS clinical subtypes.

Figure 1: Cd4 positive cells in PAPS and SLE



Disclosure: M. Gerosa, None; **P. A. Lonati**, None; **T. Ubiali**, None; **M. Cornalba**, None; **M. O. Borghi**, None; **P. L. Meroni**, None.

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Abstract Number: 2181

Antiphospholipid Antibody-Mediated Increase of Tissue Factor in Arterial Wall Is Associated with Increased Thrombus Size in a Mouse Model

Pierre Grant[1], **Rohan Willis**[2], Zurina Romay-Penabad[1], Elizabeth Papalardo[3], Mohammad Jamaluddin[4], Rajani Rudrangi[3], Emilio B Gonzalez[5] and Allan R Brasier[6], [1]University of Texas Medical Branch, Galveston, TX, [2]Rheumatology/Dept Int Med, University of Texas Medical Branch, Galveston, TX, [3]Internal Medicine, Rheumatology, University of Texas Medical Branch, Galveston, TX, [4]Institute for Translational Science, University of Texas Medical Branch, Galveston, TX, [5]Rheumatolgoy/Dept Int Med, University of Texas Medical Branch, Galveston, TX, [6]Internal Medicine and Institute for Translational Sciences, University of Texas Medical Branch, Galveston, TX

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Session Type: ACR Poster Session C
Session Time: 9:00AM-11:00AM

Background/Purpose:

Antiphospholipid syndrome (APS) is a multisystemic autoimmune disease characterized by recurrent thrombotic and adverse obstetric events in the presence of antiphospholipid antibodies (aPL). Compelling data indicate a key role for aPL-mediated induction of tissue factor (TF) expression in monocytes and endothelial cells in the pathogenesis of APS. Recent in-vivo data from our group utlizing low TF producing mice demonstrated the importance of TF in aPL-mediated thrombosis. There is however limited in-vivo data demonstrating the source of TF in the vessel wall in thrombosis resulting from aPL activity.

The aim of this study was to determine the major sources of TF expression in the arterial wall of mice subjected to passive aPL administration.

Methods:

CD1 male mice (n=5 per group) were inoculated with either purified whole IgG from an APS patient (IgG-APS) with high IgG aPL and documented aterial and venous thrombosis or with whole IgG from normal human serum (IgG-NHS). Antibodies were purified from serum using diethylaminoethanol (DEAE) sepharose and adjusted to the appropriate concentration in phosphate buffered saline and any endotoxin present was removed by a commercially available column (Thermo Scientific). Mice were treated with the IgG solutions twice intraperitoneally, the second inoculation given 48 hours after the first, and surgery to measure thrombus dynamics of thrombi induced by a standardized pinch injury to the femoral vein and to collect the aorta was done 72 hours after first inoculation. Staining for TF in the aortic wall was performed by immunohistochemistry using an anti-TF primary antibody, an Alexa-Fluor 586 conjugated secondary antibody and 4',6-diamidino-2-phenylindole(DAPI) counterstain on formalin fixed and paraffin embedded aorta specimens.

Results:

The mean thrombus size was significantly larger in IgG-APS treated mice (1747.4±362.6 um^2) compared to those given IgG-NHS (613.6±127.3um^2) ($p<0.001$). Staining for TF in the aortic wall of IgG-NHS mice revealed minimal staining in the media and moderately more intense staining in the adventitia. In IgG-APS treated mice, there was consistently intense TF staining in the adventitia and moderate staining in the media, noticeably greater than that seen in NHS treated mice.

Conclusion:

In this mouse model, IgG aPL induced significantly larger thrombi than control IgG and was associated with a noticeable increase in adventitial and medial TF, with the adventitia being the major source. Further study is needed to determine the specific cellular sources of TF important in aPL-mediated thrombosis.

Disclosure: P. Grant, None; **R. Willis**, None; **Z. Romay-Penabad**, None; **E. Papalardo**, None; **M. Jamaluddin**, None; **R. Rudrangi**, None; **E. B. Gonzalez**, None; **A. R. Brasier**, None.

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Abstract Number: 2182

Increased Risk of Livedo Reticularis Associated with Antiphospholipid Antibodies in Patients with Systemic Lupus Erythematosus: A Systematic Review and Meta-Analysis

Ersilia M. DeFilippis[1], Denis Wahl[2] and Stephane Zuily[2], [1]Department of Medicine, Brigham and Women's Hospital, Boston, MA, [2]CHU de Nancy, Vascular Medicine Division and Regional Competence Center For Rare Vascular And Systemic Autoimmune Diseases, Nancy, F-54000, France; Inserm, UMR_S 1116, Nancy, F-54000, France; Université de Lorraine, Nancy, F-54000, France, Nancy, France

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Session Time: 9:00AM-11:00AM

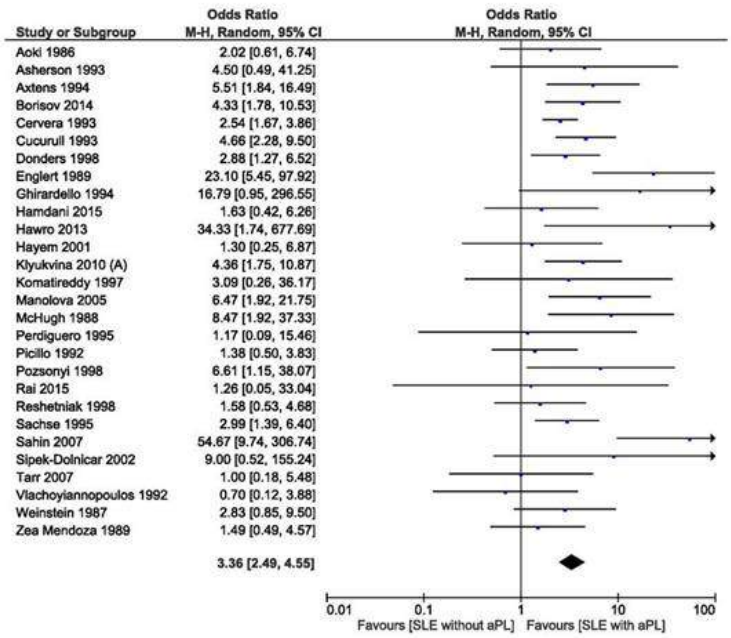
Background/Purpose : Livedo reticularis (LR) is present in patients with systemic lupus erythematosus (SLE), and the role of antiphospholipid antibodies (aPL) is controversial. Therefore our objective was to estimate the risk of LR associated with aPL in patients with SLE.

Methods : Studies were selected if they investigated the association between aPL and LR in SLE patients and if aPL-negative patients were included for comparison. Data sources were Pubmed, Embase, Cochrane Library, hand search, congress abstracts, and reference lists of studies, without language restrictions. Risk estimates were independently extracted by 2 investigators. Pooled effect estimates were obtained by using the Mantel-Haenszel method (random effects).

Results: Of 919 identified abstracts, 28 primary studies (4 cohorts, 5 case-control, 19 cross-sectional) met inclusion criteria, including 3413 SLE patients according to ACR criteria and 564 cases of LR. Prevalence of LR in aPL-positive vs. aPL-negative SLE patients was 26.5% (n=320/1207) vs. 11.1% (n=244/2206), respectively. Compared with SLE patients without LR, the overall pooled odds ratios (OR) for LR in aPL-positive SLE patients was 3.36 (95% confidence interval [CI], 2.49-4.55) (Figure 1). The risk of LR was the highest for lupus anticoagulant (LA) (5 studies, OR=4.65 [95% CI, 2.35-9.20]), anti-β_2-glycoprotein I antibodies (3 studies, OR=3.40 [95% CI, 1.53-7.52] and IgG anticardiolipin antibodies (aCL) (7 studies, OR=3.26 [95% CI, 2.18-4.88]) while IgM aCL (3 studies, OR = 1.66 [95% CI, 0.97-2.85]), anti-β_2-glycoprotein I IgM antibodies (1 study, OR 2.12 [95% CI, 0.65,6.94]) and anti-β_2-glycoprotein I IgG antibodies (2 studies, OR 2.90 [95% CI, 0.65,12.92]) did not reach statistical significance.

Conclusion : In SLE patients, aPL-positivity is associated with a significant 3- to 4-fold increased risk for livedo reticularis. These findings a) confirm that an aPL-related small vessel involvement can contribute to LR in SLE patients and b) suggest that LR could be associated with aPL in SLE patients.

Figure 1



Disclosure: E. M. DeFilippis, None; **D. Wahl**, None; **S. Zuily**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/increased-risk-of-livedo-reticularis-associated-with-antiphospholipid-antibodies-in-patients-with-systemic-lupus-erythematosus-a-systematic-review-and-meta-analysis

Abstract Number: 2183

Clinical and Epidemiological Correlates of the Adjusted Global Anti-Phospholipid Syndrome Score in a Large Cohort of Chinese APS Patients

Yu Zuo[1], Chun Li[2], David R. Karp[3] and Zhanguo Li[2], [1]Rheumatology, UT Southwestern Medical Center, Dallas, TX, [2]Peking University People's Hospital, Beijing, China, [3]UT Southwestern Medical Center, Dallas, TX

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SESSION INFORMATION

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Session Title: Antiphospholipid Syndrome: Clinical

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose:

It is well known that anti-phospholipid antibodies (aPL) are associated with an increased risk of arterial and venous thrombosis and pregnancy loss/morbidity. However, anticoagulation of aPL positive individuals is not routine due to risk of bleeding complications. The adjusted global anti-phospholipid syndrome score (aGAPSS) takes into consideration both criteria aPL and conventional cardiovascular risk factors to predict both thrombotic and pregnancy morbidity risk and may better identify patients who need more aggressive monitoring or therapy. The aGAPSS has not been evaluated in ethnically diverse subjects. This study describes the clinical relevance of aGAPSS in a Chinese APS cohort.

Methods:

This study included 98 consecutive patients who attended the rheumatology clinic at People's Hospital of Beijing University Health Science Center. All patients fulfilled the 2006 revised APS criteria. The criteria aPL profiles [anticardiolipin (aCL), anti-β2glycoproteinI (anti-β2GPI) and lupus anticoagulant (LA)] were assessed with an in-house assay. Hypertension was classified based on 8thJoint National Committee (JNC-8) guideline. Hyperlipidemia was defined as fasting total cholesterol >200 mg/dl. aGAPSS was calculated for each patient by adding points corresponding to the risk factors previously reported by Bertolaccini (3 points for hyperlipidemia, 1 point for hypertension, 5 points for aCL IgG/IgM, 4 points for anti-B2GPI IgG/IgM, 4 points for LA). Pearson Chi-squared or Fisher's exact test univariate analysis with two tailed P value was used to evaluate correlation between aGAPSS and clinical manifestations.

Results:

Patients with APS showed a baseline aGAPSS of 8.5+/-3.3 (Mean +/- SD, range 4-16). Primary and secondary APS patients showed aGAPSS of 8.0+/- 3.4 (range 4 -14) and 8.7 +/- 3.3 (range 4-16) respectively. There is no statistical difference in aGAPSS between primary and secondary patients, p=0.3021. No difference in aGAPSS was observed between male 8.6 +/- 3.2, (range 4-14) and female 8.5+/-3.4, (range 4-16) APS patients, p=0.86. Higher aGAPSS values were seen in patients who experienced thrombosis 9.4 +/- 3.2, (range 4-16) compared to those with pregnancy morbidity 6.7 +/- 2.8, (range 4 -14), p=0.0001. Patients who experienced both thrombosis and pregnancy morbidity showed higher mean aGAPSS when compared to those with pregnancy morbidity alone, but it was not statistically different, p= 0.087. There is no difference in aGAPSS score among patients who experienced thrombotic recurrence [8.7+/- 3.6, (range 4-14)] compared to those without recurrence [9.7 +/- 3.0, (range 4 – 16)], p= 0.19.

Conclusion:

All patients with APS clinical manifestations had an elevated aGAPSS. Higher aGAPSS were seen in patients who experienced thrombosis than those with only pregnancy morbidities. Previously reported differences in aGAPSS among patients with recurrent thrombosis and patients with a single thromboembolic event were not observed in this cohort of Chinese APS patients. aGAPSS may be a potential quantitative tool for APS related clinical manifestations. However, further clinical examination and validation in a large multicenter and multi-ethnicity cohort with control is warranted.

Disclosure: Y. Zuo, None; **C. Li**, None; **D. R. Karp**, None; **Z. Li**, None.

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Abstract Number: 2184

Non-Criteria Clinical Manifestations in Antiphospholipid Syndrome: Clinical Behavior and Association with Damage Accrual

Gabriela Hernandez-Molina[1], Cindy Maldonado-Garcia[1] and Antonio R. Cabral[2], [1]Immunology and Rheumatology, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico city, Mexico, [2]Immunology & Rheumatology, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico city, Mexico

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Background/Purpose: The relevance of non-criteria clinical manifestations of antiphospholipid syndrome (APS) has been less studied than its thrombotic and obstetric features. The aim of this study was to evaluate the relationship of APS non-criteria clinical manifestations with antiphospholipid antibodies and damage accrual.

Methods: We retrospectively included 176 patients with APS according to Sydney or Alarcon-Segovia's criteria. We registered demographics, antiphospholipid antibody profile, use of prednisone and immunosuppresors, thrombotic and obstetric

manifestations as well as the following so-called non-criteria clinical manifestations: cutaneous (livedo reticularis, skin ulceration,) hematological (thrombocytopenia, hemolytic anemia), renal (microangiopathy, proteinuria or renal impairment), heart valve disease, and neurological (chorea, migraine, seizures and myelitis). We scored a modified SLICC index where we also included the variables racemous livedo, adrenal insufficiency, placing of Greenfield filter and sclerosis multiple-like disease. We used descriptive statistics and logistic regression and reported OR with 95% CI.

Results: Seventy-eight percent of our patients were women with a mean age of 43.1 ± 14.7 years and median follow-up of 6.7 years. We observed thrombosis in 73%, obstetric features in 20% and 64% had non-criteria clinical manifestations (not exclusive groups). 73 patients (41.4%) had both thrombosis and a non-criteria clinical manifestation (10 concomitant, 42 post-thrombotic and 21 pre-thrombosis).The frequency of the non-criteria clinical manifestation were: hematological 64%, cutaneous 33%, neurological 27%, cardiological 8.2% and renal 6.4%. The univariate analysis showed that the prevalence of LA was higher in the non-criteria clinical manifestation group (53.2% vs. 69.5%, p=0.03). This group also used more prednisone (35.8% vs.1%, <0.0001) and immunosupressors (48.6% vs. 0%, p <0.0001) and had a higher SLICC modified score SLICC (1.69±1.9 vs. 1.1±1.5, p=0.04). Most of the weight of the SLICC score was attributed to the neurologic, pulmonar and peripheral vascular domains. The variables associated with a modified SLICC ≥ 1 were thrombosis (OR 11.5; IC 95% 4.43-30.1; P≤ 0.0001), livedo reticularis (OR 5.45; IC 95% 1.49-19.8; P=0.01) and obstetric features (OR 0.30; IC 95% 0.12-0.7; P=0.01).

Conclusion: The APS non-criteria clinical manifestations are frequent, can precede or follow thrombosis and are associated with LA. Damage accrual was mainly associated with thrombotic events followed by lived reticularis.

Disclosure: G. Hernandez-Molina, None; **C. Maldonado-Garcia**, None; **A. R. Cabral**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/non-criteria-clinical-manifestations-in-antiphospholipid-syndrome-clinical-behavior-and-association-with-damage-accrual

Abstract Number: 2185

Small but Clinically Insignificant Decreases in Antiphospholipid Antibody Titers Occur in aPL-Positive Patients during Pregnancy

Cécile Yelnik[1,2], Flint Porter[3,4], Ware D. Branch[3,4], Jill P. Buyon[5], Marta Guerra[6], Carl Laskin[7], Michael Lockshin[8], Michelle Petri[9], Joan T. Merrill[10], Lisa R. Sammaritano[11], Mary D. Stephenson[12], Mimi Y. Kim[13] and Jane E. Salmon[11,14], [1]Service de Médecine Interne, Centre National de Référence des Maladies Systémiques Rares, Hôpital Claude Huriez, CHRU Lille, Lille, France, [2]Faculté de Médecine Henri Warembourg, Université Lille Nord de France, Lille, France, [3]University of Utah, Salt Lake City, UT, [4]Intermountain Healthcare, Salt Lake City, UT, [5]NYU School of Medicine, New York, NY, [6]Rheumatology 3rd Fl Rsrch, Hospital for Special Surgery, New York, NY, [7]Medicine, Rheumatology and Obstetrics and Gynecology, University of Toronto and LifeQuest Centre for Reproductive Medicine, Toronto, ON, Canada, [8]Barbara Volcker Center for Women & Rheumatic Disease, Hospital for Special Surgery, New York, NY, [9]Johns Hopkins Lupus Center, Johns Hopkins University School of Medicine, Baltimore, MD, [10]Clinical Pharmacology, Oklahoma Medical Research Foundation, Oklahoma City, OK, [11]Rheumatology, Hospital for Special Surgery, New York, NY, [12]University of Illinois College of Medicine, Chicago, IL, [13]Albert Einstein College of Medicine, Bronx, NY, [14]Hospital for Special Surgery, New York, NY

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Background/Purpose:

The presence of aPL has been associated with pregnancy complications, but the evolution of aPL titers during pregnancy in aPL-positive patients and the utility of repeated testing during pregnancy are unclear. The primary objective of the study was to evaluate whether titers of aCL and anti-β2 Glycoprotein-1 antibodies (aβ2GP1) vary during pregnancy. The second objective was

to determine if aPL variation was associated with pregnancy outcomes.

Methods:

Data were collected from the aPL-positive patients included in PROMISSE Study, a multicenter, prospective, observational study of pregnancy outcome in women with aPL and/or SLE. Demographic and clinical data were collected at screening and patients followed monthly until delivery. aPL were tested in a core laboratory at screening [<18 weeks of gestation (WG)], 2nd trimester (20-23 WG), 3rd trimester (32-35 WG) and 12 weeks post partum (PP). Patients were considered aPL-positive if aCL and/or aβ2GP1 was ³ 40IU IgG or IgM and/or LA was positive in two determinations with at least one during pregnancy. Adverse pregnancy outcome (APO) was defined as one or more of the following: fetal death after 12 WG; neonatal death; delivery prior to 36 WG due to preeclampsia or placental insufficiency; or SGA<5th percentile.

Results:

One hundred and fifty-eight patients fulfilled inclusion criteria. Mean age was 31.9 ± 4.6 years, 84% were white, 57% had clinical APS, and 36% had SLE. During pregnancy, 28% were treated with hydroxychloroquinine, 11% steroids, 66% heparin, and 71% aspirin. At screening, 58% were IgG aCL positive, 18% IgM aCL positive, 30% aβ2GP1 IgG positive, 15% IgM aβ2GP1 positive, and 52% were LA positive. APO occurred in 30% of the patients.

Description of mean aPL titer variation is shown Figure 1. aPL IgG titers decreased through pregnancy, and the mean aCL IgG titer was significantly lower during 2nd and 3rd trimesters compared to screening, but remained in the high positive range. Mean aβ2GP1 IgG titer was significantly lower during 3rd trimester. 80% of APO occurred during the 2nd trimester when IgG titers began to fall. No significant variation in aCL or aβ2GP1 IgM was observed through pregnancy, and titers remained low.

Of note, aPL IgG titers, as well as magnitude of change in titer over the course of pregnancy, were comparable between the patients with or without APO.

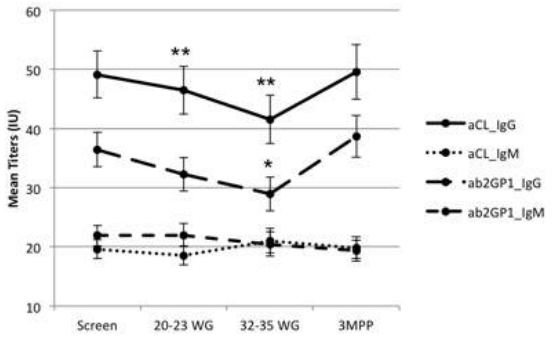

Figure1: Variation in aPL titers through pregnancy in 158 aPL-positive PROMISSE patients. Values represent mean ± SEM. Paired T-Test *p<0.05 **p<0.001 compared to mean value at screening. ab2GP1: anti-β2 Glycoprotein 1 antibodies; WG: Weeks of Gestation.

Conclusion:

In a large, prospective cohort of aPL-positive pregnant women, aCL and aβ2GP1 IgG titers decreased modestly in the course of pregnancy. Potential mechanisms for this decrease include dilutional effect, targeting of aPL to placenta, or decreased autoantibody production. Changes were modest, not clinically meaningful, and not associated with pregnancy outcomes. Our findings suggest that it is not necessary to repeat aPL testing through pregnancy.

Disclosure: C. Yelnik, None; **F. Porter**, None; **W. D. Branch**, None; **J. P. Buyon**, None; **M. Guerra**, None; **C. Laskin**, None; **M. Lockshin**, None; **M. Petri**, None; **J. T. Merrill**, Bristol-Myers Squibb, 2; **L. R. Sammaritano**, None; **M. D. Stephenson**, None; **M. Y. Kim**, None; **J. E. Salmon**, None.

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Abstract Number: 2186

The Role of Hydroxychloroquine Treatment on Pregnancy Outcome in Women

with Antiphospholipid Antibodies

Savino Sciascia[1], Beverely J Hunt[2], Eva Talavera-Garcia[3], Gloria Lliso[3], Munther Khamashta[3] and Mª Jose Cuadrado[4], [1]Department of Rare, Immunologic, Hematologic and Immunohematologic Diseases, Centro di Immunopatologia e Documentazione su Malattie rare, Torino, Italy, [2]Thrombosis & Haemostasis, Guy's & St Thomas' NHS Foundation Trust, London, UK, London, United Kingdom, [3]Louise Coote Lupus Unit, Guy's and St Thomas' NHS Foundation Trust, London, UK, London, United Kingdom, [4]Lupus Research Unit, The Rayne Institute, St Thomas' Hospital, London, United Kingdom
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Background/Purpose: With good management, around 70% of pregnant women with Antiphospholipid Syndrome (APS) will deliver a viable live infant.However, current management does not prevent all maternal, foetal and neonatal complications of APS. This observational, retrospective, single-centre cohort study aimed to assess pregnancy outcome in women with antiphospholipid antibody(aPL) treated with hydroxychloroquine (HCQ) in addition to conventional treatment during pregnancy.

Methods: One-hundred and seventy pregnancies in 96 women with persistent aPL were analysed:51 pregnancies occurred in 31 women treated with HCQ for at least six months prior to pregnancy and continued throughout gestation(group A);119 pregnancies occurred in 65 women with aPL not treated with HCQ were included as controls (group B).

Results: HCQ-treatment was associated with a higher rate of live births (67%groupA vs. 57% group B,p=0.05)and a lower prevalence of aPL-related pregnancy morbidity (47% group A vs. 63% B,p=0.004).The association of HCQ with the absence of any complication in pregnancy was confirmed after multivariate analysis (OR 2.2;95%CI 1.2-136;p=0.04). Fetal losses>10thweeks of gestation(2% vs. 11%,p=0.05)and placenta mediated complications (2% vs 11%,p=0.05)were less frequent in group A than B.Pregnancy duration was longer in group A than B(27.6 [6-40] vs. 21.5[6-40] weeks,p=0.03).There was a higher rate of spontaneous vaginal labour in HCQ-treated women compared to group B(37.3% vs. 14.3%,p=0.01).

Conclusion: Despite the heterogeneity in the two groups in terms of SLE prevalence and previous pregnancy history, our results support the concept that women with aPL may benefit from treatment with HCQ during pregnancy to improve pregnancy outcome.The addition of HCQ to conventional treatment is worthy of further assessment.

Disclosure: S. Sciascia, None; **B. J. Hunt**, None; **E. Talavera-Garcia**, None; **G. Lliso**, None; **M. Khamashta**, None; **M. J. Cuadrado**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/the-role-of-hydroxychloroquine-treatment-on-pregnancy-outcome-in-women-with-antiphospholipid-antibodies

Abstract Number: 2187

Anti-Phosholipid Antibodies and Female Infertility: A Systematic Revision of Literature

Cecilia B. Chighizola[1], Guilherme Ramires de Jesus[2] and W. David Branch[3], [1]Department of Clinical Sciences and Community Health, University of Milan, Istituto Auxologico Italiano, Cusano Milanino, Italy, [2]Department of Obstetrics, Universidade do Estado do Rio de Janeiro, Rio de Janeiro, Brazil, [3]Obstetrics and Gynecology, University of Utah and Intermountain Healthcare, Salt Lake City, UT
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SESSION INFORMATION

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Background/Purpose:

Infertility is a common condition, affecting 8-12% of couples in childbearing age. Even though the association of aPL with infertility is highly debated, infertile women are commonly screened for anti-phospholipid antibodies (aPL). Therefore, the aim of this work was to accurately review available evidence.

Methods:

A systematic PubMed search was conducted to retrieve papers addressing the: i) association between aPL positivity and infertility, ii) positivity rate of criteria and non criteria aPL in infertile women and iii) association between aPL positivity and ART outcome. aPL positivity rates in infertile women and controls were calculated as median (25-75 percentiles); differences in aPL positivity rate between patients and controls were evaluated by Wilcoxon matched-pair test. The strength of association between aPL positivity and both infertility and outcome of assisted reproduction technologies (ART) were expressed as the rate of studies confirming a positive association.

Results:

A total of 39 papers were considered in this critical analysis. There was a wide heterogeneity in the selection of study and control populations; only 10% of the studies presented a prospective design. aPL cut-offs conforming to international guidelines were used in less than 25% of studies; aPL positivity was confirmed in 11% of studies. Approximately half of the considered studies assessed non criteria aPL tests. i) According to our best estimates, the overall positivity rate of criteria aPL tests is 6% (2-8.9) among infertile women and 1% (0-2.15) among controls. Non criteria aPL tests were estimated to be positive in 3% (1.5-9) of study women and in 2% (1-7) of controls. **Table 1** reports the calculated frequencies of each of the considered tests in patients and controls. A significant difference in the positivity rate of patients versus controls emerged for anti-cardiolipin antibodies (aCL) only ($p<0.00001$, 95% CI 3.35-8.50). ii) The association rates between each aPL test and infertility are detailed in **Table 2**. iii) Only 5 of the relevant 18 studies (27.7%) reported a detrimental effect of aPL on ART outcome. Of these studies, 4 assayed only criteria aPL tests and one aCL plus non-criteria aPL tests.

Conclusion:

According to our literature revision, aPL are more frequently detected among infertile women than controls; conversely, the association between aPL and ART outcome is not supported by most studies. Data inconsistencies might be ascribed to the lack of a true association or to literature limitations; well-designed studies are warranted to produce strong evidence-based recommendations.

Table 1

aPL test	Number of studies	Number of patients/controls	Positivity rate (patients)	Positivity rate (controls)
Lupus anticoagulant	9	90 (56-137)/ 100 (80-201)	0% (0-2.5)	0% (0-0)
Anti-cardiolipin Abs	20	65 (47-131)/ 67 (34-194)	7% (3.7-13.3)	1.6% (0-3)
Anti-b2 glycoprotein I Abs	1	105/106	7.6%	2.8%
Anti- phosphatidic acid Abs	7	43(42-96)/ 45 (42-124)	6% (1.5-13.2)	5% (2-5.7)

Anti-phosphatidylcoline Abs	1	1991/205	4% (2-5.8)	1% (0.8-1.4)
Anti-phosphatydilethanolamine Abs	7	96 (42.5-1048)/ 106 (43.5-164.5)	4.2% (2-9)	2.5% (1.8-7.1)
Anti-phosphatidylglycerol Abs	5	43 (42-96)/ 45 (42-124)	3% (2-7.5)	2% (0.9-4.5)
Anti-phosphatidylinositol Abs	6	69.5 (42-103)/ 75.5 (43-119.5)	3.8% (1-5.5)	1% (0-5.7)
Anti- phosphatydilserine Abs	2	1013 (524-1502)/ 164 (144-184)	2% (0.8-2)	2.8% (0.5-6.8)
Anti-prothrombin Abs	1	69/120	31.9%	8.3%

Table 2

aPL test	Number of studies	Rate of association
Lupus anticoagulant	13	45%
Anti-cardiolipin Abs	29	31%
Anti-b2 glycoprotein I Abs	4	75%
Anti- phosphatidic acid Abs	9	44.4%
Anti-phosphatidylcoline Abs	6	83.3%
Anti- phosphatydilethanolamine Abs	12	53.3%
Anti- phosphatidylglycerol Abs	10	50%
Anti-phosphatidylinositol Abs	11	63.6%
Anti- phosphatydilserine Abs	7	/
Anti-prothrombin Abs	1	100%

Disclosure: C. B. Chighizola, None; **G. Ramires de Jesus**, None; **W. D. Branch**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/anti-phosholipid-antibodies-and-female-infertility-a-systematic-revision-of-literature

Abstract Number: 2188

Antiphospholipid Antibodies and the Risk of Damage Accrual in Systemic Lupus Erythematosus

Mara Taraborelli[1], Laura Leuenberger[2], Maria Grazia Lazzaroni[3], Nicole Martinazzi[3], Wei Zhang[4], Jane E. Salmon[2], Franco Franceschini[1], Angela Tincani[3] and Doruk Erkan[2], [1]Rheumatology and Clinical Immunology, Spedali Civili of Brescia, Brescia, Italy, [2]Rheumatology, Hospital for Special Surgery, New York, NY, [3]Rheumatology and Clinical Immunology, Spedali Civili and University of Brescia, Brescia, Italy, [4]Healthcare Research Institute, Hospital for Special Surgery, New York, NY
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Background/Purpose: A limited number of studies evaluated **t**he impact of antiphospholipid antibodies (aPL) on organ damage in Systemic Lupus Erythematosus (SLE) with contrasting conclusions. The aim of this study was to assess the relative contribution of a significant aPL positivity to organ damage in SLE patients.

Methods: SLE patients (based on American College of Rheumatology [ACR] Classification Criteria) with less than 10 years of disease duration at registry entry and at least 5 years of follow-up were identified from the SLE registry of 2 centers. Clinical information retrieved included: demographics, disease duration at registry entry, organ damage assessed by the Systemic Lupus International Collaborating Clinics/ACR Damage Index (SDI), and aPL profile. A "clinically significant" aPL profile was defined as: positive lupus anticoagulant test, anticardiolipin antibody IgG/M $\geq$ 40U, and/or anti-β_2Glycoprotein-I IgG/M $\geq$ 99thpercentile on two or more occasions, at least 12 weeks apart, within ± 1 year of registry entry. The outcome variables were any increase of SDI at 5, 10 and/or 15 years of follow-up (time 0 was defined as registry entry). For univariate analysis the demographic and clinical characteristics of patients with and without a SDI increase at 5, 10 and 15 years were compared (Chi square or Fisher's exact test for categorical data, Student t test or Mann-Whitney for continuous data as appropriate). The Generalized Estimated Equations (GEE) model was used as multivariate analysis to detect significant factors for increased SDI at 5, 10 and/or 15 years.

Results: We identified 262 patients with less than 10 years of disease duration, at least 5 years of prospective follow-up and a complete aPL profile (76% Caucasian, 8% African-American, 6% Asian, and 86% female). Mean age at diagnosis was 31 years (±12) and mean age at registry entry was 33 years (±12) with a mean disease duration of 1 year (±2). Eighty-eight (33%) patients had a clinically significant aPL profile. Twenty-one percent, 42%, and 57% of patients had new organ damage in 5, 10, and 15 years, respectively. On the univariate analysis: a) a significant aPL profile (p:0.02) and a older age at diagnosis (p:0.04) were significantly associated to any increase of SDI at 5 years; b) a shorter disease duration was significantly associated to any increase of SDI at 10 years (p:0.003) and 15 years (p:0.008); and c) male gender showed a tendency for any increase of SDI at 15 years without reaching significance (p:0.054). The GEE model showed that patients with a significant aPL profile (p:0.006,Odds Ratio, [OR]:1.9, 95% Confidence Interval,[CI]:1.2-3.1), older age at diagnosis (p:0.007, OR: 1.02, 95%CI 0.006-0.04) or male sex (p:0.017,OR: 1.9,95%CI 1.1-3.3) were more likely to experience an increase of SDI during the follow-up.

Conclusion: Our data demonstrate that: a) one-third of SLE patients have clinically significant aPL profiles; b) 21%, 42% and 57% of SLE patients have new organ damage in 5, 10 and 15 years; c) clinically significant aPL-profiles, older age at diagnosis, and male sex are associated with an increased risk of organ damage accrual during a fifteen year follow-up.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/antiphospholipid-antibodies-and-the-risk-of-damage-accrual-in-systemic-lupus-erythematosus

Abstract Number: 2189

Antiphospholipid Syndrome Alliance for Clinical Trials and International Networking Clinical Database and Repository ("Registry") Prospective Follow-up Analysis: One-Year First and Recurrent Thrombosis Risk

Doruk Erkan[1], Stephane Zuily[2], Alessandra Banzato[3], Karel De Ceulaer[4], Hannah Cohen[5], Maria Tektonidou[6], Danieli Andrade[7] and , on Behalf of APS ACTION .[8], [1]Barbara Volcker Center for Women & Rheumatic Disease, Hospital for Special Surgery, New York, NY, [2]Regional Competence Center For Rare Vascular And Systemic Autoimmune Diseases, Vascular Medicine Unit, Vandoeuvre-Les-Nancy, France, [3]Department of Cardiac Thoracic and Vascular Sciences, (2) Department of Cardiac Thoracic and Vascular Sciences, University of Padua, Padua Italy, Padua, Italy, [4]Internal Medicine, University of the West Indies, Kgn 7, Jamaica, [5]Hematology., University College London, LOndon, United Kingdom, [6]First Department of Internal Medicine, School of Medicine, National University of Athens, Athens, Greece, [7]Autoimmunity & Inflammation, Hospital for Special Surgery, New York, NY, [8]., New York, NY
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Background/Purpose: APS ACTION "Registry" was created to study the natural course of disease over 10 years in persistently antiphospholipid antibody (aPL)-positive patients with/without other systemic autoimmune diseases. Given that risk-stratified prospective data on the first or recurrent thrombosis risk in persistently aPL-positive patients are limited and controversial, our objective was to describe the thrombotic events identified during the follow-up of APS ACTION "Registry" patients, and also to determine the one-year first and recurrent thrombosis risk.

Methods: A web-based data capture system is used to store patient demographics, aPL-related history, and medications. The inclusion criteria are positive aPL (lupus anticoagulant test [LA], anticardiolipin antibody [aCL], and/or anti-β_2Glycoprotein-I antibody [aβ_2GPI]) based on the Updated Sapporo Classification Criteria at least twice within one year prior to enrollment. Patients are followed every 12±3 months with clinical data and blood collection; they also receive advice on cardiovascular disease and thrombosis prevention at each visit. In this descriptive analysis, patients who completed their one year follow-up visits are included.

Results: Of 581 patients included in the APS ACTION Registry, 350 (60%) completed their one year follow-up visits as of June 2015 (aPL/APS without any other autoimmune disease: 241 [no thrombosis: 35; thrombotic APS: 148; obstetric APS: 24; and thrombotic & obstetric APS: 34]; and aPL/APS associated with another autoimmune disease: 109 [no thrombosis: 45; thrombotic APS: 42; obstetric APS: 10; and thrombotic & obstetric APS: 12]). Table demonstrates the demographic, clinical, and laboratory characteristics of patients who had new events during the one year follow-up. Based on five new thrombotic events, the incident thrombosis risk was 1.7% and 0% per year in patients with and without history of thrombosis, respectively.

Baseline Data				One Year Follow-Up Data		
Age*/Sex/ Race	Other AIDx	aPL Profile	APS Manifestations	Recurrent Event**	aPL-related Medications*	Concomitant Thrombosis Risk Factors
18 /M/W	No	Triple aPL	DVT/PE	DVT/PE (13m)	Warfarin x 13m (INR: 2.1*)	None
46/F/A	SLE	LA, aCL	Stroke, TP, aPLN	Stroke (14m)	Cilostazol x 11m	HL, HTN, RF, Immob/postSx
47/F/UK	No	Triple aPL	DVT/PE, Critical Ischemia (lower limb), TP	DVT (arm) with IJVT (21m)	Statin Warfarin x 23m (INR<2)	Malignancy, Immob/postSx, HTN, DM, HL, Obesity, Vascular Procedure
47/F/W	SLE	Triple aPL	Stroke, DVT, Obs. APS, TP, AIHA	Stroke (180m)	Self-stopped 3m prior	PFO, RF, HL, FMHx CVD
55/F/W	No	Triple aPL	DVT	DVT (47m)	ASA x 20m	Long Flight - FMHx CVD

* At the time of the recurrent event
** The duration between the last thrombotic and recurrent event is listed in parenthesis

AIHA: autoimmune hemolytic anemia; **AIDx:** autoimmune disease; **aPLN:** aPL nephropathy; **ASA:** aspirin; **CVD:** cardiovascular disease; **DM:** diabetes mellitus; **DVT:** deep vein thrombosis; **F:** female; **HL:** Hyperlipidemia; **HTN:** hypertension; **IJVT:** internal jugular vein thrombosis; **Immob/Sx:** immobilization & postsurgical; **INR:** international randomization ratio: **M:** male; **Obs:** obstetric; **PE:** pulmonary embolism; **PFO:** patent foremen ovale; **RF:** renal failure defined as GFR < 60 ml/min; **SLE:** systemic lupus erythematosus; **TP:** thrombocytopenia defined as < 100.000/mm^3; **UK**: Unknown (unable to record due to country regulations).

Conclusion: The one year incident thrombosis risk is relatively low and commonly associated with triple aPL-positivity as well as non-aPL thrombosis risk factors in our multi-center international cohort. Annual and risk stratified analysis of APS ACTION registry will better determine the risk of thrombosis in persistently aPL-positive patients based on different risk profiles.

Disclosure: D. Erkan, New York Community Trust, 2,APS ACTION Executive Committee Co-Chair, 6; **S. Zuily**, None; **A. Banzato**, None; **K. De Ceulaer**, None; **H. Cohen**, None; **M. Tektonidou**, None; **D. Andrade**, None; **O. B. O. A. A. .**, None.

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Abstract Number: 2190

Antiphospholipid Syndrome Alliance for Clinical Trials and International Networking (APS ACTION) Core Laboratory Validation Exercise: Comparison of Enzyme-Linked Immunosorbant Assay (ELISA) and Chemiluminescence Immunoassay (CIA)

Maria Laura Bertolaccini[1], Danieli Andrade[2], Gabriella Lakos[3], Rohan Willis[4], Vittorio Pengo[5], Alessandra Banzato[6], Hannah Cohen[7], Steven Krilis[8], Doruk Erkan[9] and on behalf of APS ACTION, [1]Lupus Unit, Rayne Institute, Lupus Research Unit, The Rayne Institute, King's College London School of Medicine, St Thomas' Hospital, London, United Kingdom, [2]Rheumatology, University of São Paulo, São Paulo, Brazil, [3]INOVA Diagnostics, Inc., San Diego, CA, [4]Department of Internal Medicine, Antiphospholipid Standardization Laboratory, Division of Rheumatology, Galveston, TX, [5]Clinical Cardiology, Department of Cardiac Thoracic and Vascular Sciences, University of Padova, Padova, Italy, [6]Department of Cardiac Thoracic and Vascular Sciences, Department of Cardiac Thoracic and Vascular Sciences, University of Padua, Padua, Italy, [7]Hematology., University College London, LOndon, United Kingdom, [8]Immunology, Allergy, and Infectious Diseases, St George Hospital, Kogarah NSW, Australia, [9]Rheumatology, Barbara Volcker Center for Women and Rheumatic Diseases: Hospital for Special Surgery, New York, NY

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Background/Purpose: APS ACTION International Clinical Database and Repository was created to study the natural course of disease over 10 years in persistently aPL-positive patients with/without other systemic autoimmune diseases. The protocol involves testing for anticardiolipin antibodies (aCL) and anti-β2glycoprotein I antibodies (aβ2GPI) at five different international core laboratories in samples collected at multiple sites. Although all core laboratories use the same ELISA kits, APS ACTION core laboratory directors agreed that an exchange of samples to assess intra- and inter-laboratory variability is crucial to establish whether an acceptable agreement among the core labs can be achieved. As part of the this validation exercise, two different assays were used.

We designed this study to assess between-laboratory agreement obtained with a novel antiphospholipid (aPL) chemiluminescence immunoassay (CIA), and compare the results to those obtained with ELISA assays.

Methods: Blinded serum samples from aPL positive patients and controls (n=30) were distributed to the five APS ACTION core laboratories. All samples were tested for IgG, IgM and IgA aCL and aβ2GPI with the FDA cleared QUANTA Flash® CIA and QUANTA Lite® ELISA kits (Inova Diagnostics). For every sample, the average, SD and %CV of the values were calculated. Between laboratory precision was considered acceptable if %CV was less than 20%.

Results: Categorical agreement between the two methods was 100%, 97% and 77% for IgG, IgM and IgA aCL, respectively, and 87%, 93% and 77% for IgG, IgM and IgA aβ2GPI, respectively. The correlation between quantitative results was good (Spearman rho 0.917, 0.809 and 0.893 for IgG, IgM and IgA aCL, respectively; rho 0.938, 0.766 and 0.78 for IgG, IgM and IgA anti-β2GPI. All p values <0.0001). Only CIA met the <20% total CV acceptance criteria for all the samples with all the assays. %CV was higher for ELISA and, in some cases, well outside the acceptable range (Table).

	aCL		aβ2GPI	
	CIA	ELISA	CIA	ELISA
IgG	11% [0%-19%]	22% [7%-36%]	7% [0%-20%]	22% [8%-38%]
IgM	7% [4%-8%]	45% [30%-68%]	9% [4%-16%]	15% [3%-22%]
IgA	8% [3%-13%]	34% [25%-43%]	10% [4%-18%]	34% [4%-53%]

Conclusion: IgG and IgM aCL and aβ2GPI results showed good agreement between CIA and ELISA. Agreement was lower for IgA assays due to borderline samples being positive for CIA (a very sensitive test) and negative for the ELISA. Based on the evaluations performed in the APS ACTION Core Laboratories**,** CIA and ELISA tests displayed substantially equivalent performance for the detection of aCL and aβ2GPI. QUANTA Flash® CIA, a fully automated assay, however, showed higher level of reproducibility, making inter-laboratory comparisons more reliable.

Disclosure: M. L. Bertolaccini, None; **D. Andrade**, None; **G. Lakos**, Inova Diagnostics, Inc., 3; **R. Willis**, None; **V. Pengo**, None; **A. Banzato**, None; **H. Cohen**, None; **S. Krilis**, None; **D. Erkan**, None.

Abstract Number: 2191

Increased Risk of Acute and Chronic Renal Lesions Associated with Antiphospholipid Antibodies in Patients with Systemic Lupus Erythematosus: A Systematic Review and Meta-Analysis

Vinicius Domingues[1], DENIS WAHL[2] and Stephane Zuily[3], [1]Rheumatology, New York University School Of Medicine, New York, NY, [2]CHU de Nancy, Vascular Medicine Division and Regional Competence Centre For Rare Vascular And Systemic Autoimmune Diseases; and UMR_S U1116 Research Unit, Nancy, France, [3]CHU de Nancy, Vascular Medicine Division and Regional Competence Centre For Rare Vascular And Systemic Autoimmune Diseases; and UMR_S U1116 Research Unit, France, Nancy, France

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Background/Purpose : Renal lesions have been described in patients with antiphospholipid antibodies (aPL), however their associations with aPL are inconsistent among studies. Therefore our objective was to investigate associations between aPL and renal lesions among SLE patients.

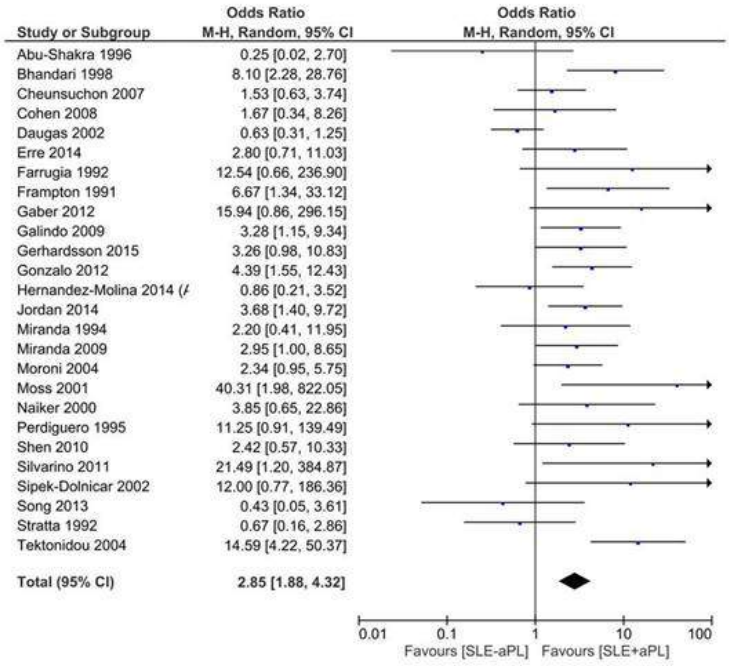
Methods : Studies were selected if they determined the association between aPL and acute (thrombotic microangiopathy including “glomerular thrombosis” and “intra-renal thrombosis”) and/or chronic (e.g. fibrous intimal hyperplasia, focal cortical atrophy) vascular renal lesions in SLE patients and if aPL-negative patients were included for comparison. Data sources were Pubmed,

Embase, Cochrane Library, hand search, congress abstracts, and reference lists of studies, without language restrictions. Risk estimates were independently extracted by 2 investigators. Pooled effect estimates were obtained by using the Mantel-Haenszel method (random effects).

Results: Of 1820 identified records, 25 published studies and 1 abstract (5 cohorts, 5 case-control, 16 cross-sectional) met inclusion criteria, including 2128 SLE patients according to ACR criteria and 482 cases of renal lesions. Prevalence of renal lesions in aPL-positive vs. aPL-negative SLE patients was 31.9% (n=243/761) vs. 17.5% (n=239/1367), respectively. Compared with SLE patients without renal lesions, the overall pooled odds ratios (OR) for renal lesions in aPL-positive SLE patients was 2.85 (95% confidence interval [CI], 1.88-4.32) (Figure 1). The risk of renal lesions was the highest for lupus anticoagulant (LA) (9 studies, OR=4.70 [95% CI, 2.36-9.36]) and IgG anticardiolipin antibodies (aCL) (4 studies, OR=3.13 [95% CI, 1.09-8.98]) while IgM aCL (2 studies, OR=1.51 [95% CI, 0.03-88.59]) and anti-β_2-glycoprotein I antibodies (aβ_2GPI) (4 studies, OR=1.66 [95% CI, 0.54-5.11] did not reach statistical significance. Furthermore, among all aPL assays, LA was the only test to be significantly associated with both acute (4 studies, OR=2.89 [95% CI, 1.10-7.60]) and chronic renal lesions (2 studies, OR for LA=3.56 [95% CI, 1.05-12.08]).

Conclusion : In SLE patients, aPL-positivity is associated with a significant 3- to 5-fold increased risk for renal lesions. This risk is mainly driven by LA and IgG aCL. While acute thrombotic renal lesions are known to be associated with aPL, our findings suggest that chronic renal lesions could be associated with aPL but with a lower level of evidence.

Figure 1



Disclosure: V. Domingues, None; **D. WAHL**, None; **S. Zuily**, None.

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Abstract Number: 2192

Increased Risk of Thrombocytopenia Associated with Antiphospholipid Antibodies in Patients with Systemic Lupus Erythematosus: A Systematic Review

and Meta-Analysis

YU PEI CHOCK[1], DENIS WAHL[2] and STEPHANE ZUILY[3], [1]KENT MEMORIAL HOSPITAL, WARWICK, RI, [2]CHU de Nancy, Vascular Medicine Division and Regional Competence Centre For Rare Vascular And Systemic Autoimmune Diseases; and UMR_S U1116 Research Unit, Nancy, France, [3]CHU de Nancy, Regional Competence Centre For Rare Vascular And Systemic Autoimmune Diseases, Vascular Medicine Division, NANCY, France

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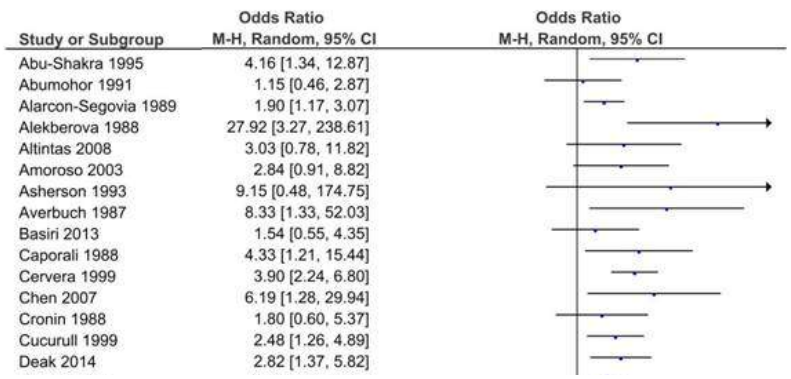
Background/Purpose : Thrombocytopenia is present in patients with systemic lupus erythematosus (SLE), and the role of antiphospholipid antibodies (aPL) is controversial. Therefore our objective was to estimate the risk of thrombocytopenia associated with aPL in patients with SLE.

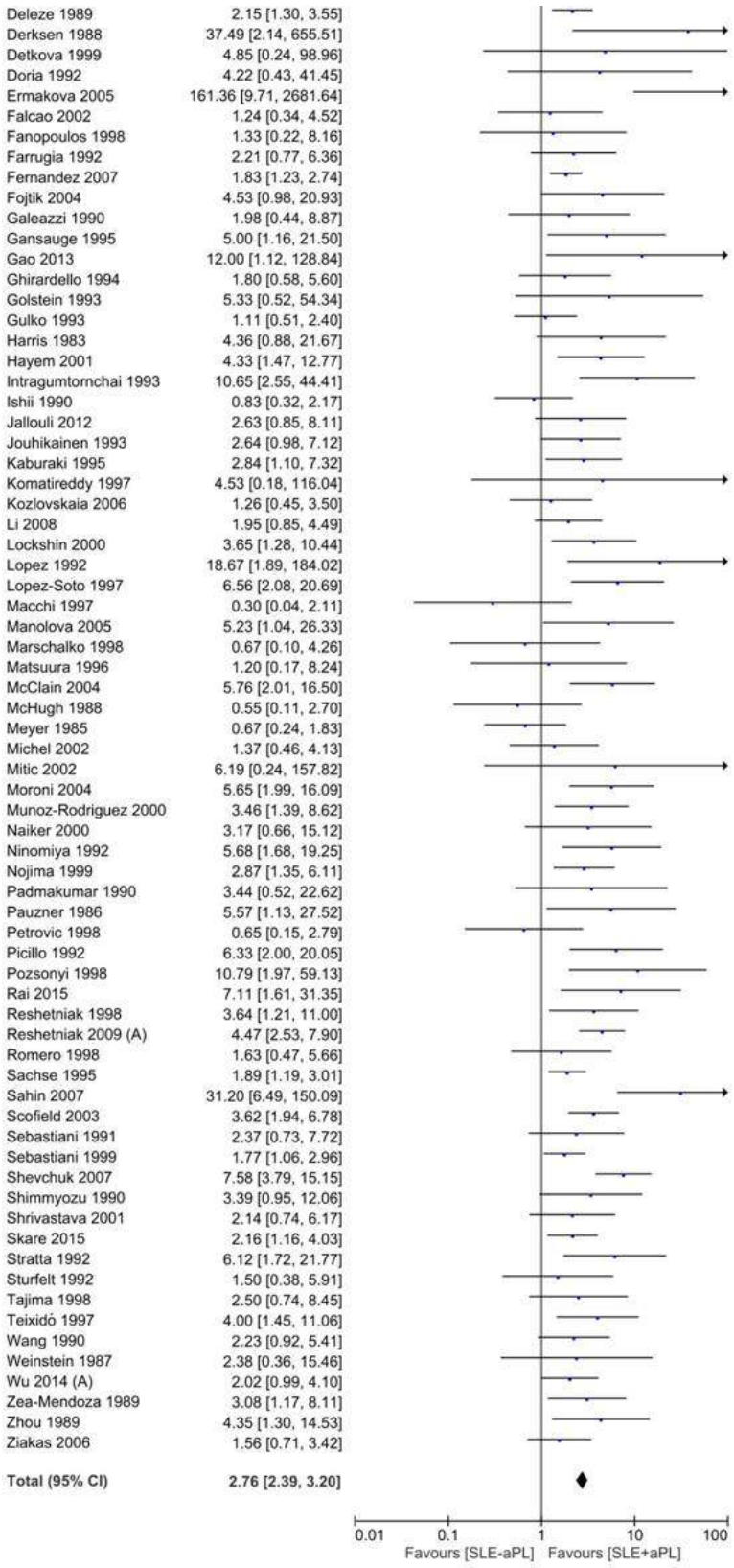
Methods : Studies were selected if they investigated the association between aPL and Thrombocytopenia in SLE patients and if aPL-negative patients were included for comparison. Data sources were Pubmed, Embase, Cochrane Library, hand search, congress abstracts, and reference lists of studies, without language restrictions. Risk estimates were independently extracted by 2 investigators. Pooled effect estimates were obtained by using the Mantel-Haenszel method (random effects).

Results: Of 2530 identified abstracts, 83 primary studies and 2 abstracts (24 cohorts, 18 case-control, 43 cross-sectional) met inclusion criteria, including 11877 SLE patients according to ACR criteria and 2399 cases of thrombocytopenia. Prevalence of thrombocytopenia in aPL-positive vs. aPL-negative SLE patients was 30.5% (n=1261/4128) vs. 14.7% (n=1138/7749), respectively. Compared with SLE patients without thrombocytopenia, the overall pooled odds ratios (OR) for thrombocytopenia in aPL-positive SLE patients was 2.76 (95% confidence interval [CI], 2.39-3.20) (Figure 1). The risk of thrombocytopenia was the highest for lupus anticoagulant (LA) (25 studies, OR=3.43 [95% CI, 2.59-4.54]). Risk of thrombocytopenia was also significantly increased in SLE patients with either IgG or IgM anticardiolipin antibodies (aCL) (27 studies, OR= 1.97 [95% CI, 1.58-2.44]; 17 studies, OR= 1.68 [95% CI, 1.34-2.12], respectively) and IgG or IgM anti-β_2-glycoprotein I antibodies (5 studies, OR=2.04 [95% CI, 1.22-3.41]; 3 studies, OR=2.68 [95% CI, 1.44-4.99], respectively). Finally, while high titers aCL were associated with an increased risk of thrombocytopenia (3 studies, OR=3.86 [95% CI, 1.05-14.23]), low titers aCL did not reach statistical significance (2 studies, OR= 0.56 [95% CI, 0.12-2.64]).

Conclusion : In SLE patients, aPL-positivity is associated with a significant 2- to 4-fold increased risk for thrombocytopenia. These findings a) confirm that an aPL-related mechanism can contribute to thrombocytopenia in SLE patients and b) suggest that thrombocytopenia could be associated with aPL in SLE patients.

Figure 1





Disclosure: Y. P. CHOCK, None; **D. WAHL**, None; **S. ZUILY**, None.

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Abstract Number: 2193

Increased Risk of Hemolytic Anemia Associated with Antiphospholipid Antibodies in Patients with Systemic Lupus Erythematosus: A Systematic Review and Meta-Analysis

OZAN UNLU[1], DENIS WAHL[2,3] and STEPHANE ZUILY[3,4], [1]Rheumatology Department, Barbara Volcker Center for Women and Rheumatic Disease, New York, NY, [2]CHU de Nancy, Vascular Medicine Division and Regional Competence Centre For Rare Vascular And Systemic Autoimmune Diseases; and UMR_S U1116 Research Unit, France, Nancy, France, [3]Inserm, UMR_S 1116, Nancy, France, [4]CHU de Nancy, Regional Competence Centre For Rare Vascular And Systemic Autoimmune Diseases, Vascular Medicine Division, NANCY, France

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Title: Increased Risk of Hemolytic Anemia Associated With Antiphospholipid Antibodies in Patients With Systemic Lupus Erythematosus: A Systematic Review and Meta-Analysis.

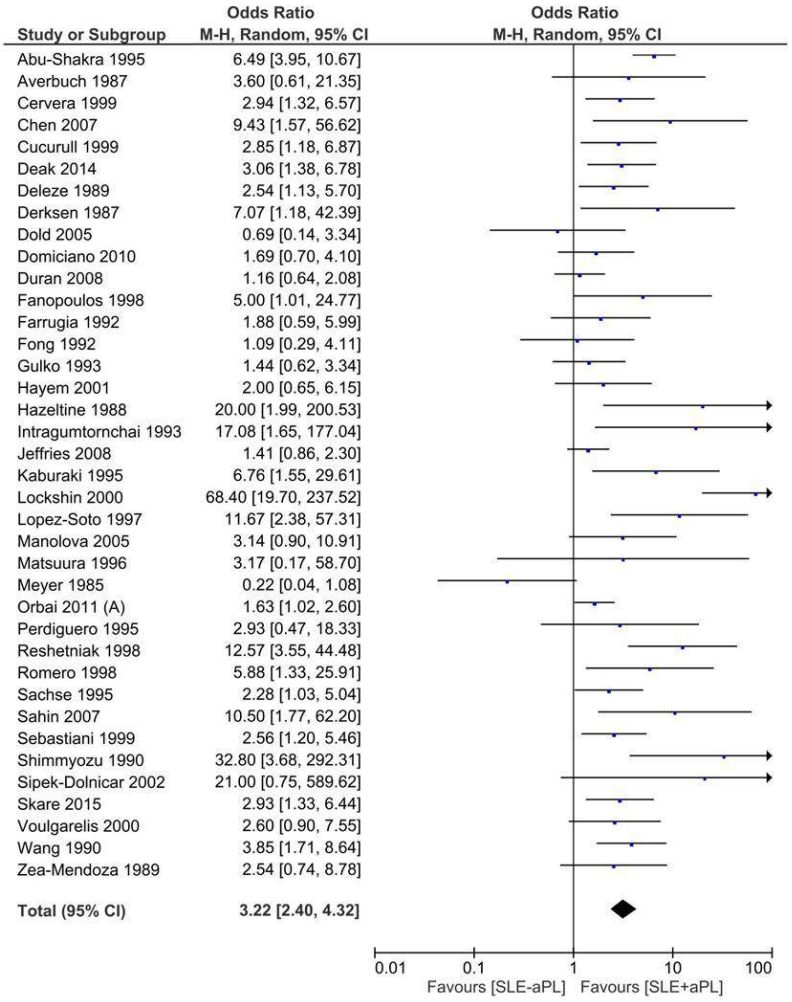
Background/Purpose : Hemolytic anemia (HA) is present in patients with systemic lupus erythematosus (SLE), and the role of antiphospholipid antibodies (aPL) is controversial. Therefore our objective was to estimate the risk of HA associated with aPL in patients with SLE.

Methods : Studies were selected if they investigated the association between aPL and HA in SLE patients and if aPL-negative patients were included for comparison. Data sources were Pubmed, Embase, Cochrane Library, hand search, congress abstracts, and reference lists of studies, without language restrictions. Risk estimates were independently extracted by 2 investigators. Pooled effect estimates were obtained by using the Mantel-Haenszel method (random effects).

Results: Of 1992 identified abstracts, 38 primary studies and 1 abstract (16 cohorts, 4 case-control, 19 cross-sectional) met inclusion criteria, including 7967 SLE patients according to ACR criteria and 974 cases of HA. Prevalence of HA in aPL-positive vs. aPL-negative SLE patients was 22.4 % (n=488/2177) vs. 8.4% (n=486/5790), respectively. Compared with SLE patients without HA, the overall pooled odds ratios (OR) for HA in aPL-positive SLE patients was 3.22 (95% confidence interval [CI], 2.40-4.32) (Figure 1). Of note, in studies explicitly reporting a positive Coombs test, the risk of HA was significantly increased (10 studies, OR=3.17 [95% CI, 1.93-5.20]). The risk of HA was the highest for lupus anticoagulant (LA) (12 studies, OR=4.58 [95% CI, 2.62-8.04]) and IgG anti-β_2-glycoprotein I antibodies (4 studies, OR=3.95 [95% CI, 1.46-10.71]). Risk of HA was also significantly increased in SLE patients with either IgG or IgM anticardiolipin antibodies (aCL) (10 studies, OR=2.27 [95% CI, 1.71-3.00]; 12 studies, OR=2.89 [95% CI, 2.16-3.87], respectively) and IgM anti-β_2-glycoprotein I antibodies (3 studies, OR=3.00 [95% CI, 1.48-6.07]).

Conclusion : In SLE patients, aPL-positivity is associated with a significant 2- to 4-fold increased risk for HA. These findings a) confirm that an aPL-related mechanism can contribute to HA in SLE patients and b) suggest that HA could be associated with aPL in SLE patients.

Figure 1



Disclosure: **O. UNLU**, None; **D. WAHL**, None; **S. ZUILY**, None.

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Abstract Number: 2194

Anticoagulation and Longterm Outcomes in Patients with Renal Artery Stenosis and Antiphospholipid Syndrome

Alina Casian[1], Shirish Sangle (joint 1st author)[2], Sotiria Manoustathopoulou[3] and David P. D'Cruz[4], [1]Louise Coote Lupus Unit, Guy's and St Thomas' Hospital, London, UK, London, United Kingdom, [2]Louise Coote Lupus Unit, Guy's and St. Thomas' Hospital, London, United Kingdom, [3]Department of Medicine, St. Thomas' Hospital, London, United Kingdom, [4]Louise Coote Lupus Unit, Guy's and St Thomas' Hospital, London, United Kingdom

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Background/Purpose: Our previous data showed renal artery stenosis (RAS) is more prevalent in antiphospholipid syndrome(APS)(26%) compared to the general hypertensive population(8%),and anticoagulation with INR>=3 was associated with initial reduction of chronic kidney disease(CKD) and hypertension.

Methods: We identified 37 patients with RAS and APS fulfilling Sapporo criteria: anticardiolipin IgG/IgM titer>40 units or >99thpercentile (or +lupus anticoagulant) on >=2 occasions >=6 weeks apart AND vascular thrombosis(or pregnancy morbidity). RAS was diagnosed by magnetic resonance angiography(MRA).

Results: 15 patients had APS alone and 22 APS associated with autoimmune conditions (13 lupus, 5 ANCA vasculitis, 4 mixed). Median age at RAS diagnosis was 48 years, 31/37(83.8%) were female and median follow-up was 10.4 years. 25/37(67.6%) had previous thrombosis. 7/37(18.9%) had bilateral RAS, 3 artery occlusion. 6/37(16.2%) had concurrent coeliac stenosis. Recanalization of RAS occurred after hydroxychloroquine in 3/37 and 9/37(24.3%) underwent angioplasty+/-stenting. MRA was repeated in 11/37(29.7%) after 2 years. 23/37(62.2%) were anticoagulated, with 9/37(24.3%) on antiplatelet therapy. 13/37(35.1%) received hydroxychloroquine, 10/22(45.5%) immunosuppressives and 18/37(48.6%) antihypertensives. 9/37(24.3%) died after a median of 10 years since RAS diagnosis. 21/37(56.8%) developed CKD: 6 endstage renal failure(ESRD) and 15 with median eGFR 39 mls/min.

Patient Group	CKD	ESRD	Death
Anticoagulation(23)	15/23	4/23	5/23
No anticoagulation(14)	6/14	2/14	4/14
p value	0.3	1.0	0.7
APS(15)	7/15	3/15	1/15
APS+autoimmune disease(22)	14/22	3/22	5/22
p	0.3	0.7	0.4
Medical therapy(28)	13/28	3/28	7/28
Angioplasty (9)	8/9	3/9	2/9
p	0.05	0.14	1

Conclusion: The majority of patients with RAS and APS were female, developed CKD and did not benefit from angioplasty. Anticoagulation was not associated with longterm reduction of ESRD or death, suggesting a non-thrombotic pathogenic process underlying RAS, e.g.intimal hyperplasia. Treatment of associated vascular risk factors and underlying autoimmune disease is paramount. Anticardiolipin antibodies and renal MRA are useful for screening hypertensive lupus patients.

Disclosure: A. Casian, None; **S. Sangle (joint 1st author)**, None; **S. Manoustathopoulou**, None; **D. P. D'Cruz**, None.

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Abstract Number: 2195

Long Term Outcome of Primary Antiphospholipid Syndrome Patients: A Multicenter Study

Francesca Dall'Ara[1], Mara Taraborelli[2], Rossella Reggia[1], Micaela Fredi[2], Maria Gerosa[3], Laura Massaro[4], Ariela Hoxha[5], Marta Tonello[5], Patrice Cacoub[6], Nathalie Costedoat-Chalumeau[7], Franco Franceschini[2], Pier Luigi Meroni[8], Jean Charles Piette[6], Amelia Ruffatti[5], Guido Valesini[4] and Angela Tincani[1], [1]Rheumatology and Clinical Immunology, Spedali Civili and University of Brescia, Brescia, Italy, [2]Rheumatology and Clinical Immunology, Spedali Civili of Brescia, Brescia, Italy, [3]Division of Rheumatology, Department of Clinical Sciences and Community Health, Ospedale Gaetano Pini, University of Milan, Milano, Italy, [4]Internal Medicine and Medical Specialties Department, Policlinico Umberto I, La Sapienza University of Rome, Roma, Italy, [5]Rheumatology Unit, Department of Medicine DIMED, University of Padua, Padova, Italy, [6]Internal Medicine Department, University Hospital “Pitié-Salpêtrière”, “Pierre et Marie Curie Paris VI” University, Paris, France, [7]Internal Medicine Department, Cochin Hospital, “René-Descartes Paris V” University, Paris, France, [8]Division of Rheumatology,

Division of Rheumatology, Istituto Ortopedico Gaetano Pini, Milan, Italy
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Background/Purpose:

Data on the long-term outcome in primary antiphospholipid syndrome (PAPS) patients (pt) are still very limited.The objectives of this work was to assess the prevalence of recurrences, organ damage, severe comorbidities (infections, hemorrhages, cancers), mortality, evolution in connective tissue disease (CTD), in long-standing PAPS.

Methods:

Medical records of PAPS pt followed in 6 centers for ≥15 years were retrospectively reviewed. Chi square for categorical and Student t test for continuous variables were used. P <0.05 was considered significant.

Results:

One hundred and sixteen pt (88% females) with PAPS followed between 1983 and 2014 with mean age at diagnosis of 33 (±10) and mean follow-up of 19 years (±3.5) were studied. Fifty-one pt (44%) had at least a thrombotic event during follow-up. Thromboses were more frequent in pt with previous thrombotic history (p:0.002,OR:4.8, 95% CI:1.6-14.7) and oral anticoagulant (OA) treatment was not protective against recurrences (p: not significant). Six pt (5%) had a catastrophic event. Fifty-two women had 87 pregnancies, that were successful in 78% of cases. Twenty-nine percent of pt had functional damage (permanent loss of function) in at least one system. Damage was significantly associated to a thrombotic history (p:0.004,OR:13.9,95% CI:1.8-288.4) and to arterial events (p<0.001,OR:7.9, 95% CI:2,7-24,3), but not to any demographical, serological or therapeutical variable. An anatomical damage (documented ischemic lesion) was present in 55% of pt. Twenty-four major bleeding episodes were recorded in 18 pt all on OA. Severe infections (4 bacterial, 2 viral) affected 6 pt (5%). A cancer (solid in 100%) was diagnosed in 8 pt (7%) at a mean age of 51 years (±6). One patient (1%) with a chronic bowel ischemia died for sepsis. Fourteen pt (12%) developed a CTD (7 Systemic Lupus Erythematosus,2 Sjogren, 5 Undifferentiated CTD).Compared to diagnosis at the end of the follow up we observed: less pt with anti-cardiolipin IgG (p:0.014) but more with antinuclear antibodies (p:0.01) and C4 reduction (p:0.025); less using estroprogestinics (p<0.001), more with hypercholesterolemia (p:0.043), hypertension (p:0.004), cancer (p:0.02); more using steroids (p:0.04), hydroxychloroquine (p<0.001), immunosuppressants (p<0.01), anticoagulants (p:0.003), anti-hypertensive drugs (p<0.001).

Conclusion:

Despite therapy, a high proportion of pt experienced new thrombotic events, while pregnancy outcome was significantly improved. Organ damage developed in a significant proportion of pt and was associated with arterial events. The risk of evolution in CTD has to be considered.

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Abstract Number: 2196

Association Between Antiphospholipid Antibodies and All-Cause Mortality Among End Stage Renal Disease Patients with and without SLE

Anna R. Broder[1], Wenzhu Mowrey[2], Mimi Kim[3], Irina Murakhovskaya[4], Joel Neugarten[5], Karen H. Costenbader[6] and Chaim

Putterman[7], [1]Rheumatology-Forchheimer 701N, Albert Einstein College of Medicine/Montefiore Medical Center, Bronx, NY, [2]Department of Epidemiology and Population Health/Division of Biostatistics, Albert Einstein College of Medicine, Bronx, NY, [3]Biostatistics and Research Design Resource, Albert Einstein Coll Med, Bronx, NY, [4]Medicine/Hametology, Albert Einstein College of Medicine/Montefiore Medical Center, Bronx, NY, [5]Medicine/Nephrology, Albert Einstein College of Medicine/Montefiore Medical Center, Bronx, NY, [6]Rheumatology, Brigham & Women's Hospital, Boston, MA, [7]Division of Rheumatology, Albert Einstein College of Medicine, Bronx, NY
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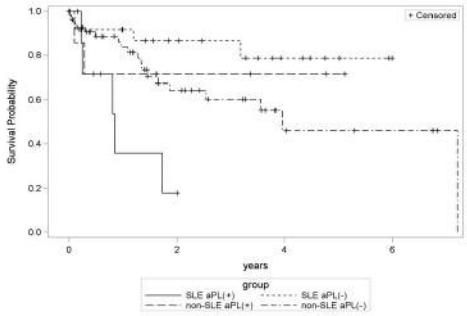
Background/Purpose: We investigated the association between the presence of antiphospholipid antibodies (aPL) and/or lupus anticoagulant (LAC) (aPL/LAC+) and all-cause mortality among end stage renal disease (ESRD) patients with and without SLE. We hypothesized that aPL/LAC+ would be associated with increased cause-mortality in ESRD, with elevated risk in SLE vs. non-SLE ESRD.

Methods: We included patients over 18 years old with ESRD, followed at an urban tertiary care center between 1/1/2006 and 1/31/2014 who had aPL measured at least once after initiating hemodialysis. All SLE patients met ACR/SLICC criteria. APL/LAC+ was defined as anti-cardiolipin IgG or IgM > 40 IU, anti-b2glycoprotein I IgG or IgM > 40 IU, or positive LAC. Age, sex, race, comorbidities, anticoagulation, and potential reasons for aPL measurement were ascertained from the medical records. Deaths through 1/31/2014 were captured in linked National Death Index data. Time to death was defined from the first aPL measurement; otherwise, subjects were censored at renal transplant, last visit date, or 1/31/2014. Kaplan-Meier survival curves and Cox proportional hazards model were used to evaluate the effects of aPL/LAC and SLE status on all-cause mortality.

Results: 34 SLE ESRD and 64 non-SLE ESRD were identified. SLE ESRD patients were younger (40.4±12.5 vs. 51.9±18.1 years, p=0.001) and more were women (88.2% vs. 54.7%, p=0.0007) compared to non-SLE ESRD. The frequency of aPL/LAC+ was 24% in SLE and 13% in non-SLE ESRD (p=0.16). Anticoagulation use was not associated with SLE or mortality. Median (IQR) follow-up time was 1.6 (0.3, 3.5) years in SLE, and 1.4 (0.4, 3.2) years in non-SLE, p=0.74. In total, 30 patients died during the study period. The median (IQR) time to death was 0.3 (0.2, 0.8) years in the aPL/LAC+ group, and 1.2 (0.2, 1.9) years in the aPL/LAC- group, p=0.22. Kaplan-Meier curves stratified by SLE and aPL/LAC status are shown in **Figure**. The survival curve for SLE aPL/LAC+ group was significantly different from the SLE aPL/LAC- group (logrank p=0.001). In Cox regression model adjusted for comorbidities, there was a multiplicative interaction between aPL/LAC and SLE with respect to mortality (p=0.05) indicating the differential effect of aPL/LAC+ in SLE and non-SLE. In SLE, the adjusted hazard ratio (HR) for death for the aPL/LAC+ vs. aPL/LAC- was 9.93 (95%CI 1.33, 74.19). In non-SLE, the adjusted HR (95%CI) for aPL/LAC+ vs. aPL/LAC- was 0.77 (0.14, 4.29).

Conclusion: SLE ESRD patients with aPL/LAC have higher risks of all-cause mortality than do SLE ESRD patients without these antibodies and non-SLE ESRD patients with these antibodies. Future studies will examine causes of death. If confirmed in prospective studies, preventive strategies could target this high risk group.

Figure 2. Kaplan-Meier curves for the 4 groups stratified by SLE and aPL status.



Abstract Number: 2197

Risk Factors for Adverse Pregnancy Outcome in First-Line Treated Pregnancies in Antiphospholip Antibodies-Positive Women According to Different Treatment Protocols: A Single Center Experience over 30 Years

Maria Grazia Lazzaroni[1], Laura Andreoli[1], Fabrizio Lupoli[1], Elena Aggogeri[1], Elisa Bettiga[2], Sonia Zatti[2], Andrea Lojacono[2], Francesca Ramazzotto[2], Micaela Fredi[3], Cecilia Nalli[4], Rossella Reggia[1], Francesca Dall'Ara[1], Mara Taraborelli[3], Roberto Gorla[3], Matteo Filippini[3], Marco Taglietti[3] and Angela Tincani[1], [1]Rheumatology and Clinical Immunology, Spedali Civili and University of Brescia, Brescia, Italy, [2]Obstetrics and Gynecology, Spedali Civili and University of Brescia, Brescia, Italy, [3]Rheumatology and Clinical Immunology, Spedali Civili of Brescia, Brescia, Italy, [4]Rheumatology and Clinical Immunology, Rheumatology and Clinical Immunology, Spedali Civili of Brescia, Brescia, Italy

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Background/Purpose: Antiphospholipid antibodies (aPL) are risk factors for Adverse Pregnancy Outcome (APO). Risk stratification may include several demographic, clinical and serological variables. Still debated is how to apply risk stratification in the therapeutic strategy to adopt in aPL-patients during pregnancy. Here we review the therapeutic approach to aPL-patients during pregnancy over 30 years of experience (1985 -2015) in our center, focusing on first-line treated pregnancies.

Methods: We collected 131 first-treated pregnancies in 131 persistently aPL-positive women (mean age 32 years) that were prospectively followed in our center by a multispecialistic team of Rheumatologists and Obstetricians. Patients were classified as Primary Antiphospholipid Syndrome (PAPS) according to Updated Sapporo criteria or as Incomplete PAPS or aPL carriers according to their clinical history or aPL status. Patients with concomitant systemic autoimmune diseases were excluded. aPL profile was defined as the combination of the 3 criteria tests for aPL. APO was defined as at least one of the followings: miscarriage (<10^{th} week), fetal death (≥10^{th} week), severe preterm delivery (≤34^{th} week) with or without preeclampsia (PE), HELLP syndrome, and perinatal death.

Results: The type of treatment was divided in 3 main categories: combination of low molecular weight heparin (LMWH) and low dose aspirin (LDA) (75, 57%), monotherapy with LDA (34, 26%) and combination of corticosteroids with LDA (22, 17%; medium prednisone-dosage 76 mg/week).

We analyzed the treatment that patients received according to clinical classification and found that those with a diagnosis according to revised criteria (Obstetric and Thrombotic PAPS) compared to Incomplete PAPS/aPL carriers, were more frequently treated with combination therapy of LMWH+LDA (67% vs.39%, p:0.0025). Regarding to serological profile, the combination therapy of LMWH+LDA was more frequently adopted in patients with a triple positive aPL profile vs. single/double positive ones (32% vs.3%, p:0.0001).

We recorded 17 APO (13%): 12 (71%) in the category of LMWH+LDA. Analyzing APO vs. non-APO pregnancies (Table 1), we found no differences in variables that could predict an APO (history of thrombosis, a previous APO or a triple positive aPL profile) in any of the 3 categories . The only predicting variable for APO in the group of LMWH+LDA was the presence of non-criteria aPL manifestations (50% vs.6%, p:0.0007).

Conclusion: Conventional treatment comprising LMWH was preferentially given to patients with recognized clinical and serological risk factors (definite APS according to criteria, triple aPL positivity). The presence of non-criteria aPL manifestations emerged as a risk factor for APO, suggesting that patients with a more severe disease phenotype may deserve additional treatments targeting aPL immunomodulation.

	Pregnancies with APO (n=17)	Pregnancies without APO (n=114)	P Value
LDA+LMWH (n=75)	**12/17(71%)**	**63/114(55%)**	
Obstetric PAPS (n=36)	6/12(50%)	30/63(48%)	
Thrombotic ± Obstetric PAPS (n=14)*	2/12(17%)	12/63(19%)	1,000
Incomplete PAPS (n=16)	1/12(8%)	15/63(24%)	
aPL carriers (n=9)	3/12(25%)	6/63(10%)	
Single positive (n=37)	5/12(42%)	32/63(51%)	
Double positive (n=14)	2/12(17%)	12/63(19%)	
Triple positive (n=24)*	5/12(42%)	19/63(30%)	0,505
Previous APO (n=56)*	7/12(58%)	49/63(78%)	0,167
Non-criteria aPL manifestations° (n=10)*	6/12 (50%)	4/63(6%)	**0,0007**
LDA in single therapy (n=34)	**2/17(12%)**	**32/114(28%)**	
Obstetric PAPS (n=7)	0/2(0%)	7/32(22%)	
Thrombotic ± Obstetric PAPS (n=0)*	0/2(0%)	0/32(0%)	1,000
Incomplete PAPS (n=11)	0/2(0%)	11/32(34%)	
aPL carriers (n=16)	2/2(100%)	14/32(44%)	
Single positive (n=25)	1/2(50%)	24/32(75%)	
Double positive (n=7)	0/2(0%)	7/32(22%)	
Triple positive (n=2)*	1/2(50%)	1/32(3%)	0,116
Previous APO (n=19)*	0/2(0%)	19/32(59%)	0,187
Non-criteria aPL manifestations° (n=4)*	0/2(0%)	4/32(13%)	1,000
Corticosteroids + LDA (n=22)	**3/17(18%)**	**19/114(17%)**	
Obstetric PAPS (n=10)	2/3(67%)	8/19(42%)	
Thrombotic ± Obstetric PAPS (n=5)*	0/3(0%)	5/19(26%)	1,000
Incomplete PAPS (n=6)	1/3(33%)	5/19(26%)	
aPL carriers (n=1)	0/3(0%)	1/19(5%)	
Single positive (n=9)	2/3(67%)	7/19(37%)	
Double positive (n=12)	1/3(33%)	11/19(58%)	
Triple positive (n=1)*	0/3(0%)	1/19(5%)	1,000
Previous APO (n=20)*	3/3(100%)	17/19(90%)	1,000
Non-criteria aPL manifestations° (n=5)*	1/3(33%)	4/19(21%)	1,000

Table 1

*variables considered for univariate analysis with Fisher's exact test (p<0.05)

°Non-criteria aPL manifestations were defined as the presence of at least one of the followings: livaedo reticularis, thrombocytopenia, headache, hemolytic anemia, cardiac valve disease, epilepsy

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Antiphospholipid Syndrome Alliance for Clinical Trials & International Networking Clinical Database and Repository Analysis: Determinants of Thrombosis in Patients Presenting with Obstetric APS

Guilherme Ramires de Jesus[1], STEPHANE ZUILY[2], Doruk Erkan[3], **Roger A. Levy**[4] and on Behalf of APS ACTION,
[1]Department of Obstetrics, Universidade do Estado do Rio de Janeiro, Rio de Janeiro, Brazil, [2]CHU de Nancy, Regional Competence Centre For Rare Vascular And Systemic Autoimmune Diseases, Vascular Medicine Division, NANCY, France, [3]Rheumatology, Hospital for Special Surgery, New York, NY, [4]Rheumatology, Department of Rheumatology, Universidade do Estado do Rio de Janeiro, Rio de Janeiro, Brazil

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Background/Purpose: APS ACTION Clinical Database and Repository ("Registry") was created to study the natural course of disease over 10 years in persistently antiphospholipid antibody (aPL)-positive patients with/without other systemic autoimmune diseases. The natural post-partum course of APS patients presenting with pure obstetric APS can be complicated by thrombosis; however, the incidence rate as well as the determinants of thrombosis are not well determined. Therefore, our objective was to compare the clinical and laboratory characteristics of the obstetric APS patients with or without thrombosis.

Methods: A web-based data capture system is used to store patient demographics, aPL-related history, and medications. The inclusion criteria are positive aPL based on the Updated Sapporo Classification Criteria at least twice within one year prior to enrollment. For the purpose of this cross-sectional baseline data analysis, we included obstetric APS patients with or without thrombosis after the initial diagnosis of pregnancy morbidity (PM) . We compared variables using Chi-Square and T-test, or non-parametric tests accordingly.

Results: Of 550 patients included in the registry as of May 2015, 173/419 (41.2%) women had any PM and 126/173 (72.8%) fulfilled the obstetric APS criteria, 74/126 (58.7%) with thrombotic APS (venous: 43; arterial: 22; and both: 9). Thrombosis occurred in 47/74 (63.5%) patients following the obstetric APS diagnosis (mean time between PM and first non-gravid thrombosis: 7.6±8.2 years). Table shows the clinical and laboratory characteristics of patients with pure obstetric APS, compared to those with presenting with obstetric APS followed by non-gravid thrombosis. Patients with obstetric APS only, compared to those with obstetric and thrombotic APS, were more likely to "ever" use aspirin and hydroxychloroquine (data not shown).

Conclusion: The cross sectional analysis of the baseline characteristics of a large scale aPL/APS registry demonstrates that: a) approximately 60% of thrombotic APS patients present initially with pregnancy morbidity; and b) earlier age during the first pregnancy morbidity, selected cardiovascular risk factors and non-criteria aPL manifestations, and lupus anticoagulant test positivity may increase the risk of future thrombosis after an aPL-related pregnancy morbidity.

Variables, n (%)	Obstetric APS only (n=52)	Obstetric APS followed by Thrombosis (n=47)	P value
Demographics Age of first pregnancy morbidity	28.94 + 6.77	26.25 + 5.52	**0.03**
Associated Autoimmune Disease No	28 (53.8%)	29 (61,7%)	0.21
SLE	12 (23.0%)	8 (17.0%)	0.22
Lupus-like disease	6 (11.5%)	2 (4.2%)	0.09
Other	6 (11.5%)	8 (17.0%)	0.43
Vascular Events			
Venous Thrombosis	NA	25 (53.1%)	NA
Arterial Thrombosis	NA	17 (36.1%)	NA
Venous and Arterial Thrombosis	NA	5 (10.6%)	NA
Cardiovascular Risk Factors*			
Hypertension on medication	11 (21.1%)	20 (42.5)	**0.01**
Diabetes on medication	1 (1.9%)	3 (6.3%)	0.13
Hyperlipidemia on medication	3 (5.7%)	8 (17.0%)	**0.03**
Obesity (BMI > 30)	6 (11.5%)	11 (23.4%)	0.059
Smoking (ever)	9 (17.3%)	18 (38.2%)	**0.009**
First Pregnancy Morbidity			
> Three (pre)-embryoic loss	4 (7.6%)	5 (10.6%)	0.30
Fetal Loss	34 (65.3%)	30 (63.8%)	0.43
Premature Birth < 34 week	14 (26.9%)	12 (25.5%)	0.43
Non-Criteria Manifestations			
Superficial Vein Thrombosis	1 (1.9%)	6 (12.7%)	**0.01**
Transient Ischemic Attack	4 (7.6%)	7 (14.8%)	0.12
Livedo	6 (11.5%)	11 (23.4%)	0.059
Thrombocytopenia	12 (23.0%)	10 (21.2%)	0.41
Hemolytic Anemia	3 (5.7%)	4 (8.5%)	0.29
Heart Valve Disease	1 (1.9%)	6 (12.7%)	**0.01**
Skin Ulcer	0	4 (8.5%)	NA
aPL-Nephropathy	2 (3.8%)	0	NA
Cognitive Dysfunction	0	0	NA
Laboratory parameters			
Lupus Anticoagulant (alone or with other autoantibodies)	35 (67.3%)	42 (89.3%)	**0.004**
Triple Positivity	17 (32.6%)	13 (27.6%)	0.29

*at the time of the registry entry

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Abstract Number: 2199

in Vivo Ubiquinol Supplementation Reduces the Pro-Atherothrombotic Status in Antiphospholipid Syndrome Patients. Preliminary Results of a Clinical Trial

Chary Lopez-Pedrera[1], Maria Ángeles Aguirre Zamorano[1], Francisco Velasco[2], Patricia Ruiz-Limon[1], Nuria Barbarroja[1], Yolanda Jiménez Gómez[1], Maria Carmen Abalos-Aguilera[1], Pedro Segui[3], Eduardo Collantes-Estevez[1], Lucia Fernandez-del Rio[4], Jose Antonio Gonzalez-Reyes[4], Jose Manuel Villalba[4], Mª Jose Cuadrado[5] and Carlos Perez-Sanchez[1], [1]IMIBIC-Reina Sofia University Hospital, Rheumatology Unit, Cordoba, Spain, [2]Hematology, IMIBIC-Reina Sofia Hospital, Hematology Unit, Cordoba, Spain, [3]IMIBIC-Reina Sofia University Hospital, Radiology Unit, Cordoba, Spain, [4]Cell Biology, Physiology and Immunology, University of Cordoba, Cordoba, Spain, [5]Lupus Research Unit, The Rayne Institute, St Thomas' Hospital, London, United Kingdom

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Background/Purpose:

To investigate the beneficial effects of *in vivo*ubiquinol (Q, reduced form of CoQ10) supplementation on athero-thrombosis prevention in APS patients, through the implementation of a prospective, randomized, double-masked, placebo-controlled study.

Methods:

The study was conducted on 20 APS patients randomized to receive either Q (200 mg/day) or placebo for one month. Blood was drawn at time 0 and at the end of the treatment. Studies were performed in plasma and purified leukocytes subsets. Plasma Q levels, various prothrombotic/proinflammatory parameters, and oxidative stress biomarkers were evaluated. Differential expression of miRNAs in monocytes was also determined using Nanostring miRNA arrays and validated by real-time RT-PCR. Ultrastructural evaluation of mitochondria in isolated monocytes was performed by electron microscopy (EM). Endothelial activity analysis was performed by Laser-Doppler measurement of post ischemic reactive hyperemia. Carotid intimae media thickness (CIMT) was measured as an early atherosclerosis marker.

Results:

Seventeen out of 20 patients completed the intervention, which increased significantly plasma Q levels. Endothelial function improved notably, as shown by the amelioration in the highest perfusion value after occlusion was released, expressed as a percentage of change vs rest flow value (RF-PF). Q treatment decreased Tissue Factor (TF), IKK and IL8 protein expression levels in monocytes. A number of other proinflammatory mediators were further reduced in monocytes and neutrophils by effect of Q treatment (VEGF, CCL3, IL-1ß, IL6, and TNFα). Comparing to controls, 57 microRNAs were found significantly altered in APS patients. Among them, 26 were reversed by effect of Q treatment. Functional classification of those miRNAs showed a preponderance of target mRNAs involved in free radical scavenging, inflammatory response, cardiovascular disease, and reproductive system disease. Q supplementation produced a reduction in both the levels of peroxides and the percentage of monocytes with altered mitochondrial membrane potential ($\Delta\Psi m$). EM analyses further indicated that Q treatment promoted an

increase in monocytes' mitochondrial size. Reduced monocyte TF expression after Q treatment was related to decreased peroxides levels, increased plasma Q levels, and improved endothelial function, which further correlated with IL8 levels. Eight out of 11 patients showing atheromatous plaques had also suffered at least one thrombotic recurrence. These pathologic processes were further linked to a poorer endothelial function compared to the remaining APS patients. Q effects were particularly relevant in those APS patients with pathologic CIMT and thrombotic recurrences, who showed a better response to Q treatment with improved endothelial function.

Conclusion:

Q supplementation at 200 mg/d significantly improved endothelial function, and reducedmitochondrial dysfunction, oxidative stress, and the expression of prothrombotic/proinflammatory proteins. Underlying epigenetic mechanisms seem to be involved. Our results support the potential impact of Qin the prevention of atherothrombosis in APS patients.Supported by: CTS-7940, PI12/01511, KANEKA.

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Abstract Number: 2200

Antiphospholipid Syndrome Alliance for Clinical Trials and International Networking Clinical Database and Repository Cluster Analysis: Identification of Different Clinical Phenotypes Among Antiphospholipid Antibody-Positive Female Patients

Stephane Zuily[1], Cecilia B. Chighizola[2], DENIS WAHL[1], Pier Luigi Meroni[3] and Doruk Erkan[4], [1]CHU de Nancy, Vascular Medicine Division and Regional Competence Centre For Rare Vascular And Systemic Autoimmune Diseases; and UMR_S U1116 Research Unit, France, Nancy, France, [2]Department of Clinical Sciences and Community Health, University of Milan, Istituto Auxologico Italiano, Cusano Milanino, Italy, [3]University of Milan, Department of Clinical Sciences and Community Health, Division of Rheumatology, Gaetano Pini Institute, Milan, Italy, [4]Barbara Volcker Center for Women & Rheumatic Disease, Hospital for Special Surgery, New York, NY

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Background/Purpose: APS ACTION International Clinical Database and Repository was created to study the natural course of persistently antiphospholipid antibodies (aPL)-positive patients ± autoimmune disorders over 10 years. Cluster analysis (CA) is a data driven method that can group patients in a way that patients in the same group (cluster) are more similar to each other than to those in other groups. Previously, we identified three different clinical phenotypes of aPL-positive patients discriminated by aPL profile, lupus, or cardiovascular (CV) risk factors (Ann Rheum Dis 2015;74(S2):813-4). As a follow-up analysis, our objective was to analyze different clinical phenotypes among female patients with a special focus on obstetric manifestations.

Methods: A secure web-based data capture system is used to store patient demographics, pertinent aPL history, and aPL profile. The inclusion criteria include aPL positivity according to updated Sapporo APS Classification Criteria. CA, using Ward's minimum-variance hierarchical method, was performed on the baseline characteristics; 15 clinical data points were included in the CA to cover a broad spectrum of aPL-positive patients. To identify differences between clusters, ANOVA and χ^2 test of independence were used with adjustment using the Bonferroni correction to identify *predominant* and *discriminant* variables

(Table).

Results: As of June 2015, of 573 aPL-positive patients recruited from 24 centers, 283 were excluded (139 male, 130 without history of pregnancy, and 14 with missing data). Finally, 290 female patients with a history of at least one pregnancy were included. Four main exclusive clusters with different combinations of features were (Table): a) Cluster 1: older female patients with arterial thrombosis and CV risk factors; b) Cluster 2: female patients with pregnancy morbidity only; c) Cluster 3: asymptomatic aPL-positive female patients with aCL/antiβ_2GPI antibodies treated with aspirin; and c) Cluster 4: female patients with venous thrombosis obesity, SLE, lupus anticoagulant, and treated with warfarin.

Conclusion: Our CA identified four different clinical phenotypes of aPL-positive female patients discriminated by pregnancy morbidity, CV risk factors, aPL profile, and lupus. Our results: a) support the heterogeneity of aPL-positive patients; and b) provide a foundation to understand disease mechanisms, create new approaches for APS classification, and ultimately to develop new management approaches.

Table 1

Variables, n (%)	Cluster 1 (n=85)	Cluster 2 (n=69)	Cluster 3 (n=92)	Cluster 4 (n=44)
Demographics				
Mean Age ± SD	**47.95 ± 9.63**[b]	38.94 ± 11.67	44.86 ± 11.74[b]	42.94 ± 11.30
White	52 (65.8)	35 (54.7)	53 (66.3)	22 (50.0)
Asian	3 (3.8)	**11 (17.2)**[a]	8 (10.0)	4 (9.1)
Latin American	22 (27.8)	16 (25.0)	12 (15.0)	12 (27.3)
Black	1 (1.3)	2 (3.1)	5 (6.3)	5 (11.4)
Past Medical History				
Clinical Criteria				
Arterial Thrombosis	**40 (47.1)**[b,d]	12 (17.4)	31 (33.7)	8 (18.2)
Venous Thrombosis	37[c] (43.5)	27[c] (39.1)	16 (17.4)	**34 (77.3)**[a,b,c]
Small Vessel Thrombosis	8 (9.4)	1 (1.4)	4 (4.3)	2 (4.5)
Fetal Death > 10th Week	30 (35.3)[c]	**58 (84.1)**[a,c,d]	3 (3.3)	11 (25.0)[c]
Premature Birth	12 (14.1)	**21 (30.4)**[d]	18 (19.6)[d]	1 (2.3)
≥ 3 Fetal Losses	7 (8.2)	5 (7.2)	8 (8.7)	3 (6.8)
Classification				
Asymptomatic aPL-carriers	11 (12.9)	3 (4.3)	**33 (35.9)**[a,b,d]	5 (11.4)
Obstetrical APS	7 (8.2)	**29 (42.0)**[a,c,d]	15 (16.3)	3 (6.8)
Thrombotic and obstetrical APS	30 (35.3)[c]	**25 (36.2)**[c]	13 (14.1)	12 (27.3)
Thrombotic APS	37 (43.5)[b]	12 (17.4)	31 (33.7)	**24 (54.5)**[b]
Other Auto-Immune Disease				
Systemic Lupus Erythematosus	21 (24.7)	11 (15.9)	20 (21.7)	**25 (56.8)**[a,b,c]
Lupus-Like Disease	7 (8.2)	4 (5.8)	15 (16.3)	0 (0.0)
Treatments				
Aspirin	32 (38.1)	32 (46.4)[d]	**57 (62.0)**[a,d]	9 (20.5)
Warfarin	56 (65.9)[c]	31 (44.9)	35 (38.0)	**33 (75.0)**[b,c]
Low Weight Molecular Heparin	7 (8.2)	4 (5.8)	7 (7.6)	2 (4.5)
Statins	**29 (34.1)**[b,d]	5 (7.2)	16 (17.4)	5 (11.4)
Hydroxychloroquine	35 (41.7)	23 (33.3)	37 (40.2)	23 (52.3)
Cardiovascular Risk Factors				
Hypertension	**42 (49.4)**[b,c]	12 (17.4)	17 (18.5)	13 (29.5)
Diabetes	4 (4.7)	3 (4.3)	5 (5.4)	2 (4.5)
Hyperlipidemia	**29 (34.1)**[b,c]	6 (8.7)	13 (14.1)	6 (13.6)
Obesity	21 (24.7)	10 (14.5)	21 (22.8)	**25 (56.8)**[a,b,c]
Smoking	14 (16.5)[b]	2 (2.9)	**16 (17.4)**[b]	5 (11.4)
Laboratory Parameters				
Antiphospholipid Antibodies				
Lupus Anticoagulant	75 (88.2)[c]	55 (79.7)[c]	53 (57.6)	**39 (88.6)**[c]
Anticardiolipin Antibodies	63 (74.1)[d]	47 (68.1)[d]	**78 (84.8)**[d]	7 (15.9)
Anti-β_2-GPI Antibodies	37 (43.5)[d]	28 (40.6)[d]	**59 (64.1)**[a,b,d]	1 (2.3)
Other Parameters				
Anti-Ro	6 (7.1)	6 (8.7)	11 (12.0)	10 (22.7)
Anti-La	1 (1.2)	2 (2.9)	2 (2.2)	4 (9.1)

[a,b,c,d] Significantly ($p<0.05$) more prevalent than Cluster 1, 2, 3 and 4, respectively.
The variable with the highest percentage, which is significantly more common compared to one other cluster only is defined as "**Predominant Variable (bold)**", and to three other clusters as "**Discriminant Variable (bold & underlined)**".

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Abstract Number: 2201

Triple Positivity of Antiphospholipid Antibody As the Main Thrombotic Factor

in a Long-Term Follow-up Study of 98 Asymptomatic Apl-Positive Carriers

Cécile Yelnik[1,2], Elodie Drumez[3], Sylvain Dubucquoi[2,4,5], Vincent Sobanski[1,2,4], Hélène Maillard[1,6], Alain Duhamel[3], David Launay[1,2,4], Eric Hachulla[1,2,4], Pierre-Yves Hatron[1,2] and **Marc Lambert**[1,2,4], [1]Service de Médecine Interne, Centre National de Référence des Maladies Systémiques Rares, Hôpital Claude Huriez, CHRU Lille, Lille, France, [2]Faculté de Médecine Henri Warembourg, Université Lille Nord de France, Lille, France, [3]CERIM, Université Lille Nord de France, Lille, France, [4]LIRIC, INSERM UMR 995, Lille, France, [5]Institut d'Immunologie, Centre de Biologie-Pathologie-Génétique, CHRU Lille, Lille, France, [6]Faculté de Médecine Henri Warembourg, Université Lille Nord de France, lille, France

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SESSION INFORMATION

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Background/Purpose:

There is limited data regarding the long-term risk of developing a first-time thrombotic event and prophylactic benefits of aspirin use in asymptomatic aPL-positive carriers. This study was designed to evaluate the long-term risk of thrombosis and the risk factors associated with the development of a first thrombotic event in asymptomatic aPL-positive carriers. We also aimed to assess the preventive effect of aspirin use.

Methods:

One hundred three of 575 patients, who consecutively tested positive in a core laboratory for aCL and/or LA in 2 determinations between 1995 and 2000, were included in a first analysis published in 2008. Patients have been evaluated for thrombosis occurrence and prophylactic benefits of aspirin use during the first study period that ended in 2005. Exclusion criteria included history of previous thrombosis and long-term anticoagulation treatment. In this study, we added data on patient's follow-up during the ten-year period following the first analysis, except for 5 patients who were lost to follow-up. Clinical and biological data were retrospectively collected until time of first thrombotic event or through July 2014 for patients who remained asymptomatic. Survival analyses were performed using Kaplan-Meier method. Cox proportional hazards analysis examined factors associated with thrombosis-free survival.

Results:

Ninety-eight patients were followed during a median follow-up period of 156 months (72-204). Population was composed of 13 men and 85 women. Median age was 40.5 years (28-55). Forty-two had SLE. Sixty-six were treated prophylactically with aspirin. Median treatment duration was 130 months (60-192). At onset, 59 patients had LA, 72 aCL and 39 anti-β2 Glycoprotein 1 antibodies (aβ2GP1) IgG or IgM, 20 were triple positive. At the end of follow-up, 22 were triple positive. A first thrombotic event occurred in 28 patients. The 15-year risk of a first thrombosis was 30%.

The univariate analysis showed that neither gender, SLE status nor biological aPL profile at onset were associated with risk of thrombosis. aCL, LA and aβ2GP1 persistence through follow-up, alone or triple positivity of aPL, were significantly associated with a higher risk of thrombosis. Conversely, aPL disappearance was associated with a lower risk of thrombosis. Despite insignificant association between aspirin prescription at diagnosis and thrombotic risk, a longer period of prescribed aspirin was associated with a lower risk of thrombosis.

In the multivariate analysis, aPL triple positivity persistence through follow-up remained the only predictive factor significantly and independently associated with the risk of thrombosis (HR 2.81; 95% CI: 1.30-6.08, *p=0.009*).

Conclusion:

The risk of developing a first-time thrombosis in asymptomatic aPL-positive carriers is significant and persistent over time. Triple positive-carriers appear to be exposed to a considerable risk of thrombosis and may justify a close follow-up. Prophylactic effects of aspirin against first thrombotic event seem to be attractive but more data are needed.

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View Abstract and Citation Information Online - http://acrabstracts.org/abstract/triple-positivity-of-antiphospholipid-antibody-as-the-main-thrombotic-factor-in-a-long-term-follow-up-study-of-98-asymptomatic-apl-positive-carriers

Abstract Number: 2202

Different Patterns of Positivity for IgG Anti-Cardiolipin, Anti-Beta-2-Glycoprotein I and Anti-Domain I Antibodies within the First Year of Disease in 501 Patients with SLE – Associations with Different Clinical Outcomes

Amrita D'Souza[1], Charis Pericleous[2], Oliver Leach[1], Karim Fouad Alber[1], Thomas McDonnell[2], Yiannis Ioannou[2], Ian Giles[3], David A. Isenberg[4] and **Anisur Rahman**[5], [1]Centre for Rheumatology Research, University College London, London, United Kingdom, [2]Rayne Institute, Centre for Rheumatology Research, UCL Division of Medicine, London, United Kingdom, [3]Rayne Intitiute, Centre for Rheumatology Research, UCL Division of Medicine, London, United Kingdom, [4]Centre for Rheumatology Research, Rayne Building, 4th Floor, Centre for Rheumatology, Department of Medicine, University College London, London, United Kingdom, [5]Centre for Rheumatology Research,Rayne Institute, 4th Floor, University College London, London, United Kingdom

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Background/Purpose:

Antiphospholipid Syndrome (APS) is an autoimmune rheumatic disorder in which antiphospholipid antibodies (aPL) cause clinical sequelae including vascular events (VE) and pregnancy morbidity (PM). The key antigen in APS is beta-2-glycoprotein I (beta2GPI), which consists of five domains. The N-terminal domain (DI) carries the main immunodominant epitope. Current clinical ELISAs used in APS test for anti-cardiolipin (CL) and anti- beta2GPI antibodies but increasing evidence suggests that anti-DI levels may be more strongly associated with VE and PM. Patients with SLE are often screened using current tests for aPL and up to 40% are positive but the implications of a positive test for future health of the patient are not clear. In this study we retrospectively explored the prevalence of IgG anti-CL, anti-beta2GPI and anti-DI antibodies in stored serum samples that had been collected prospectively within one year of diagnosis in 501 patients with SLE and analysed associations between these serological profiles and clinical outcomes.

Methods:

Samples from 501 patients with SLE, fulfilling revised ACR criteria, had been taken and stored at -20 degrees C within one year of diagnosis. All samples were tested for levels of IgG anti-CL, anti-beta2GPI and anti-DI by ELISA. **Results** were expressed in absorbance units (AU) by comparison with standard positive controls loaded on every plate. A positive test was defined as an AU level > 99th percentile of 100 healthy controls and high positive was defined as double that level. Data on VE (venous or arterial thrombosis or coronary disease) and pregnancy were obtained from medical records and patient interviews. Fisher's exact test was used to analyse statistical associations between particular serological profiles and VE or PM.

Results:

The mean (SD) age of the 501 patients was 30 (12.2) years, 91% were female and 61% white. In the early disease samples, 68 were positive for anti-CL, 24 for anti- beta2GPI and 146 for anti-DI. 30 patients were double-positive for two of these aPL and 9 were triple-positive. Using higher cut-off levels, 31, 6 and 36 were high-positive for anti-CL, anti- beta2GPI and anti-DI respectively. Mean follow-up time post-sample was 12.1 years (max 36 years). Full data on VE and PM were available for 338 and 275 patients respectively. Table 1 shows associations between particular serological profiles and occurrence of VE or PM.

Conclusion:

38% of patients were positive for one or more aPL in early disease but only 15% showed high positivity. Being double or triple-positive was most strongly associated with VE (but not PM) – 40% of the double/triple positive patients suffered VE in the follow-up period. Positivity for anti-beta2GPI was also associated with VE. High positivity for anti-DI showed the strongest association with PM.

Table 1 – Association of different serological profiles in early disease with VE or PM (* signifies statistically significant association<0.05)

aPL profile	P value for association with VE	P value for association with PM
aPL Negative vs. aPL Positive	0.25	0.41
aPL Negative/Single Positive vs. Double/Triple Positive	0.02*	1.00
aPL Negative vs. Single Positive	0.68	0.30
aPL Negative vs. Double Positive	0.09	0.33
aPL Negative vs. Triple Positive	0.04*	0.17
Anti-beta2GPI Negative vs. Anti-beta2GPI Positive	0.02*	0.33
aCL Negative vs. aCL Positive	0.07	0.84
Anti-DI Negative vs. Anti-DI Positive	0.52	0.87
Low aCL Positive vs. High aCL Positive	0.37	0.08
Low Anti-DI Positive vs. High Anti-DI Positive	0.39	0.04*

Disclosure: A. D'Souza, None; **C. Pericleous**, None; **O. Leach**, None; **K. Fouad Alber**, None; **T. McDonnell**, None; **Y. Ioannou**, None; **I. Giles**, None; **D. A. Isenberg**, Bristol-Myers Squibb, 2; **A. Rahman**, None.

Abstract Number: 2203

Loss of Wdfy3 Leads to Enhanced Osteoclastogenesis Via NF-κB Activation

Dennis J. Wu[1,2], Ran Gu[2], Ritu Sarin[2], Regina Zavodovskaya[3], Chia-Pei Chen[4], Konstantinos Zarbalis[5,6] and Iannis E. Adamopoulos[1,2,6], [1]Graduate Group in Immunology, University of California, Davis, Davis, CA, [2]Division of Rheumatology, Allergy and Clinical Immunology, University of California, Davis, Davis, CA, [3]Department of Anatomy, Physiology and Cell Biology, University of California, Davis, Davis, CA, [4]Department of Statistics, University of California, Davis, Davis, CA, [5]Department of Pathology and Laboratory Medicine, University of California, Davis, Sacramento, CA, [6]Institute for Pediatric Regenerative Medicine, Shriners Hospitals for Children, Northern California, Sacramento, CA

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Background/Purpose: Autophagy and phagocytosis are conserved cellular functions involved in the protein degradation process in immunity. Recently, autophagy-related proteins were shown to regulate osteoclast mediated bone resorption, a critical process in autoimmune diseases such as rheumatoid arthritis. Wdfy3 is a master regulator in selective autophagy for clearing ubiquitinated protein aggregates. In this study, we generated a series Wdfy3 transgenic mice (*Wdfy3*^{lacZ}, and *Wdfy3*^{loxP}) to investigate the function of Wdfy3 in osteoclast development and function.

Methods: Wdfy3 expression in *Wdfy3*^{lacZ} neonatal mice was analyzed by histology and X-gal staining. Bone marrow-derived macrophages from wild type, *Wdfy3*^{lacZ}, and Wdfy3 conditional knockout (*Wdfy3-cKO*) mice (*Wdfy3* $^{loxP/loxP}$*-LysM-Cre*$^{+}$) were differentiated into osteoclasts with macrophage colony-stimulating factor (M-CSF), and receptor activator of NF-κB ligand (RANKL). Wdfy3 expression on osteoclast-like cells was analyzed by X-gal staining and immunohistochemistry. RANKL-induced NF-κB signaling was analyzed by Western blot. Osteoclast-related genes *Ctsk*, *Acp5*, *Mmp9* were measured by qPCR. Osteoclasts were characterized by tartrate-resistant acid phosphatase staining and filamentous actin ring formation assay. Osteoclast function was evaluated by dentin resorption assay.

Results: Our data showed that Wdfy3 is up regulated in osteoclasts in *in vitro* cultures and highly expressed at the growth plate of neonatal mice. Osteoclasts derived from *Wdfy3-cKO*, showed increased osteoclast differentiation and function as evidenced by higher number and enlarged size of TRAP^{+} multinucleated cells. Western blot analysis also revealed up-regulation of TRAF6, enhanced degradation of p-IκBα and increased p-NF-κB p65 in Wdfy3-deficient osteoclasts stimulated with RANKL compared to the control cells. Consistent with these observations Wdfy3 conditional knockout mice also showed an increase in osteoclast-related genes *Ctsk*, *Acp5*, *Mmp9* and an increase of dentine resorption in *in vitro* assays. Importantly, no difference was observed in autophagic flux in Wdfy3 deficient bone marrow-derived macrophages and control cells at basal level or under starvation.

Conclusion: Taken together, our data highlight a novel role for Wdfy3 osteoclast development and function, which can be exploited for the treatment of musculoskeletal diseases.

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Abstract Number: 2204

Tankyrase Regulates Osteoclastogenesis Via SH3BP2 Expression

Tomoyuki Mukai, Shunichi Fujita, Takafumi Mito, Akiko Nagasu, Yumi Sasae, Hiroyasu Hirano and Yoshitaka Morita, Department of Rheumatology, Kawasaki Medical School, Kurashiki, Okayama, Japan
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Background/Purpose: SH3BP2, an adaptor protein, is dominantly expressed in immune cells including macrophages and regulates intracellular signaling pathways. Gain-of-function mutations in SH3BP2 cause human genetic disorder cherubism, which is characterized by jaw bone destruction. We have previously reported that SH3BP2 plays an essential role in osteoclastogenesis and controls inflammatory bone destruction in murine arthritis models (Arthritis Rheumatol. 2015, 67(3):656-67; J Bone Miner Res. 2014, 29(12):2618-35). SH3BP2 protein levels are regulated by the degradation process mediated by Tankyrase 1/2. Tankyrase 1/2, poly (ADP ribose)polymerases, has recently been reported to degrade several proteins such as SH3BP2 and beta-

catenin, however the involvement of Tankyrase in osteoclastogenesis is not well clarified. In this study, we investigated the role of Tankyrase in osteoclast differentiation and function.

Methods: Primary murine bone marrow-derived macrophages and murine pre-osteoclastic RAW264.7 cells were treated with either RANKL or TNF in the presence of Tankyrase inhibitors (IWR-1 and XAV-939) and Wnt inhibitors (IWP-2 and C59). SH3BP2 expression levels in the cells were determined by western blotting. Osteoclast differentiation was evaluated by TRAP-positive multinucleated cells (TRAP+ MNCs) formation and osteoclast-associated gene expression. Osteoclastic function was determined by resorption assay. Nuclear localization of NFATc1, a master regulator for osteoclastogenesis, was evaluated by immunofluorescence staining.

Results: SH3BP2 protein levels were elevated in Tankyrase inhibitors-treated cells but not in Wnt inhibitors-treated cells. Tankyrase inhibitors enhanced both RANKL- and TNF-induced TRAP+ MNCs formation and osteoclast-associated genes (Oscar, Acp5, and Ctsk) expression in a concentration-dependent manner. Mineral resorbing activity in response to RANKL was significantly enhanced in Tankyrase inhibitors-treated cells. NFATc1 nuclear localization was significantly induced in the Tankyrase inhibitors-treated cells. The effects of the Tankyase inhibitors on osteoclastogenesis were comparable with the culture of primary bone marrow-derived macrophages from SH3BP2 gain-of-function mouse model (P416R SH3BP2 cherubism mutation knock-in mouse).

Conclusion: These data suggest that inhibition of Tankyrase activity enhances osteoclast differentiation via elevated SH3BP2 expression but not through Wnt pathway. Tankyrase is a novel regulator of osteoclastogenesis, therefore controlling Tankyrase activity could be a therapeutic option for bone destructive disorders including rheumatoid arthritis and osteoporosis.

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Abstract Number: 2205

Inhibition of Dickkopf1 Dampens Anti Osteogenic Effect of Fibroblast-like Synoviocytes

Eiji Sugiyama, Yusuke Yoshida and Satoshi Yamasaki, Department of Clinical Immunology and Rheumatology, Hiroshima University Hospital, Hiroshima, Japan

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Background/Purpose: Fibroblast-Like Synoviocytes (FLS) play important roles in RA progression. Previous studies have revealed importance of FLS in osteoclast activation, however, the roles of FLS in osteoblast differentiation are not clear. In osteoblast differentiation, Wnt family proteins regulate transcriptions for osteoblast differentiation via stabilization of ß-catenin and TCF activation. It is now known that the Wnt pathway is blocked by several soluble proteins such as Dickkopf1 (DKK1) or Sclerostin (SOST). In this study, we aimed to determine if FLS secrete DKK1 to inhibit Wnt pathway.

Methods: The expressions of DKK1 in synovial tissue were examined by immunohistochemistry. The mRNA and protein expression in cultured FLS were detected by PCR and immuno-precipitation assay, respectively. The concentrations of DKK1 in culture media were measured by ELISA. mRNA expression was quantified by SYBR Green real-time PCR. Activity of Wnt pathway was analyzed by luciferase assay using TCF reporter plasmid that was transfected to U2OS, an osteosarcoma cell line. Anti DKK1 antibodies were used to neutralize DKK1 in FLS culture medium. siRNA was used to knock down the expressions of DKK1 in FLS.

Results: DKK1 is observed in RA synovial tissue. The mRNA and protein expressions of DKK1 in cultured FLS are comparable

to mesenchymal stem cell (MSC), which is a major source of DKK1 in human. TNF clearly induced the DKK1 secretion form FLS, however, IL-1 and IL-6 did not. FLS supernatant inhibited luciferase activities of TCF reporter induced by addition of recombinant human Wnt3a (200ng/mL). The luciferase activities were blocked by addition of anti DKK1 neutralizing antibodies. By using siRNA, we achieved 90% reduction of DKK1 secretion from FLS. As we expected, the supernatant from these siRNA treated FLS exhibited less inhibitory effect on luciferase activities of TCF reporter. Consistent with these data, FLS supernatant inhibited the RUNX2, COL1A1 mRNA expression in MSC.

Conclusion: FLS produce considerable amount of DKK1. Importantly, DKK1 secreted form FLS effectively blocks TCF activity induced by recombinant Wnt3a. Therefore, FLS may inhibit osteoblast differentiation by secreting DKK1, especially in the inflamed joint of RA, because TNF promote DKK1 production. Thus, it is possible that DKK1 inhibition allows Wnt to bind to its receptor for activation of osteoblast to repair bone erosion in RA.

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Abstract Number: 2206

Dopamine Pathway and Bone Metabolism in Arthritis

Silvia Capellino[1], Klaus W. Frommer[1], Markus Rickert[2], Jürgen Steinmeyer[3], Stefan Rehart[4], Ulf Müller-Ladner[1] and Elena Neumann[1], [1]Internal Medicine and Rheumatology, Justus-Liebig-University of Giessen, Kerckhoff-Klinik, Bad Nauheim, Germany, [2]Dept of Orthopedics and Orthopedic Surgery, University Hospital of Giessen and Marburg, Gießen, Germany, [3]Dept Orthopedics and Experimental Orthopedics, University Hospital of Giessen and Marburg, Giessen, Germany, [4]Orthopedics and Trauma Surgery, Markus-Hospital, Frankfurt, Germany

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Background/Purpose: A body of studies demonstrates the influence of the nervous system on the immune response. We recently described that dopamine, a neurotransmitter of the sympathetic nervous system, is locally produced by synovial fibroblasts of rheumatoid arthritis (RA) patients and influences *in vitro* cytokine release and inflammation. In addition, *in vivo* evidence confirmed the involvement of dopamine receptors (DR) in arthritis, and a subtype of DR was described to be expressed by *in vitro* differentiated human osteoclasts. These studies, together with the clinical evidence of an increased risk of osteoporosis in patients affected by Parkinson's disease, suggest an involvement of dopamine in joint destruction during RA. The aim of this study was therefore not only to investigate the role of the dopamine pathway on bone remodeling in RA patients, but also to unravel new pathways involved in joint destruction.

Methods: Bone tissue was obtained from osteoarthritis (OA, n=5) and RA (n=4) patients during knee joint replacement surgery. Osteoblasts were isolated from the bone spongiosa. Immunohistochemistry of paraffin-embedded bone samples and immunocytochemistry of isolated osteoblasts were performed using antibodies against the five subtypes of DR (D1 to D5). Isolated osteoblasts were treated with specific DR agonists for 24 h or 7 d. IL-6 and IL-8 were quantified after 24 h stimulation by ELISA, and expression of osteoblast activation markers was quantified after 7 d stimulation by real-time PCR. Mann Whitney test was used for statistical data analysis.

Results: Dopamine receptors D1, D3 and D4 could be detected by immunohistochemistry in the bone remodeling zone of RA patients while OA samples did not express these receptors in the bone remodeling zone. Dopamine receptor subtypes D1, D2, D3 and D5 were present on isolated osteoblasts, with stronger expression in RA compared to OA. Stimulation of DR with specific agonists induced a significant dose-dependent increase of IL-6 release in RA compared to the untreated control (D1-like agonist:

+79 ±43%, P<0.005. D2-like agonist: +70 ±49%. n=4), but no significant effects were detectable for OA osteoblasts. IL-8 release was not significantly altered in both, RA and OA osteoblasts. DR activation inhibited mRNA expression of osteocalcin, collagen type I, alkaline phosphatase and osteoprotegerin in RA osteoblasts (up to -10% compared to untreated control, n=2).

Conclusion: Dopamine receptors are upregulated in the bone remodeling zone of RA patients and their activation seems to have proinflammatory effects and to inhibit osteoblast activation. These data suggest an involvement of the dopamine pathway in bone remodeling and joint erosion in RA, and could open future perspectives to target joint destruction.

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Abstract Number: 2207

Interleukin-32Î³ Exhibited Protective Effects on Osteoporosis

Seokchan Hong[1], Eun-Jin Lee[2], Sang-Min Kim[3], Eun-Ju Chang[2], Doo-Ho Lim[4], Byeongzu Ghang[5], Wookjang Seo[6], Yong-Gil Kim[4], Chang-Keun Lee[1] and Bin Yoo[4], [1]Division of Rheumatology, Department of Internal Medicine, University of Ulsan College of Medicine, Asan Medical Center, Seoul, South Korea, [2]Department of Biomedical Sciences, University of Ulsan College of Medicine, Asan Medical Center, Seoul, South Korea, [3]Department of Biomedical Sciences, University of Ulsan College of Medicine, Seoul, South Korea, [4]Division of Rheumatology, Department of Internal Medicine, Department of Rheumatology, University of Ulsan College of Medicine, Asan Medical Center, Seoul, South Korea, [5]Division of Rheumatology, Department of Internal Medicine, Univerisy of Ulsan College of Medicine, Asan Medical Center, Seoul, South Korea, [6]Internal Medicine, Seoul Veterans Hospital, Seoul, South Korea

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Background/Purpose:

Interleukin-32 (IL-32) has been known to be implicated in the pathogenesis of various inflammatory diseases. Osteoporosis, characterized by low bone density and increases the risk of fracture, was prevalent in systemic inflammatory diseases mediated through the link between chronic inflammation and bone loss. In this study, we try to investigate the effects of IL-32γ in osteoporosis since the role of IL-32 in bone formation as well as bone resorption remains largely unknown.

Methods:

To determine whether IL-32γ affects bone formation, we examined bone volume of transgenic (TG) mice overexpressing IL-32γ by using micro-CT. Ovariectomized mice were used to know the effects of IL-32γ on osteoporosis *in vivo*. In addition, bone formation rate was evaluated by labeling with calcein, a marker of newly formed bone. To elucidate the mechanism of IL-32γ effect on bone metabolism, we measured the levels of Dickkopf-1 (DKK-1), is well-known as having an inhibitory effects on osteoblastogenesis. Further, the concentration of IL-32γ was measured in the peripheral blood from patients with osteoporosis.

Results:

Micro-CT analysis revealed that IL-32γ TG mice had an increased bone volume compared with wild-type (WT) mice. Furthermore, bone loss induced by ovariectomy was substantially attenuated in IL-32γ TG mice compared with that in WT mice. Importantly, IL-32γ TG mice had higher bone formation rate as assessed by the mineral apposition rate compared with WT mice. In addition, the level of DKK-1 was significantly lower in the IL-32γ TG mice than WT mice. Finally, we found that the concentration of IL-32γ was significantly lower in the blood of patients with osteoporosis than in those of healthy individuals.

Conclusion:

Our present study suggested that IL-32γ enhances bone formation through association with the decrease of DKK-1, which contributes to the protective effects on osteoporosis.

Disclosure: S. Hong, None; **E. J. Lee**, None; **S. M. Kim**, None; **E. J. Chang**, None; **D. H. Lim**, None; **B. Ghang**, None; **W. Seo**, None; **Y. G. Kim**, None; **C. K. Lee**, None; **B. Yoo**, None.

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Abstract Number: 2208

Macrophage Migration Inhibitory Factor: A Novel Biomarker in Ankylosing Spondylitis That Can Drive Spinal Fusion

Vidya Ranganathan[1], Ismail Sari[2], Janogini Muralitharan[3], Ammepa Anton[4] and Nigil Haroon[2], [1]University Health Network, Toronto, ON, Canada, [2]Rheumatology, Toronto Western Hospital, University of Toronto, Toronto, ON, Canada, [3]McMaster University, Hamilton, ON, Canada, [4]Rheumatology, University Health Network, Toronto, ON, Canada

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Background/Purpose: Ankylosing spondylitis (AS) is a chronic inflammatory arthritis that predominantly affects the axial skeleton. Disease progression in AS is marked by new bone formation in the spine resulting in progressive vertebral fusion. The presence of various immune cell subsets and cytokines at sites of inflammation has been reported. However their specific role in mediating bone fusion is not understood. Macrophage migration inhibitory factor (MIF) is a pro-inflammatory cytokine with pleiotropic functions and has been implicated in a variety of inflammatory diseases. Herein, we intend to identify a role for MIF in triggering bone formation in AS.

Methods: For the initial analysis, AS patients who satisfied the Modified New York Criteria and healthy controls were included. Among AS patients, non-progressors had no increase in the modified Stoke's AS Spinal Score (mSASSS) despite a minimum 4 years of follow up and progressors had ≥2 mSASSS units/year of progression and syndesmophyte formation based on sequential X-rays. MIF levels were estimated by ELISA in stored serum of AS patients and healthy controls and synovial fluid samples from AS, rheumatoid arthritis (RA) and osteoarthritis (OA) patients. The human osteosarcoma cell line Saos-2 was treated with recombinant human MIF in the presence of osteogenic conditions and the extent of mineralization was visualized by Alizarin Red S staining and quantified using Image J analysis. Active β-catenin was detected by western blotting and normalized using Glyceradehyde 3-phosphate dehydrogenase (GAPDH) as control.

Results: AS patients had significantly higher serum MIF levels as compared to healthy controls ($p<0.0001$). Baseline MIF levels were significantly higher in progressors compared to non-progressors ($p<0.04$). Saos-2 cells cultured *in-vitro* in an inflammatory milieu in the presence of recombinant human MIF showed enhanced mineralization in a dose dependent manner ($p<0.03$). Also, we found that MIF levels were markedly elevated in the synovial fluid of AS patients as compared to those suffering from RA or OA ($p<0.04$). Western blot analysis showed an induction of active β-catenin in MIF treated osteoblasts.

Conclusion: Serum MIF levels are significantly higher in AS patients compared to healthy controls. MIF levels in AS synovial fluid is higher than RA and OA. The study identifies a previously unknown role for MIF in bone formation in AS by having a direct stimulatory effect on osteoblastogenesis possibly by triggering the Wnt/β-catenin pathway.

Disclosure: V. Ranganathan, None; **I. Sari**, None; **J. Muralitharan**, None; **A. Anton**, None; **N. Haroon**, None.

Abstract Number: 2209

Stimulation of the Adenosine A2A Receptor (A2AR) Regulates the Expression of Netrin-1 (Ntn1) and Its Receptors (Unc5b, DCC) and Inhibits Wear Particle-Induced Inflammatory Osteolysis in a Model of Joint Prosthesis Loosening

Aranzazu Mediero[1], Bhama Ramkhelawon[2], Miguel Perez-Aso[3], Kathryn Moore[2] and Bruce Cronstein[4], [1]Medicine, Divison of Translational Medicine, NYU School of Medicine, New York City, NY, [2]Leon H. Charney Division of Cardiology, Department of Medicine,, NYU School of Medicine, New York, NY, [3]Provital S.A., Barberà del Vallès, Spain, [4]Medicine, Division of Rheumatology, NYU School of Medicine, NEW YORK, NY

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Background/Purpose: Ntn1 is a member of the family of axonal guidance proteins that plays a role in leukocyte function and inflammation and is critical for OC differentiation. Because A2AR ligation, either directly or indirectly following methotrexate treatment, diminishes wear particle-induced inflammatory osteolysis we asked whether A2AR activation might regulate expression of Ntn1 at sites of inflammatory osteolysis.

Methods: 1cm midline sagittal incision was made over the calvaria in C57Bl/6 mice age 6-8 weeks. Mice received no particles (Control) or 3mg of UHMWPE wear particles with 20µl of saline 0.9% or CGS21680 (A2AR agonist, 1µM, n=4 each) at the surgical site every day for 14 days. After sacrifice, calvaria were prepared for immunostaining for Ntn1/Unc5b/DCC. Protein and mRNA expression were studied by RT-PCR and western blot in mouse primary bone marrow-derived OC and OB and in RAW264.7 cells (murine cell line) in the presence/absence of CGS21680 and ZM241385 ($A_{2A}R$ antagonist) 1µM each.

Results: Wear particles stimulated increased expression of Ntn1 and Unc5b, but not DCC, in periosteal inflammatory infiltrates, an effect which was blocked by the A2AR agonist CGS21680. In *in vitro* studies RANKL induced a 25±4 and 3±0.5 fold change, respectively, in Ntn1 and Unc5b mRNA during OC differentiation, changes that were completely blocked by CGS21680 (1.17±0.1, $p<0.001$, n=4). In contrast, DCC mRNA expression did not significantly change during OC differentiation and DCC expression was unaffected by CGS21680 (1.16±0.2 fold increase vs 1.9±0.2 for RANKL, p=ns, n=4). Similar changes were observed in protein expression and secretion. When Ntn1 or Unc5b were knocked-down in RAW264.7 cells using selective shRNA, basal mRNA expression for PKA, EPAC1 and EPAC2 (cAMP signaling molecules activated by A2AR) were increased and vice versa, when PKA, EPAC1 or EPAC2 were knocked down with selective shRNA, Ntn1 and Unc5b basal mRNA levels were increased. NFkB nuclear translocation was decreased in the presence of CGS21680 or in the absence of Ntn1. There was no change in Ntn1 or Unc5b expression during OB differentiation.

Conclusion: Ntn1 expression on macrophages and OC plays a central role in wear particle-induced osteolysis and adenosine $A_{2A}R$ stimulation downregulates Ntn1expression and inhibits bony destruction at sites of wear particle-induced osteolysis. Moreover, Ntn1-unc5b and A2AR stimulation reciprocally diminish signaling by each other. These results suggest that targeting Ntn1 directly or via stimulation of adenosine $A_{2A}R$ may be a novel approach to prevent osteolysis and joint prosthesis loosening.

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Abstract Number: 2210

Immunological Dysregulation and Inadequate Hypoxia Adaptation – HIF-Stabilization As Possible Prevention of Fracture Healing Disorders in RA or Immune-Suppressed Patients

Annemarie Lang[1,2,3], Sarah Fuegener[2], Paula Hoff[1,2], Katharina Schmidt-Bleek[4], Timo Gaber[1,2] and Frank Buttgereit[2], [1]German Rheumatism Research Center (DRFZ), Berlin, Germany, [2]Department of Rheumatology and Clinical Immunology, Charité University Medicine, Berlin, Germany, [3]Berlin-Brandenburg School of Regenerative Therapies (BSRT), Berlin, Germany, [4]Julius Wolff Institut, Charité University Medicine, Berlin, Germany

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Background/Purpose: Patients suffering from rheumatoid arthritis (RA) are often affected by fracture-healing complications such as increased fracture healing time or non-unions. There is not much information whether this is a result of the disease itself and/or its treatment with glucocorticoids (GC) and other immunomodulatory drugs. Previously, we have shown that immunologically restricted patients lack an adequate adaptation to hypoxia in the fracture hematoma facilitating healing disorders (Hoff et al. 2011 Immunol Res 51(1)). The hypoxic microenvironment during the initial fracture-healing phase is known to be essential for activating the immunological reactions which induce regeneration. The hypoxia-inducible factor (HIF) is one key regulator of cellular adaption to hypoxia that can be stabilized via different factors called in the following HIF-stabilizers. Therefore, we aimed at stabilizing the hypoxic phase by application of HIF-stabilizers to facilitate bone healing.

Methods: A single-center retrospective study was conducted at the Charité University Hospital Berlin focusing on patients with long-bone fractures in order to identify factors which may affect the healing process. Obtained data were analyzed descriptively and statistically. In addition, we established an *in vitro* model simulating the inhibition of osteogenic mesenchymal stem cell (MSC) differentiation via high concentration GC treatment to test the counteracting potential of HIF-stabilizers. Furthermore, we performed an *in vivo*proof of concept study in a mouse osteotomy model (3 weeks, n=8 per group) evaluating the ratio of bone volume (BV) per total volume (TV) in the fracture gap using µCT.

Results: 266 patients were included in the retrospective study, 79 cases (fracture healing disorders) and 178 controls. The descriptive analysis showed higher frequencies of GC (6.3% vs. 1.6%) and NSAID (7.6% vs. 2.7%) administration in patients with fracture healing disorders. Statistical analysis using logistic regression showed a high significance for RA (p=0.028) and a trend for smoking (p=0.075) to negatively affect fracture healing. *In vitro*, we observed a concentration-dependent inhibitory effect of dexamethasone on osteogenesis which could be considerably antagonized by HIF-stabilizers. Both optimal combinations and concentrations of HIF-stabilizers were tested in a mouse osteotomy model. As a result, HIF-stabilizers directly administered into the fracture gap at the time of the osteotomy showed a significant positive effect on healing processes as evidenced after 3 weeks by means of increased bony callus volume (BV/TV) compared to the respective vehicle controls.

Conclusion: The results obtained so far support the hypothesis that RA indeed has a negative impact on the outcome of fracture healing. Our *in vitro* data demonstrate that HIF-stabilizers can be used to at least partially counteract the negative impact of high-dose GC on osseous differentiation. Finally, our *in vivo* data show a significant potential of HIF-stabilizers to facilitate bone healing. Therefore, this approach represents a promising strategy to prevent and overcome bone healing complications in RA patients and perhaps other immunologically restricted patients.

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Abstract Number: 2211

Extracellular Vesicles from Cow Milk Accelerate Osteoblast Differentiation into Osteocytes, However, Type I Collagen Synthesis Is Reduced and Bone Matrix Organization Is Impaired

Marina C. Oliveira[1], Onno J. Arntz[1], Esmeralda Blaney Davidson[1], Wim van den Berg[1], Adaliene V.M. Ferreira[2] and **Fons A.J. van de Loo**[1], [1]Experimental Rheumatology, Radboud university medical center, Nijmegen, Netherlands, [2]Department of Nutrition, Universidade Federal de Minas Gerais, Belo Horizonte, Brazil

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Background/Purpose: Milk consumption during childhood stimulates bone growth but the claimed beneficial effect of milk on bone at adulthood is a matter of debate. Recently extracellular vesicles (EVs) that contain proteins and RNA were discovered in milk but their effect on bone formation has not yet been determined. Our aim was to evaluate the effect of bovine milk-derived EVs (BMEVs) on the differentiation of human mesenchymal stem cells (hMSCs) into osteoblasts, and on bone formation in mice.

Methods: hMSCs in osteogenic medium were treated with BMEVs (200µg/ml protein) and healthy female DBA1/J mice received orally two different particle concentrations of BMEVs $4.7x10^6$/ml (low) or $14.3x10^6$/ml (high) in their drink water during 7 weeks.

Results: Proteomic analysis in BMEVs showed the presence of proteins with a known effect on bone formation. The exposure of hMSCs to BMEVs during 21 days resulted in less mineralization but higher cell proliferation. Interestingly, BMEVs reduced the collagen production per cell, but enhanced the expression of osteoblast genes (Runx2, ALP, osteopontin, RANKL, FGF-2) that are characteristic of immature osteoblasts. A kinetic study up to day 28 showed that BMEVs upregulated many osteogenic genes within the first 4 days of culture. However, the production of type I collagen and its genes (*COL1A1* and *COL1A2)* were markedly reduced at days 21 and 28. At day 28, BMEVs again lead to higher proliferation, but mineralization that was lower at day 21 was significantly increased at day 28. Nonetheless the formation of bone nodules was impaired at day 28 and this was corroborated by a reduction in osteonectin expression. Moreover, BMEVs increased the expression of sclerostin, a marker gene of osteocytes at the same time point. Oral delivery of BMEVs to mice did not alter the tibia trabecular bone area, however the osteocytes numbers increased independent of the dose. In addition, the highest dose of BMEVs reduced the adipose area in bone marrow of the femoral tibia bone and markedly increased the woven bone tissue and the number of osteoclasts by TRAP staining.

Conclusion: Our study showed that BMEVs on hMSCs increased osteoblast differentiation, proliferation and mineralization, probably by the induction of FGF-2 and WISP1. However, the lower type I collagen synthesis, and osteonectin expression could be explained by the presence of miR-29 in BMEVs. The net result of BMEVs exposure is impaired bone nodule formation in vitro and more woven bone formation in mice and this suggest that BMEVs could lead to more brittle bones. Our study add BMEVs to the list of milk components that can affect bone formation and may shed new light on the contradictory claims of milk on bone formation.

Disclosure: M. C. Oliveira, None; **O. J. Arntz**, None; **E. Blaney Davidson**, None; **W. van den Berg**, None; **A. V.M. Ferreira**, None; **F. A. J. van de Loo**, None.

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Abstract Number: 2212

Identification of a Novel Chemokine-Dependent Molecular Mechanism Underlying Rheumatoid Arthritis-Associated Autoantibody-Mediated Bone Destruction

Akilan Krishnamurthy[1], Vijay Joshua[2], Aase Haj Hensvold[3], Tao Jin[4], Meng Sun[3], Marianne Engström[3], Khaled Amara[1], Malin MAgnusson[4], Camilla Svensson[5], Vivianne Malmström[3], L. Klareskog[1], Heidi Wähämaa[3] and **Anca I Catrina**[3], [1]Rheumatology Unit, Department of Medicine, Karolinska Institutet, Stockholm, Sweden, [2]Unit of Rheumatology, Department of Medicine Solna, Karolinska University Hospital, Karolinska Institutet, Stockholm, Sweden, [3]Rheumatology Unit, Department of Medicine, Karolinska Institute, Karolinska University Hospital, Stockholm, Sweden, [4]Department of Rheumatology and Inflammation Research, University of Gothenburg, Gothenburg, Sweden, Gothenberg, Sweden, [5]Department of Physiology and Pharmacology, Karolinska Institutet, Stockholm, Sweden

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Background/Purpose:

Rheumatoid arthritis (RA)-specific anti-citrullinated protein/peptide antibodies (ACPAs) appear before disease onset and are associated with bone destruction. We aimed to dissect the role of ACPAs in osteoclast (OC) activation, and to identify key cellular mediators in this process.

Methods:

Polyclonal ACPA were isolated from the synovial fluid (SF) and peripheral blood (PB) of RA patients. Monoclonal ACPAs were isolated from single SF B-cells of RA patients. OCs were developed from blood cell precursors with or without ACPAs. We analyzed expression of citrullinated targets and PAD enzymes by immunohistochemistry and cell supernatants by cytometric bead array. Monoclonal ACPAs were injected into mice and bone structure was analyzed by micro-computer tomography. The effect of an anti-IL-8/CXCL8 neutralizing antibody was tested in the OC cultures and in ACPA treated mice.

Results:

Polyclonal ACPAs enhanced osteoclastogenesis from CD14-dervied macrophages of either healthy donors (fold increase of 1.6±0.4 for osteoclasts number and 2.0±0.6 for bone resorption area as compared to control IgGs) or ACPA-positive RA patients (fold increase of 1.8±0.6 for OC number and 2.3±0.7 for bone resorption as compared to control IgGs). PB derived ACPAs were equally effective with SF ACPAs. Two of the tested monoclonal ACPAs (reacting with the immunodominant cit-epitopes of enolase and vimentin, had similar effects), whereas 2 others monoclonal ACPAs (mainly reacting with cit-fibrinogen peptides) failed to induce osteoclastogenesis. Fab fragments of the active monoclonal ACPAs retained similar effects. Increased osteoclastogenesis was associated with significantly higher levels of IL-8 levels in cultures supernatants of ACPA as compared to control IgGs-treated OCs (fold increase of 2.0±0.5) and completely abolished by neutralizing anti IL-8 antibodies. Transfer of the monoclonal ACPAs into mice induced trabecular bone loss that was completely reversed by the IL-8 antagonist reparixin.

Conclusion:

We provide novel insights into the key role of IL-8 during ACPA-induced OC activation. Our results open the way for preclinical studies to test the therapeutic and preventive effect of IL-8 blocking agents in models of RA and eventually also in ACPA-positive individuals at risk of developing RA.

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dependent-molecular-mechanism-underlying-rheumatoid-arthritis-associated-autoantibody-mediated-bone-destruction

Abstract Number: 2213

RA-Associated Autoantibodies Promote Synovial Fibroblasts Migration and Adhesion through a Peptidylarginine Deiminases (PAD) Dependent Pathway

Meng Sun[1], Vijay Joshua[2], Aase Haj Hensvold[1,3], Khaled Amara[4], Vivianne Malmström[1], Heidi Wähämaa[1] and **Anca I Catrina**[1], [1]Rheumatology Unit, Department of Medicine, Karolinska Institute, Karolinska University Hospital, Stockholm, Sweden, [2]Unit of Rheumatology, Department of Medicine Solna, Karolinska University Hospital, Karolinska Institutet, Stockholm, Sweden, [3]Rheumatology Unit, Department of Medicine, Solna, Karolinska Institute, Stockholm, Sweden, Stockholm, Sweden, [4]Rheumatology Unit, Department of Medicine, Karolinska Institutet, Stockholm, Sweden

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Background/Purpose:

The presence of anti-citrullinated proteins antibodies (ACPAs) in RA is associated with a more aggressive disease phenotype and bone destruction. Synovial fibroblasts (SFs) are key players of both synovial inflammation and bone destruction in rheumatoid arthritis (RA). We aimed to invesigate the effect of ACPAs on synovial fibroblasts.

Methods:

SFs were isolated from synovial tissue of RA patients (RA SFs) by enzymatic digestion. ACPA positive and negative IgGs were separated from plasma of RA patients and monoclonal ACPAs were generated from synovial fluid single B-cells. The effect of polyclonal and monoclonal ACPAs and appropriate negative controls was tested in migration scratch assays and adhesion assays by xCELLigence System Real-Time Cell Analyzer (ACEA bioscience). Light microscopy images were analyzed using NIH ImageJ to calculate migration index. Impedance-based signals were monitored every minute for1 hour, every 5 minutes up to 13 hours and every 15 minutes up to 36 hours. Inhibition of phosphoinositide 3-kinase (PI3K), G-protein coupled receptors, focal adhesion kinase (FAK) and peptidylarginine deiminases (PAD) inhibitor were tested in migration scratch assays in the presence or absence of the antibodies.

Results:

Polyclonal ACPAs but not others IgGs than ACPAs induced a 2.6±0.5 (mean±SD) fold increase in RASFs migration ($p<0.05$). ACPAs also induced a significant fold increase in RASFs adhesion of 1.3±0.1 ($p<0.05$). Similar effects were observed with one (D10), but not others two monoclonal ACPAs, with a fold increase of 2.4±0.4 ($p<0.05$) in migration index and 1.2±0.1 ($p<0.05$) in adhesion index.

G-protein coupled receptor blockade completely abolished ACPAs effects on RA SFs migration, while PI3K blockade decreased migration to a residual fold increase of 1.4±0.4 (mean±SD) and FAK blockade had no effect. Irreversible PAD blockade and pre-incubation of antibodies with citrulinated fibrinogen abolished ACPAs effects. No difference in either cytotoxicity or proliferation rate were observed between different treatments.

Conclusion:

ACPAs directly mediate fibroblast migration and adhesion through a novel G protein coupled receptor and PAD-dependent mechanism. Our findings provide novel insights into the link between adaptive immunity and synovial fibroblasts.

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Abstract Number: 2214

Activation Feature of RANKL/RANK Signaling Pathway in Ankylosing Spondylitis Patients Compared with Healthy People

Benyong Liu[1], **Hongxiao Liu**[1], Nan Jiang[2], Yingyan Zhou[3], Xinghua Feng[1], Xiaoyan Feng[4], Heqiu Zhang[4], Quan Jiang[1], Xiaodan Wang[4], Junyao Song[1] and Ziqi Xu[1], [1]Department of Rheumatology, Guang'anmen Hospital, China Academy of Chinese Medical Sciences, Beijing, China, [2]Department of Rheumatology and Nephrology, The Second Affiliated Hospital of Tianjin University of Chinese Medicine, Tianjin, China, [3]Department of Rheumatology, Traditional Chinese Medicine Hospital of Guangdong Province, Guangzhou, China, [4]Institute of Basic Medical Sciences, Academy of Military Medical Sciences, Beijing, China

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Background/Purpose: Bone destruction is one of the main pathological features in ankylosing spondylitis (AS). This research aims to explore the role of nuclear factor kappa-B ligand (RANKL), monocyte-macrophages and RANKL/RANK pathway in AS bone destruction.

Methods: 60 AS patients (age 18-55years, BASDAI>4.0) and 30 healthy volunteers (age 18-50years) were included in the first part of the study. Use ELISA to detect the serum RANKL. The second part, hip joint synovium was used to separate monocyte-macrophages. Specimens were obtained from 10 male AS (age 25-50years) patients who underwent hip joint replacement operation and another 5 male patients (age 30-60years) who had fracture at hip joint and underwent hip joint replacement operation. Digestion and adherent culture was adopted for the primary culture of monocyte-macrophages. Identified the cells with flow cytometry. Detected the expression of protein by Western blot. Immunohistochemical methods were used to test the protein expression in the tissues.

Results: The expression of serum RANKL in the two groups were 103.74±51.09 pg/mL (normal group, n=30) and 228.16±139.15 pg/mL(AS group, n=60). Comparing with normal group, serum RANKL in AS group increased significantly, P <0.05. The correlation test showed that RANKL had no significant correlation with the clinical observation indexes (BASDAI, BASDFI, BASMI, PGA, HAQ) (P >0.05). (Table 1) In vitro, the Western blot results showed that, in AS monocyte-macrophages, the expressions of RANK, TRAF6, NF-kB, JNK, ERK, p38, NFATc1,TRAP, CATK, MMP3 were significantly higher than normal control group, P<0.05.(Table 3) Immunohistochemical results showed that TRAP positive cells in AS synovium was much more than the control group, P <0.05.

Table 1 the correlation between RANKL and BASDAI, BASDFI, BASMI, HYPNALGIA, PGA, HAQ

	RANKL	
	r	*P*
BASDAI	0.085	0.552
BASFI	0.063	0.661
BASMI	-0.083	0.560
HYPNALGIA	-0.165	0.246
PGA	-0.186	0.191
HAQ	0.030	0.835

Table 2 relative intensity of ratio of signaling molecules to b-actin

signaling molecules /b-actin	N	AS
RANK/b-actin	0.0019±0.0002	0.0031±0.0001*
TRAF6/b-actin	0.008±0.0002	0.0185±0.0014*

JNK/b-actin	0.0077±0.0005	0.0132±0.0008*
NF-kB/b-actin	0.6411±0.0442	0.7776±0.0445*
ERK/b-actin	0.0861±0.0025	0.0991±0.0069*
P38/b-actin	0.068±0.0044	0.1093±0.0108*
NFATc1/b-actin	0.0934±0.0030	0.1391±0.0158*
TRAP/b-actin	0.0083±0.0004	0.0104±0.0007*
CATK/b-actin	0.3633± 0.0754	0.5472± 0.0543*
MMP-3/b-actin	0.3988±0.0478	0.643±0.0153*

N: normal group, AS: AS group, * *P<0.05.*

Conclusion: RANKL was highly expressed in active AS patients' serum. Furthermore, experimental results suggested that the mechanism of bone destruction in AS could be: much RANKL combined with RANK, and activated RANKL/RANK pathways, then induced differentiation of monocyte - macrophages into a large number of mature osteoclasts, and eventually caused bone destruction. Serum RNAKL level could indicate the possibility of bone destruction in active AS patients, but could not reflect the progression of AS. Blocking the RANKL/RANK pathway would be an important method for treating bone destruction of AS.

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Abstract Number: 2215

Ticagrelor Regulates Osteoblast and Osteoclast Function and Promotes Bone Formation in Vivo By Increasing Adenosine Levels

Aranzazu Mediero[1], Tuere Wilder[2], Carl Whatling[3] and Bruce Cronstein[4], [1]Medicine, Divison of Translational Medicine, NYU School of Medicine, New York City, NY, [2]Dept of Med, Div of Rheum, NYU School of Medicine, New York, NY, [3]CVMD Innovative Medicine Unit, Translational Sciences, AstraZeneca R&D, Mölndal, Sweden, [4]Medicine, Division of Rheumatology, NYU School of Medicine, NEW YORK, NY

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Session Time: 9:00AM-11:00AM

Background/Purpose: The antiplatelet drugs Ticagrelor and clopidogrel are $P2Y_{12}$ antagonists but ticagrelor also inhibits cellular adenosine uptake via ENT1 and thereby increases extracellular adenosine levels. Dipyridamole induces its antiplatelet effect indirectly via adenosine, and like ticagrelor, inhibits ENT1. We have demonstrated that dipyridamole stimulates bone regeneration in mice by an A2AR-dependent mechanism. Both adenosine A2AR or A2BR stimulation inhibits osteoclast differentiation. We asked whether the antiplatelet agents ticagrelor and clopidogrel regulated osteoclast differentiation and, if so, $A_{2A}R$ or A2BR stimulation played a role in this effect.

Methods: Osteoclast and osteoblast differentiation were studied in primary murine bone marrow culture as the number of TRAP-positive or Alizarin Red-positive cells, respectively, after challenge with ticagrelor, the active metabolite of clopidrogrel or dipyridamole (1nM-100mM) (n=5 each), in the presence/absence of ZM241385 (A2AR antagonist) or GS6201 (A2BR antagonist) 1mM. Male C57Bl/6 mice were anesthetized, a trephine defect was created in the calvariae, and covered using a collagen scaffold soaked in saline or 10-100mM ticagrelor or clopidogrel (n=5 each). Animals received the appropriate treatment daily until sacrifice 4 weeks after surgery when calvariae were harvested and prepared for microCT and histology.

Results: TRAP staining reveals a dose-dependent reduction in osteoclast differentiation in the presence of ticagrelor (IC50=10μM), clopidogrel (IC50=10μM) and dipyridamole (IC50=1μM), been these concentrations above the clinical exposures.

TRAP staining revealed that ZM241385 blocked the effect of both ticagrelor and dipyridamole, whereas the effect of clopidogrel was reversed by GS6021. Alizarin Red staining revealed a slight but non-significant increase by ticagrelor, clopidogrel and dipyridamole treatment. ZM241385 reversed the effect of both ticagrelor and dipyridamole on osteoblast differentiation but the effects of clopidogrel were reversed by GS6021. microCT showed that blockade of adenosine uptake by treatment with either ticagrelor or clopidogrel markedly enhanced bone regeneration (28±1% and 27±2% respectively, vs. 15±3% in control, $p<0.01$). Bone regeneration was similar to that produced by BMP2 treatment. In ticagrelor- and clopidogrel-treated mice there was a decrease in TRAP-positive osteoclasts that correlated with a decrease in Cathepsin K immunostaining. We observed an increase in Alkaline Phosphatase immunostaining , in ticagrelor or clopidogrel treated bony defects.

Conclusion: Ticagrelor inhibits osteoclast differentiation via blockade of adenosine uptake and resulting increases in extracellular adenosine levels stimulate A2ARs, as we have previously reported for dipyridamole.. Both ticagrelor and the active metabolite of clopidogrel promoted bone regeneration in a murine trephination model. Local treatment with the antiplatelet agents ticagrelor, clopidogrel or dipyridamole may be useful for inhibition of bone destruction or promoting bone growth.

Disclosure: A. Mediero, None; **T. Wilder**, None; **C. Whatling**, None; **B. Cronstein**, Bristol-Myers Squibb, 5,Novartis Pharmaceutical Corporation, 5,Canfite Pharma, 5,Revive Therapeutics, 5,Regeneron, 5,Gismo Therapeutics, 5,Antares Pharmaceuticals, 5,Canfite Pharma, 1,Gilead Pharmaceuticals, 2,AstraZeneca, 2,Takeda, 2,Celgene, 2.

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Abstract Number: 2216

Quality Assessment of Websites Providing Educational Content about Rheumatoid Arthritis

Maria A. Lopez-Olivo[1], Ana Ojeda-Prias[2], Eric Heung[3], Amye L. Leong[4], Irmgard Willcockson[5] and Maria E. Suarez-Almazor[1], [1]General Internal Medicine, The University of Texas, MD Anderson Cancer Center, Houston, TX, [2]The University of Houston, Houston, TX, [3]Lake Erie College of Osteopathic Medicine, Erie, PA, [4]Spokesperson; Strategic Relations, BONE AND JOINT DECADE, Santa Barbara, CA, [5]School of Biomedical Informatics, The University of Texas, Houston Science Center, Houston, TX

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Background/Purpose: The Internet can support remote and immediate access to health information. It is the second most consulted information source next to physicians. Google is the preferred search engine. The purpose of this study was to evaluate the quality of currently available websites with content about rheumatoid arthritis.

Methods: We performed an environmental scan of the currently available rheumatoid arthritis education information on the World Wide Web. Three separate search engines were used: Google Advanced, Bing, and Ask.com. The term “rheumatoid arthritis” was used as the search word. The first 100 results were reviewed in each engine and separated in domains (e.g., .gov, .edu, .com, .org). Only patient education websites were included. Two independent investigators collected data regarding type of information provided, design, literacy levels (evaluated using the Flesch Grade Level readability formula), conflicts of interest, and accuracy and currency of information.

Results: We identified 36 websites. All websites provided information about the definition and prevention (disease and flare-ups) of rheumatoid arthritis. Most included material about epidemiology, diagnosis and treatment options but not enough information about prognosis, and complications. Eighty-six percent of the websites had a static design. Reading levels ranged from 6.6 to 16.6 (mean 11.5), which is higher than the governmental recommendation of 6th grade maximum readability level for patient education material. The majority of the included websites did not provide disclosure statements and only 8.3% of the

websites clearly stated to be non-profitable. References were provided by 52.8% of the websites, the rest did not report sources of information. Only 36.1% were updated to 2014.

Conclusion: Current patient information in the Internet does not comprenhensively address all educational needs of patients with rheumatoid arthritis. While websites commonly present general information about the disease and treatment choices, most fail to address prognosis and complications than can occur throughout the course of the disease. In addition, websites commonly fail to report adequate disclosure statements and sources of information and most are unsuitable for low-literacy populations.

Disclosure: M. A. Lopez-Olivo, None; **A. Ojeda-Prias**, None; **E. Heung**, None; **A. L. Leong**, None; **I. Willcockson**, None; **M. E. Suarez-Almazor**, None.

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Abstract Number: 2217

#Rheumjc: Development, Implementation and Analysis of an International Twitter-Based Rheumatology Journal Club

Christopher Collins[1], Paul Sufka[2], Jonathan S. Hausmann[3], Arundathi Jayatilleke[4], Jose Campos[5] and Suleman Bhana[6], [1]Rheumatology, Washington Hospital Center, Washington, DC, [2]Rheumatology, HealthPartners, Saint Paul, MN, [3]Rheumatology, Beth Israel Deaconess Medical Center, Boston, MA, [4]Medicine, Division of Rheumatology, Drexel University College of Medicine, Philadelphia, PA, [5]Rheumatology, Puerta de Hierro Majadahonda University Hospital, Madrid, Spain, [6]Crystal Run Healthcare, Middletown, NY

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Background/Purpose: Twitter is an increasingly popular platform for discussion and engagement amongst healthcare professionals. Here we describe the development, implementation and analysis of a rheumatology focused journal club on Twitter which utilizes the hashtag #RheumJC.

Methods: A #RheumJC development team was created, consisting of two academic rheumatologists, two private practice rheumatologists, and an adult/peds rheumatology Fellow in Training (FIT). A needs assessment survey was conducted to gauge interest and help define the structure of the proposed journal club, including preferred times and types of articles to be discussed. Prior to journal club sessions, requests were made for temporary open-access privileges to the article as well as invites to principal authors to participate. A total of 4 different journal clubs were conducted between January 29th and May 2nd, 2015, each consisting of two "live" one hour chats, occurring during the evening hours of GMT (European centric) and EST (Americas centric) respectively, as well as a full 24 hrs to allow for asynchronous participation. An analysis of the different sessions was performed to assess participant demographics and participation rates. A qualitative content analysis of the entire 96 hours of transcript (1927 tweets) was conducted with 6 coders assessing 363 tweets each (313 unique and 50 common). Inter-rater agreement was calculated using Krippendorff's alpha. A second survey was conducted after the 4th journal club to assess participant satisfaction and identify additional strengths or barriers.

Results: In total, 133 individuals from 31 different countries participated in at least one #RheumJC session. While the majority of participants were rheumatologists, over 8 different medical fields were represented. There were 13 FIT and other trainees amongst the participants. 38 individuals participated in at least 2 different journal clubs, 16 participated in at least 3, and 8 individuals were present at all four. The mean number of tweets during each of the live journal clubs sessions (n=8) was 197 (166 unique tweets, 31 re-tweets). For 2 of the journal clubs, principal authors of the manuscript were able to participate. A qualitative content analysis (inter-rater agreement alpha =0.801) revealed that the majority of the conversation was relevant with 28% of the tweets addressing the article directly (in the spirit of a "traditional" journal club) and another 62% considered "on-topic" with

tweets referencing personal experiences, opinions, and links to supporting literature. A survey conducted after the 4th journal club revealed that the majority (89%) of those who had participated were either satisfied or very satisfied with the #RheumJC initiative. Of interest, 11% of journal club participants indicated they had joined Twitter solely because of #RheumJC, and another 37% stated that #RheumJC had increased their use of Twitter as a tool for medical education.

Conclusion: #RheumJC is a novel and popular approach to the traditional medical journal club which brings together people from around the globe and across specialties to discuss current medical literature in rheumatology utilizing Twitter as a medium for medical education.

Disclosure: C. Collins, None; **P. Sufka**, None; **J. S. Hausmann**, None; **A. Jayatilleke**, None; **J. Campos**, None; **S. Bhana**, None.

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Abstract Number: 2218

A Randomized Controlled Trial to Evaluate a Multimedia Patient Education Tool in Patients with Knee Osteoarthritis. Six-Month Results

Maria A. Lopez-Olivo[1], Andrea Barbo[2], Tara Rizvi[3], Robert Volk[4], Heather Lin[5] and Maria E. Suarez-Almazor[1], [1]General Internal Medicine, The University of Texas, MD Anderson Cancer Center, Houston, TX, [2]Department of Biostatistics, The University of Texas, MD Anderson Cancer Center, Houston, TX, [3]Rheumatology, Baylor College of Medicine, Houston, TX, [4]General Internal Medicine, UT MD Anderson Cancer Center, Houston, TX, [5]Biostatistics, The University of Texas, MD Anderson Cancer Center, Houston, TX

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Background/Purpose: Video modelling is often used in patient education to improve patient outcomes. We conducted a multi-centered, open-label, parallel, randomized controlled trial that evaluated the efficacy of a multimedia patient education tool (MM-PtET) in patients with knee osteoarthritis (kOA).

Methods: Patients were recruited from 5 centers and through advertisement. Inclusion criteria were: (i) age ≥50, (ii) prior diagnosis of knee OA (unilateral or bilateral) by a physician, (iii) adequate cognitive status, and (iv) ability to communicate in English or Spanish language. Participants completed a baseline questionnaire and then were randomized through an institutional web system to receive either a MM-PtET (including storylines and testimonials) in combination with a written booklet or a written booklet alone (with the same content). Follow-up included a post-intervention, 3 and 6-month questionnaires. Primary outcome measures were: disease knowledge, decisional conflict, and role preferences. Secondary outcomes included: self-efficacy and disease management.

Results: 219 participants were randomized (n=109, MM-PtET + written booklet; n=110 written booklet alone). Mean age was 65±8 years, 76% were female, 82% had adequate health literacy, and 11% spoke Spanish. 173 (83=MM-PtET, 90=booklet) and 189 (98=MM-PtET, 91=booklet) participants returned their questionnaires at 3 and 6 months, respectively. Within groups most outcomes were improved from baseline to 3 and 6 months. At 3 months, participants receiving the MM-PtET + written booklet had lower scores on the uninformed scale of the decision conflict measure compared to those receiving the booklet alone (25.4 vs 32.7, p=0.05). Linear regression showed that Spanish-speakers patients who received the booklet had higher decisional conflict at 6 months compared to baseline (mean difference=18; p=0.04), while those who received MM-PtET had lower conflict (mean difference=-23, p=0.02) and felt less uninformed (p=0.04). Also, having a Bachelor's degree or higher was associated with improved clarity scores after 6 months (p=0.01). Greater improvement in self-efficacy was observed among English speaking patients, receiving the control, and among females, receiving the intervention (p=0.02 and p<0.05, respectively). Generalized estimating equation analysis showed that after adjusting for correlated outcome data and controlling for other variables, Caucasian

(as compared to Hispanic), and higher educated participants (p=0.009 and p=0.01) were more likely to prefer playing an active role on disease management. Also, among patients with inadequate health literacy, those who received the intervention had higher odds of choosing active role than controls (OR=5.1, 95% CI: 1.1 – 22.8, p=0.03).

Conclusion: Patients improve outcomes with any type of educational materials (either DVD or booklet) up to 6 months after being informed. Greater improvements with the use of MM-PtET compared to booklet were seen among Spanish-speakers, females, and those with inadequate health literacy.

Disclosure: M. A. Lopez-Olivo, None; **A. Barbo**, None; **T. Rizvi**, None; **R. Volk**, None; **H. Lin**, None; **M. E. Suarez-Almazor**, None.

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Abstract Number: 2219

Improving Outcomes with a Multimedia Patient Education Tool in Patients with Osteoporosis after 6 Months. a Randomized Controlled Trial

Maria A. Lopez-Olivo[1], Andrea Barbo[2], Tara Rizvi[3], Robert Volk[4], Heather Lin[5] and Maria E. Suarez-Almazor[1], [1]General Internal Medicine, The University of Texas, MD Anderson Cancer Center, Houston, TX, [2]Department of Biostatistics, The University of Texas, MD Anderson Cancer Center, Houston, TX, [3]Rheumatology, Baylor College of Medicine, Houston, TX, [4]General Internal Medicine, UT MD Anderson Cancer Center, Houston, TX, [5]Biostatistics, The University of Texas, MD Anderson Cancer Center, Houston, TX

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Background/Purpose: We conducted a 6-month multi-centered, open-label, parallel, randomized control trial to compare a multimedia-patient education tool (MM-PtET) including storylines and narratives with a written booklet for participants with osteoporosis (OP).

Methods: 225 participants were recruited from 3 outpatient clinics and newspaper advertisement. Inclusion criteria were: (i) diagnosis of osteoporosis/osteopenia, (ii) female gender, (iii) age ≥50 years (iv) at least 3 years post-menopausal, (v) adequate cognitive status, and (vi) ability to communicate in English or Spanish language. Participants were randomized through an institutional web system to either a MM-PtET or a written booklet with same content as MM-PtET. All participants completed questionnaire at baseline (pre and post), 3 and 6 months. Primary outcome measures included: disease knowledge, decisional conflict, and role preferences. Secondary outcomes were: self-efficacy and disease management.

Results: 111 participants were randomly allocated to the MM-PtET intervention and 114 to the control booklet. Mean age of participants was 64±9 years and 82% had adequate health literacy. 183 (85=MM-PtET, 98=booklet) and 189 (90=MM-PtET, 99=booklet) participants returned their questionnaires at 3 and 6 months, respectively. Within groups most outcomes were improved from baseline to 3 and 6 months. At 6 months, more participants in the MM-PtET group switched from active to passive role preference after watching the MM-PtET compared to patients reading the booklet (11% vs 3%, p=0.03). Results from linear regression on the difference between baseline and 6 month scores showed that younger age (p=0.03, p=NS, p=0.04) and receiving booklet among patients with inadequate health literacy levels (p= 0.02, p=0.009, p=0.05, p=0.02) were associated with greater improvements in the total decision conflict scale, uninformed, and clarity subscales, and self-efficacy. In contrast, receiving MM-PtET among patients with adequate health literacy levels led to greater improvements in the uninformed subscale (p=0.03). Greater improvements in the effective disease management scale were associated with younger age (p=0.03). Generalized estimating equation analysis showed that after adjusting for correlated outcome data and controlling for other variables, patients who received the intervention had higher odds of active role preference for disease management if they belonged to the inadequate

health literacy group (p=0.02). Also, the odds of active role preference among participants receiving the intervention are higher than controls but the magnitude decreases with longer disease duration (p=0.004).

Conclusion: Regardless of the delivery method, patients improve outcomes with educational materials up to 6 months after being informed. Participants with either adequate or inadequate health literacy levels improved outcomes with the MM-PtET.

Disclosure: M. A. Lopez-Olivo, None; **A. Barbo**, None; **T. Rizvi**, None; **R. Volk**, None; **H. Lin**, None; **M. E. Suarez-Almazor**, None.

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Abstract Number: 2220

Appropriate Investigations and Costs in Rheumatology: Residents' Attitudes and Knowledge

Victoria YY Xu[1], Neel Shah[2], Christine Soong[3] and Shirley Chow[4], [1]School of Medicine, Queen's University, Kingston, ON, Canada, [2]Harvard Medical School, Harvard University, Cambridge, MA, [3]Division of General Internal Medicine; Centre for Quality Improvement and Patient Safety, University of Toronto, Toronto, ON, Canada, [4]Division of Rheumatology, Sunnybrook Health Sciences Centre, University of Toronto, Toronto, ON, Canada

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Background/Purpose: With the launching of the Choosing Wisely campaign, there has been a growing emphasis in the medical community on addressing unnecessary tests and procedures and their impact on patient care, costs and resources. This study aims to: 1) assess internal medicine and rheumatology residents' attitudes towards appropriate ordering of rheumatology investigations and cost-conscious care; 2) assess residents' knowledge of costs of care in rheumatology; and 3) identify areas of need in the post-graduate rheumatology curriculum with respect to this topic.

Methods: An anonymous survey was distributed to rheumatology trainees at several academic centres and internal medicine residents rotating at one academic hospital between July 1, 2014 and December 31, 2014. Participants were asked to rate statements on a 5-point Likert-scale and estimate costs of common rheumatology investigations. Descriptive statistics were conducted using Microsoft Excel.

Results: The survey was completed by 23 of 49 eligible participants (response rate 46.9%). Fifteen participants (65%) were female. Respondents included 5 internal medicine (post-graduate year 3) residents and 18 rheumatology trainees (post-graduate year 4-5). All participants agreed or strongly agreed that all physicians should be familiar with appropriate use of investigations and costs of care. Twenty-one (91%) participants agreed or strongly agreed that residents should receive training on this topic. Fourteen (61%) felt that teaching on this topic should be mandatory. Fourteen participants (61%) consider pretest and posttest probabilities and test sensitivity/specificity in clinical decision-making, while only eight (35%) consider costs. Only 9% of responders felt confident in appropriately ordering a whole-body bone scan, and fewer than half felt confident in appropriately ordering dual X-ray absorptiometry (DXA) scans. Participants overestimated all the costs except for complete blood count (CBC). The average discrepancy between estimated and true cost was greatest for spine MRI, uric acid level, rheumatoid factor (RF) and erythrocyte sedimentation rate (ESR).

Conclusion: The results reveal areas of need in the post-graduate curriculum with regards to appropriate ordering of rheumatology investigations and costs of care. Future steps include developing a teaching tool outlining this topic for residents.

Disclosure: V. Y. Xu, None; **N. Shah**, None; **C. Soong**, None; **S. Chow**, None.

Abstract Number: 2221

Engaging Learners in Lupus Education with Pivot (Practice Improvement using Virtual Online Training), a Novel, Digital Case-Based Curriculum

Karen Law[1], Michelle Lin[2], Sheryl McCalla[3] and Maria Dall'Era[4], [1]Emory University School of Medicine, Atlanta, GA, [2]Emergency Medicine, UCSF, San Francisco, CA, [3]American College of Rheumatology, Atlanta, GA, [4]University of California San Francisco School of Medicine, San Francisco, CA

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Background/Purpose:

Lupus is one of the prototypic rheumatic diseases, yet only a small amount of time in medical school curricula is devoted to lupus-specific education. Moreover, when present, most lupus curricula focus on lists of disease characteristics, overlooking the challenging aspects of the disease, including its often elusive presentation and the social and ethnic factors that contribute to patient outcomes.

To address these concerns, we designed a library of interactive case studies titled "Practice Improvement using Virtual Online Training," or PIVOT. These cases highlight the diagnostic reasoning necessary when evaluating a patient with suspected lupus or lupus-related complications. Unlike traditional curricula, PIVOT engages learners on an interactive diagnostic journey accessible from any mobile or desktop device. Each case has 8 key clues to focus the learner as they work through the case. A point score gives feedback on learner progress. Embedded multimedia to demonstrate patient history and physical exam findings add to the case interactivity and authenticity, and introduce social themes and concepts of health disparities in lupus. Learners select which laboratories to order and interpret the results to arrive at a diagnosis. Each case is followed by a full debrief as well as the diagnostic pathway of expert clinicians as an additional learning opportunity. In this manner, PIVOT reinforces important lupus concepts including diagnosis and health disparities in a fresh, appealing format, while also piloting an innovative method of medical education.

Methods:

Twelve Fourth-year medical students from a single medical school completed PIVOT cases during their elective in rheumatology. Our primary outcome measure was learner satisfaction. Secondary outcomes included general feedback about the PIVOT platform and educational content. A descriptive analysis was performed of the data and free-text responses.

Results:

Student feedback for the PIVOT cases was positive. 100% of learners rated the PIVOT experience ³4 on a 5-point Likert scale.

Table 1: PIVOT platform and content feedback	Disagree	Neutral	Agree
The interactive nature of the cases improved the learning experience	0	7%	93%
Finding the key clues helped to engage me with the cases.	7%	20%	73%
Watching my point score helped to engage me with the cases.	27%	27%	46%
The cases increased my medical knowledge about lupus.	7%	0	93%
The cases increased my awareness of health disparities for patients with lupus.	26%	20%	54%
The cases helped me practice diagnostic reasoning and critical thinking.	0	13%	83%

Survey comments highlighted the most effective teaching points:

- "I liked having to order labs and think about how the exam and labs made certain diagnoses more or less likely"
- "[I learned about] atypical manifestations, subtle history and physical clues... what labs to look for and what else to keep in mind (viral infection, drug induced lupus, etc)"
- "There are significant health disparities in lupus that lead to morbidity that [can be] partially preventable"

Conclusion:

PIVOT, a novel, interactive digital case series, successfully engaged novice learners in lupus education. The case-based curricula richly illustrated both diagnostic reasoning and social considerations that may be overlooked by traditional curricula. Learners found the key clues and interactive lab ordering unique and appealing. These features may be augmented in future cases to further expand PIVOT's utility.

Disclosure: K. Law, None; **M. Lin**, None; **S. McCalla**, None; **M. Dall'Era**, None.

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Abstract Number: 2222

Teaching Rheumatology in Undergraduate Medical Education: What Are the Students Saying?

Amy C. Cannella[1], Gerald F. Moore[2], Ted R. Mikuls[3], James R. O'Dell[3], Sarah B. McBrien[4], Michelene Hearth-Holmes[2], Lynell W. Klassen[2], Marcus H. Snow[2], Michael G. Feely[2], Zachary D. Fowler[5], Maxwell Burchell[5] and Alan R. Erickson[6], [1]Divison of Rheumatology, University of Nebraska College of Medicine and VA Nebraska Western Iowa Health Care System, Omaha, NE, [2]Division of Rheumatology, University of Nebraska College of Medicine and VA Nebraska Western Iowa Health Care System, Omaha, NE, [3]University of Nebraska Medical Center, Omaha, NE, [4]Educational Support Office, University of Nebraska College of Medicine, Omaha, NE, [5]College of Information Science and Technology, University of Nebraska at Omaha, Omaha, NE, [6]University of Nebraska College of Medicine and VA Nebraska Western Iowa Health Care System, Omaha, NE
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Background/Purpose:

At the University of Nebraska College of Medicine (COM), rheumatology is taught in a block to second year medical students (M2s). The educational content was revised significantly in 2014. In addition to standard lectures, the following techniques were employed: faculty led live rheumatology patient encounters, student and faculty led problem and case based learning (PBL/CBL), student and faculty led Augenblick cases (pathognomic rheumatology findings), video game on gout, and independent time in the simulation lab for joint injections.

We desired to obtain student feedback regarding these teaching modalities in order to improve undergraduate rheumatology education moving forward.

Methods:

Upon completion of the rheumatology examination, students were asked to answer a voluntary 30 question evaluation. No evaluation was reviewed until final grades were determined by a grading committee. Students were asked to rate the effectiveness each teaching method using a Likert-scale response, and were given space to provide comments as free text. Free

text comments were reviewed qualitatively for prominent themes.

A chi-square test was done to compare the different teaching methods, and was adjusted for multiple comparisons.

Results:

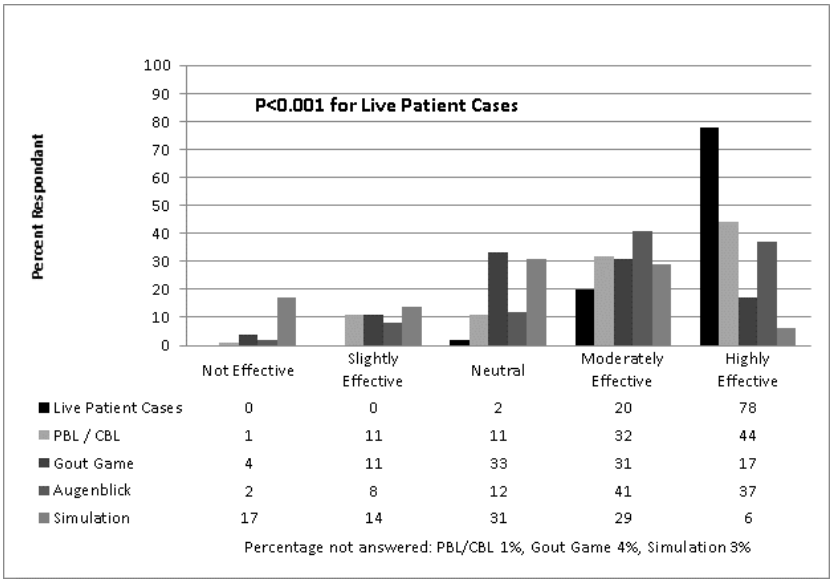
We received voluntary survey data from 114 of the 124 students participating in the block (92% response). M2 students ranked the rheumatology block the highest among all of those evaluated for the 2014-15 academic year.

Results are summarized in Table 1. Live patient encounters were deemed by students to be significantly more effective than all other modalities ($p<0.001$). With the exclusion of the simulation lab, at least 50% of the students felt the methods implemented were moderately to highly effective. Several themes emerged from the qualitative review of more than 17 pages of written feedback including: "appreciation for efforts incorporating new learning experiences" and universally positive feedback regarding faculty-led patient encounters.

Conclusion:

With a voluntary survey response rate of 92%, COM students were invested in improving learning opportunities in rheumatology. In addition to the standard lecture format, students were receptive and positive toward the novel educational methods employed. Our experience suggests that our recently developed rheumatology curriculum, blending both traditional and novel teaching methods, is highly effective in engaging medical students. Of the modalities employed, faculty-led live patient encounters appear to be particularly appealing to trainees early in rheumatology learning. With ongoing threats to a sustainable rheumatology workforce, it is vital that training curricula engage students early with goals of knowledge acquisition and learner satisfaction.

Table 1: Survey Results



Disclosure: A. C. Cannella, None; **G. F. Moore**, None; **T. R. Mikuls**, None; **J. R. O'Dell**, None; **S. B. McBrien**, None; **M. Hearth-Holmes**, None; **L. W. Klassen**, None; **M. H. Snow**, None; **M. G. Feely**, None; **Z. D. Fowler**, None; **M. Burchell**, None; **A. R. Erickson**, None.

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Abstract Number: 2223

Improving Clinical Decisions for Rheumatoid Arthritis Management Using Online Medical Simulations

Nimish Mehta[1], Keith Johnson[2], Douglas Blevins[3] and Martin Warters[3], [1]Medscape, LLC, New York, NY, [2]Medscape Education, New York, NY, [3]Medscape, LLC, Durham, NC
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Background/Purpose: In many patients with rheumatoid arthritis (RA), the disease is not adequately controlled, and only a minority of patients attain the goal of consistent remission or low disease activity. A study was conducted to determine if online, simulation-based educational interventions could improve clinical decisions made by rheumatologists regarding the management of patients with RA, including first-line and second-line biologic therapies.

Methods: A cohort of practicing rheumatologists from several countries who participated in online, simulation-based education was evaluated. The simulation consisted of two cases presented in a platform that allowed physician learners to choose from numerous lab tests and assessment scales as well as thousands of diagnoses, treatments, and procedures matching the scope and depth of actual practice. The clinical decisions made by the participants were analyzed using an artificial intelligence engine, and instantaneous clinical guidance was provided employing current evidence-based and expert faculty recommendations. Participant decisions were collected after clinical guidance and compared with each user's baseline data using a 2-tailed paired T-test ($P<0.05$ was considered statistically significant) to assess the impact of simulation-based education on the clinical decisions made by participants. Data is reflective of learners who participated in the assessment from 10/29/14 to 4/29/15.

Results:

The assessment sample consisted of 282 rheumatologists who made clinical decisions within the simulation and proceeded to the concluding, debrief section within the study period. As a result of clinical guidance (CG), significant improvements were observed in several areas of management in patients with RA (post-CG vs pre-CG) specifically:

- 33% improvement in the identification of RA flare in a patient who had stopped MTX due to intolerance ($P<.0001$)
- 34% improvement in selection of non-TNF biologic agent upon inadequate response to traditional DMARDs ($P<.0001$). Most of this improvement resulted from increase in tocilizumab monotherapy selection.
- 13% more participants correctly decided to discontinue adalimumab (baseline, $P<.02$)
- 28% increase in the decision to prescribe non-TNF biologic in an adalimumab non-responder ($P<.0001$). Most increase came from selection of tocilizumab, followed by abatacept, and rituximab.

Conclusion: This study demonstrated the success of online, simulation-based education on improving the evidence-based clinical decisions by rheumatologists in selecting appropriate treatment for first-line biologic and switching to second-line biologic agents. Simulation-based instructions that lead to improvement in physician performance in a consequence-free environment can result in more evidence-based clinical decisions for RA and improvement in patient outcomes.

Disclosure: N. Mehta, None; **K. Johnson**, None; **D. Blevins**, None; **M. Warters**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/improving-clinical-decisions-for-rheumatoid-arthritis-management-using-online-medical-simulations

Abstract Number: 2224

Tailored, Online Education on Comparative Effectiveness Studies in Rheumatoid Arthritis: Success in Improving Knowledge and Clinical Decisions

Nimish Mehta, Emilie McCardell and Kathleen Geissel, Medscape, LLC, New York, NY
First publication: September 29, 2015

SESSION INFORMATION

Session Date: Tuesday, November 10, 2015

Session Title: Education Poster II

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Analysis of past educational activities on comparative effectiveness studies in RA identified different educational needs for varying segments of rheumatologists – from interpretation of clinical results to application in practice. A study was conducted to measure the effectiveness of using responses to a single-question as a method to segment the physician audience and to provide a tailored learning approach specific to the needs of each group.

Methods: We utilized a unique online, single-question segmentation using branching logic, in order to tailor education that rheumatologists needed most regarding comparative effectiveness studies in RA. Participants were presented with a single question that tested their interpretation of results from AMPLE and ADACTA. Those who answered correctly were directed to an educational activity on applying these results in case scenarios, and those who answered incorrectly were directed to an activity on interpretation of results. Once the participants were directed to a specific activity, online survey instruments using knowledge- and case-based, multiple-choice questions were administered to compare the same participants' responses to 4 identical questions before and after each activity. McNemar's chi-squared test was used to determine statistical significance between responses. Cramer's V was used to calculate the effect sizes of education, based on the strength of association between the pre-assessment and post-assessment responses. The activities launched in December 2014 – January 2015, and data were collected through March, 2015.

Results: In total, 112 rheumatologist responses were analyzed in this study. Tailoring education designed to match individual deficiencies in knowledge and skills of rheumatologists to specific educational activities on comparative effectiveness in RA resulted in robust educational effect (effect sizes ranging from V = 0.038 to 0.134 across 4 activities, $P < .001$). Analysis of the effect of education on specific learning goals showed:

- 52% increase in the decision to add abatacept in a patient with inadequate response to MTX, based on data from AMPLE study ($P < .001$)
- 56% increase in the selection of tocilizumab based on results from ADACTA trial, in a patient who discontinued MTX due to intolerance and progressed to a DAS28 of 6.5 ($P < .001$)
- More than 38% improvement in identifying patient populations and dosage of biologics studied in ADACTA trial ($P < .05$)
- 28% improvement in the interpretation of results of AMPLE trial ($P = .057$)

Conclusion: Large, statistically significant improvements in knowledge and competence of rheumatologists regarding comparative effectiveness studies in RA demonstrated the success of using online branching logic to segment the participants and providing education on topic areas they needed the most. Recognizing that rheumatologists are at various stages of understanding and skills in application of clinical trial data from various landmark studies, this approach may be used to maximize translation of data into clinical decisions.

Disclosure: N. Mehta, None; **E. McCardell**, None; **K. Geissel**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/tailored-online-education-on-comparative-effectiveness-studies-in-rheumatoid-arthritis-success-in-improving-knowledge-and-clinical-decisions

Abstract Number: 2225

Twitter and Rheumatology: Significant and Incremental Growth in Usage

Ahmed Omar[1], Ismail Sari[1], Jonathan Chan[2], Nigil Haroon[1] and Robert D Inman[3], [1]Rheumatology, Toronto Western Hospital, University of Toronto, Toronto, ON, Canada, [2]Rheumatology, Spondylitis program, Toronto Western Hospital, University of Toronto, Toronto, ON, Canada, [3]Immunlogy and Institute of Medical Science, Toronto Western Hospital, University of Toronto, Toronto, ON, Canada

First publication: September 29, 2015

SESSION INFORMATION
Session Date: Tuesday, November 10, 2015
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Session Type: ACR Poster Session C
Session Time: 9:00AM-11:00AM

Background/Purpose:

The continued growth of social media has allowed people to rapidly communicate, share, and develop ideas and information. Twitter is an online social networking service which allows users to submit and to read short 140-character messages called "tweets". Since its creation in 2006, its user base has continued to grow with a currently estimated number of active users of half a billion. In addition, sixty million tweets are estimated to be generated each day.

Used correctly, Twitter can be a valuable portal to educate patients, share research ideas and findings and increase awareness of important health-related issues.

With regards to the subject of Rheumatology, there is lack of knowledge in terms of its online twitter presence and its development over the years.

The aim of this study is to highlight the use of Twitter in relation to Rheumatology. To the best of our knowledge, no previous research has examined this subject.

Methods:

The Symplur® healthcare analytics website was used to retrospectively examine traffic related to chosen Rheumatology-associated hashtags. Symplur® was used to generate statistics for the number of impressions, unique tweets (excluding retweets) and number of participants. Some of the hashtags that were chosen include: #Rheum, #Lupus, #Fibro, #Arthritis, #Osteoporosis, #Spondylitis (AS), #RheumatoidArthritis, and #Vasculitis. #Diabetes, #IBD (Inflammatory Bowel Disease), and #Psoriasis were also chosen as comparators. Statistics were obtained from a 5 year period (2010 to 2014).

Results:

The total number of Rheumatology-related tweets related to the major hashtags grew from only 319 tweets in 2010 to 497,595 tweets in 2014 (Fig. 1a). The #Lupus hashtag showed the most activity, followed by #Fibro (fibromyalgia), #Arthritis and #Rheum.

Between the years 2013 and 2014, there was an average growth in number of total tweets by 37%. When comparing #Diabetes with Rheumatology-related hashtags in 2014, there were a total of 1,037,211 tweets related to #Diabetes *vs* 538,186 tweets related to Rheum hashtags (Fig. 1b).

In terms of number of contributors, in 2014, there were a total of 135,237 participants using Rheumatology-related hashtags. When looking at influence, the top 10 contributors tweeting in the #lupus, #RheumatoidArthritis and #Spondylitis hashtags contributed 12.6 %, 11% and 61.4% of total number of tweets respectively.

Conclusion : Twitter usage in relation to Rheumatology has shown a dramatic growth over the last 5 years and continues to show sustained growth. These novel findings suggest that this social media portal has the potential to be a valuable tool in informing and shaping Rheumatology-related healthcare.

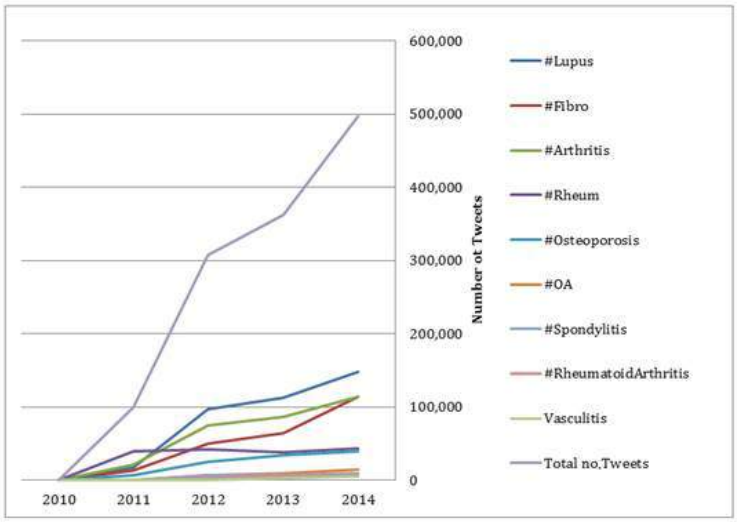

Fig 1a. Total number of tweets over a 5 year period

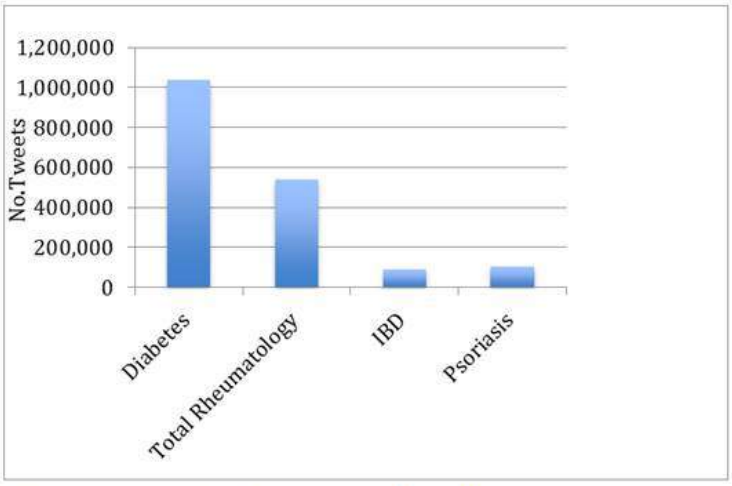

Fig 1b. Total number of tweets in 2014 for Rheumatology vs. Diabetes, IBD and Psoriasis

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Disclosure: **A. Omar**, None; **I. Sari**, None; **J. Chan**, None; **N. Haroon**, None; **R. D. Inman**, None.

Abstract Number: 2226

Enhancing Medicine Trainees' Exposure to Common Musculoskeletal Disorders through a Primary Care Musculoskeletal Clinic

Andrea M. Barker[1], Grant W. Cannon[2], Phillip Lawrence[3], Timothy A. Huhtala[4], Loren Wooldridge[5] and Michael J. Battistone[6], [1]General Internal Medicine, Salt Lake City VA Medical Center and University of Utah, Salt Lake City, UT, [2]Division of Rheumatology, Salt Lake City VA Medical Center and University of Utah, Salt Lake City, UT, [3]Pharmacology, Salt Lake City VA Medical Center and University of Utah, Salt Lake City, UT, [4]Division of General Internal Medicine, Salt Lake City VA and University of Utah, Salt Lake City, UT, [5]Physical Therapy, Salt Lake City Department of Veterans Affairs, Salt Lake City, UT, [6]Rheumatology, Salt Lake City VA Medical Center and University of Utah, Salt Lake City, UT

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Session Date: Tuesday, November 10, 2015

Session Title: Education Poster II

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose:

Musculoskeletal (MSK) disorders are common in primary care (PC), however many of these problems are referred to specialty clinics for evaluation and management. High referral rates are partly due to lack of providers' time to fully evaluate the patient during routine clinic appointments, but may also be due to lack of clinicians' experience and training in MSK diseases. To improve patient access to specialty services while aligning with current medical home models, a Primary Care MSK Clinic (PC MSK) was implemented at a Veterans Affairs (VA) Medical Center. The PC MSK Clinic has since become an integral part of our clinical training program, increasing trainees' exposure to MSK disorders.

Methods:

The PC MSK clinic was initiated by a Physician Assistant with orthopedic experience who also works in the general outpatient PC clinic. Soon after implementation, the value of this clinic to the clinical training environment was recognized. A rheumatologist clinician-scholar-educator was invited to attend, and to assist in the cultivation of this resource for rheumatology fellows and other trainees. Most recently, the clinic staffing has been expanded to include an orthopedic Doctor of Physical Therapy. The PC MSK clinic is held one-half day per week within the primary care clinical setting. One rheumatology fellow and 1-2 ambulatory residents are assigned to attend the clinic weekly. Students from medicine, physician assistant, and nurse practitioner programs may also be assigned to this clinic during their clinical rotations.

Results:

A total of 494 consults have been completed since June, 2013; details are presented in the table.

Completed Consults (n, %)	494 (100%)
Academic Year 2013-2014	223 (45%)
Academic Year 2014-2015 (through 5/2013)	271 (55%)
Predicted Academic Year 2014-2015	295
Completed Consults by Provider	494
Faculty	127 (26%)
Fellow	120 (24%)
Rheumatology	112
Geriatrics	8
Residents	247 (50%)
Internal Medicine	181
Physical Medicine & Rehabilitation	28
Med/Peds	8
Emergency Medicine	7
Orthopedics	6
Other	12
Diagnoses	750 (100%)
Shoulder disorders	297 (40%)
Knee disorders	265 (35%)
Hip/Pelvis disorders	61 (8%)
Other	56 (7%)
Osteoarthritis, not specified	38 (5%)
Neurologic/Spine disorders	33 (4%)
Procedures performed (n, % of completed consults)	262 (51%)
Procedures performed by all trainees (n, % of all procedures performed)	185 (71%)
Procedures performed by Rheumatology Fellows (n, % of all procedures performed)	77 (29%)

Conclusion:

The Primary Care MSK Clinic is a feasible and sustainable innovation that provides a unique and efficient clinical experience for medicine trainees. The clinic supplies a high volume of supervised MSK patient encounters that are not typically obtained in traditional rheumatology training experiences or other IM resident rotations. Many of these encounters also involved arthrocentesis and/or joint injections. Additionally, this clinic may serve an important role in improving patient access to appropriate care, and in helping to prioritize specialty referrals.

Disclosure: A. M. Barker, None; **G. W. Cannon**, None; **P. Lawrence**, None; **T. A. Huhtala**, None; **L. Wooldridge**, None; **M. J. Battistone**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/enhancing-medicine-trainees-exposure-to-common-musculoskeletal-disorders-through-a-primary-care-musculoskeletal-clinic

Abstract Number: 2227

Resident's Guide to Pediatric Rheumatology Mobile App: Assessing Enablers and Barriers of Use through Qualitative Focus Groups

Evelyn V. Rozenblyum[1], Niraj Mistry[2], Tania Cellucci[3], Maria Athina (Tina) Martimianakis[4] and Ronald Laxer[5], [1]Pediatrics, Hospital for Sick Children, Toronto, ON, Canada, [2]Pediatrics, University of Toronto, Toronto, ON, Canada, [3]Division of Rheumatology, The Hospital for Sick Children, Toronto, ON, Canada, [4]Faculty of Medicine, University of Toronto, Toronto, ON, Canada, [5]University of Toronto, The Hospital for Sick Children, Toronto, ON, Canada

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SESSION INFORMATION

Session Date: Tuesday, November 10, 2015

Session Title: Education Poster II

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose:

A Resident's Guide to Pediatric Rheumatology (the Guide) is currently used by trainees as an on-the-go learning and teaching resource. Research using the Technology Acceptance Model showed that the concept of developing the Guide into a mobile application (app) was well supported, with the addition of features to facilitate its use, i.e. searchable index, definitions of key terms, clinical photographs and radiology images. Graham's Knowledge-To-Action Framework was used to conduct the needs assessment to underpin the development work.

Objective: (1) To determine perceived enablers and barriers to using the Guide app; **(2)**To explore perceived uses for the Guide app and **(3)**To explore the preferred format, features, and functions of the Guide app.

Methods:

Pediatric residents, rheumatology fellows, and rheumatology staff in both academic and community settings were interviewed in 7 separate focus groups. Focus groups were digitally recorded and transcribed verbatim. Transcripts were analyzed using a combination of deductive and inductive analytical approaches to identify themes.

Results:

medication choices and aid with work-up when no pediatric rheumatologist was available at their center. Residents suggested that they would rather use the app as an on-the-go learning tool and continue with PDF or hard copy on a computer or tablet for more in-depth learning. The guide is used less as a teaching tool than initially thought: fellows and staff used different methods to teach. All groups used the medication section of the Guide regularly.

Users preferred the format of the Guide mobile app to have pictures, easy searchability, mnemonics and clinical pearls, radiographic images, videos endorsed by the section editors, links to references, and treatment algorithms. Tools that ease documentation were not necessary to promote use due to concerns regarding linking to EMR and confidentiality. Games were not a consistently desired feature of the app.

Conclusion:

Creating an easy to use Resident Guide mobile application, with interactive features, concise information, and well-indexed content will yield the most use from the app. Both fellows and staff would be more inclined to use the app as an interactive teaching tool if pictures and cases were available. Results from this needs assessment will be used to convert the sample electronic guide to a functional mobile app prototype.

Disclosure: E. V. Rozenblyum, None; **N. Mistry**, None; **T. Cellucci**, None; **M. A. Martimianakis**, None; **R. Laxer**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/residents-guide-to-pediatric-rheumatology-mobile-app-assessing-enablers-and-barriers-of-use-through-qualitative-focus-groups

Abstract Number: 2228

Brief Educational Intervention Improves Gout Patients' Understanding of Their Disease

Slavica Bobic[1], Mark Tratenberg[1], Julia Ash[1], Amy Wasserman[2] and Kirk Sperber[1], [1]Rheumatology, New York Medical College, Valhalla, NY, [2]New York Medical College, Valhalla, NY

First publication: September 29, 2015

SESSION INFORMATION

Session Date: Tuesday, November 10, 2015

Session Title: Education Poster II

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: To assess gout patients' baseline knowledge of their disease and to measure knowledge improvement after brief educational session.

Methods: In this study, 13 patients with history of gout were given a baseline telephone questionnaire with 11 questions about gout, disease management and medication side effects. Points were given for each correct answer and total score was calculated with a maximum score of 12.5. With each incorrect answer, the patient was educated according to the guideline provided by American College of Rheumatology. Time spent educating each patient was limited to no more than 10 minutes. Data was also collected on duration of disease and patient highest level of school achieved. Two weeks later each patient was called back and the same questionnaire was administered. New post-educational score was calculated using the same methodology. Post-educational activity score was compared with pre-educational activity score. The difference was recorded as a percentage of improvement.

Results: The baseline pre-educational knowledge score ranged from 1 to 11 with the mean score of 6.0. Post-educational score ranged from 4 to 11.5 with the mean score of 8.8. Eighty-five percent of patients improved their knowledge after the educational session. Mean score for patients with high school and/or college improved by 50 percent. Mean score for patients with no formal education improved by 136 percent.

Conclusion: Brief educational intervention can have significant effect on how patients with gout understand their disease and medication side effects. Patient with low educational level benefit from such activity the most. Further study is needed to determine if this improved understanding leads to better clinical outcomes and safety.

Disclosure: S. Bobic, None; **M. Tratenberg**, None; **J. Ash**, None; **A. Wasserman**, None; **K. Sperber**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/brief-educational-intervention-improves-gout-

patients-understanding-of-their-disease

Abstract Number: 2229

New Frontiers: Teaching Quality Improvement to First Year Medical Students in a Rheumatology Safety Net Clinic

Sarah Goglin[1], Mary Margaretten[2], Laura Trupin[3] and Jinoos Yazdany[2], [1]Rheumatology, University of California, San Francisco, San Francisco, CA, [2]University of California, San Francisco, San Francisco, CA, [3]Medicine/Rheumatology, University of California San Francisco, San Francisco, CA

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SESSION INFORMATION

Session Date: Tuesday, November 10, 2015

Session Title: Education Poster II

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: The UCSF Action Research Program is a course in Implementation Science started in 2012 for first and second year medical students that has created a platform for faculty to engage with UCSF medical students around critical issues in health care quality and safety. The primary goal of this program is to create a novel experiential learning program integrating a traditional preceptorship with education about health care quality and safety for first year medical students.

Methods: Four UCSF first year medical students were chosen to participate in a year-long experiential learning curriculum in the San Francisco General Hospital (SFGH) rheumatology clinic, under the leadership of two rheumatology faculty members, one rheumatology fellow, and one research analyst. The students attended weekly clinic sessions from September 2014 through June 2015. Faculty provided pre-clinic didactics on quality improvement (QI) or clinical medicine. The students participated in the team huddle at the start of clinic and then focused each week on learning clinical skills or working on their QI project. Faculty saw patients with the students and assisted with QI projects as needed during the clinic session and outside of clinic.

Results: All four of the students completed an individual QI project under the leadership of a faculty mentor and presented their projects at the annual UCSF Quality and Safety Innovations Conference. Projects focused on improving no-show rates, integrating the FRAX tool into the electronic medical record, and creating a health coaching intervention to improve patient-clinician communication and high-risk medication knowledge. Students were well integrated into the clinic and worked collaboratively in interprofessional teams to implement their projects. The primary challenge was the significant time commitment required of faculty members to create a high-quality experience for the students in addition to providing patient care. Student feedback has been overwhelmingly positive, with all four reporting this as one of the highlights of their medical school experience thus far.

Conclusion: We created a novel experiential learning program for first year medical students that integrated a traditional clinical preceptorship with education about health care quality and safety in a rheumatology safety net clinic. Students added value to the clinic and made strides in improving quality in multiple domains. Students and faculty reported high levels of satisfaction with the experience. The primary challenge is to address the need for significant faculty time commitment to ensure a sustainable program that can be carried out in other settings.

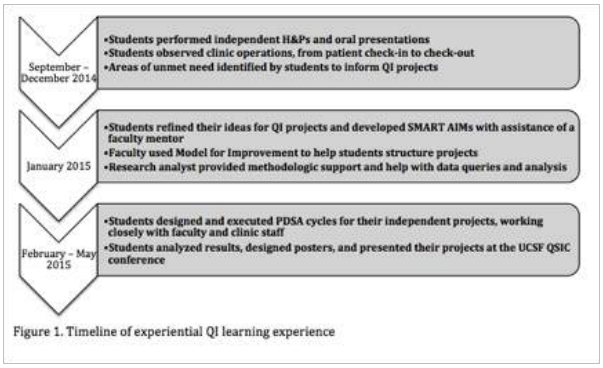

Figure 1. Timeline of experiential QI learning experience

Disclosure: S. Goglin, None; **M. Margaretten**, None; **L. Trupin**, None; **J. Yazdany**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/new-frontiers-teaching-quality-improvement-to-first-year-medical-students-in-a-rheumatology-safety-net-clinic

Abstract Number: 2230

Teaching the Teachers: Report of an Effective Mixed-Method Course Training Clinical Educators to Provide Instruction in Musculoskeletal Care to Other Providers and Learners in Primary Care

Michael J. Battistone[1], Andrea M. Barker[2], Yasuharu Okuda[3], William Gaught[3], Gregory Maida[3] and Grant W. Cannon[4], [1]Rheumatology, Salt Lake City VA Medical Center and University of Utah, Salt Lake City, UT, [2]General Internal Medicine, Salt Lake City VA Medical Center and University of Utah, Salt Lake City, UT, [3]SimLEARN National Medical Center, Veterans Health Administration, Orlando, FL, [4]Division of Rheumatology, Salt Lake City VA Medical Center and University of Utah, Salt Lake City, UT

First publication: September 29, 2015

SESSION INFORMATION

Session Date: Tuesday, November 10, 2015

Session Title: Education Poster II

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: The Veterans Affairs (VA) SimLEARN National Simulation Center, in collaboration with VA Salt Lake City, is developing a continuous professional education (CPE) program in musculoskeletal (MSK) care for clinical educators. The pilot program was presented at SimLEARN in February 2015.

Methods:

The 2-day course focused on evaluation and management of shoulder and knee pain in primary care. Curriculum included didactics, peer-teaching, standardized patients, technologically-enhanced simulation, and interactive sessions addressing clinical performance observation, effective feedback delivery, and principles of adult learning. After competency was observed by OSCE, trainees participated in a comprehensive, five-rotation objective structured teaching experience (OSTE) during which each participant was observed performing roles of simulated patient, evaluator, and learner. Learning was tracked by self-assessment using a 5-point Likert type scale (declarative knowledge) and by pre- and post-course OSCEs.

Results:

The pilot program included seven participants (four physicians, one nurse practitioner, two nurses). Post-course scores representing declarative knowledge and competence were higher than pre-course scores (4.5 vs. 2.8 for self-assessment; 4.5 vs. 0.9 for OSCE). Retrospective pre-course self-assessments were lower than prospective pre-course ratings (2.6 vs. 2.8), suggesting that participants downgraded their pre-course knowledge and skill after experiencing the course.

Conclusion:

The SimLEARN course is an effective model for CPE, demonstrating enhanced declarative knowledge and competency scores, and providing opportunities for reflective practice in education through multi-station OSTE.

Disclosure: M. J. Battistone, None; **A. M. Barker**, None; **Y. Okuda**, None; **W. Gaught**, None; **G. Maida**, None; **G. W. Cannon**, Amgen, 2.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/teaching-the-teachers-report-of-an-effective-mixed-method-course-training-clinical-educators-to-provide-instruction-in-musculoskeletal-care-to-other-providers-and-learners-in-primary-care

Abstract Number: 2231

Vitamin D Deficiency States Can be Actively Prevented. Results from a Cross-Sectional Study of over 3000 Patients with Rheumatic Diseases

Elena Nikiphorou[1], Pekka Hannonen[1], Paula Väre[1], Arto Kokko[2], Tuomas Rannio[3,4] and Tuulikki Sokka-Isler[4], [1]Jyvaskyla Central Hospital, Jyvaskyla, Finland, [2]Jyvaskyla Central Hospital, Jyväskylä, Finland, [3]Kuopio University Hospital, Kuopio, Finland, [4]Rheumatology, Jyvaskyla Central Hospital, Jyvaskyla, Finland
First publication: September 29, 2015

SESSION INFORMATION
Session Title: Epidemiology and Public Health Poster III (ACR): Gout and Non-Inflammatory Musculoskeletal Conditions
Session Type: ACR Poster Session C

Background/Purpose: Vitamin D (D25) deficiency has been an ongoing matter of concern, especially in countries at northern latitudes. The effects of D25 deficiency in patients with chronic musculoskeletal conditions could be pronounced resulting in greater disability[1].Despite this, D25 deficiency does not always represent a priority treatment in rheumatology clinics.

Methods: Register-based, cross-sectional study of adult patients (n=5857) seen in an outpatient rheumatology clinic. Calcium & D25 supplementation has been advised and prescribed routinely in this clinic for over 20 years at the first clinic review & without measuring D25 levels, especially in patients on steroids. Patients with suspected rheumatic diseases have their demographic, laboratory, clinical & patient-reported outcomes (PROs) e.g. physical status, fatigue recorded on an electronic tool as part of the normal infra-structure of the clinic. D25 is measured & recorded at baseline as part of routine care & as indicated at follow-up visits in Jan2011-Apr2015. Deficiency is defined as D25 level <50 nmol/l, severe deficiency <20; insufficiency 50-75; optimal levels >75; toxic levels >275. Statistical analysis included uni/multivariate regression models adjusting for age/gender; Spearman's correlation testing, significance assumed at 0.01(2-tailed).

Results: D25 was measured in 3203 (55%) patients (mean age 54; 68% female). Diagnoses included:RA (n=1386), unspecified arthralgia/myalgia (n=400), spondyloarthropathy (192) & psoriatic arthritis (n=138). The overall D25 mean (SD) level was 78 (31), median (IQR) 75 (55, 97). 17.8% had D25 deficiency (8.4% less than 40), only 0.7% severe (<20nmol/l). No patient had toxicity.The highest proportion of D25 deficiency was seen in patients with non-specific arthralgia/myalgia, psoriatic arthritis & fibromyalgia (>20%).The lowest mean level (66) at first visit was seen for the sarcoidosis group, highest (91) for SLE/Sjogren. Among 29 patients with darker skin, 48% had D25 deficiency, while only 8.1% among 3174 patients of Northern European origin were deficient. D25 levels were higher in women vs men, mean 79 vs 76 (p=0.044) & non-smokers vs smokers, mean 78 vs 75 (P=.005). D25 levels correlated with longer follow up in the clinic (Sp.Rho 0.101, P<.001). Higher D25 levels correlated with older age (Sp.Rho 0.205,P<.001), lower BMI (Sp.Rho -0.206, P<.001), more physical exercise (Sp.Rho 0.091, P<.001) & lower education (Sp.Rho -0.049, P=.017). None of the PROs correlated significantly with D25 levels. In multivariate analysis, younger age, non-white background, higher BMI & less frequent exercise significantly predicted D25 deficiency.Patients of non-white background were 5.4 times more likely to have D25 deficiency compared to those of white background.

Conclusion: The proportion of patients with D25 deficiency was low, supporting active calcium/D25 supplementation and patient education as an effective strategy for actively preventing D-25 deficiency. Risk groups identified included patients of non-white background, less physical exercise and higher BMI, the latter two possibly representing surrogates of less healthy lifestyle.

1.Haque UJ, Bartlett SJ. Clin Exp Rheumatol. 2010;28:745-747.

Disclosure: E. Nikiphorou, None; **P. Hannonen**, None; **P. Väre**, None; **A. Kokko**, None; **T. Rannio**, None; **T. Sokka-Isler**, None.

Abstract Number: 2232

Risk of Osteoporotic Fractures with Use of Cyclooxygenase-2 Inhibitors

Deepan Dalal[1], Devyani Misra[2], Christine Peloquin[3], Tuhina Neogi[4], Yuqing Zhang[5], David T. Felson[6] and Maureen Dubreuil[7], [1]Rheumatology, Boston Medical Center, Boston, MA, [2]Medicine, Section of, BUSM, Boston, MA, [3]Clinical Epidemiology Unit, Boston University School of Medicine, Boston, MA, [4]Clinical Epidemiology, BUSM, Boston, MA, [5]BUSM, Boston, MA, [6]Clinical Epidemiology Research and Training Unit, Boston University School of Medicine, Boston, MA, [7]Rheumatology, Boston VA HealthCare System, Boston, MA

First publication: September 29, 2015

SESSION INFORMATION

Session Title: Epidemiology and Public Health Poster III (ACR): Gout and Non-Inflammatory Musculoskeletal Conditions

Session Type: ACR Poster Session C

Background/Purpose: In animal models, cyclo-oxygenase (COX)-2 stimulates osteoclasts through prostaglandin E2 (PGE2). Therefore, non-steroidal anti-inflammatory drugs (NSAIDs) preferentially inhibiting COX-2 (ie-coxibs) should prevent bone resorption. Withdrawal of COX-2 inhibition leads to a rebound effect and excessive osteoclast stimulation which may cause fractures. There are few human studies assessing the risk of fracture with NSAID use. Thus, we examined the risk of osteoporotic fracture with NSAID use, specifically related to the duration and timing of coxib use.

Methods: We conducted a nested case control study using The Health Improvement Network, a population-based electronic medical records database from the UK. We included persons aged 40-89 with hip or knee osteoarthritis (OA). Individuals with malignancy or metabolic bone disease were excluded. NSAID use, including coxibs, was assessed using detailed prescription records.

Incident osteoporotic fracture cases were identified using Readcodes, and the date of fracture was considered the index date. Up to 4 controls were matched to each case by age, gender, year of OA diagnosis and index date.

Fracture risk is expected to depend on the cumulative dose and how recent the drug use was. Hence coxib users were categorized as: (A) Current long term users (>6 months use, and prescription within 3 months of the index date), (B) Current short term users (<6 months use and a prescription within 3 months), (C) Remote long term users (>6 months use and no prescription within 3 months), (D) Remote short term users (<6 months use and no prescription within 3 months), (E) non-selective NSAID users and (F) NSAID non-users. Coxibs included: celecoxib, etorocoxib, lumiracoxib, rofecoxib, and valdecoxib.

Potential confounders included BMI, smoking, alcohol use, history of falls, osteoporosis, other comorbidities and medication use. Conditional logistic regression was conducted to assess the risk associated with each of the coxib exposure categories compared to NSAID non-user.

Results: 4153 cases and 15040 matching controls were identified. Fracture cases had a higher prevalence of osteoporosis, anti-osteoporotic drug use and history of falls. Other baseline demographics were similar between 2 groups (Table). Each of the coxib exposure categories was associated increased risk of fractures. Current coxib use with <6 months of exposure had the highest risk of fracture (Table).

Conclusion: In this large OA population, risk of fracture was most increased with current use of COX-2 inhibitors. While confounding by indication cannot be ruled out, fracture risk was also present with remote use. This topic warrants further research.

Table. Baseline characteristics of fracture cases and matched controls, and odds of fracture with coxib exposure

		Fracture Cases	Controls
Subjects (n)		4153	15040
Age in years, mean ± SD		78.3 ± 7.5	78.0 ± 7.5
Female		3334 (80.3%)	11966 (79.6%)
Chronic Kidney Disease		690 (16.6%)	2586 (17.2%)
Diabetes		594 (14.3%)	2283 (15.2%)
History of falls		1435 (34.6%)	3191 (21.2%)
Hyperlipidemia		692 (16.7%)	2548 (16.9%)
Hypertension		2331 (56.1%)	8791 (58.5%)
Inflammatory Rheumatic Diseases*		349 (8.4%)	1195 (7.9%)
Myocardial infarction/Stroke		820 (19.7%)	2557 (17.0%)
Osteoporosis/osteopenia		554 (13.3%)	1165 (7.7%)
Anti-osteporotic drugs*		448 (10.8%)	1061 (7.1%)
Glucocorticoids		521 (12.5%)	1398 (9.3%)
HRT/SERM		39 (0.9%)	282 (1.9%)
Alcohol Use	Non-drinker	1055 (25.4%)	3781 (25.1%)
	Former drinker	112 (2.7%)	397 (2.6%)
	Current drinker	2550 (61.4%)	9181 (61.0%)
	Missing	436 (10.5%)	1681 (11.2%)
Body Mass Index (BMI)	Underweight	107 (2.6%)	276 (1.8%)
	Normal	1028 (24.8%)	2943 (19.6%)
	Overweight	1246 (30.0%)	4621 (30.7%)
	Obese	734 (17.7%)	3218 (21.4%)
	Missing	1038 (25.0%)	3982 (26.5%)
Smoking	Non-smoker	2428 (58.5%)	9053 (60.2%)
	Former smoker	1171 (28.2%)	4157 (27.6%)
	Current smoker	392 (9.4%)	1214 (8.1%)
	Missing	162 (3.9%)	616 (4.1%)

Adjusted odds of fracture with coxib exposure categories

	Fracture Cases	Controls	Adjusted odds ratio
A. Current long term coxib use	27	67	1.72 (1.08, 2.74)
B. Current short term coxib use	39	76	2.06 (1.38, 3.08)
C. Remote long term coxib use	103	304	1.31 (1.03, 1.67)
D. Remote short term coxib use	326	991	1.18 (1.02, 1.36)
E. Non-coxib NSAID use	1359	4530	1.17 (1.08, 1.27)
F. No NSAID use	2299	9072	1

Inflammatory rheumatic diseases included spondyloarthritides, psoriasis, connective tissue diseases, vasculitidies, and crystal arthropathies; Anti-osteoporotic drugs included bisophsphenates, denosumab and parathyroid hormone; HRT: hormone replacement therapy, SERM: selective estrogen

receptor modulator. Coxib: cyclooxygenase-2 inhibitor. NSAID: non-steroidal anti-inflammatory drug

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Abstract Number: 2233

Predictors of Imminent Fracture Risk in Women Aged >=65 Years with Osteoporosis

Derek Weycker[1], Richard Barron[2], Alex Kartashov[1], John Edelsberg[1], DB Crittenden[3] and A Grauer[3], [1]Policy Analysis Inc. (PAI), Brookline, MA, [2]Amgen, Inc., Thousand Oaks, CA, [3]Amgen Inc., Thousand Oaks, CA

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Background/Purpose: Fractures are the major source of morbidity among women with osteoporosis. However, evidence on factors leading to imminent risk for hip or other non-vertebral fracture within the next 12 months among women aged ≥65 years with osteoporosis is limited.

Methods: A retrospective cohort design and data from the Study of Osteoporotic Fractures (SOF)—which includes 20 years of prospectively collected data on osteoporosis care and outcomes—were employed. The study population comprised all women aged ≥ 65 years in the Caucasian cohort with osteoporosis (T-score ≤ -2.5 at total hip). Hip and other non-vertebral fractures were ascertained over a 1-year follow-up period. Potential predictors of fracture were evaluated using multivariate regression models and included anthropometric measures, BMD, cognitive function, comorbidities, drug use, fracture/fall history, lifestyle variables, medical symptoms, physical function/performance, quality of life, and vision status.

Results: The study population included 2,499 women with osteoporosis who contributed 6,811 observations. During the 1-year follow-up, 2.2% had a hip fracture and 6.6% had any non-vertebral fracture (including hip). Independent predictors of hip and/or non-vertebral fracture included impaired cognitive function, total hip T-score, falls history, fracture history, and lower physical performance (Table).

Table. Independent predictors of 1-year hip and non-vertebral fracture in osteoporotic women aged ≥ 65 years from multivariate regression models

	Hazard Ratios* (95% CI)	
Risk Factors	Hip Fracture	Non-Vertebral Fracture**
Age (vs. referent: 65-74)		
≥ 75 to 79	--	0.9 (0.6-1.3)
≥ 80 to 84	--	1.0 (0.7-1.4)
≥ 85	--	1.4 (0.9-1.9)
Total Hip T-Score (vs. referent: > -3.0 to -2.5)		
≤ -3.5	2.3 (1.5-3.7)	1.9 (1.5-2.5)
> -3.5 to -3.0	1.6 (1.0-2.6)	1.6 (1.2-2.0)
No. of Falls in Last 12 Months (vs. referent: 0)		
1	--	1.2 (0.9-1.5)
≥ 2	--	1.7 (1.3-2.2)
History of Fracture (vs. referent: no history)***		
Non-Vertebral Fracture	1.6 (1.0-2.6)	--
Any Fracture	--	1.4 (1.1-1.7)
Walking Speed (m/s) (vs. referent: >1.0)		
≤ 0.70	3.0 (1.5-5.9)	1.5 (1.1-2.1)
0.70 to 1.0	2.6 (1.4-5.0)	1.4 (1.1-1.9)
Short MMSE ≤ 23 (vs. referent: >23)	1.7 (1.2-2.4)	--
Use of Arms for Chair Stands or Poor/Very Poor Tandem Stand (vs. referent: no use of arms)	1.7 (1.1-2.6)	--
Parkinson's or Stroke (vs. referent: without conditions)	--	1.3 (1.0-1.8)
Smoker, Pack Years (continuous measure)	--	1.0 (1.0-1.0)
Bisphosphonate Use (vs. referent: non-users)	0.3 (0.1-0.9)	--
C statistic (95% CI)	0.71 (0.67-0.76)	0.62 (0.59-0.65)

MMSE: Mini-Mental State Examination

*Only hazard ratios for variables retained in the final model (i.e., those with p-values <0.10) are reported; grouped dichotomous variables were retained if any of the grouped variables had a p-value <0.10

**Includes fracture of any non-vertebral site, defined—by SOF in a composite measure—as an incident, non-traumatic fracture of ankle, clavicle, elbow, face, foot, finger, hand, heel, hip, humerus, knee, lower leg, pelvis, rib, toe, upper leg, or wrist

***After age 50 years

Conclusion: Imminent fracture risk within 12 months among osteoporotic women is higher among those with a history of fracture, history of falls, lower BMD, physical dysfunction, and/or cognitive dysfunction. Careful consideration should be given to identifying this population so that those at imminent risk may be targeted for the appropriate therapy.

Disclosure: D. Weycker, Amgen, 2; **R. Barron**, Amgen Inc., 1,Amgen Inc., 3; **A. Kartashov**, Amgen, 2; **J. Edelsberg**, Amgen, 2; **D. Crittenden**, Amgen, 1,Amgen, 3; **A. Grauer**, Amgen, 1,Amgen, 3.

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Can the Fracture Risk Assessment Tool (FRAX) Also Predict Falls in Older Women?

Shreyasee Amin[1], Elizabeth J. Atkinson[2], Sara J. Achenbach[2], Jeremy R. Crenshaw[3], Kenton R. Kaufman[3], Sundeep Khosla[4] and L. Joseph Melton III[2], [1]Rheumatology and Health Sciences Research, Mayo Clinic, Rochester, MN, [2]Department of Health Sciences Research, Mayo Clinic, Rochester, MN, [3]Orthopedics, Mayo Clinic, Rochester, MN, [4]Endocrinology, Mayo Clinic, Rochester, MN

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Background/Purpose: Falls in the elderly can lead to fragility fractures. Fall prevention targeted at those with high risk for falls could help reduce fractures. Although the fracture risk assessment tool, FRAX, does not directly incorporate fall risk, it does include some risk factors for falls. We examined whether FRAX could predict fall risk in older ambulatory women.

Methods: We studied 125 community-dwelling women, age ≥ 65 years, in whom 124 had femoral neck bone mineral density (FN BMD, g/cm^2) and US-FRAX scores (% 10-yr risk for major osteoporotic fractures [FRAX-OP] and hip fractures [FRAX-Hip]) reliably determined at baseline. Falls were tracked longitudinally every two weeks over 1 year by self-reported questionnaire. We examined fall risk for FRAX-OP and FRAX-Hip scores separately. For analyses, we created 4 groups for each FRAX score, using FRAX score cutoffs for osteoporosis [OP] treatment (≥20% for FRAX-OP and ≥3% for FRAX-Hip) as the initial basis for groupings. We then examined whether FRAX scores (by groups and also as a continuous variable) predicted falls using an Andersen-Gill model, adjusted for age and prior fall history.

Results: The median (range) age, FN BMD and FRAX scores of women were 77 (65-92 years), 0.81 (0.54-1.20 g/cm^2), 14.2 (3.3-56.9%, FRAX-OP) and 3.5 (0.1-45.8%, FRAX-Hip), respectively. There were 28 women (23%) with FRAX-OP ≥20% and 67 (53%) with FRAX-Hip ≥3%. There were 47 women (38%) who reported a fall in the year prior to their study visit. Compliance with all fall tracking questionnaires was 97.5%. Over follow-up, 73 women fell, 38 of whom had more than one fall, for a total of 157 falls over 125 person-years of follow-up [p-y] (1.3 falls/p-y). There was a trend for higher fall risk with greater FRAX score group (FRAX-OP, p=0.17; FRAX-Hip, p=0.02) **[Table]**. But the association appeared non-linear when using FRAX as a continuous variable in analyses, with decreasing fall risk in women having the very highest (>25%, FRAX-OP and >10%, FRAX-Hip) scores [data not shown]. Women with some of the highest FRAX scores were more likely to have a parent with hip fracture, increasing the FRAX score, but which may not necessarily have influenced fall risk. They also reported being less active, which may have reduced their likelihood for falling over follow-up.

Conclusion: We found a higher risk of future falls in older women with greater FRAX scores, including at some scores below the recommendations for OP treatment. That said, the non-linear association we observed at the highest FRAX scores suggests that information beyond FRAX would still be necessary to distinguish those at high vs. low fall risk.

FRAX-OP Score [%] (N per Group)	Falls/ P-Y	Hazard Ratio (95% CI)	FRAX-Hip Score [%] (N per Group)	Falls/ P-Y	Hazard Ratio (95% CI)
<10 (N=26)	0.8	referent	<1.5 (N=31)	0.8	referent
10-14.9 (N=41)	1.2	1.9 (0.8, 4.3)	1.5-2.9 (N=26)	0.9	1.3 (0.7, 2.6)
15-19.9 (N=29)	1.5	2.3 (1.1, 4.9)	3.0-5.9 (N=37)	2.0	2.5 (1.3, 4.9)
≥20 (N=28)	1.5	2.6 (1.1, 6.3)	≥6 (N=30)	1.2	1.8 (0.9, 3.9)

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Shocking? a Systematic Review of Adrenal Insufficiency in Adults on Oral Steroids

Rebecca M Joseph[1], Louise Hunter[2], David W. Ray[2] and William G Dixon[3], [1]NIHR Manchester Musculoskeletal Biomedical Research Unit, Manchester, United Kingdom, [2]Institute of Human Development, The University of Manchester, Manchester, United Kingdom, [3]Manchester Academic Health Sciences Centre, Arthritis Research UK Centre for Epidemiology, The University of Manchester, Manchester, United Kingdom

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Background/Purpose: One percent of the adult population are, at any one time, prescribed oral glucocorticoids (GC). GCs are known to be associated with hypothalamic-pituitary-adrenal axis suppression. However, there remains uncertainty regarding: (1) the prevalence of GC-induced adrenal insufficiency (AI); (2) the effects of GC dose and duration; and (3) the time course of adrenal recovery and how GCs should be withdrawn. We undertook a systematic literature review to address these questions.

Methods: Searches were performed in MEDLINE and Web of Science in November 2014. Eligible papers studied adult patients with an indication for long-term GCs, exposure to oral GCs, and adrenal function tests. Screening was performed in duplicate and additional articles identified through citation screening. Three categories each for increasing dose, duration and cumulative dose were assessed.

Results: From 645 screened papers, 42 met the inclusion criteria (14 randomised controlled trials and 28 observational studies). The prevalence of AI ranged from 0-100%. When examined within exposure categories, the prevalence still ranged from 0-100%, with medians of 33-43%. Only exposure <5mg prednisolone equivalent dose/day had reduced AI (range 0-36%, median 15%). There was evidence of persisting adrenal suppression 1-3 years after GC cessation. Only 5 studies reported weaning of GCs and these were too heterogeneous in study design to draw useful conclusions.

Conclusion: Significant variation exists in the reported prevalence of AI after oral GC therapy, irrespective of exposure category. There is evidence, albeit limited, that even low doses can suppress adrenal function, and some patients may have AI after several years of cessation. We suggest clinicians be vigilant for AI with all doses and durations of oral GC therapy. The evidence base supporting current practice, particularly with regards to withdrawal of steroids, is scant. There is imperative need for large-scale prospective studies to guide future practice.

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Abstract Number: 2236

Global Prevalence of Hyperuricemia: A Systematic Review of Population-Based Epidemiological Studies

Emma Smith[1] and Lyn March[2], [1]Department of Rheumatology, Northern Clinical School, Institute of Bone and Joint Research, Kolling Institute, University of Sydney & Department of Rheumatology, Royal North Shore Hospital, St. Leonards, Sydney, Australia, [2]Department of Rheumatology, Northern Clinical School, Institute of Bone and Joint Research, Kolling Institute, University of Sydney & Department of Rheumatology, Royal North Shore Hospital, St Leonards, Sydney, Australia

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Background/Purpose: Hyperuricemia, or raised serum uric acid (SUA), is the condition closely associated with gout due to the deposition of monosodium urate crystals in peripheral joints and soft tissues. Gout is a chronic musculoskeletal (MSK) disease affecting 1-2% of the world's population and has been identified as one of the major MSK disorders contributing to the rising MSK burden in the Global Burden of Diseases (GBD), Injuries and Risk Factors 2010 & 2013 Studies. Hyperuricemia has also been reported as an independent risk factor for coronary heart disease, the metabolic syndrome, diabetes, stroke and incident mortality. Broader dissemination of hyperuricemia prevalence data should facilitate improvement of gout and other chronic diseases prevention and management strategies.

The purpose of this study is to systematically review published literature and capture country-specific population-based data on the global prevalence of hyperuricemia.

Methods: Using the following terms: 'gout or hyperuri*' combined with the terms: 'prevalen* or epidemiolo*', literature searches were performed for the period Jan 1980 to May 2015 on MEDLINE, EMBASE, CINAHL, CAB Abstracts, WHO Library (WHOLIS) and OpenSIGLE. Inclusion and exclusion criteria were set to identify relevant population-based epidemiological studies for the data extraction. Data were extracted into an Excel spreadsheet, and grouped according to the GBD classified 21 world regions.

Results: Published population-based prevalence data of hyperuricemia were reported in 13 of the 21 GBD regions, and a total of 24 countries. Although hyperuricemia was relatively more prevalent in Asia regions, the lowest (Papua New Guinea 1%) and highest (Marshall Islands 85%) reported prevalence were both in Oceania. The widest range of prevalence was observed in East Asia. It was also noted that over two decades, the prevalence of hyperuricemia in High Income Asia Pacific (Japan) increased by 5 fold. Range of the extracted prevalence data reported by various studies are shown in the table below. The data were for both females & males combined unless specified. For the eight regions marked with "No data", no published population-based epidemiological studies on hyperuricemia were identified during the specified systematic review period.

Prevalence of Hyperuricemia in GBD Regions

GBD Region	Prevalence (%)
Central Asia	
• Mongolia	5 (Females) / 18 (Males)
East Asia	
• China	6-25
• Taiwan	10-52
High Income Asia Pacific	
• Japan	4 (1980s) / 20-26 (2000s)
• South Korea	5
South Asia	No data
Southeast Asia	
• Indonesia	18
• Philippines	25
• Seychelles	25
• Thailand	9-11
Australasia	
• New Zealand	8 (non-Maori) / 17-19 (Maori)
Caribbean	No data
Central Europe	No data
Eastern Europe	
• Russia	17
Western Europe	
• Italy	9-12
• Spain	5-11
• Sweden	10-16
Andean Latin America	No data
Central Latin America	
• Mexico	11
Southern Latin America	No data
Tropical Latin America	
• Brazil	13
North Africa and Middle East	
• Iran	8
• Saudi Arabia	8
• Turkey	12
High Income North America	
• USA	22 (Females) / 21 (Males)

Oceania	
• Marshall Islands	85
• Papua New Guinea	1
• Samoa	33
Central Sub-Saharan Africa	No data
East Sub-Saharan Africa	No data
Southern Sub-Saharan Africa	No data
West Sub-Saharan Africa	
• Nigeria	17

Conclusion: Elevation of serum uric acid (SUA) is evident throughout all regions of the world, where it has been measured, but considerable regional variation exists. Significant increases are evident in regions that have trend data available. The rising burden of gout together with increasing burden of obesity and ageing globally further emphasises the importance and urgent need for the development of prevention and management strategies for hyperuricemia and gout. Population-based epidemiological research and report on hyperuricemia and gout, particularly in regions of the world with no data, should be encouraged.

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Abstract Number: 2237

Effects of Coffee Consumption on Serum Uric Acid. a Systematic Review and Meta-Analysis

Jae-Bum Jun[1], Shin-Young Yim[2], Hyun Jung Kim[3], Kyu Yong Park[4], Hyeong Sik Ahn[3], Sun Hee Kim[4] and Eun Ji Park[4], [1]Rheumatology, Hanyang University Hospital for Rheumatic Diseases, Seoul, South Korea, [2]Department of Physical Medicine and Rehabilitation, Ajou University School of Medicine, Suwon, South Korea, [3]Department of Preventive Medicine, Korea University College of Medicine, Seoul, South Korea, [4]Department of Physical Medicine and Rehabilitation, Ajou University Hospital, Suwon, South Korea
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Background/Purpose: Findings on the effect of coffee consumption on serum uric acid has been conflicting. The aim of this systematic review and meta-analysis is to analyze the literature exploring the effect of coffee consumption on serum uric acid.

Methods: We conducted a systematic review to examine the effect of coffee consumption on serum uric acid via meta-analysis. We searched MEDLINE, EMBASE, the Cochrane library, and KoreaMed for all articles published before January 2015. Studies with quantitative data on coffee consumption and serum uric acid level were included. Coffee consumption and serum uric acid level were identified with or without prevalence of gout.

Results: Nine studies were included in the review (published between 1999 and 2014), including a total of 41,217 subjects. Six were from registry and 3 were cross-sectional study. Men showed significantly lower serum uric acid with coffee intake of 1-3 cups/day than coffee intake of <1 cup/day (-0.12 mg/dL [95% CI:-0.17 to 0.08], $I^2 = 41\%$; $p<0.00001$). Women showed significantly lower serum uric acid with coffee intake of 4-6 cups/day than coffee intake of <1 cup/day (-0.11 mg/dL [95% CI:-

0.20 to -0.02]; p=0.02). Meta-analysis showed that the amount of coffee intake of 1 cup/day or more was significant reduction of the prevalence of gout with negative correlation with the amount of daily coffee for both gender.

Conclusion: The review shows that there is lowering effect of coffee on both serum uric acid and the prevalence of gout for both genders. However, women need more coffee intake for lowering serum uric acid than men do. This is the first systematic review on the effect of coffee consumption on serum uric acid, along with gender difference in the amount of coffee for lowering effect of coffee on serum uric acid. There is a large degree of heterogeneity in the results, and the sources of this need to be investigated.

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Abstract Number: 2238

Body Mass Index Modulates the Relationship Between Sugar-Sweetened Beverage Intake and Serum Urate Concentration

Nicola Dalbeth[1], Amanda Phipps-Green[2], Meaghan House[1], Gregory Gamble[1], Anne Horne[1], Lisa K. Stamp[3] and Tony R. Merriman[2,4], [1]Department of Medicine, University of Auckland, Auckland, New Zealand, [2]University of Otago, Dunedin, New Zealand, [3]Medicine, University of Otago, Christchurch, Christchurch, New Zealand, [4]Biochemistry Dept, PO Box 56, University of Otago, Dunedin, New Zealand

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Background/Purpose: Elevated body mass index (BMI) and intake of sugar-sweetened beverages (SSB) are both modifiable risk factors for hyperuricaemia and gout. BMI can modulate the influence of non-modifiable genetic variants on serum urate. The influence of BMI may also modulate associations between modifiable factors, such as SSB intake, and serum urate. The aim of this study was to determine whether the association between SSB intake and serum urate is moderated by BMI.

Methods: The effects of chronic SSB intake on serum urate were assessed in a cross-sectional study of 12,870 people without gout from the Atherosclerosis Risk in Communities (ARIC), Framingham Heart Study (FHS) and New Zealand datasets. The effects of an acute fructose load on serum urate and fractional excretion of uric acid (FEUA) were examined over 180 minutes in a short-term intervention study. In both analyses, the responses were compared in those with BMI <25mg/kg^2 (low BMI) and ≥25mg/kg^2 (high BMI).

Results: In the cross-sectional study, increased chronic SSB intake was associated with higher serum urate in the entire group (compared with no intake, BMI-adjusted P=0.048 for low SSB intake and P=1.1x10^{-4} for high SSB intake) (Table). There was no association between SSB intake and serum urate within the low BMI group. In contrast, increased SSB intake was associated with higher serum urate in the high BMI group (P=3.9x10^{-4} for low SSB intake and P=5.3x10^{-7} for high SSB intake). The difference in serum urate between the SSB categories was significantly greater in the high BMI group than in the low BMI group ($P_{BMI\ group}$=0.005). The difference in serum urate was higher in the high BMI group for both low SSB intake ($P_{BMI\ group}$=0.002) and high SSB intake ($P_{BMI\ group}$=0.001). In the acute fructose loading study, serum urate was increased in the high BMI group at baseline and throughout the observation period ($P_{BMI\ group}$<0.0001), but there were similar serum urate changes in both BMI groups in response to the fructose load ($P_{interaction}$=0.99). The baseline FEUA was similar between the two BMI groups. However, following the fructose load, FEUA responses in the BMI groups differed ($P_{interaction}$<0.0001), with increased FEUA at 120 minutes and 180 minutes in the low BMI group and reduced FEUA at 60 minutes in the high BMI group.

Conclusion: BMI modulates serum urate responses to chronic sugar-sweetened beverage intake and renal tubular uric acid handling in response to an acute fructose load. In addition to other health benefits, avoidance of sugar-sweetened beverages may be particularly important in those with overweight/obesity to prevent hyperuricaemia and reduce gout risk.

Table. Difference in serum urate for chronic sugar-sweetened beverage intake stratified by BMI group. The difference in serum urate in the overall SSB category is the average difference from sugar-sweetened beverage category 1 to category 2 to category 3 (i.e. 0, to >0 to <2, to ≥2).

		Per SSB Category		Overall SSB Category		
	SSB drinks/day	**Difference in serum urate, 95% CI (mmol/L)**	**P compared with referent group (0 SSB drinks/day)**	**Difference in serum urate, 95% CI (mmol/L)**	**P**	**P comparing BMI < 25 & ≥25**
All participants (n=12,127)*	0	-	-	0.005 (0.003-0.007)	$4.0x10^{-5}$	-
	>0 to <2	0.004 (0.000-0.008)	0.048			
	≥2	0.009 (0.005-0.014)	$1.1x10^{-4}$			
BMI < 25 (n=4,748)	0	-	-	0.001 (-0.002-0.005)	0.494	0.005
	>0 to <2	-0.003 (-0.009-0.003)†	0.36			
	≥2	0.001 (-0.006-0.008)††	0.80			
BMI ≥25 (n=7,379)	0	-	-	0.008 (0.005-0.011)	$9.3x10^{-7}$	
	>0 to <2	0.011 (0.005-0.016)†	$3.9x10^{-4}$			
	≥2	0.017 (0.010-0.023)††	$5.3x10^{-7}$			

All analysis adjusted by sample set, age, sex, fruit intake (continuous variable), kidney disease, hypertension, relatedness.

*analysis adjusted by BMI.

† $P_{difference}$ between BMI groups =0.002, †† $P_{difference}$ between BMI groups=0.001

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View Abstract and Citation Information Online - http://acrabstracts.org/abstract/body-mass-index-modulates-the-relationship-between-sugar-sweetened-beverage-intake-and-serum-urate-concentration

Abstract Number: 2239

Prevalence of Gout and Hyperuricemia and Association with Fat Mass and Fat Free Mass: Results from a Population-Based Study

Tiffany K. Gill[1], Kimberley Ting[2], Graeme R Tucker[1], E. Michael Shanahan[3,4] and **Catherine Hill**[5,6], [1]Medicine, The University of Adelaide, Adelaide, Australia, [2]Rheumatology, The Queen Elizabeth Hospital, Adelaide, Australia, [3]Flinders University, Adelaide, Australia, [4]Repat General Hospital, Flinders University, Adelaide, Australia, [5]The Health Observatory, The University of Adelaide, Adelaide, Australia, [6]Rheumatology Unit, The Queen Elizabeth Hospital, Woodville, Australia
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SESSION INFORMATION
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Session Type: ACR Poster Session C

Background/Purpose: Gout and hyperuricemia are major co-morbid health issues worldwide, with a known association with metabolic syndrome. Only one previous study based in Vietnam, has investigated the association between body composition and

gout[1]. The aim of this study was to determine the prevalence of self-reported medically diagnosed gout and laboratory determined hyperuricemia and to examine whether fat mass and free fat mass were predictors of gout in a population-based cohort.

Methods: The North West Adelaide Health Study (NWAHS) is a longitudinal cohort study with three stages of data collection. Each stage comprised a self-complete questionnaire, clinic assessment and Computer Assisted Telephone Interview (CATI). In Stage 2 (2004-06), Dual Energy X-ray Absorptiometry (DXA) scans were undertaken on those aged 50 years and over. Additional data included demographics and body mass index (BMI). In Stage 3 (2008-10) participants were asked if a doctor had ever diagnosed them with gout, and a serum uric acid (SUA) measurement was obtained. Participants were defined as having gout if they had self-reported medically diagnosed gout or were taking any gout specific medication (allopurinol, colchicine, probenecid). Hyperuricemia was defined as a SUA >=0.45mmol/l. The association between reporting gout or hyperuricemia in Stage 3 and the measurements of BMI, fat mass, fat mass index, fat free mass and fat free mass index were all examined, using logistic regression analysis.

Results: The prevalence of gout was 9.6% (15.2% and 5.2%, $p<0.001$ for males and females respectively) and hyperuricemia was 6.8% (males vs females, 11.0% vs 3.5%, $p<0.001$). The presence of both gout and hyperuricemia was not independently associated with fat mass index but was associated with all other measures. The association with higher BMI and fat free mass index remained after adjustment for age and sex for gout, and the association with fat mass and fat mass index became significant. The association with fat free mass remained significant for hyperuricemia even after adjustment of age and sex. When adjusted for body composition, fat mass and fat mass index were significantly associated with gout (Table 1).

Conclusion:

This is the first study of body composition and gout in a Western population. The prevalence of gout and hyperuricemia is high. BMI and body composition measurements have been shown to be predictors of gout and hyperuricemia in a community sample and may need to be considered when treating these conditions.

1 Dao HH, Harun-Or-Rashid M, Sakamoto J. Body composition and metabolic syndrome in patients with primary gout in Vietnam. Rheumatology. 2010;49:2400-7.

Table 1: Unadjusted and adjusted association between gout and hyperuricemia and BMI and body composition

	BMI	Fat mass[a]	Fat mass index[a]	Fat free mass[b]	Fat free mass index[b]
Unadjusted	OR (95% CI) p-value	OR (95% CI) p-value	OR (95% CI) p-value	OR (95% CI) p-value	OR (95% CI) p-value
No gout	1.00	1.00	1.00	1.00	1.00
Gout	1.08 (1.03-1.13) 0.001	1.02 (0.99-1.04) 0.130	1.03 (0.97-1.09) 0.339	1.04 (1.02-1.06) <0.001	1.26 (1.15-1.39) <0.001
Adjusted for age and sex					
No gout	1.00	1.00	1.00	1.00	1.00
Gout	1.11 (1.06-1.17) <0.001	1.05 (1.02-1.08) <0.001	1.16 (1.07-1.24) <0.001	1.03 (0.99-1.07) 0.10	1.24 (1.08-1.41) 0.002
Adjusted for age, sex and body composition					
No gout		1.00	1.00	1.00	1.00
Gout		1.05 (1.02-1.08) 0.002	1.12 (1.04-1.22) 0.006	1.00 (0.96-1.05) 0.93	1.12 (0.96-1.30) 0.160
	BMI	**Fat mass[a]**	**Fat mass index[a]**	**Fat free mass[b]**	**Fat free mass index[b]**
Unadjusted	OR (95% CI) p-value	OR (95% CI) p-value	OR (95% CI) p-value	OR (95% CI) p-value	OR (95% CI) p-value
No hyperuricemia	1.00	1.00	1.00	1.00	1.00
Hyperuricemia	1.08 (1.02-1.14) 0.008	1.02 (0.99-1.05) 0.13	1.02 (0.95-1.09) 0.63	1.05 (1.03-1.08) <0.001	1.28 (1.15-1.43) <0.001
Adjusted for age and sex					
No hyperuricemia	1.00	1.00	1.00	1.00	1.00
Hyperuricemia	1.11 (1.04-1.18) 0.001	1.05 (1.02-1.08) 0.002	1.13 (1.04-1.23) 0.004	1.06 (1.02-1.11) 0.009	1.24 (1.06-1.44) 0.008
Adjusted for age, sex and body composition					
No hyperuricemia		1.00	1.00	1.00	1.00
Hyperuricemia		1.04 (1.00-1.07) 0.030	1.09 (1.00-1.20) 0.063	1.04 (0.99-1.09) 0.144	1.15 (0.96-1.36) 0.130

[a]Models with fat mass and fat mass index adjusted for fat free mass and fat free

mass index respectively

[b]Models with fat free mass and fat free mass index adjusted for fat mass and fat mass index respectively

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Abstract Number: 2240

Effectiveness of Allopurinol in Achieving and Sustaining Target Serum Urate: A Study Using Large Intergrated National Health Network

Jasvinder A. Singh[1], Shuo Yang[2], S. Louis Bridges Jr.[3] and Kenneth G. Saag[4], [1]Birmingham VAMC, Birmingham, AL, [2]Clinical Immunology/Rheumatology, University of Alabama at Birmingham, Birmingham, AL, [3]Clinical Immunology and Rheumatology, University of Alabama at Birmingham, Birmingham, AL, [4]University of Alabama at Birmingham, Birmingham, AL

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SESSION INFORMATION

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Session Type: ACR Poster Session C

Background/Purpose:

To comprehensively assess patient, comorbidity, physician, system, health care access and disease factors associated with the ability to achieve and maintain target serum urate (sUA) with allopurinol in patients with gout.

Methods:

We used National VA national databases from 2002-2012. Patients were eligible if they had ≥2 outpatient or ≥1 inpatient encounters with an International Classification of Diseases-ninth version (ICD-9) code 274.xx for gout, and met 12-month observability rule. Index allopurinol use was defined as the filling of a new allopurinol prescription with no allopurinol exposure in the previous 121 days. Treatment successes were defined as the achievement of: (1) post-index sUA <6 mg/dl; and (2) post-index sUA <6 mg/dl that was sustained, as defined by achievement of: (1) post-index sUA <6 mg/dl and at least one more follow-up sUA that was <6 mg/dl.

Results:

41,153 unique patients with 47,072 episodes contributed to analyses of achieving target sUA ≤ (success 1) and 17,402 unique patients with 18,323 episodes to achieving and maintaining target sUA (success 2). In multivariable-adjusted models, the following were associated with significantly higher odds of achieving both successes 1 and 2: older age, normal BMI (18.5-25 kg/m2), female sex, black/african-american race, peptic ulcer disease, severe liver disease, hypertension, rheumatologist as the main provider rather than non-rheumatologist, Midwest location for the health care facility, a lower hospital bed size, service-connection conditions of 50% or more, longer distance to the nearest VA facility, lower pre-index sUA, higher allopurinol start and end dose, higher allopurinol adherence, previous use of allopurinol with in 1 year and normal/recommended or fast allopurinol dose escalation. Diabetes with complications and paraplegia, were associated with increased odds of not achieving success 1 and 2. Additionally, increasing BMI and greater baseline sUA showed a clear linear trend toward not achieving success 1 and success 2.

Conclusion:

In this study, we identified several important factors associated with achieving and maintaining sUA <6 mg/dl. This knowledge provides several new potential modifiable targets for improving the ability to lower serum urate with allopurinol pharmacotherapy and sustain a therapeutic target in patients with gout.

Table 1. Multivariable-adjusted association of factors with the ability to achieve and maintain target sUA of < 6mg/dl*

	Success 1: Achieving post-index sUA <6 mg/dl	Success 2: Achieving and maintaining post-index sUA <6 mg/dl
	Odds Ratio (95% CI)	Odds Ratio (95% CI)
Baseline Age	**1.01 (1.01,1.02)**	**1.02 (1.01,1.02)**
Female Sex	**1.77 (1.38,2.27)**	**1.49 (1.03,2.16)**
BMI Group (Ref=18.5 to <25)		
<18.5	**0.77 (0.64,0.93)**	0.85 (0.63,1.16)
25 to <30	**0.84 (0.77,0.91)**	**0.85 (0.74,0.97)**
30 to <35	**0.73 (0.67,0.80)**	**0.70 (0.62,0.80)**
35 to <40	**0.63 (0.57,0.69)**	**0.63 (0.55,0.73)**
40 to <45	**0.55 (0.50,0.62)**	**0.52 (0.44,0.61)**
≥45	**0.51 (0.46,0.57)**	**0.54 (0.46,0.64)**
Race (Ref=White)		
Black/African-American	**1.16 (1.09,1.23)**	**1.22 (1.11,1.34)**
Hispanic	0.89 (0.80,1.00)	0.84 (0.71,1.00)
Other	0.83 (0.75,0.92)	0.73 (0.62,0.86)
Unknown	0.86 (0.76,0.98)	0.94 (0.76,1.16)
Baseline Charlson (Ref = 0)		
Peptic ulcer disease	**1.55 (1.29,1.87)**	**1.42 (1.10,1.84)**
Diabetes	**0.92 (0.88,0.98)**	**0.89 (0.82,0.97)**
Diabetes with complications	**1.20 (1.11,1.31)**	1.06 (0.94,1.19)
Paraplegia	**1.55 (1.05,2.30)**	1.45 (0.85,2.47)
Renal disease	1.01 (0.93,1.10)	**0.88 (0.79,0.99)**
Malignancy	**1.15 (1.07,1.24)**	1.00 (0.90,1.11)
Severe liver disease	**2.48 (1.54,3.98)**	**1.98 (1.02,3.83)**
Hypertension	**1.12 (1.05,1.20)**	**1.15 (1.03,1.28)**
Provider Specialty (Ref=Rheumatology)		
Other	**0.70 (0.63,0.77)**	**0.73 (0.64,0.84)**
Start Dose Group (Ref=≤100 mg/day)		
>100 to ≤200	**1.16 (1.06,1.27)**	**1.17 (1.04,1.31)**
>200 to ≤300	**1.15 (1.03,1.30)**	1.11 (0.96,1.28)
>300	1.04 (0.84,1.30)	1.03 (0.76,1.41)
End Dose Group (Ref=≤100 mg/day)		
>100 to ≤200	**2.00 (1.82,2.19)**	**2.03 (1.79,2.29)**
>200 to ≤300	**4.16 (3.70,4.67)**	**4.53 (3.93,5.22)**
>300	**4.09 (3.38,4.95)**	**4.59 (3.64,5.77)**
MPR Group (Ref, >0.8)		
<=0.4	-	-
>0.4 to ≤0.6	**0.04 (0.03,0.05)**	**0.08 (0.06,0.13)**
>0.6 to ≤0.8	**0.06 (0.06,0.07)**	**0.11 (0.10,0.13)**
Previous Usage in 1 Year Baseline (Ref=0)	**0.59 (0.56,0.63)**	**0.60 (0.55,0.66)**
Dose Escalation (Ref=No)		
Fast	**3.27 (2.27,4.70)**	**2.73 (1.43,5.22)**
Normal	**1.87 (1.53,2.30)**	**2.58 (1.91,3.48)**
Slow	**0.48 (0.44,0.53)**	**0.60 (0.54,0.68)**
Gout Duration	0.98 (0.97,1.00)	1.00 (0.98,1.01)
Baseline sUA Value Group (Ref=6 to <8)		
0 to <6	**2.71 (2.50,2.95)**	**2.50 (2.18,2.86)**
8 to <10	**0.65 (0.61,0.69)**	**0.65 (0.59,0.71)**
10 to <12	**0.46 (0.42,0.49)**	**0.44 (0.39,0.49)**
≥12	**0.37 (0.33,0.42)**	**0.40 (0.34,0.48)**

*** The following variables were significantlying associated with increased odds of achieving success 1 and success 2. (Ref= Mid-West):** Mid-Atlantic,,North East,South,West; **Operating Bed (Ref= >200):** ≤50, >50 to ≤100, >100 to ≤200; **Urban Rural (Ref=Urban)**; **Affiliated to University (Ref=No)**; **OPC Type (Ref=VAMC)**: CBOC, Other, VAMC & CBOC;

MEANS (Ref=AN): AS,C, G/N/U/X; **Service Connection (Ref=0%):** >0 to <50%, ≥50%,None;**Distance from Closest VA Facility within Network**

Disclosure: J. A. Singh, None; **S. Yang**, None; **S. L. Bridges Jr.**, None; **K. G. Saag**, Amgen, 2,Eli Lilly and Company, 2,Merck Pharmaceuticals, 2,Amgen, 5,Eli Lilly and Company, 5,Merck Pharmaceuticals, 5.

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Abstract Number: 2241

Treating to Target in Gout: The Epidemiology of Serum Urate Measurement Among Patients with Incident Gout in Usual Care Settings in the United States

Marsha Raebel[1], Liza Reifler[1], David Tabano[1], Kristin Goddard[1], Andrew Sterrett[1], T Craig Cheetham[2], Leslie Harrold[3], Daniel Sapp[4], Mark Schmidt[4], Javier Nuevo[5], Robert Morlock[6] and Gregory Nichols[4], [1]Institute for Health Research, Kaiser Permanente Colorado, Denver, CO, [2]Kaiser Permanente Southern California, Pasadena, CA, [3]Dept of Medicine, UMass Medical School, Worcester, MA, [4]Center for Health Research, Kaiser Permanente Northwest, Portland, OR, [5]AstraZeneca, Madrid, Spain, Madrid, Spain, [6]Ardea Bioscience, San Diego, CA

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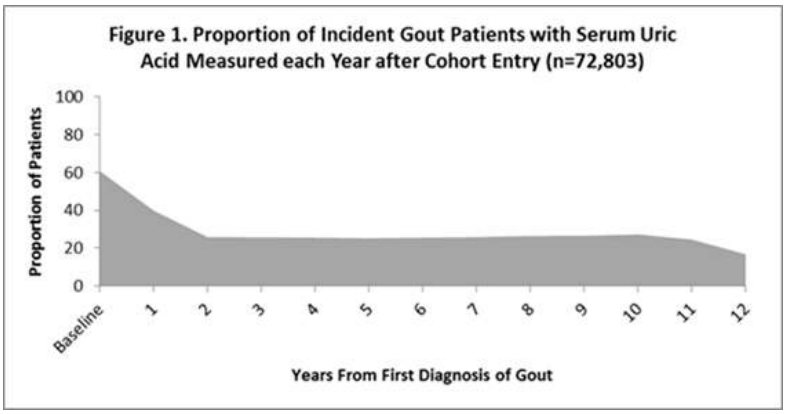
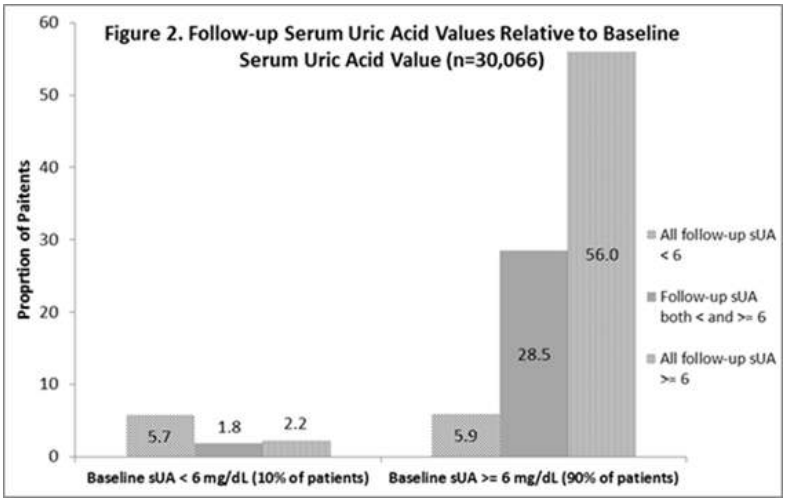
Background/Purpose: American College of Rheumatology (ACR) guidelines recommend lowering serum urate (sUA) to a target value in patients with gout to prevent crystal deposition/promote crystal dissolution. At a minimum, sUA should be reduced to <6 mg/dL; in patients with tophaceous deposits/greater disease severity, the sUA target may be <5. sUA measurement is a necessary step in the treat to target paradigm, but little is known about sUA measurement practices in usual care or attainment of target sUA. The purpose of this work was to characterize sUA measurement and sUA target attainment in patients with incident gout in usual ambulatory care settings in the United States.

Methods: This retrospective cohort study was conducted at 3 geographically, demographically, and socioeconomically diverse sites of an integrated healthcare delivery system. The source population included adults enrolled in the health plan 2001-2010. Patients with >=1 coded gout diagnosis were identified; patients with >=2 years enrollment prior to first diagnosis and with no urate-lowering medication or colchicine dispensings prior to diagnosis were considered incident cases. The participating sites have similarly formatted administrative, pharmacy, lab results, and electronic health records databases that enabled collection of demographic, clinical, medication, and sUA data for each patient from cohort entry through 2013 or until the patient was censored from the cohort, whichever occurred first. Descriptive statistics were used to characterize the cohort and to examine sUA measurement and values at baseline and over time.

Results: The cohort included 72,803 patients, mean (SD) age 60.3 (14.6); 30% female; 15% Hispanic; 57% white, 13% black, 10% Asian; 38% (n=27,780) were prescribed urate-lowering medication after diagnosis. Across mean study follow-up of 5.5 (3.1) years, 87% (n=63,366) had one or more sUA assessments. The proportion of patients with sUA measured each year after diagnosis is shown in Figure 1. The average number of sUA measurements was 3.4 (4.4) per patient, with a mean of 1.5 (1.4) years between measurements. Only 20% (n=12,491) of patients achieved mean sUA <6. As shown in Figure 2, 56% (16,827 of 30,066 with >=2 sUA) of patients never had any sUA <6.





Conclusion: Fully 80% of patients with incident gout in these usual care settings in the United States did not achieve target mean sUA <6 mg/dL. Although most patients had at least one sUA assessment, sUA assessment was infrequent. Given that most patients with incident gout do not reach target sUA, more frequent sUA measurement is urged to enable treating to target.

Disclosure: M. Raebel, AstraZeneca, 2; **L. Reifler**, AstraZeneca, 2; **D. Tabano**, AstraZeneca, 2; **K. Goddard**, AstraZeneca, 2; **A. Sterrett**, AstraZeneca, 2; **T. C. Cheetham**, AstraZeneca, 2; **L. Harrold**, AstraZeneca, 2; **D. Sapp**, AstraZeneca, 2; **M. Schmidt**, AstraZeneca, 2; **J. Nuevo**, AstraZeneca, 3; **R. Morlock**, AstraZeneca, 3; **G. Nichols**, AstraZeneca, 2.

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Abstract Number: 2242

Compliance with Allopurinol Among Hypertensive Patients with Gout Diagnosis and the Relationship to Onset of End-Stage Renal Disease

Sylvie Perreault[1], Javier Nuevo[2], Scott Baumgartner[3] and **Robert Morlock**[4], [1]University of Montreal, Montreal, QC, Canada, [2]AstraZeneca, Madrid, Spain, Madrid, Spain, [3]Ardea Biosciences, Inc., San Diego, CA, [4]4939 Directors Place, Ardea Biosciences, Inc., San Diego, CA

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Session Type: ACR Poster Session C

Background/Purpose: The risk of end-stage renal disease (ESRD) in both hypertension and gout has been examined in the clinical literature. However, the impact of allopurinol adherence on primary prevention of ESRD has not been assessed. The objective of this study was to evaluate the impact of better adherence to allopurinol therapy on ESRD onset.

Methods: A cohort of 2752 patients with gout diagnosis was reconstructed using the Québec RAMQ and MED-ECHO administrative databases. Patients were eligible if they were new users of allopurinol, aged between 45 and 85 years, had a diagnosis of hypertension and were treated with an antihypertensive drug between 1997 and 2007. A nested case-control design was used to study the occurrence of ESRD. Every case of ESRD was matched for age, sex and duration of follow-up for up to 15 controls. Adherence level was assessed as a medication possession ratio. Conditional logistic regression models were used to estimate the rate ratio (RR) of ESRD adjusting for covariables.

Results: Patients had a mean age of 68 years, 82% were men, close to 50% had ≥1 cardiovascular disorder, 33% had dyslipidemia, 21% had diabetes, 15% had chronic kidney disease, 21% were thiazides users, 33% were low-dose aspirin users, and 42% were NSAID users. Clinical characteristics among patients adherent to allopurinol were similar to those who were non-adherent. Major risk factor for ESRD onset was chronic kidney disease at stages 1 to 3 (RR: 8.00; CI: 3.16 -22.3) and the severity of hypertension (≥ 3 vs < 3 treatments with antihypertensives) was a trending risk factor as a crude estimate (RR: 1.94; CI: 0.68–5.51). Of 341 patients, cases (n=22) and controls (n=319), high adherence level (≥80%) to allopurinol therapy, compared with lower adherence level (<80%), was associated with a lower rate of ESRD onset (RR: 0.35; confidence interval [CI]: 0.13–0.91).

Conclusion: This population-based study suggests that better adherence to allopurinol may be associated with risk reduction of new-onset ESRD in the hypertensive population. Further research is needed to confirm this risk, as this study was limited by the small number of cases and potential of residual confounding factors.

Disclosure: S. Perreault, Sanofi Canada, 6; **J. Nuevo**, AstraZeneca, 3; **S. Baumgartner**, Ardea/AstraZeneca, 3; **R. Morlock**, AstraZeneca, 3.

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Abstract Number: 2243

Economic Burden of Controlled Gout, Uncontrolled Gout, and Gout Exacerbated By Common Comorbidities: Results from the 2012-2013 National Health and Wellness Survey

Robert Morlock[1], Natalia M. Flores[2], Kathy Annunziata[3], Jonathan Chapnick[4] and Javier Nuevo[5], [1]4939 Directors Place, Ardea Biosciences, Inc., San Diego, CA, [2]Kantar Health, Foster City, CA, [3]Kantar Health, Princeton, NJ, [4]Kantar Health, Horsham, PA, [5]AstraZeneca, Madrid, Spain, Madrid, Spain

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Session Type: ACR Poster Session C

Background/Purpose: Gout is one of the most common forms of inflammatory arthritis and is caused by chronic high serum uric acid (sUA) levels (ie, hyperuricemia), which leads to the deposition of urate crystals in musculoskeletal structures, kidneys, and other connective tissues. Clinical manifestations of gout include painful flares and tophi, which can lead to limited joint function and bone destruction if left untreated, as well as kidney stones and uric acid nephropathy. Recommended treatment goals include maintenance of sUA levels <6 mg/dL. However, sUA often remains elevated because of inadequate therapy or lack of response to treatment. This study aims to understand the relationship between gout control and economic burden and explores the impact of comorbidities on this relationship.

Methods: The data are from the combined 2012 and 2013 US National Health and Wellness Survey (NHWS), a representative, cross-sectional general health survey (2012 NHWS n=71,157; 2013 NHWS n=75,000) of which 3,729 self-reported being diagnosed with gout. Gout was considered "controlled" if patients reported sUA≤6 mg/dL and no flares in the past year. 344 patients were considered controlled, 2,215 uncontrolled (sUA>6 and/or ≥1 flare), and the rest (n=1,170) unknown status. Estimated total costs were calculated by adding direct costs (associated with resource use) and indirect costs (associated with work productivity loss). Those with gout and comorbidities (eg, diabetes) and their relationship with total costs were also examined. Multivariable generalized linear models were used to control for demographic and health characteristics (eg, gender, age, etc.) to assess the unique burden of uncontrolled gout.

Results: Adjusted models indicate that those with controlled gout do not statistically differ from those without gout while those with uncontrolled gout reported approximately $5,000 higher total annualized costs than those without gout ($p<0.01$). Although uncontrolled gout had $2,300 higher total cost than controlled gout, the difference was not significant. A similar pattern was observed for gout control and comorbidities. Those with diabetes and uncontrolled gout reported higher total costs than those without gout or diabetes (mean=$22,186 vs $14,256); there was no statistical difference for those with diabetes and controlled gout vs those without gout or diabetes. Furthermore, those with cardiovascular (CV) disease and uncontrolled gout reported higher total costs than those without gout or CV disease (mean=$25,912 vs $14,313). There was no significant difference between those with CV disease and controlled gout and those without gout or CV disease.

Conclusion: The findings support that uncontrolled gout results in higher total costs than for those without gout. Interestingly, those with controlled gout have a lesser burden closer to those without gout. Total cost for uncontrolled gout may be further exacerbated by comorbidities such as diabetes.

Disclosure: R. Morlock, AstraZeneca, 3; **N. M. Flores**, Kantar Health, 3; **K. Annunziata**, Kantar Health, 3; **J. Chapnick**, Kantar Health, 3; **J. Nuevo**, AstraZeneca, 3.

Abstract Number: 2244

Risk of Incident Atrial Fibrillation in Gout

Seoyoung C. Kim[1], Jun Liu[2] and Daniel H. Solomon[3], [1]Div. of Pharmacoepidemiology and Pharmacoeconomics, Div. of Rheumatology, Immunology and Allergy, Brigham and Women's Hospital, Boston, MA, [2]Division of Pharmacoepidemiology, Brigham and Women's Hospital, Boston, MA, [3]Division of Rheumatology, Immunology and Allergy, Brigham and Women's Hospital, Boston, MA

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Background/Purpose: Atrial fibrillation (AF) is the most common arrhythmia associated with cardiovascular disease and mortality. There are increasing data supporting the role of inflammation in the development and maintenance of AF. Recent observational studies report an increased risk of sinus tachycardia, AF and left atrial thrombus in patients with hyperuricemia, but little is known whether gout is associated with the risk of AF.

Methods: Using data from a US commercial insurance plan (2004-2013), we conducted a cohort study to evaluate the incidence rate (IR) of AF in patients with gout compared to osteoarthritis (OA). Patients with gout or OA were identified with ≥2 diagnosis codes and ≥1 dispensing for a gout- or OA-related drug. The index date was defined as the date of the first dispensing of a gout or OA-related drug (i.e. NSAIDs, opioids) after ≥365-days continuous enrollment. We excluded patients with a diagnosis of arrhythmia or cardiac surgery, or who used anti-arrhythmics or anticoagulants in the 365-day period prior to the index date. The OA group was then matched to the gout group on age, sex and the index date with a 3:1 ratio. Incident AF was defined as a new AF diagnosis and a dispensing for a new anticoagulant or anti-arrhythmic. Baseline ESR, CRP and serum uric acid levels were available on a subgroup of patients. We calculated the incidence rates (IR) of AF and confidence intervals (CI) in both groups. Multivariable Cox proportional hazards models compared the risk of AF in gout versus OA.

Results: We identified 70,015 patients with gout and 210,045 with OA, matched on age, sex, and the index date. The mean age was 57 years and 81% were men. Among patients with baseline ESR,CRP or uric acid levels available, 35.5% of gout and 23.4% of OA patients had elevated ESR or CRP levels and the mean (SD) uric acid level (in mg/dL) was 7.4 (2.0) in gout and 5.9 (1.4) in OA. Over the mean 2-year follow-up, the IR of AF per 1,000 person-years was 7.19 in gout and 5.87 in OA. The age and sex-adjusted HR of AF was 1.23 (95%CI 1.14-1.32) in gout versus OA. In the multivariable Cox regression adjusted for age, sex, comorbidities, medications and healthcare utilization, the HR of AF in gout was 1.13 (95%CI 1.04-1.23). In the subgroup analyses, the HR of AF in gout was 1.22 (95%CI 0.81-1.84) further adjusted for elevated ESR/CRP and 1.57 (95%CI 1.04-2.36) further adjusted for serum uric acid levels.

Conclusion: In this large population-based cohort study, gout was associated with a modestly increased risk of incident AF versus OA. It may be important to examine the role of gout treatment such as xanthine oxidase inhibitors and colchicine in the primary or secondary prevention of AF in patients with gout.

Table. Risk of incident atrial fibrillation in patients with gout compared to those with OA.

Adjustment	Hazard ratio (95% CI)
Main analysis	
Age, sex	1.23 (1.14-1.32)
Age, sex, comorbidity score and number of prescription drugs	1.19 (1.11-1.28)
Final model [a]	1.13 (1.04-1.23)
Subgroup analysis	
Final model + elevated ESR or CRP level [b]	1.22 (0.81-1.84)
Final model + serum uric acid level [c]	1.57 (1.04-2.36)

[a] The final model includes age, sex, cardiovascular disease, diabetes, other comorbidities, comorbidity index, beta-blockers, calcium channel blockers, diuretics, ACE inhibitors, angiotensin 2 receptor blockers, and other medications, and health care utilization factors.

[b] This analysis was done in a subgroup of patients with baseline ESR or CRP levels (n=15,174).

[c] This analysis was done in a subgroup of patients with baseline uric acid levels (n=20,622).

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Abstract Number: 2245

Periarticular Bone Mineral Density Predicts Structural Progression of Knee Osteoarthritis Independently of Static Alignment

Grace H. Lo[1], Jeffrey B. Driban[2], Lori Lyn Price[3], Charles Eaton[4], Michael T. Strayhorn[5] and Timothy E. McAlindon[6], [1]VA HSR&D Center for Innovations in Quality, Effectiveness and Safety; Medical Care Line and Research Care Line; Department of

Medicine, Michael E. DeBakey VA Medical Center, Baylor College of Medicine, Houston, TX, [2]Rheumatology, Tufts Medical Center, Boston, MA, [3]Clinical Care Research, Tufts Medical Center, Boston, MA, [4]Center for Primary Care and Prevention, Memorial Hospital of Rhode Island, Providence, RI, [5]VA HSR&D Center for Innovations in Quality, Effectiveness and Safety; Department of Medicine, Michael E. DeBakey VA Medical Center, Baylor College of Medicine, Houston, TX, [6]Tufts Medical Center, Boston, MA
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Background/Purpose: Individuals with a greater medial to lateral tibial periarticular bone mineral density (M:L paBMD) and static malalignment have greater risk for osteoarthritis (OA) progression. As these risk factors are inter-related, we aimed to evaluate whether M:L paBMD is associated with OA progression, independent of static alignment, which would suggest bone as a therapeutic target.

Methods: This was a study nested within two ancillary studies to the Osteoarthritis Initiative (OAI); therefore the visit for dual x-ray absorptiometry (DXA) was the OAI 30 or 36 month visit, for static alignment was mostly the 12 month visit, and for OA progression (longitudinal medial joint space narrowing (mJSN)) between the 24 and 48 month visits. Knee DXAs generated M:L paBMD using proprietary software. Hip-knee-ankle (HKA) angles (static alignment) were measured on long limb films. mJSN (OARSI grade) were assessed using PA semi-flexed radiographs. Knees with 24-month mJSN of 3 were excluded as they were not eligible for mJSN worsening.

Only evaluating one knee per person, usually the right knee unless contraindicated, we generated Pearson's correlations between HKA and M:L paBMD. We also performed logistic regression with predictors of M:L pa BMD quartiles and outcomes of worsening of mJSN between the 24 and 48 month visits (including within OARSI grade worsening). Models were adjusted for HKA quartiles, age, sex, and BMI. The Cochrane Armitage Test assessed for statistical significance of trends. We performed a sensitivity analysis of only neutrally aligned knees, defined as HKA between -2° and 2°.

To further evaluate the influence of M:L paBMD, eliminating the influence of HKA, we used the residual of M:L paBMD regressed on HKA, representing the uncorrelated aspect of M:L paBMD unrelated to static alignment in logistic regression models.

Results: 419 participants were included, with a mean age of 63.8 +9.2 years; BMI of 29.4 +4.8 kg/m^2; 52% male. At the OAI 24 month visit, 60 (14%), 68 (16%), 158 (38%), 122 (29%), and 11 (3%) had Kellgren and Lawrence grades of 0 – 4 respectively. 45% of knees were neutrally aligned.

M:L paBMD and HKA were correlated; R = 0.64 ($p<0.0001$); greater M:L paBMD was associated with greater varus alignment. Those with greater M:L paBMD had greater odds of mJSN progression, even in fully adjusted models (Table). Sensitivity analyses of only neutrally aligned knees were similar. Analyses evaluating M:L paBMD uncorrelated with HKA also supported a relationship with mJSN progression.

Table. Relationship of ML:pa BMD with mJSN progression, crude and adjusted models.					
		Prevalence of mJSN progression	Unadjusted Odds Ratios	Adjusted Odds Ratios[1]	Adjusted Odds Ratios[2]
M:L pa BMD quartiles	Quartile 1 (lowest)	3/102 (2.9%)	Referent	Referent	Referent
	Quartile 2	8/107 (7.5%)	2.7 (0.7 – 10.3)	1.7 (0.4 – 6.8)	1.5 (0.4 – 6.3)
	Quartile 3	15/104 (14.4%)	5.6 (1.6 – 19.8)	3.1 (0.8 – 11.8)	2.8 (0.7 – 10.8)
	Quartile 4 (highest)	30/106 (28.3%)	13.0 (3.8 – 44.3)	5.5 (1.5 – 20.6)	4.8 (1.2 – 18.6)
			p for trend <0.0001	p for trend = 0.0006	p for trend = 0.002
[1]Adjusted for HKA quartiles					
[2]Adjusted for HKA quartiles, age, sex, and BMI					

Conclusion: Higher relative paBMD is associated with greater structural progression, even after adjustment for static alignment, a known correlate of periarticular BMD and predictor of progression. These findings suggest that treatments targeting periarticular bone, not focused solely on static realignment, may ultimately be protective of OA progression.

Disclosure: G. H. Lo, None; **J. B. Driban**, None; **L. L. Price**, None; **C. Eaton**, None; **M. T. Strayhorn**, None; **T. E. McAlindon**, None.

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Abstract Number: 2246

Occupations Involving Manual Labor Increase the Risk for Incident Knee Osteoarthritis

Grace H. Lo[1], Michael T. Strayhorn[2], Jeffrey B. Driban[3], Lori Lyn Price[4], Charles Eaton[5] and Timothy E. McAlindon[6], [1]VA HSR&D Center for Innovations in Quality, Effectiveness and Safety; Medical Care Line and Research Care Line; Department of Medicine, Michael E. DeBakey VA Medical Center, Baylor College of Medicine, Houston, TX, [2]VA HSR&D Center for Innovations in Quality, Effectiveness and Safety; Department of Medicine, Michael E. DeBakey VA Medical Center, Baylor College of Medicine, Houston, TX, [3]Rheumatology, Tufts Medical Center, Boston, MA, [4]Clinical Care Research, Tufts Medical Center, Boston, MA, [5]Center for Primary Care and Prevention, Memorial Hospital of Rhode Island, Providence, RI, [6]Tufts Medical Center, Boston, MA

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Background/Purpose : CDC guidelines indicate regular physical activity can lead to improved health outcomes. Physically active occupations may contribute toward meeting these guidelines. The impact of this possibility toward the risk of OA has not been tested and is concerning because some jobs are associated with an increased risk of OA (e.g., military, construction, mining). The objective of this study was to evaluate the association between the extent of work-related physical activity and incident knee OA.

Methods : We performed a person-based longitudinal study using Osteoarthritis Initiative (OAI) data. PA semi-flexed knee radiographs were obtained at baseline and annual follow-up visits, centrally assessed for Kellgren-Lawrence (KL) grade (0-4).

Question 10 of the Physical Activity Scale for the Elderly (PASE) at baseline and at each annual OAI visit evaluated the prior 7 days for whether people worked (either paid or volunteer). If a participant did work, they were asked about work-related physical activity level, one of 4 levels (see table) and the number of hours worked. People with no evidence of radiographic knee OA at the baseline visit were included. Those who reported no paid or volunteer work were excluded. We performed logistic regression with the predictor being the work level (1-4), and separately, number of hours worked (<20 hours, 20-39 hours, 40-60 hours and >60 hours), with an outcome of incident person-based ROA (KL $\geq$ 2 in either knee) in the following 12 months. Those who developed ROA were censored from further analysis. We used generalized estimating equations (GEE) to adjust for correlations within person observations over time. We adjusted for age, sex, BMI, injury and the remaining PASE domains. We also tested for interactions between work level and BMI as well as work level and injury.

Results : Of 951 participants (2819 observations), 57.3% were female; baseline mean age was 59.5 (±8.7) years; BMI was 26.8 (±4.5) kg/m^2. Higher work levels were strongly and significantly associated with incident ROA, even after adjustment for BMI and knee injury, and with a significant dose response relationship (Table). However, there was no relationship with number of hours worked. In the fully adjusted model, both knee injury and BMI were also significant risk factors for incident ROA, with a significant interaction between injury and work level.

Conclusion : People who do physically intensive work have a greater odds of incident knee OA compared to those who do sedentary work. In our study, the relationship was with intensity of the work rather than number of hours worked. Strategies are needed to identify at-risk individuals engaged in heavy work, and to mitigate injuries.

Table. Associations of work-related physical activity with incident ROA.

	n = 2819 observations = 951 people	Incidence of ROA	Unadjusted OR	Adjusted OR*
Work level type	**Level 1**= Mainly sitting with slight arm movements (e.g., office worker, watchmaker, bus driver)	17/867 (2.0%)	Referent	Referent
	Level 2 = Sitting or standing with some walking (e.g., cashier, light tool and machinery worker)	30/1233 (2.4%)	1.2 (0.7 – 2.3)	1.2 (0.6 – 2.2)
	Level 3 = Walking, with some handling of materials generally weighing less than 50 pounds (e.g., mailman, waiter/waitress, construction worker)	26/649 (4.0%)	2.1 (1.1 – 3.9)	2.0 (1.1 – 3.8)
	Level 4 = Walking and heavy manual work often requiring handling of materials over 50 pounds (e.g., lumberjack, stonemason, farm laborer)	4/70 (5.7%)	3.0 (1.0 – 9.5)	2.9 (0.9 – 9.5)
			p for trend = 0.007	p for trend = 0.009

*Adjusted for age, sex, injury, BMI and the remaining components of the PASE.

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Abstract Number: 2247

Health Care Practices and Care Consumption in a Population Based Cohort of Symptomatic Knee and/or Hip OA Patients

Anne-Christine Rat[1], Alain Saraux[2], Claudine Gard[3], Francis Guillemin[4] and Bruno Fautrel[5], [1]Rheumatology, Nancy Teaching Hospital, Nancy, France, [2]Rheumatology Department, CHU de la Cavale Blanche, Brest Cedex, France, [3]APHP, Paris, France, [4]University of Lorraine, Nancy, France, [5]GRC08, Sorbonne Universités, UPMC Univ Paris 06, Paris, France, Paris, France
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Background/Purpose:

Hip and knee OA is frequent and is one of the leading causes of global disability. Population-based data of health care practices and consumption are scarce. The aim of the project was to describe health care consumption of a representative sample of patients with knee or hip symptomatic OA.

Methods:

The KHOALA (Knee and Hip OsteoArthritis Long term Assessment) cohort is a representative population-based multicenter cohort of 878 patients with symptomatic knee and/or hip OA, aged between 40 and 75 years old, established between 2007 and 2009. This study is an analysis of the 3 first years of the cohort follow-up. Patients filled in self-reported questionnaires annually.

Results:

The majority (N=698, 82%) of patients were followed up by their general practitioner and few by a rheumatologist (N=120, 14%). Twenty per cent (N=163) received NSAIDs during the past 3 months at an average of 50 to 56% of the maximal dose over time. Between 30 and 32% (N=268) of patients received grade 1 analgesic and between 20 and 23% (N=195) grade 2. Less than 15% of patients had steroids or hyaluronic injections.

Only 127 patients (15%) have been treated by physiotherapy and 59 (7%) by spa therapy. Almost 10% (N=86) of the patients used a technical aid mainly a walking stick. During the first 3 years of the cohort, between 15 and 19 total knee replacement surgeries and between 9 and 14 total hip replacement surgeries per year have been performed.

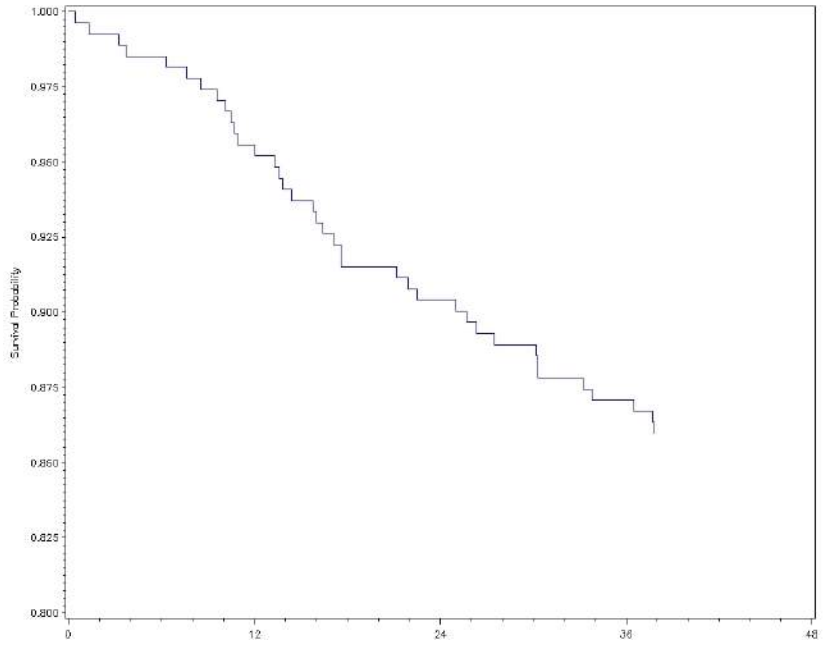
More than a third of the patients had blood tests or imaging exams, X rays being the most frequent. During the year before inclusion 120 (14%) patients have been hospitalized while during the follow up between 21 and 25% of patients have been hospitalized per year. Analgesic use was more frequent in women, in patients with a lower level of education, more comorbidities, retired, smoker and not taking alcohol more than 20g a day.

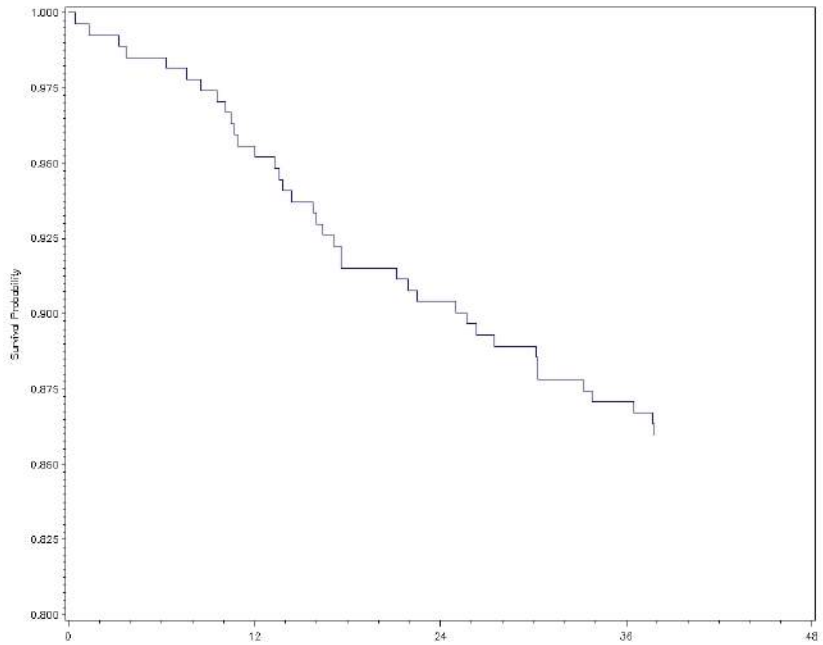
Conclusion:

These results are important data to describe current care practices and health care use in France in a representative population based cohort of patients with knee and/or hip OA.

Figure 1: survival analysis without total knee or hip surgery

Knee Hip





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Abstract Number: 2248

Knee Pain Burden Is Associated with Decreased Motor Performance: Data from the Osteoarthritis Initiative

Javad Razjouyan[1], Bijan Najafi[2], Erin Ashbeck[3], Dorothy D. Dunlop[4], Julia (Jungwha) Lee[5], Lynn Hamilton[3] and C. Kent Kwoh[6], [1]Consortium on Advanced Motion Performance (iCAMP), Department of Surgery, University of Arizona, Tucson, AZ, [2]Department of Surgery and Department of Biomedical Engineering, University of Arizona, Tucson, AZ, [3]Arthritis Center, University of Arizona, Tucson, AZ, [4]Institute for Healthcare Studies, Northwestern University Feinberg School of Medicine,

Chicago, IL, [5]Department of Preventive Medicine, Biostatistics Collaboration Center, Northwestern University Feinberg School of Medicine, Chicago, IL, [6]Rheumatology, University of Arizona, Tucson, AZ
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Background/Purpose: Knee pain is the presenting symptom in knee osteoarthritis (OA), but the impact of knee pain burden in OA has been understudied. We examined the effect of knee pain on objectively measured moderate/vigorous physical activity among community-dwelling adults with or at high risk for knee OA.

Methods: Physical activity was objectively measured by accelerometer on participants with or at risk for radiographic knee OA in the Osteoarthritis Initiative (OAI) at the 48-month clinic visit, using ActiGraph GT1M uniaxial accelerometers (ActiGraph; Pensacola, FL), and calibrated using activity definitions published by Trioano. Participants were instructed to wear the sensor for seven consecutive days for at least 10 hours per day. Analysis was restricted to those participants with four or more valid days of wear. Knee pain burden was assessed using the Higher Western Ontario McMaster Osteoarthritis Index (WOMAC) knee pain score, and categorized as no pain, and approximate quartiles of the non-zero pain score distribution. Analysis of covariance was used to estimate sex-specific means (± standard error) for time spent engaging in moderate/vigorous physical activity across the five categories of WOMAC pain, with adjustment for age, race, and body mass index (BMI). We considered the effect of WOMAC pain categories on meeting the 2008 Physical Activity Guidelines for Americans, issued by the U.S. Department of Health and Human Services (DHHS) using logistic regression to estimate adjusted odds ratios (aOR) and 95% confidence intervals (95%CI), adjusted for age, sex, race, and BMI.

Results: We included 1,907 participants, 55% female, with a mean age of 65.1(±9.1) years. As shown in Table 1, increasing knee pain burden was associated with decreasing mean average daily bout of moderate/vigorous activity among both men (p=0.0480) and women (p=<0.0001), and decreasing mean average daily minutes of moderate/vigorous activity among both men (p=0.0094) and women (p<0.0001), after adjustment for age, race, and BMI.

Participants with WOMAC pain scores of 2 to 3 had significantly lower odds of meeting the DHHS guidelines (aOR=0.63; 95%CI: 0.43, 0.93), as did participants with scores of 4 to 6 (aOR=0.61; 95%CI: 0.39, 0.96), and those with scores > 6 (aOR=0.32; 95%CI: 0.16, 0.63), as compared to participants reporting no pain. When considering the DHHS guidelines for people with arthritis, point estimates and confidence intervals were similar.

Conclusion: High knee pain burden is associated with less moderate/vigorous physical activity, and may be an impediment to meeting national physical activity guidelines. Targeted interventions to reduce knee pain among adults with or at risk of knee osteoarthritis may increase moderate/vigorous physical activity levels.

		Moderate/Vigorous Physical Activity			
		Average daily bout, minutes		**Average daily minutes**	
WOMAC pain score (non-zero quartiles)	n	Men	Women	Men	Women
0	686	11.71± 0.75	11.50± 1.20	24.28±0.96	16.88±0.89
1	285	11.50± 1.20	6.27± 1.05	24.47±1.52	13.97±1.33
2-3	395	10.12± 1.00	5.79± 0.91	21.95±1.26	13.68±1.15
4 to 6	310	9.80± 1.10	5.56± 1.04	21.29±1.39	12.72±1.32
>6	269	7.78± 1.30	4.43± 1.10	18.08±1.66	11.67±1.39

Mean ± standard error; means adjusted for age, race, and BMI

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Abstract Number: 2249

Risk and Risk Perception of Knee Osteoarthritis in the US: Population-Based Study

Griffin L. Michl[1], Jeffrey N. Katz[2] and **Elena Losina**[3], [1]Orthopaedic and Arthritis Center for Outcomes Research, Brigham and Women's Hospital, Boston, MA, [2]Brigham and Women's Hospital and Harvard Medical School, Boston, MA, [3]Orthopedics, Brigham and Women's Hospital, BU School of Public Health and Harvard Medical School, Boston, MA

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Background/Purpose: Knee osteoarthritis (OA) is increasingly diagnosed in younger adults, likely due to accumulation of risk factors such as obesity, knee injury, occupational exposure and family history. This shift in the age of the OA population suggests that prevention efforts should focus on younger individuals. However, knowledge of the disease and perceptions of risk among younger people have not been investigated formally.

Methods: We recruited a population-based cohort 25-45 years of age with no history of knee OA using Amazon's Mechanical Turk, an online marketplace used extensively for behavioral research. After collecting demographic and risk factor information, we asked participants to estimate their 10-year and lifetime risk of knee OA. We compared perceived risk with 'actual' risk derived from the OA risk calculator (OARC). OARC is an online tool built on the basis of the validated OA Policy Model. OARC matches user inputs to corresponding model outputs that include 10-year and lifetime risk of diagnosed symptomatic knee OA based on age, sex, race, obesity status, family history of OA, history of knee injury, and occupational risks. Increases in OA risk were quantified using published literature.

Results: 375 people completed the study. Mean age was 32 years; 52% were females; 21% identified as non-white; 56% had a college degree. Study participants resided in all regions of the US: 17% — Northest, 18% — Midwest, 38% — South and 27% — West. 70% reported family history of OA, 20% reported a history of knee injury, and 48% reported occupational exposure. 11% reported having 3+ risk factors for OA, 24% reported two risk factors, and 35% reported one risk factor. Using the OARC, we estimated a mean lifetime OA risk of 25% for this sample and 10-year risk of 4%. Participants estimated their lifetime and 10-year OA risk at 48% and 26%, respectively. 15% estimated their lifetime OA risk within 25% of the lifetime risk determined by the risk calculator. 61% overestimated their lifetime risk by at least 50%, while 16% underestimated their lifetime risk by at least 25%. 46% overestimated their lifetime risk of knee OA at least 2 fold, and 20% overestimated their risk 3 fold. 75% of study participants overestimated their 10 year risk by at least 2 fold and 66% by 3 fold. We found that obesity, female sex, family history of OA, history of knee injury, and occupational exposure were all significantly associated with greater perceived lifetime risk of OA.

Conclusion: Risk factors are prevalent in this relatively young cohort and subjects with risk factors perceived their risk as higher than those without risk factors. However, participants consistently overestimated their lifetime risk and showed even greater overestimation of their 10-year risk, suggesting a lack of knowledge about the timing of OA onset. Family history in particular was associated with overestimation of OA risk. Family members of OA patients may perceive knee OA as inevitable, while its contribution to the risk of knee OA has been shown to be considerably less than contribution of obesity and injury. These data offer insights for awareness and risk interventions among younger persons at risk for knee OA.

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Abstract Number: 2250

The Relationship Between Sex and Incident Knee Osteoarthritis Is Mediated By Shape

Barton L. Wise[1], Jingbo Niu[2], Yuqing Zhang[3], Felix Liu[4], Joyce H. Pang[5], John A. Lynch[6] and Nancy E. Lane[7], [1]Department of

Internal Medicine, UC Davis School of Medicine, Sacramento, CA, [2]Clinical Epidemiology Research and Training Unit, Boston University School of Medicine, Boston, MA, [3]BUSM, Boston, MA, [4]University of California at San Francisco, San Francisco, CA, [5]University of Nevada School of Medicine, Reno, NV, [6]University of California San Francisco, San Francisco, CA, [7]Center for Musculoskeletal Health, Univ of California at Davis, Sacramento, CA
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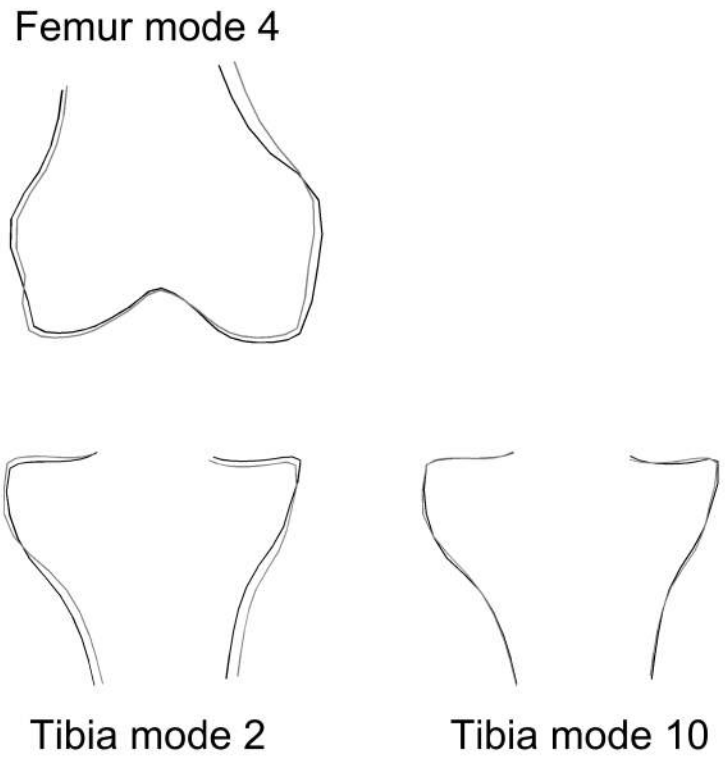
Background/Purpose: Incidence of knee osteoarthritis (OA) is higher in women than in men. We have previously shown that knee bone shape differs between men and women. The purpose of the present study was to determine whether knee bone shape is associated with risk of knee OA, and to what extent the difference in the incidence of knee radiographic OA (ROA) between men and women is mediated by bone shape.

Methods: We used data collected from the NIH-funded Osteoarthritis Initiative (OAI), a cohort of persons aged 45-79 at baseline who either had symptomatic knee OA or were at high risk of it. We randomly sampled 304 knees with incident ROA (i.e., development of Kellgren/Lawrence grade ≥2 in central readings by month 48) and 304 knees without incident ROA. We characterized distal femur and proximal tibia shape on baseline radiographs using Active Shape Modeling. Thirteen modes were derived for proximal tibial shape and for distal femoral shape, accounting for 95.5% of the total variance. We examined the relation of sex and each bone shape to the risk of incident ROA using logistic regression. If a specific bone shape was associated with the risk of incident ROA, we then performed a marginal structural model to assess the mediation effect of that bone shape on the relation of sex and risk of incident knee ROA adjusting for baseline covariates.

Results: The mean age was 60.2 years (±8.5 SD) for both cases and controls; the proportion of women was 65.1% in cases and 59.5% in controls. Women had 49% increased odds of incident knee ROA compared with men. Six shape modes were associated with risk of incident knee ROA (tibia: mode 2, 9, 10, and 12; femur: mode 4 and 10). Women had a lower value of tibial mode 2 (mean = -0.23 vs. 0.20) but a higher value of tibial mode 10 (mean = 0.25 vs. -0.21) than men among controls; and higher value of femur mode 4 (mean = 0.30 vs. -0.21) and mode 10 (mean = 0.21 vs. -0.09). The indirect effect of sex on incident OA via tibial mode 2 was negative (OR = 0.96) and the direct effect (not through this mode) was positive (OR = 1.56), suggesting there was inconsistent mediation effect of mode 2. Similar findings were also observed when assessing the mediation effect of tibia mode 10 and femur mode 4 (see Table). See Figure for images of all modes that were found to be significant mediators.

Conclusion: The shapes of the distal femur and proximal tibia that form the knee joint partially and inconsistently mediate the relationship between sex and incident knee OA. Although women had higher risk of incident ROA, their bone shape modestly protects them from even higher risk.

Table. Bone shape mode and sex, incident knee ROA				
Mode	Association of mode and incident knee ROA		Mode among knees without incident TFROA, by gender	
	OR (95% CI)*	p-value	Men mean (SD)	Women mean (SD)
tibia, mode 2	1.18(1.03,1.37)	0.021	0.20 (1.00)	-0.23 (0.94)**
tibia, mode 9	1.15(1.00,1.32)	0.042	-0.06 (1.11)	-0.09 (1.00)
tibia, mode 10	0.79(0.67,0.93)	0.006	-0.21 (0.98)	0.25 (0.98)**
tibia, mode 12	0.86(0.75,0.99)	0.031	0.00 (1.08)	0.06 (1.04)
femur, mode 4	0.85(0.73,0.98)	0.025	-0.21 (1.00)	0.30 (0.89)**
femur, mode 10	0.81(0.70,0.94)	0.005	-0.09 (0.98)	0.21 (0.95)
Mediator effect of mode on sex and incident knee ROA	Indirect effect		Direct effect	
	OR (95% CI)*	p-value	OR (95% CI)*	p-value
tibia, mode 2	0.96(0.91,1.00)	0.043	1.56(1.08,2.27)	0.019
tibia, mode 10	0.96(0.92,1.00)	0.034	1.53(1.05,2.21)	0.025
femur, mode 4	0.97(0.94,1.00)	0.045	1.50(1.03,2.17)	0.034
Total effect of sex (women vs. men): OR (95% CI)* = 1.49 (1.04, 2.12)				
*Adjusting for age, BMI, race, clinic site, knee injury and surgery ** p-value <0.05				



Disclosure: B. L. Wise, None; **J. Niu**, None; **Y. Zhang**, None; **F. Liu**, None; **J. H. Pang**, None; **J. A. Lynch**, None; **N. E. Lane**, Genzyme-Sanofi, 5,Regeneron, 5.

Abstract Number: 2251

Current Tobacco Use and the Rates of Postoperative Complications after Total Knee Arthroplasty

Jasvinder A. Singh, University of Alabama at Birmingham, Birmingham, AL
First publication: September 29, 2015

SESSION INFORMATION
Session Title: Epidemiology and Public Health Poster III (ACR): Gout and Non-Inflammatory Musculoskeletal Conditions
Session Type: ACR Poster Session C

Background/Purpose:

To our knowledge, well-designed studies that have examined the risk of post-arthroplasty implant-related complications after TKA with tobacco use are lacking. Our objective was to assess the effect of current tobacco use on surgical outcomes after primary TKA. We hypothesized that current tobacco use will be associated with an increased risk of infection, revision and wound complications after primary TKA.

Methods:

This observational cohort study included all patients who underwent primary TKA at the Mayo Clinic from 2010 to 2013 and had tobacco use status documented in the Mayo Clinic's nursing database. Current tobacco use status was the predictor of interest. It was defined based on the documentation of cigarette, cigar, pipe or smokeless tobacco use in the nursing database. Current smokers were defined as people who were using cigarettes, cigars, pipes or smokeless tobacco at the time of their surgery. They were compared to current non-smokers and former smokers with regards to post-TKA complications.

Results:

Tobacco use data at the time of TKA were available for 4,227 (95%) TKA patients and not available for 249 (5%) of the patients; mean age (67 vs. 66), BMI (33 vs. 33) and Charlson index (1.5 vs. 1.4) were similar for patients with and without tobacco use data.

There were 228 current tobacco users (5%) and 4,049 non-users (95%) among patients who underwent primary TKA. Compared to the non-users, current tobacco users who underwent primary TKA were more likely to be male, have higher Charlson index and less likely to be older than 80 years ($p<0.01$; reference $\leq$60 years). No significant differences in BMI, ASA class or implant fixation were noted.

Compared to non-smokers, smokers had 2.51 times higher hazard of any revision after primary TKA ($p=0.02$; **Table 1**). Rates of revision for infection, wound complications and any infection showed a trend towards statistical significant with hazard ratios of 2.59 ($p=0.07$) ,1.84 ($p=0.10$) and 1.94 ($p=0.12$), respectively. Rates of deep infection, superficial infection and periprosthetic fracture were higher for current smokers, but were not significantly different between current smokers and non-smokers.

Conclusion:

Current tobacco use was a risk factor for poor postoperative outcomes after total knee arthroplasty, including higher revision rates and the risk of wound complications. Perioperative smoking cessation efforts need to be incorporated into routing post-TKS care to prevent these complications after this elective surgery, aimed at improving patient's quality of life.

Table 1. Kaplan-Meier survival analyses for current smokers compared to current non-smokers (former smokers and never smokers)						
Endpoint	Variable	# events	1 year (95% CI)	2 years (95% CI)	HR (95% CI)	p-value
Any revision	Current tobacco user	7	97.8 (95.3,100)	93.3 (88.5,98.4)	2.51 (1.14,5.54)	0.02
	Past user or never used	50	98.7 (98.3,99.2)	97.7 (97.0,98.4)	1.0 (ref)	
Revision for aseptic loosening	Current tobacco user	0	100	100	1.99 (0.08,52.2)	0.68
	Past user or never used	4	100 (99.9,100)	99.8 (99.6,100)	1.0 (ref)	
Revision for infection	Current tobacco user	4	100	95.4 (91.1,99.9)	2.59 (0.92,7.31)	0.07
	Past user or never used	28	99.1 (98.6,99.5)	98.7 (98.2,99.2)	1.0 (ref)	
Revision for peri-prosthetic fracture	Current tobacco user	0	100	100	3.59 (0.09,147.8)	0.50
	Past user or never used	2	99.9 (99.8,100)	99.9 (99.7,100)	1.0 (ref)	
Complication deep infection	Current tobacco user	3	99.5 (98.5,100)	97.2 (93.3,100)	1.76 (0.54,5.77)	0.35
	Past user or never used	31	98.9 (98.5,99.4)	098.6 (98.1,99.1)	1.0 (ref)	
Complication superficial infection	Current tobacco user	3	98.3 (96.5,100)	98.3 (96.5,100)	2.12 (0.64,7.01)	0.22
	Past user or never used	25	99.2 (98.8,99.5)	99.2 (98.8,99.5)	1.0 (ref)	
Complication any infection	Current tobacco user	6	97.8 (95.7,100)	95.5 (91.8,99.4)	1.94 (0.83,4.52)	0.12
	Past user or never used	56	98.1 (97.6,98.6)	97.8 (97.2,98.4)	1.0 (ref)	
Complication wound complications	Current tobacco user	8	95.2 (92.0,98.6)	95.2 (92.0,98.6)	1.84 (0.88,3.8)	0.10
	Past user or	77	97.5 (97.0,98.1)	97.5 (96.9,98.0)	1.0 (ref)	

	never used					
Complication peri-prosthetic fracture	Current tobacco user	2	99.1 (97.9,100)	99.1 (97.9,100)	1.15 (0.27,4.78)	0.85
	Past user or never used	31	99.2 (98.9,99.5)	99.0 (98.6,99.4)	1.0 (ref)	

Disclosure: J. A. Singh, Takeda, Savient, 2,Takeda, Savient, merz, Regeneron, Allergan, Crealta, Bioiberica, 5;

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Abstract Number: 2252

Declining Post-Arthroplasty Mortality after Total Knee Arthroplasty in the U.S.: A Time-Trends Study

Jasvinder A. Singh and Rekha Ramachandaran, University of Alabama at Birmingham, Birmingham, AL
First publication: September 29, 2015

SESSION INFORMATION
Session Title: Epidemiology and Public Health Poster III (ACR): Gout and Non-Inflammatory Musculoskeletal Conditions
Session Type: ACR Poster Session C

Background/Purpose:

Total Knee Arthroplasty (TKA) is mostly an elective procedure that is effective in improving pain, function and quality of life in patients with end-stage arthritis. Our objective was to compare mortality after Total Knee Arthroplasty (TKA) over time in a nationally representative sample of patients. We also sought to compare the mortality in patients residing in urban and rural locations to see if the mortality differed by location and over time.

Methods:

We used the U.S. Nationwide Inpatient Sample from 1998-2010 to compare outcomes after total knee arthroplasty (TKA). In-hospital post-arthroplasty mortality related to the index admission was assessed as an outcome. Overall time trends in in-hospital post-TKA mortality were compared using the Cochrane-Armitage test. Rural versus urban residence was determined based on patient's residence at the time of surgery (available 2003-2010). Unadjusted and adjusted logistic regression analyses were performed comparing mortality by rural-urban location between 2003-06 to 2007-10, adjusting for age, race, gender, Charlson score and hospital TKA volume.

Results:

In-hospital post-TKA mortality decreased over time, from 197/100,000 TKA surgeries in 1998 to 97/100,000 TKA surgeries in 2010, a significant 50% reduction over time ($p<0.0001$; Table 1). The reduction was persistent over time. Similar significant time-trends in reduction in in-hospital post-TKA mortality were noted in both patients residing in rural and urban locations ($p<0.0001$ for both; Table 2). No significant rural-urban differences were noted in In-hospital post-TKA mortality in 2003-06 or 2007-10 (Table 3).

Table 1. Time-trend in in-hospital mortality after primary TKA

Year	Total Mortality	#TKA from NIS	Rate per 100,000
1998	497	252266	197
1999	491	263548	186
2000	485	282350	172
2001	501	314402	159
2002	459	351018	131
2003	653	380774	172
2004	582	432379	135
2005	564	498169	113
2006	525	497001	106
2007	455	551259	83
2008	561	616617	91
2009	446	621029	72
2010	481	658340	73

Table 2. Post-TKA in-hospital mortality over time by patient residence, rural vs. urban

Year	Location	Total Mortality	#TKA from NIS	Rate per 100,000
2003	Rural	149	86040	173
2004	Rural	127	99091	129
2005	Rural	166	113396	147
2006	Rural	122	110621	110
2007	Rural	98	121670	80
2008	Rural	96	127085	76
2009	Rural	113	134738	84
2010	Rural	102	152462	67
2003	Urban	501	293772	170
2004	Urban	455	332575	137
2005	Urban	398	384084	103
2006	Urban	399	385777	103
2007	Urban	342	410969	83
2008	Urban	459	473501	97
2009	Urban	323	466017	69
2010	Urban	373	480538	78

Rural-urban residence variable was available only from 2003 onwards; Cochran Armitage test of trend comparing the in hospital mortality rates: Rural: $p<0.0001$; Urban: $p<0.0001$

Table 3. Rural-urban differences in post-TKA in-patient mortality and time-trends

	All combined	Rural		Urban			
	2003-2010	2003-2006	2007-2010	2003-2006	2007-2010	Unadjusted p-value	Adjusted p-value*
In-hospital Mortality, n (%)	874 (0.1)	112 (0.14)	85 (0.08)	366 (0.13)	303 (0.08)	0.45 0.67 0.41	0.82 0.42 0.24

*Adjusted for age, race, gender, Charlson score, hospital TKA volume

For p-values: first p-value denotes rural/urban disparity in 2003 -2006; second the rural/urban disparity in 2007 -2010 and the third denotes the change in the disparity magnitude between 2003 – 2006 and 2007 – 2010.

Conclusion:

Significant decrease in in-hospital post-TKA mortality has occurred from 1998 to 2010 in the U.S. The magnitude of reduction is impressive. Rural and urban residing patients had similar mortality rates and reductions over time.

Disclosure: J. A. Singh, Takeda, Savient, 2,Takeda, Savient, merz, Regeneron, Allergan, Crealta, Bioiberica, 5; **R. Ramachandaran**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/declining-post-arthroplasty-mortality-after-total-knee-arthroplasty-in-the-u-s-a-time-trends-study

Abstract Number: 2253

Racial Disparities in Total Shoulder Arthroplasty Utilization and Outcomes Are Persisting

Jasvinder A. Singh and Rekha Ramachandaran, University of Alabama at Birmingham, Birmingham, AL
First publication: September 29, 2015

SESSION INFORMATION
Session Title: Epidemiology and Public Health Poster III (ACR): Gout and Non-Inflammatory Musculoskeletal Conditions
Session Type: ACR Poster Session C

Background/Purpose:

A recent study that used the 1993-2007 U.S. Nationwide Inpatient Sample (NIS) reported that Blacks had lower overall Total Shoulder Arthroplasty (TSA) utilization rates compared to Whites with a risk ratio of 0.6. It is not known, whether the racial disparity in TSA utilization is increasing or decreasing in the U.S. Our objective was to study whether racial disparities in total shoulder arthroplasty (TSA) utilization and outcomes have declined over time in the U.S.

Methods:

We used the U.S. Nationwide Inpatient Sample from 1998-2011. We used chi-squared test to compare characteristics, Cochran-Armitage test to compare utilization rates, and Cochran-Armitage test and logistic regression to compare time-trends in outcomes by race.

Results:

176,141 Whites and 7,694 Blacks underwent TSA from 1998-2011. Compared to Whites, Blacks who underwent TSA were younger (69.1 vs. 64.2 years; $p<0.0001$) and more likely to be female (54.9% vs. 71.0%; $p<0.0001$), have rheumatoid arthritis or avascular necrosis as the underlying diagnosis (1.7% vs. 3.0% and 1.7% vs. 6.1 %; $p<0.0001$ for both) and Deyo-Charlson index of 2 or higher (8.5% vs. 16.7%; $p<0.0001$). Compared to Whites, Blacks had much lower TSA utilization rate/100,000 in 1998 (2.97 vs. 0.83; $p<0.0001$) and in 2011 (12.27 vs. 3.33; $p<0.0001$); disparities increased from 1998 to 2011 ($p<0.0001$). A higher proportion of Blacks than Whites had hospital stay greater than median in 1998-2000, 62% vs. 51.4% ($p=0.02$) and in 2009-2011, 27.3% vs. 34.4% ($p<0.0001$); disparities did not change over time ($p=0.31$). These disparities were borderline significant in adjusted analyses. There were no racial differences in proportion discharged to inpatient medical facility in 1998-2000, 15.2% vs. 15.0% ($p=0.95$) and in 2009-2011, 12.3% vs. 11.1% ($p=0.37$), respectively.

Conclusion:

We found increasing racial disparities in TSA utilization. Some disparities in outcomes exist as well. Patients, surgeons and policy-makes should be aware of these findings and take action to reduce racial disparities.

Disclosure: J. A. Singh, Takeda, Savient, 2,Takeda, Savient, merz, Regeneron, Allergan, Crealta, Bioiberica, 5; **R. Ramachandaran**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/racial-disparities-in-total-shoulder-

arthroplasty-utilization-and-outcomes-are-persisting

Abstract Number: 2254

Socio-Economically Deprived Patients Have a Higher Likelihood for Having Any Type of Rheumatic and Musculoskeletal Diseases and Have Higher Healthcare Costs – Results from a Population-Based Administrative Database Including 1.9 Million Persons (Basque country, Spain)

Polina Putrik[1], Sofia Ramiro[2], Jon Orueta[3], Edurne Alonso Moran[4], Roberto Nuno Solinis[5] and Annelies Boonen[6], [1]Department of Internal Medicine, Division of Rheumatology, Maastricht University Medical Center, Maastricht, Netherlands, [2]Rheumatology, Leiden University Medical Center, Leiden, Netherlands, [3]Centro de Salud de Astrabudua, Osakidetza, Basque Health Service, Erandio, Spain, [4]O+berri, Basque Institute for Healthcare Innovation, Barakaldo, Spain, [5]Universidad Deusto, Bilbao, Spain, [6]Maastricht University Medical Center, Maastricht, Netherlands

First publication: September 29, 2015

SESSION INFORMATION

Session Title: Epidemiology and Public Health Poster III (ACR): Gout and Non-Inflammatory Musculoskeletal Conditions
Session Type: ACR Poster Session C

Background/Purpose:

Rheumatic and musculoskeletal diseases (RMDs) are prevalent and have a strong impact on health care costs. Some evidence in specific diseases indicates that patients with lower socio-economic background are at higher risk to have the disease and incur more healthcare costs. However, knowledge whether these effects of socio-economic status are comparable across all RMDs is lacking. Objective of this study was to compare the impact of socio-economic deprivation on occurrence of different RMDs and associated health care costs.

Methods:

An administrative dataset linking clinical (based on ICD codes), sociodemographics (age, gender and deprivation index) and health care utilization costs information of the entire adult (>=18 y.o.) population of the Basque Country, Spain was used. Deprivation index was based on area employment and education status, and included five categories (1 to 5 (most deprived)). Costs included primary and specialist care, planned and emergency hospital admissions, and ambulatory drug prescriptions. Thirty-six individual diseases were grouped into seven larger diagnostic groups: Rheumatoid Arthritis, Crystal Arthropathies, Osteoarthritis, Soft tissue diseases, Connective Tissue Diseases, and Vasculitis (Table). Logistic and Poisson regression models were computed to explore the relation between the deprivation index and occurrence of the disease (separately and grouped) and health care utilization costs, respectively. All models were adjusted for age and gender.

Results:

In total, data from 1,923,156 individuals were analyzed. Mean age was 49.9 (SD18:4), 49% were males. Soft tissue diseases were the most prevalent (5.5%), third most costly in terms of health care utilization costs after vasculitis and rheumatoid arthritis. Socio-economic deprivation was associated with higher likelihood to have any RMDs except vasculitis and some connective tissue diseases. The strongest socio-economic gradient was seen for occurrence of soft tissue disease (OR 1.82 [95%CI 1.78;1.85], most vs. least deprived). Deprivation was also associated with higher costs across the majority of the conditions, but a somewhat different pattern across diseases was seen, as the strongest gradients were observed in patients with Spondyloarthritis (in particular. with Ankylosing spondylitis) and Vasculitis (Table).

Table. Occurrence of diagnoses and costs by deprivation status across RMDs.				
Disease	**N(%)**	**Mean (SD) total healthcare cost per patient per year (€)**	**OR to have disease (most deprived vs least deprived)**	**IRR total costs (most deprived vs least deprived)**
Rheumatoid arthritis	**4042 (0.21%)**	**3865.93 (6296.16)**	**1.32 [1.19;1.46]**	**1.33 [1.33;1.33]**
Rheumatoid arthritis	3533 (0.18%)	4011.07 (6426.18)	1.30 [1.17;1.45]	1.38 [1.38;1.38]
Undifferentiated (poly)arthritis	536 (0.03%)	2915.41 (5112.51)	1.51 [1.13;2.01]	0.97 [0.96;0.97]
Spondyloarthritis	**1808 (0.09%)**	**2785.1 (6830.4)**	**1.43 [1.22;1.68]**	**1.66 [1.65;1.67]**
Ankylosing spondylitis	660 (0.03%)	2369.33 (6078.65)	1.72 [1.31;2.25]	2.10 [2.08;2.11]
Psoriatic arthritis	992 (0.05%)	2683.28 (6265.25)	1.35 [1.08;1.68]	1.59 [1.58;1.60]
Reactive arthritis	66 (0.00%)	5563.67 (12785.33)	0.38 [0.14;1.06]	0.77 [0.75;0.78]
Undifferentiated spondyloarthritis	110 (0.01%)	4390.99 (9363.84)	1.66 [0.91;3.04]	1.69 [1.67;1.70]
Crystal Arthropathies	**3899 (0.2%)**	**3162.69 (5987.09)**	**1.65 [1.47;1.84]**	**1.13 [1.13;1.13]**
Gout	3545 (0.18%)	3151.88 (6057.05)	1.63 [1.46;1.83]	1.09 [1.09;1.09]
Other crystal arthropathy	362 (0.02%)	3270.80 (5214.10)	1.74 [1.22;2.48]	1.44 [1.43;1.44]
Osteoarthritis	**41924 (2.18%)**	**3117.88 (4825.14)**	**1.59 [1.54;1.64]**	**1.22 [1.22;1.22]**
Knee Osteoarthritis	10559 (0.55%)	3545.09 (5205.92)	1.90 [1.78;2.03]	1.18 [1.18;1.18]
Hip Osteoarthritis	5097 (0.27%)	3711.49 (5493.39)	1.33 [1.21;1.46]	1.01 [1.01;1.01]
Hand Osteoarthritis	3599 (0.19%)	2224.09 (3397.20)	1.12 [1.01;1.25]	1.33 [1.32;1.33]
Osteoarthritis other	5304 (0.28%)	2960.97 (4612.84)	1.59 [1.45;1.74]	1.31 [1.30;1.31]
Degenerative neck disease (cervical spine)	3300 (0.17%)	2711.11 (4466.96)	1.53 [1.36;1.72]	1.33 [1.32;1.33]
Chronic low back pain (excluding degenerative)	12972 (0.67%)	3043.48 (4756.90)	1.62 [1.53;1.72]	1.26 [1.26;1.26]
Osteoarthritis generalized	7054 (0.37%)	3504.27 (5082.43)	1.61 [1.49;1.75]	1.26 [1.25;1.26]
Soft tissue diseases	**105656 (5.49%)**	**2271.56 (4027.57)**	**1.82 [1.78;1.85]**	**1.23 [1.23;1.23]**
Chronic low back pain (excluding degenerative)	66867 (3.48%)	2341.16 (4162.52)	1.86 [1.81;1.91]	1.23 [1.23;1.23]
Chronic neck pain (excluding degenerative)	17357 (0.9%)	2093.08 (3568.17)	1.99 [1.89;2.09]	1.16 [1.16;1.16]
Fibromyalgia	3056 (0.16%)	2800.76 (4477.42)	1.70 [1.51;1.91]	1.40 [1.40;1.41]

Soft tissue disease	38548 (2%)	2270.59 (3791.02)	1.67 [1.61;1.72]	1.27 [1.27;1.27]
Connective Tissue Diseases	**738 (0.04%)**	**3495.55 (5206.72)**	**1.33 [1.04;1.69]**	**1.29 [1.29;1.30]**
Systemic lupus erythematosus	590 (0.03%)	3179.44 (4908.92)	1.31 [1.00;1.72]	1.27 [1.27;1.28]
Sjogren's disease	63 (0%)	5224.62 (7098.54)	0.89 [0.37;2.12]	0.91 [0.90;0.92]
Systemic sclerosis	44 (0%)	4989.50 (5586.01)	1.98 [0.71;5.44]	3.54 [3.47;3.60]
Myositis	76 (0%)	3134.68 (3076.92)	0.99 [0.44;2.21]	0.99 [0.97;1.01]
Other connective tissue disease	51 (0%)	4149.71 (4991.57)	1.77 [0.63;4.98]	0.96 [0.95;0.98]
Vasculitis	**300 (0.02%)**	**5235.52 (7924.52)**	**1.10 [0.74;1.63]**	**1.98 [1.96;1.99]**
ANCA associated vasculitis	38 (0%)	5865.84 (6629.81)	1.55 [0.34;6.96]	3.86 [3.70;4.02]
Non-ANCA associated vasculitis	264 (0.01%)	5219.53 (8163.03)	1.08 [0.72;1.62]	1.95 [1.94;1.96]
Osteoporosis	15049 (0.78%)	2945.37 (4630.94)	1.09 [1.03;1.14]	1.34 [1.34;1.34]
Polimyalgia rheumatica	1935 (0.1%)	3828.45 (5508.66)	1.21 [1.04;1.41]	1.16 [1.16;1.16]
Undifferentiated monoarthritis	434 (0.02%)	2614.93 (3578.13)	1.48 [1.07;2.04]	1.18 [1.17;1.19]

Conclusion:

Socio-economic deprivation was consistently associated with higher occurrence and higher costs across most of the RMDs. Among major RMDs, the group of soft tissue diseases (comprising chronic low back and neck pain, fibromyalgia, and soft tissue disease), was the most prevalent and costly for the society, and occured more often in persons with lower socio-economic status.

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Abstract Number: 2255

Capillaroscopic Patterns in a Healthy Population

Génessis Maldonado[1], Christian Ferro[2], Carlos Ríos[3] and Karla Ríos[1], [1]Universidad Espíritu Santo, Guayaquil, Ecuador, [2]Universidad Católica de Santiago de Guayaquil, Guayaquil, Ecuador, [3]Centro de Reumatología y Rehabilitación CERER, Guayaquil, Ecuador

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SESSION INFORMATION

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Session Type: ACR Poster Session C

Background/Purpose: Capillaroscopy is a noninvasive and safe method that allows visualization of the capillaries in the finger nailfold, it is useful in the evaluation of Raynaud's phenomenon and collagen diseases, especially scleroderma. There are a variety of studies on the capillaroscopic findings in different collagen diseases, with the SD pattern being the characteristic finding of

scleroderma. However, some microvascular alterations can occur in the healthy population; little is known about the prevalence and distribution of capillaroscopic changes in this group.

Methods: Observational, descriptive and prospective study of healthy subjects selected by inclusion and exclusion criteria. Subjects presenting signs/symptoms or history of any collagen disease, trauma presence in the nailfold due to cosmetic treatment or nail polish, were excluded. Videocapillaroscopy of the nailfold of the nondominant hand's fourth and fifth fingers was conducted on 100 students from the Universidad Espiritu Santo. The capillaroscopy was performed by an experienced rheumatologist in a room with an ambient temperature of 20-23ºC. The fourth and fifth fingers of the nondominant hand were chosen. The capillaries were observed using a 10x magnification capillaroscope (Dino-Lite) and photographs of the last distal row of capillaries were taken. The following capillaroscopic parameters were considered: capillary diameter (ectasia and giant capillaries), crosslinked capillaries, capillary tortuosity, ramified capillaries, avascular zones, hemorrhages, dominant morphology, subpapillar venous plexus visibility, cuticulitis and SD pattern. The images were analyzed by an experienced rheumatologist. Data was analyzed using SPSS. The non-parametric correlations were performed by tau_b Kendall and values were considered statistically significant when p ²0.01 and they had two tails.

Results: 100 patients were analyzed with a mean age of 21.38 years, 50 females (50%) and 50 males (50%), most were of mixed race (87%) and caucasian (13%). Videocapillaroscopy was performed on all participants, 17% of the population didn't present capillaroscopic disorders, 86% had alterations, the most frequent were ectasias (60%), tortuous capillaries (62%) and crosslinked capillaries (59%), the mean capillary size was 42.75µm (women: 41.14µm vs. men: 45.34µm). The population was divided into two groups: smokers and nonsmokers. In the group of smokers (n = 14), the capillary mean was 46.25µm, the most frequent capillaroscopic findings were tortuous capillaries (91%), cross-linked capillaries (72%), ectasias (64%) and ramified capillaries (27%). A correlation between the presence of ramified capillaries and smoking (p <0.05, OR 7.54, 95% CI 1.35-42.11) was found. No giant capillaries nor hemorrhages were found.

Conclusion: This is the first capillaroscopic study with healthy subjects in Ecuador, healthy subjects may present microvascular alterations and this results were similar to previous studies conducted by Hoerth and Coelho Andrade.

Disclosure: G. Maldonado, None; **C. Ferro**, None; **C. Ríos**, None; **K. Ríos**, None.

Abstract Number: 2256

Clinical Characteristics, Laboratory Findings and Nailfold Capillaroscopy Microscopy Patterns in a Monocentric Series of 123 Patients with Idiopathic Pernio

Thi Phuong Uyen Doan[1], **Sara Hussein**[1], Martial Koenig[2] and France Joyal[1], [1]Université de Montréal, Montreal, QC, Canada, [2]Internal Medicine, Hôpital Notre-Dame du CHUM, Montréal, QC, Canada

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SESSION INFORMATION

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Background/Purpose:

Few studies have looked at the characteristics of patients diagnosed with pernio and the significance of the use of capillaroscopy in these patients. The objective of this study is to characterize the clinical features and laboratory findings of pernio, and to determine the nailfold capillaroscopy microscopy (NCM) patterns in patients with the diagnosis of idiopathic pernio.

Methods:

This is a single-center study of patients referred to the vascular medicine unit for evaluation of paroxystical vascular acrosyndrome. Clinical features, laboratory findings and NCM patterns of 123 patients diagnosed as having idiopathic pernio were prospectively recorded from 2005 to 2015. NCM was performed on 8 digits, using a quantitative method: images were recorded using a digital camera and further analyzed to determine capillary diameter and density, and to rule in or rule out microvasculature abnormalities. Twenty healthy patients without any vascular acrosyndrome and 22 patients with primary Raynaud's phenomenon were used to compare NCM features.

Results:

A total of 123 patients were diagnosed as having idiopathic pernio (male/female ratio 1:4.6, median age at diagnosis 42.9 years [39.7;45.6]) and compared to 20 healthy patients (male/female ratio, 1:5.6, median age 32.7 [32.3;43.7]) as well as to 22 patients with Raynaud's phenomenon (male/female ratio, 1:3.4, median age 50.7 [44.2;54.4]).

In the pernio group, the median capillary diameter was 43.4mm [43.4;48.1] as compared to 39.6mm [35.3;41.9] in healthy patients (p=0.0211). There was no other significant difference for NCM features among the three groups. There was no difference when evaluating for disease activity, status of smoking, or recurrence of illness.

Conclusion:

Increased nailfold capillary diameter was observed in patients with pernio when compared to healthy patients regardless of the disease activity, smoking status or recurrence of illness. These findings suggest that capillaroscopy shows microvascular abnormalities suggesting a vasodilation mechanism. As pernio preferentially affects the feet, further studies are needed to specifically assess the NCM pattern on feet and to determine the pathophysiology of this disease.

Disclosure: T. P. U. Doan, None; **S. Hussein**, None; **M. Koenig**, None; **F. Joyal**, None.

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Abstract Number: 2257

Decline of Lung Function Is Associated with the Presence of Rheumatoid Factor in Korean Health Screening Subjects without Clinically Apparent Lung Diseases

Jiwon Hwang[1], Jae-Uk Song[2], Hyungjin Kim[3], Hyemin Jeong[4], Yeong Hee Eun[5], Chan Hong Jeon[6], Ji-Min Oh[7], Jaejoon Lee[4], Hoon-Suk Cha[8], Eun-Mi Koh[5] and Joong Kyong Ahn[9], [1]Department of Internal Medicine, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, Seoul, South Korea, [2]Department of Internal Medicine, Kangbuk Samsung Hospital, Seoul, South Korea, [3]Department of medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea, [4]Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea, [5]Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea, [6]Department of Internal Medicine, Soonchunhyang University College of Medicine, Bucheon, South Korea, [7]Anyang SAM Hospital, Anyang, South Korea, [8]Division of Rheumatology, Department of Internal Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea, [9]Department of Medicine, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, Seoul, South Korea

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Background/Purpose: Rheumatoid factor (RF) is an autoantibody directed against the Fc component of IgG. It is present in approximately 70-80% of rheumatoid arthritis (RA) patients but also found nonspecifically in chronic inflammatory condition such as sarcoidosis, hepatitis B or C infection, and tuberculosis. It has been suggested that lung may be an important sites generating or sequestering autoantibodies by immune dysregulation. Also, RF-positive patients without inflammatory arthritis showed significantly higher frequency of inflammatory airway abnormality. However, little is known about the influence of RF on

pulmonary function in health screening subjects without any specific medical problem. This study aimed to determine the effect of the presence of RF on pulmonary function in Korean health screening subjects without any history of joint disease and clinically apparent lung diseases.

Methods: Of the 114,944 people who participated in a health checkup program in 2010, 94,438 subjects with normal chest radiography were recruited, whose results of RF and pulmonary function test (PFT) using spirometry were available. Subjects with arthralgia or the past medical history of arthritis including RA, and lung diseases were excluded based on self-reported questionnaire. Association between RF and PFT was assessed by correlation analysis.

Results: Among 94,438 people, RF was positive in 3,326 subjects (3.52%). Their mean age was 41.3 ± 8.3 (range, 21 – 83) and 43.8% were female; these characteristics were not significantly different from those of RF-negative subjects. Ever-smokers (ex- and current smokers) were 39% in RF-positive subjects while 41.2% in RF-negative subjects ($p = 0.009$). Hepatitis B surface antigen (HBsAg) and anti-hepatitis C antibodies (anti-HCV) were more frequently seen in RF-positive subjects (12.1% vs. 3.5%, $p < 0.001$ for HBsAg and 0.5% vs. 0.1%, $p < 0.001$ for anti-HCV). Regarding PFT, RF-positive subjects had lower forced vital capacity (FVC) and forced expiratory volume in on second (FEV_1) compared to RF-negative subjects (3.79 ± 0.83 L vs. 3.87 ± 0.83 L, $p < 0.001$ and 3.17 ± 0.66 vs. 3.25 ± 0.67 L, $p < 0.001$). The proportion of subjects with FVC below 82% and FEV_1 below 84% of the predicted value was significantly higher in RF-positive subjects (50.7% vs. 46.6%, $p < 0.001$ and 54.5% vs.49.4%, $p < 0.001$) but the frequency of airflow limitation ($FEV_1/FVC \leq 70\%$) did not differ between two groups (1.4% vs. 1.5%, $p = 0.47$). FVC and FEV_1 had negative correlations with the RF titers ($r = -0.053$, $p < 0.001$ in FVC and $r = -0.055$, $p < 0.001$ in FEV_1). Multivariate logistic regression analysis showed that RF positivity was an independent predictor for the reduction of FVC (adjusted OR = 1.10, 95% CI 1.01 – 1.20, $p < 0.001$) and FEV1 (adjusted OR = 1.18, 95% CI 1.08 – 1.28, $p < 0.001$).

Conclusion: The results suggest that the presence of RF could impact on pulmonary function in healthy subjects without clinically apparent lung diseases. A follow up study for the serial changes of PFT may reflect the actual influence of the raised RF titers.

Disclosure: J. Hwang, None; **J. U. Song**, None; **H. Kim**, None; **H. Jeong**, None; **Y. H. Eun**, None; **C. H. Jeon**, None; **J. M. Oh**, None; **J. Lee**, None; **H. S. Cha**, None; **E. M. Koh**, None; **J. K. Ahn**, None.

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Abstract Number: 2259

Incidence of Obesity, Diabetes and High Blood Pressure Associated with Arthritis: Analysis of the Canadian Longitudinal National Population Health Survey

Orit Schieir[1], Sheilah. Hogg-Johnson[1,2], Richard H Glazier[3,4,5,6] and Elizabeth M. Badley[1,7], [1]Dalla Lana School of Public Health, University of Toronto, Toronto, ON, Canada, [2]Institute for Work and Health, Toronto, ON, Canada, [3]Family and Community Medicine, St. Michael's Hospital, Toronto, ON, Canada, [4]Centre for Research on Inner City Health, St. Michael's Hospital, Toronto, ON, Canada, [5]Institute for Clinical Evaluative Sciences, Toronto, ON, Canada, [6]Family and Community Medicine, University of Toronto, Toronto, ON, Canada, [7]Health Care & Outcomes Research, Toronto Western Res. Institute, Toronto, ON, Canada

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Background/Purpose: While cross-sectional evidence points to a higher prevalence of cardiovascular (CVD) risk factors in persons with arthritis, longitudinal population based studies are lacking. The objective of the present study was to estimate the incidence of major CVD risk factors (obesity, diabetes and high blood pressure) associated with arthritis in a longitudinal population-based survey.

Methods: The present study was a secondary analysis of the Canadian National Population Health Survey (NPHS), a longitudinal study of 17,276 Canadians followed-up every 2 years from 1994/95 through 2010/11. Survey participants provided updated information on socio-demographic variables, self-reported physician-diagnosed chronic conditions (including arthritis, high blood pressure and diabetes), and lifestyle/health behaviors, including height & weight used to calculate body mass index (BMI) classification of obesity. Cause of death records for diabetes (ICD10 codes:E10-E14) and hypertension (ICD10 codes I10-I15) were confirmed against the Canadian Vital Statistics Database. Adult participants age 18+ and at-risk for each risk factor (i.e. those without a prior history of, or prevalent report of each risk factor at the 1994/95 baseline assessment) were eligible for analysis. Adjusted odds ratios and 95% confidence intervals (CI) conveying the odds of experiencing each risk factor event in a given time period conditional on not having experienced the event before were estimated using separate discrete time survival models. Each model included repeated measures of arthritis updated every 2 years and the following baseline covariates: age sex, race, education, smoking, physical activity, BMI, alcohol consumption, non-CVD comorbidity index, and use of pain medications. All analyses were carried out using appropriate survey weights and bootstrap standard errors to account for the complex survey design.

Results: We identified 2,284, 3,022 and 1,045 incident obesity, high blood pressure and diabetes events during the study follow up period from 1996/97 through 2010/2011. Adjusting for age and sex, arthritis was significantly associated with increased risks of each of the 3 risk factors (obesity OR (95% CI): 1.39 (1.22-1.60), high blood pressure OR (95% CI): 1.30 (1.17-1.45) and diabetes OR (95% CI): 1.25 (1.03-1.52)). In fully adjusted models controlling for all covariates, results were attenuated but remained significant for obesity (OR (95% CI): 1.20 (1.02-1.42)) and high blood pressure (OR (95% CI): 1.19 (1.05-1.34.)) but not for diabetes (OR (95% CI): 0.97 (0.83-1.12)).

Conclusion: Results of this nationally representative Canadian population based study showed that persons with arthritis had increased risks for developing major CVD risk factors. The current findings not only support arthritis as a flag for screening for existing CVD risk factors but suggest that the disease itself, its treatment and/or its consequences (i.e. pain and disability) may be implicated in the onset of obesity and high blood pressure in persons at risk for developing these conditions.

Disclosure: O. Schieir, Fonds de recherche du Québec - Santé, 2; **S. Hogg-Johnson**, None; **R. H. Glazier**, None; **E. M. Badley**, None.

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High Prevalence of Hypomagnesemia and Its Relation to BMI, Type 2 Diabetes, and Clinical Disease Measures in a VA Outpatient Rheumatology Clinic Population

Nitika Ghattaura[1], Caleb Murphy[2] and Peter Valen[2,3], [1]Rheumatology, University of Minnesota Medical School, Minneapolis, MN, [2]University of Minnesota Medical School, Minneapolis, MN, [3]Rheumatology, Minneapolis VAMC, Minneapolis, MN
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Session Type: ACR Poster Session C

Background/Purpose: Magnesium plays an essential role in multiple cellular reactions, and there is increasing interest in its role in inflammation and pain. It has been estimated that nearly half the US population consumes less than the daily requirement of magnesium, likely due in part to decreased magnesium content in processed and refined foods and purified water. There are very few studies of the prevalence of hypomagnesemia in the general population, and no studies in a Rheumatology outpatient clinic population. The purpose of this study was to determine the prevalence of hypomagnesemia in a VA Rheumatology outpatient clinic population, and explore its relationship to BMI, Type II diabetes, clinical disease measures, and potential contributing factors, including PPI use.

Methods: 100 consecutive new referrals to the Minneapolis VAMC Rheumatology clinic and 100 consecutive established inflammatory arthritis patients were included in the study. Serum magnesium (Mg), ESR and CRP were measured, and BMI was

recorded. Data regarding presence of Type 2 diabetes, rheumatoid arthritis (RA), renal function, alcohol, PPI, diuretic and vitamin supplement use was collected. In new patients, self-reported pain scores (VAS) were recorded. DAS28 scores were calculated in the subset of patients with newly diagnosed rheumatoid arthritis. Chi-square and multivariable logistic regression analysis were used for statistical analysis.

Results: 76 of 200 patients (38%) had low serum magnesium levels (< 1.8 mg /dl). There was no significant difference between new vs established patients (41 % vs 35%, p= 0.38). Magnesium levels overall tended to be in the low normal range with an overall mean of 1.8 mg/dl ±0.25. Mean Pain scores were slightly higher in the low magnesium group, but the difference was not significant (4.51 ±3.32 vs 3.76 ±2.87, p= 0.88). Mean values of ESR and CRP were not significantly different in the low vs normal Mg groups. Mean DAS28 scores were slightly higher in the RA patients with low Mg vs normal Mg (5.7±1.5 vs 3.9±1.9), however the number of patients was too small to draw statistical conclusions. Although a larger percentage of patients with low Mg were taking PPIs, the unadjusted effect of PPI use on prevalence of hypomagnesemia was small (OR 1.67, p=0.09). The concomitant use of diuretics did not significantly alter the risk. There was no significant association between reported alcohol or supplement use and hypomagnesemia. There was a weak association of BMI and hypomagnesemia (OR 1.05, p=0.04). The strongest association was with T2DM, which was an independent risk factor for hypomagnesemia (OR 3.77, p=0.001).

Conclusion: We found an alarmingly high prevalence of hypomagnesemia in a cohort of VA Rheumatology clinic outpatients. BMI and PPI use were weakly associated with hypomagnesemia. Hypomagnesemia may be associated with higher disease activity in rheumatoid arthritis. We found a strong association between T2 DM and hypomagnesemia. This study supports the need for future investigation of the prevalence and causes of hypomagnesemia in the rheumatic diseases, and its role in inflammation, pain and disease activity.

Disclosure: N. Ghattaura, None; **C. Murphy**, None; **P. Valen**, None.

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Abstract Number: 2261

Association Between Musculoskeletal Pain, Fat Mass and Fat Free Mass: Results from a Population-Based Study

Tiffany K. Gill[1], Tom P. Walsh[2,3], E. Michael Shanahan[4] and **Catherine Hill**[5,6], [1]Medicine, The University of Adelaide, Adelaide, Australia, [2]Medicine, Flinders University, Adelaide, Australia, [3]Podiatry, Repatriation General Hospital, Adelaide, Australia, [4]Flinders University, Adelaide, Australia, [5]The Health Observatory, The University of Adelaide, Adelaide, Australia, [6]Rheumatology Unit, The Queen Elizabeth Hospital, Woodville, Australia

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Background/Purpose: Musculoskeletal pain has been shown to commonly occur at multiple sites. This is likely to have a greater impact on abilities to undertake activities of daily living, work and quality of life in general. While obesity has been shown to impact on the occurrence of musculoskeletal conditions, body composition may also play a role. Few studies have examined the association between body composition and multiple pain sites although a recent study of 133 participants demonstrated that fat mass and fat mass index were associated with pain at a greater number of weight-bearing sites[1]. The aim of this study was to examine the association between pain sites and pain at weight-bearing and non-weight-bearing sites.

Methods: The North West Adelaide Health Study (NWAHS) is a longitudinal cohort study with three stages of data collection. Each stage comprised a self-complete questionnaire, clinic assessment and Computer Assisted Telephone Interview (CATI). In Stage 2 (2004-2006), Dual Energy X-ray Absorptiometry (DXA) scans were undertaken on those aged 50 years and over (n=1066), which enabled the calculation of fat mass index and fat free mass index. Additional data included demographics and body mass index (BMI). As part of the telephone interview, participants were asked if they had ever had back, hip, knee, shoulder and hand pain and/or stiffness on most days for at least a month and whether they had pain or stiffness in the feet on most days. The association with areas of pain and BMI, fat mass (kg), fat mass index, fat free mass (kg) and fat free mass index were examined

using logistic regression analysis.

Results: Among those aged 50 years and over, the prevalence of pain and/or stiffness in the feet was 20.2%, shoulder 27.8%, hip 15.6%, back 40.8%, hand 21.5% and knee 18.0%. The unadjusted and adjusted associations between areas of pain, BMI and body composition measurements are presented in Table 1. There were significant associations for both weightbearing and non-weightbearing joints between BMI and body composition variables even after adjustment for age, sex and the appropriate body composition measure.

Table 1: Unadjusted and adjusted association between areas of musculoskeletal pain, BMI and body composition

	BMI	Fat mass	Fat mass index	Fat free mass	Fat free mass index
Unadjusted ***denotes significant p<0.05**	OR (95% CI) p-value	OR (95% CI) p-value	OR (95% CI) p-value	OR (95% CI) p-value	OR (95% CI) p-value
Foot	1.07 (1.04-1.11)*	1.04 (1.02-1.05)*	1.10 (1.06-1.14)*	0.99 (0.98-1.00)	1.00 (0.94-1.06)
Shoulder	1.03 (1.00-1.06)*	1.01 (1.00-1.02)	1.03 (1.00-1.07)	1.00 (0.99-1.01)	1.03 (0.97-1.08)
Hip	1.07 (1.03-1.10)*	1.04 (1.02-1.06)*	1.11 (1.07-1.16)*	0.99 (0.97-1.00)	0.98 (0.92-1.05)
Hand	1.06 (1.02-1.09)*	1.03 (1.01-1.04)*	1.09 (1.05-1.14)*	0.98 (0.96-0.99)*	0.97 (0.92-1.03)
Back	1.06 (1.04-1.09)*	1.03 (1.02-1.05)*	1.08 (1.05-1.12)*	1.00 (0.99-1.01)	1.03 (0.98-1.08)
Knee	1.07 (1.04-1.10)*	1.03 (1.02-1.05)*	1.08 (1.04-1.12)*	1.01 (1.00-1.03)	1.07 (1.00-1.14)*
Adjusted for age and sex ***denotes significant p<0.05**	**BMI**	**Fat mass**	**Fat mass index**	**Fat free mass**	**Fat free mass index**
Foot	1.07 (1.04-1.10)*	1.03 (1.02-1.05)*	1.09 (1.05-1.14)*	1.04 (1.01-1.07)*	1.14 (1.05-1.24)*
Shoulder	1.03 (1.00-1.06)	1.01 (0.99-1.02)	1.02 (0.98-1.06)	1.03 (1.01-1.05)*	1.12 (1.04-1.21)*
Hip	1.07 (1.03-1.10)*	1.04 (1.02-1.06)*	1.11 (1.05-1.16)*	1.03 (1.00-1.06)	1.13 (1.03-1.24)*
Hand	1.06 (1.02-1.09)*	1.02 (1.00-1.04)*	1.07 (1.03-1.12)*	1.01 (0.98-1.03)	1.13 (1.04-1.23)*
Back	1.06 (1.04-1.09)*	1.03 (1.02-1.05)*	1.09 (1.05-1.14)*	1.03 (1.01-1.05)*	1.12 (1.04-1.20)*
Knee	1.07 (1.03-1.10)*	1.03 (1.02-1.05)*	1.09 (1.04-1.14)*	1.05 (1.03-1.08)*	1.18 (1.08-1.29)*
Adjusted for age and sex and relevant body composition measure ***denotes significant p<0.05**	**BMI**	**Fat mass[a]**	**Fat mass index[a]**	**Fat free mass[b]**	**Fat free mass index**
Foot		1.03 (1.00-1.05)*	1.08 (1.02-1.13)*	1.02 (0.99-1.05)	1.05 (0.95-1.16)
Shoulder		0.99 (0.98-1.01)	0.98 (0.94-1.03)	1.03 (1.01-1.06)*	1.14 (1.04-1.25)*
Hip		1.04 (1.02-1.06)*	1.10 (1.04-1.16)*	1.00 (0.96-1.03)	1.01 (0.91-1.14)
Hand		1.02 (1.01-1.04)*	1.05 (1.00-1.11)*	0.99 (0.96-1.02)	1.07 (0.97-1.18)
Back		1.03 (1.02-1.05)*	1.09 (1.04-1.13)*	1.01 (0.98-1.03)	1.03 (0.95-1.12)

Knee		1.02 (1.00-1.04)*	1.06 (1.00-1.12)*	1.04 (1.01-1.07)*	1.11 (1.00-1.23)

[a]Models with fat mass and fat mass index adjusted for fat free mass and fat free mass index respectively

[b]Models with fat free mass and fat free mass index adjusted for fat mass and fat mass index respectively

Conclusion: The prevalence of joint pain is high in community dwelling people aged 50 years and over. BMI and body composition measurements are associated with reports of pain, in both weightbearing and non-weightbearing joints. The association with fat mass and fat mass index in particular may be associated with metabolic effects. However, body composition does need to be considered when treating those with musculoskeletal pain.

1 Brady SRE et al. Body composition is associated with multisite lower body musculoskeletal pain in a community-based study. Journal of Pain. 2015, doi:10.1016/j.pain.2015.04.006

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Abstract Number: 2262

A Novel Study Instrument to Identify Household Work Related Musculoskeletal Disorders – Development and Validation

Priyanga Ranasinghe[1], Inoshi Atukorala[2], Sachitra Illangatilaka[3] and Nalika Gunawardena[4], [1]Public Health, Medical Officer, Family Health Bureau, COLOMBO 8, Sri Lanka, [2]Department of Clinical Medicine, Faculty of Medicine, University of Colombo, Consultant Rheumatologist and Senior Lecturer in Medicine, COLOMBO 8, Sri Lanka, [3]Department of Rheumatology and Medical Rehabilitation, Senior Registrar, COLOMBO 8, Sri Lanka, [4]Faculty of Medicine, University of Colombo, Senior Lecturer in Community Medicine, COLOMBO 8, Sri Lanka

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Session Type: ACR Poster Session C

Background/Purpose:

Household work is significant cause of musculoskeletal pain, particularly in the South Asian setting where household work is labour intensive and manually performed. But, the burden of this problem is unknown with the lack of a valid screening tool cited as a reason for this shortfall. This project develops and validates a novel study instrument to identify household work related musculoskeletal disorders (HWMSD) in the following nine anatomical regions – the neck, shoulder, elbow, wrist/hand, upper back, low back, hip/thigh, knee and ankles/feet.

Methods:

An interviewer -administered tool the Household Work related Musculoskeletal Disorders Questionnaire (HWMQ)) was developed. It assessed the presence/absence of musculoskeletal symptoms and household work-relatedness of these symptoms. This tool was developed by a multidisciplinary panel of experts using the Nordic Musculoskeletal Questionnaire as the base. Identification of the HWMSD was done if all absolute criteria were present for a given region in the presence of 2 or more probable symptom related *and* one or more probable household work related criteria(Table 1). The criterion validity against the diagnosis of a rheumatologist was the gold standard. Subsequently, test-retest reliability and acceptability was assessed in a sample of Sri Lankan housewives.

Results: The study cohort contained 250 full time housewives (median age 40 years, Interquartile range 35-45 years) from

Colombo, Sri Lanka. 77% were engaged in household work for >10 years with a mean of 11.3 hours (±2.8) spent daily on household work. Household work included cooking (96 %), washing clothes by hand (83.6%), sweeping and cleaning (96.4%) carrying water/firewood (72.8%) and childcare (52.8%). Acceptability was high with a response rate of 83.3%. Average time taken to complete the HWMQ was 12min (± 3min). Psychometric properties of the HWMQ were as follows: sensitivity was highest in ankle/feet and lowest in hip/thigh region and specificity was highest in low back assessment and lowest in the knee region (Table 2). Reliability by Cohen's Kappa was above 0.8 for each region.

Conclusion:

The household work related musculoskeletal disorders questionnaire is a valid and reliable instrument to screen the housewives for musculoskeletal disorders related to housework.

Table 1 Absolute and Probable Criteria to Diagnose HWMSD among Housewives

	Absolute criteria	Probable criteria
Symptoms related criteria	• Pain/ache/ discomfort for minimum of 3 consecutive days during last 3 months **(For low back region only)** • No identifiable pattern with menstruation • The pain not related to /associated with pain of sexual intercourse • Burning sensation in abdomen • Pain on passing urine • Constipation	• Pain, ache or discomfort restricts movements • Pain, ache or discomfort has limited household activities performed • Pain, ache or discomfort has worsened intermittently or continuously over time • Pain, ache or discomfort with soreness of 5 or more in the visual analogue scale of (1-10)
Household work related criteria	• The site not subjected to any injury other than household work related injury	• Onset of pain, ache or discomfort after performing household work as a housewife • Pain, ache or discomfort worsen when performing household work • pain, ache or discomfort subsides when having rest from household work

Table 2: Sensitivity and specificity of the HWMQ by region

	Sensitivity (%)(95% CI)	Specificity (%)(95% CI)
Neck	80(75.0-85.0)	99.5 (98.6-100)
Shoulder	97 (94.9-99.1)	98.6 (97.1-100)
Elbow	93.7(90.7-96.7)	98.7 (97.3-100)
Wrist/Hand	89.1 (85.2-93)	99.0 (97.8-100)
Upper back	95.5(92.9-98.1)	98.7 (97.3-100)
Lower back	94.5(91.7-97.3)	99.3 (98.3-100)
Hip/Thigh	80 (75-85)	98.0(96.3-99.7)
Knee	93.6(90.6-96.6)	89.7(85.9-93.5)
Ankle/Feet	97.6(95.7-99.5)	99 (97.8-100)

* CI- confidence interval

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Abstract Number: 2263

Construct and Convergent Validity of Four Global Measures of at-Work Productivity Loss in Patients with Rheumatic Diseases

Sarah Leggett[1], Diane Lacaille[2], Carina Mihai[3], Mihai Bojinca[4], Brendan van As[5], Suzanne M. Verstappen[6] and EULAR-PRO worker productivity group, [1]Arthritis Research UK Centre for Epidemiology, Manchester Academic Health Science Centre,The University of Manchester, Manchester, United Kingdom, [2]Arthritis Research Centre, University of British Columbia, Vancouver,

BC, Canada, [3]Internal Medicine and Rheumatology, Ion Cantacuzino Hospital, Bucharest, Romania, [4]Carol Davila University of Medicine and Pharmacy, Internal Medicine and Rheumatology, Cantacuzino Hospital, Bucharest, Romania, [5]Arthritis Research Canada, Richmond, BC, Canada, [6]Arthritis Research UK Centre for Epidemiology, The University of Manchester, Manchester, United Kingdom

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Background/Purpose:

Several global measures are available to assess at-work productivity loss in rheumatic diseases. Paucity in research exploring the construct validity of such measures contributes to a lack of consensus on which measure is optimum. The purpose of this study was to determine the construct and convergent validity of four global measures of at-work productivity loss, namely the Work Productivity Scale–Rheumatoid Arthritis (WPS-RA), Work Productivity and Activity Impairment Questionnaire (WPAI), Work Ability Index (WAI), and the Quality and Quantity questionnaire (QQ), with multi-item measures of at-work productivity and health specific measures.

Methods:

In this international study, 101 patients with inflammatory arthritis or OA in paid employment were recruited from 3 countries (UK, Canada, and Romania). Demographic, clinical, and occupational data (e.g., occupation; manual vs. non-manual) were collected. The global measures of at-work productivity loss were completed (WPAI; *0=no effect on work – 10=completely prevented from working,* WPS-RA; *0=no interference – 10=complete interference,* WAI; *0=unable to work – 10=work ability at its best,* QQ; *0= practically nothing– 10=normal quantity*), in addition to multi-item measures of at-work productivity loss (the Workplace Activity Limitations Questionnaire; WALS, & the Work Limitations Questionnaire; WLQ-25) and disease specific and health related outcomes. Spearman's correlation coefficients were used to assess the strength of the relationship between the global measures with multi-item and health related measures.

Results:

59% of the study population were female; mean age was 48 years (SD 8.8) and the mean symptom duration was 14 years (SD 10.8). 39% of the population had RA, and 52% had a non-manual occupation. Spearman correlations yielded mostly high (i.e., 0.5-0.7), with some moderate (i.e. 0.3-0.5) convergence between global and multi-item measures (Table 1). Overall, convergence was higher with the WALS (with the WPS-RA having the highest convergence; 0.73) and lower with the WLQ-25 (with the WPAI having the lowest convergence; 0.42), likely because of differences in construct measured by multi-item measures [i.e. degree of limitation (WALS) vs. amount of time limited (WLQ-25)]. Construct validity revealed mostly high, with some moderate, correlations between the global measures and health related questionnaires (Table 1).

Conclusion:

Most of the global measures demonstrated high convergence validity with multi-item measures and construct validity with disease specific measures. The strength of the relationships was variable across instruments, likely due to differences amongst global and multi-item measures (e.g., varying constructs). Overall, the results contribute to the currently sparse validity data supporting the use of global instruments to measure at-work productivity loss.

Table 1. Spearman correlations* of the four global measures with multi-item measures of at-work productivity, disease specific measures and health related measures.

	WALS	WLQ-25 index	HAQ	EQ-5D	VAS pain	VAS well-being	RAID (n=38)	PsAID (n=19)	Lequesne (n=11)	BASDAI (n=30)	BASFI (n=30)
WPAI	0.67	0.42	0.37	-0.45	0.51	0.62	0.55	0.41	0.70	0.50	0.24
WPS-RA	0.73	0.50	0.45	-0.45	0.50	0.56	0.62	0.56	0.58	0.53	0.43
WAI	-0.69	-0.56	-0.50	0.54	-0.50	-0.62	-0.34	-0.57	-0.49	-0.72	-0.57
QQ	-0.57	-0.55	-0.33	0.45	-0.36	-0.43	-0.48	-0.75	-0.32	-0.57	-0.30

*Spearman correlation coefficients: <0.1 trivial; 0.1–0.3 small; 0.3–0.5 moderate; 0.5–0.7 high; 0.7–0.9 very high; >0.9 nearly perfect.
Abbreviations: HAQ; Health Assessment Questionnaire, RAID; Rheumatoid Arthritis Impact of Disease, PsAID; Psoriatic Arthritis Impact of Disease, Lequesne; a measure of Osteoarthritis disease activity, BASDAI; Bath Ankylosing Spondylitis Disease Activity Index; BASFI; Bath Ankylosing Spondylitis Functional Index.

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Abstract Number: 2264

Prevalence and Social Burden of Active Chronic Low Back Pain in the Adult Portuguese Population – Results from a National Survey

Nelia Gouveia[1,2], Ana M. Rodrigues[1,3,4,5], Monica Eusebio[6], Pedro Machado[1,7,8], Sofia Ramiro[1,5,9], Helena Canhao[1,10,11] and Jaime C Branco[1,5,12,13], [1]EpiReumaPt Study Group, Lisbon, Portugal, [2]CEDOC - Chronic Diseases FCM NOVA, NOVA Medical School - Faculdade Ciências Médicas da UNL, Lisbon, Portugal, [3]Rheumatology Research Unit, Instituto de Medicina Molecular and Rheumatology and Bone Metabolic Diseases Department, Hospital de Santa Maria, Lisbon, Portugal, [4]Faculdade de Medicina a Universidade de Lisboa, Lisbon, Portugal, [5]CEDOC - Chronic Diseases FCM NOVA, NOVA Medical School - Faculdade de Ciências Médicas da UNL, Lisbon, Portugal, [6]Portuguese Society of Rheumatology, Lisbon, Portugal, [7]University College London - MRC Centre for Neuromuscular Diseases,, London, United Kingdom, [8]Clínica Universitária de Reumatologia, Faculdade de Medicina da Universidade de Coimbra, Coimbra, Portugal, [9]Rheumatology, Leiden University Medical Center, Leiden, Netherlands, [10]Rheumatology Research Unit, Instituto de Medicina Molecular, Lisbon, Portugal on behalf of the Rheumatic Diseases Portugal Register, Lisbon, Portugal, [11]Hospital Santa Maria - Serviço de Reumatologia, Lisboa, Portugal, [12]Serviço de Reumatologia do Hospital Egas Moniz, Centro Hospitalar Lisboa Ocidental (CHLO- E.P.E.), lisbon, Portugal, [13]NOVA Medical School/faculdade de ciências médicas, Universidade Nova de Lisboa, Lisboa, Portugal

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Session Type: ACR Poster Session C

Background/Purpose: The prevalence and burden of chronic low back pain (CLBP) were ill defined in Portugal. The aim of this study was **t**o determine, the prevalence of active CLBP (ACLBP) in the adult Portuguese population; to compare the ACLBP population with the population without ACLBP, and to explore factors associated with ACLBP.

Methods: This study was conducted under the scope of EpiReumaPt, a Portuguese population-based study including 10,661 subjects, representative of the Portuguese population. Trained interviewers undertook structured face-to-face questionnaires in participant's households that included socio-demographic, socio-economic information and medical history, as well as information on functional ability, quality of life and healthcare resources consumption. ACLBP was self-reported and considered if present on the day of the interview and for ³90 days. Prevalence estimates were calculated. Differences in quality of life, functional ability and healthcare resources consumption between subjects with and without ACLBP were evaluated. Factors associated with ACLBP were identified through logistic regression. All analyses were adjusted for possible confounders.

Results: The prevalence of ACLBP was 10.4% (95%CI 9.6%; 11.9%). The mean age was 58.9 (SD 17.2) years old and 68.7% were overweight or obese. ACLBP was significantly more prevalent among women (14.1% vs 6.3% in men).

After adjustment, ACLBP subjects were more likely to have anxiety symptoms (OR=2.66, $p<0.001$), to retire early due to the disease (OR=1.72; $p=0.006$), and to be absent from work due to the disease (OR=1.86; $p<0.001$). The presence of a self-reported rheumatic musculoskeletal disease (RMD), anxiety symptoms, female gender, older age, higher education level and higher number of self-reported comorbidities were significantly associated with the presence of ACLBP, taking potential confounders into account (BMI, NUTS II, present alcohol intake and depressive symptoms). In turn, physical exercise was inversely associated with ACLBP (table 1).

Conclusion: ACLBP is highly prevalent in the Portuguese population and is associated with disability and with a high consumption of healthcare resources. Female gender, older age, anxiety symptoms, educational level, the presence of other RMD and the number of comorbidities were independently associated with the presence of ACLBP. These factors should be taken into account when developing strategies to prevent the occurrence of ACLPB.

Table 1: Factors associated with active CLBP

Socio-demographic characteristics	**OR**	**95% CI**	**p value**
Gender (female)	**1.34**	**1.07; 1.66**	**0.009**
Age group			
26-35 y.o. vs 18-25 y.o.	2.19	1.18; 4.07	**0.013**
36-45 y.o. vs 18-25 y.o.	2.90	1.63; 5.14	**<0.001**
46-55 y.o. vs 18-25 y.o	3.04	1.70; 5.47	**<0.001**
56-65 y.o. vs 18-25 y.o.	3.04	1.64; 5.66	**<0.001**
66-75 y.o. vs 18-25 y.o.	4.41	2.25; 8.64	**<0.001**
76-85 y.o. vs 18-25 y.o.	3.39	1.75; 6.57	**<0.001**
>86 y.o. vs 18-25 y.o	6.92	3.19; 15.02	**<0.001**
BMI (kg/m^2)			
Normal vs underweight		0.40; 3.02	
Overweight vs underweight	1.10	0.47; 3.53	0.848
Obese vs underweight	1.28	0.52; 3.95	0.629
Education level	1.43		0.494
10-12 years vs >12 years	2.04	1.29; 3.21	**0.002**
5-9 years vs >12 years	1.58	0.99; 2.54	0.057
0-4 years vs >12 years	1.75	1.02; 2.99	**0.042**
NUTS II		0.66; 1.15	
Centro vs Norte	0.87	0.59; 1.10	0.331
Lisboa vs Norte	0.81	0.59; 1.23	0.182
Alentejo vs Norte	0.86	0.40; 1.11	0.404
Algarve vs Norte	0.67	0.71; 1.32	0.116
A[illegible]ores vs Norte	0.97	0.85; 1.62	0.828
Madeira vs Norte	1.17		0.336
Number of Comorbidities (0-15)	**1.11**	**1.05; 1.18**	**<0.001**
Present alcohol intake (yes/no)	**0.80**	**0.62; 1.02**	**0.068**

Physical exercise (yes/no)	**0.78**	**0.62; 0.98**	**0.030**
Anxiety symptoms (yes/no)	**2.47**	**1.88; 3.23**	**<0.001**
Depressive symptoms (yes/no)	**1.39**	**0.93; 2.07**	**0.109**
Self-report of any RMD (yes/no)	**2.82**	**2.17; 3.69**	**<0.001**

RMD-Rheumatic and musculoskeletal diseases; y.o. – years old; vs – versus; NUTS II - Nomenclature of Territorial Units for Statistics (North, Centre, Alentejo, Algarve, Lisbon, Madeira and the Azores)

Adjusted p-values<0.05.

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Abstract Number: 2265

Prevalence and Physical and Mental Health Patterns of Rheumatic and Musculoskeletal Diseases in Portugal: Results from a National Health Survey

Jaime C Branco[1], Ana M. Rodrigues[2], Nelia Gouveia[3], Leonor P Costa[4], Monica Eusebio[5], Sofia Ramiro[2,4,6], Pedro Machado[4,7,8], Filipa Mourão[4,9,10], Inês Silva[9,11], Pedro Laires[4], Alexandre Sepriano[4,12], Filipe Araújo[4,13], Sónia Gonçalves[4], Pedro S Coelho[4,14], Viviana Tavares[4], Jorge Cerol[4,15], Jorge M Mendes[4,14], Loreto Carmona[16] and Helena Canhao[17], [1]NOVA Medical School/faculdade de ciências médicas, Universidade Nova de Lisboa, Lisboa, Portugal, [2]CEDOC - Chronic Diseases FCM NOVA, NOVA Medical School - Faculdade de Ciências Médicas da UNL, Lisbon, Portugal, [3]CEDOC - Chronic Diseases FCM NOVA, NOVA Medical School - Faculdade Ciências Médicas da UNL, Lisbon, Portugal, [4]EpiReumaPt Study Group, Lisbon, Portugal, [5]Portuguese Society of Rheumatology, Lisbon, Portugal, [6]Rheumatology, Leiden University Medical Center, Leiden, Netherlands, [7]Clínica Universitária de Reumatologia, Faculdade de Medicina da Universidade de Coimbra, Coimbra, Portugal, [8]University College London - MRC Centre for Neuromuscular Diseases,, London, United Kingdom, [9]Centro Hospitalar Lisboa Ocidental (CHLO- E.P.E.), Lisbon, Portugal, [10]NOVA Medical School - Faculdade Ciências Médicas da Universidade Nova de Lisboa, Lisbon, Portugal, [11]EpiReumaPt Study Group, lisbon, Portugal, [12]Rheumatology, Hospital de Egas Moniz - CHLO, Lisbon, Portugal, Lisbon, Portugal, [13]Rheumatology, Centro Hospitalar de Lisboa Ocidental, Hospital Egas Moniz, Lisboa, Portugal, [14]NOVA Information Management School, Lisbon, Portugal, [15]Portuguese Catholic University, Lisbon, Portugal, [16]Instituto de Salud Musculoesquelética, Madrid, Spain, [17]Hospital Santa Maria - Serviço de Reumatologia, Lisboa, Portugal

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SESSION INFORMATION

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Background/Purpose:

Rheumatic and musculoskeletal diseases (MSKD) are a prevalent leading cause of disability and consume a large amount of healthcare and social resources. MSKD have been associated with low levels of physical and mental health in other countries. The purpose of this study was to estimate the national prevalence of hand, knee and hip osteoarthritis (OA), low back pain (LBP), rheumatoid arthritis (RA), fibromyalgia (FM), gout, spondyloarthritis (SpA), periarticular disease (PD) systemic lupus erythematosus (SLE), polymyalgia rheumatica (PMR) and osteoporosis (OP)) in the adult Portuguese population; to compare

physical and mental health between participants with and without MSKD.

Methods:

EpiReumaPt is a national health survey conducted from Sep'2011 to Dec'2013, which involved a three-stage approach. First, 10661 adult subjects were randomly selected. Trained interviewers undertook structured face-to-face questionnaires in participant's households that included a screening for MSKD, and the EQ5D and HAQ. Secondly, all participants screened positive for at least one MSKD plus 20% of individuals with no rheumatic complaints were invited to be seen by a rheumatologist at the local Primary Care Center for a structured evaluation. Finally, a team of 3 experienced rheumatologists revised all the clinical data and confirmed the diagnoses according to previously validated criteria. Estimates were computed as weighted proportions, in order to take into account the sampling design.

Results:

Prevalence of MSKD in the adult Portuguese population was as follows with 95% CI (table1): After adjustment, subjects with RMD had significantly lower EQ5D scores (β=-0.09; $p<0.001$) and higher HAQ scores (β=0.12; $p<0.001$) than subjects with no MSKD. Some MSKD were significantly and independently associated with worse EQ5D scores: PMR (β=-0.334), RA (β=-0.132), FM (β=-0.100), LBP (β=-0.07), Knee OA (β=-0.06) and PD (β=-0.04). Proportion of anxiety and depression symptoms among the MSKD Portuguese patients was 16.7% and 8.3%, respectively; the prevalence of anxiety symptoms was significantly higher when compared with subjects without MSKD diseases (OR= 3.4; p=0.003). Moreover, FM (OR=3.12; $p<0.001$), SpA (OR=2.82; p=0.012) and LBP (OR=1.84; p=0.007) were significantly and independently associated with the presence of anxiety symptoms; PMR (OR=18.81; p=0.006), FM (OR=3.73; p=0.001) and LBP (OR=1.55; p=0.030) were significantly and independently associated with the presence of depression symptoms.

	Total prevalence (95% CI) n=3877
LBP (n=1393)	**26.41%** (23.32%; 29.51%)
PD (n=929)	**15.76%** (13.47%; 18.04%)
Knee OA (n=981)	**12.40%** (11.00%; 13.81%)
OP (n=858)	**10.16%** (8.98%; 11.33%)
Hand OA (n=625)	**8.73%** (7.53%; 9.93%)
Hip OA (n=199)	**2.95%** (2.27%; 3.62%)
FM (n=149)	**1.70%** (1.13%; 2.08%)
SpA(n=92)	**1.63%** (1.19%; 2.08%)
Gout (n=92)	**1.28%** (0.96%; 1.60%)
RA (n=61)	**0.73%** (0.52%; 0.95%)
SLE (n=13)	**0.15%** (0.06%; 0.25%)
PMR (n=8)	**0.10%** (0.02%; 0.18%)

Conclusion: MSKDs are highly prevalent in Portugal and are associated with significant impairment of physical and mental health.

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Abstract Number: 2266

Is Rheumatic Disease Really More Severe in Indigenous Populations? a Systematic Review of Clinical Outcomes in Indigenous Populations of Canada,

the United States, Australia and New Zealand

Kelle Hurd[1] and Cheryl Barnabe[2], [1]University of Calgary, Calgary, AB, Canada, [2]Cumming School of Medicine, University of Calgary, Calgary, AB, Canada

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Background/Purpose: The Indigenous populations of Canada, the United States, Australia and New Zealand have higher disease prevalence for many inflammatory arthritis conditions and connective tissue diseases compared to the non-Indigenous populations in those countries. Phenotypic differences are believed to exist clinically. The objective of our systematic review was to summarize differences in disease characteristics, disease activity and outcomes for Indigenous populations.

Methods: A systematic search (to June 2015) was performed in Medline, EMBASE, the Bibliography of Native North Americans, Circumpolar Health Bibliographic Database, Metis Health Database, Native Health Database, Native Indigenous Studies Portal, Australian Indigenous Health InfoNet, and conference abstracts from rheumatology conferences (2012-2015) in the countries of interest and international conferences. Search terms for Indigenous populations were combined with search terms for inflammatory arthritis conditions (rheumatoid arthritis, spondyloarthropathies, juvenile idiopathic arthritis), connective tissue disorders (systemic lupus erythematosus, scleroderma, myositis, sjogren's), crystal arthritis and osteoarthritis. Studies were included if they reported disease activity measures for the condition of interest, the proportion of patients with recognized classification criteria for the condition of interest, or mortality.

Results: A total of 5,269 titles and abstracts were reviewed, of which 523 underwent full-text review, and 87 were included for extraction of clinical outcomes. Thirty-eight of the studies were published before the year 2000, and only 37% made mention of Indigenous populations collaboration on the studies. Nearly all the studies described outcomes in the North American populations (n=38 American, n=40 Canadian), with only 5 studies from Australia and 4 studies from New Zealand. Forty-four studies described RA characteristics in Indigenous populations, and 14 had a comparator group defined as Caucasian, White, Non-Aboriginal or Non-First Nations. Indigenous populations were younger at disease onset (age range 29-41 years vs 36-55 years). Disease activity measures were not frequently significantly worse in Indigenous patients, although lesser response to treatment was identified in one study. Pain levels were higher in Indigenous patients in all studies reporting this outcome (n=3 studies). No studies examined a mortality rate, but in one study Indigenous patients were younger at death (53 vs 76 years). There were 22 studies identified that described lupus characteristics and outcomes, and 13 had a comparator group. Lupus nephritis was more common in Indigenous populations, with a higher mortality rate.

Conclusion: Our synthesis highlights knowledge gaps that exist and assumptions that have been made with regards to the disease phenotype of Indigenous populations of Canada, the United States, Australia and New Zealand. Contemporary studies performed in collaboration with Indigenous populations are required to more fully understand the consequences of rheumatic disease in these countries.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/is-rheumatic-disease-really-more-severe-in-indigenous-populations-a-systematic-review-of-clinical-outcomes-in-indigenous-populations-of-canada-the-united-states-australia-and-new-zealand

Abstract Number: 2267

Rheumatology Work Force Planning in Western Countries – a Systematic Literature Review

Christian Dejaco[1], Angelika Lackner[2], Markus Narath[3] and Martin Sprenger[4], [1]Department of Rheumatology and Immunology, Medical University Graz, Graz, Austria, [2]Avenbruggerplatz 15, Medical University Graz, Graz, Austria, [3]Steiermärkische Krankenanstaltengesellschaft (KAGes), Graz, Austria, [4]Public Health School, Medical University of Graz, Graz, Austria

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Session Title: Epidemiology and Public Health Poster III (ACR): Gout and Non-Inflammatory Musculoskeletal Conditions

Session Type: ACR Poster Session C

Background/Purpose: To compare models forecasting adult and paediatric rheumatology work force requirement in Western countries

Methods: A systematic literature review (SLR) was conducted by 2 authors (CD, AL) through medical databases (Ovid MEDLINE®, Embase, CINAHL, Cochrane Library), and the homepages (and referenced links) of the departments of health, rheumatology societies and medical associations of the following countries: Austria, Germany, Switzerland, United Kingdom (UK), Ireland, Canada, USA, Australia, New Zealand. Besides, we searched the homepages of EULAR, the European Commission and related organisations. Additional articles were retrieved by reviewing the reference list of full articles, conference abstracts and by contacting the national rheumatology societies of EULAR countries, USA, Australia, New Zealand, Canada and the EU - Joint action on workforce planning and forecasting. We included only English and German articles providing an estimation of (current and/or future) adult and/or paediatric rheumatology manpower (required to serve the respective population), and describing the methods and factors underlying this calculation. Quality appraisal of included articles was not possible because no appropriate instrument is available. Any discordance between the authors (3% of the papers) was resolved by discussion. The protocol of this SLR was registered at the PROSPERO website (CRD42014013948).

Results: The initial search yielded n=5699 articles, a total of 12 articles (9 papers for adult rheumatology, 1 for paediatric and 2 for adult and paediatric rheumatology) met all inclusion criteria. Rheumatology manpower calculations were available for the USA (3 models), Canada (n=3), USA + Canada (n=1), Germany (n=2), Spain (n=1) and the UK (n=2). There was a large variance regarding the estimated number of rheumatologists ranging from 0.7 (UK, 1988) to 3.5 (Spanish projection for 2021) to serve a population of 100,000 people. For paediatric rheumatology, 1 rheumatologist per 100,000 children (Germany) or 0.7-1.0 per 1,000,000 (of the general) population (USA) were suggested. Most models used a demand (n=3) or needs (n=6) based approach whereas in 3 papers, the underlying method was unclear. The following variables were considered by ≥ 1 model: disease prevalence, proportion of patients that should be referred to a rheumatologist, clinical visits/patient/year, population development, workforce provided by one rheumatologist full time equivalent, factors influencing workforce capacity, patient flow/care sharing, effect of medical development.

Conclusion: Different methods have been applied to forecast rheumatology work force requirement in Western countries yielding highly variable results with 0.7 to 3.5 rheumatologists required to serve a population of 100,000 people.

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Abstract Number: 2268

Peripheral Joint MRI for Inflammatory Arthritis and the Choosing Wisely Campaign – Evidence for Wide Variations in Use

Gabriela Schmajuk[1], Chris Tonner[2], Sara G. Murray[3] and Jinoos Yazdany[4], [1]Medicine / Rheumatology, UCSF / San Francisco VA, San Francisco, CA, [2]Rheumatology, University of California, San Francisco, San Francisco, CA, [3]Medicine, University of California, San Francisco, San Francisco, CA, [4]Rheumatology, UCSF, SF, CA

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Background/Purpose: The Choosing Wisely campaign, which commenced in 2011, focuses on reducing medical services that are

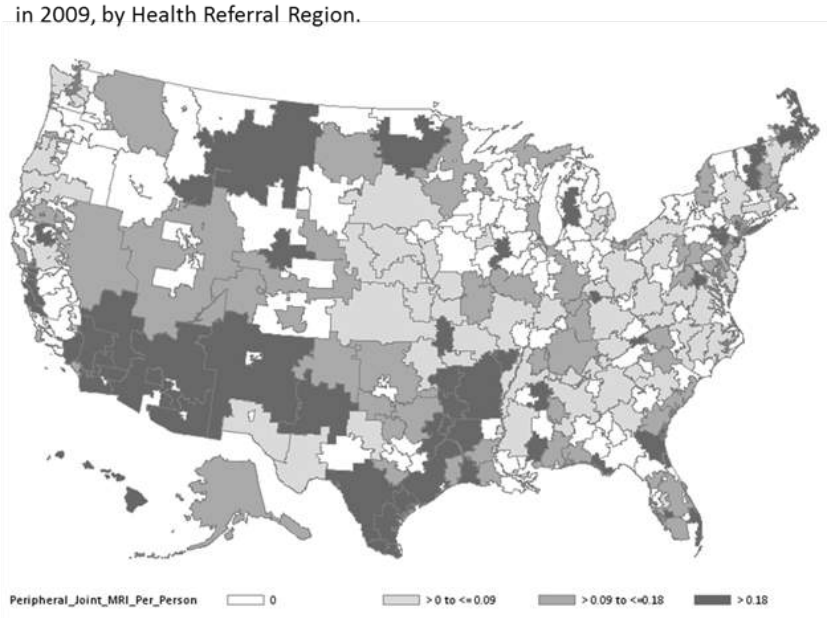
of questionable value or may be harmful. In 2013, the American College of Rheumatology published their own "Top 5" list, which included the recommendation to avoid MRI of the peripheral joints to monitor patients with inflammatory arthritis. We sought to determine the prevalence of MRI of the peripheral joints among patients with inflammatory arthritis before the "Top 5" lists were published to estimate the potential effect of the recommendations on future use of resources.

Methods: We examined use of peripheral joint MRI using data from a nationally representative 5% sample of Medicare fee-for-service claims. Using ICD9 codes we identified patients 65 years or older with at least 2 face-to-face claims for rheumatoid arthritis (714.xx) between Jan 1 and Dec 31, 2009. We used CPT codes to classify patients as having undergone MRI or plain film radiography of the peripheral joints. To assess regional variation, we estimated peripheral joint MRI use per patient by hospital referral region (HRR). We used linear regression to correlate the number of peripheral joint MRI performed in each HRR with the number of physicians or rheumatologists per Medicare beneficiary (supply data from the Dartmouth Atlas).

Results: We included 8,052 patients in our analysis. 81% were women and mean age was 76 years. 7.7% of patients underwent at least 1 peripheral joint MRI compared with 38.6% for peripheral joint plain films. Peripheral joint MRI use varied widely across 304 HRRs (range 0-2.25 per patient; interquartile range 0-0.15). High utilization areas were clustered in the southern and southwestern U.S. (see Figure). Linear regression revealed a non-significant relationship between peripheral joint MRI and HRR supply of physicians (p=0.07) or HRR supply of rheumatologists (p=0.86).

Conclusion: Before the start of the Choosing Wisely campaign, use of peripheral joint MRI for Medicare patients with known or suspected inflammatory arthritis varied widely across geographic regions. Although we cannot judge the appropriateness of each radiographic test performed, marked variation in utilization suggests that studies to assess overuse are warranted. Future analyses should also assess the impact of the Choosing Wisely campaign in reducing the variation in use of peripheral joint MRI.

Figure. Peripheral joint MRIs per rheumatoid arthritis Medicare beneficiary in 2009, by Health Referral Region.



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Abstract Number: 2269

Rheumatologists Consider Patient Preferences and Costs When Choosing Treatments for Rheumatoid Arthritis (RA) Patients. a Cross-European Discrete Choice Experiment

Monika Hifinger[1], Mickaël Hiligsmann[2], Sofia Ramiro[3], Verity Watson[4], Johan L. Severens[5], Bruno Fautrel[6], Loreto Carmona[7],

Till Uhlig[8], Ronald van Vollenhoven[9], Peggy Jacques[10], Jacqueline Detert[11], Carlo Alberto Scirè[12], Florian Berghea[13], Márta Péntek[14], Jose canas Silva[15], Andrew Keat[16] and Annelies Boonen[17], [1]Rheumatology, University of Maastricht, Maastricht, Netherlands, [2]Department of Health Services Research, University of Maastricht, Maastricht, Netherlands, [3]Rheumatology, Leiden University Medical Center, Leiden, Netherlands, [4]Health Economics Research Unit, University of Aberdeen, Aberdeen, United Kingdom, [5]Institute of Health Policy and Management, Erasmus University Rotterdam, Rotterdam, Netherlands, [6]Rheumatology, AP-HP Pitié-Salpêtrière Hospital / Pierre and Marie Curie University Paris 6 GRC-08 (EEMOIS), Paris, France, [7]Instituto de Salud Musculoesqueletica, Madrid, Spain, [8]Rheumatology, Diakonhjemmet Hospital, Oslo, Norway, [9]Rheumatology Unit, The Karolinska Institute, Stockholm, Sweden, [10]University Hospital Ghent, Ghent, Belgium, [11]Department of Rheumatology and Clinical Immunology, Charité – Universitätsmedizin Berlin, Berlin, Germany, [12]Italian Society for Rheumatology, Milan, Italy, [13]Department of Internal Medicine and Rheumatology "Sf. Maria" Hospital, University of Medicine and Pharmacy "Carol Davila", Bucharest, Romania, [14]Corvinus University of Budapest, Budapest, Hungary, [15]Rheumatology Department, Hospital Garcia de Orta, E.P.E., Almada, Portugal, [16]Northwick Park Hospital, Harrow, United Kingdom, [17]Care and Public Health Research Institute, Maastricht University Medical Center, Maastricht, Netherlands
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SESSION INFORMATION

Session Title: Epidemiology and Public Health Poster III (ACR): Gout and Non-Inflammatory Musculoskeletal Conditions
Session Type: ACR Poster Session C

Background/Purpose:

Economic considerations and patient preferences are increasingly important when choosing treatments. It is not known to what extent rheumatologists across Europe account for these factors when changing drug therapies in patients with active rheumatoid arthritis (RA).

Objectives:

To evaluate the extent to which rheumatologists across Europe consider costs, cost-effectiveness and patient preferences in addition to efficacy and safety in treatment decisions in RA.

Methods:

In a discrete choice experiment, rheumatologists were asked to choose iteratively between two unlabeled drug treatment options for a hypothetical RA patient with moderate disease activity who failed two synthetic DMARDs. The treatment options were characterized by five attributes further specified by three levels; efficacy (level of improvement and achieved state of disease activity), safety (probability of a serious adverse event), patient preference (level of agreement with proposed treatment), medication costs and cost-effectiveness (incremental cost-effectiveness ratio (ICER)).

Attributes and levels were selected based on literature data and expert consensus. An efficient experimental design was used to construct 14 treatment choices and a mixed logit model was used to estimate the relative importance of attributes.

Results:

559 rheumatologists from 12 European countries contributed to the analysis (50.2% females, mean age 48.3 years). When choosing treatments for RA patients, efficacy was the most important attribute in all participating countries (44%, range 39-52%). Overall, safety also played an important role for treatment decisions (13%) however varied between countries (2-20%). Importance of safety increased with increasing risk of severe adverse events. Patient preference contributed importantly (16%), especially when patients disagreed with the proposed treatment.

Relative importance of economic attributes varied (1) between countries and (2) among individual rheumatologists. In the majority of countries, absolute costs were more relevant for treatment decisions than relative cost-effectiveness. Contributions of attributes to treatment decision (overall and per country) are summarized in table 1.

Table 1: Contribution of selected core treatment attributes to the overall preference for a treatment choice (mean per country, in percent (%) of total explained variance)

Country/N / Treatment Attribute	BE	FR	GE	HU	IT	NL	NO	PT	RO	SE	SP	UK	All countries
	33	40	44	71	59	63	41	39	42	24	63	40	559
Efficacy *Improvement DAS28*	44%	43%	42%	46%	45%	44%	40%	39%	52%	43%	45%	39%	44%
Safety *Probability of a serious AE*	10%	20%	9%	12%	17%	1%	10%	19%	19%	11%	10%	2%	13%
Patient´s Preference	14%	21%	14%	16%	14%	17%	14%	14%	7%	19%	18%	19%	16%
Cost-Effectiveness *ICER, QALY/year*	9%	3%	14%	14%	8%	14%	12%	8%	4%	10%	17%	21%	11%
Medication costs *per year, in local currency*	23%	13%	19%	12%	15%	24%	24%	20%	18%	17%	10%	19%	17%
Model fit, R^2	0.61	0.58	0.66	0.63	0.63	0.46	0.65	0.64	0.63	0.67	0.65	0.63	0.39

BE=Belgium, FR=France, GE=Germany, HU=Hungary, IT=Italy, NL=Netherlands, NO=Norway, PT=Portugal, RO=Romania, SE=Sweden, SP=Spain, N= number of responses per country and overall, DAS28= Disease Activity Score in 28 joints, AE=Adverse Event, ICER=Incremental Cost-Effectiveness Ratio, QALY=Quality Adjusted Life Year

Conclusion:

Drug efficacy clearly remains the most important driver for treatment decisions in all European countries however rheumatologists also take into account economic aspects in their treatment decisions. In most countries, overall costs are still more important than cost-effectiveness considerations. Patient preferences are taken into account, indicating rheumatologists take steps towards patient centered care.

Disclosure: M. Hifinger, None; **M. Hiligsmann**, None; **S. Ramiro**, None; **V. Watson**, None; **J. L. Severens**, None; **B. Fautrel**, None; **L. Carmona**, None; **T. Uhlig**, None; **R. van Vollenhoven**, None; **P. Jacques**, None; **J. Detert**, None; **C. A. Scirè**, None; **F. Berghea**, None; **M. Péntek**, None; **J. canas Silva**, None; **A. Keat**, None; **A. Boonen**, None.

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Abstract Number: 2270

Cardiovascular Disease: The Hidden Risk in Persons with Rheumatoid Arthritis

Karen Soikkeli[1] and Glenn Ehresmann[2], [1]Graduate Nursing (Family Nurse Practitioner Program), Azusa Pacific University, Diamond Bar, CA, [2]Rheumatology, Keck School of Medicine, University of Southern California-Los Angeles County Medical Center, Los Angeles, CA

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Session Title: Epidemiology and Public Health Poster (ARHP)

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

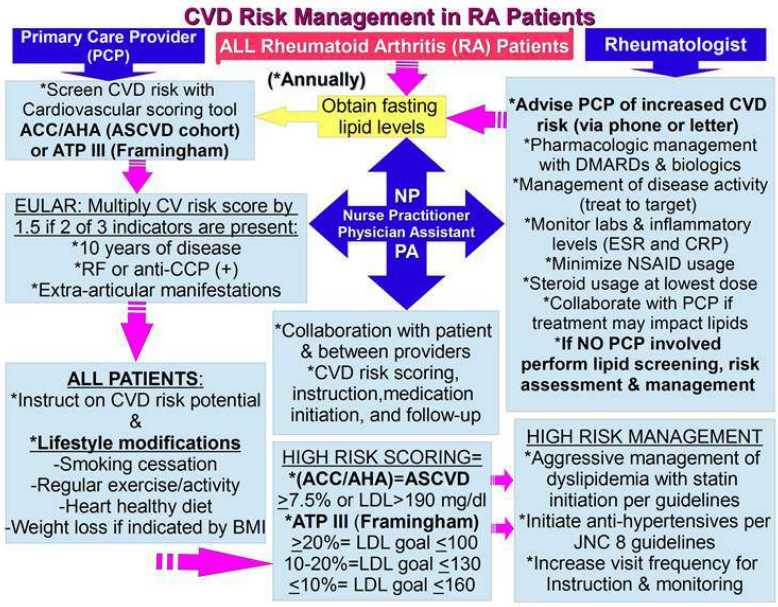
Background/Purpose: Despite the fact that patients with rheumatoid arthritis (RA) experience a 50-60% increased risk of developing cardiovascular disease (CVD), substantial gaps remain in the knowledge and application of risk prevention measures in RA patients. There is no standardized guideline or protocol for identification and management of the CVD risk in the RA population. The purpose of this study is to develop an algorithm based on current evidence with best practice measures for identification and management of CVD risk in the RA population.

Methods: An extensive review of literature was performed exploring and evaluating CVD impact in the RA population from 2009-2015 to identify current evidence based measures utilized in this population. Retrospective chart review of RA patients at a large community medical center identified the absence of consistent CVD risk screening. The American College of Cardiology/American Heart Association (ACC/AHA) guidelines and the National Cholesterol Education Program (NCEP) Adult

Treatment Panel (ATP) III guidelines were extrapolated to provide the foundation for the development of an algorithm for providers to reflect current best practice to improve patient outcome management.

Results: A review of literature reveals several barriers to the management of CVD risk in RA patients. No standardized guidelines exist relative to the CVD risk management in the RA patient, but European League Against Rheumatism (EULAR) has made recommendations. Existing CVD risk scoring tools often underestimate risk, especially in RA. Computed tomography angiography (CTA) reveals higher plaque burden in asymptomatic RA patients without pre-existing CVD. Lipid knowledge remains incomplete with respect to epidemiology and pathogenesis of RA. Chart review of 35 RA patients at a community medical center revealed that only 40% contained any recorded lipid panel results; in the past year only 11.5% of the reviewed charts contained documentation of lipid panel results. An algorithm was developed to suggest improvements in CVD risk management in the RA population. Increased collaboration between the primary care provider, rheumatologist, and nurse practitioner or physician assistant may enhance overall CVD management (see algorithm *CVD Risk Management in RA Patients*).

Conclusion: There is a paucity of identification and/or management of CVD in this population. An algorithm was developed in order to help providers identify aggressive CVD strategies, including lifestyle instruction as a standard of care in the RA population, thus improving the long term CVD outcomes. Further research is indicated and should be aimed at the development of CVD risk scoring tools specific for the RA patient, with concrete guidelines on the CVD risk in the RA population. Further studies involving the use of imaging and other alternate methods of risk identification are indicated.



Disclosure: K. Soikkeli, None; **G. Ehresmann**, Amgen, Abbvie, Genenteh, UCB, Takeda, Pfizer, Jansen, 8.

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Abstract Number: 2271

Does Arthritis in the Young Adult Life Phase Impact Involvement in Transitional Social Roles?

Arif Jetha[1,2], Kristina Theis[3] and Michael Alden Boring[3], [1]Center for Disability Research, Liberty Mutual Research Institute for Safety, Hopkinton, MA, [2]Institute for Work & Health, Toronto, ON, Canada, [3]Arthritis Program, Centers for Disease Control and Prevention, Atlanta, GA

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SESSION INFORMATION

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Session Time: 9:00AM-11:00AM

Background/Purpose:

Post-secondary schooling and/or obtaining employment are milestones of a successful transition to adulthood. It is unclear if young adults, ages 18 to 29 years, with arthritis participate in transitional roles similar to their non-arthritis peers. This study compares employment and education participation of young adults with an arthritis diagnosis ("Have you ever been told by a doctor or other health professional that you have some form of arthritis, rheumatoid arthritis, gout, lupus, or fibromyalgia?") to their peers without arthritis.

Methods:

Data from years 2009 to 2013 of the National Health Interview Survey, an ongoing in-home interview survey, nationally representative of the U.S. civilian non-institutionalized population, were analyzed. Our sample was restricted to adults aged 18-29 who were either diagnosed with arthritis (n = 951) or not (n = 28,734). Respondents who were employed or students were grouped together as those participating in transitional social roles. Demographic characteristics, health factors, and health system use were also analyzed. Weighted proportions with 95% confidence intervals (CI) were calculated accounting for complex sample design. Non-overlapping CIs indicated significant differences.

Results:

Young adults with arthritis participated in transitional roles (67.7%, 95%CI = 63.9-71.6) less frequently than their non-arthritis peers (78.5%, 95%CI = 77.7-79.2). While young adults with arthritis were employed in similar proportions (61.7%, 95%CI = 57.5-65.8) to those without arthritis (66.0%, 95%CI = 65.1-66.9), they reported being students about half as often (6.7%, 95%CI = 4.4-9.0 vs. 12.7%, 95%CI = 11.9-13.5). Young adults with arthritis also reported not participating in employment due to disability almost six times as often (11.6%, 95%CI = 9.0-14.1 vs. 2.0, 95%CI = 1.8-2.3) when compared to those without arthritis. Young adults with arthritis were more often female, married, with fair/poor health, obese, and reported more comorbid conditions. Participants with arthritis also reported attending >5 annual doctor visits more often, and less prevalence of health insurance coverage.

Conclusion:

Arthritis in young adulthood is associated with lower participation in transitional social roles and higher disability. Role participation restrictions, especially in education, may have potential long-term career consequences for young people with arthritis and may limit competitivness in a knowledge-based economy that requires specialized skills. Additional research is required to understand how work context factors, psychosocial perceptions, and relationships with close others can influence the transition to adult roles for people with arthritis.

Disclosure: A. Jetha, None; **K. Theis**, None; **M. A. Boring**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/does-arthritis-in-the-young-adult-life-phase-impact-involvement-in-transitional-social-roles

Abstract Number: 2272

Physical Performance Contributes Only Marginally in Explaining Fatigue Variation in Persons with RA Moderately Affected By Their Disease

Ingrid Demmelmaier[1], Susanne Pettersson[1], Birgitta Nordgren[1], Alyssa B. Dufour[1,2] and Christina H. Opava[1], [1]Department of Neurobiology, Care Sciences and Society, Division of Physiotherapy, Karolinska Institutet, Huddinge, Sweden, [2]Institute for

Aging Research, Hebrew SeniorLife, Harvard Medical School & Beth Israel Deaconess Medical Center, Boston, MA
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Background/Purpose:

Fatigue is a prominent problem in persons with rheumatoid arthritis (RA) and often has a detrimental effect on quality of life. Besides variables directly related to disease and disease impact, exercise and physical performance have been found to explain variation in fatigue. However, previous studies have used small samples and the role of aerobic capacity is unclear. The present study assessed the contribution of physical performance in the variation of fatigue in RA, beyond that of previously known factors related to disease and disease impact.

Methods:

This cross-sectional study used data from the Swedish Rheumatology Quality Registers and included 269 persons recruited for a physical activity intervention. They were all diagnosed with RA according to the ACR classification criteria, 82% women, mean age 60 ± 9 years, mean DAS28 2.8 ± 1.2, and mean HAQ 0.5 ± 0.5. The participants completed a questionnaire on fatigue, activity limitation, perceived health, pain, anxiety/depression and physical activity, and were tested for physical performance; lower limb function by Timed-stands Test, grip strength by Grippit, and aerobic capacity by Åstrand's submaximal bicycle test. Fatigue was rated on a visual analogue scale 0-100 with severe fatigue defined as 50-100. Variation in fatigue was analyzed in two logistic regression models including A) variables related to disease and disease impact, and B) variables related to disease, disease impact and physical performance. Multiple imputation was used to account for missing data in explanatory variables. Nagelkerke's R^2 was calculated to assess model fit.

Results:

Severe fatigue was reported by 95 persons (35%). Significant univariate associations ($p < 0.1$) between severe fatigue and disease duration, medication with biological drugs, comorbidities, activity limitation, perceived health, pain, anxiety/depression and grip strength were found and those variables were included in the adjusted models. Model fit statistics indicated that model B explained more of the variance in severe fatigue than did model A. (Nagelkerke's R^2 0.60 and 0.67 respectively, $p < .0001$). Perceived health, pain and anxiety/depression contributed significantly ($p < 0.05$) in both models and lower limb function in model B (Table 1).

Conclusion:

The results indicate that perceived disease impact variables together with lower limb function are predictors of fatigue in persons moderately affected by RA. The role of physical performance should be explored further with multidimensional assessments of fatigue in samples with larger variation in fatigue and in potential explanatory factors.

Table 1. Outcome of logistic regression for severe fatigue with odds ratios (OR) and 95% confidence intervals (CI) using multiple imputation to account for missing data. Model A includes disease-related and perceived disease impact variables and Model B also includes physical performance variables (n = 269).

Model A	OR (95% CI)	p-value	Model B	OR (95% CI)	p-value
Disease duration	0.97 (0.93, 1.01)	0.171	Disease duration	0.97 (0.93, 1.02)	0.271
Biological drugs	0.82 (0.36, 1.88)	0.642	Biological drugs	0.86 (0.36, 2.03)	0.724
Comorbidities	1.74 (0.81, 3.71)	0.154	Comorbidities	2.10 (0.94, 4.71)	0.071
Activity limitation	1.29 (0.53, 3.15)	0.576	Activity limitation	2.26 (0.83, 6.12)	0.109
Health	1.07 (1.04, 1.11)	**<0.0001**	Health	1.08 (1.04, 1.12)	**0.0001**
Pain	1.04 (1.01, 1.07)	**0.003**	Pain	1.04 (1.01, 1.07)	**0.005**
Anxiety/depression	2.40 (1.19, 4.87)	**0.015**	Anxiety/depression	2.56 (1.24, 5.27)	**0.011**
			Grip strength	1.00 (1.00, 1.01)	0.192
			Lower limb function	0.95 (0.90, 1.00)	**0.047**
			Aerobic capacity	1.01 (0.95, 1.07)	0.768

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Abstract Number: 2273

The Effect of Widespread Pain on Incident Knee Pain and Knee Osteoarthritis: The Multicenter Osteoarthritis (MOST) Study

Lisa Carlesso[1,2], Neil Segal[3], Jeffrey R. Curtis[4], Barton L. Wise[5], Laura Frey-Law[6], Michael C. Nevitt[7], Anyu Hu[8] and Tuhina Neogi[9], [1]Division of Health Care & Outcomes Research, Toronto Western Research Institute, University Health Network, Toronto, ON, Canada, [2]School of Rehabiliation, Maisonneuve Rosemont Research Institute, Université de Montréal, Montreal, QC, Canada, [3]University of Kansas, Shawnee, KS, [4]Clinical Immunology and Rheumatology, University of Alabama at Birmingham, Birmingham, AL, [5]Int Medicine, UCDMC, Sacramento, CA, [6]UIowa, Iowa City, IA, [7]Epidemiology and Biostatistics, UCSF, San Francisco, CA, [8]Clinical Epidemiology Research Unit, Boston University School of Medicine, Boston, MA, [9]Clinical Epidemiology, BUSM, Boston, MA

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Background/Purpose: Widespread pain (WSP) may be present in individuals for numerous reasons, and its presence may affect the degree to which people engage in activities. How the presence of WSP affects the risk of developing knee pain or knee osteoarthritis (OA) is unknown and could enhance the understanding of pain mechanisms in OA. For example, people with WSP may have a lower risk of developing knee OA due to less frequent loading of the knee or they may have an increased risk due to maladaptive movement patterns. The purpose of this study was to determine if WSP is associated with future consistent frequent knee pain (CFKP) or radiographic OA (ROA) two years later.

Methods: Subjects from the Multicenter Osteoarthritis (MOST) study, a NIH-funded longitudinal prospective cohort of older adults with or at risk of knee OA were assessed at the 60-month (baseline) and 84-month (follow up) visits. WSP was defined at baseline as pain on both sides of the body, above and below the waist, and axial pain, using a standard homunculus, with the exception that the knees were not included in defining WSP. Incident CFKP was defined as reporting knee pain on most days during the past month at the 84-month telephone interview and again during the clinic visit that occurred on average one month later among participants who were free of CFKP at 60 months. Incident ROA was defined as presence of Kellgren & Lawrence grade 2 or knee replacement of either knee at follow-up among those who were free of ROA (and knee replacement) at baseline. We assessed the relation of WSP to risk of CFKP and ROA respectively, using multinomial regression adjusting for baseline age, sex, BMI, comorbidities, physical activity and clinic site; the model was also adjusted for depressive symptoms, pain catastrophizing, fatigue and ROA when CFKP was the outcome, and for WOMAC pain severity when ROA was the outcome.

Results:

There were 923 eligible subjects for analysis of incident CFKP (mean age (SD); 67.4 (7.5); BMI 30.0 (5.6) kg/m^2, 56% women, 19% WSP), and 675 for incident ROA (age 65.6 (7.4); BMI 28.9 (4.7) kg/m^2, 60% women, 30% WSP). Baseline presence of WSP was associated with a non-significant 59% increased risk of incident CFKP compared with those without WSP (adjusted OR 1.59, 95% CI 0.94-2.68, p=0.08). Baseline WSP was associated with a non-significant 14% lower risk of incident ROA, (adjusted OR 0.86, 95% CI 0.46-1.63, p=0.65). WSP was associated with a non-significant 65% increased risk of unilateral CFKP vs. no CFKP (adjusted OR 1.65, 95% CI 0.92-2.96, p=0.09) and with a non-significant 35% increased risk of bilateral CFKP vs. no CFKP (adjusted OR 1.35, 95% CI 0.49-3.73, p=0.56). For both incident unilateral and bilateral ROA vs. no ROA, WSP was not statistically significantly associated; unilateral ROA had 1% lower risk (adjusted OR 0.99, 95% CI 0.51-1.92, p=0.97), and bilateral ROA had 77% lower risk (adjusted OR 0.23, 95% CI 0.02-2.53, p=0.23).

Conclusion: WSP was not significantly associated with either incident CFKP or ROA. Development of knee pain and ROA does not appear to be influenced by underlying WSP, suggesting that screening for or managing WSP will not have a meaningful influence on the development of knee pain or ROA.

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Abstract Number: 2274

Increasing Moderate-to-Vigorous Activity and Decreasing Sedentary Time Are Associated with 2-Year Weight Loss in Obese Persons with or at Risk for Knee Osteoarthritis

Christine Pellegrini[1], Jing Song[2], Rowland W. Chang[3], Pamela Semanik[4], Julia (Jungwha) Lee[5], Linda S. Ehrlich-Jones[6], Daniel Pinto[7] and Dorothy D. Dunlop[8], [1]Department of Preventive Medicine, Northwestern University Feinberg School of Medicine, Chicago, IL, [2]Institute for Healthcare Studies, Northwestern University, Chicago, IL, [3]Preventive Medicine, Northwestern University Feinberg School of Medicine, Chicago, IL, [4]College of Nursing, Rush University, Chicago, IL, [5]Department of Preventive Medicine, Biostatistics Collaboration Center, Northwestern University Feinberg School of Medicine, Chicago, IL, [6]Research CROR, Rehabilitation Institute Chicago, Chicago, IL, [7]Department of Physical Therapy & Human Movement Sciences, Northwestern University, Chicago, IL, [8]Institute for Healthcare Studies, Northwestern University Feinberg School of Medicine, Chicago, IL

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Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Moderate-to-vigorous physical activity (MVPA) is recommended for weight loss; however it is unclear how activity or sedentary changes influence long-term weight loss in obese adults. We examine if changes in MVPA, light intensity physical activity, and sedentary behavior are related to weight loss over a 2 year period in obese adults with knee osteoarthritis (OA) or knee OA risk factors.

Methods: Objectively measured body weight, physical activity, and sedentary time were obtained from 459 obese participants from the Osteoarthritis Initiative at baseline and two years. Weight change was categorized as ≥10, 5.0-9.9, 4.9 to -4.9, -5.0 to-9.9, ≤-10 lbs. The association between 2-year weight change and changes in physical activity (light and MVPA) and sedentary time from accelerometer monitoring were examined by multiple linear regression adjusted for baseline weight, demographic and health factors.

Results: Over 2 years, participants lost 3.48 ± 26.06 lbs., increased sedentary time (9.5 ± 64.5 minutes) and decreased both light and MVPA (-8.6 ± 64.5 minutes, -0.9 ± 14.2 minutes, respectively). Weight loss was associated with increased MVPA gains across five categories of weight change from ≥10lbs. loss (5.2 min), 5-9.9lbs. loss (2.4 min), ±5lbs. (1.4 min), 5-9.9lbs. gain (-0.9 min), and ≥10lbs. gain (-2.7 min) (p for trend < 0.001). Weight loss was also associated with less sedentary gain across five categories of weight change from ≥10lbs. loss (-7.1 min), 5-9.9lbs. loss (7.3 min), ±5lbs. (9.1 min), 5-9.9lbs. gain (9.5 min), and ≥10lbs. gain (25.8 min) (p for trend =0.01). Weight loss had a strong but nonsignificant trend with light activity gain (p for trend = 0.06). All models controlled for baseline weight, demographics and health factors.

Conclusion: Decreases in sedentary time over 2 years and small increases in MVPA and were associated with weight loss among obese adults with or at risk for knee osteoarthritis.

Figure 1: Two-year change in average daily time spent in sedentary behavior and physical activity based on 2-year weight change category

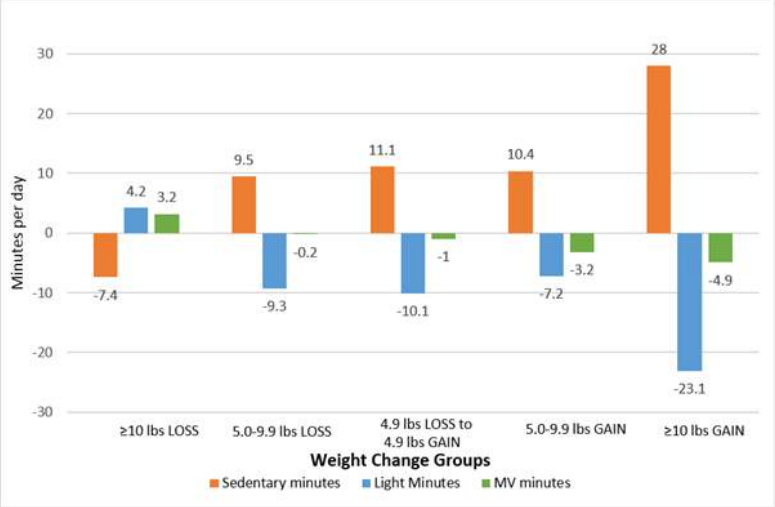

Table 1. Sedentary, light activity, and MVPA two-year change by weight change (lbs.) category in obese adults (n=459)

	Sedentary Minutes[b] Mean ± SE		Light Activity Minutes[b] mean ± SE		MVPA Minutes[b] mean ± SE	
Weight Change Category	***Change Adjusted for Age & Gender***	***Change Adjusted for SES, Health*** [a]	***Change Adjusted for Age & Gender***	***Change Adjusted for SES, Health*** [a]	***Change Adjusted for Age & Gender***	***Change Adjusted for SES, Health*** [a]
≥10 lbs LOSS (n=76)	-7.62 ± 7.83*	-7.06 ± 9.25*	3.51 ± 7.61*	1.81 ± 8.98*	4.11 ± 1.71*	5.24 ± 2.02*
5.0-9.9 lbs LOSS (n=73)	9.16 ± 7.89	7.25 ± 9.25	-9.82 ± 7.67	-9.64 ± 10.54	0.66 ± 1.73	2.39 ± 2.02
4.9 lbs LOSS to 4.9 lbs GAIN (n=193)	11.11 ± 5.53	9.13 ± 7.66	-11.09 ± 5.38	-10.55 ± 7.44	-0.03 ± 1.21	1.42 ± 1.67
5.0-9.9 lbs GAIN (n=67)	10.19 ± 8.31	9.48 ± 9.42	-7.90 ± 8.08	-8.58 ± 9.15	-2.29 ± 1.82	-0.90 ± 2.06
≥10 lbs GAIN (n=50) (Reference)	28.97 ± 9.48	25.82 ± 10.70	-23.94 ± 9.22	-23.09 ± 10.40	-4.02 ± 2.07	-2.72 ± 2.34
***P* value (trend)**	0.0055	0.0109	0.0375	0.0624	0.0005	0.0008

[a] Adjusting factors: SES (age, gender, race, education, income), Health (comorbidity, high depressive symptoms, smoking, K/L grade, WOMAC pain, knee symptoms, knee injury, hip pain, ankle pain, foot pain, baseline weight).
[b]Minutes spent in each activity level for a given day, standardized to 16 waking hours.
* Significant differences (at p<=0.05 level) in 2 year change of each activity by weight change categories compared to people with >=10 lbs weight gain (reference).

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Abstract Number: 2275

The Burden of Axial Spondyloarthritis: A Comparison of the Radiographic and Non-Radiographic Groups

Gokce Kenar[1], Pinar Cetin[1], Gercek Can[1], Sedat Capar[2], Handan Yarkan[1], Ismail Sari[1], Merih Birlik[1], Fatos Onen[1] and Nurullah Akkoc[3], [1]Rheumatology, Dokuz Eylul University Faculty of Medicine, Izmir, Turkey, [2]Dokuz Eylül University Faculty of Statistics, Izmir, Turkey, [3]Department of Rheumatology, Dokuz Eylul University, Faculty of Medicine, Izmir, Turkey
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Background/Purpose: Axial spondyloarthritis (axSpA) represents the whole clinical spectrum of ankylosing spondylitis (AS) including those at the non-radiographic (nr) stage of the disease. Although the disease burden associated with radiographic axSpA (classically known as AS) has been extensively studied, the burden associated with nr-axSpA is less well known.Our aim was to assess and compare the burden of radiographic and nr-axSpA.

Methods: This cross-sectional, observational study included consecutive AxSpA patients with varying disease severity, who attended our outpatient clinic between April 2014 and December 2014. During the visits, the following questionnaires were applied by trained health professionals:BASDAI, BASFI, HAQ-S, SF-36, ASQoL,Work Productivity and Activity Impairment (WPAI) and Work Productivity Survey (WPS).

Results:

A total of 381 AxSpA patients (279 AS) were analyzed. Nr-axSpA group, were younger (39.4 vs 43.1, p=0.007), more likely to be female (54% vs 33%, p<0.001), had a shorter disease duration (10.1 vs 16.0 years, p<0.001) and lower CRP (5.9 vs 13.2, p<0.001) and less common use of biologics (41.2% vs 26.5, p=0.008) despite higher BASDAI scores (Table). Broadly similar results were found for the other clinical outcome measures. Of all the axSpA patients, 58% were employed, with non-manual (25%), mixed (19%) and manual works (14%). Only 1.1% of the patients could not work due to arthritis. Patients with nr-axSpA reported more work productivity loss at workplace and at home over the last month, but the difference was significant only for household activities. Subgroup analysis showed that this difference was only found in females.

Conclusion: Patients with AS and nr-AxSpA demonstrate similar degree of disease burden and prodcutivity, with a greater impairment of household work in females. Low rate of inability to work due to arthritis in this population with a relatively high prevalence of anti-TNF use may be a reflection of the effectiveness of such therapies.

Table 1. Clinical variables related to disease burden in study participants. Data are presented as mean ± SD, unless otherwise stated

Variable	AS (n=279)	nr-axSpA (n=102)	P value
BASDAI (0–100)	33.2±21.8	39.5±23.1	0.014
BASFI (0–100)	30.5±24.1	29.4±24.6	0.711
HAQ-S	0.7±0.6	0.8±0.6	0.606
SF36 PCS	41.3±9.3	39.2±10	0.111
SF36 MCS	46.1±10.5	43.3±11.4	0.060
ASqoL	5.6±5.4	6.2±5.6	0.331
Work productivity and impairment index (refers to the last week)			
Absenteeism (%)*	8.7±25.5	12.3±30.3	0.374
Presenteeism (%)*	33.8±25.0	37.1±25.9	0.401
Overall work impairment (%)*	33.4±29.7	36.6±32.9	0.476
Daily activity impairment, (%)	33.5±22.9	34.6±23.6	0.672
Work productivity survey (refers to the last month)			
Days of work missed*	1.4±4.6	3.0±6.6	0.090
Days with productivity at work reduced by ≥50%*	2.6±6.3	4.6±8.2	0.090
Rate of SpA interference on work productivity*	3.2±2.3	3.8±2.6	0.109
Days of household work missed	2.5±5.6	4.8±7.6	0.010
Days with household productivity reduced by ≥50%	3.1±2.1	3.6±2.3	0.048
Days with outside help	2.7±6.5	2.8±5.9	0.815
Rate of SpA interference with household work productivity (0-10)	3.1±2.1	3.7±2.3	0.052

*Assessed in employed patients only.

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The Association of Knee Pain and Knee Osteoarthritis with Incident Widespread Pain: The Multicenter Osteoarthritis (MOST) Study

Lisa Carlesso[1,2], Neil Segal[3], Jeffrey R. Curtis[4], Barton L. Wise[5], Laura Frey-Law[6], Michael C. Nevitt[7], Anyu Hu[8] and Tuhina Neogi[9], [1]School of Rehabiliation, Maisonneuve Rosemont Research Institute, Université de Montréal, Montreal, QC, Canada, [2]Division of Health Care & Outcomes Research, Toronto Western Research Institute, University Health Network, Toronto, ON, Canada, [3]University of Kansas, Shawnee, KS, [4]Clinical Immunology and Rheumatology, University of Alabama at Birmingham, Birmingham, AL, [5]Int Medicine, UCDMC, Sacramento, CA, [6]UIowa, Iowa City, IA, [7]Epidemiology and Biostatistics, UCSF, San Francisco, CA, [8]Clinical Epidemiology Research Unit, Boston University School of Medicine, Boston, MA, [9]Clinical Epidemiology, BUSM, Boston, MA

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Background/Purpose: Widespread pain (WSP) is associated with morbidity, and poor mental and physical functioning, but its etiology is not well understood. It has been hypothesized that painful peripheral pathology may result in WSP. Previous cross-sectional studies have shown an association of knee pain and radiographic knee osteoarthritis (ROA) with WSP. However, the independent relations of knee OA and knee pain, to incident WSP is unknown. We examined the relation of ROA, symptomatic knee OA (SxOA) and consistent frequent knee pain (CFKP) to incident WSP in a large prospective cohort.

Methods: We used data from the Multicenter Osteoarthritis (MOST) Study, a NIH-funded longitudinal prospective cohort of 3026 older adults with or at risk of knee OA. ROA was defined as having radiographic tibiofemoral OA (Kellgren & Lawrence grade ≥2) on the 60-month radiographs. The definition of CFKP was met if a participant reported knee pain on most days during the past month at the 60-month telephone interview and at the clinic visit that occurred on average one month later. SxOA was defined as having both ROA and CFKP at 60 months. We also considered knee replacement as equivalent to ROA and SxOA. WSP was defined as pain above and below the waist, on both sides of the body and axially, using a standard homunculus, excluding knee pain. Incident WSP was defined as presence of WSP at 84 months among those who were free of WSP at 60 months. We assessed the relation of baseline ROA, SxOA, and CFKP, respectively, to incident WSP using logistic regression, adjusting for baseline age, sex, BMI, comorbidities, physical activity, WOMAC pain intensity, study site, depressive symptoms, pain catastrophizing and fatigue.

Results: At baseline, 1309 subjects were eligible for ROA analysis (age mean, SD; 67.3, 7.8; BMI 30.5, 6.0 kg/m^2, 56% women), 1316 for SxOA analysis (age 67.3, 7.8; BMI 30.4, 5.9 kg/m^2, 55% women) and 1383 for CFKP analysis (age 67.4, 7.8; BMI 30.5, 6.0 kg/m^2, 55% women). Baseline presence of unilateral ROA was associated with a non-significant 30% lower risk of incident WSP compared with those without ROA (adjusted OR 0.70, 95% CI 0.46-1.07, p=0.10). Similar results were found for those with bilateral ROA. Similarly, neither baseline unilateral nor bilateral SxOA were associated with risk of incident WSP compared with those without SxOA. Baseline presence of unilateral CFKP was also not significantly associated with incident WSP, while bilateral CFKP approached significance (see table).

Conclusion: Neither ROA, SxOA nor CFKP increased the risk of developing WSP. These results suggest that neither knee joint pathology nor joint pain are major factors in the onset of WSP. Further study is required to clarify what factors contribute to the onset of WSP.

Table: Risk of ROA, SxOA and CFKP to incident widespread pain

	ROA at baseline			SxOA at baseline			CFKP at baseline		
# of knees	N of subjects	Risk of incident WSP N (%)	Adjusted OR*	N of subjects	Risk of incident WSP N (%)	Adjusted OR*	N of subjects	Risk of incident WSP N (%)	Adjusted OR*
None	486	72 (14.8%)	1.0	1079	152 (14.1%)	1.0	1018	131 (12.9%)	1.0
Unilateral	365	56 (15.3%)	0.70 (0.46, 1.07) p=0.10	172	38 (22.1%)	0.92 (0.57, 1.48) p=0.72	223	49 (22.0%)	1.30 (0.84, 2.00) p=0.23
Bilateral	458	83 (18.1%)	0.75 (0.50, 1.12) p=0.16	65	19 (29.2%)	1.25 (0.65, 2.39) p=0.51	142	40 (28.1%)	1.59 (0.97, 2.61) p=0.07

[*] Adjusting for age at 60 mo, sex, BMI, comorbidities, physical activity at 60 mo, clinic site, CES-D, catastrophizing, sleep/fatigue, knee pain severity.

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Working Harder to Stay in Control: Patient Reports of Flare in Early RA Are Associated with Higher Disease Activity and More Intensive Self Management

Susan J. Bartlett[1,2], Clifton O. Bingham III[3], Daming Lin[4], Kathleen Andersen[5], Gilles Boire[6], Carol Hitchon[7], Boulos Haraoui[8], Edward C. Keystone[9], Diane Tin[10], J Carter Thorne[11], Janet E. Pope[12], VP Bykerk[4] and CATCH Investigators and OMERACT Flare Group, [1]Clinical Epidemiology, McGill University, Montreal, QC, Canada, [2]Division of Rheumatology, Johns Hopkins School of Medicine, Baltimore, MD, [3]Rheumatology, Johns Hopkins University, Baltimore, MD, [4]Rheumatology, Mount Sinai Hospital, University of Toronto, Toronto, ON, Canada, [5]Hospital for Special Surgery, New York, NY, [6]Department of Medicine/Division of Rheumatology, Université de Sherbrooke, Sherbrooke, QC, Canada, [7]Department of Rheumatology, University of Manitoba, Winnipeg, MB, Canada, [8]Institut de Rhumatologie, Montreal, QC, Canada, [9]Mount Sinai Hospital, University of Toronto, Toronto, ON, Canada, [10]The Arthritis Program, Southlake Regional Health Centre, Newmarket, ON, Canada, [11]University of Toronto, Toronto, ON, Canada, [12]University of Western Ontario, London, ON, Canada
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Background/Purpose: Early rheumatoid arthritis (ERA) patients attending office visits often report being in a disease flares. We evaluated patient reports of flare in relation to disease activity and self-management behaviors (SM) in a large Canadian ERA observational study (CATCH).

Methods: At each visit, patients provided ratings of flare severity (10 point VAS), duration, symptoms, functional impacts and SM. Joint counts were obtained, and CDAI scores were calculated. A checklist of SM strategies was developed based on international qualitative studies by the OMERACT RA Flare Group.

Results: The 474/1983 (24%) who reported being in flare were mostly female (76%), white (78%) and educated (53%>high school), with a mean (SD) age of 53 (14) yrs and symptom duration of 38 (25) months. Mean (SD) flare severity was 5.4/10 (2.4) and 67% reported duration > 7 days; flaring patients reported significantly more pain, fatigue, stiffness, disability, reduced participation, and difficulty coping (table 1). SM did not differ by sex and included using analgesics (50%) and steroids (13%); reducing (45%) and avoiding (28%) activities; selected behaviors (massage, heat/cold, exercise); 17% called their rheumatologist for help. Use of SM increased with flare severity for all activities except selected behaviors and steroid use (p<.005; Table 2); trends were evident with flare duration and use of analgesics (p=.08), avoiding activities (p=.09) and calling the rheumatologist (p=.001). Recently diagnosed patients (0-12 months) were significantly more likely to report using SM compared to those with RA >12 months (79% vs. 66%; p=.015) mostly using massage, heat and exercise (40% vs 28%, p=.04). As compared to those not on biologics, more patients on biologics reduced or avoided activities (43% vs 60%, p =.016; 25% vs 44%, p = .004). Among those with flare severity ≥ 4 and duration >7d, 80% reported SM including analgesics (57%), reducing activities (46%), behaviors (40%), avoiding activities (34%), or calling MD (19%).

Conclusion: Patient reports of RA flare are associated with higher disease activity; self-management is common, and increases with flare severity and duration. SM includes limiting participation/role activities and using additional medications and behaviors to reduce symptoms and impacts. Self-management appears to be initiated early into flares and highlight their substantial impact on quality of life.

Table 1. Symptoms and impacts of RA patients who did and did not report flares.

	Flare		No Flare		Sig
	N	Value	N	Value	
Symptoms					
Pain	474	5.4 (2.5)	1496	2.1 (2.3)	.000
Function	474	4.8 (2.8)	1509	1.8 (2.3)	.000
Fatigue	472	4.9 (3.0)	1501	2.4 (2.7)	.000
Stiffness	474	5.1 (2.6)	1498	2.0 (2.3)	.000
Functional Impact					
Physical Function	474	4.8 (2.8)	1509	1.8 (2.3)	.000
Participation	474	4.6 (3.0)	1493	1.7 (2.3)	.000
Coping	473	4.0 (2.7)	1497	1.5 (2.0)	.000
Swollen Joints (28)	444	2.4 (4.0)	1450	1.1 (2.7)	.000
Tender Joints (28)	451	4.0 (5.2)	1450	1.6 (3.3)	.000
CDAI	434	14.4 (11.2)	1413	5.8 (7.9)	.000
MD Global	444	2.4 (2.3)	1435	0.9 (1.6)	.000

Table 2. Self-management by severity and duration of flare.

	<>Severity (0-10 NRS or VAS?)				**Duration (Days)**				
N	**<4/10**	**4-6.9/10**	**7-10/10**	**Sig**	**1-3 d**	**4-7 d**	**8-14 d**	**>14d**	**Sig**
	122 (26%)	239 (51%)	108 (23%)		80 (17%)	79 (17%)	68 (14%)	247 (52%)	
Did nothing differently	41 (34%)	53 (22%)	15 (14%)	.000	23 (29%)	16 (20%)	13 (19%)	58 (23%)	.491
Reduced activities	46 (38%)	104 (48%)	61 (57%)	.005	31 (39%)	40 (51%)	34 (50%)	107 (43%)	.357
Avoided activities	17 (14%)	56 (23%)	57 (53%)	.000	14 (18%)	24 (30%)	16 (24%)	77 (31%)	.089
Massage, heat, exercise	49 (40%)	84 (35%)	46 (43%)	.750	28 (35%)	30 (38%)	21 (31%)	103 (42%)	.368
Painkillers	40 (33%)	118 (49%)	74 (69%)	.000	34 (43%)	33 (42%)	32 (47%)	136 (55%)	.083
Steroids	4 (3%)	16 (7%)	7 (7%)	.281	5 (6%)	2 (3%)	6 (9%)	14 (6%)	.431
Called rheumatologist	7 (6%)	29 (12%)	24 (22%)	.000	2 (3%)	5 (6%)	9 (13%)	46 (19%)	.001

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Abstract Number: 2278

Identification of Long-Term Physical Activity Trajectories in Individuals with Chronic Widespread Pain Who Received Exercise Treatment As Part of a Randomized Controlled Trial

Kathryn Remmes Martin[1], Katie L. Druce[1], Lucia D'Ambruoso[2] and Gary J. Macfarlane[1], [1]Musculoskeletal Research Collaboration (Epidemiology Group), University of Aberdeen, Aberdeen, United Kingdom, [2]Division of Applied Health Sciences, University of Aberdeen, Aberdeen, United Kingdom

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Background/Purpose: For individuals living with chronic widespread pain (CWP), physical activity (PA) can be an effective non-pharmacological therapy for symptom management. PA Interventions may enhance PA levels in the near term, however less is known about longer-term PA maintenance (i.e., ≥2 years) in those with CWP. This study examined PA levels over time and investigated whether subgroups followed distinct PA trajectories that could be useful in developing future stratified interventions.

Methods: Data are from individuals with CWP who took part in a 2x2 factorial randomized controlled trial with data at baseline (-6), treatment end (0), 3, 24 and 60 month post-treatment. Participants' self-report of total PA was generated from a brief two question assessment tool which queried on number of bouts of vigorous-intensity activity ≥20 minutes and on bouts of walking or moderate-intensity activity ≥30 minutes in a usual week. Analyses were conducted on 196 men and women who had either received exercise or combined exercise + cognitive behavioural therapy treatment and who had ≥3 PA data-points. Group-based trajectory modelling was used to identify latent PA trajectory groups between which descriptive statistics were used to identify whether baseline variables (e.g., demographics, chronic pain grade, self-rated health, fatigue, sleep problems, coping strategy use, kinesiophobia) differed (α=0.05).

Results: The best fitting model identified was one with three trajectories: non-maintainers (Group 1: G1), maintainers (G2) and super-maintainers (G3) (Figure 1). Overall, baseline PA levels (mean (SD)) were significantly different between groups (G1: 1.1 (1.2); G2: 4.6 (2.8); G3: 8.6 (2.7), p<0.001) and all other follow up points. While PA levels were higher for all groups (G1: 2.2 (2.2); G2: 6.2 (2.4); G3: 9.9 (1.8)) at treatment end, only G2 and G3 reached ‘adequate' or ‘high' PA levels (total activity score 5-7 or ≥8) and maintained activity over time. Non-maintainers more often reported greater BMI, higher chronic pain grade, poorer self-rated health and SF-36 PCS, as well as greater use of passive coping strategies and reduced use of active coping strategies. Groups did not vary on treatment group, age, gender or baseline employment status, SF-36 MCS, fatigue, sleep, and kinesiophobia.

Conclusion: The majority of individuals with CWP who received an exercise treatment as part of a trial were identified as long-term PA maintainers or super-maintainers. A smaller subset of participants with poorer self-reported health and behavioural response to symptoms were non-maintainers, and as such might benefit the most from intensively targeted interventions to improve long-term PA maintenance for optimal symptom management.

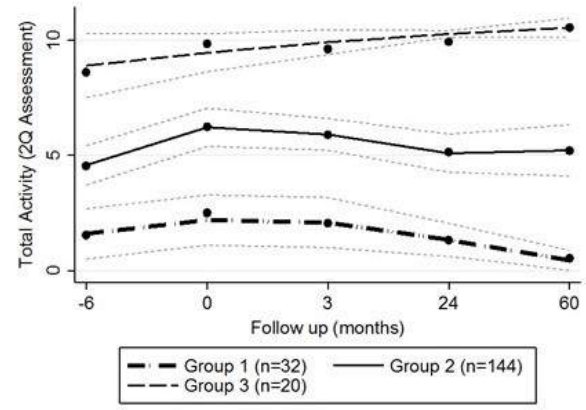

Figure 1. Physical activity trajectories (N=196)

Disclosure: K. R. Martin, None; **K. L. Druce**, None; **L. D'Ambruoso**, None; **G. J. Macfarlane**, None.

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Abstract Number: 2279

Impacts on Work: Arthritis Vs Chronic Joint Symptoms without Arthritis

Kristina A. Theis and Michael Boring, Arthritis Program, Centers for Disease Control and Prevention, Atlanta, GA
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Background/Purpose: While chronic joint symptoms are characteristic of arthritis, previous studies have shown that many people with chronic joint symptoms do not have doctor-diagnosed arthritis. These people are typically younger, more often male, and report less limitation than those with doctor-diagnosed arthritis. However, differences between the two groups have not been evaluated for the socially and economically important domain of work.

Methods: Data were obtained from ACHES, a random-digit dialed national telephone survey, conducted in 2005-06, of non-institutionalized US adults ages ≥45. We restricted analyses to 45-64 years (working ages). Respondents were classified as ARTH ('yes' to *Have you ever been told by a doctor or other health professional that you have some form of arthritis, rheumatoid arthritis, gout, lupus, or fibromyalgia*?) (n=1,006) OR CJS (joint symptoms in the past 30 days that began >3 months prior but no ARTH) (n=352). Impact on work for pay was measured by 'yes' to: 1) do arthritis or joint symptoms "now affect whether you work for pay or not," 2)"the type of work," or 3)"the amount of work" you do? Only those employed were asked type and amount. We estimated prevalence of each impact for ARTH and CJS separately and compared characteristics using weighted proportions with 95% confidence intervals (CI). All reported proportions represent statistically significant differences based on non-overlapping CIs.

Results: Overall, CJS were younger, employed more (68% vs 54%), disabled less (11% vs 22%), and had less reports of losing ≥1 workday (5% vs 13%) or activity limitations due to symptoms (33% vs 55%) compared with ARTH. Fair/poor health (19% vs 33%), severe joint pain (13% vs 31%), and daily pain (42% vs 59%) were less common among CJS vs ARTH.

Impact on whether one works and type of work were both higher for ARTH vs CJS (36% vs 20% and 43% vs 30%, respectively). Impact on amount of work was not significantly different between groups. Among ARTH greater proportions of females (35% vs 16%), those with some college education (37% vs 18%), and the obese (41% vs 23%) reported impact on whether one works

than CJS counterparts. Also among ARTH greater proportions with **no** activity limitations (55% vs 40%), **no** depression (26% vs 13%), **no** anxiety (21% vs 11%), **no** severe joint pain (23% vs 14%), and **no** bathing/dressing limitations (20% vs 9%) reported impact on whether one works compared with CJS.

Conclusion: Work impacts are high among both ARTH and CJS, despite different group patterns. ARTH work impacts are common even without severe joint pain or physical limitations. Given the economic importance of work, interventions for both groups are warranted, but ARTH identifies a priority population.

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Abstract Number: 2281

The Prediction of Fatigue in Early Rheumatoid Arthritis Patients

Margot Walter[1], T. Martijn Kuijper[2], Mieke Hazes[2,3], A.E.a.M. Weel[4] and J.J. Luime[5], [1]Rheumatology, Erasmus Medical Center, Rotterdam, Netherlands, [2]Rheumatology, Erasmus University Medical Center, Rotterdam, Netherlands, [3]Department of Rheumatology, Erasmus MC, University Medical Center, Rotterdam, Netherlands, [4]Department of Rheumatology, Maasstad Hospital, Rotterdam, Netherlands, [5]Department of Rheumatology, Erasmus Medical Centre, Rotterdam, Netherlands
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Session Title: Epidemiology and Public Health Poster (ARHP)
Session Type: ACR Poster Session C
Session Time: 9:00AM-11:00AM

The prediction of fatigue in early Rheumatoid arthritis patients

Background/Purpose:

Rheumatoid arthritis-related fatigue is a common problem with a high impact on patients. How fatigue develops over time since early diagnosis of RA is not well known. The aim of this study was i) to describe the pattern of the fatigue over time in patients with early RA under T2T ii) to identify predictive factors /determinants for evolution of fatigue over time stratified for baseline values of fatigue.

Methods: Data from the tREACH study (treatment in the Rotterdam Early Arthritis Cohort) were used. This multi-centered trial compared different initiation treatment strategies in early RA patients. Patients completed VAS and FAS on fatigue, CORS, HADS, RADAI, SF-36 and were clinically assessed by DAS every 6 month. We stratified the patients into no fatigue (FAS values 10-21) and fatigued (FAS values 22-50) and assessed the evolution of fatigue over time and the covariates using a mixed linear model with time lag. Missing covariate data was imputed using a mixed linear model.

Results:

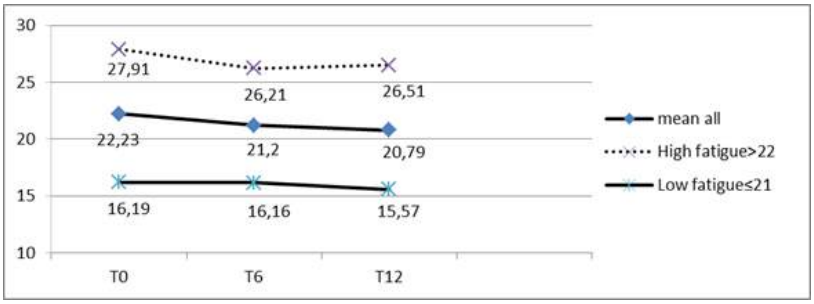
A total of 270 individuals classified as RA using the 2010 criteria, 246 could be stratified according to their baseline fatigue (24 had missing data). The sample resulted in a typical early RA population with a mean age of 53 years (SD 14.3 years) and 68% females, 73% rheumatoid factor and 77% anti-CCP antibodies positive. The percentage of patients with joint damage was 18%.The VAS fatigue was 51.4(SD 25.9) and the FAS 22.2 (SD 7.1). High fatigue at baseline was univariate associated with higher levels of the CORS, high levels of depression and anxiety, a worse physical health (SF-36) and more swollen and tender joints.Over time fatigue decreased slightly with 2-7% on average as shown in figure 1.

Significant determinants for the prediction of fatigue in the univariate and multivariate analysis are presented in table 1.

Conclusion:

About half of the early RA patients reported high levels of fatigue at baseline which for most of them consisted over time. Only better reported physical health (SF36) predicted change of fatigue. Patients with low fatigue at baseline were more likely to develop fatigue over time if they were women, had more tender joints, were more anxious and had a worse Physical SF36 scores.

Figure 1 evolution over time of fatigue



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	FAS (≤21)	FAS (>22)	Fatigud (≤21)	FAS (>22)
	Univariate analysis		Multivariate analysis	
	β-Coeff.(CI95%)	β-Coeff.(CI95%)	β-Coeff.(CI95%)	β-Coeff.(CI95%)
Sex	-2.59** (-4.21--0.97)	-1.17 (-3.61-1.27)	-2.21** (-3.59- -.833)	
Age	-0.06** (-0.12- -0.003)	-0.023 (-0.10-0.05)		
Work	1.24 (-0.40- 2.89)	1.165 (-1.00- 3.33)		
Education	0.18 (-0.83- 1.20)	0.44 (-1.03- 1.92)		
Dutch	-1.91 (-4.39-0.55)	0.47 (-2.69- 3.65)		
CRP	-0.035* (-0.06- -0.004)	-0.018 (-0.05-0 .01)		
ESR	-0.76** (-1.36- -0.15)	0.11 (-0.80- 1.02)	-0.03* (-0.07- -0.007)	
Tender joints	0.098* (0.01-0.17)	0.027 (-0.08-0.13)	0.010* (0.02-0.18)	
Swollen joints	-0.036 (-0.13- 0.06)	-0.064 (-0.186-0.057)		
VAS global	0.01 (-0.004-0.04)	-0.01 (-0.05-0 .01)		
Das28	0.054 (0-.37-0.47)	-0.19 (-0.83-0.43)		
Radai	0.34* (0.031-0.66)	-0.139 (-0.60-0.32)		
Hads depression	0.18 (-0.04-0 .41)	0.031 (-0.22-0 .28)		
Hads anxiety	0.24*	0.24	0.23*	

Table 1 Univariate and multivariate analysis divided into two groups

Disclosure: M. Walter, None; **T. M. Kuijper**, None; **M. Hazes**, None; **A. E. A. M. Weel**, None; **J. J. Luime**, None.

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Abstract Number: 2282

"Doing Every-Day Life" with Primary Sjögren's Syndrome: Factors Predicting Difficulties Performing Daily Activities and Taking on Life Roles

Katie Hackett[1], Dennis W Lendrem[2], Tim Rapley[3], Katherine Deane[4], Vincent Deary[5], Simon Bowman[6], Julia Newton[7], Wan-Fai Ng[8] and on behalf of the United Kingdom Primary Sjogren's Syndrome Registry, [1]Institute of Cellular Medicine, Newcastle University, Newcastle upon Tyne, United Kingdom, [2]Institute of Cellular Medicine (Musculoskeletal Research Group), NIHR Newcastle Biomedical Research Centre, Newcastle Hospitals Foundation Trust and Newcastle University, Newcastle upon Tyne, United Kingdom, [3]Institute of Health and Society, Newcastle University, Newcastle upon Tyne, United Kingdom, [4]University of East Anglia, Norwich, United

anxiety	(0.04-0 .44)	(-0.01-0.50)	(0.04-0.42)	
Coping pain	0.08 (-0.05-0.21)	0.076 (-0.09-0.25)		
Coping limitations	0.08* (0.009-0.15)	-0.024 (-0.14-0.093)		
Physical health (SF36)	-0.07* (-0.13- -0.013)	0.097* (0.015-0.18)	-0.08** (-0.15- -0.02)	0.09* (0.01-0.18)
Mental health (SF 36)	-.020 (-0.09-0.05)	-0.021 (-0.11-0 .07)		
Level of significance *p=0.05 /**p=0.01/ ***p=0.001 Cut point for FAS ≤21 no fatigue/ >22 fatigue				

Kingdom, [5]School of Health Psychology, Northumbia University, Newcastle upon Tyne, United Kingdom, [6]Rheumatology Dept, University Hospital Birmingham, Birmingham, United Kingdom, [7]Newcastle University, Newcastle upon Tyne, United Kingdom, [8]Newcastle-upon-Tyne Hospitals NHS Foundation Trust, Newcastle upon Tyne, United Kingdom

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Background/Purpose: Primary Sjögren's Syndrome (pSS) is an autoimmune disease which targets secretory glands and results in dryness. In addition pSS patients frequently experience symptoms of fatigue, pain, low mood and have difficulty performing daily activities and subsequently have poor quality of life. There is currently no curative treatment and medical interventions focus on the symptomatic management of dryness. The aim of this study is to identify independent predictors for each of the SF-36 domains in order to identify targets for future therapy interventions with pSS patients. The goal is to identify potential interventions to be delivered by non-medical health care professionals in order to improve the ability to perform daily activities, facilitate taking on life roles and improve quality of life.

Methods: 149 PSS patients diagnosed according to the American European Consensus Criteria were recruited from 12 sites across England. Participants completed the SF-36 questionnaire and measurements of anxiety and depression (Hospital Anxiety and Depression Scale HADs), functional status (ImprovedHAQ), pain (visual analogue scale (VAS), fatigue (VAS), mental fatigue (VAS), dryness (VAS), cognitive failures (Cognitive Failures Questionnaire) and recorded their age and disease duration. Significant correlates of each of the SF-36 domain were identified and multiple regression analysis performed for each of the domains to determine partial regression coefficients. Model robustness was determined by hierarchical regression analysis testing the sensitivity of the model to the order of inclusion.

Results: With one exception, PSS patients scored significantly worse than the norm-based scores for all domains of the SF-36, including Physical Functioning, Role Physical, Bodily Pain, Vitality, Social Functioning, Role Emotional and Mental Health ($p<0.001$). General Health was the exception and there was no significant difference between the pSS patients and the norm-based scores. All SF-36 domains correlated significantly with anxiety, depression, cognitive failures, mental fatigue, pain, fatigue and dryness ($p<0.001$).

Fatigue and depression were the main predictors of poorer Role Physical and Social Functioning domain scores (all $p\leq0.006$). Fatigue was a predictor of Bodily Pain ($p<0.001$) and pain was an independent predictor of poor Physical Functioning ($p<0.001$). Depression and pain were the main independent predictors of the Vitality domain ($p\leq0.006$) and the General Health domain ($p\leq0.043$). The main predictors of the Role Emotional domain were fatigue, anxiety and depression ($p\leq0.037$) and of the Mental Health domain were disease duration and cognitive failures ($p\leq0.026$).

Conclusion: This study demonstrates that fatigue and depression, followed by anxiety and pain are key predictors of the reduced ability to perform daily activities, take on life roles and quality of life. These factors should be addressed during therapeutic interventions with PSS patients presenting with these symptoms. This in turn could support PSS patients to carry out daily activities, take on social and physical life roles and improve their quality of life.

Disclosure: K. Hackett, None; **D. W. Lendrem**, None; **T. Rapley**, None; **K. Deane**, None; **V. Deary**, None; **S. Bowman**, Cellgene, 5,Glenmark, 5,GlaxoSmithKline, 5,Eli Lilly and Company, 5,Novartis Pharmaceutical Corporation, 5,Roche Pharmaceuticals, 5,Takeda, 5,UCB, 5; **J. Newton**, None; **W. F. Ng**, None.

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Abstract Number: 2283

Current and Lifetime Smoking Among US Adults with Arthritis: A Serious Clinical and Public Health Issue

Louise Murphy[1], Miriam G. Cisternas[2] and Teresa J. Brady[1], [1]Arthritis Program, Centers for Disease Control and Prevention, Atlanta, GA, [2]MGC Data Services, Carlsbad, CA
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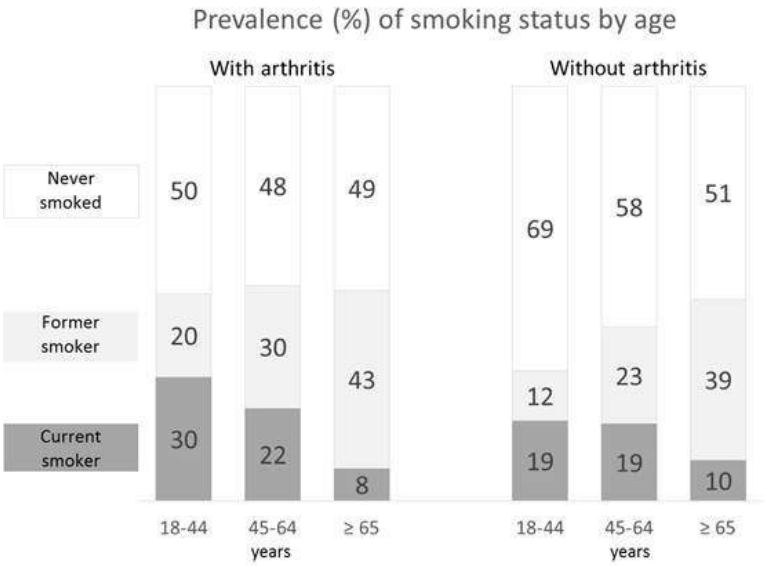
Background/Purpose: Smoking's adverse effects include increased risk of joint replacement failure and decreased medication effectiveness (e.g., methotrexate, TNF blockers). Because little is known about the epidemiology of smoking among US adults with arthritis, we examined prevalence and correlates of smoking.

Methods: We analyzed 2012 and 2013 National Health Interview Survey data for adults ≥ 18 years. Ever smoked was lifetime smoking ≥ 100 cigarettes; current smokers were "ever smokers" who currently smoked every day or some days. We estimated overall and age-specific prevalence of smoking (ever; current) by arthritis status; arthritis was "yes" to "Have you EVER been told by a doctor or other health professional that you have some form of arthritis, rheumatoid arthritis, gout, lupus, or fibromyalgia?". Among people with arthritis, we examined: 1) current smoking prevalence across socio-demographic characteristics, health status, and health behaviors; 2) associations between these characteristics and current smoking using prevalence ratios (PR) and 95% confidence intervals from multivariable logistic regression models.

Results: Ever smoking prevalence was higher among US adults with arthritis (51%) than those without (37%) overall and across all age groups (statistically significant [α=0.05])(Figure). Overall current smoking prevalence was the same for those with and without arthritis (18%); however, among young (18-44 years) and middle age (45-64 years) adults, current smoking prevalence was higher among those with arthritis than those without (statistically significant [α=0.05])(Figure). Among adults with arthritis, current smoking prevalence was at least 25% among those with the following characteristics: high (39%) or moderate (25%) serious psychological distress; unable to work because of disability (34%); young adults (30%); ≥ 2 types of non-arthritis pain (26%); or chronic pulmonary condition diagnosis (25%). In multivariable models, age and education were strongest correlates of current smoking: PRs for current smoking declined with increasing age (18-44=3.0; 45-64=2.3; referent: ≥ 65) and education (< high school=2.9, high school=2.5, and some college=2.1; referent: college degree).

Conclusion: Current smoking is a serious clinical and public health issue among adults with arthritis, especially young adults. By recommending effective and evidence-based tobacco cessation strategies, health care providers may improve treatment effectiveness.



Disclosure: L. Murphy, None; **M. G. Cisternas**, None; **T. J. Brady**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/current-and-lifetime-smoking-among-us-adults-with-arthritis-a-serious-clinical-and-public-health-issue

Abstract Number: 2284

Age and Sex Stratified Normative Data for Shoulder Range of Movement

Tiffany K. Gill[1], E. Michael Shanahan[2,3], Graeme R Tucker[1] and **Catherine Hill**[4,5], [1]Medicine, The University of Adelaide, Adelaide, Australia, [2]Rheumatology, Flinders University, Bedford Park, South Australia, Australia, [3]Repat General Hospital, Flinders University, Adelaide, Australia, [4]Rheumatology Unit, The Queen Elizabeth Hospital, Woodville, Australia, [5]The Health Observatory, The University of Adelaide, Adelaide, Australia

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Background/Purpose: Shoulder range of movement is integral to activities of daily living and the impact of pain on shoulder function has a significant effect on quality of life. However, while some studies have examined normative values for shoulder strength, few large studies have determined normative values for shoulder range of movement (ROM) across a wide age range. The aim of this study was to provide normative data for shoulder ROM, using data from a population-based cohort.

Methods: Participants for this study were part of the North West Adelaide Study (NWAHS), a longitudinal cohort study of 4056 randomly selected adults aged 18 years and over (47.7% male) at the time of recruitment. Three stages of data collection have been undertaken. Stage 1 was between 1999-2003, Stage 2, 2004-06 and Stage 3, 2008-10. As part of the Stage 2 assessment, range of flexion and abduction for both the right and left shoulders were measured using an inclinometer and standardised protocols and external rotation was measured by observation. Participants were asked if they had ever had shoulder pain or stiffness, if they had ever been told by a doctor that they had rheumatoid arthritis (RA) and were defined as having diabetes by self-report and/or a fasting plasma glucose level of >= 7.0mmol/l. Those who reported having shoulder pain and/or stiffness and those with RA were excluded from the analysis. Data were weighted by age, sex and probability of selection in the household to correct for disproportionality of response. Age group analyses were undertaken using the following groupings (<40 years, 40-49, 50-59, 60-69, 70-79, 80 years and over).

Results: Overall, there was a significant mean difference ($p<0.05$) between the right and left sides for each movement. Males had higher mean abduction and flexion and lower mean external rotation compared to females (Table 1).

Table 1: Mean shoulder ROM by sex (n=2404)

	Males	Females
	Mean (SD)	Mean (SD)
Flexion		
Right	161.5 (18.7)	158.5 (19.1)
Left	159.9 (18.1)	157.1 (18.2)
Abduction		
Right	151.5 (20.1)	149.7 (20.3)
Left	149.7 (20.3)	147.7 (20.0)
External rotation		
Right	56.8 (17.6)	60.9 (17.9)
Left	55.0 (17.9)	58.5 (17.7)

ROM generally declined with age for each movement with significant correlation between age and ROM ($p<0.05$). People with diabetes also demonstrated a significantly reduced ROM compared to those without ($p<0.05$, Table 2).

Table 2: Mean shoulder ROM for those with and without diabetes (n=2379)

	No diabetes	Diabetes
	Mean (SD)	Mean (SD)
Flexion		
Right	160.8 (18.6)	148.7 (20.9)
Left	159.4 (17.8)	146.7 (20.4)
Abduction		
Right	151.5 (19.5)	136.9 (25.8)
Left	149.6 (19.5)	135.1 (25.1)
External rotation		
Right	59.3 (17.6)	50.0 (17.9)
Left	57.2 (17.7)	47.6 (17.6)

Conclusion: This large population sample provides normative values for shoulder ROM which are important for comparison purposes, in order to determine if a level of impairment exists. Generally it is accepted that normal flexion and abduction range of movement is 180 degrees and external rotation is 90 degrees, however this does not appear to be the case. This needs to be taken into consideration when assessing and treating those with shoulder impairments.

Disclosure: T. K. Gill, None; **E. M. Shanahan**, None; **G. R. Tucker**, None; **C. Hill**, None.

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Abstract Number: 2285

Poor Quality of Sleep Is Associated with Increased Disease Activity and Fatigue in Axial Spondyloarthritis

Lana Frost[1], Jiayi Zhou[2], Lourdes Pena Castillo[2], Sean Hamilton[1], Nayef Al Ghanim[1], Proton Rahman[1] and Jennifer Burt[1], [1]Rheumatology, St. Clare's Mercy Hospital, St. John's, NF, Canada, [2]Computer Science, Memorial University of Newfoundland, St. John's, NF, Canada

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Background/Purpose: Sleep disturbance is a common occurrence in musculoskeletal disease including ankylosing spondylitis. The reasons for the sleep disturbance in rheumatic diseases are multifactorial. There are a paucity of studies examining the relationship of sleep disturbance and disease activity in axial SpA patients, with or without TNFi therapy. We set to examine the relationship between sleep quality and disease activity in axial SpA.

Methods: Consecutive patients with axial SpA satisfying the ASAS criteria were asked to fill out a HAQ and BASDAI, prior to seeing a rheumatologist or health care professional. All patients successfully completing both questionnaires at the same visit were included in our study. Demographic information, HLA-B27 status and use of biologic therapy were extracted from the charts. The assessment regarding the quality of sleep was derived from the VAS scale pertaining to a specific question on sleep in the HAQ (question number 4). Quality of sleep then was categorized into three groups based on the VAS score: 0 to 3; 3.1 to 6; and greater than 6.1. The sleep quality was compared to the total BASDAI score and fatigue, as measured by the VAS score from question number 1 from the BASDAI. Spearman's rank correlation coefficient was done between the categorical sleep score and total BASDAI and fatigue.

Results: 92 patients with axial SpA patients were included which comprised of 65 males, and 52 patients on TNFi. 40 patients had a VAS sleep score between 0-3; 25 between 3.1 to 6 and 27 between 6.1 to 10. Then mean BASDAI score respectively in these three groups were: 2.6 (sd 1.4); 4.5 (sd 1.4) and 6.2 (sd 1.7). So high VAS sleep score (poor sleep) was significantly correlated with higher BASDAI; rho 0.74; $p < 0.0001$. Patients on TNFi had a significantly lower mean BASDAI score than patients not on a TNFi, however the relationship between quality of sleep and BASDAI was similar between two groups. We observed a higher correlation between sleep pattern and BASDAI in males as compared to females (rho 0.79 vs 0.67 respectively). Sleep score was also significantly correlated with fatigue with mean scores of 2.1 (sd 1.9); 5.7 (sd 1.9) and 6.6 (sd 2.0) respectively in the three groups, rho 0.76; $p < 0.0001$.

Conclusion: A high VAS sleep score (poor sleep pattern) is associated with higher BASDI score and fatigue, irrespective of treatment with TNFi. Improving sleep hygiene may represent an alternative strategy in lowering disease activity in axial SpA, particularly in male patients.

Disclosure: L. Frost, None; **J. Zhou**, None; **L. Pena Castillo**, None; **S. Hamilton**, None; **N. Al Ghanim**, None; **P. Rahman**, Abbott, AbbVie, Amgen, BMS, Celgene, Janssen, Novartis, Pfizer and Roche, 5; **J. Burt**, None.

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Abstract Number: 2286

Correlation of Magnesium Levels and IGF-! Levels in Fibromyalgia Patients

Thomas Romano, Private Practice, Martins Ferry, OH
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Background/Purpose: To determine if there is a correlation between RBC Mg levels and IGF-! levels in Fibromyalgia (FM) patients

Methods: 60 FM patients (10 men, 50 women) Mean age 49.5 yrs for men and 42.8 yrs for women were studied. All fulfilled ACR 1990 Criteria for FM. RBC Mg levels and serum Insulin-dependent growth factor levels were measured .

Results: The mean IGF-1 level for FM patients was 159.33 ng/dl which was lower than the expected mean of 235 ng/dl. Mean

RBC Mg level for the FM patients was 4.49 mg/dl which was ststistically significantly lower than the mean for the control group of 12 Osteoarthritis patients and the laboratory standard (5.5 mg/dl for both). A correlation coefficient of 0.48 was calculated with a test statistic of 1.97.

Conclusion: There was a statistically significant positive correlation between IGF-1 levels and RBC Mg levels in the 60 FM patients studied. This has implications for treatment and further diagnostic testing.

Disclosure: T. Romano, None;

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Abstract Number: 2287

Evaluation of the Fibromyalgia Rapid Screening Tool (FiRST) Questionnaire to Screen Fibromyalgia Associated with Inflammatory Rheumatic Disease

Angélique Fan[1], Bruno Pereira[2], Anne Tournadre[3], Zuzana Tatar[1], Sandrine Malochet-Guinamand[4], Martin Soubrier[1] and **Jean-Jacques Dubost**[1], [1]Rheumatology department CHU Clermont-Ferrand, Clermont-Ferrand, France, [2]Biostatistics unit (DRCI), CHU Clermont-Ferrand, Clermont-Ferrand, France, [3]Rheumatology, UNH-UMR 1019 INRA University of Auvergne and Rheumatology department CHU Clermont-Ferrand, Clermont-Ferrand, France, [4]Rheumatology Department,, Rheumatology department CHU Clermont-Ferrand, Clermont-Ferrand, France

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Background/Purpose: Fibromyalgia (FM) is prevalent in patients with chronic inflammatory rheumatic diseases (CIRd), where it hampers diagnosis and activity assessment. No tool for screening FM associated with CIRd has ever been evaluated. The Fibromyalgia Rapid Screening Tool (FiRST) is a brief and simple self-complete questionnaire that has been validated for screening FM in patients with diffuse chronic pain. The purpose of this study was to evaluate how well FiRST performs on screening for FM associated with CIRd.

Methods: This single-center cross-sectional study was conducted between September 2014 and April 2015 on all patients with chronic pain presenting for rheumatoid arthritis (RA), spondyloarthritis (SpA), and connective tissue disease (Sjögren's syndrome (SS), systemic lupus erythematosus (SLE), scleroderma (Scl), myositis). Diagnosis of FM was based on ACR–90 classification criteria (to minimize interfering overlap between rheumatic disease-related pain and FM-related pain) and expert opinion.

Results: The population included 605 patients: 279 RA, 271 SpA (52 psoriatic arthritis, 126 radiographic axial SpA, 64 non-radiographic axial SpA, 29 peripheral SpA), 57 connective tissue disease. In total, 51 patients had FM meeting the ACR–90 criteria, and 93 patients were given a diagnosis of FM by the expert. When tested against the ACR–90 classification criteria, FiRST demonstrated a sensitivity of 74.5%, a specificity of 80.4%, a positive predictive value of 26.6% and a negative predictive value of 97.1%. Specificity was significantly weaker in the connective tissue disease group (RA: 84.4%, SpA: 80.2%, connective tissue disease: 59.6%; $p<0.001$). When tested against expert opinion, FiRST demonstrated a sensitivity of 75.8%, a specificity of 85.1%, a positive predictive value of 48.3% and a negative predictive value of 95%. FiRST underperformed on sensitivity in the SpA group compared to the connective tissue disease group (66% *vs* 94.4%; $p=0.004$). Performances varied according to item in the self-complete questionnaire.

Conclusion: The symptoms of rheumatic disease interfere with the symptoms of fibromyalgia. FiRST nevertheless manages to perform well in this population, showing an excellent negative predictive value.

Disclosure: A. Fan, None; **B. Pereira**, None; **A. Tournadre**, None; **Z. Tatar**, None; **S. Malochet-Guinamand**, None; **M.**

Soubrier, None; **J. J. Dubost**, None.

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Abstract Number: 2288

Effectiveness of Dry Needling and Exercise in Dizziness Caused By Cervical Myofascial Pain Syndrome

Tugba Aydin[1], Bahar Dernek[2], Tulin Senturk[3], Ayse Karan[4] and Cihan Aksoy[5], [1]Physiotherapy and Rehabilitation, Okmeydani Training and Research Hospital, Istanbul, Turkey, [2]Physical Medicine and Rehabilitation, Istanbul Kanuni Sultan Suleyman Education and Research Hospital, Istanbul, Turkey, [3]Department of Otolaryngology, Bagcilar Education and Research Hospital, Istanbul, Turkey, [4]Department of Physical Medicine and Rehabilitation, Istanbul University, Istanbul Faculty of Medicine, Istanbul, Turkey, [5]Department of Physical Medicine and Rehabilitation, Istanbul Medical Faculty, Istanbul Universty, ISTANBUL, Turkey

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Background/Purpose:

The aim of this study is to compare the effectiveness of dry needling therapy combined with exercise treatment (dry needling+exercise) with exercise treatment alone for alleviating the dizziness caused by cervical myofascial pain syndrome.

Methods: This is a randomized clinical study that included 61 women who complained of cervical pain and dizziness for at least three months, and who had myofascial trigger points on the clavicular side of the sternocleidomastoid muscle and/or trapezius muscle. The patients was randomized into a dry needling+exercise group (n=31) and an exercise-only group (n=30). Both groups were treated for a duration of four weeks. The patients were evaluated before treatment, at the end of one month of treatment, and at the end of four months of treatment. Myofascial pain syndrome was evaluated by cervical pain (measured using the visual analogue scale (VAS)), number of trigger points, manual palpation pain (VAS), algometric measurement, and skin rolling test values. Dizziness was evaluated by the number of dizzy attacks per week, the severity of the dizziness, fall index, and the Dizziness Handicap Inventory (DHI)

Results:

The mean age of participants in this study was 38.4±8.3 years. The severity of dizziness, severity of cervical pain, number of trigger points, severity of manual palpation pain, fall index, and DHI decreased, while algometric measurements and skin rolling test values increased in both groups after treatment. These results were statistically significant in both groups ($p<0.05$). The dry needling+exercise treatment was superior to the exercise treatment alone in decreasing the severity of cervical pain, number of trigger points, number of dizzy attacks per week, and severity of dizziness at the end of the the first and fourth months ($p<0.05$). DHI points and manual palpation trigger point pain had decreased more in the dry needling +exercise group at the end of the first month ($p<0.05$), but by the end of the fourth month there was no statistical difference between the two groups. The two groups saw similar increases in algometric measurements at the end of the first month ($p>0.05$), but dry needling+exercise treatment increased algometric measurements better than exercise treatment alone by the end of the fourth month ($p<0.05$). The fall index was statistically similar in both groups at the end of the first and fourth months ($p>0.05$).

Conclusion: Both dry needling+exercise therapy and exercise therapy alone were effective in treating cervical pain and dizziness caused by cervical myofascial pain syndrome. However, dry needling+exercise treatment was superior to exercise treatment alone in most of parameters.

Disclosure: T. Aydin, None; **B. Dernek**, None; **T. Senturk**, None; **A. Karan**, None; **C. Aksoy**, None.

Abstract Number: 2289

A Cervical Radiculopathy Can Cause Chest Pain

Robert S. Katz[1], Ben J Small[2] and Alexandra Katz Small[1], [1]Rush University Medical Center, Chicago, IL, [2]MacNeal Hospital, Berwyn, IL

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SESSION INFORMATION

Session Date: Tuesday, November 10, 2015

Session Title: Fibromyalgia, Soft Tissue Disorders, Regional and Specific Clinical Pain Syndromes Poster II

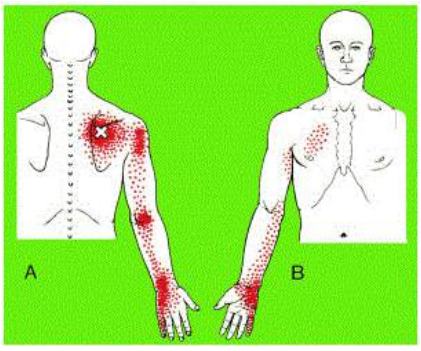
Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Chest pain has multiple etiologies, but cervical radiculopathy is not considered to be one of them. There is innervation of the chest wall from segmental nerves originating from the cervical spine.

Methods: We describe four patients who had left sided chest pain with left arm pain, whose workups demonstrated cervical radiculopathies but no evidence of coronary artery disease.

Results: Four patients, three males and one female, ages 58 to 62, each presented with left chest pain. Each patient had a negative thallium exercise stress test and an echocardiogram. Each of these four patients also described left arm discomfort. The chest and arm discomfort were often felt as a tingling or burning sensation. Each patient had an MRI demonstrating left cervical disc herniation and/or an EMG consistent with a left cervical radiculopathy.



Conclusion: These four patients demonstrate that chest pain accompanied by left arm pain may be a manifestation of a left cervical radiculopathy. Thallium stress tests and echocardiograms were normal in these patients. Each had an MRI, and some also had EMGs, consistent with a cervical radiculopathy.

These cases demonstrate that a cervical radiculopathy should be considered in the differential diagnosis of patients with chest pain especially when accompanied by left arm pain or dysesthesias.

Disclosure: R. S. Katz, None; **B. J. Small**, None; **A. Katz Small**, None.

Abstract Number: 2290

The 2011 Fibromyalgia (FM) Survey Criteria Are a Surrogate Measure of Pain Centralization

Steven E. Harte[1], Daniel J. Clauw[2], Andrew D. Clauw[1], J. Ryan Scott[1], Stephanie Moser[1] and Chad Brummett[2], [1]Department of Anesthesiology, University of Michigan, Ann Arbor, MI, [2]Anesthesiology, University of Michigan, Ann Arbor, MI
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Background/Purpose: The 2011 FM Survey Criteria can either be used as a dichotomous measure to diagnose an individual with FM, or in a continuous manner to determine the degree of "fibromyalgianess" an individual is experiencing. Used in this latter manner, studies have suggested that this measure is predictive of decreased responsiveness to opioids in the perioperative period, and decreased improvement in pain following knee and hip arthroplasty. This has led us and others to suggest that this measure is a surrogate measure of the central sensitization an individual is experiencing. However, a critical portion of the central sensitization construct is that an individual experiences pain augmentation or amplification, measured either by quantitative sensory testing (QST) or functional neuroimaging. This study examines the relationship between the FM Survey Criteria and QST findings in a cohort of individuals with osteoarthritis.

Methods: 101 individuals with osteoarthritis (ages 41 – 85, 45 male, 56 female) awaiting joint arthroplasty had a battery of self-report measures including the 2011 FM Survey Criteria. These individuals also underwent an extensive QST battery including mechanical pain threshold and tolerance, temporal summation, and conditioned pain modulation - at both the affected knee, as well as several neutral sites (including thumb and trapezius). The cohort of 101 individuals was then split into three tertiles of FM scores, from 0-3 (n = 37), 4-7 (n = 34), and 8 or greater (n = 30). ANOVA was performed comparing mean QST values in each tertile.

Results: For nearly all static QST variables, there was a stepwise change in the hypothesized direction between QST measures and FM tertiles. Most but not all of these changes reached statistical significance. The three tertiles showed a similar stepwise increase in pain intensity, even though the FM criteria do not assess pain intensity, just distribution.

Conclusion: This is the first study to demonstrate that the 2011 FM Survey Criteria show a strong relationship to QST measures in a cohort of individuals with knee osteoarthritis. This provides further evidence that this simple to administer measure may serve as a surrogate measure of pain centralization in individuals with chronic pain states.

Disclosure: S. E. Harte, MAST Device, 4,Cerephex, 5,Analgesic Solutions, 5,Merck, 5,Regeneron, 5,deCode Genetics, 5; **D. J. Clauw**, Abbott Laboratories, 5,Cerephex, 5,Eli Lilly and Company, 5,Forrest Laboratories, 5,Johnson & Johnson, 5,Merck Pharmaceuticals, 5,Pfizer Inc, 5,Purdue Pharma L.P., 5,Samumed, 5,Theravance, 5,Tonix, 5,UCB, 5,Zynerba, 5,Abbott Laboratories, 5,Cerephex, 5,Eli Lilly and Company, 5,Forest Laboratories, 5,Johnson & Johnson, 5,Merck Pharmaceuticals, 5,Pfizer Inc, 6,Purdue Pharma L.P., 6,Samumed, 5,Theravance, 5,Tonix, 5,UCB, 5,Zynerba, 5; **A. D. Clauw**, None; **J. R. Scott**, None; **S. Moser**, None; **C. Brummett**, Tonix Pharmaceuticals, 5.

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Abstract Number: 2291

The Factors That Might be Responsible for the Improvement of Fibromyalgia Patients: A Sub-Group That Improved Significantly over Three to Six Months

Robert S. Katz[1] and Lauren Kwan[2], [1]Rush University Medical Center, Chicago, IL, [2]Rheumatology Associates S.C., Chicago, IL
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Background/Purpose: In a rheumatology office practice, patients with fibromyalgia who improved significantly in their symptoms are seen commonly. We evaluated patients whose pain, fatigue, fibrofog, and functional scores were significantly better over a 3-6 month period.

Methods: Patients who had significant improvement on visual analog scales in a rheumatology office practice were further assessed and responded to a questionnaire regarding reasons for improvement.

Results: 19 patients indicated significant improvement in their fibromyalgia symptoms and are included. The mean age of the participants was 42.2 (17 years old -71 years old). 17 of the 19 (89.5%) participants were female and 2 of 19 (10.5%) participants were male. All patients met the 2010 ACR criteria for the diagnosis of fibromyalgia. The mean pain score at the last office visit was 4.8 on a 1-10 visual analog scale. The mean pain score at an office visit 3 months earlier was 7.7 and the mean pain score at an office visit 6 months earlier was 8.4. Patients were asked to list the factors they attributed to their decrease in pain scores of at least 3 points on a 1-10 visual analog scale over the last 6 months. 15 of 19 (78.9%) of patients cited medication as a reason for their improvement. These medications included cyclobenzaprine (9 of 19, 47.4%), amitriptyline (8 of 19, 42.1%), tizanidine (2 of 19, 10.5%), clonazepam (1 of 19, 5.3%), doxepin (1 of 19, 5.3%), hydrocodone (2 of 19, 10.5%), gabapentin (1 of 19, 5.3%), trazodone (1 of 19, 5.3%), chlorzoxazone (1 of 19, 5.3%), and mirtazepine (1 of 19, 5.3%).

The other common reasons cited for improvement included weather changes (5 of 19, 26.3%), increased rest (5 of 19, 26.3%), decreased stress (3 of 19, 15.8%), and improved sleep (3 of 19, 15.8%). Exercise, physical therapy, acupuncture, increased time off work, and increased knowledge about their diagnosis were other reasons occasionally cited as a reason for improvement.

Conclusion: Patients with fibromyalgia who improve significantly generally attribute that improvement to a change in their medication, but other reasons are cited, such as weather and increased rest. Medication, especially muscle relaxants and tricyclics, appears to be an effective strategy for patients with fibromyalgia who improve significantly.

Disclosure: R. S. Katz, None; **L. Kwan**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/the-factors-that-might-be-responsible-for-the-improvement-of-fibromyalgia-patients-a-sub-group-that-improved-significantly-over-three-to-six-months

Abstract Number: 2292

Improvement in Function and Pain Due to Subacromial Bursitis As Related to Dose of Triamcinolone Acetonide or Methylprednisolone Acetate

Spencer Motley[1], Bryan Ramsey[1] and Matthew Carroll[2], [1]Internal Medicine, Keesler Medical Center, Keesler AFB, MS, [2]Rheumatology, Keesler Medical Center, Keesler AFB, MS

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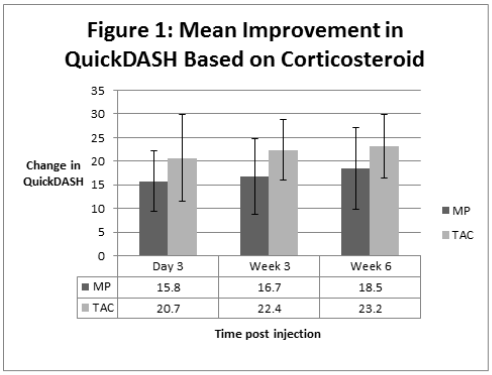
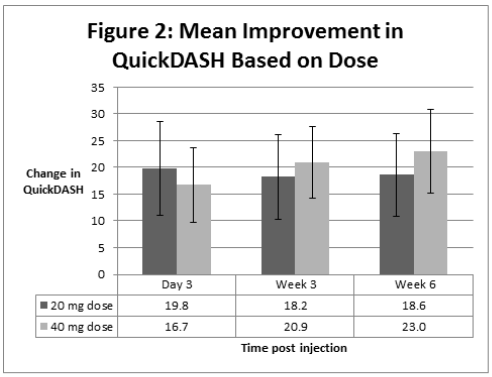
Background/Purpose: Subacromial bursitis is caused by inflammation of the bursa that separates the superior surface of the supraspinatus tendon from the overlying coraco-acromial ligament and acromion. While intra-bursal corticosteroid injection is routinely used to treat pain and help restore function in subacromial bursitis, the optimal corticosteroid dose or preparation is

currently unknown. We hypothesized that there would be no difference between subjects who received triamcinolone acetonide (TAC) or methylprednisolone acetate (MP) but there would be greater improvement with a 40 mg dose as compared to a 20 mg dose.

Methods: This single blinded study randomized subjects with at least 2 weeks of subacromial bursal pain by history and exam to receive intrabursal corticosteroid in one of four groups: TAC 20 mg, TAC 40 mg, MP 20 mg, or MP 40 mg. Concomitant with the corticosteroid injection all subjects also received 2 mL of 1% lidocaine without epinephrine and 2 mL of 0.5% bupivacaine. The Quick Disabilities of Arm, Shoulder, and Hand (or QuickDASH), subject reported pain, and adverse events were recorded at time of injection and then 3 days, 3 weeks, and 6 weeks post-injection. Primary outcome was improvement in the QuickDASH 6 weeks post-injection. Secondary outcomes were improvement in subject reported pain at 6 weeks and occurrence of adverse events. This trial is registered at www.clinicaltrials.gov (NCT02242630).

Results: Forty eight subjects were recruited. Average age was 66.8 ± 10.8 years old. Over 85% of subjects were Caucasian. Twenty left and 28 right subacromial bursa were injected. For the primary outcome, mean improvement in QuickDASH was similar between those who received TAC vs. MP (regardless of dose), shown in Figure 1. Mean improvement in QuickDASH was similar between those who received the 20 mg dose vs. 40 mg dose (regardless of preparation), shown in Figure 2.





No statistically significant differences in subject reported pain based on dose or corticosteroid preparation were noted (data not shown). No statistically significant differences in adverse events were noted between groups, although 3 subjects reported elevations in blood glucose and 2 subjects reported diarrhea.

Conclusion: With our modest sample size we have not identified any statistically significant differences for subjects with subacromial bursitis treated with either corticosteroid preparation or dose. Subject recruitment is ongoing. No significant trends in adverse outcomes were noted.

Disclosure: S. Motley, None; **B. Ramsey**, None; **M. Carroll**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/improvement-in-function-and-pain-due-to-subacromial-bursitis-as-related-to-dose-of-triamcinolone-acetonide-or-methylprednisolone-acetate

Abstract Number: 2293

What Types of Exercises Can Fibromyalgia Patients Perform?

Robert S. Katz[1] and Jessica L. Polyak[2], [1]Rush University Medical Center, Chicago, IL, [2]Rheumatology Associates S.C., Chicago, IL

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Background/Purpose: Fibromyalgia patients should exercise, but often can't. Though aerobic exercises may help, many patients find them too challenging.

Methods: We administered a questionnaire to fibromyalgia office patients. Types of exercises included aerobic exercise, muscle strengthening, stretching, yoga, and other. All patients met the 2010 ACR criteria for the diagnosis of fibromyalgia.

Results: 91 Fibromyalgia responded to a questionnaire regarding their ability to exercise. The types of exercise of fibromyalgia patients were able to perform, based 1-10 on visual analog scales, were stretching (6.75), yoga (5.82), muscle strengthening (4.92), and aerobic exercise (3.98).

Conclusion: Fibromyalgia patients identify stretching and yoga as two types of exercise they can do. Though previous studies suggest that aerobic exercise is beneficial, the majority of fibromyalgia patients find these to too challenging.

Disclosure: R. S. Katz, None; **J. L. Polyak**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/what-types-of-exercises-can-fibromyalgia-patients-perform

Abstract Number: 2294

Re-Scoring the 2011 Fibromyalgia Survey Criteria to be a Better Surrogate for Pain Centralization

Stephanie Moser[1], Chad Brummett[2], Alexander Tsodikov[3], David A. Williams[4] and Daniel J. Clauw[2], [1]Department of Anesthesiology, University of Michigan, Ann Arbor, MI, [2]Anesthesiology, University of Michigan, Ann Arbor, MI, [3]Biostatistics, School of Public Health, University of Michigan, Ann Arbor, MI, [4]Anesthseiology, University of Michigan, Ann Arbor, MI

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Background/Purpose:

The 2011 Fibromyalgia (FM) Survey Criteria is comprised of measures of widespread pain (0-19 body areas) and 6 co-morbid symptoms (scored 0-12). The measure has been termed "fibromyalgianess," which Wolfe and others have shown to be predictive of pain and disability in many rheumatic disorders. We have shown that the continuous measure is predictive of decreased opioid

responsiveness and decreased improvement in pain following arthroplasty, which we feel serves as a marker of pain centralization. We sought to develop a new scoring method for the items that would improve the predictive utility of the measure for centralized pain by re-weighting the existing items to better predict failure to improve pain following arthroplasty. **Methods:**

457 knee or hip arthroplasty patients were included. Changes in pain (WOMAC and Brief Pain Inventory (BPI)) from baseline to 6 months post-surgery and patient global impression of change (PGIC) served as outcomes. A count of 7 body zones (head, spine, trunk, arms, and legs) was compared to the count of 19 original body areas in 6 regression models. Multiple regression models with the criteria items as predictors were then conducted to determine item importance. 10-fold cross validation was used. A new scale score was formed by weighting individual items that consistently best predicted surgical outcomes. Scale scores were evaluated as predictors of surgical outcomes in regression models in the development sample and a model testing sample of 391 other knee or hip arthroplasty patients. Performance was assessed with R-square and AUROC. **Results:**

The count of 7 body zones performed as well or better than the original 19 body areas (Table 1). Thus the scoring using these zones was used in subsequent analyses. In regression models, the body zones, headache, and trouble thinking were consistently strong predictors of outcomes (Fig 1). The new scale score in which headache and trouble thinking were weighted 2X and 3X times, respectively, outperformed the original FM measure (Table 3). **Conclusion:**

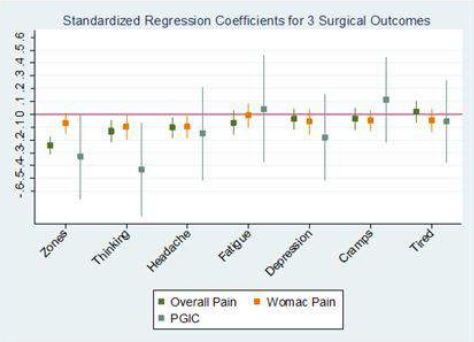
This work provides evidence that the original FM Survey Criteria can be re-scored to be a better predictor of poor response to arthroplasty. Future work is needed to determine the optimal manner to measure critical elements of FM to define a new measure of pain centralization.

Table 1. Regression coefficients and model fit statistics for individual regression models predicting BPI overall pain change, WOMAC change, and PGIC at 6 months from the count of 19 body areas or count of 7 body zones.

	BPI overall pain change		WOMAC pain change		PGIC	
	Standardized Beta	R-squared	Standardized Beta	R-squared	Odds Ratios	ROC
19 body areas	-0.28	0.46	-0.15	0.45	-0.40	0.57
7 body zones	-0.32	0.48	-0.14	0.45	-0.51	0.64

Note: Table presents results from 6 regression models predicting change in BPI overall pain from baseline to 6 months post-surgery, WOMAC pain change from baseline to 6 months post-surgery, and PGIC at 6 months post-surgery from the count of 19 body areas or the count of 7 body zones. A dichotomous variable for PGIC was created such that scores of 2 or 3 were coded as 1 and PGIC scores less than 2 were coded as 0. Linear regression was conducted for models predicting BPI overall pain change and WOMAC pain change. Baseline BPI pain scores and baseline WOMAC pain scores were included in their respective models as covariates. Logistic regression was conducted for the model predicting PGIC. 10-fold cross validation was used. Coefficient estimates and fit statistics are averages across the 10 models.

Figure 2. Standardized regression coefficients for individual regression models predicting BPI overall pain change, WOMAC change, and PGIC at 6 months from the individual ACR score items.



Note: Figure presents results from 3 regression models predicting change in BPI overall pain from baseline to 6 months post-surgery, WOMAC pain change from baseline to 6 months post-surgery, and PGIC at 6 months post-surgery from the 6 ACR criteria components: body zones, fatigue, trouble thinking, tiredness, abdominal cramps, depression, and headaches. A dichotomous variable for PGIC was created such that scores of 2 or 3 were coded as 1 and PGIC scores less than 2 were coded as 0. Linear regression was conducted for models predicting BPI overall pain change and WOMAC pain change. Baseline BPI pain scores and baseline WOMAC pain scores were included in their respective models as covariates. Logistic regression was conducted for the model predicting PGIC. 10-fold cross validation was used. Coefficient estimates are averages across the 10 models. Body zones, trouble thinking, and headache are the consistent

Table 3. Regression coefficients and model fit statistics for individual regression models predicting BPI overall pain change, WOMAC change, and PGIC at 6 months from the old and new scoring methods.

Knees & hips model development sample (n = 457)

	BPI overall pain change		WOMAC pain change		PGIC	
	Standardized Beta	R-squared	Standardized Beta	R-squared	Odds Ratio	ROC
Old scoring	-0.333	0.485	-0.221	0.492	0.866	0.621
New scoring	-0.358	0.504	-0.241	0.501	0.857	0.657

Knees & hips validation sample (n = 391)

	BPI overall pain change		WOMAC pain change		PGIC	
	Standardized Beta	R-squared	Standardized Beta	R-squared	Odds Ratio	ROC
Old scoring	-0.206	0.453	-0.159	0.545	0.769	0.734
New scoring	-0.218	0.459	-0.197	0.559	0.782	0.739

Note: Old scoring method is calculated as the sum of 19 body areas, and 6 symptom severity items. Fatigue, trouble thinking, tiredness are each assessed on a scale of 0 to 3 where 0 is no problems and 3 is severe problems. Abdominal cramps, depression, and headaches are each assessed with a binary scale where 0 is no symptoms and 1 is present symptoms. Possible score ranges from 0 to 31. New scoring method is calculated as the sum of 7 body zones (head, spine, trunk, arms, and legs), fatigue, tiredness, abdominal cramps, trouble thinking multiplied by 2 and headache multiplied by 3. Possible score ranges from 0 to 23. Scores were included in individual regression models predicting BPI overall pain change from baseline to 6 months, WOMAC pain change from baseline to 6 months, and PGIC at 6 months. Baseline BPI pain and WOMAC pain were included in the models predicting their respective change from baseline to 6 months. Scores were first tested in the original model development sample and then tested in a validation sample of 391 knee and hip arthroplasty patients.

Disclosure: S. Moser, None; **C. Brummett**, Tonix Pharmaceuticals, 5; **A. Tsodikov**, None; **D. A. Williams**, Health Focus Inc., 5; **D. J. Clauw**, Abbott Laboratories, 5,Cerephex, 5,Eli Lilly and Company, 5,Forrest Laboratories, 5,Johnson & Johnson, 5,Merck Pharmaceuticals, 5,Pfizer Inc, 5,Purdue Pharma L.P., 5,Samumed, 5,Theravance, 5,Tonix, 5,UCB, 5,Zynerba, 5,Abbott Laboratories, 5,Cerephex, 5,Eli Lilly and Company, 5,Forest Laboratories, 5,Johnson & Johnson, 5,Merck Pharmaceuticals, 5,Pfizer Inc, 6,Purdue Pharma L.P., 6,Samumed, 5,Theravance, 5,Tonix, 5,UCB, 5,Zynerba, 5.

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Abstract Number: 2295

Is There Peripheral Large Nerve Involvement in Fibromyalgia? a Systematic EMG / Nerve Conduction Study Evaluation of 55 Consecutive FM Patients

Xavier J. Caro, Robert G. Galbraith and Earl F. Winter, Southern California Fibromyalgia Research and Treatment Center, Northridge, CA

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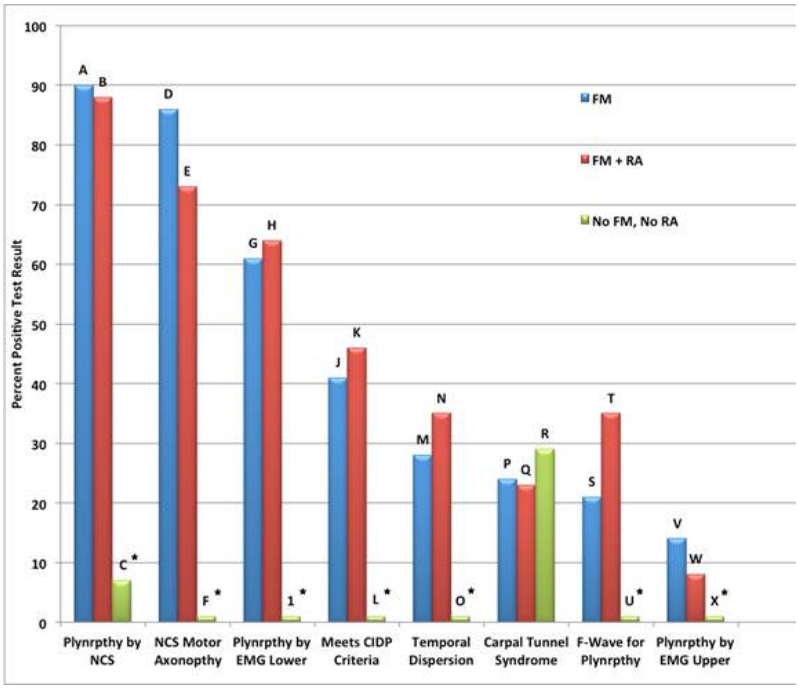
Background/Purpose: Several recent reports have implicated peripheral small fiber neuropathy (SFN) as a significant contributing factor to the pain seen in fibromyalgia (FM). Large fiber neuropathy (LFN) in this disorder has not been extensively described, however. Therefore, we retrospectively examined electromyographic (EMG) and nerve conduction study (NCS) data (collectively, "EDX") on a cohort of FM patients and controls for LFN, and clinically correlated our findings.

Methods: We reviewed clinical and EDX data from 100 consecutive patients, meeting 1990 ACR FM criteria, for study inclusion / exclusion. Subjects with a clinical disorder known to produce LFN (e.g., diabetes, Vitamin B-12 deficiency, familial neuropathy, Sjögren's syndrome, etc.) were excluded. Those with FM + RA were allowed. EDX findings from 30 "FM Only" (27 Caucasian; 23 female; mean age 59, range 21 – 90 yrs.), 25 FM + RA (20 Caucasian; 23 female; mean age 57, range 26 – 84 yrs.), and 14 control subjects with No FM & No RA (mostly incidental evaluation for carpal tunnel syndrome) were compared.

Results: All 55 FM subjects in this cohort had EDX findings of LFN (**Figure)**, with most having a sensorimotor

polyneuropathy (90%), which was demyelinating only, in 22%, axonal only, in 12%, and mixed demyelinating / axonal, in 66%. A sensorimotor polyneuropathy was seen in only 7% of control patients ($P < 0.0001$). NCS features in FM Only included temporal dispersion, prolonged duration, abnormal F-wave, or carpal tunnel syndrome in 28%, 10%, 21%, and 24% respectively. EMG in FM Only showed findings of lower extremity axonal denervation, thought most likely due to a polyneuropathy, in 61%. Clinical correlation in the FM Only group showed a significant association between EMG denervation and proximal muscle weakness ($P < 0.005$). EDX findings meeting published criteria for, at least, "possible" chronic inflammatory demyelinating polyneuropathy (CIDP) were seen in 41% of FM Only subjects, but in no control subjects ($P<0.003$). Calf epidermal nerve fiber density (ENFD) was reduced to ≤ 6.5 fibers / mm in 53% and ≤ 7.0 fibers / mm in 63% of FM Only subjects.

Conclusion: All FM subjects in our cohort had evidence of LFN, suggesting that these lesions participate in FM symptomatology. "FM Only" and FM + RA participants did not demonstrate any major between-group differences in EDX findings. EDX appeared to compliment ENFD determinations in defining the peripheral neuropathology of FM. These EDX findings probably hold important implications for the better understanding and treatment of this painful disorder.



LFN in FM: A vs. C (P value) <0.0001, B vs. C <0.0001, D vs. F <0.0001, E vs. F = 0.0001, G vs. I = 0.02, H vs. I = 0.01, J vs. L = 0.003, K vs. L = 0.002, M vs. O = 0.03, N vs. O = 0.01, S vs. U = 0.08, T vs. U = 0.01. (Fischer's Exact Test, 2 tailed) Other comparisons were NS. * Indicates 1% for illustration purposes; actual value = 0%.

Disclosure: X. J. Caro, None; **R. G. Galbraith**, None; **E. F. Winter**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/is-there-peripheral-large-nerve-involvement-in-fibromyalgia-a-systematic-emg-nerve-conduction-study-evaluation-of-55-consecutive-fm-patients

Abstract Number: 2296

Investigation of Environmental Associations of Fibromyalgia Pain Using Twitter Content Analysis

Pari Delir Haghighi[1], Yong-Bin Kang[1], Tuan Huynh[1], Rachelle Buchbinder[2], Frada Burstein[1] and **Samuel Whittle**[3], [1]Faculty of Information Technology, Monash University, Caulfield East, Australia, [2]Monash Department of Clinical Epidemiology, Cabrini Institute and Monash University, Melbourne, Australia, [3]Rheumatology Unit, The Queen Elizabeth Hospital, Woodville South, Australia

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Background/Purpose:

Little is understood about the determinants of symptom expression within individuals with fibromyalgia syndrome (FMS). While FMS sufferers often report environmental influences, including weather events, on their symptom severity, a consistent effect of specific weather conditions on FMS symptoms has yet to be demonstrated. Twitter is a popular internet-based social media platform that enables users to express their thoughts, feelings and details of their daily lives using short text-based messages (tweets) in the public domain. We used computerized content analysis of tweets to investigate the subjective experience of FMS in a large, widely distributed population and any association with coincident environmental factors.

Methods:

We performed an automated search of Twitter between January 2008 and November 2014 using the hashtags #fibromyalgia, #fibro and #spoonie as keywords. Sentiment analysis, a computerized linguistic method that uses natural language processing and text analytics to identify subjective information in written source materials, was performed using a Streamcrab Python library incorporating the Stanford CoreNLP libraries to quantify the affective content of each included tweet. The classification model was trained using two sets of pre-labelled negative and positive tweets, then used to automatically compute negative and positive sentiment scores between 0 and 100 for each tweet. The sum of the two assigned scores for each tweet is 100. A higher negative sentiment score implies a more severe pain experience. Date, time and location data for each individual tweet were used to identify corresponding climate data (temperature, humidity, wind speed, “feels like”, heat index, wind chill, and dew point) via World Weather Online. The association between negative sentiment scores (indicative of greater pain) and environmental variables was measured using Pearson correlation.

Results:

The search returned 140,432 English language tweets for which location data were available. Examples of tweets with their negative and positive sentiment analysis scores are shown in Table 1. There was a low positive correlation between humidity and negative sentiment scores which was significant at the 0.05 level ($r=0.009$, $p=0.001$). There was no significant association between the other environmental variables and negative sentiment scores.

Conclusion: Twitter users who tweet about fibromyalgia are slightly more likely to include content that suggests a higher pain burden as atmospheric humidity increases. Other local weather features, including temperature and wind speed, are not associated with changes in pain sentiment expressed via Twitter. Computerized content analysis is a novel and potentially powerful method for exploring relationships between environmental variables and the subjective experience in rheumatic and other diseases.

Table 1

Tweet Text	Positive Score	Negative Score
pain for days not going away, just broke down in tears, couldnt bear it anymore, cant be strong everyday; today is not the day #fibro #spoonie	0.0000383	**99.99996167**
Ow. Serious back #pain rn. I did too much today, didn't sleep enough, and my body is punishing me for it!! #mecfs #spoonie #insomnia	0.002235287	**99.99776471**
too tired to write, too tired to function, just too tired. i ache all over. damn #fibromyalgia. maybe epsom salt bath...	0.759179219	**99.24082078**
I'm hurting all over! Pain, pain please go away! I have 7 more hours of work to go! #spoonie	5.554535418	**94.44546458**
I'm having a good morning. If there's 1 thing I've learned from being a #spoonie it's to appreciate every good moment. :-)	99.92757658	**0.072423417**
Celebrating the very fact that I am up at 9:30 p.m. I lived through Saturday! #spoonie	99.93087439	**0.069125607**
So now I'm super duper excited 2 record the class tomorrow! I'll just do a dance session while at the mic! Yippee #spoonie #fibro #arthritis	99.96559746	**0.034402541**
I got a wonderful massage. Getting a #spoonie ready for anything requires gifted massage tech =P	99.98018133	**0.019818665**

Disclosure: P. Delir Haghighi, None; **Y. B. Kang**, None; **T. Huynh**, None; **R. Buchbinder**, None; **F. Burstein**, None; **S. Whittle**,

None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/investigation-of-environmental-associations-of-fibromyalgia-pain-using-twitter-content-analysis

Abstract Number: 2297

Dinamyx Neuromodulation in Fibromyalgia

CAMILLO GIACOMELLI, Antonino Santagati, Arianna Consensi, Alessandra Rossi and Laura Bazzichi, Division of Reumatology, Univeristy of Pisa, Pisa, Italy

First publication: September 29, 2015

SESSION INFORMATION

Session Date: Tuesday, November 10, 2015

Session Title: Fibromyalgia, Soft Tissue Disorders, Regional and Specific Clinical Pain Syndromes Poster II

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose:

Fibromyalgia (FM) is one of the most common diseases manifested by pain, tenderness and fatigue. FM is still a disorder of unknown etiology that is generally diagnosed according to the ACR criteria. According to Cochrane Reviews, **current therapy** is clearly and largely **not satisfactory (1).** Transcutaneous electrical nerve stimulation (TENS) is a non-invasive technique that is used throughout the world to manage painful conditions, although there continues to be uncertainty about efficacy and effectiveness (2). The purpose of TENS is to selectively activate low threshold peripheral afferents as this has been shown to inhibit ongoing transmission of nociceptive input in the spinal cord, leading to pain relief. A variety of TENS-like devices, that differ in design to a standard TENS device, are available to the general public without prescription although there is very little research on mechanisms, efficacy, and effectiveness. Non-invasive Interactive Neuromodulation (INM) is a relatively new TENS-like device and is sold under the trade name Dynamix®. Often pain relief lasts long after the treatment is over which hints at a neuropeptide/cytokine cascade effect and a CNS response. Manufacturers claim that non-invasive INM relieves pain and promotes healing of various injuries. The aim of our study will be evaluate the safety and efficacy of Dynamix application in FM patient.

Methods:

At the division of Rheumatology of University of Pisa, we enrolled 20 Female affected by Fibromyalgia, with a stable therapeutic regimen for at least 3 month, and we treated with Dinamix (A-circle) for 1 times at week for 6 times. Each patients completed FIQ, SF-36, FACIT-Fatigue scale, FAS Evaluation. Prior the treatment, at the end of the treatment and after 4 weeks after the end of the study. The INM treatment was applied on all the efferent nerve of the column and on the exit of trigeminal nerve (the treatment was named column basis). A tender point count with tender point index evaluation was performed by a Rheumatologist.

Results: No patient showed an adverse event during the treatment and at the follow up. We found a statistically significant reduction in FIQ, pain evaluated by VAS and SF-36 item, FAS score (both Self-Assessment Pain Scale and total FAS index), Tende Point index ($p<0.05$). Moreover we found a slight improvement of neck rotation. We don't found a significant reduction in Tender Poins number. The same results was found at follow up visit, after 4 week from the end of the treatment.

Conclusion:

The INM is a non-invasive technique that require a specific skills to obtain satisfactory results, however, the ease of use and speed of application make it a potentially useful technique in pain management. Moreover the INM is well tolerated by the patients. This is a preliminary work that underline the beneficial effects of this treatment in FM patients. The limit of the study was the absence of the control group, for example a placebo group.

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(1) Cochrane reviews: Fibromyalgia. http://www.thecochranelibrary.com/details/browseReviews/577579/Fibromyalgia. html

(2)Johnson MI,Walsh DM. Pain: continued uncertainty of TENS effectiveness for pain relief. *Nat Rev Rheumatol* 2010;6:314–

316.

Disclosure: C. GIACOMELLI, None; **A. Santagati**, None; **A. Consensi**, None; **A. Rossi**, None; **L. Bazzichi**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/dinamyx-neuromodulation-in-fibromyalgia

Abstract Number: 2298

Misdiagnosis of Fibromyalgia (FM) As Axial Spondylarthritis (SpA): Lessons from Analysis of 26 Cases

Dongfeng Liang, Jianglin Zhang and Feng Huang, Rheumatology, Chinese PLA General Hospital, Beijing, China
First publication: September 29, 2015

SESSION INFORMATION
Session Date: Tuesday, November 10, 2015
Session Title: Fibromyalgia, Soft Tissue Disorders, Regional and Specific Clinical Pain Syndromes Poster II
Session Type: ACR Poster Session C
Session Time: 9:00AM-11:00AM

Background/Purpose: Both patients with fibromyalgia (FM) and with axial spondyloarthritis (SpA) are suffering from pain. The patients with axial SpA are mainly manifested as inflammatory back pain, while widespread pain is found in the patients with FM. However for those FM patients, the commonly-seen sleep disturbance due to anxiety/depression usually amplifies the sensation of back pain during the night time, which is likely to be recognized as inflammatory back pain; thus some FM patients had been misdiagnosed as axial SpA. This study intends to further understand the modified American College of Rheumatology (ACR) 2010 diagnostic criteria for FM, increase diagnostic accuracy of axial SpA and reduce misdiagnosis of FM as axial SpA.

Methods: Clinical data of 26 patients with primary FM were collected, who had previously misdiagnosed as axial SpA by other tertiary hospitals in China. The re-diagnosis of those 26 FM patients was established based on the modified ACR 2010 criteria. Each patient was assessed by Widespread Pain Index (WPI) and Symptom Severity (SS) scale adopted by the modified ACR 2010 criteria, as well as parameters including serous C-reactive protein, erythrocyte sedimentation rate (ESR), HLA-B27 and sacroiliac joint images.

Results: Among the subjects, 8 males (30.77%) and 18 females (69.23%) complained widespread pain, most notably in the spine. None of peripheral arthritis, enthesitis, dactylitis, and limited spine motion was found. WPI median (P25-P75) was 5.0 (4.0-8.0). SS score was 9.269 ±1.589. Serous C-reactive protein (normal range: 0 - 0.8 mg/dl) was 0 in 5 cases, less than 0.348 mg/dl in 15 cases and between 0.37-0.74 mg/dl in 6 cases. ESR median (P25-P75) was 5.0 (3.0-9.0) mm/1h. HLA-B27 positivity was detected in 73.08% cases. 4 patients (15.38%, all females) were found with osteitis condensans ilii by CT and MRI, 5 patients with normal sacroiliac CT scan, 6 with normal sacroiliac MRI result, and the rest 11 with normal sacroiliac CT and MRI.

Conclusion: The modified ACR 2010 criteria for FM has adopted the criteria of WPI and SS scale replacing the tender point count and enhanced the diagnostic weight of anxiety/depression. However, in medical practice in China, it isn't uncommon to see the misdiagnosis of FM as axial SpA, which was caused by two reasons: (i) over-relying on the tender point counts indicated in ACR 1990 criteria for FM and (ii) failure to take inflammations as the priority factor of diagnosis of axial SpA. In order to increase diagnostic accuracy of FM and axial SpA, it is necessary to (i) fully investigate and evaluate somatization of anxiety/depression, instead of using tender point counts as the exclusive criterion of FM; and (ii) emphasize inflammations in diagnosis of axial SpA, i.e., at least one of the following factors should be identified: peripheral arthritis, enthesitis, dactylitis, definite sacroiliitis on imaging and elevated inflammatory biomarkers such as serous C-reactive protein and/or ESR.

Disclosure: D. Liang, None; **J. Zhang**, None; **F. Huang**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/misdiagnosis-of-fibromyalgia-fm-as-axial-spondylarthritis-spa-lessons-from-analysis-of-26-cases

Abstract Number: 2299

Association Between Catechol-O-Methyl Transferase Gene Polymorphisms and Fibromyalgia in a Korean Population: A Case-Control Study

Yi-Rang Yim[1], Dong-Jin Park[2], Seong-Ho Kim[3], Seong-Su Nah[4], Ji Hyun Lee[5], Seong-Kyu Kim[6], Yeon-Ah Lee[7], Seung-Jae Hong[8], Hyun-Sook Kim[9], Hye-Soon Lee[10], Hyoun-Ah Kim[11], Chung-Il Joung[12], Sang-Hyon Kim[13] and Shin-Seok Lee[1], [1]Chonnam National University Medical School and Hospital, Gwangju, South Korea, [2]Rheumatology, Chonnam National University Medical School and Hospital, Gwangju, South Korea, [3]Inje University Haeundae Paik Hospital, Busan, South Korea, [4]Soonchunhyang University, College of Medicine, Cheonan, South Korea, [5]Internal Medicine, Maryknoll Medical Center, Busan, South Korea, [6]Internal Medicine, Catholic University of Daegu School of Medicine, Daegu, South Korea, [7]Division of Rheumatology, Department of Internal Medicine, School of Medicine, Kyung Hee University, Seoul, South Korea, [8]Dept. of Rheumatology, #1 Hoeg, KyungHee University Medical Center, SEOUL, South Korea, [9]Internal Medicine, College of Medicine, Chosun University, Gwangju, South Korea, [10]Rheumatology, Hanyang University Hospital for Rheumatic Diseases, Seoul, South Korea, [11]Ajou University Hospital, Suwon, South Korea, [12]Internal Medicine, Konyang University Medical School, Daejeon, South Korea, [13]Division of Rheumatology, Department of Internal Medicine, Dongsan Medical Center, Keimyung University School of Medicine, Daegu, South Korea

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SESSION INFORMATION

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Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Although polymorphisms of the catechol-O-methyl transferase (COMT) gene have been implicated in altered pain sensitivity, results concerning the association between COMT gene polymorphisms and FM are equivocal. The present, large-scale case-control study assessed the associations between COMT single-nucleotide polymorphisms (SNP) and FM risk and symptom severity.

Methods: In total, 409 FM patients and 423 controls were enrolled. Alleles and genotypes at five positions [rs6269 (A>G), rs4633 (C>T), rs4818 (C>G), rs4680 (C>G) and rs165599 (A>G)] in the COMT gene were genotyped from peripheral blood DNA. Associations between COMT SNPs, FM susceptibility and FM patient clinical measures were assessed.

Results: Alleles and genotypes of the rs4818 COMT gene polymorphism were significantly associated with increased susceptibility to FM. The rs4818 GG genotype was more strongly associated with susceptibility to FM compared to the CC genotype (OR = 1.681). Although allele and genotype frequencies did not differ among groups, the rs4633 CT genotype was protective against FM following adjustment for age and sex (OR = 0.745). However, no association was observed between clinical measures and individual COMT SNPs. In haplotype analysis, there was a significant association between ACG haplotype and FM susceptibility (OR = 2.960) and the number of tender points (P = 0.046).

Conclusion: This large-scale study suggests that polymorphisms of the COMT gene may be associated with FM risk and pain sensitivity in Korean FM patients. However, our results differed to those of previous studies using Caucasian or Latin-American populations, suggesting ethnic variation in COMT gene polymorphisms in FM.

Disclosure: Y. R. Yim, None; **D. J. Park**, None; **S. H. Kim**, None; **S. S. Nah**, None; **J. H. Lee**, None; **S. K. Kim**, None; **Y. A. Lee**, None; **S. J. Hong**, None; **H. S. Kim**, None; **H. S. Lee**, None; **H. A. Kim**, None; **C. I. Joung**, None; **S. H. Kim**, None; **S. S. Lee**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/association-between-catechol-o-methyl-transferase-gene-polymorphisms-and-fibromyalgia-in-a-korean-population-a-case-control-study

Abstract Number: 2300

Polymorphisms of Transient Receptor Potential Vanilloid (TRPV) 2 and TRPV3

Gene Polymorphisms Were Associated with Fibromyalgia in a Korean Population

Yi-Rang Yim[1], Dong-Jin Park[2], Seong-Ho Kim[3], Seong-Su Nah[4], Ji Hyun Lee[5], Seong-Kyu Kim[6], Yeon-Ah Lee[7], Seung-Jae Hong[8], Hyun-Sook Kim[9,10], Hye-Soon Lee[11], Hyoun-Ah Kim[12], Chung-Il Joung[13], Sang-Hyon Kim[14] and Shin-Seok Lee[1], [1]Chonnam National University Medical School and Hospital, Gwangju, South Korea, [2]Rheumatology, Chonnam National University Medical School and Hospital, Gwangju, South Korea, [3]Inje University Haeundae Paik Hospital, Busan, South Korea, [4]Soonchunhyang University, College of Medicine, Cheonan, South Korea, [5]Internal Medicine, Maryknoll Medical Center, Busan, South Korea, [6]Internal Medicine, Catholic University of Daegu School of Medicine, Daegu, South Korea, [7]Division of Rheumatology, Department of Internal Medicine, School of Medicine, Kyung Hee University, Seoul, South Korea, [8]Dept. of Rheumatology, #1 Hoeg, KyungHee University Medical Center, SEOUL, South Korea, [9]Internal Medicine, College of Medicine, Chosun University, Gwangju, South Korea, [10]Division of Rheumatology, Department of Internal Medicine, Soonchunhyang University of Korea, Seoul, South Korea, [11]Rheumatology, Hanyang University Hospital for Rheumatic Diseases, Seoul, South Korea, [12]Ajou University Hospital, Suwon, South Korea, [13]Internal Medicine, Konyang University Medical School, Daejeon, South Korea, [14]Division of Rheumatology, Department of Internal Medicine, Dongsan Medical Center, Keimyung University School of Medicine, Daegu, South Korea

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Session Time: 9:00AM-11:00AM

Background/Purpose: Fibromyalgia (FM) is a chronic pain syndrome characterized by lowered pain thresholds and other FM-related symptoms such as fatigue, anxiety and depression. Recent studies have focused on genetic factors that influence pain sensitivity and development of FM. There are emerging evidences that transient receptor potential vanilloid (TRPV) channels have been contributed to pain hypersensitivity. However, whether polymorphisms of TRPV are associated with FM is unknown. The aim of present study was to evaluate association between polymorphisms of TRPV2 and TRPV3 gene and FM susceptibility, and FM symptoms in a Korean population.

Methods: A total of 409 patients with FM and 423 controls were enrolled from 10 medical centers which participated in the Korean nationwide fibromyalgia survey. The alleles and genotypes at 3 positions [rs3813768(C>G), rs8121(C>T) and rs1129235(C>A)] in the TRPV 2 gene and 2 positions [rs7216486 (G>A) and rs395357(C>T)] in the TRPV 3 gene were genotyped from peripheral blood DNA. The associations of TPPV 2 and TRPV3 genes polymorphisms with FM susceptibility and clinical symptoms of FM were assessed.

Results: The frequencies of alleles and genotypes of individual TRPV2 and TRPV3 genes were not significantly associated with susceptibility of FM. However, the GTA haplotype of TRPV2 gene showed protective against fibromyalgia susceptibility after age- and sex adjusted analysis (OR 0.637; 95% CI; 0.418-0.969; P=0.035). Furthermore, SNP rs395357 of TRPV3 was associated with scores of Brief Fatigue Inventory (BFI) (P=0.017) in FM patients. Although haplotypes of TRPV3 did not show different distribution between FM patients and healthy controls, haplotypes of TRPV3 was associated with BFI and the Short Form-36 Health Status Questionnaire (SF-36) physical health summary scores (P=0.036, respectively)

Conclusion: This large-scale study is the first to evaluate association of TRPV gene polymorphisms with fibromyalgia susceptibility and symptom severity of FM. Our results suggested that certain TRPV2 haplotype have a protective role against FM, and also some genotype and haplotype of TRPV3 contribute to fibromyalgia symptoms. Further researches needed to be confirmed.

Disclosure: Y. R. Yim, None; **D. J. Park**, None; **S. H. Kim**, None; **S. S. Nah**, None; **J. H. Lee**, None; **S. K. Kim**, None; **Y. A. Lee**, None; **S. J. Hong**, None; **H. S. Kim**, None; **H. S. Lee**, None; **H. A. Kim**, None; **C. I. Joung**, None; **S. H. Kim**, None; **S. S. Lee**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/polymorphisms-of-transient-receptor-potential-vanilloid-trpv-2-and-trpv3-gene-polymorphisms-were-associated-with-fibromyalgia-in-a-korean-population

Abstract Number: 2301

Facing Fibromyalgia; How Patients Describe Their Symptoms Based on a Retrospective Evaluation of a Patient Survey and Vitality Assessment in Clinical Trials

Andrew Clair[1], Lynne Pauer[2] and Elizabeth Masters[1], [1]Pfizer Inc., New York, NY, [2]Pfizer Inc, New London, CT
First publication: September 29, 2015

SESSION INFORMATION

Session Date: Tuesday, November 10, 2015

Session Title: Fibromyalgia, Soft Tissue Disorders, Regional and Specific Clinical Pain Syndromes Poster II

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Fibromyalgia (FM) is a common chronic widespread pain disorder with comorbid symptoms of fatigue, sleep disturbance, cognitive dysfunction and depression. It is believed to be a central pain processing disorder. **Results** of a recent patient survey conducted in the United States showed that those diagnosed with FM are misunderstood regarding condition severity, debilitating pain experienced and the impact it has on their lives. These factors may lead to damaged relationships, lost productivity and a general inability to perform daily tasks. In this assessment, we evaluated pain descriptors provided by FM survey respondents as well as baseline SF-36 vitality scores from 4 clinical trials to better understand the patient experience with FM pain and FM health status burden.

Methods: The Functioning with Fibro Survey was carried out in August 2013 and included 1,223 Americans ≥18 years old with fibromyalgia. Participants had received an FM diagnosis from a healthcare provider and provided survey responses through an online data collection tool. Separately, SF-36 vitality scale baseline data from 4 placebo-controlled Phase 3 FM clinical studies was assessed (range: 0-100; higher = better functioning). Subjects across the 4 clinical studies had FM diagnoses (1990 ACR criteria) with mean baseline pain scores ≥4 (0-10; higher = worse pain), and scores ≥40 mm on a Visual Analog Scale (range: 0-100; higher = worse pain).

Results: Survey results demonstrated that fibromyalgia pain is experienced differently across FM patients. In response to the survey question, "If you had to describe to a friend how your fibromyalgia pain feels, which of the following situations comes closest to what you would say?", the following was observed: radiating pain all over: 30%; getting run over by a truck: 28%; constant flu-like ache: 23%; stabbed by a knife: 10%; strenuous workout: 10%

Baseline mean SF-36 vitality scores ranged from 18.4 to 27.6 across the 4 clinical trials. For comparison, normative data for the US general population for women between ages 45–54 in 1998, was 60.6 (mean); standard deviation 21.3 (Hoffman et al. *Int J Clin Pract*. 2008:115-126).

Conclusion: Fibromyalgia patients often experience debilitating pain which may impact multiple areas of their lives. In a patient-rated survey of over 1,200 FM sufferers, pain was characterized in different ways but all were descriptive of debilitating pain. SF-36 vitality scores at baseline from 4 FM studies confirmed significant vitality impairment. These scores reflected lower vitality than what has been reported for many other health conditions widely accepted as impairing, including COPD, congestive heart failure, diabetes, clinical depression, RA, OA, SLE, primary Sjogren's Syndrome and Myofascial Pain Syndrome (Hoffman et al). Decreases in vitality scores are significantly associated with increased odds of negative outcomes, including inability to work due to health, job loss, increased hospitalization, and short and long-term mortality (Bjorner et al. *Curr Med Res Opinion.* 2007:731-739). These data underscore the important health burden in people with FM.

Disclosure: A. Clair, Pfizer Inc, 1,Pfizer Inc, 3; **L. Pauer**, Pfizer Inc, 3; **E. Masters**, Pfizer Inc, 3.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/facing-fibromyalgia-how-patients-describe-their-symptoms-based-on-a-retrospective-evaluation-of-a-patient-survey-and-vitality-assessment-in-clinical-trials

Abstract Number: 2302

The Impact of Prior Fibromyalgia Treatment on the Response to Pregabalin in Fibromyalgia Clinical Trials

Lynne Pauer[1], Andrew Clair[2], Pritha Bhadra Brown[2], Marie Ortiz[2] and Joseph Scavone[1], [1]Pfizer Inc, Groton, CT, [2]Pfizer Inc., New York, NY

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Session Date: Tuesday, November 10, 2015

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Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose:

Fibromyalgia (FM) is a chronic, widespread pain disorder for which Lyrica is an approved treatment. Antidepressants, gabapentin, muscle relaxants, and opioids are frequently used to treat FM. The impact of prior use of these treatments on the response to pregabalin treatment in FM has not been assessed. Previous work showed that FM patients respond to treatment with pregabalin with significant improvements in pain scores irrespective of prior opioid use (Argoff et al. *Clin J Pain.* 2015).

Methods:

A pooled analysis of 4 Phase 3 placebo-controlled clinical trials of pregabalin (300-600 mg/day) of 13-15 week duration in FM patients was conducted to assess the effect of prior treatment with antidepressants (including SSRIs, SNRIs, and TCAs), gabapentin, or muscle relaxants on the response to treatment with pregabalin. Patients were divided into those who had used one of these treatments prior to the trial and those who had not. Patients could have taken prior FM treatments in more than 1 category. Changes in least squares (LS) mean pain scores (assessed by NRS-Pain, a 0-10 numeric rating scale administered daily, controlled for baseline pain score) in the pregabalin and placebo groups were assessed. Last observation carried forward (LOCF) methodology was used to impute missing data.

Results:

There were 2668 patients in the analysis set, including 717 patients with prior antidepressant use, 380 with prior muscle relaxant use, and 113 with prior gabapentin use. Pregabalin improved the LS mean difference in pain score compared with placebo in patients both with and without prior use of these medications. Treatment differences (placebo adjusted) for subjects with prior use of these medications were as follows: gabapentin: -0.78 (95% confidence interval -1.56, 0.01), p=0.0522; antidepressants: -1.00 (CI -1.33, -0.67), p<.0001; and muscle relaxants: -0.96 (CI -1.46, -0.46), p=0.0002. Treatment differences (placebo adjusted) for subjects who did not previously use these medications were as follows: no prior gabapentin: -0.54 (CI -0.71, -0.37), p<.0001; no prior antidepressant: -0.40 (CI -0.59, -0.21), p<.0001; and no prior muscle relaxant: -0.49 (CI -0.67, -0.31), p<.0001. These results were statistically significant in each case apart from prior gabapentin (treatment difference -0.78, p=0.0522), likely due to the smaller size (N=113; pregabalin N=74, placebo N=39) of this cohort. Similar results compared with the overall antidepressant result were observed for SSRIs, SNRIs, and TCAs separately, based on summary statistics. In general, patients with prior FM treatment had slightly higher baseline pain scores.

Conclusion:

FM patients responded to treatment with pregabalin with improvements in pain scores relative to placebo, irrespective of prior treatment with gabapentin, muscle relaxants, or antidepressants. These results were statistically significant apart from the smallest population studied (gabapentin, N=113), which had a similar magnitude of effect. Similar conclusions were reached in previous work regarding opioids (Argoff et al). These data could inform treatment decisions for FM patients currently taking these medications.

Disclosure: L. Pauer, Pfizer Inc., 3,Pfizer Inc., 1; **A. Clair**, Pfizer Inc, 1,Pfizer Inc, 3; **P. Bhadra Brown**, Pfizer Inc., 3,Pfizer Inc., 1; **M. Ortiz**, Pfizer Inc., 1,Pfizer Inc., 3; **J. Scavone**, Pfizer Inc., 1,Pfizer Inc., 3.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/the-impact-of-prior-fibromyalgia-treatment-on-the-response-to-pregabalin-in-fibromyalgia-clinical-trials

Abstract Number: 2303

Psychometrics of Online Administration of Fibromyalgia Impact Questionnaire – Revised

Scott M. Mist[1] and Kim Jones[2], [1]Office of Research & Development, Oregon Health & Science University, Portland, OR, [2]Rsch & Develop/Mail Code SN OR, Oregon Health Sciences Univ, Portland, OR

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Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose:

The Fibromyalgia Impact Questionnaire – Revised (FIQR) [1] has been in wide use since Bennett et al revised the original FIQ[2]. While the instrument was originally validated and analyzed from questionnaires completed in person on computers, there has been no similar study of the FIQR completed in an online questionnaire. This presentation hopes to address this research gap.

Methods:

Potential participants included persons aged 21-89 with self-report of a provider diagnosis of fibromyalgia. Participants responded to an email from a fibromyalgia support and advocacy non-profit that described the study purpose and led them to a confidential link to an online survey with a unique identifier. The survey consisted of two standardized questionnaires: FIQR and the Five Facet Mindfulness Questionnaire. The sample was further profiled with a 16-item investigator-designed questionnaire that collected clinical and demographic information. Data were collected between November 2012 and January 2013. This study was approved by the Institutional Review Board of Oregon Health and Science University, Portland, Oregon. The statistical analysis from the 2009 manuscript was repeated in order to have similar comparisons. This included item analysis and questionnaire properties using basic statistics, reliability item analysis, and Cronbach alpha. Significance of specific means was analyzed using Tukey honestly significantly differences (HSD) for unequal sample size.

Results: A total of 4,986 respondents represented all 50 states in the United States and 30 countries. FIQ-R scores demonstrated moderate to severe fibromyalgia with the majority of subjects (59%) scoring ≤ 60. The mean total score was 63.4 ± 17.8 indicating that our population had a slightly higher FIQR score than originally reported. The average age was 52.2 ± 10.6. Most (74%) were symptomatic with FM for over 10 years. 53% reported not working outside the home due to their FM, despite being highly educated (47% college graduates and post graduate degrees). Individual items were compared as well as subscores. All subscores were higher than the original paper but within the standard deviations. The correlations between individual items and subscales were comparable to the original study.

Conclusion: The characteristics of the FIQR when administered online are similar to the original paper. However, our sample indicates that the population averages for the FIQR Function, Impact, and Symptom subscales as well as the Total score were all higher than originally reported.

1. Robert M Bennett, Ronald Friend, Kim D Jones, Rachel Ward, Bobby K Han and Rebecca L Ross. **The Revised Fibromayglia Impact Questionnaire (FIQR): validation and psychometric properties.** *Arthris Res Ther* 2009, **11**:R120

2. Bennett R. **The Fibromyaliga Impact Questionnaire (FIQ): a review of its development, current revision, operating characteristics and uses.** *Clin Exp Rheumatol* 2005, **23**: S154-S162.

Disclosure: S. M. Mist, None; **K. Jones**, None.

Abstract Number: 2304

Clinical, Ultrasonographic and Neurophysiological Correlation of Patients with Carpal Tunnel Syndrome in Santo Domingo, Dominican Republic

Ismely Paulino and Paulino-Izquierdo I, Paula-Mateo J, MS. Adames, Medrano-Sánchez J, Peña-Blanco R, Muñoz-Louis R, Rosario V, T. Valdez-Lorie, R. Alba-Fériz, Rheumatology, Hospital Docente Padre Billini, Santo Domingo, Dominican Republic
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Session Time: 9:00AM-11:00AM

Background/Purpose: Carpal Tunnel Syndrome (CTS) is produced by the entrapment of the median nerve (MN) in the carpal tunnel. It is characterized by pain and paresthesia in the territory of MN. It is associated with diabetes mellitus, hypothyroidism, autoimmune diseases, dyslipidemia, and etc. Tinnel and Phalen maneuvers are positive in most of the patients, with a sensitivity of 70 % and 85 %, respectively. CTS diagnosis is clinical; electromyography (EMG) with conduction velocity is considered the most objective test for the diagnosis, with sensitivity of 86 % and specificity of 95 %, ultrasound has shown an increased cross-sectional area of MN compared with healthy controls. **Purpose:** Correlate the clinical manifestations of patients with CTS with increased cross-sectional area of the MN and the neurophysiological findings.

Methods: analytical, longitudinal, prospective, study in which patients from the Rheumatology service of the Hospital Docente Padre Billini (HDPB) with clinical diagnosis of CTS were selected from August to November 2014. Ultrasound of the Carpal Tunnel was done by two rheumatologists with training in musculoskeletal ultrasound (MSU), half of the sample was evaluated by each, the result was considered pathological if they both agreed. An ultrasound SIEMENS model Acuson X150 with 13 MHz transducer was used in the study. Ultrasound images of longitudinal and transverse carpal tunnel cuts were taken and MN circumference was measured in cross section, considering a normal circumference of the MN of 10mm2. Other variables taken in consideration: sex, age, co morbidities and positive maneuvers. The diagnosis was confirmed by EMG; those patients with no EMG were excluded. The descriptive analysis was done with frequencies and percentages for categorical variables and measures of central tendency and dispersion for the number using SPSS Statistics (v20.x86). The study was approved by the ethics committee.

Results: Of a sample of 62 patients, 52 were included in the study. 51 (98.1%) were females, with a median of age of 55.2 years; 13.5% of the patients were diabetic; 13.5% had hypothyroidism; 9.6% autoimmune disease; 5.8% suffered dislipaemias; and the remaining 57.7% had no co morbidities. On physical examination, Tinel and Phalen maneuvers were positive with percentages of 90.4% and 75% respectively. As for the MN diameter, 51 patients (98.1%) had an enlarged MN circumference (>10mm^2), 90.4% bilateral. With a median 15.3mm^2 for the right MN and 13.9mm^2 for the left MN all the patients had EMG study compatible with the syndrome.

Conclusion: The ultrasonographic results of patients with CTS in the rheumatology service of the HDPB showed that the cross-sectional diameter of the MN is increased in a high percentage of the patients, and this findings are related with clinical and EMG diagnostics. We conclude that ultrasound is a very useful diagnostic tool as reported in the literature.

Disclosure: I. Paulino, None;

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Abstract Number: 2305

Relationship Between Anxiety, Depression, Sleep, Fibromyalgia and BMI in Patients with Rheumatic Disease

Shazia Bég[1] and Ali Ahmad[2], [1]Rheumatology, University of Central Florida, Orlando, FL, [2]University of Central Florida, Orlando, FL

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SESSION INFORMATION

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Background/Purpose: Patients with rheumatic diseases often have comorbidities that complicate their psychological well-being and affect prognosis. In this study, we looked at 216 patients with rheumatoid arthritis (RA), systemic lupus erythematous (SLE), psoriatic arthritis (PsA), or Sjogren's syndrome (SS) to determine (a) the prevalence of anxiety, depression, sleep disturbance, fibromyalgia (FMS), BMI greater than 23, and gastroesophageal disease (GERD) in each patient population (b) the relationship between FMS, BMI, disease activity measure known as RAPID3.

Methods: Study participants were 216 rheumatology patients seen at the UCF Pegasus Health clinic from November 2011 to May 2014 with one or more of the following diseases: rheumatoid arthritis (n=116), Sjogren's syndrome (n=20), SLE (n=27), or psoriatic arthritis (n=22). 28 were male and 88 were female. Variables that were collected included RAPID3 scores, patient demographics (age, sex), BMI, presence of GERD, and presence of FMS. Each patient was randomly assigned, unique and unidentifiable study number.

Results: Significant differences in the prevalence of anxiety and fibromyalgia were found in the study populations, with anxiety being more prevalent in Sjogren's syndrome, and fibromyalgia being more prevalent in patients with >1 diagnosis. The presence of fibromyalgia was significantly correlated with RAPID3 score in all patients except those with PsA. Significant correlations between BMI and RAPID3 score were found for patients with rheumatoid arthritis and for patients with Sjogren's syndrome who demonstrated the most pronounced relationship.

Table 1: Incidence of selected comorbidities at baseline in patients with rheumatoid arthritis, systemic lupus erythematous, psoriatic arthritis, Sjogren's syndrome, and >1 diagnosis.

	RA	SS	PsA	SLE	>1 Diagnosis	p-value
Depression	40.2%	71.4%	33.3%	30.4%	51.9%	.088
Anxiety	47.3%	78.6%	38.1%	30.4%	55.6%	.049
Sleep disturbance	78.6%	85.7%	71.4%	60.9%	77.8%	.364
Overweight or obese	71.3%	90%	90.5%	74.1%	83.9%	.245
Fibromyalgia	12.1%	20%	9.1%	18.5%	41.9%	.003
GERD	12.9%	10%	9.1%	14.8%	29%	.183

Table 2: Relationship between the presence of fibromyalgia and RAPID3 score at baseline in patients with rheumatic disease

	Correlation	p-value
All patients	.328	.000
RA	.245	.010
SLE	.763	.000
SS	.646	.013
PsA	.167	.482
>1 diagnosis	.514	.006

Table 3: Relationship between BMI and RAPID3 score at baseline in patients with rheumatic disease[a]		
	Correlation	p-value
All patients	.263	.001
RA	.246	.015
SLE	.345	.176
SS	.760	.007
PsA	.289	.261
>1 diagnosis	.420	.105
[a]Patients with fibromyalgia were excluded to as they were a confounding factor.		

Conclusion: Our study confirmed the increased prevalence of anxiety in patients with Sjogren's syndrome. Evaluation and treatment for comorbid psychiatric conditions may be pertinent in these patients. Fibromyalgia was confirmed to be related to disease activity scores. Clinically, this may incorrectly be perceived as worsening of rheumatic disease. In RA and SS patients, BMI was significantly correlated with RAPID3 scores. Studies confirm that obesity in RA patients reduces rates of remission and response to treatment.

Disclosure: S. Bég, None; **A. Ahmad**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/relationship-between-anxiety-depression-sleep-fibromyalgia-and-bmi-in-patients-with-rheumatic-disease

Abstract Number: 2306

Prevalence of Fibromyalgia in Inflammatory Rheumatic Disease. Single-Center Cross-Sectional Study in 691 Patients

Angélique Fan[1], Anne Tournadre[2], Bruno Pereira[3], Zuzana Tatar[1], Marion Couderc[1], Sylvain Mathieu[4], Martin Soubrier[1] and **Jean-Jacques Dubost**[1], [1]Rheumatology department CHU Clermont-Ferrand, Clermont-Ferrand, France, [2]Rheumatology, UNH-UMR 1019 INRA University of Auvergne and Rheumatology department CHU Clermont-Ferrand, Clermont-Ferrand, France, [3]Biostatistics unit (DRCI), CHU Clermont-Ferrand, Clermont-Ferrand, France, [4]Rheumatology Department, CHU clermont-Ferrand, Clermont-Ferrand, France

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Background/Purpose: Fibromyalgia (FM) is a prevalent syndrome in patients with inflammatory rheumatic disease. The purpose of this study was to evaluate and compare the prevalence of FM in various inflammatory rheumatic diseases.

Methods: This single-center cross-sectional study was conducted between September 2014 and April 2015. We screened for clinical signs of fibromyalgia in all patients presenting for rheumatoid arthritis (RA), spondyloarthritis (SpA), and connective tissue disease (Sjögren's syndrome (SS), systemic lupus erythematosus (SLE), scleroderma (Scl), myositis). Diagnosis of FM was based on ACR–90 classification criteria (to minimize interfering overlap between rheumatic disease-related pain and FM-related pain) and expert opinion.

Results: In total, 691 patients were included in the study: 325 RA, 298 SpA (59 psoriatic arthritis, 137 radiographic axial SpA, 64 non-radiographic axial SpA, 38 peripheral SpA), 28 SLE, 27 SS, 14 Scl, and 6 myositis. The population counted 451 women (65.3%) and 240 men (34.7%). Mean all-population age was 55.8 ± 15.5 years. Median disease duration was 11 years [IQR 5–20]. In the total population, 55 patients (8%) met the ACR–90 criteria, and 97 patients (14%) were given a diagnosis of FM by the expert doctor. Prevalence of FM meeting ACR–90 criteria was 4.9% in RA, 11.1% in SpA, and 11.3% in connective tissue disease, and was significantly higher in the SpA group than in the RA group (p=0.05). The expert settled on a diagnosis of FM for 7.7% of patients with RA, 17.5% of patients with SpA, and 28.2% of patients with connective tissue disease. The expert

diagnosed significantly more FM in SpA (p=0.003) and connective tissue disease (p=0.001) than in RA.

Conclusion: Concomitant fibromyalgia is prevalent in inflammatory rheumatic disease, especially in spondyloarthritis and connective tissue disease. The expert doctor makes the diagnosis of fibromyalgia more often than ACR–90 criteria.

Disclosure: A. Fan, None; **A. Tournadre**, None; **B. Pereira**, None; **Z. Tatar**, None; **M. Couderc**, None; **S. Mathieu**, None; **M. Soubrier**, None; **J. J. Dubost**, None.

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Abstract Number: 2307

Relationship of Sleep Quality and Fibromyalgia Outcomes in a Phase 2b Randomized, Double-Blind, Placebo-Controlled Study of Bedtime, Rapidly Absorbed, Sublingual Cyclobenzaprine (TNX-102 SL)

Harvey Moldofsky[1], R Michael Gendreau[2], Daniel J. Clauw[3], Judith Gendreau[4], Benjamin Vaughn[5], Bruce Daugherty[4], Amy Forst[6], Gregory Sullivan[7] and Seth Lederman[8], [1]Ctr for Sleep & Chronobiology, Centre for Sleep/Chronobiology, Toronto, ON, Canada, [2]Gendreau Consulting LLC, Poway, CA, [3]Anesthesiology, University of Michigan, Ann Arbor, MI, [4]Tonix Pharmaceuticals, New York, NY, [5]Statistics, Rho, Chapel Hill, NC, [6]Clinical Development, Tonix Pharmaceuticals, San Jose, CA, [7]Clinical Development, Tonix Pharmaceuticals, NEW YORK, NY, [8]Research and Development, Tonix Pharmaceuticals, Inc., New York, NY

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Background/Purpose: The importance of nonrestorative sleep in the pathophysiology of fibromyalgia (FM) suggests that treatments that improve sleep quality would address global symptoms. TNX-102 SL[1]a proprietary eutectic sublingual (SL) tablet formulation of low dose cyclobenzaprine HCl (2.8 mg) tablet designed for rapid absorption and long-term bedtime use. TNX-102 SL was assessed for its safety and efficacy in a phase 2b study of FM (the BESTFIT study).

Methods: A total of 205 FM patients who satisfied the ACR 2010 FM criteria were enrolled at 17 sites in a 12-week, double-blind, placebo-controlled trial in which participants were randomized 1:1 to receive TNX-102 SL (N=103) or placebo (N=102). Outcome measures included daily diary assessments of pain and sleep (0-10 NRS), the Fibromyalgia Impact Questionnaire-Revised (FIQ-R), Patient Global Impression of Change (PGIC), and the PROMIS Sleep Disturbance scale (PROMIS).

Results: Subjects treated with TNX-102 SL improved in all measures of sleep quality, as well as pain, FIQ-R and PGIC ratings over the 12 weeks. The PROMIS sleep disturbance scale reached statistical significance by week 4, p = 0.021, and had sustained benefit through week 12, p = 0.005 (-8.96 on TNX-102 SL v -5.13 on placebo). Daily sleep diary (change from baseline to endpoint) reached statistical significance at week 1, regained significance at week 6, p = 0.015, and was sustained through week 12; p < 0.001 (-1.85 v -0.88). The sleep quality item on the FIQ-R reached significance at week 2, p=0.012, and was sustained through week 12; p <0.001 (-2.9 v 1.2). The improvements in sleep quality preceded other FM changes. The responder analysis of daily diary pain (with =>30% improvement from baseline defined as response) was significant at week 12 p = 0.033 (34.0% response rate v 20.6%) and reached initial statistical significance at week 9, p = 0.042 (logistic regression). Improvement in sleep by PROMIS correlated with improvement in pain by 30% responder analysis (r=0.3, p=<0.001). PGIC favorable response was significant at week 12 (30.1% vs. 16.7%, p = 0.025 by logistic regression). PGIC correlated with improvement in PROMIS sleep (r=0.6, p=<0.001) and sleep diary (r=0.5, p=<0.001). FIQ-R total score became significant at week 8, p = 0.041, and was sustained through week 12, p = 0.014 (-15.6 v -8.5). FIQ-R correlated with improvement in PROMIS sleep (r=0.5, p=<0.001) and with sleep diary (r=0.6, p=<0.001).

Systemic adverse events (AEs) were infrequent. Weight gain was negligible. Local administration site reactions (transient tongue or sublingual numbness) occurred in 42% of treated patients.

Conclusion: Bedtime TNX-102 SL improved sleep quality by multiple measures of FM which is consistent with the antagonistic activity of cyclobenzaprine at 5HT2A, alpha-1 adrenergic and H-1 receptors. The improvement in sleep quality temporally preceded improvements in pain, PGIC and FIQ-R, with which sleep quality improvements were correlated. Together, these data suggest TNX-102 SL targets non-restorative sleep and provides a novel approach to treating FM.

[1]TNX-102 SL is an Investigational New Drug and has not been approved for any indication.

Disclosure: H. Moldofsky, Tonix Pharmaceuticals, 1,Tonix Pharmaceuticals, 5,Tonix Pharmaceuticals, 9; **R. M. Gendreau**, Tonix Pharmaceuticals, 1,Tonix Pharmaceuticals, 3,Tonix Pharmaceuticals, 5; **D. J. Clauw**, Pfizer Inc, 9,Lilly, 5,Tonix, 5,Cerephex, 5,Zynerba, 5,IMC, 5,Samumed, 5,Regeneron, 5; **J. Gendreau**, Tonix Pharmaceuticals, 1,Tonix Pharmaceuticals, 3; **B. Vaughn**, Tonix Pharmaceuticals, 5; **B. Daugherty**, Tonix Pharmaceuticals, 1,Tonix Pharmaceuticals, 3; **A. Forst**, Tonix Pharmaceuticals, 1,Tonix Pharmaceuticals, 3,Tonix Pharmaceuticals, 5; **G. Sullivan**, Tonix Pharmaceuticals, 1,Tonix Pharmaceuticals, 3; **S. Lederman**, Tonix Pharmaceuticals, 1,Tonix Pharmaceuticals, 3,Tonix Pharmaceuticals, 6.

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Abstract Number: 2308

Responder Compared to Mean Change Analyses in a Fibromyalgia Phase 2b Clinical Study of Bedtime Rapidly Absorbed Sublingual Cyclobenzaprine (TNX-102 SL)

R Michael Gendreau[1], Daniel J. Clauw[2], Judith Gendreau[3], Bruce Daugherty[3] and Seth Lederman[4], [1]Gendreau Consulting LLC, Poway, CA, [2]Anesthesiology, University of Michigan, Ann Arbor, MI, [3]Tonix Pharmaceuticals, New York, NY, [4]Research and Development, Tonix Pharmaceuticals, Inc., New York, NY

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Background/Purpose: Fibromyalgia (FM) is characterized by symptoms that include widespread pain and sleep disruption. Clinical studies that rely on patient self-reported outcome measures such as pain scales may be analyzed by responder analysis (comparisons of proportions of treated patients achieving a predefined clinically meaningful improvement threshold) and by group mean changes. In a Phase 2b trial of TNX-102 SL[1], a proprietary eutectic sublingual (SL) tablet formulation of low-dose cyclobenzaprine HCl (2.8 mg) in FM patients (BESTFIT), we compared these approaches to the evaluation of changes in pain and FM symptoms.

Methods: 205 FM patients who satisfied the ACR 2010 FM criteria from 17 US investigational sites were randomized in a double-blinded fashion to placebo (n=102) or TNX-102 SL (n=103) for 12 weeks. Topline results from BESTFIT are presented elsewhere. For this analysis, we compared changes in pain score, patient global impression of change (PGIC), and Fibromyalgia Impact Questionnaire-Revised (FIQ-R), analyzed by both responder analyses and group mean change from baseline techniques.

Results: For the daily pain diary, the responder analysis (=>30% improvement from baseline) resulted in 34.0% on TNX-102 SL compared to 20.6% on placebo, p=0.033. The same daily pain data when analyzed as mean change from baseline, TNX-102 SL had improvement of -1.50 units vs. -1.0 units on placebo, p=0.086. Using the FIQ-R pain item as the pain measure resulted in a response rate of 38.8% on TNX-102 SL vs. 23.5% on placebo, p=0.025, while the mean change was -1.8 on TNX-102 SL vs -0.7 on placebo, p=0.004. PGIC is a 7 point Likert scale and defining response “very much improved” or “much improved”, the

response rate was 30.1% on TNX-102 SL vs. 16.7% on placebo, p=0.025, and the mean change was 3.1 on TNX-102 SL vs 3.6 on placebo, p=0.025. The FIQ-R was evaluated as 21 discrete items, three defined domains (symptoms, overall impact and function) and a total score. The FIQ-R total score and symptom domain were statistically different between treatment groups by both responder and mean analyses. The function domain separated on the responder analysis but was not significant (p=0.059) on mean change. Systemic adverse events (AEs) were infrequent. Local administration site reactions (transient tongue or sublingual numbness) occurred in 42% of treated patients.

Conclusion: Results from this Phase 2b trial support the finding that responder analyses for analgesia[2]and other patient-reported outcomes may reveal significant and meaningful effects that are missed by group mean changes. In the particular case of the BESTFIT study of TNX-102 SL, the pain questionnaire was not specific to central or regional pain and TNX-102 SL targets non-restorative sleep with secondary improvement in pain. An ongoing confirmatory study is utilizing pain and other responder analyses as the primary and secondary endpoints which are more appropriate and sensitive measures for the evaluation of TNX-102 SL for FM.

[1]TNX-102 SL is an Investigational New Drug and has not been approved for any indication.

[2]Witter J, Simon LS, Dianne R. Are means meaningless? The application of individual responder analysis to analgesic drug development. APS Bulletin. 2003;13:4–7.

Disclosure: R. M. Gendreau, Tonix Pharmaceuticals, 1,Tonix Pharmaceuticals, 3,Tonix Pharmaceuticals, 5; **D. J. Clauw**, Pfizer Inc, 9,Lilly, 5,Tonix, 5,Cerephex, 5,Zynerba, 5,IMC, 5,Samumed, 5,Regeneron, 5; **J. Gendreau**, Tonix Pharmaceuticals, 1,Tonix Pharmaceuticals, 3; **B. Daugherty**, Tonix Pharmaceuticals, 1,Tonix Pharmaceuticals, 3; **S. Lederman**, Tonix Pharmaceuticals, 1,Tonix Pharmaceuticals, 3,Tonix Pharmaceuticals, 6.

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Abstract Number: 2309

Bedtime, Rapidly Absorbed Sublingual Cyclobenzaprine (TNX-102 SL) for the Treatment of Fibromyalgia: Results of a Phase 2b Randomized, Double-Blind, Placebo-Controlled Study

Seth Lederman[1], R Michael Gendreau[2], Daniel J. Clauw[3], Lesley M. Arnold[4], Judith Gendreau[5], Bruce Daugherty[5] and Amy Forst[6], [1]Research and Development, Tonix Pharmaceuticals, Inc., New York, NY, [2]Gendreau Consulting LLC, Poway, CA, [3]Anesthesiology, University of Michigan, Ann Arbor, MI, [4]Psychiatry, University of Cincinnati, Cincinnati, OH, [5]Tonix Pharmaceuticals, New York, NY, [6]Clinical Development, Tonix Pharmaceuticals, San Jose, CA

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Background/Purpose: Fibromyalgia (FM) is characterized by chronic widespread pain and sleep disturbance. Treatments that improve sleep quality in FM patients may improve fibromyalgia by a mechanism distinct from centrally acting analgesics. TNX-102 SL[1]is a proprietary eutectic sublingual (SL) tablet formulation of low-dose cyclobenzaprine HCl (2.8 mg) designed for rapid absorption and long-term bedtime use. This double-blind, randomized, placebo-controlled multicenter study (BESTFIT) evaluated the safety and efficacy of TNX-102 SL in FM.

Methods: A total of 205 patients who met ACR 2010 FM criteria were enrolled at 17 sites in a 12-week, double-blind, placebo-controlled trial. Patients were randomized 1:1 to receive TNX-102 SL (N=103) or placebo (N=102). Outcome measures included daily pain and sleep diaries (0-10 NRS averaged over each week), Fibromyalgia Impact Questionnaire (FIQ-R), Patient

Global Impression of Change (PGIC), and PROMIS Sleep Disturbance scale (PROMIS). Data were analyzed by mean change from baseline using Mixed Effects Model Repeated Measures (MMRM) unless otherwise noted.

Results: Patients treated with TNX-102 SL showed improvement in multiple domains of FM. Responder analysis of week 12 daily diary pain (with =>30% improvement from baseline defined as response) was statistically significant with a 34.0% pain response rate compared to 20.6% for placebo; p = 0.033. This same pain diary data showed a decrease in pain by -1.5 compared to -1.0 for placebo; p = 0.086. Pain scores reported during clinic visits (7 day recall NRS) showed significant improvement (p = 0.033) as did the pain item on the FIQ-R (7 day recall), p = 0.004.

TNX-102 SL improved the FIQ-R total score by -15.6 compared to -8.5 for placebo, p = 0.014. PGIC response rate(responses of 1 or 2 on a 7 point Likert Scale) was improved vs. placebo (30.1% vs. 16.7%, p = 0.025 by logistic regression). All measures of sleep quality improved, including PROMIS sleep disturbance with an -9.0 improvement on TNX-102 SL compared to -5.1 on placebo, p = 0.005. Sleep as measured by daily diary (change from baseline) was improved by -1.9 compared to -0.9 on placebo; p = <0.001, and the sleep quality item on the FIQ-R improved by -2.9 compared to -1.1 on placebo; p <0.001.

Systemic adverse events (AEs) were infrequent, no item was reported in >5% of TNX-102 SL- treated patients and were similar to the placebo-treated patients. Local administration site reactions (transient tongue or sublingual numbness) were commonly reported, occurring in approximately 42% of treated patients. Only 3 patients withdrew from participation in the study due to local adverse events. 86% of TNX-102 SL treated patients completed versus 83% on placebo.

Conclusion: Bedtime TNX-102 SL improved sleep quality by several measures and also improved multiple other symptoms and domains of FM. Nonrestorative sleep has been linked to central sensitization, which is characterized by changes in central pain processing. Together these findings suggest that sleep quality is a target of therapy in FM and TNX-102 SL improvement in sleep quality was well tolerated was associated with broad symptomatic improvement.

[1]TNX-102 SL is an Investigational New Drug and has not been approved for any indication.

Disclosure: S. Lederman, Tonix Pharmaceuticals, 1,Tonix Pharmaceuticals, 3,Tonix Pharmaceuticals, 6; **R. M. Gendreau**, Tonix Pharmaceuticals, 1,Tonix Pharmaceuticals, 3,Tonix Pharmaceuticals, 5; **D. J. Clauw**, Pfizer Inc, 9,Lilly, 5,Tonix, 5,Cerephex, 5,Zynerba, 5,IMC, 5,Samumed, 5,Regeneron, 5; **L. M. Arnold**, Tonix Pharmaceuticals, 9; **J. Gendreau**, Tonix Pharmaceuticals, 1,Tonix Pharmaceuticals, 3; **B. Daugherty**, Tonix Pharmaceuticals, 1,Tonix Pharmaceuticals, 3; **A. Forst**, Tonix Pharmaceuticals, 1,Tonix Pharmaceuticals, 3,Tonix Pharmaceuticals, 5.

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Abstract Number: 2310

Evaluation of Fibromyalgia Syndrome in Patients Undergoing Peritoneal Dialysis

Taskin Senturk[1], Gokhan Sargin[2] and Hakan Akdam[3], [1]Rheumatology, Adnan Menderes University School of Medicine, Aydin, Turkey, [2]Rheumatology, Adnan Menderes University Rheumatology, Aydin, Turkey, [3]Nephrology, Adnan Menderes University, Nephrology, Aydin, Turkey

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Background/Purpose: Fibromyalgia syndrome (FMS) is characterized by widespread pain, fatigue, memory problems. The syndrome is present in about %2-8 of general population. However, knowledge about this topic in specific populations is limited. Our aim was to evaluate FMS in patients undergoing peritoneal dialysis, and association between clinical and laboratory parameters.

Methods: Twenty-six patients (7 females and 19 males with mean age of 53±15,9 years) receiving peritoneal dialysis were enrolled in this study. The control group compromised 25 healthy adults (16 females and 9 males with mean age of 41±12,8 years). Diagnosis of fibromyalgia was performed according to the 1990 American College of Rheumatology (ACR) and 2011 modification of the ACR preliminary diagnostic criteria. Age, sex, causes of renal failure, dialysis duration, the level of parathyroid hormone, renal function tests and electrolites were recorded. Mann-Whitney U and chi-square test were performed as statistical analysis and $p<0.05$ was accepted as statistically significant.

Results: The etiology of renal failure was diabetes mellitus in 3 patients (11,5%), hypertension in 10 (38,5%), glomerulonephritis in 4 (15,4%), idiopathic in 5 (19,2%), polycystic kidney disease in 1 (3,8%), nephrolithiasis in 2 (7,7%), and pyelonephritis in 1 (3,8%). The mean dialysis duration was 50,42±35,19 months. One (3,84%) patients receiving peritoneal dialysis and one of 25 control subjects were diagnosed with fibromyalgia, respectively. The mean age was 53±15,9 years in dialysis group, and 41±12,8 years in control group. All of FMS was female. There was significant difference for renal function tests and electrolites between both groups ($p<0,001$). Ionized calcium and phosphorus were higher in the FMS group than in the control group ($p=0.056$, $p=0.596$, respectively). There was no association between FMS and secondary hyperparathyroidism. The level of plasma parathyroid hormone in FMS patients was significantly lower than other patients.

Conclusion: There was similar prevalence for fibromyalgia between patients on peritoneal dialysis and healty group. It may be associated with actively participate in treatment, less stress factors, and better preservation of renal functions.

Disclosure: T. Senturk, None; **G. Sargin**, None; **H. Akdam**, None.

Abstract Number: 2311

Safety of Pregabalin for Treatment of Fibromyalgia Is Comparable Between Subjects with Moderate or Severe Baseline Widespread Pain

Andrew Clair[1] and Birol Emir[2], [1]Pfizer Inc, New York, NY, [2]Primary Care Business Unit, Pfizer Global Research and Development, New York, NY

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Background/Purpose: Pregabalin has demonstrated efficacy and safety for the treatment of pain associated with fibromyalgia (FM) and is approved by the US Food and Drug Administration for this indication. Although pregabalin has been shown to be well tolerated in subjects with moderate or severe baseline pain, no studies have assessed whether its safety and tolerability differs by baseline pain severity. In this analysis, we evaluated data from subjects from 5 pooled clinical trials using pregabalin for FM-related pain to determine whether safety profiles were different in subjects with moderate versus severe baseline pain severity.

Methods: Safety data were pooled from 5, Phase III, placebo-controlled, clinical trials using pregabalin (8–15 weeks; 300 or 450 mg/day) for treatment of FM-related pain (study numbers 1008105, A0081056, A0081077, A0081100, A0081208). Subjects had FM diagnoses (1990 ACR criteria), were aged ≥18 years, had mean baseline pain scores ≥4, and had scores ≥40 mm on the Visual Analog Scale of Short-form McGill Pain Questionnaire. Descriptive statistics were used to classify adverse event (AE) profiles after 12 weeks of treatment categorized by baseline moderate (pain scores ≥4-<7) or severe (≥7-10) pain severity.

Results: Overall, the incidences of treatment-emergent AEs, treatment-related AEs, serious AEs (SAEs), and discontinuations were comparable between subjects with baseline moderate and severe pain who received the same treatment (**Table 1**).

Table 1. Safety and tolerability of pregabalin across all five clinical trials.				
Number (%) of Subjects with AEs[a]	Pregabalin (300 or 450 mg/day)		Placebo	
	Moderate (n = 785)	Severe (n = 820)	Moderate (n = 504)	Severe (n = 425)
Subjects with treatment-emergent AEs	694 (88.4)	725 (88.4)	371 (73.6)	312 (73.4)
Subjects with treatment-related AEs	588 (74.9)	613 (74.8)	234 (46.4)	192 (45.2)
Subjects with SAEs	7 (0.9)	20 (2.4)	5 (1.0)	6 (1.4)
Subjects with severe intensity treatment-emergent AEs	87 (11.1)	117 (14.3)	36 (7.1)	34 (8.0)
Subjects who permanently discontinued due to treatment-emergent AEs	134 (17.1)	130 (15.9)	44 (8.7)	35 (8.2)
Subjects with dose reduction or temporary discontinuation due to treatment-emergent AEs	52 (6.6)	47 (5.7)	19 (3.8)	11 (2.6)
[a]AEs defined by Medical Dictionary of Regulatory Activities (MedDRA) Preferred Terms.				

The incidences of the most common treatment-emergent AEs were also comparable between subjects within the same treatment group who had moderate and severe baseline pain severity (**Table 2**).

Table 2. Most common treatment-emergent AEs (≥5% incidence in any treatment group) across five pregabalin clinical trials.				
Number (%) of Subjects with AEs[a]	Pregabalin (300 or 450 mg/day)		Placebo	
	Moderate (n = 785)	Severe (n = 820)	Moderate (n = 504)	Severe (n = 425)
Constipation	66 (8.4)	57 (7.0)	27 (5.4)	8 (1.9)
Diarrhea	29 (3.7)	37 (4.5)	24 (4.8)	29 (6.8)
Dizziness	282 (35.9)	302 (36.8)	53 (10.5)	34 (8.0)
Dry mouth	59 (7.5)	54 (6.6)	8 (1.6)	6 (1.4)
Fatigue	54 (6.9)	61 (7.4)	19 (3.8)	18 (4.2)
Headache	85 (10.8)	104 (12.7)	56 (11.1)	47 (11.1)
Nasopharyngitis	51 (6.5)	57 (7.0)	51 (10.1)	27 (6.4)
Nausea	56 (7.1)	52 (6.3)	35 (6.9)	36 (8.5)
Edema peripheral	46 (5.9)	42 (5.1)	9 (1.8)	6 (1.4)
Somnolence	189 (24.1)	185 (22.6)	47 (9.3)	29 (6.8)
Vision blurred	48 (6.1)	49 (6.0)	5 (1.0)	5 (1.2)
Weight increased	96 (12.2)	94 (11.5)	16 (3.2)	10 (2.4)
[a]AEs defined by Medical Dictionary of Regulatory Activities (MedDRA) Preferred Terms.				

Conclusion: No notable differences in the safety or tolerability of pregabalin were observed between subjects with moderate and severe baseline pain severity. The treatment-emergent AEs and their incidence rates were consistent with the known safety profile of pregabalin.

Disclosure: A. Clair, Pfizer Inc, 1,Pfizer Inc, 3; **B. Emir**, Pfizer Inc, 1,Pfizer Inc, 3.

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Abstract Number: 2312

Patient Preferences for Total Knee Replacement Surgery: Two Year Follow-up

Ernest Vina[1], Di Ran[2], Erin Ashbeck[2], Said Ibrahim[3], Michael J. Hannon[4], Jin Zhou[5] and C. Kent Kwoh[1], [1]Rheumatology,

University of Arizona, Tucson, AZ, [2]Arthritis Center, University of Arizona, Tucson, AZ, [3]Medicine, University of Pennsylvania, Philadelphia, PA, [4]Medicine, University of Pittsburgh, Pittsburgh, PA, [5]Epidemiology & Biostatistics, University of Arizona, Tucson, AZ

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Background/Purpose:

Patients' preferences for total knee replacement (TKR) may determine actual receipt of TKR and may also change over time. Yet, no study has longitudinally evaluated the treatment preferences regarding joint replacement of patients with knee osteoarthritis (OA). Our objectives were to evaluate the consistency of patients' preferences for TKR with receipt of TKR surgery, and to assess patient characteristics that may influence change in willingness to undergo TKR over 2 years.

Methods:

Structured interviews were conducted to determine the socio-demographic data, clinical characteristics, and treatment preferences (i.e. willingness to undergo TKR) of patients with knee OA. Willingness was measured using a Likert scale ranging from -2 (definitely not willing) to +2 (definitely willing). Consultation with an orthopedic surgeon and receipt of TKR surgery were ascertained by medical record reviews and structured interviews at 6 months and at 2 years. Logistic regression models were conducted to assess the association between willingness and consultation with an orthopedic surgeon (or receipt of TKR), adjusted for age, sex, race, education, recruitment site, income, insurance, social support, and baseline WOMAC score. Mixed models for repeated measures were used to estimate the effects of age, sex, race, social support, change in WOMAC subscale scores, and orthopedic surgical consult on change in willingness over 2 years.

Results:

At baseline, 589 were willing, and 215 were unsure or not willing to undergo TKR surgery. Willing participants, compared to those who were unwilling, were more often White (69.4% vs. 48.4%), with more than a high school education (60.8% vs. 47.0%), employed (39.1% vs. 26.5%), and had a lower WOMAC total score (46.05 ± 16.12 vs. 50.37 ± 15.42). At 2-year follow-up, baseline willingness was not associated with having seen an orthopedic surgeon (adjusted OR 0.89, 95% CI [0.62, 1.29]) after adjustment for sociodemographic and clinical variables. The odds of having TKR was twice as high among those who were willing to have the procedure at baseline, compared to all others, but this was not a statistically significant difference (adjusted OR 2.04, 95% CI [0.92, 4.53]).

There was a general decline in willingness to undergo TKR over the follow-up period. Among those who were willing to undergo TKR at baseline, only 66.5% were still willing 2 years later. This decline in willingness was less among those who had a greater increase (> median) in WOMAC disability scores (adjusted Δ -0.34, 95% CI [-0.47, -0.20]) than those who had minimal change (≤ median) in their WOMAC disability scores (adjusted Δ -0.51, 95% CI [-0.64, -0.37]) (p=0.08). The decline in willingness was also less among those who had seen an orthopedic surgeon (adjusted Δ -0.32, 95% CI [-0.46, -0.17]) than those who did not during the study period (adjusted Δ -0.51, 95% CI [-0.63, -0.38]) (p=0.05). Other patient characteristics did not influence changes in willingness.

Conclusion:

Patients' preferences for TKR were not consistent with utilization of TKR surgery over two years of follow-up. Willingness to undergo TKR declined over time, but this decrease was mitigated by worsening OA-related disability and by consultation with an orthopedic surgeon.

Disclosure: E. Vina, None; **D. Ran**, None; **E. Ashbeck**, None; **S. Ibrahim**, None; **M. J. Hannon**, None; **J. Zhou**, None; **C. K. Kwoh**, None.

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Abstract Number: 2313

Responder Rates and Numbers Needed to Treat Based on Clinically Meaningful Improvements in Patient Reported Outcomes (PROs) Including Health-Related Quality of Life (HRQoL) after Sarilumab Treatment during a Phase III Randomized Controlled Trial (RCT)

Vibeke Strand[1], Regina Rendas-Baum[2], George J. Joseph[3], Chieh-I Chen[4], Hubert van Hoogstraten[5], T. W. J. Huizinga[6] and **Mark C. Genovese**[7], [1]Biopharmaceutical Consultant, Portola Valley, CA, [2]QualityMetric Inc, Lincoln, RI, [3]Global Health Economics & Outcomes Research (HEOR), Sanofi, Bridgewater, NJ, [4]Regeneron Pharmaceuticals, Inc., Tarrytown, NY, [5]Sanofi, Bridgewater, NJ, [6]Rheumatology, Leiden University Medical Center, Leiden, Netherlands, [7]Division of Rheumatology, Stanford University Medical Center, Palo Alto, CA

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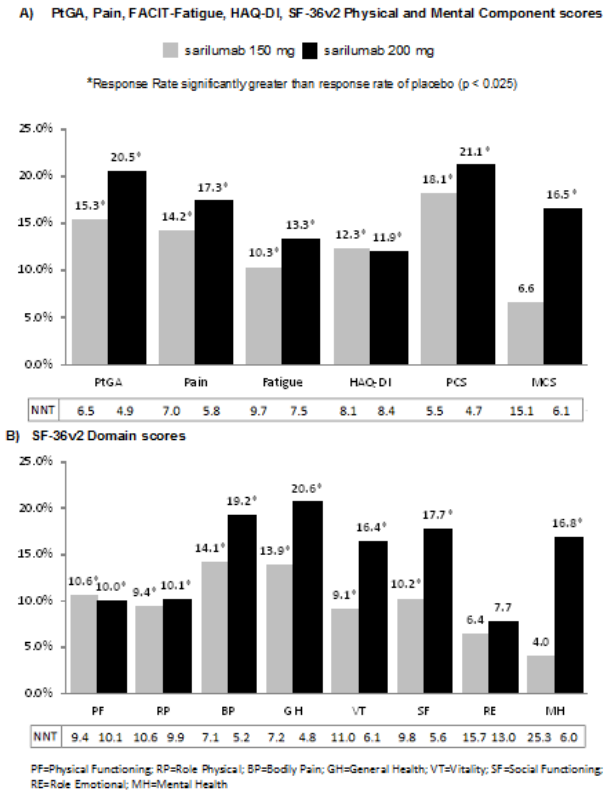
Background/Purpose: Sarilumab is a human monoclonal antibody (mAb) directed against the soluble IL-6 receptor (sIL-6R), administered subcutaneously (SC) every 2 weeks (q2w). In the phase 3 RCT MOBILITY study (NCT01061736), sarilumab 150 mg and 200 mg SC q2w+MTX demonstrated efficacy in patients (pts) with moderate-to-severe RA[1] and was generally well tolerated. Patients treated with sarilumab also experienced significantly greater improvements in HRQoL, fatigue and sleep compared with placebo.[2] Understanding the clinical importance of group differences can be enhanced by assessing treatment benefit based on the proportion of patients who report improvements meeting or exceeding minimum clinically important differences (MCID). These analyses compared the percentages of patients who reported MCIDs at week 24 across treatment groups.

Methods: The intent-to-treat population included 1,197 patients randomized 1:1:1 to placebo+MTX, sarilumab 150 mg q2w+MTX, or sarilumab 200 mg q2w+MTX. PROs included Patient Global Assessments (PtGA), Pain by VAS, HAQ-DI, SF-36v2 and FACIT-Fatigue. Patients were classified as responders if their change scores were ≥ MCID for that PRO. A binary logistic model with responder classification as the response and treatment group, prior use of biologic agents and region as fixed effects was used to estimate differences from placebo in response rates (RR) and numbers needed to treat (NNT).

Results: RRs in sarilumab were significantly better than placebo for all PROs with exception of SF-36 Mental Component Summary and Mental Health domain scores with sarilumab 150 mg and Role Emotional domain in both active treatment groups. Compared to placebo, there were an additional 15%-21% of responders by PtGA, 14%-17% by Pain-VAS, 10%-13% by Fatigue, 12% by HAQ-DI, 18%-21% by PCS and 17% by MCS (150 mg only). There were 9% - 21% more responders by 7 of the 8 SF-36v2 domains (200 mg). NNTs ranged from 4.7 (PCS; 200 mg) to 9.7 (FACIT-Fatigue; 150 mg) similarly favoring sarilumab vs placebo.

Conclusion: More patients receiving sarilumab+MTX reported changes in PROs ≥MCID, resulting in small NNTs, indicating a significantly greater likelihood of clinically meaningful improvement with active treatment than placebo+MTX.

Figure 1 Difference from placebo in the percentage of patients reporting minimally clinically important difference or better after 24 weeks of treatment with sarilumab or placebo



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Abstract Number: 2314

Minimal Important Difference in HAQ: A Validation from Health Economic Perspectives in Patient with Rheumatoid Arthritis Using Real-World Data

Chenglong Han[1], Nan Li[2] and Steven Peterson[3], [1]Outcomes Research, Janssen Global Services, LLC, Malvern, PA, [2]Janssen Global Services, LLC, Spring House, PA, [3]Janssen Global Services, LLC, Malvern, PA
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Background/Purpose: A change of 0.25 in HAQ score has been considered as clinically meaningful. This study is to evaluate the clinical meaningfulness of the HAQ change from health economic perspectives in patients with rheumatoid arthritis using real-world data.

Methods: This is a retrospective cross-sectional study using data in ADELPHI Disease-Specific Program collected in 2014 (EU5 and US). Patients with clinically diagnosed rheumatoid arthritis (N=1032) were enrolled and completed self-reported outcomes measures including physical function by Health Assessment Questionnaire-disability index (HAQ-DI), employment status, work productivity by Work Productivity and Activity Impairment Questionnaire-General Health (WPAI-GH) and general health status by EQ visual analogue scale (EQ VAS). Clinical characteristics include disease activity defined by DAS28. Correlations between HAQ-DI score and other outcomes were analyzed using univariate or multiple regression analysis.

Results: The majority of patients were female (72.1%) with average age of 55 years old and disease duration of about 9 years. The mean (SD) HAQ-DI score was 0.76 (0.69) with 42.2% having a HAQ-DI score ≥ 1, indicating moderate to severe physical disability. 58% of patients were currently unemployed. Patients with a HAQ-DI score of >1.0, 77% were unemployed with a EQ VAS of 54.2, while patients with normal HAQ score of ≤ 0.5, 40% were unemployed with a EQ VAS of 75.6. HAQ-DI score was significantly correlated with the unemployed in multivariate logistic regression model ($p<0.001$), and correlated with time lost from work ($p<0.001$) and general health status by EQ VAS ($p<0.001$) by multivariate linear regression model. After adjustment for demographic characteristics including age, gender, and disease duration, an 0.25 increase in HAQ-DI score was associated with a 30% increase in likelihood for unemployed status (OR=1.30, 95% CI=1.22, 1.39).

Conclusion: Physical function measured by HAQ-DI is a valid measure to predict employment status and general health status in patients with rheumatoid arthritis.

Disclosure: C. Han, Johnson & Johnson Pharmaceutical Services, LLC, 3; **N. Li**, Janssen Global Services, LLC, 3; **S. Peterson**, Johnson & Johnson Pharmaceutical Services, LLC, 3.

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Abstract Number: 2315

Six-Month Effects of a Multimedia Patient Education Tool in Patients with Rheumatoid Arthritis. a Randomized Controlled Trial

Maria A. Lopez-Olivo[1], Andrea Barbo[2], Tara Rizvi[3], Robert Volk[4], Heather Lin[5] and Maria E. Suarez-Almazor[6], [1]Department of General Internal Medicine, The University of Texas, MD Anderson Cancer Center, Houston, TX, [2]Department of Biostatistics, The University of Texas, MD Anderson Cancer Center, Houston, TX, [3]Rheumatology, Baylor College of Medicine, Houston, TX, [4]Health Services Research, The University of Texas, MD Anderson Cancer Center, Houston, TX, [5]Biostatistics, The University of Texas, MD Anderson Cancer Center, Houston, TX, [6]General Internal Medicine, The University of Texas, MD Anderson Cancer Center, Houston, TX
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Background/Purpose: We conducted a multi-centered, open-label, parallel, randomized controlled trial to evaluate the efficacy of a multimedia-patient education tool (MM-PtET) for patients with rheumatoid arthritis (RA) in improving outcomes immediately after the intervention and at 3 and 6 months.

Methods: Patients were recruited from 5 centers and through advertisement. Inclusion criteria were: (i) age ≥18 years (ii) diagnosis of RA by a rheumatologist (iii) disease duration ≤10 years (iii) adequate cognitive status and, (iv) ability to communicate in English or Spanish language. The efficacy of the MM-PtET was evaluated longitudinally using questionnaires on disease knowledge, decisional conflict and role preferences, self-efficacy and disease management before and after viewing the assigned materials, at 3 and 6 months. Linear regression and generalized estimating equation were used in order to determine the effective impact of correlative factors on the efficacy of the MM-PtET, including age, sex, race, education level, language in which the questionnaire was answered, health literacy and disease duration.

Results: 221 participants were randomized (111=MM-PtET, 110=written booklet). Mean age was 51±13 years, mean disease duration was 5±3 years, 85% were female 24% had inadequate health literacy levels and 46% answered the questionnaire in Spanish. 116 (64=MM-PtET, 52=booklet) and 158 (76=MM-PtET, 82=booklet) participants returned their questionnaires at 3 and 6 months, respectively. Within groups most outcomes were improved from baseline to 3 and 6 months. At 6 months, participants assigned to the intervention group had statistically significantly higher disease management scores compared to the control group (mean 81.1 vs 76.6, p=0.03). Greater improvement in knowledge scores from baseline to 6 months were observed in those participants who received the intervention (p=0.03) and those with inadequate health literacy (p=0.006). Meanwhile, among Whites, the intervention was associated with greater improvements in the decisional conflict scale and uninformed subscale (p=0.004 and p=0.02, respectively); and among males, receiving the intervention group led to improvement in the clarity subscale (p=0.02). Among younger individuals, booklet was associated with improvement in self-efficacy but among older ones, it was MM-PtET (p=0.003). Shorter disease duration, on the other hand, was associated with better disease management (p=0.009). Higher level of education (High School or above) was associated with active role played in health decision-making (p<0.003) after adjusting for correlated outcome data and controlling for other variables.

Conclusion: Our MM-PtET was more effective in improving disease management compared to reading written materials in RA patients at 6 months. The multimedia tool was associated with greater health outcomes improvement among older patients, Whites, and males. Independent factors associated with improvement include disease duration (shorter) and level of education (at least High School diploma).

Disclosure: M. A. Lopez-Olivo, None; **A. Barbo**, None; **T. Rizvi**, None; **R. Volk**, None; **H. Lin**, None; **M. E. Suarez-Almazor**, None.

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Abstract Number: 2316

An Ethnographic Observational Study of the Biologic Initiation Conversation Between Rheumatologists and Biologic Naïve Rheumatoid Arthritis Patients

Nicholas Kottak[1], Melissa Rosenberg[2], Dennis Parenti[3] and **Shelly Kafka**[3], [1]Ethnographic Solutions, Washington, DC, [2]Janssen Pharmaceuticals Inc, Horsham, PA, [3]Janssen Scientific Affairs, LLC, Horsham, PA

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Background/Purpose: To better understand how rheumatologists communicate the need to initiate biologic treatment and explain the risks and benefits, Janssen Pharmaceuticals initiated an ethnographic market research study. This initiative assessed shared decision making approaches and how modes of administration were presented to RA patients (pts).

Methods: Study participants included rheumatologists and their RA pts who were naïve to biologics. Rheumatologists and pts consented to be videotaped during their visits with one another and to be interviewed by a trained ethnographer before and after these medical visits. The study included 16 experienced rheumatologists (>2 yrs in practice and >100 RA pts/month) and 50 RA pts. Eleven rheumatologists had in-office infusion services and 5 did not. Rheumatologists selected pts who were inadequately controlled on DMARD therapy and for whom biologic therapy was being considered. One day of fieldwork by the ethnographer was conducted with each rheumatologist. The 50 videotaped physician-patient conversations were analyzed to determine content, timing and structure of the biologic initiation conversations.

Results: The mean duration of the patient visit was approximately 15 minutes, on average, with 5.7 minutes devoted to a discussion of biologic initiation. The specific discussion of mode of administration options (IV, SC, or oral) lasted approximately 30 seconds and the discussion on brands lasted <1.5 minutes. In 37% (13/48) of the patient visits, the option of IV administration was not discussed. When IV therapy was discussed, the frequency of IV administration was mentioned only half of the time (17/35). Rheumatologists often provided little description of SC or IV therapy and how they differ. When pts knew or learned more about IV therapy, they were more receptive to it. The post-visit interview also showed that many pts were confused or overwhelmed after their conversation with their HCP, including not truly understanding the benefits of initiating a biologic. When rheumatologists presented pts with a choice of biologic products, pts struggled to recall the various products mentioned and to understand their key differences.

Conclusion: These ethnographic data revealed that there was limited discussion regarding biologic treatment options, which presents challenges to a shared decision making process. Key aspects of biologic therapy options (modes of administration, dosing frequency, how products differ) were omitted or given cursory explanation. In post-visit interviews, pts also struggled to recall and understand key elements of the discussion, including their different treatment options. There are opportunities for rheumatologists and RA pts to partner more extensively on biologic therapy decisions. Educational tools may not only help rheumatologists explain complex information about biologic therapy options more efficiently, but the tools may give pts more confidence when choosing and starting a biologic therapy.

Disclosure: N. Kottak, Janssen Scientific Affairs, LLC, 5; **M. Rosenberg**, Janssen Pharmaceuticals Inc, 3; **D. Parenti**, Janssen Scientific Affairs, LLC, 3; **S. Kafka**, Janssen Scientific Affairs, LLC, 3.

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Abstract Number: 2317

Different Rheumatoid Arthritis Disease Activity Measures Often Provide Discordant Results in Clinical Practice Populations

Gary Crump[1], James Bower[2], Terrence Foley[3], **J. Timothy Harrington**[2], Nikita Hegde[4], Drew Johnson[5], Rafia Khalil[6], Edmund LaCour[7] and Robert Perhala[8], [1]Rheumatology Associates - Louisville, Louisville, KY, [2]Joiner Associates LLC, Madison, WI, [3]Terrence Foley MD Inc, Concord Twp, OH, [4]Akron General Hospital, Cuyahoga Falls, OH, [5]Crescendo Bioscience, Inc., South San Francisco, CA, [6]Rafia Khalil Arthritis & Rheumatology Center, PC, Port Huron, MI, [7]Dothan Medical Associates PC, Dothan, AL, [8]University Hospitals, Cleveland, OH

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Background/Purpose: Accurate rheumatoid arthritis (RA) disease activity assessment is required for treatment consistent with

Treat-to-Target (T2T) recommendations. Rheumatologists currently use a variety of patient-generated, physician-generated, and laboratory data to assess RA disease activity (DA). Discordance among different clinical measures, and more recently between clinical measures and a multi-biomarker test, has been documented. This study investigates discordance among DA measures in multiple clinical practice RA populations.

Methods: The Rheumatoid Arthritis Practice Performance (RAPP) Project is a voluntary collaboration of U.S. clinician rheumatologists whose goal is to provide T2T care and optimal RA disease outcomes. Of the 168 participants in the RAPP Project, 86 have enrolled their entire RA population (ICD-9 code 714.0) in a HIPAA-compliant disease population registry and are tracking DA measures in the registry. With isolated exceptions, their preferred measures include one or more of the following: RAPID3, a 0-10 Provider Global Assessment (PGA), Clinical Disease Activity Index (CDAI), and a multi-biomarker (MB) test. Table 1 reports the number of registries tracking each of these measures and the distributions of controlled, low, moderate, and high DA for each measure using the most recent assessment for each patient. Table 2 reports discordance rates between different date-matched DA results from those registries entering more than one measure, again using the most recent assessment for each patient.

Results:

Table 1. DA Distributions for Different Measures in 86 RAPP Practice Registries

	RAPID3	PGA	CDAI	MB
Registries tracking (N)	15	39	15	86
Controlled and Low DA (median %)	52%	74%	55%	22%
Moderate DA (median %)	22%	21%	27%	39%
High DA (median %)	26%	5%	19%	39%

Table 2. Discordance among Paired DA Measures

	MB vs CDAI	MB vs PGA	MB vs RAPID3
Registries included (N)	5	12	10
Measure pairs (N)	746	2162	1845
Discordance (median %)	44%	41%	33%
Discordance range	41-49%	18-59%	24-42%

	CDAI vs PGA	CDAI vs RAPID3	PGA vs RAPID3
Registries included (N)	4	5	10
Measure pairs (N)	1759	2239	3570
Discordance (median %)	17%	26%	32%
Discordance range	15-18%	15-41%	20-71%

Conclusion: 1. Different measures provide differing DA distributions within RA populations and discordant results for many individual patients. 2. Treatment decisions will likely differ based on which measures are used. 3. Factors contributing to discordance among measures at the population and patient levels appear to include patients' and providers' variable subjective perceptions, variability of joint examinations, and sub-clinical inflammation detected only by MB testing.

Disclosure: G. Crump, Crescendo Bioscience, 5,Crescendo Bioscience, 8; **J. Bower**, Crescendo Bioscience, 5; **T. Foley**, Crescendo Bioscience, 5; **J. T. Harrington**, Crescendo Bioscience, 5; **N. Hegde**, Crescendo Bioscience, 5; **D. Johnson**, Crescendo Bioscience, 3; **R. Khalil**, Crescendo Bioscience, 5; **E. LaCour**, Crescendo Bioscience, 5; **R. Perhala**, Crescendo Bioscience, 5,Crescendo Bioscience, 8.

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Abstract Number: 2318

Inflammatory Arthritis Patient Perspectives on Strategies to Support Medication Adherence: A Qualitative Study Using a Novel Group Exercise

Sharan K. Rai[1], Pavandeep Mehat[2], Anne Townsend[3], Carlo Marra[4], Harpreet Chhina[5], Rhonda Shuckett[6] and Mary A. De Vera[2], [1]Experimental Medicine, University of British Columbia, Vancouver, BC, Canada, [2]Faculty of Pharmaceutical Sciences, University of British Columbia, Vancouver, BC, Canada, [3]Medical School, University of Exeter, Exeter, United Kingdom, [4]School of Pharmacy, Memorial University, St. John's, NF, Canada, [5]Orthopedic Surgery, BC Children's Hospital, Vancouver, BC, Canada, [6]Rheumatology, University of British Columbia, Vancouver, BC, Canada
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Background/Purpose: Disappointing and inconsistent findings of adherence intervention research in inflammatory arthritis (IA) highlight the need for further work in designing interventions that promote and support treatment adherence. Patient-centered approaches to developing medication adherence interventions have shown promise in other chronic diseases, and may be particularly relevant in IA where they have scarcely been applied. We aimed to explore IA patients' perspectives on strategies to support medication adherence.

Methods: Individuals were eligible for the study if they: (1) had a rheumatologist-confirmed diagnosis of IA, (2) were taking a DMARD(s), and (3) could communicate in English. A novelty of our study, an experienced facilitator led participants through a group exercise where participants were asked to design a hypothetical tool(s)/aid(s) supporting medication use. Participants developed their tools individually using provided activity sheets and coloured cards corresponding to features of their tools, including (1) **what** (is your tool?), (2) **how** (does your tool work?), and (3) **who** (is there anybody who uses your tool with you?). They were then invited to share their tools with the group, and the facilitator used open-ended questions to promote discussion. In our qualitative analysis, we applied an iterative, thematic approach informed by aspects of grounded theory and using the constant comparison method. Three study team members independently read and annotated the transcripts, and after discussion agreed on an initial coding framework. Categories emerging from the focus groups were identified and collected under major thematic headings.

Results: Six focus groups were held with 4-6 participants each. Qualitative analyses resulted in the identification of three predominant emerging themes: (1) educational resources; (2) lifestyle modifications and adaptations; and (3) the journey of medication use. Educational resources encompassed communication with a healthcare provider (e.g., rheumatologist, pharmacist), patient group classes, pamphlets and written resources, eHealth/mHealth, and learning about medication side-effects. Lifestyle modifications and adaptations were comprised of physical reminders/prompts for medication use (e.g., blister packs, pill boxes), electronic alerts/reminders (e.g., smartphone apps), establishing a routine (e.g., taking medication with breakfast), and managing multiple medications. The journey of medication use encompassed the sequential process of patients learning about and gaining confidence in prescribed medications, and the subsequent integration of these medications into their daily life ("Once I know the med, once I'm confident in the med, it's working, then I phase it into my lifestyle").

Conclusion: To our knowledge, this is the first study to use a novel group exercise to explore patients' perspectives on strategies to support medication use in IA. Both educational resources and lifestyle modifications/adaptations were paramount to medication use among IA patients. These findings have important implications for the development of patient-centered medications adherence interventions.

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Abstract Number: 2319

Mobile Medical Documentation of Patient-Reported-Outcome

Jutta G. Richter[1], Christina Kampling[1], Gamal Chehab[1], Hasan Acar[1], Arnd Becker[2], Meike Dieckert[1] and Matthias Schneider[1], [1]Policlinic of Rheumatology, Heinrich-Heine-University Duesseldorf, Duesseldorf, Germany, [2]Ortenau Klinikum Offenburg-Gengenbach, Gengenbach, Gengenbach, Germany

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Background/Purpose: Mobile medical Applications (mApps) with integrated patient-reported outcome instruments (PROs) allow patients (pts) with rheumatoid arthritis (RA) self-monitoring and might strengthen self-management. Use of mApps might simplify PROs' information transfer between pts and physicians. Within the MiDEAR (Mobile medically supervised patient management in rheumatoid arthritis patients using DocuMed.rh and RheumaLive (RL-) App)) project we studied pts' mobile data entry of PROs using the mApp RL on an iPhone in comparison to paper-pencil versions to evaluate media bias ahead of routine clinical application.

Methods: As the project's concept relies on 'bring your own device' 271 consecutive RA out-pts were screened for App compatible devices. 156 owned App compatible devices and were thus eligible. 60 pts agreed to complete established (electronic (e)) PROs (Funktionsfragebogen Hannover FFbH/calculated HAQ; RA disease activity index (RADAI)) by using the RL-App installed on an iPhone 3 GS (installed iOS 6.1.3) owned by the clinic and as paper-pencil versions. Pts answered their questions and saved their data themselves. The quality and validity of data obtained using RL-App and the capability of disabled pts to handle it were tested; pts' experiences, App/internet use and sociodemographic respectively clinical data were assessed. Ethic approval and signed informed consents were obtained.

Results: Pts were predominantly female (78.3%), mean age was 50.1±13.1 years (yrs), mean disease duration 10.5±9.1 yrs. 50% had a high education level. 91.7% reported substantial experience with a smartphone, 68.3% with a TabletPC. 56.7% used iOS and 53.3% Android on their App compatible devices. 90.0% already used Apps. Mean confidence in Apps in general was rated 3.2±1.5 (1-6 Likert scale).

Scores obtained by pts direct data entry on the smartphone did not differ significantly from the scores obtained by the paper-pencil questionnaires, see Table1. Even when pts were splitted by FFbH groups (≤50;51-70;>70) paper-pencil and e scores did not differ significantly and correlated well.

Three pts did not complete both PRO versions. In one patient the paper-pencil version of the FFbH/HAQ could not be calculated due to too many missing values. Five pts reported problems with the data entry on the touchscreen, no other major difficulties using the RL-App for the ePROs occurred.

Score	Smartphone	Paper-pencil based	Spearman Rho#	P*
FFbH (n=56)	94.4 (17.0-100.0)	94.4 (14.0-100.0)	0.976	p>0.05
HAQ (n=56)	0.5 (0.36-2.7)	0.5 (0.36-2.8)	0.976	p>0.05
RADAI (n=57)	1.9 (0.0-7.5)	2.1 (0.0-7.8)	0.948	p>0.05

Table 1 Median scores ranges; #bivariate correlation; *Wilcoxon Rank test

Conclusion: RA pts are able to complete ePROs in a mApp on a smartphone. Thus, monitoring disease activity, disability and treatments' efficacy continuously apart from the physician visit by a mApp seems feasible. Regular and broader use of mApps offers new opportunities for tight disease control concepts. Before the mApp with PROs is used in routine care its acceptance from patients' and physicians' perspectives needs further evaluation.

M. Schneider, None.

Abstract Number: 2320

The Use of Doppler Ultrasound in Patients with Rheumatoid Arthritis Improves Patient Understanding of Disease and Adherence to Treatment and Alters Clinical Practice

Fred Joshua[1], Christine Bailey[2], Mona Marabani[3], Evange Romas[4], Raymond White[3] and Peter Wong[5], [1]Combined Rheumatology Practice and Macquarie University, Sydney, Australia, [2]AbbVie, Sydney, Australia, [3]Private Rheumatology Practice, Sydney, Australia, [4]Department of Medicine, University of Melbourne, Melbourne, Australia, [5]Mid-North Coast Arthritis Clinic and University of New South Wales Rural Clinical School, Coffs Harbour, Australia

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Background/Purpose:

Doppler ultrasound (DUS) can detect subclinical joint inflammation and can be used to predict disease relapse or flare in patients with RA. The objectives of the present study were to assess 1) the current use of DUS, 2) if DUS and visual aids with explanation improved patient understanding of disease, and 3) whether exposure to DUS alters rheumatologists' clinical practice.

Methods:

Australian rheumatologists were invited to take part in the DEDUCE Medical Practice Activity that enrolled 4−6 RA patients from each practice aged ≥18 years in DAS28 remission. Rheumatologists and patients completed a pre-activity survey assessing experience of DUS prior to DUS evaluation using the US7 score. Rheumatologists discussed results with patients using specifically developed visual aids. Patients and rheumatologists then completed post-activity questionnaires followed by a final survey six months later. Summary statistics were used as appropriate.

Results:

Eighty patients recruited by 21 rheumatologists completed pre-activity questionnaires. Patients who had previously undergone DUS found it improved their understanding of RA (18/19, 95%) and likelihood of medication adherence (16/19, 84%). Fifteen of the 21 rheumatologists had previously used DUS. Ten (67%) used DUS in patients in clinical remission and low disease activity (LDA) while 12/15 (80%) and 9/15 (60%) agreed it aided patient communication and medication adherence, respectively. The most common reasons for not using DUS were cost, inconvenience, and concern regarding usefulness and practicality.

Sixty six patients completed post-activity questionnaires. Of the 58 patients who had post-DUS discussions with their rheumatologist, 51 (88%) reported these improved understanding of their disease and 55 (95%) believed that it will encourage them to take medications as prescribed. Fifty of the 61 (82%) patients whose discussions utilised the visual aids found them useful. Overall, 56/66 (85%) of patients agreed DUS was useful in assessing disease activity.

Immediately post-activity, 20/21 (95%) of rheumatologists felt they would use DUS to guide therapeutic decisions and 16/21 (76%) found the visual aids useful for patient communication. Thirteen of 21 (62%) thought DUS would aid patient medication adherence.

Six months post-activity, all but one physician (95%) intended to continue to use DUS in their clinical practice. 15/21 (71%) of the rheumatologists had incorporated DUS into routine clinical practice, mainly for patients in LDA. Nineteen rheumatologists

(91%) believed DUS aided patient understanding and 17 (81%) believed it assisted communication with patients.

Conclusion: Almost all rheumatologists and patients who experienced DUS felt that it was a useful clinical tool. Communication of results using visual aids enabled patients to better understand their disease and increased the likelihood of medication adherence. Importantly, at 6 months the vast majority of participating rheumatologists had incorporated DUS into routine clinical practice.

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Abstract Number: 2321

Performance of Patient Reported Outcomes in the Assessment of Rheumatoid Arthritis Disease Activity: The Experience of the Espoir Cohort

Hélène Che[1], Bernard Combe[2], Jacques Morel[3], Alain G. Cantagrel[4], Laure Gossec[5] and Cédric Lukas[6], [1]Immuno-Rhumatologie, Hopital Lapeyronie, Montpellier, France, [2]Rheumatology, Hopital Lapeyronie, Montpellier, France, [3]Department of rheumatology, Lapeyronie Hospital and Montpellier University, Montpellier, France, [4]Rheumatology, INSERM CNRS UMR 1043, Paul Sabatier University Toulouse, Purpan Teaching Hospital, Toulouse, France, [5]Rheumatology, Pitié Salpetriere Hospital, Paris, France, [6]Hopital Lapeyronie, Montpellier, France

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Background/Purpose: Activity of rheumatoid arthritis (RA) can be assessed by several outcome measures : joint counts, inflammatory syndrom but also auto-questionnaires such as global patient assessment. The importance of Patient Reported Outcomes (PROs) has been recently put forward. The purpose was to determine whether patient self-assessment can reflect RA disease activity.

Methods: Data from patients included in the early arthritis ESPOIR cohort and fulfilling ACR/EULAR 2010 RA criteria at month 12 were used. The following PROs (Visual Analog Scales for fatigue, pain, patient assessment of disease activity; HAQ; SF36; EMIR-court and RAPID3) and their association with disease activity assessed by DAS28-3 variables, were measured.

DAS28-3 variables (including tender joint count, swollen joint count and erythrocyte sedimentation rate) was preferred to DAS28-4 variables in order to limit the input of subjective and patient-derived appreciation when defining the level of disease activity.

We compared the influence of disease characteristics on each PRO by Student t tests. The association between PROs and disease activity was assessed in several ways: part of explained variance, correlation and performance of each PRO in differentiating low versus higher disease activity states.

Results: 677 patients (83.2%) of the 813 patients of the ESPOIR cohort, were analyzed as they responded to the ACR/EULAR 2010 criteria of RA at month 12.Their mean age was 48.6±12.3 years with 77.4% of female, with a mean duration of disease of 3.41±1.74 months, 60.5% were rheumatoid factor or anti-citrullinated protein positives, 16.4% had anxiodepressive disorder and 15.1% had radiological lesions according to ACR/EULAR criteria. Disease activity assessed by DAS28-3 avriables was, at inclusion, 5.0±1.2, with a decrease during the follow-up.

Whatever the status of disease activity, patients with the lowest disease activity always had significantly less impaired

PROs. All analyzed PROs showed moderate correlations with RA disease activity. The PRO showing the best association with

DAS28-3v in determining RA disease activity states, was RAPID3 (Pearson correlation coefficient between 0.45-0.55, explained variance between 30-45%, sensitivity between 69-100% and specificity between 55-78%).

PROs with the highest association with disease activity were global PROs (RAPID3, EMIR-court) followed by those assessing physical function.

Conclusion: Association between PROs and RA disease activity as measured by DAS28-3 variables remains moderate. RAPID3, a global PRO, showed the best association with disease activity compared to the other analyzed PROs.

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Abstract Number: 2323

Patient Priorities in Rheumatoid Arthritis (RA) Research: An Exploration of Patient Perspectives from Those Enrolled in an Ontario RA Cohort

Laura Fullerton[1], Angela Cesta[2], Catherine Hoffstetter[3] and Claire Bombardier[2,4,5], [1]Support, Systems and Outcomes, University Health Network, Toronto, ON, Canada, [2]Toronto General Hospital Research Institute, University Health Network, Toronto, ON, Canada, [3]Patient partner, Toronto, ON, Canada, [4]Division of Rheumatology and Institute of Health Policy, Management, and Evaluation, University of Toronto, Toronto, ON, Canada, [5]Division of Rheumatology, Mount Sinai Hospital, Toronto, ON, Canada

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Background/Purpose:

Patient experiences with rheumatoid arthritis (RA) symptoms, treatments, and rheumatology care are critically important for the assessment of treatment-effectiveness and quality of care for RA. Despite recommendations for more patient-centered research, measures to evaluate the effectiveness of RA therapies often fail to reflect patient priorities.[1] The Ontario Best Practices Research Initiative (OBRI) is a clinical registry focused on improving the quality of care and health outcomes of patients with RA through long-term data collection on therapies, clinical practices, and health-care utilization. In OBRI, patient self-reported data is collected using structured interviews and validated questionnaires. The objectives of this study were to explore patient priorities in RA research, identify gaps in OBRI data collection, and explore options for improved data collection and communication with patients.

Methods:

RA patients enrolled in the OBRI clinical registry were invited to participate in 1 of 3 patient sessions in 2014 to provide feedback on how OBRI data collection could be improved to better capture patient needs/priorities. In small groups facilitated by a moderator, patients were asked to identify gaps in OBRI data collection, share experiences with RA and rheumatology care, and discuss priorities for RA research. In total, 48 RA patients participated in a facilitated discussion. After each session, patients completed a questionnaire on their use of social media.

Results:

Four overarching research priorities were identified: 1) A need for qualitative research focused on patient experiences with RA including: journeys to diagnosis, symptoms, treatment side effects, and challenges/concerns; 2) A need for qualitative research into patient satisfaction with rheumatology care including: rheumatologist accessibility, communication, and disease management;

3) A need for OBRI research questions addressing patient social support networks, strategies for coping with flares, diet and exercise, and the use of alternative therapies; and 4) A need for more information from rheumatologists on medication risks and side effects. Of those who completed the social media questionnaire, 100% reported regular use of email and 81% reported regular use of social networking sites, however only 54% reported a preference for research-related communication through email compared with regular postage.

Conclusion:

RA patients expressed that some of their most important disease-related experiences are not captured by structured questionnaires, suggesting a need for mixed-methods research to capture both qualitative and quantitative patient-reported outcomes. This study identifies patient research priorities and opportunities for improved care and communication.

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[1] Rendas-Baum, R. et al. 2014. Measuring the effect of therapy in RA clinical trials from the patient's perspective. Curr Med Res Opin. 1-13.

Disclosure: L. Fullerton, None; **A. Cesta**, None; **C. Hoffstetter**, None; **C. Bombardier**, None.

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Abstract Number: 2324

Understanding the Importance of a Patient's Role in the Management of RA: Results from a Patient-Based Survey

Ara Dikranian[1], James Galloway[2], Jörn Kekow[3], Anna Maniccia[4], Dean Spurden[5], Eustratios Bananis[6], Allan Gibofsky[7] and for the RA NarRAtives advisory panel, [1]San Diego Arthritis Medical Clinic, San Diego, CA, [2]Academic Department of Rheumatology, King´s College London, London, United Kingdom, [3]University of Magdeburg, Magdeburg, Germany, [4]Pfizer Inc, New York, NY, [5]Pfizer Inc, Tadworth, United Kingdom, [6]Pfizer Inc, Collegeville, PA, [7]Weill Cornell Medical College and Hospital for Special Surgery, New York, NY

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Background/Purpose: Rheumatoid arthritis (RA) is a chronic, debilitating condition for which there is no cure. The RA NarRAtive is a global initiative to identify patient perceptions regarding barriers to treatment and self-management.

Methods: The RA NarRAtive initiative is composed of a global advisory panel of 27 rheumatologists and patient advocacy group leaders. An online, patient-based survey, designed by the working group, was fielded across 13 countries between September 2014 and January 2015. The results are presented from all respondents who consented to the online survey.

Results: Patients from across the spectrum of disease activity (3,649) were represented, with 37% (1,346) self-reporting moderate/severe symptoms, while 12% (436) self-reported low disease activity, 4% (156) remission, and 28% (1,005) RA under control. Only 34% (1,251) described their current overall health as good/excellent. The median time since diagnosis was 7 years (range <1 to >10 years). The most frequently-cited concerns were disease progression (67% [2,437]), and impact of RA on quality of life (QoL; 62% [2,266]). Almost 50% reported stopping participation in certain activities and 29% discontinued work due to RA. Almost half of respondents seeing a healthcare provider (HCP) to manage their RA (48% [1,616/3,378]) acknowledged that dialogue/discussion with the HCP would help to manage their RA more successfully. However, over half of all respondents (62% [2,278/3,649]) felt uncomfortable raising concerns or fears with their HCP. Overall, 76% (2,764/3,649) of respondents received medication for their RA. Of those taking prescribed medication (2,139), 38% (808) were not taking this medication exactly as prescribed, although non-compliance rates varied substantially from 18–64% depending on country. The most frequently-cited reasons for non-compliance were treatment side-effects (16% [344]) and inconvenience (15% [320]).

Aspects of current, prescribed RA treatment that patients would most like to change included: number/frequency of medications (35% [742]); side-effects (34% [728]); access/cost (30% [632]); availability of monotherapy (25% [533]); alternative to subcutaneous mode of action (18% [377]); inconvenience/limitations (16% [344]); and mode of administration (12% [260]). Although 78% (1,674/2,139) of respondents were satisfied with their prescribed RA treatment, 70% (1,507) expressed a wish for fewer medications, and 56% (1,200) desired more choice. These patients defined treatment success according to: reduction of pain and/or swelling (81% [1,733]); improvements in QoL (77% [1,637]); control of disease progression (46% [992]); and treatment meeting goals/reducing medication (40% [852]).

Conclusion: These findings highlight that, while many patients are satisfied with their RA medication, non-compliance persists and there are many who would like to change certain aspects of their prescribed treatment. Furthermore, patient-HCP dialogue is important in the successful management of RA, which is clear as patients define successful treatment in terms of significant improvements in their overall symptoms and improvements in QoL.

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Abstract Number: 2325

Quantitative Clues to Recognize and Document Comorbid Fibromyalgia in Routine Care of Patients with Other Rheumatic Diagnoses on a 10 Cm Distress Visual Analog Scale Found on 1-Page Physician Rheumetric Checklist

Kathryn A. Gibson[1], Katherine J. Bryant[2] and Theodore Pincus[3], [1]Liverpool Hospital, Liverpool, Australia, [2]University of New South Wales, Sydney, Australia, [3]Rheumatology, Rush University Medical Center, Chicago, IL

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Background/Purpose: A physician global estimate (DOCGL) is commonly used to assess patients with rheumatic diseases. Fibromyalgia (FM) has been reported as a comorbidity in 10-35% of patients with rheumatoid arthritis (RA), osteoarthritis (OA), and other rheumatic diseases, and may complicate assessment and management in these patients. Formal criteria for fibromyalgia have been described and are included in many research studies. However, these formal criteria generally are not assessed in busy clinical settings, in which FM generally is diagnosed according to “gestalt,” narrative, non-quantitative descriptions. Quantitative standard data on a 1-page physician RheuMetric checklist, which is completed in 20-30 seconds, include a standard 0-10 visual analog scale (VAS) for DOCGL, and 3 further 0-10 VAS for the levels of inflammation or reversible findings (DOCINF), damage or irreversible findings (DOCDAM), and patient distress, e.g. fibromyalgia, depression (DOCDIS). We analyzed RheuMetric VAS for possible value to estimate FM in routine care.

Methods: A RheuMetric checklist is completed by one rheumatologist in all patients in routine care. Mean scores for DOCGL (0-10) and for the DOCINF (0-10), DOCDAM (0-10), and DOCDIS (0-10) subscales were compared in patients with rheumatoid arthritis (RA), other inflammatory arthritides (ankylosing spondylitis, psoriatic arthritis, inflammatory arthritis), and osteoarthritis (OA), who had or did not have a clinical diagnosis of secondary comorbid FM. Statistical significance was analyzed using 2-tailed t-tests.

Results: A total of 82 RA patients - 75 with no FM and 7 with FM, 51 with other inflammatory arthritides - 42 with no and 9 with FM, and 64 OA patients - 49 with no FM and 15 with FM, were studied (Table). Mean DOCGL scores for patients in each group

who had or did not have comorbid FM were similar: RA 2.71 vs 2.75 p=0.43; other inflammatory 3.67 vs 2.76 p=0.81; OA 3.43 vs 3.41 p=0.97 (Table). Mean DOCINF and DOCDAM estimates also did not differ significantly between patients with and with no FM in the 3 groups. Mean estimates for DOCDIS differed significantly in each of the 3 diagnostic groups in patients who had or did not have comorbid FM: RA 5.90 vs 2.38 p<0.0001; other inflammatory 5.56 vs 2.63 p=0.004; OA 5.25 vs 2.92 p=0.0008 (Table).

Conclusion: In this study, DOCDIS estimates to quantitate the degree of distress were significantly higher in patients with primary RA, OA or other inflammatory arthritides who also had comorbid FM than in those with no FM. DOCGL, DOCINF, or DOCDAM did not distinguish significantly patients who had or did not have comorbid FM. The DOCDIS scale may help clinicians to recognize and document secondary comorbid FM, without a need to administer other FM specific questionnaires, to help guide diagnosis and optimal patient care.

Table: Mean scores for physician RheuMetric scales for overall global estimate, inflammation, damage, and distress in 3 patient groups: rheumatoid arthritis, other inflammatory arthritis (Other Inflam), and osteoarthritis who do or do not have secondary fibromyalgia

	N	Overall Global Estimate	Inflammation	Damage	Distress
Rheumatoid arthritis with no comorbid fibromyalgia	75	2.75	1.79	2.74	2.38
Rheumatoid arthritis with comorbid fibromyalgia	7	2.71	2.08	1.00	5.90
p value		0.43	0.68	0.06	<0.001
Other Inflam with no comorbid fibromyalgia	42	2.76	2.28	1.75	2.63
Other Inflam with comorbid fibromyalgia	9	3.67	2.22	1.94	5.56
p value		0.81	0.93	0.81	0.004
Osteoarthritis with no comorbid fibromyalgia	49	3.41	0.45	4.50	2.92
Osteoarthritis with comorbid fibromyalgia	15	3.43	0.21	3.82	5.25
p value		0.97	0.40	0.15	0.0008

Disclosure: K. A. Gibson, None; **K. J. Bryant**, None; **T. Pincus**, Health Report Services, Inc, 4.

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Abstract Number: 2326

Patient Preferences Regarding Route of Biologic Administration in an Inflammatory Arthritis Cohort

Alysia Kwiatkowski[1], Lucas Grisanti[2], Joseph Grisanti[3] and James Hatem[4], [1]Internal Medicine, Albany Medical Center, Albany,

NY, [2]Department of Biology, College of Wooster, Wooster, OH, [3]Buffalo Rheumatology and Medicine, Orchard Park, NY, [4]BioStatistics, Buffalo Rheumatology and Medicine, Orchard Park, NY
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Background/Purpose:

Multiple biologic treatment modalities are available for managing systemic inflammatory disease states. Patient preference regarding routes of administration is frequently unclear and has not been well studied. Existing literature demonstrates that patient involvement and shared decision-making lead to greater levels of compliance and patient satisfaction (1). Additionally, correlation with demographic variables may assist the physician in tailoring individualized patient care. The goal of this study was to assess openness to and preferences for subcutaneous (SQ) versus intravenous (IV) routes of medication administration for biologic disease modifying medications in inflammatory rheumatologic disease states.

Methods:

Patients from a suburban outpatient rheumatology practice with a diagnosis of RA, PsA or AS were asked to complete a survey. Responses were reported anonymously and health care providers were blinded to results**.** Consecutive patients during a 3-month period were queried about their openness to and preferences for the use of a self administered SQ and/or IV biologic disease modifier. Data was analyzed using a two sided t-test and ANOVA. Subset analyses of gender, age and disease state were also explored.

Results:

A total of 236 subjects completed the survey and were considered for analysis (females: 73.7%; mean age: 60 years). Survey participants included 172 subjects with RA, 48 subjects with PsA and 24 subjects with AS; 107 (46.7%) were naïve to the use of a biologic DMARD. Openness to SQ and/or IV routes in subjects naïve to biologic disease modifiers can be seen in Table 1.

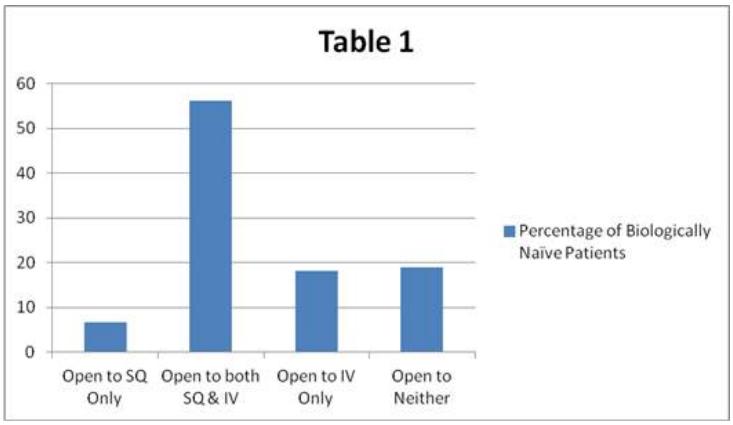
Overall, patients preferred IV to SQ route (34.2% vs. 25.3%, p=0.039) and 31.1% had no preference. Biologically naive patients preferred IV to SQ (34.0% vs. 18.9%, p=0.013), and 32.1% had no preference. Patients over the age of 60 preferred IV to SQ (41.4% vs. 12.5%, p=0.026), while those less than age 40 preferred SQ to IV (50% vs. 27.7%, p=0.008). Females preferred IV to SQ while males did not have a preference. PsA patients preferred SQ to IV (45.2% vs. 9.7%, p = 0.001) while RA patients preferred IV to SQ (36.2% vs. 23.2%, p=0.007).

Conclusion:

The results of the survey reveal that the majority of patients with inflammatory arthritis are open to the use of biologic agents. Surprisingly, in office infusion was preferred overall to subcutaneous injection. Differences exist between age groups, gender, disease and current biologic use. When considered, these variables can aid the clinician in tailoring care and may also have broader implications on future pharmacologic manufacturing.

References:

1. Lindhiem O, et al., Client preferences affect treatment satisfaction, completion, and clinical outcome: A meta-analysis. *Clin Psychol Rev*. 2014;34(6):506-517.



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View Abstract and Citation Information Online - http://acrabstracts.org/abstract/patient-preferences-regarding-route-of-biologic-administration-in-an-inflammatory-arthritis-cohort

Abstract Number: 2327

Documentation of Clinical Improvement in Patient with Polymyalgia Rheumatica According to MDHAQ/RAPID3 (Multidimensional Health Assessment Questionnaire/Routine Assessment of Patient Index Data): Longitudinal Analysis from Routine Care

Isabel Castrejón[1], Annie Huang[1], Sarah L. Everakes[2], Ailda Nika[1], Winston Sequeira[1] and Theodore Pincus[1], [1]Rheumatology, Rush University Medical Center, Chicago, IL, [2]Internal Medicine, Rush University Medical Center, Chicago, IL
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Background/Purpose: RAPID3 is an index found on the MDHAQ, which is effective in rheumatoid arthritis (RA) clinical trials and clinical care (1). MDHAQ/RAPID3 also is informative in osteoarthritis (OA), ankylosing spondylitis (AS), gout, systemic lupus erythematosus (SLE) (2), and vasculitis (3). A reported clinical composite index for polymyalgia rheumatica (PMR) includes 3 patient reported measures, which are found on MDHAQ/RAPID3 (4). We analyzed whether MDHAQ/RAPID3 would be of value to document clinical improvement in clinical status over time in patients with PMR.

Methods: All patients with all diagnoses seen at an academic rheumatology center complete an MDHAQ/RAPID3 at all visits in the waiting area, before seeing the rheumatologist. The MDHAQ includes 0-10 scores for physical function (FN), pain (PN), patient global estimate (PATGL), compiled into a 0-30 RAPID3. The MDHAQ also scores fatigue, morning stiffness, and a RADAI self-report of painful joints which queries 16 joint groups bilaterally, including shoulders and hips, as well as demographic data. Prospectively-collected MDHAQ/RAPID3 data, as well as laboratory and medication data, of PMR patients seen between 2010 and 2014 were collected retrospectively from the medical record, including MDHAQ/RAPID3 scores, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and prednisone dosage. Data from a baseline visit and most recent visit over a mean interval of 15.5 months were compared for MDHAQ/RAPID3 scores, laboratory tests and medications. Statistical significance was analyzed using paired t-tests and chi-square tests.

Results: 34 patients with PMR seen in routine care were included in the study: 59% were females, 71% Caucasian, and mean age

was 71.6 years. The mean duration from a baseline visit to most recent visit was 15.5 months (range 1 to 43 months). At initial presentation, mean RAPID3 was 12.2/30, physical function 2.2/10, pain 5.3/10, and PATGL 4.7/10, fatigue 3.9/10, and morning stiffness 63.1 minutes; 64.7% of the patients had painful hips, 79.4% had painful shoulders; 73.5% had abnormal ESR; 70.6% had abnormal CRP (Table). Significant improvement was seen between baseline and last visit in mean levels of RAPID3 and all other MDHAQ measures, except fatigue ($p<0.05$), as well as ESR and CRP (Table). The mean dose of prednisone was decreased from 12.2 at first visit to 4.3 mg at most recent visit.

Conclusion: In patients with PMR, improvement was seen according to MDHAQ/RAPID3 scores in a similar range to ESR and CRP, documenting effective response to prednisone. MDHAQ can be useful to document and monitor status of patients with PMR in busy clinical settings.

References: **1)** Pincus T, et al. Bull NYU Hosp Jt Dis. 2012;70 Suppl 1:30-6. **2)** Castrejon I, et al. J Clin Rheumatol: practical reports on rheumatic & musculoskeletal diseases. 2013;19(4):169-74. **3)** Annapureddy N, et al. Clinical rheumatology. 2015. 40. **4)** Leeb BF, Bird HA. Ann Rheum Dis 2004;63(10):1279-83.

Table: Mean MDHAQ/RAPID3 scores, laboratory measures, and medication at baseline and most recent visit (mean 15.5 months later) in 34 patients with polymyalgia rheumatica

	Baseline Visit N=34	Most Recent Visit N=34	Mean Change	% Improvement	p value
MDHAQ/RAPID3: Patient Self-report Scores					
RAPID3, mean (SD)	12.2 (7.0)	8.5 (7.2)	3.7	30.7%	0.02
MDHAQ-Function, mean (SD)	2.2 (2.1)	1.5 (1.7)	0.6	27.2%	0.03
MDHAQ-Pain, mean (SD)	5.3 (2.9)	3.4 (3.4)	1.9	35.8%	0.002
MDHAQ-PATGL, mean (SD)	4.7 (2.9)	3.1 (3.1)	1.6	34.0%	0.01
RADAI-painful hip, n (%)	22 (64.7%)	12 (35.3%)	29.4	45.4%	0.02
RADAI-painful shoulder, n (%)	27 (79.4%)	17 (50%)	10	37.0%	0.02
MDHAQ-Fatigue, mean (SD)	3.9 (3.6)	3.5 (3.3)	0.4	10.5%	0.54
Morning stiffness duration, minutes, mean (SD)	63.1 (97.7)	19.1 (34.1)	43.9	69.5%	0.05
Laboratory Measures					
Abnormal ESR, n (%)	25 (73.5%)	14 (41.1%)	32	43.5%	0.007
Abnormal CRP, n (%)	24 (70.6%)	13 (38.2%)	32	45.3%	0.007
Medication					
Prednisone dosage, mg, mean (SD)	12.2 (6.8)	4.3 (3.5)	7.9	64.7%	<0.001

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Abstract Number: 2328

The Correlation of Childhood Health Assessment Questionnaire with Disease Activity in Juvenile Idiopathic Arthritis

Watchareewan Sontichai[1,2] and Soamarat Vilaiyuk[1], [1]Division of Pediatric Rheumatology, Department of Pediatrics, Faculty of Medicine Ramathibodi Hospital, Mahidol University, Bangkok, Thailand, [2]Department of Pediatrics, Faculty of Medicine, Chiang Mai University, Chiang Mai, Thailand

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Background/Purpose: Juvenile idiopathic arthritis (JIA) is a common childhood arthritis, which is classified into 7 subtypes. Each subtype has different clinical manifestations, treatment, and disease course. The Childhood Health Assessment Questionnaire (CHAQ) is widely used for functional ability assessment. Many studies investigated the correlation between CHAQ and JIA outcomes but the correlation between CHAQ and disease activity in each JIA subtype is still obscured. Therefore, this study aims to determine the correlation between CHAQ and disease activity in each JIA subtype during active and inactive disease.

Methods: All JIA patients in pediatric rheumatology clinic at Ramathibodi hospital between January 2011 and December 2013 were included in this study. Demographic data, disease activity variables, and CHAQ were reviewed from medical records for 6 visits in each patient. Disease activity variables included active joint count, limited joint count, erythrocyte sedimentation rate, patient's global assessment (PtGA), and physician's global assessment (PGA). Juvenile Arthritis Disease Activity Score-27 (JADAS-27) was also performed by physician. The correlation between CHAQ and disease activity variables in each JIA subtype during the active and inactive disease was analyzed by Spearman's correlation.

Results: 139 JIA patients [31% enthesitis-related arthritis (ERA), 28% systemic JIA (SJIA), 17% oligoarthritis, 15% rheumatoid factor (RF) negative polyarthritis, 6% RF positive polyarthritis, and 3% undifferentiated arthritis] were enrolled into this study. Data of 812 visits were reviewed, 606 visits were in active disease while 206 visits were in inactive disease. The median of disease duration was 2.8 years. RF negative polyarthritis patients had highest CHAQ score (0.39 ± 0.66) while oligoarthritis patients had lowest score (0.20 ± 0.32). During active disease, CHAQ had moderate to strong correlation with JADAS-27, PGA, and PtGA in all JIA subtypes (p<0.05), whereas CHAQ had low correlation with disease activity variables during inactive disease. In SJIA patients, CHAQ had strong correlation with active joint count (r=0.70), whereas CHAQ in other subtypes had only moderate correlation. CHAQ also highly correlated with joint tenderness in polyarthritis (r=0.70 in RF positive group and r=0.64 in RF negative group).

Conclusion: Polyarthritis patients had the worst functional impairment, while oligoarthritis patients had the least functional impairment. CHAQ had good correlation with disease activity during active disease, whereas CHAQ had poor correlation during inactive disease in all JIA subtypes. Therefore, CHAQ is useful to assess disease activity in JIA patients only during active disease.

Disclosure: W. Sontichai, None; **S. Vilaiyuk**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/the-correlation-of-childhood-health-assessment-questionnaire-with-disease-activity-in-juvenile-idiopathic-arthritis

Abstract Number: 2329

Describe Treatments As 'new' or 'old' at Your Peril: Influences on Patient Decision Making

Mark Harrison[1,2], Carlo Marra[3] and Nick Bansback[4,5], [1]Faculty of Pharmaceutical Sciences, Vancouver, BC, Canada, [2]Centre for Health Evaluation and Outcomes Sciences, St Paul's Hospital, Vancouver, BC, Canada, [3]School of Pharmacy, Memorial University, St John's, NF, Canada, [4]St. Paul's Hospital, Centre for Health Evaluation and Outcome Sciences, Vancouver, BC, Canada, [5]School of Population and Public Health, University of British Columbia, Vancouver, BC, Canada
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Background/Purpose: Using an example of a new drug for rheumatoid arthritis which offers comparable effectiveness and side-

effect point estimates to older drugs, we explore preferences for treatments labelled 'new'. We then examine the persistence of preferences once ambiguity in the evidence base due to it being new is introduced.

Methods: We randomized a representative sample of the Canadian general population to one of three discrete choice experiment (DCE) designs which sought choices between hypothetical treatments for rheumatoid arthritis based on different levels of 7 attributes: route and frequency of administration, chance of benefit, serious and minor side-effects and life expectancy, and uncertainty in benefit and side-effect estimates. The DCEs differed in whether the treatment was 1) described as new (recently available) or older (available 5 or 10 years), 2) whether a qualitative description describing the confidence in the evidence was included instead, or 3) both the length of time available and confidence in evidence was provided. We collected characteristics of respondents including the self-reported Innovativeness scale, Subjective Numeracy Scale, and Health Risk Attitude Scale.

Results: 2837 people responded to the survey. Overall, all 6 consistent attributes (route and frequency of administration, chance of benefit, serious and minor side-effects and life expectancy) influenced preferences for treatment. An overall significant preference for less ambiguity (more confidence) in benefit and side-effect estimates was observed, but there was no preference for a treatment labelled 'new' or 'old'. However, in a subgroup analysis, early adopters (n=173) had a significant preference for 'newer' treatments relative to old treatments (B=0.157, p=0.045), preferences comparable in magnitude to preferences for reducing the risk of (rare) serious side-effects in this group. While early adopters valued reducing ambiguity in the evidence base consistently with later adopters, when the newness of the drug was combined with ambiguity in the evidence base, preferences for 'new' treatments diminished. There was evidence of a dose-response relationship across innovator categories.

Conclusion: Preferences for innovation in health care appear to exist for some potential groups of patients. However, when presented with the implications of new treatments, namely increased ambiguity in the evidence base, these preferences diminished. When communicating with patients, physicians should either avoid describing whether treatments are 'new', or be mindful to qualify the implications of a 'new' treatment in terms of ambiguity in estimates of risks and benefits.

Disclosure: M. Harrison, None; **C. Marra**, None; **N. Bansback**, None.

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Abstract Number: 2330

The Turkish Validity and Reliability of the Systemic Lupus Erythematosus Quality of Life Questionnaire (L-QoL)

M Tuncay Duruoz[1], Canan Sanal Top[2], Ilhan Sezer[3], Figen Yılmaz[4], Cagri Ünal[2], Hatica Sule Baklacioglu[5], Firat Ulutatar[6] and Pamir Atagunduz[7], [1]Dept of PM&R, Rheumatology Clinic, Marmara University Medical School, Istanbul, Turkey, [2]PM&R, Marmara University Medical School, Istanbul, Turkey, [3]Rheumatology, Physical Medicine and Rheabilitation, Antalya Education and Research Hospital, Antalya, Turkey, [4]PM&R, Sisli Hamidiye Etfal Training and Research Hospital, Istanbul, Turkey, [5]Rheumatology, Marmara University Medical School, Istanbul, Turkey, [6]Physical Medicine and Rehabilitation Department, Marmara University Medical School, Istanbul, Turkey, [7]Department of Rheumatology, Marmara University Faculty of Medicine, Istanbul, Turkey

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Background/Purpose: The Systemic Lupus Erythematosus Quality of Life Questionnaire (L-QoL) is a disease-specific measure of needs-based quality of life developed in the United Kingdom (1).

Aim: To assess the validity and reliability of the L-QoL in a Turkish population.

Methods: The L-QoL was translated into Turkish using the dual-panel process. Patients with SLE were recruited from 4 different rheumatology clinics. L-QoL administered twice with 3-4 weeks of interval to assess the test-retest reliability (intraclass correlation coefficient). Face validity was assessed via cognitive debriefing interviews with SLE patients. The convergent and divergent validities were assesed for determine the construct properties of the questionnaire. The relation of the L-QoL with subsets of Nottingham Health Profile (NHP) (energy level, pain, emotional reactions, sleep, social isolation, physical mobility) and Health Assessment Questionnaire (HAQ) were assessed for convergent validity. The relation of the L-QoL with non functional parameters such as age, disease duration, perceived general health and SLEDAI were assessed for divergent validity. Spearman's correlation coeficient (rho) was used to assessed the relation between quantitative parameters. $P<0.05$ was accepted as significant.

Results: Fifty-five SLE patients (53 female, 2 male) with 43.55 (SD:14.33) mean of age were recruited into the study. Test–retest reliability was very good (0.87), indicating low random measurement error for the scale. The measure was well accepted and the items considered understandable and relevant which showed the face validity of Turkish version of the questionnaire. The L-QoL has good correlation with subsets of NHP and HAQ were suggesting the measure assess related but distinct constructs (convergent). Its poor and not significant correlation with non functional parameters (divergent) showed its discriminative properties (Table).

Convergent validity of L-QoL	**Spearman's (rho)**	**Significance (p)**
NHP-energy level	0.52	<0.0001
NHP-pain	0.64	<0.0001
NHP-emotional reactions	0.72	<0.0001
NHP-sleep	0.65	<0.0001
NHP-social isolation	0.60	<0.0001
NHP-physical mobility	0.53	<0.0001
HAQ	0.62	<0.0001
Divergent validity of L-QoL	**Spearman's (rho)**	**Significance (p)**
Age	0.19	0.1640
Disease duration	0.18	0.1930
Perceived general health	0.32	0.0460
SLEDAI	0.29	0.1000

Conclusion: The Turkish version of L-QoL has good reliability and validity properties. It is practical and useful scale to assess the quality of life in SLE patients in Turkish population

1. L C Doward LC, McKenna SP, Whalley D et al. The development of the L-QoL: a quality-of-life instrument specific to systemic lupus erythematosus. Ann Rheum Dis 2009;68:196–200.

Disclosure: M. T. Duruoz, None; **C. Sanal Top**, None; **I. Sezer**, Abbvie, 8; **F. Yılmaz**, None; **C. Ünal**, None; **H. S. Baklacioglu**, None; **F. Ulutatar**, None; **P. Atagunduz**, None.

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Abstract Number: 2331

Agreement Between Patient's and Physician's Reported Bath Ankylosing Spondylitis Disease Activity Index in Patients with Axial Spondyloarthritis

Liana Ghukasyan[1], Adrien Etcheto[2], Anna Moltó[3] and Maxime Dougados[3], [1]Rheumatology B Department, Paris-Descartes University, Cochin Hospital, Paris, France, [2]Rheumatology B, Rheumatology B Department, Paris-Descartes University, Cochin Hospital, Paris, France, [3]Paris Descartes University, Rheumatology Department, Cochin Hospital, AP-HP. INSERM (U1153): Clinical Epidemiology and Biostatistics, PRES Sorbonne Paris-Cité, Paris, France

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Background/Purpose *:* The Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) is the more frequently used index for evaluating disease activity in Spondyloarthritis (SpA) in clinical practice. However patients frequently have questions concerning its wording or need assistance to fill it out. Despite BASDAI is a patient reported outcome, physicians often ask the questions to the patients themselves and give their own explanations. Moreover, in patients with axial SpA a short version of the BASDAI including only questions 1,2,5 and 6 has been proposed (referred here to axial-BASDAI).

These remarks prompted us to conduct this study aiming to assess the agreement between doctor's and patient's BASDAI and axial-BASDAI in the clinical evaluation of patients with SpA in daily practice.

Methods:

Study design: this was a cross-sectional study including patients with axial SpA according to the rheumatologist. Patients filled out the BASDAI questionnaire in the waiting room. Thereafter, unaware of the results provided by the patients, the rheumatologist collected another BASDAI by reading out loud the questions to the patient and giving explanations if needed.

Statistical analyses: agreement between patient and physician BASDAI and axial-BASDAI were compared by the intraclass coefficient of correlation (ICC) and its 95% confidence interval (CI) for continuous variables and by the kappa statistics (95%CI) when evaluating the percentage of patients with high disease activity (e.g. BASDAI > 4).

Results:

Of the 50 enrolled patients (mean age: 44± 10 years; disease duration: 15 ± 10 years) 32 (64%) were male, 40 (81,6%) were B27 positive and 34 (69,4%) had a radiographic sacroiliitis.

The agreement between patient's versus physician's BASDAI and axial BASDAI were excellent [ICC 0.91 [95% CI, 0.84-0.95]] and ICC 0.94 [95% CI, 0.90-0.97]] respectively. Regarding each question of the BASDAI (see table) the lowest agreement was found for Q4 (i.e. referring to enthesitis) with an ICC[95%CI] = 0.51 [0.28 – 0.69].

The agreement between patient and physician assessment of high disease activity (e.g. BASDAI > 40 yes/no) was better when considering the axial BASDAI in comparison with the total BASDAI (see table).

Table 1

	Patient	Doctors	ICC
BASDAI 1			
Mean (sd)	4.91 (2.40)	4.95 (2.38)	0.94[0.89-0.96]
BASDAI 2			
Mean (sd)	3.74 (2.34)	3.78 (2.55)	0.91[0.85-0.95]
BASDAI 3			
Mean (sd)	2.22 (2.02)	2.30 (2.29)	0.78[0.64-0.87]
BASDAI 4			
Mean (sd)	2.91 (2.31)	1.85 (2.26)	0.51[0.28-0.69]
BASDAI 5+6/2			
Mean (sd)	3.11 (2.30)	2.59 (2.08)	0.84 [0.73 - 0.91]
BASDAI total			
Mean (sd)	3.38 (1.73)	3.09 (1.75)	0.91[0.84-0.95]
“Axial” BASDAI			
Mean (sd)	39.22 (20.10)	37.75 (19.85)	0.94 [0.90 - 0.97]
BASDAI total>40			
	17/50 (34%)	13/50 (26%)	0.53[0.27-0.78]
“Axial” BASDAI>40			
	21/50 (42%)	20/50 (40%)	0.88[0.74 - 1.00]

Conclusion:

Despite an excellent agreement between the physician's and patient's total BASDAI scores, these data suggest that:

a)The fourth question of the BASDAI (e.g. relative to enthesitis) is the less concordant.

b)The physician's reported total BASDAI resulted in lower number of patients considered as active patients.

c) Such results should prompt the scientific community to revise such outcome or at least to provide clear recommendations on the optimal way to collect it.

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Abstract Number: 2332

Deriving ‘population References’ of Health Utilities for Patients with Spondyloarthritis Based on the ASAS Health Index

Ivette Essers[1,2], Mickaël Hiligsmann[3], Uta Kiltz[4], Nick Bansback[5], Juergen Braun[4], Désirée van der Heijde[6] and Annelies Boonen[1,7], [1]School for Public Health and Primary Care (CAPHRI), Maastricht University, Maastricht, Netherlands, [2]Rheumatology, Maastricht University Medical Center, Maastricht, Netherlands, [3]Department of Health Services Research, University of Maastricht, Maastricht, Netherlands, [4]Rheumazentrum Ruhrgebiet, Herne, Germany, [5]School of Population and Public Health, University of British Columbia, Vancouver, BC, Canada, [6]Rheumatology, Leiden University Medical Center, Leiden, Netherlands, [7]Maastricht University Medical Center, Maastricht, Netherlands

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Background/Purpose: The ASAS Health Index (HI) was developed to assess the impact of spondyloarthritis (SpA) on the patients' overall function and health. Utilities are a special type of health-assessment measures that reflect a ‘preference' for the different health states that patients with SpA can experience. Utilities range from 0 (death) to 1 (perfect health). While the patient's preference is increasingly recognized as resource for utilities, preferences from the general population remain the corner stone in healthcare decisions. Therefore, the aim of this study was to develop a conversion tariff for the ASAS HI to derive utility of health states of patients with SpA from the perspective of the general population. As it is known that preferences can be culturally dependent, we also derived country specific utilities.

Methods: An online survey was performed in a random sample of subject from the general population in the UK, France, Germany, the Netherlands, Spain and Italy. Subject completed first the ASAS HI. Next, two lead Time Trade Off (LTTO) experiments were performed to anchor the health states defined by the ASAS HI on a 0 to 1 utility scale. The lowest value was based on the health state ‘severe SpA' and the highest value on their ‘own ASAS-HI health state'. ‘Severe SpA' was defined by impairments in 8 items of the ASAS HI, selected previously by patients as having most impact on their health. In addition, subjects completed a Best-Worst Scaling (BWS) experiment comprising 17 choice tasks to assess the relative contribution of each item of the ASAS HI to overall health. Finally, the relative importance score of each item of the ASAS HI as derived by BWS, was used to rescale the ‘value of health' between the anchors of worst and best health defined in the LTTO.

Results: In total, a representative sample of 3,039 persons from the general population (age 46.5 years (SD 15.2), 1556 women (52.2%)) contributed to the analysis (about 500/country). As analyses showed comparable results among countries, we here present the overall results. Table 1 shows the results of the contribution of each item in the ASAS HI to the utility conversion formula. It can be seen that an individual who has no health problems related to SpA would experience a utility as 0.92. On the other hand, subjects of the general population indicate that the utility of a patient with SpA that scored problems on all 17 items of the ASAS HI would be as low as -0.37: a health state worse than death. A patient with SpA with pain, problems in sleeping, and problems with standing would be considered by society to have a utility of 0.59. Further analyses showed these results were largely comparable across countries.

Conclusion: From now onwards, a European transformation formulae is available to convert scores on the ASAS HI in a utility of the societal perspective. This makes it possible to use disease specific utilities in cost-utility analyses in patients with SpA.

Table 1: Contribution of presence of a problem for each item of the ASAS Health Index to the utility formula

Item	Contribution in Utility formula
Intercept (ASAS HI =0)	0.92
Pain	-0.13
Sleeping	-0.12
Exhausted	-0.10
Overcome difficulties	-0.10
Concentration	-0.09
Standing	-0.08
Financial changes	-0.08
Motivation to do physical effort	-0.07
Frustrated	-0.07
Walking outdoors	-0.07
Toileting	-0.07
Travelling	-0.06
Sexual relationship	-0.06
Running	-0.05
Driving	-0.05
Contact with people	-0.05
Washing hair	-0.03

Italic: items included in the health state 'SpA', which were defined in a pilot study in patients with spondyloarthritis.

BWS; best worst experiment; ASAS HI; Assessment of Spondyloarthritis International Society Health Index

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Abstract Number: 2333

Patients' Prioritization of Patient-Centered Education and Research Topics in Rheumatic Disease

Phillip Higginbotham[1], Bernadette Johnson[2], Ronan O'Beirne[1], Monica Safford[1], Seth Ginsberg[3], Ben Nowell[4] and **Jeffrey R. Curtis**[1], [1]University of Alabama at Birmingham, Birmingham, AL, [2]Immunology/Rheumatology, University of Alabama at Birmingham, Birmingham, AL, [3]CreakyJoints, New York, NY, [4]Creaky Joints/Global Healthy Living Foundation, Upper Nyack, NY

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Background/Purpose: While healthcare provider priorities often coalesce around clinical concerns, little has been done to explore which concerns are the most pressing educational concerns among the rheumatic disease patient community. This study conducted a cross-sectional analysis elicited by rheumatic disease patients using nominal groups to identify the set of topics most relevant to patients regarding their disease and care. Items were rank-ordered according to importance and used to identify the educational concerns with which rheumatic disease patients most identify.

Methods: Participants were recruited from within the membership registry of the rheumatology patient community, CreakyJoints, to participate in one of four nominal groups held in June 2015. Each of the four groups generated a set of educational topics or questions ('items'), and then rank-ordered them within each focus group. We manually reviewed all items to aggregate them into common topic groups, de-duplicating redundant items, and categorizing the topic groups in to themes according to their highest patient-ranked order.

Results: Among the 31 participants distributed across 4 nominal groups, mean (SD) age was 52.5 (9.8) years with 94% being women. Participant diseases included rheumatoid arthritis (74%), osteoarthritis (29%), osteoporosis (29%), fibromyalgia (23%), lupus (16%), ankylosing spondylitis (13%), and psoriatic arthritis (10%). Overall, 98 educational topics were suggested by the four groups, de-duplicated to 44 unique topic groups, which then were grouped into 14 representative themes. Themes consisted of 2-15 topic groups with each topic group encompassing 1-8 individual items. "Lifestyle changes and patient environment modifications" was the most valued theme, receiving 14% of votes. Medication data (drug dosing, interactions, performance, etc.), physician selection, and knowledge of disease/disease progression were also strongly emphasized with voting rank scores of 12%, 11%, and 10%, respectively. Themes of least interest included friend/family/community support, financial concerns (including insurance), and social interactions, which held vote percentages of 3%, 2%, and 1%, respectively.

Conclusion: Patients with rheumatic diseases are concerned about a variety of topics, which include lifestyle changes/patient environment modifications, medication data, and physician choice. Patient-centered research should maximally respond to addressing questions of importance to patients, and this survey is a first step in identifying and prioritizing the topics that matter most to patients.

Table 1: Top-ranked rheumatic disease educational concern themes with topic group and item examples.

Theme	Topic Group Example	Item Example
Lifestyle Changes & Patient Environment Modifications	Dietary Choices	What would be good food alternatives for reducing flares?
Medication Data (Dosing, Effects, Limitations)	Drug Effects	Drugs take a couple of months to work; don't expect an immediate fix.
Physician Selection	Finding the Right Specialist	Make sure to have a proper diagnosis by a rheumatologist.
Knowledge of Disease & Disease Progression	Disease Progression	What do you look for that indicates the condition is getting worse?
Reliable Resources	Individual Research Resources	It is important to educate yourself and do your own research.
Asking for Help & Extent of Limitations	Asking for Help	Don't be afraid to ask for help when you are having a flare.
Coping	Emotional	How do you deal with the mental and emotional problems that come with the condition?
Personalized Disease needs Personalized Treatment	Individualized Treatment Options	What are all medications/treatments available to you for your case in particular?
Alternative Treatments	Alternative Treatments	What alternative therapies that might be helpful (i.e. acupuncture and biofeedback)?
Self-Efficacy and Voicing Concerns	Self-Efficacy	Be your own advocate in your disease; trust your instincts and speak up.

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Proof of Concept Study of the Arthritis Health Journal: An Online Tool to Promote Self-Monitoring in People with Rheumatoid Arthritis (RA)

Diane Lacaille[1,2], Erin Carruthers[3], Brendan van As[3], Charles H. Goldsmith[3,4], Hilary Horlock[5], Linda Li[3,6], Anne F.

Townsend[3,7], Beverly Mitchell[8] and Paul Adam[9], [1]Rheumatology, University of British Columbia, Vancouver, BC, Canada, [2]Rheumatology, Arthritis Research Canada, Richmond, BC, Canada, [3]Arthritis Research Canada, Richmond, BC, Canada, [4]Health Sciences, Simon Fraser University, Burnaby, BC, Canada, [5]Information Management / Information Technology Services, Provincial Health Services Authority, Vancouver, BC, Canada, [6]Physical Therapy, University of British Columbia, Vancouver, BC, Canada, [7]Occupational Science and Occupational Therapy, University of British Columbia, Vancouver, BC, Canada, [8]Business Solutions and Collaboration, Provincial Health Services Authority, Vancouver, BC, Canada, [9]Rheumatology Liaison, Mary Pack Arthritis Centre, Vancouver, BC, Canada

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Background/Purpose: Patient passports have been used in chronic diseases to promote active involvement of patients in their care. In RA, patient monitoring of their disease activity could facilitate the treat to target approach by providing early warning signs when disease is not controlled. The Arthritis Health Journal (AHJ) is a patient-centered online tool that helps patients track symptoms, monitor disease activity and develop action plans. We performed a proof of concept study to assess its use in people with RA.

Methods: Participants, recruited from arthritis clinics, consumer newsletters and advertisements, were randomly assigned (1:1) to the immediate; or the delayed group, which received the intervention after 6 months. Participants were provided with online access to the AHJ and asked to use it for 6 mos (no frequency specified). The tool consists of 6 sections: 1) symptom and exercise log; 2) disease activity assessment; 3) mood assessment; 4) medical information; 5) goals and action plans; 6) health reports. On-line questionnaires every 3 months evaluated frequency of use, satisfaction, self-management, consumer effectiveness, and health status. Semi-structured interviews were conducted on a purposive sample selected to represent a range of experiences with the AHJ.

Results: 94 participants were recruited (45 immediate/49 delayed groups); mostly women (88.3%), Caucasian (78%), with post-secondary or higher education (88.3%), and a mean (SD) age of 52.9 (11.0) yrs and RA duration of 12.5 (10.6) yrs. The AHJ was used less frequently than expected, likely because participants were not instructed about how often to use it. Disease activity and mood assessment were the most frequently used sections [median (25Q; 75Q) frequency of use over 3 mos: 1.5 (0; 3) and 1.5 (0; 4), resp., with 35% not using the disease activity section over 3 mos and 29% using it > 3 times. User satisfaction was mod to high across sections (median varying from 6.0 to 7.3 on 1-10 scale), with highest satisfaction with the disease activity section. In preliminary analyses of 6-month data, no significant differences were observed in consumer effectiveness attributes or in health status. Perceived benefits of the AHJ mentioned in interviews included enhanced self-awareness, ability to see relationships between symptoms and trends over time in symptoms and disease activity, which was felt to facilitate medical-decision making during medical visits. Barriers to use included lack of perceived need when disease was stable, well-controlled or longstanding (stating they would have used it at disease onset), internal factors (e.g. fatigue, unwillingness to focus on disease, denial), external factors (lack of time due to life events). Those who found AHJ beneficial tended to use it more frequently.

Conclusion: Our proof of concept study shows that people were satisfied with the AHJ, but many did not use it frequently for a variety of reasons. No difference between groups were detected in consumer attributes or health status in preliminary analyses; however, the 6-month timeline might be short to expect such difference. A number of benefits were identified, esp. in people who used it frequently.

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Abstract Number: 2335

How Much Does Fatigue Contribute to the Physician and Patient Global Estimates in Different Rheumatic Diseases? Analysis from Routine Care on a Multidimensional Health Assessment Questionnaire (MDHAQ)

Isabel Castrejón[1], Elena Nikiphorou[2], Ruchi Jain[1], Annie Huang[1], Joel A. Block[3] and Theodore Pincus[1], [1]Rheumatology, Rush University Medical Center, Chicago, IL, [2]Rheumatology, Addenbrooke's Hospital, Cambridge, United Kingdom, [3]Rush University Medical Center, Chicago, IL

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Background/Purpose: Fatigue is an important problem for many patients with rheumatic diseases. Fatigue is associated with disease severity, psychological distress, and a poorer quality of life in rheumatoid arthritis (RA) (1), but the extent to which the level of fatigue may contribute to disease activity is controversial. A fatigue 0-10 visual analog scale (VAS) is included on a multidimensional health assessment questionnaire (MDHAQ). We analyzed possible associations between fatigue and global estimates of disease activity according to the patient (PATGL) and the physician (DOCGL) in patients with different rheumatic diseases seen in routine care.

Methods: All patients seen in one academic clinical setting complete a 2-page MDHAQ in 5-10 minutes in the waiting area, prior to seeing the rheumatologist in the infrastructure of usual care. The MDHAQ includes physical function (FN) in 10 activities of daily living, three 0-10 visual analog scale (VAS) for pain (PN), PATGL, and fatigue (FT), and demographic data. Four activity categories were defined for PATGL and DOCGL: <1 for 'inactive disease', 1-3 for 'low', 3-6 for 'moderate', and >6 for 'high'. Median values for fatigue and interquartile range (IQR) were compared in the 4 PATGL and DOCGL categories in 4 diagnostic groups: rheumatoid arthritis (RA), osteoarthritis (OA), systemic lupus erythematosus (SLE), and fibromyalgia (FM), using one-way analysis of variance; Kruskall-Wallis tests of significance were performed.

Results: The study included 612 consecutive patients, 173 with RA, 199 with OA, 146 with SLE and 94 with FM. Median fatigue scores were significantly higher in FM (7, IQR=5-8) $p<0.001$, but similar in RA (4, IQR=1-7), OA (5, IQR=2-7.5), and SLE (5, IQR=1.5-7.5). Fatigue scores were significantly higher according to disease activity categories in RA, OA and SLE patients for both PATGL and DOCGL, suggesting associations with diseases that are characterized by inflammatory or structural abnormalities (Table). By contrast, only PATGL, but not DOCGL, was associated significantly with fatigue, but a linear trend, as seen in RA, OA, and SLE, was not observed in patients with FM.

Conclusion: Fatigue scores are associated with severity of disease activity in conditions with inflammatory or structural abnormalities, such as RA, OA, and SLE, but do not appear to be similarly associated in myofascial pain syndromes. Fatigue may be due to different mechanisms in different rheumatic diseases. Fatigue is a relevant and important symptom, which may be assessed in the infrastructure of routine care as quantitative data on an MDHAQ, with no extra work for the doctor and minimal interference with clinic patient flow.

Reference: 1) Nikolaus S, et al. Arthritis Care Res (Hoboken) 2013; 65:1128-46.

Table: Fatigue in different disease activity categories according to DOCGL and PATGL													
Disease Activity Categories		**%**	**RA N=173**		**%**	**OA N=199**		**%**	**SLE N=146**		**%**	**FM N=94**	
According to DOCGL	**Remission (<1)**	13	0.5 (0-2)	p <0.001	7	0.2 (0-1.2)	p <0.001	21	1 (0-4.5)	p <0.001	2	NA	p<0.643
	Low (1-3)	33	2 (0.2-4)		17	3 (2-3.5)		35	4 (2-7.5)		8	6.7 (4.7-7.2)	
	Moderate (3-6)	39	5.7 (3.2-8)		62	6 (3-8)		34	5.5 (4-7)		69	7 (5-8)	
	High (>6)	15	6 (4-8)		14	7 (5.5-10)		10	8.2 (5.5-9.5)		22	7.5 (6-8)	
According to PATGL	**Remission (<1)**	23	0.5 (0-1.5)	p <0.001	12	1.7 (0-4)	p <0.001	25	0.5 (0-1)	p <0.001	0	NA	p<0.002
	Low (1-3)	18	2 (0.7-4.5)		12	3 (1.5-6.5)		16	2 (1.5-3.5)		8	7 (3-7.5)	
	Moderate (3-6)	28	4 (3-6.5)		33	5 (2-6)		29	5 (4-7)		25	5 (4-7)	
	High (>6)	31	7.5 (5.2-8.5)		43	7 (6-9)		30	8 (6.7-9)		67	7.75 (6-8.5)	
p values according to Kruskall-Wallis one-way analysis of variance. Data are median and interquartile range (IQR)													

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Abstract Number: 2336

Literature Review of Patient Reported Outcome and Health Related Quality of Life Measures for Biologic Therapies in the Management of Psoriatic Arthritis and Ankylosing Spondylitis

Steffen Jugl[1], Sultana Syeda[2] and Gunda Praveen[2], [1]BF I&D GPA, Health Economics and Outcomes Research, Novartis Pharma AG, Basel, Switzerland, [2]Novartis Healthcare Pvt. Ltd., Hyderabad, India, Hyderabad, India

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Background/Purpose: Psoriatic arthritis (PsA) and ankylosing spondylitis (AS) are chronic progressive conditions with substantial humanistic burden on patients and care givers. A variety of instruments, both generic and disease specific have been used in PsA and AS clinical studies. These Patient Reported Outcome (PRO) instruments allow to compare and measure impact on patient's quality of life and thus play an essential role in evaluating humanistic burden. Objective of this project was to review generic and disease specific PRO measures used in clinical studies for biologics in the management of PsA and AS.

Methods: A literature search review of literature in English language from 1996-2015 was conducted. Embase, MEDLINE®, Tuft's Cost-effectiveness Analysis registry, National Health Services Economic Evaluation Databases were searched. Inclusion criteria for review and data extraction were at least one biologic DMARD intervention, at least one utility, quality of life or patient reported outcome measure mentioned. Clinical as well as non-RCTs, observational or retrospective trials were eligible for inclusion.

Results: The literature search retrieved 3,175 articles, whereof 124 were included. Maximum articles were obtained for AS (N=73), followed by PsA (N=46). In addition five articles were included that captured both conditions. Across studies, a wide variation was observed in baseline characteristics such as age (Years, PsA: 35.5–65.0; AS: 24.4–61.0), disease duration (Years, AS: 0.7–30.2; PsA: 1.7–22.2) and gender distribution (Females, AS: 0–70%, PsA: 25–88%). The Short Form health survey 36 (SF-36) was the most commonly used generic health related quality of life (HRQoL) measure (N=27 for PsA, N=55 for AS), followed by Euro QoL 5d (EQ-5d) (N=10 PsA, N=14 AS). Variation was seen with respect to the utilization and reporting of disease specific instruments. Health Assessment Questionnaire (HAQ)/HAQ-Disability Index (N=36) was the most common in PsA while Ankylosing Spondylitis QoL (ASQoL) (N=21) was common in AS. Other common instruments reported were measured by Visual Analogue Scale (total pain, nocturnal pain, fatigue, physician global assessment etc.). Measures like Fatigue-VAS (0-10), Stiffness severity (0-100), Nottingham Health Profile (NHP)-fatigue, NHP-pain were reported the least.

Conclusion: A large variety of generic and disease specific PROs are utilized increasingly in the recent years in PsA and AS studies to measure HRQoL. This also shows the complexity and the multidimensional impact of these conditions on HRQoL. As there is no gold standard established, new tools may be needed to measure this impact holistically and reduce complexity of various measures across trials.

Disclosure: S. Jugl, Novartis Pharma AG, 3,Novartis Pharma AG, 1; **S. Syeda**, Novartis Pharma AG, 3; **G. Praveen**, Novartis Pharma AG, 3.

Abstract Number: 2337

Depression, Bad Sleep Quality, and Functional Deficit Are Independently Associated with Persistent Fatigue in Arthritic Patients with Low Disease Activity Under Biological Dmards

Vitalie Nizeica[1], Myriam Normand[2], Delphine Denarie[1], Béatrice Pallot Prades[1], Philippe Collet[1], Adamah Amouzougan[1], Hervé Locrelle[1,2], Thierry Thomas[1,2] and Hubert Marotte[1,2], [1]Rheumatology Department, University Hospital of Saint-Etienne, Saint-Etienne, France, [2]INSERM U1059/LBTO, Université de Lyon - Université Jean Monnet, Saint-Etienne, France
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Background/Purpose: In rheumatoid arthritis (RA) or axial spondyloarthritis (axSpA) patients, fatigue has been mainly related to disease activity. Current management of rheumatic inflammatory diseases aims for low disease activity as the desirable target. However, many arthritic patients with such a therapeutic response still report severe fatigue with negative consequences on their quality of life. The main objective of our study was to investigate the potential mechanisms of this fatigue by exploring factors associated with fatigue in low-activity RA and axSpA patients.

Methods: Arthritic patients with low disease activity (DAS28<3.2 for RA or BASDAI<4/10 and ASDAS<2.1 for axSpA) were enrolled in a monocentric observational and cross-sectional study. All patients were treated with a bDMARD associated or not with conventional synthetic (cs)DMARD. All patients were successively enrolled in this study. Demographic, clinical and biological patient characteristics were recorded. Fatigue was assessed by a validated self-questionnaire FACIT-F and by VAS for fatigue. Anxiety and depression were estimated by HAD scores. Physical activity was assessed by a validated score IPAQ-SF. Sleep quality was assessed using the PSQI score. Function disability was evaluated with HAQ. Function disability was evaluated with HAQ.

Results: One hundred patients were included in the study with 55 RA (86% female) and 45 axSpA (68% men), with a mean

disease duration of 11.9 ± 7.9 years. Furthermore, higher levels of physical activity together with lower functional disabilities were observed in axSpA patients compared to RA patients (Table 1). Notably, fatigue level was similar in RA and axSpA patients.

After the univariate statistical analysis, 7 parameters were statistically correlated with FACIT-F in our whole population: age, gender, sleep quality (PSQI and number of nighttime awakenings), anxiety (HAD anxiety), depression (HAD depression), and functional disability (HAQ). Four parameters remained positively associated with fatigue in the multiple linear regression: age, sleep quality (PSQI), depression (HAD depression), and functional disability (HAQ). Similar results were obtained when adding arthritic disease type (either RA or axSpA) in the multivariate analysis. Further analyses using ANCOVA test identified higher association between handicap and fatigue in axSpA patients than in RA patients. Fatigue level increased with higher handicap ($p<0.001$) and this trend was stronger in axSpA patients ($p<0.05$). Fatigue also increased with higher depression ($p<0.001$), with higher age ($p<0.05$), and sleep quality ($p<0.05$), but the strength of these associations was similar in both RA and axSpA patients.

Conclusion: Our study suggests the importance of advance care of depression, sleep quality, and functional deficit in patients with low-activity RA or axSpA in order to improve their state of fatigue and consequently to increase their quality of life.

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Abstract Number: 2338

"It Was like No One Is Listening to Me"[illegible]: A Qualitative Study of the Lived Experiences of Patients with Rheumatoid Arthritis in the Setting of Patient-Physician Discordance in Assessments of Disease Activity

John M. Davis III[1], Zoran Kvrgic[2], Melissa M. Plagge[1], Jennifer L. Ridgeway[3] and Gladys B. Asiedu[3], [1]Division of Rheumatology, Mayo Clinic, Rochester, MN, [2]Rheumatology, Mayo Clinic, Rochester, MN, [3]Center for the Science of Health Care Delivery, Mayo Clinic, Rochester, MN

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Background/Purpose: Discordance between patients with rheumatoid arthritis (RA) and their rheumatologists in their global assessments of disease activity affects around 33% of clinical encounters. The objective of this study was to understand the perspective of patients with measured discordance on issues like disease assessments and patient-provider communication.

Methods: We conducted individual interviews with 20 patients (six males and 20 females) with RA (ACR/EULAR 2010 criteria) who had patient-physician discordance as defined by a ≥25-mm absolute difference in global assessments of disease activity at the most recent rheumatology appointment within 4 weeks (median patient global assessment = 56 mm; median provider global assessment =15 mm). The interviews were audio recorded, transcribed verbatim, and checked for accuracy. Interviews were analyzed using content analysis by coding the texts, identifying themes and patterns and then grouping them into meaningful clusters. To aid interpretation of the qualitative data, the Clinical Disease Activity Index (CDAI) was collected from the most recent clinical evaluation, and participants also completed the pain visual analog scale (VAS) and the Patient Health Questionnaire-9 (PHQ-9).

Results: The average age was 63 years (range 38-85). The medians (IQRs) for CDAI, pain VAS, and PHQ-9 were 10.2 (8.3 to 22.4), 61.5 (42.8 to 77.8), and 3.5 (2 to 7.8), respectively. Qualitative data analysis yielded six key themes (Table). Many patients described being misunderstood by others, including medical and non-medical communities, and distinguished their experiences

from those with other, perhaps more objectively defined diseases. Not all patients reported feeling like their providers assessments differed from their own, but those who perceived discordance attributed it to providers' failure to listen, lack of empathy, or rushed behaviors. Many reported consternation with completing pain, disability and global activity ratings, and few reported discussions of these with providers. Other patients did not necessarily understand the meaning of disease assessments (e.g., blood tests, x-rays). Patients also described the psychosocial burden of RA on daily life, noting unmet psychosocial needs and confusion about whether these issues should be addressed with their providers.

Conclusion: The findings of this study reveal several key themes for rheumatologists to take into account in their daily approach to patients with RA. The results should inform future studies aiming to enhance patient-physician communication and to develop management approaches targeting optimal health outcomes for patients with RA, including those that acknowledge the impact that RA has on daily living, which may not be currently perceived as important to disease assessments in clinic.

Theme	Illustrative Patient Quote	Key Patient Descriptors
Being misunderstood by others	"You know, people with cancer are treated differently. People understand they have cancer; they're going through chemo or radiation. But people with RA, I think they're classified as being…I don't know…like it's all in their head? And it's not, because there is medical proof showing that I have a disease, so I'm not making this up."	Female, age 46, CDAI=43.3, PHQ-9=23, pain VAS= 80
Limitations of provider assessments	"It just seems very vague. I mean, you have a line, and you put on there what level are you at and you know the worst possible, I don't know what that looks like. I know that I'm not. Not at all. Because I feel it every day and it frustrates me every day. So you know, it's like OK, what's a five? That's what I do, I think well, I kind of put a number scale on there in my mind… I wake up in the morning and my neck hurts, my feet hurt…I mean I would always say that usually I'm somewhere between like a four and a six. That's where I would put myself on the scale… the nurse or whoever you are speaking to, because they see people who are really terrible, and then I might walk in and I look absolutely fine, and they look at me and they're like, oh, you look great, but you know you don't…it's difficult to see pain when somebody doesn't express it. Um, and do you know right now, I'm sitting here with back pain."	Female, age 38, CDAI=11.7, PHQ-9=1, pain VAS=52
Discrepancy with provider examination findings	"Well, he talks to me somewhat, but then he examines me, and that's part of why I'm here. He doesn't see that there's that much damage being done, so he doesn't…I don't that think he relates to how much it hurts…I mean, not caring…he doesn't act like oooh, you're stupid or whatever he just…I don't know, I just feel like he doesn't. And again, as far as the RA goes, maybe it isn't that bad and it's other things that are hurting."	Female, age 66, CDAI=10, PHQ-9=4, pain VA=85
Inadequate active listening	"…it was like nobody is listening to me. I can tell you what's happening to me but your… and then there was like oh I think you have rotator cuff, and so I went through all these tests and it comes back go, I guess it is your arthritis. I'm like. I know that is what I tried to tell you… I actually asked somebody else if she was new because I felt like she was just overwhelmed. I could just sense the overwhelm-ness of her. "	Female, age 64, CDAI 6.4, PHQ-9 1, pain 22
Psychosocial burden of disease	"I can either go out now and screw my employment history up completely or I can keep pissing away my savings… after 30 years I'm getting a divorce because she's tired of paying for all of the bills even though I made boohoo money and put all kinds of money into investments. Now she's tired of paying all of the bills."	Male, age 50, CDAI=10.4, PHQ-9=2, Pain VAS=71
Unmet psychosocial needs	"I just rate it how I feel. And I think a huge part of that is the stress. And, you know, fatigue, depression, so that to me rates of how you are feeling, not only physically but mentally, emotionally. So there should be your pain, physical, emotionally, you know. And that way they can say, OK, I see that, you know, you're having an extremely hard time with this emotionally, physically you're OK, your pain is tolerable. And then talk from there."	Female, age 46, CDAI 43.3, PHQ-9 23, pain 80

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View Abstract and Citation Information Online - http://acrabstracts.org/abstract/it-was-like-no-one-is-listening-to-me%ef%bf%bd-a-qualitative-study-of-the-lived-experiences-of-patients-with-rheumatoid-arthritis-in-the-setting-of-patient-physician-discordance-in-assessments-of-d

Abstract Number: 2339

Impact of Abbvie's Patient Support Program on Resource Costs in Crohn's Disease, Ulcerative Colitis, Rheumatoid Arthritis, Psoriasis, Psoriatic Arthritis, and Ankylosing Spondylitis

David T Rubin[1], **Martha Skup**[2], Matthew Davis[3], Scott Johnson[3] and Jingdong Chao[2], [1]University of Chicago Medicine, Chicago, IL, [2]AbbVie Inc., North Chicago, IL, [3]Medicus Economics, LLC, Milton, MA

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SESSION INFORMATION

Session Date: Tuesday, November 10, 2015

Session Title: Health Services Research Poster III: Patient Reported Outcomes, Patient Education and Preferences

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: AbbVie provides a Patient Support Program (PSP) to adalimumab (ADA)–treated patients to assist them with issues pertaining to medication costs, nurse support, injection training, pen disposal, and medication reminders.[1] Whether

these resources impact costs associated with healthcare utilization has not been assessed. We aimed to quantify the relationship between participation in any component of the PSP and resource costs (medical and total).

Methods: Longitudinal, patient-level data on the utilization of AbbVie's PSP were linked with Source Healthcare Analytics administrative claims data for patients initiating ADA treatment from 01/2008 to 06/2014. The sample included patients aged ≥18 years with a diagnosis of Crohn's disease, ulcerative colitis, rheumatoid arthritis, psoriasis, psoriatic arthritis, or ankylosing spondylitis who were anti-tumor necrosis factor naïve prior to initiation of ADA. Patients who enrolled in the PSP (PSP cohort) were matched to those who did not enroll (non-PSP cohort) based on age, sex, year of ADA initiation, comorbidities, diagnosis, and initiation at a specialty pharmacy. For the PSP cohort, the index date was the date of enrollment into the PSP program and their time to enrollment following initiation was used to assign index dates for the non-PSP cohort. All patients were required to have evidence of medical and pharmacy coverage for 6 months before/after their first ADA claim and for 12 months after the index date. Medical costs associated with emergency department, inpatient, physician, and outpatient visits (all-cause and disease-related) and total costs (medical costs plus drug costs) were compared at 12 months following the index date using t-tests and generalized linear models adjusting for key baseline variables. Patients with costs exceeding 5 times the standard deviation of the mean were excluded as outliers (52 for PSP, 64 for non-PSP).

Results: A total of 1,199 PSP patients and 1,187 non-PSP patients were included. Baseline characteristics were similar between cohorts. During the follow-up period, unadjusted analyses showed PSP patients had significantly lower 12-month medical costs than non-PSP patients by 23% ($18,322 vs $23,679; *P*=.003). Disease-related medical costs were 22% lower for PSP patients compared to non-PSP patients ($8,001 vs $10,201; *P*=.045). Total costs were 10% lower for PSP patients than non-PSP patients ($35,741 vs $39,713; *P*=.03). Adjusted analyses yielded similar findings.

Conclusion: AbbVie's free-to-patient PSP was associated with lowering medical costs (all-cause and disease-related) and total healthcare costs.

Reference:

[1]myHumira. Available at http://www.humira.com/global/ongoing-support.

Disclosure: D. T. Rubin, AbbVie, Emmi, Genentech, Ironwood, Janssen, Prometheus, UCB, Santarus/Salix, Takeda, Telsar, Vertex, 5,AbbVie, Elan, Prometheus, Shire, Warner Chilcott, 2; **M. Skup**, AbbVie, 1,AbbVie, 3; **M. Davis**, Medicus Economics, which received payment from AbbVie to participate in this research., 3; **S. Johnson**, Medicus Economics, which received payment from AbbVie to participate in this research., 3; **J. Chao**, AbbVie, 1,AbbVie, 3.

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Abstract Number: 2340

Improvement in Treat to Target Serum Urate Levels: Preliminary Results from a Comparison Between Two Audits of Management

Fernando Perez-Ruiz[1,2], Mariano Andres[3], Cesar Diaz-Torne[4], Eugenio De Miguel[5], Carmen Moragues[6], Francisca Sivera[7], Mercedes Jimenez[8] and Carlos Alberto Sánchez-Piedra[9], [1]BioCruces Health Research Institute, Baracaldo, Spain, [2]Servicio de Reumatologia, Hospital Universitario Cruces, Baracaldo, Spain, [3]Hospital de Alicante, Alicante, Spain, [4]Rheumatology, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain, [5]Rheumatology, University Hospital La Paz, Madrid, Spain, [6]Rheumatology Division, Hospital Universitari Bellvitge, L´Hospitalet de Llobregat, Spain, [7]Hospital de Elda, Alicante, Spain, [8]Rheumatology Division, Hospital Universitario Puerta de Hierro, Madrid, Spain, [9]Unidad de Investigación de la Sociedad Española de Reumatología, Madrid, Spain

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SESSION INFORMATION

Session Date: Tuesday, November 10, 2015

Session Title: Metabolic and Crystal Arthropathies Poster II

Session Type: ACR Poster Session C
Session Time: 9:00AM-11:00AM

Background/Purpose: 1) assess the current quality of care in gout patients and 2) compare the current management with previous audit data.

Methods: a second audit of clinical management of gout was conducted in 2014, including centers audited in 2006. The current Gout Evaluation and MAnagement-II audir included patients whose first visit was prior to the release of the ACR guidelines. In both audits, the degree of agreement was assessed according to the EULAR 2006 recommendations. The selection of patient's files for review was performed by a stratified 2-stage sampling. The number of centers per stratum was proportional to the population ≥50 years according to national statistics. In a second stage, a random sample from all patients in each participant unit with a diagnosis code of gout (ICD, R9), and who had been attended in 2006 and 2012 respectively was centrally selected. The sample size was estimated at 1,000 patients in 50 units for GEMA and then 500 patients from 40 units for GEMA-II according to previous results and expected outcomes. The main co-principal variables for GEMA-II were >50% improvement from GEMA in the rate of gold-standard diagnosis (based on crystal observation) and >50% improvement in the rate of patients at target serum urate levels (< 6 mg/dl in the last visit). In addition, an aprioristic evaluation of whether gold standard diagnosis was to be obtained in >50% of patients and target serum urate in > 50% of patients was asked from principal investigators prior to the inclusion of patient data.

Results: data from 511 randomly selected clinical records from 38 units were included. Out of the 38 units, 93% reported having a polarized microscopy facility at the office. sUA at final visit was available in 479/511 (93.7%). Samples from the two audits (GEMA and GEMA-II) did not differ in age, sex distribution or time from onset to first visit. Crystal-based diagnosis was performed in 209/803 (26.0%) and 162/511 (31.7%) in the GEMA and GEMA-II studies, not reaching endpoint. By contrast, the pre-defined improvement >50% for the rate of patients achieving target serum urate (< 6 mg/dl) was achieved (Table) for the overall population, independently of the aprioristic perception of the rate of control of target sUA. A post-hoc analysis including only patients on urate-lowering medications, the improvement in the rate of patients achieving sA target was 49.31%, very close to the >50% improvement (Table).

(Table, left columms= all patients; right columms= patients on urate-lowering medications).

sUA (mg/dl)	*< 6 mg*	*≥6 mg*		*< 6 mg*	*≥6 mg*
GEMA (N=701)	286 (40.8)	415 (59.2)	**GEMA (N= 642)**	274 (42.7)	368 (57.3)
GEMA-II (N=479)	294 (61.4)	185 (38.6)	**GEMA-II (N= 450)**	285 (63.3)	165 (37.7)

Conclusion: Overall the improvement in the rate of patients achieving target serum urate over a 6-year period exceeded 50%. The rate of gold-standard diagnosis improved, but did not reach the expected outcome. Although still under further analysis, these preliminary data show for the first time that substantial improvement has been achieved in treat to target serum urate levels strategy for gout in the Rheumatology community.

Disclosure: F. Perez-Ruiz, None; **M. Andres**, None; **C. Diaz-Torne**, None; **E. De Miguel**, None; **C. Moragues**, None; **F. Sivera**, None; **M. Jimenez**, None; **C. A. Sánchez-Piedra**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/improvement-in-treat-to-target-serum-urate-levels-preliminary-results-from-a-comparison-between-two-audits-of-management

Abstract Number: 2341

Treatment of Gout with Pharmacological Vs. Non-Pharmacological Complementary Therapy in the U.S.: An Internet Survey

Jasvinder A. Singh[1], Nipam Shah[2], N. Lawrence Edwards[3] and H. Ralph Schumacher Jr.[4], [1]University of Alabama at Birmingham, Birmingham, AL, [2]University fo Alabama at Birmingham, Birmingham, AL, [3]University of Florida, Gainsville, FL, [4]Medicine, Rheumatology, U Penn & VA Med Ctr, Philadelphia, PA
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SESSION INFORMATION
Session Date: Tuesday, November 10, 2015

Session Title: Metabolic and Crystal Arthropathies Poster II
Session Type: ACR Poster Session C
Session Time: 9:00AM-11:00AM

Background/Purpose:

The interplay of use of dietary supplement, diet modification and ULT adherence in gout management is not known. Therefore, we aimed to begin to assess the ULT adherence and choice of non-pharmacological interventions by patients with gout, using a cross-sectional online survey.

Methods:

People visiting the Gout and Uric Acid Education Society's website (http://gouteducation.org) were invited to participate in a brief anonymous Internet survey on a voluntary basis between 08/11/2014 to 04/14/2015. We collected each individual's report of their age, gender, race, physician-diagnosed gout, receipt of physician prescription of urate-lowering medication (ULT; allopurinol or febuxostat; responses were yes/no), number of days the patient forgot to take ULT in the last month, the use of cherry extract vs. diet modification vs. ULT medication as what individuals thought might be the best life-long strategy for gout and patients' likelihood of making a lifelong change to their diet (0=not at all likely to 10=extremely likely scale) for better gout management.

Results:

Of the 524 survey participants reporting a physician diagnosis of gout, 499 respondents were included in the final analysis (**Table 1)**. Mean age of survey responders was 56.3 years (standard deviation, 12.6), 50% were 41-60 years old, 74% were males, and 74% were White and 9% Asians.

57% participants responded that they were prescribed a ULT for gout, allopurinol or febuxostat. Gender, age or race were not significantly associated with the likelihood of receiving a ULT prescription. Of those who were prescribed ULT, 251/285 (88.1%) were taking ULT, 20/285 (7%) quit taking ULT, 2/285 (0.4%) were taking ULT only when they had a gout flare and 13/285 (4.5%) did not respond to this question. 197/251 (78.5%) had ULT adherence >80% and 54/251(21.5%) had ULT adherence ≤80%. In univariate and multivariable-adjusted analyses (**Table 1**), gender, race and age were not significant predictors of ULT adherence.

56% of respondents said that they preferred ULT as a lifelong treatment for gout, 24% preferred cherry extract, 16% preferred diet modification and 4% preferred none of the treatments. In multivariable-adjusted analyses, men had significantly lower odds of preferring ULT as the lifelong treatment choice for gout vs. other therapies (**p=0.03; Table 1**).

54% of participants were highly motivated to make a lifelong dietary modification to improve their gout (likelihood score of 9-10; 72.7% had score of >5). In adjusted analyses, age was significantly associated with high level of willingness to modify diet (**p=0.023; Table 1**).

Table 1. Multivariate-adjusted odds of the choice of ULT as gout treatment (ULT vs. others), adherence to ULT >80% and likelihood of lifelong diet change as treatment for gout by gender, race and age

Patient characteristics	**ULT prescribed***	**Choice of ULT as the treatment for gout****	**Urate-lowering medication adherence >80%*****	**Likelihood of diet change with score of >8 (range, 0-10)********
Gender	P= 0.58	**P=0.03**	P=0.32	P=0.41
Male	1.13 (0.74, 1.71)	**0.61 (0.39, 0.95)**[a]	0.68 (0.31, 1.47)	0.84 (0.55, 1.28)
Female	Ref	Ref	Ref	Ref
Age groups	P=0.87	P=0.16	P=0.71	**P=0.023**
21-40 years	1.39 (0.40, 4.71)	0.76 (0.22, 2.67)	0.81 (0.07, 9.05)	2.59 (0.51, 13.06)
41-60 years	1.14 (0.37, 3.53)	1.02 (0.32, 3.27)	1.01 (0.11, 9.26)	2.91 (0.63,13.58)
61-80 years	1.10 (0.34, 3.35)	0.64 (0.20, 2.08)	1.43 (0.16, 13.12)	**4.76 (1.01, 22.37)**[a]
>80 years	Ref	Ref	Ref	Ref
Race	P=0.99	P=0.60	P=0.77	P=0.48
African American	1.10 (0.41, 2.80)	0.91 (0.45, 1.85)	0.49 (0.11, 2.24)	1.35 (0.68, 2.70)
Hispanic or Latino	1.04 (0.33, 3.24)	0.92 (0.31, 2.77)	0.86 (0.09, 7.94)	1.13 (0.36, 3.54)
Asian	0.78 (0.19, 3.25)	0.59 (0.31, 1.12)	2.04 (0.76, 5.47)	0.63 (0.31, 1.29)
American Indian or Alaskan native	0.95 (0.31,2.89)	---	---	3.60 (0.31, 41.22)
Hawaiian or Pacific Islander	-----	4.15 (0.49, 35.11)	1.19 (0.13, 11.28)	2.23 (0.58, 8.52)
Other	0.96 (0.19, 4.83)	0.90 (0.34, 2.35)	1.60 (0.29, 8.76)	1.46 (0.56, 3.82)
White/Caucasian	Ref	Ref	Ref	Ref

[a]p-value <0.05

---, no odds ratio calculable since no patients in this category

* Reference category is ULT was not prescribed

** Reference category is preference for non-pharmacological treatment options (cherry extract or gout-specific diet modification) for gout

*** Reference category is urate-lowering medication adherence of ≤80% in the last month

**** Reference category is the likelihood of diet change with a score ≤8 (range 0-10)

Conclusion:

Only 57% of gout patients reported having been prescribed ULT by their healthcare providers. 40% gout patients responding to the survey said that they preferred non- pharmacological interventions. Further study would be of interest to ascertain what they expected from those interventions.

Disclosure: J. A. Singh, Takeda, Savient, 2,Takeda, Savient, merz, Regeneron, Allergan, Crealta, Bioiberica, 5; **N. Shah**, None; **N. L. Edwards**, None; **H. R. Schumacher Jr.**, None.

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Abstract Number: 2342

Uric Acid-Lowering Therapy Management Among Rural Veterans Affairs Primary Care Providers

Michael Darley[1], Grant W. Cannon[2] and Christopher Jackson[3], [1]Salt Lake City VA Medical Center and University of Utah, Salt Lake City, UT, [2]Division of Rheumatology, Salt Lake City VA Medical Center and University of Utah, Salt Lake City, UT, [3]Rheumatology, Salt Lake City VA Medical Center and University of Utah, Salt Lake City, UT

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Session Time: 9:00AM-11:00AM

Background/Purpose: ACR guidelines exist for the management of gout including the use of uric acid-lowering therapy. ACR guidelines recommend routine monitoring of uric acid levels and dose titration to achieve a uric acid goal of <6.0 mg/dL as well as regular drug safety monitoring in patients receiving uric acid lowering therapy. This study assesses the adherence of rural VA primary care providers with these ACR clinical guideline recommendations.

Methods: Patient records were examined from rural primary care provider panels. To be included in the analysis, patients were required to have been seen by their primary care provider within a one year observation period from November 1, 2013 until Oct 31, 2014 and to have been prescribed allopurinol or febuxostat. The following information was obtained for each patient: the number of uric acid determinations, the uric acid blood values, and the clinical actions that were taken if uric acid was above 6.0 mg/dL, or if the AST and ALT serum values were ≥ 2 times the upper limit of normal (74 U/L for AST and 154 U/L for ALT). If uric acid level was not at goal, or elevated AST or ALT noted, the patients' medical record was reviewed. Clinical action was considered to be appropriate for a uric acid ≥ 6.0 mg/dL if 1) an upward dose titration was documented in clinic notes or pharmacy records, 2) uric acid-lowering therapy was initiated, or 3) compliance counseling was documented in cases of suspected non-compliance. In the case of AST or ALT values ≥ 2 times the upper limit of normal, a clinical action was considered appropriate if a dose decrease or discontinuation of allopurinol or febuxostat was documented.

Results: There were 17,458 patients that had at least one primary care provider visit within the one year observation period and 772 (4.4%) of these patients had been prescribed either allopurinol or febuxostat. Of these 772 patients receiving allopurinol or febuxostat, 392 (51%) had at least one uric acid level documented during the observation period, and 738 (96%) patients had AST and/or ALT determinations. Among the 392 patients that had a uric acid level checked, 130 (33%) had a uric acid level ≥6 mg/dL. In this group of 130 patients with hyperuricemia (≥6 mg/dL), 73 (56%) had an appropriate clinical action taken. Among the 738 patients with AST and/or ALT lab determinations, 6 patients (0.8%) had an elevated AST and 1 had an elevated ALT level ≥ 2 times the upper limit of normal, and no dose adjustments or discontinuations of uric acid-lowering therapy were documented in clinical notes or pharmacy records.

Conclusion: Among rural V.A. primary care provider panel patients prescribed uric acid- lowering therapy only 51% of patients had a uric acid level checked within a year while 96% had routine AST and ALT monitoring. When the uric acid was above the goal of 6.0 mg/dL, defined appropriate action was documented in 56% of patients. There were 0.8% of patients with elevations of AST and 0.1% ALT ≥ 2 times the upper limit of normal, all of which lacked a documented adjustment of uric acid-lowering

therapy. These findings suggest the need for better education for rural VA primary care providers in the management of uric acid-lowering therapy in gout patients.

Disclosure: M. Darley, None; **G. W. Cannon**, None; **C. Jackson**, None.

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Abstract Number: 2343

Impact of Colchicine Use on the Development of Incident Coronary Artery Disease

Susanna Jeurling[1], Daria Crittenden[2], Mark C. Fisher[3], Binita Shah[4], Steven P. Sedlis[4], Craig T. Tenner[5], Svetlana Krasnokutsky Samuels[6] and Michael H. Pillinger[7], [1]Division of Rheumatology, NYU School of Medicine, New York, NY, [2]Rheumatology, NYU-HJD, New York, NY, [3]Rheumatology, New York Univ-HJD, New York, NY, [4]NYU School of Medicine, Division of Cardiology, New York, NY, [5]Medicine, NYU School of Medicine, New York, NY, [6]NYU School of Medicine, Division of Rheumatology, New York, NY, [7]Medicine/Rheumatology, NYU School of Medicine/NYU Hospital for Joint Diseases, New York, NY

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Background/Purpose: Patients with gout experience both inflammation and increased risk of cardiovascular disease (CVD). Studies suggest that colchicine reduces myocardial infarction (MI) risk, but whether colchicine reduces incident coronary artery disease (iCAD), vs. acute plaque disruption/inflammation, is unknown. We assessed colchicine's impact on iCAD in gout patients.

Methods: Patients with gout or hyperuricemia (2000-2009) were identified by ICD-9 code. We then included only subjects with 1) microscopic diagnosis of urate crystals; 2) 6/12 ACR gout classification criteria, 3) rheumatologist gout diagnosis; or 4) 4-5 ACR criteria plus a PCP gout diagnosis. Patients with a diagnosis of CAD at index date were excluded. Pharmacy records distinguished colchicine users (1 period of prescription for >30 days) vs non-users. Chart review identified iCAD, defined as first positive cardiac stress test or cardiac catheterization, PCI (stent or angioplasty) or CABG. Incident MI was also recorded.

Results: Of 7,819 patients with an ICD-9 diagnosis of gout/hyperuricemia, 446 colchicine users and 278 non-users met inclusion criteria (2,118 vs. 1,367 years of follow-up for colchicine vs control group). Baseline characteristics were generally similar across groups (Table 1). We found no increased iCAD prevalence among colchicine users vs non-users (Table 2). Inclusion of incident MI as a criterion for iCAD did not result in any significant difference between the groups. When expressed as incidence rate (events per patient-years), iCAD again did not vary between groups. The individual components of the outcome were also similar between the two groups (not shown). In multivariate models, after controlling for potential variables, colchicine use still did not impact the risk of iCAD.

Conclusion: Our data suggest that chronic colchicine use does not impact the rate of iCAD in gout patients. In conjunction with prior studies suggesting a reduction in acute cardiovascular events among colchicine users, our data suggest that colchicine is likely to act by preventing acute events (e.g., plaque rupture, or vascular occlusion post-plaque rupture), rather than by reducing iCAD.

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Table 1: Baseline characteristics of patients taking or not taking colchicine: demographics, cardiovascular risk factors, and medication use (n = 724).			
	Colchicine n= 446	No colchicine n = 278	p value
Age, yrs (mean ±SD)	72.7 ± 9.6	72.0 ± 9.8	0.34
Race			0.20
White (%)	46.2	44.6	
African-American (%)	41.7	42.1	
Asian (%)	1.79	2.16	
No response/other (%)	10.1	11.2	
Ethnicity			0.31
Hispanic (%)	10.3	9.0	
Non-Hispanic (%)	85.9	86.7	
No response/other (%)	3.6	4.3	
Diabetes mellitus (%)	23.8	24.5	0.83
Body mass index	30.2 ± 5.8	30.3 ± 6.5	0.88
Hypertension (%)	80.1	79.1	0.77
SBP, mm Hg	137.3 ± 19.6	140.1 ± 20.0	0.06
DBP, mm Hg	79.8 ± 11.4	80.9 ± 11.8	0.21
Hyperlipidemia (%)	50.2	42.1	**0.03***
LDL, mg/dl	107.9 ± 33.6	108.7 ± 34.8	0.74
HDL, mg/dl	42.8 ± 12.8	44.8 ± 13.3	**0.05***
Chronic kidney disease (%)	19.5	20.9	0.66
Serum creatinine, mg/dl	1.26 ± 0.50	1.27 ± 0.60	0.72
eGFR, ml/min	69.5 ± 26.3	67.8 ± 23.8	0.39
Active tobacco use (%)	22.0	21.9	0.99
Former tobacco use (%)	74.0	70.9	0.36
Uric acid, mg/dl	8.25 ± 1.96	7.62 ± 2.41	**< 0.01***
Allopurinol use (%)	22.9	19.8	0.33
Aspirin use (%)	20.2	23.7	0.26
Statin use (%)	27.4	29.1	0.60
Ace inhibitor use (%)	39.0	28.8	**< 0.01***
Beta-blocker use (%)	27.8	23.0	0.15
NSAID use (%)	41.0	42.5	0.71

Any antihypertensive use (%)	53.4	47.1	0.10

Table 2: Development of iCAD in colchicine users vs. non-users.

Outcome	Colchicine (N = 446)		No Colchicine (N = 278)		p value
	Percent affected (No. of patients)	*Events per 1,000 patient years*	*Percent affected (No. of patients)*	*Events per 1,000 patient years*	
iCAD	7.34 (33)	15.58	6.48 (18)	13.16	0.42
iCAD including new MI	9.19 (41)	20.78	7.55 (21)	15.36	0.44

Disclosure: S. Jeurling, None; **D. Crittenden**, Amgen Inc, 1,Amgen, Inc, 3; **M. C. Fisher**, None; **B. Shah**, Takeda Inc, 2; **S. P. Sedlis**, Takeda, 2; **C. T. Tenner**, None; **S. Krasnokutsky Samuels**, None; **M. H. Pillinger**, Takeda Inc, 2,AstraZeneca, 5.

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Abstract Number: 2344

A 3-Year Follow-up Study of Canakinumab in Frequently Flaring Gouty Arthritis Patients, Contraindicated, Intolerant, or Unresponsive to Nonsteroidal Anti-Inflammatory Drugs and/or Colchicine

Naomi Schlesinger[1], Thomas Bardin[2,3], Mark Bloch[4], Karine Lheritier[5], Uwe Machein[5], Guido Junge[5], Alexander So[6] and Rieke Alten[7], [1]Medicine, Rutgers-Robert Wood Johnson Medical School, New Brunswick, NJ, [2]Hopital Lariboisière, Paris, France, [3]Rhumatology Departement, Hôpital Lariboisière, Paris, France, [4]Holdsworth House Medical Practice, Sydney, Australia, [5]Novartis Pharma AG, Basel, Switzerland, [6]CHU Vaudois, University of Lausanne, Lausanne, Switzerland, [7]Charité Univ Medicine, Berlin, Germany

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Background/Purpose: Although anti-inflammatory drugs such as nonsteroidal anti-inflammatory drugs and colchicine are the recommended treatment options for pain and inflammation management in patients (pts) with acute gouty arthritis (GA) flares, alternative treatments are necessitated in pts with frequently flaring GA owing to contraindications, intolerance, and ineffectiveness. Safety of canakinumab (CAN), a selective, human anti-interleukin-1β antibody, vs triamcinolone acetonide (TA) over the initial 24 weeks has been reported.[1]Here we present the long-term safety of CAN over 36 months.

Methods: Pts who completed 2 phase III, multicenter, double-blind, randomized (subcutaneous [s.c.] CAN 150 mg and

intramuscular [i.m.] triamcinolone acetonide [TA] 40 mg) trials were enrolled in 2 similar design extension (E1) studies. Those completing E1 were enrolled in E2, a single arm study that was followed by an extension, E3. All in E2 and E3 received s.c. CAN 150 mg "on demand" upon a new flare. Long-term safety was assessed in terms of exposure-adjusted incidence rates per 100 patient-years (pyr) of adverse events (AEs) and serious AEs (SAEs) and efficacy was assessed by flare rate per year and high sensitivity C-reactive protein (hs-CRP) levels for a cumulative follow-up of 36 months.

Results: Of the 456 randomized in core studies, 272 pts entered the open label treatment with CAN during the extension phase E2 with re-treatment upon flare. Of those, 136 entered and 122 completed the open label treatment with CAN in E3. Overall, the exposure-adjusted incidence of AEs in CAN group was lower (264.6/100 pyr) than in TA group (308.8/100 pyr). Retreatment with CAN did not increase the incidence of AEs. Overall, the incidence of exposure-adjusted SAEs in CAN and TA groups was 17.3 and 17.7 per 100 pyr, respectively. The overall incidence of SAEs did not change in pts retreated with CAN (15.2 vs 15.1 per 100 pyr). Overall, 4 deaths—none related to study drug—were reported (2 pts in each group) due to intracranial hemorrhage [1; not retreated with CAN] and pneumonia [1; retreated with CAN] in CAN group and sudden cardiovascular death (1) and pneumococcal sepsis [1; never received CAN] in TA group. Mean flare rates/year were lower in CAN group (1.1) vs TA Group (2.5). CAN treated pts maintained clinical efficacy (pain intensity and physician's global assessment (PGA) of response to treatment) upon "on demand" retreatment over 3 years. Median hs-CRP levels remained below the upper limit of normal in pts retreated with CAN "on demand" for new GA flares from 7 days after the initial dose until end of study. Thirty % (n=12) of pts initiating or modifying urate-lowering therapies during E3 (n=40) reached target serum uric acid levels (<6 mg/mL).

Conclusion: Over 3 years, a mean "on demand" dosing of CAN was 2.68 per pt. Efficacy of CAN was demonstrated via stable pain intensity levels and PGA response scores in difficult-to-treat pts with GA. These results support the long-term safety of CAN treatment in those with frequently flaring GA pts. CAN safety profile was consistent with that observed in previous studies.

References

1. Schlesinger N., et al. *Ann Rheum Dis* 2012;71:1839–1848.

Disclosure: N. Schlesinger, Novartis, 2,Novartis, Takeda, 8,Novartis, 5,Novartis, Takeda, Pfizer, Astra Zeneca, 6; **T. Bardin**, Novartis , Gilead Sciences , ViiV Healthcare , Bristol Myers-Squibb, Merck, Romark, Abbvie, 2,Gilead Sciences, ViiV Healthcare, tol Myers-Squibb, Merck, Eli Lilly, 5,Eli Lilly, 8; **M. Bloch**, Novartis, 2; **K. Lheritier**, Novartis, 1,Novartis, 3; **U. Machein**, Novartis, 3; **G. Junge**, Novartis, 3; **A. So**, Novartis, 1; **R. Alten**, Novartis, 2,Novartis, 8.

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Abstract Number: 2345

Canakinumab Liquid Formulation in Acute Gouty Arthritis Patients: Long-Term Safety and Efficacy Results from a 36-Week Extension Study

Prashanth Sunkureddi[1], Rüdiger Moericke[2], Edith Tóth[3], Jacques P Brown[4], Uwe Machein[5], Karine Lheritier[5], Guido Junge[5] and Alan J Kivitz[6], [1]Clear Lake Rheumatology, Nassau Bay, TX, [2]Institut für Präventive Medizin & Klinische Forschung GbR, Magdeburg, Germany, [3]Flór Francis Hospital Rheumatology Department, Kistarcsa, Hungary, [4]Centre Hospitalier de l'Université Laval (CHUL), Quebec City, QC, Canada, [5]Novartis Pharma AG, Basel, Switzerland, [6]Altoona Center for Clinical Research, Duncansville, PA

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Background/Purpose: Patients with gouty arthritis (GA) experience frequent flares with pain and inflammation. The limited

available treatment options and typical comorbidities warrant effective alternative treatments[1]. A liquid formulation of canakinumab (CAN), presented as pre-filled syringe (CAN-PFS) has been developed to improve upon the lyophilized form (CAN-LYO). Efficacy and safety profile of CAN-PFS vs triamcinolone acetonide (TA) over 12 weeks in GA patients was reported earlier. Here we present the cumulative, safety, and efficacy results over 48 weeks.

Methods: Patients with GA who completed the 12-week core study[1] were enrolled in this 36-week, open-label extension (E1) study. All patients entering E1 received CAN-PFS 150 mg s.c. on demand upon new GA flare irrespective of the assigned treatment during randomization (CAN-PFS, CAN-LYO or TA 40 mg). The primary objective was to confirm the long-term safety of CAN-PFS vs TA. Secondary objectives included evaluation of CAN-PFS vs TA and CAN-LYO vs CAN-PFS for the time to first new flare over 48 weeks. Long-term safety outcomes and safety upon retreatment were assessed as the exposure-adjusted incidence rate of adverse events (AEs) and serious AEs (SAEs).

Results: Of the 397 patients randomized in the core study, 232 (58.4%) entered E1, of whom, 198 (50%) completed E1. Baseline characteristics were comparable between the treatment groups. The exposure-adjusted incidence of AEs was lower for both CAN-PFS [254.9/100 patient-years (pyr)] and CAN-LYO (224.8/100 pyr) groups vs TA (362.7/100 pyr) group over the 48 weeks. The exposure-adjusted incidence of SAEs was 14.7/100, 16.1/100, and 15.5/100 pyr in patients randomized to CAN-PFS, CAN-LYO, and TA groups, respectively. Infections and infestations were the most frequently reported SAEs in the CAN-PFS (3.4/100 pyr), CAN-LYO (3.2/100 pyr), and TA (0/100 pyr) groups. Over the 48 weeks, one death (cardiac failure), not suspected to be related to study drug, was reported in a patient randomized to CAN-PFS who was not re-treated during this period. CAN-PFS significantly delayed time to first new flare vs TA, with a relative risk reduction of 55% (hazards ratio [HR], 0.45; 95% confidence interval [CI], 0.32 to 0.64; $p<0.0001$) over 48 weeks. The mean number of new GA flares per patient was lower for both CAN-LYO (0.50) and CAN-PFS (0.76) groups than the TA group (0.96). Patients in the CAN-PFS group showed a 56% reduction in the number of new flares than the TA group (flare rate ratio, 0.44; 95% CI, 0.32 to 0.61; $p<0.0001$).

Conclusion:

These results provide evidence for the long-term safety and efficacy of CAN-PFS in patients with frequent GA flares, compared with TA. The safety profiles were consistent with those observed in the core study, and the efficacy of CAN-PFS was maintained upon retreatment.

Reference:

1. Sunkureddi P, et al. *Arthritis & Rheum*. 2013;65(10):1177.

Disclosure: P. Sunkureddi, Novartis., 2; **R. Moericke**, None; **E. Tóth**, None; **J. P. Brown**, Abvie, Amgen, Eli Lilly, Novartis, Takeda, 2,Amgen, Eli Lilly, Radius, 5,Amgen, Eli Lilly, 8; **U. Machein**, Novartis, 3; **K. Lheritier**, Novartis, 1,Novartis, 3; **G. Junge**, Novartis, 3; **A. J. Kivitz**, Novartis, 5.

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Abstract Number: 2346

Rebamipide Suppresses Monosodium Urate Crystal-Induced Interleukin-1b Production through Regulation of Oxidative Stress and Caspase-1 in THP-1 Cells

Jung-Yoon Choe[1], Minyoung Her[2] and Seong-Kyu Kim[3], [1]Division of Rheumatology, Daegu Catholic University Medical Center, Daegu, South Korea, [2]Busan Paik Hospital, Inje University, Busan, South Korea, [3]Internal Medicine, Catholic University of Daegu School of Medicine, Daegu, South Korea

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Background/Purpose: This study investigated the effect of rebamipide on activation of NLRP3 inflammasome and reactive oxygen species (ROS) in monosodium urate (MSU) crystal-induced interleukin-1b (IL-1b) production.

Methods: Human monocyte cell line THP-1 cells and human umbilical venous endothelial cells (HUVECs) were used for assessing inflammatory response to MSU crystals. NADP/NADPH activity assay was used for an alternative marker for ROS generation. Quantitative Real-time polymerase chain reaction (qRT-PCR) and western blotting was performed to evaluate levels of IL-1b, caspase-1, NLRP3, ASC, nuclear factor-kB (NF-kB), IkB, intercellular adhesion molecule 1 (ICAM-1), or vascular cell adhesion molecule 1 (VCAM-1). Experimental pharmaceuticals included rebamipide, colchicine, dexamethasone, and ascorbic acid.

Results: MSU crystals treatment to THP-1 cells induced NADP/NADPH ratio and IL-1b expression, which was potently inhibited by addition of rebamipide. Rebamipide also significantly attenuated enhanced mRNA expression of caspase-1 by MSU crystals ($p = 0.0033$), in addition to colchicine and ascorbic acid ($p = 0.0323$ and $p = 0.0266$, respectively). Western blotting demonstrated that MSU crystals stimulated only caspase-1, but not NLRP3 and ASC activation. Similarly, MSU crystals activated NF-kB pathway, which in turn was blocked by rebamipide. Increased expression of VCAM-1 and ICAM-1 by stimulation of MSU crystals to HUVECs was markedly inhibited by rebamipide, in addition to dexamethasone.

Conclusion: This study demonstrated that rebamipide inhibits IL-1b activation through suppression of ROS-mediated NF-kB and caspase-1 activation in MSU crystal-induced inflammation.

Disclosure: J. Y. Choe, None; **M. Her**, None; **S. K. Kim**, None.

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Abstract Number: 2347

Can We Predict the Dose of Allopurinol to Achieve Target Urate?

Dan Wright[1], Stephen Duffull[1], Tony R. Merriman[2], Nicola Dalbeth[3], Murray Barclay[4] and **Lisa K. Stamp**[4], [1]School of Pharmacy, University of Otago, Dunedin, New Zealand, [2]Biochemistry Dept, PO Box 56, University of Otago, Dunedin, New Zealand, [3]Department of Medicine, University of Auckland, Auckland, New Zealand, [4]Medicine, University of Otago, Christchurch, Christchurch, New Zealand

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Background/Purpose: Allopurinol is a first line urate lowering therapy in the management of gout. The observation that allopurinol hypersensitivity was associated with allopurinol dose, renal impairment and diuretics led to the suggestion that lower doses should be used in patients with renal impairment. It is well documented that many patients receiving creatinine clearance (CrCL)-based allopurinol doses fail to achieve target plasma urate. Allopurinol doses above 300mg daily are used rarely despite increasing evidence that doses higher than those based on CrCL may be safe and effective. With the introduction of new urate lowering therapies the ability to predict the dose at which a particular patient may achieve target urate may influence a clinician's decision on first line therapy.

The aims of this study were to explore factors that predict allopurinol response in patients with gout, to determine the probability of achieving the recommended plasma urate of ≤0.36mmol/L using CrCL-based doses and to predict the maintenance doses required to achieve the target plasma urate.

Methods : Data were sourced from five studies. A population analysis was conducted using NONMEM® v.7.2. Covariates included renal function, body size, sex, ethnicity, concomitant drugs, and renal transporter genotype. The final PKPD model was implemented in MATLAB (2014a). Stochastic simulations were performed under two scenarios; 1) using doses recommended by CrCL-based dosing recommendations, and 2) using daily doses sufficient to achieve target plasma urate concentrations in >75% of simulates. The model was evaluated against previously published data.

Results: A total of 1135 oxypurinol and 1178 urate plasma concentrations from 134 patients were available. A one compartment PK model with first order absorption and elimination was the best fit to the oxypurinol data. A simple direct effects (Emax) model provided an adequate description of the steady-state plasma urate data. Renal function, diuretic use, and body size were found to be significant covariates. Dose requirements were found to increase approximately 2-fold over a 3-fold range of weights and were 1.25-2 times higher in those taking diuretics. Renal function had only a relatively minor impact on allopurinol dosing. Table 1 shows the probability of achieving urate with CrCL based dose for a 70kg patient not taking diuretics and the dose predicted to achieve target urate. The model performed well when evaluated against external urate data.

Conclusion: This population PKPD model for allopurinol supports the contention that patients receiving CrCL-based allopurinol doses frequently fail to achieve target urate. The model provides a means of predicting allopurinol maintenance dose requirements for individual patients but needs to be validated against prospective data.

Table 1: Model predictions for percentage of patients achieving target urate on CrCL based doses and dose required to achieve target

CrCL ml/min	Hande allopurinol dose	% patients likely to achieve target urate based on model	CrCL	Predicted dose to achieve target urate in a 70kg patient no diuretics
0	100mg every 3 days	0		
10	100mg every 2 days	1		
20	100mg/d	12	>15-30	350mg/d
40	150mg/d	29		
60	200mg/d	44	>50-70	350mg/d
80	250mg/d	56		
100	300mg/d	64	>90	400mg/d
120	350mg/d	72		

Disclosure: D. Wright, None; **S. Duffull**, None; **T. R. Merriman**, None; **N. Dalbeth**, None; **M. Barclay**, None; **L. K. Stamp**, None.

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Abstract Number: 2349

The Efficacy and Tolerability of Febuxostat in Hyperuricemic Patients with Severe Renal Impairment

Ji Seon Oh and Seungwon Choi, Division of Rheumatology, Department of Internal Medicine, University of Ulsan College of

Medicine, Ulsan University Hospital, Ulsan, South Korea
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Background/Purpose: Febuxostat has shown to be effective and safe in the treatment of hyperuricemia in patients with mild-to-moderate renal impairment without dose adjustment. However, there are insufficient data for the use of febuxostat in patients with severe renal impairment or hemodialysis. We investigated the efficacy and tolerability of febuxostat in patients with hyperuricemia and severe renal impairment (chronic kidney disease, stage 4 or 5).

Methods: We retrospectively reviewed clinical and laboratory data from a tertiary hospital from 2012 to 2015. We included 57 patients with severe renal impairment (estimated glomerular filtration rate [eGFR] < 30 mL/min/1.73m^2) who had been treated with febuxostat. Data regarding serum uric acid and serum creatinine level before and after the start of febuxostat treatment, and clinical information including adverse events were obtained from medical records. The paired t-test was used to determine statistical significance of the effect of febuxostat on serum uric acid levels.

Results: Among 57 patients, there were 46 men (81%) and 11 women (19%). Mean age was 57.8±13.7 years (range, 28-79). Before the start of febuxostat treatment, mean serum uric acid level was 9.2±1.9 mg/dL (range, 5.6-16.4), and mean creatinine level was 4.2±2.4 mg/dL (mean eGFR 18.6±7.6 mL/min/1.73m^2; range, 3.0-29.7). Mean daily doses of febuxostat and median duration of follow-up under treatment were 54±23 mg (range, 40-160) and 15 months (range, 2-38 months), respectively. Twenty-one patients (36.8%) were on dialysis. Under treatment with febuxostat, serum uric acid levels were significanly reduced at 3 months: Mean reduction of serum uric acid levels was 5.64±3.09 mg/dL ($p<0.001$) in patients on dialysis and 3.81±2.24 ($p<0.001$) in patients not on dialysis; Eighteen of 20 patients (90%) on dialysis and 26 of 36 patients (72.2%) not on dialysis achieved a target serum uric acid level ≤6.0mg/dL. In one patient, febuxostat was stopped because of skin itching and generalized edema. In most patients (98%), febuxostat was well tolerated without withdrawals due to side effects.

Conclusion: This study showed that febuxostat was efficacious and was well tolerated in hyperuricemic patients with severe renal impairment undergoing or not undergoing dialysis.

Disclosure: J. S. Oh, None; **S. Choi**, None.

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Abstract Number: 2350

Efficacy and Safety of Febuxostat in 55 Gouty Patients with Stage 4/5 Chronic Kidney Disease: Results from a Retrospective Multicenter Study

Pierre-Antoine Juge[1], Marie-Elise Truchetet[2], Sébastien Ottaviani[3], Cécile Vigneau[4], Clotilde Loustau[5], Divi Cornec[6], Tristan Pascart[7], Emilie Cornec-Legall[8], Marine Florien[9], Florian Bailly[10], Thierry Schaeverbeke[5], Alain Saraux[11], Philippe Dieude[12], Rene-Marc Flipo[13], Georges Jean-Baptiste[14], Pascal Richette[15], Frederic Lioté[16], Thomas Bardin[17,18], Gerard H. Chales[19] and Hang-Korng Ea[20], [1]Rheumatology Department, Centre de Viggo Petersen, Lariboisère Hospital, Paris, France, [2]Rheumatology, Pellegrin Hospital, Bordeaux, France, [3]Hopital Lariboisière, Paris, France, [4]Nephrology, Rennes University Hospital, Rennes, France, [5]Rheumatology Department, Bordeaux Hospital, Bordeaux, France, [6]Department of rheumatology, Brest Occidentale University, Brest, France, [7]Rheumatology, Saint-Philibert Hospital, Lille, France, [8]Nephrology Departement, Brest Hospital, Brest, France, [9]Rheumatology Department, Pierre-Zobda-Quitman La Meynard, Fort-de-France, France, [10]Rheumatology Department, La Pitié-Salpétrière Hospital, Paris, France, [11]Rheumatology Department, CHU de la Cavale Blanche, Brest Cedex, France, [12]Rheumatology, Bichat Claude-bernard, Universitary Hospital, APHP, Paris, France, [13]Rheumatology, University Hospital, Lille, France, [14]Rheumatology and Internal Medicine, Zobda Quitman Hospital, Fort-de-France, Martinique,

[15]Université Paris Diderot, UFR médicale, Paris, France; APHP Hôpital Lariboisière, Fédération de Rhumatologie and Inserm U1132, Hôpital Lariboisière, Paris, France, [16]Rheumatology Department; Inserm UMR-S606; Paris-Diderot University, hôpital Lariboisiere, Paris, France, [17]Service de Rhumatologie, Hôpital Lariboisière, Paris, France, [18]Rhumatology Departement, Hôpital Lariboisière, Paris, France, [19]CHU RENNES, Rennes, France, [20]INSERM UMR1132, Paris Diderot University, Paris, France

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Background/Purpose: Although allopurinol is the first urate lowering therapy (ULT), its limited dosage in gouty patients with stage 4 or 5 chronic kidney disease (CKD 4/5) prevents to achieve serum urate level (sUA) target (< 6.0 mg/dL). Febuxostat is a nonpurine xanthine oxidase inhibitor with predominant hepatic metabolism and can be used without dosage adjustment in gouty patients with CKD. However, its safety and efficacy in advanced CKD have been reported in only one study and no data are available yet in patients with kidney transplantation (1).

Methods: In this retrospective multicenter study, clinical records of all gouty patients with estimated glomerular filtration rate (eGFR) ≤ 30 ml/min/1.73 m2 (MDRD formula) at febuxostat initiation and at least after 3 months follow-up period were selected. Items to be collected (demographic data, co-morbidities, renal disease, gout history and former treatments, increasing serum urate drugs, laboratory data and any adverse effects (AEs) were approved by all participant centers. Variables to be analyzed were: sUA level at initiation and last available sUA levels; variation of eGFR; percentage of patients who achieved sUA levels < 6.0 mg/dL and 5.0 mg/dL; flares under ULT and all AEs with specific attention to cardiovascular (CV) events.

Results: Fifty-five gouty patients (mean age 70.7 ± 11.1, 47 men) from 7 French rheumatology departments were included. 26 patients (47.3%) suffered from vascular CKD and 13 patients (23.6%) had received renal transplant. Mean duration of gout was 7 years. 15 patients (27.2%) had tophi and 23 (41.8%) gout arthropathies. Diuretics were used in 47 patients (85.5%). Cardiac dysfunction was present in 9 patients (16.4%). 54 patients had hypertension, 15 (27.3%) diabetes mellitus, 40 (72.3%) dyslipidemia, 19 (34.5%) CV diseases, 20 (36.3%) had past history of vascular events (stroke, myocardial infarction). Mean sUA level and eGFR at febuxostat initiation were 8.8 ± 2.7 mg/dL and 21.3 ± 6.5 ml/min (6-30 ml/min), respectively. Febuxostat initiation dosage was 80 mg daily for 36 patients (65.5%), 80 mg every 2 days for 12 patients (21.8%) and 120 mg daily for 3 patients (5.5%). At last visit (mean follow-up 72 weeks (12-260)) mean sUA level was 4.8 ± 2.2 mg/dL; 39 patients (65.5%) achieved sUA target < 6.0 mg/dL and 34 (61.8%) had sUA ≤ 50 mg/L. Renal function improved (defined by > 10% increase of eGFR from baseline) in 13 patients (23.6%) (mean eGFR change: + 8.4 ml/min), was unchanged in 16 (29.1%) and worsened (defined by > 10 decrease of eGFR from baseline) in 21 (38.2%) (mean sGFR change: -6.3 ml/min). 33 patients experienced flares under febuxostat treatment. AE was observed in one patient who had suffered from limb edema. No CV event was reported during febuxostat exposure.

Conclusion: Febuxostat appears efficient in gouty patients with stage 4/5 CKD or renal transplants. However, safety data is not yet validated with respect to renal function. Further studies with larger samples are warranted for assessing this issue.

1. Shibagaki et al. Safety, efficacy and renal effect of febuxostat in patients with moderate-to-severe kidney dysfunction. Hypertension Res 2014; 37; 919-25

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/efficacy-and-safety-of-febuxostat-in-55-gouty-patients-with-stage-45-chronic-kidney-disease-results-from-a-retrospective-multicenter-study

Abstract Number: 2351

A Study to Evaluate the Pharmacodynamics, Pharmacokinetics and Safety of Arhalofenate in Combination with Febuxostat When Treating Hyperuricemia Associated with Gout

Alexandra Steinberg, Yun-Jung Choi, Robert Martin, Charles McWherter and **Pol Boudes**, Cymabay Therapeutics, Newark, CA
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Background/Purpose: Arhalofenate is a novel Urate-Lowering Anti-Flare Therapy (ULAFT) for the treatment of gout. It lowers serum uric acid (sUA) by blocking URAT1, a tubular UA transporter, and reduces gout flares by blocking the local release of IL-1β. The study evaluated the serum uric acid (sUA) lowering effect of arhalofenate when combined with febuxostat, the potential for drug-drug interaction and safety.

Methods: This was a single-center, open label Phase 2 (NCT02252835) with two cohorts of volunteer gout subjects (n = 16 each). Subjects were treatment naïve or willing to discontinue urate lowering therapy. Dosing was once daily oral including flare prophylaxis with colchicine. One cohort received arhalofenate 600 mg for 2 weeks followed by sequential one-week co-administration of febuxostat 80 mg and 40 mg. During the final 2 weeks, febuxostat 40 mg alone was continued. The second cohort received arhalofenate 800 mg for 2 weeks, followed by sequential one-week co-administration of febuxostat 40 mg and 80 mg. During the final 2 weeks, febuxostat 80 mg alone was continued. sUA and oxypurines (xanthine, hypoxanthine, guanine) were assessed at multiple time-points. Arhalofenate (800 mg) and febuxostat (80 mg) pharmaco-kinetics were determined in the second cohort.

Results:

Thirty-two subjects were enrolled. Baseline mean sUA were 9.4 and 9.2 mg/dL, respectively. The largest decrease in sUA (63%) was seen in the arhalofenate 800 mg plus febuxostat 80 mg combination. With this treatment, 100% of subjects achieved a goal of < 6 mg/dL, 93% < 5 mg/dL and 79% < 4 mg/dL.

The mean ± SD arhalofenate acid $AUC_{(0\ \tau)}$ was 2,960 ± 730 and 3,190 ± 871 μg·h/mL in the absence and presence of febuxostat, respectively. The ratio of $AUC_{(0\ \tau)}$geometric means of the combination to arhalofenate alone was 108% (90% CI 89-131%).

The mean ± SD febuxostat $AUC_{(0\ \tau)}$ was 11,100 ± 2,940 and 9,590 ± 2,270 ng·h/mL in the absence and presence of arhalofenate, respectively. The ratio of $AUC_{(0\ \tau)}$geometric means of the combination to febuxostat alone was 87% (90% CI 74-103%).

As expected from its mechanism of action, febuxostat alone dramatically increased the plasma levels of oxypurines. These levels were unchanged, or even slightly increased, by the co-administration of arhalofenate.

Arhalofenate, either alone or in combination, was well tolerated and appeared safe. No subjects had >1.5X elevation in serum creatinine or any value above normal.

Conclusion: The combination of arhalofenate with febuxostat was well tolerated, appeared safe and was more efficacious in decreasing sUA than both drugs alone. Arhalofenate decreased the AUC of febuxostat when compared with febuxostat alone, however this was not clinically relevant as this was not associated with a decrease of oxypurines levels. Arhalofenate in combination with febuxostat is now in phase 3 to reduce sUA and prevent gout flares.

Disclosure: A. Steinberg, Cymabay Therapeutics, 3,Cymabay Therapeutics, 1; **Y. J. Choi**, Cymabay Therapeutics, 3,Cymabay Therapeutics, 1; **R. Martin**, Cymabay Therapeutics, 3,Cymabay Therapeutics, 1; **C. McWherter**, Cymabay Therapeutics, 3,Cymabay Therapeutics, 1; **P. Boudes**, Cymabay Therapeutics, 3,Cymabay Therapeutics, 1.

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Abstract Number: 2352

Efficacy and Safety in Patients with Tophaceous Gout Receiving Lesinurad and Febuxostat Combination Therapy: Interim Analysis of an Extension Study

Nicola Dalbeth[1], Graeme Jones[2], Robert Terkeltaub[3], Dinesh Khanna[4], Jeff Kopicko[5], Scott Adler[6], Nihar Bhakta[5], Maple Fung[5], Chris Storgard[5], Scott Baumgartner[5] and Fernando Perez-Ruiz[7], [1]Department of Medicine, University of Auckland, Auckland, New Zealand, [2]Musculoskeletal Unit, Menzies Institute for Medical Research, University of Tasmania, Hobart, Australia, [3]Medicine-Rheumatology, University of California, San Diego, La Jolla, CA, [4]Div of Rheumatology, University of Michigan, Ann Arbor, MI, [5]Ardea Biosciences, Inc., San Diego, CA, [6]AstraZeneca Pharmaceuticals, Wilmington, DE, [7]Servicio de Reumatologia, Hospital Universitario Cruces, Baracaldo, Spain

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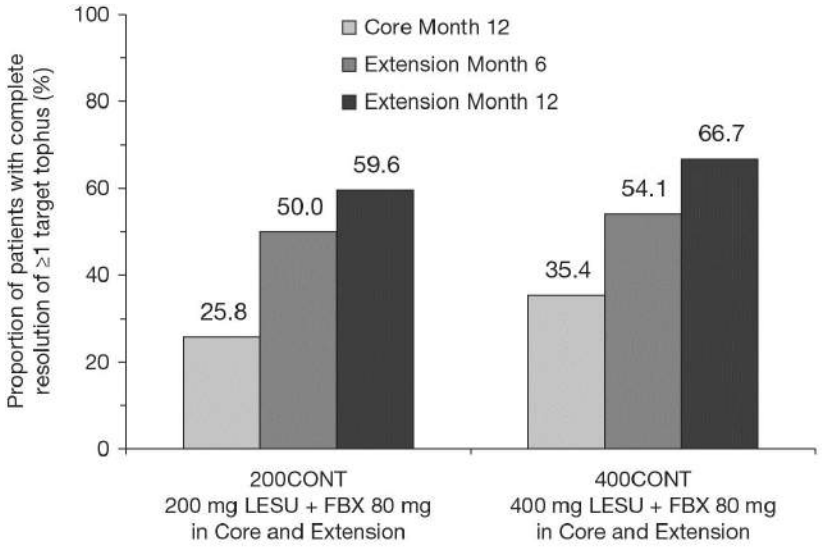
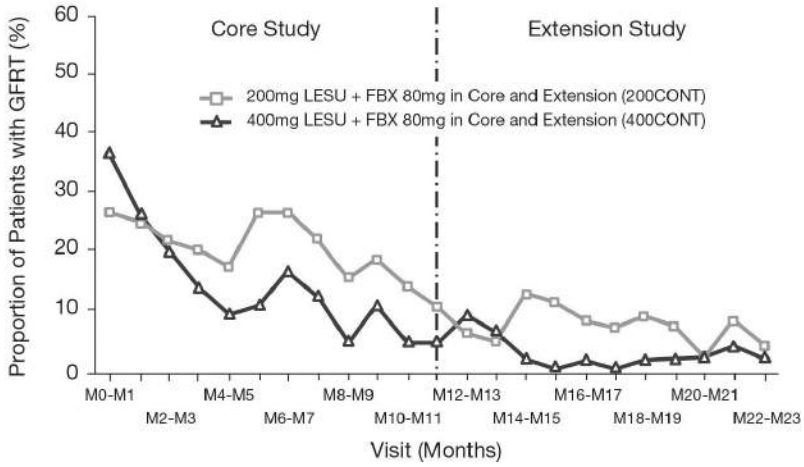
Background/Purpose: In the randomized, double-blind, placebo-controlled, Phase III CRYSTAL trial, more patients taking lesinurad 200 mg (LESU200) or 400 mg (LESU400), in combination with febuxostat (FBX) 80 mg, achieved serum uric acid (sUA) <5.0mg/dL at 6 months versus FBX + placebo (PBO). Patients completing 12 months on study could enroll in an extension study (NCT01808144). The objective was to examine efficacy and safety in patients taking lesinurad combination therapy for up to 2 years.

Methods: Patients on PBO+FBX in the core study were randomized to LESU200+FBX (200CROSS) or LESU400+FBX (400CROSS). Patients randomized to LESU200+FBX and LESU400+FBX in the core study were continued on their therapy (200CONT, 400CONT). Primary endpoint was the proportion of patients experiencing complete resolution (CR) of ≥1 target tophus (measurable tophus on hands/wrists and/or feet/ankles 5–20mm in longest diameter, using Vernier calipers) during core and extension studies by extension Month 12. The sum of areas for all target tophi, proportion of patients achieving sUA <5.0mg/dL, and proportion of patients experiencing gout flares requiring treatment (GFRT) were secondary endpoints.

Results: Of 235 patients completing the core study, 196 enrolled in the extension: 200CONT (n=64), 200CROSS (n=33), 400CONT (n=65), and 400CROSS (n=34). For those continuing core treatment (200CONT, 400CONT), 59.6% and 66.7% of patients had CR of ≥1 target tophus (Figure), with 68.3% and 72.4% reductions in the sum of areas for all target tophi, respectively, after 2 years. GFRT during extension occurred in 32.8% and 13.8% of patients, with few patients having GFRT during the second year (Figure). Target sUA levels <5.0mg/dL at Extension Month 12 were achieved in 77.1% and 88.5% of patients. For crossover groups (200CROSS, 400CROSS respectively), 43.5% and 50.0% of patients had CR of ≥1 target tophus, with 64.1% and 44.1% reductions in target tophi area after 1 year of combination therapy. GFRT rates during extension were 37.5% and 38.2%, with 79.2% and 71.4% of patients achieving target sUA <5.0 mg/dL. Treatment-emergent adverse events (TEAEs) with extended exposure to lesinurad were generally comparable between groups. The most common TEAEs for the CONT groups were serum creatinine increase (10.9%) and bronchitis (7.0%); for the CROSS groups, nasopharyngitis (13.4%) and headache (7.5%) were most common, with serum creatinine increase occurring in 6.0% of patients.

Conclusion: Patients continuing on lesinurad + FBX therapy over 2 years continued to be at sUA target, with no attenuation of sUA effect. Patients exhibited continued increase in complete resolution of tophi, additional tophi area reduction, and reduction of GFRT over the second year on study. AEs in the extension study were consistent with those observed in the core study.





Disclosure: N. Dalbeth, AstraZeneca, 2,Fonterra, 2,Novartis Pharmaceutical Corporation, 2,Savient, 8,Menarini, 8,Novartis Pharmaceutical Corporation, 8,Teijin, 8,AstraZeneca, 9,Fonterra, 9,Pfizer Inc, 9,Takeda, 9,Metabolex, 9; **G. Jones**, Abbvie, 2,Ardea Biosciences, 2,Novartis Pharmaceutical Corporation, 2,Auxilium, 2,Pfizer Inc, 9,Roche Pharmaceuticals, 9,Hospira, 9,Janssen Pharmaceutica Product, L.P., 9,UCB, 8,Roche Pharmaceuticals, 8,Janssen Pharmaceutica Product, L.P., 8,Abbvie, 8,Novartis Pharmaceutical Corporation, 8,Mundipharma, 8,Amgen, 8,Bristol-Myers Squibb, 8,Pfizer Inc, 8; **R. Terkeltaub**, ARDEA/Astra-Zeneca, 5; **D. Khanna**, AstraZeneca, 2,AstraZeneca, 5,Takeda, 5; **J. Kopicko**, Ardea/AstraZeneca, 3; **S. Adler**, AstraZeneca, 3; **N. Bhakta**, AstraZeneca, 3; **M. Fung**, AstraZeneca, 3; **C. Storgard**, Ardea/AstraZeneca, 3; **S. Baumgartner**, Ardea/AstraZeneca, 3; **F. Perez-Ruiz**, AstraZeneca, 8,Menarini, 5,AstraZeneca, 9,Menarini, 9,Cimabay, 9.

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Abstract Number: 2353

Lesinurad and Febuxostat Combination Therapy: Analysis of Treatment Based on Patient Baseline Renal Function

Nicola Dalbeth[1], Graeme Jones[2], Robert Terkeltaub[3], Dinesh Khanna[4], Jeff Kopicko[5], Scott Adler[6], Nihar Bhakta[5], Maple Fung[5], Chris Storgard[5], Scott Baumgartner[5] and Fernando Perez-Ruiz[7], [1]Department of Medicine, University of Auckland, Auckland, New Zealand, [2]Musculoskeletal Unit, Menzies Institute for Medical Research, University of Tasmania, Hobart, Australia, [3]Medicine-Rheumatology, University of California, San Diego, La Jolla, CA, [4]Div of Rheumatology, University of Michigan, Ann Arbor, MI, [5]Ardea Biosciences, Inc., San Diego, CA, [6]AstraZeneca Pharmaceuticals, Wilmington, DE, [7]Servicio

de Reumatologia, Hospital Universitario Cruces, Baracaldo, Spain
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Background/Purpose: A randomized, double-blind, placebo-controlled, Phase III clinical trial showed that lesinurad, a selective uric acid reabsorption inhibitor (SURI), in combination with febuxostat 80 mg (FBX) significantly increased the proportion of patients with tophaceous gout who achieved the serum uric acid (sUA) target of <5.0 mg/dL at 6 months compared to FBX alone. Lesinurad was generally well tolerated, with the 200 mg dose having a safety profile comparable to FBX alone, with the exception of a higher incidence in predominately reversible serum creatinine (sCr) elevations. As renal impairment and hyperuricemia frequently coexist, we aimed to analyze treatment with respect to patient baseline renal function.

Methods: Patient data was obtained from the CRYSTAL study (NCT01510769) where patients with estimated creatinine clearance (eCrCl; Cockcroft-Gault formula using ideal body weight) <30 mL/min were excluded. In current analyses, patients were analyzed by renal baseline function using eCrCl groups of <60, <90, and ≥90 mL/min; statistical analyses were unadjusted for multiplicity.

Results: In total, 324 patients were randomized and included in these analyses. Demographic characteristics, including age, gender, race, weight, and BMI, were broadly similar between patient groups stratified by baseline renal function. The proportion of patients achieving sUA target levels of <5.0 mg/dL was greater in the lesinurad 200 mg + FBX group compared with FBX alone at 12 months in those with eCrCL <90 and ≥90 mL/min (P<0.05 for both) (Table). For lesinurad 400 mg + FBX, the proportion of patients achieving <5.0 mg/dL was greater than FBX alone at Month 6 (P<0.05 for <60; P<0.001 for <90 and ≥90) and Month 12 (P<0.05 for <90 and ≥90).No consistent differences in treatment-emergent AE rates were observed based on baseline renal function (Table). sCr elevations occurred at increased rates in the lesinurad groups (particularly the 400 mg dose) versus FBX + placebo, without evident differences according to baseline renal function.

Conclusion: The results of this Phase III study subanalysis indicate that lesinurad in combination with febuxostat is efficacious in all renal function groups. Safety findings were consistent between treatment groups across all renal function categories.

Table: Efficacy and safety endpoints in CRYSTAL: stratification by baseline eCrCl <60, <90, and ≥90 mL/min

Baseline eCrCl	<60 mL/min			<90 mL/min			≥90 mL/min		
	PBO +FBX (n=25)	LESU 200 mg +FBX (n=28)	LESU 400 mg +FBX (n=22)	PBO +FBX (n=25)	LESU 200 mg +FBX (n=28)	LESU 400 mg +FBX (n=22)	PBO +FBX (n=25)	LESU 200 mg +FBX (n=28)	LESU 400 mg +FBX (n=22)
Efficacy endpoint (n, % patients)									
Proportion with sUA <5.0 mg/dL at Month 6 (LOCF)	12/25 (48.0)	19/28 (67.9)	17/22 (77.3)	41/77 (53.2)	41/66 (62.1)	53/67 (79.1)	13/29 (44.8)	25/37 (67.6)	35/39 (89.7)
Proportion with sUA <5.0 mg/dL at Month 12 (LOCF)	14/25 (56.0)	18/28 (64.3)	13/22 (59.1)	38/77 (49.4)	43/66 (65.2)	46/67 (68.7)	13/29 (44.8)	27/37 (73.0)	30/39 (76.9)
Safety endpoint (n, % patients)									
Any Adverse event	21 (84.0)	26 (92.9)	18 (81.8)	57 (73.1)	54 (78.3)	53 (79.1)	22 (71.0)	33 (89.2)	37 (88.1)
sCr elevation ≥1.5x	0	0	1 (4.5)	2 (2.6)	3 (4.3)	8 (11.9)	1 (3.2)	2 (5.4)	3 (7.1)
Unresolved* cases of sCr elevation ≥1.5x as of last study visit	0	0	1	0	0	1	0	1	0
sCr elevation ≥2.0x	0	0	1 (4.5)	0	1 (1.4)	4 (6.0)	0	2 (5.4)	2 (4.8)
Unresolved* cases of sCr elevation ≥2.0x as of last study visit	0	0	1	0	0	1	0	1	0

*sCr resolution: sCr value returned to ≤1.2x baseline

Disclosure: N. Dalbeth, AstraZeneca, 2,Fonterra, 2,Novartis Pharmaceutical Corporation, 2,Savient, 8,Menarini, 8,Novartis Pharmaceutical Corporation, 8,Takeda, 8,AstraZeneca, 9,Fonterra, 9,Pfizer Inc, 9,Takeda, 9,Metabolex, 9; **G. Jones**, Abbvie, 2,Ardea BioSciences, 2,Novartis Pharmaceutical Corporation, 2,Auxilium, 2,Pfizer Inc, 9,Roche Pharmaceuticals, 9,Hospira, 9,Janssen Pharmaceutica Product, L.P., 9,UCB, 8,Roche Pharmaceuticals, 8,Janssen Pharmaceutica Product, L.P., 8,Abbvie, 8,Novartis Pharmaceutical Corporation, 8,Mundipharma, 8,Amgen, 8,Bristol-Myers Squibb, 8,Pfizer Inc, 8; **R. Terkeltaub**, ARDEA/Astra-Zeneca, 5; **D. Khanna**, AstraZeneca, 2,AstraZeneca, 5,Takeda, 5; **J. Kopicko**, Ardea Biosciences, 3; **S. Adler**, AstraZeneca, 3; **N. Bhakta**, Ardea Biosciences, 3; **M. Fung**, Ardea Biosciences, 3; **C. Storgard**, Ardea Biosciences, 3; **S. Baumgartner**, Ardea Biosciences, 3; **F. Perez-Ruiz**, AstraZeneca, 8,Menarini, 5,AstraZeneca, 9,Menarini, 9,Cimabay, 9.

Abstract Number: 2354

The Safety and Efficacy of Lower Serum Urate Levels: A Pooled Analysis of Gout Subjects Receiving Lesinurad and Xanthine Oxidase Inhibitors

Robert Terkeltaub[1], Fernando Perez-Ruiz[2,3,4], Jeff Kopicko[5], Maple Fung[5], Scott Adler[6], Chris Storgard[7], Scott Baumgartner[5] and Nicola Dalbeth[8], [1]Medicine-Rheumatology, University of California, San Diego, La Jolla, CA, [2]Rheumatology Division, Hospital Universitario Cruces, Barakaldo, Spain, [3]BioCruces Health Research Institute, Baracaldo, Spain, [4]Servicio de Reumatologia, Hospital De Cruces, Baracaldo, Spain, [5]Ardea Biosciences, Inc., San Diego, CA, [6]AstraZeneca Pharmaceuticals, Wilmington, DE, [7]4939 Directors Place, Ardea Biosciences, Inc., San Diego, CA, [8]Department of Medicine, University of Auckland, Auckland, New Zealand

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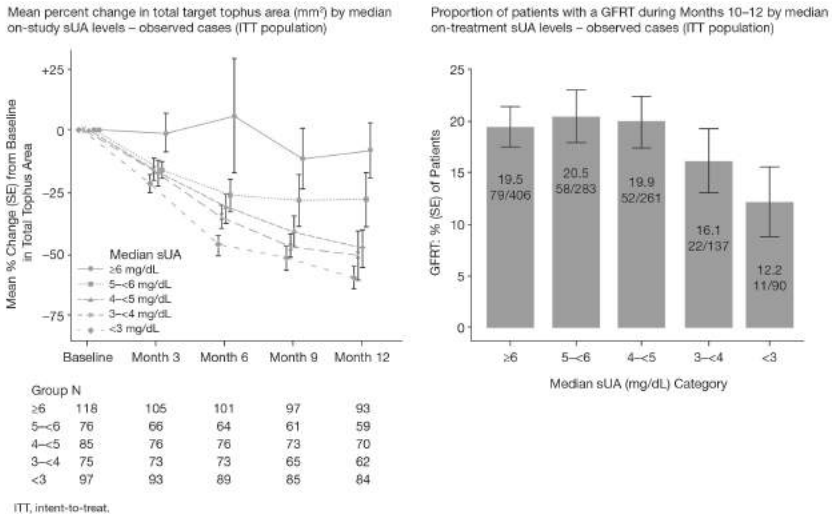
Background/Purpose: Previous studies have shown that long-term urate-lowering therapy (ULT) is required for improvements in gout flare frequency and tophi reduction, and that lower serum uric acid (sUA) levels may result in greater benefit. However, optimal sUA levels to jointly achieve these outcomes within a year using single or combination oral therapies are uncertain, as they come mostly from observational studies. Lesinurad in combination with a xanthine oxidase inhibitor (XOI) is highly effective in reducing and sustaining sUA below target levels in Phase III studies. The current analysis explored the relation between extent of reduction in sUA level and efficacy and safety endpoints in these Phase III studies.

Methods: Patient data were combined from 3 Phase III clinical studies on the efficacy and safety of lesinurad, a selective uric acid reabsorption inhibitor (SURI), in combination with an XOI (allopurinol: CLEAR 1 [NCT01510158], CLEAR 2 [NCT01493531]), or febuxostat: CRYSTAL [NCT01510769]). For the analyses, patients irrespective of treatment assignment were categorized by their on-study median sUA level, which used all scheduled post-baseline sUAs for each individual. Efficacy endpoints included clinical outcomes for ULT: tophus size reduction and proportions of patients experiencing gout flares requiring treatment (GFRT). Safety endpoints included treatment-emergent adverse events (TEAEs).

Results: In total, 1537 patients were eligible for efficacy analysis, including 474 patients with ≥1 target tophi at baseline. Patients with the lowest on-study median sUA levels achieved the greatest reduction in tophus area at Month 12 and were least likely to have GFRT during the last quarter of the study (Figure). GFRTs occurred in 11/90 (12.2%) of patients in the <3 mg/dL sUA subgroup and in 137/689 (19.9%) of patients in the ≥5 mg/dL subgroup (Figure). TEAEs occurred in 82/104 (78.8%) of patients in the <3 mg/dL sUA subgroup and in 671/886 (75.7%) of patients in the ≥5 mg/dL subgroup.

Conclusion: Based on a pooled analysis of 3 Phase III clinical studies, patients with lower median on-study sUA experienced greater reductions in tophus area, as well as a lower likelihood of having a gout flare requiring treatment. A similar safety profile was noted irrespective of the median sUA levels.



Disclosure: R. Terkeltaub, ARDEA/AstraZeneca, AstraZeneca, Takeda, Relburn, and REVIVE, 5; **F. Perez-Ruiz**, AstraZeneca, 8,Menarini, 5,AstraZeneca, 9,Menarini, 9,Cimabay, 9; **J. Kopicko**, Ardea Biosciences, 3; **M. Fung**, Ardea Biosciences, 3; **S. Adler**, AstraZeneca, 3; **C. Storgard**, Ardea Biosciences, 3; **S. Baumgartner**, Ardea Biosciences, 3; **N. Dalbeth**, AstraZeneca, 2,Fonterra, 2,Novartis Pharmaceutical Corporation, 2,Savient, 8,Menarini, 8,Novartis Pharmaceutical Corporation, 8,Teijin, 8,AstraZeneca, 9,Fonterra, 9,Pfizer Inc, 9,Takeda, 9,Metabolex, 9.

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Abstract Number: 2355

Effects of the Dietary Approaches to Stop Hypertension (DASH) Diet on Serum Uric Acid Levels: A Randomized Controlled Trial

Na Lu[1], Yuqing Zhang[2], Sharan K. Rai[3], Gary C. Curhan[4] and Hyon K. Choi[5], [1]Division of Rheumatology, Allergy and Immunology, Massachusetts General Hospital, Harvard Medical School, Boston, MA, [2]BUSM, Boston, MA, [3]Experimental Medicine, University of British Columbia, Vancouver, BC, Canada, [4]Renal Division, Brigham and Women's Hospital, Boston, MA, [5]Rheumatology, Allergy and Immunology, Massachusetts General Hospital, Harvard Medical School, Boston, MA
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Background/Purpose: There is a remarkable, increasing disease burden of gout and its associated cardiovascular-metabolic comorbidities (e.g., hypertension in 74% of cases in the US), underscoring an urgent need for holistic strategies to effectively address these conditions together. The DASH diet, which emphasizes fruits, vegetables, low-fat dairy foods, and reduced saturated and total fat, substantially reduces blood pressure and is also recommended in dietary guidelines to prevent cardiovascular disease (CVD). This approach could also lower SUA levels by its anti-hypertension effects and favorable urate-lowering components, such as low-fat dairy foods. Thus, the DASH diet holds the remarkable promise of "killing two birds with one stone" in the prevention of gout by improving both SUA outcomes and its associated CVD complications. We investigated the SUA response to the DASH diet as compared to a control diet over a 6 month period.

Methods: The DASH trial population consisted of adults with stage 1 hypertension (not on any antihypertensive agents) who received either the DASH diet, a fruit/vegetable-rich diet, or a control diet (reflective of the average American diet) over the span of 8 weeks (NEJM 1997). Sodium intake and body weight were maintained at constant levels to isolate the diet's effect. We

measured SUA levels at baseline and 8 weeks among 327 participants with complete datasets and analyzed the SUA level response. Since our central objective was to examine the potential utility of the DASH diet in the prevention of gout, our analyses had an a priori focus on high risk sub-groups for gout at baseline (i.e., those with hyperuricemia, those who were overweight/obese, and men).

Results: The mean age was 44 years and the mean BMI was 28.1 kg/m^2. Most participants (53%) were men. The overall dropout rate was <4%, and the overall rate of adherence to the diets was > 93% during the 8-week study period. The mean baseline SUA level was 5.70 mg/dL, and the DASH diet reduced SUA levels by 0.24 mg/dL more than the control diet (p = 0.01). Among the 75 subjects with hyperuricemia (men: SUA > 7mg/dL, women: SUA > 6mg/dL), the DASH diet reduced SUA levels by 0.59 mg/dL more than the control diet (p=0.005) and 0.46 mg/dL more than the fruit/vegetable group (p=0.028). Additional benefits included significant improvements in systolic and diastolic blood pressure (**Table**). For example, among 75 subjects with hyperuricemia and hypertension, the DASH diet reduced systolic and diastolic pressure by 5.0 and 3.3 mm Hg more, respectively, than the control diet (P=0.008 and P=0.012 for each).

Conclusion: Our findings suggest that the DASH diet can reduce SUA and blood pressure in high risk groups for gout. This diet offers an additional nutritional approach to preventing (and potentially treating) hyperuricemia and gout, as well as hypertension (a comorbidity present in 74% of gout patients).

Table. Comparison of Mean Changes in SUA and BP in High Risk Subgroups and All Subjects

Category	SUA Change in DASH Group Minus Change in Control Group	SBP Change in DASH Group Minus Change in Control Group	DBP Change in DASH Group Minus Change in Control Group	SUA Change in Fruit/Vegetable Group Minus Change in Control Group
Hyperuricemia (n=75)	– 0.59 (–0.99 to – 0.19)	– 5.0 (–8.6 to –1.3)	– 3.3 (–5.9 to –0.7)	– 0.13 (–0.51 to 0.25)
Overweight/Obese (n= 246)	– 0.26 (–0.47 to – 0.05)	– 5.7 (–7.8 to –3.7)	-2.9 (–4.3 to –1.4)	–0.19 (–0.39 to –0.00)
Men (n=174)	– 0.35 (–0.66 to – 0.04)	– 4.9 (–7.4 to –2.4)	– 2.7 (–4.4 to –0.9)	– 0.20 (–0.48 to – 0.08)
All Subjects (n=327)	– 0.24 (–0.43 to – 0.06)	– 5.9 (–7.7 to –4.0)	– 2.6 (–3.8 to –1.3)	– 0.20 (–0.37 to – 0.03)

SUA = serum uric acid; BP = blood pressure; SBP = systolic blood pressure; DBP = diastolic blood pressure

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Abstract Number: 2356

Major Cardiovascular Events in Gout Patients with Cardiovascular Disease or Heart Failure and Chronic Kidney Disease Initiating on Allopurinol or Febuxostat (Uloric)

JoAnne Foody[1], Robin Turpin[2], Beni Tidwell[3] and Kathy Schulman[4], [1]Brigham and Women's Hospital, Harvard Medical School, Boston, MA, [2]Medical Affairs, Takeda Pharmaceuticals International, Deerfield, IL, [3]ORS, Shrewsbury, MA, [4]Outcomes Research Solutions, Inc., Waltham, MA

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Background/Purpose:

Xanthine oxidase inhibitors (XOI) reduce both urate levels and oxidative stress in the vasculature, both of which are cardiovascular disease (CVD) risk factors. However, the impact of an individual XOI agent on major cardiovascular events (MCE) may vary based on the agent's efficacy, dosing constraints and mitigating polychronic disease.

Methods:

Gout patients (ICD-9-CM 274.xx), aged >18, with a baseline (12 months) diagnosis of stage 3/4 chronic kidney disease (CKD) and CVD (coronary artery disease (CAD), cerebrovascular disease (CBV) and peripheral vascular disease (PVD)) or heart failure were selected from the MarketScan® databases (January 2009-June 2013) upon initiating urate lowering therapy (ULT) with either allopurinol (ALO) or febuxostat (FBX). Patients were followed until disenrollment, discontinuation of the qualifying ULT or use of the alternate study agent. MCE included myocardial infarction, stroke, transient ischemic attack, non-traumatic, lower extremity (LE) amputation or coronary, cerebrovascular or LE revascularization. MCE incidence was measured per 1000 person-years (PY). Cox proportional hazards models assessed MCE risk as a function of age, gender, region, payer, CKD stage, exposure to other anti-gout medications (NSAID, colchicine, steroids, probenecid), recent CVD hospitalization and a history of CAD, CBV, PVD, heart failure (HF), diabetes or hyperlipidemia.

Results:

A total of 2,426 patients (2056 ALO, 370 FBX) met eligibility criteria (63% male; mean age 73±11). Two thirds of patients had a history of CAD, 18% CBV and 23% PVD. There were no significant differences in CVD type by cohort. Half of patients also had HF and 73% had stage 3 CKD at the time of initiation. A total of 162 MCE occurred during follow-up in 3.8% and 7.2% of FBX and ALO cohorts respectively. A total of 80 patients (3.3%) had a CAD specific MCE, 51 (2.1%) a PVD specific event and 38 (1.6%) a CBV specific event. The MCE rate per 1000 PY (95% CI) in the FBX cohort was 51.8 (28-87) as compared to 99.3 (84-117) in the ALO cohort.

Cox model results suggest significantly increased MCE risk (any MCE) among patients with baseline PVD (HR 2.7; 95% CI 1.9 – 3.7, $p<0.0001$) and baseline CVD/HF hospitalization (HR 1.7; 95% CI 1.2 – 2.5, $p=0.0023$). Model results suggest significantly decreased MCE risk amongst patients initiating on FBX (HR 0.5; 95% CI 0.3 – 0.9, $p=0.02$), with baseline history of another circulatory disorder (HR 0.5; 95% CI 0.3 – 0.85, $p=0.007$) and those receiving other baseline anti-gout medications (HR 0.7; 95% CI 0.5 – 0.998, $p=0.049$). The hazard ratio (95% CI) associated with membership in the FBX cohort on PVD specific outcomes was 0.2 (0.05 – 0.8, $p=0.026$), on CAD specific MCE was 0.6 (0.3 – 1.3, $p=0.20$) and on CBV specific MCE was 0.9 (0.4 – 2.4, $p=0.88$).

Conclusion:

Patients with moderate to severe CKD and CVD/HF initiating on FBX had a significantly lower rate of MCE than patients initiating on ALO. This may be due to the direct effects of lower sUA or the effect of reduced oxidative stress and other pleiotropic effects on the endothelium. It is unclear if this is due to channeling, greater clinical effectiveness on the part of FBX or to ALP under-dosing in renally impaired patients.

Disclosure: J. Foody, None; **R. Turpin**, Takeda Pharmaceuticals, USA, 1,Takeda Pharmaceuticals, USA, 3; **B. Tidwell**, Takeda Pharmaceuticals, USA, 5; **K. Schulman**, Takeda Pharmaceuticals, USA, 5.

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Abstract Number: 2357

Xanthine Oxidase Inhibitors for the Prevention of Cardiovascular Events: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

Markus Bredemeier[1], Matheus Augusto Eisenreich[1], Lediane Moreira Lopes[1], André Luis Bittencourt Morsch[2], Fernando da Silva Stein[2], Rui d'Avila[2] and Guilherme Gomes Dias Campos[1], [1]Rheumatology, Hospital Nossa Senhora da Conceição - Grupo Hospital Conceição, Porto Alegre, Brazil, [2]Internal Medicine, Hospital Nossa Senhora da Conceição - Grupo Hospital Conceição, Porto Alegre, Brazil

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Session Time: 9:00AM-11:00AM

Background/Purpose: There is evidence suggesting that high levels of uric acid represent an independent cardiovascular risk factor and that the use of xanthine oxidase inhibitors (XOI) may reduce the risk of major adverse cardiovascular events (MACE) (1). To date, this evidence is based mainly on observational studies (2), which are frequently subject to selection and confounding bias. Our objective in this systematic review and meta-analysis is to compare the incidence of MACE and mortality in patients enrolled in randomized controlled trials (RCTs) comparing XOI with placebo or no treatment.

Methods: A systematic review of the literature searching for RCTs was held on September 9, 2014 using PubMed, EMBASE, Cochrane Library, Web of Science, and Lilacs databases (from their inception), and hand search. The study was conducted and reported in accordance with the recommendations of the PRISMA statement (3), and the protocol was registered in PROSPERO (CRD42015016073). All RCTs comparing XOIs with placebo (or no treatment) lasting four weeks or more were eligible, independent of the presence of comorbidities or outcomes of interest in each particular study. Studies including individuals under the age of 18, as well as treatment or follow-up lasting less than 4 weeks, were excluded from the meta-analysis. The primary outcomes were the incidence of MACE (cardiovascular death, non-fatal myocardial infarction, unstable angina requiring urgent revascularization, or non-fatal stroke) and mortality; total cardiovascular events (TCE), serious adverse events (SAE), and skin rash served as secondary outcomes. Statistical analysis was made using the REVMAN 5.2 software, and associations were analyzed using the Peto or Mantel-Haenszel odds ratios (OR), depending on the frequency of events. A subgroup analysis was performed including only studies in which subjects were at high-risk for cardiovascular events.

Results: In Total, 61 RCTs including approximately 5500 individuals were considered eligible for the meta-analysis. The use of XOI was not significantly associated with the risk of MACE (OR=1.24, 95% CI 0.54 to 2.85, P = 0.61), death (0.93, 0.49 to 1.75, P = 0.82), total cardiovascular events (0.85, 0.61 to 1.18, P=0.33), and SAE (0.98, 0.74 to 1.30, P=0.90). The risk of skin rash was higher in the XOI group (1.89, 1.16 to 3.08, P = 0.01). In a subgroup analysis performed in studies including mainly individuals with high cardiovascular risk profile, there was no significant difference in the risk for MACE (1.05, 0.44 to 2.50, P=0.92), TCE (0.79, 0.57 to 1.11, P=0.18), and death (0.88, 0.46 to 1.67, P=0.70).

Conclusion: A meta-analytical pooling of the results of several RCTs performed in different clinical contexts failed to demonstrate that the use of XOIs is associated with reduced risk of major cardiovascular events, death, any adverse cardiovascular event, and serious adverse events. A small but statistically significant increase in the risk of skin rash was observed in the XOI group.

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3. Moher D, et al. BMJ 2009;339:b2535.

Disclosure: M. Bredemeier, None; **M. A. Eisenreich**, None; **L. Moreira Lopes**, None; **A. L. Bittencourt Morsch**, None; **F. da Silva Stein**, None; **R. d'Avila**, None; **G. Gomes Dias Campos**, None.

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Abstract Number: 2359

Atorvastatin-Induced Autoimmune Myopathy: An Emerging Dominant Entity in Patients with Autoimmune Myopathy Presenting with a Pure Polymyositis Phenotype

Océane Landon-Cardinal[1], Yves Troyanov[2], Marvin J. Fritzler[3], José Ferreira[1], Ira Targoff[4], Eric Rich[2], Michelle Goulet[1], Jean-Richard Goulet[1], Josiane Bourré-Tessier[2], Yves Robitaille[1], Alexandra Albert[5] and Jean-Luc Senécal[2], [1]Université de Montréal, Montréal, QC, Canada, [2]Université de Montréal, Montreal, QC, Canada, [3]Division of Rheumatology, University of Calgary, Calgary, AB, Canada, [4]University of Oklahoma, Oklahoma City, OK, [5]Université Laval, Québec, QC, Canada
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Session Time: 9:00AM-11:00AM

Background/Purpose: The classification of autoimmune myopathies (AIM) is evolving. Pure dermatomyositis (DM) and overlap myositis are dominant AIM subsets, while pure polymyositis (pPM) is uncommon and confused with myositis mimickers. Our objective was to evaluate the disease spectrum in patients presenting with a pPM phenotype and to evaluate clinical features, autoantibodies (aAbs) and membrane attack complex (MAC) in muscle biopsies of patients with treatment-responsive, statin-exposed necrotizing AIM.

Methods: Our study included all patients from the CHUM AIM Cohort with a pPM phenotype (i.e absence of DM rash, overlap features and overlap aAbs), a documented response to immunosuppression and a follow-up of at least three years. We selected statin-exposed necrotizing AIM, thus excluding patients with significant inflammatory infiltrates on muscle biopsy or no previous statin-exposure.

Results: Of 17 consecutive patients with pPM, 14 patients had a necrotizing AIM, of whom 12 were previously exposed to atorvastatin (mean duration: 38.8 months). These 12 patients were therefore suspected of atorvastatin-induced AIM (atorAIM) and selected for study. None had overlap aAbs, anti-SRP or cancer. Anti-HMGCR aAbs were present in sera of these 12 patients using addressable laser bead immunoassay.

Three clinical stages of myopathy were recognized: stage 1 (serum CK elevation, normal muscle strength, normal EMG), stage 2 (CK elevation, normal strength, abnormal EMG) and stage 3 (CK elevation, proximal weakness, abnormal EMG). At diagnosis, 10/12 patients (83%) had stage 3 myopathy (mean CK elevation: 7,247 U/L). However the presenting feature was stage 1 myopathy in 6 patients (50%) (mean CK elevation: 1,540 U/L), all of whom later progressed to stage 3 myopathy (mean delay: 37 months) despite atorvastatin discontinuation.

MAC deposition was observed in all tested muscle biopsies (n=13). Three patterns were seen: isolated sarcolemmal deposition on non-necrotic fibers, isolated granular deposition on endomysial capillaries and a mixed pattern.

Oral corticosteroids alone were unable to normalize CKs and induce remission (n=9). Ten patients (83%) received intravenous immune globulin (IVIG) as part of an induction regimen. Of 10 patients with evaluable maintenance therapy (≥ 1-year remission on stable maintenance therapy), IVIG was needed in 5 patients (50%), either with MTX monotherapy (n=3) or with combination immunosuppression (n=2). In the remaining 5 patients, MTX monotherapy (n=3) and combination therapy (n=2) maintained remission without IVIg.

Conclusion: atorAIM emerged as the dominant entity in patients with a pPM phenotype and treatment-responsive myopathy. Isolated CK elevation, i.e. stage 1 myopathy, was the initial mode of presentation of atorAIM. Thus, the new onset of isolated CK elevation on atorvastatin and persistent CK elevation on statin discontinuation should raise early suspicion for atorAIM. Three patterns of MAC deposition were seen and, while non pathognomonic, were pathological clues to atorAIM. AtorAIM was uniformly corticosteroid resistant but responsive to IVIG as induction and maintenance therapy.

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Abstract Number: 2360

The Effectiveness of Tacrolimus in Patients with Interstitial Lung Disease Secondary to Autoimmune Disease

Hina Chaudhry[1], Rochella A. Ostrowski[2] and Rodney Tehrani[3], [1]Rheumatolgoy, Loyola University Medical Center, Maywood, IL, [2]Rheumatology, Loyola University Medical Center, Maywood, IL, [3]Rheum & Immun, Loyola Univ Medical Center, Maywood, IL

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Background/Purpose:

Interstitial lung disease (ILD) secondary to connective tissue disease (CTD) is most commonly seen in systemic sclerosis followed by polymyositis and dermatomyositis. Anti-synthetase syndrome is a myositis associated with ILD and antibodies directed against tRNA synthetases. To date, there is no standard of treatment for ILD secondary to CTD, but retrospective data suggest that tacrolimus may be an effective therapeutic option. We conducted a retrospective study to assess the effectiveness of tacrolimus in patients with ILD secondary to CTD.

Methods:

A chart review was performed of adult patients with ILD secondary to CTD who received tacrolimus between December 1, 1996 and December 31, 2014 at a single center academic hospital. A diagnosis of ILD was made based on pulmonary function tests, lung biopsy, high-resolution CT of the chest, and chest radiograph. The primary endpoint was improvement or stability in pulmonary function at six months based on FEV1 (forced expiratory volume in 1 second) and diffusing capacity for carbon monoxide (DLCO). Secondary endpoints included imaging results and clinical measurements at six and 12 months.

Results:

Fifteen cases of ILD secondary to CTD treated with tacrolimus were identified. All patients had a diagnosis of polymyositis, of which two also had systemic lupus erythematosus and Sjogren's syndrome. The mean age was 53 years, 86% were females, and 46% were previous smokers. Clinical characteristics are reported in Table 1. Baseline and six month mean creatinine kinase levels (IU/L) were 794 and 97 respectively. At six months, FEV1 improved in 50% of patients who had available data and in 43% of those with anti-synthetase antibodies (Table 2). Two anti-synthetase positive patients who had DLCO measured at six months showed improvement. FK506 levels were not significantly different between responders and non-responders.

Conclusion:

Tacrolimus appears to be a well-tolerated and effective therapy for stabilizing ILD in patients with CTD, particularly anti-synthetase syndrome. Our small sample size limits the ability to determine whether these findings are statistically significant. Additionally, several patients were on concomitant mycophenolate mofetil. To date, no controlled studies have been conducted to evaluate the effectiveness of tacrolimus in the treatment of ILD secondary to CTD. Our findings warrant larger prospective randomized controlled trials to evaluate and compare the outcomes of tacrolimus therapy as adjunctive or monotherapy for ILD secondary to CTD.

Disclosures: H. Chaudhry, None; R. Tehrani, None; R. Ostrowski, None.

Table 1 Characteristics of patients treated with tacrolimus for ILD

Connective Tissue Disease	Anti-Synthetase Antibody	FEV1 improved at 6 months	FK506 level 6 months	Mean Prednisone Dose (mg)	Concomitant MMF	Concomitant AZA
SLE, PM	Anti-PL12	Yes	7.4	20	No	No
PM	Negative	N/A	5.3	22.5	No	Yes
PM	Anti-PL7	N/A	2.9	15	Yes	No
PM	Anti-JO1	N/A	8.1	13	Yes	No
PM	Anti-JO1	Yes	4.8	7.5	No	No
PM	Anti-JO1	No	5.9	8	No	No
PM	Anti-JO1	N/A	5.8	16.5	No	No
PM	Anti-JO1	Yes	2.4	35	No	No
PM	Anti-JO1	No	6.4	22.5	Yes	No
PM	Anti-JO1	No	15	10	No	No
PM	Anti-JO1	N/A	9.4	10.4	No	No
PM	Anti-JO1	N/A	4.9	15	Yes	No
Sjogrens, PM	Anti-JO1	Yes	3.3	7.5	No	No
PM	Anti-JO1	No	6.7	13.5	Yes	No
PM	Anti-JO1	N/A	3.3	24	No	No

MMF = Mycophenolate mofetil, AZA = Azathioprine, N/A=not available

Table 2 Lung function based on Pulmonary Function Test and Imaging

	Number of patients	Stable/Improved	Unstable/Not Improved
FEV1 at 6 months	8	4 (50%)	4 (50 %)
FEV1 at 12 months	7	3 (43%)	4 (57%)
DLCO at 6 months	2	2 (100%)	--
DLCO at 12 months	3	2 (67%)	1 (33%)
Imaging results at 6 months (CT chest and CXR)	13	10 (77%)	3 (23%)
Imaging results at 12 months	8	8 (100%)	--

Disclosure: H. Chaudhry, None; **R. A. Ostrowski**, None; **R. Tehrani**, None.

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Abstract Number: 2361

Abatacept in the Treatment of Adult Dermatomyositis and Polymyositis: a Randomized, Treatment Delayed-Start Trial

Ingrid E. Lundberg[1], Anna Tjärnlund[2], Quan Tang[3], Cecilia Wick[2], Maryam Dastmalchi[4], Herman F Mann[5], Jana Tomasová Studýnková[5], Radka Chura[6], Nicola J. Gullick[7], Rosaria Salerno[7], Eva Lindroos[3,8], Patrick Gordon[6] and Jiri Vencovsky[5], [1]Rheumatology Unit, Department of Medicine, Karolinska University Hospital, Solna, Karolinska Institutet, Stockholm, Sweden, [2]Rheumatology Unit, Department of Medicine, Solna, Karolinska Institutet, Stockholm, Sweden, [3]Department of Medicine, Rheumatology Unit, Department of Medicine, Karolinska University Hospital, Solna, Karolinska Institutet, Stockholm, Sweden, [4]Department of Medicine, Solna, Rheumatology Unit, Department of Medicine, Karolinska University Hospital, Solna, Karolinska Institutet, Stockholm, Sweden, [5]Institute of Rheumatology, Prague, Czech Republic, [6]Department of Rheumatology, King`s College Hospital NHS Foundation Trust, London, United Kingdom, [7]Rheumatology, Department of Rheumatology, King`s College Hospital NHS Foundation Trust, London, United Kingdom, [8]Department of Medicine, Rheumatology Unit, Karolinska University Hospital in Solna, Karolinska Institutet, Stockholm, Sweden., Stockholm, Sweden

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Session Time: 9:00AM-11:00AM

Background/Purpose:

The aim of the study was to assess the effects of abatacept, a T cell blocking agent, on disease activity and on muscle biopsy features of adult patients with dermatomyositis (DM) or polymyositis (PM).

Methods:

Patients with DM or PM with persisting signs of active disease after treatment with glucocorticoids and ≥ one immune modulating drug for ≥ 3 months were enrolled in this randomized treatment delayed-start design trial to receive either active treatment with intravenous (10 mg/kg) infusions of abatacept or delayed start for 3 months. The primary endpoint was the number of responders, defined as improved according to the International Myositis Assessment and Clinical Studies (IMACS) Group definition of improvement (DOI), after treatment for 6 months. Secondary endpoints were the number of responders in the active treatment arm compared to the delayed onset arm at 3 months, and the efficacy after 6 months treatment on the individual components of the IMACS core set measures for the disease activity, and health-related quality of life assessed by SF-36. In 6 patients muscle biopsies were taken before and after 6 months of treatment and investigated by immunohistochemistry for inflammatory cell markers including CD3, and Foxp3 (regulatory T cells) and for cytokines. Each tissue section was evaluated coded and the degree of inflammation was evaluated by digital image analysis.

Results:

Among 20 randomized patients (9 DM, 11 PM; 13 female, 7 male), 17 were included in the analyses and 8 (47%) achieved the DOI after 6 months of active treatment. No differences between DM and PM or female and male patients were seen.

At 3 months after study start, 5 (50%) patients were responders after active treatment whereas only one (14%) patient in the delayed onset arm was defined as responder. After active treatment for 6 months (n=17), significant improvement was seen in muscle strength, assessed by the manual muscle test (MMT)-8, from (median) 70 to 73 (p=0.0082), in gastrointestinal disease activity from 3 to 0 (p=0.0156), and in muscle disease activity from 18 to 10 (p=0.0133). SF-36 physical was significantly improved from median 31 at start to 36 at end of treatment (p=0.0054). Eight adverse events were regarded as related to the drug (infections, flank pain and dizziness), of which 4 were mild and 4 were moderate. There were 3 serious AE, none of which was related to the drug. These included hospitalization due to fracture, worsening in muscle weakness and pre-existing basal cell cancer. The 6 patients with repeated muscle biopsies had a significant improvement in MMT-8 (p=0.03). There was a significant increase in positively stained area for Foxp3 whereas other markers were unchanged.

Conclusion:

In this pilot study, treatment of PM and DM patients with abatacept resulted in improved muscle performance and health-related quality of life in half of the patients. In patients with repeat muscle biopsies an increased frequency of Foxp3+ cells was recorded suggesting an effect of treatment on cells in muscle tissue.

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Abstract Number: 2362

Rituximab in the Treatment of Jo-1 Antibody-Associated Antisynthetase Syndrome: Anti-Ro52 Positivity As a Marker for Severity and Treatment Response

Jutta Bauhammer[1], Norbert Blank[2], Hanns-Martin Lorenz[3], Regina Max[4], Dietmar Krause[5] and Christoph Fiehn[1], [1]ACURA Centre for Rheumatic Diseases, Baden-Baden, Germany, [2]Dept. of Internal Medicine 5, Division of Rheumatology, University of Heidelberg, Heidelberg, Germany, [3]Department of Internal Medicine 5, Division of Rheumatology, University of Heidelberg, Heidelberg, Germany, [4]Dept. of Internal Medicine 5, Division of Rheumatology, University of Heidelberg, Heidelberg, Germany,

[5]Dept. of Medical Informatics, Biometry and Epidemiology, Ruhr University Bochum, Bochum, Germany
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Background/Purpose: Rituximab (RIX) has successfully been used for the treatment of severe Jo-1 antibody-associated antisynthetase syndrome (Jo-1 ASS). The aim of this retrospective study was to evaluate the effect of RIX in severe Jo-1 ASS and to determine predictive factors for response.

Methods: 61 patients with Jo-1 ASS were identified in two centres between 2006 and 2014; 18 of these received RIX. 17 patients in a dosage of 2x1g i.v. (day 0 and 14) and 1 patient 4 weekly infusions of 375 mg/m^2 body surface. Treatment cycles were repeated every six months. One patient was lost to follow-up, but the remaining 17 RIX-patients, and 30 out of 43 patients who were treated with conventional immunosuppressive drugs, were followed for a mean of 35 and 84 months, respectively. Anti-Ro52 antibodies in serum were measured with a semiquantitative immunoblotting assay (EUROLINE, Euroimmun, Germany) and the test was validated with standard immunoprecipitation technique.

Results: Polymyositis (in 95%) and interstitial lung disease (ILD, in 67%) were the dominant clinical manifestations. Detection of anti-Ro52 antibodies (in 43%) in serum was significantly associated with acute onset ILD ($p=0.016$) with O_2 dependency, and patients with high concentrations of anti-Ro52 (in 20%) had the highest risk ($p=0.0005$). 16 out of 18 patients (89%) showed a fast and almost complete response to RIX. CK serum concentrations (mean CK was 663 U/l before treatment) dropped to normal values in all patients. Results in pulmonary functional tests improved significantly ($p<0.05$). Prednisolone-equivalent doses per day decreased from a mean of 30.4 mg/d to 6.0 mg/d. Patients received 4.6 cycles of RIX on average (range: 1–13). There were five relapses in four patients. Three of them occurred when intervals between RIX treatment cycles were extended longer than 6 months. In all these patients treatment with RIX was repeated and again had a good effect. Among those patients who were highly positive for anti-Ro52, good response to RIX was seen in 7 out of 7 cases (100%), but no response to either cyclophosphamide (n=4), cyclosporine A (n=3), azathioprine (n=9), methotrexate (n=5) or leflunomide (n=2) was observed in the patients highly positive for anti-Ro52-antibodies who did not receive RIX. One patient treated with RIX and long term medium dose prednisone died of pneumonia after the second treatment cycle. No other severe adverse events occurred during RIX therapy.

Conclusion: RIX seems to be highly effective in the treatment of severe forms of Jo-1 ASS. The presence of high anti-Ro52 antibody concentrations in these patients predicts severe acute onset ILD, non-response to immunosuppressive drugs, but good and lasting response to RIX.

Disclosure: J. Bauhammer, None; **N. Blank**, Roche Pharmaceuticals, 5; **H. M. Lorenz**, Roche Pharmaceuticals, 5; **R. Max**, None; **D. Krause**, None; **C. Fiehn**, Roche Pharmaceuticals, 5.

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Abstract Number: 2363

Efficacy and Safety of Adrenocorticotropic Hormone Gel (Acthar Gel ®) in Refractory Dermatomyositis or Polymyositis

Rohit Aggarwal[1], Galina Marder[2], Priyadarshini Loganathan[3], Diane Koontz[4], Preeya Nandkumar[5], Zengbiao Qi[6] and Chester V. Oddis[7], [1]Rheumtology, University of Pittsburgh Medical Center, Pittsburgh, PA, [2]Medicine, North Shore Long Island Health System, Great Neck, NY, [3]University of Pittsburgh Medical Center, Pittsburgh, PA, [4]University of Pittsburgh, Pittsburgh, PA, [5]North Shore Long Island Health System, Great Neck, NY, [6]Division of Rheumatology, University of Pittsburgh, Pittsburgh, PA, [7]Rheum/Clinical Immunology, University of Pittsburgh, Pittsburgh, PA
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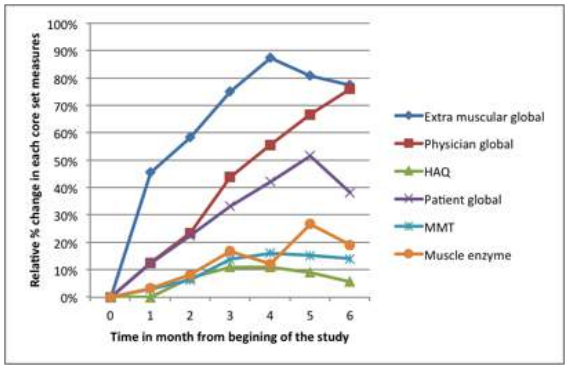
Background/Purpose: Adrenocorticotropic hormone (ACTH) gel (repository corticotropin injection) is a long-acting full sequence ACTH that may include other pro-opiomelanocortin peptides thought to have anti-inflammatory and immunomodulatory effects through melanocortin receptors. Its approval by FDA for polymyositis (PM) and dermatomyositis (DM) in 1952 was based on few case reports. We sought to evaluate the efficacy, safety, tolerability and steroid-sparing effect of ACTH gel in refractory adult PM and DM patients in a 6 month prospective, open-label uncontrolled pilot trial.

Methods: 12 adult patients (5 PM; 7 DM) were enrolled at 2 centers. ACTH gel was given as 80 U twice weekly by self-injection. One DM patient withdrew consent before study drug. The primary outcome was the proportion of patients meeting definition of improvement (DOI), defined by IMACS as improvement of ≥ 20% in 3 of 6 core set measures (CSM) with no more than 2 worsening by ≥25% [(which cannot include the manual muscle testing (MMT)]. CSM include MD global, patient global, MMT, health assessment questionnaire (HAQ), muscle enzymes and extra-muscular global assessment. Secondary endpoints included steroid-sparing effect, safety, tolerability and recently proposed myositis response criteria.

Results: Eleven patients (5 PM; 6 DM) were analyzed. Median age was 51 (IQR 37.9, 58.7), with 91% females and 46% Caucasians. All patients "failed" prednisone and a median (IQR) of 2 (2-3) additional immunosuppressive agents. Although the trial is ongoing, 8 patients completed 6 months on the drug and 3 have completed 1, 2 and 4 months in the trial, respectively. One patient stopping drug due to heart block at 2 months is considered a treatment failure. 91% (10/11) of subjects met the primary outcome by a median (IQR) of 3 (2-4) months, but the response was not sustained in 2 patients (on drug). Sustained improvement (DOI at subsequent visits) was seen in 8 (73%) patients. Median relative % improvement in MD global was 73%, 38% in patient global, 14% in MMT, 78% in extra muscular global, 13% in HAQ, 7% in muscle enzymes (Figure 1). Regarding the new myositis response criteria, 9 patients achieved minimal, 6 moderate and 4 major improvement with a median (IQR) total improvement score of 40 (25-65) on scale of 0-100. ACTH gel was safe, well-tolerated, and steroid-sparing with a drop in the median (IQR) prednisone dose from 15 mg (7.5-30) at baseline to 1.25 mg (0-4) at last visit (p=0.001). There were 4 serious adverse events in 3 patients: 2 with herpes zoster related to drug and 1 with musculoskeletal chest pain and 1 with heart block, both unrelated to study drug.

<>**Conclusion:** ACTH gel improved most enrolled myositis patients and was steroid sparing, safe and well tolerated. Viral infections require monitoring. A randomized controlled trial should be considered to further assess its efficacy in myositis.

Figure 1: Median relative percent change in core set measures on treatment with ACTH gel.



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Disclosure: R. Aggarwal, Mallinckrodt, 2; **G. Marder**, Mallinckrodt, 2; **P. Loganathan**, None; **D. Koontz**, Mallinckrodt, 2; **P. Nandkumar**, None; **Z. Qi**, Mallinckrodt, 2; **C. V. Oddis**, Mallinckrodt, 2.

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Abstract Number: 2364

Anti-3-Hydroxy-3-Methylglutaryl-Coenzyme a Reductase Positive Myopathy Patients without Statin Exposure May Have a Progressive Disease That Worsens Despite Aggressive Immunosuppressive Therapy

Eleni Tiniakou[1], Iago Pinal-Fernandez[2], Lisa Christopher-Stine[3], Jessie Werner[4], Thomas E. Lloyd[5], Julie J. Paik[6], Jemima Albayda[7], Sonye K. Danoff[8] and Andrew Mammen[9], [1]Rheumatology, Johns Hopkins University, Baltimore, MD, [2]Autoimmune Systemic Diseases Unit, Vall D'Hebron University Hospital, Universitat Autònoma de Barcelona, Barcelona, Spain, [3]Ste 4100 Rm 409, Johns Hopkins University School of Medicine, Baltimore, MD, [4]University of Maryland, School of Medicine, Baltimore, MD, [5]Neurology, Johns Hopkins, Baltimore, MD, [6]Division of Rheumatology, Johns Hopkins University School of Medicine, Baltimore, MD, [7]Rheumatology, Johns Hopkins University School of Medicine, Baltimore, MD, [8]Medicine/Pulmonary, Johns Hopkins School of Medicine, Baltimore, MD, [9]NIAMS, NIH, Bethesda, MD

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Session Time: 9:00AM-11:00AM

Background/Purpose: While the majority of myopathy patients with antibodies recognizing H 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR) have had a statin exposure, approximately one third have not. In a previous study, we reported on the evolution of antibody titers, muscle strength, and creatine kinase (CK) levels of 17 anti-HMGCR+ subjects with and without statin exposure followed longitudinally between May 2002 and July 2011. We found that (a) antibody titers correlated with CK and muscle weakness and (b) only statin-exposed patients clearly improved with immunosuppressive therapy. Here, we extend that study to these and additional anti-HMGCR+ patients followed for an additional 4 years.

Methods: Anti-HMGCR titers, CK levels, muscle strength and immunosuppressive treatment for each visit were assessed for 117 anti-HMGCR patients of the Johns Hopkins Myositis Cohort. Twenty-six patients were followed longitudinally with more than 4 visits, of which 7 were statin-unexposed.

Results: We confirmed our previous finding that statin-exposed patients experience improved strength, decreased CK levels, and decreased antibody titers with immunosuppressive therapy. Here, we demonstrate for the first time that statin-unexposed patients, despite a decrease in both anti-HMGCR titers and CK levels with immunosuppressive therapy, still have a steady decline in proximal muscle strength (deltoid, $p<0.001$ and hips, $p=0.001$) over time.

Conclusion: Unlike statin-exposed anti-HMGCR+ patients, who improve with immunosuppressive therapy, we found that statin-unexposed anti-HMGCR+ patients had a progressive decline in muscle strength despite aggressive treatement. Interestingly, the decline in muscle strength occurred even though CK levels and antibody titers decreased over time. These observations suggest that statin-exposed and statin-unexposed anti-HMGCR patients may have different underlying pathophysiological processes. Statin-exposed patients seem to have a predominantly autoimmune disease that responds to therapy. In contrast, we hypothesize that statin-unexposed patients have both an autoimmune process and an underlying myodegenerative process. The autoimmune component can be at least partially treated with immunosuppressive therapy, explaining their decreasing CK levels and antibody titers. However, we suspect that an underlying myodegenerative process does not respond to immunosuppression and causes progressive weakness. Future studies will be aimed at determining whether statin-unexposed anti-HMGCR+ patients do, indeed, have an underlying myodegenerative process, such as a muscular dystrophy.

Disclosure: E. Tiniakou, None; **I. Pinal-Fernandez**, None; **L. Christopher-Stine**, None; **J. Werner**, None; **T. E. Lloyd**, None; **J. J. Paik**, None; **J. Albayda**, None; **S. K. Danoff**, None; **A. Mammen**, None.

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Abstract Number: 2365

Use of Long Term Subscutaneous Immunoglobulins in Inflammatory Myopathies: A Retrospective Analysis of 19 Patients

Patrick Cherin[1], Cristina Belizna[2], Odile Cartry[3], Georgeta Lascu[4], Jean-Christophe Delain[5], Jean-charles Crave[6] and Eric Hachulla[7], [1]Internal Medicine, Pitié Salpêtrière Hospital, Paris, France, [2]Internal Medicine, Angers University hospital, Angers, France, [3]Internal Medicine, Clinique Mutualiste, Perpignan, France, [4]Internal Medicine, Max Fourestier Hospital, Nanterre, France, [5]Medical immunology, Octaphama France, Boulogne-BIllancourt, France, [6]Immunology, Octapharma France, Boulogne-BIllancourt, France, [7]FAI²R, Hôpital Claude Huriez, CHRU Lille, LILLE, France
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Background/Purpose:

Intravenous immunoglobulin (IVIg) therapy is recommended for patients suffering from inflammatory myopathies refractory to corticosteroids and immunosuppressive drugs. It is also recommended for patients with myositis who are unable to continue immunosuppression due to adverse reactions (ADRs) or for whom such immunosuppressive therapy is contraindicated. However, long-term IVIg therapy is associated with a risk of systemic adverse reactions, and is also associated with the need of intravenous access, surveillance and hospitalizations. Therefore, employing an alternative route of administration, subcutaneous immunoglobulin (SCIg) was made available. For the majority of patients, IVIg and SCIg are equally efficacious; however, they are not equally exchangeable.

Methods:

A retrospective analysis studied compliance, tolerance and effectiveness (using muscle testing, muscle disability scale and enzyme CK) of a 16,5% SCIg therapy in inflammatory myopathies. Between August 2011 and February 2015, 19 patients were enrolled: 10 with polymyositis (PM), 2 with dermatomyositis (DM) and 7 with inclusion body myositis (IBM).

Results:

Patients on SCIg therapy were followed on average 16.9 months (range: 1 to 42 months). Reasons to switch to the subcutaneous route were: patients being more independent (14/19), therapeutic failure (3/19), end dose effect (1/19), and poor venous access (1/19). Ten of 19 patients previously received IVIg. Average dose of SCIg was 1.7 [±0.4] g/kg/month. General regimen of SCIg treatment included two weekly administrations totalling 130.0 [±73.0] mL/week. Maximally 25 mL/site were infused at 4 sites each. All patients were followed by home delivery companies. Any deviations from the physician-defined protocol were recorded. Regarding treatment efficacy, data on muscle testing and/or functional scale were available for 9 of 12 PM/DM patients. All of these patients significantly improved (p>0,05), and 3 of them had normalized testing (88/88 on muscular testing). In IBM patients, no significant improvement was expected but 4 patients stabilized under SCIg therapy, and 2 patients with initial dysphagia recovered. Ten of 19 patients experienced adverse reactions during the follow-up period. Local reactions (skin rash, swelling, redness, induration, pain or reflux at injection site) and systemic reactions (headache, chills, hot flushes, high blood pressure, dizziness and tiredness) were reported. These ADRs resolved after decreasing the infusion rate, dose adapting or using premedication.

Conclusion:

In all patients, the use of SCIg was feasible and well-tolerated during long-term therapy. Furthermore, relevant improvement in muscle strength was observed in 8 of 14 patients. SCIg therapy allowed for reducing the daily corticoisteroid use in 3 patients and stopping the immunosuppressant therapy in 2 patients. These observations suggest that SCIg could be used as an alternative route to IVIg in auto-immune diseases.

Disclosure: P. Cherin, None; **C. Belizna**, None; **O. Cartry**, None; **G. Lascu**, None; **J. C. Delain**, None; **J. C. Crave**, None; **E. Hachulla**, None.

Abstract Number: 2366

The Anti-MDA5 Autoantibody Phenotype: Defining Clinical, Biochemical and Radiological Features Suggestive of Anti-MDA5-Associated Rapidly Progressive Interstitial Lung Disease

Sabrina Hoa[1], Yves Troyanov[1], Marvin J. Fritzler[2], Ira N. Targoff[3], Anne-Marie Mansour[1], Eric Rich[1], Hind Boudabbouz[1], Josiane Bourré-Tessier[1], Sandra Chartrand[1], Marianne Landry[1], Martin Albert[1] and Jean-Luc Senécal[1], [1]Université de Montréal, Montreal, QC, Canada, [2]Medicine, University of Calgary, Calgary, AB, Canada, [3]Veterans Affairs Medical Center, University of Oklahoma Health Sciences Center, Oklahoma City, OK

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Background/Purpose: Anti-MDA5 autoantibody associated syndrome is a novel entity within the spectrum of autoimmune myositis. It has been described as a clinical mimic of the anti-synthetase syndrome, but is associated with a characteristic cutaneous phenotype and, unlike anti-synthetase syndrome, has been associated with rapidly progressive interstitial lung disease (RPILD). This clinical picture has been primarily reported in Asians and has a poor prognosis, especially in the presence of elevated ferritin. However, in North American cohorts these associations are not as clear due to a paucity of data.

The primary goal of our study was to define clinical, biochemical and radiological features predictive of anti-MDA5-associated RPILD that would justify empirical treatment, pending confirmation of anti-MDA5 autoantibody status.

Methods: We retrospectively analyzed the clinical features of 7 patients (pts) who presented with features suggestive of anti-MDA5-associated RPILD and who were subsequently confirmed (or strongly suspected in one case) to have anti-MDA5 autoantibody, using a novel line immunoassay (Euroline, Euroimmun, Lubeck, Germany) in 3 pts.

Results: Six of the 7 pts were men; five were Caucasian. Six pts presented with dyspnea, and RPILD developed in all 7 pts. Anti-MDA5-associated cutaneous signs appeared within one month of respiratory symptoms in 6 (86%) pts, but were recognized at initial presentation in 2 pts. These included palmar or lateral finger papules (n=4), skin ulcerations (n=2), and mechanic's hands (n=4). Gottron papules and sign were sometimes psoriasiform. Shawl and V-signs were not seen, whereas periungueal erythema was always present.

Profound weight loss over 1 to 2 months (mean 21.9 lbs, range 14-37 lbs) and articular symptoms occurred in all pts. One pt had Raynaud phenomenon. Four pts were clinically amyopathic; only 1 pt had CK levels >500 U/L. Hepatic enzymes were elevated in 6 (86%) pts. The ANA test was negative for nuclear and cytoplasmic staining on HEp-2 substrate. Imaging at initial presentation showed ground glass opacities with consolidation in 6 (86%) pts, isolated ground glass opacities in 1 pt, and reticulations in 4 pts, in a bibasilar peripheral distribution in 6 pts.

Four (57%) pts died. Time from hospitalization to death ranged from 6 to 41 days. Time from initial symptoms to death ranged from 6 weeks to 4 months. Survivors received mycophenolate mofetil with or without tacrolimus, concomitantly with corticosteroids. Hyperferritinemia (>1000 mcg/L, n=4 pts) upon admission was associated with a fatal outcome (n=4 deaths).

Conclusion: In an inpatient setting, anti-MDA5-associated ILD can be a rapidly progressive condition with a high mortality. Cutaneous findings are subtle and may follow the respiratory symptoms. Dyspnea, cutaneous findings, profound weight loss, articular symptoms, normal or low CKs with elevated AST/ALT, and absence of nuclear and cytoplasmic fluorescence on ANA testing should alert the clinician to the possibility of anti-MDA5-associated RPILD. Hyperferritinemia is associated with a poor outcome. Early institution of immunosuppressive therapy may prove lifesaving.

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Abstract Number: 2367

Risk of Malignancy in Dermatomyositis with Anti-CADM-140/ Melanoma Differentiation- Associated Gene 5 Autoantibody

Shinji Sato[1], Takayoshi Kurabayashi[1], Sho Sasaki[2], Yasushi Koyama[2], Shinichi Nogi[3], Naofumi Chinen[1], Chiho Yamada[1] and Yasuo Suzuki[1], [1]Internal Medicine/ Rheumatology, Tokai University School of Medicine, Isehara, Japan, [2]Internal Medicine/Rheumatology, Tokai University School of Medicine, Isehara, Japan, [3]Division of Rheumatology, Department of Internal Medicine, Tokai University School of Medicine, Isehara, Japan

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Background/Purpose: Anti-CADM-140/ Melanoma Differentiation-Associated Gene 5 (MDA5) antibody is found specifically in patients with dermatomyositis (DM). This autoantibody is associated with clinically amyopathic DM (CADM) and rapidly progressive interstitial lung disease especially in eastern Asian population. However, the association of malignancy and anti-CADM-140/ MDA5 antibody had not been examined in detail. Aim of this study is to determine the association between cancer-associated myositis (CAM) and anti-CADM-140/ MDA5 antibody in Japanese patients.

Methods: Sixty-two patients with classic DM or CADM who were seen at our University from 2011 to 2014 were retrospectively evaluated for the associations between anti-CADM-140/ MDA5 antibody and the occurrence of malignancy. CAM was defined as a patient having a cancer within 5 years of DM diagnosis. Anti-CADM-140/ MDA5 antibody were examined by protein immunoprecipitation assay and enzyme-linked immunosorbent assay. Comparisons between two groups were made using the chi-square test.

Results: Of 62 patients, 44 patients were diagnosed as having classic DM (male/female: 15/29, a mean age ± SD: 56.8 ± 13.5) and 18 were diagnosed as having CADM (male/female: 3/15, a mean age ± SD: 54.3 ± 9.6). Sera from 3 patients with classic DM and all 18 patients with CADM were found to contain anti-CADM-140/ MDA5 antibody (6.8%; 3/44 vs. 100%; 18/18, P< 0.0001). CAM was seen in 25.0% (11/44) of classic DM as compared to 5.6 % (1/18) of CADM (P = 0.15). Malignancies in classic DM included lung (3 patients), colon (2 patients) and bladder, lymphoma, breast, oropharynx, external auditory canal and unknown (1 patient each) while CADM included colon (1 patient). CAM was found in only one patient with anti-CADM-140/ MDA5 antibody positive, whereas 11 patients with anti-CADM-140/ MDA5 antibody negative (4.8% 1/21 vs. 26.8% 11/41, P= 0.046).

Conclusion: Anti-CADM-140/ MDA5 antibody was significantly found with a high frequency in patients with CADM as compared to those with classic DM. Malignancy was significantly less found in DM patients with anti-CADM-140/ MDA5 antibody compared with those without this antibody. These results suggest that DM patients with anti-CADM-140/ MDA5 antibody might have a low risk of malignancy.

Disclosure: S. Sato, Holding a patent on anti- MDA5 antibody-measuring kit., 7; **T. Kurabayashi**, None; **S. Sasaki**, None; **Y. Koyama**, None; **S. Nogi**, None; **N. Chinen**, None; **C. Yamada**, None; **Y. Suzuki**, None.

Abstract Number: 2368

Myositis Specific-Autoantibodies: Predictors of Short-Term Good Outcome in Rituximab Treated-Refractory Idiopathic Inflammatory Myopathies

Fernando Henrique Carlos de Souza[1], **Renata Miossi**[2], Julio C. B. Moraes[1], Karina Bonfiglioli[1], Eloisa Bonfá[1] and Samuel Katsuyuki Shinjo[1], [1]Rheumatology Division, Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil, [2]Rheumatology Division, Faculdade de Medicina da Universidade de São Paulo, Sao Paulo, Brazil

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Background/Purpose: The treatment of idiopathic inflammatory myopathies (IIM) is challenging, complicated by its rarity and heterogeneity. Currently few studies have suggested the efficacy of RTX in refractory idiopathic inflammatory myopathies (IIM). The interpretation of their findings is hampered by the lack of a uniform and restrict criteria of refractory myositis. Herein, we established rigorous definition of refractory. The objective of this study was to evaluate efficacy and predictors of clinical improvement of RTX treated-refractory IIM.

Methods: This prospective single-center study included 25 consecutive adult patients with refractory IIM [7 anti-synthetase syndrome, 12 dermatomyositis (DM), 6 polymyositis (PM) - Bohan & Peter, 1975] from 2011 to 2015. Refractory myositis was defined by an inadequate response to prednisone ≥ 0.5mg/kg/day for ≥ three months and at least two other immunosuppressive or immunomodulatory drugs (azathioprine, methotrexate, cyclosporine, leflunomide, mycophenolate mofetil and/or human intravenous immunoglobulin, in their full-dose, for a minimum period of three months). These patients received two infusions of RTX (1g each, two weeks apart). After RTX initiation only one immunosuppressive was maintained and prednisone dose was tapered gradually. In six months evaluation, clinical improvement was defined as a 20% in at least three of the following six core set measures of disease activity: physician's and patient's global assessment of disease activity, manual muscle testing (MMT8), physical function (HAQ), muscle enzymes,

Results: The mean age of patients was 40.2±11.2 years, with 57.7% Caucasian, 88.5% female gender and mean disease duration of 6.4±3.2 years. Forty percent had antisynthetase (of these, 28% anti-Jo-1), 12% anti-Mi-2 and 12% other subtypes. The majority of the patients (74%) achieved clinical response. Comparison of study entry and six months after RTX revealed a reduction in mean glucocorticoid dose (26.1±16.9mg/day vs. 17.2±16.3mg/day *P*=0.008) and improvements of physician's [5.0 (4.0-6.0) vs. 4.0 (2.0-5.0), *P*=0.01) and patient's global assessment [5.0 (3.0-7.0) vs. 5.0 (2.0-5.0) , *P*=0.045) , MMT8 [70.0 (58.0-74.0) vs. 76.0 (64.0-78.0), *P*=0.006), HAQ [1.1 (0.9-1.9) vs. 0.9 (0.3-1.5), *P*=0.02), creatine kinase [481(98-1261)U/L vs. 236 (84-487)U/L, *P*=0.042], aldolase [5.3 (4.4-14.1)U/L vs. 4.1 (3.2-6.1)U/L, *P*=0.002). Further analysis of responders vs. non-responders at baseline identified that autoantibodies were more frequently detected in responder patients (75.0% *vs*. 12.5%, *P*=0.004).

Conclusion: Our study provided evidence of short-term RTX treatment efficacy for refractory IIM. We also confirmed and extended previous observations in overall IIM that myositis autoantibodies is also predictor of RTX treatment response for refractory IIM.

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Abstract Number: 2369

Dermatomyositis Associated with Anti-Melanoma Differentiation-Associated Gene 5 Antibodies: A Longitudinal Analysis

Matthew Lewis[1], Shufeng Li[1], Lorinda Chung[2] and **David Fiorentino**[1], [1]Dermatology, Stanford University, Stanford, CA, [2]Division of Immunology and Rheumatology, Stanford University School of Medicine, Stanford, CA
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Background/Purpose: Dermatomyositis (DM) patients with anti-melanoma differentiation-associated gene 5 (MDA5) antibodies are at increased risk of developing interstitial lung disease (ILD). The natural history of ILD among this subset of DM patients is poorly characterized among non-Asian populations. Skin disease studies in anti-MDA5 DM are largely cross-sectional in nature. We sought to characterize the temporal trends in ILD severity, cutaneous ulceration and calcinosis in anti-MDA5 DM patients.

Methods: We retrospectively reviewed the charts of 25 anti-MDA5 DM patients seen between July 2004 and September 2014.

Results: Of the 25 anti-MDA5 DM patients seen, 23 patients were assessed for evidence of ILD (Table 1). 17 patients (74%) had evidence of ILD corroborated by both pulmonary function tests (diffusion capacity (DLCO) less than 75% predicted or forced vital capacity (FVC) less than 80% predicted) and high-resolution chest computed tomography scans. The median time to ILD development was 5 months, (range 0-71 months), with 89% of patients developing ILD within 9 months from symptom onset.

In the 12 patients with longitudinal data, we found a small, but statistically significant increase in DLCO over time (Figure 1), 0.30% per month (95% CI 0.02-0.58%, p=.036). All 12 patients with ILD received immunosuppressive therapy.

We found a significant inverse relationship between DLCO and ulcer burden (p=0.006, Figure 2). The median times to onset of cutaneous ulceration, ulcer healing and calcinosis were 6, 22 and 30 months, respectively. Use of phosphodiesterase type 5 inhibitors, such as sildenafil, was associated with ulcer healing in 3 patients with recalcitrant cutaneous ulceration.

The proportionate mortality was significantly greater in anti-MDA5 DM patients (5/25=20%) vs non-MDA5 DM patients (7/148=4.7%) (p=.016).

Conclusion: In this cohort, 17 of 25 (74%) of anti-MDA5 DM patients developed ILD, most (89%) within 9 months of symptom onset. The ILD severity as measured by DLCO may improve over time with treatment. Among anti-MDA5 DM patients with ILD, the severity of their skin ulceration appears to correlate with ILD severity. The classic mucocutaneous feature of anti-MDA5 DM, cutaneous ulceration, appears during the onset of ILD but usually resolves and is replaced by calcinosis.

Table 1

	MDA5-	MDA5+	P
N	148	25	
age at diagnosis, mean(std)	48.73 (16.07)	47.03 (13.46)	0.6172
Follow-up, median(range)	5.09 (0.15 - 24.32)	3.03 (0.06 - 16.52)	0.6550
Died during follow-up, n(%)	7 (4.73)	5 (20)	0.0166
Female, n(%)	107 (72.30)	19 (76.00)	0.7003
Race, n(%)			0.0002
Caucasian	101(68.24)	9 (36.00)	
Asian	18 (12.16)	13 (52.00)	
African American	6 (4.05)	1 (4.00)	
Latino	23 (15.54)	2 (8.00)	
Smoker, n(%)			0.5745
no	117 (80.69)	21 (84.00)	
past	21 (14.48)	2 (8.00)	
yes	7 (4.83)	2 (8.00)	
ILD, n(%)			<0.0001
no	126 (85.71)	6 (26.08)	
yes	21 (14.29)	17 (73.91)	
Calcinosis, n(%)			0.0421
no	125 (89.93)	17 (73.91)	
yes	14 (10.07)	6 (26.09)	
Clinically amyopathic, n(%)			0.0849
no	115 (82.73)	15 (65.22)	
yes	24 (17.27)	8 (34.78)	
Cancer, n(%)			0.5368
no	117 (82.98)	21 (91.30)	
yes	24 (17.02)	2 (8.70)	
Dysphagia, n(%)			0.0462
no	70 (52.63)	15 (78.95)	
yes	63 (47.37)	4 (21.05)	
Arthralgia,arthritis, n(%)			0.0038
no	78 (60.47)	6 (27.27)	
yes	51 (39.53)	16 (72.73)	
Panniculitis, n(%)			0.0039
no	137 (98.56)	19 (82.61)	
yes	2 (1.440.71)	4 (17.39)	
All ulcers, n(%)			<.0001
no	100 (70.92)	3 (13.04)	
yes	41 (29.08)	20 (86.96)	

Figure 1

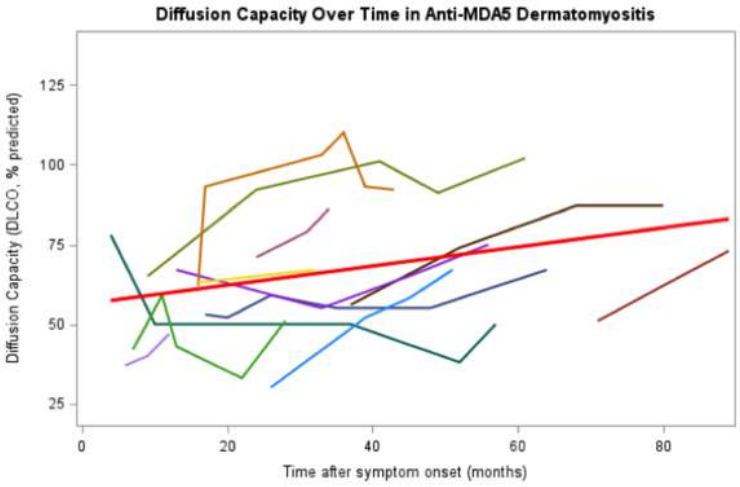
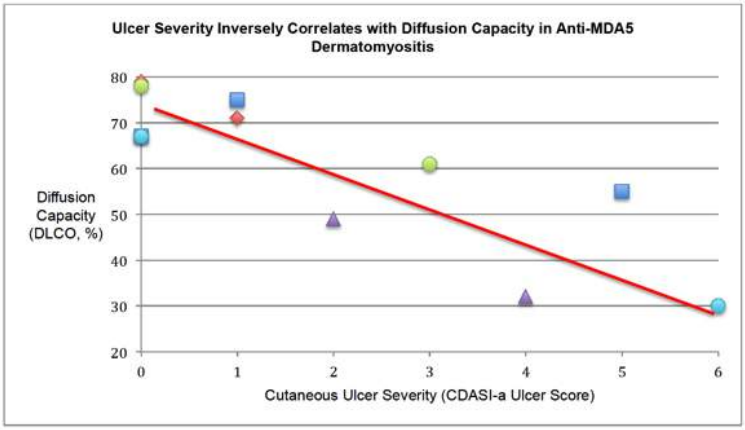


Figure 2



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Abstract Number: 2370

Clinical Characteristics of Anti-MDA5 (+) Dermatomyositis Patients in North America

Siamak Moghadam-Kia[1], Chester V. Oddis[2], Shinji Sato[3], Masataka Kuwana[4] and Rohit Aggarwal[5], [1]Medicine-Myositis Center and Division of Rheumatology and Clinical Immunology, University of Pittsburgh, Pittsburgh, PA, [2]Rheum/Clinical Immunology, University of Pittsburgh, Pittsburgh, PA, [3]Rheumatology, Tokai University School of Medicine, Isehara, Japan, [4]Division of Rheumatology, Keio University School of Medicine, Tokyo, Japan, [5]Medicine / Rheumatology, University of Pittsburgh, Pittsburgh, PA

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Background/Purpose: Clinically amyopathic dermatomyositis (CADM) patients have the classic rash (es) of DM but no objective proximal muscle weakness. Asian studies report a unique clinical phenotype in anti-MDA5 (+) CADM which has not been well described in the U.S. Our goal was to determine the clinical features associated with the anti-MDA5 autoantibody (autoAb) in CADM as compared to classic DM in U.S. patients.

Methods: CADM patients were selected consecutively from patients prospectively enrolled in a computerized university Myositis Center database between January 1985 and July 2013. CADM was defined by a typical DM rash without objective muscle weakness for at least 6 months after rash onset and no or minimal abnormalities of serum muscle enzymes [< 3 x ULN], electromyography or muscle biopsy. Classic DM was defined as probable or definite by the criteria of Bohan and Peter and 1:1 matched (gender and age +/- 5 years) to CADM patients. Clinical features were extracted from the database and supplemented with electronic medical record review when necessary.

Results: We identified 61 CADM patients (female 64%; mean age 44.8) and 61 matching classic DM controls (female 62%; mean age 48.2). Anti-MDA5 frequency was similar in both cohorts (13.1% [8/61] vs. 13.1% [8/61]). Anti-MDA5 positivity was associated with a higher likelihood of vasculitic rash and digital tip ulceration and with a trend towards more abnormal capillary microscopy and a lower frequency of Raynaud phenomenon compared to anti-MDA5 negative patients. The frequency of Gottron sign or papules, heliotrope rash and mechanic hands were similar in both groups. However, puffy fingers and dysphagia frequency were significantly higher in the anti-MDA5+ patients. Anti-MDA5 positivity was significantly associated with interstitial lung disease (ILD) ($p=0.043$), rapidly progressive ILD (RPILD) ($p<0.001$), and poor survival ($p=0.007$). Multivariate analysis suggested that anti-MDA5 positivity was predictive of poor survival even after controlling for diagnosis, age at diagnosis, gender, ethnicity, smoking, and ILD ($p=0.001$). ILD frequency was similar in CADM and classic DM (31.1% vs. 26.2%) as was RPILD (8.2% vs. 5%). CADM patients were more likely to have heliotrope rash and dysphagia as compared to classic DM patients. The remaining clinical features were similar for both CADM and classic DM cohorts (Table 1).

Conclusion: Anti-MDA5 positivity has a similar frequency in CADM and classic DM patients in the U.S. Anti-MDA5 autoAb is associated with a unique clinical phenotype consisting of ILD, RPILD, and a vasculitic rash with digital tip ulceration. CADM patients had more dysphagia and heliotrope rash as compared to classic DM, apart from obvious disease-defining features of muscle weakness and muscle enzyme.

Table 1. Clinical features of anti-MDA5 positive and CADM patients as compared to anti-MDA5 negative and classic DM patients, respectively.

Clinical features	MDA5 + (N = 16)	MDA5 – (N = 106)	p value	CADM (N = 61)	Classic DM (N = 61)	p value
ILD	50%	25.5%	0.04	31%	26%	0.46
RPILD	87.5%	3.7%	<0.001	8%	5%	0.55
Dyspnea at presentation	37.5%	27.3%	0.4	32.7%	24.5%	0.31
Pulmonary HTN	6.2%	1.8%	0.34	3.3%	1.6%	1
Cardiomyopathy	0	0	1	0	0	1
Raynaud phenomenon	12.5%	26.4%	0.35	22.9%	26.2%	0.67
Vasculitic rash	18.7%	1.8%	0.01	3.2%	4.9%	1
Abnormal capillary microscopy	43.7%	26.4%	0.15	29.5%	27.8%	0.8
Digital tip ulceration	18.7%	2.8%	0.02	4.9%	4.9%	1
Heliotrope rash	18.7%	29.2%	0.55	36%	19.6%	0.04
Gottron papules/sign	37.5%	32%	0.66	32.7%	32.7%	1
Mechanic hands	6.2%	6.6%	1	3.2%	9.8%	0.27
Arthralgia	6.2%	7.5%	1	4.9%	9.8%	0.49
Arthritis	0%	1.8%	1	1.6%	1.6%	1
Dysphagia	31.2%	10.3%	0.03	24.5%	1.6%	<0.001
Sicca	12.5%	4.7%	0.22	4.9%	6.5%	1
Puffy fingers	25%	4.7%	0.01	9.8%	4.9%	0.49
Calcinosis	0%	0%	1	0%	0%	1
Telangiectasia	0%	0.9%	1	0%	1.6%	1
Myalgia	18.7%	29.2%	0.55	34.4%	21.3%	0.1

Disclosure: S. Moghadam-Kia, None; **C. V. Oddis**, None; **S. Sato**, None; **M. Kuwana**, None; **R. Aggarwal**, None.

Abstract Number: 2371

The Clinical Features of Recurrent Interstitial Lung Disease in Dermatomyositis Patients with Anti- Melanoma Differentiation-Associated Gene 5 Antibody

Yuji Hosono[1], Ran Nakashima[1], Kosaku Murakami[2], Yoshitaka Imura[2], Naoichiro Yukawa[2], Hajime Yoshifuji[2], Koichiro Ohmura[2] and Tsuneyo Mimori[2], [1]Department of Rheumatology and Clinical Immunology, Kyoto University Graduate School of Medicine, Kyoto, Japan, [2]Department of Rheumatology and Clinical Immunology, Department of Rheumatology and Clinical Immunology, Graduate School of Medicine, Kyoto University, Kyoto, Japan

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Background/Purpose: Interstitial lung disease (ILD) is the most common cause of mortality in polymyosytis (PM) and dermatomyositis (DM). It is well known that the DM patients with anti- melanoma differentiation-associated gene 5 (MDA5) antibody (Ab) frequently develop acute progressive ILD and fatal outcome within the first year from the onset. Although survival rate of anti-MDA5-positive patients tends to be sustained after 6 months from the treatment, the characteristics of ILD-recurrent cases are still unclear. Here, we intended to investigate the characteristics of recurrent ILD among anti-MDA5-positive DM-ILD patients.

Methods: Clinical data and serum samples were collected from adult Japanese anti-MDA5-positive DM-ILD patients who visited our department from January 2006 to May 2015. 14 of 20 patients were alive after more than one year from the onset and treated with high dose glucocorticoids (GC) and intravenous cyclophosphamide (IVCY) therapy as the initial treatment. The patients who showed the recurrent symptoms after at least 6 months since the last IVCY therapy were defined as recurrence group. Anti-MDA5 was screened using the immunoprecipitation assay with [^{35}S] methionine-labelled HeLa cells.

Results: 14 patients treated with high dose GC and IVCY therapy as initial treatment survived after more than 6 months. Among these patients, 4 (29%) showed the recurrence. Among them, 3 (75%) were exacerbation of ILD and 1 (25%) was arthritis. The average duration from the last IVCY therapy to recurrence was 42.5±7.9 months. The lymphocyte counts before the initial treatment were significantly lower in recurrence group than in no-recurrence group (556±187 vs 992±118, $P<0.05$). Moreover, the total dose of IVCY until recurrence was significantly lower in recurrence group (7758±1137 vs 10364±758mg, $P<0.05$). There were no significant differences in age, sex, duration of diseases, and minimal dose of GC. 3 of 5 (60%) who were treated without calcineurin inhibitors (CNI) showed the exacerbation of ILD, whereas none of 11 who were treated with CNI ($P<0.05$).

Conclusion: Our study clarified the clinical features of recurrence among anti-MDA5-positive DM-ILD patients. The enough dose of IVCY after the induction of remission combining with CNI as well as high dose GC should be strongly recommended to prevent the recurrence of ILD in anti-MDA5-positive DM-ILD patients.

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Abstract Number: 2372

Timing of Onset and Cluster with Other Manifestations Influence the Spectrum of Arthritis in Anti Jo-1 Positive Antisynthetase Syndrome: Results from a Multicenter, International, Retrospective Study

Alberto Sifuentes Giraldo[1], Carlo Alberto Scirè[2], Santos Castañeda[3], Laura Nuño[4], Francisco Javier Lopez Longo[5], Julia Martínez-Barrio[5], Franco Franceschini[6], Ilaria Cavazzana[6], Paolo Airò[7], Elena Bartoloni Bocci[8], Javier Bachiller Corral[9], Rossella Neri[10], Simone Barsotti[11], Roberto Caporali[12], Carlomaurizio Montecucco[13], Marcello Govoni[14], Renato La Corte[14], Federica Furini[14], Florenzo Iannone[15], Margherita Giannini[16], Enrico Fusaro[17], Simone Parisi[18], Giuseppe Paolazzi[19], Giovanni Barausse[19], Raffaele Pellerito[20], Alessandra Russo[20], Lesley Ann Saketkoo[21], Norberto Ortego-Centeno[22], Luca Quartuccio[23], Christof Specker[24], Andreas Schwarting[25], Kostantinos Triantafyllias[26], Carlo Selmi[27], Fausto Salaffi[28], Marco Amedeo Cimmino[29], Annamaria Iuliano[30], Fabrizio Conti[31], Gianluigi Baiocchi[32], Elena Bravi[33], Veronica Codullo[12], Anna Ghirardello[34], Trinitario Pina[35], Miguel Angel Gonzalez-Gay[35], **Lorenzo Cavagna**[13] and AENEAS (American and European NEtwork of Antisynthetase Syndrome) collaborative group, [1]Department of Rheumatology, University Hospital Ramón y Cajal, Madrid, Spain, [2]Epidemiology Unit – Italian Society for Rheumatology (SIR), Milano, Italy, [3]Rheumatology, H.U. La Princesa, Madrid, Spain, [4]Servicio de Reumatologia, Hospital Universitario La Paz, Madrid, Spain, [5]Servicio de Reumatologia, Hospital General Universitario Gregorio Marañón, Madrid, Spain, [6]Rheumatology and Clinical Immunology, Spedali Civili and University of Brescia, Brescia, Italy, [7]Rheumatology Unit, Spedali Civili of Brescia, Brescia, Italy, [8]Rheumatology Unit, Department of Clinical & Experimental Medicine, University of Perugia, Perugia, Italy, [9]Rheumatology, University Hospital Ramón y Cajal, Madrid, Spain, [10]Rheumatology Unit, University of Pisa, Italy, Pisa, Italy, [11]Division of Rheumatology, Department of Clinical and Experimental Medicine, University of Pisa, Pisa, Italy, [12]Division of Rheumatology, University of Pavia, IRCCS Foundation

Policlinico S. Matteo, Pavia, Italy, [13]Division of Rheumatology, University and IRCCS Policlinico S. Matteo Foundation, Pavia, Italy, [14]UOC Reumatologia, Azienda Ospedaliera Universitaria S. Anna, Ferrara, Italy, [15]Interdisciplinary Department of Medicine (DIM), Rheumatology Unit, University of Bari, Bari, Italy, [16]DIM, Rheumatology Unit, Bari, Italy, [17]Department of Rheumatology, Città della Salute e della Scienza, Torino, Italy, [18]Department of Rheumatology, Città Della Salute e della Scienza, Torino, Italy, [19]Rheumatology Unit, Santa Chiara Hospital, Trento, Italy, [20]Division of Rheumatology, Mauriziano Hospital, Turin, Italy, [21]Tulane University Lung Center, New Orleans Scleroderma and Sarcoidosis Patient Care and Research Center, New Orleans, LA, [22]Systemic Autoimmune Diseases Unit, Hospital Universitario San Cecilio, Granada, Spain, [23]Clinic of Rheumatology, Department of Medical and Biological Sciences (DSMB), Santa Maria della Misericordia Hospital, University of Udine, Udine, Italy, [24]Department for Rheumatology and Clinical Immunology, St. Josef Krankenhaus, University Clinic, Essen, Germany, [25]Department of Internal Medicine, Rheumatology and Clinical Immunology, University Hospital Johannes-Gutenberg, Mainz, Germany, [26]ACURA Rheumatology Center, Bad Kreuznach, Germany, [27]Internal Medicine- Unit of Rheumatology and Clinical Immunology, Humanitas Clinical and Research Center, Rozzano, Italy, [28]Rheumatology Department, Polytechnic University of Marche, C. Urbani Hospital, Jesi,, Ancona, Italy, [29]Research Laboratory and Academic Unit of Clinical Rheumatology, Department of Internal Medicine, University of Genoa, Genoa, Italy, [30]Osp. San Camillo, Roma, Italy, [31]Rheumatology Unit, Department of Internal Medicine and Medical Specialties, Sapienza University of Rome, Rome, Italy, [32]Rheumatology Unit, Department of Internal Medicine, S.Maria Hospital –IRCCS, Reggio Emilia, Italy, [33]Internal Medicine, Rheumatology Unit, Ospedale Guglielmo da Saliceto, Piacenza, Italy, [34]Department of Medicine-DIMED, University of Padova, Padova, Italy, [35]Rheumatology, Hospital Universitario Marqués de Valdecilla. IDIVAL, Santander, Spain
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Background/Purpose: arthritis, myositis and interstitial lung disease (ILD) are reported in up to 90% of patients affected by antisynthetase syndrome (ASSD) and thus represent the most common manifestations of this rare condition. Arthritis presentation ranges from symmetrical polyarthritis to oligoarticular/asymmetrical arthritis. IgM-rheumatoid factor (RF) and anti-cyclic citrullinated peptide antibodies (ACPA) may be positive, and joint erosions mat be observed at plain radiographs of hands and feet. On this basis, in ASSD differential diagnosis with rheumatoid arthritis (RA) may be challenging. Arthritis may occur at disease onset, with or without myositis and/or ILD, or during the follow-up. The aim of this multicenter, international, retrospective study was to assess whether in ASSD the timing and the cluster of onset with other typical disease manifestations may influence arthritis characteristics

Methods: anti Jo-1 positive patients presenting with arthritis (joints swelling and tenderness required) were included in the study. Clinical, radiology and laboratory characteristics of arthritis and the occurrence of myositis and ILD, were retrospectively reviewed. Patients were divided in 3 groups: Group 1) isolated arthritis at disease onset, Group 2) arthritis associated with myositis and/or ILD at disease onset, Group 3) arthritis occurrence after disease onset

Results: the starting cohort included 252 anti Jo-1 positive ASSD. Arthritis was identified in 186 (74%) cases and it was mainly polyarticular and symmetrical (120, 65%). The remaining patients (64, 36%) had an oligoarticular/asymmetrical arthritis. RF-IgM was positive in 54/154 patients tested (30%). ACPA were positive in 19/139 patients tested (14%). Hands and feet plain radiographs were available in 179 patients, in 39 cases (22%) with evidence of erosions. Anti Ro antibodies were positive in 102/180 patients tested (57%). Patients' characteristics and statistical significances between groups are shown in table 1. Symmetrical polyarthritis was the main pattern of presentation in all groups. Ig-M RF positive and joint erosions were less common in patients without arthritis at disease onset (Group 3) than in those presenting with isolated arthritis (Group 1). ACPA and joint erosions were more common in Group 1 than in Group 2

Conclusion: in anti Jo-1 positive ASSD, the timing and the cluster of appearance influence arthritis features. According to our findings, heterogeneity within the clinical spectrum of arthritis is one of the main characteristics of anti Jo-1 positive ASSD. Typical RA features are more common at disease onset and in patients presenting with isolated arthritis

References

	Group 1 : isolated arthriris at disease onset	*Group 2: arthritis associated with myositis and/or ILD at disease onset*	*Group 3: arthritis occurrence after disease onset ^*
Number (% of total)	60 (32)	97 (52)	29 (16)
Median age in years at disease onset (IQR)	54.5 (43-62.5)	53 (43-61) **p=0.824 µ**	52 (39.5-66.5)
Median follow-up in months (IQR)	86.5 (60-150)	75 (32.5-132) **p=0.007 µ**	130 (66-225)
Males/females	***reference*** 13/47	*p=0.075** 25/72 **p=0.774**	*p=0.079** 6/23
Symmetrical polyarthritis (% of subset)	41 (68)	61 (63) **p=0.636**	17 (59)
IgM-RF positive/patients checked (% of subset)	24/59 (41)	26/93 (28) **p=0.023**	4/29 (14)
ACPA positive/patients checked (% of subset)	***reference*** 13/49 (26.5)	*p=0.147* 5/71 (7) **p=0.005**	***p=0.030*** 1/19
Joint erosions/patients checked (% of subset)	***reference*** 20/59 (34)	***p=0.007*** 16/92 (17) **p=0.013**	*p=0.107* 3/28 (11)
Anti-Ro positive/patients checked (% of subset)	***reference*** 29/60 (48)	***p=0.024*** 58/91 (64) **p=0.147**	***p=0.042*** 15/29 (52)

Table 1: different characteristics of patients according to arthritis timing of onset and cluster with other manifestions. Legend: ILD= interstitial lung disease; IQR= interquartile range; RF= rheumatoid factor; ACPA= anti-cyclic citrullinated peptide antibodies. Statistical analysis: µ Kruskal Wallis, * Mann-Whitney test, other Chi-square test.

^ median time to arthritis appearance from disease onset in Group 3: 14 months (Interquartile range 6-32).

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Abstract Number: 2373

Frequency of Antinuclear (ANA), Myositis-Specific (MSA) and Myositis-Associated Antibodies (MAA) in Patients with Idiopathic Inflammatory Myopathies (IIM) from Mexico, Central and South America Centers: Data from the Panlar Myositis Study Group.

Yelitza Gonzalez-Bello[1,2], Daniel Garcia-Cerda[3], Gabriel Medrano-Ramírez[4], José E. Navarro-Zarza[5], Lilia Andrade-Ortega[6], Marco Maradiaga-Ceceña[7], Alicia Cardenas-Anaya[8], Arnulfo H. Nava-Zavala[3,9], Gerardo Orozco-Barocio[8], Armando Rojo-Mejia[10], Esthela Loyo[11], Paola Gottschalk[11], Graciela Gómez[12], Marvin J. Fritzler[13] and Ignacio Garcia-De La Torre[8], [1]Immunology and Rheumatlogy, Universidad de Guadalajara, Zapopan, Jalisco, Mexico, [2]Immunology and Rheumatology, Hospital General de Occidente, Secretaria de Salud Jalisco, Guadalajara, Jalisco, Mexico, [3]Immunology and Rheumatology, Hospital General de Occidente, Secretaria de Salud Jalisco, Zapopan, Jal., Mexico, [4]Rheumatology, Hospital General de Mexico, Secretaria de Salud, Mexico City, Mexico, [5]Medicine, Hospital General Raymundo Abarca Alarcón, Chilpancingo, Mexico, [6]Rheumatology, Centro Medico Nacional 20 de Noviembre, ISSSTE, Mexico City, Mexico, [7]Rheumatology, Hospital General de Culiacan de la Secretaría de Salud, Culiacan, Sin., Mexico, [8]Immunology and Rheumatology, Hospital General de Occidente, Secretaria de Salud Jalisco, Zapopan, Jalisco, Mexico, [9]UMAE, Hospital de Especialidades Centro Médico Nacional de Occidente, IMSS, Guadalajara, Jalisco, Mexico, [10]Rheumatology, Clinica San Pablo, Lima, Peru, [11]Rheumatology, Hospital Regional Universitario, Santiago, Dominican Republic, [12]Rheumatology, Instituto de Investigaciones Medicas Alfredo Lanari, Buenos Aires, Argentina, [13]Medicine, University of Calgary, Calgary, AB, Canada

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Background/Purpose: Dermatomyositis (DM) and polymyositis (PM) are forms of IIM that involve skeletal muscle as well as many other organs. As in other systemic rheumatic diseases the IIM are characterized by the production of various autoantibodies that are of diagnostic and prognostic help because they are frequently associated with specific clinical subgroups. To determine the frequency of anti-nuclear antibodies (ANA), myositis specific autoantibodies (MSA) and myositis associated autoantibodies (MAA) in Latin-American patients with IIM from various centers of Mexico, Central and South America.

Methods: 155 serum samples from unselected patients with IIM were included in the study: 109 from México, 20 from Peru, 16 from Dominican Republic and 10 from Argentina. DM and PM were diagnosed according to the Bohan and Peter criteria**.** ANA were detected by IIF on HEp-2 cells (Antibodies Inc., Davis, CA, USA), MSA and MAA were tested by a line immunoassay method (Euroline Myositis Antigens Profile 3) (Euroimmun, Luebeck, Germany). In addition, anti-HMGCR was detected with an addressable laser bead immunoassay (ALBIA: Luminex)

Results: Of the 155 IIM patients, 106 (68%) had DM, 37 (24%) PM and 12 (8%) JDM. Mean age 42.4 (6-79 years), 117 (75%) were female and 38 (25%) were male. The frequency of ANA was 51%, being more frequent in Mexico (54%) than in Argentina (50%), Dominican Republic (44%), and Peru (40%); not statistically significant ($p = 0.20$; Chi square test for trend). The most frequent patterns were speckled (82%) and cytoplasmic (10%). The highest dilution (1:1,280) was present in 42% of the patients. The frequency of MSA was Mi-2 (21%), HMGCR (6%), Jo-1 (2.5%), PL-12 (2.5%), SRP (2.5%), PL-7 (1.2%), EJ (1.2%), and OJ (1.2%). Anti-Jo-1 was not present in the sera from Peru and Dominican Republic. The frequency of MAA was Ro-52/TRIM21 (18%), PM-Scl75 (3.8%), Ku (3.8%) and PM-Scl100 (1.5%); however, anti-Ro52/TRIM21 was not detected in sera from Peru and Dominican Republic.

Conclusion: This is the first study of ANA, MSA and MAA from eight centers in the PANLAR myositis study group. We observed a general prevalence of 51% of ANA by IIF, but more frequent in Mexico (54%). In relation to MSA and MAA, anti-Mi-2 was the more frequent (21%), a finding that is in contrast to studies in other geographic areas in which anti-synthetase antibodies tend to be more common. In general, we found some differences in the presence of these two groups of antibodies in the Latin-American countries included in this study.

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Abstract Number: 2374

Pulmonary Arterial Hypertension in Patients with Anti-PM-Scl Antibody

Hiromichi Tamaki[1], Ruchi Yadav[2], James Bena[3] and Soumya Chatterjee[4], [1]Department of Rheumatic and Immunologic Diseases, Cleveland Clinic Foundation, Cleveland, OH, [2]Diagnostic Radiology, Cleveland Clinic, Cleveland, OH, [3]Department of Quantitative Health Sciences, Cleveland Clinic Foundation, Cleveland, OH, [4]Cleveland Clinic Foundation, Cleveland, OH
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Background/Purpose: Pulmonary arterial hypertension (PAH) may be a disease manifestation of patients with anti-PM-Scl antibody (PM-Scl). In the 2014 ACR annual meeting we reported significantly higher prevalence of precapillary PAH proven by right heart catheterization (RHC) in our patients with PM-Scl compared to historical general population. This study aimed to further characterize PAH in our cohort of patients with PM-Scl.

Methods: All patients screened for PM-Scl between October 1999 and April 2014 were evaluated through our electronic medical record. PAH had to be established by RHC and patients were further subdivided into 'PAH with interstitial lung disease (ILD)' and 'PAH without ILD'. The patients were defined to have 'PAH with ILD' if RHC confirmed pre-capillary PAH and forced vital capacity (FVC) was < 60% of predicted. High resolution CT scans (HRCT) were reviewed by a thoracic radiologist with expertise in ILD (RY), and scored to estimate severity of ILD according to the criteria defined by Ooi et al (Acta Radiologica 2003;44:258-264). Radiographic diagnoses on HRCT [cellular non-specific interstitial pneumonia (NSIP), fibrotic NSIP, usual interstitial pneumonia (UIP), and organizing pneumonia (OP)] were determined. Also, the correlation between HRCT score and mean pulmonary artery pressure (mPAP) was analyzed.

Prevalence of PAH in the general population and in patients with SSc were identified by a systematic literature review. A meta-analysis was performed to formulate prevalence of pre-capillary PAH in SSc patients both with and without ILD. Estimates of prevalence were compared using exact binomial tests.

Results: Of the 42 patients with PM-Scl, 3 patients (7.1%) had PAH with ILD and 2 patients (4.8%) had PAH without ILD. Among the 3 patients with PAH with ILD, 2 had cellular NSIP and 1 had UIP. Due to the small sample size it was difficult to establish any significant linear correlation between mPAP and HRCT score. Systematic literature review identified 5 studies looking at prevalence of PAH in the general population, 3 evaluating PAH with ILD in SSc and 7 assessing PAH without ILD in SSc. Based on these studies the mean prevalence of PAH in the general population was 8.6/million and the maximum estimated prevalence of PAH in the general population was 13.8/million. These numbers were statistically lower than the prevalence of pre-capillary PAH in our cohort ($P<0.001$) and that of PAH without ILD ($P<0.001$). Meta-analysis revealed the estimated prevalence of pre-capillary PAH in patients with SSc was 6.3% (95%CI 4.6-8.6%), that of PAH with ILD in patients with SSc was 2.1% (95%CI 1.3-3.5%), and that of PAH without ILD in patients with SSc was 6.4% (95%CI 4.6-9.0%). In comparison to our cohort with PM-Scl no statistically significant difference was noted but there was a trend towards a higher prevalence of PAH with ILD in our cohort compared to that in SSc patients (7.1% vs 2.1%, $P=0.058$).

Conclusion: Prevalence of PAH in patients with PM-Scl may be higher than that in the general population but may be comparable to the prevalence of PAH in SSc. Prevalence of PAH with ILD may be higher in patients with PM-Scl compared to that in SSc patients. In this small study, it was difficult to ascertain any correlation between ILD severity and mPAP.

Disclosure: H. Tamaki, None; **R. Yadav**, None; **J. Bena**, None; **S. Chatterjee**, None.

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Abstract Number: 2375

Interstitial Lung Disease in Patients with Anti-PM-Scl Antibody

Hiromichi Tamaki[1], Ruchi Yadav[2], James Bena[3] and Soumya Chatterjee[4], [1]Department of Rheumatic and Immunologic Diseases, Cleveland Clinic Foundation, Cleveland, OH, [2]Diagnostic Radiology, Cleveland Clinic, Cleveland, OH, [3]Department of Quantitative Health Sciences, Cleveland Clinic Foundation, Cleveland, OH, [4]Cleveland Clinic Foundation, Cleveland, OH
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Background/Purpose: Patients with anti-PM-Scl antibody (PM-Scl) can present with several different phenotypes: polymyositis (PM), dermtomyositis (DM), systemic sclerosis (SSc), scleromyositis, or sclero-dermatomyositis. Interstitial Lung Disease (ILD) is a disease manifestation of SSc and PM/DM. However, characteristics of ILD in patients with PM-Scl have not been characterized in the published literature.

Methods: All patients screened for PM-Scl between October 1999 and April 2014 were evaluated through our electronic medical record (EMR) and patients with positive PM-Scl were identified. Data on demographics, rheumatologic diagnoses (PM, DM, SSc, PM-SSc, DM-SSc), and high resolution computed tomography (HRCT) defined interstitial lung disease (ILD) were extracted from their EMR. Available HRCT images were reviewed by a thoracic radiologist with expertise in ILD (RY). Radiographic diagnoses on thoracic HRCT scan [cellular non-specific interstitial pneumonia (NSIP), fibrotic NSIP, usual interstitial pneumonia (UIP), and organizing pneumonia (OP)] were determined. The degree of parenchymal inflammation and fibrosis were scored using the criteria defined by Ooi (Acta Radiologica. 2003;44:258-264) Comparisons between initial and follow-up scans were performed using Wilcoxon signed rank tests.

Results: PM-Scl was detected in 42 patients. Of these, ILD was described on HRCT scan in 27 patients (64.2%). HRCT images were available for review in 23 patients; 17 (73.9%) were female. The rheumatologic diagnoses of these patients include diffuse cutaneous SSc (dcSSc) (n=1), limited cutaneous SSc (lcSSc) (n=4), PM (n=6), DM (n=3), overlap of dcSSc and DM (n=1), overlap of lcSSc and PM (n=2), overlap of lcSSc and DM (n=4) and other diagnoses (n=2). HRCT diagnoses of these 23 patients include fibrotic NSIP (n=13), cellular NSIP (n=6), organizing pneumonia (OP) (n=2), UIP (n=1), and bronchiolitis (n=1). Fifteen patients had follow-up HRCT images available after a mean interval of 46.5 months. The initial HRCT scans indicated fibrotic NSIP (n=8), cellular NSIP (n=5) and OP (n=2). Of the 5 patients with initial cellular NSIP, 3 patients continued as cellular NSIP and 2 progressed into fibrotic NSIP. Two patients with initial OP developed fibrotic NSIP on follow up HRCT scan. The mean total HRCT score on the initial scan was 6 and the mean HRCT score on the follow up scan was 6.6 (P=0.14). The mean inflammation score on the initial scan was 4.9 and that of fibrosis score was 1.1. On the follow up HRCT scan the inflammation score was 4.4 (P=0.41) and the fibrosis score was 2.2 (P=0.063). All patients received immunosuppressive therapy including glucocorticoids (n=15), azathioprine (n=10), mycophenolate mofetil (n=4), methotrexate (n=3), tacrolimus (n=2), rituximab (n=2), leflunomide (n=2), cyclophosphamide (n=1) and intravenous immunoglobulin (n=4).

Conclusion: NSIP was the predominant HRCT-based subtype of ILD in our cohort of patients with PM-Scl. All patients received immunosuppressive therapy. The total lung score did not change significantly over a mean follow-up period of 46.5 months but fibrosis score showed an upward trend over the study period.

Disclosure: H. Tamaki, None; **R. Yadav**, None; **J. Bena**, None; **S. Chatterjee**, None.

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Clinical Features in Dermatomyositis Patients with Novel Autoantibody to Small Ubiquitin-like Modifier Activating Enzymes (Anti-SAE Antibody) and Relationship to Interstitial Lung Disease: A Systematic Review of 29 Cases

Sirada Panupattanapong[1], Jessica Sun[2] and Kevin Baszis[1], [1]Pediatrics, Division of Rheumatology, Washington University School of Medicine, St. Louis Children's Hospital, St. Louis, MO, [2]Pediatric, Division of Rheumatology, Washington University School of Medicine, St. Louis Children's Hospital, St. Louis, MO

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SESSION INFORMATION

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Session Title: Muscle Biology, Myositis and Myopathies Poster II: Autoantibodies and Treatments in Inflammatory Myopathies

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose:

Anti-SAE antibody is a novel myositis-specific antibody first described in 2007. SAE is an enzyme that facilitates sumoylation, leading to the formation of stable conjugates of target proteins including transcription factors. Anti-SAE is observed exclusively in dermatomyositis patients and has not been seen in other types of myositis or healthy controls.

We conducted a systematic review of case series to summarize the clinical features of this group of patients. As interstitial lung disease is a major cause of mortality in dermatomyositis, we conducted a univariate analysis to identify association of clinical features with interstitial lung disease.

Methods:

A systematic electronic search of PubMed and EMBASE was conducted, with no language restriction, from database inception through April 2015, for articles containing clinical data of patients with anti-SAE antibodies. Statistic analysis was done using Excel and SPSS version 22.0. Characterization of the features was analyzed using descriptive statistics and Fisher's exact test.

Results:

Five publications met our inclusion criteria. From 874 reported dermatomyositis cases, anti-SAE was detected in 29 cases (3.3%). There was no sex preponderance (male 41.6% and female 58.3%). The mean age of onset was 59 ± 16.3 years, except for one case of juvenile dermatomyositis, which presented at 5 years of age. The majority of patients with anti-SAE (70%) initially presented with hallmark cutaneous findings; 84% of these patients eventually developed myositis. The most common cutaneous findings were Gottron papules (81.8%), heliotrope rash (68.9%), periungual lesions (66.6%), and Gottron signs (lesions on elbows and knees, 65.5%). 56% of patients had systemic symptoms, including fever, weight loss and elevated inflammatory markers. Arthritis (13.7%), Raynaud's phenomenon (12.5%), and mechanic's hands (5.5%) are uncommon features. None developed calcinosis. Concurrent malignancy presented in 20.7% of cases (2 colon, 1 rectal and 1 ovarian cancer). 44.4% of patients had dysphagia, and 25% of them had more severe disease requiring enteral feeding. Degree of interstitial lung disease was mild and was reported in 31% of patients. In comparison between individuals with and without interstitial lung disease, periungual lesions, shawl sign and V-sign were associated with presence of interstitial lung disease (p 0.008, p 0.004, and p 0.048 respectively).

Conclusion:

The most prominent presenting features of dermatomyositis patients with anti-SAE are systemic symptoms and cutaneous findings, the majority of which eventually develop muscle involvement. Interstitial lung disease and dysphagia are fairly common. Further study from larger databases is warranted to accurately evaluate the distinct clinical features, prognosis and response to treatment of patients with this antibody.

Table 1: Clinical features and association to interstitial lung disease

Clinical features	Total (%)	ILD (%) n=9	Non-ILD (%) n =20	p-value
Arthritis	4/29 (13.7%)	0	21.0%	0.65
Calcinosis	0	0	0	-
Cancer	6/29 (20.7%)	22.2%	20.0%	0.89
Dysphagia	12/27 (44.4%)	44.4%	44.4%	1.0
Elevated CK	20/25 (80%)	75.0%	82.3%	0.672
Mechanic's hands	1/18 (5.5%)	12.5%	0	0.193
Gottron papules	18/22 (81.8%)	75%	85.7%	0.537
Gottron signs	19/29 (65.5%)	44.4%	75%	0.114
Heliotrope rash	20/29 (68.9%)	77.7%	65.0%	0.159
Muscle weakness	26/27 (96.3%)	87.5%	100%	0.112
Periungual lesions	16/24 (66.6%)	100%	52.9%	0.008
Raynaud's phenomenon	2/16 (12.5%)	0	20%	0.152
Shawl sign	11/20 (55%)	88.8%	27.2%	0.004
V-sign	13/25 (52%)	77.8%	37.5%	0.048
Isolated cutaneous findings at onset	19/27 (70.3%)	77.8%	66.6%	0.545
Cutaneous and muscular findings at onset	8/27 (29.6%)	22.2%	33.3%	0.545
Systemic symptoms	14/25 (56%)	75%	88.8%	0.181

Disclosure: S. Panupattanapong, None; **J. Sun**, None; **K. Baszis**, None.

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Anti 3-Hydroxy-3-Methylglutaryl-Coenzyme a Reductase in Systremic Sclerosis

Yael Luck and Matt Stephenson, Marie Hudson, Mianbo Wang, CSRG, Murray Baron, Marvin J. Fritzler, rheumatology, Mcgill University, montreal, QC, Canada

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Background/Purpose:

Statins are among the most frequently prescribed medications for the treatment of dyslipidemia. Amongst users, between 9-20% of

patients will develop a self- limited myopathy in which musculoskeletal symptoms may range from myalgia to rhabdomyolysis (0.4/10 000 patient years)(1-4). In the last decade, there has been considerable interest focusing on an association between statin exposure, anti-3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR) antibodies and autoimmune necrotizing myopathy. Systemic sclerosis is a highly heterogenous disease characterized, among other things, by autoantibodies and inflammatory myositis. The objective of this study was to investigate the frequency of anti- HMGCR antibodies in SSc and associations with inflammatory myositis and statin exposure.

Methods:

This was a cross-sectional, multicenter study of 306 subjects from the Canadian Scleroderma Research Group cohort who had complete data on statin exposure and history of inflammatory myositis (recorded by a study physician at baseline) and anti-HMGCR antibodies assayed by an addressable laser bead immunoassay (ALBIA, Luminex, Austin, TX (cutoff 200 units, high positive cutoff 500 units). Descriptive statistics were used to summarize the baseline characteristics of the subjects. Fisher's exact test for categorical variables and Mann Whitney U test for continuous variables were used to compute p values. All statistical analyses were performed with SAS v.9.2 (SAS Institute, USA).

Results:

Fifty-one (17%) subjects had anti-HMGCR antibodies, of which only 4 (1.3%) had high positive titers (Table 1). Subjects with high positive anti-HMGCR antibodies titers tended to be older (mean 60.3+14.9 versus 56.1+12.5 years) compared to negative subjects. They tended to have shorter disease duration (8.6+5.6 versus 11.2+9.0 years) and more diffuse skin involvement (75% versus 58%), pulmonary hypertension (67% versus 10%, p=0.03) and interstitial lung disease (75% versus 35%) compared to negative subjects. They also tended to have more severe heart disease when measured on the Medsger Disease Severity Scale (2.0+1.6 vs 0.5+0.9, p=0.005).

Of particular interest, though, none of the subjects with high positive anti-HMGCR antibodies titers had a history of inflammatory myositis, compared to 9% of those with negative titers. In addition, none of those with high positive titers had past or current exposure to statins compared to 11% of those with negative titers.

Conclusion:

High titer anti-HMGCR antibodies are rare in SSc (1.3%) but are not associated with inflammatory myositis or statin exposure. Larger studies will be required to confirm these preliminary observations. Nevertheless, we conclude that anti-HMGCR antibodies are unlikely to play a major role in inflammatory myositis in SSc and that high titers can be present in subjects without exposure to statins.

Table 1 Baseline characteristics

	(-)ve (N=255)		Low (+)ve (N=47)		High (+)ve (N=4)		-ve vs High +ve p values
	Mean or N	SD or %	Mean or N	SD or %	Mean or N	SD or %	
Mean age, years	56.1	12.5	56.4	10.8	60.3	14.9	0.650
Female, %	222	87.1%	42	89.4%	4	100%	0.578
White, %	218	90.5%	41	91.1%	4	100%	0.672
Disease duration, years	11.2	9.0	9.6	6.9	8.6	5.6	0.734
Skin subsets, %							0.354
Limited	154	60.6%	35	74.5%	3	75.0%	
Diffuse	100	39.4%	12	25.5%	1	25.0%	
Modified Rodnan skin score	9.7	9.6	9.5	8.9	13.7	4.7	0.135
Number of GI symptoms (range 0-14)	4.1	3.1	4.3	3.1	5.5	3.8	0.407
Pulmonary hypertension, %	22	10.0%	5	12.5%	2	66.7%	0.030
Interstitial lung disease, %	88	35.2%	15	32.6%	3	75.0%	0.117
FVC, %predicted	89.4	18.6	87.5	19.6	73.3	17.6	0.151
DLCO, %predicted	70.0	21.0	72.2	18.2	72.5	25.6	0.787
Inflammatory myositis, %	23	9.0%	3	6.4%	0	0%	0.688
CK (baseline)	113.8	124.0	92.2	70.3	36.8	11.1	0.004
Overlap with PM/DM, %	6	2.4%	0	0.0%	0	0%	0.910
Medsger Disease severity scores (range 0-10)							
General	0.8	1.2	0.8	1.1	1.3	1.9	0.703
Skin	1.2	0.7	1.2	0.6	1.3	0.6	0.610
Kidney	0.1	0.6	0.0	0.0	0.0	0.0	0.594
Peripheral vascular	1.5	1.3	1.6	1.2	2.3	1.7	0.297

Joint/tendon	0.7	1.2	0.9	1.4	1.0	1.7	0.893
Muscle	0.2	0.7	0.3	0.9	0.5	1.0	0.370
Gastrointestinal	1.9	0.7	1.8	0.8	2.3	0.5	0.281
Lung	1.3	1.1	1.4	1.1	2.0	1.8	0.404
Heart	0.4	0.9	0.5	0.9	2.0	1.6	0.005
Antibodies, %							
Centromere	92	36.1%	19	40.4%	3	75.0%	0.124
Topoisomerase	36	14.1%	11	23.4%	0	0%	0.548
RNA Pol-III	48	18.9%	7	14.9%	0	0%	0.437
Pm/Scl (PM1-alpha)	17	6.8%	4	18.5%	0	0%	0.758
Statins							0.631
Current	26	10.2%	7	14.9%	0	0%	
In the past	2	0.8%	1	2.1%	0	0%	
Never	227	89.0%	39	83.0%	4	100%	

Disclosure: Y. Luck, None;

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Abstract Number: 2378

Mycophenolate Mofetil As a Steroid Sparing Agent in Polymyositis and Dermatomyositis: a Systematic Review of the Literature

Janet Roberts and Stephanie O. Keeling, Medicine, University of Alberta, Edmonton, AB, Canada
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Background/Purpose:

Idiopathic inflammatory myopathies (IM's) including polymyositis (PM) and dermatomyositis (DM) are rare systemic autoimmune diseases causing chronic muscle inflammation with significant morbidity and mortality. Corticosteroids are the primary treatment; however, given the chronic nature of these conditions and the inherent risk of long term steroid use, additional immunosuppressive agents are often required. Myocophenolate mofetil (MMF) may be beneficial in the treatment of IM's with a relatively favorable side effect profile. We systematically reviewed the literature to evaluate the benefits of MMF in the treatment of PM and DM.

Methods:

A systematic review of four databases (Embase, Pubmed, Web of Science and Scopus) using keywords pertaining to IM's, DM, PM, immunosuppression and MMF was conducted. All studies up to June 2014 including patients over the age of 18 with PM or DM defined by Bohan and Peter and treated with MMF were included. Two reviewers independently reviewed the title screen

and data was extracted using a standardized form. Primary outcomes included changes in corticosteroid dose, muscle enzymes, strength, skin manifestations, and interstitial lung disease outcomes (ILD) (computed tomography (CT) scan and pulmonary function tests (PFTs)).

Results:

One hundred and ninety (190) full articles were reviewed after the title screen of 458 articles. Eighteen articles met inclusion criteria including 5 case reports, 11 case series and 2 open label trials. A total of 110 patients (PM 16; DM 46) were treated with MMF. Ninety three percent of patients were on concomitant corticosteroids (n=102), with 89% (n=91) decreasing their steroid dose after initiation of MMF. Of those with baseline elevation in muscle enzymes, 77% (n=30) showed a decrease post treatment. In 10 patients, the change in CK was not specified. In those patients with skin manifestations (n=32), 88% (n=28) showed improved skin manifestations. In the 51% (n=56) of ILD patients, improvements were noted in PFTs, perceived dyspnea and CT scan findings, including improvement in ground glass opacities and pneumonitis. Side effects (21%) were generally mild, most common being gastrointestinal upset. Only 7% (n=8) required cessation of treatment due to side effects.

Conclusion:

MMF is a potential alternative first line steroid-sparing agent in those with IM's. High quality trials are needed to further evaluate the efficacy and safety of MMF in this patient population. Lack of consensus on diagnostic approaches and outcome measures in IM research limits the ability to compare individual patients and studies. The development of core set measures by the International Myositis Assessment and Clinical Studies Groups (IMACS) will allow collaboration between multiple disciplines and centers to increase the quality and number of trials in this area.

Table 1. Change in IM outcomes with Mycophenolate Mofetil According to Study

Study	Δ in Prednisone	Muscle Manifestations	Pulmonary Manifestations	Skin Manifestations	Adverse Events (# patients)
Caramaschi et al Case report 1PM	40% ↓	CK ↓	N/A	N/A	None
Edge et al Open label trial 12 DM	94% ↓	Strength ↑ in 11	N/A	Improved in 10	Breast CA (1); Lymphoma (1); Cytopenia (2); Nausea (1) Stopped (2)
Rowin et al Case Series 10 DM	90 % ↓ 6 weaned	Strength ↑ in 5	N/A	N/A	Opportunistic Infections (3) Stopped (3)
Schneider et al Case Report 1 PM	100% ↓	Strength ↑	N/A	N/A	None
Gelber et al Case Series 4 DM	57% ↓	CK ↓ Strength ↑	N/A	Improved	Gastrointestinal upset (1) Stopped (1)

Disclosure: J. Roberts, None; **S. O. Keeling**, None.

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Tausche et al Case Series 4 DM	50% ↓	CK ↓ in 3 Strength ↑ in 3	N/A	Improved in 3	None
Bandelier et al Case Series 2 PM	50% ↑ 83% ↓	CK ↓ (90%)	N/A	N/A	Active colitis (1) Stopped X 4 mos (1)
Tsuchiya et al Case Report 1 DM	66 % ↓	N/A	Resolution of Ground Glass Opacities (31 wks) Resolution of exertional dyspnea	N/A	CMV (1)
Cozzani et al Case Report 1 DM	N/A	N/A	↓ in pneumomediastinum and parenchymal abnormalities (6 wks)	N/A	None
Danieli et al Open Label Trial 4 PM; 3 DM	87% ↓	CK ↓ (92%) Strength ↑ (39%)	N/A	Improved	Nausea (2) Headache (1)
Fischer et al Case Series 32 PM/DM	75% ↓	N/A	9.7% ↑ Forced Vital Capacity (FVC) at 156 wks (p=0.04) “similar trend DLCO" (Diffusing Lung Capacity)	N/A	Unknown
Majithia et al Case Series 3 PM; 4 DM	48% ↓	CK ↓ 88% Strength ↑	N/A	Improved	Cytopenia(1);Stopped(1) Death (1)
Marie et al Case Series 6 PM/DM	Unknown	N/A	“Improved” CT in 3 “Improved” PFT (Pulmonary Function Test) in 5	N/A	None
Mira-Avendano et al	75% ↓	N/A	No Δ in FVC after 12 mos	N/A	Non-specific (4)

Case Series 9 PM/DM			5% ↑ DLCO (p=0.17) 80% improved MMRC score (Modified Medical Research Council Dyspnea Scale)		
Morganroth et al Case Series 4 DM	73% ↓ 3 weaned	CK ↓ Strength ↑	Improved CT scan in 1 Improved DLCO and FVC in 4 Improved Total Lung Capacity in 2 Resolution of dyspnea in 3	Improved in 3	Tinea pedis (1)
Saketoo et. al Case Series 2 PM	98% ↓	CK ↓ Strength ↑	CT stable in 2 PFT ↓ in 1; stable in 1 Resolution of dyspnea in 2	N/A	Diarrhea (1)
Hervier et. al Case Report 1 DM	Slowly Withdrawn	CK ↓	"Stable improvement" PFT's	Improved	None
Pisoni et. al Case Series 6 PM/DM	38% ↓	CK ↓ 69% Strength ↑	N/A	N/A	Nausea & Headache(2)

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Abstract Number: 2379

Clinical Follow-up Predictors of Disease Pattern Change in Anti Jo-1 Positive Antisynthetase Syndrome: Results from a Multicenter, International and Retrospective Study

Franco Franceschini[1], Elena Bartoloni-Bocci[2], Santos Castañeda[3], Laura Nuno[4], Carlo Alberto Scirè[5], Francisco Javier López-Longo[6], Julia Martínez-Barrio[7], Ilaria Cavazzana[1], Paolo Airò[8], Javier Bachiller Corral[9], Alberto Sifuentes Giraldo[10], Rossella Neri[11], Simone Barsotti[12], Roberto Caporali[13], Carlomaurizio Montecucco[14], Marcello Govoni[15], Renato La Corte[15], Federica Furini[15], Florenzo Iannone[16], Margherita Giannini[17], Enrico Fusaro[18], Simone Parisi[19], Giuseppe Paolazzi[20], Giovanni Barausse[21], Raffaele Pellerito[22], Alessandra Russo[22], Lesley Ann Saketkoo[23], Norberto Ortego-Centeno[24], Luca Quartuccio[25], Christof Specker[26], Andreas Schwarting[27], Kostantinos Triantafyllias[28], Carlo Selmi[29], Fausto Salaffi[30], Marco Amedeo Cimmino[31], Annamaria Iuliano[32], Fabrizio Conti[33], Gianluigi Baiocchi[34], Elena Bravi[35], Anna Ghirardello[36], Trinitario Pina[37],

Miguel A. Gonzalez-Gay[38], Lorenzo Cavagna[39] and AENEAS (American and European NEtwork of Antisynthetase Syndrome) collaborative group, [1]Rheumatology and Clinical Immunology, Spedali Civili and University of Brescia, Brescia, Italy, [2]Department of Medicine, Rheumatology Unit, University of Perugia, Perugia, Italy, [3]Rheumatology, H.U. La Princesa, Madrid, Spain, [4]Rheumatology, Hospital Universitario La Paz, Madrid, Spain, [5]Epidemiology Unit – Italian Society for Rheumatology (SIR), Milano, Italy, [6]Rheumatology, Hospital General Universitario Gregorio Marañón, Madrid, Spain, [7]Servicio de Reumatologia, Hospital General Universitario Gregorio Marañón, Madrid, Spain, [8]Rheumatology Unit, Spedali Civili of Brescia, Brescia, Italy, [9]Rheumatology, University Hospital Ramón y Cajal, Madrid, Spain, [10]Department of Rheumatology, University Hospital Ramón y Cajal, Madrid, Spain, [11]Rheumatology Unit, University of Pisa, Italy, Pisa, Italy, [12]Division of Rheumatology, Department of Clinical and Experimental Medicine, University of Pisa, Pisa, Italy, [13]University of Pavia and IRCCS Policlinico S. Matteo Foundation, Pavia, Italy, [14]Division of Rheumatology, University of Pavia, IRCCS Foundation Policlinico S. Matteo, Pavia, Italy, [15]UOC Reumatologia, Azienda Ospedaliera Universitaria S. Anna, Ferrara, Italy, [16]Interdisciplinary Department of Medicine (DIM), Rheumatology Unit, University of Bari, Bari, Italy, [17]DIM, Rheumatology Unit, Bari, Italy, [18]Department of Rheumatology, Città della Salute e della Scienza, Torino, Italy, [19]Department of Rheumatology, Città Della Salute e della Scienza, Torino, Italy, [20]Rheumatology Unit, Santa Chiara Hospital, Trento, Italy, [21]Rheumatology, Ospedale di Trento, Trento, Italy, [22]Division of Rheumatology, Mauriziano Hospital, Turin, Italy, [23]New Orleans Scleroderma and Sarcoidosis Patient Care and Research Center, Tulane University Lung Center, New Orleans, LA, [24]Hospital San Cecilio. Granada, Granada, Spain, [25]S. Maria della Misericordia, University of Udine, Italy, Udine, Italy, [26]Department for Rheumatology and Clinical Immunology, St. Josef Krankenhaus, University Clinic, Essen, Germany, [27]Department of Internal Medicine, Rheumatology and Clinical Immunology, University Hospital Johannes-Gutenberg, Mainz, Germany, [28]ACURA Rheumatology Center, Bad Kreuznach, Germany, [29]Internal Medicine- Unit of Rheumatology and Clinical Immunology, Humanitas Clinical and Research Center, Rozzano, Italy, [30]Rheumatology Department, Polytechnic University of Marche, C. Urbani Hospital, Jesi,, Ancona, Italy, [31]Research Laboratory and Academic Unit of Clinical Rheumatology, Department of Internal Medicine, University of Genoa, Genoa, Italy, [32]Osp. San Camillo, Roma, Italy, [33]Rheumatology Unit, Department of Internal Medicine and Medical Specialties, Sapienza University of Rome, Rome, Italy, [34]Rheumatology Unit, Department of Internal Medicine, S.Maria Hospital –IRCCS, Reggio Emilia, Italy, [35]Internal Medicine, Rheumatology Unit, Ospedale Guglielmo da Saliceto, Piacenza, Italy, [36]Department of Medicine-DIMED, University of Padova, Padova, Italy, [37]Rheumatology, Hospital Universitario Marqués de Valdecilla. IDIVAL, Santander, Spain, [38]Reumatologia, Hospital Universitario Marqués de Valdecilla, IDIVAL, University of Cantabria, Santander, Spain, [39]Division of Rheumatology, University and IRCCS Policlinico S. Matteo Foundation, Pavia, Italy
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Background/Purpose: arthritis, myositis and interstitial lung disease (ILD) constitute the classic clinical triad of antisynthetase syndrome (ASSD). Even if reported in up to 90% of cases, concomitant onset of these manifestations uncommon. A recent study has shown that 60% of anti Jo-1 positive ASSD presenting without the complete triad may develop other manifestations in a very wide range of time. At baseline, the only predictor of subsequent disease pattern evolution is the onset with just one of the classic triad findings, whereas the occurrence of other ASSD typical but less frequently observed manifestations, such as Raynaud's phenomenon (RP), fever or mechanic's hands (MH), does not add further information. The aim of this multicenter, international, retrospective study is to assess whether the appearance of RP, fever or MH (defined as *accompanying features*) during the follow-up may predict the subsequent occurrence of the baseline absent classic triad manifestations

Methods: anti Jo-1 positive patients presenting with no more than 2 classic triad findings (for a practical purpose defined as *incomplete ASSD*) were included in the analysis. Clinical characteristics and different clusters of disease manifestations were retrospectively collected and analyzed

Results: we identified 170 patients (126 females, 44 males) with incomplete ASSD. The median age at disease onset was 53 years (IQR 42-64), median follow-up 88 months (IQR 48-155). Ninety-nine patients (58%) developed new classic triad manifestations and 41 (24%) new accompanying features, especially in those patients in whom isolated arthritis was the first manifestation (p=0.0049). In these 41 patients, the subsequent ex-novo appearance of classic triad features was statistically

increased (p=0.0170) and it was always concomitant or subsequent to the development of accompanying features. Furthermore, these patients had more frequently all triad manifestations (p=0.0004). The clinical characteristics of patients and statistical significances are reported in table 1 and 2

Conclusion: in anti Jo-1 positive patients with incomplete ASSD the occurrence of RP, fever or MH during the follow-up may suggest the subsequent occurrence of new classic triad manifestations

References

1. Cavagna L, et al. Ann Rheum Dis 2015;74(Suppl2): 601
2. Cavagna L, et al. Arthritis Rheum 2014;66(Suppl):550

	New accompanying features		p
	Yes	Not	
Patients number (%)	41 (24)	129 (76)	-
Female sex (% of subset)	30 (73)	96 (74.5)	0.964
Median age in years at disease onset (IQR)	54 (42-64)	49 (40.5-60.5)	0.240*
Median follow-up in months (IQR)	100 (61-167)	84 (43.5-153)	0.365*
Baseline triad manifestations			
Isolated arthritis (% of subset)	20 (49)	31 (24)	0.0049
Isolated myositis (% of subset)	6 (14.5)	22 (17)	0.970
Isolated ILD (% of subset)	3 (7)	22 (17)	0.200
Arthritis and myositis (% of subset)	6 (14.5)	21 (16.5)	0.995
Arthritis and ILD (% of subset)	2 (5)	12 (9)	0.570
Myositis and ILD (% of subset)	4 (10)	21 (16.5)	0.440
Final triad manifestations			
Isolated arthritis (% of subset)	1 (2.5)	4 (3)	0.775
Isolated myositis (% of subset)	0 (0)	5 (4)	0.454
Isolated ILD (% of subset)	1 (2.5)	14 (11)	0.180
Arthritis and myositis (% of subset)	3 (7.5)	22 (17)	0.200
Arthritis and ILD (% of subset)	4 (10)	19 (15)	0.583
Myositis and ILD (% of subset)	6 (15)	25 (19)	0.650
Arthritis, myositis and ILD (% of subset)	26 (62.5)	40 (31)	0.0004
New development of classic triad manifestations (% of subset)	33 (80.5)	66 (51)	0.0170

Table 1: overtime disease pattern changes of classic triad manifestations (eg arthritis, myositis and ILD) according to the occurrence or not of accompanying features (eg Raynaud's phenomenon, fever, mechanic's hands) during the follow-up. Legend: ILD: interstitial lung disease. *Independent Sample T test (if equal variances) or Welch-test (if unequal variances). Others: Chi-square test.

	Disease onset	Last follow-up	p*
Total Raynaud's phenomenon (%)	37 (22)	59 (35)	0.011
Total Mechanic's hands (%)	31 (18)	50 (29)	0.022
Total Fever (%)	36 (21)	57 (34)	0.015
Isolated Raynaud's phenomenon (%)	26 (15)	26 (15)	0.880
Isolated Mechanic's hands (%)	16 (9)	17 (10)	1.000
Isolated Fever (%)	29 (17)	22 (13)	0.362
Raynaud's phenomenon and Mechanic's hands (%)	4 (2)	9 (5)	0.680
Raynaud's phenomenon and Fever (%)	2 (1)	11 (6.5)	0.0237
Fever and mechanic's hands (%)	6 (4)	11 (6.5)	0.320
Raynaud's phenomenon, fever and mechanic's hands (%)	5 (3)	13 (8)	0.090
None (%)	82 (48)	61 (36)	0.0250

Table 2: prevalence and cluster of Raynaud's phenomenon, mechanic's hands and fever at baseline and at last available follow-up. * Chi-square test.

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Abstract Number: 2380

Jo-1 Positive Myositis Patients Tend to Have More Severe Muscle and Lung Involvement Than PM-Scl Positive Patients

Julie J. Paik[1], Arash Lahoutiharahdashti[2], Andrew Mammen[3] and Lisa Christopher-Stine[4], [1]Division of Rheumatology, Johns Hopkins University School of Medicine, Baltimore, MD, [2]Rheumatology, Johns Hopkins University School of Medicine, Baltimore, MD, [3]Center Tower Ste 5300, Johns Hopkins University School of Medicine, Baltimore, MD, [4]Ste 4100 Rm 409, Johns Hopkins University School of Medicine, Baltimore, MD

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SESSION INFORMATION

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Session Title: Muscle Biology, Myositis and Myopathies Poster II: Autoantibodies and Treatments in Inflammatory Myopathies

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Jo-1 positive myositis patients tend to have more severe muscle and lung involvement than PM-Scl positive patients

Background/Purpose: Jo-1 and PM-Scl positive myositis patients share many clinical features, however the differences between these two subtypes is unknown. The purpose of this study was to determine the unique phenotypes of these two subgroups.

Methods: From 5/1/2002 to 4/15/2015, 1700 patients with suspected myositis were enrolled in a longitudinal cohort study at our center. Patients were included in our analysis if they met Bohan and Peter (B&P) criteria for definite/probable polymyositis (PM)

or dermatomyositis (DM) and were positive for Jo-1 antibody or PM-Scl antibody. Only patients who had confirmed autoantibody testing at a CLIA certified lab were included. Retrospective chart review was conducted from the time of first clinic visit until 4/15/2015 or last clinical encounter. To determine the severity of disease phenotype maximum creatine kinase (CK) and aldolase, the lowest DLCO and forced vital capacity (FVC) was used to assess the severity of lung function. Muscle strength at first visit was scored on a modified 10-point scale adapted from the manual muscle strength testing scale recommended by the International Myositis Assessment and Clinical Studies Group. Right and left sided measurements were combined (range of 0-20). The presence of edema or fatty replacement on MRI of the thighs was categorized as a dichotomous variable. Pulmonary hypertension was defined by either echocardiography or cardiac catheterization and ILD on imaging findings. Differences in baseline characteristics of patients with Jo-1 vs. PM-Scl antibodies were assessed by Fisher's exact and student's t tests.

Results: A total of 91 patients were identified in our single-center database who met the B&P criteria for PM or DM and were positive for either Jo-1 or PM-Scl autoantibodies. Of the 91 patients, 60/91 (65.9%) were Jo-1 positive and 31/91 (34.1%) were PM-Scl positive. The mean follow-up time was 50.8 months for both groups. The mean age at diagnosis of the Jo-1 positive group was 45.8 ± 12.9 years vs. 47.1 ±14.3 years in the PM-Scl group. At initial visit to our center, muscle strength did not differ between the two groups. The mean maximum CK was 2197 ± 2589 IU in Jo-1 positive patients vs. 610 ± 893 IU in PM-Scl positive patients (p=0.002). ILD was found more commonly in Jo-1 positive patients (84.8% vs. 46.7%, p=<0.0001), as well as muscle edema on MRI of the thighs (79.1% vs. 25%, p=0.001). Raynaud's phenomenon and deltoid atrophy were more commonly found in PM-Scl patients and both associations were statistically significant.

Conclusion: Jo-1 positive myositis patients tended to have more severe muscle involvement with higher CK levels, more muscle edema on MRI, and more ILD when compared to PM-Scl positive patients.

Table 1. Clinical characteristics of Jo-1 positive vs. PM-Scl positive myositis patients

	Jo-1 positive (n=60)	PM-Scl positive (n=31)	p-value
Age (mean ± SD)	45.8 ± 12.9	47.1 ± 14.3	0.65
Female gender	47 (78.3%)	21 (67.7%)	0.20
White Race	40 (66.7%)	28 (90.3%)	0.10
Arm abduction (0-20)	16.3 ± 4.9	17.6 ± 4.0	0.23
Hip flexor (0-20)	16.5 ± 5.3	17.9 ± 3.3	0.13
Maximum CK (mean ± SD)	2197 ± 2588	610 ± 893	0.002
Maximum aldolase	39.6 ± 54.0	15.2 ± 13.9	0.02
MRI thighs (edema)	34 (79.1%)	3 (25%)	0.001
MRI thighs (fatty replacement)	19 (44.2%)	5 (41.7%)	0.57
Deltoid atrophy	1 (1.7%)	5 (16.1%)	0.02
Raynaud's phenomenon	27 (45%)	21 (67.8%)	0.03
Calcinosis	5 (8.3%)	6 (19.5%)	0.12
Dysphagia	22 (36.7%)	15 (48.4%)	0.20
Mechanic's hands	36 (60%)	16 (51.6%)	0.29
Interstitial lung disease	50 (84.8%)	14 (46.7%)	<0.0001
Pulmonary hypertension	11 (21.2%)	2 (7.4%)	0.10
Lowest FVC	61.5 ± 17.4	69.7 ±17.7	0.11
Lowest DLCO	55.1 ± 19.8	62.5 ± 21.9	0.21
Death	3 (5%)	1 (3.2%)	0.60

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View Abstract and Citation Information Online - http://acrabstracts.org/abstract/jo-1-positive-myositis-patients-tend-to-have-more-severe-muscle-and-lung-involvement-than-pm-scl-positive-patients

Abstract Number: 2381

Postural Stability in Adolescents with Ehlers-Danlos Syndrome (Hypermobility

Type) Following an Exercise Intervention

Jason Long[1], **Stephanie Sabo**[2], Cailee Caldwell[2] and Bailey Petersen[3], [1]Orthopaedic Surgery, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, [2]Occupational and Physical Therapy, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, [3]Kinesiology, Penn State University, State College, PA
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Background/Purpose:

Ehlers-Danlos Syndrome (EDS) comprises a group of disorders marked by abnormal collagen function. In EDS Hypermobility Type (EDS-HT), major diagnostic findings involve joint hypermobility and chronic pain. Physical therapy has been recognized for its benefits to patients with joint hypermobility. Evidence suggests that mechanical interventions may improve pain, strength and stability [1,4]. Pilot findings suggest that an intensive exercise intervention (IEI) may lead to improved joint control, loading, and symmetry [3,4]. The purpose of this study was to assess postural stability (PS) in patients before and after participation in the IEI.

Methods:

Seventeen adolescents with EDS-HT made an initial visit immediately prior to starting the IEI, and a second visit within five days of completing the IEI (a 10-day program focused in neuromuscular re-education, flexibility, strengthening, joint stabilization, and endurance). During each visit, participants underwent PS testing under Eyes Open (EO) and Eyes Closed (EC) conditions. For each trial, ground reaction force data were processed to obtain center of pressure (COP) information. Measures of interest included linear and nonlinear metrics in the A/P and M/L directions. **Results:**

Findings indicated reduced M/L position variability between the EO Pre and EO Post conditions (Fig 1). Significant increases in nonlinear postural control metrics were also observed in the M/L direction, indicating changes in the structure of the M/L position variability (Fig 2). These findings suggest improved ability to stabilize in the M/L direction, with patterns of balance demonstrating increased complexity. This may point to an increase in patients' postural adaptability.

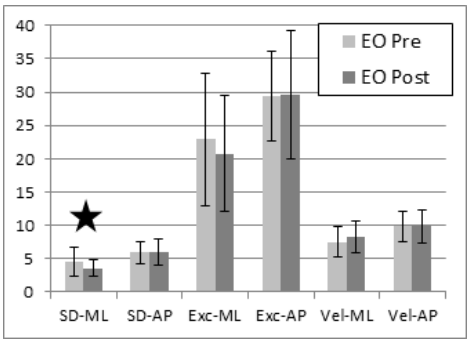

Figure 1: Linear measures of COP excursion (*SD* standard deviation, *Exc* excursion, *Vel* velocity). Star indicates significant difference ($p<0.05$).

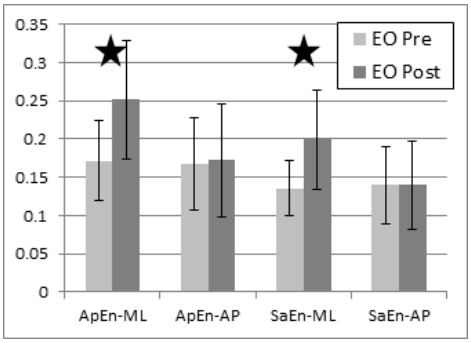

Figure 2: Approximate entropy (*ApEn*) and sample entropy (*SaEn*). Star indicates significant difference ($p<0.01$).

Conclusion:

Significant improvements in PS were observed in adolescents with EDS-HT following the IEI. Further study is warranted to learn how these changes are affected by patients' baseline characteristics (e.g. pain level, fitness level, etc.) Additional stratification by age and gender may also be useful in delineating the most appropriate intervention strategy for subsets of this population.

<>References:

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[3] Simmonds JV et al. *Man Ther* **13**, e1-e11, 2008.

[4] Greenwood NL et al. *Man Ther* **16**, 623-628, 2011.

Disclosure: J. Long, None; **S. Sabo**, None; **C. Caldwell**, None; **B. Petersen**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/postural-stability-in-adolescents-with-ehlers-danlos-syndrome-hypermobility-type-following-an-exercise-intervention

Abstract Number: 2382

An Outsourced Health-Enhancing Physical Activity Program for People with Rheumatoid Arthritis. Exploration of the Maintenance Phase

Christina H. Opava[1], Birgitta Nordgren[1], Cecilia Fridén[1], Ingrid Demmelmaier[1], Gunnar Bergström[2], Ingrid E. Lundberg[3], Alyssa B. Dufour[1,4], Thomas Nessen[1] and PARA Study Group, [1]Department of Neurobiology, Care Sciences and Society, Division of Physiotherapy, Karolinska Institutet, Huddinge, Sweden, [2]Institute of Environmental Medicine, Unit of Intervention and Implementation Research, Karolinska Institutet, Stockholm, Sweden, [3]Karolinska University Hospital, Rheumatology Unit, Department of Medicine, Solna, Karolinska Institutet, Stockholm, Sweden, [4]Institute for Aging Research, Hebrew SeniorLife, Harvard Medical School & Beth Israel Deaconess Medical Center, Boston, MA

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Session Time: 9:00AM-11:00AM

Background/Purpose: Health-enhancing physical activity (HEPA), i.e. at least 150 weekly minutes of moderate-intensity and at least twice-weekly muscle-strengthening activities, is recommended for every adult. Long-term studies on HEPA promotion in rheumatoid arthritis (RA) are scarce. Our aim was to describe HEPA levels and explore aspects of adherence and response during the second year of an outsourced two-year intervention in people with RA.

Methods: Two-hundred and twenty individuals not reaching maintained (>6 months) HEPA were included at baseline and 177 of them (81% women, mean age 60 years, mean time from disease onset 12 years) remained at the end of year two of this uncontrolled cohort study[1]. Adherence, without support from health care, to circuit training at public gyms and moderately intense daily physical activity was prompted and recorded by weekly short text messages. Bi-weekly physiotherapist-led support group meetings to facilitate behavior change during the first intervention year were replaced during year two with optional peer-support groups. Response variables included current (past week) and maintained (past six months) HEPA, socio-demographics, disease-related and psychosocial factors collected by questionnaires and performance tests of aerobic capacity and muscle function. Perceptions on the HEPA program were assessed with a study-specific questionnaire. Each participant with unchanged/improved values in general health perception (100 mm VAS) and at least two of three performance tests (aerobic capacity, grip srength and timed standing) year was considered a responder to the HEPA program.

Results: Current and maintained HEPA decreased from 82% to 75% (p=0.0141) and from 41% to 27% (p<0.0001), respectively, during the second year. Fifty-four participants were defined as total responders during the second year, while 105 were non-responders. The mean number of reported circuit-training sessions was 41 (SD 35.3) among total responders and 35 (SD 33.4) among non-responders (p=0.2708), the mean number of days with total HEPA were 194 (SD 80.8) and 171 (SD 76.9) respectively (p=0.0828) and the mean registered support group meetings 12 (SD 6.1) and 10 (SD 6.1) respectively (p=0.0943). Strategies for maintenance and relapse prevention learned during the first intervention year were reportedly used by 35% of the participants. Circuit training, daily physical activity and short text message reminders were perceived (scale 1-5) as valuable (=4), while the value of peer support groups was rated somewhat lower (=3).

Conclusion: Although maintained HEPA decreased from the end of the first intervention year, about one fourth of the originally sedentary individuals with RA still sustained their new behavior after two years. It remains unclear whether improvements in health and functioning relates to the HEPA program and its different components.

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Disclosure: C. H. Opava, None; **B. Nordgren**, None; **C. Fridén**, None; **I. Demmelmaier**, None; **G. Bergström**, None; **I. E. Lundberg**, None; **A. B. Dufour**, None; **T. Nessen**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/an-outsourced-health-enhancing-physical-activity-program-for-people-with-rheumatoid-arthritis-exploration-of-the-maintenance-phase

Abstract Number: 2383

A Qualitative Study of Barriers and Facilitators to Arthritis Patients Use of Physical Activity Monitoring Tools

Jenny Leese[1,2], Bao Chau Tran[1], Catherine Backman[3], Anne F. Townsend[4], Aileen Davis[5], Allyson Jones[6], Diane Gromala[7], J Antonio Avina-Zubieta[8] and Linda Li[9], [1]Arthritis Research Canada, Richmond, BC, Canada, [2]Rehabilitation Sciences, University of British Columbia, Vancouver, BC, Canada, [3]Occup Science & OccupTherapy, University of British Columbia, Vancouver, BC, Canada, [4]Maurice Young Centre for Applied Ethics, University of British Columbia, Vancouver, BC, Canada, [5]Health Care and Outcomes Rsrch, Toronto Western Research Institute, Toronto, ON, Canada, [6]Rehabilitation Medicine, Physical Therapy, University of Alberta, Edmonton, AB, Canada, [7]Simon Fraser University, Vancouver, BC, Canada, [8]Medicine, University of British Columbia, Department of Medicine, Division of Rheumatology, Vancouver, BC, Canada, [9]Physical Therapy, University of British Columbia, Vancouver, BC, Canada

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Background/Purpose: Physical activity participation can reduce pain, improve mobility and enhance quality of life in people with arthritis.[1] Despite these benefits, it was reported in the 2011 Canadian Community Health Survey that less than half of Canadians with arthritis are physically active.[2] While emerging evidence supports the use of some wearable physical activity monitoring tools to support an active lifestyle among patients with chronic diseases, little is known about how to integrate wearable tools to support self-management.[3] We aimed to examine the barriers and facilitators to using these wearable tools from the perspectives of arthritis patients.

Methods: Patient focus groups were conducted within a larger project that aimed to examine the context of using wearable physical activity monitoring tools to support arthritis self-management. To be eligible, patients had 1) a diagnosis of osteoarthritis (OA) and/or any type of inflammatory arthritis (IA), 2) any level of experience with wearable physical activity monitoring tools, and 3) were English-speaking. Participants were recruited via notices in hospitals and clinics of rheumatologists and rehabilitation professionals, and via online ads. An iterative, thematic analysis approach using constant comparative methods was applied to the data.

Results: In 2014 - 2015, 40 patients (31 women; 9 men) took part in 9 focus groups in-person or by teleconference. Of the 37 participants who provided information, 29 had used a wearable physical activity monitoring tool in the past. 17 (46%) had OA, 13 (35%) had IA, and 7 (19%) had OA and IA. Focus groups ranged from 3-6 participants, and the median age was 59 years (range: 23 –78). Preliminary findings revealed key barriers to patients' use of online physical activity monitors, which included: 1) an unfamiliarity with the tools, 2) a concern that the tool may be too expensive, and 3) doubts that use of the tool would be sustainable. If use was to be sustained, participants identified the importance of a tool that was user-friendly and provided information that was meaningful to their individual circumstance. Key facilitators were identified as: 1) an existing level of motivation to try out ways to be more active; 2) ease of use of the tool; 3) ongoing support from health professionals to use the tool optimally.

Conclusion: Participants identified the accessibility of wearable physical activity monitoring tools and the prospect of their long-term use as hurdles for using wearables activity monitors. The patients' perspective has also highlighted the importance of tool design and health professional support in facilitating ongoing use of these tools. These findings provide an important first step to informing future implementation strategies for patients to use wearable physical activity monitoring tools in supporting self-management.

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Disclosure: J. Leese, None; **B. C. Tran**, None; **C. Backman**, None; **A. F. Townsend**, None; **A. Davis**, None; **A. Jones**, None; **D. Gromala**, None; **J. A. Avina-Zubieta**, None; **L. Li**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/a-qualitative-study-of-barriers-and-facilitators-to-arthritis-patients-use-of-physical-activity-monitoring-tools

Abstract Number: 2384

The Comparative Efficacy of Dry Needling, Kinesio Taping and Physical Therapy in Patients with Myofascial Pain Syndrome

Alper Gumustepe[1], Pinar Borman[2], Ferda Kaygisiz[1], Figen Ayhan[1] and Aynur Karagoz[3], [1]Dept of Physical Medicine and Rehabilitation, Ankara Training and Research Hospital, Ankara, Turkey, [2]Department of Physical Medicine and Rehabilitation, University of Hacettepe Faculty of Medicine, Ankara, Turkey, [3]Dept of Physical Medicine and Rehabilitation, Ministry of Health, Ankara Training and Research Hospital, Ankara, Turkey
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Background/Purpose: The aim of this study was to compare the therapeutic effects of kinesio taping (KT),traditional physical therapy and dry needling therapy in patients with myofascial pain syndrome (MPS) at trapezius region, with regard to pain, and disability.

Methods : Sixty-eight female patients with MPS were enrolled into the study. Demographic and clinical characteristics including age, sex, duration of disease were recorded. The patients were randomized into three treatment groups receiving either a single dry needling injection to trigger points in the trapezius muscle (n=21), local physical therapy (hot pack and ultrasound) for 10 sessions (n=18) or kinesio taping performed to trapezius muscle, three times by intervals of 3 day (n=19). Visual analog scale (VAS) was used to assess pain intensity Neck Pain and Disability Index (NDI) was performed to evaluate functional disability, before treatment, at the end of therapies and four weeks after the therapies. All groups were educated for home exercise programme to perform trapezius stretching exercises.

Results : Sixty-eight female patients with a mean age of 32.1 ±10.7 years; mean disease duration of 13.1± 10.2 months were included in the study. There were no differences between the groups regarding demographic variables on entry to the study ($p>0.05$). Pain and NDI scores were improved significantly in all groups at the end of therapies and four weeks after, and these improvements were statistically similar between the groups at ANOVA analysis with Bonferroni adjustments (Table 1, $p>0.05$).

Conclusion : We imply that single dose dry needling injection, three times of kinesio taping by 3 day intervals and 10 sessions of physical therapy have favorable effects on pain and functional status in the early period (up to one month) in MPS. Although the improvements in pain and functional disability were similar between the groups, we suggest that KT may be an alternative non-invasive and time consuming method for patients suffering from MPS syndrome in the early period.

Table 1: The scores of pain intensity and neck disability index at baseline, at the end therapies and four weeks after the therapies (*improvement differences between groups,ANOVA).

	Dry needling n=21	**Kinesio taping** n=19	**Physical therapy** n=18	**P**
VAS-pain Baseline At the end of therapy 4 weeks after therapy	5.71±1.87 3.12±2.7 2.61±2.31	5.15±1.51 1.89±1.28 1.71±1.61	5.33±1.9 1.8±1.51 1.75±1.38	*>0.05
Neck Disability index Baseline At the end of therapy 4 weeks after therapy	52.4±12.9 24.8±19.7 21.33±17.2	46.4±15.1 21.4±12.8 17.8±14.8	48.38±13.2 18.05±10.7 16.11±13.6	*>0.05

Disclosure: A. Gumustepe, None; **P. Borman**, None; **F. Kaygisiz**, None; **F. Ayhan**, None; **A. Karagoz**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/the-comparative-efficacy-of-dry-needling-kinesio-taping-and-physical-therapy-in-patients-with-myofascial-pain-syndrome

Abstract Number: 2385

Arthritis Management in Primary Care and Adherence to National Guidelines – a Swedish Survey Based on the Canadian Physiotherapists Arthritis Care Questionnaire

Siv Folkhammar Andersson[1], Stefan Bergman[2,3,4] and **Ann Bremander**[3,4,5], [1]Unit of Rehabilitation, Kalmar County Council, Samrehab, Oskarshamn, Sweden, Oskarshamn, Sweden, [2]Primary Health Care Unit, Department of Public Health and Community Medicine, The Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden, [3]Department of Clinical Sciences, Lund, Section of Rheumatology, Lund University, Lund, Sweden, [4]FoU Spenshult, Halmstad, Sweden, [5]School of Business, Engineering and Science, Halmstad University, Halmstad, Sweden
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Session Type: ACR Poster Session C
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Background/Purpose:

For patients with osteoarthritis (OA) physical therapy is recommended first line treatment and performed in primary care while patients with rheumatoid arthritis (RA) may be treated in primary care at disease onset and during stable phases of the disease. This requires updated skills and evidence based knowledge of the physical therapists (PTs) in arthritis treatment. The aim of this study was to explore physical therapy arthritis practice in primary care and to study the application of evidence based care given to patients with OA or RA.

Methods:

All PTs working in primary care in one health care region in Sweden (n=70) were e-mailed a questionnaire (the Canadian Physiotherapists Arthritis Care Survey[1]) to assess the frequency of current practice, feeling of confidence, educational needs and adherence to national guidelines in managing patients with OA or RA. The questionnaire was translated and culturally adapted into Swedish according to international recommendations. Interventions supported by national guidelines were compared with reports of treatment modalities in the questionnaire. Mann-Whitney U test, Chi-square test or Fishers Exact test, were used where appropriate, to analyze differences between groups (PT management of patients with OA vs. RA).

Results:

Sixty-four PTs responded (91%), reporting a higher feeling of confidence in assessment, treatment and education for patients with OA than for RA ($p<0.001$). The total numbers of roles assumed by the PTs were higher in management of OA compared to RA ($p<0.001$). PTs who assumed a large numbers of roles also reported a higher feeling of confident in assessing OA ($p=0.036$). PTs who assumed a lower numbers of roles also reported a lower feeling of confidence in RA treatment ($p=0.045$). The recommendations in the guidelines were reported to be followed by almost all PTs in managing patients with RA and for eight out of eleven treatment modalities for patients with OA. Most PTs did provide joint mobilization and education of proper footwear for patients with OA even though Swedish national guidelines did not recommend this as treatment until further research has proven its effectiveness.

Conclusion:

PTs reported a lower feeling of confidence and to have assumed a lower numbers of roles in managing patients with RA than OA. There was a good adherence to the national guidelines for almost all listed treatment modalities. However, experienced evidence care and national guidelines did not totally agree. The results indicate a need for education in arthritis care, especially in RA.

References:

Li CL, Hurkmans EJ, Sayre EC, Vliet Vlieland TPM (2010). Continuing professional

development is associated with increasing physical therapists´ roles in arthritis management in Canada and the Netherlands. Physical Therapy 90: 629-42.

Disclosure: S. Folkhammar Andersson, None; **S. Bergman**, None; **A. Bremander**, None.

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Abstract Number: 2386

Integrating Wearable Physical Activity Monitoring Tools into Rehabilitation Practice for Patients with Arthritis: The Healthcare Professional Perspective

Graham Macdonald[1], Jenny Leese[2], Catherine Backman[3], Aileen Davis[4], Anne F. Townsend[5], J Antonio Avina-Zubieta[6], Diane Gromala[7] and Linda Li[5], [1]Occupational Science and Occupational Therapy, University of British Columbia, Vancouver, BC, Canada, [2]Rehabilitation Sciences, University of British Columbia, Vancouver, BC, Canada, [3]Occup Science & OccupTherapy, University of British Columbia, Vancouver, BC, Canada, [4]Health Care and Outcomes Rsrch, Toronto Western Research Institute, Toronto, ON, Canada, [5]Arthritis Research Canada, Richmond, BC, Canada, [6]Medicine, University of British Columbia, Department of Medicine, Division of Rheumatology, Vancouver, BC, Canada, [7]Simon Fraser University, Vancouver, BC, Canada
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Background/Purpose: Wearable physical activity monitoring tools can be used for goal-setting and progress-monitoring in rehabilitation programs for patients with arthritis. Little is known about the views of health professionals regarding the use or potential of these tools in clinical application. As part of a larger project about the barriers and facilitators to using physical activity trackers in clinical practice, this qualitative study aimed to examine the perspective of healthcare professionals on the prospect of using commercially available wearable trackers in their practice.

Methods: We conducted focus groups and one-on-one interviews to explore the views of health professionals towards physical activity trackers. Eligible participants were physiotherapists or occupational therapists with at least 40% of their caseload dedicated to arthritis. English-speaking therapists with any level of experience with online tools were considered eligible. Transcripts of the interviews and focus groups were coded and analyzed in a qualitative, theme-based examination of the views that healthcare professionals held toward these devices.

Results:

Across 5 focus groups and 3 interviews conducted in 2014-15, the sample of 25 health professionals recruited were mainly female (92%). Of the 18 participants who provided more demographic information, 94% were physiotherapists, 94% were living and working in an urban or suburban environment, with 60% of participants working full-time, and 67% working in outpatient clinics. The participant age range was between 28 and 61, with the median age of participants being 47, and the range of years in practice was between 5 and 39, with a median of 22 years. Approximately one third of participants had experience in using physical activity trackers.

The majority of healthcare professionals participating in the study regarded these devices as potentially useful tools because of the objective data they provide and their ability to facilitate the setting of and adherence to goals throughout rehabilitation. Some of the participants, however, thought that they would be of limited use due to: 1) the lesser computer literacy of older patients, who were the majority of patients with osteoarthritis; 2) their potential to be just another novelty; 3) the inaccessibility for people with

health-related challenges such as hand pain and deformity due to arthritis, or vision problems; 4) the cost of these devices for patients.

Conclusion: Therapists report activity trackers show promise for improving physical activity habits, however, some therapists are skeptical regarding the benefit for and accessibility to specific patients, particularly older adults with osteoarthritis.

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Abstract Number: 2387

The Effect of Arthroscopic Partial Meniscectomy in Patients with Osteoarthritis on Meniscal Body Extrusion

Martin Englund[1,2], Fan Zhang[3], Ali Guermazi[4], Frank W Roemer[5,6], Elena Losina[7] and Jeffrey N. Katz[8], [1]Clinical Epidemiology Unit, Orthopedics, Dept of Clinical Sciences Lund, Lund University, Lund, Sweden, [2]Clinical Epidemiology Research and Training Unit, Boston University School of Medicine, Boston, MA, [3]Orthopedics, Clinical Sciences Lund, Lund University, Lund, Sweden, [4]Boston University School of Medicine, Boston, MA, [5]Department of Radiology, University of Erlangen-Nuremberg, Erlangen, Germany, [6]Department of Radiology, Boston University School of Medicine, Boston, MA, [7]Orthopaedics, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, [8]Brigham and Women's Hospital and Harvard Medical School, Boston, MA

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Background/Purpose: Meniscal damage and extrusion are both strongly associated with the progression of knee OA. Concerns have recently been raised that arthroscopic partial meniscectomy (APM) may accelerate OA development. It is currently unclear whether performing APM or leaving a meniscal tear *in situ* affect meniscus position differently. Thus we determined the effect of APM on medial meniscal body extrusion in patients with OA and meniscal tear.

Methods: Post-hoc analysis using data from the MeTeOR trial (ClinicalTrials.gov number, NCT00597012), a multi-center randomized controlled trial that involved patients aged 45 or older with knee symptoms and meniscal tear as well as osteoarthritic changes detected on MRI (cartilage lesions) or radiography. Patients were randomized to either APM coupled with postoperative physical therapy (PT) or a standardized PT regime. Cross-over from PT to APM due to treatment failure was allowed. One orthopedic surgeon, who was blinded to treatment allocation, actual treatment received, and patient characteristics, but who had knowledge of the time sequence, performed paired meniscal measures on the baseline and 18-month mid-coronal 1.5T knee MR images. The observer measured medial meniscal body extrusion to the closest 0.1 mm using Sante DICOM Editor software. Intra-observer reliability (intra-class correlation coefficient) was 0.85 (95% CI: 0.73-0.92). We defined our primary outcome as the absolute change in mm of the position of the external medial meniscal body margin from baseline to the 18-month exam. We used the intention-to-treat (ITT) principle for the primary analysis, and we also performed a secondary as-treated analysis, i.e., taking into account the cross over after randomization (including those who crossed over from PT to APM into the APM group).

Results: The MeTeOR trial patients have mean (SD) age 59 (7.9) years at baseline and 56% were women. In this analysis we included the first 223 patients who had both baseline and 18-month follow-up knee MRIs available and readable. Of these, 108 patients were randomized to APM and 115 to standardized PT. The mean medial meniscus body extrusion at the baseline exam was similar; mean (SD) 3.2 (1.4) mm in the APM arm vs. 3.4 (1.5) mm in the physical therapy arm (p=0.34). We found no statistically significant difference in the change of extrusion of the medial meniscal body in the ITT analysis; mean (SD) change +0.47 mm (1.6) in the APM arm vs +0.40 (1.6) mm in the PT arm (p=0.72). In the PT arm, 42 patients (36.5%) crossed over to

surgery during the 18 months of follow-up, and 4 patients (3.7%) randomized to APM never had the surgery. We did not find statistically significant differences in the corresponding as-treated analysis, mean (SD) change +0.36 mm (1.5) in those having APM (n=146) vs +0.58 (1.8) mm in those patients having PT only (n=77) (p=0.32).

Conclusion: We observed on average small changes in medial meniscal body extrusion over 18 months in MeTeOR trial participants. APM of a meniscal tear in patients with knee OA does not lead to increased meniscal body extrusion as compared to non-operative management.

Disclosure: M. Englund, None; **F. Zhang**, None; **A. Guermazi**, Boston Imaging Core Lab, LLC, 1,TissueGene, 5,OrthoTrophix, 5,MerckSerono, 5,Genzyme Corporation, 5; **F. W. Roemer**, Boston Imaging Core Lab, 1; **E. Losina**, None; **J. N. Katz**, None.

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Abstract Number: 2388

Variations in Hip Morphology Are Associated with Hip Symptoms: Preliminary Results from a Large Community-Based Cohort

Amanda E. Nelson[1], Jamie L. Stiller[1], Xiaoyan A. Shi[1,2], Jordan B. Renner[3], Todd A. Schwartz[4], Nigel K Arden[5] and Joanne M. Jordan[1], [1]Thurston Arthritis Research Center, University of North Carolina, Chapel Hill, NC, [2]SAS Institute, Inc, Cary, NC, [3]Radiology, University of North Carolina, Chapel Hill, NC, [4]School of Nursing, University of North Carolina, Chapel Hill, NC, [5]Oxford NIHR Musculoskeletal Biomedical Research Unit, University of Oxford, Oxford, United Kingdom

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Background/Purpose: Alterations in hip morphology, such as femoroacetabular impingement, have been associated with incident hip OA and total hip replacement (THR), but associations of these morphologic variations with hip symptoms are less clear, and have not been studied in a community-based sample including participants with and without OA.

Methods: This preliminary analysis was performed as part of our ongoing work to determine the prevalence of morphologic features at the hip at the baseline visit for the Johnston County OA project, a large community-based cohort. At the time of this analysis, 2612 hips had been read, 120 were excluded based on excessive tilt/rotation, and 2492 hips (from 1252 individuals) were included. The outcome of hip symptoms was assessed in 3 ways: 1) response to the question "On MOST days do you have pain, aching or stiffness in your right|left hip?" (graded none, mild, moderate, or severe); 2) pain on internal rotation during clinical exam (graded none, mild, or moderate/severe); 3) self-reported groin pain (present or absent). Validated software (Oxmorf) was used to assess 27 aspects of hip morphology, and differences in means among categories of the symptom variables were assessed using GEE to account for within-person correlation (but no adjustment for any covariates in these preliminary analyses). P values <=0.05 for any difference between groups were considered significant.

Results: Of the included individuals, 37% were men, 36% were African American, with a mean age of 63.8 ± 9.8 years and BMI 28.8 ± 5.9 kg/m^2. Kellgren-Lawrence grade was 0 or 1 in 72% of hips. Reliability for all measures was acceptable (intra- [ICC 0.7-1.00] and inter-reader ICC 0.5-1.00). We focused on 10 continuous measures of hip morphology (Table). None of these was statistically significantly associated with hip pain, aching, or stiffness on most days (p>0.2 for all). However, several of the morphologic indicators (increased acetabular depth/width ratio, AP alpha angle, extrusion index, femoral shaft angle, and Gosvig ratio, as well as decreased minimum joint space width [JSW] and proximal femoral angle) were significantly associated with pain on internal rotation (Table). All but extrusion index, femoral shaft angle, and proximal femoral angle were also associated with groin pain.

Conclusion: Indicators of femoral morphology, including measures of acetabular dimension, acetabular coverage (extrusion

index), femoral angles, and indicators of cam-type lesions (AP alpha angle and Gosvig ratio), were associated with pain on internal rotation and with groin pain, but not with self-reported pain, aching and stiffness. These preliminary findings are supportive of an association between femoral morphology such as that seen in FAI and symptoms at the hip in the general population. Further study in a larger number of hips will assess differences by race, gender, and other key covariates.

TABLE. Comparison of mean (SD) values of 10 continuous morphologic measures by symptom category for pain on internal rotation and groin pain

MORPHOLOGIC MEASURES	PAIN ON INTERNAL ROTATION* None n=1144	Mild n=1122	Mod/Severe n=224	p value^	GROIN PAIN No n=2189	Yes n=303	p value^
	mean (SD)				mean (SD)		
Acetabular depth/width ratio	0.56 (0.1)	0.57 (0.1)	0.57 (0.1)	0.005	0.56 (0.1)	0.58 (0.1)	<0.001
AP alpha angle (degrees)	51.97 (15.4)	55.05 (18.0)	59.07 (19.4)	<0.001	53.11 (16.5)	60.34 (20.3)	<0.001
Minimum JSW (mm)	3.69 (0.8)	3.53 (0.8)	3.53 (1.0)	0.009	3.68 (0.8)	3.08 (0.8)	<0.001
Extrusion index	0.16 (0.1)	0.18 (0.6)	0.19 (0.1)	0.016	0.16 (0.2)	0.25 (1.2)	0.280
Femoral shaft angle (mm)	130.31 (6.5)	130.31 (6.4)	131.69 (6.8)	0.007	130.50 (6.4)	129.99 (7.4)	0.835
Gosvig ratio	0.94 (0.1)	0.94 (0.1)	0.97 (0.1)	0.007	0.94 (0.1)	0.97 (0.1)	0.009
Acetabular index (mm)	2.58 (6.0)	3.09 (9.4)	3.08 (6.8)	0.505	2.98 (6.9)	1.92 (12.4)	0.397
Lateral CEA (degrees)	29.91 (6.9)	29.77 (10.1)	29.93 (7.9)	0.603	29.78 (7.7)	30.39 (13.1)	0.133
Proximal femoral angle (mm)	80.30 (6.6)	79.59 (6.4)	79.51 (7.1)	0.003	79.91 (6.4)	79.90 (7.5)	0.155
Triangular index height (mm)	22.92 (3.4)	22.32 (3.7)	23.18 (3.9)	0.642	22.57 (3.5)	23.42 (3.9)	0.099

Underline:p<=0.05; *n=2490; ^From GEE model to account for intra-person correlation but no other covariates

Disclosure: **A. E. Nelson**, None; **J. L. Stiller**, None; **X. A. Shi**, None; **J. B. Renner**, None; **T. A. Schwartz**, None; **N. K. Arden**, None; **J. M. Jordan**, None.

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Relation of Pronated Foot Posture to Risk of Worsening Knee Pain during Gait and Compartment-Specific Knee Cartilage Damage

K. Douglas Gross[1,2], Howard J. Hillstrom[3], Emily K. Quinn[4], Michael C. Nevitt[5], Cora E. Lewis[6], James Torner[7] and David T. Felson[2], [1]Physical Therapy, MGH Institute of Health Professions, Boston, MA, [2]Clinical Epidemiology Unit, Boston University School of Medicine, Boston, MA, [3]Rehabilitation, Hospital for Special Surgery, New York, NY, [4]Clinical Epidemiology Unit, Boston University, Boston, MA, [5]Epidemiology and Biostatistics, UCSF, San Francisco, CA, [6]Preventive Medicine, University of Alabama, Birmingham, AL, [7]Epidemiology, University of Iowa, Iowa City, IA

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Background/Purpose: Pronated foot posture is prevalent in older adults with knee cartilage damage and younger adults with knee pain. Yet, there is disagreement about the role of the pronated foot in knee OA. Many footwear interventions for older adults encourage a highly pronated foot posture in an effort to redistribute provocative loads away from the medial tibiofemoral (TF) compartment. Conversely, interventions for younger adults often seek to correct the pronated foot in order to minimize painful loading of adjacent knee compartments. In adults that have or at risk of knee OA, we assessed the relation of pronated foot posture to 2-year risk of worsening knee pain during walking and stairs, and worsening medial TF, lateral TF, and patellofemoral (PF) cartilage damage.

Methods: The Multicenter Osteoarthritis Study (MOST) includes adults aged 50-79 years that have or are at risk of knee OA. At the 60 month exam, foot posture was measured by a single reader (ICC= 0.69) as Resting Calcaneal Stance Position (RCSP) from photos acquired in bipedal standing. RCSP is a validated measure, with higher values indicating a more pronated foot. From 1.0 T MRIs at 60 and 84 months, readers scored 1 knee per subject for cartilage damage in each sub-region of the medial TF, lateral TF, and PF compartments using WORMS (weighted kappa > 0.63). Worsening damage was any increase in WORMS score. Worsening knee pain during walking and stairs was defined over the same period as any increase in Likert score on corresponding questions of the WOMAC index. After forming case-based quintiles of increasing RCSP, we combined quintiles 1-4 and used logistic regression to estimate the odds of worsening knee pain or compartment-specific cartilage damage in knees with the most pronated feet (quintile 5) as compared to all others (quintiles 1-4). Adjustments were made for age, sex, and BMI. GEE accounted for non-independent knees in a person, or sub-regions in a compartment.

Results: 2021 (mean age 67.6 ± 7.7 years, BMI 30.8 ± 6.1 kg/m^2, 61.0% female) and 2412 participants contributed 2 knees each to the analysis of worsening knee pain during walking and stairs, respectively, and 1 knee each to the analysis of worsening

medial TF (1185 knees), lateral TF (1145 knees), and PF (1145 knees) cartilage damage. Mean RCSP was 5.1 ± 4.7°. Odds of worsening knee pain during walking and stairs were 23% lower (OR= 0.77, p= 0.03) and 26% lower (OR= 0.74, p< 0.01), respectively, among knees with the most highly pronated foot posture (RSCP 8.2° to 27.0°). There was no association between pronated foot posture and risk of worsening knee cartilage damage (see table).

Conclusion: In adults that have or are at-risk of knee OA, a highly pronated foot posture is protective against worsening knee pain during walking and stair climbing, but does not protect against worsening knee cartilage damage.

Table. Relative odds of worsening knee pain during walking and stairs, and worsening medial tibiofemoral (TF), lateral TF, and patellofemoral (PF) cartilage damage in knees with the most pronated Resting Calcaneal Stance Position (RCSP) compared to all others.

	Resting Calcaneal Stance Position (RCSP)		
	All Others	Most Pronated	p-value
Worsening Knee Pain Walking			
RCSP range	-28.9, 8.1	8.2, 27.0	
# knees	2415	684	
% worsening	16.5%	14.3%	
Adj OR* (95% CI)	1.00 (Reference)	0.77 (0.61, 0.98)	0.03
Worsening Knee Pain on Stairs			
RCSP range	-28.9, 8.0	8.1, 27.0	
# knees	2591	762	
% worsening	20.7%	17.2%	
Adj OR* (95% CI)	1.00 (Reference)	0.74 (0.59, 0.92)	0.007
Worsening Medial TF Cartilage Damage			
RCSP range	-28.9, 9.2	9.3, 27.0	
# knees (# sub-regions)	795 (3908)	158 (781)	
% sub-regions worsening	7.5%	9.1%	
Adj OR* (95% CI)	1.00 (Reference)	1.11 (0.74, 1.65)	0.62
Worsening Lateral TF Cartilage Damage			
RCSP range	-28.9, 9.2	9.3, 27.0	
# knees (# sub-regions)	795 (3961)	158 (781)	
% sub-regions worsening	5.7%	7.3%	
Adj OR* (95% CI)	1.00 (Reference)	1.15 (0.73, 1.82)	0.55
Worsening PF Cartilage Damage			
RCSP range	-28.9, 9.0	9.1, 27.0	
# knees (# sub-regions)	786 (2942)	167 (617)	
% sub-regions worsening	5.9%	7.0%	
Adj OR* (95% CI)	1.00 (Reference)	1.16 (0.80, 1.69)	0.43

*Adjusted for age, sex, and BMI.

Disclosure: K. D. Gross, None; **H. J. Hillstrom**, None; **E. K. Quinn**, None; **M. C. Nevitt**, None; **C. E. Lewis**, None; **J. Torner**, None; **D. T. Felson**, None.

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Abstract Number: 2390

Foot Kinematics and Foot Center of Pressure and Their Association with Medial Knee Load Reduction with Use of Flexible Shoes in Knee Osteoarthritis

Chris Ferrigno[1], Roy H. Lidtke[2], Markus A. Wimmer[3], Laura E. Thorp[4], Joel A. Block[5] and **Najia Shakoor**[2], [1]Anatomy, Rush University, Chicago, IL, [2]Rheumatology, Rush University Medical Center, Chicago, IL, [3]Orthopedic Surgery, Rush University

Medical Center, Chicago, IL, [4]Anatomy and Cell Biology, Rush University Medical Center, Chicago, IL, [5]Rush University Medical Center, Chicago, IL

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Background/Purpose: Biomechanical treatments for medial knee osteoarthritis (OA) often target the knee adduction moment (KAM). Foot-mediated biomechanical interventions for knee OA may operate through altering foot kinematics and foot center of pressure (COP). Flexible footwear has recently been shown to effectively reduce the KAM, but specific mechanisms underlying this reduction are not clear. We hypothesize that the use of flexible footwear allows increased foot pronation and medial shift in foot COP that are associated with reduction in the KAM.

Methods: Participants with symptomatic medial compartment knee OA (KL 2 and 3) were evaluated at baseline using simultaneous barefoot COP analyses and 3-D gait analyses including detailed foot kinematic modeling. All participants were provided flexible shoes (Dr. Comfort Flex-OA, Mequon, WI) and instructed to wear them at least 6 hours/day, 6 days/week. Gait and COP analyses were repeated after 12 weeks of wearing the shoes. Gait testing consisted of five trials each while barefoot, in subjects “own shoe”, and in the flexible shoe. During barefoot trials, plantar pressure distribution was acquired simultaneously by mounting a pressure platform onto a force plate and leveling the stacked assembly with the walkway. COP was quantified by determining the Medial to Lateral Pressure Index (MLPI) and normalizing to foot width, with smaller values representing more medialized COP. The primary outcomes were the peak KAM and COP during the first half of stance and foot kinematic variables. Paired samples t-tests were used to evaluate changes in kinematics and foot COP. Pearson correlations were used to evaluate the association between foot kinematics, shift in COP and percent reduction in KAM.

Results: 28 participants were evaluated (mean age 59±7 years, 21 women). At 12 weeks, the KAM in the flexible shoe was reduced compared with their own shoes at baseline (2.17± 0.82 vs 2.32±0.81%BW*Ht, p=0.030). The foot COP medialized compared with baseline (4.61±4.28 vs 5.88±4.39%FW, p=0.034). No significant correlation was found between medialization of foot COP and reduction in KAM (p=0.430). No significant changes occurred in measures of foot kinematics including rearfoot eversion (p=0.975), foot supination (p=0.372) and medial arch (p=0.841). However, lower maximal rearfoot eversion at 12 weeks correlated with both the medialization of foot COP (r=0.438, p=0.02) as well as the percent reduction in KAM with the mobility shoe at 12 weeks compared to own shoes at baseline (r=0.438, p=0.02).

Conclusion: Walking with flexible shoes for 12 weeks significantly reduces loading at the medial tibiofemoral joint in participants with knee OA and shifts the foot COP medially during walking. Interestingly, though, there was no association between the medialization in foot COP and reduction in knee loading, suggesting that both phenomena could be explained by an unidentified mechanism. Also, there were no significant differences found in foot kinematics over 12 weeks, yet less rearfoot eversion during walking at 12 weeks was associated with the extent of COP medialization and reduction in medial knee loading.

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Abstract Number: 2391

Hip Osteoarthritis As the Cause for Knee Osteoarthritis in the Multicenter Osteoarthritis Study

Chan Kim[1,2], Jingbo Niu[3], Cara Lewis[4], Mary Clancy[5], David T. Felson[3] and Ali Guermazi[6], [1]Internal Medicine and

Rheumatology, Boston Medical Center, Boston, MA, [2]Rheumatology, Boston University, Boston, MA, [3]Clinical Epidemiology Research and Training Unit, Boston University School of Medicine, Boston, MA, [4]Physical Therapy and Athletic Training, Boston University, Boston, MA, [5]Clinical Epidemiology, BUSM, Boston, MA, [6]Boston University School of Medicine, Boston, MA
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Hip Osteoarthritis as the cause for Knee Osteoarthritis in the Multicenter Osteoarthritis Study

Background/Purpose:

While the hip and knee are linked biomechanically, there have been no studies of the risk of knee OA in persons with hip OA. Unilateral hip OA has been shown to increase dynamic load and bone mineral density in the contralateral knee, thus theoretically putting the contralateral knee at risk for OA development. However, weak hip abductor muscles which can be seen in hip OA can lead to an increased knee adduction moment on the ipsilateral leg, possibly increasing risk for knee OA ipsilaterally. We examined the risk of knee OA in those with hip OA in the Multicenter Osteoarthritis Study (MOST). We secondarily tested whether hip OA increased the risk of ipsilateral or contralateral knee OA.

Methods:

MOST is a NIH funded longitudinal cohort study of risk factors for knee OA. For radiographic hip OA assessment, we used long limb films which included hip imaging obtained at baseline. For knee OA assessment, PA and lateral weight bearing films were obtained at each examination up to 84 months and read for tibio-femoral and patella-femoral OA. The exposure groups were subjects with or without radiographic hip OA at baseline, and we excluded persons with any radiographic knee OA at baseline. The outcome was incident radiographic knee OA at any of the follow-up exams (30, 60, or 84 months).

For the 1st analysis, we assessed the risk of radiographic knee OA in subjects with or without radiographic hip OA. The risks of incident radiographic knee OA were compared among the exposure groups after excluding any subjects with hip replacements during follow-up. The analysis was adjusted for knee OA risk factors including age, sex, BMI, knee injury/surgery, leg length inequality.

For the 2nd analysis, we assessed the risk of contralateral and ipsilateral knee OA in subjects with unilateral radiographic hip OA in a matched within-person analysis. We examined the risk of incident radiographic knee OA (ipsilateral vs contralateral to the affected hip).

Results:

For the 1st analysis, of the 989 subjects eligible, the risk of incident radiographic knee OA in subjects with any radiographic hip OA was greater than risk of incident radiographic knee OA in subjects without radiographic hip OA (see table). For the 2nd analysis, there was a trend for incident radiographic knee OA for the contralateral side, but this did not meet statistical significance (see table).

Conclusion:

Subjects with radiographic hip OA had an increased risk of incident radiographic knee OA. While our findings were limited by small numbers, we did not find a special association of hip OA with either contralateral or ipsilateral knee OA, suggesting that in persons with hip OA, both knees are at increased risk of OA.

Incident Radiographic Knee OA in subjects with any radiographic hip OA†					
	n/n (%)	Crude Risk Ratio	p value	Adjusted Risk Ratio*	p value
Subjects without radiographic hip OA	277/922 (30.04%)	(reference)		(reference)	
Subjects with unilateral radiographic hip OA	18/39 (46.15%)	1.54 (0.95, 2.48)	0.08	1.52 (0.93, 2.48)	0.09
Subjects with bilateral radiographic hip OA	15/28 (53.57%)	1.78 (1.06, 3.00)	0.03	1.67 (0.98, 2.84)	0.06
Subjects with any radiographic hip OA	33/67 (49.25%)	1.64 (1.14, 2.35)	0.01	1.59 (1.01, 2.30)	0.02

Incident radiographic knee OA in subjects with unilateral radiographic hip OA††					
	Knee, *n/n* (%)	Crude RR (95% CI)	p value	Adjusted RR* (95% CI)	p value
Ipsilateral Side	8/39 (20.51)	Ref		Ref	
Contralateral Side	14/39 (35.90%)	1.75 (0.73, 4.17)	0.21	1.69 (0.70, 4.08)	0.24

n/n = subjects with outcome/subjects total

Risk ratio = risk of outcome for exposure/reference risk

† Any subjects with total hip replacements or radiographic knee OA at either leg at baseline excluded

* Adjusted for age, sex, BMI, height, leg length inequality, site, knee injury/surgery

** Adjusted for knee injury/surgery

†† Any subjects with either total knee or hip replacement at either leg excluded

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Disclosure: C. Kim, None; **J. Niu**, None; **C. Lewis**, None; **M. Clancy**, None; **D. T. Felson**, None; **A. Guermazi**, Boston Imaging Core Lab, LLC, 1,TissueGene, 5,OrthoTrophix, 5,MerckSerono, 5,Genzyme Corporation, 5.

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Vibration Perception Threshold and Hip Osteoarthritis in Multicenter Ostoearthritis Study

Chan Kim[1,2], Najia Shakoor[3], Anyu Hu[4], Jingbo Niu[5], Ali Guermazi[6] and David T. Felson[5], [1]Internal Medicine and Rheumatology, Boston Medical Center, Boston, MA, [2]Rheumatology, Boston University, Boston, MA, [3]Rheumatology, Rush University Medical Center, Chicago, IL, [4]Clinical Epidemiology Research Unit, Boston University School of Medicine, Boston,

MA, [5]Clinical Epidemiology Research and Training Unit, Boston University School of Medicine, Boston, MA, [6]Boston University School of Medicine, Boston, MA

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Vibration Perception Threshold and Hip Osteoarthritis in Multicenter Ostoearthritis Study

Background/Purpose:

It is hypothesized that reduced sense of position in space leading to increased impact force and unbalanced foot strike during gait contributes to osteoarthritis (OA). In previous work from the Multicenter Osteoarthritis Study (MOST), we reported that high VPTs were associated with knee OA especially in men and women aged 65 or greater. However, the association of VPT and hip OA has not been studied for a large population. It is unclear whether sensory deficits which are mostly distal can lead to hip OA. We examined the association of vibratory sense with radiographic hip OA in participants of MOST.

Methods:

MOST is a NIH funded longitudinal study that recruited participants at risk for knee OA. We carried out a cross sectional assessment of vibration perception threshold (VPT) and hip OA at the 60 month exam. Using a protocol from knee OA studies, we measured VPT at 3 anatomical bony sites: 1st MTP, tibial tuberosity, and radial styloid. VPT measures the voltage threshold at which a subject senses vibration, thus a higher VPT threshold represents a greater sensory deficit. Long limb radiographs obtained at the same visit were read for radiographic hip OA (RHOA) using criteria devised at UCSF that incorporated features of modified Croft criteria. Symptomatic hip OA (SHOA) was defined as hips with pain and RHOA. Persons with total knee replacements, total hip replacements and diabetes were excluded from this analysis.

Because large differences in VPT exist between genders and age, men and women were evaluated separately and divided into age subgroups: <65 years and ≥65 years. The unaffected hips of persons with unilateral RHOA may be intermediate in VPT between hips with OA and normal hips without any radiographic knee OA, so a limb-based analysis was performed with three hip groups: 1) RHOA; 2) contralateral "normal" hip of unilateral RHOA; and 3) control hip (no RHOA in either hip). Statistical analysis entailed using linear regression with GEE to compare VPT between groups adjusted for age, BMI, radiographic knee OA, and accounting for the correlation between hips.

Results:

VPT was assessed in 612 men and 930 women. Of the 612 men, 72 hips were excluded from analysis (missing RHOA status due to poor quality radiographs). Of the 930 women, 99 hips were excluded. For both men and women for all age groups, VPTs were not higher for those with RHOA or SHOA compared to controls (results only shown for men age < 65 years). VPTs at the radial styloid on the non-OA side for those with unilateral RHOA and SHOA were significantly lower than controls for men age < 65 years.

Conclusion:

In MOST, RHOA was not associated with any meaningful alteration in VPT.

Radiographic hip OA for men (age < 65 years)*					
		Mean VPT (95% CI)	P value (compared to control)	Mean VPT (95% CI) adjusted for BMI and age	P value (compared to control)
MTP	RHOA	16.64 (13.66, 19.62)	0.24	16.65 (13.87, 19.44)	0.25

Disclosure: C. Kim, None; **N. Shakoor**, Dr. Comfort- Flex OA shoes, 7; **A. Hu**, None; **J. Niu**, None; **A. Guermazi**, Boston Imaging Core Lab,

	Contralateral	18.28 (13.53, 22.94)	0.90	18.16 (13.48, 22.84)	0.91	LLC, 1,TissueGene, 5,OrthoTrophix, 5,MerckSerono, 5,Genzyme Corporation, 5; **D. T. Felson**, None.
	Controls	18.60 (17.23, 19.96)		18.45 (17.14, 19.77)		
Tibial tuberosity	RHOA	20.29 (17.08, 23.51)	0.83	20.30 (17.31, 23.28)	0.89	**View Abstract and Citation Information Online -**
	Contralateral	18.00 (15.33, 20.67)	0.07	17.80 (15.21, 20.40)	0.06	
	Controls	20.67 (19.56, 21.77)		20.53 (19.48, 21.58)		
Radial styloid	RHOA	8.54 (7.79, 9.28)	0.96	8.50 (7.75, 9.25)	0.96	
	Contralateral	7.60 (6.92, 8.27)	0.02	7.54 (6.82, 8.26)	0.02	
	Controls	8.51 (8.18, 8.85)		8.52 (8.19, 8.86)		
Symptomatic hip OA for men (age < 65 years)*						
MTP	RHOA	15.32 (11.97, 18.67)	0.09	14.85 (11.94, 17.76)	0.03	
	Contralateral	15.82 (11.52, 20.12)	0.26	15.28 (11.84, 18.72)	0.10	
	Controls	18.41 (17.15, 19.67)		18.37 (17.13, 19.62)		
Tibial tuberosity	RHOA	17.18 (12.40, 21.96)	0.18	16.95 (13.10, 20.80)	0.08	
	Contralateral	15.56 (10.88, 20.24)	0.04	15.21 (11.43, 19.00)	0.01	
	Controls	20.56 (19.53, 21.59)		20.53 (19.54, 21.53)		
Radial styloid	RHOA	7.99 (6.77, 9.21)	0.43	7.89 (6.64, 9.14)	0.35	
	Contralateral	7.14 (6.03, 8.25)	0.02	7.02 (5.76, 8.28)	0.02	
	Controls	8.49 (8.19, 8.79)		8.51 (8.20, 8.81)		
* Adjusted for age, BMI, site, and knee radiographic knee OA						

http://acrabstracts.org/abstract/vibration-perception-threshold-and-hip-osteoarthritis-in-multicenter-ostoearthritis-study

Abstract Number: 2393

Validation of a Web-Based Overlay for Sectoral Scoring of Active Lesions on MRI in Hip Osteoarthritis: Femoral Bone Marrow Lesions Predict Response to Intra-Articular Hyaluronate

Damien Loeuille[1], Nicolas Deseyne[2], Jacob Jaremko[3], Ulrich Weber[4], Thierry Conrozier[5], Joel Paschke[6], **Walter Maksymowych**[7], Bernard Maillet[8] and Henri Lellouche[9], [1]Rheumatology, Department of Rheumatology, CHRU Vandoeuvre les Nancy, Vandoeuvre les Nancy, France, [2]Department of Rheumatology, CHRU Vandoeuvre les Nancy,, Vandoeuvre, France, [3]Radiology, Radiology, University of Alberta, Edmonton, AB, Canada, [4]Department of Research, King Christian 10th Hospital for Rheumatic Diseases, Graasten, Denmark, [5]Service de Rhumatologie,CHU de NANCY- Brabois, Vandoeuvre, France, [6]CaRE Arthritis, Edmonton, AB, Canada, [7]Medicine, University of Alberta, Edmonton, AB, Canada, [8]Rheumatology, Clinique Saint Odilon, Moulins, France, [9]Rheumatology, Hôpital Lariboisière, Paris, France

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Background/Purpose: Bone marrow lesions (BML) and synovitis are MRI features that have been associated with symptoms and disease progression in patients with osteoarthritis. The Hip Inflammation MRI Scoring System (HIMRISS) has been developed to specifically score these active lesions in hip OA. We aimed to conduct validation according to the OMERACT framework of a novel web-based overlay integrated to facilitate sectoral scoring of these lesions in patients receiving intra-articular hyaluronate.

Methods: We conducted MRI at baseline in patients receiving intra-articular hyaluronate for symptomatic hip OA. A circular overlay integrated with a web-based DICOM viewer was designed for use with DICOM MR images of the hip for evaluation according to the HIMRISS method. Using a mouse, the overlay can be positioned over the largest diameter of the femoral head and resized to ensure alignment with the subchondral bone. BML are assessed on coronal fluid-sensitive MR scans using an overlay comprising a circle divided into octants. The presence/absence of BML in each of the octants is scored dichotomously directly on the image display in 5 consecutive coronal slices, simply by mouse-clicking on any octants containing BML, thereby dispensing with scoring sheets. The overlay is also used to score BML in the acetabulum, assessed in 3 sectors. Synovitis is scored in 2 locations according to a grading scheme (0-2) that reflects thickness of synovitis-effusion.

Intra-class correlation coefficients (ICC) were used to assess reliability between 4 readers without any formal calibration. Correlation analysis, univariate and multivariate analyses, adjusted for age, sex, symptom duration, BMI, and baseline WOMAC pain, were used to assess the predictive capacity of baseline BML and synovitis scores for change in WOMAC pain from baseline to 12 weeks.

Results: The cohort included 60 patients, 28 (46.7%) males, mean (SD) age of 63.0 (11.2) years, mean (SD) disease duration of 31.4 (43.4) months, baseline mean (SD) WOMAC pain of 49.7 (16.3), mean (SD) change in WOMAC of -17.9 (19.2), mean (SD) femoral BML of 10.6 (13.9) (0-65 is maximum possible range), mean (SD) acetabular BML of 7.0(5.5) (0-35 is maximum possible range), mean (SD) effusion of 13.3 (8.1) (0-30 is maximum possible range).

Inter-observer ICC [95% CI] was 0.83[0.78-0.87] for femoral BML, 0.64 [0.52-0.74] for acetabular BML, 0.78 [0.65-0.86] for synovitis-effusion, and 0.86 [0.81-0.89] for total HIMRISS score. Significant correlation was evident between baseline femoral BML score and change in WOMAC pain (r =0.44, p=0.001). In univariate analysis, baseline femoral BML (β=0.58, p=0.0009) was significantly associated with change in WOMAC pain, an association which remained present in multivariate analysis (β=0.51, p=0.01). 21/55 subjects (38.2%) had a 50% reduction in WOMAC pain and 39/55 (70.9%) a 20% reduction in WOMAC pain. Baseline femoral BML predicted a WOMAC 20% response (OR [95%CI]: 0.95 [0.91-0.99], p=0.018) in multivariate logistic regression.

Conclusion: The web-based adaptation of HIMRISS facilitates reliable scoring of active lesions in hip OA and is relevant to patient symptoms and response to treatment.

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Abstract Number: 2394

B-Flow Imaging of Synovial Tissue in Osteoarthritis

Ralf G. Thiele[1], Allen P. Anandarajah[2] and Christopher T. Ritchlin[3], [1]University of Rochester Medical Center, Rochester, NY, [2]Dept of Rheumatology, Univ of Rochester Medical Ctr, Rochester, NY, [3]Allergy, Immunology and Rheumatololgy Division, University of Rochester Medical Center, Rochester, NY

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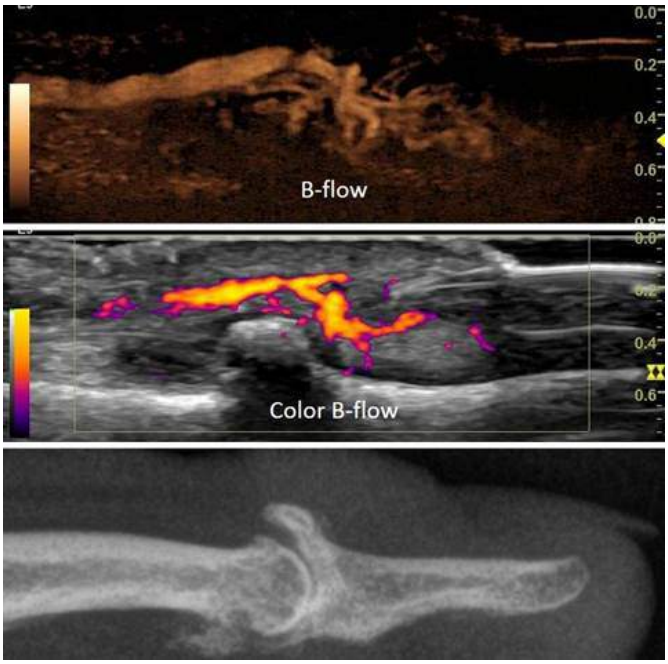
Background/Purpose: Development of disease modifying medication for osteoarthritis (OA) is desirable, but the target tissue of such treatment remains unclear. We have previously shown that proliferative and hyperemic synovial tissue is rare in joints affected by erosive osteoarthritis (EOA), if power Doppler ultrasound (US) is used as the detecting instrument. Doppler ultrasound gives indirect information about blood flow by assessing amplitude or velocity of a frequency shift. In contrast, B-flow ultrasound directly visualizes blood flow, and can visualize synovial hyperemia in a precise (flow only in the vascular lumen) and sensitive (small vessels) fashion. No previous studies have used B-flow ultrasound to assess synovial hyperemia.

The aim of this study was to assess synovial proliferation and synovial hyperemia in proximal interphalangeal and distal interphalangeal joints of patients with a radiologic diagnosis of OA or EOA using high-frequency B-mode gray scale US and B-flow US.

Methods: Joints affected by OA or EOA based on bilateral hand radiographs in 3 planes were then examined sonographically. For enrollment, the assessment of the MSK radiologist was counted. Gray scale US, native B-flow US and color B-flow still images and 3-second video clips were obtained by a rheumatologist with 20 years of experience in MSK US, certified in rheumatologic US (RT). All US and B-flow scans were performed on a GE Logiq E9 built 2014 machine, with an 18 MHz small footprint probe using a B-flow software package. Vascular factory settings were optimized for low flow in fingers. Distension of the hyperechoic, fibrous joint capsule was scored for GS synovitis from 0-3 (absent, mild, moderate, severe), analogous to scoring for RA. Intra-articular synovial blood flow was scored from 0-3 (no flow, individual signals, involving less, and equal to/ more than half the area of detected synovitis). Total scores for EOA patients were compared with OA patients.

Results: 559 still images and video clips were obtained. 84 joints of 20 consecutive OA and EOA patients were examined: DIP n=55; IP/PIP n=29. EOA patients, n=11 (55%); OA, n=9, (45%) as determined prior to US by the reading radiologist. Age range was 51-88 years; mean age 68. Female, n=16; male, n=4.

Resulting scores: Gray scale (score=n) 0=45; 1=31; 2=4; 3=2. B-flow (score=n) 0=81; 1=4; 2=1; 3=0. Mean GS score EOA=56.6; OA=53. Scores for intra-articular B-flow were too low to compare.



Conclusion: B-flow US was well suited to detect blood flow in small digital vessels. While physiologic flow in soft tissues adjacent to joints was seen in all images and video clips, intra-articular, synovial blood flow was rarely observed in OA or EOA patients. Synovial proliferation, if present, was mild and appeared to be due to mechanical distension of the joint capsule by osteophytes. No significant difference in mean GS synovitis score was observed between OA and EOA patients.

Disclosure: R. G. Thiele, None; **A. P. Anandarajah**, None; **C. T. Ritchlin**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/b-flow-imaging-of-synovial-tissue-in-osteoarthritis

Abstract Number: 2395

Predictors of and Longitudinal Factors Associated with Change in Pain, Stiffness and Physical Function over 8 Years in a Midlife Cohort with a Low Prevalence of Knee Osteoarthritis

Hussain Ijaz Khan[1], Andrew McBride[2], Louisa Chou[3], Dawn Aitken[4], Leigh Blizzard[5], Changhai Ding[6], Jean-Pierre Pelletier[7], Johanne Martel-Pelletier[8], Flavia Cicuttini[9] and Graeme Jones[6], [1]Musculoskeletal Unit, Menzies Institute of Medical Research, Hobart, Australia, [2]Musculoskeletal Unit, Menzies Institute of Medical Research, Hobart, 7000, Australia, [3]Menzies Institute of Medical Research, University of Tasmania, Hobart, 7000, Australia, [4]Muscyloskeletal Unit, Menzies Institute of Medical Research, Hobart, Australia, [5]Biostatistics, Menzies Institute of Medical Research, Hobart, Australia, [6]Musculoskeletal Unit, Menzies Institute for Medical Research, University of Tasmania, Hobart, Australia, [7]Rheumatology, Institut de recherche en rhumatologie de Montréal (IRRM), Montréal, QC, Canada, [8]Pharmacology, Osteoarthritis Research Unit, University of Montreal Hospital Research Centre (CRCHUM), Notre-Dame Hospital, Montreal, QC, Canada, [9]Department of Epidemiology and Preventive Medicine, Monash University, Melbourne, Australia

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Background/Purpose:

Knee Osteoarthritis (OA) is the most common musculoskeletal condition affecting quality of life and was one of the leading causes of the years lived with disability in the global burden of disease 2010 study by the World Health Organisation. Knee OA can result in pain and stiffness leading to impairment in routine daily activities. The aim of this study was to examine the demographic, structural and non-structural factors predicting and associated with change in knee pain, stiffness and physical function in a midlife cohort, with a low prevalence of radiographic OA, over 8 years.

Methods:

220 participants [mean age 47 (28-63); 57% female] were studied at baseline and eight years. Approximately half were the adult offspring of subjects who had a knee replacement performed for knee OA and the remaining were randomly selected controls. Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) was used to assess pain, stiffness and physical function at both baseline and follow up visits. Pain, stiffness and physical function scores were combined to get a complete WOMAC Index (WI) score representing overall morbidity. Cartilage volume/defects, bone marrow lesions (BMLs), meniscal tears/extrusion and effusion were assessed on MRI and joint space narrowing and osteophytes on radiographs. BMI was classified as normal=18.5-24.9, overweight=25-29.9 and obese=≥30.

Results:

At the baseline visit, higher BMI **(prevalence ratio (PR) for WI= +1.5 (+1.1 , +2.2), p= 0.02)**, history of knee injury **(PR for WI= +1.9 (+1.1, +3.2), p=0.01)** and patellar BMLs **(PR for WI= +1.5 (+1.1,+1.9), p=<0.01)** showed an independent cross-sectional association with the complete WI as well as each individual sub-scale. Total tibiofemoral BMLs **(PR=+1.82 (+1.2, +2.7), p=<0.01)** showed an independent association with knee stiffness only.

Baseline patellar cartilage defects **(β for WI= +6.4 (+1.0,+12.0), p=0.02)** and total (medial + lateral) body meniscal tears **(β for WI= +16.1 (+4.0. +28.0), p=0.01)** independently predicted change in WI as well as each sub-scale over 8 years. Total knee meniscal tears **(β= +1.1 (+0.2, +1.9), p=0.01)** independently predicted change in stiffness only.

Change in total knee meniscal tears **(β for WI= +6.1 (+0.2, +12.0), p=0.045)** and extrusion **(β for WI= +7.6 (+0.9, +14.3), p=0.026)** showed an independent deleterious association with change in WI and each individual sub-scale over 8 years. In unadjusted analysis change in both medial and lateral radiographic OA scores were associated with change in WI but in the fully

adjusted model, only change in lateral radiographic OA **(β for WI= +7.9 (+2.8, +13.0), p=<0.01)** was independently associated with WI and each sub-scale. Change in meniscal tears and extrusion explained most of the changes in the medial compartment on radiographs.

Conclusion:

In this midlife cohort higher BMI, history of knee injury and BMLs are associated with prevalent disability. Patellar cartilage defects and meniscal tears predicted worsening morbidity over 8 years. Change in meniscal tears/extrusion and lateral compartment radiographic OA were independently associated with worsening pain, stiffness and physical function.

Disclosure: H. I. Khan, None; **A. McBride**, None; **L. Chou**, None; **D. Aitken**, None; **L. Blizzard**, None; **C. Ding**, None; **J. P. Pelletier**, None; **J. Martel-Pelletier**, Artrotec Inc, 1; **F. Cicuttini**, None; **G. Jones**, None.

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Abstract Number: 2396

The Absence of Symptom in Subjects with Advanced Knee OA

Son Kyeong Min[1], Dong-Hyun Kim[2], Myung Hee Cho[3], Dae Gyu Jang[3] and **Hyun Ah Kim**[4], [1]Chunchun Sacred Heart Hosp, 153, Chunchun, South Korea, [2]Deparment of Social and Preventive Medicine, Hallym University College of Medicine, Chunchon, South Korea, [3]Department of Statistics, Seoul National University, seoul, South Korea, [4]Division of Rheumatology, Hanlim University Hospital, Anyang, South Korea

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Session Time: 9:00AM-11:00AM

Background/Purpose:

Although osteoarthritis(OA) is predominantly considered as a disease of cartilage, articular cartilage is an aneural tissue, and there is a consensus that the association between knee radiographic OA and knee pain is modest. To investigate the prevalence of asymptomatic subjects with advanced knee OA, we examined databases obtained from 2 Korean community residents.

Methods:

Subjects included were from Hallym Aging Study(HAS) or from the Korean National Health and Nutrition Examination Survey(KNHANES, year 2010-2012). Participants in each study were asked knee-specific questions regarding the presence of knee pain. Radiographic evaluations consisted of weight-bearing anteroposterior, semi-flexed knee radiographs. Each knee was evaluated for the presence of osteophytes, joint space narrowing, subchondral sclerosis, and cysts, and was graded for overall evidence of radiographic OA using the K-L grade. Advanced knee OA was defined as K-L grade 4(large osteophytes, severe joint space narrowing, and/or bony sclerosis). Clinical factors associated with the presence of knee pain were evaluated with multivaritate logistic regression analysis.

Results:

Included were 504 subjects from HAS and 8679 from KNHANES. Advanced knee OA was identified in 47(9.3%) and 685(7.8%) in HAS and KNHANES, respectively. The mean age of these 732 subjects were 72.5 years and 16.5% were male. Two hundred twenty five subjects(30.7%) did not report any pain despite having K-L grade 4 OA. Female, non-smoker, the presence of osteoporosis, and lower education were significantly associated with knee pain. After multivariate association, female and

osteoporosis was significantly associated with the presence of knee pain. Advanced OA Subjects without knee pain had functional status evaluated with WOMAC and chair stand not different from that of non-OA subjects.

Conclusion:

Our community study showed that 30% of subjects with K-L grade 4 OA was asymptomatic and had functional status similar with non-OA subjects. The guidance of therapeutic decision merely based on imaging study as well as treatment option focusing solely on cartilage engineering should be viewed with caution.

Disclosure: S. Kyeong Min, None; **D. H. Kim**, None; **M. H. Cho**, None; **D. G. Jang**, None; **H. A. Kim**, None.

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Abstract Number: 2397

Detection of Changes in the Serum and Synovial Fluid Levels of Resistin during Flare Ups and Remissions in Primary Knee Osteoarthritis

Hassan Bassiouni, Rheumatology, Al-Azhar University, Cairo, Egypt
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Background/Purpose: Resistin is a secreted factor that is elevated following traumatic joint injury, causing matrix degradation and it releases inflammatory cytokines from articular cartilage in vitro. This study was designed to plot changes in the levels of serum and synovial fluid (SF) resistin during flare-ups and remissions in patients with primary Osteoarthritis (OA) of the knees.

Methods: The level of resistin was measured in paired serum and SF samples from 60 patients with Primary OA of the knees during flare-ups when KOFUS $\geq$ 7, and then re-measured after remissions were attained, and from 15 controls without radiographic knee OA [Kellgren & Lawrence (K&L) =0] . Resistin levels were measured by enzyme-linked immunosorbent assay (ELISA).

Results: Serum resistin levels were higher in patients compared to controls (9.66±5.21 versus 3.31±1.04) ($P < 0.001$). In patients, serum resistin collectively was higher than in SF (9.66±5.21versus 2.45±1.04 ng/ml) ($P < 0.001$). In flare-ups serum resistin was higher than in remissions (9.66±5.21versus 5.68±3.22) ($P< 0.001$). SF resistin was higher in flare-ups than in remissions (2.45±1.04 versus1.35±0.72) ($P < 0.001$).

Conclusion: This study suggests an important involvement of resistin in OA patients considering their high serum levels compared to controls and furthermore, the up regulation of resistin during flare-ups in both serum and SF may suggest an involvement of resistin in the inflammatory component of OA.This may pave the way for using resistin as a marker of disease activity in OA.

Disclosure: H. Bassiouni, None;

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Abstract Number: 2398

Microrna Biomarker Signature in Osteoarthritis

L. A. Bennett[1], T. Coleman[1], W. Ferrell[1], J. Lockhart[2], C. Huesa[1], L. Dunning[1], B. Jones[3], M. Blyth[3], I. B. McInnes[1], M. Kurowska-Stolarska[1] and C. S. Goodyear[1], [1]Institute of Infection, Immunity and Inflammation, College of Medicine, Veterinary Medicine and Life Sciences, University of Glasgow, Glasgow, United Kingdom, [2]The Centre for Musculoskeletal Science, University of the West of Scotland, Paisley, United Kingdom, [3]Orthopedic Research Group, Orthopedic Department, Glasgow Royal Infirmary, Glasgow, United Kingdom

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Background/Purpose: Our current understanding of osteoarthritis (OA) comes mainly from late stage disease and this is partly due to when patients present with symptoms. It is therefore essential to find biomarkers indicative of OA development. One promising biomarker is circulating microRNAs, which were discovered to exist in an acellular form within the plasma and serum (1). Previous work has suggested that the level of microRNA Let7e is a potential predictor of severe hip and knee OA, with a negative correlation between expression and number of joint replacements (2). We found that microRNAs that are predicted to regulate BMP/TGFβ signalling pathways (miR24-3p and miR342-3p), are robustly expressed in the cartilage suggesting a role in the regulation of cartilage remodelling. Our current study was aimed at investigating the levels of cartilage associate candidate microRNAs in plasma of established OA.

Methods: RNA was extracted from the plasma of both end stage OA patients (mean age 69.6 years) at the point of joint replacement surgery and age/sex matched healthy controls (mean age 69.5 years) using the miRNeasy kit (Qiagen). Synovial fluid from OA patients and rheumatoid arthritis patients was extracted using the Qiagen kit. cDNA was synthesised with miScript RT kit (Qiagen). qPCR was carried out using miScript SYBR green (Qiagen) and miRNA specific primers (Qiagen). C.elegans miR-39 (Qiagen) was used as a spike in control for normalisation of RNA input.

Results: The circulating levels of miR24-3p ($p < 0.01$), miR342-3p ($p < 0.05$), miR-140 ($p < 0.05$) and Let7e ($p < 0.05$) were significantly decreased in OA patients (n=9) compared to healthy individuals (n=9). Evaluation of the synovial fluid showed that the levels of miR24-3p and miR342-3p were also decreased ($p < 0.01$) in OA (n=9) compared to rheumatoid arthritis patients (n=4) suggesting a direct involvement in OA joint remodelling. Synovial fluid levels of miR-140 and Let7e were unchanged.

Conclusion: The 4 microRNAs, differentially expressed in the OA plasma, offer a potential signature that could be used as a convenient, easily accessible OA biomarker. This circulating signature is also partially reflected in the synovial fluid where miR24-3p and miR-342-3p are distinctively changed. Further studies are underway to evaluate the predictive potential of this signature in early OA.

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Abstract Number: 2399

Baseline Fibulin3 Concentrations Are Associated with Incidence of Clinical Knee OA after 30 Months in Overweight and Obese Women

Jos Runhaar[1,2], Christelle Sanchez[3,4], Sébastien Taralla[5], **Yves Henrotin**[4,6] and Sebastia Bierma-Zeinstra[2,7], [1]PO Box 2040, Erasmus MC University Medical Center Rotterdam, Department of General Practice, Rotterdam, Netherlands, [2]D-BOARD Consortium, an European Committee FP7 project, Rotterdam, Netherlands, [3]University of Liège, Bone and Cartilage Research Unit, Arthropôle Liege, University of Liege, Liege, Belgium, [4]D-BOARD Consortium, an European Committee FP7 project, Liege, Belgium, [5]Artialis SA, Liege, Belgium, [6]Bone and Cartilage Research Unit, Arthropôle Liege, University of Liege, Liege, Belgium, [7]Erasmus MC University Medical Center Rotterdam, Department of General Practice, Rotterdam, Netherlands
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Background/Purpose: Fibulin3 is highly expressed in osteoarthritic cartilage and inhibits angiogenesis and chondrocyte differentiation. It has been demonstrated to interact with the tissue inhibitor of metalloprotease (TIMP)-3, which is a matrix bound inhibitor of matrix metalloproteinases (MMPs) and stimulates the expression of TIMP-1 and TIMP-3, but inhibits the expression and activities of MMP-2, MMP-3, and MMP-9. In the present study, the association between three Fibulin3 peptides identified by proteomics and the incidence of radiographic and clinical knee osteoarthritis (OA) in middle-aged overweight and obese women, free of radiographic and symptomatic knee OA at baseline was tested.

Methods: Women between 50 and 60 years, with a BMI ≥ 27 kg/m^2, free of knee OA were recruited through their general practitioner. At baseline, physical examination including serum collection was performed and radiographs and questionnaires on knee complaints were obtained. Using binary logistic regression, the association between baseline concentration of Fibulin (Fib)3-1, Fib3-2 and Fib3-3 and incidence of clinical and radiographic knee OA after 30 months of follow-up was tested, adjusting for age, BMI, and other potential covariates that were identified in multivariable regression analyses.

Results: Baseline serum samples and follow-up measurements were available for 242 women. Mean age was 55.9 ± 3.2 years, mean BMI was 31.6 ± 3.6 kg/m^2 and 70% was postmenopausal. All subjects were free of clinical and radiographic knee OA at baseline, but 24% had a unilateral K&L score of 1 and 33% bilaterally. Mild symptoms were present in 24% and 17% of the subjects, uni- and bilaterally respectively. Baseline concentrations of all Fib3 fragments were log-transformed for a normal distribution and z-transformed for uniformity reasons. Correlation coefficients for the baseline concentrations of the three Fib3 fragments ranged from 0.13 to 0.58. Neither of the concentrations of the three Fib3 fragments were associated with incidence of medial or lateral joint space narrowing ≥ 1.0 mm. or incidence of K&L grade 2. All three Fib3 fragments were associated with incidence of the clinical and radiographic ACR-criteria and Fib3-1 and Fib3-3 also with chronic pain at follow-up. When adjusted for the other Fib3 peptide concentrations, only Fib3-1 was significantly associated to the incidence of the ACR criteria (OR 2.5 [1.0-6.2]) and chronic pain at follow-up (OR 2.6 [1.1-5.9]).

Conclusion: Baseline Fibulin3 concentrations are associated to the incidence of clinical knee OA among middle-aged overweight and obese women. Therewith, they meet the criteria of a prognostic biomarker according to the BIPED biomarker classification for OA. Further validation of the Fibulin3 fragments seems warranted in order to better distinguish subgroups of individuals at increased risk for knee OA development.

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Abstract Number: 2400

Association Between Serum Urate and Osteoarthritis Progression in a Non-Obese Cohort

Svetlana Krasnokutsky[1], Mukundan Attur[2], Jonathan Samuels[3], Fangfei Zhang[4], Meng Chen[4], Leon Ryback[5], Steven B. Abramson[6] and Michael H. Pillinger[1], [1]Medicine/Rheumatology, NYU School of Medicine/NYU Hospital for Joint Diseases, New York, NY, [2]Rheumatology Research, NYU - Hospital for Joint Diseases, New York, NY, [3]Rheumatology, NYU - Hospital for Joint Diseases, New York, NY, [4]Medicine-Rheumatology, NYU School of Medicine-NYU Hospital for Joint Diseases, New York, NY, [5]Radiology-Musculoskeletal Radiology, New York University School of Medicine-NYU Hospital for Joint Diseases, New York, NY, [6]Dept of Rheumatology/Medicine, Hosp for Joint Diseases/NYU, New York, NY

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Background/Purpose: We recently reported an association between gout and osteoarthritis (OA) presence and severity, and a possible association between hyperuricemia and OA severity (Howard et al, JCR 2014). Others have reported that synovial fluid uric acid levels among non-gout patients correlate with OA severity (DeNoble et al, PNAS 2011). To date however, the possibility that serum UA (sUA) levels may be associated with OA progression has not been assessed. We therefore asked whether higher levels of sUA were associated with OA progression, determined as joint space narrowing (JSN), in a natural history cohort of non-obese symptomatic knee OA (SKOA) patients.

Methods: The NYU SKOA cohort consists of subjects followed for clinical, imaging and laboratory parameters for 24 months. Only patients with BMI<32 are included. From 144 completers we selected the first 80 subjects enrolled, and measured a single-point sUA level by ELISA (in duplicate) using previously banked and frozen serum. At entry and 24 months, patients underwent standardized weight-bearing fixed-flexion posteroanterior knee radiographs using the SynaFlexer™ methodology. Diseased compartment joint space width (dcJSW) and Kellgren-Lawrence (KL) grades in the signal (more painful) knee were determined by a musculoskeletal radiologist blinded to patient information (LR). Our primary outcome was extent of progression of JSN (decline in JSW in mm) over 24 months, as a function of sUA.

Results: Mean baseline KL score for all 80 subjects was 2.2, and mean baseline dcJSW was 3.5 ±1.3mm. Patients were 62% female, with a mean age of 61±10 years and mean BMI of 26.7±3.6kg/m^2. Most sUAs were <7.0 mg/dL, consistent with a non-obese, predominantly female population. Consistent with prior reports, sUA levels correlated with age (p=0.02) and BMI (p=0.04). We observed no significant associations between sUA and baseline JSW or KL score. In contrast, we observed a modest but statistically significant correlation between sUA and JSN across all patients (R=0.22;p=0.048). Additionally, when dichotomized by JSN (≥0.5 or <0.5mm/24mo), progressors demonstrated significantly higher sUA levels vs non-progressors (2.35 vs 2.92mg/dl, p=0.004). Conversely, patients with above-median sUA levels experienced more JSN compared with those below the median, though these differences did not achieve significance (0.41 vs 0.63 mm, p=0.30). When analyzed according to baseline severity (either KL grade or dcJSW quartiles) we observed non-significant trends of increasing JSN with increasing sUA in all but the KL3 and third quartile of dcJSW groups.

Conclusion: Our data suggest that increasing sUA concentrations may be associated with increased rates of JSN among non-obese patients with SKOA. If confirmed in other populations, these data would warrant investigation into the mechanisms/directions of the association, and possibly into the question of whether urate lowering in patients with early OA may be a strategy to reduce and/or prevent progression.

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Identification and Characterization of Two Osteoarthritis Phenotypes Applying Two Clinically Tested Biomarkers

Anne C. Bay-Jensen[1], Asger Bihlet[2], Inger Byrjalsen[3], Bente J. Riis[2], Claus Christiansen[2], Morten Asser Karsdal[1] and Jeppe Andersen[2], [1]Biomarkers and Research, Nordic Bioscience, Herlev, Denmark, [2]Nordic Bioscience, Herlev, Denmark, [3]Research & Development, Nordic Bioscience, Herlev, Denmark

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Background/Purpose: The osteoarthritis (OA) population is heterogeneous and it is therefore difficult to target all patients with the same intervention. Thus there is a clinical need for diagnostic tools, which can aid in identification of patients of different phenotypes. Urinary CTX-II is a biomarker of cartilage degradation, which previously have been associated with disease severity. Serum C3M is a biomarker of type II collagen remodeling, which is released from the synovial membrane when induced with pro-inflammatory cytokines. We hypothesize that patients with low cartilage degradation (low CTX-II), but a high synovial turnover (high C3M) have a synovial-driven OA, whereas patients with a high level of cartilage degradation and a low level of synovial turnover have a cartilage-driven phenotype, and that these phenotypes are markedly different. The aim of the study was to compare these two phenotypes on clinical parameters and thereby test above hypothesis.

Methods: CTX-II and C3M were measured in the urine/serum of knee OA patients (n=497) from the placebo arms of the two phase III RCTs (NCT00486434 and NCT00704847). Baseline pain questionnaires (WOMAC), as well as radiography and MRI of both knees (target (T), non-target (NT)) were recorded for each patient. Biomarker cut-offs were determined at the 75%-quartile limit. The synovial phenotype (n=89) was defined as having C3M levels above 7.3ng/mL and CTX-II levels below or equal to 345pmol/mL (creatinine corrected). The cartilage phenotype (n=99) was defined as the inverse. Difference between clinical measures and biomarkers in the two patient groups were analyzed by Mann-Whitney.

Results: There were no difference in age and BMI, nor gender distribution, in the two phenotype groups. Joint space width were significantly lower in both knees the cartilage phenotype (NT, p=0.0083; T p=0.042). The sum of Kellgren-Lawrence score was significant higher in the cartilage phenotype (p=0.0001). This corresponded to a significantly higher cartilage volume in the synovial phenotype (NT, p=0.0026; T, p=0.046). Interestingly, WOMAC pain was significantly higher in the cartilage-driven phenotype as compared to the synovial phenotype (NT, p=0.045; T, p=0.014).

Conclusion: We found the two phenotypes, defined by two biomarkers reflecting synovial and cartilage turnover, respectively, where significantly different when comparing standard clinical measures. This may indicate that non-invasive biomarkers may aid in the identification of patient phenotypes and thereby, in the future, aid in guiding treatment of patients.

Disclosure: A. C. Bay-Jensen, Nordic Bioscience Diagnostic, 1,Nordic Bioscience Diagnostic, 3; **A. Bihlet**, Nordic Bioscience Diagnostic, 3; **I. Byrjalsen**, Nordic Bioscience Diagnostic, 3; **B. J. Riis**, Nordic Bioscience Diagnostic, 4; **C. Christiansen**, Nordic Bioscience Diagnostic, 4; **M. A. Karsdal**, Nordic Bioscience Diagnostic, 1,Nordic Bioscience Diagnostic, 3; **J. Andersen**, Nordic Bioscience Diagnostic, 3.

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Comparison of Synovitis on MRI and Pain in Knee Osteoarthritis Patients with and without Chondrocalcinosis: Data from the Osteoarthritis Initiative (OAI)

Bobby Kwanghoon Han[1], Woojin Kim[2], Jingbo Niu[3], Shristi Basnyat[1], Veniamin Barshay[4], Charlene Williams[5], Sharon L. Kolasinski[6] and David T. Felson[3], [1]Division of Rheumatology, Cooper Medical School of Rowan University, Voorhees, NJ, [2]Division of Musculoskeletal Radiology, Department of Radiology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, [3]Clinical Epidemiology Research and Training Unit, Boston University School of Medicine, Boston, MA, [4]Department of Radiology, Cooper Medical School of Rowan University, Camden, NJ, [5]Department of Biomedical Sciences, Cooper Medical School of Rowan University, Camden, NJ, [6]Division of Rheumatology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA
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Background/Purpose: CPPD crystals are frequently deposited in the fibrocartilage of the meniscus and detected radiographically as linear calcification, termed chondrocalcinosis (CC). Several studies have found an association between CC and the severity of OA. However, CC has not been associated with worsening of OA, and its role in the pathogenesis of OA is not well understood. In this study, we explored whether CC was associated with synovitis on MRI or pain in patients with knee OA by examining data from the Osteoarthritis Initiative (OAI).

Methods: The study rationale and inclusion criteria for the OAI (men and women ages 45–79 with symptoms of and/or knee radiographic OA or risk factors for developing knee OA) have been described previously (http://oai.epi-ucsf.org/datarelease/). We included subjects who were 60 years and older and had Kellgren-Lawrence (KL) grade 0, 1, or 2 on baseline radiograph. We conducted a matched cohort study by selecting subjects with CC on baseline knee radiograph and age, gender, and KL grade-matched controls with no CC. We assessed each subject for synovitis by MRI Osteoarthritis Knee Score (MOAKS) on 4-year MRI. MOAKS synovitis score includes the Hoffa synovitis and effusion synovitis score. If the person had the same KL grade in both knees, we assessed one knee (left knee) per person. Wilcoxon two sample test was performed to compare MOAKS synovitis scores. Then we conducted a cohort study to assess the association between baseline CC and the Intermittent and Constant Osteoarthritis Pain (ICOAP) score at 4 years. ICOAP is a questionnaire to assess intermittent and constant pain for the past 7-day period with score ranging from 0 to 100. Linear regression was performed and the data were adjusted for age, gender, BMI, and KL grade. The correlation between two knees in a subject was controlled using generalized estimating equation.

Results: We assessed MRI of 191 knees (97 CC, 94 control) from the OAI data base. There was no difference in Hoffa synovitis score (0.9 [0.8,1.0] vs 0.9 [0.8,1.0], p=0.81) and effusion synovitis score (3.7 [3.2,4.2] vs 3.8 [3.3,4.3], p=0.60) at 4 years between the CC group and the control group. We also compared subjects within each KL grade and found there was no association with synovitis. However, there was an association between CC and ICOAP score. Knees with CC (n=138) had significantly higher intermittent pain score at 4 years compared to knees without CC (n=1760) (Table 1).

Conclusion: Knees with CC did not have higher MOAKS synovitis scores on MRI compared to knees without CC but CC was associated with significantly higher ICOAP intermittent pain scores. These results suggest that CC is associated with increased intermittent knee pain but that this pain may not be explained by an increase in synovitis.

Table 1. Chondroclacinosis (CC) and Intermittent and Constant Osteoarthritis Pain (ICOAP) at year 4

CC at BL	Crude model mean [95% CI]	p-value	Adjusted model [1] adjusted mean [95% CI]	p-value	Adjusted model [2] adjusted mean [95% CI]	p-value
ICOAP knee Intermittent Pain Score at year 4 (0-100)						
CC- (N=1760)	9.2 [8.3,10.0]	0.052	8.9 [8.1,9.7]	0.013	8.2 [7.4,9.1]	0.021
CC+ (N=138)	12.0 [9.2,14.9]		12.6 [9.7,15.4]		11.7 [8.7,14.6]	
ICOAP knee Constant Pain Score at year 4 (0-100)						
CC- (N=1760)	1.9 [1.4,2.4]	0.198	1.9 [1.4,2.4]	0.125	1.9 [1.4,2.4]	0.124
CC+ (N=138)	3.2 [1.2,5.2]		3.5 [1.5,5.5]		3.5 [1.4,5.5]	
ICOAP knee Intermittent and Constant Pain Total Score at year 4 (0-100)						
CC- (N=1759)	5.8 [5.3,6.4]	0.031	5.7 [5.1,6.3]	0.007	5.3 [4.8,5.9]	0.011
CC+ (N=138)	8.1 [6.1,10.1]		8.5 [6.5,10.5]		8.0 [6.0,10.1]	

[1]Adjusting for age, gender, BMI at baseline

[2]Adjusting for age, gender, BMI, and KL grade at baseline

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Abstract Number: 2403

Quadriceps Muscle Weakness and the Risk of Knee Cartilage Loss on MRI in a Population-Based Cohort with Knee Pain

Carson Chin[1], Eric C. Sayre[2], Ali Guermazi[3], Savvas Nicolaou[4], JM Esdaile[5], Jacek A. Kopec[6], Anona Thorne[7], Joel Singer[7], Hubert Wong[7] and Jolanda Cibere[8], [1]Department of Rheumatology, University of British Columbia, Vancouver, BC, Canada, [2]Arthritis Research Canada, Richmond, BC, Canada, [3]Boston University School of Medicine, Boston, MA, [4]Radiology, University of British Columbia, Vancouver, BC, Canada, [5]Rheumatology, Arthritis Research Canada, Richmond, BC, Canada, [6]School of Population and Public Health, University of British Columbia and ARC, Vancouver, BC, Canada, [7]Health Care and Epidemiology, University of British Columbia, Vancouver, BC, Canada, [8]Rheumatology, University of British Columbia and ARC, Vancouver, BC, Canada

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Background/Purpose:

The objective of the study was to determine whether clinically assessed baseline quadriceps weakness predicts cartilage loss on

MRI after 3 years.

Methods:

Subjects 40-79 years old with knee pain were recruited as a random population sample. Stratified sampling technique was used to achieve equal representation of age and gender. A physician examiner assessed quadriceps strength with the subject in the sitting position, using a standardized procedure, previously shown to be reliable. Quadriceps strength was graded from 0 to 2 (0: poor resistance, 1: moderate resistance, 2: full resistance). Subjects were then classified as having either normal strength (grade 2) or quadriceps weakness (grades 0 and 1). Radiographs were graded using Kellgren-Lawrence (KL) 0-4 scale with KL ≥2 considered radiographic osteoarthritis (ROA). MRI of the knees was obtained on a 1.5T magnet at baseline and at 3-year follow up. MRI cartilage was graded on a scale from 0 to 4 and bone marrow lesions (BML) were graded from 0 to 3 by an experienced musculoskeletal radiologist, blinded to time sequence and clinical information. Progression of OA was defined as worsening of cartilage damage by ≥1 MRI grade in at least 2 joint surfaces or ≥2 MRI grades in 1 joint surface. Logistic regression analysis was performed to evaluate the association of quadriceps weakness with whole knee cartilage loss (primary outcome) and with compartment-specific cartilage loss in the medial and lateral tibiofemoral (TF) and patellofemoral (PF) compartments (secondary outcomes). Crude OR, adjusted OR and 95% confidence intervals (CI) were calculated. Adjustments were included for age, sex, BMI, malalignment (varus or valgus), baseline MRI cartilage score (using the maximum cartilage score for the entire joint), baseline presence of BML and follow-up time.

Results:

Of 255 subjects, 163 were seen at a mean follow-up of 3.3 years. Of these, 24.1% had no OA (normal MRI and radiograph), 36.5% had pre-ROA (normal radiograph, abnormal MRI) and 39.4% had ROA (abnormal MRI and radiograph) at baseline. Mean (SD) age was 57.7 (10.1) years, BMI 26.1 (4.2), WOMAC pain score 19.6 (16.8) and 54% were female. Baseline quadriceps weakness was seen in 17.5% of females and 5.3% of males. Quadriceps weakness was a significant predictor of whole knee cartilage loss (OR 3.38, 95% CI 1.01-11.30). In sex-specific analyses, cartilage loss was significantly increased in females with quadriceps weakness (OR 4.91, 95% CI 1.11-21.79), not in males (OR 0.63, 95% CI 0.04-10.09). In compartment-specific analyses, quadriceps weakness was significantly associated with cartilage loss in the medial TF compartment (OR 7.12, 95% CI 1.39, 36.45), while no significant associations were seen in the lateral TF (OR 1.40, 95% CI 0.16-12.02) and PF compartments (OR 2.28, 95% CI 0.35-14.90).

Conclusion:

In this population-based cohort with knee pain, quadriceps weakness at baseline assessed by clinical examination, predicted whole knee cartilage loss in females, not males and predicted cartilage loss in the medial TF compartment after 3 years. A simple clinical test can assist clinicians to predict the risk of progression of early and advanced knee OA.

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Abstract Number: 2404

Implications of a Positive Patellar Bulge Sign of Knee Joint Effusion in Patients with Osteoarthritis: Association with MRI Signs of Inflammation and with Increased Rate of 5-Year Total Knee Arthroplasty. Data from the Osteoarthritis Initiative

Benjamin Smith[1], David McDougall[2], Robert G Lambert[3], Walter Maksymowych[4] and Jacob Jaremko[3], [1]Radiology & Diagnostic Imaging, University of Alberta, Edmonton, AB, Canada, [2]Radiology, University of Alberta, Edmonton, AB, Canada, [3]Radiology, Radiology, University of Alberta, Edmonton, AB, Canada, [4]Medicine, University of Alberta, Edmonton, AB, Canada
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Background/Purpose:

Most of our understanding of the clinical significance of a knee joint effusion is derived from trauma in young patients, with surprisingly little assessment of the meaning of an effusion in osteoarthritis (OA). It is unclear whether clinical examination of the knee for effusion is of any practical use or correlation to outcome. We sought to determine the specificity and sensitivity of clinical evaluation of knee joint effusion in OA for presence of an effusion on MRI, and the relationship of a clinical effusion to patient status and clinical outcome.

Methods:

We performed a case-control study of 80 patients with OA, with a 5 year follow-up, and validation in the Osteoarthritis Initiative dataset. This cohort study included knees from 40 subjects from the OAI dataset that had a knee corticosteroid injection within 1 year after baseline evaluation, and 40 that did not, matched by age, sex, and Kellgren-Lawrence (K-L) grade of radiographic OA.

Baseline MRI, clinical examination (patella tap and patella bulge test), Kellgren-Lawrence grading, and WOMAC scores were obtained. The MRI were evaluated for effusions by two semi-quantitative scoring systems (MOAKS and KIMRISS). The incidence of corticosteroid injection and WOMAC scores at 12 months, and of total knee replacement (TKR) within 5 years, as well as 5-year radiographic progression using K-L grade, were recorded. Pearson correlation coefficients, one-way analysis of variance (ANOVA) and multivariate logistic regression were used as appropriate to assess for significant associations.

Results:

Subjects averaged 62.3 years old (range: 45-78), 78% were women, and BMI averaged 30.3±4.6, with moderate to severe OA (K-L grade 2.8±1.0 (mean±standard deviation).

The clinical bulge test was 100% specific but only 29% sensitive for knee joint effusion as detected by MRI. The patella tap sign was only 4.8% sensitive, and not analyzed further. Bulge-positive knees were associated with higher baseline WOMAC disability (26.9 vs 18.2, p=0.02) and pain scores (5.4 vs 3.7, p=0.03) compared to bulge-negative knees. Bulge-positive knees were significantly more likely to have corticosteroid injection within 12 months (78% vs 58%, p=0.007).

An analysis of the whole OAI dataset revealed a 3-fold increase in 5 year TKR for bulge-positive patients (9% vs 3%, p<0.0001, n=9302), with bulge-positivity significantly predicting TKR using multivariate logistic regression (odds ratio 2.0 [95% CI 1.4-2.9], p<0.0001, n=4324).

Conclusion:

The patellar bulge test is a relatively insensitive but highly specific clinical marker for joint effusion in OA. A positive patellar bulge test at presentation is associated with greater pain, disability, a higher rate of corticosteroid injections and a 2- to 3-fold increase in TKR within 5 years.

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Abstract Number: 2405

Knee Sounds May Predict Osteoarthritis Severity, Symptoms and Function: Pilot Investigation Toward a Novel Dynamic Imaging System

Victoria Manning[1], Costas Yiallourides[2], Mads Brevadt[1], Alastair Moore[2], Edouard Auvinet[1], Patrick Naylor[2] and Justin Cobb[1], [1]Musculoskeletal Lab, Imperial College London, London, United Kingdom, [2]Communications and Signal Processing Group, Imperial College London, London, United Kingdom

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Background/Purpose:

Knee sounds (KS) may provide a low-cost, risk-free means of identifying presence and severity of knee osteoarthritis (KOA). Unlike static imaging, KS during dynamic activity may correlate with symptoms and function. This study aimed to explore the association between KS, KOA severity, symptoms and function.

Methods:

Adults with clinical KOA (1986 ACR) were recruited from a UK orthopedic clinic by the attending surgeon (JC). Adults (at Imperial College London) reporting no previous knee pain >2 weeks were recruited. Knees were classified as: 1) OA, 2) healthy, 3) OA healthy (contralateral KOA). Exclusion criteria were: aged <18 years, previous surgery, unable to provide consent.

Severity of OAwas assessed (single rater) using the Kellgren-Lawrence (KL) radiographic scoring method. Knee symptoms and function were assessed via self-reported Knee Injury and Osteoarthritis Outcome Scores (KOOS). KS were acquired (rate 44-48kHz) during treadmill walking (4km/h) using a contact microphone (Basik Pro, Schertler, 20Hz to 20kHz) attached to the patella, supported by a digital preamplifier (RME Babyface; PreSonus DigiMax LT).

KS features were extracted from recordings using spectro-temporal and cepstral analysis, and correlations (r) with KL and KOOS explored. Features correlating over $|r|>0.6$ were used to train binary regression decision trees to identify KS feature-combinations predictive of KOOS. Pearson's and Bland and Altman's 95% limits of agreement (LOA) were used to assess association between predicted and true values.

Results:

Twenty-eight participants were recruited; 14 knees were excluded due to previous surgery, 42 knees were included (Table 1). OA healthy knees were excluded from KOOS. Twenty knee x-rays were available dating 10±7 (all ≤ 27) weeks pre-assessment.

Of 8,141 extracted KS features, 267 exceeded $|r|>0.6$ with KL and KOOS (Figure 1). Predicted KOOS were strongly correlated with true KOOS, except quality of life (QOL) (Figure 2); mean (95% LOA) = pain -0.8 (47.2 to -48.8); symptoms 0.2 (34.6 to -34.1), activities of daily living 0.7 (40.2 to -38.8); QOL 2.1 (67.1 to -63.0).

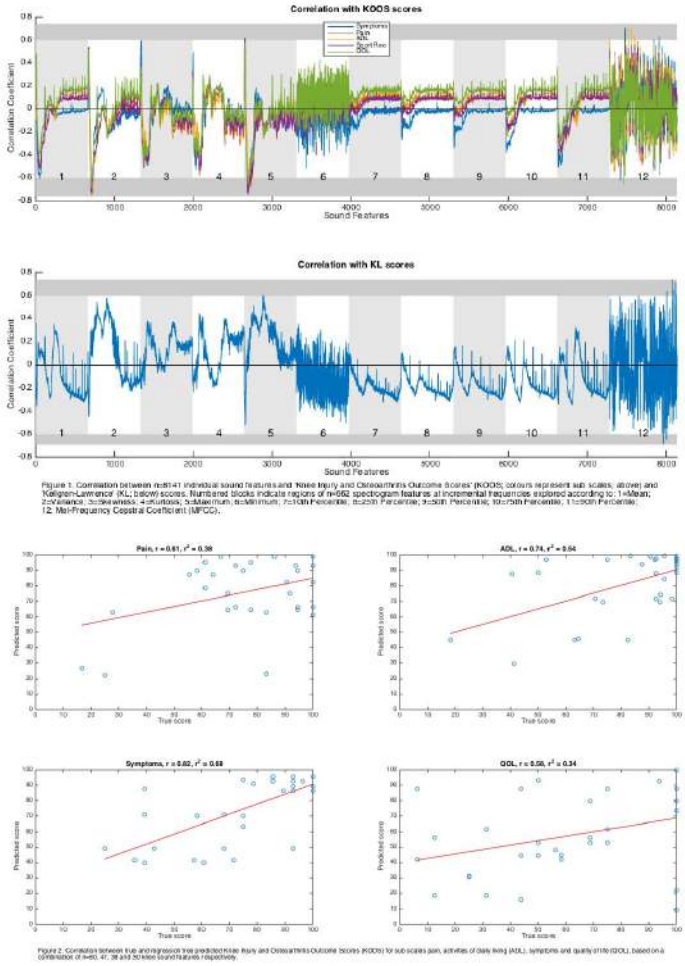
Conclusion:

These preliminary findings indicate that KS are predictive of OA symptoms and function, and possibly severity. Whilst encouraging, further investigation is required among a larger cohort.

TABLE 1. Demographical characteristics of study participants

	Healthy n=13	OA n=21	OA Healthy n=8
Age (years)	51.5 ± 21.1	62.6 ± 19.3	63.8 ± 15.5
BMI (kg/m²)	25.5 ± 3.1	29.0 ± 6.4	25.5 ± 2.4
Females (n)	4	11	2
KOOS			
Symptoms	93.5 ± 2.7	64.0 ± 21.6	99.1 ± 1.7
Pain	92.0 ± 7.5	65.6 ± 22.4	99.7 ± 22.4
ADL	96.7 ± 4.3	73.9 ± 23.4	100.0 ± 0.0
SP	84.0 ± 12.8	51.4 ± 25.7	100.0 ± 0.0
QOL	84.7 ± 17.8	44.9 ± 27.5	100.0 ± 0.0
KL* (median & range)	1 (1-1)	2 (0-4)	1 (0-2)

All numbers reported are (mean ± standard deviation), unless otherwise stated.
OA = osteoarthritis, KOOS = Knee injury and Osteoarthritis Outcome Score, ADL = Activities Daily Living, SP = Sports and Recreational activities, QOL = Quality Of Life, KL = Kellgren-Lawrence score.
* KL are based on a subset of participants with imaging available: 2 Healthy, 10 OA and 8 OA Healthy.



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Abstract Number: 2406

The 2011 Fibromyalgia (FM) Criteria Are Helpful in Identifying Central Sensitization in Knee Osteoarthritis

Steven E. Harte[1], Andrew D. Clauw[1], J. Ryan Scott[1], Daniel J. Clauw[2] and Chad Brummett[2], [1]Department of Anesthesiology, University of Michigan, Ann Arbor, MI, [2]Anesthesiology, University of Michigan, Ann Arbor, MI

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Background/Purpose: Both animal and human studies have suggested that both peripheral and central sensitization may occur in nociceptive pain states such as OA. This distinction is important since although peripheral sensitization is due to ongoing peripheral nociceptive input and would respond to more aggressive use of peripherally-directed therapies, if central sensitization or centralized pain is identified, this may indicate that treatments aimed at the central nervous system may be more helpful. Using quantitative sensory testing (QST), the presence of peripheral sensitization is suggested when there is tenderness (i.e. mechanical hyperalgesia/allodynia) localized to the knee, whereas if both the knee and a distant site are tender this is suggestive of central sensitization. Although both peripheral and central sensitization are typically identified using sophisticated pain research tools such as quantitative sensory testing (QST) or functional brain imaging, recent studies have suggested that the 2011 Survey Criteria for FM, used as a continuous rather than dichotomous variable, may be helpful in identifying individuals who have centralized pain. We hypothesized that if this was the case, individuals with knee OA with higher FM scores should have a stronger relationship between the mechanical pain threshold at the knee and that at a distant "neutral" site such as the thumb.

Methods: As part of a larger study of analgesic outcomes following total knee arthroplasty, a subset of 63 individuals (ages 42 – 81, 24 males, 39 females) scheduled to undergo arthroplasty had a mechanical pain threshold assessed at both their painful knee and dominant thumb, and also completed the 2011 FM criteria. We then performed a tertile split of the cohort using FM scores, with the lowest tertile of 22 individuals having FM scores of 0-3, the middle tertile of 23 individuals having scores of 4-7, and the highest tertile of 18 individuals having scores of 8 or greater.

Results: Using non-parametric correlations (Spearman's rho), we found that in the lowest FM tertile, there was no significant relationship between the mechanical threshold at the knee, and that measured at the thumb (r_s = .305, p = .167). The middle FM tertile showed a stronger but still statistically insignificant correlation (r_s = .352, p = .099). However, individuals with KOA in the highest FM tertile displayed a highly significant correlation between the threshold at the knee, and that measured at the thumb (r_s = .651, p =.003).

Conclusion: These data lend further evidence that the 2011 FM Survey Criteria, when used us a continuous rather than dichotomous measure, serve as a surrogate measure for the presence of central sensitization in KOA. Together with previously published studies from this same cohort suggesting that this measure is also strongly predictive of both opioid and surgery non-responsiveness, this suggests that this measure may provide useful in both research and clinical practice in identifying individual who might benefit from more centrally-directed therapies such as centrally acting analgesics, or non-pharmacological therapies.

Disclosure: S. E. Harte, MAST Device, 4,Cerephex, 5,Analgesic Solutions, 5,Merck, 5,Regeneron, 5,deCode Genetics, 5; **A. D. Clauw**, None; **J. R. Scott**, None; **D. J. Clauw**, Abbott Laboratories, 5,Cerephex, 5,Eli Lilly and Company, 5,Forrest Laboratories, 5,Johnson & Johnson, 5,Merck Pharmaceuticals, 5,Pfizer Inc, 5,Purdue Pharma L.P., 5,Samumed, 5,Theravance, 5,Tonix, 5,UCB, 5,Zynerba, 5,Abbott Laboratories, 5,Cerephex, 5,Eli Lilly and Company, 5,Forest Laboratories, 5,Johnson & Johnson, 5,Merck Pharmaceuticals, 5,Pfizer Inc, 6,Purdue Pharma L.P., 6,Samumed, 5,Theravance, 5,Tonix, 5,UCB, 5,Zynerba, 5; **C. Brummett**, Tonix Pharmaceuticals, 5.

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Abstract Number: 2407

Comparison of Knee Osteoarthritis Treatment in the Non-Obese Versus Obese Populations Across Different Medical Specialties

Kelly Forrester[1], Farah Taufiq[1] and Jonathan Samuels[2,3], [1]NYU Langone Medical Center, New York, NY, [2]Rheumatology, NYU - Hospital for Joint Diseases, New York, NY, [3]Rheumatology, NYU Langone Medical Center, New York, NY
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Background/Purpose: Knee osteoarthritis (KOA) in the obese population is underdiagnosed and routinely undertreated, as providers often attribute pain to excess weight without considering articular pathology. The literature does not speculate if obese and non-obese patients are offered the same treatment options for their KOA. Using a retrospective chart review, we compared approaches to KOA treatment across BMI subgroups as well as between physician specialties: rheumatology, orthopedics, sports medicine, physiatry, and internal medicine.

Methods: We searched the NYU electronic medical record between January 1 and December 31, 2013 for patients seen for KOA by selected physicians in the 5 specialties. From the resulting list of 4,486 patients, we reviewed the first 1,500 charts and selected for clinical and radiographic KOA while excluding patients with bilateral knee replacements, trauma within 6 weeks, or concurrent rheumatoid arthritis, psoriatic arthritis, gout, pseudogout, or bursitis. From this cohort we found 702 who met criteria (191 patients seen by rheumatology, 162 by orthopedics, 198 by sports medicine, 132 by physiatry, and 20 by internal medicine). We recorded BMIs, comorbidities, KOA characteristics, and KOA management including acetaminophen, NSAIDs/COX-2 inhibitors, physical therapy referrals, and intra-articular injections of steroids or hyaluronic acid (HA). We analyzed differences in overall KOA treatment of non-obese vs. obese patients (BMI <30 vs ≥ 30 kg/m^2), and between the 5 physician specialties regardless of patient BMI.

Results: The resulting cohort of 702 patients had an overall mean BMI of 29.1 (±7). The mean age was 60.5 (±14) with 75% females. Surprisingly, we did not find any significant differences in KOA treatment of non-obese (BMI<30) vs obese patients when aggregating scores across physician specialties; this held true when comparing the non-obese with the morbidly obese (BMI>35). Our data do suggest that rheumatologists recommend acetominophen for KOA far more often than do the combined cohort of orthopedists, physiatrists and sports medicine physicians (37% vs 3%, $p<0.001$); internists (at 43%) are even greater proponents of acetaminophen. We did not identify any significant difference between specialties in the percentage of KOA patients prescribed NSAIDs or COX-2 inhibitors, referrals to physical therapy, or the use of corticosteroid injections. With regards to HA, rheumatologists in our cohort inject less than orthopedists (17% vs 26%, $p=0.06$), sports medicine physicians (17% vs 30%, $p=0.004$), and physiatrists (17% vs 29%, $p=0.02$). We also found no reportable difference in specialty-specific KOA treatment between the BMI sub-groups.

Conclusion: In treating KOA, rheumatologists and internists are more likely to prescribe acetaminophen for KOA while orthopedists, sports medicine physicians, and physiatrists are more like to inject HA. Despite preconceived bias, we did not identify significant differences in the KOA treatment of non-obese vs obese patients, in aggregate or within any of the subspecialties. Nevertheless, identification of divergent treatment patterns between specialties warrants discussion to optimize algorithms across musculoskeletal care.

Disclosure: K. Forrester, None; **F. Taufiq**, None; **J. Samuels**, None.

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Abstract Number: 2408

The Quality of Community-Based Osteoarthritis Care Can be Improved. Results from a Systematic Review and Meta-Analysis

Kåre Birger Hagen[1], Geir Smedslund[2], Nina Østerås[2] and Gro Jamtvedt[3], [1]National Advisory Unit on Rehabilitation in Rheumatology, Department of Rheumatology, Diakonhjemmet Hospital, Oslo, Norway, [2]National Advisory Unit on Rehabilitation in Rheumatology, Department of Rheumatology,, Diakonhjemmet Hospital, Oslo, Norway, [3]The Norwegian Knowledge Center for the Health Services, Oslo, Norway

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Background/Purpose: The burden of osteoarthritis (OA) is substantial and expected to increase because people are getting older and heavier. Health care providers need to monitor and improve the quality of health services for people with OA. The purpose of this study was to evaluate the state of quality of care for OA by summarizing studies that have assessed the care provided to patients.

Methods: A systematic review of community-based observational studies that assessed the quality of care for patients living in the community with OA, by comparing actual clinical practice to a quality indicator (QI) was performed. Four databases were searched from January 2000 to November 2014. Two reviewers independently determined study eligibility, assessed risk of bias and extracted study data. The outcome was adherence to the QIs (pass rate), calculated as all instances in which recommended care was received or delivered divided by the number of times participants were eligible. No pooling of overall pass rates was performed, but when at least 50% of the studies had comparable individual QIs, the data were pooled with proportion meta-analyses.

Results: Nine studies from North America and Western Europe comprising 4037 patients were included. The Assessing Care Of Vulnerable Elders (ACOVE) indicators and RAND's Quality Assessment Tools system and were the most commonly used QI sets. The number of individual indicators in the sets used varied from 3 to 17, and data were collected from medical records in five studies, and by patient reports in four studies. The median overall pass rate across studies was 38% (ranging from 22% to 65%). Six individual indicators were similar across at least five studies, and were consequently pooled (table).

Quality Indicator	Pooled Passrate (95% CI)
Referral to orthopedic surgeon if no response to other therapy	73.5 (52.4-87.5)
Paracetamol or acetaminophen first drug used	45.9 (39.6-52.4)
Assessed for pain and/or function	45.8 (30.0-62.5)
Offered education and/or self-management	32.3 (17.8-51.3)
Referral or recommendation to exercise	30.4 (23.4-38.5)
Informed about potential risks if NSAIDs prescribed	21.4 (10.6-38.5)

Conclusion: On average, one-third of OA patients received first line non-pharmacological approaches, which was significantly lower than the nearly three-quarters referred to orthopedic surgery. This pattern seems to be consistent across North America and Western Europe, and indicates a substantial need for improvement in community-based OA care.

Disclosure: K. B. Hagen, None; **G. Smedslund**, None; **N. Østerås**, None; **G. Jamtvedt**, None.

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Abstract Number: 2409

Factors Associated with Physical Therapy Use in Osteoarthritis of the Knee:

Results from a Population-Based Study

Sicong Huang[1], Eric C. Sayre[2] and Jolanda Cibere[1,2], [1]Department of Medicine, University of British Columbia, Vancouver, BC, Canada, [2]Arthritis Research Canada, Richmond, BC, Canada
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Background/Purpose: Osteoarthritis (OA) is the most common form of arthritis. Physical therapy (PT) has previously been demonstrated to benefit patients with osteoarthritis, especially with early referral. However, few studies have investigated factors affecting PT use and none have involved a Canadian population, where the mixed private and public payer system could affect usage rates. The objective of this study is to identify factors associated with PT use in a population-based cohort with OA-associated knee pain.

Methods: 255 subjects were recruited as a random population sample (MoDEKO study) in Greater Vancouver, Canada. Inclusion criteria were: 1) age 40–79 years, 2) pain, aching, or discomfort in/around the knee on most days of the month at any time in the past, and 3) any pain, aching, or discomfort in/around the knee in the past 12 months. Exclusions were: 1) inflammatory arthritis or fibromyalgia, 2) knee arthroplasty, 3) knee injury or surgery within the past 6 months, 4) referred pain from hips or back, and 5) inability to undergo MRI. PT use during the past 12 months (dependent variable) was ascertained by self-report. Independent variables included predisposing characteristics including age, sex, ethnicity, level of education (≤/> grade 12), and median household income using the 2006 Canadian Census data based on postal codes, as well as need characteristics including body mass index (BMI), self-reported knee swelling in the past 12 months, physician diagnosis of OA, radiographic severity (Kellgren–Lawrence grading (KL) ≥2/KL <2), and pain severity on flat walking, as assessed by the Western Ontario and McMaster Universities (WOMAC) Osteoarthritis Index. Univariate logistic regression analysis was performed. Variables with $p<0.20$ were included in a multivariable logistic model to assess the association with PT use.

Results: 29 of 255 (weighted 12%) subjects reported PT use. Mean age was 57, mean BMI 26.5, mean household median income $61,560, and mean WOMAC pain 17. 56% were female, 76% Caucasian, 77% attended post-secondary education, 39% were diagnosed with OA by a physician, 38% had KL ≥2, 51% reported knee swelling. In multivariable logistic regression analysis, female gender (OR 3.19, 95% CI 1.29-7.89) and self-reported knee swelling (OR 3.51, 95% CI 1.42-8.68) were significantly associated with PT use, while household income (as a factor of $10,000, OR 1.15, 95% CI 0.97-1.37), physician diagnosis of OA (OR 1.19, 95% CI 0.53-2.71), WOMAC pain on flat walking (as a factor of 10, OR 1.11, 95% CI 0.93-1.32) were included in the multivariable model, but were not statistically significant.

Conclusion: In this population-based study of subjects with knee pain, women and those with self-reported knee swelling were three times more likely to be current PT users. Interestingly, disease severity, physician diagnosis of OA, and household income were not significantly associated with current PT usage. Further longitudinal research will be important to identify other factors affecting PT use in order to target individuals at risk of underuse and/or overuse.

Disclosure: S. Huang, None; **E. C. Sayre**, None; **J. Cibere**, None.

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Abstract Number: 2410

Report from the International Consortium of Health Outcome Measurement Hip and Knee Osteoarthritis Working Group: Consensus on an International Standard Set of Outcomes Measures for Patients with Hip or Knee Osteoarthritis.

Philip G. Conaghan[1], Lyn March[2], Ola Rolfson[3], Stephanie Wissig[4], Caleb Stowell[5], Patricia D. Franklin[6] and The ICHOM Working Group in Hip & Knee Osteoarthritis, [1]University of Leeds & NIHR Leeds Musculoskeletal Biomedical Research Unit, Leeds, United Kingdom, [2]Department of Rheumatology, Northern Clinical School, Institute of Bone and Joint Research, Kolling Institute, University of Sydney & Department of Rheumatology, Royal North Shore Hospital, St Leonards, Sydney, Australia, [3]Harris Orthopaedic Laboratory, Massachusetts General Hospital, Harvard Medical School,, International Consortium for Health Outcomes Measurement, Boston, MA, [4]ICHOM, International Consortium for Health Outcomes Measurement, Cambridge, MA, [5]14 Arrow St., Ste. #11, 3International Consortium for Health Outcomes Measurement, Cambridge, MA, [6]Orthopedics and Physical Rehabilitation, University of Massachusetts Medical School, Worcester, MA

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Background/Purpose: To define a minimum Standard Set of outcome measures and case-mix factors for monitoring, comparing, and improving healthcare for patients with clinically diagnosed hip or knee osteoarthritis (OA) with a focus on defining the outcomes that matter most to patients.

Methods: An international Working Group (WG) of patients, arthroplasty register experts, orthopedic surgeons, primary care physicians, rheumatologists, and physical therapists representing 10 countries was assembled to review existing literature and practices for assessing outcomes of pharmacological and non-pharmacological OA therapies including surgery. A series of 8 teleconferences, incorporating a modified Delphi process, were held to reach consensus.

Results: The WG reached consensus on a concise set of outcomes measures to evaluate patients' joint pain, physical functioning, health-related quality of life, work status, mortality, reoperations, readmissions, and overall satisfaction with treatment result. To support analysis of these outcome measures, pertinent baseline characteristics and risk factor metrics were defined (see Table 1). Annual outcome measurement is recommended for all patients.

Conclusion: We have defined a Standard Set of outcome measures for monitoring the care of people with clinically diagnosed hip and knee OA that is appropriate for use across in all treatment and care settings. We believe this Standard Set provides meaningful, comparable, and easy to interpret measures ready to implement in clinics and/or registries globally. We view this as an initial step that, when combined with cost data, will facilitate value-based healthcare improvements in the treatment of hip and knee OA.

Outcome Domains	Risk Factor Domains
Patient reported • Hip and/or knee function (HOOS-PS or KOOS-PS) • Pain in the hips, knees or lower back (Numeric or visual analog rating scale) • Quality of life (EQ-5D-3L or VR-12/SF-12) • Satisfaction with treatment • Work status Surgical outcomes • All cause 30-day mortality • All cause 30-day readmissions • Reoperation Disease progression • Care utilization • Treatment progression	Demographics • Age • Gender • Education level Baseline clinical status • Joint specific history • Joint specific surgical history Case-mix factors • Living status • BMI • Smoking status • Co-morbid conditions

Disclosure: P. G. Conaghan, Abbvie, BMS, Novartis Non-remunerative, 5,Abbvie, BMS, Janssen, Roche, 8; **L. March**, None; **O. Rolfson**, None; **S. Wissig**, None; **C. Stowell**, None; **P. D. Franklin**, None.

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Abstract Number: 2411

Patient Preference for Using Technology to Track and Self-Manage Osteoarthritis

Laura Khurana, **Ellen Durand**, Sarah Gary, Tony Otero, Chris Hall and Susan Dallabrida, ERT, Boston, MA

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Background/Purpose: Active and consistent self-management is essential for patients suffering from chronic diseases to improve their health. Electronic clinical (eClinical) technology may improve how patients track and manage disease. The aim of this study was to establish how subjects with osteoarthritis (OA) currently use technology to monitor and manage their health and their interest in using eClinical technology in clinical care.

Methods: Subjects aged 37-90 with OA (n=104) were surveyed as part of a mode equivalence study. Subjects were diverse in age, sex, ethnicity, and technology use. Subjects answered questions regarding how they use technology to manage disease and general health.

Results: 50% of subjects have access to a home computer, and 53% have home internet. Subjects that use the internet most commonly use a computer (71%), smartphone (22%), or tablet (7%). 48% reported using the internet daily. 39% of subjects reported that they regularly monitor or keep track of their disease. Of those subjects that do monitor their OA, 94% use paper and 6% use a computer or online forum. Subjects reported that if they need more information about managing their OA they ask their physicians (88%), use the internet (42%), and ask friends/family (35%). 48% of subjects reported searching online for information about OA and/or treatments on at least a monthly basis. With respect to OA, subjects were most likely to research information on their current treatments (83%) and the impact of diet on their disease (64%), followed by new drugs (44%), disease complications (43%), and the impact of exercise on OA (35%). With respect to their general health, subjects were most likely to search online for recommendations about diet (68%), and least likely to research how much water they should drink (12%). When asked about a potential smartphone application that provides educational messages about OA, subjects wanted messages to include information on the effects of foods/beverages on medications they are currently taking (69%), nutritional value of foods they currently eat (66%), and heathy alternatives to those foods (66%).

Conclusion: This study characterized how subjects with osteoarthritis use technology to track and research their disease. Nearly half of subjects use the internet to get information about managing their OA on a monthly basis or more. Subjects prefer to research their current treatments and the impact of diet on disease, and would like similar information provided via smartphone app. Understanding the type of information that patients track regarding their health may help identify areas for more effective intervention, and assist in the development of tools to improve patient engagement.

Disclosure: L. Khurana, ERT, 3; **E. Durand**, ERT, 3; **S. Gary**, ERT, 3; **T. Otero**, ERT, 3; **C. Hall**, ERT, 3; **S. Dallabrida**, ERT, 3.

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Abstract Number: 2412

Assessment and Comparison of Responsiveness of Four Patient Reported Outcome Measures to Assess Physical Function in Patients with Knee Osteoarthritis: WOMAC-PF Subscale Responds Best

Elien A.M. Mahler[1], Nienke Cuperus[2], Johannes W J Bijlsma[3], Thea Vliet Vlieland[4], Frank H.J. van den Hoogen[5], Alfons den Broeder[5] and Cornelia H.M. van den Ende[1], [1]Department of Rheumatology, Sint Maartenskliniek, Nijmegen, Netherlands, [2]Rheumatology Department, Sint Maartenskliniek, Nijmegen, Netherlands, [3]Rheumatology and Clinical Immunology, ARC Amsterdam; UMC Utrecht, Utrecht, Netherlands, [4]Rheumatology, Department of Rheumatology, Leiden University Medical Center, Leiden, Netherlands, [5]Rheumatology, Sint Maartenskliniek, Nijmegen, Netherlands
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Background/Purpose:

Although physical function is one of the core outcome domains in knee osteoarthritis (OA), the ability of a measurement instrument to detect changes over time in the construct (physical function) being measured, i.e. the responsiveness, has never been tested as currently recommended by the Consensus-based Standards for the selection of health status Measurement Instruments (COSMIN)[1]. The aim of the current study was to compare the responsiveness of physical function between four commonly used disease-specific patient related outcome measures in patients with knee OA following currently recommended standards.

Methods:

Patients with knee OA fulfilling the clinical ACR criteria and receiving conservative treatment following a stepped care approach were invited to complete a set of questionnaires at baseline and three months. Questionnaires included four commonly used measures of physical function ie Knee Injury and Osteoarthritis Outcome Function Short Form (KOOS-PS), the Lequesne Algofunctional index (LAI), Lower Extremity Functional Scale (LEFS), and Western Ontario and McMaster University Osteoarthritis Index Physical Function subscale (WOMAC-PF). Responsiveness of physical function was investigated according to the COSMIN standard by testing 15 a priori defined hypotheses formulated by an expert group regarding expected correlations between changes in physical function with changes in other (un)related measures (pain, fatigue, self-efficacy, coping, anxiety, depression and mental health) or expected differences in correlation. Responsiveness was considered positive if > 75% of the hypotheses could be confirmed.

Results:

Of the 161 included patients, the majority was female (61%), with a mean age of 59 years and a body mass index of 29.7 kg/m^2. We could confirm 12 out of 15 predefined hypotheses (80%) about expected correlations using the physical function subscale of the WOMAC. For the KOOS-PS, LAI and LEFS respectively 11 (73%), 10 (67%) and 11 (73%) hypotheses could be confirmed.

Conclusion:

This is the first study that evaluated and compared the responsiveness of physical function measured with KOOS-PS, LAI, LEFS and WOMAC-PF according to the latest COSMIN standards[1]. Our results suggest that the WOMAC-PF is potentially better able to detect changes over time in physical function than the LAI, LEFS and KOOS-PS in a population of patients with knee OA receiving conservative treatment. We therefore recommend the WOMAC-PF subscale should be the measure of first choice in in clinical trials evaluating the effectiveness of an intervention in knee OA patients.

None.

Abstract Number: 2413

Contributors to Walking Disability in People with Osteoarthritis: Results from a Population-Based Cohort

Lauren King[1], Tetyana Kendzerska[1,2,3] and Gillian Hawker[1,2,3], [1]Department of Medicine, University of Toronto, Toronto, ON, Canada, [2]Institute for Clinical Evaluative Sciences, Toronto, ON, Canada, [3]Women's College Research Institute, Women's College Hospital, University of Toronto, Toronto, ON, Canada

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Background/Purpose: Osteoarthritis (OA) is associated with functional limitations, including difficulty walking. However, comorbid disease is common in people with OA and may also be associated with functional limitations; this includes chronic conditions such as obesity, stroke, angina, heart failure, diabetic neuropathy, and intermittent claudication. Previous studies have demonstrated that walking disability is associated with cardiovascular (CV) events and all-cause mortality. Our aim was to examine the extent to which knee and hip OA contribute to walking disability.

Methods: A population cohort aged ≥55 years was recruited from one urban and one rural community from 1996-98. Age, sex, height and weight, joint complaints, functional limitations and self-reported medical comorbidities known to be associated with walking disability were collected by questionnaire. Subjects with inflammatory arthritis, rheumatic disease, amputation and/or reported use of a wheelchair were excluded. OA was defined as (1) swelling, pain, or stiffness in any joint lasting 6 weeks in the past 3 months; and (2) indication on the homunculus that a knee and/or hip was “troublesome”. Walking disability was defined as self-reported difficulty standing or walking in the last 3 months. Participants were classified into 4 mutually exclusive joint groups based on the presence/absence of knee and hip OA. Using logistic regression, we assessed the independent correlates of walking disability. Covariates of interest were: combined knee and hip OA, knee OA only, hip OA only, neurological disease, CV disease, diabetes and peripheral vascular disease.

Results: 20,644 participants were included: mean age 68.2±8.5 years, 58.5% female, 51.8% rural-dwelling and mean body mass index (BMI) of 25.9±4.5 kg/m^2. Self-reported walking disability was present in 5,667 (27.5%) subjects. In bivariate analysis, presence of walking disability was associated with increased age, female sex, higher BMI and all covariates of interest ($p<0.01$). In the final regression analysis, walking disability was significantly associated with older age (odds ration [OR] 1.04, 1.04 – 1.05, $p<0.01$), sex (OR 0.83, 0.77 – 0.89, $p<0.01$), BMI (OR 1.07, 1.07 – 1.08, $p<0.01$), presence of CV disease (OR 2.12, 1.88 – 2.36, $p<0.01$), diabetes (OR 1.48, 1.28 – 1.71, $p<0.01$), peripheral vascular disease (OR 6.98, 3.46 – 14.06, $p<0.01$) and neurological diseases (OR 3.67, 2.58 – 5.20, $p<0.01$). Controlling for all of these factors, knee and hip OA remained significantly associated with walking disability: knee and hip OA (OR 17.50, 15.33 – 19.97, $p<0.01$), knee OA only (OR 6.66, 6.03 – 7.37, $p<0.01$) and hip OA only (OR 7.13, 6.15 – 8.27, $p<0.01$).

Conclusion: In a large population cohort aged ≥55 years, the greatest independent contributor to walking disability was the presence of symptomatic knee and hip OA. Given the previously documented relationship between walking disability and mortality, addressing OA-associated functional limitations is important in the management of other common chronic conditions.

Disclosure: L. King, None; **T. Kendzerska**, None; **G. Hawker**, None.

Abstract Number: 2414

High-Intensity Versus Low-Intensity Physical Activity or Exercises in Patients with Hip or Knee Osteoarthritis: A Meta-Analysis

Jean-Philippe Regnaux[1,2,3], Marie-Martine Lefèvre-Colau[4], Ludovic Trinquart[3], **Christelle Nguyen**[5], Isabelle Boutron[1,3,6,7], Lucie Brosseau[8] and Philippe Ravaud[3,6,7,9], [1]METHODS team, INSERM UMR-S 1153, Paris, France, [2]EHESP Rennes, Sorbonne Paris Cité, Paris, France, [3]French Cochrane Center, Paris, France, [4]Univ. Paris Descartes, PRES Sorbonne Paris Cité, Service de rééducation et réadaptation de l'appareil locomoteur et des pathologies du rachis, Hôpital Cochin, Assistance Publique - Hôpitaux de Paris, Paris, France, Paris, France, [5]Univ. Paris Descartes, PRES Sorbonne Paris, Cité Laboratoire de Pharmacologie, Toxicologie et Signalisation Cellulaire, INSERM UMR-S 1124, UFR Biomédicale des Saints Pères, Paris, France, Paris, France, [6]Paris Descartes University, Sorbonne Paris Cité, Faculté de Médecine, Paris, France, [7]Centre d'Épidémiologie Clinique, AP-HP (Assistance Publique des Hôpitaux de Paris), Hôpital Hôtel Dieu, Paris, France, [8]Rehabilitation Sciences, University of Ottawa, Ottawa, ON, Canada, [9]METHODS team, INSERM U1153, Paris, France

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SESSION INFORMATION

Session Date: Tuesday, November 10, 2015

Session Title: Osteoarthritis - Clinical Aspects Poster II: Biomarkers, Biomechanics and Health Services Research

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Exercise or physical activity are complex interventions whose effectiveness depends on more than one component. We aimed to determine the benefits and harms of high- *vs* low-intensity exercise or physical activity programs in patients with hip or knee OA.

Methods: We searched CENTRAL, MEDLINE and EMBASE to June 2014, CINAHL, PEDro, Scopus and WHO International Clinical Registry to October 2012. We included RCTs of patients with knee or hip OA that compared high- *vs*low-intensity physical activity or exercise programs. High-intensity programs training referred to an increase in the overall amount of training time or in the amount of work or in effort/energy expenditure. Two authors independently assessed study eligibility and extracted data. The quality of the body of evidence was assessed using the GRADE approach

Results: 6 studies (N=656) were included: 5 studies recruited patients with knee OA (N=620) and 1 with hip or knee OA (N=36). In patients with knee OA, pain symptoms and physical function were more improved with high- than low-intensity exercise programs, immediately at the end of the exercise programs (from 8 to 24 weeks). Low-quality evidence indicated reduced pain on a 20-point WOMAC pain scale (mean difference [MD] -0.84, 95% confidence interval [95% CI] -1.63 to -0.04; 4% absolute reduction; NNTB 11, 95% CI 14 to 22) and improved physical function on the 68-point WOMAC disability subscale. We found no statistical difference on major outcomes at mid- or long-term follow-up. Subgroup analysis of 4 studies showed a statistical significant difference with increased exercise time on pain (MD -1.37, 95% CI -2.47 to -0.28; 7% absolute reduction; NNTB 11, 95% CI 9 to 14, very low level of evidence) and physical function (MD -4.10, 95% CI -8.12 to -0.07; 6% absolute reduction; NNTB 10, 95% CI 8 to 13; very low level of evidence). Only one study systematically monitored adverse effects. We are uncertain whether high intensity increase the number of adverse effects (Peto odds ratio 1.72, 95% CI 0.51 to 5.81; 2% absolute reduction, very low level of evidence). We found the overall quality of evidence as low to very low. Most of the studies had an unclear or high risk of bias for several domains and imprecision. Five of the six studies were at high risk for performance, detection and attrition bias.

Conclusion: We found no clear clinical benefits of high intensity *vs* low intense exercise programs for pain, function and quality of life in patients with knee or hip OA. We found no important clinical benefits depending on the type of intensity of exercise programs. Very low quality of evidence shows no difference in the rate of adverse effects. The evidence was downgraded from high to low or very low because of the risk of bias, inconsistency and imprecision. The small number of studies comparing high- *vs* low-intensity exercise programs in OA underscores the need for more studies investigating the dose-response relationship in exercise programs. In particular, further studies are needed to establish the minimal effective intensity of exercise programs needed for clinical effect and the highest intensity patients can tolerate.

Disclosure: J. P. Regnaux, None; **M. M. Lefèvre-Colau**, None; **L. Trinquart**, None; **C. Nguyen**, None; **I. Boutron**, None; **L. Brosseau**, None; **P. Ravaud**, None.

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Abstract Number: 2415

Use of Plasma Exchange for Children Hospitalized with ANCA-Associated Vasculitis in the United States

Karen James[1], Rui Xiao[2], Peter A. Merkel[3] and Pamela F. Weiss[1], [1]Rheumatology, Children's Hospital of Philadelphia, Philadelphia, PA, [2]Department of Biostatistics and Epidemiology, University of Pennsylvania, Philadelphia, PA, [3]Division of Rheumatology, University of Pennsylvania, Philadelphia, PA

First publication: September 29, 2015

SESSION INFORMATION

Session Title: Pediatric Rheumatology - Clinical and Therapeutic Aspects Posters (ACR): Imaging and Novel Clinical Interventions

Session Type: ACR Poster Session C

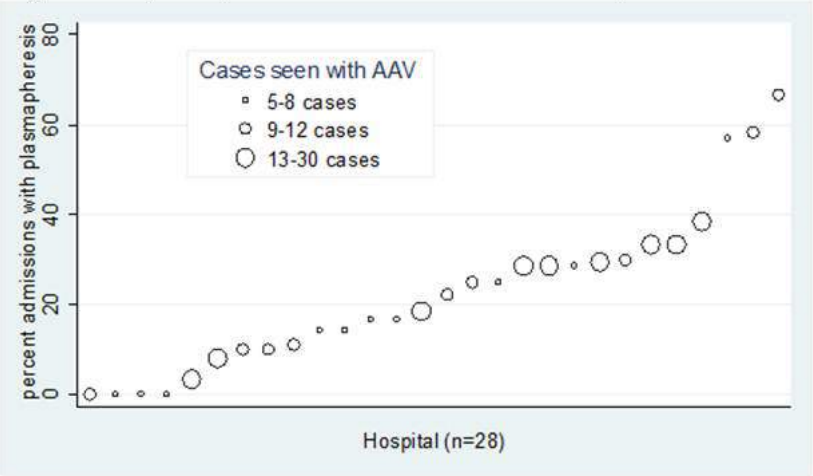
Background/Purpose: ANCA-associated vasculitis (AAV) is a group of rare systemic vasculitidies with significant morbidity and mortality. Plasma exchange (PLEX) has been shown to decrease risk for end-stage renal disease in adults with severe AAV, however there are no data in children. We aimed to characterize the use of PLEX in children with AAV hospitalized in the United States.

Methods: We conducted a retrospective cohort study of children hospitalized with AAV from 2004-2014 utilizing the Pediatric Health Information System database which contains inpatient administrative and billing data from 47 hospitals in the United States. The cohort included patients with the ICD-9-CM code 446.4 as one of the discharge diagnoses and ≥1 charge for glucocorticoids. Cyclophosphamide and rituximab exposure was determined using pharmacy billing data. Receipt of PLEX was determined using ICD-9-CM and clinical transaction classification codes. Demographics and clinical variables were summarized using count & percentage or median & interquartile range as appropriate. We built a multivariate mixed effects regression model accounting for clustering by hospital using a backwards selection model starting with preset variables (age, sex, rituximab, cyclophosphamide, mechanical ventilation, dialysis, year, & hospital case load of AAV) to determine factors associated with use of PLEX.

Results: During the study period there were 1290 admissions for 393 children with AAV at 43 hospitals. Median age at first admission was 14.6 (IQR 12.2,16.1); 60.6% were female. 236 (60%) children required readmission with a median of 2 readmissions (IQR 1, 3). The median length of stay for first admission was 9 days (IQR 4,15). The first readmission was a median of 55 days (IQR 12, 165) after initial discharge, with a median duration of 3 (IQR 2,6) days. During the first admission, 60 (15.5%) children needed dialysis, and 67 (17.1%) required mechanical ventilation. 222 (56.8%) children received cyclophosphamide, 83 (21.2%) received rituximab, 40 (10.2%) received both. Eighty-four children (21.5%) received PLEX, of whom 80 (95%) received concomitant cyclophosphamide and/or rituximab. The median proportion of children who received PLEX at each hospital with ≥5 cases of AAV was 0.20 (range 0-0.67) (Figure). There was a significant increase in the use of PLEX for new patients over the years of study (p=0.04). In multivariate regression, male sex, cyclophosphamide, rituximab, and dialysis were associated with increased odds of receipt of PLEX.

Conclusion: PLEX use for treatment of AAV in children is increasing over time, however its use varies significantly between hospitals. Use of rituximab, cyclophosphamide, and dialysis are associated with receipt of PLEX, confirming its use is reserved for children with more severe manifestations. Future studies are needed to assess the impact of PLEX on outcomes for children with AAV.

Figure. Use of plasmapheresis for children with AAV at US hospitals



Legend. Proportions of children with AAV at each hospital who received plasmapheresis during their first admission are shown. Only hospitals with at least 5 cases of AAV and who contributed data for at least 10 of the 11 years of the study are included. Size of the circle indicates the case load of patients with AAV seen at that hospital during the study period, each size category representing a tertile of case loads

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Disclosure: K. James, None; **R. Xiao**, None; **P. A. Merkel**, None; **P. F. Weiss**, None.

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Abstract Number: 2416

Pharmacokinetics, Safety, and Tolerability of Tofacitinib in Pediatric Patients from Six to Less Than Eighteen Years of Age with Juvenile Idiopathic Arthritis

Hermine I. Brunner[1], Nicolino Ruperto[2], Nikolay Tzaribachev[3], Zbigniew Zuber[4], Elena Koskova[5], Ivan Foeldvari[6], Eizbieta Smolewska[7], Gerd Horneff[8], Charles Mebus[9], Umberto Conte[10], Rong Wang[9], Christine Alvey[9], Manisha Lamba[9], Anasuya Hazra[11], Daniel Lovell[12] and Alberto Martini[13], [1]Pediatric Rheumatology Collaborative Study Group, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, [2]Istituto G. Gaslini, Pediatria II, PRINTO, Genoa, Italy, [3]Pediatric Rheumatology, Bad Bramstedt, Germany, [4]St Louis Children's Hospital ODS Rheumatology and Neurology, Krakow, Poland, [5]Institute of Rheumatic Diseases, Piestany, Slovakia, [6]Hamburger Zentrum für Kinder-und Jugendrheumatologie, Hamburg, Germany, [7]Department of Pediatric Cardiology and Rheumatology, Medical University of Lodz, Lodz, Poland, [8]Asklepios Klinik Sankt Augustin GmbH, Sankt Augustin, Germany, [9]Pfizer Inc, Groton, CT, [10]Pfizer Inc, New York, NY, [11]Pfizer Inc, Collegeville, PA, [12]Rheumatology, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, [13]Istituto G. Gaslini, Pediatria II, PRINTO, and University of Genoa, Genoa, Italy

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SESSION INFORMATION

Session Title: Pediatric Rheumatology - Clinical and Therapeutic Aspects Posters (ACR): Imaging and Novel Clinical Interventions

Session Type: ACR Poster Session C

Background/Purpose: Tofacitinib is an oral Janus kinase inhibitor for the treatment of adult patients with rheumatoid arthritis (RA). We report the pharmacokinetics (PK), safety and taste acceptability of tofacitinib following multiple oral doses in children 6 to <18 years of age with active juvenile idiopathic arthritis (JIA).

Methods: Data were obtained from an ongoing open-label, non-randomized, multi-center, Phase I study (NCT01513902) where children with JIA were given 5 mg adult equivalent (based on body weight) of tofacitinib (tablet or solution) twice daily (BID) for 5 days. There were 3 cohorts (COH) based on subject age, COH 1: 12 to <18 years, COH 2: 6 to <12 years, and COH 3: 2 to

<6 years, with a target enrollment per group of at least 8 children with JIA for a total number of at least 24 evaluable subjects completing the PK period. Patients were enrolled in a step-wise approach beginning with the older age cohort first. Subsequent younger age cohorts were enrolled following confirmation of safety and PK from the previous cohorts. PK parameters of tofacitinib were calculated using non-compartmental analysis of plasma concentration (conc)-time data.

Results: Results from the first 16 subjects from COH 1 and COH 2 were included in this analysis. Overall, subjects' age ranged from 8 to 17 years; all were white race except for one. There were 5 females and 3 males in COH 1 and in COH 2. Baseline disease characteristics were similar across both COH, except CRP; where the mean value was slightly higher in COH 2 than COH 1 (5.7 versus 3.8 mg/L). All exposure metrics including area under the conc-time curves (AUC_{tau}), maximum (C_{max}), minimum (C_{min}), predose (C_{trough}) conc were lower in COH 2 relative to those in COH 1. Apparent volume of distribution (V_z/F) was approximately 32% lower in COH 2 (71 L) relative to COH 1 (104.9 L). Average terminal half-life ($t_{½}$) was 25.5% shorter in the younger patients (1.949 hours in COH 2, to 2.616 hours in COH 1). Mean CL/F of tofacitinib in children with JIA in this study were 52.7% and 38.4% higher in COH 1 and COH 2 subjects, respectively, compared with adult patients with RA receiving tofacitinib 5 mg BID equivalent (based on allometry) dose of tofacitinib (18.4 L/h). PK parameters were similar between males and females. Tofacitinib, administered over 5 days as multiple dose tablets or solution formulation, was well tolerated and taste was found acceptable in children with active JIA. No serious adverse events or new safety signals were identified.

Conclusion: PK results from this study established dosing regimens for children aged 6 years and older to be used in the upcoming efficacy and safety studies of tofacitinib in patients with JIA. Tofacitinib was well tolerated in this study in children with JIA. Overall, subjects found the taste of the tofacitinib solution formulation to be acceptable.

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View Abstract and Citation Information Online - http://acrabstracts.org/abstract/pharmacokinetics-safety-and-tolerability-of-tofacitinib-in-pediatric-patients-from-six-to-less-than-eighteen-years-of-age-with-juvenile-idiopathic-arthritis

Abstract Number: 2417

Induction and Maintenance of Remission By Etanercept in Enthesitis Related Arthritis JIA-Patients

Gerd Horneff[1], Ivan Foeldvari[2], Kirsten Minden[3], Ralf Trauzeddel[4], J B. Kuemmerle-Deschner[5], Klaus Tenbrock[6], Gerd Ganser[7] and Hans-Iko Huppertz[8], [1]Asklepios Clinic Sankt Augustin, Sankt Augustin, Germany, [2]Hamburger Zentrum für Kinder- und Jugendrheumatologie, Hamburg, Germany, [3]DRFG, Berlin, Germany, [4]HELIOS Klinikum Berlin-Buch Klinik fuer Kinder- und Jugendmedizin, Berlin, Germany, [5]Pediatrics, University Hospital Tuebingen, Tuebingen, Germany, [6]University Aachen, Aachen, Germany, [7]Pediatric Rheumatology, Sankt Josef Stift, Sendenhorst, Germany, [8]PRINTO, IRCCS G. Gaslini, Genoa, Italy
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Session Title: Pediatric Rheumatology - Clinical and Therapeutic Aspects Posters (ACR): Imaging and Novel Clinical

Interventions

Session Type: ACR Poster Session C

Background/Purpose:

Enthesitis-related arthritis (ERA) is a juvenile idiopathic arthritis (JIA) category affecting entheses and joints. The REMINDER study to analyse the efficacy of etanercept (ETA) in active and refractory ERA pts, was used to analyse the stability of remission on and off medication (Horneff et al. Arthritis Rheumatol. 2015 Apr 17).

Methods:

In this 2-part, 48-week, randomised, placebo-controlled, double-blind withdrawal study, first, all pts received open-label ETA for 24 weeks. At week 24, pts with at least a JIA-ACR30 response entered a 24-week randomised (1:1 placebo (PLC) or ETA), double-blind withdrawal period. Remission was defined as JADAS10≤1.0. In addition, absence of tender enthesis (TE), active uveitis and spinal involvement (judged by BASDAI) were analysed.

Results:

41 pts (mean age 13.4 y, disease duration 2.8 y, active joint count 5.3, JADAS10 15.8) received open-label ETA (0.8 mg/kg bw., max.50 mg/week) for 24 weeks. 2 pts discontinued prematurely, one for intolerance and one due to a protocol violation. JIA-ACR30/50/70/90/100 response rates at week 24 were 93%/93%/80%/56% and 54%. Remission (JADAS) was reached by 14.6/35/51.3/59.0% at week 4/12/16/24. Until Week 48, 9 JIA-ACR30 flares occurred on PLC, 3 on ETA (odds ratio 6.0, p = 0.02). Until week 48, 6 of 11 (55%) pts had stable JADAS remission while continuing on ETA and 3 of 12 (25%) on PLC (OR 3.6 [0.6-21, p=0.15). An additional patient randomized to ETA achieved remission at week 28 and stayed in remission until week 48. Two pts of the ETA cohort had a disease reactivation at week 28 and week 32, which did not qualify for an ACR30 flare. They continued on double blind ETA and regained remission thereafter. The mean TE count decreased from 1.8 [range 0-7] to 0.8, 0.4, 0.2 and 0.5 and the rate of pts with no TE increased from 34% to 79/76/84/84% at week 4/8/12/24. 13/17 (76%) pts on ETA with no TE at week 24 remained without TE until week 48. 9 pts (69%) of the PLC cohort continued without a TE from week 24 to 48. The mean BASDAI score decreased from 2.6 (range 0-7.3) to 0.8/0.7/0.5/0.4 and the number of pts with a BASDAI of 0 increased from 7.8% to 31.5/34.2/36.8/50% at week 4/8/16/24. 7/10 pts on ETA with BASDAI of 0 at week 24 remained with a BASDAI of 0 until week 48. All 7 pts randomized to placebo, who had a BASDAI of 0 maintained a BASDAI of 0 until week 48 or until reset on ETA. A single uveitis event was reported in a patient randomized to ETA at week 48.

Conclusion: In this placebo-controlled randomized trial ETA proved to be effective with a high rate of pts reaching JADAS remission. Remission continued off treatment in a quarter of pts only while more pts remain in stable remission who continued treatment with ETA.

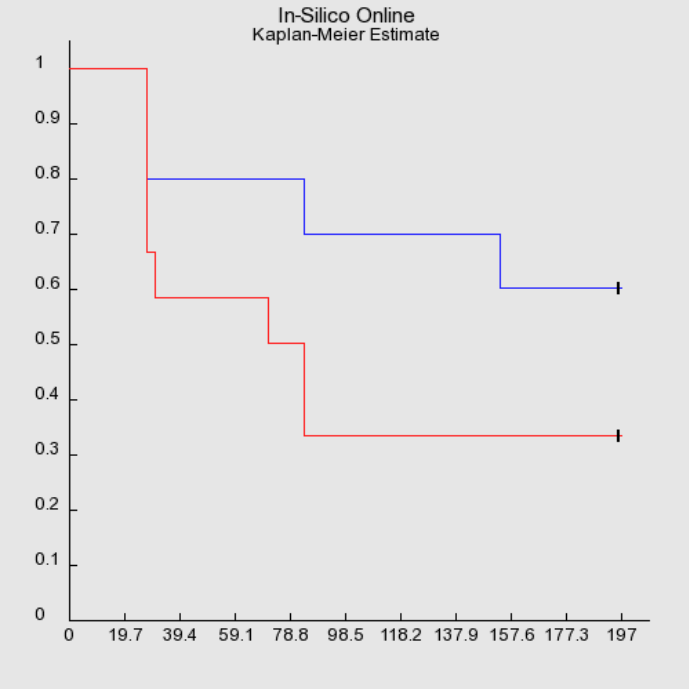

Figure 1 Kaplan Meyer curve showing stability of remission on PLC (red) and ETA (blue). Hazard ratio 2.20 [0.66-7.36], p=0.16

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Abstract Number: 2418

Pediatric Enthesitis-Related Arthritis: Variation in Disease Characteristics and Treatments Among 5 Large Centers

Sabrina Gmuca[1], Timothy Brandon[2], Rui Xiao[3], Ilaria Pagnini[4], Tracey B. Wright[5], Timothy Beukelman[6], Esi Morgan-DeWitt[7] and Pamela F. Weiss[8], [1]Pediatric Rheumatology, The Children's Hospital of Philadelphia, Philadelphia, PA, [2]Pediatrics, Children's Hospital of Philadelphia, Philadelphia, PA, [3]Department of Biostatistics and Epidemiology, University of Pennsylvania, Philadelphia, PA, [4]Department of Paediatrics, University of Florence and Anna Meyer Children's Hospital, Florence, Italy, Florence, Italy, [5]Pediatrics/Rheumatology, Univ of TX Southwestern, Dallas, TX, [6]Rheumatology, University of Alabama at Birmingham, Birmingham, AL, [7]Pediatric rheumatology, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, [8]Rheumatology, Children's Hospital of Philadelphia, Philadelphia, PA

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Session Type: ACR Poster Session C

Background/Purpose: We aimed to compare the clinical features and treatments of children with Enthesitis-related arthritis (ERA) from 5 pediatric rheumatology centers in order to determine whether pediatric ERA manifests differently and/or is treated differently based on geographical location.

Methods: We performed a retrospective multicenter cohort study that included subjects from 5 pediatric rheumatology centers who were diagnosed with ERA from 1989-2012. Baseline visit for patients was defined as the first rheumatology appointment at which the patient had enthesitis, arthritis, or symptomatic uveitis. To be included in the study, patients had to fulfill the ILAR criteria for ERA within the first 6 months from baseline visit. Patient data collected included the following: demographics, clinical features, patient reported outcomes, and medications prescribed at diagnosis and over the following 12 months. Differences across sites were compared using the Kruskal-Wallis or chi-squared test, as appropriate.

Results: 296 children with ERA were included in the study. Patients were predominantly male (69%) and Caucasian (83%). Median age at diagnosis was 12 years (IQR: 10-14) and 53% were HLA-B27 positive. The prevalence of arthritis and uveitis criteria did not differ significantly across sites. The prevalence of the remaining criteria, however, was significantly different across sites (all $p<0.001$): enthesitis (range: 40-88%); sacroiliac tenderness or inflammatory lumbosacral pain (range: 10-55%); HLA-B27 positivity (range: 30-84%); onset of arthritis in a male over 6 years (range: 47-77%); and history of HLA-B27 associated disease in a first-degree relative (range: 8-37%). The table shows medication use stratified by site and clinical features. Overall use of DMARDs and biologics differed significantly among sites ($p<0.001$ and $p<0.001$, respectively). Use of biologics for arthritis (+/- enthesitis) and sacroiliitis (+/- peripheral arthritis or enthesitis) also differed significantly among sites ($p<0.001$ and $p<0.001$, respectively).

Conclusion: Comparison of children with ERA from 5 pediatric rheumatology centers reveals significant variability in the presenting features and initial treatment strategies. The variation in presenting features may reflect either true differences by geographic location or differences between sites in assessment of particular features. Biologic use was significantly different among sites for children with arthritis and sacroiliitis. These differences highlight the need for standardized assessments for ERA as well as comparative effectiveness studies of the different treatment options.

Table. Medications Prescribed Within 3 Months of Initial ERA Clinical Feature

Medication	CLINICAL FEATURES WITHIN 3 MONTHS OF INITIAL PRESENTATION, N (%)				
	All subjects	**Enthesitis, no arthritis**	**Peripheral arthritis +/- enthesitis**	**Sacroiliitis^ +/- enthesitis or peripheral arthritis**	**Uveitis only**
ALL SITES	**296**	**18**	**235**	**40**	**3**
No DMARD, no biologic†	134 (45)	17 (94)	110 (47)	6 (15)	1 (33)
DMARD	77 (26)	1 (6)	62(26)	14 (35)	0 (0)
Biologic+/- DMARD	85 (29)	0 (0)	63 (27)	20 (50)	2 (67)
SITE 1	**118**	**14**	**88**	**14**	**2**
No DMARD, no biologic†	56 (47)	13 (93)	39 (44)	3 (22)	1 (50)
DMARD	22 (19)	1 (7)	19 (22)	2 (14)	0 (0)
Biologic+/- DMARD	40 (34)	0 (0)	30 (34)	9 (64)	1 (50)
SITE 2	**37**	**0**	**34**	**3**	**0**
No DMARD, no biologic†	3 (8)	0 (0)	3 (9)	0 (0)	0 (0)
DMARD	9 (24)	0 (0)	9 (26)	0 (0)	0 (0)
Biologic+/- DMARD	25 (68)	0 (0)	22 (65)	3 (100)	0 (0)
SITE 3	**20**	**1**	**10**	**8**	**1**
No DMARD, no biologic†	5 (25)	1 (100)	3 (30)	1 (12)	0 (0)
DMARD	1 (5)	0 (0)	1 (10)	0 (0)	0 (0)
Biologic+/- DMARD	14 (70)	0 (0)	6 (60)	7 (88)	1 (100)
SITE 4	**70**	**2**	**68**	**0**	**0**
No DMARD, no biologic†	47 (67)	2 (100)	45 (66)	0 (0)	0 (0)
DMARD	18 (26)	0 (0)	18 (26)	0 (0)	0 (0)
Biologic+/- DMARD	5 (7)	0 (0)	5 (7)	0 (0)	0 (0)
SITE 5	**51**	**1**	**35**	**15**	**0**
No DMARD, no biologic†	23 (45)	1 (100)	20 (57)	2 (13)	0 (0)
DMARD	27 (53)	0 (0)	15 (43)	12 (80)	0 (0)
Biologic+/- DMARD	1 (2)	0 (0)	0 (0)	1 (7)	0 (0)

Legend. *Differences across sites were compared using the Kruskal-Wallis or chi-squared test, as appropriate. ^Sacroiliitis by imaging. †No DMARD, no biologic category includes patients treated with non-steroidal anti-inflammatories and/or intra-articular injection(s). DMARD: disease modifying anti-rheumatic drug.

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Abstract Number: 2419

Safety and Efficacy of Etanercept in 2000 Patients with Juvenile Idiopathic Arthritis (JIA) in the JIA Biologics Register

Gerd Horneff[1], Juergen Brunner[2], Johannes Peter Haas[3], Gerd Ganser[4], Ivan Foeldvari[5], Toni Hospach[6], Kirsten Minden[7], Hans-Iko Huppertz[8], Rolf M. Kuester[9], Ralf Trauzeddel[10], Angelika Thon[11] and BIKER Study Group, [1]Asklepios Clinic Sankt Augustin, Sankt Augustin, Germany, [2]Universitätsklinik für Kinder- u. Jugendheilkunde, Innsbruck, Austria, [3]German Centre for Rheumatology in Children and Young People, Garmisch-Partenkirchen, Germany, [4]Pediatric Rheumatology, Sankt Josef Stift, Sendenhorst, Germany, [5]Hamburger Zentrum für Kinder-und Jugendrheumatologie, Hamburg, Germany, [6]Pediatrics, Olgahospital, Klinikum Stuttgart, Stuttgard, Germany, [7]DRFG, Berlin, Germany, [8]PRINTO, IRCCS G. Gaslini, Genoa, Italy, [9]Asklepios Rheumazentrum Hamburg, Hamburg, Germany, [10]HELIOS Klinikum Berlin-Buch Klinik fuer Kinder- und Jugendmedizin, Berlin, Germany, [11]Department of Pediatrics, Hannover, Germany

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SESSION INFORMATION

Session Title: Pediatric Rheumatology - Clinical and Therapeutic Aspects Posters (ACR): Imaging and Novel Clinical Interventions

Session Type: ACR Poster Session C

Background/Purpose: Treatment with Etanercept (ETA) was followed prospectively. The purpose of this interim analysis is to evaluate efficacy/ safety of ETA in routine care settings.

Methods: Documentation of pts characteristics, previous/concomitant therapy, disease activity and adverse events. The efficacy was assessed by PedACR criteria and JADAS10 (remission and minimal disease activity, MDA). A control cohort not treated with biologics was established.

Results:

Until 31.12.2014, 2000 JIA pts (67.2% fem.) started ETA. The mean/median age at baseline was 9.4/8.2, disease duration 4.5/3.3 years. The RF-Polyarthritis was the most frequent JIA category (633pts), followed by extended Oligo (396), ERA (330), RF+Poly (171), PsA (149), systemic JIA (143), persistent Oligo (111) and unclass. JIA (67). Pretreatments were performed with steroids 55.5%, methotrexate 88.2%, sulfasalazine 16.6%, azathioprine 11.6%, antimalarials 10.4, and other DMARDs (n=379) as well as 62 therapies with other biologicals (n=35 adalimumab). The initial concomitant treatment was carried out using NSAIDs 81.1%, steroids 40.9%, methotrexate 70.4% and other DMARDs (n=313). A JIA-ACR30/50/70/90 response was reached by 81%/75%/61%/40% after 12 months. A JADAS remission (JADAS10≤1) at month 12/24/36/48/60 was reached by 28%/33%/33%/26%/33% and a JADAS-MDA by 49%/51%/46%/42%/45%. Response rates according to the JIA categories are given in the table.

1225 adverse events were reported (29.1/100 PY), 158 (3.8/100 PY) were serious. Infections were the most frequent AE (350), 29 were SAE. Opportunistic infections including TB did not occur. Rates of adverse events of special interest are shown in table 2. In 1055 patients (53%) the therapy was discontinued. Reasons reported were (>1 possible) remission 409 (20%), ineffectiveness 391 (17%), patient request 342 (17%), intolerance, 124 (6%) and 174 (9%) other. 5 patients died, none during or in connection with the treatment with ETA.

Conclusion: JIA patients achieved high ACR response rates upon treatment with ETA, a JADAS-MDA was frequently reached as well. A JADAS remission was achieved only in part. Overall tolerability was good. Only a small portion discontinued therapy because of intolerance or side effects.

Table 1: Treatment response of pts reaching month 12

	sJIA	RF-PA	RF+PA	Pers.OA	Ext.OA	ERA	PsA	Unclass JIA
	n=81	n=397	n=116	n=63	n=242	n=201	n=91	n=39
JIA-ACR 30	67.9%	84.1%	74.1%	77.8%	86.4%	81.1%	76.9%	87.2%
JIA-ACR 50	59.3%	75.8%	70.7%	68.3%	80.6%	77.1%	70.3%	87.2%
JIA-ACR 70	50.6%	59.7%	57.8%	55.6%	64.9%	66.2%	54.9%	76.9%
JIA-ACR 90	30.9%	39.5%	37.1%	36.5%	40.9%	48.8%	36.3%	51.3%
JADAS10 Start Mean/Median	18.1/20	17.5/17	19.1/18	10.8/10	12.9/12	12.1/11	11.8/11	13.9/13.5
JADAS10 (Mean/Median)	8.9/3.8	5.4/3.5	5.8/3.3	3.1/1.1	3.7/2.0	3.7/.4	4.0/2.3	3.9/1.6
JADAS MDA	50.0%	51.9%	52.1%	63.3	71.7%	65.1%	60.5%	67.6%
JADAS Remission	27.3%	30.9%	28.7%	46.9	38.5%	43.8%	34.2%	38.2%

Table 2: Rate of adverse events of special interest

	ETA (4199 PY)	MTX (3099 PY)	RR (95%CI)	P (Wald-test)
SAE, n/rate/100PY	158/3.79	47/1.52	2.48(1.79-3.43)	<0.0001
SAE-Infection n/rate/100PY	29/0.69	10/0.32	2.14(1.04-4.39)	0.038
Herpes zoster n/rate/100PY	17/0.40	6/0.19	2.09(0.82-5.30)	0..12
Uveitis n/rate/100PY	79/1.88	49/1.58	1.19(0.83-1.70)	0..33
CED n/rate/100PY	12/0.29	3/0.10	2.95(0.83-10.5)	0..094
Malignancy n/rate/100PY	7/0.17	3/0.10	1.72(0.44-6.66)	0.43

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Abstract Number: 2420

Azathioprine for Glucocorticoid Resistant Non-Renal Henoch-Schönlein Purpura

Paul Tuttle IV[1], Peri Pepmueller[2] and Terry Moore[3], [1]IM-Rheumatology, Saint Louis University, St. Louis, MO, [2]Rheumatology, Saint Louis University, St. Louis, MO, [3]Division of Rheumatology and Pediatric Rheumatology, Saint Louis University School of Medicine, St Louis, MO

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Background/Purpose:

Henoch-Schönlein purpura is the most common small vessel vasculitis in childhood and has a classic presentation of palpable purpura. The disease is typically benign and self limited although some patients have gastrointestinal or renal complications requiring more aggressive therapy. Rarely, a subset of patients have persistent or recurrent musculoskeletal, gastrointestinal, and/or cutaneous symptoms without renal involvement despite use of supportive therapy, nonsteroidal anti-inflammatories, and glucocorticoids. There is a paucity of literature regarding therapy of such patients. Some patients respond well to further immunosuppression. We report a case series of three such patients.

Methods:

A retrospective chart review of patients with a diagnosis of Henoch-Schönlein purpura followed in the pediatric rheumatology clinic at Saint Louis University from 1997-2014. All patients met classification criteria for Henoch-Schönlein Purpura with the course of disease, treatment regime, and number of relapses were recorded. Patients referred to rheumatology in our institution generally had musculoskeletal, cutaneous manifestations, and /or mild gastrointestinal or renal involvement. Patients with renal or severe gastrointestinal disease are traditionally followed by those specialists.

Results:

From 1997-2014, 204 patients were seen at Cardinal Glennon Children's Medical Center in all clinics with a diagnosis of Henoch-Schönlein purpura. Twenty four patients meeting classification criteria were referred to the pediatric rheumatology clinic with musculoskeletal, gastrointestinal, and/or cutaneous manifestations. Of those 24 patients, 18 had non-renal disease and 6 had coexisting renal disease. Of those patients with non-renal disease, 15 had resolution of disease with supportive therapy, nonsteroidal anti-inflammatories, and/or one course of corticosteroids. Three patients with non-renal disease failed to control their disease with supportive measures, nonsteroidal anti-inflammatories, and/or glucocorticoids, even after 6-14 months with repeat courses of glucocorticoids at 0.5-1.0 mg/kg/day. These patients were started on azathioprine for 12-19 months which allowed successful prednisone tapering and amelioration of symptoms. Two of the three patients had cutaneous and gastrointestinal symptoms without musculoskeletal disease with remission preserved off all medications with the use of azathioprine at 1 mg/kg/day and 1.4 mg/kg/day. The third patient with cutaneous, musculoskeletal, and gastrointestinal disease was successfully tapered off his prednisone and is currently in remission on azathioprine alone at 2 mg/kg/day over the last 12 months.

Conclusion:

Azathioprine can be used successfully to treat glucocorticoid resistant non-renal Henoch-Schönlein purpura. To our knowledge this is the first published report documenting this therapy.

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Abstract Number: 2421

Experience with Adalimumab for Treatment of 568 Juvenile Idiopathic Arthritis Patients in the German JIA Biologics Register

Gerd Horneff[1], Gerd Ganser[2], Ivan Foeldvari[3], Johannes Peter Haas[4], Toni Hospach[5], Ralf Trauzeddel[6], Frank Weller-Heinemann[7], J B. Kuemmerle-Deschner[8], Angelika Thon[9] and BIKER study group, [1]Asklepios Clinic Sankt Augustin, Sankt Augustin, Germany, [2]Pediatric Rheumatology, Sankt Josef Stift, Sendenhorst, Germany, [3]Rheumatology, Scleroderma, Hamburg, Germany, [4]German Centre for Rheumatology in Children and Young People, Garmisch-Partenkirchen, Germany, [5]Pediatrics, Olgahospital, Klinikum Stuttgart, Stuttgard, Germany, [6]HELIOS Klinikum Berlin-Buch Klinik fuer Kinder- und Jugendmedizin, Berlin, Germany, [7]PRINTO, Genoa, Italy, [8]Pediatrics, University Hospital Tuebingen, Tuebingen, Germany, [9]Kinderklinik der Medizinischen Hochschule Hannover, Hannover, Germany

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Background/Purpose: Adalimumab (ADA) has become a valuable option for treatment of juvenile idiopathic arthritis (JIA), which significantly improves the outcome of patients. The aim of the German BIKER registry is surveillance of biologics. The purpose of this interim analysis is to evaluate the efficacy and safety under practical conditions.

Methods: Treatment with ADA was followed prospectively by documentation of pts' characteristics, pervious/concomitant therapy, disease activity parameters and adverse events. The efficacy was assessed by PedACR criteria and JADAS10. A control cohort not treated with biologics was established in parallel.

Results: 568 JIA pts (67.2% fem.) started ADA. The mean/median age at baseline was 12.6/13.3, disease duration 5.8/4.9 years. The RF-Polyarthritis was the most frequent JIA category (200pts), followed by extended Oligo (143), ERA (74), persistent Oligo (47), RF+Poly (45), PsA (35), systemic JIA (15), and unclass. JIA (9). Pretreatments were performed with steroids 59.3%, methotrexate 91%, sulfasalazine 12.1%, azathioprine 9.9%, leflonomide (7.2%), antimalarials 5.6%, and other DMARDs (n=47) as well as 347 therapies with other biologicals (313 with Etanercept). The initial concomitant treatment was carried out using NSAIDs 57.7%, steroids 31.3%, methotrexate 59.0% and other DMARDs (n=69). A JIAACR30/50/70/90 response was reached by 69%/66%/51%/35% after 12 months. A JADAS remission (JADAS10≤1) at month 3/6/12/18/24 was reached by 29%/34%/29%/37%</36% and a JADAS-MDA by 53%/59%/54%/56%/59%. Response rates according to the JIA categories are given in table 1.

416 adverse events were reported (57.2/100 PY), 32 (4.4/100 PY) were serious. Infections were the most frequent AE (n=133), 6 were SAE. Opportunistic infections including TB did not occur. 142 patients had had a history of uveitis before baseline. There were 30 uveitis flares. A single patient had a first uveitis upon ADA. Rates of adverse events of special interest are shown in table 2. In 168 patients (29.6%) the therapy was discontinued. Reasons reported were (several same time) remission 39 (6.9%), inefficacy 99 (17.4%), patient request 77 (13.6%), intolerance 34 (5.9%) and 21 (3.7%) other. No patients died.

Conclusion: JIA patients achieved high ACR response rates upon treatment with ADA, a JADAS-MDA was frequently reached as well. A JADAS remission was achieved only in part. Overall tolerability was good. Only a small portion discontinues therapy because of intolerance or side effects.

Table 1: JADAS10 at baseline and treatment response at month 12

	sJIA	RF-PA	RF+PA	Pers.OA	Ext.OA	ERA	PsA
JADAS baseline Mean/Median	8.2/5.0	12.7/12.8	15.4/14.6	6.7/4.4	10.4/10.4	10.4/9.7	10.9/9.4
JADAS M12 (Mean/Median)	2.1/0.4	5.1/2.9	7.8/6.5	2.7/1.9	5.6/3.0	3.8/2.5	5.4/4.4
JADAS MDA M12	80%	57.1%	10%	72.2%	54.5%	59.3%	40%
JADAS Remission M12	60%	32.4%	10%	38.9%	30.9%	33.3%	10%
JIA-ACR 30 M12	100%	69.3%	75.0%	45.5%	73.8%	64.5%	81.8%
JIA-ACR 50 M12	100%	65.9%	75.0%	45.5%	66.2%	61.3%	81.8%
JIA-ACR 70 M12	80%	54.5%	58.3%	18.2%	50.8%	51.6%	72.7%
JIA-ACR 90 M12	60%	37.5%	25.0%	13.6%	29.2%	51.6%	36.4%

Table 2: Incidence of adverse events of special interest

	ADA (723 PY)	MTX (3099 PY)	RR (95%CI)	P (Wald-test)
SAE, n/rate/100PY	32/4.43	47/1.52	2.92(1.86-4.57)	<0.0001
SAE-Infection; n/rate/100PY	18/2.49	10/0.32	7.72(3.56-16.7)	<0.0001
Herpes zoster; n/rate/100PY	3/0.41	6/0.19	2.14(0.54-8.57)	0.28
Uveitis; n/rate/100PY	30/4.15	49/1.58	2.62(1.67-4.13)	<0.0001
Psoriasis; n/rate/100PY	6/0.83	0/0.0	¥	<0.0001
Malignancy; n/rate/100PY	2/0.28	3/0.10	2.86(0.48-17.1)	0.25

Disclosure: G. Horneff, None; **G. Ganser**, None; **I. Foeldvari**, None; **J. P. Haas**, None; **T. Hospach**, None; **R. Trauzeddel**, None; **F. Weller-Heinemann**, None; **J. B. Kuemmerle-Deschner**, None; **A. Thon**, None.

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Abstract Number: 2422

Efficacy and Safety of Canakinumab in Children with Systemic Juvenile Idiopathic Arthritis: Results from the Phase 3 Extension Study

Hermine I. Brunner[1], Nicolino Ruperto[2], Pierre Quartier[3], Tamas Constantin[2], Ekaterina Alexeeva[2], Isabelle Koné-Paut[2], Katherine Marzan[1], Nico Wulffraat[2], Rayfel Schneider[1], Shai Padeh[2], Vyacheslav Chasnyk[2], Carine Wouters[2], Jasmin B. Kuemmerle-Deschner[2], Tilmann Kallinich[2], Bernard Lauwerys[4], Elie Haddad[1], Evgeny Nasonov[2], Maria Trachana[2], Olga Vougiouka[2], Karolynn Leon[5], Antonio Speziale[6], Karine Lheritier[6], Alberto Martini[2], Daniel Lovell[1,7] and on behalf of PRINTO/PRCSG, [1]PRCSG, Cincinnati, OH, [2]PRINTO-Istituto Gaslini, Genova, Italy, [3]Necker-Enfants Malades Hospital, Paris, France, [4]Cliniques Universitaires Saint-Luc and Université Catholique de Louvain, Brussels, Belgium, [5]Novartis Pharmaceuticals Corporation, East Hanover, NJ, [6]Novartis Pharma AG, Basel, Switzerland, [7]Rheumatology, Cincinnati Children's Hospital Medical Center, Cincinnati, OH

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Background/Purpose: Systemic juvenile idiopathic arthritis (SJIA) is a debilitating form of arthritis associated with systemic symptoms such as anemia, rash, leukocytosis, elevated erythrocyte sedimentation rate and acute-phase reactants. High and spiking fevers are also features of the disease. Canakinumab (CAN) leads to improvement for patients (pts) with SJIA exhibiting articular and systemic features at treatment onset.[1] However, little is known about the long-term safety and efficacy in CAN-naïve pts, including those who may not exhibit systemic fever. Here we present the long-term efficacy and safety profile of CAN in SJIA pts with and without fever at CAN initiation.

Methods: Pts aged 2-20 years with SJIA with and without SJIA associated fever at enrollment received open-label CAN 4mg/kg s.c. every 4 weeks. Efficacy was assessed every 3 months by adapted JIA ACR response criteria (aACR/JIA); juvenile arthritis disease activity score [JADAS]; clinical inactive disease; clinical remission on medication [CRM, 6 months continuous clinical inactive disease]. Safety was assessed monthly.

Results: Of 123 pts, 70 (57%) with and 52 (42%) without SJIA associated fever, were available for analysis with a median study duration of 96 weeks. At Week 4, 73% and 81% of pts with and without fever at study entry, respectively had ≥ aACR/JIA30,

increasing to 89% and 92% at Wk12. At Week 2, 23.9% and 24.5% of pts with and without fever at study entry, respectively, had inactive disease which increased to 61.5% and 59.5%, respectively, at Week 32 and thereafter. CRM was achieved in 42.3% of pts in the overall group with 26.8% maintaining it for 12 consecutive months. Median JADAS27-CRP and JADAS10-CRP scores were 6.0 (suggesting moderate disease activity) at Day 15 and 1.5 (indicating low disease activity) at the last assessment, respectively. The disease activity status at baseline and end of study for JADAS10-CRP and JADAS27-CRP are presented in Table. Adverse events (AEs) were reported in 63 (90%) and 45 (86.5%) pts with and without fever, respectively. Serious AEs were reported in 24 (34.3%) and 16 (30.8%) pts with and without fever, respectively. Overall, 8 events of MAS (pts with fever, n=6; pts without fever, n=2) were reported in both the groups. No deaths were reported during the study. No new safety signals were observed in the subgroup.

Table . Disease activity states based on JADAS27-CRP and JADAS10-CRP

	Disease state, %	SJIA patients, N=123			
		Fever at baseline			
		Yes (n=70)		No (n=52)	
		Baseline n=68	Last assessment n=70	Baseline n=52	Last assessment n=51
JADAS10-CRP	ID	0	50	0	47.1
	LDA	0	12.9	0	9.8
	MDA	10.3	5.7	9.6	19.6
	HDA	89.7	31.4	90.4	23.5
JADAS27-CRP	ID	0	50	0	47.1
	LDA	0	12.9	0	9.8
	MDA	8.8	2.9	7.7	15.7
	HDA	91.2	34.3	92.3	27.5
Cut-off values for inactive disease (ID), low disease activity (LDA) , moderate disease activity (MDA), and high disease activity (HDA), respectively for JADAS10: ≤1, >1– ≤3.8, >3.8 – ≤10.5, and >10.5; and JADAS27: ≤1, >1 – ≤ 3.8, >3.8 – ≤8.5, and >8.5					

Conclusion: Canakinumab provides similar long-term efficacy in SJIA pts, irrespective of presence of systemic fever at treatment onset. The safety profile was acceptable and similar to the pivotal program in SJIA pts with fever at enrollment.

Reference: 1. Ruperto et al. *N Engl J Med*. 2012; 367: 2396-406.

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Abstract Number: 2423

An Open-Label Extension Study to Assess the Long-Term Safety and Clinical Benefit of Etanercept on Children and Adolescents with Extended Oligoarticular Juvenile Idiopathic Arthritis, Enthesitis-Related Arthritis, or Psoriatic Arthritis: A 4-Year Update

Nicolino Ruperto[1], Tamas Constantin[2], Ivan Foeldvari[3], Jelena Vojinovic[4], Gerd Horneff[5], Rubén Burgos-Vargas[6], Irina Nikishina[7], Jonathan Akikusa[8], Tadej Avcin[9], Jeffrey Chaitow[10], Elena Koskova[11], Bernard R. Lauwerys[12], Inmaculada Calvo-Penedes[13], Berit Flato[14], Maria Luz Gamir Gamir[15], Hans-Iko Huppertz[16], Juan Jose Jaller Raad[17], Katerina Jarosova[18], Jordi Anton[19], Marie Macku[20], William Jose Otero Escalante[21], Lidia Rutkowska-Sak[22], Ralf Trauzeddel[23], Carine Wouters[24], Ronald Pedersen[25], Sameer Kotak[26], Jack F Bukowski[27], Tina Hinnershitz[28], Bonnie Vlahos[29] and Alberto Martini[30], [1]Pediatria II, PRINTO, Istituto G. Gaslini, Universita' di Genova, Genova, Italy, [2]Semmelweis University, Budapest, Hungary, [3]Hamburg Centre for Child and Adolescent Rheumatology, Hamburg, Germany, [4]Faculty of Medicine, University of Nis, Nis, Serbia, [5]Asklepios Clinic Sankt Augustin, Sankt Augustin, Germany, [6]Rheumatology, Hospital General de Mexico, Mexico city, Mexico, [7]V.A. Nasonova Research Institute of Rheumatology, Moscow, Russia, [8]Rheumatology, Royal Children's Hospital, Melbourne, Australia, [9]Allergology, Rheumatology and Clinical Immunology, University Medical Center Ljubljana, Ljubljana, Slovenia, [10]The Sydney Children's Hospital Network, Sydney, Australia, [11]National Institute of Rheumatic Diseases, Piestany, Slovakia, [12]Cliniques Universitaires Saint-Luc, Brussels, Belgium, [13]Hospital Universitario y Piltecnico La Fe, Valencia, Spain, [14]Oslo University Hospital, Oslo, Norway, [15]Rheumatology, Hospital Ramon y Cajal Unidad de Reumatologia Pediatrica, Madrid, Spain, [16]Klinikum Bremen-Mitte, Prof.-Hess-Kinderklinik, Bremen, Germany, [17]Centro de Reumatologia y Ortopedia, Barranquilla, Colombia, [18]Revmatologicky ustav, Prague, Czech Republic, [19]Unitat de Reumatologia Pediàtrica, Hospital Sant Joan de Déu, Barcelona, Spain, [20]1, Facutly Children's Hospital Brno, Brno, Czech Republic, [21]Servimed S.A.S, Santander, Colombia, [22]Instytut Reumatologii, Klinika i Poliklinika Reumatologii Wieku Rozwojowego, Warszawa, Poland, [23]HELIOS Klinikum Berlin-Buch Klinik fuer Kinder- und Jugendmedizin, Berlin, Germany, [24]UZ Leuven, Leuven, Belgium, [25]Department of Biostatistics, Pfizer, Collegeville, PA, [26]Global Health and Value, Pfizer, New York, NY, [27]Pfizer, Collegeville, PA, [28]Specialty Care MDG, Pfizer, Collegeville, PA, [29]GIPB - Clinical Sciences, Pfizer, Collegeville, PA, [30]Istituto G. Gaslini, Universita' di Genova, Genova, Italy

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SESSION INFORMATION

Session Title: Pediatric Rheumatology - Clinical and Therapeutic Aspects Posters (ACR): Imaging and Novel Clinical Interventions

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Background/Purpose:

A Phase 3b, open-label, multicenter study (CLIPPER; NCT00962741) demonstrated the efficacy of etanercept (ETN) in subjects with the extended oligoarticular (eo), enthesitis-related (ERA), and psoriatic (PsA) subtypes of juvenile idiopathic arthritis (JIA). The objective of the extension study (CLIPPER2; NCT01421069) was to assess the safety and clinical benefit of ETN in pediatric subjects with these JIA subtypes in the long term (8 years).

Methods:

127 subjects with eoJIA (2–17 yrs), ERA (12–17 yrs), or PsA (12–17 yrs) who had ≥1 dose of ETN (0.8 mg/kg QW [max. 50 mg]) and who participated for ~24 months in CLIPPER were eligible for CLIPPER2. Efficacy endpoints included the proportions of subjects achieving JIA ACR 30/50/70/90/100 and Wallace/JADAS inactive disease responses and standard measures of disease activity. Safety, including malignancy and other treatment-emergent adverse events (TEAEs) and serious TEAEs, was assessed from baseline of CLIPPER to month 48.

Results:

109/127 (86%) subjects (eoJIA n=55, ERA n=31, PsA n=23) entered CLIPPER2. Improvements from baseline in disease activity (table 1) and proportions of subjects achieving JIA ACR 30/50/70/90/100 and inactive disease responses (figure) at months 24 were largely maintained at months 48. Safety results are summarized in table 2. All 23 serious TEAEs occurred at a rate of ≤2 events each. Most frequently reported TEAEs were (number of events [N], events per patient yr [EPPY]): headache (27, 0.061), arthralgia (15, 0.034), pyrexia (14, 0.032), diarrhea (12, 0.027), and leukopenia (10, 0.023). Most commonly reported treatment-emergent (TE) infections were (N, EPPY): upper respiratory tract infection (115, 0.260), pharyngitis (73, 0.165), gastroenteritis (29, 0.066), and bronchitis (24, 0.054). TEAEs and TE infections were less frequent in months 36–48 (N, (EPPY)): 48 (0.596), 54 (0.670) than in months 0–12: 193 (1.738), 248 (2.233). One case of malignancy (Hodgkin's disease) was reported in an eoJIA subject who was treated with ETN for 27 months and methotrexate ~8 years prior to onset. No cases of active tuberculosis, demyelinating disorders, or deaths were reported.

Conclusion:

Open-label ETN treatment up to 48 months was well-tolerated and effective in treating subjects with JIA subtypes. AEs were fewer in months 36–48 versus months 0–12.

Table 1. Disease Characteristics for all JIA Subtypes.

Measure	CLIPPER			CLIPPER2		
	Mean (95% CI)					
	Baseline (n = 127)*	Month 3 (n = 123)*	Month 24 (n = 109)*	Month 36 (n = 87)*	Month 42 (n = 73)*	Month 48 (n = 64)*
PtGA	4.96 (4.6, 5.4)	2.21 (1.9, 2.5)	0.97 (0.7, 1.2)	1.16 (0.8, 1.5) n = 85	1.10 (0.7, 1.5) n = 69	1.32 (0.9, 1.8)
PGA	5.02 (4.7, 5.3)	1.50 (1.3, 1.7)	0.62 (0.5, 0.8) n = 108	0.67 (0.5, 0.9)	0.70 (0.4, 1.0)	0.67 (0.5, 0.9) n = 63
CHAQ	0.80 (0.7, 0.9)	0.32 (0.3, 0.4)	0.16 (0.1, 0.2)	0.16 (0.1, 0.2) n = 62	0.17 (0.1, 0.3) n = 46	0.14 (0.0, 0.2) n = 37
HAQ†	N/A	N/A	N/A	0.18 (0.0, 0.3) n = 24	0.21 (0.1, 0.4) n = 28	0.14 (0.0, 0.3) n = 27
CRP, mg/L	8.26 (5.7, 10.8)	2.47 (1.2, 3.8) n = 120	2.76 (1.7, 3.8) n = 103	2.97 (1.4, 4.5) n = 82	3.06 (0.9, 5.2) n = 69	2.88 (1.6, 4.1) n = 63
JADAS	17.21 (15.9, 18.5) n = 118	5.50 (4.7, 6.4) n = 120	2.28 (1.7, 2.9) n = 102	2.74 (1.8, 3.7) n = 64	2.53 (1.4, 3.7) n = 59	2.48 (1.8, 3.1) n = 61
No. active joints	6.74 (5.9, 7.6)	1.72 (1.3, 2.2)	0.61 (0.2, 1.0)	0.59 (-0.1, 1.3) n = 69	0.74 (0.1, 1.4) n = 68	0.49 (0.3, 0.7) n = 63
No. active joints (LOM)	5.72 (5.0, 6.5)	1.62 (1.2, 2.0)	1.06 (0.5, 1.6)	0.74 (0.1, 1.4) n = 69	1.16 (0.5, 1.9) n = 68	1.02 (0.6, 1.4) n = 63

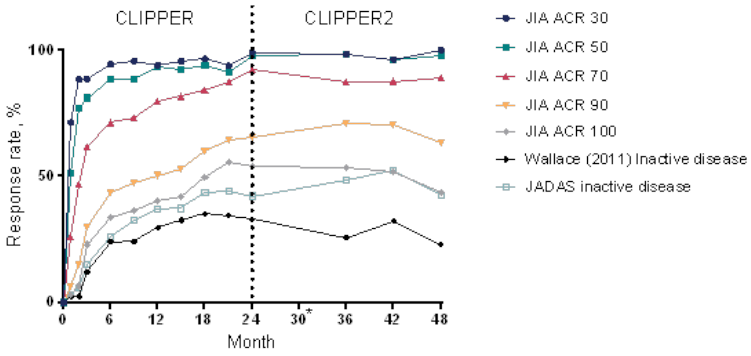
Note: Month 30 data were excluded due to the number of missing data at this time point.

*Number of patients are indicated when different to the column header.

†No subjects were assessed with HAQ in CLIPPER

PtGA, patient/parent global assessment; PGA, physician's global assessment; CHAQ, Childhood Health Assessment Questionnaire (for subjects <18 years); HAQ Health Assessment Questionnaire (for subjects ≥18 years); CRP, C-reactive protein; JADAS, Juvenile Arthritis Disease Activity Score; LOM, limitation of motion.

Figure. JIA ACR Response Rates Over Time in All JIA Subjects (Observed Cases)



*Month 30 data were excluded due to the number of missing data at this time point.
JIA, juvenile idiopathic arthritis; ACR, American College of Rheumatology; JADAS, Juvenile Arthritis Disease Activity Score.
Wallace (2011) inactive disease was defined as no joints with active arthritis; no fever, rash, serositis, splenomegaly or generalized lymphadenopathy attributable to JIA; C-reactive protein level within normal limits; a Physician Global Assessment of disease activity score of 0 on a 21-circle visual analog scale; duration of morning stiffness of ≤15 min; and no active uveitis over time.
JADAS inactive disease was defined as JADAS ≤1.

Table 2. Safety Summary up to 48 Months (CLIPPER/CLIPPER2).				
	eoJIA n = 60 EXP = 211.860 N (EPPY)*	ERA n = 38 EXP = 135.313 N (EPPY)*	PsA n = 29 EXP = 95.321 N (EPPY)*	Total n = 127 EXP = 442.494 N (EPPY)*
TEAEs†	197(0.930)	138 (1.020)	70 (0.734)	405 (0.915)
TE infections	304 (1.435)	83 (0.613)	96 (1.007)	483 (1.092)
TE ISRs	23 (0.109)	29 (0.214)	12 (0.126)	64 (0.145)
TEAEs causing withdrawal† n (%)	1 (0.005)	7 (0.052)	0	8 (0.018)
TE infections causing withdrawal, n (%)	2 (0.009)	0	1 (0.010)	3 (0.007)
Serious TEAEs†	4 (0.019)	15 (0.111)	4 (0.042)	23 (0.052)
Serious TE infections	5 (0.024)	4 (0.030)	3 (0.031)	12 (0.027)
Opportunistic infections‡	0	1 (0.007)	1 (0.010)	2 (0.005)
Infections considered preventable by vaccination in subjects not previously vaccinated	7 (0.033)	1 (0.007)	1 (0.010)	9(0.020)
Infections considered preventable by vaccination in subjects previously vaccinated	1 (0.005)µ	0	0	1 (0.002)
TE autoimmune disorders#	1 (0.005)	3 (0.022)	1 (0.010)	5 (0.011)

*All values are reported as number of events (N) per patient-year (EPPY) of exposure (EXP) to ETN, unless otherwise stated.

Year 1: Up to month 12 in CLIPPER; Year 2: from month 12 to month 24 in CLIPPER or baseline in CLIPPER2; Year 3 onwards: calendar years.

†Excluding infections and injection site reactions (ISRs).

‡Two cases of herpes zoster affecting two dermatomes (ERA) and one dermatome (PsA) were considered to be opportunistic infections and one case of latent tuberculosis (purified protein derivative conversion) was not considered to be an opportunistic infection.

µOne case of rubella.

#Two cases of uveitis, two cases of iridocyclitis, and one case of Crohn's disease were TE and one case of Crohn's disease was not.

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Abstract Number: 2424

Macrophage Activation Syndrome in Systemic Juvenile Idiopathic Arthritis Patients Treated with Canakinumab: Results from Phase 3 Trial Program

Alexei A. Grom[1], Hermine I. Brunner[1], Nicolino Ruperto[2], Alberto Martini[2], Daniel Lovell[1,3], Virginia Pascual[4], Karine Lheritier[5], Karolynn Leon[6], Ken Abrams[6] and Norman Ilowite[7], [1]PRCSG, Cincinnati, OH, [2]PRINTO-Istituto Gaslini, Genova, Italy, [3]Rheumatology, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, [4]Baylor Institute for Immunology Research, Dallas, TX, [5]Novartis Pharma AG, Basel, Switzerland, [6]Novartis Pharmaceuticals Corporation, East Hanover, NJ, [7]Pediatrics, Albert Einstein College of Medicine, Bronx, NY

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SESSION INFORMATION

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Session Type: ACR Poster Session C

Background/Purpose: Macrophage activation syndrome (MAS), a potentially fatal complication of systemic juvenile idiopathic arthritis (SJIA), was reported as an adverse event in both canakinumab and placebo group patients in Phase III trials.[1] This prompted the formation of an independent expert MAS Adjudication Committee (MASAC), to develop a methodology to identify and adjudicate potential MAS events. Here, we report frequency of MAS as adjudicated by the MASAC, in canakinumab-naïve SJIA patients[2] from the Phase III, trial program.

Methods: Potential MAS events were identified by periodic searches of the canakinumab SJIA clinical study safety and lab databases for MASAC-specified screening AE terms and lab criteria. MAS events were then adjudicated blinded to treatment by the MASAC as either probable, possible, or unlikely MAS, or insufficient information loosely based on the diagnostic criteria by Ravelli et al.[3]

Results: MASAC identified 72 potential cases for adjudication. Twenty one events in 19 patients were adjudicated as Probable MAS and 10 events in 9 patients as Possible MAS. Of the 21 Probable MAS events, 19 occurred in the canakinumab and 2 in the placebo group. The time period between the first injection of canakinumab and the onset of MAS ranged between 3 to 1359 days (median, 531 days). The rate for MASAC adjudicated Probable MAS was 2.8/100 patient-years and 7.7/100 patient-years for the canakinumab and placebo groups (Table), respectively with no statistically significant difference between groups (diff=-4.9, 95% CI, -15.6, 5.9). Three patients (canakinumab, n=2; placebo, n=1) died due to complications of MAS and full recovery was reported in the remaining patients.

Table. Exposure adjusted incidence rate of events adjudicated as Probable MAS

	Canakinumab*	Placebo	Difference canakinumab – placebo (95% confidence interval)
Number *Probable MAS* adjudicated events	19	2	
Patient- years exposure	668.61	26	
Rate of *Probable MAS* adjudicated events/ 100 PTY	2.8	7.7	-4.9 (-15.6, 5.9)

*Clinical program included studies: Phase II; Phase III Trial 1; Phase III Trial 2; Phase III Trial 2

extension; MAS = macrophage activation syndrome; MASAC = MAS Adjudication Committee

Conclusion: Canakinumab does not appear to have an effect on the frequency of macrophage activation syndrome or modify its clinical features.

Reference:

1. Ruperto et al. *N Engl J Med*. 2012;367:2396-406.
2. Ruperto et al. *Ann Rheum Dis*. 2015;74(2):608.
3. Ravelli A, et al. *J Pediatr*. 2005;146(5):598-604.

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Abstract Number: 2425

Safety of Tocilizumab in Young Adults with Juvenile Idiopathic Arthritis (JIA)

Jens Klotsche[1], Martina Niewerth[2], Johannes Peter Haas[3], Angela Zink[4], Gerd Horneff[5] and Kirsten Minden[6], [1]Programme Area Epidemiology, German Rheumatism Research Center, a Leibniz institute, Berlin, Germany, [2]Epidemiology, German Rheumatism Research Centre, Berlin, Germany, [3]German Centre for Rheumatology in Children and Young People, Garmisch-Partenkirchen, Germany, [4]Epidemiologie, Deutsches Rheuma-Forschungszentrum, Berlin, Germany, [5]Asklepios Clinic Sankt Augustin, Sankt Augustin, Germany, [6]Children's University Hospital Charite/German Rheumatism Research Centre Berlin, Berlin, Germany

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SESSION INFORMATION

Session Title: Pediatric Rheumatology - Clinical and Therapeutic Aspects Posters (ACR): Imaging and Novel Clinical Interventions

Session Type: ACR Poster Session C

Background/Purpose: Tocilizumab was recently approved for the treatment of systemic JIA (sJIA) and polyarticular JIA (pJIA). Published data on the tolerability of tocilizumab in patients with JIA are rare. The aim of the study was to investigate the safety of tocilizumab in routine care in young adults with JIA.

Methods: Patients with JIA were enrolled in the national JIA biologic register BiKeR and were prospectively followed into adulthood in the follow-up register JuMBO. All adverse events (AE) were recorded by physicians over the observation period and were categorized on the basis of MedDRA. An event was attributed to tocilizumab when the treatment was either ongoing or terminated in less than 3 months prior to the event. Rates of AE and serious AE (SAE) were calculated per 100 years of tocilizumab exposure (EY).

Results: A total of 929 JIA patients were included in the JuMBO register by the end of January 2015. The tolerability of tocilizumab could be studied in 87 patients (143 EY) who were ever exposed to tocilizumab (14 sJIA, 63 pJIA). Tocilicumab was the first-line biologic disease modifying antirheumatic drugs (DMARD) in 4 (5%) patients, the other 83 patients were treated with tocilizumab after treatment failures with other biologics (second-line bDMARD in 26%, third-line in 47%). In the majority of cases (78%) tocilicumab was first prescribed in young adulthood. At the last available JuMBO visit, 63 patients (8 sJIA, 49 pJIA) were on current treatment with tocilizumab. At treatment start with tocilizumab, patients had a mean disease duration of 13 years, a mean age of 23 years and had been treated in mean by 4.5 other DMARDs before tocilizumab. A total of 81 AE (56.6 events/100 EY) were recorded and 19 (13.3 events/100 EY) AE were rated as serious. Among the SAE, 10 surgical and medical procedures (7.0 events/ 100EY), 4 infections (2.8 events/ 100EY, herpes zoster, genital herpes, norovirus infection, pneumonia) and 2 gastrointestinal disorders (1.4 events/ 100EY) were reported.

Conclusion: Tocilizumab is often started at first time in JIA patients in young adulthood and after treatment failure with other biologic DMARDs. Thus, the JuMBO register supplements the findings about drug safety from the BiKeR register. The obtained safety data are similar to those of tocilizumab in children and of other biologics used in young adults with JIA. However, the number of observed years of drug exposure is still very limited.

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Abstract Number: 2426

Medication Taper and Risk of Relapse in Pediatric Uveitis

Sheila T. Angeles-Han[1,2,3], Courtney McCracken[3], Steven Yeh[2], Daneka Stryker[4], Kirsten Jenkins[1], Steven Tommasello[5], Scott R. Lambert[2], Carolyn Drews-Botsch[6] and Sampath Prahalad[7], [1]Children's Healthcare of Atlanta, Atlanta, GA, [2]Ophthalmology, Emory University School of Medicine, Atlanta, GA, [3]Pediatrics, Emory University School of Medicine, Atlanta, GA, [4]Pediatrics, Emory University School of Medicine and Children's Healthcare of Atlanta, Atlanta, GA, [5]University of Alabama, Birmingham, AL, [6]Epidemiology, Emory University School of Public Health, Atlanta, GA, [7]Emory University School of Medicine and Children's Healthcare of Atlanta, Atlanta, GA

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Background/Purpose: Pediatric uveitis can be vision-threatening. Treatment typically consists of ocular steroids, methotrexate, and anti-tumor necrosis factor (TNF) agents. Optimal duration of treatment and risk of relapse after medication taper is not well studied in children. Our aim is to describe the course of medication taper and discontinuation in a pediatric uveitis cohort.

Methods: There were 107 children with uveitis - JIA-associated uveitis (JIAU), idiopathic uveitis, HLA-B27 (+) uveitis, and other etiologies. Demographic and clinical data were collected. We compared children who attained remission after medication discontinuation to those who relapsed, using Wilcoxon rank-sum tests, Fisher's exact tests and Kaplan-Meier estimates.

Results: There were 28 (26%) children in whom we attempted to taper medication. Of these, 15 had JIAU, and 13 had other forms of uveitis (U). They were primarily female (82%), Caucasian (54%), and had anterior location (63%), bilateral involvement (73%), and ocular complications (72%), most commonly synechiae (57%), cataracts (54%) and macular edema (32%).

Medications were discontinued in only 6 (21%) children (4 with U, and 2 with JIAU). Of these, 5 were on methotrexate and 1 on infliximab. Median time from start of taper to discontinuation was 7 months (0-18 months). Children remained relapse-free for a median of 8 months (0 – 2.1 years).

Of 21 children who failed medication taper, 17 relapsed during taper, 2 are completing taper, 2 restarted methotrexate while on anti-TNF therapy, and 1 was lost to follow up. Comparing children with a recurrence of uveitis to those who achieved remission, those who flared were younger at uveitis diagnosis (4.1 vs. 10.3 years, $p = 0.033$). There was clinical trend of relapse in Caucasians compared to African Americans, (11/13 (85%) vs. 1/4, (25%) $p = 0.053$), those treated for a shorter duration (1.4 [0.9 – 2.3] vs. 1.8 [1.7-7.2] years), $p = 0.166$) and those with JIAU (12/17 (71%) vs. 5/17 (29%), $p = 0.162$). There were no significant differences in gender, etiology, laterality, complications, anterior chamber cells, visual acuity, or duration of uveitis before taper.

Kaplan-Meier product-limit survival estimates showed that approximately 30% failed taper within 4 months, 40% within 9 months, 50% within 10 months, and 60% within 1 year.

Conclusion: Only 21% of children achieved drug-free remission, and 60% relapsed within a year of medication taper. Older age at diagnosis may be associated with success of drug taper. Our results suggest potential differences in likelihood of remission associated with race, duration of treatment, and uveitis diagnosis. Further study of factors associated with optimal treatment of pediatric uveitis leading to disease remission are warranted.

Table 1. Comparison of Children with Uveitis who Relapsed During Medication Taper			
	No Relapse N = 6	**Relapse N = 17**	**p -value**
Gender, female	4 (66.7%)	14 (82.4%)	0.576
Race			
Caucasian	2 (33.3%)	11 (64.7%)	0.341
African American	3 (50%)	1 (5.8%)	0.040*
Other	1 (16.7%)	5 (29.4%)	1.00
Uveitis Diagnosis			
JIA-Associated Uveitis	2 (33.3%)	12 (70.6%)	0.162
Other Forms of Uveitis	4 (66.7%)	5 (29.4%)	
Age at Uveitis Diagnosis	10.3 (5.2 – 12.6)	4.1 (2.9 – 6.8)	0.033*
Duration of Disease To Date, years, median (25^{th} – 75^{th})	6.5 (4.2 – 10.2)	5.8 (3.7 – 7.6)	0.654
Duration of Uveitis Before Taper, years, median (25^{th} – 75^{th})	5.1 (2.6 – 9.2)	2.6 (1.1 – 4.7)	0.100
Duration of Treatment Before Taper, years, median (25^{th} – 75^{th})	1.8 (1.7-1.2)	1.4 (0.9-2.3)	0.166
Location			
Anterior	2 (40%)	13 (76.5%)	0.068
Intermediate	1 (20%)	--	
Posterior/Panuveitis	1 (20%)	--	
Unknown	1 (20%)	4 (23.5%)	
Bilateral Disease	6 (100%)	11 (73.3%)	0.281
Complications	4 (66.7%)	11 (64.7%)	1.00
Cataracts	3 (50%)	8 (47.1%)	1.00
Glaucoma	1 (16.7%)	6 (35.3%)	0.621
Synechiae	3 (50%)	9 (52.9%)	1.00
Macular Edema	1 (16.7%)	5 (29.4%)	0.646
Amblyopia	1 (16.7%)	2 (11.8%)	1.00
Worst LogMAR Visual Acuity, median (25^{th} – 75^{th})	0.92 (0.69 – 1.39)	1.25 (0.41 – 1.39)	0.797
Highest Anterior Chamber Cell Grade, median (25^{th} – 75^{th})	2+ (1+-2+)	2+ (1+-3+)	0.601
**p-value <0.05*			

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Abstract Number: 2427

Long-Term Efficacy and Safety of Mycophenolate Mofetil in Childhood Primary Central Nervous System Vasculitis

Alice Brambilla[1], Alessandra Cosi[2], Anna Rosati[2], Renzo Guerrini[2], Rolando Cimaz[1] and **Gabriele Simonini**[1], [1]Pediatric Rheumatology, Pediatric Rheumatology Unit, Anna Meyer Children's Hospital-University of Florence, Firenze, Italy, [2]Neurology Unit, Neurology Unit, Anna Meyer Children's Hospital-University of Florence, Firenze, Italy
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SESSION INFORMATION

Session Title: Pediatric Rheumatology - Clinical and Therapeutic Aspects Posters (ACR): Imaging and Novel Clinical Interventions

Session Type: ACR Poster Session C

Background/Purpose:

Childhood primary central nervous system vasculitis (cPANCS) is an inflammatory brain disease targeting either small (angiography-negative) or medium-large (angiography-positive) central nervous system vessels. Vascular inflammation is reversible with proper immunosuppressant treatment, preventing disabling neurologic impairment. **Objective.** To report efficacy and sustained remission in 4 children affected by cPANCS treated with MMF.

Methods: Between December 2011 and August 2014, 4 patients (median age 77 months, range 9-165) were referred to our centre due to stroke symptoms associated to focal areas of acute ischemia at brain neuroimaging. Screening for thromboembolic and metabolic diseases was negative in all patients as well as complete cardiologic evaluation. Antiplatelet and anticoagulant treatments lead to transient clinical and radiological improvement. After a median period of 7 months (range 2-11) they showed clinical and/or radiologic relapse, with documented progression of vascular involvement at magnetic resonance angiography (MRA) or cerebral angiogram. Laboratory work up for infectious diseases, inflammatory and autoimmune conditions excluded secondary causes of central nervous system vasculitis, thus prompting the diagnosis of cPANCS. Methyl-prednisolone (30mg/kg for 3-5 days) was then started, followed by administration of oral Prednisone (1-2 mg/kg/day) and induction therapy with MMF (1000 mg/m^2 divided BID). Brain MRI controls have been performed every 3-6 months according clinical history and neurological evaluation

Results: Median period of MMF treatment was 19 months (range 6-27). Steroid tapering was started after 6 weeks from the beginning and complete discontinuation was achieved within 7-8 months in 3 out of 4 patients. One patient is still on steroid tapering. Periodic clinical examination, blood tests and MRA were performed with evidence of clinical and radiological improvement or, at least, stable findings. In all children, no relapse of cerebral vasculitis occurred during the follow-up period (median 19.8 months, range 5-29). No major side effects and/or drug-related adverse events were documented during the study period of treatment.

Conclusion: Despite the restricted number of enrolled patients, we report efficacy, good tolerance along with persistent improvement and remission in children affected by cPANCS treated with MMF for up to 27 months

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Abstract Number: 2428

Efficacy and Safety of Adalimumab in Adult Patients with Polyarticular Juvenille Idiopathic Arthritis

Daniel Lovell[1,2], Nicolino Ruperto[3], Andreas Reiff[4], Lawrence Jung[5], Katerina Jarosova[6], Pierre Quartier[7], Christy Sandborg[8], John F. Bohnsack[9], Dirk Elewaut[10], Ivan Foeldvari[11], Joseph Rovensky[12], Edward H. Giannini[2], Nupun A. Varothai[13], Jasmina Kalabic[13] and Alberto Martini[14,15,16], [1]PRCSG, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, [2]PRCSG, Cincinnati, OH, [3]Paediatric Rheumatology International Trials Organization (PRINTO), Istituto Giannina Gaslini, Genova, Italy, [4]Children's Hospital, Los Angeles, CA, [5]Pediatric Rheumatology, Children's National Med Ctr, Washington, DC, [6]Revmatologicky ustav, Prague, Czech Republic, [7]Hospital Necker Enfants Malades, Paris, France, [8]Stanford University Medical Center, Standford, CA, [9]Pediatrics, University of Utah Health Sciences Center, Salt Lake City, UT, [10]Laboratory for Molecular

Immunology and Inflammation, Department of Rheumatology, VIB, Ghent University and Ghent University Hospital, Ghent, Belgium, [11]Hamburger Zentrum für Kinder-und Jugendrheumatologie, Hamburg, Germany, [12]The National Institute of Rheumatic Diseases, Piestany, Slovakia, [13]AbbVie, North Chicago, IL, [14]University of Genova, Genova, Italy, [15]Department of Pediatrics, University of Genova, Genova, Italy, [16]Istituto Gaslini-PRINTO, Genova, Italy
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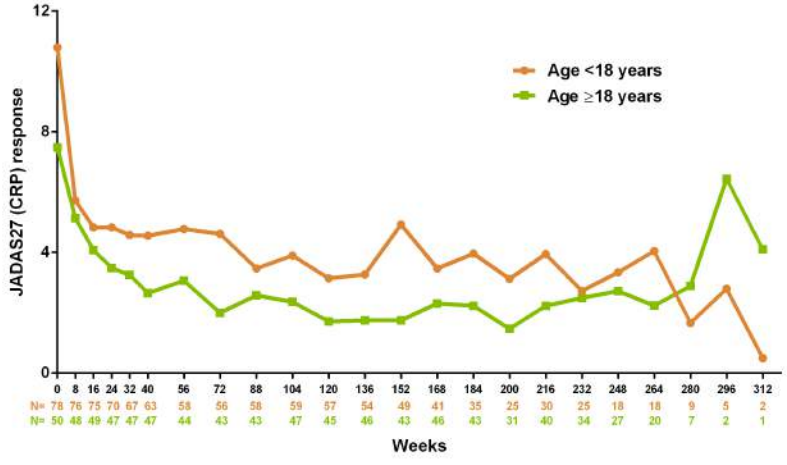
Background/Purpose: The diagnosis of polyarticular JIA (pJIA) is made in childhood but the disease and the diagnosis are carried into adulthood. Adults with pJIA have heterogeneous clinical manifestations, many of which differ from rheumatoid arthritis. These adults warrant a tailored approach for optimal management of pJIA. The objective of this study was to assess adalimumab (ADA) effectiveness and safety in pts with pJIA who turned 18 years (yrs) of age anytime during Study DE038.

Methods: This was a multicenter, phase 3, randomized, double-blind (DB), stratified study in children (4 to 17 yrs at baseline) with pJIA treated with or without MTX prior to the study entry. Pts in the MTX arm were treated concomitantly with MTX during the entire study duration. Pts in the non-MTX arm were either naïve to or withdrawn from MTX at least 2 weeks (wks) prior to study drug administration. The study consisted of 16 wk open label lead-in, a 32 wk DB phase and an open label (OL) extension phase. This post-hoc analysis assessed outcomes during the OLE for pts who turned 18 yrs anytime during the course of study in comparison to pts who remained under 18 yrs during their study participation. Twenty sevenjoint juvenile arthritis disease activity score (JADAS27), based on C-reactive protein (CRP) response was measured upto 312 wks of the OLE. Adverse events (AEs) were also monitored and compared between the two age groups throughout the study duration.

Results: 171 pts with pJIA between 4-17 yrs of age at the time of study entry were enrolled. Among them, 51(30%) turned 18 yrs of age during the course of their participation in the study and were compared to the remaining 120 pts that remained <18 yrs throughout the study participation. There were (42; <18 yrs) vs (46; ≥18 yrs) pts who received at least 4 yrs of ADA. The mean age at the time of study enrollment was 14.6 yrs vs 9.8 yrs in pts ≥18 yrs and <18 yrs respectively. The majority of pts were white (90.2% vs 92.5%) and female (74.5%; ≥18 yrs) vs 80.8%; <18 yrs). The subgroup of 51 pts that turned 18 yrs had a mean age of 19.8 ± 1.5 yrs at the time of their last dose of ADA in the study. The JADAS27(CRP) response was measured from baseline up to 312 wks and demonstrated maintainance of efficacy ($p<0.05$)from week 72 onwards, irrespective of age (Figure). The overall rate of AEs was lower in pts ≥18 yrs than pts <18 yrs (432 [95% CI, 407.6 - 458.6] vs 701 [95% CI, 672.1 - 731.0] events/100 pt-y) respectively.

Conclusion: The efficacy results based on the JASDAS27(CRP)responses demonstrated maintenance of efficacy over time for both age groups. Safety data showed the overall rate of AEs was lower in pts ≥18 yrs than pts <18 yrs. No new safety signals were observed; thus the safety profile of ADA remained unchanged. The findings from this study support a favorable benefit-risk profile of for the ADA treatment in adult pts (≥18 yrs of age) with moderately to severely active pJIA.

Figure: JADAS27 (CRP) response over time for pJIA patients <18 yrs and ≥18 yrs of age in the OL-extension phase



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Abstract Number: 2429

Varicella Vaccination in Patients with Pediatric Rheumatic Diseases Receiving Immunosuppression: Proposal of a Pre-Vaccination Checklist to Ensure Safety

Fabian Speth[1], Johannes Peter Haas[1], Susanne Loeber[1] and **Claas Hinze**[2], [1]German Center for Pediatric and Adolescent Rheumatology, Garmisch-Partenkirchen, Germany, [2]Department of Pediatric Rheumatology and Immunology, University Hospital Münster, Münster, Germany

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Session Type: ACR Poster Session C

Background/Purpose:

Varicella zoster virus (VZV) infection is a serious preventable infection in patients (pts) receiving immunosuppression (IS). The purpose of this study was to determine the safety and efficacy of administering the VV to pts with PRD on IS after passing a pre-vaccination checklist of immunologic criteria.

Methods:

In this single center study, after screening >2800 pts, 21 VZV-susceptible pts with clinically inactive PRDs, including different categories of juvenile idiopathic arthritis and connective tissue diseases between the ages of 2–18 years on low-intensity IS (LIIS) (methotrexate [MTX] ≤15mg/m2/week and/or prednisolone <10mg/day) or high-intensity IS (HIIS) (MTX>15mg/m2/week, leflunomide, mycophenolate mofetil [MMF], etanercept, tocilizumab, anakinra, abatacept, or a combination thereof) were included in this study. Prior to vaccination, pts were screened according to an immunologic checklist with predefined cut-offs, i.e. for pts on LIIS: WBC>3000/µl, ALC>1200/µl, IgG>500mg/dl, IgM>0, Tetanus toxin-IgG >0,10IU/ml, and, in addition, for pts on HIIS: CD4 >200/µl [if>5 yrs] or CD4 >500/µl [if 1-5 yrs] and positive T cell reactivity to mitogen or antigen, e.g. via TB-EliSpot positive control. Pts meeting these safety criteria received either a 1st and/or 2nd dose of VV. VZV-IgG levels were measured before applying VV and after each dose. VZV cellular mediated immunity (CMI) was measured after VV. Potential side effects and PRD flares were monitored.

Results:

Out of 9 pts receiving LIIS and 12 pts receiving HIIS none failed the immunologic checklist. Eight pts (2 LIIS, 6 HIIS) had already received their 1 dose of VV prior to this study and received a booster dose of VV only. Thirteen pts (7 LIIS, 6 HIIS) received their 1st dose of VV within the study and 7 of these 13 pts received a 2nd dose of VV. 11/13 pts demonstrated protective VZV-IgG levels of >150 IU/ml after the 1st dose of VV, and 5/7 pts of those receiving a 2nd dose of VV achieved levels of >500 IU/ml. Two pts (one on MMF one on leflunomide and abatacept) did not achieve protective VZV-IgG levels, despite otherwise adequate humoral and cellular immunity. Of those 8 pts receiving a booster dose only, all exceeded VZV-IgG levels of >500 IU/ml by far.

There was no difference in either the mean absolute or relative increase (Δ) in VZV-IgG between pts on LIIS vs. HIIS (after 1st dose of VZV Δ341 IU/ml vs. Δ378 IU/ml and 4.7-fold vs. 4.2-fold, respectively; after 2nd dose Δ745 IU/ml vs. Δ1001 IU/ml and 6.9-fold vs. 6.4-fold, respectively). Data on VZV-CMI and long-term VZV-IgG levels are pending at the time of abstract submission. There was no evidence of VV-induced varicella or other complications. None of the pts developed a PRD flare and no change in the IS regimen was required in any pt during a minimum follow-up of 4 wks. 7 pts had transient arthralgias of unclear association with VV administration.

Conclusion:

After meeting easy-to-obtain immunologic criteria, the VV could safely be applied to a diverse cohort of pts with clinically inactive PRD on IS with good immunologic response in the majority of pts.

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Abstract Number: 2430

Immunological Risk Factors after Rituximab Therapy in Patients with Pediatric Rheumatic Diseases – a Prospective Single-Center Study

Fabian Speth[1], Johannes Peter Haas[1] and **Claas Hinze**[2], [1]German Center for Pediatric and Adolescent Rheumatology, Garmisch-Partenkirchen, Germany, [2]Department of Pediatric Rheumatology and Immunology, University Hospital Münster, Münster, Germany

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Background/Purpose:

Rituximab (RTX) is used in refractory pediatric rheumatic diseases (PRD). Data regarding the effects of RTX on the immune system in children and safety in PRD is scarce. The purpose was to prospectively evaluate indicators of humoral immunity before and until 2 yrs after RTX administration.

Methods: Twenty patients (pts) with PRD (4 SLE, 3 MCTD, 3 JIA, 2 eosinophilic fasciitis, 2 juvenile dermatomyositis, 2 Sjögren-syndrome, 2 GPA (Wegener), 1 MPA, 1 PM/Scl-overlap) after excluding common variable immunodeficiency received at least 1 standard dose RTX cycle (some pts up to 3 cycles). Additional treatment consisted of prednisolone (10), hydroxychloroquin (10), mycophenolate mofetil (9), methotrexate (6), leflunomide (4), abatacept (2), everolimus (2), cyclosporin (1) and antiinflammatory doses of i.v. immunoglobulin (IVIG) (3). Lymphocyte subpopulations, IgA, IgG, IgM and IgE levels, IgG subclasses, isoagglutinins, antigen-specific IgG levels to tetanus toxin, H. influenzae type B (Hib), pneumococcus and measles, spleen size, presence of Howell-Jolly bodies (functional hyposplenism) and throat culture were obtained 6, 12 and 24 months (mos) after RTX. IgG and antigen-specific IgG levels in pts receiving IVIG were not included in the analysis. The continuous variables at time points 6, 12 and 24 mos were compared by paired T test to time point 0 mo (prior to RTX).

Results:

All pts achieved complete B cell depletion. B cells repopulated in all pts with a median of 8.5 mos. IgG and IgM levels were (mean [standard deviation] mg/dl at 0, 6, 12, 24 months) IgG 1428 [723], 1255 [653], 1075 [452], 1243 [617]; IgM 119 [61], 71 [52], 54 [39], 52 [46]. Significant reductions were observed for IgG (6/12 mos), IgM (6/12/24 mos), IgA (6/12 mos) and IgE (6/12/24 mos). Overall, 7/17 (41%) of patients received IVIG substitution based on predefined IgG and/or IgM threshold levels. One pt developed low IgG2/3, IgA and IgM levels, and 2 pts developed low IgG4 levels, at 24 mos after RTX. Tetanus toxoid IgG decreased significantly at 12 mos but not below a protective threshold in any pt. There was a non-significant decrease in pneumococcal antibodies at 12 and 24 mos. Individually, Hib-IgG and pneumococcal antibodies fell below protective thresholds

in some pts. Measles IgG levels decreased significantly at 12 and 24 mos but not below a protective threshold. There was a non-significant decrease in spleen size at 6 months. Transient Howell-Jolly bodies were observed in 8 pts, and antibiotic prophylaxis was begun. Throat culture showed colonization with C. albicans in 12, S. aureus in 3, Hib in 2, both P. aeruginosa and S. marcescens in 1, E. coli in 1 and Enterobacter in 1 pt. One pt developed fever, neutropenia, received i.v. antibiotics and recovered fully.

Conclusion:

Acquired humoral immunodeficiency occasionally occurs after RTX treatment in PRD, especially after repeated treatment cycles. Preventive strategies, including IVIG substitution and/or antibiotic prophylaxis informed by immunologic studies maybe useful in preventing serious invasive infections. We suggest at least 2 yrs of surveillance for acquired humoral immunodeficiency, incl. IgA, IgG, IgM, IgG subclasses and immunization titers after RTX treatment in PRD.

Disclosure: F. Speth, None; **J. P. Haas**, None; **C. Hinze**, None.

Abstract Number: 2431

Long-Term Safety of Adalimumab Treatment in Pediatric Patients with Polyarticular Juvenile Idiopathic Arthritis and Enthesitis-Related Arthritis

Daniel Lovell[1], Nicolino Ruperto[2], Daniel J. Kingsbury[1], Rubén Burgos-Vargas[2], Tomoyuki Imagawa[3], G Horneff[2], Pierre Quartier[4], Steven Goodman[1], Andreas Reiff[1], Edward H. Giannini[1], Anabela Cardoso[5], Jaclyn K. Anderson[6], Nupun A. Varothai[6], Jasmina Kalabic[6] and Alberto Martini[2], [1]PRCSG, Cincinnati, OH, [2]PRINTO, IRCCS G. Gaslini, Genova, Italy, [3]Kanagawa Children's Medical Center, Yokohama City, Japan, [4]Hopital Necker-Enfants Malades, Paris, France, [5]AbbVie, Amadora, Portugal, [6]AbbVie, North Chicago, IL

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Background/Purpose: The long-term safety of anti-tumor necrosis factor (TNF) drugs is particularly important in pediatric patients (pts) who may require prolonged treatment of their inflammatory disease. The purpose of the study is to evaluate long-term rates of serious adverse events (AE) and anti-TNF AEs of special interest in adalimumab (ADA) clinical trials in pediatric pts with polyarticular or polyarticular course juvenile idiopathic arthritis (pJIA) or enthesitis-related arthritis (ERA)

Methods: Safety data from pts treated with ADA, either dosed 24 mg/m^2 BSA every other week (eow) or 20 mg eow (<30 kg) to 40 mg eow (≥30 kg), in 4 clinical trials in pJIA and ERA were analyzed. Three studies in pJIA enrolled pts aged 2–17 years (yrs) treated with ADA for up to approximately 7 yrs. One study enrolled pts with ERA aged 6–17 yrs to be treated with ADA for up to 144 wks (interim results through 52 weeks were included in this analysis). AEs of special interest included malignancy, serious infections, tuberculosis (TB) and other opportunistic infections, and death. Events per 100 patient-years (PY) were calculated using AEs reported after first ADA dose through 70 days after last dose.

Results: ADA was administered to 274 pts, representing 705.0 PY of exposure. Infections, the most common AE, occurred in ≥10% of pts. Serious infection was the most frequently reported SAE (table). No cases of active or latent TB were reported. No malignancies, opportunistic infections, or deaths were reported. 7.3% of pts (20/274) discontinued study due to AE (range, 5.1% in age <5 yr to 9.6% in ages 5 - <12 yrs). Other than uveitis, liver events, and injection site-related AEs, no differences in AE rates were observed between age groups. (Table)

Conclusion: These data provide support for the long-term safety of ADA in pediatric pts aged 2–17 yrs with pJIA or aged ≥6 to <18 with ERA and demonstrate a safety profile consistent with ADA in adult pts and known information about the anti-TNF class.

Rates (E, E/100PY)	**Age <5 yr N=39**	**Age 5 - <12 yr N=104**	**Age 12 - <18 yr N=131**	**Total N=274**
Adalimumab exposure, PY	65.4	285.1	354.5	705.0
Serious AE*	8 (12.2)	31 (10.9)	64 (16.6)	103 (13.9)
Infectious AE	106 (162.1)	477(167.3)	513 (144.7)	1096 (155.5)
Serious infectious AE	2 (3.1)	7 (2.5)	10 (2.8)	19 (2.7)
Tuberculosis (latent)	0	0	0	0
New onset/worsening psoriasis	0	5 (1.8)	0	5 (0.7)
Allergic reactions	4 (6.1)	28 (9.8)	27 (7.6)	59 (8.4)
Liver events	1 (1.5)	1 (0.4)	3 (0.8)	5 (0.7)
Uveitis	2 (3.1)	3 (1.1)	1 (0.3)	6 (0.9)
Injection site-related AE	14 (21.4)	450 (157.8)	378 (106.6)	842 (119.4)

*Death, life-threatening, hospitalization or prolongation of hospitalization, persistent or significant disability, or important medical event. AEs coded by Medical Dictionary for Regulatory Activities version 16.1.

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Abstract Number: 2432

The Preventive Effect of Methotrexate on Uveitis Onset in JIA Depends on Uveitis Risk Factors

Mikhail Kostik[1], Ekaterina Gaidar[1], Margarita Dubko[1], Ludmila Snegireva[2], Vera Masalova[2], Irina Chikova[1], Eugenia Isupova[3], Tatiana Nikitina[4], Elena Serogodskaya[1], Olga Kalashnikova[1], Angelo Ravelli[5] and Vyacheslav Chasnyk[3], [1]State Pediatric Medical University, Saint-Petersburg, Russia, [2]Hospital Pediatrics, State Pediatric Medical University, Saint-Petersburg, Russia, [3]Hospital Pediatry, State Pediatric Medical University, Saint-Petersburg, Russia, [4]State Pediatric Medical University, St. Petersburg, Russia, [5]Pediatria-II, IRCCS G. Gaslini and University of Genova, Genova, Italy

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Background/Purpose:

Uveitis is the most common extra-articular manifestation of juvenile idiopathic arthritis (JIA), often entirely asymptomatic but could be sight-threatening. The main predictors of uveitis in JIA are oligoarticular (OA) subtype, ANA-positivity and younger age at the JIA onset. Methotrexate (MTX) has been able to decrease the incidence of uveitis in JIA up to 2 times [1].

Objectives: To evaluate the possibility of MTX to prevent the onset of uveitis in different JIA subgroups according to the main uveitis risk factors.

Methods:

The clinical charts of all consecutive patients who had received a stable management for at least 2 years with or without MTX were reviewed. Patients who were given systemic medications other than MTX (except NSAID) were excluded. Patients with systemic arthritis, rheumatoid factor-positive arthritis, or enthesitis-related arthritis were also excluded. In each patient, the al least 2-year follow-up period after first visit was examined to establish whether uveitis had occurred. MTX was administered in the subcutaneous injections in the dosage 15 mg/m^2/week.

Results:

A total of 281 patients with a median disease duration of 3.8 year were included. One hundred and ninety one patients (68%) were treated with MTX compare to 33.9% in previous study [1]. During the at least 2-year follow-up, 64 patients (22.8%) developed uveitis, a median of 1.6 year after the disease onset. The frequency of uveitis was lower in MTX-treated than in MTX-untreated patients (11.5% vs 46.7%, respectively, OR=6.7 (95%CI:3.7-12.3), p= 0.0000001). In previous study the frequency of uveitis was 10.5 in MTX-treated vs 20.2 in MTX-untreated patients [1]. Survival analysis confirmed that patients treated with MTX had a lower probability of developing uveitis (HR=4.35, p=0.000001). The results of preventive effect of MTX in different JIA subgroups, according to the main uveitis risk factors are shown in the table 1.

Table 1. The ability of MTX to prevent uveitis in different subgroup.

Group	MTX, Y/N	Rate (%)	OR (95% CI)	p†	HR*	p§
Boys	N	9/26 (34.6)	7.3 (2.0-26.6)	0.001*	6.7	0.0007
	Y	4/59 (6.8)				
Girls	N	19/132 (14.4)	5.9 (3.0-11.9)	0.000001	3.6	0.000001
	Y	32/64 (50.0)				
Oligoarticular course	N	37/81 (45.7)	5.7 (2.9-11.3)	0.000001	4.0	0.000001
	Y	16/125 (12.8)				
Polyarticular course	N	4/9 (44.4)	6.7 (1.5-31.2)	0.007	3.7	0.02
	Y	7/66 (10.6)				
ANA (+)ve	N	20/29 (68.9)	10.1 (3.6-28.1)	0.000002	4.4	0.00002
	Y	11/61 (18.0)				
ANA (-)ve	N	13/43 (30.2)	4.4 (1.7-11.8)	0.0016	3.6	0.003
	Y	8/90 (8.9)				
Age of JIA onset ≤ 5 y	N	23/57 (40.4)	3.5 (1.7-7.3)	0.0006	2.3	0.003
	Y	18/111 (16.2)				
Age of JIA onset > 5 y	N	15/47 (31.9)	20.6 (4.5-95.2)	0.000001	22.2	0.000001
	Y	2/90 (2.2)				

† χ2-test, §Log-Rank test, * Cox regression models

Conclusion:

Conclusions:MTX therapy may differently prevent the onset of uveitis in children with JIA depends on uveitis risk factors. Further randomized controlled trial required to confirmation our results.

References:

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Abstract Number: 2433

Anti Interferon-Gamma (IFNg) Monoclonal Antibody Treatment in a Child with NLRC4-Related Disease and Severe Hemophagocytic Lymphohistiocytosis (HLH)

Claudia Bracaglia[1], Giusi Prencipe[1], Antonio Gatto[2], Manuela Pardeo[1], Geneviève Lapeyre[3], Luigi Raganelli[1], Emiliano Marasco[2], Antonella Insalaco[2], Walter Ferlin[3], Robert Nelson[3], Cristina de Min[3] and Fabrizio De Benedetti[1], [1]Department of Pediatric Medicine, Division of Rheumatology, Ospedale Pediatrico Bambino Gesù, IRCCS, Rome, Italy, [2]Pediatric Medicine, Division of Rheumatology, Ospedale Pediatrico Bambino Gesù, IRCCS, Rome, Italy, [3]NovImmune S.A., Geneva, Switzerland
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SESSION INFORMATION

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Background/Purpose: Animal and humans data suggest that IFNγ plays a pathogenic role in HLH. A pilot trial in primary HLH with NI-0501, an anti-IFNγ monoclonal antibody, is ongoing. Mutations in *NLRC4*have recently been reported to cause recurrent macrophage activation syndrome and increased production of IL-18, that is known to induce IFNγ.

Methods: We report safety and efficacy of NI-0501 in a patient, carrying an *NLRC4*mutation with severe recalcitrant HLH.

Results: The patient presented at 20 days of age with fever, hepatosplenomegaly, pancytopenia, hypofibrinogenemia, hypertriglyceridemia, hyperferritinemia and sCD25 increase, meeting 6 HLH-criteria. Liver and subsequent multiorgan failure required ICU admission. Genes causing primary-HLH (*PRF1, UNC13D, STXBP2, STX11, RAB27A, XIAP*) and functional tests (perforin expression, degranulation assay and NK cytotoxic activity) were negative. Subsequent analysis of *NLRC4* showed a *de novo* missense mutation (T337N) located in the same codon as that reported by Canna et al (1). Elevated serum IL-18 (>30.000 pg/ml) was documented, confirming the biologic and pathogenic relevance of the *NLRC4* mutation. High-dose glucocorticoids and cyclosporine-A led to partial improvement. Development of sepsis (*C.albicans and K.pneumoniae*) triggered HLH reactivation. Etoposide and/or ATG were not considered because of the presence of active infections. Measurable IFNγ levels (6 pg/ml) and high levels of CXCL9 (5670 pg/ml) and CXCL10 (4400 pg/ml) were found. NI-0501 (compassionate use) was started on background dexamethasone (13.6 mg/m2) and cyclosporine-A. NI-0501 was administered every 3 and subsequently every 7 days according to pharmacokinetics. No infusion reaction was observed. Progressive improvement allowed rapid glucocorticoid tapering. After 6 months of treatment, the child is in excellent condition; all HLH parameters have normalized. Serum IL-18 levels remain elevated (32.000 pg/ml). High circulating levels (in the range of nanogram/ml) of IFNγ complexed with NI-0501, reflecting high IFNγ production, are detectable, and fully neutralized, as shown by undetectable levels of IFNγ-inducible chemokines (Table 1). He is receiving cyclosporine-A (6 mg/kg) and prednisone (0.3 mg/kg equivalent to 0.9 mg/m^2 dexamethasone).

Conclusion: In a patient, carrying a pathogenic *NLRC4*mutation with severe recalcitrant HLH, neutralization of IFNγ allowed control of all HLH features, while enabling glucocorticoid tapering. No safety concern emerged.

References.

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Disclosure: C. Bracaglia, None; **G. Prencipe**, None; **A. Gatto**, None; **M. Pardeo**, None; **G. Lapeyre**, Novimmune, 3; **L. Raganelli**, None; **E. Marasco**, None; **A. Insalaco**, None; **W. Ferlin**, Novimmune, 3; **R. Nelson**, NovImmune SA, 3; **C. de Min**, Novimmune, 3; **F. De Benedetti**, None.

Abstract Number: 2434

Promis Tools for Measurement of Patient-Reported Outcomes in Children with Juvenile Arthritis

Timothy Brandon[1], Brandon Becker[1], Katherine Bevans[1] and **Pamela F. Weiss**[2], [1]Pediatrics, Children's Hospital of Philadelphia, Philadelphia, PA, [2]Rheumatology, Children's Hospital of Philadelphia, Philadelphia, PA

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Background/Purpose: Child/parent perspectives on their own/their child's health are highly pertinent to disease management. PROMIS is a collection of patient-reported outcome measures that were developed to be non-disease specific. For each PROMIS domain there are "item banks" (13-29 questions) and associated "short forms" (8-10 questions) that generate a score representing the level of that trait in comparison to a sample of US children (inclusive of children with common chronic diseases). This study examines the applicability of PROMIS tools to children with juvenile idiopathic arthritis (JIA) and their parents.

Methods: A convenience sample of patients with JIA aged 8-17 years (all JIA categories) and parent proxies (5-17 years) were recruited from a single center and completed 1 to 4 PROMIS item banks. In all, 8 PROMIS items banks were administered: anger, anxiety, depression, fatigue, pain interference, mobility, upper extremity, and peer relationships. We used item response theory scoring to generate T-scores for each item bank and 8-item short form. Responsiveness of the item banks and short forms over disease activity states defined by the Juvenile Disease Activity Score (JADAS-3) was evaluated using ANOVA tests for equal variances. Standard error plots were generated for each full bank and corresponding short form. The association between child and proxy dyad responses was assessed using Spearman pairwise correlation coefficients.

Results: 229 patients (67.3% female, median age=13yrs) and 224 parents (70.5% female, median age=12yrs) completed at least one PROMIS form, resulting in 71-78 responses per item bank. Fatigue, mobility, and pain interference full item banks and short forms showed significant responsiveness to JIA disease activity (Figure; all $p<0.05$) for both patient and parent proxy report. Peer relationships, anxiety, depression, and anger had significant responsiveness (all $p<0.05$) over the disease activity levels for parent proxy but not patient report. The upper extremity instrument did not show significant responsiveness for either patient or parent proxy report. Patient and proxy PROMIS short forms exhibited comparable standard error across the range of T-scores to that seen in the full item banks. The pairwise correlations between patient and proxy dyads for the item bank scores were: **anger (r=0.38), anxiety (r=0.36), depression (r= 0.45), fatigue (r=0.65), pain interference (r=0.70), mobility (r=0.55), upper extremity (r=0.49), and peer relationships (r=0.32).**

Conclusion: Our results demonstrate that the 8-item PROMIS pediatric short forms are feasible to complete, responsive to JIA disease activity, and have comparable error to the full item banks for child and proxy report. The moderate associations between patient and proxy report are consistent with prior reports and suggest that administration of both forms should be considered.

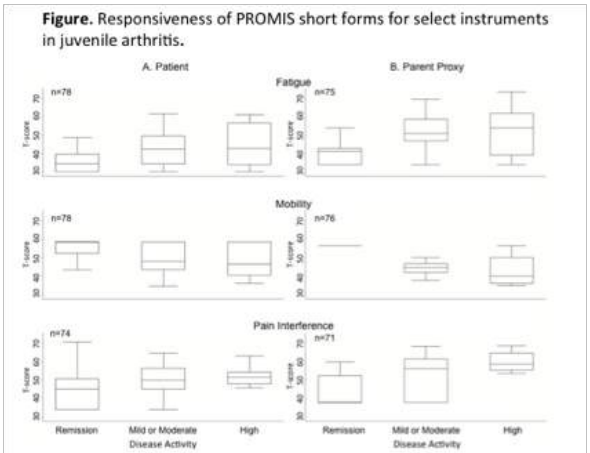

Figure. Responsiveness of PROMIS short forms for select instruments in juvenile arthritis.

Legend. Scores represent T-scores across three levels of juvenile arthritis disease activity as defined by JADAS3 for patients (A) and parent proxies (B). Mean T-score in sample of US children (inclusive of children with common chronic diseases)= 50.

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Abstract Number: 2435

Pregnancy Outcomes in Adult Juvenile Idiopathic Arthritis Patients Treated with Biologic Agents

Katerina Jarosova[1], Katerina Andelova[2], Karel Hejduk[3], Michal Uher[3] and Jiri Vencovsky[4], [1]Institute of Rheumatology, Prague, Czech Republic, [2]clinical, Institute for the Care for Mother and Child, Prague, Czech Republic, [3]Institute of Biostatistics and Analyses, Masaryk University, Brno, Czech Republic, [4]Institute of Rheumatology and Department of Rheumatology, Charles University, Prague, Czech Republic

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Background/Purpose:

Biologic drugs are effective therapeutic option in patients with juvenile idiopathic arthritis (JIA). However, data regarding the use during pregnancy and breastfeeding in adult women with JIA are rare. The purpose of this report is to summarize the pregnancy outcomes in adult female patients with JIA treated with TNF inhibitors (TNFi) and with other biologic agents.

Methods:

Pregnant patients with JIA have been prospectively followed since 2003 to 2015. The length of pregnancy, complications, preterm delivery, birth defects and disease exacerbations after delivery were entered into the database. Patients were treated with TNFi or with rituximab, abatacept and tocilizumab in recommended doses for rheumatoid arthritis. Data on disease activity, safety and doses of used medication were extracted from the Czech national registry of patients treated with biologics (ATTRA).

Results:

JIA patients were diagnosed with RF positive polyarthritis (9), RF negative polyarthritis (10), extended oligoarthritis (7), psoriatic arthritis (1) and arthritis with enthesitis (1). Twenty five live births in 28 pregnancies were observed. The age of

mothers at the onset of pregnancy was 28,1 (range 20 -40) years. Nine patients discontinued biologicals shortly before the pregnancy was confirmed. In 19 cases patients were exposed to biological drugs after conception; infliximab in 4 cases, etanercept in 9, adalimumab in 3, certolizumab in 2 and abatacept in 1. Biologic drugs were administered for 6-8 weeks during pregnancy in 17 cases. One patient who discontinued etanercept was returned on the drug at week 26 because of severe JIA relapse and the drug was administered until the delivery. One patient received etanercept throughout of pregnancy in halved dose due to a persistent activity. Two pregnancies were not planned and both patients were exposed to methotrexate in the first 6 weeks in addition to exposure to rituximab 4 and 8 months before conception.

One patient treated with infliximab had spontaneous abortion at week 7. Repeated pregnancy in this patient with the exposure to infliximab for 4 weeks was successful. Another spontaneous abortion was seen in patient exposed to adalimumab at week 6. There was one still birth terminated at week 11 in a patient on etanercept stopped at week 6 of gestation. All the other pregnancies were uneventful with just one case of hypertension. Gestation was terminated by Caesarean section in six cases (1x hypertension, 2x limited hip movement, 1x non-functional placenta, 1x JIA activity and 1x foetus defective position). There was no preterm delivery.

Birth weight was between 2470- 4000 grams. One child was born with mastocytosis.

Conclusion:

Our data from 28 pregnancies suggest that the use of biologics in the early phases of gravidity in JIA patients is safe and does not affect the gestation duration or the delivery or lead to increased frequency of birth defects.

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Abstract Number: 2436

Views and Prescribing Habits of Pneumocystis Prophylaxis in the Pediatric Rheumatology Community

Matthew Basiaga[1], Alexis Ogdie-Beatty[2] and for the CARRA Investigators, [1]Pediatric Rheumatology, The Children's Hospital of Philadelphia, Philadelphia, PA, [2]Medicine/Rheumatology, University of Pennsylvania, Philadelphia, PA

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Background/Purpose: Pneumocystis pneumonia (PCP) is a potentially devastating opportunistic infection. The incidence of PCP and the risk of adverse events secondary to prophylactic medication in children with rheumatic disease are unknown. As a result, healthcare providers must make the decision about providing prophylaxis on a case by case basis without formal guidelines. The objective of this study was to describe current prescribing habits of PCP prophylaxis among pediatric rheumatologists. We hypothesized that significant variation exists in the prescribing of PCP prophylaxis.

Methods: We performed a cross sectional survey of pediatric rheumatologists in the Childhood Arthritis & Rheumatology Alliance (CARRA). CARRA is an alliance of pediatric rheumatologists in the United States and Canada. A questionnaire was administered using REDCAP, a secure web based research platform. The anonymous survey ascertained basic demographic and PCP prophylaxis prescribing habits. After approval by the IRB and CARRA, the questionnaire was piloted and then distributed via an email in May 2015. A reminder email was sent 2 weeks later to members who had not responded to the questionnaire. Descriptive analysis was performed using STATA v 13.1 (Stat Corp; College Station TX).

Results: The questionnaire was sent to 280 pediatric rheumatologists and 76 (27%) responded; results are shown in Table. Most respondents practice at an academic medical center (N=74, 97%) and 66 (87%) of pediatric rheumatologists prescribe PCP prophylaxis. Only nine (12%) report institutional prescribing guidelines. The most common indications listed for prescribing prophylaxis were for use of cyclophosphamide (42%) or a diagnosis of Granulomatosis with Polyangiitis (38%). Trimethoprim-sulfamethoxazole was the most common first line prophylactic agent prescribed (N=68, 91%). Indications for initiation of PCP prophylaxis are diverse. Thirty-three (43%) respondents indicated prescribing in the setting of a specific medication, thirty-seven (49%) for a specific combination of medications, twenty-six (34%) a specific laboratory threshold and thirty-one (41%) for a specific disease.

Conclusion: We found significant variation in prescribing habits of PCP prophylaxis between pediatric rheumatologists in the United States and Canada. While most providers prescribe prophylaxis, we found that 13% do not. Common reasons given why prophylaxis was not prescribed include a perceived low risk of infection and that they have never seen a PCP infection before in practice. Future studies aimed at identifying the incidence of PCP in children with rheumatic disease and the incidence of adverse events associated with the prophylactic agents are needed to inform the development of evidence based guidelines for PCP prophylaxis prescribing.

Table. Characteristics of Pediatric Rheumatology Respondents and Responses (n=76)

Characteristic	N (%)
Years in Practice	
Currently in training - 5 years	30 (39%)
6 – 10 years	11 (14%)
11 – 20 years	15 (20%)
21 – 30 years	15 (20%)
30 + years	5 (6%)
Average number of patients seen per week	
0–15	24 (32%)
16-30	36 (48%)
31-45	9 (12%)
46-60	5 (7%)
60+	1 (1%)
What prompts you to start PCP prophylaxis?	
Specific medication monotherapy	33 (43%)
Specific medication combination	37 (49%)
Laboratory value threshold	26 (34%)
Specific disease	31 (41%)
Which specific monotherapy prompts you to prescribe PCP prophylaxis?	
Chronic Glucocorticoids > 20 mg daily	1 (1%)
Chronic Glucocorticoids ≥ 2 mg/kg daily	4 (5%)
Methotrexate	1 (1%)
Rituximab	7 (9%)
Mycophenolate Mofetil	1 (1%)
Cyclophosphamide	31 (41%)
Which specific medication combination prompts you to prescribe PCP prophylaxis?	
TNF Inhibitor and Methotrexate	1 (1%)
TNF Inhibitor and Glucocorticoids	2 (3%)
TNF Inhibitor and Azathioprine	2 (3%)
TNF Inhibitor and Calcineurin Inhibitor	2 (3%)
Glucocorticoids and:	
Rituximab	12 (16%)
Cyclophosphamide	33 (43%)
Calcineurin Inhibitor	5 (7%)
Methotrexate	4 (5%)
Azathioprine	4 (5%)
Mycophenolate Mofetil	7 (9%)
Anti-IL1 Therapy	2 (3%)
Anti-IL6 Therapy	3 (4%)
Which laboratory threshold prompts you to prescribe PCP prophylaxis?	
Absolute Neutrophil Count < 1000 / μL	4 (5%)
Absolute Lymphocyte Count < 1000 / μL	15 (20%)
CD4 Count < 200 / μL	11 (14%)
Which specific disease prompts you to prescribe PCP prophylaxis?	
Juvenile Dermatomyositis	6 (8%)
Systemic Lupus Erythematosus	7 (9%)
Juvenile Idiopathic Arthritis	1 (1%)
Granulomatosis with Polyangiitis	27 (36%)
Other Vasculitis	8 (11%)
When do you stop PCP prophylaxis	
Discontinuation of medication that prompted initiation	49 (65%)
Improvement in clinical condition	2 (3%)
Improvement in laboratory value that prompted initiation	15 (20%)

Legend: Responses from Pediatric Rheumatology physicians describing PCP prophylaxis prescribing habits. PCP, Pneumocystis carinii (jiroveci) Pneumonia; TNF, Tumor Necrosis Factor

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Abstract Number: 2437

Experience with Tocilizumab for Treatment of 56 Children with Systemic Juvenile Idiopathic Arthritis in the German JIA Biologics Register

Gerd Horneff[1], Gerd Ganser[2], Johannes Peter Haas[3], Toni Hospach[4], Ralf Trauzeddel[5], Hans-Iko Huppertz[6], J B. Kuemmerle-Deschner[7], Kirsten Minden[8] and BIKER Registry Study Group, [1]Asklepios Clinic Sankt Augustin, Sankt Augustin, Germany, [2]Pediatric Rheumatology, Sankt Josef Stift, Sendenhorst, Germany, [3]German Centre for Rheumatology in Children and Young People, Garmisch-Partenkirchen, Germany, [4]Pediatrics, Olgahospital, Klinikum Stuttgart, Stuttgard, Germany, [5]HELIOS Klinikum Berlin-Buch Klinik fuer Kinder- und Jugendmedizin, Berlin, Germany, [6]PRINTO, IRCCS G. Gaslini, Genoa, Italy, [7]Pediatrics, University Hospital Tuebingen, Tuebingen, Germany, [8]DRFG, Berlin, Germany

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Background/Purpose: Tocilizumab (TOC) has become a valuable option for treatment of systemic juvenile idiopathic arthritis (sJIA), which significantly improved the outcome of patients. The aim of the German BIKER registry is surveillance of biologics. The purpose of this interim analysis is to evaluate the efficacy and safety under practical conditions in childhood.

Methods: Documentation of pts' characteristics, pervious/concomitant therapy, disease activity parameters and adverse events. Treatment with TOC was followed prospectively. Efficacy was assessed by PedACR criteria and JADAS10 remission and minimal disease activity (MDA). Safety was compared to a cohort of pts treated with sJIA methotrexate only and a cohort with poly JIA treated with TOC.

Results: 56 JIA pts (54% female) started TOC. The mean/median age at baseline was 9.3/9.7, disease duration 4.9/4.1 years. 44 previous biologic therapies were performed 3 pts (Anakinra 14, Canakinumab 1,Etanercept 25, Adalimumab 3, Abatacept 1). 26 pts were biologics naïve. The initial concomitant treatment in consisted of NSAIDs 63.3%, steroids 70%, methotrexate 63.3%, other DMARDs (n=6).

Clinical response rates are given in table 1. Reported adverse events were compared to a cohort of 79 pts with polyarticular JIA and 58 sJIA pts receiving MTX onlym, both recruited and followed in parallel. 122 adverse events (AE, 83.3/100 PY) were reported, 12 (9.0/100 PY) were serious. Infections were the most frequent AE (48), 3 were serious. Opportunistic infections including TB did not occur. There were 4 events of macrophage activation syndrome in sJIA pts with TOC, none in polyJIA and 1 in sJIA controls. All resolved. Rates of other adverse events of special interest are shown in table 2. Therapy was discontinued in 32 (57%) sJIA pts due to remission (15/27%), inefficacy (7/13%), patient request (5/9%), intolerance (4/7%) and other (1/2%). No patients died.

Conclusion: sJIA pts achieved high ACR response rates upon treatment with TOC. JADAS-MDA was frequently reached. JADAS remission was achieved in about half of pts. While more serious adverse events were reported in sJIA than in controls, overall tolerability was good. Only a small portion discontinues therapy because of intolerance or side effects while remission is the leading cause of discontinuation of treatment.

Table 1: Treatment response until month 12

	Baseline	Month 3	Month 6	Month 12
Pts with active joints (n/%)	34/64.2%	7/22.3%	10/27.8%	9/30%
Pts with organomegaly (n/%)	5/10.2%	1/3.3%	0	0
Pts with serositis (n/%)	3/6.1%	0	0	0
Pts with fever (n/%)	2/4.1%	0	0	1/3.4%
JADAS 10 (mean/median)	8.7/9.4	4.9/4.5	2.2/0.7	3.5/1.0
JADAS-MDA (n/%)	12/29.3%	12/50.0%	24/80%	118/66.7%
JADAS-Remission (n/%)	7/17.1%	7/29.2%	17/56.7%	14/51.9%
JIAACR30 (%)	n.a.	66.7%	59.5%	67.7%
JIAACR50 (%)	n.a.	63.3%	54.1%	61.3%
JIAACR70 (%)	n.a	53.3%	54.1%	54.8%
JIAACR 90 (%)	n.a.	40.0%	37.8%	41.9%

Table 2: Incidence of adverse events of special interest

	sJIA TOC (n=56; 73 PY)	pJIA TOC (n=78; 59 PY)	RR (95%CI)	P (Wald-test)	sJIA MTX (n=58; 124 PY)	RR (95%CI)	P (Wald-test)
SAE, all n (rate/100PY)	10(13.7)	2(3.4)	4.04 (0.9-18.4)	0.07	3(2.4)	5.7(1.6-21)	0.008
SAE-Infection; n (rate/100PY)	3(4.1)	1(1.7)	2.4 (0.3-23.3)	0.69	0	¥	
Hypersensitivity; n (rate/100PY)	3(4.1)	1(1.7)	2.4 (0.3-23.3)	0.44	1(0.8)	5.1 (0,5-49)	0.16
MAS; n (rate/100PY)	4(5.5)	0	¥		1(0.8)	6.8(0.8-619	0.09
Cytopenias; n (rate/100PY)	2(2.7)	3(5.1)	0.5 (0.1-3.2)	0.49	0	¥	
Hepatic events; n (rate/100PY)	1(1.4)	0	¥		5/(4.0)	0.3(0.0-2.9)	0.32

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Abstract Number: 2438

Clinical Examination of the Temporomandibular Joint; A Eurotmjoint Initiative

Bernd Koos[1], Peter Stoustrup[2], Lynn R. Spiegel[3], Nikolay Tzaribachev[4], Troels Herlin[5], Thomas Klit Pedersen[6] and **Marinka Twilt**[7], [1]Orthodontics, University of Rostock, Rostock, Germany, [2]Section of Orthodontics, University of Aarhus, Aarhus C, Denmark, [3]Rheumatology/Pediatrics, The Hospital for Sick Children, Toronto, ON, Canada, [4]Pediatric Rheumatology, Center for Rheumatic Diseases, Bad Bramstedt, Germany, [5]Department of Pediatrics, Århus University Hospital Skejby, Århus, Denmark, [6]orthodontics, Aarhus University Hospital/Dental school, Aarhus, Denmark, [7]Pediatric Rheumatology Clinic, Department of Pediatrics, Aarhus University Hospital, Aarhus, Denmark

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Session Type: ACR Poster Session C

Background/Purpose:

Arthritis of the temporomandibular joint (TMJ) in patients with Juvenile Idiopathic Arthritis (JIA) is increasingly recognized. In the last decade, studies report that the frequency of TMJ involvement in JIA patients is between 45-100% depending on the population examined and the diagnostic tool used. The gold standard to diagnose TMJ arthritis is use of Gadolinium-enhanced MRI. Clinical symptoms have been shown to be unreliable for diagnosis of TMJ arthritis, however their usefulness in monitoring during the disease course needs to be determined. This study was undertaken by the Clinical Recommendation group of euroTMjoint, an international network established in 2010 to enhance mutidisciplinary, multicenter TMJ research in JIA. This study describes the reliability and reproducibility of a clinical tool that can be implemented in any practitioner.

Methods:

A clinical tool was developed based on the results of a Delphi study and expert panel. The examined tool items were: TMJ pain reported by patient; TMJ tenderness on palpation; mandibular deviation at maximal mouth opening; maximal mouth opening capacity; vertical incisal overlap; frontal facial asymmetry; facial profile. 33 patients with JIA were examined eight times, twice by four independent examiners; 2 pediatric rheumatologists and 2 orthodontists with experience in clinical examination. An independent experienced orthodontist instructed all examiners on the use of the recommendation tool. The examiners were blinded to each other's results.

Results:

The time to perform the examination differed significantly between investigators irrespective of their professional background (median 89-179 sec, $p<0.0001$), however all examiners were able to perform the exam within the 3 minutes limit. The intra- and inter-agreement was lower for questions, such as absence or present of pain, than objective measurements. Comparing pediatric rheumatologists with the more experienced orthodontists revealed a high reproducibility for the measurement items maximal mouth opening and vertical incisal overlap (Spearman rho respectively 0.81 and 0.55), indicating these items can be used by inexperienced examiners after instructions. Frontal facial asymmetry showed the least reproducibility among the items (kappa 0,23).

Conclusion:

Clinical signs and symptoms of TMJ arthritis remain controversial for diagnostic purposes; however this study does show a fair to moderate agreement for all items and a moderate to almost perfect agreement for the measured items. This study shows the possible applicability of this tool in the rheumatology clinic during the course of the disease.

Disclosure: B. Koos, None; **P. Stoustrup**, None; **L. R. Spiegel**, None; **N. Tzaribachev**, Pfizer, UCB and Roche, 2; **T. Herlin**, None; **T. K. Pedersen**, None; **M. Twilt**, None.

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Abstract Number: 2439

Methotrexate Failure in Pediatric Uveitis

Courtney McCracken[1], Steven Yeh[2], Kirsten Jenkins[3], Daneka Stryker[4], Steven Tommasello[5], Curtis Travers[1], Scott R. Lambert[2], Carolyn Drews-Botsch[6] and Sheila T. Angeles-Han[1,2,3], [1]Pediatrics, Emory University School of Medicine, Atlanta, GA, [2]Ophthalmology, Emory University School of Medicine, Atlanta, GA, [3]Children's Healthcare of Atlanta, Atlanta, GA, [4]Pediatrics, Emory University School of Medicine and Children's Healthcare of Atlanta, Atlanta, GA, [5]University of Alabama, Birmingham, AL, [6]Epidemiology, Emory University School of Public Health, Atlanta, GA

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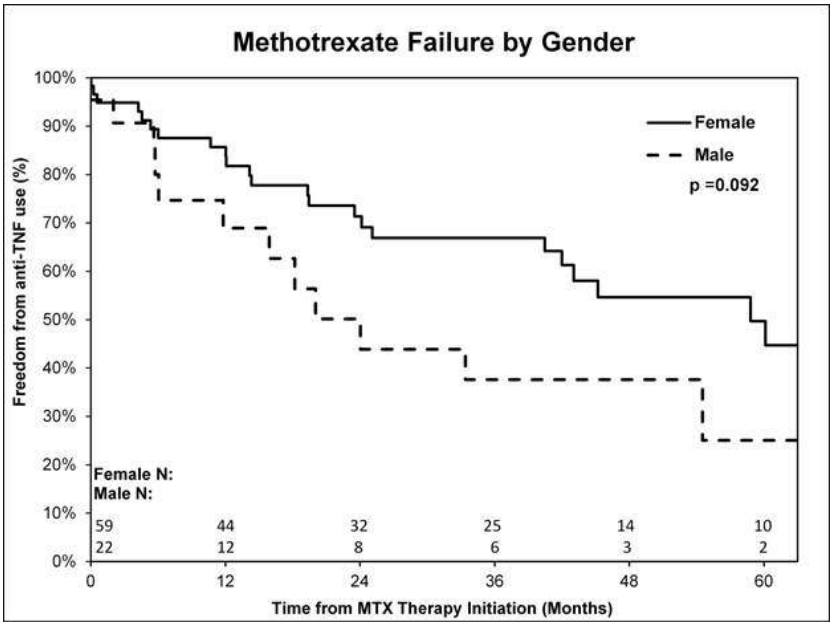
Background/Purpose: Pediatric uveitis can lead to ocular complications and vision loss. Treatment consists of steroid drops, methotrexate (MTX), and anti-tumor necrosis factor (TNF) drugs. Only 50-75% of children respond to methotrexate. Our aim was to describe the use and timing of MTX and anti-TNF drugs in pediatric uveitis.

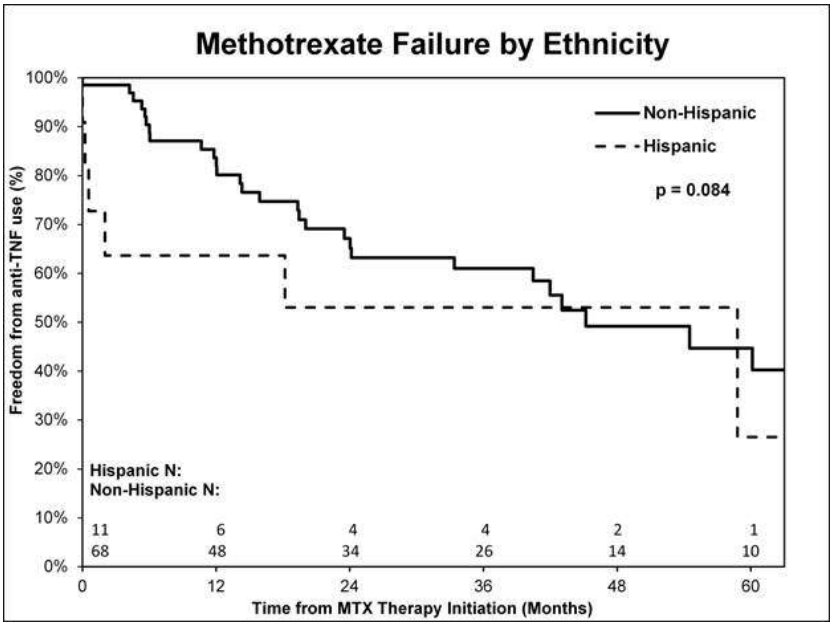
Methods: We reviewed medical records of 104 children with pediatric uveitis. We collected demographic and clinical data, and timing of initial MTX use and subsequent anti-TNF use following uveitis diagnosis. MTX failure was defined as the addition of anti-TNF agents for the treatment of uveitis. Time to MTX failure was described using survival analysis modeling strategies.

Results: There were 59 children with JIA-associated uveitis (JIAU) and 45 with other forms of uveitis (U). Of these, 85 (82%) were treated with MTX. The majority were female (69%), Caucasian (61%) or African American (29%). Most had anterior disease (76%), bilateral involvement (71%), and ocular complications (65%), commonly synechiae (45%), cataracts (40%), and macular edema (24%). More than half (51% JIAU; 60% U) were treated with MTX within 6 months of diagnosis. For children with JIAU, MTX was initiated either prior to uveitis diagnosis (27%) or within 6 months (33%).

Forty one (48%) required the addition of anti-TNF agents for uveitis at a median of 16 months following MTX use, and 2.2 years following uveitis diagnosis. The majority (60%) initially received infliximab, and 20% required a second anti-TNF drug. Kaplan-Meier estimates suggest that 13% need anti-TNF agents within 6 months of MTX treatment; 16% by 1 year; 36% by 2 years and 59% by 5 years. Data suggests that one year after MTX therapy, fewer females than males required anti-TNF agents (8/59 (14%) vs. 6/22 (27%) $p<0.1$) [Figure1], and more Hispanic children were treated with anti-TNF agents compared to non-Hispanics (4/11 (36%) vs. 10/68 (15%) $p<0.1$) [Figure2]. Timing of initial MTX use following uveitis diagnosis, type of uveitis, race, ANA positivity, complications, and age at uveitis diagnosis did not predict timing of MTX failure.

Conclusion: Most children with uveitis require therapy beyond corticosteroid treatment. Up to 82% are treated with MTX within 6 months of diagnosis, and almost 50% require an anti-TNF agent within 2.5 years of diagnosis. One in five children are treated with a second anti-TNF drug. Male gender and Hispanic ethnicity may be associated with severe uveitis requiring biologic therapy. Further elucidation of the factors associated with severe uveitis may help with optimal early treatment of disease.





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Abstract Number: 2440

Using Patient-Relevant Variables to Describe the Disease Course in Children with Juvenile Idiopathic Arthritis

Jaime Guzman[1], Andrew Henrey[2], Thomas Loughin[2], Roberta Berard[3], Natalie Shiff[4], Roman Jurencak[5], Susanne Benseler[6], Lori B. Tucker[7] and ReACCh-Out Investigators, [1]Rheumatology, Division of Rheumatology, BC Children's Hospital, Vancouver, BC, Canada, [2]Statistics and Actuarial Science, Simon Fraser University, Burnaby, BC, Canada, [3]Children's Hospital of Western Ontario, London, ON, Canada, [4]Pediatric Rheumatology, University of Saskatchewan, Saskatoon, SK, Canada, [5]University of Ottawa, Ottawa, ON, Canada, [6]Alberta Children's Hospital Research Institute/University of Calgary, Calgary, AB, Canada, [7]Rheumatology, BC Children's Hospital, Vancouver, BC, Canada

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Background/Purpose: To define distinct disease course groups among children with Juvenile Idiopathic Arthritis (JIA) based on observed changes in quality of life, pain, medication requirements, medication side-effects and active joint counts (AJC) during the first 5 years of the disease. These variables were prioritized by patients, parents and clinicians in a previous study.

Methods: We used data from the Research in Arthritis in Canadian Children emphasizing Outcomes (ReACCh-Out) prospective inception cohort. We included 618 children newly diagnosed with JIA between 2005 and 2010 with information for at least 6 of 8 study visits within the first 5 years after diagnosis. Health-related quality of life and pain were measured with 10 cm visual analogue scales. Each current medication was given a weight and weights were added to obtain a medication requirements score. Medication side effects were reported using the Juvenile Arthritis Quality of Life Questionnaire and were weighted according to how frequently they were experienced by the child to obtain a side-effects score. AJC were reported by the attending pediatric

rheumatologist. We grouped patients by course using multivariable cluster analysis and K-means clustering. Silhouette coefficients, R-Square statistics and clinical judgment were used to select the ideal number of clusters. The frequency of each disease course was described by JIA category.

Results: Four clusters provided the best discrimination: 1) Mild (43.0% of children)-almost normal quality of life throughout the disease course with initial mild pain and low AJC requiring minimal treatment, followed by normalization; 2) Moderate (33.7%)-moderate initial impact on quality of life and mild to moderate pain and AJC, followed by normalization; 3) Severe Controlled (11.6%)-moderate initial impact on quality of life and moderate pain levels with high AJC requiring aggressive treatment, followed by normalization; 4) Severe Persisting (11.6%)-persisting mayor impact on quality of life and moderate pain with moderate decreasing AJC, but ongoing treatment needs and side-effects. Children with oligoarthritis most often followed a Mild course. Almost half the children with RF negative polyarthritis, systemic and psoriatic JIA followed a Moderate course. Children with RF positive polyarthritis most often followed a Severe Controlled course. The Severe Persisting course was observed in all JIA categories but it was infrequent in systemic JIA and oligoarthritis.

Table: Proportion of children in each JIA category stratified by disease course cluster

JIA Category	Mild	Moderate	Severe Controlled	Severe Persisting
Oligoarthritis (n=228)	68.4	24.6	0.9	6.1
RF-negative polyarthritis (n=130)	21.5	46.9	17.7	13.8
Enthesitis-related (n=81)	37.0	29.6	14.8	18.5
Systemic (n=47)	23.4	48.9	25.5	2.1
Psoriatic (n=38)	36.8	47.4	2.6	13.2
RF-positive polyarthritis (n=26)	3.8	23.1	61.5	11.5
Undifferentiated (n=68)	38.2	29.4	8.8	23.5

Conclusion: Using patient-relevant variables the course of JIA can be described by four disease course groups with two of them reflecting a severe disease course, one that responded to treatment despite severe initial presentation and one with persisting impact on quality of life and pain despite moderate decreasing AJC. JIA category alone does not predict disease course.

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Abstract Number: 2441

Serum 14-3-3η Is Present in JIA and Is Not Associated with RF+ Polyarthritis

Alan M. Rosenberg[1], Walter Maksymowych[2], Yuan Gui[3] and Anthony Marotta[3], [1]Department of Pediatrics, University of Saskatchewan, Saskatoon, SK, Canada, [2]Department of Medicine, University of Alberta, Edmonton, AB, Canada, [3]Augurex Life Sciences Corp., Vancouver, BC, Canada

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Background/Purpose: Juvenile Idiopathic Arthritis (JIA) is a collective term used to denote clinically discrete subtypes, which include: Enthesitis-related arthritis, Oligoarthritis, Polyarthritis, Psoriatic arthritis, Systemic arthritis and unclassified arthritis. Polyarthritis is further categorized according to rheumatoid factor (RF) status. The International League of Associations for Rheumatology (ILAR) has devised classification criteria of JIA with specific exclusion criteria and its diagnosis is reliant upon clinical symptoms. While laboratory tests like CBC, CRP, ESR, RF, ANA, and anti-CCP add prognostic value, they have limited utility for diagnosis. Thus, markers that can assist in sub-typing JIA at presentation are imperative as this can influence patient management strategy. 14-3-3η is a joint derived, rheumatoid arthritis (RA) specific marker that informs radiographic damage. The

purpose of this study was to examine the expression of 14-3-3η in the sub-types of JIA, and to assess whether a relationship existed between 14-3-3η and RF+ polyarthritis.

Methods: 14-3-3η serum levels were measured in 60 JIA patients as shown in Table 1. One-way ANOVA analysis was used to determine if group differences existed. 14-3-3η positivity was defined using the adult RA diagnostic cut-off of ≥0.19 ng/ml. The Fisher's Exact test was employed to assess the relationship between RF and 14-3-3η positivity in polyarthritis patients.

Results: ANOVA analysis revealed differences in 14-3-3η serum levels between the groups. Patients with RF positive polyarticular disease had significantly higher serum 14-3-3η levels than the other groups. 14-3-3η positivity analysis revealed that 30% of the oligoarthritis, 53% of RF negative polyarticular, 50% of psoriatic and 57% of patients with systemic arthritis were positive for 14-3-3η. Although there were only four patients in the enthesitis group, none of them were 14-3-3η positive. Fisher's Exact testing returned no significant association between RF and 14-3-3η positive status (p-value = 0.35) indicating that the two markers may uniquely inform patient profiles within subtypes of JIA, especially since 53% of RF negative polyarticular JIA patients had positive 14-3-3η tests.

	Enthesitis	Oligo	Poly, RF-	Poly, RF+	Psoriatic	Systemic
# of Pts	4	21	19	7	2	7
Median (QR)	0.06 (0.02-0.09)	0.10 (0.02-0.23)	0.19 (0.02-0.33)	1.83 (0.09-10.59)	0.20 (0.01-0.38)	0.20 (0.01-1.54)
Mean (SD)	0.06 (0.04)	0.23 (0.35)	0.29 (0.38)	4.69 (6.51)	0.20 (0.26)	0.55 (0.69)
% Positivity (n)	0% (0)	30% (7)	53% (10)	71% (5)	50% (1)	57% (4)
ANOVA	p=0.0008					

Conclusion: 14-3-3η is a joint-derived mechanistic marker that up-regulates factors that are involved in joint damage pathogenesis. While RF+ polyarthritis patients had higher 14-3-3η levels, in JIA, 14-3-3η expression has no significant association with RF positivity and may provide insights into biochemical processes that uniquely inform JIA sub-typing.

Disclosure: A. M. Rosenberg, None; **W. Maksymowych**, Augurex Life Sciences, 5; **Y. Gui**, Augurex Life Sciences Corp, 3; **A. Marotta**, Augurex Life Sciences Corp, 3.

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Abstract Number: 2442

The Family Journey to Diagnosis with Systemic Juvenile Idiopathic Arthritis As Evidenced through Changing Social Media Presence

Renee F Modica[1], Kathleen G Lomax[2], Pamela Batzel[3], Leah Shapardanis[3], Kimberly A Compton[3] and Melissa E Elder[4], [1]UF Health Shands Children's Hospital, Gainesville, FL, [2]Medical Affairs, Immunology and Dermatology, Novartis Pharmaceuticals Corporation, East Hanover, NJ, [3]TREATO, Princeton, NJ, [4]Pediatrics, Univ of Florida, Gainesville, FL

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Background/Purpose:

Patients with systemic juvenile idiopathic arthritis (SJIA) frequently encounter delays from symptom onset to SJIA diagnosis (dx), partly due to the broad differential of fever of unknown origin, lack of provider recognition, and its rarity. Given this typical

diagnostic delay, families often seek multiple medical opinions and post to social media about their frustration. This linguistic analysis observed the changing language and social media posting behavior of parents during the time period to SJIA dx.

Methods: US-hosted English-language public social media sites were manually reviewed by linguists to identify posts consistent with an SJIA dx, divided into pre- and post-dx periods, with a linguistic analysis.

Results:

4221 posts with a date range of 7/10/01-1/7/15 on 108 sites were reviewed from 1/11-3/12/15. 283 posts (all unique authors) consistent with pre-dx SJIA patients (pts), and 722 posts (381 unique authors) involving post-SJIA dx pts were found. Parents of pre-dx pts looked to social media for answers and to share status updates, focusing on 3 site types: natural therapy forums (39%), Facebook (27%), and disease-specific forums (17%). Posts in the early pre-dx phase were characterized by language showing confidence in the healthcare provider (HCP) and trust in parental instincts, with frequent expressive language. As time passed without a dx, posts showed parents beginning to doubt their intuition and faith in the HCP's ability to dx their child. Later posts also had more objective narratives of symptoms observed with less of a child-centered emotional focus and reduced-to-absent expressive language as parents became caregivers. At later pre-dx stages, caregivers continued to post most often to alternative/natural parenting forums (22%) and Facebook (18%). Once dx of SJIA became clear, caregivers moved to disease specific websites–although they still used Facebook. At the time of dx, caregivers used dry straightforward language in their "announcement" posts. After dx, caregivers posted about renegotiating HCP relationships and usually did not explicitly solicit advice but asked for other parents' experiences, analogies and anecdotes. With initiation of treatment, posts began to show a slow return of expressive language and understanding of their "new normal."

Conclusion:

Caregiver presence on social media sites provides key indicators about the stages in the diagnostic journey for SJIA pts. Analysis of posts reveals the often delayed diagnosis of SJIA, its complex course and impact on relationships of pts and caregivers with their HCP. Caregivers use different language, references and websites pre-dx than post-dx and demonstrate gaps in caregiver/HCP communication. Importantly, post-dx parent language in social media posting did not return to the original linguistic parent frame prior to disease onset. This diagnostic process changes the parents – not just the child, as evidenced by social media posts. Furthermore, the parents' role changes from parent to caregiver, and this role fluctuates throughout the disease course and treatment. They do continue to actively develop understanding of SJIA and treatment options through social media.

Disclosure: R. F. Modica, None; **K. G. Lomax**, Novartis Pharmaceutical Corporation, 3; **P. Batzel**, Novartis Pharmaceutical Corporation, 9; **L. Shapardanis**, Novartis Pharmaceutical Corporation, 9; **K. A. Compton**, Novartis Pharmaceutical Corporation, 9; **M. E. Elder**, None.

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Abstract Number: 2443

Pediatric Tele-Rheumatology: A Pilot Project to Assess Accuracy of Physical Examination Findings and Diagnostic Concordance at a Distance

Michael Henrickson[1], Jody Raugh[2], Kelsey Hofacer[3] and Adam Furnier[4], [1]Division of Rheumatology, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, [2]Occupational and Physical Therapy, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, [3]Center for Telehealth, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, [4]Quality Improvement Systems, Cincinnati Children's Hospital Medical Center, Cincinnati, OH

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Background/Purpose: Telemedicine (TM) offers a strategic means of extending limited clinical pediatric rheumatology (PR)

workforce capacity to improve access to care for patients in remote locations. Tele-rheumatology (TR) often depends on a remote site provider to convey physical examination (PE) findings. While adult TR has diagnostic accuracy of 97% compared to in-person consultations, there are no published data for pediatric TR PE or diagnostic accuracy. This cross-sectional observational study assessed the accuracy of PE findings in 10 new PR TR consultations. Pragmatically, we envision a service delivery model involving initially inexperienced musculoskeletal examiners at remote locations. Hence, our aim was to determine the reproducibility of PE findings and diagnostic agreement. The primary outcome was comparison of the physician TR and remote examiner PE findings, and diagnostic concordance.

Methods: The physician conducted the interview within our hospital at a dedicated TM suite, then guided and documented the remote provider's PE. This examiner, a developmental pediatrics physical therapist, was physically located with the patient at our institution's PR clinic. We deliberately sought an examiner naïve to PR musculoskeletal examination. Knowing PE skills improve with repetition, we restricted the study to 10 patients to limit this effect. Patient selection focused on ensuring a variety of presenting complaints and ages. The initial 30% knew they had TR consultation scheduled; the remainder was unaware. We sought parental TM satisfaction after each session via on-line survey and/or in-person interviews. We used a Likert scale to determine the impact revised PE findings had on clinical decision-making.

Results: We identified 26 PE errors in this cohort of broad age range (14 months to 16 years). The table summarizes concordance. PE errors mainly involved biomechanical disorders with or without generalized hypermobility (7, 2) and musculoskeletal abnormalities (5). Weighted averages for diagnostic concordance varied: overall (37%), biomechanical disorders (31%), inflammatory diseases (83%) and pain amplification (0%). The practical impact on decision-making (20% none, 30% minimal, 50% moderate, 0% marked) affected 8 patients: physiotherapy orders (5), and one patient each for lab/x-ray, medication options, and additional consultation. Completed surveys (50%) indicated 100% agreed or strongly agreed with using TR again, with overall satisfaction of 100%.

Concordance for PE Findings and Diagnosis

	PE Findings Identified		Diagnostic Concordance (%)
	MD only	Both Examiners (PT & MD)	
Acrocyanosis		1	100
Complex regional pain syndrome	1	0	0
Hypermobile type Ehlers Danlos syndrome	2	4	67
Oligoarticular JIA (TMJs, peripheral joints)		2	100
Other biomechanical disorders (iliotibial band, ligament laxity, patellofemoral instability)	7	0	0
Other physical findings			
General (escutcheon)	1	0	0
Musculoskeletal (flexion contracture, joint crepitus or tenderness, malocclusion, and muscle atrophy)	5	0	0
Periodic fever syndrome		2	100
Reactive arthropathy	1	1	50

Conclusion: Pediatric TR requires a remote site examiner trained in musculoskeletal PE with an emphasis on biomechanical abnormalities which are prevalent in PR. Concerns about reliably identifying juvenile arthritis do not appear to be a major risk of TR, although errors did occur in detecting all involved joints. Pediatric TR can provide access to clinical care with high levels of satisfaction.

Disclosure: M. Henrickson, None; **J. Raugh**, None; **K. Hofacer**, None; **A. Furnier**, None.

Abstract Number: 2444

Accelerometer-Assessed Daily Physical Activity in Relation to Pain Cognitions and Quality of Life in Juvenile Idiopathic Arthritis

Mette Noergaard[1], Johanne Lomholt[2], Mikael Thastum[2], Morten Herlin[3], Marinka Twilt[4] and Troels Herlin[4], [1]Department of Physiotherapy, Aarhus University Hospital, Aarhus, Denmark, [2]Psychology and Social Sciences, Aarhus University, Aarhus, Denmark, [3]Pediatrics, Aarhus University Hospital, Aarhus, Denmark, [4]Pediatric Rheumatology Clinic, Department of Pediatrics, Aarhus University Hospital, Aarhus, Denmark

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Background/Purpose:

Juvenile Idiopathic Arthritis (JIA) has been associated with decreased physical activity (PA). However, accurate, objective measurements of PA related to potential factors limiting PA in children with JIA have been lacking. Joint pain is a primary symptom of JIA and pain has been shown to be a significant predictor of impaired physical and psychosocial function, affecting the quality of life in these patients. Therefore, it could be anticipated that pain would explain the decreased PA in JIA. The use of pain-coping strategies and pain-specific health beliefs in children with JIA has previously been found to be associated with both clinical and experimental pain reports. Beliefs about a stressor such as pain are thought to influence an individual's coping responses. We have previously reported that pain-related beliefs were significantly associated with pain in children with JIA even after controlling for disease-related variables and pain coping.

The aim was to relate accelerometer-assessed PA (PA-Acc) to disease activity, pain intensity, the use of pain coping strategies, pain-related health beliefs and health-related quality of life (HRQoL) measures in children with JIA.

Methods:

PA was assessed using the hip-worn GT1M Actigraph accelerometer during wakening hours for one week, providing at least 3 separate days of each 8 hours of valid recording accelerometry in JIA patients using 10 sec. count-time periods (epochs). Demographic, disease and pain measurements, pain coping strategies assessed with the Pain Coping Questionnaire (PCQ), pain-specific beliefs assessed with the Survey of Pain Attitudes for Children (SOPA-C), and HRQoL assessed with the Pediatric Quality of Life Inventory (PedsQL), arthritis module, were simultaneously obtained.

Results:

Accelerometer data of 61 JIA patients (60.7%) were available for analysis. Accelerometer values of mean counts per minute (c/min), minutes with moderate and high PA (>1000 c/min) and high PA (>2500 c/min) were significantly lower in patients compared to normative values. Disease activity, expressed as JADAS-27, was negatively correlated to accelerometer counts. However, PA-Acc was neither correlated to pain intensity, pain coping strategies, nor to HRQoL. Accelerometer counts were significantly correlated to the pain-specific belief that one is in control of pain ('Control'), but not to other pain-specific beliefs. In a hierarchical regression analysis 'Control' did not explain a significant unique part of the variance when controlling for JADAS-27, whereas JADAS-27 significantly explained 27% of the variance in moderate and high intensity PA when controlling for the health belief 'Control'.

Conclusion:

Accelerometer-assessed PA-levels of JIA-children were significantly lower than those of normative controls and were negatively correlated to JADAS-27. Levels of PA-Acc were not correlated to pain intensity, pain coping strategies, or HRQoL , but significantly correlated to the pain-specific belief that one is in control of pain ('Control').

Disclosure: M. Noergaard, None; **J. Lomholt**, None; **M. Thastum**, None; **M. Herlin**, None; **M. Twilt**, None; **T. Herlin**, None.

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Abstract Number: 2445

Development and Usability Testing of an Ipad-Based Psycho-Educational Game for Children with Juvenile Idiopathic Arthritis and Their Parents

Jennifer N. Stinson[1], Adam M. Huber[2], Mark Connelly[3], Nadia Luca[4], Lynn R. Spiegel[5], Argerie Tsimicalis[6], Stephanie Luca[7], Roberta Berard[8], Julie Barsalou[9], Sarah Campillo[10], Paul Dancey[11], Ciarán M. Duffy[12], Brian Feldman[13], Nicole Johnson[4], Patrick McGrath[14], Natalie J. Shiff[15], Shirley M Tse[16], Lori B. Tucker[17] and J. Charles Victor[18], [1]Anesthesia and Pain Medicine, The Hospital for Sick Children, Toronto, ON, Canada, [2]Pediatric rheumatology, IWK Health Centre, Halifax, NS, Canada, [3]Psychology, University of Kansas Medical Center, Kansas City, KS, [4]Pediatrics/Alberta Children's Hospital, Department of Pediatrics/University of Calgary, Calgary, AB, Canada, [5]Rheumatology/Pediatrics, The Hospital for Sick Children, Toronto, ON, Canada, [6]McGill University, Montreal, QC, Canada, [7]The Hospital for Sick Children, Toronto, ON, Canada, [8]Children's Hospital of Western Ontario, London, ON, Canada, [9]CHU Sainte-Justine, Université de Montréal, Montreal, QC, Canada, [10]Rheumatology, Montreal Children's Hospital, Montreal, QC, Canada, [11]Health Science Centre, Memorial University of Newfoundland, St Johns, NF, Canada, [12]Children's Hospital of Eastern Ontario and University of Ottawa, Ottawa, ON, Canada, [13]Division of Rheumatology, The Hospital for Sick Children and University of Toronto, Toronto, ON, Canada, [14]IWK Health Centre, Halifax, NS, Canada, [15]Pediatric Rheumatology, University of Saskatchewan, Saskatoon, SK, Canada, [16]Rheumatology, The Hospital for Sick Children, Toronto, ON, Canada, [17]Rheumatology, BC Children's Hospital, Vancouver, BC, Canada, [18]University of Toronto, Toronto, ON, Canada

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Session Type: ACR Poster Session C

Background/Purpose:

Juvenile Idiopathic Arthritis (JIA) is a common chronic childhood illness that can negatively impact health-related quality of life (HRQL). In younger years, children manage JIA with support from parents and health care providers. However, early childhood engagement as shared care partners can optimize disease management, assist with symptom control, including pain, and hence improve HRQL. This becomes imperative as children move into the adolescent period and are expected to a larger role in the co-management of their JIA. There is evidence to suggest that psycho-educational treatments can improve health outcomes in JIA; however, the uptake of these interventions into routine care has been slow. The vast majority of children and their parents do not receive comprehensive JIA education, disease management and coping skills training. While self-management programs for adolescents and adults with JIA do exist, to our knowledge there are no such programs for children. The aim of this current research study is to develop and assess the usability of a bilingual (English and French) interactive, iPad-based psycho-educational game for 8 to 11 year old children with JIA. The game aims to help children and parents learn disease management and coping skills using gamification mechanics to reduce pain and pain-related activity limitations and improve HRQL.

Methods:

The core game concepts were developed in collaboration with subject matter experts, patient partners, and project investigators. Usability testing of the game is being conducted in 2-3 iterative cycles with patients (8-11 years old) and parents. Participants interact with the game in a step-wise manner and errors and efficiencies of gameplay are observed and documented. Participants also provide feedback through a semi-structured interview. Data are analyzed using content analyses.

Results:

Stakeholders collaborated to create the core game concept, which entails players battling physical (i.e., pain, stiffness, and fatigue) symptoms and psychological (e.g., worry, sadness) symptoms associated with JIA. Players use appropriate treatment strategies to battle their symptoms throughout an 8-week period of game play. Usability testing has been completed for 5 English-speaking children (average age = 10.4 years; 3 male, 2 female) and 4 parents. Children and parents have responded positively to the game. Suggestions have been minor (e.g., changing specific graphics, adding more animation) and there have been no changes to core game mechanics. Minor errors are related to navigation (e.g., failure to locate functions or follow recommended screen flow) and presentation (e.g., failure to locate and properly act upon desired information).

Conclusion:

Children with JIA may benefit from educational games to teach self-management strategies in order to improve HRQL. A core game concept was developed and overall reception to the game has been positive. Based upon user suggestions, changes to the prototype will be implemented and tested using further iterative cycles. The game will be translated into French. The feasibility and overall effectiveness of the game will be evaluated using a pilot randomized control trial.

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Abstract Number: 2446

Synovial Fluid Proteins Differentiate Patients with Oligoarticular Juvenile Idiopathic Arthritis Who Are Destined to Extend from Those Who Will Remain Persistent in Course

AnneMarie C. Brescia[1], Megan M. Simonds[2], Kathleen E. Sullivan[3] and Carlos D. Rose[4], [1]Pediatric Rheumatology, Nemours A.I. duPont Hospital for Children, Wilmington, DE, [2]Nemours Research, Nemours/AI duPont Hospital for Children, Wilmington, DE, [3]Allergy Immunology, The Children's Hospital of Philadelphia, Philadelphia, PA, [4]Pediatrics, Nemours A.I. duPont Hospital for Children, Division of Pediatric Rheumatology, Thomas Jefferson University, Wilmington, DE

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Background/Purpose: Children with oligoarticular juvenile idiopathic arthritis (JIA) who have an extended course (recruitment of 5 or more joints after 6 months of disease) have a worse prognosis than those who have a persistent oligoarticular course (4 or fewer joints involved for the duration of disease). We want to predict those patients whose arthritis will ultimately extend early in the disease course, before the course has declared itself. Our goal is to identify protein biomarkers which will discriminate between patients whose involvement will remain persistently oligoarticular and those who are destined to have an extended oligoarticular course. **Methods:** As part of a separate ongoing IRB approved protocol, remnant synovial fluid was obtained from patients undergoing medically indicated arthrocenteses. Using our clinical database, JIA samples were separated into two groups: oligoarticular JIA with persistent course (PR), oligoarticular JIA with extended course (E). All samples were from steroid-na•ve joints and samples from E were obtained prior to time of extension. Using synovial fluid samples from 4 PR and 4 E patients, protein arrays were completed using RayBiotech Membrane-based Antibody Arrays. Expression of 89 cytokines, chemokines, and other inflammatory proteins were measured by calculating intensity using ImageJ. Key significant proteins were then confirmed using R&D Systems Quantikine Colorimetric Sandwich ELISAs. **Results:** Based on the analysis of the protein arrays, 20 proteins had significantly different expression levels (Table 1). Of these 20, 3 proteins were overexpressed in PR samples, while 17 were overexpressed in E samples. To confirm these results, ELISAs (Fig. 1) were performed on IL-5, a cytokine that acts as a growth and differentiation factor for B cells, Angiogenin, a potent stimulator of new blood vessels, IL-6, an interleukin with both pro- and

anti-inflammatory roles, and VEGF, a signal protein that stimulates angiogenesis. Both IL-5 and Angiogenin were significantly overexpressed on protein arrays in PR samples when compared to E samples (p-values <0.05). VEGF and IL-6 were significantly overexpressed in E samples when compared to PR samples (p-values <0.001). **Conclusion:** Samples of synovial fluid from differing courses of JIA, PR and E, taken before the ultimate course is clinically apparent, have significantly different protein levels of important chemokines and cytokines. These differences can be exploited to predict which patients may extend, allowing earlier therapeutic intervention to prevent long term disability.

Protein	p-value	Fold Change	Overexpressed
sTNFR1	0.045	1.357	Persistent
Angiogenin	0.047	1.537	Persistent
IL-5	0.002	2.891	Persistent
TGF-B2	0.008	1.228	Extended
PlGF	0.023	1.556	Extended
PARC	0.004	1.737	Extended
ICAM1	0.006	1.764	Extended
TGF-B3	0.032	1.775	Extended
IGFBP-3	0.017	1.868	Extended
IP-10	0.015	1.896	Extended
BLC	0.001	1.997	Extended
IL-6 sR	0.001	2.033	Extended
IL-4	0.033	2.634	Extended
VEGF	0.001	3.074	Extended
I-309	0.000	3.137	Extended
IL-1b	0.010	3.665	Extended
IL-8	0.001	4.292	Extended
IL-1a	0.000	4.519	Extended
IL-6	0.000	4.619	Extended
IL-3	0.000	4.704	Extended

Table 1. 20 significantly differentially expressed proteins in PR and E synovial fluid samples.

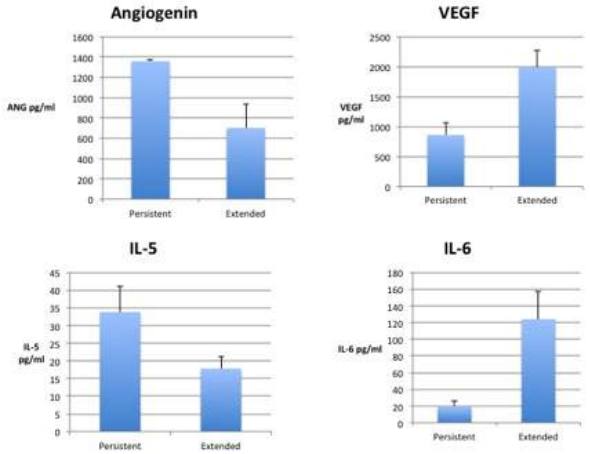

Figure 1. ELISAs confirming protein array findings.

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Abstract Number: 2447

The Juvenile Arthritis Disease Activity Score Remains the Disease Activity Marker of Choice for Adults with Polyarticular Juvenile Idiopathic Arthritis

Qiong Wu[1], **Nicola Ambrose**[1,2,3], Debajit Sen[1,2,3], Maria J. Leandro[4], Charlotte Wing[2], Nicola Daly[2], Kate Webb[1,2], Corinne Fisher[1,2], Linda Suffield[1], Francesca Josephs[1], Clarissa Pilkington[3], Despina Eleftheriou[1,3], Muthana Al-Obaidi[3], Sandrine Compeyrot-Lacassagne[3], Lucy R Wedderburn[1,3] and Yiannis Ioannou[1,2,3], [1]Arthritis Research UK Centre for Adolescent Rheumatology, University College London, London, United Kingdom, [2]Adolescent Rheumatology Department, University College London Hospital NHS Trust, London, United Kingdom, [3]Paediatric Rheumatology Department, Great Ormond Street Hospital for Children NHS Trust, London, United Kingdom, [4]Centre for Rheumatology and Bloomsbury Rheumatology Unit, University College London, London, United Kingdom

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Background/Purpose: A considerable proportion of children with polyarticular juvenile idiopathic arthritis (polyJIA) continue to experience active disease into adulthood. There is no validated disease activity measure for these adults; when children transfer to adult services they are often reclassified as having rheumatoid arthritis (RA) and assessed using the Disease Activity Score 28 (DAS28). DAS28 is validated in adults with RA to assess disease severity and in the UK a score of >5.1 defines qualification for biological drugs. However, in contrast to the Juvenile Arthritis Disease Activity Score (JADAS), the DAS28 does not include joints that are frequently affected in polyJIA. In this study, we compared the DAS28 with JADAS-10 and questioned whether DAS28 is appropriate to use in adults with polyJIA.

Methods: Tender and swollen joint counts out of 28, active joint count of all joints up to a maximum of 10, patient/parent global assessment and physician global assessment visual analogue scales were collected prospectively from paediatric, adolescent and young adult rheumatology clinics in patients aged 10 and above with polyJIA (classified by International League of Associations for Rheumatology). Erythrocyte sedimentation rate (ESR) values were taken within 30 days before or after the assessment (when unavailable, values were taken within 3 months before or after, providing the patient remained stable between the ESR test and assessment). When unavailable within these time periods, patients were excluded from analysis. DAS28 and JADAS-10 were calculated and compared using Spearman's rank correlation coefficient. A DAS28 of >5.1 constitutes high disease activity in adults with RA while a JADAS-10 of >10.5 is considered to reflect high disease activity in children with polyJIA.

Results: Forty-nine patients were analysed (range 10-27 years, median 15 years, M:F ratio 1:3.5). Thirteen out of 49 patients were classified as high disease activity by JADAS-10, while only 1 out of 49 was defined as high disease activity by DAS28. Good correlation was seen between DAS28 and JADAS-10 (Spearman r=0.6939, p<0.0001) with no considerable difference between children (range 10-15 years, median 13 years, n=25, Spearman r=0.8269, p<0.0001) and adults (range 16-27 years, median 17 years, n=24, Spearman r=0.7345, p<0.0001).

Conclusion: Discrepancy in high disease activity thresholds between DAS28 and JADAS may have implications when determining which patients qualify for biological drugs, although the absolute values correlate well. Hence the JADAS may remain the more appropriate disease activity marker to use in adults with polyJIA.

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Abstract Number: 2448

Flare Definitions for Juvenile Idiopathic Arthritis (JIA) Based on ACR Core Set Variables and Patient Reported Outcomes: Results from the Research in Arthritis in Canadian Children-Emphasizing Outcomes Prospective Cohort

Vinay Shivamurthy[1], Deborah M. Levy[2], Gilles Boire[3], Karen N Watanabe Duffy[4], Elizabeth Stringer[5], Rosie Scuccimarri[6], Rae S.M. Yeung[7], Adam M. Huber[8], Kiem Oen[9], Natalie Shiff[10], Lori B. Tucker[11], Roberta Berard[12], Kimberly Morishita[13], Ciarán M. Duffy[14] and Jaime Guzman[15], [1]Pediatrics/Rheumatology, British Columbia Children's Hospital, Vancouver, BC, Canada, [2]Rheumatology, The Hospital for Sick Children, Toronto, ON, Canada, [3]Department of Medicine/Division of Rheumatology, Université de Sherbrooke, Sherbrooke, QC, Canada, [4]Rheumatology, Children's Hospital of Eastern Ontario and University of Ottawa, Ottawa, ON, Canada, [5]Department of Rheumatology, IWK Health Centre, Halifax, NS, Canada, [6]Pediatrics, McGill University, Montréal, QC, Canada, [7]Pediatrics, Immunology and Medical Science, The Hospital for Sick Children, University of Toronto, Toronto, ON, Canada, [8]Pediatric rheumatology, IWK Health Centre, Halifax, NS, Canada, [9]University of Manitoba, Winnipeg, MB, Canada, [10]Pediatric Rheumatology, University of Saskatchewan, Saskatoon, SK, Canada, [11]Rheumatology, BC Children's Hospital, Vancouver, BC, Canada, [12]Children's Hospital of Western Ontario, London, ON, Canada, [13]Pediatric Rheumatology, BC's Children's Hospital, Vancouver, BC, Canada, [14]Children's Hospital of Eastern Ontario

and University of Ottawa, Ottawa, ON, Canada, [15]Rheumatology, Division of Rheumatology, BC Children's Hospital, Vancouver, BC, Canada

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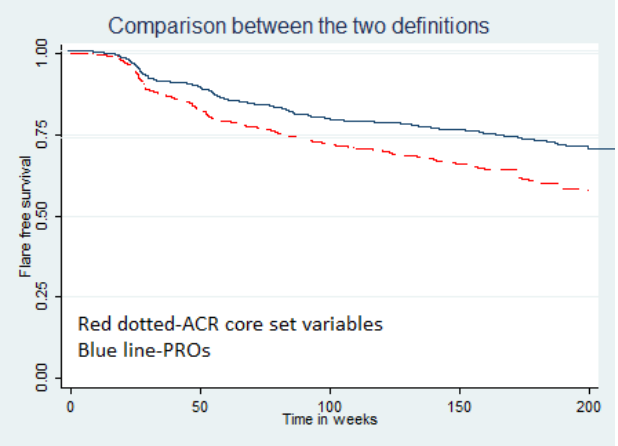
Background/Purpose: A valid flare definition is needed in clinical practice to identify a clinically relevant worsening which will guide us make treatment decisions. While the ACR core variables are primarily physician based criteria, patient reported variables could have a significant role in helping patients identify worsening early and seek medical attention sooner .Our aims were to 1) Examine the feasibility of using Patient Reported Outcomes (PROs) and ACR core set variables to define flare in children with JIA and 2) Examine the concordance between the two definitions

Methods: We studied children in the Research in Arthritis in Canadian Children emphasizing outcomes (ReACCh-Out) prospective cohort. Data were collected during routine clinical practice for newly diagnosed patients at 16 pediatric rheumatology centres enrolled between 2005 and 2010. ACR core set variables and patient reported variables were collected at 0, 6, 12, 18, 24, 36, 48 and 60 months after enrolment. The PROs included Pain visual analogue scale, functional status measured by the Childhood Health Assessment Questionnaire (CHAQ) and duration of morning stiffness. Flare was defined as: 1) PROs flare: at least 30% worsening in 2/3 PROs with minimum duration for stiffness of 30 minutes; 2) ACR Core Set flare: worsening of at least 3/6 ACR core variables by at least 30% without concomitant improvement of more than one variable by ≥ 30%. Flare status was assessed for each patient visit after the subject attained clinically inactive disease. Concordance between the two flare definitions was assessed with the Kappa statistic. The risk of first flare was estimated by Kaplan-Meier survival analysis.

Results: A total of 1146 patients were included in the study with a median follow up of 24 months after inactive disease. Of the total 6177 study visits, 2358 visits occurred after patients had attained inactive disease. Imputation was required for missing data in 42 % of visits for ACR core variables and 35 % for PROs. After imputation the definition for flare was fulfilled in 478 (20.2%) visits using ACR core variables and in 366 (15.5%) visits using PRO variables. In 231 visits flare was identified by both definitions. The overall concordance was 83.8% with kappa value of 0.45 suggesting moderate agreement (p =0.00001). Applying minimum cut-offs for ACR core variables, as done in randomized trials of polyarticular course JIA, only 278 visits would fulfill the criteria. The Kaplan Meier curves are presented in the figure.



Conclusion: A flare definition based on PROs had moderate concordance with the one based on ACR core set variables. It tended to underestimate the risk of flare. The feasibility of using both the definitions to define flare in this routine practice-based cohort was limited by missing data requiring imputation and by study visits scheduled at set intervals.

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Abstract Number: 2449

Does Antinuclear Antibodies Predict Remission in JIA ?

Mia Glerup[1], Troels Herlin[2] and Marinka Twilt[3], [1]Pediatrics, Aarhus University Hospital, Skejby, Aarhus, Denmark, [2]Department of Pediatrics, Århus University Hospital Skejby, Århus, Denmark, [3]Rheumatology, Alberta Children's Hospital, Calgary, AB, Canada

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Background/Purpose:

In the recent years the classification of Juvenile Idiopathic Arthritis (JIA) according to the ILAR criteria has been questioned as some categories still include heterogeneous conditions. One of the questions posed is if patients with a positive Antinuclear Antibody (ANA) should be a separate category. Previous studies have shown contradicting evidence to support the separation of patients based on ANA status.

The aim of this study was to evaluate disease outcome defined as remission based on ANA status. Secondary aims of the study included the clinical and disease activity features of ANA positive patients in comparison to the ANA negative patients at disease onset and last follow-up.

Methods: A retrospective cohort study; all patients diagnosed with JIA according to the revised ILAR criteria attending our Pediatric Rheumatology Center from January 2000 until May 2014 were included.

A minimum follow-up of 1 year was required. ANA positivity was defined as at least 2 positive results with a titer ≥ 1:160. ANA was measured by indirect immunofluorescence assays on HEp-2 cells. Demographic and clinical features were collected. Remission at last follow-up was defined by Wallace criteria for remission on (>6 months) and off (>12 months) medication. Descriptive analysis (Chi-square) was performed (SPSS).

Results:

A total of 625 patients met the inclusion criteria. Of these patients 229 (37%) were ANA positive. ANA positivity was correlated to a female predominance and young age at diagnosis ($p<0.05$). Joint count at diagnosis and at last follow-up showed no difference between both groups. At least half of the patients in both groups were treated with MTX. Treatment with TNF alpha blocking agents was seen more frequently in patients with a positive ANA.

Nine % of the total patient cohort had uveitis and 50% of these patients were treated with anti-TNF-alpha.

Disease outcome; remission on or off medication, showed no differences between both groups and it was irrespective of uveitis. Sub-analysing the ANA positive oligoarticular-persistent, extended and polyarticular RF-neg patients (n=200) showed a significant difference for remission on and off medication; oligoarticular-persistent patients more frequently were in remission off medication, while oligoarticular-extended and polyarticular RF-neg were more frequent in remission on medication. The latter groups also received more MTX and anti-TNF alpha treatment.

	ANA negative	ANA positive
JIA	396 (63%)	229 (37%)
Systemic JIA	48 (92%)	4 (8%)
Oligoarticular persistent	122 (57%)	93 (43%)
Oligoarticular extended	51 (50%)	50 (50%)
Polyarticular RF-neg	68 (54%)	57 (46%)
Polyarticular RF-pos	13 (62%)	8 (38%)
Psoriatic JIA	34 (83%)	7 (17%)
ERA	31 (82%)	7 (18%)
Undifferentiated JIA	29 (94%)	3 (6%)
Gender*	226 male, 169 female	50 male, 179 female
Age at diagnosis* (years)	9.2	6.4
Disease duration* (years)	5	6.4
Uveitis*	13(3%)	42 (18%)
Joint count at diagnosis	2.9	3.1
Methotrexate treatment	203 (51%)	134 (59%)
Anti-TNF alpha treatment*	86 (22%)	71 (31%)
Last follow-up		
Joint count last follow-up	< 0.1	< 0.1
Remission on medication < 6months	26 (7%)	13 (6%)
Remission on medication > 6 months	99 (25%)	61 (27%)
Remission of medication < 12 months	33 (8%)	19 (8%)
Remission of medication > 12 months	219 (55%)	115 (50%)
Active disease	22 (1%)	21 (9%)

*Statistically significant (P<0.05)

Conclusion:

Our findings show that ANA positive patients do not differ from ANA negative patients when comparing remission rate. This was independent of uveitis. However in the ANA positive group a different remission rate and medication use is seen for the different subtypes. Although ANA positive oligoarticular-extended and polyarticular RF-neg patients reach remission on medication, oligoarticular-persistent patients have a higher remission rate off medication.

Disclosure: M. Glerup, None; **T. Herlin**, None; **M. Twilt**, None.

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Abstract Number: 2450

Examination of the Clinical Significance of 14-3-3 Eta in Juvenile Idiopathic Arthritis

Lance Feller[1], **Austin M. Dalrymple**[2], Paul Tuttle IV[3], Reema H. Syed[3], Peri Pepmueller[1] and Terry Moore[4], [1]Rheumatology, Saint Louis University, St. Louis, MO, [2]Pediatric Rheumatology, St. Louis University, St. Louis, MO, [3]IM-Rheumatology, Saint Louis University, St. Louis, MO, [4]Division of Rheumatology and Pediatric Rheumatology, Saint Louis University School of Medicine, St Louis, MO

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Background/Purpose:

14-3-3 proteins are chaperonins found in all eukaryotic cells. There are multiple isoforms which are thought to be involved in intracellular signaling and transcription regulation. Recent work has implicated the η (eta) isoform as having diagnostic potential in inflammatory arthritis. Its utility and significance in juvenile idiopathic arthritis (JIA) has not been established, but our prior investigation revealed 14-3-3η positivity in some JIA patients. In this study we investigated the utility of measuring 14-3-3η in children with juvenile idiopathic arthritis.

Methods:

Measurements of 14-3-3η were obtained during evaluations of new patients with joint pain and in routine follow-up of JIA patients presenting between July 2013 and April of 2015. Rheumatoid factor (RF) and anti-cyclic citrullinated peptide antibodies (anti-CCP Ab) were measured. A chart review was later conducted to evaluate the clinical significance 14-3-3η. Joint imaging was evaluated for erosive changes.

Results:

23 JIA patients were evaluated. 10 had polyarticular disease, 3 had oligoarticular extended, 3 had seronegative spondyloarthritis (SNSA), 2 had oligoarticular, 2 were undifferentiated, 2 had enthesitis-related arthritis (ERA), and 1 had systemic-onset.

7 of 23 were 14-3-3η positive (5 had polyarticular disease, 1 with ERA, & 1 with oligoarticular). All 5 patients with polyarticular disease also were RF positive and 3 were both RF & anti-CCP Ab positive. The ERA patient was seronegative, and the oligoarticular patient was positive only for RF.

9 of the 23 had erosive disease, 4 of which were polyarticular with a positive 14-3-3η. Of those 1 was RF positive, and the remaining 3 patients were positive for RF and anti-CCP Ab. Neither the 14-3-3η positive patient with ERA nor the one with oligoarticular disease had erosions.

Conclusion:

14-3-3η can be found in polyarticular JIA and correlates with a positive RF and to a lesser extent a positive anti-CCP Ab. The majority of polyarticular JIA patients with erosions were 14-3-3η positive. We hope to expand this small study to include a larger sample and evaluate for any further relationships.

Disclosure: L. Feller, None; **A. M. Dalrymple**, None; **P. Tuttle IV**, None; **R. H. Syed**, None; **P. Pepmueller**, None; **T. Moore**, None.

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Abstract Number: 2451

Scoring Medication Requirements and Side-Effects in Juvenile Idiopathic Arthritis: Perspectives of Patients, Parents and Clinicians

Lori B. Tucker[1], Natalie Shiff[2], Susanne Benseler[3], Roberta Berard[4], Roman Jurencak[5], Thomas Loughin[6], Jaime Guzman[7] and Andrew Henrey[6], [1]Rheumatology, BC Children's Hospital, Vancouver, BC, Canada, [2]Pediatric Rheumatology, University of Saskatchewan, Saskatoon, SK, Canada, [3]Pediatrics, University of Calgary, Toronto, ON, Canada, [4]Children's Hospital of Western Ontario, London, ON, Canada, [5]University of Ottawa, Ottawa, ON, Canada, [6]Statistics and Actuarial Science, Simon Fraser University, Burnaby, BC, Canada, [7]Rheumatology, Division of Rheumatology, BC Children's Hospital, Vancouver, BC, Canada
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Background/Purpose: Medication requirements (MedReq) and medication side effects (MedSE) were found to be top priorities by patients, parents and clinicians in describing the course of the disease in children with juvenile idiopathic arthritis (JIA) in a previous study. There are no validated scales to measure these constructs in JIA. The aim of this study was to get input from patients, parents and clinicians to develop MedReq and MedSE scales in JIA.

Methods: We developed MedReq and MedSE scales, based on data available in the Research in Arthritis in Canadian Children-Outcomes cohort, and convened focus groups of youth with JIA (n=3), parents of children with JIA (n=3), and pediatric rheumatology clinicians (2 pediatric rheumatologists, 1 nurse) to evaluate the draft scales (Table). The draft MedReq scale was an ordered 11-level scale from 0=no medications to 10= Biologic, DMARD and systemic corticosteroids, with or without other medications. The MedSE scale was an 11-level scale from 0=no side effects to 10= Side-effect resulting in death or disability. Each of the proposed 11 levels for each scale was printed onto a Q card and participants were asked to rank the cards, without knowledge of the proposed order. Participants then viewed the rankings, and discussed reasons for their rankings. They could change their ranking if wanted and open discussions about JIA medications and medication side effects followed. Notes were recorded by a research assistant at each group, and data was summarized.

Results: Overall there was excellent agreement on ranking of the extreme levels of the scales (0,10) with substantial differences in the 6-9 ranks in the MedReq scale and the 3-6 ranks in the MedSE scale. MedReq scale values were changed to rank joint injection with a lower value than daily NSAID therapy. Patients own experience with side effects of prednisone and methotrexate influenced their ranking on the MedReq scale. Participants also pointed out that medication frequency has an impact on the perceived “intensity” of treatment. The MedSE scale based on the number and frequency of side-effects was said not to reflect the “real importance” of a side effect. Participants felt that future MedSE data collection must include measures of severity and impact of the side effects on daily living; information that was not available in the current data set. Additional descriptors were proposed for prednisone side-effects and inconveniences of injections.

Conclusion: Parents and patients were highly engaged and provided unique insights to the research team beyond the task they were asked to complete. The draft MedReq scale was overall well received but required weighting adjustments. Patients, parents and clinicians believe a MedSE scale should focus on the global severity and impact of experienced side-effects on daily living rather than number and frequency of side-effects.

TABLE: Proposed MedReq and MedSE items and ranking

MedReq Items	Item score	MedSE Items
No treatment at this visit	0	No side effects
Anti-inflammatory med only	1	One side effect occurring rarely
Intra-articular corticosteroid only	2	One side effect occurring some of the time
Anti-inflammatory med and intra-articular corticosteroid	3	Two side effects occurring rarely
DMARD only	4	Two side effects occurring some of the time
DMARD with anti-inflammatory and intra-articular corticosteroid	5	One side effect occurring 50% or more of the time
Multiple DMARDs	6	Two side effects occurring 50% or more of the

Multiple DMARDs	6	time
Multiple DMARDS with anti-inflammatory med and intra-articular corticosteroid	7	Three side effects occurring 50% or more of the time
DMARD and systemic corticosteroid	8	More than 3 side effects present more than 50% of the time
Biologic and DMARD	9	Side effect requiring in-hospital treatment
Biologic, DMARD, systemic corticosteroid, with or without other medications	10	Side effect resulting in death or disability

Disclosure: L. B. Tucker, None; **N. Shiff**, None; **S. Benseler**, None; **R. Berard**, None; **R. Jurencak**, None; **T. Loughin**, None; **J. Guzman**, None; **A. Henrey**, None.

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Abstract Number: 2452

Clinical and Functional Outcomes in Patients with Polyarticular Juvenile Idiopathic Arthritis Following Treatment with Adalimumab

Daniel J. Kingsbury[1], Pierre Quartier[2], G Horneff[3], Kirsten Minden[4], Mary Toth[5], Nupun A. Varothai[6], Anabela Cardoso[7] and Jasmina Kalabic[6], [1]Randall Children's Hospital at Legacy Emanuel, Portland, OR, [2]Hopital Necker-Enfants Malades, Paris, France, [3]Asklepios Klinik Sankt Augustin, Sankt Augustin, Germany, [4]Kinderklinik der Charite, Otto-Heubner Centrum, Berlin, Germany, [5]Akron Children's Hospital, Akron, OH, [6]AbbVie, North Chicago, IL, [7]AbbVie, Amadora, Portugal
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Background/Purpose: The Juvenile Arthritis Disease Activity Score (JADAS) is increasingly accepted for defining a treat-to-target strategy in patients (pts) with juvenile idiopathic arthritis (JIA)[1] The purpose of this study is to use JADAS to evaluate clinical disease activity/control, with or without functional control, in pts with polyarticular or polyarticular-course JIA (pJIA), following the initiation of adalimumab (ADA) ± concurrent methotrexate (MTX) treatment. To assess the feasibility of JADAS definition of remission (REM) and minimal disease activity (MDA) as part of a treat-to-target strategy.

Methods: Data for this post hoc analysis originated from M10-444, an open-label study in pJIA pts 2 to <4 yrs old or ≥4 yrs weighing <15 kg with moderately to severely active pJIA, in the US and EU (in the EU pts had to previously fail, have an insufficient response, or intolerance to MTX). Pts received subcutaneous ADA (24 mg/m^2 body surface area, up to 20 mg/dose), every other week (wk), for ≥24 wks, or until pts reached 4 yrs and weight ≥15 kg (in the EU, pts could continue for up to 1 additional yr). Disease activity was determined by JADAS based on C-reactive protein (CRP, normalization from 0-10), for 10 or 27 joints (JADAS10/27); functional impairment was determined by the Disability Index- Childhood Health Assessment questionnaire (DI-CHAQ). At wks 12 and 24, the proportion of pts achieving physician-assessed REM (JADAS≤2) or MDA (JADAS≤3.8), and the proportion of pts who achieved both MDA/REM and DI-CHAQ<0.5, was determined using observed cases.

Results: Out of 32 pts, 25 (78%) had received prior MTX and 27/32 (84%) received concomitant MTX during the study. At baseline, pts had a mean JADAS10 of 18.8, JADAS27 of 19.0, and DI-CHAQ of 1.2. After 12 wks on open-label ADA, improvements were observed in clinical and functional outcomes. At wks 12 and 24, the mean JADAS10 was 6.2 and 5.3; mean JADAS27 was 6.4 and 5.6; mean DI-CHAQ was 0.7 and 0.7, respectively. No pts were in REM/MDA at baseline; however after 12 and 24 wks, a sizeable proportion achieved disease control (table). After 12 and 24 wks of ADA treatment, the proportions of pts achieving both, disease control and DI-CHAQ<0.5 also increased from baseline.

Conclusion: Addition of open-label ADA treatment resulted in clinically important improvements in clinical and functional outcomes in pts with pJIA. JADAS 10 and -27 gave comparable results. JADAS REM and MDA are achievable targets with ADA

treatment.

Table: Numbers of patients who achieved disease control with/without DI-CHAQ<0.5, n/N (%)								
	JADAS27 Disease control		JADAS27 Disease control + DI-CHAQ<0.5		JADAS10 Disease control		JADAS10 Disease control + DI-CHAQ<0.5	
Week	**REM**	**MDA**	**REM**	**MDA,**	**REM**	**MDA**	**REM**	**MDA,**
0	0/31 (0.0)	0/31 (0)	0/30 (0)	0/30 (0)	0/31 (0)	0/31 (0)	0/30 (0)	0/30 (0)
12	12/29 (41.4)	14/29 (48.3)	5/22 (22.7)	5/22 (22.7)	12/29 (41.4)	13/29 (44.8)	5/22 (22.7)	5/22 (22.7)
24	10/28 (35.7)	16/28 (57.1)	2/20 (10)	4/20 (20)	9/28 (32.1)	15/28 (53.6)	2/20 (10)	3/20 (15)
REM: JADAS ≤2; MDA: JADAS ≤3.8								

References:

1. Consolaro et al, Arth & Rheum. 2012.

Disclosure: D. J. Kingsbury, AbbVie, 2; **P. Quartier**, AbbVie, Novartis, Pfizer, BMS, Chugai-Roche, Medimmune, Servier, and Swedish Orphan Biovitrum., 9; **G. Horneff**, AbbVie, Pfizer, and Roche, 2,AbbVie, Novartis, Pfizer, and Roche, 8; **K. Minden**, Pfizer and Abbvie, 2,Pfizer, Abbvie, Roche and Pharm-Allergan, 5; **M. Toth**, None; **N. A. Varothai**, AbbVie, 1,AbbVie, 3; **A. Cardoso**, AbbVie, 9; **J. Kalabic**, AbbVie, 9.

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Abstract Number: 2453

Evidence-Based Decision Support for Pediatric Rheumatology Reduces Diagnostic Errors, with the Potential to Reduce Capacity Shortage

Balu Athreya[1], Mary Beth Son[2], Jonathan S. Hausmann[3], Elizabeth Ang[4], David Zurakowski[5], Michael Segal[6] and **Robert Sundel**[7], [1]duPont Hospital for Children/Thomas Jefferson University, Wilmington, DE, [2]Division of Immunology, Children's Hospital Boston, Boston, MA, [3]Rheumatology, Children's Hospital Boston, Boston, MA, [4]Paediatrics, University Children's Medical Institute, NUH, Singapore, Singapore, [5]Departments of Anesthesia and Surgery, Boston Children's Hospital, Boston, MA, [6]SimulConsult, Chestnut Hill, MA, [7]Immunology, Childrens Hospital, Boston, MA

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Background/Purpose: This projects seeks to respond to the critical shortage of pediatric rheumatologists encapsulating the diagnostic information of the field in an advanced diagnostic decision support software (**DDSS**) tool. We present here an assessment of the benefits of such rheumatology assistance in the evaluation of actual case vignettes.

Methods: The evaluation used the SimulConsult DDSS tool, based on Bayesian pattern matching with temporal onset of each finding in each disease. The software covered 5,405 diseases, taking into account the incidence, treatability, relative frequency, age of onset and age of disappearance for each finding in each disease. The output includes a rank-ordered differential diagnosis and a display of clinical and lab findings ranked by pertinence (measured by the ability of a finding to modify the differential

diagnosis) and cost-effectiveness in distinguishing among diagnoses. Rheumatology information was entered by junior clinician curators primarily from textbook material and edited by senior clinicians. A checklist of 46 common rheumatologic findings was developed to assist in both curation of information and entry of findings in clinical use.

Results: Twenty-six testers were asked to evaluate 8 case vignettes of real patients with laboratory-established diagnoses (6 had pediatric rheumatologic diagnoses; 2 had other conditions with some rheumatologic findings). Of the 26 testers, 13 were "junior" clinicians in the final year of residency or first post-residency year. The remaining 13 had been practicing for at least 10 years ("senior"). Ten of the 26 testers were pediatric rheumatologists, 9 were pediatric emergency medicine physicians and 7 were general pediatricians. Clinician testers generated a differential diagnosis before and after using diagnostic decision support software. Overall, testers demonstrated a significant reduction in diagnostic errors following introduction of the software, from 28% unaided to 15% using decision support ($p<0.001$). Error reduction was significantly larger for emergency medicine physicians compared to generalists and rheumatologist ($p=0.013$). This error reduction occurred despite the fact that testers employed an "open book" approach to generating their initial lists of potential diagnoses, spending an average of 8.6 minutes using sources of medical information generally available on the internet before using the diagnostic software.

Conclusion: Use of DDSS can reduce diagnostic error, cutting a greater amount of error for generalists, but a greater percentage of error for rheumatologists. Junior rheumatologists equipped with decision support were able to rival the diagnostic accuracy of senior colleagues at baseline, an improvement that could further extend the availability of pediatric rheumatology consultations. These findings suggest that decision support can reduce diagnostic errors and improve use of relevant information by practitioners, potentially helping to address the shortage of experts in pediatric rheumatology and similarly underserved specialties.

Disclosure: B. Athreya, None; **M. B. Son**, None; **J. S. Hausmann**, None; **E. Ang**, None; **D. Zurakowski**, None; **M. Segal**, SimulConsult, 4; **R. Sundel**, None.

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Abstract Number: 2454

Target and Targetoid Reactions at Bacillus Calmettee-Guérin Inoculation Site Revealed By Dermatoscopy Correlate with Systemic Involvements in Patients with Kawasaki Disease

Kuo Ho-Chang and Kawasaki Disease Center, Pediatrics, Kaohsiung Chang Gung Memorial Hospital, Kaohsiung, Taiwan
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Session Type: ACR Poster Session C
Session Time: 9:00AM-11:00AM

Background/Purpose:

For the past decades, the rash at the Bacillus Calmettee-Guérin (BCG) inoculation sites has been recognized as a useful diagnostic clue in Kawasaki disease (KD). However, the detailed characterization of the BCG reaction and its correlation with systemic involvements in KD has not been evaluated. We sought to characterize the BCG reaction in KD and correlate the grade of BCG reaction with the systemic involvements in patients with KD.

Methods: History taking, laboratory examination, physical examination, and dermatoscopic examination were performed in 10 patients diagnosed with KD

Results:

We identified four dermoscopic patterns: atypical targets (targetoid) pattern in 3 patients; typical target pattern in 2 patients; faint

homogenous erythema in 3 patients; a more or less evident white patch, in the central area in 2 patients. Elevated blood level of liver enzymes is associated with the presence of typical target and atypical target pattern in patients.

Conclusion:

The dermoscopic patterns may help dermatologists and pediatrician to consolidate the diagnosis of Kawasaki disease. The target or targetoid pattern observed under dermoscope is a useful biomarker for systemic involvements in patients with KD.

Disclosure: K. Ho-Chang, None;

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Abstract Number: 2455

Utilization and Education of Nurse Practitioners in Pediatric Rheumatology

Sandra Mintz[1], Karla B. Jones[2] and Andreas Reiff[3], [1]4650 Sunset Boulevard, Mailstop 60, Children's Hospital of LA, Los Angeles, CA, [2]Rheumatology, Nationwide Children's, Columbus, OH, [3]Childrens Hosp LA MS60, Los Angeles, CA

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Background/Purpose:

Due to the shortage of subspecialty physicians there is an increasing need of adding mid-level practitioners to specialty practices (Solomon, Bitton, et.al., 2014). However there is little guidance as to best practices and standards for training a nurse practitioner (NP) or physician assistant (PA) in specialty practice. In this study we investigated the scope of practice and training for NPs in pediatric rheumatology in the United States by a nationwide survey.

Methods:

The Pediatric Nurse ListServe in the United States has an over 100 NP members and currently no known PA's. We developed an 18 question survey focused on the education, background, training and practice of Nurse Practitioners in Pediatric Rheumatology Practices. Survey monkey was utilized and sent to both the Pediatric Rheumatology and Pediatric Rheumatology Nursing List Serves. Questions included state of employment, years working a nurse prior to and as a nurse practitioner, length of training with the Rheumatologist staffing patients, focused education in the specialty, scope of practice, length of appointments, volume of clinics per week, billing practices and research engagement. The survey was sent out as an e-mail blast with two follow up reminders to practitioners.

Results:

33 NP's from 17 States in the United States responded. Response rates were evenly distributed across the country. 67.7% had a background in acute care settings as RN's with anywhere from less than 2 to over 20 years of experience prior to becoming a NP. 57% had prior experience as an NP in primary care or other specialty setting. Training with a Rheumatologist ranged from <6 months=31.0%, 6 month=31.0% and 1 year=27.6% and 10% 1-2 years. Subsequent to this, 93.7% reported seeing patients in follow up independently with an MD available, while 28.1% see the patients together with an MD; 53.1% report seeing new patients with an MD, 36.5% with a MD available. Most common diagnosis being followed: Juvenile Idiopathic Arthritis 97%, uveitis 90.9%, systemic lupus 84.8%, dermatomyositis 84.8% and linear/morphea scleroderma 81.8%. Respondents reported a broad range of acuity. 93.9% followed patients on infusion therapy. 60.6% participated in research trials although 90.6% had no protected research time. Rheumatology education of the respondents was obtained as follows: 87% within their own department, 51.5% through attending ACR/ARHP PRYSM, 54.5% by attending the ACR/ARHP Annual Meeting, 33.3% by

taking the ARHP Advanced Rheumatology Course, and 9.1% through the Rheumatology Nurses Society. 78.8% of the respondents were billing under their own name. The average job profile was 5 days a week with 43.7% averaging 3-5 half day clinics and 37.5% averaging 6-8 half day. 72.4% of the respondents had 30 minute follow up visits.

Conclusion:

Nurse Practitioner's entering pediatric sub specialty practice have a wide range of clinical background frequently with limited experience as a NP. The scope of practice and job profile appears to be broad with an average work load ranging from 3 to 8 half day clinics. There does not appear to be consistency between programs regarding length of training and educational plan. A formalized clinical training for NP's going into specialty practices is needed.

Disclosure: S. Mintz, None; **K. B. Jones**, None; **A. Reiff**, None.

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Abstract Number: 2456

Anti SRP+Ve Myositis in Childhood. Presentation and Physiotherapy Treatment of This Rare Childhood Myositis

Susan Maillard and Clarissa Pilkington, Paediatric Rheumatology, Great Ormond Street Hospital NHS Foundation Trust for Children, London, United Kingdom

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Background/Purpose: Previously it was understood that all Myositis in childhood was Juvenile Dermatomyositis. More recently Myositis specific antibodies have been discovered and these appear to be linked to specific clinical phenotypes. One of these called anti SRP+ve has been linked to a very severe form of Myositis and this review of 3 patients presents the clinical description and treatment, focusing on the physiotherapy, of these patients.

Methods: It is believed that anti SRP+ve antibodies are only present in 5% of children with Myositis**.** In the cohort of patients within the paediatric rheumatology service only 3/250 patients were found to be anti SRP+ve. The clinical case notes were reviewed and the results are presented here. The main focus of this review is during the initial presentation and treatment with specific focus upon the physiotherapy, and does not address long term outcome.

Results: Despite the rare nature of this Myositis and the relatively new recognition of this condition there have been 3 patients diagnosis within the last 1year. All 3 patients have been female aged 11-14 at time of onset. Their initial onset was rapid onset of extremely severe muscle weakness but with minimal skin involvement. CMAS score at onset ranged between 0 - 6 and MMT 8 16 – 23 and they all presented with multiple joint restrictions due to inflamed joints and muscle tightness. They have all had such severe swallowing difficulties that they were naso-gastrically fed for many weeks. The medical treatment consisted of multiple immunosuppressant agents including high dose steroids, IVIG, Methotrexate, Cyclophosphomide and Rituximab. Intensive physiotherapy was required for all and this ensured the maximum recovery of the muscle strength, muscle patterning and functional improvement. The physiotherapy was started from the initial presentation and was provided twice a day. The initial focus was on regaining range of movement and active-assisted muscle strengthening. The exercises were progressed as they were able to anti-gravity work and then into resisted work. The recovery for all 3 was very slow initially and required an extended hospital admission of many months. Two of the patients were discharged with an MMT8 of 76/80 and were able to manage full time school, walking independently and managing all activities of daily living, but did require a wheel chair for longer distances. The 3rd remains in hospital at this point but is improving significantly.

Conclusion: Anti SRP+ve Myositis in children is a very rare and severe disease presenting with profound muscle weakness and

requires both intensive physiotherapy and high dose immune-suppressants. Though long-term outcome is not known rehabilitation to restore independent function is possible.

Disclosure: S. Maillard, None; **C. Pilkington**, None.

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Abstract Number: 2457

Physical Function and Psychological Well-Being in Teens with Juvenile Idiopathic Arthritis (JIA): Characterization and Exploration of Technology-Assisted Self-Management

Carrie Shotwell[1], Paula Melson[2], Jason Long[3] and Tracy Ting[4], [1]Occupational therapy and physical terapy, Cincinnati Children's Hospital Medical Center, CINCINNATI, OH, [2]Rheumatology, Children's Hosp Medical Center, Cincinnati, OH, [3]Orthopaedic Surgery, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, [4]Rheumatology/MLC 4010, Cincinnati Children's Hosp, Cincinnati, OH

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Background/Purpose: This study sought to assess the physical function and psychological well- being of teens with juvenile idiopathic arthritis (JIA) as well as to assess social media as an effective option for peer support among teens with JIA.

Methods: Eighteen teens (age range 13-18) with medically managed JIA were recruited to participate in the study. The study team measured functional ability, functional capacity, and psychosocial wellbeing via standardized assessments. A randomly selected subgroup of the cohort were given the opportunity to wear an activity monitor, with the intent of exploring the effects of technology in promoting self-management behaviors (increased activity levels or increased awareness of activity level). All participants were invited to join a moderated online social media forum to qualitatively assess psychosocial well-being, as well as to explore social media as a potential option for peer support among teens with JIA.

Results: Study results indicate that despite the presence of a chronic condition and occasional physical limitations, there are not significant differences in functional ability or psychosocial well-being amongst teens with JIA when compared to current literature describing healthy peers. The qualitative responses from the online forum indicated difficulty with managing medications and a desire to participate in the same activities as peers, despite having pain.

Conclusion: The qualitative responses, along with the overall poor compliance with the activity monitors and online forum, may indicate that teens with JIA require continued assistance from medical professionals and caregivers to take steps towards self-management of their condition.

Disclosure: C. Shotwell, None; **P. Melson**, None; **J. Long**, None; **T. Ting**, None.

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Abstract Number: 2458

Psychostimulant-Induced Vasculopathy: A Retrospective Study in a Pediatric

Rheumatology Clinic

Freda Singletary[1], Nirupma Sharma[1] and Rita Jerath[2], [1]Pediatrics, Georgia Regents University-Children's Hospital of Georgia, Augusta, GA, [2]Dept of Pediatrics, Childrens Med Ctr Med Schl GA, Augusta, GA
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Background/Purpose: Attention-deficit/hyperactivity disorder (ADHD) is the most common neurobehavioral disorder of childhood. The first line treatment is psychostimulant medications namely, methylphenidate, amphetamines, or their derivatives. The more common side effects of psychostimulants noted in children or adolescents are insomnia, decreased appetite, weight loss, and headaches. In recent years other side effects of these medications have been noted. Our aim was to study patients who have been prescribed psychostimulants and experienced vascular changes in the spectrum of symptoms that included color change, pain, numbness to hands and feet, or similar peripheral vascular symptoms that will be globally termed peripheral vasculopathies. These symptoms are also seen in other autoimmune disorders therefore a secondary analysis of association with ANA positivity was also explored.

Methods: A retrospective chart review was completed that was derived from patients seen in Children's Hospital of Georgia's Pediatric Rheumatology clinic that were referred with complaints of peripheral vasculopathies. We searched for concurrent diagnosis of ADD/ADHD, and the use of various psychostimulants. Data was analyzed using contingency tables to derive p-values from Fisher's Exact Test, Pearson's Chi-Square, and Likelihood Ratios.

Results: Initial data collection was compiled using ICD-9 codes related to peripheral vasculopathy symptoms and psychostimulant medication usage in patients seen in the Pediatric Rheumatology Clinic over 15 months. Patient charts were then reviewed for 1) type of psychostimulants 2) length of use, 3) description of symptoms, 4) Positive ANA, 5) other Rheumatologic diagnoses, and 6) family history. Collectively 145 patients were identified in the initial data pool. Patients were excluded if they were less than 5 years old, did not have a diagnosis of a perhipheral vasculopathy, not taking psychostimulants , or had a previous rheumatologic disease. After all exclusions a total of 47 patients were used in data analysis. Chi-Square values ranged from 9.98 to 16.76 producing p-values less than 0.05. The null hypothesis in the test was taking psychostimulants and having symptoms of peripheral vasculopathy were independent of each other. Thus the null hypothesis was rejected concluding that the use of psychostimulants and presence of peripheral vasculopathy symptoms are related.

Conclusion: Our retrospective analysis demonstrated that there is a strong association between the use of psychostimulants and peripheral vasculopathy symptoms. The sample size in this analysis is larger than previously published literature thus reinforcing concern for vasculopathy as a significant side effect of psychostimulants. A larger controlled prospective study is needed to further establish the exact statistical co-relation. In conclusion, the diagnosis of ADHD and prescribing of psychostimulant medications is on a rise. Our study demonstrates the need of making prescribing physicians aware of this significant side effect so they may educate the families and also elucidate occurrence of new vascular symptoms from this patient population.

Disclosure: F. Singletary, None; **N. Sharma**, None; **R. Jerath**, None.

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Abstract Number: 2459

Personal and Environmental Factors Associated with Leisure Participation Among Children and Adolescents with Juvenile Idiopathic Arthritis

Sabrina Cavallo[1], Annette Majnemer[2], Ciarán M. Duffy[3] and Debbie Ehrmann Feldman[4], [1]École de Santé Publique, Université de Montréal, Montreal, QC, Canada, [2]School of Physical and Occupational therapy, McGill University, Montreal, QC, Canada,

[3]Children's Hospital of Eastern Ontario and University of Ottawa, Ottawa, ON, Canada, [4]School of Rehabilitation, Université de Montréal, Montreal, QC, Canada
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Background/Purpose: To identify potential disease-related, personal and environmental factors associated with leisure in children and adolescents with juvenile idiopathic arthritis (JIA) according to the International Classification of Functioning, Disability and Health for Children and Youth framework.

Methods: One hundred and seven children and adolescents (8-17 years) diagnosed with JIA followed at the Montreal Children's Hospital, McGill University Health Center completed the Children's Assessment of Participation and Enjoyment (CAPE). The CAPE measures involvement in leisure (recreation, active physical, social, skill-based, self-improvement). The disease characteristics related to JIA were abstracted from the child's medical file (JIA sub-type, active joint count, age of diagnosis), pain perception and functional status were obtained through self-report. Participants with JIA and their parents completed a series of questionnaires to gather information on the child's mastery motivation, self-concept, activity preference, and perceived social support. Parents completed questionnaires on socio-demographic data, as well as on family function and environmental barriers. Hierarchical regression analysis was used to explore factors associated with leisure in children and adolescents with JIA.

Results: Personal (age, sex, preferences for activities, motivation for gross motor tasks) and environmental (cultural background, maternal education, median household neighborhood income) factors were important in explaining leisure participation for different types of activities. Overall, included variables explained between 10.8% (self-improvement) and 29.7% (active physical) of the adjusted total variance.

Conclusion: Leisure participation in JIA is a complex phenomenon that may be explained by a multitude of factors related to the child, the family and the environment. Identification of these variables may help rehabilitation professionals ascertain those with JIA who are at greater risk for decreased participation in leisure, as well as tailor safe and effective treatment strategies to meet the child's and family's needs.

Disclosure: S. Cavallo, None; **A. Majnemer**, None; **C. M. Duffy**, None; **D. Ehrmann Feldman**, None.

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Abstract Number: 2460

B10 Cells May be Involved in Controlling Disease Activity in Polyarticular Juvenile Idiopathic Arthritis Patients

Qianzi Zhao[1] and Lawrence K. Jung[2], [1]Rheumatology, Children's National Medical Center, Washington, DC, [2]Pediatric Rheumatology, Children's National Medical Center, Washington, DC
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Background/Purpose:

In addition to antibodies production, B cells have been shown to have down-regulatory function on immune response in both mouse and human. The down-regulatory function of B cells is partially dependent on their production of Interleukin-10 (IL-10), an anti-inflammatory cytokine. IL10-producing B cells (B10 cells) are not restricted to a defined population. $CD24^{hi}CD38^{hi}$ transitional B cells and $CD24^{hi}CD27^{+}$ memory B cells have been reported to contain the majority of B10 cells in different studies. B10 cells have been demonstrated to ameliorate collagen-induced arthritis in mice. In human, very little is known about the role of B10 cells in juvenile idiopathic arthritis (JIA). In this study, we aimed to analyze the percentage and phenotypes of B10 cells in active and inactive polyarticular JIA (poly-JIA) patients and controls.

Methods:

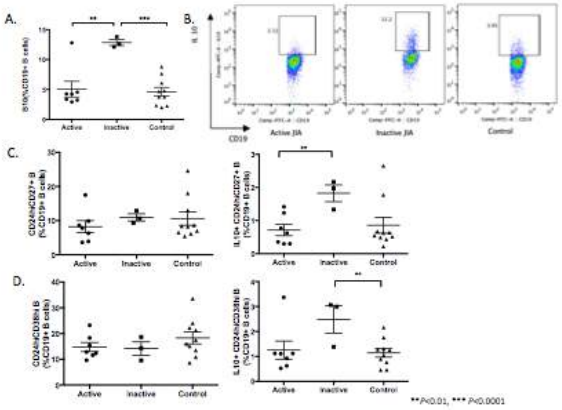
Ten poly-JIA patients (7 active and 3 inactive) and 10 children with joint pain but without arthritis were included in this study. Inactive disease was defined as an active joint count of 0, absence of uveitis and a Physician Global Assessment <10 mm with normal erythrocyte sediment rate (ESR). B10 cells were generated from peripheral blood mononuclear cells stimulated with CpG and CD40L for 48 hours, and phorbol 12-myristate 13-acetate+ionomycin+brefeldin A (PIB) for the last 6 hours. Intracellular B cell IL-10 and surface markers were assessed by flow cytometry.

Results:

The percentage of B10 cell was significantly higher in inactive poly-JIA patients than in active patients and controls (12.83±0.50 vs. 5.05±1.31, P=0.006; 12.83±0.50 vs. 4.62±0.73, P<0.0001), while there was no significant difference of B10 % between active patients and controls (P=0.762)(Figure A and B). Although there was no significant difference of the percentages of $CD24^{hi}CD27^{+}CD19^{+}$ B cells among the three groups (8.22±1.78 in active poly-JIA, 10.94±1.05 in inactive poly-JIA, and 10.60±1.96 in healthy control, P=0.623), the percentage of $\mathbf{IL10^{+}}CD24^{hi}CD27^{+}CD19^{+}$ B cells was significantly higher in inactive patients than in active patients (1.82±0.25 vs. 0.71±0.17, P=0.007), and was similar in active patients compared to controls (0.71±0.17 vs. 0.86±0.24, P=0.658)(Figure C). The percentages of $CD24^{hi}CD38^{hi}CD19^{+}$ B cells and $\mathbf{IL10^{+}}CD24^{hi}CD38^{hi}CD19^{+}$ B cells between active and inactive patients had not reached statistical difference, but the percentage of $IL10^{+}CD24^{hi}CD38^{hi}CD19^{+}$B cells in inactive patients was significantly higher than in controls (2.48±0.55 vs. 1.14±0.17, P=0.008)(Figure D). There was no correlation between B10 percentage and ESR within active poly-JIA patients.

Conclusion:

B10 cells are increased in patients whose disease is inactive, which suggests a role of them in controlling disease activity in poly-JIA pathogenesis. More samples and follow-up are needed to confirm these results.



Disclosure: Q. Zhao, None; **L. K. Jung**, OncoImmune, 5.

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Abstract Number: 2461

Identification of Target Antigens for Anti-Endothelial Cell Antibodies in Patients

with Pediatric Rheumatic Diseases Using Proteomics

Rie Karasawa[1], Mayumi Tamaki[1], Yanmin Chen[2], Kaiyu Jiang[2], Kazuo Yudoh[1] and James Jarvis[2], [1]Institute of Medical Science, St. Marianna University School of Medicine, Kawasaki, Japan, [2]Pediatrics, The University at Buffalo, Buffalo, NY
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SESSION INFORMATION
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Background/Purpose: Juvenile dermatomyositis (JDM), the most common inflammatory myopathy of childhood, is a rare systemic autoimmune vasculopathy. Juvenile idiopathic arthritis (JIA), the most common pediatric rheumatic disease, is a heterogeneous group of inflammatory diseases. The etiology of these diseases is unknown, and we lack disease and disease activity--specific biomarkers. Anti-endothelial cell antibodies (AECA) are autoantibodies against antigens on endothelial cell surface and are detected frequently in rheumatic diseases such as vasculitis. We tried to detect target proteins of AECA comprehensively by proteomics in patients with pediatric rheumatic diseases such as JIA and JDM. Furthermore we investigated relationship to these diseases in AECA from individual identified target antigens.

Methods: We separated proteins extracted from human aortic endothelial cells (HAEC) by one-dimensional electrophoresis (1DE) and two-dimensional electrophoresis (2DE) and transferred them onto membranes. By western blotting (WB) using sera from patients with pediatric rheumatic diseases and healthy donors, we detected antigens that were positive only in pediatric rheumatic disease sera but not in healthy donor sera. We next identified the detected proteins by peptide mass finger-printing.

Results: By using 1DE, 70-kDa and 88-kDa target protein of AECA were detected only in active patients without treatment. 48-kDa and 75-kDa target protein of AECA were detected only in active patients with treatment. 110-kDa target protein of AECA was detected only in active patients. These target proteins of AECA were not detected in inactive patients and healthy donors. Eighteen candidate protein spots as pediatric rheumatic diseases-specific proteins were detected in 2DE-WB. From these spots, we successfully identified 738 proteins which we functionally characterized: (1) 37% were ATP-related proteins such as proteins of the tricarboxylic acid (TCA) cycle (e.g., phosphoserine aminotransferase and methylmalonyl-CoA mutase; (2)19% were muscle-related proteins, including tropomyosin beta chain and PDZ and LIM domain protein 7; (3)13% were calcium regulated protein and/or calcium binding proteins (e.g., annexin A1 and calreticulin); (4)10% were redox related proteins (e.g., procollagen-lysine, 2-oxoglutarate 5-dioxygenase 2, and procollagen-lysine,2-oxoglutarate 5-dioxygenase 2). Furthermore 50% of the identified antigens represented membrane proteins.

Conclusion: Antibodies directed toward the proteome of HAEC are present in the sera of patients with pediatric rheumatic diseases. These antibodies recognize a broad range of cellular targets, including those associated with skeletal muscle function and inflammatory processes.

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Abstract Number: 2462

Altered Expression of IL-10 Family Cytokines in Chronic Recurrent Multifocal Osteomyelitis Result in Enhanced Inflammasome Activation

Sigrun Hofmann[1], Angela Rösen-Wolff[1], Hermann Girschick[2], Henner Morbach[3] and **Christian Hedrich**[4], [1]Children's Hospital Dresden, Dresden, Germany, [2]Children's Hospital, Berlin, Germany, [3]Children's Hospital Würzburg, Würzburg, Germany, [4]Pediatric Rheumatology and Immunology, Children's Hospital Dresden, Dresden, Germany
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Background/Purpose:

Chronic recurrent multifocal osteomyelitis (CRMO) is the most severe presentation of the autoinflammatory bone disorder chronic nonbacterial osteomyelitis (CNO). The pathophysiology of CNO remains to be determined. We recently demonstrated reduced activation of mitogen-activated protein kinases ERK1 and 2 in monocytes from CRMO patients responsible for impaired activation of the transcription factor signaling protein (Sp-)1. This resulted in failure to express the immuno-modulatory cytokine IL-10. The *IL10* gene, together with its homologues *IL19* and *IL20*, is organized in the 145 kb spanning *IL10* cytokine cluster on chromosome 1q32. In most cells, including monocytes, IL-10 cytokine family members are co-regulated in response to certain stimuli. IL-10 and IL-19 mainly have immune-modulating functions, while IL-20 acts as a pro-inflammatory cytokine contributing to inflammatory bone-loss. The NLRP3 inflammasome is a multi-protein complex forming in response to innate stimuli, subsequently mediating the cleavage and release of IL-1β. Enhanced inflammasome activation in IL-10 deficient mice was linked with bone-loss. Convincing evidence of this mechanism playing a role in CNO, however, is lacking. The aim of our study was to determine i) IL-10 cytokine family expression patterns in CRMO monocytes, ii) molecular mechanisms underlying impaired cytokine expression, and iii) potential effects on inflammasome-dependent cytokine secretion.

Methods: *Ex vivo* isolated monocytes from CRMO patients were cultured in the absence or presence of LPS. Expression patterns of cytokines were monitored on the transcriptional (mRNA) and protein level. Effects of impaired Sp-1 activation on cytokine expression were investigated through forced expression, chemical inhibition, or knock-down of Sp-1.

Results: We saw reduced expression of anti-inflammatory cytokines IL-10 and IL-19 and unaffected expression of IL-20 in CRMO monocytes when compared to controls. We for the first time demonstrate Sp-1 recruitment to the *IL19* promoter, governing IL-19 expression in monocytes. Impaired expression of IL-10 and IL-19 in CRMO monocytes was caused by reduced binding of Sp-1 to regulatory regions. Expression of IL-20 was independent of Sp-1. Reduced IL-10 and IL-19 secretion from CRMO monocytes mediated increased activity of the NLRP3 inflammasome, as assessed by IL-1β secretion. Addition of recombinant IL-10 or IL-19 reversed these findings.

Conclusion: Impaired activation of Sp-1 in monocytes from CRMO patients contributes to reduced expression of IL-10 and IL-19, resulting in an imbalance between pro- (IL-20) and anti-inflammatory IL-10 cytokine family members. Subsequently enhanced NLRP3 inflammasome activation results in IL-1β secretion which may in turn contribute to inflammatory bone-loss. A complete understanding of the molecular pathophysiology of CNO will aid in developing new disease biomarkers and therapeutic targets.

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Abstract Number: 2463

Soluble Low-Density Lipoprotein Receptor-Related Protein 1 in Juvenile Idiopathic Arthritis

Alan M. Rosenberg[1], Marianna Newkirk[2], Elham Rezaei[1], Zhenhong Li[3] and Kiem Oen[4], [1]Pediatrics, University of Saskatchewan, Saskatoon, SK, Canada, [2]Medicine, McGill University Health Centr, Montreal, QC, Canada, [3]McGill University Health Centr, Montreal, QC, Canada, [4]University of Manitoba, Winnipeg, MB, Canada

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Background/Purpose: Low-density lipoprotein receptor–related protein 1 (LRP1), a transmembrane protein, mediates endocytosis of an array of extracellular ligands. LRP1 has intracellular and extracellular domains. With inflammation the extracellular domain can shed into the circulation as soluble LRP1 (sLRP1). Increased sLRP1 has been reported in adult rheumatoid arthritis but not in childhood arthritis. This study aimed to determine, in children with juvenile idiopathic arthritis (JIA), levels of sLRP1 and correlations with age, clinical indicators of disease activity, and inflammatory biomarkers.

Methods: 111 newly diagnosed, treatment naïve children with JIA from 11 Canadian pediatric rheumatology centers were studied. Plasma was assayed for sLRP1 by ELISA and for 47 inflammation-related biomarkers by bead-based, multiplex immunoassays. Pearson correlations identified relationships between sLRP1 levels and indicators of disease activity and logarithmic transformed multiplex biomarker levels. Differences in mean sLRP1 levels in relation to presence/absence of morning stiffness were analyzed by t-tests. Comparison of sLRP1 means across JIA categories was assessed by ANOVA.

Results: Mean sLRP1 levels were highest in rheumatoid factor negative (RF-) polyarticular, oligoarticular, and psoriatic JIA and lowest in systemic JIA (Table).

JIA Subtype (n)	Mean sLRP1 + 1 SD (ng/ml)
RF– Polyarticular (41)	166.92 + 402.74
Psoriatic (9)	136.34 + 161.16
Oligoarticular (27)	120.51 + 156.97
RF+ Polyarticular (8)	67.69 + 132.77
Undifferentiated (4)	43.94 + 38.76
Enthesitis Related (8)	33.40 + 29.72
Systemic (14)	30.01 +14.48

ANOVA did not show significant mean sLRP1 differences among JIA subtypes. Groups of children stratified as < age 4 years and < age 5 years had higher levels of sLRP1 than older children (p=0.019 and 0.028 respectively). sLRP1 levels did not correlate with active joint count, presence of morning stiffness, ESR, or CRP. In oligoarticular and RF- polyarticular JIA levels of sLRP1 were positively correlated with the same 32 biomarkers encompassing a wide array of pro- and anti-inflammatory cytokines, chemokines, matrix metalloproteinases, and growth factors (p=0.026 to <0.001). An additional 2 correlations with biomarkers were found in RF- polyarticular JIA. In contrast, sLRP1 levels correlated with only a small number of the 47 biomarkers in other JIA subtypes (9 in psoriatic , 4 in RF+ polyarticular, 2 in enthesitis related arthritis, and none in systemic).

Conclusion: In this first report of sLRP1 in JIA we found correlations of sLRP1 with young age and, in oligoarticular and RF- polyarticular subtypes, with inflammation-related biomarkers. Findings suggest that oligoarticular and RF- polyarticular JIA are linked pathobiologically with respect to sLRP1 and the profile of biomarkers with which it is associated. Plasma sLRP1 could be a valuable biomarker reflective of inflammatory-mediated processes related to JIA subtype and onset age.

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Abstract Number: 2464

Characterization of the Serum Anti-Citrullinated Protein Antibody Profile in Juvenile Idiopathic Arthritis: Association with Oral Health

Sampath Prahalad[1], Lauren J. Lahey[2], Geoffrey M. Thiele[3], Lori Ponder[1], Sheila T. Angeles-Han[1], Lauren Lange[4], Aimee O. Hersh[5], Mina Rohani-Pichavant[1], Se Ryeong Jang[1], Larry B. Vogler[1], Patricia Vega-Fernandez[1], Kelly A. Rouster-Stevens[1], John F. Bohnsack[6], Ted R. Mikuls[7] and Jeremy Sokolove[8], [1]Emory University School of Medicine and Children's Healthcare of Atlanta, Atlanta, GA, [2]Medicine, VA Palo Alto HealthCare System and Stanford University, Palo Alto, CA, [3]Omaha VA Medical Center and University of Nebraska Medical Center, Omaha, NE, [4]Pediatrics, Ann and Robert H. Lurie Children's Hospital of Chicago, Chicago, IL, [5]Pediatrics/Rheumatology, University of Utah, Salt Lake City, UT, [6]Pediatrics, University of Utah Health Sciences Center, Salt Lake City, UT, [7]Veteran Affairs Nebraska-Western Iowa Health Care System and University of Nebraska Medical Center, Omaha, NE, [8]Stanford University, Palo Alto, CA

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Background/Purpose: Juvenile idiopathic arthritis (JIA) is the most common chronic childhood arthropathy. Most children with JIA phenotypically differ from adults with rheumatoid arthritis (RA) although some children resemble RA by demonstrating rheumatoid factor (RF) and anti-cyclic citrullinated peptide antibodies (CCP). Our objective was to characterize the association between anti-citrullinated protein antibodies (ACPA) and several clinical/epidemiological features in children with CCP-positive and CCP-negative JIA.

Methods: Cases were 157 children with JIA. (73 CCP-/RF-; 12 CCP-/RF+; 9 CCP+/RF-; 63 CCP+/RF+), mostly female (80%), with a mean onset age of 8.6 years. Oral health and smoking exposure history were available on 107 cases. Stored serum/plasma samples were evaluated for reactivity to 30 citrullinated peptide/protein antigens and 7 native controls using a multiplex antigen array. Significance analysis of microarrays (SAM) was used to analyze a multiplex of specific ACPAs among JIA cases to identify differences in ACPA profiles associated with variables. False-discovery corrected significance values <5% were considered statistically significant.

Results: All ACPA evaluated were significantly different between CCP-/RF-, CCP-/RF+, CP+/RF-, and CCP+/RF+ subjects with JIA (q value <0.1%). Figure 1 is a heatmap demonstrating increased levels of several antigen-specific ACPAs in seropositive JIA patients. Among CCP+ children, those who reported having no dental caries had significantly less ACPAs compared to those who reported having dental caries (Figure 2). Several other variables were also associated with significant differences in ACPA positivity among children with CCP+ JIA (Table 1).

Conclusion: Children with JIA positive for both CCP and RF demonstrate significantly increased antibody response to a variety of citrullinated antigens compared to children who are CCP and RF negative, as well as those who are positive for either CCP or RF alone. This suggests that CCP and RF-positive JIA is phenotypically similar to adult seropositive RA. Presence of dental caries may be associated with increased ACPA subtypes in children with CCP-positive JIA.

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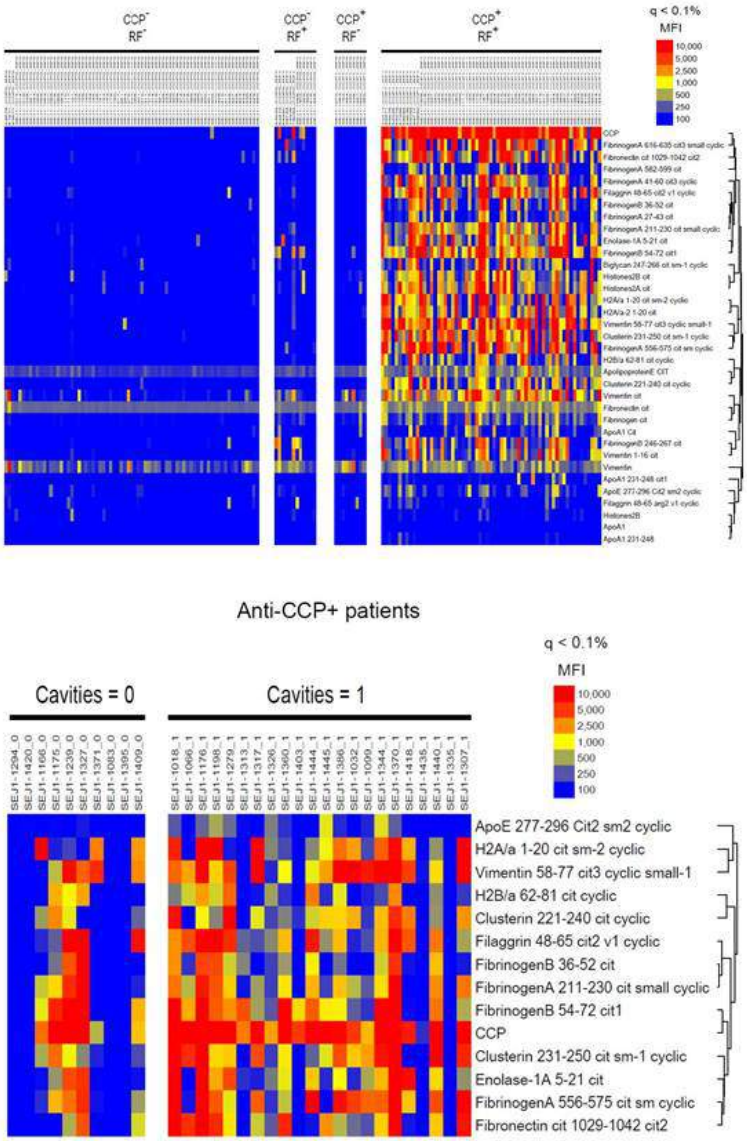
Criteria	Group 1	Group 2	Number of ACPAs	Q value
Significant associations with ACPA				
Dental caries	Absent	Present	13	<0.1%
Regular flossing	Absent	Present	9	<0.1%
Pain on chewing	Absent	Present	17	<0.1%
Regular brushing	Absent	Present	11	<0.1%
Onset age	<9	>9	7	<0.1 %
Red/swollen gums	Absent	Present	7	<0.1 %
Anti P Intermedia	Lowest ½	Highest ½	16	4.7 %
Not significantly associated with ACPA				
Anti P gingivalis	Lowest ½	Highest ½	17	NS
Anti F Nucleatum	Lowest ½	Highest ½	16	NS
Smoking exposure	Absent	Present	18	NS



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Abstract Number: 2465

Cytokine Profile Comparison of Monogenic and Complex Conditions with Interferon-Regulated Gene Signatures in Chronic Atypical Neutrophilic Dermatosis with Lipodsytrophy and Elevated Temperature (CANDLE), SAVI, Aicardi-Goutieres Syndrome, JDM, and SLE

Hanna Kim[1], Yin Liu[2], Adriana Almeida de Jesus[1], Robert Wesley[3], Yan Huang[1], Gina A. Montealegre Sanchez[1], Dawn C. Chapelle[1], Wanxia L. Tsai[4], Massimo G. Gadina[4], Frederick W. Miller[5], Sarfaraz Hasni[6], Adeline Vanderver[7], Lisa G Rider[5] and Raphaela Goldbach-Mansky[1], [1]Translational Autoinflammatory Diseases Section, NIAMS, NIH, Bethesda, MD, [2]Scientific

Review Branch, NIAMS, NIH, Bethesda, MD, [3]Clinical Center, National Institutes of Health, Bethesda, MD, [4]Translational Immunology Section, National Institute of Arthritis and Musculoskeletal and Skin Diseases, NIH, Bethesda, MD, [5]Environmental Autoimmunity Group, NIEHS, NIH, Bethesda, MD, [6]National Institute of Arthritis and Musculoskeletal and Skin Diseases, National Institutes of Health, Bethesda, MD, [7]Pediatric Neurology, Children's National Medical Center, Washington, DC
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SESSION INFORMATION
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Session Time: 9:00AM-11:00AM

Background/Purpose:

An Interferon (IFN) Regulated Gene Signature (IRS) was previously reported in patients with two complex autoimmune diseases, juvenile systemic lupus (JSLE)[1] and juvenile dermatomyositis (JDM).[2] Recently, three Mendelian conditions including CANDLE syndrome[3], STimulator of IFN Genes or STING-associated Vasculopathy with onset during Infancy (SAVI)[4], and Aicardi Goutieres syndrome (AGS)[5] have demonstrated a prominent IRS. Previous evaluations[6] found clinical phenotypic overlap such as basal ganglia calcifications (CANDLE, AGS), lipodystrophy (CANDLE, JDM), and myositis (JDM, CANDLE, SLE) raising interest in a shared role of IFN in disease-pathogenesis. This study aims to assess cytokine profile differences between IFN conditions, healthy controls and the IL-1 mediated monogenic disease, NOMID, to better understand pathogenesis and identify potential disease-specific biomarkers.

Methods:

Plasma/serum cytokine levels of 6 cytokines identified by literature review and preliminary analysis[6] were measured in 5 IFN conditions (3 Mendelian and 2 complex), the IL-1 mediated disease, NOMID, and healthy controls using a multiplex bead -based assay (Luminex/Austin, TX). Analysis of variance (ANOVA) followed by Dunnett's tests were performed to identify significant differences between each IFN condition and: 1) healthy controls and 2) NOMID (IL-1 mediated disease control). ANOVA, followed by Student-Newman-Keuls post-hoc tests, were used to assess for significant differences among the 5 IFN conditions. Statistical analysis done with Stata 12 (College Station, TX).

Results:

		IFN-mediated				*non-IFN*	
	(n)	IP10	MCP1	MIP1-alpha	RANTES	IL13	IL15
IFN conditions	CANDLE (12)	*4.16***	2.33***	0.99	4.24	1.38**	0.22
	SAVI (4)	*3.82***	2.13	0.94	4.34	1.08	0.15
	AGS (16)	2.95	2.18	*1.08**	*4.07**	1.23	0.57*
	JDM (20)	3.14*	2.25**	1.00	4.29	1.27	0.32
	SLE (16)	3.11	2.20	***1.17****	4.34	1.29	0.59*
	NOMID Control (15)	2.90	2.25	0.88	4.27	1.13	0.68
	Healthy Control (11)	2.72	1.98	0.83	4.25	1.04	0.02

*: p≤0.05 ** : p≤0.01 *** : p≤0.001

Table 1. Mean Cytokine Values (log 10 scale) by cytokine (columns) and condition (rows).
Values significantly different from healthy controls are marked by an asterisk. Number of astericks indicate level of p value. Values in italics are significantly different versus healthy controls and NOMID controls, except RANTES in AGS which is only significantly different versus NOMID controls. MIP1-alpha for SLE is bolded due to differential p values versus NOMID (0.02, **) and healthy controls (0.01, ***).

All significant values are higher in an IFN condition than NOMID or healthy controls, except RANTES which is lower in AGS versus NOMID. Most significantly elevated are IP-10 in CANDLE and SAVI, and MIP1-alpha in SLE compared to healthy controls and NOMID. Among the 5 IFN conditions, IP-10 is significantly higher in CANDLE and SAVI versus AGS, JDM, and SLE. RANTES is significantly lower in AGS versus the 4 other IFN conditions.

Conclusion:

The IFN inducible chemokine, IP-10/CXCL10, is significantly elevated in CANDLE and SAVI, even compared to AGS, JDM, SLE, and NOMID suggesting IFN-driven systemic inflammation in CANDLE and SAVI. The monocyte migration factor MCP-1/CCL2 is similarly induced in IFN diseases and the IL-1 disease, NOMID, consistent with its role in routine immunological

surveillance observed in a variety of inflammatory conditions. Significant and specific elevation of MIP1-alpha may play a role in granulocyte recruitment and activation in SLE. Distinct cytokine profiles in IFN and IL-1 mediated diseases may help in understanding organ-specific inflammatory pathogenesis and development of disease-specific biomarkers.

[1]Bennett, *Exp Med*, 2003,[2]Baechler, *Mol Med*, 2007, [3] Liu, *A&R*, 2012, [4]Liu, *NEJM*, 2014, [5] Rice, *Nat Gen*, 2012 [6] Kim, H. *A&R*, 2013

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Abstract Number: 2466

Epigenetic Traits Correlate with Clinical Activity in Juvenile Idiopathic Arthritis

Roberto Spreafico[1,2], Maura Rossetti[1,2], Carol A. Wallace[3], Daniel Lovell[4,5] and Salvatore Albani[1,6], [1]SingHealth Translational Immunology and Inflammation Centre, Singapore Health Services Pte Ltd, Singapore, Singapore, [2]Sanford-Burnham Medical Research Institute, La Jolla, CA, [3]Seattle Children's Hospital and Research Institute, Seattle, WA, [4]Cincinnati Children's Hospital Medical Center, Cincinnati, OH, [5]Rheumatology, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, [6]Duke-National University of Singapore Graduate Medical School, Singapore, Singapore

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Background/Purpose: Epigenetic regulation of gene expression is increasingly under scrutiny to understand the pathogenesis of multifactorial human diseases, such as juvenile idiopathic arthritis (JIA). Indeed, the low concordance rate between monozygotic twins (20-40%) underscores that, while this autoimmune disease has a genetic component, environmental triggers are fundamental in the disease pathogenesis. Epigenetic mechanisms are believed to integrate such non-genetic factors, and may underlie the dysregulation of the immune system.

Methods: We interrogated the DNA methylome of JIA patients before and after anti-TNF therapy withdrawal with the Infinium HumanMethylation450 BeadChip. Patients were stratified by clinical activity 8 months after withdrawal.

Results: Individual CpG sites were clustered in coherent modules without any a priori knowledge of their function. Strikingly, modules statistically associated with clinical activity were enriched in CpG sites belonging to genes that mediate T cell activation. Conversely, modules linked to age or gender controlled fundamental, non-immune functions of the cell, such as metabolism. Of note, the DNA methylome was stable, showing little variation before and after therapy discontinuation. When a similar analysis was performed on matched transcriptomic data, we found that the correlation of mRNA abundances with clinical activity was much lower than that observed for DNA methylation.

Conclusion: Our work (i) demonstrates that medically relevant information is encoded in epigenetic traits; (ii) reveals biological functions tied to clinical activity; and (iii) establishes the superiority of epigenetic markers over gene expression-based markers.

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View Abstract and Citation Information Online - http://acrabstracts.org/abstract/epigenetic-traits-correlate-with-clinical-activity-in-juvenile-idiopathic-arthritis

Abstract Number: 2467

Interaction Between Senescent T Cells and Fibrocyte-like Cells through CD31, TNFα, and IL-17 Create a Tissue Destructive Environment in the Synovium in Juvenile Idiopathic Arthritis

Ian D. Ferguson[1], Patricia Griffin[2], Hiroshi Yano[3], Joshua J. Michel[2], Jeffrey A. Dvergsten[4], Sarah L. Gaffen[5], Margalit E. Rosenkranz[1], Daniel A. Kietz[1] and **Abbe N. Vallejo**[1], [1]Department of Pediatrics, Children's Hospital of Pittsburgh, University of Pittsburgh School of Medicine, Pittsburgh, PA, [2]Department of Pediatrics, University of Pittsburgh School of Medicine, Pittsburgh, PA, [3]Department of Immunology, University of Pittsburgh School of Medicine, Pittsburgh, PA, [4]Department of Pediatrics, Duke University Medical Center, Durham, NC, [5]Division of Rheumatology and Clinical Immunology, Department of Medicine, University of Pittsburgh School of Medicine, Pittsburgh, PA

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Session Time: 9:00AM-11:00AM

Background/Purpose: T cells are considered effectors of immunopathology in JIA. In previous work, we reported dominance of senescent CD8T cells in synovial fluid of children with oligoarticular (oligo-) and polyarticular (poly-) JIA disease. Here, we examined for additional effector cells and how they shape the inflammatory microenvironment of the synovium.

Methods: Healthy children, children with oligo- and poly-JIA, and their legal guardians provided informed assent/consent. Blood samples were obtained, and where medically indicated, synovial fluids were collected from JIA patients. Cell populations were examined by flow cytometry. Cell cultures and bioassays of cell activation were performed using previously established protocols. Cytokine profiles of plasma, synovial fluids, and culture supernatants were determined by the Luminex system.

Results: The local and systemic cytokine signatures of JIA were dominated by five molecules including TNFα and IL-17. The corresponding cellular signatures included senescent $CD31^+$ CD8T cells, and $CD31^+$ double negative (DN) T cells that lack both CD4 and CD8. In synovial fluid, large numbers of fibrocyte-like cells (FLC) expressing procollagen, proline-4-hydroxylase, IL-17 receptor A, and the CD31 ligand CD38, also abound. Ligation of CD31 either with specific antibody or recombinant CD38, independent of the TCR, on synovial CD8T and DNT cells was sufficient to induce production of TNFα and IL-17. CD31 ligation alone was also sufficient to transactivate the *IL-17* gene promoter, and the *IL-17* gene transcription factor RORγT. Incubation of FLC with TNFα, IL-17, or both led to the induction of vascular endothelial growth factor, a known propagator of tissue inflammation, and three species of matrix metalloproteinases known to directly elicit cell/tissue damage. These T cell and FLC responses were abrogated by steroids, infliximab, tocolizumab, and a novel experimental small molecule inhibitor.

Conclusion: Collectively, our data indicate CD8T/DNT-FLC communication circuit via CD31 and IL-17. CD31-driven, TCR-independent induction of TNFα and IL-17 clearly demonstrate dysregulation of T cell effector function. Activation of FLC by T cell-derived TNFα and IL-17 amplifies synovial inflammatory processes. Further understanding of the control of this T cell-FLC circuit will pave way to innovative strategies to dampen immunopathology of JIA.

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Abstract Number: 2468

Antibodies to Histocompatibility Antigens in Juvenile Systemic Lupus Erythematosus Patients

Ana L Rodríguez-Lozano[1], Anne M. Stevens[2], Jessica M Foster[3], Marisa S. Klein-Gitelman[4], Hermine I. Brunner[5], Elizabeth Field[6], Ann M Reed[7] and Karen Onel[8], [1]Immunology, Instituto Nacional de Pediatria, Mexico City, Mexico, [2]Seattle Children's Res Inst, Seattle Children's Hospital, Seattle, WA, [3]Center for Immunity and Immunotherapies, Seattle Children's Research Institute, Seattle, WA, [4]Division of Rheumatology, Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, IL, [5]Cincinnati Children's Hospital Medical Center, Cincinnati, OH, [6]Internal Medicine, University of Iowa, Iowa City, IA, [7]Department of Pediatrics, Duke University, Durham, NC, [8]Pediatric Rheumatology, Univ of Chicago, Chicago, IL
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Background/Purpose: Microchimerism with HLA mismatched maternal cells can be readily demonstrated in normal individuals and is now established as a normal biological phenomenon. Pediatric SLE patients have decreased levels of blood maternal microchimerism, suggesting a loss of T-cell tolerance to maternal antigens. Because maternal MHC molecules are the most likely targets of the T-cell hyperactivity, we reasoned that pediatric lupus patients may also have B cell reactivity to maternal MHC.

Methods:

To test for loss of B-cell tolerance to maternal MHC, we measured IgG specific for HLA Class II antigens in plasma samples from children who have never been pregnant: 81 with SLE (49 (60%) with active disease, SLEDAI >4), 20 patients (24%) with nephritis. Control groups consisted of 16 systemic sclerosis (SSc), 20 juvenile idiopathic arthritis (JIA), and 78 healthy children. OneLambda, Inc. LABScreen microbeads coated with purified Class II HLA antigens were used to detect specific IgG. Data acquisition and analysis was performed using LABScan™ Statistical analysis was performed using SPSS version 16.0, Mann Whitney was used to determine median difference between groups, Correlations were tested by Spearman and associations by Likelihood ratios or Fisher Exact Test, ROC curves were constructed to test for the specificity of HLAab for lupus diagnosis and active lupus.

Results: All Subjects: The median values of 90% of specific HLAab were high in patients with SLE compared to controls. HLAab levels in JIA and SSc were similar to controls. Among the SLE patients, 27 out of 77 HLA antigens were increased in patients with active disease compared to those without active disease. Of these, a significant association was found with disease activity in 15 HLAab (see Table 1). ROC curves demonstrated specificity for active SLE in 4 HLAab, with AUC >.700: DQA1*0301-DQB1*0302 (AUC .758, 95% CI 0.66-.86, p<0.001), DQA1*0301-DQB1*0303, (AUC 0.76, 95% CI 0.66-.87, p<0.001), DQA1*0501-DQB1*0201 (AUC 0.73, 95% CI 0.61-.84, P=0.001, and DPB1*1401=DPA1*0201 (AUC 0.72, 95% CI 0.6-.84], P=0.001. Ten HLAab demonstrated a significant median difference between those with and without nephritis, and seven of those showed significant associations (Table 1).

Conclusion:

Children with SLE have high values and a considerable number of anti-HLA class II autoantibodies which seem to be specific, related with disease activity and to a lesser extent with nephritis. If confirmed, HLAab could represent useful biomarkers for disease activity.

Table 1. Significant association between HLAab with Disease Activity and Nephritis

HLAab	Disease Activity		HLAab	Nephritis
DQA*10301 DQB*10302	15.948 sig .000&		DQA1*0303 DQB1*0401	5.806 sig .020&
DQA*10301 DQB*10303	12.7888 sig .000		DQA1*0101 DQB1*0501	5.330 sig .023&
DPB1*1401 DPA1*0202	11.401 sig .001		DPB1*1001 DPA1*0201	5.131 sig .024
DQA1*0401 DPB1*0201	10.960 sig .001&		DRB5*0202	4.751 sig .045&
DPB1*1001 DPA1*0201	10.246 sig .001		DQA1*0102 DQB1*0609	4.489 sig .037&
DQA1*0302 DQB1*0301	9.773 sig .008&		DQA1*0201 DQB1*0201	4.322 sig .036&
DQA1*0601 DQB1*0301	8.608 sig .014&		DQA1*0201 DQB1*0202	4.322 sig .036&
DQA1*0303 DQB1*0301	8.608 sig .014&			
DRB1*1303	8.608 sig .014&			
DQA1*0501 DQB1*0201	8.359 sig .004			
DQA1*0201 DQB1*0303	7.906 sig .005			
DRB1*1001	7.465 sig .025&			
DPB1*0301 DPA1*0103	7.105 sig .008			

Associations between Disease Activity (SLEDAI>4) and Nephritis with HLAab are reported as Likelihood Ratios and Fisher Exact Test&

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View Abstract and Citation Information Online - http://acrabstracts.org/abstract/antibodies-to-histocompatibility-antigens-in-juvenile-systemic-lupus-erythematosus-patients

Abstract Number: 2469

The Lymphocyte Repertoire in Juvenile Dermatomyositis

Lauren A. Henderson[1], Edwin Anderson[1], Robert C. Fuhlbrigge[1,2], Luigi D. Notarangelo[1,3,4] and Susan Kim[1], [1]Division of Immunology, Boston Children's Hospital, Boston, MA, [2]Department of Dermatology, Brigham and Women's Hospital, Boston, MA, [3]The Manton Center for Orphan Disease Research, Boston Children's Hospital, Boston, MA, [4]Harvard Stem Cell Institute, Boston, MA

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Background/Purpose: In adult dermatomyositis, clonal populations of T lymphocytes with shared variable (V) gene usage have been identified, suggesting aberrant T cell responses to a common antigen. A $CD4^+$T cell subset, regulatory T (Treg) cells, has recently been identified as important mediators of muscle tissue repair. A diverse Treg repertoire is thought to be important in

maintaining Treg function and may contribute to the Treg response to muscle damage. Little is known about the T cell repertoire in juvenile dermatomyositis (JDM); further, the Treg repertoire in human inflammatory myopathies has not been evaluated. Therefore, we employed next generation sequencing to characterize the Treg and effector T (Teff) cell repertoires in JDM.

Methods: Peripheral blood (PB) was obtained from JDM patients (n=6) at disease onset and healthy children (n=3). Treg ($CD4^+CD25^+CD127^{lo}$) and Teff ($CD4^+CD25^-$) cells were isolated from PB mononuclear cells by fluorescence-activated cell sorting. The T cell receptor (TCR) β chain was amplified by multiplex PCR with genomic DNA serving as the template (ImmunoSEQ™). Illumina HiSeq platform was used for sequencing. Wilcoxon sign ranked tests were used to compare the clonality index and normalized Shannon entropy in patients and controls. 2-way ANOVA with Bonferroni correction was used to compare TCRVβ family usage in patients versus controls.

Results: Three males and 3 females with JDM, average age 7.0 years (range: 3.3-9.4 years), were studied. The average disease duration was 7 months, and the average MMT8 score was 69.6. Five of the patients were evaluated before the initiation of any immunosuppressive therapy. Treg and Teff repertoire clonality and diversity were similar in JDM patients and controls. In JDM Treg and Teff subsets, TCRVβ families 7, 19, and 28 were used more and TCRVβ families 2, 3, 5, 6 were used less than in controls ($p<0.0001$ for both Treg and Teff cells). In particular, TCRVβ7 skewing was most striking, and this Vβ family was used more than twice as often in JDM PB Treg and Teff cells compared to controls.

Conclusion: Skewed TCRVβ family usage was observed in JDM patients at disease onset. Increased usage of TCRVβ7 was observed in JDM PB Treg and Teff cells, and this Vβ family has been linked with other autoimmune conditions including type I diabetes and anti-phospholipid syndrome. Our early pilot results suggest that T cell repertoire abnormalities may contribute to disease pathogenesis in JDM. Further studies are planned to evaluate the T cell repertoire in JDM muscle and skin biopsies, as well as longitudinally over the course of disease.

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Abstract Number: 2470

Single Center Experience in Next Generation Sequencing for Genetic Diagnosis of Autoinflammatory Disorders

Antonella Insalaco[1], Elisa Pisaneschi[2], Francesca Romana Lepri[2], Daniele Minervino[2], Virginia Messia[1], Manuela Pardeo[3] and Fabrizio De Benedetti[1], [1]Division of Rheumatology, Department of Pediatric Medicine, IRCCS Ospedale Pediatrico Bambino Gesù, Rome, Italy, [2]Ospedale Pediatrico Bambino Gesù, IRCCS, Department of Cytogenetics, Roma, Italy, [3]Department of Pediatric Medicine, Division of Rheumatology, Ospedale Pediatrico Bambino Gesù, IRCCS, Rome, Italy

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Background/Purpose: Autoinflammatory disorders (AIDs) represent an expanding group of complex diseases characterized by periodic or chronic systemic inflammations. Mutations in more than 15 genes have been associated with autoinflammatory recessive or dominant syndromes (1). Next Generation Sequencing (NGS) has emerged in the last year as new diagnostic tool in this field. to share data obtained by the application of NGS in a cohort of patients affected by an autoinflammatory disease of undefined origin evaluated at our center.

Methods: In this study we enrolled 158 patients evaluated at our center from 2010 to 2014. We developed NGS approache already known to be involved in AID (Panel 1: MVK, MEFV, NRLP12, NRLP3, NOD2, TNFRSF1A and PSTPIP1 and Panel 2: IL1RN, LPIN2, IL36RN, PSMB8). Targeted resequencing was performed using customized panel and analyzed with the MiSeq®

sequencing platform (Illumina, San Diego, CA). All variants identified have been confirmed by Sanger sequencing.

Results: 48,73% of the patients present variants in genes of Panel 1. 32,46% have variants in NLRP3 gene: the most frequent variants are Q705K (56%) and V200M (32%). About 26% have variants in NOD2, the most frequent variant is R702W (25%). 30% have variants in NLRP12, the most frequent variant is F402L (65%), in two cases is homozygous. 23,37% have variants in MEFV, the most frequent variant is E148Q (22%). 4% have variants in MVK, V377I (100%). 10,38% have variants in TNFRSF1A, the most frequent variant is R121Q (75%). 9% have variants in PSTPIP1. 69% of the patients present variant in only one gene; 28,57% present variants in two different genes and two patients in three genes. We performed 15 familial study to unravel the segregation of some variants.

Conclusion: NGS leads to the identification of many genetic variants that could be associated with disease susceptibility. The major challenge is in the interpretation of the clinical relevance of identified variants (2). Some patients show variants in multiple analyzed genes: it can be assumed that different variants in different genes may cooperate to determine a pathological phenotype. This will necessitate large-scale population studies, in vitro functional assay and careful correlation of genetic information with phenotypic data (3). Crucial is, therefore, close collaboration with clinicians.

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Abstract Number: 2471

Increased Muscle Interferon-Gamma Expression Levels in Juvenile Dermatomyositis

Gian Marco Moneta[1], Adele D'Amico[2], Margherita Verardo[3], Denise Pires Marafon[4], Luisa Bracci Laudiero[5], Fabrizio De Benedetti[6] and **Rebecca Nicolai**[7], [1]Department Pediatric Medicine, Division of Rheumatology, Bambino Gesù Children's Hospital, IRCCS, Rome, Italy, [2]Department of Neuroscience,, Unit of Neuromuscular and Neurodegenrative Disease, Bambino Gesù Children's Hospital IRCCS, Rome, Italy, [3]Department of Neuroscience, Unit of Neuromuscular and Neurodegenrative Disease, Bambino Gesù Children's Hospital IRCCS, Rome, Italy, [4]Pediatric Rheumatology, IRCCS Ospedale Pediatrico Bambino Gesù, Rome, Italy, [5]Rheumatology Laboratory, Bambino Gesú Children Hospital, Rome, Italy, [6]Pediatric Rheumatology, Bambino Gesù Children's Hospital, Rome, Italy, [7]Department of Pediatric Medicine, Division of Rheumatology, Bambino Gesù Children's Hospital, IRCCS, Rome, Italy

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Background/Purpose : Juvenile dermatomyositis (JDM) is a rare autoimmune disorder characterized by muscle weakness, skin rashes and other systemic features. The immunopathogenesis of JDM is unknown, but recent biomarker studies revealed that up-regulation of several type I interferon (IFN)-related mediators might play a role in the development of JDM. In this study, we focused our attention on the inflammatory cytokine interferon-γ (IFN-γ), the only member of type II class of interferons. We analysed muscle biopsy samples of JDM-affected children to characterize IFN-γ expression levels and to identify possible correlations with clinical features.

Methods : We identified a retrospective cohort of patients diagnosed with JDM at our Center between 2001 and 2014 and for whom a muscle biopsy was performed during diagnostic work-up. Expression levels of IFN-γ, chemokine (C-X-C motif) ligand 9 (CXCL-9), chemokine (C-X-C motif) ligand 10 (CXCL-10), chemokine (C-X-C motif) ligand 11 (CXCL-11), class II major histocompatibility complex, transactivator (CIITA) were analysed by real-time PCR on muscle biopsy samples from patients with JMD (n = 18) and compared with samples from Duchenne muscular dystrophy (DMD) patients (n = 29) by Mann Withney test.

Results : Median age at diagnosis of JDM patients was 5.4 years (interquartile range, IQR: 4.2-9.1), with a median disease duration at diagnosis of 2.1 months (IQR: 1.2-6.9). For each patient we recorded clinical features at diagnosis, physician's global assessment of the patient's overall disease activity on a 100-mm visual analog scale (VAS), serum levels of muscle enzymes (CK, ALT, AST, LDH), erythrocyte sedimentation rate, C-reactive protein level, and antinuclear antibodies status. Six patients were already treated with systemic glucocorticoids before time of biopsy sampling, whereas all DMD patients were untreated. Levels of IFN-γ, CXCL-9, CXCL-10, CXCL-11 and CIITA expression were significantly higher in JDM biopsy samples compared with those of DMD patients ($p = 0.0004$, $p = 0.0004$, $p < 0.0001$, $p < 0.0001$, $p = 0.0017$, respectively). In JDM patients we found that IFN- γ mRNA levels significantly correlated with CXCL-9 and CIITA mRNA levels; on the contrary, we do not observed correlations between IFN-γ mRNA levels and clinical scores. JDM patients treated before biopsy were excluded from final statistics since the molecular analysis resulted strongly influenced by glucocorticoid therapy.

Conclusion: The increased muscle expression of IFN-γ and IFN-γ correlated genes in muscle biopsy samples of JDM patients suggests a potential pathogenic role of IFN-γ in JDM.

Disclosure: G. M. Moneta, None; **A. D'Amico**, None; **M. Verardo**, None; **D. Pires Marafon**, None; **L. Bracci Laudiero**, None; **F. De Benedetti**, None; **R. Nicolai**, None.

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Abstract Number: 2472

Highly Elevated S100A8/A9 and S100A12 Levels May Distinguish Systemic Juvenile Idiopathic Arthritis Patients with New Onset Disease and Subclinical Macrophage Activation Syndrome

Jessica Turnier[1], Ndate Fall[2], Alexei A. Grom[3], Sherry Thornton[2] and Hermine I. Brunner[4], [1]Pediatric Rheumatology, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, [2]Division of Rheumatology, Cincinnati Children's Hospital, Cincinnati, OH, [3]PRCSG, Cincinnati, OH, [4]Cincinnati Children's Hospital Medical Center, Cincinnati, OH

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Background/Purpose:

Systemic juvenile idiopathic arthritis remains a clinical diagnosis without a specific diagnostic test. Previous studies have demonstrated that extremely high levels of S100 proteins may distinguish patients with systemic juvenile idiopathic arthritis (sJIA) from patients with other inflammatory diseases or additional subtypes of juvenile idiopathic arthritis. A great degree of heterogeneity exists within the serum levels of S100 proteins amongst sJIA patients. The purpose of this study was to explore the degree of variability within S100 protein levels in sJIA patients and to correlate S100 protein levels with clinical presentation.

Methods:

A total of 189 serum samples were collected from patients with different subtypes of juvenile idiopathic arthritis, including sJIA (n=22), persistent oligoarthritis (n=28), extended oligoarthritis (n=28), rheumatoid factor positive polyarthritis (n=27), rheumatoid factor negative polyarthritis (n=28), enthesitis-related arthritis (n=29) and psoriatic arthritis (n=27). In addition, patients with sJIA were further divided into active sJIA (n=11) and clinically inactive disease (n=11). Control samples (n=90) were obtained from healthy children aged 2-18 years old. Serum samples were analyzed for protein levels of S100A8/A9 and S100A12 using commercial ELISAs (BÜHLMANN MRP8/14 and CircuLex S100A12/EN-RAGE). Clinical characteristics of the sJIA patients were examined for differences in symptoms, exam findings, lab values and treatment at the time of sample collection.

Results:

Patients with active sJIA had the highest levels of S100 proteins when compared to other subtypes of juvenile idiopathic arthritis. Patients with clinically inactive sJIA had S100 protein levels comparable to controls. A bimodal distribution was noted in both the S100A8/A9 and S100A12 levels in patients with active sJIA. Systemic juvenile idiopathic arthritis patients in the subgroup with higher levels of S100 proteins were determined to have new onset disease as well as subclinical features of macrophage activation syndrome (low hemoglobin, elevated ferritin, hepatosplenomegaly, relatively low platelets in the setting of elevated CRP). The fold difference between protein levels in new onset sJIA versus active sJIA was 29 for the S100A8/A9 levels and 31 for the S100A12 levels.

Conclusion:

Higher levels of S100A8/A9 and S100A12 proteins correlate with disease activity in systemic juvenile idiopathic arthritis as previously described. Marked heterogeneity exists in S100 protein levels amongst active sJIA patients. Active sJIA patients in the subgroup with significantly higher levels of S100 proteins could represent a unique disease subtype.

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Abstract Number: 2473

Psycho-Socio-Economic Burdens of Childhood Onset Rheumatic Diseases on Families

Sook Fun Hoh[1], Manasita Tanya[2], Justin Hung Tiong Tan[2], Lena Das[2,3] and Thaschawee Arkachaisri[2], [1]Nursing, KK Women's and Children's Hospital, Singapore, Singapore, [2]Rheumatology and Immunology, KK Women's and Children's Hospital, Singapore, Singapore, [3]Dept of Rheumatology, Cincinnati Children`s Hospital Medical Center, Cincinnati, OH
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Background/Purpose:

Rheumatic diseases (RD) in children, being complex and chronic in nature, do not only pose physical insult to the affected child, but also psychological and socioeconomic impacts to the families. Data on impact to the families are scarce. We aim to assess the financial and psychosocial impacts on family confronting with such conditions in our cohort of children with RD in Singapore.

Methods:

Patients with chronic RD were recruited. The Impact on Family (IOF) scale was completed by the caregivers. The weighted IOF score was calculated from the total of 24 items in 4 dimensions; financial burden (FB), familial/social impact (FS), personal strain (PS) and mastery (MT) with possible scores 0-4 for each domain, the higher, the more impact. In financial aid recipients, FB was collected before and after the financial helps. Nonparametric tests were used for comparative analysis. Correlation studies were performed to address the association of family factors to IOF.

Results:

139 children were recruited (55% female, median age 14.2, 7.8-20.6 years).Majority were Chinese (74%), followed by Malays (16%). The prominent diagnosis were JIA (50%) and SLE (26%). 1/3 were on biologics. 76 families (62%) earned < 5000 S$/month and 30% received financial assistance.

The internal consistency of the total IOF and subscales indicated high reliability (shown in Figure 1), except MT which posed Cronbach's alpha of 0.67.

Our RD patients' IOF scores were of milder degree (FB, FS, PS) compared to those with childhood cancers in a previous local study. FB negatively correlated to household income (rho = -0.51) but it was markedly alleviated after receiving financial aid (3.38 vs. 2.75, p< 0.001). Despite lowest income/high FB, Malay/Indian parents seemed to cope with diseases better. The highest FS, PS and total IOF were seen in CNS vasculitis (explained by debility and dependent status), while SLE affected FB the most. Lupus nephritis and sacroiliitis in JIA did not render higher family impact. Neither were age, disease duration, biologics treatment, caregiver education nor the presence of siblings associated with higher IOF.

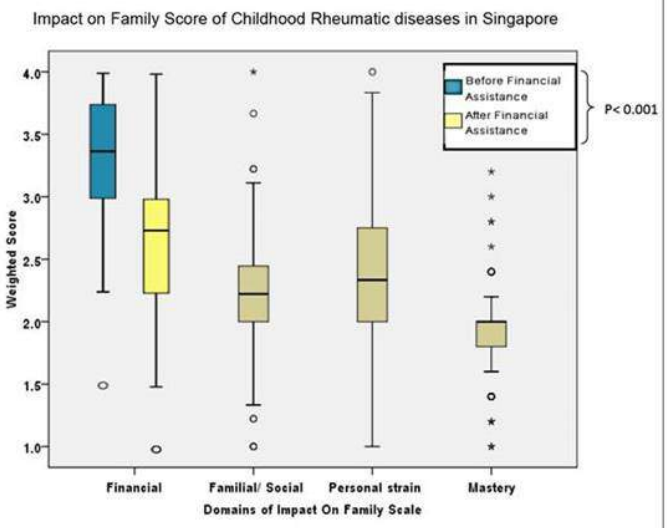
Table 1. Patient and Family Characteristics
Nominal data are presented in n (%) and continuous data are median (IQR)

Characteristics	n= 139 (%)
Age, year	14.2 (7.83-20.57)
female	76 (55)
Ethnicity	
Chinese	103 (74)
Malay	22 (16)
Indian	11 (7)
Other	4 (3)
Diagnosis	
JIA	69 (50)
With SI involvement	15 (22)
SLE/MCTD	36 (26)
With renal involvement	15 (42)
UCTD	6 (4)
Primary CNS Vasculitis	7 (5)
JDM	6 (4)
Other	15 (11)
Disease duration ,year	3.08 (1.63-5.59)
Biologic treatment	43 (31)
Main Caregiver	
Father	36 (26)
Mother	101 (73)
Other	2 (1)
Education Level	
Primary/secondary School	70 (51)
undergraduate or above	47(34)
Other	21 (15)
Household Income, S$/month	4000 (2300-8000)
< 2000	27 (22)
2001-5000	49 (40)
5000-10000	32 (26)
>10000	14 (12)
NA	17
Financial assistance recipients	42 (30)
Siblings	120 (86)

Figure 1. Impact on Family Scale and Its' Internal Consistency (Cronbach's Alpha) in Children with Chronic Illness in Singapore

IOF scale (number of items)	Weighted Impact on Family Score*			Cronbach's Alpha	
	Rheumatic Diseases (n= 139)		Cancer (n= 79)	Rheumatic Diseases (n= 139)	Cancer (n= 79)
	Median (IQR)	mean (SD)	mean (SD)		
Financial burden (4)	2.75 (2.25-3.00)	2.73(0.65)	3.41	0.83	0.69
Familial/Social Impact (9)	2.22 (2.0-2.44)	2.24 (0.50)	3.8	0.84	0.88
Personal Strain (6)	2.33 (2.0-2.83)	2.37 (0.60)	2.89	0.85	0.79
Mastery (5)	2 (1.6-2.2)	1.93 (0.42)	1.45	0.67	0.61
Total score (24)	9.19 (8.16-10.11)	9.21 (1.56)	10.74	0.88	0.64

* Calculated from the total score in each dimensions divided by the number of items. Each subscale ranges from 0 to 4 and the total IOF is 16



Conclusion:

Pediatric rheumatic diseases in Singapore affect various aspects of the family at a considerable degree. Although household income inversely correlates with FB, none of other strong associations was demonstrated between family factors and IOF scores. As we are seeking methods to minimize impact of chronic diseases on families, IOF scale seems to be a useful tool in assessing disease burdens which, overall, will help improving disease outcome and ascertain effective healthcare supporting system.

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Abstract Number: 2474

Psychometric Properties of the Social Appearance Anxiety Scale in Patients with Limited and Diffuse Systemic Sclerosis: Analysis from the Scleroderma Patient-Centered Intervention Network Cohort

Sarah D. Mills[1], Shadi Gholizadeh[1], Rina S. Fox[1], Lisa R. Jewett[2,3], Marie-Eve Carrier[3], Linda Kwakkenbos[2,3], Karen Gottesman[4], Scott C. Roesch[1,5], Brett D. Thombs[2,3], Vanessa L. Malcarne[1,5] and SPIN Investigators[6], [1]SDSU/UC San Diego Joint Doctoral Program in Clinical Psychology, San Diego, CA, [2]McGill University, Montreal, QC, Canada, [3]Lady Davis Institute for Medical Research, Jewish General Hospital, Montreal, QC, Canada, [4]Scleroderma Foundation, Los Angeles, CA, [5]Psychology, San Diego State University, San Diego, CA, [6]Scleroderma Patient-centered Intervention Network, Montreal, QC, Canada
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Background/Purpose: Despite the common appearance changes in patients with systemic sclerosis (SSc), and the potential adverse psychosocial impact of such changes, research in this area is limited. This may be, in part, because there are few validated measures evaluating the psychosocial impact of disease-related appearance changes in SSc. Thus, the goal of the present study was two-fold: 1) to evaluate the psychometric properties of the Social Appearance Anxiety Scale (SAAS), a measure that assesses fear of situations in which one's appearance will be evaluated, in a sample of SSc patients, and 2) to determine if scores from the SAAS can be meaningfully compared across limited and diffuse SSc subtypes.

Methods: The sample included SSc patients ($N = 600$; 59% limited, 41% diffuse) enrolled in the Scleroderma Patient-centered Intervention Network Cohort. Confirmatory factor analysis (CFA) was used to examine the structural validity of the measure; a one-factor model was hypothesized. Once the model with adequate fit was identified, multiple-group CFA was used to evaluate measurement invariance of the SAAS across limited and diffuse SSc patients. Internal consistency reliability was examined using Cronbach's coefficient alpha. Convergent validity was examined via Pearson product-moment correlations with the SAAS and a measure of depression, body image dissatisfaction, and two measures of social anxiety.

Results: Based on descriptive fit indices, a one-factor model showed good fit with the data using CFA (Comparative Fit Index [CFI] = 0.91, Standardized Root Mean Residual [SRMR] = 0.04, Root Mean Square Error of Approximation [RMSEA] = 0.12). The multiple-group CFA evaluated configural invariance (i.e., baseline model fitting a one-factor solution for limited and diffuse subtypes), metric invariance (i.e., factor loadings constrained to equivalence across subtypes), and factor variance invariance (i.e., factor loadings and variances constrained to equivalence across subtypes) based on descriptive fit indices (CFI, SRMR, and RMSEA), change in CFI, and the Satorra-Bentler X^2 difference test. Results from the multiple-group CFA provided support for the factor variance invariance model, suggesting a one-factor structure with equivalent response patterns and variances across limited and diffuse subtypes. Internal consistency was good for both limited ($\alpha = 0.96$) and diffuse ($\alpha = 0.97$) groups. Convergent validity was demonstrated via moderate to strong correlations with measures of depression ($r = 0.52$, $p < .01$), body image dissatisfaction ($r = 0.68$, $p < .01$), and social anxiety (2 measures; $r = 0.58$ to 0.67, $p < .01$) in the total sample.

Conclusion: Overall, results indicate that the one-factor SAAS can be used to assess fear of appearance evaluation among patients with SSc. In addition, scores on the SAAS can be meaningfully compared across limited and diffuse subtypes.

Disclosure: S. D. Mills, None; **S. Gholizadeh**, None; **R. S. Fox**, None; **L. R. Jewett**, None; **M. E. Carrier**, None; **L. Kwakkenbos**, None; **K. Gottesman**, None; **S. C. Roesch**, None; **B. D. Thombs**, None; **V. L. Malcarne**, None; **S. Investigators**, None.

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Abstract Number: 2475

Association Between Fibromyalgia and Suicidal Risk: A Systematic Review and Meta-Analysis

Sikarin Upala[1] and Anawin Sanguankeo[2], [1]Internal Medicine, Bassett Medical Center, Cooperstown, NY, [2]Bassett Medical Center, Cooperstown, NY

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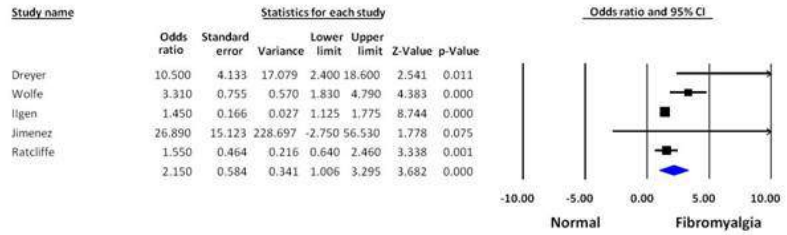
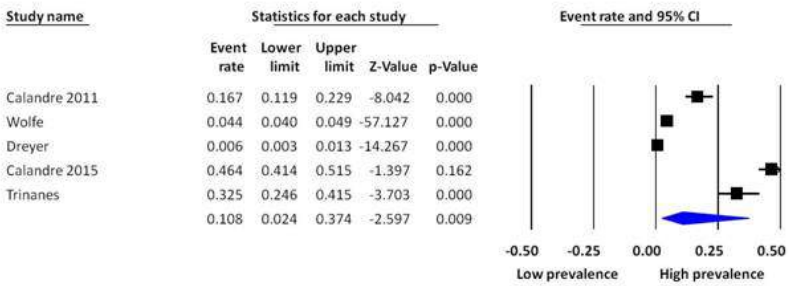
Background/Purpose: Chronic pain conditions are related poor overall health, economic burden, and mental disorders including suicidal ideation (SI), suicide attempts (SA), and completed suicides. Fibromyalgia is one of chronic pain syndrome that is a highly prevalent condition in United States. We performed a systematic review and meta-analysis of available articles that assess association between fibromyalgia and suicidal ideation or suicidal attempt.

Methods: We comprehensively searched the databases of MEDLINE and EMBASE from their dates of inception to June 2015. The inclusion criteria were published articles that reported prevalence or association of fibromyalgia and suicidal ideation or suicidal attempt. The primary outcome was the odds ratio (OR) or risk ratio (RR) of SI or SA compared between patients with and without fibromyalgia. The secondary outcome was prevalence of SI or SA in the fibromyalgia group.

Results: From 53 full-text articles, 8 studies with a total of 202 participants were included in the meta-analysis. Compared with non-fibromyalgia group, patients with fibromyalgia had significantly higher chance of SI or SA (OR=2.15, 95% CI: 1.006 to 3.30). In addition, pooled prevalence of SI or SA was high (Pooled prevalence= 0.11, 95% CI: 0.02 to 3.30).

Conclusion: We have shown that SI and SA are prevalent among patients with fibromyalgia and there is a significant association between these two conditions. These findings underscore the importance of assessment of SI and SA among the individuals presenting who have fibromyalgia.





Disclosure: S. Upala, None; **A. Sanguankeo**, None.

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Abstract Number: 2476

Patient-Reported Cognitive Impairment, Pain, and Depressive Symptoms in

Patients with Systemic Lupus Erythematosus and Comorbid Depression

Kelly Beck[1], Xing Gao[2], Yu Cheng[3] and Carol M. Greco[4], [1]School of Health and Rehabilitation Sciences, University of Pittsburgh, Pittsburgh, PA, [2]Biostatistics, University of Pittsburgh, Pittsburgh, PA, [3]Biostatistics and Psychiatry, University of Pittsburgh, Pittsburgh, PA, [4]University of Pittsburgh, Pittsburgh, PA
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Background/Purpose: Patients with systemic lupus erythematosus (SLE) frequently report cognitive impairment as well as depressive symptoms and significant pain. However, depression criteria and SLE symptoms may overlap (e.g., difficulty concentrating, low energy), and may both be exacerbated by pain. The purpose of this study is to evaluate the associations of patient-reported pain and cognitive symptoms in SLE patients with co-morbid depressive symptoms. Exploration of the relationships between these variables can better inform clinicians regarding treatment of individuals with SLE and depression.

Methods: Ninety patients with SLE (1997 Criteria) diagnosed with major depressive disorder or subsyndromal depression completed a baseline assessment for the NIH-NIAMS funded study, Reducing Depressive Symptoms in SLE (R01 AR 57338). Depressive symptoms were measured by the Center for Epidemiologic Studies Depression (CESD) scale. Self-reported ratings of pain and cognitive symptoms were collected with the PROMIS®Pain Interference short form and Cognitive Symptoms Inventory (CSI), respectively. Associations of baseline CESD total score and subscales, CSI and subscales, and Pain were evaluated cross-sectionally using Pearson's r.

Results: Participants' average age was 49 (+/- 12) years, 92% were females, and 23% were African American or other minority race. 48% had household income of < $50,000. The mean CESD score was 29.8 (SD=6). Baseline scores on the three variables of interest all met assumptions for normality and homoscedasticity. CESD total score was significantly associated with both total CSI (r = .38, p<.001) and pain (r = .38, p<.001). Specifically, the CESD somatic subscale had the strongest relationship with the attention/concentration subscale on the CSI (r = .4, p<.001). Similarly, the CESD somatic subscale was the only subscale that significantly correlated with pain (r = .36, p<.001), as the depression, positive affect, and interpersonal subscales were not significantly correlated with pain scores. Total cognitive symptoms score had a moderate positive correlation with pain scores, (r = .52, p<.001). Specifically, all of the CSI subscales were significantly correlated with PROMIS pain scores: attention/concentration (r = .49, p<.001); pattern recognition/activity management (r = .44, p<.001); immediate memory (r = .41, p<.001); and executive functioning (r = .37, p<.001).

Conclusion: In SLE patients with co-morbid depression, somatic features of depression (e.g., restless sleep, appetite disturbance) were most strongly associated with cognitive symptoms and pain, in contrast to sadness and interpersonal features of depression. Interestingly, correlation analyses indicated that the strongest relationship lies between pain and cognitive symptoms, specifically attention and concentration. The importance of pain, perceived cognitive disruption, and depressive symptoms should not be underestimated in evaluating and treating SLE.

Disclosure: K. Beck, None; **X. Gao**, None; **Y. Cheng**, None; **C. M. Greco**, None.

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Abstract Number: 2477

What Older Adults with Restricting Back Pain Worry about: Deteriorating Function, Reliance on Others, Distrust of Medications

Una E. Makris[1,2], Liana Fraenkel[3], David W Serrano[4], Jae H Yun[4], Thomas M. Gill[5] and MC Reid[6], [1]Rheumatology, Dallas

VA Medical Ctr, Dallas, TX, [2]Rheumatology, UT Southwestern Medical Center, Dallas, TX, [3]Rheumatology, Yale University School of Medicine, Veterans Affairs Connecticut Healthcare System, New Haven, CT, [4]Internal Medicine, UT Southwestern Medical Center, Dallas, TX, [5]Geriatrics, Yale School of Medicine, New Haven, CT, [6]Geriatrics, Weill Cornell Medical College, New York City, NY
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Background/Purpose: Although back pain is the most common type of pain disorder reported by older adults, its impact on the daily life of older adults remains poorly understood, particularly among racial/ethnic minorities. In this qualitative study, we explored older adults' beliefs and attitudes regarding restricting back pain (defined as back pain severe enough to restrict activity).

Methods: We conducted in-depth, one-on-one interviews and focus groups with older adults (ages ≥65 years) who reported restricting back pain within the past 3 months. We recruited participants from 3 different sources (interviews and focus groups in Connecticut and focus groups in New York City) to ensure a racially diverse sample; recruitment efforts ended once thematic saturation was achieved. A semi-structured discussion guide was used to prompt participants to discuss their beliefs, attitudes, and experiences regarding restricting back pain. Audio recordings were transcribed and analyzed (using NVivo) in an iterative process to develop and analyze thematic categories. All transcripts were independently coded (blinded to population) by four reviewers using iterative thematic analysis. Discrepancies in coding were resolved through group discussion until consensus was reached.

Results: We conducted 23 one-on-one interviews and 16 focus groups (n=70 participants), for a total of 93 participants. The majority of participants were female (68%). The median age was 83; over one-half lived alone, and 46% belonged to a minority group. We identified 3 themes related to worry and fear about restricting back pain (Table 1): (1) worry and preoccupation with deteriorating function [and need for mobility aids], (2) concerns about loss of independence and reliance on others, (3) fear of medication. Themes did not vary by race/ethnicity or by gender.

Conclusion: This study suggests that older adults with restricting back pain worry about future physical deterioration, reliance on mobility aids, and dependence on others (related to the back pain). Older adults described a common distrust of medications. A better understanding of the attitudes and beliefs, including worries and fears, of older adults with restricting back pain, will inform the development of non-pharmacological, multimodal interventions. Additionally, these data will enable clinicians and researchers to gain insight about potential barriers and facilitators to engaging in or adhering to restricting back pain management.

Table 1: Illustrative Quotes of Themes

1. Worry and preoccupation with deteriorating function including reliance on mobility aids	--I have finally succumbed to a walker and to a cane. I never…I didn't want to but I had to. --Fear appears. Is this going to get worse to the point that I can't be mobile at all?
2. Participant fear about loss of independence and reliance on others	--It makes me stop and ask somebody else to do something for me…that's very aggravating. --It has ruined my life.… I don't go anywhere alone anymore...
3. Distrust of medication	--They always want to give me medicine. I don't want medicine! Because I don't think it helps any…I don't want another medication. --First of all it makes me groggy and all I want to do is sleep and I don't want to get hooked on it so I don't want to take [the medicine].

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Abstract Number: 2478

Does Affect Predict Willingness to Take Medication?

Liana Fraenkel[1], Marilyn Stolar[2], Richard L. Street Jr.[3], Harjinder Chowdhary[2] and Ellen Peters[4], [1]Medicine, Yale University School of Medicine, New Haven, CT, [2]Yale University, New Haven, CT, [3]Department of Communication, Texas A&M University, College Station, TX, [4]Ohio State University, Columbus, OH

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Does Affect Predict Willingness to Take Medication?

Background/Purpose: Affect is known to have a significant impact on judgment and decision making. The data supporting this finding, however, are based on subjects' reactions to written materials. Our objective was to examine whether the valence and intensity of a patient's affective reactions to audible information influences their willingness to take medication.

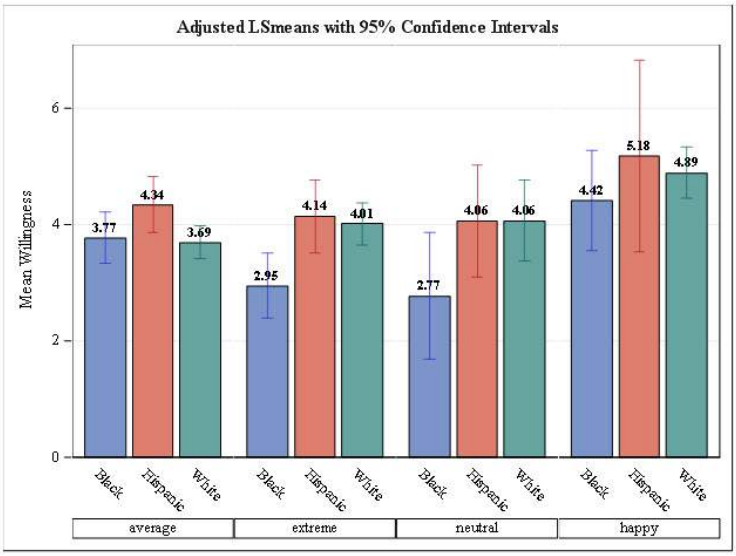
Methods: We measured affect in real time as subjects with a chronic inflammatory rheumatic disease listened to a description of a hypothetical new medication. Subjects used a joystick to indicate moment-by-moment their reaction to what they were hearing (+10= Very good, -10= Very bad, and middle position= 0 being neutral). Patterns of affect reactions were classified using a cluster analysis approach applied to time series data. After hearing the presentation, subjects rated their willingness to take the medication on a 7-point Likert rating scale. We used a multivariate linear regression model to examine the association between affect patterns and willingness, adjusting for age, numeracy, use of immunosuppressant, and patient global assessment. An

interaction between affect pattern and ethnicity was included in the model to assess whether ethnicity modified the association of affect and willingness.

Results: The mean (SD) age of the study sample (N= 382) was 55 (14) years, 75% were female, 58.4% identified themselves as being Non-Hispanic White, 23.3% as Non-Hispanic Black, and 18.3% as Hispanic. Affect reactions were classified into 4 patterns: feel consistently ‘good' (n= 58), feel consistently close to ‘neutral' (n= 33), ‘extreme' positive reaction to benefits and negative reaction to adverse events (AEs) (n= 109), and ‘average' (or expected) reaction to benefits and AEs (n= 182). Based on differences of adjusted least squares means, the patients with good patterns reported greater willingness than neutral, extreme, or average patterns (t= 2.69, p= 0.007, t= 2.98, p= 0.003, t= 2.37, p= 0.018, respectively). Black patients reported less willingness than Hispanics or Whites (t= -2.76, p= 0.006, t= -3.34, p=0.001, respectively). The interaction results revealed that Blacks were significantly less willing than Hispanics or Whites within the extreme group only (t= -2.66, p= 0.008, t= -3.36, p=0.001, respectively). Mean willingness by affect pattern and ethnicity is presented in the Figure below.

Conclusion: Patients who feel consistently good are most willing to take the new medication compared to groups with other affect reaction patterns. Black patients, particularly those with an ‘extreme' reaction pattern, are less willing. These data are consistent with recent findings demonstrating that both positive and negative affect intensity predict reluctance to accept risk, and may help explain the increased risk aversion previously documented in Black patients with rheumatic disease.

Figure. Differences of Least Squares Means Between Ethnic Groups by Affect Pattern



Disclosure: L. Fraenkel, None; **M. Stolar**, None; **R. L. Street Jr.**, None; **H. Chowdhary**, None; **E. Peters**, None.

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Abstract Number: 2479

The Association Between Social Networks, Disease Activity, and Pain in Rheumatoid Arthritis

Taysir G. Mahmoud[1], Christine Iannaccone[2], Jing Cui[2], Yvonne C. Lee[3], Michael Weinblatt[4] and N Shadick[5], [1]Division of Rheumatology, Immunology and Allergy, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, [2]Division of Rheumatology, Immunology, and Allergy, Brigham & Women's Hospital, Boston, MA, [3]Rheumatology Immunology & Allergy, Brigham and Women's Hospital, Boston, MA, [4]Division of Rheumatology, Immunology and Allergy, Brigham and Women's Hospital, Boston, MA, [5]Division of Rheumatology, Immunology & Allergy, Brigham and Women's Hosp, Boston, MA
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The Association between Social Network, Disease Activity, and Pain in Rheumatoid Arthritis

Background/Purpose: Current research suggests that high social network status is related to lower levels of reported pain in rheumatoid arthritis patients (RA). The nature of this relationship is not well known but may be related to disease activity. This study aims to examine the relationship between social network, reported pain, and disease activity.

Methods: Data collected from a single-center, prospective observational RA cohort study, including joint examinations, blood draws, and patient reported outcome measures, were analyzed cross-sectionally. Subjects completed the Berkman-Syme Social Network Index (SNI), an ordinal scale ranging from 0 to 4 where 0 indicates no social network and 4 indicates high social network. Disease activity scores were calculated using the DAS28-CRP3. Reported pain data were obtained from the pain scale in the Multidimensional Health Assessment Questionnaire (MDHAQ); a continuous scale ranging from 0 to 100 where 0 indicates no pain and 100 indicates severe pain. A multivariable linear regression model was performed using a stepwise selection approach to examine the association between social network, reported pain, and disease activity. The variables initially entered into the model included age, gender, social network, disease activity, disease duration, and seropositivity. Disease duration and seropositivity were not significant, and thus were excluded from the final model.

Results: 1053 subjects with a mean age of 57.5 (SD13.6) years and a mean disease duration of 13.8 (SD11.9) years were analyzed. In this cohort, 83% were female and 69.7% were seropositive. On average, DAS28-CRP3 score was 3.2 (SD1.5), SNI was 2.4 (SD1.0), and MDHAQ pain score was 32.0 (SD26.2). Using a univariate analysis it was found that age, disease duration, seropositivity, disease activity, and SNI were associated with reported pain. In the final multivariable linear regression model, SNI was significantly inversely associated with reported pain (β coefficient -1.8, p=0.02), after controlling for disease activity.

Conclusion: High social network status was associated with lower reported pain, in this cohort of RA patients, even after controlling for disease activity. It is unclear if high social network status has psychosocial benefits that lead to reduced pain, or if low pain promotes patients' social participation causing a high social network status. Future studies are needed to further examine the relationship between social support and reported pain, and if this association is present longitudinally.

The association of social support and disease activity with pain in RA		
	β coefficient	p-value
Social Network Index (SNI)	**-1.82**	**0.02**
Age	-0.09	0.15
Gender	3.43	0.11
DAS28-CRP3	6.14	<.0001

Disclosure: T. G. Mahmoud, None; **C. Iannaccone**, None; **J. Cui**, None; **Y. C. Lee**, Forest Research Institute, 2; **M. Weinblatt**, Bristol-Myers Squibb, 2,Crescendo Bioscience, 2,UCB, 2,Bristol-Myers Squibb, 5,Crescendo Bioscience, 5,UCB, 5; **N. Shadick**, Amgen, Questcor, Crescendo Biosciences, UCB, Bristol-Myers Squibb, 2.

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Abstract Number: 2480

The Impact of Emotional Trade-Off Difficulty on Choice

Raluca Cozmuta[1], Sonal Bhalla[2] and Liana Fraenkel[3], [1]Rheumatology, Yale University School of Medicine, New Haven, CT, [2]Yale University School of Medicine, New Haven, CT, [3]Medicine, Yale University School of Medicine, New Haven, CT
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Background/Purpose: Patients' preferences for competing treatment options can be measured using stated preference methods which require subjects to make trade-off between specific attributes. Responses can then be used to calculate the importance of specific attributes on patients' choices. Previous marketing research has found that the extent of negative emotions elicited by specific trade-offs is related to choice. Given the known literature that choice difficulty increases the likelihood of opting out or deferring, the objective of this study was to examine whether emotional trade off difficulty impacts choices after accounting for the importance of each attribute.

Methods: Women between the ages of 20 and 49 years, admitted to the hospital or infusion center, completed a discrete choice experiment (DCE) to examine preferences for a hypothetical medication for a standardized patient with joint pain, migraines and fatigue. The DCE included 4 attributes each having 3 levels: route (oral, sc, iv), benefit (35%, 45%, 75% benefit), risk of TB (1 in 1,000, 10,000, and 100,000) and cost (easy, moderately hard, or hard to afford). Subjects then rated how threatening, stressful and risky they found choices involving each attribute (measured on 7-point scales). Emotional trade off difficulty was defined as the average of these 3 items. We used multiple linear regression models to examine whether emotional trade off difficulty is associated with preference to opt out of treatment after controlling for the importance of each attribute (which sum to 100), as well as numeracy (the only characteristic found to be associated with preference in bivariate analyses).

Results: Subjects' (N=271) mean (SD) age was 34 (8) years; 94 (35%) were non-Hispanic White, 95 (35%) non-Hispanic Black, and 82 (30%) were Hispanic; 27% of all subjects had a college degree, and 45% rated their health as being fair or poor. The mean (SD) importances were; route = 16.3 (10.4), benefit = 31.3 (15.1), risk of TB = 17.6 (10.1), and cost = 34.8 (15.3). The mean (SD) emotional trade-off difficulty ratings were: route = 3.2 (1.6), benefit = 3.6 (1.5), and 4.2 (1.8) for both risk of TB and cost. The strength of preference (SE) to opt out of treatment was 24.6% (2.2) for an IV drug (with moderate benefit, risk and cost), 27.5% (2.3) for a low benefit pill (with moderate risk and cost); 28.3% (2.3) for a high TB risk pill (with moderate benefit and moderate cost), and 36.5% (2.5) for an expensive pill (with moderate benefit and moderate risk of TB). The association of emotional trade-off difficulty for each of these choices is presented in the Table.

Conclusion: Negative emotions associated with making tradeoffs predict treatment preferences even after taking into account the importance weights of each attribute. Moreover, patients experiencing greater emotional trade off difficulty are more likely to opt out of treatment.

Table. Emotional Tradeoff Difficulty and Preference to Opt Out of Treatment.

Treatment Option	Variable	t Value	Pr > |t|
IV Drug	Emotional trade-off difficulty associated with route	2.49	0.013
	Importance of route on decision making	1.76	0.079
	Numeracy	1.26	0.207
Low Benefit Pill	Emotional trade-off difficulty associated with benefit	2.86	0.004
	Importance of benefit on decision making	-0.84	0.403
	Numeracy	0.56	0.573
High Risk of TB	Emotional trade-off difficulty associated with risk of TB	2.78	0.006
	Importance of risk of TB on decision making	4.19	<.0001
	Numeracy	1.33	0.184
Expensive Drug	Emotional trade-off difficulty associated with cost	3.31	0.001
	Importance of cost on decision making	1.28	0.203
	Numeracy	2.00	0.046

Disclosure: R. Cozmuta, None; **S. Bhalla**, None; **L. Fraenkel**, None.

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Abstract Number: 2481

Work Disability in a Cohort of Patients with Psoriatic Arthritis

Cecilia Zaffarana[1], Osvaldo Luis Cerda[1], Josefina Gallino Yanzi[1], Margarita Landi[1], Emilce Schneeberger[1], Ignacio Carrillo[1], María del Carmen Gonzalez Guzmán[1], Jose A Maldonado Cocco[1], Susana Gagliardi[1] and Gustavo Citera[2], [1]Instituto de Rehabilitación Psicofisica, Buenos Aires, Argentina, [2]Rheumatology, Consultorios Reumatológicos Pampa, Buenos Aires, Argentina

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Background/Purpose: Several studies showed that unemployment and work disability are high in patients with Psoriatic Arthritis (PsA). Te purpose of this study is to evaluate work status in a cohort of patients with PsA and to identify variables associated to work disability.

Methods: A cross-sectional study was conducted including patients ≥ 18 years old with PsA according to classification criteria for Psoriatic Arthritis (CASPAR). Demographic data, disease duration, clinical features, articular and extra articular

manifestations, comorbidities and current treatment were collected. Disease activity was assessed by the 66 swollen and 68 tender joint counts, DAS28, DAPSA, BASDAI and RAPID3. Quality of life was assessed using DLQI and PsAQoL questionnaires. Functional capacity was assessed by HAQ and BASFI. Skin involvement was evaluated using PASI. Presence of dactylitis and enthesitis (MASES) were evaluated. Statistical analysis: T test, Mann Whitney, Chi^2 and Fisher exact test. Multiple logistic regression analysis to explore factors associated to work disability.

Results: 87 patients with PsA were evaluated. Median age was 52 years (IQR 40.2-61.7). 28 patients (32.2%) were unemployed and 18 of them (20.6%) were unemployed due to PsA, 10 were retired. Unemployed patients had a lower age at disease onset (33.9 ± 12.28 vs 38.87 ± 11.91, p=0.042), higher disease activity (BASDAI 5.7 ± 2.9 vs 4.06 ± 2.8, p=0.03, RAPID3 13.99 ± 7.4, vs 10.5 ± 6.27 p=0.03, DAPSA 20.5 ± 10.7 vs 16.5 ± 5.16 p=0.04, DAS28 4.2 ± 1.3 vs 3.44 ± 1.4, p=0.032), worse functional status (HAQ 1.18 ± 0.8 vs 0.68 ± 0.6, p=0.006) and worse quality of life (PsAQoL 12.1 ± 3.7 vs 6.56 ± 6, p<0.001). In the multivariate analysis, lower age [OR 0.9 (CI 95% 0.8-0.9), p=0.004] and worse functional status [HAQ OR 7.1 (IC 95% 1.9-25.7), p=0.003] were independently associated with WD.

Conclusion: In our cohort the prevalence of work disability attributed to PsA was 20.6%, and it was associated to lower age and worse functional capacity.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/work-disability-in-a-cohort-of-patients-with-psoriatic-arthritis

Abstract Number: 2482

Choosing Subserologies More Wisely: Implementing Anti-Nuclear Antibody (ANA) Reflex Testing and Education to Reduce Unnecessary Costs in an Integrated Healthcare System

David Bulbin[1], Alicia Meadows[2], Sandi Kelsey[3], Andrea Berger[4], H. Lester Kirchner[4], Harold Harrison[3] and Alfred E. Denio[5], [1]Rheumatology, Geisinger Medical Center, Danville, PA, [2]Rheumatology, Geisinger Health System, Danville, PA, [3]Dept of Pathology, Geisinger Medical Center, Danville, PA, [4]Biostatistics, Geisinger Center for Health Research, Danville, PA, [5]Dept of Rheumatology, Geisinger Medical Center, Danville, PA

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Session Title: Quality Measures and Quality of Care Poster Session

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: The American College of Rheumatology published its Top 5 List of Things Physicians and Patients Should Question as part of the American Board of Internal Medicine's Choosing Wisely campaign. First on the list was “Don't test ANA subserologies without a positive ANA and clinical suspicion of immune-mediated disease. We instituted a system to promote more cost effective subserology ordering.

Methods: We identified 101 of 1100 providers who were over utilizers (more than 2 subserologies ordered when ANA negative in a 26 month period). These providers received an email informing them of their ordering practice with explanation of ANA reflex testing, and a link to an online education module. Providers were surveyed pre and post intervention on their preferred quality improvement method. We prospectively examined for 1 year subsequent instances of unnecessary subserology ordering defined as anti-dsDNA, anti-SM/RNP, and SCL70 ordered when simultaneous ANA was negative. This was compared with the prior 26 months. If SLE was suspected, the ANA would reflex if positive to anti-ds DNA, anti-cardiolipin ab, and anti-Smith/RNP ab. For Sjogren's, the positive ANA would reflex to the SSA/SSB ab. 29/101 providers completed the non-required online education. Generalized estimating equations models were used to obtain estimates of odds ratios (OR) with their 95% confidence intervals (CI). A cluster effect by provider was included in the model to take into account the correlation within each

provider. Finally, a cost analysis based on the Medicare fee schedule was performed. This analysis assumed that when reflex testing was ordered, unnecessary subserologies were avoided.

Results: Unnecessary subserology ordering across all system providers decreased significantly after the intervention (OR 0.625, CI 0.425, 0.918, P-value 0.0167). Over the 26 month pre_intervention period, the mean percentage of unnecessary subserology ordering episodes was 44.5% when the ANA was negative. In the other 55.6%, the SSA/SSB or anti Jo1 antibodies were ordered which can be appropriate when the ANA is negative. In the 10 month post intervention period, the number of unnecessary instances decreased to 35.1% of the total. Surveyed providers preferred reflex testing and education over other practice improvement strategies. Of the 101 providers who over utilized subserologies, 26 started using ANA reflex testing. Cost analysis showed that ANA reflex testing potentially saved $8,462.50 by reducing unnecessary subserology utilization.

Conclusion: The introduction of optional ANA reflex testing with optional online education led to significant decreases in unnecessary subserology ordering when the ANA was negative across the entire integrated health system. Although, the calculated potential cost savings was not large, we only examined the instance of simultaneous ANA and subserology ordering when the ANA was negative, and not the entire spectrum of ordering practices. ANA reflex testing potentially saves providers time and patients inconvenience for 2nd phlebotomies. We expect that ANA reflex testing will be adopted by additional providers and are developing a scleroderma reflex test.

Disclosure: D. Bulbin, None; **A. Meadows**, None; **S. Kelsey**, None; **A. Berger**, None; **H. L. Kirchner**, None; **H. Harrison**, None; **A. E. Denio**, None.

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Abstract Number: 2483

Adherence to 2011 American Academy of Ophthalmology Guidelines to Perform Objective Screening Tests for Detection of Antimalarial Retinal Toxicity Is Suboptimal

Sarah Haserodt[1], Chris Tonner[2], Sara G. Murray[3], Gabriela Schmajuk[4] and Jinoos Yazdany[5], [1]Internal Medicine, California Pacific Medical Center, San Francisco, CA, [2]Rheumatology, University of California, San Francisco, San Francisco, CA, [3]Medicine, University of California, San Francisco, San Francisco, CA, [4]Medicine/ Rheumatology, UCSF/ San Francisco VA, San Francisco, CA, [5]University of California, San Francisco, San Francisco, CA

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Background/Purpose: American Academy of Ophthalmology (AAO) 2011 guidelines recommend that patients receiving hydroxychloroquine (HCQ) or chloroquine (CQ) undergo regular screening for retinal toxicity with 1 of 3 objective tests (spectral domain macula ocular CT (SD-mOCT), fundus autofluorescence (FAF), or multi-focal electroretinogram (mf-ERG)), which are sensitive for early retinal damage. In this study, we examined adherence to AAO guidelines for retinal toxicity screening in patients seen in ophthalmology clinics within a single health system who were users of HCQ or CQ.

Methods: We performed a system-wide electronic medical record (EMR) query to identify all patients seen in ophthalmology clinic between June 2012 – June 2014 who had mention of HCQ or CQ in the clinical note associated with the encounter (n=523). A chart review was performed on a random sample of these patients (n=294) to identify active users of HCQ or CQ or patients undergoing a baseline ophthalmology exam prior to starting these medications (denominator population) and to confirm

performance of SD-mOCT, mfERG and/or FAF (numerator). We also examined use of 10-2 Acute Visual Fields (AVF), the previous standard of care for antimalarial toxicity screening. Finally, we determined whether the newly recommended tests could be reliably identified through automated EMR queries since this would increase the efficiency of future quality improvement efforts.

Results: 208 patients in our sample were active users of HCQ/CQ or receiving a baseline ophthalmology exam prior to starting HCQ/CQ at the time of their ophthalmology encounter (denominator). 57.2% (n=119) had the recommended screening test performed over the study period (119 had SD-mOCT, 22 had FAF, and 7 had mf-ERG). An additional 4.3% (n=9) received only AVF screening. The automated EMR query accurately and reliably identified all 119 patients who had received the recommended objective screening. Chart review was used to determine the reasons why 42.8% (89) patients did not undergo the recommended screening tests (Table).

Table: Reasons for Not Undergoing Objective Screening for Antimalarial Retinal Toxicity

Reason for Not Undergoing Objective Screening	**Frequency**
No mention of any objective screening procedure in ophthalmology note	43.8% (n=39)
Appropriate objective screening procedure ordered but not performed	33.7% (n=30)
Documented in ophthalmology note that the patient is also followed by an outside ophthalmologist	11.2% (n=10)
Appropriate objective screening procedure mentioned but neither ordered nor performed	7.8% (n=7)
Testing was deferred because the patient planned on using HCQ/CQ for a short period of time	3.4% (n=3)

Conclusion: We found that only 57.2% of patients who were active users of HCQ or CQ underwent objective screening tests recommended by the AAO 2011 guidelines, suggesting a significant gap in quality of care. Structured query retrieval of this information was highly reliable, which will increase the efficiency of identifying care gaps for patients using these medications in future quality improvement projects.

Disclosure: S. Haserodt, None; **C. Tonner**, None; **S. G. Murray**, None; **G. Schmajuk**, None; **J. Yazdany**, None.

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Abstract Number: 2484

Use of Lean Six Sigma Methodology to Improve Time to Scheduling for New Patient Referrals to Rheumatology

Nicole Orzechowski[1], Mary Bolg[2], Rachael Bergeron[1], Christopher Dorman[2], Lauren Sanderson[2], Miranda Stark[2], Stacey Wilk[2] and Tammy Gray[3], [1]Rheumatology, Dartmouth Hitchcock Medical Center, Lebanon, NH, [2]Dartmouth Hitchcock Medical Center, Lebanon, NH, [3]White River Junction Family Practice, White River Junction, VT

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Background/Purpose: Patient satisfaction is an important driver of patient-centered care. The Section of Rheumatology was taking on average 5 days to contact and schedule new patients for consultation, with only 30-50% of patients rating the scheduling experience as excellent. Our practice was tasked by an organizational goal of Dartmouth-Hitchcock to reduce new referral scheduling time to 48-hours. The purpose of this quality improvement initiative was to develop a process to reduce referral scheduling time with a downstream impact of improving patient satisfaction.

Methods: An interdisciplinary team consisting of on-site clinicians, allied-health staff and practice managers, in addition to scheduling staff in our own practice and at referral practices met three times over a period of 6 weeks. Each meeting lasted between 4 and 7 hours. To understand the current workflow to allow for process improvement, we used the Lean Six Sigma DMAIC methodology (Define, Measure, Analyze, Improve, Control). Data was collected at baseline and at follow-up, including number of external referrals by month, number of days to triage referral, contact patient, and close referral, number of days from referral to appointment date, percent of 3rd calls that result in a scheduled appointment, and patient satisfaction on question regarding ease of scheduling.

Results: New referral scheduling dropped to less than two business days and the percent of patients rating the scheduling experience as excellent rose to 82% after process changes. Baseline process evaluation allowed us to identify considerable areas of waste including: a section-specific referral form; secretaries calling new patients up to three times prior to closing a referral when 3rd calls never resulted in an appointment being scheduled; a physician triage system resulting in batching of referrals and delays in scheduling; and secretaries hand-writing demographic information on a pre-appointment checklist. Our methodology led to the implementation of three process changes: non-urgent referrals were scheduled with the first available provider to eliminate scheduling delay due to the triage process; an electronic smartphrase eliminated the need for handwritten information and was embedded into the electronic referral containing a prior pre-appointment checklist; elimination of requiring all clinical documentation to be on hand prior to appointment scheduling but incorporated a secretarial electronic checklist to ensure all documents arrived prior to the patient's scheduled appointment.

Conclusion: Using quality improvement methodologies allowed the Section to initiate low-cost modifications to existing workflows to reduce overall scheduling times and improve patient satisfaction.

Disclosure: N. Orzechowski, None; **M. Bolg**, None; **R. Bergeron**, None; **C. Dorman**, None; **L. Sanderson**, None; **M. Stark**, None; **S. Wilk**, None; **T. Gray**, None.

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Abstract Number: 2485

Quality of Evidence of the American College of Rheumatology (ACR) Clinical Practice Guidlines

Mushabab Alghamdi[1] and Mohammed Al Mansour[2], [1]Internal Medicine, University of Bisha, Bisha, Saudi Arabia, [2]Rheumatology, King Fahad Medical City, Riyadh, Saudi Arabia
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Background/Purpose:

The American College of Rheumatology (ACR) regularly establishes and publishes guidelines for the management of various rheumatic diseases. These guidelines assist physicians in providing appropriate care to patients afflicted with rheumatic diseases. The objective of this study is to evaluate the quality of evidence supporting recommendations in the American College of Rheumatology (ACR) clinical practice guidelines.

Methods: Current guidelines for management of rheumatic diseases posted on the ACR website (http://www.rheumatology.org/) were evaluated using the methods reported by the American College of cardiology as follows: 1) for level of evidence A, data were derived from multiple RCTs or ameta-analysis, 2) for level B evidence, data were derivedfrom a single RCT or nonrandomized study, and 3) for level C evidence, data were derived from consensus, expert opinion, or case series.

Results:

At the time of our review, there were 7 guidelines posted on the ACR website, 5 of which were eligible for data analysis. Two guidelines were excluded (not followed the same quality of evidence format). The summary of the distribution is reported as the median of the percentage of all the eligible guidelines. The 5 analyzed guidelines contained a total of 191 recommendations, 56 were supported by Level A evidence (Median, 27.6(%); Inter-quartile range [IQR],15.4%-52.5%); 44 were supported by Level B evidence (Median, 18.9%; IQR,8.3%-33.8%); 91 were supported by Level C evidence (Median,45.2(%); IQR,33.2%-58.6%). (Table 1)

Table 1. Summary of All Current ACR Recommendations Level of Evidence, Number of recommendations (n), Percentage (%), Median (%) and Inter Quartile Range. 47.6% of the recommendation in the available website recommendation are supported by Level C evidence.

Level of evidence	Number	Percentage (%)	Median (%)	IQR
A	**56**	**29.3**	**27.6**	**15.4%-52.5%**
B	**44**	**23.0**	**18.9**	**8.3%-33.8%**
C	**91**	**47.6**	**45.2**	**33.2%-58.6%**

Conclusion: The ACR recommendations are supported mainly by level C evidence. These findings highlight the areas which have a paucity of high quality evidence and are not supported by either Level A or B evidence. The study highlights the limitations of current clinical rheumatological diseases research that can provide high quality of evidence. Support of high quality evidence research is crucially needed.

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View Abstract and Citation Information Online - http://acrabstracts.org/abstract/quality-of-evidence-of-the-american-college-of-rheumatology-acr-clinical-practice-guidlines

Abstract Number: 2486

Rheumatoid Arthritis Quality Measures – Automated Display of Care Gaps and Capture of Physician Decision Making at the Clinic Visit

Eric Newman[1], Tarun Sharma[2], **Alicia Meadows**[2], Jason Brown[3], Michael Rowe[4] and Shelly Vezendy[5], [1]Department of Rheumatology, Geisinger Health System, Danville, PA, [2]Rheumatology, Geisinger Health System, Danville, PA, [3]Henry Hood Center for Clinical Research, Geisinger Health System, Danville, PA, [4]Institute for Advanced Application, Geisinger Health System, Danville, PA, [5]Division of Medicine, Geisinger Health System, Danville, PA
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Background/Purpose: Rheumatoid Arthritis (RA) quality measures evaluate performance, and thus do not by themselves result in improvement. The ideal system to improve quality would provide real time actionable data by embedding the measures in the clinical workflow.

Methods: We designed a quality measurement system that 1) integrates with the electronic health record (EHR); 2) provides real-time recognition and closure of care gaps; and 3) allows easy recording of justifiable exceptions. Quality measures included RA on DMARD (Disease Modifying Anti-Rheumatic Drug), RA with MDHAQ (functional assessment), RA with CDAI (disease activity measure), RA at low disease activity, TB testing (if on biologic), flu and pneumococcal vaccination, and biologic de-escalation candidate. Color coding the measure status allowed easy recognition of an actionable item (green = measure met, red = not met/opportunity, gray = not applicable).

Using software integrated with the EHR, the RA quality measures were programmed to appear in a specific "tasks" tab. The tasks tab was user specific. The nurse tasks tab showed 1) the vaccination and TB testing measures, and 2) a decision tool where the nurse could select her decision (e.g. flu shot ordered). The rheumatologist tasks tab showed 1) all of the quality measures, 2) the nurse decision (in real time), and 3) a decision tool for RA on DMARD and biologic de-escalation. An opportunity was defined as an RA patient NOT on DMARD, or a biologic de-escalation candidate (low disease activity for at least a year). The rheumatologist used a drop-down list to easily document medical decision making for any opportunities. To reduce redundant work, each decision had an automatic "turn off" interval so that the decision tool did not appear at every visit.

Results: The tasks tabs were designed and programmed. The measures were validated against the EHR. Using PDSA (Plan Do Study Act) improvement methodology, the quality measurement system was implemented and the first cycle of data obtained regarding adoption of use and decisions made. Over the course of PDSA cycle 1 (4 weeks), 18 rheumatologists used the decision tool for 62% of the opportunities (54% for RA on DMARD, 66% for Biologic De-escalation). For RA patients NOT on DMARD, use of the tool resulted in 35% of the decisions to discuss a DMARD or add a DMARD. For biologic de-escalation candidates, use of the tool resulted in 34% of the decisions to de-escalate biologic therapy.

Conclusion: We designed, tested, and implemented a quality measurement system that integrates with the EHR, provides real time recognition of care gaps and cost reduction opportunities across a broad array of quality measures, and records provider decisions. The system was well-adopted, and early data suggests that it has facilitated improving the percent of RA patients on DMARD, as well as biologic de-escalation in well-controlled RA patients. Repeated PDSA cycles are planned to further increase tool adoption. As we gain additional data, we will explore the system's effect on improving the quality measures, and use the decision tool data to better understand modifiable barriers to improving these measures.

Disclosure: E. Newman, xG Health Solutions, 9; **T. Sharma**, None; **A. Meadows**, None; **J. Brown**, None; **M. Rowe**, None; **S. Vezendy**, None.

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Abstract Number: 2487

Clinical Practices Participating in a Quality Improvement Project Make Progress in Implementing Population Management

Erin Arnold[1], William Arnold[1], James Bower[2], Douglas Conaway[3], **J. Timothy Harrington**[2], Drew Johnson[4], James Mossell[5], Joy Schechtman[6] and Anne Winkler[7], [1]Orthopedics and Rheumatology of the North Shore, Skokie, IL, [2]Joiner Associates LLC, Madison, WI, [3]Rheumatology/Medicine, Carolina Health Specialists, Myrtle Beach, SC, [4]Crescendo Bioscience, Inc., South San Francisco, CA, [5]Arthritis and Osteo Center of South Georgia, Tifton, GA, [6]Sun Valley Arthritis Center LTD, Peoria, AZ, [7]Rheumatology, Winkler Medical Practice LLC, Springfield, MO

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Background/Purpose: Population management (PM) offers a promising approach to providing Treat-to-Target (T2T) care for rheumatoid arthritis (RA). PM depends on providing standardized, on-time disease activity (DA) assessments and coordinated care across the entire disease population, as well as for individual patients within this context. This study investigates the adoption of PM registries in rheumatology practices, the use of standardized DA measures (referred to as *signal measures*) as chosen by participating rheumatologists, and the barriers some practices are encountering as they strive to implement PM.

Methods: The Rheumatoid Arthritis Practice Performance (RAPP) Project is a voluntary collaboration of U.S. clinician rheumatologists (current N = 168) who manage more than 80,000 RA patients in total. Participating physicians are enrolling their RA patients (ICD-9 code 714.0) into a HIPAA-compliant disease population registry from practice billing records or during clinical visits. They are then collecting signal measures and current medications on these patients over time. With isolated exceptions, their preferred signal measures include one or more of the following: RAPID3, a 0-10 Provider Global Assessment (PGA), Clinical Disease Activity Index (CDAI), and a multi-biomarker (MB) test. The registry enables real-time Population Reports that track assessment timeliness (consistent with T2T recommendations) and monitor the DA distribution within each physician's enrolled RA population. Lists of overdue patients are also generated from the registry. The RAPP Project's coordinators regularly assess physicians' progress toward PM and the barriers they encounter.

Results: To this point, 86 RAPP Project physicians have fully enrolled their RA population in a population registry. Signal measure results reported by these physicians include:

Measure	Practices Reporting (Number)	Percentages of Patients Reported (Range)	Patients with Measures in All Registries (Number)
RAPID3	15	10-93%	4176
PGA	39	2-93%	8679
CDAI	15	2-93%	4151
MB Test	86	3-100%	38412

Despite strong intentions, many practices encounter barriers to implementing a population registry and PM workflows, including: 1) temporary practice or personal crises, such as partners leaving or illnesses; 2) physicians and staff lacking the time, resources, and skills to implement the necessary practice changes; and 3) administrative objections, especially in larger group practices.

Conclusion: 1. Increasing numbers of physicians and staff have been able to implement a simple yet robust population registry in their busy practice environments. 2. They are collecting one or more signal measures across their population. 3. They are using their registry data to create PM workflows and improve "on-time" DA assessment. 4. Both practice-based and health system barriers present challenges to implementing PM in many practices.

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Abstract Number: 2488

Impact of Protocolized Tight Control and Biological Dose Optimization in Daily Clinical Practice: Results of a Pilot Implementation Study

Nienke Lesuis[1], George Bruyn[2], Paul Baudoin[2], Lieke Nieboer[3] and Alfons den Broeder[1], [1]Rheumatology, Sint Maartenskliniek,

Nijmegen, Netherlands, [2]Rheumatology, MC Zuiderzee, Lelystad, Netherlands, [3]rheumatology, Sint Maartenskliniek, Nijmegen, Netherlands

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Background/Purpose:

It is possible to optimize and reduce the individual dose of biological Disease Modifying Anti-Rheumatic Drugs (bDMARDs) in patients with rheumatic diseases, in combination with tight control strategies, while maintaining adequate disease control.[1] Nevertheless, most rheumatologists in daily clinical practice do not apply these strategies. As the potential benefit for both patients (side-effects) and society (costs) is large, we aimed to implement dose optimization strategies in real clinical practice.

Methods:

This pilot implementation study was conducted at the rheumatology department of a general hospital in the Netherlands between May and October 2014. Both rheumatologists working in this center were eligible for participation. The implementation strategy comprised three steps: 1) education, feedback, and the development of guidelines on bDMARD dose optimization and tight control based treatment of rheumatoid arthritis (RA), psoriatic arthritis (PsA) and axial spondyloarthropathy (SpA), 2) individualized treatment advices of all patients using bDMARDs (written in the electronic health record of individual patients) followed by 3) monitoring and feedback after three and six months. To determine the effectiveness of this strategy, the percentage of patients with measured disease activity was assessed, i.e., the Disease Activity Score in 28 joints (DAS28), or the *Bath Ankylosing Spondylitis Disease Activity Index* (BASDAI). In addition, mean DAS28 and BASDAI scores and the percentage of patients using a reduced dose of their bDMARD were calculated. All outcomes were assessed at baseline (directly after step 1) and three and six months thereafter.

Results:

Both rheumatologists participated in this study and were present during the implementation of steps 1 through 3. At baseline, 275 patients (mean age 56 years ± 16 years; 56% female) were using a bDMARD, the most commonly prescribed bDMARDs were adalimumab (41%), etanercept (23%) and tocilizumab (13%). The majority of patients were diagnosed with RA (63%), SpA (17%), and PsA (15%). Disease activity measures and dose reduction data are listed in table 1.

Table 1 Outcomes on DAS28, BASDAI and bDMARD use

Outcome	Baseline	T = 3	T = 6
DAS28 performed* (%)	40	63	70
BASDAI performed$^{\Xi}$ (%)	20	38	40
Mean DAS28*	2.1 ± 0.9	2.4 ± 1.1	2.3 ± 0.9
Mean BASDAI$^{\Xi}$	3.6 ± 2.8	5.0 ± 1.0	3.8 ± 1.3
Using a reduced bDMARD dose† (%)	11	37	63

*Outcome only assessed in RA patients. $^{\Xi}$Outcome only assessed in SpA patients. †Outcome assessed in all patients.

Extrapolating the percentage of patients that received a reduced dose of bDMARD at six months, we estimated that total annual savings of 500,000 euros could be realized by biological dose optimization in this cohort.

Conclusion:

Based on the promising results of this pilot study, implementation of tight control based biological dose optimization may become a feasible and successful strategy in daily clinical practice, resulting in improved quality of care and a sizable reduction in bDMARD use.

References

[1]Van Herwaarden et al. BMJ 2015.

Disclosure: N. Lesuis, None; **G. Bruyn**, None; **P. Baudoin**, None; **L. Nieboer**, None; **A. den Broeder**, None.

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Abstract Number: 2489

Effects of Two Interventions on Rheumatologists Adherence to Optimal Care Recommendations in Rheumatoid Arthritis: A Combined before/after and Randomized Controlled Trial

Nienke Lesuis[1], Ronald van Vollenhoven[2], Marlies Hulscher[3] and Alfons den Broeder[1], [1]Rheumatology, Sint Maartenskliniek, Nijmegen, Netherlands, [2]ClinTRID, Department of Medicine, Karolinska Institute, Stockholm, Sweden, [3]IQ Healthcare, Radboud University Medical Centre, Nijmegen, Netherlands

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Background/Purpose:

Current treatment guidelines for rheumatoid arthritis (RA) recommend using tight control strategies.[1] Despite evidence for the benefits of this strategy, physician adherence is suboptimal.[2,3] Here we investigated two strategies to improve RA care by increasing physician guideline adherence using a multimodal intervention strategy.

Methods:

A single centre, combined before/after and randomized controlled pilot study was performed to assess effectiveness of two interventions. The first intervention combined education with feedback, whereas the second intervention comprised decision support incorporated in the Electronic Medical Record (EMR).

All clinicians (rheumatologists, residents and physician assistants; n = 20) working at the study centre during the full study period could participate. All participants received intervention 1, while intervention 2 was allocated in a 1:1 intervention vs. control randomization. .

Intervention effects were measured at the patient level using a set of 13 different dichotomous indicators for RA diagnostics, treatment and follow-up. All adult RA patients with a visit to a participating clinician in the study period were eligible for inclusion. The standardized sum score (SSS) of the indicators (indicator sum score divided by number of indicators) served as the primary outcome. The effect of intervention 1 was assessed using a before/after design; whereas the extra effect of intervention 2 was assessed using a randomized controlled design. The total study duration was 10 months (pre-intervention: 6 months; post-intervention: 4 months).

Results:

All 20 clinicians participated in this study. A total of 1050 patients was included of which 527 in the pre-intervention period and 523 in the post-intervention period.

Three out of 13 indicators improved significantly after the interventions (regular disease activity- and functional status measurements, shared care with the physician assistant) with odds ratios between the 1.8 and 3.1. Intervention 1 resulted in a significant increase in the SSS, from 0.57 before the intervention to 0.63 afterwards (difference 0.06; 95% confidence interval

(95%-CI) 0.02 to 0.10; p <0.01). In contrast, the second intervention did not result in an extra effect above intervention 1 alone (difference 0.01; 95%-CI -0.04 to 0.07; p = 0.65).

Table 1 Baseline characteristics of included clinicians

	Control group *(intervention 1; n = 10)*	**Intervention group** *(intervention 1 and 2; n = 10)*
Clinician characteristics		
Age, years (SD)	42.4 (11.1)	46.0 (11.0)
Female, n (%)	5 (50.0)	6 (60.0)
Rheumatologist, n (%)	9 (90.0)	6 (60.0)
Work experience, years (SD)	8.0 (8.0)	12.0 (9.0)
Patient characteristics		
Age, years (SD)	61.9 (12.2)	61.9 (12.6)
Female, n (%)	359 (66.1)	365 (72.0)
Disease duration, years (SD)	9.7 (8.4)	9.0 (8.5)
Rheumatoid and/or anti-CCP positivity, n (%)	364 (76.6)	276 (68.5)
Erosive disease, n (%)	250 (48.9)	202 (44.4)

Conclusion:

An intervention consisting of education and feedback, but not electronic decision support, resulted in a significant increase in guideline adherence, reflected by an increase in the indicator sum score and improvement in three out of 13 indicators.

[1]Smolen et al. Ann Rheum Dis 2014. [2]Schipper et al. Rheumatology 2012. [3]Harrold et al. Arthritis Rheum 2012.

Disclosure: N. Lesuis, None; **R. van Vollenhoven**, None; **M. Hulscher**, None; **A. den Broeder**, None.

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Abstract Number: 2490

Implementation of Disease Activity Measurement for Rheumatoid Arthritis Patients in an Academic Rheumatology Clinic

Alison Bays[1], Elizabeth R. Wahl[2], David I. Daikh[3], Jinoos Yazdany[4] and Gabriela Schmajuk[5], [1]Rheumatology, University of Washington, Seattle, WA, [2]Medicine/Rheumatology, San Francisco Veterans Affairs Medical Center, San Francisco, CA, [3]Rheumatology, UCSF/VA Medical Center, San Francisco, CA, [4]Rheumatology, UCSF, SF, CA, [5]San Francisco VA Medical Center, University of California, San Francisco, San Francisco, CA

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Session Date: Tuesday, November 10, 2015

Session Title: Quality Measures and Quality of Care Poster Session

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Session Time: 9:00AM-11:00AM

Background/Purpose:

Current recommendations for optimal rheumatoid arthritis (RA) management include routine assessment of disease activity and adjustment of medication to achieve remission or low disease activity. There are limited data describing implementation strategies for this potentially burdensome process in a real-world clinic setting. Our goal was to increase the use of disease activity measures, specifically, the Clinical Disease Activity Index (CDAI) for RA patients at an academic VA medical center rheumatology clinic using Plan-Do-Study-Act (PDSA) cycles and introduction of a simple paper form.

Methods :

Patients were diagnosed with RA by a rheumatologist. In PDSA cycle 1, a paper-based form was distributed to providers and brief one-on-one educational discussions with incoming fellows were held. The form included a patient global activity of disease visual analogue scale (VAS, 0-10cm), a physician global VAS and a 28-joint count homunculus for counting tender/swollen joints. The form also included instructions for calculation and interpretation of the CDAI. Providers were instructed to enter the total CDAI score into their clinical note. PDSA cycle 2 included two provider education talks on disease activity measurement including rationale, identification of RA patients prior to their clinic visit by investigators, inclusion of medical assistants to distribute paper forms to pre-identified patients, and separation of the form into two pages – one for the patient global (was changed from VAS to numerical in cycle 2) and one for the provider components. We generated a run chart to evaluate the effect of each PDSA cycle on the percent of RA visits with the CDAI recorded.

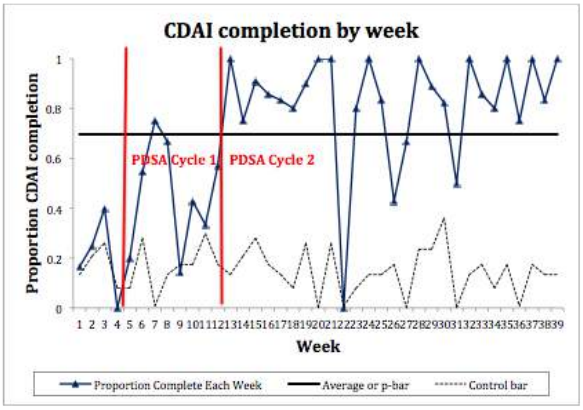
Results :

Nine rheumatology fellows, 1 nurse practitioner and 5 attending physicians participated in this quality improvement project. 107 RA patients were seen at the clinic during the study period, June 2014 through March 2015. During the 4-week pre-intervention period, there were 29 RA patient visits and 24% (n=7) had a documented CDAI. PDSA cycle 1 lasted 8 weeks with 59 visits and 44% of patients (n = 26) had a CDAI documented. Cycle 2 lasted 27 weeks with 182 visits and 85% of patients (n = 155) had a CDAI documented.

Conclusion :

We successfully increased CDAI use in an academic rheumatology clinic setting using a simple paper form coupled with brief provider education. The majority of providers were rheumatology fellows, indicating that providers can learn this skill early in their training. Our approach may be informative for other clinical settings, especially for

those without an electronic medical record or those that are unable to modify their electronic medical record to incorporate disease activity measures.



The pre-intervention, PDSA Cycle 1 and PDSA Cycle 2 separated by red bars. The dark blue line shows the proportion of CDAI completed by week. The upper control limits are not seen as they are above a proportion of 1, the lower control limit is shown and describes the variation of the denominator as different numbers of RA patients are seen in clinic each week. The p-bar is shows the average. More than six values are seen above the p-bar, indicating a successful change.

Disclosure: A. Bays, None; **E. R. Wahl**, None; **D. I. Daikh**, None; **J. Yazdany**, None; **G. Schmajuk**, None.

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Abstract Number: 2491

Documentation of Disease Activity Score As Part of a Treat to Target Strategy in Rheumatoid Arthritis

Sarah Homann[1] and Beth Scholz[2], [1]Rheumatology, University of Texas Health Sciences Center at Houston, Houston, TX, [2]University of Texas Health Sciences Center at Houston, Houston, TX

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Background/Purpose: Compared to routine care, the Treat to Target (TTT) strategy for rheumatoid arthritis (RA) has been validated to improve functional and radiographic outcomes via use of disease activity measures (DAMs) to quantify and track RA activity over time. Several DAMs have been validated for clinical use by the American College of Rheumatology (ACR), but routine use of DAMs during RA patient visits is not standard practice at the University of Texas at Houston (UT Houston) Rheumatology clinic.

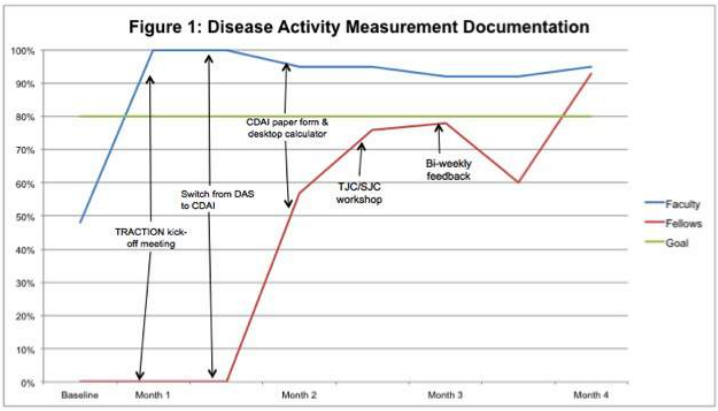
Via participation in a learning collaborative (TRACTION [Treat-to-target in Rheumatoid Arthritis: Collaboration To Improve adoptiOn and adhereNce]) we sought to increase adherence to TTT strategy in RA and to increase DAM documentation to a minimum of 80% of RA visits. Our institution adopted use of the Clinical Disease Activity Index (CDAI), which consists of a 28 tender and swollen joint count (TJC/SJC), patient global assessment of disease activity, and provider global assessment of disease activity.

Methods: The initial intervention was altering the electronic chart note template to include a dedicated line for CDAI value. Simultaneously, printed CDAI forms from the ACR website were placed in all clinic exam rooms. Electronic CDAI calculators from the ACR website were also downloaded onto clinic computers. For TRACTION, percentage of faculty visits with documented DAM is calculated by reviewing 5 charts per provider over a 2 week time period on a monthly basis.

After TRACTION faculty reached goal CDAI documentation, interventions targeted our 5 fellows. To teach proper technique for performing a 28 TJC/SJC, fellows underwent a learning session wherein they viewed a TJC/SJC instructional video and practiced TJC/SJC with simultaneous use of musculoskeletal ultrasound to verify location of the palpated joint space. Individual CDAI documentation rates based on all RA visits was provided to each fellow at baseline and then bimonthly.

Results: At baseline, faculty documented a DAM for 6/25 (24%) of RA visits. Over subsequent months, faculty documented a DAM in 20/20 (100%), 19/20 (95%), 23/25 (92%), and 19/20 (95%) of RA patient visits. At baseline, fellows documented a DAM in 0% of RA visits. Over the 8 weeks post-learning session, CDAI documentation increased to 22/29 (76%), 21/17 (78%), 14/23 (60%), and 14/15 (93%) RA visits. (See Figure 1.)

Conclusion: TTT improves outcomes in RA. Validated DAMs can assess and track RA disease activity at each visit. Use of DAM without lab value input, improved access to DAM calculating tools, and use of a template-based electronic note led to increased CDAI use and documentation among faculty. A TJC/SJC learning session for fellows with bimonthly feedback about documentation improved fellow CDAI documentation from 0% to 93% of RA visits. More time is required to assess whether our efforts will lead to a sustainable change in practice patterns.



Disclosure: S. Homann, None; **B. Scholz**, None.

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Abstract Number: 2492

Implementation of the Clinical Disease Activity Index to Treat to Target Rheumatoid Arthritis in the Ambulatory Setting: A Plan Do Study Act Quality Analysis

Irene Lazarus[1], Salahuddin Kazi[2], Alok Dwivedi[3], Christopher Dodoo[4], Riya Joseph[5], Mariela Hernandez[6], Cam Duong[7], Yasmin Sabet[8] and Kanchan Pema[9], [1]Internal Medicine, Texas Tech University Health Science Center, El Paso, TX, [2]Internal Medicine/Rheumatology, UT Southwestern Medical Center, Dallas, TX, [3]Biomedical Sciences Division of Biostatistics and Epidemiology, Texas Tech University Health Sciences Center, El Paso, TX, [4]Texas Tech University Health Sciences Center, El Paso, TX, [5]Internal Medicine, Methodist Dallas Medical Center, Dallas, TX, [6]Paul Foster Medical School, Texas Tech University Health Sciences Center, El Paso, TX, [7]Paul Foster School of Medicine, Texas Tech University Health Sciences Center, El Paso, TX, [8]Internal Medicine, Texas Tech University Health Sciences Center, El Paso, TX, [9]Internal Medicne/Rheumatology, Texas Tech University Health Science Center, El Paso, TX

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Background/Purpose: Achieving tight control of RA with reliable methods to monitor and assess disease activity in a more objective way is imperative in clinical practice to obtain treat to target results. We conducted a longitudinal study to evaluate utility, adoption, and analysis of the correlation and agreement of the Clinical Disease Activity Disease Index (CDAI) and Simple Disease Activity Index (SDAI) scores and categories of disease. We adapted our electronic health record (EHR) (Centricity) to standardize real time assessment with the CDAI in hopes to change physicians' therapeutic behavior, in order to provide better care and afford patients with a single number to understand their disease activity.

Methods: In the first seven months a total of 153 cases were included in the analysis. Spearman rank and intraclass correlation (ICC) were computed between CDAI and SDAI scores. The Kappa agreement and McNemar's test was conducted for the agreement of CDAI and SDAI disease categories. Finally one-way ANOVA was used to test the association between categorized SDAI and CDAI and selected lab variables. The quality analysis of the project was performed with quarterly meetings with rheumatologists and the information technology (IT) department to discuss implementation and data collection.

Results: The "CDAI calculator" was launched on October 2014 during this month we had a 48% documentation rate for RA patient clinical encounters, but by December we achieved a 100% EHR documentation rate. Our study was in an 87.32% Hispanic population with 84.31% being female. Based on CDAI disease activity categories, the distribution for Remission, Low, Moderate, and High activity was 43.79%, 31.37%, 15.03%, and 9.8% respectively. The association between CDAI and SDAI scores was found to be very high with a spearman value of 0.95 (p-value <0.0001) and further confirmed with the ICC of 0.987 (CI: 0.982-0.991). There was no significant difference in proportion of discordant pairs of the SDAI and CDAI categories, showing that scores that switched classification when converted were negligible (p-value 0.4815). The agreement between the CDAI and SDAI categories was high with a Kappa of 0.87 (CI: 0.81-0.94). Of note, there was a difference between the categorized SDAI versus platelets ANOVA analysis (p-value 0.053) with platelets in Remission being 272.4 (± 91.0), Low 239.9 (± 71.1), Moderate 286.8 (± 84.9), and High 293.5 (± 72.0).

Conclusion: Incorporation of the CDAI into point-of-care visits was possible with coordination of an interdisciplinary team and the continual reassessment methodology of the Plan Study Do Act approach. On analysis, the SDAI and CDAI showed that even when a CRP was not included in composite scoring the CDAI categorization was utile for proper assessment and sensitive to change. When seeing association between lab values and the indices, the SDAI categorization was able to show the theory of thrombocytosis in higher inflammation states confirming that the index can differentiate disease activity accurately. At this time, we need more follow up CDAI scores in order to objectively see treat to target changes in both patient population and physician management behavior.

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Abstract Number: 2493

Improvement of Disease Activity and Quality of Care in a Cohort of Rheumatoid Arthritis Patients Treated with Conventional Dmard Therapy Under Treat to Target Recommendations and a Model of Patient-Centered Care

Pedro Ivan Santos-Moreno[1], Ginna Saavedra[2], Rosana Ramirez[2], Laura Villarreal[2], Ana Bolena Cardozo[2], Vanessa Giraldo[2], Paola Martinez[2], Adriana Sanchez[2], Merle Sanchez[2], Danny Gomez[2] and Juan Manuel Bello[2], [1]Rheumatology, Biomab, Center for Rheumatoid Arthritis., Bogota, Colombia, [2]Rheumatology, Biomab, Center for Rheumatoid Arthritis, Bogota, Colombia, Bogota, Colombia

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Background/Purpose: Treat to Target (T2T) strategy becomes from the need to develop therapeutic targets and tools to achieve defined outcomes in rheumatoid arthritis (RA). Moreover, models of patient-centered care where multidisciplinary teams make disease management increasingly take place in rheumatology. The aim of this study was to describe change in Disease Activity Score 28 (DAS28) using T2T strategy for a 24-month period in patients with conventional DMARD therapy in a large cohort of patients from a specialized in RA center where a model of patient-centered management is used.

Methods: A descriptive cross-sectional study was performed. Records of patients in conventional DMARD therapy from specialized in RA center were reviewed; those patients were followed-up under T2T standards. Clinical follow-up was done strictly according to DAS28 as follows: every 3-5 weeks (DAS28 > 5.1), every 7-9 weeks (DAS28 ≥ 3.1 and ≤ 5.1), and every 11-13 weeks (DAS28 < 3.1). Tender joint count (TJC), swollen joint count (SJC), DAS28 and HAQ were measured on each visit. Therapy had to be adjusted with DAS28 > 3.2 unless patient´s conditions don't permit it; we considered this follow-up type as implementation of a T2T strategy in patients with RA. We divided patients in four groups: remission (Rem), low disease activity (LDA), moderate disease activity (MDA) and high disease activity (HDA) patients and the aim of the study was to look at what percentage of patients who were in moderate or high disease activity reached a low disease activity or remission after 24-month period. On the other hand, patients were followed-up by physiatrist, psychologist, nutritionist and therapists at least 3 times a year. Descriptive epidemiology was done, percentages and averages were calculated; the median of each variable was analyzed using t-Student assuming normality for DAS28 distribution and the level disease activity was analyzed using Pearson´s statistics.

Results: 1110 patients were included in this study, 826 (74.4%) women and 284 (25.5%) men. Average age was 61 y/o (15-89) with disease duration of 11 years (0.5-47). Concerning to treatment of entire cohort 76 (6.8%) patients were using Leflunomide alone, 114 (10.2%) Metothrexate alone, 100 (9.0%) Leflunomide plus Metothrexate, 98 (8.8%) Leflunomide plus other DMARDs, 519 (46,7%) Metothrexate plus others DMARDs and 203 (16.9%) "only" DMARDs without Leflunomide or Metothrexate. At 24 months 66.6% of patients got remission and 13% LDA and was observed a decrease in percentage of patients in MDA/HDA statistically significant. For the entire cohort, at beginning DAS28 was 3.6 and after 24 months of follow-up DAS28 was 2.6 showing improvement (p <0.00). In overall, 98% of patients rated the quality and accessibility of multi-disciplinary care as good or excellent.

Conclusion: There is a great improvement of DAS28 in a cohort of RA patients only receiving conventional therapy with following-up under strict T2T strategy. This is very important issue in those countries or environments with limited resources for health care. Regarding a model of patient-centered care, studies are needed to measure the impact of the multidisciplinary team on the clinical results obtained.

Disclosure: P. I. Santos-Moreno, None; **G. Saavedra**, None; **R. Ramirez**, None; **L. Villarreal**, None; **A. B. Cardozo**, None; **V. Giraldo**, None; **P. Martinez**, None; **A. Sanchez**, None; **M. Sanchez**, None; **D. Gomez**, None; **J. M. Bello**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/improvement-of-disease-activity-and-quality-of-care-in-a-cohort-of-rheumatoid-arthritis-patients-treated-with-conventional-dmard-therapy-under-treat-to-target-recommendations-and-a-model-of-patient-ce

Abstract Number: 2494

An Electronic Safety Dashboard for Rheumatology Clinics

Mary Margaretten[1], Laura Trupin[1], Sarah Goglin[2] and Jinoos Yazdany[1], [1]University of California, San Francisco, San Francisco, CA, [2]Rheumatology, University of California, San Francisco, San Francisco, CA

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Background/Purpose: Patient safety problems are increasing in rheumatology given the growing use of high-risk immunosuppressive drugs. Electronic health record "dashboards" have been utilized in research and quality improvement to evaluate provider performance. However, safety dashboards for rheumatic diseases are lacking, despite the availability of quality measures and numerous studies indicating gaps in care. Our objective was to develop an electronic safety dashboard for an outpatient rheumatology clinic using the Institute for Healthcare Improvement's Model for Improvement.

Methods: We undertook a quality improvement project using data stored in the electronic health record (EHR) of an urban safety-net hospital to develop eMeasures for a rheumatology electronic safety dashboard. The eMeasures were evidence-based, clinically actionable metrics that address high-priority patient safety risks: (1) bone health monitoring in patients taking oral

glucocorticoids, (2) screening and treatment for latent tuberculosis (TB) prior to initiation of anti-TNF-α drugs, and (3) pneumococcal vaccination in patients using high-risk immunosuppressive medications. We built prototype electronic queries to automatically extract data and adjusted clinical workflows and documentation to standardize information collection. We used Plan-Do-Study-Act cycles to create and revise clinical workflows to improve performance on each of these eMeasures. A data analyst completed training to access the EHR data warehouse and identified numerator and denominator populations of rheumatology outpatients using standardized, coded terminologies.

Results: For the bone health eMeasure, we revised our clinical workflow to include a bone health template in the clinical note, including embedding a link to a FRAX calculator. With the introduction and refinement of this template (Figure 1), performance on bone health measures increased from 0% to 27% in a three-month period. For the TB screening eMeasure, a drug safety checklist was instituted into the workflow, and results are currently being analyzed. For the pneumococcal vaccination eMeasure, a nurse-led pre-visit planning step and provider reminder sheet were instituted. This program increased vaccination rates strikingly over time (Figure 2).

Conclusion: The development of an electronic dashboard in a safety-net rheumatology clinic coupled with workflow changes to improve performance on dashboard eMeasures led to significant improvements in delivering quality measures to rheumatology patients.

Figure 1. Screen Shot of FRAX template embedded into Rheumatology Clinical Note

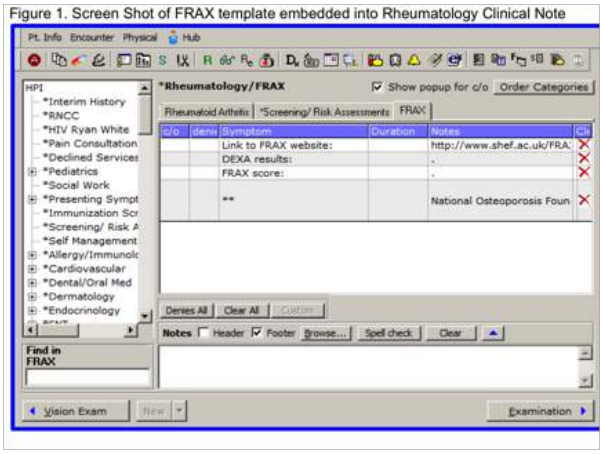
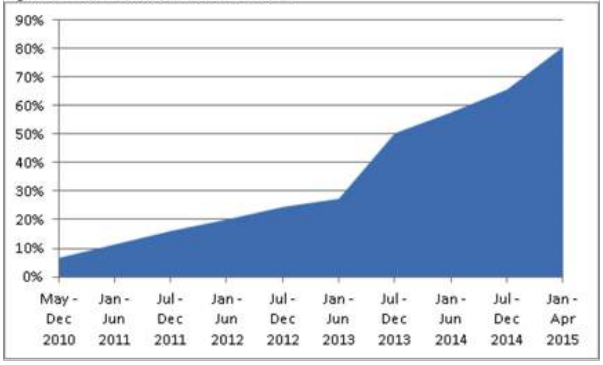


Figure 2. Pneumococcal Vaccination Rates



Disclosure: M. Margaretten, None; **L. Trupin**, None; **S. Goglin**, None; **J. Yazdany**, None.

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Abstract Number: 2495

Tele-Monitoring of Disease Activity in Rheumatoid Arthritis and Psoriatic Arthritis

Alexander Langer[1] and Hans-Eckhard Langer[2], [1]Department of Computer Science, RWTH Aachen University, Aachen, Germany, [2]RHIO (Rheumatology, Immunology, and Osteology), Duesseldorf, Germany

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Background/Purpose:

There is evidence that tight control of rheumatoid arthritis improves outcome. In daily practice this aim is constricted by logistic limitations such as a small number of rheumatologists or long distances to specialized centers. By tele-monitoring the disease activity between regular routine controls and individually tailoring control intervals, we might be able to optimize disease management. In this study, we examine the acceptance and usage of an online tele-monitoring tool.

Methods:

The tele-monitoring tool was developed as a patient empowerment platform for an internet community for patients of chronic arthritis. The program includes electronic versions of the DAS28 and the HAQ as well as a form to regularly (e.g., daily) document disease activity (scale 0-10; 0=lowest, 10=highest), pain (0-10) and fatigue (0-10), swollen and tender joints, drugs taken and any noteworthy events such as flares or special occasions in the patient's life. The monitoring data can be made available to the rheumatologist who can then react appropriately.

Between 2011 and 2015, 2732 users of the internet community signed up for the program, out of which 1233 patients voluntarily provided their age, gender and diagnosis. 616 subjects with RA (n=503) or PsA (n=114) were chosen for further analysis.

Results:

The mean age at registration was 45.0 ± 12.2 years (range 13-82); 467 (76%) subjects are female. 279 patients (45%) used the program less than two weeks. The remaining 337 patients (55%) used the program for 323.8 ± 352.5 days on average, with an average frequency of once every 32.4 ± 57.4 days.

415 patients regularly entered disease activity (totaling n=17691 entries; average of 3.07 ± 2.50), pain (n=19325 entries; average 3.27 ± 2.50), or fatigue (n=18198; average 3.42 ± 2.83). The DAS28 test was performed by 275 patients; the average score after registration was 4.68 ± 1.44 (range 0.42 - 8.91; median 4.71). The average HAQ score (333 patients) was 1.11 ± 0.67 (range 0 - 2.86; median 1.13).

Conclusion:

The tele-monitoring tool is well-received. The majority of patients that signed up continued to use it regularly. Patients seem to prefer simple scores that can be entered quickly over more involved tests such as the DAS28 or the HAQ.

It remains open why some patients discontinued the usage of the tele-monitoring tool. With additional training and support by health care providers such as the primary physician it might be possible to improve the persistency in tele-monitoring as well as the acceptance of lengthier tests such as the DAS28 or HAQ. Here we see chances and challenges for a more broader application of tele-monitoring tools.

The average user of the tele-monitoring tool is rather young, has a high disease activity and reduced functional capacity. This might be an indication that particularly patients with a severe arthritis seek help in additional tools for coping with their disease.

Disclosure: A. Langer, None; **H. E. Langer**, None.

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Abstract Number: 2496

Telerheumatology: A Technology Not Appropriate for All

Zsolt Kulcsar[1,2], Daniel Albert[3], Ellyn Ercolano[4] and John Mecchella[5], [1]Rheumatology, Dartmouth Hitchcock Medical Center, Lebanon, NH, [2]Rheumatology/Leadership Preventive Medicine Residency, Dartmouth Hitchcock Medical Center, lebanon, NH, [3]Medicine/Rheumatology, Dartmouth-Hitchcock Med Ctr, Lebanon, NH, [4]Telehealth, Dartmouth Hitchcock Center For Telehealth, Lebanon, NH, [5]Rheumatology, Dartmouth-Hitchcock Medical Center, Lebanon, NH
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Title: Telerheumatology: A Technology Not Appropriate For All

Background/Purpose: Access to Rheumatology care in New Hampshire (NH) and Vermont (VT) is limited, as a large proportion of the population lives in rural areas (60%) with limited resources. Telerheumatology services developed at Dartmouth-Hitchcock Medical Center (DHMC) brings care to these rural regions and improves access. Our previous work identified two issues with telerheumatology: 1) the quality of the patient presenter and 2) the appropriateness of the patient for a telerheumatology visit. We want to systematically assess the patient and provider experience to improve the quality of care delivered via telerheumatology.

Methods: As part of a quality improvement initiative we performed an IRB-exempt retrospective review of the charts for patients seen in the telerheumatology clinic at DHMC from October 2011 to December 2014. We also interviewed the participants: including providers, presenters and patients regarding their experience of care. We assessed both patient and provider satisfaction with the experience. We developed a web based educational series on rheumatic disease, including MSK examination, for the presenter. We used descriptive statistics to summarize our findings.

Results: Between October 2011 and December 2014, 176 patients were seen via telerheumatology between two clinical sites over the course of 244 patient visits. The top diagnosis for patients seen was inflammatory arthritis (n=156, 63.9%). 66.4% of the patients were on high risk medications including: steroids, biologics (infusion and injectable), and DMARDs. Providers filled out surveys on 9 visits for 70 patient encounters and found that 19% of patients (13) were inappropriate for the visit type for two main reasons: diagnosis unclear or diagnosis too complex. Telerheumatology afforded patients shorter travel distances and travel related money savings. 94% of patients were satisfied with the remote site staff and treating providers, and 73% of them would like to be seen via telerheumatology again. We previously provided presenter education which had no impact on the provider perceived quality of the visit.

Conclusion: The use of telerheumatology has successfully increased access to rheumatology care for patients in rural regions of NH and VT allowing for shorter travel and cost savings. 19% of the patient visits reviewed were inappropriate for the visit modality. This evaluation was performed in a setting without any pre-visit screening, which we believe could be an opportunity to triage patients to the appropriate visit modality. We propose a triage mechanism (Table 1) to pair patients appropriately with the telerheumatology visit type to ensure an overall high quality experience for patients and providers in the future.

Table 1. Triage tool to guide telemedicine in Rheumatology

Conditions	Disease State	Candidate for Tele-Health	Clinical Example
Diagnosis/Disease Well Established	Stable	Yes	Stable well-established disease (RA/PsA/SLE) on DMARD or Biologic therapy needing routine drug monitoring (labs for toxicity etc.)
	Flaring	Maybe	Patient with well-established disease (RA/PsA/SLE) experiencing flare requires escalation of therapy or short course of systemic steroids to control symptoms but no procedure needed
	Needs Procedure	No	Requiring arthrocentesis or MSK ultrasound to guide therapy
Diagnosis/Disease Complex	Complex	No	Complex multi-organ disease (i.e. Scleroderma/Dermatomyositis/Vasculitis) with worsening symptoms where diagnosis/treatment cannot be delayed/missed
Screening prior to in-person visit	Any	Yes	PCP calling for initial work-up recommendations or management questions
		No	If modality will lead to prolonged delay in follow up of complex disease
Failed Prior Tele-Health Visit	-	No	Prior bad experience or failure with modality
Hard of Hearing Or Poor Engagement	-	No	Poor ability to participate in care

RA=Rheumatoid Arthritis, PsA=Psoriatic Arthritis, SLE=Systemic Lupus erythematosus, MSK=Musculoskeletal, PCP=Primary Care Provider

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Disclosure: Z. Kulcsar, None; **D. Albert**, None; **E. Ercolano**, None; **J. Mecchella**, None.

Abstract Number: 2497

Satisfaction with the Initial Evaluation for a Rheumatologic Complaint Using Telemedicine

Tracy Nguyen-Oghalai[1], Michael Lyon[2] and Kathy Hunter[3], [1]RHEUM, VA, Palo Alto, CA, [2]Internal medicine, Stanford University, stanford, CA, [3]Internal Medicine, VA Palo Alto, Stanford, CA

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Background/Purpose: Technological advances have facilitated the use of nontraditional forms of health care encounters, such as telemedicine. The aim of this study was to describe our experience using telemedicine for the evaluation of new patients referred to the Rheumatology Clinic at the Palo Alto VA.

Methods: This is a descriptive study of the initial rheumatologic evaluation using telemedicine conducted as a VA quality assurance project. Patients were seen at a community based outpatient clinic by a nurse practitioner (KH) with a Rheumatologist (ML) participating in the encounter via Telelink from our primary site. Patients completed a satisfaction survey immediately after this initial telemedicine encounter. All patients had a second visit in person with the same Rheumatologist (ML) at the primary site. A subsequent telephone survey was conducted by a different provider (TNO) to assess patient satisfaction with both telemedicine and in-person care methods. Patients were also asked if they had a preference for one or the other care method.

Travel data (mileage) were also collected for both visits.

Results: 37 patients underwent the initial telemedicine evaluation. All of these had a second in person Rheumatologist visit and completed both questionaires. Ten had chronic autoimmune conditions such as inflammatory polyarthritis, polymyalgia rheumatica , systemic lupus erythematosus, and ankylosing spondylitis; five had crystal arthropathies. The remaining 22 patients had non-inflammatory musculoskeletal conditions. Travel miles were less for all participants for the telemedicine visits relative to the in person visit with the Rheumatologist at the primary site.

Immediately after the telemedicine encounter, all patients gave a 10/10 rating for satisfaction. During the telephone survey after their in person visit with the Rheumatologist, 30 remained highly satisfied with the telemedicine encounter, 10/10. However, among patients with chronic inflammatory conditions or crystal arthropathies, 66% (10/15) preferred the in person visit. Among patients with non-inflammatory conditions 41% (9/22) preferred the in person visit with the Rheumatologist.

Preference	In person	telemedicine	Total
Crystal	4	1	5
Chronic autoimmune	6	4	10
No chronic autoimmune	9	13	22

Conclusion: Satisfaction with telemedicine visits was high, but patients with chronic inflammatory disorders or crystalline arthopathies preferred the in-person visits, despite greater travel distances

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Disclosure: T. Nguyen-Oghalai, None; **M. Lyon**, None; **K. Hunter**, None.

Abstract Number: 2498

Barriers to Appointment Compliance and the Effect of Reminder Phone Calls on Lupus Clinic Show Rate in an Underserved Community

Anand Kumthekar[1] and Beverly Johnson[2], [1]Medicine, Albert Einstein College of Medicine/Jacobi Medical Center, Bronx, NY, [2]Jacobi Medical Center, Albert Einstein College of Medicine, Bronx, NY

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SESSION INFORMATION

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Session Type: ACR Poster Session C
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Background/Purpose:

Appointment compliance is a nationwide problem with a higher prevalence in the underserved communities. For physicians it results in lost time, decreased efficiency, and for patients it results in dissatisfaction and reduced quality of care. The primary objective of this study was to identify major barriers to appointment compliance in an underserved lupus clinic. A secondary objective was to assess appointment compliance after an intervention involving reminder phone calls.

Methods:

We retrospectively assessed the clinic show rate at our lupus clinic serving a low income population with primarily Medicare/Medicaid or no insurance from November, 2013 to July, 2014. Appointment attendance was confirmed by using electronic medical records (EMR). A survey was designed based on the perceived barriers for appointment compliance from literature review, was piloted and then administered from July 1st,2014 to August 31st,2014. An intervention involving reminder telephone calls 1-3 days prior to the visit was implemented from September 1st,2014-April 30th,2015. IRB exemption was received for this study.

Results:

We collected survey results from 43 patients. The most common reason mentioned for missed appointments was forgetting the appointment date (46.5%). 13% responded that the appointment was cancelled by the clinic and 13% said they had family issues. 12% mentioned they did not have adequate child care and 11% said they did not receive an appointment before they left the clinic. Before the intervention, 352 lupus clinic appointments were analyzed with an average show rate of 58.8%. After the telephone reminder, we analyzed 378 patient visits with a show rate of 74.86%. Using Pearson's chi square test, the improvement in clinic show rate was statistically significant (p=0.046).

Study Period	Appointments Scheduled	Clinic Show Rate
Pre-Intervention	352	207 (58.8%)
Post-Intervention	378	283 (74.86%)

Conclusion:

Our study identifies barriers to care from the patient perspective in an underserved community. Limitations include the retrospective nature of the study and the pre and post intervention states were studied at different times of the year. Our data suggests that reminder phone calls significantly improves clinic show rates, which improves quality of care. In a multidisciplinary specialized lupus clinic serving a low income population we found that clinic show rate is related to lack of appointment reminders. Reminder phone calls are a low cost intervention with the potential for significant benefit and should be considered in similar low income lupus clinics.

Disclosure: A. Kumthekar, None; **B. Johnson**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/barriers-to-appointment-compliance-and-the-effect-of-reminder-phone-calls-on-lupus-clinic-show-rate-in-an-underserved-community

Abstract Number: 2499

No More No Shows: Improving the Appointment Reminder System at an Urban County Hospital Outpatient Rheumatology Clinic

Shire Beach[1], Sarah Goglin[2], Mary Margaretten[1,2], Laura Trupin[1] and Jinoos Yazdany[2], [1]University of California, San Francisco, San Francisco, CA, [2]Rheumatology, University of California, San Francisco, San Francisco, CA
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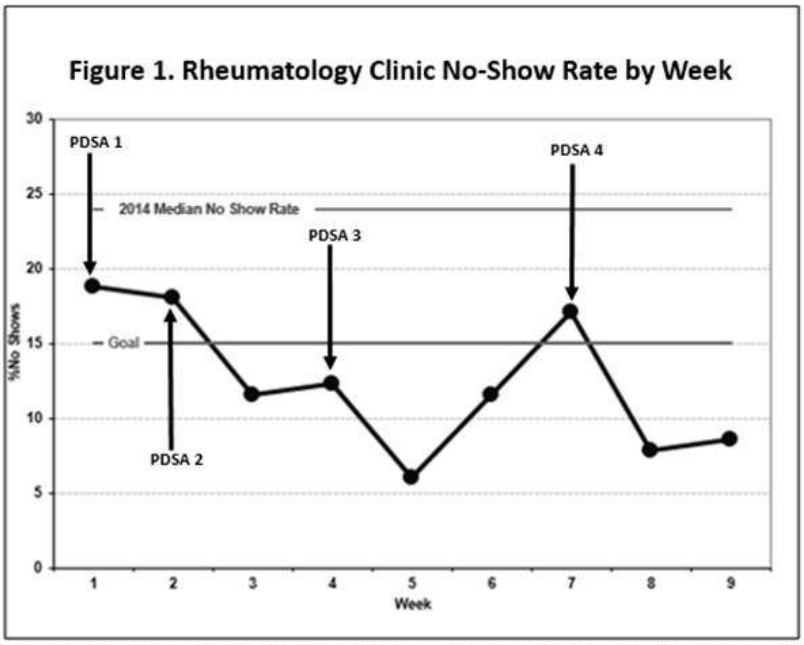
Background/Purpose: High appointment no-show rates lead to disrupted delivery of care and inefficient use of healthcare resources. Appointment reminder calls are cost-effective in lowering no-show rates. Previous studies, however, have largely been performed among English-speaking populations. We aimed to improve the reminder call system at a county hospital rheumatology clinic with an at-risk multilingual patient population (Cantonese, Mandarin, Spanish and English). Using the Institute for Healthcare Improvement's Model for Improvement, we studied no-shows in this diverse population and used Plan-Do-Study-Act (PDSA) cycles to evaluate the effect of improving the clinic's appointment reminder system. Our specific aim was to reduce the no-show rate from 24%, the clinic's 2014 average, to 15% by May 2015.

Methods: First, we studied and mapped the current appointment reminder system. We developed a survey (in English, Spanish, and Chinese) to determine how clinic patients were reminded of their most recent appointment and their preferences regarding future reminders. We then used PDSA cycles to test changes to the reminder system. A multilingual clinic staff team (English, Spanish, Cantonese, and Mandarin) was assembled to deliver language appropriate reminder calls. Ultimately, this language specific call system was scaled up to include all English, Spanish, and Chinese speaking patients.

Results: While it was assumed that most patients received both letter and phone reminders for upcoming appointments, our survey (N=50) indicated otherwise; 60.3% received a letter, 27.6% received a call, 13.8% received both, and 22.4% received no reminder. Our survey also revealed patient preferences for future letter (68%), phone (54%), and text message (25.9%) reminders. These results helped focus our PDSA cycles on improving the phone call reminder system, since letters were received more reliably, and phone calls were preferred by many patients. Baseline data revealed an average no-show rate of 24% in 2014 (Figure 1). Four PDSA cycles were completed, with the final cycle resulting in more consistent reminder calls in multiple languages. The median no show rate between February and May 2015 (N=331) following implementation of the new reminder system decreased to 11.6%.

Conclusion: Coordination across clinic staff to form a multilingual team that delivered language appropriate reminder calls measurably reduced the no-show rate in our county hospital rheumatology clinic.



PDSA 1: 2 English speaking patients contacted; follow-up appointments only. **PDSA 2:** 37 English, Spanish, and Chinese speaking patients contacted. **PDSA 3:** 126 English, Spanish, and Chinese speaking patients contacted. **PDSA 4:** 166 English, Spanish, and Chinese speaking patients contacted; follow-up and new patient appointments.

Disclosure: S. Beach, None; **S. Goglin**, None; **M. Margaretten**, None; **L. Trupin**, None; **J. Yazdany**, None.

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Abstract Number: 2500

Impact of Health Portal Enrollment and Electronic Appointment Reminders to Improve Appointment Attendance at an Academic Rheumatology Clinic

Arielle Mendel[1] and Shirley Chow[2], [1]Medicine, University of Toronto, Toronto, ON, Canada, [2]Division of Rheumatology, University of Toronto, Toronto, ON, Canada

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Background/Purpose: 'No-shows' (NS) to ambulatory care reduce the quality and efficiency of healthcare delivery. We sought to identify patient, provider, and system factors associated with NS to 5 rheumatology clinics at an academic teaching hospital. We hypothesized that an online patient portal could have a role in reducing NS through electronic reminders.

Methods: We conducted a 6-month prospective chart review of consecutive NS to the clinics of 5 rheumatologists at Sunnybrook Health Sciences Centre (SHSC). A sample of NS patients participated in semi-structured telephone interviews and qualitative themes were identified. Clinic processes were studied with administrative staff participation. Patients were encouraged to enroll in MyChart™, the online patient portal at SHSC. In one clinic, an email appointment reminder was implemented for portal users. Clinic attendees were surveyed for their portal enrollment, receipt of the reminder, and satisfaction; NS occurrences were

monitored.

Results: Over 6 months there were 110 NS; rates varied among providers (2.5% - 6.8%) with a total estimated cost of >10 000$. Eighty-six (78.2%) were follow-ups, of which 57 (66%) had systemic autoimmune conditions and 51 (59.3%) were on DMARD and/or biologic therapy; 24 (28%) had active disease or severe symptoms at last visit; 22 (26%) had portal accounts. Among 28 follow-up NS interviewed, 14 (50%) forgot or were unaware of the appointment and 7 (25%) had the wrong date. The most common theme was the request for a reminder (57%). During the intervention, 120/274 (44%) surveyed patients had portal accounts. Of these, 73 (61%) received the email reminder and 72 (99%) found the email helpful. Twenty-two patients learned of the appointment from the email alone. Ninety-six percent of email recipients wanted future reminders compared with 90% of all portal users and 42% of non-portal users. Health portal enrollment did not increase, nor was an overall improvement in appointment attendance observed 4 months into the intervention.

Conclusion: Many NS are patients with systemic autoimmune conditions taking medications that require regular monitoring. Forgetfulness and date mix-ups were the most common reasons for NS. A simple email reminder has demonstrated high patient interest and satisfaction. Patients already enrolled in the portal were more receptive to email reminders, which may relate to increased comfort levels with Internet use. Future interventions could focus on improving patient portal access and addressing new patient NS.

Disclosure: A. Mendel, None; **S. Chow**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/impact-of-health-portal-enrollment-and-electronic-appointment-reminders-to-improve-appointment-attendance-at-an-academic-rheumatology-clinic

Abstract Number: 2501

Determining the Rate of Cardiovascular Risk Assessment in Patients with Rheumatoid Arthritis at Federally Qualified Outpatient Continuity Clinic – a Performance Improvement Project

Dewan Fahima[1] and Rafah Salloum[2], [1]Internal Medicine, Monmouth Medical Center, Long Branch, NJ, [2]Rheumatology, Monmouth Medical Center, Long Branch, NJ

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Background/Purpose:

Studies have shown patients with rheumatoid arthritis (RA), a chronic inflammatory condition, have accelerated rate of coronary artery and cerebrovascular disease. Patients with RA, in particular women, are at a higher risk for silent MI. In addition to treating the underlying RA, aggressive monitoring and treatment of traditional risk factors must be addressed.

At our federally qualified health center (FQHC), as primary care physicians, while we may not prescribe biologics for our RA patients, we should focus on the traditional risk factors associated with cardiovascular disease (CVD). This performance improvement project was to examine if we as primary care physicians (PCP) at the FQHC, at the minimum, are addressing traditional modifiable risk factors for CVD in our RA patients.

Methods:

A retrospective chart review was performed. Patients were identified using clinic encounters with an associated ICD9 code for rheumatoid arthritis (714.0) in the EMR at our FQHC, from January 1, 2014 through December 31, 2014. Charts were searched to see if traditional risk factors for CVD according to the Framingham Heart Study were measured and/or addressed in 2014. They include age, diabetes mellitus (DM), smoking, systolic blood pressure, total cholesterol, HDL, and BMI. Charts were also

reviewed for documentation of smoking cessation and weight loss and lifestyle changes in patients with BMI greater than 25. The BMI was identified in one of the four categories, underweight (<18.5), healthy weight (18.5-24.9), overweight (25-29.9) and obese (>30).

Results:

A total of 78 subjects were identified. 14 were male and 64 were female. Mean age was 52 years. Of the 78 patients, 57% had their lipid profile examined and 42% did not. 17% of the RA patients had DM, of whom 79% were on anti-diabetes agent and 21% were not treated. In evaluating BMI in RA patients, 14% were healthy weight, 41% were overweight and 45% were obese. Of those who were overweight or obese, 70% had their BMI addressed and 30% did not. 26% of RA patients were smokers and of those 50% were educated regarding smoking cessation. 10% of the RA patients had documented uncontrolled hypertension either with or without anti-hypertensive agent.

Conclusion:

At FQHC as PCP, while we may not prescribe biologics to treat RA, we should at the minimum address the other modifiable risk factors such as hyperlipidemia, uncontrolled SBP, increased BMI and smoking for our RA patients. Currently, we are suboptimal at focusing in all of these factors. US Preventive Service Task Force recommends patients at higher risk for CVD, the age to begin screening lipid disorder is age 20. At our FQHC, it is only being tested 57% of the time and slightly above two thirds of the overweight or obese RA patients are being advised regarding weight loss and lifestyle modifications. Only half of the smokers were educated and informed regarding smoking cessation.

American Heart Association recognizes rheumatoid arthritis as a risk factor for atherosclerosis and increased risk of CVD. At FQHC, we need better adherence to ACR and AHA guidelines and goals of RA disease management. This may be achieved through interventions such as physician education, and use of clinical reminders in the FQHC, both of which are underway at this time.

Disclosure: D. Fahima, None; **R. Salloum**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/determining-the-rate-of-cardiovascular-risk-assessment-in-patients-with-rheumatoid-arthritis-at-federally-qualified-outpatient-continuity-clinic-a-performance-improvement-project

Abstract Number: 2502

Implementation of New Pneumococcal Vaccination Recommendations in an Academic Rheumatology Clinic

Alison Bays[1], Renuka Nayak[2], David I. Daikh[3], Jinoos Yazdany[4] and Gabriela Schmajuk[5], [1]Rheumatology, University of Washington, Seattle, WA, [2]Rheumatology, UCSF, San Francisco, CA, [3]Rheumatology, UCSF/VA Medical Center, San Francisco, CA, [4]Rheumatology, UCSF, SF, CA, [5]San Francisco VA Medical Center, University of California, San Francisco, San Francisco, CA

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Background/Purpose:

Invasive pneumococcal disease is approximately four times more common among patients with rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE) compared to healthy counterparts. In 2014, the Advisory Committee on Immunization Practices issued a new guideline recommending vaccination against pneumococcal organisms with the pneumococcal conjugate vaccine (PCV13) for all immunosuppressed patients, regardless of age, with the goal of reducing the rate of serious infections and

mortality among high-risk patients. Our goal was to increase the rate of PCV13 vaccinations in our immunosuppressed patients at an academic VA medical center.

Methods:

Plan-Do-Study-Act (PDSA) methodology was used over two cycles within a single clinic. Immunosuppressed patients were identified as those receiving any disease modifying antirheumatic drugs (DMARDs), biologic agents, or prednisone (dose > 10mg daily). PDSA Cycle 1 included (1) an investigator-led educational session for providers and (2) making the PCV13 vaccine available in the clinic. PDSA Cycle 2 involved the investigators identifying patients eligible for the PCV13 vaccine ahead of their clinic visit and pending the PCV13 order in the electronic medical record. Receipt of the vaccine was assessed via review of the electronic medication administration record. Provider recommendation of the vaccine was assessed by review of the clinical note. Reasons for patient refusal or lack of vaccine administration after provider recommendation were not consistently available.

Results:

Six rheumatology fellows and five faculty members participated in the quality improvement activity. Prior to the intervention, zero patients received a PCV13 vaccine in clinic as they were not available, with less than five patients receiving it outside of the clinic. PDSA Cycle 1 was 8 weeks long with 109 patients who were eligible for vaccination. 57 (52%) were recommended to have the vaccine and 35 (32%) received it. PDSA Cycle 2 was 6 weeks long with 44 patients who were eligible for vaccination, 36 (82%) were recommended to have the vaccine and 25 (57%) vaccinated (see Figure 1).

Conclusion:

One quality improvement lecture updating providers on new vaccination recommendations and availability of the vaccine can improve vaccination patterns amongst immunosuppressed patients. Identifying patients in need of vaccination prior to their clinic visit can improve vaccination rates even further.

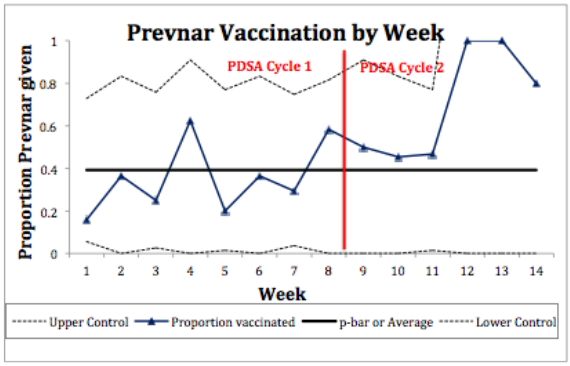

Figure 1: PDSA Cycle 1 and PDSA Cycle 2 are separated by a red bar. The dark blue line shows the proportion of patients vaccinated with PCV13. The upper and lower control limits describes the variation of the denominator as different numbers of immunosuppressed patients were seen in clinic each week. The p-bar is shows the average. More than six values are seen above the p-bar, indicating a successful change.

Disclosure: A. Bays, None; **R. Nayak**, None; **D. I. Daikh**, None; **J. Yazdany**, None; **G. Schmajuk**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/implementation-of-new-pneumococcal-vaccination-recommendations-in-an-academic-rheumatology-clinic

Abstract Number: 2503

Improved Pneumococcal Vaccination in Rheumatoid Arthritis Patients in an Urban Academic Rheumatology Clinic

Swathi B. Reddy[1], Una E. Makris[2], Kara Prescott[3] and E. Blair Solow[2], [1]Internal Medicine, Division of Rheumatic Diseases, UT Southwestern Medical Center, Dallas, TX, [2]Rheumatology, UT Southwestern Medical Center, Dallas, TX, [3]Internal Med - Rheumatology, Dallas VA Medical Center, Dallas, TX

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Session Time: 9:00AM-11:00AM

Background/Purpose:

Immunosuppressed patients are at higher risk for infections compared to the general population. Vaccines decrease morbidity and mortality, however vaccination status is not consistently addressed in clinic. It has been shown that lack of physician recommendation is a large barrier to vaccination. Pneumococcal vaccination is recommended for patients with rheumatoid arthritis (RA) by the American College of Rheumatology and Centers for Disease Control. The objective of this study was to evaluate and improve the pneumococcal vaccination rate in RA patients at an urban academic rheumatology clinic.

Methods:

A random sampling of 50 charts of patients with a diagnosis of RA from July 2013 were reviewed to determine the baseline pneumococcal vaccination rate. The rate was based on documentation in the electronic medical record (EMR) vaccination status section. Subsequently, 3 focus groups with rheumatology providers, including physicians, nurses, and medical assistants were conducted to discuss potential interventions to improve the vaccination rate. Based on this feedback, a multi-faceted approach was taken, including (1) an education program for providers regarding pneumococcal vaccination for immunosuppressed patients, (2) adding vaccination status to the EMR rheumatology note template, and (3) a pended order on patient's arrival to clinic. The protocol for the pended order begins with the medical assistant who reviews the patient's vaccination status and places a pended order if unvaccinated. The physician discusses vaccination with the patient and signs the order if in agreement, which is received by nursing who then administers the vaccine. The signed order automatically records the vaccination date in the vaccine section of the EMR. The vaccination rate for the post-intervention period in May 2014 was then determined from a random sampling of 50 charts of RA patients. The pre- and post-intervention rates were compared using a chi square test.

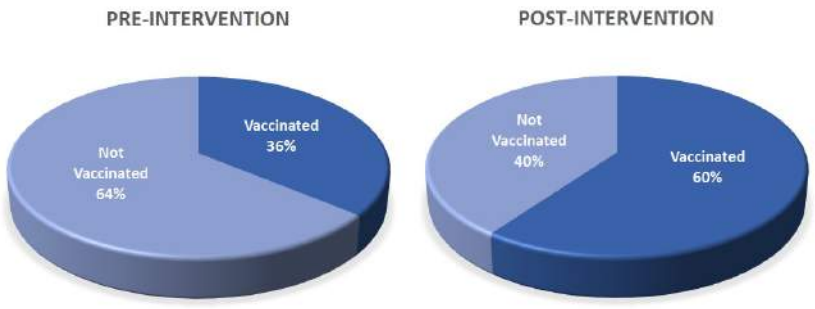
Results:

Age and gender demographics were similar in pre-intervention (mean age 52 years, 84% female) and post-intervention (mean age 57 years, 86% female) groups. The pneumococcal vaccination rate improved from 36% pre-intervention to 60% post-intervention (p=0.016), see Figure 1.

Conclusion:

This multi-faceted approach led to a statistically significant improvement in the pneumococcal vaccination rate in RA patients. The pended order and pre-loaded vaccination status section in the clinic note template both served as reminders for the physician to address pneumococcal vaccination. The education program gave providers published literature to support the decision to vaccinate. These processes have become standard in our rheumatology clinics, and we plan to extend this work to improve vaccination rates in all of our immunosuppressed patients.

Figure 1:



Disclosure: S. B. Reddy, None; **U. E. Makris**, None; **K. Prescott**, None; **E. B. Solow**, None.

Abstract Number: 2504

Zoster Vaccination in Rheumatoid Arthritis Patients: An Unmet Care Gap

Alicia Meadows[1], Carson Maynard[2], Abraham Tacang[3], Jason Brown[4] and Eric Newman[5], [1]Rheumatology, Geisinger Health System, Danville, PA, [2]Internal Medicine, Geisinger Medical Center, Danville, PA, [3]Geisinger Medical Center, Danville, PA, [4]Henry Hood Center for Clinical Research, Geisinger Health System, Danville, PA, [5]Department of Rheumatology, Geisinger Medical Center, Danville, PA

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Background/Purpose: Reactivation of the varicella zoster virus (shingles) creates a significant burden of healthcare dollars, lost work time, and extended suffering. Rheumatoid Arthritis (RA) and its treatments increase the risk of shingles 2-3x that of the general population. Despite the higher rate of reactivation and potential cost to healthcare, only about 5% of RA patients receive the zoster vaccine. Currently, the ACR recommends zoster vaccination for patients over age 60 on non-biologic DMARDs or prior to starting biologic therapy. We aimed to measure the size of our unvaccinated RA population, understand the barriers to vaccination, and develop a plan to increase shingles vaccination.

Methods: We gathered data on our RA patients over age 60 on Disease Modifying Antirheumatic (DMARD) therapy who have ever had shingles or the shingles vaccine prior to 5/29/15 using ICD-9 codes from the EPIC electronic health record. To establish why patients were un-vaccinated we surveyed RA patients at their routine clinic visits over 3 weeks. Patients were permitted to choose more than one answer. Demographics were recorded and survey results were tallied. System-wide baseline data on shingles diagnosis and vaccination rate was compared to that of our surveyed population.

Results: We surveyed 107 patients. 38 were excluded due to missing demographics, incorrectly completed surveys, not on DMARD, or < 50 years old (36%). 69 patient surveys were included for a total of 75 responses. System-wide, 211 out of 2259 RA patients on DMARD had a history of shingles (9.3%) compared to our survey group, where 5 out of 72 had a history of shingles (6.9%). System-wide, 184 out of 2259 received the vaccine (8.1%) compared to our survey group where 10 out of 72 (13.8%) received the vaccine. Of the patients who had a shingles diagnosis, 78 (40%) were on a DMARD at the time of diagnosis. Results of the survey are listed in the table below:

Survey Response	Number of Responses	Percentage
I am currently on a biologic	21	28%
I didn't know it was recommended or important	13	17.3%
It was never offered to me	13	17.3%
Other	11	14.7%
I've had the vaccine	10	13.8%
I had shingles less than 5 years ago	4	5.3%
The vaccine is too expensive	2	2.7%
I'm afraid of side effects	1	1.3%
I'm afraid of shots	0	0%
Total	75	100%

Conclusion: Our health system's zoster vaccine rate for RA patients was slightly above the national average but still leaves a considerable care gap. Since the largest unvaccinated population was started on a biologic prior to vaccination our biggest opportunity to close this care gap exists before patients start biologic. We believe a process change to integrate the zoster vaccine into pre-biologic initiation workflow would increase the vaccination rate. This coupled with a real time point-of-service quality measure tool actionable by the nurse and provider would provide timely feedback.

Disclosure: A. Meadows, None; **C. Maynard**, None; **A. Tacang**, None; **J. Brown**, None; **E. Newman**, xG Health Solutions, 9.

Abstract Number: 2505

A Fellow Led Quality Improvement Project for Improving Contraceptive Compliance in Women Receiving Teratogenic Medications

Melissa Wells[1], Victoria Lackey[2], Erica Peart[3], Nicholas Holdgate[4], Samya Mohammad[1], Stephen Balevic[1], Rebecca Sadun[4], Lisa G. Criscione-Schreiber[5], Megan E. B. Clowse[3] and Mamata Yanamadala[6], [1]Division of Rheumatology, Department of Medicine, Duke University, Durham, NC, [2]Dept of Medicine, Division of Rheumatology, Duke University, Durham, NC, [3]Rheumatology, Duke University, Durham, NC, [4]Rheumatology, Duke University Medical Center, Durham, NC, [5]Dept of Med/Rheum Div, Duke University, Durham, NC, [6]Division of Geriatrics, Department of Medicine, Duke University, Durham, NC

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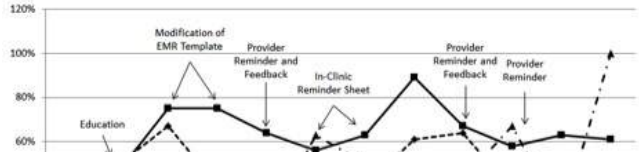
Background/Purpose: Women of child bearing age with autoimmune diseases are often prescribed teratogenic medications. Contraceptive compliance in this group of patients has been shown to be low. We conducted a quality improvement project to increase contraceptive compliance in eligible patients in the Duke Rheumatology outpatient clinic.

Methods: We reviewed charts of 18-45 year old women on teratogenic medications (methotrexate, leflunomide, mycophenolate and cyclophosphamide) to evaluate baseline contraception compliance in our practice. Contraceptive compliance was measured by reviewing documentation of 1) contraception type 2) counseling regarding contraceptives and 3) further intervention after counseling. Using Plan-Do-Study-Act (PDSA) methodology, we implemented a series of changes in our clinic based on periodic input from stakeholders. Interventions centered on inter-professional provider education, modification of the electronic medical record (EMR) templates, periodic provider reminders, in-clinic reminder sheets, and frequent feedback to providers on performance. During each monthly PDSA cycle, one week of patients' charts were reviewed for performance measurement.

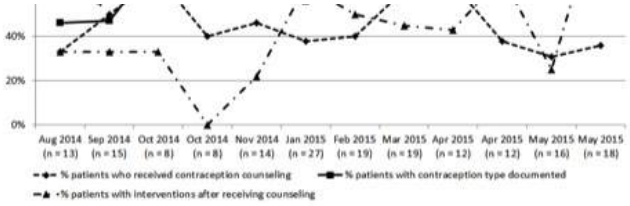
Results: At baseline, eligible patients (n = 181 out of 3003 reviewed charts) rate of documentation for contraception usage was 46%, counseling was 33%, and interventions after counseling occurred in 33%. As shown in the run chart, initial education led to a non-sustained improvement in provider compliance. Modification of the EMR template improved provider compliance, but note cloning inhibited extended improvement. In-clinic reminder sheets, frequent feedback and periodic stakeholder discussions had a mixed impact. The rate of contraception type documented at the end of the project was 61%, contraception counseling was 67%, and further intervention performed after counseling was 100%. During this project, one unintentional pregnancy that led to miscarriage occurred in a patient on teratogenic medication not using contraception.

Conclusion: Overall, documentation of contraceptive type, counseling and intervention increased, but room for improvement remains. Every woman taking teratogenic medication should be using contraception, and even during a quality improvement effort in a single clinic, 100% compliance was not achieved. Therefore more creative solutions are needed, whether EMR-based alerts, provider incentives, personalized feedback, or a combination of interventions. Discovery of a miscarriage in a patient receiving one of these medications highlights the importance of the continued discussions with our patients.

Figure: Run chart demonstrating timing of interventions and rate change in contraception compliance



Disclosure: M. Wells, None; **V. Lackey**, None; **E. Peart**, None; **N. Holdgate**, None; **S. Mohammad**, None; **S. Balevic**, None; **R. Sadun**, None; **L. G. Criscione-Schreiber**, None; **M. E. B. Clowse**, None; **M. Yanamadala**, None.



[project-for-improving-contraceptive-compliance-in-women-receiving-teratogenic-medications]

Abstract Number: 2506

Sustained Improvement in Teratogenic Risk Education in a Pediatric Rheumatology Clinic

Ashley Cooper[1], Julia Harris[2] and Mara L Becker[3], [1]Pediatric Rheumatology, Children's Mercy Kansas City, Kansas City, MO, [2]Children's Mercy Kansas City, Kansas City, MO, [3]Rheumatology, Children's Mercy Kansas City, Kansas City, MO

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Background/Purpose:

This quality improvement project was conducted to increase patient education and routine pregnancy screening in girls of childbearing age prescribed teratogenic medications in the pediatric rheumatology clinic. There is currently no standard model for providing reproductive health education to young female patients taking teratogenic medications. We aimed to adapt the education and pregnancy screening practices recommended by Mycophenolate REMS (Risk Evaluation and Mitigation Strategy) to apply to all reproductive age girls prescribed teratogenic medications in our pediatric rheumatology clinic.

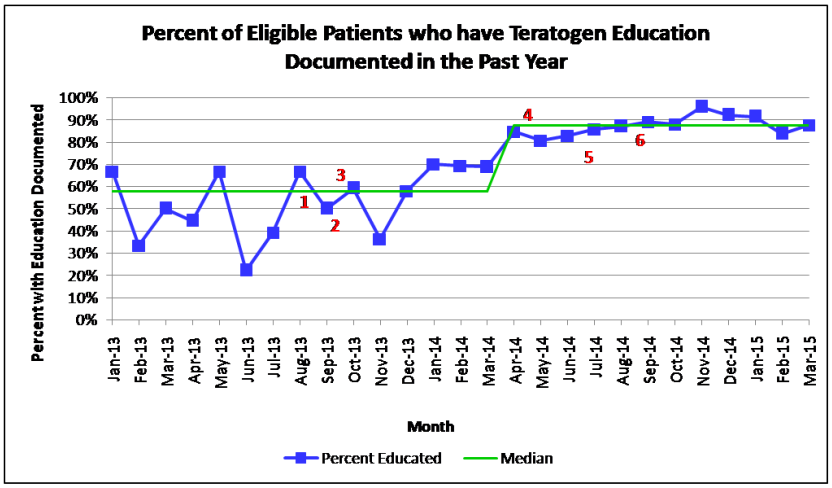
Methods:

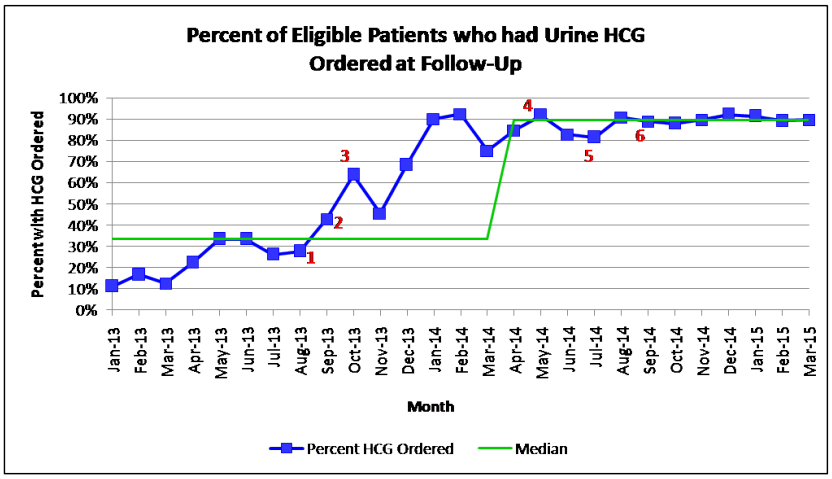
This project was initiated in a single center tertiary care rheumatology clinic comprised of 7 providers averaging 3500 visits per year. The medical records of 89 consecutive female patients age 10 and older receiving teratogenic medications were reviewed for documentation of teratogen education and pregnancy screening to establish our baseline practice. Six Plan-Do-Study-Act (PDSA) cycles were completed. Interventions included 1) visible project reminders in the clinic space, 2) targeted physician and 3) nurse education, 4) monthly progress updates, 5) pre-visit planning, and 6) development of an education template in the electronic health record (Figure 1). Ongoing chart review was performed throughout the project. Run charts were created for each aim to display improvement over time, and data reflecting overall improvement was analyzed by chi-square analysis.

Results:

At baseline, 42/89 (47.2%) female patients age 10 and older taking teratogenic medications had education documented within the last 12 months, and 21/89 (23.6%) had pregnancy screening performed at the visit. Implementation of our interventions resulted in improvement in documentation of ongoing teratogen education (616/767, 80.3%) and in routine pregnancy screening (630/767, 82.1%), both statistically significant ($p<0.0001$). Figure 1 depicts annotated run charts, which both contain shifts indicating special cause.

Figure 1. Annotated Run Charts Depicting Improvement Over Time





Intervention Key:

1) Teratogenic Medication List Posted in Clinic
2) Physician Education- Project rationale/procedures
3) Nurse Education- How to identify target patients during intake
4) Monthly Progress Updates
5) Pre-clinic Preparation Checklist
6) Education EHR Documentation Template

Conclusion:

Mindfulness of the teratogenic risks of immunosuppressive medications is important when managing adolescent patients with rheumatic disease. The interventions made through this quality improvement project increased the frequency of both teratogen education and urine pregnancy screening in these patients. Development of a simple, standardized education template in the electronic health record has helped sustain these improvements over time.

Disclosure: A. Cooper, None; **J. Harris**, None; **M. L. Becker**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/sustained-improvement-in-teratogenic-risk-education-in-a-pediatric-rheumatology-clinic

Abstract Number: 2507

A Quality Indicator for the Screening of Latent Tuberculosis Infection and the Result of Follow-up Interferon-Gamma-Release Assays in Patients with Rheumatic Disease Receiving Biologic Agents in a Japanese Hospital

Yasuhiro Suyama[1,2], Mitsumasa Kishimoto[2], Chisun Min[3], Yuko Kataoka[2], Masei Suda[2], Ryo Rokutanda[2], Yukio Matsui[2], Ken-

ichi Yamaguchi[2], Tokutaro Tsuda[2], Shunya Kaneshita[2], Hisanori Shimizu[2] and Masato Okada[2], [1]Rheumatology, JR Tokyo General Hospital, Tokyo, Japan, [2]Immuno-Rheumatology Center, St. Luke's International Hospital, Tokyo, Japan, [3]Division of Allergy and Rheumatology, St. Luke's International Hospital, Tokyo, Japan
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SESSION INFORMATION
Session Date: Tuesday, November 10, 2015
Session Title: Quality Measures and Quality of Care Poster Session
Session Type: ACR Poster Session C
Session Time: 9:00AM-11:00AM

Background/Purpose:

Infection is one of the most devastating side effects of biologic agents use, particularly early on in the course of therapy. Prevention is considered to be more important than treatment, especially in patients with known risk factors. Quality indicators (QI) has been received an increasing attention in rheumatology field and several guidelines for the prevention of biologic agents-related infections have been published, and they recommended the screening tests for hepatitis, latent tuberculosis infection (LTBI), and pneumocystis pneumonia (PCP) before starting biologic agents. However, few studies have reported the status of the implementation as well as interventions to improve its adherence in clinical settings. Herein, we repot the efficacy of monitoring for the improvement of LTBI QI for the use of biologic agents in the treatment of rheumatic disease.

Methods: We studied retrospectively all patients who had received biologic agents (TNF and non-TNF agents) for the treatment of rheumatic diseases in our department. To evaluate the adherence of a minimal standard of care for the pre-administration screening for LTBI, we monitored a LTBI bundle (chest image, tuberculosis skin test [TST] or INH prophylaxis, and interferon-gamma-release assays [IGRAs]). Since 2010, we had started a LTBI bundle for the use of biologic agents in the treatment of rheumatic disease and clinical date from January 2007 to December 2014 were collected to evaluate the proportion. In addition, we also evaluated the results of follow-up IGRA for detection of latent and newly developing tuberculosis.

Results: We identified 342 eligible patients. The analysis of data showed increases of targeted after the investigation. Adherence to the QIs improved from 82% to 99% in LTBI bundle. We also assessed 170 patients with a negative or indeterminant IGRA results in the initial LTBI screening and evaluated by follow-up IGRA test after starting biologic agents, which showed 7% of IGRA positive conversion. Active tuberculosis was not reported in our study.

Conclusion: Implementation of monitoring of quality indicators based on guidelines leads the safety for the use of biologic agents in the treatment of rheumatic disease. Our results also indicate that although the evidence for the repeated IGRA and the positive conversion after starting biologic agents in patients with rheumatic diseases is lacking, follow-up IGRA test may be useful to prevent the activation of LTBI in areas that have a high incidence of active TB such as Japan.

Disclosure: Y. Suyama, None; **M. Kishimoto**, None; **C. Min**, None; **Y. Kataoka**, None; **M. Suda**, None; **R. Rokutanda**, None; **Y. Matsui**, None; **K. I. Yamaguchi**, None; **T. Tsuda**, None; **S. Kaneshita**, None; **H. Shimizu**, None; **M. Okada**, None.

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Abstract Number: 2508

Adherence to ACR Guidelines in the Management of Lupus Nephritis – a Quality Improvement Initiative

Erik Anderson[1], Matthew Abramson[1], Sanjay Godhwani[2], Yaqi Xue[3], Jie Yang[3] and Heidi Roppelt[4], [1]Internal Medicine, Stony Brook Hospital, Stony Brook, NY, [2]Medicine/Rheumatology, Stony Brook Medicine, Setauket, NY, [3]Stony Brook University, Stony Brook, NY, [4]Rheumatology, SUNY Stony Brook Unversity Hospital, East Setauket, NY
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Background/Purpose:

Lupus nephritis not only decreases survival, but also its costs are substantial, likely due in part to deficits in care (Carls et al., 2009). A previous study by Yazdany et al (2014) showed that care varied with individual factors such as age and race.

We assessed the quality of care provided to LN patients at our rheumatology clinic according to the 2012 ACR guidelines, and analyzed whether race, age, and/or insurance status influence care.

Methods:

A retrospective chart review is performed on patients identified by the ICD9 code for LN (583.81). We exclude patients without a definite diagnosis of LN based on ACR criteria or with limited records. Since quality indicators were first published in 2009, patient data from 1/1/2010 to 10/31/2014 is collected.

Data is recorded as % adherence to the 2012 ACR guidelines (Hahn et al., 2012), which include renal biopsy indications, adjunctive treatments, and induction and maintenance therapy.

Active LN is defined by the 2012 ACR criteria, and a treatment response or relapse is defined by the 2006 ACR criteria. Inclusion and exclusion criteria, outlined by the 2012 ACR guidelines, are adhered to. Chi-squared test compares treatment compliance among insurance status, race, and age. Wilcoxon rank-sum test and Kruskal-Wallis test analyzes age as a continuous variable in relation to treatment compliance. Statistical analysis is performed using SAS 9.3®.

Results:

A total of 30 patients meeting ACR criteria for LN were included. Renal biopsy was done in 90% of patients. HCQ was offered to 100% of patients. In patients with proteinuria (n=26), 70% were treated with renin-angiotensin system blockade. A statin was given to 31% of patients (n=16), and an anti-hypertensive was given to 79% of patients (n= 14).

In patients with class III or IV disease (N=19), all patients were given appropriate induction. Maintenance glucocorticoids (GCs) were given to 95% (n=18) of patients. The majority was followed for 6 months before a treatment change (68%), and had induction within 1 month of diagnosis (68%).

In patients with class IV or IV/V disease (N=15), all patients were given appropriate induction and maintenance GCs were given to 64% (n=9) of patients, although 3 patients were not on the higher-range dosage.

In patients with class V disease (N=9), 22% of patients (n=2) were treated according to guidelines.

In patients treated with induction therapy for 6 months (N=25), 15 patients (60%) responded. Of those that did not (n=10), therapy was not switched in 5 patients (50%).

No significant association was found between race, age, or insurance type and compliance to any of the measures.

Conclusion:

There was good compliance to renal biopsy and adjunctive treatments, except for statins. This may be due to overlooking the utility of statins in LN for younger patients.

There was good compliance to initiating induction, maintenance GCs, early induction therapy, and monitoring for 6 months.

Our study was limited by its small sample size, which may have obscured significant associations.

An electronic system that collects data relevant to LN response criteria in a central location may improve therapy adjustments. Also, provider education in class V induction may improve adherence.

Disclosure: E. Anderson, None; **M. Abramson**, None; **S. Godhwani**, None; **Y. Xue**, None; **J. Yang**, None; **H. Roppelt**, None.

Abstract Number: 2509

Glucocorticoid Induced Osteoporosis Screening and Treatment: A Gender Comparison in a Cohort of Patients with Underlying Rheumatologic Diagnosis in a Tertiary Care Setting

Hajra Shah[1], Narender Annapureddy[2] and Ruchi Jain[1], [1]Rheumatology, Rush University Medical Center, Chicago, IL, [2]Rheumatology and Immunology, Vanderbilt University, Nashville, TN

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Background/Purpose: One-fourth of hip fractures occur in men. Men treated with oral glucocorticoids for at least 3 months are particularly at risk. Studies have suggested that rapid bone loss begins early in steroid use, peaks at 6 months and slows with continued usage. Inflammatory disease induced hypogonadism may also increase fracture risk by lowering testosterone secretion. Male patients over the age of 50, especially with chronic rheumatic diseases on long term steroids may not be receiving adequate osteoporosis screening or treatment compared to females.

Methods: An IRB approved retrospective chart review was performed to identify male patients ≥ 50 years with a rheumatic diagnosis to compare them to age matched women in our academic practice from 2010 to 2013. Inclusion criteria were patients on any dose of prednisone for ≥ 3 months and at least 3 clinic visits. Exclusion criteria were recognized osteoporosis and prior bisphosphonate use. Demographic data, dose and length of steroid use, timing of DXA from initiation of prednisone use, T-score and calcium and vitamin D supplementation use was collected. Optimal care was defined as screening with a baseline DXA within 6 months of initiation of prednisone, calcium and vitamin D supplementation and osteoporosis treatment or prophylaxis when indicated. Patients not meeting these criteria were defined as receiving sub-optimal care. Fisher's exact test was used to compare categorical variables. A binary logistic regression model was run to account for any differences that age, ethnicity or diagnosis may have on the outcomes between the two groups.

Results: 100 male patients met the inclusion criteria. 100 women were then randomly age matched to the men. Average age was 63.4 vs 66 (M:F); 50% vs 52% (M:F) were African American and 31% vs 32% (M:F) had Rheumatoid Arthritis. 82% of females were on calcium-vitamin D vs 53% of men (P< 0.001). 82% of women had T-scores available vs 57% of men. DXA readers ordered more scans. Faculty < 5 years from training provided more optimal care. (61% vs 33% (> 5 years); p < 0.001). Osteoporosis screening for vasculitis spectrum diseases was more likely compared to other diseases in both groups. (Figure 1) Overall **67%** woman received optimal care in comparison to **22 %** men (**p = 0.001)**.

Conclusion: To our knowledge, our study is the first to analyze trends primarily in patients with chronic inflammatory disease in a large academic rheumatology practice. Physicians who were DXA readers for the clinic were more likely to order a DXA although notably not better with optimal care. Recent graduates were better at osteoporosis management overall. Men were 8 times *less* likely to receive optimal osteoporosis management as compared to women. This highlights gender gaps in management of osteoporosis in a vulnerable population with inflammatory diseases taking steroids.

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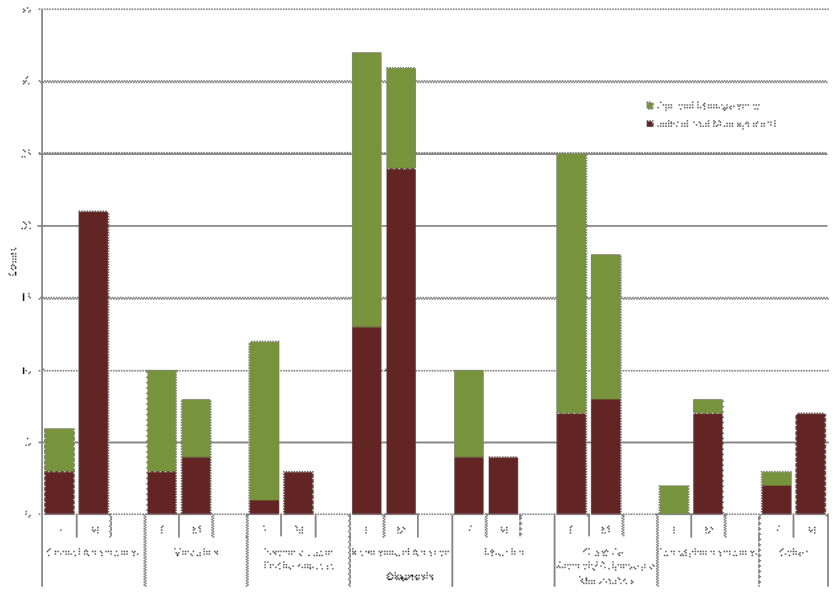

Figure 1

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Disclosure: H. Shah, None; **N. Annapureddy**, None; **R. Jain**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/glucocorticoid-induced-osteoporosis-screening-and-treatment-a-gender-comparison-in-a-cohort-of-patients-with-underlying-rheumatologic-diagnosis-in-a-tertiary-care-setting

Abstract Number: 2510

Outpatient Consultation Requests: A Failure to Communicate

Andrew Sharobeem[1], Haritha Bellam[1] and Rafael Grau[2], [1]University of Arizona, Tucson, AZ, [2]Rheumatology, University of Arizona, Tucson, AZ

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SESSION INFORMATION

Session Date: Tuesday, November 10, 2015

Session Title: Quality Measures and Quality of Care Poster Session

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Early diagnosis and intervention are central premises in the management of patients with rheumatic diseases. Nevertheless, due to the shortage of rheumatologists, patients are often subject to significant delays before consultation with rheumatology can occur. A shortage of consultants and the large demand for consultations has forced us to review consult requests and determine reasonable time periods for new outpatient referrals. We reviewed new referrals to determine if information provided was sufficient to facilitate appointment allocation and timely consultation.

Methods: We reviewed the records of 300 consecutive referral requests, over 2 months, to our service. Due to a lack of capacity, patients were triaged as routine (3 months), semi-urgent (≤2 months), urgent (≤1 month), or declined. All determinations were reviewed by a second provider (RG) and adjusted as necessary. In our review, we looked for key clinical data defined as: a referral diagnosis, mention of duration and location of pain, a musculoskeletal examination (MSK) mentioning swelling and pain (MSK), laboratory results, specifically RF, CCP, and ANA, and pertinent imaging studies. For purposes of this analysis, we

combined the urgent and semi-urgent groups. Logistic regression and multinomial logistic regression were used.

Results: The most common referral diagnosis was connective tissue disease (CTD), which included rheumatoid arthritis and systemic lupus erythematosus (43%), followed by nonspecific musculoskeletal pain (30%). Of the reviewed referrals, 58% were considered routine, 11% were either semi-urgent or urgent and 31% were declined. Information on location and/or duration of pain was provided for 55% of the referrals, examination findings of swelling and/or tenderness were provided for 38%, laboratory tests were provided for 39%, and imaging was provided for only 22%. 77% had data on at least one key clinical feature and this increased the odds of the referral being accepted ("Routine" or "Urgent") 1.64 (95% CI: [0.93-2.87]) with "Decline" as the reference. In multivariate modeling, MSK, laboratory, imaging and pain data all increased the odds of being accepted. Having information on both MSK elements increased the odds of the referral being accepted (OR=3.58 (95% CI: [1.20, 10.67], p=0.02). Imaging information also improved the odds of the referral being accepted (OR= 2.77 (95% CI: [1.11, 6.92], p=0.02).

Conclusion: We have found that referrals to our rheumatology practice often provide insufficient information to make the appropriate decisions regarding timely patient care. Targeted key information is critical and must be obtained from the referring health care providers. There is a need to improve communication with referring providers. Standardizing referral protocols can assist in facilitating timely scheduling of referrals, particularly patients with CTD.

Disclosure: A. Sharobeem, None; **H. Bellam**, None; **R. Grau**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/outpatient-consultation-requests-a-failure-to-communicate

Abstract Number: 2511

Primary Care Management of Patients with Rheumatic Diseases Prior to Rheumatologist Consultation

Jessica Widdifield[1], J Carter Thorne[2], Karen Tu[3], Debra Butt[3], Noah Ivers[4], Claire Bombardier[4], R. Liisa Jaakkimainen[5], Vandana Ahluwalia[6], J. Michael Paterson[7] and Sasha Bernatsky[8], [1]McGill University, Montreal, QC, Canada, [2]Southlake Regional Health Centre, Newmarket, ON, Canada, [3]Institute for Clinical Evaluative Sciences, Toronto, ON, Canada, [4]University of Toronto, Toronto, ON, Canada, [5]Preventive Med and Biostatisti, University of Toronto, Toronto, ON, Canada, [6]Past President, Ontario Rheumatology Association, Brampton, ON, Canada, [7]ICES, Toronto, ON, Canada, [8]Rheum/Clin. Epid., McGill MUHC/RVH, Montreal, QC, Canada

First publication: September 29, 2015

SESSION INFORMATION

Session Date: Tuesday, November 10, 2015
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Session Type: ACR Poster Session C
Session Time: 9:00AM-11:00AM

Background/Purpose: Primary care physicians (PCP) often play a central role in the early detection and referral for patients with rheumatic diseases. Our aim was to characterize referrals from PCPs to rheumatologists and investigate diagnostic and treatment patterns of PCPs prior to rheumatologist consultation.

Methods: We performed a retrospective chart review and an analysis of structured and semi-structured data within the primary care Electronic Medical Record Administrative data Linked Database (EMRALD), representing comprehensive EMR data from 168 PCPs across Ontario, Canada. We identified patients with first-time rheumatology referrals. Using a standardized data abstraction tool, PCP and rheumatology consultation records were reviewed to identify diagnoses and treatments associated with each referral. Referrals were characterized in terms of patient demographics, provisional diagnoses/clinical impressions, laboratory diagnostic tests and treatment initiated by PCPs, and other specialists seen for the complaint prior to rheumatology referral.

Results: Among 2430 patients referred to rheumatologists, 69% were female and the mean (SD) age at time of referral was 53

(16) years. Reasons for referrals included: mechanical/degenerative conditions (787; 32%), systemic inflammatory rheumatic diseases (745; 31%), regional MSK conditions (395; 16%), chronic pain conditions (346; 14%), osteoporosis/osteopenia (45; 2%), and other (e.g., abnormal labs, 112; 5%). Systemic inflammatory rheumatic disease referrals included inflammatory arthritis (287; 38%), connective tissue diseases and other systemic autoimmune rheumatic diseases (e.g., lupus, scleroderma, Sjogren's, Raynaud's) (131; 18%), gout/crystal arthropathies (122; 16%), spondyloarthropathies (120; 16%), polymyalgia rheumatica (66; 9%), and vasculitis (19; 3%). Laboratory testing done within the 3 months prior to referral is as noted in Table 1. Among the 745 systemic inflammatory patients, 22% were also seen in the emergency room for their complaint prior to seeing the rheumatologist, and 61% received treatment by their PCP (48% received NSAIDs/COXIBs, and 20% received corticosteroids). For patients diagnosed with rheumatoid arthritis, 72% received treatment by their PCP (53% received NSAIDs/COXIBs, 27% received corticosteroids, and 6% received DMARDs). The time from 1st PCP visit for the rheumatic disease complaint to date of referral exceeded 100 days for each type of systemic inflammatory rheumatic disease, except vasculitis (table).

Conclusion: We present novel data on PCP management of patients prior to rheumatology referral. Approximately 1 in 3 PCP referrals to rheumatologists were referred for a systemic inflammatory rheumatic disease. Understanding the referral patterns of PCPs can identify opportunities to improve PCP management of patients prior to rheumatology referral.

Table:

	All Patients	**Systemic Inflammatory Rheumatic Diseases n=745**								
		All	RA	IA	PsA	CTDs	AS/SpA	Crystal	PMR	Vasculitis
	n=2430	**n=745**	n=120	n=167	n=44	n=131	n=76	n=122	n=66	n=19
Age, mean (SD) years	**53 (16)**	**53 (17)**	55 (16)	51 (16)	53 (13)	45 (14)	42 (15)	61 (15)	71 (9)	53 (24)
Female	**69%**	**57%**	70%	57%	59%	82%	41%	27%	62%	52%
Diagnostic Tests[1]										
ESR done	**30%**	**45%**	52%	52%	36%	47%	43%	23%	59%	58%
ESR abnormal	**29%**	**38%**	47%	29%	38%	34%	24%	29%	67%	#
CRP done	**36%**	**53%**	63%	56%	34%	50%	50%	36%	77%	53%
CRP abnormal	**19%**	**30%**	35%	30%	#	14%	24%	36%	44%	#
RF Done	**41%**	**58%**	76%	68%	50%	57%	51%	40%	50%	26%
RF positive	**24%**	**30%**	66%	30%	#	18%	#	18%	#	#
ANA Done	**20%**	**42%**	46%	49%	36%	53%	38%	21%	47%	#
ANA positive	**11%**	**15%**	9%	10%	#	35%	#	#	#	#
PCP Initiated Treatment	**49%**	**61%**	72%	63%	64%	35%	46%	79%	79%	47%
NSAID/COXIB	**38%**	**48%**	53%	54%	61%	24%	43%	62%	44%	#
Corticosteroid	**10%**	**20%**	27%	16%	#	8%	#	18%	59%	42%
DMARD	**1%**	**2%**	6%	#	#	#	#	#	0	0
Time from 1st PCP visit for the complaint to Referral, median (IQR) days	**310 (13-324)**	**156 (12-168)**	115 (14-128)	125 (11-136)	513 (15-528)	181 (7-188)	174 (7-181)	353 (20-378)	123 (15-138)	73 (7-188)

Abbreviations: **RA**: Rheumatoid Arthritis; **IA**: Inflammatory Arthritis – other (e.g., undifferentiated); **PsA**: Psoriatic Arthritis; **CTDs**: Connective Tissue Diseases and other systemic autoimmune rheumatic diseases (e.g., lupus, scleroderma, Sjogren's, Raynaud's); **AS/SpA**: Ankylosing Spondylitis and other spondyloarthropathies; **Crystal**: Gout and other crystal arthropathies; **PMR**: Polymyalgia Rheumatica; **ESR**: erythrocyte sedimentation rate; **CRP**: c-reactive protein; **RF**: rheumatoid factor; **ANA**: antinuclear antibody; [1]denominator for abnormal tests reflects those with tests done; # not reported due low count

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Disclosure: J. Widdifield, None; **J. C. Thorne**, None; **K. Tu**, None; **D. Butt**, None; **N. Ivers**, None; **C. Bombardier**, None; **R. L. Jaakkimainen**, None; **V. Ahluwalia**, None; **J. M. Paterson**, None; **S. Bernatsky**, None.

Abstract Number: 2512

Depot Medroxyprogesterone Acetate Birth Control May Suppress Toll-like Receptor 7-Induced Interferon-Alpha Production By Plasmacytoid Dendritic Cells in Women

Yuli McCann[1], Meredith Barnes[1] and Grant Hughes[2], [1]Medicine, University of Washington, Seattle, WA, [2]Medicine/Rheumatology, University of Washington, Seattle, WA

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SESSION INFORMATION

Session Date: Tuesday, November 10, 2015

Session Title: Reproductive Issues in Rheumatic Disorders: Basic and Clinical Aspects Poster Session

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose:

Female sex steroids are important modulators of autoimmunity. Estrogen appears to favor the development of lupus autoimmunity via activation of adaptive and innate immune responses, especially type 1 interferon (IFN) (e.g., IFN-a). In contrast, progesterone may have protective effects. In mice, treatment with depot medroxyprogesterone acetate (DMPA, a widely used contraceptive) suppresses IFN-a production and the emergence of lupus-like autoimmunity. In vitro, DMPA selectively inhibits IFN-a release from human plasmacytoid DCs (pDCs), a major source of IFN-a in SLE patients. Whether DMPA suppresses IFN-a production by pDCs in humans is unknown.

Methods:

Peripheral blood mononuclear cells (PBMCs) were isolated from healthy women immediately before and 2 weeks after first dose of DMPA birth control and stimulated with toll-like receptor (TLR) 3, 7 and 9 specific ligands to induce IFN-a production, which was assayed by ELISA. Under these conditions, all measurable IFN-a induced by TLR7 and TLR9 ligands comes from pDCs. In addition, percentages and activation status of various PBMC subsets were determined by flow cytometry. Paired t-tests were used to compare pre- and post-DMPA values. RNA from PBMCs was stored for later analysis.

Results:

DMPA treatment had no statistically significant impact on IFN-a production. However, in 3 of the 4 subjects tested, DMPA markedly reduced TLR7-induced IFN-a production by pDCs, which could not be accounted for by changes in pDC numbers. In these same 3 subjects, DMPA generally increased TLR9-induced IFN-a, suggesting that DMPA can selectively suppress IFN-a production by pDCs encountering TLR7 ligands, e.g., RNA-containing lupus immune complexes or RNA viruses. There were no consistent effects on PBMC subset numbers or activation status, except in the case of B cell percentages, which were significantly increased after DMPA treatment.

Conclusion:

In healthy women, DMPA may selectively suppress TLR7-induced IFN-a production by pDCs, an innate immune pathway involved in lupus pathogenesis as well as protection against RNA viruses. Thus, DMPA could be a dual-benefit contraceptive for certain SLE patients. On the other hand, DMPA's ability to suppress protective IFN-a responses may help explain why women using DMPA in HIV-endemic areas are at increased risk of HIV infection. Further investigation into the immunomodulatory properties of this widely used form of contraception is warranted.

Disclosure: Y. McCann, None; **M. Barnes**, None; **G. Hughes**, None.

Abstract Number: 2513

Contraception Use Amongst Women Ages 18-45 Taking Known Teratogenic Medications in an Academic Rheumatology Clinic

Rebecca Sadun, Nicholas Holdgate, Melissa Wells, Megan E. B. Clowse, Lisa Criscione-Schrieber, Stephen Balevic, Victoria Lackey, Samya Mohammad and Erica Peart, Rheumatology, Duke University Medical Center, Durham, NC

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Background/Purpose: Patients with autoimmune diseases are often prescribed medications that are known to be teratogenic. Amongst women of child-bearing ages taking such medications, roughly half adhere to contraceptive guidelines. We sought to describe the contraception practices of women of child bearing age prescribed a teratogenic medication in our academic medical center outpatient rheumatology clinic.

Methods: In an academic rheumatology clinic, women ages 18 to 45 years old were screened for use of methotrexate, leflunomide, mycophenolate, and cyclophosphamide. A retrospective chart review was conducted on eligible women to determine the type of contraception documented. This project was part of an IRB-approved quality improvement project to assess rates of contraception documentation and contraceptive counseling. 3003 charts were reviewed, representing 12 one-week blocks over a period of ten. Descriptive statistics were used to quantify patient demographics and the percent of patients using each type of contraception. Women were grouped based on the relative effectiveness of contraceptive based on the pregnancy rate with 'usual use': "highly-effective"(≥95%), "moderately effective" (90-94%), or "ineffective" forms of birth control. We included abstinence in the "ineffective" group as it is only effective if practiced 100% of the time and many women in this group do not have a plan for contraception.

Results: We reviewed 3003 charts; 181 women between ages 18-45 took a teratogenic medication. The average age of eligible women was 34. Most women were receiving methotrexate (49%), followed by mycophenolate (41%), leflunomide (6%), cyclophosphamide (3%) and combination medications (2%). Of the 181 women, 67 had did not have a form of contraception documented, leaving 114 patients for whom we could describe contraception type. Of those with documented contraception, 20% were unable to conceive due to hysterectomy or menopause and another 24% were on highly effective contraception (Table). Another 29% were on effective contraception. Only 24% were on ineffective contraception and the majority of these were women who reported abstinence.

Conclusion: In this study, we found that the majority of women between ages 18-45 on teratogenic rheumatologic medications in an academic practice were either unable to conceive or on effective or highly effective contraception. Importantly, we identified a primary target cohort of patients not using any form of contraception (abstinence only) or using condoms only.

Table 1: **Type of Contraception documented (n = 106); 5-year effectiveness statistics from the Centers for Disease Control and Prevention (CDC)**		
	Number (%) of patients on type of contraception	Estimate effectiveness over a 5-year period given typical usage
HIGHLY EFFECTIVE:	***49 (46%)***	
Hysterectomy	19 (17%)	100%
Menopause	3 (3%)	n/a
Tubal Ligation	16 (14%)	99.5%
Intrauterine device (IUD)	11 (10%)	99.5%
EFFECTIVE:	***31 (29%)***	
Oral contraception pills (OCP)	15 (13%)	91%
Medroxyprogesterone acetate	14 (12%)	94%
Ring	1 (1%)	91%
Patch	1 (1%)	91%
INEFFECTIVE:	***26 (24%)***	
Abstinence	19 (17%)	n/a
Condoms only	7 (6%)	82%

Disclosure: R. Sadun, None; **N. Holdgate**, None; **M. Wells**, None; **M. E. B. Clowse**, UCB Pharma, 5; **L. Criscione-Schrieber**, None; **S. Balevic**, None; **V. Lackey**, None; **S. Mohammad**, None; **E. Peart**, None.

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Abstract Number: 2514

Subclinical Reduced Ovarian Reserve in Adult Polymiositis Patients

Fernando Henrique Carlos de Souza[1], Clovis A Silva[2], Lucas Yugo Shiguehara Yamakami[3], Vilma S. T. Viana[4], Eloisa Bonfá[5] and Samuel Katsuyuki Shinjo[1], [1]Rheumatology Division, Rheumatology Division, Faculdade de Medicina da USP, São Paulo, Brazil, [2]Pediatric Rheumatology, Faculdade de Medicina da Universidade de São Paulo, Sao Paulo, Brazil, [3]Gynecology Department, Faculdade de Medicina da Universidade de São Paulo, Sao Paulo, Brazil, [4]Rheumatology Division, University of Sao Paulo, Sao Paulo, Brazil, [5]Clínica Médica, Faculdade de Medicina da Universidade de São Paulo (FMUSP) e Hospital das Clínicas da FMUSP (HC-FMUSP), Sao Paulo, Brazil

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Background/Purpose: Polymyositis (PM) affects female gender during reproductive age. Ovarian reserve and future fertility are relevant, however there is no study performing a complete assessment of ovarian function in these patients.

Methods: From March 2011 to May 2014, 32 female PM patients (Bohan and Peter criteria, 1975), with age 18-40 years old, followed at the Outpatient Myopathy Clinic, Rheumatology Division of our tertiary center were screened. Twenty-four patients were excluded due to unwillingness to participate(n=8), hormonal contraceptive use(n=6), other autoimmune diseases(n=5), neoplasia(n=2), gynaecological surgery(n=2) and current pregnancy(n=1). Thus, a total of eight PM patients and 16 healthy

volunteer age-matched women were enrolled in the study. All PM patients and healthy controls were evaluated at early follicular phase of menstrual cycle. Follicle stimulating hormone (FSH), estradiol, inhibin B and anti-Müllerian hormone (AMH) serum levels (ELISA) were determined. Transvaginal ultrasound was performed in all PM patients and controls by a blind sonographer using a 6.5 MHz endovaginal transducer. Ovarian volumes and antral follicle count (AFC) were also assessed.

Results: PM patients and controls had comparable mean age (31.4±6.5 *vs*. 30.7±6.2 years, *P*=0.946), ethnicity and socioeconomic class (*P*>0.05). PM mean age of onset was 27.3±6.5 years and disease duration of 6.5±4.1 years. Menstrual cycles were alike in both groups with a similar frequency of age at menarche, gynecological age, duration and length of menstrual cycle (*P*>0.05). The median serum level of AMH was significantly lower in PM compared to controls [0.7(0.3-3.4) *vs*. 3.1(1.4-4.0), *P*=0.021] and AMH levels ≤1ng/mL (50%*vs*. 6.3%, *P*=0.024) and very low AFC (37.5% *vs*. 6.3%, *P*=0.037) were more frequently observed in PM. The other ovarian reserve parameters (ovarian volume, FSH, inhibin B and estradiol levels) were similar in both groups (*P*>0.05). With regard to drugs, 6/8 (75%) were exposed to potentially gonodotoxic agents, one (12.5%) was treated with intravenous cyclophosphamide with a cumulative dose of 15g and five (62.5%) were treated with high cumulative methotrexate dose (>5g/m^2). Of these six exposed patients, 4 (67%) had low AMH levels and 3 (50%) had concomitant very low AFC.

Conclusion: The present study was the first to identify a subclinical ovarian dysfunction in PM patients during reproductive ages possible associated with a gonadotoxic effect of immunosuppressive drugs on ovarian follicular pool.

Disclosure: F. H. C. de Souza, None; **C. A. Silva**, None, 2; **L. Y. S. Yamakami**, None; **V. S. T. Viana**, None; **E. Bonfá**, None; **S. K. Shinjo**, None.

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Abstract Number: 2515

MEK5/ERK5, a Lynchpin of Human Cardiac Fibroblast Transdifferentiation to a Scarring Phenotype in Autoimmune Congenital Heart Block

Andrew Markham[1], Robert Clancy[2], Mukundan Attur[3] and Jill P. Buyon[2], [1]Medicine, New York University School of Medicine, New York, NY, [2]Medicine, Division of Rheumatology, New York University School of Medicine, New York, NY, [3]Rheumatology Research, NYU - Hospital for Joint Diseases, New York, NY

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Background/Purpose:

Transplacental passage of maternal autoantibodies (Ab) reactive with the SSA/Ro-SSB/La ribonucleoprotein complex is associated with the development of cardiac injury in the fetus passively exposed to these Ab. However, antibodies are necessary but insufficient to cause disease, and the final pathway to this rapid fibrosis may be variable: kept totally in check in most fetuses (normal sinus rhythm), subclinical in others (first-degree block), and fully executed in very few (advanced block, fibrosis and macrophage infiltration). This study was initiated to evaluate a novel profibrosing candidate, MEK5/ERK5 of the mitogen activated protein kinase (MAPK) pathway, which in the context of anti-Ro antibodies may prime fetal cardiac fibroblasts toward an irreversible scarring phenotype characteristic of heart block.

Methods:

Primary human fetal cardiac fibroblasts were treated with secreted products generated from activated macrophages (an in vitro model of heart block) or TGFβ in the presence and absence of BIX 02189 (10uM), a specific MEK5/ERK5 inhibitor. The phenotype was evaluated by the profile of profibrotic genes including ACTA2, MMP-13, and PAI-1 (qRT-PCR), and expression

of α-smooth muscle actin (α-SMA, indirect immunofluorescence).

Results:

Treatment of human fetal cardiac fibroblasts with supernatants from macrophages transfected with hY3, an ssRNA associated with Ro60 (surrogate for immune complexes), induced the expression of the myofibroblast marker α-SMA, which was inhibited by co-treatment with BIX 02189 (immunofluorescence, N=3). As expected, macrophage supernatants increased fetal fibroblast mRNA expression of ACTA2, the gene encoding α-SMA, by 4-fold (24 hr), which was completely attenuated by co-treatment with BIX 02189. In parallel conditions, other profibrosing biomarkers, including MMP-13 and PAI-1 transcripts, were similarly upregulated and subsequently inhibited by BIX 02189 (MMP-13: 15.91 vs. 3.06, respectively; PAI-1: 2.27±0.1 vs. 0.84±0.1, respectively, p=0.01, N=3). Since previous work has shown that supernatants from macrophages incubated with anti-Ro immune complexes induced the fibroblast secretion of TGFβ, this cytokine was evaluated as a comparison to the fibrotic "potency" of the macrophage supernatants. TGFβ showed a similar yet less marked upregulation of the profibrotic genes MMP-13 and PAI-1, which was significantly inhibited by co-treatment with BIX 02189.

Conclusion:

These data identify the MEK5/ERK5 pathway in fetal cardiac fibroblasts as a novel and coverable target to forestall the progression of cardiac injury toward irreversible fibrosis induced by anti-Ro immune complex activated macrophages.

Disclosure: A. Markham, None; **R. Clancy**, None; **M. Attur**, None; **J. P. Buyon**, None.

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Abstract Number: 2516

Association Between Primary Sjögren's Syndrome and Pregnancy Outcome: A Systematic Review and Meta-Analysis

Sikarin Upala[1] and Anawin Sanguankeo[2], [1]Internal Medicine, Bassett Medical Center, Cooperstown, NY, [2]Bassett Medical Center, Cooperstown, NY

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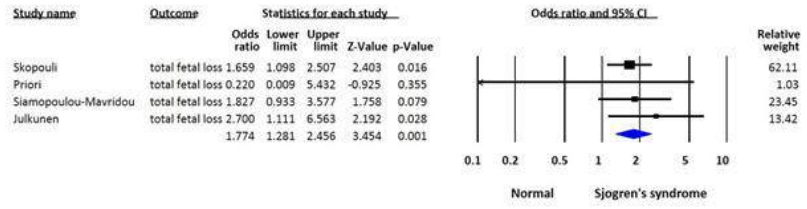
Background/Purpose: Systemic autoimmune disorders may interfere with normal reproductive function resulting in negative outcome of pregnancy. Primary Sjögren's syndrome (pSS) is a common rheumatic disease that mostly effects females. There are many reports that this condition may increase risk pregnancy complications and fetal loss. However, data regarding these adverse outcomes are scarce and inconclusive. We performed a systematic review and meta-analysis of available articles that assess association between pSS and adverse pregnancy outcome.

Methods: We comprehensively searched the databases of MEDLINE and EMBASE from their dates of inception to June 2015 and reviewed papers with validity criteria. Random-effects model were used to evaluate pregnancy complications in patients with pSS and healthy control.

Results: From 20 full-text articles, 7 studies involving 544 patients and 1586 pregnancies were included in the meta-analysis. Fetal complications included spontaneous abortion, stillbirth, neonatal deaths, and intrauterine growth retardation. Compared with healthy pregnancy, patients with pSS had significantly higher chance of neonatal deaths (pooled OR=1.77, 95% CI: 1.28 to 1.46, p=0.01). However, there were no significant association between pSS and premature birth (OR=2.10, 95%CI 0.59-7.46, p=0.25), spontaneous abortion (OR=1.46, 95%CI 0.72-2.93, p=0.29), artificial abortion (OR=1.12, 95%CI 0.52-2.61, p=0.71), and still-birth (OR=1.05, 95%CI 0.38-2.97, p=0.92).

Conclusion: There is an increased risk of fetal loss in pregnant patients with primary Sjogren's syndrome. The presented evidence further supports multidisciplinary care for these patients to prevent complications during pregnancy.



Disclosure: S. Upala, None; **A. Sanguankeo**, None.

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Abstract Number: 2517

Primary Sjögren's Syndrome and Pregnancy: Evolution of Thyroid Function, Xerostomia, Xerophthalmia and Salivary Test for Dental Caries Risk

Elisa Trujillo[1], Maria del Mar Trujillo[2], Erica Padron[3], Maria Garcia-Gonzalez[4], Lorena Exposito[5], Hiurma Sanchez[5] and Sandra Garcia[6], [1]Hospital Universitario de Canarias, Servicio de Reumatologia, Tenerife, Spain, [2]Servicio Canario de Salud., Servicio de Evaluación de tecnología Sanitaria, santa cruz de Tenerife, Spain, [3]Hospital Universitario de Canarias, Servicio de Ginecología y Obstetricia., santa cruz de Tenerife, Spain, [4]Rheumatology, Hospital Universitario de Canarias, Santa Cruz de Tenerife, Spain, [5]Hospital Universitario de Canarias, Servicio de Reumatologia, santa cruz de Tenerife, Spain, [6]Bow lane dental Group, Dentist, London, England
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Background/Purpose: 1. To study the effect of pregnancy in PSS patients on oral and ocular dryness and the salivary test for dental caries activity. 2. To study the effect of pregnancy on thyroid function in PSS patients with positive anti-thyroid antibodies (anjti-thyroglobulin and / or anti-peroxidase).

Methods: A prospective study was conducted throughout pregnancy in 12 PSS patients.

The following tests were performed at first visit and then monthly until the end of pregnancy: Schirmer tear secretion test; Whole saliva test (Heintze et al); Questionnaire on oral symptoms (Neidermaier 1998); Questionnaire on dry-eye symptoms (DEQ) (Begley et al).

To test dental caries activity, saliva samples were obtained from all patients during the first month of pregnancy and again at 3, 6 and 9 months. The following tests were performed: CRT® Buffer test was used to determine the buffering capacity of saliva to reduce pH changes; Alban® test) (0-4) was used to measure the ability of saliva to produce acid because of the microorganisms it contains; CRT bacteria system for LB and SM® was used to measure salivary levels of *Lactobacillus* (LB) and *Streptococcus mutans*(SM).

Thyroid function was prospectively studied during pregnancy in those PSS patients with positive anti-thyroglobulin and / or anti-peroxidase antibodies (n=10). At the first visit, then monthly to the end of pregnancy, TSH and free T4 were measured in all patients.

Results:

1. No significant changes in Schirmer test or whole saliva test results were observed during pregnancy. No significant changes were observed in the results of the two questionnaires.

2. The results of caries activity tests are presented in the table below:

	Patients with PSS during pregnancy (n=12)			
	1 month	3 months	6 months	9 months
CRT buffer (pH) – mean (SD)	4.9 (0.5)	4.6 (1.1)	4.3 (0.6)	4.0 (1.0)
Alban test (0-4) – mean (SD)	3.2 (0.3)	3.4 (0.4)	3.4 (0.6)	3.6 (1.1)
CRT bacteria for LB (% patients with levels ≥100.000 CFUs/mL saliva)	73.2	81.2	81.8	84.4
CRT bacteria for MS (% patients with levels ≥100.000 CFUs/mL saliva)	69.5	70.1	82.9	83.3

3. Four patients presented normal physiological changes in thyroid function during pregnancy. Three patients showed higher than normal TSH levels while maintaining normal free T4 levels. Three patients had elevated free T4 during pregnancy. Five patients were prescribed treatment with levothyroxine to maintain TSH levels within the range recommended during pregnancy.

Conclusion:

Pregnancy did not significantly alter the characteristics of xerophthalmia and xerostomia in patients with primary SS. However, periodic salivary tests for dental caries risk showed a gradual decline in the buffering capacity of these patients' saliva, as well as an increase ability to produce acid. The proportion of patients with high SM and LB values also increased as pregnancy progressed.

The presence of anti-thyroid antibodies, a common finding in patients with PSS, is a risk factor for the development of hypothyroidism during pregnancy.

Disclosure: E. Trujillo, None; **M. D. M. Trujillo**, None; **E. Padron**, None; **M. Garcia-Gonzalez**, None; **L. Exposito**, None; **H. Sanchez**, None; **S. Garcia**, None.

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Abstract Number: 2518

Does the Cytokine Pattern, Including the IL23 – IL17 Immune Axis, Change in Pregnant Women with Psoriatic Arthritis?

Andrea Pluma-Sanjurjo[1], Peter M. Villiger[2] and Frauke Förger[3], [1]Rheumatology, University Hospital Vall d'Hebron, Barcelona, Spain, [2]Professor & Head, Bern, Switzerland, [3]Rheumatology, Clinical Immunology and Allergology, Inselspital-University Hospital, Bern, Switzerland

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Background/Purpose:

During pregnancy, most patients with Psoriatic Arthritis (PsA) experience a natural improvement of their symptoms. This might be due to the immunological changes that occur in normal pregnancy to allow tolerance to the semiallogeneic fetus. Pregnancy induces a down-regulation of the adaptative immune system and generates a specific cytokine milieu. The balance between T helpers cells (Th), Th1/Th2/Th17, depends on the cytokine milieu and interleukin (IL) 23 promotes the expansion and survival of Th17 cells. The IL23-IL17 axis is up-regulated in PsA.

Objective:

The aim of our study is to investigate changes of the cytokines pattern with focus on the IL23-IL17 immune axis during and after pregnancy in PsA patients compared with non-pregnant PsA patients and healthy controls (HC).

Methods:

Nineteen PsA patients (10 pregnant, 9 non-pregnant) and 19 HC (11 pregnant and 8 non-pregnant) were prospectively studied. Clinical assessment and blood sampling was done in pregnant women before, during and after pregnancy and once in the non-pregnant group. Sera were analyzed for levels of C reactive protein (CRP) and high sensitive CRP (hsCRP) by enzyme linked immunoassay. The following cytokines and regulatory molecules were measured by magnetic bead-based multiplex immunoassay: the activation marker soluble CD40 ligand (sCD40L), the Th1 cytokines tumor necrosis factor α (TNFα) and Interleukin (IL)-1β, the Th2 cytokines IL-4, IL-10, IL-31, IL-33, IL-25 and the Th 23/17 pathway cytokines IL-6, IL-17A, IL-17F, IL-21, IL-22, IL23.

Results:

In the non-pregnant groups we observed that patients with PsA had higher levels of hsCRP, sCD40L, TNFα, IL-1β, IL-33, IL-6 and IL-22 than HC.

Though pregnant PsA patients had inactive or mild disease activity with normal CRP levels, the hsCRP levels were higher than those of pregnant HC.

In the HC group, pregnant women at the third trimester showed higher levels of IL-10, IL-33 and TNFα than at the postpartum time point. Moreover, healthy women at the third trimester had higher levels of IL-1β, IL-33 and IL-22 than age-matched non-pregnant women.

At the third trimester of pregnancy, patients with PsA displayed higher levels of hsCRP, sCD40L, TNFα and IL-6 than HC. Interestingly, pregnant PsA patients did not show any differences in the cytokine pattern compared to non-pregnant PsA patients.

Most differences appeared when comparing PsA and HC at the postpartum time point. Postpartal patients with PsA showed higher levels of sCD40L, TNFα, IL-1β,IL-10, IL-33, IL-31, IL-6 and IL-22 compared to HC.

Conclusion:

Pregnancy induces no predominance of circulating Th2 cytokines but rather a coexistence of Th1, Th2 and Th17 cytokines. Patients with PsA present a more pronounced inflammatory profile consisting of elevated hsCRP levels, Th1 and Th17 cytokines during pregnancy and postpartum. Thus, inactive disease in pregnant PsA patients was associated with persisting immunological activity including the IL-23 /Th17 immune axis.

Disclosure: A. Pluma-Sanjurjo, None; **P. M. Villiger**, None; **F. Förger**, None.

Abstract Number: 2519

Pregnancy in Psoriatic Arthritis: A Case Series

Maria Mouyis[1], Clare Thornton[1], David Williams[2,3] and Ian Giles[4], [1]Rheumatology, University College London Hospital, London, United Kingdom, [2]Institute for Women's Health, University College London, London, United Kingdom, [3]University College London, London, United Kingdom, [4]Rayne Institute, Centre for Rheumatology Research, UCL Division of Medicine, London, United Kingdom
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Background/Purpose: It is recognised that active disease in women with inflammatory arthritis is associated with adverse pregnancy outcomes. Most studies however, have focussed upon patients with rheumatoid arthritis and there is much less information on pregnancy outcomes in patients with psoriatic arthritis (PsA). Therefore, we present the outcomes of pregnancy in 14 consecutive patients, seen in a specialised obstetric rheumatology clinic – dealing with pregnancy issues in patients with rheumatic disease - over a 7-year period to explore the relationship between PsA and pregnancy.

Methods: Consecutive patients with PsA referred to the obstetric rheumatology clinic at University College London Hospital(UCLH) 2008-2014 were identified retrospectively. Their medical records six months before, during and four months after pregnancy were then examined to record: PsA disease activity, using physician global activity; medication history; plus maternal and fetal outcomes.

Results: Fourteen patients, with 16 pregnancies, were identified. Age range at delivery was 28-43 (median 34) years. Eleven had peripheral PsA; 3 had axial spondyloarthropathy and psoriasis. Previous obstetric history included 3 miscarriages and 10 live births in 8 patients. Pre-pregnancy, PsA related disease activity was: mild in 10; moderate in 2; and severe in 2 patients. Therapy pre-pregnancy included: NSAIDs alone, 4 patients; sulfasalazine (SSZ) ± prednisolone, 3 patients; anti-TNFα inhibitors ± SSZ, 8 patients; leflunomide (LEF), which was stopped and washed out pre-partum, 1 patient; and no patients on methotrexate. In line with previous recommendations, anti-TNFα was stopped during the first trimester of pregnancy. During pregnancy disease activity improved in 1 patient, remained active in 2 and worsened in 5 patients during mid to late pregnancy. In two cases this was managed with a reducing dose of prednisolone, from 20mg/day; in two other cases both prednisolone and SSZ were started. Of 16 pregnancies there were 2 spontaneous first trimester miscarriages, 14 live births and no maternal complications. Data from 11 births at UCLH revealed: mean birth weight 3.2 (range 2.9-3.8) kg; mean gestation 39.5 (range 37 to 42) weeks; 8 vaginal deliveries; 2 elective and 1 emergency caesarean section; and no congenital malformations. In 8 patients disease activity increased post-partum and was managed with reducing does of prednisolone or by restarting anti-TNF therapy. Of patients who flared, two had active disease activity antenatally which did not improve with pregnancy and the rest flared during/after pregnancy.

Conclusion: Pregnancy outcomes in these patients with PsA did not display an appreciable increase in miscarriage rate or pre-term delivery. Increased disease activity however, occurred in 5/14 patients during and 8/14 within four months post-pregnancy requiring an increase in disease specific therapy. Knowledge of alterations of disease activity in relation to pregnancy is important when counselling patients with PsA in this situation and advising continuation of disease ameliorating therapies that are compatible with pregnancy.

Disclosure: M. Mouyis, None; **C. Thornton**, None; **D. Williams**, None; **I. Giles**, None.

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Abstract Number: 2520

Psoriatic Arthritis Activity during Pregnancy and the Postpartum Period

Ari Polachek[1], Suzanne Li[2], Vinod Chandran[1] and Dafna Gladman[1], [1]Rheumatology, University of Toronto, Toronto Western Hospital, Toronto, ON, Canada, [2]University of Toronto, Toronto Western Hospital, Toronto, ON, Canada
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Background/Purpose: Psoriatic arthritis (PsA) often develops between the 3rd -4thdecades of life, including women of childbearing age. However, little is known about PsA activity during pregnancy and the postpartum period. We aimed to evaluate joint and skin activity of PsA during pregnancy and "postpartum" period.

Methods: Patients with PsA are followed prospectively according to a standard protocol. Data are stored on a computerized database. Women who had pregnancies during follow up between 1990 and 2015 and at least one clinic visit during pregnancy were identified. "Postpartum" period was defined as up to 1 year after pregnancy. PsA activity was defined by 5 states: improvement, worsening (both defined as a change in at least 2 active joints), stable low (defined as 0 or 1 active joint), stable high (defined as ≥ 2 active joints) or a combination of improvement and worsening. Skin activity was defined by 5 states: improvement, worsening (both defined as a change of 1 in the psoriatic area severity index (PASI), stable low (PASI<2), stable high (PASI ≥2) or a combination of improvement and worsening.

Results: 29 PsA women with 42 pregnancies were identified. Of the 42 pregnancies 38 (90%) resulted in live healthy babies, 2 in miscarriages (at the end of the 1sttrimester) and 2 are still pregnant. The mean age at pregnancy was 33.8 ± 4.6. The mean PsA duration was 12 ± 7.4 and the mean psoriasis duration was 19 ± 8.9 years. The mean damaged joint count was 6.3 ± 11.2 and the mean Stienbrocker score was 2 ± 5.5. The majority (24, 58.5%) of pregnancies had either PsA improvement or stable low disease activity, while 13 (31.7%) had either worsening or stable high disease activity (table 1). During the "postpartum" period, 22 (55%) had either improvement or stable low PsA disease activity, while 18 (45%) had either worsening or stable high disease activity. The skin activity during pregnancy had either improved or stayed in a stable low state in 30 (88.3%), worsened in 3 (8.8%) and initially improved with following worsening in 1 pregnancy (table 1). The skin activity during the "postpartum" period had either improved or stayed in stable low in 15 (42.9%) pregnancies, or worsened in 20 (57.1%). During pregnancy, 17 (40.5%) used NSAIDS, 18 (42.9%) used DMARDS, 7 (16.7%) used biologic treatment (6 used anti TNFα agents and 1 Ustekinumab).

Table 1: Joints and skin activity during pregnancy and "postpartum" period

Time	**Favorable course**		**Unfavorable course**		**Mixed course**
Activity in joints	**Improved**	**Stable low**	**Worse**	**Stable high**	**Improved-worse**
Pregnancy, number (%)	11 (26.8)	13 (31.7)	8 (19.5)	5 (12.2)	4 (9.8)
Total	24 (58.5)		13 (31.7)		
"Postpartum", number (%)	9 (22.5)	13 (32.5)	17 (42.5)	1 (2.5)	0
Total	22 (55)		18 (45)		
Skin activity					
Pregnancy, number (%)	14 (41.2)	16 (47.1)	3 (8.8)	0	3 (8.8)	1 (2.9)
Total	29 (88.3)				
"Postpartum", number (%)	3 (8.6)	12 (34.3)	20 (57.1)	0	20 (57.1)	0
Total	15 (42.9)				

Conclusion: The outcome of pregnancy among patients with PsA is excellent. Disease activity in both skin and joints is variable with the majority (60%) improving during pregnancy but worsening in the "postpartum" period.

Disclosure: A. Polachek, None; **S. Li**, None; **V. Chandran**, None; **D. Gladman**, None.

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Abstract Number: 2521

Pregnancies in Patients with Long-Standing Rheumatoid Arthritis and Biologic DMARD Treatment: Course of Disease during Pregnancy and Pregnancy Outcomes

Anja Strangfeld[1], Dagmar Pattloch[1], Madlen Spilka[2], Bernhard Manger[3], Brigitte Krummel-Lorenz[4], Annett Gräßler[5], Joachim Listing[6] and Angela Zink[1,7], [1]Epidemiology, German Rheumatism Research Center, Berlin, Germany, [2]German Rheumatism Research Center, Berlin, Germany, [3]Rheumatologist, Scientific Advisory Board, Erlangen, Germany, [4]Rheumatologist, Frankfurt, Germany, [5]Rheumatologist, Pirna, Germany, [6]Epidemiologiy, German Rheumatism Research Center, Berlin, Germany, [7]Rheumatology and Clinical Immunology, Charité University Medicine, Berlin, Germany

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Background/Purpose: The assumption of spontaneous remission among pregnant women with rheumatoid arthritis (RA) is common. Nevertheless, prospectively collected data describing the course of disease activity during pregnancies in women with long-standing severe RA are rare. Further, observational data suggest that biologic disease modifying anti-rheumatic drugs (bDMARDs) can be safely used until conception but the impact of bDMARD treatment during pregnancy is unclear. We aimed to study pregnancy outcomes and courses of disease activity in women with bDMARD use prior to conception.

Methods: We investigated all pregnancies and their outcomes that were reported to the German biologics register RABBIT until end of 2014. Pregnancies were stratified by treatment in A) biologic-naive, B) bDMARD stopped before or C) bDMARD exposed at time of conception. In a subgroup of patients with pregnancies reported until 2011, additional interviews with a focus on the course of disease activity and treatment during pregnancy were conducted. Descriptive statistics were applied to study associations of pregnancy outcomes, disease activity and treatment.

Results:

In 1,981 female RA patients ≤ 45 years, 106 pregnancies in 88 patients were reported. At time of conception 57 pregnancies were exposed to bDMARDs (C) (29x etanercept, 11x adalimumab, 5x tocilizumab, 4x certolizumab pegol, 3x rituximab, 3x abatacept, 1x infliximab, and 1x golimumab), 11 were biologic naive (A) and 38 had received their last bDMARD infusion or injection at least 4 weeks (rituximab 6 months) before conception (B) (12x etanercept, 9x adalimumab, 2x tocilizumab, 2x infliximab, 13x rituximab). Only 43% of the women being in remission prior to pregnancy remained in remission. From 49 women not in remission prior to conception only 7 (14%) reached remission during pregnancy. In all pregnancies of group C bDMARD treatment was stopped after awareness of pregnancy. In 13 of those (23%) bDMARDs had to be re-started during pregnancy due to high disease activity. No adverse influence of this treatment decision on the childs' health or pregnancy course was observed.

The rates of spontaneous abortions were not significantly different between treatment regimens (A: 0, B:13%, C:19%) and in range of general population rates. Induced abortions were reported in 4 out of 106 pregnancies (one due to trisomia 21 with cardiac defect in a 38 year old woman).

Among all live births one major malformation (anal atresia) was detected in a child born to a mother exposed to bDMARDs until 4 weeks prior to conception (group B). Ten premature births occurred: one in a biologic naive woman, and 4 in groups B and C, respectively. In those women disease activity during pregnancy was considerably higher compared to women with mature children.

Conclusion: Within our cohort observing women with long-standing severe RA, we could not confirm the assumption of spontaneous remission during pregnancy. A considerable proportion of women experienced ongoing or worsening disease activity or flares during pregnancy. We confirmed previous reports and found no increased risk of major malformations or other harmful consequences in patients exposed to bDMARDs at time of conception.

Disclosure: **A. Strangfeld**, AbbVie, Celltrion, Hospira, Bristol-Myers Squibb, MSD Sharp&Dohme, Pfizer, Roche, and UCB., 2,BMS, Merck-Sharp & Dohme, Pfizer, Roche, Sanofi-Aventis, 9; **D. Pattloch**, None; **M. Spilka**, None; **B. Manger**, AbbVie, 5,Bristol-Myers Squibb, 5,MSD, 5,UCB, 5,Pfizer Inc, 5,Roche Pharmaceuticals, 5; **B. Krummel-Lorenz**, None; **A. Gräßler**, None; **J. Listing**, AbbVie, Celltrion, Hospira, Bristol-Myers Squibb, MSD Sharp&Dohme, Pfizer, Roche, and UCB., 2,Pfizer Inc, 5; **A. Zink**, AbbVie, Celltrion, Hospira, Bristol-Myers Squibb, MSD Sharp&Dohme, Pfizer, Roche, and UCB., 2,BMS, Merck-Sharp & Dohme, Pfizer, Roche, UCB., 9.

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Abstract Number: 2522

High Risk of Flares during Pregnancy in Women with Rheumatoid Arthritis Who Discontinue Treatment with TNF Inhibitors at Conception

Rebecca Fischer-Betz[1], Oliver Sander[1], Christof Specker[2], Ralph Brinks[3] and Matthias Schneider[1], [1]Rheumatology, Heinrich-Heine-University, Duesseldorf, Germany, [2]Rheumatology and clinical immunology, Kliniken Essen Sued, Essen, Germany, [3]Hiller Center for Research in Rheumatology, Duesseldorf, Germany

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Background/Purpose: Optimal treatment of women with Rheumatoid Arthritis (RA) during pregnancy remains a challenge, mainly due to safety concerns. TNF inhibitors (TNFi) are now routinely used in young patients with pregnancy wish. Nevertheless it is recommended to discontinue treatment as soon as pregnancy is recognized because of lacking data concerning the long-term follow up of children exposed in utero. However, this approach may increase the risk of flares during pregnancy. We sought to explore the frequency of flare in pregnancies of women with RA who discontinue TNFi at conception. **Methods:** Pregnancies from a prospective pregnancy registry were evaluated before conception and during each trimester. Clinical characteristics, disease activity (DAS28-CRP), medication use, and pregnancy outcome were analyzed. A flare was defined as increase in clinical activity leading to intensifying treatment (new treatment with prednisolone or increase in dosage ≥5 mg/day and/or treatment with intraarticular glucocorticoids and/or (re-)treatment with DMARDS/TNFi). We applied a multivariate logistic regression model to assess the association between the use of TNFi at conception and the occurrence of flares during pregnancy. Adjustment for potential confounders was performed using logistic regression. **Results:** 42 pregnancies in women with RA were enrolled (median age 33 yrs, 71 % RF/ACPA positive). Eighteen (41%) pregnancies occurred in women with TNFi at conception. Twenty-four pregnancies in women without TNFi at conception served as controls. At conception, in 71 % disease activity was mild or in remission (DAS ≤ 3.2). We observed at least one flare in 16 pregnancies. Discontinuation of TNFi at conception was significantly associated with the occurrence of flares (OR 10.0, 95% CI 2.3-42.8, p=0.002). The strength of association was nearly constant after adjusting for age, RF, CCP, previous joint surgery, DAS28-CRP at conception, use and dosage of prednisolone during pregnancy. Twelve pregnancies had poor outcomes [10 (24%) with preterm delivery, 2 (4.7%) with preeclampsia]. The risk of preterm birth increased with every cumulative milligramme of Prednisolone [OR 1.08 (95% CI 1.02-1.15, p < 0.01)]. **Conclusion:** Women with RA who discontinue TNFi at conception face a high risk for flares during pregnancy, independently of known risk factors like sero-positivity. Flares are usually treated with Prednisolone. We found a dose-dependent significant increased risk for preterm birth associated with Prednisolone. In this era of treat-to-target management of RA, our paradigm for RA pregnancy management may need adjusting. By controlling RA activity with medications considered relatively safe in pregnancy, we may be able to improve both the pregnancy experience and pregnancy outcomes.

	All pregnancies	Pregnancies with TNFi exposure until conception	Pregnancies without TNFi exposure	P value
DAS ≤ 3.2 (1 st trim.)	30 (71 %)	12 (67 %)	18 (82 %)	0.37
DAS ≤ 3.2 (2nd trim.)	28 (66 %)	9 (50%)	19 (79%)	0.09
DAS ≤ 3.2 (3rd trim.)	28 (66%)	12 (67%)	16 (66%)	0.80
Flare	16 (38 %)	12 (67%)	4 (17 %)	0.003
Prednisolone, mg/day (median) (1st trim.)	7.5 (5-15)	9 (5-15)	8 (5-15)	0.24
Prednisolone, mg/day (median) (2nd trim.)	10 (5-20)	13 (5-20)	8 (5-15)	0.002
Prednisolone, mg/day(median) (3rd trim.)	10 (5-20)	10 (5-20)	8 (5-15)	0.02

Disclosure: R. Fischer-Betz, None; **O. Sander**, None; **C. Specker**, None; **R. Brinks**, None; **M. Schneider**, None.

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Abstract Number: 2523

Characteristics and Outcomes of Prospectively-Reported Pregnancies Exposed to Certolizumab Pegol from a Safety Database

Megan E. B. Clowse[1], Douglas C. Wolf[2], Amanda Golembesky[3], Laura Shaughnessy[4], Dirk De Cuyper[5] and Frauke Förger[6], [1]Rheumatology & Immunology, Duke University, Durham, NC, [2]Atlanta Gastroenterology Associates, Atlanta, GA, [3]UCB Pharma, Raleigh, NC, [4]8010 Arco Corporate Drive, Sui, UCB Pharma, Raleigh, NC, [5]Safety Patient Solutions BioBrands, UCB Pharma, Brussels, Belgium, [6]Rheumatology, Clinical Immunology and Allergology, Inselspital-University Hospital, Bern, Switzerland
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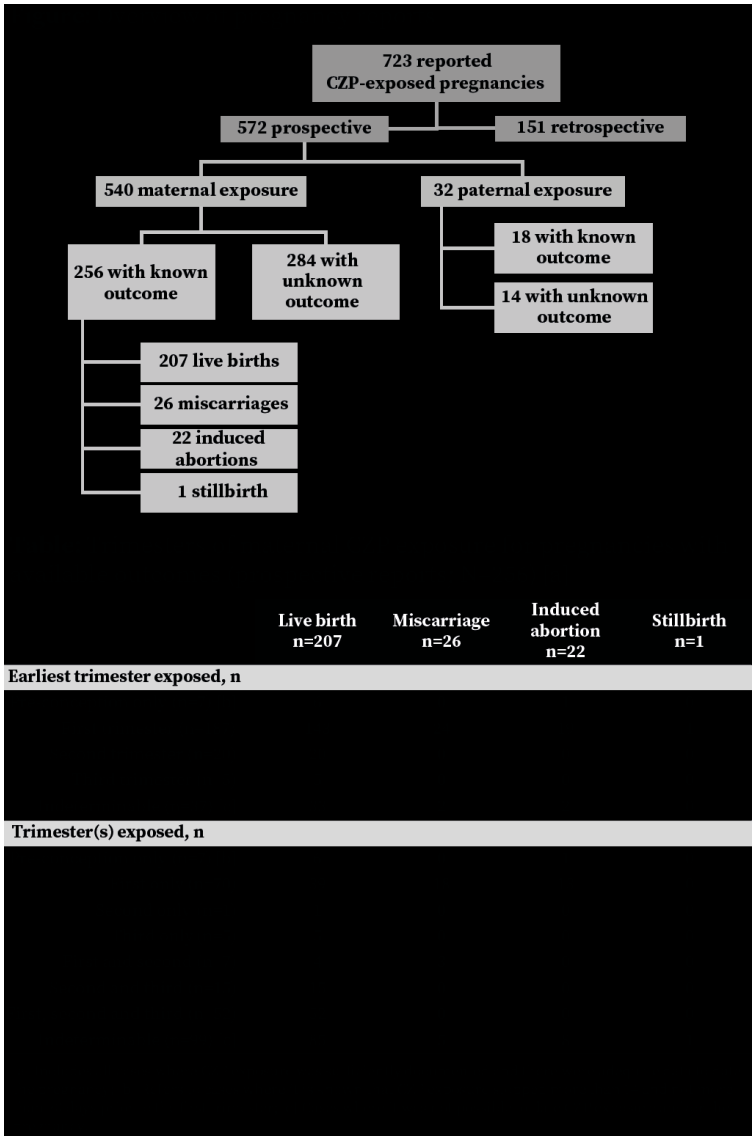
Background/Purpose: Data on the impact of anti-TNF medications on pregnancy outcomes are limited. Certolizumab pegol (CZP) is a PEGylated Fc-free anti-TNF approved in more than 50 countries for the treatment of rheumatoid arthritis (RA) and/or Crohn's disease, psoriatic arthritis (PsA) and axial spondyloarthritis (axSpA). The objective of this project is to provide information on pregnancy outcomes in women receiving CZP.

Methods: The UCB Pharma safety database was searched for CZP-exposed pregnancies through 1 February 2015. Maternal and paternal CZP exposure, prospective and retrospective reports were included. This abstract focuses on maternal exposure pregnancies that are prospectively reported to reduce bias in outcome reporting rates. Available data on CZP exposure, pregnancy dating, pregnancy outcomes, comorbidities and infant events were independently extracted by 2 internal reviewers. The number of live births, miscarriages, induced abortions and stillbirths for CZP-exposed pregnancies were examined.

Results: There were a total of 723 CZP exposed pregnancy reports, of which 572 were prospectively reported. 540 pregnancies were maternally exposed (256 with known pregnancy outcomes, 47.4%) and 32 were paternally exposed (18 with known outcomes, 56.3%). Of the 256 maternally exposed pregnancies with known outcome, there were 207 live births (80.9%), 26 miscarriages (10.2%), 22 induced abortions (8.6%), and 1 stillbirth (0.4%) (Figure). The majority of pregnancies were reported through routine surveillance (65.9%); clinical trials accounted for 9.1% of pregnancy reports. Indications for CZP use included rheumatic disease (n=100, 39.1%) and Crohn's disease (n=140, 54.7%). The mean maternal age at estimated delivery date was 31.3 (SD 5.4) years. Many pregnancies (n=70, 44.6%) were exposed only during the first trimester, when the majority of fetal organ and organ system development takes place; 52 were exposed to CZP in all 3 trimesters (Table). 9 cases of congenital malformations were prospectively reported among 210 infants (including 3 sets of twins) with no discernable pattern in the reported malformations.

Conclusion: The analysis represents a uniquely large number of pregnancies exposed to a single anti-TNF. The majority of pregnancies had first trimester CZP exposure, and up to a third of prospectively-collected pregnancies continued treatment into the second and/or third trimesters. A limitation of this study is that the majority of the data originated from spontaneous post-marketing reports, which can be affected by bias and inherent limitations due to the passive and voluntary nature of the reporting systems. The data collectively suggests that CZP exposure *in utero* does not adversely affect pregnancy outcome.



Disclosure: M. E. B. Clowse, UCB Pharma, 5; **D. C. Wolf**, Abbott, Bristol-Myers Squibb, Genentech, GIVEN Imaging, Janssen Biotech Inc., Millennium Research Group, Prometheus Laboratories, UCB Pharma, 2,Abbott, Genetech, GIVEN Imaging, Janssen Biotech Inc., Millennium Research Group, Prometheus Laboratories, Salix Pharmaceuticals, UCB Pharma, 5,Abbott, Janssen Biotech Inc., Prometheus, Salix, UCB Pharma, Warner Chilcott, 5; **A. Golembesky**, UCB Pharma, 3; **L. Shaughnessy**, UCB Pharma, 3; **D. De Cuyper**, UCB Pharma, 3; **F. Förger**, UCB Pharma, Roche, 5,UCB Pharma, Roche, 8.

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Abstract Number: 2524

Longterm Follow-up of Children Born to Mothers with Chronic Arthritides and Exposed to Anti-TNF Alfa Agents during Pregancy and Breastfeeding: A Case-Control Study

Rossella Reggia[1], Laura Andreoli[1], Chiara Bazzani[1], Maria Grazia Lazzaroni[1], Giovanna Mazza[1], Michele Agosti[1], Roberto Gorla[2], Marco Taglietti[2], Andrea Lojacono[3], Mario Motta[4] and Angela Tincani[5], [1]Rheumatology and Clinical Immunology, Spedali Civili and University of Brescia, Brescia, Italy, [2]Rheumatology and Clinical Immunology, Spedali Civili of Brescia, Brescia, Italy, [3]Obstetrics and Gynecology, Spedali Civili and University of Brescia, Brescia, Italy, [4]Neonatal Intensive Care Unit, University and Spedali Civili of Brescia, Brescia, Italy, [5]Rheumatology and Clinical Immunology Unit, Spedali Civili and University of Brescia, Brescia, Italy
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Background/Purpose: Anti-TNFalfa agents have been used to control disease activity of patients with Chronic Arthritides (Rheumatoid Arthritis, Psoriatic Arthritis, Ankylosing Spondylitis) during the wash-out period of teratogenic DMARDs and are usually discontinued at positive pregnancy index. Moderate to severe maternal disease activity during pregnancy can justify the use of the drugs in the 2nd-3rd trimester and in the postpartum period. This is a case-control study on the health and developmental conditions of children exposed in utero and/or during breastfeeding to anti-TNFalfa agents and non-exposed children born to women with the same disease.

Methods: An ad-hoc created questionnaire was submitted to women who were followed during pregnancy by a multidisciplinary team (rheumatologist, gynaecologist, neonatologist). Data on birth, lactation, weaning, growth parameters, developmental milestones, vaccinations and disease conditions were collected.

Results: The table reports the characteristics of 25 cases (9 male, 16 female) (21 exposed to etanercept, 3 to adalimumab, 1 to certolizumab) and 25 controls (12 M, 13 F). Eighteen children were exposed during the first trimester (discontinuation of anti-TNFalfa agent at positive pregnancy index), while 7 during the 2nd-3rd trimester (discontinuation at 34th-37th week, mean exposure of 13.3 weeks). Both cases and controls underwent vaccinations without any severe complications. Vaccinations were protective; only one child with periconception exposure to etanercept developed chicken-pox despite vaccination. Five children (3 cases and 2 controls) were breastfed during maternal anti-TNFalfa therapy (3 etanercept, 2 adalimumab).

Conclusion: No differences in birth parameters, congenital malformations and developmental steps in the first 24 months of life have been found between cases and controls. Growth parameters were within the curves of the general population. Cases received more vaccinations than controls: this may be due to the feeling by either parents or paediatricians that these children exposed to immunosuppressive agents could be more susceptible to infectious diseases. No relevant infectious diseases nor post-vaccine complications have been noted in the 6 children exposed to anti- TNFalfa during the 2nd-3rd trimester of gestation nor in the 5 exposed during lactation. Globally, the long-term follow-up of children supports the safety of use of anti-TNFalfa agents, either preconceptionally or during the 2^{nd}-3^{rd}trimester of pregnancy. Data on use during breastfeeding are still anecdotal but can be helpful for counseling the patients who are strongly motivated to breastfeed.

	Children exposed to anti- TNF alfa (CASES) n=25	Children not exposed to anti- TNF alfa (CONTROLS) n=25
Gestational week at birth	38 (37-39)	39 (38-40)
Birth weight (g)	3156 (2750-3520) [a,b]	3260 (3030-3735)[c]
Birth lenght (cm)	49 (48-51)	50 (48,5-51,6)
Apgar index 1 min	9 (9-9)	9 (9-10)
Apgar index 5 min	10 (9-10)	10 (9-10)
Congenital malformations at birth	1 female with Patent Foramen Ovale, pervius duct of Botallo, pulmonary hypertension; 1 female with Pierre Robin sequence + severe myopia; 1 male with cryptorchidms; 1 female with eversible metatarsal varus condition[d]	1 male with Ventricular Septal Defect, Patent Foramen Ovale, lumbar emivertebral fusion; 1 male with cardiac murmur due to 3 mild Ventricular Septal Defects; 1 male with right testicular hydrocele
Perinatal complications	1 female with emithoracical left angioma + jaundice	1 male with jaundice; 1 male with iponatriema; 1 male with neonatal cyanosis with spontaneous resolution
Maternal breastfeeding (number of children)	13 (54,2%)°	16 (66,7%)*
Age at breastfeeding discontinuation (months)	6 (3-7)	3 (2,75-7)
Weight:	7500 (7150-7683)	7600 (7180-8108)
at 6 months (g)	9500 (9163-10663)	9700 (9090-10413)
at 12 months (g)	**n.16**:12750 (10500-13620,5)	**n.18**: 12000 (11312,5-13150)
at 24 months (g)		
Length:	66 (65-67)	68 (64,6-69,3)
6 months (cm)	75 (73,5-76,9)	75,8 (73,8-76,6)
12 months (cm)	**n.16**: 85 (82,5-89,5)	**n.18**: 88 (85,8-90)
months (cm)		
Age at seated position (months)	6 (6-7)	6 (6-7)
Age at walking (months)	12 (11-13)	13 (11-14)
Age at speaking (months)	16 (13-18)	18 (12-20)
Age at June 2015 (months)	43 (30-74)	50 (32-81)

[a]1 F SGA; [b] 1 M with macrosomia; [c]1 M with IUGR; [d] exposed to MTX in the periconception period *2 children not exposed to anti-TNFalfa in utero but during breastfeeding. ° 3 children exposed to anti-TNFalfa in utero and during breastfeeding. Data reported as median value, interquartile range.

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Abstract Number: 2525

Patterns and Secular Trends in Use of Immunosuppressive Agents during Pregnancy in Women with Rheumatologic Conditions

Rishi J. Desai[1], Krista Huybrechts[2], Brian Bateman[2], Sonia Hernandez-diaz[3], Helen Mogun[2], Chandrasekar Gopalakrishnan[4], Elisabetta Patorno[4] and Seoyoung C. Kim[5], [1]Division of Pharmacoepidemiology and Pharmacoeconomics, Brigham & Women's Hospital, Harvard Medical School, Boston, MA, [2]Division of Pharmacoepidemiology and Pharmacoeconomics, Brigham and Women's Hospital, Boston, MA, [3]Harvard School of Public Health, Boston, MA, [4]Brigham and Women's Hospital, Boston, MA, [5]Div. of Pharmacoepidemiology and Pharmacoeconomics, Div. of Rheumatology, Immunology and Allergy, Brigham and Women's Hospital, Boston, MA

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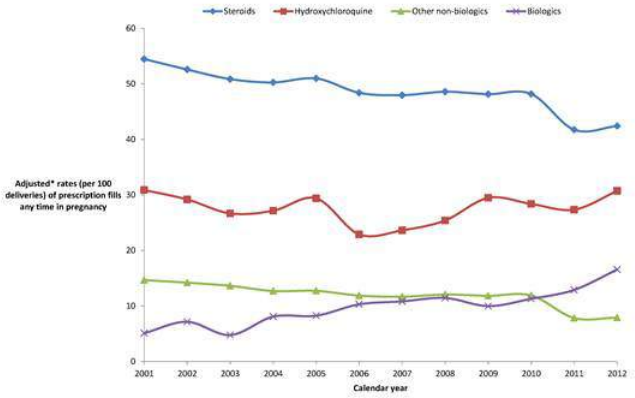
Background/Purpose: Systemic inflammatory conditions such as systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), psoriatic arthritis (PsA), and ankylosing spondylitis (AS) affect many women during their childbearing years. Empirical data describing the time-trends and patterns of use of immunosuppressive agents during pregnancy in routine practice are scarce. Therefore, we designed this study to describe patterns and secular trends in use of immunosuppressive agents in pregnant women with SLE, RA, PsA, or AS.

Methods: A cohort of women with SLE, RA, PsA, or AS enrolled in public (Medicaid, 2001-2010) or private (OptumClinformatics, 2004-2012) health insurance was identified and women filling prescriptions for immunosuppressives- including steroids, non-biologic disease-modifying agents, and biologics- in the 3-month period immediately prior to their pregnancy were included. The proportion of women continuing or discontinuing individual agents during pregnancy was reported. Annual prescription fill rates, estimated after accounting for patient characteristics and random variability from year-to-year in mixed-effect regression models, were used to conduct time-trends analysis.

Results: A total of 2,645 women actively treated with immunosuppressive agents prior to pregnancy were included. More women with PsA or AS stopped filling immunosuppressive prescriptions in pregnancy (61%) than those with SLE (26%) or RA (34.5%). From the first to the third trimester, the proportion of women filling prescriptions for immunosuppressive agents decreased across all indications. Overall, steroids (48.4%) and hydroxychloroquine (27.1%) were the most frequently used agents in pregnancy. The rates (reported per 100 deliveries in our cohort) for steroid prescription fills during pregnancy fell significantly from 54.4 to 42.4; while rates for biologics increased from 5.1 to 16.6 between 2001 and 2012 ($p<0.001$ for both trends).

Conclusion: Steroids and hydroxychloroquine remain the most widely prescribed treatment options in pregnancy; but the use of biologics is becoming increasingly common.

Figure: Time-trends in use of immunosuppressive agents during pregnancy in a cohort of women with systemic lupus erythematosus, rheumatoid arthritis, ankylosing spondylitis or psoriatic arthritis.



* Adjusted for maternal characteristics (age, region), insurance type (Medicaid or private), case-mix (underlying treatment indication-SLE, RA, PsA, or AS), and random variability across years using a mixed regression model.

Disclosure: R. J. Desai, None; **K. Huybrechts**, None; **B. Bateman**, None; **S. Hernandez-diaz**, AstraZeneca, 5; **H. Mogun**, None; **C. Gopalakrishnan**, None; **E. Patorno**, None; **S. C. Kim**, Pfizer Inc, 2,AstraZeneca, 2,Lilly, 2,Genentech and Biogen IDEC Inc., 2.

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Abstract Number: 2526

Perinatal Patterns of Medication Use in Women with Rheumatoid Arthritis: A Population-Based Study

Mary A De Vera[1,2], Eric C. Sayre[2], Nicole Tsao[1,2] and J Antonio Avina-Zubieta[2,3], [1]Faculty of Pharmaceutical Sciences, University of British Columbia, Vancouver, BC, Canada, [2]Arthritis Research Canada, Richmond, BC, Canada, [3]Medicine, University of British Columbia, Department of Medicine, Division of Rheumatology, Vancouver, BC, Canada

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Perinatal Patterns of Medication Use in Women with Rheumatoid Arthritis: A Population-based Study

Background/Purpose: Although the incidence of RA peaks during the 4th and 5th decades of life, a substantial proportion of women are also affected during the more common childbearing years. Given the limited data on perinatal medication use, including traditional and biologic DMARDs as well as other medications, our objective was to characterize real-world therapy patterns among women with RA before, during, and after pregnancy.

Methods: We linked population-based health data on all visits to health professionals and hospital admissions (01/01/1992 – 12/31/2012) and all dispensed medications, regardless of payer (01/01/1996 – 12/31/2012) with a perinatal registry capturing information on >99% of births in hospitals and homes in the province of British Columbia, Canada (01/01/2002 – 12/31/2012). Unique to this pregnancy cohort is valid, clinically-derived information on date of conception according to gestational age or date of last menstrual period as confirmed by ultrasound. The case definition for RA was 2 outpatient ICD9 codes for RA ³2 months apart and we excluded individuals with a non-RA coded subsequent visit to a rheumatologist or no subsequent RA-coded visits during the last 5 years of follow-up. Using information on prescription date and days supply, we determined the use of traditional and biologic

DMARDs, glucocorticosteroids, and NSAIDs for the following periods: **1)** pre-conception 1 (366-730 days before conception); **2)** pre-conception 2 (1-365 days before conception); **3)** 1st trimester; **4)** 2nd trimester; 5) 3rd trimester; and **6)** post-delivery (1-365 days after delivery).

Results: We identified 513 pregnancies in 414 women with RA; 80% of women were primipara and 20% multipara. At delivery, mean age was 31.3 ± 5.4 years. We tabulated the proportion of exposed pregnancies according to each period and medication class (**Table**). The majority of traditional DMARD pregnancy exposures were to hydroxychloroquine and/or chloroquine (proportion of pregnancies exposed during the 1st, 2nd, and 3rd trimester were 17.0, 10.7 and 9.2%, respectively) and the majority of biologic pregnancy exposures were to anti-TNFs (4.7, 2.1 and 2.1%). For all medications, we observed a decline in use during pregnancy followed by increased use in the year following delivery.

Conclusion: This population-based study provides data on real-world patterns of perinatal medication use among women with RA. Findings emphasize the importance of counseling women regarding childbearing decisions as well as the need for evaluation of the risk-benefit profiles of medications in pregnancy.

	Exposed RA Pregnancies (%)					
	Pre-conception 1	**Pre-conception 2**	**1st trimester**	**2nd trimester**	**3rd trimester**	**Post-delivery**
Traditional DMARDs	43.9	44.3	24.0	15.0	11.5	38.0
Biologic DMARDs	7.4	8.2	4.7	2.1	2.1	8.0
Anti-TNFs	*7.4*	*8.0*	*4.7*	*2.1*	*2.1*	*7.8*
Glucocorticosteroids	22.0	24.8	13.5	11.5	11.3	25.9
NSAIDs	41.7	42.7	12.7	4.7	3.3	40.6

Disclosure: M. A. De Vera, None; **E. C. Sayre**, None; **N. Tsao**, None; **J. A. Avina-Zubieta**, None.

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Abstract Number: 2527

Neonatal Outcome to Paternal Exposures with Anti-Rheumatic Therapy

Elisabeth Solau-Gervais[1] and **Antoine Brigaud Jr.**[2], [1]Rhumatologie, University Hospital, Poitiers, France, [2]University hospital, Poitiers, France

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Session Time: 9:00AM-11:00AM

Background/Purpose: There is a lack of studies about preconceptional paternal exposure to disease modified anti-rheumatic drugs (DMARDs) and the data of literature are controversial. The objectives are to study the difference in neonatal outcome between exposed fathers and non exposed fathers and to know information about preconceptional treatment management.

Methods: For this retrospective study, questionnaires have been sent to all the men followed in the department for rheumatic diseases (rheumatoid arthritis, spondyloarthritis or psoriatic arthritis). In this questionnaire there were questions about number of children, date of birth, treatment received during preconception, environmental factors of father and mother (tobacco, alcohol, other treatments and diseases and age) and information about preconceptional treatment management. Patients who received treatment during preconception period have been contacted to confirm their preconceptional treatment and neo-natal outcome, birth weight and term. For the neonatal outcome, two groups of patients were analyzed: paternal exposed children and non exposed children.

Results: From 407 questionnaires sent, 200 answers were received. Forty five men had a rheumatic disease diagnose at the preconceptional period. There were 77 births, 29 exposed children (11 to sulfasalazine, 7 to adalimumab, 6 to etanercept, 1 to infliximab, 1 to methotrexate and sulfasalazine, 1 to methotrexate and etanercept) and 48 non exposed children. There were 2 major birth defects in the exposed group (1 William and Beuren syndrome and 1 Turner syndrome) and no in the non exposed group, the difference was not statistically significant ($p = 0.138$). There was no statistical difference between the two groups when birth weight is concern with 3.27 kg in the exposed group versus 3.07 kg in the non exposed group ($p = 0.09$) and no difference concerning the

gestational age: 41.6 weeks in the exposed group versus 39,6 in the non exposed.

On 200 patients, 52 patients were on DMARDs and under 45 years old and only 15 (28.8%) have discussed with the practitioner about paternal exposure and 32 (61.5%) estimated not having enough information on risk of paternal exposure.

Conclusion: In this study, even if there is no increased risk in neonatal outcome after paternal exposure to DMARDs, due to a weak birth rate in this population, fathers are left behind when pregnancy is concerned

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Disclosure: E. Solau-Gervais, None; **A. Brigaud Jr.**, None.

Abstract Number: 2528

Utilization of Immune-Suppressive Medications during Pregnancy Among Women with Inflammatory Arthritis and Other Autoimmune Diseases

Jie Zhang[1,2], Jeffrey R. Curtis[3], Fenglong Xie[4], Melissa L. Mannion[5], James D. Lewis[6,7], Megan E. B. Clowse[8], Kenneth G. Saag[3], Steven Bethard[9], Jospeh Biggio[9], Gerald McGwin[9] and Timothy Beukelman[10], [1]Epidemilogy, University of Alabama at Birmingham, Birmingham, AL, [2]Division of Clinical Immunology and Rheumatology, University of Alabama at Birmingham, Birmingham, AL, [3]University of Alabama at Birmingham, Birmingham, AL, [4]Rheumatology & Immunology, University of Alabama at Birmingham, Birmingham, AL, [5]Pediatrics, University of Alabama at Birmingham, Birmingham, AL, [6]University of Pennsylvania, Philadelphia, PA, [7]Medicine, University of Pennsylvania, Philadelphia, PA, [8]Clinical Rheumatologist, Duke University Medical Center, Durham, NC, [9]UAB, Birmingham, AL, [10]Rheumatology, University of Alabama at Birmingham, Birmingham, AL
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Background/Purpose: To examine difference in the prevalence of immunosuppressive medication use during pregnancy by type of autoimmune disease and by insurance (Medicaid versus commercial) in an analysis of administrative claims databases.

Methods: We identified women who were diagnosed with rheumatoid arthritis, psoriatic arthritis, psoriasis, and inflammatory bowel disease (ulcerative colitis and Crohn's disease) and had a live birth between 2006-2010 (Medicaid) and 2005-2012 (commercial). Eligible women were identified by requiring ≥ 2 physician diagnoses for the diseases or one diagnosis plus ≥ 1 filled prescription(s) for an immunosuppressive medication at any time prior to and during pregnancy. In addition, they were required to have both medical and pharmacy coverage continuously during the 12 months period prior to delivery. We determined the use of immunosuppressive medications by examining filled prescriptions and calculated the prevalence of each medication during 4 separate time periods: preconception (90 days prior through conception), 1st trimester (day 270-180 prior to delivery), 2nd trimester (day 180-90 prior to delivery), and the 3rd trimester (day 90 prior through delivery). In addition, among biologic users during preconception with Medicaid coverage, we examined the proportion of patients who had discontinued by the 3rd trimester.

Results: We identified 5,909 pregnant women with autoimmune diseases enrolled in Medicaid and 1,104 commercially insured. Women with Medicaid coverage were younger compared to those commercially insured at time of delivery (mean age 27 versus 31 years). Biologics were the most commonly used DMARDs across all diseases and throughout the 4 time periods (Table). We observed a decline in the prevalence of biologics use from preconception to 3rd trimester in both Medicaid and commercially insured populations and across all diseases (Table). Among RA patients, 12-14% had a filled prescription during preconception compared to 3% in the 3rd trimester. Despite a lower prevalence (7-8%) of biologics use during preconception among women with inflammatory bowel disease, the prevalence (3-5%) in the 3rd trimester was similar to that among RA patients. Among biologic users during preconception enrolled in Medicaid, 83% of RA patients had discontinued by the 3rd trimester compared to 65% of IBD patients.

Conclusion: Irrespective of type of insurance, biologics were the most commonly used DMARDs during and immediately prior to pregnancy among women with inflammatory autoimmune diseases. Prevalence rates of biologics use differed by diagnoses but were not different between Medicaid and commercially insured. Further research to evaluate potential under-treatment of these diseases during pregnancy is warranted.

	Rheumatoid Arthritis		Psoriatic Arthritis		Psoriasis		Inflammatory Bowel Disease	
	Medicaid (Med)	Commercial (Com)	Med	Com	Med	Com	Med	Com
N	2177	299	137	31	1917	187	1612	400
			Preconception					
Any Biologic, %	12.4	14.0	27.7	8.6	3.8	2.4	7.0	7.5
Hydroxychloroquine, %	11.2	12.2	2.2		0.2	0.3	0.1	
Sulfasalazine, %	1.7	2.1					2.1	2.1
Azathioprine, %	0.6	0.6	0.7		0.1		2.5	0.5
Mercaptopurine, %	0.2				0.1	1.4	3.9	4.7
Methotrexate, %	8.6	3.9	8.0	2.9	0.5	0.3	0.3	
			1st Trimester					
Any Biologic, %	8.9	10.4	20.4	8.6	2.4	1.4	5.3	5.8
Hydroxychloroquine, %	8.7	6.8	2.2		0.2	0.3		
Sulfasalazine, %	1.0	1.5		2.9	0.1		1.6	2.1
Azathioprine, %	1.4	0.6	0.7		0.1		1.7	0.2
Mercaptopurine, %	0.1					0.7	2.7	4.0
Methotrexate, %	4.3	0.6	3.7		0.1		0.1	
			2st Trimester					
Any Biologic, %	3.6	3.3	10.2	5.7	1.3	1.0	4.2	5.1
Hydroxychloroquine, %	5.1	1.5	0.7		0.1			
Sulfasalazine, %	0.6	0.6					1.7	1.4
Azathioprine, %	0.3				0.1		0.8	0.5
Mercaptopurine, %						0.7	1.6	3.3
Methotrexate, %	0.8							
			3st Trimester					
Any Biologic, %	2.5	3.3	6.6	5.7	0.6	1.0	3.2	4.9
Hydroxychloroquine, %	4.0	2.1	0.7		0.2			
Sulfasalazine, %	0.5	0.6					0.7	2.3
Azathioprine, %	0.3				0.1		0.6	0.5
Mercaptopurine, %	0.1					0.7	0.9	3.7
Methotrexate, %	0.3				0.1			
% of biologic users during preconception who had discontinued by 3rd trimester								
	83%		93%		89%		65%	

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Abstract Number: 2529

Decreased Programmed Death Ligand-1 (PD-L1) in Systemic Lupus Erythematosus (SLE) Placenta

Gail Deutsch[1,2], Megan Yuasa[3] and Anne M. Stevens[4,5], [1]Pathology, Seattle Children's Hospital, Seattle, WA, [2]School of Medicine, University of Washington, Seattle, WA, [3]Seattle Children's Res Institute, Seattle Children's Research Institute, Seattle, WA, [4]Center for Immunity and Immunotherapies, Seattle Children's Research Institute, Seattle, WA, [5]Pediatrics, University of Washington, Seattle, WA

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Background/Purpose: The increased rates of preeclampsia, preterm birth, and intrauterine growth restriction in SLE pregnancy are only partially explained by the vascular effects of anti-phospholipid antibodies. SLE patients themselves are born preterm more often than expected, suggesting a heritable defect in maternal-fetal tolerance. PD-L1 is one candidate gene, in that it has been implicated in the both autoimmunity and maternal-fetal tolerance: PD-L1 is expressed on healthy antigen presenting cells to downregulate inflammatory responses, and also on placental trophoblasts at the maternal-fetal interface, where it inhibits alloreactive T cells. Peripheral blood antigen presenting cells from SLE patients are deficient in PD-L1 expression compared to remission or healthy controls. Little is known about placental costimulatory molecules in women with autoimmune diseases. This study tested the hypothesis that placental PD-L1 expression is abnormally regulated in SLE pregnancy.

Methods: Expression of PD-L1 was quantified by immunohistochemistry in placentas from full-term pregnancies of 4 SLE patients, 7 rheumatoid arthritis patients (RA) and 11 healthy control women obtained from the Global Alliance for the Prevention of Prematurity and Stillbirth Repository. PD-L1 mRNA expression was assayed by RT-PCR and normalized to GAPDH expression. PD-L1 on peripheral CD14+/CD11c+ monocytes was assayed by flow cytometry. Significant differences between groups were tested by T-test.

Results: By immunostaining, PD-L1 expression in SLE placentas was significantly reduced compared to control groups. The difference was most pronounced on the fetal side of the placenta. PD-L1 mRNA expression correlated with protein expression, although the differences were not significant. On peripheral blood monocytes, PD-L1 expression was low in juvenile SLE patients compared to healthy controls (55% of SLE monocytes v. 93% of healthy monocytes, p=0.001). Although in the normal range, mothers of SLE patients also had relatively low PD-L1 expression compared to control mothers (87% v. 94%, p=0.04).

Table 1. Relative median PD-L1 expression in the placenta in patients and controls.

	Controls	SLE	P*	RA	P**
Protein					
Overall	16.8	5.3	0.013	14.5	0.39
Fetal	19.4	7.2	0.004	14.5	0.41
Maternal	16.4	6.1	0.09	15.3	0.73
mRNA	109	72	0.21	300	0.08

*SLE versus controls; **RA versus controls.

Conclusion: PD-L1 expression is dysregulated in pregnant women with SLE (in placenta), in SLE patients, and in mothers of SLE patients (in blood). Inadequate expression of PDL-1 in the placentas of patients with SLE could result in loss of maternal-fetal tolerance, contributing to the high rate of pregnancy complications in SLE.

Disclosure: G. Deutsch, None; **M. Yuasa**, None; **A. M. Stevens**, PD-L1, 7.

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Abstract Number: 2530

A Multicenter Evaluation of Obstetric and Maternal Outcome in Prospectively Followed Pregnant Patients with Confirmed Positivity for Antiphospholipid Antibodies (aPL)

Micaela Fredi[1], Elena Aggogeri[2], Elisa Bettiga[3], Laura Andreoli[2], Maria Grazia Lazzaroni[2], Véronique Le Guern[4], Andrea Lojacono[3], Fabrizio Lupoli[2], Nathalie Morel[4], Jean Charles Piette[5], Sonia Zatti[3], Nathalie Costedoat-Chalumeau[4] and Angela Tincani[2], [1]Rheumatology and Clinical Immunology, Spedali Civili of Brescia, Brescia, Italy, [2]Rheumatology and Clinical Immunology, Spedali Civili and University of Brescia, Brescia, Italy, [3]Obstetrics and Gynecology, Spedali Civili and University of Brescia, Brescia, Italy, [4]Internal Medicine Department, Cochin Hospital, "René-Descartes Paris V" University, Paris, France, [5]Internal Medicine Department, University Hospital "Pitié-Salpêtrière", "Pierre et Marie Curie Paris VI" University, Paris, France
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Background/Purpose: Antiphospholipd antibodies (aPL) positivity is considered as a risk factors for a poor obstetric outcome. The aim of this work was to determine risk factors in patients (pts) with established aPL positivity with/without a diagnosis of primary antiphospholipid syndrome (PAPS) despite the administration of low dose aspirin (LDA) and heparin (LMWH).

Methods: Two hundred women were prospectively followed in the 3 Institutions involved between 2000 and 2014. None of the pts had a concomitant systemic autoimmune disease, while 28 had an organ autoimmune disease. Data were retrospectively collected from clinical charts using a common database. Adverse pregnancy outcome (APO) was considered the occurrence of pregnancy loss, perinatal deaths, preterm deliveries before the 34 weeks due to preeclampsia and HELLP syndrome.

Results: Among the 200 pts, 127 fulfilled the criteria for PAPS and 73 did not. During the study pts had 283 pregnancies. According to their clinical and biological characteristic we created 4 groups: 85 pts with obstetric (O-APS, 124 pregnancies), 42 thrombotic with/without obstetric (T-APS, 66 pregnancies), 39 incomplete clinical criteria (I-APS, 54 pregnancies) and 34 aPL carriers without any clinical manifestation (39 pregnancies).

The mean age at the onset of pregnancy was 32.4 years, the global rate of live births was 88%; APO was observed in 50 cases (18%). In the table 1 are reported the features statistically associated with APO at the univariate and multivariate analysis. T-APS was the group with the higher rate of APO (24%) followed by the aPL carrier and O-APS (18%), few occurred among the I-APS (9%). In table 2 we reported APO divided for clinical group and features statistically associated. We collected 14 maternal complications: 7 thrombotic events (3 DVT, 1 pulmonary embolism, 1 myocardial infarction, 2 CAPS) and 7 non-criteria manifestations (thrombocytopenia, hemolytic anemia, epilepsy). The thrombotic events occurred mostly in T-APS pts (71%), triple positive (53%) and during puerperium (53%).

Conclusion: A non-negligible considerable rate of APO and other maternal complications were observed even if the patients were treated according the recommended guidelines confirming that these pregnancies have to be considered at high risk for maternal and fetal health. With this study we identified 3 profiles of patients with a higher risk: thrombotic history, a more systemic APS phenotypes (other APS manifestations, or complement reduction) and triple positive aPL even without full criteria for APS.

	Univariate analysis		Multivariate analysis	
Demographic, clinical and serological features (number of pregnancies)	P Value	OR (95%IC)	P value	OR (95%IC)
Organ-specific autoimmune disease (thyroiditis, celiac disease, CBP, autoimmune hepatitis) (n=38)	0.016	2.51 (1.09-5.75)	0.03	2.3 (1.05-7.3)
Other aPL-related manifestations (n=48)°	0.002	2.95 (1.38-6.29)	0.019	3.2 (1.2-8.4)
LA positivity (n=125)*	0.03	1.97 (1.01-3.83)	ns	ns
aCL IgG positivity (n=153)*	0.005	2.54 (1.25-5.26)	ns	ns
Triple positivity (n=82)	0.015	2.16 (1.10-4.25)	ns	ns
Non-organ specific autoantibodies (ANA medium titer, anti-ENA, anti ds-DNA) (n=78)	0.012	2.23 (1.12-4.42)	ns	ns
Low C3 and/or C4 at beginning of pregnancy (data available for 195 pregnancies) (n=27)	0.001	4.33 (1.63-11.46)	0.03	3.0 (1.07-8.65)

Table 1. Features associated with APO, global cohort. * No statistical difference was found for isolated LA or aCL IgG positivity; ns=not significant; ° Thrombocytopenia, epilepsy, headache, livaedo reticularis, heart valve lesions and haemolytic anaemia.

	APO n (%)	Features associated with APO	LDA alone	Combination therapy (LDA+LMWH)
T-APS, 66 pregnancies	16 (24%)	Previous thrombotic event p=0.028	1 (1.5%)	60 (90.3%)
O-APS, 124 pregnancies	22 (18%)	Previous premature birth, p=0.037; Non-organ specific autoantibodies°, p=0.023; Low C3/C4, p=0.04	17 (13.7%)	107 (86.2%)
I-APS, 54 pregnancies	5 (9%)	LA positive*, p=0.03; anti-B2GPI IgG positive*, p=0.017;	23 (42.6%)	31 (57.4%)
aPL carrier, 39 pregnancies	7 (18%)	Triple positivity, p=0.022	26 (66.6%)	13 (33.4%)

Table 2. APO divided for clinical groups. * No statistical difference was found for isolated LA or aB2GPI IgG positivity; ° ANA medium titer, anti-ENA, anti ds-DNA

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Abstract Number: 2531

Hematologic Disorder during Pregnancy Associated with Adverse Pregnancy Outcomes Among Women with Systemic Lupus Erythematosus

Sara K. Tedeschi[1], Hongshu Guan[2], Alexander Fine[2], Bing Lu[1], Karen H. Costenbader[1] and Bonnie Bermas[1], [1]Rheumatology, Brigham & Women's Hospital, Boston, MA, [2]Rheumatology, Immunology and Allergy, Brigham and Women's Hospital, Boston, MA

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<>**Background/Purpose:** Previous studies have found a relationship between overall systemic lupus erythematosus (SLE) activity and adverse pregnancy outcomes. We sought to investigate whether specific types of SLE activity either in the 6 months prior to conception or during pregnancy were related to adverse pregnancy outcome. <> <>**Methods:** We identified women with confirmed SLE by 1997 ACR Revised Criteria, >2 visits to our Lupus Center, and ³1 pregnancy lasting >12 weeks from 1990-2013. Data collected from electronic medical record included demographics, SLE medications and labs, obstetric history, pregnancy outcomes, and presence of 5 specific types of SLE activity 6 months before conception and during pregnancy: hematologic (WBC <4K, hemolytic anemia, or platelets <100K), nephritis (proteinuria >0.5g/d, WBC or RBC >5, or casts), serositis (pleuritis or pericarditis), arthritis (>1 joint), and skin (discoid or malar rash). Adverse pregnancy outcome was defined as pre-eclampsia, preterm delivery (<37 weeks), spontaneous abortion ³12 weeks, or stillbirth. Univariable analyses identified predictors of adverse pregnancy outcome. Multivariable analyses evaluated each specific type of SLE activity as a primary predictor of adverse outcome, adjusting for significant univariable predictors. Generalized linear mixed models were used for both univariable and multivariable analyses to account for correlated data, as some women had >1 pregnancy. <> <>**Results:** 147 pregnancies occurred in 113 women with mean age 23.7 (SD 6.8) years at SLE diagnosis and 31.0 (SD 5.3) at conception. 68% were White, 15% Hispanic, 10% Black, 7% Asian. Five women had a history of antiphospholipid syndrome and 21 had a prior adverse pregnancy outcome. During the study period, 38 (26%) pregnancies had an adverse outcome. Hematologic disorder (16%) and nephritis (10%) were the most common types of SLE activity during pregnancy. In univariable analyses, nephritis 6 months before conception (OR 6.4, 95%CI [1.3, 32.8]) and hematologic disorder during pregnancy (OR 5.2 [1.8, 15.4]) were significantly associated with adverse outcome. Hispanic ethnicity, prior adverse pregnancy outcome, and steroid and/or azathioprine use during pregnancy were also associated with adverse outcome. In multivariable analyses, only hematologic disorder during pregnancy was associated with adverse outcome (OR 3.4 [1.1, 10.6]). (Table) <> <>**Conclusion:** The majority of pregnancy outcomes were favorable in this SLE cohort. After adjusting for ethnicity, prior adverse pregnancy outcomes, and medications during pregnancy, only hematologic disorder during pregnancy was associated with an elevated risk of adverse pregnancy outcome. Prior studies have suggested variable impact of lupus nephritis on pregnancy outcomes, but this study uniquely demonstrates an association between cytopenia during pregnancy and adverse pregnancy outcomes.

Table. Predictors of Adverse Pregnancy Outcome⁺ in 147 Pregnancies

Predictor	Univariable OR* (95% CI)	Multivariable OR* # (95% CI)
Specific Type of SLE Activity Six Months Prior to Conception		
Hematologic	2.7 (0.8, 9.1)	1.5 (0.4, 5.4)
Nephritis	**6.4 (1.3, 32.8)**	3.0 (0.5, 17.0)
Skin disease	1.1 (0.3, 4.2)	1.1 (0.3, 4.3)
Arthritis	0.8 (0.2, 3.9)	0.5 (0.1, 2.5)
Serositis	1.9 (0.2, 15.2)	1.3 (0.2, 10.4)
Specific Type of SLE Activity During Pregnancy		
Hematologic	**5.2 (1.8, 15.4)**	**3.4 (1.1, 10.6)**
Nephritis	3.4 (0.9, 12.2)	1.5 (0.4, 6.2)
Skin disease	1.5 (0.4, 6.5)	0.89 (0.2, 4.1)
Arthritis	3.4 (0.6, 17.7)	2.2 (0.4, 12.3)
Serositis	3.8 (0.7, 22.1)	2.7 (0.4, 17.0)

⁺ Adverse pregnancy outcome: pre-eclampsia, preterm delivery (<37 weeks), spontaneous abortion ≥12 weeks, or stillbirth
* OR from generalized linear mixed models to account for correlated data among 113 women carrying a total of 147 pregnancies
# Multivariable models adjusted for ethnicity (Hispanic/non-Hispanic), prior adverse pregnancy outcome, and corticosteroid and/or azathioprine use during pregnancy

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Disclosure: S. K. Tedeschi, None; **H. Guan**, None; **A. Fine**, None; **B. Lu**, None; **K. H. Costenbader**, Arthritis Care and Research, 5,International Journal of Clinical Practice, 5; **B. Bermas**, None.

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Abstract Number: 2532

Disease Activity in Women with Systemic Lupus Erythematosus during Pregnancy and the First Year Post Partum

Carina Gotestam Skorpen[1,2], Johan Skomsvoll[3], Inge-Margrethe Gilboe[4], Stian Lydersen[5] and Marianne Wallenius[3], [1]Dept of Neuroscience, Norwegian University of Science and Technology (NTNU), Trondheim, Norway, [2]Dept of Rheumatology, Trondheim

University Hospital, Norwegian National Advisory Unit on Pregnancy and Rheumatic Diseases, Trondheim, Norway, [3]Dept of Rheumatology, Trondheim University Hospital, National Advisory Unit on Pregnancy and Rheumatic Diseases, Trondheim, Norway, [4]Revmatologisk avdeling seksjon, Oslo universitetssykehus HF, Rikshospitalet, Oslo, Norway, [5]Regional Center for the health of children and adolescents, Norwegian University of Science and Technology (NTNU), Trondheim, Norway

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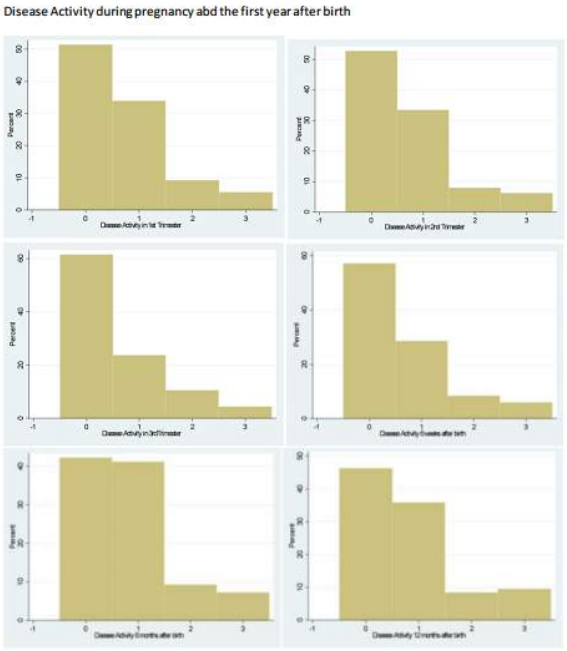
Disease Activity in women with SLE during pregnancy and the first year post partum

Background/Purpose: Disease activity measured by validated methods has been sparsely examined during and after pregnancy in women with SLE. The purpose was to examine disease activity by the Lupus Activity Index in Pregnancy(LAI-P) during pregnancy and in the first year post partum (pp).

Methods: RevNatus is a research database were patients are included nationwide at all departments of Rheumatology in Norway. Women who plan pregnancy or are already pregnant are included after informed consent. Data for the SLE- cohort was obtained in 2007 – 2015. LAI-P is a modified version of Lupus Activity Index (LAI), with a good ability to measure disease activity and diagnose disease flares in pregnancy. To explore variation in disease activity throughout pregnancy and after birth disease activity was measured by LAI-P/LAI at 6 time points: in each trimester, 6 weeks, 6 months and 12 months pp. A general mixed model was applied, using the last time point as reference, and comparing baseline (12 months post partum) with measures in each trimester, 6 weeks and 6 months pp. LAI and LAI-P measures disease activity on a continuous scale from 0 – 3; 0 indicating no disease activity and 3 indicating very high disease activity. As the assumption of normal distribution was not fulfilled, the dependant variable was categorized. We adjusted for mothers age in 1st trimester, disease duration, parity, prednisolon use and Plaquenil use .

Results: A total of 145 pregnancies in 127 women with SLE were included in the analysis. More than half (51,6%) of the measures on disease activity indicated remission and only 6,3% of the measures exceeded 0,5. A change in disease activity > 0,25 is perceived as a clinically relevant change, and the four categories chosen were no disease activity (LAI-P =0,), very low disease activity (LAI-P 0,01 – 0,25), low disease activity (LAI-P >0,25 – 0,50), and moderate disease activity or above (LAI-P>0,50), corresponding to category 0,1,2 and 3 in the figure. It illustrates the percentage of each category at the separate time points, showing that the disease activity declines during pregnancy and increase after delivery. There is a significantly increased odds of higher disease activity 6 and 12 months pp.



Conclusion: In 145 pregnancies in women with SLE, the disease activity decreased during pregnancy, but increased during the first year after delivery. This points to the importance of tight control not only during pregnancy, but also in the first year after delivery in women with SLE.

Disclosure: C. Gotestam Skorpen, None; **J. Skomsvoll**, None; **I. M. Gilboe**, None; **S. Lydersen**, None; **M. Wallenius**, None.

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Abstract Number: 2533

A Comparison of Pregnancy Outcomes before and after Lupus Diagnosis

Megan E. B. Clowse[1], Maria Dall'Era[2], Jennifer M. Grossman[3,4], Diane L. Kamen[5], Jerry McGwin[6], Robert Roubey[7] and Jill P. Buyon[8], [1]Rheumatology & Immunology, Duke University, Durham, NC, [2]University of California San Francisco School of Medicine, San Francisco, CA, [3]Medicine, UCLA David Geffen School of Medicine, Division of Rheumatology, Los Angeles, CA, [4]Rheumatology, UCLA, Los Angeles, CA, [5]Medicine, Medical University of South Carolina, Charleston, SC, [6]Deparment of Epidemiology, University Of Alabama at Birmingham, School of Public Health, Birmingham, AL, [7]University of North Carolina, Chapel Hill, NC, [8]Medicine, Division of Rheumatology, New York University School of Medicine, New York, NY
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Background/Purpose: The frequency of pregnancy complications, including miscarriage, stillbirth, preeclampsia, and preterm birth varies between lupus cohorts. This analysis compares pregnancy outcomes that occurred before and after the diagnosis of SLE.

Methods: We analyzed data from a registry of approximately 1700 patients with SLE from 17 lupus centers in the United States and Canada. At study enrollment, all women reported the outcomes of their prior pregnancies and, when known, the year of delivery. The timing of onset for each ACR criteria was obtained and the date of the accrual of the 4th criteria as the formal diagnosis of SLE. All pregnancies with a reported date of completion and in women with at least four ACR criteria at enrollment were included in this analysis. Pregnancies were divided into two groups: 1) pregnancies completed prior to the year of SLE diagnosis and 2) pregnancies delivered in the year of or the years following SLE diagnosis. Descriptive statistics, t- and chi square tests were used to compare the enrollment variables between the two groups. Generalized estimating equations were used to compare pregnancy outcomes between the groups to accommodate for multiple pregnancies in some women.

Results: A total of 2,277 pregnancies were reported in 860 women. Of these pregnancies, 499 occurred after the diagnosis of SLE, 1444 occurred before the diagnosis of SLE and 277 were unassigned due to no reported date of pregnancy completion. Compared to pre-SLE pregnancies, those after SLE diagnosis had a significantly lower risk of live birth and a higher risk of spontaneous abortions/miscarriage (see table). There was not a significant difference in the risks of fetal demise/stillbirth or in elective termination. Over a third of post-SLE pregnancies were low birth weight and/or delivered preterm. The risk of preterm birth and delivering a low birth weight infant was several-fold higher post-SLE than pre-SLE. While the pre-SLE risk of preeclampsia was similar to the general population, it was over 2.5-fold higher in the post-SLE pregnancies. The risk of preterm preeclampsia, a serious condition for both mother and infant, was almost 6-fold higher post-SLE diagnosis. Of the cases of preeclampsia, only 30.1% pre-SLE diagnosis were preterm, compared to 69.6% of those post-SLE.

Conclusion: Compared to pregnancies preceding the diagnosis of lupus, pregnancies following the diagnosis of lupus had higher risks of spontaneous abortion, preterm birth, low birth weight, preeclampsia, and preterm preeclampsia.

Table: Pregnancies before and after SLE diagnosis

Pregnancy Outcomes	Pregnancies after SLE	Pregnancies prior to SLE	Relative Risk (95% CI)	p-value
Total pregnancies	499	1444		
Live birth	316 (63.3%)	1054 (70.4)	0.87 (0.81-0.94)	<0.001
Fetal demise	13 (2.8%)	40 (2.8%)	0.89 (0.44-1.83)	0.77
Spontaneous abortions	99 (19.8%)	193 (13.4%)	1.48 (1.13-1.87)	<0.01
Termination	71 (14.2%)	157 (10.9)	1.29 (0.95-1.74)	0.09
Of LIVE BIRTHS: (with reported outcomes)	(n=316)	(n=1054)		
Low birth weight (<2500g)	108 (34.2%)	134 (12.7%)	2.69 (2.08-3.47)	<0.0001
Extreme low birth weight (<1500g)	29 (9.2%)	20 (1.9%)	4.84 (2.77-8.44)	<0.001
Preterm birth (<37 weeks)	123 (38.9%)	129 (12.2%)	3.18 (2.46-4.11)	<0.0001
Extreme preterm birth (<30 weeks)	24 (7.6%)	24 (2.2%)	3.45 (1.72-6.45)	<0.01
Neonatal lupus	8 (2.5%)	5 (0.5%)	5.34 (1.24-23.01)	0.03
Preeclampsia	56 (17.7%)	71 (6.7%)	2.58 (1.78-3.74)	<0.0001
Preterm & preeclampsia	39 (12.3%)	22 (2.1%)	5.91 (3.47-10.08)	<0.0001

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Increased Risk of Allergic Conditions in Children Born to Women with SLE

Julie Couture[1], Moshe Ben-Shoshan[1], Christian A. Pineau[2], Susan Scott[3], Ann E. Clarke[4], Sasha Bernatsky[2] and Evelyne Vinet[2], [1]McGill University Health Centre, Montreal, QC, Canada, [2]Divisions of Rheumatology and Clinical Epidemiology, McGill University Health Centre, Montreal, QC, Canada, [3]Clinical Epidemiology, Research Institute of the McGill University Health Centre, Montreal, QC, Canada, [4]Division of Rheumatology, University of Calgary, Calgary, AB, Canada

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Background/Purpose: Allergic conditions seem to be more prevalent in patients with SLE than in the general population. To date, a handful of small observational studies have evaluated the risk of allergic conditions in offspring born to women with SLE, showing a potentially increased likelihood. In a large population-based study, we aimed to determine if children born to SLE mothers have an increased risk of allergic conditions compared to children born to mothers without SLE.

Methods: The "Offspring of SLE mothers Registry (OSLER)" includes all women who had ≥1 hospitalization for delivery after SLE diagnosis, identified through Quebec's universal healthcare databases (1989-2009). OSLER also includes a randomly selected control group of women, matched at least 4: 1 for age and year of delivery, who did not have a diagnosis of SLE prior to or at the time of delivery. We identified children born live to SLE mothers and their matched controls, and ascertained allergic conditions (including asthma, allergic rhinitis, eczema, cutaneous allergy, urticaria, angioedema, and anaphylaxis) based on ≥1 hospitalization or ≥2 physician visit with a relevant diagnostic code. We performed multivariate analyses to adjust for maternal age, education, ethnicity, and obstetrical complications (i.e. preterm birth, small for gestational age), as well as calendar year of birth and sex of the child. Moreover, in a subsample analysis of children with maternal public drug coverage throughout pregnancy, we further adjusted for relevant maternal medications (i.e. antimalarials, corticosteroids, and immunosuppressive drugs).

Results: 509 women with SLE had 719 children, while 5824 matched controls had 8493 children. Mean follow-up was 9.1 (SD 5.8) years. As opposed to controls, children born to mothers with SLE experienced more allergic conditions [66.1% (95% CI 62.5, 69.5) versus 59.3% (95% CI 58.3, 60.4)]. In SLE offspring, the most frequently observed allergic conditions were eczema (43.8%) and asthma (28.5%), while anaphylaxis was the least frequent (0.8%). In control children, eczema (38.9%) and asthma (25.4%) were also the most frequent, while anaphylaxis was the least frequent (0.3%). In multivariate analysis (n=9212), children born to SLE mothers had an increased risk of allergic conditions versus control children (OR 1.36, 95% CI 1.14,1.61). In the subsample analysis further controlling for relevant maternal medications (n=1925), though a trend remained for increased risk of allergic conditions for offspring of SLE mothers versus controls, due to reduced sample size the 95% CI was wider and included the null value (OR 1.23; 95% CI 0.79, 1.91).

Conclusion: Compared to children from the general population, children born to women with SLE have an increased risk of allergic conditions. Genetic factors, shared environmental exposures, as well as in utero exposure to maternal autoantibodies and cytokines might be at play. Further research is warranted to investigate the relative importance of these potential predisposing factors.

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Increased Direct Healthcare Costs in SLE Pregnancies

Cristiano Moura[1], Sasha Bernatsky[2], Yvan St. Pierre[3], Susan Scott[3], Christian A. Pineau[4], Ann E. Clarke[5] and Evelyne Vinet[4], [1]Research Institute of the McGill University Health Centre, Montreal, QC, Canada, [2]Division of Clinical Epidemiology, Research Institute of the McGill University Health Centre, Montreal, QC, Canada, [3]Clinical Epidemiology, Research Institute of the McGill University Health Centre, Montreal, QC, Canada, [4]Divisions of Rheumatology and Clinical Epidemiology, McGill University Health Centre, Montreal, QC, Canada, [5]Division of Rheumatology, University of Calgary, Calgary, AB, Canada

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Background/Purpose: Although adverse obstetrical complications are more frequent in SLE women, no one has evaluated healthcare

costs during SLE pregnancies. Thus, we aimed to evaluate if SLE pregnancies result in higher direct healthcare cost components (including physician services during pregnancy and neonatal period, and delivery-related costs) compared to pregnancies from the general population.

Methods: We used data from the "Offspring of SLE mothers Registry (OSLER)" including all women who had ³1 hospitalization for delivery after SLE diagnosis, identified through Quebec's healthcare databases (1989-2009) which provide information on all physician services and hospitalizations in the province. OSLER also includes a randomly selected control group of women matched ³4:1 for age and year of delivery. We determined average physician costs for the SLE and non-SLE pregnancies from first gestational week until birth and the neonatal period (for both mother and child) from birth until postnatal gestational age of 44 weeks. We also estimated average hospitalization costs for the SLE and non-SLE deliveries (including inpatient physician costs). Costs were normalized to 2014 Canadian dollars.

We performed multivariate random effect log-linear and linear regression analyses to establish whether costs during pregnancy and the neonatal period were associated with SLE status, adjusting for relevant covariates.

Results: We identified 509 women with SLE who had 712 deliveries and 5824 controls who had 8363 deliveries during the study period. SLE deliveries occurred at a lower mean gestational age compared to control deliveries, and birth weight was lower in SLE offspring as opposed to unexposed offspring (Table 1). In addition, the maternal length of hospitalization for delivery was longer for SLE deliveries versus controls (Table 1).

Compared to control pregnancies, we observed substantially higher costs for both physician services and hospital stays for delivery, resulting in higher costs for SLE pregnancies [10 833$ vs 6 828$; difference 4 004$ (95% CI 3 300, 4 709)]. In multivariate analyses, SLE pregnancies had a 32% (95% CI 29, 36) increment in costs, or alternatively a 3 690$ (95% CI 2 814, 4 567) increase in costs, compared to control pregnancies (Table 2).

Conclusion: Compared to pregnancies from the general population, SLE pregnancies are associated with substantially higher direct healthcare costs, including costs for physician services and hospitalization for delivery. Our study is the first to highlight the economic burden of SLE pregnancies, identifying an area of heavy healthcare use.

Table 1. Characteristics of the mothers, deliveries, and offspring

	SLE Mean/%	**Controls** Mean/%	**Difference (SLE - controls)** Mean/% (95% CI)
Mothers (at first recorded delivery)			
n	509	5824	
Age at delivery (years)	29.8	29.9	-0.1 (-0.5, 0.4)
Education			
Years of education	14	13.8	0.2 (-0.1, 0.5)
Post-secondary education (%)	66.7	61.1	5.6 (1.2, 9.9)
16 years or more of education (%)	32.9	31.8	1.1 (-3.3, 5.4)
Married or common law (%)	91.6	92.9	-1.3 (-4.0, 1.4)
White (%)	71.3	79.2	-7.9 (-12.0, -3.9)
Rural residence (%)	16.9	20.8	-3.9 (-7.4, -0.5)
Comorbidities (%)			
Pre-gestational hypertension	6.1	1	5.1 (3.0, 7.2)
Pre-gestational diabetes	2.9	1.3	1.7 (0.2, 3.2)
Asthma	4.7	2.6	2.1 (0.3, 4.0)
Depression	1.6	0.4	1.1 (0.03, 2.2)
Deliveries			
n	712	8363	
Birth order > 1 (%)	56.9	72.2	-15.3 (-19.1, -11.6)
Twins or triplets (%)	1	1.5	-0.5 (-1.3, 0.2)
Gestational age (weeks)	37.7	38.9	-1.2 (-1.4, -1.0)
Length of stay at delivery (days)	5.2	3.3	1.9 (1.5, 2.4)
Delivery hospitalization costs (Can $)	9159	6141	3018 (2340, 3696)
Physician service costs over 44 weeks (Can $)	1674	687	986 (876, 1096)
Total costs (sum of 2 previous rows) (Can $)	10833	6828	4004 (3300, 4709)
Offspring			
n	719	8493	
Male (%)	55.9	51.5	4.4 (0.6, 8.2)
Birth weight (grams)	2976	3367	-391 (-445, -338)

Table 2. Multivariate analyses of SLE effect on direct healthcare costs related to pregnancy, including physician services and hospitalization for delivery (n=9075)

Covariates	% variation in total costs	Total costs in $*
SLE status		
Non-SLE	Reference	Reference
SLE	32 (29, 36)	3690 (2814, 4567)
Age at delivery (years)	1 (1, 1)	76 (53, 100)
Education		
<16 years	Reference	Reference
≥16 years	-3 (-5, -1)	-96 (-365, 173)**
Marital status		
Single	Reference	Reference
Married or common law	-5 (-9, -2)	-553 (-1021, -85)
Race/Ethnicity		
Other	Reference	Reference
White	4 (1, 6)	150 (-134, 434)**
Region of residence		
Urban	Reference	Reference
Rural	5 (3, 7)	380 (145, 616)
Pre-gestational hypertension		
No	Reference	Reference
Yes	33 (25, 40)	3781 (1904, 5658)
Pre-gestational diabetes		
No	Reference	Reference
Yes	25 (18, 31)	2082 (590, 3574)
Asthma		
No	Reference	Reference
Yes	12 (7, 17)	1306 (453, 2159)
Birth order		
1	Reference	Reference
≥2	-19 (-21, -17)	-1353 (-1557, -1150)
Multiple birth		
Singleton	Reference	Reference
Twins or triplets	56 (49, 63)	5265 (3822, 6710)

*Costs are normalized to 2014 Canadian dollars

** Predictors do not have a statistically significant effect

Abstract Number: 2536

The Role of Race/Ethnicity and SES in Adverse Pregnancy Outcome in SLE and Apl

Sancia Ferguson[1], Elianna Kaplowitz[2], Laura Trupin[3], Edward H. Yelin[4], Patricia P. Katz[3,5] and Jane E. Salmon[6],
[1]Medicine/Rheumatology, University of California - San Francisco, San Francisco, CA, [2]Hospital for Special Surgery, New York, NY, [3]Medicine/Rheumatology, University of California San Francisco, San Francisco, CA, [4]Medicine/Rheumatology, UC San Francisco, San Francisco, CA, [5]Arthritis Research Group, University of California San Francisco, San Francisco, CA, [6]Division of Rheumatology, Hospital for Special Surgery, Weill Cornell Medical College, New York, NY

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Background/Purpose: Women with Systemic Lupus Erythematosus (SLE) and Anti-Phospholipid Antibodies (aPL) have pregnancies with higher rates of preterm labor, preeclampsia, and fetal loss than healthy women. While 80% of pregnancies in SLE patients with quiescent disease are uncomplicated by adverse pregnancy outcomes (APOs), limited data exist on differences in pregnancy outcomes by race/ethnicity. In this study we examined rates of APOs according to race/ethnicity among women with SLE with and without aPL

and, if racial/ethnic differences in APO existed, whether socioeconomic status (SES) accounted for those differences

Methods: Analyses use data from the PROMISSE study, a multicenter, prospective observational study (2003 – 2014) of pregnant women 18 – 45 years with SLE and aPL. Subjects with SLE were enrolled by 12 weeks and subjects with aPL by 18 weeks at 9 U.S. and 1 Canadian site. Women with blood pressures of >140/90, taking prednisone ≥ 20 mg daily, or with active renal disease (> 1 gram on 24 hour urinalysis or spot, RBC casts, Cr >1.2 mg/dl) were excluded. APOs were defined as at least one of the following: fetal death after 12 weeks; neonatal death prior to hospital discharge; preterm delivery < 36 weeks due to gestational hypertension, preeclampsia or placental insufficiency; small for gestational age (<5th percentile). We examined the role of age, race/ethnicity (non-Hispanic white vs. other), self-reported disability status, percentage of visits attended, and measures of SES including level of educational attainment and median income by zip code, in a series of bivariate and multivariate logistic regression models, clustering by site. For all analyses the referent group was white patients with SLE alone.

Results: Data were available for 408 women for the analyses; 6 had missing APO data and were omitted from the analysis. Mean age was 30.9 years and 50% were racial/ethnic minorities. Seventeen percent of non-Hispanic whites and 29% of minorities met criteria for APO. Minorities with SLE alone had higher odds of APO than their white counterparts, a difference which diminished after adjustment for covariates, including measures of SES such as level of educational attainment and median income by zip code. Both white and minority women with SLE and aPL had higher rates of APO compared to white patients with SLE alone. In this SLE and aPL group, the risk of APO in minority women was more than double that of white women, and these differences remained after adjustment for covariates.

Conclusion: In minority women with SLE alone, SES appears to account for a large portion of the elevated risk of APO. In contrast, in minority women with SLE and aPL, the elevated risk of APO persisted after adjustment for SES, and large disparities in APO remained. Further evaluation of disparities including clinical measures and more robust measures of SES are needed for better understanding.

Table: Unadjusted and Adjusted Odds of Adverse Pregnancy Outcomes in Women with SLE with and without APL

	Unadjusted		Adjusted*	
	White	Minority	White	Minority
SLE	reference	2.0 (1.0,4.1)	reference	1.6 (0.7,3.4)
SLE and aPL	3.3(1.4,7.1)	8.2 (2.3, 29.4)	3.7 (1.7,8.2)	7.3 (1.8,30.2)

Reported odds Ratio (CI).

Race: individuals not self-identifying as non-Hispanic white were categorized as minorities.

*Model adjusted for (1) Education: HS education or less (completed high school education or less), beyond HS (education beyond high school). (2) Age (3) Rheumatology visits: percentage of rheumatology study visits attendance (4) Median income: derived from zip code U.S and Canadian census data. (5) Disabled: self reported disability status. SLE defined as ≥ 4 revised ACR criteria.

aPL defined as (at least one of the following on two occasions: anti-cardiolipin IgM or IgG ≥ 40 MPL units, anti-β2 glycoprotein IgM or IgG ≥ 40 MPL, positive lupus anticoagulant), both SLE and aPL:

Unit, Karolinska Institutet, Stockholm, Sweden

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Background/Purpose: There is limited information regarding medication use patterns among pregnant women with systemic lupus erythematosus (SLE). We aimed to characterize trends of medications used to treat SLE before, during, and after pregnancy, and to compare the use of other commonly used medications among SLE pregnancies with non-SLE pregnancies.

Methods: Women with pregnancies ending in live birth or stillbirth were identified from the Swedish Medical Birth Register (MBR,

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Abstract Number: 2537

Prescription Medication Use in Sweden Among Pregnant Women with Systemic Lupus Erythematosus and General Population Comparators

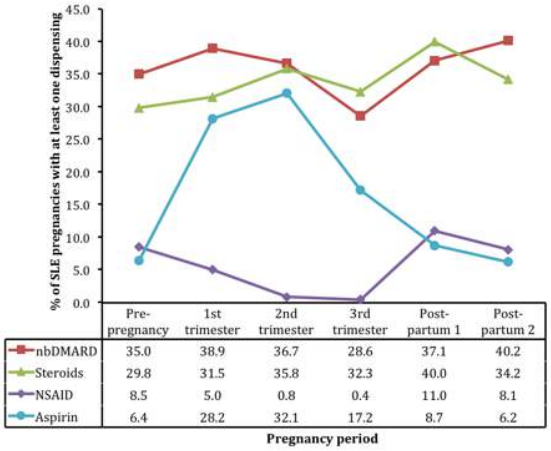
Kristin Palmsten[1], Julia F Simard[2,3], Christina D Chambers[1,4] and Elizabeth V Arkema[5], [1]Department of Pediatrics, University of California, San Diego, La Jolla, CA, [2]Division of Epidemiology, Health Research and Policy Department, and Division of Immunology & Rheumatology, Department of Medicine, Stanford School of Medicine, Stanford, CA, [3]Clinical Epidemiology Unit, Dept of Medicine, Karolinska Institutet, Stockholm, Sweden, [4]Department of Family Medicine and Public Health, University of California, San Diego, La Jolla, CA, [5]Department of Medicine, Clinical Epidemiology

2006-2012). Prevalent SLE during pregnancy was defined as 1) ³2 SLE ICD coded visits in inpatient or outpatient care in the National Patient Register (NPR) including ³1 SLE code from a specialist and ³1 SLE discharge before pregnancy or 2) ³1 SLE code from a specialist in the NPR and ³1 self-reported diagnosis of SLE in the MBR. Women without SLE were sampled from the Total Population Register. The Prescribed Drug Register was used to identify prescription medications dispensed in the 3 months pre-pregnancy, during pregnancy, each trimester, the 3 months after delivery (postpartum 1), and the 3-6 months after delivery (postpartum 2). No information was available on intravenous infusions and medications obtained over-the-counter. We reported the prevalence of non-biologic disease modifying antirheumatic drugs (nbDMARDs), systemic corticosteroids, and nonsteroidal anti-inflammatory drugs (NSAIDs; aspirin reported separately) in SLE pregnancies by pregnancy period. Then we calculated prevalence estimates of other medications (excluding vitamins) that were dispensed during pregnancy to ³10% of women with SLE and for the same medications among non-SLE pregnancies.

Results: We identified 483 pregnancies from 391 women with prevalent SLE and 5,723 pregnancies from 4,322 women without SLE. In SLE pregnancies, 49.3% had ³1 dispensing for nbDMARDs during pregnancy; the prevalence was 48.0% for corticosteroids, 40.8% for aspirin, and 6.0% for other NSAIDs and varied by period (Figure 1). Shorter exposure opportunity for preterm births contributed to decreased prevalence in the 3rd trimester. The prevalence of common medications among SLE pregnancies was 1.2 to 20-fold higher than among non-SLE pregnancies: dalteparin (20.9% vs 1.0%), paracetamol (18.2% vs 2.9%), levothyroxine (15.9% vs 4.9%), phenoxymethylpenicillin (14.3% vs 11.6%), pivmecillinam (10.8% vs 4.7%), and omeprazole (10.4% vs 2.3%).

Conclusion: In nearly half of SLE pregnancies from this population-based study, women were dispensed nbDMARDs and corticosteroids. Other commonly used medications among women with SLE had far higher prevalence estimates versus the general population. Research regarding the benefits and risks of these commonly used medications on SLE pregnancies, breast milk, and long-term offspring outcomes is needed.

Figure. Proportion of SLE pregnancies with ³1 dispensing for nbDMARDs, corticosteroids or NSAIDs by period.



	Pre-pregnancy	1st trimester	2nd trimester	3rd trimester	Post-partum 1	Post-partum 2
nbDMARD	35.0	38.9	36.7	28.6	37.1	40.2
Steroids	29.8	31.5	35.8	32.3	40.0	34.2
NSAID	8.5	5.0	0.8	0.4	11.0	8.1
Aspirin	6.4	28.2	32.1	17.2	8.7	6.2

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Abstract Number: 2538

A Population-Based Assessment of Induced Abortions in Women with Systemic Lupus Erythematosus

Evelyne Vinet[1], Emily McDonald[2], Susan Scott[3], Christian A. Pineau[1] and Sasha Bernatsky[4], [1]Divisions of Rheumatology and Clinical Epidemiology, McGill University Health Centre, Montreal, QC, Canada, [2]McGill University, Montreal, QC, Canada, [3]Clinical Epidemiology, Research Institute of the McGill University Health Centre, Montreal, QC, Canada, [4]Division of Clinical Epidemiology, Research Institute of the McGill University Health Centre, Montreal, QC, Canada

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Background/Purpose: SLE women with unplanned pregnancies might be at increased risk of both disease and pregnancy complications. Until now, there has been no population-based estimate of the induced abortion (IA) rate in women with SLE, and no one has explored disease-related factors that might affect IA rates. Thus, we determined the rate of IA in women with SLE and compared this with general population rates. In addition, in women with SLE, we investigated potential disease-related predictors of IA.

Methods: We identified women with SLE using Quebec's universal healthcare databases (01/1996-12/2011). All women with SLE, 15-45 years, were identified based on ³1 hospitalization with a SLE diagnosis, or ³2 physicians' claims for SLE within any 2-to-24-month period. We determined the number of IA during the interval, as defined by procedure codes or physicians' claims for IA. We applied age-specific and relevant calendar-period IA rates to the observed years of follow-up to determine the expected number of IA. We then calculated the standardized incidence ratio (SIR) of observed to expected IA.

To investigate predictors of IA in SLE women, we conducted a nested-case control analysis, where SLE women with an IA (i.e. cases) were matched to ³1 control SLE women (i.e. without an IA at the index date) for age, calendar time, and cohort entry. Within this nested case-control cohort, we performed a multivariate conditional logistic regression including teratogenic (i.e. mycophenolate mofetil, methotrexate, leflunomide, cyclophosphamide) and non-teratogenic (i.e. azathioprine, cyclosporine, sulfasalazine) immunosuppressive exposure, corticosteroid use, and hospitalization for SLE in the previous year. Only SLE women covered by the public drug plan for ³16 weeks prior to the index date were included in this multivariate analysis.

Results: We observed 293 IA among 2508 women with SLE, yielding an incidence rate of 17.1 IA per 1000 person-years (95% CI 15.2, 19.2). Compared to the general population, we were unable to detect a difference among women with SLE in the number of IA (SIR 1.10; 95% CI 0.98, 1.24). In the multivariate analysis, including 78 cases and 1066 corresponding SLE controls, we did not see higher rates of IA among women exposed to teratogenic immunosuppressives (RR 0.37; 95% CI 0.13, 1.07) and those using corticosteroids (RR 0.67; 95% CI 0.39, 1.16). Results were inconclusive for the effect of non-teratogenic immunosuppressive use (RR 1.12; 95% CI 0.49, 2.57) and prior hospitalization for SLE (RR 1.32; 95% CI 0.80, 2.17) on IA.

Conclusion: Our findings suggest that women with SLE have a similar rate of IA compared to the general population. Although teratogenic drug exposure was not necessarily associated with a higher IA rate, the numbers do indicate that some unplanned pregnancies occur in women exposed to teratogenic immunosuppressives. Our results should prompt further research on contraceptive counseling and practices in women with SLE.

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Abstract Number: 2539

The Validity and Reliability of Turkish Version of the Jenkins Sleep Scale in Rheumatoid Arthritis

M Tuncay Duruoz[1], Cagri Ünal[2], Firat Ulutatar[3], Canan Sanal Top[2] and Osman Hakan Gunduz[4], [1]Dept of PM&R, Rheumatology Clinic, Marmara University Medical School, Istanbul, Turkey, [2]PM&R, Marmara University Medical School, Istanbul, Turkey, [3]Physical Medicine and Rehabilitation Department, Marmara University Medical School, Istanbul, Turkey, [4]Physical Medicine and Rehabilitation, Marmara University School of Medicine, Istanbul, Turkey

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Background/Purpose: The Jenkins Sleep Scale has 4 questions to assess the estimation of sleep problems in clinical research. It was developed in USA (1).

Aim: To assess the validity and reliability of the Jenkins Sleep Scale (JSS) in a Turkish population with Rheumatoid Arthritis (RA).

Methods: The Jenkins Sleep Scale was translated from English to Turkish with back translation method. Patients with RA according to ACR 2010 criteria were recruited into the study consecutively. The internal consistency (Cronbach's alpha) was assessed for reliability. Face validity and construct validity (convergent and divergent validities) were evaluated to assess its usefulness in Turkish population. The relation of the JSS with the Pittsburgh Sleep Quality Index (PSQI), Multidimensional Assessment of Fatigue (MAF) scale, subgroups of Nottingham Health Profile (NHP) (energy level-EL, pain-P, emotional reactions-ER, sleep-S, social isolation-SI, physical mobility (PM) and Health Assessment Questionnaire (HAQ) were assessed for convergent validity. The relation of the JSS with age, disease duration, VAS-patient global and DAS28 were assessed for divergent validity. Spearman's correlation coeficient (rho) was used to assessed the relation between quantitative parameters. $P<0.05$ was accepted as significant.

Results:

Sixtyone RA patients (48 female, 13 male) with 50.52 (SD:10.84) mean of age were recruited into the study. The Cronbach's alpha of JSS was 0.80. All questions and the answer choices of the JSS were well understood by patients which showed the face validity. The JSS has good correlation with functional parameters (convergent) and it has poor or not significant correlations with non functional parameters (divergent) (Table). It means that JSS has good construct validity. The JSS has the best correlation with the Pittsburgh Sleep Quality Index (rho=0.76).

Convergent validity of JSS	**Spearman's (rho)**	**Significance (p)**
PSQI	0.76	<0.0001
NHP-EL	0.56	<0.0001
NHP-P	0.57	<0.0001
NHP-ER	0.60	<0.0001
NHP-S	0.45	<0.0001
NHP-SI	0.55	<0.0001
NHP-PM	0.56	<0.0001
HAQ	0.55	<0.0001
MAF	0.47	<0.0001
Divergent validity of JSS	**Spearman's (rho)**	**Significance (p)**
Age	0.21	0.1130
Disease duration	0.22	0.0860
VAS-patientglobal	0.38	0.002
DAS28	- 0.044	0.73

Conclusion: The Jenkins Sleep Scale is valid and reliable instrument in RA patients in a Turkish population. It is practical and non time consuming scale to use in daily practice and the clinical researches.

1. Jenkins CD, Stanton BA, Niemcryk SJ, Rose RM. A scale for the estimation of sleep problems in clinical research. J Clin Epidemiol. 1988;41(4):313-21

Disclosure: M. T. Duruoz, None; **C. Ünal**, None; **F. Ulutatar**, None; **C. Sanal Top**, None; **O. Hakan Gunduz**, None.

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Abstract Number: 2540

Construct Validity of the Promis-29 in Systemic Sclerosis: Results from the Scleroderma Patient-Centered Intervention Network (SPIN) Cohort

Linda Kwakkenbos[1], Brett D. Thombs[1], Susan J. Bartlett[2], Marie-Eve Carrier[3], Marie Hudson[1], Luc Mouthon[4], Vanessa L. Malcarne[5], Maureen Sauvé[6], **Dinesh Khanna**[7] and SPIN investigators, [1]McGill University, Montreal, QC, Canada, [2]Medicine, McGill University, Montreal, QC, Canada, [3]Lady Davis Institute for Medical Research, Jewish General Hospital, Montreal, QC, Canada, [4]Paris Descartes University, UPRES-EA 4058, Department of Internal Medicine, Cochin Hospital, Paris, France, [5]SDSU/UC San Diego Joint Doctoral Program in Clinical Psychology, San Diego, CA, [6]Scleroderma Societies of Canada and Ontario, Hamilton, QC, Canada, [7]Division of Rheumatology, University of Michigan, Ann Arbor, MI

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Background/Purpose: The Patient-Reported Outcomes Measurement Information System (PROMIS¨) initiative is a cooperative research program designed to develop, evaluate, and standardize item banks to measure patient-reported outcomes across medical conditions. The PROMIS-29 measure contains 29 items, which include four items each for domains reflecting physical function, anxiety, depression, fatigue, sleep disturbance, pain interference, and ability to perform social roles, plus a single item on pain intensity. Scores are standardized with a mean of 50 and standard deviation (SD) of 10. Higher scores represent more of the domain being measured (e.g., greater sleep disturbance, greater ability to perform social roles). The purpose of this study was to examine feasibility and construct validity of the PROMIS29 in patients with systemic sclerosis (SSc) enrolled in a large multinational study.

Methods: English-speaking patients with SSc and ³18 years of age were enrolled in the Scleroderma Patient-centered Intervention Network (SPIN) Cohort between July 2014 and June 2015 from 19 centers across Canada, the USA and the UK. Baseline medical data are provided by the enrolling physician, and SPIN Cohort patients completed the PROMIS-29 at baseline. Floor and ceiling effects were defined as >15% of patients having the lowest or highest possible domain score, respectively. To examine convergent validity of domains, hypotheses were formulated a-priori about the associations of domains and legacy measures. The magnitude of the correlations was interpreted as small (|r| ² 0.3), moderate (0.3 < |r| < 0.5), or large (|r| ³ 0.5).

Results: In total, 473 patients were included in analyses. Mean age was 55 years (SD=11.9) and mean time since onset of the first non-Raynaud symptom was 11.8 years (SD= 8.7). Most patients were female (n=411, 86.9%) and diagnosed with limited SSc (n=277, 59.1%). Means for the PROMIS-29 domains were: function 42.8 (SD=8.7), anxiety 51.5 (SD=9.6), depression 50.9 (SD=9.2), fatigue 55.9 (SD=11.2), sleep 51.8 (SD=5.0), roles 47.5 (SD=9.6), pain interference 55.9 (SD=9.8), and pain intensity 3.7 (SD=2.7). There was a floor effect for anxiety (33.6%) and depression (37.6%), and ceiling effects for function (20.5%), roles (15.2%) and pain interference (23.7%). Most hypotheses were confirmed (7 of 9) and all were in the hypothesized direction (Table 1).

Conclusion: Results of our study support the construct validity of the PROMIS-29 in patients with SSc. Future studies should examine the influence of floor- and ceiling effects for some domains, as well as other psychometric properties of the measure.

Table 1. Hypotheses and correlations of PROMIS-29 domains and legacy instruments

PROMIS-29 domain	Legacy instrument(s)	Hypothesis for correlation[1]	Pearson correlation [95% CI]
Function	Health Assessment Questionnaire-Disability Index (HAQ-DI)	Large, negative	-0.79 [-0.82, -0.75]
	Cochin Hand Function Scale	Large, negative	-0.57 [-0.63, -0.50]
Anxiety	Brief Fear of Negative Evaluation	Moderate, positive	0.49 [0.42, 0.55]
Depression	Patient Health Questionnaire (PHQ)-8	Large, positive	0.72 [0.68, 0.76]
Fatigue	PHQ-8 item 4 (Feeling tired)	Large, positive	0.80 [0.76, 0.83]
Sleep disturbance	PHQ-8 item 3 (Trouble sleeping)	Large, positive	0.55 [0.48, 0.61]
Social roles	HAQ-DI	Moderate, negative	-0.64 [-0.69, -0.59]
Pain interference	Pain interference numeric rating scale	Large, negative	-0.82 [0.79, 0.85]
Pain intensity	Pain severity numeric rating scale	Large, positive	0.89 [0.87, 0.91]

[1]The magnitude of the correlations was interpreted as small (|r| ² 0.3), moderate (0.3 < |r| < 0.5), or large (|r| ³ 0.5).

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Abstract Number: 2541

Improving Adherence with Treat to Target in Rheumatoid Arthritis through a Learning Collaborative: Rationale and Design of the Traction Trial

Daniel H. Solomon[1], Sara Lee[2], Agnes Zak[2], Jen Agosti[3], Asaf Bitton[4], Liana Fraenkel[5], Leslie Harrold[6], Elena Losina[7], Bing Lu[8], Theodore Pincus[9], Josef S. Smolen[10] and Jeffrey N. Katz[11], [1]Rheumatology, Brigham and Women's Hospital, Boston, MA, [2]Brigham and Women's Hospital, Boston, MA, [3]JRA Consulting, Andover, MA, [4]Medicine, Brigham and Women's Hospital, Boston, MA, [5]Medicine, Yale University School of Medicine, New Haven, CT, [6]Dept of Medicine, UMass Medical School, Worcester, MA, [7]Orthopedics, Brigham and Women's Hospital, BU School of Public Health and Harvard Medical School, Boston, MA, [8]Rheumatology Immunology & Allergy, Brigham & Women's Hospital, Boston, MA, [9]Medicine-Rheumatology, NYU Hospital for Joint Diseases, New York, NY, [10]Medical University of Vienna, Vienna, Austria, [11]Brigham and Women's Hospital and Harvard Medical School, Boston, MA

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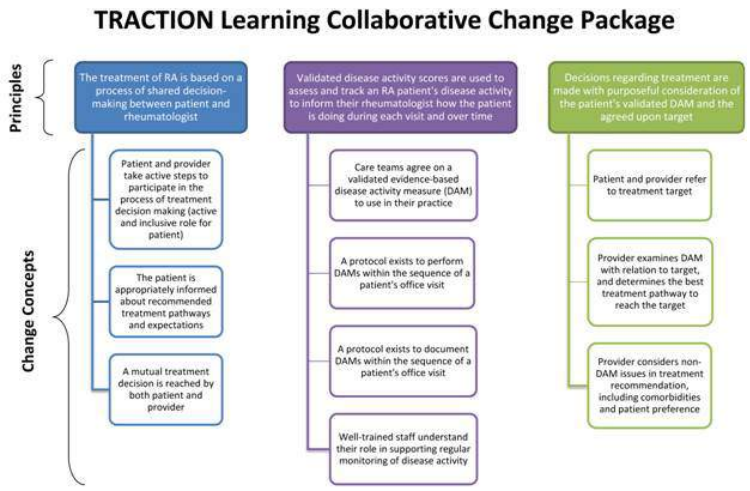
Background/Purpose: Treat to target (TTT) is a recommended paradigm in the management of rheumatoid arthritis (RA). However, various data sources suggest that TTT is implemented in only a minority of routine care settings in the US. We designed a cluster-randomized controlled trial of a Learning Collaborative (LC) to facilitate uptake of TTT.

Methods: We recruited 11 rheumatology practices from across the US using sampling. They were randomized into two groups: one is receiving the LC intervention in Phase 1 (months 1-9) and the second formed a wait-list control group to receive the intervention in Phase 2 (months 10-18). The sites were permitted to choose a disease activity index from among 6 approved by an ACR committee. The LC intervention is a modified version of the Institute for Healthcare Improvement's Breakthrough Series Collaborative method, using the Model for Improvement, a Change Package (see Figure), and monthly metrics. Phase 1 intervention practices were brought together for one face-to-face learning session. Continuous collaboration and process improvement has been facilitated by several means: monthly webinars to share results of Plan-Do-Study-Act (PDSA) cycles; a web-based tool for sites to share aggregated site-level data and PDSA results; and monthly improvement metrics collected at each practice. The wait-list control group sites have had no TTT interventions during Phase 1.

The primary trial outcome is degree of uptake of ("adherence with") TTT as measured by chart review of select patients within participating sites, comparing the differences in adherence from baseline to end of Phase 1 between patients in intervention and control practices. Specifically, the chart reviews measures 4 aspects of TTT: evidence of shared decision-making, description of a treatment target, measurement of disease activity, and response to disease activity (i.e., change in treatment if not at target or reason for no change). Secondary outcomes include: resource use, adverse events, disease activity, and sustained adherence with TTT during Phase 2.

Results: Phase 1 will finish in October 2015. All intervention sites have remained engaged in the LC with a total of 38 providers (31 physicians, 6 nurses and 1 pharmacist) participating. The primary trial outcome measures will be collected by the study team through medical record review at completion of Phase 1.

Conclusion: If this LC is an effective means for improving uptake of TTT in rheumatology practices, this process could serve as a way of disseminating TTT more widely. As well, LCs may be considered for other rheumatology quality improvement efforts.



Disclosure: D. H. Solomon, None; **S. Lee**, None; **A. Zak**, None; **J. Agosti**, None; **A. Bitton**, None; **L. Fraenkel**, None; **L. Harrold**, Corrona LLC, 3,Pfizer, AstraZeneca, 2,Genentech., 5; **E. Losina**, None; **B. Lu**, None; **T. Pincus**, Health Report Services, Inc, 4; **J. S. Smolen**, Pfizer Inc, 2,Pfizer Inc, 5; **J. N. Katz**, None.

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Abstract Number: 2542

The Multidimensional Assessment of Fatigue Scale: A 25-Year Review and Evaluation

Basia Belza[1], Christina Miyawaki[2,3], Minhui Liu[1], Xi Zhang[4] and Melissa Fessel[1], [1]University of Washington School of Nursing, Seattle, WA, [2]University of Houston Graduate College of Social Work, Houston, TX, [3]Group Health Research Institute, Seattle, WA, [4]Henan Provincial People's Hospital, Zhengzhou, China

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Background/Purpose:

The Multidimensional Assessment of Fatigue (MAF) scale was originally developed in 1990 for adults with rheumatoid arthritis. Since then, the MAF has been translated to 25 languages and used for patients with various diseases due to its relatively short, thus low burden for patients and potential for clinical usefulness. The purpose of this paper was to comprehensively review the MAF with particular attention to clinical relevance, reliability, and validity, and evaluate how the MAF has been used over the past 25 years.

Methods:

Database, and hand searches were conducted. We searched databases including CINAHL Plus, Health Source Nursing, MEDLINE, PsycINFO, and PubMed using multidimensional assessment of fatigue or MAF as key terms. All selected articles were peer-reviewed, published papers in English from January 1993 through May 2015. We located 463 articles on the topic and 98 articles met inclusion criteria.

Results:

Of the 98 articles, 79 (81%) were empirical studies and 19 (19%) were reviews/evaluations. The main purposes of the empirical studies were to 1) measure the level of fatigue in different types of disease; 2) investigate relationships between fatigue and health-related variables; and 3) assess fatigue as the outcome to evaluate efficacy, effectiveness and safety of interventions. The review/evaluation studies were comparisons of the MAF with other fatigue measures. Research was conducted in 17 countries (U.S., Turkey, U.K., Korea, Taiwan) and tested in 9 different languages (English, Turkish, Italian, Korean, Chinese) for 24 different diseases

(rheumatic diseases, osteoarthritis, depression, HIV, ankylosing spondylitis, cancer, chronic fatigue syndrome, fibromyalgia, multiple sclerosis, systemic lupus erythematosus). The sample sizes varied from 12 to 2193. The mean of global fatigue index ranged from 18.7 to 44.6, and its Cronbach's alpha was, on average, 0.93 (0.88 to 0.99). Strengths of the MAF were noted as an easy-to-use instrument with good reliability and validity in various populations, its multidimensionality, and adaptability in different languages while weakness was the needs of further validation of fatigue in more diseases and cultures.

Conclusion:

We conclude that the MAF is an appropriate assessment tool to measure fatigue, as well as intervention effectiveness in various diseases in clinical settings. Its feasibility with good internal consistency, adaptability with consistent, high reliability and validity, sensitivity to the levels of fatigue, and multidimensionality have allowed its applicability for international use. Continued use, translations, and assessments in different populations will enhance the cultural sensitivity as well as comprehensiveness of the MAF and strengthen its validity as a culturally sensitive fatigue instrument.

Disclosure: B. Belza, None; **C. Miyawaki**, None; **M. Liu**, None; **X. Zhang**, None; **M. Fessel**, None.

Abstract Number: 2543

Content Validity of the Improved Health Assessment Questionnaire in Knee Osteoarthritis Patients

Mei Chung[1], Shanshan Liu[2], Zhuxuan Fu[2], Lori Lyn Price[3], John B. Wong[4] and Chenchen Wang[5], [1]Department of Public Health and Community Medicine, Tufts University School of Medicine, Boston, MA, [2]Public Health and Community Medicine, Tufts University School of Medicine, Boston, MA, [3]Clinical Care Research, Tufts Medical Center, Boston, MA, [4]Medicine/Clinical Decision Making, Tufts Medical Center, Boston, MA, [5]Rheumatology, Tufts Medical Center, Bosotn, MA

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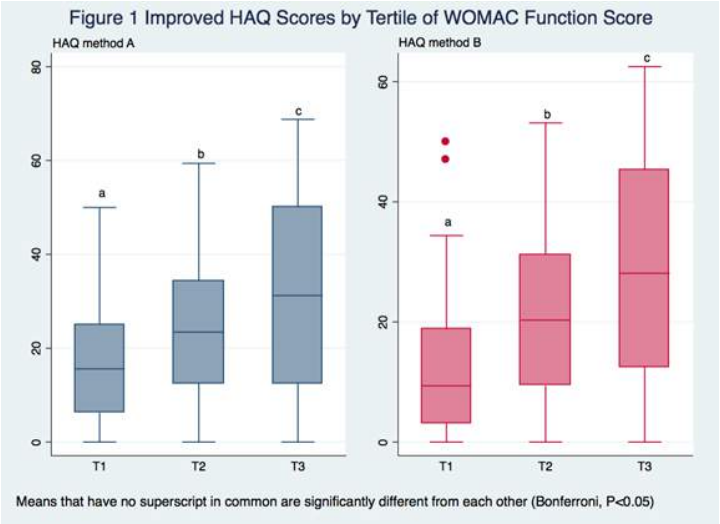
Background/Purpose: Developed in general population, rheumatoid arthritis and osteoarthritis patients, the Improved Health Assessment Questionnaire (iHAQ, formerly PROMIS HAQ) assesses physical function. The objective of this study was to evaluate the content validity of the iHAQ in patients with knee OA.

Methods: In a cross-sectional analysis using the baseline data from a Tai Chi versus physical therapy for knee osteoarthritis trial, persons meeting ACR criteria for knee OA patients self-administered the Improved HAQ, Patient Global Health Visual Analog Scale (Global VAS score range 0-10, 10=poor health), SF-36 survey (range 0-100, 100=good health), and WOMAC (range 0-1700, 1700=worst). We calculated two iHAQ scores having the same score range (0-100, 100=poor function) but based on the 20 items (method A) or 16 items (method B). To evaluate content validity, the iHAQ was compared with Global VAS, SF-36 Physical Function and Mental Health Component (PCS and MCS), and WOMAC pain and function using Spearman's rank correlation coefficients (rho). ANOVA with Bonferroni adjustment was used to test the differences in the iHAQ scores across the tertiles of WOMAC function score.

Results: In 204 knee OA patients (70% female and 53% white), the mean age was 60.2 years. The median (Interquartile Range, IQR) of iHAQ scores by the 20-item A and 16-item B methods were 21.9 (9.4, 34.4) and 18.8 (9.4, 31.3), respectively. **Table 1** summarizes iHAQ scores compared with SF-36 PCS and MCS, WOMAC pain and function, and Global VAS scores. Both iHAQ methods A and B were significantly correlated with other measures, with method B being slightly better. For physical function, higher iHAQ (poorer function) was more strongly correlated with lower SF-36 PCS scores (method A: rho=-0.66, p<.0001, method B: rho=-0.68, p<.0001) than with higher WOMAC function score (method A: rho=0.34, p<.0001, method B: rho=0.43, p<.0001). The iHAQ scores also corresponded to different levels of physical function as measured by WOMAC function (**Figure 1**). Higher iHAQ scores were however only weakly correlated with higher WOMAC pain scores (method A: rho=0.26, p=.0002, method B: rho=0.295, p<.0001), lower SF-36 MCS scores (method A: rho=-0.36, p<.0001, method B: rho=-0.37, p<.0001), and higher Global VAS scores (method A: rho=0.28, p<.0001, method B: rho=0.31, p<.0001).

Conclusion: The Improved HAQ has content validity for assessing physical function in knee OA patients. It also correlated more modestly with pain, mental health and global health status. Investigation for its longitudinal validity (responsiveness) is warranted.

Table 1. Results of Spearman's Rank Correlation Coefficients Analysis					
Instruments	**Median (IQR)**	**Method A**		**Method B**	
		rho	**P value**	**rho**	**P value**
Improved HAQ method A	21.9				
(0 best - 100 worst)	(9.4, 34.4)	1.0000	-	0.9756	<0.0001
Improved HAQ method B	18.8				
(0 best - 100 worst)	(9.4, 31.3)	0.9756	<0.0001	1.0000	-
SF-36 PCS	36.7				
(0 worst - 100 best)	(29.1, 43.5)	-0.658	<0.0001	-0.675	<0.0001
SF-36 MCS	54.6				
(0 worst - 100 best)	(46.5, 59.7)	-0.355	<0.0001	-0.372	<0.0001
WOMAC Pain	239.8				
(0 best - 500 worst)	(172.5, 325.3)	0.263	0.0002	0.295	<0.0001
WOMAC Function	905.8				
(0 best - 1700 worst)	(623.0, 1147.3)	0.340	<0.0001	0.429	<0.0001
Global VAS	5.5				
(0 good - 10 poor)	(4.7, 6.0)	0.284	<0.0001	0.306	<0.0001



Disclosure: M. Chung, None; **S. Liu**, None; **Z. Fu**, None; **L. L. Price**, None; **J. B. Wong**, None; **C. Wang**, None.

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Abstract Number: 2544

Representing the Variability in Patients' Preferences

Raluca Cozmuta[1], Sonal Bhalla[2] and Liana Fraenkel[3], [1]Rheumatology, Yale University School of Medicine, New Haven, CT, [2]Yale University School of Medicine, New Haven, CT, [3]Medicine, Yale University School of Medicine, New Haven, CT

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Background/Purpose: Data describing patients' priorities, concerns, and preferences are essential to inform important decisions in health care, including treatment planning and the development of programs to improve access and delivery of care. Traditional statistical approaches which measure the association between patient characteristics and aggregate preferences have failed to explain preference heterogeneity. In this study, we sought to examine the value of latent class analysis (LCA) as a means to describe variability in patients' preferences.

Methods: We administered a discrete choice experiment to examine preferences for a hypothetical medication varying across 4 attributes (each having 3 levels): route of administration, benefit, risk of a rare adverse events and cost for a standardized patient with joint pain, migraines and fatigue. Subjects were women, between the ages of 20 and 49 years, admitted to the hospital or infusion center. Gender and age were restricted to decrease the known influence of these factors on treatment preferences. We used LCA to calculate part-worth utilities (value computed for each level of each attribute on an interval scale), and to determine whether the importances of each attribute clustered into distinct groups.

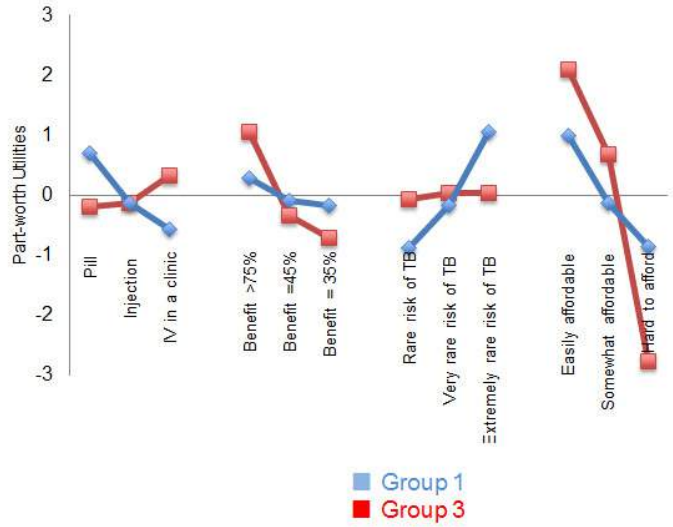
Results: Subjects' (N=271) mean age was 34 (SD=8) years; 94 were non-Hispanic White, 95 non-Hispanic Black, and 82 Hispanic, 27% of all subjects had a college degree, 41% had an annual income of at least $40,000 and 45% rated their health as being fair or poor. LCA revealed that preferences could be clustered into 4 distinct groups. Importance scores for each attribute by group membership are summarized in the Table. Subjects in Group 1 were influenced primarily by the risk of TB and cost, those in Group 2 focused mostly on benefit, while subjects in Group 3 were most concerned with cost. A distinct group of subjects (Group 4) were strongly influenced by route of administration. An illustrated example of the difference in incremental value assigned to varying levels of each attribute is provided in the Figure below. For instance, subjects in Group 1 gained utility (or value) as the risk of TB was progressively lowered, whereas subjects in Group 3 were not sensitive to changes in the risk of TB.

Conclusion: LCA is able to generate unique sets of preferences that can then be used to inform decisions. It can identify which sets of attributes are preferred by unique groups of patients and which priorities are shared across groups, thus enabling end users to allocate resources that are most likely to benefit the greatest number of patients and/ or tailor programming to focus on patients with specific needs.

Table. Attribute Importance by Group Membership

	Group 1	Group 2	Group 3	Group 4
Attribute Importance	21.7% (n= 59)	36 % (n= 97)	24.8% (n= 67)	17.6% (n= 48)
Route of administration	23	6.8	7.1	**41.7**
Benefit	8.3	**53.5**	24.3	27.4
Risk of TB	**35.1**	14.8	1.3	15.6
Cost	33.6	24.9	**67.2**	15.4

Figure. Part-Worth Utilities for Attribute Levels for Groups 1 and 3



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Abstract Number: 2545

Psychometric Testing of the Valued Life Activities Questionnaire in People with Rheumatoid Arthritis in the UK: Rasch Analysis

Yeliz Prior[1], Alan Tennant[2] and Alison Hammond[3], [1]Centre for Health Sciences, University of Salford, Greater Manchester, United Kingdom, [2]Human Functioning Sciences, ICF Unit, Swiss Paraplegic Research, Nottwil, Switzerland, [3]Centre for Health Sport & Rehabilitation Research, University of Salford, Salford, United Kingdom

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Background/Purpose: Developed in the USA, the Valued Life Activities Scale (VLAs) measures participation in daily activities. We have linguistically and culturally adopted the VLAs 33 item scale for use in the adults with RA in the United Kingdom (UK) using the recommended guidelines for cultural adaptation.

Methods: We recruited participants through 17 Rheumatology clinics in National Health Service (NHS) Hospitals across the UK. The internal construct validity (unidimensionality) was assessed using (i) Confirmatory Factor Analysis (CFA) (ii) Mokken scaling and (iii) Rasch model (including the stochastic ordering of items, unidimensionality and local independence). The RUMM2030 software was used, utilising the partial credit parameterisation of the Rasch model.

Results: Responders (n=340) had a mean age of 62 years (SD 12.1), and average disease duration was 14.4 years (SD 11.7). Of these, 73.8% were women and a third (32.3%) were employed. Just over half (55.9%) were on combination therapy, and 7.4% were on biologic drugs. A CFA failed to support a total score from the 33 items (Chi Square 3552:df 464:p<0.0001; RMSEA 0.066 (90% CI: 0.064-0.068); CFI .985; TLI 0.984); the 25 items (Chi Square 2836:df 275:p<0.0001; RMSEA 0.078(90CI: 0.076-0.081); CFI .987; TLI 0.986; or the 14 item version (Chi Square 1228:df 77:p<0.0001; RMSEA 0.099(90CI: 0.094-0.104). Based on the 25 item version the three domain structure (i.e. Obligatory, Committed and Discretionary activities) of the item set also failed (Chi Square 2693:df 272:p<0.0001; RMSEA 0.076(90CI: 0.074-0.079); CFI .987; TLI 0.986). Fit of the data from the VLA to the Rasch model is shown in Table 1. The stochastic ordering (fit) and unidimensionality assumptions were not satisfied. The VLAs was characterised by

multidimensionality and misfit, which may have been influenced by extensive clusters of residual item correlations. While reliability was high in all cases, this could be expected to be inflated in the presence of local response dependency, as identified through the residual correlation patterns. Unfortunately, out of the 1545 cases collected in this study, only 79 subjects had complete data on the items that comprise the 'activities' (obligatory + committed) and 'participation' (discretionary) domains, due to the 'does not apply to me' response option.

Table 1. Rasch Analysis of Various versions of the scale.

Scale	*Chi-Square* *	Df	P	Residual item SD	Residual Person SD	PSI/ Reliability	*Unidimensionality % t-Tests*	95% CI
RA-33	315.3	165	<0.001	2.0134	1.0995	0.95	6.67	4.3-9.5
RA-25	214.2	200	0.233	1.5988	1.1197	0.95	10.64	8.3-13.0
RA-14	141.5	112	0.031	1.7771	1.1493	0.92	8.51	6.2-10.9
Ideal			**>0.05***	**<1.4**	**<1.4**	**>0.70**	**<5.0**	**LCI <5.0**

*Bonferroni Adjusted (for 33 items fit is >0.001)

Conclusion: The UK version of the VLA, across various scales, fails to satisfy classical and modern psychometric standards. The raw score cannot be considered a valid estimate of the persons' ability within any domain. The 'does not apply to me' response option renders valid scoring impossible in routine settings. It is recommended that the VLA set of items should be reconfigured and considered as a measure of Activities and Participation, consistent with ICF terminology.

Disclosure: Y. Prior, None; **A. Tennant**, None; **A. Hammond**, None.

Abstract Number: 2546

Targeting Synovial Fibroblasts By the Intra-Articular Delivery of microRNA-140-3p and -5p Ameliorates Experimental Autoimmune Arthritis

Chrong-Reen Wang[1], Jia-Shiou Peng[2], Shih-Yao Chen[3], Chao-Liang Wu[4] and Ai-Li Shiau[5], [1]Rheum/Immun Sec/Int Med Dept, Medical Coll/Nat'l Cheng Kung, Tainan, Taiwan, [2]Institute of Basic Medical Sciences, Medical Coll/Nat'l Cheng Kung, Tainan, Taiwan, [3]Internal Medicine, Medical Coll/Nat'l Cheng Kung, Tainan, Taiwan, [4]Biochemistry and Molecular Biology, Medical Coll/Nat'l Cheng Kung, Tainan, Taiwan, [5]Microbiology and Immunology, College of Medicine, National Cheng Kung University, Medical Coll/Nat'l Cheng Kung, Tainan, Taiwan

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Background/Purpose:

Synovial fibroblasts (SF) with aberrant expression of microRNAs (miRNA) are critical pathogenic regulators of rheumatoid joint, and studies examining the effect of overexpressing or silencing miRNA expression levels in arthritis models can contribute to the development of miRNA-based therapeutics in rheumatoid arthritis (RA). We hypothesized that miR-140-3p and -5p are involved in the RA pathogenesis, and examined whether targeting SF by the intra-articular (i.a.) delivery of these molecules can ameliorate autoimmune arthritis in mice.

Methods:

Synovial tissues were obtained from RA and osteoarthritis patients, and two experimental models in mice were used in this study, collagen-induced arthritis (CIA) and collagen antibody-induced arthritis (CAIA). Recombinant lentiviral vectors were produced by transfecting 293T cells with pre-miR-140, the miR-140 precursor molecule cloned downstream of a CMV promoter, the packaging plasmid psPAX2 and the envelope plasmid pMD2.G by using a calcium phosphate precipitation method. Overexpressing miR-140-3p and -5p in SF and joints was performed by the lentivirus (LV)-mediated transfer of pre-miR-140 with a precursor scramble construct as the negative control. Quantitative real-time PCR was used to examine the expression levels of miR-140-3p and miR-140-5p in SF and synovial tissues. Clinical, histopathological and radiological scores were evaluated in CIA and CAIA joints receiving the i.a. delivery of miR-140-3p and -5p lentiviral vectors. Quantitation of sirtuin 1 (SIRT1) and stromal cell-derived factor-1 (SDF-1), target molecules

of miR-140-3p and miR-140-5p, respectively, was carried out by immunoblot/ELISA and real-time PCR in SF, and by immunohistochemical staining and real-time PCR in synovial tissues. For *in vitro* experiments with SF, cell migration, apoptosis and proliferation were analyzed with Boyden chamber, TUNEL and WST-1 assays, respectively.

Results:

Lower expression levels of miR-140-3p and -5p were detected in SF and synovial tissues from RA patients and two arthritis models. In both CIA and CAIA mice, the LV-mediated i.a. transfer of miR-140-3p and -5p significantly ameliorated arthritis by clinical, histopathological and radiological evaluations with reduced densities in SF. Overexpressing miR-140 resulted in lower expression levels with correlated kinetic patterns of SIRT1 and SDF-1 in SF and joints. *In vitro* overexpressing miR-140 in SF enhanced apoptosis, reduced migration and proliferation, and regulated the expression of miR-140 in the presence of pro-inflammatory cytokines.

Conclusion:

Our results demonstrate that targeting SF by the i.a. delivery of miR-140-3p and -5p can ameliorate autoimmune arthritis, and these findings might facilitate the pharmacological development of miRNA-based molecular therapeutics in RA.

Disclosure: C. R. Wang, None; **J. S. Peng**, None; **S. Y. Chen**, None; **C. L. Wu**, None; **A. L. Shiau**, None.

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Abstract Number: 2547

NIP-565, a Novel JAK1-Selective Inhibitor, for the Treatment of Rheumatoid Arthritis

Yuuki Hidaka[1], Takanori Nakamura[2], Tadashi Igarashi[2], Takeshi Nanya[2], Shuhei Hagiwara[2], Kazuya Takeuchi[2], Tomonori Yaguchi[3], Yutaka Kawakami[3] and Takeshi Naito[2], [1]Pharmaceutical Research Department, Nissan Chemical Industries,LTD., Saitama, Japan, [2]Nissan Chemical Industries,LTD., Saitama, Japan, [3]Keio University School of Medicine, Tokyo, Japan

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Background/Purpose:

Non-selective Janus kinase (JAK) inhibitors have shown long-term efficacy in treating rheumatoid arthritis (RA). However, clinical efficacy is limited due to concerns of dose-limiting toxicity related to JAK2/3 inhibition such as anemia, malignancies and infections. The objectives of this study were to reveal pharmacological profiles of a novel JAK1-selective inhibitor, NIP-565, and to estimate its therapeutic potential and safety in the treatment of RA patients.

Methods:

Enzyme assays and cell-based assays were conducted to assess the JAK1 selectivity of NIP-565. As therapeutic activity for RA patients, in vitro JAK1 signaling inhibitory activity was evaluated by IL-6-induced STAT1 phosphorylation using human peripheral blood. In vivo therapeutic potential of NIP-565 was evaluated the reduction of paw swelling in collagen-induced arthritic (CIA) rats. In order to estimate the risk of adverse events caused by JAK3 inhibition, NK cell numbers and NK cell cytotoxic activity were compared in the NIP-565 or tofacitinib treatment animals. The effect on erythropoietin -stimulated erythropoiesis using human bone marrow cells was examined to assume the risk of anemia caused by JAK2 inhibition. Human pharmacokinetics prediction was performed by allometric scaling methods.

Results:

NIP-565 inhibited JAK1 in the nM range, and showed more than 10-fold selectivity towards JAK2, JAK3, and Tyk2. NIP-565 inhibited IL-6-induced phosphorylation of STAT1, at sub-μM IC_{50} value. This inhibition was 37-fold stronger than the inhibitory effect on GM-CSF-induced STAT5 phosphorylation as cellular JAK2 activity, and 2-fold stronger than the inhibitory effect on IL-15-induced phospho-STAT1 production as cellular JAK1/JAK3 activity. In a rat CIA model, NIP-565 attenuated paw swelling in a dose-dependent manner after repeated oral administration once per day for 15 days. Both NIP-565 and tofacitinib completely suppressed at 30 mg/kg dosing. NK cell numbers in the peripheral blood of CIA model rats were 2-fold higher in the NIP-565-treated group than in the

tofacitinib-treated group at 30 mg/kg. In tumor-bearing mice model, NIP-565 (30 mg/kg, 2 weeks) maintained NK cell cytotoxic activity compared with control, while tofacitinib (30 mg/kg) reduced that activity. These data suggest that the risk of adverse events caused by NK cell attenuation with NIP-565 treatment may be lower than that with tofacitinib treatment. Additionally, NIP-565 showed weaker inhibitory effect than other JAK inhibitors (e.g., tofacitinib, baricitinib and peficitinib) in human erythropoiesis assay. As a result of analysis with human pharmacokinetics prediction, NIP-565 could be enough exposure to provide high therapeutic efficacy without anemia in clinical practice by once daily oral administration.

Conclusion:

NIP-565 is a novel JAK1-selective inhibitor, and expected to provide potent anti-inflammatory effects while minimizing the adverse effects that would result from JAK2/3 inhibition in the treatment of RA patients.

Disclosure: Y. Hidaka, NIissan Chemical Industries,LTD, 3; **T. Nakamura**, Nissan Chemical Industries,LTD, 3; **T. Igarashi**, Nissan Chemical Industries,LTD, 3; **T. Nanya**, Nissan Chemical Industries,LTD, 3; **S. Hagiwara**, Nissan Chemical Industries,LTD, 3; **K. Takeuchi**, Nissan Chemical Industries,LTD, 3; **T. Yaguchi**, NIissan Chemical Industries,LTD, 2; **Y. Kawakami**, NIissan Chemical Industries,LTD, 2; **T. Naito**, Nissan Chemical Industries,LTD, 3.

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Abstract Number: 2548

M-CSF-R Is a Critical Determinant for the Differentiation of Classical to Non-Classical Monocytes

Philip J. Homan[1], Alexander Misharin[1], Carla Cuda[2], Salina Dominguez[2], Rana Saber[2], Fu-Nien Tsai[3] and Harris R. Perlman[4], [1]Medicine-Rheumatology, Northwestern University, Chicago, IL, [2]Northwestern University, Chicago, IL, [3]Medicine, Rhuematology, Northwestern University, Chicago, IL, [4]Feinberg School of Medicine, Northwestern University, Chicago, IL

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Background/Purpose:

Colony-stimulating factors (CSF) are simply defined as haemotopoitec growth factors. However, CSFs have been implicated to have additional functions in various autoimmune diseases. Specifically M-CSF has been shown to effect the progression of CIA, a murine model of RA. Additional studies have also shown that M-CSF is required to maintain the monocyte derived macrophage population in the ankle. However, all of these studies utilized M-CSF or MCSFR knockout or mutant mice. Here we generated MCSFR conditional mice that lack the receptor in myeloid cells. We hypothesize that M-CSF is integral to the development of monocytes and subsequent macrophage differentiation, and will affect the development of other autoimmune diseases.

Methods:

We generated mice lacking M-CSF-R specifically in myeloid cells (M-CSF-$R^{fl/fl}Cre^{LysM}$) and assessed mice at 4 months of age for characterization of RA-like disease. Monocyte turnover/proliferation and differentiation were examined *in vivo*using flow cytometric analyses.

Results:

M-CSF-$R^{fl/fl}Cre^{LysM}$ displayed a normal response and recovery to RA in our K/BxN serum transfer arthritis (STIA) model. However flow cytometry analysis revealed differential cell populations in multiple tissues within M-CSF-$R^{fl/fl}Cre^{LysM}$ mice compared to M-CSF-$R^{fl/fl}$ mice. We observed a marked decreased in the non-classical monocytes in which the M-CSF-$R^{fl/fl}$ was deleted. Since blood monocytes are directly linked to the formation of tissue inflammatory macrophages we also examined synovial macrophages in the ankle. We previously characterized synovial macrophages as $MHCII^-$, tissue resident macrophages, and $MHCII^+$ macrophages. M-CSF-$R^{fl/fl}Cre^{LysM}$ mice showed a significant decrease in $MHCII^+$macrophages.

Conclusion:

M-CSF plays a central role in both monocyte differentiation in the blood and MHCII^{+} macrophage proliferation in the ankle. The lack of M-CSF-R depletion in both intermediate and non-classical monocytes, in the blood, suggests that expression of M-CSF-R is required for classical monocytes to differentiate into non-classical monocytes. This data also suggest that M-CSF can act as either an active or passive participant in the replenishment of synovial macrophages. M-CSF could be directly required for the differentiation of monocytes into synovial macrophages. The decrease in MHCII^{+} cells could also be due to the decreased ability of classical monocytes to differentiate into non-classical monocytes, suggesting that non-classical monocytes directly replenish the synovial macrophage populations. The M-CSF-R$^{fl/fl}$Cre^{LysM} provides an important model to study autoimmune disease and identify the specific role of M-CSF in classical and non-classical monocyte differentiation and their ability to replenish both tissue resident and bone marrow derived macrophages during the progression of disease.

Disclosure: P. J. Homan, None; **A. Misharin**, None; **C. Cuda**, None; **S. Dominguez**, None; **R. Saber**, None; **F. N. Tsai**, None; **H. R. Perlman**, None.

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Abstract Number: 2549

Characterizing the RPTPσ Mediated Proteoglycan Switch As a Target for Rheumatoid Arthritis Therapy

Karen M. Doody[1], Stephanie M. Stanford[1], Mattias N. D. Svensson[1], Cristiano Sacchetti[1], Gary S. Firestein[2], A. Radu Aricescu[3] and Nunzio Bottini[1,4], [1]Cellular Biology, La Jolla Institute for Allergy and Immunology, La Jolla, CA, [2]Division of Rheumatology, Allergy and Immunology, University of California, San Diego, La Jolla, CA, [3]Division of Structural Biology, Wellcome Trust Centre for Human Genetics, University of Oxford, Oxford, United Kingdom, [4]Division of Cell Biology, La Jolla Institute for Allergy and Immunology, La Jolla, CA

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Background/Purpose: RPTPσ (gene *PTPRS*) is a protein tyrosine phosphatase that binds heparan sulfate- and chondroitin sulfate-containing proteoglycans with its extracellular immunoglobulin domains 1 and 2 (Ig1&2). RPTPσ is expressed at minimal or low levels in immune cells, while in neurons the competition between heparan sulfate and chondroitin sulfate for RPTPσ binding controls axon outgrowth and is called the proteoglycan switch. We recently reported that RPTPσ is highly expressed in fibroblast-like synoviocytes (FLS) and the proteoglycan switch exists in these cells. Treatment of FLS with decoy RPTPσ Ig1&2 competes with surface heparan sulfate proteoglycans, which flips the proteoglycan switch and reduces rheumatoid arthritis (RA) FLS migration, invasion and attachment to cartilage. Systemic administration of RPTPσ Ig1&2 reduces arthritis severity and cartilage damage in the K/BxN serum transfer mouse model of RA. To further characterize RPTPσ Ig1&2 as a putative FLS-targeting treatment for RA, we tested its selectivity for FLS, as well as its effectiveness in an additional mouse model of arthritis.

Methods: Migration was assessed using a scratch-wound assay with RA FLS and normal human dermal fibroblasts (NHDF). Collagen production in NHDF was assessed by measuring collagen 1A2 mRNA expression in TGFβ-stimulated cells. RPTPσ and heparan sulfate proteoglycan mRNA expression were measured by qPCR. Surface expression of heparan sulfate was assessed by flow cytometry. Collagen antibody-induced arthritis (CAIA) was induced by injection of mice with an anti-collagen antibody cocktail (ArthritoMab®).

Results: RPTPσ Ig1&2 decreased migration of RA FLS by 27%, but did not affect migration of NHDF. This was not due to differences in *PTPRS* expression; however, surface heparan sulfate levels and expression of heparan sulfate proteoglycans were higher in RA FLS (> 4-fold and > 2-fold increase, respectively). RPTPσ Ig1&2 did not affect collagen production by NHDF upon TGFβ stimulation, a characteristic function of these cells important for wound-healing. Finally, RPTPσ Ig1&2 administration decreased arthritis severity by 30% in the CAIA mouse model of RA.

Conclusion: RPTPσ Ig1&2 treatment ameliorates arthritis in multiple models by selectively targeting FLS due to their high expression of heparan sulfate proteoglycans. These results support further testing of RPTPσ Ig1&2 alone and in combination with conventional immune-targeting RA therapies.

Disclosure: K. M. Doody, None; **S. M. Stanford**, None; **M. N. D. Svensson**, None; **C. Sacchetti**, None; **G. S. Firestein**, None; **A. R.**

Aricescu, None; **N. Bottini**, None.

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Abstract Number: 2550

Metabolomic Profiling of Joints in Murine Models of Inflammatory Arthritis

Ilya gertsman[1], Jesus Rivera-Nieves[2], Maripat Corr[2], Bruce Barshop[1] and **Monica Guma**[3], [1]pediatrics, University of California, San Diego, La Jolla, CA, [2]Medicine, University of California, San Diego, La Jolla, CA, [3]Pharmacology, University of California, San Diego, La Jolla, CA

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Background/Purpose: Given the complexity and heterogeneous nature of rheumatoid arthritis (RA), it is unlikely that a single biomarker may provide sufficient discrimination; therefore biomarker signatures may represent more realistic approach for the future of personalized medicine in RA. These signatures may represent different subsets in this heterogeneous disease. The study of metabolomics represents a new approach to develop biomarker signatures. Given that metabolism and metabolome are similar between species, biomarkers field might benefit from animal models studies in which pathogenic mechanisms can be controlled, and correlations with joint metabolome can be evaluated.

Methods: Ankles from 10 weeks old K/BxN mice (an IL-1b-driven mouse model of arthritis; n=6) and from 10 weeks old TNFARE mice (a TNF-driven mouse model of arthritis; n=6) and its corresponding littermates, were snap frozen, pulverized and then homogenized using a biphasic chloroform/methanol/water extraction method for polar and lipid metabolite analysis. The phases were separated, dried, and then reconstituted before injection and analysis on a 5600 Triple-TOF LC-MS (MS; AB Sciex). Peak integration, alignment, and statistical analysis were performed using Markerview software (AB Sciex).

Results: Multivariate statistical analysis of the MS spectra successfully discriminated between inflamed joints samples and controls. Several metabolites were upregulated in both mouse models compared to their respective littermates. Among them, metabolites in purine (AMP, GMP, xanthosine and deoxyinosine), pyrimidine (uridine and thymidine), TCA cycle (malate, fumarate and citrate), and phospholipid (lysophosphatidylcholine) pathways were statistically increased in joints from both murine models, which suggest that there may be common metabolic perturbations in these disease models. However, some metabolites were upregulated uniquely in the K/BxN model such as metabolites in phenylalanine/tyrosine metabolism, branched chain amino acid metabolism (leucine, isoleucine and valine) and eicosanoid metabolism (15-HEPE, 13-HOTrE, 12-oxo-ETE).

Conclusion: The differences between up-regulated metabolites in both murine models suggest different metabolic signatures secondary to different pathogenic pathways. More metabolic profiles studies using controlled animal models are needed to determine if metabolic signatures can distinguish subsets of RA patients and help in diagnoses, prognosis and predicting drug choice in this disease.

Disclosure: I. gertsman, None; **J. Rivera-Nieves**, None; **M. Corr**, None; **B. Barshop**, None; **M. Guma**, None.

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Abstract Number: 2551

Antibodies to Malondialdehyde-Acetaldhyde Adducts Are Increased in the Serum of Mice Following Infection with P. Gingivalis and/or Injection of Citrullinated Mouse Type II Collagen: a Model of Human Disease Response

Geoffrey M. Thiele[4], Einstein Juma[1], Roxanne Haslam[1], Michael J. Duryee[2], Anand Dusad[3], Carlos D. Hunter[2], James R. O'Dell[4], Lynell W. Klassen[4], Ted R. Mikuls[4] and Geoffrey M. Thiele[4], [1]University of Nebraska Medical Center, Omaha, NE, [2]Internal Medicine Division of Rheumatology, University of Nebraska Medical Center, Omaha, NE, [3]Rheumatology, University of Nebraska

Medical Center, Omaha, NE, [4]Veteran Affairs Nebraska-Western Iowa Health Care System and University of Nebraska Medical Center, Omaha, NE
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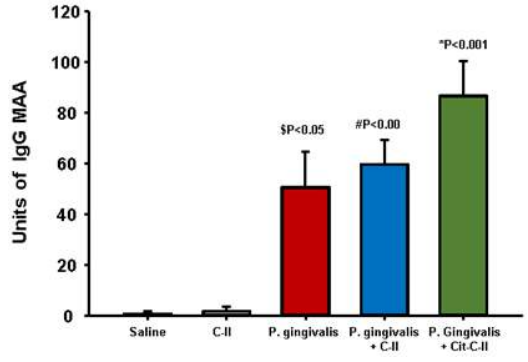
Background/Purpose: Patients with RA complicated by periodontal disease (PD) have been shown to have higher anti-citrullinated protein antibody (ACPA) levels, which have also become predictive markers of the disease and its severity. Recent studies by our group have shown that Malondialdehyde-Acetaldehyde Adducts (MAA) are present in synovial tissues and antibodies to MAA are detected in the serum of patients with RA. Also, the presence of these antibodies in serum correlated with the severity of the disease. Therefore, it was the purpose of this study to determine whether animal models of RA in the context of *P. gingivalis* (Pg) infection results in the development of anti-MAA antibodies.

Methods: DBA/1J mice were subjected to sulpha-methoxazole in their water for 10 days and then gavaged with Pg 3 times over a 1 week period. Control mice were subjected to antibiotics in the absence of Pg and injected with mouse type II collagen (C-Il) or citrullinated Col (Cit-C-II) in parallel as previously published. Serum was tested for the presence of antibody to C-II, Cit-C-CII, Pg outer membrane antigen (PGMA), CCP, and MAA.

Results: At week 6, Pg infected (3.25) and Cit-C-II immunized mice 3.25 ($P \leq 0.001$) had higher inflammation indexes as compared to controls. There was nearly a 2-fold increase in serum CCP in the Pg infected mice (11.2 U/ml) compared to uninfected controls (6.89 U/ml) ($p=0.002$). There were fairly high concentrations of IgM anti-MAA antibodies in the serum of mice injected with nothing or C-II (954 ± 139 and 1025 ± 230 U/ml, respectively). These values increased when Pg (1578 ± 153 U/ml) was administered to the mice in the presence of C-II (1458 ± 262 U/ml) or Cit-C-II (1250 ±161 U/ml). In contrast, IgG anti-MAA levels (Figure) were only increased in mice infected with Pg (51 ± 19 U/ml), and were further increased only in the presence of Cit-C-II (86 ± 30 U/ml), but not C-II (59 ± 19 U/ml). Thus, it appears that the IgG anti-MAA responses were affected by the addition of these two unique antigens. Finally, IgG anti-MAA antibodies in Pg infected mice correlated with CRP levels ($p = 0.019$), and mice infected and immunized with Cit-C-II correlated with both CRP ($p = 0.01$) and CCP (0.012) levels.

Conclusion: These data show that following infection with Pg and immunization with C-II or Cit-C-II anti-CCP response is not increased. However, serum IgG anti-MAA antibody responses increased when Cit-C-II immunization was coupled with Pg infection. More importantly, IgG anti-MAA antibody significantly correlate with CRP levels in this same group of animals. A correlation that also is prevalent in the serum of patients with RA. Thus, this animal model appears to mimic many of the interactions of anti-MAA, CCP, and Pg, observed in humans and may be useful for further investigations into these interactions with respect to inflammatory responses in RA.



View Abstract and Citation Information Online - http://acrabstracts.org/abstract/antibodies-to-malondialdehyde-acetaldhyde-adducts-are-increased-in-the-serum-of-mice-following-infection-with-p-gingivalis-andor-injection-of-citrullinated-mouse-type-ii-collagen-a-model

Abstract Number: 2552

Alterations in the Colonic Microbiome Precede the Development of Murine Inflammatory Arthritis

Jason Hendrickson[1], Gaurav Mehta[2], NIRMAL BANDA[1] and Kristine A. Kuhn[1], [1]University of Colorado School of Medicine, Aurora, CO, [2]Division of Rheumatology, University of Colorado School of Medicine, Aurora, CO
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Background/Purpose: Alterations in resident bacteria, termed dysbiosis, is present in patients in early stages of rheumatoid arthritis, psoriatic arthritis, and spondyloarthritis. However, it remains unclear if dysbiosis is causative or occurs as a result of the disease. Using the collagen-induced arthritis (CIA) model in mice, we aimed to determine if microbiome changes occur and, if so, at what point during the development of disease.

Methods: DBA1/j mice were injected intradermally with bovine type II collagen emulsified in complete Freund's adjuvant at days 0 and 21 to induce CIA. Fecal pellets were harvested from the mice at days 0, 21, and 39 after immunization. The microbial DNA was extracted from the feces using a commercially available kit. 16S rRNA sequencing was performed and the sequences aligned using SINA with a reference taxonomic database Silva 111 NR. Microbial ecology such as diversity and relative abundance of the 16S rRNA sequences was evaluated using Explicet software. Statistical analyses of the changes in identified species were done by non-parametric ANOVA.

Results: The mean arthritis severity in our cohort of mice at day 39 after immunization was 6.67 ± 1.05 (based on a scale of 0-12); no mice had observable arthritis before day 24. Our microbiome sequencing results demonstrate significant differences in the beta diversity of the microbial community at day 0 (1.000) compared to day 21 (0.866) and at day 39 (0.920). We now plan to evaluate the relative abundance of specific bacterial species at each of our time points.

Conclusion: These data indicate that dysbiosis occurs during the initial stages of CIA, when immune responses that lead to disease are developing. Such findings suggest that dysbiosis may be causative in pathogenesis of disease rather than reflective of the disease presence. An interesting finding was that beta diversity was most affected at day 21 compared to day 39. This is consistent with microbiome studies in patients with RA in which dysbiosis were most pronounced in new-onset patients compared to those with established disease. With our additional analyses, we expect to identify changes in specific bacterial species that may shed light on the role of the microbiome in developing arthritis.

Disclosure: J. Hendrickson, None; **G. Mehta**, None; **N. BANDA**, None; **K. A. Kuhn**, None.

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Abstract Number: 2553

Involvement of M2 Macrophages in the Pathogenesis of Arthritis in a Mouse Model

Shinjiro Kaieda[1], Naomi Yoshida[2], Yukiko Kunitake[3], Daisuke Wakasugi[4], Yukio Fujiwara[5], Yoshihiro Komahara[6], Hiroaki Ida[7] and Tomoaki Hoshino[2], [1]Department of Medicine, *Division of Respirology, Neurology and Rheumatology, Kurume University School of Medicine, kurume, Japan, [2]Department of Medicine, Division of Respirology, Neurology and Rheumatology, Kurume University School of Medicine, Kurume, Japan, [3]Kurume University School of Medicine, Kurume, Japan, [4]Medecine, Division of Respirology, Neurology and Rheumatology, Kurume University School of Medicine, Kurume, Japan, [5]Cell Pathology, Graduate School of Medical Sciences, Kumamoto University, Kumamoto, Japan, [6]Cell Pathology, Graduate School of Medical Sciences, Kurume University, Kumamoto, Japan, [7]Respiorogy, Neurology and Rheumatology, Kurume University School of Medicine, Kurume, Japan
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Background/Purpose:

Synovial lining macrophages play an important role in initiating and maintaining joint inflammation in arthritis. Classically activated pro-inflammatory macrophages and alternatively activated anti-inflammatory macrophages are generally referred to as M1 and M2 macrophages, respectively. The CD163, CD204, and CD206 proteins are predominantly expressed by M2-phenotype macrophages. Monocyte/macrophage-restricted expression of CD163 has been confirmed and observed in affected joint tissues of patients with RA

and spondyloarthropathy. However, the pathogenic role of M2 macrophages in inflammatory arthritis remains unclear. We investigated the involvement of M2 macrophages in the development of arthritis in mice.

Methods:

Collagen antibody-induced arthritis (CAIA) was induced using a combination of monoclonal anti-type II collagen antibodies and lipopolysaccharide. C57BL/6 (B6) background CD163 knockout (KO) mice and BALB/c background CD204 KO mice were used in an autoantibody-induced RA mouse model. Arthritis was graded using a 0–16 clinical scale (0–4 per paw). Histological assessment was conducted using paraffin-embedded 4-mm sections stained with hematoxylin and eosin. Total RNA was isolated from mouse ankle joints. Gene expression of M2 macrophage markers including CD163, CD204, and CD206 and the pro-inflammatory cytokines IL-1β and IL-6 was determined before and 10 days after CAIA induction by quantitative RT-PCR.

Results:

CD163 gene expression in inflamed synovium was significantly lower than that in normal synovium. In contrast, CD204 mRNA expression was significantly greater in inflamed synovium. No significant differences in CD206 mRNA expression were observed between normal and inflamed synovium. Thus, we focused our attention on involvement of CD163- and CD204-positive macrophages in the development of arthritis. CD163 KO mice exhibited significantly higher clinical scores for arthritis than did control wild-type B6 mice. Histomorphometric quantification of arthritic changes in the joint tissues confirmed the clinical assessment, with higher inflammation in CD163 KO mice. Correspondingly, mRNA expression of IL-1β and IL-6 was significantly up-regulated in inflamed ankle joints of CD163 KO mice compared to those of control mice. CD204 KO mice were found to be normally susceptible to arthritis.

Conclusion:

In the present study, we aimed to identify the involvement of M2 macrophages in CAIA. CD163 deficiency exacerbated disease severity in autoantibody-induced arthritis via up-regulation of synovial tissue IL-1β and IL-6 expression. Thus, CD163-positive M2 macrophages may play a role in inhibiting the pathogenesis of RA.

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Abstract Number: 2554

Inhibition of IL6 Receptor Improves Arthritis and Atherosclerosis in a Mouse Model of Rheumatoid Arthritis

Amy Archer[1], Carla Cuda[2], Alexander Shaffer[2], Emily Alex Waters[3], Chad Haney[4], Rana Saber[2], George Kenneth Haines III[5], Jason Low[6] and **Harris R. Perlman**[7], [1]Rheumatology, Northwestern University, Chicago, IL, [2]Northwestern University, Chicago, IL, [3]Chemistry of Life Processes Institute, Northwestern University, Evanston, IL, [4]Center for Advanced Molecular Imaging, Northwestern University, Evanston, IL, [5]Mount Sinai, New York, NY, [6]Genentech, San Francisco, CA, [7]Feinberg School of Medicine, Northwestern University, Chicago, IL

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Background/Purpose: Rheumatoid arthritis is a chronic, systemic, autoimmune disease associated with an increased risk of cardiovascular disease. However, it is unclear what role patients' dyslipidemia plays in enhancing this cardiovascular risk. Moreover, the impact that treatments for rheumatoid arthritis have on both dyslipidemia and cardiovascular disease is under investigation. Anti-IL6 receptor (aIL6R) therapy is an effective treatment for rheumatoid arthritis but can be associated with an unfavorable lipid profile. Our study examines whether treatment with aIL6R is able to improve both inflammatory arthritis and early atherosclerosis in a mouse model of rheumatoid arthritis (K/BxA^{g7}).

Methods: K/BxA^{g7}mice on a high fat diet were treated with a murine aIL6R monoclonal antibody (cMR16-1) three times a week for 12 weeks. Arthritis was histologically assessed by a blinded pathologist and with SPECT/CT. Atherosclerosis was determined with whole mount sudan IV staining, sections though the aortic root and MRI. Serum cholesterol levels and cytokine levels were determined

via enzymatic and luminex assays respectively.

Results: Our data show that cMR16-1 improves both articular and extra-articular inflammation, but does not influence bone resorption. In addition, sudan IV staining showed a decrease in the area of early atherosclerosis by 30%. As expected there was an associated increase in serum IL6. We also observed an increase in adiponectin, leptin, VEGF and RANTES, as well as a decrease in GRO-alpha. However, in our model treatment with cMR16-1 was not associated with any changes in the lipid profile of the K/BxA^{g7} mice.

Conclusion: Thus our data suggest that cMR16-1 is able to improve arthritis and early atherosclerosis in the absence of changes to the lipid profile in our mouse model of rheumatoid arthritis. This suggests that changes to the standard lipid profile may not be the ideal parameter to monitor in assessing the ability of treatments for rheumatoid arthritis to improve atherosclerosis.

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Abstract Number: 2555

14-3-3η As a Novel RA Drug Target: Anti-14-3-3η Monoclonal Antibody Delays the Onset and Mitigates the Severity of Arthritis in CIA Mice

Abedelnasser Abulrob[1], Mario Mercier[1], Slavisa Corluka[1], Roger MacKenzie[1], Shalini Raphael[1], Sara Michienzi[2], Jane Savill[2], Yuan Gui[2], Walter Maksymowych[3] and **Anthony Marotta**[2], [1]National Research Council of Canada, Ottawa, ON, Canada, [2]Augurex Life Sciences Corp., Vancouver, BC, Canada, [3]Department of Medicine, University of Alberta, Edmonton, AB, Canada

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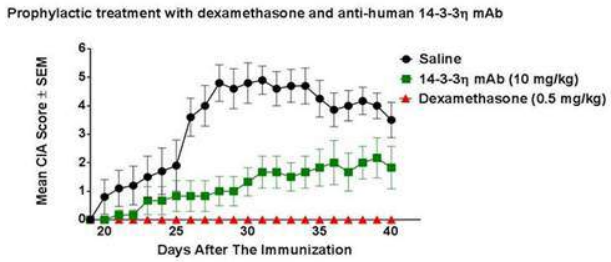
Background/Purpose: As an extracellular ligand, 14-3-3η potently and concentration-dependently upregulates the expression of multiple factors including TNFα, IL-6, and RANKL and its clinical detection is associated with joint damage progression risk. Several disease modifying agents are available for the treatment of RA with remission efficacy rates around 30%. Since RA is driven by multiple factors to varying degrees, within and between patients along the disease course, personalized medicine that enables the specific targeting and measurement of disease potentiators, such as 14-3-3η, is highly desirable. This study evaluated the *in vivo* feasibility of targeting 14-3-3η with a monoclonal antibody to mitigate the onset and severity of collagen-induced arthritis (CIA) in mice.

Methods: 27 DBA/1 mice were randomized to four study groups: non-induced mice (negative control, N=5), 0.5 mg/kg of dexamethasone group (positive control, N=6), saline injected mice (placebo group, N=10), and the treatment arm that was administered 10 mg/kg of 14-3-3η mAb (N=6). Treatments were initiated 2 days prior to immunization with collagen and administered daily for 6 weeks. A collagen booster was injected on day 18 of the study for all immunized mice. Arthritis scores were determined daily by an established and standardized chart evaluating inflammation and swelling of each paw (0 to 4). All animals were sacrificed 42 days after the beginning of the treatments. Paws were further analysed by x-ray. Student t-test was performed to examine differences (onset CIA, maximum, and end scores, and paw scores) amongst the two groups. Kruskal Wallis test was used to compare group daily score differences over the course of disease.

Results: Non-induced and dexamethasone mice did not develop visible signs of arthritis over the course of disease while 100% of the mice within the saline arm did. 17% of the mice in the 14-3-3η mAb group did not develop any signs of arthritis. The CIA score for the 14-3-3η mAb arm had significantly lower onset scores (0.83 ±0.41 vs 2.7 ±1.57, p=0.0119), maximum scores (2.33 ±1.75 vs 5.3 ±1.83, p=0.0052), and end scores (1.83 ±1.84 vs 4.3 ±1.7, p=0.0197) than the saline treated groups. Figure 1 further demonstrates that 14-3-3η mAb treated mice have significantly lower disease over the disease course than animals in the saline group, $p<0.01$, with x-ray paw analysis also demonstrating significance (p=0.0041).



Conclusion: 14-3-3η is a mechanistic joint damage factor involved in the pathogenesis of RA. A research program to exploit modifying the 14-3-3η pathway is underway to develop improved antibody therapeutics for delaying the onset and reducing the severity of this disease.

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Abstract Number: 2556

Functional Genetics of PTPN2 in Rheumatoid Arthritis: Haploinsufficiency of PTPN2 Promotes Severity of CD4+ T-Cell Mediated Autoimmune Arthritis

Mattias N.D Svensson[1], Karen M. Doody[1], Cristiano Sacchetti[1], Dennis J. Wu[1], Gisen Kim[2], Annelie Hellvard[3], Brith Bergum[3], Piotr Mydel[3], Mitchell Kronenberg[2], Michel L. Tremblay[4] and Nunzio Bottini[1], [1]Cellular Biology, La Jolla Institute for Allergy and Immunology, La Jolla, CA, [2]Developmental Immunology, La Jolla Institute for Allergy and Immunology, La Jolla, CA, [3]Clinical Science, Broegelmann Research Laboratory, Bergen, Norway, [4]Goodman Cancer Centre, McGill University, Montréal, QC, Canada
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Background/Purpose: Several genome-wide associations studies have in recent years linked polymorphisms in the *PTPN2* locus to rheumatoid arthritis (RA) and other autoimmune diseases. *PTPN2* encodes for the tyrosine phosphatase TC-PTP, an important regulator of cytokine signaling in hematopoietic cells. Complete loss of TC-PTP has previously been shown to result in development of spontaneous erosive arthritis in mice. Also, recent work has reported that lack of TC-PTP in T-cells leads to systemic autoimmunity in mice. Disease-associated variants of *PTPN2* are believed to result in a partial loss of protein expression. To model the functional genetics of RA-associated *PTPN2* variants in mice, we studied the effect of *PTPN2* haploinsufficiency in the SKG mouse, a spontaneous $CD4^+$T-cell-driven model of autoimmune arthritis.

Methods: Mice homozygous for the SKG Zap-70^{W163C} mutation develop IL-17 dependent spontaneous arthritis, which is due to reduced TCR signaling resulting in altered thymic selection and emergence of autoreactive $CD4^+$ T-cells. Arthritis in SKG mice can also be induced by administration of the fungal cell wall component mannan. Development of both spontaneous and mannan-induced arthritis was assessed in $PTPN2^{+/+}$ and $PTPN2^{+/-}$ SKG mice. Also, CD4 T-cells isolated from $PTPN2^{+/+}$ and $PTPN2^{+/-}$ SKG mice were transferred to $RAG2^{-/-}$mice and development of spontaneus arthritis was monitored. Clinical scoring of arthritis was followed by histological scoring and micro-CT analysis. Flow cytrometry was used to asses thymic T-cell development and T-cell effector populations in arthritic joints.

Results: Haploinsufficiency of *PTPN2* significantly increased the severity of arthritis in SKG mice. Importantly, transfer of $PTPN2^{+/-}$ $CD4^+$ T-cells to $RAG2^{-/-}$ mice was sufficent to increase severity of arthritis when compared to transfer of $PTPN2^{+/+}$ $CD4^+$ T-cells. Further investigation into the effect of *PTPN2* haploinsufficiency in T-cell function revealed no alterations in thymocyte development or

selection; however, arthritic *PTPN2*$^{+/-}$ SKG mice showed an increased accumulation of Th17 cells in arthritic joints.

Conclusion: Haploinsufficiency of *PTPN2* enhances CD4^{+} T-cell mediated autoimmune arthritis in mice.

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Abstract Number: 2557

Comparable Therapeutic Potential of Umbilical Cord Mesenchymal Stem Cells in Collagen Induced Arthritis with Anti-Tumor Necrosis Factor or Anti-CD20

Yue Sun, Wei Kong, Weiwei Chen, Genhong Yao, Xuebing Feng and **Lingyun Sun**, Department of Rheumatology and Immunology, The Affiliated Drum Tower Hospital of Nanjing University Medical School, Nanjing, China
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Background/Purpose: Tremendous progress has been made in the development of non-conventional therapies for rheumatoid arthritis (RA). Mesenchymal stem cells (MSC) present multiple immunosuppressive capacities and may have the potential to exert therapeutic effect in RA. In this study, the effects of MSC transplantation on established collagen-induced arthritis (CIA) were evaluated and compared with two kinds of biologic agents, anti-tumor necrosis factor (TNF) and anti-CD20 antibody.

Methods: CIA was induced with the immunization of type Ⅱ collagen (CⅡ) in DBA/1 mice. Human umbilical cord derived MSC (5×10^6), anti-TNF antibody (100μg) and anti-CD20 antibody (200μg) were injected i.p. into mice on day 28 after the immunization, respectively. The control group was treated with PBS or human fibroblasts (5×10^6). All mice were sacrificed 3 weeks later and arthritis severity was assessed by clinical and histology scoring. The frequency of CD4^{+} T cell subsets, B cells and plasma cells in spleen was analyzed by flow cytometry. Serum levels of autoantibody to mouse CⅡ were also determined. The ability of MSC to regulate the balance of T helper cell subsets in CⅡ stimulated CIA CD4^{+} T cells was assessed *in vitro*.

Results: MSC treatment significantly decreased the severity of arthritis and pathology scores, which was comparable to anti-TNF or anti-CD20 treatment. All of the three treatments resulted in a decrease in Th1 subset, but none of them altered the percentage of Th2 subset. Except anti-CD20 treatment, both MSC and anti-TNF treatment significantly decreased Th17 subset. Anti-CD20 treatment depleted nearly half of B220+ cells, and markedly reduced the frequency of plasma cells and serum levels of autoantibody compared to the control group [(738±187) U/ml vs (1817±447) U/ml, $P<0.001$]. The decrease of autoantibody level was also detectable in the group of anti-TNF treatment (663±336 U/ml) or MSC treatment (1057±362 U/ml), but neither of these two treatments showed significant effect on the percentage of B cells or plasma cells. MSC inhibited the generation of T follicular helper (Tfh) cells which play a key role for supporting B cells and antoantibody production. MSC treatment also enhanced the proportion of regulatory T (Treg) cells compared to the control group. In vitro MSC inhibited the generation of IL17^{+} or IFNγ^{+} T cells, induced Foxp3^{+} T cells, and also reduced pathogenic IL17^{+}IFNγ^{+} or IL-17^{+}Foxp3^{+} T cells.

Conclusion: These results indicated that MSC may have a role in preventing the pathogenic plasticity of CD4^{+} T cell subsets in arthritic milieu. Umbilical cord (UC)-MSC could exert comparable effects to biologic agents and effectively correct the immune imbalance in CIA. UC-MSC may provide a promising approach for the treatment of RA.

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Abstract Number: 2558

The Role of Leukocyte Associated Immunoglobulin-like Receptor-1 (LAIR-1) in Collagen-Induced Arthritis

Seunghyun Kim[1], John E. Coligan[2], Jeoung-Eun Park[3], John M. Stuart[4], Andrew Kang[5] and Linda Myers[5], [1]Rheumatology, University of Tennessee Health Science Center, Memphis, TN, [2]NIH, Bethesda, MD, [3]University of Tennessee, Memphis, TN, [4]University of Tennessee/Veterans Affairs, Memphis, TN, [5]University of Tennessee Health Science Center, Memphis, TN
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Background/Purpose: Several observations implicate a critical role for T cell dysregulation as a central problem in RA. We present a method for suppressing T cell activation by activating natural inhibitory receptors called leukocyte associated immunoglobulin-like receptor-1 (LAIR-1). We used the collagen-induced arthritis model and DR-1 tg mice to study the importance of LAIR-1 in autoimmune arthritis.

Methods: a.) *Murine* splenocytes (LAIR-1 +/+ or LAIR-1 -/-) were stimulated with soluble CD3 in the presence or absence of collagen and supernatants were collected for cytokine analysis. b.) DR-1 mice were immunized with CII/CFA to induce arthritis and were injected intra-articularly with 0.3mg of either the stimulatory monoclonal antibody to LAIR-1 or a hamster IgG control. c.) DR1/LAIR-1 -/- and DR1/LAIR-1 +/+ mice were immunized to induce arthritis and mean severity scores were recorded thrice weekly.

Results: a.) In the presence of LAIR-1, CD3-induced cytokine secretion was significantly suppressed in the presence of collagen, while LAIR-1 -/- cells had no attenuation. b.) Treatment with the stimulatory monoclonal antibody to LAIR-1 attenuated CIA in the mice (severity scores 1.5 ± 1.9 vs. 6.4 ± 2.4, $p = 0.007$). c.) DR1/LAIR-1-/- mice that were immunized with CII developed more severe arthritis and had a greater percentage of limbs affected with arthritis than did the wild type (DR1/LAIR-1 +/+) group ($p<0.05$).

Conclusion: Taken together, these data demonstrate that collagen can suppress T cell cytokine response in the presence of LAIR-1. Treatment with stimulating mLAIR-1 antibodies suppresses CIA while DR1/LAIR-1 -/- mice develop more severe arthritis than wild type controls. These data suggest that LAIR-1 may be a potential therapeutic target for suppressing RA.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/the-role-of-leukocyte-associated-immunoglobulin-like-receptor-1-lair-1-in-collagen-induced-arthritis

Abstract Number: 2559

PRO-Resolving Mediators Issued from Apoptotic CELL Efferocytosis (SUPERMAPO) Modulate Antigen Presenting CELL Properties Toward a Tolerogenic Profile: Efficacy in the Treatment of Collagen- Induced Arthritis

Francis Bonnefoy[1], Romain Vallion[2], Mélanie Couturier[3], Anna Daoui[3], **Eric Toussirot**[4] and Sylvain Perruche[1], [1]UMR1098 INSERM, EFS Bourgogne Franche Comté, Besançon, France, [2]INSERM UMR 1098, EFS Bourgogne Franche Comté, Besançon, France, [3]INSERM UMR1098, EFS Bourgogne Franche Comté, Besançon, France, [4]Service de Rhumatologie, CHU J Minjoz, Besancon, France
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Background/Purpose: Pro-resolving mediators produced by macrophages eliminating apoptotic effector cells during the resolution of inflammation have been shown to stop inflammation, favor tissue repair and return to homeostasis. In immune-mediated inflammatory diseases such as rheumatoid arthritis (RA), one may believe that reintroducing proresolving mediators would allow the control of the

disease. We have developed a cell culture system of macrophages and apoptotic cells that mimics this phase of resolution. The supernatant of this cell culture system called SuperMApo (SUPERnatant issued from Macrophage APOptotic cell culture) is enriched in pro-resolving factors including anti-inflammatory cytokines like TGF-b.

Objectives: to evaluate the effects of SuperMApo in the treatment of collagen-induced arthritis (CIA).

Methods: SuperMApo is obtained after 48h of culturing macrophages from peritoneal cavity with apoptotic cells obtained from thymus after X-ray irradiation. CIA was used as a model of RA. SuperMApo (200 µL of 5x concentrated SuperMApo,IV, for 2 days) was injected in score 8 CIA mice. The effect of SuperMApo was first evaluated on APC and T cells from naïve mice in terms of phenotype, profile and properties such as maturation of APC before or after TLR-ligand stimulation and T cell polarization assays. Then, SuperMApo was evaluated in vivo in CIA mice.

Results: Macrophages, cDC and pDC submitted to SuperMApo demonstrated robust insensitivity to TLR ligand-induced activation, particularly in terms of co-stimulatory molecules expression. Spleen cells cultured with SuperMApo demonstrated a strong Treg increase. This was confirmed using naïve CD4+CD25– T cells cultured in the presence of SuperMApo showing Foxp3 expression. CIA mice received 2 injections of SuperMApo (over 48h) and demonstrated a significant long term decrease of CIA (joint score before and after SuperMApo: 8-10 and 1-4, respectively; sustained response to 60 days). This clinical improvement was associated with a higher suppressive function of Treg. Treg transfer from mice treated by SuperMApo to arthritic mice induced joint improvement. Finally, we tested SuperMApo effect on PBMC issued from 4 patients with RA, with and without TLR ligand activation. Our results were that monocytes from 3 patients showed a decreased inflammatory phenotype after overnight exposure to SuperMApo (CD80, CD86, CD40 and HLA-DR expression).

Conclusion: these data demonstrated that macrophages eliminating apoptotic cells produced pro-resolving mediators affecting Antigen Presenting Cell properties therefore allowing the control of arthritis in the CIA model

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Abstract Number: 2560

The Mer Tyrosine Kinase Receptor Plays a Protective Role in Joint Inflammation By Mediating Efferocytosis

Claire E.J. Waterborg[1], Silke Beermann[1], Miranda B. Bennink[1], Carla V. Rothlin[2], Greg Lemke[3] and Fons A.J. van de Loo[1], [1]Experimental Rheumatology, Radboud university medical center, Nijmegen, Netherlands, [2]Department of Immunobiology, Yale University School of Medicine, New Haven, CT, [3]Molecular Neurobiology Laboratory, Salk Institute for Biological Studies, La Jolla, CA

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Background/Purpose:

Rheumatoid arthritis (RA) is a chronic autoimmune disease characterized by a hyper-inflammatory response in synovial joints. In joints of patients with active RA, few apoptotic cells are detected, and experimental data suggest that apoptotic cells delivered into the joint are protective. One of the receptors involved in uptake of apoptotic cells, a process called efferocytosis, is the Mer tyrosine kinase receptor. In addition, the Mer receptor is involved in an anti-inflammatory natural feedback mechanism. The local role of Mer during arthritis, however, has not been elucidated.

Methods: One day after the booster injection of collagen-induced arthritis (CIA) in mice, a commercially available antibody against Mer was injected intravenously or an adenovirus overexpressing the Mer ligand Protein S (Pros1) was injected intra-articularly into the knee joints. Mice were macroscopically scored until they were euthanized at day 30 or 31, respectively. Knee joints were taken for histology and synovial biopsies were isolated for cytokine profiling. The KRN serum transfer model was induced by two injections of serum on day 0 and 2 in either Mer-deficient mice or in wild type mice that overexpress Pros1 in their knee joints. Mice were macroscopically scored for 7 days or 14 days, respectively, and knee joints were taken for histology.

Results:

CIA mice treated with anti-Mer antibodies showed increased incidence and higher macroscopic knee score compared to those receiving an isotype control (IgG). Histological analysis showed significantly enhanced synovial inflammation, and higher synovial expression of the apoptosis marker caspase 3 after anti-Mer treatment. This indicates reduced efferocytosis in the anti-Mer treated animals. On the other hand, anti-Mer antibody treatment induced phosphorylation of the Mer receptor in these mice and upregulated synovial expression of the suppressor of cytokine signaling (SOCS) 1 and 3 genes. This could, however, not reduce the synovial expression of matrix-metalloproteinases (MMPs) 3, 9, and 13 and the pro-inflammatory mediator TNFα. In concordance with these data, CIA mice which locally overexpressed Pros1, a ligand that bridges apoptotic cells to the Mer receptor, in the knee joint showed a significant reduction in knee inflammation and expression of TNFα and several MMPs. Resolution of joint inflammation in the KRN-serum arthritis model is dependent on the development of apoptotic cells. We found that in Mer-deficient mice, induction of passive KRN arthritis caused an accelerated onset of disease and enhanced the macroscopic score in both knee and ankle joints. In contrast, intra-articular overexpression of Pros1 before KRN serum injections markedly reduced arthritis severity in wild type mice.

Conclusion: These data indicate the importance of Mer in controlling the severity and resolution of inflammation in experimental arthritis. Our data suggest that promoting Mer-mediated uptake of apoptotic cells in the arthritic joint might be therapeutically beneficial.

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Abstract Number: 2561

TAS5315, a Novel Bruton's Tyrosine Kinase (BTK) Inhibitor, Demonstrates Potent Efficacy in an Animal Model of Rheumatoid Arthritis

Fumihito Hosoi, Youhei Yoshiga, Satoru Iguchi, Ryuusuke Kaneko, Yoshinori Nakachi, Daichi Akasaka, Kazuhiko Yonekura, Teruhiro Utsugi, Eiji Sasaki and Yoshikazu Iwasawa, TAIHO PHARMACEUTICAL CO., LTD., TSUKUBA, Japan

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Background/Purpose: Bruton's tyrosine kinase (BTK) is a member of the Tec family kinases, and is expressed in B cells, monocytes/macrophages, mast cells, basophils and osteoclast[1,2]. BTK regulates cell proliferation and survival of B cells, and the expression of inflammatory factors in macrophages[3]. In osteoclast, RANKL (receptor activator of NF-kB ligand) binds to its receptor RANK, and induces differentiation and bone resorption of osteoclast through BTK-PLCγ signaling pathway[4]. These various effector cells are reported to be associated with disease progression of rheumatoid arthritis[4,5]. Therefore, BTK would be a potential target for a therapeutic agent in rheumatoid arthritis.

Methods: The phosphorylation of BTK and the expression of CD69 on B cells, which were stimulated by anti-IgM, were examined using western blotting or flow cytometry. In macrophages, the expression of inflammatory factors induced by IgG was measured with ELISA assay. The bone resorption activity of mouse osteoclast was evaluated using osteoclast culture kit. To establish collagen-induced arthritis, male DBA/1 mice were injected on day-27 and-6 with an emulsion of complete Freund's adjuvant and bovine type II collagen. On day 0, mice were randomized into treatment groups. TAS5315 was administrated orally once daily for 15 consecutive days. Disease severity was evaluated by clinical score of paw swelling, and the bone destruction of ankle was also measured by micro-CT imaging analysis at the end of treatment period. The scoring of inflammation, pannus, cartilage and bone damage in four joints of the CIA mice was performed by a single blinded pathologist using a modified Mankin score system.

Results: TAS5315 showed a potent inhibitory activity against anti-IgM-induced phosphorylation of BTK with an IC50 in sub nmol/L range. The up-regulation of CD69 on stimulated mouse splenic B cells was suppressed by TAS5315 in a dose-dependent manner (IC50 = 0.2 nmol/L). TAS5315 inhibited the expression of TNFα and CCL3 stimulated by IgG in macrophages, and also suppressed bone resorption activity of osteoclast induced by RANKL. In a mouse collagen-induced arthritis model, TAS5315 dose-dependently and significantly decreased the clinical score in arthritic mice compared with that in vehicle-treated mice, with an ED50 value of 0.12 mg/kg. In the histopathological analysis, TAS5315-treated mice had a marked reduction in the severity of inflammation, pannus, cartilage destruction and bone destruction in a dose-dependent manner. TAS5315-treated mice also showed a remarkable recovery of

bone mineral density compared with vehicle-treated mice by the micro CT analysis of hind paws of CIA mice.

Conclusion: Our study demonstrates that a novel BTK inhibitior, TAS5315, shows significant efficacy in an animal model of rheumatoid arthritis. These data suggests that TAS5315 could be a promising novel therapeutic agent for RA by inhibiting inflammation and bone destruction.

References: 1. Curr Opin Immunol. 2000;12, 282-288, 2. Int Arch Allergy Immunol. 2004; 134, 65-78, 3. Rheumatology (Oxford). 2013; 52, 1155-1162, 4. Arthritis Res Ther. 2011; 13, 3380-3391, 5. Nat Rev Immunol. 2007; 7, 191-201

Disclosure: F. Hosoi, TAIHO PHARMACEUTICAL CO., LTD., 3; **Y. Yoshiga**, TAIHO PHARMACEUTICAL CO., LTD., 3; **S. Iguchi**, TAIHO PHARMACEUTICAL CO., LTD., 3; **R. Kaneko**, TAIHO PHARMACEUTICAL CO., LTD., 3; **Y. Nakachi**, TAIHO PHARMACEUTICAL CO., LTD., 3; **D. Akasaka**, TAIHO PHARMACEUTICAL CO., LTD., 3; **K. Yonekura**, TAIHO PHARMACEUTICAL CO., LTD., 3; **T. Utsugi**, TAIHO PHARMACEUTICAL CO., LTD., 3; **E. Sasaki**, TAIHO PHARMACEUTICAL CO., LTD., 3; **Y. Iwasawa**, TAIHO PHARMACEUTICAL CO., LTD., 3.

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Abstract Number: 2562

The Inhibition of Wnt/Beta-Catenin Signaling Pathway Via Paricalcitol and Pyrvinium Ameliorates Experimental Arthritis

Suleyman Serdar Koca[1], Servet Yolbas[2], Ahmet Yildirim[2], Ahmet Tektemur[3], Zulfinaz Betul Celik[3], Ebru Etem Onalan[3], Ibrahim Hanifi Ozercan[4] and Mustafa Akin[4], [1]İnternal Medicine Division of Rheumatology, Firat University, Faculty of Medicine, Elazig, Turkey, [2]Rheumatology, Department of Rheumatology, Firat University, Elazig, Turkey, [3]Department of Medical Biology Faculty of Medicine, Firat University, Elazig, Turkey, [4]Department of Pathology, Faculty of Medicine, Firat University, Elazig, Turkey
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Background/Purpose: Rheumatoid arthritis (RA) is an inflammatory joint disorder, the progression of which leads to the destruction of cartilage and bone. Fibroblast-like synoviocytes (FLS) display an important role in the pathogenesis of RA. Wnt signaling pathway act several important biological functions, such as cell differentiation, embryonic development, limb development and joint formation. Accumulated evidence has suggested that this signaling pathway plays a key role in the FLS activation, bone resorption and joint destruction in RA. The purpose of this study was to investigate the therapeutic effect of lapatinib on collagen-induced arthritis (CIA) in rats.

Methods: Forty Wistar albino female rats were randomized to 4 groups (n=10 in each group): Group-I as the control group, Group-II as the arthritis (sham) group, Group-III as the Paricalcitol group and Group-IV as the Pyrvinium group were assigned. Arthritis was induced by intradermal injection of chicken type II collagen combined with incomplete Freund's adjuvant. One day after the onset of arthritis, paricalcitol (0.3 µg/kg/day) was injected subcutaneously, and pyrvinium (5 mg/kg/day) was given via oral gavage, until they were killed on day 29. Animals were sacrificed at the 15th day after the onset of arthritis. The paws of the rats were obtained for further analysis. Perisynovial inflammation and cartilage-bone destruction were determined histopathologically in the paws. Tissue axin-2, Wnt-5a and DKK1 mRNA expressions were determined by real-time polymerase chain reaction (RT-PCR).

Results: Arthritis was clinically developed at 12 to 13 days after the injection of collagen (Figure). The 29th day scores were decreased in the paricalcitol and pyrvinium groups compared to the own 13th day score ($p<0.05$ for both), while it was increased in the sham group ($p<0.05$). Histopathological analysis demonstrated the extensive perisynovial inflammation and marked cartilage-bone destruction in sham group rats. Paricalcitol and pyrvinium treatments decreased the perisynovial inflammation and cartilage-bone destruction in the paws. Moreover, the tissue mRNA expressions of axin-2 (22 folds), Wnt5a (11 folds) and DKK1 (3 folds) were increased in the sham group compared to the control group. Their mRNA expressions in paricalcitol and pyrvinium groups were similar in the control group.

Conclusion: The present study shows that Wnt signaling pathway is active in CIA model. Moreover, paricalcitol and pyrvinium those are inhibit Wnt pathway ameliorate CIA. These agents may be candidate to further research in human RA.

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Disclosure: S. S. Koca, None; **S. Yolbas**, None; **A. Yildirim**, None; **A. Tektemur**, None; **Z. B. Celik**, None; **E. E. Onalan**, None; **I. H. Ozercan**, None; **M. Akin**, None.

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Abstract Number: 2563

Immune Regulation By Migrating Mesenchymal Stem Cells Ameliorate Inflammatory Arthritis in Mice

Seung Min Jung, Yoojun Nam and Ji Hyeon Ju, Division of Rheumatology, Department of Internal Medicine, College of Medicine, The Catholic University of Korea, Seoul, South Korea

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Session Time: 9:00AM-11:00AM

Background/Purpose: Mesenchymal stem cells (MSCs) function as immune regulators in inflammatory conditions. However, it is unclear how to control local inflammation by systemically administered MSCs. We aimed to evaluate the therapeutic effect of human MSCs on inflammatory arthritis and to delineate the underlying mechanisms.

Methods: Mice with collagen antibody induced arthritis (CAIA) were intraperitoneally injected with human bone marrow-derived MSCs (5×10^6 cells/500 µl of PBS, two times at three-day interval) or control vehicle. The clinical score and histological features of tarsal joints were compared between two groups. The synovial and spleen tissues of CAIA mice were stained with human anti-nuclear antibody (ANA) to confirm the migration of injected human MSCs. After analysis of multiple cytokines on peritoneal cells, migration assay of MSCs was performed in the presence of SDF-1a and/or CCL5. We evaluated the effect of MSCs on induction of regulatory T cells by coculture system *in vitro* and mRNA profiling *in vivo*.

Results: Treatment with human MSCs alleviated the joint inflammation of CAIA mice. The clinical score was consistently lower in mice injected with MSCs compared to control mice. Histological analysis also revealed the conserved articular structure by MSCs. The joints and spleens of CAIA mice treated with human MSCs were positively stained with human ANA, suggesting recruitment of MSCs to inflamed tissues. Peritoneal lavage cells in mice treated with MSCs expressed a higher level of SDF-1a and CCL5, known as chemoattractants. MSCs migrated more easily in the presence of SDF-1a and/or CCL5. The synovia and spleens of CAIA mice treated with MSCs showed the upregulated expression of FOXP3 mRNA, which was supported by enhanced differentiation into regulatory T cells in coculture of CD4+ T cells and MSCs.

Conclusion: This study suggests that MSCs would directly induce the differentiation of regulatory T cells through migration into inflamed tissues. Systemic administration of MSCs can be a therapeutic option for rheumatoid arthritis.

Disclosure: S. M. Jung, None; **Y. Nam**, None; **J. H. Ju**, None.

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Abstract Number: 2564

Nuclear Receptor 4A2 Is Selectively Upregulated in the Human TNF-Alpha Transgenic Model of Rheumatoid Arthritis

Jackeline Araujo, Cullen Lilley and **Kimberlee Mix**, Biological Sciences, Loyola University New Orleans, New Orleans, LA

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Background/Purpose: The orphan nuclear receptor 4A2 (NR4A2 / NURR1) is emerging as a critical transcription factor in chronic inflammatory joint diseases. We have demonstrated elevated expression of NR4A2 in joint tissues from patients with arthritis, and this receptor promotes synovial hyperplasia and cartilage degradation *in vitro*. NR4A2 transactivates the MMP-13, IL-8, and prolactin promoters in synovial fibroblasts and may therefore contribute to the onset and progression of arthritis. TNF-alpha rapidly and potently induces NR4A2 expression and nuclear localization, suggesting that NR4A2 controls transcriptional responses to inflammation *in vivo*. The current study tests the hypothesis that NR4A2 is an early transcriptional mediator of synovial inflammation in the human TNF-alpha transgenic mouse model of rheumatoid arthritis.

Methods: The hTNF-alpha transgenic model exhibits deregulated expression of the human proinflammatory cytokine due to incorporation of the beta-globin 3' UTR which stabilizes the transcript (Taconic Biosciences, Model 1006). Mice develop severe polyarthritis by 10 weeks of age with 100% penetrance. To address early changes in gene expression, RNA was extracted from 8-week old male hTNF-alpha and wild-type mice and NR4A1-3 mRNA was detected by RT-qPCR. Gene expression patterns were compared between hTNF-alpha and wild-type joints using RT-qPCR panels specific for 88 genes involved in RA pathogenesis and housekeeping controls.

Results: Joints from 8-week old hTNF-alpha mice lacked clinical signs of arthritis, yet several genes involved in pathogenesis were upregulated: CCL5 (15-fold), IL-1-beta (13-fold), TNFRSF1b(10-fold), ICAM1 (7-fold), CCR5 (5-fold), TNF (5-fold), IL-6 (4-fold), NF-kappa-B (3-fold), and CREB (2-fold). All three NR4A receptors were expressed at detectable levels by RT-qPCR, however only NR4A2 was selectively increased by 50% in the forepaws and hindpaws of hTNF-alpha mice relative to wild-type controls ($p<0.05$).

Conclusion: Upregulation of NR4A2 mRNA precedes clinical signs of arthritis in the hTNF-alpha model, suggesting that NR4A2 is an early transcriptional mediator of synovial inflammation. In line with this, several genes involved in inflammation and cell signaling are expressed at elevated levels, demonstrating that molecular pathogenesis is underway. Future studies will examine the expression and distribution of NR4A2 throughout the course of disease and examine the therapeutic potential of targeting NR4A2 in the hTNF-alpha model of RA.

Disclosure: J. Araujo, None; **C. Lilley**, None; **K. Mix**, None.

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Abstract Number: 2565

ACPA Specific IVIG Attenuate Collagen Induced Arthritis in Mice

Shaye Kivity[1], Nina Svetliscky[1], Qusim Odeh[1], Smadar Gertel[1], Howard Amital[1], Omer Gendelman[1], Iris Barshack[2], Alexander Volkov[2], Eran Bar-Meir[3], Miri Blank[1] and Yehuda Shoenfeld[4], [1]Sheba Medical Center, Zabludowicz Center for Autoimmune Diseases, affiliated to Sackler Faculty of Medicine, Tel-Aviv University, Ramat Gan, Israel, [2]Sheba Medical Center, Institute of Pathology, affiliated to Sackler Faculty of Medicine, Tel-Aviv University, Ramat Gan, Israel, [3]Plastic surgeon Poria Medical Center affiliated to Faculty of medicine in the Galilee Bar-Ilan university, Poria, Israel, [4]Sheba Medical Center, Zabludowicz Center for Autoimmune Diseases, affiliated to affiliated to Sackler Faculty of Medicine, Tel-Aviv University, Ramat Gan, Israel

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Background/Purpose:

Administration of intravenous-immunoglobulin (IVIg) is a recognized safe and efficient immunomodulatore therapy for many autoimmune diseases. Anti-idiotypic antibody binding to pathogenic autoantibodies was proposed as one of mechanisms attributed to the protective activity of IVIg in autoimmunity. The aim of this study was to fractionate the anti-anti-citrullinated protein anti-idiotypic-antibodies (anti-ACPA) from a IVIg preparation and to test it as a treatment for collagen-induced arthritis in mice.

Methods:

IVIg was loaded on an ACPA column. The eluted fraction was defined as ACPA-specific-IVIg (ACPA-sIVIg). Collagen-induced-arthritis (CIA) was induced in mice. Mice were treated weekly with ACPA-sIVIg, low-dose-IVIg, high-dose-IVIg and PBS. Sera-ACPA titers, anti-collagen Abs and cytokine levels were analyzed by ELISA; antibody-forming-cell activity by ELIspot assay; expansion of T-regulatory cell (Treg) population by FACS.

Results:

ACPA-sIVIg inhibited ACPA binding to citrullinated-peptides (CCP) *in-vitro* 100 times more efficiently than the IVIg compound. ACPA-sIVIg was significantly more effective than IVIg-preparation in attenuating development of collagen-induced arthritis. Splenocytes from CIA mice treated with ACPA-sIVIg reduced the ACPA and anti-collagen-antibody titers including the number of anti-collagen and ACPA antibody-forming cells. In parallel, splenocytes from ACPA-sIVIg treated mice secreted higher levels of anti-inflammatory cytokines and lower proinflammatory cytokines. The ACPA-sIVIg inhibitory potential was accompanied with expansion of the Treg population. Low dose IVIg did not affect the humoral and cellular response in the CIA-mice, in comparison to PBS treated mice.

Conclusion:

Based on our results, IVIg may be considered as a safe compound for treating patients with rheumatoid-arthritis by neutralizing pathogenic autoantibodies , reducing proinflammatory cytokines and expanding Treg population.

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Abstract Number: 2566

Novel Therapeutic Compound Tuftsin-Phosphorylcholine Attenuate Collagen Induced Arthritis

Tomer Bashi[1], Miri Blank[1], Jasna Omersel[2], Alexander Volkov[3], Iris Barshack[3] and **Yehuda Shoenfeld**[1], [1]Sheba Medical Center, Zabludowicz Center for Autoimmune Diseases, affiliated to affiliated to Sackler Faculty of Medicine, Tel-Aviv University, Ramat Gan, Israel, [2]Faculty of pharmacy, University of Ljublijana, Ljublijana, Slovenia, [3]Sheba Medical Center, Institute of Pathology, affiliated to Sackler Faculty of Medicine, Tel-Aviv University, Ramat Gan, Israel

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Background/Purpose:

Treatment with helminthes and ova from helminthes, improved clinical findings of several autoimmune diseases in patients and in animal models. We aimed to decipher the tolerogenic potential of Tuftsin- Phosphorylcholine (TPC), a helminth based compound in collagen induced arthritis (CIA) a mouse model of rheumatoid arthritis (RA).

Methods:

CIA DBA mice were treated with TPC, subcutaneously (5 µg/0.1 ml) or orally (250 µg/0.1 ml), starting 3 days before disease induction. The control groups were treated with PBS. Collagen antibodies were tested by ELISA, cytokines protein levels by DuoSet ELISA and T and B-regulatory cells phenotypes by FACS.

Results:

TPC treated mice had a significantly lower arthritis score 1.5 with comparison to the control mice 11.8 ($p<0.0001$) in both the subcutaneous and orally treated groups at Day 31. Moreover, histology analysis demonstrated highly inflamed joints in the CIA DBA mice, whereas the TPC treated mice maintained normal joint structure. Moreover, TPC decreased the titers of circulating collagen II antibodies in the sera of the mice ($p<0.0001$) as well as enhanced the expression of IL-10 ($p < 0.001$), and inhibited the production of

TNFα, IL-17 and IL-1β ($p < 0.0001$). TPC significantly expanded the CD4+CD25+FOXP3+ T-regulatory (Treg) cells and CD19+IL-10^{high}+$CD5^{high}CD1d^{high}$TIM-1^{+} B-regulatory (Breg) cells phenotypes ($p < 0.0001$) in the treated mice.

Conclusion:

Our data indicate that treatment with TPC attenuate CIA development in DBA mice which was exemplified by a low arthritic score, normal joints histology, reduced pro-inflammatory cytokines and increased anti-inflammatory cytokine expression, as well as expansion of Treg and Breg cells. Our results may lead to a new approach for a natural therapy for early RA patients.

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Abstract Number: 2567

SPACIA1/SAAL1-Deficient Mice Show Reduced Disease Progression in Collagen-Induced Arthritis

Ryoji Fujii[1], Iwao Seki[2], Rie Komatsu[1], Tomomi Kohara[2], Miwa Takai[2], Tomoo Sato[3], Koji Konomi[2], Hiroyuki Aono[2], Kazuo Yudoh[1], Kusuki Nishioka[4] and Toshihiro Nakajima[5], [1]Institute of Medical Science, St. Marianna University School of Medicine, Kanagawa, Japan, [2]Santen Pharmaceutical Co. Ltd., Nara, Japan, [3]Molecular Medical Science, St. Marianna University School of Medicine, Kanagawa, Japan, [4]Institute of Medical Science, Tokyo Medical University, Tokyo, Japan, [5]Department of Locomotor Science/Future Medical Science, Institute of Medical Science, integrated Gene Editing Section (iGES), Tokyo Medical University, Tokyo, Japan
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Background/Purpose: *SPACIA1/SAAL1* is a gene associated with abnormal synovial proliferation. We previously showed that *SPACIA1/SAAL1* small interfering RNA inhibited the proliferation of rheumatoid arthritis synovial fibroblasts *in vitro* and that *SPACIA1/SAAL1* transgenic mice exhibited early onset and rapid progression of collagen-induced arthritis (CIA). Therefore, SPACIA1/SAAL1 could be involved in the progression of synovitis. In the present study, we generated *SPACIA1/SAAL1*-deficient mice and investigated the gene's potential as a druggable target.

Methods: To ablate the functional mouse *SPACIA1/SAAL1* locus, we deleted its exon 4 in the C57BL/6 genome using the Cre/loxP system to cause a frameshift mutation. After backcross mating with the DBA/1J strain for 8 generations, we examined the effect of SPACIA1/SAAL1 in CIA. In *SPACIA1/SAAL1*-deficient and wild-type (control) mice, the serum levels of anti-type II collagen antibody and the bone destruction score were measured on day 56 after the first collagen injection.

Results: Heterozygous ($SPACIA1^{+/-}$) and homozygous ($SPACIA1^{-/-}$) mice systemically lacking SPACIA1/SAAL1 developed normally and did not show abnormalities. In the $SPACIA1^{-/-}$ mice, the incidence of arthritis and its score were significantly reduced on days 35 and 56, respectively, when compared with values in wild-type mice. However, all tested mice developed CIA eventually. The mean anti-type II collagen antibody level and bone destruction score in the $SPACIA1^{-/-}$ mice decreased by half compared with those in wild-type mice, but this difference was not significant.

Conclusion: Consistent with our previous study of CIA using *SPACIA1/SAAL1* transgenic mice, this study also indicated that SPACIA1/SAAL1 may be involved in the progression of CIA. However, we conclude that there is almost no potential for SPACIA1/SAAL1 itself as a druggable target, although SPACIA could be related to regulation of crucial factors in CIA. We previously found that SPACIA1/SAAL1 is related to cyclin-dependent kinase 6 expression, at least in cultured rheumatoid arthritis synovial fibroblasts. We are currently studying downstream targets of SPACIA1/SAAL1, including cyclin-dependent kinase 6, to find potential druggable targets.

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progression-in-collagen-induced-arthritis

Abstract Number: 2568

The Osteoimmunological Mechanistic Basis of Low-Dose Radiotherapy in TNF Driven Arthritis

Lisa Deloch[1], Anja Derer[1], Axel J. Hueber[2], Barbara Happich[3], Rainer Fietkau[1], Benjamin Frey[1] and Udo S. Gaipl[1], [1]Department of Radiation Oncology, University of Erlangen-Nuremberg, Erlangen, Germany, [2]Department of Internal Medicine 3, Rheumatology & Immunology, University of Erlangen-Nuremberg, Erlangen, Germany, [3]Internal Medicine 3, Rheumatology and Immunology, University of Erlangen-Nuremberg, Erlangen, Germany

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Background/Purpose: Today many treatment options for Rheumatoid Arthritis (RA) and degenerative inflammatory musculoskeletal diseases are available, however, not all patients respond properly or have to reduce or stop their medication due to adverse reactions. In such cases treatment with low dose-radiotherapy (LD-RT) with X-rays can be beneficial to attenuate inflammation, reduce pain and improve the quality of life, as suggested by studies by Ott et al. (2012-2014) and Seegenschmiedt et al. (1998). Preclinical *in vitro* models have revealed that doses of X-ray ranging from 0.1 Gray (Gy) to 1.0 Gy have an impact on immune cells and reduce the inflammatory phenotype of endothelial cells, neutrophils, and macrophages. A dose of 0.5 Gy has been shown to be the most efficient. Even though these mechanisms are well known and accepted, health care professionals and patients often refrain from low LD-RT. The main reasons for that are fear of radiation, lack of randomized trials and lack of *in vivo* examinations with inflammatory animal models. We therefore aimed to examine the impact of local LD-RT with 0.5 Gy on inflammation and bone homeostasis in human *TNF-α* transgenic (h*TNF-α*tg) mice.

Methods: Inflamed joints of h*TNFα* tg mice were locally irradiated (0.5 Gy, 250 kV, 15mA) and monitored over a time course of 30 days. Afterwards, paw sections were analyzed using histomorphological methods and the OsteoMeasure™ Software. In an *ex vivo* setting, we investigated the effects of LD-RT on bone marrow-derived osteoclasts (OC) of h*TNFα*tg mice as well as on murine and human fibroblast-like synoviocytes (FLS) using qPCR, ELISA and flow cytometry.

Results: A significant improvement of grip strength over 30 days in mice treated locally with 1x 0.5 Gy of X-rays was observed. Further histological analysis of irradiated paws showed a significant reduction of the inflammatory area as identified by decrease of leukocyte infiltration, reduction of bone loss, and OC numbers in comparison to mock treated control animals. *Ex vivo* differentiation of h*TNFα*tg mice derived OCs was also significantly reduced after exposure to X-rays in the dose range of 0.5 to 2.0 Gy. Further, OC function seems to be down-regulated after an irradiation with 2x 0.5 Gy as indicated by qPCR analysis. Irradiation of human RA FLS resulted in a dose-dependent reduction of cell growth and increased numbers of apoptotic cells.

Conclusion: On a mechanistic preclinical osteoimmunlogical basis our findings support that LD-RT can influence TNF dependent arthritis. The results from our OC experiments further imply that LD-RT does not only have a considerably decelerating effect on inflammation, but also on bone erosion. Future placebo controlled studies in humans need to address its effect in RA patients.

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Abstract Number: 2569

Regulation of SIRT1 Maybe a Perfect Strategy in Treatment of Rheumatoid Arthritis

Sang-Yeob Lee[1], Sung Won Lee[2], Won Tae Chung[2], Jae Ho Bae[3], So Youn Park[4] and Chi Dae Kim[4], [1]Division of Rheumatology,

Department of Internal Medicine, Dong-A University College of Medicine, Busan, South Korea, [2]Rheumatology, Dong-A University Hospital, Busan, South Korea, [3]Biochemistry, Pusan national university, Yong -San, South Korea, [4]Medical Research Center for Ischemic Tissue Regeneration, Pusan national university, Yong -San, South Korea
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Background/Purpose: Monocyte may differentiate to osteoclasts in bone and macrophages in joint. so, blocking of monocyte differentiation maybe effective target in RA (rheumatoid arthritis) treatment. in this study, we interrupted monocyte differentiation via SIRT1 and proposed potential strategy in treatment of RA.

Methods: In this study, monocytes from synovial fluid of RA patients (RAMCs), THP-1 monocytes, bone marrow–derived monocytes (BMDCs) from mice and RAW 264.7 cells were studied. Expression of macrophages surface markers (CD11b, CD14 and CD36) were analysis by real-time PCR. TNF-α, IL-1β and IL-6 levels were measured in the conditioned medium by ELISA. The effects of SIRT1 on osteoclast formation were detected TRAP activity and pit formation. In addition, RANKL [receptor activator of nuclear factor kappa B (RANK) ligand]-induced RANK expression in bone marrow–derived monocyte/macrophage precursors (BMMs) and RAW 264.7 cells were measured using western blot. Anti-arthritic effects of SIRT1were evaluated in CIA mice.

Results: PMA-induced expression of macrophages surface markers (CD11b, CD14 and CD36) and proinflammatory cytokines (TNF-α, IL-1β and IL-6) secretion was inhibited by resveratrol, SIRT1 activator in RAMCs. BMDCs from SIRT1 TG mice were inhibited differentiation by PMA than control BMDCs from C57BL/6 mice. These effects were associated with decrease in proinflammatory cytokines (TNF-α, IL-1β and IL-6) secreation by decreasing mRNA expression in BMDCs from SIRT1 TG mice. Further, resveratrol suppressed the PMA-induced PU.1 activation, which is critical transcription factor for macrophages differentiation. SIRT1 activity and expression were elevated by cilostazol. Cilostazol inhibits monocytes to macrophages differentiation through the down-regulates PU.1 activity and cilostazol elevated SIRT1 mRNA and protein levels in 12 - 24 h and increased SIRT1 activity, and these effects were also inhibited by sirtinol, a SIRT1 inhibitor. Furthermore, the RANKL-induced nuclear expression of PU.1 was suppressed by cilostazol, a SIRT1 activator. In addition, marked RANKL-induced RANK immunofluorescence staining in Raw264.7 cells was strongly attenuated by cilostazol and by rSIRT1, and these attenuations were prevented by sirtinol. Extensive RANK staining of knee synovial tissues in a mouse model of collagen-induced arthritis (CIA) was also markedly reduced by cilostazol (30 mg/kg/day), and in BMMs both RANKL- and M-CSF-induced differentiation of BMMs to multinucleated $TRAP^+$ giant cells and resorption pit formation were inhibited by cilostazol in association with a decrease in TRAP (a marker enzyme of osteoclasts) activity.

Conclusion: SIRT1 have dual a role in anti-osteoclast formation BMMs of RA bone and inhibiting differentiation monocyte to macrophage in RA synovium. so, regulation of SIRT1 maybe a potential strategy for perfect RA treatment.

Abstract Number: 2570

Comparative Analysis of Collagen-Antibody Induced Arthritis and the Arthritis Inhibitory Potential of Specific ACPA in Two Mouse Subspecies Genetically Separated about One Million Years Ago

Christina Grimm[1], Bianka Marklein[1], Zoltan Konthur[2], Gerd Burmester[1] and **Karl Skriner**[1], [1]Department of Rheumatology and Clinical Immunology, Charité - Universitätsmedizin Berlin, Berlin, Germany, [2]Department of Vertebrate Genomics, Max Planck Institute for Molecular Genetics, Berlin, Germany
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Background/Purpose:

Rheumatoid arthritis (RA) is believed to be induced by environmental, genetic and immunological factors. Monoclonal Anti-citrullinated protein/peptide autoantibodies (ACPA) target different citrullinated proteins years before RA is diagnosed but their role is still largely unknown. As a prerequisite to identify genetic factors involved in rheumatoid arthritis, we analyzed the susceptibility of PWD Mus musculus musculus subspecies, separated from Mus musculus domesticus about one million years ago to collagen antibody-induced arthritis (CAIA) and the role of ACPA antibodies in the CAIA model of arthritis.

Methods:

Collagen antibody-induced arthritis (CAIA antibody cocktail provided by Modiquest GmbH) was induced by administration of collagen antibodies followed by lipopolysaccharide injection. Two genetically distinct mouse strains, representatives of the subspecies *Mus musculus domesticus* and *Mus musculus musculus* as well as their F1 hybrids, and consomis strains thereof were analyzed for the development of clinical and histological signs of arthritis upon CAIA treatment. ACPA antibodies were tested by adding it to the CAIA cocktail and their autoantigenic profile was analysed using protein macroarrays as previously described (**Leidinger et al., 2009)**

Results:

The wild-derived mouse strain PWD/Ph was highly susceptible to CAIA induced arthritis, whereas the classical laboratory strain C57BL/6J was resistant (2mg CAIA cocktail). Mice carrying chromosomes 5 or 12 from PWD on a B6 background display a B6-like phenotype in the CAIA model as well as the F1 hybrids (B6xPWD and PWDxB6) implicating the presence of dominant resistance modifiers in the C57BL/6J genetic background. The two mouse strains differ highly in their autoantigenic profile induced and the PWD strain shows decrease of B-cells and IgA, IgG, IgM levels.

Injecting specific monoclonal ACPAs reactive with the citrullintated H1 and H4 were able to block the CAIA induced arthritis. This inhibition can be explained in part by a Toll dependent inhibition of osteoclasts. Moreover we show the first time that TLR2 activation via Porphyromonas gingivalis LPS or vesicles and lipomannan treated animals show a 80% reduction of arthritis score compared to E. coli LPS in a C57BL/6J CAIA model.

Anti-collagen specific antibodies are increased in both strains B6 and PWD when arthritis is induced. Rheumatoid factor RF was not detected in PWD or B6 mice before and after the CAIA-treatment nor in the LPS-treated control animals. Interestingly, the commercial CCP2 ELISA detected ACPA in some animals regardless of the treatment. Using the arginine and citrulline containing peptides as control shows that this response is directed to the arginine containing peptide and in most of the animals citrullination downregulates the antigenicity of the autoantibody targeting of uncitrullinated proteins or peptides.

Conclusion:

The *Mus musculus musculus* derived mouse strain PWD/Ph is a highly susceptible CAIA mouse strain to study new genetic arthritis markers. TLR2 activation of P. gingivalis LPS blocks CAIA and specific ACPAs inhibit osteoclast activation and may be used as therapeutic antibodies in the future that protect from RA destructive development.

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View Abstract and Citation Information Online - http://acrabstracts.org/abstract/comparative-analysis-of-collagen-antibody-induced-arthritis-and-the-arthritis-inhibitory-potential-of-specific-acpa-in-two-mouse-subspecies-genetically-separated-about-one-million-years-ago

Abstract Number: 2571

Anti-IL-6 Receptor Antibody Prevents Loss of Bone Strength in a Mouse Model of Collagen-Induced Arthritis

Hiroto Yoshida, Yuanyuan Bi, Miho Suzuki, Keisuke Tanaka and Yoshihiro Matsumoto, Product Research Department, Chugai Pharmaceutical Co., Ltd., Gotemba, Japan

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Background/Purpose: Rheumatoid arthritis (RA) is a disease that typically induces secondary osteoporosis, which increases the risk

of bone fractures and, consequently, mortality. Bone fracture is induced not only by lower bone mineral density (BMD) but also by deterioration in bone structure. Anti-IL-6 receptor antibody is used as RA treatment, however its effect on bone strength is not clear. The purpose of this study is to clarify the influence of IL-6 on the changes of bone strength in arthritis, using a mouse model of collagen-induced arthritis (CIA). Additionally, we analyzed what correlates with bone strength in CIA mice.

Methods: CIA was immunized in DBA/1J mice by an intradermal injection of bovine type II collagen on Days 0 and 21. Mice were injected intraperitoneally with anti-mouse IL-6 receptor antibody (MR16-1) on Days 0 and 21. Urine and serum were sampled on Day 33-35. Urinary collagen type 1 cross-linked C-telopeptide (CTX), a bone resorption marker, and serum procollagen type 1 N-terminal propeptide (P1NP), a bone formation marker, were measured by ELISA. Femurs and feet were excised on Day 35, the peak of swelling of joints. As the bone structure, trabecular bone volume (BV/TV) of distal femur, and cortical bone thickness (Ct) of femur shaft, BMD of femur shaft and foot were analysed by micro-computed tomography (μCT). The bone strength of femur shaft was measured a maximum load by bending test.

Results: In CIA mice, urinary CTX and serum P1NP were significantly higher and lower, respectively, than in non-immunized mice. All parameters of bone structure (BV/TV of the distal femur, Ct of the femur shaft, BMD of the femur shaft and the foot) in CIA mice significantly decreased than in non-immunized mice. Moreover, maximum load of the femur shaft in CIA mice was significantly lower than in non-immunized mice. Maximum load of the femur shaft more strongly correlated with Ct of the femur shaft than BMD of the femur shaft and swelling score in hind limb. On the other hand, swelling score in the hind limb most strongly correlated with BMD of the foot, but did not correlate with Ct of the femur shaft. MR16-1 suppressed the development of arthritis. An increase in urinary CTX and a decrease in serum P1NP during development of CIA were suppressed by MR16-1. MR16-1 treatment significantly prevented a decrease in BV/TV of the distal femur, BMD of the foot and maximum load of the femur shaft by CIA induction.

Conclusion: We demonstrated that CIA induced loss of bone strength through a deterioration of bone structure and that cortical thickness has possibility of playing the most important role in bone strength. Moreover, our results indicated that IL-6 played an important role in bone strength because anti-IL-6 receptor antibody prevented the loss in bone strength in CIA.

Disclosure: H. Yoshida, None; **Y. Bi**, None; **M. Suzuki**, None; **K. Tanaka**, None; **Y. Matsumoto**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/anti-il-6-receptor-antibody-prevents-loss-of-bone-strength-in-a-mouse-model-of-collagen-induced-arthritis

Abstract Number: 2572

Protective and Therapeutic Effects of Growth Hormone on Collagen-Induced Arthritis

Ricardo J. Villares[1], Gabriel Criado[2], Rosa P Gomariz[3], Yasmina Juarranz[3], Javier Leceta[3], Graciela Cascio[4], Jose L. Pablos[5] and Mario Mellado[6], [1]Immunology & Oncology, Centro Nacional de Biotecnología-CSIC, Madrid, Spain, [2]Servicio de Reumatología, Instituto de Investigación Hospital 12 de Octubre (i+12), Madrid, Spain, [3]Cellular Biology, School of Biology. Universidad Complutense de Madrid, Madrid, Spain, [4]Immunoloy & Oncology, Centro Nacional de Biotecnología-CSIC, Madrid, Spain, [5]Instituto de Investigacion Hospital, Madrid, Spain, [6]Immunology and Oncology, Centro Nacional de Biotecnología. CNIC, Madrid, Spain
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Background/Purpose: Inflammatory (M1) macrophages and T helper 17 (TH17) cells are central to rheumatoid arthritis (RA) pathogenesis. Although the growth hormone [GH]/insulin-like growth factor 1 axis is involved in joint repair, little is known of the GH function in control of innate and adaptive immunity. To analyze the potential clinical and immunological effects of GH treatment in RA, we use a murine collagen-induced arthritis (CIA) model, compile data on disease development, and study the molecular and cellular mechanisms involved.

Methods:

We tested the *in vivo*inhibitory effect of GH in a murine CIA model. Disease was induced in 8- to 10-week-old transgenic C57BL/6J mice expressing bovine GH (Tg-bGH), Wild type (WT) littermates, and DBA1 mice, by intradermal immunization with 200 mg chicken type II collagen (CII) in complete Freund's adjuvant.

To assess clinical effectiveness in DBA1 mice, we administered recombinant human (rh)GH subcutaneously for 20 days as a

therapeutic regime. At disease onset, DBA1 mice with a clinical arthritis score >1 (scale: 0-12) were randomized to receive rhGH treatment (100 mg/kg/day; n = 10) or vehicle (n= 10). Statistical differences were analyzed by ANOVA and Mann-Whitney U-test. P values <0.05 were considered significant.

GH effect was analyzed by flow cytometry (FC) to detect Treg (FoxP3+), Th1 (IFNg+) and Th17 (IL17+) CD4 T cells in secondary lymphoid tissues. T cell responses were evaluated *in vitro*by CII-induced proliferation as measured by incorporation of the colorimetric reagent WST-1. Serum levels of anti-CII antibodies were determined by ELISA. T cell differentiation was determined in various tissues by quantitative PCR using probes for the specific transcription factors t-bet, RORgT and FoxP3, and for Th1/Th17/Treg-specific cytokines. To test the ability of dendritic cells (DC) from WT and Tg-bGH mice to present antigen to T cells from OT-II mice, we loaded DC with the ovoalbumin peptide 329-337 and assessed T cell activation and proliferation by FC and CellTrace Violet dilution.

Results:

We found significant reduction in GH transgenic compared to control mice in disease incidence (25% vs. 70%) and onset time (34.5±1.7 vs. 23.2±3.5; p<0.001), and a tendency to lower clinical scores (1.5±0.7 vs. 3.8±1.8 at day 37 post-immunization, p=0.13). GH treatment of arthritic DBA1 mice ameliorated disease, with a reduced cumulative arthritis score (2.5±0.8) compared to the vehicle group (4.0±0.6)(p=0.06).

The molecular mechanism involves an increased Treg/Th17 ratio and a shift to a non-pathogenic phenotype in Th17 cells and in joint-infiltrated macrophages in Tg-bGH mice; these mice had a M2 (non-inflammatory) macrophage profile compared to M1 in WT counterparts. Although serum anti-CII antibodies and *in vitro*collagen-induced T cell proliferation were low in Tg-bGH mice, DC showed no differences in phenotype or in antigen-presenting activity; anti-CD3+IL2-induced T cell activation was similar in both mouse groups.

Conclusion: GH prevents and has therapeutic effects in CIA by modulating macrophage and Th17 cell differentiation. Targeting the GH signaling pathway could thus be a therapeutic approach to RA treatment.

Disclosure: R. J. Villares, None; **G. Criado**, None; **R. P. Gomariz**, None; **Y. Juarranz**, None; **J. Leceta**, None; **G. Cascio**, None; **J. L. Pablos**, None; **M. Mellado**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/protective-and-therapeutic-effects-of-growth-hormone-on-collagen-induced-arthritis

Abstract Number: 2573

Confirmatory Analysis of Methylome Signatures in Rheumatoid Arthritis Using an Independent Dataset

Rizi Ai[1], Deepa Hammaker[2], Wei Wang[3] and Gary S. Firestein[4], [1]University of California San Diego, La Jolla, CA, [2]Division of Rheumatology, Allergy and Immunology, UCSD School of Medicine, La Jolla, CA, [3]Chemistry and Biochemistry, University of California, San Diego, La Jolla, CA, [4]Div of Rheumatology, UCSD School of Medicine, La Jolla, CA

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Background/Purpose:

Epigenetics can contribute to the pathogenesis of rheumatoid arthritis (RA). A DNA methylation signature that distinguishes RA fibroblast-like synoviocytes (FLS) from osteoarthritis (OA) FLS has been characterized in previous studies using RA, OA and normal samples. To confirm the pattern, we evaluated DNA methylation patterns of an independent group of 19 RA and 5 OA FLS and compared them to previous findings.

Methods:

Genomic DNA from FLS was isolated from 19 RA and 5 OA syovia obtained at the time of total joint replacement. Methylation levels were measured using Illumina HumanMethylation450 chip. Differentially methylated loci (DMLs) were identified using Welch's t-test and mapped to gene promoter regions to define differentially methylated genes (DMGs). Both sets of DMLs and DMGs were compared to our previously characterized methylation patterns. To confirm enriched biological pathways, Ingenuity pathway analysis was applied.

Hierarchical clustering and principal component analysis (PCA) were performed to assess the relationships between 19 RA and 5 OA FLS and also the combined dataset (30 RA/16 OA).

Results:

2,956 DMLs were identified between 19 RA and 5 OA, and 72.5% were overlapped with DMLs identified in previously reported data; after mapping DMLs to gene promoter region, 71.5% of 450 DMGs were overlapped (p-value = 4.26e-284). With established DMLs, distinct methylation patterns were confirmed between RA and OA. 13 out of 31 significantly enriched pathways were overlapped with pathways identified previously (p value < 0.05). Interestingly, "Role of Osteoblasts, Osteoclasts and Chondrocytes in Rheumatoid Arthritis" ranked No.1 among them. Additional overlapped pathways such as "Role of Macrophages, Fibroblasts and Endothelial Cells in Rheumatoid Arthritis", "Atherosclerosis Signaling", "Leukocyte Extravasation Signaling", and "Angiopoietin Signaling" suggested the DMGs contribute to inflammation, immunity and joint destruction. With the combined dataset (30 RA/16 OA), 13,577 DMLs in 1,714 DMGs were found, and 43 out of 66 significantly enriched pathways overlapped with previous data, especially in pathways involving inflammation and immune responses. Using hierarchical clustering and PCA, the 30 RA and 16 OA segregated into two groups (Figure 1).

Conclusion:

The significantly overlapped DMLs/DMGs between the new and previously reported FLS lines confirmed the consistency of DNA methylation signatures and FLS imprinting. In addition, overlapping enriched biological pathways suggest that the methylation patterns might contribute to the pathogenesis of RA. With the expanded dataset, DNA methylation signatures of RA become more powerful and can provide insights into pathogenesis of the disease and identify potential therapeutic targets.

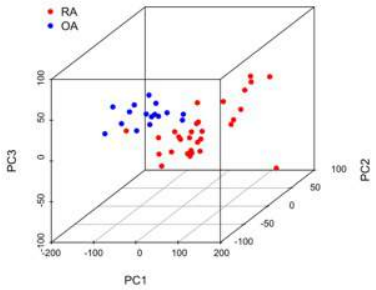

Figure 1. PCA analysis on 30 RA and 16 OA using 13,577 DMLs.

Disclosure: R. Ai, None; **D. Hammaker**, None; **W. Wang**, None; **G. S. Firestein**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/confirmatory-analysis-of-methylome-signatures-in-rheumatoid-arthritis-using-an-independent-dataset

Abstract Number: 2574

Rheumatoid Arthritis Leads to Altered Gene Expression in the Brain and Behavioral Changes in Mice

Karin ME Andersson[1], Lovisa Leifsdottir[2], Malin Erlandsson[1], Marcela Pekna[3], Milos Pekny[3], Kjell Olmarker[4] and **Maria Bokarewa**[5], [1]Rheumatology and Inflammation Research, University of Gothenburg, Gothenburg, Sweden, [2]Department of Rheumatology and Inflammation Research, Institute of Medicine, Sahlgrenska University Hospital, University of Gothenburg, Gothenburg, Sweden, [3]Center for Brain Repair and Rehabilitation, Department of Clinical Neuroscience and Rehabilitation, Institute of Neuroscience and Physiology, Sahlgrenska University Hospital, University of Gothenburg, Gothenburg, Sweden, [4]Musculoskeletal Research, Department of Medical Chemistry and Cell Biology, Institute of Biomedicine, Sahlgrenska University Hospital, University of Gothenburg, Gothenburg, Sweden, [5]Rheumatology and Inflammation Research, Göteborgs University, Göteborg, Sweden

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Background/Purpose: Rheumatoid arthritis (RA) is an autoimmune disorder characterized by joint inflammation and destruction. Pain is the major symptom in RA, which often persists despite resolution of inflammation. This indicates a deregulation of central nervous system processing of pain in RA, but the underlying mechanisms remain largely unexplored.

The aim of this study was to examine whether joint inflammation was associated with changes in the brain. Expression of genes involved in inflammation and neuroprotection was studied.

Methods: Arthritis was induced in DBA/1 mice by immunization with collagen type II. Development of arthritis and behavioral pattern of each mouse were followed clinically by regular assessment and filming. Behavioral pattern including locomotion, rearing, grooming, minor movements, and immobility, was compared to that of naïve healthy siblings, recorded simultaneously. Quantification of gene expression by RT-PCR was performed in cerebellum, medulla, basal ganglia and motor cortex.

Results: Arthritis decreased locomotion and rearing, and increased periods of minor movements. These changes were apparent already in early arthritis, and increased with the arthritis severity. The brain of arthritic mice showed increased expression of inflammatory cytokine IL-1, which correlated with duration of minor movements. mRNA levels of CD68, a marker of activated microglia, were increased, predominantly in the motor cortex. The expression of IGF1R and S100A4, known to be important for neuroprotection and regeneration, was down-regulated with arthritis. The alterations in gene expression correlated with changes of behavior of the arthritic mice.

Conclusion: Arthritis changes the behavior of mice potentially by altering gene expression in the brain. The expression of inflammatory and microglia activation marker genes were increased, and the expression of neuroprotective genes was decreased, resembling the situation in neurons during Alzheimer's disease.

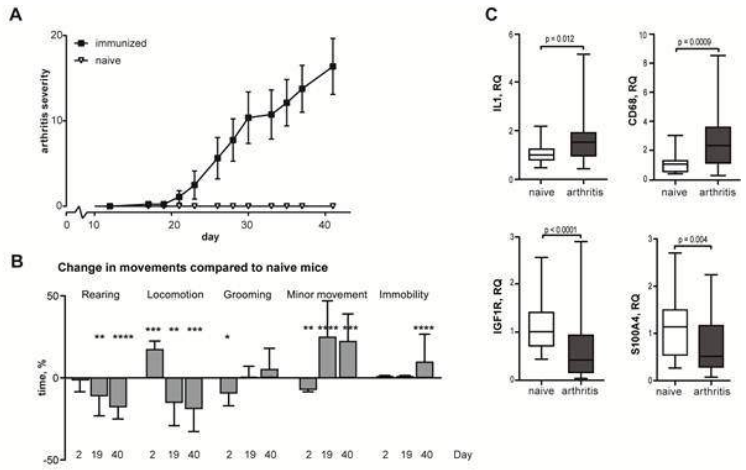

Figure 1. Arthritis affects the behavioral pattern. DBA1 mice where immunized twice with collagen II, resulting in polyarthritis, judged clinically (A). The mice were filmed after immunization (day 2), at early arthritis (day 19), and at overt arthritis (day 40). Change in movement pattern compared to naïve mice shown (B). Arthritis induced change in gene expression of in the brain, as measured by real time-PCR, day 40 (C).

Disclosure: K. M. Andersson, None; **L. Leifsdottir**, None; **M. Erlandsson**, None; **M. Pekna**, None; **M. Pekny**, None; **K. Olmarker**, None; **M. Bokarewa**, None.

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Abstract Number: 2575

The Effect of mPGES-1 Deletion on Platelet Function in Mice

Joan Raouf[1], Fariborz Mobarrez[2], Karin Larsson[1], Per Johan Jakobsson[1] and Marina Korotkova[1], [1]Medicine, Department of Medicine, Rheumatology Unit, Karolinska University Hospital, Karolinska Institutet S-171 76, Stockholm, Sweden, Stockholm, Sweden, [2]Department of Medicine, Karolinska Institutet, Rheumatology Unit, Karolinska University Hospital, Stockholm, Sweden

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Session Time: 9:00AM-11:00AM

Background/Purpose:

Microsomal prostaglandin E synthase-1 (mPGES-1) is an essential player in inflammation and has an indispensible role in the generation and maintenance of autoimmune disease such as rheumatoid arthritis (RA). It is an inducible terminal synthase that generates PGE_2. Pharmacological inhibition and genetic deletion of mPGES-1 has been proven to be protective in experimental models of inflammation. Platelets play a vital role in homeostasis and modulation of inflammatory processes by releasing a diversity of cytokines, chemokines and other lipid mediators. It has been recognized that activated platelets and formation of platelet-derived microparticles (PMPs) play a major role in RA pathogenesis. We hypothesize that mPGES-1/PGE_2 pathway may contribute to platelet activation and mPGES-1 inhibition might have beneficial effects on platelet-mediated functions during inflammation. The aim of the study was to investigate the outcome of mPGES-1 deletion on platelet function in mice stimulated with LPS.

Methods:

mPGES-1 wild type (WT) and knockout (KO) DBA mice were injected with 2µg LPS i.p, for 24h. Mice were anesthetized and blood was slowly drawn from the heart by a syringe containing 100µl 3.8% sodium citrate and was transferred to tubes. The numbers and activation of platelets and PMPs were measured in whole blood by flow cytometry. Briefly, blood samples were labeled with CD61-Alexa 488 together with CD62P-PE and CD154-APC. The platelet and PMP numbers where defined by their size characteristics and CD61 expression. The platelets were then investigated for co- expression of CD62P or CD154 respectively. In addition, platelet-leukocyte interaction was also measured in the leukocyte gate. To investigate platelet aggregation, a flow cytometry–based platelet aggregation assay (FCA) was used. Briefly, whole blood is divided into two tubes and labeled with either CD61-Alexa 488 or CD61-PE. After incubation, the tubes were combined and platelets were activated with ADP (6.5µM). Platelets expressing both markers were considered as platelet aggregates.

Results:

Upon LPS stimulation the number of platelets in WT mice was significantly reduced compared to KO mice ($p<0.001$). Platelet activation (assessed by CD62P and CD154 expression) was significantly higher in WT mice compared to KO mice upon treatment with LPS ($p<0.01$ for both). Moreover, the levels of platelet-leukocyte interaction were higher in WT mice ($p<0.05$). PMP numbers were also higher in WT mice compared to KO ($p<0.01$). In addition, platelet aggregation measured with the FCA assay, yielded significantly higher numbers of platelet aggregates in WT compared to KO mice ($p<0.001$).

Conclusion:

mPGES-1 deletion affects platelet concentration and activation as well as PMP formation in LPS stimulated WT mice. The data suggest possible role of mPGES-1 in platelets function in inflammation.

Disclosure: J. Raouf, None; **F. Mobarrez**, None; **K. Larsson**, None; **P. J. Jakobsson**, None; **M. Korotkova**, None.

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Abstract Number: 2576

Treatment of Inflammatory Arthritis with a Hybrid Compound, LLP2A-Ale, Can Prevent Joint Destruction

Nancy E. Lane[1], Wei Yao[2] and Maripat Corr[3], [1]Center for Musculoskeletal Health, Univ of California at Davis, Sacramento, CA, [2]University California, Davis Medical Center, Internal Medicine, Sacramento, CA, [3]Medicine, University of California, San Diego, La Jolla, CA

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Background/Purpose: Nearly 2% of the US population suffers from inflammatory arthritis, and while there are effective treatments that reduce the joint destruction, over 20% of affected individuals to do derive benefit from currently available treatments. We have previously described the bone sparing effect of a stem cell recruiting peptide (LLP2A) chemically linked to the osteoaffinity compound

alendronate. The goal of this experiment was to determine if the hybrid compound, LLP2A-Ale, alone or in combination with concomitantly administered mesenchymal stem cells (MSCs) could reduce inflammatory joint destruction in the collagen induced arthritis model and if there was an immunomodulating role of MSCs in the inflammatory joint and in the lymphoid tissues.

Methods: 8-week-old DBA1/J male mice were immunized with CFA/100 µg chicken collagen (Chondrex Inc) and on Day 21 boosted with 100 µg chicken collagen in IFA subcutaneously. On Day 22 the mice were randomized into groups and received the individual treatments: PBS, vehicle (2% DMSO), alendronate 500ug/kg ip, LLP2A-Ale 250 ug/kg iv, LLP2A-Ale 500 ug/kg, MSC $2x10^6$, MSC+LLP2A-Ale 250 ug/kg iv, or MSC+ LLP2A-Ale 500ug/kg iv. On Day 24 all mice received 50ug LPS in NS and were sacrificed on day 48. Study endpoints included ankle thickness assessed with microcalipers, 28 joint count for swelling, histologic assessment of right hind limbs (erosion, cartilage thickness, inflammation), bone volume assessed by microCT of left hind limb, levels of anti-CII antibodies and serum cytokines by Luminex. Lymph nodes and spleen were analyzed by flowcytometry. Each experiment was performed on two occasions.

Results: Mice developed clinically detectable arthritis on day 23 (two days after the boost with IFA/CII) and the swelling resolved by day 35. Arthritis developed in all immunized groups; however all of the treatment groups had statistically significantly less swelling and lower joint scores than the mice treated with vehicle (AUC for swelling $p<0.001$ for all treated groups from vehicle). There was a trend toward lower levels of anti-CII antibodies in the treatment groups compared to the vehicle control. There were no significant differences in the number of CD4+CD25+FoxP3+ T regs in the draining lymph nodes or in the splenic B220+, CD4+ or CD8+ populations. There was an incresae in splenic Gr1+ cells. The vehicle treated group had significant histological changes compared to nonarthritis controls, but was not statistically difference than other treated mice. Erosive changes were confirmed in microCT scans of the knee joints; however there were no significant differences in the bone volume density of the distal femur, proximal tibia and the paws. There was an overall trend toward increased cytokine production in mice treated with MSCs.

Conclusion: reatment of CIA with LLP2A-Ale with and without MSCs appeared to reduce joint swelling, with modest effects on immune modulation and joint tissue destruction.

Disclosure: N. E. Lane, Genzyme-Sanofi, 5,Regeneron, 5; **W. Yao**, None; **M. Corr**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/treatment-of-inflammatory-arthritis-with-a-hybrid-compound-llp2a-ale-can-prevent-joint-destruction

Abstract Number: 2577

Ablation of Fc Gamma Receptors Leads to a Decreased Bone Erosion in Experimental Arthritis Not By Altering Osteoclast Numbers within the Inflamed Joint but By Inhibiting Osteoclast Activation

Irene Di Ceglie[1], Sjef Verbeek[2], Peter van der Kraan[1], Wim van den Berg[1] and Peter van Lent[1], [1]Experimental Rheumatology, Radboud university medical center, Nijmegen, Netherlands, [2]Human Genetic, Human Genetic, Leiden University Medical Center, Leiden, Netherlands

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Background/Purpose:

Rheumatoid arthritis is characterized by immune complex dependent chronic joint inflammation and severe cartilage and bone destruction. In earlier studies we showed that Fcγ receptors (FcγRs) are crucial in regulating cartilage destruction during immune complex mediated antigen induced arthritis (AIA)(1,2). In this study we investigated the role of FcγRs in osteoclast-mediated bone erosion comparing development of AIA between mice lacking all FcγRs (FcγRI,II,III,IV $^{-/-}$) and their wild type controls.

Methods:

AIA was induced by injection of 60 µg mBSA into the knee joint of FcγRI,II,III,IV$^{-/-}$and wild type (WT) control mice previously immunized with mBSA/CFA. Joint inflammation and bone destruction was determined in total knee joints sections. mBSA antibody titers were measured using ELISA and T cell response monitored with a lymphocyte stimulation test. The percentage of osteoclast precursors in the bone marrow was defined through FACS analysis. Gene expression was measured using RT-PCR and protein levels measured with ELISA or Luminex. S100A8 positive cells in the synovium were detected with immunostaining.

Results:

In FcγRI,II,III,IV $^{-/-}$ mice the development of bone erosion in knee joints was significantly reduced both at days 7 and 21 after induction of AIA (30% and 25% lower) when compared to WT controls. The immune response against mBSA (serum level of specific anti mBSA (total IgG, IgG1, IgG2a, IgG2b) and mBSA specific T-cell response) was comparable between the two strains. The percentage of osteoclast precursor population within the bone marrow (CD11b $^{low\text{-}neg}$/ Ly6C ^{high}, described to be upregulated during arthritis) was comparable between FcγRI,II,III,IV $^{-/-}$ and WT controls. Moreover FcγRI,II,III,IV $^{-/-}$ bone marrow cells showed the same ability to differentiate towards osteoclasts upon stimulation with M-CSF and RANK-L *in vitro*.

At day 7 after AIA induction, the decrease in bone erosion in FcγRI,II,III,IV $^{-/-}$ was associated with a significantly decrease in the number of inflammatory cells present within the joint (infiltrate and exudate 29% and 27% lower respectively compared to WT control). Interestingly no differences were present in the number of mature osteoclasts present at locations of bone erosion along patella, femur and tibia (32 +/- 13 osteoclasts/section in FcγRI,II,II,IV-/- versus 28 +/- 9 osteoclasts/section in WT). Gene expression of osteoclast activation factors (RANK-L, IL-1β, S100A8) within the synovium were however significantly lower in FcγRI,II,III,IV-/- (ddCt -2.7, -2.6, -3, respectively). IL-1β and S100A8 were decreased also at the protein level in the synovium wash out and the immunostaining showed a significantly lower amount of S100A8-producing cells in the synovium of FcγR I,II,III,IV -/- animals compared to the WT.

Conclusion:

FcγRs promote bone erosion in AIA not by increasing the number of osteoclasts present on the bone surface but by enhancing influx and activation of inflammatory cells within the synovium thereby releasing factors able to stimulate osteoclast activity.

(1) van Lent PL et al., Am J Pathol., 2001

(2) van Lent PL et al., Arthritis Rheum., 2010

Disclosure: I. Di Ceglie, None; **S. Verbeek**, None; **P. van der Kraan**, None; **W. van den Berg**, None; **P. van Lent**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/ablation-of-fc-gamma-receptors-leads-to-a-decreased-bone-erosion-in-experimental-arthritis-not-by-altering-osteoclast-numbers-within-the-inflamed-joint-but-by-inhibiting-osteoclast-activation

Abstract Number: 2578

Cardiovascular Effects of Etanercept in an Animal Model of Rheumatoid Arthritis: Mechanisms Involved

Perle Totoson[1], Katy Maguin-Gaté[1], Alice Monnier[2], Anne Tessier[2], Christine Marie[2], Frank Verhoeven[3], Clément Prati[3], Daniel Wendling[4] and Céline Demougeot[1], [1]EA 4267 FDE, FHU INCREASE, Université de Bourgogne Franche-Comté, Besançon, France, [2]INSERM U1093, Université de Bourgogne Franche-Comté, Dijon, France, [3]Service de Rhumatologie, CHRU J Minjoz, Besançon, France, [4]Université de Franche-Comté, Besançon, France

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SESSION INFORMATION

Session Date: Tuesday, November 10, 2015

Session Title: Rheumatoid Arthritis - Animal Models Poster

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose:

Rheumatoid arthritis (RA) is associated with increased cardiovascular (CV) morbidity and mortality secondary to endothelial dysfunction (ED). Growing evidence suggests that TNFα-inhibitors may reduce ED in RA patients, but the underlying mechanisms are still unclear. In this study, we investigated the impact of Etanercept on endothelial function and related pathways as well as on traditional CV risk factors in the adjuvant-induced arthritis (AIA) rat model.

Methods:

AIA was induced by an intradermal injection of *Mycobacterium butyricum* in the tail of male Lewis rats. At the first signs of arthritis (day 11 post-immunization), Etanercept (10 mg/kg/3 days, sc) was administered for 21 days. AIA control rats received saline. Body

weights and arthritis scores were daily monitored. At the end of treatment, blood pressure was measured by invasive method. Blood was collected to measure triglycerides, cholesterol and glucose levels. Endothelial function was studied in aortic rings relaxed with cumulative concentrations of acetylcholine (Ach, 10^{-11}-10^{-4} moles/liter) in the presence or not of inhibitors of nitric oxide synthase (eNOS), cyclooxygenase-2 (COX-2), Arginase, endothelium-derived hyperpolarizing factor (EDHF) and superoxide anions ($O_2^{-\circ}$) production. Aortic expression of eNOS, phospho-ser1177-eNOS, COX-2, Arginase-2, p22phox and p47phox was evaluated by western blotting analysis.

Results:

As compared to control AIA, Etanercept significantly improved Ach-induced relaxation ($p<0.05$) as a result of increased NOS activity, decreased COX-2 and arginase activities, and decreased $O_2^{-\circ}$ production. These functional effects relied on increased eNOS expression and phosphorylation, decreased COX-2, Arginase-2 and p22phox expressions, respectively. By contrast, there was no change in EDHF production and p47phox expression. Etanercept reduced arthritis score by about 34% ($p<0.001$). Of note, no correlation was found between arthritis score and Ach-induced relaxation ($r=-0.195$; $p=0.246$, all AIA rats). The treatment did not affect triglycerides, cholesterol and glucose levels but significantly increased systolic blood pressure ($p<0.05$).

Conclusion:

Our data show the involvement of the NOS, Arginase, COX-2 and NADPH oxidase pathways in Etanercept-induced improvement in endothelial in AIA even though the pivotal common effector of these pathways remains to be identified. They also reveal that the beneficial effect on endothelial function is disconnected from its impact on traditional CV risk factors which are worsened or unchanged. This latter result, associated with a lack of correlation between endothelial function and arthritic scores suggests that the vascular effect of Etanercept is, at least in part, independent on the reduction of disease severity and other traditional CV risk factors. From a therapeutic point of view, they suggest that Etanercept could be a good choice in RA patients at high risk of CV events.

Disclosure: P. Totoson, None; **K. Maguin-Gaté**, None; **A. Monnier**, None; **A. Tessier**, None; **C. Marie**, None; **F. Verhoeven**, None; **C. Prati**, None; **D. Wendling**, None; **C. Demougeot**, None.

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Abstract Number: 2579

Effect of Tacrolimus on Endoplasmic Reticulum Stress-Mediated Osteoclastogenesis in a Collagen-Induced Arthritis Mouse Model

Won-Seok Lee[1], Yun Jung Choi[2], Myong-Joo Hong[3], Chang-Hoon Lee[4,5], Myeung Su Lee[6], Young Sun Suh[7], Sang-Il Lee[8] and Wan-Hee Yoo[9], [1]Division of Rheumatology, Department of Internal Medicine, Chonbuk National University Medical School and Research Institute of Clinical Medicine of Chonbuk National University Hospital-Chonbuk National University, jeonju, South Korea, [2]Division of Rheumatology, Department of Internal Medicine, Chonbuk National University Medical School and Research Institute of Clinical Medicine of Chonbuk National University Hospital-Chonbuk National University, JeonJu, South Korea, [3]Internal Medicine, Presbyterian Medical center, Jeonju, South Korea, [4]Department of Internal Medicine, School of Medicine, Wonkwang University, Iksan, Chonbuk, South Korea, [5]Rheumatology, Department of Internal Medicine, School of medicine, Wonkwang university, Iksan, Chonbuk, South Korea, [6]Internal Medicine, School of Medicine, Wonkwang University, Iksan, Chonbuk, South Korea, [7]Division of Rheumatology, Department of Internal Medicine, School of Medicine, The Catholic University of Korea, Seoul St. Mary's Hospital, Seoul, South Korea, [8]Division of Rheumatology, Department of Internal Medicine, Gyeongsang National University School of Medicine, Jinju, South Korea, [9]Division of Rhuematology, Department of Internal Medicine, Chonbuk National University Medical School and Research Institute of Clinical Medicine of Chonbuk National University Hospital-Chonbuk National University, Jeonju, South Korea

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Session Title: Rheumatoid Arthritis - Animal Models Poster

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Although the effects of tacrolimus on T cells are well known, its direct effects on osteoclastogenesis remain unclear. We previously revealed that thapsigargin (TG)-induced endoplasmic reticulum (ER) stress modulates receptor activator of nuclear factor kappa-B ligand (RANKL)-mediated osteoclastogenesis in vitro. We have also shown that tacrolimus downregulates ER-

mediated osteoclastogenesis *in vitro*. We examined whether the regulatory effect of tacrolimus on ER stress-mediated osteoclastogenesis and inflammation could be detected in collagen-induced arthritis (CIA).

Methods: CIA was induced by immunization of female Lewis rats with an emulsion of bovine type II collagen and incomplete Freund's adjuvant. Tacrolimus at doses of 3.2 mg/kg or a placebo formulation were orally administered to rats for 28 days from the day after immunization. The histopathological changes in osteolysis and the expression of specific ER stress-mediated inflammatory signaling pathway biomarkers (IRE1α, GRP78/Bip, c-Fos, and NF-κB) were examined. In addition, pro-inflammatory cytokines and osteoclastogenic molecules (RANKL and M-CSF) were assessed in the knee and ankle joints in the CIA mouse model. Changes in bone mass and structure were assessed based on micro-CT scans of ankle and knee joints.

Results: In the mouse model, tacrolimus administration resulted in a dramatic amelioration of osteolysis and a significant reduction in ER stress intensity. Simultaneously, tacrolimus lessened inflammatory cell infiltration, reduced osteoclastogenesis capability, and reduced the inflammatory response via reduced levels of IRE1α, GRP78/Bip, c-Fos, and NF-κB. Based on the Micro-CT analysis, bone erosion on the hind paw in CIA was augmented compared with that of CIA + tacrolimus mice.

Conclusion: These findings suggest that tacrolimus has the potential to inhibit the progression of joint damage by inhibiting ER stress and has anti-inflammatory effects in established rheumatoid arthritis.

Disclosure: W. S. Lee, None; **Y. J. Choi**, None; **M. J. Hong**, None; **C. H. Lee**, None; **M. S. Lee**, None; **Y. S. Suh**, None; **S. I. Lee**, None; **W. H. Yoo**, None.

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Abstract Number: 2580

Age-Related Differences in Collagen-Induced Arthritis: Clinical, Imaging and Biological Characteristics in Juvenile Compared to Adult Animals

Tracy Wilson-Gerwing[1], Arash Panahifar[2], David M.L. Cooper[2] and Alan M. Rosenberg[1], [1]Pediatrics, University of Saskatchewan, Saskatoon, SK, Canada, [2]Anatomy and Cell Biology, University of Saskatchewan, Saskatoon, SK, Canada

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SESSION INFORMATION

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Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Arthritis is among the most common chronic diseases in both children and adults. Joint inflammation is a feature in both age groups but there are age-related disparities in clinical manifestations, disease courses, and treatment efficacy and safety. Collagen-Induced Arthritis (CIA) in rodents is a model of arthritis that has utility in assessing pathogenic processes and efficacy of treatments. However, the CIA model has been applied to adult animals but not to juveniles. This study compared clinical, imaging and biologic characteristics of CIA in adult and juvenile animals. Determining age-related differences of CIA should improve understanding of age-specific inflammatory processes and help design treatment interventions tailored to age.

Methods: Juvenile (5 wks old) and young adult (13 wks old) male Wistar rats were immunized with an emulsion of bovine type II collagen/incomplete Freund's adjuvant. Naïve juvenile and adult rats served as controls. Baseline measures included paw thickness, thermal and mechanical thresholds and footprint analysis. Following arthritis onset, measures were repeated every 3 days. For each animal, the Maximum Daily Arthritis Index (MAI) score and daily weight were measured. Fourteen days after arthritis onset, animals were euthanized and blood and tissues collected. Paws were imaged by Micro-CT and quantified with a 6 point scale to rate bone destruction and density. Plasma was assayed by enzyme immunoassay with a rat 27-plex cytokine/chemokine array. Dorsal root ganglia and spinal cord immunohistochemistry assessed pro-inflammatory high mobility group box-1 (HMGB1), receptor for advanced glycation end products (RAGE) and the resolvin D1 receptors G-protein coupled receptor 32 (GPR32) and formyl peptide receptor 2 (FPR2).

Results: Juvenile CIA rats had significantly lower MAI compared to adults ($p<0.0001$). Adult CIA rats had significant increases in the thickness of the ankle ($p=<0.0001$), the paw distal to the tarsus ($p=<0.0001$) and the phalanges ($p=<0.0001$) while juvenile rats had significant increase only in paw thickness distal to the tarsus ($p=<0.0001$). Analysis of chemokine/cytokine profiles revealed that Juvenile CIA rats had lower levels of interleukin-10 ($p=0.04$); and higher levels of the chemokine fracktalkine ($p=0.02$). Levels of HMGB1 and RAGE were highest in adult CIA rats while juvenile rats had higher levels of GPR32 and FPR2. Adult CIA rats had a decrease in toe spread compared to juvenile CIA rats ($p<0.0001$). Micro-CT scores were not significantly different between the two groups ($p=0.40$).

Conclusion: Adult rats have more severe CIA than juveniles. Our results indicate age-related differences in arthritis severity are related to the balance between HMGB1 and resolvins and their respective receptors with the balance favouring promotion of inflammation in adults associated with higher levels of HMGB1 and lower levels of resolvins. Juveniles produce more resolvins that may impede transition from acute to chronic arthritis. We postulate that anti-inflammatory effects of endongenous resolvins are mediated by impeding production of HMGB1 and/or HMGB1 binding to its receptors.

Disclosure: T. Wilson-Gerwing, None; **A. Panahifar**, None; **D. M. L. Cooper**, None; **A. M. Rosenberg**, None.

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Abstract Number: 2581

TNF-Alpha Receptor II Signaling Plays an Important Role in Maintaining the Expression of Forkhead Box P3 in Murine Regulatory T Cells

Wen-Yi Tseng[1,2], Kay McNamee[1], Adam Cribbs[3], Anviti Vyas[1] and Richard O. Williams[1], [1]Kennedy Institute of Rheumatology, University of Oxford, Oxford, United Kingdom, [2]Division of Rheumatology, Allergy and Immunology, Chang Gung Memorial Hospital at Keelung, Keelung, Taiwan, [3]Computational Genomics and Training Centre, MRC Functional Genomics Unit, University of Oxford, Oxford, United Kingdom

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Session Date: Tuesday, November 10, 2015

Session Title: Rheumatoid Arthritis - Animal Models Poster

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: TNF-α is a key regulator of inflammation, which induces signal transduction by binding to two structurally and functionally distinct receptors on target cells: TNF receptor 1 (TNFR1) and TNF receptor 2 (TNFR2). The development of TNF inhibitors has revolutionized the management of rheumatoid arthritis, ankylosing spondylitis, Psoriatic arthritis and inflammatory bowel disease. However, previous studies have suggested a positive role for TNFR2 signaling in maintaining the numbers and function of regulatory T cells (Tregs). The aim of this study was to further investigate the role of TNFR1/2 signaling in Tregs.

Methods: To study the influence of TNF signaling on Tregs, we first isolated splenic cells, thymus and lymph node cells from na•ve TNFR1$^{-/-}$, TNFR2$^{-/-}$ and wild-type mice. The number of Tregs was measured by flow cytometry. The gene expression profiles of Treg related markers in spleen and thymus were then compared by real-time qPCR.

Results: Flow cytometry analysis showed that neither TNFR1 nor TNFR2 altered the number of regulatory T cells. However, there was a significant decrease in Foxp3 expression intensity in Tregs from TNFR2$^{-/-}$ mice (Figure 1), which was confirmed in the gene expression study of Treg related markers from spleen (Figure 2) and thymus (Figure 3). The gene expression study of spleen and thymus showed no significant difference of CTLA-4, GITR, IL-10 and IL-4, but a marked decrease of TGF-β in TNFR2$^{-/-}$ mice compared to wild type mice.

Conclusion: Our data reveal that TNFR2 signaling is critical in maintaining the expression of Foxp3 in Tregs in healthy mice, and we are currently exploring its role in arthritis. We hypothesize that TNF signaling affect the expression of Foxp3 through decreased production of TGF-β. Our data suggest that the use TNF inhibitors may affect the phenotype and function of Tregs in which may influence treatment response in some patients.

Figure 1

Figure 1

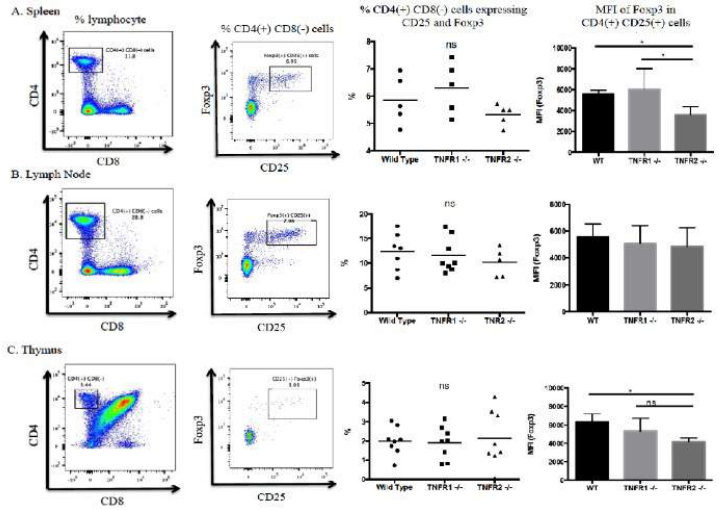


Figure 2

Figure 2

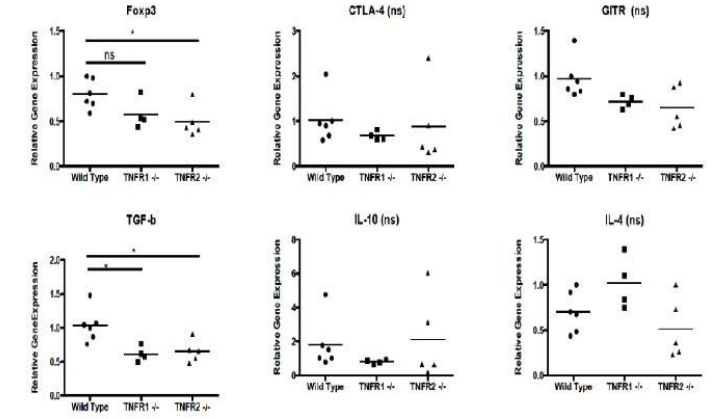
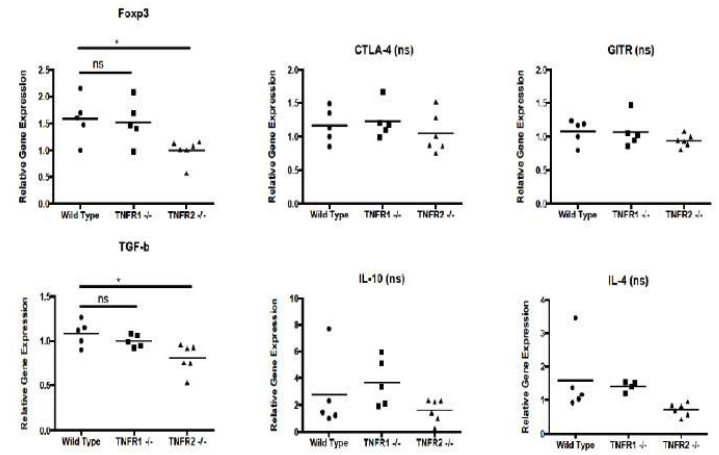


Figure 3

Figure 3



Disclosure: W. Y. Tseng, None; **K. McNamee**, None; **A. Cribbs**, None; **A. Vyas**, None; **R. O. Williams**, None.

Abstract Number: 2582

Increased Morbidity and Mortality in Female Versus Male Tumor Necrosis Factor-Transgenic Mice

Richard Bell[1], Ronald Wood[2], Joe Chakkalakal[3], Christopher T. Ritchlin[4], Edward Schwarz[5] and **Homaira Rahimi**[6], [1]Pathology, University of Rochester, Rochester, NY, [2]University of Rochester, Rochester, NY, [3]Orthopaedics, University of Rochester, Rochester, NY, [4]Allergy, Immunology and Rheumatology, University of Rochester, Rochester, NY, [5]Orthopedeatrics, University of Rochester, Rochester, NY, [6]Rheumatology, University of Rochester/Golisano Children's Hosp, Rochester, NY

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SESSION INFORMATION

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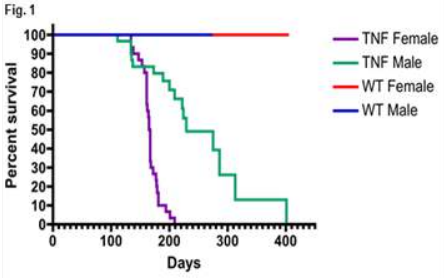
Session Title: Rheumatoid Arthritis - Animal Models Poster

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Rheumatoid arthritis (RA) is a chronic debilitating condition with a 2-3 fold greater prevalence in women than men. Additionally, women have worse disease outcomes and a suspected increased mortality. However, the etiology of sex differences in RA remains unclear. Tumor necrosis factor-transgenic (TNF-Tg) mice, a model of inflammatory arthritis, display similar sex differences as RA patients. To formally test the hypothesis that female TNF-Tg mice have greater morbidity and mortality versus male littermates, we assessed arthritic signs, function and time to death in a large cohort of TNF-Tg mice and wild type (WT) controls. **Methods:** Male (n=30) and female (n=38) TNF-Tg mice (3647 line) and WT littermates (n=33) were monitored over six months, and dates of death were recorded for Kaplan-Meier analysis. Grip strength, as an indicator of arthritis, and weight was measured in male and female TNF-Tg mice with active arthritis at five months of age. The same measurements were taken in a cohort of mice at two months of age, prior to onset of clinical signs, and four weeks later when frank arthritis was present. **Results:** Female TNF-Tg mice have significantly shorter median lifespans than males (5.9 vs 8.1 months, $p<0.05$) (Fig. 1). Male and female TNF-Tg mice have significantly decreased normalized grip-strength at five months of age compared to WT sex-matched controls (0.05±0.001 vs 0.03±0.004 vs 0.10±0.01 vs 0.01±0.001, $p<0.0001$). At two months of age, female TNF-Tg mice have decreased normalized grip-strength compared to age-matched male TNF-Tg and female WT mice (0.079±0.01 vs 0.095±0.02 vs 0.10±0.01, $p<0.05$). Interestingly, there was no clinical evidence of arthritis at this time. However, four weeks later, tarsal joint swelling and an inability to splay digits was noted in hind limbs of TNF-Tg mice, which was indistinguishable between sexes. Moreover, female TNF-Tg displayed a significantly decreased rate of weight gain measured from two months to three months of age compared to male TNF-Tg and female WT mice (1.01±1.71% vs 7.11±1.18% vs 12.53±2.08%, $p<0.001$). **Conclusion:** We show for the first time that TNF-Tg female mice with chronic inflammatory arthritis have shorter lifespans than male littermates. Grip-strength was decreased in female TNF-Tg earlier than age-matched TNF males, indicating earlier onset of disease, although gross signs of arthritis between sexes were not noted. Similarly, rate of growth as measured by change in weight gain was decreased in female TNF-Tg mice at the earliest manifestations of disease compared to male TNF-Tg mice. This is similar to RA in which females are suggested to have increased morbidity and mortality compared to males. Potential implications include sex hormone interactions during TNF-mediated inflammation, raising the possibility that modulating the hormonal environment could lessen the burden of RA in women.

Fig. 1



Disclosure: R. Bell, None; **R. Wood**, None; **J. Chakkalakal**, None; **C. T. Ritchlin**, None; **E. Schwarz**, None; **H. Rahimi**, None.

Abstract Number: 2583

Important Role of CD11c+ Dendritic Cells in Inflammatory Arthritis

Antonia Puchner[1], Victoria Saferding[2], Eliana Goncalves-Alves[3], Gerhard Krönke[4], Rene Pfeifle[4], Silvia Hayer[5], Josef S. Smolen[6], Kurt Redlich[3,7] and Stephan Blüml[3], [1]Department of Rheumatology, Medical University of Vienna, Vienna, Austria, [2]Rheumatology, Medical University of Vienna, Vienna, Austria, [3]Division of Rheumatology, Medical University of Vienna, Vienna, Austria, [4]Universitätsklinikum Erlangen, Erlangen, Austria, [5]Department of Internal Medicine III, Division of Rheumatology, Medical University of Vienna, Vienna, Austria, [6]Department of Medicine 3, Division of Rheumatology, Medical University Vienna, Vienna, Austria, [7]Medical University Vienna, Dpt. of Rheumatology, Vienna, Austria

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Session Type: ACR Poster Session C
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Background/Purpose: Dendritic cells (DCs) play an important role in bridging the innate and the adaptive immune response by serving as antigen presenting cells and are therefore implicated in the initiation of chronic autoimmune diseases, including rheumatoid arthritis. Using two different models of inflammatory arthritis, K/BxN serum transfer arthritis as well as hTNFtg arthritis, both depending only on the innate immune system, we investigated the innate role of dendritic cells in inflammatory arthritis

Methods:

We analyzed histological sections of K/BxN serum transfer arthritis as well as hTNFtg arthritis for the presence of $CD11c^+$ cells by immunohistochemistry. We also performed synovial biopsies and analyzed the cellular composition of the inflammatory infiltrate with respect to DCs. We used CD11c-diphteria toxin receptor (DTR) transgenic mice, which express the human diphtheria-toxin receptor under the CD11c promoter, allowing for specific depletion of $CD11c^+$cells by administration of diphtheria toxin (DT). K/BxN serum transfer arthritis was induced, and mice were given either DT or PBS or in wt and BATF3 deficient mice. In addition CD11c DTR mice were crossed into hTNFtg animals and also received either DT or PBS. The severity of arthritis was determined clinically and histologically.

Results:

We show that $Cd11c^+$ cells are present in significant numbers in the synovia of K/BxN and TNF driven arthritis. Both myeloid dendritic subsets, $CD8^+CD11c^+$ and $CD11b^+CD11c^+$, can be found in synovial tissue. In K/BxN serum transfer arthritis, clinical scores showed that CD11c-DTR transgenic mice that received DT had significantly reduced paw swelling and loss of grip strength compared to PBS treated animals. Histological analysis found reduced inflammation after the depletion of $CD11c^+$ cells in K/BxN arthritis. In addition local bone destruction and the number of osteoclasts was significantly reduced. To exclude unspecific effects of DT in mice, wild type animals received DT showed identical clinical and histological signs of arthritis as PBS treated animals. Analysis of K/BxN arthritis in wt mice and $BATF3^{-/-}$ mice, which lack $CD8^+CD11^+$ DCs revealed no difference in arthritis severity between the two groups. In addition to K/BxN arthritis, we found that also in TNF-driven arthritis depletion of $CD11c^+$cells led to a significant reduction of synovial inflammation, as well as local bone erosions.

Conclusion:

These data show that in addition to initiating an adaptive immune response, $CD11c^+$ dendritic cells are also involved in innate effector mechanisms of inflammatory arthritis and suggest that dendritic cells could be an important therapeutic target for patients suffering from inflammatory arthritis.

Disclosure: A. Puchner, None; **V. Saferding**, None; **E. Goncalves-Alves**, None; **G. Krönke**, None; **R. Pfeifle**, None; **S. Hayer**, None; **J. S. Smolen**, AbbVie, Janssen, Eli Lilly and Company, MSD, Pfizer, Roche, 2,Abbvie, Amgen, Astra-Zeneca, Astro, Celgene, Glaxo, ILTOO, Janssen, Lilly, Medimmune, MSD, Novartis-Sandoz, Novo-Nordisk, Pfizer, Roche, Samsung, Sanofi, UCB, 5; **K. Redlich**, None; **S. Blüml**, None.

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Abstract Number: 2584

Prediction of Disease Relapses By Multi-Biomarker Disease Test Activity in

Rheumatoid Arthritis Patients Tapering DMARD Treatment

Juergen Rech[1], Axel J. Hueber[2], Matthias Englbrecht[2], Stephanie Finzel[3], Judith Haschka[4,5], Bernhard Manger[2], Arnd Kleyer[3], Michaela Reiser[3], Hans-Peter Tony[6], Stefan Kleinert[7], Martin Feuchtenberger[8], Martin Fleck[9], Karin Manger[10], Wolfgang Ochs[11], Matthias Schmitt-Haendle[12], Joerg Wendler[13], Florian Schuch[13], Monika Ronneberger[13], Hanns-Martin Lorenz[14], Hubert Nüßlein[15], Rieke Alten[16], Jayme Fogagnolo Cobra[17], Joerg C. Henes[18], Klaus Krüger[19] and Georg A. Schett[20], [1]medical clinic 3, University of Erlangen-Nuremberg, Erlangen, Germany, [2]Department of Internal Medicine 3, Rheumatology & Immunology, University of Erlangen-Nuremberg, Erlangen, Germany, [3]Department of Internal Medicine 3, University of Erlangen-Nuremberg, Erlangen, Germany, [4]Medical Department 3, Rheumatology & Immunology, University of Erlangen-Nuremberg, Erlangen, Germany, [5]Medical Department II, Medical University of Vienna, St. Vincent Hospital Vienna,, Vienna, Austria, [6]University Hospital Würzburg, Würzburg, Germany, [7]Rheumatologische Schwerpunktpraxis Erlangen, Erlangen, Germany, [8]Rheumatologie/Klinische Immunologie, Kreiskliniken Altötting-Burghausen, Burghausen, Germany, [9]Department of Internal Medicine I, University of Regensburg, 93042 Regensburg, Germany, [10]Rheumatology Practice Bamberg, Bamberg, Germany, [11]Rheumatologist in Private Practice, Bayreuth, Germany, [12]Rheumatology Practice, Bayreuth, Germany, [13]Schwerpunktpraxis Rheumatologie, Erlangen, Germany, [14]University Hospital Heidelberg, Heidelberg, Germany, [15]University Erlangen, Nürnberg, Germany, [16]Internal Medicine, Rheumatology & Clinical Immunology, Schlosspark-Klinik, University Medicine Berlin, Berlin, Germany, [17]Instituto de Reumatologia de Sao Paolo, Sao Paolo, Brazil, [18]Department of Internal Medicine II, Rheumatology Division, University Hospital Tuebingen, Tuebingen, Germany, [19]Praxiszentrum St. Bonifatius, München, Germany, [20]University of Erlangen-Nuremberg, Erlangen, Germany

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Session Title: Rheumatoid Arthritis - Clinical Aspects Poster Session III
Session Type: ACR Poster Session C
Session Time: 9:00AM-11:00AM

Background/Purpose: To analyze the role of multi-biomarker disease activity (MBDA) in predicting disease relapses in rheumatoid arthritis (RA) patients in sustained remission, tapering disease modifying anti-rheumatic drug (DMARD) therapy in a prospective randomized controlled trial.

Methods: Twelve individual inflammation markers were analyzed from baseline serum samples of 100 patients from the RETRO study by the standardized MBDA test (Vectra® DA). MBDA scores range from 1-100 and are categorized as low (<30), moderate (30-44) or high (>44). The scores were calculated and compared between patients relapsing or remaining in remission when tapering DMARDs. Demographic and disease-specific parameters were recorded and included in multivariate logistic regression analysis for defining predictors of relapse.

Results: Moderate to high MBDA scores were found in 35% of RA patients, with doubling in patients relapsing (58.3%) than those remaining in stable remission (25%). Baseline MBDA scores were significantly higher in RA patients relapsing than those remaining in stable remission, when analyzing the entire population (N=100; p=0.0034), those tapering (N=36; p=0.0017) or stopping DMARDs (N=28; p=0.0036). Multivariate regression analysis identified MBDA scores as independent predictors for relapses next to anti-citrullinated protein antibody (ACPA) status. Relapse rates were low (13%) in MBDA-/ACPA- patients, moderate in MBDA+/ACPA- (33.3%) and ACPA+MBDA- (31.8%) patients and high in MBDA+/ACPA+ patients (76.4%). (Figure 1)

Conclusion: MBDA score improves the prediction of relapses in RA patients in stable remission undergoing DMARD tapering. If combined with ACPA testing, MBDA allows a correct case classification of relapse in more than 80% of the patients.

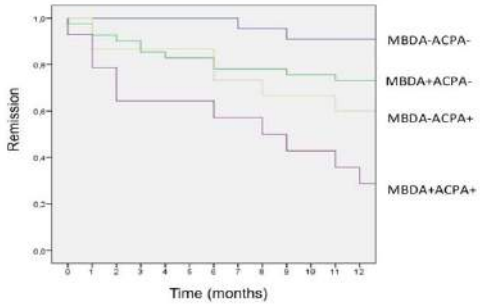

Figure 1. Relapse rates of RA dependent on ACPA and MBDA status: Kaplan-Meier curves indicate loss of remission over 12 months in patients with rheumatoid arthritis in relation to ACPA and MBDA status: (blue) ACPA/MBDA double-negative, (green) ACPA+/MBDA-, (yellow) ACPA-/MBDA+ and (purple) ACPA/MBDA double positive. Y-axis indicates the percentage of patients with rheumatoid arthritis in sustained remission (100% at baseline). X-axis indicates time.

Disclosure: J. Rech, None; **A. J. Hueber**, None; **M. Englbrecht**, None; **S. Finzel**, None; **J. Haschka**, None; **B. Manger**, None; **A. Kleyer**, None; **M. Reiser**, None; **H. P. Tony**, None; **S. Kleinert**, None; **M. Feuchtenberger**, None; **M. Fleck**, None; **K. Manger**, None; **W. Ochs**, None; **M. Schmitt-Haendle**, None; **J. Wendler**, None; **F. Schuch**, None; **M. Ronneberger**, None; **H. M. Lorenz**, None; **H. Nüßlein**, None; **R. Alten**, Horizon Pharma USA, Inc, 5,Horizon Pharma USA, Inc, 2; **J. F. Cobra**, None; **J. C. Henes**, None; **K. Krüger**, None; **G. A. Schett**, None.

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Abstract Number: 2585

Serum 14-3-3η Is an RA Specific Mechanistic Marker

Bidisha Dasgupta[1], Yauheniya Cherkas[1], Sarah Lamberth[1], Karen Hayden[1], Carrie Brodmerkel[1], Anthony Marotta[2] and Mark Curran[1], [1]Janssen Research & Development, LLC., Spring House, PA, [2]Augurex Life Sciences Corp., Vancouver, BC, Canada

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Session Title: Rheumatoid Arthritis - Clinical Aspects Poster Session III

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Background/Purpose: 14-3-3η is an emerging soluble Rheumatoid Arthritis (RA) biomarker that activates intracellular pathways that lead to the upregulation of inflammatory and joint damage factors. It is reported to be highly specific and sensitive for RA as a diagnostic marker, higher levels are associated with greater joint damage progression risk[1,2] and 14-3-3η's modulation with treatment suggests a role in disease monitoring. In this study, we examine the specificity of 14-3-3η in an independent, clinically well-characterized cohort of moderate to severe RA and disease control subjects.

Methods: Serum 14-3-3η levels were measured in a total of 147 patients using the Augurex 14-3-3η ELISA. The patient set comprised 36 with RA and 111 controls consisting of 20 with asthma (A), 20 with Crohn's Disease (CD), 12 presumed healthy (H), 16 with psoriasis (PsO), 20 with sarcoid arthritis (S), and 23 with spondylarthropathies (SpA). Sample testing was done independently of Augurex. Mann-Whitney testing together with Kruskal-Wallis analysis with the post-hoc Dunn's multiple comparison test was performed to assess group differences. Receiver operator characteristic curve (ROC) analysis was performed to assess the specificity of 14-3-3η for RA.

Results: Median (IQR) serum 14-3-3η levels were significantly higher in RA [2.35ng/ml (0.28-19.41)] than all controls [0 (0-0)],

p<0.0001. ROC curve analysis further underscored this differential expression yielding a significant area under the curve (AUC) of 0.86, p<0.0001. At the diagnostic positivity cut-off of ≥0.19 ng/ml, the ROC curve delivered a sensitivity of 81% with a corresponding specificity of 84%. Kruskal-Wallis testing revealed that serum 14-3-3η levels were significantly higher in RA in comparison to all other diseases, p<0.0001. This differential expression is illustrated in Figure 1.

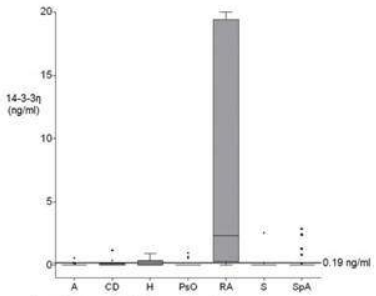

Figure 1. Serum 14-3-3η Expression by Disease.

Conclusion: Serum 14-3-3η is a highly specific RA biomarker. As a novel mechanistic disease factor, 14-3-3η is expected to provide new insights and approaches to RA management and clinical studies.

References: [1]Arthritis Res Ther 2014; 16(2):R99; [2]J Rheumatol 2014; 41(11):2104.

Disclosure: B. Dasgupta, Janssen R & D, LLC, 3; **Y. Cherkas**, Janssen R & D, LLC, 3; **S. Lamberth**, Janssen R & D, LLC, 3; **K. Hayden**, Janssen R & D, LLC, 3; **C. Brodmerkel**, Janssen R & D, LLC, 3; **A. Marotta**, Augurex Life Sciences Corp, 3; **M. Curran**, Janssen R & D, LLC., 3.

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Abstract Number: 2586

Cardiac Magnetic Resonance Imaging Reveals Myocardial Damage in Patients with Active Rheumatoid Arthritis

Miia Holmström[1], Riitta Koivuniemi[2], **Tarja Tiippana-Kinnunen**[2], Antti Kuuliala[3], Marjatta Leirisalo-Repo[2] and Sari Kivistö[1], [1]Radiology, HUS Medical Imaging Center, University of Helsinki and Helsinki University Hospital, Helsinki, Finland, [2]Rheumatology, University of Helsinki and Helsinki University Hospital, Helsinki, Finland, [3]Bacteriology and Immunology, University of Helsinki and Helsinki University Hospital, Helsinki, Finland

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Background/Purpose:

In rheumatoid arthritis (RA), cardiac involvement is common and frequently subclinical. We used cardiac MRI to identify myocardial abnormalities in patients with active RA, free of symptoms and signs of cardiac disease.

Methods:

Sixty female patients with active RA under age of 70 years (31 patients with early RA awaiting the start of treatment with conventional DMARDs and 29 patients with chronic RA awaiting the start of treatment with biological therapy) and 21 sex and age-matched control subjects (10 patients with FM and 11 healthy volunteers) underwent either 1.5T or 3T cardiac MRI for analyses of T1 relaxation times, late gadolinium enhancement (LGE), volumes and function of both ventricles.

Table 1. Clinical features of RA patients

	Early RA	Chronic RA	p-value
Age, years; mean ± SD	48 ± 15	48 ± 14	0.57
RF positivity; n (%)	26 (84)	23 (85)	1.000
ACPA positivity; n (%)	27 (87)	26 (93)	0.673
CRP; mean + SD	16 + 26	7 + 7	0.076
Number of swollen joints; median (IQR)*	8 (4-10)	6 (2-7)	0.037
Number of tender joints; median (IQR)*	7 (3-12)	6 (2-11)	0.726
DAS28-CRP; mean ± SD	3.7 ± 1.05	3.4 ± 1.15	0.267
Extra-articular manifestations; n (%)	5 (16)	14 (48)	0.007
Erosions on radiographs; n (%)	5 (17)	23 (85)	<0.001
Duration of symptoms, years; median (IQR)	0.4 (0.3-0.8)	13.0 (4-26)	<0.001
BMI, kg/m^2; mean ± SD	23.7 ± 4.1	25.5 ± 3.6	0.069

* 66/68 joints evaluated

Results:

By using 1.5T cardiac MRI, native left ventricular (LV) septal T1 time averaged 1010 ± 45 ms in 20 RA patients v.s. 977 ± 18 ms in 11 controls (p = 0.045). With 3T cardiac MRI, the T1 time measured 1170 ± 33 ms in 29 RA patients v.s. 1047 ± 113 ms in 9 controls (p = 0.002). Myocardial LGE was detected in 55% of RA patients, but in none of FM controls. Increased likelihood of LGE was associated with increasing DAS28-CRP (OR 1.87, 95% CI 1.05 to 3.35, p=0.035) and increasing age (OR 1.05, 95% CI 1.00 to 1.09, p=0.040) in multivariate logistic regression model, but not with disease duration or ACPA positivity. Compared with controls, RA patients had impairments in systolic and diastolic function of both ventricles (Table 2). In patients with early RA, right ventricular (RV) dysfunction was more obvious (Table 3).

Table 2. Cardiac MRI findings in RA patients and controls

Variable	RA patients = 60 Mean ± SD Median (IQR)	Controls together = 21 Mean ± SD Median (IQR)	p-value
LVEF, %	58.9 ± 4.3	66.7 ± 6.8	<0.001
LVEDV-index, ml/m2	82.3 ± 11.6	75.1 ± 11.0	0.022
LVESV-index, ml/m2	34 (30-40)	25 (21-29)	<0.001
LVSV-index, ml/m2	47 ± 11	43 ± 6	0.24
LVPFR/EDV, 1/s	2.95 ± 0.85	3.44 ± 0.70	0.012
LV mass-index, g/m2	51.3 ± 7.6	53.1 ± 7.2	0.29
RVEF, %	59 ± 6	58 ± 6	0.65
RVEDV-index, ml/m2	82 ± 13	74 ±8	0.03
RVESV-index, ml/m2	34 ± 9	31 ± 6	0.21
RVSV-index, ml/m2	44 (40-45)	48 (45-49)	0.02

SD = standard deviation, IQR = interquartile range, LV = left ventricle, EF = ejection fraction, EDV = end-diastolic volume, ESV = end-systolic volume, SV = stroke volume, PFR = peak filling rate, RV = right ventricle

Table 3. Cardiac MRI findings in early and chronic RA

Variable	Early RA Mean (±SD) Median (IQR)	Chronic RA Mean (±SD) Median (IQR)	p-value
LV EF %	57 (56-58)	60 (59-61)	0.05
LV EDV-index ml/m2	83±11	81±13	0.56
LV ESV-index ml/m2	35±7	33±6	0.13
LV SV-index; ml	48±6	46±14	0.96
LV PFR/EDV; 1/s	3.04±1.67	3.21±0.88	0.61
LV mass-index; g/m2	51±8	52±8	0.86
RV EF %	57±5	61±6	0.008
RV EDV-index ml/m2	84±12	79±13	0.16
RV ESV-index ml/m2	37±8	32±8	0.02
RV SV-index ml/m2	47±5	48±7	0.49

Conclusion:

Patients with active RA show myocardial abnormality on cardiac MRI: prolonged myocardial T1 relaxation times suggesting diffuse inflammation or fibrosis and LGE indicating local myocardial scars. RA patients also had impairments of LV and RV systolic and diastolic functions. Inflammatory activity observed in patients with early RA with lower systolic ventricular functions compared to patients with chronic RA can reflect systemic inflammation.

Disclosure: M. Holmström, None; **R. Koivuniemi**, None; **T. Tiippana-Kinnunen**, None; **A. Kuuliala**, None; **M. Leirisalo-Repo**, None; **S. Kivistö**, None.

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Abstract Number: 2587

CRP and 14-3-3η Are Each Associated with Joint Damage Progression, Their Titres Do Not Correlate and Are Better Predictors of Progression Together Than Alone

Gilles Boire[1,2], Nathalie Carrier[3], Artur de Brum-Fernandes[1,4], Patrick Liang[1,4], Ariel Masetto[2,5], Yuan Gui[6], Jane Savill[6], Sara Michienzi[6], Henri Ménard[7], Walter Maksymowych[8] and Anthony Marotta[6], [1]Rheumatology Division, Centre Hospitalier Universitaire de Sherbrooke, Sherbrooke, QC, Canada, [2]Department of Medicine/Division of Rheumatology, University of Sherbrooke, Sherbrooke, QC, Canada, [3]Division of Rheumatology, Université de Sherbrooke, Sherbrooke, QC, Canada, [4]Department of Medicine/Division of Rheumatology, Université de Sherbrooke, Sherbrooke, QC, Canada, [5]Department of Medicine/Division of Rheumatology, Université de Sherbrooke, Centre Hospitalier Universitaire de Sherbrooke, Sherbrooke, QC, Canada, [6]Augurex Life Sciences Corp., Vancouver, BC, Canada, [7]MSK Research Axis, McGill University Health Center Research Institute, Montreal, QC, Canada, [8]Department of Medicine, University of Alberta, Edmonton, AB, Canada

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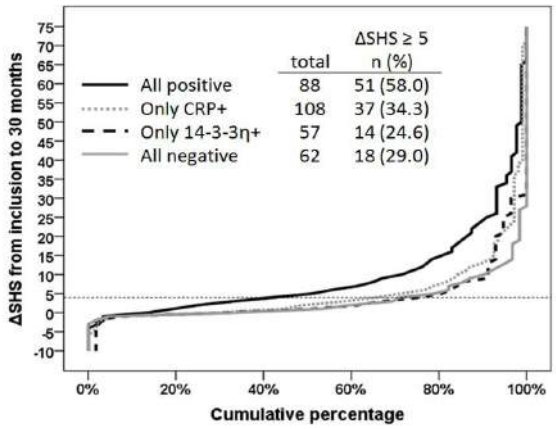
Background/Purpose: As a marker of inflammation and an acute phase reactant, C-reactive protein (CRP) is routinely used in clinical practice and in RA classification criteria. Higher or sustained levels of CRP are associated with a worse prognosis. 14-3-3η is a joint derived mechanistic marker that up-regulates factors that perpetuate disease. Similar to CRP, higher or persistent levels of 14-3-3η are associated with a worse prognosis, and lower circulating levels are associated with better clinical outcomes. Inflammation and joint damage are now understood to be processes that uncouple along the course of disease and treatment strategies have been tightened to achieve both clinical and joint damage remission. The aim of this study was to examine both the independent and combined effects of CRP and 14-3-3η on radiographic progression.

Methods: Baseline (BL) serum 14-3-3η titres were assessed in 331 recent onset polyarthritis patients from the Sherbrooke EUPA Cohort with 5 years of radiographic follow-up data. Patients were DMARD naïve at BL, median age was 60 years, and 62% were female. CRP and 14-3-3η positivity were defined as >8mg/L and ≥0.19ng/ml, respectively. Spearman correlation was performed to assess the relationship between 14-3-3η and CRP titres. Radiographic changes (change in total Sharp/van der Heijde (ΔSHS) score over 30 months were assessed in relation to CRP and 14-3-3η co-expression using ANOVA analysis. Chi-square was used to assess the relationship between CRP positivity with radiographic changes at 30 months based on ΔSHS ≥1, 3, and 5 unit cut-offs.

Results: Of 331 patients, 207 (63%) and 153 (46%) were CRP and 14-3-3η positive at BL, respectively. Spearman correlation revealed that titres of CRP and 14-3-3η did not correlate, r= -0.00025 p=0.996. As noted in Table, Chi-square analysis returned both CRP and 14-3-3η as significantly associated with radiographic changes.

	ΔSHS BL to Year 3 ≥ 1		ΔSHS BL to Year 3 ≥ 3		ΔSHS BL to Year 3 ≥ 5	
	n = 233		n = 168		n= 120	
Variable	OR	p-value	OR	p-value	OR	p-value
CRP positivity	1.73	0.034	2.47	<0.001	2.22	0.001
14-3-3η positivity	1.69	0.046	1.74	0.016	1.70	0.023
CRP and 14-3-3η positivity	2.82	0.002	3.68	<0.001	3.16	<0.001

The cumulative probability plot illustrates that patients who were positive for both CRP and 14-3-3η had the significantly greatest increase in radiographic progression (p<0.001) with over 50% of patients having ΔSHS≥5 over the 30 month period.



Conclusion: CRP and 14-3-3η are both associated with joint damage progression at 3 years and titres do not correlate consistent with their distinct roles in RA disease processes. Interaction analysis further reveals that the combination of these two markers is a better predictor of future radiographic damage than either marker alone. Concomitant serial testing of both these modifiable markers may assist with tight control RA treatment strategies.

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Disclosure: G. Boire, None; **N. Carrier**, None; **A. de Brum-Fernandes**, None; **P. Liang**, None; **A. Masetto**, None; **Y. Gui**, Augurex Life Sciences Corp, 3; **J. Savill**, Augurex Life Sciences Corp, 3; **S. Michienzi**, Augurex Life Sciences Corp, 3; **H. Ménard**, None; **W. Maksymowych**, Augurex Life Sciences, 5; **A. Marotta**, Augurex Life Sciences Corp, 3.

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Abstract Number: 2588

Survivin Links Smoking and High Prevalence of Rheumatoid Arthritis in Women

Minna Turkkila[1], Apostolos Bossios[2], Malin Erlandsson[3], Karin ME Andersson[3], Sofia Töyrä Silfverswärd[4], Maria Rolf[5], Linda Ekerljung[2], Carina Malmhäll[2], Bo Lundbäck[2] and **Maria Bokarewa**[6], [1]University of Göteborg, Göteborg, Sweden, [2]The Krefting Research Centre, University of Gothenburg, Gothenburg, Sweden, [3]Rheumatology and Inflammation Research, University of Gothenburg, Gothenburg, Sweden, [4]Department of Rheumatology and Inflammation Research, Gothenburg University, Gothenburg, Sweden, [5]Department of Rheumatology and Inflammation Research University of Gothenburg, Gothenburg, Sweden, [6]Rheumatology and Inflammation Research, Göteborgs University, Göteborg, Sweden

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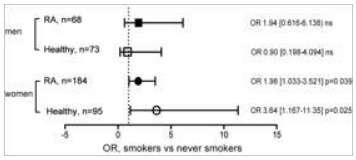
Background/Purpose : Patients with rheumatoid arthritis (RA) are predominantly female, smokers and positive for autoantibodies, rheumatoid factor and antibodies to citrullinated peptides. The oncoprotein survivin has recently emerged as an early marker for RA being frequently found in seropositive patients. High levels of survivin may be measured in serum several years before disease onset. Presence of survivin in serum is also a risk factor for an aggressive and treatment resistant disease. This study elucidates associations between smoking and survivin.

Methods : To study if smoking contributes to higher levels of survivin in serum we measured survivin in 252 (184 women, 68 men) RA patients and 168 healthy controls (95 women, 73 men)**.** Information about smoking habits was collected via extended questionnaire. Serum survivin was analysed with a sandwich ELISA, where the level >0.45ng/ml was considered positive. Production of survivin isoforms of wild type, survivin-2B and survivin-deltaExon3 and estrogen receptor alpha (ERa) by peripheral blood mononuclear cells (PBMC) was measured by qPCR.

Results: The prevalence (43% vs 22.8%, $p<10^{-5}$) and the absolute levels of serum survivin were significantly higher in smokers compared to never smokers (p=0.0024). In women, the estimated risk to be survivin-positive was significantly higher for healthy smokers (OR 3.64[1.17-11.35], p=0.025) and for RA patients (OR 1.98[1.03-3.52], p=0.039). In contrast, no significant increase in risk was found in men.



High serum levels of survivin were associated with combined expression of all three survivin isoforms in PBMC. To study gender-dependent effects of smoking, we compared ERa transcription in PBMC of smoking and non-smoking women RA patients. We observed a smoking-dependent increase of ERa in young women (age <50 years) compared to the older women (p=0.0056). Also, young survivin-positive smokers had higher ERa compared to survivin-negative non-smokers (p=0.0137). Finally, these young survivin-positive women had higher estimated risk for the combined expression of all three survivin isoforms (p=0.012). Functional studies in mouse model proved synergistic effect of smoking and ERa on survivin transcription in leukocytes.

Conclusion: Smoking significantly increases risk for high serum levels of survivin in healthy women and in women with RA potentially decreasing the threshold for the disease. ERa has experimentally been shown as a mediator of survivin production in leukocytes predisposing to an active and proliferating phenotype of these cells.

Disclosure: M. Turkkila, None; **A. Bossios**, None; **M. Erlandsson**, None; **K. M. Andersson**, None; **S. Töyrä Silfverswärd**, None; **M. Rolf**, None; **L. Ekerljung**, None; **C. Malmhäll**, None; **B. Lundbäck**, None; **M. Bokarewa**, None.

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Abstract Number: 2589

Associations Between 49 Susceptibility SNPs and Disease Activity Including Radiographic Damage in Early Untreated Rheumatoid Arthritis

Christian G. Ammitzbøll[1], Rudi Steffensen[2], Martin Bøgsted[3,4], Kaspar Rene Nielsen[2], Torkell Ellingsen[5], Merete Lund Hetland[6], Peter Junker[5], Jan Pødenphant[7], Mikkel Østergaard[8], Julia Johansen[9], Kim Hørslev-Petersen[10] and Kristian Stengaard-Pedersen[1], [1]Department of Rheumatology, Aarhus University Hospital, Aarhus, Denmark, [2]Department of Clinical Immunology, Aalborg University Hospital, Aalborg, Denmark, [3]Department of Haematology, Aalborg University Hospital, Aalborg, Denmark, [4]Department of Mathematical Sciences, Aalborg University, Aalborg, Denmark, Aalborg, Denmark, [5]Department of Rheumatology, Odense University Hospital, Odense, Denmark, [6]DANBIO, Center for Rheumatology and Spine Diseases, Rigshospitalet, Glostrup, Glostrup, Denmark, [7]Department of Rheumatology, Copenhagen University Hospital at Gentofte, Glostrup, Denmark, [8]Rigshospitalet-Glostrup, Copenhagen Center for Arthritis Research, Center for Rheumatology and Spine Diseases, Rigshospitalet - Glostrup, Glostrup, Denmark, [9]Departments of Medicine and Oncology, Copenhagen University Hospital at Herlev, Copenhagen, Denmark, [10]Rheumatology, Research Unit at King Christian X Hospital for Rheumatic Diseases, Graasten, Graasten, Denmark
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Background/Purpose:

Genome-wide association studies (GWAS) and meta-GWAS studies have identified >50 single nucleotide-polymorphisms (SNPs) that are associated with susceptibility to rheumatoid arthritis (RA). It is, however, not known whether these susceptibility SNPs are also associated with disease activity in early RA. The purpose of this study was to analyze for associations between 49 susceptibility SNPs and disease activity including radiographic damage in early untreated RA patients.

Methods:

315 patients with DMARD naïve RA and disease duration <6 months were included from two randomized controlled trials (1,2), Table 1. The two trials had similar inclusion and exclusion criteria, which resulted in similar demographic and clinical characteristics and thus, the two cohorts were combined in the analysis. We genotyped 49 SNPs previously associated with disease susceptibility in two large meta-GWAS studies (3,4) with the TaqMan OpenArray system, Table 2 shows rs-numbers. The genotype associations with disease activity score of 28 joints (DAS28) and radiographic damage (modified Total Sharp Score, mTSS) were evaluated using linear regression analysis adjusted for age, sex, treatment, anti-CCP status and smoking.

Results:

Baseline characteristics were similar in the two cohorts, Table 1. Table 2 shows the linear regression analysis between the 49 SNPs and DAS28 and mTSS at baseline and after one year. Three SNPs were associated with mTSS at both baseline and year one (rs13315591 *PXK*, rs26232 *C5orf30*, rs2793108 *ZEB1*) and neither with DAS28 at baseline nor at year one. There were modest effects on radiographic damage judged by a β ranging from 1.04 to 2.43, with *PXK* having the strongest effect. In summary, we found 12 P values <0.05 in 8 SNPs, but none had a P value ≤0.001. Five associations were found with DAS28 and 7 with mTSS. None of the 196 associations tested were significant when using the Bonferoni's or Sidak's adjustment for multiple testing (both P=0.00026).

Conclusion:

We found three out of 49 susceptibility SNPs to be associated with radiographic damage in 315 early RA patients before and after one year's treatment. No SNPs were consistently associated with DAS28. The results should be interpreted with some reservation due to the large number of associations investigated.

References:

(1) Hetland ML et al. *Arthritis Rheum* 2006, **54:** 1401-1409.

(2) Horslev-Petersen K et al. *Ann Rheum Dis* 2014, **73:** 654-661.

(3) Zhernakova A et al. *PLoS Genet* 2011, **7:** e1002004.

(4) Stahl EA et al. *Nat Genet* 2010, **42:** 508-514.

Table 1. Patient characteristics of the two cohorts included

Baseline	Cohort 1 (n = 180)	Cohort 2 (n = 135)	P-value
Age	55(27–78)	52(26–71)	0.11
Female sex, %	66	65	0.91
Disease duration, days	84(42–162)	98(48–175)	<0.001
Rheumatoid factor positive, %	72	68	0.54
Anti-CCP positive, %	65	60	0.41
Tender joint count 28	11(3–26)	9(2–22)	0.07
Swollen joint count 28	8(2–23)	8(2–20)	0.41
Patient's global assesment, mm	67(13–98)	50(10–91)	<0.001
CRP, mg/liter	14(1–132)	20(2–105)	0.04
DAS28	5.6(3.8-7.7)	5.3(3.2-7.1)	0.02
HAQ	1.1(0.1-2.5)	1(0–2.3)	0.02
Erosive disease (mTSS≥1), %	75	61	0.005
mTSS	2(0-19)	3(0-20)	0.93
Year one			
CRP, mg/liter	2(0.5-19)	7(0.7-33)	<0.001
DAS28	2.0(1.7-4.3)	2.0(1.3-5.1)	0.13
mTSS	3(0-19)	3(0-24)	0.88
DmTSS (year 1 - baseline)	0(-2-6)	0(0-6)	0.76

Values are medians with 5-95% percentile values in parentheses, unless otherwise stated. Anti-CCP = anti-cyclic citrullinated peptide, DAS28 = disease activity score 28 joints, HAQ = Health Assessment Questionnaire. Fisher's exact test and Mann–Whitney rank sum test were used when appropriate. Cohort 1 = OPERA(2), Cohort 2 = CIMESTRA(1)

Tabel 2. Linear regression analysis of 49 SNPs with DAS28 score and modified Total Sharp Score at baseline and year one in 335 early untreated RA patients

		DAS28 baseline		DAS28 Year 1		mTSS baseline		mTSS Year 1	
rs number	gene	β	P	β	P	β	P	β	P
rs10488631	IRF5	0.03	0.82	0.15	0.25	0.50	0.49	0.35	0.68
rs10499194	TNFAIP3	0.12	0.27	-0.02	0.84	0.29	0.61	-0.13	0.85
rs10865035	AFF3	0.01	0.87	-0.03	0.74	-0.88	0.07	-0.61	0.29
rs10919563	PTPRC	0.11	0.41	-0.17	0.18	1.10	0.13	1.65	0.05
rs11203203	UBASH3Ac	-0.02	0.82	-0.01	0.90	-0.15	0.77	0.12	0.84
rs11586238	CD2_CD58	-0.17	0.10	-0.01	0.91	-0.58	0.28	-0.58	0.36
rs11594656	IL2RAc	0.09	0.42	0.08	0.42	-0.23	0.69	-0.67	0.33
rs11676922	AFF3	0.00	0.99	-0.02	0.85	-0.82	0.08	-0.54	0.34
rs12746613	FCGR2A	-0.11	0.41	0.02	0.84	-0.22	0.77	-0.56	0.51
rs13031237	REL	-0.08	0.39	0.04	0.62	-0.02	0.97	-0.38	0.52
rs13119723	IL2_IL21c	0.00	1.00	-0.09	0.45	0.33	0.63	0.74	0.35
rs13315591	PXK	-0.18	0.32	0.16	0.33	2.40	0.01	2.43	0.03
rs1678542	KIF5A	-0.01	0.88	-0.16	0.08	0.22	0.66	0.45	0.46
rs1980422	CD28	-0.06	0.61	0.01	0.94	0.10	0.87	-0.15	0.83
rs2104286	IL2RA	0.00	0.98	-0.05	0.64	-0.36	0.53	-0.31	0.65
rs2397084	IL17F	0.31	0.03	0.16	0.23	0.02	0.98	-0.64	0.50
rs2476601	PTPN22	0.23	0.09	0.15	0.23	1.05	0.15	0.57	0.51
rs26232	C5orf30	0.03	0.77	-0.01	0.89	1.04	0.04	1.21	0.04
rs2736340	BLK	-0.05	0.65	-0.09	0.35	-0.05	0.93	-0.43	0.50
rs2793108	ZEB1	-0.04	0.66	0.18	0.03	-1.17	0.01	-1.29	0.03
rs2812378	CCL21	-0.03	0.71	-0.01	0.87	-0.59	0.23	-0.46	0.44
rs2872507	IKZF3c	-0.14	0.13	-0.04	0.62	-0.17	0.73	-0.09	0.87
rs3087243	CTLA4	-0.11	0.24	0.03	0.72	0.26	0.61	0.53	0.36
rs3093023	CCR6	0.14	0.10	0.08	0.33	0.71	0.13	1.17	0.03
rs3184504	SH2B3	-0.16	0.08	-0.08	0.33	-0.32	0.50	-0.65	0.26
rs3218253	IL2RB	-0.06	0.52	-0.04	0.63	-0.60	0.26	-0.28	0.65
rs3761847	TRAF1_C5	0.07	0.45	-0.01	0.88	0.19	0.70	0.07	0.90
rs3890745	TNFRSF14	0.09	0.38	-0.08	0.39	-0.53	0.33	-0.25	0.70
rs394581	TAGAP	0.26	0.02	-0.08	0.45	0.26	0.68	0.01	0.99
rs4750316	PRKCQ	0.12	0.33	-0.02	0.86	-0.54	0.41	-0.73	0.34
rs4810485	CD40	0.05	0.64	0.02	0.81	-0.63	0.27	-0.58	0.38
rs4819388	ICOSLG	-0.02	0.85	0.13	0.20	-0.71	0.22	-0.22	0.74
rs5029937	TNFAIP3	0.04	0.86	0.34	0.17	-0.57	0.67	-0.18	0.91
rs540386	TRAF6	-0.28	0.05	-0.06	0.67	0.04	0.95	0.93	0.30
rs548234	PRDM1	-0.02	0.87	-0.06	0.54	-0.23	0.66	-0.59	0.34
rs5754217	UBE2L3	0.00	0.98	0.22	0.10	0.56	0.45	0.02	0.99
rs6822844	IL2_IL21	-0.10	0.42	-0.10	0.38	-0.02	0.98	0.50	0.53
rs6859219	IL6ST	-0.25	0.03	0.13	0.23	-0.54	0.39	-0.12	0.88
rs6920220	TNFAIP3	0.05	0.63	0.15	0.12	0.02	0.97	0.11	0.87
rs706778	IL2RA	-0.11	0.22	0.02	0.79	0.48	0.31	0.45	0.42
rs7155603	BATFc	0.03	0.77	0.14	0.17	0.90	0.12	1.03	0.14
rs7543174	IL6R	-0.19	0.11	-0.17	0.13	-0.40	0.53	-0.87	0.25
rs7574865	STAT4	-0.02	0.86	-0.05	0.62	0.08	0.90	-0.20	0.78
rs763780	IL17F	0.13	0.51	-0.12	0.51	-0.60	0.57	-0.90	0.47
rs8045689	CD19	-0.16	0.10	0.06	0.49	-0.54	0.29	-0.13	0.83
rs840016	CD247	0.11	0.25	0.03	0.74	0.43	0.37	0.56	0.33
rs874040	RBPJ	-0.19	0.05	-0.05	0.57	-0.17	0.75	0.07	0.91
rs934734	SPRED2	-0.01	0.94	0.00	1.00	-0.12	0.80	0.05	0.93
rs951005	CCL21	-0.08	0.57	0.04	0.73	-0.44	0.54	-0.33	0.70

Linear regression analyses are corrected for treatment, age, gender, anti-CCP status and smoking(never/ever). mTSS=modified Total Sharp Score, β=correlation coefficient, P values <0.05 are marked by shading, SNPs are listed in ascending order by their rs number.

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Abstract Number: 2590

Anti-Citrullinated Protein Antibody and Radiographic Disease Progression in Rheumatoid Arthritis

Brian Coburn[1], Geoffrey M. Thiele[1], Michael J. Duryee[2], Fang Yu[3], Harlan Sayles[4], Jeremy Sokolove[5], WH Robinson[6], Alan Erickson[7], Mary Brophy[8], James R. O'Dell[1] and Ted R. Mikuls[1], [1]Omaha VA Medical Center and University of Nebraska Medical Center, Omaha, NE, [2]Internal Medicine Division of Rheumatology, University of Nebraska Medical Center, Omaha, NE, [3]Public Health, University of Nebraska Medical Center, Omaha, NE, [4]University of Nebraska Medical Center, Omaha, NE, [5]Stanford University, Palo Alto, CA, [6]VA Palo Alto Health Care System and Stanford University, Palo Alto, CA, [7]University of Nebraska College of Medicine and VA Nebraska Western Iowa Health Care System, Omaha, NE, [8]VA Boston Heathcare System, Boston, MA

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Background/Purpose:

Anti-citrullinated protein antibody (ACPA) positivity is associated with more rapid radiographic progression in rheumatoid arthritis (RA). A majority of prior studies, however, have assessed ACPA status using only the commercially available anti-CCP2 antibody assay. Thus, it is unknown to what extent any antigen-specific ACPA might drive this relationship. The objective of this study was to simultaneously evaluate the association between anti-CCP2 antibody and antigen-specific ACPA with radiographic disease progression in a well-characterized cohort.

Methods:

This is a secondary analysis of the 48-week Rheumatoid Arthritis Comparison of Active Therapies (RACAT) trial. RA patients with active disease despite methotrexate (MTX) were randomized to receive triple therapy (MTX + sulfasalazine/hydroxychloroquine) or MTX + etanercept. Baseline serum was tested for anti-CCP2 using a commercially available ELISA and 29 antigen-specific ACPA using a multiplex peptide array (Table footnote). Radiographs from baseline, 24- and 48-weeks were scored by blinded experts using a modified Sharp score. Generalized linear mixed effects models assuming a negative binomial distribution were used to model associations of ACPA with Sharp scores over time. Models were adjusted for age, gender, race, smoking status, BMI and disease duration. Statistical significance was defined at a p-value < 0.05 after adjusting for multiple comparisons using the Benjamini-Hochberg method.

Results:

RA patients (n=281) had a mean (± SD) age of 56 (12) years, 88% were white and 58% were male. Although not reaching statistical significance, anti-CCP2 positive patients had higher baseline Sharp scores compared with anti-CCP2 negative patients (16.1 vs. 11.1; p=0.45). In adjusted analyses modeling for Sharp scores, anti-CCP2 positivity was associated with 1.14 to 1.18 times the radiographic progression of anti-CCP2 negative patients at 24 and 48 weeks (p=0.01) (Table). Assessing ACPA fine specificity, only antibody to citrullinated histone 2A concentration was associated radiographic progression; each natural log unit increase was associated with 1.05 and 1.06 times higher Sharp score changes from baseline to 24 and 48 weeks, respectively (p=0.0007). No other antigen-specific ACPA were significantly associated with radiographic scores after adjusting for multiple comparisons.

Conclusion:

These novel findings suggest that the well-described association of ACPA positivity with structural joint damage in RA, may at least in part of driven by autoantibody targeting citrullinated histone 2A. In addition to required verification in an independent cohort, future efforts will be needed to identify the “source” of this autoantigen and mechanisms underpinning the relationship of this antigen-specific ACPA with radiographic disease progression.

Table 1 Associations of ACPA with change in modified Sharp scores over time.

Variable	Visit	Exponential of Coefficient‡	P
Anti-CCP2 Positive	24 Weeks	1.14	0.01
	48 Weeks	1.18	
Histone 2A [1-20] cit cyclic†	24 Weeks	1.05	0.0007*
	48 Weeks	1.06	
Histone 2B [62-81] cit cyclic†	24 Weeks	1.05	0.006**
	48 Weeks	1.05	
Histone 2A [1-20] cit sm2 cyclic†	24 Weeks	1.04	0.007**
	48 Weeks	1.05	

‡ Represents an interaction with visit date indicating a significant difference in Sharp score changes over time by anti-CCP2 status or log-transformed ACPA level. † Numbers in brackets indicate the amino acid sequence of the peptide. The Histone 2A peptides are homologous with differing cyclization chemistry. * $p < 0.05$ after Benjamini-Hochberg adjustment; ** $p \geq 0.05$ after Benjamini-Hochberg adjustment.

Citrullinated peptides / proteins examined: Fibrinogen (n=10); Apolipoprotein A1 (n=2); Apolipoprotein E (n=2); Enolase 1A (n=1); Vimentiin (n=3); Histone 2A (n=3); Histone 2B (n=2); Filaggrin (n=1); Clusterin (n=2); Biglycan (n=1) and Fibronectin (n=2).

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Abstract Number: 2591

Ultrasound Residual Synovitis Has an Impact on the Time to Relapse in RA Patients Considered in Clinical Remission: A Real Life Study of 211 Patients

Pascal Zufferey[1], Myriam Riek[2], Giorgio Tamborrini[3], Laure Brulhart[4], Martin Toniolo[5], Sandra Blumhardt[6], Burkhard Moeller[7,8] and Hans Ruedi Ziswiler[9], [1]Rhu /Dal .Chuv, Rheumatology, Lausanne, Switzerland, [2]SCQM Registry, Zurich, Switzerland, [3]Rheumatologie, Bethesda spital, Basel, Switzerland, [4]médecine, hôpital neuchateulois, La chaux de fond, Switzerland, [5]Department of Rheumatology, University Hospital of Zurich, Zurich, Switzerland, [6]rheumatology, USZ, zurich, Switzerland, [7]Rheumatology, Inselspital-University Hospital, Bern, Switzerland, [8]Rheumatology, Inselspital University Hospital, Bern, Switzerland, [9]Osteorheuma, Bern, Switzerland

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Background/Purpose:

Previous publications have suggested that patients in clinical remission with residual ultrasound (US) synovitis flare more often and do not stay in remission as long as those without residual US synovitis[1]. Those studies have been performed in single centers by a few highly skilled operators. Before recommending the use of US as a predictor of flare in daily practice, those observations need to be

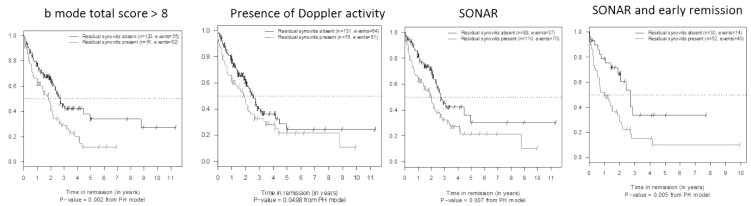
confirmed in real life studies.

The objective of this study was to investigate the predictive value of US residual synovitis on loss of remission in a national cohort of patients followed in real life by many different rheumatologists operating on many different US machines

Methods: US significant residual synovitis has been defined on the Swiss SONAR score, which adopted the single joint definition of pathologies according to OMERACT for 22 joints. Recently, the SONAR score was validated against clinical disease activity parameters and the ACR/EULAR remission status in a large cross-sectional setting among patients in the Swiss RA registry (SCQM) [2]. For each patient we identified the first visit in clinical remission (defined as a DAS28 < 2.6) belonging to the first remission phase during which an assessment of residual US synovitis was available as the baseline and analyzed time to relapse during follow-up. Relapse was defined as a DAS28 >= 2.6, start of a biologic, start of an sDMARD, or start of glucocorticosteroid (GC) therapy or an intensification of GC therapy, whatever occurred first.

Results:

Up to 211 RA patients had US synovitis data and a follow-up. The majority of patients received a biological treatment at baseline. Significant residual US synovitis was present in 110 of 198 patients based on SONAR and in 91 of 211 patients considering only b and in 76 of 207 considering only Doppler mode for defining residual synovitis. Median time to relapse was 2 yrs (95% CI: 1.4, 2.6) for SONAR+, and 2.7 yrs (95% CI: 2.4, not estimable) for SONAR-. When we restricted the analysis to the 82 patients who were known to have been in remission for at most 6 months at baseline (confirmed early remission), median times to relapse were 1 year (95% CI: 0.7, 2) for SONAR+ and 2.7 yrs (95% CI: 2.1, not estimable) for SONAR-. The same conclusions were obtained with b or Doppler mode only defined residual synovitis. The figure displays Kaplan-Meier plots of time to relapse for SONAR+ and SONAR- (all patients and subgroup of confirmed early remission patients) and for b mode and Doppler mode only defined residual synovitis.



Conclusion:

Our study in real life patients supports the earlier finding that residual US synovitis is predictive of duration of remission in RA in particular in early remission.

References 1 : Rheumatology . 2014 Nov;53(11):2110-8, 2: Joint Bone Spine. 2014 Oct;81(5):426-32

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Abstract Number: 2592

Rheumatoid Arthritis Patients with Many Autoantibodies Have Different Characteristics at Presentation Compared to Patients with Few Autoantibodies

Veerle F.A.M. Derksen[1], Sofia Ajeganova[2], Annette H.M. van der Helm- van Mil[1], Ingiäld Hafström[3], T. W. J. Huizinga[1], René E. M. Toes[1], Leendert A. Trouw[1], Björn Svensson[4] and **Diane van der Woude**[1], [1]Rheumatology, Leiden University Medical Center, Leiden, Netherlands, [2]Rheumatology unit, Department of Medicine,, Karolinska Institutet at Karolinska University Hospital Huddinge, Stockholm, Sweden, [3]Unit of Rheumatology, Department of Medicine, Karolinska Institutet at Karolinska University Hospital Huddinge, Stockholm, Sweden, [4]Section of Rheumatology, Institution of Clinical Science, Lund University, Lund, Sweden
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Background/Purpose: Patients with rheumatoid arthritis (RA) are frequently positive for one or several autoantibodies like rheumatoid factor (RF), anti-citrullinated protein antibodies (ACPA) and anti-carbamylated protein antibodies (Anti-CarP). Seropositive and seronegative patients differ in respect of risk factors and disease outcome.[1,2] However, it is unclear whether these patients differ at baseline. Therefore, this study aimed to investigate whether the number of autoantibodies is associated with phenotypic characteristics at presentation in RA patients.

Methods: Two independent cohorts of early RA patients were analysed: the Leiden Early Arthritis Cohort (EAC) (845 patients) and the Swedish BARFOT (Better Anti-rheumatic Farmaco-therapy) study (805 patients). All patients fulfilled the 1987 ACR criteria for RA and had a symptom duration of less than 24 months. Autoantibody status was determined at baseline. RF was measured with commercial enzyme linked immunosorbent assays (ELISAs) in the EAC and with commercial agglutination tests in the BARFOT. Commercial ELISAs were also used to determine anti-CCP2 status in both cohorts. Antibodies against carbamylated fetal calf serum (Anti-CarP) were measured for both cohorts in Leiden using in-house ELISAs. Baseline characteristics between patients with few (0 or 1) and many (2 or 3) autoantibodies were compared using logistic regression. Variables with a univariate p <0.10 were included in a multivariate model. The multivariate analysis was repeated after exclusion of highly correlated variables and variables with >15% missing values.

Results: The distribution of the autoantibodies in both cohorts was similar. In both cohorts, patients with many RA-associated antibodies were younger, more often smokers, had a longer symptom duration, more often an intermittent onset of symptoms and a higher erythrocyte sedimentation rate (ESR) compared to patients with few autoantibodies (Table 1). Furthermore, patients having many autoantibodies differed with respect to distribution of affected joints and swollen joint count in the EAC (Table 1). Other variables which were significantly associated with the number of autoantibodies in univariate analysis, were BMI, family history of RA and HAQ in the EAC, and C-reactive protein (CRP), SHS and erosions at baseline in the BARFOT study. When these variables were included in the multivariate model, only erosions was significant: OR 2.62 (1.63-4.21).

Conclusion: Patients carrying few and many autoantibodies differ with regard to initial clinical presentation. Patients with many RA-associated autoantibodies are younger, more often smokers, have a longer symptom duration, more often an intermittent onset of symptoms and a higher ESR compared to patients with few autoantibodies.

1. Aletaha D. et al. 2010 Arthritis Rheum. 62(9): 2569-81.

2. Shi J. et al. 2011 PNAS. 108(42): 17372-7.

Cohort	Baseline Characteristics	OR	95% CI	p
EAC	Age in years	**0.98**	**0.97-0.99**	**<0.001**
(n=610)	Smoked ever	**1.67**	**1.19-2.35**	**0.003**
	Symptom duration in months	**1.05**	**1.01-1.09**	**0.006**
	Intermittent onset of symptoms	**5.80**	**1.29-26.07**	**0.022**
	ESR in mm/hour	**1.01**	**1.01-1.02**	**0.001**
	Symmetry start of symptoms	0.60	0.40-0.91	0.015
	Start of symptoms in both extremities	2.02	1.40-2.91	<0.001
	Swollen joint count in 66 joints	0.97	0.95-0.99	0.006
BARFOT	Age in years	**0.98**	**0.97-0.99**	**0.002**
(n=753)	Smoked ever	**1.83**	**1.34-2.48**	**<0.001**
	Symptom duration in months	**1.09**	**1.03-1.14**	**0.001**
	Intermittent onset of symptoms	**2.20**	**1.04-4.66**	**0.040**
	ESR in mm/hour	**1.02**	**1.01-1.03**	**<0.001**

Table 1

Disclosure: V. F. A. M. Derksen, None; **S. Ajeganova**, None; **A. H. M. van der Helm- van Mil**, None; **I. Hafström**, None; **T. W. J. Huizinga**, None; **R. E. M. Toes**, None; **L. A. Trouw**, None; **B. Svensson**, None; **D. van der Woude**, None.

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Abstract Number: 2593

Relationship Between Index of Activity Speed (Time Up and Go test) and Patient-Reported Outcome in Patients with Long-Standing Rheumatoid Arthritis: Multicenter Prospective Cohort Study for Evaluation of Joint Surgery on Physical

Function

Toshihisa Kojima[1], Hajime Ishikawa[2], Keiichiro Nishida[3], Sakae Tanaka[4], Nobuhiko Haga[5], Jun Hashimoto[6], Hisaaki Miyahara[7], Yasuo Niki[8], Masayo Kojima[9] and Naoki Ishiguro[10], [1]Department of Orthopedic Surgery, Nagoya University Hospital, Nagoya, Japan, [2]Orthopedic Surgery, Niigata Rheumatic Center, Niigata, Japan, [3]Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama city, Japan, [4]Orthopaedic Surgery and Spinal Surgery, The University of Tokyo Hospital, Tokyo, Japan, [5]Rehabilitation Medicine, The University of Tokyo Hospital, Tokyo, Japan, [6]Dept of Rheumatology, Osaka-Minami Medical Center, Kawachinagano City, Japan, [7]Orthopedic Surgery, National Hospital Organization Kyushu Medical Centre, Fukuoka, Japan, [8]Orthopedic Surgery, Keio University School of Medicine, Tokyo, Japan, [9]Nagoya City University Graduate School of Medical Sciences, Nagoya, Japan, [10]Department of Orthopedic Suregery, Nagoya University Hospital, Nagoya, Japan
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Background/Purpose:

Total management including reconstructive joint surgery and rehabilitation should be needed for further improvements of physical function for long-standing RA patients. It is very important to set treatment goal for those management using index of activity speed [Time Up and Go (TUG)] and range of motion (ROM). The purpose of this study is to explore the characteristics of functional impairment and relationship TUG and physical function in RA patients who were needed joint surgery using multicenter prospective cohort.

Methods:

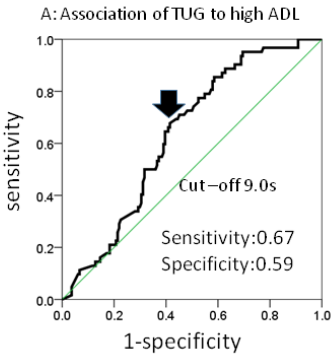
We started the prospective study in September, 2012 (Study registration: UMIN000012649). We collected data at pre- and post-operation (0.5 years, 1 year) on age, sex, disease duration, drug therapies, and disease activity. Functional evaluations were made using the TUG, HAQ-DI, DASH (upper limb function), and patient subjective evaluations using the EQ-5D (QOL) and BDI-II (depression). Joint range of motion was also measured as part of this evaluation.

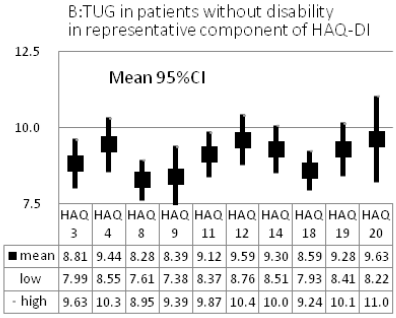
Results:

347 surgical patients were registered. Mean values for age, disease duration, and sex were 65.2 years, 18 years, and 88% female, respectively. Actually, even long-standing RA patients who were needed joint surgery had remission or low disease activity in this baseline data (median values for DAS28 (3.0) and CRP (0.33 mg/dl). 23.8% of the patients were treated with biologics. We confirmed the significant correlation between TUG and disease duration, HAQ-DI, patient-reported outcome (EQ-5D, BDI-II) and range of motion (hip, knee, shoulder ankle). We also found significant relationship between TUG and the level of disability in 18 of 20 components in HAQ-DI. TUG was significantly associated with high ADL status (total HAQ point <6/60: upper quartile value of study population) based on ROC curve (Fig. A). Cut-off value of TUG for high ADL status was 8.98 seconds (sensitivity 67%, specificity 59%).Cut-off of TUG (9 seconds) was associated with the TUG value of patients without disability of HAQ-DI component (Fig.B). As for total knee and hip arthroplasty, TUG was significantly improved after operation (14.0 s to 11.1 s). TUG before operation significantly associated with that after operation. To achieve TUG=9 seconds after operation, the cut-off of TUG before operation was 10.3 s (sensitivity 74%, specificity 82%).

Conclusion:

TUG was significantly associated with many kinds of daily activity and patient-reported outcome. The information should be important for assessment of disability in patients with long-standing RA. TUG as shown in this study could provide target of surgical procedure and rehabilitation program and index of timing for better outcome of joint arthroplasty.





	HAQ 3	HAQ 4	HAQ 8	HAQ 9	HAQ 11	HAQ 12	HAQ 14	HAQ 18	HAQ 19	HAQ 20
■mean	8.81	9.44	8.28	8.39	9.12	9.59	9.30	8.59	9.28	9.63
low	7.99	8.55	7.61	7.38	8.37	8.76	8.51	7.93	8.41	8.22
· high	9.63	10.3	8.95	9.39	9.87	10.4	10.0	9.24	10.1	11.0

Disclosure: T. Kojima, None; **H. Ishikawa**, None; **K. Nishida**, None; **S. Tanaka**, None; **N. Haga**, None; **J. Hashimoto**, None; **H. Miyahara**, None; **Y. Niki**, None; **M. Kojima**, None; **N. Ishiguro**, None.

Abstract Number: 2594

Multi-Biomarker Disease Activity Score As a Predictor of Flare in Patients with Rheumatoid Arthritis Who Stop TNF-Alpha-Inhibitor Therapy

Femke Lamers-Karnebeek[1], Marjan Ghiti Moghadam[2], Harald E. Vonkeman[3], Janneke Tekstra[4], Annemarie Schilder[5], Henk Visser[6], Peter M. ten Klooster[7], Eric H. Sasso[8], David Chernoff[9], Willem Lems[10], Dirkjan van Schaardenburg[11], Robert Landewé[12], Iet Van Albada[13], T.R.D.J. Radstake[14], Piet van Riel[15], Mart A.F.J. van de Laar[16] and Tim Jansen[17], [1]Rheumatology, Radboudumc, Nijmegen, Netherlands, [2]rheumatology, Medisch Spectrum Twente - Arthritis Center Twente, Enschede, Netherlands, [3]Ariensplein 1, Medisch Spectrum Twente - Arthritis Center Twente, Enschede, Netherlands, [4]Dept. Rheumatology & Clinical Immunology, University Medical Center Utrecht, Utrecht, Netherlands, [5]Rheumatology, Medisch Centrum Leeuwarden, Leeuwarden, Netherlands, [6]Rheumatology, Alysis Care Group, Arnhem, Netherlands, [7]Pcgr, University of Twente, Enschede, Netherlands, [8]Crescendo Bioscience Inc., South San Francisco, CA, [9]Crescendo Bioscience, Inc., South San Francisco, CA, [10]Amsterdam Rheumatology and immunology Center, location VU University Medical Center, Department of Rheumatology, Amsterdam, Netherlands, [11]Rheumatology, Amsterdam Rheumatology and immunology Center, Academic Medical Center, Amsterdam, Netherlands, [12]Department of Rheumatology, Amsterdam Rheumatology Center, Amsterdam, The Netherlands, Amsterdam, Netherlands, [13]Meander MC, Amersfoort, Netherlands, [14]Laboratory for Translational Immunology, University Medical Center Utrecht, Utrecht, Netherlands, [15]Rheumatology, Radboud University Nijmegen Medical Centre, Nijmegen, Netherlands, [16]Rheumatology, Medisch Spectrum Twente - Arthritis Center Twente, Enschede, Netherlands, [17]VieCuri Medical Center, Venlo, Netherlands
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Background/Purpose:

Prediction which rheumatoid arthritis (RA) patients in low disease activity (LDA) can successfully discontinue TNF inhibition (TNFi) may improve the cost-effectiveness of RA management. We evaluated the multi-biomarker disease activity (MBDA) score, which is based on 12 serum biomarkers, as a predictor of flare after TNF-i discontinuation.

Methods:

Data were used from the 439 RA patients who were randomized to stop TNFi treatment in the Dutch multi-center POET trial. All patients had been in DAS28 LDA for ≥12 months. In the study TNFi was allowed to be restarted if RA flared according to reimbursement criteria: DAS28 exceeding the 3.2 again, but patients and/or physicians were allowed if DAS increase was minor to escalate the dose from the conventional disease modifiers. In our current analysis 4 definitions of flare were assessed during the 12 months from TNFi discontinuation: 1) re-initiating TNFi treatment, 2) escalation of any medication and 3) physician-reported flare. MBDA score, which measures RA disease activity on a scale of 1 to 100 with validated levels of low (<30), moderate (30 to 44) and high (>44), was assessed at baseline. Associations between baseline MBDA score and each definition of flare by 12 months post-TNFi discontinuation were evaluated using univariate analysis and multivariate logistic regression.

Results: At baseline, 50.1%, 35.3% and 14.6% of patients had low, moderate or high MBDA scores and 94.1%, 5.9%, 0% had low, moderate high DAS28. Within 12 months, 49.9% of patients who discontinued TNFi treatment at baseline had restarted TNFi medication, 59.0% had escalation of any medication and 57.2% had experienced at least one physician-reported flare. MBDA scores at baseline were predictive for each definition of flare. At least one definition of flare was observed by 12 months in 59.5%, 68.4% and 81.3% of patients with low, moderate, or high MBDA score at baseline, respectively (*P*=0.004) (Table 1). Adjusted for baseline DAS28-ESR, disease duration, BMI and erosions, high MBDA scores (>44) were associated with an increased risk for TNFi re-initiation (OR=1.85, 95% CI 1.00–3.40), medication escalation (OR=1.99, 95% CI 1.01–3.94) and physician-reported flare (OR=2.00, 95% CI 1.06–3.77).

Table 1: Occurrence of flare by four definitions at 12 months for patients classified by baseline MBDA score

Flare definition	**Low (<30) n=220**	**Moderate (30–44) n=155**	**High (>44) n=64**	**P-value**
TNF-inhibitor re-initiation	102 (46.4%)	74 (47.7%)	43 (67.2%)	0.011
Medication escalation	117 (53.2%)	92 (59.4%)	50 (78.1%)	0.002
Clinician-reported flare	116 (52.7%)	87 (56.1%)	48 (75.0%)	0.006
Any flare	131 (59.5%)	106 (68.4%)	52 (81.3%)	0.004

Any flare = TNFi re-initation, medication escalation, clinician-reported flare or DAS28 flare. P-value by Pearson χ^2test.

Conclusion:

In RA patients with DAS28 LDA, a high MBDA score at baseline was an independent predictor of flare within 12 months of discontinuing TNFi therapy. The MBDA score may be a clinically useful tool for identifying a subgroup of patients at higher risk of flare when stopping TNFi treatment.

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Abstract Number: 2595

Autoantibodies to Citrullinated Fibrinogen, Anti-CCP2 and Anti-MCV Antibodies in Early Rheumatoid Arthritis Patients with Rapid Radiographic Progression at 1-Year

Yannick Degboé[1], Arnaud Constantin[2], Delphine Nigon[3], Gabriel Tobon[4], Martin Cornillet[5], Thierry Schaeverbeke[6], Gilles

Chiocchia[7], Pascale Nicaise-Roland[8], Leonor Nogueira[9], Guy Serre[5,10,11], Alain G. Cantagrel[12] and Adeline Ruyssen Witrand[13,14], [1]Rheumatology, Rheumatology Center, Purpan University Hospital, Toulouse, France, [2]Inserm U558, Rheumatology Center, Purpan University Hospital, Toulouse, France, [3]CHU Purpan, Toulouse, France, [4]Rheumatology Department, la Cavale Blanche Hospital, Brest, France, [5]Service de Biologie Cellulaire, C.H.U. Purpan, Toulouse, France, [6]CHU Bordeaux, Bordeaux, France, [7]Immunology-Rheumatology, INSERM U1173, paris, France, [8]Immunology Department, Bichat Claude-bernard, Universitary Hospital, APHP, Paris, France, [9]Immunology, UMR CNRS 5165, INSERM 1056, Toulouse, France, [10]Cell Biology, Purpan University Hospital, Toulouse, France, [11]Unité Différenciation Épidermique et Autoimmunité Rhumatoïde, Unité Mixte de Recherche, INSERM,Toulouse, France, Toulouse, France, [12]Rheumatology, Centre Hospitalier Universitaire, Toulouse Purpan, Toulouse, France, [13]Rheumatolgy, CHU Purpan - Hôpital Pierre-Paul Riquet, Toulouse, France, [14]UMR 1027, Inserm, Toulouse, France
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Background/Purpose: We compared the ability of anti-CCP2, anti-mutated citrullinated vimentin (anti-MCV) and anti-citrullinated fibrinogen (AhFibA) antibodies to predict 1-year rapid radiographic progression (RRP; total Sharp score variation ≥ 5 points), in early rheumatoid arthritis (RA).

Methods: We analyzed 566 patients from the ESPOIR cohort with early RA fulfilling the 2010 ACR/EULAR criteria at inclusion. Prediction of 1-year RRP was analyzed by receiver operating characteristic (ROC) curves for the 3 ACPA assayed by ELISA on baseline sera. One-year RRP risk was assessed by ACPA titers. Logistic multivariate regression was used to analyze RRP risk in terms either of positivity or of titer: high, >3 times the cut-off (>3N) and low (1 to 3N).

Results: 333 patients were positive for at least one of the three ACPA tests and 145 patients displayed RRP (Table 1). The areas under the ROC curves were similar for the 3 antibodies, about 0.60. Low+ anti-MCV titers were not associated with RRP (Odds ratio (OR) 0.68; 95% confidence interval (95%CI) 0.29-1.59), whereas low+ anti-CCP2 titers (OR 3.80; 95%CI 1.11-13.10) and low+ AhFibA titers (OR 2.39; 95%CI 1.04-5.49) were significantly associated (Table 2). In multivariate analysis, 1-year RRP was associated with high anti-MCV titers (OR 2.17; 95%CI 1.45-3.24), with anti-CCP2 positivity (OR 2.14; 95%CI 1.43-3.21) and with AhFibA positivity (OR 2.39; 95%CI 1.57-3.63) (Table 3).

Conclusion: Anti-CCP2 antibodies and AhFibA were predictive of 1-year RRP in early RA whatever their titer was, whereas only high anti-MCV antibodies titers were predictive potentially making them more discriminant to predict 1-year RRP risk.

Table 1. Demographic, biologic and radiographic data for patients with early rheumatoid arthritis

	Patients (n = 566)	Patients without RRP at 1 year (n = 421)	Patients with RRP at 1 year (n = 145)	P value
DEMOGRAPHIC DATA				
Age, years, median (IQR)	50.5 (40.2-57.0)	49.9 (40.0-56.7)	52.4 (41.7-58.6)	NS
Women, no. (%)	445 (78.6)	336 (79.8)	109 (75.2)	NS
Smokers, no. (%)	272 (48.1)	204 (48.5)	68 (46.9)	NS
Disease duration, months, median (IQR)	5.0 (3.1-7.4)	4.8 (3.0-7.1)	5.2 (3.5-7.8)	NS
BIOLOGIC DATA				
ESR, mm/1h, median (IQR)	22 (12-37)	20 (12-34)	27 (14-49)	0.0063
CRP level, mg/L, median (IQR)	9 (0-21)	8 (0-18)	14 (5-36)	< 0.0001
≥ 1 allele encoding *HLADRB1* SE, no. (%)	292 (54.0%)	205 (50.9)	87 (63.0)	0.0133
RF+, no. (%)	307 (54.2)	208 (49.4)	99 (68.3)	< 0.0001
Anti-CCP2 titers, no. (%) negative low high	295 (52.1) 11 (1.9) 260 (45.9)	242 (57.5) 6 (1.4) 173 (41.1)	53 (36.5) 5 (3.4) 87 (60.0)	< 0.0001
Anti-MCV titers, no. (%) negative low high	268 (47.3) 51 (9.0) 247 (43.6)	217 (51.5) 44 (10.4) 160 (38.0)	51 (35.2) 7 (4.8) 87 (60.0)	< 0.0001
AhFibA titers, no. (%) negative low high	272 (48.1) 30 (5.3) 264 (46.6)	225 (53.4) 20 (4.8) 176 (41.8)	47 (32.4) 10 (6.9) 88 (60.7)	< 0.0001
RADIOGRAPHIC DATA				
Baseline mTSS, median (IQR)	3 (0-7)	2 (0-7)	3 (0-8)	NS
mTSS at 1 year, median (IQR)	6 (2-12)	4 (2-8)	13 (8-19)	< 0.0001
mTSS progression, median (IQR)	2 (0-5)	0 (0-2)	8 (6-11)	< 0.0001

RRP = rapid radiographic progression; SE = presence of at least one allele of the shared epitope of HLA-DRB1; ESR = erythyocyte sedimentation rate; CRP = C-reactive protein; IQR = interquartile range; RF = rheumatoid factor; mTSS = van der Heijde modified Total Sharp Score

Table 2. One-year rapid radiographic progression (RRP) and baseline ACPA titers (anti-CCP2, anti-MCV, AhFibA)

Antibody titers	**No. of patients with RRP(%)**	**OR [95%CI]**	**p value (χ^2)**
Anti-CCP2			
Negative	53 (18.0)	1	-
Low titer (≤3N)	5 (45.5)	3.80 [1.11–13.10]	0.0226
High titer (>3N)	87 (33.5)	2.30 [1.54–3.43]	< 0.0001
p value (OR trend)	$2.9\ 10^{-5}$		
Anti-MCV			
Negative	51 (19.0)	1	-
Low titer (≤3N)	7 (13.7)	0.68 [0.29–1.59]	NS
High titer (>3N)	87 (60.0)	2.31 [1.54–3.48]	< 0.0001
p value (OR trend)	$3.0\ 10^{-5}$		
AhFibA			
Negative	47 (17.3)	1	-
Low titer (≤3N)	10 (33.3)	2.39 [1.04–5.49]	0.0332
High titer (>3N)	88 (33.3)	2.39 [1.58–3.62]	< 0.0001
p value (OR trend)	$2.1\ 10^{-5}$		

p value = χ^2 test, with negative ACPA rates as the reference. p value (OR trend) = test of trend

Table 3. Multivariate analysis of variables associated with 1-year RRP

	OR	95%CI	P value
Model 1: assessing anti-CCP2			
AUC 0.6491 (95%CI 0.5978–0.7003)			
Anti-CCP2 positivity	2.15	1.43–3.21	<0.0001
CRP level (> 10 mg/L)	1.73	1.15–2.58	0.007
Erosions at baseline	1.50	1.00–2.25	0.049
Model 2: assessing anti-MCV			
AUC 0.6304 (95%CI 0.5784–0.6825)			
Anti-MCV positivity	Discarded during logistic regression		
RF positivity	2.12	1.40–3.20	<0.0001
CRP level (> 10 mg/L)	1.80	1.21–2.67	0.004
Model 3: assessing AhFibA			
AUC 0.6536 (95%CI 0.6017–0.7055)			
AhFibA positivity	2.39	1.57–3.63	<0.0001
CRP level (> 10 mg/L)	1.68	1.13–2.51	0.011
Age at RA onset	1.02	1.00–1.04	0.031
Model 4: assessing high ACPA titer (>3N)			
AUC 0.6480 (95%CI 0.5958–0.7003)			
High anti-CCP2 or AhFibA titers	Discarded during logistic regression		
High anti-MCV titers	2.17	1.45–3.24	<0.0001
CRP level (> 10 mg/L)	1.69	1.13–2.53	0.010
Erosions at baseline	1.50	1.00–2.25	0.049

AUC = area under (the receiver operating characteristic) curve

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Abstract Number: 2596

Less Musculoskeletal Ultrasound Power Doppler Activity Seen in Obese Rheumatoid Arthritis

Erin Bauer[1], Ami Ben-Artzi[2], Erin Duffy[1], David Elashoff[1], Cesar Olmos[3] and Veena K. Ranganath[3], [1]Medicine, David Geffen School of Medicine, Los Angeles, CA, [2]David Geffen School of Medicine, Los Angeles, CA, [3]Medicine, Division of Rheumatology, David Geffen School of Medicine, Los Angeles, CA

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Background/Purpose: Studies report that obese and overweight patients with rheumatoid arthritis (RA) are less likely to attain remission and more likely to have limited therapeutic response, as compared to non-obese RA patients. Our objective was to determine the association between synovitis musculoskeletal ultrasound measures (Power Doppler [PDUS]) and disease activity measures (DAS28) in obese RA patients.

Methods: Cross sectional clinical and ultrasound data was collected on 43 RA patients, and divided into three groups based on their

body mass index (BMI): <25, 25 to 30, and >30. Clinical joint assessments included patient global visual analogue scale (VAS), physician global VAS and 28 swollen and tender joint counts. The sedimentation rate, anti-cyclic citrullinated pepide (ACPA) and rheumatoid factor (RF) were also measured. DAS28/ESR-4 item and clinical disease activity index (CDAI) were calculated. Ultrasound of the wrist, metacarpalphalangeal joints 2, 3 and 4, proximal interphalgeal joints 2 and 3 and metatarsalphalangeal joints 2 and 5 included synovitis assessments with gray scale (GSUS) and PDUS of the most affected side. GSUS and PDUS were categorically scored as per OMERACT published guidelines on a scale of 0-3. We then categorized the 0-3 scale into two PDUS groups 0/1=non-active, 2/3=active synovitis. Demographic and clinical characteristics were compared across BMI groups with Kruskal-Wallis test (KW) for continuous variables and chi-square tests for categorical variables. Mixed effects models were used to evaluate the relationship between BMI and the PPV and NPV.

Results: Demographic characteristics and disease activity were similar among BMI groups; however, PDUS scores significantly differed as seen in the Table. Using PDUS activity as the gold standard for synovitis and clinically swollen joints (SJ) as the test, the positive predictive value (PPV) of SJ was lower in higher BMI groups and significantly different across the BMI groups in KW analysis (0.71 in BMI<25, 0.58 in BMI 25-30 and 0.44 in BMI<30) (p= 0.01). Similarly, the negative predicative value (NPV) was significantly higher in higher BMI groups (p=0.04). In the mixed effects models, BMI was significantly predictive of PPV and a one unit increase in BMI was associated with a 0.1 unit decrease in PPV (p=0.02). BMI was not significantly predictive of NPV in the mixed effects model.

Conclusion: This study suggests that for obese RA subjects, clinically swollen joints have a higher PPV and a trend for lower NPV for true synovitis, while the opposite is found for normal BMI patients. This implies that clinically assessed swollen joints are less likely to represent true synovitis in obese RA patients. Therefore, RA disease activity may be overestimated by CDAI and DAS28 calculations in this subpopulation.

	BMI <25 N= 17		**BMI 25-30 N= 12**		**BMI>30 N=14**		**p-value**
Background characteristics							
	Median	**(IQR)**	**Median**	**(IQR)**	**Median**	**(IQR)**	
Age (years)	52.00	(26.0)	55.00	(11.5)	49.00	(17.0)	0.30
Disease duration (years)	5.00	(6.0)	3.00	(0.0)	8.00	(14.0)	0.05
	N	**(%)**	**N**	**(%)**	**N**	**(%)**	
Sex							
Male	0	(0%)	4	(33%)	2	(14%)	0.02
Female	17	(100%)	8	(67%)	12	(86%)	
RF or CCP Positive	11	(69%)	3	(25%)	7	(54%)	0.55
Ultrasound and Clinical Joint Measures							
	Median	**(IQR)**	**Median**	**(IQR)**	**Median**	**(IQR)**	
GSUS	5	(3)	4	(3.5)	5.5	(2)	0.42
PDUS	3	(3)	1	(3.5)	0	(2)	0.02
SJC	5	(2)	4	(2.5)	4	(2)	0.40
TJC	4	(3)	3	(3)	4	(4)	0.57
DAS28/ESR-4 item	6.63	(1.54)	6.25	(0.99)	6.07	(1.67)	0.44
CDAI	37	(24)	35	(28)	40	(29)	0.67
ESR	37	(24)	35	(28)	40	(29)	0.77
Physician Global	6	(2)	5	(2)	6	(2)	0.25
Patient Global	7	(3)	5.5	(3)	5.5	(3)	0.41
Predictive Values							
PPV	0.71		0.58		0.44		0.01
NPV	0.62		0.71		0.81		0.04

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Abstract Number: 2597

Fine Specificity of Anti-Citrullinated Peptide Antibodies Is Associated with Left

Ventricular Mass Index in Rheumatoid Arthritis Patients without Cardiovascular Disease

Laura Geraldino-Pardilla[1], Jon T. Giles[2], Jeremy Sokolove[3], Afshin Zartoshti[4], WH Robinson[5] and Joan M. Bathon[6], [1]Division of Rheumatology, Columbia University College of Physicians & Surgeons, New York, NY, [2]Division of Rheumatology, Columbia University, College of Physicians & Surgeons, New York, NY, [3]Medicine, VA Palo Alto HealthCare System and Stanford University, Palo Alto, CA, [4]Rheumatology, Columbia University Medical Center, NY, NY, [5]Medicine, Division of Immunology and Rheumatology, Stanford University School of Medicine, Stanford, CA, [6]Rheumatology, Columbia University College of Physicians & Surgeons, New York, NY

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Background/Purpose: Heart failure (HF) is a leading cause of excess deaths in RA. We previously found an association between left ventricular mass index (LVMI) and anti-citrullinated peptide antibodies (ACPA) in rheumatoid arthritis (RA) patients without CVD. Our objective was to validate these findings in a different RA cohort of patients without CVD.

Methods: Seventy-four patients without known CVD from underwent 3D Echocardiography and concurrent serum testing of a panel of 30 specific ACPAs using a custom Bio-Plex bead array. With a high ACPA level defined as $\geq 75^{th}$ percentile, a cross-sectional analysis of the association of specific ACPAs and LVMI was performed. Traditional CVD risk factors and RA characteristics were adjusted for.

Results: The mean age of the patients was 54 years (±13), with 85% being females and 36% self-identified as non-Hispanic White. The median disease duration was 7 years (IQR: 3-17), 67% had a positive anti-CCP antibody, and the mean current RA disease activity, based on the DAS28-CRP, was 3.9 (IQR: 2.9-4.5). Forty percent were hypertensive, 11% had diabetes, and 7% were current smokers. Except for a higher proportion of patients with rheumatoid factor level> 40units, no differences were seen between those with high vs. low anti-CCP titers. High anti-citrullinated fibrinogen, anti-citrullinated vimentin, and anti-citrullinated fibronectin antibody levels were associated with a higher LVMI compared to low levels of these antibodies (68 vs. 58 g/m^2, p=0.02; 67 vs. 58 g/m^2, p=0.003; and 69 vs. 57 g/m^2, p=0.004; respectively). These associations remained significant in the adjusted analyses (69 vs. 58 g/m^2, p=0.04; 67 vs. 58 g/m^2, p=0.004; 72 vs. 57 g/m^2, p=0.009; respectively) (figure 1).

Conclusion: In concordance with our previous findings, specific ACPAs were associated with a higher LVMI in RA patients without CVD. This independent association suggests a link between autoimmunity and cardiac structure in RA.

Figure 1. Association of ACPA status with Left Ventricular mass index.

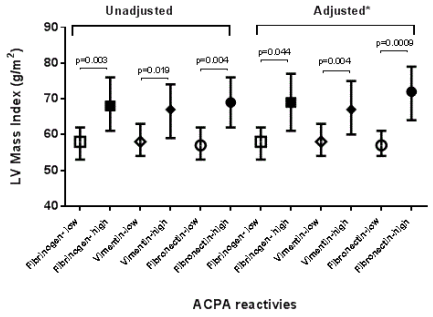

Figure 1. High anti-citrullinated-vimentin, anti-citrullinated-fibrinogen, and anti-citrullinated fibronectin antibody levels were associated with higher LVMI. *Adjusted for hypertension.

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Abstract Number: 2598

Neutrophil Extracellular Trap Levels Measured By Cell Free Nucleosome ELISA in Serum Are Highly Specific and Sensitive for Rheumatoid Arthritis

Paul Hasler[1], Stavros Giaglis[1], Ulrich A. Walker[2], Erik Deman[1], Christoph Hemmeler[1], Christina Ryser[1], Samuel Kretzschmar[1], Guenther Schaefer[3], Juliane Franz[1] and Sinuhe Hahn[4], [1]Rheumatology, Kantonsspital Aarau, Aarau, Switzerland, [2]Rheumatology, University Hospital, Basel, Basel, Switzerland, [3]Dept. of Biomedicine, Laboratory of Prenatal Medicine, University Hospital Basel, Basel, Switzerland, [4]Dept. of Biomedicine, Laboratory for Prenatal Medicine, University Hospital Basel, Basel, Switzerland
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Background/Purpose: Rheumatoid factor (RF) or anti-citrullinated peptide antibody (ACPA) detection have limited clinical utility for the diagnosis of rheumatoid arthritis (RA), as the specificity and sensitivity of RF is low and ACPAs seem restricted to a subgroup of RA patients. Neutrophil extracellular trap (NET) formation, the extracellular extrusion of chromosomal components from the nucleus upon specific stimulation, reported principally as a response to infectious agents, has also been linked to the pathogenesis of autoimmune and inflammatory diseases such as preeclampsia (PE), systemic lupus erythematosus (SLE), and recently RA[1,2]. We have previously observed that serum samples from RA patients showed significantly higher cell-free DNA levels than those of healthy controls and that the serum concentration of cell free nucleosomes (cfNucs) is a surrogate marker for NET formation[3,4].

Our aim was to validate cfNuc measurement in the serum for the diagnosis of RA and to assess its potential to differentiate rheumatoid arthritis cases from similar autoimmune inflammatory conditions and healthy controls.

Methods: Serum from healthy controls and groups of patients with RA, SLE, psoriatic arthritis (PsA) and ankylosing spondylitis (AS) were analyzed for cfNuc levels by ELISA. Healthy and disease control groups were compared by one way ANOVA. Receiver operator characteristic (ROC) curves were calculated with the standard errors. The results presented are from an interim analysis of a targeted 120 cases with RA and 30 each with SLE, PsA and AS.

Results: The mean cfNuc level of the healthy control group (n=47) was 0.3244, of the RA patients 1.813 (n=64), of the SLE patients 0.5753 (n=18), of the PsA patients 0.4684 (n=6) and of the patients with AS 0.6328 (n=10).

The difference between healthy controls and RA was significant at $P<0.0001$, between RA and SLE 0.0011, between RA and PsA 0.0007, and between RA and AS 0.0001.

Significance between RA and all disease controls and between RA and all controls was $P<0.0001$. The ROC area under the curve (AUC) for RA versus healthy controls was > 97%, the sensitivity and specificity being 87.5% and 91.5%, respectively, at a 0.58 cutoff. The ROC AUC for distinguishing RA from SLE was 88%, from PsA 92%, from AS 86% and disease controls as a group 88% (sensitivity 81.25%, specificity 80-89% at a cutoff of 0.78). For RA versus all controls, the ROC AUC was 93% (sensitivity 81.25%, specificity 93% at a cutoff of 0.78).

Conclusion: The detection of cell free nucleosomes in the serum of patients with autoimmune conditions can be utilized to discriminate between healthy controls and cases with RA with remarkable sensitivity and specificity. Sensitivity and specificity against disease controls, albeit less, were in a similar range. Upon reaching our target case numbers, we intend to analyze whether cfNuc could provide a tool to monitor and/or predict the response of RA patients to treatment with biologics and to optimize the ELISA assay.

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Abstract Number: 2599

The Effect of Daily Low Dose Prednisone (divided daily versus single daily dose) in the Treatment of African Americans (AA) with Early Rheumatoid Arthritis (RA)

Athan Tiliakos[1], Kirk Easley[2], Gaobin Bao[3], Shuling Liu[4], S. Louis Bridges Jr.[5], Leigh F. Callahan[6], Larry W. Moreland[7] and Doyt L. Conn[1], [1]Rheumatology, Emory Univ School of Medicine, Atlanta, GA, [2]Biostatistics, Emory University, Atlanta, GA, [3]Medicine, Emory University, Atlanta, GA, [4]Biostatistics and Bioinformatics, Emory University School of Medicine, Atlanta, GA, [5]Clinical Immunology and Rheumatology, University of Alabama at Birmingham, Birmingham, AL, [6]Thurston Arthritis Research Center, University of North Carolina, Chapel Hill, NC, [7]Rheumatology & Clinical Immunology, University of Pittsburgh, Pittsburgh, PA
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Background/Purpose:

To describe the longitudinal changes in the number of swollen and tender joints and HAQ scores in 345 African Americans with early RA and to assess factors influencing improvement and side effects of medications.

Methods:

This is a prospective observational cohort study of African American RA patients with early disease (<2 years) taken from the CLEAR1 registry who were followed longitudinally for up to 5 years after diagnosis. A total of 626 clinical visits were performed on 345 subjects (~54% of subjects had the 5 year disease duration visit). Clinical outcome data (number of tender and swollen joints based on 28 joints and HAQ scores) were subjected to repeated measures analysis. The statistical models were adjusted simultaneously for 7 baseline covariates (gender, age, BMI, family history of RA, smoking status, poverty and education level) and 5 time-dependent covariates (prednisone therapy divided daily and single daily, methotrexate treatment, diabetes, hypertension and osteopenia/osteoporosis).

Results:

The mean age at enrollment was 51 years, 82% of the cohort was female, and the mean disease duration at enrollment was 12 months. The prevalence of low dose oral prednisone use at baseline was 77% (265/345) and median prednisone dose at baseline was 10 mg/day. AA with early RA had significant reduction during follow-up in number of swollen joints, tender joints and in HAQ scores (all $p < 0.001$, univariable analyses). At baseline, 18% of patients had diabetes mellitus, 56% hypertension, 45% osteopenia and 5% osteoporosis. During follow-up approximately 5% of the patients developed diabetes mellitus, hypertension or new osteoporosis.

Multivariable analyses indicated similar improvement in number of swollen joints and HAQ scores for patients on divided daily low dose oral prednisone (n=x) or single daily low dose oral prednisone (n=y). However, the adjusted mean tender joint count was lower for patients on a divided daily dose of prednisone (covariate-adjusted mean= 7.1) compared to a single daily dose of prednisone (covariate-adjusted mean= 9.6) with a mean difference (divided daily minus single daily) in number of tender joints=-2.5 joints (95% CI: -2.8 to -2.2; $P < 0.01$). The adjusted mean number of tender joints for patients not on prednisone was approximately 9 tender joints.

Conclusion:

During the 5 years of follow-up, clinical outcomes improved in AA patients with early RA. Reduced number of tender joints appears to be associated with divided daily low dose prednisone treatment. The development of new diabetes mellitus, hypertension and osteoporosis was uncommon and not related to prednisone use.

Disclosure: A. Tiliakos, None; **K. Easley**, None; **G. Bao**, None; **S. Liu**, None; **S. L. Bridges Jr.**, None; **L. F. Callahan**, None; **L. W. Moreland**, None; **D. L. Conn**, None.

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Abstract Number: 2600

Signs of Immune Activation and Local Inflammation Are Present in the Bronchial Tissue of Patients with Untreated Early Rheumatoid Arthritis

Gudrun Reynisdottir[1,2], Helga Olsen[3], Vijay Joshua[4], Marianne Engström[2], Magnus Skold[3], Anders Eklund[5], Johan Grunewald[3] and **Anca I Catrina**[2], [1]Rheumatology Unit, Department of Medicine, Karolinska University Hospital and Karolinska Institutet, Stockholm, Sweden, [2]Rheumatology Unit, Department of Medicine, Karolinska Institute, Karolinska University Hospital, Stockholm, Sweden, [3]Department of Medicine, Division of Respiratory Medicine, Karolinska University Hospital, Karolinska Institute, Stockholm, Sweden, [4]Unit of Rheumatology, Department of Medicine Solna, Karolinska University Hospital, Karolinska Institutet, Stockholm, Sweden, [5]Division of Respiratory Medicine, Karolinska University Hospital, Karolinska Institute, Stockholm, Sweden

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SESSION INFORMATION

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Background/Purpose:

Events in the lungs might contribute to generation of anti citrullinated protein antibodies (ACPA) in rheumatoid arthritis (RA). We investigated if signs of immune activation are present in the bronchial biopsies and bronchoalveolar lavage (BAL) of early-untreated RA patients in the absence of concomitant lung pathology.

Methods: 24 RA patients with symptom duration less than one year and naïve to disease-modifying antirheumatic drugs (DMARD) were subjected to bronchoscopy where bronchoalveolar lavage (BAL) and mucosal large bronchial biopsies were retrieved. For comparison 15 bronchial biopsies and 79 BAL samples from healthy volunteers were available. Histological examination was performed to evaluate lymphocyte infiltration, presence of immune cells (T and B cells, plasma cells, dendritic cells and macrophages) and immune activation markers. Cells composition of BAL samples was analyzed by differential counting and flow cytometry.

Results:

Lymphocyte infiltration was more frequently found in ACPA-positive patients (9 out of 18 patients, 50%) as compared to ACPA-negative patients (1 our of 6, 17%, $p>0.05$) and controls (2 out of 15, 13%, $p<0.05$). Occasional formation of germinal center like structures was observed only in ACPA-positive RA patients (2 out of 18, 11%). These structures were positive for B cells markers and activation-induced cytidine deiminase and stained positively with biotinylated cit-enolase.

B cells and plasma cells were only found in ACPA-positive patients, while T cells were more frequently detected in bronchial biopsies of ACPA-positive (median 2, range 1-3) as compared to ACPA-negative (median 1, range 1-3) RA patients. Similar, expression of immune activation markers was higher in ACPA-positive as compared to ACPA-negative RA patients for both HLA-DR (median of 3, range 2-3 as compared to a median of 2, range 1-3, $p<0.05$) and HLA-DQ (median of 2, range 0-3 as compared to a median of 1, range 1-3, $p<0.05$). BAL samples of ACPA-positive but not ACPA-negative RA patients had significantly higher relative numbers of lymphocytes and expressed higher levels of activation markers compared to controls.

Conclusion:

Signs of immune cell accumulation and activation are present in the bronchial tissue of untreated early-RA patients without concomitant lung pathology, strengthening the role of the lung compartment as a critical initiating factor in the development of ACPA-positive RA.

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Abstract Number: 2601

The Multi-Biomarker Disease Activity Score in a TNF Inhibitor Tapering Study in Rheumatoid Arthritis Patients: Predictive Value for Successful Tapering, Flaring and Radiographic Progression

Chantal A.M. Bouman[1], Aatke van der Maas[1], Noortje van Herwaarden[1], Eric H. Sasso[2], Frank H.J. van den Hoogen[1] and Alfons A. den Broeder[1], [1]Rheumatology, Sint Maartenskliniek, Nijmegen, Netherlands, [2]Crescendo Bioscience Inc., South San Francisco, CA
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Background/Purpose:

We evaluated the predictive value of the multi-biomarker disease activity (MBDA) score for clinical outcomes and radiographic progression in a TNFi tapering study in RA patients with sustained low disease activity.

Methods:

DRESS is an 18-month randomised trial on non-inferiority of tapering of adalimumab or etanercept compared with usual care (UC). TNFi was tapered every 3 months until stopping or clinical flare (ΔDAS28-CRP >1.2 or >0.6 if current DAS28-CRP ≥3.2; major flare: >3 months). Patients were assessed every 3 months and at flare. For flares, TNFi was restarted or escalated. X-rays of hands and feet were scored with modified Sharp-van der Heijde score (mSHS) at baseline (BL) and 18 months. Correlations between MBDA score and DAS28-CRP were determined at BL, 9, 18 months and first flare. MBDA scores at BL, 9 and 18 months and ΔMBDA score from BL to 9 months were analysed for successful stopping, successful tapering, and no tapering possible. AUROC evaluated the predictive value of: 1) BL MBDA score for a) successful tapering vs. no tapering possible, b) stopping vs. no tapering possible, c) occurrence of (major) flares, d) incidence of radiographic progression (RP); 2) ΔMBDA score from BL to 9 months for clinical outcomes and RP; 3) MBDA scores at first and second visits preceding a flare for occurrence of that flare; 4) ΔMBDA score between first and second visits preceding a flare for occurrence of that flare.

Results:

Of 180 patients, 171 (115 tapering, 56 UC) had serum and month 18 outcomes available: 64% female, mean disease duration 12.1 (SD 8.3) years, 73.3% ACPA positive. TNFi had been successfully stopped in 19%, tapered in 44%, and re-escalated to baseline dose in 37%. MBDA scores and DAS28-CRP are summarized in Figure 1. Correlation of DAS28-CRP and MBDA score was greatest at 18 months (Spearman's $r=0.45$, $p<0.01$) and lowest at BL ($r=0.19$, $p<0.01$). AUROCs for predicting successful stopping, tapering and flare by BL MBDA score were not significant. AUROC for major flare by BL MBDA score was significant in the UC group (10% flared; AUROC 0.72, 95% CI 0.56-0.88) and not the taper group (12% flared). RP (ΔmSHS >0.5 from BL to 18 months) occurred in 26% of 167 patients with available data and was not predicted by MBDA score. ΔMBDA score from BL to 9 months was not predictive for clinical outcomes or RP. MBDA scores at first and second visit preceding a flare were not predictive for any flare. AUROC for ΔMBDA score between first and second visit preceding a flare was borderline significant (0.56, 95% CI 0.50-0.63).

Conclusion:

Neither BL MBDA score nor ΔMBDA score from BL to 9 months was predictive for successful stopping; tapering; occurrence of flare; or radiographic progression. However, exploratory analyses showed that: 1) BL MBDA score was predictive for flare in patients who received UC and 2) ΔMBDA score between visits preceding a flare was borderline significant for predicting flare.

Figure 1. Mean MBDA scores and DAS28-CRP at BL, 9 and 18 months, and change from BL to 9 months†

Outcome at 18 months (n=171)	Mean MBDA baseline (SD)	Mean DAS28-CRP baseline (SD)	Mean MBDA 9 months (SD)	Mean DAS28-CRP 9 months (SD)	Mean MBDA 18 months (SD)	Mean DAS28-CRP 18 months (SD)	Change MBDA BL to 9M (SD)
Successful stopped (n=22)	33.6 (13.1)	2.05 (0.62)	39.7 (12.0)	2.07 (0.66)	40.8 (11.4)	2.14 (0.70)	6.09 (14.0)
Successful tapered (n=51)	34.4 (11.3)	2.08 (0.60)	39.6 (11.1)	2.48 (0.98)	36.6 (12.8)	2.08 (0.86)	4.61 (11.1)
No tapering possible (n=42)	33.3 (13.7)	2.34 (0.70)	40.5 (13.2)	2.70 (1.02)	36.5 (13.3)	2.48 (0.99)	7.60 (13.1)
Usual care (n=56)	33.4 (12.0)	2.15 (0.76)	36.2 (12.1)	2.08 (0.78)	32.3 (13.7)	2.10 (0.91)	3.06 (14.5)

†Successful stopped, Successful tapered and No tapering possible are non-overlapping groups of patients who began tapering TNFi therapy at baseline.

Disclosure: C. A. M. Bouman, None; **A. van der Maas**, None; **N. van Herwaarden**, None; **E. H. Sasso**, Myriad Genetics, 1,Crescendo Bioscience, 3; **F. H. J. van den Hoogen**, None; **A. A. den Broeder**, None.

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Abstract Number: 2602

CCP Antibody Negativity Is Associated with Higher Fatigue in Rheumatoid Arthritis

Laura Cappelli[1], Susan J. Bartlett[2,3], Michelle Jones[4] and Clifton Bingham[4], [1]Ste 4500, Johns Hopkins University, Baltimore, MD, [2]Division of Rheumatology, Johns Hopkins School of Medicine, Baltimore, MD, [3]Medicine , Divisions of Clinical Epidemiology, Rheumatology, Respirology, McGill University, Montreal, QC, Canada, [4]Johns Hopkins University, Baltimore, MD
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Background/Purpose: Fatigue in rheumatoid arthritis (RA) is common and highly debilitating. Emerging evidence suggests that seronegative RA patients differ from their seropositive peers in genetic susceptibility, immunology, and clinical characteristics. One pathway shown to have increased activity in seronegative RA patients is the IL-6/STAT3 signaling pathway. We hypothesized that selected symptoms (fatigue, pain, sleep) and impacts (physical function and social participation) would be worse in CCP negative participants.

Methods: Data are from a prospective cohort study of patients receiving guideline-based RA care in an academic clinic. Baseline visits conducted from 10/12 to 1/14 were included in this cross sectional analysis. Patients meeting ACR criteria for RA and for whom information on CCP status was available were included in this study. Selected symptoms and impacts were assessed using The NIH Patient Reported Outcome Measurement Information System (PROMIS) computer adaptive tests and compared by CCP status with t-tests. Linear regression models were used to evaluate the impact of CCP status on fatigue after adjusting for potential confounders.

Results: The 165 participants were 82% female with mean age of 56 (SD 13.1). CCP negative and positive participants differed only by disease duration, with CCP negative patients having shorter duration (Table 1). Exploratory analysis evaluating average T-scores of eight PROMIS domains and pain VAS showed statistically significantly higher levels of fatigue in CCP negative patients as compared to their CCP positive counterparts (table 1). Similar trends with higher anxiety levels and pain interference, and impairments in physical function and participation were seen in the CCP negative group ($p<.10$). Associations between greater fatigue and CCP negativity persisted after adjustment for sociodemographic and other characteristics (table 2).

Conclusion: In RA, CCP negativity is a robust independent predictor of greater fatigue and may be associated with greater impairments in disability and participation. These results suggest that some symptoms are associated with autoantibody status and may indicate differential activity of IL-6/STAT3 signaling.

Table 1. Participant characteristics by CCP status (n = 165) .

Characteristic	CCP- n = 54	CCP+ n= 111	Sig
Age	58.2 (14.6)	55.1 (12.2)	0.16
Sex- n (%)	Male- 7 (13%)	Male- 22 (20%)	0.28
Race- n (%)	White- 46 (85%) Black- 6 (11%) Other- 2 (4%)	White- 89 (80%) Black- 15 (14%) Other- 6 (54%)	0.78
Disease duration (yrs)	9.3 (6.9)	13.0 (10.6)	**0.02**
Swollen joints (28)	2.3 (3.7)	2.0 (2.9)	0.65
Tender joints (28)	1.6 (3.2)	1.1 (2.4)	0.20
MD Global	14.4 (16.2)	12.5 (13.7)	0.42
Patient Global	29.0 (26.6)	28.7 (27.5)	0.94
Clinical Disease Activity Index (CDAI)	8.6 (8.0)	6.9 (7.2)	0.18
Fatigue	56.0 (9.2)	52.4 (10.1)	**0.03**
Pain VAS	31.2 (27.7)	29.7 (28.9)	0.76
Pain Interference	55.3 (8.8)	52.8 (9.7)	0.06
Sleep Disturbance	52.5 (9.7)	50.8 (9.4)	0.30
Sleep Impairment	51.7 (8.9)	50.8 (9.6)	0.58
Depression	49.8 (8.9)	48.5 (8.4)	0.37
Anxiety	51.9 (8.5)	50.0 (7.6)	0.08
Physical Function	41.5 (9.1)	44.2 (8.9)	0.07
Ability to Participate in Social Roles	48.4 (8.8)	51.3 (8.9)	0.05
Values are the mean (SD) unless otherwise indicated			

Table 2. Relationship between CCP status and outcome of PROMIS fatigue (Crude and adjusted coefficients)

	Crude (95% CI)	Adjusted (95% CI)
CCP-	**3.66** (0.45, 6.87)	**3.53** (0.35, 6.72)
Age	0.0002 (-0.12, 0.12)	-0.03 (-0.15, 0.08)
Female sex	-0.63 (-4.50, 3.24)	-1.21 (-5.23, 2.80)
Minority vs. white	3.75 (-.017, 7.68)	3.54 (-0.02, 7.48)
Swollen joints	**0.74** (0.29, 1.20)	**0.74** (0.27, 1.23)

Disclosure: L. Cappelli, None; **S. J. Bartlett**, PCORI, 2,NIH, 9; **M. Jones**, None; **C. Bingham**, NIH, 2,PCORI, 2.

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Abstract Number: 2603

What Is the Variability of HAQ over Time in Patients with Rheumatoid Arthritis Treated with Anti-TNF?

Regan Arendse[1], Boulos Haraoui[2], Denis Choquette[3], John Kelsall[4], Philip Baer[5], Dalton Sholter[6], William G. Bensen[7], Mary J. Bell[8], Michelle Teo[9], Emmanouil Rampakakis[10], Eliofotisti Psaradellis[11], Brendan Osborne[12], Cathy Tkaczyk[12], Karina Maslova[13], Francois Nantel[14] and Allen J Lehman[13], [1]University of Saskatchewan, Saskatoon, SK, Canada, [2]Institut de Rhumatologie de Montréal and University of Montreal, Montreal, QC, Canada, [3]Rheumatology Department, Institut de Rhumatologie de Montréal and University of Montreal, Montreal, QC, Canada, [4]Mary Pack Arthritis Centre, Vancouver, Vancouver, BC, Canada, [5]Section on Rheumatology, Ontario Medical Association/Journal of the Canadian Rheumatology Association, Toronto, ON, Canada, [6]Rheumatology Associates, Edmonton, AB, Canada, [7]St Joseph's Healthcare Hamilton, Hamilton, ON, Canada, [8]Rheum Div, Sunnybrook Health Sciences Centre/University of Toronto, Toronto, ON, Canada, [9]Rheumatology, Penticton Regional Hospital, Penticton, BC, Canada, [10]JSS Medical Research, St-Laurent, QC, Canada, [11]JSS Medical Research, Montreal, QC, Canada, [12]Medical Affairs, Janssen Inc., Toronto, ON, Canada, [13]Janssen Inc., Toronto, ON, Canada, [14]19 Green belt Dr, Janssen Inc., Toronto, ON, Canada

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Background/Purpose :

The Health Assessment Questionnaire (HAQ) remains the gold standard for measuring patient-reported functional status in rheumatoid arthritis (RA) and is included among the measures suggested by the American College of Rheumatology for making treatment decisions in routine care. We have previously shown that significant variability exists in the correlation of individual HAQ questions with patient-reported and clinical outcomes. The aim of this analysis was to assess, in routine care, the timelines of HAQ improvement as compared to clinical improvement and to examine possible differences in the improvement of individual questions.

Methods :

BioTRAC is an ongoing, prospective registry of patients initiating treatment for RA, ankylosing spondylitis, or psoriatic arthritis with infliximab (IFX) or golimumab (GLM). Eligible people for this analysis included RA patients treated with IFX who were enrolled since 2002 or with GLM enrolled since 2010. Time to achieving minimal important difference (MID; $\Delta \geq 0.22$) in HAQ, HAQ$\leq$1, minimal disease (MD) in individual HAQ questions (no or some difficulty), CDAI low disease activity (LDA), or CDAI remission was assessed with the Kaplan-Maier estimator of the survival function and cox regression.

Results:

A total of 1205 patients (75.3% female) were included with mean (SD) age of 56.0 (13.6) years and disease duration of 8.4 (8.9) years at baseline. Mean (SD) HAQ and CDAI were 1.55 (0.72) and 33.8 (17.4), respectively.

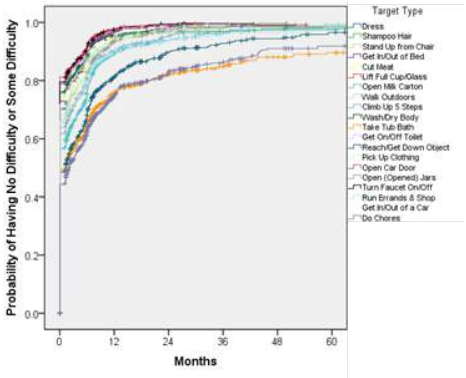
Statistically significant and clinically meaningful improvements in both HAQ and CDAI were observed over time. The cumulative probability of achieving HAQ MID, HAQ$\leq$1, CDAI LDA, and CDAI remission by 12 months was 69.5%, 54.5%, 54.1%, and 18.1%, respectively. Time to achieving HAQ MID [Hazard Ratio (95% CI): 3.6 (3.2-4.2)], HAQ$\leq$1 [2.9 (2.6-3.4)], and CDAI LDA [3.1 (2.7-3.6)] was significantly lower as compared to CDAI remission.

With respect to individual HAQ questions, at baseline, the most predominant usual activities that patients were unable to do were taking a tub bath (27.9% of patients), reaching and getting down a 5-pound object from the head (21.8%), and doing chores such as vacuuming or yard work (23.2%). In accordance, time to having no or some difficulty in these activities was significantly higher compared to the remaining HAQ items (Figure 1).

Conclusion:

The results of this analysis show that the timelines for achieving HAQ targets in routine care is comparable to that of achieving CDAI LDA. Significant differences were observed in terms of improvement in individual HAQ items with the inability to take a tub bath, getting heavy overhead objects down, and doing chores being the most persistent.

Figure 1. Time to Having No Difficulty or Some Difficulty in Individual HAQ Questions



Disclosure: R. Arendse, Janssen Inc., 5; **B. Haraoui**, Janssen Inc.,, 5; **D. Choquette**, Janssen Inc., 5,AbbVie, 5,Amgen, 5,Celgene, 5,BMS, 5,Pfizer Inc, 5; **J. Kelsall**, Janssen Inc., 5; **P. Baer**, Janssen Inc., 5,AbbVie, 5,Amgen, 5,BMS, 5,Pfizer Inc, 5,Roche Pharmaceuticals, 5; **D. Sholter**, Janssen Inc., 5; **W. G. Bensen**, Janssen Inc., 5; **M. J. Bell**, Janssen Inc., 5; **M. Teo**, Janssen Inc., 5; **E. Rampakakis**, JSS Medical Research, a Contract Research Organization, 3; **E. Psaradellis**, JSS Medical Research, 3; **B. Osborne**, Janssen Inc., 3; **C. Tkaczyk**, Janssen Inc., 3; **K. Maslova**, Janssen Inc., 3; **F. Nantel**, Janssen Inc., 3; **A. J. Lehman**, Janssen Inc., 3.

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Abstract Number: 2604

Evaluation of Serum Undercarboxylated Osteocalcin in Premenopausal Rheumatoid Arthritis Patients; Its Correlation with Disease Activity and Bone Mineral Density

Heba Esaily[1], Abd El Samad Al Hewala[2], Samar Soliman[3], Eman Galbat[4] and Dalia Abo Al- Ela[5], [1]Physical Medicine and Rehabilitation,, Faculty of Medicine, Menoufia University, Menofia, Egypt, [2]Department of Rheumatology, Faculty of Medecine, Zagazigue University, Al Sharquia, Egypt, [3]Physical Medicine and Rehabilitation, Faculty of Medicine, Menoufia University, Menoufia,, Egypt, [4]Physical Medicine and Rehabilitation, Faculty of Medicine, Menoufia University, Menoufia, Egypt, [5]Clinical Pathology, Faculty of Medicine, Menoufia University, Menofia, Egypt

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Background/Purpose:

The role of vitamin K and undercarboxylated osteocalcin (ucOC) on BMD in RA is present. Up to our knowledge no other works have discussed the relationship between ucOC and BMD in premenopausal RA patients and its correlation with disease activity.

Methods:

Sixty Premenopausal rheumatoid arthritis female patients and thirty healthy premenopausal controls with matched age were included in this study.All were subjected to demographic data , clinical examination, Laboratory investigations:-including serum level of ucOC, disease activity assessment by DAS 28 score and bone mineral density measurement in the lumbar spine L2–4 ,hip and distal radius by dual-energy X-ray absorptimetry (DEXA) equipment.

Results:

In our study the level of ucOC was significantly higher in patients of RA than controls ($p < 0.001$). BMD in patients was found to be

significantly lower than controls in spine,femoral neck and distal radius areas. The most frequent osteoporotic site according to Z score was spine(16.7%) followed by femoral neck (8.3 %) then distal radius (6.7%).While the commonest osteopenic site according to (Z score ≤ -1) was spine(31.7%) followed by femoral neck (21.7 %)then (16.7%)in the distal radius. Our work showed that ucOC level was found to be high in premenopausal RA patients with higher DAS values than those with lower DAS value ($p<0.001$) . In our work BMD measured by DEXA scan was found to be lower with higher DAS values and vice versa.

Conclusion:

Serum level of ucOC (which is amirror of vitamin K defficency) was found to be higher in premenopausal RA patients than control and correlated positively with disease activity and inversely with BMD measurement.

Disclosure: H. Esaily, None; **A. E. S. Al Hewala**, None; **S. Soliman**, None; **E. Galbat**, None; **D. Abo Al- Ela**, None.

Abstract Number: 2605

14-3-3η Positive Status and Higher Titres Are Associated with More Severe RA

Shintaro Hirata[1], Kentaro Hanami[2], Anthony Marotta[3] and Yoshiya Tanaka[4], [1]The First Department of Internal Medicine, University of Occupational & Environmental Health, Japan, Kitakyushu, Japan, [2]The First Department of Internal Medicine, University of Occupational and Environmental Health, Japan, Kitakyushu, Japan, [3]Augurex Life Sciences Corp., Vancouver, BC, Canada, [4]The First Department of Internal Medicine, University of Occupational and Environmental Health, Kitakyushu, Japan

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Background/Purpose: Serum 14-3-3η is an RA diagnostic marker that is associated with radiographic progression risk. *In vitro* studies describe 14-3-3η's potent, dose-dependent up-regulation of factors that perpetuate inflammation and joint damage. In this study we investigated the association of 14-3-3η cut-points with standard RA disease activity measures at a treatment-change clinical juncture.

Methods: Serum 14-3-3η levels were measured in 149 Japanese RA patients prior to the initiation of therapy (BL) and at Yr1. 14-3-3η positivity was defined at 3 cut-points: the diagnostic cut-off of ≥0.19 ng/ml, and 2x and 4x this cut-off, 0.40 and 0.80 ng/ml respectively. Contingency analysis provided the relationship between 14-3-3η positivity and DAS, CDAI and SDAI categorization. Patients were grouped into 4 categories based on the Yr1 14-3-3η positivity (≥0.19 ng/ml): remaining negative (RN), becoming positive (BP), remaining positive (RP) or becoming negative (BN). Non-parametric ANOVA analysis and the Mann Whitney U-test were utilized to assess group differences in disease activity measures. The Fisher Exact Test was used to assess 14-3-3η's association with Good EULAR response.

Results: The mean (SD) age was 57 (15) years and 86% of the patients were female. The median (IQR) disease duration was 51 (9-150) months. At the diagnostic cut-point of ≥0.19 ng/ml, 14-3-3η positive patients had worse disease based on significantly higher median DAS28ESR [5.62 (4.64-6.57) vs. 4.77 (4.10-5.86), p=0.010], CDAI [24.7 (16.2-36.3) vs 16.0 (11.5-27.0), p=0.015], and SDAI [26.8 (16.7-38.6) vs 18.8 (11.7-32.7), p=0.024]. Titres of 14-3-3η correlated significantly with DAS28ESR [r=0.29], CDAI [r=0.25], SDAI [r=0.24], TJC28 [r=0.21], SJC28 [r=0.26] and JSN [r=0.18]. As shown in Table 1, a stronger and more significant association with DAS28, CDAI and SDAI categorization was observed at higher 14-3-3η positivity cut-offs.

Table 1. Baseline 14-3-3η positivity and association with Disease State.

	BL DAS Category		BL SDAI Category		BL CDAI category	
BL Cut-point	LR	p-value	LR	p-value	LR	p-value
≥ 0.19ng/ml	10.6	0.0011	3.7	0.16	6.2	0.045
≥ 0.40ng/ml	16.3	<0.0001	9.7	0.0077	8.8	0.012
≥ 0.80 ng/ml	25.2	<0.0001	16.3	0.0003	14.0	0.0009

The match pairs t-test revealed that the 14-3-3η serum concentrations significantly decreased from 0.70 ng/ml [0.17-5.96] at BL to 0.37 ng/ml [0.11-1.82] at Yr1 ($p<0.0001$). At BL and Yr1, 110 (74%) and 97 (65%) were 14-3-3η +ve. At Yr 1, 18 of the 110 patients that

were BL +ve were BN and 92 RP. In the BL-ve group, 5 patients sero-converted (BP) and 34 were RN at Yr1. ANOVA and the U-test revealed that median Yr1 DAS28ESR was significantly lower in the 18 BN patients compared to the 92 RP patients [2.0 (1.6-2.8) vs 2.7 (2.0-3.8), p=0.004]. The unpaired t-test, assuming equal variances, revealed that mean DAS28ESR Yr1 levels were significantly lower in the 18 BN patients compared to 5 BP patients [2.1 vs 3.1, p=0.033].

Conclusion: Serum 14-3-3η is a mechanistic marker that is involved in the pathogenesis of RA. Patients who present with higher 14-3-3η titres reflect a higher disease status and may be considered for a post-treatment measurement of 14-3-3η toward negative levels.

Disclosure: S. Hirata, None; **K. Hanami**, None; **A. Marotta**, Augurex Life Sciences Corp, 3; **Y. Tanaka**, None.

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Abstract Number: 2606

Serum Myeloid Related Protein 8/14 Levels in Rheumatoid Arthritis: Marker of Disease Activity and Response to Methotrexate in DMARD Naïve Patients

Pradeepta Sekhar Patro, Ankita Singh, Ramnath Misra and Amita Aggarwal, Clinical Immunology, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, India

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Background/Purpose:

MRP8/14 are calcium binding proteins produced by myeloid cells. Recently baseline serum levels of MRP8/14 have been shown to predict response to biologicals in rheumatoid arthritis (RA). Since methotrexate (MTX) is the first line therapy in RA we studied if MRP8/14 levels can predict response to MTX.

Methods:

Patients with RA (ACR 2010 criteria), DMARD naïve with active disease were enrolled. All patients were treated with MTX by gradually increasing dose to a maximum of 25mg/week or the maximal tolerated dose.No corticosteroids were given. Patients were followed up monthly telephonically and 2 monthly in the clinic. At 4 months disease activity was measured by DAS 28 and EULAR response was assessed.All patients who needed rescue therapy after 2 months or did not respond at 4 months were classified as non-responders.

Results:

90 patients were enrolled in the study, of which 3 were excluded(discontinued MTX within 4-6 weeks due to toxicity). Thus 87 patients (74 females) with mean age 40.8±12.1yr, mean duration of disease 28±25.5months and mean DAS28 4.5±0.7) were analyzed. The mean serum MRP 8/14 level at baseline was 27.612±21.353µg/ml.The serum MRP8/14 had good correlation with DAS28CRP (r = 0.35; p=0.001).The MRP8/14 levels fell significantly after 4 months of treatment (12.734 ± 9.966µg/ml; p<0.001).

Among 87 patients 69 were classified as responders (good 43, moderate 26) while 18 were non- responders. The mean baseline level of MRP 8/14 was higher among responders as compared to non- responders (29.280 ± 20.411µg/ml vs 19.152 ± 23.341µg/ml; p=0.002). Comparing the fall in responders and non-responders separately, the levels reduced significantly only in the responders(29.280 ± 20.411 µg/ml to 12.487± 9.987 µg/ml; p<0.001), but not in the non-responders(19.152 ± 23.341µg/ml to 15.173±10.189 µg/ml; p=0.687).Receiver-operation characteristic (ROC) analysis showed that MRP8/14 was a good predictor of response with an area under curve(AUC)of 0.719 better than that of DAS28CRP(AUC-0.635) and DAS28ESR (AUC-0.489).

Conclusion:

MRP8/14 is a good biomarker of disease activity in RA and higher levels predict response to MTX.

Disclosure: P. S. Patro, None; **A. Singh**, None; **R. Misra**, None; **A. Aggarwal**, None.

Abstract Number: 2607

Anti-Cyclic Citrullinated Peptide Antibodies and Rheumatoid Factor in Rheumatoid Arthritis Hispanics Exposed to Biomass Smoke

Raymundo Vera-Pineda[1], Alberto Cardenas-de La Garza[2], Jorge Esquivel-Valerio[3], Dionicio A. Galarza-Delgado[2], Jose Ramon Azpiri-Lopez[4], Iris J. Colunga-Pedraza[2], Mario Alberto Garza-Elizondo[2] and Jesus Zacarias Villarreal-Pérez[5], [1]Cardiology., Hospital Universitario, UANL., Monterrey, Mexico, [2]Rheumatology, Hospital Universitario, UANL., Monterrey, Mexico, [3]Rheumatology, Hospital Universitario.UANL, Monterrey, Mexico, [4]Cardiology, Hospital Universitario, UANL., Monterrey, Mexico, [5]Endocrinology, Hospital Universitario, UANL., Monterrey, Mexico

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Session Time: 9:00AM-11:00AM

Background/Purpose:

Tobacco smoke has been associated to anti-cyclic citrullinated peptide (anti-CCP) antibodies positivity. Recently, in wood-smoke-induced chronic obstructive pulmonary disease (COPD) patients without rheumatoid arthritis (RA), anti-CCP antibody higher titers have been reported than in healthy individuals and tobacco-induced COPD. The anti-CCP and rheumatoid factor (RF) titers have not been examined in rheumatoid arthritis patients with biomass smoke exposure. The objective of the present study is to report the correlation between anti-CCP, IgG, IgM and IgA RF to biomass exposure index (BEI).

Methods:

A cross-sectional study was designed based on a cohort of Hispanic RA patients recruited from September 2014 to April 2015. All fulfilled the 1987 ACR and the 2010 ACR/EULAR classification criteria for RA. Biomass smoke exposure was expressed with the BEI calculated as the average hours of exposure per day multiplied by the number of years. Patients with a minimum exposure of 1 BEI were included. RF and Anti-CCP were measured by ELISA with cutoff points of <5U/mL and <20U/mL respectively. Sample calculation expecting a 0.5 correlation determined the need of at least 30 subjects.

Results:

Out of the 102 patients in the cohort, 46 (44.6%) had a BEI equal to or higher than 1 and were included in the analysis. A total of 41 (89.1%) were women with a mean age of 61.06 ±8.82 years and mean disease duration of 12.47 years ±8.81. None had renal or pulmonary disease at baseline. Activity by DAS28 ESR was 3.69 ±1.50 (moderate activity). The median BEI was 42 (p25=30, p75=80.25). All of the exposure was due to in-house cooking with wood. Anti-CCP positivity was present in 33 (71.7%) with a median titer of 150.10 U/mL (p25=2.74, p75=200). IgG RF was present in 11 (23.9%) at a median titer of 8.88 U/mL (p25=4.31, p75=19.98), IgA in 28 (60.9%) with a mean titer of 79.75 U/mL ±77.93, and IgM in 41 (89.1%) with a median of 112.91 U/mL (p25=67.77, p75=200). Spearman's rho correlation showed no significant correlation between BEI and anti-CCP (p=0.386, rho= -0.131), IgG RF (p=0.147, rho= -0.217), IgA RF (p=0.501, rho= -0.102) and IgM RF (p=0.874, rho=-0.024). Additionally, no difference was found between exposed and not exposed patients regarding anti-CPP (p=0.715), IgG (p=0.335), IgA (p=0.954) and IgM (p=0.433) RF within the cohort.

Conclusion:

In this Hispanic cohort of established rheumatoid arthritis patients with moderate disease activity exposed to biomass smoke, no correlation was found between BEI and anti-CCP, IgG RF, IgA RF, or IgM RF.

Disclosure: R. Vera-Pineda, None; **A. Cardenas-de La Garza**, None; **J. Esquivel-Valerio**, None; **D. A. Galarza-Delgado**, None; **J. R. Azpiri-Lopez**, None; **I. J. Colunga-Pedraza**, None; **M. A. Garza-Elizondo**, None; **J. Z. Villarreal-Pérez**, None.

Abstract Number: 2608

The "Rheumatoid Arthritis Impact of Disease" Score Correlates with Other Patient Reported Outcomes and with Disease Activity Scores in Patients with RA and Its Patient Acceptable Symptom State Is More Stringent Than DAS28-Remission

Ricardo J.O. Ferreira[1,2], Cátia Duarte[1,3], Sylvie Batista[3], Catarina Medeiros[3], J.P. Sousa[3], Gisela Eugénio[1], Carlos Costa[1], Pedro Carvalho[1], Joana F. Ferreira[1], Margarida Coutinho[1,4], Maria J. Salvador[1,4], Laure Gossec[5] and J.A.P. da Silva[3,6], [1]Rheumatology, Centro Hospitalar e Universitário de Coimbra - Hospitais da Universidade de Coimbra, EPE, Coimbra, Portugal, [2]Health Sciences Research Unit: Nursing (UICISA: E), Coimbra, Portugal, [3]Faculty of Medicine, Universidade de Coimbra, Coimbra, Portugal, [4]Clínica Universitária de Reumatologia, Faculty of Medicine, Universidade de Coimbra, Coimbra, Portugal, [5]Rheumatology, Pitié Salpetriere Hospital, Paris, France, [6]Centro Hospitalar e Universitário de Coimbra - Hospitais da Universidade de Coimbra, EPE, Coimbra, Portugal

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Background/Purpose: The "Rheumatoid Arthritis Impact of Disease" (RAID) score is a Patient Reported Outcome (PRO) that comprises seven domains of disease[1], that may reflect the patient's perspective more widely than other PROs. A cut-off corresponding to the patient acceptable symptom state (PASS) has been defined as RAID score <=2 [2]. This study aims: 1) to assess the associations between the RAID and established measures used in RA (disease activity measures and other PROs); 2) to analyse the relationship between clinical remission and PASS by RAID.

Methods: Consecutive RA patients (ACR/EULAR 2010 or ACR 1987 criteria) followed in a tertiary rheumatology department were included in this cross-sectional study. Patient demographics and clinical data collected were: DAS28, SDAI, CDAI and HAQ; patient and physician global assessment (PGA and PhGA); the Hospital Anxiety and Depression Scale (HADS), the Happiness Scale (HS) and the EuroQOL (EQ5D) score. RAID and DAS28 (4vCRP) scores were classified according to PASS and remission definitions (<=2 and <=2.6, respectively). We used Spearman correlation coefficient, Qui-square and Kappa as statistic tests.

Results: 101 patients were included (82% females, 58.8±12.4 years and 13.0±8.6 years of disease duration). Disease impact and activity were moderate: mean RAID=4.8±2.2 and mean DAS28(4vCRP)=2.9±1.2. RAID showed moderate correlations with most of the established combined indices of disease activity, with the HAQ having the highest correlation (r=0.66). Regarding other PROs, RAID was strongly correlated with PGA (r=0.70) and moderately with the remaining (Table 1).

Table 1 – Spearman's correlations between RAID and Disease Activity scores, Patient and Physician Global Assessment and other PROs (n=101)

	DAS283vESR	DAS284vESR	DAS283vCRP	DAS284vCRP	SDAI	CDAI	HAQ
RAID	0.28*	0.43*	0.32*	0.54*	0.61*	0.62*	0.66*
	PGA	**PhGA**	**Happiness**	**EQ5D**	**HADS-D**	**HADS-A**	--
RAID	0.70*	0.26*	-0.41*	-0.45*	0.55*	0.63*	--

*p<0.05

Out of 50 patients in DAS28 remission, 11 had a RAID score consistent with PASS but 39 had higher scores. Of the 51 patients not in remission, only one patient had a RAID score consistent with PASS (Table 2). This difference of proportions was statistically significant (X2(1)=9.684; p=0.002; Kappa=0.20).

Table 2 – Proportion of RA patients in PASS and in remission (n=101)

			DAS28(4vCPR)		
			Remission	Non Remission	Total
RAID	PASS	Count	11	1	12
		% of Total	10,9%	1,0%	11,9%
	Non PASS	Count	39	50	89
		% of Total	38,6%	49,5%	88,1%
Total		Count	50	51	101
		% of Total	49,5%	50,5%	100,0%

Conclusion: RAID correlates well with different PROs and moderately with disease activity scores. Its use in clinical practice may allow a better representation of the global impact of RA in patient's lives.

As disease remission by DAS and PASS by RAID are in disagreement for a considerable percentage of patients, further research on this

topic is warranted.

References:

1. Gossec L, et al. Ann Rheum Dis 2011;70(6):935-42.

2. Dougados M, et al. Arth Res & Ther 2012;14(3):R129.

Disclosure: R. J. O. Ferreira, None; **C. Duarte**, None; **S. Batista**, None; **C. Medeiros**, None; **J. P. Sousa**, None; **G. Eugénio**, None; **C. Costa**, None; **P. Carvalho**, None; **J. F. Ferreira**, None; **M. Coutinho**, None; **M. J. Salvador**, None; **L. Gossec**, None; **J. A. P. da Silva**, None.

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Abstract Number: 2609

The Measurement of the Skin Autofluorescence As an Indicator of Disease Progression in Rheumatoid Arthritis Patients

Slawomir Jeka[1], Pawel Zuchowski[2], Katarzyna Kolossa[3], Marta Dura[4] and Rafal Wojciechowski[5], [1]Clinic of Rheumatology and Connective Tissue Diseases, University Hospital Nr 2 Dr. Jan Biziel, 85-168 Bydgoszcz, Collegium Medicum in Bydgoszcz, Nicolaus Copernicus University in Torun, Poland, Bygdoszcz, Poland, [2]Independent Section of Scientific Research Coordination and Didactic Activity, University Hospital Nr 2 Dr. Jan Biziel, 85- 168 Bydgoszcz, Poland, Bygdoszcz, Poland, [3]Clinic of Rheumatology and Connective Tissue Diseases, University Hospital Nr 2 Dr. Jan Biziel, 85- 168 Bydgoszcz, Poland, Bygdoszcz, Poland, [4]Department of Radiology and Medical Imaging, University Hospital Nr 2 Dr. Jan Biziel, 85- 168 Bydgoszcz, Poland, Bygdoszcz, Poland, [5]Clinic of Rheumatology and Connective Tissue Diseases, University Hospital Nr 2 Dr. Jan Biziel, 85-168 Bydgoszcz, Poland, Bydgoszcz, Poland

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Background/Purpose: In course of rheumatoid arthritis (RA) ther is often impaired glucose metabolism, which leads to the development of diabetes mellitus (DM). One of the parameters allowing to assess the risk of DM and cardiovascular disease (CVD) is the concentration of advanced glycation end products (AGE). In rheumatoid arthritis patients increase in the level of AGE also occurs due to the underlying disease. The aim of the study was to assess correlation of AGE skin concentration with other laboraotry tests and to compare the levels of AGE concentration between RA patients and healthy subjects.

Methods: The study involved 148 patients divided into three groups: Group I - patients with RA (n = 102, 79F / 23M, average age 51.5), group II - patients with RA and DM (n = 21, 14F / 7M average age: 51.9), group III - healthy persons (n = 25, 16F / 9M, average age 48.8). Each patient had a skin test using the AGE Reader, which allows the assessment of AGE skin concentration by evaluation of skin autofluorescence (SAF) signal and a laboratory tests panel including total cholesterol, HDL, LDL, triglycerides and HbA1C and the calculated body mass index (BMI).

Results: Average SAF value in arbitrary units [au] was: group I 2.54 au and group II 2.74 au, group III 1.96 au. The average SAF value in the group III differed significantly from the average SAF value in group I and II ($p < 0.1$ and $p < 0.05$ respectively). There was no statistically significant difference between the mean AF values for Groups I and II. Based on AGE Reader tests risk groups of developing DM and CVD can also be separated. Significant differences in the distribution of patients in each risk group between the group III and group I and II ($p < 0.001$) was observed. There was a correlation between an increased SAF value in groups I and II and the following laboratory results compared to the group III: HDL (mean values in the groups were as follows: 60.52 mg/dl, 57.48 mg/dl, 84.08 mg/dl) and Hb1AC (mean values in the groups were respectively 5.5 mm/hr, 5.6 mm/h and 5.3 mm/h) ($p < 0.01$). In case of groups II and III a significant differences between the results of ESR (average values were 24 mm/h and 13 mm/h) and triglycerides concentration (mean values were 135 mg/dl and 95 mg/dL) ($p < 0.01$. were also observed.

Conclusion: These results confirm that the value of AGE skin concentration is associated with increased RA activity and may be an important indicator in the assessment of disease progression and its potential complications.

Disclosure: S. Jeka, None; **P. Zuchowski**, None; **K. Kolossa**, None; **M. Dura**, None; **R. Wojciechowski**, None.

Abstract Number: 2610

Real-World Use of Tocilizumab in Rheumatoid Arthritis Patients: Cardiovascular Risk, Concomitant Treatment, and Outcomes over 6 Months of Follow-up

Boulos Haraoui[1], Shahin Jamal[2], Vandana Ahluwalia[3], Tarang Manchanda[4] and Majed M. Khraishi[5], [1]Institut de Rhumatologie de Montréal and University of Montreal, Montreal, QC, Canada, [2]Vancouver Coastal Health, Vancouver, BC, Canada, [3]Brampton Civic Hospital, Brampton, ON, Canada, [4]Hoffmann-La Roche Canada, Mississauga, ON, Canada, [5]Nexus Clinical Research, St Johns, NF, Canada

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Background/Purpose: Tocilizumab (TCZ) is approved for the treatment of adults with rheumatoid arthritis (RA) either as monotherapy or in combination with disease-modifying antirheumatic drugs (DMARDs). However, to date, data on its real-world utilization and durability are limited. The aim of this analysis was to describe its real life use over 6 months and assess its safety in Canada.

Methods: ACT-UP CARE (ACT-UP Canadian Physician Observance of RA Patients on TCZ [CARE]) is an ongoing, multi-national, observational study with TCZ. As of January 2015, 1,432 patients have been enrolled from 18 countries. In this analysis, data from the 200 Canadian patients participating in ACT-UP are presented. The Framingham Cardiovascular (CV) Risk Score (FCRS) was measured at baseline (BL) as an exploratory assessment. Within-group changes in disease parameters were evaluated with the paired-samples t-test. Safety was described with the incidence of adverse events (AEs).

Results: The mean (SD) RA disease duration was 12.6 (10.4) years, and 79% of patients were on a previous biologic. Low, moderate and high FCRS category was reported for 52.6%, 36.8%, and 10.5%, respectively, of patients with available data. The most frequent CV risk factors were hypertension (36.7%), hyperlipidemia (21.6%), and current smoking (18.6%). Concomitant methotrexate (MTX) use was reported for 51.5% of patients at BL (mean dose: 19.5 mg/week) and 57.7% of patients over 6 months of treatment (mean dose: 18.7 mg/week). Corticosteroid use was reported for 40.5% of patients at BL (mean prednisone dose: 10.8 mg/day). Among patients on prednisone at BL, stable dose was reported for 50.6%, decreased dose for 22.8%, increased dose for 10.1%, and steroid discontinuation for 16.5% over 6 months. Mean (SD) disease and lipid parameters at BL and 6 months are shown in Table 1.

There were 20 (10.0%) discontinuations due to: AEs (n=6), lack of efficacy (n=5), withdrawal of consent (n=5), other (n=3), and death (n=1), without any significant differences based on prior use of a biologic (10.8% for bio-experienced vs. 7.1% for bio-naïve; P=0.772) and presence of comorbidities (8.7% for presence vs. 17.9% for no presence; P=0.168). A total of 351 AEs were reported by 144 (72.7%) patients (353.0 events /100 PYs), the majority of which (93.4%) were non-serious. Most frequently reported AEs included upper respiratory tract infection (n=14, 7.1%), headache (n=9, 4.5%), and fatigue (n=8, 4.0%). Serious infections were reported by 5 (2.5%) patients. One death due to pneumonia was reported which was judged by the treating physician as not related to TCZ.

Conclusion: The results of this real-world Canadian study show that TCZ is well tolerated and effective in significantly improving clinical parameters and patient reported outcomes as early as 6 months of treatment.

Table 1: Disease and Lipid Parameters over 6 Months			
	Baseline	**Month 6**	**P-Value**
Disease Parameter, Mean (SD)			
CRP: mg/L	19.8 (37.4)	4.3 (9.1)	<0.001
SJC	9.4 (5.2)	3.5 (4.4)	<0.001
TJC	12.6 (7.1)	4.6 (5.9)	<0.001
DAS28	5.6 (1.2)	2.9 (1.5)	<0.001
DAS28 Remission*	3 (1.6)	54 (41.5)	<0.001
AM Stiffness: minutes	58.4 (22.9)	38.7 (26.6)	<0.001
Patient Global (PtGA): VAS mm	62.5 (21.4)	41.2 (25.5)	<0.001
Pain: VAS mm	63.3 (22.9)	39.8 (27.6)	<0.001
Fatigue: VAS mm	62.8 (24.3)	43.8 (28.3)	<0.001
Lipid Parameter, Mean (SD)			
Total Cholesterol: mmol/L	4.8 (1.1)	5.1 (1.1)	0.294
LDL-C: mmol/L	2.7 (0.9)	3.0 (0.8)	0.315
HDL-C: mmol/L	1.6 (0.8)	1.8 (0.7)	0.073
Triglycerides: mmol/L	1.4 (1.1)	1.3 (0.9)	0.548
Total Cholesterol/HDL-C Ratio	3.4 (1.4)	3.3 (1.2)	0.225
*Proportions are based on total number of patients with available data			

Disclosure: B. Haraoui, AbbVie, Amgen, Bristol-Myers-Squibb, Celgene, Janssen Pharmaceutica Product, L.P., Pfizer Inc, Roche Pharmaceuticals, UCB, 2,AbbVie, Amgen, Bristol-Myers-Squibb, Celgene, Janssen Pharmaceutica Product, L.P., Pfizer Inc, Roche Pharmaceuticals, UCB, 5; **S. Jamal**, None; **V. Ahluwalia**, None; **T. Manchanda**, None; **M. M. Khraishi**, Janssen Inc., 5.

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Abstract Number: 2611

Circulating Monocyte Count Is Significantly Associated with Interstitial Pneumonia in Biologic-Naive Patients with Rheumatoid Arthritis: A Single-Center Prospective Cohort Study (Keio First-Bio Cohort Study)

Keisuke Izumi[1], Misato Hashizume[2], Yuko Kaneko[3], Keiko Yoshimoto[1] and Tsutomu Takeuchi[1], [1]Division of Rheumatology, Department of Internal Medicine, Keio University School of Medicine, Tokyo, Japan, [2]Product Research Department, Fuji-Gotemba Research Laboratories, Chugai Pharmaceutical Co., Ltd., Gotemba, Japan, [3]Division of Rheumatology, Keio University School of Medicine, Tokyo, Japan

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SESSION INFORMATION

Session Date: Tuesday, November 10, 2015

Session Title: Rheumatoid Arthritis - Clinical Aspects Poster Session III

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Background/Purpose : Interstitial pneumonia (IP) is one of the most critical complications in rheumatoid arthritis (RA). Severe IP is developed in zymosan-treated SKG mice, and this IP is completely blocked by neutralization of granulocyte macrophage colony-stimulating factor (GM-CSF) (Shiomi A, et al. J Immunol. 2014;15;193(2):849-59). GM-CSF induces expression of soluble vascular endothelial growth factor (VEGF) receptor-1 from human monocytes (Eubank TD, et al. Immunity. 2004;21(6):831-42). Here we aimed to explore the associations between IP and biomarkers including GM-CSF, VEGF, and circulating monocyte count in biologic-naive patients with RA.

Methods : Consecutive biologic-naive patients with RA were enrolled in our prospective cohort study at the timing of initiating biologics. Our cohort started in February 2010, and the patients were analysed as of April 2012. Before initiating biologics, we evaluated chest X-rays for all of the patients, and if IP was suspected, a chest computed tomographic (CT) scan was taken. At the enrollment of our cohort we assessed variables including the patients' characteristics (sex, age, disease duration, prednisolone dose, methotrexate dose, Clinical Disease Activity Index, Health Assessment Questionnaire-Disability Index) and blood biomarkers (GM-CSF [pg/mL], VEGF [pg/mL], TNF-α [pg/mL], Interleukin(IL)-6 [pg/mL], IL-17 [pg/mL], osteopontin [ng/mL], C-reactive protein

[mg/dL], white blood cell count [/μL], neutrophil count [/μL], and monocyte count [/μL]) to extract factors associated with CT scan-proven IP using univariate analyses. The extracted factors were entered into a multivariate logistic regression model to obtain factors associated with IP.

Results : A total of 127 patients (108 females and 19 males) were included in our study. The mean age and disease duration of the patients were 56.2±12.9 years and 6.7±7.7 years, respectively. CT scan-proven IP was noted in 17 patients. Prednisolone was used in 33 patients and methotrexate was used in 110. In the univariate analyses, sex, age, prednisolone dose, methotrexate dose, GM-CSF, VEGF, and monocyte count were significantly associated with IP ($P<0.05$). In the multivariate analyses, age (OR 1.081, 95% CI 1.010-1.174), methotrexate dose (OR 0.820, 95% CI 0.686-0.970), and monocyte count (OR 1.005, 95% CI 1.001-1.010) were identified as factors associated with IP.

Conclusion : The large number of circulating monocytes as well as advanced age and low methotrexate dose is significantly associated with IP in biologic-naive patients with RA.

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Abstract Number: 2612

Impact of a Multibiomarker Disease Activity Score in Patients with Rheumatoid Arthritis Treated in a Real World Setting

Sergio Schwartzman[1], Keith Knapp[2], Gary Craig[3], Karen Ferguson[4] and Howard Kenney[5], [1]Rheumatology, Hospital for Special Surgery, New York, NY, [2]Arthritis Northwest, Spokane, WA, [3]Discus Analytics, Inc., Spokane, WA, [4]Arthritis Northwest PLLC., Spokane, WA, [5]Rheumatology, Arthritis Northwest, Spokane, WA

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Background/Purpose: A number of composite outcome measures have been validated to quantify disease activity in Rheumatoid Arthritis (RA). Few studies have been published on the use of a multi-biomarker disease activity (MBDA) blood test (Vectra DA®) in a real world setting. The published articles that attempt to define the impact of this test in clinical practice have been an exercise on the use of the MBDA in RA case vignettes and a study evaluating the effect of the MBDA on treatment decisions. As there are no published studies using the MBDA in a true clinical practice compared to a validated outcome measure, in this study we compared the MBDA to the CDAI using the clinical registry JointMan® (JM).

Methods: This is a retrospective, observational study. JM captures RA diagnostic criteria and selected disease features, formal joint counts, outcome measures, serology, medication efficacy and safety and reason for discontinuation of medications. Due to the retrospective analysis methodology not all data was available.

Results:

Over 5700 unique RA patients and 133,000 encounters have been recorded since 2009.

The total distinct Vectra patient count was 687 and the total number of Vectra results was 1079. The total JM entries where a Vectra and CDAI score are within 20 days of each other was 436. Total distinct Vectra patients with more than one Vectra score was 274.

We calculated three correlation coefficients: the Pearson, the Cohen-Kappa, and the Weighted Kappa. The correlation coefficients are delineated in **Table 1**. The results demonstrate a Cohen Kappa estimate of 0.093 ($p<0.006$), a Weighted Kappa of $\kappa = 0.298$ ($p<0.001$)

and a Pearson score, ρ = 0.4185 (P<0.001). **Table 2.** Contains the distribution of the paired data.

Table 1.

	Lower CI	Estimate	Upper CI
Unweighted Kappa (κ)	0.035	0.093	0.15
Weighted Kappa (κ)	0.213	0.298	0.38
Pearson (ρ)	0.338	0.419	0.493

Table 2.

		Vectra			
		High	**Moderate**	**Low**	**Remission**
CDAI	**High**	59	29	3	12
	Moderate	67	51	7	29
	Low	37	52	6	15
	Remission	4	26	10	29

Conclusion: This is the first study using the MBDA in a true clinical practice setting. In this study the MBDA was compared to CDAI. The Cohen Kappa indicates "slight" agreement, whereas the weighted score of K = .298, is a "fair" correlation according to Landis and Koch. The Vectra DA score achieved almost 3/10 of the way between the expected accuracy (random) and perfect classification accuracy (CDAI being the standard). The Pearson ρ score of 0.4185 (P<0.001) falls into the category of a strong positive linear relationship between Vectra and CDAI scoring metrics. The qualitative nominal interpretations of the scores indicate that there is a valid, yet incompletely characterized relationship between the metrics. Additional prospective studies are needed in real world settings are needed to continue to define the role of the MBDA score.

Disclosure: S. Schwartzman, Discus Analytics, 9,Discus Analytics, 1,Crescendo, 9,Crescendo, 5,Crescendo, 8; **K. Knapp**, Discus Analytics, 1,Discus Analytics, 3; **G. Craig**, Discus Analytics, 1,Discus Analytics, 9; **K. Ferguson**, Discus Analytics, 1; **H. Kenney**, Discus Analytics, 1,Discus Analytics, 9,Crescendo, 8.

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Abstract Number: 2613

Patient Reported Physical Capacity Correlates with Phenylalanine Serum Levels in Patients with Early Untreated Rheumatoid Arthritis

Aulikki Kononoff[1], Leena Arstila[1,2], Hannu Kautiainen[3,4], Pia Elfving[1], Elina Savolainen[5], Helena Niinisalo[6,7] and Oili Kaipiainen-Seppanen[1], [1]Department of Medicine, Kuopio University Hospital, Kuopio, Finland, [2]Iisalmi Hospital, Iisalmi, Finland, [3]Unit of Primary Health Care, Kuopio University Hospital, Kuopio, Finland, [4]Unit of Primary Health Care, Helsinki University Central Hospital, Helsinki, Finland, [5]Kuopio Municipal Hospital, Kuopio, Finland, [6]Suonenjoki Health Center, Suonenjoki, Finland, [7]Varkaus Hospital, Varkaus, Finland

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Background/Purpose:

Lipolysis is increased in rheumatoid arthritis (RA), and lipid-induced insulin resistance coincides with anabolic resistance. Ability to maintain skeletal muscle mass is impaired in insulin-resistant conditions. Low grade inflammation prevents protein synthesis in peripheral muscles. Phenylalanine is associated with whole body protein turnover; protein synthesis and break down.We have investigated the relationship between amino acids and patient reported outcomes: general health (GH, patient global estimate, VAS), pain (VAS) and HAQ, among patients with newly diagnosed RA in a population based cohort.

Methods:

For quantification of amino acids and alpha-1-acyl glycoprotein (GP) levels serum nuclear magnetic resonance platform operating at 500 MHz was used in native serum samples from patients with RA participating in Northern Savo 2010 Study. Crude, age and BMI adjusted correlations between HAQ, phenylalanine, and inflammatory parameters were counted.

Results:

Serum samples from 63 patients, 34 females and 29 males with RA satisfying the ACR/Eular 2010 classification criteria, were studied. The mean age (SD) of the patients was 59.1 (12.0) years and the mean BMI 27.3 (5.4) kg/m². 69.8 % had anti-CCP antibodies. The mean DAS28(ESR) was 4.4 (1.3), GH 52.7 (25.7), pain 56.4 (29.1), HAQ 0.70 (0.65), and GP 1.62 (0.29) mmol/L. DAS28(ESR) correlated with HAQ 0.41 (0.18 to 0.59), $p < 0.01$, with ESR 0.36 (0.12 to 0.56), $p < 0.05$, GH 0.38 (0.13 to 0.57), $p<0.05$, and physical function (HAQ) 0.61 (0.43 to 0.75), $p< 0.001$. HAQ-levels increased with increasing phenylalanine serum levels, adjusted for age, gender, BMI, duration of symptoms, tender joint count, swollen joint count, Charlson comorbidity index score, GP level and seropositivity, p for linearity = 0.029.

Conclusion:

Patient reported physical function correlates with phenylalanine serum levels in untreated RA. The result reflects changes in muscle metabolism in RA, in which inflammation induces protein break down and prevents protein synthesis in peripheral muscles.

Disclosure: A. Kononoff, None; **L. Arstila**, None; **H. Kautiainen**, None; **P. Elfving**, None; **E. Savolainen**, None; **H. Niinisalo**, None; **O. Kaipiainen-Seppanen**, None.

Abstract Number: 2614

Single Academic Center Experience with 14-3-3 Eta in the Evaluation of Inflammatory Arthritis

Lance Feller[1], **Paul Tuttle IV**[2], Austin M. Dalrymple[3], Srikanth Bathula[4], Katherine Temprano[5], Reema H. Syed[6], Rama Bandlamudi[7], Kathryn Coulson[8], Peri Pepmueller[9] and Terry Moore[10], [1]Internal Medicine/Rheumatology, Saint Louis University, Saint Louis, MO, [2]Saint Louis University, Saint Louis, MO, [3]Pediatric Rheumatology, St. Louis University, St. Louis, MO, [4]Rheumatology, Saint Louis University, Saint Louis, MO, [5]Medicine/Rheumatology, Saint Louis University, St. Louis, MO, [6]IM-Rheumatology, Saint Louis University, St. Louis, MO, [7]Internal Medicine/Rheumatology, St. Louis Univ Health Sciences, St. Louis, MO, [8]Rheumatology/ 213A, St. Louis University, St. Louis, MO, [9]Rheumatology, Saint Louis University, St. Louis, MO, [10]Division of Rheumatology and Pediatric Rheumatology, Saint Louis University School of Medicine, St Louis, MO

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Background/Purpose:

14-3-3 proteins are chaperonins found in all eukaryotic cells. There are multiple isoforms which are thought to be involved in intracellular signaling and transcription regulation. Among their targets are phosphatases, kinases and transmembrane receptors. There are seven known isoforms in mammals. The η (Eta) isoform has been implicated as having diagnostic potential in inflammatory arthritis. In this study we investigated the utility of measuring 14-3-3η when evaluating inflammatory arthritis.

Methods:

Measurements of 14-3-3η were obtained during evaluation of joint pain in patients presenting between July 2013 and April of 2015. Rheumatoid factor (RF) and anti-cyclic citrullinated peptide antibodies (anti-CCP Ab) were measured. Joint imaging was evaluated for erosive changes and use of biologics was recorded. A chart review was later conducted to evaluate the utility of standard measures versus 14-3-3η.

Results:

214 patients were evaluated. 49 had a diagnosis of rheumatoid arthritis (RA), 17 had psoriatic arthritis (PsA). 43 patients had

connective tissue disease (CTD), 8 had undifferentiated inflammatory arthritis, and 97 had other rheumatological disorders.

Of the 49 RA patients, 37 were RF positive, 36 were anti-CCP Ab positive, and 25 were 14-3-3η positive. Of the 25 who were 14-3-3η positive, 22 were both anti-CCP Ab and RF positive, 2 were RF positive but anti-CCP Ab neg, and 1 was negative for both RF and anti-CCP Ab. Of the 24 who were 14-3-3η negative, 12 were both RF and anti-CCP Ab positive, 2 were only anti-CCP Ab positive, 1 was only RF positive, and 9 were seronegative. 20 patients in total had erosive disease of which 13 were positive for 14-3-3η, 10 were positive for all three markers, 1 was positive for just RF, and 1 was negative for both RF and anti-CCP Ab. Of the RA patients with erosive changes on biologic medication, 5 were 14-3-3η positive and 8 were 14-3-3η negative.

All 17 patients with PsA were seronegative with one exception, who was 14-3-3η positive. 6 PsA patients had joint erosions and they were seronegative. Of the 43 patients with CTD, 6 were 14-3-3η positive. 2 patients had enteropathic arthritis and were seronegative.

	14.3.3η alone	RF and CCP	Triple Positive	14.3.3η and RF	14.3.3η and CCP	Any seropositivity
RA sensitivity	0.51	0.69	0.45	0.49	0.45	0.82
RA specificity	0.90	0.97	0.98	0.94	0.98	0.79
RA PPV	0.49	0.50	0.50	0.50	0.50	0.49
RA NPV	0.88	0.92	0.86	0.87	0.86	0.95

Conclusion:

The 14-3-3η protein can be detected in inflammatory arthritis, with the highest percentage in RA patients. However, there was no correlation between 14-3-3η titers with RF or anti-CCP Ab. No significant association was found with PsA patients in our small sample. There was also no correlation with biologic use. One 14-3-3η positive patient who was negative for RF and anti-CCP Ab had erosive disease.

Disclosure: L. Feller, None; **P. Tuttle IV**, None; **A. M. Dalrymple**, None; **S. Bathula**, None; **K. Temprano**, None; **R. H. Syed**, None; **R. Bandlamudi**, None; **K. Coulson**, None; **P. Pepmueller**, None; **T. Moore**, None.

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Abstract Number: 2615

Changes in a Patient-Reported Measure of Physical Function, PF-10a, Are Most Strongly Associated with Changes in the Patient Global Assessment Portion of a Composite Measure of RA Disease Activity

Elizabeth R. Wahl[1,2], Andrew Gross[2], Vladimir Chernitskiy[2], Patricia P. Katz[2] and Jinoos Yazdany[3], [1]Medicine/Rheumatology, San Francisco Veterans Affairs Medical Center, San Francisco, CA, [2]Medicine/Rheumatology, University of California San Francisco, San Francisco, CA, [3]University of California, San Francisco, San Francisco, CA

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Background/Purpose: A brief patient-reported measure of physical function, the PROMIS PF-10a, is sensitive to changes in disease activity among patients with rheumatoid arthritis (RA). However, less is known about which components of composite disease activity measures--swollen and tender joint counts, patient and provider global assessments, pain, or inflammatory markers--are most strongly associated with reported changes in physical function. Better understanding the impact of each of these domains on physical function is critical to interpreting changes in PF-10a and understanding its role in the clinical setting. The current study evaluates the relative contribution of patient and provider assessments, pain, and inflammatory markers, on self-reported physical function.

Methods: Clinical and demographic data were abstracted from the electronic health record for all patients seen at a university-based rheumatology clinic between February 2013 and February 2015 with at least two ICD-9 codes for RA. All patients had PF-10a and Clinical Disease Activity Index (CDAI) scores recorded on at least two occasions. Pain was assessed at each visit using a visual

analog scale (0-10cm). The inflammatory marker C-reactive protein (CRP) was assessed at least every 3 months. Mixed effects linear regression was used to model the relationship between change in CDAI score over baseline and change in PF-10a score, and then to model the relationship between changes in each component of the CDAI (patient global assessment (PGA), evaluator global assessment (EGA), swollen (SJC) and tender joint count (TJC)) and changes in PF-10a score over time. The model was adjusted for age, gender, pain, and CRP.

Results: Of 326 patients, 82% were women with a mean (SD) age of 59 (14). The group was racially/ethnically diverse. About half of patients had moderate-severe CDAI scores (≥ 10) at baseline. In an unadjusted model, changes in CDAI and PF-10a were significantly associated ($p<0.001$); a 12-point increase in CDAI, the Minimal Clinically Important Improvement threshold, was associated with an average 3.3 point decrease in PF-10a, 95% CI (2.7-3.8). In the multivariate model, changes in CDAI remained significantly associated with changes in PF-10a; changes in pain but not CRP were associated with changes in PF-10a score (Table). In a model isolating CDAI components, changes in PGA and pain level were associated with changes in PF-10a score, while changes in EGA, SJC, TJC, and CRP were not.

Conclusion: Changes in the patient global assessment and in pain levels were significantly associated with reported changes in physical function as measured by the PROMIS-PF10a, while changes in the evaluator global assessment, tender and swollen joint count, and CRP level were not. These findings suggest that PF-10a measures a distinct construct, self-reported physical function, that may reflect patients' global assessment and pain level but is unrelated to provider assessments.

Table. Mixed effects linear regression model coefficients (95% CI) representing the association between average change in physical function score (PF-10a) and change in CDAI components, pain, and CRP for 326 RA clinic patients.

	Adjusted Models*	
	Composite CDAI Model	Component CDAI Model
CDAI score (0-76)	**-0.1 (-0.2 -- -0.04)**	
Patient Global Assessment (0-10)		**-0.8 (-1.2 -- -0.5)**
Provider Global Assessment (0-10)		-0.4 (-0.8 -- -0.0004)
Tender Joint Count (0-28)		0.05 (-0.1 -- 0.2)
Swollen Joint Count (0-28)		-0.05 (-0.3 -- 0.2)
Pain score, VAS (0-10)	**-1.2 (-1.5 -- -1.0)**	**-0.6 (-0.9 -- -0.3)**
CRP, mg/L	-0.01 (-0.04 -- 0.01)	-0.01 (-0.04 -- .01)

*Models adjusted for age and gender. Results from the unadjusted model were similar.

Higher PF-10a scores reflect better function and lower CDAI scores reflect less disease activity.

Bolded covariates reached statistical significance, $p<0.05$

Disclosure: E. R. Wahl, None; **A. Gross**, None; **V. Chernitskiy**, None; **P. P. Katz**, None; **J. Yazdany**, None.

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Abstract Number: 2616

Study of Anti-Carbamylated Protein Antibody in the Rheumatoid Patients Who Were Clinically Active and Under Treatment with Biological Dmards

Kazuko Shiozawa[1] and Shunichi Shiozawa[2], [1]Rheumatic Diseases Center, Konan Kakogawa Hospital, Kakogawa, Japan, [2]Department

of Medicine, Rheumatic Diseases Unit, Kyushu University Beppu Hospital, Beppu, Japan
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Background/Purpose: A newly discovered anti-carbamylated protein antibody (anti-CarP) is found prior to disease-onset, associates with the conversion towards arthralgia and with a more severe disease course in patients negative for ACPA. We here studied anti-CarP in 141 rheumatoid patients who were clinically active and under treatment with biological DMARDs with reference to anti-CCP2 protein antibody2 (ACPA2) and ACPA3.

Methods: ACPA2, ACPA3, anti-CarP-Fetal Calf Serum (aCarPFCS) and anti-CarP-Fibrinogen (aCarPFib) were measured by using ELISA in sera of 141 Japanese patients with RA who were clinically active (fulfilling either DAS-CRP > 4.0 or DAS-ESR > 4.2 and either CDAI > 22 or SDAI >26) and under treatment with biological DMARDs (53 with ETN, 40 with IFX, 19 with TCX, 15 with ADA, 8 with ABA, and 6 with GLM). Data were compared by classifying into ACPA2b (0~0.6 U/mL; below assay limit), ACPA2n (0.7~4.4; negative) or ACPA2p (4.5~20; low positive) subgroups.

Results: Among ACPA2b group (n=41), ACPA3, aCarPFCS and aCarPFib were positive in 8 (19.5%), 0 (0%) and 4 (9.8%), respectively. Likewise, among ACPA2n group (n=31), they were positive in 16 (51.6%), 3 (9.7%) and 6 (19.4%). Among ACPA2p group (n=69), they were 64 (92.8%), 26 (37.7%) and 18 (26.1%). Within ACPA2b and ACPA3-positive groups (n=8), aCarPFCS and aCarPFib were 0 and 3 (37.5%). Within ACPA2n and ACPA3-positive groups (n=17), they were 3 (17.6%) and 2 (11.8%). Within ACPA2p and ACPA3-positive groups (n=64), they were 24 (37.5%) and 17 (26.6%). It was noted that among ACPA2b and ACPA3-negative groups (n=1) and ACPA2n and ACPA3-negative groups (n=2), aCarPFCS was all negative, however, aCarPFib was positive in 1/1 (100%) and 2/2 (100%), respectively. These 3 anti-CarP sole positive patients were with DAS28-ESR3: 5.1, 7.0, and 5.4, and ΔTSS: 4, 0, 4.

ACPA3	aCarPFCS	aCarPFib	ACPA2below	ACPA2negative	ACPA2positive
-	-	-	32	12	3
+	-	-	5	12	31
+	+	-	0	1	16
+	+	+	0	2	8
+	-	+	3	2	9
-	+	-	0	0	1
-	+	+	0	0	1
-	-	+	1	2	0
Total			41	31	69

Conclusion: Anti-CarP was positive in a substantial fraction of ACPA2 negative subset, in which most of them were also ACPA3 positive. There existed 3 patients who were sole positive for anti-CarP whose disease was clinically active despite treatment with biological DMARDs.

This study is a co-work with Drs. Verheul MK and Trouw LA, Department of Rheumatology, Leiden University, Netherlands.

Disclosure: K. Shiozawa, None; **S. Shiozawa**, None.

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Abstract Number: 2617

Serum 14-3-3eta Protein Elevation in Osteoarthritis Suggests Misclassification or Concurrent Inflammatory Arthritis

Olga S. Zhukov[1], Jonnielyn G. Rivera[1], Rania W. Abolhosn[1], Robert J. Lagier[2], Charles M. Rowland[3], Joanna M. Popov[1], Kaleb Michaud[4] and **Stanley J. Naides**[1], [1]Immunology, Quest Diagnostics Nichols Institute, San Juan Capistrano, CA, [2]Research Support, Alameda, Quest Diagnostics Alameda, Alameda, CA, [3]Research Support, Quest Diagnostics Alameda, Alameda, CA, [4]Rheumatology & Immunology, University of Nebraska Medical Center and National Data Bank, Omaha, NE

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Background/Purpose: Tissue distribution of the chaperonin 14-3-3η (eta) is limited to synovial tissue and brain. Synovium releases proinflammatory 14-3-3η into synovial fluid and serum in rheumatoid arthritis (RA) patients and, to a lesser extent, erosive psoriatic arthritis (PsA) patients. Serum measurement aids RA diagnosis (sensitivity 64% in early RA and 77% in established RA) and prognosis, and may have utility in assessing disease activity.[1,2] Differentiating RA or PsA from osteoarthritis (OA), or identifying inflammatory arthritis in the presence of co-existing OA can be difficult. The purpose of this study was to estimate the specificity of 14-3-3η among a cohort of subjects with physician-confirmed OA.

Methods: Participants in the U.S.-based Arthritis Internet Registry (AIR) were surveyed by questionnaire. Physician and/or medical records were queried. Serum samples from patients with physician-confirmed diagnoses of OA (n=169) were tested for C-reactive protein (CRP) and rheumatoid factor (RF) by nephelometry, cyclic citrullinated peptide antibody (CCP) by ELISA, and 14-3-3η by a proprietary laboratory-developed ELISA test.

Results: Of 169 physician-diagnosed OA patients tested, 11 (6.5%; 95% CI 3.3% to 11.3%) were positive for 14-3-3η. However, for 1 of the 11, CRP was 0.3 mg/dL, (normal, <0.8 mg/dL), RF was 123 IU/ml (normal <14 IU/mL), CCP was >250 Units (normal, <20 Units), and 14-3-3η was 1.9 ng/mL (normal, <0.2 ng/mL); the subject was subsequently reclassified as RA. Another subject's CRP, RF, and CCP were nomral, but 14-3-3η was 3.1 ng/mL; subsequently, the subject was diagnosed with PsA based on new onset dactylitis in 2 fingers, joint pain, and changes in fingernails, all in the absence of prior psoriasis. A third subject had previously been treated for RA with methotrexate and entanercept; CRP was 4.4 mg/dL, RF was >1,200 IU/mL, CCP was >250 Units, and 14-3-3η was >20 ng/mL. Excluding the 3 subjects with subsequent diagnoses of RA or PsA, 8 of 166 OA subjects were 14-3-3η positive, or 4.8% (95% CI 2.1% to 9.3%). The specificity in OA subjects for 14-3-3η as a marker of inflammatory arthritis was 95.2% (95% CI 90.7% to 97.9%).

Conclusion: In the present study, the low frequency of 14-3-3η in a cohort of individuals with OA supports the high specificity of 14-3-3η observed for RA. Further, 14-3-3η may be used to help identify RA or PsA patients amongst those being followed for OA. 14-3-3η may be particularly useful in the primary care setting to screen OA patients for misclassification of RA or PsA as OA, or for concurrent inflammatory arthritis in the setting of OA.

References: 1. Maksymowych, et al. *J Rheum*. 2014;41:2104-13; 2. Maksymowych, et al. *Clin Exp Rheum*. 2014;32(Suppl 85):S35-9.

Disclosure: O. S. Zhukov, Quest Diagnostics, 3; **J. G. Rivera**, Quest Diagnostics, 3; **R. W. Abolhosn**, Quest Diagnostics, 3; **R. J. Lagier**, Quest Diagnostics, 3; **C. M. Rowland**, Quest Diagnostics, 3; **J. M. Popov**, Quest Diagnostics, 3; **K. Michaud**, None; **S. J. Naides**, Quest Diagnostics, 3.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/serum-14-3-3eta-protein-elevation-in-osteoarthritis-suggests-misclassification-or-concurrent-inflammatory-arthritis

Abstract Number: 2618

Methotrexate Dose May Associated with the Frequency of Lymphoproliferative Disorders in Rheumatoid Arthritis

Hiroaki Dobashi[1], Tomohiro Kameda[1], Masayuki Inoo[2], Ikuko Onishi[2], Noriyuki Kurata[2], Miharu Izumikawa[1], Yohei Takeuchi[3], Shusaku Nakashima[1], Hiromi Shimada[1], Hiroki Ozaki[1], Risa Wakiya[1] and Norimitsu Kadowaki[4], [1]Internal Medicine Division of Hematology, Rheumatology, and Respiratory Medicine, Kagawa University, Kagawa, Japan, [2]Utazu hospital, Kagawa, Japan, [3]Internal Medicine Division of Endocrinology and Metabolism, Hematology, Rheumatology and Respiratory Medicine, Kagawa University, Kagawa, Japan, [4]Department of Internal Medicine, Division of Hematology, Rheumatology and Respiratory Medicine, Faculty of Medicine, Kagawa University,, Kagawa, Japan

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SESSION INFORMATION

Session Date: Tuesday, November 10, 2015

Session Title: Rheumatoid Arthritis - Clinical Aspects Poster Session III

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose:

Rheumatoid arthritis (RA) is a systemic inflammatory disease that is characterized by synovitis and the destruction of articular structures of multiple joints. The goal of treatment for RA is to control the progression of these articular lesions. MTX is an antirheumatic drug that is expected to have an excellent suppressive effect on articular destruction. Recently, MTX has been used as an anchor drug for the treatment of RA (1). On the other hand, RA patients have a high risk of onset of lymphoproliferative disorders (LPD) (2). Although MTX-LPD occurs mainly in RA patients, it has not been established if MTX administration is an independent risk factor for LPD in RA patients.

We examined the clinical characteristics of MTX-LPD in Japanese RA patients and attempted to determine the risk factors for MTX-LPD development.

Methods: We performed a nested case-control study on RA patients. We enrolled 5,873 RA patients from Kagawa Prefecture, Japan between June 2003 and May 2015. Patients were diagnosed according to American College of Rheumatology 1987 classification criteria, and treated with disease modifying antirheumatic drugs (DMARDs) including MTX. In age and gender matched patients, we separated patients who did not develop LPD under MTX treatment (MTX non-LPD group) from those that did (MTX-LPD group), and conducted a comparative examination. We used multivariate analysis to determine the independent risk factors for MTX-LPD onset.

Results:

There were 36 patients in the MTX-LPD group and 158 patients in the MTX non-LPD group. The number of patients with DMARDs (except MTX) treatment showed no significant difference in two groups. Furthermore, there was no difference between two groups about that with corticosteroid and biologics treatment. Also, the complication rates for Sjögren's syndrome did not differ significantly. Using univariate analysis, significant differences were found in the duration of RA disease, total MTX dose and mean MTX dose between the two groups. Furthermore, multivariate analysis of the parameters extracted by univariate analysis revealed that the mean MTX dose was a risk factor for MTX-LPD after adjusting for age.

Conclusion:

We revealed the mean MTX dose was demonstrated to be an independent risk factor regarding MTX-LPD onset in RA patients. This data strongly suggest that the treatment with higher MTX dose promotes LPD onset in Japanese RA patients.

Disclosure: H. Dobashi, None; **T. Kameda**, None; **M. Inoo**, None; **I. Onishi**, None; **N. Kurata**, None; **M. Izumikawa**, None; **Y. Takeuchi**, None; **S. Nakashima**, None; **H. Shimada**, None; **H. Ozaki**, None; **R. Wakiya**, None; **N. Kadowaki**, None.

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Abstract Number: 2619

Clinical Usefulness of Periodic Detection of Serum 14-3-3Î· for Predicting Efficacy of Tocilizumab in RA

Akira Sagawa[1], Takuya Isayama[2], Makoto Kaneda[3], Yuan Gui[4], Anthony Marotta[5] and Jiro Arai[2], [1]Sagawa Akira Rheumatology Clinic, Sapporo, Japan, [2]Medical and Biological Laboratories Co., Ltd., Ina, Japan, [3]MBL Europe, Diegem, Belgium, [4]Augurex Life Sciences Corp., North Vancouver, BC, Canada, [5]1423 Dempsey Road, Augurex Life Sciences Corp., North Vancouver, BC, Canada
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Session Time: 9:00AM-11:00AM

Background/Purpose: Serum 14-3-3η is a diagnostic marker for RA. Recent *in vitro* evidence indicates that it may play a casual role in the pathogenesis of RA. As such the clinical usefulness of 14-3-3η is being more extensively investigated to include prediction of RA in arthralgia subjects and efficacy of drugs used to treat RA. In this study, we investigated whether serum 14-3-3η level is useful as a marker to predict therapeutic efficacy of tocilizumab (TCZ) in RA.

Methods: Sera 14-3-3η were measured in 41 patients (median age 54 yrs, range 20–78 yrs) with RA before and 3, 6, and 12 months after treatment with TCZ (8 mg/kg iv every 4 weeks), using the 14-3-3η ELISA kit (Augurex). 14-3-3η positivity was defined as ≥ 0.19

ng/ml. Median DAS28-ESR (DAS28) and clinical disease acrivity index (CDAI) before treatment were 5.1 (range 2.1–7.5) and 22.7 (range 10.4–60.8), respectively. 31 of 41 patients were ACPA positive, 37 were MMP3 positive and 1 was negative for both markers. Mann-Whitney U-tests and Fisher's exact tests were performed for comparison between treatment groups. A regression analysis was performed to determine if serum 14-3-3η was an independent predictor of diseases activity scores by comparison to DAS28 and CDAI.

Results: At pre-treatment, 28 of 41 patients were 14-3-3η positive and the 14-3-3η positive group tended to have higher baseline DAS28 (4.5 *vs* 5.3, $p = 0.055$) and CDAI (20.0 *vs* 25.4, $p = 0.046$). The 14-3-3η levels were significantly lower post-treatment with TCZ (4.7 *vs* 3.7, $p = 0.028$). The patient group with decreased 14-3-3η after 3months of treatment had significantly greater changes in MMP3 levels compared to the group with no decrease (54.8 *vs* 8.0, $p = 0.027$). According to the EULAR response criteria, the good responder group ($n = 17$) had significantly lower pre-treatment 14-3-3η levels compared to the moderate and non-responder group ($n = 24$), 0.37 *vs* 1.76 ng/ml, $p = 0.0252$. Similarly, the pre-treatment 14-3-3η levels were significantly lower in the group of patients that achieved remission by DAS28 < 2.6 and CDAI ≤ 10 (as remission and low diseases activity), after treatment. Neither ACPA nor MMP-3 levels were different between these responder groups. Fisher's exact testing revealed an association ($p = 0.045$) between DAS28 remission and 14-3-3η negativity delivering an odds ratio (OR) of 3.4 (95% CI: 0.9–13.3). Regression analysis controlling for baseline DAS28 revealed that 14-3-3η levels were an independent predictor of remission yielding a likelihood ratio (LR) of 7.8, $p= 0.0052$.

Conclusion: Serum 14-3-3η is a potential marker for predicting efficacy of TCZ treatment for RA. Further study is being achieved to establish the usefulness of 14-3-3η in longer term administration of TCZ.

Disclosure: A. Sagawa, None; **T. Isayama**, MBL Co., Ltd., 3; **M. Kaneda**, MBL Co., Ltd, 3; **Y. Gui**, Augurex Life Sciences Corp, 3; **A. Marotta**, Augurex Life Sciences Corp, 3; **J. Arai**, MBL Co., Ltd., 3.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/clinical-usefulness-of-periodic-detection-of-serum-14-3-3i%c2%b7-for-predicting-efficacy-of-tocilizumab-in-ra

Abstract Number: 2620

Predictive Value of Anti-Carbamylated Protein Antibodies in Patients with Early Arthritis

Cristina Regueiro[1], Diana Peiteado[2], Laura Nuño[3], Alejandro Villalba[4], Dora Pascual-Salcedo[5], Ana Martínez[6], Alejandro Balsa[4] and **Antonio Gonzalez**[7], [1]Instituto Investigacion Sanitaria - Hospital Clinico Universitario de Santiago, Santiago de Compostela, Spain, [2]Instituto de Investigación Hospital Universitario La Paz (IDIPAZ), Madrid, Spain, [3]Servicio de Reumatologia, Hospital Universitario La Paz, Madrid, Spain, [4]Rheumatology, La Paz University Hospital-Rheumatology Department, Madrid, Spain, [5]Immunology Unit, La Paz University Hospital-Immunology, Madrid, Spain, [6]Immunology Unit, La Paz University Hospital-IdiPaz, MADRID, Spain, [7]Instituto Investigacion Sanitaria-Hospital Clinico Universitario de Santiago, Santiago de Compostela, Spain

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Background/Purpose:

Anti-carbamylated protein (anti-CarP) antibodies have been described as a new type of autoantibodies specific of patients with rheumatoid arthritis (RA). They seem useful as a new biomarker of disease severity with independence of anti-CCP antibodies (1). In addition, they could also be a biomarker of future development of RA, at least, among patients with arthralgia (2). The aim of this study was to explore the predictive value of anti-CarP antibodies in early arthritis (EA) patients. Identification of the subgroup of EA at high risk of developing RA is a priority for prevention of joint damage and achievement of long-term remission.

Methods:

All the EA patients from a dedicated clinic with a minimum follow-up of two years have been included. These patients were recruited if they have shown 2 or more swollen joints for at least 4 weeks and symptoms for less than a year. Classifiation as RA was done according with the 1987 ACR criteria. Baseline sera from 552 EA patients were analyzed for anti-CarP fetal calf serum (FCS) antibodies by ELISA. Anti-CarP titre was obtained after subtracting reactivity to native FCS from the reactivity to carbamylated FCS. We used as a cut-off the 95 % percentil of 208 healthy donors.

Results:

Near half of the 552 patients (45.6%) fulfilled RA criteria at the end of the 2 years of follow-up. Baseline anti-CarP was 53.4% sensitive and 79.5% specific for RA at study end. These antibodies were found in 65.0% of the RA patients, which is similar to the percentage found in established RA. Presence of anti-CarP was significantly correlated with anti-CCP antibodies and with RF status. However, we observed that 13.0% of the anti-CCP negative RA patients tested positive for anti-CarP antibodies. Baseline anti-CCP and RF combination resulted in 91.9% positive predictive value (PPV) and a 79.6% negative predictive value (NPV) for RA. These values did not change by the addition of anti-CarP antibodies (91.5 and 81.6 %, respectively). In the anti-CCP negative RA patients, anti-CarP antibodies were 49.2% sensitive and 64.4% specific, and their combination with RF antibodies increased only modestly the PPV (from 36.3 with RF to 47.6% with the combination) withouth changing the NPV for RA (from 79.6% to 81.6%). Analysis of the 66 incident RA patients (fullfiling RA criteria by 2 years, but not at baseline) showed similar PPV and NPV with the inclusion of anti-CarP to the obtained with RF and anti-CCP antibodies alone (PPV = 70.6 with the three antibodies, and 72.9 with anti-CCP and RF, and NPV 90.9% in the two analyses). No association was found between anti-CarP status and smoking or DAS28 values.

Conclusion:

Anti-CarP antibodies were present in EA patients and their presence was associated with RA, both prevalent RA at baseline and incident RA during follow-up. However, they did not add to the prediction of RA available with the already known antibodies except for a modest increase in PPV among the anti-CCP negative patients.

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2. Shi, J., et al. Arthritis Rheum. 2013; 65(4): 911-5

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Abstract Number: 2621

Characteristics of Histopathology and Clinical Course of 19 Cases That Developed a Lymphoproliferative Disease (LPD) during Methotrexate (MTX) Treatment.

Noriyuki HAYASHI[1], Kae HAMAMOTO[2], Kouichiro YODA[2], Maki YODA[2], Shinsuke YAMADA[3], Hitoshi GOTO[2] and Masaaki INABA[2], [1]Rheumatology, Osaka City University Graduate School of Medicine, Osaka, Japan, [2]Second Department of Internal Medicine, Osaka City University Medical School, Osaka, Japan, [3]Rheumatology, Osaka City University Graduate School of Midicine, Osaka, Japan

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Session Time: 9:00AM-11:00AM

Background/Purpose:

We examined the clinical features of the cases after discontinuation or decrease of dosage of MTX in the MTX-LPD.

Methods:

We retrospectively examined a patient background, a clinical presentation, a histopathology, and clinical course in 19 patients of Osaka City University Hospital rheumatology clinic from 2006 through 2014.

Results:

These cases were average age 64.5 y.o. (37-81), 3 male/16 female , 8.1 mg/week of MTX average dosage, 1,510 mg (312-6110 mg) of MTX average total doses, and mean DAS28(CRP) of 3.65 (2.3-5.46) at the MTX-LPD onset.

Lymph node biopsy performed in 16 patients showed reactive lymphadenopathy syndrome 6, Diffuse large B-cell lymphoma (DLBCL) 5, Hodgkin's lymphoma 3, primary effusion lymphoma (PEL) 1, and non-specific Peripheral T-cell lymphoma 1. Epstein-Barr virus (EBV) DNA in blood specimen was examined in 4 cases resulting 2 positive, 2 negative.

16 cases improved by discontinuation of MTX spontaneously, but 3 cases required chemotherapy. It is reported that MTX-LPD often showed EBV-positive in histopathology, and the pathological type of EBV-positive LPD could show both the B-cell and the T-cells. One of 16 patients which performed lymph node biopsy was diagnosed T-cell lymphoma, and EBV was proved even in this case histologically. This case also improved spontaneously after discontinuation of MTX. The mechanism is not revealed, but the EBV infects both B-cells and T-cells.

Conclusion:

There was no difference in the ratio of the histopathology compared with malignant lymphoma besides iatrogenic immunodeficiency-associated lymphproliferative disorders. Contribution of the EBV infection is suggested in MTX-LPD development. In this study, it is suggested that the mechanism is applicable in T-cell lymphoma, although all cases are not EBV-positive in histopathology. Further study is necessary on revealing the mechanism of pathogenesis of MTX-LPD, and EBV infection to T-cells.

Disclosure: N. HAYASHI, None; **K. HAMAMOTO**, None; **K. YODA**, None; **M. YODA**, None; **S. YAMADA**, None; **H. GOTO**, None; **M. INABA**, None.

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Abstract Number: 2622

Serum RANKL Levels, Associate with Anti Citrullinated Proteins Antibodies (ACPA) in Early-Untreated Rheumatoid Arthritis and Is Modulated Following Methotrexate

Aase Haj Hensvold[1], Vijay Joshua[1], K. Lundberg[2], Nadine A. Defranoux[3], Saedis Saevarsdottir[4] and Anca I Catrina[2], [1]Rheumatology Unit, Department of Medicine, Solna, Karolinska Institute, Stockholm, Sweden, Stockholm, Sweden, [2]Rheumatology Unit, Department of Medicine, Karolinska Institutet, Stockholm, Sweden, [3]Crescendo Bioscience Inc., South San Francisco, CA, [4]Department of Medicine, Rheumatology Unit, The Karolinska Institute and Karolinska University Hospital, Stockholm, Sweden

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Background/Purpose:

Receptor Activator of Nuclear factor Kappa-b Ligand (RANKL) is a key regulator of bone metabolism. Anti-citrullinated (cit) protein antibodies (ACPA) have been suggested to cause bone destruction by osteoclast activation. We investigated the relationship between RANKL and ACPA in early-untreated rheumatoid arthritis (RA) patients.

Methods: Patients with newly diagnosed untreated RA (n=183) were analysed at baseline and 3 months after initiating methotrexate (MTX) treatment. Serum RANKL (total RANKL), ACPA (anti-CCP2) and ACPA specificities (anti cit-vimentin, anti cit-enolase and anti cit-fibrinogen) were determined by enzyme-linked immunosorbent assay (ELISA). Synovial RANKL expression was evaluated by immunohistochemistry in a subgroup of patients (N=15). The relationship between anti cit-vim antibodies and bone destruction was further validated in 1116 RA patients included in the EIRA cohort. Pearson’s Chi-Square test, Wilcoxon rank sum test, Wilcoxon signed rank test and linear regression models were used.

Results: Serum RANKL concentration was significantly higher ($p < 0.05$) in ACPA-positive (median: 689 pmol/L, IQR 342-1253) compared with ACPA-negative (median: 159 pmol/L, IQR 96-243) patients and this difference was also seen for synovial RANKL expression. Serum RANKL associated with ACPA and bone erosions in rheumatoid factor (RF) negative patients ($p < 0.05$). Among ACPA specificites, anti-cit-vim was associated with higher RANKL concentration and higher prevalence of bone erosion ($p < 0.05$). Significant reductions in both serum RANKL and ACPA levels were observed after 3 months of MTX treatment ($p < 0.05$).

Conclusion:

RANKL was elevated in ACPA-positive and in anti cit-vimentin positive early untreated RA patients and associated with bone erosions. These findings give further support for an early direct pathogenic link between ACPA and bone destruction in RA.

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Abstract Number: 2623

DAS28-ESR and DAS28-CRP Are Not Exchangeable in Daily Clinical Practice: Data from a Large Outpatient Cohort

Alexander Langer[1], Oliver Wiemann[2], Stephanie G. Werner[2], Felicitas Spiecker[3], Sabine Mettler[3], Gudrun Lind-Albrecht[2] and Hans-Eckhard Langer[4], [1]Department of Computer Science, RWTH Aachen University, Aachen, Germany, [2]RHIO (Rheumatology, Immunology, Osteology), Duesseldorf, Germany, [3]RHIO (Rheumatology, Immunology, Osteology) Duesseldorf, Duesseldorf, Germany, [4]RHIO (Rheumatology, Immunology, and Osteology), Duesseldorf, Germany
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Background/Purpose:

The original DAS28 is based on the erythrocyte sedimentation rate (ESR). An alternative formulation uses the C-reactive protein (CRP). Previous research[1,2,3] suggests that in comparison the DAS28-CRP underestimates disease activity, and therefore new thresholds[4,5] for levels of disease activity should be used. In this study, we compare the DAS28-ESR and DAS28-CRP data of patients from our outpatient center and derive a formula to convert between the two formulations.

Methods:

A total of 996 patients with RA (n=399, 307 female), PsA (n=356, 235 female) and undifferentiated arthritis (n=242, 176 female) were included in this retrospective study. A sub-cohort with early-arthritis (disease duration ≤ 2 years) includes 248 subjects (206 female) with a definite diagnosis of RA (n=200) or PsA (n=48). For each patient and each visit, the DAS28-ESR and the DAS28-CRP were computed. The mean, standard deviation and skewness were used to obtain a normalization formula to convert the DAS28-CRP scores via

$$\text{DAS28-conv} = 13.1 * (((\text{DAS28-CRP} - 2.53) * 1.15 + 2.91)^{0.2} - 1)$$

For 5254 individual DAS28 records, we computed the number of patients with remission, low, medium and high disease activity for the DAS28-BSG and the converted DAS28-CRP ("DAS28-conv") using the standard DAS28-ESR thresholds, and the number of patients in remission and with low disease activity using the cut-off-points for DAS28-CRP (<2.4, ≤ 2.9) suggested by Fleischmann et al[4].

Results:

The results are summarized in the following table (r/l/m/h = remission/low/medium/high disease activity)

cohort / n. entries	DAS28-ESR	DAS28-CRP	correlation	DAS28-conv	DAS28-ESR r/l/m/h	Fleischmann et al. cut-offs r/l	DAS28-conv r/l/m/h
all patients n=5254	2.91 ± 1.22	2.53 ± 1.06	0.89 p < 0.001	2.91 ± 1.31	2331/995/1652/276	2013/871	2292/813/1848/301
female n=4154	2.99 ± 1.89	2.57 ± 1.04	0.88 p < 0.001	2.97 ± 1.29	1697/819/1419/219	1482/691	1702/661/1559/232
male n=1100	2.58 ± 1.27	2.39 ± 1.10	0.89 p < 0.001	2.70 ±1.35	634/176/233/57	531/180	590/152/289/69
RA n=2285	3.04 ± 1.26	2.62 ± 1.12	0.90 p < 0.001	3.00 ± 1.36	911/453/760/161	830/340	941/328/848/168
PsA n=1467	2.93 ± 1.22	2.61 ± 1.06	0.89 p < 0.001	3.01 ± 1.29	659/270/459/79	531/232	605/223/550/89
undiff. arthritis n=1502	2.69 ± 1.12	2.33 ± 0.92	0.85 p < 0.001	2.67 ± 1.21	761/272/433/36	652/299	746/262/450/44
early arthritis n=3241	2.77 ± 1.14	2.41 ± 0.96	0.87 p < 0.001	2.77 ± 1.14	1560/632/941/108	1356/586	1540/538/1040/123

Conclusion:

Our data confirms earlier findings that the DAS28-CRP underestimates the disease activity. On the other hand, the new DAS28-CRP cut-off points of Fleischmann et al. seem to be too strict with significantly fewer patients in remission and low disease activity.

The data suggests that a normalization formula can be used to convert between the two formulations, resulting in higher classification agreement within our cohort. More research is needed to validate the formula against larger datasets.

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Disclosure: A. Langer, None; **O. Wiemann**, None; **S. G. Werner**, None; **F. Spiecker**, None; **S. Mettler**, None; **G. Lind-Albrecht**, None; **H. E. Langer**, None.

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Abstract Number: 2624

Preliminary Content Validation of the Patient Reported Outcomes Measurement Information System (PROMIS) Short Forms in People Living with Rheumatoid Arthritis

Anna Kristina Gutierrez[1], Michelle Jones[2], Susan J. Bartlett[1,3,4] and Clifton O. Bingham III[2], [1]Division of Rheumatology, Johns

Hopkins University, Baltimore, MD, [2]Johns Hopkins University, Baltimore, MD, [3]Division of Rheumatology, Johns Hopkins School of Medicine, Baltimore, MD, [4]Medicine , Divisions of Clinical Epidemiology, Rheumatology, Respirology, McGill University, Montreal, QC, Canada

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Background/Purpose: The process of patient reported outcome (PRO) validation requires demonstration that the concept being measured and the patient experience of the corresponding symptom or impact are aligned. The NIH Patient Reported Outcomes Measurement Information System (PROMIS) provides standardized measures across the illness continuum of domains of physical, mental, and social health. Whether items contained within PROMIS item banks and short forms (SF) are felt to be relevant to people living with rheumatoid arthritis (RA) has not been previously reported.

Methods: We administered surveys to RA patients (pts) seen for routine care in an academic rheumatology practice. Routine clinical (MD global, joint count, pt global, pain, and fatigue VAS) and demographic data were collected. Surveys included PROMIS SFs for Physical Function (PF) 20a; Pain Interference (PI) 8a, Fatigue 7a and 8a, Ability to Participate in Social Roles and Activities 8a (PSRA), and Depression 8a. Pts also completed the PROMIS Profile 29 v 2.0, which contains 4 item assessments for these domains. For each domain, patients rated the relevance of items within the SF to their disease experience and the importance of the symptom to their disease. We also queried how much patients were able to separate their overall symptom experience from that due to RA (e.g., "How much of your fatigue is due to your RA?"). Mean PROMIS T-scores were calculated.

Results: Fifty two pts (86.5% female, 88.5% Caucasian, 31% HS education or less) were surveyed with a mean (SD) age of 52.5 (13.5) yrs, disease duration of 14.7 (11.4) yrs, and CDAI 9.7 (15). PROMIS T-scores were similar using SF of different lengths, though the magnitude of difference was greatest for the PF measures. RA patients had worse PF, PI, and Fatigue that exceeded 0.4SD from the general population norm of 50 (Table 1). More than 60% of respondents reported that the SF items in a domain completely or mostly reflected their experience due to their RA. For PF and PSRA almost half of patients considered *both* their symptom in general and their symptom due to RA when answering items (55.8 and 48.1%). When answering items on PI, 51.9% were thinking only of their RA. However, most (>88 %) would not have responded differently to the questions if instead asked "due to their RA". Most patients attribute problems with PF and PI to their RA, but not problems with sleep, emotional health, or PSRA. Most patients (>75%) considered all domains very important. Almost all (>85%) did not feel that additional questions needed to be asked regarding these symptoms.

Conclusion: These results provide preliminary evidence of the content validity in terms of importance and relevance of selected PROMIS domains and SF items from the perspective of people living with RA. Additional studies in a broader group of pts are needed.

Table 1. PROMIS short form T-scores for each domain.

Domain/Symptom	Short Form		
Physical Function (PF)	**4a**	**20a**	
	43.9 (10.2)	41.9 (11.5)	
Pain Interference (PI)	**4a**	**8a**	
	56.3 (9.8)	55.9 (9.9)	
Fatigue	**4a**	**7a**	**8a**
	54.1 (13.4)	54.5 (11.3)	54.5 (13.5)
Ability to Participate in Social Roles and Activities (PSRA)	**4a**	**8a**	
	48.9 (10.5)	48.8 (11.1)	
Depression	**4a**	**8a**	
	51.1 (10.7)	50.2 (11.5)	
Anxiety 4a	50.3 (10.5)		
Sleep 4a	51.4 (9.8)		
Legacy PROs	**Mean (SD)**		
Patient Global VAS	34 (29.9)		
Pain VAS	3.8 (3.5)		
Fatigue VAS	4.5 (4)		

Disclosure: A. K. Gutierrez, None; **M. Jones**, None; **S. J. Bartlett**, PCORI, 2; **C. O. Bingham III**, NIH, 2,PCORI, 2.

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reported-outcomes-measurement-information-system-promis-short-forms-in-people-living-with-rheumatoid-arthritis

Abstract Number: 2625

SDAI 50 Is More Stringent Than the EULAR Response Measure and a Better Predictor of Low Disease State/Remission in Early Rheumatoid Arthritis: Results from an Early Arthritis Cohort

Mohammed Omair[1], Edward C. Keystone[2], VP Bykerk[3], Boulos Haraoui[4], Gilles Boire[5], J Carter Thorne[3], Janet E. Pope[6], Daming Lin[7], Carol Hitchon[8] and **Pooneh S.Akhavan**[9], [1]Rheumatology, Mount Sinai hospital, Toronto, ON, Canada, [2]University of Toronto/Rebecca MacDonald Centre for Arthritis and Autoimmune Disease, Toronto, ON, Canada, [3]University of Toronto, Toronto, ON, Canada, [4]Institut de Rhumatologie de Montréal and University of Montreal, Montreal, QC, Canada, [5]Department of Medicine/Division of Rheumatology, Université de Sherbrooke, Sherbrooke, QC, Canada, [6]St. Joseph's Health Care, London, ON, Canada, [7]mount Sinai Hospital, Toronto, ON, Canada, [8]University of Manitoba, Winnipeg, MB, Canada, [9]mount sinai hospital, Toronto, ON, Canada

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SESSION INFORMATION

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Session Title: Rheumatoid Arthritis - Clinical Aspects Poster Session III
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Background/Purpose:

To compare the sensitivity of the EULAR and SDAI50 response measures (RMs) and their impact on future response to treatment in patients with early rheumatoid arthritis (RA).

Methods: Biologic naïve RA patients from the Canadian early ArThritis CoHort (CATCH) who had baseline, 3 and 6 months complete data were evaluated. Kappa statistics & Spearman correlation were used to assess the correlation between the EULAR and SDAI50 RMs. The RMs at 3 months were also compared for their ability to predict low disease state (LDAS) or remission (REM) at 6months.

Results: A total of 419 patients were evaluated. Of those, 198 (47.2%) and 206 (49.1%) patients failed to achieve a EULAR and SDAI50 RMs respectively. A strong correlation was observed between the EULAR and SDAI50 RMs with a Kappa of 0.66 (95% CI 0.58- 0.73) and Spearman coefficient of 0.66 ($p < 0.0001$). Throughout the range of disease activity, the SDAI50 response was shown to be more stringent than the EULAR response. Multivariate linear regression analysis demonstrated that SDAI50 at 3 months had a more significant impact on achieving low disease state or remission at 6 months compare to the EULAR response.

Conclusion: Our results suggest there is a strong overall correlation between the EULAR and SDAI50 RMs however a minority of patients can be identified with discordant RMs at the two ends of disease activity spectrum at baseline. Nevertheless the SDAI response at 3 month was a better predictor of outcomes at 6 months than the EULAR response.

Disclosure: M. Omair, Pfizer Inc, 2,Roche Pharmaceuticals, 9,newbridge, 9,Bristol-Myers Squibb, 9; **E. C. Keystone**, Janssen Inc., 2,Abbott/AbbVie, 5,Amgen, 2,Bristol-Myers Squibb, 5,Janssen Inc., 5,Hoffmann-La Roche, Inc., 5,Janssen Inc., 2,Janssen Inc., 5,Merck Pharmaceuticals, 5,Merck Pharmaceuticals, 5,Pfizer Pharmaceuticals, 5,Pfizer Pharmaceuticals, 5; **V. Bykerk**, None; **B. Haraoui**, Abbott, Amgen, BMS, Janssen, Pfizer, Roche and UCB Pharma, 2,Abbott, Amgen, BMS, Janssen, Pfizer, Roche and UCB Pharma, 5,Abbott, Amgen, BMS, Janssen, Pfizer, Roche and UCB Pharma, 8; **G. Boire**, None; **J. C. Thorne**, Amgen, Canada, 5; **J. E. Pope**, None; **D. Lin**, None; **C. Hitchon**, None; **P. S.Akhavan**, None.

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Abstract Number: 2626

Disease Activity Predicts ABCB1 and ABCG2 Drug-Efflux Transporters Function in Rheumatoid Arthritis (RA) Patients

Yemil Atisha-Fregoso[1], Guadualupe Lima[2], Virginia Pascual-Ramos[3], Juan Jakez-Ocampo[4], Hilda Fragoso-Loyo[5], Miguel Baños[6],

Luis Llorente[7] and Irazú Contreras-Yáñez[8], [1]Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubiran, Mexico City, Mexico, [2]Immunology and Rheumatology, Instituto Nacional de Ciencias Medicas y Nutricion, Mexico City, Mexico, [3]Mexican Accreditation Council of Rheumatology, A.C., Mexico City, Mexico, [4]Immunology and Rheumatology, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, México, Mexico, [5]Vasco de Quiroga 15 Col Seccio, INNCMSZ-Departamento de Inmunología y Reumato, Mexico, Mexico, [6]Immunology and Rheumatology, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico, Mexico, [7]Immunology and Rheumatology, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico, [8]Inmunología y Reumatología, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico
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Background/Purpose: ABCB1 (P-gp) and ABCG2 (BCRP1) are part of the adenine triphosphate (ATP)-binding cassette transporter proteins. These proteins can modulate inflammatory responses and mediate efflux of drugs from cells. Several disease modifying anti-rheumatic drugs are among the substrates of ABC transporters.

The objectives of this study were to compare drug efflux function of ABCB1 and ABCG2 transporters in patients with active and inactive RA and investigate the impact of disease activity and treatment on transporter function.

Methods: Seventeen patients with RA (ACR/EULAR criteria) active (DAS28 ≥3.2 at study inclusion) and 17 with inactive RA (DAS28<2.6) were selected from the Early Arthritis Clinic (Dec 2013-January 2015). Patients were paired according to age, gender and disease duration. All patients had medical evaluation and serum sample at study inclusion. Furthermore, 27 of them had an additional sample and clinical evaluation after six-months.

ABCB1 and ABCG2 functional activity was measured in peripheral mononuclear cells by flow cytometry. The percentage of cells able to extrude substrates for ABCB1 (daunorubicin) and ABCG2 (mitoxantrone) were recorded in the presence or absence of the selective ABCB1 (verapamil) or ABCG2 (KO143) inhibitors. Efflux activity was defined as a percentage greater than the mean in 30 healthy controls plus two standard deviations, i.e. 1.67% (range 0.26% to 1.98%).

The study was approved by our internal review board. All patients signed informed consent.

Statistical analysis. Appropriate tests were used according to variable distribution and linear regression model to establish the association between disease activity and transporter´s function.

Results:

Data from 34 patients (94.1% women) were analyzed. Mean ± SD age: 41.6 ± 11 years, disease duration was 6.3 ± 3.5 years; patients with active disease (DAS28: 4.8 ± 1.3) had significantly higher baseline and cumulative corticosteroids doses than inactive patients (DAS28: 1.2 ± 0.6): 10.1±5 vs. 6.3±2.1 mg/day, p=0.03 and 4041±1849 vs. 2348.5±859.5 mg, p=0.004, respectively. No other remarkable differences were seen.

Active patients had higher ABCB1 activity, median (25-75 IQR): 7.1% (1.4-29.3) vs. 1.6% (0.7-3.5); p=0.02 and ABCG2 activity: 6.2% (1.3-22.4) vs. 1.3% (0.7-2); p=0.007.

The ABCB1 and ABCG2 activity correlated with DAS28: rho=0.45, p=0.008 for ABCB1 and rho=0.52, p=0.002, for ABCG2. No correlation was found with cumulative corticosteroids or other treatment.

Linear regression model applied to the 34 patients at baseline showed DAS28 as the only predictor of both ABCB1 (beta coefficient: 0.50; 95%CI: 1.6-6.7; p=0.002; R2=0.23) and ABCG2 (beta coefficient: 0.48; 95CI%: 1.4-6.8; p=0.004; R2=0.21) function.

Disease activity increased in 14.8% of the patients at 6 month follow-up, while 48.1% remained stable and 37.1% improved. DAS28 changes at this time correlated with shift in ABCB1 (r=0.35, p=0.07) and ABCG2 (r=0.33, p=0.09) function.

Conclusion:

Patients with active RA have a higher efflux function of ABCB1 and ABCG2 compared with those in remission at baseline. ABCB1 and ABCG2 behavior is conditioned by disease activity.

Abstract Number: 2627

Does 14-3-3 ETA Protein Offer Any Additional Diagnostic Value in Rheumatoid Arthritis?

Andrew Vasconcellos[1], Seema Chittalae[2] and Petros Efthimiou[3], [1]Methodist, New York Methodist Hospital, Brooklyn, NY, [2]Medicine, New York Methodist Hospital, Brooklyn, NY, [3]Med/Rheumatology, New York Methodist Hospital/Weill Cornell Medical College Affiliate, Brooklyn, NY

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Background/Purpose:

Serum 14-3-3 eta has been described to have diagnostic utility and in established RA an association has been established between the levels of this marker and the degree of joint damage. The η isoform of 14-3-3 is expressed extracellularly in much higher concentration than the ϒ isoform or MMP 1 and 3 levels in the synovial fluid and serum of patients with rheumatoid arthritis compared to the normal population. Rheumatoid factor (RF) is known to be sensitive and anti-CCP highly specific for RA, but a high number of patients remain seronegative .There is a need for a biomarker to prevent underdiagnosis in this subset.

The purpose of the study was to investigate if serum 14-3-3 η enhanced the detection of RA over RF or anti-CCP in RA patients. We also studied the utility of 14-3-3 eta as a diagnostic test by comparing presence of this protein in RA v/s non-RA patients.

Methods:

A retrospective chart review study was conducted in RA patients at an outpatient rheumatology clinic in an inner city population at a community teaching hospital serving a large immigrant population. 90 RA patients were identified who satisfied the 2010 ACR diagnostic criteria and 37 non RA patients seen in the clinic for other rheumatologic conditions were chosen as the control group. Serum 14-3-3η protein was measured by ELISA. The positive threshold range using Quest Diagnostic for RF was 15 International Unit/ml, Anti CCP was 20 Units and for 14-3-3 eta was 0.2 ng/mL. The chi-square goodness-of-fit test was used to analyze the frequency of eta positivity in the RA population while kappa was calculated to compare the RA and non RA patients.

Results:

Of the 90 RA patients, 75.8 % were females and mean age was 58 (range 28- 90) years. The population was predominantly Hispanic (75%). In the non-RA group, 9% had psoriatic arthritis and 14% lupus, 73% were females, 76% Hispanic and the mean age was 54 (range 19-93) years. In the non-RA population, 22 patients were ETA positive, of these 11 patients were also RF positive and 9 were ACPA positive. In the RA population, 1 RF negative patient was ETA positive, while 47 patients were both ETA and RF positive. Further 1 patient was found to be ETA positive with a negative ACPA, while 47 patient's were both ETA and ACPA positive.

Table I: Non-Rheumatoid Arthritis Patients

	ETA Negative		ETA Positive		
Variable	N	%	N	%	Chi-sq test
Gender					
male	5	[18.5]	6	[55]	0.0377
female	22	[81.5]	5	[45]	
Race					
hispanic	21	[77.8]	8	[72.7]	1
not hispanic	6	[22.2]	3	[27.3]	
RF					
0	25	[92.6]	0	[0]	6.48E-008
1	2	[7.41]	11	[100]	
ACPA					
0	24	[88.9]	2	[18.2]	6.09E-005
1	3	[11.1]	9	[81.8]	

Table II: Rheumatoid Arthritis Patients

	ETA Negative		ETA Positive		
Variable	N	%	N	%	Chi-sq test
Gender					
male	6	[14.3]	15	[31.2]	0.0804
female	36	[85.7]	33	[68.8]	
RACE					
hispanic	29	[69]	38	[79.2]	0.336
not hispanic	13	[31]	10	[20.8]	
RF					
0	25	[59.5]	1	[2.08]	4.27E-010
1	17	[40.5]	47	[97.9]	
ACPA					
0	21	[50]	1	[2.08]	0.00E+000
1	21	[50]	47	[97.9]	

Conclusion:

In our population, measurement of 14-3-3η ETA offered limited additional diagnostic value when compared to RF and ACPA. Furthermore, it was found to offer no additional value in differentiating RA from other inflammatory arthropathies where RF can also be found positive.

Disclosure: A. Vasconcellos, None; **S. Chittalae**, None; **P. Efthimiou**, Crescendo Bioscience, 5.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/does-14-3-3-eta-protein-offer-any-additional-diagnostic-value-in-rheumatoid-arthritis

Abstract Number: 2628

Identifying Anxiety and Depression Among Rheumatoid Arthritis Patients Using the Multidimensional Health Assessment Questionnaire

Naoto Yokogawa[1], Tetsuji Kaneko[2], Yoshiki Nagai[1], Takahiro Nunokawa[3], Toshioki Sawaki[3], Katsuaki Shiroto[3], Kota Shimada[3] and Shoji Sugii[3], [1]Department of Rheumatic Diseases, Tokyo Metropolitan Tama Medical Center, Tokyo, Japan, [2]Division of Clinical Research Support Center, Tokyo Metropolitan Children's Medical Center, Fuchu, Japan, [3]Department of Rheumatic Diseases, Tokyo Metropolitan Tama Medical Center, Fuchu, Japan

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Background/Purpose:

The Multidimensional Health Assessment Questionnaire (MDHAQ) was designed to assess quality of life impairment including psychological distress in rheumatoid arthritis (RA) patients. In addition to ten questions addressing the patient's physical activity (Q1-10), MDHAQ also includes the following three questions (4-point scale: 0, 1, 2, and 3), which address the psychological state of the patient: "Get a good night's sleep?"(Q11), "Deal with feelings of anxiety or being nervous?"(Q12), and "Deal with feelings of depression or feeling blue?"(Q13). The utility of these questions has yet to be investigated.

The purpose of the study is to identify RA patients suffering from anxiety and depression using MDHAQ in daily clinical practice

Methods:

A previously validated Japanese version of MDHAQ was used in this study [1]. Hospital Anxiety and Depression Scale (HADS) was used to detect RA patients suffering from anxiety and depression. The validation of MDHAQ (Q11, Q12, and Q13) included test-retest reliability, content validity, and concurrent validity.

Results:

A total of 348 patients were included in this study. Mean (SD) age and disease duration in the validation study population were 65.2 (12.1) years and 11.4 (10.5) years, respectively.

The proportion of cases with possible anxiety (HADS-Anxiety (HADS-A) ≥8) and probable anxiety (HADS-A ≥11) was 7.9% and 21.4%, respectively, whereas the proportion of cases with possible depression (HADS-Depression (HADS-D) ≥8) and probable depression (HADS-D ≥11) was 7.9% and 24.7%, respectively.

The test-retest reliability of Q11, Q12, and Q13 (50 patients) was 0.730, 0.757, and 0.708 (Spearman's rank correlation coefficient), respectively. The internal reliability of Q11, Q12, and Q13 was 0.930, 0.628, and 0.680 (Chronbach's α), respectively. The correlation between Q11 and 12, Q11 and 13, and Q12 and 13 was 0.503, 0.463, and 0.891 (Spearman's rank correlation coefficient), respectively. The correlation between Q12 and HADS-A, and Q13 and HADS-D was 0.557 and 0.420 (Spearman's rank correlation coefficient), respectively.

In screening for patients with probable anxiety, Q12 ≥1 showed a sensitivity of 82.6 % and a specificity of 40.6% while Q12 ≥2 showed a sensitivity of 21.7% and a specificity of 98.6%. In screening for cases with probable depression, Q13 ≥1 showed a sensitivity of 62.5% and a specificity of 68.7% while Q13 ≥2 showed a sensitivity of 8.3% and a specificity of 97.9%. Among the 7 ACR Core Data Set measures, all 3 patient-reported outcomes (patient global assessment, pain VAS, and HAQ) and tender joint counts were significantly worse in patients with Q13 ≥1 than in patients with Q13=0 but other 3 ACR Core Data Set measures (swollen joint count, physician global assessment, and acute phase reactants) were similar for both groups.

Conclusion:

MDHAQ was found to be suitable for use in daily practice for identifying RA patients with probable anxiety and depression.

Reference:

[1] Yokogawa N, et al. Validation of RAPID3 using a Japanese version of Multidimensional Health Assessment Questionnaire with Japanese rheumatoid arthritis patients: characteristics of RAPID3 compared to DAS28 and CDAI. Mod Rheumatol 2015;25(2):264-9.

Disclosure: N. Yokogawa, None; **T. Kaneko**, None; **Y. Nagai**, None; **T. Nunokawa**, None; **T. Sawaki**, None; **K. Shiroto**, None; **K. Shimada**, None; **S. Sugii**, None.

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Abstract Number: 2629

The Most Frequent Fears and Beliefs of 226 Patients with Rheumatoid Arthritis or Spondyloarthritis, Using a Novel Questionnaire

Laure Gossec[1,2], Pierre Chauvin[3,4], Christophe Hudry[5], Florence Mathoret-Philibert[6], Maud Poussière[7], Thibault de Chalus[8], Francoise Russo-Marie[9], Jean-Michel Joubert[8], Alain Saraux[10] and Francis Berenbaum[1,11], [1]Rheumatology Department, Sorbonne Universités, Université Pierre et Marie Curie, Paris, France, [2]Rheumatology Department, AP-HP, Hôpital Pitié Salpêtrière, Paris,

France, [3]Department of Social Epidemiology, Sorbonne Universités, Université Pierre et Marie Curie, Paris, France, [4]Department of Social Epidemiology, Pierre Louis Institute of Epidemiology and Public Health, Paris, France, [5]Rheumatology, AP-HP, Hôpital Cochin, Paris, France, [6]Clinical Psychology Department, AP-HP, Hôpital Cochin, Paris, France, [7]Independent Researcher, Paris, France, [8]UCB Pharma, Colombes, France, [9]Arthritis Foundation Courtin, Neuilly-sur-Seine, France, [10]Rheumatology Department, CHU de la Cavale Blanche, Brest Cedex, France, [11]Rheumatology Department, AP-HP, Hôpital Saint-Antoine, Paris, France
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Background/Purpose: Patients with chronic inflammatory disorders such as rheumatoid arthritis (RA) or spondyloarthritis (SpA) create personal sets of fears and beliefs related to their disease. These fears and beliefs may influence the patient-physician relationship and potentially treatment adherence. Little is known about these fears and beliefs in the era of biologics.[1] The purpose of this study was to describe the most frequent fears and beliefs in RA and SpA patients.

Methods: These analyses used cross-sectional assessment of unselected patients with a diagnosis of RA (ACR/EULAR criteria) or axial SpA (axSpA)(ASAS criteria) in France in 2014. The study was proposed to all rheumatologists in France and consecutive patients recruited through the first 51 rheumatologists agreeing to participate. A self-reported 44-item questionnaire (25 items on fears, 19 on beliefs) was built and preliminarily validated for this study. Each item was scored 0–10 (10 indicating higher fears/beliefs).[2] The analysis was descriptive for the 5 fears and the 5 beliefs, most frequently scored as ≥7/10, in both RA and axSpA patients.

Results: Overall, 226 patients (161 RA and 65 axSpA; 64.4% female) were analyzed: patients had a mean disease duration of 11.9 vs 13.8 years and mean patient global assessment was 31/100 vs 41/100 for RA vs axSpA patients, respectively. Of 25 fear items, the 6 most frequently-reported fears were: “afraid of suffering again” (66.7% scored this as ≥7/10), “afraid of losing control and autonomy” (61.4%), “afraid of being a burden for relatives” (59.6%), “afraid of losing all joint mobility” (58.9%), “afraid of the spread of the disease to other joints” (58.6%) and “afraid of the consequences of my disease on my professional activity” (58.6%). Of 19 belief items, the 5 most frequently-reported beliefs were: “flares are triggered by fatigue” (41.7%), “physical activity reduces flares” (38.7%), “flares are triggered by changes in the weather” (37.3%), “flares are triggered by physical effort” (37.1%) and “the disease is linked to a genetic cause” (36.9%).

Conclusion: This study highlights the main fears and beliefs from a patient perspective using a novel questionnaire specific for chronic inflammatory arthritis. Consistent work needs to be performed to better document the effect of these fears and beliefs on adherence, disease care and progression.

References:

1. Gossec L. Rheumatology 2014;53(7):1274–8;

2. Berenbaum F. PLoS ONE 2014;9(12) [Epub]

Disclosure: L. Gossec, None; **P. Chauvin**, UCB Pharma, 5; **C. Hudry**, None; **F. Mathoret-Philibert**, None; **M. Poussière**, None; **T. de Chalus**, UCB Pharma, 3; **F. Russo-Marie**, None; **J. M. Joubert**, UCB Pharma, 3; **A. Saraux**, None; **F. Berenbaum**, None.

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Abstract Number: 2630

Rheumatoid Arthritis Patients with Carotid Plaque: 10-Year Follow-up

Raymundo Vera-Pineda[1], Alberto Cardenas-de La Garza[2], Dionicio A. Galarza-Delgado[2], Jose Ramon Azpiri-Lopez[3], Iris J. Colunga-Pedraza[2], Jorge Munoz De Hoyos[2], Griselda Serna-Peña[4], Brenda B Tovar-Jasso[2], Mario Alberto Garza-Elizondo[2] and Gerardo Ornelas[5], [1]Cardiology., Hospital Universitario, UANL., Monterrey, Mexico, [2]Rheumatology, Hospital Universitario, UANL., Monterrey, Mexico, [3]Cardiology, Hospital Universitario, UANL., Monterrey, Mexico, [4]Internal Medicine, Hospital Universitario, UANL., Monterrey, Mexico, [5]Radiology, Hospital Universitario, UANL., Monterrey, Mexico
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Background/Purpose:

The main cause of mortality in patients with rheumatoid arthritis (RA) is atherosclerotic cardiovascular disease (ASCVD). RA patients have a 10-year decrease in life expectancy when compared to healthy controls. Reports of ASCVD outcomes in Hispanic RA patients is scarce. The objective of the present study is to determine the mortality of a Hispanic RA cohort followed for a 10-year period, and its relation to the presence of carotid plaque (CP) after initial carotid ultrasound evaluation.

Methods:

An observational, longitudinal, descriptive study was designed based on a cohort that included 124 Hispanic patients with RA who fulfilled the ACR 1987 classification criteria. A telephonic questionnaire was applied to the subjects or family members to determine ASCVD-related mortality and new onset of comorbidities (hypertension, diabetes, dyslipidemia, acute myocardial infarction, stroke, arrhythmias, heart failure, angina, and chronic kidney disease). A descriptive analysis of current and past comorbidities was carried out. Survival analysis was performed with Kaplan-Meier curves. Log-Rank test was used to compare between patients with and without carotid plaque (CP), considering statistically significant a difference in mortality if a value of $p<.05$ was obtained.

Results:

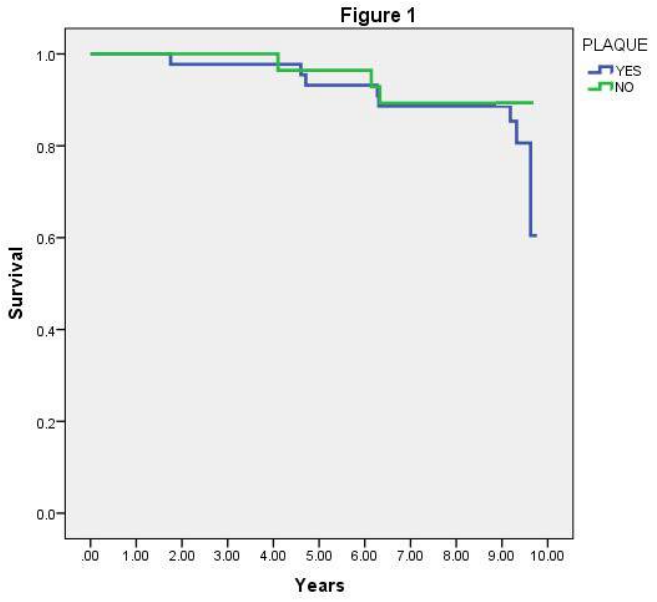
The original cohort included 124 subjects of which 52 were lost to follow-up. A total of 72 patients were included in the analysis (Table 1). CP was present in 44 (61.11%) of the patients. Of the 72 patients, 11 (15.3%) had died: 7 (9.7%) of them due to ASCVD (4 myocardial infarctions, 2 strokes, 1 heart failure), 2 of non-cardiovascular causes and 2 in traffic accidents. Diabetes mellitus type 2 was diagnosed in 6 (10.6%) of the remaining patients, hypertension in 24 (39.34%) and dyslipidemia in 12 (25%). Only 1 patient had a non-lethal myocardial infarction. In the CP group, 8 (18%) had died against 3 (10.7%) of the patients without CP (Figure 1). The majority of ASCVD-related deaths occurred in patients with CP, although there was no difference in mortality (p=.373).

Conclusion:

ASCVD was the most frequent cause of death in this cohort. In a 10-year period, there was no difference in mortality in RA in relation to the presence of CP. Prospective studies with a greater sample are necessary to corroborate this finding.

Table 1. Demographical data at baseline. Comorbidities at baseline and at follow up

Feminine, n (%)	68 (94.4)
Age (yo), mean ± SD	55.35 ± 11.99
Duration of disease (yo), mean ± SD	11.87 ± 9.92
Carotid Plaque at baseline, n (%)	44 (61.11)
Diabetes mellitus type 2 at baseline, n (%)	12 (16.7)
Hypertension at baseline, n (%)	6 (8.3)
Dyslipidemia at baseline, n (%)	12 (16.7)
Current smoking at baseline, n (%)	29 (40.3)
ESR at baseline, mean ± SD	26.09 ± 11.17
Total cholesterol at baseline (mg/dl), mean ± SD	191.4 ± 35.7
HDL cholesterol at baseline (mg/dl), mean ± SD	55.6 ± 12.9
Prevalence of CP at baseline, n (%)	44 (61.1)
Type 2 Diabetes mellitus at follow up, n (%)	6 (10.16)
Hypertension at follow up, n (%)	24 (39.34)
Dyslipidemia at follow up, n (%)	12 (25)



Disclosure: **R. Vera-Pineda**, None; **A. Cardenas-de La Garza**, None; **D. A. Galarza-Delgado**, None; **J. R. Azpiri-Lopez**, None; **I. J. Colunga-Pedraza**, None; **J. Munoz De Hoyos**, None; **G. Serna-Peña**, None; **B. B. Tovar-Jasso**, None; **M. A. Garza-Elizondo**, None; **G. Ornelas**, None.

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Abstract Number: 2631

Rheumatologists More Likely to Perform Tobacco Cessation Counselling in Uncontrolled Rheumatoid Arthritis Visits

Andrew Vreede[1], Katya Voelker[2], Joanna Wong[3] and **Christie M. Bartels**[4], [1]Internal Medicine, University of Wisconsin Hospitals and Clinics, Madison, WI, [2]University of Wisconsin School of Medicine and Public Health, Madison, WI, [3]Tufts School of Medicine, Boston, MA, [4]Medicine, Rheumatology, University of Wisconsin School of Medicine and Public Health, Madison, WI
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Background/Purpose: Tobacco use is a risk factor for developing rheumatoid arthritis (RA) and a predictor of more severe disease and heightened cardiovascular disease (CVD) risk. Despite these known health effects, there is significant variation in rheumatologists performing tobacco cessation counseling. Herein we examine the frequency and predictors of tobacco discussions in RA visits among a cohort of RA patients with at least one additional CVD risk factor. We hypothesized that tobacco cessation counseling would occur more frequently in patients with well-controlled RA due to fewer competing demands for clinical time.

Methods: Electronic health records were used to identify RA patients with either high cholesterol or uncontrolled blood pressure in 3 rheumatology clinics (2004-2011) within an academic center for a prior study. Uncontrolled cholesterol was defined as LDL >100 in individuals with diabetes, CVD or chronic kidney disease or LDL>130 without one of these conditions. Uncontrolled blood pressure was defined according to JNC-7. Trained abstractors reviewed clinic notes using a standardized tool to identify CVD risk discussions including tobacco counselling, and to assess perceived RA control. Perceived RA control was defined as subjectively stated by a rheumatologist in the visit note. We used logistic regression to calculate the odds ratios (OR) and 95% confidence intervals reflecting RA control as a predictor of tobacco cessation counseling after controlling for sociodemographics, comorbidity (ACG score) and clinic.

Results: 3707 RA visits were abstracted, of which 360 visits involved active tobacco users. RA tobacco users had a mean age of 53 years, 73% were female, 79% white and BMI of 29 ± 7 (mean ± SD). Physician-perceived well-controlled RA was present in 31% of

tobacco user visits (42% of non-user). Of the 360 visits, documentation of smoking status occurred in 43% of visit notes. Counseling was only documented in 10% of total visits (n=37). In contrast to our hypothesis, patients with well-controlled RA were less likely to receive tobacco cessation counseling (OR 0.25, 0.09-0.68; Table 1). Obese BMI was an additional negative univariate predictor. Positive univariate predictors of tobacco cessation counseling included CVD, pulmonary disease, hypertension, or anxiety-depression at baseline. In a multivariate model RA control remained significant, as did pulmonary disease, and obesity. Limitations of our study include small size and reliance upon physician documentation for occurrence of counseling events.

Conclusion: Perceived uncontrolled RA predicted more likely tobacco cessation counseling by rheumatologists, but overall rates were low. Given the clear negative health effects of smoking on patient's RA disease severity and CVD risk, systematic efforts are needed to employ evidence based practices for promoting tobacco in rheumatology clinics.

Table 1: Univariate & multivariate predictors of tobacco counseling (n=360 visits)

	OR	95% CI	p
Univariate			
RA Control	0.4	0.1-0.9	0.022*
Age: 40-59yo (18-39 Ref)	1.5	0.2-11.5	0.35
>59yo	2.2	0.3-18.1	0.47
Sex: Female	1.2	0.5-2.5	0.734
Race: Black (White Ref)	0.3	0.1-1.1	0.06
Other	1.5	0.3-7.3	0.6
Language: Non-English	0.4	0.1-2.6	0.31
Non-Married	0.5	0.2-1.3	0.17
Medicaid (ever)	0.8	0.4-1.7	0.57
BMI Underweight (Normal Ref)	1.6	0.4-5.6	0.49
BMI Overweight	0.9	0.3-2.1	0.36
BMI Obese	0.4	0.1-0.9	0.02*
ACG Middle Tertile (Lowest Ref)	0.6	0.3	0.23
Highest Tertile	0.6	0.2	0.24
Cardiovascular disease**	2.8	1.3-6.2	0.009*
Diabetes mellitus	1.6	0.7-3.7	0.29
Hyperlipidemia	1.2	0.6-2.5	0.69
Hypertension	2.8	1.4-5.8	0.02*
Pulmonary disease	3.5	2.7-18.9	<0.001*
Anxiety/Depression	2.4	1.2-5.0	0.02*
Multivariate Model			
RA Control	0.3	0.1-1.0	0.04*
Pulmonary disease	5.0	1.7-14.4	0.003*
BMI Underweight	0.6	0.2-2.5	0.53
BMI Overweight	0.5	0.1-1.8	0.29
BMI Obese	0.3	0.1-0.9	0.04*

*p <0.05 ** CVD includes CHF, PVD TIA/Stroke, Ischemic Heart Disease

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Development and Validation of a Questionnaire Assessing the Fears and Beliefs of Patients Suffering from Chronic Rheumatic Diseases

Laure Gossec[1,2], Alain Saraux[3], Christophe Hudry[4], Florence Mathoret-Philibert[5], Maud Poussière[6], Thibault de Chalus[7], Francoise Russo-Marie[8], Jean-Michel Joubert[7], Pierre Chauvin[9] and Francis Berenbaum[1,10], [1]Rheumatology Department, Sorbonne Universités, Université Pierre et Marie Curie, Paris, France, [2]Rheumatology Department, AP-HP, Hôpital Pitié Salpêtrière, Paris, France, [3]Rheumatology Department, CHU de la Cavale Blanche, Brest Cedex, France, [4]Rheumatology, AP-HP, Hôpital Cochin, Paris, France, [5]Clinical Psychology Department, AP-HP, Hôpital Cochin, Paris, France, [6]Independent Researcher, Paris, France, [7]UCB Pharma, Colombes, France, [8]Arthritis Foundation Courtin, Neuilly-sur-Seine, France, [9]Department of Social Epidemiology, Sorbonne Universités, Université Pierre et Marie Curie, Paris, France, [10]Rheumatology Department, Hôpital Saint-Antoine, Paris, France

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Background/Purpose: Questionnaires assessing the beliefs of patients with chronic rheumatic diseases mainly focus on medications.[1] A validated questionnaire evaluating patients' fears and beliefs towards their disease and therapeutic strategy could improve specific counseling and educational programs. The purpose of this study was to develop and validate a patient-reported questionnaire to assess the fears and beliefs of patients suffering from rheumatoid arthritis (RA) or spondyloarthritis (SpA).

Methods: Step 1: qualitative research (individual patient interviews: 25 RA, 25 axial SpA [axSpA]).[2] Step 2: all fears and beliefs appearing in more than 10% of interviews rephrased as questions by an expert group including a patient-partner. Each question scored 0–10 (10=higher fears/beliefs). Step 3: preliminary questionnaire tested by cognitive debriefing (5 RA and 5 axSpA patients), and reproducibility through a test-retest procedure among 28 patients (13 RA, 15 axSpA). Step 4: psychometric validation through a cross-sectional study of 226 patients. Internal consistency assessed by Cronbach's alpha, principal components analysis and descending hierarchical classification. Step 5: scoring results: descriptive presentation of the number of patients with scores ≥7/10, for ≥50% of the questions for a given domain, based on the psychometric validation.[3]

Results: Steps 1–3: development and adaptation of a self-reported 44-item questionnaire on a 0–10 scale of fears and beliefs. Step 4: in the study of 226 patients (161 RA, 65 axSpA), mean DAS28 was 2.5/10 (RA patients) and the mean BASDAI was 25.9/100 (axSpA patients). Based on the psychometric validation, the following domains were identified: fears of the disease progression or consequences (18 items), fears about treatment (5), beliefs related to: psychological influence (2), genetic influence (2), physical influence (4), diet influence (4), lifestyle (3) and diverse opinions (4). Step 5: the 3 domains with the highest number of patients with scores ≥7/10, for ≥50% of the questions for a given domain were: fears of the disease progression or consequences (55.3%), beliefs related to psychological influence (48.2%) and fears about treatment (46.9%).

Conclusion: This analysis indicates the internal consistency of the questionnaire developed. The questionnaire and the scoring results by domain should help physicians to better understand their patients' perceptions of their disease, thus improving the patient-physician dialogue and eventually leading to a better adherence to treatment.

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Abstract Number: 2633

Association of Medication Beliefs, Self-Efficacy, and Adherence in a Diverse Cohort of Adults with Rheumatoid Arthritis

Caroline McCulley[1], Patricia P. Katz[2], Laura Trupin[2], Edward H. Yelin[3] and Jennifer Barton[4,5], [1]Internal Medicine, Providence Portland Medical Center, Portland, OR, [2]Rheumatology, UCSF, SF, CA, [3]University of California, San Francisco, San Francisco, CA, [4]Rheumatology, OHSU, Portland, OR, [5]Rheumatology, VA Portland Healthcare System, Portland, OR
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Background/Purpose:

Adherence to disease-modifying anti-rheumatic drugs (DMARDs) among rheumatoid arthritis (RA) patients ranges from 30% to 107%, leading to potential adverse outcomes. Patient beliefs about medications and self-efficacy have been associated with decision-making and adherence. The aim of this study was to assess the association among medication beliefs, self-efficacy, and adherence to oral DMARDs among diverse populations with RA.

Methods:

Data were derived from RA patients enrolled in a longitudinal observational cohort (Rheumatoid Arthritis Outcomes Study; RAOS). Subjects completed a telephone interview in 2012-2013 in English or Spanish that included measures of self-reported adherence (missing ≥1 dose in past week was considered to be poor adherence) and the Beliefs about Medicine Questionnaire (BMQ). The BMQ consists of two 5-question subscales (specific necessity scale and specific concerns scale), which are scored from 1 to 5 (agree strongly to disagree strongly), summed and averaged. Higher scores indicate greater belief in medication necessity or stronger concerns (e.g., beliefs about potential long-term effects of taking medication). Logistic regression was used to estimate the association of poor adherence with the BMQ subscales, with and without adjustment for depressive symptoms, self-efficacy (Self-Efficacy for Managing Chronic Disease 6-item Scale), demographics (race/ethnicity, age, gender, education) and RA disease activity (global assessment).

Results:

Of 438 patients, 88% were female, 29% Latino, mean age 61±13 years, 32% had high school education or less, 75% reported taking a synthetic DMARD. Only 14% reported poor adherence to oral DMARDs. In terms of medication beliefs, 64% reported that having to take medicines worries them, 81% reported they sometimes worry about long-term effects of medicines, and 47% reported worrying about becoming dependent on their medicines. However 91% agreed with the statement "my health, at present, depends on my medicines" and 92% agreed that "my medicines will protect me from becoming worse." In multivariate analyses, the BMQ necessity score – but not the concerns subscale – was associated with lower odds of poor adherence. Self-efficacy conversely was associated with higher odds of poor adherence (table).

Conclusion:

In a diverse cohort of patients with RA, our data suggest that patients who report stronger beliefs in the necessity of medication are more likely to adhere to their DMARDs. Higher self-efficacy scores were associated with greater odds of poor adherence. Given the often sub-optimal adherence to DMARDs, providers can play an important role in enforcing positive patient beliefs about medications to improve adherence and ultimately health outcomes. Further research is needed to explore how best to inform positive medication beliefs among diverse populations with RA.

Table. Unadjusted and adjusted odds ratios of poor self-reported adherence to oral synthetic DMARDs among a diverse cohort of adults with RA

	Unadjusted OR (95% confidence interval)	Adjusted* OR (95% CI)
BMQ concerns subscale	1.24 (0.96-1.61)	0.96 (0.68-1.35)
BMQ necessity subscale	0.89 (0.65 – 1.23)	**0.68 (0.47-0.99)**
Self-efficacy	1.09 (0.95-1.26)	**1.25 (1.03-1.53)**

*Includes: age, gender, self-efficacy, race, education, depressive symptoms, RA disease activity VAS, mean BMQ subscale as indicated

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Associations Between Health Literacy, Ethnicity, Communication Quality and Beliefs about Medicines in Rheumatoid Arthritis

Jennifer Barton[1,2], Patricia P. Katz[3], Laura Trupin[4], Somnath Saha[5], Dean Schillinger[6] and Edward H. Yelin[4], [1]VA Portland Health Care System, Portland, OR, [2]Medicine/Rheumatology, Oregon Health & Science University, Portland, OR, [3]Rheumatology, UCSF, SF, CA, [4]University of California, San Francisco, San Francisco, CA, [5]Medicine, VA Portland Health Care System, Portland, OR, [6]Medicine, UCSF, San Francisco, CA

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Background/Purpose:

Vulnerable populations with rheumatoid arthritis (RA) experience poorer health outcomes despite access to current therapies. These disparities may result from limited health literacy, cultural barriers, or mood disorders leading to negative beliefs and concerns about medications, which are in turn associated with poor medication adherence. RA patients with limited health literacy also report suboptimal patient-provider communication and shared decision making, suggesting missed opportunities to address negative beliefs about medications. Prior research has demonstrated these pathways to disparities in other conditions such as HIV but has not been studied in RA. Our objective was to examine associations between health literacy, ethnicity, communication with physicians, and mood, with beliefs about medicine in a diverse population with RA.

Methods:

Data were derived from RA patients enrolled in a longitudinal observational cohort (Rheumatoid Arthritis Outcomes Study or RA OS). Subjects completed a telephone interview in either English or Spanish that included measures of patient-provider communication, health literacy, depressive symptoms (PHQ), demographics and the Beliefs about Medicine Questionnaire (BMQ). Linear regression was performed to identify correlates of the two subscales of the BMQ – necessity of taking RA medications and concerns about medication use and long-term effects.

Results:

Of 438 patients, 88% were female, 29% were Latino, 32% had high school education or less and 30% had limited health literacy. Mean age was 61 (SD 13) years and mean disease duration was 23 (SD 12) years. Subjects with limited health literacy were more likely than those with adequate literacy to be female, of Latino ethnicity, have high school or less education, and have depressed mood. More than half of subjects with adequate health literacy reported their doctor “always” spent enough time with them (63%) compared to only 48% of those with limited health literacy ($p=0.006$). Subjects with limited health literacy had more concerns about medicines compared to those with adequate literacy ($p<0.001$) as did those who did not report that their doctor always spend enough time with them ($p<0.001$). In multivariate linear regression, limited health literacy, depression, Latino ethnicity, female gender, younger age and reports that the doctor did not “always” spend enough time were associated with stronger concerns about medicines. None of these factors was associated with perceived necessity of medicines.

Conclusion:

Among a diverse cohort of adults with RA, limited health literacy, Latino ethnicity, depressed mood and lower perceived quality of communication with the doctor were independently associated with stronger concerns about medicines. This may in turn be associated with poorer adherence and poorer outcomes in these vulnerable populations who also have significant barriers to communication. Future research should focus on knowledge transfer, including evidence based risk and benefit information, and promotion of patient engagement in shared decision making to reduce disparities.

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Validating Arthroscopic Findings Using Histology, Status for Erosive Disease, and CRP in RA

Carl Orr[1], Trudy McGarry[2], Francis Young[3], Ursula Fearon[2] and Douglas J. Veale[1], [1]St Vincent's University Hospital, Centre for Arthritis and Rheumatic Diseases, Dublin Academic Medical Centre, Dublin 4, Ireland, [2]St. Vincent's University Hospital, Centre for Arthritis and Rheumatic Diseases, Dublin Academic Medical Centre, Dublin 4, Ireland, [3]Centre for Arthritis and Rheumatic Diseases, Dublin Academic Medical Centre, Dublin 4, Ireland

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Background/Purpose:

The utility of synovial biopsy has been confirmed as an important research tool in increasing our understanding of the pathogenesis of RA, evaluating new treatments and identifying potential therapeutic targets.[1, 2] However, no scoring system for the assessment of synovitis at knee arthroscopy has been validated against the histological grade of inflammation observed in the synovial biopsies retrieved.

Furthermore, the power that arthroscopy may have in identifying patients with active inflammation despite normal CRPs has not been reported. Finally, we currently understand only 32% of the variance in factors that predict joint destruction,[3] and macroscopic findings at arthroscopy may present an additional opportunity in assessing those most at risk of this disease course.

Aims

To validate synovitis scores at arthroscopy with histology scores, CRP levels and erosive disease on radiographs.

Methods:

141 patients with RA were recruited to undergo arthroscopy, and serum CRP levels were measured at the same time. The most recent set of hands and feet radiographs were assessed for the presence or absence of erosions. A macroscopic score of synovitis, graded at 5 unit intervals between 0-100, was recorded by the operator at each arthroscopy.

Synovitis scores were analysed using Pearson's test for correlation, with categorical data for histology findings (no inflammation, mild inflammation, and moderate-severe inflammation).The same test was used to determine if there was a correlation between synovitis scores and CRP levels.

The Chi-square test was employed to test for a relationship between categorical synovitis scores (4 quartiles), and the presence or absence of erosions.

Results:

A correlation was observed between synovitis scores and histology findings ($p=0.0014$, $r=0.2943$).

There was no correlation with synovitis scores and CRP levels. 49 (34.8%) patients had normal CRP levels (0-5mg/l), with 29 (59.2%) having synovitis scores >50%.

An association was also observed with higher synovitis scores and the presence of erosions ($p=0.0173$).

Conclusion:

Synovitis can be reliably assessed by scores at arthroscopy, which correlate with subsequent histological findings. Arthroscopy has the power to identify patients with synovitis, where CRP levels are normal, favouring the concept that not all RA phenotypes manifest elevated CRP levels during active disease. Furthermore, those with high synovitis scores are more likely to have erosions on radiographs.

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Comparison of Arterial Health in Patients with Rheumatoid Arthritis to a Population-Based Cohort

Caroline Ball[1], John M. Davis III[2], Cynthia S. Crowson[3], Iftikhar Kullo[4], Eric L. Matteson[5] and Rekha Mankad[6], [1]Internal Medicine, Mayo Clinic, Rochester, MN, [2]Division of Rheumatology, Mayo Clinic, Rochester, MN, [3]Health Sciences Research, Mayo Clinic, Rochester, MN, [4]Department of Internal Medicine, Division of Cardiovascular Diseases, Mayo Clinic, Rochester, MN, [5]Division of Rheumatology, Department of Internal Medicine and Department of Health Sciences Research, Mayo Clinic, Rochester, MN, [6]Cardiovascular Diseases, Mayo Clinic, Rochester, MN

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Title: Comparison of Arterial Health in Patients with Rheumatoid Arthritis to a Population-based Cohort

Background/Purpose: Patients with rheumatoid arthritis (RA) have increased risk of cardiovascular disease (CVD). Vascular stiffness is associated with increased cardiovascular risk in the general population. We aim to characterize the differences in arterial health, including vascular stiffness and endothelial function between patients with RA and no history of CVD and a population-based cohort of non-RA patients without a known history of CVD or RA.

Methods: A set of arterial health tests were carried out in patients with RA who were seen in our institution's Cardio-Rheumatology Clinic as part of a cardiovascular risk assessment. Assessment included 2-D carotid artery ultrasound, brachial artery reactivity, and arterial tonometry. Data from these patients were compared to normative data from the institution's cardiovascular healthcare clinic. Each patient with RA was matched on age and sex to 10 subjects from the comparison cohort. Diagnosis of RA was made by rheumatologists according to the 2010 American College of Rheumatology/ European League Against Rheumatism criteria. Comparisons between cohorts were performed using conditional logistic regression.

Results: The study cohort included 28 patients with RA (mean age: 58.1 [SD:10.4] years; 82% female) compared to 280 controls (mean age: 58.4 [SD:9.7] years; 82% female). Flow-mediated dilation (FMD) was higher in the patients with RA (8.7±6.3 vs 6.2±4.9, p=0.014; Table) than controls. Hyperemic flow was marginally higher in the patients with RA (458±255 vs 403±169, p=0.067). Among our RA cohort, treatments included methotrexate in 61%, corticosteroids in 39% and biologics in 54% at the time of arterial health studies.

Conclusion:

In subjects without a history of CVD, vascular stiffness is similar in patients with treated RA compared with subjects without RA. Patients with RA show a trend toward decreased augmentation pressure, augmentation index and pulse wave velocity, consistent with increased arterial stiffness. Flow-mediated dilation was increased in patients with RA, suggesting better endothelial function. Hyperemic response was similar in both cohorts. It is possible that endothelial function in this population is affected by RA therapies. These measures of arterial stiffness may also have prognostic values for prediction of risk for CVD and lead to more targeted prevention strategies to reduce this risk in this population that is already at higher risk for CVD.

Table

	Control	RA Patients	p-value
	N=280	N=28	
Augmentation Pressure (mmHg)	14.6 ± 7.5	14.1 ± 7.5	0.65
Aortic Pulse Pressure (mmHg)	43.2 ± 14.3	44.7 ± 16.5	0.59
Augmentation Index (%)	32.5 ± 10.1	30.2 ± 10.6	0.23
Pulse Wave Velocity (m/s)	9.5 ± 2.8	8.7 ± 2.0	0.14
Brachial Artery Diameter (mm)	3.5 ± 0.7	3.4 ± 0.8	0.20
Basal Flow (mL/min)	59.0 ± 62.6	71.4 ± 61.6	0.30
Hyperemic Flow (mL/min)	403.4 ± 169.2	458.3 ± 254.6	0.067
Flow Mediated Dilation (%)	6.2 ± 4.9	8.7 ± 6.3	0.014
Hyperemic flow response	0.15 ± 0.12	0.15 ± 0.08	0.75

Disclosure: C. Ball, None; **J. M. Davis III**, None; **C. S. Crowson**, None; **I. Kullo**, Fukuda, 2; **E. L. Matteson**, None; **R. Mankad**, None.

Abstract Number: 2637

Prevalence of Unacceptable Pain and the Risk of Fatigue and Sleeping Problems in Early Rheumatoid Arthritis Patients

Joakim Lindqvist[1], Maria Sandberg[2,3], Saedis Saevarsdottir[4], Reem Altawil[4], Lars Klareskog[5], Lars Alfredsson[6] and Jon Lampa[7], [1]Rheumatology Unit, Department of Medicine, Karolinska Institute, Stockholm, Sweden, [2]Unit of Cardiovascular Epidemiology, Institute of Environmental Medicine, Karolinska Institutet, Karolinska Institutet, Stockholm, Sweden, [3]The Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden, [4]Rheumatology Unit, Karolinska University Hospital, Karolinska Institutet, Stockholm, Sweden, [5]Rheumatology Unit, Karolinska University Hospital, Stockholm, Sweden, [6]Unit of Cardiovascular Epidemiology, Institute of Enviornmental Medicine, Karolinska Institutet, Karolinska Institutet, Stockholm, Sweden, [7]Dep of Medicine, Rheumatology unit, Karolinska Institute, Karolinska Institute, Stockholm, Sweden

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Background/Purpose: Pain is a commonly reported cause of affliction in RA-patients, also after adequate anti-rheumatic treatment. The objective of this study was to investigate the prevalence of unacceptable pain in early RA-patients with good inflammation control after anti-rheumatic treatment and also how this condition may affect the risk of long-term fatigue, sleeping problems and continuous pain.

Methods: Data was compiled from the population-based case control study Epidemiological Investigation of Rheumatoid Arthritis (EIRA) and linked to the Swedish Rheumatology Quality Register (SRQ). All patients were diagnosed with RA according to the 1987 ACR criteria. Early RA-patients with follow-up data both from diagnosis, 1 year and 3 years after diagnosis were included (N=186; 75% women, median age at diagnosis 56 years). Unacceptable pain in spite of good inflammation control at the 1 year follow-up (in the following named “refractory pain”), was defined using the previously validated definition of unacceptable pain (Patient Acceptable Symptom State (PASS) VAS pain ≥ 40) (1), combined with CRP <10 g/L (depicting good inflammatory control). The associated risk for significant fatigue (VAS ≥40), sleeping problems (defined as quite big/very big problem by the patient) and current pain, minimal pain and maximal pain (VAS ≥40, VAS ≥20 and VAS 75th percentile in the group; respectively) at 3 years follow-up was calculated using logistic regression, adjusted for age and sex.

Results: Although a majority of patients (85%) reached good inflammatory control at the 1 year follow-up, 28% of them had unacceptable pain according to PASS. After 3 years, 17% of all patients had sleeping problems and 26% had significant fatigue. Median VAS pain at 3 years was 11 mm. Refractory pain at 1 year was associated with an increased risk of fatigue OR= 2.80 [95% CI:

1.36-5.78] and sleeping problems OR= 4.64 [95% CI: 1.96-10.98] 3 years after diagnosis. Refractory pain also associated with an increased risk of both current pain at the 3 year follow-up OR= 5.17 [95% CI: 2.33-11.47], as well as minimal pain level OR= 5.32 [95% CI: 2.34-12.11] and maximal pain level OR= 5.38 [95% CI: 2.56-11.31] at the 3 year follow-up.

Conclusion: Approximately a quarter of RA-patients have unacceptable pain despite good inflammation control 1 year after diagnosis. This condition strongly predicts fatigue, sleeping problems and continuous pain 2 years later. These findings highlight the insufficiency of anti-rheumatic treatment to suppress long-term pain and fatigue, and support the importance of early acknowledgement and treatment of pain also in patients with good inflammation control.

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Abstract Number: 2638

Multiple Psychosocial Factors Influence Subjective Assessments of Disease Activity in Rheumatoid Arthritis

Ying L. Liu[1], Joan M. Bathon[2,3] and Jon T. Giles[4], [1]Internal Medicine, Columbia University Medical Center, New York, NY, [2]Medicine, Columbia University, College, New York, NY, [3]Rheumatology, Columbia University College of Physicians & Surgeons, New York, NY, [4]Division of Rheumatology, Columbia University, College of Physicians & Surgeons, New York, NY

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Background/Purpose: Measuring disease activity in rheumatoid arthritis (RA) is important in evaluating efficacy of treatments, but many tests are subjective and lead to discordance in patient and physician assessments. Identifying factors contributing to discordance may allow disease activity to be assessed more accurately from patient-centered assessments.

Methods: In 195 patients with RA, demographic information, measures of disease activity, and use of therapeutic agents were assessed by questionnaire. Patient Global Assessment (PtGA) and Physician Global Assessment (PhGA) were assessed by marking level of disease activity on a standard 100mm line with higher scores reflecting more disease activity (range 0-100). Discordance in global assessment (PtGA-PhGA) was stratified into tertiles. Multiple validated scales for an array of psychosocial comorbidities (depression, chronic life stressors, anxiety/anger, social support, discrimination/hassles) were assessed. Quality of life and fatigue were assessed using SF36 and FACIT scores respectively. Multivariable (MV) linear regression was used to fit models predicting discordance in global assessments.

Results: Tertiles of discordance in global assessment were defined as “Physician Higher than Patient (Ph>Pt)” [PtGA<PhGA -52 to -9 (n=65)], Concordant [PtGA=PhGA -8 to +8 (n=66)], and “Patient Higher than Physician (Pt>Ph)” [PtGA>PhGA +9 to +92 (n=64)]. Compared with the Pt>Ph and concordant groups, the Ph>Pt group had significantly higher DAS28 scores with more swollen/tender joints. In contrast, the Pt>Ph group had higher HAQ and pain/pain catastrophizing scores and was more likely to be on no DMARDs compared with the Concordant group. Also, the Pt>Ph group had significantly higher job stress and fatigue, depression, and anxiety scores and lower SF36 total, physical and mental health scores along with slower walking pace and a trend towards less physical activity. In MV models, male gender, slower walking pace, no DMARD use, job and health stress, higher FACIT and lower SF36 Total scores were associated with more discordance in which the PtGA was higher than the PhGA, and more tender/swollen joints, use of a biologic and higher anger scores were associated with more discordance in which the PhGA was higher than the PtGA. Together, these variables explained 51% of the discordance between patients and physicians. The psychosocial variables made up 9.4% of the explainable variability, and tender/swollen joints and slow walking speed were the largest contributors to discordance.

Conclusion: Psychosocial comorbidities, fatigue, quality of life, tender/swollen joints, functional status and type of therapy may explain some, but not all, of the discordance in patient and physician assessments of disease activity in RA.

Table: Selected RA variables and Psychosocial Comorbidities According to Concordance/Discordance of Patient and Physician Global Assessments

	1- More physician PtGA<PhGA (-52 to -9) n=65	2 - Concordant PtGA=PhGA (-8 to +8) n=66	3 - More Patient PtGA>PhGA (+9 to +92) n=64	1 v. 2 p-value	3 v. 2 p-value	1 v. 3 p-value
Age (years)	58 ± 7	61 ± 9	59 ± 9	0.068	0.11	0.98
Male	25 (38%)	25 (38%)	29 (45%)	0.95	0.39	0.43
Pain (0-100mm)	18 (5-39)	14 (4-36)	26 (17-41)	0.46	0.0043	0.037
Physical Activity (met-hrs/wk)	17.5 (4-44)	17 (0-43)	11.4 (0-25)	0.62	0.12	0.037
Slow Walking Pace	26 (40%)	23 (35%)	36 (57%)	0.54	0.011	0.052
DAS28	4.0 (3.2-4.8)	3.6 (2.9-4.1)	3.3 (2.7-4.0)	0.03	0.52	0.009
Swollen Joints	10 (7-14)	6 (2-8)	5 (2-8)	<0.001	0.64	<0.001
Tender Joints	9 (3-19)	5 (2-10)	5 (3-10)	0.01	0.6	0.01
CRP	2.3 (0.9-5.4)	3.3 (1.3-8.3)	2.1 (1.2-6.7)	0.19	0.25	0.74
HAQ	0.62 (0.12-1.12)	0.44 (0-1.75)	0.94 (0.38-1.31)	0.75	0.08	0.04
Biologics Ever	39 (60%)	31 (47%)	39 (47%)	0.14	0.94	0.16
No DMARD	2 (3%)	4 (6%)	6 (10%)	0.68	0.52	0.16
Pain Catastrophizing Total Score	5 (1-13)	6 (2-12)	9 (4-18)	0.56	0.02	0.009
Rumination	2 (0-5)	3 (0-5)	4 (2-7)	0.34	0.05	0.004
Magnification	1 (0-3)	2 (0-2)	2 (0-4)	0.74	0.07	0.06
Helplessness	2 (0-5)	2 (0-4)	3 (1-8)	0.58	0.004	0.04
FACIT Score	9 (5-17)	9 (6-16)	16 (10-24)	0.88	0.002	0.004
SF36 Total Score	59 (51-64)	60 (54-64)	54 (49-62)	0.64	0.002	0.010
Total Physical	60 (50-66)	60 (51-65)	51 (45-61)	0.75	0.002	0.007
Total Mental	62 (52-67)	63 (55-68)	55 (49-63)	0.73	0.0007	0.005
CESD Score	5 (3-9)	4 (2-9)	9 (4-15)	0.35	0.007	0.04
Anxiety Score	15 (12-17)	14 (11-18)	16 (13-21)	0.80	0.03	0.05
Anger Score	14 (12-17)	13 (12-16)	14 (13-16)	0.38	0.06	0.46
Stress, Health	30 (48%)	16 (25%)	34 (57%)	0.01	<0.001	0.32
Stress, Caregiver	23 (36%)	20 (32%)	18 (31%)	0.62	0.88	0.52
Stress, Job	9 (14%)	7 (11%)	20 (33%)	0.53	0.002	0.013
Stress, Financial	7 (11%)	7 (11%)	9 (15%)	1.0	0.50	0.50
Stress, Relationship	12 (18%)	8 (12%)	9 (15%)	0.33	0.66	0.61
Total Stress	1.26 ± 1.15	0.92 ± 1.07	1.44 ± 1.15	0.08	0.012	0.37

*Continuous Variables are shown with medians and 25th and 75th percentiles, except for age/total stress which are mean ± SD. Categorical variables are counts and percentages with ttest and Kwallis or chi-squared/Fischer's exact p-values.
** HAQ = Health Assessment Questionnaire, DMARD = Disease Modifying Anti-Rheumatic Drug, FACIT = Fatigue Score, CESD = Center for Epidemiologic Studies Depression Scale, Anxiety Score = State Trait Anxiety Inventory, Anger Score = State Trait Anger Inventory

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Abstract Number: 2639

Towards Patient-Centeredness of the Treat-to-Target Paradigm: Development of a Framework for Evaluation of Patients with Rheumatoid Arthritis in the Setting of Patient-Physician Discordance

John M. Davis III[1], Tim Bongartz[2], Zoran Kvrgic[2], Melissa M. Plagge[1], Cynthia S. Crowson[3], Eric L. Matteson[4], Thomas G. Mason II[2], Scott T. Persellin[5], Clement J. Michet Jr.[2], Theresa Wampler Muskardin[1] and Kerry Wright[2], [1]Division of Rheumatology, Mayo Clinic, Rochester, MN, [2]Rheumatology, Mayo Clinic, Rochester, MN, [3]Division of Rheumatology and Department of Health Sciences Research, Mayo Clinic, Rochester, MN, [4]Division of Rheumatology, Department of Internal Medicine and Department of Health Sciences Research, Mayo Clinic, Rochester, MN, [5]Department of Rheumatology, Mayo Clinic Rochester, Rochester, MN
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Background/Purpose: A great challenge in managing rheumatoid arthritis (RA) is the scenario of patient-physician discordance, in which despite seeming control of inflammation, patients suffer from undifferentiated symptoms of pain, fatigue, psychosocial distress, and functional disability. Our aim was to explicate the etiologic domains underlying patient-physician discordance.

Methods: We identified consecutive patients with RA fulfilling the ACR/EULAR 2010 criteria from our outpatient practice. Patients with ≥25-mm difference between patient and provider global assessments (0-100) of disease activity were identified. We abstracted electronic records for RA disease characteristics and comorbidities. Disease activity was classified according to Clinical Disease Activity Index (CDAI). In a sub-study, 50 discordant and 20 concordant patients (10 each with CDAI ≤10 and >10) completed several validated health status instruments (e.g., pain visual analog scale (VAS), Health Assessment Questionnaire II (HAQ-II), Fibromyalgia Research Survey, and the Patient-Reported Outcome Measures Information System (PROMIS) Pain Interference and Ability to Participate surveys) and underwent grayscale (GS) and power Doppler (PD) ultrasonography of the dominant hand, wrist and foot. Differences between discordant and concordant groups were evaluated using chi-square and rank sum tests.

Results: Patient-physician discordance affected 118 (34%) of 351 consecutive visits. The study cohort included 141 of these patients (mean age 61 years, 73% female), with discordant global assessments in 68 (48%). Of the discordant patients, 63 (93%) rated their disease activity as greater than their provider, with median (range) patient global assessment of 57 (2-87) and provider global assessment of 15 (0-80). Discordance was associated with seronegativity (p=0.008 for rheumatoid factor and p=0.035 for anti-cyclic citrullinated peptide (anti-CCP) antibodies), lack of joint erosions (p=0.013), and the presence of comorbid osteoarthritis (p=0.005), depression (p=0.004), and fibromyalgia (p=0.011). The proportion of patients with CDAI >10 was significantly higher in the discordant than concordant group (50% vs. 33%, p<0.001). While usage of RA therapies was similar between groups, discordant patients had greater usage of opioids (p=0.015), antidepressants (p<0.001), and fibromyalgia medications (p=0.018). In the sub-study, higher values for the pain VAS, HAQ-II disability, Fibromyalgia widespread pain index, PROMIS Pain Interference, and PROMIS Ability to Participate questionnaires distinguished the discordant group. On sonographic examination, the discordant group had 66% GS synovitis ≥2 and 38% PD synovitis ≥1.

Conclusion: Our findings demonstrate that a comprehensive framework for evaluation of patient-physician discordance should include domains of seronegativity, fibromyalgia, depression, comorbid osteoarthritis, and persistent synovitis. Further work is necessary to develop a standardized approach for patient-centered evaluation and shared decision-making to improve outcomes for patients with RA in the setting of patient-physician discordance.

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Abstract Number: 2640

Factors Influencing Treatment Adjustments in RA Patients – Biologic DMARD Treatment Start and Options

Peter C. Taylor[1], Emma Sullivan[2], Robert Wood[3], James Piercy[3], Rieke Alten[4], Juan J Gomez-Reino[5], Philippe Bertin[6], Roberto Caporali[7], Radu Vasilescu[8], Dean Spurden[9] and Jose Alvir[10], [1]Kennedy Institute of Rheumatology, Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences, University of Oxford Botnar Research Centre, Oxford, United Kingdom, [2]Adelphi Real World, Manchester, United Kingdom, [3]Adelphi Real World, Macclesfield, United Kingdom, [4]Internal Medicine, Rheumatology & Clinical Immunology, Schlosspark-Klinik, University Medicine Berlin, Berlin, Germany, [5]Desarmen of Rheumatology, Unit Hospital Clinico Universitario, Santiago, Spain, [6]Rheumatology, CHU Dupuytren, Limoges, France, [7]University of Pavia and IRCCS Policlinico S. Matteo Foundation, Pavia, Italy, [8]Medical Affairs, Pfizer Inc, Brussels, Belgium, [9]Pfizer Inc, Tadworth, United Kingdom, [10]Global Health and Value, Pfizer Inc, New York, NY
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Background/Purpose: Current recommendations for pharmacologic management of rheumatoid arthritis (RA) advise dose titration or switching treatment if goals of remission or low disease activity are not met.

Our objective is to describe factors causing treatment change and choice of drug from non-biologic DMARD to a biologic DMARD (bDMARD), and subsequent progression in bDMARD therapy, in real-world practice.

Methods: Data were drawn from the Adelphi 2014 RA Disease Specific Programme, a survey of rheumatologists and their RA patients in France, Germany, Italy, Spain and UK. Rheumatologists provided patient demographics, clinical details and treatment history including reasons for switching treatment. In bDMARD-naïve patients physicians provided reasons why they would initiate a bDMARD. Summary statistics were used to describe the decision-process of physicians at varying stages of treatment, and to compare bDMARD vs. non-bDMARD patients who were eligible for bDMARD therapy at initiation of current therapy.

Results: 307 rheumatologists provided data for 2536 patients, 71% female, a mean age of 52.8 years and 72.6 months since diagnosis. 63.5% of patients had never received bDMARD therapy (bDMARD naïve), 36.5% had received bDMARD therapy (33.9% currently receiving, 2.6% on a treatment break or had discontinued). 24.8% of patients had only ever received 1 bDMARD.

The main reasons prompting initiation of a bDMARD in naïve patients were worsening of RA severity as assessed by the physician (60.6%) and failure of non-bDMARD therapy (32.5%). bDMARD patients had been diagnosed longer compared to bDMARD-eligible patients who had not received a bDMARD (103.4 vs. 80.3 months), had a more severe condition at initiation of therapy (% rheumatologist perceived ‘severe': 51.7 vs. 26.5), experienced more pain at initiation (mean score [1=none; 10=worst]: 7.1 vs. 6.4); all $p<0.01$). When selecting which bDMARD therapy to prescribe first, physicians report ‘strong overall efficacy' as the main reason for bDMARD selection (70.8%) followed by ‘convincing efficacy in clinical trials' (54.9%).

The main reasons for switching from previous bDMARD to current bDMARD are physician assessed worsening of condition (45.8%) and loss of response over time (38.4%). The main reasons for second bDMARD choice were similar to first: strong overall efficacy (73.8%), convincing efficacy in clinical trials (50.2%), and in addition ‘inhibits disease progression' (50.2%). Reasons were relatively consistent regardless of bDMARD switched to (TNF inhibitor (TNFi) or non-TNFi).

Conclusion: Worsening severity of RA, rather than high baseline RA activity, is the main reason for treatment escalation regardless of the stage in the treatment pathway, suggesting current treatment approaches are not sustainably maintaining disease control in all patients. Furthermore, there is a need for clinical and laboratory biomarkers that could better inform the selection of first and subsequent bDMARDs. These findings emphasise the importance of early and optimum disease control where feasible, and physicians may therefore benefit from additional guidance and clarity on appropriate sequencing of bDMARD treatments.

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Correlation of Rheumatologists’ Perceptions of RA Severity with Observed Disease Activity, Patient Impact and Treatment Patterns

Peter C. Taylor[1], Juan J Gomez-Reino[2], Roberto Caporali[3], Rieke Alten[4], Philippe Bertin[5], Emma Sullivan[6], Robert Wood[7], James Piercy[7], Radu Vasilescu[8], Dean Spurden[9] and Jose Alvir[10], [1]Kennedy Institute of Rheumatology, Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences, University of Oxford Botnar Research Centre, Oxford, United Kingdom, [2]Desarmen of Rheumatology, Unit Hospital Clinico Universitario, Santiago, Spain, [3]University of Pavia and IRCCS Policlinico S. Matteo Foundation, Pavia, Italy, [4]Internal Medicine, Rheumatology & Clinical Immunology, Schlosspark-Klinik, University Medicine Berlin, Berlin, Germany, [5]Rheumatology, CHU Dupuytren, Limoges, France, [6]Adelphi Real World, Manchester, United Kingdom, [7]Adelphi Real World, Macclesfield, United Kingdom, [8]Medical Affairs, Pfizer Inc, Brussels, Belgium, [9]Pfizer Inc, Tadworth, United Kingdom, [10]Global Health and Value, Pfizer Inc, New York, NY

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Background/Purpose: Efforts have been made in recent years to standardize the clinical assessment of RA patients with increased focus on objective measures, such as the DAS28.

The objective of the current study was to compare physicians' perceptions of the severity of their patients' RA against the patients' DAS28, treatment, and quality of life.

Methods: Data were drawn from the Adelphi 2014 RA Disease Specific Programme, a survey of rheumatologists and their RA patients in France, Germany, Italy, Spain and UK. Rheumatologists provided patient clinical details including DAS28, physician perceived disease severity (mild/ moderate/ severe) and treatment history. Patients completed the EuroQoL 5-Dimension Health Questionnaire (EQ-5D) and Work Productivity Activity Impairment (WPAI) questionnaire. Three cohorts were created based on the physician's perceived severity of the patient's RA: mild, moderate, severe and were compared across DAS28 (as reported by the physician), treatment history, EQ-5D and WPAI. Appropriate univariate tests were used to compare subgroups statistically.

Results: 307 rheumatologists provided records for 2,536 patients, of whom 68.8% were perceived to have currently mild RA, 27.1% moderate RA and 4.2% severe RA. Comparisons of mean DAS28 scores across groups showed an increase in mean score as severity worsened (DAS28: 2.48, 3.81, 5.45 for mild, moderate and severe, respectively; $p<0.01$). When DAS28 was categorized based on agreed definitions of remission (<2.6), low disease activity (LDA; ≥2.6 and ≤3.2) and active disease (>3.2) the percentage of mild patients in each DAS28 category was 53.2%, 34.5% and 12.3%, respectively; moderate patients: 9.2%, 22.4% and 68.3%; and severe patients: 5.6%, 2.8% and 91.7% ($p<0.01$). 47.2% of patients who are currently severe have been prescribed a biologic DMARD (bDMARD) therapy, which was higher than for patients who are currently moderate (39.1%) or mild (34.9%).

Higher disease activity scores were associated with lower EQ-5D scores indicating worse quality of life (EQ-5D: 0.81, 0.60, 0.21 for mild, moderate and severe, respectively; $p<0.01$), and overall work impairment increased (18.8%, 37.6% and 55.9% for mild, moderate and severe, respectively; $p<0.01$).

Conclusion: Results showed that in general rheumatologists' labels of mild, moderate and severe RA correlate with more objective measures of disease activity (DAS28) and impact on the patient (EQ-5D and WPAI), although the finding that some patients classed as 'mild' have active RA (DAS28 >3.2) implies active disease can still be overlooked and potentially undertreated.

Additionally, the finding that less than half of patients who are currently severe had received a bDMARD therapy suggests a certain population of patients may not receive bDMARD therapy regardless of the severity of their RA, and may benefit from an alternative efficacious treatment option.

Disclosure: P. C. Taylor, UCB Pharma, GSK, 2,Pfizer, UCB Pharma, Lilly, BMS, AbbVie, Celltrion, Hospira, Merck, Jannsen, Galapagos NV, Sandoz, 5; **J. J. Gomez-Reino**, None; **R. Caporali**, UCB Pharma, Roche, 8,AbbVie, Pfizer Inc, MSD, 5; **R. Alten**, Pfizer Inc, 2,Pfizer Inc, 5,Pfizer Inc, 8; **P. Bertin**, MSD, Pfizer Inc, Reckitt Benckiser, Roche, 5; **E. Sullivan**, Adelphi Real World, 3,Pfizer Inc, 9; **R. Wood**, Adelphi Real World, 3,Pfizer Inc, 9; **J. Piercy**, Adelphi Real World, 3,Pfizer Inc, 9; **R. Vasilescu**, Pfizer Inc, 1,Pfizer Inc, 3; **D. Spurden**, Pfizer Inc, 1,Pfizer Inc, 3; **J. Alvir**, Pfizer Inc, 1,Pfizer Inc, 3.

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Patient Reported Outcome Assessment of Rheumatoid Arthritis Patients Experience with IV Administered Biologic Therapy

Norman B. Gaylis[1], Joanne Sagliani[1], Danny Tuccitto[2], Shawn Black[3], Kehzen Tang[4], Raphael Dehoratius[3,5] and Dennis Parenti[3], [1]Arthritis & Rheumatic Disease Specialties, Aventura, FL, [2]AARDS Research, Inc, Aventura, FL, [3]Janssen Scientific Affairs, LLC, Horsham, PA, [4]Janssen Research & Development, LLC, Spring House, PA, [5]Kimmel School of Medicine, Thomas Jefferson University, Philadelphia, PA

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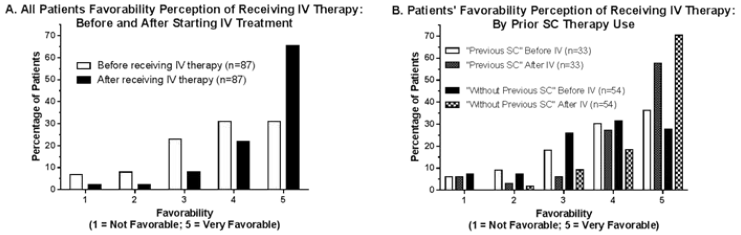
Background/Purpose: Patient-reported outcomes (PRO) are used to assess patient related benefit in clinical trials. Rheumatoid

arthritis (RA) patients are equally receptive to intravenous (IV) or subcutaneous (SC) biologic treatment[1]. The objective of this study was to obtain PRO data to understand characteristics of patients who receive IV biologic agents for RA.

Methods: This was a questionnaire-based study conducted at a single rheumatology practice with extensive clinical trial experience. A total of 100 patients will be enrolled; 87 patients are included in this interim analysis. The inclusion criteria were: a diagnosis of RA with IV biologic use for ≥3 mo; ≥18 yrs age; able to read, write and speak English, willing to complete the questionnaire and a signed informed consent form. IV biologic treatment was per clinical practice; there were no treatment assignments and study drug was not supplied. The questionnaire had 30 questions; patients completed the questionnaire prior to receiving a regularly scheduled dose of IV biologic. Data collected 1-2Q2015.

Results: The mean (±SD) age of patients in this interim analysis was 57.9 (±14.5) yrs with a mean disease duration of 10.6 (±8.5) yrs (range 0.7-45 yrs). Patients were Caucasian (36.8%), African American (28.7%), Latino/Hispanic (20.7%), Asian/Pacific Islander (1.1%) and 12.6% not identified. IV biologics used were infliximab (68%), rituximab (13%), tocilizumab (10%), abatacept (7%), golimumab (1%) and other (1%). The mean duration of current IV therapy was 4.0 (±3.2) yrs (range 0.1 to 16.0 yrs). Patients' favorability (1=Not Favorable, 5=Very favorable) perception of IV therapy BEFORE and AFTER starting IV therapy is shown in Figures A and B. Amongst all patients (A), "Very Favorable" increased ($p<0.05$) from 31% to 65% after receiving IV therapy; the increase in "Very Favorable" was evident in patients with or without previous SC therapy (B).



The favorability scores (mean ±SD) of current IV therapies were: infliximab 4.7 (±0.6), abatacept 4.7 (±0.5), rituximab 4.3 (±1.0), golimumab 5 (n=1) and tocilizumab 3.9 (±1.5). Prior SC biologic users had similar responses to questions identifying advantages or disadvantages associated with receiving IV biologic therapy as those patients who were not previous SC biologic users.

Conclusion: These interim results suggest that among patients receiving IV biologic therapy for treatment of RA, there is a high degree of patient satisfaction, including a similar favorability perception of IV therapy among patients who switched from an SC to an IV biologic. Our results support the concept that when there is a shared decision making discussion with patients regarding biologic treatments, the option of IV therapies should be an essential part of that discussion and that the RA patient's perspective should be given meaningful consideration.

[1]Bolge SC et al Arthritis Rheum 2013;65 Suppl 10:1023

Disclosure: N. B. Gaylis, Janssen Scientific Affairs, LLC, 2; **J. Sagliani**, Janssen Scientific Affairs, LLC, 2; **D. Tuccitto**, Janssen Scientific Affairs, LLC, 2; **S. Black**, Janssen Scientific Affairs, LLC, 3; **K. Tang**, Janssen R & D, LLC, 3; **R. Dehoratius**, Janssen Scientific Affairs, LLC, 3; **D. Parenti**, Janssen Scientific Affairs, LLC, 3.

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Decreased Pain Level with Aging Leads to Underestimation of Disease Activity in Rheumatoid Arthritis

Yong Gil Hwang[1], Juan (June) Feng[2], Heather Eng[3], Jason Lyons[4], Anthony Fabio[5] and Larry W. Moreland[6], [1]Department of Medicine, University of Pittsburgh, Pittsburgh, PA, [2]Epidemiology Data Center, University of Pittsburgh, Graduate School of Public Health, Pittsburgh, PA, [3]Epidemiology, Univ of Pittsburgh, Pittsburgh, PA, [4]School of Public Health, Department of Epidemiology, University of Pittsburgh, Pittsburgh, PA, [5]Department Of Epidemiology, Graduate School of Public Health, University of Pittsburgh, Pittsburgh, PA, [6]Rheumatology & Clinical Immunology, University of Pittsburgh, Pittsburgh, PA

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Background/Purpose: Rheumatoid arthritis (RA) is most prevalent in those who are 60 years of age or older. It has not been clearly established whether pain perception is different according to age in RA patients. We investigated whether there is any difference in pain level to similar synovial inflammation with aging using Modified Disease Activity Score (MDAS), which was shown to have superior correlation with Magnetic Resonance Image (MRI) detected synovitis.

Methods: For RA subjects enrolled in the University of Pittsburgh Rheumatoid Arthritis Comparative Effectiveness Registry (RACER), a cross-sectional analysis was performed for all first visits available. Levels of inflammation were calculated by MDAS28 score (=0.49 x ln(C-reactive protein (CRP)) + 0.15 x Swollen joint count 28 (SJC) + 0.22 x Physician global assessment (PhGA) +1). Spearman's correlations among pain (visual analog scale, VAS), disease characteristics, comorbidities and American College of Rheumatology (ACR) Core Data Set measures were calculated. Univariate and multivariate analyses were performed to investigate association between pain level and age. Age was categorized into 2 groups (younger RA <60, older RA ≥ 60) in regression models. Mann-Whitney U test was used to detect differences between two age groups.

Results: For the 740 subjects analyzed, subject age was 61.2 ±13.7 (median ±SD) years with disease duration of 14.4 ±12.4 years. In multivariate analyses, pain level had significant negative association with age even after adjustment for race, gender, comorbidities, and inflammation. (Table.1) In subjects with moderate inflammation (defined by MDAS28 score above 50 percentile, N=370), older RA subjects (age ≥ 60, N=189) had lower pain level, Tender Joint Count (TJC), Patent Global Assessment (PtGA), PhGA, , Routine Assessment of Patient Index Data 3 (RAPID3), Disease Activity Score (DAS) 28-CRP than younger subjects (age < 60, n=157) but SJC, physical health by 12-Item Short Form Health Survey (SF12) were not different between them. SF12-Mental Health was better in older RA subjects. (Table.2). There were no significant differences between two age groups in subjects with lower levels of inflammation (MDAS ≤ 50 percentile, N=370).

Conclusion: Decreased pain level in older RA patients with a similar degree of joint inflammation as younger RA patients leads to under-estimation of disease activity measured by either patient reported outcome (RAPID3) or composite disease activity index (DAS28-CRP). This suggests that current clinical disease activity measurements may not fully reflect the severity of disease in older RA patients.

Table.1 Multiple regression analyses of the associations of pain level with age adjusted for influences of covariates. Model 1 was adjusted for race, gender, comorbidities, and disease duration. Model 2 was adjusted as model 1 plus MDAS28. Model 3 was adjusted as model 2 plus physical & mental health (β: unstandardized coefficient, SE: Standard Error, MDAS28: Modified Disease Activity Score, 12-Item Short Form Health Survey (SF12)- Physical Health(PCS), Mental Health (MCS))

Model	Variables	β	SE	p value
1	Age	-0.722	.008	0.014
	Race	1.199	.349	0.003
	Gender	-0..122	.259	.684
	Charlson Score	0.174	.083	.016
	Disease duration	-0.122	.000	.848
2	Age	-0.700	0.270	.010
	Race	.989	.334	.003
	Gender	-0.171	.238	.474
	Charlson Score	0.146	.075	.053
	Disease duration	0.000	.0.000	0.366
	MDAS28	0.735	.065	.000
3	Age	-.602	.163	.000
	Race	.619	.253	.015
	Gender	-.016	.187	.931
	Charlson score	.050	.060	.404
	Disease duration	0.000	.001	.961
	MDAS28	.314	.055	.000
	SF12-PCS	-.147	.008	.000
	SF12-MCS	-.071	.007	.000

Table. 2 Comparisons between younger (age<60,n=157) and older (age>=60, n=189) RA patients with moderate inflammation (MDAS28 >50 percentile) (SJC: Swollen Joint Count, TJC: Tender Joint Count, PtGA: Patient Global Assessment, PhGA: Physician Global Assessment, SF12-PCS/MCS: 12-Item Short Form Health Survey (SF12)- Physical Health(PCS), Mental Health (MCS), DAS28-CRP: Disease Activity Score 28-C-Reactive Protein, RAPID3: Routine Assessment of Patient Index 3)

	Unadjusted (Mean ± SD)			Adjusted (Mean ± SD)		
	Age < 60	Age ≥ 60	p value*	Age < 60	Age ≥ 60	p value*
Pain (VAS)	6.36 (2.59)	5.14 (2.75)	<0.001	6.16 (1.87)	5.06 (1.80)	<0.001
SJC	6.76 (5.92)	6.88 (6.00)	0.963	7.36 (3.85)	7.06 (3.59)	0.521
TJC	6.74 (6.65)	4.20 (5.46)	<0.001	6.70 (2.89)	4.84 (2.71)	<0.001
PtGA	5.56 (2.35)	4.44 (2.50)	<0.001	5.35 (1.78)	4.52 (1.67)	<0.001
PhGA	4.89 (2.37)	3.97 (2.27)	<0.001	4.64 (1.67)	4.03 (1.56)	<0.001
RAPID3	4.51 (1.17)	3.98 (1.09)	<0.001	4.79 (1.62)	4.04 (1.56)	<0.001
DAS28-CRP	4.94 (2.01)	4.04 (2.02)	<0.001	4.38 (1.02)	3.97 (0.96)	<0.001
SF12-PCS	34.77 (9.88)	35.27 (10.34)	0.697			
SF12-MCS	44.27 (11.58)	49.27 (10.93)	<0.001			

*** p values < 0.0056 were considered statistically significant using the Bonferroni correction for multiple comparisons**

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Abstract Number: 2644

The Relationship Between Disease Activity and Cognitive Impairment in Patients with Rheumatoid Arthritis

Sang-Il Lee[1], Young Sun Suh[1], Yun-Hong Cheon[1], Hyun-Ok Kim[1], Hyun-Su Yang[2], Ki-Soo Park[2], Eun-Kyoung Park[3], Seung-Geun Lee[4], Chang-Nam Son[5], Ji-Min Kim[5] and Sang-Hyon Kim[6], [1]Division of Rheumatology, Department of Internal Medicine, Gyeongsang National University School of Medicine, Jinju, South Korea, [2]Department of Preventive Medicine, Gyeongsang National University School of Medicine, Jinju, South Korea, [3]Division of Rheumatology, Department of Internal Medicine, Pusan National University School of Medicine, Busan, South Korea, [4]Division of Rheumatology, Department of Internal Medicine, Busan National University School of Medicine, Busan, South Korea, [5]Division of Rheumatology, Department of Internal Medicine, Dongsan Medical Center, Keimyung University School of Medicine, Daegu, South Korea, [6]Division of Rheumatology, Department of Internal Medicine, Keimyung University School of Medicine, Daegu, South Korea

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Background/Purpose: Only few studies investigated the prevalence and risk factors of cognitive impairment in patients with rheumatoid arthritis (RA), however, results are controversial. Therefore we performed this study to determine the prevalence and risk factors of cognitive impairment and their association with RA disease activity.

Methods: Patients with RA and osteoarthritis (OA) were recruited from 3 university hospitals and physical, psychosocial, laboratorial, and medication statuses were assessed. Patients under 45 years old or with illiteracy were excluded. The activity and functional status of RA were assessed by Disease activity score (DAS)-ESR and Routine Assessment of Patient Index Data 3 (RAPID 3) score. Cognitive function was evaluated by Korean version of Mini-Mental State Examination (MMSE-K). Cognitive impairment was defined as MMSE-K scores ≤ 23.

Results: A total of 506 RA and 202 OA patients were recruited. Cognitive impairment was observed in 10.5%in RA and 13.4% in OA (*P*=0.272). In subgroup analysis between RA patients with cognitive impairment (n=53) or not (n=453), education level (OR 0.72, 95% CI 0.64-0.80), marriage status (OR 2.12, 95% CI 1.02-4.41), and high disease activity (OR 2.84, 95% CI 1.08-7.48) were independently predicted cognitive impairment after multivariate analysis controlling for age, hypertension, exercise, RAPID 3 score, fatigue, depression, and medication use. In subgroup analysis between RA patients with high disease activity (DAS28-ESR>5.1, n=55) or without (n=448), high disease activity was strongly associated with cognitive impairment (25.5% vs 8.5%, P=0.001). The education level was 63.8±9.96 and 62.1±8.51 (*P*=0.250) and age was 7.9±4.42 and 8.8±3.82 (*P*=0.111). In addition, DAS28-ESR score showed negative correlation with MMSE-K score (ρ=-0.110, *P*<0.05).

Conclusion: High disease activity is strongly associated with cognitive impairment in patients with RA. Thus, controlling disease activity may help preserving cognitive function in RA.

Abstract Number: 2645

Changes in Clinical Disease Activity Index and Changes in Sleep Among RA Patients Initiating Disease Modifying Antirheumatic Drugs

Alyssa Wohlfahrt[1], ChihChin Liu[2], Yuanyu Lo[1], Clifton Bingham[3], Marcy B. Bolster[4], Tuhina Neogi[5], Kristine Phillips[6] and Yvonne C. Lee[7], [1]Rheumatology, Immunology and Allergy, Brigham and Women's Hospital, Boston, MA, [2]Brigham and Women's Hospital, Boston, MA, [3]Johns Hopkins University, Baltimore, MD, [4]Rheumatology, Allergy, Immunology, Massachusetts General Hospital, Harvard Medical School, Boston, MA, [5]Clinical Epidemiology, BUSM, Boston, MA, [6]Rheumatology, University of Michigan, Ann Arbor, MI, [7]Rheumatology Immunology & Allergy, Brigham and Women's Hospital, Boston, MA

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Background/Purpose: Sleep problems affect over 60% of RA patients, but little is known about the relationship between sleep and inflammation in RA. Our primary objective was to identify associations between changes in sleep and changes in disease activity among RA subjects starting DMARDs. We also examined differences in these associations among those starting non-biologic vs. biologic DMARDs.

Methods: Individuals with active RA were recruited from 4 academic medical centers and assessed before and 12-weeks after starting a new DMARD. Subjects had to be starting a DMARD due to active disease, meet 2010 ACR criteria for RA, and be taking ≤ 10 mg of prednisone daily. Primary outcomes were changes in the PROMIS computerized adaptive test scores for Sleep-Related Impairment and Sleep Disturbance, reported as T-scores with a general population mean of 50 ± 10 and higher scores indicating worse sleep. The primary predictor was change in the Clinical Disease Activity Index (CDAI). The minimal clinically important improvement in CDAI is 6 for those with moderate baseline disease activity and 12 for those with high baseline disease activity (Curtis 2015). Multivariable linear regression models, adjusted for age, race, gender, RA duration and baseline sleep measures, were used to identify associations between changes in CDAI and changes in sleep. These associations were also examined in subgroup analyses stratified by those starting non-biologic vs. biologic DMARDs.

Results: Of the 58 RA subjects seen to date, 23 (39.7%) started non-biologic DMARDs, and 35 (60.3%) started biologic DMARDs. The mean baseline CDAI was 23.1 ± 14.0. After 12 weeks of DMARD treatment, the mean change in CDAI was -9.6 ± 13.5. Decreases in CDAI were associated with decreases in sleep-related impairment (β = 0.25; *P* = 0.01) but not with changes in sleep disturbance (β = 0.18; *P* = 0.11). In subgroup analyses, subjects who started non-biologic DMARDs had greater, though not statistically significant, decreases in CDAI (-12.9 ± 15.5), sleep disturbance (-3.8 ± 13.4) and sleep-related impairment (-4.5 ± 9.8) than subjects who started biologic DMARDs (CDAI: -7.5 ± 11.8; sleep disturbance: -3.1 ± 7.4; sleep-related impairment: -2.7 ± 10.2) despite similar baseline values. Decreases in CDAI were significantly associated with decreases in sleep disturbance and sleep-related impairment for those who started biologic DMARDs. No associations were observed in those starting non-biologic DMARDs (Table).

Conclusion: The magnitude of association between change in CDAI and change in sleep disturbance and sleep-related impairment differed among those who started non-biologic DMARDs vs. biologic DMARDs. These differences may reflect different mechanisms underlying improvements in sleep. A large, randomized clinical trial, directly comparing different types of DMARDs, is needed to elucidate the link between changes in inflammation and changes in sleep in RA.

Table. Associations between changes in disease activity and changes in sleep over 12 weeks among RA patients starting, switching, or adding a DMARD.

Cohort	Change in Sleep Disturbance		Change in Sleep-Related Impairment	
Primary Predictor	β-coefficient	P-value	β - coefficient	P-value
All DMARD initiators (N = 58)				
Change in CDAI	0.18	0.11	0.25	0.01
Non-Biologic DMARD initiators (N = 23)				
Change in CDAI	-0.14	0.61	0.05	0.79
Biologic DMARD initiators (N = 35)				
Change in CDAI	0.29	0.009	0.45	0.001

All models adjusted for age, race, gender, RA duration, and baseline sleep measures.

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Abstract Number: 2646

Different Wording of the Patient Global Assessment Scale Leads to Different Rating of Disease Activity

Helga Radner[1], Paul Studenic[2], Stanley B. Cohen[3], N Shadick[4], C Iannaccone[5], Elisabeth Lie[6], Maria Dahl Mjaavatten[6], Meredith Leigh Cohen[3], Josef S. Smolen[7] and Daniel Aletaha[8], [1]Department of Internal Medicine III; Division of Rheumatology, Medical University of Vienna, Vienna, Austria, [2]Department of Internal Medicine 3, Division of Rheumatology, Medical University Vienna, Vienna, Austria, [3]Metroplex Clinical Research Center, Dallas, TX, [4]Division of Rheumatology, Immunology & Allergy, Brigham and Women's Hosp, Boston, MA, [5]Division of Rheumatology, Immunology and Allergy, Brigham and Women's Hospital, Boston, MA, [6]Dept. of Rheumatology, Diakonhjemmet Hospital, Oslo, Norway, [7]Dept of Medicine 3, Division of Rheumatology, Medical Univ Vienna, Vienna, Austria, [8]Rheumatology, Medical University Vienna, Vienna, Austria

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Background/Purpose: The patient global assessment of disease activity (PtGA) is a key variable in assessing RA disease activity and remission (REM). Typically assessed on a 10cm visual analogue scale (VAS), its widely employed wording is: *ÔConsidering all of the ways your arthritis has affected you, how do you feel your arthritis is today?Ô.* This wording may be misinterpreted by patients, not addressing symptoms related to RA in detail. We investigated how different wordings of the question influence results obtained for the PtGA.

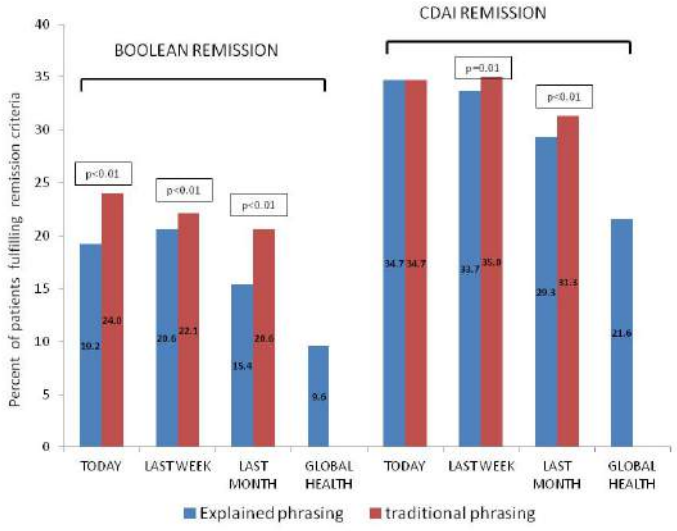
Methods: In 4 international centers, RA patients filled in VAS of 6 differently phrased PtGA covering 2 aspects: one set using the traditional phrasing (PtGA_trad; see above), and one using a version including a detailed explanation of RA disease activity *("Active arthritis can cause joint swelling OR stiffness, pain OR discomfort in your joints. WITH ACTIVE ARTHRITIS, You CAN BE tired during the day, even when you've slept well*"; PtGA_expl); each set was divided into 3 questions with different reference periods: *today (TD), last week (LW)* or *last month (LM)*. Questions were on a separate page, and the order of the questions was random. Also, one question on global health was added (PtGA_GH).

To assess agreement of different PtGAs we calculated intra-class correlation (ICC); mean values of different PtGA were compared using paired t-test. The percentage of patients fulfilling Boolean defined REM (SJC²1; TJC²1; EGA²10mm; PtGA²10mm) and CDAI REM (²2.8) was calculated using different PtGA.

Results: 105 randomly selected patients (age 57.7±13.1 years, disease duration 17.9±10.4 years; 84.8% female, 91.4% white, 81% seropositive) participated in the study. Disease specific characteristics at baseline were: swollen joint count 1.5±2.4; tender joint count 1.6±3.9; pain 21.2±22.3 mm; fatigue 26.7±25.3 mm; HAQ 0.44±0.51; evaluator global (EGA) 15.3±15.8 mm. ICC was high across different PtGA (ICC 0.83 to 0.94; p<0.01), with lower ICCs between GH and the other 6 PtGA (0.53 to 0.65; p<0.05). Paired T-test revealed significantly higher mean values for PtGA_expl as compared to PtGA_trad, independent of the reference period (TD: 27.3±23.2 vs. 23.7±21.7; LW: 26.5±22.3 vs. 24.0±20.8; LM: 30.8±25.5 vs. 24.5±21.2; p<0.01 PtGA_expl vs. PtGA_trad respectively). In the total cohort, the percentage fulfilling either CDAI or Boolean REM was lowest when using PtGA_GH (Boolean REM 9.6%; CDAI REM 21.6%). By using PtGA_expl significantly fewer patients fulfilled CDAI and Boolean REM criteria compared to using the traditional phrasing of PtGA (**figure**).

Conclusion: Against our expectations, a more detailed explanation of "disease activity" led to higher ratings on the PtGA scale, and lower REM rates. It appears to increase awareness of and attention to specific symptoms related to RA disease activity, which would otherwise be discounted.

Figure. Percentage of patients fulfilling CDAI REM and Boolean REM using different wording of PtGA



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Correlations Between Personality Types, Disease Activity and Quality of Life in As and RA Patients

Teodora Donisan[1], Madalina Dobrin[2], Denisa Predeteanu[3,4], Violeta Claudia Bojinca[4,5], Mihai Bojinca[6,7], Dinu Valentin Balanescu[1], Laura Grosanu[3,5], Florian Berghea[4,5], Cosmin Constantinescu[4,5], Daniela Opris[3,4], Andreea Borangiu[3,8], Ruxandra Ionescu[3,4] and **Andra Rodica Balanescu**[4,5], [1]University of Medicine and Pharmacy "Carol Davila", Bucharest, Romania, [2]Department of Internal Medicine and Rheumatology "Sf. Maria" Hospital, Department of Internal Medicine and Rheumatology "Sf. Maria" Hospital, Bucharest, Romania, [3]University of Medicine and Pharmacy "Carol Davila", Department of Internal Medicine and Rheumatology "Sf. Maria" Hospital, Bucharest, Romania, [4]Department of Internal Medicine and Rheumatology "Sf. Maria" Hospital, Bucharest, Romania, [5]Department of Internal Medicine and Rheumatology "Sf. Maria" Hospital, University of Medicine and Pharmacy "Carol Davila", Bucharest, Romania, [6]Department of Internal Medicine and Rheumatology "Dr. I. Cantacuzino" Hospital, University of Medicine and Pharmacy "Carol Davila", Bucharest, Romania, [7]Department of Internal Medicine and Rheumatology "Dr. I. Cantacuzino" Hospital, Bucharest, Romania, [8]University of Medicine and Pharmacy "Carol Davila", Department of Internal Medicine and Rheumatology "Sf. Maria" Hospital, Romania, Bucharest, Romania

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Background/Purpose: It is well established that health related quality of life (HRQoL) is low in patients (pts) with RA and AS. Type C and D behavior patterns negatively influence perceptions on HRQoL, but there is little evidence on the relationship between personality types and clinical outcomes in RA and AS.

Methods: 194 pts from two Rheumatology Departments (104 with RA: 7.7% men, 92.3% women, mean age 59.08 years old, mean duration of disease 12.77 years; 90 with SA: 75.6 men, 22.4 women, mean age 43.63 years old, mean duration of disease 12.7 years) participated in a questionnaire study. HRQoL was evaluated with Medical Outcome Study Short-Term 36 (SF-36v2), analyzing all subscales (Physical function-PF, Social function-SF, Role limitations due to physical problems-RP, Role limitations due to emotional problems-RE, Mental health-MH, Vitality-VT, Bodily Pain-BP and Global Health-GH, including the summary physical component scores-PCS and mental component scores-MCS), personality type A/B with Jenkins Activity Survey (JAS-13), type C with State-Trait Anger Expression Inventory Anger-in Scale (AIS), type D with Type D Personality Scale (DS-14) and disease activity with DAS28 for RA and BASDAI for AS. Pearson's correlation coefficient and independent samples t-tests were used and results were considered statistically significant at $p<0.05$.

Results: In the RA group, type D pts have significant correlations with 7/12 SF36 components, exhibiting limited functional status (higher RP and RE, lower SF), welfare (higher BP, lower VT and MH) and overall decreased GH. These associations are stronger for AS pts, type D personality being linked with deficits in all SF36 subscales, including PCS and MCS. Furthermore, negative affectivity (NA, type D subcomponent) independently influences PF, RP, BP, SF and PCS in AS negatively. Type D is also related with more active disease forms for both RA and AS, not only regarding the total scores in DAS28 and BASDAI, but also with some subcomponents and with other disease activity indicators not included in standard scores, like patient global assessment (PGA), ESR and CRP for AS pts. NA and SI correlate independently with higher DAS28 and BASDAI as well. The same pattern was identified for type C pts. All HRQoL subscales are affected in AS pts, whereas for RA pts, only 7/12 correlations were significant (SF, VT, MH, RP, RE, PCS, MCS). Both RA and AS type C pts have more active disease forms. In the RA group, type A personality did not significantly correlate with HRQoL, but it did positively influence pain visual analog scale (VAS) scores. In AS pts, however, this personality type was found to be linked with better HRQoL (greater VT, better PF, lower RP and RE, overall better PCS and GH) and with less active disease types (lower BASDAI scores, PGA and pain VAS).

Conclusion: Type C and D personality types were found to be strongly correlated with decreased HRQoL and with higher disease activity levels in both RA and AS pts, whereas type A appeared to be linked with less active disease forms in AS pts and with less pain in RA pts. A longitudinal study should be done to establish the causality of these associations, as personality types might be one of the parameters influencing clinical outcomes.

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Abstract Number: 2648

Vitality, Presenteeism, and Their Determinants in Patients with Early Rheumatoid Arthritis Treated with a 6-Month Induction Infliximab Therapy Added on a Triple Combination Therapy

Vappu Rantalaiho[1], Marjatta Leirisalo-Repo[2], Hannu Kautiainen[3], Petri Mankinen[4], Janne Martikainen[5] and Kari Puolakka[6], [1]Department of Internal Medicine, Center for Rheumatic Diseases, Tampere University Hospital, Tampere, Finland, [2]Rheumatology, University of Helsinki and Helsinki University Hospital, Helsinki, Finland, [3]Unit of Primary Health Care, University of Helsinki and Helsinki University Hospital, Helsinki, Finland, [4]Pharmacoeconomics & Outcomes Research Unit (PHORU), School of Pharmacy, University of Eastern Finland, Kuopio, Finland, [5]Pharmacoeconomics and Outcomes Research Unit, School of Pharmacy, University of Eastern Finland, Kuopio, Finland, [6]Department of Medicine, South Karelia Central Hospital, Lappeenranta, Finland
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Background/Purpose: To evaluate vitality, reduced paid and unpaid work ability, and productivity losses for patients with early rheumatoid arthritis (RA) available for work force at baseline and treated with an add-on 6-month induction infliximab therapy versus a combination of three DMARDs and prednisolone**.**

Methods: In the NEO-RACo trial 99 patients with early, DMARD-na•ve RA were treated with a combination of three DMARDs and prednisolone (FIN-RACo) and randomised to receive either infliximab (FIN-RACo+IFX) or placebo (FIN-RACo+PLA) infusions during the first 6 months. The patients were assessed clinically at weeks 0, 4, 6, 10, 14, 18, 22, 26, and at months 8, 10, 12, and thereafter 3-monthly. Patient-reported SF-36 subscales for vitality (0-100, 100=full vitality) and presenteeism, i.e., decreased work productivity while at work (0-100, 100=full presenteeism, i.e. complete decrease of productivity) were gathered at baseline, and at 8, 12, and 24 months, and the mean values were estimated with an area under the curve (AUC) approach.

Results: During the 24-month follow-up, vitality improved significantly in both groups, with no between-group differences. However, the mean score of presenteeism decreased more from baseline to 8 months in the FIN-RACo+IFX group than in the FIN-RACo+PLA group (-46 vs. -32, p=0.004); by 24 months the difference between the groups had levelled out (Figure 1). A negative curvilinear correlation was found between vitality and presenteeism (Figure 2). A higher body mass index and self-reported depressive symptoms were associated with lower vitality and higher level of presenteeism (Table 1).

Conclusion : Vitality (antithesis of fatigue) manifests itself in better work productivity while at work. BMI and depressive symptoms at baseline were found to be the significant determinants of decreased vitality and increased presenteeism.

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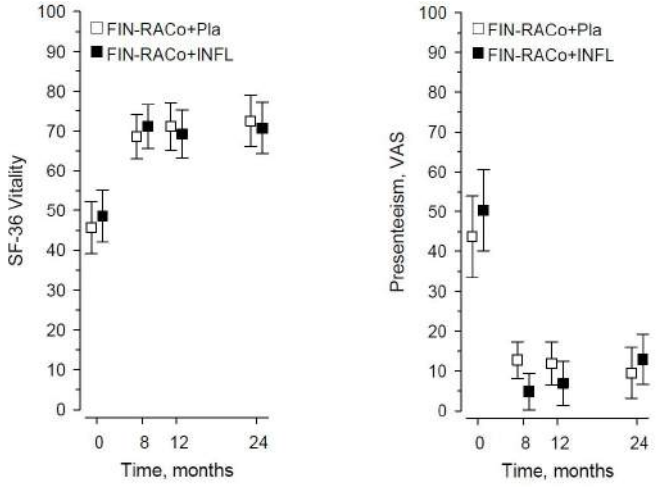

Figure 1. The development of SF-36 vitality and presenteeism scores from baseline to 24 months.

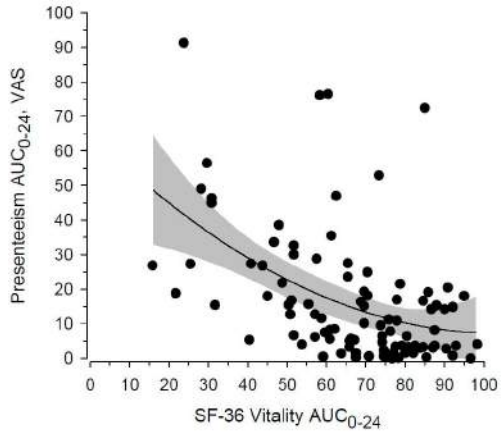

Figure 2. Curvilinear (quadratic) relationship between vitality and presenteeism in patients with early RA over 2 years follow up. Sex- and age-adjusted r= 0.51 (95%CI 0.29 to 0.67).

Table 1. Determinants of vitality and presenteeism in patients with early RA

	SF-36 Vitality AUC0-24		Presenteeism AUC0-24, VAS	
	β (95% CI)	P-value	β (95% CI)	P-value
Treatment IFX	0.01 (-0.17 to 0.19)	0.91	-0.02 (-0.19 to 0.15)	0.80
Male	0.13 (-0.05 to 0.31)	0.16	0.07 (-0.10 to 0.25)	0.41
Age	-0.04 (-0.23 to 0.15)	0.67	0.16 (-0.01 to 0.34)	0.069
Duration of symptoms	-0.06 (-0.24 to 0.13)	0.55	-0.05 (-0.23 to 0.12)	0.56
Rheumatoid factor present	0.02 (-0.16 to 0.21)	0.81	-0.01 (-0.18 to 0.17)	0.92
DAS28	0.03 (-0.21 to 0.27)	0.79	0.17 (-0.06 to 0.39)	0.15
Physician's global assessment	-0.09 (-0.33 to 0.15)	0.47	0.23 (-0.01 to 0.46)	0.051
Sharp-van der Heijde score	0.03 (-0.15 to 0.22)	0.71	-0.16 (-0.33 to 0.01)	0.072
Body Mass Index	-0.21 (-0.39 to -0.04)	0.018	0.21 (0.04 to 0.38)	0.016
Depressive Symptoms	-0.41 (-0.57 to -0.26)	<0.001	0.21 (0.04 to 0.37)	0.015

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Abstract Number: 2649

Test-Retest Reliability of the 5-Item Compliance Questionnaire Rheumatology and Factors Influencing Its Assessment of Adherence in Patients with Rheumatoid Arthritis

Raquel Sweezie[1], Mary J. Bell[2], Charles Goldsmith[3], Imy Chiu[1], Anna Gutlin[1] and Sharron Sandhu[1], [1]Rheumatology, Sunnybrook Health Sciences Centre, Toronto, ON, Canada, [2]Rheum Div/Univ of Toronto, University of Toronto, Toronto, ON, Canada, [3]Faculty of Health Sciences, Simon Fraser University, Vancouver, BC, Canada

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Background/Purpose: Adherence to disease modifying anti-rheumatic drug (DMARD) therapy is suboptimal in patients with rheumatoid arthritis (RA). Efficient, low-cost measures are required for optimal monitoring of medication adherence in the rheumatology clinic. Self-report tools are the most efficient and cost-effective measures available. Recently, a 5-item version of the Compliance Questionnaire Rheumatology (CQR5) was developed from the original 19-item version to reduce patient burden[1]. Reliability of CQR5 over time has not been evaluated, nor has its association with other factors that can impact medication taking. In a sample of RA patients, we investigated 1) test-retest reliability of CQR5 and 2) correlation of CQR5 with psychosocial and physical factors known to influence adherence.

Methods: RA patients (disease duration ≥ 1 yr) taking at least one DMARD were randomly selected from a rheumatology clinic database. Patients were assessed at baseline and 2 weeks. Demographic data were collected at baseline. At each visit, medication adherence was assessed with CQR5. Each item on the CQR5 was scored on a 4-point Likert scale (1 = strongly disagree, 4 = strongly agree). Scores for each item were summed into a total score which varied between 0 and 20. Higher scores indicated greater adherence. Psychosocial measures were evaluated using 1) Beliefs about Medicines Questionnaire (BMQ)[2], which examines beliefs around necessity of and concern with taking medications (high scores reflect strong beliefs) and 2) RA Self-Efficacy Questionnaire (RASE)[3] (high scores reflect high self-efficacy). Physical factors were assessed using 1) multi-dimensional HAQ (MDHAQ)[4] (high numbers indicate poor general health and worse symptoms) and 2) disease activity measured by the Composite Disease Activity Index (CDAI)[5](high scores indicate high disease activity). Intraclass correlation coefficients (ICC) were used to evaluate test-retest reliability of CQR5 scores measured at baseline and 2 weeks. Bivariate correlations (Pearson's r) were performed to determine relationships between psychosocial factors and medication adherence measured by CQR5 at baseline.

Results: 100 RA patients, [age, mean (SD) = 60.75(12.67) yrs], were recruited. In this sample, the CQR5 demonstrated excellent test-retest reliability (ICC=0.78). Adherence measured by CQR5 had a strong positive correlation with BMQ necessity scores ($r = 0.64$, $p<0.001$) and a weak negative correlation with BMQ concerns scores ($r = -0.22$, $p<0.05$). Correlations between the CQR5 and RASE, MDHAQ, and CDAI were negligible ($r<0.17$, $p>0.05$).

Conclusion: The CQR5 demonstrates excellent reliability over time. Adherence measured by the CQR5 is associated with beliefs about medicines, especially around the necessity of taking medications. A more in-depth investigation of the CQR5, including its validation against a gold standard for measuring medication adherence, is currently underway.

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Disclosure: R. Sweezie, None; **M. J. Bell**, None; **C. Goldsmith**, None; **I. Chiu**, None; **A. Gutlin**, None; **S. Sandhu**, None.

Abstract Number: 2650

Impact of Patient Education on the Satisfaction of Rheumatoid Arthritis Patient : A Randomized Trial of Nurse-Led Vs. Physician-Led Education

Soo-Kyung Cho[1], Dam Kim[1], Jeongim Choi[1], Seung Lee[2], Seung Taek Song[2], GaEun Bae[3], Hyeon Kyung Kim[1] and **Yoon-Kyoung Sung**[1], [1]Department of Rheumatology, Hanyang University Hospital for Rheumatic Diseases, Seoul, South Korea, [2]Hanyang University Hospital for Rheumatic Diseases, Seoul, South Korea, [3]Rheumatology, Hanyang University Hospital for Rheumatic Diseases, Seoul, South Korea

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Background/Purpose: Early, more aggressive treatment of rheumatoid arthritis (RA) has resulted in greatly improved outcomes compared to past decades. However, because of heterogeneity and complexity of RA disease course and potential toxicity of therapies, shared decision-making (SDM) between physician and patient is central to patient safety and outcomes. Patient education (PE) is a useful tool for patient empowerment, since patients should aware of their disease course, treatment target, medications and their adverse effects. However, it is uncertain that how we can measure the clinical benefits of PE and who should be responsible for educating patients. This study aims to examine the impact of PE on the patients' satisfaction in RA patients and to compare the nurse-led education with physician-led education for RA patients.

Methods: Patients were enrolled by categorizing in three according to their clinical characteristics: early RA patient (<2 years of disease duration) with conventional DMARDs (Group I), established RA patients (≥ 2 years of disease duration) with conventional DMARDs (Group II), and RA patients treated with biologic DMARDs (Group III). After constructing two groups of nurse-led and physician-led education, stratified randomization was performed by randomly assigning the two education groups separately within each group by characteristics. Patient education materials were composed of the characteristics and outcomes of RA, T2T, treatment options with side effects, and comorbidities. Two times of face-to-face education was performed and changes in patient satisfaction before and after PE were assessed using visual analogue scale (VAS, 0-100mm) and Leeds Satisfaction Questionnaire (LSQ) score. Changes of patients' outcomes were measured using DAS28-ESR, HAQ-DI, and EQ-5D scores. Changes of patients' satisfaction and disease outcomes between before and after PE were compared using paired t-test, and the comparison between nurse-led and physician-led education was analyzed using independent t-test.

Results: A total of 120 RA patients, 40 patients from each groups, were randomized to receive either nurse-led or physician-led education. Among them, 113 patients completely received twice face-to-face education and final assessment with 1 or 2 month interval: 38, 36, and 39 patients in group I, II, and III, respectively. In total patients, patients' satisfaction by PE was significantly increased from 87.8 (± 13.1) to 92.3(± 8.8) in VAS ($p<0.01$), and from 3.7 (± 0.4) to 4.0 (± 0.4) in LSQ score ($p<0.01$). The improvement of patients' satisfaction measured with LSQ was highest in group I (0.45 ± 0.45) and followed by group II (0.22 ± 0.34) and group III (0.19 ± 0.38). However, there was no improvement in DAS28-ESR, HAQ, or quality of life after PE. Improvement of patients' satisfaction by LSQ after nurse-led education was 0.37 ± 0.37 and it was higher than 0.27±0.45 after physician-led education, but it was not statistically different (P =0.25).

Conclusion: Patient education in outpatient clinic for RA patients improved patients' satisfaction, especially in patients with early stage. Nurse-led education showed comparable improvement in patients' satisfaction with physician-led education.

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Abstract Number: 2651

Evaluation of the Impact of Disease-Modifying Antirheumatic Drugs on Anti-Cyclic Citrullinated Peptide Autoantibody Levels in Clinical Practice

E Alemao[1], KK Gandhi[1], C Iannaccone[2], M Frits[2], JS Coblyn[2], N Shadick[2] and Michael Weinblatt[2], [1]Bristol-Myers Squibb, Princeton, NJ, [2]Brigham and Women's Hospital, Boston, MA
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Background/Purpose: Testing for anti-citrullinated peptide antibodies (ACPA) is included in the 2010 ACR classification criteria for RA. ACPA concentration, beyond ACPA positivity, is indicative of more aggressive radiographic progression. Biologic (b)DMARDs such as abatacept have been shown to reduce ACPA levels in clinical trials; however, there are limited data on the impact of DMARDs on ACPA in clinical practice. **Methods:** Data were analyzed from patients (pts) enrolled in a large, US RA registry established in 2003. The registry comprises pts with established RA who were evaluated annually for multiple clinical and laboratory measures, and semi-annually for multiple pt-reported outcomes and resource utilization parameters. The current analysis is based on pts enrolled in the registry with ACPA values at the time of initiating DMARDs (baseline ACPA levels). Baseline and follow-up ACPA levels were measured using a validated ELISA (Inova Diagnostics) until its discontinuation in 2011; the Euro-Diagnostica assay (distributed by IBL-America, Minneapolis, MN), which supplied the 'capture' antibody for the original Inova Diagnostics ELISA, has been used since (correlation between the two assays: 0.984). Mean ACPA level and mean change from baseline to Year (Yr) 1 and Yr 2 were compared between conventional (c)DMARDs, TNF-inhibitors (TNF-Is) and abatacept. To control for baseline differences in clinical and laboratory measures, additional ACPA comparisons between groups were conducted based on a 1:1 matched cohort of TNF-I and abatacept pts. **Results:** Overall, 1316 (98%) registry pts with ACPA levels at therapy initiation were included in the analysis; 45, 49 and 6% of pts were initiated on cDMARDs, TNF-Is or abatacept, respectively. The mean (SD) age (yrs) was 58.7 (14.1), 54.7 (13.6) and 59.3 (11.4) for cDMARD, TNF-Is and abatacept cohorts, respectively. The average (SD) disease duration (yrs) in the abatacept cohort was 20.5 (12.0) (vs 12.5 [12.6] for cDMARDs and 14.2 [11.4] for TNF-Is). The abatacept group also had higher mean (SD) disease activity (24.3 [15.7] vs 19.9 [15.5] in cDMARDs and 20.1 [17.3] in TNF-Is). ACPA values at baseline, Yr 1 and Yr 2 by treatment group are shown in Table 1. The pt characteristics of the matched abatacept and TNF-I groups, and ACPA values in Yr 1 and Yr 2 are shown in Table 2. Pts treated with abatacept showed a lowering of the ACPA values during follow-up, while similar reductions in ACPA values were not seen in pts treated with TNF-Is or cDMARDs.

Conclusion:

These results from a real-world clinical setting support observations from clinical trials that abatacept treatment leads to a reduction of ACPA levels, which is not seen with TNF inhibitors.

Table 1. Baseline and follow-up ACPA levels (U/mL) in pts treated with cDMARDs, TNF-Is and abatacept				
	N	**Mean (SD)**	**Change from baseline**	
			Median	**Mean (SE)**
cDMARDs				
Baseline	591	99.8 (133.0)	–	–
Yr 1	333	103.7 (138.8)	0.00	2.1 (3.0)
Yr 2	263	130.6 (168.1)	1.34	29.0 (4.2)
TNF-Is				
Baseline	651	157.1 (162.5)	–	–
Yr 1	380	155.8 (151.5)	–0.01	3.3 (3.6)
Yr 2	323	175.0 (162.4)	3.40	26.2 (4.6)
Abatacept				
Baseline	74	169.1 (225.3)	–	–
Yr 1	30	89.7 (122.9)	–0.47	–20.5 (20.3)
Yr 2	19	112.5 (135.4)	–11.18	–55.1 (29.4)

Table 2. Baseline characteristics and follow-up ACPA levels in matched cohorts of pts treated with TNF-Is and abatacept			
	TNF-Is (n=66)	**Abatacept (n=66)**	**p-value**
Baseline age, mean (SD)	57.0 (11.7)	58.9 (11.4)	0.34
Female, %	84.8	81.8	0.64
Baseline disease duration, mean (SD)	19.1 (11.3)	20.0 (11.3)	0.64
Baseline DAS28 (CRP), mean (SD)	3.9 (1.5)	4.0 (1.5)	0.51
Baseline SDAI, mean (SD)	24.3 (16.5)	24.3 (15.7)	0.99
Baseline ACPA, mean (SD)	167.7 (227.2)	167.1 (227.1)	0.99
Follow-up ACPA levels (U/mL)	**TNF-Is**	**Abatacept**	
1-yr follow-up ACPA			
N	33	27	
Mean (SE)	165.8 (36.7)	84.5 (23.8)	
Median	78.8	29.4	
Interquartile range (IQR)	12.3 to 272.7	3.7 to 97.0	
ACPA change from baseline to Yr 1			
N	33	27	
Mean (SE)	4.20 (23.2)	–11.4 (19.3)	
Median	–0.23	–0.45	
IQR	–12.7 to 20.1	–12.3 to 4.8	
2-yr follow-up ACPA			
N	29	16	
Mean (SE)	155.1 (30.4)	97.5 (32.2)	
Median	113.8	48.7	
IQR	3.3 to 310.2	11.2 to 97.2	
ACPA change from baseline to Yr 2			
N	29	16	
Mean (SE)	18.2 (14.4)	–40.5 (27.7)	
Median	0.0	–40.5	
IQR	–6.1 to 49.2	–33.0 to 0.23	

Disclosure: E. Alemao, Bristol-Myers Squibb, 3,Bristol-Myers Squibb, 1; **K. Gandhi**, Bristol-Myers Squibb, 1,Bristol-Myers Squibb, 3; **C. Iannaccone**, None; **M. Frits**, None; **J. Coblyn**, None; **N. Shadick**, Amgen, Questcor, Crescendo Biosciences, UCB, Bristol-Myers Squibb, 2; **M. Weinblatt**, Amgen, Abbvie, Bristol-Myers Squibb, Lilly, Novartis, Merck, Pfizer, Roche, Crescendo, Myriad Genetics, UCB, 5,Bristol-Myers Squibb, Myriad Genetics, UCB, 2.

Abstract Number: 2652

Power Doppler Ultrasound Features in Rheumatoid Arthritis Patients in Clinical Remission: Reclassifying Disease Activity?

Facundo Vergara[1], Santiago Ruta[1], Maria de los Angeles Gallardo[1], Emmanuel Bertiller[2], Josefina Marin[1], Javier Rosa[3], Ricardo Garcia-Monaco[4] and Enrique R. Soriano[5], [1]Rheumatology Unit, Internal Medicine Service, Hospital Italiano de Buenos Aires, Buenos Aires, Argentina, [2]Rheumatology Unit, Internal Medicine Service, Hospital Italiano de Buenos Aires, Instituto Universitario Hospital Italiano de Buenos Aires, and Fundacion PM Catoggio, Buenos Aires, Argentina, [3]Rheumatology, Hospital Italiano de Buenos Aires, Buenos Aires, Argentina, [4]Radiology and Imagenology Department, Hospital italiano de Buenos Aires, Buenos Aires, Argentina, [5]Internal Medicine, Hospital Italiano de Buenos Aires, Buenos Aires, Argentina

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Background/Purpose: Many studies have shown disparity between clinical and ultrasound (US) findings in rheumatoid arthritis (RA). US appears to detect subclinical synovitis in patients in clinical remission. The aim of the present study was to compare clinical and US activity in patients with RA in clinical remission, applying different US definitions of an active joint, and to evaluate whether replacing clinical by US assessment would change patients' disease activity state.

Methods: We included consecutive patients with RA according to 2010 ACR/EULAR criteria in clinical remission by DAS28 (<2.6). US examinations were performed by the same rheumatologist, using a MyLab 70 machine equipped with 6-18 MHz broad band multi-frequency linear transducer. The following 20 joints of both hands were assessed: wrist, first to fifth MCP joints and second to fifth proximal PIP joints. Power Doppler (PD) US signal was evaluated on a semi-quantitative scale from 0 to 3 (0= no PD signal; 1= a single PD signal; 2= confluent PD signal in less than 50% of intra-articular area; 3= PD signal in more than 50% of intra-articular area). Three different US DAS28 (US DAS28) were constructed, replacing the clinical swollen joint count by the PD US joint count (clinical examination was used for joints not included in US assessment) using PD grade ≥ 1, ≥ 2 or ≥ 3, respectively.

Results: Eighty six patients were included. Sixty-five (75.5%) were female; mean age (SD) was 58.5 (13.8) years; and mean disease duration (SD) was 7.2 (7.9) years. Mean DAS28 (SD) was 2.1 (0.37). Twenty-three (26.7%) patients had at least one joint with abnormal vascularization by PD US (PD ≥ 1). Among these, 14 (60.8%) had only one joint with abnormal vascularization by PD ≥ 1; 6 (26.1%) had two; 2 (8.7%) had three and 1 (4.3%) had four. Mean (SD) US DAS28 were 2.18 (0.47); 2.16 (0.45) and 2.1 (0.4) using the number of joints with PD grade ≥ 1; ≥2 and ≥3, respectively. Thirteen out of 86 (15%) patients were reclassified to low disease activity using US DAS28 with PD ≥ 1. Using US DAS28 with PD ≥ 2, only nine (10.5%) patients were reclassified to low disease activity, and US DAS28 with PD ≥ 3 did not reclassify any patient. No patients were reclassified into moderate or high disease activity using any of PD grades (Table). Correlation between clinical DAS28 and US DAS28 was excellent (Spearman's rho: 0.8271; 0.8470 and 0.8701 for US DAS28 using PDUS grade ≥ 1; ≥ 2 and ≥3, respectively).

Table. Clinical and US DAS28 scores in patients with at least one joint with PD signal.

	Clinical DAS28	Number of joints with PD Grade 1	Number of joints with PD Grade 2	Number of joints with PD Grade 3	US DAS28 with PD grade ≥ 1	US DAS28 with PD grade ≥ 2	US DAS28 with PD grade ≥ 3
1	2,36	0	1	0	**2,64**	**2,64**	2,36
2	1,64	0	0	1	1,64	1,64	1,64
3	2,44	0	1	0	**2,72**	**2,72**	2,44
4	2,17	0	2	0	2,57	2,57	2,17
5	2,52	0	3	0	**2,72**	**2,72**	2,52
6	2,5	1	0	0	**2,78**	2,5	2,5
7	2,42	0	3	0	**2,91**	**2,91**	2,42
8	2,06	0	1	0	2,34	2,34	2,06
9	2,38	1	0	0	**2,66**	2,38	2,38
10	2,57	1	0	0	**2,85**	2,57	2,57
11	2,52	1	0	0	**2,8**	2,52	2,52
12	2,43	3	1	0	**2,99**	**2,71**	2,43
13	2,57	0	2	0	**2,96**	**2,96**	2,57
14	1,64	0	1	1	2,04	2,04	1,92
15	2,59	0	1	0	2,59	2,59	2,31
16	2,24	0	2	0	**2,63**	**2,63**	2,24
17	2,34	1	1	0	**2,74**	**2,62**	2,34
18	1,25	0	1	0	1,53	1,53	1,25
19	2,31	0	1	0	2,59	2,59	2,31
20	2,08	0	1	0	2,36	2,36	2,08
21	2,06	0	1	0	2,34	2,34	2,06
22	0,4	1	1	0	0,4	0,28	0,0
23	2,5	0	1	0	**2,78**	**2,78**	2,5

PGA: patient global assessment; **ESR**: erythrosedimentation rate.

Conclusion: Although around one quarter of patients with RA in clinical remission showed PD US features indicating residual activity, a low percentage of these patients were reclassified to a DAS28 low disease activity state, and none to either moderate or high disease activity, using PD US assessment. There was a very good correlation between clinical and US assessment.

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Abstract Number: 2653

Diagnostic Value of the Prednisolone Test in Patients with Possible Rheumatoid Arthritis

Uta Kiltz[1], Christine von Zabern[1], Xenofon Baraliakos[1], Frank Heldmann[1], Bernhard Mintrop[1], Michael Sarholz[1], Martin van Werde[1], Claudia Klink[2], Dietmar Krause[2], Friedrich Dybowski[3], Ludwig Kalthoff[3], Liane Hein[3] and Juergen Braun[1], [1]Rheumazentrum Ruhrgebiet, Herne, Germany, [2]Private rheumatology office, Gladbeck, Germany, [3]Private rheumatology office, Herne, Germany
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Background/Purpose:

In patients with tender and swollen finger joints, the differential diagnosis between rheumatoid arthritis (RA) and osteoarthritis (OA) of

the hands can be initially difficult. In a previous pilot study we have shown that the positive response to a 3-day-course of 20 mg prednisolone (the 'pred-test') differentiates between RA and OA of the hands. An subjective percentage of improvement of 40% was found to discriminate best. The objective is to study the diagnostic value of the pred-test in patients with possible RA.

Methods:

Consecutive patients with hand pain referred because of suspected RA (n=100) were included in the study. Clinical examination by one experienced rheumatologist, laboratory tests, and magnetic resonance imaging (MRI) were regularly performed. All patients received 1g paracetamol/day for 5 days. On days 3-5 a morning dose of 20 mg of prednisolone was added. Hand pain was quantified on a numerical rating scale (NRS 0–10) and the subjective percentage of improvement recorded. The predefined cut-off of 40% improvement was applied to differentiate between responders and non-responders. Diagnoses were made by the expert who was unaware of the treatment result. Patients were reexamined at week 12 to confirm the diagnosis.

Results:

There were 95 patients with complete data (Tab.1). RA was diagnosed in about half of the patients. RA patients had more swollen joints, higher CRP levels and a comparable HAQ (Tab.1). The pred test was positive in 42.1% of the patients (40/95). The median percentage of improvement after 3 days of 20 mg of prednisolone was higher in RA than in OA: 50% (IQR 30%-60%) vs. 20% (IQR 10%-30%), $p<0.001$. The sensitivity and specificity of the pred-test was 65.9% (31/47) and 81.2% (39/48), and the positive and negative predictive value was 0.77 and 0.70, respectively.

Table 1: Clinical characteristics of patients with RA and OA (mean±SD)

	RA (n=47)	OA (n=48)
mean age	57.6±12.2	54.5±9.2
sex (female)	85%	68%
pain	6.1±1.6	5.8±1.6
HAQ	1.15±0.5	1.13±0.4
Swollen joint count (66/68)	2.3±2.4	1.4±2.3
Tender joint count (68/68)	13.0±8.5	13.9±10.5
CRP (mg/dl)	0.5±0.6	0.2±0.3

Conclusion:

This is the first evaluation of the widely used pred-test that has ever been performed. We found that this test has a moderate sensitivity and good specificity. We propose that rheumatologists use this test in uncertain clinical situations to be able to better differentiate between inflammatory arthritis and osteoarthritis. Finally, we hope that a negative test result will prevent patients to receive unnecessary glucocorticoid treatment, while a positive test will help to identify patients with inflammatory arthritis who can then receive proper treatment.

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Abstract Number: 2654

The Influence of Patient Reported Morning Stiffness on Patient Global Assessment in Rheumatoid Arthritis Patients Not Achieving ACR/EULAR Boolean Remission in a Large US Registry

Dimitrios A. Pappas[1,2], Robert J. Holt[3], Ying Shan[4], Jeffrey D. Kent[5], John T. Nguyen[4], Joel M. Kremer[6] and Jeffrey D. Greenberg[2,7], [1]Columbia University, New York, NY, [2]Corrona, LLC, Southborough, MA, [3]University of Illinois - Chicago, Chicago, IL, [4]Corrona, LLC., Southborough, MA, [5]Horizon Pharma USA, Inc., Deerfield, IL, [6]Albany Medical College and The Center for Rheumatology, Albany, NY, [7]NYU School of Medicine, New York, NY

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SESSION INFORMATION

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Background/Purpose: The ACR/EULAR Boolean definition of remission is expected to be used as an outcome measure in randomized clinical trials for rheumatoid arthritis (RA). Boolean defined remission requires satisfaction of all of the following: (TJC≤1, SJC≤1, CRP≤1 mg/dl and patient global assessment (PGA) ≤1 (0-10 scale) (1).The extent to which PGA may be driven by the presence and the duration of morning stiffness and thus the ability to meet Boolean based remission criteria has not been investigated.

Methods: Patients enrolled in the Corrona RA registry were analyzed. Data from the most recent visit for the components of Boolean remission criteria were used. The percentage of patients in Boolean based remission was calculated. Morning stiffness data (presence or not, and duration) as reported by the patient at each registry visit were utilized. We investigated the prevalence and the duration of morning stiffness in RA patients in remission and for those not meeting the remission criteria due to PGA>1 while all other components (TJC, SJC, CRP) were ≤1.

Results: Out of 24,170 patients, Boolean defined remission was met in 4,856 (20.09%) patients at the most recent visit. Boolean remission was not met in 19,314 (79.91%) patients and 4,371 (18.08%) patients did not meet remission criteria due to PGA>1. Morning stiffness was present in 39.4% of patients in remission (and PGA≤1) while it was reported in 78.4% of patients not in remission because PGA>1 ($p<0.001$). The median duration of stiffness at most recent visit was 0.33(IQR: 0.17-0.5) hours for patients in remission while it was 0.75(0.33-1.5) hours for patients not in remission because of PGA>1($p<0.001$). 8.9% of patients had morning stiffness >1 hour in the former group while 26.3% of patients reported a similar duration in the latter group ($p<0.001$).

Conclusion: PGA may be affected by several factors and may not allow patient to meet remission criteria based on the Boolean definition. In this analysis, 18.08% of patients did not meet remission criteria because PGA>1. Morning stiffness duration was longer in these patients compared to patients in remission. This finding suggests that morning stiffness is an important contributor to the PGA and likely plays a role in patients' inability to meet the remission criteria.

Reference: 1. Bykerk VP, Massarotti EM. The new ACR/EULAR remission criteria: rationale for developing new criteria for remission. *Rheumatol* 2012;51 :vi16–vi20.

Disclosure: D. A. Pappas, Corrona, LLC, 3,Novartis, 9; **R. J. Holt**, Horizon Pharma USA, 5; **Y. Shan**, Corrona, LLC., 3; **J. D. Kent**, Horizon Pharma USA, 3; **J. T. Nguyen**, Corrona, LLC., 3; **J. M. Kremer**, Corrona, LLC., 3,Corrona, LLC., 1,AbbVie, Amgen, BMS, Genentech, Lilly, Pfizer, 5; **J. D. Greenberg**, Corrona, LLC., 3,Corrona, LLC., 1,AstraZeneca, Pfizer, Celgene, Novartis, Genentech, Janssen, 5.

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Abstract Number: 2655

Clinically Important Worsening (CIW) of RA Disease Activity Requiring an Increase in Therapy Can be Identified Using a Combined Patient and Physician Report of Flare

VP Bykerk[1,2], Clifton O. Bingham III[3], Ernest H. Choy[4], Daming Lin[2], Rieke Alten[5], Robin Christensen[6], Daniel E. Furst[7], Francis Guillemin[8], Sarah Hewlett[9], Amye L. Leong[10], Lyn March[11], Thasia Woodworth[12], Gilles Boire[13], Carol Hitchon[14], Shahin Jamal[15], Edward C. Keystone[16], Janet E. Pope[17], J Carter Thorne[18], Diane Tin[19], Susan J. Bartlett[20,21,22] and CATCH Investigators and OMERACT Flare Group, [1]Rheumatology, Hospital for Special Surgery, New York, NY, [2]Rheumatology, Mount Sinai Hospital, University of Toronto, Toronto, ON, Canada, [3]Rheumatology, Johns Hopkins University, Baltimore, MD, [4]Cardiff University, Institute of Infection and Immunity, Tenovus Building, University Hospital of Wales, Cardiff, United Kingdom, [5]Internal Medicine, Rheumatology & Clinical Immunology, Schlosspark-Klinik, University Medicine Berlin, Berlin, Germany, [6]The Parker instutute, RC, Copenhagen, Denmark, [7]Medicine, University of California, Los Angeles, David Geffen School of Medicine, Los Angeles, CA, [8]University of Lorraine, Nancy, France, [9]Academic Rheumatology, University of West of England, Bristol, United Kingdom, [10]Spokesperson; Strategic Relations, BONE AND JOINT DECADE, Santa Barbara, CA, [11]Department of Rheumatology, Northern Clinical School, Institute of Bone and Joint Research, Kolling Institute, University of Sydney & Department of Rheumatology, Royal North Shore Hospital, St Leonards, Sydney, Australia, [12]Medicine, Division of Rheumatology, David Geffen School of Medicine, Los Angeles, CA, [13]Department of Medicine/Division of Rheumatology, Université de Sherbrooke, Sherbrooke, QC, Canada, [14]Department

of Rheumatology, University of Manitoba, Winnipeg, MB, Canada, [15]Vancouver Coastal Health, Vancouver, BC, Canada, [16]Mount Sinai Hospital, University of Toronto, Toronto, ON, Canada, [17]Monsignor Roney Bldg/Rheum, University of Western Ontario, St Joseph Health Care, London, ON, Canada, [18]University of Toronto, Toronto, ON, Canada, [19]The Arthritis Program, Southlake Regional Health Centre, Newmarket, ON, Canada, [20]Medicine , Divisions of Clinical Epidemiology, Rheumatology, Respirology, McGill University, Montreal, QC, Canada, [21]Division of Rheumatology, Johns Hopkins University, Baltimore, MD, [22]Division of Rheumatology, Johns Hopkins School of Medicine, Baltimore, MD
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Background/Purpose: A reference point for clinically important worsening (CIW) of RA disease activity requiring retreatment or escalation is needed for randomized trials of treatment withdrawal. These studies are usually performed in patients (pt) in states of low disease activity (LDA) or remission (REM). Restarting RA therapy needs a Pt-MD concordant assessment of worsening ("flare") to maximize adherence. Here we examine the construct and convergent validity of a combined Pt-MD concordant report of flare that indicates CIW in pts who are in LDA/REM.

Methods: CATCH (Canadian early ArThritis CoHort) Pts were eligible for study if they were in DAS28 REM or LDA at first (V1) of 2 sequential visits (3 or 6 months apart). RA flare was assessed at the 2nd visit (V2). Pts reported if their RA was flaring (yes/no) and if yes the severity and duration. Concurrently, MDs classify them as flaring (yes/no). Changes in disease activity and treatment, OMERACT core flare domains, MD measures, inflammatory markers, and DAS28 were assessed in pts reporting flare, MDs classifying flare, and when Pt-MDs were concordant in identifying flare**.**

Results: Of 849 RA pts who completed OMERACT flare questions twice between 11/2011-10/2014, 360 (42%) were in LDA or REM at the 1st of paired visits. Pts most often reported a flare duration lasted >14 days in Pt-MD concordant flares with mean (SD) severity rating of 5.0 (2.3)(Table 1). DAS28 worsening was less in MD-report of flare DAS28 0.9 (1.3) vs 1.8 (1.2) in Pt-MD concordant flare. Prior treatment reduction/withdrawal was observed in 36% of Pt-MD flares with subsequent treatment addition in 61% at/after the 2nd "Flare". Mean differences in measures of RA disease activity, (PROs, clinical, and laboratory assessments), were significant in pt-reported flare, and of greater magnitude with concordant Pt-MD flare. This was notable for all measures in the existing RA core set for monitoring disease activity and the expanded OMERACT Flare Core Set (Table 2).

Conclusion: A concordant Pt-MD report of flare can provide a feasible assessment of CIW of RA disease activity associated with worsening in ACR RA core set measures and domains in the expanded OMERACT Flare core set. This anchor for CIW is often associated with stopping or reducing treatment and with subsequent increases in therapy. These data provide a rationale for using this Pt-MD anchoring construct to identify CIW for existing and new RA disease activity measures.

Table 1: Patient and MD Reported Flare Characteristics, DAS28 worsening, and changes in treatment.			
Patients Previously in DAS28 LDAS or REM (N=360)	**Patient Flare (Yes)**	**MD Flare**	**Patient Flare Yes/ MD Flare**
	N=58 (16%)	N=71 (20%)	N=28 (8%)
Flare severity (0-10) (mean SD)	4.4 (2.1)	4.5 (2.6)	5.0 (2.3)
Duration of flare			
1-3 days	12 (21%)	5 (18%)	5 (18%)
4-7 days	6 (10%)	4 (14%)	4 (14%)
8-14 days	12 (21%)	6 (21%)	6 (21%)
>14 days	28 (48%)	13 (46%)	13 (46%)
Change in DAS28:			
DAS28 at time of flare	3.2 (1.4)	3.0 (1.4)	3.9 (1.4)
DAS28 at previous visit	2.1 (0.7)	2.1 (0.6)	2.1 (0.7)
Worsening of DAS28	1.1 (1.4)	0.9 (1.3)	1.8 (1.2)
Treatment Reduced/Stopped Before Flare Assessment			
Recent Treatment Reduction (from visit 1)	22 (38%)	29 (41%)	9 (32%)
Recent Treatment Cessation (from visit 1)	19 (33%)	28 (39%)	7 (25%)
Recent Treatment Reduction or Cessation (from visit 1)	24 (41%)	34 (48%)	10 (36%)
Treatment Increase with Flare			
MD Intent to increase Treatment Increase (at 2nd Visit)	25 (45%)	37 (53%)	17 (61%)
Observed Treatment Increase (Visit 2 or next visit):			
Non MTX DMARDS	9 (16%)	10 (14%)	7 (25%)
MTX added/increased (dose or po to sc)	2 (6%)	3 (7%)	1 (7%)
Biologics added/switched (not due to side effect)	2 (3%)	3 (4%)	2 (7%)
Steroids (po/IM or IA; not used in prior visit)	7 (12%)	7 (10%)	4 (14%)
NSAIDs added (not used in the prior visit)	3 (5%)	3 (4%))	2 (7%)

Table 2: Changes in ACR Core Set and OMERACT Flare Core Set Domains with Patient-MD Report of Flare.						
Patients Previously in DAS28 LDAS or REM	**Patient Flare (yes) ***		**Mean Difference of Change**	**Pt Yes Flare / MD Yes Flare**	**Pt No Flare / MD No Flare**	**Mean Difference of Change**
Domains	Yes	No				
	N = 58	N = 302	**(95% CI)**	N = 28	N = 219	**(95% CI)**
OMERACT Flare Questionnaire Items (0-10)						
Pain	1.7 (2.4)	-0.4 (1.8)	2.0 (1.4, 2.7)	2.3 (2.6)	-0.5 (1.7)	2.7 (1.7, 3.8)
Stiffness	1.3 (3.0)	-0.3 (1.7)	1.6 (0.8, 2.4)	2.1 (3.1)	-0.4 (1.7)	2.5 (1.3, 3.7)
Function	1.6 (2.7)	-0.3 (1.9)	1.9 (1.2, 2.6)	1.8 (2.7)	-0.4 (1.8)	2.2 (1.1, 3.2)
Fatigue	0.6 (3.1)	-0.3 (2.1)	0.9 (0.1, 1.8)	1.6 (3.0)	-0.5 (1.9)	2.1 (0.9, 3.3)
Participation	1.5 (2.7)	-0.3 (1.8)	1.8 (1.1, 2.5)	1.8 (2.7)	-0.4 (1.6)	2.2 (1.1, 3.3)
Pt Global	1.9 (3.0)	-0.3 (2.1)	2.2 (1.3, 3.0)	2.6 (2.8)	-0.3 (2.2)	3.0 (2.1, 3.9)
Physician Measures						
MD Global (0-10)	1.2 (2.3)	-0.1 (1.3)	1.3 (0.7, 2.0)	2.7 (2.1)	-0.3 (1.2)	3.0 (2.1, 3.8)
MD TJC28	2.8 (4.5)	0.3 (2.4)	2.4 (1.2, 3.7)	4.8 (5.5)	0.2 (1.9)	4.6 (2.4, 6.7)

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MD SJC28	1.6 (4.0)	0.0 (1.4)	1.6 (0.5, 2.7)	3.4 (5.0)	-0.1 (1.2)	3.6 (1.6, 5.5)
Acute Phase Reactants						
CRP (mg/L)	3.0 (11.0)	0.1 (5.9)	2.9 (-0.2, 6.1)	5.8 (15.0)	-0.1 (5.6)	5.9 (-0.4, 12.1)
ESR (mm/Hr)	4.3 (11.6)	0.6 (8.7)	3.7 (0.4, 7.0)	6.3 (14.1)	0.4 (8.5)	5.9 (0.2, 11.5)

Biogen IDEC Inc., 2,UCB, 2,Abbvie, 5,Actelion Pharmaceuticals US, 5,Amgen, 5,Bristol-Myers Squibb, 5,Cytori, 5,Janssen Pharmaceutica Product, L.P., 5,Gilead, 5,GlaxoSmithKline, 5,NIH, 5,Novartis Pharmaceutical Corporation, 5,Pfizer Inc, 5,Roche Pharmaceuticals, 5,Genentech and Biogen IDEC Inc., 5,UCB, 5,Abbvie, 8,Actelion Pharmaceuticals US, 8,Bristol-Myers Squibb, 2,Amgen, 2,Actelion Pharmaceuticals US, 2,Abbvie, 2,UCB, 8; **F. Guillemin**, None; **S. Hewlett**, None; **A. L. Leong**, None; **L. March**, None; **T. Woodworth**, None; **G. Boire**, None; **C. Hitchon**, Health Sciences Centre Foundation, 2; **S. Jamal**, None; **E. C. Keystone**, Janssen Inc., 2,Abbott/AbbVie, 5,Amgen, 2,Bristol-Myers Squibb, 5,Janssen Inc., 5,Hoffmann-La Roche, Inc., 5,Janssen Inc., 2,Janssen Inc., 5,Merck Pharmaceuticals, 5,Merck Pharmaceuticals, 5,Pfizer Pharmaceuticals, 5,Pfizer Pharmaceuticals, 5; **J. E. Pope**, None; **J. C. Thorne**, Amgen, Canada, 5; **D. Tin**, None; **S. J. Bartlett**, PCORI, 2,NIH, 9.

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Abstract Number: 2656

Analysis of Morning Stiffness Response in Rheumatoid Arthritis Patients with Low Disease Activity Receiving Delayed-Release Prednisone Plus Dmards As Compared to Placebo Plus Dmards

Rieke Alten[1], **Robert J. Holt**[2], Jeffrey D. Kent[3] and Frank Buttgereit[4], [1]Charité Univ Medicine, Berlin, Germany, [2]College of Pharmacy, University of Illinois-Chicago, Vernon Hill, IL, [3]Medical Affairs, Horizon Pharma, Inc, Deerfield, IL, [4]Charité-Universitätsmedizin Berlin, Free University and Humboldt University of Berlin, Berlin, Germany

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Session Time: 9:00AM-11:00AM

Background/Purpose: Patient reported outcomes such as morning stiffness are reported frequently in rheumatoid arthritis (RA) patients. But little has been reported about the presence and the treatment of it in patients who have achieved low disease activity (LDA) (1). The CAPRA-2 study demonstrated previously absolute and relative reductions in morning stiffness in RA patients on DMARDs and concomitantly treated with low dose delayed-release (DR-) prednisone as compared to placebo/DMARDs over 12 weeks (2). Herein we report the relative and absolute changes in morning stiffness from the CAPRA-2 study in patients who achieved, and did not achieve, LDA.

Methods: RA patients with moderate disease on non-biologic DMARDs previously randomized to receive DR-prednisone or placebo were evaluated at baseline, 2, 6, and 12 weeks for relative and absolute changes in morning stiffness and LDA status (DAS28 $\leq$3.2).

Results: Patients who attained LDA at 12 weeks had similar demographics at the beginning of the trial to those who did not achieve LDA. By week 12, patients who received DR-prednisone and attained LDA (N=62) had significantly higher absolute ($p<0.05$) and relative reductions ($p<0.001$) in morning stiffness as compared to patients who received DR-prednisone and did not reach LDA (N=153). There were no differences in the placebo treated LDA (N=17) and non-LDA (N=90) groups. Of the patients attaining LDA status the DR-prednisone group had longer duration of disease, greater severity of morning stiffness and greater pain upon awakening, but similar DAS scores, at baseline compared to the placebo group. Despite this, there were significant differences from baseline found in both absolute ($p<0.0001$) and relative reductions ($p<0.0001$) in morning stiffness in those treated with DR-prednisone (n=62) which was not observed with placebo patients reaching LDA (n=16). (Figure 1)

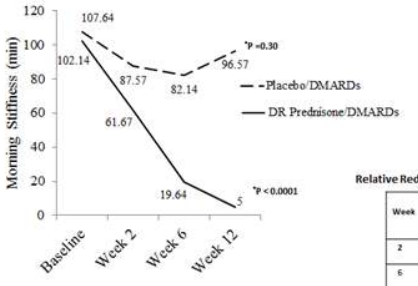
Conclusion: Attainment of LDA is not accompanied by decreasing morning stiffness in patients on DMARD monotherapy but is with DR prednisone/DMARDs, indicating the potential lack of construct validity between the two outcomes in the absence of glucocorticoid therapy. Glucocorticoid/DMARD treatment had a profound suppressing effect (-95%) on morning stiffness in patients who reached low disease activity. It is unknown whether this construct validity exists with other commonly used therapies in RA.

References:

(1) van Tuyl, et al. BMC Musculoskeletal Disorders 2014;15:28-33.

(2) Buttgereit, et al. Ann Rheum Dis 2013;72:204–210.

Figure 1. Change in Morning Stiffness in Low Disease RA Patients



Relative Reduction in Morning Stiffness (%)

Week	Delayed Release Prednisone	Placebo
2	-35	-28
6	-78	-48
12	-95 *p < 0.0001	-30 *P = 0.23

Baseline observation carried forward imputation algorithms were implemented up to the next visit following the last diary data. Baseline is the value recorded at week -1.Duration of morning stiffness is the average of the morning stiffness duration (minutes) over the last 7 days prior to visit day (including day of visit). If more than 4 assessments are missing then the duration is set to missing. All patients were on stable DMARDs. *P-value, Wilcoxon Signed Rank Test Week 12 versus baseline

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Disclosure: R. Alten, Horizon Pharma USA, Inc, 5,Horizon Pharma USA, Inc, 2; **R. J. Holt**, Horizon Pharma USA, Inc, 5; **J. D. Kent**, Horizon Pharma USA, Inc, 3; **F. Buttgereit**, Horizon Pharma formerly Nitec Pharma and Mundipharma International LTD, 5,Horizon Pharma formerly Nitec Pharma and Mundipharma International LTD, 9,Horizon Pharma, formerly Nitec Pharma, and Mundipharma International LTD, 9,Horizon Pharma, 2.

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Abstract Number: 2657

Influence of Anxiety and Depression on the Swollen to Tender Joint Count Ratio: In Pursuit of a Phenotype of RA Patients with Somatic Complaints in a U.S. Veteran Population

Iris Navarro-Millan[1], Archana Jain[1], Rebecca Belsom[1], Angelo L. Gaffo[2], Shuo Yang[3], Ted R. Mikuls[4] and Jeffrey R. Curtis[5], [1]Rheumatology, University of Alabama at Birmingham, Birmingham, AL, [2]Rheumatology, Birmingham VA Medical Center, Birmingham, AL, [3]Clinical Immunology/Rheumatology, University of Alabama at Birmingham, Birmingham, AL, [4]Medicine, University of Nebraska Medical Center, Omaha, NE, [5]Clinical Immunology and Rheumatology, University of Alabama at Birmingham, Birmingham, AL

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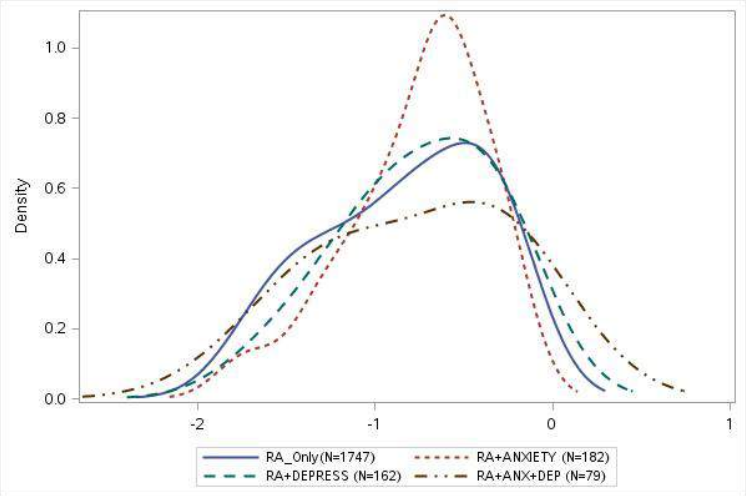
Background/Purpose: The utilization of a swollen (SJC) to tender joint count (TJC) ratio (STR = (SJC/TJC)) has been proposed in the past to identify a phenotype of rheumatoid arthritis (RA) patients that may have somatic complaints that do not reflect active RA. The influence of comorbidities such as depression and anxiety concomitant with RA, may influence the tender joint count and may be an important factor moderating the STR. To evaluate the influence of anxiety and depression on the distributions of TJC, SJC and the STR within the Veterans' Affairs Rheumatoid Arthritis cohort (VARA),

Methods: Four mutually exclusive RA patient groups were identified: 1) RA without anxiety or depression; 2) RA and depression only; 3) RA and anxiety only; 4) RA and Anxiety and Depression. We used Kolmogorov-Smirnov test to determine differences in the distribution of the STR by patient group.

Results: There were 2,170 RA patients within VARA. Mean age was 63 ± SD 10.9, 90% were men with an overall STR median (IQR) = 0.55 (0-1.30). The median (IQR) of the STR for the RA only group was 0.57 (0-1.4); RA + depression 0.55 (0-1.3), RA + anxiety 0.25 (0-1.0) and RA + anxiety + depression 0.54 (0-1.0). When comparing the actual distribution of the STR only RA + Anxiety compared to RA only was significantly different (p-value = 0.029). There was no difference between the RA + Depression group or the RA + Depression and Anxiety when compared to the RA only group (p-value = 0.17, 0.13, respectively) (Figure). The proportion of patients with STR ratio <0.5 was 43% (RA only), 54%, (RA+Anxiety), 45% (RA+Depression), and 43% (RA+both), p<0.038.

Conclusion: The distribution of the swollen to tender joint count ratio (STR) appears to be influenced by different comorbidities. While the tender joint count is part of many disease activity metrics, our study suggest that the tender to swollen joint count ratio may identify a phenotype of RA patients with less active disease with somatic complaints. Typical RA disease activity metrics may be overestimated in such patients.

Figure: Distribution of Swollen to Tender Joint Count Ratio in RA patients with and without concomitant anxiety and depression



Disclosure: I. Navarro-Millan, None; **A. Jain**, None; **R. Belsom**, None; **A. L. Gaffo**, None; **S. Yang**, None; **T. R. Mikuls**, None; **J. R. Curtis**, Roche/Genentech, UCB, Janssen, CORRONA, Amgen, Pfizer, BMS, Crescendo, AbbVie, 2,Roche/Genentech, UCB, Janssen, CORRONA, Amgen, Pfizer, BMS, Crescendo, AbbVie, 5.

Abstract Number: 2658

Low Disease Activity Is Associated with Higher HDL and a Trend to Lower Insulin Resistance in Rheumatoid Arthritis Patients

Androniki Bili[1], Debra Webb[1], Cynthia Matzko[2], Andrea Berger[3], Eric Newman[4], Thomas Olenginski[4], H. Lester Kirchner[3], Jon Giles[5] and Mary Chester M. Wasko[6], [1]Rheumatology, Geisinger Medical Center, Danville, PA, [2]Rheumatology MC 13-41, Geisinger Medical Center, Danville, PA, [3]Biostatistics, Geisinger Center for Health Research, Danville, PA, [4]Department of Rheumatology, Geisinger Medical Center, Danville, PA, [5]Columbia University Medical Center, New York, NY, [6]West Penn Allegheny Health System, Temple University School of Medicine, Pittsburgh, PA

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Background/Purpose: Treat to target (T2T) trials in RA to date have focused on the effect of T2T on articular disease without directly addressing cardiovascular risk. The aim of this study was to examine if a T2T strategy is associated with improved cardiometabolic risk factors in patients with newly diagnosed RA.

Methods: Patients were participants in TACARRA (TArgeting CArdiometabolic Risk in Rheumatoid Arthritis) and had RA based on 2010 ACR criteria with symptoms <2 years, were DMARD- and biologic-naïve (except hydroxychloroquine), took corticosteroid equivalent of prednisone ≤10 mg daily, had clinical disease activity index (CDAI) >10 and did not have known diabetes. The patients were treated according to a predetermined structured protocol that mandated treatment escalation for CDAI >10. The primary outcome was insulin resistance as assessed primarily by the homeostatic model assessment 2 for insulin resistance (HOMA2-IR) and secondarily by the 2 hour glucose tolerance test (GTT). Secondary outcomes were lipid levels and body composition measurements by dual energy xray absorptiometry (Hologic). Differences between outcome data at 52 weeks and baseline was tested using the Wilcoxon

signed rank test. Differences of the change between 52 weeks and baseline in patients with low (CDAI ≤10) and higher (CDAI >10) disease activity at 52 weeks were compared using exact Wilcoxon tests.

Results: Of the 25 patients who entered the study, the 16 completing 52 week follow-up were included in the analysis. 44% were female with median age 55 years. 75% were RF and 62.5% ACPA positive respectively, with median body mass index (BMI) 29 kg/m^2. Patient characteristics and outcome measures at baseline and week 52 are shown in Table. At week 52, 10 patients had low and 6 patients had higher disease activity. Median change in HOMA2-IR levels was -0.43 (-0.65, 0.02) vs.1.45 (0.78, 2.18), p=0.06, and median change in HDL was 2.5 (0.0, 12.0) vs. -11.5 (-19.0, -6.0), p< 0.01 in the low and higher disease activity groups respectively. The low disease activity patients at 52 weeks were more likely to be on hydroxychloroquine and had a smaller increase in BMI between 52 weeks and baseline. Change in HOMA2-IR according to disease activity at 52 weeks is shown in Figure.

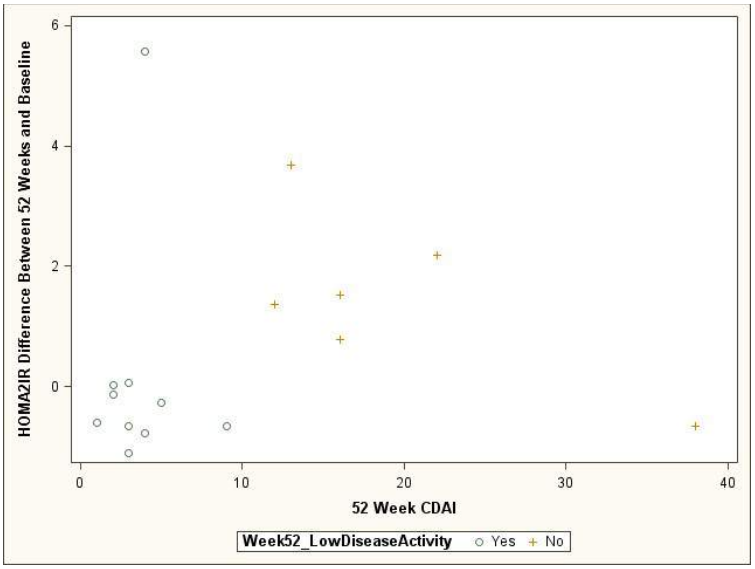
Conclusion: Newly diagnosed RA patients who reach low disease activity (CDAI ≤10) by 1 year of treatment have higher HDL and a trend to lower insulin resistance than patients with higher disease activity. Although our findings need confirmation in larger trials, they provide evidence that T2T is associated with decreased cardiometabolic risk factors in RA.

Table. Patient characteristic of RA patients at baseline and week 52 (n=16)

	Baseline	52 Week	Week 52 - Baseline Difference Median (IQR)	Baseline to 52 Week Difference P-value
Age, median (IQR)	55.0 (49.5, 67.5)			
Female	7 (43.8%)	-		
RF Positive	12 (75.0%)			
CCP Positive	10 (62.5%)			
CDAI, median (IQR)	32.0 (22.0, 39.5)	4.5 (3.0, 14.5)	-25 (-31, -18)	< 0.001
DAS28, median (IQR)	4.6 (4.3, 5.9)	2.2 (2.0, 3.9)	-2.1 (-2.6, -1.2)	< 0.001
MHAQ, median (IQR)	5.0 (1.5, 11.0)	0.5 (0.0, 5.5)	-2.5 (-5.5, 0.0)	0.006
BMI, median (IQR)	28.8 (24.4, 35.4)	31.4 (25.2, 38.6)	0.8 (0.4, 2.6)	0.006
ESR, median (IQR)	29.0 (22.0, 48.5)	18.0 (10.0, 29.0)	-12.0 (-22.5, -5.5)	< 0.001
2hour GGT mg/dL, median (IQR)	131.0 (107.0, 153.0)	109.0 (89.5, 136.5)	-11.0 (-27.5, 2.0)	0.11
HOMA2 IR, median (IQR)	1.67 (1.55, 2.07)	1.77 (0.92, 3.43)	-0.06 (-0.65, 1.45)	0.46
HDL, median (IQR)	59.0 (48.5, 67.0)	54.5 (43.0, 65.0)	0.0 (-9.5, 5.0)	0.50
LDL, median (IQR)	88.0 (78.0, 114.5)	89.0 (75.5, 99.0)	-7.5 (-14.5. 7.0)	0.21
Total Cholesterol, median (IQR)	178.5 (156.0, 204.5)	165.0 (149.5, 177.0)	-0.5 (-29.5, 10.5)	0.40
Triglycerides, median (IQR)	101.0 (72.0, 166.0)	109.0 (87.5, 130.0)	-16.5 (-30.5, 25.5)	0.64
Total Body % Fat, median (IQR)*	35.7 (31.2, 48.5)	36.1 (32.7, 48.9)	0.4 (-1.0, 2.4)	0.14
Total Lean Mass in the Limbs, median (IQR) *	23,234 (18,014, 28,799)	23,334 (19,154, 29,079)	786 (-234, 1261)	0.02
Trunk Fat Mass, median (IQR)*	17,913 (9114, 24,373)	16,880 (8574, 25,616)	82 (-937, 2364)	0.33

*n=15

Figure. Change in HOMA2-IR according to RA activity at 52 weeks.



Disclosure: A. Bili, None; **D. Webb**, None; **C. Matzko**, None; **A. Berger**, None; **E. Newman**, None; **T. Olenginski**, None; **H. L. Kirchner**, None; **J. Giles**, None; **M. C. M. Wasko**, None.

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Abstract Number: 2659

Poor Correlation Between Vectra DA and DAS28 Scores in Patients with Rheumatoid Arthritis

Marcia S. Genta[1], Amnon Sonnenberg[2] and Robert M. Genta[3], [1]Dallas Arthritis Center, Dallas, TX, [2]Medicine - Gastroenterology, Portland VAMC - Oregon Health & Science University, Portland, OR, [3]Laboratory, Dallas Arthritis Center, Dallas, TX

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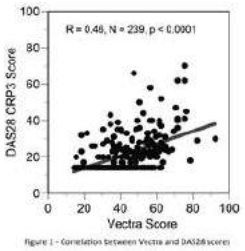
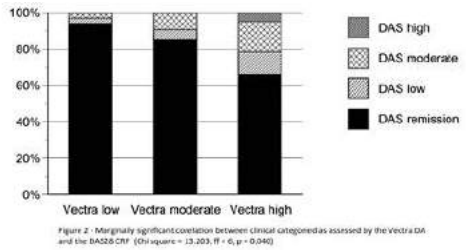
Background/Purpose: Vectra DA, a blood test that integrates the blood levels of 12 biomarkers into a single score (1-100), is claimed to provide an objective measurement of disease activity in RA patients. There is considerable controversy on whether it adds actionable information to that provided by joint examination, CRP, and ESR, and the resulting DAS scores. The purpose of this investigator-initiated non-sponsored study was to evaluate the correlation between Vectra DA and DAS28 CRP scores in RA patients followed in a solo practice.

Methods: Patients with an established diagnosis of RA underwent the Vectra DA test; the DAS28 CRP activity score was calculated at the time of the examination, when Vectra DA scores were unknown. Scores from each test were analyzed by multivariate linear regression. Levels of disease activity associated with the scores for each test were compared by the chi-square test.

Results: Vectra DA and DAS28 CRP scores were available for 239 unique patients (mean age 63.4 years, SD 13.2; 79% women; 40% African American, 36% Hispanic, and 25% White). RF was positive in 159 patients (67%) and CCP in 125 (52%); 129 patients were on DMARDs only (54%); 19 (8%) had only biologics; 72 (30%) were on combinations of DMARDs and biologics; and 19 (8%) had prednisone only or no therapy. There was a significant but weak correlation between Vectra DA score and the DAS28 CRP score (r^2 = 0.2102 or r = 0.4584; Figure 1), which was unaffected by age, sex, or ethnicity. In a multivariate linear regression analysis that included the type of therapy, the correlation improved slightly (r^2 = 0.321). In concordance with this weak correlation, the relationship between the 3 Vectra DA and the 4 DAS categories (Figure 2) also yielded a marginally significant chi-square (chi-square = 13.203, df = 6, p = 0.040). However, only 6 of 120 patients in a high Vectra clinical category were also in a high DAS category (concordance =

5%); of the 204 patients with a DAS in remission or low, only 32 were in the low Vectra category (concordance = 16%).





Conclusion: In a previous validation study Vectra DA scores showed a significant correlation with DAS28 scores. While our study confirmed a statistically significant but weak correlation, it also showed that when clinical categories rather than raw scores were used, the concordance between the two tests was minimal. Since therapeutic decisions based on a test that may not accurately reflect a patient's clinical status would be inappropriate, cost effectiveness and benefits of this expensive test should be reevaluated.

Disclosure: M. S. Genta, None; **A. Sonnenberg**, None; **R. M. Genta**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/poor-correlation-between-vectra-da-and-das28-scores-in-patients-with-rheumatoid-arthritis

Abstract Number: 2660

Elevated 14-3-3η Serum Protein Levels Increase RA Confirmation Rates in Recent-Onset Polyarthritis Patients

Nathalie Carrier[1], Anthony Marotta[2], Artur de Brum-Fernandes[3,4], Patrick Liang[3,4], Ariel Masetto[5,6], Yuan Gui[2], Jane Savill[2], Sara Michienzi[2], Henri Ménard[7], Walter Maksymowych[8] and Gilles Boire[4], [1]Division of Rheumatology, Université de Sherbrooke, Sherbrooke, QC, Canada, [2]Augurex Life Sciences Corp., Vancouver, BC, Canada, [3]Department of Medicine/Division of Rheumatology, Université de Sherbrooke, Sherbrooke, QC, Canada, [4]Rheumatology Division, Centre Hospitalier Universitaire de Sherbrooke, Sherbrooke, QC, Canada, [5]Department of Medicine/Division of Rheumatology, Université de Sherbrooke, Centre Hospitalier Universitaire de Sherbrooke, Sherbrooke, QC, Canada, [6]Department of Medicine/Division of Rheumatology, University of Sherbrooke, Sherbrooke, QC, Canada, [7]MSK Research Axis, McGill University Health Center Research Institute, Montreal, QC, Canada, [8]Department of Medicine, University of Alberta, Edmonton, AB, Canada

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Background/Purpose: The 14-3-3 family of conserved regulatory proteins consists of seven isoforms: α/β, γ, δ/ζ, ε, η, θ/τ and σ. These proteins exist as intracellular adapters that interact with more than 200 intracellular proteins to modulate their activities. Extracellular 14-3-3η at concentrations found in patient serum activates key signalling cascades and induces factors associated with Rheumatoid Arthritis (RA) pathogenesis.[1] The purpose of this study was to determine if 14-3-3η serum levels are additive to available RA-associated autoantibodies to identify RA patients in a cohort of recent-onset polyarthritis cohort (EPA).

Methods: Using the manufacturer's (Augurex 14-3-3η) ELISA, serum 14-3-3η levels were measured at baseline in 331 patients with EPA from the Sherbrooke EUPA cohort. All 331 had completed a follow up of at least 5 years. Patients were rapidly and intensively treated with DMARDs and/or biologics to achieve clinical remission defined as 0 swollen joint among 66. The manufacturer's reported diagnostic cut-off of ≥0.19 ng/ml was used. Anti-CCP2 (EuroImmun and Inova Diagnostics) and IgM RF (RapiTex, Dade-Behring) were determined using commercial assays and Anti-Sa/citrullinated vimentin (Sa), using an in-house assay previously described.[2]

Results: Median age was 60 y.o. and 62% were female; median time of symptom duration was 4 months. Up to 92% were treated with DMARDs between baseline and the 18-month follow up; 23 also received biologic agents over that period. 14-3-3η was positive at baseline in 153 (46%) of patients and RF, anti-CCP2 and anti-Sa were positive respectively in 146 (44%), 132 (39.9%) and 73 (22%). When 14-3-3η protein was combined with antibodies, the proportion of patients with at least one positive test increased to 54.8% (RF or 14-3-3η), 55% (anti-CCP2 or 14-3-3η) and 49.7% (anti-Sa or 14-3-3η), corresponding to an incremental benefit in sensitivity of 25%, 38% and 126%, respectively. When combining 14-3-3η with all 3 antibodies, the number (proportion) of positive patients for at

least one marker increased from 164 (51.0%) to 194 (58.6%).

Conclusion: Serum 14-3-3η positive status in recent-onset polyarthritis adds significant sensitivity to currently available RA-associated antibodies. Since higher 14-3-3η titres are associated with an increased risk of joint damage progression, our data support measuring it in early inflammatory polyarthritis to assist with patient stratification.

References: [1]Maksymowych et al. Arthritis Research & Therapy 2014, 16:R99; [2]Boire G et al. 2005. Arthritis Research & Therapy, 7:R592-R603

Disclosure: N. Carrier, None; **A. Marotta**, Augurex Life Sciences Corp, 3; **A. de Brum-Fernandes**, None; **P. Liang**, None; **A. Masetto**, None; **Y. Gui**, Augurex Life Sciences Corp, 3; **J. Savill**, Augurex Life Sciences Corp, 3; **S. Michienzi**, Augurex Life Sciences Corp, 3; **H. Ménard**, None; **W. Maksymowych**, Augurex Life Sciences, 5; **G. Boire**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/elevated-14-3-3-serum-protein-levels-increase-ra-confirmation-rates-in-recent-onset-polyarthritis-patients

Abstract Number: 2661

Assessing Information Needs for Chronic Disease Management in Rheumatoid Arthritis

Marylou Cardenas-Turanzas[1], Elsa Gonzalez[2], Maithili Shethia[1], Maria A. Lopez-Olivo[3], Pratibha Nayak[4] and **Maria E. Suarez-Almazor**[3], [1]Department of General Internal Medicine, The University of Texas, MD Anderson Cancer Center, Houston, TX, [2]Higher Education Administration, Texas A&M University, Corpus Christi, TX, [3]General Internal Medicine, The University of Texas, MD Anderson Cancer Center, Houston, TX, [4]National Institutes of Health, Atlanta, GA
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Background/Purpose: Patients with chronic disease are increasingly using social networking to share experiences about their disease, and receive peer support. As part of an educational intervention we conducted a qualitative needs assessment to evaluate the information needs of patients with RA and to determine the acceptability of the Internet, and specifically social networking tools such as Facebook (FB), as a source of information and interaction among peers.

Methods: We conducted 20 semi-structured cognitive interviews with adult participants with RA who were diagnosed by a rheumatologist, had ongoing or prior treatment with disease-modifying anti-rheumatic drugs or biologic agents, disease duration <=10 years, and had internet access. Themes explored included: (1) health information needs, (2) use of self-management health behaviors, (3) use of internet resources for disease management, (4) role of peer support in health self-management, and (5) use of social networking sites (SNS) such as FB in disease management. Data was organized, sorted and interpreted from the participant's verbatim responses using *Dedoose*, a web application to analyze qualitative data.

Results: Participants included 85% females. The majority were White (65%) and 50% were 51-65 years old. Categories identified by the themes mentioned above were (see table): (1) important aspects that patients' needs to know, source of information, useful information but difficult to get, advice giving to others; (2) self-management health condition and practices, dealing with ongoing health needs and stress, managing medication regularly, support from family and friends; (3) definition of uses of internet such as getting familiar/getting started, frequency of use, familiar or not with internet, self-management/use of internet, daily use, self-management/useful information, preferred learning vehicles; (4) forms of online communication, type of social networking site, purpose and frequency of use, information on, and support from SNS.

Conclusion: Although the dominant theme was RA information needs, the rest of the themes contribute in supporting the robust emergence of Internet media in informing patients about their health. In searching for useful information to manage their condition including activities as exploration of internet sites and interest for FB as support tool, participants are authenticating their need for accurate information on RA to help them managing their condition. The interpretation of these findings will inform the choices and format of educational and self-management materials to be considered for online educational, self-management and social networking tools.

Theme (Num. Units)	Categories (Num. Units)
1 (387)	Important aspects that patients' needs to know (150)
	Source of Information (170)
	Useful information but difficult to get (26)
	Advice giving to others (41)
2 (438)	Self-management health condition (15)
	Self-management health practices (108)
	Dealing with ongoing health needs & stress (72)
	Managing medication regularly (52)
	Support from family and friends (21)
	Other actions (67)
	Successful management strategies (62)
	Goal of self- management (41)
3 (356)	Definition of uses of internet - getting familiar/getting started (26)
	Frequency of use (46)
	Familiar or not (26)
	Self-management/use of internet (21)
	Daily use (41)
	Self-management/useful information (77)
	Preferred learning vehicles (119)
4 (526)	Forms of online communication (5)
	Type of social networking site (41)
	Purpose of use (21)
	Frequency of use (31)
	Information on SNS (31)
	Support from SNS
	• Getting support from SNS (31)
	• Getting useful information from SNS (10)
	• Sharing issues/ asked questions on SNS (52)
	• Perception of use SNS for health (144)
	• Expected information on SNS (98)
	• Perception of moderator on SNS (31)
	• Suggestions developing support group on FB (31)
5 (299)	Support from doctors (36)
	Support from family and friends (31)
	Perception towards to peer support (98)
	Use internet to share information (46)
	Preferred support (21)
6 (15)	Problems using internet

Disclosure: M. Cardenas-Turanzas, None; **E. Gonzalez**, None; **M. Shethia**, None; **M. A. Lopez-Olivo**, None; **P. Nayak**, None; **M. E. Suarez-Almazor**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/assessing-information-needs-for-chronic-disease-management-in-rheumatoid-arthritis

Abstract Number: 2662

Validation of the Quickdash in the Assessment of Rheumatoid Arthritis Disease Activity

Cassandra Craig[1] and Matthew Carroll[2], [1]Internal Medicine, Keesler Medical Center, Keesler AFB, MS, [2]Rheumatology, Keesler Medical Center, Keesler AFB, MS

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SESSION INFORMATION

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Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Rheumatoid Arthritis (RA) is a chronic inflammatory arthritis associated with substantial morbidity and mortality. Measuring disease activity in RA is important as it facilitates a treat-to-target approach. The purpose of this study was to determine whether the modified version of the Disabilities of Arm, Shoulder, and Hand (DASH), the QuickDASH, was valid in measuring disease activity in RA. Validity was assessed by correlation with the Routine Assessment of Patient Index Data 3 (RAPID3).

Methods: This prospective cohort study gathered commenced July 2014 at a single academic facility Rheumatology Clinic. Subjects with a diagnosis of RA based on 1987 or 2010 American College of Rheumatology (ACR) Classification Criteria, depending on year diagnosed, were enrolled. When seronegative, subjects with polyarticular symptoms and synovitis or erosions on MRI established diagnosis. Primary endpoint was establishing validity of QuickDASH in routine clinical assessment of RA disease activity through correlation with RAPID3.

Results: From a cohort of 98 subjects, 89 had at least 2 data points available for analysis and 178 data points were used in paired analysis. The average patient age was 62.3 ± 13.7 years old. Slightly more than 70% of study participants were women and alomst 75% were Caucasian. Seropositivity was 72.4% and 74.5% had erosive disease.

Test-retest reliability of the QuickDASH was excellent with an intraclass correlation coefficient (ICC) of 0.915 (95% Confidence Interval (CI): 0.871, 0.945). Assessed by the Pearson correlation coefficient, the strength of the relationship between the QuickDASH and RAPID3 questionnaire was high ($r = 0.834$, $p < 0.0001$). The interclass reliability of the QuickDASH to correlate with the RAPID3 was moderate with an ICC of 0.627 (95% CI: 0.498, 0.722).

Linear regression analysis yielded the equation QuickDASH score = (2.801* RAPID3 score) + 3.542. Using the established disease activity ranges for the RAPID3 questionnaire, we developed similar ranges for the QuickDASH, as noted in the Table:

TABLE

	RAPID3 (raw score)	QuickDASH
Remission	0 – 3.0	0 - 12.0
Low Disease Activity	3.1 – 6.0	12.1 – 20.0
Moderate Disease Activity	6.1 – 12.0	20.1 – 37.0
High Disease Activity	≥ 12.1	≥ 37.1

For the 4 categorical measurements of QuickDASH and RAPID3 as defined in the Table, reliability of testing yielded an average Inter-Item Correlation of 0.786 ($p < 0.001$). Cronbach's α was 0.879 (95% CI: 0.838, 0.910, $p < 0.001$). The measurement of agreement assessed by Kappa testing showed moderate agreement with a Kappa of 0.481 ($p < 0.001$) for the QuickDASH ranges established.

Conclusion: This study demonstrated that the QuickDASH was very reliable and internally consistent in the measurement of RA disease activity. The QuickDASH moderately correlates with established ranges of RA disease activity established by the RAPID3 and could potentially be used as a surrogate for the RAPID3 in clinical practice.

Disclosure: C. Craig, None; **M. Carroll**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/validation-of-the-quickdash-in-the-assessment-of-rheumatoid-arthritis-disease-activity

Abstract Number: 2663

Evaluation of Anti-Cyclic Citrullinated Peptide Autoantibody Levels in Clinical Practice and Its Association with Disease Activity

E Alemao[1], KK Gandhi[1], C Iannaccone[2], M Frits[2], JS Coblyn[2], N Shadick[2] and Michael Weinblatt[2], [1]Bristol-Myers Squibb, Princeton, NJ, [2]Brigham and Women's Hospital, Boston, MA

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Session Time: 9:00AM-11:00AM

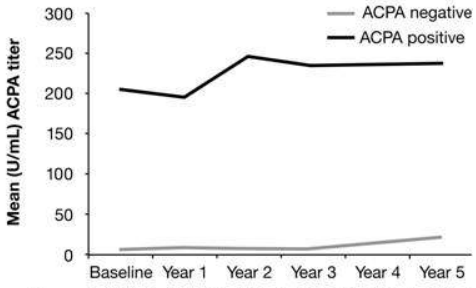
Background/Purpose: Testing for anti-citrullinated peptide antibodies (ACPA) is included in the 2010 ACR classification criteria for RA. ACPA concentration, beyond ACPA positivity, is indicative of more aggressive radiographic progression. However, there is limited information on ACPA levels in clinical practice settings and its association with disease activity measures. **Methods:** Data were analyzed from patients (pts) enrolled in a large, US RA registry established in 2003. The registry mostly comprises pts with established RA who were evaluated semi-annually for multiple clinical PROs and resource utilization parameters. The current analysis is based on pts enrolled in the registry with ACPA values at the time of baseline visit. Baseline and follow-up ACPA levels were based on a well-documented and validated ELISA from Inova Diagnostics until its discontinuation in 2011; the Euro-Diagnostica assay (distributed by IBL-America, Minneapolis, MN), which supplied the 'capture' antibody for the original Inova Diagnostics ELISA, has been used since. In assessments, the correlation between the two assays was 0.984. Mean changes from baseline over the first 5 years (yrs) of enrolling into the registry were calculated. Four categories of ACPA change from baseline were created based on quartiles of the distribution of ACPA change to Yr 1. Multivariate regression analyses controlling for baseline covariates were conducted to evaluate associations between ACPA change from baseline quartiles and disease activity measures defined by CDAI, SDAI, DAS28 (CRP) and joint counts.

Results: Overall, 1309 (97%) registry pts were included in the current analysis. The mean (SD) age of the cohort was 56.01 (14.04) yrs and 83.2% were females. Figure 1 represents the mean of ACPA levels up to Yr 5. The mean (SD) change in ACPA in ACPA+ pts was –0.5 (71.3) U/ml, 50.8 (93.9) U/ml, 33.1 (123.1) U/ml, 33.9 (132.0) U/ml, 40.6 (122.4) for Yr 1 through Yr 5, respectively. The ACPA mean change to Yr 1 quartiles had the following cut-off values: Q1 >–488.1 to ≤–13.6 U/ml; Q2 >–13.6 to ≤0.0 U/ml; Q3 >0 to ≤8.8 U/ml; Q4 >8.8 U/ml. The mean reductions in disease activity based on CDAI, SDAI and joint counts were greatest for Q1 (Figure 2). Similar patterns of change in disease activity were observed after controlling for baseline covariates in multivariate analysis.

Conclusion:

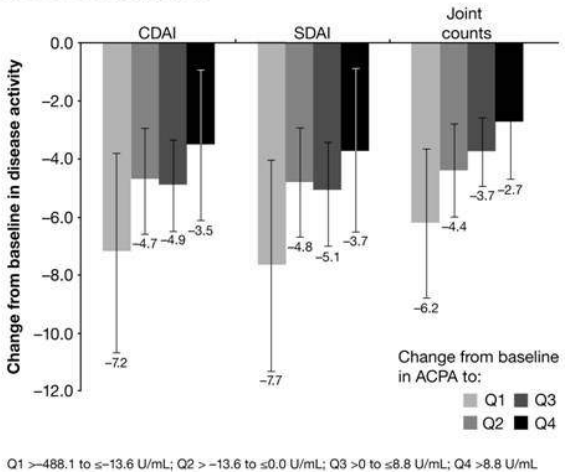
We observed that ACPA titers change over time and ACPA increase is primarily observed in ACPA+ pts with higher ACPA values at baseline. Pts with reduction in ACPA show a numerically greater reduction in disease activity levels.

Figure 1. Mean ACP titer over time



ACPA positive, n	803	530	467	388	295	342
ACPA negative, n	506	307	252	208	141	156

Figure 2. Association between change from baseline in ACPA levels and change in disease activity levels



Q1 >−488.1 to ≤−13.6 U/mL; Q2 > −13.6 to ≤0.0 U/mL; Q3 >0 to ≤8.8 U/mL; Q4 >8.8 U/mL

Disclosure: E. Alemao, Bristol-Myers Squibb, 3,Bristol-Myers Squibb, 1; **K. Gandhi**, Bristol-Myers Squibb, 1,Bristol-Myers Squibb, 3; **C. Iannaccone**, None; **M. Frits**, None; **J. Coblyn**, None; **N. Shadick**, Amgen, Questcor, Crescendo Biosciences, UCB, Bristol-Myers Squibb, 2; **M. Weinblatt**, Amgen, Abbvie, Bristol-Myers Squibb, Lilly, Novartis, Merck, Pfizer, Roche, Crescendo, Myriad Genetics, UCB, 5,Bristol-Myers Squibb, Myriad Genetics, UCB, 2.

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Abstract Number: 2664

Flares Occur Frequently in RA Patients Undergoing Arthroplasty

Susan M. Goodman[1], Rivka Friedlander[2], Caroline Figgie[2], Anh Hoang[1], Kathleen Andersen[3], Alessandra B. Pernis[4], Cristina T. Rozo[5], Edward F. DiCarlo[6], Mark P. Figgie[7], Laura T. Donlin[8] and VP Bykerk[3], [1]Rheumatology, Hospital for Special Surgery, New York, NY, [2]Research, Hospital for Special Surgery, New York, NY, [3]Hospital for Special Surgery, New York, NY, [4]Autoimmunity & Inflammation, Hospital for Special Surgery, New York, NY, [5]535 East 70th Street, Hospital for Special Surgery, New York, NY, [6]Laboratory Medicine, Hospital for Special Surgery, New York, NY, [7]Orthopaedics, Hospital for Special Surgery, New York, NY, [8]Arthritis and Tissue Degeneration Program and the David Z. Rosensweig Genomics Research Center, Hospital for Special Surgery, New York, NY

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Background/Purpose: RA patients are at risk for disease worsening (flare) after joint surgery, as medication is withdrawn to mitigate infection risk. We aimed to describe rates and characteristics of RA flare within 6 weeks of total hip (THA) and total knee arthroplasty (TKA).

Methods : RA patients undergoing TKA/THA were queried every week about any change in RA status including pain and function (MDHAQ, HOOS/KOOS ADL). Baseline (BL) characteristics, BL and 6 week DAS-28, were collected. RA Flare was defined by Patient Report (yes/no, “Are you in a flare?”). Flare classification was determined by concordance between patient report of flare and MD assessment of flare, by chart review including joint counts, excluding the surgical joint. Medication use was standard of care: biologic DMARDs stopped; steroids and MTX continued.

Results : Of 37 RA pts recruited, most were female, white and had undergone THA **(Table 1)**. Mean (SD) time to flare was 2.9(2.0) wks in 23/37 (62%) patients, with a self-rated flare severity of 6.3(2.4), duration >4 days in 74%. All but 6 stopping biologics flared. Numerically, more flarers took steroids, MTX and biologics. Disease activity at baseline and 6 weeks remained moderate for both groups **(Table 2)**. Though numerically higher in flares disease activity and function at BL and change over 6 weeks was similar. At 6 weeks, patients reporting flare had significantly higher tender joint counts [RADAI 14.5(8.3) vs. 7.6(6.1), p=0.02], rescored to remove the surgical joint [RADAI 13.3(7.7) vs. 6.5(6.1), p=0.02]. Worse MDHAQ [4.0(1.7) vs. 2.9(1.2), p=0.07] and RAPID3 [13.8(5.3) vs.

14.7(8.2), p=0.09] approached significance.

Conclusion: Post-op flares are frequently reported, and rated as severe in RA patients undergoing THA/TKA. Numerically, flares are more frequent in patients stopping biologics. Increased RA related worsening joint pain and function seen in those whose RA worsens after surgery may contribute to poor long-term outcomes for RA patients undergoing THA/TKA. Further studies of post-op flare are needed.

This study was supported by the Clinical Translational Science Center (CTSC) (UL1-TR000457-06)

Table 1: Cohort Characteristics	All (n=37)	Flare (n=23)	Non-Flare (n=14)	p-value
Age, mean (SD)	58 (12)	56 (12)	60 (11.5)	0.50
Female (%)	29 (78%)	19 (83%)	10 (71%)	0.44
Race: White	28 (76%)	16 (70%)	12 (86%)	0.22
ACPA+ and/or RF+	16 (43%)	13 (57%)	3 (21%)	0.12
Total Hip Arthroplasty	22 (59%)	15 (65%)	7 (50%)	0.49
Total Knee Arthroplasty	15 (41%)	8 (35%)	7 (50%)	
Meets either 1987 or 2010 criteria	27 (73%)	17 (74%)	10 (71%)	1.00
Education: college/university	32 (86%)	19 (83%)	13 (93%)	0.63
BMI	28.9 (6.6)	29.1 (7.8)	28.6 (4.2)	0.89
Ex-smokers	17 (46%)	8 (35%)	9 (64%)	0.22
Baseline steroid use	14 (38%)	10 (43%)	4 (29%)	0.49
Week 6 steroid use	11 (32%)	8 (40%)	3 (21%)	0.29
Baseline Methotrexate use	22 (59%)	14 (61%)	8 (57%)	0.48
Week 6 Methotrexate use	18 (53%)	12 (60%)	6 (43%)	0.49
Baseline Non-MTX DMARDs	9 (24%)	6 (26%)	3 (21%)	1.00
Week 6 Non-MTX DMARDs	9 (26%)	7 (35%)	2 (14%)	0.25
Baseline TNFi use	16 (43%)	12 (52%)	4 (29%)	0.19
Week 6 TNFi use	9 (26%)	5 (25%)	4 (29%)	1.00
Baseline Biologics use	22 (59%)	16 (70%)	6 (43%)	0.17
Week 6 biologics use	12 (35%)	7 (35%)	5 (36%)	1.00
Weeks biologic stopped	3.2 (3.9)	3.4 (4.4)	2.8 (2.6)	1.00
Dosing intervals missed	1.9 (2.0)	2.1 (2.3)	1.5 (1.0)	0.97
Time to Flare, wks		2.9 (2.0)		
Flare Severity, 0-10		6.3 (2.4)		
Flare duration: >4 days		17 (74%)		
Change over past week: Worse/Much Worse Slightly worse Same/Slightly better Better/Much Better		6 (26%) 8 (35%) 5 (22%) 4 (17%)	0 (0%) 3 (21%) 10 (71%) 1 (7%)	

Table 2	Baseline*			At Flare	Week 6		
Disease Activity Measures	All	Flare	Non-Flare	Flare (only)	Flare	Non-Flare	p-value[a]
DAS-28 CRP	4.0 (1.2)	4.2 (1.1)	3.6 (1.2)		4.2 (1.4)	3.3 (1.1)	0.17
CRP, mg/dL	2.0 (3.6)	2.7 (4.4)	0.9 (0.5)		3.3 (5.0)	1.2 (0.6)	0.33
MD TJC (0-28)	4.8 (6.0)	5.1 (6.0)	4.2 (6.1)		**9.3 (9.3)**	**2.9 (6.1)**	**0.03**
MD SJC, 0-28	5.1 (5.5)	6.0 (5.8)	3.8 (4.7)		5.4 (6.7)	3.0 (4.8)	0.12
MD Global, 0-10	4.0 (1.8)	4.5 (1.8)	3.3 (1.6)		3.8 (2.5)	2.3 (1.2)	0.16
Patient TJC, 0-40	10.4 (10.1)	11.4 (10.1)	8.9 (10.2)	15.9 (13.0)	12.5 (12.4)	7.4 (9.9)	0.23
Patient SJC, 0-40	7.3 (9.2)	6.5 (8.3)	8.4 (10.7)	7.2 (8.6)	8.0 (9.2)	3.2 (3.4)	0.14
Patient Global, 0-10	6.0 (2.5)	6.6 (2.2)	5.0 (2.6)	4.0 (2.6)	4.1 (2.4)	2.9 (2.3)	0.10
Pain Global, 0-10	6.8 (2.6)	7.3 (1.9)	5.9 (3.3)	5.9 (2.5)	5.1 (2.3)	3.6 (2.6)	0.10
RADAI JC, 0-48	14.3 (8.7)	15.8 (9.5)	12.1 (7.0)	14.2 (8.3)	**14.5 (8.3)**	**7.6 (6.1)**	**0.02**
RADAI JC Adjusted, 0-45[b]	11.6 (8.3)	12.9 (9.2)	9.7 (6.7)	12.7 (7.7)	**13.3 (7.7)**	**6.5 (6.1)**	**0.02**
MD HAQ, 0-10	3.9 (1.6)	4.2 (1.4)	3.3 (1.7)	4.2 (1.4)	4.0 (1.7)	2.9 (1.2)	0.07
Sum PROs, 0-60[c]	32.8 (14.6)	37.1 (12.6)	26.7 (15.5)	31.7 (14.6)	**28.0 (13.6)**	**14.7 (8.2)**	**0.01**
HOOS/KOOS ADL, 0-100	42.0 (21.5)	38.4 (19.3)	47.9 (24.2)		59.8 (19.6)	64.0 (19.4)	0.58
T/S JC Tender/Swollen Joint Count; *Values Mean (SD), no significant differences noted; comparisons tested by Wilcoxon 2-sample test statistical test; **a** calculated comparing flare and non-flare; **b** excluded surgical joint in calculation; **c** Sum of patient reported pain, fatigue, and stiffness intensity, global function impairment, worsening in participation and coping;							

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Abstract Number: 2665

Improved Flare/ Remission Pattern in Rheumatoid Arthritis over the Recent Decades

Elena Myasoedova[1], Sherine E. Gabriel[2], Eric L. Matteson[3], John M. Davis III[4] and Cynthia S. Crowson[5], [1]Internal Medicine and Rheumatology, Mayo Clinic, Rochester, MN, [2]Rutgers Robert Wood Johnson Medical School, New Brunswick, NJ, [3]Rheumatology, Mayo Clinic, Rochester, MN, [4]Division of Rheumatology, Mayo Clinic, Rochester, MN, [5]Health Sciences Research, Mayo Clinic, Rochester, MN
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Background/Purpose: Flare or episodic worsening of disease activity is an important aspect of the disease experience for patients with rheumatoid arthritis (RA), with significant impact on quality of life, well-being, joint damage and comorbidity. Improving trends towards lower RA disease activity have been suggested in recent years as compared to previous decades. However, long-term data on flare and remission rates in RA over calendar time are lacking. We aimed to assess trends in the occurrence of flares and remission in RA over the last decades.

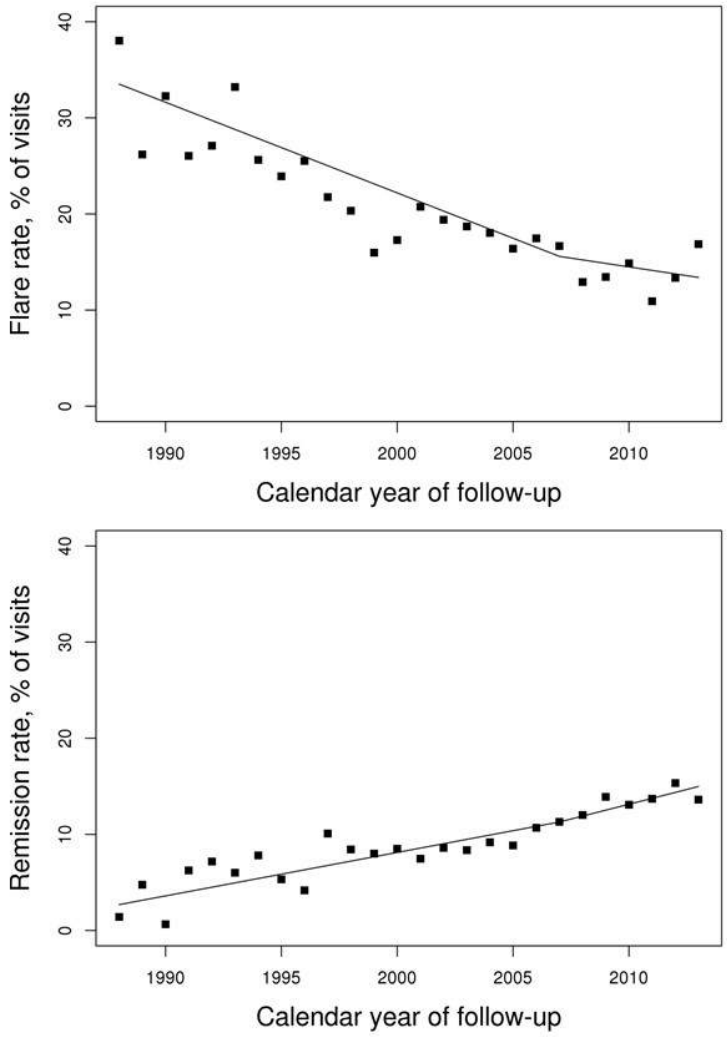
Methods: In a population-based cohort of patients with RA (age≥30 years; 1987 ACR criteria met in 1988-2007) we performed a retrospective medical records review of each clinical visit to estimate flare and remission status. RA flare was defined as any worsening of RA activity leading to initiation/change/increase of therapy (OMERACT 9). Remission was defined as the absence of disease activity (i.e. tender joint count [TJC] = 0 + swollen joint count [SJC] = 0 + ESR ≤ 10 mm/hr) (OMERACT 7). All subjects were followed until death, migration or July 1, 2012. Flare and remission rates were calculated as the percentage of visits in flare or remission in each calendar year. Time spent in flare was calculated as days in flare divided by days of follow-up in each calendar year.

Results: The study included 525 RA patients (mean age 54.5 years; 71% female) with mean follow up of 10.1 years. Flare/ remission status was collected for a total of 15,649 clinical visits. Patients were flaring in 2829 (18%) visits and were in remission in 1545 (10%) visits. The median duration of flare was 2.4 months (Q1 1, Q3 5.4 months). The figure shows trends in flare and remission occurrence in RA patients over time.

There has been a statistically significant decline in the RA flare rate over calendar time, from 32% of visits per year in 1990 to 15% of visits per year in 2010 ($p<0.001$). In contrast, remission rates went up from 0.6% of visits per year in 1990 to 13.1% of visits per year in 2010 ($p<0.001$). During the study period, there has been a statistically significant annual decline in the percentage of time spent in flare (3.6% per year, $p<0.001$), while the percentage of time spent in remission has been increasing by 3.0% per year ($p<0.001$).

Conclusion: Our findings show significant decline in flare occurrence and concurrent increase in remission rates in patients with RA over the last two decades, likely reflecting improved control of RA activity and possibly milder RA disease course in the recent time. Concordantly, there has been a decrease in time spent in RA flare accompanied by an increase in remission time over the years. These positive trends are highly relevant to patients with RA and rheumatology health care providers and have potentially important impact on health care organization and management of RA. The implications of this improved trend on outcomes and mortality in RA require further study.

Figure. Occurrence of flares (upper panel) and remissions (lower panel) in patients with RA over calendar time



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Abstract Number: 2666

Trajectories of EQ-5D in RA Patients Treated with Biologics Using the IORRA Cohort

Daisuke Hoshi, Eiichi Tanaka, Eisuke Inoue, Yoko Shimizu, Naoki Sugimoto, Kumi Shidara, Ayako Nakajima, Shigeki Momohara, Atsuo Taniguchi and Hisashi Yamanaka, Institute of Rheumatology, Tokyo Women's Medical University, Tokyo, Japan

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Background/Purpose: Patient-reported outcomes are recognized as important for evaluating the disease status of rheumatoid arthritis

(RA). The EuroQol 5-dimensional descriptive system (EQ-5D) has been used to assess health-related quality of life (HR-QOL) in clinical research and pharmacoeconomical studies. RA is a chronic disease associated with pain, fatigue, disability, and functional loss, which can markedly decrease a patients' quality of life (QOL). Treatment strategies for RA have changed greatly since the introduction of biological DMARDs (bDMARDs). The QOL of RA patients can be evaluated using EQ-5D in daily practice.

We analyzed a clinical database of a large prospective observational cohort of patients with RA. Subclasses with distinct patterns were identified in the Japanese version of EQ-5D in RA patients who received biologics. The clinical features of patients whose QOL improved after use of biologics in daily practice was then examined.

Methods: Since October 2000, we have established a large observational cohort of RA patients in our institute, the Institute Of Rheumatology, Rheumatoid Arthritis (IORRA). Essentially, all RA patients who attend our clinic are asked every 6 months to answer questionnaires including the EQ-5D, disease activity score 28 (DAS28), and Japanese version of the health assessment questionnaire (J-HAQ). More than 5,000 RA patients are included in the cohort, with 813 patients who received bDMARDs being enrolled in this study. The EQ-5D scores of these 813 patients were recorded biannually for 2.5 years and the latent classes of time trends in EQ-5D score based on posterior probability examined after initiation of bDMARDs. The clinical characteristics of each latent class were then compared.

Results: The 813 patients were classified into 4 classes based on time-related changes in EQ-5D score: Class 1, patients with persistent high score of around 0.9 (n=301); Class 2, patients whose score improved from about 0.7 to 0.9 after use of bDMARDs (n=73); Class 3, patients with a persistent moderate score of around 0.7 (n=348); and Class 4, patients with a persistent low score of under 0.6 in spite of use of bDMARDs (n=166). The patients in Class 2 were younger and had a shorter disease duration (p<0.05), higher DAS28 (p<0.001), lower J-HAQ (p<0.05) and more frequent use of non-steroidal agents (p<0.05) than the patients in Class 3.

Conclusion: This study suggests that QOL is less likely to improve in patients with RA whose disability and deterioration of QOL has already become established despite the use of bDMARDs. We also determined the clinical features of RA patients whose QOL improved after daily use of biologics.

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Clinical Characteristics and Health Outcomes of RA Patients Not Adequately Controlled By Current Treatment

Peter C. Taylor[1], Rieke Alten[2], Philippe Bertin[3], Roberto Caporali[4], Juan J Gomez-Reino[5], Emma Sullivan[6], Robert Wood[7], James Piercy[7], Radu Vasilescu[8], Dean Spurden[9] and Jose Alvir[10], [1]Kennedy Institute of Rheumatology, Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences, University of Oxford Botnar Research Centre, Oxford, United Kingdom, [2]Internal Medicine, Rheumatology & Clinical Immunology, Schlosspark-Klinik, University Medicine Berlin, Berlin, Germany, [3]Rheumatology, CHU Dupuytren, Limoges, France, [4]University of Pavia and IRCCS Policlinico S. Matteo Foundation, Pavia, Italy, [5]Desarmen of Rheumatology, Unit Hospital Clinico Universitario, Santiago, Spain, [6]Adelphi Real World, Manchester, United Kingdom, [7]Adelphi Real World, Macclesfield, United Kingdom, [8]Medical Affairs, Pfizer Inc, Brussels, Belgium, [9]Pfizer Inc, Tadworth, United Kingdom, [10]Global Health and Value, Pfizer Inc, New York, NY

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Background/Purpose: Despite an increasing armamentarium of efficacious treatments for Rheumatoid Arthritis (RA), sustained remission remains an unrealistic expectation for many patients, with most experiencing ongoing disease activity and flares of varying frequency. The aim of the current study is to describe the patients who are inadequately controlled (DAS28>3.2) on their current therapy

and identify common features associated with this population.

Methods: Data were drawn from the Adelphi 2014 RA Disease Specific Programme, a survey of rheumatologists and their RA patients in France, Germany, Italy, Spain and UK. Rheumatologists provided patient demographics, comorbidities, satisfaction with RA control and clinical details including current DAS28. Patients reported their satisfaction, and completed the EuroQOL 5-Dimension Health Questionnaire (EQ-5D) and Work Productivity and Activity Impairment (WPAI) Questionnaire. Of the patients who had been on their current therapy for at least 3 months, two patient cohorts were created based on the physician-reported DAS28: adequately and inadequately controlled (DAS28 ≤3.2 and >3.2 respectively). Univariate tests were performed to compare the cohorts.

Results: A total of 1147 patients had been on current therapy for at least 3 months and had DAS28 scores reported, 74% were female, with a mean age of 52 years, and mean time since RA diagnosis of 84 months. The table demonstrates that compared with the adequately controlled cohort, inadequately controlled patients were more affected clinically, had higher rates of depression, worse quality of life and greater work and activity impairment. There were also lower satisfaction rates among the patients and their physicians.

	Adequately controlled	Inadequately controlled*
n:	839 (73%)	308 (27%)
Rheumatologist reported clinical profile		
Perceived severity: ‘mild' (%)	87.4	31.2
Perceived severity: ‘moderate' (%)	11.9	58.1
Perceived severity: ‘severe' (%)	0.7	10.7
RA currently ‘improving' (%)	31.1	22.1
RA currently ‘stable' (%)	65.3	38.3
RA currently ‘unstable / deteriorating' (%)	3.6	39.6
Physician reports patient is currently ‘in remission' (%)	68.2	13.6
Current level of pain (mean, 1 none – 10 worst)	2.3	4.6
Patient ever experiences flares: yes (%)	41.4	67.3
Comorbidities (%):		
Depression	5.4	15.6
No comorbidities	56.9	34.7
BMI (mean)	24.9	25.8
Treatment		
Months receiving current therapy (mean)	25.9	24.8^
Ever received a bDMARD (%)	44.0	51.0
Status of bDMARD (% of patients prescribed a bDMARD):		
Currently receiving 1st bDMARD therapy	68.0	52.9
Impact on the patient		
Quality of life: EQ-5D score (mean)	0.77	0.53
Employment: Full time employed (%)	46.0	29.2
WPAI: % Overall work impairment (mean)	18.4	33.5@
WPAI: % Presenteeism (mean)	16.5	32.2
WPAI: % Activity impairment (mean)	26.7	48.2
Satisfaction with RA control (%)		
Physician ‘satisfied'	88.4	31.2
Patient ‘satisfied'	84.6	55.1

*: Variables significantly different from ‘adequately controlled' cohort, $p<0.01$ unless indicated by @: $p=0.0146$, or ^: not significant

Conclusion: Results show that almost a third of RA patients are insufficiently controlled despite current therapy. Even though these patients are more affected clinically, more impacted in their daily lives and less satisfied overall, the data indicated that in some cases physicians may perceive these patients to be ‘mild', or ‘in remission'. The discordance between physicians' perceptions and the objective DAS28 in some patients may result in less than optimal therapeutic management, the result of which may be sustained periods of unnecessary active disease. Furthermore, over half of patients who are not adequately controlled report being satisfied with the control their RA therapy provides, suggesting they too may be accepting sub-optimal outcomes and not look to change treatment.

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Effect of Anti-Cyclic Citrullinated Peptide 2 Immunoglobulin M Serostatus on Efficacy Outcomes Following Treatment with Abatacept Plus Methotrexate

T. W. J. Huizinga[1], SE Connolly[2], A Johnsen[2], J Zhu[2], Daniel E. Furst[3], VP Bykerk[4], Gerd Burmester[5], BG Combe[6], DA Wong[2], LA Trouw[1], René E. M. Toes[1] and Paul Emery[7], [1]Leiden University Medical Center, Leiden, Netherlands, [2]Bristol-Myers Squibb, Princeton, NJ, [3]Medicine, University of California, Los Angeles, David Geffen School of Medicine, Los Angeles, CA, [4]Weill Cornell Medical College, New York, NY, [5]Department of Rheumatology and Clinical Immunology, Charité - Universitätsmedizin Berlin, Berlin, Germany, [6]Montpellier University, Montpellier, France, [7]University of Leeds, Leeds, United Kingdom
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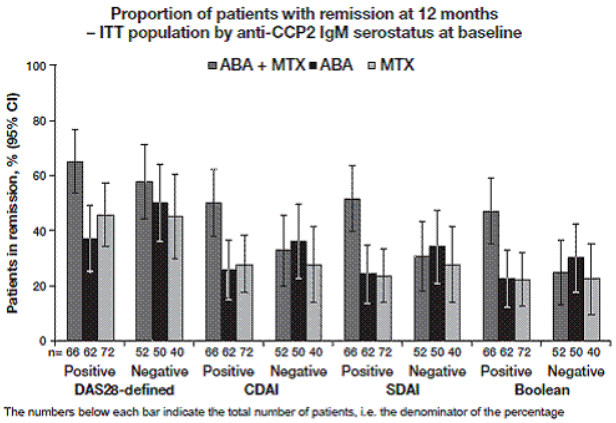
Background/Purpose: Anti-citrullinated protein antibodies (ACPA) are a marker of RA, and the presence of the immunoglobulin M (IgM) isotype indicates an ongoing immune response involving the recruitment of naïve B cells.[1] Abatacept (ABA) modulates T-cell co-stimulation and has been shown to impact ACPA maturation, including seroconversion of IgM, in the AVERT (Assessing Very Early Rheumatoid arthritis Treatment) trial.[2] The objective of this analysis was to assess the efficacy of treatment with ABA+MTX, ABA monotherapy or MTX alone in patients (pts) from the AVERT trial based on their anti-cyclic citrullinated peptide 2 (CCP2; a surrogate for ACPA) IgM serostatus at baseline (BL), and seroconversion (anti-CCP2 IgM positive to negative) through 1 year. **Methods:** The AVERT trial has been described previously.[3] In this *post hoc* analysis, pt samples were analysed by ELISA to determine anti-CCP2 IgM serostatus. Efficacy outcomes analyzed by BL anti-CCP2 IgM serostatus included remission rate at 12 mths (CDAI, SDAI, Boolean and DAS28 [CRP] <2.6-defined remission), and adjusted mean change in DAS28 (CRP) and HAQ-DI over time (samples taken every 28 days up to Mth 12 and analyzed with a longitudinal repeated-measures model). Boolean remission was analyzed in pts who seroconverted. **Results:** In the ABA+MTX treatment arm, a higher proportion of pts who were anti-CCP2 IgM positive at BL achieved remission by all indices compared with pts who were BL IgM negative (Figure). This trend was most clearly observed in the stringent indices of CDAI, SDAI and Boolean remission, compared with DAS28 (CRP)-defined remission. This trend was not observed in either the ABA monotherapy or MTX alone arms. Mean improvement in DAS28 (CRP) and HAQ-DI over time was also greatest in BL anti-CCP2 IgM-positive pts treated with ABA+MTX. A numerically higher proportion of pts who seroconverted from anti-CCP2 IgM positive at BL to negative at Mth 12 achieved Boolean remission versus pts who remained seropositive in the ABA+MTX and ABA



The numbers below each bar indicate the total number of patients, i.e. the denominator of the percentage

	Proportion of BL anti-CCP2 IgM-positive pts who achieved Boolean remission, by serostatus at Mth 12	
Treatment group	BL positive to Mth 12 negative	BL positive to Mth 12 positive
ABA+MTX	61.5% (16/26)	41.2% (14/34)
ABA	44.4% (4/9)	23.8% (10/42)
MTX	28.6% (4/14)	27.9% (12/43)

Proportion of pts is expressed as: % (number of pts with remission/total number of pts)

monotherapy arms (Table).

Conclusion: Abatacept in combination with MTX had greater clinical efficacy in pts who were anti-CCP2 IgM positive at BL than in those who were anti-CCP2 IgM negative at BL, and in those who seroconverted over time than those who did not, suggesting that the impact on ACPA is associated with clinical benefit.

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2. Huizinga TWJ, et al. *Arthritis Rheum* 2014;**66**:S666. Poster 1515.

3. Emery P, et al. *Ann Rheum Dis* 2015:**74**:19–26.

4. This abstract was first presented at the EULAR Congress, 10–13 June 2015, Rome, Italy (THU0114) and published in the corresponding supplement of *Ann Rheum Dis*.

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Abstract Number: 2669

Persistency of Patient Reported Morning (AM) Stiffness in a Large US Registry Cohort of Rheumatoid Arthritis (RA) Patients Initiating New DMARD Therapy

Vibeke Strand[1], Robert J. Holt[2], Heather J. Litman[3], Jeffrey D. Kent[4], Hristina Pashova[5], John T. Nguyen[3] and Carol J. Etzel[6,7], [1]Division of Immunology/Rheumatology, Stanford University School of Medicine, Portola Valley, CA, [2]University of Illinois - Chicago, Chicago, IL, [3]Corrona, LLC., Southborough, MA, [4]Horizon Pharma USA, Inc., Deerfield, IL, [5]Axio Research, LLC., Seattle, WA, [6]The University of Texas MD Anderson Cancer Center, Houston, TX, [7]Corrona, LLC, Southborough, MA

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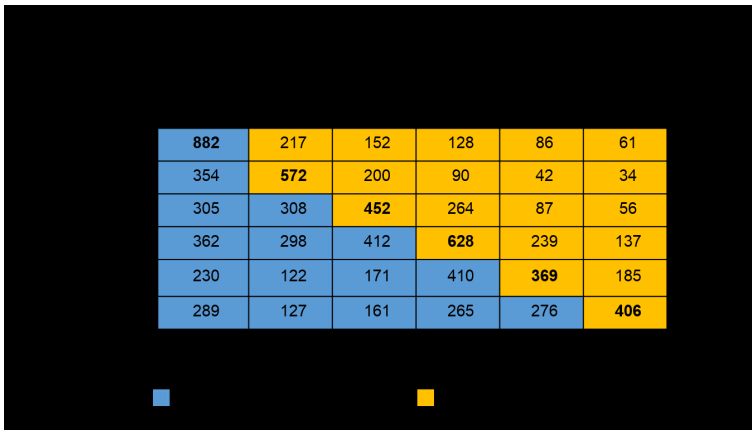
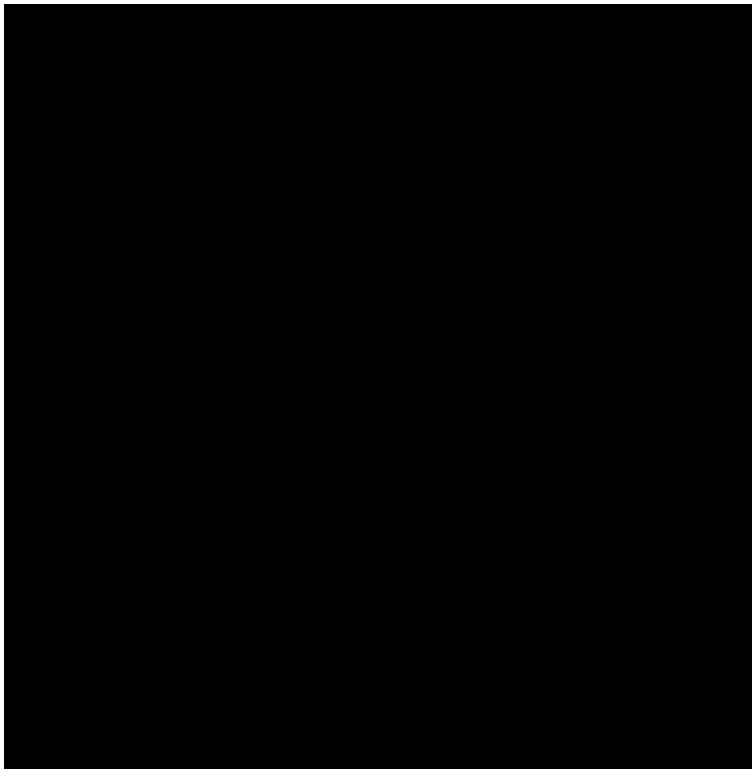
Background/Purpose: AM stiffness is a common yet under-appreciated symptom in RA. The longitudinal impact of AM stiffness has not been previously investigated. This study evaluated persistency of AM stiffness over time and prevalence of improvement based on decreases in stiffness duration following initiation of new DMARD therapy in the Corrona RA Registry.

Methods: Adult patients enrolled as of December 31, 2014 who initiated new biologic or synthetic DMARDs and maintained treatment for ≥90 days were analyzed and followed until last visit. The proportion and frequency of patients who reported none or decreased duration of AM stiffness were compared with those with persistent or increased duration at last visit. Among patients with AM stiffness at treatment initiation, baseline characteristics and categorical improvement in stiffness duration were evaluated. Patients reporting <1hr of AM stiffness were considered improved if they had no stiffness; those reporting 1-<2hrs were improved if <0.5 hours and those with 2-<3 and ≥3hrs improved if <1hr by last visit.

Results: Of 9377 total patients, 4972 (53%) continued stiffness free or reported decreased duration and 4405 (47%) had persistent or worsened duration of stiffness at last visit (Table 1). 644 (42.2%) with no stiffness at treatment initiation reported stiffness by last visit. Among 7851 with AM stiffness at treatment initiation, a large majority were biologic DMARD naïve (56.5%) and initiated combination therapy (56.4%) (Table 2). When categorical improvement in stiffness duration criteria were analyzed, 5432 (69.2%) among patients reporting AM stiffness at treatment initiation reported no improvement at last visit.

Conclusion: In this analysis, longitudinal and categorical change data demonstrate that AM stiffness is a recurring symptom which persists as an unmet need in a large majority of RA patients despite initiation of new DMARD therapy. Further research is needed to evaluate clinically meaningful metrics from the patients' perspective for improvement in AM stiffness duration. Clinical factors associated with improved responses should be evaluated to address persistency of AM stiffness that continues to affect a large number of RA patients.





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Abstract Number: 2670

Comparison of M-DAS and DAS28, Two Composite Scores for Prediction of Structural Damages in Rheumatoid Arthritis: Data from the Espoir Cohort

Marion Couderc[1], Bruno Pereira[2], B G Combe[3], Valerie Devauchelle[4], Xavier Mariette[5] and Martin Soubrier[1], [1]Rheumatology department CHU Clermont-Ferrand, Clermont-Ferrand, France, [2]Biostatistics unit (DRCI), CHU Clermont-Ferrand, Clermont-Ferrand, France, [3]Hospital Lapeyronie, Immuno-Rheumatology, Montpellier, France, [4]Service de Rhumatologie, CHU Brest, Brest, France, [5]Université Paris-Sud, AP-HP, Hôpitaux Universitaires Paris-Sud, Paris, France

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Background/Purpose: Numbers of composite scores are available to assess disease activity in rheumatoid arthritis (RA), the most widely used being the Disease-Activity-Score in 28 joints (DAS28), the Simplified-Disease-Activity-Index (SDAI), and the Clinical-Disease-Activity-Score (CDAI). Baker et al. have recently developed a modified version of these scores (M-DAS28, M-CDAI, M-SDAI) based on widely available clinical measures (swollen joint count [SJC] evaluator global assessment of disease activity [EvGA] and CRP level). (1) These scores demonstrated superior correlation with MRI detection of synovitis and more accurately predicted radiographic progression after 1 year than DAS28 and SDAI.The objective of the study was to evaluate the performance of new composite disease activity scores (M-DAS28, M-SDAI and M-CDAI]) compared to conventional measures (DAS28, SDAI and CDAI)

to predict radiographic progression in rheumatoid arthritis patients from the ESPOIR cohort.

Methods: The French multicentric ESPOIR cohort included a total of 664 patients with early (< 6 months) unclassified arthritis. This study was conducted on the patients fulfilling the ACR/EULAR 2010 classification criteria for RA. The M-DAS28, M-SDAI, and M-CDAI were respectively compared to the DAS28, CDAI and SDAI for predicting radiographic progression (estimated after 1 year by The Sharp/van der Heidje [SHS] scoring system).

Results: A total of 590 RA patients (women 78%, age 48.8 years, symptoms duration 16 weeks, SJC 8, tender joint count 9, ESR 29 mm at the first hour, CRP level 22 mg/L, DAS28-ESR 5.2, DAS28-CRP 5.0, SDAI 30.4, CDAI 28.3) were included.

Ability to predict radiographic progression after 1 year was the same between baseline M-DAS28-ESR and DAS28-ESR (Area under the curve [AUC]: 0.53 [0.49–0.58] *vs* 0.53 [0.48–0.58] respectively), M-DAS28-CRP and DAS28-CRP (AUC : 0.54 [0.49–0.59] *vs* 0.52 [0.47–0.57] respectively), M-SDAI and SDAI (AUC : 0.52 [0.47–0.57] *vs* 0.51 [0.46–0.56] respectively), M-CDAI and CDAI (AUC: 0.51 [0.47–0.56] *vs.* 0.50 [0.45–0.55] respectively).

Conclusion: In conclusion, modified disease activity scores (M-DAS28-ESR, M-DAS28-CRP, M-CDAI and M-SDAI), based on clinical measures of disease activity, did not prove superiority to original disease activity scores on ability to predict structural progression in patients with RA.

Reference :

1 - Baker JF, Conaghan PG, Smolen JS, Aletaha D, Shults J, Emery P, et al. Development and validation of modified disease activity scores in rheumatoid arthritis: Superior correlation with MRI synovitis and X-ray progression. Arthritis Rheum. 2014;66:794-802

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Abstract Number: 2671

Male Gender and Higher Hemoglobin Predict Response to Methotrexate in Rheumatoid Arthritis

Abhijeet Danve[1], Harlan Sayles[2], Ted R. Mikuls[3] and James R. O'Dell[2], [1]Internal Medicine - Rheumatology, University of Nebraska Medical Center, Omaha, NE, [2]University of Nebraska Medical Center, Omaha, NE, [3]Internal Medicine, University of Nebraska Medical Center, Omaha, NE

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Background/Purpose:

Methotrexate (MTX) is routinely used as the first-line drug for rheumatoid arthritis (RA). About 1 in 3 RA patients achieve excellent RA control with MTX monotherapy. Identifying predictors of MTX response could allow treatment optimization, avoid drug toxicities and treatment delays while saving costs.

Methods:

Potential baseline clinical predictors were studied in two cohorts: Rheumatology & Arthritis Investigational Network (RAIN) Early Predictors Study and Treatment of Early Aggressive Rheumatoid Arthritis (TEAR) trial. RAIN is a 16-week, open-label study where RA patients are started on weekly po MTX 15mg and escalated to 20 mg at 8 weeks if not in remission (DAS-28 ESR< 2.6). Clinical and laboratory parameters are collected at baseline, 8, and 16 weeks. TEAR was a randomized, double-blind study using 4 treatment arms: two arms with immediate combination therapy and two step-up arms. We analyzed patients from TEAR step-up arms who initially were on po MTX monotherapy. Primary outcome was absolute change in DAS-28 (baseline to 16 weeks for RAIN and baseline to 12 weeks for TEAR) adjusted for the baseline. Low disease activity (LDA; DAS28 <3.2) was a secondary outcome. Data were analyzed using ordinary least squares and logistic regression.

Results:

Eighty-three patients (75% female, 89% white) completed the 16-week RAIN trial. Mean (SD) change in DAS-28 from baseline to 16 weeks was -1.90 (1.50) with LDA achieved by 51%. Male gender (p=0.015), white race (p=0.019) and lower baseline neutrophil (BNC) count (p=0.011) were associated with significant improvement in DAS-28ESR (Table). Male gender, higher hemoglobin and lower BNC were significantly associated with achieving LDA (not shown).

Patients (n=297) who received MTX monotherapy during TEAR were also analyzed (70% female, 81% white). Mean (SD) change in DAS-28 from baseline to 12 weeks was -1.28 (1.19) with LDA achieved by 20%. Male gender (p=0.016), lower baseline tender joint counts (p=0.037) and lower baseline aspartate transaminase (p=0.020) were associated with primary outcome (Table). Lower BNC showed a non-significant trend towards DAS28 improvement. Male gender, lower swollen joint count and higher hemoglobin were associated with LDA (not shown).

Conclusion:

In both cohorts, male gender and white race were associated with significant improvement in DAS28ESR with MTX monotherapy; higher baseline hemoglobin was also associated with achieving LDA. Lower BNC was associated with good response (absolute change and LDA) to MTX in RAIN cohort, but only showed a trend in the TEAR cohort. Larger studies with a focus on pharmaco-genetics may be required to identify the RA patients who are ideal candidates for MTX monotherapy.

Table - DAS28ESR Change from 0 to 16 Weeks (RAIN) or 12 Weeks (TEAR) Controlling for Baseline DAS28ESR

	RAIN N=83			TEAR N=297		
Characteristic	**Coefficient**	**SE**	**p value**	**Coefficient**	**SE**	**p value**
Male gender	-0.789	0.318	**0.015**	-0.356	0.147	**0.016**
White race	-1.070	0.448	**0.019**	-0.339	0.175	0.054
Tender joint count	-0.021	0.029	0.471	0.030	0.014	**0.037**
Neutrophils	0.013	0.005	**0.011**	0.079	0.043	0.068
Platelet count	-0.002	0.002	0.349	0.001	0.001	0.329
Aspartate Transaminase	-0.002	0.025	0.947	0.018	0.008	**0.020**

*Non-significant factors examined included age, disease duration, smoking status, diabetes, baseline HAQ score, swollen joint count, ESR, hemoglobin, WBC, platelet count, albumin, and creatinine

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Abstract Number: 2672

Determinants of Patient- Physician Discordance in Assessment of Global Disease Activity in Latinos with Rheumatoid Arthritis in the United States

George A. Karpouzas[1], Taylor Draper[2], Elizabeth Hernandez[1] and Sarah Ormseth[1], [1]Rheumatology, Harbor-UCLA Medical Center, Torrance, CA, [2]Psychology, Loma Linda University, Loma Linda, CA

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Background/Purpose: Patients and physicians often differ in their perceptions of disease activity in Rheumatoid arthritis (RA) as described by patients' and evaluators' global assessments (PGA and EGA respectively), mostly assessed in Caucasians. We evaluated determinants of PGA and EGA and their proportionate contributions in Latinos with RA in the US. We further explored predictors of discrepancies between PGA and EGA, and interrogated the frequencies of concordant and discordant assessments of changes in PGA and EGA longitudinally.

Methods: We assessed 333 Latinos with RA and follow up in a single center. EGA and PGA were captured on a 0-10 cm visual analogue scale; discordance was defined as difference >2 cm between the 2 assessments. Linear regression models evaluated predictors of PGA and EGA, and relative importance weights were calculated for their proportionate contribution to PGA and EGA variance. Logistic regression models interrogated predictors of both patient and physician higher ratings respectively.

Results: Our models explained 66% of variability in PGA and 83% of the variability in EGA. Main, multivariate determinants for PGA were fatigue (23.7%), pain (21.2%), depression (18%), and sedimentation rate- ESR (3.2%). EGA was mainly predicted by swollen joint counts (44.4%), tender joint counts (30.2%), ESR (5.2%) and fatigue (3.5%). Concordance was observed in 142 (43%), higher patient ratings in 147 (44%), and higher physician ratings in 44 (13%). Fatigue and pain predicted higher patient ratings, while swollen joints, tender joints, and prednisone use predicted higher physician ratings (table 1). At follow up, EGA improved in 31.7%, remained unchanged in 50.9% and worsened in 17.4%. Respective trends for PGA were 28.6%, 44.1% and 27.3%. The lowest concordance was seen for worsening disease, where PGA showed only 27% concordance with the EGA, compared to 59% and 52% for unchanged or improved disease respectively.

Conclusion: Highly divergent parameters shape patients' and physicians' perceptions of disease activity in Latinos with RA in the US; fatigue and pain contribute mainly to higher patient assessments, while swollen and tender joint counts predict higher physician assessments. Patient education of what determines long-term disability, and a better physician grasp of the patient perspective will likely foster shared decision-making and compliance with treat to target initiative.

Table 1: Predictors of discordant Patient –Physician Assessments of global disease activity

	Higher PGA (PGA - EGA > 2cm)				Higher EGA (EGA - PGA > 2cm)			
	Unadjusted OR (95% CI)		Adjusted OR (95% CI)		Unadjusted OR (95% CI)		Adjusted OR (95% CI)	
Age	1.02	(1.00 - 1.04)			1.01	(0.98 - 1.04)		
Gender	1.29	(0.61 - 2.73)			0.86	(0.32 - 2.34)		
Disease duration	0.98	(0.95 - 1.01)			0.99	(0.95 - 1.03)		
RF positive	0.46	(0.19 - 1.09)			0.32	(0.11 - 0.93)	0.56	(0.11 - 2.81)
CCP positive	0.64	(0.31 - 1.34)			0.53	(0.20 - 1.43)		
Erosions	1.04	(0.66 - 1.65)			1.61	(0.80 - 3.23)		
IAD present	1.25	(0.75 - 2.10)			0.72	(0.31 - 1.63)		
Fibromyalgia	1.87	(1.01 - 3.48)	0.90	(0.38-2.10)	0.47	(0.13 - 1.68)		
n-TJC	0.94	(0.89 - 0.99)	0.87	(0.79 - 0.95)**	1.21	(1.13 - 1.29)	1.16	(1.05 - 1.28)**
n-SJC	0.80	(0.73 - 0.88)	0.64	(0.54 - 0.75)***	1.38	(1.25 - 1.52)	1.34	(1.18 - 1.53)***
ESR	1.00	(0.99 - 1.01)			1.02	(1.00 - 1.03)	1.00	(0.98 - 1.02)
Prednisone	1.23	(0.75 - 2.02)			3.13	(1.56 - 6.29)	3.14	(1.15 - 8.55)*
n-DMARDs	0.97	(0.77 - 1.23)			0.81	(0.57 - 1.14)		
Biologics	1.17	(0.73 - 1.88)			1.63	(0.83 - 3.22)		
HAQ-DI	1.80	(1.35 - 2.41)	1.31	(0.84-2.04)	1.72	(1.16 - 2.57)	1.21	(0.61 - 2.4)
Pain-VAS	2.07	(1.53 - 2.79)	2.06	(1.23 - 3.46)***	1.55	(1.01 - 2.38)	0.29	(0.12 - 0.69)**
PHQ-9	1.10	(1.06 - 1.15)	1.05	(0.99 - 1.12)	1.02	(0.96 - 1.08)		
FACIT	1.26	(1.16 - 1.37)	1.30	(1.12 - 1.49)***	1.09	(0.97 - 1.22)		

*p<0.05, **p<0.01, ***p<0.001

Abstract Number: 2673

Association Between Anxiety and Depression and Rheumatoid Disease Severity: Results from an Established Rheumatoid Arthritis Cohort

Faith Matcham[1], Sam Norton[2,3], Nicola Goodson[4], Samantha Hider[5], Matthew Hotopf[6] and James Galloway[7], [1]Psychological Medicine Clinical Academic Group, King's College London, London, United Kingdom, [2]Department of Psychological Medicine, King´s College London, London, United Kingdom, [3]Institute of Psychiatry, King's College London, London, United Kingdom, [4]Rheumatology, University of Liverpool, Liverpool, United Kingdom, [5]Research Institute for Primary Care and Health Sciences, Keele University, Keele, United Kingdom, [6]Department of Psychological Medicine, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, United Kingdom, [7]Academic Department of Rheumatology, King´s College London, London, United Kingdom

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Background/Purpose:

Depression is highly prevalent in RA. In trials, depression has been found to be associated with higher disease activity and impaired treatment response. However data are limited and subject to methodological limitations such as being derived from highly selected trial populations. Our aim was to examine the long-term association between depression and RA disease outcomes in routine care.

Methods:

Data were collected using electronic records from an inner city hospital in London, UK. The presence of depression/anxiety was identified using PHQ9 and GAD7 respectively. Patients were included in this analysis if they had completed a PHQ9/GAD7 on at least 2 occasions. The first ever PHQ9/GAD7 record was taken as the baseline visit. Follow up included all visit information over the subsequent 12-months. The relationship between anxiety/depression and DAS outcome was analysed using two approaches: 1) we calculated the likelihood of an individual achieving remission during follow up using Cox proportional hazards, adjusted for age, gender, disease duration and disease activity; 2) we modelled DAS trajectory using generalised estimating equations (GEE).

Results:

From a total cohort of 1,375, 385 patients were eligible for analysis. The mean age was 59 (SD 15), with 81% female (see table). At baseline, depression/anxiety were associated with higher disease activity and disability. The presence of depression/anxiety at baseline was associated with significantly higher disease activity throughout follow-up (b= 0.92, SE= 0.15, p<0.001, 95%CI: 0.53 to 1.21), after adjusting for age, gender and disease duration. Using a GEE model DAS was significantly higher for patients with anxiety or depression (b=.85; 95% CI:.54 to 1.16), but reduced slightly over time (b/year=-.11 95% CI: -.21 to -.01). This change may reflect more aggressive treatment of patients with anxiety or depression that have higher DAS, the correlation between a change in DAS and anxiety or depression status of r=.28. Patients with baseline anxiety or depression were less likely to attain a state of remission (adjusted hazard ratio: 0.51, 95%CI: 0.35 to 0.75).

Conclusion:

Our data reveal a high prevalence of psychological comorbidity in RA. The presence of depression/anxiety associated with larger differences in patient reported components of outcomes (tender joint count, patient global, HAQ) than objective measures. Patients with baseline anxiety/depression had higher disease activity that remained high during follow up. Comparing change in DAS over time revealed no material difference in the DAS trajectory in patients with or without anxiety or depression. It is clear that psychological factors are linked to the clinical outcome measures used in rheumatology. However, how depression/anxiety influence prognosis is unclear.

Table

		No anxiety/ depression	Probable anxiety/ depression	p-value*
Total = 385	N	279	106	
Age	Mean(SD)	59 (15)	57 (15)	0.27
Female gender	n(%)	223 (80)	88 (83)	0.49
Seropositive	n(%)	318 (78)	129 (79)	0.85
Baseline DAS28	Mean(SD)	3.9 (1.5)	5.0 (1.4)	<0.0001
Baseline swollen joint count	Mean(SD)	2.6 (3.4)	3.5 (3.6)	0.0112
Baseline tender joint count	Mean(SD)	5.6 (6.2)	9.7 (8.2)	<0.0001
Baseline ESR	Mean(SD)	24 (20)	31 (24)	0.0201
Baseline patient global	Mean(SD)	40 (23)	62 (23)	<0.0001
Baseline HAQ score	Mean(SD)	1.2 (0.8)	1.9 (0.6)	<0.0001
Baseline fatigue	Mean(SD)	45 (25)	65 (20)	<0.0001
Baseline pain VAS	Mean(SD)	39 (26)	64 (22)	<0.0001
*Wilcoxon's rank sum- any anxiety depression vs no anxiety depression				

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Abstract Number: 2674

Patient Global Assessment in Evaluating Boolean-Based Remission in Rheumatoid Arthritis-Is It Really Required Instead of Physician Global Assessment? a

Comparative Study with Ultrasound

Gulsen Ozen[1], Ali Ugur Unal[1], Atakan Topcu[2], Pamir Atagunduz[1], Haner Direskeneli[1] and Nevsun Inanc[1], [1]Department of Rheumatology, Marmara University Faculty of Medicine, Istanbul, Turkey, [2]Department of Internal Medicine, Marmara University Faculty of Medicine, Istanbul, Turkey

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Background/Purpose: Patient global assessment (PtGA) is included in all the current remission definitions for RA despite the fact that PtGA is not exclusively related to disease activity and may be influenced by noninflammatory or psychological processess. In this study in order to objectively identify whether patient's assessment is better than physician's (Ph) or not, we compared disease activities assessed with ultrasound (US) of Boolean remission patients with PtGA and Boolean remission patients with PhGA but not PtGA.

Methods: RA patients in clinical remission (DAS28-ESR<2.6) for at least 3 months were included. Boolean based remission definition and modified versions by substitution of PtGA with PhGA and by omitting PtGA were determined. A standard gray scale (GS) and power Doppler (PD) US examination of 28 joints (included in DAS28) for the presence of synovitis was performed by an experienced sonographer (NI) blinded to clinical data. US synovitis GS and PD signals were semiquantitatively graded from 0 to 3 and were recorded as sum scores of PD and GS, respectively.

Results: A total of 55 out of 302 RA patients (18.2%) in DAS28 remission were enrolled (F/M=35/20, mean age 52.2±12.0, disease duration 11.011.0±6.5 years, bDMARDs 43.6%, RF/Anti-CCP positivity 76.4%). Of 55 patients, 25 (45.5%) fulfilled the Boolean criteria. When PtGA was substituted with PhGA, remission rate increased to 72.7% (n=40) and when PtGA was omitted remission rate increased to 89.1% (n=49) (P<0.001 for both). Regarding US disease activity no PD, no GS and no PD+GS signals were observed in 9 (36%) vs 12 (30%), 7 (28%) vs 8 (20%) and 6 (24%) vs 7 (17.5%) patients in Boolean remission with PtGA and PhGA, respectively (P>0.05 for all). When PD and GS signals ≥ grade 2 were taken into account, % of patients without PD, GS or both signals were also similar (respectively, 16 [64%] vs 25 [62.5%], 12 [48%] vs 18 [45%] and 12 [48%] vs 17 [42.5%]). US disease activity parameters of Boolean PtGA remission and nonremission patients were compared as well, no significant difference was observed. On the other hand patients in Boolean PhGA remission had significantly lower PD scores (without grade 1) compared to Boolean PhGA nonremission (Table 1). In comparison of US disease activity of patients in Boolean PtGA remission and in Boolean remission with PhGA but not PtGA, the median PD and GS synovitis sum scores and the % of patients with no PD or GS signals were not statistically different.

Conclusion: RA patients in Boolean remission with PhGA do not have higher disease activity that is verified by US, compared to patients in Boolean remission with PtGA. Furthermore Boolean remission with PhGA better differentiates patients with US evinced inflammation. These data suggest that PtGA might be substituted with PhGA in Boolean criteria. Prospective follow up and recruitment of more patients will clarify the consistency of these results over time and impact of this substitution on functionality.

Table 1. US disease activity parameters of remission and nonremission patients according to Boolean based criteria with PtGA and PhGA*

	Boolean remission with PtGA (n=25)	Boolean non-remission with PtGA (n=30)	*P* value	Boolean remission with PhGA (n=40)	Boolean non-remission with PhGA (n=15)	*P* value
PD synovitis sum score (0-84)	1 (0-4.5)	2.5 (0-6.2)	0.26	1 (0-4)	4 (0-7)	0.26
PD synovitis sum scores (without counting grade 1 signals)	0 (0-3)	1 (0-6)	0.20	0 (0-3.5)	4 (0-6)	**0.045**
GS synovitis sum score (0-84)	3 (0-6.5)	4 (1-8.2)	0.32	3.5 (1-8)	4 (1-9)	0.59
GS synovitis sum scores (without counting grade 1 signals)	2 (0-5)	2 (0-7.2)	0.39	2 (0-6)	4 (0-8)	0.58
US joint count with PD signal (0-28)	1 (0-3)	2 (0-3.2)	0.32	1 (0-3)	2 (0-4)	0.36
US joint count with PD signal (without counting grade 1 signals)	0 (0-1.5)	0.5 (0-3)	0.21	0 (0-1.7)	2 (0-3)	**0.090**
US joint count with GS signal (0-28)	2 (0-4.5)	3 (1-4)	0.37	2 (1-4)	3 (1-4)	0.73
US joint count with GS signal (without counting grade 1 signals)	1 (0-2.5)	1 (0-3.2)	0.39	1 (0-3)	3 (1-4)	0.61
USDAS28PD	2.35 (1.82-2.91)	2.55 (2.26-2.8)	0.32	2.47 (1.99-2.83)	2.50 (2.31-2.83)	0.35
USDAS28GS	2.35 (1.88-3.03)	2.69 (2.3-2.9)	0.31	2.54 (2.02-2.99)	2.60 (2.40-2.90)	0.49

**The values were presented as median (25-75).*

Disclosure: G. Ozen, None; **A. U. Unal**, None; **A. Topcu**, None; **P. Atagunduz**, None; **H. Direskeneli**, None; **N. Inanc**, None.

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Abstract Number: 2675

Has the Relationship Between Disease Activity and Disability in Rheumatoid Arthritis Changed?

Aneela Mian[1], Fowzia Ibrahim[2,3], Ian C. Scott[4], Sardar Bahadur[5], Maria Filkova[6], Louise Pollard[7], Gabrielle H. Kingsley[8], Sophia Steer[9], David L. Scott[6] and James Galloway[10], [1]Academic Rheumatology, King's College London, London, United Kingdom, [2]Academic Rheumatology Dept, King's College, London, United Kingdom, [3]Academic Rheumatology Dept, King's College London, London, United Kingdom, [4]Louise Coote Lupus Unit, St Thomas' Hospital, London, United Kingdom, [5]Guys' and St Thomas' NHS Trust, London, United Kingdom, [6]Academic Department of Rheumatology, King´s College London, London, United Kingdom, [7]University

Hospital Lewisham, London, United Kingdom, [8]Rheumatology, Kings College London, London, United Kingdom, [9]Rheumatology Dept, Kings College Hospital, London, United Kingdom, [10]King's College Hospital, London, United Kingdom
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Background/Purpose: Rheumatoid arthritis (RA) management paradigms have changed over the last two decades. Evidence now supports aggressive immunosuppression with early use of combination disease modifying anti rheumatic drugs (DMARDs) and biologics when standard DMARDs fail. The use of composite tools to measure disease activity has become standard assessment tools in the clinic with an aim of achieving remission or low disease activity. We set out to study the changing patterns of disease activity and disability in RA over the last 20 years.

Methods: Retrospective cross-sectional surveys were undertaken at four time points from two secondary care rheumatology departments in London. Patients included had a diagnosis of RA by the 1987 criteria of the American College of Rheumatology. The surveys collected data between (i) 1996-97; (ii) 2001-3; (iii) 2009-10; (iv) 2012-14. Data collected comprised demographic details (age, sex and disease duration), 28 joint disease activity score (DAS28) and its component parts. Disability measures using the Health Assessment Questionnaire (HAQ) scores were also available for the first, second and fourth cohorts.

Results: Overall 1324 patients were studied. The groups had similar demographic features (76-80% were female; their mean ages were 58-60 years; and their mean disease durations were 9.1-10 years. Disease activity fell over time, with the proportion of patients in remission significantly increasing from 8% in the earliest cohort to 28% in the most recent. The proportion with severe disease fell from 50% in the earliest cohort to 18% in the most recent, whilst the proportion with moderate disease remained constant (38-42%). Although the number of swollen joints has decreased in each DAS28 group over time, the more objective tender joint counts and patient global scores have increased or remained stable. In contrast, there was no fall in disability levels over time. Mean HAQ scores were 1.30 in 1996-97 and 1.32 in 2012-14, with a slightly higher mean HAQ of 1.52 in 2001-03. Comparing disability change over time across the disease activity groups, mean HAQ scores in patients in remission and low disease activity states increased. The correlation between disease activity and disability became weaker over time; in 1996-97 Spearman's rho was 0.56, in 2001-03 it was 0.55 and in 2012-14 it was 0.44.

Conclusion: Our data add to the existing evidence base, confirming that the trends towards milder disease are continuing. There is a widening gap between the subjective and objective components of DAS, with climbing tender joint counts in the face of reduced numbers of swollen joints. Other factors such as comorbidity including psychological disease, may be very relevant. Depression and anxiety are highly prevalent in RA. Our data show that the relationship between disease activity and disability has changed over time. Further research is needed to understand how to best manage non-severe RA, that now makes up the largest burden of clinic attenders. Strategies to address comorbidity and mental health needs should to be evaluated.

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Abstract Number: 2676

Is It Useful to Determine All Rheumatoid Factors Isotypes to Enhance Rheumatoid Arthritis Detection? a Clinical Laboratory Perspective

Alejandro Garza-Alpirez[1], Mario Alberto Garza-Elizondo[2], David Vega-Morales[2], Cassandra Skinner-Taylor[2], Ricardo Ramírez[3], Roberto Negrete-López[4], Jorge Esquivel-Valerio[2], Miguel Villarreal-Alarcon[2] and Andrés Mendiola[1], [1]Servicio de Reumatología, Departamento de Medicina Interna del Hospital Universitario " Dr. José Eleuterio González". Universidad Autónoma de Nuevo León, Monterrey, Mexico, [2]Servicio de Reumatología, Departamento de Medicina Interna del Hospital Universitario "Dr. José Eleuterio González", Universidad Autónoma de Nuevo León, Monterrey, Mexico, [3]Rheumatology, Hospital Universitario, UANL., Monterrey, Mexico, [4]Servicio de Reumatología, Departamento de Medicina Interna del Hospital Universitario, Monterrey, Mexico
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Background/Purpose: Rheumatoid arthritis (RA) diagnosis includes determination of autoantibodies and, their presence can represents 33% (2/6) to 50% (3/6) of the 2010 ACR/EULAR classification criteria [1]. Rheumatoid factor has three isotypes, of which IgM is the most used because of its sensitivity and specificity [2]. The aim of this study is to evaluate the performance of RF isotypes alone and in combination with anti-cyclic citrullinated peptide (anti-CCP) antibodies in the RA diagnosis.

Methods: An observational, retrospective and analytical study was made. We selected all results of RF and anti-CCP sent to our laboratory between March 2014 and March 2015 with an inflammatory arthritis suspicion. We collected final diagnosis according to medical records and classified patients with RA (2010 ACR-EULAR), Osteoarthritis (OA, ACR), Systemic lupus erythematosus (SLE,1987 ACR criteria) and Primary Sjögren syndrome (pSS, 2012 American-European-Consensus-Group (CETA) criteria). RF isotypes evaluated was IgA, IgM and IgG measured by ELISA (ORGENTEC®) with a cut-off > 20 IU and anti-CCP2 antibodies by ELISA (ORGENTEC®) with a cut-off> 25 IU. We made a descriptive analysis of the seropositivity according to different diseases. Then, we performed an analysis of sensitivity and specificity using autoantibodies alone and in different combinations for the final RA diagnosis.

Results: We included 62 (44.3%) RA patients, 10 (7.1%) patients with SS, 5 (3.5%) patients with SLE, and 52 (37.1%) patients with OA. In table 1 we described autoantibodies frequencies according to different diseases. Sensitivity and specificity to RA diagnosis was represented in Table 2 with autoantibodies combinations.

Conclusion: The combination of the four autoantibodies increased sensitivity for RA detection, although we observed a decreased of global specificity of the test.

References: 1.Aletaha D, Neogi T, Silman AJ, et al. Arthritis Rheum 2010;62:2569-81. 2. Sun J, Zhang Y, Liu L, et al. Clin Exp Rheumatol 2014;32:11-21

Table 1. Frequencies of autoantibodies according different diseases

Test	RA n, (%)	OA n, (%)	pSS n, (%)	SLE n, (%)
IgM RF	54 (62.8)	12 (23.1)	6 (66)	3 (60)
IgA RF	46 (53.5)	7 (13.5)	3 (33.3)	4 (7.8)
IgG RF	44 (51.2)	10 (19.2)	4 (44)	1 (20)
anti-CCP	43 (44)	6 (11.5)	5 (50)	1 (20)

RA: Rheumatoid Arthritis, OA: Osteoarthritis, pSS: Primary Sjögren Syndrome, SLE: Systemic Lupus Erythematosus. RF: Rheumatoid Factor, anti-CCP: anti-Cyclic Citrullinated Peptide antibodies

Table 2. Sensitivity and specificity according to autoantibodies and their combinations for RA detection

Test	Sensitivity (%)	Specificity (%)
IgG RF	49.4	89.7
Anti-CCP	49.4	96.2
IgA RF	54	90.6
IgM RF	62.1	90.6
IgA+, IgG+	65.1	83
CCP+, IgA+	66.3	86.8
CCP+, IgG+	67.4	84.9
CCP+, IgM+	68.6	86.8
IgM+, IgG+	69.8	83
IgM+, IgA+	72.1	83
IgM+, IgA+, IgG+	76.7	77.4
IgM+, IgA+, IgG+, CCP+	**81.4**	**73.6**

RF: rheumatoid factor, Anti-CCP: anti-cyclic citrullinated peptide antibodies

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Abstract Number: 2677

Targeting Biomarkers of Nitric Oxide and Endothelial Dysfunction in Patients with Rheumatoid Arthritis

Ankita Satpute[1], Stanley Hazen[2,3], WH Wilson Tang[3] and **M. Elaine Husni**[4], [1]Case Western Reserve University School of Medicine, Cleveland, OH, [2]Cell Biology, Cell Biology, Cleveland Clinic Foundation, Cleveland, OH, [3]Cardiology, Cardiology, Cleveland Clinic Foundation, Cleveland, OH, [4]Rheumatology Dept A50, Cleveland Clinic Foundation, Cleveland, OH
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Background/Purpose:

Numerous studies have reported increased cardiovascular morbidity and mortality in rheumatoid arthritis (RA) patients that cannot be explained by traditional risk factors. In a non-RA cohort, our collaborators identified specific biomarkers of nitrative stress which act to impair endothelium dependent nitric oxide function and were found to be predictive of future CV events in an at risk population. These biomarkers [asymmetric dimethylarginine (ADMA), symmetric dimethylarginine (SDMA), and N-mono-methylarginine (MMA)] are produced by methylation of arginine, the sole nitrogen source for NO synthesis. We believe these biomarkers of subclinical endothelial dysfunction may serve as an early non-invasive predictor of accelerated atherosclerosis in RA patients. The aim of this study is to investigate if these biomarkers of endothelial dysfunction are increased in patients with RA compared to healthy controls and to examine the effects of disease modifying treatments, statin therapy, and seropositive status on levels of these biomarkers.

Methods:

The plasma from 119 RA patients (83.6% female, 60.2± 13.6 yrs of age) seen in a tertiary care center from October 2014 to April 2015 was analyzed for ADMA, SDMA and MMA levels by stable isotope dilution HPLC with online electrospray ionization tandem mass spectrometry compared to controls. The Arginine Methylation Index (ArgMI) was estimated by the ratio of [(ADMA+SDMA)/MMA]. The effects of statin and DMARD therapy, as well as seropositivity (anti-CCP antibody or RF>20) on these biomarkers were evaluated. The Student t test or Wilcoxon Rank sum test for continuous variables and chi squared test for categorical variables were used in statistical analysis.

Results:

ADMA and SDMA biomarker levels and ArgMI were statistically larger in the RA cohort ($p<.0001$) when compared with their age and gender matched healthy controls (see Table 1). Surprisingly, seronegative patients exhibited statistically significant higher ArgMI compared with seropositive patients. Statin and DMARD therapy showed no significant effect on any nitrative stress biomarkers.

Conclusion:

These elevated nitrative stress biomarkers in RA patients suggest an important avenue for detecting subclinical endothelial dysfunction in RA. Surprisingly, DMARD treatment, known to decrease systemic inflammation, did not suppress biomarkers of nitrative stress, which points towards a disconnect between systemic inflammation and endothelial dysfunction. Furthermore the elevated ArgMI seen in seronegative patients, a group that is perceived as having a more benign course and CV risk phenotype, warrants additional study. Future studies which prospectively follow patients for CV outcomes have the potential to identify RA patients at increased CV risk and provide them with appropriate preventative intervention.

Table 1.

Nitrative Stress Biomarkers	Healthy Controls (n=244)	Rheumatoid Arthritis (n=119)	P Value
ADMA, (µmol/L)	0.62 (0.55-0.69)	0.76 (0.68-0.82)	**<0.0001**
SDMA, (µmol/L)	0.46 (0.39-0.53)	0.52 (0.45-0.58)	**<0.0001**
MMA, (µmol/L)	0.20 (0.17-0.25)	0.20 (0.17-0.25)	0.9816
ArgMI,	5.30 (4.40-6.40)	6.21 (5.33-7.00)	**<0.0001**

Data represented as Median (IQR)

Disclosure: A. Satpute, None; **S. Hazen**, Abbott Diagnostics, Cleveland Heart Lab, Esperion, Lilly, Liposcience Inc, Merck Pharmaceuticals, Pfizer Inc, 5,Abbott Laboratories, Cleveland Heart Lab, Liposcience Inc, Pfizer, 2,Abbott Laboratories Inc, Cleveland Heart Lab, Esperion, Frantz Biomarkers, LLC, Liposcience Inc, Siemens, 7; **W. W. Tang**, None; **M. E. Husni**, None.

Abstract Number: 2678

Vitamin D Serum Level in Early Arthritis Patients: Association with Disease Activity, Disability and Severity in the Espoir Cohort

Etienne Gamon[1], Gaël Mouterde[2], Cédric Lukas[3], Mattea Orsini[4], Raphaèle Seror[5] and Bernard Combe[6], [1]Immunologie Rhumatologie, Hopital Lapeyronie, Montpellier, France, [2]Rheumatology Department, Hopital Lapeyronie, Montpellier, France, [3]Hopital Lapeyronie, Montpellier, France, [4]Epidemiology Unit, Hopital Lapeyronie, Montpellier, France, [5]Rheumatology, AP-HP Bicêtre Hospital / Paris-Sud University, Le Kremlin-Bicêtre, France, [6]Rheumatology, Hopital Lapeyronie, Montpellier, France
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Background/Purpose: Environmental factors may play a crucial role in auto-immune diseases. Besides tobacco, other factors like vitamin D are suspected to impact the onset and the subsequent activity of inflammatory arthritis including rheumatoid arthritis (RA), but its association with severity of the disease has not been evaluated yet. The purpose of the study was to examine the association of baseline vitamin D serum level with RA severity, disability, disease activity, response to treatment over the first year in early arthritis patients.

Methods: Patients presenting with synovitis of at least 2 joints for 6 weeks to 6 months were included in the multicenter French ESPOIR cohort. 25OH vitamin D2 and D3 was measured at baseline and then separated into 3 groups: deficiency (<10 ng/ml), insufficiency (10-30 ngl/mL), normal level (≥30ng/mL). Correlation between vitamin D levels and DAS28, HAQ and van der Heijde modified total Sharp score (mTSS) were assessed at baseline by a Spearman correlation analysis. Bivariate analyses of the association between baseline vitamin D level and other outcomes were conducted: radiographic progression (defined by an increase of at least 1 point of the mTSS at 12 months); disability (defined by an HAQ≥1); disease activity (DAS28) and RA diagnosis (2010 ACR/EULAR criteria) at baseline, 6 and 12 months; response to treatment (EULAR response) at 6 and 12 months. Forward stepwise multiple logistic regression was used to evaluate independent association between baseline variables and formerly described outcomes.

Results: Among 813 patients included in the cohort, 810 were analyzed and 138 (16.97%), 522 (64.21%), 150 (18.45%) had vit D<10, 10-30 and ≥30ng/mL respectively. Vitamin D levels were found to be correlated with DAS28, mTSS and HAQ at baseline (Rho=-0.11, p=0.0016; Rho=-0.07, p=0.0335 and Rho=-0.11, p=0.0016 respectively). In bivariate analyses, patients with vitamin D deficiency had more radiographic progression at 12 months compared to vitamin D normal group (OR=1.82 95% CI 1.05-3.15, p=0.0323). Patients with a HAQ ≥ 1 were more frequent in deficiency group compared to normal group at baseline and 6 months (OR=1.89 95% CI 1.18-3.03, p=0.008 and OR=2 95% CI 1.15-3.49 p=0.0146 respectively). Patients with DAS28>5.1 were more frequent in deficiency group compared to normal group at baseline (OR=1.84 95%CI 1.15-2.87 p=0.011). There was no link between vitamin D level and RA diagnosis at baseline, 6 and 12 months nor with response to treatment at 6 and 12 months. In multivariate analysis, radiographic progression at 12 months was associated with vitamin D deficiency (OR=1.82 95% CI 1.01-3.06, p<0.001), age, ACPA, CRP, sex, alcohol consumption and smoking status. Likewise, disability at baseline was associated with vitamin D deficiency (OR=1.73 95% CI 1.05-2.85, p=0.03), age, CRP, corticosteroid use and disease duration; furthermore disability at 6 months was associated with vitamin D deficiency (OR=2.01 95% CI 1.15-3.52, p=0.025), age and sex.

Conclusion: Vitamin D deficiency may be predictive of radiographic progression at 1 year and is associated with increased disability at baseline and 6 months in early arthritis patients.

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Abstract Number: 2679

Development and Validation of a HAQ-Derived Tool to Detect Muscle Mass Deficits in Rheumatoid Arthritis

Giorgos Loizidis[1,2], Patricia P. Katz[3], Erik Jorgenson[4], Jon Giles[5] and Joshua F. Baker[6,7], [1]Rheumatology, University of Pennsylvania, Philadlphia, PA, [2]Internal Medicine, Pennsylvania Hospital of the University of Pennsylvania, Philadelphia, PA, [3]Medicine/Rheumatology, University of California San Francisco, San Francisco, CA, [4]Statistics and Epidemiology, University of Pennsylvania, Philadelphia, PA, [5]Rheumatology, Columbia University Medical Center, NY, NY, [6]Rheumatology, University of Pennsylvania, Philadelphia, PA, [7]Medicine/Rheumatology, University of Pennsylvania and Philadelphia VAMC, Philadelphia, PA
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Background/Purpose:

Rheumatoid Arthritis (RA) is associated with loss of muscle mass, exacerbating impairments in physical function. The 20-question Health Assessment Questionnaire (HAQ) is an accepted measure of physical function. However it only demonstrates modest correlations with muscle mass. The aim of this study was to develop and validate a tool that consists of a subset of questions from HAQ that demonstrate superior correlation with muscle deficits.

Methods:

Three cohorts of patients with RA with data on body muscle mass, fat mass and HAQ scores were included from three large independent academic centers in the United States. Whole-body DXA measures of skeletal muscle [appendicular lean mass index (ALMI)] and fat mass index (FMI) were converted to age, sex, and race specific Z-Scores using NHANES reference ranges. Associations between individual HAQ questions and ALMI Z-Score were assessed in a development cohort (consisting of the two larger cohorts) adjusting for age, sex, and FMI Z-Score. HAQ questions independently associated with ALMI in multivariable models ($p<0.1$) after stepwise deletion, were included and a simple estimating equation was developed based on regression coefficients. The performance of the muscle-HAQ was tested in the validation cohort (consisting of the third, smaller cohort). A low lean mass for age was defined as a standard or fat-adjusted ALMI Z-Score of ≤ -1.

Results:

In the development cohort (n=320), eight questions were independently associated with ALMI Z-Score. Specifically, having difficulty 1) lifting a cup, 2) running errands, 3) bathing, 4) self-hygiene and 5) opening a car's door were associated with lower ALMI whereas difficulty 6) climbing stairs, 7) dressing and 8) washing were associated with higher ALMI. [Muscle-HAQ= (1*climb+1*dress+1*wash-1*cup-1*errands-1*bath-1*hygiene-1*caropen -4)*-1]. In the validation cohort (n=85), the standard HAQ was not associated with ALMI or fat-adjusted ALMI Z-Score while the muscle-HAQ was strongly associated (Table 1). Patients with a muscle-HAQ ≥ 6 (n=16/85) had ALMI Z and fat adjusted ALMI Z Scores approximately 1 SD lower (Figure1) and greater odds of a low ALMI and fat adjusted ALMI Z-Score [OR 4.54 (1.38, 14.9) p=0.01 / OR 4.36 (1.25, 15.19) p=0.02]

Conclusion:

The muscle-HAQ demonstrates superior correlation with muscle mass deficits in RA, potentially capturing a domain of disability. These observations add new utility to the HAQ in clinical practice and research as a screening tool for muscle deficits or outcome in interventional studies.

Table 1	Age and sex-adjusted associations between unadjusted/fat-adjusted measures of ALMI with HAQ/Muscle HAQ score in the validation cohort.			
	ALMI-Z		Fat-Adjusted ALMI	
	Spearman's rho	p	Spearman's rho	p
HAQ	-0.05	0.66	-0.19	0.08
Muscle HAQ	-0.29	0.007	-0.35	0.0004

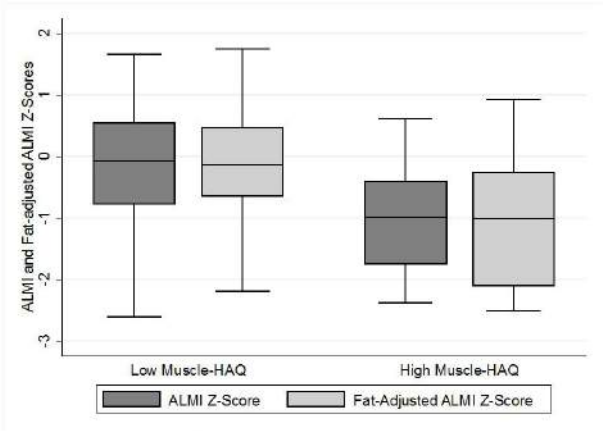

Figure 1: Box plot of ALMI Z-Scores and Fat-Adjusted ALMI Z-Scores adjusted for age and sex among patients with high/low Muscle-HAQ scores demonstrating lower skeletal muscle estimates among those with scores ≥6.

Disclosure: G. Loizidis, None; **P. P. Katz**, None; **E. Jorgenson**, None; **J. Giles**, None; **J. F. Baker**, None.

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Abstract Number: 2680

Severity of Morning Stiffness Is Associated More Strongly with Disease Activity in Patients with Rheumatoid Arthritis

Belén Barrios[1], Rafael Chaparro del Moral[2], Oscar Luis Rillo[2], Silvia Beatriz Papasidero[1], María Alejandra Medina[2], Sergio Paira[3] and Carolina Sandobal[4], [1]Rheumatology Department, Hospital General de Agudos Dr. E. Tornú, Buenos Aires, Argentina, [2]Rheumatology Section, Hospital General de Agudos Dr. E. Tornú, Buenos Aires, Argentina, [3]Rheumatology, Hospital Jose Maria Cullen, Santa Fe, Argentina, [4]Hospital Jose Maria Cullen, Santa Fe, Argentina

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Morning stiffness (MS) is a complex symptom involving pain and functional limitation. It is not included in the ACR/EULAR 2010 classification criteria for rheumatoid arthritis (RA) nor is a component of Disease Activity Scores, which generally serve as the primary outcome measures to assess efficacy of therapies for RA. However, this symptom at first presentation is a risk factor for more severe disease reflected by structural damage or disease persistence. Despite this, the best way to evaluate morning stiffness has been controversial.

Background/Purpose: To compare the severity and duration of MS, assessed by physician and by a self-report questionnaire, with disease activity and functional disability in a cohort of patients with RA.

Methods: We conducted a cross-sectional observational study that included consecutively patients with established RA (ACR 1987 criteria) from two rheumatology centers. Patients were assessed for MS: approximately half of them were asked about the duration (in minutes) and the rest of them were evaluated using a self reported questionnaire which included the intensity (VAS) and duration (in minutes and Likert Scale) of MS. Physician global assessment, pain and global status by VAS, functional disability (HAQ-DI), tender and swollen joint count (total of 28), erythrocyte sedimentation rate and disease activity (DAS28 and CDAI) were evaluated. Regression models were used to estimate possible associations between these variables and morning stiffness.

Results: One hundred and eleven patients were included, 88% were women (n=96). Mean age was 52 years (SD 13) and median disease duration was 8 years (IQR 4-12)**.** Fifty seven patients (51%) reported MS, 27 out of 52 were asked by the physician and 30 out of 59 were assessed by the questionnaire. MS measured in minutes by the physician showed a significant correlation with functional disability scores HAQ-DI (r= 0.72, p<0.001), whereas there was an acceptable correlation (r=0.61, p<0.001) between DAS28 and severity of MS measured by VAS (TABLE). When intensity of MS was evaluated by VAS (assessment in both numerical and non-numerical scales), we observed that a value ³ 5.5 centimeters (0-10) was associated to severe disease activity (DAS28 > 5.1) with a sensitivity of 44% and specificity of 100% (AUC 0.76).

Conclusion: Duration of morning stiffness evaluated through patient interview appears to reflect functional disability while the severity of morning stiffness was associated more strongly with inflammatory activity in this cohort of RA patients.

Table: MS correlation (assessed by different methods) with DAS28, CDAI and HAQ-DI

MORNING STIFFNESS		DAS 28	CDAI	HAQ-DI
PHYSICIAN EVALUATION	Minutes	0.63*	0.60*	0.72*
SELF-ADMINISTERED QUESTIONNAIRE EVALUATION	Minutes	0.38*	0.32*	0.01
	Likert's Scale	0.37*	0.30	0.001
	VAS	0.61*	0.55	0.33*
	VAS nº	0.61*	0.57	0.30

***p < 0.05**

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Abstract Number: 2681

Physical Function, Sleep, Depression but Not CRP Level Is Associated with Fatigue in Patients with Established Rheumatoid Arthritis

Yong Gil Hwang[1], Juan (June) Feng[2], Heather Eng[2], Jason Lyons[2], Anthony Fabio[3] and Larry W. Moreland[4], [1]Department of Medicine, University of Pittsburgh, Pittsburgh, PA, [2]Epidemiology Data Center, University of Pittsburgh, Graduate School of Public Health, Pittsburgh, PA, [3]Department Of Epidemiology, Graduate School of Public Health, University of Pittsburgh, Pittsburgh, PA, [4]Rheumatology & Clinical Immunology, University of Pittsburgh, Pittsburgh, PA

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Background/Purpose: Rheumatoid arthritis (RA) is characterized by inflammation of the joints and fatigue. Although many studies have identified risk factors for RA-associated fatigue, few studies have comprehensively examined the role of C - reactive protein (CRP) on fatigue. We investigated the association of CRP on fatigue using the Patient Reported Outcomes Measurement Information System

(PROMIS) in a cohort of patients with RA.

Methods: RA subjects enrolled in the University of Pittsburgh Rheumatoid Arthritis Comparative Effectiveness Registry (RACER) and who completed the PROMIS29 questionnaire were included (N=180). RA specific risk factors (disease activity measured by the Clinical Disease Activity Index [CDAI], physical function, RA treatment [conventional Disease Modifying Anti-Rheumatic Drugs (DMARD), anti - tumor necrosis factor [TNF], other biologics, disease duration, pain level), non-RA risk factors (sleep, anxiety, depression, Charlson comorbidity index) as well as CRP were assessed using descriptive statistics to summarize the distribution of the variables. Fatigue identified by PROMIS29 was the primary outcome. Spearman correlations and univariate analyses were first conducted to evaluate associations with fatigue. Multiple linear regression analyses were performed to investigate whether CRP is an independent predictor of fatigue. Mediation analysis was performed to explore if there is any indirect relationship between CRP level and factors associated with fatigue.

Results: Mean (±SD) subject age was 63.9 (±12.2) years with disease duration of 7.7 (± 0.8) years. Univariate analyses identified 7 covariates (age, CDAI score, global pain intensity, physical function, sleep, anxiety, depression) initially as potential predictors of fatigue. In multivariate analyses, physical function, sleep, and depression were independently associated with fatigue, but CRP or RA treatments did not have significant association with fatigue. (Table.1) CRP was inversely correlated with physical function ($\rho = -0.23$, $p=0.016$). However, there was no mediation effect between CRP and physical function in association with fatigue.

Conclusion: Out study suggests that poor sleep, decreased physical function, and depression have significant effect on fatigue. CRP level was not associated with fatigue directly or indirectly.

Table.1 Rheumatoid arthritis (RA)-specific and non -RA specific risk factors for fatigue (CDAI: Clinical Disease Activity Index, CRP: C-Reactive Protein, TNF: Tumor Necrosis Factor)

		Mean (SD) or N
RA specific risk factors	CDAI	10.28 (8.14)
	Disease duration	18.03 (13.52)
	CRP (mg/dL)	0.77 (0.92)
	Pain level (global pain intensity 0-10)	4.30 (2.54)
	Treatment	
	DMARD (N)	96
	Anti-TNF (N)	11
	Non-TNF biologics (N)	9
Non-RA risk factors	Sleep (t score)	50.82 (8.09)
	Anxiety (t score)	51.04 (9.56)
	Depression (t score)	49.53 (8.80)
	Comorbidity index	2.32 (2.00)

Table.2 Associations of fatigue with RA specific and non-RA specific factors by multiple linear regression analyses. Among RA associated and non-RA associated risk factors, 4 variables identified by univariate analyses were included in Model 1. Model 2 was adjusted as model 1 plus CRP and RA treatment. (β unstandardized coefficient, SE : Standard Error).

Model	Variables	Fatigue		
		β	SE	p value
1	Physical function	-0.38813	0.07199	. <.0001
	Age	-0.11267	0.04882	0.0223
	Sleep	0.31284	0.07318	<.0001
	Depression	0.37075	0.07060	<.0001
2	Physical function	-0.40934	0.09867	<.0001
	Age	-0.11650	0.06712	0.0856
	Sleep	0.35516	0.09857	0.0005
	Depression	0.39728	0.09954	0.0001
	CRP	-1.13464	0.82493	0.1720
	DMARD	-0.47791	1.54109	0.7571
	Anti-TNF	0.36249	4.05218	0.9289
	Non-TNF biologics	2.43892	4.16328	0.5593

Disclosure: Y. G. Hwang, None; **J. Feng**, None; **H. Eng**, None; **J. Lyons**, None; **A. Fabio**, None; **L. W. Moreland**, None.

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Abstract Number: 2682

A Brief Patient-Reported Measure of Physical Function Is Sensitive to Changes in a Composite Disease Activity Measure in a Diverse Rheumatoid Arthritis Clinic Setting

Elizabeth R. Wahl[1,2], Andrew Gross[2], Vladimir Chernitskiy[2], Laura Trupin[2], Jinoos Yazdany[3] and Patricia P. Katz[2], [1]Medicine/Rheumatology, San Francisco Veterans Affairs Medical Center, San Francisco, CA, [2]Medicine/Rheumatology, University of California San Francisco, San Francisco, CA, [3]University of California, San Francisco, San Francisco, CA

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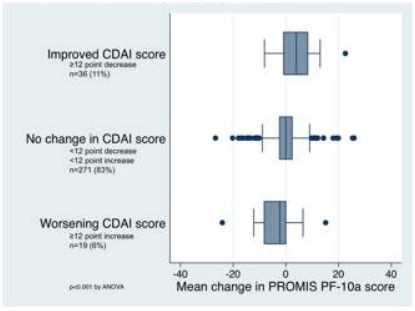
Background/Purpose: Rheumatoid arthritis (RA) patients' physical function is a strong predictor of clinical outcomes. A brief patient-reported measure of physical function, the PROMIS PF-10a (PF-10a), is increasingly being used to measure physical function in RA patients, but its sensitivity to changes in disease activity has not been described in a real world clinical setting. In this study, we assess the relationship between changes in a commonly used measure of disease activity, the clinical disease activity index (CDAI), and changes in PF-10a.

Methods: Clinical and demographic data were abstracted from the electronic health record for all patients seen at a university-based rheumatology clinic between February 2013 and February 2015, who had at least two ICD-9 codes for RA. All patients had PF-10a and CDAI scores documented on at least two occasions. We categorized changes in CDAI score as improved, stable, or worse using Minimally Important Difference (MID) criteria of a 12-point change in score, and compared changes in PF10a scores across these three groups. We then evaluated sensitivity to change by modeling the relationship between changes in disease activity (CDAI) and changes in PF-10a over time with multilevel mixed effects linear regression.

Results: Of 326 individuals included in the analysis, mean age (SD) was 59 (14), 83% were women, 53% were Caucasian, and 48% had moderate or severe disease activity by CDAI. Using MID criteria, CDAI scores were improved in 11% of encounters, were stable in 83%, and worse in 6%. Among those whose disease activity improved, PF-10a score improved by 4.4 ± 6.0 points (mean ± SD). Among those with stable disease activity, mean PF-10a score did not change (-0.1 ± 6.3 points), and among those with worsening disease activity, PF-10a scores worsened by 3.6 ± 8.1 points (Figure). These differences were significant (ANOVA p=0.0001). In a multivariate model adjusting for starting CDAI, age, and gender, changes in CDAI score were associated with changes in PF-10a scores ($p<0.001$).

Conclusion : The PROMIS-PF10a, a patient-reported measure of physical function, appears sensitive to changes in RA disease activity as measured by CDAI, suggesting it could play an important role in the clinical setting. Future studies should evaluate discordance between measures of function and disease activity by evaluating the role of disease duration, disability, and comorbidities such as chronic pain or depression.

Figure. Relationship between change in CDAI and change in PF-10a between 2 encounters for 326 RA patients



Disclosure: E. R. Wahl, None; **A. Gross**, None; **V. Chernitskiy**, None; **L. Trupin**, None; **J. Yazdany**, None; **P. P. Katz**, None.

Abstract Number: 2683

Contribution of Subjective Patient Reported Components of Disease Activity Scores Differs in Disease Activity Measures and Their Changes over Time Are Closely Associated with Objective Measures

Yong Gil Hwang[1], Juan (June) Feng[2], Heather Eng[2], Jason Lyons[2], Anthony Fabio[3] and Larry W. Moreland[4], [1]Department of Medicine, University of Pittsburgh, Pittsburgh, PA, [2]Epidemiology Data Center, University of Pittsburgh, Graduate School of Public Health, Pittsburgh, PA, [3]Department Of Epidemiology, Graduate School of Public Health, University of Pittsburgh, Pittsburgh, PA, [4]Rheumatology & Clinical Immunology, University of Pittsburgh, Pittsburgh, PA

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Background/Purpose: Patient reported measures are influenced by many non-rheumatoid arthritis (RA) factors and they are reflected variably among various composite disease activity scores (DAS). We investigated relative contribution of patient reported measures and changes over time in two most widely used DAS.

Methods: For RA subjects enrolled in the University of Pittsburgh RA Comparative Effectiveness Research (RACER), cross-sectional and longitudinal analyses were performed to compare relative contribution of subjective patient reported components to DAS28-C-Reactive Protein (CRP) and Clinical Disease Activity Index (CDAI). Relative of the contribution of the patient reported measures (Tender Joint Count (TJC) and Patient Global Assessment (PtGA) in DAS28-CRP (DAS-P) and CDAI (CDAI-P) were calculated at baseline and follow-up visit within 3 months. DAS28-CRP changes was categorized by European League Against Rheumatism (EULAR) response criteria and CDAI changes were grouped into major (improvement ≥ 14), moderate (≥ 6), mild (<6). Wilcoxon signed ranks tests were performed for comparison. Univariate and multivariate regression analyses were performed to investigate factors associated with changes of subjective domains.

Results: For the 740 subjects analyzed, age was 60.2 ±13.7 (Mean±SD) years with disease duration of 14.4 ±12.4 years. 312 subjects had follow up visit within 3 months (1.7 ± 2.2 month). DAS-P was increased linearly with higher disease activity score. In contrast, CDAI-P remains similar with wider variation in remission or low disease activity (CDAI ≤ 10) (Figure.1). Significant reduction in the DAS28-P score was observed at follow up visit in all response groups, with greater reduction of DAS28-P in good responders. However, CDAI-P did not differ between the index and follow up visit (Figure.2). Multivariate analyses showed Swollen Joint Count (SJC) and Physician Global Assessment (PhGA) at the index visit had significant association with DAS-P changes at the follow up visit. CDAI-P changes were also significantly associated with HAQ (Table.1).

Conclusion: Contribution of patient reported components and their changes over time are substantially different between DAS28-CRP and CDAI. Objective findings such as SJC and PhGA predict changes of subjective patient reported measures at the follow up visit.

Figure.1 Scatterplot at index visit: (a) DAS-P(%) vs DAS28-CRP (a), (b) CDAI-P (%) vs CDAI, contribution of subjective patient reported components by disease activity categories (remission, mild, moderate, severe): (c) DAS-P(%) vs DAS28-CRP, (d) CDAI-P (%) vs CDAI (DAS-P: Subjective components of DAS28 relative to the total DAS28, CDAI-P: Subjective components of CDAI relative to the total CDAI)

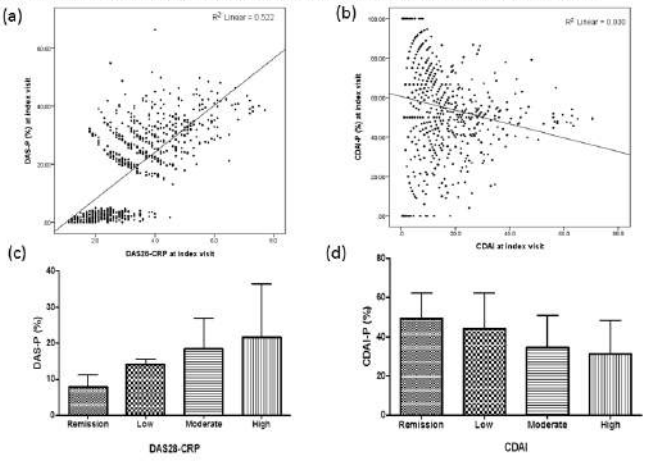

Figure.2 Changes of contribution of subjective patient reported components over time by treatment response criteria: (a) DAS-P (%) changes by EULAR response criteria, (b) CDAI-P (%) changes by CDAI response criteria (DAS-P: Subjective components of DAS28 relative to the total DAS28, CDAI-P: Subjective components of CDAI relative to the total CDAI)

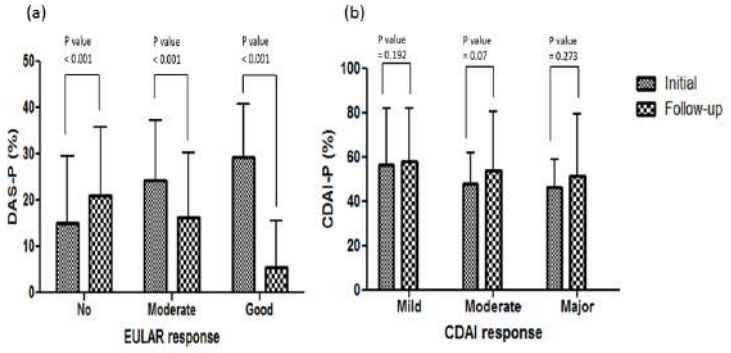

Table.1 Associations of subjective patient reported component changes with clinical variables at baseline by multiple linear regression analyses (β unstandardized coefficient, SE: Standard Error, DAS-P: Subjective components of DAS28 relative to the total DAS28, CDAI-P: Subjective components of CDAI relative to the total CDAI, SJC: Swollen Joint Count, PhGA: Physician Global Assessment, HAQ: Health Assessment Questionnaire)

	DAS-P change			CDAI- P change		
	β	SE	P value	β	SE	P value
SJC	-.029	.008	.001	-.293	.065	.000
PhGA	-.069	.022	.002	-.502	.171	.004
HAQ	-.181	.096	.061	-2.070	.758	.007

Disclosure: Y. G. Hwang, None; **J. Feng**, None; **H. Eng**, None; **J. Lyons**, None; **A. Fabio**, None; **L. W. Moreland**, None.

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Abstract Number: 2684

Association Between Anxiety and Depression and Rheumatoid Arthritis Outcome: Results from an Inception Early Rheumatoid Arthritis Cohort

Sizheng Zhao[1,2], Samantha Hider[3], Christopher Sparks[2], Faith Matcham[4], James Galloway[5], Cristina Estrach[1] and Nicola Goodson[1,2], [1]Department of Rheumatology, Aintree University Hospital, Liverpool, United Kingdom, [2]Musculoskeletal Biology I, Institute of Ageing and Chronic Disease, University of Liverpool, Liverpool, United Kingdom, [3]Research Institute for Primary Care and Health Sciences, Keele University, Keele, United Kingdom, [4]Psychological Medicine Clinical Academic Group, King's College London, London, United Kingdom, [5]Academic Department of Rheumatology, King´s College London, London, United Kingdom
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Background/Purpose: Anxiety and depression (A&D) are important comorbid conditions that affect patients with rheumatoid arthritis (RA). It is not known whether they impact on disease outcome in early RA (eRA). The aim of this study was to understand if A&D are: 1) associated with disease activity (DAS28) or disability at time of eRA diagnosis, 2) predictors of DAS28 and disability after 12 months of treatment.

Methods: An inception cohort of eRA patients was studied. At baseline, patients completed a detailed questionnaire recording self-rated quality of life (EQ5D) and disability (modified health assessment questionnaire (HAQ)). A categorical variable for level of anxiety and depression (A&D) was created from the EQ5D (0=none, 1=moderate, and 2=extreme levels of self-reported A&D). Disease activity (DAS28), DAS28 remission (<2.6), and HAQ were recorded at baseline and at 12 month review. Associations with A&D were explored: 1) at baseline using simple descriptive statistics, and 2) with 12-month outcomes using age and gender adjusted logistic regression.

Results: At baseline, 126 eRA patients had complete data. 36 (28.6%) patients reported moderate levels, and 14 (11.1%) extreme levels of A&D. Increasing A&D was significantly associated with elevated HAQ, and DAS28 at baseline (Table 1).

Age and gender adjusted logistic regression revealed that baseline A&D predicted a reduced likelihood of: 1) DAS28 remission (OR_{adj} 0.38 [95%CI 0.18, 0.81]), and 2) good EULAR response (OR_{adj} 0.41 [95%CI 0.13, 1.03]), at 12 months. No difference was observed in initial DMARD therapy. Baseline A&D was not significantly associated with mean change in DAS28 (OR_{adj} 1.06 [95%CI 0.85, 1.32]), or minimal clinically significant improvement in HAQ (OR_{adj}1.95 [95%CI 0.91, 4.20]). However, those reporting extreme level A&D at baseline were 5 times more likely to report HAQ above 1.0 at 12-months compared to without A&D (OR_{adj} 5.78 [95%CI 1.72, 19.52]).

Conclusion: Anxiety and depression at diagnosis of eRA is a strong predictor of poor outcome (disease activity and disability) at 12 months. Whilst A&D predict reduced likelihood of good EULAR response, no significant associations were observed with absolute change in HAQ or DAS28 after 12 months of DMARD therapy. This suggests that patients with A&D may benefit from additional treatment, targeted to reduce A&D, combined with usual DMARD treatment in order to optimise outcomes. Understanding the impact of confounding effect of anxiety and depression is important when assessing DMARD response in eRA.

Table 1 Disease characteristics at baseline by level of anxiety/depression.

	Anxiety and depression			P-value
	None (n=76)	Moderate (n=36)	Extreme (n=14)	
Mean age (SD)	58 (15.0)	55.7 (16.9)	54.4 (16.2)	0.287
Female (%)	47 (61.8%)	30 (83.3%)	10 (71.4%)	0.031
Smoke (%)	23 (30%)	8 (22.2%)	4 (28.6%)	0.442
Obese (%)	19 (25.0%)	10 (27.8%)	4 (28.6%)	0.707
Rheumatoid factor positive (%)	48 (63.2%)	22 (61.1%)	11 (78.6%)	0.744
CCP positive (%)	50 (65.8%)	23 (63.9%)	8 (57.1%)	0.664
High CRP (>14 [median])	36 (49.3%)	14 (40.0%)	9 (64.3%)	0.796
Median DAS28 [IQR]	4.8 [3.9, 5.5]	4.8 [4.3, 5.9]	6.4 [5.9, 7.4]	0.046*
High DAS28 (>5.1)	31 (40.8%)	13 (36.1%)	12 (85.7%)	0.309
Median HAQ [IQR]	0.75[0.25, 1.25]	1.25 [0.875, 1.5]	2.0 [1.125, 2.125]	0.000*
High HAQ (≥1.0)	30 (39.5%)	24 (66.7%)	11 (78.6%)	0.003
High TJC (>6)	34 (49.3%)	13 (44.8%)	9 (81.8%)	0.564
High SJC (>3)	26 (37.7%)	14 (48.3%)	7 (63.6%)	0.132
High ESR (>33)	40 (52.6%)	18 (50.0%)	9 (64.3%)	0.880
High Global VAS (>55)	35 (46.1%)	20 (55.6%)	12 (85.7%)	0.048
Initiated triple DMARD therapy	11 (14.5%)	7 (19.4%)	1 (7.1%%)	0.536

Table 2 Response at 12 months by level of anxiety/depression.				
	Anxiety and depression			P-value
	None (n=76)	Moderate (n=36)	Extreme (n=14)	
Median DAS28 at 1yr	2.3[1,7, 3.3]	3.0[2.1, 3.5]	3.5[2.0, 4.8]	0.046 *
DAS28 remission (<2.6)	47 (71.2%)	14 (21.2%)	5 (7.6%)	0.008
Good EULAR response	53 (69.7%)	19 (52.8%)	6 (42.9%)	0.025
Median change in DAS28 (from baseline)	2.2 [1.3, 3.1]	2.3 [1.0, 3.0]	2.7 [0.9, 4.7]	0.697
Median HAQ at 1yr	0.25 [0.0, 0.75]	0.5 [1.25, 1.0]	1.0[0.75, 2.0]	0.005 *
HAQ improvement (>0.25 above baseline)	39 (51.4%)	25(69.4%)	9(64.3%)	0.063

*Wilcoxon's ranksum - any anxiety depression vs no anxiety depression

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Disclosure: S. Zhao, None; **S. Hider**, None; **C. Sparks**, None; **F. Matcham**, None; **J. Galloway**, None; **C. Estrach**, None; **N. Goodson**, None.

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Abstract Number: 2685

High Levels of 25(OH)D Are Associated with Lower Disease Activity in Patients with Newly Diagnosed Rheumatoid Arthritis

Linda Rasch[1], Nicole Konijn[1], Yvonne Krul-Poel[2], Lilian van Tuyl[1], Hennie Raterman[1], Marieke ter Wee[1], Debby den Uyl[1], Suat Simsek[2], Michael Nurmohamed[1,3] and **Willem Lems**[1,3], [1]Amsterdam Rheumatology and immunology Center, location VU University Medical Center, Department of Rheumatology, Amsterdam, Netherlands, [2]Department of Internal Medicine, Medical Center Alkmaar, Alkmaar, Netherlands, [3]Amsterdam Rheumatology and immunology Center, location Reade, Amsterdam, Netherlands
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Background/Purpose: Vitamin D deficiency is highly common in patients with rheumatoid arthritis (RA) (1). In vitro, vitamin D has anti-inflammatory effects and vitamin D has been linked to disease activity in RA due to its immuno-modulatory properties (1,2). The aim of this study is to investigate the association between vitamin D status and disease activity in newly diagnosed RA patients before start of therapy.

Methods: Consecutive patients with active, newly diagnosed RA (symptom duration <2 years), were randomized for treatment with COBRA or COBRA-light therapy (3). Before start of therapy, baseline values were determined, including Disease Activity Score (44 joints; DAS) and serum 25-hydroxy vitamin D (25(OH)D) levels. Based on the widely used cutoff values, patients were stratified into three groups based on baseline serum 25(OH)D levels: <50 nmol/l, 50-74 nmol/l, and ≥75 nmol/l.

Results: Baseline serum 25(OH)D levels were determined in 147 of 164 included RA patients in the COBRA-light trial (90% of trial population). Serum 25(OH)D levels of the different groups are presented in Table 1. Patients with a baseline serum 25(OH)D level ≥75 nmol/l had a significant lower mean DAS compared to patients with a baseline serum 25(OH)D <75 nmol/l (p=0.001). Vitamin D deficient patients (<50 nmol/l) had a significant shorter symptom duration (p=0.003), and were more often rheumatoid factor positive (p=0.015) compared to patients with sufficient serum 25(OH)D levels.

Table 1. Vitamin D status and disease related factors of patients with newly diagnosed rheumatoid arthritis before start of therapy

	Serum 25(OH)D <50 nmol/l (n=62; 42%)	Serum 25(OH)D 50-74 nmol/l (n=50; 34%)	Serum 25(OH)D ≥75 nmol/l (n=35; 24%)
Disease Activity Score (DAS, 44 joints)	4.2 (0.7)	4.0 (0.9)	3.6 (0.7)*
Symptom duration (weeks)	12 [8,21]*	18 [8,49]	25 [13,36]
Health Assessment Questionnaire Score (HAQ, 0 to 3)	1.5 (0.8)	1.3 (0.6)	1.2 (0.6)
Serum 25(OH)D (nmol/l)	36 [25,46]	61 [54,67]	87 [81,100]
Rheumatoid factor positive (n(%))	44 (72)†	22 (45)	20 (57)
aCCP positive (n(%))	44 (71)	26 (53)	25 (71)

*Values are reported as mean (SD) or median [IQR], unless otherwise specified; * Differs significantly from both other groups (p-value<0.05); † Differs significantly from serum 50-74 nmol/l (p-value<0.05); 25(OH)D: 25-hydroxy vitamin D; aCCP: antibodies against cyclic citrullinated peptides.*

Conclusion: Newly diagnosed RA patients with serum 25(OH)D levels ≥75 nmol/l demonstrate a significant lower disease activity than patients with a serum 25(OH)D level <75 nmol/l before start of therapy. This study cannot distinguish whether a lower DAS at baseline is caused by immuno-modulatory properties due to higher serum 25(OH)D levels, or that higher serum 25(OH)D levels are caused by more frequent outdoor activities related to a lower DAS. Since 75% of the newly diagnosed RA patients have insufficient serum 25(OH)D levels (<75 nmol/l), vitamin D supplementation should be considered in every newly diagnosed RA patient.

References: (1) Grazio S, et al. Am J Med Sci 2014; (2) Baker JF, et al. Clin Exp Rheumatol 2012; (3) Den Uyl D, et al. Ann Rheum Dis 2013.

Disclosure: L. Rasch, None; **N. Konijn**, None; **Y. Krul-Poel**, None; **L. van Tuyl**, None; **H. Raterman**, None; **M. ter Wee**, None; **D. den Uyl**, None; **S. Simsek**, None; **M. Nurmohamed**, None; **W. Lems**, None.

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Abstract Number: 2686

No Clear Association Between the Presence of Ultrasound Synovitis and Patient Reported Outcomes in Rheumatoid Arthritis Patients in Remission

Myrthe van der Ven[1], T. Martijn Kuijper[1], Andreas Gerards[2], I. Tchetverikov[3], A.E.a.M. Weel[1,4], Derkjen van Zeben[5], Mieke Hazes[1] and J.J. Luime[1], [1]Rheumatology, Erasmus University Medical Center, Rotterdam, Netherlands, [2]Rheumatology, Vlietland Hospital, Schiedam, Netherlands, [3]Albert Schweitzer Ziekenhuis, Dordrecht, Netherlands, [4]Department of Rheumatology, Maasstad Hospital, Rotterdam, Netherlands, [5]Rheumatology, Sint Franciscus Gasthuis, Rotterdam, Netherlands

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Background/Purpose: Several studies assessed disease activity with ultrasound in rheumatoid arthritis (RA) patients who were in clinical remission. These studies found ultrasound synovitis in 48-73% of the patients. Ultrasound synovitis is associated predicts short-term relapse in RA patients. So far, little is known about the association between ultrasound synovitis and patient reported outcomes (PROs). Our first objective was to evaluate the frequency of ultrasound synovitis in RA patients in clinical remission while they are continuing synthetic and biological DMARDs. Our second objective was to compare PROs between patients in clinical remission with and without ultrasound synovitis.

Methods: RA patients who are treated with the combination of a synthetic DMARD and biological DMARD (adalimumab or etanercept) and have low disease activity (DAS44<2.4 and SJC ≤1) were examined by ultrasound at baseline and after three months

follow-up. Ultrasound examination included 26 joints (MCP2-5, PIP2-5, wrists, MTP2-5) graded on greyscale (GS;0-3) and power Doppler (PD;0-3). A joint with ultrasound synovitis was defined as GS>1 and/or PD>0. Data on clinical and psychological characteristics, demographics, pain scores, functional ability (HAQ) and health-related quality of life (SF-36) were collected at baseline and at three months. Coping (Pain Coping and Cognition List [PCCL]), depression/anxiety symptoms (Hospital Anxiety and Depression Scale[HADS]) and fatigue (Bristol RA Fatigue Multi-Dimensional Questionnaire [BRAF-MDQ] and Fatigue Assessment Scale [FAS]) were collected at three months follow-up. Ultrasound synovitis positive and negative patients were compared on their PROs using the Wilcoxon-Mann-Whitney test and Chi-square test.

Results: At baseline, 89 RA patients were included of which 71 patients had had their three months evaluation. Ultrasound revealed synovitis in 64% of the patients at baseline and in 68% at three months. In 44% of the patients ultrasound synovitis was detected at both measurements. Table 1 shows baseline characteristics and patient reported outcomes at baseline and after three months. No clear pattern emerged on the PROs scores between ultrasound synovitis positive and negative patients. At baseline functional ability differed between the two groups while health-related quality of life was similar. At three months similar levels were observed for functional ability, health-related quality of life, coping, depression symptoms and fatigue. HADS anxiety differed at 3 months.

Conclusion: Ultrasound synovitis is common in RA patients in clinical remission while they continue synthetic and biological DMARDs. In our study population we could not find a clear association between ultrasound synovitis and PROs.

Table 1 Baseline characteristics and patient reported outcomes

Clinical and demographic characteristics (n=89)						
Age, mean ±sd years	55 (12)					
Women	66%					
Time since diagnose, mean ±sd years	5 (3.4)					
DAS44, mean ±sd	1.1 (0.5)					
DAS44 remission (DAS44<1.6)	82%					
BSE, median (IQR)	8 (3-16)					
RF positive	55%					
ACCP positive	69%					
Patient reported outcomes	*Visit 1*			*Visit 2*		
	US negative (n=35)	US positive (n=54)	p-value*	US negative (n=23)	US positive (n=48)	p-value*
HAQ (range 0-3), median (IQR)	0.3 (0-0.9)	0.6 (0.1-1.4)	0.029	0.3 (0-0.6)	0.3 (0-0.6)	0.928
SF36 (range 0-100), median (IQR)						
PCS	49 (44-52)	44 (38-50)	0.084	48 (44-52)	46 (40-52)	0.780
MCS	54 (49-59)	57 (54-59)	0.134	55 (41-59)	58 (54-61)	0.054
HADS anxiety >7 (range 0-21)				24%	2%	0.004
HADS depression >7 (range 0-21)				14%	2%	0.056
BRAF (range 0-70), median (IQR)				21 (13-26)	14 (6-23)	0.070
Fatigue (FAS; range 10-50), median (IQR)				21 (18-23)	18 (14-23)	0.160
PCCL (range 1-6), median (IQR)				1.8 (1.3-2.5)	1.4 (1.1-2.4)	0.264

US = Ultrasound; HAQ = Health Assessment Questionnaire; SF-36 = Short Form 36; HADS = Hospital Anxiety and Depression Scale; BRAF = Bristol RA Fatigue Multi-Dimensional Questionnaire; FAS = Fatigue Assessment Scale; PCCL = Pain Coping and Cognition Scale; sd = standard deviation; IQR = interquartile range; *Wilcoxon-Mann-Whitney test for continuous scales, Chi-square test for binary scales

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Abstract Number: 2687

Clinical Significance of Patient-Reported Pain and Stiffness at Each Joint Level in the Evaluation of Patients with Rheumatoid Arthritis

Ayako Hirata, Takehisa Ogura, Norihide Hayashi, Sayaka Takenaka, Hideki Ito, Kennosuke Mizushina, Yuki Fujisawa, Munetsugu Imamura, Naoko Yamashita and Hideto Kameda, Department of Rheumatology, Toho University Ohashi Medical Center, Tokyo, Japan

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Session Time: 9:00AM-11:00AM

Background/Purpose:

Patient-reported outcome has been considered as an important aspect in the evaluation of patients with rheumatoid arthritis (RA). Recently, ultrasonography (US) has been used as a valid and objective tool for joint assessment for both joint synovitis and tenosynovitis. Therefore, the objective of this study was to elucidate the clinical significance of self-reported joint pain and stiffness of each joint by examining the association of those subjective findings with US joint synovitis and tenosynovitis.

Methods:

A total of 40 patients with RA were enrolled in this study between October 2014 and June 2015. All the patients reported the presence of pain and/or stiffness in each joint of hands including bilateral interphalangeal (IP) joints of the thumb, proximal interphalangeal (PIP) joints, metacarpophalangeal (MCP) joints and wrist joints. They also received joint examination by rheumatologists for the presence of tenderness and swelling, and US joint examination for the presence of joint synovitis and tenosynovitis. The medical records were reviewed for the patient characteristics and laboratory data.

Results: The median age was 66.5 years and the median disease duration was 3.7 years. The median DAS28-ESR was 2.7. Thirty-two patients (80%) were seropositive for either rheumatoid factor or anti-cyclic citrullinated peptide antibody. Although joint pain and stiffness were similarly observed among IP/PIP, MCP and wrist joints (pain in 9-11% of joints and stiffness in 5-6% of joints), US joint synovitis was detected in 6% of IP/PIP joints, 16% of MCP joints and 38% of wrist joints, and US tenosynovitis in 2% of IP/PIP joints, 8% of MCP joints and 18% of wrist joints, respectively (Table 1). The concordance defined by κ value indicated poor correlation of subjective joint pain with US synovitis (κ=0.19) and tenosynovitis (κ=0.03), as well as joint stiffness with US synovitis (κ=0.13) and tenosynovitis (κ=-0.04), respectively, although joint swelling showed a moderate correlation with US synovitis (κ=0.43).

Conclusion:

Patient-reported joint symptoms, especially joint stiffness, were not sensitive enough, and they did not correlate well with US joint findings.

Table 1. The presence rate of clinical findings at each joint level.

	Pain	Stiffness	Swelling	US joint synovitis	US tenosynovitis
IP/PIP	9%	5%	5%	6%	2%
MCP	10%	6%	7%	16%	8%
Wrist	11%	5%	20%	38%	18%
Total	9%	5%	7%	13%	6%

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Abstract Number: 2688

Socioeconomic Status, Ethnicity/Race, and Autoantibody Status in Rheumatoid Arthritis

Mercedes Quinones[1], Sharon Dowell[1], Gail S. Kerr[2], Christopher Swearingen[3], Yusuf Yazici[4], Luis Espinoza[5], Ignacio Garcia-Valladares[6], Edward L. Treadwell[7], Theresa Lawrence Ford[8], Yvonne Scherrer[9], Angelia Mosley-WIlliams[10], Rodolfo Perez Alamino[11], Akgun Ince[12], John Amatruda[13] and Jorge Flautero Arcos[14], [1]Howard University Hospital, Washington, DC, [2]Washington DC VAMC, Georgetown University Hospital, Howard University Hospital, Washington, DC, [3]Pediatrics & Biostatistics, University of Arkansas, Little Rock, AR, [4]Department of Medicine, Division of Rheumatology, New York University School of Medicine, New York, NY, [5]Medicine-Section of Rheumatology, LSU Medical Center, New Orleans, LA, [6]Immunology & Rheumatology, Hospital General de Occidente, Zapopan, Jalisco, Mexico, [7]Dept Medicine Div of Rheum, E Carolina Univ Sch of Med, Greenville, NC, [8]North

Georgia Rheumatology Group, PC, Lawrenceville, GA, [9]Center for Rheumatology & Immunology Arthritis, Fort Lauderdale, FL, [10]John Dingell VAMC, Detroit, MI, [11]Rheumatology, Lousiana State University and LSU Medical Center, New Orleans, LA, [12]Arthitis Consultants Inc, St. Louis University, St. Louis, MO, [13]Rheumatology, Howard University, Washington, DC, [14]Rheumatology, Howard University Hospital, Washington, DC

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Session Type: ACR Poster Session C

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Background/Purpose:

Ethnic disparities in outcomes of RA patients have been attributed to delayed presentation to specialty care and access to DMARDs, greater disease burden, and less years of education. Recent literature supports a role for socioeconomic status (SES) as a determinant of RA disease status, including clinical disease activity measures, mortality, seropositivity, and treatment delays. The purpose of this analysis was to delineate the association of SES versus race/ethnicity with RA autoantibody status in a diverse cohort of RA patients.

Methods:

Ethnic Minority RA Consortium (EMRAC) participants with recorded anti-CCP positive markers at time of enrollment visit were abstracted for analysis; demographics (age, gender, race, years of education), clinical features (tobacco use, erosions, disease duration), and clinical outcomes (RAPID3) were also abstracted. An estimate of SES was derived from the median housing income of the city of each enrollment site. Median incomes less than two-fold the 2014 poverty line ($47,700) defined lower SES status. Logistic regression was used to model risk factors and their association with positive anti-CCP.

Results:

346 EMRAC participants with self-reported race/ethnicity were abstracted for analysis; 284 (82%) were female. The average values for the following parameters were: age 56.1 (±15.6) years, disease duration 9.4 (±10.1) years, and education 13.8 (±3.7) years. Ninety-nine (28.6%) of EMRAC participants were enrolled at sites servicing lower than the twice poverty line. With this SES indicator, significant differences in participants' disease duration, education years, clinical features, and outcomes were observed (**Table**). In logistic regression modelling, being below the twice poverty line was significantly associated with the presence of anti-CCP [13-fold increase; odds ratio=14.2] (**Figure**). Both African-American and other race participants also had increased odds of the presence of anti-CCP compared to Caucasian subjects, but less than that for low SES. Tobacco use and erosions could not be modeled due to missing clinical data. However, in a full model with both smoking and erosion indicators, lower SES remained the strongest risk factor associated with positive anti-CCP.

Conclusion:

In a diverse ethnic cohort, disparity in income as an estimate of SES was a stronger risk factor of RA autoantibody status than race/ethnicity. As autoantibody status is a poor prognosticator, policies that improve access to specialty care and RA medications must be paralleled by improvements in overall SES of individuals in order to minimize the impact of disease.

Figure. Odds Ratio Ladder Plot with 95% Confidence Intervals Depicting Logistic Regression Model Associating Risk Factors with Positive Anti-CCP

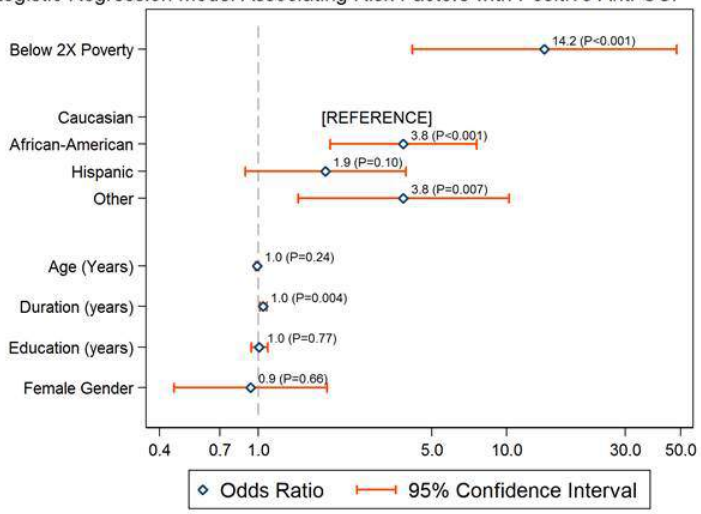

Table. Demographics, Clinical Features and Outcomes by SES Indicator

	Twice 2014 Poverty Line		
	Higher	Lower	P
N	247	99	
Age (years)	55.4 (16.4)	58.0 (13.0)	0.16
Duration (years)	7.9 (9.9)	13.3 (9.7)	<0.001
Education (years)	14.5 (3.8)	12.1 (2.6)	<0.001
RAPID [0-30]	10.8 (7.1)	13.8 (5.8)	<0.001
Female	207 (84%)	77 (78%)	0.19
Race			<0.001
Caucasian	81 (33%)	3 (3%)	
African.American	80 (32%)	55 (56%)	
Hispanic	61 (25%)	6 (6%)	
Other	22 (9%)	25 (25%)	
CCP+	134 (54%)	96 (97%)	<0.001
Hx of Smoking	61 (42%)	20 (20%)	<0.001
Hx of Erosions	45 (42%)	28 (28%)	0.02

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Abstract Number: 2689

Discrepancies Between Patients and Physicians in Their Perceptions of Rheumatoid Arthritis Disease Activity Are Multifactorial in Early Rheumatoid Arthritis

Cécile Gaujoux-Viala[1], Nathalie Rincheval[2], Laure Gossec[3], Francis Guillemin[4], Maxime Dougados[5], Jean-Pierre Daures[6] and BG Combe[7], [1]Nîmes University Hospital, Rheumatology Department; EA 2415, Montpellier University, Nîmes, France, [2]Biostatistic, EA 2415, Epidemiology unit, Montpellier, France, [3]Rheumatology, Pitié Salpetriere Hospital, Paris, France, [4]University of Lorraine,

Nancy, France, [5]Paris Descartes University, Rheumatology Department, Cochin Hospital, AP-HP. INSERM (U1153): Clinical Epidemiology and Biostatistics, PRES Sorbonne Paris-Cité, Paris, France, [6]Biostatistic, EA 2415 Epidemiology unit, Montpellier, France, [7]Lapeyronie, Montpellier, France
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Background/Purpose:

Patients and physicians often differ in their perceptions of rheumatoid arthritis (RA) disease activity, as quantified by the patient's global assessment (PGA) and by the evaluator's global assessment (EGA).

The aim of this study was to explore the extent and reasons for this discordance.

Methods:

-Patients: from the French cohort of early arthritis ESPOIR (at least 2 swollen joints for less than 6 months, DMARD naïve), fulfilling the ACR-EULAR criteria for RA at baseline

-Analyses: At baseline, agreement between PGA and EGA (Bland-Altman plot) was assessed. Multivariate linear regression was used to analyze data to determine the patient and early arthritis features independently associated with discordance (calculated as PGA - EGA). Logistic regression was used to analyze discordance as $\left|\text{PGA} - \text{EGA}\right| \geq 20$.

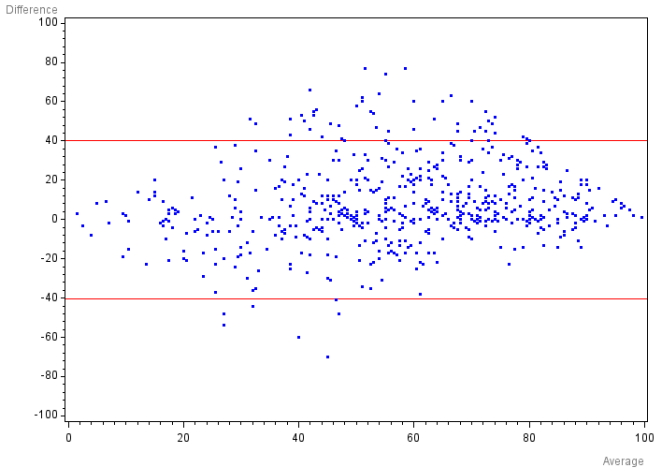
Results:

In 645 patients with early RA (mean age=48.8±12.2 years, 77% female, 48.7% ACPA +) agreement was better at both ends of the spectrum of the disease activity perception, especially for patients with high disease activity. The direction of the discrepancy usually points toward a higher rating by the patients than by physicians themselves.

In multivariate linear regression center-adjusted, higher PGA has been found to be associated with absence of fulfilling ACR 1987 revised criteria for RA (p=0.0005), higher level of fatigue (p<0.0001) and lower number of swollen joint counts (SJC) (p=0.0022). With logistic regression center-adjusted, low number of SJC (OR 95%CI=0.522 [0.343-0.794]), low mental component of the SF-36 (OR 95%CI=0.550 [0.371-0.815]) and living alone (OR95%CI=0.595 [0.388-0.914]) were associated with discordance between PGA and EGA.

Conclusion:

In early RA, the discordance between PGA and EGA is multifactorial with objective measures like low SJC and absence of fulfilling ACR 1987 revised criteria for RA, but also patient reported outcomes like high level of fatigue and low mental status, and environmental factor: living alone. Understanding the reasons for a discordant view of disease activity will help to facilitate the sharing of decision-making in the management of RA. In addition, our findings represent a call to treat fatigue and anxiety-depression, as this may create better consensus about the course of treatment.



Bland-Altman Plot : baseline PGA and PhGA

Disclosure: C. Gaujoux-Viala, None; **N. Rincheval**, None; **L. Gossec**, None; **F. Guillemin**, None; **M. Dougados**, None; **J. P. Daures**, None; **B. Combe**, Pfizer, Roche-Chugai, 2,BMS, Merck, Pfizer, Roche-Chugai, UCB, 8.

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Abstract Number: 2690

The Effects of Disease of the Joints on Modified Health Assessment Questionnaire Scores in Rheumatoid Arthritis Patients: A Retrospective Study Using the National Database of Rheumatic Diseases By Ir-Net in Japan

Kumiko Ono[1], Satoru Ohashi[2], Hiroyuki Oka[3], Yuho Kadono[4], Yasunori Omata[5], Takumi Matsumoto[6], Sakae Tanaka[1] and Shigeto Tohma[7], [1]Orthopaedic Surgery and Spinal Surgery, The University of Tokyo Hospital, Tokyo, Japan, [2]Department of Orhopaedic Surgery, Sagamihara Hospital, National Hospital Organization, Kanagawa, Japan, [3]Department of Joint Disease Research, 22nd Century Medical & Research Center, faculty of medicine,the university of Tokyo, Tokyo, Japan, [4]Department of Orthopaedic Surgery, The University of Tokyo Hospital, Tokyo, Japan, [5]Department of Orthopaedic Surgery and Spine Surgery, The University of Tokyo Hospital, Tokyo, Japan, [6]Department of orthopaedic Surgery, The University of Tokyo Hospital, Tokyo, Japan, [7]Sagamihara Hospital, National Hospital Organization, Sagamihara, Japan

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Background/Purpose: Few studies of which joints most affect physical function in rheumatoid arthritis (RA) patients have been conducted. The present study investigated the effect of bilateral and unilateral disease in the shoulder, elbow, wrist, hip, knee, ankle, finger, and toe joints on Modified Health Assessment Questionnaire (MHAQ) scores using the National Database of Rheumatic Diseases by iR-net in Japan (NinJa), a multicenter, rheumatic disease database.

Methods: The subjects were the 9,212 patients (1,766 men, 7,466 women) with complete medical records among the 10,367 patients registered in NinJa in 2011. The presence or absence of disease in each joint (swelling and pain were considered as disease) and whether the disease was bilateral or unilateral were investigated. At least one metacarpophalangeal joint or proximal interphalangeal joint were considered as finger and toe joint's disease. The correlations between bilateral and unilateral disease of each joint and MHAQ scores were investigated using logistic regression analysis.

Results:

Patients were aged 63.2±12.9 years and their duration of symptoms was 12.2±10.7 years. The majority of subjects had moderate disease activity (mean baseline 28-joint Disease Activity Score, 3.3±1.3). The MHAQ scores median were 0.25. The 2 most frequently affected joints were the finger joints (42.2%) and wrist (36.6%) joint, followed by the knee (21.2%), ankle (20.9%), toe joints (18.7%), elbow (17.8%), shoulder (11.5%). In contrast, the frequencies of hip joint involvements were small (2.0%). Significant correlations were observed between the MHAQ scores and bilateral and unilateral disease of all joints apart from bilateral disease of the hip and bilateral and unilateral disease of the toes. The odds ratio for each joint (95% confidence interval) bilaterally and unilaterally, respectively, were as follows: shoulder, 4.0 (2.9 to 5.6) and 1.8 (1.5 to 2.1) ; elbow, 2.6 (2.1 to 3.4) and 1.8 (1.5 to 2.1); wrist, 1.9 (1.7 to 2.2) and 1.5 (1.3 to 1.7); hip, 1.7 (0.7 to 4.7) and 3.0 (2.0 to 4.7) ; knee, 2.6 (2.2 to 3.2) and 1.9 (1.7 to 2.2) ; ankle, 2.3 (1.9 to 3.0) and 2.0 (1.8 to 2.4) ; finger, 1.4 (1.2 to 1.5) and 1.2 (1.0 to 1.3) ; and toe, 1.0 (0.8 to 1.3) and 1.1 (0.9 to1.3). Regarding the odds ratio, an integer score was assigned to each identified risk factor as follows: each joint (bilaterally/unilaterally) points, shoulder (4/2); elbow(3/2); wrist(2/2); finger(1/1); hip(0/3); knee(3/2); ankle(2/2). The total risk scores for each patient ranged from 0 to 18. The results of the ROC analysis were as follows: cut-off value, 3 points; area under the ROC curve, 0.709; sensitivity 58.6%; and specificity, 72.8%.

Conclusion: While MHAQ scores were significantly affected by disease in almost all joints, a greater effect was exerted by the major joints, in increasing order of ankle, knee, elbow and shoulder. Bilateral disease tended to have a greater effect than unilateral disease in these major joints and the wrist

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Abstract Number: 2691

Musculoskeletal Ultrasound in Multi-Center Rheumatoid Arthritis Clinical Trials: Methodology for Optimizing Reliability of Acquisition and Real-Time Scoring

Veena K. Ranganath[1], Yossra Suliman[1,2], Jenny Brook[3], David Elashoff[3], Ami Ben-Artzi[4], Cesar Olmos[1], Nabeel Borazan[3], Thasia Woodworth[1] and Gurjit S. Kaeley[5], [1]Medicine, Division of Rheumatology, David Geffen School of Medicine, Los Angeles, CA, [2]Rheumatology and Rehabilitation department, Assiut university, Faculty of Medicine,, Assiut, Egypt, [3]Medicine, David Geffen School of Medicine, Los Angeles, CA, [4]David Geffen School of Medicine, Los Angeles, CA, [5]University of Florida, Jacksonville, FL
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Background/Purpose: Rheumatoid arthritis (RA) musculoskeletal ultrasound (MSUS) literature reports good reliability of scoring still images with training, but inconsistent reliability of scoring during acquisition, likely a key factor for reproducibility and sensitivity to change. The aim of this study was to systematically optimize MSUS acquisition and real-time scoring reliability prior to conducting a multicenter MSUS-based RA study.

Methods: This two-site MSUS study evaluated the following joints: bilateral radio-carpal, intercarpal, radioulnar, MCP 1-5, PIP 1-5, knees and MTP 2-5. Reliability among three ultrasonographers with >5 years MSUS experience was assessed in 2 stages: 1) face-to-face 1 [F2F1] Aug 2014, and 2) face-to-face 2 [F2F2] Feb 2015. A reference MSUS RA atlas was modified during serial teleconferences and multiple reliability still-image exercises. After each reliability exercise, the most discrepant images were discussed and the draft atlas was updated. Factors affecting discordance were identified and comprehensively addressed prior to F2F2: *Environment and Machine* (consensus of room temperature, lighting, machine settings); *B-Mode Optimization* (permitting adjustment of frequency, depth, focus, and positioning of deformed joints); *Power Doppler Optimization* (standardization of gel layer, strict adherence to Doppler settings, color map adjustment to accommodate color blindness); *Scoring Optimization*(consensus rules on scoring cutoffs, scoring rules on compound joints such as the wrist). Intra- and inter-reader reliability was examined using weighted-kappa, intraclass correlation coefficient (ICC), and Spearman correlation. Reliability statistics were compared between stages using permutation tests to compute empirical distributions for differences in those statistics.

Results: Acquisition intra-reader reliability improved from F2F1 (0.52-0.71) to F2F2 (0.7-0.86) for weighted kappa, ICC and Spearman correlation (Table). Ultrasonographer-1 (US-1) achieved significant improvement in reliability from F2F1 to F2F2 ($p<0.05$). Inter-reader reliability also improved from 0.5-0.66 to 0.64-0.74 as a result of between-meeting consensus activities. Improvement was

statistically significant for inter-reader reliability between F2F1 to F2F2 for weighted kappa (p=0.03) and a trend for Spearman correlation (p=0.07).

Conclusion: By determining and addressing factors that influence acquisition and scoring, improved real-time scoring reliability can be achieved.

Table: Acquisition and Real-Time Scoring Reliability

Intra- reader						**Inter**- reader			
		Weighted Kappa	ICC	Spearman correlation			Weighted Kappa	ICC	Spearman correlation
F2F-1	US-1	0.63	0.71	0.67		US-1/US-2	0.51	0.66	0.59
	US-2	0.52	0.59	0.64					
F2F-2	US-1	0.80	0.86	0.86		US-1/US-3	0.66	0.75	0.73
	US-3	0.72	0.81	0.81					
	Difference US-1	-0.17	-0.15	-0.19		Difference	-0.16	-0.09	-0.14
	p-value	0.02	0.02	0.008		p-value	0.03	0.22	0.07
ICC: intraclass correlation coefficient; F2F: face-to-face; US: ultrasonographer									

Disclosure: V. K. Ranganath, Genentech and Biogen IDEC Inc., 2,Pfizer Inc, 2,Bristol-Myers Squibb, 2,Bristol-Myers Squibb, 5; **Y. Suliman**, None; **J. Brook**, None; **D. Elashoff**, None; **A. Ben-Artzi**, None; **C. Olmos**, None; **N. Borazan**, None; **T. Woodworth**, None; **G. S. Kaeley**, None.

Abstract Number: 2692

The Patients Evaluation of Pain and Disease Activity As Well As Improvement during One-Year Follow-up on Etanercept Treatment Is Highly Associated to Subjective Factors and Not to Objective Assessments Including Ultrasound

Hilde Berner Hammer[1] and Jon Lampa[2], [1]Rheumatology, Diakonhjemmet Hospital, Oslo, Norway, [2]Dep of Medicine, Rheumatology unit, Karolinska Institute, Karolinska Institute, Stockholm, Sweden

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SESSION INFORMATION

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Background/Purpose:

Patient reported outcomes (PROs) are important for evaluation of treatment response in patients with rheumatoid arthritis (RA). Ultrasound (US) is a sensitive method for assessing inflammation, including grey scale synovitis (GS) and vascularization (power Doppler (PD)). The present objective was to explore the associations during biologic treatment between subjective evaluations of disease activity and more objective assessments of inflammation including US.

Methods:

93 patients with RA (mean (SD) age 50 (13) years, disease duration 8 (7) years, 77% women, 76% anti-CCP positive) were included when starting etanercept 50 mg/week (79% biologic naïve, 54% using prednisolone). The patients were assessed at baseline and after 1, 2, 3, 6 and 12 months with PROs (joint pain VAS, patient's global disease activity VAS, Rheumatoid Arthritis (RA) Impact of Disease (RAID) score, MHAQ), clinical examination (assessor's disease activity VAS, tender and swollen joints (of 32) performed by a study nurse) and laboratory variables (ESR and CRP). DAS28 and CDAI were calculated. Pain catastrophizing was assessed by the

sum of two questions from the Coping Strategies Questionnaire (CSQ, score 0-6) and Swollen/Tender Ratio of 28 joints (STR) was calculated to assess the pain component of arthritis. All US examinations (semi-quantitative scoring (0-3) of GS and PD (PIP 2-3, MCP 1-5, wrist (RC, IC, RU), elbow, knee, talo-crural, MTP 1-5 and ECU/TP tendons bilaterally) were performed by one rheumatologist (HBH) (Siemens Acuson Antares, excellence version, 5-13 MHz probe, optimized settings). Last observation carried forward was used for missing data. Correlations were explored by use of Spearman's, Wilcoxon explored changes from baseline and Mann-Whitney examined differences between two independent groups.

Results:

The 62 patients fulfilling 12 months treatment showed decrease in all variables during the study ($p \leq 0.001$, table). The correlations between patient's global VAS and number of swollen joints, ESR, CRP and US sum scores were low during the study (median (range) r= 0.13 (0.00-0.33). Patients with pain catastrophizing (score 3-12) and low STR (<1.0) had significantly higher subjective variables, but there were no different objective assessments of disease activity (table).

Conclusion:

Subjective evaluations of disease activity were weakly associated with objective assessments of inflammation. Patients with catastrophizing and low STR may not reach DAS28 remission in spite of objectively decreased disease activity. The different expression of pain and PRO scoring in these patients should be acknowledged during biologic treatment.

	Baseline, median (range)	**1 month, median (range)**	**2 months, median (range)**	**3 months, median (range)**	**6 months, median (range)**	**12 months, median (range)**
Joint pain	33 (11-57)	14 (5-32)	14 (5-25)	8 (2-24)	9 (3-22)	8 (4-25)
Patient global VAS	45 (20-66)	14 (9-32)	14 (4-30)	15 (2-29)	14 (3-28)	11 (4-36)
Sum score RAID	3,8 (2.2-5.3)	2.2 (1.0-3.7)	1.9 (0.9-3.4)	1.7 (0.7-3.2)	1.8 (0.8-3.4)	2.1 (0.5-4.0)
Sum score catastrophizing	4 (2-6)	2 (0-5)	2 (0-4)	2 (0-4)	2 (0-4)	2 (0-4)
MHAQ	0.38 (0.13-0.88)	0.13 (0-0.38)	0.13 (0-0.38)	0.13 (0-0.38)	0.13 (0-0.35)	0.07 (0-0.38)
DAS28	4.1 (3.1-4.8)	3.2 (2.5-4.2)	3.0 (2.2-4.0)	3.0 (2.0-3.8)	2.8 (2.0-3.5)	2.6 (1.9-3.5)
Tender joints (of 32)	4 (1-9)	3 (1-6)	2 (0-6)	1 (0-5)	1 (0-4)	1 (0-3)
Swollen joint (of 32)	5 (3-9)	4 (2-7)	3 (1-6)	2 (0-6)	2 (0-4)	1 (0-3)
Assessor's global VAS	25 (15-35)	19 (10-25)	15 (10-22)	12 (5-20)	11 (8-18)	12 (6-19)
Sum score GS	28 (18-40)	22 (14-32)	21 (12-34)	18 (10-28)	17 (10-23)	16 (10-23)
Sum score PD	10 (4-22)	7 (2-16)	4 (2-16)	4 (1-11)	3 (1-8)	3 (1-7)

	Not catastrophizers (score 0-2) / Catastrophizers (score 3-12) (median (p value))						Number of patients Swollen/Tender count Ratio ≥ 1.0 / <1.0 (median (p value))					
	Baseline	**1 month**	**2 months**	**3 months**	**6 months**	**12months**	**Baseline**	**1 month**	**2 months**	**3 months**	**6 months**	**12 months**
No patients	30 / 63	40 / 51	46 / 39	48 /37	43 / 30	41 / 21	60 / 33	68 / 24	59/26	62/24	48/25	42/19
Joint pain VAS	10 / 51 (p<0.001)	9 / 29 (p<0.001)	7 / 28 (p<0.001)	5 / 25 (p<0.001)	5 / 22 (p<0.001)	5 / 27 (p<0.001)	32/ 51 (NS)	12/34 (p<0.001)	10/28 (p=0.001)	7/26 (p<0.001)	7/22 (p=0.001)	5/24 (p=0.004)
Patient's global VAS	22 /56 (p<0.001)	10 / 25 (p<0.001)	8 / 30 (p<0.001)	7 / 31 (p<0.001)	7 / 27 (p<0.001)	6 / 32 (p<0.001)	45/61 (p=0.008)	12/29 (p=0.001)	10/34 (p<0.001)	8/30 (p<0.001)	10/20 (p0.009)	7/27 (p=0.016)
Sum score RAID	2.4 / 5.1 (p<0.001)	1.1 / 3.5 (p<0.001)	1.2 / 3.2 (p<0.001)	1.2 / 3.3 (p<0.001)	1.3 / 3.5 (p<0.001)	0.9 / 4.0 (p<0.001)	3.3 /5.3 (p=0.003)	1.5/3.7 (p<0.001)	1.5/3.6 (p<0.001)	1.2/3.4 (p<0.001)	1.8/2.8 (p=0.049)	0.9/3.4 (p=0.001)
MHAQ	0.25 0.75 (p<0.001)	0.00/0.38 (p<0.001)	0.00/0.38 (p<0.001)	0.00 /0.25 (p<0.001)	0.00/0.25 (p=0.001)	0.00/0.38 (p=0.001)	0.38/0.75 (NS)	0.00/0.38 (p<0.001)	0.12/0.38 (p=0.005)	0.00/0.38 (p<0.001)	0.07/0.25 (NS)	0.00/0.38 (p=0.002)
DAS28 (ESR)	3.3 / 4.6 (p<0.001)	2.7 / 3.8 (p =0.003)	2.4 / 3.8 (p<0.001)	2.6 / 3.8 (p<0.001)	2.5 / 3.5 (p=0.009)	2.2 / 3.6 (p<0.001)	3.9/ 5.1 (p<0.001)	2.9/4.2 (p<0.001)	2.6/4.1 (p<0.001)	2.7/4.1 (p<0.001)	2.4/3.5 (p<0.001)	2.3/3.6 (p<0.001)
CDAI	11 / 16 (p<0.001)	8 / 11 (p=0.03)	5 / 12 (p=0.001)	5 / 11 (p<0.001)	6 /9 (p=0.003)	4 / 9 (p=0.002)	13/20 (p=0.008)	8/13 (p=0.003)	6/15 (p<0.001)	6/11 (p<0.001)	6/9 (p=0.001)	4/10 (p=0.001)
No tender joints (of 32)	3 / 5 (p=0.034)	2 / 5 (p=0.001)	1 / 6 (p<0.001)	1 / 3 (p=0.018)	1 / 3 (NS)	0 / 3 (p=0.001)	3/10 (p<0.001)	2/7 (p<0.001)	1/8 (NS)	1/8 (p<0.001)	1/5 (p<0.001)	0/5 (p<0.001)
No swollen joints (of 32)	4 / 5 (NS)	4 / 3 (NS)	3 / 3 (NS)	2 / 3 (NS)	1 / 2 (NS)	1 / 2 (NS)	5 /4 (NS)	4/3 (NS)	3/3 (NS)	2/2 (NS)	2/2 (NS)	1/2 (NS)
Assessor's global VAS	22 / 25 (p=0.028)	15 / 17 (NS)	15 / 17 (NS)	10 / 18 (p=0.001)	10 / 17 (p=0.015)	10/15 (p=0.016)	25/25 (NS)	15/16 (NS)	15/18 (NS)	11/14 (NS)	10/14 (NS)	11/15 (NS)
ESR	16 / 23 (p=0.041)	14 / 13 (NS)	11 / 14 (NS)	15 / 18 (NS)	11 / 15 (NS)	10 / 16 (NS)	21/20 (NS)	13/13 (NS)	12/11 (NS)	16/17 (NS)	12/12 (NS)	13/14 (NS)
CRP	3/ 5 (NS)	2 / 2 (NS)	1 / 2 (NS)	2 / 2 (NS)	1 / 3 (p=0.044)	1 / 1 (NS)	4 /5 (NS)	2/2 (NS)	1 /2 (NS)	2/2 (NS)	2/2 (NS)	1/2 (NS)
Sum score GS	27 / 26 (NS)	21 / 20 (NS)	20 / 15 (NS)	17 / 17 (NS)	17 / 18 (NS)	16 / 16 (NS)	28/19 (NS)	23/18* (p=0.041)	20/17 (NS)	20/14 (NS)	17/16 (NS)	16/16 (NS)
Sum score PD	9 / 8 (NS)	5 / 5 (NS)	5 / 3 (NS)	4 / 5 (NS)	3 / 3 (NS)	3 / 3 (NS)	11/6 (NS)	7/2* (p=0.009)	5/3 (NS)	4/2 (NS)	3/3 (NS)	4/3 (NS)

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Abstract Number: 2693

Comparing Eight Year Clinical and Radiographic Outcome in Two Cohorts of Patients with Rheumatoid Arthritis

Maria LE Andersson[1], Kristina Forslind[2] and Ingiäld Hafström[3], [1]R&D Centre Spenshult,Halmstad, Halmstad, Sweden, [2]Department of Medicine, Helsingborgs Lasarett, Section of Rheumatology, Helsingborg, Sweden, [3]Rheumatology Dept, Karoliska Institute, Stockholm, Sweden

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Background/Purpose: To compare patient and disease characteristics over the first 8 years of disease in a large inception cohort of early RA patients included 1992 to 1999 and 2000 to 2006, respectively.

Methods: In all 1911 RA patients from the early BARFOT prospective multi-centre observational study, who had completed the 8 year follow-up, were recruited. All patients fulfilled the ACR 1987 criteria. The patients were divided into two groups, group 1 (N=928, 68% women) included 1992 to 1999 and group 2 (N=1010, 70% women) included 2000 to 2006. DAS28, VAS pain, HAQ and radiographs of the hands and feet scored by the van der Heijde modified Sharp method (SHS) were assessed during the 8 years. Statistical comparisons between groups were done by t-test and Chi2.

Results: At inclusion, the women in group 2 were, compared with those in group 1, older, mean (SD) 55 (15) vs 52 (14) years, $p<0.001$, were more frequently RF positive, 64% vs. 58%, $p=0.031$ and had worse radiographic score, mean total SHS (SD) 5 (9) vs 3 (6), $p<0.001$, whereas the men did not differ in these aspects.

Over time DAS28 decreased in both groups, and as from 6 months in men and 12 months in women the mean DAS28 was significantly lower in group 2 compared with group 1 and remained so during the 8 year follow-up. HAQ and VAS pain decreased similarly in the two groups with no differences between women at any time point. Men in group 1 had higher mean VAS pain at 6 months and at 2 years follow-up, with no differences between the groups at 8 years.

In both groups women and men progressed radiographically over 8 years, $p<0.001$ respectively. Women in group 1 had more progression than women in group 2, mean (SD) change SHS 20 (27) vs. 16 (20), $p=0.009$. In men there were no difference in mean change SHS over 8 years 16 (19) vs 14 (18), $p=0.186$.

The patients in group 1 started with methotrexate (MTX) in 26%, with sulphasalazine (SAL) in 30%, and with other DMARDs in 10%, the corresponding figures for group 2 were 61%, 19% and 3%. After 8 years patients in group 1 got MTX in 32%, combination therapy in 8% and biologics in 13%, in group 2 the corresponding figures were 40%, 7% and 26%.

Conclusion: Women diagnosed in the 2000s had higher disease activity, more pain and worse radiographic joint damage at inclusion than those diagnosed in the 1990s. They achieved lower disease activity and less radiographic progression over 8 years compared with the women included in the 1990s. This difference may reflect the more active medical treatment in the 2000s. Despite that, HAQ and pain did not differ between women in the two groups during follow-up.

Men diagnosed in the 2000s had higher disease activity and more tender joints at inclusion than those diagnosed in the 1990s. As for women disease activity decreased more in those diagnosed in the 2000s, though there was no difference in radiographic progression between the groups, neither in HAQ or pain reduction at the 8-yearfollow-up. HAQ and pain seems thus not solely depend on inflammatory activity or radiological damage in either gender.

Disclosure: M. L. Andersson, None; **K. Forslind**, None; **I. Hafström**, None.

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Abstract Number: 2694

Variations in the Metabolome in Response to Disease Activity of Rheumatoid Arthritis

Zuzana Tatar[1], Carole Migne[2], Mélanie Petera[3], Estelle Pujos Guillot[4], Philippe Gaudin[5,6], T Lequerré[7], Hubert Marotte[8], Jacques Tebib[9] and Martin Soubrier[1], [1]Rheumatology department CHU Clermont-Ferrand, Clermont-Ferrand, France, [2]Metabolomic Plateform INRA, Theix-Clermont-Ferrand, France, [3]Metabolomic Plateform, INRA, Theix -Clermont-Ferrand, France, [4]Metabolomic Plateform, INRA, Theix-Clermont-Ferrand, France, [5]Rheumatology, University Hospital, Grenoble, France, [6]Rheumatology Department, CHU Hôpital Sud, Grenoble Teaching Hospital, Echirolles, France, [7]Rheumatology Department and INSERM U 905, CHU Hôpitaux de Rouen, Rouen, France, [8]INSERM 1059 / LBTO, Université de Lyon, Saint-Etienne; Rheumatology Department, Saint-Etienne, France, [9]Rheumatology Department, Centre Hospitalier Lyon-Sud, Pierre-Bénite Lyon, France

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Background/Purpose:

Anti-TNF-alpha therapies are able to control rheumatoid arthritis (RA) disease activity and to limit structural damage. Nevertheless, no predictive factor of response to anti-TNF-alpha, has yet been identified. The metabolic profile can vary in response to different inflammatory rheumatisms and hence determining this profile can considerably improve diagnosis and, consequently, prognosis.

The aim of this study was to determine, by mass spectrometry, whether there is a variation in the metabolome in patients treated with anti-TNF alpha in order to predict the therapeutic response.

Methods:

Blood samples were taken before (M0) the initiation of anti-TNF-alpha treatment in 140 patients with active RA. Plasma was deproteinised, extracted and analysed by coupled reverse phase chromotography / QToF mass spectrometry. Extracted and normalized ions were considered in univariate and ANOVA analysis and were confronted to PLS-DA (partial least-squares regression-discriminant analysis). An OSC (Orthogonal Signal Correction) were also used in order to filter data from unwanted non-related effects. Disease activity scores, obtained at M0 and M6, and metabolome variation findings were correlated to identify a metabolite that is predictive of therapeutic response to anti-TNF-alpha.

Results: After 6 months of anti-TNF therapy, 100 patients were considered as good responders and 40 patients as non-responders according to EULAR criteria. Metabolomic investigations suggested two different metabolic fingerprinting splitting good responders group and non-responders group. A global effect of discriminative ions is concrete even if we could not report one single discriminating biomarker that could simplify the daily management of RA. The univariate analysis in positive mode revealed 24 significant ions ($p < 0,05$) and 31 significant ions in negative mode ($p < 0,05$). Once intersected with PLS results, only 35 ions remained. Especially, carbohydrate derivates seemed to be determining of therapeutic response.

Conclusion: This is the first study describing metabolic profiling in response to anti-TNF-alpha treatments using plasma samples. Our study highlighted two different metabolic fingerprinting splitting good responder group and non-responder group.

Disclosure: Z. Tatar, None; **C. Migne**, None; **M. Petera**, None; **E. Pujos Guillot**, None; **P. Gaudin**, None; **T. Lequerré**, None; **H. Marotte**, None; **J. Tebib**, None; **M. Soubrier**, None.

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Abstract Number: 2695

Th17 Cell Related Cytokines and Microarray Expression Profiles in Patients with Early Rheumatoid Arthritis

Youngkyun Kim[1], Kijun Lee[2], Hae-Rim Kim[3], Sang Heon Lee[4], Ji Hyeon Ju[5] and **HO-YOUN KIM**[6], [1]1Convergent Research Consortium for Immunologic Disease, The Catholic University of Korea, Seoul, South Korea, [2]The Catholic University of Korea, Seoul, South Korea, [3]Konkuk University Medical Center, Seoul, South Korea, [4]Konkuk University Hospital, Seoul, South Korea, [5]Division of Rheumatology, Department of Internal Medicine, College of Medicine, The Catholic University of Korea, Seoul, South Korea, [6]Konkuk university hospital, Seoul, South Korea

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Background/Purpose: The purpose of this study is to explore new biomarkers for early diagnosis of rheumatoid arthritis (RA). For better discrimination power, we especially investigated the samples of early RA (eRA) patients whose onset of RA were less than 1

year.

Methods: We examined the serum cytokines and the gene expression profiles of peripheral mononuclear cells from early rheumatoid arthritis (eRA). eRA samples were compared with advanced RA (aRA, disease duration more than 1 year) and osteoarthritis. Serum obtained from 44 patients with eRA were evaluated for cytokine panels, including IFN-r, IL-12, IL-2, IL-4, IL-10, IL-17 and IL-6. Gene expression profiles of eRA (n=11), using microarray analysis, were compared with OA (n=8) and aRA (n=7). Biomarker candidates were positively selected by pathway analysis using NCBI database about Th17 cell differentiation genes.

Results: Mean age of eRA and aRA were 51.9 and 58.1 respectively. CRP level was higher in aRA than eRA (3.27 vs 1.19 mg/dL, *P<0.02*). Th17 cell-related cytokines like IL-6 and IL-17 were prominent than other cytokines in eRA patients. IL-17 concentration was statistically higher in eRA than aRA. Positive percentage of IL-6 was more than 50% in eRA patients. IL-6 were well correlated with ESR (r=0.3, *P=0.006*) and CRP (r=0.6, *P<0.001*). Interestingly, IL-17 levels were correlated with disease activity DAS28 (r=0.45, *P=0.003*). 255 genes were upregulated in eRA (|F.C|>1.3, *P<0.05*). 10 genes were selected from 255 genes by association analysis with Th17 differentiation as followings, TMEM140 (transmembrane protein 140), NUAK2 (NUAK family, SNF1-like kinase 2), SULT1A3 (sulfotransferase family, cytosolic, 1A, phenol-preferring, member 3), HIST1H4H (histone cluster 1, H4h), NAPSB (napsin B aspartic peptidase pseudogene), FEN1 (flap structure-specific endonuclease 1), PROS1 (protein S alpha), RPS6KA2 (ribosomal protein S6 kinase, 90kDa, polypeptide 2), CDKN3 (cyclin-dependent kinase inhibitor 3), JAM3 (junctional adhesion molecule 3).

Conclusion: Th17-related cytokines were dominant at early stage of RA and associated with disease activity. Th17-related candidate genes could give a new insight as biomarkers for early diagnosis and therapeutic target for eRA.

Disclosure: Y. Kim, None; **K. Lee**, None; **H. R. Kim**, None; **S. H. Lee**, None; **J. H. Ju**, None; **H. Y. KIM**, None.

Abstract Number: 2696

Geography and Association Between Patient Reported Outcomes and Disease Activity (DAS28) Components in Patients with Rheumatoid Arthritis, Among 17 Countries

Raluca Dumitru[1], Elizabeth M.A. Hensor[1], Ihsane Hmamouchi[2], Paul Emery[3], Maxime Dougados[4] and Maya H. Buch[5], [1]University of Leeds, Leeds Institute of Molecular Medicine and LMBRU, Leeds, United Kingdom, [2]El Ayachi Hospital, Rabat, Morocco, [3]Academic Section of Musculoskeletal Disease, University of Leeds, Leeds Institute of Molecular Medicine and LMBRU, Leeds, United Kingdom, [4]Service de Rhumatologie B, GHU Cochin, F-75014 France, PARIS, France, [5]Division of Rheumatic and Musculoskeletal Disease, University of Leeds, Leeds Institute of Molecular Medicine and LMBRU, Leeds, United Kingdom

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Background/Purpose: 28 joints-disease activity score (DAS28) is routinely used in clinical practice to assess disease activity in rheumatoid arthritis (RA). DAS28, particularly its subjective components [patient visual analogue scale (VAS), tender joint count (TJC)] might not always reflect inflammation. No study to date has assessed the relationship between PRO and the DAS28 components in a large cohort of patients, among different countries. The main objective of this study is to assess the associations between patient and physician reported outcomes and the objective components of DAS28 across different geographical populations, using the COMORA dataset[1]('Prevalence of Comorbidities in Rheumatoid Arthritis and evaluation of their monitoring: results of an international, cross-sectional study'). The study will also assess the relationship between patient and physician perception of disease activity, and PRO and number of comorbidities.

Methods: Demographics, clinical characteristics, including DAS28 and PRO, treatment and comorbidities were recorded. Using Spearman's rho, we assessed pairwise correlations among patient global, patient fatigue, physician global, quality of life (EQ5D) and the DAS28 components for each country. We then looked at the inter-relationship of patient/physician reported outcomes. Finally, the correlation between PRO and comorbidities was calculated.

Results: 3674 patients from 17 countries were included in the analysis (mean age 56 years; 82% female). Mean (SD) DAS28 was moderate at 3.72 (1.55). DAS28, SJC, TJC and ESR varied significantly between countries. ESR showed very weak correlation with all PRO for the majority of the countries. SJC correlated moderately with PRO and the association varied between countries, but

showed good correlation with physician global for almost all assessed countries(r>0.5 for 16/17). TJC had good correlation with patient global, physician global and EQ5D and showed little variation between countries. TJC and patient fatigue correlation varied between countries. Patient and physician global correlated with each other. No significant correlation was found between number of comorbidities and PRO.

Conclusion: PROs generally associated well with the more subjective components of DAS28 whilst physician global seemed more consistent with the objective elements and this was observed across most countries. Geographical variation however was particularly observed with tender joint and patient-reported fatigue. This might have implications in the interpretation and applicability of International clinical trials.

References: 1.Dougados M, Ann Rheum Dis, 2014

Table 1: Ranges of Spearman's rho coefficients

	Physician global	Patient global	Fatigue VAS	EQ5D
ESR	-0.15 to 0.57	-0.07 to 0.36	-0.04 to 0.28	-0.35 to 0.02
SJC	0.25 to 0.84	0.13 to 0.61	0.05 to 0.61	-0.58 to -0.13
TJC	0.46 to 0.82	0.32 to 0.71	0.18 to 0.59	-0.56 to -0.32
Patient global	0.33 to 0.83	n/a	0.48 to 0.79	-0.78 to -0.53
Comorbidities	n/a	-0.08 to 0.36	-0.06 to 0.35	-0.25 to 0.01

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Abstract Number: 2697

Phenome-Wide Association Study of Rheumatoid Arthritis Subgroups Identifies Association Between Seronegative Disease and Fibromyalgia

Jayanth Doss[1], Huan Mo[2], Leslie J. Crofford[1] and Joshua C. Denny[2], [1]Rheumatology, Vanderbilt University School of Medicine, Nashville, TN, [2]Biomedical Informatics, Vanderbilt University School of Medicine, Nashville, TN
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SESSION INFORMATION
Session Date: Tuesday, November 10, 2015
Session Title: Rheumatoid Arthritis - Clinical Aspects Poster Session III
Session Type: ACR Poster Session C
Session Time: 9:00AM-11:00AM

Background/Purpose: The differences between seronegative and seropositive rheumatoid arthritis (RA) have not been widely reported. We performed an electronic health record (EHR)-based phenome-wide association study (PheWAS) to identify disease associations that differ between seropositive and seronegative RA.

Methods: A validated algorithm identified RA subjects from the de-identified EHR (1). Serotypes were determined by values of rheumatoid factor (RF) and anti-cyclic citrullinated peptide antibody (ACPA). A PheWAS uses logistic regression to identify ICD9 codes that are more likely to be present in one group of patients versus another. A PheWAS comparing seropositive and seronegative patients was performed and identified disease associations (i.e. ICD9 codes) for each serotype. Following PheWAS, select disease associations were manually reviewed and fibromyalgia was specifically evaluated using a validated algorithm.

Results: A total of 2199 individuals were identified with RA and with serologic testing. Of these, 1382 (63%) were seropositive. Seronegative RA was associated with “Myalgia and Myositis” (odds ratio [OR] 2.1, $P=3.7x10^{-10}$) and back pain. A manual record review showed 80% of Myalgia and Myositis codes were used for fibromyalgia, and follow-up with a specific EHR algorithm for fibromyalgia confirmed that seronegative RA was associated with fibromyalgia (OR=1.8, $P=4.0x10^{-6}$). Seropositive RA was associated with Chronic Airway Obstruction (OR=2.2, $P=1.4x10^{-4}$), tobacco use (OR=2.1, $P=3.8x10^{-4}$), and other pulmonary

phenotypes.

Conclusion: This PheWAS study in RA patients identifies a strong association between seronegativity and fibromyalgia. It also replicates a well-known association between seropositivity and chronic airway obstruction related to tobacco use. These findings demonstrate the utility of the PheWAS approach to discover novel phenotype associations within different subgroups of a disease.

Table 1

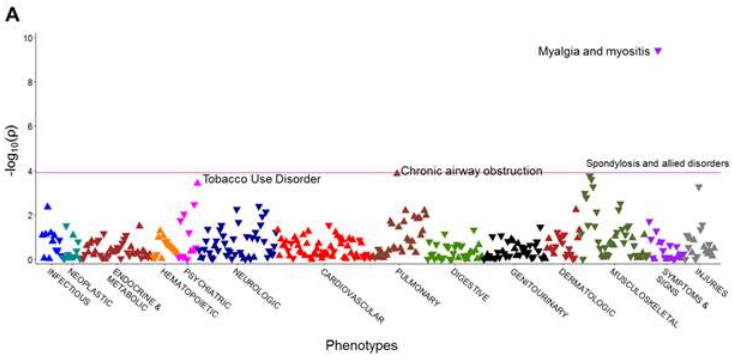
	All Patients (n = 2199)	Seropositive (n = 1382)	Seronegative (n = 817)
Demographic Characteristics			
Age, mean ± SD years	52.1 ± 14.5	53.17 ± 13.4	51.7 ± 14
Sex, no. (%) female	1669 (76)	1012 (73)	657 (80)
Race, no. (%)			
White	1711 (78)	1063 (77)	648 (79)
Black	176 (8)	127 (9)	50 (6)
Other	22 (1)	14 (1)	7 (1)
Unknown	290 (13)	178 (13)	112 (14)
Electronic Health Record (EHR) Encounter Data			
Median EHR time in years (IQR)	8 (5 – 14)	8 (5 – 13)	8 (5 – 14)
Median EHR time with RA ICD9 Codes in years (IQR)	6 (3 – 8)	6 (3 – 9)	5 (3 – 8)
Median EHR Billing Encounters (IQR)	29 (14 – 60)	29 (14 – 60)	29 (14 – 60)
Median EHR Billing Encounters with RA ICD9 Codes (IQR)	16 (8 – 28)	17 (8 – 29)	14 (7 – 26)

Table 2. PheWAS results adjusted for age and sex

	Cases	Controls	OR	CI (95%)	p
Associations favoring seronegative RA					
Myalgia and Myositis *	346	1642	2.1	1.7 – 2.7	3.7×10^{-10}
Spondylosis and allied disorders	104	1725	2.2	1.4 – 3.2	1.7×10^{-4}
Spondylosis without myelopathy	96	1725	2.2	1.4 – 3.3	2.5×10^{-4}
Intervertebral disc disorders	191	1725	1.7	1.3 – 2.3	5.2×10^{-4}
Internal Derangement of Knee	38	2032	3.4	1.7 – 6.8	5.3×10^{-4}
Polymyalgia Rheumatica	35	2140	3.2	1.6 – 6.6	1.1×10^{-3}
Spinal Stenosis	102	1725	1.9	1.3 – 2.9	1.7×10^{-3}
Associations favoring seropositive RA					
Chronic Airway Obstruction	149	1842	2.2	1.5 – 3.4	1.4×10^{-4}
Tobacco Use Disorder	143	1885	2.1	1.4 – 3.1	3.8×10^{-4}
Staphylococcus Infection	32	2051	5.7	1.7 – 18.8	4.3×10^{-3}
Chronic Ulcer of Skin	51	2104	2.8	1.3 – 5.8	5.8×10^{-3}
Diseases of Respiratory System	29	2112	7.5	1.8 – 31.6	6.2×10^{-3}
Post-Inflammatory Pulm Fibrosis	65	1880	2.4	1.3 – 4.4	6.3×10^{-3}
Symptoms Involving Resp System	26	2138	6.6	1.6 – 28.1	1.1×10^{-2}

* p-value reaches Bonferroni threshold of 1.3×10^{-4}

Figure 1. PheWAS Manhattan plots of RA patients comparing seropositive and seronegative phenotypes



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1. Carroll RJ, et al. Portability of an algorithm to identify rheumatoid arthritis in electronic health records. J Am Med Inform Assoc JAMIA. 2012 Jun;19(e1):e162–9.

Disclosure: J. Doss, None; **H. Mo**, None; **L. J. Crofford**, None; **J. C. Denny**, None.

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Abstract Number: 2698

Follicular Helper T Cells in Peripheral Blood of Patients with Rheumatoid Arthritis

Alicia Beatriz Costantino[1], Laura Onetti[2], Melina del Valle Cloquell[3], Cristina del Valle Acosta[1], Eduardo Mussano[2], Isaac Ignacio Cadile[2], Cecilia María Rodriguez[3], Stefania Santo[1] and Paola Virginia Ferrero[1], [1]Córdoba, Laboratorio de Inmunología. Hospital Nacional de Clínicas. Facultad de Ciencias Médicas. Universidad Nacional de Córdoba, Córdoba, Argentina, [2]Córdoba, Servicio de Reumatología. Hospital Nacional de Clínicas. Facultad de Ciencias Médicas. Universidad Nacional de Córdoba, Córdoba, Argentina, [3]Córdoba, Laboratorio de Oncohematología, Hospital Nacional de Clínicas, Facultad de Ciencias Médicas, Universidad Nacional de Córdoba, Córdoba, Argentina

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Session Time: 9:00AM-11:00AM

Background/Purpose: RA is an autoimmune, inflammatory and chronic disease which aetiology is unknown. It presents different autoantibodies such as RF and ACPA. A population of CD4 T cells expressing CXCR5, Bcl6, PD-1, ICOS, CD40L and IL-21, named Follicular helper T cells (Tfh), collaborates with B cells to produce antibodies. Increased levels of peripheral blood Tfh cells have been implicated in the development of systemic autoimmunity. Differential expression of CXCR3 and CCR6 whitin $CD4^+CXCR5^+$ T cells defines three mayor subset: $CXCR3^+CCR6^-$ (Tfh1), $CXCR3^-CCR6^-$ (Tfh2) and $CXCR3^-CCR6^+$ (Tfh17). The aim is to ascertain if differents subsets of $CD4^+CXCR5^+$ T cells are alterated in RA patients and if their percentages correlate with disease activity.

Methods: In this study participated RA patients (n=24), healthy controls (HC) (n=22) and undifferentiated arthritis (UA) patients (n=16) (Table 1). Percentage of $CD4^+CXCR5^+$ T cells and their subsets $CXCR3^+CCR6^-$, $CXCR3^-CCR6^-$ and $CXCR3^-$ $CCR6^+$ from PBMCs were analysed by flow cytometry. Pearson or Spearman correlation coefficients were used for statistics.

Results: Figure 1 shows flow cytometry analysis. No differences were found in the % of $CD4^+CXCR5^+$ T cells between RA vs HC or RA vs UA (mean±SD, RA 12,89±7,73; HC 10,48±3,9; UA 11,71±5,04). Either in the % of Tfh1 (12,75 ± 9,72; 11,22 ± 7,48; 12,81 ± 6,13), or Tfh2 (32,66 ± 11,46; 39,53 ± 12,12; 27,56 ± 11,25), or Tfh17 subsets (37,94 ± 11,34; 40,79 ± 8,17; 37,34 ± 7,16) between previous groups (Figure 2). There was not correlation between $CD4^+CXCR5^+$ T cells (r=-0,19 p=0,37), or Tfh1 (r=0,09 p=0,68), or Tfh2 (r=0,36 p=0,09), or Tfh17 (r=-0,20 p=0,35) vs DAS-28, like either between each subset and ESR (r=-0,18 p=0,39, r=-0,08 p=0,71, r=-0,01 p=0,97, r=-0,25 p=0,23, respectively). Unexpectedly, there was positive correlation between Tfh17 cells and CRP

r=0,47 *p*=0,021. Finally, there was not correlation between $CD4^+CXCR5^+$ T cells vs mutated citrullinated vimentin (MCV) r= 0,38 *p*=0,07, either between Tfh1, Tfh2 and Tfh17 subsets vs MCV(r=-0,04 *p*=0,84, r=-0,14 *p*=0,51, r=-0,19 *p*=0,37, respectively) or all of them vs RF (r=0,30 *p*=0,15, r=-0,18 *p*=0,39, r= -0,15 *p*=0,46, r=0,01 *p*=0,98, respectively).

Conclusion: In concordance with our results, $CD4^+CXCR5^+$ T cells and their subsets would not be involved in the RA development.

TABLE 1. Summary of Patients and Donors in the Study

	RA (n=24)	HC (n=22)	UA (n=16)	RA vs HC *p* value	RA vs UA *p* value
Sex, F/M	21/3	19/3	13/3	0,77#	0,93#
Age,* years	51 ± 10	49 ± 10	52 ± 11	>0,05	>0,05
WBC,* n°.10⁹/L	6,98 ± 1,85	7,23 ± 1,96	6,84 ± 1,74	>0,05&	>0,05 &
Hgb, *g/L	12,6 ± 1,91	12,6 ± 0,98	12,96 ±1,07	>0,05§	>0,05§
Plat* n°.10⁹/L	255 ± 80	254 ± 41	249 ± 59	>0,05§	>0,05§
ESR,*mm/h	25 ± 21	9 ± 6	14 ± 12	<0,01§	>0,05§
CRP,* mg/L	18 ±14	9 ±2	14 ± 8	<0,01§	>0,05§
RF +, n (%)	19 (79)	0 (0)	0 (0)	<0,0001#	<0,0001#
MCV**, UI/L	75,0(7,7-530,0)	2,8(2,3-5,3)	2,9(2,5-3,8)	<0,001§	<0,001§
IgG*, mg%	1310 ± 338	1325 ± 257	1212 ± 336	>0,05#	>0,05#
IgM*, mg%	220 ± 88	169 ± 55	179 ± 60	<0,05#	>0,05#
IgA*, mg%	363 ± 126	313 ± 80	261 ± 114	>0,05#	<0,05#
C3*, mg%	112 ± 33	119 ± 26	130 ± 30	>0,05#	>0,05#
C4*, mg%	24 ± 9	26 ± 7	31 ± 8	>0,05#	<0,05#
DAS-28*	5,16 ± 1,35	----------	----------	----------	----------

*Value given in mean ± SD
** Value given in median and interquartile range (P_{25-75})
# Chi-square test
& One- way ANOVA test (post test Bonferroni)
§ Kruskal-Wallis test (post test Dunn)
Satatistically significant p values (p<0,05) are shown in bold
RA: Rheumatoid Arthritis, HC: Healthy Control, UA: Undifferentiated Arthritis, WBC: White Blood Cell, Hgb: Hemoglobin, Plat: Platelets, ESR: Erythrocyte Sedimentation Rate, CRP: C-Reactive Protein,
RF: Rheumatoid Factor, MCV: anti-Mutated Citrullinated Vimentin, Ig: Immunoglobulin. DAS-28: Disease Activity Score in twenty-eight joints

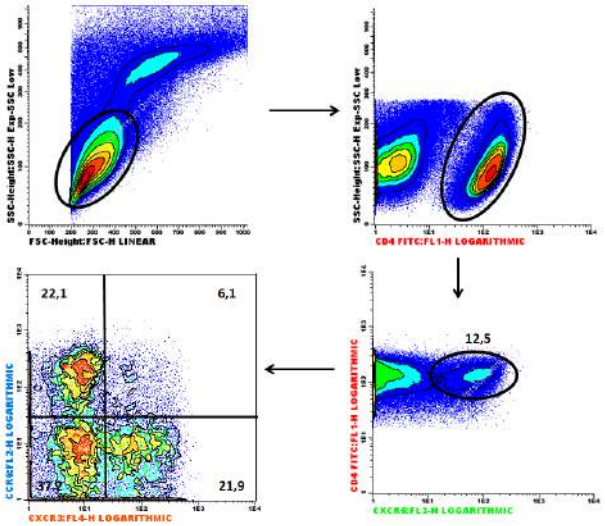

Figure 1. Density contour graph 2D showing gate strategy of a representative experiment from a patient with RA

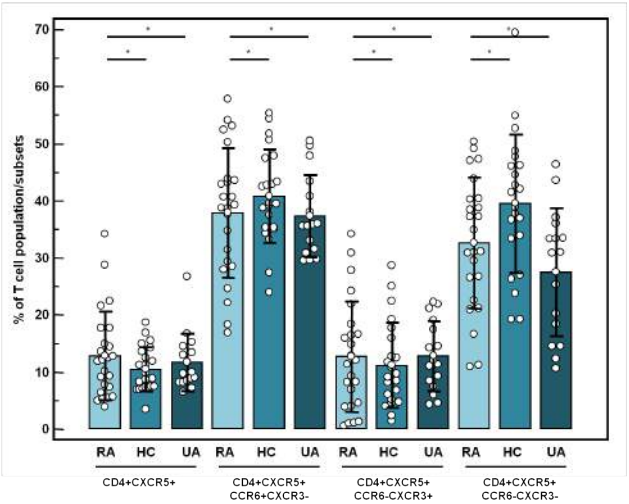

Figure 2. Percentages of CD4+CXCR5+ T cell population and each subset in PBMCs from RA patients, Healthy Controls (HC) and Undifferentiated Arthritis (UA) patients. One-way ANOVA test and Bonferroni post test , * *p*>0,05

Disclosure: **A. B. Costantino**, None; **L. Onetti**, None; **M. D. V. Cloquell**, None; **C. D. V. Acosta**, None; **E. Mussano**, None; **I. I. Cadile**, None; **C. M. Rodriguez**, None; **S. Santo**, None; **P. V. Ferrero**, None.

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Abstract Number: 2699

Muscle Inflammation Relates to Disease Activity and Disability but Not Insulin Resistance in Rheumatoid Arthritis

Ryan Jessee[1], Rachel Narowski[2], Monica Hubal[3], Janet Huebner[4], Virginia Kraus[5], William Kraus[6] and Kim Huffman[2,7], [1]Internal Medicine, Duke University Medical Center, Durham, NC, [2]Duke Molecular Physiology Institute, Duke University Medical Center, Durham, NC, [3]Research and Education, George Washington University School of Medicine and Health Sciences, Washington, DC, [4]Duke Molecular Physiology Institute,, Duke University Medical Center, Durham, NC, [5]Duke Molecular Physiology Institute, Duke University School of Medicine, Durham, NC, [6]Division of Cardiology, Duke University Medical Center, Durham, NC, [7]Durham Veterans Affairs Medical Center, Durham, NC

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Background/Purpose: Rheumatoid arthritis (RA) is associated with increased cardiovascular disease, insulin resistance, and disability. Our objectives were to analyze levels of skeletal muscle inflammatory cytokines and gene expression pathways in RA patients compared to controls without RA in order to determine whether increased muscle inflammation was related to disease activity, insulin resistance, and/or disability. We hypothesized that greater disease activity would be associated with greater muscle inflammation and worse insulin resistance

Methods: 39 individuals with RA were matched with 39 individuals based on age, gender, race, and BMI. Exclusion criteria included diabetes, cardiovascular disease, recent medication changes, and prednisone use greater than 5 mg/d. All underwent measurements of disease activity (DAS-28), disability (HAQ-DI), glucose tolerance, plasma inflammatory cytokines, thigh CT imaging, physical activity (accelerometry), and vastus lateralis muscle biopsies. ELISAs were used to measure muscle (m) inflammatory markers: interleukin (mIL)-1β, mIL-6, mIL-8, tumor necrosis factor-alpha (mTNFα), and Toll-like receptor 4. Gene expression was measured in muscle from 5 matched case-control sets using Illumina Expression BeadChips. Differentially expressed genes were identified with Partek and used in pathway analyses performed with Ingenuity Pathway Analysis.

Results: Despite elevated systemic inflammation (C-reactive protein, IL-6, TNFα; $P<0.05$) in RA compared to controls, the only muscle cytokine with higher concentrations was mIL-6 ($P=0.006$). Nonetheless, in RA, higher mIL-1β and mIL-8 were correlated with higher DAS-28 ($r=0.35$, $r=0.30$, $P<0.05$). Higher mIL-1β and mIL-6 levels were associated with higher HAQ-DI ($r=0.33$, $r=0.33$, $P<0.05$). Higher concentrations of mIL-1β, mIL-6, and mIL-8 were associated with less exercise ($r=-0.38$, $r=-0.40$, $r=-0.38$, $P<0.05$), while higher mIL-1β and mIL-6 were related to less physical activity ($r=-0.35$, $r=-0.33$, $P<0.05$). Muscle cytokines had minimal correlation with insulin resistance and serum cytokines ($P>0.05$). Pathways with the most differences in muscle gene expression ($P<0.05$) had central molecules associated with the NF-kB and Ras/MapK pathways.

Muscle Inflammation Relationships in RA (n=39)

Variable	mIL-1β	**mIL-6***	mIL-8	mTNFα	mTLR-4
Age (years)	-0.308	-0.222	-0.003	0.013	**-0.326†**
Body Mass Index (kg/m^2)	**-0.339†**	-0.042	-0.273	0.024	-0.194
Disease Activity (DAS_{ESR}-28)	**0.348†**	0.229	**0.297†**	0.140	-0.005
Disability (HAQ-DI)	**0.325†**	**0.329†**	0.190	0.085	0.119
Pain (Visual Analog Score)	**0.392†**	0.147	0.169	**0.292†**	**0.474†**
DMARD Use (Yes=1; No=0)	0.210	-0.038	-0.071	0.031	0.079
Biologic Use (Yes=1; No=0)	-0.330	-0.246	**-0.369†**	0.208	0.008
Comorbidity Index	0.262	0.168	0.115	0.166	-0.083
Insulin Sensitivity (x10-5 min-1/[pmol/L])	-0.094	-0.197	-0.190	-0.061	-0.175
hsCRP (mg/L)	-0.033	0.202	0.066	0.113	-0.168
IL-1β (pg/mL)	-0.137	0.008	-0.070	-0.071	-0.119
IL-6 (pg/mL)	-0.006	-0.032	0.113	0.123	-0.097
IL-8 (pg/mL)	0.140	-0.109	0.062	0.113	0.017
TNF-α (pg/mL)	-0.230	**-0.369†**	-0.149	0.020	-0.077
IL-18 (pg/mL)	-0.240	-0.081	-0.121	-0.019	0.058
Thigh Muscle Density (Hu)	0.155	-0.044	-0.095	0.057	**0.295†**
Thigh subcutaneous adiposity (cm^2)	-0.092	**0.310†**	-0.067	-0.106	-0.112
Exercise (min/w)	**-0.381†**	**-0.400†**	**-0.376†**	-0.051	-0.114
Physical Activity (METs/w)	**-0.354†**	**-0.331†**	-0.260	0.099	-0.145
***P* < 0.05 for comparison with matched controls** **†*P* < 0.05 for correlation coefficient**					
DAS_{ESR}-28 = Disease activity score with 28 joint count and ESR=erythrocyte sedimentation rate; HAQ-DI= Health Assessment Questionnaire Disability Index; DMARD=Disease Modifying Anti-Rheumatic Drug; hsCRP = High sensitivity C-reactive protein; IL = Interleukin; Hu= Hounsfield units; TNF=Tumor Necrosis Factor; TLR-4=Toll-like receptor 4; Hu= Hounsfield units; METs= Metabolic Equivalents					

Conclusion: While muscle inflammation is not a recognized feature of RA and does not relate to insulin resistance, higher levels of muscle inflammatory cytokines were related to worse disease activity, disability, and pain, as well as less physical activity. MapK and NF-kB are both important transcription factors that may activate signaling cascades resulting in higher levels of mIL-6 in RA patients. Further analyses are ongoing to better understand the role of skeletal muscle inflammation in RA.

Disclosure: R. Jessee, None; **R. Narowski**, None; **M. Hubal**, None; **J. Huebner**, None; **V. Kraus**, None; **W. Kraus**, None; **K. Huffman**, None.

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Abstract Number: 2700

Trabecular Thinning in Metacarpophalangeal Joints of Anticitrullinated Peptide Antibody Positive Patients with Arthralgia

Kresten Krarup Keller[1], Jesper Skovhus Thomsen[2], Kristian Stengaard-Pedersen[1], Andreas Wiggers Nielsen[1], Berit Schiøtz-Christensen[3], Lone Svendsen[4], Merete Graakjær[5], Peter Mosborg Pedersen[6], Barbara Unger[7], Bente Langdahl[8] and Ellen-Margrethe

Hauge[1], [1]Rheumatology, Aarhus University Hospital, Aarhus, Denmark, [2]Aarhus University, Aarhus, Denmark, [3]Spine Centre of Southern Denmark, Middelfart, Denmark, [4]Private Practice in Rheumatology, Skanderborg, Denmark, [5]Clinic of Rheumatology Aarhus, Aarhus, Denmark, [6]Randers Hospital, Randers, Denmark, [7]Horsens Hospital, Horsens, Denmark, [8]Endocrinology, Aarhus University Hospital, Aarhus, Denmark
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Background/Purpose:

Rheumatoid arthritis (RA) is characterized by synovitis leading to bone erosions and joint destruction, but little is known about bone structure in the joints of patients before they are diagnosed with RA.

High Resolution peripheral Quantitative Computed Tomography (HR-pQCT) is a new imaging technique allowing detailed automatic evaluation of bone structure.

The aim was to quantify the cortical and trabecular bone structure in the metacarpophalangeal (MCP) joints of anticitrullinated peptide antibody (ACPA) positive patients with arthralgia and compare with healthy controls.

Methods:

Using a cross-sectional study design patients were recruited from local rheumatologists and controls from a website for test subjects. All individuals underwent medical history interview, clinical examination, and biochemical screening including ACPA. Patient inclusion criteria were positive ACPA and arthralgia. Exclusion criteria were fulfillment of the 2010 ACR/EULAR criteria for RA and other rheumatologic or metabolic bone diseases. Exclusion criteria for controls were known rheumatologic or metabolic bone disease, current or prior arthralgia, arthritis, and positive ACPA.

The right hand MCP joints were imaged with HR-pQCT using an isotropic voxel size of 82 µm.

A region of 1.2 cm located proximal to the articular surface of the MCP head was evaluated in the 2nd and 3rd finger using a semiautomatic program. Volumetric bone mineral density (vBMD), bone volume fraction (BV/TV), trabecular number (Tb.N), trabecular thickness (Tb.Th), trabecular separation (Tb.Sp), average cortical thickness (Ct.Th), and cortical area (Ct.Ar) were evaluated. Nine patients were rescanned after repositioning and the coefficient of variation (CV) was calculated. Values are mean(SD).

Results:

Twenty-six ACPA positive patients without clinical arthritis (age 50.4(13.8)) and 26 healthy controls (age 49.9(14.5)) were included. CV of the HR-pQCT parameters was 0.64–3.53%.

The overall bone density was similar in the groups since vBMD and BV/TV did not differ. In addition, the cortical bone was not affected in patients, as we found no difference in Ct.Th and Ct.Ar between the groups. In contrast, the trabeculae were significantly ($p <$ 0.05) thinner in both 2nd (87.7(9.7) µm vs 93.3(9.8) µm) and 3rd (83.7(9.7) µm vs 89.9(10.2) µm) MCP head compared with controls, whereas Tb.N and Tb.Sp did not differ.

Conclusion:

It has earlier been demonstrated that inflammation of the synovium and bone marrow is crucial for development of erosions in RA. In the present study we demonstrate that the trabecular thickness is affected very early, i.e. before the onset of clinical arthritis. Therefore, up-regulation of bone resorption in the bone marrow may be an early feature of RA. Bone loss before clinical RA warrants earlier diagnosis and treatment.

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Abstract Number: 2701

An Expansion of Rare Lineage Intestinal Microbes Characterize Rheumatoid

Arthritis

Jun Chen[1], John M. Davis III[2], Eric L. Matteson[3] and **Veena Taneja**[4], [1]Health Sciences Research, Mayo Clinic, Rochesert, MN, [2]Division of Rheumatology, Mayo Clinic, Rochester, MN, [3]Division of Rheumatology, Department of Internal Medicine and Department of Health Sciences Research, Mayo Clinic, Rochester, MN, [4]Immunology, Mayo Clinic, Rochester, MN

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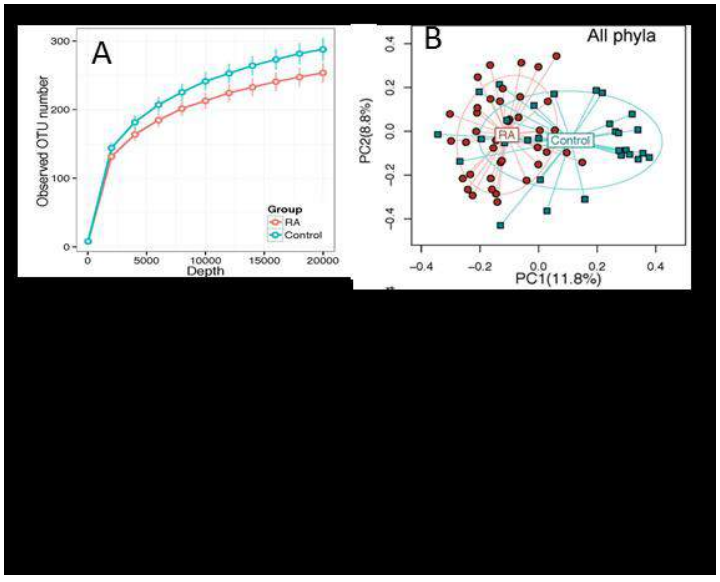
Background/Purpose: The adaptive immune response in Rheumatoid arthritis (RA) is influenced by an interaction between host genetics and environment, particularly the host microbiome. To define the role of host microbiome, we characterized intestinal microbiome signatures in patients with RA.

Methods: To identify an RA biomarker profile, fecal samples from 40 RA patients and 32 healthy non-RA comparator subjects were sequenced for the 16S ribosomal DNA. Bray-Curtis distances were constructed and PERMANOVA was used to test for an association between variables of interest and the overall microbiota composition. PICRUSt was used to infer the abundance of functional categories (KEGG pathways) based on the 16S rRNA data, depending upon which differential abundance analysis was performed. Differential abundance analysis was also performed using LEfSe software. The machine learning algorithm 'Random Forest' was used to build a predictive model, and identify the most discriminatory taxa between patients and controls.

Results: Patients with RA exhibited decreased gut microbial diversity compared to controls. Increased rheumatoid factor levels and disease duration were associated with decreased species richness and diversity ($P<0.05$ and $P<0.1$ respectively) (Fig 1A). PERMANOVA based on Bray-Curtis distance showed that the structure of the microbiota of patients with RA differed significantly from control subjects (Fig 1B). A taxon-level analysis suggested an expansion of the rare taxa, Actinobacteria, with a decrease in abundant taxa in patients with RA compared to controls. The abundance of Actinobacteria correlated strongly with high levels of IL-17A. Prediction models based on the Random Forests algorithm suggested that 3 genera segregated with RA. Increased abundance of Actinobacteria was associated with decrease in the expression of tight junction protein in epithelial cells and abundance of metabolite alpha aminoadipic, a marker for age-associated changes in collagen.

Conclusion: These observations suggest dysbiosis in patients with RA resulting from the abundance of certain rare bacterial lineages. A correlation between the intestinal microbiota and metabolic signatures could determine a predictive profile for disease causation, progression, and drug efficacy.



Disclosure: J. Chen, None; **J. M. Davis III**, None; **E. L. Matteson**, Novartis/Sanofi/Centocor-Jansen/Celgene/Amgen/Roche/Genentech/Mesoblast/Pfizer, 2; **V. Taneja**, None.

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Abstract Number: 2702

Immunophenotyping of Rheumatoid Arthritis Reveals the Linkage Between HLA-DRB1 Genotype, CXCR4 Expressions on Memory CD4+ T Cells, and Disease Activity

Yasuo Nagafuchi[1], Hirofumi Shoda[1], Shuji Sumitomo[1], Shinichiro Nakachi[1], Rika Kato[2], Yumi Tsuchida[2], Haruka Tsuchiya[2], Keiichi Sakurai[2], Norio Hanata[2], Shoko Tateishi[2], Hiroko Kanda[2], Keishi Fujio[1] and Kazuhiko Yamamoto[1], [1]Department of Allergy and Rheumatology, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan, [2]Graduate School of Medicine, The University of Tokyo, Tokyo, Japan

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Background/Purpose: The HLA-DRB1 is the strongest genetic risk factor for rheumatoid arthritis (RA). Although this fact suggests a pivotal role for adaptive immunity in RA, the linkage between HLA-DRB1 genotype and lymphocytes activation remains unclear.

Methods: We analyzed 91 HLA-DRB1 genotyped RA patients and 110 healthy donors by 24-subset immunophenotyping of peripheral blood mononuclear cells (PBMC) combined with CXCR4 expression analysis, HLA-DR quantification, and multiplex serum cytokine analysis. The correlation between these biomarkers and clinical parameters, such as the titer of anti-citrullinated peptide antibody (ACPA) and DAS28esr, was examined. 20 RA patients were analyzed at the initiation of CTLA4-Ig treatment and after 6-months of treatment. PBMC of healthy donors were cultured for 5 days with IL-21 and anti-HLA-DR antibody to assess CXCR4 expression on $CD4^+$ T cells.

Results: The frequency of CXCR4-expressing memory $CD4^+$ T cells, not that of classical Th1 or Th17 cells, was significantly associated with DAS28esr and the titer of ACPA. RA patients with susceptible haplotype of HLA-DR (shared epitope: SE) displayed significantly higher frequency of memory $CD4^+$ T cells and higher positivity for CXCR4 on memory $CD4^+$ T cells than healthy donors and RA patients without SE. Moreover, the frequency of CXCR4-expressing memory $CD4^+$ T cells displayed a significant correlation to the expression level of HLA-DR on B cells, which was elevated in RA patients with SE. In vitro experiments indicated that the increased CXCR4 expression on RA memory CD4+ T cells was dependent both on IL-21 and HLA-DR expression on antigen presenting cells. In clinic, higher frequency of CXCR4-expressing memory $CD4^+$ T cells predicted better therapeutic effects of CTLA4-Ig.

Conclusion: These findings demonstrate a potential contribution of HLA-DR on B cells to the development of memory $CD4^+$ T cells which is associated with disease activity. Identification of CXCR4 on memory T cells as a biomarker may promote the understanding of the linkage between genetic risk factor and adaptive immunity in RA.

Disclosure: Y. Nagafuchi, None; **H. Shoda**, None; **S. Sumitomo**, None; **S. Nakachi**, None; **R. Kato**, None; **Y. Tsuchida**, None; **H. Tsuchiya**, None; **K. Sakurai**, None; **N. Hanata**, None; **S. Tateishi**, None; **H. Kanda**, None; **K. Fujio**, Astellas, BMS, Daiichi-Sankyo, MitsubishiTanabe, Pfizer, Santen, Takeda, Chugai, Eisai, Taisho Toyama, UCB, and Janssen., 2; **K. Yamamoto**, UCB Pharma, Pfizer, Abbott, Santen, Mitsubish-Tanabe, Eisai, 2,UCB Pharma, Pfizer, Abbott, Bristol-Myers Squibb, Roche, Chugai, Mitsubish-Tanabe, Eisai, 5.

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Abstract Number: 2703

Reduction in Matrix Metalloproteinase-1 and -2 Secretion from Fibroblast-like Synoviocytes after Induction of Adipogenesis By a Natural Peroxisome Proliferator-Activated Receptor Gamma Ligand, Arterpilin-C

Eiji Sugiyama[1], Satoshi Yamasaki[1] and Je-Tae Woo[2,3], [1]Department of Clinical Immunology and Rheumatology, Hiroshima University Hospital, Hiroshima, Japan, [2]Department of Biological Chemistry, Chubu University, Aichi, Japan, [3]JT WOO, Okinawa Research

Center Co., Ltd, Okiawa, Japan
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Background/Purpose: Fibroblast-like synoviocytes (FLS) play important roles in rheumatoid arthritis (RA) by producing matrix metalloproteinase (MMP) and cytokines, and hence, these cells are a therapeutic target. Another unique characteristic of FLS is their ability to differentiate into mesenchymal multilineage cells, such as osteoblasts, chondrocytes, and adipocytes. Based on this characteristic, we proposed that the induction of adipogenesis in FLS would ameliorate RA activity by reducing cytokine and protease secretion from the cell. Thus, in this study, we treated FLS with plant-derived natural PPARγ ligands—arterpilin-C —to induce adipogenesis in FLS and evaluated the MMP secretion from FLS following adipogenesis induction.

Methods: The FLS derived from RA patients (Articular Engineering, USA) were maintained in Dulbecco's Modification of Eagles Medium with 10% fetal bovine serum. To induce adipogenesis via FLS, we added arterpilin-C to the culture medium in the presence or absence of dexamethasone. Lipid deposition in FLS was examined by using Oil red O or LipidTOX™ (Molecular Probes, USA) staining. To confirm adipogenic differentiation, we used anti-fatty acid binding protein 4 antibodies for immunostaining. A quantitative polymerase chain reaction using SYBR Green was performed to determine the expression levels of the transcripts.

Results: Droplets were observed in the cytoplasm of FLS after a 3-week culture with arterpilin-C (30 μM) in the presence of dexamethasone. Oil red O or LipidTOX staining confirmed adipogenesis by FLS. The expression of FABP4, an adipocyte-specific protein, was also noted in the cells with droplets by immunostaining. However, adipogenesis by arterpilin-C was achieved only in the presence of dexamethasone in a dose-dependent manner. The minimum dexamethasone concentration required for adipogenesis induction by arterpilin-C in FLS was 10^{-7} M. PPARγ protein expression was clearly enhanced in FLS treated with a dexamethasone concentration of 10^{-7}M. Moreover, the MMP1 and MMP2 mRNA expressions were lower in the FLS following adipogenesis induced by arterpilin-C, compared to the FLS treated only with dexamethasone.

Conclusion: These data suggest that the natural PPARγ ligands, arterpilin-C , can be used to induce adipogenesis in FLS. Importantly, the expressions of MMP1 and MMP2 were significantly reduced in FLS following adipogenesis induced by these natural PPARγ ligands. Since these proteinases are important in RA disease progression, induction of adipogenesis in FLS may contribute to inhibiting joint destruction in RA.

Disclosure: E. Sugiyama, Santen Pharmaceutical Co.,Ltd, Astellas Pharma Inc., Pfizer Inc., Chugai Pharmaceutical Co.,Ltd., AbbVie GK (AbbVie Godo Kaisha), TEIJIN PHARMA LIMITED., Mitsubishi Tanabe Pharma Corporation, Eisai. Co.,Ltd., Taisho Toyama Pharmaceutical Co.,Ltd., Kissei, 2; **S. Yamasaki**, Eli Lilly K.K., 2; **J. T. Woo**, JT WOO, Okinawa Research Center Co., Ltd, 4.

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Abstract Number: 2704

Neutrophil-Derived Lactoferrin Regulates the Activity of NFAT5 in Rheumatoid Arthritis Synovial Fibroblasts Via Toll-like Receptor 4

Kunihiko Umekita, Shunichi Miyauchi, Kazuyoshi Kubo, Hajime Nomura, Kazumi Umeki, Koushou Iwao, Mao Komura and Akihiko Okayama, Department of Rheumatology, Infectious Diseases and Laboratory Medicine, University of Miyazaki, Miyazaki, Japan
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Background/Purpose: Damage-associated molecular patterns (DAMPs) are proposed to drive aberrant stimulation of Toll-like receptors (TLRs) in the rheumatoid arthritis (RA) joints resulting in increased expression of proinflammatory cytokines and chemokines. In the current study we investigated the role of the neutrophil-derived lactoferrin (LTF), as an endogenous ligand for TLR4

in the inflammatory response of RA synovial fibroblasts (RASF).

Methods: Recombinant human neutrophil-derived LTF was purchased from Sigma. LTF solution was screened for lipopolysaccharide contamination before using. RASF were treated with LTF and/or TNFα, and the expression of proinflammatory cytokines in RASF was measured by real-time quantitative PCR and multi-cytokine assay system. The levels of phosphorylated p38 mitogen associated phosphokinase (MAPK) in RASF stimulated with LTF were determined by immune blotting. To repress the TLR4 signaling pathway, TAK243, a small molecular inhibitor of TLR4, was used. The role of the nuclear factor of activated T cells 5 (NFAT5) in the TLR4 signaling pathway in RASF was investigated using a small interfering RNA targeting NFAT5.

Results: Stimulation of RASF with LTF significantly increased the mRNA and protein expression of proinflammatory cytokines, such as IL-6, IL-8 and CCL20 ($p=0.01$). Furthermore, LTF enhanced the expression of IL-6, IL-8, and CCL20 mRNA in RASF stimulated by TNFα ($p=0.01$). The phosphorylation of p38MAPK increased in LTF-stimulated RASF. TAK243, the TLR4 inhibitor, repressed the expression of proinflammatory cytokines and chemokines in RASF stimulated by LTF. Silencing of NFAT5 significantly decreased the expression of proinflammatory cytokines and chemokines in RASF treated by LTF ($p= 0.01$).

Conclusion: This is the first study to demonstrate that LTF can induce the proinflammatory response in RASF mediated by TLR4 and the activation of NFAT5. Neutrophil derived LTF is is an endogenous ligand for TLR4 in RASF. The activity of NFAT5 is important in the inflammatory response of RASF induced by LTF via TLR4.

Disclosure: K. Umekita, None; **S. Miyauchi**, None; **K. Kubo**, None; **H. Nomura**, None; **K. Umeki**, None; **K. Iwao**, None; **M. Komura**, None; **A. Okayama**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/neutrophil-derived-lactoferrin-regulates-the-activity-of-nfat5-in-rheumatoid-arthritis-synovial-fibroblasts-via-toll-like-receptor-4

Abstract Number: 2705

AAA-Atpase p97-HDAC6 Controlled Poly-Ubiquitin Turnover Regulates Apoptotic and Autophagy-Associated Cell Death in Arthritis

Masaru Kato[1], Kerstin Klein[2], Caroline Ospelt[2], Christoph Kolling[3], Michihito Kono[1], Shinsuke Yasuda[1], Renate E. Gay[4], Steffen Gay[5] and Tatsuya Atsumi[1], [1]Division of Rheumatology, Endocrinology and Nephrology, Hokkaido University Graduate School of Medicine, Sapporo, Japan, [2]Center of Experimental Rheumatology, University Hospital Zurich, Zurich, Switzerland, [3]Schulthess Clinic, Zurich, Switzerland, [4]Center of Experimental Rheumatology, University Hospital Zurich, Switzerland, Zurich, Switzerland, [5]Center of Experimental Rheumatology, University Hospital Zurich, University Zurich, Zurich, Switzerland

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Background/Purpose: The AAA-ATPase valosin containing protein (p97) and histone deacetylase 6 (HDAC6) interact with each other and are implicated in the degradation of ubiquitin-labelled proteins. We recently described a resistance to apoptotic cell death induced by proteasome inhibition and a hypersensitivity to autophagy-associated cell death under conditions of severe endoplasmic reticulum (ER) stress in rheumatoid arthritis synovial fibroblasts (RASF) compared to osteoarthritis synovial fibroblasts (OASF). The objective of this study was to investigate the role of p97-HDAC6 controlled poly-ubiquitin turnover in apoptotic and autophagy-associated cell death in RASF and in an *in vivo* arthritis model.

Methods: p97, HDAC6 and poly-ubiquitinated proteins were evaluated by immunohistochemistry, Real-time PCR, immunoblotting and proximal ligation assay. RASF were transfected with siRNA targeting p97 or HDAC6 or treated with the selective p97 inhibitor DBeQ (5 μM). To induce cell death, RASF were treated with TRAIL (100 ng/ml) for 24 hours or the ER stress inducer thapsigargin (TG, 5 nM-5 μM) for 72 hours. 3-methyladenine (5 mM) was used as an autophagy inhibitor. Cell death was evaluated by flow cytometry using annexin V/ propidium iodide staining and a caspase-3 activity assay. Collagen-induced arthritis (CIA) was induced in Lewis rats. Scrambled or p97 siRNA-atelocollagen complexes were injected into ankle joints of rats. CIA was scored according to paw thickness and ankle diameter. Bone erosion was assessed by micro-CT. Proliferation of fibroblasts in rat synovial tissue was quantified by immunolabeling for Hsp47.

Results: The expression of p97 and the expression of HDAC6 were restricted to the lining layer of synovial tissues and were similarly detected in RA and OA patients. The expression of p97 in RASF and OASF was positively related with the expression of HDAC6 at both mRNA ($R^2 = 0.77$, $n = 31$) and protein ($R^2 = 0.77$, $n = 14$) level. Interactions of p97-ubiquitin, HDAC6-ubiquitin and p97-HDAC6

were detected in RASF. The siRNA-mediated knockdown of p97 in RASF decreased the expression of HDAC6 but not vice versa. Knockdown of p97 in RASF increased cell death induced by TRAIL ($p = 0.009$, $n = 6$), accompanied by caspase-3 activation. Both knockdown and inhibition of p97 in RASF boosted cell death induced by 5 μM TG, accompanied by a massive cytoplasmic vacuolization and the formation of poly-ubiquitinated protein aggregates, and cell death was inhibited by 3-methyladenine. Smaller amounts of TG (50 or 500 nM) induced a cytoplasmic vacuolization and the formation of poly-ubiquitinated protein aggregates in p97-inhibited RASF but not in control RASF. Intra-articular injection of p97 siRNA significantly suppressed CIA ($p = 0.002$, $n = 6$), bone erosion ($p = 0.02$), cartilage destruction ($p = 0.03$) and proliferation of synovial fibroblasts ($p = 0.004$) in rats.

Conclusion: Our data indicate that the inhibition of the ATPase p97 promotes both apoptotic and autophagy-associated cell death in RASF and suppresses CIA and proliferation of synovial fibroblasts *in vivo*. The p97-HDAC6 controlled poly-ubiquitin turnover may be a new potential target in the treatment of arthritis.

Disclosure: M. Kato, None; **K. Klein**, None; **C. Ospelt**, None; **C. Kolling**, None; **M. Kono**, None; **S. Yasuda**, None; **R. E. Gay**, None; **S. Gay**, None; **T. Atsumi**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/aaa-atpase-p97-hdac6-controlled-poly-ubiquitin-turnover-regulates-apoptotic-and-autophagy-associated-cell-death-in-arthritis

Abstract Number: 2706

3D Location of Erosions in an Early Rheumatoid Arthritis Population: An MRI Study Using Statistical Shape Models with Implications for Pathogenesis

Michael A. Bowes[1], Gwenael Guillard[1], Z. Xie[2], Bethanie Wilkinson[2] and Philip G. Conaghan[3], [1]Imorphics, Manchester, United Kingdom, [2]Pfizer Inc, Groton, CT, [3]University of Leeds & NIHR Leeds Musculoskeletal Biomedical Research Unit, Leeds, United Kingdom

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Background/Purpose: Concepts of erosion pathogenesis in rheumatoid arthritis (RA) have been based on radiographs, although MR images are much better able to visualise erosions. Statistical shape models (SSM) allows bones and erosions to be aligned, correcting for size and patient shape, allowing the 3D study of systematic effects. This study employed SSMs to visualise the spatial distribution of erosions, and their probability of arising at a particular location, in a population of early RA patients.

Methods: 90 baseline MR images were selected at random from an exploratory Phase 2 multicentre study (NCT01164579). Inclusion criteria were as follows: MTX-naïve adult patients with early RA (duration ≤ 2 years); diagnosis using ACR criteria, unequivocal evidence of radiographic erosion, and clinical evidence of synovitis. 7 images were not analysed due to image quality.

Bones and erosions were manually segmented and independently reviewed. 3D bone and erosion surfaces were generated, and rigidly warped to the mean bone shape. A population image was created; containing the number of times that each voxel was found within an erosion. Voxels which were present in >2 erosions were displayed along with the mean bones. (Figure 1)

Results: Erosions were present in low numbers of patients. In 18 patients there were no erosions visible in MR despite reported radiographic erosions. Over half had only 0 to 2 bones with an erosion. Erosions exhibited a clear spatial pattern. In the metacarpals, the erosions were most prevalent in MCP2 and 3 (Table 2). In the wrist, there were typically 20 erosions per bone for half of the bones; the trapezium, trapezoid and proximal metacarpals had ~10. Erosions occurred at consistent sites, with only one or 2 sites within each bone where the erosion was found in >2 patients.

Conclusion: This is the first study to provide an accurate 3D visualisation of erosion sites in early RA. Erosions occurred at only a small number of entheseal sites. Erosions in the metacarpals occurred in the area containing the collateral ligament and capsular attachments. In the wrist, the erosions were located primarily on the palmar side of the bone, and had a more complex arrangement. Although multiple ligament, capsular and tendon attachments exist in close proximity on each bone, we observed that erosion sites were usually those in which there was a deep attachment site in non-eroded patients. This suggests that the attachments which will generate an erosion are those which experience the highest mechanical load. Further careful study will be required to pursue the detail of these anatomical locations, and will significantly help our understanding of the pathogenesis of RA erosions.

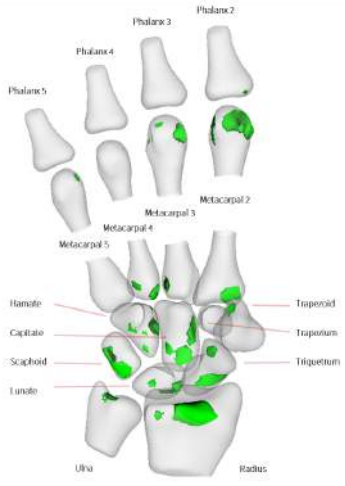

Figure 1: Erosions occurring in more than 2 patients

Mean bone surfaces are shown as partly transparent, viewed from the palmar direction. Maximum numbers of erosions for each bone are provided in Table 1

Bone	Number of erosions
MCP	
Phalanx 2	6
Phalanx 3	2
Phalanx 4	1
Phalanx 5	1
Metacarpal 2	31
Metacarpal 3	26
Metacarpal 4	8
Metacarpal 5	17
WRIST	
Metacarpal 2	13
Metacarpal 3	11
Metacarpal 4	10
Metacarpal 5	2
Hamate	18
Capitate	29
Trapezium	11
Trapezoid	12
Scaphoid	21
Lunate	21
Triquetrum	23
Radius	24

Table 1: Number of erosions by bone

Disclosure: M. A. Bowes, None; **G. Guillard**, None; **Z. Xie**, None; **B. Wilkinson**, Pfizer Inc, 1,Pfizer Inc, 3; **P. G. Conaghan**, Abbvie, BMS, Novartis Non-remunerative, 5,Abbvie, BMS, Janssen, Roche, 8.

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Abstract Number: 2707

An in Vitro Bovine Bone Chip Model with Micro-CT: A Model for the Assessment of Autoantibody Mediated Bone Resorption

Manpreet Kaur Sethi[1], Anand Dusad[1], Andy Hollins[2], Carlos D. Hunter[3], Michael J. Duryee[3], Ted R. Mikuls[2], Geoffrey M. Thiele[4] and Ellen M. Gravallese[5], [1]Rheumatology, University of Nebraska Medical Center, Omaha, NE, [2]University of Nebraska Medical Center, Omaha, NE, [3]Internal Medicine Division of Rheumatology, University of Nebraska Medical Center, Omaha, NE, [4]Omaha VA Medical Center and University of Nebraska Medical Center, Omaha, NE, [5]Lazare Research Bldg Ste 223, University of Massachusetts Medical School, Worcester, MA

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Background/Purpose: Anti-citrullinated protein antibodies (ACPAs) are specific to rheumatoid arthritis (RA) and are associated with disease severity. Although ACPAs are associated with disease progression, mechanisms driving this relationship are not well understood. The objective of this study was develop an *in vitro* model incorporating bovine bone chips and micro-CT (μ-CT) to investigate the effects of ACPA on bone remodeling.

Methods: PBMCs were isolated from the blood of normal controls. Osteoclasts (OCs) were generated by culture in α-MEM media containing 1% penicillin/streptomycin and 10% heat inactivated FBS along with RANKL (1 ng/ml) and MCSF (10 ng/ml) for 14 days. Sera from ACPA positive RA patients was obtained and IgG was isolated using Staph Protein G columns. Antibody to citrullinated type II human collagen (Cit-C-II) was purified using CNBR Sepharose beads coupled with Cit-C-II. F(ab')2 and Fc fragments were generated using pepsin columns and were added to differentiated OCs in the presence and absence of C-II and Cit-C-II and incubated with bone chips for 3 days (n=3 chips/group). Bone chips were then scanned with μ-CT for bone mineral density (BMD) and pit volume (PV). Bone specific alkaline phosphatase (BAP) and cathepsin-K (CTPK) were measured on media using ELISA. BAP/CTPK ratios served as the primary measure of bone turnover.

Results: Activated OCs in the absence of ACPA increased PV and decreased BMD (Figure), although these differences did not reach

significance. Compared to OCs stimulated with F(ab')2 + C-II + Cit-C-II, the substitution of Fc fragments for F(ab')2 led to significant increases in BAP (4.24 vs. 1.89 ng/ml, p=0.006) and CTPK (7.07 vs. 2.83 ng/ml, p = 0.011); BAP/CTPK ratio was higher, but not significantly, in OCs incubated simultaneously with Fc and F(ab')2 antibodies along with C-II and Cit-C-II as compared to OCs alone (Figure; p= 0.181 and p= 0.071, respectively). Across groups, BAP values were positively correlated with PV (r= 0.52, p=0.015). Addition of the F(ab')2 or Fc fragments led to a numeric increase in PV and decreased BMD, although differences compared to OCs alone did not reach significance.

Conclusion: The differential effects of Fc and F(ab')2 fragments of anti-Cit-C-II antibody along C-II and Cit-C-II antigens suggests that the action on bone could be mediated by both the type of antibody fragments and the amount and type of antigen present. Additional studies with a larger number of samples will be needed to perform more robust statistical comparisons including the evaluation of alternative doses and different ACPA. This novel model, incorporating bovine bone chips with µ-CT, appears to be a practical and reproducible approach for studying the osteoimmunology of ACPA and citrullinated antigens.

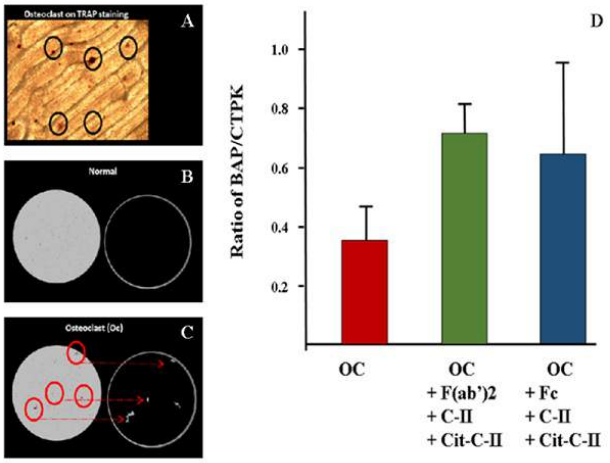

Figure: A) OCs detected on bovine bone chip; TRAP staining; B) normal bone chip by µ-CT; C) bone chip with OCs resulting in decreased BMD (p= 0.163) and increased PV (p= 0.096); and D) Increased BAP/CTPK ratios in OCs vs. OCs + F(ab')2 + C-II + Cit-C-II (p=0.071) vs. OCs + Fc + C-II + Cit-C-II (p=0.181).

Disclosure: M. K. Sethi, None; **A. Dusad**, None; **A. Hollins**, None; **C. D. Hunter**, None; **M. J. Duryee**, None; **T. R. Mikuls**, None; **G. M. Thiele**, None; **E. M. Gravallese**, None.

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Abstract Number: 2708

Correlation of Peripheral Blood Th-17 and Th-1 with Synovitis and Osteitis By MRI in Recent Onset Rheumatoid Arthritis

Sukesh Edavalath[1], Ankita Singh[1], Namita Mohindra[2], Sunil Kumar[2] and Ramnath Misra[1], [1]Clinical Immunology, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, India, [2]Radiodiagnosis, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, India

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Background/Purpose: An increased expansion of Th17 cells in the synovial membrane have shown to play a key role in causing persistent synovitis leading to cartilage and bone destruction in RA. MRI is superior to conventional X-rays in detecting erosions in early disease. In this study we sought to see the association of level of peripheral circulatory Th-17 and Th-1 cells with MRI changes in RA

Methods:

RA patients satisfying ACR Criteria 2010 with active disease (DAS28 >3.2) and within 3 years of onset who had not received prior DMARDs or steroids were recruited. MRI of dominant hand and wrist was done using 0.2 Tesla extremity MRI and was scored using OMERACT RA MRI Scoring system 2002 by two radiologists. Peripheral blood Th1 (CD3+ CD4+ IFNγ +) and Th17 (CD3+ CD4+ IL17+) were enumerated by flow cytometry. Th-1and Th-17 levels were measured in 25 healthy controls. Statistical analysis was done by non-parametric tests using SPSS statistics 21version software.

Results:

Thirty-two consecutive patients (26 females and 6 males) with RA after obtaining consent were included. The median age at presentation was 38.5 years (Range 19 – 65 years) with median disease duration of 11.5 months (Range 1-36 months). The median DAS 28 score was 4.35 (Range 3.22 – 6.24). All the patients were seropositive. MRI evaluation revealed synovitis in 93.8%(30/32), Osteitis in 31.3%(10/32) and erosions in 75% (24/32) of patients. On subgroup analysis erosions were present in 67% (12 /18) of cases of early (≤ 1year) RA and in 86% (12/14) of established (> 1 year) RA. OMERACT RA MRI scoring revealed a significantly ($p<0.05$) higher erosion score (17.8 ± 19.9) in established RA compared to early RA (5.4 ± 11.4) whereas synovitis and osteitis were similar in both groups. Synovitis score showed modest correlation with ESR (r= 0.43, p =0.02), CRP(r= 0.38, p =0.03), and DAS28 (r= 0.43, p =0.02), while osteitis and erosion score did not correlate with the same.Percentage of Th17 cells in serum were significantly ($p<0.05$) elevated in patients (1.57 ± 0.69) compared to healthy controls (0.84 ± 0.45) while Th1 cells did not differ between the groups. However, the increased frequency of Th17 cells did not show any correlation with acute phase reactants, DAS28 score and MRI proven synovitis or osteitis.

Conclusion: Peripheral blood Th17 subset was significantly elevated in patients with RA, though they did not correlate with the synovitis, osteitis or erosions in MRI.

Disclosure: S. Edavalath, None; **A. Singh**, None; **N. Mohindra**, None; **S. Kumar**, None; **R. Misra**, None.

Abstract Number: 2709

Immediate Release of Peripheral Neutrophil Myeloperoxidase and Elastase and Formation of Extracellular Traps to Cigarette Smoking in Rheumatoid Arthritis

Juliane Franz[1], Stavros Giaglis[1,2], Guenther Schaefer[3], Erik Deman[1], Andreas Thueler[4], Sinuhe Hahn[2] and **Paul Hasler**[1],
[1]Rheumatology, Kantonsspital Aarau, Aarau, Switzerland, [2]Biomedicine, Laboratory of Prenatal Medicine, University Hospital Basel, Basel, Switzerland, [3]Dept. of Biomedicine, Laboratory of Prenatal Medicine, University Hospital Basel, Basel, Switzerland, [4]Rheumatology, Kantonsspital Baden, Baden, Switzerland

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Background/Purpose:

Smoking represents an independent risk factor for rheumatoid arthritis (RA) (1). In response to infectious agents, neutrophil granulocytes can extrude their nuclear contents as nucleoprotein threads, known as neutrophil extracellular traps (NETs) (4). Recently, it has been shown that RA neutrophils show a vastly greater propensity to form NETs than those from normal controls (2,3). Since NETs are pro-inflammatory and immuno-stimulatory, and neutrophils show increased activity in inflammatory lung conditions, we investigated the responsiveness of peripheral blood neutrophils in RA and controls to cigarette smoke exposure.

Methods:

Regular smokers without (n=8) and with (n=6) RA were examined at baseline and after a 16 hour abstinence from smoking. Then they smoked two cigarettes within 10 min and measurements were repeated at 30, 60 and 120 min. Parameters measured were exhaled carbon monoxide (CO), myeloperoxidase (MPO), neutrophil elastase (NE) and cell free nucleosomes by ELISA. Routine laboratory tests included blood counts, CRP, BSR and clotting parameters. In addition, neutrophils from healthy donors were incubated with cigarette smoke extract (CSE) for assessing NET formation by SytoxGreen extracellular DNA staining and combined immunohistochemistry (ICH) with anti-MPO, anti-cit-H3 and DAPI.

Results:

RA smokers started from higher baseline CO levels, but showed similar courses as the controls after re-exposure to cigarette smoke. They exhibited higher baseline MPO, NE and nucleosomes compared to controls. Re-exposure caused a pronounced increase of peripheral blood leucocytes and neutrophils in RA smokers compared to controls. No changes were observed concerning parameters of inflammation and clotting.

Re-exposure of RA patients to cigarette smoke led to a 3- fold rise of MPO und NE at 30 minutes after exposure and a subsequent gradual reduction of serum levels up to 120 min. Unexpectedly, this was paralleled by a sharp reduction in circulatory cell free nucleosomes with a decrease to the baseline at 120 min.

Freshly isolated control neutrophils showed diminished PMA-driven NET release in vitro after 3 hours of treatment with CSE. This was confirmed by MPO and citrullinated H3 ICH and morphometric analysis. Activated neutrophils with a delobulated citH3 positive nuclear phenotype were also remarkably higher in CSE-treated neutrophils.

Conclusion:

RA smokers show increased peripheral blood markers of neutrophil pre-activation compared to non-RA smokers. Cigarette smoking causes a rapid increase of MPO and NE, indicating the systemic release of neutrophil granular contents, and a rapid concomitant decrease of cell free nucleosomes. This is paralleled by the in vitro reduction of CSE-induced NET formation. Our findings provide evidence that cigarette smoking in RA patients provokes the immediate release of toxic neutrophil granular enzymes into the circulation and that NET formation is transiently reduced in the immediate aftermath of smoke inhalation.

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Abstract Number: 2710

Necrox-7 Inhibits Cell Aggressiveness By Suppressing of NF-Kappa B Activation and Reactive Oxygen Species Generation in Human Rheumatoid Arthritis Fibroblast-like Synoviocytes

Hyun Jung Yoo[1,2], Jin Kyun Park[2], Eun Young Lee[2], Eun Bong Lee[2] and Yeong Wook Song[2,3], [1]Department of Molecular Medicine and Biopharmaceutical Sciences, BK21 plus Graduate School of Convergence Science and Technology, and College of Medicine or College of Pharmacy, Seoul National University, Seoul, South Korea, [2]Division of Rheumatology, Department of Internal Medicine, Seoul National University Hospital, Seoul, South Korea, [3]Department of Molecular Medicine and Biopharmaceutical Sciences, Graduate School of Convergence Science and Technology and College of Medicine Seoul National University, Seoul, South Korea

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Background/Purpose: Rheumatoid arthritis (RA) is characterized by hyperplastic synovial pannus tissue, which mediates destruction of cartilage and bone. Fibroblast-like synoviocytes (FLS) are a key component of the invasive pannus and have a major role in the initiation and perpetuation of destructive joint inflammation. NecroX-7 is a small chemical compound that exhibits cytoprotective effects and anti-oxidant activity. We investigated the inhibitory effects of NecroX-7 on the aggressiveness of TNF-α stimulated RA-FLS.

Methods: RA-FLS were cultured from synovial specimens obtained from RA patients undergoing joint replacement therapy. The cell viability was determined using CCK-8 colorimetric assay. The wound healing and transwell migration assay were performed to evaluate the effects of NecroX-7 on the migration of RA-FLS. Intracellular reactive oxygen species (ROS) generation was assessed by fluorometric assay. Matrix metalloproteinase-2 (MMP-2) and MMP-9 activity was measured using gelatin zymography. The expression of p-ERK1/2, p-p38, p-JNK and p-IκB was detected by Western blot analysis. The location of NF-κB p65 in RA-FLS was detected by immunofluorescence microscope.

Results: NecroX-7 had no significant cytotoxicity and inhibited migration of RA-FLS activated by TNF-α *in vitro*. NecroX-7 suppressed TNF-α-induced NF-κB activation by inhibiting ERK1/2 phosphorylation and IκB degradation and it prevented the nuclear translocation of NF-κB p65 with subsequent decrease in synthesis of MMP-2 and MMP-9. NecroX-7 reduced the generation of intracellular ROS (hydrogen peroxide, mitochondrial superoxide, cytosolic superoxide and peroxynitrite) in TNF-α-treated RA-FLS.

Conclusion: NecroX-7 reduces activities of MMP-2 and MMP-9 via inhibition of NF-κB signaling pathway and intracellular ROS formation in activated RA-FLS, suggesting that NecroX-7 might suppress the aggressiveness of RA-FLS *in vivo*. NecroX-7 may provide a new therapeutic option in treatment of RA.

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The Lung Microbiome in Rheumatoid Arthritis and Associated Local/Systemic Autoimmunity

Jose U. Scher[1], Vijay Joshua[2], Carles Ubeda[3], Alejandro Artacho[3], Leopoldo Segal[4] and Anca I Catrina[5], [1]Department of Medicine, Division of Rheumatology, New York University School of Medicine, New York, NY, [2]Cmm L8:04, Karolinska Institutet, Stockholm, Sweden, [3]Institute for Research in Public Health, Valencia, Spain, [4]Medicine, Pulmonay Division, NYU School of Medicine, New York City, NY, [5]Department of Medicine, Solna, Unit of Rheumatology, Karolinska University Hospital, Karolinska Institutet, Stockholm, Sweden

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Background/Purpose: Rheumatoid arthritis (RA) is a complex autoimmune disorder in which several genetic and environmental factors play a role. Recent data suggest that the gut and oral microbiome might potentially contribute to the priming of an aberrant systemic immune response characteristic of RA. Among studied microbiota, both *Porphyromonas gingivalis* in the oral cavity and *Prevotella copri* in the gut have been implicated. Intriguingly, airway abnormalities and increased lung tissue citrullination is found in both RA patients and individuals at at-risk for the development of disease. This suggests the possibility that the lung could be yet another site of autoimmunity generation in RA. Our objective was to study whether the RA lung microbiome contains distinct taxonomic features associated with local and/or systemic autoimmunity.

Methods: Bronchoalveolar lavage (BAL) samples from 20 subjects with RA, 10 with sarcoidosis and 24 healthy controls were obtained by research bronchoscopy. 16S rDNA sequencing was performed to define microbiota composition. Levels of arginine/citrulline were measured in BAL fluid using GC-MS for all samples. Autoantibodies, including anti-CCP, RF and ACPAs were also measured in BAL and sera of RA subjects. Statistical analysis was performed using wilcoxon test and Spearman correlation.

Results: There were no differences in demographic or clinical characteristics (including smoking status) between groups. 16S sequencing data showed similar alpha/beta diversity between RA and DC groups, but significantly different from controls. Taxonomic comparison between groups was performed using LEfSe, which revealed several significant differences (LDA score>2). Multiple taxa, including *Rhanella* and *Rhodanobacter* were present only in the RA and DC groups, but completely absent from healthy subjects ($p<0.001$). While RA BAL samples were enriched with *Sphingobacteria*, sarcoidosis BAL was enriched with *Bacteroidia*, *Rhizobiales*, *Nitrospirales*, and *Campylobacter*. GC-MS showed similar levels of arginine and citrulline in BAL for the sarcoidosis and RA groups. Raoultella and Barnesiella correlated with CCP2 levels in BAL (rho= 0.49 and 0.47; p-value= 0.026 and 0.032 respectively). Serum levels of CCP-IgA had a negative correlation with Massilia and Tannerella (rho= -0.63 and 0.53; p-value 0.003

and 0.016, respectively), and a positive correlation with Vagococcus and Lactobacillus (rho= 0.59 and 0.54; p-value 0.006 and 0.014, respectively). Unclas_Lactobacillales also had a positive correlation with serum levels of RF-IgA (rho= 0.71; p-value <0.001). Serum levels of anti-CCP2 antibodies had a positive correlation with *Porphyromonas*, *Rahnella* and *Chryseobacterium*(rho=0.46, 0.46 and 0.45; p-value= 0.03, 0.03 and 0.04 respectively).

Conclusion: Despite the relatively small number of samples analyzed, several taxonomic differences were noted between groups. Correlations between relative abundance of specific taxa in RA BAL with serum autoantibodies (i.e., anti-CCP) support an association between the lung microbiome and the host immune phenotype in RA. Further evaluation of functional aspects of this microbiome may provide further insights into its possible contribution to RA.

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Abstract Number: 2712

Intracellular O-Glc-Nac Alterations in Mononuclear Blood Cell of Rheumatoid Arthritis Patients

Jose Luis Montiel Hernandez[1,2], **Daniel Xibille-Friedmann**[3], Gerardo-Jossue Contis-Corrales[1], Maritza-E. Castillo-Gregorio[1], Carolina Bustos-Rivera Bahena[4] and Donaji Domínguez-Zuñiga[5], [1]Faculty of Pharmacy, Universidad Autonoma del Estado de Morelos, Cuernavaca, Mexico, [2]Cytokines and Autoimmunity Laboratory, Faculty of Pharmacy, Universidad Autónoma del Estado de Morelos, Cuernavaca, Mexico, [3]Rheumatology, Hospital General de Cuernavaca, Cuernavaca, Mexico, [4]Universidad Autonoma del Estado de Morelos, Instituto de Dinamica Celular, Cuernavaca, Mexico, [5]Faculty of Medicine, Universidad Autonoma del Estado de Morelos, Cuernavaca, Mexico

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Background/Purpose: Although it has been traditionally assumed that most glycosylation occurs on membrane or secreted proteins and lipids, it is well known that cytoplasmic or even nuclear proteins can be glycosylated, through an O-GlcNAc (O-linked β-N-acetylglucosamine) modification coupled to Ser or Thr residues. Its evaluation in diseases such as cancer or metabolic syndrome has led to the suggestion that they play an active role both in cell metabolism, intracellular signaling and transcription regulation. However, there are still no studies comparing the level of O-GlcNAc between Rheumatoid Arthritis (RA) patients and healthy donors. To compare the levels of O-GlcNAc in the cytoplasm of peripheral blood mononuclear cells (PBMC) of healthy donors and patients with RA, as well as its possible relationship with clinical parameters.

Methods: Patients were evaluated at the Hospital General de Cuernavaca, SSM. RA disease activity was evaluated through DAS28. The donor blood samples were obtained from the sate blood bank. After isolating the PBMC (Ficoll Hypaque), cytosolic proteins were recovered, in the presence of protease inhibitors. Levels of O-GlcNAc were evaluated using Western blot, employing a specific LR2 antibody. The levels of O-GlcNAc transferase (OGT) and O-GlcNAcase (OGA) expression, responsible for the addition and elimination of the GlcNAc group, were evaluated in parallel. Differences between groups were evaluated using Student's t and Mann Whitney's test and their correlation with DAS28 was evaluated using Spearman's test.

Results: 21 patients with RA and 20 healthy donors were included. A global comparison showed that patients had significantly less immunoreactivity than donors. The glycosylation pattern was clearly different in patients compared to donors, where the 73 and 112 kDa glycoproteins seem to be exclusive of RA patients. These results were consistent with a greater OGT/OGA balance in donors with respect to patients. On the other hand, levels of O-GlcNAc showed a significant negative correlation with DAS28 (rho=-0.579, p<0.008).

Conclusion: The results seem to suggest that patients with RA present a reduced ratio of OGT:OGA expression, as well as less O-GlcNAc glycosylation, compared to donors. The relationship between the levels of O-GlcNAc and DAS28 suggests that this glycosylation patterns could reflect a functional state of PBMC in patients with RA. Study financed by CB-2010-2#155392 (CONACyT).

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Abstract Number: 2713

A Novel Paradigm in the Clinical Context of Rheumatoid Arthritis: Role of Tfh and Th17 Cells in Autoimmunity

Magdalena Budziakowska[1], Arif Shahzad[1], Jerry Pounds[1], Shikha Singla[1], Jerald M. Zakem[1,2], Kismet Collins[1], Tamika Webb-Detiege[1], William E. Davis[1,2], Zongbing You[3], Robert Quinet[1,2] and Xin Zhang[4], [1]Rheumatology, Ochsner Medical Center, New Orleans, LA, [2]University of Queensland School of Medicine, Brisbane, Australia, [3]Tulane University Health Science Center, New Orleans, LA, [4]Laboratory of Cellular Immunology, Institution of Translational Research, Ochsner Medical Center, New Orleans, LA
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Background/Purpose:

Rheumatoid Arthritis (RA) is an autoimmune disease characterized by chronic inflammation of synovium, which causes progressive joint destruction and reduction in quality of life for patients. The Th1/Th2 paradigm is a model for the induction and regulation of immune responses. Th1 cells participate in cell-mediated immunity whereas Th2 cells support humoral immunity. Recently, Tfh and Th17 cells have emerged as the novel T cell subsets controlling autoimmunity. Identifying their roles may break the Th1/Th2 axis dichotomy, bridge the knowledge gap of T cell lineages on RA immunopathogenesis, and lead to novel therapeutic approaches for RA patients. We examined the frequency of Tfh and Th17 cells in RA patients, and investigated their correlation with disease activity, autoantibody levels, and inflammation.

Methods:

Peripheral blood was collected from 51 RA patients meeting 2010 ACR/EULAR RA classification criteria and 51 age-/gender-matched healthy donors. Clinical disease activity was quantified using the Disease Activity Score in 28 joints (DAS-28). RA patients were divided into remission (DAS-28<2.6) and active disease groups (DAS-28>2.6) based on their DAS-28. Serum laboratory measurements including Rheumatoid Factor (RF), Anti-cyclic Citrullinated Peptide antibody (anti-CCP), Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) were obtained. The frequency of Tfh cells ($CD4^+CXCR5^+ICOS^+$ $PD\text{-}1^+$) and Th17 cells ($CD4^+CCR4^+CCR6^+$) were measured by flow cytometry and analyzed by sequential gating. The plasmablasts ($CD20^{lo}CD38^+CD138^-$) in the peripheral blood were measured by flow cytometry. Correlation of the frequency of circulating Tfh cells and Th17 cells with DAS-28, plasmablasts, and laboratory parameters were statistically determined.

Results:

Both circulating Tfh cells ($CD4^+CXCR5^+ICOS^+$ $PD\text{-}1^+$) and Th17 cells ($CD4^+CCR4^+CCR6^+$) were significantly increased in RA patients, expecially in moderate/severe patients ($p<0.05$), comparing to healthy donors. The frequency of circulating Tfh cells correlated with the percentage of plasmablasts and the level of pathogenic anti-CCP antibody, whereas the frequency of circulating Th17 cells correlated with the serum level of RF and CRP as well as DAS-28.

Conclusion:

Our data suggests that Tfh and Th17 cells may play different roles in RA pathogenesis. Tfh cells may contribute to B cell differentiation and autoantibody production, while Th17 cells may be involved in the inflamation and pathogenesis of RA. Thus, disrupting the signals provided by Tfh and Th17 cells may offer new therapeutic stategies for severe RA patients and shift their immune system toward homeostasis.

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Abstract Number: 2714

Rheumatoid Arthritis Synovial Fibroblast Potentiates Mast Cell Degranulation and Migration Independent of Cell-to-Cell Contact

Hee-suk Lim[1], Jiyong Choi[2,3], Yeong Wook Song[4] and Kichul Shin[1], [1]Division of Rheumatology, Department of Internal Medicine, Seoul Metropolitan Government-Seoul National University Boramae Medical Center, Seoul, South Korea, [2]Division of Rheumatology, Department of Internal Medicine, Seoul National University Hospital, Seoul, South Korea, [3]Department of Internal Medicine, Seoul National University College of Medicine, Seoul, South Korea, [4]Division of Rheumatology, Department of Internal Medicine, Seoul National University College of Medicine, Seoul, South Korea

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Background/Purpose:

A number of studies have shown that synovial mast cells (MCs) are activated, and elicit a pro-inflammatory role in rheumatoid arthritis (RA). Synovial MCs are located around the microvasculature, but also adjacent to the synovial lining and subsynovium where synovial fibroblasts (SFs) reside. Despite that mediators produced by MCs have been demonstrated to activate SF, the effector function of SF on MC activation is not well known.

Methods:

In vitro SF cultures were obtained from knee synovium of RA patients. Co-culture of SF ($2.5x10^4$ cells) and human mast cell (HMC)-1 line was done with IMEM phenol red free media including 10% fetal bovine serum in a 24 well plate. We used the b-hexosaminidase (HXSA) assay as the readout for MC degranulation (1, 6, 12, 24 hours) after direct/indirect co-culture or PMA/ionomycin treatment. HMC-1 was treated with SF conditioned medium (SFCM) to study migration, cytoskeletal rearrangement, proliferation, and degranulation. Antibody based proteins array was utilized to assay cytokines increased after SF/HMC-1 co-cultures.

Results:

Indirect, as well as direct co-culture of SF/HMC-1 showed significantly increased activity of b-HXSA compared with controls. HMC-1 primed in SFCM for 48 hours burst out 3.6 times of b-HXSA activity compared with naïve HMC-1. In addition, HMC-1 transformed into a spindle-shaped cell after cultured in SFCM for 24 hours; surface adherence increased up to 58.3 times compared with cells in control media (figure). Moreover, not proliferation, but HMC-1 migration was induced in the SFCM environment; 2.3 times more than controls. Co-culture of SF/HMC-1 significantly induced soluble interleukin 1 receptor-like 1 (or ST2) and cytokines associated with cell migration or adhesion (endoglin, urokinase receptor (uPAR)).

Conclusion:

Our data indicate that interactions between RA SFs and MCs, independent of direct contact, result in activating MCs into migratory, innate effector cells in the synovium.

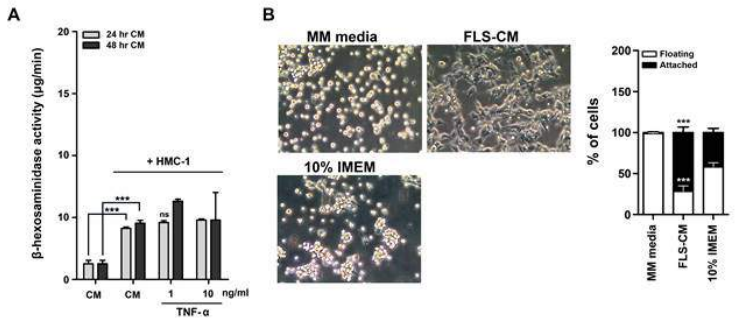

Figure. (A) Increased HMC-1 b-hexosaminidase activity (24 hours) after treated with rheumatoid arthritis synovial fibroblast conditioned media (CM). (B) Transformed HMC-1 cells after treated with CM (24 hours).

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Abstract Number: 2715

Increased Frequency of Dysfunctional Hematopoietic Stem and Progenitor Cell Subpopulations in Treatment Naïve Rheumatoid Arthritis Patients

Natalia Regine de Franca Shimabukuro[1], Kelsey Ann O'Hagan Wong[2], Marie Hudson[3], Sabrina Fallavollita[1] and **Ines Colmegna**[2], [1]Rheumatology, McGill University, Montreal, QC, Canada, [2]McGill University, Montreal, QC, Canada, [3]McGill University, Jewish General Hospital, Montreal, QC, Canada

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Background/Purpose: Hematopoietic stem and progenitor cells (HSPC) are responsible for the lifelong production of immune cells. Accumulation of DNA damage occurs in HSPC during normal ageing, impacts immune regeneration and has been implicated in the increased risk of malignant transformation. Similarly, age-independent premature accumulation of DNA damage occurs in HSPC from rheumatoid arthritis (RA) patients. Among HSPC the $CD34^+CD38^-$immunophenotype defines a rare primitive subpopulation of progenitor cells, enriched in their colony forming unit ability, and which numbers are increased in the elderly. In this study we characterized the frequency, phenotype and function of HSPC subpopulations in treatment naïve rheumatoid arthritis (RA) patients.

Methods: Peripheral blood circulating $CD34^+$ cells were isolated from treatment naïve, recent onset, ACPA positive RA patients (n=19) and from age/sex matched healthy controls (HC, n=19). The frequency of viable HSPC subpopulations ($7AAD^-/CD34^+/CD38^{+/-}$) and their proliferative responses (CFSE) were assessed by FACS. Clonogenicity was assessed in colony-forming cell (CFC) assays and DNA damage was quantified by single cell gel electrophoresis assay (comet assay). All results are shown as mean ± SEM, non-parametric tests were used for group comparisons.

Results: Treatment naïve RA patients have an increased proportion of circulating $CD34^+CD38^-$ HSPC (5.30 ± 0.84 % vs 2.83 ± 0.76 % respectively, $p<0.05$, n=9). The frequency of $CD34^+CD38^-$ does not change following 6 months of methotrexate treatment (5.21 ± 2.39 % vs 5.49 ± 2.20 %, p=0.375, n=3). Compared to HC, RA-CD34 produced fewer colonies (n=7) [CFU-GEMM (1.82 ± 0.37 vs 4.71 ± 1.10 respectively, $p<0.05$), CFU-GM (6.89 ± 1.01 vs 18.54 ± 3.97 respectively, $p<0.05$) and BFU-E (10.71 ± 1.95 vs 15.43 ± 3.57 respectively, $p>0.05$)]; accrued DNA damage (32.25 ± 5.27% vs 7.63 ± 2.57% DNA in tail respectively, $p<0.0001$), and had impaired proliferative responses to hematopoietins (Day 4 expansion index (EI): 3.21 ± 0.20 vs 4.28 ± 0.28, $p<0.01$, n=11); and increased number of $CD34^+$ that remained non-proliferating (generation 0: 27.42 ± 4.06 % vs 18.65 ± 2.74 % respectively, $p<0.05$, n=11). The EI of RA-$CD34^+CD38^-$HSPC was significantly reduced (3.61 ± 0.48 vs 5.00 ± 0.62 expansion index respectively, $p<0.05$, n=10).

Conclusion: The function of the most primitive HSPC subpopulations in treatment naïve RA patients is impaired mimicking the HSPC phenotype of healthy elderly individuals. The disruption of HSPC homeostasis is an early event in RA with potential implications in immune-regeneration and carcinogenesis.

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Abstract Number: 2716

Dysregulated Osteoclastogenesis Is Related to Natural Killer T Cell Dysfunction in

Rheumatoid Arthritis

Seung-Jung Kee[1], Hye Mi Jin[2], Jeong-Hwa Kang[2], Young-Nan Cho[2], Ki-Jeong Park[2], Hyun-Ju Jung[2] and Yong-Wook Park[2], [1]Laboratory Medicine, Chonnam National University Medical School and Hospital, Gwangju, South Korea, [2]Rheumatology, Chonnam National University Medical School and Hospital, Gwangju, South Korea

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Background/Purpose: The aims of the present study were to investigate the role played by natural killer T (NKT) cells in osteoclastogenesis and their effects on inflammatory bone destruction.

Methods: Patients with RA (n=25) and healthy controls (n=12) were enrolled in this study. *In vitro* osteoclastogenesis experiments were performed using peripheral blood mononuclear cells (PBMCs) in the presence of M-CSF and receptor activator of nuclear factor kB ligand (RANKL). PBMCs were cultured *in vitro* with α-galactosylceramide (αGalCer), and proliferation indices of NKT cells were estimated by flow cytometry. *In vivo*effects of αGalCer-stimulated NKT cells on inflammation and bone destruction were determined in collagen-induced arthritis (CIA) mice.

Results: *In vitro*osteoclastogenesis was found to be significantly inhibited by αGalCer in healthy controls, but not in RA patients. Proliferative responses of NKT cells and STAT-1 phosphorylation in monocytes in response to αGalCer were impaired in RA patients. Notably, αGalCer-stimulated NKT cells inhibited osteoclastogenesis mainly via interferon-g production, in a cytokine-dependent manner (not by cell-cell contact), and down-regulated osteoclast-associated genes. αGalCer-treated mice showed less severe arthritis and reduced bone destruction. Moreover, proinflammatory cytokine expression in arthritic joints was found to be reduced by αGalCer treatment.

Conclusion: This study primarily demonstrates that αGalCer-stimulated NKT cells have a regulatory effect on osteoclastogenesis and a protective effect on inflammatory bone destruction. However, it also shows that these effects of αGalCer are diminished in RA patients, and that this is related to NKT cell dysfunction. These findings provide important information for those searching for novel therapeutic strategies to prevent bone destruction in RA.

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Abstract Number: 2717

Stf-083010, the Inhibitor of ER Stress Transducer IRE1, Suppresses Rheumatoid Synovitis

Soutarou Izumi[1], Tomoyuki Nakasa[2], Shigeru Miyaki[3] and Mitsuo Ochi[1], [1]Orthopaedic Surgery, Hiroshima University, Hiroshima, Japan, [2]Orthopaedic Surgery, Matsuyama Redcross Hospital, Matsuyama, Japan, [3]Translational Research Medical Center, Hiroshima, Japan

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Background/Purpose: Endoplasmic reticulum (ER) stress is a cellular signal, which is triggered by the failure to fold newly synthesized ER proteins. ER stress plays an important role in the pathogenesis of some human diseases. Recently it was revealed that the rheumatoid arthritis (RA) causes synovial cell tolerance against ER stress during secretion of inflammatory cytokines. ER stress transducer IRE1 is one of the canonical transducers. The activation of IRE1 was identified in RA. Here, we report that IRE1 is a master

regulator of the unfolded protein response in RA synovium. And, we demonstrated that the tolerance for ER stress was reduced by inhibiting IRE1 in RA synovial cells. Furthermore, this is the first report to apply STF-083010, a novel small-molecule inhibitor of IRE1, for treatment of RA synovitis.

Methods: Synovial fibroblasts from the knee joint of RA patient who underwent total knee replacement were prepared by digestion with collagenase. We assessed the ER-related genes in the RA patient's primary cultured synovial fibroblasts.

To investigate the effectiveness of suppressing the synovitis by IRE1 inhibitor, we prepared antigen induced arthritis (AIA) mice model. To prepare the AIA mouse model, arthritis was induced in knee joints of 8-week-old wild-type mice by intra-articular injection of methylated bovine serum albumin (mBSA; Sigma) in mice preimmunized with mBSA. On day 1, mice were preimmunized by a 100 μL intradermal injection at the base of the tail with an emulsion containing 100 μg of mBSA and an equal volume of Freund's complete adjuvant (Sigma). On day 10, animals were treated with intra-articular mBSA injected into the left and right knee joints. On day 17, the knee joints were harvested and processed using standard procedures.

Results: Although all ER stress transducers were up-regulated with the time, IRE1 exhibited dynamic up-regulation in response to inflammatory stimulation in RA synovial fibroblast group. To assess the effectiveness of IRE1 inhibitor, STF-083010, we also performed TUNEL staining using RA patient's synovial fibroblasts. We found that the TUNEL-positive cells were significantly increased especially in the STF-083010-treated group. The synovitis of AIA was significantly suppressed in STF-083010-treated AIA group.

Conclusion: STF-083010 inhibited IRE1 activity through ER stress shown in both *in vitro* and *in vivo* assays. Treatment with STF-083010 resulted in a significant reduction in cell viability in primary cultured human RA synovial fibroblasts. Similarly, STF-083010 successfully suppressed synovial activity in AIA mouse models as the result of less tolerated to ER stress. This procedure could be considered 'the molecular targeted synovectomy'. The application of this novel IRE1 inhibitor supports the hypothesis that IRE1 is a promising target for alternative therapy in RA synovitis.

Disclosure: S. Izumi, None; **T. Nakasa**, None; **S. Miyaki**, None; **M. Ochi**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/stf-083010-the-inhibitor-of-er-stress-transducer-ire1-suppresses-rheumatoid-synovitis

Abstract Number: 2718

Along Those Lines: Synoviocyte Cell-to-Cell Communication Via Nanotubes

Ruth Byrne[1], Karolina von Dalwigk[2], Isabel Olmos Calvo[3,4], Felix Kartnig[3], Mario Rothbauer[4], Verena Charwat[5], Thomas Karonitsch[6], Peter Ertl[4], Gunter Steiner[7], Christian Schöfer[8], Johannes Holinka[9], Josef S. Smolen[10], Clemens Scheinecker[11] and **Hans Peter Kiener**[12], [1]Rheumatology, Internal Medicine III, Medical University of Vienna, Vienna, Austria, [2]Department of Medicine III, Division of Rheumatology, Medical University of Vienna, Vienna, Austria, [3]Inner Medicine III, Rheumathology, Medical University of Vienna, Vienna, Austria, [4]Nanotechnology, Austrian Institute for Technology, Vienna, Austria, [5]Department of Nanotechnology, Austrian Institute for Technology, Vienna, Austria, [6]Internal Medicine III, Vienna Medical University, Vienna, Austria, [7]Internal Medicine III, Division of Rheumatology, Medical University of Vienna, Vienna, Austria, [8]Department of Cell and Developmental Biology, Medical University of Vienna, Vie, Austria, [9]Department of Orthopedics, Medical University of Vienna, Vienna, Austria, [10]Dept of Medicine 3, Division of Rheumatology, Medical Univ Vienna, Vienna, Austria, [11]Divison of Rheumatology, Medical University of Vienna, Vienna, Austria, [12]Division of Rheumatology, Medical University of Vienna, Vienna, Austria
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Background/Purpose: The synovium is primarily formed by fibroblast-like synoviocytes (FLS). Its multicellularity requires precise coordination to generate a tissue that confers specialized functions critical to joint homeostasis. Cell-to-cell communication facilitates the concerted behavior of FLS within the synovium. Using a 3D model of the synovium, we analyzed FLS capacity for exchange of cytoplasmic content.

Methods: Human FLS were prepared from synovial tissues obtained as discarded specimens following joint arthroplasty. Cells were cultured in spherical matrigel micromasses with an average size of 2 mm Ø. Data was acquired by confocal live cell imaging and transmission electron microscopy. Analysis of the resulting 4D movies was done with Imaris® software.

Results: To examine intercellular cytoplasmatic transfer, we labeled 50% of FLS with red cell tracker dye and loaded the other 50 % with green non-degradable microspheres. In a time series (8 days), we found that microspheres do indeed appear in red labeled cells. First evidence was found on Day 1 and over the course of the following days microspheres accumulated in red labeled cells with a transfer rate of 10 % of newly affected cells/day. Additionally, red vesicles also appeared in green labeled cells. They first occurred on day 1, however, their transfer rate reached a steady state at about 20%, presumably due to degradation following transfer in the receiving cell. A similar experiment in 2D demonstrated microsphere movement within interconnecting nanotubes. Transfer rates for microspheres into red cells were identical. By contrast, rates for red vesicles into green cells were much higher than in 3D cultures. Thus, cells in 2D culture may have easier access to released vesicles as compared to 3D tissues. Transmission Electron Microscopy revealed transfer via exocytosed vesicles as well as open intercellular connections.

Conclusion: These studies suggest transfer of cytoplasmic cargo between FLS. We identified two ways for cytoplasmic transfer between cells; 1) through vesicles and 2) through interconnecting open nanotubes. Further studies will demonstrate the significance of directed cargo exchange for cellular cooperation and the function of the normal as well as the diseased synovium.

Disclosure: R. Byrne, None; **K. von Dalwigk**, None; **I. Olmos Calvo**, None; **F. Kartnig**, None; **M. Rothbauer**, None; **V. Charwat**, None; **T. Karonitsch**, None; **P. Ertl**, None; **G. Steiner**, None; **C. Schöfer**, None; **J. Holinka**, None; **J. S. Smolen**, Abbvie, Janssen, MSD, Pfizer, Roche, UCB, 2,Abbvie, Amgen, Astra-Zeneca, Astro, Celgene, Glaxo, ILTOO, Janssen, Lilly, Medimmune, MSD, Novartis-Sandoz, Novo-Nordisk, Pfizer, Roche, Samsung, Sanofi, UCB, 5; **C. Scheinecker**, None; **H. P. Kiener**, None.

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Abstract Number: 2719

Track Along: Monocytes Follow Fibroblast-like Synoviocyte Network for Movement and Rest within the Synovial Tissue

Ruth Byrne[1], Karolina von Dalwigk[2], Gunter Steiner[3], Johannes Holinka[4], Reinhard Windhager[4], Josef S. Smolen[5], Hans Peter Kiener[6] and Clemens Scheinecker[7], [1]Rheumatology, Internal Medicine III, Medical University of Vienna, Vienna, Austria, [2]Department of Medicine III, Division of Rheumatology, Medical University of Vienna, Vienna, Austria, [3]Internal Medicine III, Division of Rheumatology, Medical University of Vienna, Vienna, Austria, [4]Department of Orthopedics, Medical University of Vienna, Vienna, Austria, [5]Dept of Medicine 3, Division of Rheumatology, Medical Univ Vienna, Vienna, Austria, [6]Division of Rheumatology, Medical University of Vienna, Vienna, Austria, [7]Divison of Rheumatology, Medical University of Vienna, Vienna, Austria
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Background/Purpose: The synovial lining tissue consists of fibroblast-like synoviocytes (FLS) and monocyte-derived macrophage-like synoviocytes (MLS) within a self-built meshwork of dense extracellular matrix (ECM) components. FLS are thought to direct ECM synthesis, assembly and degradation. Whether FLS themselves or the ECM network serve as guiding structures for MLS migration is incompletely understood. We studied the dynamics of tissue modeling as well as MLS migratory behavior using a 3D synovial tissue in vitro model.

Methods: Human FLS were prepared from synovial tissues obtained as discarded specimens following joint arthroplasty. CD14+ monocytes (MO) were isolated from peripheral blood. Fluorescently labeled FLS and MO were cultured in spherical extracellular matrix micromasses with an average size of 1.5 mm for up to two weeks. Second harmonic generation was used for the visualization of collagen fibers (ECM). Cell migration was monitored by real-time confocal/multi-photon microscopy.

Results: FLS spontaneously formed a synovial lining-like layer at the surface of the 3D cell culture within 3 days. The first signs of collagen fibers co-localized with FLS clusters and appeared as early as day 1. ECM density increased during the establishment of the lining layer.

The majority (98%) of MO was found to be in close contact with the FLS network with low tendency for migration. On the surface of 3D cultures at the tissue/medium interface a minor fraction of MO displayed directed cell movement with an impressive maximum speed of up to 15 mcm/min. MO migration occurred in intimate contact with FLS but did not necessarily follow individual FLS of the network. Inside the synovial tissue, MO migration followed the FLS network rather than the ECM fibers. For both MO contact with FLS seemed to be more important than contact with the ECM.

Conclusion: The 3D synovial tissue culture system allows for monitoring and analyzing the dynamics of synovial lining modeling. Both, FLS and MO appear to cooperate in the organization of the synovial lining tissue with subtle migration patterns of MO in relation to the organized synovial lining architecture. Ongoing experiments address molecular mechanism(s) of MO – FLS interaction in order to identify potential targets for future therapeutic intervention in arthritis.

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Abstract Number: 2720

Crucial Role of Nuclear Factor of Activated T Cell 5 (NFAT5), an Osmo-Protective Factor, in Migration and Invasion of Rheumatoid Synoviocytes

Saseong Lee[1], Seung-Ah Yoo[1], Ki-Jo Kim[2], Chong-Hyeon Yoon[3], Wan-Uk Kim[4] and Bong Ki Hong[1], [1]Institute of Bone and Joint Diseases, The Catholic University of Korea, Seoul, South Korea, [2]St. Mary's Hospital, Seoul, South Korea, [3]Division of Rheumatology, Department of Internal Medicine, College of Medicine, The Catholic University of Korea, Seoul, South Korea, [4]Internal Medicine, Seoul St. Mary's Hospital, The Catholic University of Korea, Seoul, South Korea

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Background/Purpose:

Fibroblast-like synoviocytes (FLS) play an important role in the progression of rheumatoid arthritis (RA). Particularly, FLS of RA patients (RA-FLS) exhibit pro-migratory and invasive characteristic reminiscent of cancer cells, destroying cartilage and bone. However, key regulators or signaling molecules responsible for this characteristic are not fully documented. Recently, we have demonstrated that nuclear factor of activated T cell 5 (NFAT5), an osmo-protective transcription factor, is crucial to the development of experimentally-induced arthritis in mice (Kim WU, et al. Arthritis Rheum 2011). Here, we investigated if NFAT5 controls migration and invasion of RA-FLS.

Methods:

The FLS were obtained from synovial tissues of RA patients. Messenger RNA (mRNA) in RA-FLS and embryonic fibroblasts, which were deficient of NFAT5 gene, were profiled using microarray technology. NFAT5 expression in the presence of interleukin 1β (IL-1β) or transforming growth factor β (TGFβ) was analyzed by western blot analysis and real-time PCR. The expression levels of tissue factor and CCL2 were measured by flow cytometry analysis and ELISA, respectively. Wound migration assay and invasion assay using matrigel chamber were conducted *in vitro*.

Results:

The mRNA profiling of RA-FLS transfected with NFAT5 short interfering RNA (siRNA) and embryonic fibroblasts of NFAT5 knockout mouse revealed that NFAT5 is involved in the migration and invasion in RA-FLS. Transcriptome analysis also suggested that tissue factor and CCL2 were the key target genes of NFAT5 responsible for these processes. Consistent with these results, NFAT5 was up-regulated in RA-FLS stimulated with pro-migratory and pro-invasive cytokines, including IL-1β and TGFβ. Interestingly, tissue factor and CCL2 were independently increased by TGFβ and IL-1β, respectively, although both of which were commonly regulated by NFAT5. Moreover, knockdown of NFAT5 or tissue factor using siRNAs resulted in a marked suppression of migration and invasion of RA-FLS; particularly, TGFβ-induced RA-FLS invasion and lamellipodia formation were blocked by knockdown of NFAT5 or tissue factor transcripts. SB203580, a p38 inhibitor, down-regulated TGFβ-induced NFAT5 expression, suggesting that p38 is an up-stream regulator of NFAT5 under high TGFβ conditions.

Conclusion:

The present study demonstrates first that NFAT5 is a critical regulator responsible for the migration and invasion of RA-FLS. These data also provide the evidence for a novel role of the TGFβ-NFAT5-tissue factor axis in RA-FLS invasiveness, which could be a

potential target for anti-FLS therapy retarding cartilage and bone destruction.

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Abstract Number: 2721

Elevated Subgingival Levels of Periodontal Pathogens in Rheumatoid Arthritis Patients, Particularly Leptotrichia species in New-Onset Disease

Sheila Arvikar[1], Hatice Hasturk[2], Daniel Nguyen[2], Klemen Strle[3], Marcy B. Bolster[4], Deborah Collier[5], Allen C. Steere[6] and Alpdogan Kantarci[2], [1]Division of Rheumatology, Allergy & Immunology, Massachusetts General Hospital, Harvard Medical School, Boston, MA, [2]Department of Applied Oral Health Sciences, Forsyth, Cambridge, MA, [3]Center for Immunology and Inflammatory Diseases, Massachusetts General Hospital, Harvard Medical School, Boston, MA, [4]Rheumatology, Allergy, Immunology, Massachusetts General Hospital, Harvard Medical School, Boston, MA, [5]Rheumatology, Allergy, and Immunology, Massachusetts General Hospital, Harvard Medical School, Boston, MA, [6]Center for Immunolgy and Inflammatory Diseases, Massachusetts General Hospital, Harvard Medical School, Boston, MA

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Background/Purpose:

Periodontitis, a polymicrobial infectious and inflammatory disease of tooth-supporting structures, shares pathogenic mechanisms with rheumatoid arthritis (RA) and may trigger its onset. Most studies have focused on *Porphyromonas gingivalis* (*Pg*), and serologic responses to periodontal pathogens, rather than direct detection of organisms. One prior study by Scher et al. found enrichment of *Prevotella* and *Leptotrichia* species in the oral microbiota of new-onset RA patients, irrespective of periodontal disease status. Here we studied the subgingival plaque biofilm of patients with new-onset and chronic RA.

Methods:

43 subjects, 23 RA patients, all meeting 2010 ACR/EULAR criteria, and 20 age- and gender-matched healthy subjects without periodontitis or RA completed standardized dental examination performed by a single periodontist. Dental parameters were measured at 6 sites per tooth. A total of 86 subgingival plaque samples (2 per subject) were evaluated for the presence of 41 bacterial taxa associated with periodontitis biofilms by checkerboard DNA-DNA hybridization.

Results:

Typical of RA cohorts, the 23 patients were mainly female (87%) with median age of 48; 15 had DMARD-naive early disease. The majority (61%) was seropositive for ACPA, 43% were positive for rheumatoid factor, and they had a range of disease activity from mild to severe. None were current smokers. All but one patient received routine dental care with cleanings every 6 months.

Of the 23 patients, 10 (43%) had gingivitis, a precursor of periodontitis, 9 (39%) had periodontitis, and only 4 patients (17%) had healthy periodontal tissue. Compared with the 20 healthy subjects, the 23 RA patients had significantly increased pocket depth ($P<0.000001$), clinical attachment loss ($P=0.001$), and bleeding on probing ($P=0.0001$). There were no differences in dental parameters between former vs. never smokers.

The RA patients had a distinct subgingival biofilm. Accounting for multiple comparisons, 10 of 41 pathogens had higher DNA probe counts (levels) in RA patients versus controls ($P \leq 0.002$). Although RA patients had higher levels of classic “red-complex” pathogens (*P. gingivalis, Tannerella forsythia,* and *Treponema denticola*) than healthy controls, differences were not significant. Compared with chronic RA, new-onset patients had significantly higher levels of several pathogens, including *Gemella morbillorum, Propionybacterium acnes, Streptococcus gordonii,* and *Leptotrichia buccalis* ($P \leq 0.05$), regardless of whether they had periodontitis on examination. *L. buccalis* was present in 67% of new-onset RA patients versus only 13% of those with chronic RA ($P=0.02$). Finally, levels of *L. buccalis* and *P. acnes*tended to correlate with multiple disease activity measures ($P \leq 0.07$).

Conclusion:

Despite routine dental care, most of our patients had gingivitis or periodontitis on examination and abundance of periodontal pathogens in subgingival plaque. Although *P. gingivalis*, a classic periodontal pathogen is of interest in RA pathogenesis, several other organisms including the previously implicated *Leptotrichia* species, may be more specifically associated with new-onset RA and may warrant further study as candidate triggers of RA.

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Abstract Number: 2722

Cyclic Phosphatidic Acid (CPA) Suppresses Expression of Cartilage Degrading Enzymes Such As MMP-3, MMP-13 and Adamts-4 in Inflammatory Synovial Fibroblasts and Articular Chondrocytes Induced By IL-1 Beta and/or TNF ALFA

Ikuko Masuda[1,2], Kodo Okada[3], Hisashi Yamanaka[1] and Shigeki Momohara[1], [1]Institute of Rheumatology, Tokyo Women's Medical University, Tokyo, Japan, [2]Rheumatology, Jyujyo Takeda Rehabilitation Hospital, Kyoto, Japan, [3]SANSHO, Co. Ltd., Tokyo, Japan
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Background/Purpose: Cyclic phosphatidic acid (cPA) is one of bioactive lipid, has been implicated as an mediator of various biological effects including inhibitory effects of proliferation, invasion and metastasis of cancer cells. We have previously confirmed that cPA stimulated HAS-2 production on human osteoarthritic chondrocytes and synovial fibroblasts (SFs) in vitro. Furthermore, intra-articular administration of cPA has shown its suppressing effect of pain, swelling, and articular cartilage destruction in rabbit experimental osteoarthritis. We have shown that cPA might had direct inhibitory effect of cartilage degrading enzymes on rheumatoid synovial fibroblasts (SFs) in vitro. Inflammatory arthritis such as rheumatoid arthritis and early stage of OA involves synovial inflammation and subsequent production of cartilage degrading enzymes. cPA is naturally occurring mediator even exists in human serum. cPA may be possible another therapeutic option for degenerative arthritis. The aim of this study was to evaluate the direct effects of cPA on cartilage matrix degrading enzymes using SFs and articular chondrocytes under influence of inflammatory cytokines.

Methods: In vitro studies were performed using SFs and chondrocytes obtained from arthritis patients at joint replacement surgery. cPA 0-25 μM was added to cell cultures and effects of cPA on ADAMTS-4, -5, MMP-3, -13, TIMP-3 expression were assessed by real time PCR using specific primers to corresponding genes. SFs or chondrocytes were also cultured with IL-1β (2.5ng/ml) and/or TNF-α (10 ng/ml), to study attenuated effect of cPA. Beta-actin was used as endogenous expression control for PCR. Newly synthesized MMP-3, -13, TIMP-3 from SFs or chondrocytes in cultured media were measured by sandwich ELISA.

Results: cPA itself repressed cartilage degrading enzymes, ADAMTS-4, ADAMTS-5, MMP-3, and MMP-13 expression in both SFs and chondrocytes was all repressed by low dose of cPA, even after these expressions was stimulated by cytokines. Expression of these enzymes were repressed more in chondrocytes by cPA. ELISA results also confirmed the inhibitory effect of cPA on MMP-3, MMP-13, and PGE2 production.

Conclusion: The in vitro results confirmed that cPA had suppressing effect of cartilage degrading enzymes on SFs and chondrocytes, supports the hypothesis that cPA might have played direct role to suppress inflammation and also protect articular cartilage in arthritic condition. Molecular mechanism of cPA to prevent cartilage degradation remains to be elucidated, however, further study should be warranted for cPA as a novel candidate for therapeutic agent of arthritis.

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2,Eisai, 2,Mitsubishi Tanabe, 2,Nakashima Medical Co., Ltd., 2,Santen Pharmaceutical Co., Ltd., 2,Taisho Toyama Pharmaceutical Co. Ltd, 2,Takeda, 2.

Abstract Number: 2723

Basal STAT5 Signaling Is Elevated in Multiple Peripheral Blood Cell Subsets in Rheumatoid Arthritis and Is Markedly Downregulated By IFN-Î³ in T Lymphocytes

Molly Boland[1], Yanna Ding[2], Surabhi Vinod[3], S. Louis Bridges Jr.[4] and Chander Raman[1], [1]Medicine/Division of Clinical Immunology and Rheumatology, University of Alabama at Birmingham, Birmingham, AL, [2]Medicine/Division of Clinical Immunology and Rheumatology, University of Alabama Birmingham, Birmingham, AL, [3]University of Alabama at Birmingham, Birmingham, AL, [4]Clinical Immunology and Rheumatology, University of Alabama at Birmingham, Birmingham, AL

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Background/Purpose: The importance of type I interferons (IFN-α and others) as a driver of pathogenesis in autoimmunity, including rheumatoid arthritis (RA) is well recognized. However, in this context, the contribution of type II interferons (IFN-γ) has been ambiguous. The interferon gamma receptor (IFNGR) is a heterodimer of proteins encoded by *IFNGR1* and *IFNGR2*. The expression of *IFNGR2*, not plasma levels of INF-γ, has been shown to be the limiting factor for receptor binding. We recently reported a strong association between the presence of RA and the level of expression of the INF-γ receptor gene *IFNGR1* in peripheral blood mononuclear cells (PBMC). We also analyzed 576 RA patients and found that *IFNGR2* in PBMC strongly associated with radiographic severity (P=0.03 for erosions, P=0.04 for joint space narrowing, and P=0.03 for total radiographic score). These data implicate and important pathogenetic function of the IFN-γ signaling pathway in RA.

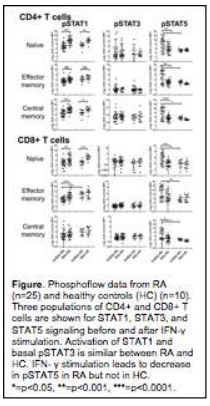

Figure. Phosphoflow data from RA (n=25) and healthy controls (HC) (n=10). Three populations of CD4+ and CD8+ T cells are shown for STAT1, STAT3, and STAT5 signaling before and after IFN-γ stimulation. Activation of STAT1 and basal pSTAT3 is similar between RA and HC. IFN- γ stimulation leads to decrease in pSTAT5 in RA but not in HC. *=p<0.05, **=p<0.001, ***=p<0.0001.

Methods: We sought to determine the mechanistic significance of the elevated expression of INF-γ receptors within subpopulations of CD4 and CD8 T cells, B cells, and monocytes. To address this question, we used a phosphoflow approach (high-definition multi parameter flow cytometry with simultaneous evaluation of activation of multiple STAT signaling molecules). We analyzed STAT1, STAT3, and STAT5 cell signaling in na•ve and memory CD4+ and CD8+ T cells (differentiated by CD45RA and CCR7), Tfh cells (CD4+/CXCR5-), na•ve and memory B cells, and monocytes (CD11b+) in PBMC of RA (n=25) and healthy controls (HC) (n=10).

Results: Although STAT1 is the primary STAT activated following stimulation with INF-γ, we found no difference in the activation of STAT1 between RA and HC in all cell populations. However, we found that basal active STAT5 (as assessed by phosphorylated tyrosine at position 694 [pY694-STAT5]) was elevated in RA compared to HC (p=<0.05). Strikingly, this active basal pSTAT5 was down-modulated following stimulation with INF-γ in CD4 and CD8 T cell populations but not in B cell populations or monocytes from RA (see figure).

Conclusion: Our novel preliminary findings suggest that decreased levels of pSTAT5 following stimulation of T cell populations and Tfh cells with INF-γ contribute to the pathogenesis of RA and its severity. Ongoing studies reveal that this down-modulation of STAT5 may render cells hyporesponsive to regulatory cytokines such as IL-2.

Disclosure: M. Boland, None; **Y. Ding**, None; **S. Vinod**, None; **S. L. Bridges Jr.**, None; **C. Raman**, None.

Abstract Number: 2724

Methotrexate Treatment Could Modulate the Abnormal CD4+T Lymphocyte Subset

Distribution in NaÏve Rheumatoid Arthritis Patients

Cristina Bohórquez Heras[1], Lucía Ruiz Gutiérrez[1], Carolina Garcia Torrijos[2], Ana Turrión Nieves[1], Ana Pérez Gómez[1], Ana Sánchez Atrio[1], Eduardo Cuende[1], Atusa Movasat[1], Fernando Albarrán Hernández[1], Henry Moruno[1], M José León[1], David Diaz[2], Jorge Monserrat[2] and Melchor Álvarez de Mon[1,2], [1]University Hospital Príncipe de Asturias, Immune System Diseases, Rheumatology department, Alcalá de Henares, Madrid, Spain, [2]Laboratory of Immune System Diseases, Department of Medicine, University of Alcalá, Alcalá de Henares, Madrid, Spain
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Background/Purpose:

Mechanisms regulating the chronic autoimmune response in rheumatoid arthritis (RA) are not well understood. However, activated T CD4+ play a pivotal role initiating and perpetuating the chronic inflammation characteristic for the disease. The objetive is evaluate the number and distribution of circulating CD4+ T lymphocytes and their CD4+ naïve T cells (TN), central memory (TCM), non-terminated effector memory (TNTEM) and terminated effector memory (TTEM) T cells subsets in a population of recently diagnosed DMARD naive RA patients before and along the first 6 months of methotrexate (MTX) treatment.

Methods: The number of circulating CD4+ T lymphocytes, and of their TN, TM, TCM and TEM subsets in fifty untreated patients with RA before MTX treatment and at 3 and 6 months of treatment were assayed using a multiparametric flow cytometry. We also studied twenty-four age- and sex-matched healthy subjects as controls.

Results:

RA naïve patients show a significant ($p<0.05$) expansion of the circulating CD4+ TNTEM subset. MTX non responder naïve RA patients show from basal conditions a significative expansion of CD4+ TNTEM lymphocytes and develop significant expansion of CD4+ TCM, and CD4+ TEM lymphocyte subsets along MTX treatment.

Conclusion: Recently diagnosed DMARD naive RA patients show involvement of the circulating CD4+ T lymphocytes activation/differentiation stage subsets. MTX treatment show immunomodulatory effects on CD4+ T lymphocyte compartment with different behavior in responder and non-responder patients.

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Abstract Number: 2725

Secular Trends in Use of Disease Modifying Anti-Rheumatic Drugs for the Treatment of Rheumatoid Arthritis in the United States

Rishi J. Desai[1], Daniel H. Solomon[2], Jun Liu[3] and Seoyoung C. Kim[4], [1]PharmacoEpidemiology & PharmacoEconomics, Brigham and Women's Hospital, Boston, MA, [2]Rheumatology, Brigham and Women's Hospital, Boston, MA, [3]Division of Pharmacoepidemiology, Brigham and Women's Hospital, Boston, MA, [4]Div. of Pharmacoepidemiology and Pharmacoeconomics, Div. of Rheumatology, Immunology and Allergy, Brigham and Women's Hospital, Boston, MA
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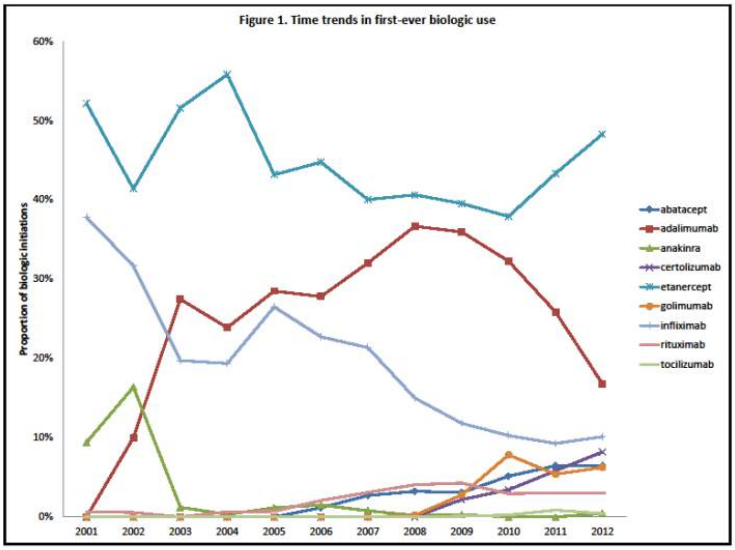
Background/Purpose: Treatment of rheumatoid arthritis (RA) with disease modifying anti-rheumatic drugs (DMARDs) has undergone major advances in last two decades. More than 10 non-biologic DMARDs and 9 biologic DMARDs are currently approved in the United States for the indication of RA. Yet, little is known about the population level time-trends in use of these agents. Therefore, we described secular trends in use of DMARDs for initial and subsequent treatment of RA in publicly and privately insured patients.

Methods: Claims data derived from private (United HealthCare, 2004-2013) or public (Medicaid Analytic eXtract (MAX), 2000-2010) insurance programs were used to conduct a retrospective cohort study. RA patients were identified from either data source based on at least two medical claims with ICD-9 code of 714.xx and classified into three groups by their DMARD use in a 12-month baseline period: 1) DMARD-naïve patients, 2) biologic-naïve patients, or 3) biologic-exposed patients. In a 12-month follow-up period, we identified initiation of the first ever DMARD among DMARD-naïve patients, initiation of the first ever biologic agent among biologic-naïve patients, and initiation of a second or later biologic agent among biologic-exposed patients. Among the patients initiating the new DMARD of interest during follow-up in each group, we calculated the proportion of patients initiating individual DMARDs for all available calendar years and reported time-trends.

Results: A total of 75,545 RA patients with private and 95,624 with public insurance were identified as eligible for this study. Mean age (SD) the cohort was 48 (12) years and 78% of the patients in the cohort were female. Among DMARD-naïve RA patients, methotrexate (42%), hydroxychloroquine (32%), and sulfasalazine (9%) were the three most commonly used agents as the first-ever DMARD during our study period. Among biologic-naïve patients, etanercept (45%) was the most commonly initiated agent as the first-ever biologic, followed by adalimumab (25%) and infliximab (20%). A decreasing trend for infliximab was observed between 2001 and 2012 as the first ever biologic agent; while newer agents, abatacept and certolizumab, showed increasing trend in use since their introduction ($p<0.05$) (**Figure 1**). Among biologic-exposed patients, a decreasing trend in the use of adalimumab and infliximab, while an increasing trend for abatacept, golimumab, and certolizumab as the second-line biologic of choice was noted since their introduction ($p<0.05$ for all trends).

Conclusion: Use of etanercept as the most common first-line agent has remained relatively stable over the past decade; however, use of adalimumab and infliximab is decreasing and the use of newer biologics, especially abatacept, golimumab, and certolizumab, is increasing as both first-line and second-line agents in recent years.



Disclosure: **R. J. Desai**, None; **D. H. Solomon**, None; **J. Liu**, None; **S. C. Kim**, Pfizer Inc, 2,AstraZeneca, 2,Lilly, 2,Genentech and Biogen IDEC Inc., 2.

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Abstract Number: 2726

The Effect of Prior Disease Duration and Prior DMARD Use on Treatment Outcomes in Patients with Early or Established Rheumatoid Arthritis

Josef S. Smolen[1], Daniel Aletaha[2], Su Chen[3] and Stefan Florentinus[3], [1]Department of Rheumatology, Medical University of Vienna, Vienna, Austria, [2]Division of Rheumatology, Department of Internal Medicine III, Medical University of Vienna, Vienna, Austria, [3]AbbVie Inc., North Chicago, IL

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Background/Purpose: A delay in effective treatment is known to negatively affect long term treatment outcomes in patients (pts) with rheumatoid arthritis (RA). The purpose of this study was to compare the effects of disease duration and the number of prior failed disease modifying anti-rheumatic drugs (DMARDs) before effective treatment, on the achievement of long term outcomes in pts with early or established RA.

Methods: Data from two randomized controlled trials, PREMIER and DE019, were used. In PREMIER, pts with mean RA duration < 1 year (yr), who were TNF inhibitor-(TNFi) and MTX-naïve received adalimumab (ADA), methotrexate (MTX), or ADA+MTX. In DE019, TNFi-naïve pts with mean RA duration 11 yrs, and an insufficient response to MTX received 20 mg/40mg ADA every other week +MTX, or PBO+MTX. The association of either variable (prior disease duration or prior DMARDs) with the endpoints was modeled while controlling for the other variable using linear or logistic regression. RA duration and number of prior DMARDs were grouped and the groups were treated as ordinal variables. For PREMIER, RA duration groups were ≤1yr, >1 to ≤2yr and >2yr and for prior DMARDs, groups were: 0 or ≥1 DMARD. For DE019, RA duration groups were: ≤1yr, >1 to ≤5yr and >5 to ≤10 yr, and >10yr, and for prior DMARDs groups were: MTX+0 or 1 DMARD, MTX + 2 DMARDs and MTX +>2 DMARDs. The effect of RA duration/ exposure to prior DMARDs was determined for the following endpoints: week (wk) 52 ACR 20/50/70 response rates, mean DAS28 / SDAI / CDAI and HAQ; and mean changes from baseline (BL) to wk 52 in DAS28 / SDAI / CDAI/ HAQ (for changes from BL, a positive regression coefficient indicates a smaller change) .

Results: In PREMIER, in the ADA+MTX arm (268 pts), longer RA duration led to a smaller change from BL to wk 52 in CDAI and SDAI (2.95 and 3.59 respectively; $p<0.05$); higher absolute DAS28, CDAI and SDAI scores, and lower ACR response rates at wk 52. In DE019, for pts receiving ADA 40 mg +MTX (207 pts), an exposure to a larger number of prior DMARDs was significantly associated ($p<0.05$) with increased (by 0.21) DAS28 scores at wk 52, and a smaller (by 0.15) change in HAQ scores from BL to wk 52 ($p<0.01$). Longer RA duration was significantly associated ($p<0.05$) with an increase of 0.13 in wk 52 HAQ scores. Larger number of prior DMARDs or longer RA duration were associated, although not significantly, with lower ACR response rates at week 52.

Conclusion: In early RA, disease duration but not number of prior DMARDs, was significantly associated with a smaller change from BL to wk 52 in SDAI and CDAI, higher CDAI and SDAI scores and lower ACR response rates at wk 52.

Table: Association of wk 52 outcomes with number of prior DMARDs or disease duration. Regression coefficient estimate (95% CI)

PREMIER				
Wk 52 outcome	**# prior DMARDs**		**Disease duration**	
	ADA+MTX	**MTX**	**ADA+MTX**	**MTX**
ACR20	-0.37 (-1.25, 0.50)	-0.05 (-1.05, 0.95)	-0.22 (-0.78, 0.35)	0.50 (-0.23, 1.23)
ACR50	-0.49 (-1.18, 0.21)	0.39 (-0.34, 1.13)	-0.05 (-0.52, 0.42)	-0.12 (-0.57, 0.33)
ACR70	-0.60 (-1.22, 0.02)	0.26 (-0.44, 0.97)	-0.03 (-0.45, 0.39)	0.05 (-0.39, 0.49)
DAS28	0.07 (-0.29, 0.44)	0.10 (-0.37, 0.57)	0.10 (-0.14, 0.35)	-0.17 (-0.46, 0.12)
CDAI	-0.30 (-3.44, 2.84)	0.05 (-4.51, 4.61)	1.75 (-0.40, -3.90)	-1.44 (-4.23, 1.35)
SDAI	-0.78 (-4.16, 2.6)	0.17 (-4.64, 4.99)	1.87 (-0.43, 4.17)	-1.55 (-4.52, 1.42)
ΔDAS	-0.02 (-0.42, 0.39)	0.14 (-0.36, 0.63)	0.19 (-0.08, 0.47)	-0.11 (-0.41,0.20)
ΔCDAI	0.12 (-4.16, 4.41)	1.83 (-3.32, 6.97)	2.95* (0.00, 5.90)	-0.45 (-3.60, 2.71)
ΔSDAI	-0.91 (-5.80, 3.98)	2.0 (-2.81, 7.81)	3.59* (0.26, 6.93)	-0.33 (-3.91, 3.25)

DE019 (ADA 40mg + MTX)		
	# prior DMARDs	Disease duration
ACR20	-0.06 (-0.44, 0.32)	-0.02 (-0.35, 0.31)
ACR50	-0.21 (-0.57, 0.15)	-0.15 (-0.46, 0.16)
ACR70	-0.31 (-0.72, 0.09)	-0.13 (-0.47, 0.22)
DAS28	0.21* (0.00, 0.43)	-0.01 (-0.19, 0.17)
SDAI	2.00 (-0.01, 4.00)	-0.09 (-1.78, 1.60)
HAQ	0.08 (-0.05, 0.21)	0.13* (0.02, 0.24)
ΔDAS	0.21 (-0.01, 0.42)	0.00 (-0.18, 0.19)
ΔSDAI	1.73 (-0.87, 4.32)	-0.09 (-2.28, 2.10)
ΔHAQ	0.15* (0.04, 0.25)	0.03 (-0.06, 0.12)
*p<0.05; Δ, change		

Disclosure: J. S. Smolen, AbbVie Inc, 2,AbbVie Inc, 5; **D. Aletaha**, AbbVie, Pfizer, Grünenthal, Merck, Medac, UCB, Mitsubishi/Tanabe, Janssen, and Roche, 2,AbbVie, Pfizer, Grünenthal, Merck, Medac, UCB, Mitsubishi/Tanabe, Janssen, and Roche, 5; **S. Chen**, AbbVie, 1,AbbVie, 3; **S. Florentinus**, AbbVie, 1,AbbVie, 3.

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Abstract Number: 2727

BI 695501, a Proposed Biosimilar for Adalimumab, Shows Bioequivalence to Adalimumab Reference Products in a Randomized, Double-Blind Phase I Trial in Healthy Subjects

Christopher Wynne[1], Magdalena Petkova[2], **Ferdinand Rombout**[3], Niklas Czeloth[3], Mario Altendorfer[3], Benjamin Lang[4], Francois-Xavier Frapaise[3] and Rod Ellis-Pegler[5], [1]Christchurch Clinical Studies Trust, Christchurch, New Zealand, [2]SGS, CPU Antwerpen, Antwerp, Belgium, [3]Boehringer Ingelheim, Ingelheim, Germany, [4]Boehringer Ingelheim, Biberach an der Riss, Germany, [5]Auckland Clinical Studies Limited, Auckland, New Zealand

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Background/Purpose: BI 695501 is a proposed adalimumab biosimilar currently in development and was evaluated for pharmacokinetic (PK) similarity to both US-licensed and EU-approved reference products.

Methods: Healthy male subjects aged 18 to 55 years (N = 327) were randomized to receive one dose of either BI 695501 40 mg/0.8 mL, or US-licensed adalimumab or EU-approved adalimumab 40 mg/0.8 mL (NCT02045979). In each treatment group, 108 subjects received the trial medication, which was administered by subcutaneous injection. Primary and secondary PK endpoints included were total drug exposure as measured by the area under the concentration–time curve (AUC) from time zero to infinity ($AUC_{0\text{-}inf}$), AUC from time zero to the last measurable concentration ($AUC_{0\text{-}tz}$), and maximum observed plasma concentration (C_{max}), as well as several time truncated AUCs. Statistical PK similarity of BI 695501 vs. US licensed and vs. EU approved adalimumab was assessed by an ANCOVA model on the log-transformed primary PK parameters (with fixed effects for treatment and trial site as well as age and body weight as continuous covariates) for the ratios of the geometric means for each treatment and compared with the pre-specified boundaries of 80% to 125%. Safety and immunogenicity were also evaluated.

Results: Demographics and baseline characteristics were similar between the three treatment groups. Mean plasma concentration–time profiles for BI 695501, US-licensed and EU approved adalimumab were similar over the entire profiling interval (See figures). Body weight at baseline was a statistically significant predictor of C_{max} and AUC ($P < 0.0001$ for all pairwise analyses). Subject age was a statistically significant predictor of C_{max} ($P < 0.026$ for all pairwise analyses) but not for AUC ($P > 0.149$ for all pairwise analyses). Based on the predefined hypothesis test, the primary and secondary endpoints were met. PK parameters were similar for all comparisons of BI 695501 vs. US-licensed and vs. EU-approved adalimumab. Single subcutaneous doses of BI 695501, US-licensed or EU-approved adalimumab were generally well tolerated, and there were no notable differences in safety between the three treatment groups. Immunogenicity was also comparable and will be reported elsewhere.

Conclusion: BI 695501, US-licensed, and EU approved adalimumab are bioequivalent and have similar safety and tolerability profiles.

Figure A. Arithmetic mean (±SD) plasma concentration–time profiles for BI 695501 vs. US-licensed adalimumab

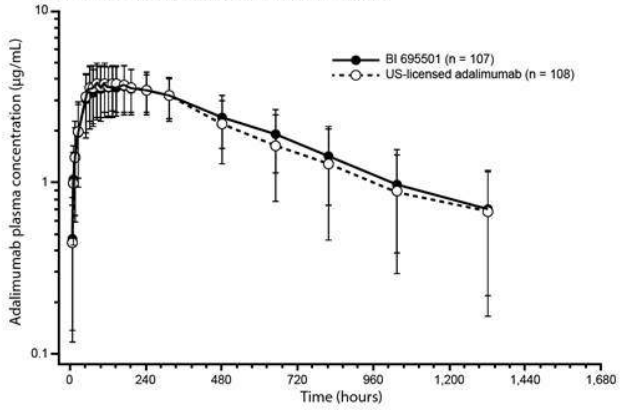
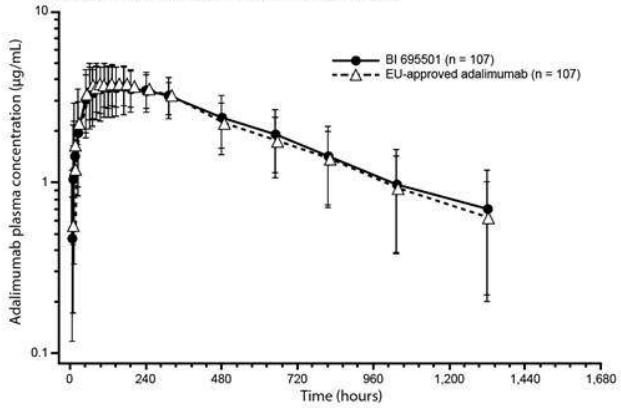


Figure B. Arithmetic mean (±SD) plasma concentration–time profiles for BI 695501 vs. EU-approved adalimumab



Disclosure: C. Wynne, Boehringer Ingelheim, 2; **M. Petkova**, None; **F. Rombout**, Boehringer Ingelheim, 3; **N. Czeloth**, Boehringer Ingelheim, 3; **M. Altendorfer**, Boehringer Ingelheim, 3; **B. Lang**, Boehringer Ingelheim, 3; **F. X. Frapaise**, Boehringer Ingelheim, 3; **R. Ellis-Pegler**, Boehringer Ingelheim, 2.

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Abstract Number: 2728

Baseline Characteristics and Changes in Disease Activity at 12 Months in Patients Treated with Abatacept Versus Other Biologic Disease-Modifying Antirheumatic Drugs in Clinical Practice Setting

E Alemao[1], S Joo[2], M Frits[3], C Iannaccone[3], N Shadick[3] and Michael Weinblatt[3], [1]Bristol-Myers Squibb, Princeton, NJ, [2]Bristol-Myers Squibb, Hopewell, NJ, [3]Brigham and Women's Hospital, Boston, MA

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Background/Purpose: Biologic (b)DMARDs have advanced the standard of care in RA, reducing unmet needs and increasing remission rates. Abatacept (ABA) is approved for the management of moderate-to-severe RA. In clinical trials, ABA showed efficacy similar to TNFi.[1] In clinical practice, TNFi are the predominantly used bDMARDs in the management of RA, but data comparing ABA to bDMARDs are limited. The primary objective was to assess baseline (BL) characteristics of RA patients (pts) receiving ABA or other bDMARDs in clinical practice. The secondary objective was to evaluate changes from BL to Month 12 in disease activity measures (DAS28 [CRP], CDAI and SDAI) and pt-reported outcomes (PROs; physical functioning [modified Health Assessment Questionnaire (mHAQ)], quality of life [EQ-5D] and arthritis active/pain today). **Methods:** Data from pts enrolled in the Brigham and Women's Hospital RA Sequential Study (BRASS) registry, established in 2003, were analyzed. The registry comprises mostly pts with established RA who were evaluated annually on clinical measures and semi-annually on multiple clinical PROs and resource utilization parameters. The current analysis is based on pts who had exposure to bDMARDs and available data on at least one disease activity measure during 12-month follow-up in the registry. Descriptive statistics were used to summarize BL differences in demographics, disease activity measures and laboratory measurements between RA pts prescribed ABA vs other bDMARDs. Mean change from BL to 12 months in disease activity measures and PROs were assessed using univariate and multivariate regression analyses that controlled for BL covariates, including BL ABA vs bDMARD treatments. **Results:** 748 pts were included in the analysis: 102 (13.6%) received ABA and 646 (86.4%) received other bDMARDs; 83% of ABA pts had prior exposure to bDMARDs. At BL, ABA pts (vs other bDMARD patients) were older (mean [SD] age: 59.5 [10.7] vs 54.8 [14.2] yrs; p=0.0015), with higher CRP levels (17.09 [41.5] vs 8.1 [19.2] mg/L; p=0.0004), higher DAS28 (CRP) (4.42 [1.58] vs 3.68 [1.65]; p≤0.001), higher mHAQ (0.59 [0.52] vs 0.37 [0.47]; p≤0.001) and lower EQ-5D (0.71 [0.15] vs 0.80 [0.17]; p≤0.001). After controlling for BL covariates, the mean changes from BL to 12 months in disease activity measures and PROs were comparable in ABA and other bDMARD pts (Table).

Table: Change from baseline to 12 months between ABA vs bDMARD on disease activity and patient-reported outcomes*

	bDMARD patients	ABA patients	p-value
	Mean (95% CI)	Mean (95% CI)	
DAS28 (CRP)	–0.915 (–1.276, –0.554)	–0.606 (–1.123, –0.090)	0.147
CDAI	–8.406 (–11.819, –4.992)	–5.098 (–10.238, 0.042)	0.119
SDAI	–8.673 (–12.353, –4.994)	–7.004 (–12.348, –1.659)	0.299
mHAQ	–0.023 (–0.085, 0.039)	–0.038 (–0.137, 0.062)	0.239
EQ-5D	0.003 (–0.022, 0.028)	0.022 (–0.018, 0.063)	0.231
Arthritis active today	–0.285 (–0.708, 0.138)	–0.709 (–1.357, –0.061)	0.904
Arthritis pain today	–0.199 (–0.585, 0.187)	–0.595 (–1.187, –0.003)	0.944

*Negative values indicate a reduction in disease activity and improvement in patient-reported outcomes except for EQ-5D, where positive values indicate an improvement

Conclusion: RA pts prescribed abatacept (vs other bDMARDs) in clinical practice tend to be older, with longer disease duration, higher disease activity scores, higher acute-phase reactant and most had prior bDMARD exposure. Despite this, mean changes from BL to 12 months in disease activity measures and PROs in pts on abatacept and other biologic therapies were comparable.[2]

1. Schiff M, et al. *Ann Rheum Dis* 2014;**73**:86–94.

2. This abstract was first presented at the EULAR Congress, 10–13 June 2015, Rome, Italy (AB0448) and published in the corresponding supplement of *Ann Rheum Dis*.

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Abstract Number: 2729

Clinical and Radiographic Outcome of Iguratimod for Rheumatoid Arthritis

Tsuneo Kondo, Akiko Shibata, Ryota Sakai, Jun Kikuchi, Kentaro Chino, Ayumi Okuyama, Hirofumi Takei and Koichi Amano, Department of Rheumatology and Clinical Immunology, Saitama Medical Center, Saitama Medical University, Saitama, Japan
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Background/Purpose:

Iguratimod is a new small-molecular drug for rheumatoid arthritis (RA), which was approved on June, 2012 in Japan. The agent inhibits the production of immunoglobulins and various inflammatory cytokines (interleukin-1, -6 and -8 and TNF), and exerts anabolic effects on bone metabolism by stimulating osteoblastic differentiation and inhibiting osteoclastogenesis in mice through inhibiting the nuclear transcription factor NF-κB, but not its inhibitor, IκBα. In addition this agent is very cheap (1.5$/25 mg tablet) , so 50 mg/day iguratimod therapy costs only 3$/day. A few clinical efficacies have been reported, while radiographic efficacy have never reported. In this study, We evaluate the clinical and radiographic efficacy of iguratimod for RA patients.

Methods:

62 patients who were administered iguratimod at a dosage of 25mg qd during the first month, then 50mg qd thereafter, and followed up for 24 weeks were enrolled. Efficacy was evaluated by composite measures such as DAS28, SDAI, HAQ-DI and modified Total Sharp Score (mTSS), and safety was evaluated by adverse events.

Results: The mean age was 61.3 years and 75.8% of patients were female. MTX was used in 46.8%, the average dose was 8.6±2.9 mg/week. LOCF analysis revealed that DAS28-ESR and SDAI decreased significantly from 4.49±1.33 to 3.12±1.08 and from 18.5±10.9 to 8.3±6.34 in 52 weeks respectively (P<0.01). Remission and LDA rate in DAS28-ESR were 29.0% and 24.2%. HAQ-DI score also decreased from 1.2±0.8 to 0.85±0.79. The percentage of patients with no radiographic progression(ΔmTSS <0.5) was 56.8%, while that of rapid radiographic progression(ΔTSS >5) was 13.5%. The mean estimated yearly progression was 9.9 ± 15.6 at baseline. After 52 weeks of IGU treatment, the mean change was significantly reduced to 1.2 ± 2.5(P<0.01).The difference between the efficacy of igurarimod with and without MTX was not significant. 35.5%(n=22) of the patients discontinued iguratimod within 52 weeks. The reason of cessation consisted of adverse events (21.0%) and lack of efficacy (6.5%). Adverse events were digestive symptom (n=6), liver dysfunction (n=4), nasal hemorrhage (n=2) and so on. There's no severe adverse event.

Conclusion:

IGU reduced disease activity and radiographic progression with RA patients. IGU is generally safe and tolerable and may have a good cost effectiveness. So iguratimod be a new useful option as small molecule DMARDs.

Disclosure: T. Kondo, None; **A. Shibata**, None; **R. Sakai**, None; **J. Kikuchi**, None; **K. Chino**, None; **A. Okuyama**, None; **H. Takei**, None; **K. Amano**, None.

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Abstract Number: 2730

Patient-Reported Outcomes from a Phase 3 Study of Baricitinib in Patients with Rheumatoid Arthritis with Inadequate Response to Conventional Synthetic Disease-Modifying Antirheumatic Drugs

Paul Emery[1], Carol L. Gaich[2], Amy M. DeLozier[3], Stephanie de Bono[2,4], Jiajun Liu[2], Cecile Chang[2] and Maxime Dougados[5], [1]Division of Rheumatic and Musculoskeletal Disease, University of Leeds, Leeds Institute of Molecular Medicine and LMBRU, Leeds, United Kingdom, [2]Eli Lilly and Company, Indianapolis, IN, [3]Lilly Corporate Center, Eli Lilly and Company, Indianapolis, IN, [4]Eli Lilly and Company, Cookham, United Kingdom, [5]Paris-Descartes University, Paris, France
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Background/Purpose:

Baricitinib (bari) is an oral Janus kinase (JAK) 1 /JAK2 selective inhibitor, representing a potentially effective treatment for patients with moderately to severely active rheumatoid arthritis (RA). This study evaluated the effect of bari 2 and 4 mg on patient-reported outcomes (PROs) in patients with RA with an inadequate response or intolerance to conventional synthetic disease-modifying antirheumatic drugs (csDMARDs), including methotrexate, and who have not previously been treated with a biologic DMARD (bDMARD). This study has previously shown that bari improved signs and symptoms of RA (Dougados M et al, Ann Rheum Dis 2015;74(S2):79).

Methods:

In this multicenter, double-blind, double-dummy, outpatient study, patients aged ≥18 yrs with active RA were randomized in a 1:1:1 ratio to placebo (PBO) or bari (2 or 4 mg, once a day) for 24 weeks. PRO measures assessed with daily patient diaries through 12 weeks included duration and severity of morning joint stiffness (MJS), worst tiredness and worst joint pain. PROs assessed at study visits included the Health Assessment Questionnaire-Disability Index (HAQ-DI), Functional Assessment of Chronic Illness Therapy Fatigue (FACIT-F) scale, Short Form 36 (SF–36), European Quality of Life-5 Dimensions-5 Level (EQ-5D), Patient's Global Assessment of Disease Activity, and patient's assessment of pain. PRO data from treatment groups were compared at Week 12 for diary data and at Weeks 12 and 24 for study visits. Analyses were conducted on an intention-to-treat basis.

Results:

684 patients were randomized. **After 12 and 24 weeks of therapy, bari-treated patients achieved statistically significant improvements in most PROs compared with PBO (Tables). For PROs collected via daily patient diaries, bari-treated patients achieved statistically significant improvements at Week 12 in MJS duration, severity, tiredness, and joint pain.**

Conclusion:

In this phase 3 study of patients with RA with an inadequate response to csDMARDs, and not previously treated with a bDMARD, treatment with bari produced significant clinical improvements in disease activity. This analysis showed that treatment with bari also resulted in significant improvement in patient-reported outcomes across different domains including pain, functional disability and fatigue.

PRO Data Collected By Daily Patient Diaries

PRO measures	Day 1 (mean, unless stated otherwise)			Week 12 (LSM, unless stated otherwise)		
	PBO (N=228)	Bari 2 mg (N=229)	Bari 4 mg (N=227)	PBO (N=228)	Bari 2 mg (N=229)	Bari 4 mg (N=227)
Median duration of MJS, minutes	60.0	80.0	75.0	60.0	44.4**	34.6***
Severity MJS, NRS	5.5	5.5	5.3	4.1	3.5 **	3.4 ***
Worst Tiredness, NRS	5.8	5.7	5.7	4.5	4.1 *	4.0*
Worst Joint Pain, NRS	5.8	5.9	5.7	4.7	3.8 ***	3.8 ***

*p≤0.05; **p≤0.01; ***p≤0.001 vs. placebo at Week 12

Abbreviations: LSM: least squares mean; MJS: morning joint stiffness; NRS: numeric rating scale

PRO Data Collected at Study Visits

PRO measures, LSM change from baseline, unless noted otherwise	Week 12			Week 24		
	PBO (N=228)	Bari 2 mg (N=229)	Bari 4 mg (N=227)	PBO (N=228)	Bari 2 mg (N=229)	Bari 4 mg (N=227)
Physical function (HAQ-DI), LSM % change from baseline	-21.9	-38.2***	-36.6***	-21.9	-42.4***	-40.3***
% achieving MCID (≥0.22)	54.4	69.0***	64.3*	41.7	64.2***	60.4***
Fatigue (FACIT-F)	7.5	8.5	9.1	7.9	9.2	10.1*
% achieving MCID (≥3.56)	58.8	63.3	64.8	42.5	59.0***	59.9***
QoL (SF-36)						
Physical Component Score	4.3	8.0***	7.2***	5.3	9.0***	9.1***
% achieving MCID (≥5)	40.4	56.8***	53.3**	33.8	55.5***	55.9***
Mental Component Score	3.2	3.1	3.5	2.6	2.5	3.4
% achieving MCID (≥5)	36.0	38.4	36.1	28.1	31.4	32.6
EQ-5D						
Health State Index Score, US algorithm	0.066	0.117***	0.112***	0.062	0.111***	0.131***
Health State Index Score, UK algorithm	0.092	0.165***	0.162***	0.091	0.157***	0.186***
VAS	4.5	13.5***	11.3***	7.9	13.9**	11.0
Patient's Global Assessment of Disease Activity, LSM, % change from baseline	3.2	-34.9	-8.7	-15.6	-40.4	-15.0
Patient Assessment of Pain (VAS), LSM, % change from baseline	-6.6	-40.0***	-32.2**	-23.2	-41.6**	-38.3*

*p<0.05; **p≤0.01; ***p≤0.001 vs. placebo
Abbreviations: EQ-5D: European Quality of Life-5 Dimensions; FACIT-F: Functional Assessment of Chronic Illness Therapy-Fatigue; HAQ-DI: Health Assessment Questionnaire-Disability Index; LSM: least-squares mean; MCID: minimum clinically important difference; QoL: quality of life; VAS: visual analog scale

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Abstract Number: 2731

Persistency of Tocilizumab As Monotherapy or Combination Therapy in Patients with Rheumatoid Arthritis–Real-World Analyses from the US Corrona Registry

Dimitrios A. Pappas[1,2], Ani John[3], Carol J. Etzel[2,4], Chitra Karki[2], YouFu Li[5], Joel M. Kremer[6], Tmirah Haselkorn[3] and Jeffrey D. Greenberg[2,7], [1]Columbia University, New York, NY, [2]Corrona, LLC, Southborough, MA, [3]Genentech, Inc, South San Francisco, CA, [4]The University of Texas MD Anderson Cancer Center, Houston, TX, [5]University of Massachusetts Medical School, Worcester, MA, [6]Albany Medical College and The Center for Rheumatology, Albany, NY, [7]NYU School of Medicine, New York, NY

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Background/Purpose: For patients with rheumatoid arthritis (RA), there are limited real-world data on factors that predict persistency on biologic therapy or whether use of biologics as monotherapy vs in combination with conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) affects persistency. This analysis compared persistency of the interleukin-6 receptor α inhibitor tocilizumab (TCZ) initiated as combination therapy vs monotherapy and evaluated predictors of persistency in patients with RA.

Methods: Corrona is a US-based, prospective, observational cohort of nearly 40,000 patients with RA. Patients who newly initiated TCZ on or after October 1, 2008, within the Corrona registry and who had ≥ 1 follow-up visit were included in this analysis. Persistency was defined as time to the switch to a new biologic, regardless of possible gaps between TCZ discontinuation and switch to a new biologic. Kaplan-Meier analyses estimated the persistency for all eligible TCZ initiations and by combination therapy vs monotherapy. Multivariable Cox proportional hazards models evaluated associations of type of therapy (combination therapy vs monotherapy) and other baseline factors with persistency of treatment.

Results: Of the 1001 initiations of TCZ included in this analysis, 80.7% of patients were female, median (IQR) age was 58 (49-66) years and median (IQR) duration of RA was 9 (5-17) years. At the time of TCZ initiation, 33.0% initiated TCZ as monotherapy, 52.6% had high disease activity (Clinical Disease Activity Index > 22) and 90.8% had received prior tumor necrosis factor inhibitors (TNFis). The overall median (95% CI) time to switch from TCZ to a new biologic was 33.5 (28.0-41.0) months (**Table**). In patients who initiated TCZ as monotherapy, the median (95% CI) time to switch was comparable with those who initiated TCZ in combination with csDMARDs (36.4 [29.6-not estimable] months vs 28.0 [22.4-40.0] months, respectively; $P = 0.162$). Compared with initiation of TCZ as monotherapy, initiation of TCZ as combination therapy was not associated with an increased likelihood of switching from TCZ to a new biologic (adjusted hazard ratio [HR; 95% CI], 0.81 [0.64-1.04]; $P = 0.100$). Previous and current smokers were significantly more likely to switch to a new biologic (HR [95% CI], 1.32 [1.02-1.73] and 1.50 [1.10-2.06]; $P = 0.040$ and 0.010, respectively), while prior use of 1 TNFi was significantly associated with a 47% decreased likelihood of switching compared with TNFi-naive patients (HR [95% CI], 0.53 [0.34-0.81]; $P = 0.003$).

Conclusion: In this real-world setting of patients with RA, persistency on TCZ was similar when initiated as monotherapy or as combination therapy. Among TCZ initiators, prior use of 1 TNFi was associated with a decreased likelihood of switching to another biologic compared with those with no prior TNFi exposure, whereas smoking was associated with an increased likelihood of switching to another biologic.

Table. Median Time to End of Persistency by Type of Therapy in Patients Initiating TCZ

	N	Persistency of TCZ, Median (95% CI), Months[a]	*P*-value[b]
Overall persistency	1001	33.5 (28.0-41.0)	
Persistency by type of therapy at initiation			
Monotherapy	220	36.4 (29.6-NE[c])	0.162
Combination with csDMARDs	671	28.0 (22.4-40.0)	
Persistency within TCZ combination therapy groups			
TCZ + MTX alone	413	36.4 (29.0-NE[c])	0.757
TCZ + other csDMARDs	72	NE[c] (22.7-NE[c])	
TCZ + other csDMARDs (excluding MTX)	186	33.4 (26.0-NE[c])	
Persistency by number of csDMARDs[d]			
TCZ + 1 csDMARD	568	35.0 (29.0-NE[c])	0.595

csDMARD, conventional synthetic disease-modifying antirheumatic drug; MTX, methotrexate; NE, not estimable; TCZ, tocilizumab.
[a] End of persistency was the *switch* to a new biologic regardless of possible gaps between TCZ discontinuation and switch to a new biologic.
[b] *P*-value from log-rank statistic comparing Kaplan-Meier estimates of median time to discontinuation for combination therapy vs monotherapy and for combination therapy subgroups.
[c] Median or upper CI values NE due to censoring.
[d] The median (95% CI) persistency of TCZ + ≥ 2 csDMARDs (n = 103) was NE.

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Abstract Number: 2732

The Effect of Adrenocorticotropin Gel (HP Acthar Gel) in Combination with MTX in Newly Diagnosed RA Patients from a Clinical and Structural Perspective

Norman B. Gaylis[1], Steven Needell[2] and Joanne Sagliani[1], [1]Arthritis & Rheumatic Disease Specialties, Aventura, FL, [2]Boca Radiology Group, Boca Raton, FL

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Background/Purpose: Although adrenocorticotropin (ACTH) gel was approved by the FDA for the treatment of RA in 1952, data on its clinical and structural benefits for the treatment of RA are limited. Emerging evidence related to the melanocortin system suggests that mechanisms of ACTH gel, in addition to steroidogenesis, may produce anti-inflammatory and immunomodulatory effects,[1] which can have a significant impact in the management of inflammatory disorders such as RA. The objective of this study was to evaluate the effects of ACTH gel on the widely accepted clinical and structural endpoints in patients with early RA.

Methods: Fourteen patients with early RA, were enrolled in a 24-week, open-label study using 15 mg methotrexate (MTX) weekly and 80 U ACTH gel weekly or biweekly. Each subject had a minimum of 6 tender and swollen joints, a Clinical Disease Activity Index (CDAI) score of >6.0 (with a mean score of 39.3) and presence of at least 1 of the following: osteitis, synovitis, or erosions on MRI (Esaote 0.3T) upon enrollment.

Results: We report interim results on 7 patients dosed weekly and 7 patients dosed biweekly with 80 U ACTH gel. In the biweekly-dosed group, all patients showed a clinical response, with an average of 84% improvement in CDAI score after 6 months (Table 1). Two patients in this group achieved remission, 3 low disease activity, and 2 medium disease activity. In the weekly-dosed group, 5 of 7 patients showed a clinical response, with a group average of 61.1% improvement in CDAI score after 6 months (Table 1). One patient remained at high disease activity and 1 patient terminated early due to lack of efficacy. Taking into consideration both groups, 12 of 14 patients showed a clinical response beginning at 3 months (71.2% CDAI improvement), which persisted through 6 months of treatment (71.0% CDAI improvement).

Structural MRI findings varied between treatment groups. In the biweekly-dosed group, 5 patients showed regression in synovitis, while 2 patients showed regression in osteitis. In the weekly-dosed group, 3 patients showed regression in synovitis and 3 patients showed regression in osteitis. Overall, erosions were unchanged or regressed in 9 patients and progressed in 3 patients. No significant adverse events were reported.

Conclusion: The results of this interim analysis suggest a clinical and structural benefit with the use of ACTH gel in combination with MTX in early RA. It appears that the biweekly-dosed group obtained a more robust clinical and structural response; at 6 months this group showed an improved, sustained outcome. These data suggest that use of ACTH gel may result in a very effective treatment combination with MTX for early RA, possibly reducing the need for step-up biologic therapy over time. Further research is needed to determine if these results can be maintained on MTX therapy alone after discontinuation of ACTH gel.

1. Levine T, Drug Des Devel Ther. 2012:6:131–139

Table 1

	Patient	CDAI			Disease Activity	% Improvement at 6 months
		Baseline	3 months	6 months		
Once Weekly	1	25.3	2.7	19.6	MDA	22.5
	2	35.8	16.7	9.5	LDA	73.5
	3	49.5	ET	ET	ET	ET
	4	36.6	12.6	9.3	LDA	74.6
	5	48.3	18.8	41.4	HDA	14.3
	6	49.8	18.3	5.5	LDA	89.0
	7	19.0	1.0	2.9	LDA	84.7
Average		37.8	11.7†	14.7†		59.8 †
	Patient	CDAI			Disease Activity	% Improvement at 6 months
		Baseline	3 months	6 months		
Twice Weekly	1	34.4	5.1	15.9	MDA	53.8
	2	55.9	7.2	5.4	LDA	90.3
	3	37.7	14.1	0.7	Rem	98.1
	4	44.8	0.8	0	Rem	100
	5	42.2	5.3	12.1	MDA	71.3
	6	45.9	15.0	4.4	LDA	90.4
	7	24.8	25.4	7.2	LDA	71.0
Average		40.8	10.4	6.5		82.1
Total Average*		39.3	11.0	10.6		71.0

*Average of once weekly and twice weekly dosing.

†Average of 6 patients as 1 patient terminated the study early.

Early Termination (ET); Low Disease Activity (LDA) [2.9 – 10.0]; Moderate Disease Activity (MDA) [10.1 – 22.0]; High Disease Activity (HAD) [>22.1]; Remission (Rem) [≤2.8]

Disclosure: N. B. Gaylis, Questcor, Janssen, Pfizer, 2,Janssen Pharmaceutica Product, L.P., 8; **S. Needell**, None; **J. Sagliani**, None.

Abstract Number: 2733

Effect of Abatacept on Telomerase Activity of Lymphocytes of Patients with Rheumatoid Arthritis

Kazuhiro Otani[1], Haruyasu Ito[1], Kenichiro Hirai[2], Kentaro Noda[2], Ken Yoshida[2], Isamu Kingetsu[2] and Daitaro Kurosaka[2], [1]Internal Medicine, Jikei University School of Medicine, Tokyo, Japan, [2]Division of Rheumatology, Department of Internal Medicine, Jikei University School of Medicine, Tokyo, Japan

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Background/Purpose:

Telomere is a component of chromosome, and protects end of chromosome from various stress. Telomere shortens during cell division, and telomerase maintains telomere length. It was reported that telomerase activity of lymphocytes is upregulated when the lymphocytes are activated.

Abatacept suppress the activation of T lymphocytes which are involved in pathogenesis of rheumatoid arthritis. Therefore we investigated effect of abatacept on telomerase activity of lymphocytes of patients with rheumatoid arthritis.

Methods:

This study included 16 patients who were diagnosed with rheumatoid arthritis based on ACR 2010 criteria and received treatment of abatacept from August 2012 to August 2013. We collected their clinical data and peripheral blood samples before starting abatacept, 4, 12, 24, and 52 weeks after the treatment. Then we extracted peripheral blood mononuclear cells using ficoll. And CD3 positive lymphocytes and CD19 positive lymphocytes were sorted by magnetic beads. Using these cells, we measured telomerase activity by Telomeric Repeat Amplification Protocol.

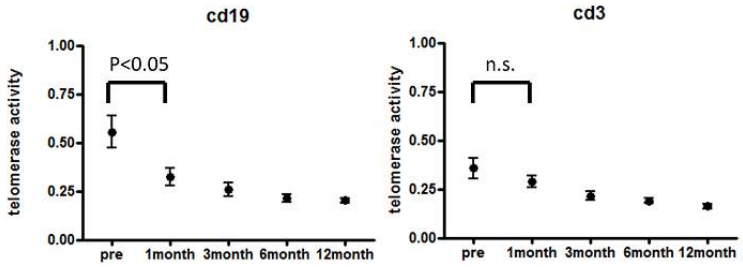
Results:

Mean age of patients was 59.2. Before using abatacept, patients were received various treatment including prednisolone, conventional disease-modifying anti-rheumatic drugs and biologic therapy. DAS28-CRP before treatment of abatacept was 3.43, and that after the treatment was 1.54.

Telomerase activity of CD3 positive lymphocytes declined from 0.413 to 0.156 ($p<0.05$) at 52 weeks after the treatment, and that of CD19 positive lymphocytes also declined from 0.755 to 0.187 ($p<0.05$). Telomerase activity of CD19 positive lymphocytes was significantly downregulated at 4 weeks after the treatment, although that of CD3 positive lymphocytes was not significantly downregulated. (figure)

Conclusion:

Treatment of rheumatoid arthritis including abatacept suppressed the activition of T lymphocytes and B lymphocytes. Telomerase activity of B lymphocytes was downregulated before that of T lymphocytes. It is suggested that abatacept directly suppress the activation of B lymphocytes.



Disclosure: K. Otani, Bristol-Myers Squibb, 2; **H. Ito**, None; **K. Hirai**, None; **K. Noda**, None; **K. Yoshida**, None; **I. Kingetsu**, None; **D. Kurosaka**, Bristol-Myers Squibb, 2.

Abstract Number: 2734

Validation and Comparison Study of Immunoassays for the Measurement of Golimumab and Antibodies to Golimumab in Rheumatic Patients

Sergio Martín[1,2], Ainhoa Ruiz del Agua[1], Nerea Torres[1], Dora Pascual-Salcedo[3], Chamaida Plasencia[4], Teresa Jurado[5], Begoña Ruiz-Argüello[1], Antonio Martínez[1], Rosaura Navarro[6] and **Daniel Nagore**[1], [1]R&D, Progenika-Grifols, Derio, Spain, [2]Department of Physiology, Medicine and Dentistry School, University of the Basque Country UPV/EHU (Convocatoria ZabaldUZ, UPV/EHU; Departamento de Educación, Universidades e Investigación del Gobierno Vasco, Ref. IT687-13), Leioa, Spain, [3]Immunology Unit, La Paz University Hospital-Immunology, Madrid, Spain, [4]Rheumatology Unit, La Paz University Hospital-Rheumatology, Madrid, Spain, [5]Immunology, La Paz University Hospital-Idipaz, Madrid, Spain, [6]Department of Physiology, Medicine and Dentistry School, University of the Basque Country UPV/EHU, Leioa, Spain

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Background/Purpose: The options for treatment of rheumatoid arthritis (RA) with tumour necrosis factor (TNF) inhibitors is constantly growing. As a consequence monitoring of drug levels (DL) and Anti-Drug Antibodies (ADA) in clinical practice is advisable in order to complement clinical assessment and optimize patient treatment. However, a common objection that limits implementation of measurements in medical practice is the claim that assay standardization is lacking. The purpose of this study was to validate new assays to monitor golimumab (GLM) and antibodies to GLM (ATG), and evaluate the correlation and agreement between different commercially available technologies to monitor GLM therapy in patients with rheumatic diseases.

Methods: Trough levels of GLM and ATG were analysed in a retrospective cohort of 48 rheumatic patients (102 serum samples) initiating or under maintenance therapy with GLM for up to three years. Samples were assayed using Promonitor-GLM and Promonitor-Anti-GLM ELISA kits (Progenika, Spain), and in parallel with ELISA and radioimmunoassay (RIA) offered by Sanquin Blood Supply (Amsterdam, The Netherlands) to measure GLM levels and ATG, respectively. Promonitor tests were validated according to Clinical & Laboratory Standards Institute (CLSI) guidelines. Spearman and Mann-Whitney tests were used to study correlation and difference between the two DL tests; the difference (bias) in values obtained with both GLM assays was also assessed with Bland-Altman analysis. Percentage of positive and negative agreement was used to study the association between the ADA methods.

Results: Promonitor tests met performance criteria as recommended in the CLSI guidelines. Both types of ELISA for GLM determination showed a statistically significant relationship (Spearman´s r=0.98, $p<0.0001$). There was no significant difference between the two assays (median 575 vs 600 ng/mL, IQR 0 - 1614 vs 0 - 1600 ng/mL; t-test $p=0.907$ for Promonitor-GLM and Sanquin, respectively). Bland-Altman analysis showed a perfect agreement between both assays (bias -33.4 ng/mL 95% CI -92.3 to 25.3; $p>0.05$). Both tests gave identical results for ATG analysis (positive and negative percentage agreement of 100%). Antibodies were detected in 3 samples (3 patients, 6%) regardless of the test used. ELISA sensitivity proved to be equal to RIA for the detection of ATG

in this cohort.

Conclusion: Validation according to CLSI guidelines proved adequate Promonitor ELISA performance for an in vitro diagnostic setting. Despite different reagents and technologies, no significant differences in GLM and ATG levels were observed between assays, suggesting that future development of optimal ranges values is viable and not influenced by the type of assay, and therefore both methods should result in similar correlations with clinical outcomes and comparable therapeutic actions.

Disclosure: S. Martín, Progenika-Grifols, 2; **A. Ruiz del Agua**, Progenika-Grifols, 3; **N. Torres**, Progenika-Grifols, 3; **D. Pascual-Salcedo**, None; **C. Plasencia**, None; **T. Jurado**, None; **B. Ruiz-Argüello**, Progenika-Grifols, 3; **A. Martínez**, Progenika-Grifols, 3; **R. Navarro**, None; **D. Nagore**, Progenika-Grifols, 3.

Abstract Number: 2735

Is Disease Duration an Independent Predictor of Treatment Response Among Patients with Rheumatoid Arthritis Initiating Abatacept?

Leslie Harrold[1,2], KK Gandhi[3], H Litman[4], S Kelly[3], YF Li[2], E Alemao[3], S Deveikis[1] and J Kremer[5], [1]Corrona, LLC, Southborough, MA, [2]University of Massachusetts Medical School, Worcester, MA, [3]Bristol-Myers Squibb, Princeton, NJ, [4]Corrona, LLC., Southborough, MA, [5]Albany Medical College and The Center for Rheumatology, Albany, NY

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Background/Purpose: It has been postulated that patients with longstanding RA have more treatment-resistant disease. We propose to examine whether disease duration is an independent predictor of treatment response among patients with RA initiating abatacept in a US national observational cohort. **Methods:** Using the Corrona RA registry, we identified new initiators of abatacept between February 2006 and January 2014, with a follow-up visit at 1 year (±3 months), and assessment of disease activity using CDAI at both the time of initiation and the 1-year follow-up, stratified by disease duration (0–2, 3–5, 6–10, >10 years). The primary outcome was mean Δ in CDAI, with a secondary outcome as achievement of low disease activity (LDA; CDAI ≤10) among those who initiated abatacept in moderate or high disease activity, or achievement of remission (CDAI ≤2.8) in those who initiated abatacept in low, moderate or high disease activity. For patients who switched agents before 1 year, the last observation before the switch was used to calculate mean Δ in CDAI. Switchers were imputed as non-responders for calculation of LDA and remission. **Results:** We identified 1746 abatacept initiators who met inclusion criteria (disease duration 0–2 years: 243; 3–5 years: 313; 6–10 years: 431; >10 years: 759). Patients with longer disease duration were more likely to be older, not working (including disabled and retired), more impaired (based on modified Health Assessment Questionnaire), and with a greater number of prior biologics used (Table 1). Unadjusted mean Δ in CDAI at 1 year ranged from –9.8 in those with 0–2 years' disease duration to –5.9 in those with >10 years ($p<0.001$; Table 2). Unadjusted rates of LDA occurred in 44.7% of those with 0–2 years' disease duration but diminished to 30.1% of those with >10 years ($p=0.002$). Similarly, unadjusted rates of remission were observed in 20.8% of those with 0–2 years' disease duration but diminished to 11.7% of those with >10 yrs ($p=0.005$). These differences were attenuated in multivariable models and lost significance. The proportion of patients remaining on abatacept at 1 year among those with 0–2 years' disease duration was 70% compared with 63.9% of those with >10 years' disease duration ($p=0.07$). **Conclusion:** Treatment with abatacept was associated with significantly greater improvement in those with shorter disease duration in unadjusted analyses. This significance was lost in adjusted models, but the trend remained. Further exploration is needed to assess whether earlier treatment with abatacept is independently associated with better outcomes.

Table 1. Baseline characteristics					
	Disease duration, years				
	0–2	**3–5**	**6–10**	**>10**	**p-value**
Baseline characteristics	**N=243**	**N=313**	**N=431**	**N=759**	
Mean age (SD), years	56 (13.9)	57 (13.3)	57.2 (12.6)	61.7 (11.5)	0.001
Female, n (%)	195 (80.2)	255 (81.5)	349 (81.0)	632 (83.3)	0.640
Smoking status					0.020
Current, n (% of m*)	37 (15.4)	68 (21.8)	77 (17.9)	103 (13.6)	
Mean BMI (SD), kg/m^2	30.0 (6.9)	29.9 (6.9)	29.5 (6.7)	29.5 (7.1)	0.22
Work status, n (% of m*)†					0.001
Full time	114 (46.9)	102 (33.2)	159 (37.1)	209 (27.7)	
Part time	26 (10.7)	32 (10.4)	41 (9.6)	70 (9.3)	
Not working outside home	29 (11.9)	38 (12.4)	48 (11.2)	68 (9.0)	
Student	4 (1.6)	10 (3.3)	9 (2.1)	13 (1.7)	
Disabled	20 (8.2)	47 (15.3)	72 (16.8)	158 (21)	
Retired	50 (20.6)	78 (25.4)	99 (23.1)	236 (31.3)	
Medicare, n (%)	63 (25.9)	101 (32.3)	142 (32.9)	363 (47.8)	0.001
Median mHAQ (IQR)	0.38 (0.75)	0.38 (0.75)	0.38 (0.75)	0.5 (0.75)	
Median CDAI (IQR)	20.5 (18.2)	19.8 (19.5)	19 (19.6)	18.3 (19.2)	0.45
Number of prior biologics/small molecules, n (%)					0.001
0	107 (44.0)	45 (14.4)	50 (11.6)	79 (10.4)	
1	85 (35.0)	130 (41.5)	161 (37.4)	244 (32.1)	
2	42 (17.3)	105 (33.5)	132 (30.6)	246 (32.4)	
3+	9 (3.7)	33 (10.5)	88 (20.4)	190 (25.0)	
IQR=interquartile range; mHAQ=modified Health Assessment Questionnaire *m=number of patients with non-missing data; †P-value for number disabled vs others.					

Table 2. Outcomes					
	Disease duration, years				
	0–2	**3–5**	**6–10**	**>10**	
	N=243	**N=313**	**N=431**	**N=759**	
Primary outcome	**Mean (SE)**	**Mean (SE)**	**Mean (SE)**	**Mean (SE)**	**p-value**
Δ in CDAI	–9.8 (0.93)	–8.7 (0.82)	–7.0 (0.70)	–5.9 (0.52)	<0.001
Adjusted Δ in CDAI Model 1*	–8.2 (0.80)	–7.9 (0.68)	–7.2 (0.58)	–6.6 (0.45)	0.30
Adjusted Δ in CDAI Model 2†	–7.9 (0.81)	–7.9 (0.68)	–7.2 (0.58)	–7.0 (0.45)	0.64
Secondary outcome	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**p-value**
	N=206	**N=259**	**N=336**	**N=585**	
Unadjusted achievement of LDA/remission‡	92 (44.7)	89 (34.4)	111 (33.0)	176 (30.1)	0.002
	OR (95% CI)	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**	
Unadjusted likelihood of LDA	Reference	0.65 (0.45, 0.94)	0.61 (0.43, 0.87)	0.53 (0.38, 0.74)	0.003
Adjusted likelihood of LDA, Model 1*	Reference	0.80 (0.54, 1.18)	0.78 (0.53, 1.13)	0.67 (0.46, 0.96)	0.18
Adjusted likelihood of LDA, Model 2†	Reference	0.90 (0.60, 1.35)	0.83 (0.56, 1.22)	0.75 (0.51,1.09)	0.44
*Adjusted for age, sex, baseline CDAI and the number of prior biologic/targeted synthetic DMARDs used †Adjusted for age, sex, CDAI, number of prior biologics/targeted synthetic DMARDs used, smoking status, BMI, work status, Medicare, and mHAQ ‡Among those in moderate or high disease at initiation LDA=low disease activity (CDAI ≤10); mHAQ=modified Health Assessment Questionnaire; OR=odds ratio					

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Reduction of Disease Burden on Workplace and Household Productivity Following 52 Weeks of Treatment with Certolizumab Pegol in Combination with Methotrexate in DMARD-Naïve Patients with Active, Severe, Progressive Rheumatoid Arthritis

VP Bykerk[1], Clifton Bingham[2], Gerd Burmester[3], Daniel E. Furst[4], Xavier Mariette[5], Oana Purcaru[6], Brenda VanLunen[7], Michael Weinblatt[8] and Paul Emery[9], [1]Hospital for Special Surgery, New York, NY, [2]Johns Hopkins University, Baltimore, MD, [3]Department of Rheumatology and Clinical Immunology, Charité - Universitätsmedizin Berlin, Berlin, Germany, [4]Medicine, University of California, Los Angeles, David Geffen School of Medicine, Los Angeles, CA, [5]Université Paris-Sud, AP-HP, Hôpitaux Universitaires Paris-Sud, Paris, France, [6]Outcomes & Access Immunology, UCB, Brussels, Belgium, [7]UCB Pharma, Raleigh, NC, [8]Rheumatology Immunology & Allergy, Brigham and Women's Hospital, Boston, MA, [9]Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds, Leeds, United Kingdom

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Background/Purpose: Rheumatoid arthritis (RA) is associated with work disability and lower employment rates (evidence shows 20–30% of pts are work disabled in the first 3 yrs and up to 40–50% in the first 10 yrs of RA). Improvements in workplace/household productivity with certolizumab pegol (CZP)+MTX have been reported in established RA.[1] Here we estimate the RA burden on work disability in DMARD-naïve early RA vs established RA and assess the CZP+MTX effect on workplace/household productivity in DMARD-naïve early RA pts over 52 wks.

Methods: C-EARLY (NCT01519791) is a phase 3 study assessing efficacy and safety of CZP in DMARD-naïve pts with severe, active and progressive RA (≤1 yr since diagnosis) and poor prognostic factors.[2] RAPID1 (NCT00152386) and RAPID2 (NCT00160602) reported efficacy and safety of CZP in pts with active RA of ≥6 months' duration on MTX for ≥6 months prior to baseline (BL).[1] The burden of early/established RA on workplace and household productivity was assessed at study BL in C-EARLY (full analysis set [FAS]) and pooled RAPID1/2 studies (intent-to-treat [ITT] population), using the validated arthritis specific Work Productivity Survey (WPS).[3] WPS responses (LOCF imputation) in C-EARLY were compared between groups using a non-parametric bootstrap-t method.

Results: At BL, mean age, disease activity and functioning were similar between early and established RA pts (early/established RA: age 50.6/52 yrs; DAS28(ESR) 6.7/6.9; HAQ-DI 1.6/1.6) with differences in mean disease duration since diagnosis (early/established RA: 2.9 months/6.1 yrs) and mean prior synthetic DMARD use (early/established RA: 0/1.3). More early RA pts were employed vs established RA; (52.2% vs 40.9%); more established RA pts were RA work disabled vs early RA (22.3% vs 10.5%) (Table A). High RA burden was reported at BL in both early and established RA pts with >2 wks of paid work (mean 13.3 vs 11.4 days), >2 wks of household duties (mean 18.9 vs 18.1 days), and mean 5.2 vs 5.6 days of social activities affected over previous month, respectively (Table A). At Wk52 in DMARD-naïve pts, greater improvements were reported in CZP+MTX arm vs PBO+MTX in household productivity, and in absenteeism and presenteeism (employed pts only) (Table B).

Conclusion: DMARD-naïve pts with early severe RA and poor prognostic factors have a similar high burden on workplace and household productivity to that reported in established RA, which could lead to large financial burden for pts and society. CZP+MTX showed greater improvements at 1 yr in workplace and household productivity in DMARD-naïve pts with severe, active, progressive RA (≤1 yr since diagnosis), which could reduce the economic burden of this disease.

References:

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2. Emery P. Ann Rheum Dis 2015;74(S2):712

3. Osterhaus J. Arthritis Res Ther 2009;11:R7

Table A: Disease burden on workplace and household productivity at study baseline in early RA DMARD-naïve patients (C-EARLY study, overall FAS) and in patients with established RA (pooled RAPID1 and RAPID 2 studies, overall ITT)

	Early RA (C-EARLY) [a] N=868	Established RA (Pooled RAPID 1 and RAPID 2) [b] N=1601
Employment status at baseline, n (%)		
Employed	446 (52.2)	615 (40.9)
Unable to work due to arthritis	90 (10.5)	336 (22.3)
Retired	152 (17.8)	351 (23.3)
Other not employed status [c]	167 (19.5)	203 (13.5)
Burden of disease on workplace productivity (over the previous month), employed patients only		
Work days affected per month [d], mean	13.3	11.4
Level of arthritis interference on work productivity (0–10 scale) [f], mean	5.6	5.3
Burden of disease on household productivity and daily activities (over the previous month), all patients		
Household work days affected per month [e], mean	18.9	18.1
Family, social or leisure days missed due to arthritis, mean	5.2	5.6
Level of arthritis interference on household work productivity (0–10 scale) [f], mean	6.1	6.1

Results shown for patients who completed the WPS survey at study baseline. [a] C-EARLY, FAS: full analysis set; [b] Pooled RAPID1 and RAPID2 studies, ITT: intent-to-treat; [c] "Other not employed status" category includes homemaker, unable to work due to non-arthritis health problems, student, other not employed; [d] Includes full days missed (absenteeism) and days with productivity reduced by at least 50% (presenteeism); the estimated maximum paid work days affected/month is 20 days; [e] Includes days with no household work and days with household productivity reduced by at least 50%, the estimated maximum household work days affected/month is 30 days; [f] 0=no interference, 10=complete interference.

Table B: C-EARLY study: Improvements in patient workplace and household productivity and reduction in need for regular assistance with daily activities (FAS)

		PBO+MTX (n=213)	CZP+MTX (n=655)
Productivity at the workplace [a] (employed patients only)			
Work days missed due to arthritis per month	Baseline [b]	4.0	4.4
	Week 52 [c]	0.9	0.6
Days with work productivity reduced by ≥50% per month due to arthritis[d]	Baseline [b]	8.8	6.4*
	Week 52 [c]	1.8	1.0*
Level of arthritis interference with work productivity per month (0-10 scale, 0=no interference)	Baseline [b]	5.8	5.5
	Week 52 [c]	1.9	1.4*
Productivity in home and daily activities [a] (all patients)			
Household work days missed per month	Baseline [e]	10.4	8.8*
	Week 52 [f]	3.0	1.9*
Household work days with productivity reduced by ≥50% per month [d]	Baseline [e]	10.6	9.4
	Week 52 [f]	3.0	2.1*
Level of arthritis interference with household work productivity per month (0-10 scale, 0=no interference)	Baseline [e]	6.4	6.0*
	Week 52 [f]	2.5	1.9*

*p<0.05, **p<0.01, CZP+MTX vs PBO+MTX (non-parametric bootstrap t method, p-values are nominal); Full analysis set; Mean WPS responses, LOCF imputation; [a] Assessed through the arthritis-specific Work Productivity Survey (WPS); [b] n=108 (PBO+MTX), n=338 (CZP+MTX); [c] n=106 (PBO+MTX), n=351 (CZP+MTX); [d] Does not include work days missed counted in the previous question; [e] n=209 (PBO+MTX), n=646 (CZP+MTX); [f] n=206 (PBO+MTX), n=640 (CZP+MTX).

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Abstract Number: 2737

Consistency of Treatment Effects Across Different High-Risk Clinical Phenotypes in the Tofacitinib Clinical Program

Jeffrey R. Curtis[1], Ara Dikranian[2], Alan Mendelsohn[3], Koshika Soma[4], Haiyun Fan[3] and Chudy Nduaka[3], [1]University of Alabama at Birmingham, Birmingham, AL, [2]San Diego Arthritis Medical Clinic, San Diego, CA, [3]Pfizer Inc, Collegeville, PA, [4]Pfizer Inc, Groton, CT

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Background/Purpose: Tofacitinib is an oral Janus kinase inhibitor for the treatment of RA. Patients (pts) with RA often have comorbidities that may affect treatment response. This post-hoc analysis evaluated whether predefined clinical phenotypes influenced treatment response, as assessed by different efficacy and safety outcomes.

Methods: Data from Phase 3 randomized studies of tofacitinib 5 mg BID in RA as monotherapy (ORAL Solo [NCT00814307], ORAL Start [NCT01039688]) or with background conventional synthetic DMARDs (csDMARDS; mainly methotrexate [MTX]) (ORAL Scan [NCT00847613], ORAL Sync [NCT00856544], ORAL Standard [NCT00853385]) were included. Pts in ORAL Start were MTX-naïve while pts in other studies had an inadequate response to biologic or csDMARDs, mostly MTX. Efficacy and safety of tofacitinib was evaluated in subgroups of monotherapy and combination therapy populations with different high-risk comorbidities: diabetes (history of diabetes and/or treatment with anti-diabetic medication at baseline [BL]); obesity (BMI $\geq$30 kg/m^2) and hypertension (history of hypertension and/or treatment with antihypertensive medication at BL); or obesity and dyslipidemia (total cholesterol >2g/L and/or treatment with lipid-lowering medication at BL). Efficacy outcomes at Month 3 included the proportion of pts achieving low disease activity (DAS28-4(CRP) $\leq$3.2); ACR50 response; and mean change from BL in Health Assessment Questionnaire-Disability Index (HAQ-DI) score. Safety outcomes included incidences of serious adverse events (SAEs) up to Month 3, discontinuations due to AEs, and serious infections (SIEs).

Results: In total, 616 pts received tofacitinib 5 mg BID monotherapy (243 from ORAL Solo and 373 from ORAL Start) and 840 pts received tofacitinib 5 mg BID with background csDMARDs. Efficacy and safety outcomes by pt subgroups are presented in the Table. Tofacitinib 5 mg BID was similarly efficacious across different high-risk clinical phenotypes.

Incidence rates for discontinuations due to AEs were numerically higher for the csDMARD group than the monotherapy group.

Efficacy and safety outcomes in these subpopulations were within the ranges of the overall populations for the respective Phase 3 studies.

Conclusion: These findings suggest that tofacitinib 5 mg BID, when administered as monotherapy or combination therapy, has a consistent efficacy and safety profile up to Month 3 in RA pts with different high-risk clinical phenotypes, such as diabetes. Although these pts are at high risk of further AEs, they appear to experience a short-term safety profile with tofacitinib similar to the overall clinical program population. Limitations include the relatively few pts in each clinical phenotype subgroup, and that the monotherapy group included MTX-naïve pts, whereas the csDMARD group included DMARD inadequate responders only.

Table. Efficacy and safety outcomes at Month 3							
		Monotherapy			Background csDMARDs		
		Diabetes	Obese and hypertension	Obese and dyslipidemia	Diabetes	Obese and hypertension	Obese and dyslipidemia
Total, n/N (%)	Tofacitinib 5 mg BID	47/616 (7.6)	77/616 (12.5)	121/616 (19.6)	68/840 (8.1)	108/840 (12.9)	166/840 (19.8)
	Placebo*	3/122 (2.5)	23/122 (18.9)	28/122 (23.0)	34/427 (8.0)	45/427 (10.5)	83/427 (19.4)
DAS28-4(CRP) ≤3.2 n/N (%) [CI]	Tofacitinib 5 mg BID	14/43 (32.6) [19.1, 48.5]	24/70 (34.3) [23.4, 46.6]	37/113 (32.7) [24.2, 42.2]	18/64 (28.1) [17.6, 40.8]	29/99 (29.3) [20.6, 39.3]	37/151 (24.5) [17.9, 32.2]
	Placebo*	0/2	2/20 (10.0) [1.2, 31.7)	4/26 (15.4) [4.4, 34.9]	2/31 (6.5) [0.8, 21.4]	3/38 (7.9) [1.7, 21.4]	2/76 (2.6) [0.3, 9.2]
ACR50 response n/N (%) [CI]	Tofacitinib 5 mg BID	19/43 (44.2) [29.1, 60.1]	24/71 (33.8) [23.0, 46.0]	39/114 (34.2) [25.6, 43.7]	21/64 (32.8) [21.6, 45.7]	28/99 (28.3) [19.7, 38.2]	40/152 (26.3) [19.5, 34.1]
	Placebo*	1/2 (50.0) [1.3, 98.7]	4/21 (19.1) [5.5, 41.9]	7/27 (25.9) [11.1, 46.3]	4/31 (12.9) [3.6, 29.8]	2/38 (5.3) [0.6, 17.8]	6/76 (7.9) [3.0, 16.4]
HAQ-DI, mean change from BL (SD)	Tofacitinib 5 mg BID	-0.6 (0.6)	-0.6 (0.7)	-0.5 (0.7)	-0.5 (0.6)	-0.3 (0.5)	-0.4 (0.5)
	Placebo*	-0.3 (0.7)	-0.2 (0.7)	-0.4 (0.7)	-0.3 (0.7)	-0.3 (0.5)	-0.2 (0.5)
Discont. due to AEs, IR (95% CI)	Tofacitinib 5 mg BID	8.9 (3.4, 23.8)	1.2 (0.2, 8.6)	3.4 (1.4, 8.2)	14.3 (7.9, 25.7)	13.5 (8.1, 22.3)	12.3 (8.1, 18.7)
	Placebo*	0	18.9 (2.7, 134.0)	0	0	7.3 (1.0, 51.5)	3.7 (0.5, 25.9)
SAEs, n/N (%)	Tofacitinib 5 mg BID	1/47 (2.1)	2/77 (2.6)	2/121 (1.7)	5/68 (7.4)	7/108 (6.5)	8/166 (4.8)
	Placebo*	1/3 (33.3)	2/23 (8.7)	2/28 (7.1)	0/34	0/45	0/83
SIEs, IR (95% CI)	Tofacitinib 5 mg BID	6.8 (2.2, 21.1)	0	1.4 (0.3, 5.5)	3.9 (1.2, 12.0)	6.3 (3.0, 13.2)	4.5 (2.2, 8.9)
	Placebo*	0	0	0	9.2 (1.3, 65.6)	0	0
IR, incidence rate: pts with events/100 pt-years *For monotherapy studies, only ORAL Solo had a placebo arm							

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Abstract Number: 2738

A Comparison of EQ5D Index from the UK, US, and Japan Preference Weights Model, and Mapping Algorithm from Clinical Outcomes in Patients with Rheumatoid Arthritis: Results from Golimumab Intravenous Study

Chenglong Han[1], Clifton O. Bingham III[2], Rene Westhovens[3], Michael Weinblatt[4], Lilianne Kim[5], Daniel Baker[5], Steven Peterson[6] and Elizabeth C. Hsia[5,7], [1]Outcomes Research, Janssen Global Services, LLC, Malvern, PA, [2]Johns Hopkins University, Baltimore, MD, [3]Rheumatology, UZ Gasthuisburg, Leuven, Belgium, [4]Brigham & Women's Hospital, Boston, MA, [5]Janssen Research & Development, LLC, Spring House, PA, [6]Janssen Global Services, LLC, Malvern, PA, [7]University of Pennsylvania, Philadelphia, PA
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Background/Purpose: To compare the EQ5D index from the UK, US, and Japan preference weights models in patients with rheumatoid arthritis (RA), and to examine the relationship of each index with clinical outcomes for developing mapping algorithm.

Methods: GO-FURTHER was a multicenter, randomized, placebo-controlled study. Adult patients with active RA were randomized to PBO + MTX (PBO group) or GLM (2mg/kg) plus MTX at wk 0, 2, and every 8 wk thereafter (GLM group). Patients in PBO group with <10% improvement in tender and swollen joint count from baseline at wk 16 entered early escape (EE) and received a 2 mg/kg GLM infusion at wks 16 and 20. Clinical and patient-reported outcomes measures including EQ5D domains, EQ VAS scale, Health Assessment Questionnaire (HAQ) were collected. The EQ-5D index was calculated using preference weights from the US (D1) [1], UK (N3)[2], and Japanese [3]population weights. Pearson's correlation and linear regression model were used to test correlation and established mapping algorithms. Comparisons between groups in EQ5D index were performed using t-test.

Results: The study population had moderate to severe RA with a HAQ score of 1.6 and DAS28 score of 5.9 at the baseline. The UK model predicted a lower EQ5D index (0.36 ±0.33), compared to the US model (0.54 ±0.21) and Japan model (0.52 ±0.13).The differences in EQ5D index between UK and US or Japan model were moderate in patients with mild to moderate disability (HAQ-DI<1) (0.64 vs. 0.72 and 0.64), but were more than twofold in patients with severe disability (HAQ-DI>1.5) (0.19 vs.0.42 and 0.45). The Pearson's correlations coefficient of EQ5D index from the US model with HAQ, DAS28 score, pain, SF-36 PCS and MCS was -0.70, -0.40, -0.51, -0.57, -0.55, respectively (all p value <0.001), and were highly consistent across 3 models and sensitive to change. Comparing mapping algorithms based on linear regression models, HAQ model was equally predictive to each EQ5D index. However, the UK N3 model was more responsive to active treatment compared to US D1 or Japan model. Compared to PBO+MTX group, the change in EQ5D index in GLM+MTX group at wk24 were 0.26±0.32 vs. 0.11±0.37 in UK model (p<0.001), 0.17±0.21 vs. 0.11±0.23 in US model (p<0.01), and 0.13±0.16 vs. 0.05±0.17 in Japan model (p<0.001).

Conclusion: Although HAQ was highly predictive to EQ5D index derived from US, UK or Japan model, the EQ5D scores from each model were not equivalent, and were significantly influenced by disease severity, warranting caution in the cost-utility analysis across trials.

[1]Dolan P: *Med Care* 1997, **35:**1095-1108; [2]Shaw JW, et al: *Med Care* 2005, **43:**203-220; [3]Tsuchiya A, et al *Health Econ* 2002, **11:**341-345

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Abstract Number: 2739

Survival of Etanercept (ETN) Responders after Methotrexate (MTX) Failure When ETN Is Initiated As Mono or Combination Therapy or after MTX Withdrawal from

ETN/MTX Combination in Long Standing Rheumatoid Arthritis (RA). a Single Center Retrospective Study

Edward C. Keystone[1], Abdulaziz ALKhalaf[2,3], Sabri ALSaeedi[4,5], Mosaab Makkawy[4,6], Deborah Weber[7] and Daming Lin[8], [1]Mount Sinai Hospital, University of Toronto, Toronto, ON, Canada, [2]Rheumatology Division, Medicine Department, UNIVERSITY OF TORONTO/Mount Sinai Hospital, Toronto, ON, Canada, [3]Rheumatology Division, Medicine Department, King Saud University, Riyadh, Saudi Arabia, [4]Rheumatology Division, Medicine Department, UNIVERSITY OF TORONTO/ Mount Sinai Hospital, Toronto, ON, Canada, [5]Rheumatology Division, Medicine Department, King Fahd Hospital, Jeddah, Saudi Arabia, [6]Rheumatology Division, Medicine Department, Prince Mohammad Bin Abdulaziz Hospital, Riyadh, Saudi Arabia, [7]Advanced Therapeutics, Mt Sinai Hosp 2nd Floor 02-205, Toronto, ON, Canada, [8]Rheumatology, Mount Sinai Hospital, University of Toronto, Toronto, ON, Canada
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Background/Purpose: The long term sustainability of ETN as monotherapy (mono) or in combination (combo) with methotrexate (MTX) is uncertain in patients with longstanding RA responding to ETN after MTX failure.

Objectives: The purpose of this study was to evaluate the long term sustainability of ETN for efficacy in ETN responsive patients after MTX failure when initiated as mono or combo therapy.

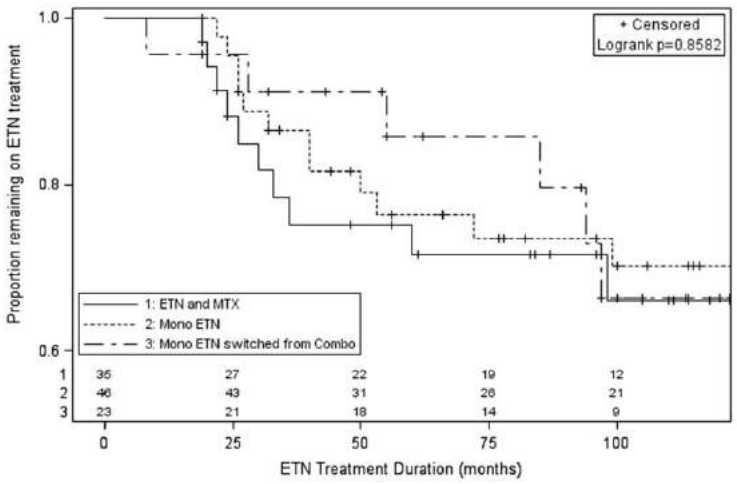
Methods: A retrospective cohort based on a chart review of 140 pts from a single rheumatology center who initiated ETN as their first biologic was carried out. Only data from 104 (74.3%) pts who had achieved DAS 28 low disease or remission by 18 months (mo.) were considered for analysis in order to more stringently define secondary ETN efficacy failures in the survival analysis. Pts discontinuing ETN before 18 mo or for adverse effects at any time were excluded from the long term survival analysis. Three groups of pts were included in the long term survival analysis: (i) pts initiating combo ETN plus MTX, (ii) patients initiating ETN mono because of prior intolerance to MTX, (iii) patients initiating ETN mono after withdraw of MTX from the ETN/ MTX combo.

Results: Of the 140 total ETN treated pts, 36(25.7%) discontinued ETN for efficacy before 18 mo: 11 (7.9%) before 6 mo, 17 (12.1%) between 6-12 mo and 8 (5.7%) between 12-18 mo. In the 104 pts achieving low disease or remission for 18 mo, 93(82%) were women, mean (SD) age 52.4(12.6) with a disease duration of 22.4(9.7) years of which 71(77.2%) were seropositive. Baseline disease activity (at ETN initiation) of the 46 pts initiating ETN mono revealed a tender joint count (tjc) of 4.9(7.0) a swollen joint count (sjc) of 7.5(5.9), an ESR of 29.5(21.3) and DAS28 score of 4.3(1.4). Of 35 patients adding ETN to the MTX combo, the baseline (at MTX initiation) tjc was 4.9(5.1), sjc 9.1(5.9), ESR 40.4(31.1) and DAS28 score of 4.8(0.9). A separate population of 23 pts receiving combo therapy withdrew MTX (mean (SD) time from withdrawl was 21.8 (19.3) mo with a median of 16 mo). The baseline (at MTX initiation) tjc was 2.52(3.8), sjc 9.1(4.5), ESR 25.6(14.3) and DAS28 score of 3.8 (1.1) The results of the survival analysis of the 104 pts (figure 1) revealed comparable survival of the all 3 groups at 10 years (log rank 0.8582). Survival of ETN after MTX withdrawl appeared greater than the other groups but its survival analysis was initiated 18 months after MTX withdrawl.

Conclusion: In this preliminary analysis of extremely long standing RA pts, ETN responders who achieve low disease or remission by18 months have a high likelihood of ETN sustainability whether initiating ETN as mono or combo therapy or withdrawing MTX from the combo. Larger pt populations need to be studied for confirmation of the results.

Image:

Survival curves in RA pts achieving low disease or remission after 18 months for biologic naïve patients initiating ETN mono therapy or adding ETN in combination with MTX, or initiating ETN mono after discontinuing MTX from combo therapy.



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Abstract Number: 2740

ACPA Positivity in the Elderly and Concomitant MTX Use in Younger May be Useful Predictive Factors for Superior Clinical Efficacy with Abatacept in Japanese Biological-Naïve RA Patients

Masahiro Sekiguchi[1], Takao Fujii[2], Masayasu Kitano[1], Kiyoshi Matsui[1], Kenji Miki[3], Hideo Hashimoto[4], Akira Yokota[5], Aihiro Yamamoto[6], Takashi Fujimoto[7], Toshihiko Hidaka[8], Naoki Shimmyo[9], Keiji Maeda[10], Takanori Kuroiwa[11], Ichiro Yoshii[12], Kosaku Murakami[13], Koichiro Ohmura[13], Satoshi Morita[14], Yutaka Kawahito[6], Norihiro Nishimoto[15], Tsuneyo Mimori[16] and Hajime Sano[1], [1]Division of Rheumatology, Department of Internal Medicine, Hyogo College of Medicine, Nishinomiya, Japan, [2]Dept of Rheum/Clinical Immun, Kyoto University Graduate School of Medicine, Kyoto, Japan, [3]Department of Orthopaedic Surgery, Amagasaki Central Hospital, Amagasaki, Japan, [4]Rheumatology, Rinku Hashimoto Rheumatology Orthopaedics, Izumisano Osaka, Japan, [5]Yokota Clinic for Rheumatology, Osaka, Japan, [6]Inflammation and Immunology, Graduate School of Medical Science, Kyoto Prefectural University of Medicine, Kyoto, Japan, [7]Nara Medical University, Kashihara, Japan, [8]Zenjinkai Shimin-no-Mori Hospital, Miyazaki, Japan, [9]Department of Rheumatology, Kashiba Asahigaoka Hospital, Kashiba, Japan, [10]Division of Allergy, Rheumatology and Connective Tissue Diseases, Department of Internal Medicine, NTT West Osaka Hospital, Osaka, Japan, [11]Department of Internal Medicine, Yukioka Hospital, Osaka, Japan, [12]Department of Orthopaedic Surgery, Yoshii Hospital, Shimanto, Japan, [13]Rheumatology & Clin Immunology, Kyoto University Graduate School of Medicine, Kyoto, Japan, [14]Department of Biomedical Statistics and Bioinformatics, Kyoto University Graduate School of Medicine, Kyoto, Japan, [15]Osaka Rheumatology Clinic, Osaka, Japan, [16]Dept of Rheum & Clinical Immun, Kyoto University Graduate School of Medicine, Kyoto, Japan

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Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose:

Sustained clinical remission is crucial in the RA. However, baseline predicting factors for sustained clinical remission in RA patients treated with abatacept (ABT) are little known.The ABROAD (ABbatacept Research Outcomes as a first-line biological Agent in the real worlD) study is the prospective multicenter observational cohort study, in which 43 institutions in the west side of Japan participate to investigate both efficacy and safety of ABT in biologic-naïve RA patients. The purpose of the present study was to

determine the useful markers associated with sustained clinical remission by the intravenous ABT infusion treatment in different age groups (age ≥ 65 vs < 65 years old).

Methods:

Two-hundred and seventy-seven RA patients with high or moderate disease activity (female = 84.8%, mean age at the ABT initiation = 63.2 years old, disease duration = 7.9 years) were enrolled. DAS28-CRP remission rate at 24, 36, and 48 weeks after the initiation of ABT treatment were examined. Then, patient profiles, disease activity, concomitant drug use, and laboratory findings at baseline associated with sustained clinical remission (>12 weeks) during the last 24 weeks in the whole treatment period (48 weeks) were determined by logistic regression analysis.

Results:

The proportion of patients, who achieved DAS28-CRP-defined clinical remission at 24 and 48 weeks, were 35.1% and 36.5% in elderly patients (≥ 65 years old) and 34.9% and 43.4% in younger patients (< 65 years old), respectively. In elderly patients, ACPA positivity (Odds ratio [OR] = 5.378, 95% confidence interval [CI] = 1.225-38.512, p = 0.0241) was significantly associated with sustained clinical remission. In elderly patients without ACPA, a significant change in DAS28-CRP was observed only 4 weeks from baseline. However, the DAS28-CRP improved persistently until 24 weeks in the elderly patients having ACPA. On the other hand, in younger patients, concomitant MTX use (OR = 4.981, 95% CI = 1.426-23.621, p = 0.0103) was the predictive factors for sustained clinical remission. Significant improvement in the DAS28-CRP score was observed from the baseline to 12 weeks in younger patients without MTX use, while in younger patients who did use MTX, improvement was noted from the baseline to 24 weeks. Mean DAS28-CRP values were similar throughout the entire study period regardless of the presence or absence of ACPA in the younger patients group, and any concomitant MTX use in elderly patients.

Conclusion:

The efficacy of ABT in biologic-naïve RA patients was equivalent between elderly and younger patient groups, while the baseline clinical characteristics in association with clinical remission were totally different. ACPA positivity in elderly and concomitant MTX use in younger patients may be the useful predicting factors for achieving sustained clinical remission with ABT. We recommend treatment with ABT particularly for biologic-naïve RA patients who are elderly and have ACPA, and also for those who are younger and have received MTX.

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Abstract Number: 2741

An Analysis of the Efficacy of Tofacitinib Monotherapy in MTX-Naïve Patients with Early RA Compared with Patients with Established RA

Roy Fleischmann[1], T. W. J. Huizinga[2], Arthur Kavanaugh[3], Bethanie Wilkinson[4], Kenneth Kwok[5], Ryan DeMasi[5] and Ronald F. van Vollenhoven[6], [1]Metroplex Clinical Research Center, Dallas, TX, [2]Leiden University Medical Center, Leiden, Netherlands, [3]University of California, San Diego School of Medicine, LaJolla, CA, [4]Pfizer Inc, Groton, CT, [5]Pfizer Inc, New York, NY, [6]The Karolinska Institute, Stockholm, Sweden

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Background/Purpose: Tofacitinib is an oral Janus kinase inhibitor for the treatment of RA. In a Phase 3 study (ORAL Start; NCT01039688), tofacitinib monotherapy in MTX-naïve patients demonstrated significant, durable, and clinically meaningful improvements in RA signs and symptoms and physical functioning, and inhibition of progression of structural damage, vs MTX over 24 months.[1] Here, we present a post-hoc analysis of ORAL Start to assess the efficacy and safety of tofacitinib monotherapy in patients

with early RA or established RA as defined by disease duration. Interim data have previously been presented.[2] **Methods:** Patients were randomized 2:2:1 to tofacitinib 5 mg twice daily (BID), tofacitinib 10 mg BID, or MTX (mean MTX dose at end of titration [Month 3], 18.5 mg/week). Clinical efficacy was assessed in cohorts of patients with disease duration at baseline <1 (early RA) and ≥1 year (established RA), using ACR20/50/70, Disease Activity Score (DAS)28-4(ESR)<2.6 (DAS28-4[ESR]-remission) and ≤3.2 (low disease activity), and HAQ-Disability Index (HAQ-DI). Safety assessments included recording the incidence and severity of all adverse events (AEs). **Results:** Although not pre-defined in the original study, a total of 515 patients had early RA (N=201, N=207, and N=107 for tofacitinib 5 mg BID, tofacitinib 10 mg BID, and MTX, respectively) and 441 patients had established RA (N=172, N=190, and N=79 for tofacitinib 5 mg BID, tofacitinib 10 mg BID, and MTX, respectively). For all efficacy parameters at Month 12 and Month 24 within each cohort, response rates and improvements from baseline were significantly greater ($p<0.05$) for both tofacitinib doses vs MTX, except for patients with established RA treated with tofacitinib 5 mg BID (ACR20, ACR50, and ACR70 at Month 12; change from baseline in HAQ-DI, DAS28-4(ESR)≤3.2, and DAS28-4(ESR)<2.6 at both Month 12 and Month 24) and tofacitinib 10 mg BID (DAS28-4(ESR)<2.6 at Month 12). Numerically more tofacitinib-treated patients with early RA achieved ACR20/ACR50/ACR70 responses, DAS-defined remission and low disease activity and numerically greater changes from baseline in HAQ-DI at both Month 12 and Month 24 compared with patients with established RA (Table 1). Odds ratios for early RA vs established RA were greater than 1 for all efficacy parameters from Month 1 through Month 24. In general, there was no difference in AEs or discontinuations due to AEs when patients were sub-grouped by baseline disease duration. **Conclusion:** Tofacitinib monotherapy significantly improved signs and symptoms and physical function vs MTX in MTX-naïve patients with early (<1 year) and established (≥1 year) disease. There were generally greater numerical improvements observed in patients with shorter disease duration. AEs and discontinuations due to AEs were similar between groups. **References:** 1. Lee EB et al. N Engl J Med 2014; 370: 2377-2386.

2. Huizinga TWJ et al. Ann Rheum Dis 2013; 72: 241.

Table 1. Clinical efficacy and safety parameters in patients with baseline disease duration <1 year (early RA) and ≥1 year (established RA)

Parameter	Tofacitinib 5 mg BID		Tofacitinib 10 mg BID		MTX	
	Early RA (N=201)	Established RA (N=172)	Early RA (N=207)	Established RA (N=190)	Early RA (N=107)	Established RA (N=79)
ACR20 response rate, %						
Month 12	70.41	65.29	71.43	71.28	49.06	53.95
Month 24	68.88	58.24	66.01	62.77	47.17	36.84
ACR50 response rate, %						
Month 12	52.04	47.65	58.13	52.13	30.19	38.16
Month 24	54.08	42.94	53.20	45.21	32.08	23.68
ACR70 response rate, %						
Month 12	33.67	22.94	40.39	35.11	16.04	14.47
Month 24	40.82	26.47	40.89	34.04	15.09	15.79
DAS28-4(ESR)≤3.2 rates, %						
Month 12	37.23	27.81	41.54	40.23	16.67	21.92
Month 24	42.02	25.17	38.97	32.76	16.67	15.07
DAS28-4(ESR)<2.6 rates, %						
Month 12	22.34	13.91	24.62	21.84	9.38	15.07
Month 24	25.00	15.23	21.54	22.99	11.46	8.22
LS mean change from baseline in HAQ-DI						
Month 12	-0.95	-0.86	-1.03	-0.97	-0.66	-0.79
Month 24	-0.99	-0.86	-1.08	-1.00	-0.74	-0.73
Adverse events at Month 24, n (%)	165 (82.1)	132 (76.7)	175 (84.5)	159 (83.7)	83 (77.6)	64 (81.0)
Discontinuations due to adverse events at Month 24, n (%)	22 (10.9)	18 (10.5)	21 (10.1)	20 (10.5)	14 (13.1)	11 (13.9)

N numbers are for all treated patients; therefore, N numbers per endpoint and timepoint could have fewer patients due to data collection and availability.

BID, twice daily; DAS, disease activity score; HAQ-DI, HAQ-Disability Index; LS, least squares

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Abstract Number: 2742

Efficacy and Safety of Tofacitinib Monotherapy Versus Combination Therapy in a Latin American Subpopulation of Patients with Rheumatoid Arthritis: A Pooled Phase 3 Analysis

Cristiano Zerbini[1], Sebastiao Radominski[2], Mario H. Cardiel[3], Oswaldo Castañeda[4], Ferope Romero[5], Gustavo Citera[6], Oscar Neira[7], Dario Ponce de Leon[8], Elaine Hoffman[9] and Ricardo Rojo[10], [1]Centro Paulista de Investigação Clinica, São Paulo, Brazil, [2]Universidade Federal do Paraná, Curitiba, Brazil, [3]Centro de Investigacion Clinica de Morelia, Morelia, Mexico, [4]Clínica Angloamericana, Lima, Peru, [5]Hospital Arzobispo Loayza, Lima, Peru, [6]Rheumatology, Instituto de Rehabilitación Psicofísica, Buenos Aires, Argentina, [7]Hospital del Salvador, Clínica Alemana, Santiago, Chile, [8]Pfizer Inc, Lima, PA, Peru, [9]Pfizer Inc, Groton, CT, [10]Pfizer Inc, New York, NY

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Session Title: Rheumatoid Arthritis - Small Molecules, Biologics and Gene Therapy Poster III
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Background/Purpose: Tofacitinib is an oral Janus kinase inhibitor for the treatment of RA. This post-hoc pooled analysis was designed to assess the efficacy and safety of tofacitinib, as monotherapy or combination therapy with nonbiologic DMARDs, in Latin American (LA) patients with an inadequate response to prior DMARDs.

Methods: Phase 3 data were pooled from LA patients receiving tofacitinib 5 or 10 mg BID or placebo as monotherapy (ORAL Solo [NCT00814307]) or combination therapy (ORAL Scan [NCT00847613], ORAL Sync [NCT00856544] and ORAL Standard [NCT00853385]). Patients included in the analysis were from Brazil, Dominican Republic, Colombia, Mexico, Chile, Peru, Argentina, Venezuela and Costa Rica. Efficacy outcomes assessed at 3 months were ACR20, 50 and 70 responses, and the health assessment questionnaire – disability index (HAQ-DI). Adverse events (AE) and clinical laboratory parameters were also assessed.

Results: 451 patients were included in the pooled analysis with a mean age (range) of 49.2 (18-75) years in the combination therapy arm and 50.4 (22-77) years for monotherapy. Tofacitinib 5 and 10 mg BID as monotherapy or combination therapy had higher ACR20, 50 and 70 response rates than placebo, with similar response rates between monotherapy and combination therapy for both doses of tofacitinib (Table). Mean change from baseline in HAQ-DI score was similar for monotherapy and combination therapy with either dose. Adverse events occurred more frequently with tofacitinib 5 and 10 mg BID compared with placebo, and numerically more events with combination therapy were noted compared with monotherapy in some parameters (Table). Seventeen tofacitinib treated patients withdrew due to adverse events (monotherapy, 4; combination, 13), and four patients withdrew due to infection (monotherapy, 1; combination, 3). Patients receiving combination therapy were more likely to develop elevations in liver enzymes. No patients developed severe neutropenia or lymphopenia, with either monotherapy or combination therapy.

Conclusion: In this short-term post-hoc analysis of pooled, Phase 3 data from LA patients with RA, tofacitinib demonstrated similar efficacy as monotherapy or combination therapy and patients on tofacitinib monotherapy appeared to have fewer discontinuations due to adverse events and fewer elevations in liver enzymes compared with combination therapy over Months 0-3. These data are consistent with data from the global population of tofacitinib-treated patients.[1]

Reference: 1. Keystone et al. Ann Rheum Dis. 2013;72(S3):242.

Table. Efficacy and Safety Outcomes Over 3 Months

Parameter	Monotherapy			Combination		
	Tofacitinib 5 mg BID	Tofacitinib 10 mg BID	Placebo	Tofacitinib 5 mg BID	Tofacitinib 10 mg BID	Placebo
	N=62	N=68	N=36	N = 118	N=112	N=55
ACR20 response rate, n (%)	43 (69.4)	53 (81.5)	12 (37.5)	76 (70.4)	76 (73.8)	16 (33.3)
ACR50 response rate, n (%)	29 (46.8)	30 (46.2)	6 (18.8)	51 (47.2)	54 (52.4)	9 (18.8)
ACR70 response rate, n (%)	12 (19.4)	13 (20.0)	4 (12.5)	19 (17.6)	26 (25.2)	1 (2.1)
HAQ-DI, mean change from baseline (SD)	-0.58 (0.70)	-0.68 (0.63)	-0.26 (0.58)	-0.66 (0.67)	-0.82 (0.63)	-0.32 (0.54)
AEs, n (%)	46 (74.2)	56 (82.4)	27 (75.0)	100 (84.7)	97 (86.6)	39 (70.9)
Discontinuations due to AEs, n (%)	2 (3.2)	2 (2.9)	1 (2.8)	5 (4.2)	8 (7.1)	2 (3.6)
Discontinuation due to	0	1	0	2	1	0

infection, n	0	1	0	2	1	0
Serious infection, n (%)	0	1 (1.5)	0	2 (1.7)	3 (2.7)	0
Neutropenia <500cells/mm^3, n	0	0	0	0	0	0
Lymphopenia <500 cells/mm^3, n	0	0	0	0	0	0
AST, n (%)						
>1 ULN	7 (11.3)	7 (10.3)	0	21 (17.8)	24 (22.0)	5 (9.1)
>2 ULN	2 (3.2)	0	0	0	2 (1.8)	0
>3 ULN	0	0	0	0	0	0
ALT, n (%)						
>1 ULN	7 (11.3)	6 (8.8)	1 (2.8)	28 (23.7)	21 (19.3)	5 (9.1)
>2 ULN	2 (3.2)	2 (2.9)	0	2 (1.7)	5 (4.6)	0
>3 ULN	0	0	0	0	2 (1.83)	0
LDL, mean mg/dL						
Baseline	107.82	107.85	108.15	107.21	108.27	119.71
Month 3	124.00	127.33	111.90	125.03	126.87	115.91
HDL, mean mg/dL						
Baseline	59.52	59.90	59.28	57.29	55.95	56.31
Month 3	63.27	65.98	52.91	58.76	60.87	52.38

All data are at 3 months unless otherwise stated.

ACR, American College of Rheumatology response rate; AE, adverse event; ALT, alanine transaminase; AST, aspartate aminotransferase; HAQ-DI, health assessment questionnaire – disability index; HDL, high density lipoprotein; LDL, low density lipoprotein; ULN, upper limit of normal

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Abstract Number: 2743

Treatment Target Status at 6 Months and Long-Term Outcomes at 5 Years: Analysis of Methotrexate-Naïve Patients with Rheumatoid Arthritis

Paul Emery[1], Roy Fleischmann[2], Stephen Xu[3] and Elizabeth C. Hsia[3,4], [1]Division of Rheumatic and Musculoskeletal Disease, University of Leeds, Leeds Institute of Molecular Medicine and LMBRU, Leeds, United Kingdom, [2]Rheumatology, Metroplex Clinical Research Center, Dallas, TX, [3]Janssen Research & Development, LLC, Spring House, PA, [4]University of Pennsylvania, Philadelphia, PA

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Background/Purpose*:* Management guidelines recommend patients (pts) with RA should be treated with the intent of reaching a clinical target of low disease activity or remission at 6 months. To compare long-term efficacy outcomes for MTX-naïve RA pts in the GO-BEFORE trial grouped by their treatment target status at week 24 using DAS28-CRP score (<2.6, 2.6 to ≤ 3.2, >3.2) and SDAI

(≤3.3, >3.3 to ≤11, >11).

Methods: In GO-BEFORE, 637 MTX-naïve pts with active RA were randomized to placebo (PBO)+MTX, golimumab (GLM)100mg +PBO, GLM 50mg+MTX, or GLM 100mg+MTX. Most PBO+MTX pts crossed over to GLM 50mg+MTX at wk52. In this analysis, pts were grouped by their treatment target status at wk24 using DAS28-CRP score (<2.6, 2.6 to ≤ 3.2, >3.2) and SDAI (≤3.3, >3.3 to ≤11, >11). Efficacy outcomes at 5 years (wk256) were evaluated for these mutually exclusive groups using observed data.

Results: At wk24, 150 pts had DAS28-CRP <2.6, 85 had DAS28-CRP 2.6 to ≤3.2, and 368 had DAS28-CRP >3.2. Of these, 23%, 31%, and 31%, respectively, discontinued treatment before wk256; 3%, 2%, and 3%, respectively, were due to lack of efficacy. Greater proportions of patients treated with GLM+MTX than patients treated with PBO+MTX improved from having DAS28-CRP >3.2 at wk24 to DAS28-CRP <2.6 at wk 52. Among pts achieving treatment targets at wk24, the majority either maintained a DAS28-CRP <2.6 (80%) or improved to DAS28-CRP< 2.6 (72%) at week 256. Over 50% of pts with DAS28-CRP >3.2 at wk24 achieved treatment targets at wk256. Pts with DAS28-CRP≤3.2 at wk 24 had less progression in vdH-S scores and lower HAQ, SJC, TJC, pain, and pt/physician global assessment of disease (GAD) scores at wk 256 vs. patients with DAS28-CRP >3.2 at wk 24 (Table). Also, pts with DAS28-CRP 2.6 to ≤3.2 at wk24 had higher TJC (but not SJC), pain, and pt/physician GAD scores at wk256 than pts with DAS28-CRP <2.6 at wk 24. HAQ and change in vdH-S at wk256 were not significantly different between pts who achieved either DAS28-CRP <2.6 or DAS28-CRP 2.6 to ≤3.2 at wk 24. Of note, CRP levels at wk256 were similar among the three groups. Similar results were observed using SDAI scores (Table).

Conclusion: In GO-BEFORE, the majority of patients who achieved DAS28-CRP or SDAI score treatment targets at wk24 maintained or had improvement in clinical response at 5 years. At wk 256, efficacy outcomes, including clinical, functional, and radiographic scores, but not CRP level, at wk256 were significantly better among pts who had achieved DAS28-CRP <2.6 at wk24 vs pts with DAS28-CRP >3.2 at wk24. More subjective outcomes (TJC, pain, and pt/physician GAD) were also better at wk 256 for pts with DAS28-CRP <2.6 at wk 24 vs pts with DAS28-CRP 2.6 to ≤3.2 at wk24.

Table. Efficacy outcomes at week 256 according to DAS28-CRP and SDAI treatment target status at week 24

	Treatment Target Status at Week 24		
	DAS28-CRP <2.6	DAS28-CRP 2.6 to ≤3.2	DAS28-CRP >3.2
Outcome at week 256			
Pts	115	59	253
HAQ	0.35 ± 0.44	0.48 ± 0.60	0.90 ± 0.67*
Change in vdH-S	0.73 ± 3.49	0.11 ± 1.93	1.91 ± 6.34**
SJC	0.80 ± 1.60	1.53 ± 2.95	2.61 ± 4.60*
TJC	1.44 ± 3.68	2.79 ± 4.28**	7.00 ± 10.09*
CRP	0.57 ± 0.65	0.60 ± 0.97	0.71 ± 0.90
Pain VAS	1.20 ± 1.72	1.89 ± 2.08**	3.00 ± 2.36*
Pt Global Disease Assessment	1.20 ± 1.58	1.79 ± 2.05**	3.04 ± 2.37*
Physician Global Disease Assessment	0.55 ± 0.76	1.09 ± 1.40**	1.64 ± 1.66*

Data presented as mean ±SD. *p<0.0001 vs. pts with DAS28-CRP <2.6.

**p<0.05 vs. pts with DAS28-CRP <2.6

	Treatment Target Status at Week 24		
	SDAI ≤3.3	SDAI 3.3 to ≤11	SDAI >11
Outcome at week 256			
Pts, n	56	130	241
HAQ	0.24 ± 0.33	0.48 ± 0.57**	0.92 ± 0.67*
Change in vdH-S	0.55 ± 3.22	0.67 ± 3.84	1.91 ± 6.24**
SJC	0.60 ± 1.47	1.34 ± 3.11	2.63 ± 4.46*
TJC	1.44 ± 3.60	2.24 ± 4.83**	7.17 ± 10.10*
CRP	0.63 ± 0.75	0.63 ± 0.88	0.69 ± 0.86
Pain VAS	0.73 ± 1.20	1.80 ± 2.11*	3.04 ± 2.33*
Pt Global Disease Assessment	0.72 ± 0.96	1.77 ± 2.07*	3.09 ± 2.34*
Physician Global Disease Assessment	0.50 ± 0.83	0.78 ± 1.12**	1.72 ± 1.66*

Data presented as mean ±SD. *p<0.0001 vs. pts with SDAI ≤3.3.

**p<0.05 vs. pts with SDAI ≤3.3

Disclosure: P. Emery, Janssen R & D, LLC, 2; **R. Fleischmann**, Janssen R & D, LLC, 2; **S. Xu**, Janssen R & D, LLC, 3; **E. C. Hsia**, Janssen R & D, LLC, 3.

Abstract Number: 2744

What Is the Treatment Durability and Safety Profile of Rheumatoid Arthritis Patients Treated with Infliximab Plus Methotrexate and/or Leflunomide? an Analysis from a Real-World Registry

Rafat Faraawi[1], Raman Joshi[2], William G Bensen[3], Denis Choquette[4], Wojciech Olsynzynski[5], Regan Arendse[5], Maqbool Sheriff[6], Proton Rahman[7], Emmanouil Rampakakis[8], Eliofotisti Psaradellis[9], Francois Nantel[10], Allen J Lehman[11], Susan Otawa[11], Cathy Tkaczyk[11] and Brendan Osborne[11], [1]McMaster University, Hamilton, ON, Canada, [2]William Osler Health Centre-Brampton Civic Hospital, Brampton, ON, Canada, [3]St Joseph's Healthcare Hamilton, Hamilton, ON, Canada, [4]Rheumatology Department, Institut de Rhumatologie de Montréal and University of Montreal, Montreal, QC, Canada, [5]University of Saskatchewan, Saskatoon, ON, Canada, [6]Nanaimo Regional General Hospital, Nanaimo, BC, Canada, [7]Medicine, Memorial University, St John's, NF, Canada, [8]JSS Medical Research, St-Laurent, QC, Canada, [9]JSS Medical Research, Montreal, QC, Canada, [10]Janssen Inc., Toronto, ON, Canada, [11]Medical Affairs, Janssen Inc., Toronto, ON, Canada

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Background/Purpose: Clinical trials of anti-TNF therapies have shown that concurrent methotrexate (MTX) therapy enhances the efficacy of TNF inhibitors. A scarcity of data exists on the benefits of combination therapy with IFX and MTX vs. leflunomide (LEF) in a real-world setting; therefore the BioTRAC Registry database was used to explore this question.

Methods: BioTRAC is an ongoing, prospective registry of patients initiating treatment for RA, AS, or PsA with IFX or golimumab as first biologics or after having been treated with a biologic for <6 months. RA patients treated with IFX who were enrolled between 2002-2014 were included in this analysis. Treatment durability was assessed with the Kaplan Meier (KM) estimator of the survival function and Cox regression.

Results: 723 RA patients were included; at baseline 516 (71.4%) were on IFX+MTX, 115 (15.9%) on IFX+LEF, and 92 (12.7%) on IFX+MTX+LEF. The mean (SD) age was 55.5 (13.6) years, 76.2% were female and mean (SD) disease duration was 8.7 (9.2) years. The majority of patients were from Ontario (50.6%), followed by Western Canada (25.8%), and Quebec (20.9%). There were 217 (30.0%) patients who discontinued due to lack/loss of response, disease progression, adverse event (AE) or change in therapy with a KM-based mean (SE) time to discontinuation of 83.9 (3.0) months. Upon adjusting for potential confounders, higher durability was observed for the IFX+MTX group vs. IFX+LEF [hazard ratio -HR- (95% CI): 0.50 (0.25-1.01), P=0.055]. Moreover, factors independently associated with premature treatment termination were earlier enrolment period [HR2006-09 vs. 2002-05 (95% CI): 0.15 (0.02-1.15, P=0.068; HR2010-2014 vs. 2002-05 (95% CI): 0.09 (0.01-0.70), P=0.021], shorter baseline disease duration [HR (95% CI): 0.97 (0.93-1.00), P=0.054], and increased baseline pain levels [HR (95% CI): 1.14 (1.03-1.26), P=0.013]. 2,016 AEs were reported by 343 patients (106.8 events/100 patient-years) and 156 SAEs by 96 patients (8.3 events/100 patient-years). The incidence density ratio (IDR) (95% CI) was higher in the groups IFX+MTX vs. IFX+LEF for both AEs and SAEs with 1.44 (1.25-1.67) and 1.60 (0.94-2.73), respectively, however the latter was not statistically significant. When examining the triple combination therapy (IFX+MTX+LEF), higher durability was observed compared to both IFX+MTX [HR (95% CI): 3.68 (1.14-11.92); P=0.030] and IFX+LEF [HR (95% CI): 6.34 (1.72-23.34); P=0.006].

Conclusion: The results of this real-world observational study have shown that combination therapy with IFX+MTX is associated with significantly higher treatment durability compared to IFX+LEF in RA patients with increased risk for AEs but not for SAEs.

Disclosure: R. Faraawi, Janssen Inc., 5; **R. Joshi**, Janssen Inc, 5; **W. G. Bensen**, Janssen Inc., 5; **D. Choquette**, None; **W. Olsynzynski**, Janssen Inc, 5; **R. Arendse**, Janssen Inc., 5; **M. Sheriff**, Janssen Inc, 5; **P. Rahman**, None; **E. Rampakakis**, JSS, 3; **E. Psaradellis**, JSS Medical Research, 3; **F. Nantel**, Janssen Inc., 3; **A. J. Lehman**, employee of Janssen Inc., 3; **S. Otawa**, Employee of Janssen Inc., 3; **C. Tkaczyk**, Janssen Inc., 3; **B. Osborne**, Janssen Inc., 3.

Abstract Number: 2745

Real World Evaluation of Patients with Rheumatoid Arthritis Initiating Tofacitinib Vs. Adalimumab and Etanercept

Benjamin Chastek[1], James Harnett[2], Jeffrey R. Curtis[3], Robert Gerber[4], David Gruben[4], Rui Song[5] and Andrew Koenig[6], [1]Optum Insight, Eden Prairie, MN, [2]Pfizer Inc, New York, NY, [3]University of Alabama at Birmingham, Birmingham, AL, [4]Pfizer Inc, Groton, CT, [5]Optum Insight, Reston, VA, [6]Pfizer Inc, Collegeville, PA

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Background/Purpose: In November 2012, the first oral Janus kinase (JAK) inhibitor tofacitinib was approved in the US for the treatment of RA with or without methotrexate. Given its recent introduction to the market, limited real world data are available in patient (pts) with RA receiving tofacitinib vs. TNFi. Here, we compare characteristics of pts with RA initiating tofacitinib vs. adalimumab (ADA) and etanercept (ETN) in a US administrative claims database and describe the feasibility of matching treatment cohorts to yield comparable pts for an outcomes evaluation.

Methods: This was a retrospective cohort study of pts aged ≥18 years at index with an RA diagnosis (ICD9: 714.0x-714.4x and 714.81) newly initiating tofacitinib in the Optum Research Database (11/12-7/14). Pts starting TNFi were also selected. Pts were continuously enrolled for ≥12 months (mos) pre-index and ≥6 mos post-index (tofacitinib or TNFi start). Pts with index medication use in prior 12 mos were excluded. Initial propensity score matching (1:1) was conducted among biologic-naïve and biologic-experienced subgroups (using a variable-length [VL] baseline starting 12/06) based on demographics, 12-mo pre-index total RA-related costs and opioid use, and number of prior biologics in the VL baseline (for biologic-experienced subgroup).

Results: Prior to matching, 647 tofacitinib pts, 703 ADA pts, and 1864 ETN pts met the cohort selection criteria. Tofacitinib pts had significantly ($p<0.001$ all comparisons) higher 12-mo pre-index mean RA-related costs ($20,067 vs. $4,405 and $4,305) and opioid use (72% vs. 58% and 60%), VL baseline biologic experience (81% vs. 22% and 14%) and index monotherapy regimen use (55% vs. 41% and 41%). After matching (Table) among biologic-naïve pts, those initiating tofacitinib had significantly higher VL baseline RA-related out-of-pocket costs, more rheumatologist visits (vs. ADA), more Medicare Advantage pts (vs. ETN), and greater use of monotherapy (vs. ADA) and leflunomide. In matched biologic-experienced cohorts, 49% (ADA) – 53% (ETN) of pts had prior experience with the respective index treatment. Significantly more ADA and ETN pts had prior ETN and ADA use, respectively, while more tofacitinib pts had abatacept, certolizumab pegol (vs. ETN) and tocilizumab (vs. ETN) use.

Conclusion: Tofacitinib was more likely to be used as monotherapy and in biologic-experienced pts vs. ETN and ADA. Initial attempts to match treatment cohorts were not feasible given prior treatment history with respective TNFi comparators and channeling bias with tofacitinib.

Table. Summary of propensity score matched cohorts						
	Tofacitinib	ADA	*P-value*	tofacitinib	ETN	*P-value*
Biologic-naïve, n (%)	121 (100)	121 (100)		123 (100)	123 (100)	
Monotherapy, n (%)	64 (53)	42 (35)	0.004	65 (53)	53 (43)	0.126
Medicare Advantage, n (%)	51 (42)	50 (41)	0.896	53 (43)	34 (28)	0.011
RA-related out-of-pocket costs*, mean (SD)	$1,424 ($1,683)	$1,007 ($1,440)	0.039	$1,454 ($1,685)	$986 ($1,297)	0.015
Rheumatologist visits among those with ≥1 visit*, mean (SD)	10 (9)	8 (6)	0.044	10 (9)	9 (7)	0.258
Conventional synthetic DMARD use*, n (%)	113 (93)	109 (90)	0.350	114 (93)	111 (90)	0.494
Leflunomide*, n (%)	40 (33)	24 (20)	0.020	41 (33)	25 (20)	0.021
Biologic-experienced*, n (%)	106 (100)	106 (100)		155 (100)	155 (100)	
Monotherapy, n (%)	66 (62)	47 (44)	0.009	95 (61)	79 (51)	0.067
ADA*, n (%)	37 (35)	52 (49)	0.037	39 (25)	63 (41)	0.004
Certolizumab pegol*, n (%)	16 (15)	9 (8)	0.136	26 (17)	9 (6)	0.002
ETN*, n (%)	33 (31)	37 (35)	0.559	50 (32)	82 (53)	<0.001
Tocilizumab*, n (%)	7 (7)	5 (5)	0.552	18 (12)	4 (3)	0.002
Abatacept*, n (%)	29 (27)	8 (8)	<0.001	54 (35)	17 (11)	<0.001
*using variable length baseline						

Disclosure: B. Chastek, Optum Insight, 3; **J. Harnett**, Pfizer Inc, 1,Pfizer Inc, 3; **J. R. Curtis**, Roche/Genentech, UCB, Janssen, CORRONA, Amgen, Pfizer, BMS, Crescendo, AbbVie, 2,Roche/Genentech, UCB, Janssen, CORRONA, Amgen, Pfizer, BMS, Crescendo, AbbVie, 5; **R. Gerber**, Pfizer Inc, 1,Pfizer Inc, 3; **D. Gruben**, Pfizer Inc, 1,Pfizer Inc, 3; **R. Song**, Optum Insight, 3; **A. Koenig**, Pfizer Inc, 1,Pfizer Inc, 3.

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Abstract Number: 2746

Comparison Study of Tests Available to Monitor Tocilizumab Therapy in Rheumatic Patients

Sergio Martín[1,2], Ainhoa Ruiz del Agua[2], Nerea Torres[2], Dora Pascual-Salcedo[3], Chamaida Plasencia[4], Teresa Jurado[5], Alejandro Balsa[6], Begoña Ruiz-Argüello[2], Antonio Martínez[2], Rosaura Navarro[7] and **Daniel Nagore**[2], [1]Department of Physiology, Medicine and Dentistry School, University of the Basque Country UPV/EHU (Convocatoria ZabaldUZ, UPV/EHU; Departamento de Educación, Universidades e Investigación del Gobierno Vasco, Ref. IT687-13), Leioa, Spain, [2]R&D, Progenika-Grifols, Derio, Spain, [3]Immunology Unit, La Paz University Hospital-Immunology, Madrid, Spain, [4]Rheumatology Unit, La Paz University Hospital-Rheumatology, Madrid, Spain, [5]Immunology, La Paz University Hospital-Idipaz, Madrid, Spain, [6]Rheumatology, La Paz University Hospital-Rheumatology Department, Madrid, Spain, [7]Department of Physiology, Medicine and Dentistry School, University of the Basque Country UPV/EHU, Leioa, Spain

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Background/Purpose: The options for treatment of rheumatic diseases is constantly growing. Tocilizumab (TCZ) is an anti-interleukin 6 receptor monoclonal antibody indicated for the treatment of severe active and progressive rheumatoid arthritis (RA) and active systemic juvenile idiopathic arthritis (sJIA). Monitoring of drug levels (DL) and anti-drug antibodies (ADA) in clinical practice is highly advisable in order to establish normal therapeutic ranges, complement clinical assessment and optimize patient treatment. As a consequence several tests and technologies have been developed. However, a common objection that limits implementation of biological drug monitoring in medical practice is the claim that the magnitude of measurements varies among assays and that assay standardization is lacking. The purpose of this study was to evaluate the correlation and agreement between different commercially

available tests to measure TCZ and antibodies to TCZ (ATT) in patients with rheumatic diseases.

Methods: Trough levels of TCZ and ATT were analyzed in a retrospective cohort of 26 rheumatic patients (42 serum samples, 88% RA and 12% sJIA) under maintenance therapy with TCZ for up to two years. Samples were assayed using Promonitor-TCZ and Promonitor-ANTI-TCZ ELISA kits (PR, Progenika, Spain), LISA-TRACKER Duo Tocilizumab ELISA kit (LT, Theradiag, France), and by Sanquin Blood Supply testing service (SQ, Amsterdam, The Netherlands) that uses ELISA and RIA technologies to measure TCZ and ATT levels, respectively. One-way analysis of variance (ANOVA) and Spearman´s test was used to study correlation between the DL tests; the difference (bias) in values obtained with DL assays was also assessed with Bland-Altman analysis. Percentage of positive and negative agreement was used to study the association between the ADA assays.

Results: TCZ trough level in patients are much higher than other biological treatments like anti-TNF infliximab and adalimumab. ANOVA analysis showed that the differences in the median values among the three DL assays are not statistically different (median 4.4 vs 4.7 vs 5.4 µg/mL, IQR 0 – 8.7 µg/mL vs 0 – 7.8 µg/mL vs 0 – 9.4 µg/mL for Promonitor-TCZ, LISA-TRACKER and Sanquin ELISA tests, respectively, p=0.693). Spearman´s coefficient showed a very high correlation between the each pair of assays (r=0.951, 0.935 and 0.944 for PR vs LT, PR vs SQ and LT vs SQ, respectively, p<0.0001). Bland-Altman analysis shows an excellent association between each pair of DL assays with no significant difference in bias (-0.3, -0.5 and -0.2 µg/mL for PR vs LT, PR vs SQ and LT vs SQ, p>0.05). Antibodies to TCZ were not detected with any of the assays in the patient cohort confirming the low immunogenicity of TCZ.

Conclusion: Despite different reagents, assay formats and technologies, all tests studied here provide exactly the same results and measure the same magnitude of TCZ in rheumatic patients. Assays can be safely exchanged in a clinical setting even in the absence of a gold standard test, and should lead to similar drug therapeutic ranges and actions.

Disclosure: S. Martín, Progenika-Grifols, 2; **A. Ruiz del Agua**, Progenika-Grifols, 3; **N. Torres**, Progenika-Grifols, 3; **D. Pascual-Salcedo**, None; **C. Plasencia**, None; **T. Jurado**, None; **A. Balsa**, None; **B. Ruiz-Argüello**, Progenika-Grifols, 3; **A. Martínez**, Progenika-Grifols, 3; **R. Navarro**, None; **D. Nagore**, Progenika-Grifols, 3.

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Abstract Number: 2747

Study Completion and Etanercept Retention in Patients with Rheumatoid Arthritis Treated with Etanercept Monotherapy Versus Etanercept and Methotrexate Combination Therapy

Janet E. Pope[1], Edward C. Keystone[2], J Carter Thorne[3], Melanie Poulin-Costello[4], Krystene Phan-Chronis[4] and Boulos Haraoui[5], [1]University of Western Ontario, London, ON, Canada, [2]Mount Sinai Hospital, University of Toronto, Toronto, ON, Canada, [3]Southlake Regional Health Centre, Newmarket, ON, Canada, [4]Amgen Canada Inc., Mississauga, ON, Canada, [5]University of Montreal Hospital Centre, Montreal, QC, Canada

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Background/Purpose:

The CAnadian Methotrexate and Etanercept Outcome (CAMEO) study, an open-label trial in patients with active rheumatoid arthritis (RA), revealed that patients achieving low disease activity (LDA) after 6 months of etanercept (ETN) plus methotrexate (MTX) therapy had similar clinical outcomes at 12 months if they continued ETN+MTX, or switched to ETN alone, at month 6 (M6). Conversely, those who did not achieve LDA at M6 had a reduced response after switching to ETN monotherapy. This analysis assessed the different discontinuation rates between treatment arms in the CAMEO trial by examining study completion and ETN retention over 25 months, and the association between ETN discontinuation and disease activity.

Methods:

Anti-TNF naïve patients with active RA (≥ 3 swollen joints, disease activity score [DAS28] ≥ 3.2), despite MTX treatment (≥ 15 mg/week or 10 mg/week if intolerant) for > 12 weeks, were enrolled. After 6 months of ETN (50 mg/week subcutaneously) + MTX treatment, patients were randomized (1:1) to ETN+MTX or ETN alone for another 18 months. ETN retention was assessed by physician prescribing information at the end of study. Cox regression analysis determined associations of study completion and ETN retention

with DAS28 score at M6 (continuous variable; not dichotomized to LDA and moderate/high disease activity), reimbursement type, and demographics.

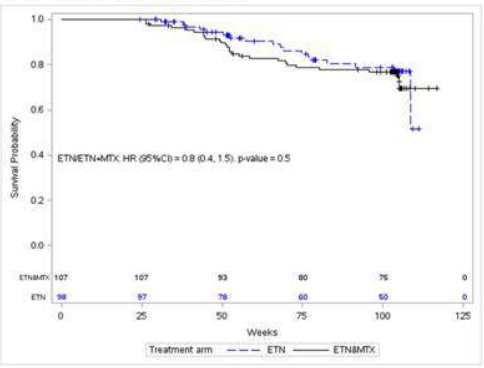
Results:

A total of 258 patients enrolled (76% female, mean age 54.7 ± 12.5 years, disease duration 8.9 ± 8.4 years, baseline DAS28 5.4 ± 1.1) and 205 (79%) were randomized at M6 (98 ETN, 107 ETN+MTX). Of the 205 patients randomized, 50 (51.0%) and 75 (70.1%) in the ETN and ETN+MTX groups completed the study, respectively, with the remainder discontinuing due to adverse events, lack of efficacy, or other reasons**.** Patients on ETN alone were twice as likely to discontinue the study as those on ETN+MTX (HR [95% CI] 2.0 [1.2, 3.1], p=0.004), and with increasing DAS28 score at M6, the chance of study discontinuation increased by 20% in both treatment arms (HR [95% CI] 1.2 [1.1, 1.5], p=0.005). Of the 205 patients randomized, 80 (81.6%) and 80 (74.8%) in the ETN and ETN+MTX groups, respectively, continued ETN at the end of the study but some randomized to ETN alone restarted MTX. ETN retention did not differ between treatment arms (HR [95% CI] 0.8 [0.4, 1.5], p=0.5), but higher DAS28 at M6, increased the chance of discontinuing ETN in both groups (HR [95% CI] 1.4 [1.1, 1.8], p=0.0017). Reimbursement and demographics were not associated with study and/or ETN discontinuation.

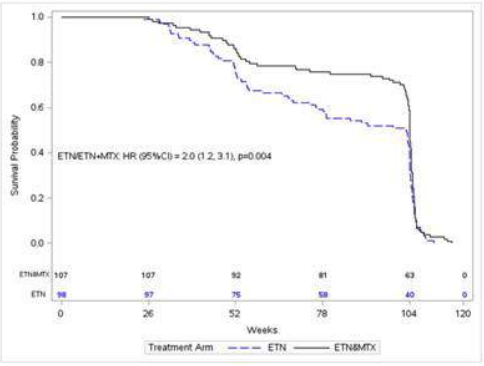
Conclusion:

Lower disease activity at M6 increased the chance of study completion and ongoing ETN treatment. Patients on ETN+MTX vs. ETN alone, and those achieving LDA at M6, regardless of treatment group, were more likely to complete the study. Both treatment arms had high ETN retention rates at the end of the study, with those reaching LDA at M6 being more likely to remain on ETN.

Time to ETN discontinuation:



Time to study discontinuation:



Disclosure: J. E. Pope, Abbott/AbbVie, 2,Abbott/AbbVie, 5,Amgen, 2,Amgen, 5,Actelion Pharmaceuticals Ltd., 2,Actelion Pharmaceuticals Ltd., 5,Bristol-Myers Squibb, 2,Bristol-Myers Squibb, 5,Hoffmann-La Roche, Inc., 2,Hoffmann-La Roche, Inc., 5,Hospira, 5,Janssen Inc., 2,Novartis Pharmaceutical Corporation, 5,Pfizer Pharmaceuticals, 2,Pfizer Pharmaceuticals, 5,UCB, 2,UCB, 5; **E. C. Keystone**, Abbott/AbbVie, 5,Amgen, 2,Bristol-Myers Squibb, 5,Hoffmann-La Roche, Inc., 5,Janssen Inc., 2,Janssen Inc., 5,Merck Pharmaceuticals, 5,Pfizer Pharmaceuticals, 5; **J. C. Thorne**, Abbott/AbbVie, 2,Abbott/AbbVie, 5,Amgen, 2,Amgen, 5,Bristol-Myers Squibb, 2,Bristol-Myers Squibb, 5,Celgene, 2,Celgene, 5,Centocor Inc., 2,Centocor Inc., 5,Medac, 5,Medexus, 5,Merck Pharmaceuticals, 2,Merck Pharmaceuticals, 5,Novartis Pharmaceutical Corporation, 2,Novartis Pharmaceutical Corporation, 5,Pfizer Pharmaceuticals, 2,Pfizer Pharmaceuticals, 5,Roche Pharmaceuticals, 2,Roche Pharmaceuticals, 5,UCB, 2,UCB, 5; **M. Poulin-Costello**, Amgen, 3; **K. Phan-Chronis**, Amgen, 3; **B. Haraoui**, Abbott AbbVie, 2,Abbott/AbbVie, 5,Amgen, 2,Amgen, 5,Bristol-Myers Squibb, 2,Bristol-Myers Squibb, 5,Merck Pharmaceuticals, 5,Janssen Inc., 2,Pfizer Pharmaceuticals, 2,Pfizer Pharmaceuticals, 5,Roche Pharmaceuticals, 2,Roche Pharmaceuticals, 5,UCB, 2,UCB, 5.

Abstract Number: 2748

Evaluation of Patient-Reported Outcomes By Baseline Disease Duration: 6-Month Data from Two Clinical Trials of Patients with Early Rheumatoid Arthritis Treated with Abatacept

Daniel E. Furst[1], VP Bykerk[2], Gerd Burmester[3], BG Combe[4], T. W. J. Huizinga[5], E Alemao[6], A Johnsen[6] and Paul Emery[7], [1]Medicine, University of California, Los Angeles, David Geffen School of Medicine, Los Angeles, CA, [2]Weill Cornell Medical College, New York, NY, [3]Department of Rheumatology and Clinical Immunology, Charité - Universitätsmedizin Berlin, Berlin, Germany, [4]Montpellier University, Montpellier, France, [5]Leiden University Medical Center, Leiden, Netherlands, [6]Bristol-Myers Squibb, Princeton, NJ, [7]University of Leeds, Leeds, United Kingdom

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Background/Purpose: Patients with RA and longer disease duration generally do not respond as well to treatment with DMARDs as patients with shorter duration of disease. It has been reported that long-term disease control can be improved with earlier use of biologic DMARDs.[1,2] Patient-reported outcomes (PROs) that are of particular importance to those with RA were compared in patients with varying lengths of disease duration enrolled in the AGREE (Abatacept study to Gauge Remission and joint damage progression in MTX naïve patients with Early Erosive RA),[1] and the AVERT (Assessing Very Early Rheumatoid arthritis Treatment)[3] trials. Both studies evaluated the efficacy of abatacept + MTX versus MTX alone. **Methods:** In each study, PROs analyzed were fatigue (visual analog scale), HAQ-DI, activity limitation (Activity Participation Questionnaire [APaQ]), and physical and mental function (short form-36 health survey [SF-36]). This *post hoc* analysis included all randomized and treated patients (last observation carried forward). PROs were evaluated in patients with early RA and ≤3 months' disease duration compared with those with >3 months' disease duration after treatment with SC abatacept + MTX or MTX alone. The mean changes in PRO from baseline to Month 6 (Day 169) were calculated for each trial with adjustment based on analysis of covariance, with treatment as a factor and baseline value as a covariate. Combined weighted means were then calculated.

Results:

Irrespective of baseline disease duration, changes from baseline in PROs for fatigue, HAQ-DI response, activity limitation (APaQ), and SF-36 physical component summary (PCS) and mental component summary (MCS) scores for the AGREE and AVERT trial data were generally greater for patients treated with abatacept + MTX than MTX alone at 6 months (Table). Patients treated with abatacept + MTX with shorter disease duration (≤3 months) demonstrated reduced fatigue, improved physical function (HAQ-DI) and mental function (MCS) compared with those with longer disease duration (>3 months; Table).

Conclusion:

Although patients with RA of both short and longer disease duration benefited, those with shorter disease duration (≤3 months) generally reported improved PROs compared with those with longer duration (>3 months) following treatment with abatacept + MTX for 6 months. These results support the use of abatacept earlier in the course of RA.

1. Westhovens R, et al. *Ann Rheum Dis* 2009;**68**:1870–7.

2. Emery P, et al. *Ann Rheum Dis* 2010;**69**:510–6.

3. Emery P, et al. *Ann Rheum Dis* 2014;**73**(Suppl 2):69.

	Weighted average mean changes in PRO from AVERT and AGREE combined (Baseline to Month 6)			
	ABA + MTX ≤3 months	**MTX** ≤3 months	**ABA + MTX** >3 months	**MTX** >3 months
Fatigue	(n=156; 133; 23) –30.47	(n=153; 119; 34) –22.98	(n=184; 117; 67) –25.69	(n=174; 128; 46) –24.49
HAQ-DI	(n=156; 133; 23) –0.91	(n=157; 120; 37) –0.67	(n=189; 117; 72) –0.75	(n=177; 129; 48) –0.58
Activity limitation (APaQ)	(n=154; 131; 23) –9.11	(n=156; 122; 34) –7.29	(n=184; 117; 67) –9.58	(n=174; 127; 47) –7.09
PCS (SF-36)	(n=164; 133; 31) 10.82	(n=161; 119; 42) 7.14	(n=192; 117; 75) 10.91	(n=182; 128; 54) 7.83
MCS (SF-36)	(n=164; 133; 31) 8.44	(n=161; 119; 42) 6.17	(n=192; 117; 75) 6.21	(n=182; 128; 54) 5.82
n=total number of patients from both trials with available data; n from AGREE; n from AVERT				

Disclosure: D. E. Furst, Gilead, 2,GlaxoSmithKline, 2,NIH, 2,Novartis Pharmaceutical Corporation, 2,Pfizer Inc, 2,Roche Pharmaceuticals, 2,Genentech and Biogen IDEC Inc., 2,UCB, 2,Abbvie, 5,Actelion Pharmaceuticals US, 5,Amgen, 5,Bristol-Myers Squibb, 5,Cytori, 5,Janssen Pharmaceutica Product, L.P., 5,Gilead, 5,GlaxoSmithKline, 5,NIH, 5,Novartis Pharmaceutical Corporation, 5,Pfizer Inc, 5,Roche Pharmaceuticals, 5,Genentech and Biogen IDEC Inc., 5,UCB, 5,Abbvie, 8,Actelion Pharmaceuticals US, 8,Bristol-Myers Squibb, 2,Amgen, 2,Actelion Pharmaceuticals US, 2,Abbvie, 2,UCB, 8; **V. Bykerk**, Genentech, BMS, UCB, BIPI, 2,Amgen, Abbvie, BMS, UCB, Antares, Regeneron, Genentech, 5,Novartis and Biogen, 3; **G. Burmester**, Abbvie, Pfizer, UCB, Roche, 2,Abbvie, BMS, Pfizer, Merck, MedImmune, UCB, Roche, 5,Abbvie, BMS, Pfizer, Merck, UCB, Roche, 8; **B. Combe**, Pfizer, Roche-Chugai, 2,BMS, Merck, Pfizer, Roche-Chugai, UCB, 8; **T. W. J. Huizinga**, Merck, UCB, BMS, Biotest AG, Pfizer, GSK, Novartis, Roche, Sanofi-Aventis, Abbott, Crescendo Bioscience, Nycomed, Boehringer, Takea, Zydus, and Eli Lilly., 5,Roche & Abbott, 9; **E. Alemao**, Bristol-Myers Squibb, 3,Bristol-Myers Squibb, 1; **A. Johnsen**, Bristol-Myers Squibb, 1,Bristol-Myers Squibb, 3; **P. Emery**, Abbott/Abbvie, Bristol-Myers Squibb, Pfizer, UCB, MSD, Roche, Novartis, Samsung, Takeda, Lilly, 5.

Abstract Number: 2749

A Phase 1 Study of FPA008, an Anti-Colony Stimulating Factor 1 Receptor (anti-CSF1R) Antibody in Patients (pts) with Rheumatoid Arthritis (RA): Preliminary Results

Lei Zhou[1], Robert Sikorski[1], Seema Rogers[1], Stefan Costin[2], Mariusz Korkosz[3], Maria Jaraczewska-Baumann[4], Péterfai Éva[5], Bernadette Rojkovich[6], Janos Bartalos[7], Emma Masteller[1], Hong Xiang[1], Brian Wong[1] and Julie Hambleton[1], [1]Five Prime Therapeutics, Inc., South San Francisco, CA, [2]PRA Heath Sciences, Berlin, Germany, [3]Malopolskie Centrum Medyczne, The University Hospital in Krakow, Krakow, Poland, [4]MedPolonia Sp. z o.o, Poznan, Poland, [5]Drug Research Center, Balatonfüred, Hungary, [6]Hospitaller Brothers of St. John of God, Budapest, Hungary, [7]PRA Hungary Ltd, Budapest, Hungary
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Background/Purpose: FPA008 is a humanized IgG4 anti-CSF1R antibody that blocks the binding of CSF1 and IL34 ligands to CSF1R, resulting in inhibition of the activation and survival of inflammatory macrophages and osteoclasts, thus providing a potential therapeutic benefit in RA. Data from healthy volunteers in this 3-part Phase 1 study were reported previously (***J Hambleton et al., ACR Annual Meeting 2014***). Here, we report preliminary results from Part 3 in RA pts.

Methods: Part 3 consists of open-label dose escalation and randomized portions. In the open-label portion, FPA008 is being evaluated at 1, 3, and 6 mg/kg IV every 14 days for 2 or 3 doses. Three to 9 RA pts without adequate response to biologic or nonbiologic disease modifying anti-rheumatic drugs (DMARDs) are treated in each dose cohort. All pts are required to be on stable dose methotrexate (MTX) during the study. ACR 20/50/70, EULAR responses as well as change in DAS 28 from baseline and MRI are assessed at wks 4 and 12. The randomized portion will be based upon the open-label results.

Results: As of May 13, 2015, 3 pts each were treated with FPA008 at 1 or 3 mg/kg for 2 doses. The median age was 59, ranging from 53 to 66 yrs old. Five were female and one was male. No pts had prior biologic DMARDs. Median MTX dose was 17.5 mg, ranging from 10 mg to 25 mg wkly with 3 pts requiring methylprednisolone 2 to 4 mg daily. All 3 pts receiving 1 mg/kg completed the study (through Study Day 141) and all 3 pts receiving 3 mg/kg completed the Study Day 85 visit. Reduction in CD14+CD16++ nonclassical monocytes were observed as expected. Reported treatment-related AEs were periorbital edema/eyelid edema in the 3 mg/kg cohort and all were self-limiting. Expected, reversible dose-dependent asymptomatic elevations of AST, ALT, LDH and CK were noted, but not associated with abnormalities in total bilirubin, troponin, aldolase or EKGs.

Preliminary efficacy data are reported below:

FPA008 Dose Cohort		**Day-1**	**Week 4**					**Week 12**				
Dose regimen	Subjects	DAS28CRP	ACR 20/50/70	ACR hybrid	EULAR	DAS28CRP	DAS28 change	ACR 20/50/70	ACR Hybrid	EULAR	DAS28CRP	DAS28 change
1 mg/kg x 2 doses	3101	3.44	0	-5.14%	no	3.74	-0.31	0	-6.00%	no	3.83	-0.39
	3102	4.35	0	11%	moderate	3.26	1.09	0	6.29%	moderate	3.22	1.13
	3103	7.06	ACR50	52.86%	moderate	3.87	3.19	ACR50	53.86%	moderate	5.22	1.83
3 mg/kg x 2 doses	3104	4.17	ACR 20	49.99%	good	2.94	1.23	0	19.99%	moderate	3.55	0.62
	3105	5.40	0	19.99%	good	2.28	3.12	0	8.57%	moderate	4.44	0.96
	3106	4.50	0	-1.43%	no	4.13	0.37	0	8.71%	moderate	3.73	0.77

Conclusion: FPA008 was well tolerated up to 3 mg/kg in RA pts with no new safety signals. Dose escalation is ongoing. Updated safety, PK/PD and preliminary efficacy from open-label dose escalation will be presented.

Disclosure: L. Zhou, Five Prime Therapeutics, 5; **R. Sikorski**, Five Prime Therapeutics, 1,Five Prime Therapeutics, 3; **S. Rogers**, Five Prime Therapeutics, 1,Five Prime Therapeutics, 3; **S. Costin**, None; **M. Korkosz**, None; **M. Jaraczewska-Baumann**, None; **P. Éva**, None; **B. Rojkovich**, None; **J. Bartalos**, None; **E. Masteller**, Five Prime Therapeutics, 1,Five Prime Therapeutics, 3; **H. Xiang**, Five Prime Therapeutics, 1,Five Prime Therapeutics, 3; **B. Wong**, Five Prime Therapeutics, 1,Five Prime Therapeutics, 3; **J. Hambleton**, Five Prime Therapeutics, 1,Five Prime Therapeutics, 3.

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Abstract Number: 2750

Tocilizumab Is Effective As 1st, 2nd and 3rd-Line Biologic DMARD in Patients with Rheumatoid Arthritis

Adrian Richter[1], Anja Strangfeld[2], Joern Kekow[3], Arnold Bussmann[4], Andreas Krause[5], Carsten Stille[6], Joachim Listing[7] and Angela Zink[8], [1]German Rheumatism Research Center, Berlin, Germany, [2]Epidemiology, German Rheumatism Research Center, Berlin, Germany, [3]University of Magdeburg, Magdeburg, Germany, [4]Rheumatologist, Geilenkirchen, Germany, [5]Rheumatologist, Berlin, Germany, [6]Rheumatologist, Hannover, Germany, [7]Epidemiology, DRFZ, Berlin, Germany, [8]Epidemiologie, Deutsches Rheuma-Forschungszentrum, Berlin, Germany

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Background/Purpose: In Germany, treatment with Tocilizumab (TCZ) is primarily used in rheumatoid arthritis patients with previous failures of biologic DMARDs. Effectiveness and adherence of TCZ in patients with multiple bDMARD failures has rarely been investigated.

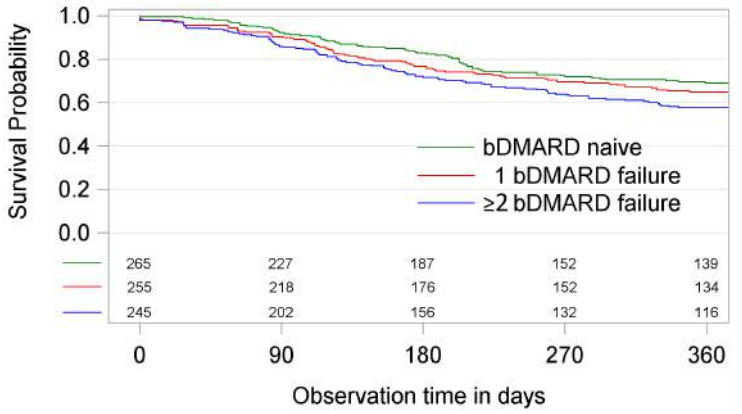
Methods: We included 765 RA patients enrolled between 2009 and 2015 in the German biologics register RABBIT (**R**heumatoid **a**rthritis: O**b**servation of **bi**ologic **t**herapy) starting with TCZ. Patients were stratified according to the number of bDMARD failures prior to the initiation of TCZ: biologic naive (n=265), 1 bDMARD failure (n=255) and ≥2 bDMARD failures (n=245). Therapy discontinuation within 12 month after the start of TCZ was investigated using Kaplan-Meier and Cox-proportional hazard regression. Discontinuation was defined as the stop of TCZ therapy. Effectiveness regarding control of disease activity (DAS28-ESR) after 3, 6 and 12 month were examined with linear mixed effects models.

Results: Compared to biologic naive patients those with prior bDMARD failures at start of TCZ were younger (1 failure: -1.6y (p=0.09); ≥2 failures: -2.8y (p=0.01)), had significantly longer disease duration (8.1 vs. 11.4 vs. 14.1 years; p<0.01) and more csDMARDs failures (p<0.01). Loss of physical function, pain and fatigue were significantly higher in patients with bDMARD failures (p<0.01). No differences were found regarding the initial composite score DAS28 (5.2 vs 5.3 vs 5.3), its components: TJC and SJC and the concomitant use of csDMARDs (p=0.3). During follow-up disease activity (DAS28) was significantly reduced in all treatment strata. At month 3, 6 and 12 differences between treatment strata were statistically not significant (Table).

Crude survival on TCZ therapy was significantly lower if patients had bDMARD failures, unadjusted hazard ratios (HR) compared to bDMARD-naive patients were 1.17 (p=0.34) and HR=1.50 (p<0.01) (Figure). Adverse events were the most frequent reason for discontinuation, particularly in patients with prior bDMARD failures.

Table: Means of DAS28 [95% confidence interval] at month 3, 6 and 12 after enrollment with TCZ. Estimates were adjusted for age, disease duration, physical function, comorbidities and concomitant use of csDMARDs (yes vs. no).

	DAS28 at month 3	DAS28 at month 6	DAS28 at month 12
bDMARD naive	3.02 [2.82; 3.22]	2.84 [2.63; 3.04]	2.88 [2.66; 3.10]
1 bDMARD failure	3.19 [3.01; 3.38]	3.04 [2.84; 3.24]	3.07 [2.87; 3.28]
≥2 bDMARD failure	3.37 [3.17; 3.56]	3.21 [3.00; 3.42]	3.06 [2.82; 3.29]



Conclusion: Treatment with TCZ is effective in patients with and without prior bDMARD failures, the majority of patients achieves low disease activity (DAS28<3.2) within 6 month and maintains controlled disease activity throughout month 12. However, the higher susceptibility of adverse events in patients with prior bDMARD failures needs further investigation.

Disclosure: A. Richter, None; **A. Strangfeld**, AbbVie, Celltrion, Hospira, Bristol-Myers Squibb, MSD Sharp&Dohme, Pfizer, Roche, and UCB., 2,BMS, Merck-Sharp & Dohme, Pfizer, Roche, Sanofi-Aventis, 9; **J. Kekow**, None; **A. Bussmann**, None; **A. Krause**, None; **C. Stille**, None; **J. Listing**, AbbVie, Celltrion, Hospira, Bristol-Myers Squibb, MSD Sharp&Dohme, Pfizer, Roche, and UCB., 2,Pfizer Inc, 5; **A. Zink**, AbbVie, Celltrion, Hospira, Bristol-Myers Squibb, MSD Sharp&Dohme, Pfizer, Roche, and UCB., 2,BMS, Merck-

Sharp & Dohme, Pfizer, Roche, UCB., 9.

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Abstract Number: 2751

Assessment of the Effect of CYP3A Inhibition, CYP Induction, OATP1B Inhibition and Administration of High-Fat Meal on the Pharmacokinetics of the Potent and Selective JAK1 Inhibitor ABT-494

Mohamed-Eslam Mohamed[1], Steven Jungerwirth[2], Armen Asatryan[1], Ping Jiang[2] and Ahmed Othman[1], [1]AbbVie, North Chicago, IL, [2]AbbVie Inc., North Chicago, IL

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Background/Purpose:

ABT 494 is an oral selective JAK1 inhibitor that is being developed for treatment of rheumatoid arthritis and Crohn's disease. ABT-494 is metabolized by cytochrome P450 (CYP) enzymes including CYP3A and approximately 20% of the dose is eliminated unchanged in urine. The objectives of this work were to assess the effect of high-fat meal, ketoconazole (a strong CYP3A inhibitor), and rifampin (a broad CYP inducer and an OATP1B inhibitor) on the pharmacokinetics of ABT-494 in humans.

Methods:

Two studies were conducted. In the first study, using a randomized, two sequence, cross-over design, healthy adult subjects (N = 12) received a single dose of 3 mg ABT-494 in three different occasions: after 10 hours of fasting, 30 minutes after starting a high-fat breakfast, and on Day 4 of a 6-day regimen of once daily ketoconazole (400 mg) under fasting condition. In the second study, healthy adult subjects (N = 12) received single doses of 12 mg ABT-494 on three sequential occasions: alone, with the 1st, and with the 8thdose of a 9-day regimen of once daily rifampin (600 mg). Serial blood samples were collected to determine ABT-494 plasma concentrations and safety and tolerability were monitored. Pharmacokinetic parameters for ABT-494 were calculated using non-compartmental analyses.

Results:

Relative to administration under fasting conditions, high-fat meal delayed ABT-494 T_{max} by approximately 1 hour, decreased ABT-494 C_{max} by 23% and had no impact on ABT-494 AUC. Administration of ABT-494 with repeated doses of ketoconazole increased ABT-494 C_{max} and AUC by 70% and 75%, respectively. Repeat-dose administration of rifampin decreased ABT-494 $C_{max}$and AUC by 51% and 61%, respectively, whereas single dose co-administration of rifampin had no effect on ABT-494 AUC. ABT-494 was well tolerated by subjects.

Conclusion:

Food has no clinically meaningful effect on ABT-494 plasma exposure. Strong inhibition of CYP3A results in a limited increase in ABT-494 exposure (i.e. weak pharmacokinetic interaction). The broad CYP inducer rifampin reduces ABT-494 exposure by approximately half, while lack of effect of the first dose of rifampin on ABT-494 AUC suggests no interaction of ABT-494 with OATP1B inhibitors.

Disclosure: M. E. Mohamed, AbbVie, 1,AbbVie, 3; **S. Jungerwirth**, AbbVie, 1,AbbVie, 3; **A. Asatryan**, AbbVie, 1,AbbVie, 3; **P. Jiang**, AbbVie, 1,AbbVie, 3; **A. Othman**, AbbVie, 1,AbbVie, 3.

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Abstract Number: 2752

Profile of Joint Involvement over Time in Rheumatoid Arthritis and Psoriatic Arthritis Patients Treated with Anti-TNF in a Real-World Setting

Algis Jovaisas[1], Michael Starr[2], Denis Choquette[3], Michel Zummer[4], Regan Arendse[5], Dalton Sholter[6], Rafat Faraawi[7], Jude Rodrigues[8], Emmanouil Rampakakis[9], John S. Sampalis[9], Francois Nantel[10], Allen J Lehman[11], Susan Otawa[11], May Shawi[10] and Karina Maslova[10], [1]Capital North Therapeutics & Research, Ottawa, ON, Canada, [2]Rheumatology, McGill University, Montreal, QC, Canada, [3]Rheumatology, Institut de recherche en rhumatologie de Montréal (IRRM), Montréal, QC, Canada, [4]Université de Montréal, Quebec, QC, Canada, [5]University of Saskatchewan, Saskatoon, SK, Canada, [6]Rheumatology Associates, Edmonton, AB, Canada, [7]McMaster University, Hamilton, ON, Canada, [8]Jude Rodrigues Medicine Professional Corporation, Windsor, ON, Canada, [9]JSS Medical Research, St-Laurent, QC, Canada, [10]Janssen Inc., Toronto, ON, Canada, [11]Medical Affairs, Janssen Inc., Toronto, ON, Canada

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Background/Purpose: :

Unlike rheumatoid arthritis (RA), the pattern of joint involvement in psoriatic arthritis (PsA) is usually asymmetric. Furthermore, PsA may demonstrate oligoarthritis or polyarthritis, while RA usually manifests in multiple joints. The aim of this study was to describe the most commonly affected joints in patients with RA and PsA at baseline and after 6 months (mos) of treatment with infliximab (IFX) in a clinical practice setting.

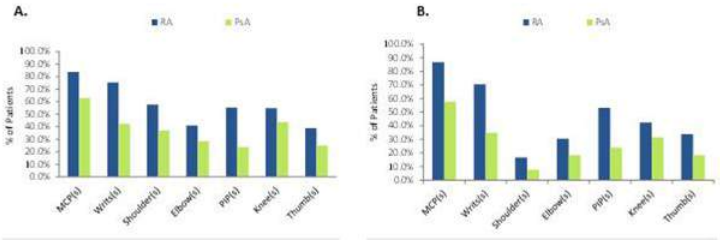
Methods :

BioTRAC is an ongoing, prospective registry of patients initiating treatment for RA, ankylosing spondylitis, or PsA with IFX as first biologics or after having been treated with a biologic for <6 mos. RA patients treated between 2002-2012 and PsA patients treated with IFX between 2005-2012 were included. Based on the 28-joint involvement 7 groups were created: shoulder(s), elbow(s), metacarpophalangeal (MCP(s)), wrist(s), proximal interphalangeal (PIP(s)), knee(s), and thumb(s). The impact of treatment on joint swelling/tenderness was assessed with the McNemar test while the Chi-square test was used to compare the affected joints between disease groups.

Results:

832 RA patients (mean age: 55.8 yrs disease duration: 10.2 yrs) and 92 PsA patients (age: 48.7 yrs; disease duration: 6.8 yrs) were included. At baseline, mean DAS28, SJC28 and TJC28 in RA vs. PsA patients were 5.8 vs. 4.1 ($P<0.001$), 10.7 vs. 4.0 ($P<0.001$), and 12.6 vs. 5.9 (<0.001), respectively. Among RA patients, the joints most commonly swollen at baseline were MCPs (86.8% of patients), wrists (70.5%), and PIPs (53.2%). Knees, thumbs, elbows and shoulders were swollen in 42.3%, 33.7%, 30.5%, and 16.7% of patients, respectively (Figure 1A). With respect to tenderness, MCPs were tender in 83.8% of patients, wrists in 75.3%, shoulders in 57.8%, knees in 54.8%, PIPs in 55.3%, thumbs in 38.8%, and elbows in 41.0% (Figure 1B). Statistically significant differences were observed between RA and PsA patients both in the frequency of joint swelling/tenderness, which were lower in PsA, and the profile of affected joints. Among PsA patients, MCPs, wrists, and knees were the joints most commonly swollen, affected in 57.6%, 34.8%, and 31.5% of patients, respectively; MCPs, knees, and wrists were the joints most commonly tender (63.0%, 43.5%, and 42.4% of patients, respectively). Upon 6 mos of treatment, significant improvement in swelling/tenderness in all the most commonly affected joints in both RA and PsA patients was observed. The joints most resistant to treatment, still remaining affected at 6 mos, were MCPs in both patient groups.

Figure 1. Types of Swollen (A) and Tender (B) Joints at Anti-TNF Treatment Initiation in RA and PsA



Conclusion:

Significant differences exist in both the frequency and the profile of swollen and tender joints in RA and PsA patients although both diseases shared the MCPs as the joint most commonly affected and most resistant to treatment. Treatment with IFX for 6 mos resulted in a significant reduction in the 28-swollen and tender joint counts in both RA and PsA patients

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Disclosure: A. Jovaisas, Janssen Pharmaceutica Product, L.P., 5; **M. Starr**, Janssen Inc.,, 5; **D. Choquette**, Janssen Inc., 5,AbbVie, 5,Amgen, 5,Celgene, 5,BMS, 5,Pfizer Inc, 5; **M. Zummer**, Janssen Inc.,, 5; **R. Arendse**, Janssen Inc., 5; **D. Sholter**, Janssen Inc., 5; **R. Faraawi**, Janssen Inc., 5; **J. Rodrigues**, Janssen Inc., 5; **E. Rampakakis**, JSS, 3; **J. S. Sampalis**, JSS Medical Research, 3; **F. Nantel**, Janssen Inc., 3; **A. J. Lehman**, Janssen Inc., 3; **S. Otawa**, Janssen Inc., 3; **M. Shawi**, Janssen Inc., 3; **K. Maslova**, Janssen Inc., 3.

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Abstract Number: 2753

Effectiveness and Safety of Tocilizumab in Biologics-Naive RA Patients – Postmarketing Surveillance for Investigating Success in Achieving Clinical and Functional Remission and Sustaining Efficacy with Tocilizumab in Biologics-Naive RA Patients (FIRST Bio) Study

Naoki Ishiguro[1], Tatsuya Atsumi[2], Masayoshi Harigai[3], Tsuneyo Mimori[4], Norihiro Nishimoto[5], Takayuki Sumida[6], Tsutomu Takeuchi[7], Yoshiya Tanaka[8], Nobuhiro Takagi[9], Ayako Nakasone[10] and Hisashi Yamanaka[11], [1]Department of Orthopedic Suregery, Nagoya University Hospital, Nagoya, Japan, [2]Division of Rheumatology, Endocrinology and Nephrology, Hokkaido University Graduate School of Medicine, Sapporo, Japan, [3]Department of Phamacovigilance, Tokyo Medical and Dental University, Tokyo, Japan, [4]Dept of Rheum & Clinical Immun, Kyoto Univ Grad Schl of Med, Kyoto, Japan, [5]Osaka Rheumatology Clinic, Osaka, Japan, [6]Department of Internal Medicine, Faculty of Medicine, University of Tsukuba, Tsukuba, Japan, [7]Keio University School of Medicine, Tokyo, Japan, [8]The First Department of Internal Medicine, University of Occupational and Environmental Health, Kitakyushu, Japan, [9]Medical Science, Chugai Pharmaceutical, Tokyo, Japan, [10]Chugai Pharmaceutical Co. Ltd, Tokyo, Japan, [11]Institute of Rheumatology, Tokyo Women's Medical University, Tokyo, Japan

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Background/Purpose: The all-patient postmarketing surveillance (PMS) of tocilizumab (TCZ; PMS7901), which followed 7901 rheumatoid arthritis (RA) patients for 28 weeks (wks), showed that patients with high probability of remission and low probability of developing serious infections (SIs) were most likely to be those in early and less advanced stages of RA and who had not received biologics previously. The FIRST Bio study aimed to evaluate the overall effectiveness and safety of TCZ in biologics-naïve RA patients in the real clinical setting.

Methods: The FIRST Bio study was a 52-wk PMS. Patients who met the ACR/EULAR 2010 classification criteria and experienced inadequate response or were intolerant to ≥1 DMARDs received 8 mg/kg intravenous (IV) TCZ every 4 wks with or without DMARDs. Paired *t*-test was used for comparisons of continuous variables and X-squared test was used for categorical variables.

Results: Overall, 839 patients were observed. Patients from the FIRST Bio study had shorter mean disease duration (FIRST Bio, 7.5 years [y]; PMS7901, 10.4 y), and a higher percentage had less advanced Steinbrocker's stage and class than those in PMS7901. At Wk 52, 72.3% of patients continued to receive IV TCZ (total, 718.4 patient-years [pty]). The mean Clinical disease activity index (CDAI) improved from baseline (23.3) to Wk 52 (6.6; p<0.0001). At Wk 52, CDAI remission rate was 36.8% and Boolean remission rate was 33.1%. Boolean remission rate was better in the FIRST Bio study at Wk 24 (27.7%) than in PMS7901 at Wk 28 (15.1%). The mean HAQ score improved from baseline (1.0) to Wk 52 (0.5; p<0.0001); in 65.1% patients, HAQ-DI score was ≤0.5 at Wk 52. While the CDAI remission rate was significantly higher in the <2-y vs ≥10-y disease duration categories at Wk 24 (p<0.0001), it increased in the ≥10-y group after Wk 24, making the difference not statistically significant at Wk 52 (Table). However, the remission rate in patients with HAQ score ≤0.5 was higher in the <2-y vs ≥10-y disease duration categories at Wk 24 and Wk 52. The incidence (events/100 pty) of total adverse events (AEs) and serious AEs (SAEs) was 75.7 and 18.1, respectively. Infections were the most frequent AEs (17.8) and SAEs (5.8). The incidence rates of SAEs and SIs were lower in FIRST Bio than in PMS7901 (PMS7901: SAEs, 27.4; SIs, 8.6). The mean dose of concomitant MTX decreased from baseline (9.1 mg/wk) to Wk 52 (6.4 mg/wk), and 19.3% patients discontinued MTX. The mean dose of concomitant glucocorticoid (GC) also decreased from baseline (5.4 mg/day) to Wk 52 (2.6 mg/day), and was suspended in 34.0% of patients. CDAI remission rate did not decrease in patients who discontinued MTX or GC.

Conclusion: The FIRST Bio study confirmed the high effectiveness and safety of TCZ in the real clinical setting in patients with less advanced RA who had not received biologics previously.

Table. Changes in CDAI and HAQ-DI remission rates over time in the FIRST Bio study

		Week 0	Week 12	Week 24	Week 36	Week 52
CDAI remission rate (%)	Total (*n*=722)	0.4	17.9	31.1	33.2	36.8
	<2 y (*n*=240)	0.8	21.6	40.2	40.4	42.9
	≥10 y (*n*=176)	0	12.6	20.5	27.3	33.5
HAQ-DIremission (≤0.5) rate (%)	Total (*n*=559)	34.3	59.8	62.0	64.9	65.1
	<2 y (n=183)	33.9	69.69	69.36	75.41	77.6
	≥10 y (*n*=140)	30.0	48.8	48.5	50.0	46.4

Disclosure: N. Ishiguro, AbbVie, Chugai, Daiichi-Sankyo, Eisai, Mitsubishi Tanabe, Pfizer and Takeda, 5,AbbVie, Chugai, Daiichi-Sankyo, Eisai, Mitsubishi Tanabe, Pfizer and Takeda, 8; **T. Atsumi**, Chugai, Eisai, Bristol-Myers Squibb, Astellas, Daiichi-Sankyo, Mitsubish-Tanabe, 2,Astellas, Mitsubish-Tanabe, 8; **M. Harigai**, AbbVie, Astellas, Chugai, Eisai, Mitsubishi Ono, Tanabe, Takeda and UCB, 2,Bristol-Myers Squibb, Chugai and Janssen, 5,AbbVie, Astellas, Bristol-Myers Squibb, Chugai, Eisai, Janssen, Mitsubishi Tanabe, Ono, Takeda, UCB and Pfizer, 8; **T. Mimori**, Asahi Kasei, Astellas, Bristol-Myers Squibb, Chugai, Daiichi Sankyo, Eisai, Mitsubishi Tanabe, MSD, Nippon Kayaku, Nippon Shinyaku, Santen and Takeda, 2,Astellas, Bristol-Myers Squibb, Chugai, Mitsubishi Tanabe and Taisho Toyama, 8; **N. Nishimoto**, Chugai and Eisai, 2,Chugai, 3,Chugai, 5,Chugai, 7; **T. Sumida**, Chugai, 2,Chugai, 8; **T. Takeuchi**, AbbVie, Asahi Kasei, Asahi Kasei Medical, Astellas, Astra Zeneca, Bistol-Myers Squibb, Chugai, Daiichi-Sankyo, Eisai, Eli Lilly, Janssen, Mitsubishi Tanabe, Novartis, Pfizer, Santen, SymBio, Takeda, Taishyo Toyama and Teijin, 5,AbbVie, Asahi Kasei, Asahi Kasei Medical, Astellas, Astra Zeneca, Bristol-Myers Squibb, Chugai, Daiichi-Sankyo, Eisai, Eli Lilly, Janssen, Mitsubishi Tanabe, Novartis, Pfizer, Santen, SymBio, Takeda, Taishyo Toyama and Teijin, 8; **Y. Tanaka**, Abbvie, Daiichi-Sankyo, Chugai, Takeda, Mitsubishi-Tanabe, Bristol-Myers, Astellas, Eisai, Janssen, Pfizer, Asahi-kasei, Eli Lilly, GlaxoSmithKline, UCB, Teijin, MSD, Santen, 8; **N. Takagi**, Chugai, 3; **A. Nakasone**, Chugai, 3; **H. Yamanaka**, Abbvie, Daiichi-Sankyo, Chugai, Takeda, Mitsubishi-Tanabe, Bristol-Myers, Astellas, Eisai, Janssen, Pfizer, Asahi-kasei, Eli Lilly, GlaxoSmithKline, UCB, Teijin, MSD, Santen, 5,AbbVie, Astellas, Bristol-Myers Squibb, Chugai, Daiichi-Sankyo, Mitsubishi Tanabe, Nippon Kayaku, Pfizer, Takeda, Teijin and UCB, 8.

Abstract Number: 2754

Safety, Tolerability, Pharmacokinetics (PK) and Pharmacodynamics of BI 655064, an Antagonistic Anti-CD40 Antibody Following Single-Dose Administration in Chinese and Japanese Healthy Volunteers

Jiyoon Kim[1], **Yasuhiro Tsuda**[2], Kazuhiko Yamamoto[3], Ralf Thiedmann[4], Corinna Schoelch[4], Stephen Norris[5], Steven Padula[6], Juergen Steffgen[4] and In-Jin Jang[7], [1]Boehringer Ingelheim Korea Ltd., Seoul, South Korea, [2]Clinical PK/PD department, Nippon Boehringer-Ingelheim.Co.,Ltd., Kobe, Japan, [3]Department of Allergy and Rheumatology, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan, [4]Boehringer Ingelheim Pharma GmbH & Co. KG, Biberach, Germany, [5]Boehringer Ingelheim Pharmaceuticals, Inc., Ridgefield, CT, [6]Boehringer Ingelheim Pharma GmbH & Co. KG, Ingelheim, Germany, [7]Seoul National University Hospital, Seoul, South Korea

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Session Time: 9:00AM-11:00AM

Background/Purpose: The CD40-CD40L pathway may play a major role in autoimmune disorders like rheumatoid arthritis or SLE. Blocking this pathway may be a promising new treatment for patients suffering from autoimmune diseases. BI 655064 is a novel humanized antagonistic anti-CD40 monoclonal antibody free of agonistic activity and without antibody-dependent cellular- or complement- dependent cytotoxicity. Safety, tolerability, PK and CD40 receptor occupancy (RO) were investigated in a single ascending dose study in Asian male healthy volunteers.

Methods: This was a randomized, double-blind within dose groups, placebo-controlled, two-sites, single rising dose trial evaluating single subcutaneous (SC) doses (80, 120, 180 and 240 mg) of BI 655064. Blood samples were taken for analysis of PK, immunogenicity and CD40 RO throughout the entire trial duration (10 weeks).

Results: Thirty-two Chinese and 32 Japanese subjects, mean age 26.8 years, were treated: 48 received BI 655064 and 16 received placebo. All doses of BI 655064 were well tolerated in both ethnicities. There was no-drug related serious adverse event (AE) or significant AE reported. All AEs were mild, except 1 moderate (Chinese 120 mg; contusion), and all recovered. The percentage of subjects reporting any AE was the same (31.3%) for subjects treated with BI 655064 or placebo. AEs did not show a dose relationship. Nineteen of the 20 subjects that reported at least 1 AE during the treatment phase were Chinese. The most frequently reported AEs were upper respiratory tract infections (reported in 8.3% subjects on BI 655064 vs. 12.5 % on placebo). AEs rated as drug –related by the investigator were only reported in Chinese subjects and did not show a dose relationship. The only drug-related AE that was reported for more than 1 subject was diarrhoea (1 Chinese in each 80 mg and 240 mg treatment). There was no evidence of thromboembolism or bleeding, hypersensitivity reaction, cytokine release and relevant change in safety laboratory tests including coagulation parameters.

Plasma concentrations of BI 655064 increased gradually after a single SC administration of BI 655064, reached a peak at 96 to 144 hours post dose and then declined with the terminal half-life ranging from 105 to 242 hours. The exposure increased more than proportionally with the dose indicating target mediated drug disposition. Single dose of 120 mg SC resulted in >90% CD40-RO and the duration of >90% CD40-RO increased with increasing dose. Anti-drug antibodies were detected in most of the subjects (45 out of 48 subjects) who received BI 655064 with relatively low to moderate titer (mostly ≤ 400, median titer ≤ 80) and median onset time of 41 days.

Conclusion: These data demonstrate that BI 655064 has a favorable clinical safety profile and high potential to block the CD40-CD40L pathway in Chinese and Japanese population. This is in line with results in Caucasians and supports the inclusion of Asian subjects in global clinical trials with BI 655064.

Disclosure: J. Kim, Boehringer Ingelheim, 3; **Y. Tsuda**, Boehringer Ingelheim, 3; **K. Yamamoto**, Boehringer Ingelheim, UCB, Eisai, Toyoma-chemical, Pfizer, Taisho Toyama, 5,Boehringer Ingelheim, Astellas, AbbVie, Eisai, Pfizer, Bristol-Myers, Janssen, UCB, Asahikasei, Santen, Ono, Taisho Toyama, Daiichisankyo, Chugai, Mitsubishi Tanabe, Eli Lilly Japan, Nipponkayaku, Takeda, 8,Immunofuture, 1,Immunofuture, 6,Astellas, TEIJIN, Bristol-Myers, Pfizer, AbbVie, Daiichisankyo, Nipponkayaku, Chugai, Mitsubishi Tanabe, Janssen, Eisai, Santen, 2; **R. Thiedmann**, Boehringer Ingelheim, 3; **C. Schoelch**, Boehringer Ingelheim, 3; **S. Norris**, Boehringer Ingelheim, 3; **S. Padula**, Boehringer Ingelheim, 3; **J. Steffgen**, Boehringer Ingelheim, 3; **I. J. Jang**, Boehringer Ingelheim, 2.

Abstract Number: 2755

Evaluating Pharmacokinetic Predictors of Tofacitinib Clinical Response in Rheumatoid Arthritis

Manisha Lamba[1], Daniel E. Furst[2], Ara Dikranian[3], Martin Dowty[1], Matthew M Hutmacher[4], Daniela Conrado[1], Thomas Stock[5], Chudy Nduaka[5] and Sriram Krishnaswami[1], [1]Pfizer Inc, Groton, CT, [2]Medicine, University of California, Los Angeles, David Geffen School of Medicine, Los Angeles, CA, [3]San Diego Arthritis Medical Clinic, San Diego, CA, [4]Ann Arbor Pharmacometrics Group, Ann Arbor, MI, [5]Pfizer Inc, Collegeville, PA

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Background/Purpose: Tofacitinib is an oral Janus kinase inhibitor for the treatment of RA. A modified-release (MR) formulation to provide a once-daily (QD) dosing alternative to the available 5 mg twice-daily (BID) immediate-release (IR) formulation has been developed.[1] The objective was to determine the most relevant pharmacokinetic (PK) parameter driving the clinical response of tofacitinib to inform clinical development of the MR formulation.

Methods: Clinical efficacy data (DAS and ACR 20/50/70 responses) from 5 Phase 2 RA dose-ranging studies of IR 1-30 mg BID and IR 20 mg QD across ~1,500 patients were analyzed. Dose and exposure-response (E-R) models were developed to characterize the time course of changes in DAS, including quantifying the delay between concentration and response, and to compare the predictive abilities of various PK parameters (total drug exposure as measured by area under the concentration-time profile [AUC], and peak [C_{max}] and minimum [C_{min}] plasma concentrations). Non-clinical efficacy data from a dose-fractionation study of multiple IR QD and BID doses using the murine collagen-induced arthritis (mCIA) model were also analyzed to delineate the predictive ability of PK parameters. The relationship between tofacitinib exposure metrics and incidence of safety outcomes were explored using linear logistic models.

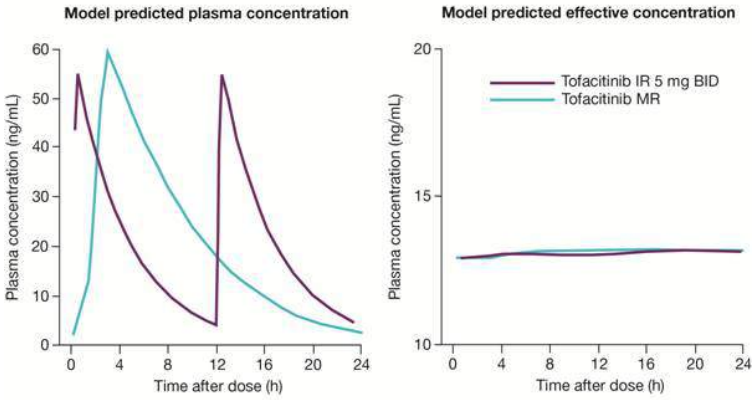
Results: The E-R model yielded an equilibration half-life of 3.2 weeks for changes in DAS, substantially longer than the PK half-life of tofacitinib (~3 hours). Application of this model to plasma PK profiles of MR and IR yielded predicted effective superimposable concentrations for both regimens (Fig 1). In a dose-ranging Phase 2 study, analyses of the IR 20 mg QD dose (similar AUC to the IR 10 mg BID dose, but 86% lower C_{min} and ~2-fold higher C_{max}) demonstrated similar efficacy to the IR 10 mg BID dose. DAS mean [standard error] change from baseline was -1.72 [0.14] for IR 20 mg QD vs -1.82 [0.15] for IR 10 mg BID; ACR 20/50/70 rates were 56/36/24% for IR 20 mg QD vs 58/28/12% for IR 10 mg BID, respectively, at Week 12. Statistical comparison of PK parameters favored AUC as a better predictor ($p<0.05$) of DAS changes than C_{max} or C_{min}, with little added value of C_{max} or C_{min}. In the mCIA model, BID and QD E-R curves were well aligned for AUC as the predictor, as demonstrated by concordance of concentrations producing 50% of maximum response. Comparing the predictive ability of AUC, C_{max}, and C_{min} for safety events of interest (eg serious infections) also supported AUC as the most relevant PK parameter (data not shown).

Conclusion: Collectively, these analyses support AUC as the relevant predictor of tofacitinib clinical response and inform clinical development of an MR formulation of tofacitinib for QD dosing.

Reference

1. Lamba M et al. Ann Rheum Dis 2015; 74(S2): 626.

Figure 1. Predicted Steady-State Tofacitinib Concentration-Time Profiles in Plasma and in the Virtual Effect Compartment Following IR 5 mg BID Doses and MR Doses in RA Patients



BID, twice daily; IR, immediate-release; MR, modified-release

Disclosure: M. Lamba, Pfizer Inc, 1,Pfizer Inc, 3; **D. E. Furst**, Gilead, 2,GlaxoSmithKline, 2,NIH, 2,Novartis Pharmaceutical Corporation, 2,Pfizer Inc, 2,Roche Pharmaceuticals, 2,Genentech and Biogen IDEC Inc., 2,UCB, 2,Abbvie, 5,Actelion Pharmaceuticals US, 5,Amgen, 5,Bristol-Myers Squibb, 5,Cytori, 5,Janssen Pharmaceutica Product, L.P., 5,Gilead, 5,GlaxoSmithKline, 5,NIH, 5,Novartis Pharmaceutical Corporation, 5,Pfizer Inc, 5,Roche Pharmaceuticals, 5,Genentech and Biogen IDEC Inc., 5,UCB, 5,Abbvie, 8,Actelion Pharmaceuticals US, 8,Bristol-Myers Squibb, 2,Amgen, 2,Actelion Pharmaceuticals US, 2,Abbvie, 2,UCB, 8; **A. Dikranian**, Pfizer Inc and AbbVie, 8,Pfizer Inc and AbbVie, 9; **M. Dowty**, Pfizer Inc, 1,Pfizer Inc, 3; **M. M. Hutmacher**, Pfizer Inc, 5; **D. Conrado**, Pfizer Inc, 1,Metrum Research Group, 3; **T. Stock**, Pfizer Inc, 1,Pfizer Inc, 3; **C. Nduaka**, Pfizer Inc, 1,Pfizer Inc, 3; **S. Krishnaswami**, Pfizer Inc, 1,Pfizer Inc, 3.

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Abstract Number: 2756

Impact of Tocilizumab Monotherapy on Patient-Reported Quality of Life Outcomes in the US Corrona Registry

Leslie Harrold[1,2], Ani John[3], George W. Reed[2,4], Chitra Karki[2], YouFu Li[4], Joel M. Kremer[5], Tmirah Haselkorn[6] and Jeffrey D. Greenberg[2,7], [1]Department of Orthopedics and Medicine, University of Massachusetts Medical School, Worcester, MA, [2]Corrona, LLC, Southborough, MA, [3]Genentech, Inc., South San Francisco, CA, [4]University of Massachusetts Medical School, Worcester, MA, [5]Albany Medical College, Albany, NY, [6]Genentech, Inc, South San Francisco, CA, [7]NYU School of Medicine, New York, NY
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Background/Purpose: The objective of this real-world analysis was to examine the impact of the interleukin-6 receptor α inhibitor tocilizumab (TCZ) on patient-reported outcomes (PROs) in a US observational cohort of > 40,000 patients with rheumatoid arthritis (RA; Corrona).

Methods: Between October 1, 2010, and March 31, 2015, patients with RA who newly initiated TCZ monotherapy while not in remission (based on Clinical Disease Activity Index) and had a follow-up visit at 1 year (± 3 months) were identified. Changes in PROs, assessed 1 year from baseline and stratified by prior tumor necrosis factor inhibitor (TNFi) use, included patient global assessment of disease, pain and fatigue (0-100); morning stiffness (hours); modified Health Assessment Questionnaire (mHAQ; 0-3); and Euro Quality of Life 5 dimensions questionnaire (EQ-5D). Improvement in EQ-5D domains was defined as patients improving from moderate to no disability or severe to moderate or no disability. Outcomes between the 1 and ≥ 2 prior TNFi groups were compared using chi-square or *t*-tests, as appropriate.

Results: Of the 255 TCZ monotherapy initiators included, 24 (9%) were TNFi naive, 93 (37%) received 1 prior TNFi and 138 (54%) received ≥ 2 prior TNFis. Baseline PROs showed that patients were substantially impacted by their disease, with similar scores

reported across TNFi exposure groups (**Table**). Patients reported median (IQR) global disease activity, pain, fatigue and mHAQ scores of 55 (40-75), 60 (40-76), 60 (33-80) and 0.63 (0.25-1.00), respectively, and a median (IQR) of 1 (0.5-2.5) hour of morning stiffness at baseline. Baseline proportions of patients reporting difficulties in EQ-5D domains are shown (**Table**). At 12 months, improvements were reported in all PROs with no significant differences across TNFi exposure groups. Median (IQR) improvements in patient global, pain and fatigue were 10 (-5-30), 10 (-5-30) and 5 (-10-23), respectively. 46% of patients reported no reduction in morning stiffness, 35% reported 1-60 minutes reduction and 19% reported > 60 minutes reduction. Improvement in EQ-5D is shown (**Figure**). A significantly lower proportion of patients with ≥ 2 prior TNFis had improvement in walking and usual activities compared with patients with 1 prior TNFi.

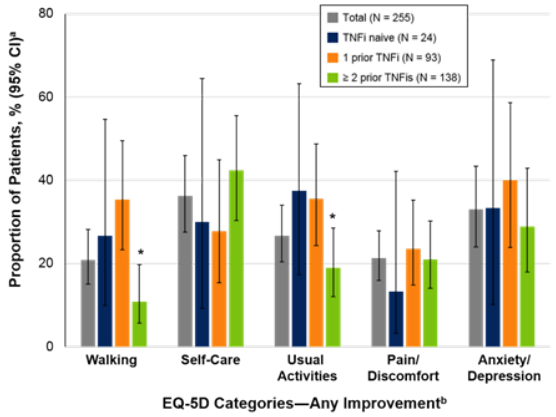
Conclusion: Real-world data showed that quality of life in patients with RA newly initiating TCZ monotherapy was substantially impacted by their disease. Improvements at 1 year were reported in all measures, regardless of prior TNFi history; however, patients who received TCZ therapy earlier in the line of treatment had better response with respect to walking and usual activities than those treated with ≥ 2 prior TNFis.

Table. Baseline EQ-5D Measures Among TCZ Monotherapy Initiators

	Total N = 255	TNFi Naive N = 24	1 Prior TNFi N = 93	≥ 2 Prior TNFis N = 138	*P*-value[a]
Patients experiencing at least some difficulty in EQ-5D categories, % (n/N)					
Walking	72.9 (151/207)	78.9 (15/19)	72.6 (53/73)	72.2 (83/115)	0.45
Self-care	51.7 (106/205)	58.8 (10/17)	50.0 (37/74)	51.8 (59/114)	0.19
Usual activity	81.6 (168/206)	88.9 (16/18)	80.8 (59/73)	80.9 (93/115)	0.58
Pain/discomfort	94.1 (190/202)	88.9 (16/18)	94.5 (69/73)	94.6 (105/111)	0.94
Anxiety/depression	43.8 (91/208)	47.4 (9/19)	41.1 (30/73)	44.8 (52/116)	0.87

EQ-5D, Euro Quality of Life 5 dimensions questionnaire; TCZ, tocilizumab; TNFi, tumor necrosis factor inhibitor.
[a] *P*-value represents the comparison between those with 1 prior TNFi and those with ≥ 2 prior TNFis.

Figure. Improvement in the EQ-5D at 12 Months Among TCZ Monotherapy Initiators Stratified by Prior TNFi Experience



EQ-5D, Euro Quality of Life 5 dimensions questionnaire; TCZ, tocilizumab; TNFi, tumor necrosis factor inhibitor.
[a] Percentage of patients reporting improvement among those patients who reported difficulty in each measure at baseline.
[b] Improvement in the EQ5D domains was defined as either patients improving from moderate to no disability, or those with severe disability improving to moderate or no disability.
* $P < 0.05$; *P*-value represents the comparison between those patients with 1 prior TNFi versus those with ≥ 2 prior TNFis.

Disclosure: L. Harrold, Corrona, LLC, 3; **A. John**, Genentech, Inc, 3; **G. W. Reed**, Corrona, LLC, 3; **C. Karki**, Corrona, LLC, 3; **Y. Li**, University of Massachusetts Medical School, 3; **J. M. Kremer**, Corrona, LLC, 1,Corrona, LLC, 3,Genentech, Inc, 5,Genentech, Inc, 2; **T. Haselkorn**, Genentech, Inc, 3; **J. D. Greenberg**, Corrona, LLC, 1,Corrona, LLC, 3,AstraZeneca, Celgene, Novartis and Pfizer, 5.

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Abstract Number: 2757

Secondary Efficacy Endpoints: Results from a Phase 3 Study Comparing ABP 501 with Adalimumab in Subjects with Moderate to Severe Rheumatoid Arthritis

Alan K. Matsumoto[1], Karel Pavelka[2], Warren Rizzo[3], Ramesh Gupta[4], William Shergy[5], Pawel Heycaj[6], Nan Zhang[7] and Primal P. Kaur[8], [1]Rheumatology, Arthritis & Rheumatism Assoc, Wheaton, MD, [2]Charles University, Prague, Czech Republic, [3]Advanced Arthritis Care & Research, Scottsdale, AZ, [4]Private Practice, Rheumatology, Memphis, TN, [5]RANA Clinical Research Center, Huntsville, AL, [6]Rheumatology and Clinical Immunology, Poznañ University of Medical Sciences, Poznan, Poland, [7]Biosimilars, Amgen, Inc., Thousand Oaks, CA, [8]Amgen, Inc., Thousand Oaks, CA
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Background/Purpose:

ABP 501 is being developed as a biosimilar candidate to adalimumab (Humira®), a fully human recombinant monoclonal antibody. Evidence from analytical and pharmacokinetic comparisons indicates that ABP 501 is highly similar to adalimumab. Primary efficacy endpoints and safety results from a phase 3 study comparing ABP 501 with adalimumab in subjects with rheumatoid arthritis (RA) are reported separately. Here we report the secondary efficacy endpoints of the study. The objective was to evaluate and compare American College of Rheumatology 20% response criteria (ACR20), ACR50, and ACR70, as well as the change from baseline in Disease Activity Score in 28 joints using C-reactive protein (DAS28-CRP) over weeks 2–24 for ABP 501 and adalimumab based on results from a phase 3 study.

Methods:

This was a randomized, double-blind, active-controlled study in adult subjects with moderate to severe RA who had an inadequate response to methotrexate. Subjects were randomized in a 1:1 ratio (ABP 501: n=264; adalimumab: n=262) to receive either ABP 501 or adalimumab 40 mg subcutaneously every 2 weeks. The primary endpoint was risk ratio (RR) of ACR20 assessed at week 24 with a safety follow-up to week 26 (end of study). Here we report descriptive results of the secondary efficacy endpoints that included risk difference (RD) of ACR20, RR of ACR50 and ACR70, and difference in change from baseline of DAS28-CRP over the entire study.

Results:

Baseline characteristics were well balanced between groups. The table shows the response rate for ACR20, ACR50, and ACR70 throughout the study. At week 24, the RD of ACR20, ACR50 and ACR70 for ABP 501 vs adalimumab was 2.60% (2-sided 90% CI, –3.728% to 8.936%), –2.84% (90% CI, –10.220 to 4.547) and 3.15% (90% CI, –3.177 to 9.470), respectively. The RR of ACR50 and ACR70 was 0.95 (90% CI, 0.819–1.097) and 1.13 (90% CI, 0.872–1.464), respectively, at week 24. The differences in mean change from baseline in DAS28-CRP between ABP 501 and adalimumab were –0.08 (90% CI, –0.24 to 0.08) at week 8, –0.09 (90% CI, –0.26 to 0.07) at week 12, –0.09 (90% CI, –0.25 to 0.08) at week 18, and –0.01 (90% CI, –0.18 to 0.17) at week 24. The overall safety and immunogenicity profile of ABP 501 was comparable to that of adalimumab and is reported separately.

Table. Response Rate (%) of ACR20, ACR50, and ACR70 by Visit and Treatment

	ACR 20		ACR 50		ACR 70	
Week	ABP 501	adalimumab	ABP 501	adalimumab	ABP 501	adalimumab
2	35.4	24.5	11.0	6.2	0.8	1.9
4	51.5	45.0	19.5	17.8	5.1	3.9
8	63.5	62.5	31.1	28.5	10.4	10.2
12	74.6	65.5	41.3	43.5	15.3	13.3
18	77.3	75.9	50.0	47.2	19.6	22.8
24	74.6	72.4	49.2	52.0	26.0	22.9

Conclusion:

Along with the primary endpoint, these data support the results that efficacy of ABP 501 was similar to adalimumab.

Disclosure: A. K. Matsumoto, Abbvie, Amgen, Pfizer, Takeda, 2; **K. Pavelka**, None; **W. Rizzo**, None; **R. Gupta**, None; **W. Shergy**, None; **P. Heycaj**, None; **N. Zhang**, Amgen, 3; **P. P. Kaur**, Amgen, 3.

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Abstract Number: 2758

Clinical Utility and Factors Associated with Certolizumab Pegol Drug Levels and Anti-Drug Antibodies in the Long-Term Treatment of Rheumatoid Arthritis

Meghna Jani[1], Hector Chinoy[1,2], John Isaacs[3], Ann W. Morgan[4], Anthony Wilson[5], Kimme L. Hyrich[6], Darren Plant[1,2] and Anne Barton[1,7], [1]Centre for Musculoskeletal Research, University of Manchester, Manchester, United Kingdom, [2]NIHR Manchester Musculoskeletal Biomedical Research Unit, Manchester Academy of Health Sciences, Manchester, United Kingdom, [3]National Institute for Health Research Newcastle Biomedical Research Centre, Newcastle upon Tyne Hospitals NHS Foundation Trust and Newcastle University, Newcastle, United Kingdom, [4]NIHR-Leeds Musculoskeletal Biomedical Research Unit, Leeds & Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds, Leeds, United Kingdom, [5]Infection & Immunity, University of Sheffield, Sheffield, United Kingdom, [6]Arthritis Research UK Centre for Epidemiology, The University of Manchester, Manchester, United Kingdom, [7]NIHR Manchester Musculoskeletal Biomedical Research Unit, Central Manchester Foundation Trust and University of Manchester, Manchester Academy of Health Sciences, Manchester, United Kingdom

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Background/Purpose:

Up to 40% of RA patients on anti-TNF agents fail to respond either due to primary or secondary inefficacy. One explanation is immunogenicity leading to the development of anti-drug antibodies (ADAb) and low drug levels, observed with monoclonal antibodies (adalimumab and infliximab). Data from prospective studies on the value of pharmacological testing in certolizumab-treated RA patients is lacking. An additional challenge is the practicality of obtaining trough drug levels and impact on service delivery. Our aims were to evaluate (i) the association between random certolizumab drug levels, ADAbs and treatment response in patients with RA; (ii) factors associated with ADAbs and certolizumab drug levels.

Methods:

115 patients on certolizumab were selected from the Biologics in RA Genetics and Genomics Study Syndicate prospective cohort. Serum samples were collected at 3, 6 and 12 months following initiation of therapy. ADAbs were measured using RIA and drug levels using ELISA assays at 3, 6 and 12 months. Disease activity (DAS28) scores were measured at each visit and 12 month EULAR response was calculated. Patient self-reported adherence was collected longitudinally. Ordinal logistic regression and generalised estimating equation (GEE) were used to test the association between random drug levels on treatment response, between ADAbs and drug levels, and factors associated with drug levels.

Results:

253 serial samples were tested for certolizumab drug levels (n=230 suitable for ADAb measurement). Mean age: 56 ± 13 years; 75% female; baseline DAS28 score: 5.9 ± 0.8; median BMI 27.5 (IQR 23.6-32.3). 87% were on a DMARD (58% MTX). ADAbs were detected in 37% (cut off ≥20 AU/ml; 42/112 patients at ≥1 time points by 12 months). The presence of ADAbs were significantly associated with lower drug levels over 12 months using GEE (β=-0.037, 95% confidence interval [CI]-0.055 to -0.018, $p<0.0001$) but not independently with 12 month EULAR response (β=0.0013 [95% CI:-0.0032, 0.00061], p=0.18). Drug level was associated with 12 month EULAR response (β=0.035 [95% CI: 0.0018-0.069], p=0.039). Patients who developed ADAbs had longer disease duration (8.3 years [5.7-15.3]) vs. patients who did not (6.0 years [3.3-12.4], p=0.01). Factors associated with certolizumab drug level in the univariate GEE analysis were gender, adherence, BMI, CRP and ADAb level (Table). In the multivariate model after adjustment of confounders, ADAb level and adherence remained significant (Table).

Table: Predictors of drug levels in certolizumab treated RA patients using generalised estimating equation		
Variable	**β Coefficient (95% confidence intervals)**	**P value**
Univariate analysis		
Age	0.14 (-0.017, -0.29)	0.08
Gender*	4.76 (0.21, 9.29)	0.040
BMI*	-0.46 (-0.89, -0.041)	0.032
CRP *	-0.099 (-0.17, -0.029)	0.005
Methotrexate use	-0.11 (-0.47, 4.47)	0.96
Anti-drug antibody level*	-0.037 (-0.055, -0.018)	<0.0001
Adherence*	10.43 (4.76, 16.11)	<0.0001
Multivariate model †		
Anti-drug antibody level*	-0.044 (-0.059 to -0.028)	<0.0001
Adherence*	7.08 (0.71, 13.45)	0.029
Gender	1.77 (-4.21, 7.76)	0.56
BMI	-0.13 (0.66, 0.43)	0.65
CRP	-0.065 (-0.14, 0.013)	0.102
*p <0.05; †Adjusted for variables significant in the univariate analysis		

Conclusion:

Drug levels in certolizumab-initiated patients may be clinically useful even in the absence of trough levels to determine treatment response. Adherence and ADAb levels are associated with low certolizumab drug levels, whilst high disease duration prior to biologic initiation associated with ADAbs. ADAb measurement may help determine the aetiology of a low drug level, but were not associated with 12 month EULAR response.

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Abstract Number: 2759

Long-Term Survival of Biological Therapy in Rheumatoid Arthritis Elderly Patients in Clinical Practice

Cristina Lajas[1], Alejandro Gomez-Gomez[1], Luis Rodriguez-Rodriguez[2], Leticia Leon[2], Cristina Vadillo[1], Dalifer Freites Núñez[1], Pilar Macarrón[1], José María Leal Pozuelo[2], Juan A Jover[1] and Lydia Abasolo[2], [1]Rheumatology, Hospital Clínico San Carlos, Madrid, Spain, [2]Instituto de Investigación Sanitaria San Carlos (IdISSC), Madrid, Spain

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Background/Purpose: With the increasingly widespread use of biological agents (BA), a thorough knowledge of their long-term behavior in clinical practice is fundamental. The purpose of our study was to assess and compare the long-term survival of Biological Agents (BA) in elderly patients with Rheumatoid Arthritis (RA) in clinical practice. Factors associated to discontinuation were also investigated.

Methods: Observational longitudinal study from 1999 to 2013 was conducted. RA patients followed in outpatient clinic at Hospital Clínico San Carlos, which started BA treatment after 65 years of age, were included. Primary outcome: BA (Etanercept; Infliximab; Adalimumab; Rituximab; and other BA [including Golimumab, Certolizumab, Abatacept and Tozilizumab]) discontinuation due to: adverse drug reaction (ADR), inefficacy, and other causes. Covariables: sociodemographic, clinical and therapy. Incidence rates of discontinuation (IR) per 100 patient-years were estimated using survival techniques with their respective 95% confidence interval [95% CI]. Comparison between BA discontinuation rates and other associated factors were run by Cox regression models.

Results: We included 286 courses of BA therapy in 146 patients (604 patient-years). Of these, 78% were women with a mean age at diagnosis of 66.5 ± 7 years and a median time to the start of the first BA of 6 ± 4 years. Adalimumab (27.3%), followed by Infliximab (22.4%), Etanercept (21.3%), and Rituximab (19.2%) were the most frequently used. Treatment was suspended in 199 cases (IR: 33 [28.6 -37.8]), 21.7% due to inefficacy (IR: 10.2 [8-13.5]), 39% to ADRs (IR: 18.4 [15.2- 22.1]), 2.8% to patient choice and 2.8% to improvement. In the first year of therapy 60% continued on BA, and after ten years, the retention rate didn´t exceed 5%. The crude IR of discontinuation was higher for Rituximab (IR: 39.2 [28-54]) compared to TNF- antagonists. In the multivariate analysis, after adjusting with calendar time, age and sex, we did not find differences between Adalimumab, Etanercept, Infliximab and Rituximab. Concomitant therapy with Disease Modifying Antirheumatic Drugs or corticoids, functional loss, positive anti–citrullinated protein antibodies and specific comorbidities were independent factors associated to discontinuation.

Conclusion: After several years of BA treatment in clinical practice, the survival in our cohort was low, mainly as a result of ADRs and inefficacy. We did not find any statistical differences between Adalimumab, Etanercept, Infliximab and Rituximab discontinuation rate. But we have found other clinical and therapy factors that modify their survival. This study contributes to increasing knowledge of long-term survival of these drugs in RA patients over 65 years and in real life conditions.

Disclosure: C. Lajas, None; **A. Gomez-Gomez**, None; **L. Rodriguez-Rodriguez**, None; **L. Leon**, None; **C. Vadillo**, None; **D. Freites Núñez**, None; **P. Macarrón**, None; **J. M. Leal Pozuelo**, None; **J. A. Jover**, None; **L. Abasolo**, None.

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Abstract Number: 2760

Efficacy and Safety of Sarilumab Plus MTX in Subgroups of Patients with Rheumatoid Arthritis in a Phase 3 Study

Arthur Kavanaugh[1], Alan J. Kivitz[2], P Miranda[3], Stefano Fiore[4], Jonathan Fay[5], Chunpeng Fan[6], Janet van Adelsberg[7] and T. W. J. Huizinga[8], [1]University of California San Diego, La Jolla, CA, [2]Altoona Center for Clinical Research, Duncansville, PA, [3]Centro De Estudios Reumatológicos, Santiago, Chile, [4]Sanofi, Bridgewater, NJ, [5]Regeneron Pharmaceuticals, Inc., Tarrytown, NY, [6]Biostatistics, Sanofi, Bridgewater, NJ, [7]Clinical Science, Regeneron Pharmaceutials, Inc., Tarrytown, NY, [8]Rheumatology, Leiden University Medical Center, Leiden, Netherlands

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Background/Purpose: The investigational drug sarilumab is a human mAb directed against the IL-6 receptor.[1] The phase 3 part of MOBILITY (NCT01061736) examined sarilumab + MTX vs placebo + MTX in patients with active, moderate-to-severe RA with inadequate response to MTX.[1] Both sarilumab doses (150 and 200 mg subcutaneously every 2 weeks [q2w]) were generally well tolerated and demonstrated statistically significant improvements in signs and symptoms of RA, improvements in physical function, and inhibition of radiographic progression. The incidence of treatment-emergent adverse events (TEAEs) was greater with sarilumab than placebo. The most common TEAEs were infections, neutropenia, injection-site reactions, and increased transaminases. In the present study, efficacy of sarilumab across prespecified subpopulations from MOBILITY was assessed.

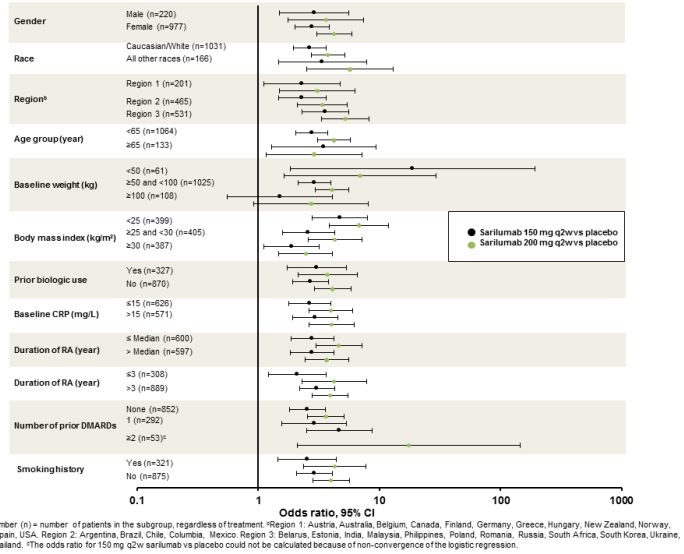
Methods: The MOBILITY study design and methods have previously been reported.[1] Incidence of ACR20 at week 24 and least-squares mean difference in change from baseline in HAQ-DI at week 16, coprimary endpoints in MOBILITY, were evaluated for placebo (n=398), sarilumab 150 mg q2w (n=400), and sarilumab 200 mg q2w (n=399) in prespecified subpopulations. Treatment-by-subgroup interactions were assessed by a logistic regression model for ACR20 at week 24 and by a mixed-effect model for repeated measures for HAQ-DI at week 16.

Results: No treatment-by-subgroup interactions were observed in the proportion of patients achieving ACR20 response at week 24 (Table), indicating that, across all subgroups, the efficacy of sarilumab was consistent with the overall study findings. There appeared to be a trend toward lower efficacy in patients with increasing weight and BMI, particularly in the sarilumab 150 mg q2w group (Figure). No treatment-by-subgroup interactions were observed for HAQ-DI improvements at week 16, and the trends observed with ACR20 response in regards to lower efficacy with increased weight and BMI were not observed.

Conclusion: ACR20 and HAQ-DI responses with sarilumab were generally consistent across all subgroups in MOBILITY, although ACR20 responses may be decreased in patients with increasing weight and BMI.

1. Genovese et al. *Arthritis Rheumatol*. 2015;67:1424-1437.

Table. Incidence of ACR20 Response at Week 24: Treatment by Subgroup Interactions	
Subgroup	***P* value (interaction)[a]**
Gender	0.79
Race	0.48
Region[b]	0.57
Age group	0.47
Baseline weight	0.53
BMI	0.05
Prior biologic use[c]	0.86
Baseline CRP	0.91
Duration of RA	0.84
Duration of RA	0.39
Number of prior DMARDs	0.42
Smoking history	0.89
BMI, body mass index; CRP, C-reactive protein; DMARD, disease-modifying antirheumatic drug; RA, rheumatoid arthritis. [a]Logistic regression model with terms of treatment, prior biologic use, region, subgroup, treatment-by-subgroup. [b]Logistic regression model with terms of treatment, prior biologic use, region, treatment-by-region. [c]Logistic regression model with terms of treatment, prior biologic use, region, treatment-by-prior biologic use.	



[a]Patient number (n) = number of patients in the subgroup, regardless of treatment. [b]Region 1: Austria, Australia, Belgium, Canada, Finland, Germany, Greece, Hungary, New Zealand, Norway, Portugal, Spain, USA. Region 2: Argentina, Brazil, Chile, Columbia, Mexico. Region 3: Belarus, Estonia, India, Malaysia, Philippines, Poland, Romania, Russia, South Africa, South Korea, Ukraine, Taiwan, Thailand. [c]The odds ratio for 150 mg q2w sarilumab vs placebo could not be calculated because of non-convergence of the logistic regression.

Figure. Odds ratio for ACR20 response of sarilumab versus placebo at week 24 by subgroup.[a]

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Abstract Number: 2761

IL-6R Blockade with Sarilumab Plus Methotrexate Results in Changes in Clinical and Laboratory Parameters Associated with Chronic Inflammation in Patients with Moderate-to-Severe RA in a Phase 3 Study

Maxime Dougados[1], Ernest H. Choy[2], Hideto Kameda[3], Janet van Adelsberg[4], Jonathan Fay[5], Stefano Fiore[6], Chunpeng Fan[7] and Georg Schett[8], [1]Paris-Descartes University, Paris, France, [2]Cardiff University, Institute of Infection and Immunity, Tenovus Building, University Hospital of Wales, Cardiff, United Kingdom, [3]Dep of Rheumatol/Clin Immun, Saitama Medical Ctr, Kawagoe, Japan,

[4]Clinical Science, Regeneron Pharmaceutials, Inc., Tarrytown, NY, [5]Regeneron Pharmaceuticals, Inc., Tarrytown, NY, [6]Sanofi, Bridgewater, NJ, [7]Biostatistics, Sanofi, Bridgewater, NJ, [8]Department of Internal Medicine 3 and Institute for Clinical Immunology, University of Erlangen-Nuremberg, Erlangen, Germany

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Background/Purpose: Chronic inflammation in RA is characterized by biochemical changes, including decreased hemoglobin, elevated CRP, changes in lipid metabolism, and hypoalbuminemia.[1] Some parameters, including CRP, are associated with RA disease activity, rapid structural disease progression, and comorbidities (eg, cardiovascular disease).[2,3] Chronic inflammation in RA is also associated with non-focal complaints[4]; some, like weight loss, are not measured by response-to-treatment measures routinely used in clinical studies. In the phase 3 MOBILITY study (NCT01061736), investigational agent sarilumab (150 or 200 mg every 2 wks [q2w]) + MTX demonstrated efficacy vs placebo (Pbo) in adults with active, moderate-to-severe RA with inadequate response to MTX.[5] The most common treatment-emergent adverse events with sarilumab included infections, neutropenia, injection site reactions, and increased transaminases. Laboratory abnormalities were consistent with IL-6 blockade. In the present analysis of MOBILITY, effect of sarilumab on laboratory parameters associated with chronic inflammation was assessed.

Methods: Changes in laboratory parameters from baseline through 52 wks with Pbo (n=427), sarilumab 150 mg q2w (n=431), and sarilumab 200 mg q2w (n=424) were assessed.

Results: Laboratory parameters remained relatively unchanged in the Pbo group through wk 52 (Table). Decreases in serum amyloid A, fibrinogen, and CRP were observed in the sarilumab group beginning at wk 2 and remained below baseline through wk 52. Increases in hemoglobin and albumin were also observed. An increase in total cholesterol levels was observed starting at ~4 wks in all 3 groups (mean increase of ~20 mg/dL for both sarilumab groups) and remained at these levels through wk 52. Low-density lipoprotein (LDL) cholesterol increased from <160 to ≥160 mg/dL in more patients treated with sarilumab (27.8% in 200 mg, 21.1% in 150 mg vs 11.5% in Pbo). Slight weight gain was observed with either dose of sarilumab (1.32 and 1.85 vs Pbo, 0.07 kg), with more patients treated with sarilumab 150 or 200 mg (32.7% and 34.2%, respectively) experiencing a ≥5% increase from baseline (vs 15.0% with Pbo).

Conclusion: Inhibition of IL-6 signaling via sarilumab was associated with changes in parameters associated with chronic inflammation including a decrease in CRP, an increase in hemoglobin, normalization of albumin and fibrinogen, and an increase in total and LDL cholesterol. Increase in weight was also observed in both sarilumab groups across the 52-wk study.

1. Yoshida et al. *BioMed Res Int.* 2014;2014:698313.

2. Scott. *J Rheumatol.* 2004;69;55-65.

3. Yeh. *Circulation.* 2004;109(suppl II):II11-II14.

4. Suresh. *J R Soc Med.* 2004;97:421-424.

5. Genovese et al. *Arthritis Rheumatol.* 2015;67:1424-1437.

Table. Change From Baseline to Week 52 in Laboratory Parameters Associated With Chronic Inflammation Following Treatment With Sarilumab in MOBILITY

Laboratory assessment, mean (SD)	Placebo + MTX (n=427)	Sarilumab 150 mg q2w + MTX (n=431)	Sarilumab 200 mg q2w + MTX (n=424)
Hemoglobin, g/L	-0.58 (10.40)	9.15 (10.96)	9.81 (11.06)
Serum amyloid A protein, mg/L	3.01 (69.47)	-58.87 (89.61)	-63.36 (85.80)
Fibrinogen, g/L	-0.15 (1.37)	-2.14 (1.60)	-2.24 (1.54)
Albumin, g/L	0.67 (2.81)	4.23 (3.86)	4.71 (3.57)
Total cholesterol, mg/dL	0.52 (27.60)	20.73 (31.56)	22.96 (32.08)
CRP, mg/L	1.01 (23.33)	-16.91 (26.70)	-18.42 (21.93)

CRP, C-reactive protein; MTX, methotrexate; q2w, every 2 weeks; SD, standard deviation.

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Abstract Number: 2762

Sarilumab Dose Reduction to Manage Laboratory Abnormalities in an Open-Label Extension Study in RA Patients

Gerd Burmester[1], Anju Garg[2], Hubert van Hoogstraten[2], Neil Graham[3], Alex Boddy[2], Janie Parrino[4] and Mark C. Genovese[5], [1]Department of Rheumatology and Clinical Immunology, Charité - Universitätsmedizin Berlin, Berlin, Germany, [2]Sanofi, Bridgewater, NJ, [3]Regeneron Pharmaceuticals, Inc., Tarrytown, NY, [4]Merck & Co., Inc., Whitehouse Station, NJ, [5]Division of Rheumatology, Stanford University Medical Center, Palo Alto, CA

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Background/Purpose: The investigational agent sarilumab is a human mAb directed against the IL-6 receptor. In the phase 3 MOBILITY study (NCT01061736), sarilumab (150 or 200 mg every 2 wks [q2w] + MTX) demonstrated efficacy in adults with active, moderate-to-severe RA with inadequate response to MTX.[1] The most common treatment-emergent adverse events (TEAEs) with sarilumab included infections, neutropenia, injection site reactions, and increased transaminases. Lab changes observed were consistent with IL-6 signaling blockade. This analysis examined dose reduction of sarilumab that occurred during an open-label, long-term, follow-up study (EXTEND, NCT01146652) that evaluates long-term safety and efficacy of sarilumab with or without concomitant non-biologic DMARDs. Eligible patients were adults with RA who participated in prior sarilumab studies.

Methods: Patients initially entering EXTEND received sarilumab 150 mg every week (qw). Following dose selection for phase 3 studies, patients were switched to or initiated on sarilumab 200 mg q2w. Per protocol, investigators could have reduced the dose to sarilumab 150 mg q2w for absolute neutrophil count (ANC) ≥0.5 to 1.0 Giga/L in the absence of infection, platelet count ≥50 to 100 Giga/L in the absence of bleeding, or alanine aminotransferase (ALT) ≥3 to 5 × ULN. The majority of patients included in these analyses were enrolled from MOBILITY; efficacy data from EXTEND were analyzed after dose reduction in these patients (n=138).

Results: The study is ongoing. As of April 2015 interim analysis, dose reduction from 200 to 150 mg sarilumab q2w occurred in 15% of patients. The most common reasons for sarilumab dose reduction were decrease in neutrophil counts (9.5%) and elevations in ALT (3.3%) (Table 1). Infection was the most common non-laboratory reason for dose reduction (0.4%). Approximately 76% of patients who dose reduced are continuing treatment, with a mean duration of treatment after dose reduction of 1.5 years. Improvements in ANC and ALT were observed over the 6 months following dose reduction (Table 2). Efficacy of sarilumab in MOBILITY patients was maintained following dose reduction in EXTEND as assessed by ACR20 response at wk 24: 83%.

Conclusion: In this study, reducing the dose from 200 mg q2w to 150 mg q2w to manage laboratory abnormalities allowed the majority of patients to continue in the study for a mean duration of >1.5 years. For patients continuing in the study, these laboratory abnormalities improved during the 6 months following dose reduction, and efficacy was maintained.

1. Genovese et al. *Arthritis Rheumatol*. 2015;67:1424-1437.

Table 1. Reasons for Dose Reduction

	Patients on 200 mg q2w (N=1843)	
		n (%)
Patients who dose reduced from 200 mg q2w to 150 mg q2w		276 (15%)
Decrease in neutrophil count		175 (9.5%)
Neutrophil count <1.0 Giga/L and ≥0.5 Giga/L	92 (5.0%)	
Precautionary measure to avoid ANC <1.0 Giga/L	83 (4.5%)	
Increase in ALT level		61 (3.3%)
ALT increase >3 times ULN and ≤5 times ULN	54 (2.9%)	
Precautionary measure to avoid ALT increase >3 times ULN	7 (0.4%)	
Decrease in platelet count		19 (1.0%)
Platelet count ≥50 Giga/L and <100 Giga/L	8 (0.4%)	
Precautionary measure to avoid platelet count <100 Giga/L	11 (0.6%)	
Other AE		16 (0.9%)
Other reason		5 (0.3%)

AE, adverse event; ALT, alanine aminotransferase; q2w, every 2 weeks; ULN, upper limit of normal.

Table 2. Laboratory Parameters Following Dose Reduction

	Prior to dose reduction n (%)	1 month after dose reduction n (%)	3 months after dose reduction n (%)	6 months after dose reduction n (%)
Absolute neutrophil count				
≥0.5 to 1.0 Giga/L	95/175 (54%)	17/121 (14%)	17/146 (12%)	8/131 (6%)
<0.5 Giga/L	0/175	3/121 (3%)	1/146 (1%)	0/131
ALT				
>3 and ≤5 times ULN	50/61 (82%)	7/34 (21%)	1/46 (2%)	2/46 (4%)
>5 and ≤10 times ULN	2/61 (3%)	1/34 (3%)	0/46	0/46

ALT, alanine aminotransferase; ULN, upper limit of normal.

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Abstract Number: 2763

Filgotinib (GLPG0634), a Selective JAK1 Inhibitor, Shows Similar Pharmacokinetics and Pharmacodynamics Profiles in Japanese and Caucasian Healthy Volunteers

Namour Florence[1], Béatrice Vayssière[1], René Galien[2], Liesbeth Fagard[3], Annegret Van der Aa[3], Sandy Goss[4], Pille Harrison[3] and Chantal Tasset[3], [1]Galapagos SASU, Romainville, France, [2]102 Avenue Gaston Roussel, Galapagos SASU, Romainville, France, [3]Galapagos NV, Mechelen, Belgium, [4]Abbvie, Chicago, IL

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Background/Purpose: Filgotinib is an oral, selective Janus kinase 1 (JAK1) inhibitor combining clinical efficacy and a rapid onset of action with a good safety profile in patients with rheumatoid arthritis (RA). Its once-daily oral administration is supported by the long half-life of an active metabolite with the same JAK1 selectivity profile as the parent compound. Given genetics may cause differences in drug metabolism and pharmacokinetics (PK), and pharmacodynamics (PD) resulting in variability in clinical response, filgotinib was studied in Japanese healthy volunteers to evaluate the potential for different dosing requirements compared to Caucasians/ Compare the PK, PD and safety of filgotinib between Japanese and Caucasian healthy volunteers after repeated dosing of 200 mg filgotinib.

Methods: In a single-center Phase 1 study, 10 Japanese (1st and 2nd generation residing outside Japan for less than 5 years) and 10 Caucasian healthy volunteers received once daily 200 mg filgotinib or placebo for 10 days. The PK of filgotinib and its main active metabolite were evaluated, and the overall PD effect was assessed in whole blood using *ex vivo* IL-6 induced phosphorylation of STAT1 (pSTAT1) as biomarker for JAK1 activity and GM-CSF induced phosphorylation of STAT5 (pSTAT5) for JAK2 activity. Standard safety assessments were performed throughout the study duration.

Results: Steady state in plasma concentrations for filgotinib and its active metabolite was attained after 2 to 3 days of administration in both Japanese and Caucasian volunteers. Overall exposures for filgotinib and its metabolite were similar in the two groups, with the main active metabolite showing plasma concentrations well exceeding those of filgotinib. Both in Japanese and Caucasians, IL-6 induced pSTAT1 was inhibited over the entire 24 hour post-dosing period, with maximum inhibition observed between 1 and 5 hours post dose. No relevant inhibition of JAK2 activity was observed in any group, confirming filgotinib's selective inhibition of JAK1 over JAK2. In Japanese and Caucasian healthy volunteers, filgotinib was generally safe and well tolerated with no relevant differences in safety profile among the ethnic groups.

Conclusion: Filgotinib showed comparable PK, PD and safety profiles in Japanese and Caucasian healthy volunteers. The similarity in the PK and PD response suggests that there are no relevant differences among the groups in drug metabolism or selective inhibition of JAK1. These data support that filgotinib may be administered at similar doses in Japanese and Caucasian RA patients.

Disclosure: N. Florence, GALAPAGOS, 3; **B. Vayssière**, GALAPAGOS, 3; **R. Galien**, Galapagos, 3; **L. Fagard**, GALAPAGOS, 3; **A. Van der Aa**, Galapagos, 3; **S. Goss**, AbbVie, 3; **P. Harrison**, Galapagos, 3; **C. Tasset**, Galapagos, 3.

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Abstract Number: 2764

Head-to-Head Comparison of the Retention Rate of First Biologics in Elderly Patients with Rheumatoid Arthritis in Japanese Clinical Practice: Results from the Multicenter Biologic Registry

Masatoshi Hayashi[1], Toshihisa Kanamono[2], Hiroyuki Matsubara[3], Toshihisa Kojima[4], Koji Funahashi[5], Nobunori Takahashi[4] and Naoki Ishiguro[6], [1]Departments of Orthopedic surgery and Rheumatology, Nagano Red Cross Hospital, Nagano, Japan, [2]Reumatology, Nagano Red Cross Hospital, Nagano, Japan, [3]Department of Orthopedic Surgery and Rheumatology, Nagano Red Cross Hospital, Nagano, Japan, [4]Department of Orthopedic Surgery, Nagoya University Hospital, Nagoya, Japan, [5]Nagoya University, Nagoya, Japan, [6]Department of Orthopedic Suregery, Nagoya University Hospital, Nagoya, Japan
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Background/Purpose: The objective of this report was to clarify and compare the retention rate of first biologics used to treat elderly Japanese patients with rheumatoid arthritis (RA).

Methods: A prospective analysis was performed on 289 patients of age over 65 years with RA followed up in our multicenter registry after September 2010 (approval date of abatacept as the 5th biologic agent for RA, two years after tocilizumab in Japan). We assessed the age, sex, disease duration, Steinblocker's Stage and Class, Disease Activity Score 28-Erythrocyte Sedimentation Rate, past

operation history, complications, methotrexate use and dose, and corticosteroid use and dose as baseline characteristics, and compared cumulative survival and reasons of discontinuation among patients treated with the TNF-inhibitors (TNF-i), abatacept, and tocilizumab.

Results: Of the 289 patients, 146 (50.5%) were treated with TNF-i, 117 (40.5%) with abatacept, and 26 (9.0%) with tocilizumab. The patients in the abatacept group had older age and longer disease duration, worse stage and class, fewer complications, and lower methotrexate use than those in the TNF-i group (see table). However, the cumulative survival was longer in the abatacept group than in the TNF-i group (P = 0.013, log-rank test).

Conclusion: In our cohort of elderly patients with RA, the abatacept group, despite a relatively worse RA presentation at baseline, had better retention rate compared with the TNF-i group. This result provides valuable information in managing active RA in elderly patients.

Table. Demographic and clinical characteristics of patients of age over 65 years with rheumatoid arthritis who received first biologic treatments after September 2010

Characteristics	Total	TNF-i	Abatacept	Tocilizumab	P-value†
Number (%)	289 (100)	146 (50.3)	117 (40.3)	26 (9.0)	
Age, years	72.17 ± 5.26	71.08 ± 4.95	73.80 ± 5.33	70.96 ± 4.85	<0.001*
Female, %	77	81	79	50	0.757
RA disease duration, years	10.84 ± 11.12	9.30 ± 9.84	13.50 ± 12.75	8.58 ± 8.73	0.014*
Steinblocker's Stage III or IV, %	59	51	69	52	0.010*
Steinblocker's Class 3 or 4, %	38	26	56	24	<0.001*
DAS28ESR	5.20 ± 1.21	5.08 ± 1.19	5.23 ± 1.27	5.71 ± 1.00	0.360
Past operations, %	17	22	15	9	0.226
Complications, %	66	71	53	83	0.043*
MTX use, %	62	77	44	72	<0.001*
MTX dose, mg/week	8.32 ± 3.22	8.58 ± 3.06	7.72 ± 3.51	8.56 ± 3.20	0.091
Oral corticosteroids use, %	54	56	53	50	0.695
PSL-equivalent dose, mg/day	4.87 ± 2.74	4.90 ± 2.88	4.73 ± 2.75	5.42 ± 1.79	0.895
AE as reason of discontinuation, no. (%)	81 (37)	52 (31)	22 (41)	7 (71)	0.430

The data are reported as mean ± standard deviation. †P-values are calculated between TNF-i and abatacept with suitable statistics. RA rheumatoid arthritis, TNF-i tumor necrosis factor inhibitor, DAS disease activity score, ESR erythrocyte sedimentation rate, MTX methotrexate, PSL prednisolone, AE adverse events

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Disclosure: M. Hayashi, None; **T. Kanamono**, None; **H. Matsubara**, None; **T. Kojima**, Takeda Pharma Corporation, 2,Janssen Pharmaceutical, 2,Astellas Pharma Corporation, 2,Mitsubishi Tanabe Pharma Corporation, 8,Takeda Pharma Corporation, 8,Eisai Pharma Corporation, 8; **K. Funahashi**, Abbvie Japan Co. Ltd, 8,Eisai Co. Ltd, 8,UCB Japan Co. Ltd, 8,Mitsubishi Tanabe Pharma Co., 8,Takeda pharmaceutical Co. Ltd, 8,Pfizer Co. Ltd, 8,Chugai Pharma Co. Ltd, 8,Janssen Pharma KK, 8,Bristol-Myers Squibb, 8; **N. Takahashi**, None; **N. Ishiguro**, Takeda, Mitsubishi-Tanabe, Astellas, Chugai, Abbott, Bristol-Myers Squibb, Eisai, Janssen, Kaken, Pfizer, 2,Takeda, Mitsubishi-Tanabe, Astellas, Chugai, Abbott, Bristol-Myers Squibb, Eisai, Janssen, Kaken, Pfizer, Taisho-Toyama, Otsuka, 8.

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Abstract Number: 2765

Long-Term Retention Rate of First Biologics in Patients of Age over 75 Years with Rheumatoid Arthritis in Japanese Clinical Practice: Results from the Multicenter Biologic Registry

Masatoshi Hayashi[1], Toshihisa Kanamono[2], Hiroyuki Matsubara[3], Toshihisa Kojima[4], Koji Funahashi[5], Nobunori Takahashi[4] and Naoki Ishiguro[6], [1]Department of Orhtopedic Surgery and Rheumatology, Nagano Red Cross Hospital, Nagano, Japan, [2]Reumatology, Nagano Red Cross Hospital, Nagano, Japan, [3]Department of Orthopedic Surgery and Rheumatology, Nagano Red Cross Hospital, Nagano, Japan, [4]Department of Orthopedic Surgery, Nagoya University Hospital, Nagoya, Japan, [5]Nagoya University, Nagoya, Japan, [6]Department of Orthopedic Suregery, Nagoya University Hospital, Nagoya, Japan

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Background/Purpose: The objective of this report was to clarify and compare the retention rate of first biologics used to treat elderly Japanese patients with rheumatoid arthritis (RA) in clinical practice.

Methods: A prospective analysis was performed on 197 patients of age over 75 years with RA who were followed up in our multicenter registry since its establishment. We assessed the age, sex, disease duration, Steinblocker's Stage and Class, Disease Activity Score 28-Erythrocyte Sedimentation Rate (DAS28ESR), past surgical history, complications, methotrexate use and dose, and corticosteroid use and dose as baseline characteristics, and compared cumulative survival and reasons for discontinuation among patients treated with TNF-inhibitors (TNF-i), abatacept, and tocilizumab.

Results: Of the 197 patients, 140 (71%) were treated with TNF-i, 48 (24%) with abatacept, and 9 (5%) with tocilizumab. Patients in the abatacept group were older and had worse Steinblocker's Class, fewer complications, and lower methotrexate use than those in the TNF-i group; however, they had similar DAS28ESR at baseline (see table). As a result, the abatacept group was superior to the TNF-i group in terms of cumulative survival (p = 0.002, log-rank test).

Conclusion: In our cohort of patients of age over 75 years with RA, the abatacept group, despite a relatively worse RA presentation at baseline, had a better retention rate than the TNF-i group. This result should be valuable in managing active RA in elderly patients.

Table. Demographic and clinical characteristics of patients of age over 75 years with Rarheumatoid arthritis who received first biologic treatments.

Characteristics	total	TNF-i	abatacept	tocilizumab	P value†
Number (%)	197 (100)	140 (71)	48 (24)	9 (5)	
Age, years	78.3 ± 3.2	78.0 ± 3.1	79.1 ± 3.4	78.4 ± 2.7	0.030*
Female, %	76	75	81	56	0.434
RA duration, years	11.0 ± 11.4	11.0 ± 11.1	12.7 ± 13.2	4.2 ± 4.4	0.781
Steinblocker's Stage III or ‡W, %	62	65	59	33	0.585
Steinblocker's Class 3 or 4, %	46	42	64	22	0.014*
DAS28ESR	5.42 ± 1.19	5.36 ± 1.20	5.36 ± 1.18	6.31 ± 0.79	0.928
Past operations, %	27	31	19	0	0.135
Complications, %	81	91	43	86	<0.001*
MTX use, %	59	68	36	75	<0.001*
MTX dose, mg/weeks	6.8 ± 2.1	6.9 ± 1.8	6.7 ± 3.2	6.0 ± 1.3	0.482
Oral corticosteroids use, %	60	66	49	57	0.068
PSL-equivalent dose, mg/day	3.0 ± 3.1	3.4 ± 3.2	2.2 ± 2.8	3.6 ± 3.5	0.059
AE as reason of discontinuations, no. (%)	42 (48)	39 (48)	2 (50)	1 (33)	1.000

Data are mean ± standard deviation. †P values are calculated between TNF-i and abatacept with suitable statistics. RA rheumatoid arthritis, TNF-i tumor necrosis factor inhibitor, DAS disease activity score, ESR erythrocyte sedimentation rate, MTX methotrexate, PSL prednisolone, AE adverse events.

Disclosure: M. Hayashi, None; **T. Kanamono**, None; **H. Matsubara**, None; **T. Kojima**, Takeda Pharma Corporation, 2,Janssen Pharmaceutical, 2,Astellas Pharma Corporation, 2,Mitsubishi Tanabe Pharma Corporation, 8,Takeda Pharma Corporation, 8,Eisai Pharma Corporation, 8; **K. Funahashi**, Abbvie Japan Co. Ltd, 8,Eisai Co. Ltd, 8,UCB Japan Co. Ltd, 8,Mitsubishi Tanabe Pharma Co., 8,Takeda pharmaceutical Co. Ltd, 8,Pfizer Co. Ltd, 8,Chugai Pharma Co. Ltd, 8,Janssen Pharma KK, 8,Bristol-Myers Squibb, 8; **N. Takahashi**, None; **N. Ishiguro**, Takeda, Mitsubishi-Tanabe, Astellas, Chugai, Abbott, Bristol-Myers Squibb, Eisai, Janssen, Kaken, Pfizer, 2,Takeda, Mitsubishi-Tanabe, Astellas, Chugai, Abbott, Bristol-Myers Squibb, Eisai, Janssen, Kaken, Pfizer, Taisho-Toyama, Otsuka, 8.

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Abstract Number: 2766

Glucocorticoid-Sparing Effects of Abatacept in Real Life Practice: Data from a Paneuropean Analysis of RA Registries

Jacques Gottenberg[1], Xavier Mariette[2], Maria Victoria Hernandez[3], Florenzo Iannone[4], Elisabeth Lie[5], Helena Canhão[6], Karel Pavelka[7], Carl Turesson[8], Merete Lund Hetland[9] and Axel Finckh[10], [1]Hautepierre, Strasbourg, France, [2]Université Paris-Sud, AP-HP,

Hôpitaux Universitaires Paris-Sud, Paris, France, [3]Biobadaser, Barcelona, Spain, [4]Bari University, Rheumatology, Bari, Italy, [5]Dept. of Rheumatology, Diakonhjemmet Hospital, Oslo, Norway, [6]Rheumatology, Lisbonne, Portugal, [7]Charles University, Prague, Czech Republic, [8]Lund University, Rheumatology, Dept. of Clinical Sciences,, Malmö, Sweden, [9]DANBIO, Copenhagen Center for Arthritis Research, Center for Rheumatology and Spine Diseases, Rigshospitalet, Glostrup, Denmark, [10]Rheumatology Division, University Hospital of Geneva, Geneva, Switzerland
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Background/Purpose:

Despite disease modifying anti-rheumatic drugs (bDMARDs), glucocorticoids (GCs) are still widely prescribed in rheumatoid arthritis (RA). GCs are associated with numerous potential side effects, in particular for prolonged use and high doses. Thus, tapering GC to the minimal required dose remains a major therapeutic objective in RA management. GC sparing effects in real life practice have been demonstrated with anti-TNF agents, but only few studies have analyzed this effect with non-anti-TNF agents. The objective of this study was to investigate the impact of abatacept (ABA) on the evolution of concomitant GC dose in patients with RA

Methods:

This is a pooled observational database analysis of 9 European RA registries (ARTIS-SE, ATTRA-CZ, BIOBADASER-ES, DANBIO-DK, GISEA-IT, NOR-DMARD-NO, ORA-FR, SCQM-CH, Reuma.PT). Inclusion criteria for this analysis were a diagnosis of RA, initiation of ABA and available information on time-varying GC use. The primary endpoint was mean GC dose over time. Because GC dose was not normally distributed and there were a significant number of zeros (non GC users), we used a 'Hurdle Model' to analyze the longitudinal evolution of mean GC dose over time.

Results:

We identified 2409 patients initiating ABA with 5054 pt-years (PY) of follow-up with complete time-varying information on concomitant GC use. At baseline, the mean age was 58.6 years, 78% were female, and mean BMI was 26.4 kg/m^2. Disease characteristics suggest long-standing RA with severe disease (mean disease duration of 13.4 yrs, DAS28 5.0, HAQ score 1.32, ESR 31 mm/h, RF positive 72%, anti-CCP positive 68%). Most patients have failed several biotherapies before starting ABA (prior N° of biotherapies: 2 [IQR: 1 – 3]) and several conventional synthetic DMARDs (prior N° of csDMARDs; 2 [IQR: 1 – 4]).

At initiation of ABA, 87.4% of patients received concomitant GCs at a mean dose of 7.8 (95% CI: 0 – 18) mg (median dose [IQR] of 6.4 [5.0 -10.0] mg) of prednisone per day. The average GC dose slowly but continuously decreased after ABA initiation at a mean rate of -0.6 mg/year per patient. After one year, 11.5% of patients had stopped concomitant GC altogether. Significant predictors of lower concomitant GC use were female sex, older age, lower baseline disease activity, and less prior biotherapy failures.

Conclusion:

Data from this Pan-European registry analysis reveals that concomitant GC use is very common in patients starting ABA, with established and severe RA and a history of multiple failures on biotherapies. The average GC dose and the proportion of patients requiring GC decreases continuously after ABA initiation, demonstrating indirectly the effectiveness of ABA in this population. GC dose reduction in patients responding to ABA may contribute to a decrease in the burden of co-morbidities.

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Abstract Number: 2767

Comparative Analysis of Drug Effects on Primary Human Coronary Artery Endothelial Cells Activated By Serum Amyloid a

Katja Lakota[1], Dolores Hrušovar[2], Katjusa Mrak-Poljšak[3], Polona Žigon[1], SaÂša Čučnik[1,2], Borut BoÂžiÄ[2,3], Matija Tomšič[1] and Snezna Sodin Semrl[1,4], [1]Department of Rheumatology, University Medical Centre Ljubljana, Ljubljana, Slovenia, [2]Faculty of Pharmacy, University of Ljubljana, Ljubljana, Slovenia, [3]University Medical Centre Ljubljana, Ljubljana, Slovenia, [4]Faculty of Mathematics, Natural Science and Information Technology, University of Primorska, Koper, Slovenia

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Background/Purpose: In certain chronic diseases, such as rheumatoid arthritis (RA), atherosclerosis is more prevalent. RA patients have a higher incidence of cardiovascular disease and at least two-fold enhanced cardiovascular risk, as compared to the general population. This is in part due to persistently present inflammation shown to be a risk factor for atherosclerosis. Serum amyloid A (SAA) is an acute phase protein, highly upregulated in sera of RA patients and reported to activate endothelial cells. Our aim was to determine the effects of medications used in RA patients on selected adhesion molecules, cytokines and chemokines involved in atherosclerosis and coagulation in human coronary artery endothelial cells (HCAEC) following stimulation with SAA. **Methods:** Primary HCAEC at passage 5, grown to confluency in 6-well plates were preincubated for 30 min with medications from sterile ampules at indicated final concentrations (Dexamethasone 1µM, Methotrexate 1µM, Certolizumab pegol 100µg/ml, Etanercept 100µg/ml, Meloxicam 100µM, Diclofenac 10µM) or dissolved in medium (Captopril 10µM) or DMSO (Fluvastatin 10µM, Etoricoxib 100µM, Rosiglitazone 30µM). Human recombinant SAA1/2 (Peprotech, London, UK) was used to stimulate HCAEC at a final 1000 nM concentration. After 24 hours, supernatants were collected, centrifuged and frozen at -20 C. IL-6, IL-8, sVCAM-1, PAI-I were measured by ELISA. The number of viable cells was determined by colorimetry (CellTiter MTS assay, Promega). **Results:** SAA-stimulated levels of released IL-6, IL-8 and VCAM-1 in HCAEC supernatants were significantly attenuated by Methotrexate, Fluvastatin and Etoricoxib. Both Certolizumab pegol and Etanercept significantly decreased PAI-1 by an average of 43%. Captopril did not significantly alter either the cytokine or chemokine profile released by SAA stimulation of HCAEC. Rosiglitazone caused only slight lowering of IL-6, but significantly inhibited VCAM-1 by 58%. Among the NSAID group of medications, Diclofenac and Etoricoxib showed a trend towards lowering IL-6 and IL-8, while Meloxicam showed just the opposite. Diclofenac and Etoricoxib significantly attenuated VCAM-1 released supernatant levels, while Meloxicam was less effective. Diclofenac and Etoricoxib increased PAI-1, which was significantly reduced by Meloxicam. **Conclusion:** The most successful agent in lowering cytokine production was Fluvastatin. None of the medications significantly influenced cell viability. Methotrexate also showed strong beneficial effects on lowering released cytokine/chemokine/adhesion molecule levels from SAA-treated HCAEC. An interesting duality was observed in the NSAID group of medications, with Meloxicam exhibiting opposite effects from Diclofenac and Etoricoxib.

Table 1: Influence of medications used in RA patients on released IL-6, IL-8, sVCAM-1, PAI-1 protein levels and viability of SAA-activated HCAEC compared with the influence of SAA alone

	IL-6		IL-8		sVCAM-1		PAI-1		viability	
	Average	SD	Average	SD	Average	SD	Average	SD	Average	SD
B	0.05	0.05	0.07	0.05	0.13	0.11	0.76	0.24	0.97	0.05
SAA 1000nM	1	0	1	0	1	0	1	0	1	0
Dexametasone 1uM	0.09	0.07	0.10	0.11	0.17	0.17	0.96	0.38	0.99	0.07
Dexametasone +SAA	**0.94**	0.23	**0.93**	0.19	**0.94**	0.36	**1.04**	0.26	**0.98**	0.07
Metotrexate 1uM	0.06	0.07	0.10	0.10	0.17	0.06	0.74	0.31	1.01	0.03
Metotrexate + SAA	**0.68**	0.23	**0.77**	0.08	**0.69**	0.19	**0.88**	0.21	**1.07**	0.02
Certolizumab pegol 100ug/ml	0.04	0.04	0.06	0.02	0.23	0.21	0.39	0.12	0.98	0.00
Certolizumab pegol + SAA	**0.93**	0.21	**1.08**	0.17	**1.13**	0.56	**0.58**	0.07	**0.99**	0.04
Etanercept 100ug/ml	0.06	0.04	0.06	0.03	0.19	0.30	0.35	0.04	1.02	0.06
Etanercept + SAA	**0.85**	0.15	**0.88**	0.15	**1.06**	0.45	**0.57**	0.04	**1.05**	0.06
Captopril 10uM	0.05	0.04	0.04	0.02	0.09	0.09	0.92	0.42	0.95	0.03
Captopril + SAA	**1.20**	0.13	**1.01**	0.14	**1.15**	0.32	**1.04**	0.13	**0.92**	0.02
Fluvastatin 10uM	0.01	0.00	0.01	0.00	0.08	0.08	0.77	0.46	0.80	0.18
Fluvastatin + SAA	**0.59**	0.22	**0.25**	0.09	**0.42**	0.11	**0.73**	0.21	**0.77**	0.14
Rosiglitazon 30uM	0.13	0.16	0.19	0.16	0.17	0.16	1.28	0.18	1.08	0.03
Rosiglitazon+SAA	**0.80**	0.07	**1.06**	0.04	**0.42**	0.37	**1.24**	0.24	**1.17**	0.03
Diclofenac 10uM	0.03	0.00	0.10	0.08	0.08	0.03	1.20	0.06	1.09	0.10
Diclofenac + SAA	**0.97**	0.41	**0.92**	0.32	**0.46**	0.12	**1.52**	0.16	**1.07**	0.25
Meloxicam 100uM	0.05	0.04	0.07	0.03	0.07	0.06	0.39	0.11	0.92	0.01
Meloxicam + SAA	**1.14**	0.12	**1.47**	0.26	**0.67**	0.24	**0.71**	0.22	**0.91**	0.03
Etoricoxib	0.14	0.11	0.16	0.14	0.20	0.22	0.78	0.22	1.04	0.22
Etoricoxib + SAA	**0.68**	0.15	**0.52**	0.27	**0.29**	0.10	**1.10**	0.33	**1.01**	0.24

p<0.05
p<0.01

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Trend and Factors Associated with Switching Treatment after Initial Anti-TNF Therapy Among Patients with Rheumatoid Arthritis

Wenhui Wei[1], **Emma Sullivan**[2], Chieh-I Chen[3], James Piercy[2] and Stuart Blackburn[2], [1]Sanofi-Aventis, Bridgewater, NJ, [2]Adelphi Real World, Manchester, United Kingdom, [3]Regeneron Pharmaceuticals, Inc., Tarrytown, NY

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Background/Purpose: Among rheumatoid arthritis (RA) patients who progress beyond their first biologic disease-modifying antirheumatic drug (bDMARD), in-class cycling between different tumor necrosis factor inhibitors (TNFi) has been common practice. The introduction of newer bDMARDs targeting other mechanisms of action (MOA) offer additional treatment options and could introduce changes in clinical practice guidelines that directly impact real-world clinical practice. This analysis aims to examine the trend of US RA patients who switch bDMARD treatment following an initial TNFi, and to identify patient and physician factors associated with switching to a bDMARD with a different MOA rather than in-class cycling to a second TNFi.

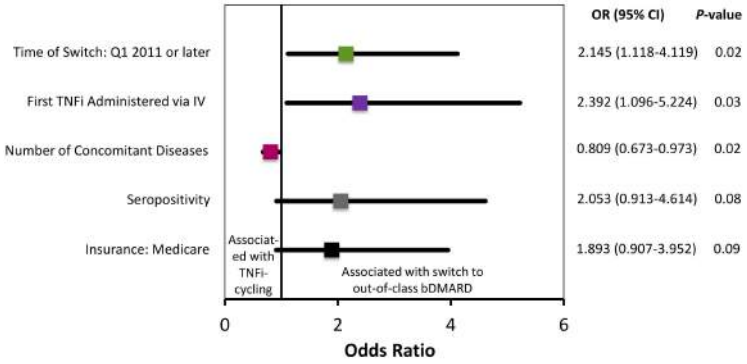
Methods: Data were drawn from the Adelphi RA-DSP, a cross-sectional geographically diverse survey of US rheumatologists about their RA patients using samples from the 1st quarter (Q1) of 2011 and Q1 2014. Rheumatologists provided patient demographics, clinical details, and treatment history. All patients had previously received a TNFi bDMARD as their first bDMARD therapy. Patients who subsequently cycled in-class to a second TNFi were compared to those switching to a bDMARD with a different MOA. Multivariate analysis was performed to identify independent patient and physician characteristics associated with switching to a bDMARD with a different MOA as the second treatment strategy rather than in-class cycling to a second TNFi.

Results: Included in the analysis were 246 RA patient cases that had previously received a TNFi as their first bDMARD therapy and had progressed onto a second bDMARD: mean age 56.0 years, 74.0% female, 83.1% RA-seropositive, 63.3% commercially insured, 25.3% Medicare, and 8.2% Medicaid. The main reasons for discontinuing the first TNFi therapy included: loss of efficacy (55.2%), lack of response (43.6%), adverse events (17.8%), and cost reasons (4.3%).

Comparing patient cases collected in 2011 and 2014, a significant increase was observed in switching to bDMARDs with a different MOA (compared to in-class cycling to a second TNFi), from 30% in 2011 to 43.1% in 2014 ($P = 0.035$). Multivariate analysis indicated that patients were more likely to switch to a bDMARD with a different MOA if the switch occurred after Q1 2011 and if they had received their first line of TNFi intravenously, but less likely to switch to bDMARDs with a different MOA when they had a high number of concomitant conditions (Figure).

Conclusion: This study suggests that when switching between bDMARDs occurred, US physicians increasingly switched their RA patients to a bDMARD with a different MOA rather than in-class cycling to a second TNFi.

Figure: Forest Plot Describing Patient Factors Associated with bDMARD Switching After First TNFi Therapy.
IV = intravenous, OR = odds ratio.



Disclosure: W. Wei, Sanofi US, 1,Sanofi US, 3; **E. Sullivan**, Adelphi Real World, 3,Sanofi US, 9; **C. I. Chen**, Regeneron Pharmaceuticals, Inc., 1,Regeneron Pharmaceuticals, Inc., 3; **J. Piercy**, Adelphi Real World, 3,Sanofi US, 9; **S. Blackburn**, Adelphi Real World, 3,Sanofi US, 9.

Abstract Number: 2769

Factors Associated with TNF Switching: a Retrospective Real-World Study of Patients with Rheumatoid Arthritis

Wenhui Wei[1], Keith Knapp[2], Li Wang[3], Chieh-I Chen[4], **Gary Craig**[2], Karen Ferguson[2] and Sergio Schwartzman[5], [1]Sanofi-Aventis, Bridgewater, NJ, [2]Discus Analytics, Inc., Spokane, WA, [3]Director, Analytic Research, STATinMED Research, Plano, TX, [4]Regeneron Pharmaceuticals, Inc., Tarrytown, NY, [5]Hospital for Special Surgery, New York, NY
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Background/Purpose: Switching of disease-modifying antirheumatic drugs (DMARDs) in rheumatoid arthritis (RA) patient treatment is common in real-world clinical practice. The context for why patients switch has not been well described and various factors may impact switching behavior. The purpose of this analysis is to characterize factors associated with DMARD switching using an US clinical RA registry, JointMan®. This database provides a practical outcome tool to manage patients with RA in a traditional office-based setting.

Methods: A retrospective analysis using the JointMan®registry was conducted in RA patients (N = 5,817) diagnosed by rheumatologists. Adult RA patient inclusion parameters were: a physician prescription record of a tumor necrosis factor inhibitor (TNFi) (infliximab, etanercept, adalimumab, golimumab, certolizumab) from April 1, 2010 through March 31, 2015; and a subsequent follow-on prescription of TNFi or a novel mode of action (MOA) DMARD (abatacept, anakinra, rituximab, tocilizumab, tofacitinib). Patients were divided into 2 cohorts: those who switched from previous TNFi to another TNFi (TNF cyclers), and those who switched to a novel MOA DMARD. Differences in baseline characteristics and reasons for discontinuing prior TNFi were analyzed using bivariate analysis. Multiple logistic regression was used to identify independent factors associated with switching.

Results: 519 adult RA patients were included in the study: mean age 56.5 years, 79.4% women, 86.3% Caucasian, 95.8% US West Coast resident, clinical disease activity index (CDAI) 22.8, mean prior TNFi treatment duration 29.4 months. Reasons for discontinuing prior TNFi therapy were primary lack of efficacy (38.9%), secondary loss of efficacy (20.0%), adverse events (12.1%), cost/insurance-related reasons (5.6%), and 23.3% other. After discontinuing index TNFi, more than half of patients switched to another TNFi (n = 278, 53.6%) rather than novel MOA DMARDs (n = 241, 46.4%). Patients switching to a novel MOA DMARD were older (57.8 vs. 55.4 years, $P = 0.0332$), less likely to be commercially insured (61.51% vs. 50.21%, $P = 0.001$), and more likely to be Medicare insured (46.06% vs. 35.61%, $P = 0.0156$) than patients cycling to another TNFi.

Multivariate analysis showed that patients were more likely to switch to a novel MOA DMARD than cycling to another TNFi if the first TNFi was administered intravenously (adjusted odds ratio [aOR] [95% CI] = 4.18 [2.50-6.99], $P < 0.0001$). Additionally, those with positive rheumatoid factor (aOR = 2.13 [1.28-3.56], $P = 0.0038$) and those with higher CDAI (aOR = 1.02 [1.01-1.04], $P = 0.008$) were more likely to switch to a novel MOA DMARD. Patients were less likely to switch to novel MOA DMARDs than to another TNFi if the reason for discontinuing the prior TNFi was insurance/cost-related (aOR = 0.30 [0.32-0.95], $P = 0.0094$) or loss of efficacy (aOR = 0.50 [0.32-0.95], $P = 0.0321$).

Conclusion: TNF cycling in RA treatment is common in clinical practice. The main reasons for discontinuation of prior TNFi therapy were lack or loss of efficacy. Increased understanding of switching patterns in RA patients may help improve patient care and foster further definition of drug development.

Disclosure: W. Wei, Sanofi US, 1,Sanofi US, 3; **K. Knapp**, Arthritis Northwest, 3,Discus Analytics, 3; **L. Wang**, STATinMED Research, 3,Sanofi US, 9; **C. I. Chen**, Regeneron Pharmaceuticals, Inc., 1,Regeneron Pharmaceuticals, Inc., 3; **G. Craig**, Arthritis Northwest, 4,Discus Analytics, 4,Discus Analytics, 1,Discus Analytics, 6; **K. Ferguson**, Arthritis Northwest, 3,Discus Analytics, 4,Discus Analytics, 1,Discus Analytics, 6; **S. Schwartzman**, Discus Analytics, 1,Discus Analytics, 6.

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Abstract Number: 2770

Efficacy of Sarilumab Plus Methotrexate in Achieving Clinical Remission, Using 4 Different Definitions, in Patients with Active, Moderate-to-Severe Rheumatoid Arthritis in a Phase 3 Study

Mark C. Genovese[1], Marina Stanislav[2], Hubert van Hoogstraten[3], Renata Martincova[4], Chunpeng Fan[5] and Janet van Adelsberg[6], [1]Division of Rheumatology, Stanford University Medical Center, Palo Alto, CA, [2]Research Institute of Rhumato, Moscow, Russia, [3]Sanofi, Bridgewater, NJ, [4]Sanofi Czech Republic, Prague, Czech Republic, [5]Biostatistics, Sanofi, Bridgewater, NJ, [6]Clinical Science, Regeneron Pharmaceutials, Inc., Tarrytown, NY

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Background/Purpose: Remission is an important clinical outcome in RA[1] and is associated with improved physical function and health-related quality of life.[2] Several definitions of remission have been proposed on the basis of score thresholds of disease activity measures.[3] Recent ACR/EULAR updates to the criteria for remission found a Boolean-based definition (categorical in structure) and SDAI (composite index of RA activity) to be more clinically relevant.[3] In the phase 3 MOBILITY study (NCT01061736), both doses of sarilumab (150 or 200 mg every 2 weeks [q2w]) + MTX) demonstrated statistically significant improvement in signs and symptoms of RA, improvement in physical function, and inhibition of radiographic progression.[4] The most common treatment-emergent adverse events (TEAEs) with sarilumab included infections, neutropenia, injection site reactions, and increased transaminases. Laboratory changes were consistent with IL-6 signaling blockade. The objective of this prespecified analysis was to assess the ability of sarilumab to induce remission in patients with active, moderate-to-severe RA using 4 different disease activity measures.

Methods: Remission was defined as DAS28-CRP <2.6, CDAI ≤2.8, SDAI ≤3.3, and Boolean-based ACR/EULAR remission, which includes tender joint count and swollen joint count (28 joint count) ≤1, CRP ≤10 mg/L, and patient global VAS ≤10. Patients who started rescue medication or discontinued study were considered not in remission. Differences in incidence of DAS28-CRP, CDAI, SDAI, and Boolean remissions between the active treatment arms and placebo in the ITT population were assessed using 2-sided Cochran-Mantel-Haenszel tests stratified by prior biologic use and region.

Results: Baseline demographics and disease characteristics were generally similar between patients who achieved remission and the general ITT population with 2 exceptions: patients with remission had slightly shorter RA duration and fewer patients had used prior biologic therapies. Proportion of patients achieving DAS28-CRP, CDAI, SDAI, and Boolean-based remission at week 24 was higher in the sarilumab-treated groups vs the placebo group (all $P<0.006$, except for Boolean remission in the sarilumab 150 mg q2w group), and these observations were maintained at week 52 (Table). In all groups, DAS28-CRP remission had the highest and Boolean-based remission had the lowest frequency.

Table. Incidence of Clinical Remission in ITT population

	Placebo + MTX (n=398)	Sarilumab 150 mg q2w + MTX (n=400)	Sarilumab 200 mg q2w + MTX (n=399)
DAS28-CRP remission			
Week 24, n (%)	40 (10.1)	111 (27.8)	136 (34.1)
P value vs placebo		<0.0001	<0.0001
Week 52, n (%)	34 (8.5)	124 (31.0)	136 (34.1)
P value vs placebo		<0.0001	<0.0001
CDAI remission			
Week 24, n (%)	20 (5.0)	41 (10.3)	55 (13.8)
P value vs placebo		0.0053	<0.0001
Week 52, n (%)	19 (4.8)	59 (14.8)	72 (18.0)
P value vs placebo		<0.0001	<0.0001
SDAI remission			
Week 24, n (%)	19 (4.8)	41 (10.3)	52 (13.0)
P value vs placebo		0.0032	<0.0001
Week 52, n (%)	16 (4.0)	60 (15.0)	74 (18.5)
P value vs placebo		<0.0001	<0.0001
Boolean-based ACR/EULAR remission			
Week 24, n (%)	15 (3.8)	26 (6.5)	42 (10.5)
P value vs placebo		0.0810	0.0002
Week 52, n (%)	12 (3.0)	42 (10.5)	56 (14.0)
P value vs placebo		<0.0001	<0.0001

ITT, intent-to-treat; MTX, methotrexate; q2w, every 2 weeks.

Conclusion: Sarilumab plus MTX induced clinical remission at weeks 24 and 52 as defined by DAS28-CRP, CDAI, SDAI, and Boolean-based remission, although Boolean-based remission was not achieved for sarilumab 150 mg q2w at week 24. Remission at week 24 was maintained at week 52.

1. Smolen et al. *Ann Rheum Dis*. 2015 [Epub ahead of print].

2. Radner et al. *Arthritis Res Ther*. 2014;16:R56.

3. Felson et al. *Ann Rheum Dis*. 2011;70:404-413.

4. Genovese et al. *Arthritis Rheum*. 2015;67:1424-1437.

Disclosure: M. C. Genovese, Amgen, Eli Lilly and Company, Sanofi, Regeneron, 2,Amgen, Eli Lilly and Company, Sanofi, Regeneron, 5; **M. Stanislav**, None; **H. van Hoogstraten**, Sanofi, 1,Sanofi, 3; **R. Martincova**, Sanofi, 3; **C. Fan**, Sanofi, 1,Sanofi, 3; **J. van Adelsberg**, Regeneron, 1,Regeneron, 3.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/efficacy-of-sarilumab-plus-methotrexate-in-achieving-clinical-remission-using-4-different-definitions-in-patients-with-active-moderate-to-severe-rheumatoid-arthritis-in-a-phase-3-study

Abstract Number: 2771

Impact of Tocilizumab Monotherapy in Patients with Moderate to High Disease Activity: Real-World Analyses from the US Corrona Registry

Leslie Harrold[1,2], Ani John[3], George W. Reed[1,4], Chitra Karki[1], YouFu Li[4], Joel Kremer[5], Tmirah Haselkorn[6] and Jeffrey D. Greenberg[1,7], [1]Corrona, LLC, Southborough, MA, [2]Department of Orthopedics and Medicine, University of Massachusetts Medical School, Worcester, MA, [3]Genentech, Inc., South San Francisco, CA, [4]University of Massachusetts Medical School, Worcester, MA, [5]Albany Medical College and The Center for Rheumatology, Albany, NY, [6]Genentech, Inc, South San Francisco, CA, [7]NYU School of Medicine, New York, NY

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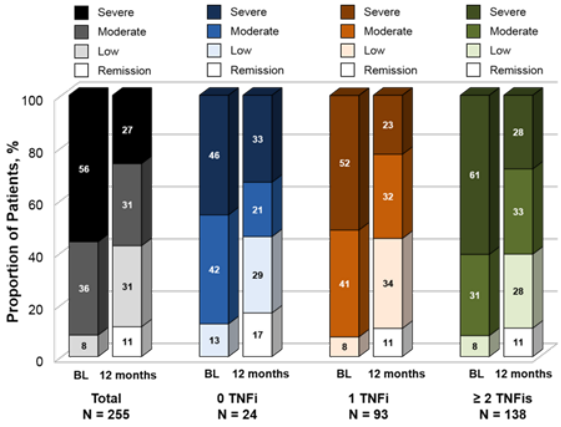
Background/Purpose: Little is known regarding the real-world use and effectiveness of the interleukin-6 receptor α inhibitor tocilizumab (TCZ) as monotherapy. The effectiveness of TCZ monotherapy in patients with rheumatoid arthritis (RA) was evaluated using a US national observational registry with > 40,000 patients with RA (Corrona).

Methods: Between October 1, 2010, and March 31, 2015, patients with RA who newly initiated TCZ monotherapy while not in remission (based on the Clinical Disease Activity Index [CDAI]), and who had a follow-up visit at 1 year (± 3 months) with CDAI measurements at both visits were identified. Outcomes assessed at 1 year included change in disease activity (median change in CDAI), meaningful improvement in the modified Health Assessment Questionnaire (mHAQ; change > 0.25) and achievement of a modified American College of Rheumatology (mACR)20/50/70 response from baseline in all TCZ initiators and were stratified by prior tumor necrosis factor inhibitor (TNFi) use. Outcomes between the 1 and ≥ 2 prior TNFi groups were compared using chi-square tests or *t*-tests, as appropriate.

Results: Of the 255 patients who newly initiated TCZ monotherapy, 24 (9.4%) were TNFi naive, 93 (36.5%) received 1 prior TNFi and 138 (54.1%) received ≥ 2 prior TNFis. At baseline, median (IQR) CDAI was 19.5 (13.0-34.5), 22.2 (14.0-30.0) and 25.2 (19.0-34.1) in patients who were previously treated with 0, 1 and ≥ 2 TNFis, respectively. At 12 months, there was improvement in the proportion of patients who achieved remission or low disease activity in the overall cohort and across all TNFi groups (**Figure**). CDAI remission occurred in 16.4%, 10.8% and 10.9% of patients in the 0, 1 and ≥ 2 TNFi groups, respectively. The overall median decrease in CDAI from baseline to 1 year and decreases stratified by TNFi group each exceeded the minimal clinically important difference, with similar improvement in both those with 1 and ≥ 2 prior TNFis (**Table**). Meaningful improvement in mHAQ and mACR20/50/70 responses were also observed overall, with no statistically significant differences across TNFi groups. Overall, the rate of serious infections was 2.1 per 100 patient-years (PY) and the rate of cardiovascular events was 1.0 per 100 PY; no differences were observed by prior exposure to TNFis.

Conclusion: In this real-world cohort of TCZ monotherapy initiators with primarily moderate to high disease activity and prior TNFi exposure, substantial improvements in all clinical outcomes were observed, with > 40% of patients overall achieving remission or low disease activity (46%, 45% and 39% for patients with 0, 1 or ≥ 2 prior TNFis, respectively).

Figure. Changes in CDAI From Baseline to 12 Months in Patients Newly Initiating TCZ Monotherapy Stratified by Prior TNFi



BL, baseline; CDAI, Clinical Disease Activity Index; TCZ, tocilizumab; TNFi, tumor necrosis factor inhibitor.
Remission was defined as CDAI ≤ 2.8; low disease activity as CDAI > 2.8 to ≤ 10; moderate disease activity as CDAI > 10 to ≤ 22; and severe disease activity as CDAI > 22.

Table. Improvement in Disease Activity at 12 Months in Patients Newly Initiating TCZ Monotherapy Stratified by Prior TNFi

	Total N = 255	TNFi Naive N = 24	1 Prior TNFi N = 93	≥ 2 Prior TNFis N = 138	*P*-value[a]
CDAI, median change (IQR)[b]	9.8 (8.2-11.4)	7.4 (1.7-13.0)	10.6 (7.7-13.6)	9.6 (7.6-11.6)	0.55
mACR20, % (95% CI)	37.8 (32-44)	45.8 (26-67)	25.3 (25-46)	38.1 (30-47)	0.66
mACR50, % (95% CI)	24.5 (19-30)	29.2 (13-51)	25.3 (17-35)	23.1 (16-31)	0.71
mACR70, % (95% CI)	11.6 (8-16)	25.0 (10-47)	11.0 (5-19)	9.7 (5-16)	0.75
Meaningful improvement in mHAQ (> 0.25), % (95% CI)	26.1 (21-32)	29.2 (13-51)	28.6 (20-39)	23.9 (17-32)	0.43

CDAI, Clinical Disease Activity Index; IQR, interquartile range; mACR, modified American College of Rheumatology; mHAQ, modified Health Assessment Questionnaire; TCZ, tocilizumab; TNFi, tumor necrosis factor inhibitor.
[a] The *P*-value represents comparison between those patients with 1 prior TNFi versus those with ≥ 2 prior TNFis.
[b] The overall minimal clinically important difference was defined as a decrease in CDAI of ≥ 6 (Curtis JR, et al. Abstract presented at the 2013 ACR Annual Meeting; October 25-30, 2013; San Diego, CA [Abstract 2866]).

Disclosure: L. Harrold, Corrona, LLC, 3; **A. John**, Genentech, Inc, 3; **G. W. Reed**, Corrona, LLC, 3; **C. Karki**, Corrona, LLC, 3; **Y. Li**, University of Massachusetts Medical School, 3; **J. Kremer**, Corrona, LLC, 1,Corrona, LLC, 3,Genentech, Inc., 5,Geneltech, Inc., 2; **T. Haselkorn**, Genentech, Inc, 3; **J. D. Greenberg**, Corrona, LLC, 1,Corrona, LLC, 3,AstraZeneca, Celgene, Novartis and Pfizer, 5.

Abstract Number: 2772

Activated Memory B Cells in Rheumatoid Arthritis and Relationship to Anti-TNF Treatment

Jennifer Barnard[1], Nida Meednu[2], Kelly Callahan[1], Andreea Coca[1], Bethany A. Marston[1], Ralf G. Thiele[1], Darren Tabechian[1], Marcy Bolster[3], Jeffrey R. Curtis[4], Meggan C. Mackay[5], Jonathan D. Graf[6], Richard Keating[7], Edwin Smith[8], Karen Boyle[9], Lynette Keyes-Elstein[9], Beverly Welch[10], Ellen Goldmuntz[11] and **Jennifer H. Anolik**[1], [1]University of Rochester Medical Center, Rochester, NY, [2]Medicine- Allergy, Immunology and Rheumatology, University of Rochester Medical Center, Rochester, NY, [3]MUSC, Charleston, SC, [4]University of Alabama at Birmingham, Birmingham, AL, [5]Autoimmune & Musculoskeletal Disorders, The Feinstein Institute for Medical Research, Manhasset, NY, [6]Rosalind Russell / Ephraim P. Engleman Rheumatology Research Center, University of California, San Francisco, San Francisco, CA, [7]University of Chicago, Chicago, IL, [8]Dept of Med Div of Rheum, MUSC, Charleston, SC, [9]Rho Federal Systems, Inc., Chapel Hill, NC, [10]6610 Rockledge Dr., NIAID/NIH, Bethesda, MD, [11]DAIT, NIAID/NIH, Bethesda, MD
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Background/Purpose: TNF blockade is a mainstay of treatment for rheumatoid arthritis (RA), but a significant proportion of patients fail to respond to treatment or lose clinical response over time. B cells play a critical role in the disease process and can become activated in germinal center (GC) reactions in secondary lymphoid tissue and ectopic GCs in synovium. TNF and lymphotoxin (LT) blockade have been shown to alter GC reactions in mouse models, but the potential impact of anti-TNF therapy on the B cell compartment remains controversial. The purpose of this study is to characterize the peripheral B cell compartment longitudinally during anti-TNF therapy in RA and determine the relationship between B cells and treatment response.

Methods: We randomized subjects in a 2:1 ratio to receive standard dosing regimens of etanercept or adalimumab for 24 weeks. Eligible subjects met the 1987 ACR criteria for RA, had clinically active RA (DAS28>4.4), and were on methotrexate. Disease activity and response was assessed based on DAS28-CRP. B cells from 54 patients were analyzed by multi-color flow cytometry at baseline and longitudinally at 12 and 24 weeks. The primary endpoint was the change in memory B cell fraction in the peripheral blood from baseline to week 12. All B cell results are expressed as a mean percent (+/- SE) of the CD19+ or parent population.

Results: Of the 63 eligible subjects, 43 and 20 were randomized to etanercept and adalimumab, respectively. The mean DAS at baseline was 5.3. After 12 weeks of treatment, 43% (n=24) of patients were identified as good responders, 45% (n=25) moderate responders, and 13% (n=7) non-responders (NR). The primary endpoint was not met as B cell subsets remained remarkably stable over the course of the study regardless of treatment group, and the remainder of the results report secondary endpoints. Repeated measures

analysis of variance (with unstructured covariance) was used to compare trends over time between NR and moderate or good responders (R). In NRs, the mean % CD27-IgD- (DN) memory B cells was significantly higher than R over all visits (R: baseline 6.2±0.4, WK12: 5.3±0.4, WK24: 5.1±0.4; NR: baseline: 8.7±1.1, WK12: 8.6±1.1, WK24: 7.6±1.1; p=0.01 over all visits, p<0.05 by visit). There was a significantly higher frequency of CD21- activated B cells over all visits in both SM (NR: baseline 11.8±2.1, WK12 13.9±1.9, WK24 15.2±2.3; R: baseline 8.5±0.8, WK12 8.7±0.7, WK24 8.6±0.8, p=0.02 over all visits, p<0.05 at WK12, WK24) and DN B cells (NR: baseline 36±5.2, WK12 34.1±4.6, WK24 37.5±4.8; R: baseline 19.0±2.0, WK12 19.1±1.7, WK24 19.0±1.8, p=0.001 over all visits, p<0.05 at each visit) in NRs vs. Rs.

Conclusion: Our results suggest a relationship between activated memory B cells and the response to anti-TNF treatment, with higher activated memory associated with a less robust response. Examination of peripheral lymphoid and target tissue may be necessary to define changes in B cell subsets with anti-TNF.

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Abstract Number: 2773

Novel Mechanisms of Action for Methotrexate and Doxycycline: Prevention of Protein Adduct Formation and Free Radical Scavenging

Daniel Anderson[1], Michael J. Duryee[2], Matthew Zimmerman[3], Jun Tian[3], Cleofes Sarmiento[3], Lynell W. Klassen[4], James R. O'Dell[1], Geoffrey M. Thiele[5] and Ted R. Mikuls[1], [1]University of Nebraska Medical Center, Omaha, NE, [2]Internal Medicine Division of Rheumatology, University of Nebraska Medical Center, Omaha, NE, [3]Cell Biology and Physiology, University of Nebraska Medical Center, Omaha, NE, [4]Dept of Internal Medicine, Omaha VA Medical Center and University of Nebraska Medical Center, Omaha, NE, [5]Omaha VA Medical Center and University of Nebraska Medical Center, Omaha, NE

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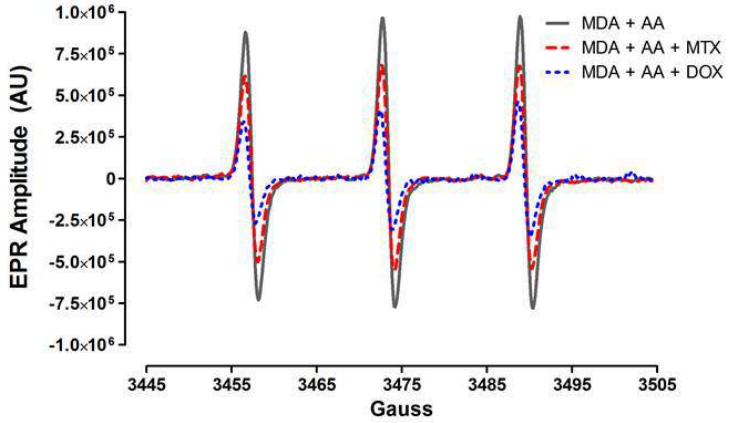
Background/Purpose: Oxidative stress and free radical formation play an important pathogenic role in rheumatoid arthritis (RA) and a number of other inflammatory diseases. Oxidative stress promotes the formation of malondialdehyde-acetaldehyde (MAA) protein adducts, leading to robust inflammatory responses and tolerance loss. We have previously demonstrated that MAA adducts are markedly over-expressed in inflammatory synovitis and that anti-MAA immune responses are strongly associated with both anti-citrullinated protein antibody (ACPA) and RA disease activity. Whether disease-modifying therapies used to treat RA impact MAA adduct formation or exhibit free radical scavenging properties is unknown. In this study, we sought to examine whether the prevention of MAA adduct formation or free radical scavenging could represent novel mechanisms of action for RA treatments, utilizing both methotrexate (MTX) and doxycycline (DOX).

Methods: Molar equivalents of MTX or DOX were incubated in the presence of acetaldehyde, malondialdehyde (substrates in MAA formation) and albumin at pH 3.0, 5.0, and 7.0 for 1-3 days at 37^0C. Fluorescent activity of MAA was measured at 398 nm to quantify adduct formation. To measure free radical levels in the above reactions, electron paramagnetic resonance (EPR) spectroscopy and the EPR spin probe 1-hydroxy-3-methoxycarbonyl-2, 2, 5, 5-tetramethylpyrrolidine (CMH) were utilized.

Results: Incubation of human albumin with MDA and AA resulted in MAA-adduction of 8×10^4 fluorescent units (FU). MAA adduct formation was significantly reduced in the presence of both MTX (5.6×10^4 FU; P<0.05) and DOX (1.5×10^3 FU; P<0.001). When these reactions were evaluated for free radical levels by EPR, DOX and MTX reduced the levels of free radicals generated by MDA and AA at the different pH levels tested. For example, at pH 5 .0 MDA + AA resulted in 1.74×10^6 EPR arbitrary units (AU). In contrast, addition of MTX (1.23×10^6 EPR AU) or DOX (7.19×10^5 EPR AU) to the reaction significantly decreased the free radical levels by 30% and 41%, respectively (see figure).

Conclusion: MTX and DOX significantly decreasing MAA-adduction of proteins (human albumin in this case) *in vitro* is highly important given the known effect of MAA adduction on tolerance loss and the promotion of both humoral and cell-mediated immunity. Moreover, our data suggest that these agents have the capacity to directly scavenge free radicals *in vitro*, an effect that has not

previously been reported. For the first time, these results lend insight into novel mechanisms of action for two agents routinely used in the treatment of RA and other inflammatory diseases. The degree to which these agents' disease-modifying properties are dependent on direct free radical scavenging requires further investigation.



Disclosure: D. Anderson, None; **M. J. Duryee**, None; **M. Zimmerman**, None; **J. Tian**, None; **C. Sarmiento**, None; **L. W. Klassen**, None; **J. R. O'Dell**, None; **G. M. Thiele**, None; **T. R. Mikuls**, None.

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Abstract Number: 2774

Longterm Outcome of Patients Switched from Iv to Sc Formulation of Abatacept: A Monocentric Study

Rossella Reggia[1], Ilaria Cavazzana[1], Angela Tincani[2] and Franco Franceschini[1], [1]Rheumatology and Clinical Immunology, Spedali Civili and University of Brescia, Brescia, Italy, [2]Rheumatology and Clinical Immunology Unit, Spedali Civili and University of Brescia, Brescia, Italy

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Background/Purpose: Abatacept is a selective T cell costimulation modulator indicated for active Rheumatoid Arthritis (RA). Since August 2013, in Italy, the drug has also been available in a subcutaneous(sc) formulation, consisting in a fixed weekly dose of 125 mg. Aim of our study was to analyze the clinical response and the longterm outcome of a series of patients (pts) with RA previously treated with monthly iv infusion and then converted to the sc formulation based on their subjective preference about the way of administration.

Methods: We have retrospectively included 49 pts with RA, converted to sc Abatacept from October 2013 to April 2014. We divided them into two groups, depending on their need to return to the iv administration for the appearance of a disease flare. The main clinical and serological features of the two groups were compared using the Chi-square, T-test or the Mann-Whitney test.

Results: Fifteen pts (30.6%) returned to the iv administration due to a disease flare (mean DAS28: 4.8 vs 2.1, p:<0.001), after a mean of 15 injections (range 4-48): in these pts it has been observed a significant increase of the CRP values (mean:0.29 vs 0.86 mg/dl, p:0.004) and of the number of painful (mean:0.6 vs 4.9, p:<0.001) and swollen joints (mean 0.5 vs 4.2, p:<0.001).The remaining 34 pts (69.4%) continued with the sc formulation. The compared parameters between the two groups are summarized in Table 1. In pts with arthritis flare, disease activity decreased again (mean DAS28: 4.16 vs 2.43, p:<0.001) after returning to the iv infusion, with a significant decrease in the CRP values (mean 0.9 vs 0.4 mg/dl, p:0.04) and in the number of painful (mean:4.9 vs 1.7, p:0.003) and swollen joints (mean:4.2 vs 1.2, p:0.003).One patient discontinued the sc formulation for the onset of headache and nausea, not reported with the iv administration.Twelve months after the switch we have evaluated the persistence in treatment with Abatacept of the original cohort: 32 of the 34 patients (94%) were still treated with sc Abatacept (one withdrawn for sustained remission and one for repeated infections) while only 10 over the 15 (67%) pts who returned to iv Abatacept were still treated with the drug because 5 of them were swapped to other biologics for reactivation of arthritis (p:0.0368).

Conclusion: Although the safety profile of the sc Abatacept seems to confirm the data previously obtained with the iv use of the drug, a high rate of our patients complained a reduced efficacy, also confirmed by the subanalysis of the objective components of the DAS28 index (CRP values and joints involvement). We failed to identify clear risk factors that may help toward the selection of pts to which propose the formulation switch, however, if an arthritic flare occurs, the return to the iv administration seems to ensure a good control of the disease again. Nevertheless the switch failure seems to predict a reduced persistence efficacy of abatacept during time.

Tab1.

Analyzed features:	Patients who maintained the sc formulation	Patients who returned to iv infusions	p:
	n=34 (69.4%)	**n=15 (30.6%)**	
Mean age (years) [SD]	58.8 [14.4]	57.1 [13.1]	ns
Positivity for Rheumatoid Factor (RF)	n:31/34; (91.2%)*	n:9/12; (85.7%)*	ns
Positivity for anti-citrullinated proteins antibodies (ACPA)	n:20/27; (74.1%)*	n:9/11; (81.8%)*	ns
Mean disease duration (months) [SD]	132 [116.5]	111.9 [86.4]	ns
Previous iv therapy duration (months) [SD]	22.4 [20]	16.4 [17]	ns
Body Mass Index: BMI [SD]	24.6 [4.9]	25.2 [5]	ns
Smokers	n:4; (11.8%)	n:2; (12.5%)	ns
DMARDs in association	n:31; (91.2%)	N:13; (86.7%)	ns
Previous use of biological agents	n:24; (66.7%)	N:11; (73.3%)	ns
N' of different biological agents used in the past: mean; [SD]	1.4; [1.4]	2.2; [2.2]	ns
Abatacept as first biological agent	n:12; (33.3%)	N:4; (26.7%)	ns
Remission of the disease at sc therapy start (DAS28 <2.6)	n:27; (79.4%)	N:11; (73.3%)	ns
DAS28 at sc therapy start: mean; [SD]	1.9; [0.8]	2.1; [0.9]	ns

** percentage based on available data*

Disclosure: R. Reggia, None; **I. Cavazzana**, None; **A. Tincani**, None; **F. Franceschini**, None.

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Abstract Number: 2775

What Factors Are Associated with Starting an Intravenous Vs. Sub-Cutaneous Biologic in Patients with RA?

Kaleb Michaud[1,2], **Sofia Pedro**[2] and Steven Peterson[3], [1]Internal Medicine, University of Nebraska Medical Center, Omaha, NE, [2]National Data Bank for Rheumatic Diseases, Wichita, KS, [3]Janssen Global Services, LLC, Malvern, PA

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Background/Purpose:

To characterize which factors are associated with RA patients' preferences for biologic administration: sub-cutaneous or intravenous.

Methods:

Using a large US observational cohort, the National Data Bank for Rheumatic Diseases (NDB), we characterized RA patients who were on a biologic from Jan 2006 onwards, one year after Medicare changed reimbursement policies to cover more biologics than infliximab. Only the patient's first biologic or second (if already on their first biologic) were considered. Patients were assigned into 3 groups based on biologic administration: intravenous (IV), sub-cutaneous (SC), or "both" if they had taken IV and SC biologics in the same 6-month period. All patients enrolled via FDA-mandated drug safety registries were excluded, as well as those who had not had any change on biologic use after enrollment.

One–way Anova and chi-squared tests were used when applicable, with 5% significance level. Polytomous logistic regression models were used, with SC as reference, controlling for confounders, and results were presented as relative risk ratios (RRR). All explanatory variables were 6-month lagged, including: socio-economic status, marital status, markers of clinical status such as HAQ, Patient Activity Score, SF-36 physical component summary score, and dependency on others for help.

Results:

From 4,318 eligible RA patients, 1,609 (37.3%) were taking an IV biologic, 2,562 (59.3%) were on a SC biologic and 147 patients (3.4%) were on both (Figure 1). Patients in the IV group tended to be older, have longer RA duration, more likely on Medicare, and depended less frequently on others for help (Table 1). They also tended to have greater disability and worse disease activity (IV vs. SC RRR for HAQ, 1.21 [1.09-1.34]; both vs. SC, 1.61 [1.23; 2.12]).

Patients who switched between IV and SC were more likely to have uncontrolled disease activity. Most patients on biologics (70.8%) did not switch between classes, and the most common order of switching was from SC to IV (62.3%). which is consistent with the premise that patients/physicians may have preferences for one format over the other.

Conclusion:

Our results consistently characterized patients on IV biologics as more likely to choose and/or require the professional help that comes with IV administration. As most patients did not switch, this may indicate overall preferences by the patient and/or physician.

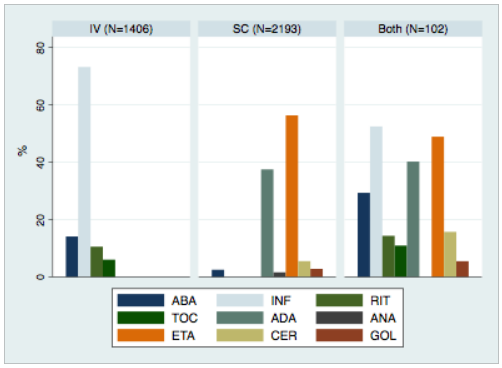

Figure 1. Biologic distribution by form of administration (%).

Table 1. Multivariate polytomous logistic regression of IV vs. SC patients (N=4,002)

Variables	RR	95% Conf. Interval		P-value
How often do you depend on other for help?				
None (referent)	1			
A little of the time	1.26	1.04	1.52	0.02
Some of the time	1.16	0.94	1.42	0.16
Most of the time	1.34	0.98	1.82	0.06
All of the time	1.70	0.79	3.62	0.17
Age (yrs)	1.03	1.01	1.03	0.00
RA duration (yrs)	0.99	0.99	1.00	0.04
Comorbidity index	1.01	0.97	1.06	0.55
Total income (US$1000)	1.00	1.00	1.00	0.17
Education (yrs)	1.01	0.98	1.05	0.42
Male sex	0.97	0.81	1.16	0.75
Employed	0.94	0.79	1.13	0.51
Medical Insurance				
Private (referent)				
Medicare*	1.91	1.56	2.33	0.00
Medicaid	1.18	0.87	1.62	0.29
None	0.65	0.36	1.17	0.15
Constant	0.13	0.07	0.25	0.00

Disclosure: K. Michaud, None; **S. Pedro**, None; **S. Peterson**, Johnson & Johnson Pharmaceutical Services, LLC, 3.

Abstract Number: 2776

Profiling Compounds in Human Primary Cell-Based Disease Models Guide Indication Selection

Jason Ptacek, Ellen L. Berg and Alison O'Mahony, BioSeek, a division of DiscoveRx Corp., South San Francisco, CA

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Background/Purpose: In vitro co-cultures of human primary cells, including immune cells, fibroblasts, smooth muscle, keratinocytes, epithelial or endothelial cells were developed to capture the complexity of various disease states. Compound effects on protein biomarkers in these assay systems were used to generate phenotypic signatures to inform how drugs may behave in these settings. These activity profiles could also be used to help guide indication selection for either novel compounds or repurposing of approved drugs. With a library of clinically validated and experimental compounds in the BioMAP reference database, novel compounds can be mapped to the current therapeutic landscape as well as help guide indication expansion.

Methods: Three benchmark RA drugs, a DMARD (Methotrexate, MTX), an anti-TNFα antibody (Adalimumab, Humira, ADA), and a small molecule JAK kinase inhibitor (Tofacitinib, Xeljanz, TOF) were profiled across a panel of 12 human primary cell based systems to generate phenotypic profiles. Drug effects on a broad scope of disease relevant readouts related to immune cell activation, proliferation, vascular inflammation, epithelial cell activation, matrix remodeling, fibrosis, and tissue remodeling were used to generate sentinel effects consistent with the RA indication. Three development candidates, BIRB-796 (p38MAPK inhibitor), apremilast (PDE IV inhibitor), and idelalisib (PI3Kδ inhibitor) were similarly profiled to assess indication selection.

Results: ADA and TOF were broadly anti-inflammatory with decreased cytokines (TNFα, IL-17F) and inflammation markers (VCAM-1, Eotaxin-3). In contrast, MTX was more selectively active in a system modeling T cell dependent B cell activation (BT). Correlation of activities with impact on disease relevant processes such as vascular inflammation, immune cell activation and proliferation, modulation of matrix, and epithelial activation was used to confirm RA as a primary indication best suited to these drugs. Analysis of the developmental compounds BIRB-796, apremilast, and idelalisib, was performed to assess which compound best mapped to which indication. BIRB-796 and apremilast, but not idelalisib, suppressed TNFα production from LPS-stimulated monocytes, similar to ADA. Although analysis of BIRB-796 revealed impacts on RA relevant processes, there were additional pro-inflammatory activities in a wound-healing model using dermal fibroblasts. Skin adverse events (AEs) have been reported in clinical trials of BIRB-796 and other p38 MAPKi. The data support the repositioning of p38 inhibitors for indications such as lung disease including COPD. Conversely to

the broad activities of BIRB-796, idelalisib's anti-inflammatory activities were selective to the BT system, similar to MTX and TOF. These data suggest that idelalisib may be better suited for indications such as lupus or oncology (CLL) where B cell dysfunction is of greater importance with respect to the disease.

Conclusion: These in vitro human primary cell-based model systems provide a phenotypic screening platform that can used to evaluate indication-related efficacy, dosing, and safety.

Disclosure: J. Ptacek, DiscoveRx, 3; **E. L. Berg**, DiscoveRx, 3; **A. O'Mahony**, DiscoveRx, 3.

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Abstract Number: 2777

Drug Retention Rates of Biologic Monotherapies for Patients with Rheumatoid Arthritis Receiving TNF Inhibiting Fusion Protein Agent and Antibody Agent; From Multicenter Registry in Japan

Hiroyuki Matsubara[1], Masatoshi Hayashi[2], Nobunori Takahashi[3], Toshihisa Kojima[3], Koji Funahashi[3] and Naoki Ishiguro[4], [1]Department of Orthopedic Surgery and Rheumatology, Nagano Red Cross Hospital, Nagano, Japan, [2]Department of Orhtopedic Surgery and Rheumatology, Nagano Red Cross Hospital, Nagano, Japan, [3]Department of Orthopedic Surgery, Nagoya University Hospital, Nagoya, Japan, [4]Department of Orthopedic Suregery, Nagoya University Hospital, Nagoya, Japan
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Background/Purpose: In general, drug retention rate reflects the effectiveness and tolerability of the drug. TNF inhibitors include fusion protein agent such as etanercept (ETN) and antibody agent such as adalimumab(ADA),golimumab(GLM). There is few data comparing the retention rates between these biological therapies without concomitant methotrexate(MTX) for RA patients in daily clinical practice. The purpose of this study is to compare the drug retention rates of biological therapies with different TNF inhibitors that include fusion protein agent and antibody agent without MTX.

Methods: We collected the data from the patients who started ETN, ADA, GLM as first-biologics without MTX since 2008 and registered in the multicenter, large cohort of RA patients (Tsurumai Biologics Communication Registry; TBCR). We devided patients into two groups including ETN group and antibody group(ADA,GLM).We surveyed the following information: demographic data, disease activity (DAS28-CRP) at the baseline of each biological treatment. Drug retention rates were calculated by the Kaplan-Meier analysis and compared using the log-rank test among two groups. We investigated drug retention rates for discontinuation due to insufficient effectiveness and adverse events.

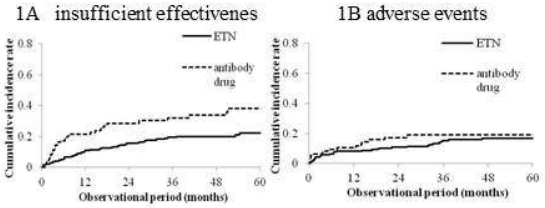
Results: We analyzed 356 patients of 2324 patients registered in TBCR until March 2013 (244 patients in the ETN group, 112 patients in the antibody group including, 78 patients with ADA,34 patients with GLM). The mean follow up time was 34.7 months. Table shows baseline characteristics of the groups (Table). Cumulative incidence rate for discontinuation due to insufficient effectiveness was significantly lower in the ETN group (p=0.0017, Fig.1A). There was no significant difference in cumulative incidence rate for discontinuation due to adverse events (p=0.342, Fig.1B).

Conclusion: We demonstrated that ETN therapy without concomitant MTX had a lower discontinuation rate due to insufficient efficacy compared with antibody agent without concomitant MTX.

Table

Variables	ETN (n=244)	Antibody drug (n=112)	P value
Age, years	62.5 ± 14.0	60.1 ± 14.7	0.217
Female (%)	81.2	82.6	0.768
Disease duration (years)	11.3 ± 10.3	11.5 ± 9.8	0.700
Disease duration ≤2years (%)	17.9	16.5	0.803
Steinbrocker's Stage III or IV (%)	67.7	65.6	0.774
Steinbrocker's Class 3 or 4 (%)	42.5	36.0	0.319
Oral corticosteroids use (%)	63	78.6	0.046
PSL-equivalent dose (mg/day)	3.4 ± 3.3	4.2 ± 3.0	0.061
DAS28-CRP	4.45 ± 1.12	4.05 ± 1.52	0.114

The data are reported as mean±stndard deviation. P-value are calculated between etanercept and antibody drug with suitable statistics. ETN etanercept PSL prednisolone, DAS disease activity score



Disclosure: H. Matsubara, None; **M. Hayashi**, None; **N. Takahashi**, None; **T. Kojima**, Takeda Pharma Corporation, 2,Janssen Pharmaceutical, 2,Astellas Pharma Corporation, 2,Mitsubishi Tanabe Pharma Corporation, 8,Takeda Pharma Corporation, 8,Eisai Pharma Corporation, 8; **K. Funahashi**, None; **N. Ishiguro**, Takeda, Mitsubishi-Tanabe, Astellas, Chugai, Abbott, Bristol-Myers Squibb, Eisai, Janssen, Kaken, Pfizer, 2,Takeda, Mitsubishi-Tanabe, Astellas, Chugai, Abbott, Bristol-Myers Squibb, Eisai, Janssen, Kaken, Pfizer, Taisho-Toyama, Otsuka, 8.

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Abstract Number: 2778

Abatacept-Treated Rheumatoid Arthritis Patients Have Better Drug-Survival Rate When Abatacept Is the First or Second Line Biologic Agent with an Excellent Overall Safety Profile: A Single Center Experience

Irini Flouri[1], Argyro Repa[2], Antonis Fanouriakis[2], Nikolaos Kougkas[2], Ioannis Papalopoulos[2], Eleni Kampouraki[2], Dimitrios Boumpas[3], Nestor Avgoustidis[2], George Bertsias[2] and **Prodromos Sidiropoulos**[2], [1]Rheumatology, Clinical Immunology, Allergy, University of Crete, Medical School, University Hospital, Heraklion, Greece, [2]Rheumatology, Clinical Immunology, and Allergy, University of Crete, Medical School, University Hospital, Heraklion, Greece, [3]Biomedical Research Foundation, Academy of Athens, Athens, Greece

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Background/Purpose:

Long-term prospective observational studies are complementary to controlled clinical trials in exploring the effectiveness and safety of biological therapies in rheumatoid arthritis (RA). We sought to study abatacept survival, reasons of discontinuation and clinical responses in everyday clinical practice.

Methods:

Prospective, observational, single-center study at the Rheumatology Clinic, University Hospital of Heraklion, Greece. Patient demographics, co-morbidities and disease characteristics were recorded at baseline, while drug discontinuations, disease activity and adverse events were monitored during follow-up, All patients who received abatacept intravenously between 29/6/2017 till 31/8/2014 were analyzed.

Results:

243 RA patients (84% women, 44% with destructive arthritis) with median (IQR) age 61 (15) years (37% aged >65 years), disease duration 7.9 (11) years and DAS28 5.9 (1.6) at baseline were included. Total follow-up time was 407 patient-years [median (IQR): 1.4

(1.3) years per patient]. Abatacept was used as first, 2nd or 3rdbiologic agent in 28%, 34%, and 38% of the patients, respectively.

Forty percent of the patients discontinued therapy after median (IQR) 1.0 (1.1) years. Reasons for discontinuation were treatment failure in 88 patients, adverse events in 8, other reasons in 3. In multivariable regression analysis controlling for potential possible confounding factors (demographic, disease characteristics, treatments), independent predictors of abatacept survival were male sex, older age, abatacept used as 1st or 2nd (as compared to ≥3rd) biologic agent, lower CRP and higher DAS28 and HAQ at baseline.

Regarding responses at 6 (12) months of therapy, 5.7% (13.2%) of patients had good and another 46.3% (47.6%) had moderate EULAR response, while 10.8% (16.5%) and 5.9% (7.8%) of the patients had DAS28 ≤3.2 or remission, respectively. The response rate at 12 months was higher in patients who received abatacept as 1st or 2nd as compared to ≥3rdbiologic agent (p= 0.021).

257 adverse events were registered, 43 being serious adverse events (SAE). The rate of total or serious infections was 37 and 2.7 per 100 patients/year respectively, while the median (IQR) time to first serious infection was 1.3 (1.8) years. SAE (including 5 cancers and 11 infections, mainly of the respiratory tract) occurred more frequently in geriatric RA patients (p=0.05).

Conclusion:

In this large, single-center observational study with abatacept-treated RA patients, nearly 60% of the patients remained on therapy and only 9% of drug discontinuations were due to adverse events. The majority of patients discontinued therapy due to inadequate response, mainly when abatacept was the third or more biologic agent administered. Abatacept when used as 1st or 2nd line biologic agent has better survival and efficacy profile.

Disclosure: I. Flouri, None; **A. Repa**, None; **A. Fanouriakis**, None; **N. Kougkas**, None; **I. Papalopoulos**, None; **E. Kampouraki**, None; **D. Boumpas**, None; **N. Avgoustidis**, None; **G. Bertsias**, None; **P. Sidiropoulos**, None.

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Abstract Number: 2779

Better Drug Survival of Non-TNFi Compared to TNFi Biologics after Non-TNFi Failure in RA Patients: A Single Center Experience

Konstantinos Thomas, Christos Koutsianas, Argyro Lazarini, Christina Tsalapaki, Chrisoula Hatzara, Anna Kandili, Katerina Antonatou and Dimitrios Vassilopoulos, University of Athens Medical School, Clinical Immunology and Rheumatology Unit, 2nd Department of Medicine and Laboratory, Athens, Greece

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Background/Purpose:

There are sparse data in the literature regarding the drug survival of TNFi vs. non-TNFi biologics in rheumatoid arthritis (RA) patients who have already failed non-TNFi treatment in a real-life setting. We studied the drug survival of non-TNFi versus TNFi biologics in RA patients after failure of the first non-TNFi biologic in daily clinical practice.

Methods:

Data were collected retrospectively in RA patients treated with different biologics in our center from January 1, 2003 to June 1, 2015. Analyses were stratified by the first type of biologic agent after the 1st non-TNFi failure and then by RF status, csDMARD and corticosteroid co-administration and previous TNFi use. Kaplan-Meier survival analysis and log-rank test of equality pairwise over strata were performed.

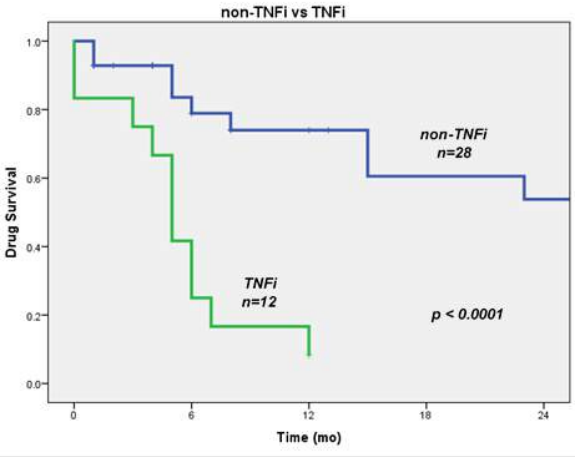
Results:

Among 237 biologic treated RA patients, 40 patients with non-TNFi failure (rituximab-RTX n=16, abatacept-ABA n=16, tocilizumab-TCZ n=8) were included; 28/40 (70%) had previously failed TNFi, 39/40 (97.5%) were women, 20/40 (50%) were RF and/or anti-CCP+, their mean age was 61.8 ± 11.3 years with a mean follow-up of 27.2 ± 23.4 months (median 17.5). 70% of patients (28/40) were

switched to a 2nd non-TNFi (TCZ n=17, RTX n=6, ABA n=5) and 30% (12/40) to an TNFi. The baseline characteristics did not differ significantly between the 2 groups with the exception of previous TNFi exposure [non-TNFi: 25/28 (89%) vs. TNFi: 3/12 (25%), p<0.0001]. The mean estimated drug survival after switching to a 2nd non-TNFi was significantly longer (33.8 ± 5.8 months) compared to switching to a TNFi (5.4 ± 1.1 months) (p<0.0001). The corresponding survival rates at 12 months were 74% vs 8.3% and at 24 months 53.8% vs 0%, respectively (p<0.0001). This difference in survival maintained its statistical significance when the groups were stratified according to RF positivity and csDMARD co-administration. All 3 non-TNFi drug classes (RTX, TCZ, ABA) had significantly better survival when compared to TNFi.

Conclusion:

In this observational real life study, in RA patients who had failed the 1st non-TNFi, switching to a 2nd non-anti-TNFi was associated with better drug survival compared to switching to a TNFi, regardless of serological status or csDMARD co-administration.



Disclosure: K. Thomas, None; **C. Koutsianas**, None; **A. Lazarini**, None; **C. Tsalapaki**, None; **C. Hatzara**, None; **A. Kandili**, None; **K. Antonatou**, None; **D. Vassilopoulos**, None.

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Abstract Number: 2780

Relationship Between Immunogenicity, Hypersensitivity Reactions and Skin Tests Against Infliximab, Etanercept and Adalimumab in Patients with Rheumatoid Arthritis and Ankylosing Spondylitis

Firas Doghanji[1], **Sebnem Ataman**[2], Ali Erhan Ozdemirel[2], Recep Bülent Seckin[1], Ayse Peyman Yalcin[1] and Sevim Bavbek[3], [1]Physical Medicine and Rehabilitation, Ankara University Faculty of Medicine, Ankara, Turkey, [2]Rheumatology Department, Ankara University Faculty of Medicine, Ankara, Turkey, [3]Immunology and Allergy, Ankara University Faculty of Medicine, Ankara, Turkey

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Relationship between immunogenicity, hypersensitivity reactions and skin tests against Infliximab, Etanercept and Adalimumab in patients with rheumatoid arthritis and ankylosing spondylitis

Background/Purpose:

Anti-TNF drugs can cause systemic or local hypersensitivity reactions.In this study, we aimed to investigate relationships between serum antidrug antibody (ADA), systemic hypersensitivity or local injection site reactionsduring anti-TNF drugs treatmentand to detect the role of skin tests in the diagnosis of hypersensitivity reactions to anti-TNFs.

Methods:

According to 1984 Modified New York Criteria and 1987 ACR classification criteria, 69 AS patients who were using Infliximab, Adalimumab, and Etanercept (n=25, 21, and 23 respectively) and 46 RA patients who were using Infliximab, Adalimumab, and Etanercept (n=9, 20, and 17 respectively) were enrolledin the study.Demographical data, ESR and CRP levels in the serum of the patients were determined, and BASDAI for AS patients and DAS28 for RA patients were assessed.Serum levels of anti-TNFs and ADA to these agents were measured with ELISA methods (Progenika Biopharma SA, Derio Spain). The patients withanti-TNF associated hypersensitivity reactions were evaluated withskin prick (full strenght)/ intradermal tests (1/1000 to 1/10 dilutions) with implicated anti-TNF agents..Readings were conducted after 15 min and 24, 48, and 72 hoursand considered positive if the size of the initial wheal had increased by at least 3 mm in diameter and was surrounded by erythema.

Results:

In total, 28.6% of patients had a history of hypersensitivity reaction to the anti-TNF drugs. Statistically significant relation was identified between hypersensitivity reactions and skin test positivity in all patients (p=0,001) (Table 1). Statistically significant relation was identified between injection site reactions and skin test positivity in patients using Etanercept and Adalimumab (p=0,001, p=0,02 respectively). No relation was found between skin test positivity and the presence of ADAto Anti-TNFs, and disease activity scores.Skin testswith anti-TNFs results in significantly more positive in patients with normal drug levelscompared with patients with low drug levels (table 2).

Conclusion:

This study demonstrates that patients whoexhibit a hypersensitive reaction to anti-TNF drugs produce notably positive results to skin testing without maintaining a direct relationship to serum levels of ADA. There is a need for more comprehensive studies in this field.

Table 1. Relationship allergic reactions and skin test positivity

	Skin test negative		Skin test positive		P
	Number	%	Number	%	
No history of allergy in Infliximab users	24	70,6			
History of allergy	10	29,4			
Total	34	100			
No history of allergy in Adalimumab users	21	65,6	2	22,2	**0,020**
History of allergy	11	34,4	7	77,8	
Total	32	100	9	100	
No history of allergy in Etanersept users	15	83,3	6	27,3	**0,001**
History of allergy	3	16,7	16	72,7	
Total	18	100	22	100	
No history of allergy	60	71,4	8	25,8	**0,001**
History of allergy	24	28,6	23	74,2	
Total	84	100	31	100	

Table 2. Relationship between drug level and skin prick test

	Normal drug level in blood (n=83)		Low drug level in blood (n=32)		P
	Number	%	Number	%	
Skin test negative	55	66,3	29	90,6	**0,008**
Skin test positive	28	33,7	3	9,4	
Total	83	100	32	100	

Disclosure: F. Doghanji, None; **S. Ataman**, Roche Pharmaceuticals, 5,Pfizer Inc, 5,UCB, 5,Mustafa Nevzat, 5,BMS, 5,MSD, 5; **A. E. Ozdemirel**, None; **R. B. Seckin**, None; **A. P. Yalcin**, None; **S. Bavbek**, None.

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Abstract Number: 2781

Absence of Effects of Filgotinib on Erythrocytes, CD8+ and NK Cells in Rheumatoid Arthritis Patients Brings Further Evidence for the JAK1 Selectivity of Filgotinib

René Galien[1,2], Reginald Brys[3], Annegret Van der Aa[3], Pille Harrison[3] and Chantal Tasset[3], [1]Galapagos SASU, Romainville, France, [2]102 Avenue Gaston Roussel, Galapagos SASU, Romainville, France, [3]Galapagos NV, Mechelen, Belgium

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SESSION INFORMATION

Session Date: Tuesday, November 10, 2015

Session Title: Rheumatoid Arthritis - Small Molecules, Biologics and Gene Therapy Poster III

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose:

The distinct role of JAK family members (JAK1, JAK2, JAK3 and TYK2) in signaling for cytokines and growth factors has established these kinases as therapeutic targets for inflammatory diseases and cancer. JAK1 plays a dominant role in signalling for inflammatory cytokines, JAK2 signals for erythropoietin and thus is central to haematopoiesis, and JAK3 is key to the adaptive immune system. We hypothesized that inhibiting JAK1 would provide an efficacious treatment for rheumatoid arthritis (RA), while avoiding effects associated with the inhibition of other JAKs. Filgotinib (GLPG0634) demonstrated selectivity for inhibition of JAK1 over JAK2, JAK3 and TYK2 in biochemical and cell assays. In phase 2 clinical trials, filgotinib rapidly improved signs and symptoms of RA within 1 week with good tolerability and safety. The data presented here bring additional evidence for its clinical JAK1 selectivity in RA patients.

Methods:

RA patients (n=91) with insufficient response to MTX were randomized to receive placebo or 30, 75, 150, or 300 mg filgotinib once-daily orally for 4 weeks as add-on to MTX in a double-blind phase 2a study. Blood was sampled pre-dose and on the last day of treatment. CRP, Chitinase-3 L1 (CHI3L1) and VEGF plasma concentrations were measured using an ELISA assay from R&D Systems and the Myriad RBM InflammationMAP© assay. Hemoglobin concentration was measured using the Siemens Advia technology. Red blood cell (RBC) and reticulocyte counts as well as $CD8^+$ and natural killer (NK: $CD3^-$ $CD16^+$ $CD56^+$) cell percentages were measured by flow cytometry.

Results:

4 weeks of treatment with filgotinib decreased plasma concentrations of the inflammatory disease markers CRP, CHI3L1/YKL-40 and VEGF, whose expressions are controlled by STAT factors. The mean blood concentration of haemoglobin increased by up to 0.4 g/dL at 300 mg (from 12.5 g/dL to 12.9 g/dL), while reticulocyte and RBC counts, which are all directly controlled by erythropoietin, were not impacted by treatment, indicating that JAK2 activity was not inhibited at these doses and regimen. Similarly, no effects were observed on blood $CD8^+$and NK cell percentages, suggesting that the gamma chain signalling, mostly dependent on JAK3 signalling, was not inhibited by filgotinib.

Conclusion:

In patients with active RA, 4 weeks of treatment with filgotinib, a selective inhibitor of JAK1, reduced plasma concentrations of inflammatory markers. This correlates well with the previously reported improvement in signs and symptoms of RA. Treatment did not adversely influence erythrocytes and reticulocytescounts and showed a mean improvement in haemoglobin, supporting the hypothesis that JAK2 signalling was not inhibited. There were no effects on CD8+ or NK cell counts, which are regulated by JAK3 signalling. Thus, these data provide further evidence for the JAK1 selectivity of filgotinib in RA patients. Future studies will need to establish potential clinical correlates of the observed increase in haemoglobin, such as an improvement in fatigue or lower rates of infections with less decrease in immune cells.

Refrence:

O'Shea J, Schwartz D, Villarino A, Gadina M, McInnes I and Laurence A. Annu. Rev. Med. 2015.66:311-328

Disclosure: R. Galien, Galapagos SASU, 3,AbbVie, 2; **R. Brys**, Galapagos NV, 3,AbbVie, 2; **A. Van der Aa**, Galapagos NV, 3,AbbVie, 2; **P. Harrison**, Galapagos NV, 3,AbbVie, 2; **C. Tasset**, Galapagos NV, 3,AbbVie, 2.

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Abstract Number: 2782

Not Only 5 but Also 6 Weeks Intervals of Tocilizumab Infusion Induce Clinical Remission in Patients with Active Rheumatoid Arthritis

Hiroshi Uda[1], Koji Shigematsu[2], Yoshitaka Ishizaki[2] and Osamu Saiki[1,3], [1]Rheumatology, Higashiosaka City General Hospital,

Higashiosaka, Japan, [2]Orthopedics, Higashiosaka City General Hospital, Higashiosaka, Japan, [3]Rheumatology, Shiraishi Hospital, Imabari, Japan

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Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose:

For active rheumatoid arthritis patients with inadequate response to synthetic disease modifying antirheumatic drugs (DMARDs), biologic agents are indicated. However, the cost of biologics, including tocilizumab (TCZ), is very high, which makes it difficult for all patients to receive biologics because of the associated expenses. A period of 4 weeks has been recommended as the interval between TCZ infusions in active rheumatoid arthritis patients (1). In our clinical experience, however, we observed that longer intervals could also be effective. The aim of the present study was to clarify that not only 5 but also 6 weeks intervals of TCZ infusion induce clinical remission in patients with active rheumatoid arthritis.

Methods:

The rheumatoid arthritis patients who showed inadequate response to synthetic DMARDs and the patients who showed inadequate response to TNF inhibitors and who agreed with TCZ therapy of six weeks interval were enrolled in the present study. Initially, active rheumatoid arthritis patients were infused with 8 mg/kg of TCZ every 6 weeks with oral medicines. The patients who did not achieve clinical remission after 6 months of TCZ infusions at 6 weeks intervals were administered TCZ infusions every 5 weeks or 4 weeks, along with the same doses of the oral medicines. After one year of treatment with same intervals, we evaluated the clinical conditions. The disease activities were evaluated with clinical symptoms, VAS, CRP, and DAS28 score, and clinical remission was estimated as DAS28 score less than 2.6.

Results: In total, 103 patients were enrolled in the present study, and 82% of patients achieved clinical remission with TCZ infusion. Twelve patients did not achieve clinical remission even at 4 weeks intervals. Seven patients dropped out from the study because of personal reasons. Among the patients who achieved clinical remission with TCZ infusion, 71% of patients were with 6 weeks intervals, and 24% were with 5 weeks intervals. To our surprise, the patients who needed 4 weeks intervals of TCZ infusions to achieve remission were less than 5%. In patients who achieved remission with 6 weeks intervals of TCZ infusion, 27% could discontinue both prednisolone (PSL) and methotrexate (MTX), 43% received PSL (5 to 1mg), and 3% received MTX, and 27% received PSL and MTX. Severe adverse events that led to the discontinuation of treatment, including tuberculosis and death, did not occur, and the frequency of other adverse events with infusions at 6 weeks intervals was lower than that at 4 weeks intervals.

Conclusion:

The present study has provided evidence that not only 5 but also 6 weeks intervals of TCZ infusion induce clinical remission in patients with active rheumatoid arthritis, and the finding should be of great interest for patients for both financial and labor reasons.

Reference:

(1) Roshe Registration Limited. RoACTEMRA 20 mg/ml concentrate for solution for infusion. Welwyn Garden City, UK: Roshe Registration Limited, 2012

Disclosure: H. Uda, None; **K. Shigematsu**, None; **Y. Ishizaki**, None; **O. Saiki**, None.

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Abstract Number: 2783

What Is the Rate of Primary and Secondary Failure of Anti-TNF in RA Patients? Data from a Rheumatoid Arthritis Cohort

Edward C. Keystone[1], Mohammad Movahedi[2,3], Angela Cesta[2], Xiuying Li[2], Sandra Couto[2], Emmanouil Rampakakis[3], John S. Sampalis[3,4], Claire Bombardier[2,5,6] and OBRI Investigators, [1]The Rebecca MacDonald Centre For Arthritis, Mount Sinai Hospital, Toronto, ON, Canada, [2]Toronto General Hospital Research Institute, University Health Network, Toronto, ON, Canada, [3]JSS Medical Research, St-Laurent, QC, Canada, [4]McGill University, Montreal, QC, Canada, [5]University of Toronto, Department of Medicine

(DOM) and Institute of Health Policy Management, and Evaluation (IHPME), Toronto, ON, Canada, [6]Division of Rheumatology, Mount Sinai Hospital, Toronto, ON, Canada

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SESSION INFORMATION

Session Date: Tuesday, November 10, 2015

Session Title: Rheumatoid Arthritis - Small Molecules, Biologics and Gene Therapy Poster III

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Although the majority of RA patients respond to treatment with anti-TNF agents, some patients present with refractory disease (1ry failure) while others show some initial clinical response and eventually lose responsiveness (2ry failure). Assessing primary and secondary failure, and thus the extent of non-response to anti-TNF agents, is complex due to the use of different definitions and variations in the timing of patient assessment in routine clinical care. The purpose of this analysis was to assess the rate of non-response based on different definitions among RA patients treated with anti-TNF in a large observational cohort.

Methods: Patients enrolled in the Ontario Best Practices Research Initiative (OBRI) that were treated with an anti-TNF agent and had available information on treatment discontinuation were included in the analysis. Those who discontinued anti-TNF due to 1ry failure, 2ry failure, or an adverse event (AE) as per the judgment of the treating physician were classified in three different types of failure, based on (i) time of failure (<6 months, 6-12 months, >12 months); (ii) response to treatment, i.e. whether they achieved DAS28 low disease activity (LDA) prior to discontinuation, and; (iii) time and response criteria. Time to treatment discontinuation and time to LDA were assessed with the Kaplan-Meier (K-M) estimator of the survival function.

Results:

953 patients (81.6% female) were included with a mean (SD) age at OBRI enrolment of 56.0 (12.5) and disease duration of 9.8 (9.5). Mean (SD) disease parameters were: DAS28: 4.6 (1.2); SJC: 6.1 (5.2); TJC: 6.8 (6.5); physician global: 4.8 (2.5) cm; patient global: 5.2 (2.7) cm.

After a mean (SD) follow-up of 32.8 (30.6) months, 259 (27.2%) patients were discontinued due to some type of failure; 187 (19.6%) due to non-response and 72 (7.6%) due to safety reasons with mean (SD) K-M-based time to failure of 9.3 (0.4) years. Table 1 summarizes the incidence of each type of failure by type of definition. Among patients failing anti-TNF treatment after 12 months half achieved DAS28 LDA before failure after a median of 37 months.

Table 1: Rates of 1ry and 2ry Anti-TNF Failure Based on Different Definitions

	Failure Definition					
% of patients	**Time Criteria**		**Response Criteria**		**Time & Response Criteria**	
1ry Failure	<6 mos	5.6%	No LDA	14.9%	No LDA	14.9%
Partial Response	6-12 mos	4.5%	-	-	<12 mos + LDA or >12 mos + LDA after 12 mos	2.0%
2ry Failure	>12 mos	9.5%	LDA	4.7%	>12 mos + LDA before 12 mos	2.7%
Safety	-	-	AE	7.6%		-
Early Safety	<6 mos	3.3%	-	-	<6 mos + AE	3.3%
Intermediate Safety	6-12 mos	1.7%	-	-	6-12 mos + AE	1.7%
Late Safety	>12 mos	2.6%	-	-	>12 mos + AE	2.6%

Conclusion: The results of this analysis have shown that the rate of primary failure to anti-TNF treatment may range from 6% to 15% depending on the failure definition used highlighting the need for standardization. Furthermore, approximately half of the patients showing some initial clinical response can achieve LDA over a 3-year period.

Disclosure: E. C. Keystone, Abbott Laboratories, Amgen Inc., AstraZeneca Pharmaceuticals LP, Bristol-Myers Squibb, F. Hoffmann-La Roche Inc, Janssen Inc, Lilly Pharmaceuticals, Novartis Pharmaceuticals, Pfizer Pharmaceuticals, Sanofi-Aventis, UCB., 2,Abbott Laboratories, AstraZeneca Pharma, Biotest, Bristol-Myers Squibb Company, F. Hoffmann-La Roche Inc, Genentech Inc, Janssen Inc, Lilly Pharmaceuticals, Merck, Pfizer Pharmaceuticals, UCB., 5,Abbott Laboratories, Astrazeneca LP, Bristol-Myers Squibb Canada, F. Hoffmann-La Roche Inc., Janssen Inc., Pfizer Pharmaceuticals, UCB, Amgen., 6; **M. Movahedi**, JSS Medical Research, a Contract Research Organization, 3; **A. Cesta**, None; **X. Li**, None; **S. Couto**, None; **E. Rampakakis**, JSS Medical Research, a Contract Research Organization, 3; **J. S. Sampalis**, JSS Medical Research, a Contract Research Organization, 3; **C. Bombardier**, Abbvie, Amgen, Bristol

Myers Squibb, Hospira, Janssen, Roche, Pfizer, UCB, 2.

Abstract Number: 2784

Faecal Levels of Calprotectin Are Increased in Patients with Primary Sjögren's Syndrome and Correlates with Disease Activity

Thomas Mandl[1], Bodil Ohlsson[2] and Kristofer Andreasson[3], [1]Dept of Rheumatology, Skåne University Hospital Malmö, Lund University, Malmo, Sweden, [2]Dept of Internal Medicine, Skane University Hospital Malmo, Lund University, Sweden, Malmo, Sweden, [3]Dept of Rheumatology, Skane University Hospital Lund, Lund University, Sweden, Lund, Sweden
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SESSION INFORMATION
Session Title: Sjögren's Syndrome: Translational Insights into Sjögren's Syndrome
Session Type: ACR Poster Session C

Background/Purpose: FC is a validated biomarker differentiating inflammatory bowel disease from irritable bowel syndrome. We have evaluated faecal levels of calprotectin (FC) in patients with primary Sjögren's syndrome (pSS) in reference to patient reported indices of gastrointestinal discomfort as well as clinical features of pSS.

Methods: Fourty-four consecutive pSS patients (median 62 (IQR 55, 69) years, 43 females), diagnosed according to the American-European Classification Criteria (AECC), were recruited from the open clinic at the Dept of Rheumatology, Malmö, Sweden and included in the study. Patients were evaluated by patient reported indices of GI disease (the Rome III diagnostic questionnaire for the adult functional GI disorders and Scoring Algorithm) and Sjögren's syndrome (the EULAR Sjögren's syndrome patient reported index, ESSPRI). Disease activity was evaluated by the EULAR Sjögren's syndrome disease activity index (ESSDAI). FC was measured in stool samples with a commercially available ELISA using a monoclonal antibody (Bühlmann Laboratories, Schönenbuch, Switzerland). For comparison, FC levels were evaluated in 21 healthy hospital workers (median age 56 (IQR 47, 58) years, 17 females), not currently treated with non-steroidal anti-inflammatory drugs or proton pump inhibitors.

Results: pSS patients displayed significantly increased levels of FC in comparison to healthy controls (41 mg/g (20, 118) vs. 20 mg/g (20, 53); p=0.036). Of the pSS patients, 39% fulfilled the Rome III criteria for IBS. FC levels correlated significantly with the ESSDAI total score (rs=0.40; p=0.008) whilst not with the ESSPRI total score. Furthermore, patients fulfilling Rome III criteria for IBS had significantly increased ESSDAI (10 (7,10) vs. 5 (0, 9); p=0.028) and ESSPRI total scores (7 (6, 9) vs. 6 (4, 7); p=0.029), but did not show any increased levels of FC (47 mg/g (20, 70) vs. 41 mg/g (20, 128); p=0.415).

Conclusion: FC levels are moderately increased in pSS patients and show a moderate association with disease activity. pSS patients fulfilling the criteria for IBS did not show increased levels of FC but had higher disease activity as well as increased scores in the Sjögren's syndrome patient reported index. We suggest that FC has potential as an objective biomarker in pSS.

Disclosure: T. Mandl, None; **B. Ohlsson**, None; **K. Andreasson**, None.

Abstract Number: 2785

Association of Anti-Glutamate Receptor Subunit NR2 Antibody and Psychiatric Disorder in Patients with Primary Sjögren Syndrome

Yoshiyuki Arinuma[1,2], Yuko Sakuma[3], Eisuke Ogawa[2], Tatsuhiko Wada[4], Tatsuo Nagai[2], Sumiaki Tanaka[2] and Shunsei Hirohata[2], [1]Center for Autoimmune and Musculoskeletal Diseases, The Feinstein Institute for Medical Research, Manhasset, NY, [2]Rheumatology and Infectious Diseases, Kitasato University School of Medicine, Kanagawa, Japan, [3]Department of Rheumatology and Infectious Diseases, Kitasato University School of Medicine, Kanagawa, Japan, [4]Department of Rheumatology and Infectious Diseases, Kitasato University School of Medicine, Sagamihara, Japan
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SESSION INFORMATION

Session Title: Sjögren's Syndrome: Translational Insights into Sjögren's Syndrome

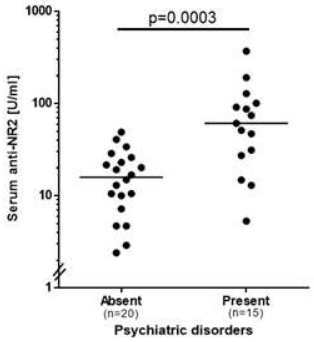
Session Type: ACR Poster Session C

Background/Purpose: Sjögren syndrome (SjS) is one of the autoimmune disease characterized by the production of autoantibodies. Patients with SjS frequently observe psychiatric manifestation such as depression, anxiety and cognitive dysfunction as is often seen in patients with systemic lupus erythematosus (SLE). Anti-glutamate receptor subunit NR2 antibodies (anti-NR2) is one of the pathogenic autoantibodies related to psychiatric disorder (PD) in patients with SLE. However, anti-NR2 in patients with SjS has not been clarified. The aim of this study is to investigate the association of anti-NR2 and PD in patients with primary SjS (pSjS).

Methods: We examined 35 patients with pSjS, 17 patients with rheumatic diseases other than SLE or SjS as disease control (DC) and 36 healthy individuals (HC). Anti-NR2 in serum were measured by ELISA.

Results: The level of anti-NR2 in serum was significantly elevated in patients with pSjS (47.3±69.4U/ml), compared to those with DC (14.0±16.6, p=0.0043) or HC (16.8±9.6, p=0.0226). In pSjS patients with PD, the serum anti-NR2 level was significantly higher than that in patients without PD (p=0.0003). Also, the positivity of anti-NR2 in serum from patients with pSjS was found to be a significant risk factor for PD in pSjS patients (OR 38.0, 95%CI 5.5-789.3, p=0.0018) by logistic regression analysis.

Conclusion: Anti-NR2 are significantly associated with PD in patients with pSjS.



Disclosure: Y. Arinuma, None; **Y. Sakuma**, None; **E. Ogawa**, None; **T. Wada**, None; **T. Nagai**, None; **S. Tanaka**, None; **S. Hirohata**, None.

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Abstract Number: 2786

miR200b-5p: A Possible Predictor of Lymphoma Development in Sjögren's Syndrome (SS)?

Efstathia K. Kapsogeorgou[1,2], Vasiliki C. Gourzi[1] and Athanasios G. Tzioufas[1], [1]Pathophysiology, School of Medicine, National University of Athens, Athens, Greece, [2]Pathophysiology, School of Medicine, National University of Athens, Greece, Athens, Greece

First publication: September 29, 2015

SESSION INFORMATION

Session Title: Sjögren's Syndrome: Translational Insights into Sjögren's Syndrome

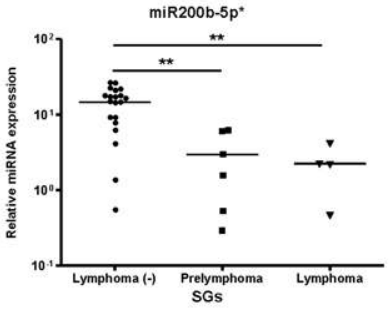
Session Type: ACR Poster Session C

Background/Purpose: miR200b miRNAs (miR200b-3p and miR200b-5p) are critical regulators of the expression of oncogenes and tumour suppressor genes. Herein, we sought to investigate whether their expression in salivary gland tissues (SG) is related to SS-related lymphoma development.

Methods: miR200b-3p and miR200b-5p expression in SG tissues was analyzed by real-time PCR in total RNA from 30 SS patients (all women), including 20 patients that did not develop SS-lymphoma during follow up (lymphoma(-); median follow up time since biopsy performance, range: 3.8yrs, 3.4-10yrs), 6 patients that develop MALT-lymphoma in the future (prelymphoma; median follow up time till lymphoma diagnosis, range: 4.0yrs, 1.0-5yrs) and 4 patients that had MALT-lymphoma at the time of biopsy (lymphoma). Significant differences in miR expression between SS subgroups were analysed by Tukey's multiple comparison test, whereas associations with other histologic futures by Mann-Whitney test.

Results: miR200b-5p, but not miR200b-3p, was significantly down-regulated in SG tissues of prelymphoma ($p \leq 0.01$) and lymphoma ($p \leq 0.01$) SS patients compared to lymphoma(-) SS patients (mean relative expression±SE: 2.97±1.09, 2.24±0.75 and 14.67±1.76, respectively) (Figure). On the contrary, miR200b-3p levels in SGs were significantly reduced in SS patients with SG infiltrates that organize into ectopic germinal centres (GC) compared to those without (1883±682 vs 51090±28330, p=0.05, respectively).

Conclusion: The significantly lower expression of miR200b-5p in SS patients that had or developed SS-related MALT lymphoma in the future implicates it in lymphomagenesis, whereas its significant downregulation in prelymphoma SGs possibly suggests that miR200b-5p represents a potential prognostic marker for future lymphoma development. Evaluation of its expression in a larger cohort is needed. Finally, considering that GC formation has been linked to lymphomagenesis, the deregulated expression of its paired miRNA, miR200b-3p, in SS patients with GCs could represent a continuum of lymphomagenesis.



Disclosure: E. K. Kapsogeorgou, None; **V. C. Gourzi**, None; **A. G. Tzioufas**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/mir200b-5p-a-possible-predictor-of-lymphoma-development-in-sjogrens-syndrome-ss

Abstract Number: 2787

Expression of Interferons Lambda in Salivary Glands of Patients with Sjögren's Syndrome

Eirini Apostolou[1], Efstathia K. Kapsogeorgou[1], Orsia D. Konsta[1], Maria Ioanna Saridaki[2], Evangelos Andreakos[2] and Athanasios G. Tzioufas[1], [1]Pathophysiology, Faculty of Medicine, School of Health Sciences, National and Kapodistrian University of Athens, Athens, Greece, [2]Clinical, Experimental Surgery and Translational Research, Biomedical Research Foundation Academy of Athens, Athens, Greece

First publication: September 29, 2015

SESSION INFORMATION

Session Title: Sjögren's Syndrome: Translational Insights into Sjögren's Syndrome

Session Type: ACR Poster Session C

Background/Purpose: Type I and II interferons (IFNs) have been implicated in the pathophysiology of Sjögren's Syndrome (SS). Recently a new family of IFNs, namely type III IFNs or Interferons lambda (IFNλs), has been identified, containing three distinct members; IFNλ1/IL29, IFNλ2/IL28A and IFNλ3/IL28B. IFNλs share IFNλR1/IL10R as a common signaling receptor. Despite the fact that their function and regulation has not been completely understood, they exhibit significant antiviral activity. Initial studies implicate IFNλs in several human disorders, including cancer and autoimmune diseases. In this study we sought to investigate the pattern of their expression in SS patients.

Methods: The expression of all IFNλs and their common IFNλR1 receptor was investigated in salivary gland (SG) biopsies from 45 patients with primary SS (according to the American–European Consensus Group criteria) that had variable degree of infiltration (mild, intermediate or severe) and 17 non-SS sicca complaining controls. mRNA and secreted IFNλ levels were measured from salivary gland epithelial cells (SGECs), both resting or following polyinosinic-polycytidylic acid (polyI:C) treatment, in representative samples from the aforementioned groups.

Results: Expression of all IFNλs and their common IFNλR1 receptor was detected in SGs of both SS patients and controls. IFNλ1 (IL29) was detected in ductal epithelia, displaying higher intensity in SGs from SS patients and particularly those with intermediate lesions. IFNλ2 (IL28A) and IFNλ3 (IL28B) were expressed in both ductal and acinar epithelia, as well as in infiltrating Mononuclear Cells (MNCs). Interestingly, regarding IFNλ2, higher expression was observed in the epithelia of SS patients compared to controls. The common receptor IFNλR1 is expressed in all types of cells except fibroblasts, and in higher levels in SGs from SS patients. Importantly, high expression of IFNλR1 was additionally identified to infiltrating plasmatocytoid Dendritic Cells (pDCs). Moreover, TLR3

stimulation by polyI:C treatment, produced high levels of IFNλ1/IL29, IFNλ2/IL28A and IFNλ3/IL28B in all SGECs.

Conclusion: Our findings implicate IFNλs in SS pathophysiology. Identification of all IFNλs and their common signaling receptor locally in SG suggests a potential role for IFNλs in autoimmune responses that govern SS. Further studies are needed to elucidate the role of IFNλs in SG physiology and SS.

Disclosure: E. Apostolou, None; **E. K. Kapsogeorgou**, None; **O. D. Konsta**, None; **M. I. Saridaki**, None; **E. Andreakos**, None; **A. G. Tzioufas**, None.

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Abstract Number: 2788

DNA Microarray Analysis of Labial Salivary Glands in Patients with Sjögren's Syndrome: Comparison with IgG4-Related Disease

Hiroyuki Takahashi[1], Hiroto Tsuboi[1], Mana Iizuka[1], Hiromitsu Asashima[1], Tomoya Hirota[1], Yuya Kondo[1], Isao Matsumoto[1], Takayuki Sumida[1], Seiji Nakamura[2], Sachiko Furukawa[2], Masafumi Moriyama[3], Yuji Nakai[4], Keiko Abe[4] and Toshio Yoshihara[5], [1]Department of Internal Medicine, Faculty of Medicine, University of Tsukuba, Tsukuba, Japan, [2]Faculty of Dental Science, Kyushu University, Fukuoka, Japan, [3]Section of Oral and Maxillofacial Oncology, Division of Maxillofacial Diagnostic and Surgical Sciences, Faculty of Dental Science, Kyushu University, Fukuoka, Japan, [4]Functional Food Science and Nutrigenomics, Graduate School of Agricultural and Life Sciences, The University of Tokyo, Tokyo, Japan, [5]Department of Otolaryngology, Tokyo Women's Medical University, Tokyo, Japan

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SESSION INFORMATION

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Background/Purpose: The previous reports showed that DNA microarray in Sjögren's syndrome (SS) identified the genes associated with mononuclear infiltrates such as immunoglobulin, human leukocyte antigen, T cell receptor and interferon-inducible genes. However, it is possible that the results might reflect nonspecific gene expression due to inflammatory cell infiltration, since the controls were healthy individuals. Therefore, we conducted DNA microarray analysis in labial salivary glands (LSGs) of SS patients and those of IgG4-related disease (IgG4-RD) patients, which also show inflammation, to compare gene expression in LSGs of SS patients with IgG4-RD patients and to identify genes specifically involved in the pathogenesis of SS.

Methods:

1) Gene expression was analyzed by DNA microarray in LSGs of SS patients (n=5), IgG4-RD patients (n=5) and healthy controls (HC) (n=3). All patients with SS and IgG4-RD fulfilled the Japanese Ministry of Health criteria for the diagnosis of SS (1999) and the comprehensive diagnostic criteria for IgG4-RD (2011), respectively. Moreover, all of the patients had not received steroids or any immunosuppressive agents. After the obtained microarray data were normalized by FARMS algorithm, Differentially expressed genes (DEGs) upregulated in SS than in IgG4-RD were identified in pairwise comparisons (false discovery rate<0.05) by rank products method. Approval for this study was obtained from the local ethics committee and a signed informed consent was obtained from each subject.

2) Validation of the results was performed by quantitative PCR using LSGs obtained from other patients with SS (n=11), IgG4-RD (n=11), and HC (n=3) than those examined by DNA microarray.

3) The protein production of validated genes and expressing cells in LSGs from SS patients and IgG4-RD patients were examined by immunofluorescence assay.

4) Functional analysis of the DEG was performed using $CD4^+$ T cells isolated from peripheral blood mononuclear cells (PBMCs) by comparing the gene expression of the DEG in peripheral $CD4^+$ T cells and the population of Th17 cells differentiated from peripheral $CD4^+$ T cells in Th17 polarizing conditions between patients with SS and HC.

Results:

1) In patients with SS, 1785 up-regulated probe sets (corresponding to 1320 up-regulated genes) were identified as DEGs in comparison with those with IgG4-RD.

2) CXCL9, NR4A2, DPP4, SGK1, and PDK1 were selected as candidate genes for validation, according to rank<150, high expression levels, small variance and relation to T cell functions. PCR validated significantly higher expression of NR4A2 and DPP4 in SS patients than in IgG4-RD patients.

3) Immunofluorescence staining in LSGs revealed higher production of NR4A2 and DPP4 in SS patients than in IgG4-RD patients and localization of NR4A2 in IL-17$^+$ CD4$^+$ T cells of SS patients.

4) Peripheral CD4$^+$ T cells of patients with SS showed significantly higher expression of NR4A2, and more preferably differentiated into Th17 cells than those of HC.

Conclusion:

The gene expression pattern of LSG in patients with SS was different from that in those with IgG4-RD.

NR4A2 might be a novel molecule involved in the pathogenesis of SS via Th17 differentiation.

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Abstract Number: 2789

Blood and Salivary Gland BAFF-Driven B-Cell Hyperactivity in Rituximab Non-Responder Patients with Primary Sjögren's Syndrome

Divi Cornec[1], Sebastian Costa[2], Valerie Devauchelle[3], Sandrine Jousse-Joulin[4], Pascale Marcorelles[5], Jean-Marie Berthelot[6], laurent chiche[7], Eric Hachulla[8], Pierre-Yves Hatron[9], Vincent Goeb[10], O Vittecoq[11], Alain Saraux[12] and Jacques-Olivier Pers[13], [1]Department of rheumatology, Brest Occidentale University, Brest, France, [2]anatomopathological department, Brest university hospital, Brest, France, [3]Service de Rhumatologie, CHU Brest, Brest, France, [4]Rheumatology, CHu La cavle Blanche, Brest, France, [5]anatomopathological department, Brest university hospital, CHU Morvan, Brest, France, [6]Rhumatologie, CHU Nantes, Nantes, France, [7]internal medicine, Hopital Europeen, Marseille, France, [8]Department of Internal Medicine, University Lille Nord-de-France, Lille, France, [9]Service de Médecine Interne, Centre National de Référence des Maladies Systémiques Rares, Hôpital Claude Huriez, CHRU Lille, Lille, France, [10]Rhumatologie, CHU Amiens, Amiens, France, [11]University Hospital, Rouen, France, [12]Rheumatology Department, CHU de la Cavale Blanche, Brest Cedex, France, [13]EA2216/ERI29 UBO, Brest, France
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SESSION INFORMATION
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Background/Purpose: To determine whether B-cell markers (blood and minor salivary gland (SG) B-cell depletion (BCD), autoantibodies, BAFF) are associated with clinical response to rituximab in patients with primary Sjögren's syndrome (pSS).

Methods: 45 pSS patients were included: 14 who received low-dose rituximab (two 375 mg/m² infusions) in an open-labelled study (group I); and 17 who received full-dose rituximab (two 1000 mg infusions) from a randomized-controlled study (group II), as well as their 14 placebo. SG B-cell proportion was assessed using a pixel-based software analysis of digitized double-immunostained (CD3/CD20) whole SG slides. Response was defined at W24 according to the Sjögren's Syndrome Responder Index (SSRI)-30.

Results: Response rate was 50% in both groups of rituximab-treated patients. Duration of blood BCD was similar in the 2 groups despite the difference in rituximab dosage, and was highly correlated with residual serum rituximab levels as lately as W16. SG B-cell dynamics mirrored blood B-cell levels, with a drastic SG B-cell proportion decrease at W12 (group I), but an increase at W24 in half of the patients from group II who had already experienced blood B-cell return. Duration of BCD was not associated with the clinical response, but responders had lower baseline SG B-cell proportion. Baseline serum BAFF level correlated with SG B-cell proportion, as well as with other B-cell activation markers (serum free-light chains, serum IgG, beta-2 microglobulin, or auto-antibody levels). This global B-cell hyperactivation was associated with the clinical response, with higher serum BAFF levels in non-responders.

Conclusion: In pSS patients, intense BAFF-driven B-cell activation is associated with nonresponse to a single rituximab course.

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Abstract Number: 2790

Leflunomide/Hydroxychoroquine Combination Treatment Additively Inhibits T Cell Receptor/Toll-like Receptor 9-Triggered Th1 and Th17 Cytokine Secretion

E.H.M. van der Heijden[1,2], S.A.Y. Hartgring[1], S. Hiddingh[1], A.A. Kruize[2], T.R.D.J. Radstake[1,3] and J.A.G. van Roon[1], [1]Laboratory for Translational Immunology, University Medical Center Utrecht, Utrecht, Netherlands, [2]Rheumatology and Clinical Immunology, University Medical Center Utrecht, Utrecht, Netherlands, [3]Department of Rheumatology & Clinical Immunology, University Medical Center Utrecht, Utrecht, Netherlands

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SESSION INFORMATION

Session Title: Sjögren's Syndrome: Translational Insights into Sjögren's Syndrome

Session Type: ACR Poster Session C

Background/Purpose: Primary Sjögren's Syndrome (pSS) is a systemic auto-immune disease, leading to an exocrinopathy of mainly salivary and lachrymal glands. T- and B-cell-driven immunity is critically involved in its immunopathology. Recently we demonstrated synergistic T- and B-cell activation upon T-cell triggering and TLR7/9-driven B-cell activation in pSS patients, accompanied by synergistic induction of immunoglobulins and IFNγ- and IL-17- producing T-cells. In addition, TLR7/9-expressing activated pDCs associated with increased type I IFNs and IFN-inducible genes are increased pSS patients. Several studies have shown that the DMARDs leflunomide (LEF) and hydroxychloroquine (HCQ) inhibit immune activation in pSS, but given separately only show moderate efficacy[(1-4)]. However, LEF and HCQ target different pathways with overlapping, but also potentially additive mechanisms, where LEF primarily targets T- and B-cells and HCQ TLR7/9-driven B-cell and pDC activation.

Objective: To assess the additive effects of LEF and HCQ on CD4 T- and B-cell activation and Th cytokine and IFN-α secretion *in vitro,* employing T cell receptor/TLR9-triggered PBMC.

Methods: PBMCs from healthy persons and pSS patients were cultured with antigen (SEB), TLR9-agonist (CPG-C) and their combination (n=11), in presence or absence of different dosages of LEF, HCQ and their combination (at least n=4). Proliferation of T- and B-cells (using Cell Trace Violet) and release of IFN-α, IFN-γ and IL-17 was measured (Luminex).

Results: In line with robust T and B cell activation, IFN-γ and IL-17 production and synergistic IFN-α production, indicative of pDC activity, was achieved by a combination of SEB and TLR9 ((all $p<0.001$). Both HCQ and LEF potently and dose-dependently inhibited B- and T-cell proliferation and IFN-α production. Mean inhibition of IFN-a was 99% and 85% at 10 µM HCQ and 100 µM LEF, resp and 100% using LEF/HCQ combination (both $p<0.05$). At the latter concentrations HCQ and LEF additively inhibited IFN-γ production (mean: HCQ 41%, LEF 35%, and combination 75%, all $p<0.05$; both HCQ and LEF vs combination $p<0.05$) and IL-17 production (mean: HCQ 68%, LEF 77%, and combination 85%, all $p<0.05$, HCQ vs combi $p=0.05$ and LEF vs combi $p=0.19$). Both T- and B-cell proliferation were additively and significantly inhibited by a combination of HCQ and LEF (all $p<0.05$).

Conclusion: HCQ and LEF robustly inhibited lymphocyte proliferation and cytokine production with additive inhibition of Th1 and Th17 cytokine secretion (IFN-γ and IL-17) and T- and B-cell proliferation. These findings could indicate the potential surplus value of combination therapy with HCQ and LEF for patients with pSS.

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Abstract Number: 2791

TREX-1 Variants in Sjögren's Syndrome Related Lymphomagenesis

Panagiota Makri[1], Adrianos Nezos[2], Michael Voulgarelis[3], Haralampos M. Moutsopoulos[4] and **Clio Mavragani**[5], [1]Physiology,

Department of Physiology, School of Medicine, University of Athens, Athens, Greece, [2]Physiology, Department of Experimental Physiology, School of Medicine, National Kapodistrian University of Athens, Athens, Greece, [3]Pathophysiology, Department of Pathophysiology, Medical School of Athens, Athens, Greece, [4]Department of Pathophysiology, Medical School of Athens, Department of Pathophysiology, Athens, Greece, [5]Physiology, Department of Physiology, School of Medicine, National Kapodistrian University of Athens, Athens, Greece
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Background/Purpose:

Three prime Repair Exonuclease 1 (TREX-1) is an exonuclease involved in DNA repair preventing genomic instability. TREX-1 variants have been previously associated with activation of type I interferon (IFN) pathway in patients with Aicardi-Goutieres syndrome, as well as in Familial chilblain lupus. Primary Sjogren's syndrome (SS) -a chronic autoimmune disorder affecting the exocrine glands with a high predilection for B-cell lymphoma development- is also characterized by the presence of type I IFN signature in approximately half of affected individuals. The goal of the present study was to explore whether TREX-1 variants rs11797 (A>G, p.Y177Y), 5'UTR rs3135941 (C>T, NG_009820.1:g.5439T>C) and rs3135945 (intronic, G>A) polymorphisms could influence the risk of SS and SS related lymphoma.

Methods:

Three single nucleotide polymorphisms (SNPs) of the TREX-1 gene (rs11797, rs3135941 and the rs3135945) were evaluated in 229 SS-non lymphoma, 89 SS-lymphoma (19 non-MALT, 70 SS-MALT) and 240 healthy controls (HC) by PCR-based assays. All patients were followed in the Department of Pathophysiology, School of Medicine and the Department of Rheumatology, General Hospital of Athens between 2008-2014 and fulfilled the 2002 American/European criteria for the classification of primary SS. Allele and genotype frequencies in primary SS patients and HC were determined by SHEsis and SNPStats software.

Results:

No statistically significant differences were detected in the frequency of the above SNPs tested between SS-non lymphoma, SS-lymphoma patients and HC ($p>0.05$). However, SS non-MALT lymphoma patients had significantly increased prevalence of the SNP rs11797 G allele compared to HC (OR: 2.28, $p=0.02$). Of interest, the presence of the GC haplotype (rs11797 and rs3135941) conferred increased susceptibility for SS-non MALT lymphoma patients compared to both HC and SS-non lymphoma patients [OR 95% (CI): 2.33 (1.01-5.36), $p=0.04$ and 1.53 (1.02-2.28), $p=0.04$, respectively). The TREX-1 SNP rs3135945 was observed in 1/257 SS patients but not in the HC group.

Conclusion:

Increased frequency of the TREX-1 GC haplotype (rs11797 and rs3135941) in SS individuals complicated by non-MALT lymphoma may imply impaired DNA repair as an additional mechanism for SS-related lymphomagenesis.

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Abstract Number: 2792

Not Only Sjögren's Syndrome. EBV Infection Reactivation As a Risk Factor of the Dryness Symptome Development

Maria Maslinska[1] and Anna Zuk-Wasek[2], [1]Clinic of Early Arthritis, Institute of Rheumatology, Warsaw, Poland, [2]2. National Institute of Public Health – National Institute of Hygiene (NIPH – NIH, Warsaw, Poland
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SESSION INFORMATION
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Background/Purpose:

The glandular cell apoptosis in Epstein-Barr virus (EBV) infection may play role in primary Sjögren's Syndorme (pSS) development, possibly causing progressive gland damage and dysfunction, reflected by the reduced secretion and classic clinical symptoms. The aim of the study was to investigate: (i) EBV infection status in healthy individuals and patients with confirmed pSS or isolated dryness symptoms; (ii) searching for differences in salivary gland imaging among these individuals.

Methods:

We evaluated 3 groups of individuals: (i) 58 patients with established diagnosis of pSS (mean age 52±15), that included 49 (84%) female (F) and 9 (16%) males (M); (ii) 36 subjects with symptoms of eye or/and mouth dryness [mean age 55±12; 34 (94%) F, 2 (6%) M] and (iii) 20 healthy volunteers [mean age 45±11; 15 (75%) F and 5(25%)M]. Profile of IgM/IgG antibodies specific to EBV proteins was determined by ELISA test, allowing indication of recent/past EBV infection or reactivation. Sjögren's specific antibodies A (SS-A) and B (SS-B), anti-nuclear antibodies (ANA), rheumatoid factor (RF) were also identified. The ocular tests included Schirmer test and corneal staining (fluorescein and lissamine green). In 93(88%) patients the salivary gland ultrasonography (SGUS) examination was performed. Differences between groups were analyzed using the χ2-square test (categorical variables) or U Mann-Whitney test (continuous variables). Statistical significance was set at $p<0.05$. The study was approved by Ethics Committee; subjects gave informed consent.

Results:

The majority of patients with pSS (n=44; 76%) had reactivation of EBV infection, with 11 (19%) having markers of past infection, 2 (3%) of primary infection, and only 1(2%) was without EBV exposure. By contrast, in healthy volunteers EBV reactivation was stated in 40% (n=8), past infection was found in 50%(n=10), one person (5%) had primary infection and another one was not exposed to EBV. The differences in EBV infection status between pSS and healthy control group were statistically significant (p-value >0,031). All patients with dryness symptoms without pSS, were exposed to EBV and 83%(n=30) had EBV reactivation, 11% (n=4) past infection, 6% (n=2) primary infection. There were no statistically significant differences between patients with pSS with EBV reactivation and ones with past EBV infection as to the presence of SS-A/SS-B antibodies or RF, the ocular test values or the degree of focus score in histopathological evaluation. Parenchymal heterogeneity was more frequent in pSS group than in patients with symptoms of dryness alone: 77% vs 23% (p<0,001). There was no change in SGUS allowing differentiation of patients with EBV infection or reactivation.

Conclusion:

EBV reactivation is significantly more often observed in individuals with pSS or dryness symptoms, than in healthy volunteers. There were no differences in SGUS in patients with past exposure or reactivation of EBV. SGUS of pSS patients confirmed previous observations of parenchymal heterogeneity as most common abnormality.

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Abstract Number: 2793

IL35 Serum Level Is Decreased in Patients with Primary Sjogren Syndrome, Essentially in Patients with the More Active Disease Data from the French Prospective Assess Cohort

Olivier Fogel[1], Raphaèle Seror[2], Gaetane Nocturne[3], Elodie Rivière[4], Saida Boudaoud[5], Jacques Gottenberg[6], Véronique Le Guern[7], Xavier Mariette[8], Jean-Jacques Dubost[9] and Corinne Miceli-Richard[10], [1]INSERM U1012, Paris Sud University, Le Kremlin Bicêtre, France, [2]Rheumatology, AP-HP Bicêtre Hospital / Paris-Sud University, Le Kremlin-Bicêtre, France, [3]INSERM U1012, Université Paris Sud, Le Kremlin Bicêtre, France, [4]Unité INSERM 1184 Université Paris Sud, le Kremlin Bicetre, France, [5]INSERM U1012 - Université Paris XI, Le Kremlin Bicêtre, France, [6]Hautepierre, Strasbourg, France, [7]National Referral Center for Rare Systemic Autoimmune Diseases, Hôpital Cochin, AP–HP, Université Paris Descartes, Paris, France, [8]Université Paris-Sud, AP-HP, Hôpitaux Universitaires Paris-Sud, Paris, France, [9]Rheumatology department CHU Clermont-Ferrand, Clermont-Ferrand, France, [10]Rheumatology, Hôpitaux Paris Sud & INSERM U1184, Le Kremlin Bicêtre, France

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Background/Purpose: Primary Sjögren's Syndrome (pSS) is an autoimmune disease mediated by B-cells as evidenced by the occurrence of non-Hodgkin lymphoma and increased B-cell markers in salivary glands and serum of pSS patients. Interleukin 35 (IL35) is a new anti-inflammatory and immunosuppressive cytokine secreted by B-regulatory cells that could play a major role in controlling autoimmune diseases. We decided to study the link between IL35 and disease activity in pSS patients.

Methods: IL35 serum level was quantified using an ELISA kit (BioLegend®) on 385 patients from the French multicentric pSS ASSESS cohort and 50 healthy controls. The difference in IL35 serum level between patients and controls was assessed using a Mann Whitney test. The association between IL35 level and several subsets of patients was assessed using a chi-square test. IL35 high level has been defined as the upper quarter of cytokine level in ASSESS cohort.

Results: IL35 serum level was significantly decreased in pSS patients compared to healthy controls (p=0.0001, mean 7.31 [5.75-8.82] ng/ml and 8.66 [4.45-12.86] ng/ml, respectively). Within the cohort, we observed a higher proportion of patients with low disease activity defined by an ESSDAI score <5 in the group with high level of IL35 compared to those with low level of IL35 (72% and 60%, respectively; p=0.05). We observed that 99% of patients with high serum levels of IL35 did not developed lymphoma *versus*93% in the group with low IL35 (p=0.03).

Conclusion: This study suggests that the level of the immunosuppressive cytokine IL35, usually secreted by regulatory B cells and plasma cells, is decreased in the serum of patients with pSS and essentially in patients with the more active disease. Further studies in pSS on regulatory B cells and plasma cells as well as in animal models of autoimmune diseases assessing the effect of recombinant IL35, would help to decipher whether this regulatory cytokine could be of interest for future therapeutic approaches.

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Abstract Number: 2794

A New Scoring System for Ultrasonographic Evaluation of Salivary Gland in Sjogren: Multireader Reliability

Sandrine Jousse-Joulin[1], Malin V. Jonsson[2], Nicoletta Luciano[3], Elke Theander[4], Vera Milic[5], Alojzija Hocevar[6], Jacqueline Brown[7], Andrew Carr[8], Divi Cornec[9], Marina Carotti[10], Benjamin A. Fisher[11], Joel Fradin[12], John Rout[13], Alain Saraux[14], Alja Stel[15], Arjan Vissink[16], Simon Bowman[17], Alan N. Baer[18], Matija Tomšič[6], Wan-Fai Ng[19], Chiara Baldini[3] and Valerie Devauchelle[20], [1]Rheumatology, CHu La cavle Blanche, Brest, France, [2]Department of Clinical Dentistry, Section for Oral and Maxillofacial Radiology,, University of Bergen, Bergen, Norway, [3]Rheumatology Unit, University of Pisa, Italy, Pisa, Italy, [4]Skåne University Hospital Malmö, Lund University, Malmo, Sweden, [5]rheumatology, belgrade university, belgrade, Serbia, [6]Department of Rheumatology, University Medical Centre Ljubljana, Ljubljana, Slovenia, [7]dental division, Tower Wing Guy's hospital, london, United Kingdom, [8]departement of radiology, University of Newcastle, New castle, United Kingdom, [9]Department of rheumatology, Brest Occidentale University, Brest, France, [10]Istituto di Radiologia, Ospedali Riuniti di Ancona, Ancona, Italy, [11]Kennedy Institute of Rheumatology, Imperial College London, London, United Kingdom, [12]Department of Radiology and Radiological Science, Johns Hopkins University School of Medicine, Baltimore, MD, [13]Birmingham Dental Hospital, Birmingham, United Kingdom, [14]Rheumatology Department, CHU de la Cavale Blanche, Brest Cedex, France, [15]Hanzeplein 1, University Medical Center Groningen, University of Groningen, Groningen, Netherlands, [16]Department of Oral and Maxillofacial Surgery, University of Groningen, University Medical Center Groningen, Groningen, Netherlands, [17]Rheumatology Dept, University Hospital Birmingham, Birmingham, United Kingdom, [18]Division of Rheumatology, Johns Hopkins University School of Medicine, Baltimore, MD, [19]Institute of Cellular Medicine, Newcastle University, Newcastle upon Tyne, United Kingdom, [20]Service de Rhumatologie, CHU Brest, Brest, France

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SESSION INFORMATION

Session Title: Sjögren's Syndrome: Translational Insights into Sjögren's Syndrome

Session Type: ACR Poster Session C

Background/Purpose: A new consensual scoring system for Ultrasonography (US) of the salivary gland in pSS is required and endorsed by an international group of experts (US-pSS Study group).

The objectives were to define and validate relevant ultrasonographic components of the salivary glands in Sjogren.

Methods: A consensus exercise about definitions of the different ultrasonographic components of the salivary glands was done and discussed between experts on the field of US pSS during 2 annual meetings. Using these preliminary definitions, a reliability exercice was done on static images (60 images of both parotid and submandibular glands were read twice). Then an interreliability exercise was performed by a group of 5 experts with acquisition on 20 pSS patients. On this basis, we selected the most relevant US components, to build the new US-pSS score

Results: Eight different components evaluating the abnormal parenchyma of salivary glands were defined (echogenicity, homogenicity, presence or absence of hyperechoic bands, number of hypoechoic ares, and location of hypoechoic areas, lymph nodes, presence or absence of calcifications, visualisation of posterior border) in Sjögren. Concerning reliabilities, the web exercise demonstrated good inter and intra observers agreements applying these definitions on US parotid gland and submandibular glands (table 1) particularly in taking homogeneity as the principal important item in this definition. In contrast posterior border or presence of calcification had low agreement. The inter reliability exercice on pSS patients showed good kappa values concerning parotids glands but very low for submandibular glands

Conclusion: This is the first consensus-based US definitions on salivary glands and its elementary components. These results of the reliability exercice on static images showed good results and permit to apply these preliminary definitions on pSS patients with good results in parotids glands. With these results, a new US score could be assessed and used in routine practice

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Abstract Number: 2795

Fatigue in Primary Sjögren's Syndrome: Clinical, Laboratory, Psychometric and Biological Associations

Theofanis Karageorgas[1], Sofia Fragkioudaki[2], Adrianos Nezos[3], Dimitris Karaiskos[4], **Clio Mavragani**[5] and Haralampos M. Moutsopoulos[6], [1]Clinical Immunology and Rheumatology, "Attikon" University Hospital of Athens, Athens, Greece, [2]Physiology, Medical School of Athens, Department of Physiology, Athens, Greece, [3]Physiology, Department of Experimental Physiology, School of Medicine, National Kapodistrian University of Athens, Athens, Greece, [4]Physiology, School of Medicine, University of Athens, Athens, Greece, Athens, Greece, [5]Physiology, Department of Physiology, School of Medicine, National Kapodistrian University of Athens, Athens, Greece, [6]Department of Pathophysiology, Medical School of Athens, Department of Pathophysiology, Athens, Greece
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SESSION INFORMATION
Session Title: Sjögren's Syndrome: Translational Insights into Sjögren's Syndrome
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Background/Purpose: To identify independent predictors of fatigue in primary Sjogren's Syndrome (pSS) patients taking into account clinical, laboratory and psychological features and to explore the potential role of interferon (IFN)-induced gene indoleamine 2,3-dioxygenase (IDO-1), anti-21 hydroxylase [anti-21(OH)] antibodies and soluble B-cell activating factor (sBAFF).

Methods: Detailed clinical and laboratory characteristics were recorded for 106 pSS patients. FACIT-F, Zung Depression Scale, State-Trait Anxiety Inventory, Eysenck Personality Questionnaire Scale and Athens Insomnia Scale were adopted to assess fatigue, depression, anxiety and sleep disturbances respectively. Peripheral whole blood expression levels of IDO-1, as well as type I and II IFN-induced genes were calculated using qRT-PCR. Serum anti-21(OH) antibodies and sBAFF levels were determined by a radioimmunoassay and an ELISA, respectively. Univariate and multivariate models were performed to identify determinants of fatigue.

Results: Fatigue was detected in 32 out of 106 (30.2%) of pSS patients. In univariate analysis, fatigue was associated with arthralgias/myalgias, hydroxychloroquine therapy, both state and trait anxiety scores, depression and neuroticism, as well as impaired sleep patterns. Multivariate analysis revealed neuroticism [OR=6.0 (95%CI:1.5-23.8)], depression [OR=3.4 (95%CI:1.0-12.2)] and state anxiety [OR=3.0 (95%CI:0.9-10.6), as independent predictors of fatigue. sBAFF levels, anti-21(OH) autoantibodies and IDO-1 mRNA expression did not significantly differ between fatigued and non-fatigued pSS patients.

Conclusion: Depression, anxiety and neuroticism play a major role in pSS-associated fatigue and should be addressed, in clinical practice, with active collaboration between rheumatologists and mental health professionals. Further studies are warranted in order to

explore underlying pathophysiological pathways that might explain fatigue in the setting of pSS.

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Elevated Serum Immunoglobulin G Is a Prognostic Factor for Progression of Interstitial Lung Disease in Primary Sjögren's Syndrome

Eriko Ishioka[1], Katsuya Suzuki[2], Naoshi Nishina[2], Hidekata Yasuoka[3], Kunihiro Yamaoka[2] and Tsutomu Takeuchi[2], [1]Division of Rheumatology, Department of Internal medicine, Keio University School of Medicine, Tokyo, Japan, [2]Division of Rheumatology, Department of Internal Medicine, Keio University School of Medicine, Tokyo, Japan, [3]Division of Rheumatology, Keio University School of Medicine, Tokyo, Japan

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Background/Purpose: Lung involvement is a systemic manifestation of primary Sjögren's syndrome (pSS), however, the prevalence in pSS is various (9-75 %) and details are still unclear. In addition, interstitial lung disease (ILD) associated with pSS shows several radiographic patterns such as nonspecific interstitial pneumonia (NSIP) and usual interstitial pneumonia (UIP). Although UIP pattern is known as a prognostic determinant in idiopathic interstitial pneumonia, risk factors for progression of ILD in pSS has not been established.The aim of this study is to investigate clinical features of lung involvement in pSS and prognostic factors for exacerbation of pSS-ILD.

Methods: Total 300 consecutive patients with pSS diagnosed according to the 1999 revised Japanese criteria for the diagnosis of pSS, between January 2012 and September 2014 at our division were enrolled after exclusion of secondary SS. Clinico-radiographic characteristics were retrospectively investigated and statistically analyzed. ILD progression was defined by exacerbation on chest computed tomography (CT) image or pulmonary function test.

Results: To screen lung involvements, chest X-ray was underwent in 239 patients and chest CT was evaluated in 111 patients. Lung involvements were confirmed in 31.4%. Mean age was 68.5 years old. This included ILD (n=23, 9.6%), chronic airway lesion (n=11, 4.6 %), cystic lesion (n=3, 1.3 %), and malignant lymphoma (n=3, 1.3 %). Notably, the prevalence of smoking history (≥10 cigarettes per day, p=0.03), and elderly (≥65 years old, p<0.01) were higher in pSS with lung involvement than pSS without lung involvement. Radiological patterns of 23 pSS-ILD were followings: 17 for NSIP (73.9%), 5 for UIP (21.7%) and 1 OP (4.35%). 9 were progressive and 17 were stable during observation periods. Comparing ILD progressive group with stable group, serum immunoglobulin (Ig) G were significantly elevated (2263 +/- 479 vs 1726 +/- 519 mg/dl, p=0.02) and ESSDAI was higher (10.8 +/- 1.9 vs 6.1 +/- 1.3, p<0.01).There was no significant difference in the extent of reticular abnormality, ground glass attenuation, consolidation, and micronodules between two groups. On the other hand, UIP patterns having honeycombing were significantly higher in ILD-progressive group (p=0.04). Remarkably, serum IgG levels were significantly elevated in the progressive case with UIP pattern (p=0.02), but not with NSIP pattern.

Conclusion: This study demonstrated that serum IgG levels was elevated in progressive group in pSS-ILD and a prognostic factor particularly in pSS-ILD patients with UIP pattern. In the pSS patients with UIP pattern and serum IgG elevation, careful observation should be needed for appropriate management of ILD.

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factor-for-progression-of-interstitial-lung-disease-in-primary-sjogrens-syndrome

Abstract Number: 2797

Identification of Serum Biomarker for the Glandular Dysfunction of Primary Sjögren's Syndrome

Ayumi Nishikawa[1], Katsuya Suzuki[1], Yoshiaki Kassai[2], Yuumi Gotou[3], Takahiro Miyazaki[4], Maiko Takiguchi[4], Rimpei Morita[5], Akihiko Yoshimura[5] and Tsutomu Takeuchi[1], [1]Division of Rheumatology, Department of Internal Medicine, Keio University School of Medicine, Tokyo, Japan, [2]Takeda Pharmaceutical Company, Fujisawa, Japan, [3]Inflammation Drug Discovery Unit, Pharmaceutical Research Division, Takeda Pharmaceutical Company Limited, Tokyo, Tokyo, Japan, [4]Inflammation Drug Discovery Unit, Pharmaceutical Research Division, Takeda Pharmaceutical Company Ltd., Kanagawa, Japan, [5]Department of Microbiology and Immunology, Keio University School of Medicine, Tokyo, Japan

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SESSION INFORMATION

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Background/Purpose: Primary Sjögren's syndrome (pSS) is a systemic autoimmune disease characterized by dry eye and mouth. Measurements of un-stimulated salivary flow and Schirmer's test are classically used as assessment of salivary and lachrymal gland dysfunction. However, these tests tend to be easily affected by environmental and psychological factors, and thus development of more stable and effective surrogate marker has been strongly desired for the objective evaluation in the clinical setting. In this study, we investigated novel serum protein biomarkers for the salivary dysfunction of pSS patients.

Methods: Serum protein concentrations were measured by comprehensive high throughput proteomics assay (SOMAscan™). Candidate biomarkers positively correlated with glandular dysfunction of pSS patients were statistically analyzed. As objective indicators represents glandular dysfunction, uptake and excretion rate (%) of parotid gland (PG), submandibular gland (SMG) examined by 99m Tc schintigraphy and Greenspan's grade score, and other clinical information were also applied to the study.

Results: A total of 1128 serum proteins in 30 pSS and 30 untreated rheumatoid arthritis (RA) patients, and 30 healthy controls were comprehensively screened using SOMAscan™. We first screened differentially up- and down-regulated proteins among the three groups, 55 proteins were statistically extracted ($p<0.05$ in the U-test, and fold change ≥ 1.2 or ≤ 0.83). To then extract biomarker for the glandular dysfunction, the correlation between protein levels and data of schintigraphy or lip biopsy in pSS patients. Next, we calculated association 55 up-regulated proteins in pSS with intake and excretion rate. Finally, we identified that LAG3, TNF-R2, LKHA4, MMP-12, granzyme A, β2-microglobulin, HCG, PF-4 were negatively correlated with intake and excretion rate of salivary gland scintigraphy. Greenspan's grade was positively correlated with β2-microglobulin, MCP-3, EPHB2, CCL28, and TRAIL-R4.

Conclusion: We successfully identified novel serum proteins associated with salivary dysfunction of pSS. These proteins may be potential therapeutic targets for salivary dysfunction.

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Abstract Number: 2798

Increased Frequency of the PTPN22W* Variant in Primary Sjögren's Syndrome-Association with Low Type I IFN Scores in Peripheral Blood

Nikolaos Vlachogiannis[1], Eliona Gkioka[2], Adrianos Nezos[3] and **Clio Mavragani**[4], [1]Physiology, Department of Physiology, School of Medicine, National Kapodistrian University of Athens, Athens, Greece, Athens, Greece, [2]Physiology, Department of Experimental

Physiology, School of Medicine, National Kapodistrian University of Athens, Athens, Greece, Athens, Greece, [3]Physiology, Department of Experimental Physiology, School of Medicine, National Kapodistrian University of Athens, Athens, Greece, [4]Physiology, Department of Physiology, School of Medicine, National Kapodistrian University of Athens, Athens, Greece
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SESSION INFORMATION

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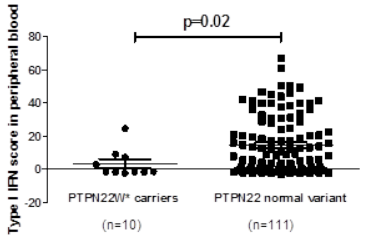
Background/Purpose: Protein tyrosine phosphatase non-receptor 22 (PTPN22) gene encodes a protein tyrosine phosphatase previously shown to inhibit antigen-receptor signaling in T cells and promoting type I interferon (IFN) production by myeloid cells. PTPN22W* represents a single nucleotide polymorphism (SNP), namely C1858T (rs 2476601), which has been previously shown to increase susceptibility of various autoimmune diseases including Type 1 Diabetes, SLE and RA. In regard to Sjögren's Syndrome (SS), available data so far is rather inconclusive. SS is a chronic autoimmune disease, with a prominent peripheral type I IFN signature in approximately half of patients. In the present study, we sought to explore whether the PTPN22W* risk variant would influence the risk of primary SS in a Greek population and investigate potential associations with clinical, laboratory features as well as type I IFN scores in peripheral blood.

Methods: PTPN22W* was identified with Real-Time PCR by TaqMan SNP genotyping assay in peripheral blood DNA samples derived from 326 patients with primary SS (91 SS-lymphoma and 235 SS non-lymphoma) according to the 2002 revised version of the European criteria proposed by the American-European Consensus Group, as well as from 448 unrelated healthy controls (HC) of similar age and sex distribution. Available peripheral blood from 121 SS patients was subjected to Real-Time PCR for 3 interferon inducible genes (IFIGs) preferentially induced by type I IFN and a type I IFN score was determined. Clinical characteristics, demographics and laboratory parameters were analyzed for possible associations with PTPN22W* using SPSS 21.0.

Results: Increased prevalence of the PTPN22W* variant was detected in primary SS population compared to HC [32/326, 9.8% vs 21/448, 4.7%, OR 95% (CI): 2.2 (1.3-3.9), p-value: 0.006]. Of interest, the presence of the PTPN22W* variant was associated with lower type I IFN scores in peripheral blood (Figure 1). After we stratified primary SS patients into low and hi IFN subgroups, the corresponding frequencies were 12.7% and 3.4%, respectively. PTPN22W* carriers had a 3-fold increased risk for low-IFN SS development compared to HC [OR 95% (CI): 3.0 (1.2-7.0), p=0.01]. No association with autoantibody status or presence of lymphoma was observed.

Conclusion: PTPN22W* may be involved in SS genetic predisposition implying an additional shared etiological origin in autoimmune disorders. Association of PTPN22W* with low IFN scores in peripheral blood of SS patients provides further evidence of the role of genetic contributors as determinants of distinct IFN patterns in patients with autoimmune diseases.

Figure 1



Disclosure: N. Vlachogiannis, None; **E. Gkioka**, None; **A. Nezos**, None; **C. Mavragani**, None.

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Abstract Number: 2799

Varicella Zoster Reactivation in Patients with Primary Sjögren's Syndrome and SLE

Eliza F. Chakarvarty[1], Jacy Odell[2], Astrid Rasmussen[3], Kathy L. Sivils[2], Joel M. Guthridge[2] and Judith A. James[4], [1]Arthritis and Clinical Immunology, Oklahoma Medical Research Foundation, Oklahoma City, CA, [2]Arthritis and Clinical Immunology, Oklahoma Medical Research Foundation, Oklahoma City, OK, [3]Arthritis and Clinical Immunology Research Program, Oklahoma Medical Research Foundation, Oklahoma City, OK, [4]Arthritis and Clinical Immunology, University of Oklahoma Health Sciences Center and

Oklahoma Medical Research Foundation, Oklahoma City, OK
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Background/Purpose: Increasing data has suggested that individuals with systemic lupus (SLE) are at increased risk of herpes zoster (HZ) reactivation compared to healthy controls and patients with rheumatoid arthritis, although the immunological basis of increased risk remains unknown. Primary Sjogren's syndrome (PSS) shares several immunologic abberations with SLE, but disease manifestations are often less severe and are less likely to be treated with immunosuppression: risks of HZ in this population has remained unstudied.

Methods: We mailed a single-page self-completing questionnaire to participants of 3 established Oklahoma Cohorts: the Oklahoma Lupus Cohort, the Sjogren's Research Cohort, and the Oklahoma Community Engagement Cohort (individuals without autoimmune diseases recruited to serve as control subjects). Questionnaires covered questions about recall of chicken pox infection, HZ reactivation, complications, and therapy, as well as receipt of the Zostavax vaccine. Stored blood samples from respondents were analyzed for cytokines using the xMAP bead assays for 12 cytokines from eBiosciences using a Bio-Rad Bioplex 200 system and BLyS levels were assessed by ELISA to identify cytokines that may be associated with HZ susceptibility.

Results: Completed questionnaires were returned from 635 participants: 350 healthy controls (HC), 163 with PSS and 122 with SLE. The mean age of respondents was 53 years, and the majority were Caucasian women. Fewer than 20% of HC reported HZ reactivation, compared to 30.7% of PSS and 36.4% of SLE subjects. The mean age at development of first HZ episode was 10 years younger for SLE than for PSS or HC (39 vs 49 years, $p<0.001$). Although many cytokine concentrations were higher in SLE than PSS or HC, these differences were not statistically significant (Table 1). Multivariate logistic regression found the Odds Ratio for HZ was 1.03 (95% CI 1.02-1.05) for each year of age, 1.8 (95% CI1.2-2.8) for PSS, and 2.7 (1.7-4.3) for SLE. Ro positivity, but not age, was associated with HZ in SLE patients; both age and anti-Ro status were relevant in pSS. Among SLE patients, Ro positivity was predictive of earlier age of HZ; this was not seen for pSS. Tested cytokines were not associated with development of HZ.

Conclusion: Subjects with PSS have increased rates of HZ compared to healthy individuals, although less so and at older ages than SLE patients. Ro seropositivity, but not cytokines, was associated with development of HZ in both SLE and pSS.

Table 1: Characteristics and cytokine levels of Respondents by Disease Group

Variable	Healthy	Sjogrens	SLE
n	350	163	122
age	52.2 (12.0)	56.7 (12.6)	50.0 (13.0)
%female	81.7	94.5	94.2
%Caucasian	86.6	91.4	73.8
% recall Chicken Pox	93.9	96.7	94.7
% Shingles *	18.4	30.7	36.4
Age at Shingles	49.5 (15.5)	49.9 (17.2)	39.6 (11.8)*
% Vaccinated (age>50)	28.9	28.3	13.6**
% Ro+	-	55	37
BLyS (pg/mL)	789 (329)	1071 (454)	1015 (706)
MIP-1beta	0.64 (0.69)	1.52 (2.51)	2.00 (6.48)
E-selectin	0.32 (0.31)	0.18 (0.26)	0.43 (0.31)
CxCL-13	3.37 (7.58)	2.99 (4.88)	10.18 (16.62)
IFN-alpha	1.72 (3.00)	1.84 (4.99)	2.82 (6.88)
Il-1alpha	1.41 (3.17)	3.30 (7.07)	3.53 (10.81)
IP-10	1.00 (1.12)	0.88 (1.35)	2.29 (4.34)
IFN-gamma	2.75 (4.18)	3.51 (8.52)	3.59 (7.38)

*P <0.001
**p<0.05

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Abstract Number: 2800

Bone Microarchitecture and Bone Strength in Patients with Primary Sjögren's Syndrome: A Case-Control Study Using HR-pQCT

Sandra Gofinet Pasoto[1], Kristopherson Lustosa Augusto[1], Jackeline Couto Alvarenga[2], Liliam Takayama[1], Valéria Caparbo[3], Ricardo M. Oliveira[4], Eloisa Bonfá[1] and Rosa M R Pereira[1], [1]Rheumatology Division, Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil, [2]Division of Rheumatology, Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil, [3]Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil, [4]RDO Diagnósticos Médicos, São Paulo, Brazil
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Background/Purpose: To evaluate bone mineral density (BMD), microarchitecture, strength and prevalence of vertebral fractures (VF) in primary Sjögren's syndrome (pSS).

Methods:

We evaluated 71 female pSS patients and 71 healthy age-, race-matched women. In this case-control study, demographic and clinical data including the risk factors for osteoporosis (OP)/fragility fractures were collected through a standardized protocol. BMD and VF were analyzed by dual-energy X-ray absorptiometry (DXA). Bone microarchitecture was assessed by high-resolution peripheral quantitative computed tomography (HR-pQCT) at radius and tibia.

Results:

Patients and controls had comparable age, body mass index, daily calcium intake, smoking, menopausal status and family history of hip fracture ($p>0.05$). OP/low BMD for age (33.8% vs. 5.6%, $p<0.0001$) and FV (19.7% vs. 5.6%, $p=0.043$) were more frequent in patients than controls. In addition, HR-pQCT showed deterioration of cortical and trabecular microarchitecture components and strength at radius, and a deficit on cortical compartment at tibia ($p<0.05$) in pSS patients compared to controls. Further analysis revealed that prednisone use duration, and deterioration of bone microarchitecture on cortical and trabecular components and strength were significantly higher in pSS patients with OP/low BMD for age than pSS patients without OP/low BMD for age ($p<0.05$). Multivariate logistic regression analysis revealed that these alterations in bone microarchitecture and strength were independent factors associated with OP/low BMD for age ($p<0.05$). pSS patients with VF presented cortical bone deterioration (density and thickness) compared with pSS patients without VF ($p<0.05$).

Conclusion: This study shows increased frequencies of OP and VF associated with cortical and trabecular bone microarchitecture and strength deterioration in pSS. The identification that cortical deterioration is the most important abnormality detected by HR-pQCT in patients with VF suggests that this parameter may be involved in pathogenesis of VF in pSS.

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Abstract Number: 2801

Tofacitinib Suppresses Lymphocytic Infiltration in the Salivary Gland of Non-Obese Diabetic Mice; The Animal Model of Sjögren's Syndrome

Jennifer Lee[1], Ji Yeon Lee[2], Jung Hee Koh[3], Min Kyung Chung[4], Ji Hun Kim[1], Seung-Ki Kwok[5], Ji Hyeon Ju[2] and Sung-Hwan Park[6], [1]Division of Rheumatology, Department of Internal Medicine, College of Medicine, Seoul St. Mary's Hospital, The Catholic University of Korea, Seoul, South Korea, [2]Division of Rheumatology, Department of Internal Medicine, College of Medicine, The Catholic University of Korea, Seoul, South Korea, [3]Division of Rheumatology, Department of Internal Medicine, School of Medicine, The Catholic University of Korea, Seoul St. Mary's Hospital, Seoul, South Korea, [4]Division of Rheumatology, Department of Internal Medicine, School of Medicine, The Catholic University of Korea, Seoul St. Mary's Hospital, Seoul, South Korea, [5]seungki73@catholic.ac.kr, Division of Rheumatology, Department of Internal Medicine, College of Medicine, The Catholic University of Korea, Seoul, South Korea, [6]Division of Rheumatology, Department of Internal Medicine, Seoul St. Mary's Hospital, Seoul, South

Korea
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Background/Purpose: Interferon signatures are upregulated in patients with primary Sjogren's syndrome (pSS) and interferons are considered to have a pathogenic role in pSS. As Janus kinase (JAK) mediates interferon signaling pathway, we investigated whether tofacitinib would ameliorate disease-related parameters in non-obese diabetic (NOD) mice, the animal model SS.

Methods: Tofacitinib (1.5mg/kg or 15mg/kg) or vehicle (10% DMSO) was intraperitoneally injected twice per week from 8 weeks after birth. Salivary flow rate (SFR) and serum level of immunoglobulin(Ig) were addressed on 8 weeks, 12 weeks and 16 weeks. Histologic analysis was performed on 16 weeks. Various T and B cell subpopulations were evaluated using FACS and RT PCR with *ex vivo* splenocytes and cervical lymph node cells.

Results: The SFR of NOD mice all three groups decreased over time. On 16 weeks, the salivary flow rates of tofacitinib-treated mice were higher than those of controls. Serum level of IgM was also lower in tofacitinib-treated mice on 16 weeks. Histologic evaluation of the salivary gland revealed that the lymphocytic infiltration of salivary gland was markedly reduced in the mice treated with tofacitinib. Tofacitinib suppressed Th1 differentiation *in vitro* and the expression of B cell activation markers (Bcl-6, AID) was lower in ex vivo B cells of tofacitinib-treated mice compared with controls.

Conclusion: Tofacitinib suppressed lymphocytic infiltration in the salivary gland of NOD mice, which suggests the therapeutic potential of tofacitinib in pSS.

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Abstract Number: 2802

Co-Occurence of Anti-Ro52/TRIM21 and Anti-TRIM38 Autoantibodies Is Associated with Higher Severity of Dry Eye in Sjögren's Syndrome

Nina Wolska[1], Paulina Rybakowska[1], Arkadiusz Klopocki[1], Michael Brown[1], Courtney G. Montgomery[2], Kiely Grundahl[1], Astrid Rasmussen[1], Robert Hal Scofield[3], Lida Radfar[4], Donald U Stone[5], Juan-Manuel Anaya[6,7], John Ice[2], Christopher Lessard[3], David M. Lewis[8], Nelson L. Rhodus[9], Raj Gopalakrishnan[10], Andrew Huang[11], Pamela J Hughes[12], Michael D. Rohrer[13], Michael Weismann[14], Swamy Venuturupalli[15], Joel M. Guthridge[3], Judith A. James[16], Kathy L. Sivils[3], Harini Bagavant[17], **Umesh S Deshmukh**[17] and , [1]Arthritis and Clinical Immunology Program, Oklahoma Medical Research Foundation, Oklahoma City, OK, [2]Arthritis and Clinical Immunology Research Program, Oklahoma Medical Research Foundation, Oklahoma City, OK, [3]Oklahoma Medical Research Foundation, Oklahoma City, OK, [4]University of Oklahoma Health Sciences Center, Oklahoma City, OK, [5]Dean McGee Eye Institute, Oklahoma City, OK, [6]Rheumatology, Center for Autoimmune Diseases Research (CREA), Rosario University, Bogotá, Colombia, [7]Cell Biol and Immunogenetics, CIB-Rosario University, Medellin, Colombia, [8]College of Dentistry, Department of Oral and Maxillofacial Pathology, University of Oklahoma Health Sciences Center, Oklahoma City, OK, [9]Department of Oral Surgery, University of Minnesota School of Dentistry, Minneapolis, MN, [10]Diagnostic and Biological Sciences, Division of Oral Pathology, University of Minnesota, Minneapolis, MN, [11]Washington University,, St Louis, MO, [12]Division of Oral and Maxillofacial Surgery, University of Minnesota, Minneapolis, MN, [13]Hard Tissue Research Laboratory, University of Minnesota School of Dentistry, Minneapolis, MN, [14]Cedars-Sinai Medical Center, Los Angeles, CA, [15]Cedars-Sinai Medical Center, West Hollywood, CA, [16]Arthritis & Clinical Immunology Research Program, Oklahoma Medical Research Foundation, Oklahoma City, OK, [17]Arthritis and Clinical Immunology, Oklahoma Medical Research Foundation, Oklahoma City, OK
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Session Type: ACR Poster Session C

Background/Purpose: Autoantibodies reactive with Ro52/TRIM21 are detected in almost 70% of primary Sjögren's syndrome (pSjS)

patients and their presence is associated with higher severity of the disease. However, anti-TRIM21 are also present in patients with systemic lupus erythematosus, dermatomyositis, primary biliary cirrhosis, and in mothers of children with congenital heart block. How immune responses to Ro52 exert pathogenic effects in such a diverse group of autoimmune disorders is not clear. TRIM21 belongs to a large and structurally conserved C-IV family of the tripartite motif containing (TRIM) proteins. Two other proteins within this family, TRIM38 and TRIM68, have been previously reported to be autoantigens in pSjS. This study investigates the hypothesis that auto-reactivity against multiple TRIM proteins is associated with the pathogenesis of pSjS. In this study, the frequency and clinical relevance of autoantibodies reactive with TRIM38 was investigated in pSjS patients.

Methods: Serum samples from pSjS patients (n=225) and controls (n=50) were analyzed for reactivity to *in vitro* transcribed and translated TRIM38 and TRIM21 proteins. The association of anti-TRIM38 with different clinical parameters of disease such as: anti-Ro/SSA, van Bijsterveld scores, Schirmer's test scores, minor labial salivary gland biopsy scores, and unstimulated whole saliva volume were evaluated. To analyze antibody cross-reactivity, affinity purified anti-TRIM38 antibodies were used to immunoprecipitate TRIM21. To analyze cross-reactivity at T cell epitope level, TRIM21 reactive T cell hybridomas generated in HLA-DR3 transgenic mice were used.

Results: TRIM38 reactive autoantibodies were detected in the sera of 24/225 pSjS patients and in 2/50 controls. The presence of anti-TRIM38 was significantly associated with the presence of anti-Ro/SSA. Almost 20% of anti-TRIM21 positive patients had anti-TRIM38 and all patients with anti-TRIM38 were positive for anti-TRIM21. Clinically, the co-occurrence of anti-TRIM38 and anti-TRIM21 was significantly associated with higher van Bijsterveld scores and reciprocally lower Schirmer's test scores. In contrast, anti-TRIM38 did not worsen the clinical measures of salivary gland disease. Despite the structural homology between TRIM38 and TRIM21, affinity purified anti-TRIM38 antibodies did not immunoprecipitate TRIM21. Interestingly, a T cell hybridoma reactive with $TRIM21_{300\text{-}312}$ peptide was stimulated by $TRIM38_{138\text{-}150}$ peptide.

Conclusion: Our data demonstrate that the co-occurrence of anti-TRIM38 and anti-TRIM21 is specifically associated with higher severity of dry eye in pSjS patients. Anti-TRIM38 is a distinct autoantibody specificity arising in a subset of pSjS patients and T cell cross-reactivity might be involved in the diversification of autoantibody responses from TRIM21 to TRIM38. Our data also suggests that the heterogeneity of clinical manifestations accompanying anti-TRIM21 in different rheumatic disorders might be associated with the co-existence of autoantibodies reactive with other TRIM proteins.

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Abstract Number: 2803

Systemic Interferon Type I and Type II Signatures Present in Distinct Subsets of Primary Sjögren's Syndrome: En Route Towards More Selective Targeting

Naomi I Maria[1], Cornelia G. van Helden-Meeuwsen[1], Eline C. Steenwijk[1], Arne S. IJpma[2], Zana Brkic[1], Paul L. van Daele[1,3], P. Martin van Hagen[1,3], Peter J. van der Spek[2], Hemmo A. Drexhage[1], Wan-Fai Ng[4] and Marjan A. Versnel[1], [1]Immunology, Erasmus Medical Center, Rotterdam, Netherlands, [2]Bioinformatics, Erasmus Medical Center, Rotterdam, Netherlands, [3]Internal Medicine, Erasmus Medical Center, Rotterdam, Netherlands, [4]Institute of Cellular Medicine, Newcastle University, Newcastle upon Tyne, United Kingdom

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SESSION INFORMATION

Session Title: Sjögren's Syndrome: Translational Insights into Sjögren's Syndrome

Session Type: ACR Poster Session C

Background/Purpose: Primary Sjögren's syndrome (pSS) is a systemic autoimmune disease with a large heterogeneity in clinical phenotype. The IFN type I signature is present in over half of PSS patients, associated with higher disease activity [Brkic Z. et al. Ann Rheum Dis 2013]. Novel evidence in pSS salivary glands indicates IFN activation to be also partly attributed to IFN type II [Hall J.C. *et al.* PNAS 2012]. Furthermore, a large modular analysis revealed distinct Type I and Type II IFN signatures related to disease severity in systemic lupus erythematosus (SLE) [Chiche L. *et al.* Arthritis Rheumatol 2014]. Increasing interest in development of therapeutic interventions to target the IFN signalling pathway is emerging. To date, clinical trials with anti-IFNα monoclonal antibodies in SLE have generated mixed results. Better understanding the molecular pathways causal to the IFN signature is essential for specific therapeutic targeting. Thus, identifying the pathways responsible for the sustained IFN overactivation in pSS could lead to a more

selective, targeted therapy. The aim of this study was to investigate the contribution of IFN type II, to the IFN signature in pSS.

Methods: Here we used previous findings from the modular transcriptional repertoire analysis described by Chiche *et al.*, the 3 IFN-annotated modules: M1.2=mild (predominantly IFNα), M3.4=moderate (predominantly IFNβ), and M5.15=strong (also IFNβ and IFNγ), in a class comparison to find overlapping genes in pSS. Differentially expressed genes were considered significant using a cut-off: $p<0.05$ and Fold change≥2. Whole blood mRNA expression of the top genes was validated in a cohort of 36 healthy controls (HC), and 55 pSS patients fulfilling the 2002 AE-criteria (stratified in 20 IFNnegative and 35 IFNpositive pSS).

Results: Class comparison analyses between pSS genome wide microarray data, and the genes annotated for the IFN modules M1.2, M3.4 and M5.12, revealed n=19 genes overlapping in M1.2, n=31 genes in M3.4 and n=10 genes in M5.12. For M1.2 most genes were already previously validated to determine the IFN type I signature, thus predominantly driven by IFNα (MxA ($p<0.0001$), IFI44L ($p<0.0001$), IFIT3 ($p<0.0001$) e.g.). Interesting genes validated for M3.4 were amongst others ZBP1 ($p<0.001$), GBP1 ($p<0.001$), PKR ($p<0.001$), IFIH1 ($p<0.0001$) and for M5.12 ISG20 ($p<0.01$), IFI16 ($p<0.001$) and TAP1 ($p<0.001$), all significantly upregulated in IFNpositive compared to HC and IFNnegative pSS. Similar to findings in SLE, only a subset of IFN type I positive pSS patients showed upregulation of M3.4 genes and an even smaller subset for M5.12 genes. We are currently assessing the relation of these findings to disease activity and other aspects of disease such as fatigue and depression. Data will be further validated using the gene expression data from the UK pSS registry (n=29 HC and n=133 pSS).

Conclusion: Here we find evidence for the presence of complex IFN signatures driven by IFN type I and IFN type II in pSS. Subtyping pSS patients according to distinct IFN signature modules might aid in more selective therapeutic targeting, as well as better disease monitoring and control.

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Abstract Number: 2804

The Global miRNA Whole Blood Profile of Ankylosing Spondylitis

Carolina Mejia Otero[1], Shervin Assassi[1], Michael H. Weisman[2], Michael M. Ward[3], Lianne S. Gensler[4], Matthew A. Brown[5], Minghua Wu[1], John Hagan[6], John D. Reveille[7] and Gloria Salazar[1], [1]Rheumatology, University of Texas Medical School at Houston, Houston, TX, [2]Rheumatology, Cedars-Sinai Medical Center, Los Angeles, CA, [3]NIH/NIAMS, Bethesda, MD, [4]Medicine/Rheumatology, University of California, San Francisco, San Francisco, CA, [5]The University of Queensland Diamantina Institute, Brisbane, Australia, [6]Neurosurgery, University of Texas at Houston, Houston, TX, [7]Internal Medicine/Rheumatology, University of Texas Medical School at Houston, Houston, TX

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SESSION INFORMATION

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Session Time: 9:00AM-11:00AM

Background/Purpose:

MicroRNA (miRNA) are small non-coding RNAs that play an important role in posttranscriptional gene regulation and their involvement in the pathophysiology of several autoimmune diseases has been proposed. The role of miRNA in Ankylosing spondylitis (AS) has not been well studied. Recent advances in quantitative polymerase chain reaction (qPCR) allow simultaneous measurement of hundreds of miRNAs. The objective of this study is to use this technology to identify differentially expressed whole blood miRNA in AS patients compared to healthy controls. We hypothesize that AS patients have a distinct whole blood miRNA profile that has potential predictive and pathophysiological significance.

Methods:

We investigated the miRNA profile in AS whole blood compared to controls using a multiplex qPCR platform. We obtained whole blood samples from 10 AS patients from the Prospective Study of Outcomes in Ankylosing Spondylitis (PSOAS) cohort and 10 age-, gender- and ethnicity matched unaffected controls. All patients met modified New York Criteria for AS. Blood was obtained at each study visit for disease activity, genetic markers.Total RNA was isolated using PAXgene blood miRNA kit and examined by Exiqon LNA-enhanced miRNA qPCR platforms. Levels of 752 miRNAs were determined. Patient and control sample miRNA levels were compared using univariate t-test at $p<0.05$. In this hypothesis generating study, a correction for multiple comparisons was not

performed.

Results:

Whole blood profiling of miRNA revealed a list of 20 miRNA with differential expression in AS patients (table 1). Interestingly the main finding was the high expression of miR-204-5p (12 fold higher than controls, *p 0.004*). This miRNA has been described particularly in the oncology literature (dysregulation was observed in colon, gastric and pancreatic cancer). Studies in this field show an important role as a regulator of autophagy pathways. Considering the recent discovery of the importance that autophagy pathways play in the pathophysiology of AS this miRNA might play an important role in the pathogenesis of AS.

Conclusion:

AS patients have a whole blood miRNA "signature" based on specific dysregulated miRNA compared to healthy controls. In our study, we found that there is a high expression of miR-204-5p in AS patients compared to controls and this could have implications in the pathophysiology of AS. MiRNA analysis of a larger study population is required to further characterize potential epigenetic factors that may have a role in AS susceptibility.

Table 1. Dysregulated miRNA in Ankylosing Spondylitis patients compared to healthy controls.

	miRNA	Location	Fold change	*p*
1	**miR-204-5p**	**9q21.12**	**12.45**	**0.004**
2	miR-432-3p	14q32.2	4.08	0.010
3	miR-513a-5p	xq27.3	0.75	0.014
4	miR-200c-3p	12p13.31	0.69	0.019
5	miR-373-5p	19q13.42	0.39	0.022
6	miR-654-5p	14q32.31	4.49	0.025
7	miR-28-3p	3q28	1.45	0.026
8	miR-1911-3p	xq23	2.76	0.027
9	miR-210	11p15.5	0.57	0.029
10	miR-141-3p	12p13.31	0.29	0.030
11	miR-421	xq13.2	0.75	0.030
12	miR-504	xq26.3	2.35	0.032
13	miR-340-5p	5q35.3	0.54	0.037
14	miR-187-3p	18q12.2	3.24	0.039
15	miR-875-3p	8q22.2	0.94	0.039
16	miR-595	7q36.3	0.68	0.042
17	miR-93-5p	7q22.1	0.57	0.044
18	miR-33b-5p	22q13.2	0.45	0.044
19	miR-638	19p13.2	0.51	0.045
20	miR-146a-3p	5q34	2.52	0.047

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Abstract Number: 2805

Enteric Flora in Newly Diagnosed Spondyloarthritis: A Collaborative Study

Matthew L. Stoll[1], Pamela F. Weiss[2], Jennifer E. Weiss[3], Peter A. Nigrovic[4], Marilynn G. Punaro[5], Charles H. Spencer[6], Kenneth N. Schikler[7], Casey D Morrow[8] and Elliot J. Lefkowitz[9], [1]University of Alabama at Birmingham, Birmingham, AL, [2]Rheumatology, Children's Hospital of Philadelphia, Philadelphia, PA, [3]Hackensack Univ Med Ctr, Hackensack, NJ, [4]Department of Medicine, Division of Rheumatology, Immunology and Allergy, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, [5]Texas Scottish Rite Hospital, Dallas, TX, [6]Rheumatology, Nationwide Childrens Hospital/OSU, Columbus, OH, [7]Pediatrics, University of Louisville, Louisville, KY, [8]Cell, Developmental, and Integrative Biology, University of Alabama at Birmingham, Birmingham, AL, [9]Microbiology, University of Alabama at Birmingham, Birmingham, AL

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Session Time: 9:00AM-11:00AM

Matthew L Stoll, Pamela F Weiss, Jennifer E Weiss, Peter A Nigrovic, Lynn Punaro, Charles Spencer, Ken Schikler, Casey Morrow, Elliot Lefkowitz

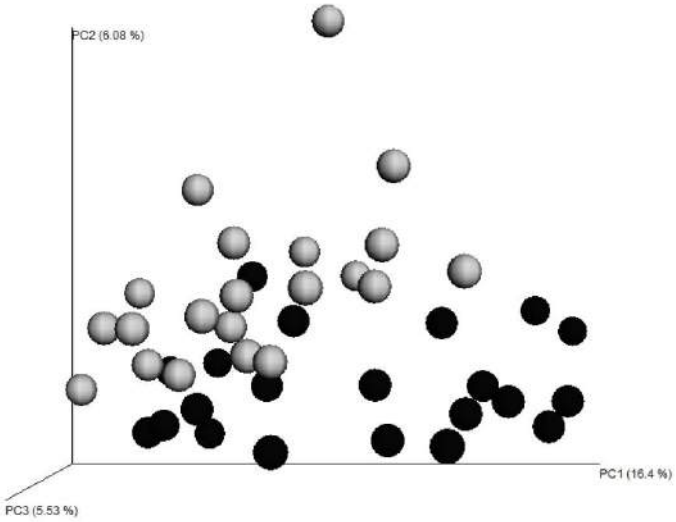
Enteric flora in newly diagnosed spondyloarthritis: a collaborative study

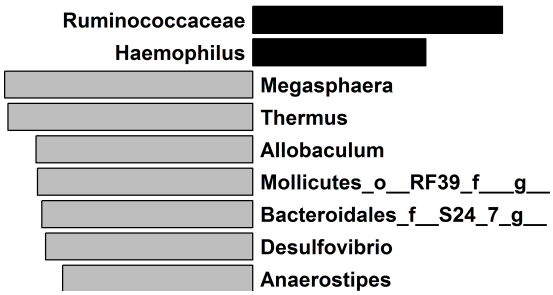
Background/Purpose: Spondyloarthritis (SpA) affects 1% of the population in the United States. We have previously shown altered microbiota in children with established as well as newly diagnosed juvenile SpA (enthesitis-related arthritis; ERA). A limitation of this study is that many of the subjects had been exposed to long-term immunosuppressive therapy. Thus, through the CARRA network, we designed a study in which newly diagnosed subjects with ERA from around the country submitted fecal specimens for assessment of baseline microbiota. We hypothesized that we would identify similar alterations in microbiota in these newly diagnosed ERA subjects.

Methods: This is a collaborative study with nine participating sites. At each site, subjects newly diagnosed with ERA and unexposed to systemic immunosuppressive therapy are enrolled. Each site also enrolls normal healthy controls. Stool specimens are collected at home and shipped overnight to the PI via commercial carrier. Purified DNA undergoes PCR amplification using primers designed to the conserved region flanking the variable IV region from the 16S rDNA gene. The PCR products are run on the MiSeq flowcell. Analysis is performed with the Quantitative Insight into Microbial Ecology (QIIME) suite, and taxonomic comparisons are performed with LEfSe.

Results: Nine sites agreed to participate in the study. So far, six sites have enrolled a total of 24 subjects, of whom 17 have submitted fecal specimens. Nine of them, along with 12 newly diagnosed ERA subjects from Childrens of Alabama and 21 controls matched for age and sex, underwent 16S sequencing. Preliminary analysis shows no obvious clustering from samples from different sites, supporting the validity of pooling their specimens; however, principal coordinates analysis revealed that there was substantial clustering by diagnosis (Figure 1). Diminished alpha diversity was observed among ERA patients, consistent with findings at the taxonomic level of decreases in a number of rare bacteria among this group (Figure 2.) This result is consistent with a recent study in adults with psoriatic arthritis.

Conclusion: Although we have not so far been able to replicate previous findings of decreased *F. prausnitzii* levels in ERA, our data does suggest that diminished microbial diversity may be part of disease pathogenesis.





Disclosure: M. L. Stoll, None; **P. F. Weiss**, None; **J. E. Weiss**, None; **P. A. Nigrovic**, None; **M. G. Punaro**, None; **C. H. Spencer**, None; **K. N. Schikler**, None; **C. D. Morrow**, None; **E. J. Lefkowitz**, None.

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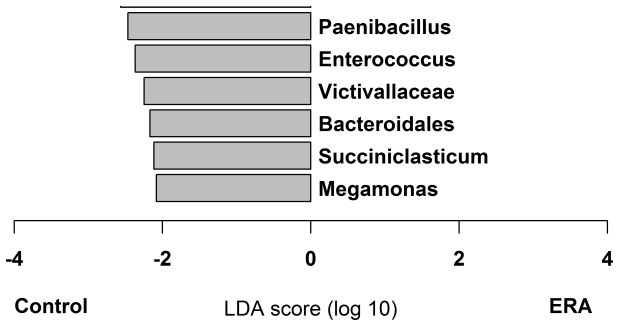
Abstract Number: 2806

Bacterial Skin Microbiome in Psoriatic Arthritis Ã¢â‚¬â€œ Pilot Data from Psoriatic Plaques on Dry Skin Sites from Patients with Psoriasis (PsC) and Psoriatic Arthritis (PsA)

Madhura Castelino[1], Stephen Eyre[2], Mauro Tutino[2], John Moat[3], Paul Martin[2], Umer Ijaz[4], Christopher Quince[5], Pauline Ho[1], Mathew Upton[6] and Anne Barton[1,7], [1]NIHR Manchester Musculoskeletal Biomedical Research Unit, Manchester Academic Health Science Centre, Manchester, United Kingdom, [2]Arthritis Research UK Centre for Genetics and Genomics, University of Manchester, Manchester,



United Kingdom, [3]Microbiology and Virology Unit, University of Manchester, Manchester, United Kingdom, [4]School of Engineering, University of Glasgow, Glasgow, United Kingdom, [5]Warwick Medical School, University of Warwick, Coventry, United Kingdom, [6]Plymouth University Peninsula Schools of Medicine and Dentistry, Plymouth, United Kingdom, [7]Arthritis Research UK Centre for Genetics and Genomics, Centre for Musculoskeletal Research, Manchester Academic Health Science Centre, The University Of Manchester, Manchester, United Kingdom

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Background/Purpose:

In complex traits like psoriasis (PsC) and psoriatic arthritis (PsA) interactions between genetics and environmental factors are thought to result in the development of disease. Among candidate environmental triggers, the microbial flora in immediate contact with the immune system at several sites, including the skin, are likely to be influential in disease. Topographical diversity exists in the microbial flora based on the skin niche: dry (extensor surfaces of the limbs), sebaceous (scalp, trunk) and moist (flexural surfaces), and bacterial microbiota differ in psoriatic plaques from normal skin. We present data for the bacterial microbiota in psoriatic plaques from the dry skin niche of individuals with psoriatic arthritis and psoriasis, to determine whether the bacterial microbiota are consistent both temporally and from different physical sites

Methods:

Twelve individuals with PsA and 9 individuals with plaque psoriasis were recruited from three centres in North West England, UK. Informed written consent was obtained; skin swabs from multiple psoriatic plaques on the extensor surfaces of the upper and/or lower limbs of each individual were collected and DNA extracted using the MoBio PowerSoil DNA Isolation Kit. The V3-V4 hypervariable region of the 16S rRNA gene was amplified. The samples were sequenced using the MiSeq. OTUs were generated using QIIME 1.6 after quality checks and chimera removal. The data was analysed using R 3.2.0.

Results:

Table 1. Baseline Demographics

Demographic variables	PsC (n=9)	PsA (n=12)
Age mean (range) yrs	48 (22-79)	56 (40-66)
Gender Female (%)	4 (44)	3 (25)
Duration of Psoriasis mean (median) yrs	20.3 (23)	21.7 (20.5)
Type 1 Psorasis (Age at onset <40yrs) (%)	7 (77)	7 (58)

39 skin samples comprising 25 samples from PsA and 14 from PsC individuals were available analysis. There was no significant difference in the alpha (Shannon) diversity index between the two groups (Wilcoxon rank sum test: W=163, p-value=0.7855).

The data was analysed using unweighted UniFrac for the principal co-ordinate analysis (PCoA) and the Bray-Curtis method for the Non-metric Multidimensional Scaling (NMDS). Samples from two time points for clinically stable individuals (n=3) clustered together, as did skin samples from the same individual taken from different dry sites (n=14).

Multivariate analysis using the Adonis method was carried out based on UniFrac and Bray-Curtis distance. Inter-individual differences accounted for most of the variance (>70%), regardless of PsA/PsC status ($p<0.001$; $F=3.4268$ and 5.7337; $R^2=0.76$ and 0.84). A statistically significant ($p<0.015$; $F=1.9237$;$R^2= 0.053$) difference was observed when samples were grouped for disease (PsA vs PsC) using the UniFrac metric but only explained ~5% of the variance.

Conclusion:

In our study, the skin microbiota from psoriatic plaques is consistent for the dry skin type regardless of the physical site and time of

sampling in clinically stable individuals. We found no significant differences in the bacterial skin microbiota from the dry skin plaques of individuals with PsA vs PsC.

Disclosure: M. Castelino, None; **S. Eyre**, None; **M. Tutino**, None; **J. Moat**, None; **P. Martin**, None; **U. Ijaz**, None; **C. Quince**, None; **P. Ho**, None; **M. Upton**, None; **A. Barton**, None.

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Abstract Number: 2807

Transcriptome Profiling of Synovium from Patients with Psoriatic Arthritis or Osteoarthritis Using RNA Sequencing Provides Insights into Disease Mechanisms Involved in Heterotopic Ossification with Potential Therapeutic Implications

Jennifer Belasco[1], Steven R. Goldring[2], Kelly McHugh[3], James G. Krueger[4], Areille Fein[2], Sandra Garcet[5], Mayte Suarez-Farinas[4], Lisa Mandl[6] and Yupu Liang[5], [1]Krueger Laboratory, Rockefeller University, New York, NY, [2]Hospital for Special Surgery, New York, NY, [3]Rheumatology, Hospital for Special Surgery, New York, NY, [4]Krueger Laboratory, The Rockefeller University, New York, NY, [5]The Rockefeller University, New York, NY, [6]Department of Rheumatology, Hospital for Special Surgery, New York, NY
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Session Time: 9:00AM-11:00AM

Background/Purpose: Up to 44% of patients undergoing total hip arthroplasty (THA) show radiographic evidence of heterotopic ossification (HO). Patients with psoriatic arthritis (PsA) and a subset of patients with osteoarthritis (OA) demonstrate an increased risk of HO after THA. The molecular and cellular mechanisms responsible for HO are poorly defined. We conducted a comprehensive genomic and molecular comparison of synovium taken from patients at the time of THA. We compared three groups of patients: osteoarthritis (OA) patients who had developed HO after a previous THA, OA patients who had not developed HO after a previous THA, and PsA patients undergoing a first THA.

Methods: Synovium samples were obtained at the time of THA from three groups: OA patients with previous HO after a primary THA (n= 7), or OA patients without HO (n=7) after a primary THA; and patients with PsA undergoing an initial THA (n=7). RNA-seq was performed to identify shared and differentially expressed genes (DEGs). DEGs were considered with a cut-off of fold change >2.0 and false discovery rate <0.05. Ingenuity Pathway Analysis (IPA) was utilized to identify canonical pathways among shared and DEGs.

Results: A comparison of PsA vs. OA and HO vs. OA transcripts revealed 631 differentially expressed genes unique to the PsA vs. OA group and 91 differentially expressed genes unique to the HO vs. OA group. 76 genes were shared between these groups. When PsA is directly compared to HO there are 386 shared genes. The top canonical pathways from IPA based on these shared genes include IL12 signaling and production in macrophages, 4-IBB signaling in T lymphocytes, Inhibition of angiogenesis by TSP1, Nitric oxide signaling in the cardiovascular system, Leptin signaling in obesity, BMP signaling pathway, and TGFβ signaling.

Conclusion: In this study we show similarities and differences in gene expression of synovium from patients with OA with HO, OA without HO, and PsA. To our knowledge, this is the first study to use RNA-seq to define the transcriptomes of synovium in these conditions. It is also the first study to compare these populations. Genes shared between HO and PsA might suggest a common bone anabolic pathway and direct future therapies for these conditions.

Disclosure: J. Belasco, None; **S. R. Goldring**, Fidia Farmaceutici, Janssen Pharmaceutical,BoneTherapeutics,Novartis, 5; **K. McHugh**, None; **J. G. Krueger**, None; **A. Fein**, None; **S. Garcet**, None; **M. Suarez-Farinas**, None; **L. Mandl**, Boehringer Ingelheim, 2; **Y. Liang**, None.

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Abstract Number: 2808

Genetic Variants at Chromosome 5q15 Associated with Immune-Mediated Diseases Influence Gene Expression and Isoform Profile of the Endoplasmic Reticulum Aminopeptidase

Aimee Hanson[1], Katelin Haynes[2], Gethin Thomas[2], Thomas Cuddihy[2], Paul Leo[2] and **Matthew A. Brown**[1], [1]The University of Queensland Diamantina Institute, Brisbane, Australia, [2]University of Queensland Diamantina Institute, Brisbane, Australia
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Session Time: 9:00AM-11:00AM

Background/Purpose: Polymorphisms in the endoplasmic reticulum aminopeptidase genes *ERAP1* and/or *ERAP2* are strongly associated with the diseases AS, psoriasis, IBD and Behcet's disease. Robust genetic interaction exists between *ERAP1* and the HLA Class I alleles HLA-B27 and –B40 (associated with AS), -Cw6 (in psoriasis), and -B*51 (in Behcet's disease). In AS, two *ERAP1* haplotypes are disease associated, tagged either by rs30187 (thought to be directly disease-associated) or rs10050860 (which lies on a disease-associated haplotype). Protective alleles of rs30187 are associated with reduced peptidase activity. We hypothesized that other AS-associated *ERAP1* and *ERAP2* genetic variants would also either lead to reduced function or expression of the respective gene.

Methods: RNA sequencing was performed on PBMC derived total RNA from 54 AS cases and 70 healthy controls. This data was analysed to investigate the gene and isoform expression profiles of *ERAP1* and *ERAP2*. The consequences of *ERAP1* variants on the protein level were then validated by mass spectrometry.

Results: Considering markers in linkage disequilibrium with rs30187, multiple showed effects on expression of *ERAP1* ($P=5.27x10^{-7}$ for lead variant rs39840), with protective variants invariably leading to reduced ERAP1 expression. The same property was noted for multiple protective *ERAP2* variants associated with ERAP2 expression (lead SNP rs2910686, $P=1.71x10^{-6}$, after correction for rs2248374 which leads to nonsense mediated decay of ERAP2 transcripts). On the second *ERAP1* haplotype tagged by the SNP rs10050860, a subset of variants alter the expression of two isoforms of the gene. The risk allele at the lead putative splice altering polymorphism, rs7063, correlated with a significant increase in expression of the canonical 19-exon ERAP1 isoform ($P=8.7x10^{-12}$, expression level 2x greater in AS-risk genotype carriers), and a significant decrease in the expression of a second 20-exon isoform ($P=1.0x10^{-17}$, expression level 0.47x lower in risk genotype carriers). The proportion of the 19-exon isoform was also significantly greater in cases than controls (P=0.047). The correlation between *ERAP1* disease risk genotype and isoform profile was replicated at the protein level. Protein expression of the second isoform was greatly reduced, rendering individual carrying the protective genotype at rs7063, with predominant production of this transcript variant, with significantly less total *ERAP1* overall ($P =1.58x10^{-6}$).

Conclusion: *ERAP1* and *ERAP2* genetic variants operate by effects on protein function, expression and sequence to influence the risk of developing AS and related diseases.

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Abstract Number: 2809

Increased Frequencies of IL-23R Positive T Cells and IL-22 and IL-17 Producing MAIT Cells in the Peripheral Blood of Patients with Ankylosing Spondylitis: Preliminary Results.

Eric Toussirot[1], Caroline Laheurte[2], Béatrice Gaugler[3] and Philippe Saas[4], [1]Service de Rhumatologie, CHU J Minjoz, Besancon, France, [2]Etablissement Français du Sang/ Université de Franche Comté / CBT506 / CHRU, INSERM UMR1098 / Plateforme Biomonitoring, Besançon, France, [3]EFS Bourgogne Franche Comté, INSERM UMR1098 / Etablissement Français du Sang / Université de Franche Comté, Besançon, France, [4]Etablisement Français du Sang ; Université de Franche Comté, INSERM UMR1098, Besançon, France

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Background/Purpose: Ankylosing spondylitis (AS) is the prototypic and most common form of spondyloarthritis (SpA). It was recently suggested that IL-23 could play a pivotal role in the pathophysiology of SpA. Indeed, there is a strong genetic association of SpA with polymorphisms of the *IL-23* receptor (IL-23R) gene. In experimental models, IL-23 is produced during the misfolding phenomenon of HLA-B27 heavy chain in the endoplasmic reticulum. Furthermore, in animal models, IL-23 overexpression induced a SpA-like disease *via* resident IL-23$^+$ T cells infiltrating entheseal structures and producing IL-17 and IL-22. In addition, there is an increased number of circulating cells producing IL-17 in patients with AS. Recent data also suggested that IL-17A is a potential target in the treatment of patients with AS.

Objectives: Cells that expressed IL-23R, as well as those producing IL-17 and/or IL-22 have been poorly characterized in AS and/or SpA. Thus, we aimed to better delineate the peripheral blood T cells that expressed IL-23R and the IL-17 and IL-22 producing cell subsets, notably conventional T cells as well as mucosal-associated invariant T cells (MAIT) in patients with AS.

Methods: 36 patients with AS (modified NY criteria; 27 M; age: 44.7 ± 2.6, disease duration: 12.7 ± 1.6; all under NSAIDs or traditional DMARDs) and 31 healthy controls (HC) (8 M; age: 46 ± 2.3) were evaluated. For each subject, peripheral blood T cell subsets were assessed using multi-color flow cytometry. Intracellular cytokine IL-17A, IL-22 and IFN-γ were evaluated after phorbol myristate acetate and ionomycine activation and permeabilization and analysed by flow cytometry. MAIT cells were identified by using TCRVα7.2 specific monoclonal antibodies. IL-22 serum levels were determined by ELISA using commercially available kit.

Results: the number and percentage of CD3$^+$ T cells, CD3$^+$CD4$^+$ and CD3$^+$CD8$^+$ T cells were comparable between patients and HC. Circulating IL-22 levels did not differ between patients and HC (22.6 ± 8.4 *vs* 15.1 ± 4.4 pg/ml, p = 0.7). IFN-γ producing CD4$^+$ and CD8$^+$ T cells were decreased in AS compared to HC (4.6 ± 1.7 *vs* 11.4 ± 2.5 % and 23.3 ± 1.9 *vs* 34.3 ± 2.3 %, respectively, p = 0.005 and p = 0.002). CD8$^+$ T cells expressing IL-23R were significantly increased in AS: 72.8 ± 1.5 *vs* 65.2 ± 2 % (p = 0.009). The percentage of MAIT T cells did not differ between patients and HC but we found an increased percentage of MAIT cells that produced IL-17 and IL-22: MAIT IFN-γ$^-$ IL-17$^+$: 0.43 ± 0.1 *vs* 0.12 ± 0.008 %, p = 0.006; MAIT IFN-γ$^-$ IL-22$^+$: 0.83 ± 0.1 *vs* 0.3 ± 0.1 %, p = 0.004. No correlation was found between the percentage of IL-23R$^+$ CD8$^+$ T cells and measurements of disease activity, as well as between IL-17$^+$ or IL-22$^+$ MAIT cells and disease activity.

Conclusion: These preliminary results suggest that the peripheral blood of patients with AS is enriched in IL-23R$^+$ CD8$^+$ T cells, as well as IL-17 and IL-22 producing MAIT cells. Since MAIT cells are involved in antibacterial immunity and bacterial agents are potentially involved in SpA, our preliminary data suggest that this T cell subset could potentially play a role in AS *via* IL-17 and IL-22 production. This remains to be clarified by future and complementary studies.

Disclosure: E. Toussirot, None; **C. Laheurte**, None; **B. Gaugler**, None; **P. Saas**, None.

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Abstract Number: 2810

The Presence of HLA-B27 Increases Severity of Arthritis but Does Not Appear to Influence New Bone Formation in Different in Vitro and in Vivo Models

Barbara Neerinckx[1], Kerri Heritage[2], Jacqueline Shaw[3], S. Kollnberger[3], Paul Bowness[3] and Rik Lories[1], [1]Rheumatology, UZ Leuven, Leuven, Belgium, [2]Laboratory of Tissue Homeostasis and Disease, Skeletal Biology and Engineering Research Center, KU Leuven and University Hospitals Leuven., Leuven, Belgium, [3]Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences, University of Oxford, Oxford, United Kingdom

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Background/Purpose: The strong genetic association between the HLA-B27 gene and ankylosing spondylitis (AS) has been known for over 40 years. Among AS patients, HLA-B27 positivity is associated with worse disease outcome. The long-term outcome of AS is determined by both inflammation and structural damage. The latter is characterized by new cartilage and bone formation, often leading to ankylosis. In this study, we investigated the *in vitro* and *in vivo* impact of HLA-B27 (over)expression in model systems of cartilage and bone formation.

Methods:

We used different *in vitro* systems mimicking endochondral bone formation. We set up micromasses with ATDC5 cells and human periosteal derived cells (hPDCs) transduced with a HLA-B27 or HLA-B7 (as a control) lentiviral vector. Micromasses were kept for 21 (ATDC5) or 14 (hPDCs) days in culture. RNA extraction and colorimetric tests were performed at different time points (d1, d7, d14, d21). For the ATDC5 cells, after 14 days the chondrogenic medium was switched to mineralization medium. To specifically study osteogenesis in hPDCs, cells were kept in monolayer for 28 days and stimulated with osteogenic media. We also set up micromasses from limb bud cells derived from HLA-B27 transgenic and wild-type (WT) C57BL/6 mice embryos at day 12.5E. These cells are also known to undergo endochondral bone formation *in vitro*. Samples were taken for RNA extraction at d1, d7 and d14. Chondrogenesis (Col II, Aggrecan, Col X) and osteogenesis associated markers (OSC, ALP, Runx2) were studied by quantitative RT-PCR. Stainings with alcian blue, alizarin red, picosirius red and safranin O were performed to measure proteoglycans, mineralization and collagens. For the *in vivo*study, we induced collagen antibody induced arthritis (CAIA) in HLA-B27 transgenic and WT C57BL/6 mice (n=10 in each group). Clinical scoring was performed twice a week. µCT scans were performed at baseline and 3 and 6 weeks after disease induction to study new bone formation. Statistical analyses were performed by 2 way ANOVA taking into account repeated measurements as appropriate.

Results: There was no difference in expression of Col II, Aggrecan or Col X in the HLA-B27 ATDC5 micromasses compared to the HLA-B7 micromasses. There was no difference between the stainings at the different time points. For the hPDC micromasses, there was no difference in expression of the chondrogenesis markers between HLA-B27 and HLA-B7 micromasses. Stainings with alcian blue could not show any difference between the two conditions. Expression of osteogenesis markers en alizarin red staining was comparable in the HLA-B27 and the HLA-B7 hPDCs in monolayer. The limb bud micromasses showed no difference in expression of chondrogenesis associated genes between HLA-B27 transgenic and WT embryos. In the CAIA experiment, the HLA-B27 transgenic mice showed more severe arthritis compared to WT mice. µCT analysis showed no increased bone formation in the post-inflammatory phase when HLA-B27 transgenic mice were compared to WT.

Conclusion: The presence of HLA-B27 seems to enhance joint inflammation in the CAIA model in C57BL/6 mice. These *in vivo* and the *in vitro*data do not support a direct role for HLA-B27 in new cartilage or bone formation leading to ankylosis.

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Abstract Number: 2811

Higher Serum Level of Leptin Protects from Radiographic Spinal Progression in Patients with Ankylosing Spondylitis

Agnes Hartl[1], Kay-Geert Hermann[1], In-Ho Song[1,2], Joachim Listing[3], Martin Rudwaleit[1,4], Joachim Sieper[1] and **Denis Poddubnyy**[1], [1]Charité Universitätsmedizin Berlin, Berlin, Germany, [2]Abbvie, Chicago, IL, [3]German Rheumatism Research Centre, Berlin, Germany, [4]Klinikum Bielefeld, Bielefeld, Germany
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Background/Purpose:

Fat tissue synthesizes and releases a series of biologically active substances (adipokines), which are involved in bone metabolism through effects on bone formation and resorption. Leptin, one of the most important adipokines derived from fat tissue, seems to be

responsible for the major part of effects of adipose tissue on bone.

The aim of this study was to investigate the role of leptin serum levels as a predictor of radiographic spinal progression in patients with ankylosing spondylitis (AS).

Methods:

Altogether 120 patients (82 men and 38 women) from the Effects of NSAIDs on Radiographic Damage in AS (ENRADAS) trial who completed the study per protocol were included into the analysis. Spinal radiographs (lumbar and cervical spine, lateral views) were scored independently by two trained readers in a concealed and randomly selected order according to the modified Stoke Ankylosing Spondylitis Spine Score (mSASSS) scoring system. Radiographic spinal progression was defined as 1) mSASSS worsening by ≥2 units after 2 years, and 2) development of at least one new syndesmophyte or progression of existing syndesmophytes (i.e., formation of a bridging syndesmophyte) after 2 years. Leptin serum levels were measured at baseline by ELISA.

Results:

Mean baseline leptin levels were significantly lower in patients with mSASSS worsening by ≥2 units after 2 years (n=29) as compared to those without progression (n=91): 10.3±8.8 vs. 15.9±13.7 ng/ml, respectively, p=0.002, and in patients with syndesmophyte formation (n=25) as compared to those without syndesmophyte formation (n=95): 10.1±9.6 vs. 15.7±13.4 ng/ml, respectively, p=0.002. This difference was especially evident in males, but not in females. Remarkably, in females the serum level of leptin at baseline was significantly higher than in males: 30.0±21.0 vs. 10.7±8.2 ng/ml, p<0.001.

In the ROC analysis leptin had an area under the curve (AUC) of 0.69 (95% CI 0.57-0.81) for no mSASSS worsening by ≥2 units and 0.70 (95% CI 0.57-0.82) for no syndesmophyte formation. Leptin serum level of >7.5 ng/ml had a sensitivity of 78%, a specificity of 55%, and an odds ratio (OR) = 4.2 (95% CI 1.7-10.6) as a protector from mSASSS worsening by ≥2 units after 2 years (after adjustment for baseline syndemophytes, elevated CRP, smoking, body mass index, sex, and NSAIDS intake index, the OR increased to 9.2, 95% CI 2.5-34.0). The same serum level of leptin demonstrated a sensitivity of 77%, a specificity of 56%, and an OR = 4.2 (95% CI 1.7-10.6) as a predictor from syndesmophyte formation (after adjustment for the same variable as above, OR = 11.7, 95% CI 2.8-47.8).

In the logistic regression analysis with baseline leptin serum level as a scale variable, a protective role of higher leptin serum level regarding radiographic spinal progression was confirmed: OR = 1.15 (95% CI 1.02-1.3) for no mSASSS worsening by ≥2 units, and OR = 1.28 (95% CI 1.1-1.5) for no syndesmophyte formation.

Conclusion:

Higher serum levels of leptin seem to protect patients with AS from radiographic spinal progression. Interestingly, female patients with AS have significantly higher leptin levels that might explain lesser extent of structural damage in the spine in female AS patients in general.

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Abstract Number: 2812

Cytokine Secretion By Peripheral Blood Mononuclear Cells in Patients with Axial Spondyloarthritis and the Effect of Thymoquinone on Cytokine Profile

Erkan Kilic[1], Cagri Sakalar[2], Huriye Aksu[3], Mustafa Cakir[3], Gamze Kilic[1] and **Salih Ozgocmen**[4], [1]Dept. PRM, Erciyes University, Faculty of Medicine,Division of Rheumatology, Kayseri, Turkey, [2]Genome and Stem Cell Center (GEN-KOK), Erciyes University, Faculty of Medicine, Medical Biology, Kayseri, Turkey, [3]Genome and Stem Cell Senter (GEN-KOK), Erciyes University, Faculty of Medicine, Medical Biology, Kayseri, Turkey, [4]Dept.PRM, Erciyes University, Faculty of Medicine,Division of Rheumatology, Kayseri, Turkey

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Background/Purpose: Axial spondyloarthritis (axSpA) defines a group of chronic inflammatory diseases which includes non-radiographic axSpA (nr-axSpA) who do not have definite sacroiliitis on pelvic X-rays. Disease burden seems to be similar between nr-axSpA and AS, however differences or similarities in disease progress and pathogenesis are not completely clear. Thymoquinone (TQ) is the active ingredient of *Nigella sativa* and it's anti-inflammatory, anticancer and immunoregulatory role has been demonstrated in various diseases. The aim of this study was to investigate the cytokine production of peripheral blood mononuclear cells (PBMC) in pts with axSpA (AS and nr-axSpA) and the effect of thymoquinone on the cytokine profile.

Methods: Pts with axSpA who met the ASAS axSpA classification criteria and age-matched healthy controls (HC) were enrolled in this study. Pts were DMARD naive (biologic or synthetic), and 23 pts were using only NSAIDs (19 on demand, 5 regular full dose). All of the pts had pure axial involvement and none had peripheral arthritis or psoriasis or IBD. Peripheral blood mononuclear cells (PBMCs) were cultured in RPMI medium with and without TQ (12.5 µM). PBMCs were stimulated for 48 hours with 10 µg/ml phytohemagglutinin and secretion of TNF-α, interleukin-4 (IL4), IL6, IL8, IL10, IL17 and VEGF was measured in the supernatant by ELISA (lab investigators were blind to pts/controls clinical diagnosis/variables).

Results: Twenty-nine pts with axSpA (14 male, 37.2±12.6 yrs) and age- and gender-matched 14 healthy controls (7 male, 35.6±9.6 yrs) were included. In axSpA group 15 pts were nr-axSpA (mean symptom duration; 5.3±6.7 yrs) and 14 pts were AS (10.4±8.6 yrs). Disease activity assessed by BASDAI and ASDAS-CRP were similar in pts with AS (4.4±2.3 and 2.9±1.3) and nr-axSpA (3.8±1.9 and 2.6±1.1). Cytokine levels without TQ are given in Table 1. Interleukin-4 (Il-4), Il-8, TNF-α and VEGF were significantly different in pts with axSpA compared to HCs. Cytokine profiles were similar in pts with AS and nr-axSpA. TQ supressed cytokine secretion in pts with axSpA and HCs (Table 2). However VEGF secretion increased with TQ, particularly in pts with AS (nr-axSpA 18.4±5.1 vs AS 29.1±13.2 pg/ml, p=0.011).

Conclusion: This is the first study reporting similar cytokine profile of stimulated PBMCs in patients with AS and nr-axSpA and the suppressive effect of TQ on cytokine production of PBMCs. Also our results showed increased production of VEGF by PBMCs despite TQ particularly in patients with AS.

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Table 1. Cytokine levels between axial spondyloarthritis and healthy controls (HCs) (pg/ml, mean±SEM)

	HCs (n=14)	axSpA (n=29)	P	AS(n=14)	p	nr-axSpA (n=15)	p
IL-4	226.7 ± 12.8	203.5 ± 18.2	**0.022**	216.2 ± 33.3	0.250	191.7 ± 17.3	0.060
IL-6	1906.8 ± 305.8	2806.1 ± 420.3	0.328	3667.5 ± 688.5	0.054	2002.2 ± 420.6	0.694
IL-8	13095.2± 2063.9	26257 ± 859.1	**<0.0001**	26908.2 ± 719.0	**<0.0001**	25649.3 ± 1533.3	**<0.0001**
IL-10	1091.2 ± 233.2	1641.8 ± 52.2	0.106	1686.4 ± 306.7	0.108	1600.2 ± 275.3	0.163
IL-17	432.5 ± 84.8	350.1 ± 40.7	0.857	319.6 ± 50.6	0.383	378.6 ± 63.8	0.777
TNF-α	739.9 ± 77.4	578.1 ± 52.2	**0.009**	506.4 ± 56.55	**0.029**	645.0 ± 84.3	0.432
VEGF	6.9 ± 3.1	20.6 ± 4.6	**0.001**	27.0 ± 8.7	**0.001**	14.6 ± 3.5	**0.007**

Table 2. Comparisons of cytokine levels with and without thymoquinone in HCs and axSpA (pg/ml, mean±SEM)

pg/ml mean±SEM	HCs+TQ (n=14)	HCs vs HCs+TQ p	axSpA+TQ(n=29)	axSpA vs axSpA+TQ p
IL-4	159.5 ± 7.5	**0.002**	190.7 ± 8.6	0.754
IL-6	31.8 ± 2.9	**0.001**	24.7 ± 4.5	**0.002**
IL-8	357.4 ± 19.9	**0.001**	679.4 ± 273.8	**0.002**
IL-10	5.2 ± 1.7	**0.001**	3.3 ± 0.8	**0.002**
IL-17	9.6 ± 4.3	**0.001**	7.1 ± 2.4	**0.002**
TNF -α	246.6 ± 12.3	**0.001**	270.1 ± 17.54	**0.002**
VEGF	18.0 ± 4.5	**0.002**	23.6 ± 2.1	0.859

Disclosure: E. Kilic, None; **C. Sakalar**, None; **H. Aksu**, None; **M. Cakir**, None; **G. Kilic**, None; **S. Ozgocmen**, None.

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Abstract Number: 2813

IL-17 Induces Skin Inflammation Independently of IL-23R+ T Cells and Is Protected By Conditional Deletion of Wdfy3 in Neutrophils

Erika Suzuki[1], Emanual Maverakis[2], Laura Bouchareychas[1], Vijay K. Kuchroo[3], Frank Nestle[4] and Iannis E. Adamopoulos[1], [1]Internal Medicine, University of California, Davis, Sacramento, CA, [2]Dermatology, University of California, Davis, Sacramento, CA, [3]Center of Neurological Disease, Harvard Medical School, Boston, MA, [4]Mary Dunhill Chair of Cutaneous Medicine and Immunotherapy Division of Genetics and Molecular Medicine St Johns Institute of Dermatology, King's College London, London, England
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Background/Purpose: IL-17 is elevated in both the lesional skin and arthritic joints of psoriatic arthritis (PsA) patients, however, the direct effect of IL-17 on myeloid cells in PsA is less understood. We recently identified a unique molecule, Wdfy3, associated with IL-17 and neutrophil-driven epidermal hyperplasia. Using a cre-lox system to selectively ablate Wdfy3 in myeloid cells, we report the effect of Wdfy3 in protecting against epidermal hyperplasia.

Methods: We performed gene transfer of IL-17 by hydrodynamic delivery of minicircle (MC) DNA in control (C57BL/6) mice and mice treated with topical imiquimod. The psoriatic features were analyzed and scored for disease progression histologically. Further phenotypic analysis of cell populations was performed by flow cytometry, RT-qPCR, and *in vivo* imaging using nanoprobes in *Il23r*$^{-/-}$*Rag*$^{-/-}$, *Tcrd*$^{-/-}$ and Wdfy3-LysM^{Cre} transgenic mice.

Results: Histological analysis of dorsal skins from IL-17 MC-injected Wdfy3-LysM^{Cre} at day 4 revealed reduced skin thickness and absence of epidermal hyperplasia and Munro's microabscesses in contrast to IL-17 MC-injected WT controls. Consistent with the histology findings we observed a reduction in gene expression of *K16, S100a8, Cxcl1, Cxcr2 and Ltb4r1* in IL-17 MC-injected Wdfy3-LysM^{Cre} dorsal skins compared to IL-17 MC-injected WT mice. Histological analysis of dorsal skins from IL-17 MC-injected Wdfy3-LysM^{Cre} at day 4 showed reduced apoptotic cells compared to IL-17 MC-injected WT controls. We found that deletion of *Wdfy3* in Ly6G^{+} cells resulted in reduced NET formation, which was consistent with a reduction in NET-associated neutrophil elastase compared to WT or LysM^{Cre} controls.

Conclusion: Collectively, our data underscore the importance of IL-17 in IL-23 and T cell independent skin pathology and its direct association with neutrophil activation and Wdfy3 in epidermal hyperplasia; a pathological feature of various skin diseases and paves the way for the design of novel therapeutics to combat this disabling condition.

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Abstract Number: 2814

IL-10 May Mitigate Cardiovascular Risk in Psoriatic Arthritis Via an Anti-Atherosclerotic Effect on Cellular Cholesterol Transport

Lucas McCaffrey[1], Iryna Voloshyna[2], Michael J. Littlefield[2], Eduard Zhurov[3], Steven E. Carsons[4], Elise Belilos[5], Kristina Belostocki[6], Lois Bonetti[7], Gary Rosenblum[6] and Allison B. Reiss[2], [1]Medicine, Division of Rheumatology, Winthrop-University Hospital, Mineola, NY, [2]Medicine, Winthrop University Hospital, Mineola, NY, [3]Winthrop-University Hospital, Mineola, NY,

[4]Rheumatology, Allergy and Immunology, Winthrop University Hospital, Mineola, NY, [5]Winthrop University Hospital, Mineola, NY, [6]Rheumatology, Winthrop University Hospital, Mineola, NY, [7]Rheum & Immun, Winthrop University Hospital, Mineola, NY
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Session Time: 9:00AM-11:00AM

Background/Purpose: The increased risk of major adverse cardiovascular events (MACE) in patients who suffer from systemic inflammatory conditions such as Rheumatoid Arthritis (RA), Systemic Lupus Erythematosus (SLE), and Psoriatic Arthritis (PsA) is well established. A recent population-based cohort study quantified the risk of MACE among patients with RA, PsA, and psoriasis compared to the general population after adjusting for traditional cardiovascular risk factors. The risk of MACE was elevated by 40-50% in patients with RA but only 20% in patients with PsA. Our group has explored potential mechanisms to explain the attenuated risk of MACE in PsA compared to RA. Previous clinical studies have suggested that increased serum levels of IL-10 are associated with a more favorable prognosis in patients with acute coronary syndromes. Murine models have shown IL-10 to have atheroprotective effects. IL-10 has also been shown to favorably effect reverse cholesterol transport in THP-1 macrophages via increases in the expression of ABCA1, ABCG1, and Liver X receptor α. We sought to determine if IL-10 present in PsA plasma modulated the expression of the major cellular cholesterol transport proteins ABCA1 and CD36, and prevented foam cell formation.

Methods: The study was performed under a Winthrop University Hospital IRB-approved protocol. Level of IL-10 was evaluated by ELISA (Milliplex). THP-1 differentiated macrophages (10^6/ml, phorbol dibutyrate, 100nM, 48h), were incubated (37^0C, 5% $C0_2$, 18h) ± 1, 10, 50 and 100 pg/ml of recombinant human IL-10 ± 100 ng/ml of anti-IL10 (R&D) for neutralization. Macrophages were exposed to 10% plasma from 8 PsA±100 ng/ml of anti-IL10 (R&D). Expression of major cholesterol transport proteins: ATP binding cassette transporter (ABC) A1 and CD36 were quantified by real-time PCR, foam cells were identified by oil-red-O staining.

Results: Purified IL-10 had a bimodal effect on expression of the cholesterol efflux gene ABCA1. ABCA1 was increased by IL-10 1.3±0.04 fold at 10 pg/ml and reaching 2.4±0.2 fold at 50 pg/ml (n=3, $P<0.05$) but had no effect at 100 pg/ml. Neutralization of IL-10 by anti-IL10 antibody decreased the expression of ABCA1 to the baseline level of untreated cells. CD36 expression was not affected.

In THP-1 macrophages exposed to 10 % PsA plasma (~24 pg/ml) inhibition of IL-10 binding significantly decreased expression of ABCA1 71±9.0% (n=8, $P<0.001$) with expression in macrophages exposed to PsA plasma set at 100%. In addition, neutralization of IL-10 increased expression of CD36 to 133.4±6.9% (n=8, $P<0.001$). Results were confirmed by Western blot. Consequently, neutralization of IL-10 increased foam cell formation by 20%.

Conclusion: Compared to pro-atherogenic changes induced by RA plasma, PsA plasma displays a modest pro-atherogenic pattern consistent with the clinically observed attenuated risk of MACE in PsA compared to RA. IL-10 in PsA plasma demonstrates an artheroprotective effect on cellular cholesterol transport. This study suggests a role for IL-10 in the attenuation of MACE observed in PsA.

Disclosure: L. McCaffrey, None; **I. Voloshyna**, None; **M. J. Littlefield**, None; **E. Zhurov**, None; **S. E. Carsons**, None; **E. Belilos**, None; **K. Belostocki**, None; **L. Bonetti**, None; **G. Rosenblum**, None; **A. B. Reiss**, None.

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Abstract Number: 2815

A Comparison of Th17 Gene Expression in Psoriatic Arthritis Synovial Fluid and Peripheral Blood

Fatima Abji[1], Remy Pollock[2], Kun Liang[3], Vinod Chandran[4] and Dafna Gladman[4], [1]Rheumatology, Toronto Western Hospital and University of Toronto, Toronto, ON, Canada, [2]University of Toronto, Toronto Western Hospital, Toronto, ON, Canada, [3]Department of Statistics and Actuarial Science, University of Waterloo, Waterloo, ON, Canada, [4]Rheumatology, University of Toronto, Toronto Western Hospital, Toronto, ON, Canada
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Background/Purpose: Psoriatic arthritis (PsA) is a destructive inflammatory arthritis that develops in approximately 30% of patients with cutaneous psoriasis. Th17 cells infiltrate psoriatic skin and joints and are central to the pathogenesis of PsA. The aim of this study was to identify Th17 cell signaling genes that are dysregulated in the affected joint of PsA patients and if these differences are detected in peripheral blood.

Methods: Synovial fluid cells from 8 PsA and 4 gout patients undergoing routine joint aspirations were obtained and stored in TRIzol reagent. RNA was isolated by phenol-chloroform extraction and purified with RNeasy miniprep kits. Peripheral blood from 24 PsA and 19 controls was stored in Tempus tubes and total RNA was extracted according to the manufacturer's instructions. Quantitative RT-PCR arrays were used to profile expression of 84 genes related to the Th17 regulatory network in synovial and peripheral blood cells. Expression was quantified by the ΔΔCt method and fold change differences were compared in synovial cells by logistic regression and in peripheral blood by Student's t test ($p<0.05$).

Results: Out of 16 genes significantly dysregulated in PsA compared to gout synovial cells, 15 genes were up-regulated and one gene (STAT4) was down-regulated (Table 1). In peripheral blood, 5 genes (IL-15, CXCL6, CLEC7A, CD3D and TLR4) were elevated and 21 genes, including IL-8, IL-17C, CD4, STAT3, NFKB1 and TGFB1, were reduced in PsA compared to controls. Five genes (CD4, CLEC7A, CXCL6, NFKB1 and IL8) were significantly altered in both synovial and peripheral blood cells of PsA patients compared to controls (gout or normal). Additionally, gene expression was compared in paired synovial and peripheral blood cells in 4 PsA patients. Eight genes were increased and 13 genes were reduced in PsA synovial cells compared to peripheral blood cells (Table 2).

Conclusion: We identified gene expression differences that may distinguish PsA from other inflammatory arthritides such as gout. Five genes (CD4, CLEC7A, CXCL6, NFKB1 and IL8) were altered in both synovial fluid and peripheral blood, potentiating their use as biomarkers of PsA. Differences between synovial and peripheral blood cells contribute to our understanding of the biology of PsA and warrant further investigation.

Table 1: Differences in expression of Th17 signaling genes ($p<0.05$) in synovial cells obtained from patients with PsA compared to that obtained from gout

Gene	Description	Fold Change	P-Value	FDR
IL6	Interleukin 6	10.68	0.009	0.139
CD4*	Cluster of differentiation 4	6.21	0.017	0.139
MMP9	Matrix metallopeptidase 9	5.44	0.021	0.139
CLEC7A*	C-type lectin domain family 7, member A	5.15	0.043	0.175
CCL1	Chemokine (C-C motif) ligand 1	5.13	0.010	0.139
CXCL6*	Chemokine (C-X-C motif) ligand 6	4.63	0.034	0.160
IL4	Interleukin 4	4.58	0.025	0.140
TIRAP	Toll-interleukin 1 receptor (TIR) domain containing adaptor protein	3.73	0.023	0.139
SOCS3	Suppressor of cytokine signaling 3	2.95	0.012	0.139
NFKB1*	Nuclear factor of kappa light polypeptide gene enhancer in B-cells 1	2.92	0.047	0.178
IL12RB1	Interleukin 12 receptor, beta 1	2.66	0.021	0.139
IL8*	Interleukin 8	2.54	0.019	0.139
TRAF6	TNF receptor-associated factor 6, E3 ubiquitin protein ligase	2.22	0.042	0.175
CD3E	CD3 antigen, epsilon polypeptide	1.84	0.017	0.139
SOCS1	Suppressor of cytokine signaling 1	1.75	0.030	0.151
STAT4	Signal transducer and activator of transcription 4	0.31	0.016	0.139

*Denotes genes that were dysregulated in synovial and peripheral blood of PsA vs. controls (gout or normal)

Table 2: Expression of Th17 signaling genes ($p<0.05$) in paired synovial and peripheral blood cells of PsA patients

Gene	Description	Fold Change	P-Value	FDR
CCL1	Chemokine (C-C motif) ligand 1	1302.31	0.002	0.027
MMP13	Matrix metallopeptidase 13	413.92	0.007	0.045
CCL22	Chemokine (C-C motif) ligand 22	48.71	0.035	0.098
ICAM1	Intercellular Adhesion Molecule 1	33.24	0.008	0.045
CCL20	Chemokine (C-C motif) ligand 20	24.91	0.035	0.098
IL17RC	Interleukin 17 receptor C	3.84	0.029	0.097
STAT4	Signal transducer and activator of transcription 4	3.37	0.022	0.097
TRAF6	TNF receptor-associated factor 6, E3 ubiquitin protein ligase	2.06	0.027	0.097
GATA3	GATA binding protein 3	0.42	0.004	0.035
IL17D	Interleukin 17D	0.41	0.034	0.098
CD28	Cluster of differentiation 28	0.35	0.028	0.097
MMP9	Matrix metallopeptidase 9	0.29	0.004	0.035
SOCS3	Suppressor of cytokine signaling 3	0.28	0.042	0.102
TLR4	Toll-like receptor 4	0.28	0.041	0.102
CD3D	CD3d molecule, delta (CD3-TCR complex)	0.22	0.038	0.102
NFKB1	Nuclear factor of kappa light polypeptide gene enhancer in B-cells 1	0.22	0.003	0.035
TIRAP	Toll-interleukin 1 receptor (TIR) domain containing adaptor protein	0.12	0.005	0.035
IL27	Interleukin 27	0.095	0.010	0.050
MMP3	Matrix metallopeptidase 3	0.065	0.026	0.097
CSF2	Colony stimulating factor 2 (granulocyte-macrophage)	0.043	0.001	0.020
CXCL12	Chemokine (C-X-C motif) ligand 12	0.008	0.0004	0.020

Abstract Number: 2816

Is the Gender Difference in As Linked to IL-23?

Johannes Nossent[1] and **Gunnstein Bakland**[2,3], [1]Medicine, University of Western Australia, WA, Australia, [2]Dept. of Rheumatology, University Hospital Northern Norway, Tromsø, Norway, [3]University of Tromsø, The Arctic University of Norway, Tromsø, Norway
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Background/Purpose:

Ankylosing Spondylitis (AS) has traditionally been portrayed as a disease where male patients outnumber female patients by a factor 3 to 4. It has also been suggested that female patients have a less severe disease course and a longer diagnostic delay due to a more protracted radiological progression. We wanted evaluate several SNPs with an acknowledged association to AS to identify a possible influence of gender on the distribution among patients.

Methods:

We identified 306 patients with AS according to the modified New York criteria in a population of northern European descent

(Northern Norway). The distribution of 10 different SNPs where evaluated in the population using Taqman RT-PCR. These SNPs were describing variation in ERAP-1, IL-1, TNF and IL-23R The statistical analyses where performed using SNPstats (http://bioinfo.iconcologia.net/SNPstats).

Results:

We could only find a correlation to gender within the IL-23R-gene, and only two SNPs (rs11209032 and rs10489629) in the IL23R-gene showed a distribution significantly associated with gender, p=0.016 and 0.026 respectively. There was no association with the examined SNPs from ERAP1, IL1 or TNF. We could not find a correlation between IL-23 levels and SNP distribution.

Conclusion:

Our data suggest that a variation of rs11209032 and rs10489629 is associated with gender distribution in AS. Considering IL23 has been identified as a cytokine central to active inflammation in enthesitis, this could be the link to the observed gender difference in AS. To our knowledge, this correlation has not previously been reported. However, studies reporting on radiographic progression in AS find that male patients have a more rapid progression and pronounced tendency to syndesmophyte formation. We suggest that this observation might be linked to IL23, but future studies are needed. Given the difference in gender distribution reported in radiographic and non-radiographic axial Spondyloarthritis, this could be a population where a study of IL-23/IL-23R could bring further understanding to the pathogenesis of the spondyloarthritidis.

Disclosure: J. Nossent, None; **G. Bakland**, None.

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Abstract Number: 2817

The Microbiome of Reactive Arthritis in a Guatemalan Cohort

Alexis Ogdie-Beatty[1], Carles Ubeda[2], Helga Raquel Garcia Ferrer[3], Joan Von Feldt[4], A Garcia Kutzbach[5] and **Jose U. Scher**[6], [1]Medicine/Rheumatology, University of Pennsylvania, Philadelphia, PA, [2]Institute for Research in Public Health, Valencia, Spain, [3]Society for Worldwide Med Exchange, North Bay Village, FL, [4]University of Pennsylvania, Philadelphia, PA, [5]Internal Medicine, Rheumatology Unit (AGAR), Francisco Marroquin University, School of Medicine, Guatemala City, Guatemala, [6]Department of Medicine, Division of Rheumatology, New York University School of Medicine, New York, NY

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Background/Purpose: Reactive arthritis (ReA) is an inflammatory arthritis that typically follows infection. Several agents microbial agents have been implicated, particularly *Shigella, Salmonella, Campylobacter* in the gastrointestinal tract and *Chlamydia trachomatis* in the genitourinary tract. However, the intestinal microbiome in these patients has never been characterized. The objective of this study was to determine the community composition of pathogenic and commensal gut microorganisms of ReA subjects from a highly prevalent region.

Methods: We performed a prospective case-control study among patients with an infection (urogenital or gastrointestinal) in the 3-6 months prior to enrollment (January through October 2014). ReA was defined using the ASAS peripheral SpA criteria. Cases were identified in the AGAR rheumatology clinic. Controls were recruited from primary care clinics in the same hospital system in Guatemala. Fecal samples from 33 subjects with ReA and 31 controls were obtained and bacterial DNA was extracted. 16S rDNA amplicons targeting V4 region were sequenced using MiSeq (Illumina) to define the microbiota composition. The obtained 16S rRNA sequences were analyzed using the Quantitative Insights into Microbial Ecology (QIIME) pipeline for analysis of community sequence data.

Results: There were no significant differences in age, gender, HLA-B27 positivity or type of infections between the groups. 16S sequencing data showed that ReA patients had significantly less intestinal microbial diversity compared to controls, as calculated by chao ($p<0.05$) and phylogenetic tree ($p<0.05$; Figure 1). Taxonomic comparison between groups was performed using LEfSe, which revealed a few significant differences (LDA score>2). While ReA microbiome samples were enriched with *Bifidobacteriaceae* ($p<0.05$), there was a notable and significant decrease in intestinal *Peptococcaceae* ($p<0.001$; Figure 2). At the operational taxonomic unit (OTU) level, there was a virtual absence of *Paraprevotellaceae* in the ReA group ($p<0.01$).

Conclusion: Despite the relatively small number of samples analyzed, the intestinal microbiome of ReA patients appears to be less

diverse than that of controls. Taxonomic differences were also noted between groups, including the lower abundance of gut pathobionts *(i.e., Peptococcaceae)*. Further evaluation of functional aspects of this microbiome and its relationship to intestinal commensals and pathogens in various patients' phenotypes may provide further insights into its possible contribution to ReA.

Figure 1. Phylodiversity Tree

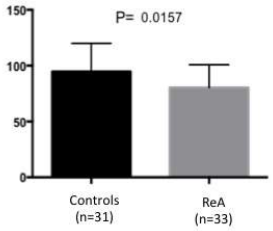
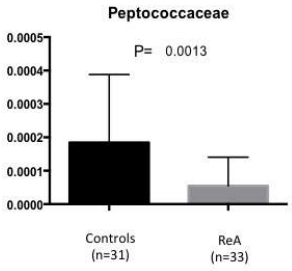


Figure 2. Relative abundance of intestinal *Peptococcaceae*



Disclosure: A. Ogdie-Beatty, None; **C. Ubeda**, None; **H. R. Garcia Ferrer**, None; **J. Von Feldt**, None; **A. Garcia Kutzbach**, None; **J. U. Scher**, None.

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Associations of IL23R, BMP6 and PTGS1 Polymorphisms with Radiographic Severity of Ankylosing Spondylitis

Gulsen Ozen[1], Rabia Deniz[2], Fatih Eren[3], Can Erzik[3], Ali Ugur Unal[1], Sibel Z. Aydin[4], Nevsun Inanc[1], Haner Direskeneli[1] and Pamir Atagunduz[1], [1]Department of Rheumatology, Marmara University Faculty of Medicine, Istanbul, Turkey, [2]Marmara University Faculty of Medicine, Istanbul, Turkey, [3]Department of Medical Biology, Marmara University Faculty of Medicine, Istanbul, Turkey, [4]Department of Rheumatology, Koc University Faculty of Medicine, Istanbul, Turkey

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Background/Purpose: Ankylosing spondylitis (AS) is an inflammatory disease affecting spine which may lead to new bone formation and disability. However, the radiographic severity of AS shows great variance. The genetic determinants for the new bone formation and for this great variance have not been fully understood yet. By using a well-categorized group of patients representing two extreme ends of AS radiographic severity, we aimed to determine the effects of interleukin-23 receptor (*IL23R),* bone morpogenetic protein-6 *(BMP6)* and prostaglandin endoperoxide synthase-1 (*PTGS1)* gene variants on radiographic severity of AS.

Methods: rs11209026 (*IL23R*), rs1235192 and rs270378 (*BMP6*), and rs1236913 (*PTGS1*) single nucleotide polymorphisms (SNPs) were genotyped in 241 AS patients (F/M=97/144, mean age 42.0±11.0 years, 60.6% HLA-B27[+]) fulfilling the modified New York criteria. Patients were classifed as mild and severe radiographic AS according to modified Stoke AS spinal score (mSASSS). Mild AS is defined as having mSASSS of "0" despite ≥10 years of disease duration. Whereas severe AS is defined as having mSASSS of >20 (without counting scores with "1") regardless of the disease duration.

Results: Seventy (29%) and 171 (71%) patients were classified as severe and mild radiographic AS, respectively (mean mSASSS 48.2±17.3 vs 0, *P*<0.0001). Severe AS patients were mainly male and significantly older, had longer disease duration, more extra-articular and coxofemoral joint involvement, smoking rates, HLA-B27 positivity and ever TNFi usage. The genotype distributions and allele frequencies of the 4 SNPs were not different in severe group compared to mild group. After adjustment for clinical differences between two groups by logistic regression analysis none of the alleles in those SNPs were found to be associated with radiographic severity of the AS (Table 1). The genotype frequencies also did not change when groups were categorized according to gender and HLA-B27 status. However, HLA-B27 was associated with radiographic severity only in male patients (OR=3.23, 95% CI [1.11 to 9.41], *P*=0.032). No association with these SNPs and other clinical manifestations of AS, coxofemoral joint involvement, uveitis and enthesitis, could be demonstrated. Severe group patients had higher CRP levels, likewise patients with elevated CRP had higher mSASSS scores (22.1±26.9 vs 10.4±22.4, *P*=0.001). However no difference was identified.in genotype distributions and allele frequencies of patients with and without elevated CRP.

Conclusion: In a radiographically well-categorized AS cohort *IL23R* rs11209026, *BMP6* rs1235192 and rs270378 and *PTGS1*rs1236913 SNPs are not found to be associated with radiographic severity of AS. HLA-B27 is associated with radiographic severity only in male AS patients.

Table 1. The distribution of allele frequencies of *IL23R, BMP6* and *PTGS1* SNPs of mild and severe radiographic AS patients*

	Mild radiographic AS (n=171)	Severe radiographic AS (n=70)	*P* value	OR (95% CI)
	Allele frequency			
***IL23R* rs11209026**			**0.42**	**0.28 (0.058 to 1.36)**
G	**156 (91.2)**	**66 (94.3)**		
A‡	**15 (8.8)**	**4 (5.7)**		
***BMP6* rs1235192**			**0.69**	**1.14 (0.53 to 2.48)**
A	**100 (58.5)**	**39 (55.7)**		
C‡	**71 (41.5)**	**31 (44.3)**		
***BMP6* rs270378**			**0.86**	**0.92 (0.30 to 2.75)**
T	**23 (13.5)**	**10 (14.3)**		
C‡	**148 (86.5)**	**60 (85.7)**		
***PTGS1* rs1236913**			**0.92**	**1.10 (0.39 to 3.08)**
C	**145 (84.8)**	**59 (84.3)**		
T‡	**26 (15.2)**	**11 (15.7)**		

**Values are provided as n (%).* ‡ *Risky allele*

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Abstract Number: 2819

Rorc Antagonism Inhibits IL-23-Dependent Aberrant Bone Formation in Vivo

Mark Panzenbeck[1], Kathleen Hoyt[1], Donald Souza[2], Gregg Davis[1], Elizabeth Glynn[1], Thomas Wieckowski[1], Michael Turner[1], Robert Hughes[1], Dustin Smith[1], Christian Harcken[1], Gerald Nabozny[3] and **Mark Labadia**[4], [1]Boehringer Ingelheim Pharmaceuticals Inc., Ridgefield, CT, [2]Immunology & Inflammation, Boehringer Ingelheim Pharmaceuticals Inc., Ridgefield, CT, [3]Immunology and Inflammation, Boehringer Ingelheim Pharmaceuticals Inc., Ridgefield, CT, [4]Immunology, Boehringer Ingelheim Pharmaceuticals Inc., Ridgefield, CT

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Background/Purpose: RORγt is a nuclear hormone receptor expressed in Th_{17} cells and distinct subsets of lymphoid cells, including innate lymphoid cells (ILC), and γδ T-cells. RORγt is required for Th_{17} cell and innate lymphocyte differentiation and regulates the transcription of the effector cytokines genes including IL17A and IL22. Ankylosing spondylitis (AS) is characterized by a peripheral oligoarthritis and enthesitis. A key feature of AS is the imbalance between bone resorption and formation leading to aberrant bone formation and ankylosis. The contribution of IL23/IL17 axis to the pathogenesis of AS is supported by several lines of evidence. The protective IL23R variant (R381Q) is associated with decreased expression of Th_{17} genes. Elevated levels of serum IL23 and IL17 and increased numbers of circulating Th_{17} cells have been reported in AS patients. Finally, anti IL17A antibody (Secukinumab) therapy has been demonstrated to be efficacious in AS. Overexpression of IL23 using minicircle DNA technology is characterized by a rapid and pronounced skin and rheumatic phenotype characterized by synovitis, enthesitis, and aberrant bone formation in the B10RIII mouse (Sherlock et al.). Furthermore, significant expression of IL23 pathway associated genes including IL17A and IL22 was observed in the entheses tissue. The potent and selective RORγt antagonist (Compound A), was utilized to test the hypothesis that antagonism of RORγt can inhibit the IL23 pathway in the context of synovial and entheseal inflammation and subsequent bone remodeling.

Methods: Adult B10RIII female mice were administered 1.5 mg/mL (3 mg dose) of IL23 minicircle DNA via hydrodynamic injection on day 1. Starting on day 2, mice received a 10 mg/kg dose of Compound A, p.o. *bid*for 28 days. Mice were monitored daily for signs of arthritis. Arthritis severity was graded using a 0-4 score per paw for a maximum score of 16. Upon sacrifice (Day 28) serum was collected for cytokine analysis. Enthesis tissue was collected for biomarker analysis and paws were collected for histologic assessment (Bolder Biopath, Boulder, CO). Medullary trabecular and cortical bone were assessed for erosion. Presence of osteoclasts was also incorporated in the bone erosion score. The distribution and widths of periosteal bone proliferation were used to assess aberrant bone formation.

Results: Administration of 10 mg/kg Compound A, p.o. *bid* for 28 days resulted in significant inhibition (49 ± 7%) of arthritic score (AUC). Entheses tissue biomarkers including IL-17A, IL-22, S100a8 and S100a9 were significantly inhibited (>80%) at the 10 mg/kg dose. In addition, biomarkers of bone erosion including RANKL and MMP9 were inhibited 99 ± 1% and 94 ± 3% respectively at day 28. Histological analysis demonstrated a significant inhibition of both synovitis and enthesitis. Finally, bone erosion and aberrant bone formation were inhibited 95 ± 4% and 98 ± 2% respectively at day 28.

Conclusion: These data support the hypothesis that antagonism of RORγt can attenuate IL23-dependent inflammation in entheseal tissue and attenuates both bone erosion and aberrant bone formation in the joint in vivo. Correlations between entheseal tissue biomarker responses and bone endpoints are being established.

Disclosure: M. Panzenbeck, Boehringer Ingelheim, 3; **K. Hoyt**, Boehringer Ingelheim, 3; **D. Souza**, Boehringer Ingelheim, 3; **G. Davis**, Boehringer Ingelheim, 3; **E. Glynn**, Boehringer Ingelheim, 3; **T. Wieckowski**, Boehringer Ingelheim, 3; **M. Turner**, Boehringer Ingelheim, 3; **R. Hughes**, Boehringer Ingelheim, 3; **D. Smith**, Boehringer Ingelheim, 3; **C. Harcken**, Boehringer Ingelheim, 3; **G. Nabozny**, Boehringer Ingelheim, 3; **M. Labadia**, Boehringer Ingelheimhringer Ingelheim Pharmaceuticals, 3.

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Abstract Number: 2820

Multi-Omics Studies of Gut Microbiota in Enthesitis-Related Arthritis Identify

Diminished Microbial Diversity and Altered Typtophan Metabolism As Potential Factors in Disease Pathogenesis

Matthew L. Stoll[1], Landon S. Wilson[2], Stephen Barnes[3], Ranjit Kumar[4], Anna Genin[5], Randy Q. Cron[1], Charles O. Elson[6], Casey D Morrow[7] and Elliot J. Lefkowitz[8], [1]Pediatric Rheumatology, University of Alabama at Birmingham, Birmingham, AL, [2]Pharmicology / Toxicology, University of Alabama at Birmingham, Birmingham, AL, [3]Pharmicology, University of Alabama at Birmingham, Birmingham, AL, [4]Center for Clinical and Translational Sciences, University of Alabama at Birmingham, Birmingham, AL, [5]Pediatrics, University of Alabama at Birmingham, Birmingham, AL, [6]Dept of Medicine, University of Alabama at Birmingham, Birmingham, AL, [7]Cell, Developmental, and Integrative Biology, University of Alabama at Birmingham, Birmingham, AL, [8]Microbiology, University of Alabama at Birmingham, Birmingham, AL

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Background/Purpose: Children with enthesitis-related arthritis (ERA) and adults with spondyloarthritis are at risk for intestinal inflammation. We have previously shown altered microbiota in children with ERA similar to inflammatory bowel disease. However, the mechanisms by which an altered microbiota might predispose to arthritis and intestinal inflammation remain unclear. Therefore, we explored expression profiles from fecal samples of children with ERA.

Methods: Fecal samples were obtained from patients with ERA and healthy controls. For metabolomics, samples were subjected to acid extraction and analyzed by nanoscale liquid chromatography coupled to tandem mass spectrometry (MS). Data analysis was performed with the mummichog for metabolomics program on the output of the positive and negative modes MS analyses, comparing metabolites identified by mass : charge ratio with at least a 1.5 fold difference between patients and controls, and a p-value of <0.05. This was repeated on a second cohort of largely newly diagnosed ERA patients and healthy controls. For metagenomics, fecal samples from a subset of the second cohort (10 with ERA & 8 controls) were subject to DNA purification and shotgun sequencing using MiSeq.

Results: The initial metabolomics run involved 12 ERA patients and 11 controls. Among the negative mode ions, pathway analysis revealed 5 pathways relatively under-represented in patients: metabolism of biopterin, tryptophan, glycerophospholipid, urea cycle, and tyrosine. The repeat run was performed on 15 non-overlapping patients with largely newly diagnosed ERA and 11 controls. Tryptophan metabolism again emerged as under-represented in patients among the negative mode ions, as did the butanoate pathway. Additionally, both runs revealed far more ions over-represented in controls as compared to patients. Metagenomics analysis was generally consistent with the metabolomics: more genes and pathways were represented in the controls compared to patients. In addition, the patients had less taxonomic diversity.

Conclusion: Multi-omics analysis of children with ERA compared to healthy controls indicates lower functional metabolic potential and activity in ERA patients, decreased taxonomic diversity, and possible differences in the fecal microbial metabolism of tryptophan. Thus, we have identified functional correlates to the diminished microbial diversity seen in many disease states. Also, tryptophan metabolism has been linked to the balance between Th17 and regulatory T cells; thus, it appears that the fecal microbiota may affect T cell development towards a pro- or anti-inflammatory phenotype. This may help to explain findings of intestinal inflammation and arthritis in children with ERA.

Disclosure: M. L. Stoll, None; **L. S. Wilson**, None; **S. Barnes**, None; **R. Kumar**, None; **A. Genin**, None; **R. Q. Cron**, None; **C. O. Elson**, None; **C. D. Morrow**, None; **E. J. Lefkowitz**, None.

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Abstract Number: 2821

Increased CD4 T Cell GM-CSF Production in Spondyloarthritis

M Hussein Al-Mossawi[1], Jelle De Wit[2], Anna Ridley[3] and Paul Bowness[1], [1]Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences, University of Oxford, Oxford, United Kingdom, [2]Nuffield Department of Orthopaedics Rheumatology and Musculoskeletal Sciences, University of Oxford, Oxford, United Kingdom, [3]Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Science, University of Oxford, Oxford, United Kingdom

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Background/Purpose:

Immunological, genetic and therapeutic studies have implicated the IL-17A/IL-23 inflammatory axis in SpA. GM-CSF is emerging as a cytokine that marks out a pathogenic subset within this inflammatory axis, and inhibition of this cytokine pathway is currently in clinical trials for rheumatoid arthritis. We sought to investigate the role of GM-CSF in SpA pathogenesis.

Methods:

Blood, synovial fluid and synovial tissue from patients with SpA was studied ex-vivo and in-vitro using SpA joint tissue explant assays. GM-CSF production from different cell types were characterised using multi-colour flow cytometry (FACS) and time-of-flight cytometry (CyTOF).

Results:

CyTOF analysis revealed ex-vivo GM-CSF production from multiple lymphoid but not myeloid cell lineages with CD4 cells clearly the main producers upon whole PBMC stimulation (Fig. 1). CyTOF findings were validated with flow cytometry (fig 2). The percentage of CD4 cells producing GM-CSF was significantly increased in AS PBMCs ex-vivo compared to healthy controls (mean 6.89% vs 3.30% n=31, p=0.006). Further characterisation of GM-CSF-producing T cells showed overlap with both classical Th1 and Th17 phenotypes. The mean percentage of GM-CSF-positive CD4 cells from ex-vivo synovial fluid mononuclear cells (SFMCs) was 34.27% and significantly higher compared to matched PBMCs (n=3, p=0.0391). CD4 cells from SpA synovial tissue mononuclear cell explant cultures also showed high levels of GM-CSF production by CD4 cells (n=6).

Conclusion:

Increased numbers of CD4 T cell produce GM-CSF in the blood and joint in SpA. GM-CSF may be a key pathogenic cytokine in SpA and can potentially be targeted therapeutically. Anti-GM-CSF monoclonal antibodies are already in phase three clinical trials for other inflammatory diseases and have shown an acceptable safety profile.

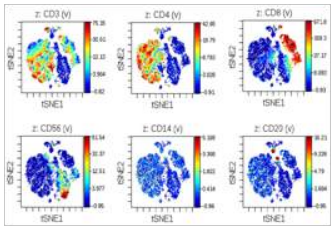

Figure 1: CyTOF shows CD4 cells to be the main producers of GM-CSF upon ex-vivo PBMC stimulation in AS.

Representative multi-dimensional viSNE analysis of all GM-CSF producers upon ex-vivo AS PBMC stimulation shows CD4 cells to be the predominant GM-CSF producing population. GM-CSF is also produced by populations of CD8, $CD56^{+}$ NK cells.

Figure 2: Flow cytometry confirms CD4 cells to be the predominant GM-CSF producers upon ex-vivo PBMC stimulation in AS.

Pooled sunburst analysis (Cytobank) from ex-vivo stimulated PBMCs of AS patients (n=5). CD4 cells account for greater than 50% of all GM-CSF production with smaller contributions from the CD8, γd-T Cell and $CD56^{+}$ NK cells.

Disclosure: M. H. Al-Mossawi, None; **J. De Wit**, None; **A. Ridley**, None; **P. Bowness**, None.

Abstract Number: 2822

Increased Peripheral Blood CCR6+/IL-23R+ Gamma Delta T Cells Are Associated with High Disease Activity in Patients with Axial Spondyloarthritis

Elizabeth Mainolfi[1], Susan M. Goodman[2], Shawn Anderson[3], Jon Hill[4], Thakker Paresh[5], Meera Ramanujam[6], Rivka Friedlander[7], Elli Kim[7], Dalit Ashany[8], Ed Purdue[9], Christine Averill[9], Michael Nevid[9], Allison Shaber[9], Lisa Mandl[10], Steven R. Goldring[11], **Gerald Nabozny**[1] and VP Bykerk[2], [1]Immunology and Inflammation, Boehringer Ingelheim Pharmaceuticals Inc., Ridgefield, CT, [2]Rheumatology, Hospital for Special Surgery, New York, NY, [3]Immunology, Boehringer Ingelheim Pharmaceuticals Inc., Ridgefield, CT, [4]Scientific Knowledge Discovery, Boehringer Ingelheim Pharmaceuticals Inc., Ridgefield, CT, [5]Transl. Medicine & Clin. Pharmacology, Boehringer Ingelheim Pharmaceuticals Inc., Ridgefield, CT, [6]Boehringer Ingelheim Pharmaceuticals Inc., Ridgefield, CT, [7]Department of Medicine, Rheumatology Division, Hospital for Special Surgery, New York, NY, [8]Rheumatic Disease, Hospital for Special Surgery, New York, NY, [9]Osteolysis Research Laboratory, Hospital for Special Surgery, New York, NY, [10]Department of Rheumatology, Hospital for Special Surgery, New York, NY, [11]Hospital for Special Surgery, New York, NY

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Background/Purpose: The IL-23 axis and Th17 type immunity has been implicated in the pathogenesis of Ankylosing Spondylitis (AS) and an enrichment of gamma delta (gd) T cells expressing IL-23R in AS patients has previously been reported (Kenna et al Arthritis Rheum. 2012). However, the relationship of these cells with clinical phenotype remains to be determined. We aimed to deepen the understanding of the relationship between the IL-23 axis, gd T cells and clinical phenotype in the immunopathogenesis of axial spondyloarthritis (axSpA) by examining cellular expression of IL-23 axis molecules on gd T cells in peripheral blood of highly active biologic naïve AS subjects.

Methods: Thirty nine patients diagnosed with active AS meeting ASAS criteria with sacroiliitis by imaging were recruited to a longitudinal observational study and phenotypically characterized using disease activity (ASDAS-CRP), radiographic vs. MRI only imaging changes, HLAB27, extraspinal features and medication use in first 6 months. Peripheral blood was obtained at baseline and multicolor flow cytometry performed to determine the expression of IL-23R and the IL-23 axis molecule CCR6 on gd T cells relative to healthy volunteer (HV) controls (n=20) .

Results: Of the 39 patients studied, 18 (46%) were male, mean (SD) age was 41.7 (15.3), symptom duration 9.6 (8.3) yrs, 15 (38%) were HLA-B27+, CRP (1.5 (1.4) mg/dl and ASDAS-CRP 2.7 (0.7). 11 (52%) of those with follow-up started TNFi therapy within 6 months. All had confirmed sacroiliitis, 15 (38%) by radiographs (rad), 18 (46%) by MRI (non-rad) sacroiliitis, and 6 (15%) by both. There were no significant clinical differences between sexes or those with radiographic/MRI findings. Similar to previously published studies, an increase in the % gd TCR+ cells was observed in SPA subjects vs control. Moreover, analysis of CCR6 expression on the gd subset demonstrated that 61.5% of SpA patients showed increased levels (mean % ± 2 s.d vs. HV) of CCR6+, gd + T cells in peripheral blood (CCR6 Hi) while 38.5% of the subjects were similar to HV controls (CCR6 Lo). The percentage of IL-23R+, gd T cells was also significantly increased in CCR6hi patients vs. CCR6lo patients (Table 1). Also, a correlation between the density of IL-23R and % CCR6+ gd cells in the SpA subjects was observed (r = 0.422, p=0.0074). Analysis of ASDAS-CRP scores showed that within the CCR6 Hi, gd subjects, 21% of the patients demonstrated severe disease (score >3.5) versus 6.6% in the CCR6 Lo group. Also, a trend towards increased CCR6 receptor expression on gd cells and severity of ASDAS-CRP was seen in CCR6 Hi subjects (r = 0.43)

Expression in Peripheral Blood

Cell Type	Marker	HV Control N=20	Mean ± SEM axSpA CCR6^{LO} N=15	axSpA CCR6^{HI} N=24
gd TCR+ CD3+ T cells	%CCR6+	21.60 ± 2.04	20.86 ± 3.11	65.32 ± 3.31
gd TCR+ CD3+ T cells	%IL-23R+	2.50 ± 0.83	1.22 ± 0.46	10.31 ± 3.36
gd TCR+ CD3+ T cells	IL-23R (MESF)*	66.25 ± 36.46	81.79 ± 22.57	299.30 ± 63.85

*** Molecules of Equivalent Soluble Fluorochrome**

Conclusion: These data sugg est that CCR6+, IL-23R+ gd T cells play a role in more active AS. Further understanding of how these cells contribute to the disease phenotype may lead to improved strategies for patient selection and treatment approaches for AS.

Disclosure: E. Mainolfi, Boehringer Ingelheim, 3; **S. M. Goodman**, Boehringer Ingelheim, 2; **S. Anderson**, Boehringer Ingelheim, 3; **J. Hill**, Boehringer Ingelheim, 3; **T. Paresh**, Boehringer Ingelheim, 3; **M. Ramanujam**, Boehringer Ingelheim, 3; **R. Friedlander**, Boehringer Ingelheim, 2; **E. Kim**, Boehringer Ingelheim, 2; **D. Ashany**, Boehringer Ingelheim, 2; **E. Purdue**, Boehringer Ingelheim, 2; **C. Averill**, Boehringer Ingelheim, 2; **M. Nevid**, Boehringer Ingelheim, 2; **A. Shaber**, Boehringer Ingelheim, 2; **L. Mandl**, Boehringer Ingelheim, 2; **S. R. Goldring**, Boehringer Ingelheim, 2; **G. Nabozny**, Boehringer Ingelheim, 3; **V. Bykerk**, Boehringer Ingelheim, 2.

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Abstract Number: 2823

Gut Inflammation in HLA-B27 Transgenic Rats Alters the Monocyte Compartment and Its Osteoclastogenic Potential

C. Ansalone, L. Utriainen, S. W. F. Milling and C. S. Goodyear, Institute of Infection, Immunity and Inflammation, College of Medicine, Veterinary Medicine and Life Sciences, University of Glasgow, Glasgow, United Kingdom

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Background/Purpose: Human HLA-B27 and β_2-microglobulin transgenic rats (B27 rats), an animal model for spondyloarthropathies, spontaneously develop inflammatory colitis and bone loss. We have previously demonstrated that B27 rats lack specific myeloid cell populations but it is not known whether gut inflammation drives systemic symptoms. Here we have examined central and peripheral myeloid cells, focusing on osteoclast precursors. To investigate the link between colitis and the peripheral disease we have assessed the effects of oral antibiotic treatment on intestinal pathology, and the subsequent systemic impacts.

Methods: Bone marrow (BM) and blood, from 14-16 week old B27 and control (B7) rats, were evaluated by flow cytometry for expression of CD90, CD3, CD45RA, Igκ, CD172a, CD43, and CD11b, and uptake of fluorescent M-CSF and CCL2. Plasma CCL2 levels were measured by ELISA. Monocytes from BM and blood were FACS sorted and cultured in pro-osteoclastogenic medium to evaluate osteoclastogenic potential. Mature osteoclasts, tartrate-resistant acid phosphatase positive multinucleated cells, were counted. Some B27 rats were given oral antibiotics for 4 weeks. Guts were collected for H&E staining and monocytes were analysed by flow cytometry. BM cells were cultured in pro-osteoclastogenic medium ± TNF-α and the generated osteoclasts were counted.

Results: Rat central and peripheral monocytes comprise two main subsets: $Lin^-(CD90^-CD3^-CD45RA^-Ig\kappa^-)CD172a^+CD11b^+CD43^{hi}$

and $Lin^-CD172a^+$ $CD11b^+CD43^{low}$. A $Lin^-CD172a^+CD43^{low}CD11b^{low}$ BM monocyte subset has also been described. In B27 rats, there was a substantial increase in the number of circulating $Lin^-CD172a^+CD43^{low}$ monocytes, which significantly correlated with higher levels of plasma CCL2. Interestingly, this population of monocytes (in BM and blood) has the greatest *in vitro* osteoclastogenic potential. Antibiotic treatment of rats substantially reduced colitis, plasma CCL2 levels, and the number of central and circulating $Lin^-CD172a^+CD11b^+CD43^{low}$ monocytes. Finally, antibiotic treatment also prevented the previously described TNF-α enhanced osteoclastogenesis observed in transgenic B27 rats.

Conclusion: B27 rats have increased numbers of myeloid osteoclast progenitors in the circulation and bone marrow, and higher levels of the monocyte chemokine CCL2, potentially contributing to enhanced inflammation and bone loss. Importantly, antibiotic treatment not only reduced gut inflammation but also decreased circulating levels of CCL2 and $Lin^-CD172a^+CD11b^+CD43^{low}$ cells. This study therefore provides a link between colitis and systemic inflammation, and a mechanism connecting these with altered bone homeostasis.

Disclosure: C. Ansalone, None; **L. Utriainen**, None; **S. W. F. Milling**, None; **C. S. Goodyear**, None.

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Abstract Number: 2824

Autoantibodies Against CD74 – a New Diagnostic Marker for Spondyloarthritis (SpA)

Bruno Larida, AESKU.DIAGNOSTICS INC, Oakland, CA
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Background/Purpose:

Spondyloarthritis (SpA) is a common debilitating inflammatory disorder. The pathogenesis of axial spondyloarthritis (axSpA) including ankylosing spondylitis (AS), although known to be strongly associated with genes such as the human leukocyte antigen HLA-B27, is still largely unclear. Establishing the diagnosis is difficult, since abnormalities in conventional X-rays develop with a latency of several years and only HLA-B27 is used as a laboratory marker. Additionally, the presence of radiographic sacroiliitis is now essential for the diagnosis of SpA. Furthermore, to prevent destructive effects of the disease, early diagnosis and intervention in patients with SpA may be important. Therefore, the goal of our study was to evaluate antibodies to the human leukocyte antigen class II-associated invariant chain peptide (anti-CD74) as a diagnostic marker of SpA.

Methods:

Sera of SpA and non-SpA patients were analyzed for IgA and IgG antibodies against CD74 by ELISA. Sera for the ELISA were obtained from 117 patients with axial SpA. Sera of 38 blood donors served as controls. All donors provided informed consent for the study, which was approved by the local ethics committee (project number 4928).

Results:

We analyzed 155 sera from 117 SpA and 38 non-SpA patients. SpA patients were more often male and younger. HLA-B27 status was available in 112 patients. Anti-CD74 antibodies were detected in 85.1% of the SpA patients but only in 5% of the non-SpA patients ($p \leq 0.0001$). The detection of both IgG and IgA anti-CD74 antibodies for diagnosing SpA revealed a sensitivity of 77% and a specificity of 90%. Remarkably, IgA autoantibodies against CD74 alone had a sensitivity of 67% and a specificity of 95%, the likelihood ratio (LR) LR+ was 12.7 and LR- was 0.35. Moreover, IgA anti-CD74 antibodies were even more frequent in SpA patients with short disease duration and significantly correlate with more advanced radiological sacroiliitis and reduced spinal mobility.

Conclusion:

Anti-CD74 IgA antibodies were strongly associated with SpA. Antibodies against CD74 could provide an important additional tool for diagnosis of SpA.

Disclosure: B. Larida, None;

Abstract Number: 2825

Characterization of Mesenchymal Stem Cells Generated from Axial Spondyloarthritis Patient-Derived Induced Pluripotent Stem Cells

Gerlinde Layh-Schmitt[1], Shajia Lu[1], Emily Lazowick[1], Stephen Brooks[1], Massimo Gadina[1] and Robert A. Colbert[2], [1]NIAMS/NIH, Bethesda, MD, [2]National Institute of Arthritis and Musculoskeletal and Skin Diseases, National Institutes of Health, Bethesda, MD

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Background/Purpose: Ankylosing spondylitis (AS) is an immune-mediated inflammatory disease associated with trabecular bone loss and concomitant aberrant bone formation in the spine. Over 40 genes or genetic regions have been associated with the risk of developing AS. The impact of these genes on disease pathogenesis and the cell types that mediate these effects remain largely unknown. To begin to address these questions we generated induced pluripotent stem cells (iPSCs) from fibroblasts of axial spondyloarthritis (AxSpA) patients and healthy controls (HC), differentiated them into disease-relevant cell lineages like mesenchymal stem cells (MSCs) and osteoblasts (OBs), and analyzed comprehensive gene expression patterns and expression levels of AS risk genes in iPSCs and MSCs using whole blood as a comparison.

Methods: Dermal fibroblasts from two AxSpA patients and one HC were reprogrammed using a Sendai virus vector encoding OCT4, SOX2, KLF4 and MYC. Virus-free iPSCs were differentiated into MSCs using a TGF-β inhibitor. MSCs were differentiated into osteoblasts, by culturing them in cell type specific differentiation media. Immunofluorescence microscopy and flow cytometry were conducted to evaluate the expression of lineage specific markers. Genome-wide gene expression patterns in iPSCs and MSCs were compared with whole blood using RNA-Seq followed by Principle Components Analysis (PCA) and Ingenuity Pathway Analysis (IPA).

Results: Reprogrammed lines expressed iPSC-specific genes and proteins, and iPSCs were successfully differentiated into functional MSCs. Gene expression analysis revealed distinct cell type-specific clusters and differentially expressed pathways identified by IPA. The expression of known AS risk genes in iPSCs and MSCs was compared to peripheral blood, revealing several genes that were highly enriched in MSCs (e.g. EDIL3, ANO6, HAPLN1) or expressed at high levels, but comparable to blood (TNFRSF1, TYK2, SH2B3, and STAT3). MSCs were further differentiated into osteoblasts. Differences in osteoblast mineralization potential between subject-derived lines were consistent in duplicate iPSC derivations, with the AxSpA patient exhibiting 3-fold higher mineralization than the HC along with increased expression of alkaline phosphatase (ALP) mRNA in patient lines, whereas other genes associated with osteoblast differentiation (etc. RUNX2, Osterix) were expressed equally in all lines.

Conclusion: AxSpA patient-derived iPSCs demonstrated pluripotency, lineage-specific gene expression patterns, and could be differentiated into disease-relevant cell types. A subset of risk genes was expressed predominantly in MSCs, underscoring the potential utility of these cells in studying pathogenic mechanisms. Moreover, enhanced OB mineralization potential was reproducible in separate iPSC derivations from the same individuals. We are currently generating more lines to determine whether this is a disease characteristic. In summary, skin fibroblast-derived iPSCs provide a powerful system to explore the functional genomics of AS risk genes that may impact bone formation.

Disclosure: G. Layh-Schmitt, None; **S. Lu**, None; **E. Lazowick**, None; **S. Brooks**, None; **M. Gadina**, None; **R. A. Colbert**, None.

Abstract Number: 2826

Stimulation of Autophagy Reduces Misfolded HLA-B27 in a Rat Model of Spondyloarthritis

Fatemeh Navid[1], Gerlinde Layh-Schmitt[1] and Robert A. Colbert[2], [1]NIAMS/NIH, Bethesda, MD, [2]National Institute of Arthritis and Musculoskeletal and Skin Diseases, National Institutes of Health, Bethesda, MD

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Background/Purpose: HLA-B27/human $\beta_2$microglobulin transgenic rats develop spondyloarthritis (SpA) characterized by inflammation in the gut and peripheral joints by mechanisms that remain poorly defined, but do not require CD8+ T cells. HLA-B27 has a tendency to misfold and dimerize, and when upregulated, aberrant forms can accumulate in the endoplasmic reticulum (ER) and on the cell surface. ER accumulation can activate an unfolded protein response (UPR), which promotes pro-inflammatory cytokine production, and cell surface accumulation may trigger effector immune cells expressing certain killer immunoglobulin receptors (KIRs), both of which may contribute to disease. Here, we examined whether autophagy is involved in the degradation of HLA-B27 in transgenic rats and whether alteration of this pathway may affect accumulation of aberrant forms and the generation of ER stress.

Methods: Bone marrow-derived macrophages (MΦ) were obtained from HLA-B27-transgenic (TG), HLA-B7-TG and Lewis wild type (WT) rats and autophagy was induced with rapamycin treatment for 2 hours. Chloroquine or bafilomycin were used to block autophagic flux. The level of autophagy was measured by the amount of cytosolic microtubule-associated protein 1 light chain 3B-II (LC3B-II) expression detected by western blot (WB), flow cytometry (FACS) or immunofluorescence (IF). Expression of HLA-B27 was determined by WB analysis of cell lysates or after immunoprecipitation (IP) with the HC10 antibody. XBP1 mRNA splicing was used as an early marker to determine whether the UPR is activated after stimulation with IFNγ and TNFα in the presence or absence of bafilomycin or rapamycin.

Results: There was no difference in autophagy in HLA-B27-expressing MΦ compared to WT and HLA-B7-expressing cells based on WB and FACS analysis of LC3B-II expression upon stimulation of autophagy (rapamycin) or inhibition of autophagic flux (chloroquine). LC3B-II expression determined by IF showed a cytosolic vesicular pattern in all cells confirming LC3B-II localization in autophagic vesicles. However, inhibition of autophagic flux (bafilomycin) during upregulation of HLA expression with IFNγ resulted in an accumulation of HLA heavy chains, and in particular misfolded forms of HLA-B27. There was also significant exacerbation of ER stress (which itself is induced by blocking autophagic flux) as measured by XBP1 mRNA splicing. In contrast, activation of autophagy with rapamycin reduced the accumulation of aberrant forms of HLA-B27 induced by IFNγ, and resulted in diminished XBP1 splicing.

Conclusion: These results demonstrate that blocking autophagic flux causes ER stress, and that HLA-B27 expression exacerbates this response. More importantly, induction of autophagy can reduce the accumulation of misfolded forms of HLA-B27, and may alleviate ER stress. Current studies are assessing effects of autophagy on the cellular distribution of aberrant forms of HLA-B27. Alteration of the autophagic pathway may be a promising therapeutic tool worthy of further investigation in the treatment of SpA.

Disclosure: F. Navid, None; **G. Layh-Schmitt**, None; **R. A. Colbert**, None.

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Abstract Number: 2827

Analysis of HLA-B27 Transgenic Rats Reveals Specific Gut Transcriptome and Microbiome Signatures Associated with Inflammation

Tejpal Gill[1], Mark Asquith[2], Stephen Brooks[1], James T. Rosenbaum[3] and Robert A. Colbert[4], [1]NIAMS/NIH, Bethesda, MD, [2]OHSU, Portland, OR, [3]Devers Eye Institute, Legacy Hospital system, Portland, OR, [4]National Institute of Arthritis and Musculoskeletal and Skin Diseases, National Institutes of Health, Bethesda, MD

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Background/Purpose: HLA-B27 and human beta 2-microglobulin expression in rats (transgenic; TG) induces a spontaneous inflammatory disease resembling human spondyloarthritis (SpA) with associated gastrointestinal inflammation. While aspects of rat SpA have been studied in detail, our understanding of gut inflammation remains limited. We recently showed that HLA-B27 affects the

gut microbiota in TG rats. Therefore, the aim for our current project was to determine the association between intestinal microbiota and host gut transcriptome among TG rats developing SpA-like disease. Lewis (LEW), Fischer (F344), and Dark Agouti (DA) rats with same transgene locus (33-3) at 2, 3 and 6 months of age along with strain-specific controls were studied. TG LEW and F344 rats develop SpA beginning with colitis at about 8 weeks of age, while TG DA rats are disease resistant. Arthritis develops later in LEW and F344 TG animals, and is more variable.

Methods: To determine gut inflammation, tissue samples from cecum and colon were stained with H&E and scored for histology. Gut transcriptome differences were analyzed using Illumina HiSeq 2000 and differential gene expression was assessed. To characterize microbial profiles, 16SrRNA gene from gut microbiota was amplified and sequenced using Illumina MiSeq. Data were quality-filtered using Quantitative Insights Into Microbial Ecology (QIIME) and relative frequency was calculated.

Results: Inflammation in the cecum and colon occurred earlier and was more severe in F344 TG rats compared to LEW based on histology scores. Differential gene expression in LEW and F344 TG animals revealed marked up-regulation of IL-17 (A, F) as well as upregulation of *Il23a.* Interferon (IFNg) and IFN response genes were upregulated in TG rats, as were apoptotic signaling and oxidative stress pathways (upregulation of *Gpx2, Nox1*, *Duox2* and downregulation of *Apoa1*). Although there was no significant gut inflammation in DA TG rats, we observed upregulation of many of these genes at 2-3 months, followed by return to normal at 6 months of age. Microbial profiling revealed increased relative frequency of *Akkermansia* in F344 TG and LEW TG rats. Increased abundance of *Candidatus Arthromitus*, a segmented filamentous bacteria (SFB) implicated in inducing Th17 responses, was detected in the F344 and LEW animals. Interestingly we were unable to detect SFB in DA, which could account for the lack of Th17 cytokines and absence of SpA including gut inflammation.

Conclusion: Transcriptome analysis of the HLA-B27 TG reveals upregulation of interferon and Il23/Il17 mediated pathways suggesting a proinflammatory shift in the immune microenvironment of the gut. In TG rats, microbial dysbiosis is associated with a decrease in *Firmicutes*, and an expansion of *Proteobacteria, Prevotella spp.* and *Akkermansia muciniphila.* Protective effects of DA background may be linked to the absence of SFB in the gut. Ongoing analyses underway correlating microbial communities with activation of the IL-23/IL-17 axis, IFN signaling, and oxidative stress pathways will establish links with disease severity. This should increase our understanding of SpA associated IBD and generate mechanistic hypotheses as well as potential biomarkers for diagnosis and treatment.

Disclosure: T. Gill, None; **M. Asquith**, None; **S. Brooks**, None; **J. T. Rosenbaum**, None; **R. A. Colbert**, None.

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Abstract Number: 2828

Profiling Immunogenic Bacteria within the Microbiota of ZAP-70 Mutant SKG Mice Associated with Spondyloarthritis and Ileitis Using IgA-SEQ

Linda Rehaume[1], Alicia Kang[1], Olga Zbarskaya[1], Jane Mullaney[1], Matthew Kim[1], Paraic O Cuiv[1], Nicola Angel[2], Philip Hugenholtz[2], Mark Morrison[1] and Ranjeny Thomas[1], [1]Translational Research Institute, The University of Queensland Diamantina Institute, Brisbane, Australia, [2]Australian Centre for Ecogenomics, The University of Queensland, Brisbane, Australia

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Session Time: 9:00AM-11:00AM

Background/Purpose:

IgA production is the main barrier mechanism of mucosal surfaces. High affinity IgA is generated through T cell-dependent mechanisms and preferentially binds to invasive or pathogenic bacteria, whereas low affinity IgA is T cell-independent and binds commensal bacteria. Next-generation sequencing of IgA-coated bacteria (IgA-SEQ) identified consortia of bacteria from mouse or human gut microbiota that exacerbate murine colitis, including unclassified *Prevotella* and *Bacteroides* species. The colitogenic species, *Prevotella copri,* was associated with new-onset rheumatoid arthritis, and *Prevotella spp*. were increased in the cecum of HLA-B27 transgenic rats. BALB/c ZAP-70^{W163C} (SKG) mutant mice treated with beta-glucan (curdlan) develop an IL-23-dependent disease recapitulating human spondyloarthritis, in which ileitis is microbiota-dependent. SKG mice housed in specific pathogen-free (SPF) conditions have a dysbiosis in which Gram negative bacteria are over-represented. Furthermore, ileitis severity is decreased in TLR4-deficient SKG mice. Our aim was to study SKG mice colonized with a limited bacterial consortium or an unrestricted microbiota to define bacteria driving dysbiosis and the development of ileitis in a genetically susceptible host.

Methods:

Fecal and tissue samples were collected from germ-free (GF) SKG and GF-BALB/c mice recolonized with a limited bacterial consortium known as altered Shaedler microbiota (ASM) (*Eubacterium plexicaudatum*, *Lactobacillus murinus*, *Mucispirillum schaedleri*, 2 *Clostridium* sp., *Lactobacillus* sp., *Parabacteroides* sp., *Firmicutes* bacterium). Fecal samples were collected from naive SKG mice housed under SPF conditions and IgA-coated bacteria were enriched by magnetic-activated cell sorting, then the IgA^{bright} and IgA^{dim} bacteria were enriched by fluorescence-activated cell sorting. Real-time PCR identified the fecal microbiota composition in ASM mice. IgA-, IgA^{dim} and IgA^{bright} bacteria were identified by deep sequencing.

Results:

After colonization of GF mice with ASM, four bacterial strains were detected in ASM-SKG and ASM-BALB/c mice: *Clostridium* sp., *Lactobacillus murinus*, *Mucispirillum schaedleri*, *Parabacteroides* sp. ASM-SKG microbiota exhibited dysbiosis relative to ASM-BALB/c in that the Gram positive *Clostridium* sp. and Gram negative *Parabacteroides* sp. were decreased in SKG faces. However, the dominant bacterial species in both strains of mice was the *Parabacteroides* sp. In naive SKG mice housed under SPF conditions, Gram negative *Prevotellaceae* were enriched among IgA^{bright} bacteria, while Gram negative *Lactobacillaceae* were diminished. Conversely *Lactobacillaceae* were enriched among IgA^{dim} bacteria and *Prevotellaceae* were diminished.

Conclusion:

Interaction of the microbiota with the immune system of SKG mice alters the composition of both a limited consortium and an unrestricted bacterial community. The most immunogenic IgA^{bright} bacteria within the microbiota of naïve SKG mice are enriched in *Prevotellaceae*, which have been associated with rheumatoid arthritis and inflammatory bowel disease. IgA-SEQ is a powerful tool to identify potentially immunogenic bacteria from a highly diverse microbiota.

Disclosure: L. Rehaume, None; **A. Kang**, None; **O. Zbarskaya**, None; **J. Mullaney**, None; **M. Kim**, None; **P. O Cuiv**, None; **N. Angel**, None; **P. Hugenholtz**, None; **M. Morrison**, None; **R. Thomas**, None.

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Abstract Number: 2829

Enhanced Expression of the Transcription Factor T-Bet Alters Pro-Inflammatory Cytokine Profile in Ankylosing Spondylitis

Max C. Lau[1], Patricia Keith[1], Mary-Ellen Costello[1], Linda A. Bradbury[1], Kelly A. Hollis[1], Gethin P. Thomas[2], **Matthew A. Brown**[1,3] and Tony J. Kenna[1], [1]The University of Queensland Diamantina Institute, Brisbane, Australia, [2]Translational Reserch Institute, The University of Queensland Diamantina Institute, Brisbane, Australia, [3]Translational Research Institute, Brisbane, Australia
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SESSION INFORMATION
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Session Title: Spondylarthropathies and Psoriatic Arthritis - Pathogenesis, Etiology Poster II
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Session Time: 9:00AM-11:00AM

Background/Purpose: *TBX21* encodes T-bet, a T-box transcription factor, and lies within a locus with genome-wide significant association with AS (rs11657479, odds ratio=1.13, $P=6.16x10^{-10}$). T-bet is implicated in both innate and adaptive arms of immunity. However, the role of T-bet in AS pathogenesis is unclear

Methods:

We examined the role of T-bet in disease development and progression in peripheral blood mononuclear cells (PBMCs) from 172 AS cases and 83 healthy control (HC) carrying either risk or protective alleles of rs11657479, the peak AS-associated *Tbx21* SNP, by qPCR and flow cytometry. We also examined kinetics and localization of T-bet expression in the SKG mouse model of spondyloarthropathy, and the impact of *Tbx21* knockout on arthritis development in SKG mice.

Results:

T-bet expression by qPCR was increased in AS cases compared with HC ($P=3.6x10^{-5}$), and was associated with rs11657479

genotypes in AS cases (P=0.0017), with risk genotype carriers having higher expression (ΔΔCt=0.064±0.074) than protective (ΔΔCt=0.022±0.020, P=0.0003) genotypes. The proportion of cells expressing T-bet was increased in both CD3-positive and -negative PBMCs in AS vs HC (CD3- 1.3x increase, P=0.0012; CD3+ 3.9x increase, $P<10^{-4}$). A marked expansion of T-bet CD3+ CD4- CD8+ T cells was seen in AS cases (31.47±8.45%) compared with healthy controls (3.00±2.54%)(P<0.0001), with all AS cases studied having higher proportions of these T-bet expressing cells than all controls studied. This increase in AS case T-bet expression was particularly prominent in interleukin-17- (IL-17) producing NK cells (3.4x increase % cells expressing T-bet, P=0.0005) and cytotoxic T ($T_C17.1$) cells (5.6x increase % cells expressing T-bet, $P<10^{-4}$). In curdlan-treated SKG mice, T-bet expression increased early after disease initiation and persisted, from 7 days onward, throughout the course of AS-like disease. In Tbx21-/- compared with wild-type SKG mice, there was marked reduction in both gut and peripheral joint inflammation, and reduced numbers of $T_C17.1$ cells.

Conclusion: *Tbx21* genetic variants operate to increase the risk of AS through effects on T-bet expression. T-bet, through influences on the function of innate and adaptive immune cells, plays a major role in the pathogenesis of spondyloarthropathy in humans and mice.

Disclosure: M. C. Lau, None; **P. Keith**, None; **M. E. Costello**, None; **L. A. Bradbury**, None; **K. A. Hollis**, None; **G. P. Thomas**, None; **M. A. Brown**, Abbvie, Pfizer, UCB, Wyeth, Leo Pharma, NIAMS, NHMRC, Arthritis Australia, Qld Government, 2,Pfizer, Abbvie, UCB, 5,Pfizer, Abbvie, UCB, 8; **T. J. Kenna**, None.

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Abstract Number: 2830

Synovial Fluid T Cells of Patients with Reactive Arthritis and Undifferentiated Spondyloarthropathy Respond to Salmonella Typhimurium Outer Membrane Protein a and Induces IL17 and IL23 Production By Synovial Fluid Mononuclear Cells

Ramnath Misra[1], Smriti Chaurasia[1], Ajit K Shashny[2] and Amita Aggarwal[3,4], [1]Clinical Immunology, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, India, [2]Central Institute of Medicinal and Aromatic Plants, Scientist, Lucknow, India, [3]Clinical Immunology, Additional Professor Sanjay Gandhi Post Graduate Institute of Medical Sciences, Lucknow, Lucknow, India, [4]Department of Clinical Immunology, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, India

First publication: September 29, 2015

SESSION INFORMATION

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Session Title: Spondylarthropathies and Psoriatic Arthritis - Pathogenesis, Etiology Poster II

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Background/Purpose: We have previously shown that synovial fluid mononuclear cells (SFMCs) of patients with Reactive arthritis (ReA) and undifferentiated Spondyloarthropathy (uSpA) proliferated to low molecular weight fractions of outer membrane proteins (OMP) of *S typhimurium*. Proteomic analysis of the the stimulatory fractions predicted to consist of 10 proteins including OMPA and OMPD . In this study, we examined the *in vitro*immunogenecity of recombinant (r) OMP A and D by measuring frequency of antigen specific CD4+ and CD8+ T cells against rOMP A and D in the synovial fluid (SF) of patients with ReA/uSpA. Further, induction of proinflammatory cytokines (IFN- γ, IL-17 and IL-23) were measured by SFMC stimulated by rOMPA and rOMP D in these patients.

Methods: Patients presenting with typical clincial picture of asymmetric lower limb oligoarthritis with a history of preceding diarrhoea within 4 weeks were labelled as Rea and uSpA patients fulfilled ESSG criteria. Synovial fluid were aspirated from inflammed knee joint prior to steroid injections and monnonuclear cells (SFMC) were isolated and cultured with crude extract of s typhimurium OMP and rOMPA/D for flow cytometry, ELISPOT and cytokines in the culture supernatant. Intracellular IFN-γ and IL17 producing SF T (CD4+CD69+ and CD8+ CD69+) cells was enumerated by Flow cytometry (Beckman Coulter, USA) Antigen specific IFN-γ producing T cells were also measured by ELISPOT. A positive response was taken if the ratio of % cells or mean spots/well with antigen/Control ≥ 3. IFN-γ (BD,USA) , IL17 and IL23 (ebioscinces, USA) levels were measured by commericial ELISA in the culture supernatant of antigen treated SFMCs.

Results: Out of 20 patients recruited, 17 were males with a median age 27.6 years (range 15-65 year). Eleven patients were ReA. The median duration of current episode was 15 days (range 3-180) days. HLA B27 were positive in 13/19 patients. Thirteen out of 20 patients with ReA/uSpA, showed a CD8+CD69+IFN+ response to crude OMP suggesting triggered by *S. typhimurium*. Of these 13, 9 patient's SF CD8+CD69+T cells positive for intracellular γ-IFN in response to rOMPA as compared to 4 patients who responded to rOMPD. The mean frequency (%) of antigen specific CD8+CD69+ T cells were 0.56±0.5 to rOMPA and 0.24±0.15 to rOMPD in

comparison to blank 0.18±0.17. Regarding CD4+T cell response, 6 out of 15 were postive against crude OMP and of these 4 responded to rOMPA and only 2 responded to rOMPD. By ELISPOT assay 13, 7 and 3 patients showed increased IFN-γ producing T cells to crude OMP, rOMPA and rOMPD respectively. Only 1 RA patients SF CD8+T cells showed response to crude OMP. SFMC upon stimulation with rOMP A and not rOMP D produce significant IFN-γ, IL-17 and Il-23 in comparison to non treated cells (Table)

Table . Induction of pro inflammatory cytokines by SFMC stimulated by rOMP A /D

Cytokine (pg/ml)	Blank, (a)	rOMP A (b)	Significance b vs a	rOMP D c	Significance c vs a
IFN γ	691.98±999.27	3129.4±5365.48	P<0.05	1793.2±2842.79	No signifiance
IL17	36.42±62.64	74.33±129.27	P<0.05	41.58±72.54	No significance
IL23	44.86±41.98	208.59±269.56	P<0.05	49.87±59.43	No significance

Conclusion: OMPA is a major antigenic target in patients with *Salmonella* triggered ReA/uSpA.

Abstract Number: 2831

A Subset of Natural Killer Cells Are Expanded in Synovial Fluid of Patients with Reactive Arthritis and Undifferentiated Spondyloarthritis

Abhra Chandra Chowdhury, Smriti Chaurasia, Amita Aggarwal and Ramnath Misra, Clinical Immunology, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, India

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Background/Purpose:

We have previously shown that there is an increase in IL-17 in the synovial fluid of patients with Reactive arthritis(ReA) and undifferentiated spondyloarthropathy(uSpA). Besides Th17 cells, IL-17 is produced by several innate cells such as NK, NKT , γδT and double negative T cells(DNT) To account for increased IL-17 we have enumerated these innate cells in the peripheral blood and synovial fluid of patients with ReA/uSpA.

Methods:

Patients were labelled as Reactive arthritis if they had a typical clinical history of acute or subacute onset of asymmetrical oligoarthritis with a preceding history of diarrhoeal illness within 4 weeks and as uSpA if patients fulfilled ESSG criteria but didnot fit into any defined spondyloarthropathy. 10 to 30 ml of Synovial fluid was aspirated from the inflammed knee joint prior to corticosteroid injection along with peripheral blood in EDTA for cell analysis. Peripheral blood (PB) of 28 patients with ReA/uSpA and paired synovial fluid (SF)in 20 patients were collected between September 2014 and June 2015 for analysis. The percentage of NK cells(CD56+CD3-)/NK cells($CD56^{bright}$) / NK cells($CD56^{dim}$) / NKT cells(CD3+/CD56+) , DNT cells($CD4^-/CD8^-$ αβTCR+CD3+)and γδT cells(γδTCR+CD3+) were determined by flow cytometry (Beckman Coulter, USA) using a panel of monoclonal antibodies (BD biosciences, USA) In paired samples the percentage of cells were compared between the synovial fluid and peripheral blood by non parametric tests(Wilcoxon signed ranks test)

Results:

28 patients(male-25 female–3) with a median age 24(IQR 20-31) years were recruited .Of these 12 were ReA and 16 were uSpA.4 patients had chronic symptoms whereas 24 had acute episode.Knee was the most common joint involved followed by ankle.11 patients had evidence of enthesitis (most common-achilles tendinitis)whereas 3 patients had extra-articular involvement. The median frequency and interquartile range of various cell population in the peripheral blood and synovial fluid are presented in Table 1.

Table 1. Percentage (median and interquartile range) of various innate cells in peripheral blood and synovial fluid

Innate cells	Peripheral blood % median(interquartile range)	Synovial Fluid % median(interquartile range)
NK cells(CD56+CD3-)	8 (6.3-10.5)	10.6(5.7-13)
CD56 ^{bright}NK cells	0.5 (0-0.9)	4.4(0.35-8.45)**
CD56 ^{dim} NK cells	6.8 (0-10.3)	1.35(0.15-2.80)**
NKT cells	3.3(1.2-5.6)	2.2(1.40-3.75)
DNT cells	1.7(0.9-2.0)	1.8(1.2-2.2)
γδT cells	3.3(1.4-5.4)	1.5(0.85-3.15)*

** $p < 0.005$ * $p < 0.05$

CD56 ^{bright} NK cells was significantly increased in synovial fluid(p=.000) and CD56 ^{dim}NK cells was significantly decreased in synovial fluid(p=0.001) in comparison to peripheral blood. As it is known that CD56 bright NK cells can produce IL17 , these cells can be a innate source of IL17 in the inflamed joints.Also γδT cells was significantly increased in peripheral blood (P=.022).

Conclusion:

CD56 ^{bright} NK cells which are cytokine producers are expanded in the synovial compartment as compared to peripheral blood and may be contributing to the production of IL-17 in ReA and uSpA. The increase of peripheral blood γδT cells is most likely related to its origin from the gut.

Disclosure: A. Chandra Chowdhury, None; **S. Chaurasia**, None; **A. Aggarwal**, None; **R. Misra**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/a-subset-of-natural-killer-cells-are-expanded-in-synovial-fluid-of-patients-with-reactive-arthritis-and-undifferentiated-spondyloarthritis

Abstract Number: 2832

Characterization of Leukocyte Subsets in Ankylosing Spondylitis Patients

Yolanda Jiménez Gómez, Chary Lopez-Pedrera, Pilar Font, Patricia Ruiz-Limon, Carlos Perez-Sanchez, Nuria Barbarroja, M. Carmen Castro Villegas, Jerusalem Calvo-Gutierrez, MariCarmen Abalos-Aguilera, Alejandro Escudero-Contreras and Eduardo Collantes-Estevez, IMIBIC-Reina Sofia University Hospital, Rheumatology Unit, Cordoba, Spain

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Session Time: 9:00AM-11:00AM

Background/Purpose:

AS is a chronic inflammatory disease, of unknown aetiology, characterized by pathological ossification. We aimed: 1) To analyze the profile of inflammation, oxidative status and bone turnover in plasma and leukocyte subsets, as well as the endothelial function (EF) in AS patients. 2) To evaluate the relationship among those biomarkers and their correlation with disease activity.

Methods:

Thirty AS patients and 30 healthy donors were included in the study. Disease function and activity status were analyzed by BASFI and BASDAI indexes. EF was determined by the post occlusive hyperaemia test. Biomarkers of oxidative stress, inflammation, thrombosis and bone turnover were analyzed in lymphocytes, neutrophils and monocyte subsets (MON1: $CD14^{+}/CD16^{-}$; MON2: $CD14^{+}/CD16^{+}$; MON3: $CD14^{dim}/CD16^{+}$) by RT-PCR and flow cytometry. Antioxidant enzyme activities, nitric oxide (NO) and total antioxidant capacity (TAC) of plasma were measured by specific kits.

Results:

Compared to healthy donors, a significant EF alteration was observed in AS patients. The analysis of inflammatory markers showed increased expression of TNFα and signal transducter and activator of transcription 3 (STAT3) in neutrophils, and of IL6, IL23, IL2 and STAT3 in lymphocytes. The monocyte analysis demonstrated a reduction in %MON1, along with an increase in %MON2. MON1 showed a specific alteration of STAT3, I kappa B kinase (IKK), TNFα and IL6, whereas MON2+MON3 displayed elevated levels of IL23, macrophage inflammatory protein-1α, tissue factor and IKK. Osteogenic markers significantly elevated in neutrophils were ALP and dickkopf (DKK)-1. Lymphocytes displayed reduced levels of DKK1 and osteoprotegerin (OPG) whereas MON1 showed an alteration of BMP2, DKK1, OPG and TGFß1. Oxidative stress study showed that leukocyte subsets from patients display an increase in oxidative stress markers and mitochondrial dysfunction, along with an alteration of TAC and NO at plasma level. *In vitro* treatment of healthy leukocyte subsets with pooled serum from patients displaying structural damage and low inflammation status caused a significant increase in oxidative stress markers, as well as prominent changes in inflammatory and osteogenic gene expression.

Correlation studies showed that AS development was associated with endothelial dysfunction, inflammation and osteogenesis. Oxidative stress and mitochondrial dysfunction were associated with inflammatory and osteogenic markers. Endothelial dysfunction was correlated with inflammation and mitochondrial dysfunction. Osteogenesis was associated with inflammatory markers.

Conclusion:

1) AS patients show an endothelial dysfunction directly associated with the inflammatory profile and disease progression. 2) Circulating leukocyte subsets in AS patients seem to contribute to the inflammatory and bone turnover processes, so that neutrophils and MON1 seem to mediate both processes whereas lymphocytes and MON2+MON3 seem to be more associated with the inflammatory process. 3) The oxidative stress and, particularly, the mitochondrial dysfunction, might also mediate the inflammation and ossification processes present in AS

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View Abstract and Citation Information Online - http://acrabstracts.org/abstract/characterization-of-leukocyte-subsets-in-ankylosing-spondylitis-patients

Abstract Number: 2833

Negative Regulator, MiR-23a, Down-Regulated in Psoriatic Arthritis. Implications for Disease Pathogenesis

Sarah Wade[1], Michelle Trenkmann[1], Trudy McGarry[1], Douglas J. Veale[2] and Ursula Fearon[1], [1]St. Vincent's University Hospital, Centre for Arthritis and Rheumatic Diseases, Dublin Academic Medical Centre, Dublin 4, Ireland, [2]St Vincent's University Hospital, Centre for Arthritis and Rheumatic Diseases, Dublin Academic Medical Centre, Dublin 4, Ireland

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Background/Purpose: Psoriatic Arthritis (PsA) is a chronic immune-mediated inflammatory disease, characterised by proliferation of synovial tissue and progressive destruction of articular cartilage/bone associated with psoriasis. These processes may be governed by microRNA (miRNA), a class of small non-coding RNAs which exert their function through suppression of specific target genes. Altered miR-23a expression has been previously associated with angiogenic and pro-inflammatory mechanisms in other diseases. To date, altered miRNA expression and regulation has not been examined in PsA.

Methods: Synovial tissue biopsies were obtained under direct visualisation from site of inflammation by needle arthroscopy, along with peripheral blood mononuclear cells (PBMC) from PsA (n=8), osteoarthritis (OA) (n=7), and healthy controls (n=8). To examine possible factors involved in regulating miRNA expression, primary PsA synovial fibroblasts (SFC) were isolated and cultured with candidate pro-inflammatory stimuli including TLR ligands: Pam3CSK4 (1 µg/ml), LPS (1 µg/ml), polyIC (10 µg/ml) and pro-inflammatory cytokines: IL-1β (1 ng/ml), TNFα (10 ng/ml) and IL-17 (20ng/ml). Total RNA was extracted using the Qiagen miRNeasy kit, and expression of miR-23a was measured by Sybr Green real-time PCR. In parallel, IL-6, IL-8 and MCP-1 were quantified in culture supernatants by ELISA. Clinical demographics such as CRP, TJC, SJC and patient global were also assessed.

Results: A significant increase in miR-23a expression was demonstrated in PsA PBMC versus OA (p=0.0476) and HC (p=0.0186). In contrast, a significant decrease in miR-23a expression was observed in PsA synovial tissue compared to OA (p=0.0172). In PsA, synovial miR-23a expression negatively correlated with matched PBMC miR-23a (r=-1.00, p=0.0167), demonstrating a dissociation in miR-23a expression between systemic and local inflammation. Furthermore, miR-23a expression in PsA synovial biopsies inversely correlated with DAS28-CRP (r= -0.5294, p=0.035). TLR activation *via* PolyIC (TLR3) and LPS (TLR4) significantly decreased miR-23a expression in primary PsA SFC (all $p<0.05$), with no effect observed for pro-inflammatory cytokines. This was paralleled by a significant induction of IL-6, IL-8 and MCP-1 in response to LPS and PolyIC (all $p<0.05$). Finally, *in silico* analysis identified putative targets for miR-23a including PDE4B and PTK2B, which are known to be involved in multiple immune pathways, osteoclast function and angiogenic mechanisms.

Conclusion: This is the first report of altered expression and regulation of miRNA in PsA, levels of which were inversely associated with increased joint inflammation. MiR-23a may be an important regulator of pathogenesis in PsA and may represent a potential target for therapeutic strategies. Further work will examine the functional role of miR-23a and it's implications on disease pathogenesis in PsA.

Disclosure: S. Wade, None; **M. Trenkmann**, None; **T. McGarry**, None; **D. J. Veale**, None; **U. Fearon**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/negative-regulator-mir-23a-down-regulated-in-psoriatic-arthritis-implications-for-disease-pathogenesis

Abstract Number: 2834

CXCL10 Expression Is Elevated in Synovial Fluid of Psoriatic Arthritis Patients

Anastasiya Muntyanu[1], Fatima Abji[2], Kun Liang[3], Vinod Chandran[4] and Dafna Gladman[4], [1]Toronto Western Hospital, University of Toronto, Toronto, ON, Canada, [2]Rheumatology, Toronto Western Hospital and University of Toronto, Toronto, ON, Canada, [3]Department of Statistics and Actuarial Science, University of Waterloo, Waterloo, ON, Canada, [4]Rheumatology, University of Toronto, Toronto Western Hospital, Toronto, ON, Canada

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Background/Purpose: Psoriatic arthritis (PsA), an inflammatory musculoskeletal disease, develops in approximately 30% of patients with psoriasis. We previously identified C-X-C motif chemokine 10 (CXCL10) as a predictive biomarker of PsA in patients with psoriasis. This study explores the expression of CXCL10 in the joint of PsA patients.

Methods: Synovial fluid (SF) was obtained from patients with PsA, osteoarthritis (OA) and gout undergoing routine joint aspirations. PsA patients with paired SF and serum samples were identified from the cohort of patients followed prospectively. The expression of CXCL10, TNFα, IL-17A and IFNγ were measured using the Milliplex MAP human chemokine/cytokine magnetic bead panel (EMD Millipore), according to the manufacturer's instructions. Data was acquired using the Luminex 200 system and analyzed with the Bio-Plex Manager software (Bio-Rad Laboratories). Statistical differences in protein levels between groups were identified by Wilcoxon signed rank test for paired samples and by Wilcoxon rank sum test for comparison between PsA patients and controls ($p<0.05$ was accepted as significant).

Results: Cytokine and chemokine expression was measured in SF from 40 patients with PsA and 17 controls (OA and gout). CXCL10 (5.87 ± 4.53 vs. 1.73 ± 2.08 ng/ml, $p=4.6x10^{-5}$) and IL-17A (14.3 ± 11.6 vs. 3.13 ± 3.1 pg/ml, p=0.0001) were significantly elevated in PsA patients compared to controls (Figure 1). In paired samples from 11 PsA patients (mean age 43 years, 91% males, psoriasis duration 17 years, PsA duration 11 years, PASI 7.7, tender joint count 2, swollen joint count 2), CXCL10 was significantly (p=0.001) increased in SF (6.3 ± 4.3 ng/ml) compared to serum (0.4 ± 0.3 ng/ml) while both TNFα (53.7 ± 68.0 vs. 9.0 ± 6.5 pg/ml, p=0.001) and IFNγ (154.3 ± 318.6 vs. 16.3 ± 24.3 pg/ml, p=0.01) were significantly reduced. Additionally, we measured the change in CXCL10, TNFα, IL-17A and IFNγ in SF from 15 PsA patients after follow-up, however no significant differences were found.

Conclusion: This study confirms previous reports of elevated synovial CXCL10 and IL-17A in PsA patients. The differences in SF and serum levels of CXCL10, TNFα and IFNγ that were observed may be important in the pathogenesis of PsA.

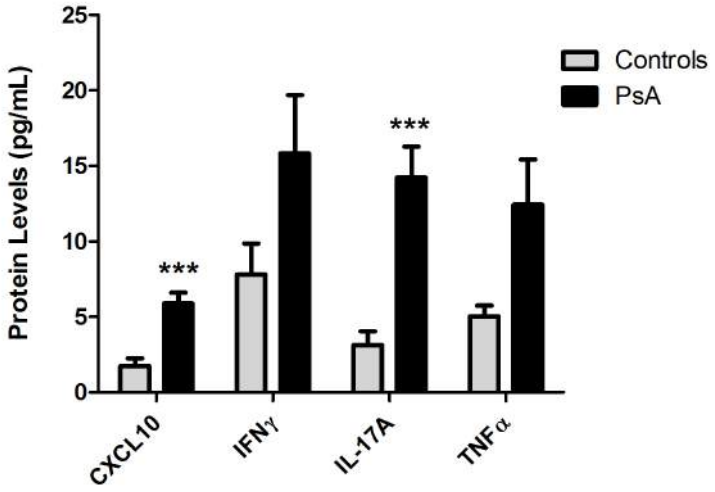

Figure 1: Histogram of CXCL10, IFNγ, IL-17A and TNFα expression in SF from 40 PsA patients and 17 controls (OA and gout). ***indicates a significant difference compared to controls. CXCL10 concentration was converted to ng/ml.

Disclosure: A. Muntyanu, None; **F. Abji**, None; **K. Liang**, None; **V. Chandran**, AbbVie, 2; **D. Gladman**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/cxcl10-expression-is-elevated-in-synovial-fluid-of-psoriatic-arthritis-patients

Abstract Number: 2835

Long-Term Improvements with Certolizumab Pegol in Joints and Extra-Articular Manifestations of Psoriatic Arthritis in Patients with and without Prior Anti-TNF Exposure

Dafna D. Gladman[1], Alice B. Gottlieb[2], Bengt Hoepken[3], Luke Peterson[4] and Oliver FitzGerald[5], [1]Toronto Western Research Institute, Toronto, ON, Canada, [2]Dermatology, Tufts Medical Center, Boston, MA, [3]UCB Pharma, Monheim, Germany, [4]UCB Pharma, Raleigh, NC, [5]Department of Rheumatology, St. Vincent's University Hospital, UCD School of Medicine and Medical Sciences and Conway Institute of Biomolecular and Biomedical Research, University College Dublin, Dublin, Ireland
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Session Time: 9:00AM-11:00AM

Background/Purpose:

Previous reports of RAPID-PsA (NCT01087788) have demonstrated the efficacy of certolizumab pegol (CZP) in patients (pts) with psoriatic arthritis (PsA) over 96 weeks (wks),[1] and have shown that improvements in ACR responses and skin manifestations were similar regardless of prior anti-TNF exposure.[2] Here we report the efficacy of CZP for the treatment of joint and extra-articular manifestations (EAMs) of PsA in pts with and without prior anti-TNF exposure over 96 wks of the RAPID-PsA trial.

Methods:

RAPID-PsA was double-blind and placebo-controlled to Wk24, dose-blind to Wk48 and open-label to Wk216. Pts had active PsA, had failed ≥1 DMARD, and ≤40% pts could have received 1 prior anti-TNF. 409 pts were randomized at baseline (BL) to either placebo or CZP (200 mg Q2W/400 mg Q4W, following 400 mg loading dose at Wks 0, 2, 4). The primary clinical endpoint was Wk12 ACR20

response.[3] Joint disease activity was assessed in all pts using the tender joint count (TJC), swollen joint count (SJC) and DAS28(CRP). EAMs were assessed in pts with BL involvement and included nail psoriasis (modified nail psoriasis severity index [mNAPSI], BL involvement = BL mNAPSI >0; for some pts the nail analyzed was different at one or more visit to Wk96), enthesitis (Leeds enthesitis index [LEI], BL involvement = BL LEI >0) and dactylitis (Leeds dactylitis index [LDI], BL involvement = at least 1 digit affected and with a difference in circumference ≥10% compared to the contralateral digit). Observed data are presented for all pts originally randomized to CZP with and without prior anti-TNF exposure.

Results:

There were 409 pts randomized, 273 received CZP from Wk0, of whom 54 (19.8%) had prior anti-TNF exposure. Of the 273 CZP-randomized pts, 197 (72.2%) had BL nail psoriasis, 172 (63.0%) BL enthesitis and 73 (26.7%) BL dactylitis. BL scores for joints and EAMs were similar in pts with and without prior anti-TNF exposure (Table).

By Wk4, CZP treatment was associated with rapid improvements in all measures of joint disease activity, including TJC, SJC and DAS28(CRP). Improvements in all outcomes continued through to Wk96 and were very similar in pts with and without prior anti-TNF exposure (Table). Similarly, improvements in nail psoriasis, enthesitis and dactylitis were seen to Wk96 of CZP treatment in PsA pts regardless of their prior anti-TNF exposure (Table). However, these analyses were limited by the low number of pts with prior anti-TNF exposure.

Conclusion:

Improvements in joint outcome measures and EAMs of PsA were observed over 96 wks of CZP treatment. These improvements were seen across multiple joint outcome measures and in all EAMs assessed, including nail psoriasis, enthesitis and dactylitis. Similar improvements were observed in pts with and without prior anti-TNF exposure.

References:

1. Mease P. Arthritis Rheum 2014;66(S10):S237–8

2. Khraishi M. Ann Rheum Dis 2015;74(S2):353–4

3. Mease P. Ann Rheum Dis 2014;73(1):48–55

Table: Efficacy of CZP over 96 weeks for the treatment of joint and extra-articular manifestations of PsA in patients with and without prior anti-TNF exposure (observed data)

	Patients with prior anti-TNF exposure (n=54)				Patients without prior anti-TNF exposure (n=219)			
	Week0	Week4	Week24	Week96	Week0	Week4	Week24	Week96
Data shown as mean score (number of patients)								
Tender joint count (TJC) [a]	21.4 (54)	15.1 (52)	11.4 (50)	5.6 (39)	20.3 (219)	13.5 (215)	7.4 (199)	5.1 (178)
Swollen joint count (SJC) [b]	12.7 (54)	5.6 (52)	3.4 (50)	1.9 (39)	10.3 (219)	5.3 (215)	2.8 (199)	1.2 (178)
DAS28(CRP)	5.2 (54)	3.7 (53)	3.1 (50)	2.6 (39)	5.0 (219)	3.8 (215)	3.0 (199)	2.5 (179)
Nail psoriasis (mNAPSI) [c]	2.9 (38)	2.0 (38)	1.2 (37)	0.6 (29)	3.4 (159)	3.0 (158)	1.4 (142)	0.7 (129)
Enthesitis (LEI) [d]	2.9 (39)	1.6 (38)	1.3 (37)	0.8 (27)	3.0 (133)	1.8 (131)	1.0 (121)	0.7 (104)
Dactylitis (LDI) [e]	52.5 (17)	17.7 (17)	7.3 (16)	0.0 (11)	50.9 (56)	17.1 (55)	0.8 (49)	0.0 (46)

[a] TJC scale: 0–68; [b] SJC scale: 0–66; [c] mNAPSI scale for affected nail: 0–13; [d] LEI scale: 0–6; [e] LDI measured as: percent difference between the circumference of the affected digit and the contralateral digit, multiplied by tenderness score (0 for non-tender, 1 for tender). Final LDI score = sum of results from all digits with dactylitis.

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Abstract Number: 2836

Early Clinical Response Is a Better Predictor of Long-Term Remission Than Baseline Disease Characteristics Following Adalimumab Treatment in Peripheral Spondyloarthritis

Filip van Den Bosch[1], Philip J. Mease[2], Joachim Sieper[3], Dominique Baeten[4], Nupun A. Varothai[5], Aileen L. Pangan[5] and In-Ho Song[5], [1]Ghent University Hospital, Ghent, Belgium, [2]Swedish Medical Center and University of Washington School of Medicine, Seattle, WA, [3]Charité Universitätsmedizin Berlin, Berlin, Germany, [4]Academic Medical Center, University of Amsterdam, Amsterdam, Netherlands, [5]AbbVie Inc., North Chicago, IL

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Background/Purpose: ABILITY-2 has demonstrated the efficacy of adalimumab (ADA) vs. placebo (PBO) over 12 weeks (wk) in patients (pt) with peripheral spondyloarthritis (pSpA)[1] and sustained response following up to 2 years (yr) of ADA. The purpose of this study is to determine predictors of long-term remission in pts with pSpA.

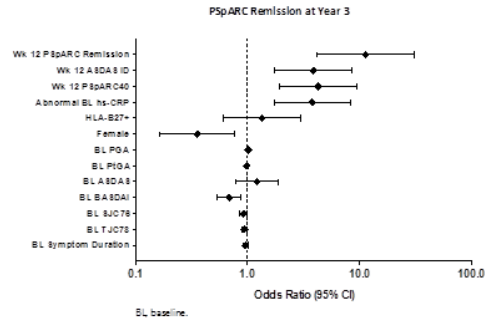
Methods: In ABILITY-2 pts were randomized to receive ADA 40 mg every other wk or PBO during a 12-wk double-blind period, followed by an open-label period of up to 3 yrs of treatment. PSpARC1 remission was defined as SJC ≤1 plus 4/5 of the following: Physician's Global Assessment (PGA) of Disease Activity ≤20 mm (visual analog scale, VAS); PGA-pain ≤20 mm VAS, TJC ≤1, enthesitis count ≤1, dactylitis count ≤1. ASDAS inactive disease (ASDAS ID) was ASDAS score <1.3. Possible predictors for remission at 1 and 3 yrs of ADA treatment were selected a priori. Categorical variables included symptom duration, abnormal baseline (BL) hs-CRP, HLA-B27+, and response at wk 12 for BASDAI50, PSpARC, and ASDAS categories. Continuous variables included BL values for TJC, SJC, enthesitis count, BASDAI, ASDAS, Patient Global Assessment of disease activity (PtGA), PGA, and hs-CRP. Univariate logistic regression was used to evaluate predictors for remission variables at yrs 1 and 3. Multivariate analysis was done to determine predictors of achieving sustained (≥ 3 consecutive visits) remission at any time during the study.

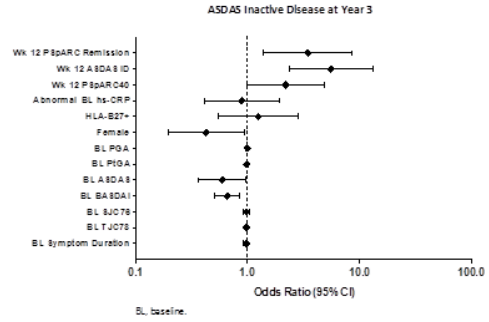
Results: 165 pts (ADA 84/PBO 81) were randomized. Among pts completing both yr 1 and 3, 48.2% (54/112) of pts achieved PSpARC remission and 58.9% (63/107) were in ASDAS ID at yr 3. Univariate analysis showed that wk 12 responses were more consistent predictors of remission at yr 1 or 3 (Figure) than most BL disease characteristics. Abnormal BL hs-CRP was a predictor of PSpARC remission at yr 3, but not at yr 1. Furthermore, abnormal BL hs-CRP was not a predictor of ASDAS ID at yr 1 or 3. 44.9% (74/165) and 57.6% (95/165) achieved sustained PSpARC remission and ASDAS ID, respectively, during the 3-yr study. Multivariate analysis demonstrated that PSpARC remission at wk 12 predicted sustained PSpARC remission (Odds ratio (OR) 95.96, *P*=0.0023) and ASDAS ID at wk 12 predicted sustained ASDAS ID (OR 46.29, *P*=0.0084).

Conclusion: Early response to ADA in pSpA patients is a better predictor of long-term remission for up to 3 years, whether at a single point in time or sustained over time, than baseline disease characteristics.

Reference

1. Mease P et al. Arthritis Rheumatol 2014;Accepted Dec 29. DOI 10.1002/art.39008.





Disclosure: F. van Den Bosch, AbbVie, Celgene, Janssen, Merck, Novartis, Pfizer, and UCB, 2,AbbVie, Celgene, Janssen, Merck, Novartis, Pfizer, and UCB, 8,AbbVie, Celgene, Janssen, Merck, Novartis, Pfizer, and UCB, 5; **P. J. Mease**, Abbott, AbbVie, Amgen, BiogenIdec, BMS, Celgene, Crescendo, Genentech, Janssen, Eli Lilly, Merck, Novartis, Pfizer, UCB Pharma, 2,Abbott, AbbVie, Amgen, BiogenIdec, BMS, Celgene, Covagen, Crescendo, Genentech, Janssen, Eli Lilly, Merck, Novartis, Pfizer, UCB Pharma, 5,Abbott, AbbVie, Amgen, BiogenIdec, BMS, Celgene, Crescendo, Genentech, Janssen, Lilly, Pfizer, UCB Pharma, 8; **J. Sieper**, AbbVie, Merck, Pfizer, and UCB, 2,AbbVie, Merck, Pfizer, and UCB, 5,AbbVie, Merck, Pfizer, and UCB, 8; **D. Baeten**, AbbVie, BMS, Boehringer Ingelheim, Centocor, Janssen, MSD, Novartis, Pfizer, and UCB, 2,AbbVie, BMS, Boehringer Ingelheim, Centocor, Janssen, MSD, Novartis, Pfizer, and UCB, 5,AbbVie, BMS, Boehringer Ingelheim, Centocor, Janssen, MSD, Novartis, Pfizer, and UCB, 8; **N. A. Varothai**, AbbVie, 1; **A. L. Pangan**, AbbVie, 1,AbbVie, 3; **I. H. Song**, AbbVie, 1,AbbVie, 3.

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Abstract Number: 2837

Sulfasalazine Comedication: A Predictor of Reduced Long-Term Anti-TNF Switch in Ankylosing Spondylitis

Andrea Y. Shimabuco, Celio R. Gonçalves, Julio C. B. Moraes, Mariana G Waisberg, Percival D Sampaio-Barros, Cláudia Goldenstein-Schainberg, Eloisa Bonfá and Carla G.S. Saad, Rheumatology Division, Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil

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Background/Purpose: Anti-TNF agents are efficacious in the treatment of ankylosing spondylitis (AS). The switch to another TNF blockage can be an alternative in cases of lack or loss of efficacy and side effects. There are, however, no clear evidence for a beneficial effect of co-therapy with conventional synthetic DMARDs in AS. The aim of this study was to determine the efficacy and predictors of anti-TNF switch in the long-term follow-up of AS patients, in a routine clinical care center.

Methods: Data from an ongoing longitudinal electronic database of AS patients under anti-TNF therapy between June 2004 and August

2013 were assessed. Demographic and clinical parameters, concomitant therapy and treatment responses by ASDAS were recorded. ASDAS remission(<1.3) and ASDAS inactive/moderate(<2.1) were analyzed to characterize the switch of TNF blockage. Final assessment of switch response excluded patients who underwent anti-TNF therapy less than 24 weeks and patients that stopped a given anti-TNF treatment course due to non-adherence, adverse events or infection (without further drug introduction).

Results: Of 117 AS patients treated with anti-TNF (mean treatment duration: 39.4 ± 30.1 months) 69(59%) received solely the first anti-TNF, 48(41%) switched to a second anti-TNF (58% failure and 42% side effects) and 13(11%) to a third anti-TNF (62% failure and 38% side effects).The choice of the second anti-TNF did not influence the maintenance of the therapy; it was comparable among patients who started and switched to monoclonal antibody (infliximab or adalimumab) and those who started with monoclonal antibody and switched to etanercept (66% vs. 77%, p=0.72). At the final assessment, 42 patients still under the first anti-TNF (non-switcher group) achieved more frequently ASDAS remission-ESR (62% vs. 36%, p=0.04) and ASDAS inactive/moderate-ESR (88% vs. 58%, p=0.03) than patients treated with more than one anti-TNF. The switch to a third anti-TNF resulted in a lower response rate with 25% reaching inactive/moderate disease activity (p<0.001) and 12.5% achieving ASDAS remission (p=0.03). Duration of the last anti-TNF treatment was comparable in all groups (p=0.24). Non-switchers achieved lower BASDAI (p=0.04) and BASFI (p=0.03) than switcher groups. Switchers due to failure or adverse effects were comparable regarding demographic and clinical parameters at baseline and at final assessment. The analysis of predictors at baseline revealed that non-switchers were more often treated with sulfasalazine (SSZ) (63.8% vs. 41.7%, p=0.02) than switcher patients. Further evaluation of the use of this drug revealed that non-switchers with pure axial involvement also used more frequently SSZ than switchers (70.8% vs.15% vs. p=0.03). In contrast, the frequency of SSZ use was comparable in non-switchers and switchers AS patients with peripheral involvement (58.1% vs. 48.7%, p=0.51).

Conclusion: This study provides novel evidence that SSZ comedication reduces anti-TNF switch in AS patients, particularly in those with pure axial disease. The underlying mechanism remains unknown and may involve the prevention of anti-drug antibodies formation and/or an additional anti-inflammatory effect.

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Abstract Number: 2838

Evidence of Serological IL-23/IL-17 Axis Activation in Ankylosing Spondylitis Patients with Long-Term TNF Blockade: The Missing Therapy Target?

Fernanda M. Milanez[1], **Carla G.S. Saad**[1], Vilma S. T. Viana[1], Julio C. B. Moraes[1], Grégory V. Périco[2], Celio R. Gonçalves[1] and Eloisa Bonfá[1], [1]Rheumatology Division, Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil, [2]Unidade Radiologica Criciuma, Criciuma, Brazil

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Background/Purpose: Spondyloarthritis (Spa) is a group of inflammatory diseases in which ankylosing spondylitis (AS) is the prototype. Despite recent advances in pathophysiology and treatment, this group is still a challenge, particularly regarding the understanding of the inflammatory pathways involved, predictors of anti-TNF response and risk factors for radiographic progression. The aim of our study was to investigate the long-term influence of TNF-blockage in IL-23/IL-17 axis of ankylosing spondylitis (AS) patients.

Methods: Eighty-six AS anti-TNF naïve patients, 47 referred for anti-TNF therapy (active-AS; BASDAI ≥4) and 39 with BASDAI<4 (control-AS) were included. The active group was evaluated at baseline, 12-months and 24-months after TNF blockage and compared at baseline to control-AS group and to 47 age- and gender-matched healthy controls. Plasma levels of IL-17A, IL-22, IL-23 and PGE2 were measured. Radiographic severity and progression was assessed by mSASSS.

Results: At baseline, active-AS group presented higher IL-23 and PGE2 levels compared to control-AS group (p<0.001 and p=0.008) and to healthy controls (p<0.001 and p=0.02). After 24-months of TNF blockage, IL-23 and PGE2 remained elevated in which group (I suppose active-AS but you don't mention control-AS here) with higher levels compared with the healthy group (p<0.001 and p=0.03) in spite of significant improvements in all clinical/inflammatory parameters(p<0.001). Further analysis of 27 anti-TNF-treated patients who achieved a good response(ASDAS-CRP<2.1,with a drop≥1.1) at 24-months revealed that IL-23 plasma levels remained higher than healthy controls(p<0.001) and higher than control-AS group with similar disease activity (ASDAS-CRP<2.1, p=0.01). In active-

AS group(n=47), there was a strong positive correlation between IL-23 and IL-17A at baseline, 12-months and 24-months after anti-TNF therapy($p \leq 0.001$).

Conclusion: This study provides novel data demonstrating that IL-23/IL-17 axis is not influenced by TNF blockage in AS patients despite clinical and inflammatory markers. In this context, the IL-23/IL-17 blockage emerges as a potential additional target in AS.

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Abstract Number: 2839

Disease Activity and Safety during Long-Term (104-Week) Treatment with Apremilast, an Oral Phosphodiesterase 4 Inhibitor, in Patients with Psoriatic Arthritis: Results from a Phase III, Randomized, Controlled Trial and Open-Label Extension

Christopher J. Edwards[1], Francisco J. Blanco[2], Jeffrey Crowley[3], ChiaChi Hu[4], Kamal Shah[4] and Charles A. Birbara[5], [1]University Hospital Southampton, Southampton, United Kingdom, [2]Osteoarticular and Aging Research Lab. Proteomics Unit - Associated Node to ProteoRed, Rheumatology Division, Proteomics Group-ProteoRed/ISCIII, INIBIC-CHUAC, A Coruña, Spain, [3]Bakersfield Dermatology, Bakersfield, CA, [4]Celgene Corporation, Warren, NJ, [5]University of Massachusetts Medical School, Worcester, MA
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Session Time: 9:00AM-11:00AM

Background/Purpose: Apremilast (APR), an oral phosphodiesterase 4 inhibitor, acts to regulate immune responses in psoriatic arthritis (PsA). PALACE 3 compared the efficacy and safety of APR with placebo (PBO) in patients with active PsA, including active skin disease, despite prior conventional DMARDs and/or biologics. We report the efficacy and safety of APR treatment over 104 weeks in PALACE 3.

Methods: Patients were randomized (1:1:1) to PBO, APR 30 mg BID (APR30), or APR 20 mg BID (APR20) stratified by baseline DMARD use (yes/no) and psoriasis involvement of the body surface area (<3%/≥3%). The PBO-controlled phase continued to Week 24, with an early escape option at Week 16. At Week 24, all remaining PBO patients were re-randomized to APR30 or APR20. Double-blind APR treatment continued to Week 52; subsequently, patients could continue APR for up to 4 additional years in an open-label extension study.

Results: 505 patients were randomized and received ≥1 dose of study medication (PBO: n=169; APR30: n=167; APR20: n=169); 82% of patients entering the second year of APR therapy completed 104 weeks of treatment. Patients receiving APR at Week 104 demonstrated sustained decreases in disease activity. At baseline, 65.7% and 27.7% of APR30 patients and 61.8% and 28.6% of APR20 patients had moderate (DAS-28 [CRP]): ≥3.2 to ≤5.1) and severe (DAS-28 [CRP]: >5.1) disease, respectively; 43.4% (APR30) and 44.0% (APR20) achieved DAS-28 (CRP) remission at Week 104 (Table). Sustained relief of signs/symptoms and improvements in physical function were demonstrated by the swollen/tender joint count mean percent change, HAQ-DI mean change, proportion of patients with HAQ-DI score exceeding the minimal clinically important difference (MCID) ≥0.30 threshold, modified ACR20/ACR50/ACR70 response rates, and PASI-75/PASI-50 response rates (Table). No new safety concerns were observed with treatment through Week 104; long-term findings indicate that APR tolerability improved with long-term exposure. During Weeks >52 to ≤104, adverse events (AEs) occurring in ≥5% of APR-exposed patients were nasopharyngitis and upper respiratory tract infection; most AEs were mild/moderate in severity. Serious AEs occurred in 5.8% (APR30) and 6.2% (APR20) during Weeks 0 to ≤52 and 8.7% (APR30) and 7.5% (APR20) over Weeks >52 to ≤104. Fewer discontinuations due to AEs occurred during Weeks >52 to ≤104 (3.5%) than during Weeks 0 to ≤52 (7.5%).

Conclusion: Over 104 weeks, APR demonstrated sustained, clinically meaningful improvements in PsA disease activity, physical function, and associated psoriasis. APR continued to demonstrate a favorable safety profile and was generally well tolerated.

Outcomes at Week 52 and Week 104 (Data as Observed)				
	Week 52		Week 104	
	APR30 n=194*	APR20 n=178*	APR30 n=161*	APR20 n=135*
DAS-28 (CRP) <2.6, n/m (%)	64/194 (33.0)	53/178 (29.8)	69/159 (43.4)	59/134 (44.0)
DAS-28 (CRP), mean change	-1.37	-1.24	-1.59	-1.56
Swollen joint count, mean % change	-67.6	-63.8	-74.7	-72.6
Tender joint count, mean % change	-55.3	-51.3	-66.5	-59.2
HAQ-DI (0-3), mean change	-0.35	-0.33	-0.41	-0.36
HAQ-DI MCID ≥0.30§, n/m (%)	103/194 (53.1)	86/178 (48.3)	83/161 (51.6)	67/135 (49.6)
ACR20, n/m (%)	119/194 (61.3)	97/172 (56.4)	105/158 (66.5)	84/133 (63.2)
ACR50, n/m (%)	59/192 (30.7)	45/174 (25.9)	59/158 (37.3)	47/132 (35.6)
ACR70, n/m (%)	23/192 (12.0)	22/175 (12.6)	33/157 (21.0)	29/134 (21.6)
PASI-75‡, n/m (%)	35/99 (35.4)	26/87 (29.9)	39/79 (49.4)	23/68 (33.8)
PASI-50‡, n/m (%)	54/99 (54.5)	47/87 (54.0)	50/79 (63.3)	35/68 (51.5)

*The n reflects the number of patients treated with APR30 and APR20 (regardless of whether treatment started at Week 0, 16, or 24) and who had data available at the specific time point; actual number of patients available for each end point may vary. §Pre-specified MCID threshold, based on the literature (Mease PJ, et al. *Ann Rheum Dis.* 2004;63[Suppl 1]:391) at the time of protocol and analysis. ‡Examined among patients with psoriasis involvement of the body surface area ≥3% at baseline and data at the specific time point.
n/m=number of responders/number of patients with sufficient data for evaluation.

Disclosure: C. J. Edwards, Abbvie, Pfizer, Lilly, Celtrion, Mundipharma, Samsung, Anthera, UCB, Celgene, Roche, Bristol-Myers Squibb, Janssen, 8; **F. J. Blanco**, Pfizer, Bioiberica, and Gebro Pharma, 5; **J. Crowley**, AbbVie, Amgen, Celgene, Janssen, Lilly, Maruho, Merck, Pfizer, Regeneron,, 5; **C. Hu**, Celgene Corporation, 3; **K. Shah**, Celgene Corporation, 3; **C. A. Birbara**, Amgen, Lilly, Pfizer, Incyte, Merck, and Bristol-Myers Squibb, 2.

Abstract Number: 2840

Long-Term (104 Week) Safety Profile of Apremilast, an Oral Phosphodiesterase 4 Inhibitor, in Patients with Psoriatic Arthritis: Pooled Safety Analysis of Three Phase III, Randomized, Controlled Trials

Philip J. Mease[1], Adewale O. Adebajo[2], Dafna D. Gladman[3], Juan J. Gomez-Reino[4], Stephen Hall[5], Arthur Kavanaugh[6], Eric Lespessailles[7], Georg A. Schett[8], Kamal Shah[9], Lichen Teng[9] and Jürgen Wollenhaupt[10], [1]Clinical Professor, University of Washington School of Medicine, Seattle, WA, [2]University of Sheffield, Sheffield, United Kingdom, [3]Toronto Western Research Institute, Toronto, ON, Canada, [4]Rheumatology, Hospital Clinico Universitario de Santiago, Santiago de Compostela, Spain, [5]Monash University, Melbourne, Australia, [6]University of California, San Diego School of Medicine, LaJolla, CA, [7]University of Orléans, Orléans, France, [8]University of Erlangen-Nuremberg, Erlangen, Germany, [9]Celgene Corporation, Warren, NJ, [10]Schön Klinik Hamburg Eilbek, Hamburg, Germany

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Background/Purpose: Apremilast (APR), a phosphodiesterase 4 inhibitor, helps regulate the immune responses in psoriatic arthritis (PsA). PALACE 1-3 compared APR efficacy/safety with placebo in patients with active PsA despite prior conventional disease-modifying antirheumatic drugs (DMARDs) and/or biologics. We report the safety of APR treatment during Weeks 0 to ≤104.

Methods: Patients were randomized (1:1:1) to placebo, APR 30 mg BID (APR30), or APR 20 mg BID (APR20) stratified by baseline DMARD use (yes/no). The placebo-controlled phase continued to Week 24, with an early escape option at Week 16. Double-blind APR treatment continued to Week 52; patients could continue to receive APR during an open-label, long-term treatment phase.

Results: 1,493 patients were randomized and received ≥1 dose of study medication (placebo: n=495; APR30: n=497; APR20: n=501). A total of 1,441 (1,209.3 patient-years) patients received APR in Weeks 0 to ≤52, with 1,028 (907.7 patient-years) continuing treatment during Weeks >52 to ≤104. Of the 1,441 patients randomized, 698 (48.4%) had a full 2 years of exposure. During Weeks 0 to ≤52, adverse events (AEs) occurring in ≥5% of APR-exposed patients were diarrhea, nausea, headache, upper respiratory tract infection, and nasopharyngitis (Table). Most diarrhea and nausea events were reported within the first 2 weeks of treatment and usually resolved in 4 weeks without medical intervention. Most AEs were mild or moderate in severity during the Weeks 0 to ≤104 APR-exposure

period; no increase was seen in the incidence and severity of AEs with longer term exposure. During Weeks >52 to ≤104, diarrhea (2.9%), nausea (1.8%), and headache (3.0%) occurred at lower rates vs. Weeks 0 to ≤52 (Table). Reported serious AEs (SAEs) with APR30 between 0 to ≤52 and >52 to ≤104 weeks were comparable at 6.5% and 6.3%, respectively. Reported SAEs were higher with APR20 at 7.5% between >52 to ≤104 weeks compared with 5.6% between 0 to ≤52 weeks with no cluster indicating any specific organ involvement. Most SAEs were reported by 1 patient each. The cardiac, malignant neoplasm, opportunistic infection, or psychiatric disorder related SAEs were comparable between 0 to ≤52 and 52 to ≤104 weeks, and no cases of tuberculosis (new or reactivation) were reported with either APR dose. Discontinuations due to AEs occurred at a lower rate (2.3%) during Weeks >52 to ≤104 than during Weeks 0 to ≤52 (7.5%). Marked laboratory abnormalities were infrequent, and most returned to baseline with continued treatment or were associated with a concurrent medical condition.

Conclusion: APR demonstrated a favorable safety profile and was well tolerated for up to 104 weeks. These data continue to support the lack of a need for specific laboratory monitoring with APR. No new safety concerns were identified with long-term exposure to apremilast.

	APR-Exposure Period* Weeks 0 to ≤52		APR-Exposure Period* Weeks >52 to ≤104	
	APR30 n=721	APR20 n=720	APR30 n=520	APR20 n=508
Patients, n (%)				
≥1 AE	524 (72.7)	505 (70.1)	308 (59.2)	315 (62.0)
≥1 SAE	47 (6.5)	40 (5.6)	33 (6.3)	38 (7.5)
AE leading to drug withdrawal	56 (7.8)	52 (7.2)	13 (2.5)	11 (2.2)
Death	0 (0.0)	1§ (0.1)	1‡ (0.2)	0 (0.0)
AEs in ≥5% of patients, any treatment group, n (%)				
Diarrhea	112 (15.5)	88 (12.2)	20 (3.8)	10 (2.0)
Nausea	108 (15.0)	69 (9.6)	11 (2.1)	7 (1.4)
Upper respiratory tract infection	60 (8.3)	71 (9.9)	27 (5.2)	40 (7.9)
Headache	75 (10.4)	61 (8.5)	17 (3.3)	14 (2.8)
Nasopharyngitis	41 (5.7)	48 (6.7)	31 (6.0)	29 (5.7)
Select marked abnormalities in clinical laboratory parameters n/m (%)ǂ				
ALT >3× ULN	9/713 (1.3)	8/713 (1.1)	2/518 (0.4)	1/502 (0.2)
Creatinine >1.7× ULN	1/713 (0.1)	1/713 (0.1)	0/518 (0.0)	0/502 (0.0)
Leukocytes <1.5, 10^9/L	0/713 (0.0)	0/712 (0.0)	0/517 (0.0)	0/503 (0.0)
Neutrophils <1, 10^9/L	2/713 (0.3)	4/712 (0.6)	3/517 (0.6)	2/502 (0.4)
Platelets <75, 10^9/L	0/713 (0.0)	0/712 (0.0)	0/517 (0.0)	1/503 (0.2)
Hemoglobin, male <10.5 g/dL, female <8.5 g/dL	5/713 (0.7)	5/712 (0.7)	3/517 (0.6)	0/503 (0.0)

*Includes all patients who received APR during the time interval relative to the start of APR. §Multiorgan failure not suspected to be treatment related. ‡Patient died in a motor vehicle accident on Study Day 489 while receiving APR30. ǂn/m=number of patients with ≥1 occurrence of the abnormality at any time point/number of patients with ≥1 post-baseline value. ALT=alanine aminotransferase; ULN=upper limit of normal.

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Abstract Number: 2841

Changes in Treatment Patterns in Psoriatic Arthritis Patients Newly Initiated on Biologic and Non-Biologic Therapy Enrolled in a North American Clinical Registry

Philip J. Mease[1], Tamara Lesperance[2], Neil Accortt[2], David Collier[2], Mei Liu[3], Marc Mason[4] and Sabrina Deveikis[4], [1]Clinical Professor, University of Washington School of Medicine, Seattle, WA, [2]Amgen, Inc., Thousand Oaks, CA, [3]352 Turnpike Rd, Corrona, LLC, Southborough, MA, [4]Corrona, LLC., Southborough, MA

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Background/Purpose: Over the past decade, the treatment of PsA has improved significantly. The purpose of this study was to describe real-world treatment patterns among PsA patients following initiation of TNF inhibitor (TNFi) and non-biologic (MTX) therapy over time to understand if increasing clinical evidence for the benefit of TNFi therapy has led to changes in treatment patterns.

Methods: Using data on PsA patients from Corrona, a national multicenter registry of RA and PsA patients, PsA patients were identified between 1/1/2004 and 12/31/2012 and stratified into 3 cohorts; those who had initiated TNFi monotherapy (mono), MTX monotherapy or combination (combo) therapy (TNFi and MTX). Patients with at least 6 months of follow-up data after first therapy initiation were included. The 3 patient cohorts were further stratified over three different time periods (2004-2006, 2007-2009, and 2010-2012) based on year of initiation. Baseline demographic and clinical characteristics were assessed at drug initiation. The key outcome measures of interest were persistence on index medication therapy; gaps in therapy and therapy restarts; therapy changes, including treatment switches and add-on therapy; and length of time on therapy. Persistence was defined as continuous use of therapy over a 12-month period.

Results: There were 520 PsA patients who met inclusion criteria. The 3 groups differed demographically in terms of baseline characteristics. The proportion of patients initiating TNFi mono has decreased over time, while the proportion starting combination therapy has remained steady (Table). Over the three time periods, patients were noted to start TNFi earlier in their disease course; however, time to initiating TNFi mono was longer than time to initiating combo therapy. Mean CDAI at initiation was highest among the combo group and has remained above 12 for all therapy groups in all time periods. Time on initial therapy decreased as the time period cohorts became more contemporary, but persistence on TNFi mono was higher than the other two cohorts across all time periods (in 2010-2012 persistence was 53% on TNFi mono, 34% on MTX mono, and 36% on combo therapy). Patients appear less likely to remove MTX from their combo therapy in recent years (70% in 2004-2006, 34% in 2010-2012), yet no patients dropped TNFi from their combo therapy. In the most recent time period, 11% of mono TNFi users became combo users, whereas 28% of mono MTX users became combo users.

Conclusion: Treatment patterns in PsA patients have changed from 2004-2012, including earlier TNFi initiation and more cycling. This may be due to the increasing number of treatment options available and increased focus on achievement of low disease activity state. However, physicians do not appear to be more likely to initiate patients on TNFi monotherapy even though the clinical evidence supporting their effectiveness has increased over this same time period and patients remain more persistent with it.

Table. Patient characteristics at drug initiation and persistency patterns for PsA patients who enrolled into Corrona 2004-2012 and initiated mono TNFi or mono MTX or combo TNFi/MTX at enrollment or during the follow-up

	2004-2006	2007-2009	2010-2012
Treatment initiation (%)			
TNFi monotherapy	46.4	36.0	32.1
MTX monotherapy	32.7	43.2	45.0
Combination therapy	20.9	20.8	22.9
PsA duration (time to initiation, years)			
TNFi monotherapy	8.4	6.7	6.6
MTX monotherapy	2.8	4.3	2.7
Combination therapy	7.6	7.2	4.2
CDAI score at initiation (mean score)			
TNFi monotherapy	12.8	12.6	14.4
MTX monotherapy	16.8	14.4	14.9
Combination therapy	17.7	17.7	17.9
Treatment persistence (%)			
TNFi monotherapy	71	70	53
MTX monotherapy	64	59	34
Combination therapy	52	65	36
Duration of persistence (time on initial therapy, months)			
TNFi monotherapy	46	31.8	19.6
MTX monotherapy	38.3	30.2	17.5
Combination therapy	46	31.2	21.3

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Abstract Number: 2842

Tumor Necrosis Factor Alpha Inhibition in Ankylosing Spondylitis and Non Radiographic Axial Spondyloarthritis: Treatment Response, Drug Survival and Patient Outcome

Justine Corli[1], Rene-Marc Flipo[1], Peggy Philippe[2], Anne Bera-Louville[2], Cecile Wibaux[2] and Julien Paccou[2], [1]Rheumatology, Hopital R Salengro CHRU, Lille, France, [2]Hopital R Salengro CHRU, Lille, France

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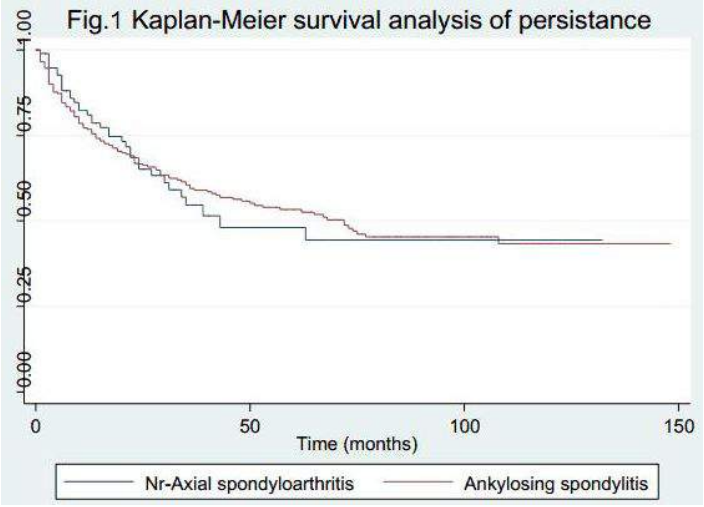
Background/Purpose: Several studies have demonstrated that Tumor Necrosis Factor Inhibitors (TNFi) are efficient in non-radiographic axial spondyloarthritis (Nr-AxSpA). However, few investigations have directly compared ankylosing spondylitis (AS) patients with Nr-AxSpA patients, and fewer still have compared response rates to first line TNFi treatment. The purpose of this study, which involved a tertiary care cohort, was to (i) evaluate baseline characteristics of Nr-AxSpA and AS treated by TNFi; (ii) assess the response to first-line TNFi treatment; (iii) compare drug-survival.

Methods: Inclusion criteria were patients with axial SpA (ASAS criteria) who initiated first-line TNFi treatment between April 2001 and July 2014 and followed up for at least 3 months. Efficacy criteria at 3 months were an improvement of at least 2 points (on a 0 –10 scale) or a 50% improvement in BASDAI. Baseline characteristics, responses at 12 months, and drug survival were compared between AS and Nr-AxSpA.

Results:

A total of 361 patients were included in the study (AS: n=263; Nr-AxSpA: n=98). AS patients were more often male (65.02% vs. 45.92%; p=0.001) and had longer symptom duration (11.71 ±9.52 vs. 7.34 ± 9.30; p<0.001). Median levels of acute-phase reactants (CRP and ESR) were significantly higher in AS patients (p<0.001 for both). Median BASDAI scores at first line TNFi initiation were not higher in Nr-AxSpA patients than in AS patients (59 [49-70] vs. 60 [50- 70]; p=0.73). BASDAI 20 and BASDAI 50 response rates at 12 months were not statistically different between AS patients and Nr-AxSpA patients (74.58% vs. 64.58%; p=0.19 and 61.02% vs. 50.00%; p=0.19 respectively). No statistically significant difference in terms of survival was observed between AS and Nr-AxSpA patients (p=1.00) (Figure 1).

Conclusion: Treatment response, drug survival and patient outcome in our study were similar in patients with AS and Nr-AxSpA after first line TNFi initiation.



Disclosure: J. Corli, Pfizer Inc, 2; **R. M. Flipo**, Pfizer Inc, 2,Abbvie, 2; **P. Philippe**, None; **A. Bera-Louville**, None; **C. Wibaux**, None; **J. Paccou**, Pfizer Inc, 2.

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Abstract Number: 2843

Long-Term (156-Week) Efficacy and Safety Profile of Apremilast, an Oral Phosphodiesterase 4 Inhibitor, in Patients with Psoriatic Arthritis: Results from a Phase III, Randomized, Controlled Trial and Open-Label Extension (PALACE 1)

Arthur Kavanaugh[1], Adewale O. Adebajo[2], Dafna D. Gladman[3], Juan J. Gomez-Reino[4], Stephen Hall[5], Eric Lespessailles[6], Philip J. Mease[7], Georg A. Schett[8], Kamal Shah[9], Lichen Teng[9] and Jürgen Wollenhaupt[10], [1]University of California, San Diego School of Medicine, LaJolla, CA, [2]University of Sheffield, Sheffield, United Kingdom, [3]Department of Medicine, Division of Rheumatology, University of Toronto, Toronto, ON, Canada, [4]Hospital Clinico Universitario, Santiago, Spain, [5]Monash University, Melbourne, Australia, [6]University of Orléans, Orléans, France, [7]Rheumatology Research, Swedish Medical Center, Seattle, WA, [8]University of Erlangen-Nuremberg, Erlangen, Germany, [9]Celgene Corporation, Warren, NJ, [10]Schön Klinik Hamburg Eilbek, Hamburg, Germany
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Background/Purpose: Apremilast (APR), an oral phosphodiesterase 4 inhibitor, has demonstrated clear efficacy and good tolerability in psoriatic arthritis (PsA) and psoriasis. Longer term data are crucial for chronic diseases such as PsA. PALACE 1 compared APR efficacy and safety with placebo (PBO) in patients with active PsA despite prior conventional disease-modifying antirheumatic drugs (DMARDs) and/or biologics. We evaluated the longer term efficacy and safety of APR treatment over 156 weeks.

Methods: Patients were randomized (1:1:1) to PBO, APR 30 mg BID (APR30), or APR 20 mg BID (APR20) stratified by baseline DMARD use (yes/no). The PBO-controlled phase continued to Week 24, with an early escape option at Week 16. At Week 24, all remaining PBO patients were re-randomized to APR30 or APR20. Double-blind APR treatment continued to Week 52; patients could continue APR for up to 4 additional years. Efficacy assessments in Years 2 and 3 were conducted at Weeks 65, 78, 91, 104, 117, 130, 143, and 156.

Results: 504 randomized patients received ≥1 dose of study medication (PBO: n=168; APR30: n=168; APR20: n=168). In an "as observed" analysis, 53.2% of APR30 patients and 59.6% of APR20 patients achieved a modified ACR20 response at Week 52 (Table), regardless of whether APR was started at Week 0, 16, or 24; 65.3% (APR30) and 60.9% (APR20) of patients showed these responses at Week 104. Of the patients entering the third year of therapy, 92% (260/284) completed the Week 156 visit; this is overall 52% (260/504) of patients randomized at baseline. Patients receiving APR at Week 156 demonstrated sustained improvements, as shown by ACR20/ACR50/ACR70 response rates modified for PsA by the addition of the distal interphalangeal joints of the toes and the carpometacarpal joints to the total joint count, swollen/tender joint count mean percent improvement, HAQ-DI mean change, proportion of patients with HAQ-DI exceeding the minimal clinically important difference (MCID) ≥0.30 threshold, mean change in DAS-28 (CRP), achievement of DAS (CRP) <2.6, and PASI-50/PASI-75 responses (Table). No new safety concerns were identified with up to 156 weeks of APR treatment. During Weeks >104 to ≤156 of APR exposure, the only adverse event (AE) occurring in ≥5% of patients was upper respiratory tract infection; most AEs were mild/moderate in severity. Diarrhea (2.1%) and nausea (2.1%) occurred at low rates in Weeks >104 to ≤156. Serious AEs occurred in 6.9% (APR30) and 6.4% (APR20) of patients, and few discontinuations (0.7%) due to AEs occurred over Weeks >104 to ≤156.

Conclusion: Over 156 weeks, among patients remaining in the study on treatment, APR demonstrated sustained and clinically meaningful improvements in PsA signs/symptoms, including physical function and associated psoriasis. APR continued to demonstrate an acceptable safety profile and was generally well tolerated.

	Outcomes at Week 52 and Week 156 (Data as Observed)			
	Week 52		Week 156	
	APR30 n=193*	APR20 n=186*	APR30 n=139*	APR20 n=129*
ACR20, n/m§ (%)	101/190 (53.2)	109/183 (59.6)	89/137 (65.0)	85/125 (68.0)
ACR50, n/m§ (%)	49/191 (25.7)	45/180 (25.0)	56/138 (40.6)	55/125 (44.0)
ACR70, n/m§ (%)	27/191 (14.1)	21/179 (11.7)	32/138 (23.2)	22/124 (17.7)
SJC, mean % change	-50.5	-61.8	-81.2	-80.6
TJC, mean % change	-45.1	-59.9	-73.2	-74.2
HAQ-DI (0-3), mean change	-0.31	-0.33	-0.37	-0.35
HAQ-DI MCID, ≥0.30‡, n/m (%)	85/193 (44.0)	81/184 (44.0)	71/139 (51.1)	60/127 (47.2)
DAS-28 (CRP), mean change	-1.26	-1.42	-1.90	-1.92
DAS-28 (CRP) <2.6, n/m (%)	41/189 (21.7)	56/185 (30.3)	57/136 (41.9)	64/129 (49.6)
PASI-50, n/m (%)‖	52/95 (54.7)	39/78 (50.0)	38/67 (56.7)	25/47 (53.2)
PASI-75, n/m (%)‖	31/95 (32.6)	17/78 (21.8)	24/67 (35.8)	15/47 (31.9)

n/m=number of responders/number of patients with sufficient data for evaluation. *The n reflects the number of patients treated with APR30 and APR20 (regardless of whether treatment started at Week 0, 16, or 24) and who had data available at the specific time point; actual number of patients available for each end point may vary. §Denominators vary slightly due to availability of sufficient data for each level of ACR response assessment. ‡Pre-specified MCID threshold, based on the literature (Mease PJ, et al. *Ann Rheum Dis.* 2004;63[Suppl 1]:391) at the time of protocol development and definition of analysis. ‖Examined among patients with psoriasis involvement of the body surface area ≥3% at baseline and data at the specific time point.

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Abstract Number: 2844

Secukinumab Reduces the Burden of Nail and Skin Disease in Patients with Psoriasis and Patients with Psoriatic Arthritis: Results from Two Phase 3 Studies

Alice B. Gottlieb[1], Kristian Reich[2], Zailong Wang[3], Marina Milutinovic[4] and Shephard Mpofu[4], [1]Dermatology, Tufts Medical Center, Boston, MA, [2]Dermatologikum Hamburg and Georg-August-University Göttingen, Hamburg, Germany, [3]Novartis Pharmaceuticals Corporation, East Hanover, NJ, [4]Novartis Pharma AG, Basel, Switzerland

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Background/Purpose: Nail psoriasis is associated with decreased finger mobility and pain in patients (pts) with moderate to severe plaque psoriasis and psoriatic arthritis (PsA).[1,2] Secukinumab, a fully human IgG1κ monoclonal antibody to interleukin-17A, provides significant and sustained improvements in the signs and symptoms of psoriasis and PsA.[3–5] Here we report the efficacy of secukinumab on skin and nail disease in two randomized, double-blind, placebo (PBO)-controlled phase 3 studies: TRANSFIGURE (NCT01807520), a study in pts with moderate to severe psoriasis with significant nail involvement, and FUTURE 2 (NCT01752634), a study in pts with PsA, a subset of whom had nail involvement.

Methods: In TRANSFIGURE, 198 pts with nail psoriasis were randomized (1:1:1) to subcutaneous (s.c.) secukinumab 300 mg, 150 mg, or PBO at baseline (BL), Weeks (Wks) 1, 2, and 3, and then every 4 wks (q4wk) from Wk 4. In FUTURE 2, 279/397 enrolled pts had nail psoriasis (nail subset) and 192/397 had ≥3% body surface area affected by psoriasis (psoriasis subset) at BL. Pts were randomized (1:1:1:1) to s.c. secukinumab 300 mg, 150 mg, and 75 mg or PBO at BL, Wks 1, 2, and 3, and then q4wk from Wk 4. In TRANSFIGURE, the primary endpoint was the percentage change from BL in total fingernail NAil Psoriasis Severity Index (NAPSI) score at Wk 16. In FUTURE 2, the primary endpoint was the proportion of pts achieving a ≥20% improvement from BL in ACR response criteria at Wk 24, with change from BL in total fingernail modified NAPSI (mNAPSI) score a pre-specified exploratory endpoint in the nail subset. Both studies included additional pre-specified assessments of psoriasis burden, including PASI 90.

Results: The primary endpoints were met in both studies. In TRANSFIGURE, the mean percentage change from BL in NAPSI was superior with both doses of secukinumab vs. PBO at Wk 16 (P<0.0001). At Wk 16, mean NAPSI score improved (decreased) from BL by 45.3%, 37.9%, and 10.8% for secukinumab 300 mg, 150 mg, and PBO, respectively. In FUTURE 2, mNAPSI scores at Wk 24 were improved vs. PBO with all secukinumab doses (all P<0.01). At Wk 24, mean mNAPSI score improved (decreased) from BL in the nail subset by 66.5%, 55.9%, and 61.6% for secukinumab 300 mg, 150 mg, and 75 mg, respectively, vs. 28.0% with PBO. PASI 90 responses at Wk 16 in TRANSFIGURE were 72.5%, 54.0%, and 1.7% for 300 mg, 150 mg and PBO, respectively; all P<0.0001). In FUTURE 2, PASI 90 responses at week 24 in the subset of pts with psoriasis were 48.8%, 32.8%, 12.0%, and 9.3% for 300 mg, 150 mg, 75 mg, and PBO, respectively (all P<0.01).

Conclusion: Secukinumab improved nail and skin symptoms in pts with psoriasis with significant nail involvement and in pts with concomitant PsA and nail involvement.

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Abstract Number: 2845

A Randomized, Clinical Trial to Assess the Relative Efficacy and Tolerability of Two Doses of Etoricoxib in Patients with Ankylosing Spondylitis

Eva Balazcs[1], Désirée van der Heijde[2], Narinder Rawal[3], Joachim Sieper[4], Boyd Scott[5], Kara Bickham[6], Nancy Frontera[6], Paul Stryszak[6], Dimitris Papanicolaou[6], Zoran Popmihajlov[6] and Paul Peloso[6], [1]Department of Neuromusculoskeletal Rehabilitation, Sima F, Szentes, Hungary, [2]University Hospital, Maastricht, Netherlands, [3]Orebro University Hospital, Orebro, Sweden, [4]University Clinic Benjamin Franklin, Berlin, Germany, [5]Merck Sharp & Dohme Corp., Whitehouse Station, NJ, [6]Merck & Co., Inc., Kenilworth, NJ

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Session Title: Spondylarthropathies and Psoriatic Arthritis - Clinical Aspects and Treatment Poster III: Therapy
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Session Time: 9:00AM-11:00AM

Background/Purpose:

Etoricoxib 90 mg, a selective COX-2 inhibitor, provides symptom relief in ankylosing spondylitis (AS) patients. A prior study established etoricoxib 90 mg as safe and effective in treating AS symptoms. The current study was conducted to determine the efficacy and safety of etoricoxib 60 mg in AS patients.

Methods:

This was a 2-part, double-blind, active comparator-controlled non-inferiority study in AS. Part I (6 weeks) assessed the efficacy of etoricoxib 60 mg and 90 mg compared to naproxen 1000 mg. Part II (6 weeks) evaluated whether subjects with inadequate pain relief on etoricoxib 60 mg in Part I benefited from increasing to etoricoxib 90 mg in Part II. Patients were ≥18 years of age with AS as classified by the Modified New York criteria and a history of clinical response with NSAIDs. Patients were required to have a disease flare after NSAID washout prior to randomization. Eligible patients were randomized to naproxen; etoricoxib 60 mg in Part I & II; etoricoxib 60 mg in Part I 90 mg in Part II; or etoricoxib 90 mg in Part I & II in a 4:9:9:4 ratio respectively. The primary objective was to compare the effect on spinal pain intensity (SPI) score (0 to 100 mm VAS) after 6-weeks of treatment in Part I. The non-inferiority margin was set at 8 mm for the SPI measure based on prior literature findings. The overall safety and tolerability of etoricoxib in AS patients was assessed including independent adjudication of all thrombotic cardiovascular and serious upper GI AEs.

Results:

In total, 1015 patients were randomized; 70.9% were male; the mean age was 45.2 years, 84.6% were Caucasian, 919 patients completed Part I and all continued to Part II. In Part I, both etoricoxib doses were non-inferior to naproxen based on change in SPI score from baseline (Table 1A). There was a mean decrease of ~2 mm SPI score for etoricoxib 90 mg versus 60 mg; (Table 1B). Patients who had inadequate pain response in Part I with 60 mg, had a small but significant improvement in SPI score after switching to 90 mg (Table 1C). In both Part I and II, the incidences of AEs, drug-related AEs, and SAEs were similar between the 3 treatment groups. Independently adjudicated AEs were also similar between treatment groups).

Conclusion:

Both doses of etoricoxib were non-inferior to naproxen. Etoricoxib 60 mg and 90 mg had similar efficacy in relieving the pain associated with AS. Among inadequate responders to etoricoxib 60 mg, dose escalation to 90 mg daily resulted in a statistically significant decrease in SPI score as compared to those subjects remaining on 60 mg. Both etoricoxib 90 mg and 60 mg were well tolerated, and no new safety signals were identified.

SPI (0 to 100 mm VAS) time-weighted average change from baseline

A Part I (Non-Inferiority: Per-protocol Population)			
Treatment (6 weeks)	N	LS Mean change†	Between etoricoxib and naproxen difference in LS mean change† (95% CI)
Etoricoxib 60 mg	660	-29.0	1.59 (-2.19, 5.37)
Etoricoxib 90 mg	144	-31.23	-0.64 (-5.47, 4.19
Naproxen 1000 mg	143	-30.59	
B Part I (Non-Inferiority: Modified Intention to Treat Population)			
Treatment (6 weeks)	N	Between Etoricoxib doses	
		Difference in LS Mean Change† (80% CI)	P-Value†
Etoricoxib 60 mg	694		
Etoricoxib 90 mg	153	-1.58 (-3.96, 0.81)	0.396
C Part II Average Change from Week 6 at Weeks 10 and 12 in SPI among Pain Inadequate Responders from Part I (Superiority: Modified Intention to Treat Population)			
Treatment Sequence (weeks 10 and 12)	N	LS Mean (95% CI)	Difference in LS Mean (80% CI)	p-Value
Etoricoxib 60 mg/60 mg	175	-7.26 (-9.73, -4.80)		
Etoricoxib 60 mg/90 mg	178	-9.97 (-12.42, -7.51)	-2.70 (-4.88, -0.52)	0.112

† The LS means, CIs, and p-values were derived from the analysis of covariance model with terms for treatment, chronic peripheral arthritis (presence, absence) and baseline values as a covariate. LS = Least Squares, CI = Confidence intervals

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Abstract Number: 2846

Modifications to Biologic Therapy and Economic Implications in Psoriatic Arthritis Patients

Jacqueline B. Palmer, Yunfeng Li, Vivian Herrera, Minlei Liao and Zafer Ozturk, Novartis Pharmaceuticals Corporation, East Hanover, NJ

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Background/Purpose: Limited information exists on the long term real-world treatment patterns of biologics for psoriatic arthritis (PsA) in the US population. We assessed medication persistence and drug switching with biologics in PsA and estimated the economic costs of different treatment sequences.

Methods: We conducted a retrospective analysis of medical and pharmacy claims data from the MarketScan database (United States). The study included PsA patients >= 18 years of age, biologic-naïve (no biologic therapy in the previous 6 months), who initiated a biologic during the period from October 1, 2009 to September 30, 2010 and were continuously enrolled in a medical and pharmacy benefits program for a 3-year follow-up period. Treatment persistence, switching, modification of treatment (i.e., biologic dose adjustment or any change in concomitant DMARD therapy), and medical and pharmacy costs were analyzed for each line of biologic therapy during the 3 year follow-up period. Line of therapy was defined by the number of biologics a patient used in the follow-up peroid.

Results: Among the 990 PsA patients identified 89.0% of patients used only one line of biologic, 7.3% had a second-line biologic, and 3.7% tried 3 or more lines of biologic therapy. For all the lines of therapy, the first biologics used were: etanercept (n = 435; 43.9%), adalimumab (n = 437; 44.1%), infliximab (n = 77; 7.8%), and golimumab (n = 41; 4.1%). The discontinuation rates by line of therapy were as follows: 71.6% (n = 631) for patients who only used one line of biologics; 50.0% (n = 36) for those with second-line biologic and 18.9% (n = 7) for those who tried 3 or more biologics.The time patients spent on the first biologic was shorter for those who switched to a second-line biologic (348 days) or third-line biologic (325 days) compared to those those who only used one biologic (522 days). Overall time to treatment modification became shorter with each line of therapy; the shortest was 42 days for patient on their third line of therapy, 137 days for those on their second line, and 146 days in the first line. The most common treatment modifications in the first-line of biologic therapy were DMARD dose increase (21.1%), add-on (9.0%) and removal (7.4%). Monthly medical costs (hospitalizations, office visits, emergency department visits) per member per month were higher for patients using only one line of biologic ($322) than for those who received second-line ($167) or third-line ($217) treatment, whereas monthly pharmacy costs per member per month were lower for patients using only one line of biologic ($1985) than for those on second-line ($2045) or third-line ($2539) biologics.

Conclusion: Approximately two thirds of PsA patients discontinued their first biologic therapy. Of those who were continuous users and and moved on to second- and third-line therapies, the time of discontinuation from their first-biologic was shorter, indicating non-responders were identified early in the treatment course. Monthly medical costs were higher for those who did not switch biologic therapy, but pharmacy costs increased with the number of biologic switches. This may be because of treatment add-ons or worsening disease severity.

Disclosure: J. B. Palmer, Novartis Pharmaceutical Corporation, 3; **Y. Li**, Novartis Pharmaceutical Corporation, 3; **V. Herrera**, Novartis Pharmaceutical Corporation, 1,Novartis Pharmaceutical Corporation, 3; **M. Liao**, Novartis Pharmaceutical Corporation, 3; **Z. Ozturk**, Novartis Pharmaceuticals Corporation, 3.

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Abstract Number: 2847

Predictors of Therapeutic Response in Ankylosing Spondylitis Patients Initiating Therapy with Adalimumab in a German Non-Interventional Study

Michaela Koehm[1,2], Frank Behrens[1,3], Eva C. Scharbatke[4], Marc Schmalzing[5], Holger Gnann[6], Gerd Greger[7], Bianca Wittig[8], Hans Peter Tony[9] and Harald Burkhardt[3,10], [1]Clinical Research, Fraunhofer Institute for Molecular Biology and Applied Ecology IME, Project Group Translational Medicine & Pharmacology TMP, Frankfurt/Main, Germany, [2]Rheumatology, Goethe-University Frankfurt, Frankfurt/Main, Germany, [3]Rheumatology, Goethe-University Frankfurt, Frankfurt, Germany, [4]Rheumatology/Immunology, University of Würzburg, Würzburg, Germany, [5]Rheumatology/Immunology, University Würzburg, Würzburg, Germany, [6]Abteilung Biostatistik, GKM Gesellschaft für Therapieforschung mbH, München, Germany, [7]AbbVie Deutschland GmbH & Co.KG, Wiesbaden, Germany, [8]Abbott GmbH & Co KG, Wiesbaden, Germany, [9]Rheumatology / Clinical Immunology, University Hospital Würzburg, Würzburg, Germany, [10]Fraunhofer Institute for Molecular Biology and Applied Ecology IME, Project Group Translational Medicine & Pharmacology TMP, Frankfurt/Main, Germany

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Background/Purpose:

Ankylosing spondylitis (AS) is associated with a significant burden of illness and has limited treatment options. The identification of predictors of response to anti-tumor necrosis factor (TNF) therapy may help clinicians select therapy and address patient expectations.

Methods:

We analyzed data from a large German multicenter, prospective, observational study of patients with active AS who initiated adalimumab (ADA) therapy during routine clinical care. Multiple regression models were used to evaluate significant predictors of improvement at month 12 in the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and the Bath Ankylosing Spondylitis Functional Index (BASFI). For both indices, higher scores indicate greater disease activity/impairment.

Results:

Patients in the full analysis set (N = 3756) had a mean age of 43.0 ± 12.2 years and a mean disease duration of 14.2 ± 10.9 years. During ADA therapy, mean BASDAI scores improved from 5.5 ± 1.9 at baseline to 3.1 ± 2.1 at month 12 and BASFI scores improved from 4.9 ± 2.4 at baseline to 3.2 ± 2.4 at month 12 in evaluable patients remaining on therapy. Although both HLAB27 status and baseline erythrocyte sedimentation rate (ESR) were positive predictors of therapeutic response for BASDAI and BASFI (Table), the strongest positive predictors were not shared between these two indices (dactylitis and baseline BASDAI for BASDAI, baseline BASFI and employment for BASFI). In contrast, most of the negative predictors of response were shared between the BASDAI and BASFI, including the two strongest predictors, mental disorder/depression and a greater number of previous biologics.

Conclusion:

AS patients showed marked improvement in BASDAI and BASFI during 12 months of treatment with ADA in routine clinical practice. Positive predictors of response to ADA therapy differ between BASDAI and BASFI in AS patients, but negative predictors are generally shared.

Disclosure: M. Koehm, Pfizer Inc, 2,MSD; Pfizer, 5,Janssen Pharmaceutica Product, L.P., 8; **F. Behrens**, AbbVie Deutschland GmbH & Co KG; Chugai; Pfizer; Roche, 5,Pfizer Inc, 8; **E. C. Scharbatke**, AbbVie Deutschland GmbH Co.KG; Baxter; Chugai; Roche, 5,Chugai, 8; **M. Schmalzing**, AbbVie Deutschland GmbH Co.KG; Actelion; Chugai; Pfizer; Roche; UCB, 5; **H. Gnann**, Abi Deutschland GmbH Ko.KG, 5; **G. Greger**, AbbVie Deutschland GmbH + Co.KG, 3; **B. Wittig**, AbbVie Deutschland GmbH + Co.KG, 3; **H. P. Tony**, None; **H. Burkhardt**, AbbVie Deutschland; Pfizer; BMS; UCB; Chugai, 5,Pfizer Inc, 2.

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Abstract Number: 2848

Network Meta-Analysis of Tumor Necrosis Factor, Interleukins, and Phosphodiesterase-4 Inhibitor in the Treatment of Psoriatic Arthritis

Vibeke Strand[1], M. Elaine Husni[2], William Reichmann[3], Keith Betts[4], Jenny Griffith[5], Yan Song[3], Marci Beppu[6] and Arijit Ganguli[5], [1]Biopharmaceutical Consultant, Portola Valley, CA, [2]Rheumatology Dept A50, Cleveland Clinic Foundation, Cleveland, OH, [3]Analysis Group Inc., Boston, MA, [4]Analysis Group, Inc., Boston, MA, [5]AbbVie Inc., North Chicago, IL, [6]Abbvie, Newcastle, WA

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Background/Purpose:

Multiple disease-modifying therapies for treatment of psoriatic arthritis (PsA) are available. However, there are limited data directly comparing these biologic therapies and the recently approved phosphodiesterase-4 (PDE-4) inhibitor. In the absence of head-to-head

trials, it is difficult for decision makers to make treatment choices in real world scenarios. The aim of this study was to conduct a network meta-analysis (NMA) to indirectly compare the efficacy of biologic agents and apremilast for treatment of active PsA.

Methods:

A systematic literature review was conducted to identify Phase III randomized controlled trials (RCTs) for tumor necrosis factor inhibitors (TNFi's: adalimumab, infliximab, golimumab, etanercept, and certolizumab), interleukin inhibitors (ustekinumab and secukinumab), and a PDE-4 inhibitor (apremilast) for active PsA. The relative probabilities of achieving ACR20 and PASI75 responses at week 24 with each agent were estimated via a Bayesian network meta-analysis. All arms of the network meta-analysis included FDA-approved doses for PsA except secukinumab, where all three doses examined in RCTs: 75, 150, and 300 mg every 4 weeks were included. Numbers needed to treat (NNT) were calculated as the reciprocal of the incremental response rate of each treatment versus placebo. Analyses were repeated among subgroups of patients without prior biologic therapy.

Results:

Seventeen RCTs were identified, 14 included ACR20 and/or PASI75 responses at Week 24. Among all patients and biologic-naive patients, adalimumab, golimumab, infliximab, and secukinumab (300 and 150 mg) had NNTs <3 for ACR20 responses at Week 24, and adalimumab the lowest NNT of 2.32 (95% credible interval [CrI] 1.78, 3.22; Figure 1). Among all patients and biologic-naive patients, infliximab, golimumab, and adalimumab had NNTs <2 for PASI75 responses at Week 24, and infliximab the lowest NNT of 1.53 (1.25, 2.01; Figure 2). PASI75 responses among biologic-naïve patients were not available for secukinumab, certolizumab, and apremilast.

Conclusion:

At Week 24, adalimumab, golimumab, secukinumab 300 mg, and infliximab had the lowest NNTs per ACR20 and/or PASI75 responders among all patients as well as among biologic-naïve patients.

Figure 1. Numbers needed to treat to achieve one additional ACR 20 responder

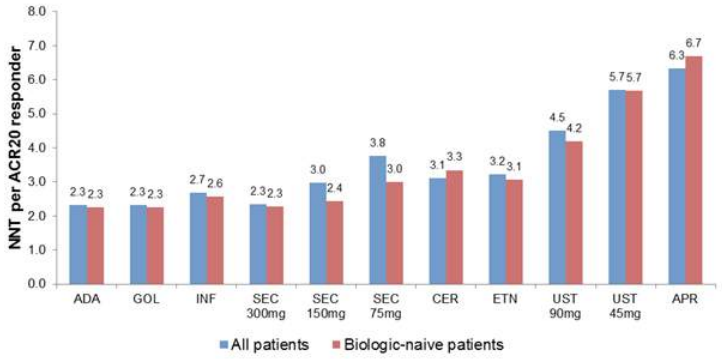

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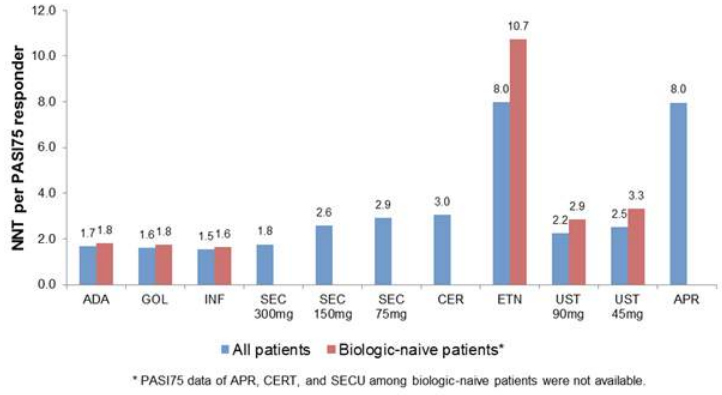
Figure 2. Numbers needed to treat to achieve one additional PASI 75 responder



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Disclosure: V. Strand, Abbvie, Alder, Amgen, Anthera, AstraZeneca, BiogenIdec, Bristol-Myers Squibb, Genentech, GSK, Janssen, MerckSerono, Novartis, Pfizer Inc, Sanofi-Aventis, and UCB, 2; **M. E. Husni**, Celgene, Abbvie, Genentech, Bristol Myers Squibb, Pfizer, Novartis, and Janssen, 9; **W. Reichmann**, Analysis Group, and received payment from AbbVie to assist with research, 3; **K. Betts**, Analysis Group, and received payment from AbbVie to assist with research, 3; **J. Griffith**, AbbVie, 3,AbbVie, 1; **Y. Song**,

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Abstract Number: 2849

Apremilast, an Oral Phosphodiesterase 4 Inhibitor, Is Associated with Long-Term (104-Week) Improvement in Fatigue in Patients with Psoriatic Arthritis: Pooled Results from 3 Phase 3, Randomized, Controlled Trials

Arthur Kavanaugh[1], Dafna Gladman[2], Christopher J. Edwards[3], Airi Poder[4], Frederic Liote[5], Paul A. Bird[6], Georg Schett[7], Melissa McIlraith[8], Lichen Teng[8] and Philip J. Mease[9], [1]University of California, San Diego School of Medicine, LaJolla, CA, [2]Toronto Western Research Institute, Toronto, ON, Canada, [3]University Hospital Southampton, Southampton, United Kingdom, [4]Clinical Research Centre Ltd, Tartu, Estonia, [5]University Paris Diderot, Paris, France, [6]University of New South Wales, Sydney, Australia, [7]Department of Internal Medicine 3 and Institute for Clinical Immunology, University of Erlangen-Nuremberg, Erlangen, Germany, [8]Celgene Corporation, Warren, NJ, [9]Swedish Medical Center and University of Washington School of Medicine, Seattle, WA
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Background/Purpose: Patients (pts) with active psoriatic arthritis (PsA) have disease involvement across multiple domains. Pts can have substantial fatigue, which is increasingly being recognized as important to pts, particularly those with chronic diseases, and can affect QoL.[1] The 2014 OMERACT PsA Working Group identified fatigue measurement as an important outcome to consider including in PsA core assessments.[2] PALACE 1-3 compared apremilast (APR) efficacy/safety with placebo (PBO) in pts with active PsA despite prior conventional DMARDs and/or biologics, including assessment of fatigue levels. We report the impact of APR treatment on fatigue over 104 wks in a pooled PALACE 1-3 analysis.

Methods: Pts were randomized (1:1:1) to PBO, APR 30 mg BID (APR30), or APR 20 mg BID (APR20) stratified by baseline DMARD use (yes/no). The PBO-controlled phase continued to Wk 24, with a Wk 16 early escape option. At Wk 24, all remaining PBO pts were re-randomized to APR30 or APR20. Double-blind APR treatment continued to Wk 52; pts could then continue to receive APR for up to an additional 4 years during an open-label extension phase. Fatigue was assessed using the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) v4, a 13-item questionnaire initially developed to assess anemia-associated fatigue.[3] Questions are scored from 0-4. Total FACIT-F scores range from 0-52, with higher scores denoting lower levels of fatigue. As a point of reference, mean fatigue scores of 40.1-43.6 in the general population, 35.8 in PsA patients,[4] and 23.9 in anemic cancer pts have been reported[5,6]; FACIT-F MCID in pts with rheumatoid arthritis (RA) is 3-4.[7]

Results: Baseline mean FACIT-F scores in pts receiving APR at Wks 52 and 104 ranged from 29.2-31.2, which are markedly below population norms and indicative of fatigue-related impaired QOL. Long-term improvement in fatigue was seen in APR pts at 52 wks, as shown by improvement in FACIT-F score (Table). At Wk 104, APR30 pts had sustained improvements in fatigue (mean FACIT-F=35.0), marking a shift toward population FACIT-F norms. APR30 mean change was 5.6, which exceeded the MCID for this measure in RA pts; 50.9% of APR30 pts achieved MCID for FACIT-F. APR30 mean % change in FACIT-F was 44.5%. Wk 104 findings were similar with APR20. Over 104 wks, most adverse events (AEs) were mild/moderate; in general, no increase was seen in AE incidence/severity with longer term exposure.

Conclusion: Over 104 wks, APR continued to improve fatigue in PsA pts. APR demonstrated an acceptable safety profile and was generally well tolerated up to 104 wks.

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FACIT-F at Wk 52 and Wk 104 (Data as Observed)				
	Wk 52		Wk 104	
FACIT-F	APR30 n=559	APR20 n=541	APR30 n=454	APR 20 n=430
Baseline, mean	29.2	31.2	29.5	31.2
Mean at time point	34.0	35.1	35.0	35.7
Mean change from baseline	4.8	3.9	5.6	4.5
Mean % change from baseline	35.4	21.5	44.5	26.1
Proportion (%) of pts achieving MCID	50.6	49.0	50.9	50.5
The n represents the number of pts who completed 52 wks and 104 wks of treatment, respectively, regardless of when treatment started (Wk 0, 16, or 24), with a baseline value and a post-baseline value at the time point.				

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Abstract Number: 2850

Etanercept Treatment in Psoriatic Arthritis: Need for Co-Medication?

Brigitte Michelsen[1], Dag Magnar Soldal[2], Arthur Kavanaugh[3] and Glenn Haugeberg[1,4,5], [1]Rheumatology, Hospital of Southern Norway Trust, Kristiansand, Norway, [2]Rheumatology, Hospital of Southern Norway, Kristiansand, Norway, [3]University of California San Diego, La Jolla, CA, [4]Rheumatology, Martina Hansens Hospital, Gjettum, Norway, [5]Rheumatology, The Norwegian University of Science and Technology, Trondheim, Norway

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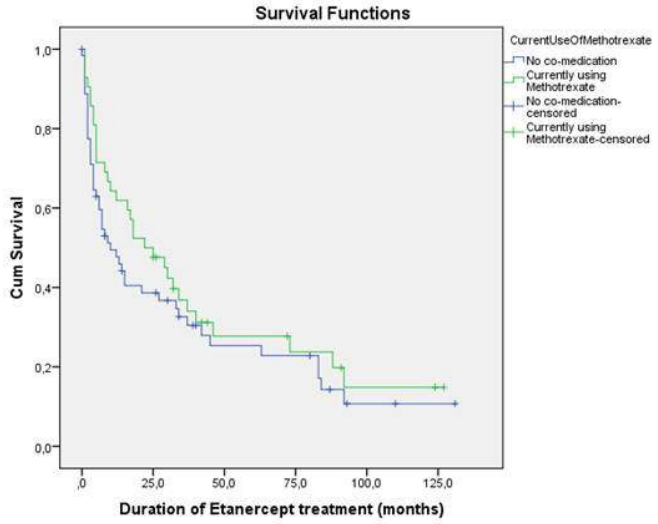
Session Time: 9:00AM-11:00AM

Background/Purpose: The role of co-medication e.g. with conventional synthetic disease-modifying antirheumatic drugs (csDMARDs), among patients with psoriatic arthritis (PsA) who are receiving tumor necrosis factor inhibitors (TNFi) remains unclear. Some studies have indicated a beneficial role in the longevity of treatment, potentially by reducing the formation of anti-drug antibodies. Etanercept has generally been found to be less immunogenic than monoclonal antibody TNFi. This study aimed to investigate the role of concomitant methotrexate on drug survival of etanercept in psoriatic arthritis (PsA).

Methods: We included consecutive PsA patients from a Norwegian out-patient clinic. Baseline characteristics and drug survival were compared between patients with and without methotrexate co-medication. The X^2 test, independent t-test and Mann-Whitney U test were applied as appropriate for group comparisons. Drug survival was explored by Kaplan-Meier analysis, and patients receiving and not receiving co-medication were compared using the log rank test. Cox regression analysis was used to identify predictors of discontinuation.

Results: We included 105 patients treated with etanercept, 42 receiving co-medication with methotrexate. Mean (SD) age was 54,3 (11,0) years, years of education 13,1 (3,7), disease duration 13,4 (8,8) years, body mass index 28,2 (4,8) kg/m^2, baseline CRP 11,1 (23,4), baseline swollen joints 2,9 (3,4), 42,9% were female and 21,9% currently smoking. Overall, 31 (29,5%) patients were previously treated with TNFi. Baseline characteristics were similar for patients with and without co-medication. Drug survival of etanercept was similar for patients receiving versus not receiving concomitant methotrexate (log rank test p=0,277, figure). In the Cox regression analysis the only identified predictor for etanercept discontinuation was previous use of TNFi. Separate analyses for first time TNFi users did not change the primary outcome.



Conclusion: In our population of etanercept treated PsA patients, we found similar drug survival for patients with and without co-medication with methotrexate. The only identified predictor for etanercept discontinuation was previous use of TNFi.

Disclosure: B. Michelsen, None; **D. M. Soldal**, None; **A. Kavanaugh**, None; **G. Haugeberg**, Pfizer Norway, 2.

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Abstract Number: 2851

Anti-TNF Therapy Is Associated with an Increase in Serious Infections in Patients with Spondyloarthritis (SpA), Especially during the First 12 Monts of Treatment: Results from the GISEA Registry

Fabiola Atzeni[1], Marco Sebastiani[2], Valentina Panetta[3], Fausto Salaffi[4], Antonio Marchesoni[5], Roberta Ramonda[6], Florenzo Iannone[7], Roberto Gorla[8], Elisa Gremese[9], Marcello Govoni[10], Pier Carlo Sarzi-Puttini[11], Gianfranco Ferraccioli[12], Giovanni Lapadula[13] and on behalf of GISEA group, [1]Rheumatology Unit, L. Sacco University Hospital of Milan, Milan, Italy, [2]SC Reumatologia, Dipartimento di Medicine, Medicina d'Urgenza e Specialità Mediche, Azienda Ospedaliero-Universitaria di Modena, Modena, Italy, [3]L'altrastatistica -Consultancy & Training- Biostatistics office., Rome, Italy, [4]Rheumatology Department, Polytechnic University of Marche, C. Urbani Hospital, Jesi,, Ancona, Italy, [5]Day Hospital of Rheumatology, G. Pini Orthopedic Institute, Chair of Rheumatology of Milan, Milan, Italy, [6]Cattedra, Voc Rheumatology, University of Padua, Padova, Italy, [7]Interdisciplinary Department of Medicine (DIM), Rheumatology Unit, University of Bari, Bari, Italy, [8]Rheumatology and Immunology Unit, Spedali Civili di Brescia, Brescia, Italy, [9]Division of Rheumatology, Institute of Rheumatology, Catholic University of the Sacred Heart, Rome, Italy, [10]Department of Medical Sciences, UOC of Rheumatology, Azienda Ospedaliero-Universitaria S. Anna-Ferrara, University of Ferrara, Cona Ferrara, Italy, [11]Rheumatology Unit, University Hospital L Sacco, Milan, Italy, [12]Rheumatology and Internal Medicine, Catholic University of the Sacred Heart, Rome, Italy, [13]Bari University, Rheumatology, Bari, Italy

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Session Time: 9:00AM-11:00AM

Background/Purpose: Infection is by far the most common and most important adverse effect of TNF inhibitors (TNFI) in the treatment of rheumatoid arthritis (RA) and spondyloarthritis (SpA). The aim of this study was to evaluate the risk of SIs in the TNFI-treated SpA patients in the Gruppo Italiano Studio Early Arthritis (GISEA) Registry, and assess the predictors of their occurrence.

Methods: The Registry, which is designed to collect real-world clinical data concerning RA and SpA patients receiving biological drugs as part of routine care, was approved by local Ethics Committees, and enrols patients aged ≥18 years who have given their written informed consent. The baseline information includes demographics, disease duration, HAQ, DAS-28, BASDAI, BASFI and BASMI scores, steroid use (defined as actively receiving oral steroids at the time of recruitment), smoking history and comorbidities.

Results: The analysis involved 3321 SpA patients (1731 males, 52.2%; mean age 47±13 years; median disease duration three years, interquartile range [IQR] 0, 8 years): 1065 (32%) treated with infliximab (IFN), 1052 (32%) with adalimumab (ADA), and 1204 (36%) with etanercept (ETN). Two thousand, one hundred and five (63.4%) had a median of one comorbity (IQR 0, 2], the most frequent being hypertension (701), thyroid diseases (281), diabetes mellitus (207), cardiopathy (189), and osteoporosis (145). In combination with the biological drug, 919 patients (27.7%) received steroids and 2451 (79.9%) at least one DMARD. The median follow-up was three months (IQR 12 years). During 12 years of TNFI treatment, 259 patients experienced at least one of 391 microbiologically diagnosed SIs, 32% of which were recorded in the first 12 months. Overall incidence was 43.9/1000 patient-years of follow-up (95% CI 39.6–48.4): 29.9/1000 (95% CI 23.1–38.1) among those treated with ADA; 36.1/1000 (95% CI 30.0–43.1) among those treated with ETN; and 61.4/1000 (95% CI 53.3–70.5) among those treated with IFN. The most frequent were lower respiratory tract infections (pneumonia and bronchitis), followed by cutaneous infections. Bacteria were the most frequent micro-organisms (228, 58.3%), followed by fungal infections (40, 10.2%) and viral infections including herpes zoster (22, 5.6%). Univariate analysis showed that female gender (p=0.019) and comorbidities (p<0.001) were associated with a high risk of SI, and that the use of ETN or ADA rather than IFN (p<0.001 and p0.001) was associated with a lower risk of SI. Multivariate models showed that the number of comorbidities (hazard ratio [HR] 1.29, 95%CI 1.2–1.4; p<0.001), age at the start of anti-TNF treatment (HR 0.99, 95%CI 0.97-0.99; p=0.030), steroid use (HR 1.40, 95%CI 1.1–1.8; p=0.012), male gender (HR 0.72, 95%CI 0.5-0.9; p=0.012) were statistically significant predictors of infection. The factors independently associated with a decreased risk of SIs were the use of ETN (HR 0.52, 95%CI 0.4-0.7; p<0.001) or ADA (HR 0.59, 95%CI 0.4-0.8; p=0.002) rather than INF.

Conclusion: These data add to currently available evidence suggesting that TNFI therapy is associated with a small but significant overall risk of SI in SpA patients.

Disclosure: F. Atzeni, None; **M. Sebastiani**, None; **V. Panetta**, None; **F. Salaffi**, None; **A. Marchesoni**, None; **R. Ramonda**, None; **F. Iannone**, None; **R. Gorla**, None; **E. Gremese**, None; **M. Govoni**, None; **P. C. Sarzi-Puttini**, None; **G. Ferraccioli**, None; **G. Lapadula**, None.

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Abstract Number: 2853

Secukinumab Improves Skin Symptoms and Physical Functioning Compared with Ustekinumab in Patients with Moderate to Severe Psoriasis with Concomitant Psoriatic Arthritis: Subanalysis of a Randomized, Double Blind, Parallel-Group, Active Comparator-Controlled Phase 3b Trial

Alice B. Gottlieb[1], Diamant Thaci[2], Andrew Blauvelt[3], Marina Milutinovic[4] and Shephard Mpofu[4], [1]Tufts Medical Center and Tufts University School of Medicine, Boston, MA, [2]Comprehensive Center for Inflammation Medicine, University Hospital Schleswig-Holstein, Lübeck, Germany, [3]Research Excellence & Personalized Patient Care, Oregon Medical Research Center, Portland, OR, [4]Novartis Pharma AG, Basel, Switzerland

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SESSION INFORMATION

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Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Psoriatic arthritis (PsA) is a common comorbidity in patients (pts) with psoriasis. In the ongoing Phase 3b CLEAR study (NCT02074982), secukinumab, a fully human anti-interleukin (IL)-17A monoclonal antibody, demonstrated superior efficacy (PASI 90) to ustekinumab (an IL-12/23 inhibitor) in pts with moderate to severe plaque psoriasis.[1]Here we report results of a pre-defined sub-analysis which evaluated 16-week (wk) outcomes in pts in the study who had concomitant PsA.

Methods: Pts, stratified by body weight (≤ 100 and > 100 kg), were randomized 1:1 to receive subcutaneous (s.c.) secukinumab 300 mg or ustekinumab (for pts ≤ 100 kg, 45 mg s.c.; > 100 kg, 90 mg s.c.). Secukinumab was administered at baseline (BL), Wks 1, 2, 3, and every 4 Wks from Wk 4; ustekinumab was administered at BL and Wk 4, and then every 12 wks from Wk 16. The primary end-point

was the proportion of pts achieving at least a 90% reduction from BL in Psoriasis Area and Severity Index score (PASI 90) at Wk 16. Changes from BL in the Health Assessment Questionnaire-Disability Index (HAQ-DI; score range of 0–3) were reported in the subgroup of psoriasis pts with concomitant PsA.

Results: The overall study population consisted of 676 pts. Concomitant PsA was reported in 69/337 (20.5%) pts in the secukinumab group and 54/339 (15.9%) pts in the ustekinumab group. In the overall population, a PASI 90 response at Wk 16 was achieved by 79.0% pts receiving secukinumab vs. 57.6% pts receiving ustekinumab ($P < 0.0001$) and a PASI 100 (clear skin) response at Wk 16 was achieved by 44.3% pts receiving secukinumab vs. 28.4% pts receiving ustekinumab ($P < 0.0001$). In the subgroup of pts with concomitant PsA, a higher proportion of pts in the secukinumab group achieved a PASI 90 response at Wk 16 compared with ustekinumab; 79.1% vs. 65.4%, respectively (p=0.063). A PASI 100 response at Wk 16 was achieved by 35.8% pts in the secukinumab group vs. 28.8% pts in the ustekinumab group (p=0.336). Improvements in physical function in the PsA sub-group were greater with secukinumab vs. ustekinumab; mean change from baseline in HAQ-DI at Wk 16 was –0.29 (-47.6%) with secukinumab vs. –0.13 (-37.7%) with ustekinumab. A higher proportion of pts receiving secukinumab achieved a clinically meaningful improvement in HAQ-DI (defined as at least a 0.3 decrease from baseline at Wk 16 vs. ustekinumab (34.9% vs. 26.5%, respectively).

Conclusion: Secukinumab was superior to ustekinumab at improving skin symptoms in patients with moderate to severe plaque psoriasis. In the small sub-group of patients with psoriasis and concomitant PsA, secukinumab showed a trend for improving skin symptoms and physical functioning compared with ustekinumab.

Reference:

1. Thaci D, et al. Oral Presentation at AAD Annual Meeting 2015, San Francisco, USA Late breaking abstract.

Disclosure: A. B. Gottlieb, Amgen Inc., Astellas, Akros, Centocor (Janssen), Inc. Celgene Corp., Bristol Myers Squibb Co., Beiersdorf, Inc., Abbott Labs. (Abbvie), DUSA, TEVA, Actelion, UCB, Novo Nordisk, Novartis, Dermipsor Ltd., Incyte, Pfizer, Canfite, Lilly, Coronado, Vertex, Ka, 5,Centocor (Janssen), Amgen, Abbott (Abbvie), Novartis, Celgene, Pfizer, Lilly, Coronado, Levia, Merck, Xenoport, 2; **D. Thaci**, AbbVie, Amgen, Biogen-Idec, Celgene Corp., Eli Lilly, Janssen-Cilag, Leo Pharma, MSD, Novartis, Pfizer, Regeneron, and Sanofi, 5,AbbVie, Amgen, Biogen-Idec, Celgene Corp., Eli Lilly, Janssen-Cilag, Leo Pharma, MSD, Novartis, Pfizer, Regeneron, and Sanofi, 6,AbbVie, Amgen, Biogen-Idec, Celgene Corp., Eli Lilly, Janssen-Cilag, Leo Pharma, MSD, Novartis, Pfizer, Regeneron, and Sanofi, 9; **A. Blauvelt**, Abbott, Amgen, Astellas, Boehringer Ingelheim, Celgene, Centocor, Eli Lilly, Galderma, Janssen, Merck, Novartis, Pfizer, and Sandoz, 5; **M. Milutinovic**, Novartis Pharmaceutical Corporation, 3; **S. Mpofu**, Novartis AG, 3,Novartis AG, 1.

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Abstract Number: 2854

Long-Term Tolerability and Efficacy of Golimumab in Active Nonradiographic Axial Spondyloarthritis: Results from the Open-Label Extension of a Randomized, Double-Blind Study

Désirée van der Heijde[1], Maxime Dougados[2], Walter Maksymowych[3], Gina Bergman[4], Sean P. Curtis[4], Anjela Tzontcheva[4], George Philip[4], Susan Huyck[4] and Joachim Sieper[5], [1]Leiden University Medical Center, Leiden, Netherlands, [2]Paris-Descartes University, Paris, France, [3]University of Alberta, Edmonton, AB, Canada, [4]Merck & Co., Inc., Kenilworth, NJ, [5]University Clinic Benjamin Franklin, Berlin, Germany

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SESSION INFORMATION

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Session Title: Spondylarthropathies and Psoriatic Arthritis - Clinical Aspects and Treatment Poster III: Therapy

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: The tolerability and efficacy of golimumab (GLM) as a treatment for nonradiographic axial spondyloarthritis (nr-axSpA) were recently investigated in a randomized, double-blind (DB), placebo (PBO)-controlled, phase 3 study (GO-AHEAD).[1] We report the findings from an open-label extension (OLE) of GO-AHEAD that evaluated the long-term use of GLM in patients with nr-axSpA.

Methods: Patients completing the 16-week DB study were eligible to receive open-label GLM 50 mg every 4 weeks during the 44-week extension (36-week treatment period; 8-week safety follow-up). Safety evaluations included the incidence/severity of adverse

events (AEs). Efficacy evaluations included ASAS 20, ASAS 40, BASDAI 50, ASAS partial remission (PR; ≤20 mm score in all 4 domains), and ASDAS-C at weeks 20, 24, 32, 40, and 52. Quality of life evaluations included EQ-5D and percentage of work impairment (WPAI) at weeks 16 and 52. Data were summarized descriptively; all patients were included. Non-responder imputation was used for missing ASAS 20, ASAS 40, and ASAS PR values. BASDAI required 3 of 5 responses; LOCF imputation was used for missing values. ASDAS-C was only calculated if all components were available.

Results: Of the 197 subjects treated in the DB study, 189 entered the OLE (GLM/GLM, 93/97 [96%]; PBO/GLM, 96/100 [96%]). In total, 174/189 (92%) patients completed all visits (GLM/GLM, 85/93 [91%]; PBO/GLM, 89/96 [93%]). There were no notable differences in the number/types of AEs between the GLM/GLM and PBO/GLM groups (Table). For ASAS 20, ASAS 40, BASDAI 50, and ASAS PR, the PBO/GLM group showed notable improvement in these measures after switching to GLM in the OLE, while the proportions of responders in the GLM/GLM group remained higher than the PBO/GLM group throughout the study (Figure). For week 52 vs week 16, mean changes from baseline (BL) in ASDAS-C were similar or better in the GLM/GLM group (–2.2 vs –1.7) and were improved in the PBO/GLM group after switching to GLM (–1.7 vs –0.6). At week 52, the mean change from BL in EQ-5D Health State VAS score was 3.2 cm in the GLM/GLM group and 2.3 cm in the PBO/GLM group, and the mean change from BL in the percentage of work impairment while working was –28.1% in the GLM/GLM group and –22.8% in the PBO/GLM group.

Table. Summary of Adverse Events in the GO-AHEAD OLE

AEs,[a] n (%)	GLM/GLM N=93	PBO/GLM N=96	Total N=189
Treatment-emergent AE	39 (41.9)	52 (54.2)	91 (48.1)
Treatment-related AE[b]	12 (12.9)	16 (16.7)	28 (14.8)
Nasopharyngitis	2 (2.2)	3 (3.1)	5 (2.6)
Upper respiratory tract infection	2 (2.2)	2 (2.1)	4 (2.1)
Headache	2 (2.2)	2 (2.1)	4 (2.1)
Discontinuation due to AE[c]	1 (1.1)	2 (2.1)	3 (1.6)
Serious AE[d]	2 (2.2)	3 (3.1)	5 (2.6)
Fatal AE	0	0	0

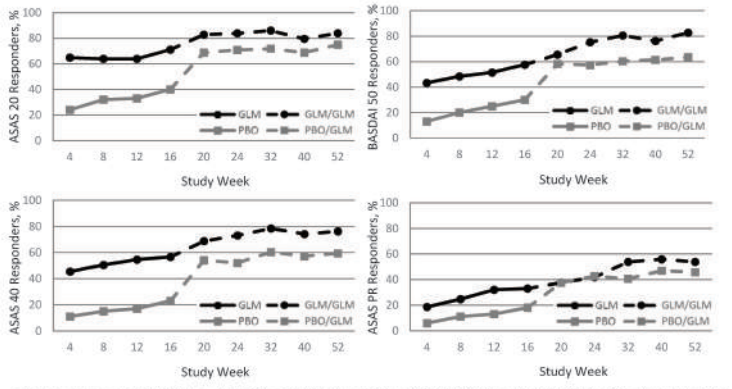
[a]Includes patients who received ≥1 dose of study drug.

[b]The most common AEs considered treatment-related (occurring in ≥3 pts in total) are shown.

[c]GLM/GLM: acute tonsillitis and treatment-related bacterial infection (n=1); PBO/GLM: hepatitis, treatment-related rhinitis (each n=1).

[d]GLM/GLM: bacterial infection, duodenitis (each n=1); PBO/GLM: treatment-related migraine, uterine polyp, staphylococcal infection (each n=1).

Figure. Proportion of Responders Over Time by Efficacy Endpoint and Treatment Group in the GO-AHEAD OLE*



*DB study (up to week 16): GLM, n=97; PBO, n=100. OLE (weeks 20 to 52): GLM/GLM, n=93; PBO/GLM, n=96. At weeks 16, 20, 24, and 32, the number of responders in the GLM/GLM group was 69, 77, 78, and 80, respectively.

Conclusion: Consistent with results of the GO-AHEAD randomized trial,[1] treatment with GLM in the OLE was generally well tolerated in patients with nr-axSpA. Improvements in disease activity were retained in patients who received GLM in the OLE and in patients

who switched from PBO to GLM.

Reference

1. Sieper J, et al. *Arthritis Rheum*. 2014;66:S1283-S1284.

Disclosure: D. van der Heijde, AbbVie, Amgen, AstraZeneca, Augurex, BMS, Boehringer Ingelheim, Celgene, Centocor, Chugai, Covagen, Daiichi, Eli-Lilly, Galapagos, GSK, Janssen Biologics, Merck, Novartis, Novo-Nordisk, Otsuka, Pfizer, Roche, Sanofi-Aventis, UCB, Vertex, 5,Imaging Rheumatology BV, 3; **M. Dougados**, AbbVie, Lilly, Novartis, Pfizer, Roche, Sanofi, UCB, 2; **W. Maksymowych**, AbbVie, Janssen, Pfizer, 2,AbbVie, Amgen, UCB, Pfizer, Merck, Janssen, Eli Lilly, Celgene, Synarc, Boehringer, 1; **G. Bergman**, Merck & Co., Inc., Kenilworth, NJ, USA, 3,Merck & Co., Inc., Kenilworth, NJ, USA, 1; **S. P. Curtis**, Merck & Co., Inc., Kenilworth, NJ, USA, 3,Merck & Co., Inc., Kenilworth, NJ, USA, 1; **A. Tzontcheva**, Merck & Co., Inc., Kenilworth, NJ, USA, 3,Merck & Co., Inc., Kenilworth, NJ, USA, 1; **G. Philip**, Merck & Co., Inc., Kenilworth, NJ, USA, 3,Merck & Co., Inc., Kenilworth, NJ, USA, 1; **S. Huyck**, Merck & Co., Inc., Kenilworth, NJ, USA, 3,Merck & Co., Inc., Kenilworth, NJ, USA, 1; **J. Sieper**, AbbVie, Eli Lilly, Janssen Biologics, Merck, Novartis, Pfizer, Roche, UCB, 5.

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Abstract Number: 2855

Non-Response to Antitnf Treatment in Psoriatic Arthritis Can be Predicted By an Objective Automated Measurement of Fluorescence-Signal Intensities in Fluorescence-Optical Imaging Technique – the First Interims Analysis of the Xplore-Study

Michaela Koehm[1,2], Tanja Rossmanith[3], Ulf Henkemeier[4], Peer Aries[5], Rieke Alten[6], Hans-Eckhard Langer[7], Harald Burkhardt[8,9] and Frank Behrens[1,9], [1]Clinical Research, Fraunhofer Institute for Molecular Biology and Applied Ecology IME, Project Group Translational Medicine & Pharmacology TMP, Frankfurt/Main, Germany, [2]Rheumatology, Goethe-University Frankfurt, Frankfurt/Main, Germany, [3]Fraunhofer Institute for Molecular Biology and Applied Ecology IME, Project Group Translational Medicine & Pharmacology TMP, Frankfurt, Germany, [4]Centre of Innovative Diagnostics and Therapeutics Rheumatology/Immunology at Goethe-University, Frankfurt, Germany, [5]Rheumatologie im Struenseehaus, Hamburg, Germany, [6]Internal Medicine, Rheumatology & Clinical Immunology, Schlosspark-Klinik, University Medicine Berlin, Berlin, Germany, [7]RHIO (Rheumatology, Immunology, Osteology) Duesseldorf, Duesseldorf, Germany, [8]Fraunhofer Institute for Molecular Biology and Applied Ecology IME, Project Group Translational Medicine & Pharmacology TMP, Frankfurt/Main, Germany, [9]Rheumatology, Goethe-University Frankfurt, Frankfurt, Germany

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Session Time: 9:00AM-11:00AM

Background/Purpose: Psoriatic arthritis (PsA) is a chronic inflammatory disorder. AntiTNF-therapy is initiated after failure of NSAID and DMARD-treatment. Up to 30-40% of the patients are primary not responding adequately to the induced therapy. In daily practice, response is assessed by improvement of disease activity measured by clinical examination and using composite indices (ACR20 response or DAS28). Earliest after 3 months, a decision for response is made. Feasible and robust biomarkers for early prediction of therapeutic response are still missing.

Methods: Fluorescence optical imaging technique (FOI) is used as method for detection of changes in vascularisation of the hands as inflammatory marker. ICG is injected as fluorescence colour agent, stimulated by light in a specific wave length and recorded by a specific camera in the device. Overall fluorescence-signals and their intensities are measured by an automated computer-based reading of the disease activity (DACT). In a prospective multicentre study, value of FOI in measurement of disease activity and sensitivity to change in newly treated PsA patients (n=80) with Etanercept is investigated (XPLORE-study). In this first interims analysis (n=13), early changes of DACT (baseline to week 4) are measured and correlated to the clinical response (achievement of at least low disease activity: DAS28 ² 3.2) after 12 weeks of treatment.

Results: All of the patients (mean age 55 years, female:male 1:1, mean DAS28 4.6, mean PASI 5.6, mean SJC 6.4, mean TJC 12.9 (66/68 joint count) at baseline) who did not reach at least 45% improvement in fluorescence intensities after 4 weeks of treatment did

not achieve the threshold of low disease activity (DAS28 ² 3.2) at week 12. The treatment regime of most of those patients was changed after week 12. Only one patient without the described improvement was qualified as responder by DAS28 change of -3.0.

	%DACT change BL to W4	DAS28 BL	DAS28 W12	SJC BL	SJC W12	TJC BL	TJC W12	Treatment Change after 12 weeks [y/n]
01	-59	5.0	2.7	9	2	9	0	n
02	-50	2.4	2.3	6	4	4	4	n
03	>+100	5.1	4.2	5	3	22	4	y
04	-49	3.5	1.0	2	1	3	1	n
05	-14	4.3	3.5	5	8	7	11	y
06	>+100	5.9	5.5	5	4	16	19	y
07	>+100	5.8	3.6	3	4	25	0	n
08	0	4.5	1.5	1	0	1	0	n
09	-65	5.9	2.8	18	0	18	0	n
10	>+100	4.5	4.2	2	2	10	12	n
11	-35	4.1	3.8	9	20	1	8	y
12	-51	4.3	2.6	19	9	5	15	y
13	>+100	4.5	4.8	9	4	18	57	n

Conclusion: Preliminary data of the first interims analysis of the XPLORE study illustrate high sensitivity in patients newly treated with Etanercept-therapy. Achievement of improvement of at least 45% in fluorescence intensity shows already after 4 weeks a high discriminative value for prediction of later clinical response at week 12. Only one patient was qualified as responder although he did not meet the criteria for response in fluorescence signalling. In this case, disease activity seems to be driven by other factors than inflammatory arthritis (only 1 SJC/TJC at baseline). Early change in fluorescence signalling seems to be a promising marker for prediction of clinical response in newly initiated biological treatment.

Disclosure: M. Koehm, Pfizer Inc, 2,MSD; Pfizer, 5,Janssen Pharmaceutica Product, L.P., 8; **T. Rossmanith**, Pfizer Inc, 2; **U. Henkemeier**, None; **P. Aries**, Pfizer Inc, 8,Pfizer Inc, 2; **R. Alten**, Pfizer Inc, 5,Pfizer Inc, 2,Pfizer Inc, 8; **H. E. Langer**, Pfizer Inc, 2; **H. Burkhardt**, AbbVie Deutschland; Pfizer; BMS; UCB; Chugai, 5,Pfizer Inc, 2; **F. Behrens**, AbbVie Deutschland GmbH & Co KG; Chugai; Pfizer; Roche, 5,Pfizer Inc, 8.

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Abstract Number: 2856

Efficacy and Safety of Ustekinumab in Psoriatic Arthritis Patients with Spondylarthritis As Well As Peripheral Arthritis: Results from 2 Phase 3, Multicenter, Double-Blind, Placebo-Controlled Study

Arthur Kavanaugh[1], Luis Puig[2], Alice B. Gottlieb[3], Christopher T. Ritchlin[4], Yin You[5], Shu Li[5], Michael Song[5], Bruce Randazzo[5], Proton Rahman[6] and Iain. B. McInnes[7], [1]University of California San Diego, La Jolla, CA, [2]Universitat Autònoma de Barcelona, Barcelona, Spain, [3]Tufts Medical Center, Boston, MA, [4]Allergy, Immunology and Rheumatololgy Division, University of Rochester Medical Center, Rochester, NY, [5]Janssen Research & Development, LLC, Spring House, PA, [6]Rheumatology, Memorial University of Newfoundland, St Johns, NF, Canada, [7]Institute of Infection, Immunity and Inflammation, College of Medicine, Veterinary Medicine and Life Sciences, University of Glasgow, Glasgow, United Kingdom

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Background/Purpose: To evaluate ustekinumab(UST) in a subgroup of psoriatic arthritis (PsA) pts with physician diagnosed spondylarthritis, as well as peripheral arthritis, from the PSUMMIT 1 & 2 trials.

Methods: Adult PsA pts with active disease were randomized to UST45mg, 90mg, or PBO at wks 0,4, and q12wks, thereafter. PBO-

pts crossed over to UST45mg at wks24 and 28 followed by q12wk dosing. At wk16, pts with <5% improvement in TJC & SJC entered blinded early escape [EE]. This post hoc analysis evaluated efficacy and safety in the subgroup of PsA patients with physician diagnosed spondylarthritis at baseline from the PSUMMIT trials (PSUMMIT 1 [bio-naïve] and PSUMMIT 2 [bio-naïve and bio-experienced]). BASDAI scores were collected at baseline and wks12 and 24; BASDAI question (#2) related to overall level of axial disease neck, back or hip pain was also assessed separately.

Results: 256 (28% of PSUMMIT 1 &2 population, including 32 bio-experienced) randomized pts (92 PBO, 164 UST combined) had spondylarthritis at baseline. In this sub-group 80.5% had enthesitis and 51.6% had dactylitis at baseline; in the overall population, 71.4% and 45.6% had enthesitis and dactylitis, respectively. Consistent with the overall population, at baseline, about 50% of patients used MTX, 77% NSAIDs, and 20.7% low dose oral corticosteroids. More UST-treated pts achieved BASDAI20/50/70 responses vs PBO at wk24(Table). The observed changes in the median score of the BASDAI question related to the overall level of axial disease neck, back or hip pain were also similar to the total BASDAI score changes for both groups, -0.45 vs -1.65, between PBO and combined UST groups, respectively. Other clinical efficacy and radiographic progression data in this subgroup are summarized (Table). During the PBO-controlled period, AE rates for PBO vs combined UST-treated groups were 41.3% vs 34.8%; SAEs were 2.2% vs 1.2% discontinuations due to AEs were 3.3% vs 0.6%; and infections were 16.3% vs 13.4%). Through 1yr, safety was consistent with the overall PsA population.

Conclusion: In this post-hoc analysis, UST significantly improved axial symptoms in a subgroup of PsA patients who also had physician diagnosed spondylarthritis. Reponses in other PsA domains and safety were similar to that observed in the overall PsA study population.

Table: PSUMMIT 1 and 2-Efficacy Outcomes in Patients with Spondylitis and Peripheral Joint Involvement at Baseline (BL)

	Wk 24		Wk 52	
	PBO	UST Combined	PBO→ 45mg	UST Combined
	92	164	81	156
BASDAI20/50/70†	N=92 32.9%/11.4%/0%	N=164 54.8%/29.3%/15.3%	-	-
Change in BASDAI score (median)	N=92 -0.51	N=164 -1.60	-	-
Mean % change (median) from BL entheses score (MASES index)*	N=63 -16.01(-26.67)	N=132 -46.66(-50.00) P=0.017	N=60 -53.06(-87.50)	N=127 -54.76(-73.33)
Mean % change(median) from BL dactylitis score**	N=41 -11.03(0.00)	N=83 -57.48(-88.89) P<0.001	N=39 -69.76(-100.00)	N=82 -68.94(-100.00)
ACR20 /ACR50/ ACR70 (%)	N=92 22.8/3.3/1.1	N=164 43.9^/25.6/11.0 ^P=0.001	N=81 65.4/39.5/16.0	N=156 62.8/34.6/19.2
Mean (SD) change from BL HAQ-DI	N=92 -0.11(0.39)	N=164 -0.33(0.53) P<0.001	N=81 -0.39(0.42)	N=156 -0.37(0.55)
PASI 75 response***	N=69 11.6%	N=137 63.5% P<0.001	N=61 65.6%	N=129 70.5%
Total vdH-S mean change from BL (peripheral joints)	1.51(6.41)	0.00(1.69) P=0.003	3.04(11.86)	0.25(2.13)

Pts who did not receive UST excluded. †BASDAI not collected at wk 52 ^ACR20 only, *enthesitis and dactylitis **with spondylitis and peripheral joint involvement at BL; *** pts with ≥3% BSA psoriasis involvement with spondylitis and peripheral joint involvement at BL

Disclosure: **A. Kavanaugh**, Janssen R & D, LLC, 2; **L. Puig**, Janssen R & D, LLC, 2; **A. B. Gottlieb**, Janssen R & D, LLC, 2; **C. T. Ritchlin**, Janssen Scientific Affairs, LLC, 2; **Y. You**, Janssen R & D, LLC, 3; **S. Li**, Janssen R & D, LLC, 3; **M. Song**, Janssen R & D, LLC, 3; **B. Randazzo**, Janssen R & D, LLC, 3; **P. Rahman**, Janssen R & D, LLC, 2; **I. B. McInnes**, Janssen R & D, LLC, 2.

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Abstract Number: 2857

The 8-Year Retention Rate of the First TNF-Inhibitor in the Treatment of Spondyloarthropathies: Real-Life Data from Three Local Registries

Ennio Giulio Favalli[1], Andrea Becciolini[1], Martina Biggioggero[2], Enrico Fusaro[3], Simone Parisi[3], Alarico Ariani[4], Daniele Santilli[4], Antonio Marchesoni[1] and Pier Luigi Meroni[2], [1]Department of Rheumatology, Gaetano Pini Institute, Milan, Italy, [2]University of Milan, Department of Clinical Sciences and Community Health, Division of Rheumatology, Gaetano Pini Institute, Milan, Italy, [3]Città della salute e della Scienza, Turin, Italy, [4]Department of Internal Medicine and Rheumatology, University of Parma, Parma, Italy
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Background/Purpose: Long-term data on drug survival of TNF inhibitors (TNFi) in the treatment of spondyloarthropathies are still lacking. The aim of the study is to analyze in a setting of real-life the 8-year retention rate of the first TNFi for the treatment of psoriatic arthritis (PsA) and axial spondyloarthritis (ax-SpA) and to compare the between-group discontinuation rates for each TNFi (infliximab [IFX], etanercept [ETN], and adalimumab [ADA]).

Methods: Data were retrospectively extracted from three local registries including all patients affected by PsA and ax-SpA treated with a biologic drug between January 2002 and May 2014. The analysis was limited to patients treated with IFX, ETN, or ADA as first-line biologic agent, with at least 1-year follow-up period. The 8-year drug survival was evaluated by Kaplan-Meier method and the risk for discontinuation among the 3 treatment groups was compared by a stratified log-rank test. The comparison of reasons for drug withdrawal among treatment subgroups was performed by the Fischer's exact test.

Results: The study population (594 patients) included 322 ax-SpA (69.2% male, median age [±SD] 42 [±12.2] years, median disease duration 5.2 [±8] years), treated with ADA (n=99), ETN (n=40), or IFX (n=183); and 272 PsA (53.7% male, median age 47.9 [±12.2] years, median disease duration 9.1 [±7.3] years), treated with ADA (n=98), ETN (n=75), or IFX (n=99). The overall median survival on treatment of the whole study population was 103.6 months (105.2 and 102.6 months for ax-SpA and PsA, respectively; p=0.3768). The overall retention rate was 62.8% (68.4% versus 59.7% in axSpA and PsA, respectively) at 5 years and 53.3% (56.1% versus 52.4% in axSpA and PsA, respectively) at 8 years. No significant differences emerged in the comparison among ADA, ETN, and IFX in both ax-SpA group (p=0.1113) and PsA group (p=0.4783). The main reported reasons for treatment discontinuation were drug inefficacy (18.2% in ax-SpA versus 25.6% in PsA; p=0.0357) and adverse events (16.4% in ax-SpA and 19.2% in PsA; p=0.45).

Conclusion: In a real-life setting, the 8-year retention rate of the first TNFi in the treatment of spondyloarthropathies was about 50%, with no significant difference between ax-SpA and PsA. The risk of stopping IFX, ETN, and ADA treatment was similar in both ax-SpA and PsA group.

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Abstract Number: 2858

A Phosphodiesterase 4 Inhibitor for Psoriatic Arthritis: Systematic Review and

Meta-Analysis

Ignacio-Alfredo Valerio-Morales[1], **Maria A. Lopez-Olivo**[2], Xin Pan[3] and Maria E. Suarez-Almazor[4], [1]Rheumatology, National Institute of Rehablitation, Mexico, Mexico, [2]Department of General Internal Medicine, The University of Texas, MD Anderson Cancer Center, Houston, TX, [3]Department of Rheumatology, Shuguang Hospital, Shanghai University of Traditional Chinese Medicine, Shanghai, China, [4]General Internal Medicine, The University of Texas, MD Anderson Cancer Center, Houston, TX
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Background/Purpose: Inhibition of phosphodiesterase (PDE) family enzymes is now recognized as target to develop new psoriatic arthritis (PsA) drugs. We conducted a systematic review to evaluate the benefits and harms of the first PDE4 inhibitors approved by the FDA (i.e., apremilast) for the treatment of PsA.

Methods: We searched electronic databases (i.e., The Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, and Web of Science) from inception to October 2014 with no restrictions. We also searched of ClinicalTrials.gov and the list of references of relevant citations to identify any additional citations not otherwise found. We included any controlled trials comparing treatment with apremilast alone or in combination with any DMARD versus placebo or other synthetic or biologic DMARD. Our primary outcome was the ACR modified response criteria for 50% improvement. Secondary outcomes included function measured by the health assessment questionnaire (HAQ), quality of life measured by the SF-36, disease activity, withdrawals, and serious adverse events. We calculated relative risks (RR) and their 95% confidence intervals (95%IC).

Results: Out of 246 citations, 5 double-blind, randomized controlled trials (RCTs) were included. All studies were funded by the manufacturer of the drug. The studies included a total of 2,005 patients (1,336 assigned to apremilast plus standard of care, and 669 to placebo plus standard of care). Mean age of participants ranged from 48.8 to 51.4 years; mean disease duration ranged from 6. 8 to 16.5 years; and between 45.5% to 52.6% were male. All studies were judged to have high risk of performance and detection bias since apremilast was compared to placebo until week 16, and then placebo non-responders received apremilast. At 16 weeks, ACR50 response rates were statistically significantly improved with apremilast 20 and 30 mg compared with control (RR 2.3, 95%CI 1.6-3.2 and 2.2, 1.6-3.2, respectively. HAQ scores were statistically significantly better with apremilast 20 and 30 mg than with control (MD -0.11, 95% CI -0.16, -0.06 and -0.16, 95% CI -0.21, -0.11, respectively). Quality of life scores were similar between apremilast 20 mg and control, but were significantly better in the apremilast 30 mg versus placebo (MD 2.6, 95%CI 1.7-3.4). There was a statistically significant reduction from baseline in the DAS28 in favour of apremilast 20 and 30 mg (MD -0.42, 95%CI -0.53, -0.31 and -0.48, 95%CI -0.59, -0.37, respectively). No differences were observed in the withdrawals rates or serious adverse events between groups. These differences were sustained even after 24 weeks (Table).

Conclusion: Our findings suggest that apremilast (either 20 or 30 mg) in combination with standard of care is significantly more efficacious than standard of care alone for improving the symptoms of PsA. Further studies are needed to evaluate its effects in preventing disease progression (structural damage).

	20 mg	**30 mg**
ACR50	RR 2.2, 95%CI 1.6-3.0	RR 2.2, 1.6-3.1
HAQ	MD -0.58, 95%CI -0.63, -0.53	MD -0.17, 95%CI -0.21, -0.12
SF-36 (PCS)	not significant	MD 2.9, 95%CI 2.0-3.8
DAS28(ESR)	MD -0.42, 95%CI -0.54, -0.31	MD -0.50, 95%CI -0.62, -0.38
Withdrawals (total)	not significant	not significant
Serious adverse events	not significant	not significant

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Abstract Number: 2859

Effect of Weight on Efficacy of Certolizumab Pegol in Patients with Axial Spondyloarthritis

Atul A. Deodhar[1], Joachim Sieper[2], Owen Davies[3], Tommi Nurminen[4] and Philip J. Mease[5], [1]Division of Arthritis & Rheumatic Diseases, Oregon Health & Science University, Portland, OR, [2]University Hospital Charité, Berlin, Germany, [3]UCB Pharma, Slough, United Kingdom, [4]UCB Pharma, Monheim, Germany, [5]Swedish Medical Center and University of Washington School of Medicine, Seattle, WA

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Background/Purpose:

Recent studies suggest that patients' (pts') body weight impacts response to anti-TNF treatment in pts with spondyloarthropathies[1] including axial spondyloarthritis (axSpA).[2] Here we investigate whether efficacy of certolizumab pegol (CZP), a PEGylated Fc-free anti-TNF, is affected by weight in axSpA pts.

Methods:

RAPID-axSpA (NCT01087762) was double-blind and placebo (PBO)-controlled to Week (Wk) 24. Pts fulfilled ASAS criteria and had active axSpA. At baseline (BL), pts were randomized 1:1:1 to PBO, or CZP 200 mg Q2W/CZP 400 mg Q4W. The primary endpoint was the Wk12 ASAS20 response.[3] In this post-hoc analysis, data from the overall population were summarized by subgroups according to median BL weight (80 kg); further analyses considered BL weight ≥100 kg. Efficacy by BL BMI (<25 kg/m^2, normal weight; ≥25–<30 kg/m^2, overweight; ≥30 kg/m^2, obese) was also explored. Missing ASAS data were imputed as non-responders; LOCF was used for continuous measures.

Results:

Of 325 pts randomized, 218 received CZP from Wk0, and 107 PBO. BL characteristics, including disease activity measures, were similar between populations, though more males weighed ≥80 kg (76.5% male vs 46.2% male in <80 kg group) and CRP was higher in heavier pts (median CRP [mg/L]: pts <80 kg, 11.5; pts ≥80 kg, 14.5; pts ≥100 kg, 15.0). At BL, pt numbers between BMI categories were similar (normal weight: 114; overweight: 111; obese: 94).

At Wk12, ASAS20 and ASAS40 response rates and treatment differences were similar regardless of BL weight (Table, Figure). Similarly, there was no decreasing trend in Wk12 response rates or treatment differences for ASAS20 and ASAS40 across increasing BMI categories (Figure; CZP dose combined: ASAS20, normal weight: 56.3% CZP [n=80] vs 38.2% PBO [n=34]; overweight: 72.6% CZP [n=73] vs 42.1% PBO [n=38]; obese: 55.0% CZP [n=60] vs 35.3% PBO [n=34]; ASAS40, normal weight: 46.3% CZP vs 20.6% PBO; overweight: 53.4% CZP vs 26.3% PBO; obese: 40.0% CZP vs 5.9% PBO).

Comparable improvements with CZP treatment were observed across weight categories in clinical and pt-reported outcomes, as well as laboratory measures of inflammation (Table); though pts weighing ≥100 kg had lower BASFI improvements, possibly as a result of the independent effect of weight on function.

Similar efficacy was maintained to Wk24 regardless of pt weight, with similar outcomes observed with both CZP dose regimens (data not shown).

Conclusion:

In RAPID-axSpA, improvements to Wk12 of CZP treatment in composite clinical outcomes, pt-reported and laboratory outcome measures were similar regardless of pt weight. These results were maintained over 24 wks of CZP treatment with both CZP dose regimens.

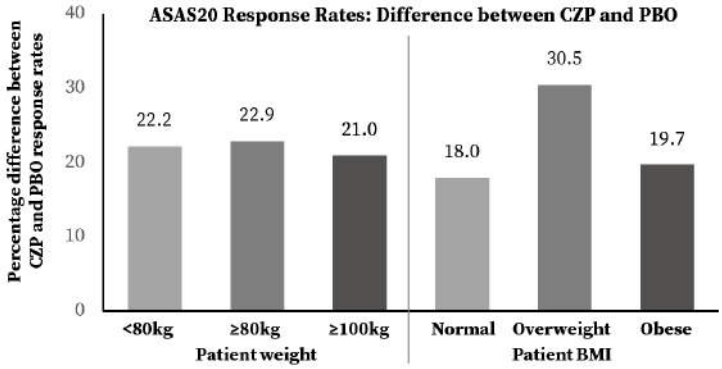
References:

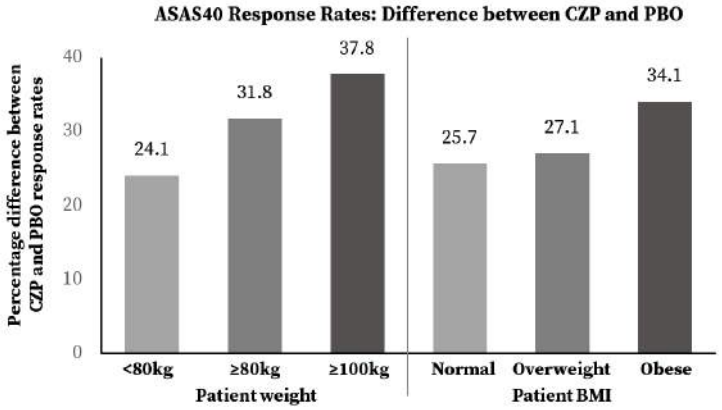
1. Ferraccioli G. Arthritis Rheum 2010;62(S10):297

2. Gremese E. Rheumatology 2014;53:875–81

3. Landewé R. Ann Rheum Dis 2014;73:39–47

Figure: Difference between CZP and PBO response rates at Week 12 for ASAS20 and ASAS40 by weight or BMI at baseline





Data shown as percentage difference between CZP (dose-combined) and PBO response rates. Missing data were imputed using NRI. BMI categories: normal weight, <25 kg/m²; overweight, ≥25–<30 kg/m²; obese, ≥30 kg/m².

Table: Efficacy of CZP at Week 12 of the RAPID-axSpA trial by patient weight at baseline

		Weight <median (80 kg) (N=158)		Weight ≥median (80 kg) (N=166)		Weight ≥100 kg (N=51)	
		PBO n=50	CZP n=108	PBO n=57	CZP n=109	PBO n=14	CZP n=37
Week 12, n (%) [NRI]							
ASAS20 response rate		19 (38.0)	65 (60.2)	22 (38.6)	67 (61.5)	5 (35.7)	21 (56.8)
ASAS40 response rate		12 (24.0)	52 (48.1)	7 (12.3)	48 (44.0)	0	14 (37.8)
Week 12, mean (SD) [LOCF]							
ASDAS	**Mean score**	3.3 (1.1)	2.2 (1.1)	3.6 (1.1)	2.2 (1.0)	3.6 (0.9)	2.4 (0.9)
	CFB	-0.5 (0.8)	-1.7 (1.2)	-0.5 (0.7)	-1.7 (1.1)	-0.8 (0.8)	-1.5 (1.0)
BASDAI	**Mean score**	5.3 (2.3)	4.0 (2.5)	5.4 (2.2)	3.6 (2.2)	5.7 (1.8)	4.1 (2.0)
	CFB	-1.1 (1.7)	-2.7 (2.4)	-1.2 (1.8)	-2.7 (2.2)	-1.2 (1.2)	-2.2 (2.0)
BASFI	**Mean score**	4.6 (2.5)	3.5 (2.8)	5.3 (2.4)	3.3 (2.6)	5.7 (1.8)	3.7 (2.6)
	CFB	-0.5 (1.7)	-2.0 (2.4)	-0.6 (1.8)	-1.9 (2.2)	-1.2 (1.1)	-1.4 (1.6)
Pain	**Mean score**	5.3 (2.4)	4.0 (2.8)	6.1 (2.4)	4.0 (2.6)	6.6 (2.3)	4.4 (2.4)
	CFB	-1.4 (2.1)	-3.2 (2.7)	-1.3 (2.0)	-2.7 (2.8)	-1.6 (2.3)	-2.4 (2.3)
Fatigue	**Mean score**	5.6 (2.3)	4.8 (2.7)	5.7 (2.5)	4.2 (2.4)	6.3 (1.9)	4.8 (2.3)
	CFB	-0.8 (2.0)	-2.2 (2.4)	-0.9 (2.4)	-2.2 (2.4)	-0.8 (2.5)	-2.1 (2.6)
PGADA	**Mean score**	5.5 (2.4)	4.2 (2.9)	5.8 (2.6)	3.8 (2.6)	6.4 (2.7)	4.1 (2.4)
	CFB	-1.0 (2.6)	-2.9 (3.1)	-1.3 (2.5)	-3.2 (2.8)	-1.9 (3.3)	-3.0 (2.9)
Log(CRP [mg/L]+1)	**Mean score**	2.4 (1.0)	1.5 (0.8)	2.8 (0.8)	1.6 (0.7)	2.6 (0.6)	1.8 (0.7)
	CFB	-0.1 (0.8)	-0.9 (0.8)	-0.1 (0.7)	-1.0 (0.8)	-0.3 (0.9)	-0.9 (0.8)

One CZP-treated patient did not have a valid baseline weight measurement and was excluded from these analyses. CFB: change from baseline; PGADA: Patient's Global Assessment of Disease Activity.

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Abstract Number: 2860

Clinical Responses in Joint and Skin Outcomes and Patient-Reported Outcomes Are Associated with Increased Productivity in the Workplace and at Home in Psoriatic Arthritis Patients Treated with Certolizumab Pegol

Arthur Kavanaugh[1], Dafna Gladman[2], Désirée van der Heijde[3], Oana Purcaru[4] and Philip J. Mease[5], [1]University of California San Diego, La Jolla, CA, [2]University of Toronto, Toronto, ON, Canada, [3]Leiden University Medical Center, Leiden, Netherlands, [4]UCB Pharma, Brussels, Belgium, [5]Rheumatology Research, Swedish Medical Center, Seattle, WA

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Background/Purpose:

Compared to the general population, patients (pts) with psoriatic arthritis (PsA) suffer greater amounts of disability and substantially lower employment rates.[1] Few studies have evaluated the association between improvements in workplace and household productivity and symptom relief with available therapies in PsA pts. Here we evaluate the association between improvements in clinical and pt-reported outcomes (PROs) and improvements in productivity in the workplace and at home in PsA pts treated with certolizumab pegol (CZP).

Methods:

Associations between clinical outcomes or PROs and work and household productivity outcomes were compared using Week (Wk) 24 data from the double-blind and placebo-controlled period of RAPID-PsA (NCT01087788).[2] Clinical outcomes included achievement of ACR20/50, PsARC and PASI75 responses, and DAS28 remission (DAS28<2.6). PROs included achievement of MCID for HAQ-DI (≥0.3 decrease from baseline [BL]), pain (≥10 mm decrease from BL) and fatigue (≥1 decrease from BL). Responders and non-responders at Wk24 for clinical outcomes and PROs were compared in terms of change from BL (CFB) in workplace and household productivity, as assessed using the validated arthritis-specific Work Productivity Survey (WPS).[3] Analyses were carried out for pts originally randomized to CZP. Groups were compared using a non-parametric bootstrap-t method. Missing data were imputed using last observation carried forward for WPS outcomes and non-responder imputation for clinical outcomes and PROs.

Results:

273 CZP pts entering RAPID-PsA were included in Wk24 analyses. 61.9% of pts were employed at Wk24. Overall, pts achieving a clinical or PRO response at Wk24 also reported greater improvements in workplace and household productivity than non-responders (Table). Improvements in both joint and skin symptoms, and clinically meaningful reductions in disability, pain and fatigue were associated with improved workplace absenteeism and presenteeism. Responders also reported greater improvements in their participation in family, social and leisure activities (data not shown). Results should be interpreted with caution due to differences in the number of pts between responder and non-responder groups, and because the analyses were not adjusted for differences in BL productivity between these groups.

Conclusion:

Clinical responses in joint and skin outcomes as well as clinically meaningful improvements in PROs are associated with improved workplace and household productivity in PsA pts treated with CZP.

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1. Mau W. J Rheumatol 2005;32:721–8

2. Mease P. J. Ann Rheum Dis 2014;73:48–55

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Table: Change from baseline in workplace and household productivity at Week 24 of RAPID-PsA in CZP-treated patients (randomized set) by responder status for clinical outcomes and PROs

		Workplace productivity [a], mean CFB (SD)				Household productivity [b], mean CFB (SD)			
		n	Days missed [c]	Days with productivity reduced by ≥50% [d]	Level of arthritis interference on productivity [e]	n	Days missed [c]	Days with productivity reduced by ≥50% [d]	Level of arthritis interference on productivity [e]
ACR20	Responders	106	-1.4 (3.6)	-4.1 (8.2)	-2.5 (2.9)*	164	-3.9 (7.1)	-5.8 (8.0)***	-3.2 (2.9)***
	Non-responders	54	-0.5 (5.3)	-1.6 (7.9)	-1.4 (2.9)	109	-2.1 (9.2)	-1.0 (9.2)	-1.7 (2.9)
ACR50	Responders	77	-1.2 (3.4)	-4.4 (8.1)	-2.7 (2.8)*	115	-3.9 (6.8)	-6.3 (8.4)***	-3.5 (2.9)***
	Non-responders	83	-0.9 (4.9)	-2.2 (8.1)	-1.7 (3.0)	158	-2.7 (8.8)	-2.1 (8.7)	-1.9 (2.9)
PsARC	Responders	131	-1.1 (3.9)	-3.4 (8.3)	-2.2 (3.0)	212	-3.7 (7.3)	-5.1 (8.2)***	-3.0 (2.8)***
	Non-responders	29	-1.2 (5.7)	-2.5 (7.2)	-1.9 (2.8)	61	-1.5 (10.0)	0.2 (9.6)	-1.2 (3.1)
PASI75 [f]	Responders	65	-1.9 (5.7)*	-3.5 (7.7)	-2.3 (3.4)	102	-3.0 (6.2)	-5.5 (9.2)***	-2.7 (3.1)
	Non-responders	32	-0.4 (1.3)	-2.3 (5.0)	-1.6 (2.0)	64	-4.4 (8.5)	-0.9 (7.6)	-1.8 (2.8)
DAS28 remission	Responders	81	-1.5 (4.9)	-3.9 (7.8)	-2.6 (2.9)*	115	-3.6 (7.0)	-5.1 (7.8)*	-3.1 (3.0)*
	Non-responders	79	-0.6 (3.5)	-2.5 (8.5)	-1.6 (3.0)	158	-2.9 (8.7)	-3.0 (9.4)	-2.3 (3.0)
HAQ-DI MCID	Responders	82	-1.7 (4.7)*	-5.4 (9.6)***	-2.8 (3.1)**	133	-4.7 (7.8)**	-6.0 (9.4)***	-3.2 (3.1)**
	Non-responders	78	-0.5 (3.7)	-0.9 (5.5)	-1.5 (2.7)	140	-1.7 (8.0)	-1.9 (7.7)	-2.1 (2.7)
Pain MCID	Responders	124	-1.2 (4.2)	-3.4 (8.3)	-2.2 (3.1)	189	-3.7 (7.7)	-5.1 (8.8)***	-3.0 (3.0)**
	Non-responders	36	-0.7 (4.4)	-2.6 (7.5)	-1.8 (2.6)	84	-2.0 (8.6)	-1.3 (8.4)	-1.8 (2.9)
Fatigue MCID	Responders	107	-1.3 (4.8)	-4.4 (8.8)**	-2.5 (3.1)*	176	-3.7 (8.2)	-5.1 (8.9)**	-3.0 (3.0)**
	Non-responders	53	-0.7 (2.8)	-0.9 (6.0)	-1.3 (2.6)	97	-2.2 (7.7)	-1.7 (8.3)	-1.8 (2.9)

Nominal p values for the difference in mean CFB between responders and non-responders: *p<0.05, **p<0.01 and ***p<0.001. [a] Workplace productivity results shown for Week 24 employed patients (n=160); [b] Household productivity results shown for Week 24 patients overall (n=273); [c] CFB in the number of days missed due to arthritis in the last month; [d] CFB in the number of days with productivity reduced by ≥50% due to arthritis in the last month; [e] CFB in the rate of arthritis interference on productivity in the last month, as measured on a 0–10 point scale (0=no interference, 10=complete interference); [f] PASI75 results shown for patients with ≥3% body surface area affected at baseline (at Week 24, n=166 patients overall and n=97 employed patients).

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Abstract Number: 2861

Treatment Patterns of Subcutaneous Biologic Agent Use Among Patients with Ankylosing Spondylitis

Sergio Schwartzman[1], Yunfeng Li[2], Huanxue Zhou[3], Vivian Herrera[2] and Jacqueline B. Palmer[2], [1]Hospital for Special Surgery, New York, NY, [2]Novartis Pharmaceuticals Corporation, East Hanover, NJ, [3]KMK Consulting Inc, East Hanover, NJ

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Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Ankylosing spondylitis (AS) is characterized by chronic debilitating inflammation of the spine and/or sacroiliac joints. Several biologic agents have been approved for the treatment of AS. In some instances, physicians and patients may discontinue or switch biologics during the course of therapy. These treatment patterns are not well characterized and have potential clinical implications. The objective of this study was to characterize and understand the treatment patterns of AS patients on subcutaneous biologics therapy.

Methods: We conducted a retrospective analysis of medical and pharmacy claims data from the MarketScan commercial claims database (United States). Biologic-naïve AS patients (no biologic therapy in the previous 12 months) were identified who initiated a biologic agent (etanercept, adalimumab, or golimumab) during the period from January 1, 2011, to December 31, 2012, and were continuously enrolled in a prescription drug benefit program for 12 months prior to, and 18 months following, their first biologic use. Demographic, clinical, and treatment information were analyzed.

Results: 382 AS patients met the criteria for analysis (index biologic: adalimumab, n=202 [52.9%]; etanercept, n=157 [41.1%]; golimumab, n=23 [6.0%]). They had a mean age 42.5 yrs and 66.5% male. The most common comorbidities were hypertension (18.8%), hyperlipidemia (12.6%), depression (8.9%), and uveitis (7.9%). During the follow-up period, 214 patients (56.0%) were continuous users of the index treatment (no gaps in therapy >180 days or no therapy switches for 12 months), while 168 (44.0%) discontinued (had a gap in therapy >180 days with the index therapy or switched to another therapy). Among patients who discontinued their index therapy, 53 (13.9% of the total group) switched to another agent with a treatment gap of ≤180 days; 14 (3.7%) had a gap in therapy >180 days, but restarted on their index therapy while 6 (1.6%) restarted with a different biologic therapy after discontinuation of index biologic. Among continuous users (no gap >180 days) dose escalation was infrequent: adalimumab, 9 patients (7.6%) with above label dosing (>40 mg every 2 weeks); etanercept, 1 patient (1.1%) (>50 mg/wk); golimumab 0 patients (0%) received a (>50 mg/month).

Conclusion: Almost half of AS patients will discontinue their index biologics in the year following initiation of use. Of those who continued therapy adherence was high and the approved label dosing was frequently used. Future studies are needed to further define treatment patterns, the reasons for discontinuation of the index biologic, switching and importantly the pharmacoeconomic impact of these patterns.

Disclosure: S. Schwartzman, Novartis Pharmaceutical Corporation, 5; **Y. Li**, Novartis Pharmaceutical Corporation, 3; **H. Zhou**, Novartis Pharmaceutical Corporation, 5; **V. Herrera**, Novartis Pharmaceutical Corporation, 1,Novartis Pharmaceutical Corporation, 3; **J. B. Palmer**, Novartis Pharmaceutical Corporation, 3.

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Abstract Number: 2862

Is Anti-TNF Tapering Possible in Patients with Axial Spondyloarthritis? a Systematic Literature Review

Victoria Navarro-Compán[1], Chamaida Plasencia-Rodriguez[2], Eugenio De Miguel[1], Alejandro Balsa[1], Emilio Martín-Mola[1], Daniel Seoane-Mato[3] and Juan D. Cañete[4], [1]Rheumatology, University Hospital La Paz, Madrid, Spain, [2]Rheumatology Department, La Paz University Hospital-Rheumatology Department, Madrid, Spain, [3]Research Unit, Spanish Society of Rheumatology, Madrid, Spain, [4]Rheumatology, Hospital Clinic and IDIBAPS, Barcelona, Spain

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Background/Purpose: Anti-TNF therapy is successful for achieving low disease activity (LDA) or clinical remission in patients with axial spondyloarhritis (axSpA). Nevertheless, this therapy has not clearly shown to slow or inhibit radiographic progression in these patients. Based on this, it is unclear what therapeutic attitude should be adopted once remission has been achieved in patients with

axSpA. The aim of this study was to evaluate if anti-TNF tapering is efficacious for maintaining remission or LDA in patients with axSpA.

Methods: A systematic literature review until August 2014 was performed using Medline, EMBASE and Cochrane databases. The research question was formulated according to the PICOS method: Population (axSpA patients); Intervention (anti-TNF dose tapering); Comparator (continue with standard dose of anti-TNF); Outcome (flare or change on disease activity); and Study design (longitudinal studies with at least 6 months of follow up after dose adjustment). Data was extracted independently by two reviewers using a form developed for this purpose.

Results: In total, 8 studies from 763 citations were included. All studies included patients with ankylosing spondylitis from single centers and no study included patients with non-radiographic axSpA. The study design was observational (n=6) and interventional (n=2). In these studies, patients receiving standard doses of anti-TNF therapy who were in remission (BASDAI<2 and normal CRP) or with LDA (BASDAI<4 and normal CRP) reduced anti-TNF therapy dose according to an established protocol (n=5) or to the physician«s criterion (n=3). Total number of patients on low-dose regimen ranged between 8 and109 patients and the follow-up period after anti-TNF tapering between 6-21 months. Administered anti-TNF therapy was etanercept (n=5), infliximab (n=1) and adalimumab/etancercept/infliximab (n=2). Data extracted for each study are shown on the table.

The percentage of patients maintaining LDA or remission after reducing anti-TNF dose was reported in 5 out of the 7 studies. These were 67%, 75%, 53-81%, 86% and 100%. The remaining three studies reported mean change in disease activity measures after reducing anti-TNF therapy. Mean BASDAI in these studies before reducing anti-TNF dose was 2.3, 1.6 and 2.1 and at the end of the study was 0.6, 1.4 and 3.2, respectively. Mean CRP (mg/L) before reducing anti-TNF dose was 0.1, 1.0 and 8 and at the end of the study was 0.1, 1.3 and 8, respectively. Anti-TNF tapering was most frequently done increasing the interval between drug administrations than decreasing the dose of the injection/infusion.

Conclusion: Published data indicates that anti-TNF therapy tapering is successful in maintaining remission or LDA during at least one year in a high number (>50%) of patients with AS. Further data are required to identify which patients with axSpA are included within this group.

Table: Results for quantitative variables are mean values.

	Lee et al	Navarro-Compán et al	Paccou et al	Cantini et al	Mörck et al	Borrás-Blasco et al	De Stefano R et al	Závada J et al
Characteristics of the study								
Year	2010	2011	2012	2013	2013	2014	2014	2014
Journal	Clin Rheumatol	Clin Rheumatol	J Rheumatol	Biologics: Targets and Therapy	Mediators of Inflammation	Expert Opin Biol Ther	Clin Rheumatol	Ann Rheum Dis
Design	retrospective	prospective	retrospective	RCT	Clinical trial	retrospective	prospective	Prospective
Total number pts	109	51	65 (49)	43	19	8	21	136
Pts with dose reduction	109	16	49	22	19	8	21	53
Follow-up (months)	21	at least 6 (mean 26)	at least 6 (mean 30)	21	12	6	9	12
Characteristics of patients								
Age (years)	35	43	45	37	40	-	44	41
Male	90%	87%	79%	79%	74%	-	76%	75%
Disease duration (yr)	9	8	14	13	8	-	3	9
HLA-B27+	91%	87%	80%	-	80%	-	87%	75%
Anti-TNF	etanercept	etanercept	Adalimumab(5), etanercept(17), infliximab(25)	etanercept	infliximab	etanercept	etanercept	adalimumab, etanercept o infliximab
Time on anti-TNF (m)		17			12	32	3	35
Reduction	protocol	physician	physician	protocol	protocol	protocol	protocol	physician
Outcome								
Remision or LDA	-	BASDAI <4 & PCR ø	BASDAI <2, no peripheral symptoms & PCR ø	BASDAI <4, no peripheral symptoms & PCR ø	-	BASDAI<2	ASAS partial remission	BASDAI<4
Time in remission after dose reduction (months)	-	>6	≥3	-	-	-	<3	≥6 mean 27
Remission maintenance	-	-	At month 12: 80%adalimumab 53% etanercept 81% infliximab	86%	-	100%	67%	75%
Most freq regimen	↑ interval (25mg/12 days)	25 mg /wk	40 mg/3wk 25 mg/wk 5mg/kg/8wk	50 mg/2wk	3 mg/kg/8 wk	25 mg /wk	25 mg /2wk	↑interval
Level of evidence								
CEBM Oxford	4	4	4	2b	4	4	4	4

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Abstract Number: 2863

Discontinuation of Anti-TNF Therapy in Patients with Axial Spondyloarthritis. a Systematic Literature Review

Victoria Navarro-Compán[1], Chamaida Plasencia-Rodriguez[2], Eugenio De Miguel[1], Alejandro Balsa[3], Emilio Martín-Mola[1], Daniel Seoane-Mato[4] and Juan D. Cañete[5], [1]Rheumatology, University Hospital La Paz, Madrid, Spain, [2]Rheumatology Department, La Paz University Hospital-Rheumatology Department, Madrid, Spain, [3]Rheumatology, La Paz University Hospital-Rheumatology Department,

Madrid, Spain, [4]Research Unit, Spanish Society of Rheumatology, Madrid, Spain, [5]Rheumatology, Hospital Clinic and IDIBAPS, Barcelona, Spain

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Background/Purpose: In patients with axial spondyloarthritis (axSpA), anti-TNF therapy is successful for clinically improving signs and symptoms of the disease. However, there is no clear evidence of the capability of this therapy to slow or inhibit radiographic progression. Based on this, it is unclear whether or not this treatment should be indefinitely sustained once the clinical goal is achieved in these patients. The aim of this study was to evaluate if discontinuation of anti-TNF therapy is successful to maintain clinical response in patients with axSpA.

Methods: A systematic literature review until August 2014 was performed using Medline, EMBASE and Cochrane databases. The research question was formulated according to the PICOS method: Population (axSpA patients); Intervention (discontinuation of anti-TNF); Comparator (continue with standard dose of anti-TNF); Outcome (flare); and Study design (longitudinal studies with at least 6 months of follow-up after anti-TNF discontinuation). Flare was assessed according to the definition employed by each study, usually BASDAI ³4 & Physician«s assessment ³4 or ÆBASDAI ³2. Exclusion criteria were: less than 12 weeks on anti-TNF treatment before discontinuation or no clinical improvement achieved during the treatment. Data were independently extracted by two reviewers using a form developed for this purpose.

Results: Five studies out of 763 citations were included, with a total of 220 patients (84% AS and 16% nr-axSpA). The study design was: observational study following participation on a RCT (n=4) and RCT (n=1). In these studies, patients receiving standard doses of an anti-TNF drug discontinued this therapy and were followed in order to assess the appearance of flare. Discontinued therapy was etanercept (n=3), infliximab (n=1), and adalimumab (n=1). Sample size ranged between 17 and 111 patients and follow-up period after discontinuation between 36 and 52 weeks. Data extracted for each study are shown on the table. The percentage range of patients developing flare during the follow-up period was 69-100%. Specifically, the percentage and corresponding period for each study were as follows: 100% (within 36 weeks), 98% (within 48 weeks), and 69%, 79% and 79% (all three within 52 weeks). Median (range) time to flare was 16 (6-24) weeks. Additionally, in 4 studies patients with flare were re-treated later using the same anti-TNF. Overall, similar response to the one achieved after the initial treatment was observed for most clinical outcomes.

Conclusion: Published data indicates that discontinuation of anti-TNF therapy in patients with axSpA leads to the appearance of flare within a few months in most cases. However, most of the published evidence is based on studies including patients with established disease. Therefore, it still remains to be evaluated whether or not this high frequency of flares is observed in patients with shorter disease duration.

Table:

	Brandt et al	Baraliakos et al	Song et al	Deng et al	Haibel et al
Characteristics of the study					
Year	2003	2005	2012	2013	2013
Journal	Arthritis Rheum	Arthritis Res & Ther	Ann Rheum Dis	Rheumatol Int	Arthritis Rheum
Design	Prospective, observational after RCT	Prospective, observational after RCT	Prospective, observational after RCT	RCT	Prospective, observational after RCT
Period	2001	2003	2003	-	-
Country	Germany	Germany	International	China	Germany
Nº pts (AS/nr-axSpA)	26/0	42/0	6/11	111/0	0/24
Pts with discontinuation	26	42	17	111 (talidomida vs SSZ or NSAID)	24
Control group	no	no	no	no	no
Follow-up (weeks)	36	52	52	52	52
Characteristics of patients					
Age (years)	37	40	34	18-57	38
Male	77	65	71	-	45
Disease duration (yr)	14 (9)	15 (9)	<5 symp dur	9	7-8
HLA-B27+	89	-	94	100	67
Peripheral arthritis		-	-	-	30
DMARDs	0	-	-	-	-
Anti-TNF	etanercept	infliximab	etanercept	etanercept	adalimumab
Time on anti-TNF (m)	3	36	11	2.5	12
Definition to discontinue anti-TNF	≥ 20% improvement in BASDAI	all patients (at least they all had ≥ 30% improvement in BASDAI)	prASAS and remission on MRI	ASAS20 response	ASAS40 response
Outcome					
Flare definition	BASDAI≥4 & PhGV≥4	BASDAI≥4 & PhGV≥4	BASDAIΔ 2 versus baseline	BASDAIΔ 2 or 80% of BASDAI prior to treatment	Loss of ASAS40 response vs baseline
Nº pts with flare	75% at 12wk, 100% at 36 wk	24% at 12wk, 98% at 48wk	76% at wk52	79% at wk52	79% at wk52
Time to flare (weeks)	6.2 (3.0)	17 (8)	24	14 (9)	15 (5.5)
Predictor of flare	-	No prASAS, high BASDAI or high CRP at discontinuation	-	CRP, PtGV, spinal inflammation	Not found
Response after retreatment	58% BASDAI50 31% ASAS after 54 weeks	Similar to initial (BASDAI 6.1 at reinfusion vs 2.9 after 12 wk)	Similar to initial except for ASASpr that was less frequently achieved	-	ASAS40 was achieved by 63% after 1 year and 74% after 2 years
Level of evidence					
CEBM Oxford	4	4	4	4	4

Disclosure: V. Navarro-Compán, None; **C. Plasencia-Rodriguez**, None; **E. De Miguel**, None; **A. Balsa**, None; **E. Martín-Mola**, None; **D. Seoane-Mato**, None; **J. D. Cañete**, None.

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Abstract Number: 2864

Long-Term Work Productivity Improvement Associated with Apremilast, an Oral Phosphodiesterase 4 Inhibitor, in Patients with Psoriatic Arthritis: Pooled Analysis of 3 Phase 3 Studies

Frank Zhang[1], Zoe Clancy[2] and Stan Li[3], [1]Pricing and Market Access, I&I, Celgene Corporation, Warren, NJ, [2]33 Technology Drive, Celgene Corporation, Warren, NJ, [3]Celgene Corporation, Warren, NJ

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Background/Purpose: Studies have shown that patients with psoriatic arthritis (PsA) have significantly compromised physical health and quality of life, and negative effect on work productivity has been seen (Tillett W, et al. *Rheumatology [Oxford]*. 2012;51:275-283). The Work Limitations Questionnaire (WLQ) is a reliable tool for assessing limitations on work productivity in patients with chronic health conditions and was used in the PALACE 1, 2, and 3 trials, which compared the efficacy and safety of apremilast (APR), an oral phosphodiesterase 4 inhibitor, with placebo in patients with active PsA despite prior conventional disease-modifying antirheumatic drugs (DMARDs) and/or biologics. Our objective was to assess the effect of APR on work productivity and work limitations over 52 weeks in a pooled analysis of 802 patients in PALACE 1-3.

Methods: Patients were randomized (1:1:1) to receive placebo, APR 30 mg BID (APR30), or APR 20 mg BID (APR20). Early escape to active treatment was possible at Week 16 for placebo patients, and at Week 24, all patients remaining on placebo were re-randomized to APR30 or APR20. The WLQ, a 25-item questionnaire that assesses the impact of chronic health conditions on work performance and productivity, was administered at baseline, Week 16, and Week 52. Work limitations were categorized into 4 domains: physical demands (PDS), mental demands (MDS), time management demands (TMS), and output demands (ODS). An overall WLQ Productivity Score is calculated and expressed as the percentage loss in productivity associated with illness

Results: Patient demographics (age, sex, geographic region) were similar across treatment groups for patients who completed at least 1 domain of the WLQ at baseline. At Week 16, both APR30 and APR20 were associated with a greater mean change from baseline in PDS, MDS, TMS, and ODS vs. placebo, resulting in an improvement from baseline in work productivity loss. Productivity improvements in PDS, MDS, TMS, and ODS were also maintained among patients receiving APR30 and APR20 to Week 52 (Table).

Conclusion: APR30 and APR20 treatment increased work productivity and improved work limitations among patients in the PALACE 1-3 studies. Improvements in productivity loss were maintained through 52 Weeks of treatment.

	PALACE 1-3 Pooled Analysis		
	Placebo n=273	APR30 n=267	APR20 n=262
Week 16 (ITT Population, LOCF), Mean Change From Baseline			
PDS	n=226 -0.75	n=209 -2.45	n=218 -1.66
MDS	n=230 1.29	n=209 -4.83	n=226 -3.23
TMS	n=219 -0.88	n=198 -8.03	n=215 -4.64
ODS	n=223 0.28	n=202 -8.26	n=221 -3.97
WLQ Index	n=209 0.00	n=184 -0.02	n=208 -0.01
Productivity loss, %	n=209 -0.03	n=184 -1.83	n=208 -0.91
Week 52 (Data as Observed), Mean Change From Baseline			
PDS	N/A	n=163 -7.49	n=174 -6.26
MDS	N/A	n=171 -4.95	n=180 -3.39
TMS	N/A	n=159 -9.56	n=171 -8.11
ODS	N/A	n=165 -7.20	n=173 -4.31
WLQ Index	N/A	n=148 -0.02	n=162 -0.01
Productivity loss, %	N/A	n=148 -1.82	n=162 -1.33

ITT=intent to treat; LOCF=last observation carried forward; N/A=not applicable.
Negative changes from baseline indicate improvement.

Disclosure: F. Zhang, Celgene Corporation, 3; **Z. Clancy**, Celgene Corporation, 3; **S. Li**, Celgene Corporation, 3.

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Abstract Number: 2865

Methotrexate and Leflunomide Survival in Patients with Psoriatic Arthritis

Margarita Landi[1], Cecilia Zaffarana[1], Osvaldo Luis Cerda[1], Josefina Gallino Yanzi[1], Emilce Schneeberger[1], Ignacio Carrillo[1], María del Carmen Gonzalez Guzmán[1], Jose A Maldonado Cocco[1] and Gustavo Citera[2], [1]Instituto de Rehabilitación Psicofísica, Buenos Aires, Argentina, [2]Rheumatology, Instituto de Rehabilitación Psicofísica, Buenos Aires, Argentina
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Background/Purpose:

Disease Modifying Anti-Rheumatic Drugs (DMARDs) are frequently used in Psoriatic Arthritis (PsA), however there is limited data regarding their survival rates. This study attempts to estimate the survival rate of the most frequently used DMARDs in a cohort of PsA patients and to determine the main causes of drug discontinuation as well as factors associated with a higher survival rate.

Methods:

Patients with PsA according to CASPAR criteria, ≥ 18 years of age, belonging to the RAPSODIA cohort were studied. Socio-demographic and clinical data were collected. Peripheral, cutaneous and axial involvement were assessed along with functional status, quality of life and disease activity. Data regarding treatment was gathered by a direct interview with the patient and from medical records in order to reduce forgetfulness bias. *Statistical analysis:* Continuous variables were compared using Mann Whitney or T test with Levene's test for homogeneity of variance, and categorical data by Chi^2 or Fisher's exact test. Kaplan Meier survival curves and log rank were used to analyse and compare drugs' survival rate. Cox proportional analysis was performed to determine associated factors with drug survival.

Results:

A total of 87 patients with PsA were included in the analysis, with a median age of 52 years (IQR 40.2-61.7) and a slight female predominance (52.9%). Median disease duration was 10 years (IQR 6-17). Seventy patients (80.5%) received methotrexate (MTX), 23 (32.9%) had to discontinue it due to adverse events (65%) or treatment failure (35%). The median survival time of MTX was 13 years (range 8.5-17.4). The cumulative survival rate after 10 years of treatment was 55%, being significantly higher among patients receiving concomitant steroid therapy (X̄16.4±2.3 years vs X̄10±2 years, p=0.01).

Of the 16 patients receiving leflunomide (LFN), 56.25% had to discontinue, estimating a median survival time of 6 years (Range 1.6-10.3). The main reasons for discontinuation were adverse events (44.5%) and treatment failure (33.3%). The cumulative survival rate after 10 years was 35%. Patient's age had a mayor impact in LFN survival; using a cut-off value of 50 years, elderly patients had higher drug survival (X̄5.5±1.5 years vs X̄3.3±1 years, p=0.03).

Conclusion:

In this cohort of PsA patients, MTX was the most frequently DMARD used, followed by LFN. MTX cumulative survival was greater than that of LFN and was favoured by concomitant steroid therapy. LFN survival was higher amongst patients with more than 50 years of age. The main reasons for drug discontinuation in both scenarios were adverse events and loss of efficacy.

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Abstract Number: 2866

Effectiveness and Safety of Golimumab in the Treatment of Psoriatic Arthritis over a 12 Month Period

Proton Rahman[1], Michel Zummer[2], William G Bensen[3], Isabelle Fortin[4], Dalton Sholter[5], Milton F. Baker[6], Regan Arendse[7], Eliofotisti Psaradellis[8], Emmanouil Rampakakis[9], Francois Nantel[10], Allen J Lehman[10], Cathy Tkaczyk[11], Karina Maslova[10] and Brendan Osborne[11], [1]Medicine, Memorial University, St John's, NF, Canada, [2]Rheumatology, Hôpital Maisonneuve-Rosemont and University of Montreal, Montreal, QC, Canada, [3]St Joseph's Healthcare Hamilton, Hamilton, ON, Canada, [4]Centre de Rhumatologie de l'Est du Québec, Rimouski, QC, Canada, [5]Rheumatology Associates, Edmonton, AB, Canada, [6]VIHA, Victoria, BC, Canada, [7]University of Saskatchewan, Saskatoon, SK, Canada, [8]JSS Medical Research, Montreal, QC, Canada, [9]JSS Medical Research, St-Laurent, QC, Canada, [10]Janssen Inc., Toronto, ON, Canada, [11]Medical Affairs, Janssen Inc., Toronto, ON, Canada
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Background/Purpose: The efficacy and tolerability of golimumab (GLM) in patients with psoriatic arthritis (PsA) has been demonstrated in several controlled clinical trials. Longitudinal observational studies assessing the real-life effectiveness of anti-TNF agents are essential to demonstrate true population-based benefits. The objective of this analysis was to assess the 12-month outcomes in PsA patients treated with GLM in Canadian routine clinical practice.

Methods: BioTRAC is an ongoing, prospective registry of patients initiating treatment for rheumatoid arthritis, ankylosing spondylitis, or PsA with infliximab or GLM. Eligible participants for this analysis included PsA patients treated with GLM enrolled since 2010. Descriptive statistics were produced for clinical outcome measures and patient reported outcomes over 12 months. Within-group changes were assessed for statistical significance with the paired-samples Student's t-test and the McNemar test. Safety was assessed with the incidence of adverse events (AEs)/100 patient-years.

Results:

There were 151 patients included in this analysis with a mean (SD) age of 51.3 (13.4) years and a disease duration since diagnosis of 4.3 (5.0) years. The proportion of males and females was even (50%). Six-month and 12-month follow-up was available for 109 (72.2%) and 69 (45.7%) patients, respectively. Upon six months of treatment, statistically significant and clinically meaningful improvements were observed for all disease parameters and were sustained over 12 months of treatment. Mean (SD) disease parameters at baseline and 12 months of treatment are shown in Table 1.

The proportion of patients with minimal disease activity (MDA) was 9.8% at baseline, 52.1% at 6 months, and 50.0% at 12 months. The prevalence of enthesitis decreased from baseline to 12 months from 27.8% to 18.8% (P=0.791), while a considerable decrease was observed for dactylitis from 27.8% to 2.9% (P<0.001), respectively. The incidence of new enthesitis cases and new dactylitis cases at 12 months was 11.1% and 1.9%, respectively.

A total of 216 AEs (172.6 events/100 patient-years) were reported by 78 (51.7%) patients and 22 serious AEs (SAEs) (17.6 events/100 patient-years) by 12 (7.9%) patients. The incidence of serious infections and malignancies were 4 (3.2 events/100 patient-years) and 5 (4.0 events/100 patient-years), respectively. There was one death reported during the course of the study judged as not related to GLM by the treating physician.

Conclusion: The results of this Canadian longitudinal observational study have shown that a significant burden of illness is observed at GLM initiation in PsA patients. Treatment with GLM was well tolerated and effective in reducing symptom severity and improving disease outcomes in PsA patients over 12 months.

Table 1: Disease Parameters Over 12 Months of Treatment with GLM

Disease Parameter, mean (SD)	Baseline	12 Months	P-Value
Enthesitis count	1.5 (3.1)	0.8 (2.2)	0.738
Enthesitis count among patients with enthesitis	5.4 (3.8)	4.6 (3.2)	0.093
Dactylitis count	1.3 (3.1)	0.03 (0.17)	0.003
Dactylitis count among patients with dactylitis	4.7 (4.5)	1.0 (1.0)	NC
Morning Stiffness, Minutes	34.4 (39.5)	14.3 (21.2)	0.012
SJC28	4.9 (4.2)	0.9 (2.0)	<0.001
TJC28	6.9 (6.8)	2.6 (5.0)	<0.001
Pain, mm VAS	49.2 (26.3)	26.3 (25.1)	<0.001
PtGA, mm VAS	49.3 (26.5)	25.7 (23.0)	<0.001
MDGA, 0-10 NRS	4.9 (2.2)	1.7 (1.7)	<0.001
HAQ	1.0 (0.7)	0.7 (0.7)	0.003
PASI	2.3 (3.9)	0.6 (1.0)	0.008
DAS28-CRP	4.1 (1.4)	2.5 (1.0)	<0.001

NC=not computable

Disclosure: P. Rahman, None; **M. Zummer**, Janssen Inc, 5; **W. G. Bensen**, Janssen Inc., 5; **I. Fortin**, Janssen Inc., 5; **D. Sholter**, Janssen Inc., 5; **M. F. Baker**, Janssen Inc., 5; **R. Arendse**, Janssen Inc., 5; **E. Psaradellis**, employee of JSS Medical Research, 3; **E. Rampakakis**, JSS, 3; **F. Nantel**, Janssen Inc., 3; **A. J. Lehman**, employee of Janssen Inc., 3; **C. Tkaczyk**, Janssen Inc., 3; **K. Maslova**, Employee of Janssen Inc., 3; **B. Osborne**, Janssen Inc., 3.

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Abstract Number: 2867

Impact of Timely Versus Delayed Use of Anti-Tumor Necrosis Factor (TNF) Biologics in the Treatment of Psoriatic Arthritis: Results from a Modeling Study

Vibeke Strand[1], M. Elaine Husni[2], Zheng-Yi Zhou[3], James Signorovitch[3], Jenny Griffith[4], Yichen Zhong[3] and Arijit Ganguli[4], [1]Stanford University, Palo Alto, CA, [2]Rheumatology Dept A50, Cleveland Clinic Foundation, Cleveland, OH, [3]Analysis Group, Inc., Boston, MA, [4]AbbVie Inc., North Chicago, IL

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Background/Purpose: Progression of psoriatic arthritis (PsA) can lead to irreversible joint damage and functional impairment. TNF inhibitors (TNFi's) have been shown to improve signs and symptoms of PsA and, in contrast to apremilast, a phosphodiesterase-4 inhibitor, inhibit radiographic progression. The clinical impact of using apremilast prior to a TNFi is not fully understood. This study evaluated clinical responses associated with timely vs delayed use of TNFi's among patients with PsA.

Methods: A Markov model was developed to evaluate improvements in joint and skin symptoms in patients with moderate-to-severely active PsA (≥3 swollen joints and ≥3 tender joints) treated with TNFi's (adalimumab, etanercept, infliximab, or golimumab) and/or apremilast over a 1-year time horizon. In the model, PsA patients received either TNFi (timely use) or apremilast (delayed use) as initial treatment. Those who did not achieve ACR20 responses in the first 12 weeks of treatment or lost responses in the subsequent weeks either switched to a different TNFi (after timely use of first TNFi) or initiated a first TNFi (representing delayed use). Subsequent non-responses or loss of responses were followed by palliative care (both arms). Joint responses (achievement of ACR20 responses) were evaluated for all patients; skin responses (defined by 75% improvement in Psoriasis Area and Severity Index score [PASI75]) were evaluated in a subgroup of patients with moderate-to-severe psoriasis (affected body surface area [BSA] ≥3%). Efficacy inputs and distributions of patients treated with anti-TNFs were based on randomized controlled trials and market share data, respectively. Certolizumab, which was only recently approved, was excluded. Outcomes included ACR20/PASI75 response rates at year 1, mean time with ACR20/PASI75 responses, and number needed to treat (NNT) with timely vs. delayed TNFi use for achievement of ACR20/PASI75 responses in 1 patient.

Results: After one year, patients who initiated a TNFi had higher ACR20 response rates, more prolonged times as ACR20 responders and lower NNTs (**Table**) vs those initiating apremilast. Results were similar in the subgroup of patients with comorbid moderate-to-severe psoriasis: those who initiated a TNFi vs apremilast had higher combined ACR20/PASI75 response rates, more time as combined ACR20/PASI75 responders, and lower NNTs for combined responses.

Conclusion: Based on this modeling approach**,** timely use of TNFi's was a more effective strategy for management of PsA compared with delayed use of TNFi's due to sustained improvements in both joint and skin symptoms.

Outcomes at 12 Months Among PsA Patients with Timely vs Delayed Anti-TNF Use

	Arm A (timely TNFi use)	Arm B (delayed TNFi use)
Overall Population		
Joint response rates (ACR20), %[a]	70.4%	59.6%
Number needed to treat (NNT)[b]	1.42	1.68
Mean time as ACR responders, years	0.60	0.48
Subpopulation with Baseline Psoriasis		
Combined joint and skin response rates, %[a]	41.0%	30.0%
Number needed to treat (NNT)[b]	2.44	3.33
Mean time in ACR20/PASI75 responses, years	0.35	0.24

[a]Joint responses were defined as ACR20 responders; skin responses as PASI75 responders.

[b]NNT was defined as the average number of patients to be treated to gain one additional responder.

Disclosure: V. Strand, AbbVie, Alder, Amgen, BMS, Celgene, Genentech, Janssen, Novartis, Pfizer, and UCB, 5,Abbvie, Amgen, BMS, Celgene, Genentech, Janssen, Novartis, Pfizer, and UCB, 9; **M. E. Husni**, Celgene, Abbvie, Genentech, Bristol Myers Squibb, Pfizer, Novartis, and Janssen, 9; **Z. Y. Zhou**, Analysis Group, which has received consulting fee from AbbVie to partner on this research, 3; **J. Signorovitch**, Analysis Group, which has received consulting fee from AbbVie to partner on this research, 3; **J. Griffith**, AbbVie, 3,AbbVie, 1; **Y. Zhong**, Analysis Group, which has received consulting fee from AbbVie to partner on this research, 3; **A. Ganguli**, AbbVie, 3,AbbVie, 1.

Abstract Number: 2868

Relative Efficacy of Adalimumab Versus Secukinumab in Active Psoriatic Arthritis: A Matching-Adjusted Indirect Comparison

Keith A. Betts[1], Manish Mittal[2], Avani Joshi[2], Jinlin Song[1] and Yanjun Bao[2], [1]Analysis Group, Inc., Boston, MA, [2]AbbVie Inc., North Chicago, IL

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Background/Purpose: The phase 3 FUTURE 1 and FUTURE 2 trials demonstrated efficacy of secukinumab (SEC) for active psoriatic arthritis (PsA). However, there is limited data comparing the effectiveness of SEC with established PsA treatments. This study compared the relative efficacy of adalimumab (ADA) 40mg versus SEC 150mg and 300mg for the treatment of PsA.

Methods: An indirect comparison was conducted using individual patient data from the ADA pivotal trial (ADEPT) and published data from FUTURE 1 and 2. To adjust for the cross-trial differences, individual patients in ADEPT were re-weighted to match the mean baseline characteristics in the FUTURE trials.[1,2] Specifically, age, weight, gender, race, baseline methotrexate use, psoriasis ≥ 3% body surface area, baseline PASI score, presence of dactylitis and enthesitis, and HAQ-DI were included in the baseline matching. The ACR 20/50/70 and PASI 75/90 response rates relative to placebo at week 24 were compared. Numbers needed to treat (NNTs) to achieve one additional ACR 20 and PASI 75 responder were also calculated.

Results: After matching, mean baseline characteristics were balanced across the ADEPT and FUTURE 1 and 2 trial populations. For all outcomes, ADA demonstrated a higher relative efficacy to placebo when compared to SEC 150mg (n=302) (Figure 1). Specifically, the mean differences (95% confidence interval) between ADA and SEC 150mg in relative ACR 20/50/70 response rates were 9.5% (-4.3%, 23.3%), 3.0% (-10.1%, 16.0%), and 6.0% (-4.4%, 16.5%), respectively. The mean differences in relative PASI 75/90 response rates were 13.1% (-0.5%, 26.7%) and 6.7% (-6.4%, 19.9%). Similarly, ACR 20/50/70 and PASI 75 were higher with ADA vs SEC 300mg (n=100) (Figure 2). The NNTs to achieve one additional ACR 20 responder were 2.3 for ADA vs 3.0 for SEC 150mg and 2.7 for SEC 300mg. The NNTs to achieve one additional PASI75 responder were also lower for ADA (1.7) vs SEC 150mg (2.2) and SEC 300mg (1.9).

Conclusion: In the absence of head to head trials comparing ADA and SEC, the current indirect comparison which adjusts for differences across trial populations provides valuable and reliable evidence for physicians and payers. After adjusting for cross-trial differences in baseline characteristics, ADA was associated with higher relative ACR and PASI rates and lower NNTs compared with SEC 150mg or 300mg at week 24 among patients with PsA.

[1] Signorovitch et al. *Pharmacoeconomics* 2010; 28 (10): 935-945.

[2] Signorovitch et al. *Value in Health* 2012; 15 (6), 940-947.

Figure 1 ACR 20/50/70 and PASI 75/90 relative to placebo of ADA 40mg vs. SEC 150mg

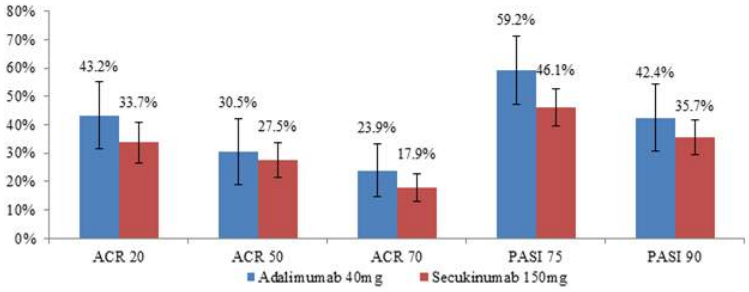
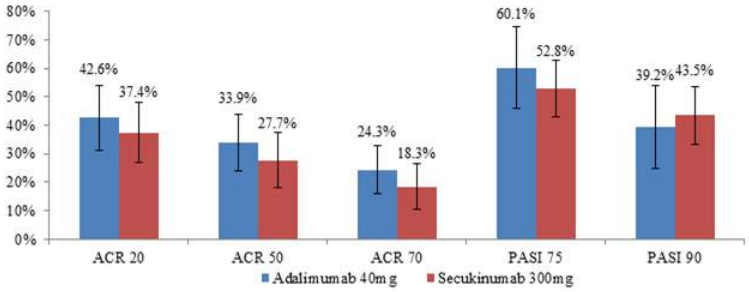


Figure 2 ACR 20/50/70 and PASI 75/90 relative to placebo of ADA 40mg vs. SEC 300mg



Disclosure: K. A. Betts, AbbVie, 5; **M. Mittal**, AbbVie, 1,AbbVie, 3; **A. Joshi**, AbbVie, 1,AbbVie, 3; **J. Song**, AbbVie, 5; **Y. Bao**, AbbVie, 1,AbbVie, 3.

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Abstract Number: 2869

Impact of Methotrexate on the Real-World Effectiveness of Golimumab in Psoriatic Arthritis

Louis Bessette[1], Proton Rahman[2], Denis Choquette[3], John Kelsall[4], Maqbool Sheriff[5], Emmanouil Rampakakis[6], Eliofotisti Psaradellis[7], Allen J Lehman[8], Karina Maslova[8], Francois Nantel[9,10], Brendan Osborne[11] and Cathy Tkaczyk[11], [1]Centre d'Ostéoporose et de Rhumatologie de Québec (CORQ), Québec, QC, Canada, [2]Medicine, Memorial University, St John's, NF, Canada, [3]Rheumatology Department, Institut de Rhumatologie de Montréal and University of Montreal, Montreal, QC, Canada, [4]Mary Pack Arthritis Centre, Vancouver, Vancouver, BC, Canada, [5]Nanaimo Regional General Hospital, Nanaimo, BC, Canada, [6]JSS Medical Research, St-Laurent, QC, Canada, [7]JSS Medical Research, Montreal, QC, Canada, [8]Janssen Inc., Toronto, ON, Canada, [9]Schering Plough Canada Inc., Janssen Inc., Kirkland, QC, QC, Canada, [10]19 Green belt Dr, Janssen Inc., Toronto, ON, Canada, [11]Medical Affairs, Janssen Inc., Toronto, ON, Canada

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Background/Purpose: : Previous controlled clinical trials have shown that concurrent methotrexate (MTX) therapy may enhance the efficacy of anti-TNF agents. However, real-world data on the benefits of combination therapy with MTX and golimumab (GLM) are scarce. This aim of this analysis was to compare the baseline profile of patients initiating MTX+GLM compared to patients treated with GLM monotherapy and to assess the impact of concomitant MTX treatment on GLM effectiveness.

Methods: Biologic Treatment Registry Across Canada (BioTRAC) is an ongoing, prospective registry of patients initiating treatment for rheumatoid arthritis, ankylosing spondylitis, or PsA with infliximab or GLM. PsA patients treated with GLM enrolled since 2010 were included in this analysis. Descriptive statistics were produced for clinical outcome measures and patient reported outcomes at baseline, 6 and 12 months of treatment. Within-group changes were assessed for statistical significance with the Wilcoxon t-test.

Results:

There were 152 PsA patients included in this analysis. Mean (SD) age was 51.3 (13.4) years and disease duration was 4.3 (5.0) years. The majority of patients (94.7%) in the GLM+MTX group received a high MTX dose (≥15 mg/week). 51.8% of patients had a MTX history for the GLM group vs 64.2% for the GLM+MTX group. Baseline patient characteristics and disease parameters were comparable for GLM vs. GLM+MTX although a higher proportion in the GLM group had dactylitis (39.3% vs. 21.1%. P=0.023). Statistically significant and clinically meaningful improvements were observed upon 6 months of treatment in both groups for all disease parameters which were sustained over 12 months of treatment, with the exception of PASI and HAQ-DI in the GLM group which did not reach statistical significance (Table 1). Upon adjusting for baseline levels, patients in the GLM+MTX group experienced greater improvements in most disease parameters although statistical significance was achieved only for TJC.

Table 1: Disease parameters for GLM vs. GLM+MTX at baseline and 12 months

	Group: GLM N=57			Group: GLM+MTX N=95			Between Group
Parameter, mean (SD)	Baseline	12 Months	P-value[1]	Baseline	12 Months	P-value[1]	P-value[2]
SJC	5.21(4.65)	1.73(3.06)	***<0.001***	4.71 (4.00)	0.51 (1.01)	***<0.001***	0.123
TJC	6.88 (6.82)	3.43 (5.07)	***0.007***	6.93 (6.85)	1.16 (1.68)	***<0.001***	***0.013***
Pain	47.26 (25.18)	26.05 (25.11)	***0.009***	50.47 (26.96)	26.37 (25.42)	***<0.001***	0.819
PASI	2.66 (4.48)	0.45 (0.70)	0.093	2.09 (3.56)	0.74 (1.16)	***0.020***	0.331
PtGA	46.88 (24.37)	24.24 (20.64)	***0.038***	50.68 (27.77)	26.44 (24.27)	***<0.001***	0.731
MDGA	5.08 (1.96)	2.39 (1.92)	***<0.001***	4.78 (2.34)	1.36 (1.38)	***<0.001***	0.112
DAS28	4.07 (1.47)	2.91 (1.22)	***0.015***	4.15 (1.32)	2.30 (0.82)	***<0.001***	0.106
HAQ-DI	0.96 (0.67)	0.76 (0.62)	0.087	1.03 (0.67)	0.67 (0.68)	***0.019***	0.726

[1] Represents within group P-value assessed with Wilcoxon test

[2] Represents between group P-value at 12 months of treatment assessed with linear regression adjusting for baseline disease parameters

The proportion of patients achieving minimal disease activity (MDA) was comparable between groups with GLM=56.0% vs. GLM+MTX=50.0% at 6 months, and GLM=47.1% vs. GLM+MTX=51.4% at 12 months.

Conclusion: The results of this analysis have shown that treatment with GLM, with or without MTX, is effective in reducing symptom severity and improving disease outcomes over a 12 month period in PsA patients. However, concomitant treatment with MTX may confer additional benefits. Additional analyses with larger sample sizes are required.

Disclosure: L. Bessette, Janssen Inc., 5; **P. Rahman**, None; **D. Choquette**, Janssen Inc., 5,AbbVie, 5,Amgen, 5,Celgene, 5,BMS, 5,Pfizer Inc, 5; **J. Kelsall**, Janssen Inc., 5; **M. Sheriff**, Janssen Inc, 5; **E. Rampakakis**, JSS, 3; **E. Psaradellis**, JSS Medical Research, 3; **A. J. Lehman**, Janssen Inc., 3; **K. Maslova**, Janssen Inc., 3; **F. Nantel**, Janssen Inc., 3; **B. Osborne**, Janssen Inc., 3; **C. Tkaczyk**, Janssen Inc., 3.

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Abstract Number: 2870

Predictors of Early Minimal Disease Activity in Psa Patients Treated with Anti-TNF in a Real-World Registry

Michel Zummer[1], Proton Rahman[2], Regan Arendse[3], Michael Starr[4], John Kelsall[5], J Antonio Avina-Zubieta[6], Philip Baer[7], Dalton Sholter[8], Michelle Teo[9], Emmanouil Rampakakis[10], Eliofotisti Psaradellis[11], Brendan Osborne[12], Karina Maslova[13], Francois Nantel[14], Allen J Lehman[13] and Cathy Tkaczyk[12], [1]Rheumatology, Hôpital Maisonneuve-Rosemont and University of Montreal, Montreal, QC, Canada, [2]Medicine, Memorial University, St John's, NF, Canada, [3]University of Saskatchewan, Saskatoon, SK, Canada, [4]Rheumatology, McGill University, Montreal, QC, Canada, [5]Mary Pack Arthritis Centre, Vancouver, Vancouver, BC, Canada, [6]Arthritis Research Canada / University of British Columbia, Vancouver, BC, Canada, [7]Section on Rheumatology, Ontario Medical Association/Journal of the Canadian Rheumatology Association, Toronto, ON, Canada, [8]Rheumatology Associates, Edmonton, AB, Canada, [9]Rheumatology, Penticton Regional Hospital, Penticton, BC, Canada, [10]JSS Medical Research, St-Laurent, QC, Canada, [11]JSS Medical Research, Montreal, QC, Canada, [12]Medical Affairs, Janssen Inc., Toronto, ON, Canada, [13]Janssen Inc., Toronto, ON, Canada, [14]19 Green belt Dr, Janssen Inc., Toronto, ON, Canada

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Background/Purpose: Early achievement of minimal disease activity (MDA) is recommended as a valid treat-to-target approach in psoriatic arthritis (PsA). The purpose of the current analysis was to evaluate predictors of MDA achievement in PsA patients treated with anti-TNF agents in Canadian routine clinical care.

Methods:

Biologic Treatment Registry Across Canada (BioTRAC) is an ongoing, prospective registry of patients initiating treatment for rheumatoid arthritis, ankylosing spondylitis, or PsA with Infliximab (IFX) or Golimumab (GLM). Eligible people for this analysis included PsA patients treated with IFX who were enrolled since 2005 or with GLM enrolled since 2010 and with available MDA information at baseline, 6 months, and/or 12 months. MDA was defined as the fulfillment of ≥5 of the following criteria: TJC28≤1, SJC28≤1, PASI≤1 or BSA≤3, Pain (VAS)≤15mm, PtGA (VAS)≤20mm, HAQ ≤0.5, tender entheseal points ≤1. Independent predictors of MDA achievement were assessed with logistic regression.

Results:

A total of 196 patients (51.4% male and 87.2% bionaive) were included with a mean (SD) age and disease duration of 49.8 (11.1) and 5.4 (6.3) years, respectively. The proportion of patients with MDA was 11.7% at baseline, 43.5% at 6 months, 44.8% at 12 months, and 49.1% at either 6 or 12 months. Among patients with MDA at 6 months, 75.7% had sustained MDA at 12 months. Patients achieving MDA during follow-up had significantly lower disease activity at baseline; mean (SD) disease parameters were: SJC28: 3.24 (3.58) vs. 5.47 (4.31), P<0.001; TJC28: 3.75 (4.00) vs. 8.66 (6.53), P<0.001; pain: 35.39 (25.11) vs. 55.70 (22.93), P<0.001; PtGA: 38.51 (25.00) vs. 56.15 (25.13), P<0.001; HAQ-DI: 0.71 (0.61) vs. 1.33 (0.57), P<0.001; MDGA: 4.25 (2.38) vs. 5.84 (2.07), P<0.001); enthesitis count: 2.62 (1.60) vs. 4.97 (3.48), P=0.008.

Multivariate logistic regression analysis showed that lower baseline HAQ (OR=0.243; P<0.001), lower TJC28 (OR=0.889; P=0.008), and lower enthesitis count (OR=0.817; P=0.817) were significant predictors of MDA achievement over 12 months of treatment.

Conclusion: The results of the current analysis have shown that 50% of patients treated with IFX or GLM in routine clinical care achieve MDA within the first year of treatment. Lower baseline HAQ, lower TJC28, and lower enthesitis count were identified as significant predictors of MDA achievement.

Disclosure: M. Zummer, Janssen Inc, 5; **P. Rahman**, None; **R. Arendse**, Janssen Inc., 5; **M. Starr**, Janssen Inc, 5; **J. Kelsall**, Janssen Inc., 5; **J. A. Avina-Zubieta**, Janssen Inc., 5; **P. Baer**, Janssen Inc., 5,AbbVie, 5,Amgen, 5,BMS, 5,Pfizer Inc, 5,Roche Pharmaceuticals, 5; **D. Sholter**, Janssen Inc., 5; **M. Teo**, Janssen Inc., 5; **E. Rampakakis**, JSS, 3; **E. Psaradellis**, JSS Medical Research, 3; **B. Osborne**, Janssen Inc., 3; **K. Maslova**, Janssen Inc., 3; **F. Nantel**, Janssen Inc., 3; **A. J. Lehman**, Janssen Inc., 3; **C. Tkaczyk**, Janssen Inc., 3.

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Abstract Number: 2871

Effectiveness and Safety of Golimumab in the Treatment of Ankylosing Spondylitis over a 12 Month Period

Denis Choquette[1], Proton Rahman[2], Maqbool Sheriff[3], Wojciech Olszynski[4], Emmanouil Rampakakis[5], Eliofotisti Psaradellis[6], Francois Nantel[7], Brendan Osborne[8], Allen J Lehman[9], Karina Maslova[9] and Cathy Tkaczyk[8], [1]Rheumatology Department, Institut de Rhumatologie de Montréal and University of Montreal, Montreal, QC, Canada, [2]Medicine, Memorial University, St John's, NF, Canada, [3]Nanaimo Regional General Hospital, Nanaimo, BC, Canada, [4]University of Saskatchewan, Saskatoon, SK, Canada, [5]JSS Medical Research, St-Laurent, QC, Canada, [6]JSS Medical Research, Montreal, QC, Canada, [7]19 Green belt Dr, Janssen Inc., Toronto, ON, Canada, [8]Medical Affairs, Janssen Inc., Toronto, ON, Canada, [9]Janssen Inc., Toronto, ON, Canada

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Background/Purpose: Although the efficacy and tolerability of golimumab (GLM) in patients with ankylosing spondylitis (AS) has been demonstrated in several controlled clinical trials, it is essential to assess the real-life effectiveness of therapeutic interventions in order to demonstrate true population-based benefits. The aim of this analysis was to describe the real-life effectiveness of GLM in AS patients in a Canadian routine clinical practice setting.

Methods: Biologic Treatment Registry Across Canada (BioTRAC) is an ongoing, prospective registry of patients initiating treatment for rheumatoid arthritis, ankylosing spondylitis, or PsA with infliximab or GLM. Eligible people for this analysis included AS patients treated with GLM enrolled since 2010. Descriptive statistics were produced for clinical outcome measures and patient reported outcomes over 12 months of treatment. Within-group changes were assessed for statistical significance with the paired-samples Student's t-test. Safety was assessed with the incidence of adverse events (AEs)/100 patient-years.

Results: A total of 206 AS patients were included in this analysis with a mean (SD) age of 45.6 (13.9) years and disease duration since diagnosis of 5.7 (10.2) years, the majority were male (61.2%) and 93.2% were biologic naïve. After six months of treatment, statistically significant (P<0.001) and clinically meaningful improvements were observed for all disease parameters and were sustained over 12 months of treatment (P<0.001). Mean (SD) disease parameters at baseline and 12 months of treatment are shown in Table 1. Clinically important improvement in ASDAS (change ≥1.1) by 6 and 12 months was 46.6% and 40.0%, respectively; major improvement (change ≥2.0) was achieved by 13.8% and 25.0% respectively. The proportion of patients who achieved ASDAS inactive disease (ASDAS <1.3) increased from 2.6% at baseline to 21.2% at 12 months; while very high disease activity (ASDAS >3.5) decreased from 44.4% to 21.2%, respectively. A total of 282 AEs (215.8 events/100 patient-years) were reported by 105 (51.0%) patients and 23 serious AEs (SAEs) (17.6 events/100 patient-years) by 20 (9.7%) patients. The incidence of serious infections and malignancies were 2 (1.5 events/100 patient-years) and 1 (0.8 events/100 patient-years), respectively. There were no deaths reported during the course of the study.

Table 1: Disease Parameters Over 12 Months of GLM Treatment

Parameter **Mean (SD) / %**	**Baseline** **(n=206)**	**Month 12** **(n=77)**	**P-Value**
AM stiffness: minutes	55.17 (45.29)	24.19 (30.76)	<0.001
HAQ-DI	1.02 (0.60)	0.68 (0.62)	<0.001
Patient Global (PtGA): VAS mm	55.08 (25.96)	32.41 (28.36)	<0.001
Physician Global (MDGA): NRS 0-10	5.32 (2.20)	2.42 (2.40)	<0.001
BASFI	5.10 (2.49)	3.33 (2.80)	<0.001
BASDAI	5.86 (2.13)	3.64 (2.58)	<0.001
ASDAS	3.33 (0.96)	2.46 (1.20)	<0.001
ASDAS Disease Activity (DA) *Inactive Disease* *Moderate DA* *High DA* *Very High DA*	 2.6% 9.3% 43.7% 44.4%	 21.2% 23.1% 34.6% 21.2%	<0.001
ASDAS Clinically Important Improvement (Δ≥1.1)	N/A	46.6%	N/A
ASDAS Major Improvement (Δ≥2.0)	N/A	40.0%	N/A

Conclusion: The results of this Canadian longitudinal observational study have shown that GLM is well tolerated and effective in reducing symptom severity and improving disease outcomes in AS patients over a 12 month period.

Disclosure: D. Choquette, Janssen Inc., 5,AbbVie, 5,Amgen, 5,Celgene, 5,BMS, 5,Pfizer Inc, 5; **P. Rahman**, None; **M. Sheriff**, Janssen Inc, 5; **W. Olszynski**, Janssen Inc., 5; **E. Rampakakis**, JSS, 3; **E. Psaradellis**, JSS Medical Research, 3; **F. Nantel**, Janssen Inc., 3; **B. Osborne**, Janssen Inc., 3; **A. J. Lehman**, Janssen Inc., 3; **K. Maslova**, Janssen Inc., 3; **C. Tkaczyk**, Janssen Inc., 3.

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Abstract Number: 2872

Two-Year Clinical Response to Brodalumab, an Anti-Interleukin-17 Receptor Antibody, in Patients with Psoriatic Arthritis

Mark C. Genovese[1], Philip J. Mease[2], Maria Greenwald[3], Christopher T. Ritchlin[4], Andre Beaulieu[5], Atul A. Deodhar[6], Richard

Newmark[7], JingYuan Feng[8], Ngozi Erondu[9] and Ajay Nirula[10], [1]Division of Rheumatology, Stanford University Medical Center, Palo Alto, CA, [2]Rheumatology Research, Swedish Medical Center, Seattle, WA, [3]Desert Medical Advances, Palm Desert, CA, [4]Allergy, Immunology and Rheumatololgy Division, University of Rochester Medical Center, Rochester, NY, [5]Faculty of Medicine, University of Laval, Quebec, QC, Canada, [6]Division of Arthritis & Rheumatic Diseases, Oregon Health & Science University, Portland, OR, [7]Clinical Affairs, Amgen, Thousand Oaks, CA, [8]Amgen Inc., Thousand Oaks, CA, [9]Inflammation, Amgen, Inc., Thousand Oaks, CA, [10]Amgen Inc, Thousand Oaks, CA
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Background/Purpose: The interleukin-17 (IL-17) cytokine family plays a key role in the pathogenesis of psoriatic diseases of skin and joint. Brodalumab is a fully human anti–IL-17 receptor monoclonal antibody that blocks the activity of IL-17A, IL-17F, and IL-17A/F. Here, we evaluate the long-term safety and efficacy of brodalumab in patients with psoriatic arthritis (PsA) in an open-label extension (OLE) of a phase 2 study.

Methods: In a phase 2 study (NCT01516957), adults (18–75 years) with active PsA were randomized to brodalumab (140 or 280 mg) or placebo at weeks 0, 1, 2, 4, 6, 8, and 10. At week 12, patients could enter an OLE and receive brodalumab 280 mg every 2 weeks (Q2W); a protocol amendment in November 2013 resulted in dosage reduction to 210 mg Q2W for all patients. Outcome measures based on observed data through week 108 included percentages of patients with 20% and 50% improvement in American College of Rheumatology criteria (ACR20 and ACR50) and changes in ACR components and Psoriasis Symptom Inventory (PSI) score. Safety was assessed by adverse events (AEs).

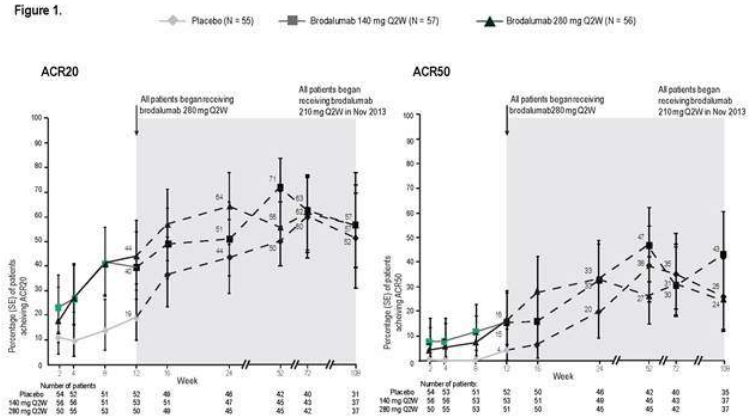
Results: At baseline, patients were 64% female, 94% white, with mean age and weight of 52 years and 91 kg, respectively. Mean PsA duration was 9 years, 92% were rheumatoid factor negative, and mean PSI score was 12.7. Of 168 patients randomized at baseline, 156 (52 placebo, 53 brodalumab 140 mg, and 51 brodalumab 280 mg) entered the OLE and 109 (70%) remained at week 108.

Through week 108, 149 (96%) patients reported an AE and 23 (15%) reported a serious AE (SAE). The most frequent SAEs (n=2 each) were coronary artery disease, cholelithiasis, and cellulitis; the most frequent AEs (≥10% of all patients) were nasopharyngitis, upper respiratory tract infection, psoriatic arthropathy, urinary tract infection, arthralgia, diarrhea, sinusitis, and bronchitis. Exposure-adjusted AE rate (per 100 patient-years) for all patients was 526; exposure-adjusted SAE rate was 14. There were no deaths, 1 laboratory report of neutropenia, 1 case of suicidal ideation, and 11 cases of oral candidiasis.

At week 12 of the study (double-blind phase), percentages of patients with ACR20 and ACR50 (non-responder imputation [NRI] analysis) were significantly greater in each brodalumab group than placebo: ACR20 37% (140 mg) and 39% (280 mg) vs 18% (placebo); ACR50 14% and 14% vs 4%. Through week 108 of the OLE, we continued to observe meaningful clinical benefit in ACR20 and ACR50 (Figure 1, as observed). Continued clinical benefit was also demonstrated by NRI analysis. Responses for other outcome measures were also sustained from week 12 to 108 in patients remaining in the OLE.

Conclusion: Treatment with brodalumab resulted in a safety profile comparable to the overall safety profile of biologics approved for PsA and meaningful clinical benefit that was maintained through week 108 in patients with PsA in this ongoing OLE.

Figure 1.



Disclosure: M. C. Genovese, Amgen, 5; **P. J. Mease**, Amgen Inc., 2; **M. Greenwald**, Amgen Inc., 2; **C. T. Ritchlin**, Amgen Inc., 2; **A. Beaulieu**, Amgen Inc., 2; **A. A. Deodhar**, Amgen Inc., 9,Amgen Inc., 2; **R. Newmark**, Amgen Inc., 1,Amgen Inc., 3; **J. Feng**, Amgen

Inc., 1,Amgen Inc., 3; **N. Erondu**, Amgen Inc., 1,Amgen Inc., 3; **A. Nirula**, Amgen Inc., 1,Amgen Inc., 3.

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Abstract Number: 2873

Pharmacological Treatment of Psoriatic Arthritis (PSA): Systematic Literature Review for the Update of the EULAR Recommendations for the Management of PSA

Sofia Ramiro[1], Josef S. Smolen[2], Robert B.M. Landewé[3], Désirée van der Heijde[1], Maxime Dougados[4], Paul Emery[5], Maarten de Wit[6], Maurizio Cutolo[7], Susan Oliver[8] and Laure Gossec[9], [1]Rheumatology, Leiden University Medical Center, Leiden, Netherlands, [2]Department of Rheumatology, Medical University of Vienna, Vienna, Austria, [3]Department of Rheumatology, Amsterdam Rheumatology Center, Amsterdam, Netherlands, [4]Rheumatology Department, Cochin hospital, Paris-Descartes University, Paris, France, [5]Section of Musculoskeletal Disease, Leeds Institute of Molecular Medicine, University of Leeds, Leeds, United Kingdom, [6]EULAR Social Leagues, Zurich, Switzerland, [7]Division of Clinical Immunology, Dept Internal Medicine, University of Genova, Genova, Italy, [8]Independent Nurse Consultant, North Devon, United Kingdom, [9]Rheumatology, Pitié Salpetriere Hospital, Paris, France
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Background/Purpose: As part of the update of the EULAR recommendations for the management of PsA, we performed a systematic literature review to assess the efficacy and safety of pharmacological agents for the management of PsA.

Methods: Randomised controlled trials (RCTs), including long-term extensions, comparing any two pharmacological interventions for the management of patients with PsA, were identified by searches in Medline, Embase and Cochrane datasets (2010-2014), supplemented by searches in 2013-2014 EULAR and ACR abstracts. Pharmacological interventions were defined as any biological (bDMARD), synthetic DMARD (sDMARD) either conventional or targeted, NSAID, glucocorticoid or any combination and they could be compared to any of them or placebo (PBO). Strategy trials were also included. The main efficacy outcomes were ACR20, ACR50, PASI75 and radiographic progression, and the main safety outcome was withdrawals due to adverse events. Risk of bias (RoB) was assessed according to the Cochrane tool. Multiple studies of the same intervention were meta-analysed with random effects analysis in RevMan.

Results: Of 2,278 articles and 387 conference abstracts screened, 42 (24 papers and 18 abstracts) met the inclusion criteria. A total of 19 articles/abstracts focused on 3 new drugs for the management of PsA: ustekinumab (UST), apremilast (APR) and secukinumab (SEC). All were PBO-compared trials and met their primary endpoint, ACR20; RoB was low (UST, SEC) or unclear (APR). For achieving ACR20, absolute responses are in the Table. Risk ratios (RR) versus PBO were respectively for UST90mg and UST45mg of 2.17 (95%CI 1.71-2.76) and 1.95 (1.52-2.50); for APR30mg and APR20mg of 2.06 (1.67, 2.54) and 1.84 (1.51-2.25); and for SEC300mg, SEC150mg and SEC75mg, of 3.31 (2.04-5.36), 5.82 (1.56-21.71) and 4.47 (0.66-30.26). The 3 drugs showed efficacy on dactylitis and enthesitis, with APR apparently showing less pronounced effects. These new drugs showed slightly more SAEs and withdrawals due to AEs than PBO. Eleven articles/abstracts on golimumab and certolizumab pegol demonstrated the efficacy and safety of these drugs with respect to all outcomes. A strategy trial, TICOPA, has shown better ACR responses with tight control compared to standard care. No studies were found on NSAIDs or glucocorticoids.

Table - Main efficacy outcomes of the new drugs for the treatment of PsA, at time point of the trial's primary endpoint

Trial, time point	Treatment arm	ACR 20 (%)	ACR 50 (%)	PASI 75 (%)	delta mTSS
PSUMMIT 1 24 Weeks	UST 90mg	49.5	27.9	62.4	0.4 (2.4)*
	UST 45mg	42.4	24.9	57.2	0.4 (2.1)*
	PBO	22.8	8.7	11.0	1.0 (3.9)*
PSUMMIT 2 24 Weeks	UST 90mg	43.8	22.9	55.6	**
	UST 45mg	43.7	17.5	51.3	**
	PBO	20.2	6.7	5.0	**
PALACE 1 16 Weeks	APR 30mg	38.1	NA	NA	NA
	APR 20mg	30.4	NA	NA	NA
	PBO	19.0	NA	NA	NA
PALACE 2 16 Weeks	APR 30mg	34.4	NA	NA	NA
	APR 20mg	38.4	NA	NA	NA
	PBO	19.5	NA	NA	NA
PALACE 3 16 Weeks	APR 30mg	42.8	NA	NA	NA
	APR 20mg	29.4	NA	NA	NA
	PBO	18.9	NA	NA	NA
PALACE 4 16 Weeks	APR 30mg	29.2	NA	NA	NA
	APR 20mg	32.3	NA	NA	NA
	PBO	16.9	NA	NA	NA
FUTURE 1 24 Weeks	SEC 150mg	50.0	34.7	61.1	0.13
	SEC 75mg	50.5	30.7	64.8	0.02
	PBO	17.3	7.4	8.3	0.57
FUTURE 2 24 Weeks	SEC 300mg	54.0	35.0	63.4	NA
	SEC 150mg	51.0	35.0	48.3	NA
	SEC 75mg	29.3	18.2	28.9	NA
	PBO	15.3	7.1	16.3	NA

*Results reflect a pooled analysis of PSUMMIT 1 and 2, as *a priori* pre-defined

Conclusion:

UST, APR and SEC are new drugs with efficacy demonstrated for the treatment of PsA. No major safety signals arise, but long-term studies are needed. Studies with new TNFi confirm the efficacy of these drugs. Treatment set to a therapeutic target achieves better outcome than non-targeted therapy. This review informs the update of the EULAR recommendations for the management of PsA.

Disclosure: S. Ramiro, None; **J. S. Smolen**, Consultant for: AbbVie Inc., Amgen, AstraZeneca, Astro, BMS, Celgene, Centocor-Janssen, Glaxo, Lilly, Pfizer, MSD, Novo-Nordisk, Roche, Samsung, Sandoz, and UCB, 5; **R. B. M. Landewé**, Consultant for: AbbVie, Amgen, AstraZeneca, Augurex, BMS, Boehringer Ingelheim, Celgene, Centocor, Chugai, Covagen, Daiichi, Eli-Lilly, Galapagos, GSK, Janssen Biologics, Merck, Novartis, Novo-Nordisk, Otsuka, Pfizer, Roche, Sanofi-Aventis, UCB, Vertex Di, 5; **D. van der Heijde**, Consultant for: AbbVie, Amgen, AstraZeneca, Augurex, BMS, Boehringer Ingelheim, Celgene, Centocor, Chugai, Covagen, Daiichi, Eli-Lilly, Galapagos, GSK, Janssen Biologics, Merck, Novartis, Novo-Nordisk, Otsuka, Pfizer, Roche, Sanofi-Aventis, UCB, Vertex Di, 5; **M. Dougados**, Consultant for: AbbVie, Pfizer, UCB, Novartis, Sanofi, Lilly, Merck, BMS, 5; **P. Emery**, Abbvie, Pfizer, MSD, UCB, Roche, Novartis, BMS, 5; **M. de Wit**, Consultant for: AbbVie, BMS, Celgene, Eli-Lilly, Novartis, Roche, 5; **M. Cutolo**, Consultant for: BMS, Actelion, Celgene, Celltrion, Horizon, Mundipharm, 5; **S. Oliver**, Consultant for: AbbVie, MSD, Pfizer, Regeneron, Roche and UCB, 5; **L. Gossec**, Consultant for: Abbvie, Amgen, Celgene, Chugai, Janssen, MSD, Novartis, Pfizer, Regeneron, Roche and UCB, 5.

Abstract Number: 2874

Two-Years Survival of Golimumab in Patients with Rheumatoid Arthritis, Psoriatic Arthritis, and Axial Spondyloarthritis and Predictors Thereof in Real-Life Settings

Leonardo Santo[1], Angelo Semeraro[2], Carmelo Zuccaro[3], Maria Grazia Anelli[4], Romano Bucci[5], Antonio Marsico[6], Laura Quarta[7], Giorgio Carlino[8], Francesco Paolo Cantatore[9], Annamaria Gaudio[10], Fabio Cacciapaglia[11], Oriana Casilli[12], Paola Chiara Francesca Falappone[13] and Florenzo Iannone[14], [1]DSS4 Barletta, ASL BT Andria - Rheumatology Service, Barletta, Italy, [2]Unità Operativa di Reumatologia ASL Taranto, Taranto, Italy, [3]U.O.of Geriatrics, Outpatient clinic of Rheumatology, Brindisi, Italy, [4]DIM, Rheumatology Unit, Bari, Italy, [5]A.O.U., Rheumatology Hospital Unit, Foggia, Italy, [6]Outpatient clinic of Rheumatology, Taranto,, Italy, [7]Department of Rheumatology, "V.Fazzi" Hospital, San Cesario di Lecce, Italy, [8]ASL LE - DSS Casarano and Gallipoli, Rheumatology Service, Gallipoli, Italy, [9]Department of Rheumatology, University of Foggia,, Foggia, Italy, [10]Department of Rheumatology, University of Foggia, Foggia, Italy, [11]Internal Medicine Unit and Outpatient clinic of Rheumatology, “N. Melli” Hospital, San Pietro Vernotico (BR), Italy, [12]Department of Rheumatology, "Vito Fazzi" Hospital, San Cesario di Lecce, Italy, [13]Internal Medicine Unit - Outpatient clinic of Rheumatology,, "S. Camillo de' Lellis" Hospital, Mesagne (BR), Italy, [14]Interdisciplinary Department of Medicine (DIM), Rheumatology Unit, University of Bari, Bari, Italy

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Background/Purpose:

It has previously been shown that the survival of anti-TNF drugs was lower in Rheumatoid arthritis (RA) than in other chronic arthritis[1]. The objective of this study was to investigate the drug retention of Golimumab (GOL) and its effectiveness in patients affected with axial Spondyloarthritis (AxSpA), Psoriatic arthritis (PsA) and RA. Furthermore, the impact of possible baseline predictors was also evaluated.

Methods:

This is a multicenter prospective observational study of unselected patients with AxSpA, PsA and RA starting GOL because of their active disease despite prior treatment with conventional disease modifying drugs (DMARDs) or biological DMARDs (bDMARDs) in the settings of standard care from 11 rheumatologic centres of Apulia (Southern Italy). The primary endpoint was GOL drug retention at 2 years. A secondary endpoint was clinical outcomes based on DAS28 and BASDAI reduction. Time to discontinuation was defined as the time between drug initiation and last administration plus one dispensation interval. Kaplan-Meier curve analysis was used to assess drug retention, and a Cox proportional regression model, adjusting for potential confounders, including prior bDMARD exposure, patient demographics and disease characteristics, for the analysis of predictors.

Results: To date, 357 patients (PsA 154, AR 80, AxSpA 123) have been enrolled, 151 (42.3%) were “biologic-naïve”. Disease duration was 6.7 ±6 yrs for PsA, 8.1 ±7 for RA, and 7.0 ±6 for AxSpA, respectively. At 2 years (Fig.1), the crude survival rate was 74.8% (21.1 ± 0.5 months) for AxSpa, 67.5% (20.2 ± 0.8 months) for RA and 63.6% (18.8 ± 0.6 months) for PsA, being the difference not statistically significant. Analysis of predictors showed that female gender strongly correlated with GOL discontinuation (hazard ratio (HR) (95% CI): 3.82, (1.54-9.51)), while the lack of extra-articular manifestations was a negative predictor (HR (95% CI): 0.21, (0.49-0.91) for AxSpA patients. No predictors of drug survival for RA and PsA were found. Additionally, GOL was effective in all patients with a significant reduction of DAS28 and BASDAI at 12 and 24 months compared to baseline (Table 1).

Conclusion:

Unlike previous studies on TNF inhibitors, GOL seems to have similar drug survival in different chronic arthritides regardless of prior bDMARD treatment. Female AxSpA patients with extra-articular manifestations have higher hazard to discontinue the therapy .

REFERENCES:

1. Carmona L. et al. Arthritis Res Ther 2006; 8:3, R72

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Abstract Number: 2875

Anti-TNF Therapy Is Not Associated with an Increase in Neoplasias in Patients with Spondyloarthritis (SpA): Results from the GISEA Registry

Fabiola Atzeni[1], Antonio Carletto[2], Marco Sebastiani[3], Valentina Panetta[4], Fausto Salaffi[5], Florenzo Iannone[6], Elisa Gremese[7], Marcello Govoni[8], Antonio Marchesoni[9], Roberto Gorla[10], Roberta Ramonda[11], Pier Carlo Sarzi-Puttini[12], Gianfranco Ferraccioli[7], Giovanni Lapadula[13] and on behalf of GISEA group, [1]Rheumatology Unit, L. Sacco University Hospital of Milan, Milan, Italy, [2]Rheumatology Unit, University of Verona, Verona, Italy, [3]SC Reumatologia, Dipartimento di Medicine, Medicina d'Urgenza e Specialità Mediche, Azienda Ospedaliero-Universitaria di Modena, Modena, Italy, [4]L'altrastatistica -Consultancy & Training-Biostatistics office., Rome, Italy, [5]Rheumatology Department, Polytechnic University of Marche, C. Urbani Hospital, Jesi,, Ancona, Italy, [6]Interdisciplinary Department of Medicine (DIM), Rheumatology Unit, University of Bari, Bari, Italy, [7]Division of Rheumatology, Institute of Rheumatology, Catholic University of the Sacred Heart, Rome, Italy, [8]Department of Medical Sciences, UOC of Rheumatology, Azienda Ospedaliero-Universitaria S. Anna-Ferrara, University of Ferrara, Cona Ferrara, Italy, [9]Rheumatology Unit, Orthopedic Institute G. Pini, Milano, Italy, [10]Rheumatology and Immunology Unit, Spedali Civili di Brescia, Brescia, Italy, [11]Cattedra, Voc Rheumatology, University of Padua, Padova, Italy, [12]Rheumatology Unit, L. Sacco University Hospital, Milan, Italy, [13]Bari University, Rheumatology, Bari, Italy

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Session Time: 9:00AM-11:00AM

Background/Purpose: The use of TNF inhibitors (TNFIs) has led to efficient control of the signs and symptoms of SpA and rheumatoid arthritis (RA), and significantly improved the patients' quality of life. However, as most patients need often indeterminately long-term treatment (especially those with SpA), rheumatologists must be aware of treatment side effects such as malignances, even though nine clinical trials of etanercept in SpA patients did not find an increased risk. The aim of this study was to evaluate the risk of malignances in the TNFI-treated SpA patients in the Gruppo Italiano Studio Early Arthritis(GISEA) Registry, and assess predictors of malignancies

Methods: The Registry, which is designed to collect real-world clinical data concerning RA and SpA patients receiving biological drugs as part of routine care, was approved by local Ethics Committees, and enrols patients aged ≥18 years who have given their written informed consent. The baseline information includes demographics, disease duration, HAQ, DAS-28, BASDAI, BASFI and BASMI scores, steroid use (defined as actively receiving oral steroids at the time of recruitment), smoking history and comorbidities.

Results:

The analysis involved 3321 SpA patients (1731 males, 52.2%; mean age 47±13 years; median disease duration three years, interquartile range [IQR] 0, 8 years): 1065 (32%) treated with infliximab (IFN), 1052 (32%) with adalimumab (ADA), and 1204 (36%) with etanercept (ETN). Two thousand, one hundred and five (63.4%) had a median of one comorbity (IQR 0, 2], the most frequent being hypertension (701), thyroid diseases (281), diabetes mellitus (207), cardiopathy (189), and osteoporosis (145). In combination with the biological drug, 919 patients (27.7%) received steroids and 2451 (79.9%) at least one DMARD. The median follow-up time was three months (IQR 12 years). During 12 years of TNFI treatment, 50 patients experienced at least one of 56 neoplasias, 28% of which occurred during the first 12 months. Overall incidence was 6.3/1000 patient-years of follow-up (95% CI 4.7–8.2): 7.3/1000 (95% CI 4.1–11.8) among those treated with ADA; 6.1/1000 (95% CI 3.8–9.4) among those treated with ETN; and 5.8/1000 (95% CI 3.5–9.1) among those treated with IFN. Univariate analysis showed that age at the start of anti-TNF treatment (p=0.001), the number of comorbidities (p<0.001), and HAQ score (p=0.002) were associated with a high risk of malignancy. Multivariate models showed that male gender (hazard ratio [HR] 4.5, 95%CI1.3-16.0; p=0.020), age at the start of anti-TNF treatment (HR 1.1, 95%CI 1.01-1.11; p=0.020), and HAQ score (HR 2.8, 95%CI1.5-5.3; p=0.002) were statistically significant predictors of malignances. Ten of the 50 patients experiencing a neoplasia had had a previous solid cancer (HR 11.2, 95%CI 4.4-28.4; p<0.001).

Conclusion: TNFI therapy is not associated with a significant overall risk of malignances in SpA patients, but having had a previous solid cancer is predictive of a new neoplasia.

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Abstract Number: 2876

Baseline Demographic and Disease Characteristics Associated with Response to Golimumab in Patients with Active Nonradiographic Axial Spondyloarthritis

Maxime Dougados[1], Gina Bergman[2], Walter Maksymowych[3], Sean P. Curtis[2], Susan Huyck[2], Anjela Tzontcheva[2] and Joachim Sieper[4], [1]Paris-Descartes University, Paris, France, [2]Merck & Co., Inc., Kenilworth, NJ, [3]University of Alberta, Edmonton, AB, Canada, [4]University Clinic Benjamin Franklin, Berlin, Germany

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SESSION INFORMATION

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Session Title: Spondylarthropathies and Psoriatic Arthritis - Clinical Aspects and Treatment Poster III: Therapy

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Background/Purpose: Subgroup analyses can be used to investigate the size and direction of treatment effects across a range of demographic and disease characteristics. The purpose of this study was to explore response consistency in subgroups of patients with nonradiographic axial spondyloarthritis (nr-axSpA) who received golimumab (GLM) or placebo for 16 wks.

Methods: GO-AHEAD was a double-blind, randomized, placebo (PBO)-controlled trial of GLM in patients with active nr-axSpA (ASAS criteria and centrally read sacroiliac (SI) joint X-rays and MRIs; disease duration ≤5 years; chronic back pain; high disease activity [total back pain ≥40 mm on a 0–100 mm Visual Analogue Scale and BASDAI ≥4 cm]; and inadequate response/intolerance to NSAIDs). Patients were randomized 1:1 to subcutaneous GLM 50 mg or PBO every 4 wks. Estimated between-group treatment differences and 95% CIs for ASAS 20 and ASAS 40 response at wk 16 were calculated for prespecified patient subgroups. Treatment and subgroup differences were compared by stratified Miettinen–Nurminen methods with baseline inflammation by SI joint MRI and screening C-reactive protein (CRP) level as stratification factors. No multiplicity control was applied.

Results: A total of 197 patients were treated (GLM=97; PBO=100). Overall, ASAS 20 at wk 16 was achieved by 71.1% of GLM patients and 40.0% of PBO patients (P <.0001). Although size of response differed somewhat across the subgroups, responses were greater to GLM than PBO in most patient subgroups (P<.05; Table). Because of the small numbers of patients within subgroups and because subgroups may not represent randomized samples, results should be considered exploratory and interpreted with caution. Treatment group differences appeared to be larger in patients with objective signs of inflammation (MRI SI or CRP>ULN). The results for ASAS 40 were very similar to those for ASAS 20.

Table. ASAS 20 Attainment at Week 16 by Treatment Group and Baseline Characteristics			
Subgroup	**GLM n/N (%)**	**PBO n/N (%)**	**Difference vs PBO[a] % (95% CI)**
Gender			
Female	21/36 (58.3)	20/48 (41.7)	14.8 (–6.9, 35.4)
Male	48/61 (78.7)	20/52 (38.5)	40.0 (21.8, 55.6)
Age			
≤30 years	41/56 (73.2)	16/45 (35.6)	39.6 (20.4, 56.0)
>30 years	28/41 (68.3)	24/55 (43.6)	26.1 (5.6, 43.7)
Disease duration			
>median	38/48 (79.2)	18/51 (35.3)	43.3 (24.1, 59.3)
≤median	31/49 (63.3)	22/49 (44.9)	18.2 (–1.4, 36.3)
HLA-B27			
Negative	8/16 (50.0)	7/18 (38.9)	11.1 (–23.3, 43.5)
Positive	61/81 (75.3)	33/82 (40.2)	35.0 (20.2, 48.2)
MRI sacroiliitis			
Yes	48/65 (73.8)	25/66 (37.9)	36.0 (19.3, 50.7)
No	21/32 (65.6)	15/34 (44.1)	21.6 (–2.6, 43.0)
CRP			
≤ULN	35/58 (60.3)	25/59 (42.4)	17.9 (–0.3, 35.0)
>ULN	34/39 (87.2)	15/41 (36.6)	50.6 (30.5, 66.6)
MRI sacroiliitis (+) or CRP >ULN	60/78 (76.9)	30/80 (37.5)	39.6 (24.6, 52.6)
MRI sacroiliitis (–) and CRP ≤ULN	9/19 (47.4)	10/20 (50.0)	–2.6 (–32.7, 27.9)
[a]Differences derived from the statistical model.			

Conclusion: Overall, patients with active nr-axSpA who received GLM were more likely to achieve ASAS 20 at wk 16 than those treated with PBO across a variety of baseline characteristics, including those with baseline objective signs of inflammation (eg, MRI SI or CRP >ULN).

Disclosure: M. Dougados, AbbVie, Lilly, Novartis, Pfizer, Roche, Sanofi, UCB, 2; **G. Bergman**, Merck & Co., Inc., Kenilworth, NJ, USA, 3,Merck & Co., Inc., Kenilworth, NJ, USA, 1; **W. Maksymowych**, AbbVie, Janssen, Pfizer, 2,AbbVie, UCB, Pfizer, Merck, Janssen, Eli Lilly, Celgene, Synarc, 5; **S. P. Curtis**, Merck & Co., Inc., Kenilworth, NJ, USA, 3,Merck & Co., Inc., Kenilworth, NJ, USA, 1; **S. Huyck**, Merck & Co., Inc., Kenilworth, NJ, USA, 3,Merck & Co., Inc., Kenilworth, NJ, USA, 1; **A. Tzontcheva**, Merck & Co., Inc., Kenilworth, NJ, USA, 3,Merck & Co., Inc., Kenilworth, NJ, USA, 1; **J. Sieper**, AbbVie, Eli Lilly, Janssen Biologics, Merck, Novartis, Pfizer, Roche, UCB, 5.

Abstract Number: 2877

What Is the Location of Enthesitis in Ankylosing Spondylitis and Psoriatic Arthritis Patients and How Do They Respond to Anti-TNF Treatment?

John Kelsall[1], Denis Choquette[2], Proton Rahman[3], Regan Arendse[4], Michelle Teo[5], Isabelle Fortin[6], J Antonio Avina-Zubieta[7],

Emmanouil Rampakakis[8,9], Eliofotisti Psaradellis[9], Karina Maslova[10], Brendan Osborne[11], Cathy Tkaczyk[11], Francois Nantel[12] and Allen J Lehman[10], [1]Mary Pack Arthritis Centre, Vancouver, Vancouver, BC, Canada, [2]Rheumatology Department, Institut de Rhumatologie de Montréal and University of Montreal, Montreal, QC, Canada, [3]Medicine, Memorial University, St John's, NF, Canada, [4]University of Saskatchewan, Saskatoon, SK, Canada, [5]Rheumatology, Penticton Regional Hospital, Penticton, BC, Canada, [6]Centre de Rhumatologie de l'Est du Québec, Rimouski, QC, Canada, [7]Arthritis Research Canada, Richmond, BC, Canada, [8]JSS Medical Research, St-Laurent, QC, Canada, [9]JSS Medical Research, Montreal, QC, Canada, [10]Janssen Inc., Toronto, ON, Canada, [11]Medical Affairs, Janssen Inc., Toronto, ON, Canada, [12]19 Green belt Dr, Janssen Inc., Toronto, ON, Canada
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Background/Purpose:

Enthesitis is characterized by inflammation at the insertion of ligaments, tendons, joint capsule, or fascia to bone, and represents a well-known characteristic feature of ankylosing spondylitis (AS) and related spondyloarthropathies.

Methods:

BioTRAC is an ongoing, prospective registry of patients initiating treatment for rheumatoid arthritis, AS, or psoriatic arthritis (PsA) with infliximab (IFX) or golimumab (GLM). Eligible people for this analysis included AS and PsA patients treated with IFX who were enrolled since 2005 or with GLM enrolled since 2010 who had available information on enthesitis. The paired sampled t-test was used to compare the enthesitis count at baseline and 12 months.

Results:

A total of 260 AS patients and 261 PsA patients were enrolled with a mean (SD) age at baseline of 46.1 (13.0) vs. 50.0 (12.0) years, respectively, and disease duration of 6.4 (9.8) vs. 5.2 (6.8) years. Among patients with AS, 28.1%, 21.7%, 22.4% had enthesitis at baseline, 6 months and 12 months, respectively. For PsA these numbers were 32.2%, 19.7%, and 22.6%, respectively. The presence of enthesitis by anatomical site and visit are described in Table 1 with higher proportions observed for the greater trochanter (GT) in AS patients and the lateral epicondyle humerus (LEH) in PsA patients.

Table 1: Presence of Enthesitis by Anatomical Site

	AS			PsA		
	Baseline (N=260)	6 Months (N=203)	12 Months (N=134)	Baseline (N=261)	6 Months (N=189)	12 Months (N=133)
LEH, %	10.8	6.9	7.5	16.1	8.5	6.8
MEH, %	8.1	5.9	4.5	12.6	7.4	6.8
PA, %	10.8	5.4	3.0	13.0	6.4	6.8
GT, %	14.2	8.4	10.4	10.7	9.0	6.0
IPF, %	7.7	3.4	4.5	11.9	5.3	3.8
SI, %	11.5	8.9	7.5	10.7	8.0	8.3
QIP, %	6.9	3.9	1.5	9.6	5.9	6.0
PATT, %	6.9	4.4	1.5	13.8	5.9	8.3

LEH: Lateral epicondyle humerus; MEH: Medial epicondyle humerus; PA: Proximal achilles; GT: Greater trochanter; IPF: Insertion plantar fascia; SI: Suprapsinatus insertion; QIP: Quadriceps insertion patella; PATT: Inferior pole patella or tibial tubercle

Presence of enthesitis in all anatomical sites was significantly associated with higher HAQ among AS and PsA patients. The mean (SD) enthesitis count at baseline and 12 months was 4.4 (3.4) vs. 2.6 (2.3) (P=0.061) among AS patients and 5.0 (3.8) vs. 3.8 (3.0) (P=0.006) in PsA patients, respectively.

Conclusion: A considerable proportion of PsA and AS patients had enthesitis at anti-TNF initiation in this Canadian real-world cohort. Overall, presence of enthesitis was associated with significantly higher functional disability. Treatment with IFX or GLM for 12 months was associated with significant reduction in the mean enthesitis count.

Disclosure: J. Kelsall, Janssen Inc., 5; **D. Choquette**, Janssen Inc., 5,AbbVie, 5,Amgen, 5,Celgene, 5,BMS, 5,Pfizer Inc, 5; **P. Rahman**, None; **R. Arendse**, Janssen Inc., 5; **M. Teo**, Janssen Inc., 5; **I. Fortin**, Janssen Inc., 5; **J. A. Avina-Zubieta**, None; **E.**

Rampakakis, JSS, 3; **E. Psaradellis**, JSS Medical Research, 3; **K. Maslova**, Janssen Inc., 3; **B. Osborne**, Janssen Inc., 3; **C. Tkaczyk**, Janssen Inc., 3; **F. Nantel**, Janssen Inc., 3; **A. J. Lehman**, Janssen Inc., 3.

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Abstract Number: 2878

Treating Axial Spondyloarthritis to Target: Influence of the Population Characteristics and Comorbidities in Reaching Ankylosing Spondylitis Disease Activity Score (ASDAS) Inactive Disease in a Cohort of Patients Treated with Tnfalpha Inhibitors Agents

Sara Monti, Veronica Codullo, Vittorio Grosso, Silvia Breda, Carlomaurizio Montecucco and Roberto Caporali, Division of Rheumatology, University of Pavia, IRCCS Foundation Policlinico S. Matteo, Pavia, Italy

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Session Time: 9:00AM-11:00AM

Background/Purpose: The treat to target strategy (T2T), aiming at inactive disease (ID), has become the recommended approach also in the field of axial-SpA (axSpA) (1). Using the composite disease activity index "*Ankylosing Spondylitis Disease Activity Score*" (ASDAS) we assessed the real life feasibility of the T2T strategy in our cohort of axSpA patients treated with TNFα inhibitors (TNFi). We analyzed potential differences among the Ankylosing Spondylitis (AS) and the non-radiographic Ax-SpA (nr-ax-SpA) group and the influence of the population characteristics and comorbidities in reaching ID.

Methods: The study population was selected from outpatients with axSpA on a stable TNFi treatment for at least 6 months. Disease activity was cross-sectionally evaluated in terms of BASDAI and ASDAS-CRP during the latest follow up visit. ID was defined as ASDAS-CRP< 1.3. Extra-articular manifestations and comorbidities were assessed. Statistical analysis performed with STATA.

Results: General characteristics of the 125 enrolled patients are presented in Table 1. Female sex, prevalence of fibromyalgia and frequency of concomitant DMARDs were significantly more represented in the nr-ax-SpA group. On the other hand, the time from TNFi initiation was significantly shorter in nr-ax-SpA. ASDAS-CRP ID was reached by n=51 (40.8%) of our population, while a good disease control would have been reached by n=89 (71.2%) of patients in terms of BASDAI. There were no differences in the two groups, with a slightly higher prevalence of ID in the nr-ax-SpA group not reaching statistical significance (Figure 1). Multivariate logistic regression demonstrated a negative correlation of fibromyalgia (OR 0.14; CI95% 0.02-0.77), higher *Bath Ankylosing Spondylitis Metrology Index* (BASMI) (OR 0.6; CI95% 0.41-0.89) and number of previous TNFi (OR 0.36; CI95% 0.15-0.89) with the chances of reaching ID. ID achievement resulted independent from sex, age, disease duration, DMARDs, NSAIDs and other comorbidities.

Conclusion: The recommended T2T strategy represents a new challenge in the management of ax-SpA, with recently introduced methods of measuring disease activity being significantly more stringent. The prevalence of ID was not influenced by the type of disease (nr-Ax-SpA Vs AS) but was significantly influenced by the presence of concomitant fibromyalgia, decreased spine mobility and the previous number of TNFi lines of treatment.

References

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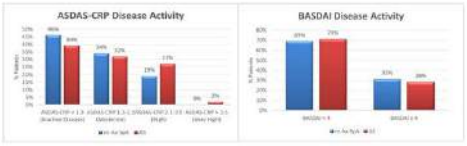
Figure 1. Differences in Disease activity (ASDAS-CRP and BASDAI) among nr-ax-SpA and AS patients.

Table 1. General characteristics of the study population

Variable (Number / Mean ± SD, %)	Total	Nr-AxSpA	AS	P
Total number of patients	125	26 (20.8%)	99 (79.2%)	
Male	72 (57.6%)	8 (30.7%)	64 (64.6%)	0.002
Female	53 (42.4%)	18 (69.2%)	35 (35.3%)	
Age at symptoms onset	36.3 (± 12)	38.6 (± 11)	35.7 (± 12)	Ns
Age at diagnosis	39.4 (± 13)	41.2 (± 12)	39.1 (± 13)	Ns
Disease duration (years)	10.3 (± 8)	8.9 (± 8)	10.6 (± 8)	Ns
Extra-articular involvement*	62 (49.6%)	11 (42.3%)	51 (51.5%)	Ns
Comorbidities **	73 (58.4%)	12 (46.1%)	61 (61.6%)	Ns
Fybromyalgia	25 (20%)	14 (53.8%)	11 (11.1%)	< 0.0001
Previous TNFi	27 (29.6%)	4 (15.3%)	33 (33.3%)	Ns
Concomitant NSAIDs intake	74 (59.2%)	14 (53.8%)	60 (60.6%)	Ns
DMARD combination therapy	62 (49.6%)	18 (69.2%)	44 (44.4%)	0.024
Time from anti-TNFα treatment initiation (months)	34.7 (±30)	19.4 (± 11)	38.8 (± 32)	0.001

*Extra-articular involvement: uveitis, psoriasis, enthesitis, dactylitis, IBD; ** Comorbidities: mainly cardiovascular, diabetes, pulmonary



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Conflict of interest and financial funding: NONE

Disclosure: S. Monti, None; **V. Codullo**, None; **V. Grosso**, None; **S. Breda**, None; **C. Montecucco**, None; **R. Caporali**, UCB Pharma, Roche, 8,AbbVie, Pfizer Inc, MSD, 5.

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Abstract Number: 2879

What Is the Location of Dactylitis in Ankylosing Spondylitis and Psoriatic Arthritis Patients and How Do They Respond to Anti-TNF Treatment?

Regan Arendse[1], Proton Rahman[2], Denis Choquette[3], J Antonio Avina-Zubieta[4], Michel Zummer[5], Milton F. Baker[6], Jacqueline Stewart[7], Isabelle Fortin[8], Michelle Teo[9], Emmanouil Rampakakis[10], Eliofotisti Psaradellis[11], Brendan Osborne[12], Cathy Tkaczyk[12], Karina Maslova[13], Francois Nantel[14] and Allen J Lehman[13], [1]University of Saskatchewan, Saskatoon, SK, Canada, [2]Computer Sciences, Memorial University of Newfoundland, St. John's, NF, Canada, [3]Rheumatology Department, Institut de Rhumatologie de Montréal and University of Montreal, Montreal, QC, Canada, [4]Medicine, University of British Columbia, Department of Medicine, Division of Rheumatology, Vancouver, BC, Canada, [5]Rheumatology, Hôpital Maisonneuve-Rosemont and University of Montreal, Montreal, QC, Canada, [6]VIHA, Victoria, BC, Canada, [7]Penticton Regional Hospital, Penticton, BC, Canada, [8]Centre de Rhumatologie de l'Est du Québec, Rimouski, QC, Canada, [9]Rheumatology, Penticton Regional Hospital, Penticton, BC, Canada, [10]JSS Medical Research, St-Laurent, QC, Canada, [11]JSS Medical Research, Montreal, QC, Canada, [12]Medical Affairs, Janssen Inc., Toronto, ON, Canada, [13]Janssen Inc., Toronto, ON, Canada, [14]19 Green belt Dr, Janssen Inc., Toronto, ON, Canada
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Background/Purpose: Dactylitis is one of the most commonly reported features in spondyloarthritis. It has been hypothesized that dactylitis is a functional enthesitis at the proximal interphalangeal joints, resulting in synovitis, tenosynovitis, bone and soft tissue

oedema to the digit, and may simultaneously involve more than one digit.

Methods: BioTRAC is an ongoing, prospective registry of patients initiating treatment for rheumatoid arthritis (RA), ankylosing spondylitis (AS), or psoriatic arthritis (PsA) with infliximab (IFX) or golimumab (GLM). Eligible people for this analysis included AS and PsA patients treated with IFX who were enrolled since 2005 or with GLM enrolled since 2010 who had available information on dactylitis. The McNemar (paired Chi-square) test was used to compare the presence of dactylitis over time.

Results: A total of 260 AS patients and 261 PsA patients were enrolled with a mean (SD) age at baseline of 46.1 (13.0) vs. 50.0 (12.0) years, disease duration of 6.4 (9.8) vs. 5.2 (6.8) years, and proportion of females 40.6% vs. 48.5%, respectively. Among patients with AS, dactylitis was reported in 6.2% and 2.2% of patients at baseline and 6 months, respectively; at 6 months of treatment 73.3% of AS patients with dactylitis at baseline had no dactylitis and 1.6% developed dactylitis (P=0.057). For PsA higher proportions of dactylitis were observed with 30.7%, and 12.7%, respectively; at 6 months of treatment 69.0% of PsA patients with dactylitis at baseline had no dactylitis and 4.6% developed dactylitis (P<0.001). The distribution of dactylitis amongst digits is described in Table 1 with the highest prevalence observed for feet in AS and PsA patients.

Table 1: Distribution of Dactylitis amongst Digits in AS and PsA

	AS		PsA	
	Baseline (N=260)	6 Months (N=207)	Baseline (N=261)	6 Months (N=189)
HD1, %	1.9	0.5	4.2	2.6
HD2, %	3.1	1.0	9.2	5.3
HD3, %	3.1	2.4	8.0	5.3
HD4, %	1.5	1.0	8.0	2.6
HD5, %	1.5	1.4	5.4	3.2
FD1, %	2.7	0.5	8.0	1.1
FD2, %	3.8	0.5	12.6	3.7
FD3, %	2.3	0.5	11.1	3.2
FD4, %	2.3	1.0	14.9	5.3
FD5, %	1.5	0.0	10.0	1.6

HD=hand digit; FD=foot digit

Presence of dactylitis in hands or feet (any digit) was associated with significantly higher HAQ in AS and PsA (AS: ΔHAQ=1.36 (P≤0.001); PsA: ΔHAQ=0.64 (P≤0.001)).

Conclusion: A considerable proportion of PsA patients had dactylitis at anti-TNF initiation in this Canadian real-world cohort. Although a lower proportion of patients had dactylitis among AS patients, the presence of dactylitis was associated with higher functional disability in both AS and PsA patients. Treatment with IFX or GLM for 6 months was associated with significant reduction in the prevalence of dactylitis.

Disclosure: R. Arendse, Janssen Inc., 5; **P. Rahman**, None; **D. Choquette**, Janssen Inc., 5,AbbVie, 5,Amgen, 5,Celgene, 5,BMS, 5,Pfizer Inc, 5; **J. A. Avina-Zubieta**, Janssen Inc., 5; **M. Zummer**, Janssen Inc, 5; **M. F. Baker**, Janssen Inc., 5; **J. Stewart**, Janssen Inc., 5; **I. Fortin**, Janssen Inc., 5; **M. Teo**, Janssen Inc., 5; **E. Rampakakis**, Bristol-Myers Squibb, 2; **E. Psaradellis**, JSS Medical Research, 3; **B. Osborne**, Janssen Inc., 3; **C. Tkaczyk**, Janssen Inc., 3; **K. Maslova**, Janssen Inc., 3; **F. Nantel**, Janssen Inc., 3; **A. J. Lehman**, Janssen Inc., 3.

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Abstract Number: 2880

Real-World Impact of Anti-TNF Medication Use on Patient Reported Outcomes in a Prospective Cohort of Patients with Ankylosing Spondylitis

Walter Maksymowych[1], Annelies Boonen[2], Helena Marzo-Ortega[3], Marina N. Magrey[4], Manish Mittal[5], Michael Halpern[6], Jeanette Renaud[6], Yanjun Bao[5] and Avani D. Joshi[5], [1]Medicine, University of Alberta, Edmonton, AB, Canada, [2]Maastricht University Medical Center, Maastricht, Netherlands, [3]LMBRU, Chapel Allerton Hospital, and University of Leeds, Leeds, United Kingdom, [4]Case Western Reserve University at MetroHealth Medical Center, Cleveland, OH, [5]AbbVie Inc., North Chicago, IL, [6]RTI International, Washington, DC

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Session Time: 9:00AM-11:00AM

Background/Purpose: Clinical trial results have demonstrated benefits of anti-TNF therapy in improving clinical outcomes, including overall health-related quality of life (HRQoL) in patients with ankylosing spondylitis (AS)[1]. We aimed to understand how consistency of anti-TNF use in the real-world impacts patient-reported outcomes, including measures of disease activity, functional impairment, depression, HRQoL, and work productivity.

Methods: A prospective Patient Reported Outcomes Survey of Employment in Patients with AS (PROSE-AS) was conducted at rheumatologists' practices in Canada, the Netherlands, the United Kingdom, and the United States. Patients ≥18 years of age completed surveys assessing sociodemographic and clinical characteristics, drug use, and several patient reported outcomes at 3 month intervals (12 months follow-up; 5 visits total). Anti-TNF history prior to the baseline visit was not assessed. Disease activity and functional impairment were assessed using the Bath AS Disease Activity Index (BASDAI) and Bath AS Functional Index (BASFI) scales, respectively; depression with the Center for Epidemiological Studies Depression (CES-D) scale; overall HRQoL with the Short Form 36 Health Survey (SF-36) and AS Quality of Life (ASQoL) questionnaires; and work outcomes with the Work Productivity and Activity Impairment (WPAI) questionnaire. Associations between anti-TNF use (occasional vs intermittent or continuous; defined as use in 1–2, 3–4, and 5 of 5 visits, respectively) and outcomes at 12 months were assessed with multivariable regression analyses, after controlling for baseline characteristics.

Results: Of 555 patients enrolled, 227 who had ≥1 visit with anti-TNF use during study period (20 occasional, 63 intermittent, and 144 continuous) were included in the analysis. Mean age was 46 years, 93.4% were white, and 30.8% were female. At baseline, mean AS duration was 14 years; mean BASDAI and BASFI scores were both 4.4; and mean SF-36 Physical Component Summary (PCS) and ASQoL scores were 37.3 and 8.2, respectively. Of the 227 anti-TNF users, 182 (8 occasional, 30 intermittent, and 144 continuous) were on anti-TNFs at baseline. Among 149 (65.6%) patients who were employed at baseline, 30 (20.1%) reported baseline absenteeism. At month 12, patients with intermittent or continuous anti-TNF use reported significantly better BASDAI, BASFI, SF-36 PCS, and ASQOL scores than patients with occasional use; they were also significantly less likely to be depressed and to report absenteeism (**Table**). Improvements were generally greater with increasing anti-TNF use.

Conclusion: In this real-world, multi-country, prospective study of patients with AS, continuous and intermittent vs occasional use of anti-TNF medication was associated with better clinical, psychological, and HRQoL outcomes, and lower absenteeism.

Reference:

1. van der Heijde D et al, *Rheumatology* (Oxford). 2014 Dec 25. pii: keu438.

Association Between anti-TNF Use Category and Outcome Variables at 12 Months[a]

Outcome Variables (Continuous)	Intermittent vs Occasional (β, 95% CI)	Continuous vs Occasional (β, 95% CI)
BASDAI Score (n=227, scale 0–10)	-1.33 (-2.27 to -0.39)[b]	-1.68 (-2.58 to -0.78)[b]
BASFI Score (n=227, scale 0–10)	-0.96 (-1.85 to -0.06)[b]	-1.09 (-1.95 to -0.23)[b]
SF-36		
(a) PCS Score (n=227, scale 0–100)	4.14 (-0.05 to 8.33)	5.87 (1.88 to 9.86)
(b) MCS Score (n=227, scale 0–100)	2.94 (-1.97 to 7.84)	2.96 (-1.67 to 7.6)
ASQoL Score (n=227, scale 0–18)	-3.17 (-5.05 to -1.3)[b]	-2.9 (-4.68 to -1.12)[b]
Outcome Variables (Categorical)	**Intermittent vs Occasional (OR, 95% CI)**	**Continuous vs Occasional (OR, 95% CI)**
CES-D (scale 0–60)		
Depressed (≥16, n=85) vs not depressed (<16, n=142)	0.11 (0.02 to 0.49)	0.11 (0.02 to 0.46)
WPAI		
(a) Absenteeism (n=30) vs no absenteeism (n=117)	0.05 (0.004 to 0.82)	0.06 (0.004 to 0.78)

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Abstract Number: 2881

Infliximab in Spondyloarthritis Patients: Utility of Drug Level Monitoring

(b) Presenteeism (n=121) vs no presenteeism (n=26)	0.23 (0.01 to 5.50)	0.14 (0.01 to 2.88)
(c) Overall work impairment (n=120) vs no overall work impairment (n=25)	0.23 (0.01 to 5.51)	0.14 (0.01 to 3.04)
(d) Activity impairment (n=206) vs no activity impairment (n=21)	1.09 (0.07 to 17.34)	0.56 (0.04 to 7.29)

[a]Results from multivariate regression adjusted for age, sex, race, country, education, number of comorbidities, use of NSAIDs and non-biologic DMARDs, AS duration, and outcome at baseline.

[b]Lower score indicates better outcome.

CI, confidence interval; DMARD, disease-modifying antirheumatic drug; MCS, Mental Component Summary; NSAID, non-steroidal antiinflammatory drug; OR, odds ratio; PCS, Physical Component Summary; β, regression coefficient.

Claudia Deaconu[1], Diana Mazilu[2], Laura Grosanu[2], Ioana Saulescu[2], Andreea Borangiu[2], Cecilia Gainaru[3], Cosmin Constantinescu[2], Violeta Bojinca[2], Violeta Vlad[1], Andra Balanescu[2], Denisa Predeteanu[2], Ruxandra Ionescu[2] and Daniela Opris[2], [1]Department of Internal Medicine and Rheumatology "Sf. Maria" Hospital, Bucharest, Romania, [2]University of Medicine and Pharmacy "Carol Davila", Department of Internal Medicine and Rheumatology "Sf. Maria" Hospital, Bucharest, Romania, [3]"Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania

First publication: September 29, 2015

SESSION INFORMATION

Session Date: Tuesday, November 10, 2015

Session Title: Spondylarthropathies and Psoriatic Arthritis - Clinical Aspects and Treatment Poster III: Therapy

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Spondyloarthritides, a heterogeneous group of chronic, inflammatory disorders with overlapping organ and joint targeting, share the same therapeutic approach in regard to biological therapy. Anti-tumor necrosis factor (anti-TNF) agents have highly proved their efficacy in lowering overall disease activity. However, a number of patients who initially responded to therapy fail to maintain a satisfactory disease evolution curve. Loss of response to TNF-inhibitors in spondyloarthritis (SpA) might be due to undetectable drug serum level. Determining infliximab (IFX) serum levels in SpA patients and adjusting dose or interval administration in a personalized manner might lead to a better disease outcome.

Methods: During a period of six months (January – June 2015), thirty-three consecutive patients with established SpA were enrolled in this study, while on regular hospital visit for IFX infusion. Patient data was gathered together with serum drug levels measured by enzyme linked immunosorbent assay (ELISA), using Progenika kits (Promonitor-IFX). The statistical analysis was performed using the SPSS statistical software, version 20.0, with a standardized p value of 0.05. Differences between groups were recorded with the aid of Student t-test, whereas Spearman test was used for correlations.

Results: Out of the 33 enrolled patients (90% males; mean age 37.8 years), all presented HLA B27 antigen positivity. Mean disease duration was 89 months (SD +/- 56). Detectable IFX serum levels were measured in 60% of patients (20 patients) while 40% (13 patients) had unmeasurable drug titers. The latter had significantly higher disease activity scores such as BASDAI (mean 3.01, p .023), ASDAS-ESR (mean 2.77, p .000) and ASDAS-CRP (mean 2.48, p .001) when compared to patients with detectable serum drug (1.52, 1.39 and 1.34 respectively). Inflammatory markers determined at the same visit showed higher ESR and CRP levels in IFX-negative patients (mean ESR 37 versus 9.5 with laboratory reference values ranging 2-20 mm/h, p .000; mean CRP 25 versus 4 with normal values between 0 to 5 mg/L, p.032). Serum IFX detection correlated to ASDAS scores (r -.583 p .000 for ASDAS-ESR; r -.512 p .002 for ASDAS-CRP) and to inflammatory biomarkers (r -.607 p .000 for ESR; r -.573 p .000 for CRP). In the IFX-positive group, mean drug persistence was of 64 (SD +/-32.5) months while lower for the IFX-negative group (45 months, SD +/- 21.7, p .066), the time frame being positively correlated to drug detection (r .352, p .045). Treatment persistence also correlated to disease duration (r .719, p .000). Dosage regimen was not significantly different between the two groups (5.11mg/kg in undetectable IFX group compared to 5mg/kg for the second group) and the maintenance drug administration interval, whether at 6 or 8 weeks, positively correlated to quantitative serum IFX levels.

Conclusion: In our study, IFX serum level correlated with patient's disease activity measured through ASDAS score. Moreover, correlations to inflammatory tests highlight their importance on follow-up visits. Monitoring IFX levels might represent a useful tool in assessing patients' evolution.

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Abstract Number: 2882

Baseline Extent of Damage at the Spine Predicts Radiographic Progression in Korean Patients Using Golimumab for Ankylosing Spondylitis

Jeong Seok Lee[1], Dae Young Yu[2], Stephen Xu[3] and Eun Young Lee[4], [1]Division of Rheumatology, Department of Internal Medicine, Seoul National University Hospital, Seoul National University Hospital, Seoul, South Korea, [2]Medical Affairs, Janssen Korea, Seoul, South Korea, [3]Janssen Research & Development, LLC, Spring House, PA, [4]Division of Rheumatology, Department of Internal Medicine, Seoul National University Hospital, Seoul, South Korea

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Session Time: 9:00AM-11:00AM

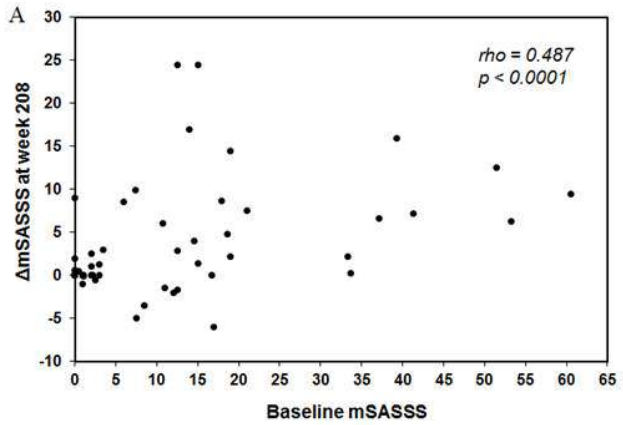
Background/Purpose: Ankylosing spondylitis (AS) is a chronic rheumatic disease associated with radiographic damage of the spine. Golimumab had consistent efficacy in controlling disease activity through 5 years but the benefit in preventing radiographic progression was obscure at 4-year. To predict radiographic progression, we analyzed baseline characteristics of AS patients in Korean population.

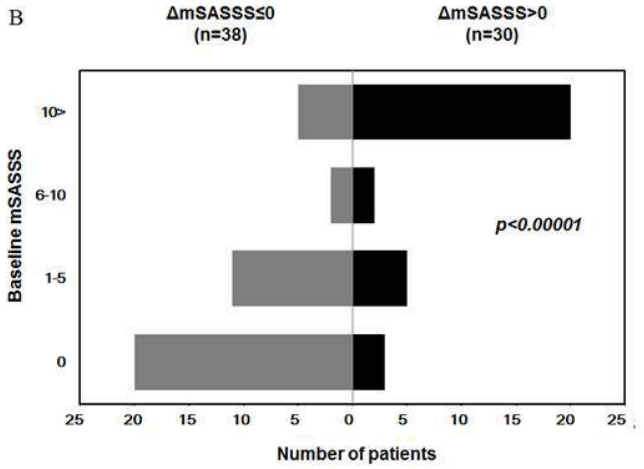
Methods: All 68 Korean patients with AS participated in the phase 3, multicenter, randomized, placebo-controlled, double-blind trial which was previously described. Radiographic evaluations were performed at baseline, week 104 and 208. Baseline modified Stoke AS spine score (mSASSS) and change in mSASSS from baseline (¥ÄmSASSS) were compared in the patients of Korea and other countries. Baseline characteristics were compared between the patients with ¥ÄmSASSS>0 and ¥ÄmSASSS°Â0. The correlation between baseline mSASSS and ¥ÄmSASSS was also analyzed.

Results: Korean patients had lower baseline mSASSS and maintained consistently higher retention rate to treatment (91.6% vs. 68.1%, p<0.0002) and assessment in AS partial remission rate (44.4% vs. 31.3%, p=0.036) till week 256 when compared to the patients in other countries. However, ¥ÄmSASSS was larger in Korean patients at week 104 and 208 without statistical significance. Korean patients who did not undergo radiographic progression of spinal lesion of AS were younger when diagnosed and had shorter symptomatic duration, lower Bath AS functional and metrology index, more chest expansion and lower baseline mSASSS. The baseline mSASSS and ¥ÄmSASSS had positive correlation in Korean AS patients (Spearman's rho= 0.487, p<0.0001) (Figure 1A). Radiographic progression was more prevalent (80%) when baseline mSASSS>10 and less common (13%) with baseline mSASSS=0 (Figure 1B).

Conclusion: Korean patients with AS receiving golimumab had distinctive patterns of spinal lesion progression detected by simple radiograph at week 208. This bipolar pattern of progression could be predicted reliably by the initial severity of spinal lesion. Given this result, this study implicated the value of early and active treatment before appearance of overt spinal damage.

Figure 1. Correlation between baseline mSASSS and ¥ÄmSASSS at week 208 (Spearman's rho) (A). Population distribution stratified by baseline mSASSS and ¥ÄmSASSS at week 208 analyzed by Freeman-Halton extension of the Fisher exact probability test (B).





Disclosure: J. S. Lee, None; **D. Y. Yu**, Janssen Korea Ltd., 3; **S. Xu**, Janssen Research & Development, LLC, 3; **E. Y. Lee**, None.

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Abstract Number: 2883

Relationship Between Improvements in Fatigue and Signs & Symptoms of Active Psoriatic: Arthritis a Sub-Analysis of a Phase 3 Study with Secukinumab

Laure Gossec[1], Tore K. Kvien[2], Philip G. Conaghan[3], Mikkel Østergaard[4], Juan D. Cañete[5], C. Gaillez[6], Shephard Mpofu[6], Bintu Sherif[7] and Steffen Jugl[8], [1]Rheumatology Department, Paris 06 University,Hôpital Pitié Salpêtrière, Paris, France, [2]Dept of Rheumatology, Diakonhjemmet Hospital, Oslo, Norway, [3]University of Leeds & NIHR Leeds Musculoskeletal Biomedical Research Unit, Leeds, United Kingdom, [4]Center for Rheumatology and Spine Diseases, Glostrup Hospital, Copenhagen Center for Arthritis Research (COPECARE), Center for Rheumatology and Spine Diseases, Rigshospitalet - Glostrup, University of Copenhagen, Denmark, Glostrup, Denmark, [5]Rheumatology, Hospital Clinic and IDIBAPS, Barcelona, Spain, [6]Novartis Pharma AG, Basel, Switzerland, [7]RTI Health Solutions, Durham, NC, [8]BF I&D GPA, Health Economics and Outcomes Research, Novartis Pharma AG, Basel, Switzerland
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Session Type: ACR Poster Session C
Session Time: 9:00AM-11:00AM

Background/Purpose: Fatigue is highly important to patients (pts) with psoriatic arthritis (PsA). Secukinumab, an anti-interleukin-17A monoclonal antibody, significantly improved the signs and symptoms of active PsA in the phase 3 FUTURE 2 study (NCT01752634).[1]Here we present the results of a post-hoc analysis assessing the impact of secukinumab on fatigue according to prior anti-tumor necrosis factor (anti-TNF) therapy status. The relationship between fatigue and baseline disease characteristics, as well as to other assessments of PsA response to therapy, are also presented.

Methods: Pts with active PsA were randomized to receive subcutaneous (s.c.) secukinumab (300 mg, 150 mg, or 75 mg) or placebo (PBO) at baseline, Wks 1, 2, 3, and 4, and every 4 wks thereafter. Fatigue was assessed at baseline and Wks 4, 8, 12, 16, and 24 using the Functional Assessment of Chronic Illness Therapy–Fatigue (FACIT-F) scale. Mean change in FACIT-F score from baseline up to Wk 24 was assessed using mixed model repeated measures analysis with visit, weight, and baseline FACIT-F score as covariates. A minimum clinically important difference (MCID) >4 was used to define fatigue response. A logistic regression model was used to investigate baseline predictors of FACIT-F improvement at Wk 16. The relationship between FACIT-F and ACR 20, PASI 75, PASI 90, DAS28-CRP low disease activity (LDA; ≤ 3.2) and remission (< 2.6), and Psoriatic Arthritis Response Criteria (PsARC) was assessed at Wks 8 and 16. The secukinumab 75 mg s.c. group was excluded from this analysis as it did not meet any pre-defined secondary endpoints.

Results: Of 298 pts included in this analysis, 193 were anti–TNF-naive and 105 anti–TNF-inadequate responders (IR). Mean changes from baseline in FACIT-F were improved with secukinumab 150 and 300 mg vs. placebo in both anti-TNF-naïve and anti-TNF-IR populations at the majority of timepoints up to Wk 24 with mean changes exceeding the MCID at all timepoints (Table). In a logistic

regression model of FACIT-F response at Wk 16, age was the only baseline factor found to be a significant covariate ($P<0.05$). ACR 20 responses correlated with improvements in FACIT-F at Wk 16; no relationship was seen between FACIT-F and PASI 75, PASI 90, DAS28-CRP, LDA and remission criteria, or PsARC.

Conclusion: Secukinumab improved fatigue in patients with active PsA regardless of prior anti-TNF therapy. A relationship between improvement in fatigue and improvements in the signs and symptoms of PsA was only shown for ACR 20 response and not for other assessments of disease. These results suggest that fatigue in PsA is not strongly related to disease activity but was still improved by secukinumab.

References:

1. McInnes IB, et al. ACR/ARHP Annual Meeting, Boston, MA, USA. November 14–19, 2014. Oral Presentation L1.

Table: Mean changes in FACIT-F in anti–TNF-naïve and anti–TNF-IR patients up to Week 24

Mean (± SD) Change from Baseline (p-value vs. placebo)	Week 4	Week 8	Week 12	Week 16	Week 24
Anti–TNF-naïve					
Secukinumab 300 mg (N = 67)	–4.42 ± 0.94 (0.2)	–5.14 ± 1.04 (0.047)	–5.51 ± 1.09 (0.02)	–6.18 ± 1.10 (0.009)	–5.13 ± 1.15 (0.098)
Secukinumab 150 mg (N = 63)	–5.51 ± 0.94 (0.04)	–5.72 ± 1.04 (0.02)	–7.67 ± 1.09 (0.0003)	–7.90 ± 1.11 (0.0003)	–8.17 ± 1.16 (0.001)
Placebo (N = 63)	–2.79 ± 0.93	–2.20 ± 1.05	–1.97 ± 1.10	–2.00 ± 1.13	–1.98 ± 1.50
Anti–TNF-IR					
Secukinumab 150 mg (N = 37)	–5.44 ± 1.25 (0.2)	–7.45 ± 1.40 (0.01)	–8.45 ± 1.52 (0.05)	–7.25 ± 1.63 (0.03)	–8.26 ± 1.60 (0.03)
Secukinumab 300 mg (N = 33)	–5.28 ± 1.33 (0.2)	–7.23 ± 1.47 (0.02)	–7.36 ± 1.61 (0.2)	–6.22 ± 1.73 (0.09)	–8.25 ± 1.68 (0.03)
Placebo (N = 35)	–3.10 ± 1.28	–2.25 ± 1.42	–4.07 ± 1.59	–2.05 ± 1.73	–2.23 ± 2.15

Disclosure: L. Gossec, UCB Pharma, 2,AbbVie, 5,Bristol-Myers Squibb, 5,Celgene, 5,Chugai, 5,Janssen, 5,Novartis, 5,Pfizer, 5,Roche, 5,UCB Pharma, 5,OMERACT Executive Commitee, 6; **T. K. Kvien**, AbbVie, BMS, MSD, Pfizer, Roche and UCB, 2,AbbVie, BMS, Celgene, Celltrion, Eli Lilly, Hospira, Merck-Serono, MSD, Novartis, Orion Pharma, Pfizer, Roche, Sandoz and UCB, 5; **P. G. Conaghan**, Abbvie, Merck, Roche, Pfizer, Novartis, and UCB, 5,Abbvie, Merck, Roche, Pfizer, Novartis, and UCB, 8; **M. Østergaard**, Abbvie, BMS, Boehringer-Ingelheim, Celgene, Eli-Lilly, Centocor, GSK, Hospira, Janssen, Merck, Mundipharma, Novartis, Novo, Orion, Pfizer, Regeneron, Schering-Plough, Roche, Takeda, UCB, and Wyeth, 5,Abbvie, BMS, Boehringer-Ingelheim, Celgene, Eli-Lilly, Centocor, GSK, Hospira, Janssen, Merck, Mundipharma, Novartis, Novo, Orion, Pfizer, Regeneron, Schering-Plough, Roche, Takeda, UCB, and Wyeth, 2; **J. D. Cañete**, Abbvie, Amgen, Celgene, Janssen-Cilag, Novartis, Novo Nordisk, Merck Sharpe & Dohme, and Pfizer, 5; **C. Gaillez**, Novartis Pharma AG, 3,Novartis Pharma AG, 1; **S. Mpofu**, Novartis AG, 3,Novartis AG, 1; **B. Sherif**, RTI Health Solutions, NC, USA, 3; **S. Jugl**, Novartis Pharma AG, 3,Novartis Pharma AG, 1.

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Abstract Number: 2884

Epidemiological Parameters Affecting Therapeutic Response in Psoriatic Arthritis Patients

Michail P. Migkos[1], George Somarakis[2], Evripidis Kaltsonoudis[3], Theodora E. Markatseli[4], Paraskevi V. Voulgari[5,6] and **Alexandros**

A. Drosos[7], [1]Rheumatology Clinic, Department of Internal Medicine, Medical School, University of Ioannina, 45110, Fellow in Rheumatology, Ioannina, Greece, [2]Rheumatology Clinic, Department of Internal Medicine, Medical School, University of Ioannina, 45110, University of Ioannina, Rheumatology Clinic, Ioannina, Greece, [3]Rheumatology Clinic, Department of Internal Medicine, Rheumatologist, Ioannina, Greece, [4]Rheumatology Clinic, Department of Internal Medicine, Fellow in Rheumatology, Ioannina, Greece, [5]Rheumatology Clinic, Department of Internal Medicine, Assistant Professor of Rheumatology, Ioannina, Greece, [6]Rheumatology Clinic, Department of Internal Medicine, Medical School, University of Ioannina, 45110, Assistant Professor of Rheumatology, Ioannina, Greece, [7]Rheumatology Clinic, Department of Internal Medicine, Medical School, University of Ioannina, 45110, Professor of Medicine/Rheumatology, Ioannina, Greece
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Session Title: Spondylarthropathies and Psoriatic Arthritis - Clinical Aspects and Treatment Poster III: Therapy
Session Type: ACR Poster Session C
Session Time: 9:00AM-11:00AM

Background/Purpose: Published data have shown that epidemiological parameters such as Body Mass Index (BMI), gender and disease duration may affect the therapeutic response in psoriatic arthritis patients receiving disease modifying antirheumatic drugs (DMARDs) conventional or biologic.

Methods: We retrospectively studied 260 patients diagnosed with psoriatic arthritis (PsA) fulfilling the Assessment of SpondyloArthritis international Society (ASAS) criteria for those with axial involvement and additionally the Classification Criteria for Psoriatic Arthritis (CASPAR) for those with peripheral joint involvement. We studied the effect of BMI, gender, disease duration, and treatment in therapeutic response. The patients were followed up at predefined time points (baseline, 6 months, 1 and 5 years). The treatment response was assessed by using Bath Ankylosing Spondylitis Activity Index (BASDAI), Bath Ankylosing Spondylitis Functionality Index (BASFI), Disease Activity Score in 28 joints-CRP (DAS28-CRP), Disease Activity Score in 28 joints -TKE (DAS28-TKE) and Health Assessment Questionnaire (HAQ). The patients were categorized in two groups according their treatment: group A patients treated with biological DMARDs (anti-TNFa agents) and group B patients treated with conventional DMARDs (methotrexate, leflunomide, cyclosporine).

Results: Disease duration was positively correlated in all time points ($p<0,005$) with all disease activity scores (BASDAI, BASFI, DAS28-CRP, DAS28-TKE and HAQ). Statistical significant differences with respect to gender were observed for DAS28-CRP (3,055 - 2,616 $p=0,015$) and DAS28-TKE (3,543 – 2,640 $p<0,0001$) at 6 months. More specifically, females showed significant higher DAS28-TKE and DAS28-CRP than males in all cases. BMI was not significantly correlated with the disease activity (BASDAI, BASFI, DAS-CRP, DAS-TKE, HAQ) at any time point. Finally the two treatment groups did not differ significantly with respect to disease activity scores at any time point.

Conclusion: In the current study longer disease duration was associated with higher disease activity. Females showed higher DAS28-CRP and DAS28-TKE scores than males early on the disease course. BMI as well as treatment options did not show any significant effect in the therapeutic response.

Disclosure: M. P. Migkos, None; **G. Somarakis**, None; **E. Kaltsonoudis**, None; **T. E. Markatseli**, None; **P. V. Voulgari**, None; **A. A. Drosos**, None.

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Abstract Number: 2885

Long-Term Effects of Etanercept on Patient-Reported Outcomes in Early Non-Radiographic Axial Spondyloarthritis: 104-Week Results of a Phase III Study

Filip van Den Bosch[1,2], Edit Drescher[3], Jan Rosa[4], Ronald Pedersen[5], Randi Bonin[6], Bonnie Vlahos[7], Jack F Bukowski[6] and Sameer Kotak[8], [1]Department of Rheumatology, Ghent University Hospital, Ghent, Belgium, [2]Rheumatology, Ghent University Hospital, Ghent, Belgium, [3]Csolnoky Ferenc Hospital, Veszprém, Hungary, [4]Mediscan Group, Prague, Czech Republic, [5]Department of Biostatistics, Pfizer, Collegeville, PA, [6]Clinical Affairs, Pfizer, Collegeville, PA, [7]GIPB - Clinical Sciences, Pfizer, Collegeville, PA, [8]Global Health and Value, Pfizer, New York, NY
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Session Time: 9:00AM-11:00AM

Background/Purpose: In patients with active, NSAID-resistant, non-radiographic axial spondyloarthritis (nr-axSpA) who participated in the multiphase, randomized, placebo (PBO)-controlled EMBARK study (ClinicalTrials.gov identifier: NCT01258738), health-related quality-of-life (HRQoL) and other patient-reported outcomes (PROs) were evaluated after 12 wks of double-blind (DB) etanercept (ETN) treatment[1] and 92 wks of open-label (OL) ETN.

Methods: Patients who fulfilled Assessment of SpondyloArthritis international Society classification criteria for axSpA, but not modified New York radiographic criteria for ankylosing spondylitis, and were unresponsive to ≥2 NSAIDs were randomized to receive ETN 50 mg/wk or PBO for 12 wks, followed by ETN 50 mg/wk to wk 104 (ETN/ETN or PBO/ETN). Background NSAID therapy was continued in all patients. Analyses of a binary endpoint (ie, minimal clinically important difference [MCID; ≥0.05] in EQ-5D utility score at wk 12) and continuous endpoints (changes from wk 0 to wk 12 and wk 104 in pain/fatigue [nocturnal back pain, MFI general fatigue], HRQoL [SF-36, ASQoL], utility [EQ-5D], and work productivity [WPAI-AS]) were conducted in the modified intent-to-treat (mITT) population (all patients with wk-12 efficacy data who continued into OL period, received ≥1 ETN dose in OL period, and had been included in DB mITT population) with observed cases. The Cochran-Mantel-Haenszel chi-square test was used for between-group comparisons of the binary endpoint; ANCOVA was used for between-group comparisons of continuous endpoints.

Results: Of 215 randomized patients (DB mITT), 205 patients entered the OL phase (ETN/ETN, n=100; PBO/ETN, n=105 [OL mITT]) and 169 patients completed it (n=83; n=86). Improvements from wk 0 to wk 12 in most pain/fatigue, HRQoL, utility, and work productivity assessments favored ETN versus PBO (table). In the OL phase, improving trends from wk 0 to wk 104 were observed in the ETN/ETN group, whereas improvements seen in patients who switched from PBO to ETN were comparable to or greater than those in the former group. At wk 12, significantly greater proportions of patients receiving ETN vs PBO achieved MCID in the EQ-5D utility score (59% [52/88] vs 45% [42/94]; $P<0.05$, between-groups); at wk 104, 76% (57/75) and 81% (64/79) of patients in the ETN/ETN and PBO/ETN groups achieved this endpoint.

Table. Long-term effects of ETN on PROs in patients with nr-axSpA in the EMBARK study*				
	Mean (SD) at Wk 0 / Mean (SE) D from Wk 0 to Wk 12		**Mean (SE) D from Wk 0 to Wk 104**	
Endpoint	**ETN**	**PBO**	**ETN/ETN**	**PBO/ETN**
Nocturnal back pain	5.5 (2.6) / –2.0† (0.4)	5.4 (2.5) / –0.9 (0.4)	–3.8 (0.4)	–3.7 (0.3)
MFI general fatigue	14.7 (3.5) / –1.2 (0.5)	15.0 (3.5) –0.9 (0.4)	–3.3 (0.5)	–3.0 (0.5)
SF-36, PCS (0-100)	37.8 (8.9) / 6.2‡ (1.0)	37.2 (8.1) / 3.8 (0.9)	10.0 (1.0)	10.4 (1.0)
SF-36, MCS (0-100)	42.3 (11.9) / 2.4 (1.3)	43.5 (11.1) / 1.6 (1.2)	4.9 (1.3)	3.7 (1.1)
ASQoL (0-18)	8.6 (4.8) / –1.9 (0.5)	8.4 (4.8) / –1.4 (0.5)	–4.7 (0.5)	–4.0 (0.5)
EQ-5D VAS (0-100)	56.5 (21.0) / 9.3‡ (3.0)	56.4 (20.6) / 3.3 (2.8)	19.8 (2.5)	23.7 (2.7)
EQ-5D utility score (0-1)	0.52 (0.34) / 0.14 (0.04)	0.57 (0.30) / 0.08 (0.03)	0.29 (0.04)	0.25 (0.03)
WPAI-AS, absenteeism# (0-100%)	9.1 (25.0) / –0.2 (4.4)	11.8 (27.7) / –4.9 (4.3)	–6.4 (3.5)	–10.4 (4.7)
WPAI-AS, presenteeism¶ (0-100%)	44.9 (26.7) / –21.2‡ (4.7)	42.2 (26.3) / –12.1 (4.7)	–25.5 (3.7)	–22.5 (3.5)

*mITT population; observed cases.

†$P<0.01$; ‡$P<0.05$, between-group comparisons.

#% work time missed; ¶% impairment while working.

ASQoL, AS quality of life; EQ-5D, EuroQol 5 Dimensions; MFI, Multidimensional Fatigue Inventory; SF-36: 36-item Short Form Health Survey; WPAI-AS: Work Productivity and Activity Index in ankylosing spondylitis.

Conclusion: Patients with early, active nr-axSpA and an inadequate response to NSAIDs achieved sustained improvement in pain/fatigue, HRQoL, utility, and work productivity over 104 weeks of etanercept treatment in the EMBARK study. At study end, health outcome responses were generally comparable regardless of original treatment assignment, suggesting that etanercept has a favourable long-term impact on PROs in patients with nrAxSpa.

Reference: 1. Dougados M, et al. *Arthritis Rheum* 2014;66:2091-102.

Disclosure: F. van Den Bosch, AbbVie, 5,Celgene, 5,Merck Pharmaceuticals, 5,Novartis Pharmaceutical Corporation, 5,Pfizer Inc, 5,UCB, 5,Celgene, 8,Merck Pharmaceuticals, 8,UCB, 8; **E. Drescher**, None; **J. Rosa**, None; **R. Pedersen**, Pfizer Inc, 1,Pfizer Inc, 3; **R. Bonin**, Pfizer Inc, 1,Pfizer Inc, 3; **B. Vlahos**, Pfizer Inc, 1,Pfizer Inc, 3; **J. F. Bukowski**, Pfizer Inc, 3; **S. Kotak**, Pfizer Inc, 1,Pfizer Inc, 3.

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Abstract Number: 2886

Secukinumab Safety and Tolerability in Patients with Active Psoriatic Arthritis and Psoriasis: Results from a Pooled Safety Analysis

Philip J. Mease[1], Iain B. McInnes[2], Alice B. Gottlieb[3], Albert Widmer[4], Luminita Pricop[5] and Shephard Mpofu[4], [1]Rheumatology

Research, Swedish Medical Center, Seattle, WA, [2]Immunology, Infection and Inflammation, University of Glasgow, Glasgow, United Kingdom, [3]Dermatology, Tufts Medical Center, Boston, MA, [4]Novartis Pharma AG, Basel, Switzerland, [5]Integrated Hospital Care (IHC) Franchise, Novartis Pharmaceuticals Corporation, East Hanover, NJ

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SESSION INFORMATION

Session Date: Tuesday, November 10, 2015

Session Title: Spondylarthropathies and Psoriatic Arthritis - Clinical Aspects and Treatment Poster III: Therapy

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Secukinumab, a fully human anti–interleukin-17A monoclonal antibody, has been shown to improve the signs and symptoms of psoriasis and psoriatic arthritis (PsA).[1–3] Here, we describe the safety profile of secukinumab from a large cohort of patients (pts) with psoriasis (PsO) and pts with psoriatic arthritis (PsA), using pooled data from phase 3 studies.

Methods: Safety data were pooled from five double-blind, randomized, placebo (PBO)-controlled phase 3 studies in pts with PsO (ERASURE [NCT01365455], FIXTURE [NCT01358578], SCULPTURE [NCT01406938], FEATURE [NCT01555125] and JUNCTURE [NCT01636687]), and two double-blind, randomized, PBO-controlled, phase 3 studies in pts with active PsA (FUTURE 1 [NCT01392326] and FUTURE 2 [NCT01752634]). In the FUTURE 1 study, pts received 10 mg/kg secukinumab i.v. loading followed by s.c. maintenance dosing (75 mg or 150 mg). In all other studies pts received s.c. loading and maintenance with secukinumab (300, 150, or 75 mg). All randomized pts were included in the pooled safety analysis. Data were pooled at the patient level, and safety analyses were performed for the entire treatment period (≥ 52 weeks for FUTURE 1; Week 52 for ERASURE, FIXTURE, SCULPTURE, FEATURE and JUNCTURE; ≥ 24 weeks for FUTURE 2)

Results: 3928 pts received ≥1 dose of secukinumab (3225 pt-years of exposure, respectively). Baseline demographics, disease/medical history and concomitant medications were similar between the pooled secukinumab and PBO populations. Exposure-adjusted incidence rates for AEs/SAEs across the entire safety period (mean exposure: 299.8 days secukinumab; 105.7 days PBO) were, 240.5/7.9 and 329.6/9.9 per 100 pt-years with secukinumab and PBO, respectively; 115 (2.9%) pts discontinued secukinumab treatment due to AEs. There were four deaths in secukinumab-treated pts: one due to intracranial hemorrhage; one due to cardio-respiratory arrest; one due to alcohol intoxication; and one of unknown cause. There were two (0.05%) cases of suicidality with secukinumab; one attempted suicide and one case of suicidal ideation. Nasopharyngitis and upper respiratory tract infections were the most frequently reported AEs with secukinumab. The incidence of inflammatory bowel disease (IBD)/Crohn's, infections, neutropenia, major adverse cardiac events (MACE) and malignancy with secukinumab was low (Table).

Conclusion: Secukinumab was well tolerated in a large cohort of 3928 patients across 7 phase 3 studies with PsA and PsO. The safety profile was consistent with previous reports.

References

1. Mease P, et al. *Arthritis Rheumatol*. 2014;66:S423–4.

2. Mclnnes IB, et al. ACR/ARHP Annual Meeting, Boston, MA, USA. November 14-19, 2014. Oral Presentation L1.

3. Langley RG et al. *N Engl J Med*. 2014;371:326–38

Table. Summary of pooled safety across PsO and PsA studies

	Any secukinumab N=3928	**Placebo N=994**
Exposure, mean days (SD)	299.8 (131.1)	105.7 (56.8)
Min–max exposure, days	1–721	8–377
	Events per 100-pt years (95% confidence interval)	
Any AE	240.5 (231.9–249.4)	329.6 (302.3–358.7)
Any SAE	7.9 (6.9–8.9)	9.9 (6.6–14.3)
AEs of special interest		
Infections and infestations	92.8 (88.7–97.0)	93.9 (82.1–107.0)
IBD	0.3 (0.1–0.6)	0.3 (0.0–1.9)
Crohn's	0.1 (0.0–0.3)	0.3 (0.0–1.9)
Neutropenia	1.5 (1.1–2.0)	2.4 (1.0–5.0)
MACE (unadjudicated)	0.6 (0.4–1.0)	0.0 (0.0–1.3)
Malignant or unspecified tumors	0.8 (0.6–1.2)	1.4 (0.4–3.6)

Disclosure: P. J. Mease, Abbvie, Amgen, BMS, Celgene, Crescendo Bioscience, Genentech, Janssen, Lilly, Merck, Novartis, Pfizer,

UCB, 2,Abbvie, Amgen, BMS, Celgene, Crescendo Bioscience, Genentech, Janssen, Lilly, Merck, Novartis, Pfizer, UCB, 5,Abbvie, Amgen, BMS, Celgene, Crescendo Bioscience, Genentech, Janssen, Lilly, Merck, Novartis, Pfizer, UCB, 9; **I. B. McInnes**, Abbvie, Amgen, BMS, Celgene, Janssen, Lilly, Novartis, Pfizer, UCB, 5,Abbvie, Amgen, BMS, Celgene, Janssen, Lilly, Novartis, Pfizer, UCB, 2,Abbvie, Amgen, BMS, Celgene, Janssen, Lilly, Novartis, Pfizer, UCB, 9; **A. B. Gottlieb**, Amgen Inc., Astellas, Akros, Centocor (Janssen), Inc. Celgene Corp., Bristol Myers Squibb Co., Beiersdorf, Inc., Abbott Labs. (Abbvie), DUSA, TEVA, Actelion, UCB, Novo Nordisk, Novartis, Dermipsor Ltd., Incyte, Pfizer, Canfite, Lilly, Coronado, Vertex, Ka, 5,Centocor (Janssen), Amgen, Abbott (Abbvie), Novartis, Celgene, Pfizer, Lilly, Coronado, Levia, Merck, Xenoport, 2; **A. Widmer**, Novartis AG, 3; **L. Pricop**, Novartis Pharmaceutical Corporation, 3; **S. Mpofu**, Novartis AG, 3,Novartis AG, 1.

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Abstract Number: 2887

Safety and Tolerability of Secukinumab in Patients with Active Ankylosing Spondylitis: Pooled Safety Analysis of Two Phase 3, Randomized, Controlled Trials

Atul A. Deodhar[1], Dominique Baeten[2], Joachim Sieper[3], Brian Porter[4], Albert Widmer[5] and Hanno Richards[5], [1]Division of Arthritis & Rheumatic Diseases, Oregon Health & Science University, Portland, OR, [2]Clinical Immunology and Rheumatology, Academic Medical Center/University of Amsterdam, Amsterdam, Netherlands, [3]University Clinic Benjamin Franklin, Berlin, Germany, [4]Novartis Pharmaceuticals Corporation, East Hanover, NJ, [5]Novartis Pharma AG, Basel, Switzerland

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SESSION INFORMATION

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Session Title: Spondylarthropathies and Psoriatic Arthritis - Clinical Aspects and Treatment Poster III: Therapy

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Secukinumab, an anti–interleukin-17A monoclonal antibody, improved the signs and symptoms of ankylosing spondylitis (AS) in 2 Phase 3, randomized, double-blind, placebo (PBO)-controlled studies, MEASURE 1 (NCT01358175) and MEASURE 2 (NCT01649375).[1,2]We report the safety of secukinumab in AS through ≥52 weeks (wks) using pooled data from these 2 studies.

Methods: Both studies enrolled patients (pts) with active AS with radiological evidence fulfilling the modified New York Criteria. In MEASURE 1, 371 pts were randomized to secukinumab or PBO. Pts on secukinumab received 10 mg/kg intravenously (IV) at baseline (BL), Wk 2 and 4, followed by 75 or 150 mg subcutaneously (SC) every 4 wks (q4w) from Wk 8. PBO was given according to the same IV to SC schedule. In MEASURE 2, 219 pts were randomized to receive SC secukinumab (75 or 150 mg) or PBO at BL, Wk 1, 2, and 3, and q4w starting from Wk 4. At Wk 16, PBO pts were re-randomized to receive secukinumab 150 or 75 mg SC q4w. Anti-drug antibodies (ADAs) were assessed using a Meso Scale Discovery bridging assay. Safety data were pooled at the pt level, with a data cut-off of Wk 52 visit of the last pt enrolled in each study.

Results: 571 pts received ≥1 dose of secukinumab (691.1 pt-years of exposure). Baseline demographic and disease characteristics were well-balanced in the pooled secukinumab and PBO populations. The incidence of adverse events (AEs)/serious AEs (SAEs) during the 16-wk PBO-controlled period was 65.7/3.3% and 58.7/4.1% in the secukinumab and PBO groups, respectively. Exposure-adjusted AE/SAE rates across the entire safety period (mean exposure: secukinumab, 442.1 days; PBO, 118.5 days) were 206.8/7.9 and 359.5/12.8 per 100 pt-years with secukinumab and PBO, respectively; 27 (4.7%) pts receiving secukinumab and 11 (5.6%) receiving PBO discontinued due to AEs during the study. Three deaths were reported: 1 suicide (PBO); 1 due to respiratory failure (IV→75 mg) and 1 due to an acute myocardial infarction (75 mg), both in pts with multiple cardiovascular risk factors. Nasopharyngitis was the most frequent AE with secukinumab (11.2% with secukinumab vs 6.1% with PBO during the 16-wk PBO-controlled period; 17.9 vs 19.5 per 100 pt-years during the entire study period). The incidence of inflammatory bowel/Crohn's disease, *Candida*infections, neutropenia, major adverse cardiac events, and malignancy was low with secukinumab (Table). Uveitis AEs were reported in 7 (1.2%) pts on secukinumab and 2 (1.0%) on PBO. Treatment-emergent ADAs were detected in 2 (0.3%) pts, with no associated loss of efficacy. There were no suicidality-related AEs with secukinumab.

Conclusion: Secukinumab was well-tolerated in pts with active AS, with a low incidence of SAEs and discontinuations due to AEs.

References:

1. Baeten D, et al. *Arthritis Rheumatol* 2014; 66 (11Suppl):S360
2. Sieper J, et al. *Arthritis Rheumatol.* 2014;66(11Suppl):S232

Table: Summary of pooled safety across the MEASURE 1 and MEASURE 2 studies				
	Placebo-controlled period: 16 wks		Entire safety period:	
	Any secukinumab dose N=394	Placebo N=196	Any secukinumab dose N=571[a]	Placebo N=196
Exposure (days), mean (SD)	112.1 (14.3)	108.6 (22.5)	442.1 (142.8)	118.5 (32.8)
Minimum–maximum exposure (days)	8-195	1-176	8-757	1-206
	Number of pts with event (%)		Number of events per 100 pt-years (95% CI)	
Any AE	259 (65.7)	115 (58.7)	206.8 (188.4- 226.4)	359.5 (297.6-430.5)
Any SAE	13 (3.3)	8 (4.1)	7.9 (5.9-10.3)	12.8 (5.5-25.2)
AEs of special Interest				
Infections and infestations	121 (30.7)	35 (17.9)	68.8 (61.2-77.0)	63.8 (44.7-88.4)
Candida infections	2 (0.5)	0 (0.0)	0.9 (0.3-1.9)	0.0 (0.0-5.8)
IBD	3 (0.8)	0 (0.0)	1.2 (0.5-2.3)	0.0 (0.0-5.8)
Crohn's disease	2 (0.5)	0 (0.0)	0.7 (0.2-1.7)	0.0 (0.0-5.8)
MACE[b]	1 (0.3)	0 (0.0)	0.4 (0.1-1.3)	0.0 (0.0-5.8)
Malignancy	1 (0.3)	1 (0.5)	0.6 (0.2-1.5)	1.6 (0.0-8.8)
Neutropenia	10 (2.5)	1 (0.5)	4.1 (2.7-5.9)	1.6 (0.0-8.8)

[a]Includes PBO pts re-randomized to secukinumab; [b]Adjudicated events

AE, adverse event; CI, confidence interval; IBD, inflammatory bowel disease; MACE, major adverse cardiac events; pts, patients; SAE, serious adverse event; SD, standard deviation; wks, weeks

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Disclosure: A. A. Deodhar, AbbVie, Amgen, Janssen, Pfizer, Novartis, UCB, 2,Abbvie, Amgen, Janssen, Pfizer, Novartis, UCB, 5,Boehringer Ingelheim, 9; **D. Baeten**, Boehringer Ingelheim, Janssen, MSD, Novartis, Pfizer, 2,AbbVie, Boehringer Ingelheim, BMS, Eli Lilly, Janssen, MSD, Novartis, Pfizer, Roche, UCB, 5; **J. Sieper**, AbbVie, Boehringer Ingelheim, Janssen, Novartis, Merck, Lilly, Pfizer, and UCB, 2,AbbVie, Boehringer Ingelheim, Janssen, Novartis, Merck, Lilly, Pfizer, and UCB, 9; **B. Porter**, Novartis, 3,Novartis, 1; **A. Widmer**, Novartis Pharmaceutical Corporation, 3; **H. Richards**, Novartis, 3.

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Abstract Number: 2888

Apremilast, an Oral Phosphodiesterase 4 Inhibitor, Is Associated with Long-Term (104-Week) Improvements in Enthesitis and Dactylitis in Patients with Psoriatic Arthritis: Pooled Results from Three Phase III, Randomized, Controlled Trials

Dafna D. Gladman[1], Arthur Kavanaugh[2], Adewale O. Adebajo[3], Juan J. Gomez-Reino[4], Jürgen Wollenhaupt[5], Maurizio Cutolo[6], Georg A. Schett[7], Eric Lespessailles[8], Melissa McIlraith[9], ChiaChi Hu[9], Christopher J. Edwards[10], Charles A. Birbara[11] and Philip J. Mease[12], [1]Toronto Western Hospital, Toronto, ON, Canada, [2]University of California, San Diego School of Medicine, LaJolla, CA, [3]University of Sheffield, Sheffield, United Kingdom, [4]Hospital Clinico Universitario, Santiago, Spain, [5]Schön Klinik Hamburg Eilbek, Hamburg, Germany, [6]University of Genova, Genova, Italy, [7]University of Erlangen-Nuremberg, Erlangen, Germany, [8]University of Orléans, Orléans, France, [9]Celgene Corporation, Warren, NJ, [10]University Hospital Southampton, Southampton, United Kingdom, [11]University of Massachusetts Medical School, Worcester, MA, [12]Rheumatology Research, Swedish Medical Center, Seattle, WA

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Background/Purpose: Apremilast (APR), a PDE4 inhibitor, helps regulate immune responses in psoriatic arthritis (PsA). PALACE 1, 2, and 3 compared apremilast (APR) efficacy/safety with placebo (PBO) in patients (pts) with active PsA despite prior conventional DMARDs and/or biologics, including efficacy assessments across multiple disease aspects. Enthesitis and dactylitis, hallmark features of PsA, lead to pain and disability. We report the impact of APR treatment over 104 wks on enthesitis and dactylitis in a pooled analysis of the PALACE 1-3 studies.

Methods: Pts were randomized (1:1:1) to PBO, APR 30 mg BID (APR30), or APR 20 mg BID (APR20) stratified by baseline DMARD use (yes/no). The PBO-controlled phase continued to Wk 24, with an early escape option at Wk 16. At Wk 24, all remaining PBO pts were re-randomized to APR30 or APR20. Double-blind APR treatment continued to Wk 52; pts could then continue to receive APR for up to an additional 4 years during an open-label extension phase. Data were pooled across PALACE 1-3 at Wk 24, as prespecified in the protocol, to allow for analysis of robust numbers of pts with pre-existing enthesopathy and/or dactylitis. Enthesitis was evaluated based on the Maastricht Ankylosing Spondylitis Enthesitis Score (MASES) (range: 0-13), which indicates the number of painful entheses out of 13 entheses sites. The dactylitis count (range: 0-20) is the number of digits (hands/feet) with dactylitis present; each digit is rated as 0 (absence) or 1 (presence). Analyses at Wk 24 used last observation carried forward for missing values; Wk 52 and Wk 104 were based on data as observed.

Results: At Wk 24, mean change in MASES was -1.3 (APR30, *P*=0.0194 vs PBO), -1.2 (APR20), and -0.9 (PBO); MASES=0 was achieved by 27.5% (APR30), 27.4% (APR20), and 22.5% (PBO) of pts. Mean change in dactylitis count was -1.8 (APR30, *P*=0.0097 vs PBO), -1.6 (APR20), and -1.3 (PBO); dactylitis count of 0 was achieved by 46.2% (APR30), 45.9% (APR20), and 39.0% (PBO) of pts. Long-term improvement in enthesitis and dactylitis severity was seen in pts with enthesitis and/or dactylitis at baseline who were receiving APR at 104 wks, as shown by reductions in MASES and dactylitis counts (Table). Mean % changes in MASES were -57.5% (APR30) and -55.1% (APR20) at Wk 104. MASES of 0, indicating no pain at any of the entheses assessed, was achieved by 48.7% (APR30) and 51.5% (APR20) of pts. Mean % changes in dactylitis count were -80.0% (APR30) and -75.8% (APR20) at Wk 104. Dactylitis counts decreased to 0 in 77.5% (APR30) and 72.9% (APR20) of pts. Over 104 wks, most AEs were mild or moderate in severity; in general, no increase was seen in AE incidence and severity with longer term exposure.

Conclusion: Over 104 wks, APR continued to demonstrate efficacy in PsA treatment, including improvements in enthesitis and dactylitis. APR demonstrated an acceptable safety profile and was generally well tolerated for up to 104 wks.

Enthesitis and Dactylitis at Wk 24 (LOCF), and Wks 52 and 104 (Data as Observed)

	Wk 24			Wk 52		Wk 104	
MASES*	**PBO n=302**	**APR30 n=315**	**APR20 n=298**	**APR30 n=377**	**APR20 n=326**	**APR30 n=302**	**APR 20 n=260**
Baseline, mean	4.8	4.4	4.6	4.4	4.5	4.3	4.6
Mean change from baseline	-0.9	-1.3‡	-1.2	-2.0	-2.2	-2.6	-2.6
Mean % change from baseline	-7.0	-23.6‡	-19.3	-43.5	-42.2	-57.5	-55.1
Median % change from baseline	-21.1	-50.0‡	-40.0	-66.7	-66.7	-100.0	-100.0
Pts achieving score of 0, %	22.5	27.5	27.4	37.7	41.1	48.7	51.5
Dactylitis count§	**PBO n=194**	**APR30 n=214**	**APR20 n=202**	**APR30 n=249**	**APR20 n=225**	**APR30 n=200**	**APR20 n=181**
Baseline, mean	3.3	3.2	3.4	3.4	3.3	3.4	3.2
Mean change from BL	-1.3	-1.8‡	-1.6	-2.5	-2.3	-2.9	-2.4
Mean % change from baseline	-38.2	-48.6	-43.2	-67.9	-70.2	-80.0	-75.8
Median % change from baseline	-66.7	-79.3	-75.0	-100.0	-100.0	-100.0	-100.0
Pts achieving score of 0, %	39.0	46.2	45.9	67.5	66.7	77.5	72.9

The n at Week 24 represents pts with a baseline value and at least one post-baseline value at or prior to Week 24. The n at Weeks 52 and 104 represents the number of pts taking APR (regardless of when treatment started [baseline, Wk 16, or Wk 24]) with a baseline value >0 and a value at Wk 52 or Wk 104.
*MASES ranges from 0 to 13, with 0 indicating no pain at any assessed entheses and 13 indicating pain at all assessed entheses. §Dactylitis count is the sum of all scores for each of the 20 digits, with each digit scored as 0=absence or 1=presence of dactylitis. ‡*P*<0.05 vs PBO.

Disclosure: D. D. Gladman, Abbvie, 2,Amgen, 5,BMS, 5,Celgene, 2,Eli Lilly and Company, 5,Janssen Pharmaceutica Product, L.P., 2,Novartis, 2,Pfizer Inc, 5,UCB, 2; **A. Kavanaugh**, Abbott, Amgen, BMS, Pfizer, Roche, Janssen, UCB Pharma, 2; **A. O. Adebajo**, None; **J. J. Gomez-Reino**, Bristol-Myers Squibb, Pfizer Inc, Roche, Schering-Plough, and UCB SA, 8; **J. Wollenhaupt**, Roche, Chugai Pharma, Pfizer Inc, Abbott, and UCB, 5,Roche, Chugai Pharma, Pfizer Inc, Abbott, and UCB, 8; **M. Cutolo**, Actelion, Bristol-Myers Squibb, and Sanofi-Aventis, 2,Actelion, Bristol-Myers Squibb, and Sanofi-Aventis, 5; **G. A. Schett**, Abbott, Celgene Corporation, Roche, and UCB, 5; **E. Lespessailles**, Amgen, Eli Lilly, Novartis, and Servier, 2; **M. McIlraith**, Celgene Corporation, 3; **C. Hu**, Celgene Corporation, 3; **C. J. Edwards**, Celgene Corporation, Pfizer Inc, Roche, and Samsung, 2,Celgene Corporation, Pfizer Inc,

Roche, and Samsung, 5,Abbott, Glaxo-SmithKline, Pfizer Inc, and Roche, 8; **C. A. Birbara**, Amgen, Lilly, Pfizer, Incyte, Merck, and Bristol-Myers Squibb, 2; **P. J. Mease**, Celgene, Merck, Novartis, Abbvie, Amgen, BiogenIdec, BMS, Genentech, Janssen, Lilly, Pfizer, UCB, 2,Celgene, Merck, Novartis, Abbvie, Amgen, BiogenIdec, BMS, Crescendo, Genentech, Janssen, Lilly, Merck, Pfizer, UCB, Vertex;, 5,Abbvie, Amgen, BiogenIdec, BMS, Crescendo, Genentech, Janssen, Lilly, Pfizer, UCB, 8.

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Abstract Number: 2889

Apremilast, an Oral Phosphodiesterase 4 Inhibitor: Improvements in Nail and Scalp Psoriasis and Psoriasis Area and Severity Index in Patients with Moderate to Severe Plaque Psoriasis

Kim Papp[1], Jeffrey Crowley[2], Carle Paul[3], Melinda Gooderham[4], Kristian Reich[5], ChiaChi Hu[6], Robert M. Day[6] and Christopher E.M Griffiths[7], [1]Probity Medical Research, Waterloo, ON, Canada, [2]Bakersfield Dermatology, Bakersfield, CA, [3]Toulouse University, Hôpital Larrey, Toulouse, France, [4]SKiN Centre for Dermatology and Probity Medical Research, Peterborough, ON, Canada, [5]SCIderm Research Institute and Dermatologikum Hamburg, Hamburg, Germany, [6]Celgene Corporation, Warren, NJ, [7]Dermatology Centre, University of Manchester, Manchester, United Kingdom

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Background/Purpose: Scalp and nail psoriasis are difficult-to-manage manifestations of psoriasis and psoriatic arthritis (PsA). Nail involvement occurs in ~80% of pts with PsA and can negatively affect daily/work activities, thereby impacting pt quality of life. ESTEEM 1 and 2 are phase 3, randomized, controlled trials evaluating apremilast (APR) efficacy/safety in pts with moderate to severe plaque psoriasis. Of 1,255 pts randomized in the ESTEEM trials, 65.7% had nail and 66.3% had moderate to severe scalp involvement at baseline (BL).

Methods: Pts were randomized 2:1 to APR 30 mg BID (APR30) or placebo (PBO). At Wk 16, PBO pts switched to APR30. All pts were treated with APR30 through Wk 32, followed by a randomized treatment withdrawal phase up to 52 wks in pts randomized to APR30 at BL and identified as responders at Wk 32. The primary endpoint was the proportion of pts achieving PASI-75 at Wk 16. Nail and scalp involvement were assessed through Wk 52 in pts with Nail Psoriasis Severity Index (NAPSI) ≥1 in the target nail and Scalp Physician Global Assessment (ScPGA) ≥3 at BL.

Results: Improvements in mean PASI score occurred as early as Wk 2 in ESTEEM 1 and 2 with APR30 (-22.3% and -24.3%, respectively) vs PBO (-6.5% and -7.5%). At Wk 16, significantly more pts achieved PASI-75 in ESTEEM 1 and 2 with APR30 (33.1% and 28.8%, respectively) vs PBO (5.3% and 5.8%; both $P<0.0001$). Improvements in mean percent change in NAPSI score and NAPSI-50 achievement rates were also significantly greater with APR30 vs PBO at Wk 16 (Table). Similarly, a higher proportion of pts achieved an ScPGA of 0 (clear) or 1 (minimal) at Wk 16 with APR30 ($P<0.0001$, both studies; Table). At Wk 32, mean percent change in NAPSI as well as NAPSI-50 and ScPGA 0 or 1 achievement were sustained in pts randomized to and continuing treatment with APR30 (Table). Among pts randomized to APR30 at BL who were randomized to continue APR30 (with no addition of other treatments) through Wk 52, mean improvement in PASI score at Wk 52 was -80.5% in ESTEEM 1 and -74.4% in ESTEEM 2. Improvements in NAPSI outcomes were maintained in these pts over 52 wks: mean percent change in NAPSI was -60.2% in ESTEEM 1 and -59.7% in ESTEEM 2; achievement of NAPSI-50 was 70.7% and 68.6%, respectively. In this pt group, ScPGA 0 or 1 was reached by 83.3% of pts in ESTEEM 1 and 62.5% of pts in ESTEEM 2. AEs occurring in ≥5% of pts treated with APR30 were diarrhea, nausea, URTI, nasopharyngitis, tension headache, and headache up to 16 wks. Most AEs were mild or moderate in severity, with no increase in incidence or severity with up to ≥52 wks of treatment.

Conclusion: In the ESTEEM plaque psoriasis studies, APR30 was effective in improving skin involvement and the difficult-to-manage manifestations of nail and scalp psoriasis, with maintenance of these improvements over time. APR30 was generally well tolerated, with the most common tolerability issues occurring early and resolving with continued treatment.

Table*

	Placebo-Controlled Phase (Wk 16)				Active Treatment Phase (Wk 32)§	
	ESTEEM 1		ESTEEM 2		ESTEEM 1	ESTEEM 2
	PBO	APR30	PBO	APR30	APR30/ APR30	APR30/ APR30
NAPSI (0-8)						
NAPSI ≥1 at BL, n	195	363	91	175	363	175
BL NAPSI, mean	4.4	4.3	4.4	4.2	4.3	4.1
% change from BL, mean	6.5	-22.5‡	-7.1	-29.0‡	-43.6	-60.0
NAPSI-50, n (%)	29 (14.9)	121 (33.3)‡	17 (18.7)	78 (44.6)‡	164 (45.2)	97 (55.4)
ScPGA (0-5)						
ScPGA ≥3 at BL, n	189	374	93	176	374	176
ScPGA 0 or 1, n (%)	33 (17.5)	174 (46.5)‡	16 (17.2)	72 (40.9)‡	140 (37.4)	57 (32.4)
PASI (0-72)						
FAS, n	278	559	136	269	425	191
% improvement from BL, mean	-16.7	-52.1‡	-15.8	-50.9¶	-61.9	-58.8

*Data are presented for those pts who had data at BL and (Wk 16) at least one post-BL value (last observation carried forward) or (Wk 32) a value at the study wk (data as observed).
§Pts who were randomized to APR30 at BL and continued to take APR30 through Wk 32.
‡$P<0.0001$; ¶$P=0.0052$. BL=baseline; FAS=full analysis set.

Disclosure: K. Papp, Abbott, Amgen, Celgene, Eli Lilly, and Janssen, 2,Abbott, Amgen, Celgene, Eli Lilly, and Janssen, 5; **J. Crowley**, AbbVie, Amgen, Celgene, Janssen, Lilly, Maruho, Merck, Pfizer, Regeneron,, 5; **C. Paul**, AbbVie, Amgen, Celgene, Eli Lilly, Janssen, Leo Pharma, Novartis, and Pfizer, 5; **M. Gooderham**, AbbVie, Amgen, Astellas, Galderma, Janssen, Leo Pharma, Novartis, and Pfizer, 8,AbbVie, Allergan, Celgene, Eli Lilly, Galderma, Kythera, Leo Pharma, Merck, Novartis, and Pfizer, 9; **K. Reich**, Abbott, AbbVie, Amgen, Basilea, Biogen-Idec, Celgene, Centocor, Eli Lilly, Forward Pharma, GlaxoSmithKline, Janssen-Cilag, LEO Pharma, Medac, MSD (Essex Pharma, Schering-Plough), Novartis, Ocean Pharma, Pfizer (Wyeth), and UCB, 2,Abbott, AbbVie, Amgen, Basilea, Biogen-Idec, Celgene, Centocor, Eli Lilly, Forward Pharma, GlaxoSmithKline, Janssen-Cilag, LEO Pharma, Medac, MSD (Essex Pharma, Schering-Plough), Novartis, Ocean Pharma, Pfizer (Wyeth), and UCB, 5,Abbott, AbbVie, Amgen, Basilea, Biogen-Idec, Celgene, Centocor, Eli Lilly, Forward Pharma, GlaxoSmithKline, Janssen-Cilag, LEO Pharma, Medac, MSD (Essex Pharma, Schering-Plough), Novartis, Ocean Pharma, Pfizer (Wyeth), and UCB, 8; **C. Hu**, Celgene Corporation, 3; **R. M. Day**, Celgene Corporation, 3; **C. E. M. Griffiths**, Abbott, Celgene, Eli Lilly, Janssen, LEO, Novartis, and Pfizer, 2,Abbott, Celgene, Eli Lilly, Janssen, LEO, Novartis, and Pfizer, 8,Abbott, Celgene, Eli Lilly, Janssen, LEO, Novartis, and Pfizer, 5.

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Abstract Number: 2890

Secukinumab Provides Sustained Improvements in the Signs and Symptoms of Active Ankylosing Spondylitis in Anti-TNF-Naïve Patients and Those Previously Exposed to Anti-TNF Therapy: 52-Week Results from Two Randomized, Double-Blind, Placebo-Controlled Phase 3 Trials

Dominique Baeten[1], Ricardo Blanco[2], Piet Geusens[3], Joachim Sieper[4], Tseng Jui-Cheng[5], Ruvie Martin[6], Brian Porter[6] and Hanno Richards[7], [1]Academic Medical Center/ University of Amsterdam, Amsterdam, Netherlands, [2]Rheumatology, Hospital Universitario Marqués de Valdecilla. IDIVAL, Santander, Spain, [3]Maastricht University, Maastricht, Netherlands, [4]University Clinic Benjamin Franklin, Berlin, Germany, [5]Kaohsiung Veterans General Hospital, Kaohsiung, Taiwan, [6]Novartis Pharmaceuticals Corporation, East Hanover, NJ, [7]Novartis Pharma AG, Basel, Switzerland

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Session Time: 9:00AM-11:00AM

Background/Purpose:

Anti–TNFs are the only biologics currently approved for ankylosing spondylitis (AS). There is a significant unmet need in those patients (pts) with an inadequate response/intolerance to these agents. The efficacy and safety of secukinumab, an anti–interleukin-17A monoclonal antibody, has been assessed in two Phase 3 studies in pts with active AS, MEASURE 1 (NCT01358175) and MEASURE 2 (NCT01649375).[1,2] Here, we present the efficacy and safety of secukinumab by anti-TNF history in pts enrolled in these 2 studies.

Methods:

In MEASURE 1, 371 pts were randomized to secukinumab or placebo (PBO). The secukinumab group received 10 mg/kg intravenously (iv) at baseline (BL) and Weeks (Wks) 2 and 4, followed by subcutaneous (sc) 150 (IV→150 mg) or 75 mg (IV→75 mg) every 4 wks (q4w) from Wk 8; PBO was given according to the same dosing schedule. In MEASURE 2, 219 pts were randomized to receive secukinumab 150 or 75 mg sc or PBO at BL, Wks 1, 2, and 3, and q4w starting from Wk 4. Randomization was stratified by anti-TNF history: anti-TNF-naive, or inadequate response/intolerance to not more than one anti-TNF agent (anti-TNF-IR). The primary endpoint for both studies was ASAS20 response at Wk 16. Secondary endpoints were ASAS40, hsCRP, ASAS 5/6, BASDAI, SF-36 PCS, ASQoL, and ASAS partial remission. Wk 16 analyses used non-responder imputation (binary variables) and mixed-model repeated measures (continuous variables). Wk 52 data are as observed. Analysis of primary and secondary endpoints stratified by anti-TNF history was pre-specified.

Results:

At BL, 73% and 61% of pts were anti–TNF-naïve in MEASURE 1 and MEASURE 2, respectively. Compared with PBO, ASAS20 response rates at Wk 16 were higher with all secukinumab doses, except for the 75 mg sc dose in MEASURE 2, in both anti–TNF-naïve and anti–TNF-IR pts (Table). Improvements with secukinumab were observed for all secondary endpoints in anti–TNF-naïve pts, except ASAS partial remission in MEASURE 2, and for most secondary endpoints in anti–TNF-IR pts. No incremental increase in efficacy was observed with the IV→150 mg or IV→75 mg doses versus 150 mg sc, despite the greater exposure conferred by iv loading. At Wk 52, 319 (86.0%) pts remained in MEASURE 1 and 181 (82.6%) in MEASURE 2. Clinical responses to secukinumab were sustained or continued to improve through 52 wks of therapy in both anti–TNF-naïve and anti–TNF-IR pts (Table). Responses were generally higher in anti-TNF-naïve vs anti–TNF-IR pts. ASAS40 response rates at Wk 52 in anti-TNF-naïve and anti-TNF-IR pts were 67.1% and 45.8% with IV→150 mg, 48.8% and 50.0% with IV→75 mg, 64.1% and 45.5% with 150 mg, and 47.6% and 26.3% with 75 mg.

Conclusion:

Secukinumab 150 mg provided sustained improvements in the signs and symptoms of AS in both anti–TNF-naïve and anti–TNF-IR pts.

Reference:

1. Baeten D et al. *Arthritis Rheumatol* 2014; 66 (11Suppl):S360.
2. Sieper J et al. *Arthritis Rheumatol*. 2014;66(11Suppl):S232.

Table: Efficacy at Week 16[a] and 52[b]							
		MEASURE 1			MEASURE 2		
		Secukinumab			Secukinumab		
		IV→150 mg	IV→75 mg	PBO	150 mg	75 mg	PBO
Anti–TNF-Naïve							
ASAS20, % responders	Wk 16	66.3*	60.0†	32.6	68.2†	51.1	31.1
	Wk 52	78.5	73.8	N/A	82.1	71.4	N/A
ASAS40, % responders	Wk 16	48.9*	34.4§	15.7	43.2‡	31.1	17.8
	Wk 52	67.1	48.8	N/A	64.1	47.6	N/A
BASDAI (Mean change from BL)	Wk 16	−2.72*	−2.61*	−0.72	−2.56§	−2.27‡	−1.15
	Wk 52	−3.32	−2.93	N/A	−3.33	−2.86	N/A
Anti–TNF-IR							
ASAS20, % responders	Wk 16	45.5‡	58.8†	18.2	50.0‡	25.0	24.1
	Wk 52	70.8	64.3	N/A	59.1	47.4	N/A
ASAS40, % responders	Wk 16	21.2	29.4‡	6.1	25.0§	17.9‡	0.0
	Wk 52	45.8	50.0	N/A	45.5	26.3	N/A
BASDAI (Mean change from BL)	Wk 16	−1.72‡	−2.19§	−0.65	−1.60	−1.38	−0.59
	Wk 52	−2.77	−2.67	N/A	−2.80	−2.13	N/A

*$P<0.0001$; †$P<0.001$; §$P<0.01$; ‡$P<0.05$ vs. PBO. [a]NRI (binary variables) and LS Mean via MMRM (continuous variables) data presented at Wk 16; [b]Observed data presented at Wk 52; LS, least squares; N/A, not applicable.

MEASURE 1: At Wk 16/52, in anti–TNF-naïve pts: secukinumab IV→150 mg, n = 92/79; secukinumab IV→75 mg, n = 90/80 (except for BASDAI at Wk 52 where n = 81); PBO, n = 89/NA; anti–TNF-IR pts: secukinumab IV→150 mg, n = 33/24; secukinumab IV→75 mg, n = 34/28; PBO, n = 33/NA

MEASURE 2: At Wk 16/52, in anti–TNF-naïve pts: secukinumab 150 mg, n = 44/39; secukinumab 75 mg, n = 45/42; PBO, n = 45/NA; anti–TNF-IR pts: secukinumab 150 mg, n = 28/22; secukinumab 75 mg, n = 28/19; PBO, n = 29/NA

Disclosure: D. Baeten, Boehringer Ingelheim, Janssen, MSD, Novartis, Pfizer, 2,AbbVie, Boehringer Ingelheim, BMS, Eli Lilly, Janssen, MSD, Novartis, Pfizer, Roche, UCB, 5; **R. Blanco**, None; **P. Geusens**, Pfizer, Abbott, Lilly, Amgen, MSD, Will, and Roche, 2,Amgen, 5,Amgen and Lilly, 8; **J. Sieper**, AbbVie, Pfizer, Merck, UCB and Novartis, 5,AbbVie, Pfizer and Merck, 2,AbbVie, Pfizer, Merck and UCB, 8; **T. Jui-Cheng**, Novartis, 3; **R. Martin**, Novartis, 3; **B. Porter**, Novartis, 3,Novartis, 1; **H. Richards**, Novartis, 3.

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Abstract Number: 2891

Assessment of Disability Levels in a Cohort of 1,489 Patients with Active Psoriatic Arthritis, and the Effect of Apremilast Treatment: Pooled Data from Three Phase III, Randomized, Controlled Trials

Philip J. Mease[1], Jürgen Wollenhaupt[2], Stephen Hall[3], Filip van Den Bosch[4], Eric Lespessailles[5], Melissa McIlraith[6], Lichen Teng[6] and Christopher J. Edwards[7], [1]Rheumatology Research, Swedish Medical Center, Seattle, WA, [2]Schön Klinik Hamburg Eilbek, Hamburg, Germany, [3]Monash University, CabriniHealth, Melbourne, Australia, [4]Rheumatology, Ghent University Hospital, VIB, Ghent, Belgium, [5]University of Orléans, Orléans, France, [6]Celgene Corporation, Warren, NJ, [7]University Hospital Southampton, Southampton,

United Kingdom

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Session Time: 9:00AM-11:00AM

Background/Purpose: PsA, a chronic systemic inflammatory disease, reduces physical function and QOL. Treatment improves/maintains functionality. PALACE 1-3 compared apremilast (APR) efficacy/safety with placebo (PBO) in patients (pts) with active PsA despite prior conventional DMARDs and/or biologics, providing one of the largest databases (N=1,489) examining physical disability in moderate to severe PsA pts. The impact of APR 30 mg BID (APR30) treatment over 104 wks on disability was assessed using the HAQ-DI in a pooled analysis of the PALACE 1-3 database.

Methods: Pts were randomized (1:1:1) to PBO, APR30, or APR 20 mg BID (APR20) stratified by baseline (BL) DMARD use (yes/no). At Wk 24, all remaining PBO pts were re-randomized to APR30 or APR20. HAQ-DI scores were collected at BL and Wks 16, 24, 40, 52 65, 78, 91, and 104. Data are analyzed by ITT, LOCF methodology for Wk 16, and described as data as observed to Wk 104, with LOCF analysis done to confirm results. HAQ-DI MCID decreases ≥0.13 and ≥0.30 were prespecified; a post hoc analysis for the most recently published MCID ≥0.35 was done. Disability categories were calculated using HAQ-DI cutoff levels ≤1.0 (clinically significant disability[1]) and ≤0.5 (MDA criteria[2]); assessments included proportion reaching levels ≤0.25. Shift categories of scores were examined with increments of 0.25 to clarify pt disability level and category shifts.

Results: Pts exhibited significant physical disability at BL (mean HAQ-DI=1.2); 60% of APR30 pts had >1.0, and 31% had >1.5, noting marked difficulty/need for assistive devices in performing activities of daily living. Major disability was noted in up to 13% with BL HAQ-DI >1.875. As early as Wk 16, physical function improved with APR30; pts exhibited a mean HAQ-DI change of -0.21 (vs. -0.07 PBO; *P*<0.0001), 56% achieved HAQ-DI ≤1.0 at Wk 16 (vs. 48% PBO pts), and 29% achieved HAQ-DI ≤0.5 (vs. 25% PBO pts). Fewer PBO vs. APR30 pts reached MCID of -0.13 (37% vs. 47%; *P*<0.005) and -0.30 and -0.35 (26% vs. 36%; *P*<0.005). At Wk 52, decreases in disability were maintained (APR30 mean change in HAQ-DI=-0.33); 48% of APR30 pts achieved MCID -0.30 and 48% MCID -0.35. Importantly, at Wk 52, 59% of all APR30 pts achieved HAQ-DI ≤1.0, 35% ≤0.5, and 25% ≤0.25 (Table). Among pts with greater BL disability (HAQ-DI ≥1.5), 64% improved by ≥1 shift category and 48% by ≥2. At Wk 104, 50% of APR30 pts achieved MCID -0.30 and MCID -0.35, with 64% achieving HAQ-DI ≤1.0, 40% ≤0.5, and 29% ≤0.25.

Conclusion: In APR30 pts, physical function improved and was sustained with long-term treatment. Most pts achieved HAQ-DI MCID -0.30 or -0.35 and HAQ-DI scores ≤1.0, with many obtaining HAQ-DI ≤0.5, defined as minimal disease in recently developed criteria. These data indicate improvement and long-term maintenance of functionality with APR treatment.

References: 1. Sokka T, et al. *Arthritis Rheum.* 2003;48:59-63. 2. Coates LC, et al. *Ann Rheum Dis.* 2010;69:48-53.

Patients Achieving Improvement in Physical Function, by HAQ-DI Category

	Wk 52*	Wk 104*
% Pts Achieving HAQ-DI Disability Threshold	APR30 n=569	APR30 n=458
≤1.0	59	64
≤0.5	35	40
≤0.25	25	29

HAQ-DI=Health Assessment Questionnaire-Disability Index (HAQ-DI) ≤1.0=disability not clinically significant; ≤0.5=disability remission.
*Wk 52 and Wk 104 were based on data as observed.

Disclosure: P. J. Mease, Celgene, Merck, Novartis, Abbvie, Amgen, BiogenIdec, BMS, Genentech, Janssen, Lilly, Pfizer, UCB, 2,Celgene, Merck, Novartis, Abbvie, Amgen, BiogenIdec, BMS, Crescendo, Genentech, Janssen, Lilly, Merck, Pfizer, UCB, Vertex;, 5,Abbvie, Amgen, BiogenIdec, BMS, Crescendo, Genentech, Janssen, Lilly, Pfizer, UCB, 8; **J. Wollenhaupt**, Roche, Chugai Pharma, Pfizer Inc, Abbott, and UCB, 5,Roche, Chugai Pharma, Pfizer Inc, Abbott, and UCB, 8; **S. Hall**, Celgene Corporation, Pfizer, UCB, Bristol-Myers Squibb, Glaxo-Smith Kline, Roche, Janssen, Novartis, Merck, 5,Celgene Corporation, Pfizer, UCB, Bristol-Myers Squibb, Glaxo-Smith Kline, Roche, Janssen, Novartis, Merck, 2; **F. van Den Bosch**, Abbvie, Celgene, Novartis, Pfizer, UCB, 5,Abbvie, Celgene, Janssen, Novartis, Pfizer, UCB, 8; **E. Lespessailles**, Amgen, Eli Lilly, Novartis, and Servier, 2; **M. McIlraith**, Celgene Corporation, 3; **L. Teng**, Celgene Cororation, 3; **C. J. Edwards**, Abbvie, Pfizer, Lilly, Celtrion, Mundipharma, Samsung, Anthera, UCB, Celgene, Roche, Bristol-Myers Squibb, Janssen, 8.

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Abstract Number: 2892

Statin Treatment in Patients with Ankylosing Spondylitis

Grunde Wibetoe[1], Eirik Ikdahl[1], Tore K. Kvien[2], Silvia Rollefstad[1] and Anne Grete Semb[3], [1]Preventive Cardio-Rheuma Clinic, Department of Rheumatology, Diakonhjemmet Hospital, Oslo, Norway, [2]Dept. of Rheumatology, Diakonhjemmet Hospital, Oslo, Norway, [3]Preventive Cardio-Rheuma clinic, Department of Rheumatology, Diakonhjemmet Hospital, Oslo, Norway
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Background/Purpose: Patients with ankylosing spondylitis (AS) have increased risk of cardiovascular disease (CVD). In the general population, CVD risk reduction can be achieved by lipid lowering therapy (LLT). We aimed to evaluate the effect of statins in AS patients and factors associated with the changes (Δ) in low-density lipoprotein cholesterol (LDL-c) and total cholesterol (TC).

Methods: In this longitudinal, observational study, 108 patients with AS underwent CVD risk evaluation. Of these, 48 patients had an indication for LLT and received statin treatment which was adjusted until lipid targets were achieved. Variables obtaining a p-value of < 0.25 in a univariate analyses were entered in forward, stepwise, linear regression models with ΔLDL-c and ΔTC as the dependent variables and were adjusted for age and gender, as well as baseline LDL-c levels (for ΔLDL-c) and intensity of LLT (for ΔTC).

Results: At first visit, median (IQR) age was 61.5 (56.0, 66.8) years, 72.9 % were male, median disease duration was 27 (17.8, 32.8) years, 12.5 % smoked daily, 70.8 % had hypertension (HT), mean (SD) body mass index (BMI) was 26.0 (3.50) kg/m^2, mean LDL-c and TC, were 3.82±1.02 and 6.04±1.16mmol/L and 70.8 % had carotid plaque(s). Twenty patients were treated with low or moderate intensity LLT (simvastatin 20 mg or 40 mg, rosuvastatin <40 mg or atorvastatin <40 mg), while the remaining 28 received intensive LLT (rosuvastatin 40 mg or atorvastatin >40 mg). LDL-c goals (50% reduction in LDL-c and /or LDL-c <2.5 /<1.8 mmol/L, for primary (n=10) or secondary prevention (n=38), respectively) were achieved in 85.4% of patients (90.0% and 84.2% for primary and secondary prevention, respectively). Reductions in LDL-c and TC were 1.60+0.41 mmol/L and 2.42+1.15 mmol/L (p<0.001 for both). Predictive variables explaining 86.5% (R^2) of the ΔLDL-c included erythrocyte sedimentation rate (ESR), established CVD and HT. Only ESR (p=0.03) and baseline LDL-c (p<0.001) contributed significantly to the final model. ESR was inversely related to ΔLDL-c. In addition, higher baseline LDL-c levels were associated with larger LDL-c reduction. The final model for ΔTC, accounting for 33.0% (R^2) of the variation, included ESR, waist circumference, BMI, non-steroidal anti-inflammatory drugs, and use of biologic and synthetic disease modifying anti-rheumatic drugs. Intensive LLT and high waist circumference were predictive of greater TC reductions (p=0.002 and 0.04, respectively).

Conclusion: Lipid lowering with statins was highly effective in AS patients. Inflammation measured by ESR was inversely related to change in LDL-c, possibly due to the suppressive effect on lipid levels. Further studies are needed to elucidate if the anti-inflammatory effect of rheumatic medication influence the lipid lowering effect of statins in patients with AS.

ΔLDL-c, R^2=0.865			ΔTC, R^2=0.330		
	B (95% CI)	p-value		B (95% CI)	p-value
Age	0.004 (-0.01, 0.02)	0.56	**Age**	0.02 (-0.02, 0.05)	0.39
Sex (gender)	-0.05 (-0.31, 0.21)	0.70	**Sex (gender)**	-0.03 (-0.88, 0.83)	0.95
LDL-c at baseline	-0.78 (-0.89, -0.66)	<0.01	**LLT (statin dose)**	-1.09 (-1.74, -0.43)	>0.01
ESR	0.01 (0.00, 0.02)	0.03	**ESR**	0.01 (-0.02, 0.03)	0.61
CVD	0.20 (-0.12, 0.52)	0.21	**Waist circumference**	-0.06 (-0.12, -0.00)	0.04
Hypertension	-0.16 (-0.42, 0.11)	0.25	**BMI**	0.14 (-0.06, 0.33)	0.16
			NSAIDs	-0.33 (-1.08, 0.42)	0.37
			Biologic DMARDs	-0.34 (-1.06, 0.39)	0.35
			Synthetic DMARDs	0.18 (-0.87, 1.23)	0.73

Disclosure: G. Wibetoe, None; **E. Ikdahl**, None; **T. K. Kvien**, None; **S. Rollefstad**, None; **A. G. Semb**, None.

Abstract Number: 2893

Quality of Life in Patients with Active Nonradiographic Axial Spondyloarthritis after 16 Weeks of Golimumab Treatment

Walter Maksymowych[1], Sean P. Curtis[2], Maxime Dougados[3], Gina Bergman[2], Susan Huyck[2], Anjela Tzontcheva[2] and Joachim Sieper[4], [1]Medicine, University of Alberta, Edmonton, AB, Canada, [2]Merck & Co., Inc., Kenilworth, NJ, [3]Paris-Descartes University, Paris, France, [4]University Clinic Benjamin Franklin, Berlin, Germany

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Background/Purpose: Chronic inflammation, back pain, and progressive spinal stiffness associated with axial spondyloarthritis (axSpA) can decrease quality of life (QoL). The purpose of this study was to determine whether golimumab (GLM) is superior to placebo (PBO) in improving the QoL of patients with nr-axSpA.

Methods: GO-AHEAD was a double-blind, randomized, PBO-controlled trial of GLM in patients with active nr-axSpA (ASAS criteria and centrally read sacroiliac joint X-rays and MRI; disease duration ≤5 years; chronic back pain; high disease activity [total back pain ≥40 mm on a 0–100 mm VAS and BASDAI ≥4 cm]; and inadequate response/intolerance to NSAIDs). Patients were randomized 1:1 to SC GLM 50 mg or PBO every 4 wk. Secondary outcomes related to QoL included the 36-item Short Form Health Survey (SF-36), Ankylosing Spondylitis Quality of Life (ASQoL), EuroQoL 5-Dimension (EQ-5D) Index and Health State (0–10 cm

VAS), and Work Productivity and Activity Impairment (WPAI) questionnaire scores at wk 16. Treatment group differences for all patients and for the objective signs of inflammation (OSI) population (baseline inflammation by centrally evaluated SI MRI and/or elevated CRP) were compared using a constrained longitudinal data analysis for continuous endpoints and Mann–Whitney test for WPAI scores.

Results: Of 197 treated patients (GLM=97; PBO=100), mean age was 31 years; 57% were male. At wk 16, patients treated with GLM had greater improvements from baseline QoL than patients treated with PBO, as measured by all scales of the ASQoL, EQ-5D, and SF-36 (Table). GLM patients also had greater improvements than PBO patients in percentages of WPAI overall work impairment (−21.1 vs −11.7, *P*=.0391) and activity impairment (−24.9 vs −8.6, *P* < .0001); impairment while working and work time missed were not significantly different between groups. Results for QoL and WPAI measures were similar in the OSI population, except that patients in the GLM group also had greater improvements in percentage of impairment while working than the PBO group (*P*=.0194).

Table. QoL Outcomes From Baseline to Week 16

	All Patients as Treated			OSI Population		
	GLM N=97[a] Mean (SD)	PBO N=100[a] Mean (SD)	Difference vs PBO[b] Mean (95% CI)	GLM N=78[a] Mean (SD)	PBO N=80[a] Mean (SD)	Difference vs PBO[b] Mean (95% CI)
ASQoL[c]						
Baseline	11.1 (4.6)	10.2 (4.6)		10.9 (4.4)	10.2 (4.8)	
Wk 16	5.6 (5.2)	8.6 (5.1)	−3.5 (−4.7, −2.2)[d]	5.6 (5.2)	8.6 (5.1)	−3.4 (−4.8, −2.0)[d]
EQ-5D Index						
Baseline	0.41 (0.32)	0.44 (0.33)		0.41 (0.32)	0.42 (0.34)	
Wk 16	0.68 (0.28)	0.54 (0.31)	0.15 (0.08, 0.22)[d]	0.68 (0.29)	0.53 (0.32)	0.16 (0.07, 0.24)[e]
EQ-5D VAS, cm						
Baseline	4.5 (2.2)	5.1 (2.1)		4.6 (2.2)	5.2 (2.1)	
Wk 16	6.8 (2.4)	5.5 (2.3)	1.5 (0.9, 2.1)[d]	6.7 (2.5)	5.5 (2.3)	1.5 (0.8, 2.2)[d]
SF-36 physical						
Baseline	32.9 (8.1)	35.0 (8.7)		33.0 (8.3)	35.1 (8.9)	
Wk 16	43.4 (10.2)	38.3 (9.6)	6.6 (4.3, 8.8)[d]	43.6 (10.2)	38.4 (9.9)	6.7 (4.2, 9.2)[d]
SF-36 mental						
Baseline	41.1 (11.9)	41.6 (11.1)		40.9 (11.4)	42.2 (11.0)	
Wk 16	47.1 (11.1)	43.1 (11.8)	4.2 (1.4, 7.1)[f]	46.8 (11.6)	42.9 (12.0)	4.5 (1.3, 7.8)[g]

[a]Sample size may vary due to unavailable data; [b]Differences derived from the statistical model; [c]Decrease from baseline indicates improvement; [d]*P* <.0001; [e]*P*=.0004; [f]*P*=.0034; [g]*P*=.0065.

Conclusion: Patients with active nr-axSpA who received GLM treatment had greater improvement in QoL and work productivity outcomes at wk 16 than those who received PBO; however, the mean values indicate that some degree of impairment remained.

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Abstract Number: 2894

The Majority of Patients with Moderate to Severe Psoriatic Arthritis Had Existing Structural Damage, Predisposing Them to Further Progression, Which Was Markedly Inhibited By Adalimumab

Pranav Sheth[1], Philip J. Mease[2], Yihan Li[3], Fabiana Ganz[4] and Maja Hojnik[5], [1]Group Health Associates, Trihealth, Cincinnati, OH, [2]Seattle Rheumatology Associates, Seattle, WA, [3]AbbVie Inc., North Chicago, IL, [4]Neuhofstrasse 23, AbbVie AG, Baar, Switzerland, [5]AbbVie, Ljubljana, Slovenia
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Background/Purpose:

Patients (pts) with psoriatic arthritis (PsA) may experience structural damage if not appropriately treated. The purpose was to determine 1) the frequency of radiographic structural damage in PsA pts at baseline (BL), and BL patient and disease characteristics associated with having BL structural damage 2) the risk of further radiographic progression in PsA pts with/without BL structural damage 3) the inhibition of radiographic progression by adalimumab (ADA) in PsA pts with/without BL structural damage.

Methods:

The analysis used data from the ADEPT trial[1], which was a 24-week (wk) randomized placebo (PBO)- controlled trial that evaluated efficacy and safety of ADA in pts with moderate to severe PsA (mean duration of approx. 9.5 years). Pts with available radiographs of hands and feet at BL and wk 24 were included in the present analyses. Radiographic damage at BL was defined as modified Total Sharp Score (mTSS) >0.5; radiographic progression was defined as a change in mTSS by >0.5 over 24 wks. In each treatment group (ADA or PBO), the proportion of pts with radiographic progression (progressors) from BL to wk 24 was determined among pts with/without BL structural damage. The association of the following BL characteristics with radiographic damage at BL was determined by univariate and multivariate logistic regression: age, weight, swollen joint count at 28 joints (SJC28), tender joint count at 28 joints (TJC28), duration of psoriasis or PsA, C-reactive protein (CRP), and Psoriasis Area Severity Index (PASI).

Results:

Out of 313 pts randomized in the ADEPT trial (151 to ADA, 162 to PBO), 296 pts (95%) had radiographic data available at BL and wk 24. Eighty-one percent (81%; 239/296 pts) had radiographic damage at BL; 83% of pts with PsA duration ≥2 years and 72% of pts with PsA duration <2 years. Among 239 pts with BL damage, significantly fewer pts in the ADA-treated group (13/118, 11.0%) vs the PBO-treated group (43/121, 35.5%) experienced radiographic progression by wk 24 ($p<.001$). The treatment effect of ADA in pts with BL damage was larger than the treatment effect of ADA in the overall population (24.5% vs 19.2% of non-progressors). Among pts without BL damage, 1/26 (3.8%) and 1/31 (3.2%) pts in the ADA and PBO group, respectively, had further damage by wk 24. Multivariate analysis indicated that higher CRP and age at BL were associated with an increased risk of having existing BL structural damage ($p<.01$).

Conclusion:

The majority of PsA pts had radiographic damage at BL, even with < 2 years of disease duration. Pts with BL structural damage had a greater risk for further progression overall, while the inhibitory effect of ADA on radiographic progression was more pronounced in pts with BL damage. Higher CRP and age at BL were associated with BL damage. The data suggests that effective treatment to prevent further radiographic damage would be particularly beneficial in pts with existing damage, who in the ADEPT trial constituted the majority.

Reference: 1) Mease P et al, *Arthritis Rheum* 2005;52:3279-89

Disclosure: P. Sheth, None; **P. J. Mease**, AbbVie, Amgen, Biogen Idec, Bristol Myers, Celgene, Genentech, Janssen, Lilly, Merck, Novartis, Pfizer, and UCB., 9; **Y. Li**, AbbVie, 1,AbbVie, 3; **F. Ganz**, AbbVie, 1,AbbVie, 3; **M. Hojnik**, AbbVie, Amgen, BMS, Celgene, Eli Lilly, Janssen, Novartis, Pfizer, UCB., 9.

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Abstract Number: 2895

Intraarticular Sacroiliac Corticosteroid Injections in Ankylosing Spondylitis

Seunghun Lee[1], Sung Won Lee[2], Yoonah Song[1], Il-Hoon Sung[3] and Tae-Hwan Kim[2], [1]Department of Radiology, Hanyang University College of Medicine, Seoul Hospital, Seoul, South Korea, [2]Department of Rheumatology, Hanyang University Hospital for Rheumatic Diseases, Seoul, South Korea, [3]Department of Orthopaedic Surgery, Hanyang University Hospital for Rheumatic Diseases, Seoul, South Korea

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Background/Purpose: Ankylosing spondylitis (AS) is a chronic inflammatory disease which involves axial skeleton. NSAIDs are drug of choice and biologic disease-modifying anti-rheumatic drugs (DMARDs) are strongly recommended in case of NSAIDs failure. But some AS patients have intermittent, migratoy pain and inflammatory pain could last several days or weeks. Intraarticular injections of sacroiliac joints are recommended in these cases.

The goal of this study was to analyze the effectiveness of a fluoroscopy-guided intraarticular corticosteroid injection for the treatment of sacroiliac joint pain in patients with AS.

Methods: Between March 2012 and February 2015, a total of 62 fluoroscopy-guided intraarticular corticosteroid injections in the sacroiliac joints were performed in 58 patients with AS (37 males, 21 females; mean age 29.1 years, range 12 to 66 years). All patients had been previously diagnosed with AS according to the modified New York criteria And there were findings of active inflammation in their sacroiliac joints confirmed by pelvic magnetic resonance imaging (MRI).

The mixture of triamcinolone acetonide 40 mg and normal saline 0.5 mL was injected under floroscopic guidance.

Results: The mean disease duration before injection was 26.7 months (range 0 to 151 months) and the mean follow-up after injection was 15.1 months (range 0 to 35 months). After injection, BASDAI score and levels of acute phase reactant were decreased. The mean BASDAI score before injection was 6.26 (range 2.3 to 10.0) and the mean BASDAI score after injection was 4.81 (range 1.0 to 9.2). BASDAI 50%/20mm response rate was 27.4% (17/62). In 24 out of 62 cases (39.0%), the BASDAI score were below 4 which means optimal control of disease. No initiation of biologic DMARDs and additional intervention was required in 39 out of 54 patients (72.2%).

But 4 out of 58 patients (6.9%) needed a second injection. 3 patients already was on biologic DMARDs before injection, 15 patients newly started biologic DMRADs after injection due to their high disease activity and lack of effectiveness of intraarticular injection. There were neither discontinuity nor change of biologic DMARDs. There was no bilateral injection at once and no complication associated with the procedure. There was no significant difference between dose of medications which is prescribed before and after injection.

Conclusion: Fluoroscopy-guided corticosteroid injection into sacroiliac joint could be considered as one of treatment options instead of starting biologic DMARDs or dose escalation of medications, when AS patients complain of abrupt and severe pain in their sacroiliac joints.

Abstract Number: 2896

Secukinumab Provides Sustained Improvements in the Signs and Symptoms of Active Ankylosing Spondylitis: 2-Year Efficacy and Safety Results from a Phase 3, Randomized, Double-Blind, Placebo-Controlled Trial

Dominique Baeten[1], Jurgen Braun[2], Joachim Sieper[3], Maxime Dougados[4], Atul A. Deodhar[5], Xenofon Baraliakos[6], Brian Porter[7], Yankun Gong[8] and Hanno Richards[9], [1]1Academic Medical Center / University of Amsterdam, Amsterdam, Netherlands, [2]Rheumazentrum Ruhrgebiet, Herne, Germany, Herne, Germany, [3]University Clinic Benjamin Franklin, Berlin, Germany, [4]Paris-Descartes University, Paris, France, [5]Oregon Health and Sciences University, Portland, OR, [6]Rheumazentrum Ruhrgebiet, Herne, Germany, [7]Novartis Pharmaceuticals Corporation, East Hanover, NJ, [8]Beijing Novartis Pharma Co. Ltd., Beijing, China, [9]Novartis Pharma AG, Basel, Switzerland

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Background/Purpose: Secukinumab, an anti–interleukin-17A monoclonal antibody, improved the signs and symptoms of ankylosing spondylitis (AS) over 52 weeks (wks) in the randomized, double-blind, placebo (PBO)-controlled, Phase 3 MEASURE 1 study (NCT01358175).[1] Here, we report the long-term (104 wks) efficacy and safety of secukinumab in this study.

Methods: 371 patients (pts) with active AS were randomized to secukinumab or PBO. Pts on secukinumab received a 10 mg/kg intravenous (i.v.) loading dose at baseline, Wks 2 and 4, and then subcutaneous (s.c.) 150 mg (IV→150 mg) or 75 mg (IV→75 mg) every 4 wks from Wk 8. PBO was given on the same schedule. PBO pts were re-randomized to secukinumab 150 or 75 mg s.c. based on ASAS20 response at Wk 16, with non-responders switched at Wk 16 and responders at Wk 24. Assessments at Wk 104 included ASAS20/40, hsCRP, ASAS5/6, BASDAI, SF-36 PCS, ASQoL, and ASAS partial remission. Wk 104 data are presented as observed. Pre-specified exploratory endpoints included assessment of spinal x-ray (modified Stoke Ankylosing Spondylitis Spinal Score [mSASSS]) and sacroiliac joint x-ray and magnetic resonance imaging.

Results: 97/125 (77.6%) pts randomized to IV→150 mg and 103/124 (83.1%) pts randomized to IV→75 mg completed 104 wks. Using observed data, ASAS 20/40 response rates at Wk 104 were 79.3/64.4 % and 72.1/53.5 % with IV→150 mg and IV→75 mg, respectively (Table). Clinical improvements with secukinumab were sustained through Wk 104 across all other endpoints (Table). Sustained improvements were observed in pts naïve to anti-tumor necrosis factor (anti-TNF) therapy and in those with an inadequate response/intolerance to not more than one agent (anti-TNF-IR). ASAS 20/40 response rates at Wk 104 (observed data) in anti-TNF-naïve pts were 85.5/69.6% and 72.3/52.3% with IV→150 mg and IV→75 mg, respectively; corresponding rates in anti-TNF-IR pts were 55.6/44.4% and 71.4/57.1%. mSASSS progression over 2 years was 0.3 units for both treatment arms. Across the entire study period (mean secukinumab exposure: 631.6 days), the exposure-adjusted incidence rate (EAIR) for serious infections with secukinumab was 1.0 per 100 pt-years. No cases of TB were reported. The EAIR for inflammatory bowel disease was 0.8, malignant or unspecified tumours 0.6, and major adverse cardiac events 0.4, per 100 pt-years, respectively.

Conclusion: Secukinumab provided sustained improvement through 2 years in the signs and symptoms of AS and improved physical function and quality of life. These sustained improvements were observed regardless of anti-TNF status. The safety profile was consistent with that previously reported.

Reference:

1. Baeten D, et al. *Arthritis Rheumatol* 2014; 66 (11Suppl):S360.

Table. Summary of 104-week Efficacy Results (Observed Data)

	Secukinumab IV → 150 mg	Secukinumab IV → 75 mg
ASAS20 response, n/N (%)	69/87 (79.3%)	62/86 (72.1%)
ASAS40 response, n/N (%)	56/87 (64.4%)	46/86 (53.5%)
hsCRP, change from baseline score (Mean ± SD)	–11.14 ± 24.38	–8.90 ± 18.62
ASAS5/6, n/N (%)	56/87 (64.4%)	49/86 (57.0%)
BASDAI, mean change from baseline score (Mean ± SD)	–3.41 ± 2.12	–3.04 ± 1.81
SF-36 PCS, mean change from baseline score (Mean ± SD)	8.06 ± 8.08	7.41 ± 6.83
ASQoL, mean change from baseline score (Mean ± SD)	–4.82 ± 4.83	–4.58 ± 4.44
ASAS partial remission, n/N (%)	28/87 (32.2%)	20/86 (23.3%)

ASAS, Assessment of Spondyloarthritis International Society; ASQoL, ankylosing spondylitis quality of life; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; hsCRP, high sensitivity C-reactive protein; n, number of pts meeting criteria; N, total number of pts in the analysis; SD, standard deviation; SF-36 PCS, short form-36 health survey physical component summary

Disclosure: D. Baeten, Boehringer Ingelheim, Janssen, MSD, Novartis, Pfizer, 2,AbbVie, Boehringer Ingelheim, BMS, Eli Lilly, Janssen, MSD, Novartis, Pfizer, Roche, UCB, 5; **J. Braun**, Abbvie (Abbott), Amgen, BMS, Boehringer, Celgene, Celltrion, Centocor, Chugai, EBEWE Pharma, Medac, MSD (Schering-Plough), Mundipharma, Novartis, Pfizer (Wyeth), Roche, Sanofi-Aventis and UCB, 9,Abbvie (Abbott), Amgen, BMS, Boehringer, Celgene, Celltrion, Centocor, Chugai, EBEWE Pharma, Medac, MSD (Schering-Plough), Mundipharma, Novartis, Pfizer (Wyeth), Roche, Sanofi-Aventis and UCB, 9,Abbvie (Abbott), Amgen, BMS, Boehringer, Celgene, Celltrion, Centocor, Chugai, EBEWE Pharma, Medac, MSD (Schering-Plough), Mundipharma, Novartis, Pfizer (Wyeth), Roche, Sanofi-Aventis and UCB, 5; **J. Sieper**, AbbVie, Pfizer, Merck, UCB and Novartis, 5,AbbVie, Pfizer and Merck, 2,AbbVie, Pfizer, Merck and UCB, 8; **M. Dougados**, AbbVie, BMS, Eli Lilly, Merck, Pfizer, 2,Eli Lilly and Company, 5; **A. A. Deodhar**, AbbVie, Boehringer Ingelheim Celgene, Janssen, Novartis, Pfizer and UCB, 2,AbbVie, Boehringer Ingelheim Celgene, Janssen, Novartis, Pfizer and UCB, 5; **X. Baraliakos**, AbbVie, Merck, Pfizer, UCB, Novartis, and Chugai, 2,AbbVie, Merck, Pfizer, UCB, Novartis, and Chugai, 5,AbbVie, Merck, Pfizer, UCB, Novartis, and Chugai, 8; **B. Porter**, Novartis, 3,Novartis, 1; **Y. Gong**, Novartis, 3; **H. Richards**, Novartis, 3.

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Abstract Number: 2897

Predictors of Organ Damage Progression and Impact on Health-Related Quality of Life in Systemic Lupus Erythematosus

Alexandra Legge[1], Steve Doucette[2] and John G. Hanly[3], [1]Department of Medicine, Dalhousie University, Halifax, NS, Canada, [2]Dalhousie University and Capital Health, Halifax, NS, Canada, [3]Rheumatology, Division of Rheumatology, Capital Health and Dalhousie University, Halifax, NS, Canada

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Background/Purpose:

To describe cumulative organ damage in a longitudinal cohort of SLE patients and to evaluate the impact of key disease-related factors, medical therapies, demographic variables, and serological biomarkers on the rate of damage accrual. The relationship between cumulative organ damage and health-related quality of life (HRQoL) was also examined.

Methods:

A longitudinal database of SLE patients followed for up to 14 years was analyzed. Patients were assessed at enrollment and annually for (i) cumulative organ damage (Systemic Lupus International Collaborating Clinics (SLICC)/ACR Damage Index (SDI)) and (ii) HRQoL (Medical Outcome Survey Short Form-36 (SF-36) subscales and summary scores). The impact of demographic, disease-related and treatment-related factors on damage progression was examined using multivariable Cox proportional-hazards models. The impact of changes in SDI scores on HRQoL was assessed using linear mixed-effects modeling.

Results:

There were 273 SLE patients with a mean (SD) follow-up of 7.3 (4.3) years. Seventy-seven patients (28.2%) had preexisting damage (baseline SDI > 0) and during follow-up, 126 patients (46.1%) had an increase in SDI scores. Multivariate analysis revealed that older age, 8 or more ACR classification criteria, immunosuppressive drugs, cigarette smoking, and higher C-reactive protein (CRP) levels up to time of first SDI change were associated with an increase in SDI scores (*Table 1*). Changes in SDI scores were associated with initial declines in SF-36 scores at the time that damage occurred, with subsequent change in HRQoL comparable to that seen in patients without damage progression *(Table 2)*.

Conclusion:

Pre-existing organ damage and other risk factors, some modifiable, predict additional damage accrual in SLE patients. The negative impact of damage progression on HRQoL emphasizes the need to target modifiable risk factors and develop effective prevention and treatment strategies to reduce organ damage over time.

Table 1.
Univariate and multivariate analyses of predictors for earlier time to first change in SDI score.

	Univariate		Multivariate	
	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Older Age	1.03 (1.02-1.05)	**<0.001**	1.03 (1.01-1.05)	**<0.001**
Female gender	0.86 (0.50-1.46)	0.57		
Disease duration (per day)	1.03 (1.01-1.05)	**0.01**	1.00 (0.98-1.02)	0.90
Baseline SDI				
0 at baseline	Reference			
1+ at baseline	2.09 (1.44-3.01)	**<0.001**	1.42 (0.93-2.19)	0.11
Number of ACR criteria				
< 8 at baseline	Reference			
≥8 at baseline	2.39 (1.24-4.63)	**0.01**	2.29 (1.09-4.82)	**0.03**
Mean SLEDAI-2K score	1.05 (0.97-1.14)	0.22		
Corticosteroid use	1.36 (0.89-2.07)	0.16		
Average visit dose of steroids	0.99 (0.97-1.01)	0.50		
Antimalarial use	0.96 (0.55-1.65)	0.87		
Immunosuppressive use	1.80 (1.23-2.63)	**0.002**	1.82 (1.21-2.73)	**0.004**
Presence of antiphospholipid antibodies at baseline	0.95 (0.65-1.41)	0.81		
Mean ESR up to first change in SDI	1.01 (1.00-1.02)	**0.001**		
Mean CRP up to first change in SDI	1.01 (1.00-1.02)	**<0.001**	1.01 (1.00-1.02)	**0.002**
Hypertension	1.41 (0.82-2.41)	0.21		
Diabetes	1.51 (0.70-3.24)	0.29		
Smoking Status				
Never	Reference			
Past or Current	2.07 (1.37-2.98)	**<0.001**	1.69 (1.1-2.6)	**0.02**
Education				
Did not complete high school	Reference			
Completed high school	0.80 (0.51-1.25)	0.32	1.21 (0.74-1.97)	0.44
Completed college	0.56 (0.35-0.92)	**0.02**	0.98 (0.56-1.71)	0.94
ACR criteria				
Serositis	1.47 (1.01-2.15)	**0.045**	0.83 (0.53-1.28)	0.40
Mucocutaneous manifestations	1.28 (0.82-2.00)	0.28		
Arthritis	0.89 (0.60-1.33)	0.58		
Renal manifestations	0.87 (0.57-1.32)	0.51		
Neurological manifestations	1.21 (0.56-2.60)	0.63		
Hematological manifestations	1.10 (0.75-1.62)	0.63		
Immunological manifestations	1.06 (0.64-1.78)	0.81		

Table 2.
Impact of changes in SDI scores on HRQoL as measured by the SF-36 subscales and summary scores. (Model parameter estimates (SE), *p*-value)

	Visit Number	Patient Age at Baseline	Change in SDI (one unit)	Change SDI/Visit interaction term
Physical component summary score (PCS)	-0.12 (0.1), p=0.25	-0.28 (0), **p=<0.001**	-0.72 (0.3), **p=0.036**	
Mental component summary score (MCS)	0.16 (0.1), p=0.11	0.11 (0), **p=0.015**	-0.64 (0.4), p=0.079	
General Health	0.18 (0.2), p=0.32	-0.18 (0.1), p=0.050	-3.92 (0.9), **p=<0.001**	0.26 (0.1), **p=0.008**
Body Pain	-0.25 (0.2), p=0.24	-0.23 (0.1), **p=0.007**	-1.38 (0.7), p=0.063	
Mental Health	0.17 (0.1), p=0.25	0.05 (0.1), p=0.48	-1.19 (0.5), **p=0.026**	
Physical Function	-0.16 (0.2), p=0.47	-0.65 (0.1), **p=<0.001**	-1.55 (0.7), **p=0.024**	
Emotional Role	0.55 (0.3), p=0.07	0.04 (0.1), p=0.75	-2.39 (1.2), **p=0.038**	
Physical Role	-0.11 (0.4), p=0.75	-0.62 (0.1), **p=<0.001**	-2.99 (1.3), **p=0.021**	
Social Function	0 (0.2), p=0.999	-0.07 (0.1), p=0.43	-1.49 (0.8), p=0.059	
Vitality	0.01 (0.2), p=0.95	-0.14 (0.1), p=0.101	-1.38 (0.7), **p=0.040**	

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Abstract Number: 2898

Erythrocytes, Acanthocytes, and Proteins in Urine Reflect Lupus Nephritis Histology

Marco Ulises Martinez-Martinez[1], Lilia Llamazares-Azuara[2], David Martínez-Galla[3], Francisco Valadez-Castillo[4], Peter Mandeville[4], Jaime Antonio Borjas García[5] and Carlos Abud-Mendoza[1], [1]Unidad de Investigaciones Reumatológicas, Hospital

Central & Facultad de Medicina, Universidad Autónoma de San Luis Potosí, San Luis Potosí, Mexico, [2]Laboratorio Renal, Universidad Autónoma de San Luis Potosí, San Luis Potosí, Mexico, [3]Patología, Hospital Central & Facultad de Medicina, Universidad Autónoma de San Luis Potosí, San Luis Potosí, Mexico, [4]Faculty of Medicine, Universidad Autónoma de San Luis Potosí, San Luis Potosí, Mexico, [5]Regional Unit of Rheumatology and Osteoporosis, Faculty of Medicine, Universidad Autónoma de San Luis Potosí and Hospital Central, San Luis Potosí, Mexico
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SESSION INFORMATION

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Background/Purpose: Hematuria in lupus nephritis (LN) is secondary to the passage of red blood cells (RBCs) through glomerular abnormalities. Dysmorphic RBCs are associated with glomerulonephritis, and particularly the acanthocytes that are the typical dysmorphic-glomerular RBCs. Kidney biopsy (KB) in LN–that informs the activity (Austin et al[1].), and the LN class– is helpful guiding treatment and prognosis. **Objectives:** To evaluate the correlation between the activity (in KB) and the count of total RBCs/acanthocytes in urine of patients with LN. Secondary objective was to assess if the count of RBCs, and the percentage of acanthocytes discriminate among the LN classes.

Methods: Patients with LN undergoing KB were invited to participate in our study. The morning before the KB, a urine sample was obtained and evaluated (after centrifugation) for the number of RBCs in a Neubauer chamber; the percentage of acanthocytes was also determined. KBs were evaluated by a nephro-pathologist who evaluated the class and activity of LN (0-24 points for proliferative classes); non-proliferative forms of LN were assigned as 0 of activity. Correlation was evaluated with Spearman's rho and median difference with Mann-Whitney's U. A classification tree was performed to distinguish between proliferative (III, IV, III/V, IV/V), pure membranous (V) or other classes of LN (I,II). Statistical analysis was performed using R version 3.2.0.

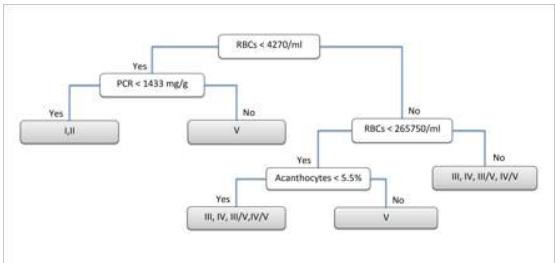
Results: We included 39 patients, 28 women (71.8%); three patients (7.7%) had LN class I, 3 (7.7%) class II, 5 (12.8%) class III, 13 (33.3%) class IV, 11 (28.2%) class V, 3 (7.7%) class III/V and 1 (2.6%) class IV/V. The median activity of LN was 4 (0-18). The RBCs count had a positive correlation with the LN activity ($r=0.7058$, $p<0.0001$); the number of acanthocytes had also a positive correlation with activity of LN ($r= 0.6460$, $p<0.0001$). Patients with proliferative LN had higher count of RBCs than non-proliferative LN (434,000 vs 29,000, $p<0.001$) and higher total count of acanthocytes (27,350 vs 2,860, $p= 0.0005$). The classification tree (Figure 1) shows that RBCs, the protein/creatinine ratio (PCR), and the acanthocytes percentage can be helpful for predicting LN class; the misclassification error rate of this tree was 17.95%.

Conclusion: Evaluation of urine abnormalities is a window of LN histopathology, particularly RBCs, acanthocytes, and PCR.

References

1. Austin HA, et al. Kidney Int. 1984;25(4):689–95.

Figure 1. Classification tree for predicting class of LN.



Disclosure: M. U. Martinez-Martinez, None; **L. Llamazares-Azuara**, None; **D. Martínez-Galla**, None; **F. Valadez-Castillo**, None; **P. Mandeville**, None; **J. A. Borjas García**, None; **C. Abud-Mendoza**, None.

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Abstract Number: 2899

Mortality Related to Pediatric Systemic Lupus Erythematosus: A Multiple Cause-of-

Death Analysis in France

laurent chiche[1], sarah malaekah[2], alexandre belot[3], Brigitte Bader-Meunier[4], gregoire rey[5], Noémie Jourde-Chiche Sr.[6] and mireille eb[5], [1]internal medicine, Hopital Europeen, Marseille, France, [2]pediatry, CHU Lyon, Lyon, France, [3]Pediatric Rheumatology, CHU lyon, Hospices Civils de Lyon, HFME, lyon, France, [4]Hopital Necker-Enfants Malades, Paris, France, [5]cepidc, paris, France, [6]Nephrology, Aix-Marseille Université - APHM, Marseille, France
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Background/Purpose:

Although regarded as a disease of adulthood, SLE is also seen in children, and is associated with an increased risk for aggressive clinical course and major organ damage in comparison to adults. However, mortality rates and causes of death are under reported in the pediatric population, so that most of our understanding derived from generalizations of the adult literature. In France, a previous retrospective multicenter survey conducted on a ten-year period (1996-2006) identified 12 deaths in pediatric SLE patients. A better knowledge of the causes of death and the related comorbidities is pivotal to improve strategies to prevent death in children suffering SLE. The aim of the MORTALU-Ped study was to analyze the mortality profile related to pediatric SLE in France using a multiple cause-of-death analysis.

Methods:

For the 2000-2011 period, data was collected from the database of the French Epidemiological Center of Medical Causes of Death (CepiDc, Inserm) corresponding to death certificates (DC) on which SLE was listed as an underlying or non-underlying cause of death (ICD-10 code L93 or M32) were analyzed for all patients under the age of 18 years. Gender, age, sex-ratio, as well as the causes of death were assessed.

Results:

Overall, 35 DC were identified, of which 5 were excluded from further analyses (Age at death < 1 year; diagnosis of neonatal lupus with congenital heart block n=3; polymalformative syndrome n=1; cerebral hemorrhage n=1). Among the 30 remaining DC, SLE was notified as an underlying cause in 24 (80 %) and as a non-underlying cause of death in 6 (20 %). Mean number of causes of death reported on DC was 3.7 [2; 6]. The patients had a median age at death was 15 years [2; 17] and a sex ratio of 3 (23 female and 7 male). The median number of annual death was 3 [0; 5], relatively stable over time during the study period. Deaths were distributed across 20 French departments, with 1 or 2 DC by department, except for n°78 (Yvelines, n=3) and n°97 (ovserseas separtments, n=6).

For half patients (n=15), at least one severe SLE manifestation was reported: neurologic (n=4), cardiac (n=4), nephritis (n=3), hematologic (n=3), pancreatic (n=2) and pulmonary (n=1). Severe infections was reported in 9/30, 2 in a context of aplasia. Reported pathogens were Streptococcus pneumoniae (n=2), methicillin-resistant Staphylococcus aureus (n=1), Gram negative bacteria (n=1), histoplasmosis (n=1), crytpococcosis (n=1). Other noticeable causes of death were pulmonary embolism (n=1) and associated severe autoimmune condition (autoimmune cirrhosis).

Conclusion:

To our knowledge, this is the first mortality study using a multiple cause-of-death analysis in pediatric SLE. This study shows the interest of such approach to collect a more important number of cases of death in the context of a rare condition such as pediatric SLE. In pediatric SLE patients, the causes leading to death seem to be dominated by severe disease manifestations as well as by severe and/or opportunistic infections and lower sex ratio compared to the living pediatric population suggests higher severity in young male patients.

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Abstract Number: 2900

Phospholipase A2 Receptor 1 Antibody in Membranous Lupus Nephritis

Amy Sandford[1], Malvika Gulati[2], Ademola Oliatan[3], Angela Pakozdi[2], Ravindra Rajakariar[4], Andrea Cove-Smith[4] and Dev Pyne[2], [1]Barts Health NHS trust, London, United Kingdom, [2]Rheumatology, Barts Health NHS Trust, London, United Kingdom, [3]Barts Health NHS Trust, London, United Kingdom, [4]Renal Medicine, Barts Health NHS Trust, London, United Kingdom
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Background/Purpose:

Recently phospholipase A2 receptor 1 (PLA2R1) has been found to be the antigenic target for primary membranous nephropathy (pMN) (1). Circulating anti-PLA2R1 autoantibody can be used as a marker for diagnosis and monitoring of pMN, and due to their high specificity, PLA2R1 antibody detection is useful in discriminating patients with pMN from those with secondary MN. A recent review calculated an overall PLA2R1 prevalence of 4.4% in membranous lupus nephritis (mLN)(2). PLA2R1 has been described in mLN patients with Chinese origin but not in Caucasians, raising the possibility of ethnic differences (3). We therefore sought to define the frequency of anti-PLA2R1 antibody in our ethnically diverse mLN population.

Methods:

This was a retrospective analysis of blood samples taken from lupus patients meeting ACR classification criteria with biopsy proven pure WHO class V or overlap (class III/V or IV/V) LN. ELISA was used to detect the presence or absence of the PLA2R1 antibody. Urinary protein : creatinine ratio (PCR) , erythrocyte sedimentation rate (ESR), dsDNA and complements were measured.

Results:

38 patients with biopsy proven mLN were tested for PLA2R1 antibody. There were 17 (44.7%) South-Asian, 14 (36.8%) Afro-Caribbean, 5 (13.2%) Caucasian, 1 South-East Asian and 1 Mixed. 5 of the 38 patients were Male (F:M ratio 6.6:1), and age range was from 21-60. 60% of the total group had significant proteinuria (uPCR>50), of whom 9 (23.7%) were in the nephrotic range. Median PCR was 91. 11 (29%) had active renal disease at the time of measurement of PLA2-R1 antibody based on significant increase of proteinuria warranting consideration of escalation of immunosuppression. 13 (39%) patients had elevated dsDNA titres, 8 (21%) patients had low complement levels and 18 (47%) patients had raised ESR >20. All patients were negative for the PLA2R1 antibody.

Conclusion:

Our results support the high reported specificity for PLA2R1 antibodies for pMN. The previously reported finding of PLA2R1 antibodies in SLE is most likely due to a chance co-occurrence of primary MN rather than ethnic differences. Since PLA2R1 has therapeutic and prognostic implications in pMN, its measurement should be considered in proteinuric lupus patients who are older and male since this is the group most likely to present with pMN.

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Disclosure: A. Sandford, None; **M. Gulati**, None; **A. Oliatan**, None; **A. Pakozdi**, None; **R. Rajakariar**, None; **A. Cove-Smith**, None; **D. Pyne**, None.

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Abstract Number: 2901

Anti-dsDNA Antibodies Measured By Chemiluminescent Immunoassay Show Strong Association with Active Lupus Nephritis

Gabriella Lakos[1], John G. Hanly[2], Peter Martis[1], Chelsea Bentow[1], Milagros Garcia[3], Odette Viñas[3], Gerard Espinosa[4], Ricard

Cervera[4] and **Michael Mahler**[5], [1]Research, Inova Diagnostics, San Diego, CA, [2]Rheumatology, Division of Rheumatology, Capital Health and Dalhousie University, Halifax, NS, Canada, [3]Immunology, Hospital Clinic of Barcelona, Barcelona, Spain, [4]Department of Autoimmune Diseases, Hospital Clínic, Barcelona, Spain, [5]Inova Diagnostics, San Diego, CA
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Background/Purpose:

Anti-dsDNA antibodies support the diagnosis of systemic lupus erythematosus (SLE), and their quantification is useful for the assessment of lupus nephritis (LN) and the disease activity in LN patients. However, the standardization of anti-dsDNA antibodies in terms of diagnostic accuracy and utility to measure disease activity is still poor and different test systems yield different results. Using a large cohort of well characterized SLE patients, we analyzed the usefulness of a novel anti-dsDNA microparticle chemiluminescent immunoassay (CIA) for the association with LN, and compared the assay to two traditional ELISA methods.

Methods:

Samples from 457 SLE patients from three cohorts (Canada, Spain, USA) were tested with the QUANTA Flash dsDNA CIA (Inova Diagnostics, San Diego, USA). Of these 457 SLE patients, 132 (28.9%) had LN at the time of the blood draw, or had the history of LN. Data obtained with the QUANTA Lite dsDNA SC ELISA and with the QUANTA Lite HA dsDNA ELISA (Inova Diagnostics) were available for samples from the Canadian and USA cohort (n=305), and results obtained with the HA dsDNA ELISA were available for samples from the Canada cohort only (n=234). The data were statistically evaluated using Analyse-it software (Version 3.90.1; Leeds, UK). Wilcoxon-Mann-Whitney was used to analyze the titer difference between different groups. Fisher Exact test was used to analyze antibody prevalence in different categories and p values < 0.05 were considered significant for all statistical methods.

Results:

In the total SLE group (n=457), the dsDNA CIA was positive in 59.3% of all SLE patients and in 70.5% with LN (n=132) (Fisher Exact p=0.002 compared to non-LN SLE). Anti-dsDNA antibody levels, as measured by CIA were significantly higher in LN patients compared to the rest of the SLE patients (median 67.5 *vs.* 32.4 IU/mL; p<0.0001, See Table). SLE patients who tested positive on CIA had an odds ratio (OR) of 2.0 (95% Confidence Interval, CI 1.3-3.0) for LN. Within the Canadian cohort, there was a significant difference between active *vs.* inactive LN for both the prevalence (p=0.0170) and the level (median 50.0 *vs.* 28.7 IU/mL; p=0.0160) of anti-dsDNA antibodies. When compared to the ELISA methods, the dsDNA CIA results showed the strongest correlation with LN (See Table).

	dsDNA CIA		**SC dsDNA ELISA**		**HA dsDNA ELISA**	
	Anti-dsDNA antibody level	Anti-dsDNA positivity	Anti-dsDNA antibody level	Anti-dsDNA positivity	Anti-dsDNA antibody level	Anti-dsDNA positivity
Canada (n=234)	p=0.0006	p=0.009	p=NS*	p=NS*	p=0.02	p=NS*
Spain (n=152)	p=0.0017	p=0.0226	N/A	N/A	N/A	N/A
USA (n=71)	p=NS*	p=NS*	p=NS*	p=NS*	N/A	N/A
All Cohorts (Canada + USA + Spain)	*p<0.0001*	0.002	N/A	N/A	N/A	N/A

*NOTE: NS = not significant. A p-value greater than 0.05 was considered not significant.

Conclusion:

Our results show that the measurement of anti-dsDNA antibodies obtained with the dsDNA CIA is superior to other more conventional assays for the occurrence of LN and assessment of active disease in LN patients.

Disclosure: G. Lakos, Inova Diagnostics, Inc., 3; **J. G. Hanly**, None; **P. Martis**, Inova Diagnostics, Inc., 3; **C. Bentow**, Inova Diagnostics, Inc., 3; **M. Garcia**, None; **O. Viñas**, None; **G. Espinosa**, None; **R. Cervera**, None; **M. Mahler**, Inova Diagnostics, Inc., 3.

chemiluminescent-immunoassay-show-strong-association-with-active-lupus-nephritis

Abstract Number: 2902

The Initial Presentation of Cerebrovascular Disease Attributed to Lupus Is Most Frequent Early in the Disease Course: Results from an International, Inception Cohort Study

John G. Hanly[1], Qiuju Li[2], Li Su[3], Murray Urowitz[4,5], Juanita Romero-Diaz[6], C. Gordon[7], Sang-Cheol Bae[8], Sasha R Bernatsky[9], Ann Clarke[10], Daniel J Wallace[11], Joan T. Merrill[12], David A. Isenberg[13], Anisur Rahman[14], Ellen M. Ginzler[15], Michelle Petri[16], Ian N. Bruce[17], Mary Anne Dooley[18], Paul Fortin[19], Dafna D. Gladman[20], Jorge Sanchez-Guerrero[21], Kristján Steinsson[22], Rosalind Ramsey-Goldman[23], Munther Khamashta[24], Cynthia Aranow[25], Graciela S. Alarcon[26], Barri J. Fessler[27], Susan Manzi[28], Ola Nived[29], Gunnar K. Sturfelt[30], Asad Zoma[31], Ronald F. van Vollenhoven[32], Manuel Ramos-Casals[33], Guillermo Ruiz-Irastorza[34], S. Sam Lim[35], Kenneth C. Kalunian[36], Murat Inanc[37], Diane L. Kamen[38], Christine A. Peschken[39], Søren Jacobsen[40], Anca Askanase[41], Chris Theriault[42] and Vernon Farewell[43], [1]Rheumatology, Division of Rheumatology, Capital Health and Dalhousie University, Halifax, NS, Canada, [2]MRC Biostatistics Unit, Institute of Public Health, University Forvie Site, Cambridge, United Kingdom, [3]Nova Scotia Rehab Site, Division of Rheumatology, Capital Health and Dalhousie University, Halifax, NS, Canada, [4]Rheumatology, TWH, Toronto, ON, Canada, [5]Rheumatology, U of Toronto, Toronto Western Hospital, Toronto, ON, Canada, [6]Immunology and Rheumatology, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico city, Mexico, [7]School of Immunity and Infection, College of Medical and Dental Sciences, University of Birmingham, Birmingham, United Kingdom, [8]Rheumatology, Hanyang University Hospital for Rheumatic Diseases, Seoul, South Korea, [9]Division of Rheumatolog, McGill Unversity Health Cener, Montreal, QC, Canada, [10]Division of Rheumatology, Department of Medicine, University of Calgary, Calgary, AB, Canada, [11]Cedars-Sinai Medical Center, West Hollywood, CA, [12]Clinical Pharmacology, Oklahoma Medical Research Foundation, Oklahoma City, OK, [13]Rayne Institute, Centre for Rheumatology Research, UCL Division of Medicine, London, United Kingdom, [14]Centre for Rheumatology Research, U College of London, London, United Kingdom, [15]Medicine/Box 42, SUNY-Downstate, Brooklyn, NY, [16]Rheumatology, Johns Hopkins University Hospital, Baltimore, MD, [17]Stopford Building, Arthritis Research UK Centre for Epidemiology, Centre for Musculoskeletal Research, Institute of Inflammation and Repair, Manchester Academic Health Science Centre, The University of Manchester, Manchester, United Kingdom, [18]UNC Kidney Centre, Chapel Hill, NC, [19]Medicine, Division of Rheumatology, Centre Hospitalier Universitaire de Quebec et Universite Laval, Quebec, QC, Canada, [20]Department of Medicine, Division of Rheumatology, University of Toronto, Toronto, ON, Canada, [21]Rheumatology, Toronto Western Hospital, Toronto, ON, Canada, [22]Rheumatology, Univ. Hospital, Reykjavik, Iceland, [23]Northwestern University Feinberg School of Medicine, Chicago, IL, [24]Graham Hughes Lupus Research Laboratory, The Rayne Institute, St Thomas' Hospital, London, United Kingdom, [25]Feinstein Institute for Medical Research, Manhasset, NY, [26]Medicine, University of Alabama at Birmingham, Birmingham, AL, [27]UAB, Birmingham, AL, [28]Rheumatology, Allegheny Health Network, Pittsburgh, PA, [29]Rheumatology, Inst of Clinical sciences, Lund, Sweden, [30]Department of Rheumatology, Univ Hospital Lund, Lund, Sweden, [31]Rheumatology, Hairmyres Hospital, East Kilbride, United Kingdom, [32]Department of Medicine, Unit for Clinical Therapy Research, Inflammatory Diseases (ClinTRID), The Karolinska Institute, Stockholm, Sweden, [33]Autoimmune Diseases, IDIBAPS, Hospital Clinic, Barcelona, Spain, [34]Universidad del Pais Vasco, Servicio de Medicina Interna, Hospital de Cruces, Bizkaia, Spain, [35]Emory University School of Medicine, Atlanta, GA, [36]Division of Rheumatology, Allergy & Immunology, UCSD School of Medicine Center for Innovative Therapy, La Jolla, CA, [37]Department of Internal Medicine, Division of Rheumatology, Istanbul University, Istanbul Faculty of Medicine, Istanbul, Turkey, [38]Medicine, Medical University of South Carolina, Charleston, SC, [39]Rheumatology, Univ of Manitoba, Winnipeg, MB, Canada, [40]Rheumatology, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark, [41]Columbia University College of Physicians & Surgeons, New York, NY, [42]Dept of Medicine, Queen Elizabeth II Health Sciences Centre and Dalhousie University, Halifax, NS, Canada, [43]Medicine, Division of Rheumatology, Capital Health and Dalhousie University, Halifax, NS, Canada

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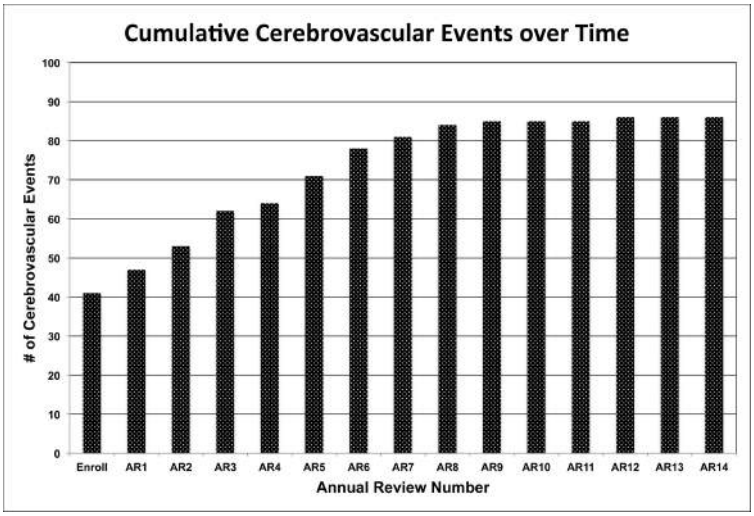
Background/Purpose: Neuropsychiatric (NP) disease in patients with SLE includes cerebrovascular events. We determined the frequency, characteristics and attribution in a large, multi-ethnic/racial, inception cohort of SLE patients.

Methods: A prospective study of new onset SLE patients was performed by an international network of 32 academic centers in 11 countries. Patients were evaluated at enrollment and annually for up to 14 years. Data were collected at each assessment on demographic and clinical manifestations, medications, SLE disease activity index-2000 (SLEDAI-2K) and Systemic Lupus International Collaborating Clinics (SLICC)/ACR damage index (SDI). Nervous system events were recorded using the ACR case definitions for 19 NP syndromes. These include cerebrovascular events and consisted of: (i) Stroke; (ii) Transient ischemia; (iii) Chronic multifocal ischemia; (iv) Subarachnoid and intracranial hemorrhage; (v) Sinus thrombosis. Pre-defined rules determined the attribution of NP events to SLE and non-SLE causes.

Results: Of 1,826 SLE patients, 88.8% were female, 48.8% Caucasian with mean±SD age 35.1±13.3 years. At enrollment, mean SLE duration was 5.6±4.2 months, SLEDAI-2K was 5.3±5.4, SDI was0.31±0.74. The mean follow-up was 5.8±3.8 years. Over the study 912 (49.9%) patients had 1,770 NP events of which 537 (30.3%) were attributed to SLE. Cerebrovascular events were the fourth most frequent NP event: 69/1,826 (3.8%) patients had 86 events of which 82/86 (95.3%) were attributed to SLE. Eleven (15.9%) patients had ≥ 2 cerebrovascular events (9 attributed to SLE and 2 to non-SLE factors) and other NP events occurred concurrently in 42/69 (60.8%) patients. The predominant cerebrovascular events were stroke [45/86 (52.3%)] and transient ischemia [23/86 (26.7%)] followed by subarachnoid and intracranial hemorrhage [9/86 (10.5%)], chronic multifocal ischemia [7/86 (8.1%)] and sinus thrombosis [2/86 (2.3%)]. Forty-one of 86 (47.7%) cerebrovascular events were identified at the enrollment assessment and by the fifth annual assessment 71/86 events (82.6%) had occurred (Figure).



Conclusion: Cerebrovascular events are the fourth most frequent NP event in lupus patients and are usually attributable to SLE. Over 80% of cases present in the first 5 years following the diagnosis of SLE.

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Abstract Number: 2903

Late-Onset Neutropenia Following Rituximab Treatment in Patients with Systemic Lupus Erythematosus

Ioannis Parodis, Frida Söder, Ronald F. van Vollenhoven, Elisabet Svenungsson and Iva Gunnarsson, Department of Medicine, Rheumatology Unit, Karolinska Institutet, Stockholm, Sweden

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SESSION INFORMATION

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Session Type: ACR Poster Session C

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Background/Purpose: The incidence and clinical consequences of rituximab-mediated late-onset neutropenia (LON) have been studied in various diseases, but data from Systemic Lupus Erythematosus (SLE) are limited. We studied the prevalence, consequences and predisposing factors for LON following treatment with rituximab in patients with SLE.

Methods: Ninety-two patients from the Karolinska SLE cohort treated with rituximab were enrolled in this retrospective observational study. Rituximab was given according to the lymphoma course (weekly for four weeks; 73 cycles), the arthritis course (at week 0 and 2; 94 cycles), or as a single infusion (16 cycles), with (60 cycles) or without (123 cycles) cyclophosphamide. LON was defined as an absolute neutrophil count <1,500 cells/µL, corresponding to a neutropenia of grade II–IV according to the National Cancer Institute Common Terminology Criteria for Adverse Events, occurring four weeks to two years after initiation of rituximab treatment, provided that other apparent causes were excluded. Cases of grade II-IV neutropenia occurring later than two years after treatment initiation, but during sustained B cell depletion, were also considered cases of LON.

Results: Thirty-two of 92 patients developed LON (17 patients developed grade II neutropenia, 7 developed grade III, and 8 patients developed grade IV neutropenia) after a median time of 222 days (range: 28–1990 days). Twenty-two patients were asymptomatic. Thirteen patients were admitted to the hospital (median hospital stay: 6 days; range: 1–47 days), either due to suspicion of infection, or for observation and/or treatment with Granulocyte-Colony Stimulating Factor. Three patients were hospitalised due to other causes during the incidence of LON. Ten patients presented with fever, and three of them developed critical conditions and had positive microbiological cultures (*Staphylococcus aureus* sepsis, *Pseudomonas aeruginosa* sepsis, *Streptococcus*fasciitis). Except for one febrile patient with grade III neutropenia, all patients with fever were treated with intravenous broad-spectrum antibiotics. The infections resolved with antibiotics; however, one patient required admission to an Intensive Care Unit. Nine patients were retreated with rituximab after the incidence of LON, and three of them developed LON following these subsequent cycles.

There was no association between neutropenia grade and severity of complications. No predictors for LON were identified among dosages of rituximab, prednisone equivalent or cyclophosphamide (concurrent or accumulated), preceding neutropenia, sex, age, and disease duration.

Conclusion: SLE patients had a higher prevalence of rituximab-mediated LON (35%) compared with patients with lymphoma (3–27%) and rheumatoid arthritis (3%). Although this phenomenon is typically self-limiting, our results demonstrate that it is a common complication in SLE patients, which can lead to life-threatening conditions, and underscore the importance of monitoring these patients for neutrophil counts, fever and infections.

Disclosure: I. Parodis, None; **F. Söder**, None; **R. F. van Vollenhoven**, AbbVie, Amgen, BMS, GSK, Pfizer, Roche, UCB, 2,AbbVie, Biotest, BMS, Celgene, Crescendo, GSK, Janssen, Lilly, Merck, Novartis, Pfizer, Roche, UCB, Vertex, 5; **E. Svenungsson**, None; **I. Gunnarsson**, None.

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Abstract Number: 2904

Utility of Untimed Single Urine Protein/Creatinine Ratio As a Substitute for the 24 Hour Proteinuria for the Assessment of Proteinuria in Systemic Lupus Erythematosus

Jorge Medina-Rosas[1], Dafna Gladman[2], Jiandong Su[2], Arthy Sabapathy[3] and Murray Urowitz[2,4], [1]Medicine, University of Toronto, Toronto Western Hospital, Toronto, ON, Canada, [2]Rheumatology, University of Toronto, Toronto Western Hospital, Toronto, ON, Canada, [3]University of Toronto, Toronto Western Hospital, Toronto, ON, Canada, [4]Rheumatology, U of Toronto, Toronto Western Hospital, Toronto, ON, Canada

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Background/Purpose: To determine the utility of an untimed Sample of Urine Protein/Creatinine ratio (S-UPCR) as a screening test for proteinuria and its ability to accurately measure the level of proteinuria in Systemic Lupus Erythematosus (SLE).

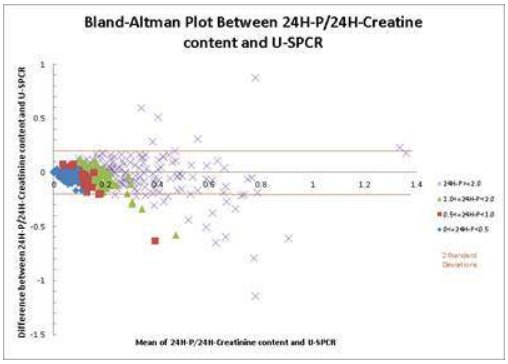
Methods: Analysis was performed on the data available from a single SLE cohort between May 2008-December 2014. Proteinuria was measured in a 24 hour urine sample collection (24H-P) and with the S-UPCR. Based on the 24H-P, samples were divided into: Group I: < 0.5, group II: 0.5-0.99, group III: 1-1.99, and group IV: ≥2g/day. Correlation between 24H-P and S-UPCR was measured.

Agreement was determined by Intraclass Correlation Coefficient (ICC), Concordance Correlation Coefficient (CCC) and Bland-Altman plot between 24H P/C and S-UPCR. The best cut-offs for S-UPCR predicting a 24H-P of 0.5, 1.0 and 2.0 g/day were determined with the receiver operating characteristics curve.

Results: The correlation of 24H-P and S-UPCR for all the samples overall was high, but the correlation for groups I, II, III and IV was low-moderate. The agreement for all urine samples overall was appropriate but poor for groups I, II, III and IV. On the Bland-Altman plot, the dots corresponding for groups III and IV are outside 2 Standard Deviations signifying poor agreement (Figure 1). S-UPCR cut-offs for 24H-P of 0.5, 1.0 and 2.0 g/day were 0.08, 0.16 and 0.35 g/mmol

Conclusion: S-UPCR can be used as a screening test for proteinuria, and the best cut off value to predict a 24H-P of 0.5 g/day is 0.08 g/mmol (800 mg/g). S-UPCR is not a valid test to quantify proteinuria. The accurate level of proteinuria should be measured by the gold standard test, 24H-P.

Figure 1. Bland-Altman plot for 24H-P/creatinine content and S-UPCR



Disclosure: J. Medina-Rosas, None; **D. Gladman**, None; **J. Su**, None; **A. Sabapathy**, None; **M. Urowitz**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/utility-of-untimed-single-urine-proteincreatinine-ratio-as-a-substitute-for-the-24-hour-proteinuria-for-the-assessment-of-proteinuria-in-systemic-lupus-erythematosus

Abstract Number: 2905

Urinary Protein:Urinary Creatinine Ratio in an Untimed Urine Specimen and Estimated Glomerular Filtration Rate Are Reliable Measures of Proteinuria and Renal Function in Patients with Lupus Nephritis

Yasuhiro Katsumata, Hirokazu Nishina, Masanori Hanaoka, Yasushi Kawaguchi, Kae Takagi, Akiko Tochimoto, Yuki Ichimura and Hisashi Yamanaka, Institute of Rheumatology, Tokyo Women's Medical University, Tokyo, Japan

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Session Time: 9:00AM-11:00AM

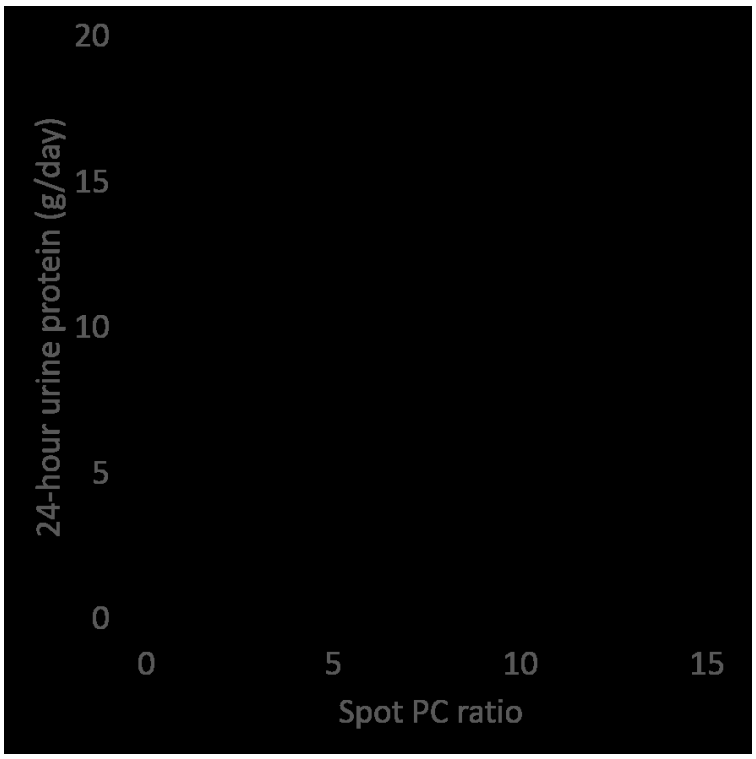
Background/Purpose: Renal Disease Subcommittee of the American College of Rheumatology (ACR) Ad Hoc Committee on Systemic Lupus Erythematosus (SLE) has recommended the urinary protein level in a spot (untimed) urine specimen (determined as urinary protein:urinary creatinine ratio; spot PC ratio) over a 24-hour urine protein excretion, because it is more easily and reliably obtained. In addition, the committee stated that renal function refers to the estimated glomerular filtration rate (GFR) and selected the abbreviated Modification of Diet in Renal Disease (MDRD) study equation. Accordingly, complete renal remission was defined by the ACR subcommittee as an estimated GFR of >90 ml/minute/1.73 m^2 and a urinary PC ratio of <0.2 and inactive urinary sediment. However, recent work suggests that the spot PC ratio may be inaccurate in the assessment of the degree of proteinuria in lupus nephritis (LN) as compared with other forms of chronic glomerular disease. In addition, there is no consensus as to which estimating equation is preferred for estimated GFR. In the present study, we aimed to ensure the reliability of spot PC ratio and estimated GFR as measures of

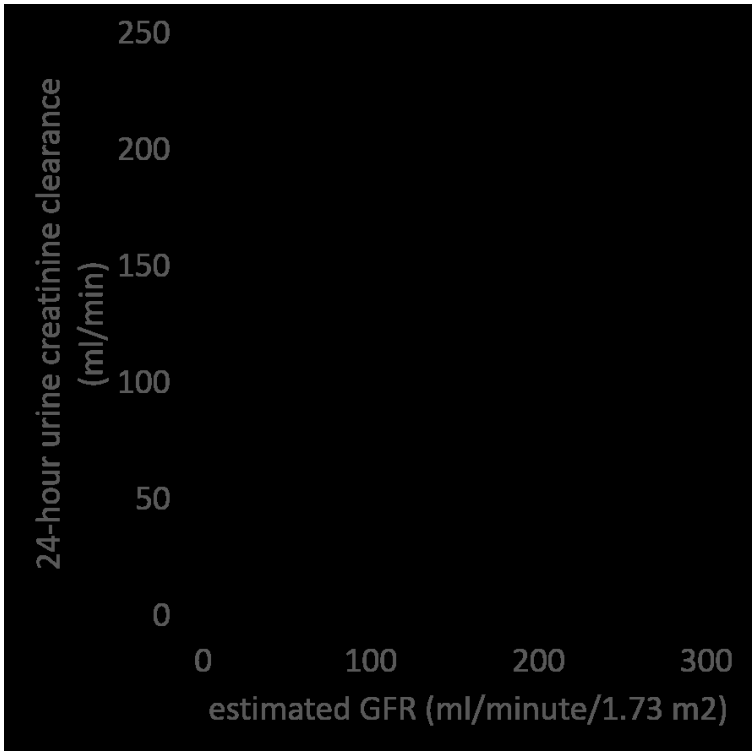
proteinuria and renal function in patients with LN.

Methods: A total of 46 patients with active lupus nephritis who were admitted to our hospital from 2010 through 2014 were included. All the patients met the revised ACR classification criteria for SLE. LN was pathologically confirmed in 44 patients and renal biopsy was not performed in the other 2 patients. Clinical and laboratory data were retrospectively collected from the medical records and statistically analyzed.

Results: The spot PC ration and the 24-hour urine protein excretion were highly correlated (n = 23, Pearson's $r = 0.80$). Agreement of the PC spot ratio >0.5 and the 24-hour urine protein excretion >0.5g was good (Cohen's kappa = 0.60). The 24-hour urinary protein:urinary creatinine ratio is also highly correlated with the 24-hour urine protein excretion (n = 32, Pearson's $r = 0.87$). The estimated GFR by the abbreviated MDRD study equation and the 24-hour urine creatinine clearance were moderately correlated (n = 38, Pearson's $r = 0.68$).

Conclusion: Our results supported the reliability of spot PC ratio and estimated GFR by the abbreviated MDRD study equation as measures of proteinuria and renal function in patients with LN. Larger and prospective studies are needed to confirm and validate these findings.





Disclosure: Y. Katsumata, None; **H. Nishina**, None; **M. Hanaoka**, None; **Y. Kawaguchi**, None; **K. Takagi**, None; **A. Tochimoto**, None; **Y. Ichimura**, None; **H. Yamanaka**, None.

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Abstract Number: 2906

Can Immunosuppressive Drug Treatment Reduce Mortality in Patients with Systemic Lupus Erythematosus (SLE): A Propensity Score Analysis of a Longitudinal Cohort of 803 Patients?

Chi Chiu Mok[1], Sau Mei Tse[1] and Ling Yin Ho[2], [1]Medicine, Tuen Mun Hospital, Hong Kong, Hong Kong, [2]Dept of Medicine, Tuen Mun Hospital, Hong Kong SAR, Hong Kong

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Session Time: 9:00AM-11:00AM

Background/Purpose:

To evaluate the association of the use of immunosuppressive agents and mortality in a longitudinal cohort of SLE patients

Methods:

Patients who fulfilled >=4 1997 ACR criteria for SLE and followed in our rheumatology clinics between 1995 and 2014 were longitudinally followed. Data on demographic characteristics, clinical manifestations and ever use of immunosuppressive agents were retrieved from our database. A propensity score for the use of individual immunosuppressive agent was calculated for each patient based on the odds ratios obtained from separate logistic regression models, with different drugs being the outcome variables. Cox regression models were established to study the effect of the use of various immunosuppressive agents and mortality of our patients over time, with adjustment by the propensity score, age at onset of SLE and sex.

Results:

803 SLE patients were studied (742 women, 92%). All were ethnic Chinese. The mean age of onset of SLE was 33.2±14 years and the mean follow-up time of the entire cohort of patients was 10.8±7.7 years. The cumulative manifestations of SLE, in decreasing order of frequency, were musculoskeletal (70.3%), renal (52%), facial rash (46%), leukopenia (36%), photosensitivity (26%), thrombocytopenia (25%), hemolytic anemia (21%) and serositis (19%). The frequencies of patients who were ever treated with various immunosuppressive drugs were as follows: prednisolone (85%), azathioprine (AZA) (63%), cyclophosphamide (CYC) (25%), mycophenolate mofetil (MMF) (27%), calcineurin inhibitors (CNI) (23%) and hydroxychloroquine (HCQ) (69%). 97 patients (12%) died (mean time to death 9.8±8.0 years) and 56 (7%) patients were lost to follow-up. The commonest causes of death were: infection (44%), cerebrovascular events (12%), cardiovascular events (10%), malignancy (8.2%), pulmonary hypertension (7.2%), interstitial lung disease (3.1%) and uncontrolled SLE activity (3.1%). Cox regression analyses adjusted for age, sex and vascular risk factors (current / past smoking, hypertension, diabetes mellitus, LDLc/HDLc >3.0) revealed that the ever use of MMF (hazard ratio [HR] 1.89[1.19-3.02]; p=0.007), CYC (HR 1.67[1.04-2.68]; p=0.04) and HCQ (HR 0.52[0.35-0.79]; p=0.002) was significantly associated with mortality. Conversely, the use of CNI (HR 1.10[0.67-1.82]; p=0.71), AZA (HR 0.98[0.64-1.50]; p=0.92), or prednisolone (HR 1.06[0.51-2.01]; p=0.85) was not significantly associated with SLE mortality. After further adjustment for the propensity scores, it was demonstrated that the ever use of HCQ (HR 0.53[0.34-0.84]; p=0.006) and AZA (HR 0.55[0.34-0.89]; p=0.02) was significantly associated with a reduction in SLE mortality (47% and 45%, respectively). The use of MMF (HR 1.42[0.87-2.32]; p=0.17) and CYC (HR 1.24[0.75-2.04]; p=0.40) was no longer significantly associated with an increase in mortality.

Conclusion:

In this longitudinal cohort of Chinese SLE patients, the ever use of HCQ and AZA was significantly associated with lower mortality. However, treatment with prednisolone, CYC, MMF or the CNIs was not associated with a benefit of survival.

Disclosure: C. C. Mok, None; **S. M. Tse**, None; **L. Y. Ho**, None.

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Abstract Number: 2907

The Natural History of Thrombotic Events in Systemic Lupus Erythematosus and Associated Risk Factors

Katharine Hickman[1], Laurence S Magder[2] and Michelle Petri[3], [1]University College London, London, United Kingdom, [2]University of Maryland School of Medicine, Baltimore, MD, [3]Rheumatology, Johns Hopkins University Hospital, Baltimore, MD

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Background/Purpose: Prospective cohort studies of the natural history of thrombosis in SLE, including events before diagnosis are rare. No previous study has identified risk factors prospectively for both venous and arterial thrombosis. In this study we used a large prospective SLE cohort to assess the natural history of both arterial and venous thrombosis before and after the diagnosis of SLE.

Methods: 2305 SLE patients were enrolled in a prospective cohort. Medical records were reviewed to identify the occurrence of arterial and venous thrombosis prior to cohort entry. During participation in the Lupus Cohort, arterial thrombosis was diagnosed by patient history, diagnostic enzymes tests and imaging, including arteriogram, and venous thrombosis by ultrasound, CT or venography. We calculated the rate of thrombosis per person-year in periods of follow-up defined by time since diagnosis with SLE.

Results:

The highest rates of both venous thrombosis and arterial thrombosis were observed in the 2 years before and the 2 years after diagnosis: 8.9-10.5 per 1000 patient years for arterial thrombosis and 11.4-12.5 per 1000 patient years for venous thrombosis. A second peak in incidence of arterial thrombosis (11.8 per 1000 patient years) was observed later in the course of SLE.

Table 1: Rates of Venous and Arterial Thrombosis by Time since SLE Diagnosis

	Venous Thrombosis				Arterial Thrombosis			
Time since SLE diagnosis	# Events	Number of Person-Years	Rate of events per 1000 person-years	Rate Ratios (95% CI) adjusted for age	# Events	Number of Person-Years	Rate of events per 1000 person-years	Rate Ratios (95% CI) adjusted for age
> 5 years before SLE diagnosis	49	39,704	1.2	1.0 (Ref. Grp)	16	40,128	0.4	1.0 (Ref. Grp)
2-5 years before SLE diagnosis	15	6,490	2.3	1.5 (0.8, 2.7)	12	6,610	1.8	3.5 (1.6, 7.4)
0-2 years before SLE diagnosis	50	4,370	11.4	7.0 (4.7, 10.5)	40	4,472	8.9	15.9 (8.8, 28.8)
0-2 years after SLE diagnosis	51	4,087	12.5	7.4 (5.0, 11.1)	44	4,194	10.5	17.7 (9.9, 31.9)
2-5 years after SLE diagnosis	35	5,194	6.7	3.9 (2.5, 6.1)	24	5,364	4.5	7.2 (3.7, 13.8)
5+ years after SLE diagnosis	139	15,274	9.1	5.0 (3.5, 7.2)	183	15,481	11.8	15.8 (9.2, 27.3)

Conclusion: This large cohort study indicated that prevention of both venous and arterial thrombosis is important around the time of diagnosis of SLE. Monitoring for thrombosis should occur throughout the disease course, being mindful of the arterial thrombosis risk with longer duration of SLE. Our results suggest that the mechanism of events before diagnosis is not just accelerated atherosclerosis as suggested by some investigators. Accelerated atherosclerosis would not explain the increase in both arterial and venous events that occurs before and at diagnosis. Hypercoagulability appears to be the major explanatory mechanism.

Disclosure: K. Hickman, None; **L. S. Magder**, None; **M. Petri**, None.

Abstract Number: 2908

Diagnostic and Screening Accuracy of Spot Urinary Protein-Creatinine Ratio Compared to Protein Content in a 24 Hour-Urine Collection in Systemic Lupus Erythematosus: Systematic Review and Meta-Analysis

Jorge Medina-Rosas[1], Kristy Yap[2], Melanie Anderson[3], Jiandong Su[2] and Zahi Touma[2], [1]Medicine, University of Toronto, Toronto Western Hospital, Toronto, ON, Canada, [2]Rheumatology, University of Toronto, Toronto Western Hospital, Toronto, ON, Canada, [3]Library and Information Services, University Health Network, University Health Network, Toronto, ON, Canada

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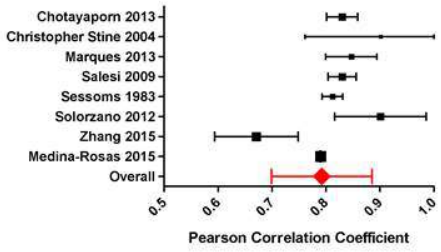
Background/Purpose: To systematically review literature on the utility of spot urinary protein-creatinine ratio (PCR) as a screening test for proteinuria and its ability to accurately measure proteinuria compared with 24 hour urine collection (24H-P) in patients with Systemic Lupus Erythematosus (SLE).

Methods: Literature search (1900 – 2015) for articles comparing PCR and 24H-P in SLE patients in the databases Medline, Web of Science and Embase. Included studies and their results were critically appraised and analyzed.

Results: 13 studies (1001 patients; 84.01% women) were included. 10 studies reported on Pearson correlation (range: 0.67-0.94); 3 studies reported on Spearman correlation (range: 0.78-1). The meta-analysis of studies with Pearson correlation showed a high overall correlation of 0.80 between 24H-P and PCR (Figure 1) however with high heterogeneity (I^2=97.2%). Correlation analysis is not sufficient to evaluate the utility of a new test against the gold standard test and analysis on agreement is required. Seven studies reported on agreement: 3 studies analyzed Concordance Correlation Coefficient (0.48-0.94); 3 Intraclass Correlation Coefficient (0.66-0.95) and 1 kappa (0.58). These results confirmed that the agreement between 24H-P and PCR was inappropriate. Three studies included Bland-Altman plot and the results also demonstrated poor agreement between both tests.

Conclusion: The PCR has a utility as a screening test for proteinuria in SLE patients. The studies' results of 24H-P and PCR showed poor agreement between both tests signifying that PCR should not substitute the gold standard test (24H-P) to accurately measure proteinuria.

Figure 1. Forest plot of correlations for the 8 studies included in the meta-analysis for the overall correlation of 24H-P and PCR



Disclosure: J. Medina-Rosas, None; **K. Yap**, None; **M. Anderson**, None; **J. Su**, None; **Z. Touma**, None.

Abstract Number: 2909

A Systematic Review and Meta-Analysis of Cutaneous Manifestations in Late Versus Early-Onset Systemic Lupus Erythematosus

Jennifer Medlin[1], Karen E. Hansen[2], Sara Fitz[3] and Christie M. Bartels[4], [1]Internal Medicine, University of Wisconsin Hospitals and Clinics, Madison, WI, [2]Rheumatology/Medicine, Univ of Wisconsin, Madison, WI, [3]Department of Dermatology, Mercy Medical Center, Dubuque, IA, [4]Medicine, Rheumatology, University of Wisconsin School of Medicine and Public Health, Madison, WI
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Background/Purpose: Systemic lupus erythematosus (SLE) is commonly diagnosed in females of reproductive age, with those diagnosed after the age of 50 referred to as late-onset SLE. Most prior studies comparing late and early-onset SLE manifestations were limited by small sample sizes. The last meta-analysis (Ward 1989) included just 9 studies. Given that more than one third of SLE classification criteria are cutaneous, we performed a systematic literature review and meta-analysis to assess the clinical differences in cutaneous manifestations between late and early-onset SLE.

Methods: Systematic review of the literature from inception through August 2013 was performed using PubMed, CINAHL, Web of Science, and Cochrane Library. We excluded studies that did not require the ACR SLE classification criteria, had no early-onset controls, defined late-onset SLE as <50 years of age, or were non-English language. The quality of the eligible studies was evaluated using Newcastle Ottawa Quality Scale. Forest plots were created using random effects models to compare rates of cutaneous manifestations by age of onset. Study heterogeneity was assessed using I^2.

Results: Thirty five studies, representing 1,727 late-onset and 11,189 early-onset SLE patients, met eligibility criteria. The female: male ratio was smaller in the late-onset group (5:1 versus 8:1, p<0.001, I^2 7.5%). Most cutaneous manifestations were less prevalent in the late-onset group, including malar rash (OR 0.43 (0.35, 0.52)), photosensitivity (OR 0.72 (0.59, 0.88)), alopecia (OR 0.63 (0.48; 0.82)), and Raynaud's phenomenon (OR 0.84 (0.71-0.99)). By contrast, sicca was more common in late versus early-onset SLE (OR 2.45 (1.91, 3.14)). Other cutaneous manifestations including mucosal ulcerations, discoid rash, cutaneous vasculitis, livedo, and subacute cutaneous lupus did not differ significantly. The mean Newcastle Ottawa Quality Scale score was 6.3±0.5 out of 9 possible points.

Conclusion: Many cutaneous manifestations were less common overall in late-onset SLE patients with the exception of sicca symptoms, consistent with prior studies. Increased sicca in late-onset lupus was also reported in a meta-analysis restricted to that topic (Yao 2012). Late-onset SLE with sicca symptoms might represent a distinct disease entity with characteristic features including milder disease course. Future studies should investigate etiologies for these phenomena including roles of genes, gender, immune senescence, environment, and isolated cutaneous versus systemic lupus prevalence in older adults.

Table 1: Meta-analysis summary statistics for 10 cutaneous manifestations in Late vs Early-onset SLE

Cutaneous Manifestation	Total cases n= 12,916	Late-onset n= 1,727	Early-onset n= 11,189	OR (95% CI)	Heterogeneity I^2 (%), p-value
Malar rash	**12,731**	**1,691**	**11,040**	**0.43 (0.35,0.52)**	**64, <0.001**
Mucosal ulcerations	11,697	1,616	10,081	0.88 (0.74, 1.04)	22, 0.14
Discoid rash	10,997	1,520	9,477	1.11 (0.91, 1.34)	9, 0.33
Photosensitivity	**12,318**	**1,698**	**10,620**	**0.72 (0.59, 0.88)**	**54, <0.001**
Sicca	**5,489**	**833**	**4,656**	**2.45 (1.91, 3.14)**	**13, 0.31**
Raynaud phenomenon	**8,515**	**1,194**	**7,321**	**0.84 (0.71, 0.99)**	**14, 0.26**
Alopecia	7,290	992	6,298	**0.63 (0.48, 0.82)**	36, 0.06
Cutaneous vasculitis	3,711	480	3,231	0.78 (0.49, 1.26)	37, 0.11
Livedo reticularis	1,619	197	1,422	0.63 (0.17, 2.31)	62, 0.03
Subacute cutaneous lupus	1,060	120	940	0.92 (0.43, 1.98)	0, 0.80

I^2 interpretation: low heterogeneity between studies ≤25%, moderate 50%, and high >75%

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Abstract Number: 2910

How Accurate Is Spot Urine Protein/Creatinine Ratio in Measuring the Change over Time in Proteinuria Level Compared to the 24 Hour Proteinuria Test?

Jorge Medina-Rosas[1], Murray Urowitz[2,3], Jiandong Su[2], Dafna Gladman[2] and Zahi Touma[2], [1]Medicine, University of Toronto, Toronto Western Hospital, Toronto, ON, Canada, [2]Rheumatology, University of Toronto, Toronto Western Hospital, Toronto, ON, Canada, [3]Rheumatology, U of Toronto, Toronto Western Hospital, Toronto, ON, Canada
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Background/Purpose: The Protein/Creatinine ratio in a spot urine sample (PCR) has been accepted as a substitute for the protein content in a 24 hours urine collection (24H-P), but there is not enough evidence on its usefulness for the prospective follow up of lupus patients. The purpose of this study was to determine if PCR can accurately measure the change in proteinuria level over time when compared to the "gold standard" test 24H-P.

Methods: Analysis on data from a single lupus centre between May 2008 and December 2014 was conducted. **Results** of concurrent urine samples for PCR and 24H-P were identified. Patients with diabetes mellitus, end stage kidney disease and kidney transplantation were excluded.

The gold standard test in this study is 24H-P. At baseline visit, urine samples with abnormal 24H-P (³0.5 g/day) and normal 24H-P (<0.5 g/day) were identified. In the group with abnormal 24H-P, the first follow up visit for each patient with 50 and 100% improvement, based on 24H-P, was identified and compared to the PCR results at this visit. In the group with normal 24H-P, the first follow up visit for each patient with worsening (³0.5 g/day) based on 24H-P was identified and compared to the PCR results at this visit. Abnormal PCR is >0.05 g/mmol.

Standardized Response Mean (SRM) for 24H-P and PCR for 50 and 100% improvement and for worsening were calculated. We hypothesized that both tests (24H-P and PCR) will change in the same direction but the effect captured by 24H-P is larger than PCR.

Results:

1188 paired samples from 230 patients.

- 24H-P 100% improvement: 60 patients started with abnormal 24H-P (³0.5 g/day) and had 100% improvement on follow up. Mean duration for improvement: 17.5 months. Among this group, only 53.3% had 100% improvement based on PCR. SRM for 24H-P: -1.00 (95% CI: -1.31 to -0.69) (large effect). SMR for PCR: -0.69 (95%CI: -0.97 to -0.41) (moderate effect).
- 24H-P 50% improvement: 64 patients started with abnormal 24H-P (³0.5 g/day) and had 50% improvement on follow up. Mean duration for improvement: 13.6 months. Among this group, only 56% of patients had 50% improvement based on the PCR. SRM for 24H-P: -1.27 (95% CI: -1.61 to -0.95) (large effect). SMR for PCR is -0.63 (95% CI: -0.90 to -0.36) (moderate effect).
- 24H-P worsening: 43 patients started with normal 24H-P (<0.5 g/day) and became abnormal (³0.5 g/day) on follow up. Mean duration for worsening of proteinuria: 10.5 months. At first visit all patients had normal 24H-P but 34.9% had abnormal PCR (≥0.5 mg/g). At the first visit with abnormal 24H-P, only 79.1% of these patients had abnormal results by PCR. SRM for 24H-P: 0.81 (95% CI: 0.46 to 1.15) (large effect). SMR for PCR: 0.53 (95%CI: 0.21 to 0.85) (moderate effect).

Magnitude of change for improvement (50 and 100%) and worsening: $SRM_{24H\text{-}P} > SRM_{PCR}$

Conclusion: PCR is not as accurate as 24H-P in determining clinically important change in proteinuria levels (50, 100% improvement and 100% worsening) in lupus nephritis. Thus 24 H-P should be used to monitor improvement or deterioration in LN in clinical practice.

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Abstract Number: 2911

Tubulointerstitial Involvement in Lupus Nephritis

Angela Pakozdi[1], Ravindra Rajakariar[2], Michael Sheaff[3] and Dev Pyne[1], [1]Rheumatology, Barts Health NHS Trust, London, United Kingdom, [2]Renal Medicine, Barts Health NHS Trust, London, United Kingdom, [3]Histopathology, Barts Health NHS Trust, London, United Kingdom

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Background/Purpose: Tubulointerstitial disease is frequent in lupus nephritis (LN) with immune deposits being present in up to one third of patients.[1,2] Lesions including interstitial infiltration, tubular atrophy and interstitial fibrosis are all independent risk factors for LN renal outcome.[3] The aim of this retrospective study was to analyze tubulointerstitial changes on a series of repeat renal biopsies (RB) and to identify correlations with clinical variables.

Methods: Histopathological changes of 39 LN patients were analysed using the revised Austin's semi-quantitative scoring system, using a grading system of 0 to 3 (0, normal; 1, mild <25%, 2, moderate between 26 and 50%; 3, severe >50% of the interstitium affected).[4] With a similar method, chronicity indices were also calculated and included scores for glomerular sclerosis, fibrous crescents, tubular atrophy and interstitial fibrosis. Spearman's rank-order correlation was run to determine relationship between clinical variables and histological findings.

Results: Compared to the initial biopsy, we found a progression in both tubular atrophy (p=0.001) and interstitial scarring (p<0.001), but not in inflammatory cell infiltration (p=1.000) by the time of RB. The mean total tubulointerstitial score (± SD) has progressed from

2.69 ± 2.03 to 3.78 ± 2.03 (p=0.001). There was a positive correlation between serum creatinine level and the severity of tubular atrophy at time of both reference biopsy (r=0.33, p=0.048) and RB (r=0.56, p<0.001). In addition serum creatinine at time of RB showed a strong correlation with interstitial scarring (r=0.60, p<0.001). We found no association between any of the other clinical variables and the tubulointerstitial pathology. A trend was identified between the severity of interstitial inflammation on reference biopsy and the amount of tubular atrophy and interstitial scaring on RB (r=0.349, p=0.19; r=0.385, p=0.009, respectively). The mean chronicity index (CI, ± SD) increased from 3.58 ± 2.64 to 5.11 + 2.96 by the time of RBs. Patients with proliferative histopathology on initial biopsy had higher CI at both the reference biopsy (4.03 ± 2.48 vs. 2.57 ± 2.79, proliferatives vs. non-proliferatives, mean score ± SD, p=0.047) and RBs (5.77 ± 2.94 vs. 3.64 ± 2.53, proliferatives vs. non-proliferatives, mean score ± SD, p=0.019). Treatment decisions did not seem to be influenced by the progression of CI (treatment escalation in 60.9% vs. 61.1%, increased CI vs. stable/reduced CI, respectively, p=0.982).

Conclusion: Not only the glomerular pathology, but tubulointerstitial lesions are also important in LN, and they show progression in time illustrated by our study using RBs. Serum creatinine level showed good correlation with the severity of tubulointerstitial lesions. Correlation was also demonstrated between the amount of interstitial inflammation on reference biopsies and the severity of tubular atrophy and interstitial scaring on RBs, suggesting a possible predictive role of damage.

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Abstract Number: 2912

Concomitant Kidney Disease in Patients with Lupus Nephritis

Paul Hoover[1], Jose A. Gomez Puerta[2], Alexander Fine[1], Helmut Rennke[3] and Karen H. Costenbader[4], [1]Rheumatology, Immunology and Allergy, Brigham and Women's Hospital, Boston, MA, [2]Grupo de Inmunología e Inmunogenética, GICIG, Universidad de Antioquia, Medellín, Colombia, Medellín, Colombia, [3]Pathology, Brigham and Women's Hospital, Boston, MA, [4]Rheumatology, Immunology & Allergy, Brigham and Women's Hospital, Boston, MA

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Background/Purpose:

The most common and clinically and histologically best-characterized SLE kidney disease is lupus nephritis (LN). However, other forms of kidney disease can and do occur concomitantly with LN, although their prevalence, clinical features and impact on disease course and response to therapy are not well described. We sought to determine the prevalence of other concomitant kidney pathology among patients with newly diagnosed LN, and to compare demographic and clinical features between patients with and without concomitant kidney findings.

Methods:

We identified patients age ≥18 years with ≥1 visit for LN and a kidney biopsy reviewed at our large academic hospital from 1992 to 2014. (For those with > 1 biopsy, we analyzed only the first) We ascertained demographics, clinical factors, and reviewed kidney biopsy reports for International Society of Nephrology/Kidney Pathology Society class (ISN/RPS) and concomitant findings. We calculated the prevalence of concomitant kidney diseases in this group of LN patients. Data were stratified by the type of kidney disease and analyzed to determine demographics, classification of lupus nephritis, median activity and chronicity index, HIV and antiphospholipid antibody status before or at the time of kidney biopsy. To compare those with and without concomitant kidney disease, Fisher's exact tests were used for categorical variables and Wilcoxon rank-sum tests for continuous variables.

Results:

We identified 76 patients with LN confirmed on kidney biopsy. Overall, the median age at biopsy was 37 years old (range 18-71) and racial breakdown was: Asian 6%, Hispanic 16%, Black 25%, White 29%, other/unknown 23%. The major concomitant kidney pathologic findings were thrombotic microangiopathy (TMA, 10, 13%) and collapsing glomerulonephropathy (GN, 15, 20%). Four patients (5%) had both TMA and collapsing GN. Comparisons of the demographic and clinical factors among those with and without concomitant kidney disease are given in the **Table**. Compared to those without concomitant pathology, patients with collapsing glomerulonephropathy and those with TMA were more likely to be Black (**Table**). Distributions of lupus nephritis class were different across the 3 groups defined by presence of collapsing GN or TMA or not, but there were no significant differences in median activity or chronicity indices. No patients were HIV positive. There were no differences in the proportions who had antiphospholipid antibodies. Other findings included interstitial nephritis (6, 8%), tubular injury (5, 7%) and vascular injury (10, 13%).

Conclusion:

Other concomitant pathology occurred in a substantial number of LN kidney biopsies in this population. The clinical and prognostic implications of these findings deserve further study. In future analyses, we will investigate variation in treatment and outcomes among those with and without other concomitant kidney pathologies.

Table. Comparison of SLE patients with Classical ISN/RPS Lupus Nephritis Alone vs. with Concomitant Kidney Pathology on Kidney Biopsy

	LN without CGN or TMA (n=53)	**LN with Collapsing Glomerulo-nephropathy (n=15)**	**p value[a]**	**LN with Thrombotic Microangiopathy (n=10)**	**p value[b]**
Median Age at Biopsy, years (range)	36 (22-61)	42 (18-71)	0.57	39 (24-65)	0.34
% Female	87	87	0.40	100	**0.001**
Race/Ethnicity					
% Black	19	47	**<0.001**	40	**<0.001**
% White	32	20		20	
% Hispanic	17	13		10	
% Asian	9	0		0	
International Society of Nephrology/Renal Pathology Society (ISN/RPS) Class					
% Class 2	16	27	**<0.001**	40	**<0.001**
% Class 3	17	27		20	
% Class 4	30	13		40	
% Class 5	36	26		0	
Median Activity Index (range)	5 (0-16)	3 (1-11)	0.71	2 (2-21)	0.82
Median Chronicity Index (range)	3 (0-24)	6 (2-9)	0.02	6 (2-9)	0.03
% +HIV	0%	0%	1	0%	1
% +APLA[c]	20%	20%	1	33%	0.53

Fisher's exact tests or Chi squared tests for categorical data and Wilcoxon Rank sum tests for continuous data (1 person added to each zero cell in order to calculate)

[a] p-value comparing those without other findings vs. those with Collapsing GN

[b] p-value comparing those without other findings vs. those with Thrombotic Microangiopathy

[c] APLA= antiphospholipid antibodies

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Abstract Number: 2913

Intensified Treatment of B Lymphocyte Depletion (ITBLD) without Immunosuppressive Maintenance Treatment As a Rescue Therapy in Refractory Lupus Nephritis (LN): A 4-Year Observation

Dario Roccatello[1], Savino Sciascia[2], Daniela Rossi[1], Carla Naretto[3], Simone Baldovino[3], Mirella Alpa[3], Ilaria Salussola[3] and Vittorio Modena[3], [1]Department of Medicine and Experimental Oncology, CMID - Center of Research of Immunopathology and Rare Diseases, Turin, Italy, [2]Department of Rare, Immunologic, Hematologic and Immunohematologic Diseases, Centro di Immunopatologia e Documentazione su Malattie rare, Torino, Italy, [3]CMID, Torino, Italy
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Background/Purpose: B-lymphocytes (BL) play a critical role in Systemic Lupus Erythematosus (SLE). BL depletion therapy still remains an attractive option, despite the disappointing results of randomized controlled trials (RCTs).

Methods: Twelve SLE patients [2 males, mean age 43.8 yrs (29-54)] with polyarthralgia and multiorgan involvement including class IV or III/V (ISN/RPS) glomerulonephritis (9 cases), skin lesions (9 cases, with necrotizing ulcers in 3), polyneuropathy (7 cases), CNS involvement (2), lymphoadenopathy (6) e polysierositis (5) have been treated with an IBLD protocol: Six patients were refractory or intolerant to conventional immunosuppressive therapy. Six patients were given the following induction regimen as a front line therapy. Protocol: Rituximab (RTX) 375 mg/sm on days 1, 8, 15, 22, and 2 more doses after one and two months, associated with 2 IV administrations of 10 mg/kg of cyclophosphamide, and 3 methylprednisolone pulses (15 mg/kg) followed by oral prednisone (0.8 mg/die, rapidly tapered to 5 mg/day 12 weeks). No further immunosuppressive maintenance therapy has been given.

Results: ITBLD obtained a complete depletion of CD20+ BL for 12-18 months. Patients had been followed-up for 48.9 (25-93) months. Significant decreases ($p<0.05$) were found in the levels of ESR (baseline mean value: 54.2 mm; 3 months: 33; end of follow-up: 14.9), anti-dsDNA antibodies (baseline: 192 U; 3 months: 112; end of follow-up: 17), and proteinuria (baseline: 4.9 g/24 hours; 3 months: 0.97; end of follow-up: 0.22). C4 values (baseline 11 mg/dl) significantly increased ($p<0.05$) after 3 months (22 mg/dl) and at the end of the follow-up (20 mg/dl). Three patients relapsed after 36, 41 and 72 months, respectively. They showed again a complete remission after re-treatment over 13-48 months of observation

Conclusion: A promising role of RTX in an intensified protocol of induction therapy can be envisaged in patients for whom avoiding immunosuppressive maintenance therapy and sparing steroids are particularly appealing. Moreover, our data confirm the opportunity to reconsider the regimens of BL depletion in the treatment of the most severe or refractory forms of SLE despite the disappointing results of RCTs.

Disclosure: D. Roccatello, None; **S. Sciascia**, None; **D. Rossi**, None; **C. Naretto**, None; **S. Baldovino**, None; **M. Alpa**, None; **I. Salussola**, None; **V. Modena**, None.

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Abstract Number: 2914

Modifiable and Non-Modifiable Correlates of Satisfaction with Care in Systemic Lupus Erythematosus

Syed Alam[1], Nisarg Gandhi[2], Alana Nevares[1], Ailda Nika[2], Winston Sequeira[2] and Meenakshi Jolly[3], [1]Internal Medicine, Cook County Hospital, Chicago, IL, [2]Rheumatology, Rush University Medical Center, Chicago, IL, [3]Department of Medicine, Section of Rheumatology, Rush University Medical Center, Chicago, IL
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Background/Purpose: Systemic Lupus Erythematosus (SLE) a chronic disease, predominantly of young women, which may involve various organs, and is marked by periods of disease flares, activity and damage. It may interfere with training, work, social life, and performance of important roles in life. Its treatment may involve use of corticosteroids and immunosuppressive medications which may cause side effects. SLE can adversely impact various aspects of one's life and may significantly impair quality of life of patients and their loved ones. With the aim of improving patient care, we sought to determine significant modifiable and non-modifiable correlates of satisfaction with care (SC) in SLE.

Methods: Fifty consenting SLE patients fulfilling ACR classification criteria were given self-administered surveys (FACIT-Fatigue, Self-reported Fibromyalgia Tender Point, Pain, Insomnia Severity Index for Sleep, Perceived Stress Scale-4, Patient Health Questionnaire-9 for depression, LupusPRO) at routine care visits. Disease activity and damage were assessed using SELENA-SLEDAI (SS) and SLICC/ACR (SDI). Non-modifiable variables of interest were age, gender, education, marital status, disease duration, number of ACR criteria, damage, lupus nephritis (LN) diagnosis and fibromyalgia (FM) diagnosis. Modifiable variables of interest included disease activity, current use and current dose of corticosteroids, specific SLE medications, self-reported FM tender point count, pain, insomnia, fatigue, depression and stress. SC was measured using the LupusPRO SC domain items. Univariate and multivariate regression modeling was done, with SC as a dependent variable and with the above variables of interest. P value of ≤ 0.05 on two tailed test was significant. Bonferroni correction was used for the final model, and a $p \leq 0.006$ was significant on two tailed test.

Results: Mean (SD) age was 41.4+13 years, 90% participants were women. Ethnic background was as follows: 56% Blacks, 24% Whites, 10% Asians and 10% Others. Median (IQR) values of Physician Global Assessment (PGA), total SS, and SDI were 0.5 (0.8), 4.0(6.0) and 1.0(1.0), respectively. Age, education, disease duration, damage, FM diagnosis and LN diagnosis were the non-modifiable, while disease activity, current corticosteroid dose and fatigue were the modifiable correlates of SC (Table 1). Greater disease activity, disease duration and FM were associated with better SC. Together these 8 variables accounted for 51% variance in SC. After Bonferroni correction, age, education and FM were not significant in the model, but rest remained significant.

Conclusion: Fatigue and current daily dose of steroids are significant and modifiable correlates of satisfaction with care in SLE, even after adjusting for FM. We suggest proactive assessment and interventions targeted towards addressing fatigue and steroid dose reduction at each visit for SLE patients.

Table 1: Multivariate Model for Satisfaction with Care

Variable	Standardized Beta	95% CI	P value
			*significant after Bonferonni correction for multiple comparisons
Non-modifiable			
Age	-0.32	-1.28, -0.10	0.024
Education	-0.39	-23.94, -3.53	0.010
Disease duration	0.38	0.44, 2.60	0.007
Lupus nephritis	-0.63	-53.25, -17.50	0.0001*
Fibromyalgia	0.37	3.85, 50.46	0.024
Modifiable			
Disease activity	0.55	1.32, 4.89	0.001*
Fatigue	-0.45	-1.73, -0.40	0.003*
Daily prednisone dose	-0.41	-1.17, -0.21	0.006*

Disclosure: S. Alam, None; **N. Gandhi**, None; **A. Nevares**, None; **A. Nika**, None; **W. Sequeira**, None; **M. Jolly**, Pfizer Inc, 7.

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Abstract Number: 2915

The Utility of Lupus Serology in Predicting Outcomes of Renal Transplantation in Lupus Patients: Systematic Review and Analysis of a Large Lupus Cohort

Kristy Yap[1], Murray Urowitz[1,2], Quenby Mahood[3], Jorge Medina-Rosas[4], Arthy Sabapathy[5], Daeria Lawson[4], Jiandong Su[1], Dafna Gladman[1] and Zahi Touma[1], [1]Rheumatology, University of Toronto, Toronto Western Hospital, Toronto, ON, Canada, [2]Rheumatology, U of Toronto, Toronto Western Hospital, Toronto, ON, Canada, [3]Library Services, Institute of Work and Health, Toronto, ON, Canada, [4]Medicine, University of Toronto, Toronto Western Hospital, Toronto, ON, Canada, [5]University of Toronto, Toronto Western Hospital,

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Background/Purpose: To study the utility of lupus serology as a predictor for kidney graft outcome in: a) a systematic review (SR) of the literature and b) a lupus cohort.

Methods: For the SR, a literature search in Medline and Embase (inception-2014) was performed to identify the articles reporting on the serology at RT and on the outcome of RT. Included studies were critically appraised using the Newcastle Ottawa Scale (NOS).

Patients who underwent RT in the identified. RT outcomes included: a) nonfunctional graft requiring dialysis ≤ 3 weeks, b) graft failure requiring permanent dialysis after 3 weeks, c) graft survival not requiring dialysis d) death. The patients were grouped into graft failure and survival. The duration of graft failure was defined as the time between RT and subsequent dialysis. The duration of graft survival was defined as the time between RT and recipient death or the end of the study with functioning graft.

Results:

The literature search identified 539 references, excluding 119 duplicates. Of the 539, 534 were not relevant to the research question. 5 studies in addition to our lupus cohort data (n= 77 patients) were included in the SR. The majority of the grafts survived to at least 1 year regardless of whether the serology was positive or negative pre transplant which is consistent with the results of our lupus cohort (Table 1). The quality assessment of the studies using the NOS revealed limitations in the domains of outcome and selection due to small sample size and a short follow up period.

32 of 1783 patients in our lupus cohort had a RT. 2 patients had a nonfunctional graft, 5 patients had graft failure (2 patients had failure <5 years and 3 ≥5 years) and 25 patients had graft survival (11 had survival ≥5 years). 1 year prior to RT, 40% of the graft failures had positive serology compared to 52% in the graft survival (Table 2). Both failure and survival groups demonstrated no clinical disease activity at 1 year prior to RT. The time to graft failure (n=5) was 9.2 ± 6.77 years. In the failure group, 2 patients died by 12.1 ± 1.0 years, 2 patients are still alive and 1 was lost to follow-up. In the graft survival group, 5 patients died by 7.1 ± 5.6 years and 1 patient was lost of follow-up. Cause of death was ischemic heart disease in 3 patients, sepsis in 2 patients and unknown in 1 patient.

Table 1: Survival of the graft in patients with positive and negative serology at RT

	Seropositive patients n=33				**Seronegative patients n=38**					
	Failure at 6 months		**Failure at 1 year**		**Failure at 6 months**		**Failure at 1 year**		**Failure at 5 years**	
Author	**Yes**	**No**	**Yes**	**No**	**Yes**	**No**	**Yes**	**No**	**Yes**	**No**
Yap 2015	0	15	0	15	0	13	0	0	1	11
Dong 2005	0	3	0	2	0	10	0	9	1	3
Rivera 1990	NA	NA	NA	NA	0	4	0	4	0	3
Amend 1977	2	6	2	6	0	2	0	2	NA	NA
Bitker 1993	0	4	0	4	NA	NA	2	4	NA	NA
Goss 1991	0	3	1	2	0	9	0	9	2	2
Total	**2**	**31**	**3**	**29**	**0**	**38**	**2**	**28**	**4**	**19**

Table 2. Characteristics of graft failure and survival patients in our lupus cohort

	Graft Failure n=5	Graft survival n=25	Total Grafts n=30
Sex (F)	100%	84%	86.7%
Age at lupus diagnosis (yr)	27.14 ± 9.66	22.28 ± 7.43	23.09 ± 7.87
Age at RT (yr)	33.79 ± 14.01	39.14 ± 8.83	38.25 ± 9.79
Lupus duration at 1st clinic visit (yr)	6.21 ± 4.19	7.60 ± 8.94	7.37 ± 8.30
Lupus duration at RT (yr)	6.65 ± 4.82	16.86 ± 8.22	15.16 ± 8.61
DNA +ve in 1 year prior	1/5	6/24 (NA n=1)	7/29
Low complements in 1 year prior	2/5	13/25	15/30
DNA +veand low C3/C4 in 1 yr prior	1/5	4/23 (NA n=2)	5/28
DNA +ve and/or low C3/C4 in 1 yr post RT	3/4 NA n=1	12/25	15/29
AMS-(serology) 1 yr prior to RT	4.90 ± 2.54	3.75 ± 4.59	3.90 ± 4.36
SDI at RT	4.00 ± 0.82	4.48 ± 2.43	4.41 ± 2.28
Months on dialysis prior to RT	33.43 ± 17.54	56.25 ± 45.55	51.86 ± 42.34
Source of allograft (Cadaver or Living)	2/5 Cadaver 1/5 Living 2/5 Unknown	11/25 Cadaver 13/25 Living 1/25 Unknown	13/30 Cadaver 14/30 Living 3/25 Unknown

Conclusion: The results of this SR found that the persistence of serological abnormalities at the time of RT was not associated with graft failure. These results are consistent with the results of our lupus cohort.

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Abstract Number: 2916

Analysis of Risk Factors of the Progression to Chronic Kidney Disease and Comorbidities in Lupus Nephritis

Yoichiro Akiyama, Takeo Sato, Takamasa Murosaki, Katsuya Nagatani, Masahiro Iwamoto and Seiji Minota, Division of Rheumatology and Clinical Immunology, Jichi Medical University, Tochigi, Japan

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Background/Purpose: Many studies have reported long-term outcomes including morbidity, mortality, and end stage kidney disease (ESKD) in patients with lupus nephritis (LN). We aimed to elucidate the risk factor of the progression to chronic kidney disease (CKD) in patients with lupus nephritis, and the development of comorbidity and its impact on the renal function.

Methods: We collected 116 patients with a diagnosis of LN who were hospitalized in our division from 2005 to 2013, and were followed up for at least 1 year or died within 1 year. We retrospectively examined the demographics, the clinical course, and the progression to CKD (defined as equal to or severer than G3bA1, G3aA2, or G2A3 by the classification for CKD). We performed COX hazard regression analysis to elucidate the risk factor of the progression to CKD and examined the impact of acute kidney injury (AKI) and acute decompensated heart failure (ADHF) on the renal function and the incidence of vascular event.

Results: The ratio of female to male was 8.7 : 1 and the median age of LN onset was 32 year-old. LN as one of the first symptoms was 54%, and 52% of LN showed proteinuria ≥ 3.5 g/day at least one time during the clinical course. Clinical symptoms and laboratory data included arthritis or arthralgia (41%), facial erythema (40%), serositis (20%), neurological symptoms (12%), hematological abnormality (22%), positive anti-double stranded DNA antibody (86%), and positive anti-phospholipid antibody (30%). In 98 renal biopsy-proven patients (86%), the pathological diagnoses (WHO classification) were class II (7%), IV (III) (45%), V (32%), and IV (III)+V (16%). Kaplan-Meier analysis showed survival, ESKD (introduction of dialysis or renal transplantation)-free, and CKD-free rate at 20 years were 0.761, 0.677, and 0.433, respectively (Figure 1). Multivariate COX hazard regression analysis revealed the hazard ratio of proteinuria ≥ 3.5 g/day for the progression to CKD was 2.01 (95% confidence interval, 1.06 to 3.81; p = 0.03). ADHF, AKI, and vascular events developed in 6, 9, and 12 patients, respectively. All patients with ADHF and 8 of 9 patients with AKI progressed to CKD eventually. There was a tendency that the cumulative incidence of vascular events in patients with CKD was higher than in those with non-CKD in the late phase (0.45 vs. 0.24, Figure 2).

Conclusion: Nephrotic proteinuria was a risk factor of CKD, and ADHF and AKI may have a deteriorating impact on the subsequent renal function. In the late phase, vascular events should be cared for patients with LN who progressed to CKD.

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Abstract Number: 2917

Combined Proliferative and Membranous Lupus Nephritis: Is the Prognosis Really Poor?

Ryota Sakai[1], Akiko Shibata[1], Kentaro Chino[1], Jun Kikuchi[2], Tsuneo Kondo[1], Ayumi Okuyama[1], Hirofumi Takei[1] and Koichi Amano[1], [1]Department of Rheumatology and Clinical Immunology, Saitama Medical Center, Saitama Medical University, Saitama, Japan, [2]Rheumatology and Clinical Immunology, Saitama Medical Center, Saitama Medical University, Saitama, Japan
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Background/Purpose: Using light microscopy (LM) or immunofluorescence (IF), combined proliferative and membranous lupus nephritis (LN) is defined as an active proliferative class III/IV lesion and diffusely distributed membranous lesion (involving >50% tuft of >50% glomeruli) in ISN/RPS 2003. A mixed-type LN was reported to show poor prognosis[1,2]; however, an interesting case report on corticosteroid-free treatment regimen of rituximab and mycophenolate mofetil is recently published[3]. We examined the renal outcome of mixed-type LN based on renal remission, end-stage renal disease (ESRD), and death.

Methods: We retrospectively evaluated 66 cases constituting class III and IV lesions, including 22 showing mixed-type LN on renal biopsy, during 2005–2014. Mixed-type LN were divided into 2 groups; membranous findings on LM + IF (LM group; n = 18) and those on IF only (IF group; n = 4). Renal remission was defined as a spot urine protein/creatinine ratio <0.5 g/g Cr and normal or near-normal eGFR (within 10% of normal eGFR) in EULAR/ERA-EDTA recommendations and KDIGO guidelines.

Results: Clinical findings were mean age 40.6 ± 15.8 years (male:female = 6:16), disease duration 5.2 ± 5.2 years, and observation period 2.2 ± 2.0 years and concentration of urine protein 3.5 ± 2.9 g/day, serum creatinine 0.93 ± 0.49 mg/dl, dsDNA 225.2 ± 745.6 IU/ml, C3 57.6 ± 24.0 mg/dl, and C4 9.9 ± 7.0 mg/dl. Pathological findings were activity index 6.0 ± 3.1, chronicity index 2.4 ± 2.6, cellular crescents 54.6%, fibrinoid necrosis 22.7%, and chronicity of glomeruli 72.7%. Twenty of 22 cases were class IV + V and 2 cases were class III + V. Most cases received a high dose of corticosteroids (0.6–1.0 mg/kg/day) and various immunosuppressants such as cyclophosphamide, tacrolimus, azathioprine, cyclosporine, and mizoribine for remission induction and maintenance therapy. IF group cases had a tendency toward shorter disease duration than LM group cases; there were no chronic lesions. The IF group cases achieved renal remission at the last observation and no ESRD or death. The LM group cases had a statistically significant lower remission rate of 27.8%; two cases developed ESRD and death.

Conclusion: This retrospective clinico–pathological study shows that mixed-type LN, defined as per findings of LM + IF, has a poor prognosis. However, mixed-type LN determined by IF only has an unexpectedly high remission rate, probably because of early detection of membranous lesions without morphological alterations.

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Disclosure: R. Sakai, None; **A. Shibata**, None; **K. Chino**, None; **J. Kikuchi**, None; **T. Kondo**, None; **A. Okuyama**, None; **H. Takei**, None; **K. Amano**, None.

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Abstract Number: 2918

Do Patients with Lupus Nephritis Who Achieve Complete Proteinuria Recovery at 2 Years Have Better Long Term Outcomes Compared to Patients with Partial Proteinuria Recovery?

Zahi Touma[1], Murray Urowitz[2,3], Jorge Medina-Rosas[4], Jiandong Su[1] and Dafna Gladman[1], [1]Rheumatology, University of Toronto, Toronto Western Hospital, Toronto, ON, Canada, [2]University of Toronto, Toronto, ON, Canada, [3]Rheumatology, U of Toronto, Toronto Western Hospital, Toronto, ON, Canada, [4]Medicine, University of Toronto, Toronto Western Hospital, Toronto, ON, Canada
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Background/Purpose: The tempo of Complete Proteinuria Recovery (CPR) in Lupus Nephritis (LN) is slow and while 28% achieve CPR at year 1 this increases to 52% at year 2. The long term outcomes of patients who achieve CPR or Partial Proteinuria Recovery (PPR) of≥ 50% at 2 years is not well studied.

To determine the prognostic value of PPR and CPR at 2 years on long term outcomes compared to patients who did not recover proteinuria ≥ 50% on the standard of care therapy.

Methods: All patients that are registered at a large lupus clinic from 1970–2015 were reviewed (n=1782) and patients with LN were identified. LN was defined as: Proteinuria ≥0.5g/24 hours or spot Urine Protein Creatinine Ratio≥ 0.6mg/mg on 2 consecutive occasions within one year. Patients who achieved PPR or CPR within 2 years and have at least 5 years of follow up since the onset of LN were studied.

*Endpoints:*CPR was defined as proteinuria <0.5g/24 hours or PCR<0.6 mg/mg at least on 2 occasions. PPR was a decrease of ≥50% but not to normal levels. Not recovered was defined as <50% improvement.

*Long term outcomes:*Death, eGFR<15, dialysis or kidney transplant, damage [SLICC Damage Index (SDI)] >0 and >3) and atherosclerotic events occurring after achieving PPR or CPR.

*Analyses:*Non-parametric tests, survival analyses and simple cox regression were used to study the effect of PPR/CPR on outcomes.

Results: 326 patients (85% F) with LN were studied. The age at LN onset was 34.56 ± 12.19 yrs and lupus duration at LN onset was 5.72 ± 6.71 yrs. Follow up duration from lupus nephritis was 14.97 ± 8.95 yrs.

Endpoints at 2 years: 178 had CPR, 43 PPR and 105 did meet the endpoints.

The prevalence of comorbidities(except damage) was the lowest in the CPR group, slightly higher in the PPR group and the highest in the no remission group (table 1).

Although CPR protects against the development of comorbidities (death, end stage kidney disease, dialysis and transplant, and

atherosclerosis), PPR does not. Damage accrual was not protected by CPR or PPR.

Table 1. Long term outcomes among 3 groups

Outcomes	No remission N = 105 (n and %)	PPR N = 43 (n and %)	CPR N = 178 (n and %)
Death	25 (23.8)	7 (16.3)	21 (11.8)
eGFR < 15	17 (16.2)	9 (20.9)	10 (5.6)
Dialysis or Transplant	15 (14.3)	8 (18.6)	10 (5.6)
SDI > 0	86 (81.9)	36 (83.7)	129 (72.5)
SDI > 3	30 (28.6)	20 (46.5)	44 (24.7)
Atherosclerotic Events	22 (20.9)	5 (11.6)	21 (11.8)

Table 2. Effects of CPR and PPR on long term outcomes (simple cox regression)

Outcomes	Comparisons	Hazard Ratio	95% CI	P value
Death	**PPR to no remission**	0.68	0.29-1.57	0.36
	CPR to no remission	0.54	0.30-0.96	0.035
eGFR < 15	**PPR to no remission**	1.27	0.56-2.84	0.57
	CPR to no remission	0.33	0.15-0.72	0.005
Dialysis or Transplant	**PPR to no remission**	1.31	0.55-3.08	0.54
	CPR to no remission	0.41	0.19-0.92	0.03
SDI > 0	**PPR to no remission**	0.98	0.66-1.45	0.93
	CPR to no remission	0.91	0.69-1.19	0.48
SDI > 3	**PPR to no remission**	1.43	0.80-2.53	0.23
	CPR to no remission	0.838	0.52-1.34	0.46
Atherosclerotic Events	**PPR to no remission**	0.434	0.16-1.18	0.10
	CPR to no remission	0.509	0.27-0.95	0.033

Conclusion: Achieving CPR at 2 years, from the onset of LN, protects against comorbidities. PPR at 2 years doesn't protect against comorbidities, thus physicians should aim to achieve CPR to prevent comorbidities in LN patients.

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Abstract Number: 2919

Effect of Thrombotic Microangiopathy on Clinical Outcomes in LUPUS Nephritis

Krishan Gupta[1], Manish Rathi[2], Navin Pattanashetti[3], Ritambhra Nada[4] and Aman Sharma[5], [1]Nephrology, Postgraduate Institute of Medical Education and Research, Chandigarh, India, [2]Department of Nephrology,, Postgraduate Institute of Medical Education and Research, Chandigarh, India, [3]Internal Medicine, Junior Resident, Chandigarh, India, [4]Histopathology, Professor, Chandigarh, India, [5]Internal Medicine, Postgraduate Institute of Medical Education and Research, Chandigarh, India

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Background/Purpose:

In addition to glomerular lesion, renal vascular lesion is also an important prognostic marker of lupus nephritis (LN). Among various vascular changes thrombotic microangiopathy (TMA) presents with severe clinical manifestations and high mortality. The aim of this study was to assess the spectrum and impact of TMA on the outcomes of LN.

Methods: In this prospective observational study of one and half year duration, clinical and renal histopathological data of 102 patients with biopsy proven LN were noted and in addition evaluatation for antiphospholipid syndrome (APS) as cause of TMA in LN was also carried out. Study subjects were followed up actively for six months and various outcomes were noted. Cases were divided into two groups as LN with TMA and LN without TMA, and various features were compared between two groups. Renal TMA was defined as intertubular artery and glomerular capillary response including endothelial cell swelling, lumen narrowing or obstruction & thrombi formation by light microscopy. Swelling of glomerular endothelial cells, detachment from glomerular basement membrane and widening of sub-endothelial space were identified by electron microscopy. Outcomes noted were complete response, partial response, failure and death.

Results: In the 102 patients with lupus nephritis, 26 patients were diagnosed as co-existing with renal TMA based on strict pathological criteria. Among the 26 patients three patients were found to have concomitant APS (11.5%). As compared to cases without TMA, patients with TMA had significantly higher rates of arthralgia, malar rash, advanced renal injury i.e. serum creatinine >3mg/dl(34.6% Vs 11.84% with P= 0.008), higher percentage of fibrocellular+fibrous crescents (P= 0.018) and tubular atrophy (P= 0.006),. Even though the rates of endocapillary proliferation (73.1% Vs 56.5%), hyaline thrombhi(19.2% Vs 7.9%), and glomerular sclerosis(46.2% Vs 30.3%) were higher in TMA group compared to cases without TMA, but failed achieve statistical significance.. Patients of Lupus nephritis with TMA had poorer outcomes i.e higher rates of failure to treatment(P=0.011) and lower rates of complete response(P=0.031) compared to non TMA group. Renal TMA group is significantly associated with 7.26 times more likely poor outcomes than non TMA group(Odds ratio7.262, 95% confidence interval:1.585 to 31.303, P= 0.008).

Conclusion: Presence of TMA in lupus nephritis is associated with adverse clinicopathological presentation and poorer outcome.

Disclosure: K. Gupta, None; **M. Rathi**, None; **N. Pattanashetti**, None; **R. Nada**, None; **A. Sharma**, None.

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Abstract Number: 2920

Time to Recovery of Individual Lupus Manifestations on Standard of Care Treatment

Zahi Touma[1], Dafna Gladman[1], Jiandong Su[1] and Murray Urowitz[2,3], [1]Rheumatology, University of Toronto, Toronto Western Hospital, Toronto, ON, Canada, [2]University of Toronto, Toronto, ON, Canada, [3]Rheumatology, U of Toronto, Toronto Western Hospital, Toronto, ON, Canada

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Background/Purpose: Musculoskeletal, dermal and renal systems are the most commonly represented systems in lupus clinical trials. Thus, it is very important to study the time to recovery in each individual system on standard of care treatment in longitudinal studies of lupus patients. The objective of this study was to compare the time to recovery in individual lupus manifestations on standard of care treatment.

Methods: Consecutive lupus patients with active disease (SLEDAI-2K ≥6 at first visit) who attended the Lupus Clinic between 2000 and 2012 were studied. The analysis was conducted on patients who had: 1) At least 1 of the following 3 systems active by SLEDAI-2K criteria – renal (proteinuria), musculoskeletal (arthritis) or dermal (mucosal ulcers, rash and/or alopecia) and 2) started or

increased prednisone therapy. All patients had to have at least one year follow-up.

The analysis was focused on the group of patients who improved their disease activity which is defined as a decrease in SLEDAI-2K by ≥4. Time to recovery in each individual system among these patients was determined using the Kaplan-Meier curves.

Results: 158 patients fulfilled the inclusion criteria and were further studied. Of the 158 patients and at the last visit (9-12 months), 109 (69%) patients showed overall improvement and they were further studied. In 109 patients, at first visit, musculoskeletal system was present in 48 patients, renal (proteinuria) in 42 patients and dermal in 48 patients.

Time to improvement in individual lupus manifestations (Figure 1):

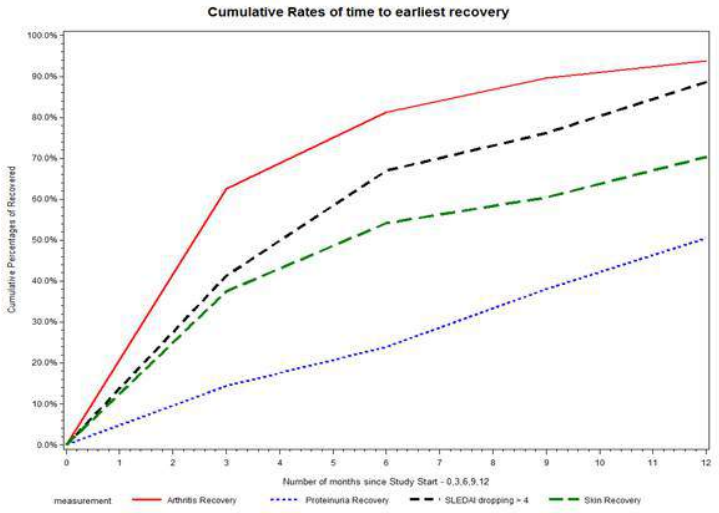
-Arthritis: 50% of the patients recovered by 3 months (95% CI: 3-6 months) and at 12 months, 45 out of 48 (94%) recovered. 3 patients did not recover by the last visit.

-Dermal system: 50% of the patients recovered by 6 months (95% CI: 3-12 months) and at 12 months 33 out of 48 (69%) patients recovered. 15 patients did not recover at the last visit.

-Renal (proteinuria):48% improved by 12 months (95% CI: 9-12 months). 22 patients did not recover proteinuria at the last visit.

Conclusion: The time to recovery of individual lupus manifestations on standard of care therapy varies among organ systems. Arthritis was the fastest to recover followed by the mucocutaneous manifestations and then proteinuria. These facts should be taken into consideration when determining the length of clinical trials with new agents.

Figure 1. Time to recovery in individual manifestations of lupus



Disclosure: Z. Touma, None; **D. Gladman**, None; **J. Su**, None; **M. Urowitz**, None.

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Abstract Number: 2921

Lupus Nephritis: An Exploration of Management Style

Abhishek Nandan[1], Huzaefah Syed[2], Christen Vagts[1] and Jason Kidd[1], [1]Virginia Commonwealth University Medical Center, Richmond, VA, [2]Rheumatology, Virginia Commonwealth University Medical Center, Richmond, VA

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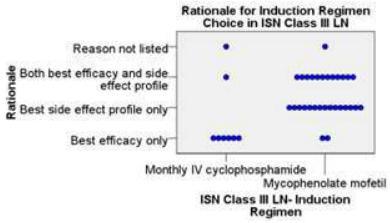
Background/Purpose: We aim to evaluate the differences and rationale behind the diagnostic and therapeutic approaches to proliferative lupus nephritis (LN) among nephrologists and rheumatologists.

Methods: A de-identified, multiple-choice survey was distributed to nephrologists and rheumatologists in the United States. The survey consisted of a demographic questionnaire and two case vignettes exploring the decision of when to biopsy for the diagnosis of LN, management of International Society of Nephrology (ISN) Class III LN, and management of refractory ISN Class IV LN.

Results: There were 38 respondents to the survey: 12 rheumatologists and 26 nephrologists. Work setting: 81% academic, 19% non-academic. Management of abnormal urinalysis findings in an asymptomatic lupus patient: 33% of rheumatologists versus 76% of nephrologists chose to biopsy. Induction regimen of ISN Class III LN: 79% of all providers chose mycophenolate mofetil (MMF) and 21% chose IV cyclophosphamide.

Choice of Induction Regimen in ISN Class III LN per Specialty

	Mycophenolate Mofetil	IV Cyclophosphamide	Total
Nephrology	18	8	26
Rheumatology	12	0	12
Total	30	8	38



Maintenance regimen of ISN Class III LN: all surveyed rheumatologists chose MMF as a sole maintenance agent compared to 32% of nephrologists who elected the addition of low-dose corticosteroids to MMF. Choice of an adjunctive agent in refractory ISN Class IV LN: 68% of all providers chose rituximab, 14% chose tacrolimus, 5% chose abatacept, and 14% elected not to add any agents listed.

Conclusion: The results of this survey suggest a significant difference among rheumatologists and nephrologists on the decision to perform initial kidney biopsy and management of ISN Class III LN. The results suggest that perception of side effect profiles play an important role in the choice of therapeutics. This study emphasizes the need for a multi-disciplinary approach toward renal disease in lupus patients. We continue to recruit subjects to complete this survey.

Disclosure: A. Nandan, None; **H. Syed**, None; **C. Vagts**, None; **J. Kidd**, None.

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Abstract Number: 2922

HLA-Specific Antibody Profile in Renal Transplant Patients with Systemic LUPUS Erythematosus

Diana Girnita[1], Paul Brailey[2] and Alin Girnita[3], [1]Division of Immunology, Allergy & Rheumatology, University of Cincinnati Medical Center, Cincinnati, OH, [2]Transplant Immunology Division, University of Cincinnati Medical Center -Hoxworth Blood Center, cincinnati, OH, Oman, [3]Transplant Immunology Division, University of Cincinnati Academic Health Center, Hoxworth Blood Center, Cincinnati, OH

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Background/Purpose: End stage renal disease due to Systemic lupus erytematosus (SLE) is one of the autoimmune disorder leading to renal transplantation. In this single-center study we sought to describe the sensitization profile in renal transplant patients with end stage renal disease due to SLE.

Methods: A retrospective single center analysis in the last ten years revealed 26 renal transplant patients with SLE (20 females and 6 males). This group was matched to a 53 patient control group, without SLE, but matched for gender and age distribution. The detection and specificity of anti-HLA antibody was achieved by single-antigen bead (Luminex) assays. The HLA polymorphism for A, B, C, DRB1, DRB3/4/5, DQB1, DQA1, DPB1 was performed by reverse SSO for intermediate resolution in all patients, while high resolution SBT (Sanger) was used for 12 cases. The auto-crossmatches were performed both by complement-dependent cytotoxicity, and by flowcytometry.

Results: The HLA typing in SLE group has shown a higher (19/26, 73%) prevalence of HLADRB13/4/5 antigens when compared to control group (8/53, 15%, $p<0.05$). Furthermore, 4 SLE patients (15%) exhibited a positive cytotoxic and flow auto-crossmatch, compared to only 1 (2%) in controls ($p<0.01$). The distribution of HLA-specific antibody was 20/26 (77%) in SLE versus 18/53 in controls (33%), $p<0.01$ The class distribution in SLE group was: 19 anti-class I, and 11 anti class II, versus 11 class I and 7 class II in controls. 22 patients in SLE group exhibited anti-HLA antibody towards public epitopes resulting in a calculated PRA > 50%, while 19 SLE patients exhibited anti-HLA antibody towards public epitopes resulting in a calculated PRA > 80%. The control group had a significantly lower proportion of strong antibody towards public epitopes (4/18 and 2/18, respectively, $p<0.01$).

Conclusion: Renal transplant patients with SLE exhibited a higher prevalence of HLADRB13/4/5 self antigens, and a higher prevalence of positive auto crossmatches and strong HLA antibody towards public epitopes. This might explain their worse transplant outcomes due to higher prevalence of antiHLA antibodies in these patients.

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Abstract Number: 2923

The Effects of Disease Activity and Mood Disorders on Cognitive Function in Systemic Lupus Erythematosus

Michelle Barraclough[1,2], Rebecca Elliott[2,3], Shane McKie[2,3], Ben Parker[1,2] and **Ian N. Bruce**[1,2], [1]Stopford Building, Arthritis Research UK Centre for Epidemiology, Centre for Musculoskeletal Research, Institute of Inflammation and Repair, Manchester Academic Health Science Centre, The University of Manchester, Manchester, United Kingdom, [2]Central Manchester University Hospital NHS Foundation Trust and Manchester Academic Health Science Centre, NIHR Manchester Musculoskeletal Biomedical Research Unit, Manchester, United Kingdom, [3]Stopford Building, Neuroscience and Psychiatry Unit, Institute of Brain and Behaviour and Mental Health, Manchester Academic Health Science Centre, The University of Manchester, Manchester, United Kingdom

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Session Title: Systemic Lupus Erythematosus - Clinical Aspects and Treatment Poster Session III

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose:

Cognitive dysfunction (CD) significantly affects SLE patients with many contributing causal factors. The effect of disease activity on cognitive function remains unclear and currently there is no definitive measure for CD in SLE. Functional magnetic resonance imaging (fMRI) provides a sensitive measure of brain functionality during cognitive tasks. The limited studies using fMRI in SLE have shown that SLE patients employ compensatory brain mechanisms to maintain adequate cognitive function. The aim of this study is to investigate fMRI as a potential biomarker for CD in SLE and examine other factors that affect CD in SLE.

Methods:

Data from 12 healthy controls (HC), 9 SLE patients with active disease (SLE-F) and 15 stable SLE patients (SLE-S) were analysed. SLE patients met ACR 1997 criteria. Basic demographic, disease and mood variables were collected. We also performed two fMRI tasks; the n-back (working memory task) and the facial emotional recognition task (FERT). The n-back had three levels (0-, 1-, and 2-back) with the 2-back being the most difficult. The FERT displayed faces expressing different emotions: happiness, sadness, fear and neutral. Both tasks were preprocessed and modelled using SPM12. The out of scanner variables and region of interest (ROI) data

extracted from the fMRI tasks were analysed using SPSS 22.

Results:

Participants were matched on demographic and clinical variables except for the SLEDAI score and steroid dose where, as expected, the SLE-F group scored higher. The SLE-F patients had significantly higher depression scores than the SLE-S and HC. The FERT mean results for the amygdala (sad vs neutral condition) were significantly different when comparing all SLE participants to the HC group. The n-back task showed a significant difference in the blood-oxygen-level dependent (BOLD) response for the 2- vs 0-back condition in the middle frontal gyrus (MFG), with an increased response for the SLE-F group compared to the other two groups.

Conclusion:

We found an increased BOLD response using the n-back in the MFG but only in the SLE-F group. This combined with the FERT amygdala result suggests that CD in SLE is affected by both disease activity and mood disorders. Functional MRI biomarkers may help differentiate features of CD in SLE patients related to disease activity and aid better targeting of relevant pathways for interventions in this condition.

This independent research is funded by Genzyme in the context of the ISS Program.

Table 1: Group comparisons of demographic, disease and mood variables

Variable	SLE-F (n=9) Mean (SD) Median (IQR)	SLE-S (n=15) Mean (SD) Median (IQR)	HC (n=12) Mean (SD) Median (IQR)	Test statistic	Post hoc - significant results
Demographics					
Age (yrs)*	39 (20.5, 48.5)	40 (33.3, 50.8)	36 (32.3, 49.5)	$H(2) = 1.71$, $p=0.42$	n/a
Sex (% female)	100	100	100	n/a	n/a
Handedness (% right-handed)	78	81	92	χ^2 (2) = 0.86, $p=0.65$	
Disease					
Disease duration (yrs)	8.56 (4.53)	13.00 (8.08)	n/a	$F(1, 23) = 2.29$, $p=0.14$	n/a
ACR criteria ever	7.11 (1.27)	5.94 (1.44)	n/a	$F(1, 23) = 4.16$, $p=0.05$	n/a
SLEDAI-2K	5.78 (3.53)	1.50 (1.59)	n/a	$F(1, 23) = 17.62$, **$p<0.001$**	n/a
Steroid dose (mg)*	5 (20)	0 (3.8)	0	$H(2) = 9.385$, **$p=0.01$**	HC vs SLE-F
Mood					
BDI score*	22 (13, 26.5)	7.5 (0, 11.8)	1 (0, 3.8)	$H(2) = 15.85$, **$p<0.001$**	HC vs SLE-F SLE-S vs SLE-F
MADRS*	9.5 (2.8, 13.5)	1 (0, 5.5)	1 (1, 0)	$H(2) = 8.55$, **$p=0.01$**	HC vs SLE-F

**Post-hoc statistics: significant p-value set to 0.167 to account for multiple comparisons.*

ACR: American College of Rheumatology SLE criteria

SLEDAI: Systemic Lupus Erythematosus Disease Activity Index

BDI-II: Beck's Depression Inventory II

MADRS: Montgomery Asberg Depression Rating Scale

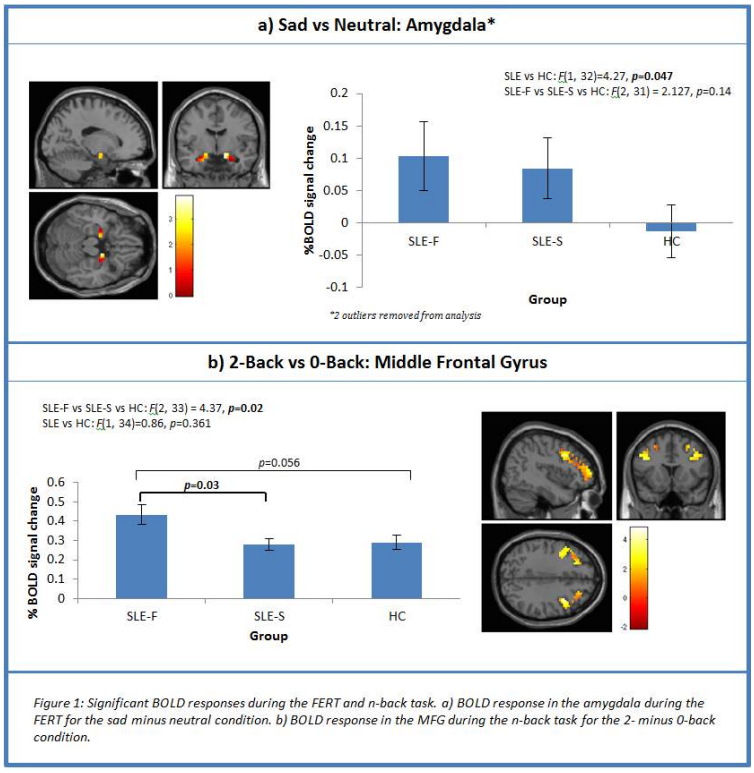

Figure 1: Significant BOLD responses during the FERT and n-back task. a) BOLD response in the amygdala during the FERT for the sad minus neutral condition. b) BOLD response in the MFG during the n-back task for the 2- minus 0-back condition.

Disclosure: M. Barraclough, Genzyme Corporation, 2,GSK, 5; **R. Elliott**, Genzyme, 2,Pfizer Inc, 2,Johnson & Johnson, 2; **S. McKie**, Genzyme Corporation, 2,Pfizer Inc, 2,Autifony, 2,Sunovion, 2; **B. Parker**, Genzyme Corporation, 2; **I. N. Bruce**, Genzyme Corporation, 2.

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Abstract Number: 2924

Determinants of Damage in an SLE Cohort: Real World Data

Maria Francisca Moraes-Fontes[1], Eliana Silva[2], Nuno Riso[3] and Margarida Jacinto[4], [1]Autoimmune Diseases Unit, Serviço Medicina 7.2, Hospital de Curry Cabral, Centro Hospitalar Lisboa Central, Lisbon, Portugal, [2]Patologia Clínica, Instituto Português de Oncologia, Francisco Gentil, Lisboa, Portugal, [3]Serviço de Medicina 7.2, Hospital de Curry Cabral, Centro Hospitalar Lisboa Central, Lisbon, Portugal, [4]Medicina Interna - Serviço 1, Hospital Espírito Santo - Évora, Évora, Portugal
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SESSION INFORMATION
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Background/Purpose: Across the spectra of autoimmune diseases RA stands out, as biomarkers present from the onset are associated with severity and can be a guide to therapy. In contrast, in SLE, genetic susceptibility has no clinical applicability, specific autoantibodies do not predict disease course, determinants of target organ remain unknown and clinical outcome is unpredictable for individual patients. In practice, damage accrual is therefore the best measure which is used to define SLE disease severity, found to predict future mortality. The objective of this study was to test the validity of damage determinants in a single-centre cohort.

Methods: Prospectively followed SLE female patients (defined by the identification of at least 4 SLE ACR criteria - fulfillement 100%, n=76) over the past 5 years. Age of onset, ethnicity, disease duration, number of ACR criteria at the end of follow-up, cumulative: renal, neuropsychiatric and articular phenotypes, hypertension, dyslipidemia, smoking, hydroxychloroquine, immunosuppressive use and SLEDAI 2K were correlated to the presence and degree of irreversible damage, as measured by SLICC/SDI in its several domains. Accumulation of ACR criteria was measured in a sub-group of patients followed from disease onset (within a year of the first symptom ascribed to SLE) (n=39 - 51%); SLEDAI and SLICC were performed bi-annualy and annualy, respectively. Univariate statistical analysis was performed using the Wilcoxon Mann-Whitney, Chi-Square tests and bivariate analysis for non-parametric distributed data (Sig. 2-tailed $p < 0,05$).

Results: SLICC SDI index > 0 was present in 43/76 (56.6%) and significantly associated to a longer disease duration, a higher number of ACR criteria and a neuropsychiatric (NP) phenotype when compared with those with no damage. There was no effect from any other demographic or clinical features (Table I). The final number of ACR criteria accrued was positively correlated to a higher disease activity over the past 5 years of follow-up (Spearman´s rho 0.02). Mean disease activity (SLEDAI 2K ≥ 3) over the past 5 years was not correlated to damage accrual at the end of follow-up according to disease duration: ≤ 5 and < 10y (n=17); ≥ 10 and < 20y (n=32); ≥ 20 (n=27).

Table I: Univariate analysis comparing patients with and without damage according to SLICC SDI index

Characteristic	SLICC < 1 (n=43)	SLICC ≥ 1 (n=33)	P value (Sig*)	Statistical Test
Age at disease onset (years) (mean ± SD)	32 ± 11	31 ± 13	0.653	Mann Whitney (MW)
Non-Caucasian (n, %)	4 (44.4)	5 (55.6)	0.610	Pearson Chi-square (PCS)
Disease Duration (years) (mean ± SD)	14 ± 7	19 ± 8	0.007*	MW
Hypertension (n, %)	16 (36.4)	27 (61.4)	0.338	PCS
Dyslipidemia (n, %)	12 (34.3)	22 (62.9)	0.201	PCS
Smoking (n, %)	7 (43.8)	9 (56.2)	1.000	PCS
Malignancy (n, %)	0 (0)	6 (100)	0.111	PCS
Infection (n, %)	16 (39)	24 (58.5)	0.809	PCS
Neuropsychiatric (n, %)	2 (11.1)	16 (88.9)	0.004*	PCS
Renal (n, %)	13 (41.9)	17 (54.8)	0.614	PCS
Articular (n, %)	22 (39.3)	33 (58.9)	0.631	PCS
Anti-nuclear Ab (n, %)	32 (42.1)	43 (56.6)	1.000	PCS
Anti-dsDNA (n, %)	24 (41.4)	33 (56.9)	1.000	PCS
Mean SLEDAI (bi-annual, past 5 years)	2.2 ± 2.0	3.6 ± 2.9	0.054	MW
Cumulative ACR criteria - first 6 months after disease onset (n available)	4.1 ± 1.3 (n=21)	3.7 ± 1.5 (n=18)	0.280	MW
Cumulative ACR criteria - end of follow-up	5.0 ± 1.1	5.6 ± 1.4	0.046*	MW

Conclusion: Disease duration and number of ACR criteria predict SLICC SDI as previously reported[1]. In our cohort, NP disease has a major impact on damage accrual.

References: [1]Bruce IN et al. doi:10.1136/annrheumdis-2013-2051-71

Disclosure: M. F. Moraes-Fontes, None; **E. Silva**, None; **N. Riso**, None; **M. Jacinto**, None.

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Abstract Number: 2925

Factors Associated with Early Damage Accrual in Patients with Systemic Lupus Erythematosus: 12-Month Preliminary Results from the Inception Cohort of the Multicenter Early Lupus Project

Matteo Piga[1], Fabiana Figus[1], Francesca Bellisai[2], Silvano Bettio[3], Alessandra Bortoluzzi[4], Laura Coladonato[5], Fabrizio Conti[6], Andrea Doria[3], Mauro Galeazzi[2], Marcello Govoni[4], Florenzo Iannone[7], Annamaria Iuliano[8], Marta Mosca[9], Imma Prevete[8], Gian Domenico Sebastiani[8], Francesca Romana Spinelli[10], Chiara Tani[9] and Alessandro Mathieu[1], [1]University of Cagliari, Cagliari, Italy, [2]University of Siena, Siena, Italy, [3]Department of Medicine-DIMED, University of Padova, Padova, Italy, [4]University of Ferrara, Ferrara, Italy, [5]DIM, Rheumatology Unit, Bari, Italy, [6]Rheumatology Unit, Department of Internal Medicine and Medical Specialties, Sapienza University of Rome, Rome, Italy, [7]Interdisciplinary Department of Medicine (DIM), Rheumatology Unit, University of Bari, Bari, Italy, [8]Osp. San Camillo, Roma, Italy, [9]University of Pisa, Pisa, Italy, [10]Sapienza University of Rome, Rome, Italy

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Background/Purpose:

Preventing organ damage is a major challenge in management of Systemic Lupus Erythematosus (SLE). Few data are available on factors related to development of damage in early stages of the disease. This study aim to evaluate the early damage accrual and factors associated with development of damage in the Early Lupus Project, a prospectively followed-up inception cohort of SLE patients diagnosed within 12 months since fulfillment of four or more 1997 ACR classification criteria

Methods:

The development and progression of damage assessed by the SLICC/ACR Damage Index (SDI) were prospectively recorded during the first year of the disease. SDI represent irreversible damage occurred after onset of SLE and being present for at least 6 months; by definition, it scores 0 at disease onset.

Using univariate analysis, we assessed the contribution of covariates collected at baseline (demographic, serological, clinical by BILAG2004 domains, disease activity by ECLAM index) in the development of damage (SDI from 0 to ≥1) within 12 months since disease onset. Stepwise regression models were fitted with covariates with $p<0.1$ to identify factors independently associated with development of damage.

Results:

A total of 119 patients (93.3% Caucasians, 18 males) were eligible for this study having available data at 12 months of disease. Mean age and mean disease duration since recognition of 4 ACR criteria were 36.7±14.1 years and 2.5±3.9 months (median = 1 month; IR 0-3.1), respectively. Twenty-eight (23.5%) and 31 (26.0%) patients, had an SDI score ≥1 after 6 and 12 months since disease onset (Table 1), respectively.

Univariate analysis revealed that dyslipidemia ($p=0.01$), anti-Beta2glicoproteinI antibodies positivity ($p=0.01$), active cardiorespiratory involvement ($p=0.02$) and high disease activity calculated by ECLAM ($p=0.05$) registered at baseline were associated with development of damage. However, older age at diagnosis ($p<0.01$; OR 1.1 95% CI 1.0-1.3), higher number of active BILAG2004 clinical domain ($p<0.01$; OR 1.7 95% CI 1.2 – 2.4) and neuropsychiatric involvement at baseline ($p<0.01$; OR 6.7 95% CI 1.4-32.2) were the only independent risk factors for early development of damage in this cohort.

No influence of active renal involvement and medications prescribed at baseline was detected in our cohort, likely because they most contribute to development of late-onset damage.

Table 1. Distribution at 6 and 12 months and prevalence of organ damage stratified according to the SDI domains at 12 months of disease.

	Prevalence (patients)
SLICC 6 Months (median; IR range)	**0 (0-0)**
SLICC = 0	76.5% (91)
SLICC = 1	16.8% (20)
SLICC > 1	6.7% (8)
SLICC 12 Months (median; IR range)	**0 (0-1)**
SLICC = 0	73.9% (88)
SLICC = 1	18.5% (22)
SLICC > 1	7.6% (9)
SDI domains	
Neuropsychiatric	**10.1% (12)**
Cerebrovascular accident	5.9% (7)
Cognitive impairment	3.4% (4)
Peripheral neuropathy	1.7% (2)
Psychosis	0.8% (1)
Ocular	**5.9% (7)**
Cataract	3.4% (4)
Retinal change	2.5% (3)
Miscellanea	**5.0% (6)**
Malignancy	4.2% (5)
Diabetes	0.8% (1)
Cardiac	**3.4% (4)**
Pericarditis or pericardiectomy	1.7% (2)
Myocardial infarction	0.8% (1)
Valvular disease	0.8% (1)
Peripheral Vascular	**3.4% (4)**
Venous thrombosis with swelling, ulceration	3.4% (4)
Pulmonary	**2.5% (3)**
Pleural fibrosis	2.5% (3)
Pulmonary fibrosis	0.8% (1)
Musculoskeletal	**2.5% (3)**
Deforming or erosive arthritis	1.7% (2)
Muscle atrophy or weakness	0.8% (1)
Renal	**2.5% (3)**
Proteinuria ≥3.5 gm/24hours	1.7% (2)
Estimated or measured glomerular filtration rate<50%	0.8% (1)
Mucocutaneous	**1.7% (2)**
Scarring chronic alopecia	1.7% (2)
Gastrointestinal	**0**

Conclusion:

Development of organ damage begins early in patients with SLE. In order to prevent damage accrual in the early stage of SLE it is

necessary to identify which clinical manifestations and risk factors are associated with it.

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Abstract Number: 2926

Cytochrome P450 Polymorphisms on Blood Hydroxychloroquine Levels in Patients with Systemic Lupus Erythematosus

Ji Yeon Lee[1], Min Kyung Chung[2], Ji Hun Kim[2], Jung Hee Koh[3], Seung Min Jung[4], Jennifer Lee[2], Seung-Ki Kwok[5], Ji Hyeon Ju[6], Kyung-Su Park[7] and Sung-Hwan Park[2], [1]Division of Rheumatology, Department of Internal Medicine, School of Medicine, Catholic University of Korea, Seoul St. Mary's Hospital, Seoul, South Korea, [2]Division of Rheumatology, Department of Internal Medicine, College of Medicine, Seoul St. Mary's Hospital, The Catholic University of Korea, Seoul, South Korea, [3]Division of Rheumatology, Department of Internal Medicine, School of Medicine, The Catholic University of Korea, Seoul St. Mary's Hospital, Seoul, South Korea, [4]Division of Rheumatology, Department of Internal Medicine, school of medicine, The catholic university of Korea, Seoul, South Korea, [5]seungki73@catholic.ac.kr, Division of Rheumatology, Department of Internal Medicine, College of Medicine, The Catholic University of Korea, Seoul, South Korea, [6]Division of Rheumatology, Department of Internal Medicine, College of Medicine, The Catholic University of Korea, Seoul, South Korea, [7]Division of Rheumatology, Internal Medicine, Seoul St. Mary's Hospital, The Catholic University of Korea, Seoul, South Korea

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Background/Purpose:

Hydroxychloroquine (HCQ) is a safe and effective treatment for systemic lupus erythematosus (SLE), and its blood concentration is known to be closely related to the treatment response [1, 2]. However, blood HCQ concentration has been found to be widely variable in patients taking the medication at same dose and frequency [1-4], and the reason is not well understood. We sought to evaluate the association of genetic polymorphisms in Cytochrome P450 (CYP) 2D6, 3A5, 3A4 and blood concentration of HCQ and its metabolite, N-desethylhydroxychloroquine (DHCQ), in patients with SLE.

Methods: Patients meeting the 1997-updated 1982 revised SLE criteria or the SLICC classification criteria who have been taking HCQ > 3 months were recruited and were genotyped for four SNPs in CYP2D6*10, CYP3A5*3, and CYP3A4*18B. Blood HCQ and DHCQ concentrations ([HCQ] and [DHCQ]) were measured and their association with corresponding genotypes was investigated.

Results: Total 194 patients were included in the analysis. The mean patient age was 39.2 ±0.83 years, 93.8% were female, and the average daily HCQ dose per weight was 4.48mg/kg/day. The mean time between the last HCQ dose and the blood draw was 15.58 ±0.86 hours. The mean SLEDAI score was 3.44±0.2. The mean [HCQ] and [DHCQ] were 575.05±26.33 ng/ml and 449.83±21.78 ng/ml, respectively. The allele frequencies of the 2 SNPs in CYP2D6*10 were relatively frequent among our participants. However, the other SNPs in the CYP3A4 and CYP3A5 isoforms were infrequent. CYP2D6*10 polymorphisms (rs1065852 and rs1135840) were significantly associated with the ratio of [DHCQ]/[HCQ] when adjusted for age, sex, dose per weight and SLEDAI score (p=0.03 and p<0.01, respectively)(Table). The ratio of [DHCQ]/[HCQ] was the highest in patients with G/G type of CYP2D6*10 (rs1065852) polymorphism and the lowest in those with A/A type (p=0.03). Similarly, the ratio was the highest in patients with C/C type of CYP2D6*10 (rs1135840) polymorphism and the lowest in those with G/G type (p<0.01). CYP2D6*10 (rs1065852) polymorphism was significantly related to [DHCQ] (p=0.01). However, polymorphism of CYP3A5*3 and CYP3A4*18B did not show any significant association with [HCQ], [DHCQ] or the ratio which could be due to small allele frequencies.

Table. Associations between CYP genotypes and HCQ concentration

	[HCQ]*	[DHCQ]*	Ratio
rs1065852(CYP2D6*10)			
A/A	424.6(352.3,511.7)	280.6(230.6,341.4)	0.72±0.05
A/G	524.9(457.5,602.3)	405.4(350.8,468.4)	0.83±0.03
G/G	409.5(340.1,493.2)	340.7(280.2,414.2)	0.89±0.04
p value	0.06	**0.01**	**0.03**
rs1135840(CYP2D6*10)			
C/C	403(309.2,525.3)	349.4(264.5,461.7)	0.94±0.06
C/G	481.9(413.1,562.2)	391.6(333,460.4)	0.86±0.03
G/G	453.3(389.4,527.7)	305.9(260.7,358.8)	0.73±0.03
p value	0.51	0.11	**<0.01**
rs776746(CYP3A5*3)			
C/C	402.9(309,524.8)	330.5(288.3,378.9)	0.79±0.03
T/C	481.9(412.8,562.1)	380.5(320.3,452)	0.87±0.04
T/T	453.3(389.2,527.6)	255.2(140.2,464.5)	0.74±0.13
p value	0.68	0.27	0.21
rs28371759 (CYP3A4*18B)			
A/G	317.1(158.2,635.7)	304.4(145.7,636.2)	0.99±0.16
A/A	461.8(416.3,512.3)	351.9(315.2,392.8)	0.82±0.02
p value	0.29	0.70	0.32

Adjusted for age, sex, SLEDAI score, dose per weight per day

*Log transformed

Ratio: [DHCQ]/[HCQ]

Conclusion: Our study showed that the ratio of HCQ and its metabolite, DHCQ, was related to CYP2D6 polymorphisms in Korean lupus patients taking oral HCQ. CYP polymorphisms may explain why there is wide variation in blood HCQ concentration levels. Therefore, it is important to consider the role of an individual's CYP polymorphisms when one prescribes oral HCQ.

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Abstract Number: 2927

Disease Activity Patterns over Time in Patients with SLE – a Retrospective Descriptive Analysis of the Hopkins Lupus Cohort

Noémi Györi[1], Katerina Chatzidionysiou[2], Laurence S Magder[3], Ronald F. van Vollenhoven[1] and Michelle Petri[4], [1]Department of Medicine, Unit for Clinical Therapy Research, Inflammatory Diseases (ClinTRID), The Karolinska Institute, Stockholm, Sweden, [2]Department of Medicine, Unit of Rheumatology, Department of Medicine Solna, Karolinska University Hospital, Karolinska Institutet, Stockholm, Sweden, [3]Johns Hopkins University School of Medicine, Devision of Rheumatology, Baltimore, MD, [4]Division of Rheumatology, Johns Hopkins University School of Medicine, Baltimore, MD

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Background/Purpose: Systemic Lupus Erythematosus (SLE) is a multi-systemic inflammatory disease, characterized by an extreme variability of its expression, both between and within individuals, over time. Overall disease activity is a predictor of both mortality

and organ damage. It is therefore important to understand the burden of disease course over time among patients with SLE. We aimed to discern and describe SLE disease activity patterns over time by analyzing data from the Hopkins Lupus Cohort.

Methods: Disease activity was retrospectively studied in a cohort of 2386 SLE patients followed up quarterly for 1-28 yrs (10 367 person-yrs of F/U). SLE disease activity patterns were defined using 1) Physician Global Assessment (PGA) and 2) SLE Disease Activity Index (SLEDAI), including serology: Long Quiescent (LQ), SLEDAI/PGA=0 for 1 yr at all visits; Relapsing-Remitting (RR), periods of disease activity (SLEDAI/PGA>0) interspersed with periods of disease inactivity (SLEDAI/PGA=0) at 1 or more visits during 1 yr; Chronic Active (CA), SLEDAI/PGA scores are >0 for 1 yr at all visits. Disease activity at yearly intervals ("1-yr blocks") was readily classified into 1 of the 3 major patterns for each patient. The pattern in each patient of 3 consecutive F/U years ("3-yr blocks") was also determined: Persistent Long Quiescent (pLQ), LQ pattern in each of the 3 yrs; Persistent Remissing-Remitting (pRR), RR pattern in each of the 3 yrs; Persistent Chronic Active (pCA), CA pattern in each of the 3 yrs; Mixed, at least 2 different patterns during 3 consecutive yrs. The frequency of different pattern groups (LQ, RR, CA) in each "1-yr-block" and pattern subgroups (pLQ, pRR, pCA, Mixed) in each "3-yr-block" of F/U was examined.

Results: Three major patterns of SLE disease activity were identified: LQ, RR, and CA. The RR pattern accounted for the greatest proportion of F/U time for both the SLEDAI and PGA, representing 48% and 52**%** of total person-yrs, respectively. The CA pattern was the second most frequent pattern observed. The least prevalent pattern was the LQ, indicating that 655 patients experience 1674 LQ "1-yr-blocks", and 352 patients experience 981 LQ "1-yr-blocks", using SLEDAI and PGA, respectively. When disease activity was defined within 3-yr intervals, the Mixed pattern was the most common for both the SLEDAI and PGA, representing 55% of total "3-yr blocks". The pRR and pCA patterns were intermediate and similar in frequency. The pLQ was the least frequent subgroup. The SLEDAI was more likely to depict the LQ pattern than was the PGA.

Conclusion: In this large cohort, the three major patterns of SLE disease activity as originally identified by Barr et al. were confirmed. In the present study, the RR pattern appeared to be the most prevalent pattern type. Long quiescence was achieved in a subset of patients. Over a 3-yr perspective almost half the patient maintained their disease activity pattern.

	1-YEAR-BLOCKS			3-YEAR-BLOCKS			
	RR	CA	LQ	pRR	pCA	pLQ	Mixed
PGA	52%	38.5%	9.5%	21%	20.6%	3%	55.4%
SLEDAI	48%	35.5%	16%	18%	21%	5.7%	55%

Frequencies of different disease activity pattern groups observed at both 1-year-, and 3-year intervals.

Disclosure: N. Györi, None; **K. Chatzidionysiou**, None; **L. S. Magder**, None; **R. F. van Vollenhoven**, None; **M. Petri**, None.

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Abstract Number: 2928

Persistent Disease Activity over Time in a Large Canadian Cohort of Prevalent Lupus Patients

Christine A. Peschken[1], Willy Wynant[2], Michal Abrahamowicz[3], Janet E. Pope[4], Earl Silverman[5], Amyn Sayani[6], Sandra Iczkovitz[6], Jorge A. Ross[6], Christian Pineau[7], C Douglas Smith[8], Marie Hudson[7], Michel Zummer[9], Lori B. Tucker[10], Deborah M. Levy[11], Gaëlle Chédeville[12], Adam M. Huber[13], Hector Arbillaga[14], Carol Hitchon[15], Paul R. Fortin[16] and CaNIOS 1000 Faces Investigators, [1]Arthritis Center, University of Manitoba, Winnipeg, MB, Canada, [2]McGill University, Quebec, QC, Canada, [3]Department of Epidemiology and Biostatistics., McGill University, Montreal, QC, Canada, [4]University of Western Ontario, London, ON, Canada,

[5]Division of Rheumatology, Hospital for Sick Children and University of Toronto, Toronto, ON, Canada, [6]Medical Affairs, GlaxoSmithKline, Mississauga, ON, Canada, [7]Medicine, McGill University, Montreal, QC, Canada, [8]The Arthritis Centre, TOH Riverside Campus, Ottawa, ON, Canada, [9]Rheumatology, Hôpital Maisonneuve-Rosemont and University of Montreal, Montreal, QC, Canada, [10]Rheumatology, BC Children's Hospital, Vancouver, BC, Canada, [11]Rheumatology, The Hospital for Sick Children, Toronto, ON, Canada, [12]Rheumatology, McGill University, Montreal, QC, Canada, [13]Pediatric rheumatology, IWK Health Centre, Halifax, NS, Canada, [14]Calgary Rheumatology, Calgary, AB, Canada, [15]University of Manitoba, Winnipeg, MB, Canada, [16]Medicine, CHU de Québec - Université Laval, Québec, QC, Canada
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SESSION INFORMATION

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Background/Purpose:

Treatment of systemic lupus erythematosus (SLE) aims at controlling disease activity to prevent damage. In a large multi-centre cohort of prevalent SLE patients we previously described a high proportion of patients with active disease and requiring steroid treatment. We examined changes in disease activity over time in this cohort.

Methods:

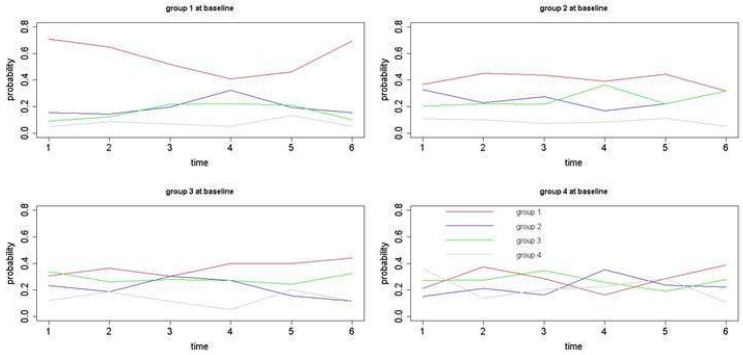
Predictors of changes in disease activity over the follow-up period, including symptoms, sociodemographic characteristics, and treatment were described in our cohort. Four groups were created based on their SLEDAI score at cohort entry (T0): 1: no or low (<4); 2: moderate (4 to <6); 3: active (6 to <10) and 4: highly active (≥10). Linear and mixed regression models) were used to identify predictors of changes in SLEDAI over time.

Results:

Among 2,048 participants, 1314, 553, 271, 183 and 146 had follow-up data at 1, 2, 3, 4 and 5 years, respectively. At T0, for all patients, mean (sd) age was 42 years (17), age at diagnosis was 31 (15), disease duration 11 (10) years. There were 90% females, 84 % had completed high school, and 63% were Caucasians. At T0, almost half of the patients were in Group 1 (n=898, 44%; 95%CI: 42-46%), 1/5 were in Group 2 (n=406, 20%; 95%CI: 18-22%) or Group 3 (n=447, 22%; 95%CI: 20-24%), while 287 (14%; 95%CI: 13-16%) were in Group 4. The probability that patients in Group 1 at T0 would move to a higher disease activity level was 30% at 1 year, 36% at 2 years, 49% at 3 years, 59% at 4 years and 54% at 5 years; transitions shown in Figure 1. In linear regression of changes in the 1st year, higher SLEDAI at T0 was a very significant predictor of higher SLEDAI at year 1 (0.3 unit increase for each additional SLEDAI unit at T0; p<0.00001). Higher Income was associated with lower SLEDAI at Yr 1 (0.5 unit decrease per each higher of 5 income categories, p=0.002), but there were no demographic or clinical predictors of disease activity changes. In mixed model analyses of i. longitudinal data across follow-up, and ii. if/how variables at previous visits predict changes in SLEDAI scores at the next visit, higher T0 SLEDAI was the single significant predictor of higher SLEDAI across the follow-up (1 unit increase in Yr 0 is associated with 0.3 increase in Yr1, p=0.001; and 0.3 increase per 1 unit increase at previous visit, p<0.0001), again without significant demographic or clinical predictors of disease activity changes.

Conclusion:

In our analyses more than 1/2 the patients had active disease at T0, and 116 (64.1%) of 181 patients with moderate to high disease activity at T0, who had at least 3 years of follow-up remained in this category for at least 3 years. Higher SLEDAI was the single major independent predictor of higher SLEDAI over time. Our data support persistence of active disease over the disease course in a significant subset of patients, even in those with longstanding disease. This highlights gaps in the optimal treatment of lupus and the need for additional therapies.



Disclosure: **C. A. Peschken**, Glaxo SmithKline Canada, 2; **W. Wynant**, GlaxoSmithKline Canada, 2; **M. Abrahamowicz**, Glaxo SmithKline Canada, 2; **J. E. Pope**, Amgen, 2; **E. Silverman**, None; **A. Sayani**, GlaxoSmithKline, 3; **S. Iczkovitz**, GlaxoSmithKline, 3; **J. A. Ross**, GlaxoSmithKline, 3; **C. Pineau**, None; **C. D. Smith**, None; **M. Hudson**, None; **M. Zummer**, Janssen Inc, 5; **L. B. Tucker**, None; **D. M. Levy**, None; **G. Chédeville**, None; **A. M. Huber**, None; **H. Arbillaga**, None; **C. Hitchon**, None; **P. R. Fortin**, GlaxoSmithKline, 2,GlaxoSmithKline, 5,Eli Lilly and Company, 5,AbbVie, 5.

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Abstract Number: 2929

Diet and Glucocorticoid Treatment in Patients with SLE

Cecilia Lourdudoss[1], Johan Frostegård[2] and Ronald F. van Vollenhoven[3], [1]Dept. of Medicine, ClinTRID, Karolinska institutet, Stockholm, Sweden, [2]Karolinska Institutet, Section of Immunology and chronic disease, Institute of Environmental Medicine, Stockholm, Sweden, [3]Department of Medicine, Unit for Clinical Therapy Research, Inflammatory Diseases (ClinTRID), The Karolinska Institute, Stockholm, Sweden

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Background/Purpose:

Relatively little is known about the link between diet and treatment results in SLE. Glucocorticoids (GC) are used to control active SLE but minimized whenever possible in order to avoid long-term side effects. The aim of this study was to investigate whether diet influences GC treatment in SLE patients.

Methods:

This study included 111 SLE patients from SLE Vascular Impact Cohort (SLEVIC), Karolinska institutet, Stockholm, Sweden. We linked dietary data from food frequency questionnaires with data on GC treatment from medical records for the year preceding and the year following the food survey. Associations between diet and GC treatment during the two years period were analyzed with logistic regression, adjusted for age and gender. GC treatment was considered a proxy for more active SLE; unchanged or increased GC doses were considered unfavorable outcomes.

Results:

Patient characteristics	N=111
Age (years), mean ± SD	47.9
Female, n (%)	100 (87.7)
BMI (Kg/m^2), mean ± SD	25.0 ± 4.5
Smokers, n (%)	46 (40.4)
CRP (mg/L), mean ± SD	4.9 ± 6.5
SLAM, median (IQR)	6 (4-9.25)
SLEDAI, median (IQR)	2 (0-6)
SLICC, median (IQR)	1 (0-3)
GC use at inclusion, n (%)	69 (61.6)
- Dose, (mg/day) mean ± SD	6.2 ± 3.9
GC use at -1year, n (%)	66 (63.5)
- Dose, (mg/day) mean ± SD	5.9 ± 2.5
GC use at +1year, n (%)	66 (66.0)
- Dose, (mg/day) mean ± SD	7.7 ± 7.7

Higher dietary intake of vitamin D was more common in patients treated with GC (OR=2.9). Alcohol was inversely associated with GC treatment (OR=0.3-0.4). Higher intake of vitamin B12, retinol, and calcium were related to unchanged/increased GC dose (OR=3.0-4.6), but higher intake of fatty acid C18:2 and beta-carotene were found in patients with decreased GC dose during year -1 to inclusion (OR=0.3 and 0.2 respectively). Finally, a positive association was seen between higher intake of several nutrients and GC dose levels of >2.5, >5.0, and >7.5 mg/day.

Conclusion:

Higher dietary intake of vitamin D did not protect against lupus activity. Higher intake of C18:2 (omega-6) and beta-carotene (anti-oxidant) may protect against unfavorable outcomes (need for increases in GC dose). The inverse association between alcohol intake and GC treatment/lupus activity may provide a partial explanation for the link between moderate alcohol intake and improved cardiovascular health in rheumatic diseases. The association between higher dietary intake and higher GC dose levels indicated GC's influence on increasing appetite.

Disclosure: C. Lourdudoss, None; **J. Frostegård**, None; **R. F. van Vollenhoven**, None.

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Abstract Number: 2930

Outcome of Patients with Systemic Lupus Erythematous (SLE) after Thrombotic Events

Samar Alharbi[1], Jiandong Su[2], Stacey E. Morrison[3], Mohammed Attar[4], Khawla Al-Ghanim[5], Murray Urowitz[6,7], Dafna Gladman[2] and Jorge Sánchez-Guerrero[8], [1]Rheumatology, University Health Network, Toronto, ON, Canada, [2]Rheumatology, University of Toronto, Toronto Western Hospital, Toronto, ON, Canada, [3]Div Rheumatology Rm MP-10-304, Toronto Western Hospital, Toronto, ON, Canada, [4]Rheumatology, Toronto Western Hospital, Toronto, ON, Canada, [5]Rheumatology, TWH, Toronto, ON, Canada, [6]University of Toronto, Toronto, ON, Canada, [7]Rheumatology, U of Toronto, Toronto Western Hospital, Toronto, ON, Canada, [8]Rheumatology, Mount Sinai Hospital and University Health Network, Toronto Canada, Toronto, ON, Canada

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Background/Purpose: To assess the impact of thrombotic events (TE) on 1) mortality, 2) SLE-related damage accrual; and 3) health-related quality of life (HRQoL) in patients with SLE.

Methods: We included patients participating in a prospective cohort (1990-2014). Demographic, SLE-related clinical and laboratory data were extracted. The TE group included patients with any venous or arterial event occurring after enrollment in the cohort. The non-TE group included those with no TE ever. Chi-Square test, t-tests, and Kaplan-Meier survival analysis were used to identify the differences between those with and without TE in terms of: 1) mortality by all causes; 2) damage accrual since TE using the SLICC/ACR Damage Index (SDI) excluding all vascular domains (mod-SDI); and 3) HRQoL using the mental (MCS) and physical (PCS) component summary scores of the SF-36 questionnaire.

Results: A total 1015 SLE patients were included in analysis. A univariate comparison of TE (n = 151) vs non-TE (n = 864) showed: older age at SLE diagnosis (33.8 ± 14.2 vs 30.9 ± 13.1 years, P = 0.01); lower proportion of females (82.8% vs 88.7%, P = 0.04); higher frequency of antiphospholipid antibody positivity (20.5% vs 14.1%, P = 0.04); no difference in time from SLE diagnosis to first visit to the clinic (13.8 ± 17.6 vs 14.9 ± 17.4 months, P = 0.45); no difference in survival time (75% survival time: 22 vs 27 years, P = 0.70); and more non-vascular damage (mod-SDI >0: 80.8% vs 56.9%, P ≤ 0.0001; mean mod-SDI: 1.8 ± 1.8 vs 1.1 ± 1.5, P ≤ 0.0001). Among 44 patients with TE, no differences in HRQoL MCS or PCS were observed between the groups. These results did not differ by type of TE.

Conclusion: Compared to those without TE, SLE patients with TE accrued more chronic non-vascular damage. We found no difference in mortality, and in the subgroup of TE patients assessed, HRQoL did not differ between the groups.

Abstract Number: 2931

Is Pregnancy a Risk Factor for the Onset of Systemic Lupus Erythematosus (SLE) in Women of the Reproductive Age: A Population Based Case-Control Study?

Chi Chiu Mok[1], Sau Mei Tse[1], Ling Yin Ho[2] and Kar Li Chan[1], [1]Medicine, Tuen Mun Hospital, Hong Kong, Hong Kong, [2]Dept of Medicine, Tuen Mun Hospital, Hong Kong SAR, Hong Kong
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Background/Purpose: To evaluate whether pregnancy is a risk factor for the onset of SLE in women of the reproductive age.

Methods:

Female patients who had first onset of SLE during pregnancy between the age of 15 and 49 years were identified from our SLE cohort database (year 1999-2013). The incidence of SLE during pregnancy in women of the reproductive age was calculated by the ratio of pregnancy-onset SLE and the total number of obstetric deliveries in our hospital within the same study period (data retrieved from the obstetric registry). The observed incidence of SLE onset during pregnancy was compared with the expected incidence of SLE in women of the reproductive age (age 15-49 years) in the general population (data retrieved from a clinical registry of all public hospitals in Hong Kong using the diagnostic codes of SLE and its related complications, and the population census data in the years 2001, 2006 and 2011) by the Chi-square test (95% asymptotic confidence intervals calculated). The clinical presentations, course and prognosis of pregnancy-onset SLE were compared with other non-pregnancy-onset female SLE patients.

Results:

742 female SLE patients were in our cohort; 15 patients had first onset of SLE during their pregnancies (age of onset 29.5±5.3 years; 13% in first trimester, 47% in second trimester, 40% in third trimester). Compared to non-pregnancy-onset female SLE patients (N=727), there were more renal disease, thrombocytopenia and central nervous system involvement as initial manifestations of

pregnancy-onset SLE. Three (20%) patients also qualified the diagnosis of the obstetric antiphospholipid syndrome. Fetal outcome was poor in patients with onset of SLE during pregnancy: intrauterine death (13%), spontaneous or therapeutic abortion (33%) and preterm delivery (13%). The maternal prognosis of pregnancy-onset SLE, however, was generally good, with good response to treatment and very infrequent disease flares on follow-up. The SDI damage score was significantly lower in pregnancy-onset than non-pregnancy-onset SLE patients (0.33±0.49 vs 1.09±1.6; p<0.001). There was no mortality in pregnancy-onset SLE patients (compared to 11.4% in the remaining cohort). The total number of deliveries registered in our hospital in women of the age 15-49 years between 1999 and 2013 was 71224. The observed incidence of SLE during pregnancy was 0.014/1000 person-year. During the same time period, the incidence of new onset SLE in all public hospitals in Hong Kong relative to the mean female population (15-49 years of age) from 1999 to 2013 was 0.077/1000 person-year. The odds ratio (OR) of having new onset SLE during pregnancy was 0.22 (95%CI 0.13-0.39; p<0.001).

Conclusion:

In women of the reproductive age, pregnancy protects against the development of SLE. First onset of SLE during pregnancy often leads to poor fetal outcome. However, the maternal outcome of pregnancy-onset SLE is generally good, with good response to treatment, infrequent relapse of organ manifestations and smaller risk of organ damage in the long run.

Disclosure: C. C. Mok, None; **S. M. Tse**, None; **L. Y. Ho**, None; **K. L. Chan**, None.

Abstract Number: 2932

A Retrospective Observational Study of Patients with Lupus Nephritis Treated with Rituximab in Combination with Cyclophosphamide

Nídia Oliveira[1], Mónica Ibañez[2], Natalia Ciang[3] and David A. Isenberg[4], [1]Internal Medicine Department, Hospital Pedro Hispano, Matosinhos, Portugal, London, United Kingdom, [2]Rheumatology Department, Hospital Son Llàtzer, Palma de Mallorca, Spain, London, United Kingdom, [3]Rheumatology Department, Queen Eliazbeth Hospital, Hong Kong, London, United Kingdom, [4]Rayne Institute, Centre for Rheumatology Research, UCL Division of Medicine, London, United Kingdom

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Background/Purpose:

Lupus nephritis (LN) is a major cause of morbidity. Many patients with refractory disease can not tolerate conventional immunosuppressive therapy. The aims of this study were to describe the comorbidities at baseline, most relevant manifestations at diagnosis, concomitant medications used with disease-modifying anti-rheumatic drugs and prednisolone in lupus patients given Rituximab (RTX). Additionally, we identified what variables are associated with renal response at 12 months.

Methods:

A 13 year retrospective analysis was completed on 42 LN patients treated with combination therapy of RTX and cyclophosphamide (CYC). We defined Renal flare (RF), Complete (CR) and Partial (PR) Renal Response according to the EULAR/ERA-EDTA criteria. The response was defined at 12 months after the treatment with RTX.

Results:

Based on 42 patients treated with RTX 2g in combination with CYC 750 mg for active LN: 38 patients were female with a median age at diagnosis of 38 years, interquartile range [IQR: 25 – 46]. 12 (28.6%) were Caucasian, 17 (40.5%) Black, and 10 (23.8%) South-Asian. The most frequent comorbidities were high blood pressure (52.4%), dyslipidaemia (26.2%), depression (23.8%), skin (26%), pulmonary (26%) and infectious disease (28.6%). 6 (14.3%) had associated autoimmune diseases (APS 7%; Sjögren's Syndrome 4.8%). The main manifestations at diagnosis were: constitutional in 36 (85.7%), mucocutaneous in 39 (93%), musculoskeletal in 38 (90.5%), hematological in 22 (52.4%), cardiorespiratory in 19 (45.2%), gastrointestinal in 9 (21.4%), neuropsychiatric in 13 (31%) and renal in 38 (90.5%). Prior RTX administration, the most frequently medications used were: MMF in 19 patients (45%), Hydroxychloroquine in 15 (35.7%), Azathioprine in 9 (21.4%) and Prednisone <10mg/d in 25 (60%) and 11-30 mg/d in 13 (31%).

2 patients had class II, 7 class III, 20 class IV, 8 class V, and 4 with mixed (II+III; IV+V; V+III) LN.

At 12 months post-RTX therapy, 14 patients achieved renal response and 15 patients were non responders. 9 patients had a new flare before 12 months, 2 had no retrievable information and 2 patients died at 4 and 5 months post-RTX.

22 out of 42 were retreated due to a flare (Renal/Non renal). Patients with GN type 4 were more prone to flare and required re-treatment with B cell depletion.

The time between first dose of RTX and second treatment was 25 ± 22.4 months.

We found a significant association between renal response at 12 months post-RTX and age (35.64 vs 42.87; $p<0.05$); lower levels of serum creatinine (91.07 vs 120.38; $p<0.05$) and higher levels of dsDNA (1063 vs 474; $p<0.05$) at baseline; absence of dyslipidemia (15.4%; $p<0.05$) or anaemia (15.4%; $p<0.05$); absence of cardio-respiratory (23.1%; $p<0.05$) and ocular involvement (0%; $p<0.05$) at diagnosis. We determined that there was no difference with ethnicity, gender, concomitant treatments, type of GN or levels of complement.

Conclusion:

We have shown that patients who achieved a Renal Response at 12 months post-RTX were younger, had a lower levels of creatinine and higher levels of dsDNA at baseline.

More prospective studies and randomized control trials are needed to understand better this complex disease

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Disclosure: N. Oliveira, None; **M. Ibañez**, None; **N. Ciang**, None; **D. A. Isenberg**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/a-retrospective-observational-study-of-patients-with-lupus-nephritis-treated-with-rituximab-in-combination-with-cyclophosphamide

Abstract Number: 2933

Low Prevalence of PCP in Hospitalized Patients with SLE: Review of a Clinical Database Warehouse

Teja Kapoor[1], Jianhua Li[2], Sameer Malhotra[3], Joan Bathon[4] and Anca Askanase[5], [1]Columbia University, New York, NY, [2]Columbia University Medical Center, New York, NY, [3]Weill Cornell Medical Center, New York, NY, [4]Rheumatology, Columbia University Medical Center, NY, NY, [5]Columbia University College of Physicians & Surgeons, New York, NY

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Background/Purpose : The risk of Pneumocystis carinii pneumonia (PCP) in Systemic Lupus Erythematosus (SLE) is not well-established. Accordingly, this study aims to establish the prevalence of PCP in hospitalized SLE patients.

Methods : This is a retrospective cohort study evaluating the prevalence of PCP in hospitalized patients with SLE. Data was obtained from the Columbia University Medical Center (CUMC) Clinical Data Warehouse from January 2000 to September 2014. HIV-positive patients and patients with renal transplant were used as controls.

Results : Patients with SLE were identified by searching the database for an ICD-9 of 710.0; as such, 4,800 patients were identified. Chart review of a sample of 107 charts (roughly 3% of the identified 4,800) was used to verify the diagnosis of SLE. Of the 107 charts reviewed, SLE case definitions were assigned: a) met 4 out of 11 ACR or SLICC SLE criteria = 58 patients (54%), b) has 2-3 SLE criteria along with Lupus medications and/or Lupus auto-antibodies or met only 1 SLE criteria but had a previous diagnosis of SLE by a rheumatologist and were treated with SLE medication = 21 patients (20%), c) had a history of Lupus (usually "Lupus in remission") without criteria verification, of which half had +ANA = 7 (7%). 21/107 (20%) of patients in the sample did not have SLE but had a diagnosis of another autoimmune disease, such as Sjogren's syndrome, RA, scleroderma, vasculitis, or polymyositis. We decided to consider only the first two groups that met the most stringent SLE case definition to represent the true SLE cases, i.e 74% as of the 4800 patients (3,552) were extrapolated as having SLE, which is consistent with other studies of administrative databases.

A total of 9 cases of PCP in SLE patients were identified. The diagnosis of PCP was made based on clinical and radiographic evidence. PCP Gomori methenamine silver stain was negative in 8/9.

Prevalence of PCP in SLE, renal transplant, and HIV patients is presented in the following table.

PATIENTS:	PCP DIAGNOSIS based on hospital discharge
SLE, N=3,552	N=9 (0.25%)
SLE with HIV, N=40	N=3 (7.50%) P<0.05
HIV, N=9,060	N=542 (5.98%) P<0.05
Renal transplant, N=5,885	N=36 (0.61%) P=0.01

Of the 9 cases of PCP, 8 patients met SLE criteria as defined above, and 1 patient had a confirmed historical diagnosis of SLE. In addition, 3/9 patients had co-existing AIDS with a median CD4 count of 31.

All patients were treated with IV trimethoprim-sulfamethoxazole and discharged; no deaths occurred. None of the patients were on PCP prophylaxis prior to admission, which is not routinely done for SLE patients at CUMC.

Conclusion : The risk of PCP in SLE is low compared to other immunosuppressed patients, such as HIV or renal transplant. All patients responded to treatment with trimethoprim-sulfamethoxazole. This data does not substantiate the need for PCP prophylaxis, except for patients with SLE-HIV. Although rare, SLE patients admitted with bilateral infiltrates should have a low threshold for initiating PCP treatment.

Disclosure: T. Kapoor, None; **J. Li**, None; **S. Malhotra**, None; **J. Bathon**, None; **A. Askanase**, None.

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Abstract Number: 2934

Endothelial Dysfunction in SLE-the Role of Platelets and Type I Interferon

Helena Tydén[1], Christian Lood[2], Birgitta Gullstrand[3], Andreas Jönsen[4] and Anders A. Bengtsson[5], [1]Department of Clinical Sciences, Division of Rheumatology Lund University and Skane University Hospital Lund Sweden, Lund University, Lund, Sweden, [2]Department of Clinical Sciences, Division of Rheumatology, Lund University and Skane University Hospital Lund Sweden, Lund University, Lund, Sweden, [3]Department of Clinical Sciences, Division of Rheumatology Lund University and Skane University Hospital, Lund University, Lund, Sweden, [4]Department of Rheumatology, Lund University Hospital, Lund, Sweden, [5]Rheumatology, Inst of Clinical sciences, Lund, Sweden

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Background/Purpose:

Type I interferon (IFN) may affect endothelial progenitor cells leading to endothelial dysfunction in SLE. SLE patients have a type I IFN signature in platelets associated with cardiovascular disease (CVD). The objectives were to investigate if there is an association between type I IFN activation, endothelial dysfunction and platelet activation in SLE and if young SLE patients have increased arterial stiffness and impaired endothelial function.

Methods:

SLE patients n=148,(n=144 fulfilling≥ 4 ACR classification criteria for SLE, 87% women, mean age 49 years old) and 79 sex- and age matched healthy controls (HC) were tested. Endothelial dysfunction (ED) and Augmentation Index (AI) were measured by EndoPAT 2000 (Itamar Medical, Israel). Elevated AI indicates increased arterial stiffness and a low Reactive Hyperemia Index (RHI) value indicates ED. Surrogate markers for ED; sVCAM-1 and vWF were measured with ELISA. Type I IFN activity was measured by a

serum IFN-reporter gene expression assay (s-IFN score), type I IFN signature was assessed in peripheral blood mononuclear cells (PBMCs) as PBMC- IFN and the type I IFN regulated protein G3BP was measured by ELISA.

Platelet activation was measured as levels of platelet C4d deposition (p-C4d dep), platelet- monocyte complex (p-mc compl) and platelet- granulocyte complex (p-gc compl), measured by flow cytometry.

Results:

A low RHI was seen in SLE patients with ongoing type I IFN activity compared to HC (OR 2.61 CI 95% 1.04-6.53 p= 0.04). No differences were seen when comparing all SLE patients with HC (OR 1.30 CI 95% 0.66-2.58 p=0.450).

ED (low RHI and/or high sVCAM-1) was seen in SLE patients with ongoing type I IFN activity measured as IFN score, G3BP and high PBMC-IFN signature.

High sVCAM-1, was seen in patients with a high value of s-IFN score (OR 6.12 CI 95% 2.21-16.93 p<0.001), a high G3BP level (OR 3.38 CI 95% 1.41-8.06 p=0.006) and high levels of PBMC- IFN (OR 7.89 CI 95% 2.87-21.7 p<0.0001). ED measured with a low RHI was seen in patients with high s-IFN score (OR 2.53 CI 95% 1.07-5.97 p=0.035) and high G3BP (OR 2.36 CI 95% 1.025-5.45 p=0.044)

Young SLE patients seemed to have increased arterial stiffness compared to HC, since AI was clearly increased (OR 2.95 CI 95% 1.24-7.02 p=0.015) in SLE patients 18-45 years of age.

High levels of p-C4d dep and p-mc compl were seen in SLE compared to HC (OR 13,5 CI 95% 4.07-45.1 p<0.000) and (OR 2.84 CI 95% 1.19-6.8 p=0.019), respectively, demonstrating more activated platelets in SLE. SLE patients with low RHI had increased levels of p-mc compl (OR 2.92 CI 95% 1.22-6.99 p=0.016). SLE patients with high sVCAM-1 had increased p-gc compl and p-C4d dep (OR 3.39 CI 95% 1.19-9.66 p=0.022) and (OR 3.33 CI 95% 1.58-7.03 p= 0.002), respectively showing more activated platelets in SLE patients with ED.

Conclusion:

Increased arterial stiffness was seen in young SLE patients, suggesting that early primary preventive treatment might be important already in younger patients.

SLE patients with activated type I IFN system have impaired endothelial function. This may act together with activated platelets due to injured endothelium, in the development of CVD in SLE.

Disclosure: H. Tydén, None; **C. Lood**, None; **B. Gullstrand**, None; **A. Jönsen**, None; **A. A. Bengtsson**, None.

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Abstract Number: 2935

Disease Evolution in Late Onset and Early Onset Systemic Lupus Erythematosus (SLE)

Roa'a Al Johani[1], Dafna Gladman[2], Jiandong Su[2] and Murray Urowitz[2,3], [1]Medicine, University of Toronto, Toronto Western Hospital, Toronto, ON, Canada, [2]Rheumatology, University of Toronto, Toronto Western Hospital, Toronto, ON, Canada, [3]Rheumatology, U of Toronto, Toronto Western Hospital, Toronto, ON, Canada

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SESSION INFORMATION

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Background/Purpose: To compare clinical features, disease activity and outcome in late onset versus early onset SLE over 5 years of follow up.

Methods: Patients with SLE are followed prospectively according to standard protocol and tracked on a computerized database. Patients entering the cohort within one year of diagnosis constitute the inception cohort. Patients with late onset (age at diagnosis ≥ 50 were identified and matched 1:2 based on gender and first clinic visit (+/- 5) years with patients with early disease onset (age at

diagnosis 18- 40 years). Groups were compared at baseline and 5-year follow up. Disease activity was measured by the SLE Disease Activity Index (SLEDAI-2K) and Damage was assessed by the Systemic Lupus International Collaborating Clinics/American College of Rheumatology(SLICC/ACR) damage index. All information is collected prospectively in the database.

Results: A total of 86 patients with late onset disease (84.9% female,81.4% Caucasian ,mean age ±SD 58.05 ± 7.30) and 169 patients with early onset disease (86.4% were female , 71% Caucasian, mean age± SD 27.80 ± 5.90) were identified.

Variables	At baseline			5 years		
	Late (N= 86)	Early (N=169)	P value	Late (N= 86)	Early (N=169)	P value
ACR criteria*	4.92 ± 1.05	5.32 ± 1.15	0.001	5.60 ± 1.17	6.31 ± 1.34	0.0001
SLEDAI-2K score*	4.58 ± 4.68	6.18 ± 6.24	0.006	3.41 ± 4.84	4.09 ± 4.40	0.173
Total SDI*	0.15 ± 0.43	0.17 ± 0.60	0.928	0.98 ± 1.28	0.69 ± 1.16	0.005
SLICC ≥ 1	9(10.4%)	17(10.1%)	-	43(50.1%)	88(36.1%)	-
IS use	11 (12.8%)	43 (25.4%)	0.001	19 (22.1%)	61 (36.1%)	0.001
Steroid use	60 (69.8%)	102 (60.4%)	0.083	44 (51.2%)	95 (56.2%)	0.340
Average steroids dose in mg/d	22.53 ± 13.07	30.23 ±19.35	0.021	12.58 ± 6.60	15.18±8.51	0.004
* Mean ± SD ; IS= immunosuppressive						

At enrollment, late onset SLE had a lower total number of ACR criteria, less renal and neurologic manifestations. Mean SLEDAI-2K scores were lower in late onset SLE, especially renal features and anti-DNA positivity. Over 5 years, mean SLEDAI-2K scores decreased in both groups, while mean SDI scores increased more significantly in the late onset group ; they developed more cardiovascular, renal and ocular damage , had higher prevalence of hypertension and hypercholesterolemia.

Conclusion: Although late onset SLE group had a milder presentation and less active disease, with the evolution of disease, they developed more organ damage likely a consequence of cardiovascular risk factors and aging.

Disclosure: R. Al Johani, None; **D. Gladman**, None; **J. Su**, None; **M. Urowitz**, None.

Abstract Number: 2936

Evolution of Disease Burden over 7 Years in a Multicentre Inception SLE Cohort

Murray Urowitz[1,2], Dafna Gladman[1], Nicole Anderson[3], Jiandong Su[1] and Systemic Lupus Erythematosus International Collaborating Clinics (SLICC), [1]Rheumatology, University of Toronto, Toronto Western Hospital, Toronto, ON, Canada, [2]Rheumatology, U of Toronto, Toronto Western Hospital, Toronto, ON, Canada, [3]Division of Rheumatology, University of Toronto, Toronto Western Hospital, Toronto, ON, Canada

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Background/Purpose: The evolution on an annual basis of disease activity and damage and the annual accrual of ACR criteria and key autoantibodies in patients with SLE is not well described. We report the annual occurrence of these features in an inception cohort of patients with SLE.

Methods: An international research network comprising 33 centres from 11 countries has followed an inception cohort of SLE patients yearly according to a standardized protocol between 2000 and 2014. Of these, 748 patients followed for a minimum of 7 years constitute the study population. Clinical disease activity was assessed using SLEDAI-2K and disease damage using the SLICC/ACR

Damage Index (SLICC/DI). ANA, Anti-DNA and anticardiolipin, antibody levels, the presence of the lupus anticoagulant were assessed at each visit. Descriptive statistics were used.

Results: Of the 748 patients followed for at least 7 years, 90.2% were female, 49.1% were Caucasian, 14.8% were Black, 16.3% were Asian, 15.9% Hispanic and 3.9% other. 40.8% were married and 57.2% had at least College education. Their mean age at enrolment was 34.7±13.4years and SLEDAI-2K at enrolment was 5.6±5.7. The duration from diagnosis to enrolment was 5.5±4.2 months.

Table 1: Mean SLEDAI-2K, SDI and ACR Accumulation in the First 7 Years of Follow-up

FU	Annual SLEDAI-2K		SDI		Cumulative ACR Criteria	
	N	Mean ± std	N	Mean ± std	N	Mean ± std
0	745	5.62±5.70	632*	0.14±0.49	748	5.05±1.13
1	679	3.75±4.33	678	0.44±0.88	679	5.42±1.25
2	660	3.57±4.32	660	0.55±1.01	660	5.65±1.34
3	636	3.28±3.56	637	0.68±1.12	637	5.84±1.39
4	605	3.50±3.95	625	0.80±1.22	625	5.93±1.37
5	619	3.35±3.94	621	0.92±1.35	621	6.04±1.42
6	619	3.39±3.95	621	1.00±1.42	621	6.14±1.46
7	620	3.17±3.57	624	1.08±1.45	624	6.16±1.43

*SDI performed only in those patients with > 6 months disease duration

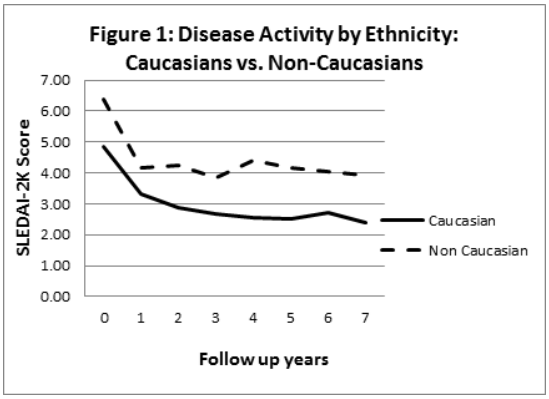

Table 2: Auto-Antibodies and Lupus Anticoagulant Over 7 Years

	Anti-Nuclear Antibody		Anti-DNA		Anticardiolipin		Lupus Anticoagulant	
FU	N	%	N	%	N	%	N	%
0	748	96.2	637	41.2	584	14.7	618	21.8
1	679	97.4	624	31.7	498	12.0	499	19.7
2	660	97.4	649	30.9	440	11.9	440	20.9
3	637	97.4	633	28.5	375	9.5	377	24.2
4	625	97.5	620	31.6	263	11.7	266	20.3
5	621	98.1	615	33.3	195	8.0	201	23.2
6	621	98.0	612	35.5	178	8.6	174	15.9
7	624	98.1	606	34.5	119	9.6	115	11.6

Mean SLEDAI-2K decreases to low levels in the first year and then remains low. SLEDAI-2K was significantly lower at each year in Caucasians compared to Non-Caucasians. Mean SLICC/DI increases progressively over the 7 years but there was no significant difference at each year between Caucasians and Non-Caucasians. Mean ACR criteria accumulation gradually increases over 7 years, with Caucasians accumulating less ACR criteria in the first 2 years of disease as compared to Non-Caucasians.

Although ANA positivity is high at enrolment, the percent positivity remains stable over 7 years. Frequency of anti-DNA positivity is high at enrolment and decreased by almost 7% over 7 years. Anticardiolipin antibody and the lupus anticoagulant decreases by 5% and 10% over 7 years respectively.

Conclusion: As expected disease activity in newly diagnosed patient's decreases over their first 7 years but disease damage increases. Similarly, key antibody levels with the exception of ANA positivity decreased over the first 7 years of disease.

Disclosure: M. Urowitz, None; **D. Gladman**, None; **N. Anderson**, None; **J. Su**, None.

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Abstract Number: 2937

Treatment Patterns Differ Based on Age of Systemic Lupus Erythematosus Onset: A Comparison of Azathioprine and Mycophenolate on the Prevention of Lupus Nephritis

J. Madison Hyer[1], Bethany Wolf[1], Jim Oates[2], Gary S. Gilkeson[3] and Diane L. Kamen[2], [1]Public Health Sciences, Medical University of South Carolina, Charleston, SC, [2]Medicine, Medical University of South Carolina, Charleston, SC, [3]Department of Rheumatology, Medical University of South Carolina, Charleston, SC

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Background/Purpose: Lupus nephritis (LN) is a major cause of morbidity and mortality among patients with systemic lupus erythematous (SLE). Studies have demonstrated efficacy and safety for mycophenolate mofetil (MMF) in LN, but use of MMF for extra-renal manifestations of SLE has not been as well-described as for azathioprine (AZA). This study was conducted to assess whether use of either MMF or AZA for extra-renal manifestations of SLE protects against development of future LN and whether treatment affects vary depending on age of SLE onset.

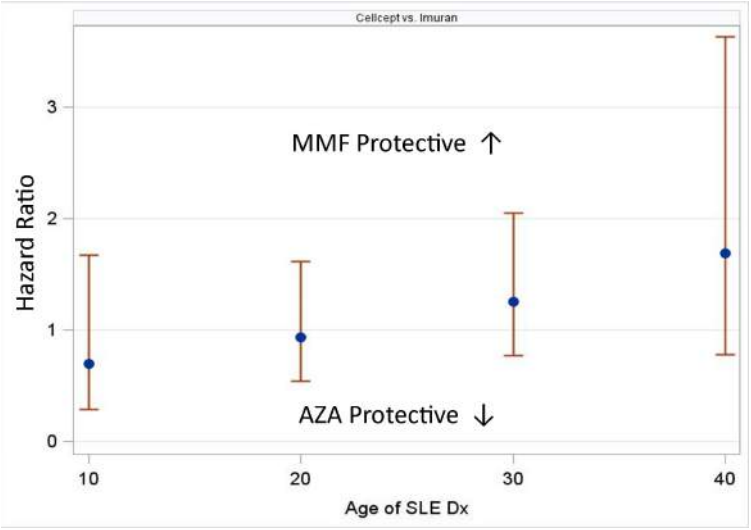
Methods:

Data was collected on patients with SLE consented and enrolled in a longitudinal registry started in 2003. Data included, but were not limited to, medication use and changes over time, medical history, and demographics. To assess the effects of treatment and the potential modification of treatment effect by age of SLE onset, Cox proportion-hazards modeling, controlling for gender, race, and hydroxychloroquine use, was utilized- allowing treatment to vary over time.

Results:

Of the 533 patients with SLE, 90.4% were female and 76.7% were African American. The average age at SLE onset was 30.4 years (sd = 13.7) with a range of 3 to 76 years of age. Among those diagnosed with LN (n = 251, 47.1%), the average time between diagnosis of SLE and LN was 6.3 years (sd = 5.4) with a range of less than a year to more than thirty years.

When comparing patients taking MMF or AZA to those not taking either: there is no increased risk of developing LN for patients taking either medications at decade-ages 10 and 20; for MMF, there was no statistically or clinically significant increased risk of developing LN at decade-ages 30 and 40; for AZA, there is a clinical risk and, at decade-age 40, a statistically significant risk of developing renal disease; for both, AZA and MMF, there is an upward trend of the risk estimates as age of SLE onset increases. When comparing AZA to MMF usage, there was no clinical or statistical difference found at any decade-age. Moreover, when comparing AZA to MMF usage, there is trend from indifference in treatment benefit to MMF benefit over AZA around decade-ages 30 and 40.



Conclusion:

Within a large registry of patients with SLE, we found increasing use of MMF for extra-renal manifestations of SLE. For patients diagnosed with SLE at a later age, our data suggests that MMF has a protective effect over AZA in preventing future LN. Although this same protective effect was not seen within patients with childhood-onset SLE, MMF was prescribed to patients across all ages who were at higher risk of LN, suggesting a possible protective effect which should be explored in prospective studies.

Disclosure: J. M. Hyer, None; **B. Wolf**, None; **J. Oates**, None; **G. S. Gilkeson**, None; **D. L. Kamen**, None.

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Abstract Number: 2938

Baseline Predictors of Remission and Low Disease Activity Using Recently Defined International Criteria in a Multi-Center Lupus Registry Cohort

Kichul Ko[1], Alana B. Levine[2], Russell Griffin[3], Olga Dvorkina[4], Saira Sheikh[5], Jinoos Yazdany[6], Richard Furie[7] and Cynthia Aranow[8], [1]Section of Rheumatology and Gwen Knapp Center for Lupus and Immunology Research, University of Chicago, Chicago, IL, [2]Rheumatology, Hospital for Special Surgery, New York, NY, [3]University of Alabama at Birmingham, Birmingham, AL, [4]Medicine, SUNY Health Science Center at Brooklyn, Brooklyn, NY, [5]University of North Carolina, Chapel Hill, NC, [6]Rheumatology, University of California, San Francisco, San Francisco, CA, [7]Division of Rheumatology, North Shore - LIJ Health System, New York, NY, [8]Feinstein Institute for Medical Research, Mahasset, NY

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Background/Purpose: Treating to a target of remission or low disease activity state (LDAS) is an attractive potential therapeutic approach in SLE. Recently, LDAS and remission in SLE have been proposed by the Asia-Pacific Lupus Collaboration (APLC) and the Definitions of Remission in SLE (DORIS) consensus panel, respectively. We identified 1228 of the 1506 patients who completed enrollment in a real-world SLE registry composed of 17 centers in the United States and Canada who had at least ≥ 1 follow-up visit through one year following enrollment, and we evaluated the incidence and predictors of achieving these outcomes.

Methods: Using definitions created by the APLC and DORIS, subjects were classified into 4 mutually exclusive groups based on the lowest remission or LDAS category they reached and maintained for ≥ 1 year: 1) **Not optimally controlled:** SLEDAI > 4, prednisone > 7.5 mg/d OR physician global assessment (PGA) > 1.0; 2) **LDAS**: SLEDAI ≤ 4, prednisone ≤ 7.5 mg/d AND PGA ≤ 1.0 with

immunosuppressive drugs being allowed; 3) **Remission On Therapy:** Prednisone ≤ 5mg and/or maintenance immunosuppressive agents allowed, SLEDAI = 0 AND PGA ≤ 0.5; 4) **Remission Off Therapy**: No steroids or immunosuppressive agents, SLEDAI = 0 AND PGA ≤ 0.5. Characteristics of subjects at baseline were compared using chi-square and analysis of variance tests (Table 1). A multinomial logistic regression (ordered logit) ranking outcomes from remission off therapy (lowest) to not optimally controlled disease (highest) was used to examine the multivariable association between baseline predictors and ordered outcome.

Results: Among 1228 patients, 91.6 % were female, mean age was 41.1 years (±13.3 y) and median duration of disease was 9.8 years (interquartile range [IQR] 4.96 – 16.34 y). At follow-up (median duration of 2.05 years [IQR 1.54 – 2.44 y]); 930 (75.7%) patients were classified as not optimally controlled; 139 (14.9%) achieved LDAS; and 93 (7.57%) and 66 (5.37%) achieved remission on or off therapy, respectively, for ≥ 1 year. Among the groups, statistically significant differences were observed for age at diagnosis, steroid and immunosuppressive usage, PGA, patient global assessment of disease, SELENA-SLEDAI scores and ACR criteria count (Table 1). In multivariable analysis, decreased odds of a more desirable ordered outcome category were observed for increasing SELENA-SLEDAI scores (odds ratio [OR] 0.89, 95% CI 0.84-0.94), steroid usage (OR 0.74, 95% CI 0.84-0.94) and increasing patient global assessment (OR 0.993, 95% CI 0.987-0.999).

Conclusion: Optimal control of SLE disease activity through one year, defined as LDAS or remission on/off therapy, was achieved in 24.3 % of patients in the LCTC cohort. Baseline predictors of better control of SLE at follow-up included lower SELENA-SLEDAI scores, no steroids and lower patient global assessment of disease.

Table 1. Comparison of enrollment demographic, medication, and clinical characteristics by disease activity group

	Not optimally controlled	Low disease activity	Remission on meds	Remission off meds	p-value*
N	930	139	93	66	
DEMOGRAPHICS					
Age at diagnosis					
Mean	28.9±12.1	30.3±13.8	29.7±12.4	34.6±12.5	0.0046
Category (%)					
0-20 years	29.1	27.5	26.4	16.1	0.0273
21-35 years	44.2	41.3	45.1	35.5	
36-50 years	21.1	21.0	22.0	40.3	
≥51 years	5.6	10.1	6.6	8.1	
Sex (%)					
Male	8.3	7.3	7.7	12.9	0.5836
Female	91.7	92.7	92.3	87.12	
Race					
White Non-Hispanic	39.2	29.7	36.3	45.2	0.4454
White Hispanic	7.7	6.5	11.0	4.8	
Black Hispanic	1.1	2.2	0.0	1.6	
Black Non-Hispanic	35.2	41.3	31.9	27.4	
Asian	9.3	8.7	11.0	12.9	
Other	7.4	11.6	9.9	8.1	
Smoking status (%)					
Current	8.8	6.5	5.5	3.2	0.4266
Former	19.0	23.9	19.8	24.2	
Never	72.2	69.6	74.7	72.6	
Insurance (%)					
None	4.3	4.6	1.1	0.0	0.1204
Medicaid	11.8	19.2	10.1	13.8	
Medicare	9.2	10.0	7.9	3.5	
Commercial/HMO	59.7	55.4	60.7	60.3	
Multiple	15.0	10.8	20.2	22.4	
MEDICATIONS					
Plaquenil (%)	69.9	69.8	78.5	72.7	0.3609
Steroids (%)	58.9	66.2	53.8	13.6	<0.0001
Immunosuppresants (%)	54.78	62.6	66.7	6.1	<0.0001
CLINICAL					
Mean physician global assessment	0.71±0.70	0.81±0.61	0.35±0.51	0.22±0.47	<0.0001
Mean patient global assessment	30.87±26.58	30.81±25.41	22.62±21.24	13.86±18.46	<0.0001
Mean SLEDAI	3.24±3.52	3.67±3.18	1.13±1.66	0.65±1.39	<0.0001
Mean SLICC	1.26±1.75	1.30±1.64	1.63±2.50	1.29±2.11	0.3493
Mean disease duration	11.51±8.87	11.03±9.57	13.06±9.99	12.45±10.64	0.3219
Mean ACR criteria count	5.58±1.53	5.73±1.62	5.51±1.64	5.08±1.41	0.0464
Malar rash (%)	50.7	52.5	52.7	43.9	0.6736
Renal disorder (%)	41.2	48.9	47.3	21.2	0.0013
Oral ulcers (%)	38.0	39.6	37.6	19.7	0.0264
Antinuclear antibody (%)	91.2	94.2	93.6	92.4	0.5767
Serositis (%)	32.3	35.3	26.9	25.8	0.3918
Photosensitivity (%)	41.9	38.1	45.2	43.9	0.7218
Hematologic disorder (%)	57.0	59.7	51.6	62.1	0.5294
Immunologic disorder (%)	75.3	87.8	77.4	72.7	0.0106
Discoid rash (%)	15.1	17.3	12.9	13.6	0.8082
Neurologic disorder (%)	11.3	13.0	18.3	13.6	0.2465
Arthritis (%)	81.3	82.7	75.3	68.2	0.0334

*Estimated from chi-square and analysis of variance for categorical and continuous variables, respectively

Disclosure: **K. Ko**, None; **A. B. Levine**, None; **R. Griffin**, None; **O. Dvorkina**, None; **S. Sheikh**, None; **J. Yazdany**, None; **R. Furie**, None; **C. Aranow**, None.

activity-using-recently-defined-international-criteria-in-a-multi-center-lupus-registry-cohort

Abstract Number: 2939

The Impact of Tabalumab on the Kidney in Systemic Lupus Erythematosus: Results from Two Phase 3 Randomized Clinical Trials

Mary Anne Dooley[1], Brad H. Rovin[2], Jai Radhakrishnan[3], Ellen M. Ginzler[4], Tammy Forrester[5] and Pamela Anderson[6], [1]Medicine-Rheumatology-Immun, U of NC at Chapel Hill, Chapel Hill, NC, [2]Ohio State University Medical Center, Columbus, OH, [3]Presbyterian Hospital, Columbia University, New York, NY, [4]Medicine/Box 42, SUNY-Downstate, Brooklyn, NY, [5]Eli Lilly & Company, Indianapolis, IN, [6]Eli Lilly & Co, Indianapolis, IN
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Background/Purpose: Tabalumab is a monoclonal antibody that neutralizes membrane and soluble B-cell activating factor. Two 52-week, randomized, double-blinded, placebo-controlled Phase 3 trials, designated BCDS and BCDT, were done to evaluate the safety and efficacy of tabalumab in non-renal disease manifestations in patients with systemic lupus erythematosus (SLE).

Methods: Patients with moderate-severe active SLE but without severe active lupus nephritis (defined as a urine protein/creatinine ratio of >200 mg/mmol or an estimated creatinine clearance of <30 mL/min) were randomized 1:1:1 to receive tabalumab (120 mg subcutaneously every 4 weeks or 120 mg subcutaneously every 2 weeks) or placebo for 52 weeks. Serum creatinine, glomerular filtration rate, urine protein/creatinine ratio, and renal adverse events were determined monthly. Data were analyzed for the intent-to-treat population and for intent-to-treat patients with a baseline urine protein/creatinine ratio >20 mg/mmol using an ANCOVA model.

Results: The trials enrolled 2262 patients. At baseline, demographics, SLE disease activity, use of SLE drugs, serum creatinine, glomerular filtration rate, and urine protein/creatinine ratio were similar among the treatment arms. In the two populations, there were no differences between treatment arms in baseline-to-endpoint change in serum creatinine, glomerular filtration rate, and urine protein/creatinine ratio (Tables 1-2). Renal adverse events were not different among treatment arms.

Conclusion: Compared to placebo, tabalumab did not significantly affect serum creatinine, glomerular filtration rate, and urine protein/creatinine ratio over 52 weeks in the intent-to-treat population or intent-to-treat patients with a baseline urine protein/creatinine ratio >20 mg/mmol. There were no significant renal safety signals.

TABLE 1: Change in Renal Laboratory Parameters, Baseline to Week 52: Intention-to-Treat Set

	BCDS				BCDT				BCDS+BCDT		
	TAB Q2W (N=301)	TAB Q4W (N=293)	PBO (N=287)		TAB Q2W (N=296)	TAB Q4W (N=290)	PBO (N=288)		TAB Q2W (N=597)	TAB Q4W (N=583)	PBO (N=575)
ΔSCr (umol/L)	0.90±10.2	0.03±8.5	-0.19±10.5		0.18±11.1	0.19±11.0	0.81±12.2		0.54±10.7	0.11±9.8	0.31±11.4
p-value vs PBO	.153	.758			.731	.924			.549	.897	
ΔGFR (MDRD) (mL/min/bsa)	-1.28±17.3	1.30±14.3	0.36±17.3		1.63±17.8	-0.06±15.3	0.41±15.9		0.17±17.6	0.63±14.8	0.38±16.6
p-value vs PBO	.239	.574			.595	.396			.622	.805	
ΔuPCR (mg/mmol)	4.46±67.8	-0.20±61.9	3.78±56.5		-3.68±32.5	-0.40±38.7	-0.02±27.7		0.44±53.4	-0.30±51.6	1.87±44.4
p-value vs PBO	.998	.412			.468	.834			.718	.517	

TAB Q2W=tabalumab 120 mg every 2 weeks; TAB Q4W=tabalumab 120 mg every 4 weeks; PBO=placebo

SCr=serum creatinine; GFR=glomerular filtration rate (GFR); uPCR=urine protein/creatinine ratio; bsa=body surface area

mean± SD

Table 2: Change in Renal Laboratory Parameters, Baseline to Week 52: Intention-to-Treat Set with Baseline uPCR >20

mg/mmol

	BCDS				BCDT				BCDS+BCDT		
	TAB Q2W (N=70)	TAB Q4W (N=66)	PBO (N=58)		TAB Q2W (N=47)	TAB Q4W (N=50)	PBO (N=33)		TAB Q2W (N=117)	TAB Q4W (N=116)	PBO (N=91)
ΔSCr (umol/L)	3.31±11.4	2.23±9.0	2.00±14.5		-0.74±15.0	0.36±15.4	4.00±14.3		1.68±13.0	1.42±12.1	2.73±14.4
p-value vs PBO	.685	.900			.136	.360			.471	.655	
ΔGFR (MDRD) (mL/min/bsa)	-3.67±17.3	-0.52±13.5	-2.07±21.5		3.29±20.6	1.35±18.9	-2.26±19.7		-0.87±18.9	0.29±16.0	-2.14±20.7
p-value vs PBO	.983	.597			.321	.602			.604	.559	
ΔuPCR (mg/mmol)	-2.34±91.0	-6.58±127.9	3.50±117.2		-28.12±75.5	-12.35±87.9	-26.93±68.4		-12.52±85.8	-9.08±111.8	-7.53±102.9
p-value vs PBO	.316	.282			.879	.776			.383	.434	

TAB Q2W=tabalumab 120 mg every 2 weeks; TAB Q4W=tabalumab 120 mg every 4 weeks; PBO=placebo

SCr=serum creatinine; GFR=glomerular filtration rate (GFR); uPCR=urine protein/creatinine ratio; bsa=body surface area

mean± SD

Disclosure: M. A. Dooley, Lilly, 9,Aurinia, 9,GSK, 5,Genentech and Biogen IDEC Inc., 5,EMD Serono, 5,Medimmune, 5,UCB, 5; **B. H. Rovin**, Lilly, 5; **J. Radhakrishnan**, Lilly, 5; **E. M. Ginzler**, None; **T. Forrester**, Eli Lilly and Company, 3; **P. Anderson**, Eli Lilly and Company, 3.

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Abstract Number: 2940

Risk Factors for Late-Onset Thrombosis in Systemic Lupus Erythematosus (SLE)

Khawla Al-Ghanim[1], Jiandong Su[2], Stacey E. Morrison[3], Samar Alharbi[4], Mohammed Attar[5], Dafna Gladman[2], Murray Urowitz[6,7] and Jorge Sánchez-Guerrero[8], [1]Rheumatology, TWH, Toronto, ON, Canada, [2]Rheumatology, University of Toronto, Toronto Western Hospital, Toronto, ON, Canada, [3]Div Rheumatology Rm MP-10-304, Toronto Western Hospital, Toronto, ON, Canada, [4]Rheumatology, University Health Network, Toronto, ON, Canada, [5]Rheumatology, Toronto Western Hospital, Toronto, ON, Canada, [6]University of Toronto, Toronto, ON, Canada, [7]Rheumatology, U of Toronto, Toronto Western Hospital, Toronto, ON, Canada, [8]Rheumatology, Mount Sinai Hospital and University Health Network, Toronto Canada, Toronto, ON, Canada
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Background/Purpose: Thrombotic events (TE) cause great morbidity and mortality in SLE patients. Studies of TE in SLE focus on early-onset TE. While the incidence of TE remains increased during later-stage disease, no study has assessed the risk factors for late-onset TE. The purpose of this study is to: a) assess the characteristics and risk factors associated with late-onset TE (> 5 years after diagnosis) in SLE; and b) compare these with early-onset TE (< 5 years after diagnosis).

Methods: One hundred and fifty-one SLE patients who developed TE after enrolment in a prospective lupus cohort from 1970 to 2014 were identified. They were matched for age, sex and disease duration with non-TE SLE patients (early-onset TE controls: n=151; and late- onset TE controls: n=77). The demographic (age, ethnicity), clinical (disease duration, ACR criteria, SLE manifestations), lab (anti-dsDNA antibody, C3, C4, nuclear antigens, lupus anticoagulant, anti-cardiolipin antibody), disease activity (SLEDAI-2K), disease damage [SLICC Damage Index with cardiovascular items removed (mod-SDI)] and treatment (prednisone, immunosuppressants, antimalarials, anti-inflammatories), as well as TE type [arterial (ATE), venous (VTE)] and traditional TE risk factor (smoking, cholesterol levels and hypertension) variables were recorded.

Results: Fifty (33%) patients developed late-onset and 101 (67%) early-onset TE. In comparison with early- onsetTE, late-onset TE

were predominantly ATE (62.0% vs 45%, *P=0.02*). In univariate analysis, significant variables associated with late-onset TE were hypertension (OR 3.97, P<*0.01*), oral/nasal ulcers (OR 2.56, *P=0.03*), CNS manifestations (OR 5.40, *P=0.01*), vasculitis (OR 3.48, *P<0.01*), elevated total cholesterol (OR 2.58, *p<0.01*), and prednisone dose within 3 years of TE (OR 1.07, *P*=0.02).

In multivariate analysis, significant predictors of late-onset TE were hypertension (OR 2.85, *P=0.03*), CNS manifestations (OR = 6.66, *P=0.04*), vasculitis (OR = 2.96, *P=0.049*), lupus anti-coagulant (OR = 4.73, *P=0.02*). Risk factors associated with late ATE included a combination of traditional TE risk factor and lupus-related factors; whereas in late VTE risk factors included predominantly lupus-related factors. Variables associated with early-onset TE were also a mixture of traditional and lupus-related risk-factors.

Conclusion: Late-onset TE in SLE is predominantly arterial, and result from both traditional and SLE-related risk factors. The risk of thrombosis remains elevated throughout the course of SLE, resulting from the combination of traditional and SLE-related risk factors. In order to reduce the burden of TE, these risk factors need to be continuously evaluated and controlled throughout the disease course.

Disclosure: K. Al-Ghanim, None; **J. Su**, None; **S. E. Morrison**, None; **S. Alharbi**, None; **M. Attar**, None; **D. Gladman**, None; **M. Urowitz**, None; **J. Sánchez-Guerrero**, None.

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Abstract Number: 2941

Outcomes in Lupus Nephritis Patients Previously Randomized to Receive Either Low Dose Cyclophosphamide Versus Oral Mycophenolate Mofetil on Azathioprine Maintenance

Manish Rathi[1], Ajay Jaryal[2], Ajay Goyal[2], Aman Sharma[3], Pramod Gupta[4] and Krishan Gupta[2], [1]Department of Nephrology,, Postgraduate Institute of Medical Education and Research, Chandigarh, India, [2]Nephrology, Postgraduate Institute of Medical Education and Research, Chandigarh, India, [3]Internal Medicine, Postgraduate Institute of Medical Education and Research, Chandigarh, India, [4]Biostatistics, Postgraduate Institute of Medical Education and Research, Chandigarh, India

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Background/Purpose: Management of SLE and lupus nephritis is challenging as it is always a trade off between remission, prevention of relapse and long term adverse effects of drugs. No previous trial has compared oral mycophenolate mofetil (MMF) with low dose intravenous cyclophosphamide (CYC) as induction agent followed by azathioprine as maintenance agent in the treatment of less severe lupus nephritis (LN).

Methods: This study is a follow-up study of previous open label, ongoing prospective, randomized trial comparing the efficacy and safety of low dose CYC (Euro-lupus regimen) and oral MMF in subjects with class III, IV, V, III+V, or IV+V LN. Subjects with crescentic LN, serum creatinine >3mg/dl, neurological or pulmonary lupus, ongoing infection, pregnancy and prior CYC or MMF use were excluded. The dose of MMF was 2–3 gm/day for 6 months, while CYC was administered as six fortnightly infusions of 500 mg each. All subjects also received three consecutive intravenous methylprednisolone injections initially followed by oral steroids at 1mg/kg up to 2 months and then tapered to a dose of 5-7.5 mg/day. After completion of induction treatment, all subjects were prescribed azathioprine (2 mg/kg) with low dose steroid.

Results: A total of 100 subjects were randomized, of which 69 completed one year of maintenance treatment with azathioprine after receiving either MMF or CYC as induction agent. Out of these 69 subjects, thirty four (n=34) received CYC and thirty five received MMF (n=35) as an induction agent. Baseline characteristics were similar except for a higher 24 hour protein excretion in the CYC group. Sixty one of total subjects, i.e.88.4%, (n=32 in CYC and n =29 in MMF, p=ns) achieved treatment response, of which fifty seven subjects achieved remission. Mean duration to achieve remission in CYC arm was 21.81 weeks and 19.47 weeks in MMF arm. Eight patients had resistant disease (MMF =6, CYC=2), six deaths (MMF=5, CYC=1), four lost to follow up (MMF=1, CYC=3) and one patient deviated from protocol. Four subjects, 3 in MMF and 1 in CYC arm had nephrotic flare during follow up and none had nephritic flare. Gastrointestinal symptoms were more frequent in the MMF group; however there was no difference in other adverse events. Main adverse events during maintenance phase were cytopenia in one patient, herpes zoster in one and avascular necrosis of femoral head in one patient. The treatment cost of MMF was ten times more than the CYC therapy.

Conclusion: One year outcome of maintenance phase with azathioprine were similar in low dose intravenous CYC and oral MMF arm

in treatment of less severe lupus nephritis.

Disclosure: M. Rathi, None; **A. Jaryal**, None; **A. Goyal**, None; **A. Sharma**, None; **P. Gupta**, None; **K. Gupta**, None.

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Abstract Number: 2942

Longitudinal Analyses of Progression of Brain Athrophy in Childhood-Onset Systemic Lupus Erythematosus

Aline Tamires Lapa[1], Nailu A. Sinicato[2], Mariana Postal[1], Fernando Cendes[3], Roberto Marini Sr.[4] and **Simone Appenzeller**[5], [1]Medicine, State University of Campinas, Campinas, Brazil, [2]Pediatrics, State University of Campinas, Campinas, Brazil, [3]State University of Campinas, Campinas, Brazil, [4]Pediatric Rheumatology Unit, State University of Campinas, São Paulo, Brazil, [5]Division of Rheumatology, Faculty of Medical Science, State University of Campinas, São Paulo, Brazil

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Background/Purpose: The CNS involvement in cSLE has been described to occur from 25-90% in childhood-onset systemic lupus erythematosus (cSLE). The aim of the study was to investigate the progression of brain and corpus callosum atrophy in cSLE patients.

Methods: We included consecutive cSLE patients followed in the pediatric rheumatology unit at the State University of Campinas. All patients had 2 magnetic resonance imaging (MRI) done during the follow-up period. MRI scans were obtained through a standardized protocol. Volumes ≤2 standard deviation (SD) from the means of controls were considered abnormal. Neurological manifestations were analyzed according to the ACR classification criteria. SLE patients were further assessed for clinical and laboratory SLE manifestations, disease activity [SLE Disease Activity Index (SLEDAI)], damage [Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index (SDI)] and current and cumulative drug exposures. Non-parametric-tests were used for statistical analysis.

Results: We included 44 cSLE patients (mean age 17.1±3.8 years). The control group consisted of 66 healthy volunteers (mean age 17.3±4.4 years) (p=0.15). At study entry, we observed smaller cerebral (mean volume 1073.1±123.8 cm^3) and corpus callosum (CC) (mean volume 11.5 ±1.7 cm^3) volumes in cSLE patients when compared to controls [mean cerebral volume 1182.9±118.9 cm^3; p<0.001 (mean difference (MD): -1139.0 cm^3; 95%CI 1114.1-1163.9)] and mean CC volume 13.6±2.1; cm^3 p<0.001 (MD -12.8 cm^3; 95%CI 12.4-13.2). Cerebral volumes were associated with anxiety (p=0.016), depression (p=0.002), antinuclear antibody (p=0.026) and anti-Sm antibody (p=0.013) in cSLE. CC volumes were associated with psychosis (p=0.039), acute confusional state (p=0.035) and low complement levels (p=0.01). After a mean follow-up mean period of 20.7±9.1 months we observed significant reduction in cerebral volume [mean 1060.6±128.9 cm^3; p<0.001 (MD -1066.8 cm^3; 95%CI: 1040.2-1093.5)] and CC volumes [mean volume 11.3±1.3 cm^3; p<0.001 (MD-11.4 cm^3; 95%CI: 11.1-11.7)] in cSLE patients. Reduction of cerebral volume was associated with corticosteroid dose per kilogram (p=0.035) and reduction of CC volume with nephritis (p=0.033) and low complement (p=0.046). Cerebral and CC volumes were stable in controls over time (p=0.3). Cerebral atrophy was observed in 9 (20.4%) cSLE patients and 1 (1.5%) controls at study entry and in 10 (22.7%) cSLE patients during the follow-up period (p=0.62). CC atrophy was observed in 9 (20.4%) cSLE patients and 1(1.5%) controls at study entry and in 10 (22.7%) cSLE patients during the follow-up period (p=0.62). Cerebral atrophy was associated with anxiety (p=0.008), depression (p=0.014) and anti-Sm antibody (p=0.04) and CC atrophy with low complement levels (p=0.002) in cSLE.

Conclusion: We observe progression of cerebral and CC volume loss in cSLE patients, although the number of patients with atrophy did not increase. Corticosteroid dose and disease activity (nephritis and low complement) were variables associated with progression of volume loss in cSLE.

Disclosure: A. T. Lapa, None; **N. A. Sinicato**, None; **M. Postal**, None; **F. Cendes**, None; **R. Marini Sr.**, None; **S. Appenzeller**, None.

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Abstract Number: 2943

Preliminary Population-Based Incidence and Prevalence Estimates of Systemic Lupus Erythematous from the Manhattan Lupus Surveillance Program

Peter M. Izmirly[1], Isabella Wan[2], Sara Sahl[1], Jill P. Buyon[3], H. Michael Belmont[4], Jane E. Salmon[5,6], Joan M. Bathon[7], Anca Askanase[8], Laura Geraldino-Pardilla[9], Yousaf Ali[10], Ellen M. Ginzler[11], Chaim Putterman[12], Caroline Gordon[13], Charles G. Helmick[14] and Hilary Parton[15], [1]Medicine, Division of Rheumatology, New York University School of Medicine, New York, NY, [2]Rheumatology, New York University School of Medicine, New York, NY, [3]Department of Medicine, Division of Rheumatology, New York University School of Medicine, New York, NY, [4]New York University School of Medicine, New York, NY, [5]Dept of Medicine, Hospital for Special Surgery, Weill Cornell Medical College, New York, NY, [6]Rheumatology, Hospital for Special Surgery, New York, NY, [7]Rheumatology, Columbia University College of Physicians & Surgeons, New York, NY, [8]Columbia University College of Physicians & Surgeons, New York, NY, [9]Division of Rheumatology, Columbia University College of Physicians & Surgeons, New York, NY, [10]Icahn School of Medicine at Mount Sinai, New York, NY, [11]Medicine/Box 42, SUNY-Downstate, Brooklyn, NY, [12]Division of Rheumatology, Albert Einstein College of Medicine, Bronx, NY, [13]School of Immunity and Infection, College of Medical and Dental Sciences, University of Birmingham, Birmingham, United Kingdom, [14]Arthritis Program, Centers for Disease Control and Prevention, Atlanta, GA, [15]Bureau of Epidemiology Services, New York City Department of Health and Mental Hygiene, Long Island City, NY

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Background/Purpose: Given widely varying estimates of the incidence and prevalence of Systemic Lupus Erythematous (SLE) in the US and the absence of data for certain demographic groups attention has turned to obtaining a better epidemiologic understanding of SLE across key ethnic/racial groups. Recently the Centers for Disease Control and Prevention supported four local health departments as well as the Indian Health Service to more rigorously capture cases SLE through the implementation of a population-based registry, the Manhattan Lupus Surveillance Program (MSLP), comprised of SLE patients treated in New York County. The primary goal of the MLSP is to capture information that can be used to determine the prevalence of SLE in 2007 and incidence of SLE during 2007-09 among Manhattan residents. Of specific interest are SLE rates among Hispanics and Asians where epidemiologic data are very limited.

Methods: Potential MLSP cases were identified from Manhattan-based hospitals and rheumatologists, and state population databases. More than 75,000 potential SLE patients were initially identified by screening for key ICD-9 codes. After additional screening based on Manhattan residence and deduplication, trained medical abstractors performed detailed medical chart review on the remaining ~6,400 patients for information on SLE and related conditions. Preliminary MLSP estimates of SLE were calculated based on two current criteria developed by the ACR and the Systemic Lupus International Collaborating Clinics (SLICC). Cases were defined as fulfilling 1) > 4/11 of the ACR classification criteria or 2) the SLICC criteria. Prevalence rates, based on SLE diagnosis by 2007, and incidence rates, based on new SLE diagnosis in 2007-09, and associated 95% confidence intervals (CI) were calculated using denominators obtained from the US Census data (revised 2000-2009 intercensal population files) for Manhattan.

Results: Based on the ACR criteria, the preliminary age-adjusted overall prevalence and incidence rates of SLE in New York County were 63.2 and 4.3 per 100,000 population, respectively. The overall prevalence and incidence rates were 10 times higher in females than males (Table 1). The highest prevalence of SLE was observed among black women (195.3), followed by Hispanic women (132.5), Asian women (89.5) and white women (61.9). Using the SLICC criteria generated age-adjusted overall prevalence and incidence rates of 70.4 and 5.5 per 100,000 population, respectively. Incidence and prevalence rates for all demographics were higher using the SLICC criteria for SLE than the ACR criteria (Table 1).

Conclusion: Using a more complete case finding methodology, the MLSP revealed substantial gender, ethnic and racial disparities in SLE among Manhattan residents. Black women had the highest prevalence rate of SLE followed by Hispanic, Asian and white women. The SLICC criteria provided higher SLE prevalence and incidence rates than the ACR criteria.

Preliminary Prevalence and Incidence Rates (per 100,000) of SLE in New York (Manhattan), NY

	Prevalence (2007) Age-adjusted Estimate (95% CI)		Incidence (2007-2009) Age-adjusted Estimate (95% CI)	
Race/Ethnicity, Sex	ACR Criteria	SLICC Criteria	ACR Criteria	SLICC Criteria
	63.2 (59.5	70.4 (66.5	4.3 (3.7	

Disclosure: P. M. Izmirly, None; **I. Wan**, None; **S. Sahl**, None; **J. P. Buyon**, None; **H. M. Belmont**, None; **J. E. Salmon**, None; **J. M. Bathon**, None; **A. Askanase**, None; **L. Geraldino-Pardilla**, None; **Y. Ali**, None; **E. M. Ginzler**, None; **C. Putterman**, None; **C. Gordon**, None; **C. G. Helmick**, None; **H. Parton**, None.

Overall	63.2 (59.5 - 66.9)	70.4 (66.5 - 74.3)	4.3 (3.7 - 4.9)	5.5 (4.9 - 6.1)
Female	106.5 (99.9 - 113.1)	119.7 (112.7 - 126.7)	7.3 (6.3 - 8.3)	9.2 (8.1 - 10.3)
Male	13.2 (10.7 - 15.7)	13.5 (10.9 - 16.1)	0.9 (0.5 - 1.3)	1.3 (0.8 - 1.8)
Black	120.4 (106.3 - 134.5)	132.8 (118.0 – 147.6)	9.2 (6.9-11.5)	11.1 (8.6 - 13.6)
Female	195.3 (171.0 - 219.6)	216.2 (190.7 – 241.7)	15.6 (11.5 - 19.7)	17.9 (13.5 - 22.3)
Male	31.5 (20.6 - 42.4)	32.3 (21.3 - 43.3)	2 (0.4 - 3.6)	3.2 (1.2 - 5.2)
White	34.4 (30.6 - 38.2)	38.4 (34.4 - 42.4)	3 (2.4 - 3.6)	3.7 (3.0 - 4.4)
Female	61.9 (54.8 - 69.0)	68.7 (61.2 - 76.2)	5.5 (4.3 - 6.7)	6.6 (5.3 - 7.9)
Male	4.3 (2.3 - 6.3)	5.2 (3.0 – 7.4)	0.4 (0.1 - 0.7)	0.7 (0.2 - 1.2)
Hispanic	82.0 (73.2 - 90.8)	85.9 (76.9 – 94.9)	3.3 (2.3 – 4.3)	4.0 (2.9 – 5.1)
Female	132.5 (117.4 - 147.6)	139.6 (124.1 – 155.1)	5.0 (3.3 - 6.7)	6.3 (4.4 – 8.2)
Male	18.9 (12.4 - 25.4)	19.5 (13.0 – 26.0)	1.2 (0.3 - 2.1)	1.2 (0.3 - 2.2)
Asian	55.4 (45.0 - 65.8)	67.5 (56.0 – 79.0)	3.8 (2.2 - 5.4)	6.1 (4.1 – 8.1)
Female	89.5 (71.6 - 107.4)	112.5 (92.5 – 132.5)	6.5 (3.7 - 9.3)	9.8 (6.4 – 13.2)
Male	12.3 (5.3 – 19.0)	11.4 (4.9 - 17.9)	0.5 (-0.5 - 1.5)	1.5 (-0.2 - 3.2)

Data reflects cases abstracted as of 5/31/2015. These estimates do not include all Manhattan cases for the study period. Data abstraction is expected to be completed in mid-2015.

Denominator data for NYC rates is based on NYC DOHMH intercensal population estimates.

NYC data are age adjusted to the US 2000 Standard Population.

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Abstract Number: 2944

Presepsin (sCD14 subtype) Concentration Is Elevated and Reflects Disease Activity in Systemic Lupus Erythematous Patients

Kohei Tsujimoto[1], Masaaki Fujita[2], Yutaka Shinkawa[2], Iku Shirasugi[1], Masashi Taniguchi[1], Saori Hatachi[3] and Masato Yagita[4], [1]Department of Clinical Immunology and Rheumatology, Tazuke Kofukai Foundation, Medical Research Institute, Kitano Hospital, Osaka, Japan, [2]Department of Clinical Immunology and Rheumatology C, Tazuke Kofukai Foundation, Medical Research Institute, Kitano Hospital, Osaka, Japan, [3]Department of Rheumatology, Tazuke Kofukai Foundation, Medical Research Institute, Kitano Hospital, Osaka, Japan, [4]Tazuke Kofukai Foundation, Medical Research Institute, Kitano Hospital, Osaka, Japan

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Background/Purpose: Presepsin (sCD14 subtype) has recently been identified as a novel biomarker for predicting sepsis. Because presepsin is produced as a consequence of cellular phagocytosis, it may reflect monocyte activation. Recent evidence indicates that monocytes play an extremely important role in systemic lupus erythematosus (SLE). Little is known regarding presepsin in patients with SLE. Therefore, we tested the hypothesis that presepsin concentrations are elevated and associated with disease activity in patients with SLE without infection.

Methods: Thirty-three patients with SLE (4 men, 29 women) with a mean age of 46.6 and 22 healthy controls (5 men, 17 women) with a mean age of 48.1 were enrolled in this study. No patient had an apparent infection. Concentrations of plasma presepsin, serum C3, C4, and total hemolytic complement (CH50) levels were measured. The plasma presepsin concentration was measured using a chemiluminescent enzyme immunoassay. The levels were compared between the groups. The SLE disease activity index (SLEDAI) was calculated in the SLE group. Eight out of 33 SLE patients who underwent intensified immunosuppressive therapy were tested twice at 2 weeks after treatment.

Results: Patients with SLE had higher concentrations of presepsin [238.5 (48–741) pg/mL] than the healthy controls [118.4 (74–270) pg/mL; $P = 0.0003$]. The mean SLEDAI of all SLE patients was 10.8 (0–30). In patients with SLE, the concentration of presepsin was significantly correlated with disease activity, as assessed by SLEDAI scores ($R^2 = 0.77$; $P < 0.0001$; Fig. 1). There were significant correlations between presepsin and compliment CH50 ($R^2 = 0.12$; $P = 0.046$) and C4 ($R^2 = 0.034$; $P = 0.034$) but not between presepsin and C3 ($R^2 = 0.073$; $P = 0.12$). The concentration of presepsin was significantly decreased after treatment (before: 351.3 pg/mL; after: 134.0 pg/mL; $P = 0.016$; Fig. 2). The ROC curve analysis was conducted to compare the predictive values of presepsin. Area under the curve of presepsin was 0.7803. According to the ROC analysis, the optimal cut-off value of presepsin for the diagnosis of SLE was 156.5 pg/mL. Using this cut-off value, the sensitivity and specificity were 66.67% and 86.36%, respectively.

Conclusion: Measurements of plasma presepsin can be useful in assessing the disease activity of SLE and may be used to monitor treatment.

Figure 1

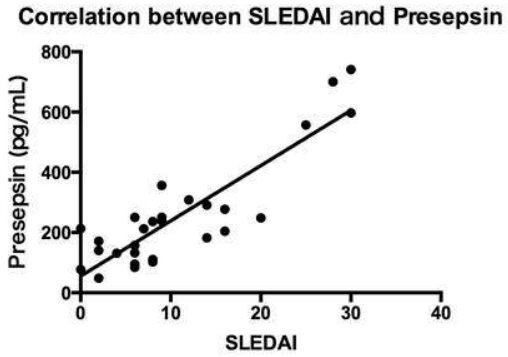
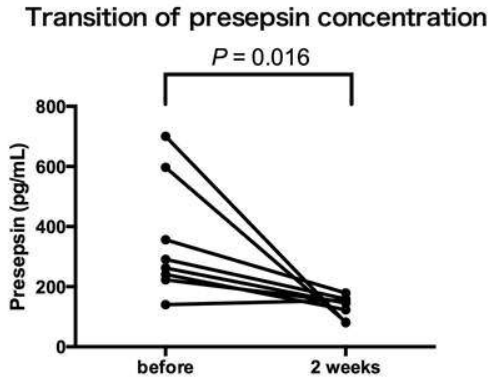


Figure 2



Disclosure: K. Tsujimoto, None; **M. Fujita**, None; **Y. Shinkawa**, None; **I. Shirasugi**, None; **M. Taniguchi**, None; **S. Hatachi**, None; **M. Yagita**, None.

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Abstract Number: 2945

Diffuse Alveolar Hemorrhage in SLE: Risk Factors, Response to Therapy, and Survival

Nayef M. Kazzaz[1], Patrick S. Coit[2], Emily E. Lewis[3], W Joseph McCune[4], Amr H. Sawalha[2] and Jason S. Knight[2], [1]Rheumatology, University of Michigan, Ann Arbor, MI, [2]Division of Rheumatology, University of Michigan, Ann Arbor, MI, [3]University of Michigan, Ann Arbor, MI, [4]Int Med/ Rheum, University of Michigan, Ann Arbor, MI

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Background/Purpose: While diffuse alveolar hemorrhage (DAH) is recognized as a life-threatening complication of SLE, little is known about its risk factors and response to therapy. Here, we describe 22 cases of DAH in a U.S. lupus cohort of ~1,000 patients, and compare them to 66 controls from the same outpatient cohort.

Methods: All patients met ACR classification criteria for SLE. We first captured variables pertaining to diagnoses of SLE and secondary antiphospholipid syndrome (APS) and analyzed them by Chi square (univariate) testing. Those variables with p values <0.05 were then further considered in a multivariate model. Kaplan-Meier curves were constructed for each group, and survival was analyzed by Log-rank test.

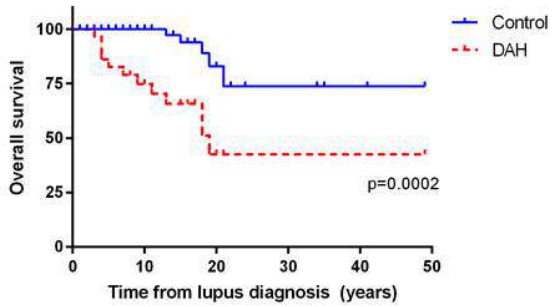
Results: Of the 22 DAH patients, 59% were diagnosed with DAH within 5 years of SLE diagnosis. By univariate analysis, several manifestations of SLE and APS were more common in DAH patients as compared to controls (**Table**). After building a multivariate model, history of thrombocytopenia and low C3 were maintained as independent risk factors. While a remarkable 19/22 DAH patients had a history of thrombocytopenia, only 5 had thrombocytopenia at the time of the DAH episode (and only 2 with platelet counts <50,000/µl), arguing that DAH was not simply a hemorrhagic complication of the low platelets. Interestingly, all patients survived their initial episode of DAH. All were treated with increased immunosuppression, including various combinations of corticosteroids, plasmapheresis, cyclophosphamide, rituximab, and mycophenolate mofetil. While the DAH patients did well in the short-term, their long-term survival was significantly worse compared to the control group (**Figure**). Interestingly, despite the history of both thrombocytopenia and DAH, several of the deaths were attributable to thrombotic complications after recovering from the DAH episode.

Conclusion: To our knowledge, this is the largest case-control study of lupus DAH reported to date. While a history of thrombocytopenia was strongly predictive of DAH (odds ratio ~40), only 2 patients had platelet counts <50,000/µl at the time of hemorrhage. A number of APS manifestations correlated with DAH in univariate testing (but not a multivariate model), and deserve further consideration in larger studies. In the short-term, this cohort of patients was treated aggressively for their DAH and fared quite well. However, over time, their survival was significantly reduced as compared to controls.

Table DAH vs. controls (univariate analysis)

History of:	Odds ratio	P-value
Thrombocytopenia *	43.2	<0.0001
Cardiac valve disease	22.1	<0.0001
Low C3 *	19.3	<0.0001
Leukopenia	13.4	0.0004
Neuropsychiatric	9.20	0.001
Hemolysis	5.85	0.0007
Arterial thrombosis	6.42	0.005
Lupus anticoagulant	5.36	0.004
Secondary APS	4.47	0.04
Low C4	3.32	0.03

* Remains significant in a multivariate model



Disclosure: N. M. Kazzaz, None; **P. S. Coit**, None; **E. E. Lewis**, None; **W. J. McCune**, None; **A. H. Sawalha**, None; **J. S. Knight**, None.

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Abstract Number: 2946

Mortality Among SLE Patients in the National Data Bank for Rheumatic Diseases

Kaleb Michaud[1], Sofia Pedro[2] and Patricia P. Katz[3], [1]Internal Medicine, University of Nebraska Medical Center, Omaha, NE, [2]National Data Bank for Rheumatic Diseases, Wichita, KS, [3]Medicine/Rheumatology, University of California San Francisco, San Francisco, CA

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Background/Purpose: To investigate risk of mortality among SLE patients cohort in the NDB.

Methods: Systemic lupus erythematous (SLE) and non-inflammatory rheumatic disease (NIRD) patients were studied from 1998 through 2011 in the National Data Bank for Rheumatic Diseases (NDB), a longitudinal observational study following patients from all regions of the US through biannual questionnaires. Patients were required to have at least 2 observations or 1 observation and died before 2012. Mortality was confirmed through National Death Index-matched death records. We calculated standardized mortality ratios (SRRs) of SLE vs. NIRD based on age-, race- and sex-stratified US population data (CDC.gov). Cox regression models with time varying covariates were used to investigate the risk of mortality among diagnoses. A second Cox regression model was done at last observation using SLE specific variables.

Results: 2,374 SLE and 5,603 NIRD patients were studied. The mean (median) time in the study for SLE patients was: 2.52 (1.71) years with a total of 5,981 patient-years of follow-up, and for NIRD, 3.77 (2.12) years with a total of 21,090 patient-years of follow-up. At a random observation, SLE patients were described as: mostly male (93.3%), with an average of 50.4 (SD 13.5) years, white (73.0%), married (59%), mostly high-graduated (93.9%), with worse disease activity measures compared to NIRD (P<0.001 for the majority). At last observation, the BILD score was 3.36 (SD 2.08), PHQ8 scale 5.67 (SD 5-04) and GAD2 0.93 (SD 1.36).

The overall SRM were: 2.88 (95% CI 2.42-3.44) and 1.46 (95% CI 1.37-1.55) for SLE and NIRD patients, respectively. After multivariate adjustment (including demographic and disease severity outcomes), the hazard ratio comparing diagnoses was 0.96 (95%CI 0.74 -1.24). Among SLE patients, univariate preditors of mortality (age, age-squared and sex adjusted) were presented in Table. Almost all disease severity variables were associated with an increased risk of mortality among the SLE cohort.

Conclusion: Predictors of mortality were studied among SLE patients. Worse disease severity, more comorbidities and smoking habits were all important factors to an increased risk of mortality, among others. When comparing diagnoses, the risk of mortality did not seem to differ. The use of treatment will be further investigated in future works.

Table - Age, age-squared and sex adjusted predictors of mortality among SLE patients.

Cox regression	**HR**	**95% CI**	
Age	0.90	0.84	0.97
Age- squared	1.00	1.00	1.00
Sex	2.37	1.47	3.83
White	0.61	0.40	0.94
Married	0.70	0.50	0.99
Widowed	1.96	1.14	3.37
Employed	0.38	0.23	0.63
Educational level (yrs)	0.90	0.84	0.96
Past smoker	1.49	1.03	2.16
Current smoker	1.86	1.10	3.15
BMI (Kg/m^2)	1.02	1.00	1.05
HAQ disability (0-3)	2.30	1.82	2.90
VAS pain scale (0-10)	1.18	1.11	1.25
VAS Global (0-10)	1.19	1.11	1.27
VAS Fatigue scale (0-10)	1.14	1.08	1.21
PAS (0-10)	1.29	1.19	1.39
SF-36 PCS (0-100)	0.94	0.92	0.96
SF-36 MCS (0-100)	0.98	0.96	0.99
Comorbidity index (0-9)	1.26	1.15	1.37
VAS function scale (0-10)	1.17	1.12	1.22
Symptom intensity scale (0-10)	1.09	1.06	1.12
SLAQ score*	1.09	0.99	1.19
SLAQ flares*			
Yes, mild flare	2.68	0.41	17.40
Yes, moderate flare	2.53	0.19	34.25
Yes, severe flare	14.11	1.59	124.92

* Model performed at last observation, not using time-varying covariates.

Disclosure: K. Michaud, None; **S. Pedro**, None; **P. P. Katz**, None.

Abstract Number: 2947

Association of Anti-NR2 and U1RNP Antibodies with Neurotoxic Inflammatory Mediators in Cerebrospinal Fluid from Patients with Neuropsychiatric Systemic Lupus Erythematosus

Seiko Kondo-Ishikawa[1], Takao Fujii[2], Nozomi Ishigooka[1], Kosaku Murakami[1], Ran Nakashima[1], Yoshitaka Imura[1], Motomu Hashimoto[2], Naoichiro Yukawa[1], Hajime Yoshifuji[1], Koichiro Ohmura[1] and Tsuneyo Mimori[1], [1]Department of Rheumatology and Clinical Immunology, Department of Rheumatology and Clinical Immunology, Graduate School of Medicine, Kyoto University, Kyoto, Japan, [2]Department of the Control for Rheumatic Diseases, Department of the Control for Rheumatic Diseases, Graduate School of Medicine, Kyoto University, Kyoto, Japan

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Background/Purpose: Autoantibodies (auto Abs) in cerebrospinal fluid (CSF) and inflammatory mediators (IMs) may be involved in the pathogenesis of neuropsychiatric systemic lupus erythematosus (NPSLE). Previous studies revealed that auto Abs such as anti-NMDA(N-methyl *D*-aspartate) receptor NR2 subunit (NR2) Abs are linked to a certain kind of NPSLE. We reported the association between NPSLE and CSF-anti-U1RNP Abs. What kinds of IMs in the central nervous system are stimulated by these Abs, however, remains unknown. The aim of the present study is to determine the association of both Abs with neurotoxic IMs.

Methods: Serum and CSF samples were obtained from NPSLE patients with diffuse NPSLE (n=39) or focal NPSLE (n=35), and non-NPSLE patients (control, n=13). Serum- and CSF-anti-NR2 Abs were determined by ELISA. Serum- and CSF-anti-U1RNP Ab positivity and titer were determined by RNA-immunoprecipitation assay and ELISA, respectively. CSF-IL-6, IL-8, and monokine induced by IFN-γ(MIG), which were reported to be neurotoxic, were measured by quantitative multiplex cytokine analysis. To elucidate the possibility that these IMs pass through blood-brain barrier (BBB), the permeability of BBB was evaluated by albumin quotient (Q*alb*).

Results: 1) IL-6 (67.4 vs. 17.5 pg/mL, p=0.02) and MIG (4307 vs. 109 pg/mL, p=0.03) levels, but not IL-8, were higher in CSF-anti-NR2 Ab-positive patients than controls. IL-6 level was higher in serum-anti-NR2 Ab-positive patients than in controls (50.0 vs. 17.4 pg/mL, p=0.03). There was no association of CSF-IMs with serum- and CSF-anti-NR2 Ab titer. CSF-anti-NR2 Ab positivity and titers were correlated with an increased permeability of BBB, as previously reported. 2) MIG level, but not IL-6 or IL-8, was higher in CSF-anti-U1RNP Ab-positive patients than in controls (2142 vs. 109 pg/mL, p=0.04). CSF-IMs were not correlated with serum-anti-U1RNP Ab titer. MIG level tended to positively correlated with CSF-anti-U1RNP Ab titer (r=0.49, p=0.07). 3) All the NPSLE patients were divided into 4 groups: CSF-anti-NR2 Ab +/U1RNP+ (double positive [DP], n=7), anti-NR2 Ab+/U1RNP- (NR2, n=18), anti-NR2-/U1RNP+ (U1RNP, n=9), anti-NR2 Ab-/U1RNP- (double negative [DN], n=40). In CSF-DP group, IL-6 and MIG levels, but not IL-8, were higher than in NR2 and U1RNP groups. 4) Q*alb* was positively correlated with IL-8 (r=0.45, p<0.0001) and MIG (r=0.56, p<0.0001) levels. Elevated CSF-IL-6 level, however, was not associated with an increased permeability of BBB. 5) The frequency of diffuse NPSLE in CSF-DP group (71%) tended to be higher than in the other groups. Auto Ab positivity was not associated with the brain MRI abnormalities.

Conclusion: CSF-IL-6 level was closely associated with the presence of CSF-anti-NR2 Abs, but not correlated with the BBB permeability. CSF-MIG level was associated with the presence of CSF-auto Abs and the BBB permeability. CSF-IL-8 level might be dependent of the BBB permeability alone. Thus, the involvements of auto Abs in CSF and BBB permeability in neurotoxic IM activation of NPSLE patients are different one another. The present study also suggests that NPSLE with both anti-NR2 and U1RNP Abs in CSF may have more severe manifestations.

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Abstract Number: 2948

How Do Patients with Newly Diagnosed SLE Present? a Multicenter Cohort Analysis

to Inform the Development of New Classification Criteria for SLE

Marta Mosca[1], Zahi Touma[2], Karen H. Costenbader[3], Bimba F. Hoyer[4], Chiara Tani[1], Alexander Fine[5], Sara Tedeschi[3], Jorge Medina-Rosas[6], Valentina Lorenzoni[7], Gian Domenico Sebastiani[8], Thomas Dorner[9] and on behalf of the SLE Classification Criteria Steering committee, [1]University of Pisa, Pisa, Italy, [2]Rheumatology, University of Toronto, Toronto Western Hospital, Toronto, ON, Canada, [3]Division of Rheumatology, Immunology and Allergy, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, [4]Charité University Medicine, Department of Medicine/Rheumatology and Clinical Immunology and German Rheumatism Research Centre Berlin (DRFZ), Berlin, Germany, [5]Rheumatology, Immunology and Allergy, Brigham and Women's Hospital, Boston, MA, [6]University of Toronto, Toronto, ON, Canada, [7]SSSUP, Pisa, Italy, [8]Osp. San Camillo, Roma, Italy, [9]Department of Medicine/Rheumatology and Clinical Immunology and German Rheumatism Research Centre Berlin (DRFZ), Charité University Medicine, Berlin, Germany

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Background/Purpose:

SLE onset may be insidious with clinically evident disease developing over years. Current SLE classification criteria may not classify patients with early SLE well. The ability of SLE classification criteria to include patients with earlier stages of SLE would allow studies of disease progression and the testing of therapies aimed at the prevention of organ involvement and damage. The aim of this multicenter study was to describe the characteristics of patients with early SLE to inform for the development of classification criteria which would capture patients with earlier stages of disease.

Methods:

Clinical and laboratory data at disease onset of patients newly diagnosed with SLE in the past 3 years (1/1/2012-12/31/2014) at 4 referral centers in Europe (2) and North America (2) were collected. All patients were diagnosed by SLE clinical experts. A data extraction form with all current ACR and SLICC items, as well as an additional list of 30 items (clinical and laboratory), was developed. Patients' medical records were reviewed and reviewers were encouraged to add to the existing list of items any other presenting manifestations. Two-step cluster analysis followed by discriminant analysis were used to identify potential subgroups of patients with distinct SLE presentations, and to identify the important variables contributing to SLE diagnosis.

Results:

Two hundred and thirty one patients (F 203; M 27) were identified, of these 73% were White, 10.5% Black and 9.5% Asian and 7% of mixed ethnicities. Mean age at first symptoms was 32.3 ±12.6 and at diagnosis 34.5 ± 12.8 years. At diagnosis, 48% of patients had < 3 ACR classification criteria, 52% had > 4. The most common clinical manifestations and serologies at diagnosis are in **Table**. Less common manifestations were oral ulcers (18%), discoid lesions (9%), CNS involvement (6%). Less than 5% of patients had alveolar hemorrhage, myocardial infarction, livedo reticularis, thrombosis, subacute cutaneous lesions and thrombocytopenia. Although the numbers were small, no statistically significant differences in manifestations at onset were observed in ANA positive (96%) vs. ANA negative (4%) patients. Twenty nine (12.6%) ANA positive patients, had no more specific serologies. Cluster analysis identified a group of 58 younger patients (29.0 vs. 33.5 years for others) with SLE onset characterized by constitutional symptoms (weight loss, fatigue, fever), thrombosis, anti-dsDNA antibodies, Coomb's test, and renal involvement.

Conclusion:

Almost half of patients had < 3 ACR criteria at diagnosis, mean duration of symptoms was 2.2 years, and 4% of patients were ANA negative. There may be a group of young patients presenting with a specific pattern of disease onset. Additional analyses are required to understand the manifestations most likely found in early SLE.

Table. The Most Common Manifestations and Serologies at Diagnosis of SLE in 4 Large Academic Referral Centers, 2012-2014	
Clinical manifestations	Prevalence (%)
Arthritis	65
Malar rash	45
Leukopenia	40
Fatigue	34
Renal abnormalities	33
Photosensitivity	29
Serositis	29
Fever	28
Raynaud's	20
Serologies and Complement	
ANA	96
Anti-dsDNA	70
Anti-SM	27
Antiphospholipid Antibodies	28
Hypocomplementemia	68

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Disclosure: M. Mosca, None; **Z. Touma**, None; **K. H. Costenbader**, None; **B. F. Hoyer**, None; **C. Tani**, None; **A. Fine**, None; **S. Tedeschi**, None; **J. Medina-Rosas**, None; **V. Lorenzoni**, None; **G. D. Sebastiani**, None; **T. Dorner**, None.

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Abstract Number: 2949

Differential Serum Cytokine Profile in Patients with Systemic Lupus Erythematosus and Posterior Reversible Encephalopathy Syndrome: A Single-Center Study

Jorge Alcocer-Varela[1], Diana Gómez-Martín[1], Javier Merayo-Chalico[2] and Ana Barrera-Vargas[1], [1]Department of Immunology and Rheumatology, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico, [2]Immunology and Rheumatology, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico

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Background/Purpose:

Patients with systemic lupus erythematosus (SLE) are susceptible to the development of posterior reversible encephalopathy syndrome (PRES). The main theory about the physiopathology of PRES suggests there is brain-blood barrier damage, which is associated with endothelial dysfunction, and characterized by vasogenic edema. However, to date there is no evidence about serologic markers associated with the development of PRES in SLE patients. The aim of this study was to determine whether PRES/SLE patients show a specific cytokine profile.

Methods: A transversal study was performed from November 2012 to March 2015 at the Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán in Mexico City. We included four groups of subjects: healthy controls (n=6), SLE patients in remission (n=6), SLE patients with SLEDAI scores >6 (n=6, neurological activity and infections were excluded) and patients with PRES/SLE (n=14). All SLE patients fulfilled at least 4 ACR criteria and PRES was defined as reversible neurological manifestations (seizures, visual abnormalities, acute confusional state, among others) associated with changes by magnetic resonance (iso or hypointensity in T1 and hyperintensity in T2/FLAIR). Serum samples were obtained during the first 48 hours after the PRES episode and they were analyzed by Cytometric Bead Array (Th1, Th2, Th17) and ELISA for CD40L and VEGF.

Results:

Table 1 shows clinical, laboratory and demographic patient features. IL-6 and IL-10 levels were significantly higher in PRES/SLE patients when compared to the rest of the groups (see table). There were no differences between groups regarding sCD40L levels (p=0.80), nor VEGF in SLE patients (p=0.77). There were no differences in platelets, leukocytes or hemoglobin among groups. Other analyzed cytokines (IL 2, 3, 4, 16, 17A, 18, and 12p40; IFNγ and TNFα) did not show significant differences among groups.

Conclusion:

SLE patients with PRES had higher IL-6 and IL-10 levels when compared to other SLE patients and healthy controls. Enhanced IL-6 serum levels could be associated with vascular endotelial cells activation, which might play a key role in the pathogenesis of PRES-related vasogenic edema. Moreover, increased IL-10 levels could act as a counterregulatory mechanism to contend with the inflammatory response driven by IL-6, which might explain the reversibility of the clinical manifestations that characterizes PRES. Prospective studies that include serial measurements of these serum cytokines, correlation with their levels in cerebrospinal fluid and the reversibility of image abnormalities, are needed to confirm our findings.

Table 1. Demographic, serologic and clinical characteristics

Groups (n)	*Age (years) Mean ±SEM*	*SLEDAI (points) Mean ±SEM*	*Platelets (cells/µl x10^3) Mean ±SEM*	*VEGF (pg/ml) Mean ±SEM*	*CD40L (pg/ml) Mean ±SEM*	*IL-6 (pg/ml) Mean ±SEM*	*IL-10 (pg/ml) Mean ±SEM*	*IL-2 (pg/ml) Mean ±SEM*	*IL-4 (pg/ml) Mean ±SEM*
Healthy controls (6)	36±4.10	N/A	N/D	653±275	3923±1200	2.55±0.65	0.83±0.09	0.07±0.04	0.17±0.15
Remission SLE (6)	39.1±4.88	0	224±19.3	153±62	2724±1296	2.04±0.62	1.001±0.14	0.08±0.05	0.23±0.11
¶Active SLE (6)	34.6±4.20	**17±3.07¥**	233±68.9	223±116	1445±1252	4.58±1.84	1.59±0.52	0.35±0.27	0.32±0.27
PRES/SLE(14)	33.3±2.96	7.8±1.48	190±31.4	**173±66¥¥**	2620±773	**21.2±6.85***	**4.24±1.06***	0.43±0.31	0.36±0.27

N/A= Not Applicable; N/D= Not Determined. Values in bold are statistically significant

¶Without neurological involvement ¥p<0.0001 vs PRES/SLE ¥¥p=0.041 vs healthy controls *p<0.05 vs other groups

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Disclosure: J. Alcocer-Varela, None; **D. Gómez-Martín**, None; **J. Merayo-Chalico**, None; **A. Barrera-Vargas**, None.

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Abstract Number: 2950

Using Electronic Health Record Algorithms to Accurately Identify Patients with Systemic Lupus Erythematosus

April Barnado[1], Joshua C. Denny[2] and Leslie J. Crofford[1], [1]Medicine, Vanderbilt University, Nashville, TN, [2]Biomedical Informatics, Medicine, Vanderbilt University, Nashville, TN

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Background/Purpose: To harness the data in electronic health records (EHRs) and administrative databases to study systemic lupus erythematosus (SLE), it is important to identify patients accurately. Currently, there is no validated EHR algorithm specifically for SLE. This study sought to develop and validate a novel EHR algorithm that uses International Classification of Diseases, Ninth Revision

(ICD-9) billing codes, lab values, and medications to identify SLE patients accurately.

Methods: We used Vanderbilt's research electronic database called the Synthetic Derivative (SD). The SD contains 2.5 million records with de-identified clinical data from the EHR. There were 5959 potential SLE cases with at least one SLE ICD-9 code of 710.0. Of these potential subjects, 200 were randomly selected for chart review to identify the true cases. A subject was defined as a case if the subject fit the ACR SLE criteria or was diagnosed by a rheumatologist. Positive predictive values (PPVs) and sensitivity were calculated for combinations of SLE ICD-9 code counts, a positive anti-nuclear antibody (ANA) (titer $\geq$ 1:40), ever use of antimalarials, corticosteroids, and disease-modifying antirheumatic drugs (DMARDs), and a keyword of "lupus" in the subjects' problem lists. PPVs were also calculated for excluding ICD-9 codes for systemic sclerosis (SSc) of 710.1 and dermatomyositis (DM) of 710.3. The algorithm with the highest PPV was internally validated using an additional, randomly selected 100 of the remaining potential 5959 SLE cases. **Results:** The algorithms with the highest PPVs are shown in Table 1. Excluding the SSc and DM ICD-9 codes improved the PPV as did adding ever antimalarial use, ever DMARD use, and a positive antinuclear antibody (ANA) to the SLE ICD-9 code. The algorithm with the best PPV at 95% was 3 or more ICD-9 codes and ANA positive and ever DMARD and ever steroid use while excluding SSc and DM ICD-9 codes. Using this algorithm to randomly select 100 subjects for cross-validation, 91 of the 100 subjects were classified as a case resulting in an internally validated PPV of 91%. **Conclusion:** We have designed a novel algorithm that incorporates not only ICD-9 codes but also lab values and medications to identify SLE patients with a PPV of 91% on an independent test set. Being able to identify SLE cases accurately within the EHR will expand the ability to study more SLE patients from diverse settings. Follow-up studies are ongoing to externally validate the algorithm in other institutions' EHRs.

Table 1. Positive Predictive Values of Electronic Health Record Algorithms to identify SLE cases.

Algorithm	Positive Predictive Value (PPV)	PPV (excluding dermatomyositis and systemic sclerosis)	Sensitivity
3 or more ICD-9 codes AND ANA positive AND ever DMARD AND ever steroid use	91%	95%	40%
4 or more ICD-9 codes AND ANA positive AND ever DMARD AND ever steroid use	90%	95%	38%
4 or more ICD-9 codes AND ever antimalarial use AND ANA positive	89%	92%	70%
4 or more codes AND ever antimalarial use	89%	92%	61%
3 or more codes AND ever antimalarial use	88%	91%	66%
3 or more codes AND ever steroid use AND ever DMARD use	86%	91%	34%
4 or more codes AND ever steroid use AND ever DMARD use	86%	91%	33%

Disclosure: A. Barnado, None; **J. C. Denny**, None; **L. J. Crofford**, None.

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Abstract Number: 2951

Anti-NR2 Antibody and Blood-Brain Barrier Disruption in Systemic Lupus Erythematosus Patients with Cognitive Dysfunction

Gaurav Gulati[1], Philip Iffland[2], Damir Janigro[2], Bin Zhang[3] and Michael Luggen[4], [1]Division of Immunology, Allergy and Rheumatology, University of Cincinnati College of Medicine, Cincinnati, OH, [2]Cleveland Clinic Lerner College of Medicine, Cleveland, OH, [3]Cincinnati Children's Hospital and Medical Center, Cincinnati, OH, [4]Division of Immunology, University of Cincinnati Medical Center, Cincinnati, OH

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Background/Purpose: Cognitive Dysfunction (CD) is one of the most common manifestations of neuropsychiatric SLE (NPSLE) and one of the most devastating. The pathogenesis of CD in SLE is not known, but in animal models, antibody to the NR2 subunit of the N-methyl D- aspartate receptor (aNR2) can cause memory impairment. However, this effect can only be demonstrated if the blood brain barrier (BBB) has been disrupted or if the antibody is introduced intrathecally. Several studies in SLE patients have failed to find an association of aNR2 with CD. None, however, has assessed the integrity of the BBB as a potential pathogenic cofactor. S100B protein is an astrocyte specific protein that has been used as biomarker of BBB disruption in traumatic brain injury and some neurodegenerative disorders. And, antibodies to this protein may indicate previous exposure to this immunologically privileged protein and might be used as an indicator of preceding BBB disruption. We hypothesized that aNR2 antibody is pathogenic in SLE patients only if there evidence of previous or ongoing BBB disruption as indicated by increased levels of S100B or anti-S100B.

Methods: Patients who fulfilled the revised American College of Rheumatology (ACR) criteria for SLE and were stable for at least 4 weeks were recruited from three different settings. Basic demographic, clinical and laboratory data was collected. The Automated Neuropsychological Assessment Metrics (ANAM), a computerized and validated tool, was utilized to measure cognitive function. The Total Throughput Score (TTS = number of correct responses/time) was used as the primary outcome measure. CD was defined as a score of less than 1.5 SD below the age, sex, and race matched RA population mean. Patients also had assessment of fatigue, depression, SLE activity and SLE damage using the FACIT fatigue score, Becks Depression Inventory (BDI), SLEDAI 2K, and SLICC respectively. Serum was analyzed by established ELISA techniques for anti-NR2 antibody, anti-S100B antibody and intact serum S100B protein.

Results: A total of 57 patients were evaluated. Twelve patients had CD. The age, ethnicity, and family income were significantly different between the two groups ($p<0.05$) **[TABLE 1]**. In a multiple regression model adjusting for the above independent variables together with simple reaction time and opioid use, no significant effects of aNR2, S100B, or aS100B on decreasing TTS were found. And, when the effects of aNR2 antibodies were evaluated at high levels of S100B and aS100B, no significant influence on TTS was found.

Conclusion: Serum antibodies to NR2 do not appear to play a role in the pathogenesis of CD in SLE even when analyzed in the context of BBB integrity. This would suggest that, if these antibodies are pathogenic, they are produced within the CNS and peripheral antibody measurements do not adequately reflect their intrathecal levels.

TABLE 1: Patient Demographics and Biomarkers Values: Dichotomized By CD

(* Indicates a significant difference between the CD and no-CD groups (p <0.05))

Variable	All Subjects (n = 57)	CD (n = 12)	No – CD (n = 45)
Age (Years (SD))	**49.9 (11.2)**	**54.9 (8.8)**	**48.5 (11.5)***
Caucasians (%)	**36.8**	**8.3**	**44.4***
Family Income < USD 20k (%)	**45.6**	**75.0**	**37.8***
Females (%)	92.9	83.3	95.6
Education < 12 years (%)	36.8	50.0	33.3
SLE Disease Duration (Years)	13.1 (10.1)	17.5 (13.9)	12.0 (8.6)
SLEDAI (Mean (SD))	3.6 (3.4)	3.2 (4.3)	3.8 (3.3)
SLICC (Mean (SD))	2.75 (2.4)	3.4 (2.1)	2.4 (2.4)
Pain (100 mm VAS - Patient)	40.0 (28.2)	49.6 (29.1)	36.2 (27.7)
Global Assessment (100 mm VAS - Patient)	53.7(22.6)	58.8 (22.6)	52.3 (22.7)
BDI II (Depression) (Mean (SD))	16.0 (12.3)	17.6 (10.2)	14.4 (12.6)
FACIT (Fatigue) (Mean (SD))	24.6 (13.5)	26.1(10.8)	23.3 (14.3)
APL Positive (%)	38.6	25.0	42.2
Current Prednisone Use (%)	53.7	54.5	53.9
Prednisone > 20 mg/d (%)	15.8	25.0	13.3
Immunosuppressant Use (%)	48.2	36.4	51.2
Plaquenil Use (%)	70.0	50.5	74.4
Warfarin (%)	14.8	18.2	14.0
Aspirin (%)	38.9	27.3	41.9
Antidepressants (%)	31.5	36.4	30.2
Opioid (%)	25.9	45.5	20.9
NSAID (%)	22.2	18.2	23.3
Serum anti-NR2 Antibody (SD)	0.41 (0.24)	0.45 (0.19)	0.40 (0.26)
Serum anti-S100B Antibody (SD)	0.57 (0.11)	0.58 (0.09)	0.57 (0.11)
Serum S100B Protein (SD)	0.09 (0.05)	0.09 (0.05)	0.09 (0.05)

Disclosure: G. Gulati, None; **P. Iffland**, None; **D. Janigro**, None; **B. Zhang**, None; **M. Luggen**, None.

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Diagnosis of Primary Neuropsychiatric Systemic Lupus Erythematosus: Attribution Models Versus Physician Judgment

Antonis Fanouriakis[1,2], Cristina Pamfil[3], Simona Rednic[3], Prodromos Sidiropoulos[1], George Bertsias[4,5] and Dimitrios Boumpas[5,6,7], [1]Rheumatology, Clinical Immunology, and Allergy, University of Crete, Medical School, University Hospital, Heraklion, Greece, [2]Foundation of Research and Technology, University of Molecular Biology and Biotechnology, Heraklion, Greece, [3]Rheumatology, University of Medicine and Pharmacy, Cluj-Napoca, Romania, [4]Rheumatology, Clinical Immunology, and Allergy, University of Crete, Heraklion, Greece, [5]Institute of Molecular Biology and Biotechnology, Foundation of Research and Technology-Hellas, Heraklion, Crete, Greece, [6]Biomedical Research Foundation, Academy of Athens, Athens, Greece, [7]Clinical Immunology and Rheumatology, National And Kapodistrian University of Athens, Medical School, Athens, Greece

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Background/Purpose: Attribution of neuropsychiatric manifestations to systemic lupus erythematosus *per se* ("primary NPSLE") is challenging and depends largely on physician judgment based on clinical and neuroimaging results. To facilitate physicians, attribution models have been proposed but their diagnostic performance has not been validated. We compared attribution of neuropsychiatric events as per physician judgment against different attribution models.

Methods: SLE patients with neuropsychiatric involvement were retrospectively identified. All neuropsychiatric manifestations were classified as attributed to SLE, not attributed to SLE, or uncertain, according to physician judgment. **Results** were compared against three published attribution models: the Systemic Lupus International Collaborating Clinics (SLICC) models A (most stringent) and B (less stringent), and a recently proposed algorithm by the Italian study group on NPSLE (total score 0-10). Sensitivity and specificity for each model was calculated against physician judgment. For the Italian algorithm, a receiver operating curve (ROC) analysis was also performed to calculate the area under the curve (AUC) using dichotomous outcome (attributed vs. not attributed/uncertain).

Results: A total of 242 neuropsychiatric manifestations, experienced by 191 patients, were included in the study. According to physician judgment, 136 events were attributed and 96 not attributed to SLE; for 10 events, attribution was considered uncertain. Using the SLICC models, only a small proportion of the events were attributed to SLE [34 events (14.0%) with model A, 67 events (27.7%) with model B]. Consequently, when compared with physician judgment, both models showed high specificity, but poor sensitivity (Table 1). Exclusion of so-called 'minor' neuropsychiatric manifestations (ie. cases of headache, mild depression, mild cognitive dysfunction and polyneuropathy without electrophysiologic confirmation), which are *a priori* not attributed to SLE in the SLICC models, led to moderate increases in sensitivity (27.7% and 42.0% for models A and B, respectively), but specificity was reduced especially in SLICC model B (94.8% and 65.5% for models A and B, respectively).

The AUC of the ROC curve for the Italian study group algorithm was 0.859, indicating good reliability as a diagnostic test for NPSLE attribution. When serial cut-offs of total score were tested, values ≥ 7 showed the best combination of sensitivity and specificity (82.4% and 82.9%, respectively [Table 1]).

Conclusion: Attribution models show varying levels of sensitivity and specificity, related to physician judgment. A recently proposed attribution score performs well and may be suitable for use in real-life clinical settings. SLICC model A shows the highest specificity and can be used for confirmation of doubtful cases.

Table 1. Sensitivity and specificity of different attribution models for neuropsychiatric SLE

Model	Sensitivity	Specificity	Positive predictive value	Negative predictive value
Italian model				
Score ≥ 8	42.6%	93.3%	89.2%	55.7%
Score ≥ 7	82.4%	82.9%	86.1%	78.4%
Score ≥ 6	87.5%	68.6%	78.3%	80.9%
SLICC model A (*stringent*)	22.8%	97.2%	91.2%	49.5%
SLICC model B (*less stringent*)	34.6%	80.6%	79.1%	48.2%

Disclosure: A. Fanouriakis, None; **C. Pamfil**, None; **S. Rednic**, None; **P. Sidiropoulos**, None; **G. Bertsias**, None; **D. Boumpas**, None.

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Abstract Number: 2953

The Emergency Room and SLE: What Characteristics Are Associated with Increased Emergency Room Utilization in Lupus Patients?

Kimberly Trotter[1], Kichul Ko[1], Gabrielle Liu[1] and Tammy Utset[2], [1]Medicine, University of Chicago, Chicago, IL, [2]University of Chicago, Chicago, IL

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Background/Purpose: There is sparse data examining the characteristics of SLE patients who frequent the emergency room (ER). Data suggest that lupus patients with certain sociodemographic risk factors and possibly lack of access to preventive care are more likely to go to the ER. We sought to explore which characteristics were associated with ER utilization in our lupus cohort.

Methods: 125 patients fulfilling the ACR criteria for SLE were recruited during routine ambulatory visits between November 2013 and December 2014. Demographics, disease duration, preventive care, healthcare utilization, reason for ER visit, who referred the patient to the ER, disposition, and prevention of ER visits were elicited via a patient reported questionnaire. Patients also completed the Medication Adherence Self-Report Inventory (MASRI), Visual Analog Scale (VAS) for pain, Short Form 36 Health Survey (SF-36), Beck depression Inventory, and Interpersonal Support Evaluation List (ISEL). We compared patients with no ER visits versus ≥ 1 ER visit in the past year. Categorical variables were evaluated using chi-square while continuous variables were evaluated using two-tailed Student's unpaired *t*-test, Wilcoxon rank-sum test, or logistic regression analysis.

Results: Patients with ≥ 1 ER visit were more likely to be younger, non-Caucasian, single, non-college graduates, and have Medicaid. ER utilizers also had higher pain scores, worse overall mental and physical health, and increased depression. Patients who utilized the ER were also less likely to have ever had a lipid panel (Table 1). There was no difference in frequency of PCP or rheumatology appointments, mammograms, flu shots, pap smears. In a multivariate analysis, only younger age was found to be associated with ≥ 1 ER visit.

In regards to characteristics associated with each ER visit, 57.3% of patients went to the ER due to lupus. 73% of patients self-directed themselves to the ER and felt nothing could have prevented the ER visit. Only 23.4% of these ER visits actually resulted in admission. The majority of ER visits were reportedly due to pain/arthritis (26.5%) and cardiopulmonary complaints (20.5%).

Conclusion: Frequent ER utilization was shown to be associated with certain sociodemographic features and worse self-reported outcomes. Studies from the general population have also found an association with frequent ER use and poor access to medical care. Conversely, our data showed that access to primary care, rheumatology, and preventive services was equivalent between the two groups. This suggests that access to care may not be associated with ER utilization in the SLE population. Lastly, given the majority of patients self-directed themselves to the ER and were not admitted to the hospital, we need to educate them to call their physician first to determine the utility of an ER evaluation.

Table 1

Characteristics of study population by ER Visits

Variables	No ER Visits (n=53)	Any ER Visits (n=56)	*P* Value
Percent of total sample	48.6 %	51.4 %	
Demographics			
Age, mean (standard deviation)(SD)	47.3 (10.3)	40.5 (11.9)	0.002
Race/Ethnicity			0.007
Caucasian, %	43%	20%	
Non- Caucasian, %	57%	80%	
Education, %			0.04
< College degree	39.6%	58.9%	
≥ College degree	60.4%	41.1%	
Employed, %	53%	48%	0.63
Married, %	62%	35%	0.006
Insurance, %			
Private	54.7%	40%	
Medicare	24.5	36.4%	0.01
Medicaid	5.7%	21.8%	
Health Maintenance Organization (HMO)	13.2%	1.8%	
Other (self-pay)	1.9%	0%	
Disease characteristics			
Disease duration, mean years (SD)	14.5 (9.5)	11.7 (10.4)	0.06
MASRI, mean score (SD)	9 (1.4)	8.9 (1.8)	0.55
VAS, pain, mean score (SD)	4 (2.8)	5.7 (2.8)	0.003
SF-36, mental mean score (SD)	47.6 (11)	42 (10.8)	0.01
SF-36, physical mean score (SD)	40.4 (10.4)	34.9 (10.6)	0.007
ISEL, mean score (SD)	93.3 (16.2)	85.4 (21)	0.06
Becks, mean score (SD)	8.6 (7.8)	14.5 (9)	0.0006
Primary Care Physician (PCP), %	87%	91%	0.48
PCP visits, mean (SD)	2.6 (2.6)	3 (2.7)	0.3
Rheumatology visits, mean (SD)	2.9 (1.2)	3.6 (2.1)	0.18
Frequency missed PCP visits, %			0.18
0	50.6%	49.4%	
≥1	33.3%	66.7%	
Missed Rheumatology visits, %			0.6
0	49.3%	50.7%	
≥ 1	43.3%	56.7%	
Preventive Care			
Lipids ever, %	83%	66%	0.04
Lipids last 5 years, %	76%	67%	0.34
Flu shot, %	69%	62%	0.46
Pap smear, (q3/q1 years) %	28/54%	28/59%	0.85
Mammogram (yearly), %	67%	46%	0.19

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Serum and CSF Biomarkers of Neuropsychiatric Involvement in Primary Sjogren Syndrome and Systemic Lupus Erythematosus

Maria Boge Lauvsnes[1], Anne Bolette Tjensvoll[2], Ingeborg Kvivik[3], Roald Omdal[4] and Chaim Putterman[5], [1]Clinical Immunology Unit, Stavanger University Hospital, Stavanger, Norway, [2]Department of Neurology, Stavanger University Hospital, Stavanger,

Norway, [3]Reasearch Department, Stavanger University Hospital, Stavanger, Norway, [4]Clinical Immunology Unit, Department of Internal Medicine, Stavanger University Hospital, Stavanger, Norway, [5]Division of Rheumatology, Albert Einstein College of Medicine, Bronx, NY

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Background/Purpose: Neuropsychiatric manifestations are commonly observed in both SLE and primary Sjšgren's syndrome (pSS). However, making an accurate diagnosis can be challenging. Multiple serum and CSF biomarkers have been studied, but have not yet entered into routine clinical practice. Studies of the pathogenesis of neuropsychiatric involvement in SLE and pSS have suggested new biomarker candidates, including mediators of inflammation (TWEAK), pathogenic antibodies (anti-NMDA receptor subunit 2 (NR2)), and indicators of increased BBB permeability (S100b).

Methods: In a population-based Caucasian cohort of 52 SLE and 54 pSS patients (fulfilling ACR and AECG criteria, respectively), neuropsychiatric manifestations were categorized according to the ACR classification scheme for lupus neuropsychiatric syndromes. TWEAK and anti-NR2 antibodies (ab) were measured in the serum and CSF and S100b was measured in the CSF, using ELISA. IgG index and Q-albumin were calculated by standard methods.

Results: SLE patients were significantly younger than patients with pSS, yet had longer disease duration. There was no difference in serum TWEAK between the SLE and pSS groups. While CSF TWEAK (cTWEAK) and S100b were significantly higher in pSS, patients with SLE displayed significantly higher serum (but not CSF) anti-NR2 antibody titers (Table 1).

The associations between cS100b and anti-NR2 ab and selected laboratory variables in the SLE and pSS patient cohorts were further explored by multivariable regression models (Table 2). The levels of serum and CSF TWEAK were not related to mood disorders, fatigue, psychosis, acute confusional state, headache, seizures, or cerebrovascular disorders. Analysis of possible associations with various cognitive functions is currently underway.

cS100b demonstrated significant correlation with cTWEAK in both SLE and pSS. Furthermore, cS100b was associated with higher BBB permeability in SLE but not in pSS patients. CSF and serum anti-NR2 antibodies correlated in pSS but not in SLE (Table 2).

Conclusion: Although a normal control group was not available for comparison, high cTWEAK in pSS points to a possible role of this cytokine in the pathogenesis of neuropsychiatric manifestations. In pSS, cTWEAK, serum anti-NR2 ab, and IgG index influence anti-NR2 ab in the CSF, suggesting that both leakage through the BBB and as well as intrathecal production contribute to CSF anti-NR2 ab titers. Finally, although this relationship deserves further study, an interesting and significant association was revealed between S100b and TWEAK in the CSF in both SLE and pSS.

Table 1:

Demographic and selected laboratory data in 52 SLE and 54 pSS patients

	SLE	pSS	p-value
Age in years (SD)	43 (13)	57 (12)	<0.001
Female (%)	45 (87)	46 (85)	0.8
Disease duration in years (SD)	12 (9)	6 (5)	<0.001
TWEAK in serum, mean (SD)	862 (787)	947 (211)	0.5
TWEAK in CSF, mean (SD)	1027 (395)	1689 (1106)	<0.001
Anti-NR2 ab in serum, median (range)	0.9 (0.3-3.6)	0.6 (0.3-4.6)	0.05
Anti-NR2 ab in CSF, median (range)	0.4 (0.1-2.2)	0.4 (0.2-3.0)	0.4
Q-albumin, mean (SD)	4.9 (2.4)	4.7 (1.8)	0.8
IgG index, mean (SD)	0.56 (0.15)	0.61 (0.32)	0.3
S100b in CSF, mean (SD)	232 (79)	284 (92)	0.002

TWEAK, pg/mL; S100b, pg/ml; ab, antibodies; anti NR2 ab values given as a ratio against an internal calibrator with defined signal intensity; p-values based on independent samples t-test, or Chi-squared test as indicated.

Table 2:

Multivariable regression model of association between S100b and anti-NR2-antibody level in cerebrospinal fluid and selected laboratory variables in 52 SLE and 54 pSS patients

	Variables	β	*P*-value	
S100b (SLE)	cTWEAK	0.09	<0.001	
	Q-albumin	13.6	0.001	
	IgG index	-172	0.3	
	Adjusted R^2 for the model			0.43
S100b (pSS)	cTWEAK	0.03	0.004	
	Q-albumin	15.8	0.1	
	IgG index	13.8	0.7	
	Adjusted R^2 for the model			0.26
Anti-NR2 ab (pSS)	Anti-NR2 ab in serum	1.2	<0.001	
	Interaction	<0.001	<0.001	
	cTWEAK	<0.001	0.08	
	IgG index	0.8	<0.001	
	Adjusted R^2 for the model			0.6

cTWEAK, TWEAK in CSF in pg/ml; anti NR2 ab values given as a ratio against an internal calibrator with defined signal intensity; interaction, interaction between anti-NR2 ab in serum and TWEAK in CSF

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Cognitive Impairment in Lupus Patients: Identification of the Best Screening Test and Assessment for Associated Factors

Stephanie Nantes[1], Murray Urowitz[2,3], Dafna Gladman[2], Jiandong Su[2], Ashneet Dhaliwal[1] and Zahi Touma[2], [1]University of Toronto, Toronto Western Hospital, Toronto, ON, Canada, [2]Rheumatology, University of Toronto, Toronto Western Hospital, Toronto, ON, Canada, [3]Rheumatology, U of Toronto, Toronto Western Hospital, Toronto, ON, Canada

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Background/Purpose: There is an unmet need for a screening test of cognitive function that can be administered in clinic in patients with SLE. We aimed to determine the: 1) validity of Montreal Cognitive Assessment (MoCA) and Mini-Mental State Examination (MMSE) as screening tests of Cognitive Impairment (CI) in SLE and 2) associated factors with CI.

Methods: Consecutive patients followed at a single centre and seen since Feb 2014 were included. Screening tests were administered by 2 trained assessors: Hopkins Verbal Learning Test-Revised (HVLT-R), Controlled Oral Word Association Test (COWAT) via telephone interview and MoCA and MMSE via face-to-face assessment.

Patients completed Centre of Epidemiologic Studies Depression Scale (CES-D), Beck Anxiety Inventory (BAI), and Reynolds Intellectual Screening Test (RIST), and scores were compared in patients with and without CI.

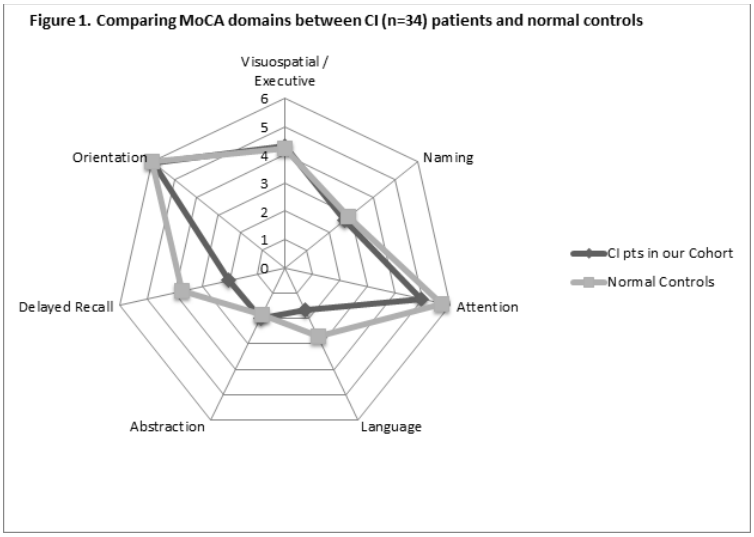
Sensitivity/Specificity, Positive Predictive Value (PPV)/Negative Predictive Value (NPV) and Likelihood Ratio (LR) of MoCA and MMSE in detecting CI (HVLT-R external construct) were determined. Pearson correlation of MoCA and MMSE with HVLT-R were studied. Regression analyses were performed to test for possible associations with CI.

Results: Of 86 patients, 45% had CI using MoCA, 40% using HVLT-R, 16% using COWAT and 14% using MMSE. Sensitivity was higher for MoCA (65%) compared to MMSE (21%), though MMSE was more specific (90%) than MoCA (67%). PPV and LR were similar in MoCA and MMSE (PPV: 56% & 58%; LR: 2.0 & 2.1, respectively), but NPV was higher in MoCA (75%) than MMSE (64%). HVLT-R correlated with MoCA ($r=0.43$, $p<0.0001$). Attention, delayed recall and language domains of MoCA were lower than normal (Figure 1).

Univariate analyses: CI patients had higher CES-D scores (ie. more depressive symptoms) than those without CI (22.1±13.7 vs. 15.9±10.6, $p=0.02$). This did not hold in multivariate analysis. There were no significant differences in BAI scores, diabetes, cardiovascular events, dyslipidemia, hypertension, smoking status or antiphospholipid antibodies in patients with and without CI.

Multivariate analyses: Patients with CI had shorter SLE disease duration than patients without CI (OR=0.94; CI 95% 0.90-0.99; $p=0.01$). Each one year of SLE follow up reduces the probability of CI by 6%. More education years and high RIST score were protective against CI (OR=0.81; CI 95% 0.66-0.98; $p=0.03$ and OR=0.93; CI 95% 0.88-0.98; $p=0.006$, respectively). Each one-year increase in education decreases the chance of developing CI by 19%. Each 1 score increase in RIST decreases the chance of developing CI by 7.5%.

Conclusion: CI among SLE patients was highly prevalent (45%) using MoCA. Considerations of cost/administrative burden and appropriate psychometric properties make MoCA the preferential screening test for CI in SLE. Shorter SLE disease duration increases risk while education and high intelligence scores protect against CI.



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Abstract Number: 2956

Patients' Reported Perceived Deficits Questionnaire – 5-Item Is Not Valid to Screen for Cognitive Impairment in Lupus

Stephanie Nantes[1], Murray Urowitz[2], Dafna Gladman[2], Ashneet Dhaliwal[1] and Zahi Touma[2], [1]University of Toronto, Toronto Western Hospital, Toronto, ON, Canada, [2]Rheumatology, University of Toronto, Toronto Western Hospital, Toronto, ON, Canada
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Background/Purpose: It is unclear whether cognitive complaints in patients with SLE are indicative of true Cognitive Impairment (CI) or underlying depression or anxiety.

To determine: 1) the validity of the patient-reported outcome on CI (Perceived Deficits Questionnaire – 5-item [PDQ-5]) and 2) the association of PDQ-5 with self-reported symptoms of depression and anxiety.

Methods: Consecutive patients followed at a single centre and seen between Feb 2014 and May 2015 that agreed to participate were included in this study. Patients completed PDQ-5, which assessed perceived cognitive deficits from the patient's perspective. PDQ-5 included five questions representing four subscales: Attention/Concentration, Retrospective Memory, Prospective Memory, and Planning/Organization. Total PDQ-5 score consists of the sum of the raw scores on these 5 items and could range from 0-20 with higher scores indicating greater perceived deficit.

Patients underwent two cognitive screening tests by two trained assessors: Hopkins Verbal Learning Test-Revised (HVLT-R) via telephone interview and MoCA via face-to-face assessment. Patients also completed Center of Epidemiologic Studies Depression Scale (CES-D) and Beck Anxiety Inventory (BAI).

Prevalence of self-reported cognitive deficits (PDQ-5), depression and anxiety were determined and scores from these questionnaires were compared in patients with and without CI (based on HVLT-R). Sensitivity (Se)/specificity (Sp) and Positive Predictive Value (PPV)/Negative Predictive Value (NPV) of PDQ-5 in detecting CI (based on HVLT-R and MoCA), depression (CES-D) and anxiety (BAI) were studied.

Results: Of 71 patients, 46% self-reported cognitive difficulties occurring 'often' or 'almost always' in at least one of PDQ-5's four subscales. 45% reported depressive symptoms by CES-D, and 24% reported moderate-severe anxiety by BAI.

CES-D showed higher scores in CI patients compared to those without CI (22.1±13.7 vs. 15.9±10.6, p=0.02) [higher scores = more depressive symptoms]. There were no significant differences in BAI or PDQ-5 scores between patients with and without CI.

Se, Sp, PPV and NPV were high in both CES-D (Se 69%, Sp 75%, PPV 63%, NPV 79%) and BAI (Se 94%, Sp 69%, PPV 48%, NPV 97%) signifying that PDQ-5 is detecting anxiety and depression.

PDQ-5 was less predictive of objective CI (MoCA: Se 58%, Sp 60%, PPV 53%, NPV 65%; HVLT-R: Se 48%, Sp 52%, PPV 41%, NPV 59%) (Table 1)

TABLE 1. Sensitivity, specificity, PPV and NNP of PDQ-5 in detecting CI (HVLT-R and MoCA), depression (CES-D) and anxiety (BAI)

	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
MoCA	58	60	53	65
HVLT-R	48	52	41	59
BAI	94	69	48	97
CES-D	69	75	63	79

Conclusion: The PDQ-5 self-report questionnaire is not a valid test to screen for CI in SLE. Depression and anxiety among SLE patients was highly prevalent using CES-D (46%) and BAI (24%) and depression was associated with CI. Patients' cognitive complaints reported in PDQ-5 scores were not reliably associated with performance on MoCA or HVLT-R, but rather were influenced by the presence of depression and anxiety.

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Abstract Number: 2957

25-Hydroxyvitamin D3 Deficiency Independently Predicts Cognitive Impairment in Patients with Systemic Lupus Erythematosus: Results from a Controlled Study

Sen Hee Tay[1,2] and Anselm Mak[2,3], [1]National University of Singapore, Singapore, Singapore, [2]National University Health System, Singapore, Singapore, [3]Medicine, National University of Singapore, Singapore, Singapore

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Background/Purpose:

Cognitive dysfunction has been reported in 20-80% of systemic lupus erythematosus (SLE) patients. Converging evidence has indicated the importance of vitamin D as a neuro-immuno-modulator for normal cognitive function. In this study, we evaluated the relationship between vitamin D, traditional neuropsychological and SLE-specific risk factors as predictors for cognitive dysfunction.

Methods:

Consecutive SLE patients who fulfilled ≥ 4 American College of Rheumatology 1997 revised classification criteria and healthy controls (HC) matched for age and gender were administered the Automated Neuropsychological Assessment Metrics (ANAM) to assess cognitive function in this cross-sectional study. The primary outcome was the mean total throughput score (TTS), defined as the total of the throughput scores for 8 ANAM subtests. Cognitive dysfunction was defined as a TTS < -1.5 SD of the HC mean. Anxiety and depression were measured using the Hospital Anxiety and Depression Scale (HADS). Levels of 25-hydroxyvitamin D [$25(OH)D_3$ and total 25(OH)D] were measured using Liquid Chromatography-Tandem Mass Spectrometry. Vitamin D status was defined as deficiency < 10 ng/mL, insufficient 10 – 29 ng/mL and sufficient ≥ 30 ng/mL. Association between cognitive function and vitamin D levels or

status was explored using linear regression models.

Results:

In total, 61 SLE patients and 61 HC were studied. SLE patients had the following characteristics: 83.6% female; median age 36.0 (Q1; Q3 26.0; 48.5); SLE duration 6.0 years (Q1; Q3 0.0; 12.0); SELENA-SLEDAI 4.0 (Q1; Q3 2.0; 5.0)]. HADS-Anxiety, -Depression and -Total scores were significantly higher in SLE patients compared to HC [HADS-Anxiety: 8.0 (Q1; Q3 4.5; 9.0) versus 5.0 (Q1; Q3 2.5; 8.0), $p = 0.001$; HADS-Depression: 3.0 (Q1; Q3 2.0; 6.0) versus 2.0 (Q1; Q3 1.0; 3.0), $p < 0.001$; HADS-Total: 11.0 (Q1; Q3 7.5; 15.0) versus 7.0 (Q1; Q3 3.0; 10.5), $p < 0.001$]. After adjusting for age, education, gender, ethnicity and HADS-Total, SLE patients scored significantly lower than HC in 4 ANAM subtests [code substitution (learning) ($p = 0.013$), code substitution (immediate memory) ($p = 0.012$), code substitution (delayed memory) ($p = 0.025$), matching to sample ($p = 0.026$)] and in the TTS ($p = 0.004$). Cognitive dysfunction was identified in 21 (34.4%) SLE patients and 1 (1.6%) HC ($p < 0.001$). There were no statistically significant differences in $25(OH)D_3$ levels, total 25(OH)D levels and total 25(OH)D deficiency between SLE patients and HC. However, more SLE patients had $25(OH)D_3$ deficiency compared to HC [12 (19.7%) versus 2 (3.3%), $p = 0.003$] contributed by vitamin D_2 supplementation [8 (13.1%) versus 0 (0.0%), $p < 0.001$]. Deficiency of $25(OH)D_3$ ($\beta = -63.667$, SE = 27.456, $p = 0.025$), but not the other vitamin D variables, independently predicted worse TTS after adjusting for age, education, gender, ethnicity, HADS-Total, duration of SLE, SELENA-SLEDAI and cumulative steroid dose in SLE patients. Age ($\beta = -4.261$, SE = 0.866, $p < 0.001$) was the only predictor of TTS after adjusting for education, gender, ethnicity, HADS-Total, vitamin D levels or status in HC.

Conclusion:

Deficiency of $25(OH)D_3$, a potentially modifiable risk factor, independently predicts cognitive impairment in SLE patients.

Disclosure: S. H. Tay, None; **A. Mak**, None.

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Abstract Number: 2958

Vitamin D, Cognition and Cerebral Structural Abnormalities in Childhood- Onset Systemic Lupus Erythematosus

Nailu A. Sinicato[1], Mariana Postal[2], Aline Tamires Lapa[2], Bruna B Siqueira[3], Karina Pelicari[2], Paula T Fernades[3], Roberto Marini Sr.[4] and **Simone Appenzeller**[5], [1]Pediatrics, State University of Campinas, Campinas, Brazil, [2]Medicine, State University of Campinas, Campinas, Brazil, [3]State University of Campinas, Campinas, Brazil, [4]Pediatric Rheumatology Unit, State University of Campinas, São Paulo, Brazil, [5]Division of Rheumatology, Faculty of Medical Science, State University of Campinas, São Paulo, Brazil
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Background/Purpose: About 16-95% of SLE patients have vitamin D insufficiency. Vitamin D levels, especially vitamin D deficiency, are associated with cognitive performance in adults. We aimed to analyze the association of vitamin D levels, cognitive impairment and cerebral structures in childhood-onset Systemic Lupus Erythematosus (cSLE).

Methods: We screened consecutive cSLE patients, disease-onset before the age of 18 years followed in the pediatric rheumatology unit at the State University of Campinas. Controls were matched for age, sex and demographic background. Levels of 25-hydroxyvitamin D3 were measured in serum samples, using a commercial enzyme-linked immunosorbent assay; vitamin D levels were considered deficient (<10pg/mL), insufficient (10-29pg/mL), sufficient (30-100pg/mL) and toxic (>100pg/mL). cSLE patients were assessed for disease activity by Systemic Lupus Erythematosus disease activity index (SLEDAI) and damage [Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index (SDI)]. Cognitive evaluation was performed in all participants using Wechsler Intelligence Scale, according to age and validated in Portuguese. Cognitive dysfunction was defined when scores were ≤-2 standard deviations (SD) from controls in 1 or more subtests. Magnetic resonance imaging scans were performed using a standardized protocol and volumetric 1mm T1 weighted images were used for analysis. Volumes ≤ 2 SD from the means of controls were considered abnormal. White matter (WM) lesions were analyzed in T2-weighted images using a semiautomatic computer program (Neuroline®). Non-parametric tests were used for statistical analysis.

Results:

We included 100 cSLE patients (mean age 16.8 years (SD±4.4) and 37 controls (mean age 18.7 years (SD±4.8). The mean vitamin D level was 32.4±18.7pg/ml in cSLE and 36.5±19.8pg/ml in controls (p=0.22). Cognitive impairment was observed in 27 (47%) cSLE patients and 6 (25%) controls (p=0.001). No association between vitamin D levels and cognitive impairment (p=0.219), SLEDAI (p=0.469), SDI (p=0.915) and corticosteroid use (p=0.486) was observed.

Forty-seven (47%) cSLE patients and 13 (35%) controls had vitamin D insufficiency (p=0.08). Vitamin D insufficiency was not associated with cognitive impairment (p=0.24). When analyzing individual cognitive tests, we observed that vitamin D levels were associated with forward digits span (p=0.04) and correlated indirectly with cubes (r=-0.265;p=0.05) in cSLE patients. No association with structural abnormalities [hippocampal (p=0.466), cerebral (p=0.610) and cerebellum (p=0.475) atrophy] and WM lesion (p=0.601) was observed.

Conclusion: Vitamin D insufficiency was frequent in both cSLE and controls. Although vitamin D levels were not associated with cognitive impairment and cerebral structural abnormalities, we observed an association of vitamin D insufficiency and cognitive subtests associated with retention of immediate memory, analytical skills, visual-motor-spatial coordination, perceptual speed and organization in cSLE patients. Therefore vitamin D levels may contribute to cognitive dysfunction in cSLE and should be followed closely and corrected when indicated.

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Abstract Number: 2959

Patterns of Vascular Brain Injury in Systemic Lupus Erythematosus Patients with Ischemic Stroke: Impact on Neuropsychological, Neurobehavioral and Physical Function Outcome

Jamal A. Mikdashi[1], Marcia Wozniak[2], Umran Ashraf[3] and William Regenold[4], [1]Div of Rheumatology, Univ of Maryland Schl of Med, Baltimore, MD, [2]Neurology, University of Maryland School of Medicine, Baltimore, MD, [3]Radiology, University fo Maryland, Baltimore, MD, [4]Psychiatry, Univeristy of Maryland School of Medicine, Baltimore, MD

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Background/Purpose: Ischemic strokes in Systemic lupus erythematosus (SLE) patients contribute to increased morbidity and mortality. Little is known however, about the patterns of ischemic brain injury in SLE and how this issue impacts the clinical outcome. Our objective is to investigate the neuropsychological, neurobehavioral and physical function in SLE patients with ischemic stroke, and correlate findings with the type of arterial ischemic injury.

Methods: Consecutive SLE patients presented with first-ever ischemic stroke drawn from the Maryland Lupus Cohort from 2000 to 2014 were observed. Ischemic brain injury was categorized based on brain magnetic resonance imaging (MRI/ MRA) into infarctions of large territorial, lacuanar, localized cortical and borderzone. Angiographic findings were staged to assess severity of arterial stenotic lesion. Comparison was made to age- and gender -matched SLE patients with no stroke, and non SLE ischemic stroke subjects. Primary outcomes determined at 6 months post stroke included, cognitive dysfunction, mood disorders, emotion/ affective disorders and physical function.

Results: 56 SLE patients with stroke (mean age 35.7 years, 82 % women, 84 % African American, mean duration of SLE 5.5 years), 44 SLE patients with no stroke (mean age 32.9 years, 93 % women, 77 % African American, mean duration of SLE 6.5 years) and 20 Non SLE stroke subjects (mean age 37.5 years, 80 % women, 90 % African American) were included. There was no significant statistical difference among the three groups regarding demographic and clinical features, phospholipid syndrome, disease activity, co-morbid conditions, treatment or stroke rehabilitation care.

Poor cognitive performance in SLE patients with stroke was frequently associated with subcortical damage with and without white matter intensity (p value < 0.003), as compared to major cortical syndrome in non SLE stroke subjects (P value < 0.010), after adjusting for vascular risk factors. Cognitive domains of memory, orientation, language, and attention were more defective in SLE

patients with stroke when compared with SLE patients with no stroke or non SLE stroke subjects.

Post stroke depression and emotional incontinence were associated with cognitive impairment among SLE patients with stroke and non SLE stroke subjects, regardless of coping style, anti-depressant intake, severity of steno-occlusive disease, or phospholipid syndrome. Post stroke depression was associated with cortical (OR: 1.5, 95 % CI: 1.0- 2.7), and subcortical lesions (OR: 12.0, 95 % CI: 1.8-78.2) among SLE patients, compared to right hemispheric lesion (OR: 1.2, 95 % CI: 1.0- 2.6) in non SLE stroke subjects.

Functional impairment was greater among SLE patients with focal brain injury (OR: 2.2, 95% CI: 1.1-25.6), and those with cognitive impairment (OR: 3.0, 95% CI: 1.7- 14.8), after adjusting for co-morbid condition and severity of stroke.

Conclusion: Ischemic brain injury in SLE is associated with cognitive impairment, depression, emotional incontinence and physical disability. Better understanding of the mechanism of vascular brain injury in SLE will improve patient care and facilitate the development of therapeutic options and effective rehabilitative measures.

Disclosure: J. A. Mikdashi, None; **M. Wozniak**, None; **U. Ashraf**, None; **W. Regenold**, None.

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Abstract Number: 2960

Sodium Thiosulfate in Calcinosis

Eliza Pelrine[1], Jessica K. Gordon[2], Murray Baron[3] and Robert F. Spiera[2], [1]Hospital for Special Surgery, New York, NY, [2]Rheumatology, Hospital for Special Surgery, New York, NY, [3]Rheumatology, McGill University, Jewish General Hospital, Montreal, QC, Canada

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Background/Purpose:

Calcinosis occurs in ~25% of patients with Systemic Sclerosis (SSc) and causes pain, morbidity, and decreased quality of life. The treatment of calcinosis is a major challenge in the treatment of patients with SSc. The pathogenesis of calcinosis is not fully understood but shares similarities to calciphylaxis, an ischemic vasculopathy with arteriolar calcification seen in end-stage renal disease, which has been successfully treated with intravenous sodium thiosulfate (STS). Suggested mechanisms of action of STS include calcium chelation, reduction of pro-inflammatory cytokines through anti-oxidant properties, and vasodilation. Previous case studies have reported positive outcomes for calcinosis patients treated with intravenous (IV) or intralesional STS. We report here a retrospective chart review of calcinosis patients in our practice treated with STS.

Methods:

We included all patients at our site that had been treated with STS (topical and IV) and had follow-up data available. Patient charts were reviewed for clinical and demographic data. X-rays were retrospectively assessed by a physician blinded to pre or post treatment status using the SCTC Calcinosis Working Group's scoring system accounting for density of calcinosis and relative area involved. A paired t-test was used to assess significance.

Results:

A total of 5 patients were identified, 4 of whom met 2013 ACR/EULAR criteria for SSc and 1 met criteria for juvenile dermatomyositis. All SSc patients were treated with topical STS while the dermatomyositis patient was treated with IV STS. Table 1 summarizes clinical and demographic characteristics of patients. Treatment time ranged from 3-7 months. 1 patient (STS 4) discontinued use after 2 days due to erythema and inflammation of ulcerating calcinosis. No significant change in calcinosis scores was seen between baseline and follow-up x-rays (Table 2, p=0.24).

Conclusion:

In this small retrospective study no significant changes in radiographic calcinosis score were observed, but the duration of treatment was relatively short and STS was generally well tolerated. Further evaluation of STS in calcinosis may be considered recognizing the limitations of this study, in particular the relatively short treatment period.

Table 1-Clinical and Demographic Data

Study ID	Age	Sex	Race	Disease Duration (Years)	Disease Type	SSc Antibodies	Location of Calcinosis	Concomitant Medications
STS 1	65	F	White	13	Limited SSc	RF	L & R wrists	omeprazole, minocycline, atorvastatin, diltiazem, escitalopram,
STS 2	67	F	White	14	Diffuse SSc	Pol3	R wrist	omeprazole
STS 3	52	F	White	5	Limited SSc	centromere	R Thumb and 5th digit, L wrist	esomeprazole (40mg QD), famotidine (40mg QD), colchicine (0.6 QD), eletriptan (prn)
STS 4	61	F	White	8	Limited SSc	centromere	L & R Hips	amlodipine (2.5mg QD), omeprazole (20mg BID)
STS IV	25	F	Asian	5	Juvenile Dermatomyositis	N/A	Diffuse (thighs, hips, arms)	methotrexate (5mg SQ weekly), alendronate

Table 2-Radiographic Scores*

Study ID	Baseline	3-months	6-months
SSc Patients			
STS 1	177.375	250.25	246
STS 2	42.75	51.25	N/A
STS 3	53.25	N/A	65.75
Juvenile Dermatomyositis Patient			
STS IV-Hands	3.5	5.75	N/A
STS IV-Right Thigh	20%†	20%†	N/A
STS IV-Left Thigh	5%†	5%†	N/A
STS IV-Feet	1-2%†	1-2%†	N/A

*reported as composite scores for both right and left hands according to the SCTC Calcinosis Working Group scoring system. A t-test was performed on the mean change in score giving p=0.24, NS.
†SCTC scoring system is only applicable to hand radiographs. Thus, the blinded assessor scored these images on percent involvement.
N/A = Not Available

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Reliability and Validity of the Total Joint Count and Swollen Joint Count in Early Diffuse Systemic Sclerosis

Jessica K. Gordon[1], Veronica J. Berrocal[2], Gandikota Girish[3], Meng Zhang[4], Chris Hatzis[1], Shervin Assassi[5], Elana J. Bernstein[6], Robyn T. Domsic[7], Faye N. Hant[8], Monique E. Hinchcliff[9], Elena Schiopu[10], Virginia D. Steen[11], Tracy M. Frech[12] and Dinesh Khanna[13], [1]Rheumatology, Hospital for Special Surgery, New York, NY, [2]Div of Rheumatology, University of Michigan, Ann Arbor, MI, [3]Radiology, University of Michigan, Ann Arbor, MI, [4]Epidemiology and Biostatistics, Hospital for Special Surgery, New York, NY, [5]Rheumatology, University of Texas Medical School at Houston, Houston, TX, [6]Rheumatology, Columbia University College of Physicians & Surgeons, New York, NY, [7]Medicine - Rheumatology, University of Pittsburgh, Pittsburgh, PA, [8]Dept of Medicine, Medical University of South Carolina, Charleston, SC, [9]Division of Rheumatology, Division of Rheumatology, Northwestern University, Feinberg School of Medicine, Chicago, IL, [10]University of Michigan, Ann Arbor, MI, [11]Rheumatology, Georgetown University Medical Center, Washington, DC, [12]Div of Rheumatology, University of Utah, Salt Lake City, UT, [13]Division of Rheumatology, University of Michigan, Ann Arbor, MI

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Background/Purpose: Arthropathy and tendinopathy in Systemic Sclerosis (SSc) contribute to disability and are associated with disease progression. Clinical trials in SSc sometimes include the tender joint count (TJC) and swollen joint count (SJC) as outcome measures; however, these outcomes have not yet been validated in SSc. We assessed inter and intrarater reliability of TJC and SJC and compared joint examinations with musculoskeletal ultrasound (MSK US) to determine criterion validity.

Methods: Seven patients enrolled in the Prospective Registry of Early Systemic Sclerosis (PRESS) cohort participated. Two separate 28 joint count TJC and SJC were performed on a single day by 10 rheumatologists. On the same day patients had MSK US of the bilateral hands and wrists (22 joints) which were read by a MSK radiologist for synovitis, synovial thickening, and erosions. For TJC and SJC, we computed inter and intra-rater reliability. The following values represent the following degrees of agreement: <0 – poor; 0-0.2 – slight; 0.21- 0.4 – fair; 0.41- 0.6 – moderate; 0.61-0.8 – substantial; and 0.81-1.0 – almost perfect agreement. For the validation exercise we compared the initial physician assessment of swelling or tenderness of the individual 22 joints to the MSK US. We calculated the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) for each physician compared to MSK US as a gold standard and present the mean (SD).

Results: The mean age of the patients was 41.6 ± 19.8 years and the mean disease duration from the first non-Raynaud's symptom was 2.7 ± 0.8 years. All had diffuse cutaneous (dc)SSc; 3 were female and 4 male. The mean modified Rodnan Skin Score was 14.67 ± 4.04.

The mean TJC was 4.2 ± 2.0 (0-28 count). The interobserver reliability for the TJC was 0.97, and the intraobserver reliability for the TJC was 0.99, showing almost perfect agreement. The mean SJC was 1.3 ± 0.8 (0-28 count). The interobserver reliability for the SJC was 0.24, showing fair agreement, and the intraobserver reliability for the SJC was 0.71 denoting substantial agreement.

9.7% (15/154) of joints showed synovitis or synovial thickening on MSK US. 2% (3/150) of physician examinations of joints noted to abnormal on MSK US noted swelling, and 9.3% (14/150) noted tenderness. Additionally, in the joints that were normal on MSK-US, 4.4% (57/1302) of examinations noted swelling and 21.7% (282/1302) noted tenderness.

	Sensitivity – mean (SD)	Specificity – mean (SD)	PPV – mean (SD)	NPV – mean (SD)
Swelling of joint	0.020 (0.045)	0.956 (0.028)	0.039 (0.076)	0.894 (0.009)
Tenderness of joint	0.093 (0.034)	0.778 (0.033)	0.046 (0.014)	0.881 (0.013)

Table 1. Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) for the initial physician assessment of swelling and tenderness for each physician compared to the MSK US as the reference standard. These were calculated for 10 physicians and are presented as mean (SD) for the group of physicians.

Conclusion: We noted excellent inter and intrarater reliability for the TJC, substantial intrarater reliability for SJC, and fair interrater reliability for SJC in patients with early dcSSc. Examination of the joint for swelling or tenderness showed low sensitivity, but high specificity when compared with MSK US. This cohort had low prevalence of MSK US abnormalities, and this may account for the low PPV observed. Further study should assess the factors associated with SJC and TJC in early dcSSc.

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Abstract Number: 2962

Efficacy of Mycophenolate As a Maintenance Therapy Following the Administration of Cyclophosphamide in the Treatment of Interstitial Lung Disease Associated with Systemic Sclerosis

Javier Narváez[1], Helena Borrell Paños[2], Ivan Castellvi[3], Sergi Heredia[2], Milena Millan[3], Susana Herrera[4], Eulalia Armengol[2], Josep María LLobet[3], Joan Miquel Nolla[2], María Molina[5] and Juan José Alegre[6], [1]Rheumatology, Hospital Universitario de Bellvitge,

Barcelona, Spain, [2]Department of Rheumatology, Hospital Universitario de Bellvitge, Barcelona, Spain, [3]Rheumatology Unit. Hospital de la Santa Creu i Sant Pau, Barcelona, Spain, [4]Deparment of Pneumology, Hospital Universitario Dr Peset, Valencia, Spain, [5]Department of Pneumology, Hospital Universitario de Bellvitge, Barcelona, Spain, [6]Rheumatology Department, Hospital Universitario Doctor Peset, Valencia, Spain

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Background/Purpose: Treatment with cyclophosphamide (CYC) for 12 months stabilizes lung function parameters and improves respiratory symptoms of patients with systemic sclerosis and diffuse interstitial lung disease (ILD-SSc). After stopping treatment, this beneficial effect on lung function disappears at 24 months, hence the need to establish maintenance therapy after CYC. Our objective was to investigate the efficacy of mycophenolate mofetil (MMF) as a maintenance therapy following the administration of CYC in the management of ILD-SSc

Methods: An ambispective observational study was performed in 14 patients with SS (ACR/EULAR 2013 criteria) and secondary ILD confirmed by high-resolution thoracic CT (HRCT), who were treated with CYC due to severity criteria. The primary efficacy outcome was the change in pulmonary function tests (PFT) at the end of follow-up according to the following definitions from the American Thoracic Society: *a) improvement:* if an increase in FVC ≥ 10% or DLCO ≥ 15% is observed; *b) stabilization:* if changes in FVC are less than 10% or 15% in DLCO; and *c) worsening:*if FVC decreases ≥ 10% or DLCO ≥ 15%.

Results: Of the 14 included patients (12 women, mean age 58 ± 10 years), 11 had diffuse SS, one had limited SS, and two had systemic sclerosis sine scleroderma.

Regarding ILD subtypes, 13 cases corresponded to NSIP (nonspecific interstitial pneumonitis; two of them fibrosing) and one to UIP (usual interstitial pneumonitis). All had been treated with intravenous CYC having achieved, at minimum, stabilized lung function parameters: 10 patients had been administered CFM for a minimum of 12 months (six monthly boluses, followed by two to four quarterly boluses) and four patients for six months (six monthly boluses). The dose administered in the bolus was 750 mg/m^2 or 500 mg/m^{2}body surface as tolerated. MMF doses ranged from 1.5 to 2 g per day.

During follow-up, nine (64%) patients showed ILD-SSc progression with clinical and functional decline, ultimately requiring rescue treatment with rituximab (RTX). The elapsed time from the start of MMF to treatment with RTX (mean ± SD) was 21 ± 8 months (range, 8-28). The evolution of PFT values in this subgroup of patients is shown in the following table:

	Baseline (onset of MMF treatment	**End of MMF treatment**	**% of change from baseline**
FVC %	65.7 ± 20.5	51.2 ± 18.4	-22.07%
TLC %	69.2 ± 10.9	61.6 ± 9.2	-10.98%
DLCO%	51.8 ± 15.5	40.2 ± 13.6	-22.39%

In the four (36%) remaining patients, MMF stabilized PFT. The mean follow-up time in this subgroup was 18 ± 8 months (range, 8-28).

Conclusion: Maintenance therapy with MMF only manages to preserve the beneficial effect achieved with CYC in approximately one-third of cases. Despite advances in the early diagnosis of ILD-SSc, the results obtained with available treatments remain disappointing.

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Abstract Number: 2963

Correlations Between Microvasculature Changes and Angiogenic Factors in Systemic Sclerosis – Data from a Single Center Registry

Radim Becvar[1], Simona Skacelova[2], Jiri Stork[3], Hana Hulejová[4], Ivana Putova[5], Michal Tomcik[6] and Marie Jachymova[7], [1]Institute of Rheumatology, Department of Rheumatology, 1st Faculty of Medicine, Charles University, Prague, Czech Republic, [2]Institute of Rheumatology, Department of Rheumatology, 1st Faculty of Medicine, Charles University, Prague, Prague, Czech Republic, [3]Clinic of

Dermatology and Venerology, Prague, Czech Republic, [4]Institute of Rheumatology, Department of Rheumatology of the First Faculty of Medicine, Charles University in Prague, Prague, Czech Republic, [5]Institute of Rheumatology and Department of Rheumatology of the 1st Faculty of Medicine, Charles University, Prague 2, Czech Republic, [6]Institute of Rheumatology and Department of Rheumatology, First Faculty of Medicine, Prague, Czech Republic, [7]Second Internal Clinic – Clinic of Cardiology and Angiology, General University Hospital,, Prague, Czech Republic
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Background/Purpose: Histopathological hallmarks of systemic sclerosis (SSc) are perivascular infiltrates and a reduced capillary density, which precede the excessive accumulation of extracellular matrix components in the later stages of the disease. The reduced capillary density leads to a slower blood flow, to tissue ischemia. Tissue hypoxia usually initiates the formation of new blood vessels from the pre-existing microvasculature. Despite the reduced blood flow and lower oxygen pressure levels, there is no evidence for a sufficient angiogenesis in the skin of patients with SSc. Nailfold capillaroscopy (NVC) is a safe, noninvasive method for the microvascular investigation. It allows us to distinguish between primary and secondary Raynaud's phenomenon.The aim was to assess whether blood levels of angiogenic biomarkers are associated with microvasculature changes in SSc patients.

Methods: Microvasculature changes were assessed using NVC which was performed by two independent examiners. The obtained images were analysed anonymously by two investigators blinded for the clinical and serum status of SSc patients and classified as early, active and late pattern (1). Serum or plasma levels of soluble vascular adhesion molecule-1 (sVCAM-1) and soluble intercellular adhesion molecule-1 (sICAM-1) were measured by ELISA, big endothelin-1 (BET-1) concentrations using competitive enzyme-immunoassay and von Willebrand factor antigen (vWFAg) concentrations using ELISA kit were measured. As potential disease activity markers soluble receptor of interleukin-2 (sIL-2r) and interleukin-6 (IL-6) serum levels using commercial kits were assayed. For statistical evaluation Pearson's correlation coefficient and univariate analysis were used.

Results:

Total 40 patients (38 females) were investigated: 30 individuals with limited form, 5 with diffuse, 3 patients with sclerosis sine scleroderma, 1 with overlap syndrome and 1 with undifferentiated connective tissue disease. The mean age ± standard deviation (SD) of the whole cohort was 51±22 years and the mean disease duration ± SD was 10±7 years. 3 patients (7.5%) had early NVC pattern, 12 patients (30%) had active, 10 (58%) late pattern, and 15 (37.5%) had nonspecific changes or normal picture. The patients with late NVC pattern exhibited higher vWFAg levels than patients with active pattern ($p<0.01$). BET-1 and sICAM-1 serum levels were higher in the active pattern compared with late pattern ($p<0.01$ and $p<0.05$, respectively). When correlating these potential biomarkers with SSc-related clinical characteristics we found only these associations: vWFAg levels with heart arrhythmias and modified Rodnan skin score ($p<0.01$, $p<0.05$, respectively).

Conclusion: VWFAg and ET-1 increase in the late NVC pattern can be considered as an attempt to support deficient vasculogenesis. Further studies are needed to determine the role of other potential biomarkers of endothelial injury and repair in SSc.

Disclosure: R. Becvar, Actelion Pharmaceuticals US, 5; **S. Skacelova**, None; **J. Stork**, None; **H. Hulejová**, None; **I. Putova**, None; **M. Tomcik**, None; **M. Jachymova**, None.

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Abstract Number: 2964

Influences of Various Factors on Survival of Patients Treated with Pulmonary Arterial Hypertension-Specific Drugs Combination Therapy in Patients with Connective Tissue Diseases

Sumiaki Tanaka[1], Yu Matsueda[2], Eisuke Ogawa[1], Jun Okada[3] and Shunsei Hirohata[1], [1]Rheumatology and Infectious Diseases, Kitasato University School of Medicine, Kanagawa, Japan, [2]Rheumatology and Infectious diseases, Kitasato University School of Medicine, Kanagawa, Japan, [3]Rheumatology, Kitasato University Hospital, Sagamihara, Japan
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Background/Purpose: In patients with connective tissue disease (CTD), especially systemic sclerosis (SSc), several mechanisms have been implicated for the development of pulmonary hypertension (PH), including pulmonary arterial hypertension (PAH), PH with interstitial lung disease (PH-ILD) and PH with left heart disease (PH-LHD). The combination of such different mechanisms lead to the complexity of pathogenesis that might possibly result in less efficacy of combination therapy using PAH-specific drugs (CoTpy) for survival in PH-CTD than in idiopathic PAH. The present study therefore aimed to analyze the factors that influence the effect of CoTpy on survival of PH-CTD.

Methods: We performed a retrospective-cohort study of 118 patients with PH-CTD, including 56 SSc, 29 MCTD or 24 SLE patients, who were followed up between January 1980 and March 2015 in our hospital. PH was diagnosed based on heart catheterization (HC). Patients with PH-ILD had been confirmed to have ILD on chest CT scan. Patients with PH-LHD had been confirmed to have LHD by HC or biopsy. There were 97 PAH, 47 PH-ILD and 9 PH-LHD patients. Our CoTpy strategy for PH intended to achieve the following goals: 1) improvement in WHO-functional class and 2) reduction of serum BNP level of less than 100 pg/ml, based on our previous study as well as on the results demonstrated by Hoeper et. al, (Eur Respir J 2005; 26: 858–863). The PAH-specific drugs, including bosentan, ambrisentan, sildenafil, tadalafil, epoprostenol, and beraprost (an oral prostacyclin analog that is only available in Japan), were switched from drug to drug or adopted in combination so as to achieve these predetermined therapeutic goals once a month. We performed Cox's proportional hazard analysis for survival measured from the date of the diagnosis of PH using propensity score (PS) methods. PS for CoTpy was estimated from a variety of factors, including sex, age at diagnosis of PH and CTD, causes for PH, and complicated CTD, using logistic regression.

Results: Fifty-nine patients were treated under our CoTpy strategy. The PAH-specific medications in this group at the last observation are shown in table 1. Multivariative study demonstrated that CoTpy significantly reduced the risk for death (HR 0.324, 95%CI: 0.163-0.610) in PH-CTD. Estimated survival curves of patients with PH-CTD under CoTpy are shown in Figure 1. Thus, coexistence of PH-ILD and PAH significantly increased the risk for death (HR 1.88, 95%CI: 1.08-3.26) compared with PAH alone. Moreover, coexistence of PH-ILD and PH-LHD in addition to PAH increased the risk for death (HR 5.11, 95%CI: 0.822-24.62) compared with PAH alone.

Conclusion: The results demonstrate that combination therapeutic strategy using PAH-specific drugs markedly improved survival of patients with PH-CTD. Moreover, the data indicate that appropriate management of PH-ILD and/or PH-LHD is important for improving survival of PH-CTD patients treated with PAH-specific drugs combination therapy.

Table. Use of PAH-specific drugs in combination therapy (Cotpy)

Combination	Number(%)	
• *Mono*		*18(30.5)*
- BPS	16 (27.2)	
- BOS	0 (0.0)	
- SIL	0 (0.0)	
- TAD	1 (1.4)	
- EPO	1 (1.4)	
• *Comb(2)*		*26(44.1)*
- BPS + BOS	6 (10.2)	
- BPS + AMB	1 (1.4)	
- BPS + SIL	7 (11.9)	
- BPS + TAD	2 (3.4)	
- BOS + TAD	3 (5.1)	
- BOS + SIL	1 (1.4)	
- AMB + TAD	1 (1.4)	
- EPO + AMB	2 (3.4)	
- EPO + SIL	3 (5.1)	
- EPO + TAD	2 (3.4)	
• *Comb(3)*		*12(20.3)*
- BPS + BOS + SIL	4 (6.8)	
- BPS + BOS + TAD	3 (5.1)	
- BPS + AMB + SIL	1 (1.4)	
- BPS + AMB + TAD	4 (6.8)	
• *Non*	*3 (5.1)*	
Total	59 (100)	*59 (100)*

BPS: beraprost, BOS: bosentan, SIL: sildenafil, TAD: tadalafil, EPO: epoprostenol, AMB: ambrisentan

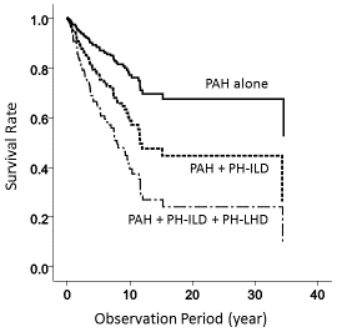

Figure. Estimated survival rate of PH-CTD patients treated with PAH-specific drugs combination therapy

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Abstract Number: 2965

Might Troponin be a Marker for Subclinical Scleroderma Heart Involvement (SHI)?

Chiara Stagnaro[1], Anna d'Ascanio[1], Alice Parma[2], Umberto Conti[3], Michele Emdin[4], Alessandra Della Rossa[1] and Marta Mosca[1], [1]Internal Medicine, University of Pisa, Pisa, Italy, [2]University of Pisa, Pisa, Italy, [3]Cardiotoracico, Cardiologia 2, Pisa, Italy, [4]Fondazione Toscana Gabriele Monasterio, UOC Cardiologia e Medicina Cardiovascolare, Pisa, Italy
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Background/Purpose: Systemic sclerosis (SSc) is a rare connective tissue disease with pronounced alterations of the microvascular system, frequent cellular and humoral immunity abnormalities and fibroblast dysfunction. All these events result in an overproduction of collagen with possible involvement of skin and internal organs. Cardiac involvement is common in SSc; it is often asymptomatic and insidious, but almost invariably associated with ominous outcome. For this reason it is essential to identify markers useful to early recognize any sort of SHI. The aim of this study was to investigate if high sensitivity troponin (HSTn) could be helpful to identify subclinical SHI.

Methods: for this purpose we analyzed data of 65 consecutive SSc patients (M:F = 4:61; mean age 59,4 years, range 24-95 years; mean disease duration 10,3 years; 33 with lcSSc, 32 with dcSSc) followed at our unit. Among all our SSc patients admitted in the last two years, we selected only those who underwent the following laboratory and instrumental investigations: HSTn, electrocardiogram and an echocardiogram within six months of HSTn test. Most of patients performed also N-terminal segment of proBNP (NT-proBNP) test and three patients underwent cardiac magnetic resonance imaging (cMRI). We excluded from our study patients with overt pulmonary arterial hypertension since it could alter cardiac markers. For six of the selected patients we collected data in more than one occasion. Furthermore we defined as SHI the presence of one or more of these conditions, in the absence of any other causes: diastolic dysfunction (at least grade II or grade I if patient is younger than 50 years or in presence of other manifestations of SHI), pericardial effusion, conduction abnormalities (bundle branch block or atrioventricular block) or arrhythmias, edema and/or T2 weighted non ischemic pattern showed by cMRI. Correlation between laboratory data and instrumental measurements were performed by non parametric tests for continuous variables and contingency tables for categorical variables (Stat-View, SAS). Fisher exact test was applied when indicated.

Results: among the analyzed patients 13 showed SHI and 23 and 29 had respectively high levels of HSTn and of NT-proBNP. SHI seems to be correlated only with high levels of HSTn (p 0,02) with a significant difference between the HSTn values of patients with or without SHI (59 versus 13ng/ml; p 0,0097). Moreover we observed a strictly correlation between NT-proBNP and HSTn: among patients with abnormal NT-proBNP, 18 had also out of range HSTn (spearman rank correlation 0,5; p <0.0001).

Conclusion: Our data shows a close relationship between HSTn and NT-proBNP in SSc patients with SHI. However, if we consider these 2 serological parameters independently, we observe that HSTn might be a marker of SHI while NT-proBNP seems to be a less specific index of heart dysfunction. Since SHI is often subclinical, but anyway associated with a significantly increased morbidity and mortality, a serological marker would be very useful not only to early diagnose SHI but also to select patients who need additional investigations such as cMRI. However further studies are necessary to confirm these preliminary results.

Abstract Number: 2966

Pulmonary Involvement in Systemic Sclerosis at Initial Presentation: A Single Center Experience

Ranadeep Mandhadi[1] and Santhanam Lakshminarayanan[2], [1]Division of Rheumatology, The University of Connecticut Health Center, Farmington, CT, [2]Division of Rheumatology, University of Connecticut Health Center, Farmington, CT
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Background/Purpose:

Systemic Sclerosis (SSc) is a rare heterogeneous autoimmune connective tissue disease**.**Pulmonary involvement is the major cause of mortality and morbidity in Systemic sclerosis. The aim of the study is to provide a single center experience of SSc patients diagnosed at a tertiary care center over a continuous period of 10 years, in regards to the extent and characteristics of interstitial lung disease at the time of initial presentation

Methods:

Retrospectively reviewed the charts of all the SSc patients who presented to The University of Connecticut Health Center Rheumatology clinic for the first time from April,2004 to March, 2014. All patients fulfilled the 2013 ACR/EULAR classification criteria for SSc, applied retrospectively at the time of chart review. Information about patient's demographics, laboratory, imaging studies and procedures including chest x- ray (CXR), high resolution CT (HRCT) of lung , pulmonary function tests (PFT's) and esophageal transit time (ETT) done at the time of their initial presentation were collected

Results:

128 patients were identified with either limited cutaneous (111) or diffuse cutaneous (17) variant SSC, of whom 120 (94%) were female and 95 (74%) were white**.** SCL-70 was positive in 18% and anti-centromere antibody was positive in 32% of patient's. Complete report of the PFT's was available in 104 patients. FVC was less than 70% in 20 (19%) patients. Of these, 4 had normal HRCT of the lung and 16 patients had interstitial changes. DLCO was less than 70% in 16 of the 20 patients with abnormal FVC. Of the remaining 84 patients with normal FVC, 10 (12%) patients had abnormal CXR and of the 62 patients with both normal FVC and normal CXR, 15 (24%) patients had an abnormal HRCT**.**

Among the 122 patients who had HRCT lung, 52 (43%) had abnormal HRCT including the 18 patients with only minimal ground glass changes and 34 patients with honeycombing and or fibrosis mostly limited to the subpleural space . Among the 52 patients with abnormal HRCT 28 (54%) patients had either an abnormal CXR or FVC. The remaining 24 patients with an abnormal HRCT had a normal FVC and CXR which accounts for 20% of total patients.

Of the 52 patients with abnormal HRCT lung, ETT was normal in 16 (30%) patients and abnormal in 35 (67%) patients. Of the 70 patients with normal HRCT, ETT was normal in 31(44%) patients and abnormal in 36 (51%) patients. No statistically significant difference was seen in the incidence of ETT in people with and without HRCT lung abnormalities (2 tailed p value was 0.129 using Fisher's exact test)

Conclusion:

Majority of patients presenting to University of Connecticut Health Center had limited cutaneous variant of SSc .Interstitial lung disease as diagnosed with HRCT lung was seen in more than 40% of patients with Systemic Sclerosis at the time of diagnosis. More than one third of these patients had only minimal ground glass opacities. Even though HRCT lung was abnormal in one fourth of the patients with normal FVC and chest x-ray**,** none of the patients had ILD severe enough to require treatment. Esophageal dysmotility is seen more often in patients with HRCT lung abnormalities but it was not statistically significant.

Disclosure: R. Mandhadi, None; **S. Lakshminarayanan**, None.

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Abstract Number: 2967

Musculoskeletal Involvement in SSc Correlates with Poor Short Form 36 and SSc Health Assessment Questionnaire Scores As Well As Lower TNF-Alpha Gene Expression in PBMCs

Eliza Pelrine[1], Marie-Dominique Ah-Kioon[1], Meng Zhang[2], Franck J. Barrat[3], Robert F. Spiera[3] and Jessica K. Gordon[3], [1]Hospital for Special Surgery, New York, NY, [2]Epidemiology and Biostatistics, Hospital for Special Surgery, New York, NY, [3]Rheumatology, Hospital for Special Surgery, New York, NY
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Background/Purpose:

Systemic Sclerosis (SSc) is characterized by a wide variety of symptoms and disease manifestations including joint pain, gastrointestinal dysfunction, interstitial lung disease, and cardiomyopathy. Using the Scleroderma Health Assessment Questionnaire (SHAQ) and Short Form-36 (SF-36) we explored how patient-reported physical health, mental health, and functional status related to these clinical characteristics and to cytokine levels in our scleroderma patient cohort.

Methods:

This was an observational study including 274 patients enrolled in our center's SSc registry. From those we included patients who had completed both questionnaires and had clinical data available (n=185). A subsection of 32 patients was included for cytokine analysis. Interleukin-6 (IL-6), Interleukin-1β (IL1ß), and Tumor Necrosis Factor-α (TNFα) levels were measured by Luminex and ELISA assays. Gene expression of these cytokines was measured by qPCR. Analysis was carried out using descriptive statistics, Spearman, Kruskal Wallis, and ANOVA tests as appropriate.

Results:

Musculoskeletal (MSK) involvement, as defined by the presence of myalgias, myositis, arthritis, and/or joint pain, correlated with lower (worse) SF-36 scores (χ^2=11.32,p<0.01) and higher (worse) SHAQ scores (χ^2=11.54,p<0.01). High SHAQ scores also correlated with high modified Rodnan Skin Scores (mRSS) (ρ=0.21,p<0.01). SF-36 and SHAQ scores were also compared to age, gender, race, disease duration, disease type, and other organ system involvement and no significant interactions were observed. Lower TNFα expression in peripheral blood mononuclear cells (PBMC) correlated with MSK involvement (F=103.21,p<0.01) SF-36 Mental Health component scores positively correlated with IL-6 levels in PBMC (ρ=0.81,p<0.05). Disease duration negatively correlated with TNFα expression in PBMC (ρ=-0.9,p<0.05). No other significant interactions were seen between clinical characteristics and cytokine levels.

Conclusion:

In our cohort, MSK involvement was the only clinical feature to be strongly associated with both decreased quality of life and worse functional status. Surprisingly, subjects with musculoskeletal symptoms expressed lower levels of TNFα in their PBMCs. These associations are topics for further study.

Table 1- Demographics & Clinical Data (n=185)

Age (avg. ± SD)	51.5 ± 13.9	
Gender (% female)	82.2	
Race (%)		
White	67.2	
Black	14	
Hispanic	9.7	
Asian	4.7	
Other	2.1	
Disease Type (%)		
Diffuse	65.4	
Limited	29.7	
Other	4.9	
Disease Duration (avg. ± SD)	5.96 ± 6.1	
	Diffuse	**Limited**
mRSS (avg. ± SD)	22.5 ± 10.8	6.0 ± 4.3
Disease Manifestations-% (out of n)		
ILD	64.9 (111)	17.6 (51)
PAH	12.2 (115)	15.1 (53)
GI	76.8 (142)	71.9 (64)
SRC	4.4 (113)	0 (48)
Ulcers	52.8 (123)	28.3 (53)
Raynaud's	89.3 (122)	94 (50)
Cardiac Edema	11.1 (99)	10 (50)
Pericardial Effusion	6.2 (97)	0 (47)
Arhythmia	5.1 (99)	8.2 (49)
Myalgias	25.8 (89)	23.6 (55)
Myositis	0 (67)	2.2 (45)
Arthritis	17.3 (52)	8.3 (24)
Joint Pain	50.6 (81)	52 (50)

Table 2-Clinical Characteristic Correlations						
	SF-36 Mental		SF-36 Physical		SHAQ	
	Mean ± SD, n	*p-value*	*Mean ± SD, n*	*p-value*	*Mean ± SD, n*	*p-value*
Gender						
Male	54.7 ± 26.8, 24	0.76	46.8 ± 25.8, 27	0.62	0.99 ± 0.91, 27	0.92
Female	56.9 ± 22.4, 155		48.6 ± 23.7, 158		0.97 ± 0.85, 148	
Race						
White	59 ± 22.6, 114		51 ± 23.9, 117		0.92 ± 0.79, 112	
African American	55.5 ± 21.8, 22		53.5 ± 24.9, 23		0.86 ± 0.91, 22	
Hispanic	43.9 ± 24.6, 12	0.08	36.1 ± 21.1, 12	0.08	1.25 ± 1.04, 12	0.83
Asian	49.2 ± 21, 12		39.3 ± 23.3, 13		1.17 ± 0.95, 13	
Mixed/Other	72 ± 18.6, 4		58.5 ± 22.4, 4		1.01 ± 0.52, 4	
Disease Type						
Limited	58.3 ± 25.8, 59		51.1 ± 25.2, 59		0.92 ± 0.85, 56	
Diffuse	55.1 ± 22.1, 92	0.63	48.4 ± 23, 97	0.18	1.06 ± 0.84, 92	0.13
Other	57.4 ± 19.0, 9		36.4 ± 23.9, 9		0.53 ± 0.47, 7	
ILD						
Present	52.4 ± 23.3, 33	0.26	43.5 ± 21.3, 34	0.11	1.07 ± 0.94, 36	0.53
Not Present	57.7 ±23.8, 82		51.8 ± 26.3, 84		0.92 ± 0.86, 76	
PAH						
Present	51.8 ± 22.3, 18	0.38	42.1 ± 21.3, 19	0.26	1.28 ± 1.09, 18	0.36
Not Present	56.3 ± 23.5, 104		49.8 ± 25.2, 106		0.96 ± 0.79, 99	
GI						
Involved	55.7 ± 22.8, 116	0.6	47.5 ± 24, 117	0.3	1.07 ± 0.89, 107	0.12
Uninvolved	57.1 ± 25.2, 39		51.2 ± 23.8, 39		0.83 ± 0.76, 42	
Cardiac				0.05		
Involved	51.3 ± 23.9, 25	0.44	40 ± 24, 26	0.05	1.34 ± 1.09, 21	0.1
Uninvolved	54.9 ± 23.7, 94		50.4 ± 24.5, 96		0.89 ± 0.77, 97	
Musculoskeletal						
Involved	50.2 ± 23.8, 76	0.0008	41.9 ± 23.3, 77	<0.0001	1.18 ± 0.94, 74	0.0007
Uninvolved	67.7 ± 21.5, 32		63.3 ± 21.2, 34		0.52 ± 0.48, 34	

Disclosure: E. Pelrine, None; **M. D. Ah-Kioon**, None; **M. Zhang**, None; **F. J. Barrat**, None; **R. F. Spiera**, None; **J. K. Gordon**, None.

Abstract Number: 2968

Interrater Reliability of Nailfold Capillaroscopy in Systemic Sclerosis Using Widefield Microscopy

Jessica K. Gordon[1], Meng Zhang[2], Shervin Assassi[3], Elana J. Bernstein[4], Robyn T. Domsic[5], Faye N. Hant[6], Monique E. Hinchcliff[7], Dinesh Khanna[8], Ami A. Shah[9], Victoria K. Shanmugam[10,11], Virginia D. Steen[12] and Tracy M. Frech[13], [1]Rheumatology, Hospital for Special Surgery, New York, NY, [2]Epidemiology and Biostatistics, Hospital for Special Surgery, New York, NY, [3]Rheumatology, University of Texas Medical School at Houston, Houston, TX, [4]Rheumatology, Columbia University College of Physicians & Surgeons, New York, NY, [5]Medicine - Rheumatology, University of Pittsburgh, Pittsburgh, PA, [6]Dept of Medicine, Medical University of South Carolina, Charleston, SC, [7]Division of Rheumatology, Division of Rheumatology, Northwestern University, Feinberg School of Medicine, Chicago, IL, [8]Division of Rheumatology, University of Michigan, Ann Arbor, MI, [9]Rheumatology, Johns Hopkins University School of Medicine, Baltimore, MD, [10]Director, Division of Rheumatology, The George Washington University, Washington, DC, [11]Division of Rheumatology, The George Washington University, Washington, DC, [12]Rheumatology, Georgetown University Medical Center, Washington, DC, [13]Div of Rheumatology, University of Utah, Salt Lake City, UT

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Background/Purpose:

The presence of nailfold capillary (NFC) abnormality is part of the 2013 ACR/EULAR Classification Criteria for Systemic Sclerosis (SSc). NFC findings include the presence of capillary dilation, hemorrhage, and neoangiogenesis, and it has been shown that these patterns have prognostic value. Patients in the Prospective Registry of Early Systemic Sclerosis (PRESS) cohort (diffuse SSc patients with < 2 years disease duration) have NFC evaluation using widefield microscopy (WM) at eleven centers in the United States. Our objective in this study was to assess the interrater agreement of the PRESS investigators assessment of NFC abnormalities by WM in

order to ensure the quality of our data collection.

Methods:

Investigators from the PRESS registry assessed 26 cases of patients with SSc without macrovascular changes or significant hand contractures who had been photographed using WM. The PRESS Investigators have attended training exercises to learn the capillaroscopic techniques, but no specific training was provided prior to this exercise. Each case was assessed for NFC dilation, hemorrhage, and neoangiogenesis (defined as bushy capillaries) and rated as normal, mild, moderate, or severe for each of these categories. Data were captured via surveymonkey and analyzed in two ways: 1.) using all 4 categorical variables and 2.) using a simplified approach where the variables were collapsed to normal vs abnormal. Krippendorf's alpha reliability estimate was used to assess the interrater agreement between these categorical variables. The following values represent the following degrees of agreement: <0 – poor; 0-0.2 – slight; 0.21- 0.4 – fair; 0.41- 0.6 – moderate; 0.61-0.8 – substantial; and 0.81-1.0 – almost perfect agreement.

Results:

Intrarater reliability ranged from substantial to almost perfect agreement for NFC hemorrhage to substantial agreement for dilation of NFC loops to fair agreement for neoangiogenesis. Assessment with four variables showed improved agreement when compared to 2 variables. Results are presented in Table 1.

Interrater Reliability		
	4 variables (normal, mild, moderate, severe)	2 variables (normal/abnormal)
NFC Hemorrhage - alpha (95% CI)	0.7991 (0.7528, 0.8403)	0.8205 (0.6801, 0.9262)
Dilated Capillary Loops - alpha (95% CI)	0.6538 (0.5930, 0.7093)	0.4869 (0.2846, 0.6934)
Neoangiogenesis - alpha (95% CI)	0.3738 (0.2820, 0.4644)	0.2706 (0.0879, 0.4527)

Table 1. Krippendorf's alpha reliability estimate using 4 variables (normal, mild, moderate, severe) and using 2 variables for the 3 categories of NFC abnormality assessed.

Conclusion:

Fair inter-rater reliability was observed for neoangiogenesis, moderate to substantial reliability was observed for dilated capillary loops, and substantial to near perfect agreement was noted for reading of WM photomicrographs for NFC hemorrhage among PRESS investigators. This attests to quality data collection for this procedure. Classification of specific NFC abnormalities using the terms normal, mild, moderate, and severe is feasible and can be used reliably in registries. Whether NFC abnormalities carry prognostic significance in patients with early diffuse SSc is a subject for future study in the PRESS registry.

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Abstract Number: 2969

X-Ray Diffraction of Spontaneously Draining Calcinosis in Patients with Scleroderma

Vivien Hsu[1], Thomas Emge[2] and Naomi Schlesinger[3], [1]Medicine, Rutgers University, New Brunswick, NJ, [2]Dept of Chemistry and Chemical Biology, Rutgers- the State University, Piscataway, NJ, [3]Medicine, Rutgers-Robert Wood Johnson Medical School, New Brunswick, NJ

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Background/Purpose: Calcinosis is caused by deposition of calcified materials in the soft tissues (1). Hydroxyapatite (HA) is reported to be its major constituent (2). Mechanical stress and local tissue hypoxia are believed to be important in its pathogenesis (3). Our aim was to analyze spontaneously draining material from calcinosis sites in scleroderma (SSc) patients using x-ray diffraction.

Methods: In this IRB-approved study, we enrolled SSc patients meeting the American College of Rheumatology criteria for definite SSc (4). Pertinent clinical data was collected. Xray diffraction data were used to determine solid phase present (e.g., HA *versus* other Ca phosphate phase) and to approximate the % amorphous and % crystalline components using a Bruker HiStar multi-wire area detector.

Results: Ten female subjects (see Table 1) with advanced SSc were enrolled with mean disease duration 16 years; 6 had diffuse SSc. Calcinosis occurred later in the disease course and 7 had extensive calcinosis affecting multiple sites. Draining calcinosis was collected from multiple sites, most commonly the hand. X-ray diffraction confirmed HA of varying percentages in all but one specimen. Solid samples generally contained higher amounts of HA.

Conclusion: By using x-ray diffraction, our study corroborates previous published reports (2, 3) that HA crystal deposition is the main constitute of SSc-related calcinosis. Solid samples contained higher amounts of HA crystals; fluid samples observed by optical microscopy to contain solids, including HA in suspension. Further research is needed to characterize the amorphous materials associated with HA deposition in SSc patients with calcinosis.

Table 1: SSc clinical characteristics and crystal analysis:

Patient #	SSc type	SSc/ calcinosis onset (in years)	Auto-antibodies	sites	State	Crystalline component
1	D*	15/9	ANA/Nucleolar/ Scl70	elbow thigh groin	liquid* liquid liquid	HA** (25%) HA (20%) HA (20%)
2	D	19/9	ANA/Scl70	belly	liquid	HA (3%)
3	L**	15/3	ANA/ACA	groin	liquid	HA (2%)
4	L	19/5	ANA/ACA/RNP	finger	liquid	HA (8%)
5	L	16/3	ANA	Elbow over 3 days	solid liquid solid	HA (40%) HA (40%) HA (4%)
6	D	14/3	Scl70/RNApol3	finger	solid	HA (15%)
7	D	11/9	Scl70	finger over 3 days	solid liquid liquid	HA (50%) HA (7%) HA (10%)
8	D	9/4	Scl70/ANA	shoulder	Solid mass	HA (3%)
9	L	29/4	ANA/RNApol3/	Belly	Solid***	calcite (<1%)

*Diffuse **Limited

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1. Steen et al *Arthritis Rheum* 1984; 27:125.
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4. Hoogen et al., *Ann Rheum Dis* 2013;72:1747 & *Arthritis Rheum* 2013;65(11):2737-57.

Disclosure: V. Hsu, None; **T. Emge**, None; **N. Schlesinger**, Novartis Pharmaceutical Corporation, 2,Takeda, novartis, 8,Novartis, Astra Zeneca, Pfizer, 5.

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Abstract Number: 2970

Primary Care Assessment of Capillaroscopy Abnormalities in Patients with Raynaud's Phenomenon

Rebecca Overbury[1], Maureen Murtaugh[2], Aryeh Fischer[3] and Tracy M. Frech[4], [1]Internal Medicine and Pediatrics, University of Utah, Salt Lake City, UT, [2]Internal Medicine-Division of Epidemiology, University of Utah School of Medicine, SLC, UT, [3]University of Colorado School of Medicine, Aurora, CO, [4]Div of Rheumatology, University of Utah Medical Ctr, Salt Lake City, UT

			nucleolar	finger	solid	HA (2%)
10	D	10/2	ANA	finger	solid	HA (43%)

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Session Title: Systemic Sclerosis, Fibrosing Syndromes and Raynaud's - Clinical Aspects and Therapeutics Poster III

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Background/Purpose: Raynaud's phenomenon is a clinical symptom that can commonly present to a primary care provider or generalist. Proper identification of an underlying connective tissue disease in a patient with Raynaud's could allow for the prevention of possible critical digital ischemia. Capillaroscopy is a tool which can identify abnormalities associated with connective tissue disease.

Methods: Patients presenting with a complaint of Raynaud's phenomenon were assessed with capillaroscopy. In twenty consecutive Raynaud's patients 8 digits were assessed by a 200X magnification dermatoscope and an image was obtained. Each image was assessed for the following abnormalities: drop-out (<9 capillaries in 1 mm); micro-hemorrhage; dilated loops; and neoangiogenesis. These 160 images were then shown to 20 primary care physicians, who assessed these same abnormalities. The interrater reliability, a measure of agreement, of individual primary care providers with the expert provider was assessed using kappa statistics.

Results: The total agreement from the 20 primary care providers was moderate (kappa =0.50, 95% CI: 0.49, 0.55). Three raters had slight agreement (in the range 0 to 0.20), one rater had fair agreement (0.21 to 0.40), 11 raters had moderate agreement (0.41 to 0.60), 5 raters had substantial agreement (0.61 to 0.80), and no rater had almost perfect agreement (0.81 to 1.00) For the four providers with slight to fair interrater reliabilities, the most common disagreement was providing a positive diagnosis when the expert rater diagnosed the digit negative. Ten of the 20 primary care providers provided at least one additional diagnosis following an abnormal diagnosis (n= 35 digits or 35% of the 1,556 abnormal ratings by the primary care providers). The four providers with the poorest interrater reliabilities were not among the 10 providers who participated in making these additional specific diagnoses. These providers achieved the moderate agreement with the expert provider for diagnoses of micro-hemorrhage (kappa = 0.64, 95% CI: 0.57, 0.70), but fair agreement with the expert provider for diagnoses of dilated loops (kappa = 0.27, 95% CI: 0.20, 0.34) and neoangiogenesis (kappa = 0.22, 95%CI: 0.13, 0.31).

Conclusion: Capillaroscopy is a potentially contributive clinical exam skill that could assist primary care providers and generalists in identifying and qualifying changes associated with the common presentation of Raynaud's disease. However, formal training is needed to ensure accuracy and reproducibility. Furthermore, training and scoring systems should address time constraints of busy primary care practitioners.

Disclosure: R. Overbury, None; **M. Murtaugh**, None; **A. Fischer**, Genentech and Biogen IDEC Inc., 2,Actelion Pharmaceuticals US, 5,GlaxoSmithKline, 5,Boehringer Ingelheim, 1,Gilead Sciences, 5,Seattle Genetics, 5,Bristol-Myers Squibb, 5; **T. M. Frech**, None.

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Abstract Number: 2971

Raynaud Phenomenon Subjects with Abnormal Capillary Dilations Show a Risk Threshold Diameter Value for the Transition to the Capillaroscopic Early Scleroderma Pattern: A Case Control Study

Maurizio Cutolo[1], Carmen Pizzorni[2], Marianna Meroni[2], Vanessa Smith[3], Sabrina Paolino[2], Barbara Ruaro[2], Alberto Sulli[2], Bruno Seriolo[2] and Amelia Chiara Trombetta[2], [1]Department of Internal Medicine, University of Genova, Genova, Italy, Research Laboratory and Academic Division of Clinical Rheumatology, Department of Internal Medicine, University of Genova, Genova, Italy, [2]Research Laboratory and Academic Division of Clinical Rheumatology, Department of Internal Medicine, University of Genova, Genova, Italy, [3]Department of Rheumatology, Ghent University Hospital, Ghent University, Ghent, Belgium

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Background/Purpose: Nailfold Video Capillaroscopy (NVC) is a reliable method to qualitatively differentiate Primary (PRP) from Secondary Raynaud Phenomenon (SRP) through diagnosis of the “early scleroderma pattern” (1, 2). Quantitative evaluation by NVC was demonstrated to be of great value for the analysis of abnormal capillary parameters (2). The purpose was to assess the presence and localization of capillary diameter abnormalities (>20µm),before the transition to SRP. Moreover, to find a threshold value for those dilations, associated to the development of giant capillaries (>50 µm), pathognomonic for the “early scleroderma pattern” (SSc).

Methods: We realized a case-control study, over a total population of 191 RP subjects with a NVC follow-up of 42.77±35.80 months. Two gruoups were identified, uniform for demographic characteristics (gender, age), RP duration (p= 0.98), treatments (p=0.13) and comorbidities (p=0.13). RP subjects were classified as SRP SSc-associated, based on the appearance of the “early” scleroderma pattern and/or ANA positivity, or confirmed with PRP. One operator performed the NVC and results were separately checked by two experts with an inter-rater/intra-rater proportion of agreement of 90% and 96%, respectively. Another observer measured on NVC images the major dilation of capillary branches (arterial, venous, apical) using a dedicated software (Videocap, DS MediGroup, Milan, Italy). More then 6112 images were analyzed. The mean diameter value for each enlarged branch (arterial, venous, apical) and the total mean diameter, were calculated. Statistics were performed by non-parametric tests. ROC curve was performed to find the SSc development associated threshold value.

Results: A statistically significant difference was found in SRP subjects, before the transition, compared to PRP subjects, for diameter values of dilations in both arterial (35.30 ± 8.79 VS 27.84 ± 5.52 µm; p<0.0001) and venous (37.19 ± 6.58 VS 28.86 ± 4.48 µm; p<0.0001) branches. No significant differences were observed for apical dilations (32.64 ± 5.77 VS 30.81 ± 6.35 µm; p=0.07). ANAs were observed in 56.2% of SRP patients (p= <0.0001). No confounding effect was observed for other demographic and clinical data. Kaplan-Meier analysis showed that 50% of SRP patients evolved to SSc in 20 months. The threshold value associated with SSc development was 30.16 µm, determined through ROC curve, with a sensitivity/specificity of 0.85/0.63 respectively, a negative predictive value (NPV) of 0.92 and a positive predictive value (PPV) of 0.44.

Conclusion: Abnormal dilations of arterial and/or venous branches, at baseline, are detectable by NVC, and are significantly more often expressed in RP subjects that will develop a SRP.Progression to “giant” capillaries (>50 µm) pathognomonic for the “early” NVC scleroderma pattern seem to be unlikely for subjects affected by RP with mean capillary diameter lower then 30.16 µm (NPV 0.92). Therefore, it is advisable to perform always the qualitative/quantitative integrated NVC during the follow up of all patients affected by RP.

References: 1) Cutolo M et al. 2000;27:155–60. 2) Cutolo M et al. Best Pract Res Clin Rheumatol. 2013;27(2):237-48. 3) Smith V at al. J Rheumatol. 2013;40:2023-8

Disclosure: M. Cutolo, None; **C. Pizzorni**, None; **M. Meroni**, None; **V. Smith**, None; **S. Paolino**, None; **B. Ruaro**, None; **A. Sulli**, None; **B. Seriolo**, None; **A. C. Trombetta**, None.

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Abstract Number: 2972

Cardiopulmonary Exercise Testing in Patients with Systemic Sclerosis: Unexplored Mechanisms of Dyspnea

Sara R. Schoenfeld[1], George Alba[2], Josanna Rodriguez-Lopez[3], Richard N. Channick[3], Flavia V. Castelino[4] and Marcy B. Bolster[4], [1]Rheumatology, Allergy and Immunology, Massachusetts General Hospital, Harvard Medical School, Boston, MA, [2]Department of Pulmonary and Critical Care, Massachusetts General Hospital, Harvard Medical School, Boston, MA, [3]Pulmonary and Critical Care, Massachusetts General Hospital, Harvard Medical School, Boston, MA, [4]Rheumatology, Allergy, Immunology, Massachusetts General Hospital, Harvard Medical School, Boston, MA

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Background/Purpose:

Patients with systemic sclerosis (SSc) experience dyspnea for multiple reasons. Cardiopulmonary exercise testing (CPET), an important tool in the evaluation of undifferentiated dyspnea, provides integrated metabolic and hemodynamic measures during exercise. Few

studies have utilized CPET in SSc.[1] In this study we evaluated exercise limitations in SSc patients as determined by CPET combined with invasive hemodynamic measurements (level 3 CPET).

Methods:

This was a single center, retrospective review of all SSc patients who underwent level 3 CPET between February 2006 and February 2015. Level 3 CPET consists of graded exercise on a cycle ergometer with metabolic cart and simultaneous measurement of pulmonary and systemic arterial hemodynamics. Primary reasons for exercise limitation include left ventricular diastolic dysfunction (LVDD), a peripheral limit (impairment in the ability of the muscles to extract and use oxygen), a pulmonary vascular limit (PVL, i.e. PAH) or a pulmonary mechanical limit. Demographic and clinical information was extracted from medical records.

Results:

Eleven patients were included in this analysis. Nine of the eleven patients met the 2013 ACR SSc classification criteria. Two had missing information that precluded the definitive classification as SSc, but fell within the spectrum of SSc disease. Baseline characteristics are shown in **Table 1**. 91% of patients were female and the mean age was 61 years. Seven of eleven (64%) patients had a peripheral extraction limitation; the remaining four had LVDD or PVL **(Table 2)**. Three of the seven patients with a peripheral limit to exercise were anemic, defined by hemoglobin <12 g/dL, the lower limit of normal in our laboratory.

Conclusion:

Our findings provide novel insight into less explored etiologies of dyspnea and exercise limitation in SSc patients. Only one prior study reported findings similar to ours, but that study did not employ invasive CPET.[2] Of note, only three of the seven patients with a peripheral limit in our study were anemic, suggesting alternative mechanisms for impaired peripheral oxygen extraction. The systemic vasculopathy characteristic of SSc is likely present in muscle and may contribute to impaired oxygen utilization. Our findings call for larger studies to address the possible mechanisms of peripheral limitation in SSc patients, and even suggest a potential therapeutic role for agents with vascular targets that may improve peripheral extraction, resulting in improved dyspnea and exercise tolerance in SSc patients.

References

1. *J. Rheum*. 2010. 37:1871.

2. *Am J Med*. 1993. 95:413.

Table 1. Baseline Characteristics of SSc Patients

Variable	N (%)
Age, mean +/- SD, years	61 +/- 15
Female	10 (91%)
BMI, mean +/- SD, kg/m^2	26.5 +/- 7.8
Antibody profile	
Anti-Scl-70 antibodies	2 (18%)
Anti-centromere antibodies	3 (27%)
Nucleolar pattern of ANA	3 (27%)
Positive ANA alone	2 (18%)
Missing	1 (9%)
Smoking History	
Never	8 (73%)
Past	3 (27%)
Current	0
Other Medical History	
Asthma	1 (9%)
COPD	0
HTN	2 (18%)
Diabetes	1 (9%)
CAD	0
CHF	2 (18%)
Medication Use	
Calcium Channel Blocker	4 (36%)
Beta Blocker	3 (27%)
Aspirin	4 (36%)
Phosphodiesterase Inhibitor	0
Endothelin Receptor Antagonist	0
Reason for CPET Referral	
Dyspnea on exertion	11 (100%)
Concern for exercise PAH	2 (18%)
Left Ventricular Ejection Fraction	
Normal (≥50%)	10 (91%)
Abnormal (<50%)	0
Echocardiogram estimated RVSP	
Normal (<40 mmHg)	6 (55%)
Abnormal (≥40 mmHg)	3 (27%)
FVC/DLCO ratio	
≥1.6	5 (45%)
<1.6	6 (55%)
DLCO	
≥60%	6 (55%)
<60%	5 (45%)
BNP, mean +/- SD, pg/mL	214.9 +/- 130.1
Hemoglobin, mean +/- SD, g/dL	12.6 +/- 1.4

Table 2. Selected CPET Parameters for Each Individual Patient

Patient	Indication for CPET	DLCO (%)	FVC (%)	Peak VO2 (% predicted)	VAT[1] (% predicted peak)	O2 Pulse Peak[2] (ml/beat)	A-a Gradient Peak	Ca-v O2 Peak[3]	mPAP/PCWP[4] Rest	mPAP/PCWP Peak	Hgb[5](g/dL)	Primary Exercise Limitation
1	DOE,[6] possible exercise PAH[7]	26	59	54	38	5.4	61	10.4	25/7	41/12	12.6	PVL[8]
2	DOE	71	112	87	42	7.2	18.4	9.4	13/9	31/25	11.3	Peripheral
3	DOE	58	100	71	36	10.6	35	10.7	14/4	27/11	12.7	Peripheral
4	DOE	44	61	50	29	5.3	19	9.1	21/4	27/13	12.5	Peripheral
5	DOE, possible exercise PAH	46	83	54	24	8.7	59	12.3	32/10	56/22	13.6	PVL
6	DOE	67	110	100	58	9.5	NR	12.4	13/6	41/23	NR[9]	LVDD[10]
7	DOE	44	80	65	NR	5.6	44	7.4	20/6	37/11	9.8	Peripheral
8	DOE	64	66	64	28	10.4	60	8.4	13/3	29/11	14.4	PVL
9	DOE	82	91	72	42	9.4	5	10.9	17/3	27/7	13.9	Peripheral
10	DOE	65	99	55	35	6.6	9	8.1	11/2	25/15	12.9	Peripheral
11	DOE	64	84	63	32	7.4	NR	8.2	15/4	27/17	11.5	Peripheral

1 VAT=ventilatory anaerobic threshold; 2 O2 pulse = VO2/heart rate, the product of stroke volume and arterial-mixed venous blood oxygen content difference; 3 Ca-VO2= arteriovenous oxygen difference, indicator of peripheral oxygen extraction; 4 mPAP=mean pulmonary artery pressure, PCWP=pulmonary capillary wedge pressure; 5 Hgb=hemoglobin; 6 DOE=dyspnea on exertion; 7 PAH=pulmonary arterial hypertension; 8 PVL=pulmonary vascular limit; 9 NR=not recorded; 10 LVDD=left ventricular diastolic dysfunction

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Abstract Number: 2973

Exercise Intolerance Evaluated By Invasive Cardiopulmonary Exercise Testing in Connective Tissue Disease: Beyond Pulmonary Hypertension

Rudolf Oliveira[1,2], David Systrom[2], Julie Tracy[2], Abbey Karin[2], Aaron Waxman[2], Paul Dellaripa[3] and Paul Hoover[3], [1]Medicine, Division of Respiratory Disease, Federal University Of São Paulo, São Paulo, Brazil, [2]Pulmonary and Critical Care Medicine, Brigham and Women's Hospital, Boston, MA, [3]Rheumatology, Immunology and Allergy, Brigham and Women's Hospital, Boston, MA
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Background/Purpose:

Exercise intolerance is common in patients with connective tissue disease (CTD) and may be related to pulmonary hypertension (PH). However, determining the exact etiology of the exercise limitation in these patients is challenging due to the multiorgan involvement of CTDs. The invasive cardiopulmonary exercise testing (iCPET) combines the non-invasive evaluation of an incremental symptom-limited cycling CPET with simultaneous pulmonary and radial artery-derived invasive hemodynamics measurements, and therefore differentiate among cardiovascular, respiratory, metabolic and peripheral limitations to exercise. In the current study, we evaluated patients with CTD and exertional intolerance (with or without interstitial lung disease, ILD) who underwent iCPET. Our aim was to determine the relative contributions of central cardiac and peripheral mechanisms underlying exertional intolerance in CTD patients. We hypothesized that CTD without ILD would have multifactorial reasons for exertional intolerance, beyond PH.

Methods:

683 clinically indicated iCPETs performed at Brigham and Women's Hospital between 2011-2015 were evaluated. Based on established diagnostic criteria 50 patients had confirmed CTD (18 SSc, 15 RA, 4 UCTD, 3 SLE, 3 antisynthetase syndrome, 2 CREST, 2 MCTD, 1 psoriatic arthritis, 1 Sjögren's, 1 Still's). ILD was defined by the presence of fibrosis on CT scans of the lungs and a forced vital capacity < 70% predicted.

Results:

From the 50 patients evaluated, 15 had CTD-ILD, of which 14 (93%) had PH. Among the 35 patients without ILD, 23 (66%) had a reduced aerobic capacity defined by maximum oxygen uptake (VO_{2MAX}) < 80% predicted. Out of these 23 patients, 10 (43%) had PH and 13 (57%) had a non-PH related exercise diagnosis, most commonly a peripheral limitation to exercise (10 of 13). Subgroup analysis of systemic sclerosis (SSc) patients revealed 10 of 18 (56%) with ILD, and PH was the most common diagnosis. SSc patients without ILD and a reduced VO_{2MAX} were more likely to have a peripheral limitation to exercise (5 of 7, Figure 1). VO_{2MAX} was 62±15% predicted for the CTD-ILD group, 60±16% for CTD without ILD with PH-related limitation to exercise, and 63±12% for CTD without ILD and a non-PH disease. There were no significant differences regarding VO_{2MAX} among these three groups ($p>0.05$).

Conclusion:

With direct measures from iCPET, we conclude that while CTD-ILD patients are more likely to present a PH-related limitation to exercise, CTD patients without ILD have a higher prevalence of peripheral limitation manifested by impaired systemic O_2 extraction. We speculate the latter may be related to skeletal muscle mitochondrial dysfunction and/or peripheral microvascular dysfunction.

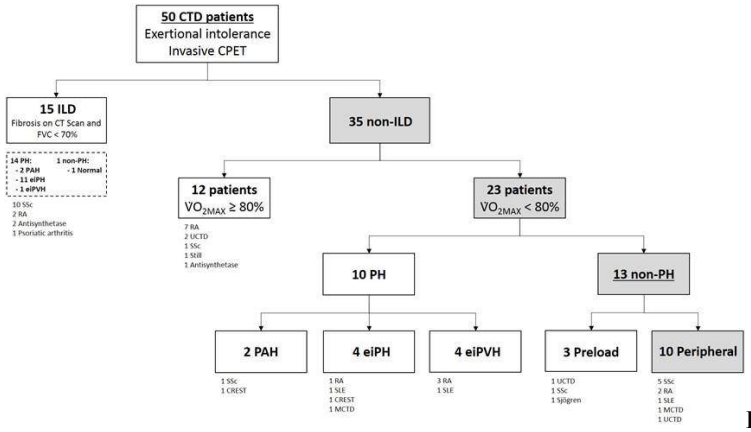

Figure 1.

Disclosure: R. Oliveira, None; **D. Systrom**, None; **J. Tracy**, None; **A. Karin**, None; **A. Waxman**, None; **P. Dellaripa**, None; **P. Hoover**, None.

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Abstract Number: 2974

Insulin Resistance Is Associated with the Digital Ulcer in Patients with Systemic Sclerosis

Seung-Geun Lee[1], Eun-Kyoung Park[2], Dong-Wan Koo[2], Geun-Tae Kim[3], Hee-Sang Tag[3] and Joung-Wook Lee[4], [1]Division of Rheumatology, Department of Internal Medicine, Busan National University School of Medicine, Busan, South Korea, [2]Division of Rheumatology, Department of Internal Medicine, Pusan National University School of Medicine, Busan, South Korea, [3]Division of Rheumatology, Department of Internal Medicine, Kosin University College of Medicine, Busan, South Korea, [4]Divsion of Rheumatology, Department of Internal Medicine, Busan St. Marys center, Busan, South Korea

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Background/Purpose: Growing evidence supports the view that systemic sclerosis (SSc) is a vascular disease mediated by autoimmunity and evolving into progressive tissue fibrosis. Several vascular biomarkers have been studied, but little is known about the role of metabolic derangement in vasculopathy in SSc. Our study aimed to investigate the relationship between insulin resistance and the digital ulcer (DU) in patients with SSc.

Methods: With a cross-sectional design, 69 female patients with SSc and 109 age-matched (± 2 years) female healthy subjects were consecutively recruited at a university-affiliated rheumatology center from June 2014 to May 2015. The magnitude of insulin resistance was evaluated by the homeostatic model assessment of insulin resistance (HOMA-IR) which was calculated as [fasting serum insulin (μIU/mL) × fasting serum glucose (mg/dL) / 405] and DU ever included active and healed ulcers. Skin fibrosis in SSc patients was assessed by modified Rodnan skin thickness score (MRSS).

Results: HOMA-IR in SSc patients was significantly higher than that in healthy subjects (1.09 (0.79-2.1) vs 0.72 (0.47-0.99), p<0.001). In SSc group, the mean age was 52.8 years, the median disease duration was 84 months and 33 patients (47.8%) had diffuse SSc. Nineteen patients (27.5%) had DU ever (6 active DU, 13 healed DU). SSc patients with DU ever had a significantly higher HOMA-IR (1.95 (1.22-2.8) vs 0.99 (0.71-1.75), p=0.002) and MRSS (15 (9-22) vs 9.5 (4.8-14), p=0.004) than those without DU ever. As shown in Table 1, in multivariable logistic regression analyses, increased log-transformed HOMA-IR showed a significant association with the presence of DU ever after adjustment of confounding factors such as MRSS (OR=2.42, 95% CI=1.01-5.8, p=0.047).

Conclusion: Increased insulin resistance was independently associated with the presence of digital ulcer in patients with SSc. Our data suggest that insulin resistance may contribute to the pathogenesis of vascular damage in SSc.

Table 1. Logistic regression models for the presence of digital ulcer in patients with systemic sclerosis

Variables	Crude OR (95% CI)	p	Adjusted OR [a] (95% CI)	p
Log-transformed HOMA-IR	2.96 (1.28-6.88)	0.011	2.42 (1.01-5.8)	0.047
MRSS	1.13 (1.04-1.24)	0.005	1.12 (1.02-1.22)	0.018
ILD	1.85 (0.96-3.53)	0.064		
Disease duration, months	1.01 (0.99-1.01)	0.097		
Age, years	0.96 (0.92-1.01)	0.130		
CRP, mg/dL	0.78 (0.17-3.64)	0.746		

HOMA-IR; homeostatic model assessment of insulin resistance, MRSS; modified Rodnan skin thickness score, ILD; interstitial lung disease, CRP; C-reactive protein

[a] Estimated using multivariable logistic regression model with backward selection including log-transformed HOMA-IR, MRSS, ILD and disease duration.

Disclosure: S. G. Lee, None; **E. K. Park**, None; **D. W. Koo**, None; **G. T. Kim**, None; **H. S. Tag**, None; **J. W. Lee**, None.

Abstract Number: 2975

Induced Sputum Analysis in Systemic Sclerosis Patients

Irena Litinsky[1], Elizabeth Fireman[2], Ari Polachek[1], Adi Broyde[1], Amir Sharabi[1], Marina Anouk[1], Daphna Paran[1] and Ori Elkayam[1], [1]Rheumatology, Tel Aviv Sourasky Medical Center and the Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel, [2]Institute of Pulmonary and Allergic Diseases, Tel Aviv Sourasky Medical Center and the Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

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Background/Purpose:

Induced sputum (IS) is a noninvasive tool, aimed at collecting cellular and soluble materials from lung airways. IS is well accepted by patients, safer than bronchoalveolar lavage (BAL) and easily repeated. IS sampling has been validated in chronic obstructive as well as in various interstitial lung disorders (ILD). Very few studies have evaluated the role of IS analysis in SSc.

Purpose

To evaluate IS cellular analysis in SSc patients compared to healthy controls and its possible relationship with disease manifestations.

Methods:

Twenty consecutive SSc patients and 16 healthy controls underwent pulmonary Function testing (PFT) (Jaeger Masterlab spirometer), single breath diffusion capacity of carbon monoxide (DLCO) and analysis of induced sputum (IS) cytology. IS was recovered after 20 min inhalation of 3% saline with an ultrasonic nebulizer by the selecting plugs method.

Results:

Group 1(SSc) : 13 (65%) with diffuse type,7 (35%) with CREST syndrome, 19 (95%) women, mean age 52.25+17.08, disease duration 8.69+7.56 years, Raynaud duration 10.3+9.22 years , eight (40%) patients had a history of ILD and none had pulmonary artery hypertension .

.Group 2 (controls): 16 healthy volunteers: 13 women (81.25%), mean age 57.93 ± 10.4years.

Lung tests:

TLC, FVC and DLCoVA were significantly lower within Group 1 vs controls . Seven patients in Group1 had a restrictive pattern.

SSc patients IS contained higher neutrophils count (p=0.091) and lower lymphocytes count (p=0.045) compared to the control group. No difference in IS cytology was found between types of SSc.

Within Group 1, a statistically significant positive correlation was

found among several clinical, PFT and IS findings (mRss score – CD3 (p=0.044); mRss –CD4 (p=0.04); mRss - % neutrophils (0.059); FVC-% neutrophils (0.002)). Neutrophils counts in IS were significantly inversely associated with TLC and FVC.

IS samples from SSc patients with PFT restrictive pattern contained a significantly lower percentage of lymphocytes (p=0.004) and CD4/CD8 ratio (0.028) compared with controls.

Among SSc, the statically significant high CD4/CD8 ratio was associated with restrictive PFT pattern (p=0.05).

A positive correlation was found between restrictive subtype of Group 1 IS cytology count and several clinical, laboratory PFT parameters (disease duration- CD4/CD8 ratio(p=0.033), TLC- CD3(p=0.053), TLC and FVC - % macrophages (p=0.033,p=0.052 respectively), DLCoVA – % macrophages (p=0.032), CRP - % lymphocytes ,% macrophages and neutrophils (p=0.019 and p= 0.008 and p= 0.006 respectively). A Negative correlation was shown between TLC and neutrophils count (p=0.043).

Conclusion:

IS analysis of SSc patients, including patients with restrictive lung disease, shows changes in cellular pattern in comparison to healthy controls and correlation with several clinical and PFT parameters.

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Abstract Number: 2976

Ambrisentan Dose Migration over 3 Years in Patients with Connective Tissue Disease-Associated Pulmonary Arterial Hypertension (CTD-PAH)

James Tislow[1], Chris Blair[2] and Hunter Gillies[3], [1]Medical Affairs, Gilead Sciences, Inc., Foster City, CA, [2]Biostatistics, Gilead Sciences, Inc., Foster City, CA, [3]Clinical Research - Cardiovascular, Gilead Sciences, Inc., Foster City, CA

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Background/Purpose:

Pulmonary arterial hypertension (PAH) is an important complication in patients with connective tissue disease and may lead to increased morbidity and early mortality. Ambrisentan, an orally active endothelin A receptor selective antagonist, has demonstrated safety and efficacy in patients with WHO Group I PAH. Due to the chronic, long-term nature of treatment, dose adjustments are often desired to enhance efficacy or attenuate adverse events. We analyzed the ARIES database to determine dose adjustments in patients with CTD-PAH treated with ambrisentan over a three year period.

Methods:

Data from the combined ARIES 1 & 2 placebo-controlled studies (ARIES-C) as well as the long-term extension study (ARIES-E) were evaluated. Available ambrisentan dosages in ARIES-C were 2.5mg, 5mg, and 10mg once daily. Patients randomized to placebo in ARIES-C who continued to ARIES-E were re-randomized to active treatment. ARIES-E was open-label; however subjects and investigators were blinded to dose for the first 24 weeks of treatment during which a single, blinded dose reduction was permitted in the case of study drug intolerance. After 24 weeks, dosage adjustments were permitted at the discretion of the investigator. The dosage of ambrisentan was recorded at each study visit for all patients continuing in the study and on therapy. At the end of 3 years, survival status was collected retrospectively for patients no longer participating in the study.

Results:

There were 124 patients with CTD-PAH who received at least one dose of ambrisentan. The numbers of patients randomized to receive each initial dose were: 2.5mg = 30, 5mg = 60, and 10mg = 34. Annual patient disposition is outlined in Table 1. Over the course of three years, approximately 40% (n=49) of patients continued to receive ambrisentan therapy in ARIES-E. Reasons for discontinuation included transitioning out of the study (n=28, 23%) or terminating participation (n=45, 36%). Retrospectively collected survival status at 3 years revealed 83 patients (67%) were still alive, 29 patients (23%) had died, and survival status was unknown in 12 patients (10%). Dose adjustments of ambrisentan over the course of three years are represented in Figure 1.

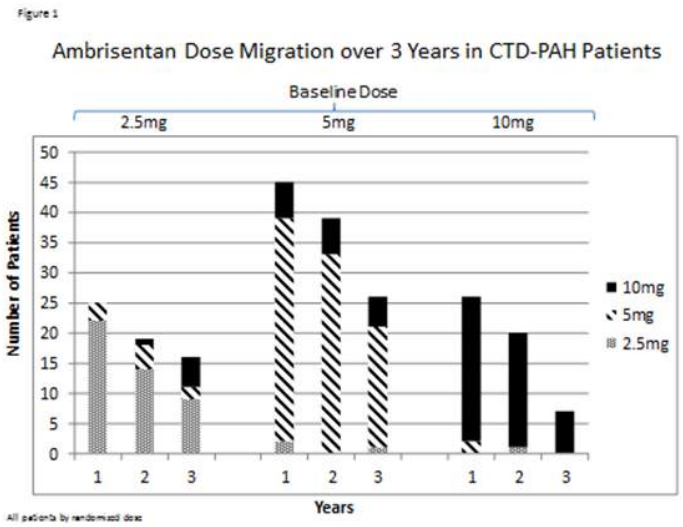
Conclusion:

Through three years of treatment with ambrisentan, those patients with CTD-PAH remaining in ARIES-E predominately remained on the dosages they were originally randomized to.

Table 1

	Year 1		Year 2		Year 3	
	Ongoing	Not Ongoing*	Ongoing	Not Ongoing*	Ongoing	Not Ongoing*
2.5mg (n = 30)	25	5	19	11	16	14
5mg (n = 60)	45	15	39	21	26	34
10mg (n = 34)	26	8	20	14	7	27

*Values of patients not ongoing for each dosage are cumulative



Disclosure: J. Tislow, Gilead Sciences, Inc., 3; **C. Blair**, Gilead Sciences, Inc., 3; **H. Gillies**, Gilead Sciences, Inc., 3.

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Abstract Number: 2977

A Meta-Analysis of Phosphodiesterase 5 Inhibitors for the Treatment of Raynaud's Phenomenon

Janet E. Pope[1], Fadumo Rirash[2], Paul Tingey[3], Sarah Harding[4], Lara J. Maxwell[5], Jordi Pardo[6], Elizabeth Ghogomu[7], Peter Tugwell[8] and George A. Wells[9], [1]University of Western Ontario, London, ON, Canada, [2]Medicine/Rheumatology, University of Western Ontario, London, ON, Canada, [3]Faculty of Medicine, University of Queensland, Brisbane, Australia, [4]ERLanger, ERLanger, KY, [5]Centre for Global Health, Institute of Population Health, University of Ottawa, Ottawa, ON, Canada, [6]University of Ottawa, Ottawa, ON, Canada, [7]University of Ottawa, Cochrane Musculoskeletal Group, Ottawa, ON, Canada, [8]Center For Global Health, Institute of Population Hlth, Ottawa, ON, Canada, [9]Cardiovascular Research Reference Centre, University of Ottawa Heart Institute, Ottawa, ON, Canada

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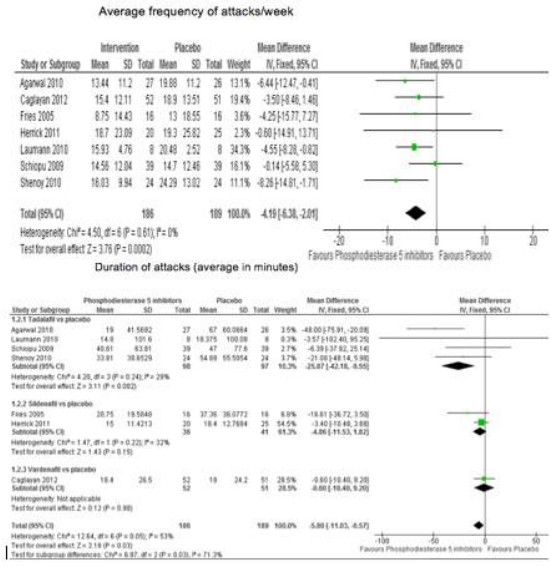
Background/Purpose: To assess the benefits and harms of phosphodiesterase 5 inhibitors (PDE5) for the treatment of Raynaud's phenomenon (RP).

Methods: The Cochrane library, MEDLINE, EMBASE and Clinicaltrials.gov were searched to June 2014 for randomized controlled trials (RCTs) examining RP with PDE5. Outcomes of interest were: Frequency of RP attacks, Duration of attacks, Severity of attacks, Pain, Patient global, Withdrawals and Serious adverse events. Fixed effects models were used to calculate mean differences (MD) or standardized mean differences (SMD) for continuous outcomes and pooled risk ratios (RR) for dichotomous outcomes. Heterogeneity was determined and was considered significant if I^2>50%.

Results: Seven trials (4 with tadalafil, 2 sildenafil, 1 vardenafil) with an average duration of 5 weeks totaling 255 subjects were included; 97% had RP secondary to systemic sclerosis; SSc). Trial quality ranged from low to moderate. Many individual trials were not significantly different from placebo. PDE5 reduced the frequency of attacks by 4.2 attacks/week (95% CI 2.01-6.38) from a baseline of 26 attacks/week, or relative %change in the frequency of attacks of 22% reduction (95% CI 10-33%). Duration of attacks decreased by 6 minutes (95% CI 0.5-11); relative %reduction of 24% (95% CI 2-47%). Severity of RP attacks was assessed in one trial. Raynaud's Condition Score (RCS) improved by 0.49 cm (95% CI 0.02-0.95). Pain (VAS 0-10) improved by 1.06 (95% CI 0.09-2.03) with 25% decrease in relative %pain. The relative %reduction in disability was 39% (95% CI 18-60%). The relative risk of withdrawals was 4.42 (higher in PDE5 group). The number needed for an additional harmful outcome (NNTH) was 32 (95% CI 7 to 717). Figure shows the reduction of RP frequency and duration of attacks. Samples were too small to detect differences between PDE5 drugs.

Conclusion: PDE5 medications seem to be effective in treating RP associated with SSc.



Disclosure: J. E. Pope, None; **F. Rirash**, None; **P. Tingey**, None; **S. Harding**, None; **L. J. Maxwell**, None; **J. Pardo**, None; **E. Ghogomu**, None; **P. Tugwell**, None; **G. A. Wells**, None.

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Abstract Number: 2978

Longitudinal Assessment of Gastrointestinal Symptoms in the Prospective Registry of Early Systemic Sclerosis Cohort

Tracy M. Frech[1], Maureen Murtaugh[2], Jessica K. Gordon[3], Robyn T. Domsic[4], Ami A. Shah[5], Faye N. Hant[6], Shervin Assassi[7], Monique E. Hinchcliff[8], Elana J. Bernstein[9], Virginia D. Steen[10], Victoria K. Shanmugam[11,12] and Dinesh Khanna[13], [1]Div of Rheumatology, University of Utah, Salt Lake City, UT, [2]University of Utah, Salt Lake, UT, [3]Rheumatology, Hospital for Special Surgery, New York, NY, [4]Medicine - Rheumatology, University of Pittsburgh, Pittsburgh, PA, [5]Rheumatology, Johns Hopkins University School of Medicine, Baltimore, MD, [6]Dept of Medicine, Medical University of South Carolina, Charleston, SC, [7]Rheumatology, University of Texas Medical School at Houston, Houston, TX, [8]Division of Rheumatology, Division of Rheumatology, Northwestern University, Feinberg School of Medicine, Chicago, IL, [9]Columbia University, New Yory, NY, [10]Rheumatology, Georgetown University Medical Center, Washington, DC, [11]Director, Division of Rheumatology, The George Washington University, Washington, DC, [12]Division of Rheumatology, The George Washington University, Washington, DC, [13]Division of Rheumatology, University of Michigan, Ann Arbor, MI

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Background/Purpose: The Prospective Registry of Early Systemic Sclerosis (PRESS) is a multicenter incident cohort study of patients with early diffuse cutaneous systemic sclerosis (dcSSc; < 2 years duration). We previously reported that gastrointestinal tract (GIT) symptoms are common at baseline in this cohort and are not associated with the choice of immunosuppressant agent. The goal of this study was to analyze the longitudinal assessment of GIT symptoms in early dcSSc as captured by the GIT 2.0.

Methods: PRESS data was collected longitudinally at various SSc centers using REDCap, a NIH funded database including demographics, disease characteristics, physical exam data, and patient-reported outcomes. PRESS patients who had a complete gastrointestinal tract questionnaire (GIT 2.0), a validated instrument for evaluation of patient-reported outcomes involving the GIT, at baseline and at one and/or two-years were included in this analysis. Statistical analysis was performed using SAS version 9.4.

Results: A total of 83 of 92 PRESS patients had a GIT 2.0 completed at the baseline visit. Thirty-seven of 15 and 12 of 15 had GIT 2.0 at one- and two- year follow-up respectively. At baseline, the mean age of this patient population was 48.9 (SD 15.1) years. Fifty-eight were women. The average BMI was 25.9 (SD 4.8). At baseline, upper GIT symptoms were more common than lower GIT symptoms. Medication use did not account for these baseline GIT 2.0 severity differences (proton pump inhibitors p=0.47; methotrexate p=1; or mycophenolate mofetil p=0.27). At one-year follow-up, 13 had worse scores for total GIT 2.0, 2 remained the same and 13 had improved scores. At two-year follow-up 6 had worse scores for total GIT 2.0 and 7 had improved total scores (Table 1). No medication changes accounted for these changes. Soilage was not present at baseline in our population, but developed in some patients at the two-year follow-up (Table 2). No PRESS patients reported a complete absence of GIT symptoms.

Conclusion: Gastrointestinal symptoms captured by the GIT 2.0 are universal in early dcSSc. Variability in change of GIT 2.0 scores may reflect variation in disease progression and GIT involvement; however the pathogenesis of developing soilage in this population wants further study.

Table 1: Severity of GIT Illness in the PRESS Population

Total GIT 2.0	Baseline (n=83)	Year 1 (n=37)	Year 2 (n=12)
Mild to Moderate	58	28	10
Moderate	17	4	0
Severe to Very Severe	8	5	2

Table 2: PRESS patient gastrointestinal symptoms captured as components of GIT 2.0 (median, Interquartile range*)

	Baseline (n=83)		Year 1 (n=37)		Year 2 (n=12)	
Variable	**Median**	**IQR***	**Median**	**IQR**	**Median**	**IQR**
Total GIT 2.0	0.32	0.45	0.19	0.33	0.26	0.34
Reflux	0.38	0.75	0.63	0.75	0.5	0.56
Distention/Bloating	0.5	1.25	0.75	0.75	0.63	0.63
Fecal Soilage	0	0	0	0	0	0.5
Diarrhea	0	0.5	0.0	0.5	0	0
Social Functioning	0	0.5	0.17	0.5	0	0.25
Emotional Well-being	0	0.22	0	0.22	0.06	0.22
Constipation	0	0.5	0	0.5	0	0.5

Disclosure: T. M. Frech, None; **M. Murtaugh**, None; **J. K. Gordon**, Bayer, 5; **R. T. Domsic**, Biogen-Idec, 5,Bayer, 5; **A. A. Shah**, None; **F. N. Hant**, None; **S. Assassi**, None; **M. E. Hinchcliff**, None; **E. J. Bernstein**, None; **V. D. Steen**, None; **V. K. Shanmugam**, None; **D. Khanna**, Bristol-Myers Squibb, 2,EMD Serono, 2,Genentech and Biogen IDEC Inc., 2,Bayer, 5,Biogen Idec, 5,Cytori, 5,EMD Serono, 5,Forward, 5,Genentech and Biogen IDEC Inc., 5,Gilead, 5,Lycera, 5,Seattle Genetics, 5.

Abstract Number: 2979

Laser Speckled Imaging and Videomicroscopy Assessment of Sublingual Perfusion in Systemic Sclerosis and Healthy Controls

Mark Sievert[1], Daniel R. Machin[2], Anthony J. Donato[2], Maureen Murtaugh[3], John D. Pauling[4], Robyn T. Domsic[5], Lee S. Shapiro[6] and Tracy M. Frech[7], [1]University of Utah, Salt Lake City, UT, [2]University of Utah and Salt Lake Veterans Affair Medical Center, Salt Lake, UT, [3]University of Utah, Salt Lake, UT, [4]Upper Borough Walls, Royal National Hospital for Rheumatic Disease, Bath, United Kingdom, [5]Medicine - Rheumatology, University of Pittsburgh, Pittsburgh, PA, [6]Steffens Scleroderma Center, Albany, NY, [7]Div of Rheumatology, University of Utah, Salt Lake City, UT

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Background/Purpose: Our group has previously described the sublingual frenulum abnormalities in systemic sclerosis (SSc, scleroderma). The goal of this project was to assess microvascular abnormalities in SSc by comparing perfusion of the frenulum using laser speckle contrast imaging (LSCI) in patients with SSc and healthy controls (HC). As we have observed sublingual microvascular abnormalities in SSc patients using a different technique (i.e., video-microscopy) we compared the inter-day variability of LSCI and video-microscopy of the sublingual mucosa by the Glycocheck Measurement device and software analysis in the HC.

Methods: Ten patients fulfilling 2013 ACR/EULAR classification criteria for SSc and 17 HC were recruited from the University of Utah SSc clinic and local community. Baseline perfusion (in arbitrary flux units [fu]) of the frenulum was assessed using LSCI in patients with SSc during a clinical visit and HC. Video-microscopy was assessed in 7 HC, and microvascular health was determined by penetration of red blood cells into the microvessel wall barrier region (perfused barrier region, PBR) using the Glycocheck Measurement device and software. To determine inter-day variability, HC subjects completed LSCI and video-microscopy on an additional day. All subjects were at least 2 hours without any exercise, caffeine, or food.

Results: The mean age of the SSc population was 55.1 (SD 13.7) years. Median SSc disease duration from first non-Raynaud symptom was 9.9 years (SD 9.9). When LSCI was applied to the frenulum, the perfusion index was 2308 fu (1810-3203). The perfusion index correlated negatively with disease duration, -0.64 ($p < 0.05$), but the was not significantly different from the healthy control population (2794 fu; 1368-5292). The mean age of the healthy control population was 35.9 (SD 6.25). In the healthy control population the coefficient of variation for the LSCI was 37.8±29.1% vs. coefficient of variation for Glycocheck PBR score is 5.0±2.3% ($p=0.011$).

Conclusion: This feasibility study suggests perfusion of the sublingual frenulum can be assessed by both LSCI and videomicroscopy. Although we have previously shown a decrement in microvascular health in SSc compare with HC using videomicroscopy, there were

no differences between SSc and HC using LSCI. Considering the differences in measurement variability, proper perfusion measurement of the sublingual frenulum microvasculature may be assessed more accurately by use of videomicroscopy

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Disclosure: M. Sievert, None; **D. R. Machin**, None; **A. J. Donato**, None; **M. Murtaugh**, None; **J. D. Pauling**, None; **R. T. Domsic**, Biogen-Idec, 5,Bayer, 5; **L. S. Shapiro**, None; **T. M. Frech**, None.

Abstract Number: 2980

Assessment of Sublingual Frenulum Perfusion in Systemic Sclerosis

Tracy M. Frech[1], Daniel R. Machin[2], Phillip E. Gates[2], Robyn T. Domsic[3], Lee S. Shapiro[4], John D. Pauling[5] and Anthony J. Donato[2], [1]Div of Rheumatology, University of Utah, Salt Lake City, UT, [2]University of Utah and Salt Lake Veterans Affair Medical Center, Salt Lake, UT, [3]Medicine - Rheumatology, University of Pittsburgh, Pittsburgh, PA, [4]Steffens Scleroderma Center, Albany, NY, [5]Upper Borough Walls, Royal National Hospital for Rheumatic Disease, Bath, United Kingdom

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Background/Purpose: SSc is characterized by vasculopathy that precedes fibrosis and progresses to end-stage vascular manifestations such as malnutrition due to gastro-intestinal tract (GIT) involvement. Clinical management of SSc is a challenge because of limited information on the underlying pathophysiology. In this preliminary study, we aimed to determine if there were differences in sublingual microvascular health in SSc patients with/without sublingual frenulum abnormalities. We also examined the association between microvascular health and GIT scores in a pooled subset of patients.

Methods: Twenty-four patients fulfilling the 2013 ACR/EULAR classification criteria for SSc were recruited from the SSc clinic at the University of Utah. Patients had their sublingual frenulum assessed as previously described by our group and completed the GIT 2.0 validated questionnaire. Patients were grouped according to absence/presence of sublingual frenulum thickening/shortening (Fren-/Fren+, respectively). The Glycocheck videomicroscopic sublingual device was used to image the sublingual frenulum in SSc patients. This device is equipped with software that identifies > 3000 vascular segments and automatically starts when image quality is within acceptable range and automatically stops when a sufficient number have been collected. The device provides measurements of the number of well perfused vessels / mm^2 tissue surface, total number of vessels / mm^2 tissue surface, longitudinal vessel fraction that is filled with red blood cells (RBC), the fraction of vessels out of the total number that are well perfused (Dval/Dvot), RBC filled vessel density, penetration of red blood cells into the microvessel wall barrier region (perfused barrier region, PBR), and a MicroVascular Health score (MVH) which is a combined effect of these parameters (low MVH Score reflects low density and/or high PBR value = poor microvascular health). Additionally, a clinical feature of disease, SCTC GIT 2.0 was recorded examined for association across variables of microvascular health. Two tailed independent samples t-test; one-tailed Pearson correlation; mean±SE; alpha $P<0.05$.

Results: Twelve patients were recruited to each group (age, years): Fren- 57±3; Fren+ 59±4; one male per group). There were significant differences between groups in valid microvascular density (Fren- 240±23, Fren+ 149±22, $p<0.05$), total microvascular density (Fren- 328±30; Fren+ 210±29, $p<0.05$) and MVH score (Fren- 1.01±0.14; Fren+ 0.57±0.12, $p<0.05$). There were no differences in RBC filling, PBR, or Dval/Dtot (all $p>0.05$). GIT 2.0 score was negatively associated with valid microvascular density ($r=-0.39$, $p<0.05$), RBC filling ($r=-0.39$, $p<0.05$), and MVH score ($r=-0.44$, $p<0.05$). There was a trend for a negative association with total microvascular density ($r=-0.34$, $p=0.08$), PBR ($r=-0.29$, $p=0.11$), and Dval/Dtot ($r=-0.26$, $p=0.14$).

Conclusion: This feasibility study confirms that the sublingual frenulum may be indicative of perfusion abnormalities in SSc. Moreover, GIT heath scores were inversely associated with variables of microvascular health. The functional significance and pathogenesis of this abnormality warrants further study.

Disclosure: T. M. Frech, None; **D. R. Machin**, None; **P. E. Gates**, None; **R. T. Domsic**, Biogen-Idec, 5,Bayer, 5; **L. S. Shapiro**, None; **J. D. Pauling**, None; **A. J. Donato**, None.

Abstract Number: 2981

Measurement of Tissue Damage in Scleroderma Using Digital Mammographic Xrays: A Proof of Concept Study

John Highton[1], Terence Doyle[2] and Simon Stebbings[3], [1]Dept of Medicine, University of Otago, Dunedin, New Zealand, [2]Medicine, University of Otago, Dunedin, New Zealand, [3]Dunedin School of Medicine, University of Otago, Dunedin, New Zealand
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Background/Purpose: We have used digital mammographic soft tissue Xrays of the fingers from patients with Scleroderma and related conditons to show damage related to the disease. Images clearly show skin thickening, fibrosis of subcutaneous tissues, calcinosis, tuft resorption and loss of tissue from the finger tips. In this study we developed a scoring sytem to give a semi-quantitative measure of these changes to investigate the hypothesis that this method could be used as a damage index and outcome measure in Scleroderma.

Methods: A Sectra Microdose C30 machine was used to take digital soft tissue images with four-finger AP views and lateral views of the index and middle fingers. Images were viewed by 2 authors and consensus reached on mild, moderate and severe changes (scored 1,2,3) for fibrosis, calcinosis and tuft resorption. Skin thickness was measured at 3 sites in each finger and averaged. Loss of tissue at the fingertip was measured according to Yune et al. Measurements were converted to scores for consistency.

Results: Xrays were scored for 6 normal subjects, 15 with lcSSc, 1 MCTD (included with lcSSc) and 7 dcSSc. Scores for calcification were higher in lcSSc for calcification: 1.2 vs 0.8 for dcSSc. Scores for tuft resorption and skin thickening were higher in dcSSc vs lcSSc: 1.8 vs 1.1 and 1.9 vs 1.1. Total damage scores were 0.17±0.1, 6.3±3.8 and 7.6±3.0 for normals, lcSSc and dcSSc respectively. These values were not statistically different. However, subjects with dcSSc had significantly more damage per year of disease duration: 1.2±0.8 vs 0.4±0.3, p=0.03.

Conclusion: We have explored the possibility that soft tissue Xrays of the fingers taken using digital mammographic methods could be used to produce a semiquantitative measure of tissue damage in Scleroderma, akin to a Sharp Index in RA. The fact that we were able to demonstrate significantly faster accumulation of damage with dcSSc compared to lcSSc even in a small number of subjects provides proof of the concept and warrants further development of this method as an outcome measure in Scleroderma.

Disclosure: J. Highton, None; **T. Doyle**, None; **S. Stebbings**, None.

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Abstract Number: 2982

Blood Perfusion in Different Skin Areas of Hands in Primary Raynaud's Phenomenon and Systemic Sclerosis Patients

Alberto Sulli[1], Barbara Ruaro[1], Amelia Chiara Trombetta[1], Vanessa Smith[2], Carmen Pizzorni[1], Sabrina Paolino[1] and Maurizio Cutolo[1], [1]Research Laboratory and Academic Division of Clinical Rheumatology, Department of Internal Medicine, IRCCS A.O.U. San Martino-IST, University of Genova, Genoa, Italy, Genoa, Italy, [2]Department of Rheumatology, Ghent University Hospital, Ghent University, Ghent, Belgium
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Background/Purpose: Peripheral blood perfusion is reduced in patients affected by both primary (PRP) or secondary Raynaud's

phenomenon (SRP) (1-2). The objective of this study was to investigate blood perfusion (BP) in different skin areas of patients with PRP, SRP to systemic sclerosis (SSc), and healthy subjects (CNT), looking for differences between the groups.

Methods: Seventy SSc patients (new ACR/EULAR criteria) (3) (mean age 63±12 years, mean disease duration 6±5 years), 31 PRP patients (LeRoy criteria) (4) (mean age 48±18 years, mean Raynaud duration 3±2 years) and 68 CNT (mean age 59±19 years) were enrolled during winter time, after informed consent. BP was assessed by Laser speckle contrast analysis (LASCA) at the level of fingertips, periungual areas, dorsal and palmar aspect of 3rd finger bilaterally, dorsum and palm of both hands, and the average BP calculated as perfusion units (PU) (1). Nailfold videocapillaroscopy (NVC) was also performed to distinguish between PRP and SRP, and to detect the proper pattern of nailfold microangiopathy ("early", "active" or "late") (5). Patients were not taking vasodilator drug since al least two weeks.

Results: Both PRP and SSc patients showed a statistically significant lower BP than CNT at the level of fingertips (median 86, 88, 186 PU, respectively, $p<0.0001$), periungual (median 75, 76, 142 PU, respectively, $p<0.0001$), palmar aspect of 3rd finger (median 71, 81, 134 PU, respectively, $p<0.0001$), and palm areas (median 61, 78, 112 PU, respectively, $p<0.0001$). On the contrary, the three groups displayed similar BP values at the level of other areas of hands. Of interest, PRP patients showed lower BP values than SSc patients in all areas of hand, even if BP was found statistically different only at the level of both palmar aspects of 3rd finger ($p=0.04$) and palm of hands ($p=0.008$). The gradients of BP fingertip-phalanx-palm and periungual-phalanx-dorsum were significantly lower in PRP than in SSc patients ($p<0.0001$), as well as significantly higher in CNT when compared with both PRP and SSc patients ($p<0.0001$). A statistically significant progressive decrease of BP was observed in SSc patients with progressive pattern of nailfold microangiopathy ("early", "active", and "late") at the level of fingertips, periungual, palmar aspect of 3rd fingers and palm areas ($p<0.05$). Moreover, BP was significantly lower in PRP than in SSc patients with the "early" pattern of microangiopathy in all areas ($p<0.04$), with the exception of dorsal phalanx and hand dorsum.

Conclusion: By considering a small cohort of patients, BP of hand was found lower in PRP than in SSc patients with the "early" NVC pattern of microangiopathy. Also the gradients of perfusion between distal and proximal areas of hand were significantly lower in PRP than in SSc patients. The clinical value of this new early finding is matter of further analysis**.**

References: 1. Ruaro B, et al. Ann Rheum Dis 2014;73:1181-5. 2. Rosato E, et al. Rheumatology 2009;36:2257-63. 3. van den Hoogen F, et al. Ann Rheum Dis 2013; 72:1747-55. 4. LeRoy EC, et al. Clin Exp Rheumatol.1992;10:485-8. 5. Sulli A, et al. Arthritis Rheum. 2012;64:821-5.

Disclosure: A. Sulli, None; **B. Ruaro**, None; **A. C. Trombetta**, None; **V. Smith**, None; **C. Pizzorni**, None; **S. Paolino**, None; **M. Cutolo**, None.

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Abstract Number: 2984

Scleroderma Bronchoalveolar Lavage Fluid Thrombin Activity: Correlation with Pulmonary Function

Merrideth Ashley Morris[1], Tanjina Akter[2], Paul Nietert[3], Galina S. Bogatkevich[2] and Richard Silver[4], [1]Medical University of South Carolina, Charleston, SC, [2]Division of Rheumatology & Immunology, Medical University of South Carolina, Charleston, SC, [3]Division of Public Health Science, Medical University of South Carolina, Charleston, SC, [4]Division of Rheumatology and Immunology, Medical University of South Carolina, Charleston, SC

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SESSION INFORMATION

Session Date: Tuesday, November 10, 2015

Session Title: Systemic Sclerosis, Fibrosing Syndromes and Raynaud's - Clinical Aspects and Therapeutics Poster III

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose:

Multiple lines of evidence identify thrombin as an important mediator of lung fibrosis in systemic sclerosis (SSc). In addition to demonstrating dramatically high levels of thrombin activity in SSc bronchoalveolar lavage fluid (BALF), increased expression of the thrombin receptor PAR-1 in SSc-ILD tissue has also been shown. Previous studies established that after brief exposure to thrombin *in vitro*, normal lung fibroblasts differentiate to a SSc-like myofibroblast phenotype. In addition, it has been demonstrated that a direct thrombin inhibitor, dabigatran etexilate, prevents cleavage of the extracellular domain of the PAR-1 receptor, and in doing so inhibits thrombin-induced differentiation of lung fibroblasts to the myofibroblast phenotype, while also decreasing CTGF, α-SMA, and collagen

type I in SSc lung fibroblasts. Although there is much evidence to support a central role for thrombin in SSc-ILD, to date there has been no attempt to correlate thrombin activity to pulmonary function. Our goal is to determine if the correlation between thrombin activity and decline in pulmonary function does exist.

Methods:

Thrombin activity was measured using a fluorometric assay (Morita, et al.). Samples were analyzed in duplicate. Samples included existing specimens from MUSC patients, as well as stored BALF specimens from Scleroderma Lung Study (SLS-1) subjects (treated and untreated) for whom there were serial PFT data (baseline and every 3 months for up to 24 months). A Wilcoxon rank sum test was used to compare the thrombin levels between cases and controls, and Spearman correlations were calculated to investigate the associations between thrombin and PFT metrics at various time points. General linear mixed models (GLMMs) were also constructed to assess whether thrombin was associated with decline in PFT metrics over time among the SSc patients.

Results:

BALF samples were obtained from 75 patients with SSc. All patients fulfilled the 2013 ACR/EULAR classification for systemic sclerosis. Four samples from patients without SSc served as controls. Eighty-five percent of patients in our cohort were female, and the proportion of Caucasian and African American patients was equal (49%; 2% Hispanic). As shown in the past, the thrombin level for cases was significantly higher than controls (p=0.02). Thrombin levels were not meaningfully correlated with any of the PFT metrics at any point in time (all correlations <0.3, all p-values >0.15), and thrombin levels were not significantly (all p-values >0.22) associated with declines in PFT metrics over time.

Conclusion:

Thrombin activity may not be a useful biomarker for decline in pulmonary function, but is increased in SSc cases when compared to controls.

Disclosure: M. A. Morris, None; **T. Akter**, None; **P. Nietert**, None; **G. S. Bogatkevich**, None; **R. Silver**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/scleroderma-bronchoalveolar-lavage-fluid-thrombin-activity-correlation-with-pulmonary-function

Abstract Number: 2985

Mycophenolate Mofetil (MMF) Use in Systemic Sclerosis (SSc) Patients with a Designation of Elevated Systolic Pulmonary Artery Pressure (sPAP): Forced Vital Capacity (FVC), Outcomes and Survival from the European Scleroderma Trials and Research (EUSTAR) Database

Lesley Ann Saketkoo[1], Dörte Huscher[2], Christopher P. Denton[3], Gabriela Riemekasten[4], Virginia D. Steen[5], Oliver Distler[6] and EUSTAR member centres, [1]Tulane University Lung Center, New Orleans Scleroderma and Sarcoidosis Patient Care and Research Center, New Orleans, LA, [2]Charité-University Hospital and German Rheumatism Research Centre, Berlin, Germany, [3]Rheumatology and Connective Tissue Diseases, University College London, London, United Kingdom, [4]Clinic of Rheumatology, University of Luebeck, Lübeck, Germany, [5]Rheumatology, Georgetown University Medical Center, Washington, DC, [6]Research of Systemic Autoimmune Diseases, Division of Rheumatology, University Hospital Zurich, 8952 Schlieren, Switzerland
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Session Time: 9:00AM-11:00AM

Background/Purpose : SSc related PH carries a high mortality; with SSc-PH related to restrictive lung disease (RLD) having worse prognosis and more rapid time to death.Speculation regarding potential MMF anti-fibrotic and anti-remodeling effects on parenchymal lung and vascular intimal fibrosis were supported by two prior large observational studies from the US and the UK. Here, we analyzed predictive markers of mortality of SSc patients with PH stratified for RLD and for MMF use in the prospective EUSTAR database of > 12,000 SSc patients.

Methods : SSc patients with a registry designation of elevated sPAP by either right heart catheterization (RHC) or, in absence of RHC, by echocardiography were subsequently stratified by an FVC of >70% or ≤ 70% predicted near the time of designationand by MMF

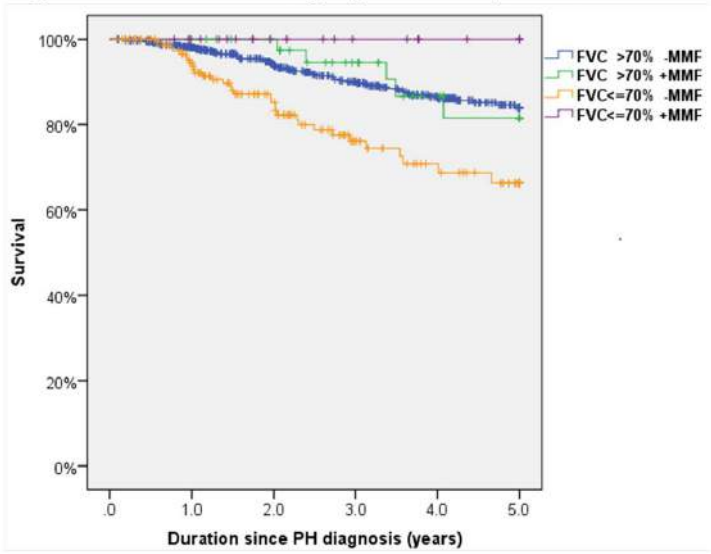
use. MMF <6 months or cyclophosphamide use were excluded. Calculations are derived from one-way ANOVA. Categorical variables were compared with Chi square. Comparison of survival was done with Kaplan-Meier analysis.

Results : Of 11,721 patients fulfilling ACR-EULAR criteria, 1,264 matched criteria and had baseline FVC results coincident with PH diagnosis, of those 965 had a baseline FVC of >70% with 43 on MMF and 927 without; and 294 had a baseline FVC≤70% with 22 on MMF and 272 without. Overall, diagnosis was made by RHC in 263/1264 patients and in the remaining patients by echo. There were no differences in disease duration. The FVC≤70 MMF+ was significantly younger with worse NYHA status and disease activity. In the FVC≤70 (RLD) groups, FVC, DLCO and FVC:DLCO ratio were significantly lower while the presence of fibrosis on HRCT and diffuse SSc subtype were significantly higher. Survival assessed numerically and by Kaplan-Meier analysis was significantly the worse in the FVC≤70 without MMF and the best in the FVC≤70 with MMF across years 2 (p=0.001) and 3, 4, 5 years (p<0.0001) despite a significantly worse disease activity score and NYHA class over the 4 groups.

Table 1. Comparison between the baseline characteristics of the four groups at time of PH diagnosis. Values reported in mean, unless otherwise stated.

	FVC >70% +MMF	FVC >70% - MMF	FVC <=70% +MMF	FVC <=70% - MMF	
Number (1264 total)	43	927	22	272	
Age – yrs, mean	59±11.6	63.4±12	47.9±11.2	58.3±13	p<0.001
Disease Duration yrs, mean	8.9±10.4	11.5±9.2	9.2±7.7	10.2±8.6	p=0.075
Female sex%(n)	65.1 (28)	86 (803)	63.6 (14)	80.1 (218)	p<0.001
EScSG Disease Activity Index >=3	20.9%(9)	23.9%(222)	50.0% (11)	38.6%(105)	p<0.001
Diffuse cutaneous %(n)	48.8 (21)	21.6 (198)	68.2 (15)	53% (142)	P<0.001
Skin score, mean	9.1+6.9	7.7+6.8	12.8±8.4	10.8±9.1	p<0.001
Scl-70 Antibody	40(16)	24.3(198)	66.7(14)	56.8(134)	
Presence of Fibrosis on HRCT %(n)	63.6 (21)	44.2 (258)	85.7 (18)	77.5 (162)	p<0.001
NYHA Class III/IV %(n)	27.5(11)	23.1(199)	66.7 (14)	49.8 (123)	p<0.001
FVC% predicted	89.2±15	97.8±17.6	56.0±9.4	56.5±10.4	p< 0.001
DLCO % predicted	50.8±17.1	62.1±20.2	40.9±13	43±17	p<0.001
FVC:DLCO Ratio	2.0±0.7	1.7±0.6	1.5±0.5	1.5±0.5	p<0.001
RHC performed %(n)	25.6 (11)	21.2 (196)	40.9 (9)	24.6 (67)	

Diagram 1. Survival across all groups stratified by FVC and MMF use.



Conclusion : Data trends in this registry survey suggest MMF might be associated with beneficial survival in SSc PH. Limitations of the study include mixed diagnostic methods of PH diagnosis given challenges of accuracy of echocardiogram as well as inability to assess hemodynamics in non-RHC diagnoses and therefore inability to assign WHO PH Group classification. These findings warrant further analysis of international PH-SSc cohorts to determine whether a prospective controlled trial may be developed to test the mechanisms and impact of MMF in treating this important complication of SSc.

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Abstract Number: 2986

Systemic Sclerosis Patients on Intensive Care Unit – Reasons for Admission and Determinants of Outcome

Svetlana I. Nihtyanova[1], Francesco Figorilli[2], Christopher P. Denton[3], Banwari Agarwal[2] and Voon H. Ong[1], [1]Rheumatology, UCL Division of Medicine, London, United Kingdom, [2]ITU, Royal Free Hospital, London, United Kingdom, [3]Rheumatology and Connective Tissue Diseases, University College London, London, United Kingdom

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Session Time: 9:00AM-11:00AM

Background/Purpose:

Little has been published on systemic sclerosis (SSc) patients requiring admission to Intensive Care Unit (ICU) for organ support; published results suggest respiratory failure due to end-stage lung disease the most frequent reason for admission and need for mechanical ventilation a significant predictor of poor outcome.

Methods:

Retrospective case note review of consecutive SSc patients admitted to ICU over a fifteen year period was analysed for patient demographic and disease characteristics, acute precipitating event, end organ damage requiring organ system support on ICU and outcome.

Results:

Fifty-one SSc patients were identified, 80% female, 43% with diffuse cutaneous SSc and 41% with overlap syndromes; 24% (n=12) had clinically significant pulmonary fibrosis (PF), 12% (n=6) had pulmonary hypertension (PH), 14% (n=7) had cardiac SSc, 29% (n=15) had SSc renal crisis (SRC) and 12% (n=6) had severe SSc bowel involvement.

Sepsis (37%, n=19), pneumonia in particular (n=16), accounted for the single most frequent precipitant requiring ICU admission. Other primary reasons for admission included SRC (8%, n=4), cardiac (4%, n=2), neurological (6%, n=3) and non-infective pulmonary causes (6%, n=3). A large proportion of patients (29%, n=15) were on ICU post elective surgery.

All surgical, neurological or SRC admissions survived to ICU and hospital discharge. Sepsis on the other hand was associated with nearly 4 times higher risk of death within 1 year from ICU admission (HR 3.8, p=0.002) with 52% of these patients dying while on ICU compared to 13% of the other admissions (p=0.003).

Elective surgical patients spent up to 3 days on ICU, while the medical (n=33) and emergency surgical admissions (n=3) spent between 1 and 45 days (median 4, IQR 1, 19). On the day of admission 22% (n=8) required non-invasive mechanical ventilation, 61% (n=22) invasive mechanical ventilation, 22% (n=8) renal replacement therapy and 36% (n=13) vasopressors. Fourteen (39%) died while on ICU. While the use of mechanical ventilation and renal replacement therapy was not associated with negative short-term outcome, patients who needed vasopressor therapy were at nearly 6 times higher odds of dying while on ICU (OR 5.7, p=0.011).

Overall survival from ICU admission was 67% on day 7, 56% at 1 month and 44% at 1 year. Gender, subset, antibody specificities and overlap features did not associate with survival after ICU admission. On the other hand, compared to patients without significant organ involvement, those with PH had nearly 8 time increase of the risk of death (HR 7.7, p=0.024) and those with severe bowel disease had more than 5 times increase in the risk of death (HR 5.5, p=0.020). SRC on the other hand, was associated with good prognosis (HR 0.2, p=0.010).

Conclusion:

ICU outcomes of patients with underlying SSc seem to be better than previously reported, with best prognosis observed in post-surgical and SRC patients. Sepsis and pneumonia are most common medical precipitating events and are associated with poor prognosis. Mechanical ventilation and renal replacement therapy need is likely to reflect severity of underlying chronic disease and acute derangement and their use therefore should be guided by the overall clinical context.

Disclosure: S. I. Nihtyanova, None; **F. Figorilli**, None; **C. P. Denton**, GlaxoSmithKline, 2,Actelion Pharmaceuticals US, 5,GlaxoSmithKline, 5,Serono, 5,Inventiva, 5,CSL Behring, 2,Bayer, 5; **B. Agarwal**, None; **V. H. Ong**, None.

reasons-for-admission-and-determinants-of-outcome

Abstract Number: 2987

An EULAR Study Group Pilot Study on Reliability of Simple Capillaroscopic Definitions to Describe Capillary Morphology in Rheumatic Diseases

Vanessa Smith[1], **Sam Beeckman**[2], Ariane L. Herrick[3], Saskia Decuman[4], Ellen Deschepper[5], Filip De Keyser[6], Oliver Distler[7], Ivan Foeldvari[8], Francesca Ingegnoli[9], Ulf Müller-Ladner[10], Valeria Riccieri[11], Gabriela Riemekasten[12], Alberto Sulli[13], Alexandre E. Voskuyl[14] and Maurizio Cutolo[13], [1]Department of Rheumatology, Ghent University Hospital, Ghent University, Ghent, Belgium, [2]Department of Rheumatology, Ghent University, Ghent University Hospital,, Ghent, Belgium, [3]Centre for Musculoskeletal Research, University of Manchester, Manchester Academic Health Science Centre, Manchester, United Kingdom, [4]Department of Rheumatology, UGent, Ghent, Belgium, [5]Biostatistics Unit, Biostatistics Unit, Ghent University, Ghent, Belgium, [6]Rheumatology, Ghent University Hospital, Ghent, Belgium, [7]Research of Systemic Autoimmune Diseases, Division of Rheumatology, University Hospital Zurich, 8952 Schlieren, Switzerland, [8]Hamburger Zentrum für Kinder-und Jugendrheumatologie, Hamburg, Germany, [9]Division of Rheumatology, Istituto Gaetano Pini, Department of Clinical Sciences & Community Health, University of Milano, Milano, Italy, [10]Internal Medicine and Rheumatology, Justus-Liebig-University of Giessen, Kerckhoff-Klinik, Bad Nauheim, Germany, [11]Cattedra di Reumatologia, Dip Clinica e Terapia Medica, Sapienza Università di Roma, Roma, Italy, [12]Clinic of Rheumatology, University of Luebeck, Lübeck, Germany, [13]Research Laboratory and Academic Division of Clinical Rheumatology, Department of Internal Medicine, IRCCS A.O.U. San Martino-IST, University of Genova, Genoa, Italy, Genoa, Italy, [14]Rheumatology, Amsterdam Rheumatology and immunology Center, location VU University medical center, Amsterdam, Netherlands

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Session Time: 9:00AM-11:00AM

Background/Purpose: The EULAR study group on Microcirculation in Rheumatic Diseases (RD) aims to build an international network of centres of excellence to facilitate collaboration and exchange knowledge within Europe. One of its aims is to study natural evolution of microvascular morphology in RD. To this end standardisation of morphological interpretation across diseases is paramount. Hence, the objective is to propose simple capillaroscopic definitions for interpretation of single capillaroscopic morphologies and assess their interrater reliability. **Methods:** The simple definitions to assess morphology were: 1) “normal”: hairpin, tortuous or crossing; 2) “abnormal”: not hairpin, tortuous or crossing; 3) “not evaluable”: whenever rater doubted in classifying between normal and abnormal (figure 1). Based upon an aimed kappa of 0.80 and default prevalences of normal (0.4), abnormal (0.4) and not evaluable (0.2) capillaries, 87 capillaries evaluated by two raters were necessary to obtain a half width of the 95% confidence interval (CI) of no larger than 0.2. Consequently, 90 single capillaries were presented to 3 groups of raters: experienced independent raters, n = 5; attendees to the 6th EULAR course on capillaroscopy, n = 34; novices after a 1 hour course, n = 11. Interrater agreement was assessed by calculation of proportion of agreement and by kappa coefficients. **Results:** Mean kappa was 0.47 (95% CI: 0.39-0.54) for expert raters, 0.40 (0.36-0.44) for attendees and 0.46 (0.41-0.52) for novices, with overall agreements of 67% (63-71), 63% (60-65) and 67% (63-70) respectively. Comparing only “normal” vs. “abnormal and not evaluable” capillaries did increase the kappa: 0.51 (0.37-0.65), 0.53 (0.49-0.58), and 0.55 (0.49-0.62). On the condition that the capillaries were classifiable, the mean kappa was 0.62 (0.50-0.74) for expert raters (n = 65), 0.76 (0.69-0.83) for attendees (n = 20) and 0.81 (0.74-0.89) for novices (n = 44). **Conclusion:** This study shows moderate reliability of “simple” capillaroscopic definitions to describe morphology of individual capillaries by rheumatologists with different expertise on the topic. Novices are capable to distinguish normal from abnormal capillaries by means of a 1-hour training session. Consequently, when encountering an abnormal capillary, they may refer the patient to an expert in nailfold videocapillaroscopy.

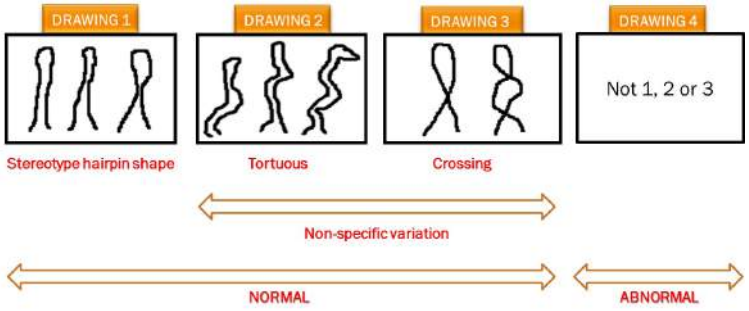

Figure 1: Information given to the raters concerning the definitions of normal and abnormal capillaries

Disclosure: V. Smith, None; **S. Beeckman**, None; **A. L. Herrick**, None; **S. Decuman**, None; **E. Deschepper**, None; **F. De Keyser**, None; **O. Distler**, None; **I. Foeldvari**, None; **F. Ingegnoli**, None; **U. Müller-Ladner**, None; **V. Riccieri**, None; **G. Riemekasten**, None; **A. Sulli**, None; **A. E. Voskuyl**, None; **M. Cutolo**, None.

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Abstract Number: 2988

Novel Use of Musculoskeletal Ultrasound (MSUS) to Measure Ulcers in the Skin of Systemic Sclerosis (SSc) Patients.

Yossra Suliman[1,2], Veena K. Ranganath[2], Suzanne Kafaja[3] and Daniel E. Furst[4], [1]Rheumatology and Rehabilitation department, Assiut university, Faculty of Medicine,, Assiut, Egypt, [2]Medicine, Division of Rheumatology, David Geffen School of Medicine, Los Angeles, CA, [3]Medicine/Rheumatology, University of California Los Angeles, David Geffen School of Medicine, Los Angeles, CA, [4]Medicine, University of California, Los Angeles, David Geffen School of Medicine, Los Angeles, CA

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Session Time: 9:00AM-11:00AM

Background/Purpose:

1) To describe the role of MSUS, using both grey scale (GS) and Power Doppler (PD), to detect skin ulcers in SSc patients. 2) To look for initial indications that MSUS may be useful to guide therapy for SSc-ulcers.

Methods:

We examined a convenience sample of 7 SSc patients with skin ulcers by MSUS which was performed using General Electric Logic E9 scanner using a 5-16 MHz linear array transducer. PD settings: pulse repetition frequency 800 Hz, frequency 10 mHz and low wall filter. We proposed preliminary definitions of Ulcer characteristics based on normal skin reference (1). Pain and ulcer measures were obtained using 100 mm visual analogue scales (VAS).

Results:

7 SSc patients met 2013 EULAR /ACR criteria for SSc. Median (range) for mRSS: 14 (9-25). 5 patients had diffuse SSc. The 7 patients had 16 clinically apparent skin ulcers. We categorized them on GS as **a) skin ulcer (GS-SU);** characterized by loss of skin thickness both epidermal and dermal layers, or loss of epidermal layer with irregular hyper-echoic granulation tissue below the level of the surrounding epidermis (figure 1a, b), **b) Non-ulcer lesions (GS-NUL);** show no loss of epidermal layer but show irregular hyper-echoic tissue at the same or above the level of epidermis (figure 1c).

Twelve GS-SU/NUL (75%) were on the PIPs, 2 (13%) on the legs, 1 (6%) on the DIP and 1(6%) on the elbow. Two ulcers in one patient demonstrated high PD signals (presumed underlying infection). After treatment for 15 days with Ciprofloxacin, PD signal was reduced, and both pain and ulcer VASs decreased from 100 mm to 40mm (fig 2a,b). Five lesions showed underlying calcinosis (3 of 5 lesions with calcinosis had evidence of positive PD signals). Variable ulcer depths and dimensions were detected. The highest pain and ulcer VASs (100mm) were recorded in the ulcers with the highest PD signal (table 1).

Conclusion:

This is the first study to show a promising role of MSUS in evaluating skin ulcers in SSc patients. MSUS may have a role in identifying depth and underlying pathology (i.e. infection and calcinosis) of the lesion. Hence, MSUS can add clinical information and help in guiding treatment. Future studies are warranted with more SSc patients to further validate our preliminary findings.

Ref (1)Wortsman X. Sonography of Cutaneous and Ungual Lumps and Bumps Ultrasound Clin 7 (2012) 505–523

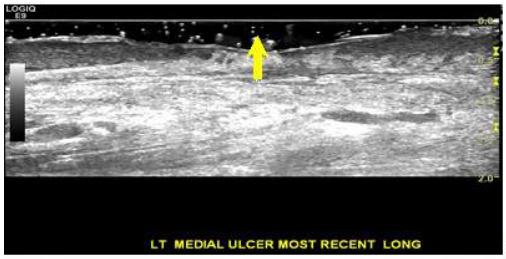

fig. 1(a)

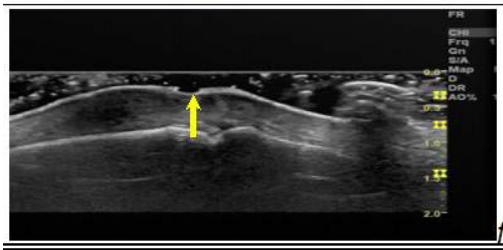

fig. 1(b)

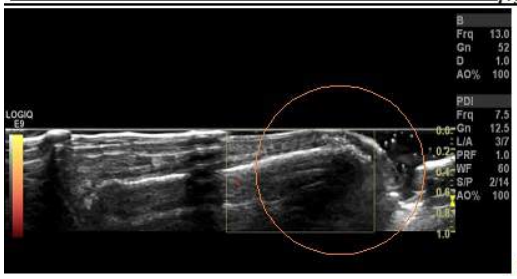

fig. 1(c)

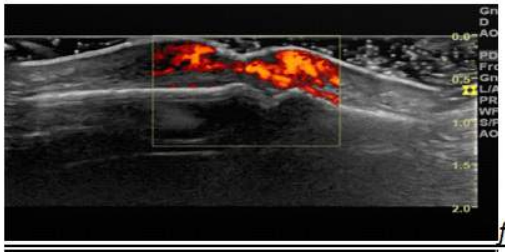

fig. 2 (a)

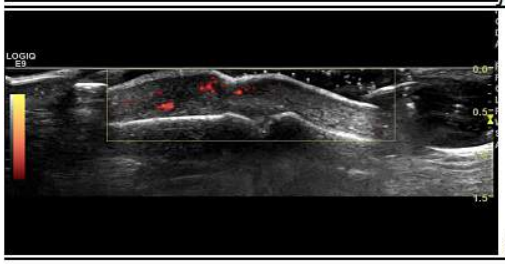

fig.2 (b)

Table1: Characteristics of the examined ulcers

	Number ulcers*	Site	Depth By GS	Dimensions measured by tape	PD#	Underlying calcinosis	Ulcer VAS 7 days	Pain VAS 7days
1	2	Rt 3rd PIP	1mm	6X3 mm	Yes 3	No	10	10
		Lt 3rd PIP	2.5mm	9x4 mm	Yes 3	No	10	10
2	2	Med Lt leg	3mm	5x2.5 cm	No	No	5	5
		Ant Lt leg	2.5mm	2x1.7 cm	No	No	5	5
3	1	Rt 3rd PIP	0	0.4 cm	no	no	5	4.5
4	2	Lt 3rd PIP	0	1.2x1.5cm	no	no	6	2
		Lt 4th PIP	0	1.5x1.5cm	no	no	6	2
5	2	Lt 3rd DIP	0	3mm	no	no	5	7
		Rt elbow	0	4mm	no	no	5	7
6	6	Lt 2nd PIP	0	2mm	No	yes	0	7
		Lt 3rd PIP	0	4mm	yes1	Yes	0	7
		Lt5th PIP	0	1mm	yes1	yes	0	7
		Rt 3rd PIP	0	1mm	yes 1	yes	0	7
		Rt4th PIP	0	4mm	no	yes	0	7
		Rt 5th PIP	0	2mm	N0	no	0	7
7	1	RT 4th PIP	0	3 mm	no	no	0	3

*Number of ulcers scanned. #The semi quantitative findings of soft tissue PDUS activity were scored as follows: grade 0 - no color signal, grade 1 - up to 3 small color signals or 2 single and 1 confluent signal in the area, grade 2 - greater than grade 1 to -50% of the area filled with color signals, and grade 3 – greater than 50% of the area filled with color signals

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Abstract Number: 2989

A Romanian Version of the University of Californa at Los Angeles Scleroderma Clinical Trial Consortium Gastrointestinal Tract (UCLA SCTC GIT 2.0) Instrument

Marilena Gorga[1], Alina Soare[1], Rucsandra Dobrota[1], Ana Maria Gherghe[1], Victor Stoica[2] and **Carina Mihai**[3], [1]Carol Davila University of Medicine and Pharmacy, Internal Medicine and Rheumatology, Cantacuzino Hospital, Bucharest, Romania, [2]Internal Medicine and Rheumatology, Cantacuzino Hospital, Carol Davila University of Medicine and Pharmacy, Bucharest, Romania, [3]Internal Medicine and Rheumatology Departement, Cantacuzino Hospital, Carol Davila University of Medicine and Pharmacy, Bucharest, Romania

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SESSION INFORMATION

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Session Title: Systemic Sclerosis, Fibrosing Syndromes and Raynaud's - Clinical Aspects and Therapeutics Poster III

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose:

UCLA Scleroderma Clinical Trial Consortium Gastrointestinal Tract (UCLA SCTC GIT 2.0) Instrument is a comprehensive, self-administered survey for the assessment of gastrointestinal involvement in patients with systemic sclerosis (SSc), developed and validated in English. This study aimed to translate and validate a Romanian version of the UCLA SCTC GIT 2.0.

Methods:

Translation from English into Romanian has been performed by the forward-backward method. Sixty-four patients with SSc satisfying the 2013 ACR/EULAR classification criteria, attending a referral centre as part of an extensively studied cohort, have been approached in a consecutive manner for administration of the questionnaire. We evaluated the internal consistency, construct validity and discriminative capacity of the translated questionnaire (Romanian GIT). Reproducibility was assessed by retesting the questionnaire over a period of 8-14 days in patients who did not suffer any significant intervention during this time.

Results:

Fifty-four patients (91% females, mean age 52.4±12.1 years, median [range] of disease duration since first non-Raynaud symptom 78.5 [43-148] months, diffuse cutaneous SSc 26%) returned completed questionnaires. The median total GIT score [range] was 0.35 [0-1.51]. Internal consistency was demonstrated by Cronbach's alpha coefficient (0.931); for all subscales Cronbach's alpha was ≥0.7, with the exception of the diarrhea subscale (alpha=0.581). Construct validity was supported by moderate, but significant correlations (Spearman) of the Romanian GIT total score with the Mental Component Summary (MCS) of SF-36 (r=0.541) and among subscales, by significant correlations with the Scleroderma Health Assessment Questionnaire (SHAQ) total score (r=0.559) and a strong correlation with the gastrointestinal subscale of the SHAQ (r=0.726). Reproducibility was good with correlation indices >0.7. Divergent validity was supported by significant differences between patients with or without a clinical diagnosis of gastrointestinal disease (see table).

Romanian GIT scores and total SHAQ score for patients with/without clinical diagnosis of gastrointestinal (GI) disease

	No GI diagnosis	≥1 GI diagnosis	p
Reflux	0.250 (0.125-0.375)	0.625 (0.250-1.375)	0.016
Distension/ bloating	0.500 (0.000-1.000)	1.000 (0.500-1.625)	0.012
Fecal soilage	0.000 (0.000-0.000)	0.000 (0.000-0.000)	1.000
Diarrhea	0.000 (0.000-0.000)	0.000 (0.000-0.500)	0.021
Social Functioning	0.000 (0.000-0.330)	0.245 (0.000-0.660)	0.022
Emotional well-being	0.000 (0.000-0.550)	0.550 (0.000-1.550)	0.021
Constipation	0.250 (0.000-0.750)	0.500 (0.000-1.000)	0.208
Total GIT score	0.221 (0.042-0.378)	0.589 (0.221-0.839)	0.002
SHAQ total score (0-3)	0.884 (0.385-1.154)	1.154 (0.653-1.500)	0.160

Medians and interquartile ranges (25-75th percentiles). p values <0.05 are considered significant (Mann-Whitney U test).

Conclusion: The Romanian GIT has acceptable reliability and validity. This questionnaire can be used for the assessment of gastrointestinal involvement in patients wih SSc.

Disclosure: M. Gorga, None; **A. Soare**, None; **R. Dobrota**, None; **A. M. Gherghe**, None; **V. Stoica**, None; **C. Mihai**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/a-romanian-version-of-the-university-of-californa-at-los-angeles-scleroderma-clinical-trial-consortium-gastrointestinal-tract-ucla-sctc-git-2-0-instrument

Abstract Number: 2990

Assessment of NT-Pro BNP As a Potential Marker for Pulmonary Hypertension in

Systemic Sclerosis: Data from a Large, Prospective and Unselected Patient Cohort

Anna-Maria Hoffmann-Vold[1,2], Oyvind Midtvedt[1], Torhild Garen[3], May Brit Lund[4], Arne Andreassen[5] and Øyvind Molberg[6], [1]Rheumatology, Oslo University Hospital, Oslo, Norway, [2]Institute of clinical medicine, University of Oslo, Oslo, Norway, [3]Rheumatology, Department of Rheumatology, Oslo University Hospital, Oslo, Norway, [4]Respiratory Diseases, Oslo University Hospital, Oslo, Norway, [5]Cardiology, Oslo University Hospital, Oslo, Norway, [6]Department of Rheumatology, Institute of Clinical Medicine, Oslo University Hospital, Oslo, Norway

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Session Time: 9:00AM-11:00AM

Background/Purpose: In Systemic Sclerosis (SSc), pulmonary arterial hypertension (PAH) is often diagnosed at an advanced stage. Serum levels of N-terminal pro-brain natriuretic peptide (NT-proBNP) are typically elevated in established SSc-PAH, but it is not known if the serum levels rise prior to PAH diagnosis, and it is not known if NT-proBNP levels differ between PAH and pulmonary hypertension secondary to interstitial lung disease (PH-ILD); which is resistant to treatment. Here, we utilized serial serum samples from a large, prospective and unselected SSc cohort, and approached these two questions by testing NT-proBNP levels in sera obtained before and after PAH or PH-ILD diagnoses.

<>**Methods:** The study cohort included patients from the prospective, observational Oslo University Hospital SSc cohort (n=298) who met the 2013 ACR/EULAR classification criteria and had (A) baseline and follow-up serum samples available for NT-proBNP analyses, (B) baseline and follow-up data on systolic pulmonary artery pressure (sPAP) by echocardiography (ECHO) and diffusion capacity for carbon monoxide (DLCO), and (C) follow-up data on PAH and PH-ILD diagnoses by right heart catheterization (RHC).

<>**Results:** The study cohort included 298 consecutive SSc patients (243 female, 78 diffuse cutaneous SSc) aged 48 ± 15.4 years at disease onset. During an observation period of 11.5 ± 8.0 years 52/298 patients developed PH, of those 32/52 were diagnosed with PAH, and 20/52 had PH-ILD. Serum levels of NT-pro-BNP obtained at baseline (mean 1.4 years before PH diagnoses) did not differ between cases with and without PH (Table 1). There was, however, a difference in NT-proBNP levels between PH and non-PH cases in serum samples obtained at follow-up, mean 2.6 years after the PH diagnoses. Development of PH was positively associated with sPAP values obtained at baseline, mean 1.6 years before PH diagnosis, and at follow-up: Likewise, PH was also associated with DLCO at baseline and at follow-up (Table 1). None of these parameters could significantly segregate PAH from PH-ILD.

<>**Conclusion:** In this prospective SSc cohort we did not find any difference in baseline NT-proBNP levels between PH and non PH cases; indicating that NT-proBNP analyses are not useful for predicting PH development. In contrast, we found that the values of sPAP and DLCO differed between PH and non PH cases both at baseline and follow-up. None of the markers tested could differentiate between PAH and PH-ILD. Hence, we are still missing predictive biomarkers for the development of PAH.

Table 1: Associations between PH and baseline and follow up characteristics

	No PH N=246	PH N=52	p-value
NT-proBNP; mg/ml, SD			
A. Baseline	64.1 ± 325.9	116.1 ± 172.6	0.265
B. Follow-up	155.8 ± 546.1	399.4 ± 666.3	0.018
sPAP by ECHO in mmHg, SD			
A. Baseline	22.9 ± 10.5	50.2 ± 30.8	<0.001
B. Follow-up	26.6 ± 13.4	69.3 ± 25.2	<0.001
DLCO, % of value expected, SD			
A. Baseline	71.8 ± 20.0	51.3 ± 21.7	<0.001
B. Follow-up	64.6 ± 19.0	37.9 ± 14.8	<0.001

Disclosure: A. M. Hoffmann-Vold, None; **O. Midtvedt**, None; **T. Garen**, None; **M. B. Lund**, None; **A. Andreassen**, None; **Molberg**, None.

Abstract Number: 2991

Evaluation of Serum Levels of Adipokines and Interleukines in Pericardial Effusion Related to Systemic Sclerosis

Angela Chialà[1], Cinzia Rotondo[1], Maria Grazia Anelli[1], Emanuela Praino[1], Luca Cantarini[2], Crescenzio Scioscia[1], Margherita Giannini[1], Giovanni Lapadula[1] and Florenzo Iannone[1], [1]DIM, Rheumatology Unit, Bari, Italy, [2]Univ Siena, Siena, Italy
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Background/Purpose: Pericardial involvement is common in rheumatic disease, as rheumatoid arthritis, lupus erythematosus, mixed connective disease and systemic sclerosis. Few data are available about pathogenesis of pericardial effusion in systemic sclerosis. This study aimed at evaluating the differences in serum levels of adipokines and interleukins (IL) in systemic sclerosis (SSc) patients with and without pericardial effusion.

Methods: A total of 87 outpatients (84 female, mean age of 52,6±14,2 ys, and disease duration of 8,2±6,7 ys), who fulfilled the ACR/EULAR 2013 SSc classification criteria, were recruited in this study. The anthropometric measures, as body mass index (BMI), demographic, clinical and laboratoristic characteristics and SSc related manifestations were assessed in each patient. The presence of pericardial effusion (PE) was evaluated by means of echocardiographic techniques (the presence of fluid ≥ 5 cc was considered pathologic). Sera levels of adiponectin, leptin, resistin, visfatin, tumor necrosis factor α (TNF-α), interferon g (INF-g), IL-2, IL-10 and IL-17 were measured in SSc patients, using Multiplex Immunoassay (Bioplex 200 System), by means of two kits (Bioplex ProTM Cytokine/Chemokine and Growth Factor Assay e Bioplex Pro Diabetes Assay). The data normality was verified using Kolmogorov-Smirnov Test; the comparisons between SSc patients groups were evaluated by Mann-Whitney U test and t-student test, where appropiate. Statistic significance was set at p≤0,05. The results are expressed as median and interquartile range (IQR) or means ±1standard deviation. The data analysis were assessed using IBM SPSS statistic 20.

Results: 11 SSc patients had pericardial effusion (PE). The SSc patients groups (with and without PE) did not differ in age (46,5±13,8 ys vs 53,5±14,2 ys), sex and BMI (24,4±5,5 vs 23,62±4,12). 11 SSc patients were obese (BMI≥30) (2 with PE and 9 without PE). We observed significant differences between SSc patients with PE and without PE in sera levels of visfatin (1546,9 (8590,9) vs 388,8 (103); p=0,036), adiponectin (2845000 (4132900,0) vs 5272100,0 (8243600,0); p=0,027) and IL-17 (1,33 (3,5) vs 0,05 (0,56); p=0,45). Moreover higher leptin/adiponectin ratio was found in patients with PE (0,006 (0,01) vs 0,0017 (0,00); p= 0,032). The sera levels of adipokines and IL did not change in SSc patients with interstitial lung disease or pulmonary arterial hypertension, different videocapillaroscopy pattern, limited or diffuse skin subset.

Conclusion: The visfatin and adiponectin could play an important role in pathogetic mechanism in pericardial effusion in systemic sclerosis. Futher study are necessary to unravel a role of visfatin and adiponectin as biomarkers of SSc pathology.

Disclosure: A. Chialà, None; **C. Rotondo**, None; **M. G. Anelli**, None; **E. Praino**, None; **L. Cantarini**, None; **C. Scioscia**, None; **M. Giannini**, None; **G. Lapadula**, None; **F. Iannone**, None.

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Abstract Number: 2992

Identification of a New Set of Activity Criteria for Systemic Sclerosis. Preliminary Report

Gabriele Valentini[1], Michele Iudici[2], Veronika K. Jaeger[3], Christopher P. Denton[4], Oliver Distler[5], Otylia M. Kowal-Bielecka[6], Ulf Müller-Ladner[7], Gabriela Riemekasten[8], Ulrich A. Walker[3], Suzana Jordan[5], Elise Siegert[8], Serena Vettori[2] and Yannick Allanore[9], [1]Department of Clinical and Experimental Medicine, Rheumatology Unit, Rheumatology Unit, Second University of Naples, Naples, Italy, [2]Department of Internal and Experimental Medicine, Rheumatology Unit, Second University of Naples, Naples, Italy, [3]Department of Rheumatology, University Hospital Basel, Basel, Switzerland, [4]Rheumatology and Connective Tissue Diseases, University College

London, London, United Kingdom, [5]Department of Rheumatology, University Hospital Zurich, Zurich, Switzerland, [6]Department of Rheumatology and Internal Medicine, Medical University in Bialystok, Bialystok, Poland, [7]Internal Medicine and Rheumatology, Justus-Liebig-University of Giessen, Kerckhoff-Klinik, Bad Nauheim, Germany, [8]Rheumatology and Clinical Immunology, Charité – University Hospital, Berlin, Berlin, Germany, [9]Department of Rheumatology, University Paris Descartes and Cochin Hospital, Paris, France
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Session Type: ACR Poster Session C
Session Time: 9:00AM-11:00AM

Background/Purpose: The European Scleroderma Study Group (EScSG) Activity Index developed in 2001 has some limitations due to the procedure underlying its development and the inclusion of hypocomplementemia, that was criticized for its poor face validity. The present study is devoted to overcome such limitations.

Methods: Ninety seven clinical charts of patients with SSc, all of whom satisfying 1980 ACR criteria for the disease, were retrieved from a large database. Three investigators (CD, OKB, YA) external to the enrolling centres assigned a disease activity score to each chart on a 0-10 visual analogue scale, providing a reliable scoring tool (ICC=0.786; 95%CI=0.716-0.844). The median score served as the disease activity gold standard. Another investigator (GV) evaluated disease activity as inactive, moderately active, active, and very active. Univariate and multivariate linear regression analyses were used to assess the performance of sets of criteria in predicting the "gold standard" and to identify the weight of each variable. Pending the final validation in a replication cohort, the resulting preliminary activity index was validated by the jackknife statistical procedure i.e.by leaving out one patient a time. Receiver operating curves served to assess the efficiency of the index in separating active-very active disease from inactive-moderately active disease.

Results: A preliminary weighted 10-point activity index was identified: Δ (ie. patient-assessed worsening during the previous month)-skin= 1.25, Δ- heart-lung= 0.75, modified Rodnan skin score >18=1.25; digital ulcers=1.75; tendon friction rubs=1.5; erythrocyte sedimentation rate >50 mm/h=1.0; C reactive protein >1 mg/dl= 1.5; Diffusing Lung Capacity for CO <70% of predicted=1. A cut-off ≥1.75 identified patients with active-very active disease. It resulted to be more sensitive and specific than the currently used EScSG index in identifying SSc patients with active disease in the 97 SSc patients considered for this part of the study.

Conclusion: A preliminary revised activity index has been developed. It is feasible and has face validity. It is going to be validated in a replication cohort

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Abstract Number: 2993

Serum CXCL4 Increase in Patients with Undifferentiated Connective Tissue Disease at Risk for Systemic Sclerosis Is Associated with Anti-Scl70 Antibodies and ICAM-1, a Marker of Endothelial Activation

Serena Vettori[1], Rosaria Irace[2], Veronica Giacco[2], Antonella Riccardi[2], Lucia Vicedomini[2], Luciana Pellecchia[2] and Gabriele Valentini[2], [1]Department of Internal and Experimental Medicine, Rheumatology Unit, Second University of Naples, Naples, Italy, [2]Internal and Experimental Medicine, Rheumatology Unit, Second University of Naples, Naples, Italy
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Session Title: Systemic Sclerosis, Fibrosing Syndromes and Raynaud's - Clinical Aspects and Therapeutics Poster III

Session Type: ACR Poster Session C
Session Time: 9:00AM-11:00AM

Background/Purpose: CXCL4 is a pleiotropic antiangiogenic and immunomodulatory chemokine, that has been shown to be increased in the sera of patients with systemic sclerosis (SSc) as well as in patients previously referred to as early SSc, at present labeled as undifferentiated connective tissue disease (UCTD) at risk for SSc. We aimed to search for relationships between CXCL4 serum levels and demographic, serological, and clinical features in patients with UCTD at risk for SSc, that is patients with Raynaud's phenomenon (RP) and SSc marker autoantibodies and/or nailfold capillaroscopy (NVC) scleroderma pattern, who do not satisfy the 2013 ACR/EULAR criteria for SSc classification.

Methods: Serum levels of CXCL4 were measured in 24 autoantibody positive UCTD patients at risk for SSc and 24 osteoarthritis/fibromyalgia controls by a fluorescence-based suspension immunoassay. All patients were investigated for preclinical and clinical organ involvement, SSc marker autoantibodies, and NVC abnormalities. The new 2013 ACR/EULAR classification score for SSc was calculated for each patient at baseline and at the end of follow-up.

Results: Median serum levels of CXCL4 were increased in UCTD patients at risk for SSc (6.79 ng/ml, interquartile range - IQR- 3.4-13.8 vs 1.44 ng/ml, IQR 0.14-3 in controls, $p < 0.0001$). CXCL-4 resulted to be correlated to ICAM-1 serum levels ($r=0.44$, $p < 0.05$); had higher levels in the 6 anti-Scl70 positive patients (median 16.27 ng/ml, IQR 10.25-33.5) than in the 17 ACA positive patients (5, IQR 2.9-8.1 ng/ml, $p < 0.01$) and exceeded the 95° percentile of control values (12.24 ng/ml) in 5/15 (33.3 %) of patients who progressed to definite SSc vs 1/9 (10%) of those who did not at the end of the follow-up period (median follow-up: 2.75 years, range 0.4-8.4) ($p = 0.3$). Moreover, CXCL4 positively correlated with serum levels of soluble ICAM-1 ($r = 0.44$; $p < 0.05$).

Conclusion: Here we confirm that patients with UCTD at risk for SSc have increased serum levels of CXCL4. Moreover, we point out an association with anti-Scl70 positivity and a correlation with serum ICAM-1, a marker of endothelial activation. The predictive role, if any, of CXCL4 in patients with UCTD at risk for SSc awaits to be assessed in larger series of patients.

Disclosure: S. Vettori, None; **R. Irace**, None; **V. Giacco**, None; **A. Riccardi**, None; **L. Vicedomini**, None; **L. Pellecchia**, None; **G. Valentini**, None.

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Abstract Number: 2994

The Global Microrna Profile of Systemic Sclerosis Whole Skin/Dermal Fibroblasts and the Role of the Xq26.3 miRNA Cluster As a TGF-b Pathway Positive Feedback Mechanism

Gloria Salazar[1], John Hagan[2], Minghua Wu[3], Xinjian Guo[4], Xiaodong Zhou[4], Julio Charles[1], Maureen D Mayes[1] and Shervin Assassi[1], [1]Rheumatology, University of Texas Medical School at Houston, Houston, TX, [2]Neurosurgery, University of Texas at Houston, Houston, TX, [3]Feinberg School of Medicine, Northwestern University, Chicago, IL, [4]Internal Medicine, University of Texas Medical School at Houston, Houston, TX
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Session Time: 9:00AM-11:00AM

Background/Purpose:

MicroRNA (miRNA) are critical gene regulators that frequently play central roles in disease. Here, we report the miRNA expression signatures of systemic sclerosis (SSc) skin and dermal fibroblasts and examined the role of Xq26.3 miRNA cluster in the exaggerated fibrotic process observed in SSc.

Methods:

The global miRNA profiles of skin (10 early SSc samples and matched controls) were determined using a highly sensitive, comprehensive multiplex qPCR platform (Exiqon LNA-enhanced qPCR array) that interrogates 752 miRNAs. Similarly, global miRNA expression was investigated for early passage dermal fibroblasts from 5 SSc patients and unaffected controls. SSc patients had disease

duration < 5 years and were not treated with immunosuppressive agents. Based on these studies, we then performed targeted qPCR for 3 miRNAs located in a cluster on X-chromosome in 5 SSc and control fibroblast cell lines unstimulated and stimulated with TGF-b and 8 other key Th1/Th2/Th17 cytokines for 24 hours. Additionally, we performed global gene expression microarrays of the 5 unstimulated/stimulated control fibroblasts.

Results:

Global miRNA profile of SSc whole skin samples revealed 26 dysregulated miRNAs, 3 of which were part of a miRNA cluster located in Xq26.3. The global miRNA profiling of dermal fibroblasts revealed 24 differentially expressed miRNAs in SSc. Similar to skin studies, Xq26.3 cluster miRNA were also significantly increased in SSc dermal fibroblasts. Notably, 3 of these miRNA (miR 424-5p, miR 424-3p and miR 503-5p) are predicted to target SMAD7 per in silico algorithms, therefore we investigated them further.

The fibroblast stimulation experiments in SSc and control fibroblast cell lines revealed that these 3 miRNA were significantly upregulated after stimulation by TGF-b (compared to paired unstimulated cells). Furthermore, the highest levels of these miRNA were observed after TGF-b stimulation compared to 8 cytokines (IFNa, IFNg, IL10, IL13, IL17a, IL22, MCPI, TNFa). A similar stimulation pattern was observed in SSc and control cell lines.

As predicted in silico, Xq26.3 miRNA levels were inversely correlated with SMAD7 mRNA levels (as miRNA levels increased SMAD7 levels decreased) (mir424-5p spearman r=-1 p=<0.0001, miR424-3p r=-0.9 p=0.03, miR503-5p r=-0.9 p=-0.03). No significant correlations were observed with other gene transcripts such as SMAD4 or after stimulation with other cytokines. Furthermore, there were no significant correlations with a control miRNA (miR25).

Conclusion:

This is the first comprehensive and unbiased examination of miRNAs in SSc skin and fibroblasts. Increased miRNA from the Xq26.3 cluster were observed in both sample types. TGF-b upregulates these miRNA. Moreover, there is a strong inverse relationship between their levels and the predicted target in the TGF-b pathway (SMAD7). These miRNA are likely part of a positive feedback mechanism which is activated by TGB-b to target its natural inhibitor (SMAD7) keeping the pathway activated. Given the strong female predilection of SSc, this miRNA cluster, located on the X-chromosome, could have important ramifications for understanding SSc pathophysiology and drug development.

Disclosure: G. Salazar, None; **J. Hagan**, None; **M. Wu**, None; **X. Guo**, None; **X. Zhou**, None; **J. Charles**, None; **M. D. Mayes**, None; **S. Assassi**, None.

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Abstract Number: 2995

Genome Wide Analysis in Scleroderma Renal Crisis: Defining Genetic Risk in Patients with RNA Polymerase III Auto-Antibodies

Maria C Fonseca[1], Sandra Guerra[1], Edward Stern[1,2], Svetlana I. Nihtyanova[1], David Abraham[3], Aine Burns[2], Mark Harber[2] and Christopher P. Denton[4], [1]Rheumatology, UCL Division of Medicine, London, United Kingdom, [2]Nephrology, Royal Free Hospital, London, United Kingdom, [3]Centre for Rheumatology and Connective Tissue Disease, University College London, London, United Kingdom, [4]Rheumatology and Connective Tissue Diseases, University College London, London, United Kingdom
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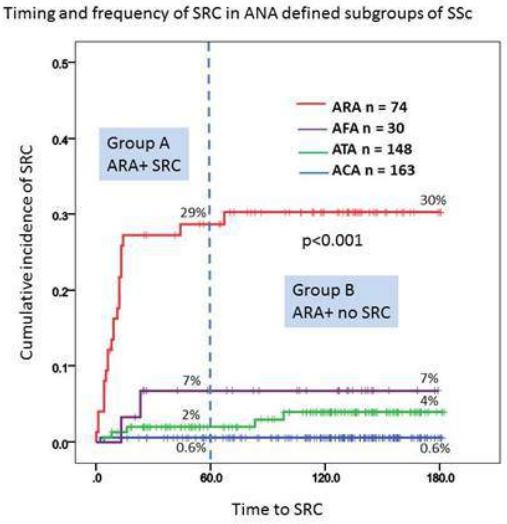
Background/Purpose: Scleroderma renal crisis (SRC) is a severe complication of systemic sclerosis (SSc). Most SSc cases demonstrate a disease-specific antinuclear antibody including anti-RNA polymerase III (ARA), anti-fibrillarin (AFA), anti-topisomerase-1 (ATA) or anticentromere (ACA). ARA defines a distinct sub-phenotype characterised by diffuse skin disease and risk of complications including SRC and pulmonary arterial hypertension. We used the strong association between ARA and SRC and the predominant occurrence of SRC early in disease to develop an extreme phenotype strategy for defining genetic factors in susceptibility to renal crisis.

Methods: First we analysed SRC in a well characterised group of SSc cases followed at our centre (n=415). Informed by this, 50

patients with confirmed SRC and ARA+ and another 50 SSc ARA+ that had never developed SRC were identified from our larger SSc cohort. These cases, all with Northern European ancestry, were genotyped across approximately one million SNPs using the Illumina Human Omni-express bead array chip. All data underwent quality control checks for Hardy-Weinberg equilibrium and genotyping rate in PLINK (HWE $p < 0.001$, and genotyping rate > 90%). After filtering of SNPs, a logistic regression was performed in PLINK comparing patients with or without SRC to determine the genetic signature difference between these two groups of patients.



Results: Initial analysis confirmed a strong association between ARA and SRC with 30% ARA+ SSc developing SRC compared with 7% AFA, 4% ATA and 1% ACA ($p < 0.001$). Moreover in ARA+ cases almost all SRC occurred within 18 months of disease onset, and SRC after 5 years of follow up was very rare. Thus we could define a group with SRC and another at very low risk. This dichotomy formed the basis of our genetic analysis comparing ARA+ patients with SRC history (Group A) to the control group, who had been followed for > 60 months without SRC (Group B). We performed GWAS analysis on these two groups. Quality control checks removed 2309 SNPs for missingness (GENO > 0.1) and 77122 failed MAF filters (MAF < 0.01). In total 641,489 SNPs were analysed. The logistic regression analysis identified a number of SRC associated SNPs within genes and gene regions. Top associations were found in the complement region (P= 1.66x10-5), and in other genes including EPHA5 (P= 1.87x10-5), GRIA3 (P= 2.16x10-5), HECW2 (P= 2.71x10-5) and CTNND2 (P= 2.92x10-5).

Conclusion: We present a novel study using extreme phenotypes of ARA+ SSc to identify genetic association of SRC in cases that are serologically and clinically otherwise homogeneous. We identified genes including Caterin cadherin-associated protein delta 2 (CTNND2) which is known to regulate adhesion molecules relevant to fibrosis. Genes identified from this analysis may have general relevance to SSc vasculopathy or other forms of hypertensive thromobotic microangiopathy. Additional functional and genetic replication studies are needed.

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Abstract Number: 2996

Evaluation of Systemic Sclerosis Risk Genes in the Turkish Population

Javier Martín[1], Francisco David Carmona[2], Tamara Fernández-Aranguren[1], Alberto Serrano-Fernández[3], Ahmet Mesut Onat[4], Gema Robledo[5], Enrique Raya[6], Haner Direskeneli[7], Amr H. Sawalha[8] and Sule Yavuz[9], [1]Instituto de Parasitología y Biomedicina López-Neyra, IPBLN-CSIC, PTS-Granada, Granada, Spain, [2]Instituto de Parasitología y Biomedicina López-Neyra, IPBLN-CSIC, PTS-Granada, Granada, Spain, [3]Immunology, Instituto de Parasitología y Biomedicina López-Neyra, IPBLN-CSIC, Armilla, Spain, [4]Ä °nternal Medicine Division of Rheumatology, Gaziantep University, Faculty of Medicine, Gaziantep, Turkey, [5]Immunology, Instituto de Parasitología y Biomedicina López-Neyra, IPBLN-CSIC, Granada, Spain, [6]Rheumatology, Hospital Clínico San Cecilio, Granada, Spain, [7]Department of Rheumatology, Marmara University Faculty of Medicine, Istanbul, Turkey, [8]Division of Rheumatology, University of Michigan, Ann Arbor, MI, [9]Rheumatology, Istanbul Bilim University, Faculty of Medicine,Department of Rheumatology, Istanbul, Turkey

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Background/Purpose: The use of high-throughput genotyping platforms has allowed a better understanding of the genetic background underlying systemic sclerosis (SSc). Sixteen non-HLA genes have been consistently associated with SSc at the genome-wide level of significance, with *IRF5*, *STAT4*, *CD247*, *DNASE1L3*, *IL12A* and *ATG5* representing the top signals in the two most powered large-scale analyses on SSc performed to date (a genome-wide association study and an Immunochip study in Europeans). We aimed to evaluate for the first time the possible role of the above mentioned genes in SSc susceptibility in the Turkish population.

Methods: We genotyped a total of 355 SSc patients and 718 unrelated healthy controls from Turkey for the SSc-associated lead genetic variants *IRF5* rs10488631, *STAT4* rs3821236, *CD247* rs2056626, *DNASE1L3* rs35677470, *IL12A* rs77583790, and *ATG5* rs9373839. The genotyping of the whole SSc group and part of the control group (219 samples) was performed by TaqMan assays, whereas the remaining control data (499 samples) was obtained using the Immunochip platform. To test for association, we compared the minor allele frequencies of every polymorphism between cases and controls by performing 2x2 contingency tables and x2 tests.

Results: The overall analysis evidenced statistically significant associations of the global SSc with *IRF5* (P=1.48E-05, OR=1.76, CI 95%=1.36-2.27) and *CD247* (P=2.20E-03, OR=0.75, CI 95%=0.62-0.90). Trends of association were also suggested for *STAT4* (P=0.066, OR=1.21, CI 95%=0.99-1.48), *IL12A* (P=0.080, OR=4.06, Ci 95%=0.74-22.23), and *DNASE1L3* (P=0.100, OR=1.41, CI 95%=0.93-2.11). Interestingly, the subphenotype analysis showed subtype- and autoantibody-specific associations, that is, *CD247* was specifically associated with the diffuse form of the disease (diffuse SSc vs controls: P=4.91E-04, OR=0.64, CI 95%=0.49-0.82; diffuse SSc vs limited SSc: P=0.065, OR=0.75, CI 95%=0.55-1.02), and *IRF5* with the presence of anti-topoisomerase autoantibodies (ATA+ SSc vs controls: P= 8.84E-08, OR=2.28, CI 95%=1.68-3.11; ATA+ SSc vs ATA- SSc: P=8.43E-03, OR=1.70, CI 95%=1.14-2.52).

Conclusion: We were able to replicate the associations of *IRF5* rs10488631 and *CD247* rs2056626 with SSc in the Turkish population, thus confirming the relevant role that these genes may have in the pathophysiology of this disease.

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Abstract Number: 2997

A Genome-Wide Association Study of a Hispanic Systemic Sclerosis Cohort

Lara Bossini-Castillo[1], Enrique Raya[2], John D. Reveille[3], Shervin Assassi[4], Olga Y Gorlova[5], Dinesh Khanna[6], Daniel E. Furst[7], Suzanne Kafaja[8], Robert W. Simms[9], Robert Lafyatis[9], Tracy M. Frech[10], Virginia D. Steen[11], Barri J. Fessler[12], Jerry A. Molitor[13], Marta Alarcón-Riquelme[14,15], Javier Martín[16] and Maureen D Mayes[4], [1]Instituto de Parasitología y Biomedicina López-Neyra, IPBLN-CSIC, PTS Granada, Granada, Spain, [2]Rheumatology, Hospital Clínico San Cecilio, Granada, Spain, [3]Internal Medicine/Rheumatology, University of Texas Medical School at Houston, Houston, TX, [4]Rheumatology, University of Texas Medical School at Houston, Houston, TX, [5]Department of Community and Family Medicine, Geisel School of Medicine at Dartmouth, Hanover, NH, [6]Division of Rheumatology, University of Michigan, Ann Arbor, MI, [7]Medicine, University of California, Los Angeles, David Geffen School of Medicine, Los Angeles, CA, [8]Rheumatology, University of California Los Angeles, Los Angeles, CA, [9]Rheumatology, Boston University School of Medicine, Boston, MA, [10]Div of Rheumatology, University of Utah, Salt Lake City, UT, [11]Department of Rheumatology, Georgetown University Medical Center, Washington, DC, [12]Rheumatology, Department of Medicine, University of Alabama at Birmingham, Birmingham, AL, [13]Rheumatology, University of Minnesota, Minneapolis, MN, [14]Arthritis and Clinical Immunology Program, Oklahoma Medical Research Foundation, Oklahoma, OK, [15]Centre for Genomics and Oncological Research (GENYO), Pfizer–University of Granada–Junta de Andalucia, Parque Tecnológico de la Salud (PTS), Granada, Spain, [16]Instituto de Parasitología y Biomedicina López- Neyra, IPBLN-CSIC, PTS-Granada, Granada, Spain

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Background/Purpose: Genome-wide association studies (GWASs) have resulted in the identification of several genetic *loci* involved in systemic sclerosis (SSc) susceptibility. However, GWASs are normally focused in white European ancestry populations. Indeed, in the case of SSc this hypothesis-free approach has not been followed in mixed populations such as Hispanic Americans. It should be considered that the genetic polymorphisms described in whites do not cover all the variation observed in other ethnic groups. Moreover, due to the difference linkage-disequilibrium patterns, the analysis of cohorts of multiple ancestries contributes to fine-mapping and causal variant identification. Therefore, the aim of our study was to analyze for the first time the genetic background of SSc in a Hispanic American population.

Methods: Our study comprised a total of 285 SSc patients and 261 ethnically matched healthy controls. All SSc cases and 131 controls were recruited in Houston (Texas, USA) and genotyped using the HumanOmni2.5-8 Illumina Array. Statistical power was increased by adding 130 additional controls of Hispanic descent, recruited in Oklahoma City (Oklahoma, USA) and genotyped using the HumanOmni1-Quad Illumina BeadChip. After stringent per variant and per individual quality controls, 307,939 single-nucleotide polymorphisms (SNPs) were included in our analysis. Despite the mixed ancestry of the Hispanic population in the USA, the majority of the analyzed individuals in our study, both cases and controls, were of Mexican origin. Nevertheless, stringent principal component analysis filters were applied to verify case-control overlap. Significance was calculated using 2x2 contingency tables and Fisher's exact test or χ 2 when necessary, to obtain p-values, odds ratios and 95% confidence intervals using PLINK (v1.07) software. Genomic correction was used to correct for multiple testing.

Results: We observed genome-wide level associations in the HLA region, specifically in the HLA class II region (between the *HLA-DRB1* and the *HLA-DQA1 loci*). However, we did not report any signal outside the HLA region that reached the genome-wide significance threshold. Nevertheless, we found nominally associated SNPs in a number of SSc-related *loci*, identified in white populations. The regions showing nominal associations included: *IRF5*, *STAT4*, *CD247*, *BLK*, *BANK1, IRF8*, *IRF7*, *IL12A*, *ATG5*, *PPARG*. It should be noted that, despite the replication of firm SSc-risk factors in the Hispanic population, the most associated variants for each *loci* were not normally the same than in white populations.

Conclusion: Our findings support a common genetic background for SSc susceptibility between white European and Hispanic populations. Nonetheless, our results also revealed that the associated variants were not necessarily the same in both populations. These findings may be a basis for causal variant identification in the shared *loci*.

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Abstract Number: 2998

Microchimerism Is Present in Systemic Sclerosis Lung and Includes CD31-Positive Cells

Coline GENTIL[1], Julie Randolph-Habecker[2], David. K. Madtes[3,4], Min FANG[5], Hilary S. Gammill[6], Corinne L. Fligner[7], McGarry, A. Houghton[3,8] and J. Lee Nelson[9,10], [1]Clinical Division, Fred Hutchinson Cancer Research Center, SEATTLE, WA, [2]Histopathology, Fred Hutchinson Cancer Research Center, SEATTLE, WA, [3]Clinical Research, Fred Hutchinson Cancer Research Center, SEATTLE, WA, [4]University of Washington, SEATTLE, WA, [5]Cytogenetics, Seattle Cancer Care Alliance, SEATTLE, WA, [6]Obstetrics and Gynecology, University of Washington, Seattle, WA, [7]Pathology, University of Washington, SEATTLE, WA, [8]Pulmonary medicine, University of Washington, SEATTLE, WA, [9]Clinical Research Division, Fred Hutchinson Cancer Research Center, Seattle, WA, [10]University of Washington, Seattle, WA
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Background/Purpose: Microchimerism (Mc), harboring a small number of cells (or DNA) that originated in a different individual, occurs commonly due to bi-directional maternal-fetal exchange during pregnancy and long-term persistence decades later. Mc has been implicated in some autoimmune diseases, especially systemic sclerosis (SSc), but any role in pathogenesis remains unclear. We sought to identify and characterize Mc at the site of disease pathology in SSc lung.

Patients and **Methods:**

SSc lung specimens were obtained from autopsy. Of 9 patients, 7 had diffuse and 2 limited SSc; 6 were female, 3 male. SSc onset age ranged from 25 to 56 (mean 45.6) and disease duration 1 to 8 years (mean 3.1). Causes of death were primarily pulmonary (interstitial fibrosis, hemorrhage), however 3 patients had cancer (1 lung, 2 breast) and cause of death was unclear for 1 patient. 3 had undergone autologous hematopoietic cell transplants and 2 cord blood transplants. For comparison, healthy tissue from surgical lung cancer resections are being studied, to date 2 females and 2 males.

To identify and characterize Mc, two approaches were employed. When family members were available, a non-shared polymorphism of the putative Mc source was identified and DNA extracted from lung tissue interrogated for the specific polymorphism by quantitative-polymerase chain reaction (qPCR). When the Mc source was sex mismatched, fluorescence in situ hybridization (FISH) was employed with X- and Y-chromosome specific probes. Concomitant immunohistochemistry (IHC) was added for CD31, CD45, cytokeratin and SMA-α to determine cell phenotype. Cells with two distinct signals within one nucleus were counted and analyzed under bright field for IHC staining.

Results: Molecular studies indicated multiple Mc sources are detected in SSc lung, i.e. maternal, fetal and possibly sibling Mc. By polymorphism specific qPCR concentrations ranged from 1 to 144 microchimeric cell equivalents per 10^5 cell tested. By FISH 3/3 male lungs had female cells (mean: 9.3/2000, range 3-19) and 4/5 female lungs had male cells (mean: 5.8/2000, range 1-13). Among controls, 3/4 had Mc (mean: 5/2000, range 1-8). Interestingly, in male SSc patients, half or more of maternal Mc was positive for the endothelial cell marker CD31. 10% were positive for SMA-α. In females, 36% of the male Mc was positive for CD31, 9.5% for SMA-α and 3.5% for cytokeratin. No microchimeric cell was positive for CD45.

Conclusion:

These results indicate SSc lung contains Mc from multiple different sources. Microchimeric cells in the lung were not hematopoietic. The most common phenotype was endothelial, of potential additional interest in light of early endothelial cell injury in SSc. While other studies are needed, these results, along with other literature, [1] indicate that Mc can adopt different cell phenotypes so that loss of tolerance to our natural immigrants could contribute to an "auto" immune disease.

Acknowledgements: This work was supported by a grant from the Scleroderma Foundation.

[1] Reviewed in: Nelson JL. The Otherness of Self: Microchimerism in health and disease. *Trends in Immunol* 33(8):421-7, 2012.

Disclosure: C. GENTIL, None; **J. Randolph-Habecker**, None; **D. K. Madtes**, None; **M. FANG**, None; **H. S. Gammill**, None; **C. L. Fligner**, None; **M. A. Houghton**, None; **J. L. Nelson**, None.

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Abstract Number: 2999

Maternal Microchimerism Is Increased in Multiple Cellular Subsets of Patients with Systemic Sclerosis Compared to Healthy Controls

Sami B. Kanaan[1], Whitney Harrington[2,3], Laurence S. Loubiere[4], Tessa M. Aydelotte[1] and J. Lee Nelson[1,5], [1]Clinical Research Division, Fred Hutchinson Cancer Research Center, Seattle, WA, [2]Seattle Children's Hospital, Seattle, WA, [3]Department of Pediatrics, University of Washington School of Medicine, Seattle, WA, [4]University of Birmingham, Birmingham, United Kingdom, [5]University of Washington, Seattle, WA

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Background/Purpose: Microchimerism (Mc) is naturally acquired through bi-directional exchange of small amounts of cells or DNA between mother and fetus during pregnancy. Higher amounts of maternal Mc (MMc) have been reported in peripheral blood of patients suffering from autoimmune diseases such as systemic sclerosis (SSc), compared to healthy controls (1,2), however, it is unknown what cell type(s) is responsible for this increase. We investigated the frequencies and quantitative levels of MMc within cellular subsets isolated from peripheral blood mononuclear cells (PBMC) in patients with SSc and compared results to healthy controls.

Methods : 69 subjects were studied for MMc in T cells, B cells, NK cells and monocyte/macrophages, including 27 female patients with SSc and 42 healthy controls (32 female and 10 male). To detect and identify MMc, HLA-specific primers and fluorogenic probes were used in quantitative polymerase chain reaction (Q-PCR), targeting the non-inherited, non-shared maternal HLA allele. Therefore, HLA genotyping was performed for all the subjects and their mothers. When non-inherited maternal HLA was indistinguishable from subject's HLA, primers and probes targeting non-HLA polymorphisms developed for this purpose were used. Using fluorescence-activated cell sorting, PBMC were sorted into: T, B, and NK cells, and monocyte/macrophages to an average purity of 98.6%. The specific Q-PCR assays were then undertaken on DNA extracted from individual subsets. Prevalence of MMc was analyzed using logistic regression, and negative binomial regression model was used to asses MMc quantitative levels, with adjustment for total number of genome equivalents tested.

Results: MMc was identified in at least one cellular subset in 44.4% of SSc patients and 40.5% of healthy subjects, without a significant difference between patients and controls overall, or when comparing each subpopulation separately. However, MMc levels were significantly higher in SSc patients compared to controls, with an incidence rate ratio (IRR) of 47.4 ($P < 0.001$). Interestingly, the difference in MMc levels was greater in the adaptive immune subpopulations ($IRR_{[T\ cells]} = 109.1$ and $IRR_{[B\ cells]} = 51.2$; $P < 0.001$) compared to those of the innate immune cells ($IRR_{[NK\ cells]} = 29.8$; $P = 0.001$ and $IRR_{[Monocytes]} = 6.3$; $P = 0.117$).

Conclusion : We found higher amounts of MMc especially in adaptive immune cellular subsets in women with SSc compared to healthy controls. This incites further investigation of the immunologic functionality of MMc in health and disease, which is currently under way.

References:

1. Lambert, et al. *Arthritis Rheum*. 2004 Mar;50(3):906-14
2. Nelson JL. *Trends Immunol*. 2012 Aug;33(8):421-7

Disclosure: S. B. Kanaan, None; **W. Harrington**, None; **L. S. Loubiere**, None; **T. M. Aydelotte**, None; **J. L. Nelson**, None.

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Abstract Number: 3000

Intrinsic Gene Expression Subset Predicts Improvement in Systemic Sclerosis Patients during Dasatinib (SprycelTM) Therapy

Viktor Martyanov[1], Jonathan Goldin[2], Kim Hyun[3], Oumar Sy[4], Wendy Hayes[4], Shuyan Du[4], Michael Whitfield[1] and John Varga[5], [1]Department of Genetics, Geisel School of Medicine at Dartmouth, Hanover, NH, [2]David Geffen School of Medicine, University of California, Los Angeles, Los Angeles, CA, [3]Radiology, David Geffen School of Medicine, University of California, Los Angeles, Los Angeles, CA, [4]Bristol-Myers Squibb, Princeton, NJ, [5]Division of Rheumatology, Northwestern University, Feinberg School of Medicine, Chicago, IL

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Background/Purpose:

Intrinsic gene expression subsets are molecular pathway-driven subtypes of systemic sclerosis (SSc) that have been reproduced across multiple cohorts of SSc patients. The goal of this study was to determine if intrinsic subset assignment could identify SSc patients who improved with treatment in an open-label clinical trial of dasatanib, the broad spectrum tyrosine kinase inhibitor.

Methods:

Biopsies of lesional forearm skin were performed on days 1 and 169 of the study. RNA was isolated and used for intrinsic subset assignment, differential gene expression and pathway enrichment analyses. Clinical response was determined by modified Rodnan Skin Score (mRSS) and pulmonary function was assessed at baseline and day 169. Improvement was defined by a decrease in mRSS of >5 or >20% from baseline. Quantitative image analysis of high-resolution computed tomography (HRCT) scans of the chest was performed and quantitative lung fibrosis (QLF) and ground class (QGG) scores were obtained at baseline and 6-month follow-up. Categorical variables were analyzed via Fisher's exact test and continuous variables via Mann-Whitney and Wilcoxon signed-rank test.

Results:

Among twelve subjects with baseline and post-treatment skin biopsies, three were classified as improvers and nine as non-improvers. Intrinsic gene analysis identified 3207 probes (2532 unique genes) at False Discovery Rate (FDR)<1.1% which organized study samples into fibroproliferative, inflammatory and normal-like groups. Based on the intrinsic subset assignment, improvers were normal-like or fibroproliferative while 7/9 non-improvers were inflammatory at baseline (p=0.0455). Consistent with these results, improvers were enriched in cell cycle genes (e.g. EGFR, TOP1 and TOP3A) and growth-related pathways (e.g. intracellular signal transduction and kinase cascade). Non-improvers were enriched in immune response genes (IL6, TLR2 and CCR2) and inflammatory pathways (e.g. defense response and leukocyte migration). Improvers showed stable pulmonary function (as measured by forced vital capacity (FVC) and diffusing capacity for carbon monoxide (D_LCO)) and stable QLF score post-treatment (as measured on HRCT). In contrast, non-improvers showed a trend towards decrease in FVC, a decrease in D_LCO (p=0.1289 and p=0.0156, respectively) and progression in QLF (p=0.0313). Moreover, non-improvers at baseline had a higher QGG score (p=0.0364) and tended to have a higher interstitial lung disease (ILD) score than improvers (p=0.1212).

Conclusion:

Our results indicate that the intrinsic gene expression subset of SSc may be associated with those patients most likely to respond to therapy. In this trial of dasatinib, patients classified as inflammatory at baseline displayed worse clinical outcomes in terms of skin score, pulmonary function and lung fibrosis than patients from other intrinsic subsets. To our knowledge, this is the first report showing that SSc patients from the inflammatory subset show a distinct lack of response to a drug treatment. Molecular subset information may improve clinical trial design and guide the development of personalized therapies for rare and difficult to treat diseases, such as SSc.

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Abstract Number: 3001

Exome Sequencing for Identification of Potential Causal Variants for Diffuse Cutaneous Systemic Sclerosis

Angel CY Mak[1], Paul LF Tang[2], Clare Cleveland[3,4], M Kari Connolly[5], Tamiko Katsumoto[3,4], Paul Wolters[6], Pui-Yan Kwok[2,5] and Lindsey A. Criswell[7], [1]Cardiovascular Research Institute, University of California, San Francisco, San Francisco, CA, [2]Institute for Human Genetics, University of California, San Francisco, San Francisco, CA, [3]Rosalind Russell Medical Research Center for Arthritis, University of California, San Francisco, San Francisco, CA, [4]Department of Medicine, University of California, San Francisco, San Francisco, CA, [5]Department of Dermatology, University of California, San Francisco, San Francisco, CA, [6]Pulmonary Division, Department of Medicine, University of California, San Francisco, San Francisco, CA, [7]Rosalind Russell / Ephraim P. Engleman Rheumatology Research Center, University of California, San Francisco, San Francisco, CA

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Background/Purpose:

Scleroderma is a genetically complex autoimmune disease with substantial phenotypic heterogeneity. Previous genome-wide association studies (GWAS) have identified a large number of gene regions associated with disease risk. However, GWAS directly capture only common genetic variants that are presumably in linkage disequilibrium with causal variants, some of which may be rare

variants more frequently found in the disease population. Our goal was to identify potentially causal variants by comparing whole exome sequencing data between cases and controls. We focused on patients with severe disease, and specifically those with diffuse cutaneous systemic sclerosis (dcSSc), to limit disease heterogeneity.

Methods:

We produced whole exome sequencing data from 32 dcSSc patients on the Illumina HiSeq2500 platform with the Nimblegen SeqCap EZ v3.0 exome enrichment protocol. Paired-end 2 X 100 bp sequencing reads were generated with a mean coverage of 51X on the 64Mb of targeted exome regions. Control data came from 17 healthy control subjects whose data were produced using comparable methods, and from the 1000 Genomes and the NHLBI-ESP6500 Projects. Exome sequencing reads were processed according to the GATK Best Practices for DNAseq variant analysis. Variants were annotated and filtered with ANNOVAR and Variant Tools. We applied a gene mutation burden test to identify genes that were enriched with deleterious variants in dcSSc patients compared to controls.

Results:

We identified 96 genes that were enriched with deleterious variants in the dcSSc patients. Among the 96 genes, 10 genes (*NOTCH4, BANK1, BLK, GRB10, IRF8, KCNA5, NMNAT2 and TNFSF4*) are in previously identified scleroderma susceptibility loci or pathways implicated in scleroderma pathogenesis. In addition, we identified novel genes and 3 new pathways associated with scleroderma, including pathways related to ABC-family proteins mediated transport, extracellular matrix organization and the CD320-dependent methylmalonic aciduria.

Conclusion:

Using exome sequencing and gene mutation burden analysis, we identified 96 genes that contain functionally deleterious variants that may contribute to the development of dcSSc. This study demonstrates the potential value of whole exome sequencing for the identification of causal variants that contribute to scleroderma risk and/or severity. The candidate genes we discovered are potential targets for in-depth functional study or therapeutics development.

Disclosure: A. C. Mak, None; **P. L. Tang**, None; **C. Cleveland**, None; **M. K. Connolly**, None; **T. Katsumoto**, None; **P. Wolters**, None; **P. Y. Kwok**, None; **L. A. Criswell**, None.

Abstract Number: 3002

The Regulatory Role of Gammadelta T Cells in Bleomycin-Induced Pulmonary Fibrosis

Seiji Segawa[1], Daisuke Goto[2], Akira Iizuka[3], Masahiro Yokosawa[3], Shunta Kaneko[3], Yuya Kondo[3], Isao Matsumoto[3] and Takayuki Sumida[3], [1]Division of Clinical Immunology, Doctoral Program in Clinical Sciences,, University of Tsukuba, Tsukuba, Japan, [2]Division of Clinical Immunology, Doctoral Program in Clinical Sciences, Graduate School of Comprehensive Human Sciences, University of Tsukuba, Tsukuba, Japan, [3]Department of Internal Medicine, Faculty of Medicine, University of Tsukuba, Tsukuba, Japan

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Background/Purpose: Interstitial pneumonia (IP) is a chronic progressive interstitial lung disease associated with high mortality and poor prognosis. However, the exact mechanism of IP remains elusive. Recently, the pathological role of gdT cells was reported in several IP mice models. The γδT cells could produce a wide variety of cytokines, chemokines and growth factors and these cells have an important role in the regulation of the initial immune responses. In human, we previously reported that γδT cells might concern the pathogenesis of IP in systemic sclerosis patients. However, there are no reports on the properties and functional characteristics of γδT cells in pulmonary fibrosis. The purpose of this study is to clarify the role of γδT cells in bleomycin-induced IP model mice.

Methods: 1.C57BL/6 (WT) mice were injected with bleomycin (1.25mg/kg, intratracheally). After 3, 7, 14 and 21 days, the phenotypes of pulmonary γδT cells were examined by flow cytometry (FCM). 2.WT and TCRδ deficient ($TCR\delta^{-/-}$) mice were injected with bleomycin and the pathological findings were examined. 3.WT and $TCR\delta^{-/-}$ mice were injected with bleomycin. At 3, 7, 14, 21 days,

pulmonary Th17 (IL-17A$^+$ CD4$^+$ T) and Treg (Foxp3$^+$ CD4$^+$) cells were analyzed by FCM. 4.Splenic CD4$^+$T cells isolated from WT mice were co-cultured with γδT cells in condition of Th17 cell differentiation.

Results: 1.The number of pulmonary γδT cells increased at day3, 7, 14 after bleomycin exposure ($p<0.05$, $p<0.05$ and $p<0.05$, respectively). At 3 days after bleomycin exposure, pulmonary IFN-γ$^+$ γδT cells increased ($p<0.05$). On the other hands, pulmonary IL-17A$^+$ γδT cells increased at 7, 14 and 21 days after bleomycin exposure ($p<0.05$, $p<0.05$ and $p<0.05$, respectively). 2.TCRδ$^{-/-}$ mice showed pronounced hypercellularity and intimal thickening in lung parenchyma, and overproduction of collagen in lungs compared with WT mice. 3.In TCRδ$^{-/-}$ mice, pulmonary IL-17A$^+$ CD4$^+$ T cells increased at day 7 and 14 after bleomycin exposure compared with WT mice ($p<0.05$ and $p<0.05$, respectively). Pulmonary Foxp3$^+$ CD4$^+$ T cells were not significantly difference between WT and TCRδ$^{-/-}$ mice. 4.After co-cultured with γδT cells, the rate of IL-17A production in CD4$^+$ T cells and the number of IL-17A$^+$ CD4$^+$T cells were significantly decreased ($p<0.05$ and $p<0.05$, respectively).

Conclusion: Pulmonary γδT cells might play a regulatory role in the generation of bleomycin induced IP model mice via the suppression of IL-17 production.

Disclosure: S. Segawa, None; **D. Goto**, None; **A. Iizuka**, None; **M. Yokosawa**, None; **S. Kaneko**, None; **Y. Kondo**, None; **I. Matsumoto**, None; **T. Sumida**, None.

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Abstract Number: 3003

Increased Heparanase Expression in Keratinocytes Promotes Dermal Fibrosis in Scleroderma

In-Woon Baek[1], Wan-Uk Kim[2], Chul-Soo Cho[1] and Ki-Jo Kim[3], [1]Internal Medicine, Yeouido St. Mary's Hospital, The Catholic University of Korea, Seoul, South Korea, [2]Internal Medicine, Seoul St. Mary's Hospital, The Catholic University of Korea, Seoul, South Korea, [3]Internal Medicine, St. Vincent's Hospital, The Catholic University of Korea, Suwon, South Korea
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Background/Purpose: Interactions between keratinocyte and dermal fibroblast via paracrine loop play an important role in wound repair and keloid formation. In this study, we investigated heparanase expression in activated keratinocyte, and tested its effect on the survival of dermal fibroblasts.

Methods: Plasma heparanase levels were measured in scleroderma patients, and heparanase expression was evaluated in the skin of bleomycin-induced fibrosis mice and HaCaT keratinocyte (HaCaT). Dermal fibroblasts were cocultured with HaCaT separated by transwell insert under serum starvation, and apoptosis was determined using APOPercentage assay.

Results: Plasma heparanase levels were significantly higher in 26 scleroderma patients than in 10 healthy subjects, and positively correlated with plasma TGF-β levels. In bleomycin-induced fibrosis mice, increased heparanase expression was observed in keratinocyte layer, but not in dermal layer. Treatment of HaCaT with hypoxia resulted in significant increase in heparanase expression, and this increase was accompanied by concomitant increase of matrix metalloproteinase-9, both of which are known to degrade epidermal basement membrane components. Coculture of dermal fibroblasts and HaCaT in the presence of hypoxia significantly protected the apoptosis of dermal fibroblasts induced by serum starvation, but it was abolished by anti-heparanase antibody or transfection of HaCaT with heparanase siRNA. Dermal fibroblasts cocultured with HaCaT exposed to hypoxia exhibited increased Akt phosphorylation, and pretreatment of dermal fibroblasts with LY294002, an inhibitor of phosphatidylinositol 3-kinase, significantly abolished anti-apoptotic effect of heparanase on dermal fibroblasts.

Conclusion: These data indicate that hypoxia, caused possibly by microvascular alteration, increases heparanase production in keratinocytes, which may promote fibrosis in scleroderma by inhibiting the apoptosis of dermal fibroblasts.

Disclosure: I. W. Baek, None; **W. U. Kim**, None; **C. S. Cho**, None; **K. J. Kim**, None.

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Abstract Number: 3004

Scleroderma Keratinocytes Promote Fibroblast Activation Independent of TGF-ß

Sara S McCoy[1], Tamra J Reed[1], Pei-Suen Tsou[2], Dinesh Khanna[3], J. Michelle Kahlenberg[4] and Celine C. Berthier[5], [1]Division of Rheumatology, Division of Rheumatology, University of Michigan Medical Center, Ann Arbor, MI, [2]Division of Rheumatology, University of Michigan Medical Center, Ann Arbor, MI, [3]Division of Rheumatology, University of Michigan, Ann Arbor, MI, [4]Internal Medicine, Division of Rheumatology, Division of Rheumatology, University of Michigan Medical Center, Ann Arbor, MI, [5]Nephrology, Division of Nephrology, University of Michigan Medical Center, Ann Arbor, MI
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Background/Purpose: Systemic sclerosis (SSc) is a devastating fibrosing disease that primarily involves the skin, but may have life-threatening effects on the heart, lungs, gastrointestinal tract, and kidney. Although the exact pathogenesis of SSc remains unclear, one identified mechanism is the excessive extra cellular matrix (ECM) produced by fibroblast activation. Keratinocytes have recently been shown to influence fibroblast function; thus, we hypothesized that SSc keratinocytes may contribute to fibroblast activation and subsequent ECM production.

Methods: All SSc subjects fulfilled the ACR/EULAR criteria for SSc and were classified as limited cutaneous (lc) SSc and diffuse cutaneous (dc) SSc. Keratinocytes were cultured from the isolated epidermis of two 4mm forearm punch biopsies for two passages, and conditioned media was collected at passage 2. Keratinocyte population purity was assessed by morphology. Studies were performed on at least 3 lcSSc, 3 dcSSC, and 4 normal samples for each assay. Normal primary fibroblasts were stimulated for 24 or 72 hours with conditioned keratinocyte media in the presence or absence of TGF-β neutralizing antibody. Fibroblast activation was measured by expression of αsmooth muscle actin (SMA) and type 1 collagen expression via RT-PCR and with αSMA staining via immunofluorescent microscopy. Affymetric Human Gene ST2.1 microarrays were completed on cultured SSc and control keratinocytes. Pathway analysis was performed using Genomatix software.

Results: Stimulation of normal primary fibroblasts with keratinocyte conditioned media from lcSSc and dcSSc samples yielded increased collagen (lcSSc 1.6-4.5 fold, $p<0.0001$; dcSSc 1.2-4.4 fold,$p<0.0002$)and αSMA mRNA expression (lcSSc 6.6-12.5 fold,$p<0.0001$; dcSSc 6.2-13 fold;$p<0.0001$). αSMA expression was also increased on immunofluorescent staining of normal fibroblasts after exposure to scleroderma keratinocyte conditioned media. Microarray analyses and confirmation by RT-PCR demonstrated decreased TGF-β expression in both dcSSc and lcSSc keratinocytes. The addition of TGF-β neutralizing antibody to keratinocyte conditioned media did not decrease induction of αSMA or collagen expression by normal fibroblasts.

Conclusion: These results demonstrate that unstimulated scleroderma, but not control, keratinocytes are able to promote fibroblast activation, as measured by αSMA and collagen expression, independent of TGF-β production. Identification of the mediator of this activation may provide novel targets for prevention or treatment of fibrosis for SSC patients

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Disclosure: S. S. McCoy, None; **T. J. Reed**, None; **P. S. Tsou**, None; **D. Khanna**, None; **J. M. Kahlenberg**, None; **C. C. Berthier**, None.

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Abstract Number: 3005

Pulmonary Arterial Hypertension-Associated Single Nucleotide Polymorphisms of Hypoxia-Inducible Factor-3a Gene Cause Constitutive Activation of the Endothelin-1 Gene Promoter

Katsutoshi Mizumoto[1], Kyohei Takatori[1], Sayaka Takatori[1], Ryota Yoshimoto[1], Kohei Eguchi[1], Daisuke Fujishiro[1], Satoru Kodama[1], Atsushi Kobayashi[1], Kensaku Okamoto[1], Yasushi Kawaguchi[2], Masakazu Haneda[1] and Yuichi Makino[1], [1]Division of Metabolism and

Biosystemic Science, Department of Medicine, Asahikawa Medical University, Asahikawa, Japan, [2]Institute of Rheumatology, Tokyo Women's Medical University, Tokyo, Japan
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Background/Purpose: Pulmonary arterial hypertension (PAH) is a progressive and fatal complication in the patients with connective tissue diseases (CTD). Elevation of endothelin-1 (ET-1) levels in pulmonary arteries is suggested as one of the pathogenesis of PAH, however, mechanism for ET-1 induction in the disease circumstances is still elusive. A driving force for ET-1 synthesis is hypoxia and ET-1 has been known as a target gene of hypoxia-inducible factors (HIFs). HIFs are heterodimeric transcription factors composed of α subunit (HIF-1α or HIF-2α or HIF-3α) and β subunit (HIF-1β), operating in gene regulation in adaptive response to hypoxic condition. We have demonstrated ablation of HIF-3α gene in mice resulted in an increase in ET-1 production by pulmonary endothelial cells and human PAH-like cardio-pulmonary phenotype such as right ventricular enlargement and pulmonary arteriole musculalizations, indicating an implication of HIF-3α in the pathogenesis of PAH. In the present study, we aimed to explore the role of genetic defect or anomalies of HIF-3α in the pathogenesis of CTD-PAH.

Methods: Using genomic DNA form patients with systemic sclerosis (SSc) without PAH, SSc complicated with PAH, and normal healthy controls, we analyzed the incidence of coding single nucleotide polymorphisms (SNPs) in HIF3A gene reported in NCBI dbSNP database by PCR-direct sequencing. The m×n χ^2–test was applied to examine statistical significance of the incidence of the SNPs. Functional validations of the HIF-3α carrying the SNPs (SNP-HIF3α) were performed in the cells overexpressing SNP-HIF3α. Effect of SNP-HIF3α on ET-1 gene promoter was analyzed by reporter gene assays and chromatin immunoprecipitation assays.

Results: We found coding SNPs in HIF3A gene with significantly higher incidence in the SSc patients complicated with PAH compared to the SSc patients without PAH. Overexpression of HIF-3α carrying the SNPs (SNP-HIF3α) in the cells resulted in induction of ET-1 mRNA even under normoxic condition, indicating an implication of SNP-HIF3α in dysregulation of ET-1 production. SNP-HIF3α showed higher affinity to HIF-1β and to ET-1 gene promoter irrespectively of oxygen concentrations compared to wild type HIF-3α. Interestingly, SNP-HIF3α seemed to employ an additional cis-acting DNA sequence proximity to hypoxia response element in ET-1 gene promoter for transcriptional activation of the gene.

Conclusion: PAH-associated coding SNPs confer a novel function on HIF-3α at ET-1 gene promoter, which might contribute to the derangement of ET-1 gene regulation in patients with CTD-PAH.

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Abstract Number: 3006

Cell-Free Circulating DNA in Systemic Sclerosis: Increased Levels and Global Cytosine Hypomethylation

Shadia Nada[1], Omar Oraibi[2], Farouk Abu Alhana[2], Nawaf Almeshal[2], Yongqing Wang[2], **Nezam Altorok**[3] and Bashar Kahaleh[4], [1]Internal Medicine, Divison of Rheumatology, The University of Toledo, Toledo, OH, [2]The University of Toledo, Toledo, OH, [3]Internal Medicine, Division of Rheumatology, The University of Toledo, Toledo, OH, [4]Medicine/Rheumatology, The University of Toledo, Toledo, OH
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Background/Purpose: Systemic sclerosis (SSc) is an autoimmune disease characterized by endothelial dysfunction, vascular injury,

and activation of fibroblasts leading to organ fibrosis. The precise etiology of SSc is not clear. We sought to study circulating cell-free DNA (cfDNA) and characterize it in an initial effort to determine if cfDNA is a useful biomarker in SSc.

Methods: We measured levels of cfDNA in the serum of 20 patients with SSc (13 limited cutaneous SSc, 7 diffuse cutaneous SSc) compared to 20 age-, sex-, and ethnicity-matched controls. The average age was 57.8 and 52.3 years for patients with SSc and controls, respectively (P= 0.10). The majority of subjects in this study were female (n= 17), and Caucasians (n= 19). Modified Rodanan's skin score (mRSS) was 6.5 and 20.2 for patients with limited cutaneous SSc (lcSSc) and diffuse cutaneous SSc (dcSSc), respectively. Moreover, we measured global methylation level of Cytosine in cfDNA by directly quantifying levels of 5-methylcytosine using 5-methylcytosine specific capture antibody.

Results: We demonstrate an increase in cfDNA level in patients with SSc (262.1 ng/ml) compared to healthy controls (65.9 ng/ml) (P= 0.027). The average level of cfDNA in lcSSc was (134.03 ng/ml) (P = 0.004), and (463.76 ng/ml) in dcSSc (P= 0.022). We did not find a correlation between level of cfDNA and mRSS in each subset, clinical manifestations, or type of organ involvement. We used same amount of cfDNA from each sample to measure 5-methylcytosine, and we demonstrate that cytosine methylation was significantly lower in patients with SSc (29.1%) compared to controls (54.3%) (P = 0.047). There was no significant difference in cytosine methylation between the two subsets of SSc.

Conclusion:

We demonstrate increased level of cfDNA in sera of patients with SSc, especially in patients with dcSSc in association with global hypomethylaiton of cytosine. We did not find a correlation between level of cfDNA and mRSS and/or clinical features of SSc. The origin, functional effect and suitability of cfDNA as a biomarker in SSc need further investigation.

Disclosure: S. Nada, None; **O. Oraibi**, None; **F. Abu Alhana**, None; **N. Almeshal**, None; **Y. Wang**, None; **N. Altorok**, None; **B. Kahaleh**, None.

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Abstract Number: 3007

Cold Receptor Expression and Function in Human Dermal Fibroblast: Possible Role in the Pathogenesis of Scleroderma Fibrosis

Yongqing Wang[1], John Sun[1], Shadia Nada[2], Nezam Altorok[3] and **Bashar Kahaleh**[4], [1]The University of Toledo, Toledo, OH, [2]Internal Medicine, Divison of Rheumatology, The University of Toledo, Toledo, OH, [3]Internal Medicine, Division of Rheumatology, The University of Toledo, Toledo, OH, [4]Medicine/Rheumatology, The University of Toledo, Toledo, OH
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Background/Purpose:

Enhanced cold sensitivity is an early and consistent phenomenon in scleroderma (SSc). We previously demonstrated increased expression of the transient receptor potential melastatine 8 (TRPM8) in SSc microvascular endothelial cells. TRPM8 protein is a cold- and menthol-sensing calcium (Ca^{2+}) ion channel. To date, TRPM8 expression, function and intracellular signaling have not been characterized in human dermal fibroblasts (FB). In this study we evaluated TRPM8 expression in normal and SSc FB and in skin biopsies. We also investigated the effects of TRPM8 activation on selected FB fibrotic gene expression, intracellular calcium concentration ($[Ca^{2+}]_i$), intracellular reactive oxygen species (ROS) generation and SMAD3 phosphorylation.

Methods:

FB were isolated from involved SSc skin and matched control subjects. The expression of TRPM8 was determined by RT-PCR, immunocytochemistry (ICC) and western blot (WB) analysis. TRPM8 activation in FB was triggered by the TRPM8 agonist menthol (MT) or by exposure of cells to cold (18C°). The $[Ca^{2+}]_i$ was determined by Ca^{2+} calcium imaging system using Ca^{2+} indicator dye Fura 2 or Fura4. The mRNA and protein expression levels of *COL1, aSMA, FN, CTGF* and phosphoSMAD3 were determined by q PCR and WB. The production of ROS was detected by fluorescent indicator dye dihydroethidium (DHE). SMAD3 binding to CTGF promoter region was detected by chromatin immunoprecipitation assay (ChIP).

Results:

TRPM8 gene and protein expression in dermal FB was determined by RT-PCR, WB and ICC. TRPM8 mRNA and protein expression were significantly higher in SSc-FB and SSc-skin biopsies. Calcium image studies show that MT increased $[Ca^{2+}]_i$ and this response was blocked by capsazepine (CapZ), an antagonist of TRPM8. The activation of the TRPM8 by MT or cold exposure resulted in increased expression of *COL1, aSMA*, and *FN*. SSc-FB were more sensitive to MT or cold than normal FB. These effects were blocked by the addition of CapZ or TRPM8 siRNA. Furthermore, MT evoked production of intracellular ROS, which could be abolished by Ca^{2+} free solution or CapZ. The increased expression of *COL1, FN*, *aSMA* and *CTGF* by MT were inhibited by BAPTA-AM (intracellular calcium chelator) or by antioxidants (a mixture of superoxide dismutase, catalase and N-acetycysteine amide). Additionally, MT induced intracellular SMAD3 phosphorylation and facilitated nuclear accumulation of SMAD3. Finally, Chip assay confirmed that SMAD3 is recruited to the CTGF promoter after MT stimulation in FB. The addition of SB431542 and CTGF antibody partly block the *COL1* expression induced by MT.

Conclusion: Functional TRPM8 is expressed in human dermal FB and enhanced expression was observed in SSc FB and skin. The activation of TRPM8 mediated enhanced expression of the profibrotic genes *COL1*, aSMA, *FN and CTGF* via calcium influx, ROS production and SMAD3 transcription activation. SSc-FB were more sensitive to MT or cold exposure than normal FB, implicating potential involvement of TRPM8 in the pathogenesis of scleroderma fibrosis and suggesting that the blockade of TRPM8 may be a novel target for therapeutic intervention in SSc.

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Abstract Number: 3008

Role of PTP4A1 Tyrosine Phosphatase in Systemic Sclerosis

Cristiano Sacchetti[1], Stephanie Stanford[2], Yunpeng Bai[3], Zhong-Yin Zhang[4], Amin Gholami[5], Gregory Seumois[6], Maria Piera-Velazquez[7], Sergio A. Jimenez[8] and Nunzio Bottini[1], [1]Cellular Biology, La Jolla Institute for Allergy and Immunology, La Jolla, CA, [2]Cell Biology, La Jolla Institute for Allergy and Immunology, La Jolla, CA, [3]Indiana University, School of Medicine, Indianapolis, IN, [4]Biochemistry and Molecular Biology, Indiana University School of Medicine, Indianapolis, IN, [5]Bioinformatics Core, La Jolla Institute for Allergy and immunology, La Jolla, CA, [6]Sequencing Facility, La Jolla Institute for Allergy and immunology, La Jolla, CA, [7]Dermatology and Cutaneous Biology, Jefferson Medical College, Philadelphia, PA, [8]Div Connective Tissue Diseases, Thomas Jefferson Univ, Philadelphia, PA

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Background/Purpose: Systemic sclerosis (SSc) is a multi-system autoimmune connective tissue disorder that leads to fibrosis of the skin and internal organs, resulting in significant patient morbidity and mortality. The fibroblast is considered a key target cell type for possible therapies aimed at modifying excessive deposition of extracellular matrix in affected organs. Several studies have assessed the role of protein tyrosine kinases (PTKs) in the pathophysiology of SSc fibroblasts and fibrosis. However the role of protein tyrosine phosphatases (PTPs), a family of enzymes that naturally balance the action of PTKs in signal transduction, in fibrosis remains mostly unexplored.

Methods: We analyzed the mRNA expression profile of all the PTPs (109 genes) in primary dermal fibroblasts from 9 patients with diffuse SSc compared to 9 healthy subjects. Whole transcriptome analysis by Next Generation Sequencing (NGS) was performed on normal human dermal fibroblasts (NHDF) subjected to silencing of the *PTP4A1* gene. In NHDF we investigated the effects of *PTP4A1* silencing on TGFbeta1 stimulated *COL1A2* and *ACTA2* gene expression and on SMAD3 and alphaSMA protein level by qPCR and immunoblotting, respectively. Luciferase assays were performed using a SMAD reporter in HEK 293T cell and *in vivo* experiments were carried out in mice using a bleomycin-induced fibrosis model.

Results: *PTP4A1* gene displayed increased expression in SSc dermal fibroblast lines studied (Mann-Whitney test, $p<0.05$). NGS of normal dermal fibroblasts showed that silencing of *PTP4A1* correlated with reduced expression of human pro-fibrotic genes and in particular of *SMAD3,* which pointed to a possible role of PTP4A1 in the TGFbeta-dependent pro-fibrotic pathway. NGS data for SMAD3 and other pro-fibrotic genes were confirmed at the protein level by immunoblotting. Co-transfection of HEK 293T with a

human *PTP4A1*-encoding pCDNA4 vector together with a luciferase SMAD reporter showed that PTP4A1 enhances activation of SMAD signaling after TGFbeta1 stimulation (Mann-Whitney test, $p<0.05$). *In vivo* experiments showed that knockout of PTP4A1 significantly attenuates bleomycin-induced fibrosis model in mice.

Conclusion: These results suggest that PTP4A1, a PTP overexpressed in SSc dermal fibroblasts, plays a role in the pathogenesis of SSc by promoting pro-fibrotic TGFbeta/SMAD3 signaling.

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Abstract Number: 3009

Fli1 Deficiency Contributes to the Downregulation of Endothelial Protein C Receptor in Systemic Sclerosis: A Possible Role in Pro-Thrombotic Condition

Ryosuke Saigusa[1], **Yoshihide Asano**[2], Takashi Taniguchi[2], Takashi Yamashita[2], Takehiro Takahashi[2], Yohei Ichimura[2], Tetsuo Toyama[2], Ayumi Yoshizaki[2], Tomomitsu Miyagaki[2], Makoto Sugaya[2] and Shinichi Sato[2], [1]7-3-1 Hongo, Bunkyo-ku, University of Tokyo Graduate School of Medicine, Tokyo, Japan, [2]Dermatology, University of Tokyo Graduate School of Medicine, Tokyo, Japan
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Background/Purpose: Systemic sclerosis (SSc) is a multisystem connective tissue disease characterized by fibrosis of the skin and certain internal organs due to the constitutive activation of fibroblasts following immune attacks and vascular injury. Although the pathogenesis of SSc still remains unknown, a variable degree of luminal thrombosis following vascular injury may contribute to impaired peripheral circulation and the activation of vascular cells and fibroblasts. Endothelial protein C receptor (EPCR) predominantly expressed on endothelial cells plays a critical role in the regulation of coagulation system and also mediates various cytoprotective effects by binding and activating protein C. Since the role of EPCR has not been studied in SSc, we here investigated the potential contribution of EPCR to the development of this disease by utilizing clinical samples and its animal models.

Methods: EPCR expression was examined in skin samples and cultivated dermal microvascular endothelial cells by immunostaining and/or quantitative reverse transcription PCR. Fli1 binding to the *EPCR* promoter was assessed by chromatin immunoprecipitation. Serum EPCR levels were determined by enzyme-linked immunosorbent assay in 65 SSc and 20 healthy subjects.

Results: EPCR expression was markedly decreased in dermal small vessels of SSc lesional skin compared with those of healthy control skin. Transcription factor Fli1, whose deficiency is implicated in SSc vasculopathy, occupied the *EPCR* promoter and EPCR expression was suppressed in Fli1 siRNA-treated human dermal microvascular endothelial cells and dermal small vessels of *Fli1*$^{+/-}$ mice. In SSc patients, decreased serum EPCR levels were associated with diffuse skin involvement, interstitial lung disease and the current and past history of digital ulcers, all of which are associated with hyper-coagulation status. Furthermore, serum EPCR levels inversely correlated with plasma levels of plasmin-a2-plasmin inhibitor complex (PIC), suggesting that reduced expression of endothelial EPCR truly induces hyper-coagulation status in SSc. Moreover, circulating EPCR and PIC levels were normalized in parallel with the up-regulation of Fli1 and EPCR in endothelial cells after the treatment with bosentan, a potential disease modifying drug preventing the development of digital ulcers in SSc.

Conclusion: This is the first report demonstrating the potential contribution of reduced EPCR to the development of SSc. The present findings further reinforce the notions that endothelial Fli1 deficiency is a key feature underlying the induction of structural and functional abnormalities of SSc vasculopathy and that bosentan has a potential to reverse the vascular phenotype related to Fli1 deficiency. The reversal of impaired coagulation/fibrinolysis system is a possible mechanism underlying the preventive effect of bosentan on digital ulcers in SSc.

Disclosure: R. Saigusa, None; **Y. Asano**, Actelion Pharmaceuticals JAPAN, 9; **T. Taniguchi**, None; **T. Yamashita**, None; **T. Takahashi**, None; **Y. Ichimura**, None; **T. Toyama**, None; **A. Yoshizaki**, None; **T. Miyagaki**, None; **M. Sugaya**, None; **S. Sato**, None.

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Abstract Number: 3010

Estrogens Inhibit the Profibrotic Effects of Transforming Growth Factor-Beta and Protect from the Development of Experimental Dermal Fibrosis

Jerome Avouac[1], Léa Baudoin[2], Anne Cauvet[2], Barbara Ruiz[2] and Yannick Allanore[3], [1]Rheumatology A department and INSERM U1016, Paris Descartes University, Cochin Hospital, Paris, France, [2]INSERM U1016, Paris Descartes University, Cochin Hospital, Paris, France, [3]Paris Descartes University, Rheumatology A department, Cochin Hospital, And Eular Scleroderma Trials And Research (EUSTAR) Board, Paris, France

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Background/Purpose: Systemic sclerosis (SSc) primarily affects postmenopausal women. This sex bias could partly be explained by the action of estrogens on the immune system and/or fibrogenesis. Since little is known about their direct role in fibrogenesis, our aim was to evaluate the effects of estrogens i) on the pathological activation of dermal fibroblasts induced by transforming growth factor-b (TGF-β) and ii) in the development of experimental dermal fibrosis.

Methods: SSc dermal fibroblasts were stimulated with TGF-β and incubated with different concentrations of 17-β-estradiol and/or tamoxifen, a selective estrogen receptor modulator that display anti-estrogenic properties. Collagen release from fibroblasts was evaluated by mRNA levels of col1a1 and col1a2 and by measuring the concentrations of collagen in cell culture supernatants with the SirCol collagen assay. Differentiation of fibroblasts into myofibroblasts was assessed by the expression of alpha smooth muscle actin (α-SMA). Activation of the TGF-β pathway was evaluated by the expression of phospho-smad-2/3. Effects on estrogen inhibition by gene inactivation (knockout mice for the estrogen receptor-α, ERKOa) or targeted molecular strategy (tamoxifen) were evaluated in the mouse model of bleomycin-induced dermal fibrosis and in the tight skin (Tsk-1) mouse model.

Results: Treatment of SSc dermal fibroblasts with 17-β-estradiol or tamoxifen did not change significantly baseline collagen production and fibroblast differentiation. In SSc fibroblasts stimulated by TGF-β, treatment with 17-β-estradiol led to a significant reduction of COL1A1 and COL1A2 mRNA levels, as well as collagen release in cell culture supernatant. In addition, decreased α-SMA mRNA and protein levels were observed upon treatment with 17-β-estradiol in TGF-b stimulated dermal fibroblasts. 17-β-estradiol also led to a significant reduction of TGF-b dependent phosphorylation of phospho-Smad2/3. In fibroblasts stimulated with TGF-b and treated with 17-β-estradiol, the addition of tamoxifen restored TGF-b signaling and its profibrotic effects on collagen synthesis and fibroblast differentiation.

Estrogen inhibition led to more a severe dermal fibrosis induced by bleomycin. Upon bleomycin injections, ERKO-a mice and mice treated with tamoxifen had a significant increase of dermal thickness (17%, p=0.03 and 20%, p=0.04), hydroxyproline content mice (16%, p=0.02 and 36%, p=0.003, respectively) and number of myofibroblasts (22%, p = 0.01 and 20%, p = 0.04 respectively) compared to control mice. In Tsk-1 mice, treatment with tamoxifen led to significantly enhanced skin fibrosis, with a 31±8% increase of hypodermal thickening (p=0.03) and a 17% increase of hydroxyproline content (p=0.01) compared to control mice.

Conclusion: Our results demonstrate a beneficial effect of estrogen in dermal fibrosis. Estrogens reduce TGF-b dependent activation of SSc dermal fibroblasts and estrogen inhibition leads to a more severe experimental dermal fibrosis. These findings may partly explain the occurrence of SSc in postmenopausal women and the greater severity of the disease in men and open avenue to potential hormonal therapies.

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Abstract Number: 3011

The Homeoprotein Engrailed-1 Regulates Canonical TGF Beta Signaling in Experimental Systemic Sclerosis

Tatjana Mallano[1], Katrin Palumbo-Zerr[1], Christian Beyer[1,2], Clara Dees[1], Jingang Huang[1], Thomas Wohlfahrt[1], Oliver Distler[3], Georg Schett[1] and Jeorg HW Distler[1,2], [1]Department of Internal Medicine 3 and Institute for Clinical Immunology, University of Erlangen-Nuremberg, Erlangen, Germany, [2]Department of Internal Medicine 3, University of Erlangen-Nuremberg, Erlangen, Germany, [3]Department of Rheumatology, Center of Experimental Rheumatology and Zurich Center of Integrative Human Physiology, University Hospital Zurich, Zurich, Switzerland

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Background/Purpose: Systemic sclerosis (SSc) is a chronic fibrotic connective disease of unknown etiology that affects the skin and internal organs. Transforming growth factor-β (TGFβ) has been characterized as a key-mediator of fibroblast activation in SSc. However, the intracellular signaling cascades that control TGFβ signaling and the TGFβ-induced activation of fibroblasts are still incompletely understood. Homeobox containing transcription factor, Engrailed-1 plays a key role in embryonic development and has also been linked to disease, including cancer. EN-1 is induced by proinflammary cytokines and oxidative stress which play an important role in Systemic Sclerosis (SSc).

Methods: The expression of EN-1 in skin tissue and in human dermal fibroblasts was determined by real-time PCR, Western blot and immunohistochemistry. Knock-down and overexpression strategies were used to evaluate the effect of EN-1 on fibroblast activation. The outcome of mice with fibroblast-specific knockout of EN-1 (EN1 fibKO) was evaluated in bleomycin-induced skin fibrosis; fibrosis induced by overexpression of a constitutively active TGF-β receptor I (TBRIact) and in the Tsk model which resembled the later stages of SSc. Co-IP and CAGA Reporter assay were performed to study the physical and functional interaction between EN-1 and Smad3.

Results: A five-fold increased expression of EN-1 was detected in the upper layer of the dermis of SSc patients on fibroblasts double stained for EN-1 and anti-prolyl-4-hydroxylase. EN-1 expression was induced by TGF-β in cultured fibroblasts and treatment with the TBR inhibitor SD-208 prevented the induction of EN-1 by two-fold decrease in experimental fibrosis. Fibroblasts lacking EN-1 were less sensitive to the pro-fibrotic effects of TGF-β with impaired induction of collagen mRNA and protein. Additionally, overexpression of EN-1 enhanced the profibrotic effect of TGF-β with myofibroblast differentiation and increased collagene release. Function studies demonstrated that EN-1 interacts with Smad3 to regulate the pro-fibrotic effects of TGF-β. Co-IP demonstrated that TGF-β induces binding of EN-1 to Smad3. Reporter study and analyses of the expression of classical Smad target genes such as PAI-1 demonstrated that the binding of EN-1 to Smad3 stimulates the transcriptional activity of Smad3. In the model of bleomycin-induced fibrosis dermal thickening, hydroxyproline content and myofibroblast counts were significantly decreased in EN1 fibKO mice as compared to wildtype littermates. EN1 fibKO also protected from TBRIact-induced fibrosis and ameliorated fibrosis in the Tsk1 model.

Conclusion: We demonstrate for the first time a role of EN-1 in fibroblast activation and tissue fibrosis. Deficiency in EN-1 reduced the stimulatory effect of TGF-β on fibroblasts by interfering with canonical Smad and protected from experimental fibrosis in different mouse models. Considering the potent anti-fibrotic effects observed in this study, EN-1 might be a candidate for molecular targeted therapies of SSc.

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Abstract Number: 3012

Over-Expression of Ubiquitin-Specific Peptidases in Systemic Sclerosis Fibroblasts Increases Responses to TGF-Beta

Christine Galant, Joëlle Marchandise, Julie Ducreux, Maria Stoenoiu, Frédéric A. Houssiau and **Bernard R. Lauwerys**, Pôle de pathologies rhumatismales inflammatoires et systémiques, Institut de Recherche Expérimentale et Clinique, Université catholique de Louvain, Brussels, Belgium

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Background/Purpose: Ubiquitination of proteins leads to their degradation by the proteasome, and is regulated by a small number of ubiquitin ligases, and a large number of susbtrate-specific ubiquitin-specific peptidases (USP). The ubiquitination process is not only key to protein recycling, and cell survival but plays also important roles in the regulation of cell metabolism and cell cycle. Here, we found that the expression of several USP is increased in systemic sclerosis tenosynovial biopsies, and we demonstrated that USP inhibition decreases TGFβ signaling in primary fibroblast cell lines.

Methods: HGU133 Plus2.0 arrays were hybridized with total RNA obtained from 5 tenosynovial samples obtained in patients with SSc and overt tenosynovial involvement, and compared to disease control synovial biopsies. Primary fibroblast cell lines were obtained from the skin of SSc patients or controls, and cultured in the presence of DMOG, a HIF1α hydroxylase inhibitor or in the presence of TGFβ +/- USP inhibitor NS-632839. HEK293 cells were stably transfected with an USP15-encoding expression plasmid.

Results: Transcriptomic profiles of tenosynovial biopsies from SSc patients were characterized by the expression of genes involved in known pathogenic pathways : fibrosis, Wnt signaling, but also by the over-expression of several USP (USP15, 16, 18, 25, 31, 36, 37, 45, 48). Immunohistochemistry experiments on the same samples confirmed the presence of USP15 in SSc biopsies.

Culture of primary fibroblast cell lines in the presence of DMOG, a HIF1α-hydroxylase inhibitor that mimics the effects of hypoxia, results in a significant induction of TGFβ, USP25 and USP36 gene expression, but not USP15.

USP15 is known to specifically deubiquinate SMAD3, and we confirmed that over-expression of USP15 in HEK293 cells results in increased SMAD3, and SMAD3 phosphorylation in response to TGFβ stimulation. Conversely, exposure of cultured fibroblasts to NS-632839, a pan-USP inhibitor decreased SMAD3 expression and phosphorylation, and expression of COLIAI, COL3A1 and fibronectin gene expression in response to TGFβ stimulation. The effect of the USP inhibitor resulted in increased SMAD3 ubiquitination (as proven by SMAD3 immunoprecipitation experiments), and was blocked by epoxomicin, a proteasome inhibitor, thereby confirming the specificity of its action.

Conclusion: Over-expression of several USP, including USP15, is observed in tenosynovial biopsies from SSc patients, and is not fully explained by the effects of hypoxia. USP15 amplifies fibrotic responses induced by TGFβ, and is a potential therapeutic target in SSc.

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Abstract Number: 3013

Adipose Loss of Co-Repressor Ncor Attenuates Bleomycin-Induced Skin Fibrosis By Enhancing PPAR-Gamma Signaling

Benjamin Korman[1], Roberta Goncalves Marangoni[1], Warren Tourtellotte[2] and John Varga[3], [1]Division of Rheumatology, Northwestern University, Chicago, IL, [2]Department of Pathology, Ward, Northwestern University, Chicago, IL, [3]Division of Rheumatology, Northwestern University, Feinberg School of Medicine, Chicago, IL

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Background/Purpose: The adipogenesis master regulator PPAR-gamma (PPARg) is regulated by repressors such as NCoR. Systemic sclerosis (SSc) is associated with impaired PPARg expression and function and altered adipokine homeostasis. Loss of intradermal adipose tissue is prominent in the skin in SSc, as well as in mouse models of skin fibrosis.

Methods: To test the hypothesis that decreased adipose PPARg has a pathogenic role in dermal fibrosis and to ask whether rescuing its function might be beneficial, we characterized skin fibrosis in mice with adipocyte-specific NCoR ablation using the bleomycin model.

Results:

Adipocyte-NCoR null mice on a high-fat diet showed PPARg activation, enhanced insulin sensitivity and alterations in serum adipokines. Moreover, NCoR null mice were resistant to bleomycin-induced changes in adipocyte size and function and loss of intradermal adipose tissue. Importantly, NCoR null mice had attenuated skin fibrosis measured both histologically and biochemically, which was reversed by the pharmacological inhibitor of PPARg GW9662. Taken together, these findings suggest that enhanced dermal adipogenesis mediated by tissue-specific PPARg activation modulates skin fibrosis.

Conclusion: These results strongly suggest that intradermal adipose plays an active role in skin fibrosis. Targeting adipogenesis might therefore represent an innovative approach to control skin fibrosis in SSc

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Abstract Number: 3014

Endotrophin: A Novel Adipokine Linking Adipose Tissue and Skin Fibrosis in Systemic Sclerosis

Roberta Goncalves Marangoni[1], Jun Wei[2], Monique E. Hinchcliff[1], Philipp E. Scherer[3] and John Varga[2], [1]Division of Rheumatology, Division of Rheumatology, Northwestern University, Feinberg School of Medicine, Chicago, IL, [2]Division of Rheumatology, Northwestern University, Feinberg School of Medicine, Chicago, IL, [3]University of Texas Southwestern Medical Center, Dallas, TX

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Background/Purpose: Adipocytes and their progenitor cells are embedded in a network of extracellular matrix that plays a role in regulating its function. Type 6 collagen (COL6) is the most highly expressed collagen in differentiated adipocytes and its expression is upregulated in the skin in systemic sclerosis (SSc). The cleavage product of COL6α3, endotrophin, is secreted by mature adipocytes. The recently described adipokine, endotrophin, exerts a major influence locally in adipose tissue and has potential effects on triggering fibrosis and inflammation in both metabolic dysfunction and in growing solid tumors. In SSc, recent findings point to an unrecognized connection between adipose tissue, adipokines, and fibrosis. We, therefore, hypothesize that in SSc abnormal endotrophin expression contributes to dermal fibrosis.

Methods: To examine COL6 expression in SSc skin, we first queried a publicly available data set comprising genome-wide expression data from SSc and healthy control skin biopsy samples. COL6 mRNA expression was also examined in explanted fibroblasts from SSc skin biopsies and healthy controls. Tissue levels of endotrophin protein in skin biopsy samples from SSc patients with diffuse subtype and healthy controls were examined by immunohistochemistry.

Results: Levels of COL6 mRNA were found to be significantly increased ($p < 0.001$) in skin biopsy samples mapping to the diffuse-proliferative and inflammatory intrinsic subsets compared to normal-like subsets. Expression levels of COL6α3 mRNA were positively correlated with the total skin score (MRSS) ($R=0.39$, $p<0.001$). Elevated COL6 mRNA expression in SSc skin biopsy samples was confirmed by real-time qPCR ($p=0.02$). Endotrophin was markedly increased in both dermis and intradermal adipose tissue of diffuse SSc patients as compared to healthy controls ($p=0.002$).

Conclusion: Endotrophin and COL6 expression are both highly expressed in the skin in SSc. Endotrophin has potential effects on fibrosis in SSc and might be a potential target of therapy.

Disclosure: R. G. Marangoni, None; **J. Wei**, None; **M. E. Hinchcliff**, None; **P. E. Scherer**, None; **J. Varga**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/endotrophin-a-novel-adipokine-linking-adipose-tissue-and-skin-fibrosis-in-systemic-sclerosis

Abstract Number: 3015

Characterization of the Profibrotic/Antifibrotic Profile of microRNA Contained in Exosomes Isolated from Cultured Normal Human Dermal and Lung Microvascular Endothelial Cells Undergoing Endothelial Mesenchymal Transition in Vitro

Sergio A. Jimenez[1], **Sonsoles Piera-Velazquez**[2], Peter J. Wermuth[3] and Kerri Fasino[4], [1]Jefferson Institute of Molecular Medicine, Division of Connective Tissue Diseases and Scleroderma Center,Thomas Jefferson University, Philadelphia, PA, [2]Jefferson Institute of Molecular Medicine, Thomas Jefferson Univ, Philadelphia, PA, [3]Jefferson Institute of Molecular Medicine, Division of Connective Tissue Diseases and Scleroderma Center, Thomas Jefferson University, Philadelphia, PA, [4]Jefferson Institute of Molecular Medicine and Division of Connective Tissue Diseases, Thomas Jefferson University, Philadelphia, PA

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Background/Purpose: Systemic Sclerosis (SSc) is characterized by progressive fibrosis of skin and multiple internal organs, severe alterations in the microvasculature, and numerous immunological abnormalities. Recently it has been suggested that endothelial to mesenchymal transition (EndoMT) may be involved in SSc vasculopathy and tissue fibrosis. Exosomes are 30-150 nm lipid bilayer bound microvesicles released from all human cells into their surrounding intercellular space and into the circulation and contain numerous macromolecules including mRNAs, miRNAs, proteins, cytokines, chemokines and growth factors. Exosomes are capable of carrying complex signals to sites removed from the cell of origin. We propose that EndoMT-activated EC induce phenotypic changes in normal/healthy fibroblasts and EC and that these effects are mediated by exosomes released into the circulation that reach normal fibroblasts and EC, fusing with them, and transferring their miRNA contents rendering them profibrotic. We examined here whether exosomes isolated from Endo-MT-activated normal human dermal and lung microvascular EC display alterations in their miRNA content that may be capable of inducing a profibrotic phenotype in normal fibroblasts and EC.

Methods: Normal human dermal or lung microvascular EC were expanded in monolayer cultures until reaching confluency, then they were cultured under control conditions or in the presence of 10 ng/ml of TGF-β1 or TGF-β2 for 48h to induce EndoMT. Following treatment the cells were washed and incubated in exosome-free culture media for additional 24h. The culture media were collected and exosomes were isolated using the ExoQuick polymer exosome purification procedure. The exosomes were pelleted by centrifugation. Exosome miRNA were isolated by lysis of the pellet and RNA purification using SeraMir RNA spin columns. cDNA was synthesized by polyadenlyation of RNA followed by reverse transcription substituting a miRNA 3' adaptor oligonucleotide in place of Oligo-dT. The resulting single-stranded miRNA-derived cDNA was utilized in qPCR profiling of profibrotic and antifibrotic miRNAs. Exosomal miRNA levels were normalized to levels of the small nucleolar RNA SNORD25.

Results: Exosomes were successfully isolated from culture media samples and sufficient RNA was extracted for RTPCR performance and relative miRNA quantification. The quantification of profibrotic and antifibrotic miRNA in the exosomes isolated from the culture media of both cell types is shown in Figure 1.

Conclusion: Exosomes were successfully isolated and purified from the culture media of human EC. TGF-β1 or TGF-β2-mediated *in vitro* induction of EndoMT in normal human dermal or lung microvascular EC resulted in a marked increase in profibrotic miRNA and a marked decrease in antifibrotic miRNA contained in exosomes released by these cells into the culture media.

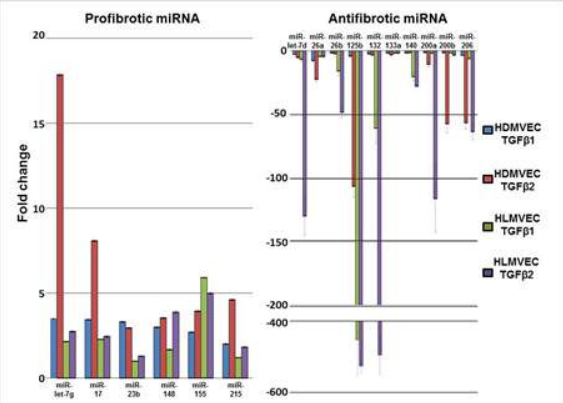

Figure 1. Levels of **miRNA contained in exosomes isolated from culture media from normal human dermal microvascular EC (HDMVEC) or normal human lung microvascular EC (HLMVEC) treated with either TGF-β1 or TGF-β2 assessed by real time PCR.** Values represent the mean (+/- SD) fold change levels of three replicates of exosomes isolated from each cell line. Content levels in samples of untreated cells were arbitrarily set at 1 fold.

Disclosure: S. A. Jimenez, None; **S. Piera-Velazquez**, None; **P. J. Wermuth**, None; **K. Fasino**, None.

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Abstract Number: 3016

Bromodomain Inhibitor JQ1 Modulates Smooth Muscle Cell Switching and Ameliorates Chronic Hypoxia/SU5416-Induced Pulmonary Arterial Hypertension in Mice

Sarah L. Trinder[1], Adrian Gilbane[2], Robert Good[2], Emma C. Derrett-Smith[3], Christopher P. Denton[4], David Abraham[5] and **Alan M. Holmes**[2], [1]Centre for Rheumatology and Connective Tissue Diseases, UCL, London, United Kingdom, [2]Centre for Rheumatology and Connective Tissue Diseases, UCL Medical School, London, United Kingdom, [3]Centre for Rheumatology and Connective Tissue Diseases,, UCL Division of Medicine, London, United Kingdom, [4]Rheumatology and Connective Tissue Diseases, University College London, London, United Kingdom, [5]Centre for Rheumatology and Connective Tissue Disease, University College London, London, United Kingdom

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Background/Purpose: Pulmonary arterial hypertension (PAH) represents a serious co-morbidity affecting up to 10% of systemic sclerosis (SSc) patients. Cardinal features of PAH include inflammation and vascular remodelling, the latter resulting from alterations in proliferation, matrix production, chemokine and cytokine expression by resident cells including pulmonary arterial smooth muscle cells (PASMCs). Previously we have shown an inhibitor of the epigenetic BET bromodomain proteins, JQ1 can antagonise the pro-inflammatory phenotype of SSc dermal fibroblasts. In this study we assessed the role of BET inhibition on PASMC cell contractile to synthetic switching, and the *in vivo* effects on vascular remodelling and development of PAH in the hypoxia/SU5416 mouse model.

Methods: The effects of siRNA knockdown and pharmacological inhibition using JQ1 on contractile and synthetic PASMCs switching and proliferation, matrix deposition and inflammatory chemokine secretion assessed by crystal violet, Western Blot and ELISA respectively. Using the hypoxia/SU5416 model of PAH, female C57BL/6 mice were maintained in a hypoxic (10% O_2) chamber and given 3 weekly doses of 20mg/kg SU5416 to induce PAH. Animals were treated with JQ1 at 15 or 60 mg/kg/day ($n \geq 6$), and haemodynamics, cardiac hypertrophy and vascular remodelling were assessed after 21 days. The effect on circulating inflammatory chemokines was determined by multiplex ELISA.

Results: Synthetic PASMCs secrete significantly ($p<0.05$) elevated IL-6, IL-8 and MCP-1 compared to contractile PASMCs (n=3).

Administration of JQ1 significantly inhibited in a concentration dependent manner, secretion of MCP1 ($P<0.01$) and IL-6 ($P<0.01$) but not IL-8 from PASMCs. Further, elevated collagen type I deposition observed in synthetic PASMCs was significantly inhibited by JQ1. Systemic administration of JQ1 *in vivo* in the pre-clinical model of hypoxia/SU5416 induced PAH, significantly attenuated right ventricular systemic pressure in a dose dependent manner ($P<0.05$) and attenuated vascular remodeling ($P<0.05$). JQ1 had no effect on mean systemic arterial pressure or heart rate at the doses tested. Furthermore, pro-inflammatory cytokines including IL-6 and IL-8 were significantly reduced in serum from JQ1-treated mice compared to hypoxia/SU5416 control (Table I). Consistent with this, JQ1 significantly attenuated the synthetic PASMC phenotype, significantly reducing IL-6 and MCP-1 secretion ($P<0.001$), as well as enhanced type-I collagen and CTGF expression.

Conclusion: This data supports a key role for BET bromodomain proteins in the pathological switching of PASMCs. Consistent with this, JQ1 inhibited vascular remodeling and the development of PAH in the hypoxia/Su5416 mouse model of PAH. Suggesting targeting of bromodomain proteins may represent a novel therapeutic approach to targeting SSc-PAH.

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Abstract Number: 3017

TYK2 and Systemic Sclerosis Susceptibility: a New Associated Locus in the IL-12 Pathway

Elena Lopez-Isac[1], Lara Bossini-Castillo[2], Sandra G Guerra[3], Shervin Assassi[4], Carmen P. Simeón[5], Patricia E. Carreira[6], Norberto Ortego-Centeno[7], Paloma García de la Peña[5], Lorenzo Beretta[8], Alessandro Santaniello[9], Chiara Bellocchi[10], Claudio Lunardi[11], Gianluca Moroncini[12], Armando Gabrielli[13], Gabriela Riemekasten[14], Torsten Witte[15], Nicolas Hunzelmann[16], Alexander Kreuter[17], Jorg HW. Distler[18], Alexandre E. Voskuyl[19], J.K. de Vries-Bouwstra[20], Ariane L. Herrick[21], Jane Worthington[22], Christopher P. Denton[23], Carmen Fonseca[3], T.R.D.J. Radstake[24], Maureen D Mayes[25] and Javier Martín[1], [1]Institute of Parasitology and Biomedicine López-Neyra, IPBLN-CSIC, Granada, Spain, [2]Instituto de Parasitología y Biomedicina López-Neyra, IPBLN-CSIC, PTS Granada, Granada, Spain, [3]Centre for Rheumatology, Royal Free and University College Medical School, London, United Kingdom, [4]Rheumatology, University of Texas Medical School at Houston, Houston, TX, [5]Rheumatologist, Granada, Spain, [6]Rheumatology, Hospital Universitario 12 de Octubre, Madrid, Spain, [7]Systemic Autoimmune Diseases Unit, Hospital Universitario San Cecilio, Granada, Spain, [8]Rheumatology, Milan, Italy, [9]Referral Center for Systemic Autoimmune Diseases, Fondazione IRCCS Ospedale Maggiore Policlinico, Mangiagalli e Regina Elena and University of Milan, Italy, Milan, Italy, [10]Referral Center for Systemic Autoimmune Diseases, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico di Milano, Milan, Italy, [11]Department of Medicine, Università degli Studi di Verona, Verona, Italy, [12]Dipartimento di Scienze mediche e Chirurgiche, Università politecnica delle Marche, Ancona, Italy, [13]Clinica Medica, Università Politecnica delle Marche, Ancona, Italy, [14]Clinic of Rheumatology and Clinical Immunology, Berlin, Germany, [15]Department of Immunology and Rheumatology, Hannover Medical School, Hannover, Germany, [16]Department of Dermatology, University of Cologne, Cologne, Germany, [17]Department of Dermatology, Venereology, and Allergologie, HELIOS St. Elisabeth Hospital, Oberhausen, Germany, [18]Department of Internal Medicine 3 and Institute for Clinical Immunology, University of Erlangen-Nuremberg, Erlangen, Germany, [19]Rheumatology, Amsterdam Rheumatology and immunology Center, location VU University medical center, Amsterdam, Netherlands, [20]Rheumatology, Leiden University Medical Center, Leiden, Netherlands, [21]Centre for Musculoskeletal Research, University of Manchester, Manchester Academic Health Science Centre, Manchester, United Kingdom, [22]Arthritis Research UK Epidemiology Unit, Manchester Academic Health Science Centre, The University of Manchester, Manchester, United Kingdom, [23]Rheumatology and Connective Tissue Diseases, University College London, London, United Kingdom, [24]Department of Rheumatology & Clinical Immunology, University Medical Center Utrecht, Utrecht, Netherlands, [25]University of Texas - Houston Medical School, Houston, TX

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Session Title: Systemic Sclerosis, Fibrosing Syndromes and Raynaud's - Pathogenesis, Animal Models and Genetics Poster II

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Background/Purpose: Systemic sclerosis (SSc) is a complex autoimmune disease. The aetiology of the disease is largely unknown, although both environmental and a genetic factors are thought to be involved in the disease development. The genetic susceptibility of SSc has been well-addressed by powered genetic association studies. The results of these studies clearly support an important role of the immune system. In this regard, several interleukin-12 (IL-12) pathway-related genes have been identified as susceptibility factors for SSc (*IL12RB1*, *IL12RB2*, *IL12A*, *STAT4*). *TYK2* is a tyrosine kinase protein that mediates several family cytokines signaling, including IL-12, and constitutes a common risk factor for autoimmunity. On this base, we aimed to analyze the association of the *TYK2* locus with SSc susceptibility.

Methods: The complete set of individuals enrolled for this study comprised a total of 7,103 SSc patients and 12,220 healthy controls of Caucasian ancestry from Spain, USA, Germany, The Netherlands, Italy and the United Kingdom. We performed an initial screening of *TYK2* genetic region in a previously published large-scale genetic study (Immunochip). Four *TYK2*single-nucleotide polymorphisms (SNPs) were selected for follow-up (V362F [rs2304256], P1104A [rs34536443], I684S [rs12720356] and A928V [rs35018800]). Association and dependence analyses were performed by the means of logistic regression and conditional logistic regression. Meta-analyses were performed using the inverse variance method.

Results: Genome-wide significance level was reached for *TYK2* V362F common variant in our pooled analysis ($P = 3.08x10^{-13}$, OR = 0.83), while the association of P1104A, A928V and I684S rare and low-frequency missense variants remained significant with nominal signals ($P = 2.28x10^{-3}$, OR= 0.80; $P = 1.27x10^{-3}$, OR= 0.59; $P = 2.63x10^{-5}$, OR= 0.83, respectively). Interestingly, dependence and allelic combination analyses clearly supported that the highly significant association observed for V362F with SSc was a spurious signal driven by P1104A, A928V and I684S. This results are consistent with previous *in vitro* and *in silico*studies, which revealed that P1104A, A928V, and I684S were damaging mutations and impaired the catalytic activity of TYK2, leading to a reduced TYK2 response and decreasing pro-inflammatory cytokines signaling, such as IL-12.

Conclusion:

The present study reports for the first time robust evidence for the implication of *TYK2* in SSc susceptibility. These results reinforce the crucial involvement of IL-12 signaling axis in the disease pathophysiology. Thus, target therapies blocking this pathway might represent an effective treatment for the disease.

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Abstract Number: 3018

Paracrine Effect of Proteins Secreted By Normal Lung Microvascular Endothelial Cells Undergoing Endothelial Mesenchymal Transition on the Expression of Genes Associated with Tissue Fibrosis in Normal Human Lung Fibroblasts

Sonsoles Piera-Velazquez[1], Kerri Fasino[2] and Sergio A. Jimenez[3], [1]Jefferson Institute of Molecular Medicine, Thomas Jefferson Univ, Philadelphia, PA, [2]Jefferson Institute of Molecular Medicine and Division of Connective Tissue Diseases, Thomas Jefferson University, Philadelphia, PA, [3]Div Connective Tissue Diseases, Thomas Jefferson Univ, Philadelphia, PA
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Background/Purpose: Progressive tissue fibrosis and microvascular alterations are the hallmarks of Systemic Sclerosis (SSc). The mechanisms involved in SSc pathogenesis are complex and have not been fully elucidated. One notable feature of SSc is the extension of the pathologic process to normal tissues. The mechanisms involved in this topographic extension have remained elusive. Recent studies suggested that the phenotypic transition of endothelial cells (EC) into mesenchymal cells (endothelial to mesenchymal transition; EndoMT) may be involved in the progressive tissue fibrosis and fibroproliferative vasculopathy in SSc although the mechanisms

involved have not been elucidated. We here suggest that one potential mechanism may be that EndoMT activated EC exert paracrine effects on normal/healthy fibroblasts and EC and induce them to express a profibrotic phenotype and transdifferentiate into activated profibrotic cells. The purpose of the study was to evaluate whether secreted molecules released by microvascular lung EC undergoing EndoMT exert paracrine effects on normal human pulmonary fibroblasts inducing them to become profibrotic.

Methods: Normal human lung fibroblasts and microvascular EC were isolated from normal lung tissues by enzymatic digestion with collagenase. The isolated cell suspension was incubated with CD45 microbeads to remove leukocytes. Fibroblasts and EC were isolated employing anti-human CD31 antibody magnetic beads. The CD31- fibroblasts and the CD31+ EC were expanded separately. For EndoMT induction the lung microvascular EC were treated with TGF-β1 or TGF-β2 for 48 h. Following a change of media to serum-free media for 24h the supernatants were collected and aliquotes added to triplicate wells of normal human lung fibroblasts. After 24h, culture supernatants were isolated for Western blot analysis. The cells were lysed and total fibroblast RNA isolated and cDNA generated. Expression of various fibrosis-associated +genes was assessed by quantitative real time PCR. Validation of the gene expression results was performed employing Western blot analysis of secreted and intracellular proteins.

Results: RTPCR results showed a marked increase in levels of COL1A2, COL3A1, FN1, CTGF and TGFβ1 mRNA in normal lung fibroblasts treated with supernatants from normal lung microvascular EC pretreated with TGF-β1 or TGF-β2 compared to medium from untreated EC. Increased amounts of fibronectin were found in the media of lung fibroblasts treated with supernatants from the lung microvascular EC treated with TGF-β1 or TGF-β2.

Conclusion: Treatment of normal lung fibroblasts with proteins released by cultured human lung microvascular EC induced to undergo EndoMT *in vitro* resulted in a profound change in the expression of numerous profibrotic genes. The results demonstrated potent paracrine effects of EndoMT-activated lung microvascular EC on normal target lung fibroblasts and suggest a novel mechanism for the progression of SSc-associated pulmonary fibrosis.

Disclosure: S. Piera-Velazquez, None; **K. Fasino**, None; **S. A. Jimenez**, None.

Abstract Number: 3019

The CD4+CD52low T Cell Contributes to Disease Activity and Autoantybody Production in Systemic Lupus Erythematosus

Masataka Umeda[1], Tomohiro Koga[1], Kunihiro Ichinose[2], Toru Michitsuji[1], Toshimasa Shimizu[2], Shoichi Fukui[3], Ayako Nishino[3], Yoshikazu Nakashima[4], Yoshiro Horai[1], Takahisa Suzuki[1], Shin-ya Kawashiri[3], Naoki Iwamoto[1], Toshiyuki Aramaki[5], Mami Tamai[1], Yasuko Hirai[1], Hideki Nakamura[1], Kazuo Yamamoto[6], Tomoki Origuchi[7,8], Yukitaka Ueki[9] and Atsushi Kawakami[1], [1]Department of Rheumatology, Unit of Translational Medicine, Graduate School of Biomedical Sciences, Nagasaki University, Nagasaki, Japan, [2]Department of Immunology and Rheumatology, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan, [3]Department of Immunology and Rheumatology, Nagasaki University, Nagasaki, Japan, [4]Department of Rheumatology, Nagasaki University, Nagasaki, Japan, [5]Department of Rheumatology, Sasebo Chuo Hospital, Sasebo, Japan, [6]Biomedical Research Support Center, Nagasaki University School of Medicine, Nagasaki, Japan, [7]Department of Rehabilitation Sciences, Nagasaki University, Nagasaki, Japan, [8]Department of Rehabilitation Sciences, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan, [9]Kyushu multicenter rheumatoid arthritis ultrasound prospective observational cohort study group, Nagasaki, Japan
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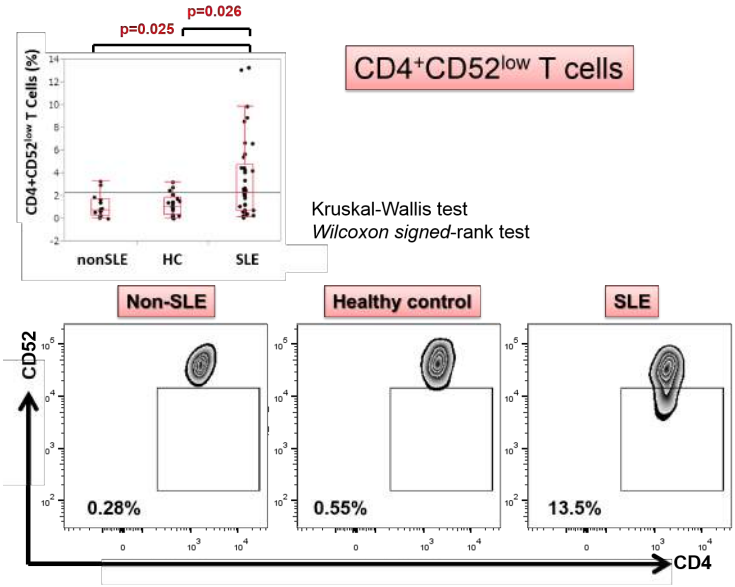
Background/Purpose: CD52 is a cell-surface glycoprotein that is widely expressed in lymphocytes, monocytes and eosinophils. The anti-CD52 antibody has been used to treat multiple autoimmune diseases, and its effectiveness has been reported. $CD4^{+}CD52^{high}$ T cells inhibit the activation of $CD4^{+}CD52^{low}$ T cells through the release of cell-surface CD52. Soluble CD52, which is cleaved from $CD4^{+}CD52^{high}$ T cells, works as a ligand of siglec-10 on $CD4^{+}CD52^{low}$ T cells (Nat Immunol. 2013 Jul;14(7):741-8.). $CD4^{+}CD52^{high}$ T cells were reported as distinct population from conventional regulatory T cells. The role of the immune regulation of $CD4^{+}CD52^{high}$ T cells in systemic lupus erythematosus (SLE) is unknown. We evaluated the $CD4^{+}CD52^{high}$ and $CD4^{+}CD52^{low}$ T cells in the human peripheral blood mononuclear cells (PBMCs) of SLE patients and clarified their roles in the pathogenesis of SLE.

Methods: We isolated the PBMCs of 40 SLE patients, 14 non-SLE patients (11 with rheumatoid arthritis, 3 with mixed connective-tissue disease) and 22 healthy controls (HCs). The expressions of $CD4^+CD25^+CD127^-$ T cells (Tregs), $CD4^+CD52^{high}$ T cells and $CD4^+CD52^{low}$ T cells were analyzed by flow cytometry. We also analyzed the correlations with clinical parameters including SLEDAI, anti-ds-DNA antibody titer and complement titer. The soluble CD52 was also analyzed in an ELISA among the SLE and non-SLE patients and HCs.

Results: We found that the expression of $CD4^+CD52^{low}$ T cells in the SLE patients was significantly higher than HC (p=0.003) and non-SLE (p=0.003) (Figure). The expression of $CD4^+CD52^{low}$ T cells of the SLE group were significantly correlated with SLEDAI (p-value=0.002, r=0.481803), anti-ds-DNA antibody (p-value=0.01, r=0.420842) and IgG (p-value=0.018, r=0.392004). Soluble CD52 measured by ELISA was found to be decreased in the SLE group versus the other groups (vs. HC: p=0.001; vs. non-SLE: p=0.014). No significant difference was found in the population of $CD4^+CD25^+$ $CD127^-$ cells among the groups. There was no correlation between Tregs and $CD4^+CD52^{high}$ T cells in SLE.

Conclusion: Collectively, our data suggest that increased $CD4^+CD52^{low}$ T cells along with decreased soluble CD52 are involved in the pathogenic autoantibodies production highlighting its potential as a therapeutic target for SLE.



Disclosure: M. Umeda, None; **T. Koga**, None; **K. Ichinose**, None; **T. Michitsuji**, None; **T. Shimizu**, None; **S. Fukui**, None; **A. Nishino**, None; **Y. Nakashima**, None; **Y. Horai**, None; **T. Suzuki**, None; **S. Y. Kawashiri**, None; **N. Iwamoto**, None; **T. Aramaki**, None; **M. Tamai**, None; **Y. Hirai**, None; **H. Nakamura**, None; **K. Yamamoto**, None; **T. Origuchi**, None; **Y. Ueki**, None; **A. Kawakami**, None.

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Abstract Number: 3020

IL-21 Abrogates CD4+CD25+FOXP3+ Treg Differentiation in Part By Suppressing Treg GATA-3 Expression in SLE

Hiroshi Kato[1] and Andras Perl[2], [1]Division of Rheumatology/Internal Medicine, SUNY Upstate Medical University, Syracuse, NY, [2]Department of Medicine, SUNY Upstate Medical University, Syracuse, NY

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Background/Purpose: Previous studies point to qualitative and quantitative Treg insufficiencies underlying aberrant T-cell activation in SLE. GATA-3 is critical in lineage commitment and functions of murine Treg, whereas IL-21 tips the balance from Treg towards Th17 differentiation through STAT3 phosphorylation in mice. IL-21 and IL-21 receptor polymorphisms confer risk for SLE. However, roles of GATA-3 in lupus Treg biology and mechanisms by which IL-21 regulates human Treg development remain undefined.

Methods: $CD3^+$ T cells were isolated from 9 pairs of matched SLE and healthy control (HC) subjects. A part of the $CD3^+$ T cells were stained with CD4, CD25, FOXP3, and GATA-3. The remainder was cultured in RPMI culture media with 10% FCS in the presence of plate-bound anti-CD3, soluble anti-CD28 with/without 100 nM rapamycin. After 3 days in culture, IL-21 secretion in the supernatants was quantified by LUMINEX assay. Naïve $CD4^+$ T cells were isolated from 5 pairs of matched SLE and HC subjects and cultured for 3 days in the presence of anti-CD3/CD28, TGF-β, and IL-2 with/without IL-21. A portion of cells were stained with CD25, FOXP3, and GATA-3 to determine the frequency of $CD4^+CD25^+FOXP3^{hi}$ Tregs and GATA-3 expression in the $CD4^+CD25^+FOXP3^+$ Tregs by flow cytometry. Cell lysates were saved for immunoblotting with antibodies against STAT3, $pSTAT3^{Y705}$, Akt, and $pAkt^{Ser473}$. Signal intensity was normalized to actin. Statistical analysis was made using Student's t-test.

Results: GATA-3 expression in Tregs was reduced in SLE as compared with HC (relative mean fluorescence intensity: 0.81±0.09, p=0.032) in freshly isolated $CD3^+$ T cells, whereas IL-21 secretion appears to be increased in culture supernatants of SLE T cells (SLE: 415.37±207.62 pg/ml, HC: 147.38±45.28 pg/ml, p=0.10). Under Treg-polarizing conditions, IL-21 suppressed $CD4^+CD25^+FOXP3^+$ Treg differentiation in SLE (frequency of $CD4^+CD25^+FOXP3^{hi}$ cells; control: 57.06±3.35%, IL-21-treated cells: 34.80±2.13%, p=0.0002) and HC (control: 45.30±6.66%, IL-21-treated cells: 30.43±2.84%, p=0.03). IL-21 suppressed GATA-3 expression in $CD4^+CD25^+FOXP3^+$ Tregs in SLE (control 58.31±7.93%, IL-21-treated cells 26.57±5.40%, p=0.001) and HC (control: 59.53±5.32%, IL-21-treated cells: 38.47±8.51%, p=0.045). Mechanistically, IL-21 phosphorylated STAT3 (relative intensity: 1.48±0.19, p=0.033) as well as Akt (relative intensity: 1.48±0.20, p=0.037) in SLE $CD4^+$T cells cultured under Treg-skewing conditions. Rapamycin suppressed IL-21 secretion by SLE T cells stimulated with anti-CD3/CD28 (control: 415.37±207.62 pg/ml, rapamycin: 8.23±3.01 pg/ml, p=0.047).

Conclusion: The data indicate that IL-21 phosphorylates STAT3 and Akt and inhibits Treg differentiation in SLE, possibly via the suppression of GATA-3. Suppression of T-cell IL-21 secretion emerges as one of the mechanisms by which rapamycin promotes Treg expansion in SLE.

Disclosure: H. Kato, None; **A. Perl**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/il-21-abrogates-cd4cd25foxp3-treg-differentiation-in-part-by-suppressing-treg-gata-3-expression-in-sle

Abstract Number: 3021

The Adaptor Protein Crkii Regulates Rap1 Activation in the Immunological Synapse

Adam Mor[1] and Inbar Alfaguter[2], [1]Rheumatology and Pathology, NYU Langone Medical Center, New York, NY, [2]NYU, New York, NY
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Background/Purpose:

Crk proteins are a family of adaptors that play an important role in regulating multiple T cell functions. The two main Crk isoforms are CrkII and CrkL that are encoded by separate genes. Similar to other adaptors, they bind to phosphorylated tyrosine motifs of many proteins via their SH2 domain to recruit additional effectors utilizing their SH3 domain. One of these effectors is C3G, a guanine nucleotide exchange factor regulating Rap1 activation and subsequent adhesion. T cells adhere to multiple cells including endothelial cells and antigen presenting cells (APC). The interphase between T cell and APC is known as the immunological synapse (IS). It is made of multiple T cell receptors that interact with adhesion molecules and ligands presented on the surface of the APC. The distribution of these molecules is characterized by a specific organization that can be divided into central supermolecular activation clusters (cSMACs) and peripheral SMAC (pSMAC).

Methods:

The goal of this study was to uncover the mechanism by which Crk proteins regulate Rap1 activation within the IS of primary human T cells using lipid bilayer and TIRFm microscopy.

Results:

We determined that activation of T cells trough the antigen receptor led to polarization of activated Rap1 toward the IS. Unlike other GTPases, Rap1 was excluded from the cSMAC. Notably, C3G was recruited to the same compartments as Rap1. Although both CrkII and CrkL populated both compartments of the IS, their distribution was phosphorylation dependent. While phosphorylated (and inactive) CrkII was limited to the cSMAC, CrkL phosphorylation resulted in pSMAC distribution. Subsequent biochemical and genetic studies confirmed that signaling initiated by the antigen receptor resulted in CrkII dephosphorylation that was mediated by the phosphatase SHP2.

Conclusion:

In summary, we discover a new signaling pathway where signals downstream the T cell receptor result in recruitment of SHP2 to dephosphorylate and activate the adaptor CrkII. Activated CrkII travel to pSMAC where it recruits C3G, leading to Rap1 activation and LFA-1 mediated adhesion.

Disclosure: A. Mor, None; **I. Alfaguter**, None.

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Abstract Number: 3022

Characterizing a Novel Gene, Mosaic, and Its Role in Mediating a Multisystem Autoimmunity

Alice Chan[1], Emily Brown[2], Oded Foreman[3], Anita Oberbauer[4], Angela Hughes[5], Shelly Burton[6], Hong-Erh Liang[7], Mark Anderson[8] and Danika Bannasch[9], [1]Pediatric Rheumatology, University of California San Francisco, San Francisco, CA, [2]Population Health and Reproduction, School of Veterinary Medicine, University of California Davis, Davis, CA, [3]Genentech, Inc, South San Francisco, CA, [4]Department of Animal Science, School of Veterinary Medicine, University of California Davis, Davis, CA, [5]Mars Veterinary, Gaithersburg, MD, [6]Pathology and Microbiology, Atlantic Veterinary College, University of Prince Edward Island, Charlottetown, PE, Canada, [7]Medicine, University of California San Francisco, San Francisco, CA, [8]Diabetes Center, University of California San Francisco, San Francisco, CA, [9]Department of Population Health and Reproduction, School of Veterinary Medicine, University of California Davis, Davis, CA
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Background/Purpose: A novel candidate gene, *Mosaic* (Multi-Organ System Autoimmunity in Canines), was identified as the culprit causing an early and severe multiorgan autoimmunity in a purebred canine population. This unique dog breed develops early onset Addison's disease, arthritis, autoimmune cytopenias, hepatitis and uveitis. Little is known about the function of this gene. It is conserved across all known vertebrae species including humans and mice. The affected dogs possess a single point mutation resulting in an amino acid change of a proline to leucine residue in a highly conserved region. This gene is expressed in immune cells with particularly high abundance in T regulatory (Treg) cells. Thus, we hypothesized that the deficiency in *Mosaic*disrupts normal Treg cell function in maintaining immune tolerance and leads to multiorgan autoimmunity.

Methods: The cDNA for *Mosaic*was cloned into an expression vector and transfected into 293 cells to assess cellular localization. A knockout mouse was generated carrying a reporter cassette allowing tracing of the endogenous gene expression pattern. Heterozygous knockout mice were used for flow cytometry to identify immune subsets that expressed this gene.

Results: Wild-type and mutant *Mosaic*showed nuclear localization by immunohistochemistry and western blotting in transfected cells. Heterozygous knockout mice were assessed by flow cytometry and showed expression in multiple immune cell lineages including high expression in Treg cells and activated T cells.

Conclusion: *Mosaic* was identified as the causal gene mediating a multi-organ system autoimmunity in a unique breed of dogs. This protein is localized to the nucleus suggesting a role in modifying gene expression and is expressed in multiple immune cell subsets. Further characterization of these mice will shed light on the role of this novel gene in mediating early-onset and severe multi-organ autoimmunity.

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Abstract Number: 3023

Decreased Intracellular Calcium Flux in Follicular Helper T Cells after T Cell Receptor Stimulation

Abhinav Seth[1], Edward I. Herman[2], Jason S. Weinstein[1], Jin Young Choi[3] and Joseph E. Craft[4], [1]Department of Internal Medicine (Rheumatology), Yale University School of Medicine, New Haven, CT, [2]Department of Immunobiology, Yale University School of Medicine, New Haven, CT, [3]Internal Medicine, Section of Rheumatology, Yale University School of Medicine, New Haven, CT, [4]Dept of Internal Med/Rheum, Yale University School of Medicine, New Haven, CT

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Background/Purpose:

Follicular helper T (Tfh) cells are a specialized subset of CD4+ helper T cells that are required for B cell maturation in germinal centers and subsequent antibody formation following infection or immunization with thymus dependent antigens. Tfh cells have also been implicated in mediating pathogenic autoantibody production in lupus and modulation of their function has been shown to ameliorate end organ disease in murine models of lupus. Understanding the molecular determinants of Tfh cell function may allow for the development of specifically targeted immunomodulating therapies for lupus and other autoantibody mediated diseases. In this study, we have systematically characterized the ability of Tfh cells from a variety of physiologic and pathologic settings to flux calcium in response to T cell receptor stimulation.

Methods:

B6 mice were immunized in bilateral foot pads with a mixture of papain and 4-Hydroxy-3-nitrophenylacetyl conjugated to ovalbumin (NP-OVA). After 5 days, inguinal and popliteal lymph nodes were harvested and lymphocytes were labeled with fluorophore-conjugated antibodies

to allow identification of different T cell subtypes by flow cytometry. Cells were loaded with the calcium sensitive dyes Fluo4 and FuraRed to allow ratiometric imaging of intracellular calcium. Cells were stimulated with anti-CD3 antibodies to initiate T cell receptor (TCR) signaling and the intracellular calcium concentration was monitored in naïve T cells, Tfh cells and other effector T cells subtypes. Similar experiments were conducted using T cells obtained from the spleens of 1) B6 mice infected with the helminth *Nippostrongylus brasiliensis*, 2) B6 mice acutely infected with lymphocytic choriomeningitis virus or 3) 6 month old lupus-prone, B6.*Sle1*.Yaa, mice.

Results:

Tfh cells, relative to naïve T cells or to their Th1 or Th2 counterparts, exhibit significantly reduced calcium flux upon TCR stimulation in the context of NP-OVA immunization (2.4-fold reduction, $p < 0.0001$), helminth infection (3.7-fold reduction, $p < 0.0001$), viral infection (2.3-fold reduction, $p < 0.0001$) or autoimmune activation in lupus-prone mice (3.3-fold reduction, $p < 0.0001$). These findings are not due to generalized defects in signaling as Tfh cells retain the ability to activate MAP kinases following TCR stimulation, suggesting a specific alteration in the ability of Tfh cells to handle calcium.

Conclusion:

Our results demonstrate that Tfh cells, in physiologic or pathogenic settings, have a selective defect in calcium mobilization upon TCR stimulation. The altered calcium handling profile of Tfh cells likely contributes to the unique molecular program of these specialized cells. These results have important implications for designing therapeutic strategies to selectively target Tfh cells in autoimmune disease.

Disclosure: A. Seth, None; **E. I. Herman**, None; **J. S. Weinstein**, None; **J. Y. Choi**, None; **J. E. Craft**, AbbVie, 2.

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Abstract Number: 3024

FcÎ³riiia Mediated Signal Cause Epigenetic Changes in Human Naive CD4+ T-Cells

Ye Bi[1], Chen Chen[2], Terry Moore[3] and **Anil K. Chauhan**[4], [1]Internal Medicine, Saint Louis University, St. Louis, MO, [2]Biostatistics and Epidemiology, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, [3]Division of Rheumatology and Pediatric Rheumatology, Saint Louis University School of Medicine, St Louis, MO, [4]Internal Medicine-Rheumatology, Saint Louis University, St Louis, MO

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SESSION INFORMATION

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Background/Purpose: Signals that trigger epigenetic changes in $CD4^+$ T-cells are unknown. To examine a role for FcγRIIIa mediated co-signal in causing epigenetic changes in human $CD4^+$ T-cells. GWAS studies have shown hypomethylation of IFN promoter region in $CD4^+$ T-cells. During IFN signaling multiple genome sites are hypomethylated. Procainamide and hydrazine, which inhibit DNA (cytosine-5)-methyltransferase 1 (DNMT1), predispose individuals to drug-induced systemic lupus erythematosus (SLE). We examined whether immune complexes (ICs) by ligating FcγRIIIa on $CD4^+$ T-cells cause epigenetic changes.

Methods:

We activated peripheral human naïve $CD4^+$ T-cells using plate bound anti-CD3+anti-CD28 and anti-CD3+ICs+C5b-9. Thereafter, we cultured these cells in T_H17 polarizing conditions. On day nine, we harvested the cells and prepared cDNA. PCR array was performed using chromatin modification array (n=6) (Applied Biosystems) and Human Epigenetic Chromatin Modification Enzyme RT^2Profiler PCR array (n=5) (SA Biosciences). We compared the relative change in DNA and histone modifying enzyme genes from ICs+C5b-9 co-stimulation over CD28 co-stimulation. Epigenetic marks were examined by ChiP assay.

Results:

In six donors analyzed by AB array, hierarchical cluster analysis showed a strong correlation among DNMT1, RBBP7, CHD4, and MBD2, which are part of deacetylases complex. All enzymes of this complex were repressed by ICs ligation to $CD4^+$ T-cells. A dramatic decrease (4.5 fold) was observed in co-activator associated arginine methyl transferase and nuclear receptor co-activator (NCOA6) (7.14 fold), which remodels chromatin with HAT1. A 7.37-fold increase was observed in activating transcription factor 2 (ATF2), which acetylates H2B and H4 histones during DNA damage response, from ICs ligation of FcγRIIIa on $CD4^+$ T-cells compared to CD28 co-stimulation. ATF2/c-Jun regulated IFN-β gene and IFN-γ production. K(lysine) acetyl transferase 6A (KAT6A) was increased 6-fold, which acetylate H3 and H4 histones. KAT6A

is a transcriptional co-activator of Runx1 and Runx2. Both T-bet and Runx generate pathogenic IFN-γ producing T_H17 cells. In addition, a 6.16-fold increase in SET domain containing lysine methyltransferases (SETD)-7, a transcription activator that generates H3K4 mark was observed. Also other SET domain proteins SET4, SET8 that generate H4K2me1 mark and SET1 that generates H3K9 mark were upregulated. Relative increase in the expression of ATF2, KAT6A, and SEDT7 was seen in both arrays.

Conclusion:

Epigenetic modifications contribute to multistep differentiation and plasticity of in vitro and in vivo-derived helper T-cells. Our results show that signal via FcγRIIIa in $CD4^+$ T-cells modulates both histones and DNA modifying enzymes. Ligation of FcγRIIIa by ICs lead to the development of IFN-γ^{high} subset. ATF2 and c-Jun bind to -53 CpG in the IFN-γ promoter in T_H1 and not in T_H2 cells. Persistent signaling from IC ligation to FcγRIIIa by up-regulating ATF2 will continue to generate IFN-γ producing cells.

Disclosure: Y. Bi, None; **C. Chen**, None; **T. Moore**, None; **A. K. Chauhan**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/fci%c2%b3riiia-mediated-signal-cause-epigenetic-changes-in-human-naive-cd4-t-cells

Abstract Number: 3025

FcγRIIIa-Psyk Signaling up-Regulates TLR3 and TLR5 in Human Naïve CD4+ T-Cells

Chen Chen[1], Ye Bi[2], Terry Moore[3] and **Anil K. Chauhan**[4], [1]Rheumatology/Internal Medicine, Saint Louis University, St. Louis, MO, [2]Internal Medicine, Saint Louis University, St. Louis, MO, [3]Division of Rheumatology and Pediatric Rheumatology, Saint Louis University School of Medicine, St Louis, MO, [4]Internal Medicine-Rheumatology, Saint Louis University, St Louis, MO
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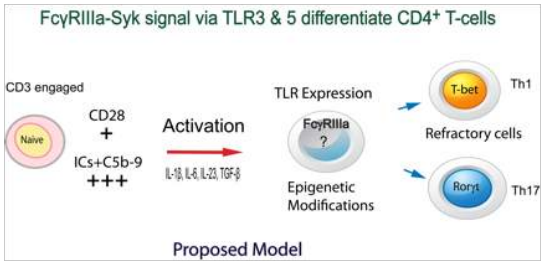
Background/Purpose: To delineate mechanism of FcγRIIIa-pSyk signal in T_H17 and IFN-γ^{high} subset development. To examine whether Toll-like receptor signaling play a role in $CD4^+$ T-cell differentiation upon FcγRIIIa ligation by immune complexes (ICs).

Methods: Purified naïve $CD4^+CD45RA^+$ T-cells were co-stimulated with plate bound ICs+C5b-9 or anti-CD28 in the presence of anti-CD3 and polarized in T_H17 cytokine milieu. Flow analysis was performed for IFN-γ, IL-17A, IL-22 cytokines and pSyk. The $CD4^+$ T-cells from SLE patients (n=40) were analyzed for pSyk and CD25, CD69 and CD98. TLR signaling genes were analyzed by RT^2 Profiler QT-PCR arrays. Association of HMGB1 and MyD88 with FcγRIIIa was examined using IP and Western blotting. Cell staining was performed for co-localization of HMGB1, MyD88, TLR3, and TLR5 with labeled ICs.

Results: We show that the activated naïve $CD4^+$ T-cells express FcγRIIIa, which upon IC ligation signals via pSyk and drive $CD4^+$ T-cell differentiation in vitro. In SLE patients activated $CD4^+$ T-cells that express CD25, CD69 and CD98 show pSyk. These $pSyk^+$ cells express ICOS but not PD1. Both MyD88 dependent and independent TLRs, 2 (5.50-fold), 3 (9.89), 5 (5.17), 8 (5.09), and 10 (5.16) were upregulated. TLR7 and 9 did not show significant increase. Adaptor and TLR interacting proteins BTK, HMGB1, HRAS, and MyD88 were upregulated. Labeled ICs co-localize with HMGB1 and MyD88 in $CD4^+$ T-cells. Western blots of IPs generated with anti-FcγRIIIa antibody show association of HMGB1 and MyD88 with these receptors. These results suggest a role for FcγRIIIa-pSyk signaling by upregulation of TLR pathway in defining adaptive immune responses in autoimmune pathology.



Conclusion: Recently TLR-dependent T-cell activation in autoimmunity has been documented. While TLR2 provide a co-stimulatory signal to

$CD4^+$ T-cells, TLR4 enhance activation and persistence of T_H17 and T_H1 cells. TLR3 contribute to the development of T_H1 cells. We observed up-regulation of TLR-signaling pathway genes in $CD4^+$ T-cells from FcγRIIIa ligation by SLE-ICs. The $pSyk^+$ $CD4^+$T-cells in SLE patients produce IFN-γ and IL-17A suggesting a role of ICs in driving T-cell mediated disease pathology. A role for FcγRIIIa was further confirmed from in vitro generation of T_H1 and T_H17 like population. We propose that FcγRIIIa-pSyk signal drives the generation of refractory T_H1 and T_H17 cells that override the suppression from Tregs. Such cells are produced in response to activation from anti-CD3+anti-CD28 co-stimulation and LPS. Further MyD88 ablation impairs both T_H1 and T_H17 responses. Our data describe a new role for FcγRIIIa-pSyk mediated signaling in production of pro-inflammatory $CD4^+$ T-cells that are refractory to suppression by Tregs.

Disclosure: C. Chen, None; **Y. Bi**, None; **T. Moore**, None; **A. K. Chauhan**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/fcriiia-psyk-signaling-up-regulates-tlr3-and-tlr5-in-human-nave-cd4-t-cells

Abstract Number: 3026

The Effects of Lrg on the Differentiation of Naïve T Cells

Hayato Urushima[1], Minoru Fujimoto[2], Chiharu Iwahashi[1], Tomoharu Ohkawara[2], Hiromi Honda[2], Satoshi Serada[1] and Tetsuji Naka[2], [1]Laboratory for Immune Signal, National Institute of Biomedical Innovation, Health and Nutrition, Ibaraki, Japan, [2]Laboratry of immune signal, National Institute of Biomedical Innovation, Health and Nutrition, Ibaraki, Japan

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Background/Purpose: Previously, we have identified leucine-rich alpha 2 glycoprotein (LRG) as a disease marker of Rheumatoid arthritis(RA). Although LRG is produced in site of inflammation such as synovial tissues, its function is still unclear. Recently, LRG has been reported to modulate TGF-β signaling. TGF-β is essential for differentiation of Th17 and Treg, and these cells play important roles in the pathogenesis of RA, for example, by regulating osteoclast differentiation. So, LRG is may be involved in the pathogenesis of RA through the regulation of T lymphocyte differentiation. In this study, we aimed to elucidate the function of LRG on T lymphocyte differentiation and to examine the involvement of LRG in the pathogenesis of RA.

Methods: Naïve T lymphocyte were isolated from WT mice to examine the effects of LRG on the differentiation into Th17 and Treg. Male C57BL/6 mice and LRG KO mice were subjected to collagen-induced arthritis (CIA).

Results: In the presence of TGF-β alone, the differentiation of Treg was promoted by LRG. However, in the presence both TGF-β and IL6, LRG enhanced the differentiation into Th17 by increasing STAT3 phosphorylation. In CIA model, the numbers of Th17 in regional lymph nodes and serum levels of IL17 were significantly lower in LRG KO mice than in WT mice.

Conclusion: We propose that LRG promote differentiation of Th17 by enhancing phosphorylation of STAT3 and Smad in naïve T cells in the presence both TGF-b and IL6, and might involve in the arthritis pathology.

Disclosure: H. Urushima, None; **M. Fujimoto**, None; **C. Iwahashi**, None; **T. Ohkawara**, None; **H. Honda**, None; **S. Serada**, None; **T. Naka**, None.

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Abstract Number: 3027

Hyperactivated State of Mucosal Associated Invariant T Cells Due to Activation Potency of Monocytes in Systemic Lupus Erythematous

Goh Murayama[1], Asako Chiba[2], Ken Yamaji[3], Naoto Tamura[3], Yoshinari Takasaki[3] and Sachiko Miyake[2], [1]Department of Internal Medicine and Rheumatology,, Juntendo University School of Medicine, Tokyo, Japan., Tokyo, Japan, [2]Division of Immunology/NCNP, Natl Institute of Neuroscience, Kodaira Tokyo, Japan, [3]Department of Internal Medicine and Rheumatology, Juntendo University School of Medicine, Tokyo, Japan

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Background/Purpose: Mucosal-associated invariant T (MAIT) cells are innate-like lymphocytes that express a semi-invariant TCRα chain: Vα7.2-Jα33 in humans and Vα19-Jα33 in mice. MAIT cells are restricted by the MHC-related molecule-1 (MR1) and uniquely recognize microbial-derived vitamin B metabolites presented by MR1. Like other innate-like lymphocytes, MAIT cells have been suggested to play both proinflammatory and regulatory roles in autoimmune models. Although MAIT cells are rare in mice, human MAIT cells are more abundant and constitute approximately 5% of peripheral blood T cells, suggesting possible roles of MAIT cells in human autoimmune diseases. Previously we demonstrated that MAIT cells underwent activation-induced cell death and their frequency was markedly reduced in patients with systemic lupus erythematous (SLE). In this study, we aimed to investigate the mechanism by which MAIT cells are activated in SLE.

Methods: Peripheral blood was collected from SLE patients and healthy volunteers. Informed consent was obtained from all individuals according to institutional ethical guidelines. Peripheral blood mononuclear cells (PBMC) of SLE patients as well as healthy volunteers were stained with anti-human monoclonal antibodies against CD3, γδTCR, Vα7.2TCR, CD161, and CD69. MAIT cells were identified as $CD3^{+}gdTCR^{-}Va7.2TCR^{+}CD161^{high}$ cells by flow cytometetry. The activation status of MAIT cells was assessed by the expression of CD69. MAIT cells were sorted from PBMC of healthy individuals by using magnetic cell sorting (MACS) and FACS Aria. $CD19^{+}$B cells or $CD14^{+}$monocytes were isolated from PBMC of healthy controls (HC) or SLE patients by using MACS. MAIT cells were co-cultured with B cells or monocytes in the presence of MR1 ligand (MR1L), and the expression of CD69 on MAIT cells stimulated with MR1L was evaluated by FACS. The serum cytokine levels were measured by ELISA or magnetic bead-based assays. PBMC were cultured in the presence of various cytokines, and CD69 expression on MAIT cells was analyzed by FACS.

Results: MAIT cells from lupus patients with active disease expressed high levels of CD69. Although B cells from SLE patients and healthy controls equally activated MAIT cells in the presence of MR1L, the activation capacity of lupus monocytes was greatly augmented compared to healthy controls. The serum levels of cytokines including IL-12 and IL-18 were increased in active SLE and MAIT cells were activated by cytokines in the absence of exogenous antigens in vitro.

Conclusion: Monocytes and inflammatory cytokines may contribute to the hyperactivated state of MAIT cells in SLE.

Disclosure: G. Murayama, None; **A. Chiba**, None; **K. Yamaji**, None; **N. Tamura**, None; **Y. Takasaki**, None; **S. Miyake**, None.

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Abstract Number: 3028

CD1d Regulates iNKT Cell Autoreactivity

Meng Zhao[1,2] and Mitchell Kronenberg[2], [1]Medicine, UC-San Diego, La Jolla, CA, [2]Developmental Immunology, La Jolla Institute for Allergy and Immunology, La Jolla, CA

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Background/Purpose:

Invariant Natural Killer T (iNKT) cells are a unique population of lymphocytes that express an invariant TCR alpha chain, and react to lipid antigens presented by non classical MHC class I like molecule CD1d. There is highly homologous population in human. iNKT cells carry out innate-like responses and produce large amount of diverse cytokines, including IFNgamma, IL-4, IL-17 and IL-21. Therefore, iNKT cells are involved in numerous inflammatory and pathological conditions, including rheumatic diseases such as SLE and RA.

iNKT cells are autoreactive, and it is not clear how their autoreactivity is regulated. This is an important question, especially relevant for understanding the pathogenesis of many human autoimmune diseases. Our discoveries, therefore, will potentially identify novel drug targets for the treatment of patients with SLE, RA and other autoimmune diseases in which abnormal activation of iNKT cells is observed.

Methods:

We use primary iNKT cell line as a model system to study iNKT cell autoreactivity. Microarray and RNA-seq were carried out to identify new regulators of iNKT autoreactivity.

Results:

We have found that the short-term cultured iNKT cells have greatly increased sensitivity to CD1d-lipid complexes derived from multiple sources. APCs that express a tail-deleted form of CD1d are defective to stimulate the iNKT cell lines *in vitro*. iNKT cell lines distinguish previously identified self lipid Ags from their structural homologs. Transfer experiments revealed that CD1d in the periphery down regulates the autoreactivity. However, tail-deleted CD1d is unable to completely control the reactivity of iNKT cells. RNAseq identified several candidate genes that may act down stream of CD1d-TCR interaction to regulate the function of iNKT cells, one of which is PTPN6/SHP1. The development of iNKT cells is impaired in the conditional knockout mice of SHP1, thus it prevents us from directly evaluating the role of SHP1 in the pheripheral iNKT cells. However, we observed several T cell exhaustion markers, such as PD-1 and FR4, express at higher level in SHP1 deficient iNKT cells. It is consistent with our hypothesis that SHP1 acts downstream of TCR and controls the reactivity of iNKT cells.

Conclusion:

We have designed a new a reliable system that demonstrates iNKT cell autoreactivity for CD1d in bulk populations with diverse TCR beta chains, rather than requiring a single hybridoma. iNKT cell autoreactivity is modulated by CD1d in the periphery and depends on the endolysosomal localization of CD1d. Gene expression profiling reveals new regulators of iNKT cell reactivity, for example, SHP1/PTPN6.

Disclosure: M. Zhao, None; **M. Kronenberg**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/cd1d-regulates-inkt-cell-autoreactivity

Abstract Number: 3029

Increased Plasticity of Non-Classic Th1 Cells Towards the Th17 Phenotype

Antonia Klose[1], Fausto Pirronello[1], Hendrik Schulze-Koops[1], Jan Leipe[2] and Alla Skapenko[1], [1]Division of Rheumatology and Clinical Immunology, University of Munich, Munich, Germany, [2]Division of Rheumatology, University of Munich, Munich, Germany
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Background/Purpose: Mechanisms underlying the predominance of Th17 cells observed in RA are not fully understood. Th cell plasticity is a potential mechanism leading to enrichment of Th populations under certain conditions. Recently, two distinct subtypes of Th1 cells named classic (IFNγ+RORC-CD161-CCR6-) and non-classic (IFNγ+RORC+CD161+CCR6+) Th1 cells were described. Given that non-classic Th1 cells share several characteristics with Th17 cells, we hypothesized that non-classic Th1 cells might show an enhanced plasticity towards the Th17 phenotype. Increased frequencies of non-classic Th1 cells in RA might therefore potentially contribute to the Th17 shift in RA.

Methods: CD4 memory T cells were isolated from patients with early active and untreated RA and age- and sex-matched healthy controls (HC) by MACS. Frequencies of the *in vivo*-generated Th1 cell populations were assessed after cytokine secretion assay for IFNγ and IL-17 and surface staining for CD161 and CCR6. Viable Th1 cells (IFNγ+IL-17-) were FACS-sorted into classic Th1 (CD161-CCR6-) and non-classic Th1 (CD161+CCR6+). Sorted Th1 cell populations were trans-differentiated under Th0-, Th1-, Th2- and Th17-inducing conditions. Plastic changes were assessed *ex vivo*by analyzing the cytokine and transcription factor profile by flow cytometry on the protein and by qPCR on the mRNA level.

Results: Trans-differentiation of non-classic Th1 cells under inflammatory Th17-inducing conditions resulted in markedly high frequencies of IL-17-producing cells, Th17 cells and Th1/Th17 cells (IL-17+IFNγ+), whereas no substantial plasticity towards a Th17 phenotype was observed for classic Th1 cells (Th17 cells: 3.9% vs 0.9%, p=0.045; Th17/Th1 cells: 16.6% vs. 0.9%, p=0.00003). In marked contrast, classic Th1 cells showed higher plasticity towards IL-4-producing cells, most of them being Th1/Th2 cells (IFNγ+/IL-4+), compared to non-classic Th1 cells (Th1/Th2 cells: 8.4% vs. 3.0%, p=0.015). Consistently, for RORC higher expression was found in non-classic Th1 and for GATA-3 in classic Th1 cells *ex vivo*. The frequencies of classic and non-classic Th1 cells did not differ significantly between RA patients and healthy individuals.

Conclusion: Non-classic Th1 cells demonstrate a general substantial plasticity towards the Th17 phenotype, which might contribute to their pathogenicity, whereas classic Th1 cells show the propensity to acquire a Th2 phenotype and might therefore give rise to a less pathogenic

phenotype. Similar frequencies of *ex vivo* non-classic and classic Th1 cells between RA and HC suggest a conserved phenotype of the populations after their *in vivo* generation and might argue against the contribution of non-classic Th1 cells to Th17-biased RA phenotype.

Disclosure: A. Klose, None; **F. Pirronello**, None; **H. Schulze-Koops**, None; **J. Leipe**, None; **A. Skapenko**, None.

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Abstract Number: 3030

Increased Localization of Spleen Tyrosine Kinase (Syk) in Lipid Rafts of in Vitro TCR/CD3-CD28 Activated Lupus T Cells

Noymar Luque[1], **Nursamaa Abdoel**[1], Héctor Rojas[2], Martín Rodríguez[1], Gloria Vásquez[3] and Ana Blasini[1], [1]Centro Nacional de Enfermedades Reumáticas. Hospital Universitario de Caracas, Caracas, Venezuela, [2]Instituto de Inmunología, Escuela de Medicina, Universidad Central de Venezuela, Caracas, Venezuela, [3]Grupo de Inmunología Celular e Inmunogenética. Universidad de Antioquia, Medellin, Colombia

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Background/Purpose: Numerous alterations in signal transduction in SLE T cells have been previously reported. Diminished expression of the ζ chain of the TCR/CD3 complex has been shown to be accompanied by the substitutive assembly of FcεRIγ chain and coupling to Syk PTK (Protein Tyrosine Kinase), rewiring downstream signaling to produce alternative functional outcomes in lupus T cells. Syk is 100-fold times enzymatically more potent than ZAP-70. In this study we examined the localization of ZAP-70 and Syk in lipid rafts of lupus T cells; lipid raft is the site in membranes where signaling molecules preferentially associate to form signalosomes.

Methods: SLE patients were diagnosed according to the American College of Rheumatology 1987 criteria. Healthy donors were recruited from the blood bank of Hospital Universitario de Caracas. All individuals signed an informed consent previously approved by the Hospital Bioethics Committee. Highly enriched T cells, obtained from peripheral blood samples and subjected to RosetteSep^{TM} isolation, were adhered to poly-L-lysine coated slides and activated for 5 and 15 minutes at 37°C, with 4.5 µm superparamagnetic polystyrene beads coated with antibodies against CD3ε and CD28. The cells were fixed, permeabilized and stained with antibodies recognizing ZAP-70, Syk and Cholera Toxin Subunit B as a lipid raft marker. The cell-bead complexes were evaluated by confocal microscopy and densitometries were obtained using ImageJ, 1.49t (National Institutes of Health, USA).

Results: We observed similar localization of Syk in lipid rafts of unstimulated lupus T cells as compared to healthy controls (0.216 ± 0.045 vs. 0.287 ± 0.056; Pearson's r ± SME, n= 6). In contrast, there was a diminished localization of ZAP-70 in unstimulated lupus T cells as compared to healthy controls (0.383 ± 0.035 vs. 0.488 ± 0.037; Pearson's r ± SME, n= 6; Student's t-test, p= 0.046,). After CD3-CD28 costimulation during 15 minutes, we observed an increased localization of Syk in lipid rafts of lupus T cells as compared to healthy controls (0.352 ± 0.033 vs. 0.235 ± 0.042; Pearson's r ± SME, n= 6; Student's t-test, p= 0.034), whereas ZAP-70 localization in lipid rafts after costimulation was similar in both groups (0.433 ± 0.040 vs. 0.402 ± 0.031; Pearson's r ± SME, n= 6).

Conclusion: Our findings suggest an abnormal pattern in the localization of key tyrosine kinases in lipid rafts after activation of SLE T cells, with a predominant translocation of Syk over the typical T-cell kinase, ZAP-70. This abnormal response may contribute to known signaling abnormalities such as displacement of transmembrane protein Linker for Activation of T cells (LAT) from lipid rafts and downstream deficient activation of Extracellular Signaling Regulated Kinases (ERK), as previously shown in our laboratory.

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Disclosure: N. Luque, None; **N. Abdoel**, None; **H. Rojas**, None; **M. Rodríguez**, None; **G. Vásquez**, None; **A. Blasini**, None.

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Abstract Number: 3031

Dalazatide (ShK-186), a Kv1.3 Channel Inhibitor That Targets Effector Memory T Cells: Ex Vivo Studies in Pediatric Systemic Lupus Erythematosus

Megan Yuasa[1], David Peckham[2], Anne M. Stevens[3], Shawn P. Iadonato[2] and Ernesto J. Muñoz-Elías[4], [1]Seattle Children's Res Institute, Seattle Children's Research Institute, Seattle, WA, [2]Kineta Inc, Seattle, WA, [3]Seattle Children's Res Inst, Seattle Children's Hospital, Seattle, WA, [4]Translational Immunology & Preclinical Development, Kineta, Inc., Seattle, WA

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Background/Purpose:

The voltage-gated potassium channel Kv1.3 is highly expressed on activated T effector memory cells (TEM), is essential for T cell activation, and thus is a novel target for the treatment of autoimmune disorders. ShK-186 (dalazatide) is a specific, highly potent peptide inhibitor of Kv1.3 that has recently entered clinical development. Previous reports associated TEM activation with the pathogenesis of SLE, suggesting a potential for dalazatide efficacy in SLE.

Methods:

Peripheral blood from pediatric patients with SLE and healthy controls were studied. *Ex vivo* Kv1.3 expression was assayed on T lymphocyte subsets by flow cytometry. The effect of dalazatide on cytokine expression after no stimulation or following short term stimulation by PMA and thapsigargin or ionomycin was evaluated by flow cytometry.

Results:

Kv1.3 was up-regulated on $CD4^{+}$TEM from SLE patients with active disease (mean MFI 370) compared to and to patients with inactive disease (mean MFI 265, p=0.08), or to controls (mean MFI 208, p=0.005). A larger effect on Kv1.3 expression was detected in CD8+TEM (active SLE 311, inactive SLE 185, p=0.02; controls 140, p=0.005). Dalazatide at concentrations of 10 pM-1nM decreased proinflammatory cytokine production *ex vivo* in a dose-dependent fashion in TEM, but not naïve cells from SLE patients and healthy controls. In the CCR7low CD45RO+ CD4+ TEM subset, inhibition of TNF-a (mean 33-43%), interferon-g (33-55%), and IL-17 (28-53%) was detected.

Conclusion:

In vitro studies suggest that Kv1.3 on TEM may be a treatment target for SLE. In addition, Kv1.3 expression may be useful as a biomarker of disease activity in SLE.

Disclosure: M. Yuasa, None; **D. Peckham**, kineta inc, 3; **A. M. Stevens**, None; **S. P. Iadonato**, Kineta Inc, 3; **E. J. Muñoz-Elías**, Kineta, Inc., 3.

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Abstract Number: 3032

Role of Adenosine and Neutrophils in Inflammation Associated with Mutations in CECR1 Gene

Kyawt W. Shwin[1,2], Carmelo Carmona-Rivera[3], Wanxia Tsai[4], Chya-chia Richard Lee[5,6], Elaine Novakovich[7], Deborah L. Stone[8], Amanda K. Ombrello[8], Raphaela Goldbach-Mansky[9], Massimo Gadina[10], Daniel Kastner[11], Ivona Aksentijevich[12,13], Mariana J. Kaplan[7] and Peter C. Grayson[14,15], [1]NIAMS, National Institutes of Health, BETHESDA, MD, [2]Translational Autoinflammatory Diseases Section, National Institutes of Health, Bethesda, MD, [3]Systemic Autoimmunity Branch/ NIAMS, National Institutes of Health, Bethesda, MD, [4]Translational Immunology, Office of Science and Technology, National Institutes of Health, Bethesda, MD, [5]National Cancer Institute, National Institutes of Health, Bethesda, MD, [6]Laboratory of Pathology, NCI, National Institutes of Health, BETHESDA, MD, [7]Systemic Autoimmunity Branch, NIAMS, National Institutes of Health, Bethesda, MD, [8]National Human Genome Research Institute, National Institutes of Health, Bethesda, MD, [9]Translational Autoinflammatory Diseases Section, NIAMS, NIH, Bethesda, MD, [10]Translational Immunology, Office of Science and Technology, NIAMS, National Institutes of Health, Bethesda, MD, [11]Inflammatory Disease Section, NHGRI, National Institutes of Health,

Bethesda, MD, [12]NIH/NHGRI, Metabolic, Cardiovascular, and Inflammatory Disease Genomics Branch, Bethesda, MD, [13]Inflammatory Disease Section, National Human Genome Research Institute, Bethesda, MD, [14]National Institute of Arthritis and Musculoskeletal and Skin Diseases, National Institutes of Health, Bethesda, MD, [15]NIAMS Systemic Autoimmunity Branch, National Institutes of Health, Bethesda, MD
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Session Type: ACR Poster Session C
Session Time: 9:00AM-11:00AM

Background/Purpose:

The phenotype of patients afflicted by deficiency of adenosine deaminase 2 (DADA2) due to mutations in *CECR1*encoding ADA2 protein shares many features with idiopathic polyarteritis nodosa (PAN), including abundant neutrophilic infiltration in affected tissues. Immune cell responses following treatment with TNF inhibitors and the specific role of neutrophils were studied in a family consisting of 2 children with DADA2 and several family members afflicted by various autoimmune diseases including idiopathic PAN.

Methods:

Candidate-gene sequencing of the *CECR1*gene was performed in 2 children who had lacunar infarcts, livedoid rash and biopsy-proven vasculitis. Histopathology characterization was performed on affected skin and small bowel tissues. Neutrophils and low-density granulocytes (LDGs) were isolated during active disease. Neutrophil extracellular traps (NETs) were quantified and visualized by fluorescence microscopy. Neutrophils were incubated with graded concentrations of adenosine +/- ADA2 enzyme and resultant NET formation was quantified. Evaluations were conducted during active disease and 4 months later during disease remission after treatment with etanercept. Immune cell subsets before and after treatment were quantified by multi-panel flow cytometry.

Results:

Both children were compound heterozygotes for G358R and G47R mutations in the *CECR1* gene. The mother was a carrier for G358R mutation and had a history of unexplained lacunar infarct at age 45. A maternal great grandmother had a history of biopsy-proven PAN onset at age 60, and a maternal great uncle had a history of autoimmune colitis and livedo reticularis. The father was a carrier for G47R mutation and had a history of Guillian-Barré syndrome. Fibrinoid necrosis of medium-sized blood vessels, intravascular thrombi, and dense perivascular infiltrates of netting neutrophils and macrophages were visualized in affected skin and small bowel sections from children. Immunohistochemistry showed aggregates of MPO, CD163 and CD3 positive cells in the deep dermis and perivascular region. An abundance of circulating LDGs prone to spontaneous NET formation was observed during active disease and also in clinically unaffected heterozygous carriers of *CECR1* mutation. LDG numbers normalized when remission was achieved using anti-TNF agents. Various concentrations of adenosine [0.2, 0.5, 16 μM] stimulated robust NET formation, and this was inhibited by addition of recombinant ADA2. Following treatment with etanercept, there were decreases in $CD14^+/CD16^+$ monocytes (8% vs 2%), increases in memory T_{reg} cells (12% vs 23%), activated T_{reg}(2% vs 7%) and B cells (2% vs 19%).

Conclusion:

Neutrophils may play pathogenic roles in DADA2. LDGs and NETs are observed during active disease in children with DADA2 and their parents. Deficiency of ADA2 may increase risk for adenosine-induced NET formation, which is a novel mechanism of NETosis. Alterations in the adenosine-mediated signaling pathway may contribute to the pathogenesis of DADA2. The autoimmunity observed in this family suggests that carriers of *CECR1*gene mutation may have increased risk for autoimmune diseases and that DADA2 and idiopathic PAN may be genetically related.

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View Abstract and Citation Information Online - http://acrabstracts.org/abstract/role-of-adenosine-and-neutrophils-in-inflammation-associated-with-mutations-in-cecr1-gene

Abstract Number: 3033

Polyarteritis Nodosa and Cutaneous Arteritis: Are They Distinct Diseases?

Fatma Alibaz-Oner[1], Matthew J. Koster[2], Cynthia S. Crowson[3], Ashima Makol[2], Steven R. Ytterberg[2], Eric L. Matteson[2] and Kenneth J. Warrington[2], [1]Department Rheumatology, Marmara University Faculty of Medicine, Istanbul, Turkey, [2]Rheumatology, Mayo Clinic, Rochester, MN, [3]Health Sciences Research, Mayo Clinic, Rochester, MN

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Background/Purpose: Polyarteritis nodosa (PAN) is a rare systemic necrotizing vasculitis predominantly targeting medium-sized visceral arteries. Cutaneous arteritis (CA) is generally limited to the medium-sized vessels in the skin. Although previously categorized as cutaneous PAN, it is now included as a form of single organ vasculitis in the revised 2012 International Chapel Hill Consensus Conference Nomenclature of Vasculitides. In this study, we aimed to evaluate and compare the demographics, clinical characteristics, treatment, and outcome of patients with systemic PAN and CA.

Methods: Retrospective cohorts of patients with PAN and CA evaluated in 1986-2014 were assembled. The demographics, clinical characteristics, treatment and outcomes of patients were abstracted from medical records. Birmingham Vasculitis Activity Score (BVAS) and the prognostic Five Factor Score (FFS) were calculated. Chi-square and rank sum tests were used to compare characteristics between the groups.

Results: The study cohort included 29 patients with PAN and 39 patients with CA. Only 1 patient presenting as CA evolved to systemic PAN during disease course. Sixteen of 29 patients with PAN and all patients with CA had histologically proven vasculitis involving medium-sized vessels. Mean follow-up duration was 6.0±5.9 years in PAN group, 5.8±4.4 years in the CA group. Angiographic abnormalities consistent with PAN were present in 16 patients. Most cases of PAN were idiopathic. Three patients in the PAN group and 2 patients in CA group had hepatitis B. One patient in the PAN group had Hepatitis C. Clinical characteristics of the groups are presented in Table 1. All patients with PAN and 90% of patients with CA were treated with glucocorticoids (GC). Additional immunosuppressive (IS) agents were used in 62% of PAN and 33% of CA. Dapsone was used in 8 (20.5%) patients in CA group. Twenty patients with PAN and 16 patients with CA were followed for at least 6 months. BVAS and FFS scores were higher among patients with PAN. However, the relapse rate was significantly higher in the CA group compared to PAN (9.8 vs 0.9 per 100 person-years; Rate ratio:7.88; 95% confidence interval:1.81-112.73). While no deaths were observed in the CA group, survival in the PAN group was 66% at 10-years.

Conclusion: Our results suggest that CA is a distinct disease rather than a limited expression of systemic PAN. Progression of CA to systemic PAN is rare. Patients with CA have a higher relapse rate compared to those with systemic PAN, possibly due to lower use of IS agents in CA.

Table 1: Baseline clinical and laboratory characteristics

	Systemic PAN (n=29)	Cutaneous Arteritis (n=39)	P value
Demographics			
Age at diagnosis, years*	56.7±18.2	48.7±19.3	0.10
Female	13 (45%)	25 (64%)	0.11
Laboratory parameters			
Sedimentation rate (mm/hour)*	55.3±41	32.7±26.6	**0.042**
C-reactive protein(mg/l)†	9.1(0.6-117)	6.9(0.7-42)	0.53
Proteinuria(>400gm/24 hours)	4/27 (15%)	0/34	**0.02**
Constitutional symptoms			
Fever	9/29 (31%)	6/39 (15%)	0.12
Weight loss	10/29 (34%)	2/38 (5%)	**0.002**
Clinical manifestations			
Musculoskeletal	19/29 (66%)	20/39 (51%)	0.24
Neurologic	15/29 (52%)	2/39 (5%)	**<0.001**
Urologic	4/28 (14%)	0/38	**0.001**
Hypertension	8/29 (28%)	0/39	**<0.001**
Cutaneous	16/29 (55%)	39/39 (100%)	**<0.001**
Gastrointestinal	12/29 (41%)	0/39	**<0.001**
Cardiac	1/29 (3%)	0/39	0.24
Vascular	3/29 (10%)	1/39 (3%)	0.18
Ocular	1/27 (4%)	0/36	0.24
Pulmonary	1/29 (3%)	0/39	0.24
ENT	1/26 (4%)	0/39	0.22
Disease assessment			
BVAS score*	11.3±5.2	2.5±1.8	**<0.001**
Five Factor Score =0	16/29 (55%)	38/39 (97%)	
=1	11/29 (38%)	1/39 (3%)	
≥2	2/29 (7%)	0/39	**<0.001**

PAN: Polyarteritis nodosa; ENT: Ear, Nose, Throat; BVAS: Birmingham Vasculitis Activity Score *Mean ±SD; †Median (Interquartile range)

Disclosure: F. Alibaz-Oner, None; **M. J. Koster**, None; **C. S. Crowson**, None; **A. Makol**, None; **S. R. Ytterberg**, None; **E. L. Matteson**, Novartis/Sanofi/Centocor-Jansen/Celgene/Amgen/Roche/Genentech/Mesoblast/Pfizer, 2; **K. J. Warrington**, None.

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Abstract Number: 3034

A Comparative Metabolomic Evaluation of Behcet's Disease with Arthritis and Seronegative Arthritis Using Synovial Fluid

Joong Kyong Ahn[1], Sooah Kim[2], Jungyeon Kim[2], Jiwon Hwang[3], Hyungjin Kim[4], Hyemin Jeong[5], Yeong Hee Eun[6], Chan Hong Jeon[7], Jaejoon Lee[5], Eun-Mi Koh[5], Kyoung Heon Kim[2] and Hoon-Suk Cha[8], [1]Department of Medicine, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, Seoul, South Korea, [2]Department of Biotechnology, Korea University Graduate School, Seoul, South Korea, [3]Department of Internal Medicine, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, Seoul, South Korea, [4]Department of medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea, [5]Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea, [6]Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of

Medicine, Seoul, South Korea, [7]Department of Internal Medicine, Soonchunhyang University College of Medicine, Bucheon, South Korea, [8]Division of Rheumatology, Department of Internal Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea
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Background/Purpose: Behcet's disease (BD) is a chronic, complex systemic vasculitis of unknown etiology characterized by orogenital ulcers, uveitis, and arthritis. Arthritis and arthralgias in BD are known to be the most common rheumatologic findings with a prevalence ranging from 40 to 70%. However, arthritis in BD is often confused with seronegative arthritis (SNA) including seronegative spondyloarthropathy (SNSpA) and seronegative rheumatoid arthritis (SNRA) because of shared clinical symptoms and the lack of definitive biomarkers for BD. The purpose of this study was to evaluate the metabolomic profiling of synovial fluid (SF) from patients with arthritis in BD and SNA to investigate possible metabolic patterns and potential biomarkers for arthritis in BD.

Methods: SF samples were collected from BD patients with arthritis (n = 6, mean age 34.8 ± 16.4 years), SNSpA (n = 13, mean age 30.9 ± 11.0 years), and SNRA (n = 5, mean age 65.8 ± 10.7 years). Metabolomic profiling was performed by gas chromatography/time-of-flight mass spectrometry in conjunction with univariate and multivariate statistical analyses.

Results: A total of 123 metabolites were identified from samples. Orthogonal partial least square-discriminant analysis showed clear discrimination between arthritis in BD and SNA. A set of 11 metabolites were identified as potential biomarkers for arthritis in BD using variable importance for projection values and the Wilcoxon-Mann-Whitney test. Compared with SNA, arthritis in BD exhibited relatively high levels of glutamate, valine, citramalate, leucine, methionine sulfoxide, glycerate, phosphate, lysine, isoleucine, urea, and citrulline. There were two markers identified, elevated methionine sulfoxide and citrulline, that were associated with increased oxidative stress, providing a potential link to BD-associated neutrophil hyperactivity. Glutamate, citramalate, and valine were selected and validated as putative biomarkers for arthritis in BD (sensitivity, 100%; specificity, 61.1%).

Conclusion: This is the first report to present potential biomarkers from SF for discriminating arthritis in BD from SNA. The metabolomics of SF may be helpful in searching for potential biomarkers and elucidating the clinicopathogenesis of arthritis in BD.

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Abstract Number: 3035

HLA B51 and Possible Associated Autoimmune Disorders Other Than Behcets Disease: A Retrospective Cohort Study

Luis Salayandia[1], Wilmer Sibbitt Jr.[1], Arthur Bankhurst[2], Roderick Fields[3], Gladys Cook[4], Konstantin Konstantinov[5] and Suzanne Emil[1], [1]Rheumatology, University of New Mexico, Albuquerque, NM, [2]Rheum/ MSC 105550, University of NM Med Ctr, Albuquerque, NM, [3]Rheumatology, University of New Mexico, Albquerque, NM, [4]Rheumatology, UNM, Albuquerque, NM, [5]1 University Of New Mexico, University of New Mexico, Albuquerque, NM
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Background/Purpose: The diagnostic utility of HLA B51 in association with Behcet's disease has been clearly identified; however the correlation of HLA B51 with other autoimmune disorders has not been well established to date. This study aims to assess the correlation

between the presence of HLA B51 with other autoimmune disorders, prevalence of Behcet's in our population and most common presenting symptoms and serologic markers.

Methods: Retrospective analysis of autoimmune conditions other than Behcet's disease in patients with HLA B51 allele, which is measured in all incoming patients to our consultation service.

Results: At our tertiary reference center, from approximately 1200 screened patients, we identified 55 patients who were HLA B 51 positive. Out of these 55 patients, 14 (25.5%) met ICBD criteria for Behcet's disease, 22 (30.7%) had history of oral ulcers, 35 (63.6%) had arthralgias, 12 (21.8%) had history of uveitis, 16(29.1%) had cutaneous features such as cutaneous vasculitis, cutaneous ulcers, digital ulceration, Erythema nodosum, positive pathergy test, papulopostules, acne or folliculitis. Mean follow-up was 3 years. Only 2 out of 55 were cocaine users. Our demographics showed 45 females (81.8%) and 32 Hispanics (58.2%), 17 Northern European (30.9%) and 4 Native American (7.3%). Regarding specific autoimmune disorders, we had 6(10.9%) patients who met SLE criteria, 4 (7.3%) that met RA criteria, 2 (3.6%) that met PMR criteria, 4 (7.3%) that met Sjogren's syndrome criteria, 5 (9.1%) spondyloarthropathies, 4 (7.3%)with scleroderma/CREST, and 1 with Dermatomyositis (1.8%). No patient had giant cell arteritis, granulomatosis with polyangiitis, Microscopic polyangiitis or eosinophilic granulomatosis with polyangiitis in this study. Thus, in this cohort 31% of HLA-B51patients had autoimmune disease other than Behcet's disease; this is remarkable, as HLA-B51 is present in only 0.2-1.5% of reference populations.

Conclusion: Our study demonstrates that 25.5% of HLA-B51 subjects in our population have Behcet's disease, but 31% of HLA-B51 positive individuals have other classic autoimmune diseases compared to 0.2-1.5% of reference populations. Thus, the results of this study confirms that HLA B51 is associated with Behcet's disease, but these data also suggest that HLA-B51 may also play a hereto unrecognized role in either inducing, modulating, or upregulating other forms of autoimmune disease to cause a 20 fold increase in HLA-51 prevalence from reference populations.

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Abstract Number: 3036

The Association Between Behcet's Disease, Myelodysplastic Syndrome and Trisomy 8

Won-Seok Lee[1], Yun Jung Choi[2], Myong-Joo Hong[3], Chang-Hoon Lee[4], Myeung Su Lee[5], Young Sun Suh[6], Sang-Il Lee[7], Yong Gon Cho[8] and Wan-Hee Yoo[9], [1]Division of Rheumatology, Department of Internal Medicine, Chonbuk National University Medical School and Research Institute of Clinical Medicine of Chonbuk National University Hospital-Chonbuk National University, jeonju, South Korea, [2]Division of Rheumatology, Department of Internal Medicine, Chonbuk National University Medical School and Research Institute of Clinical Medicine of Chonbuk National University Hospital-Chonbuk National University, JeonJu, South Korea, [3]Internal Medicine, Presbyterian Medical center, Jeonju, South Korea, [4]Department of Internal Medicine, School of Medicine, Wonkwang University, Iksan, Chonbuk, South Korea, [5]Internal Medicine, School of Medicine, Wonkwang University, Iksan, Chonbuk, South Korea, [6]Division of Rheumatology, Department of Internal Medicine, School of Medicine, The Catholic University of Korea, Seoul St. Mary's Hospital, Seoul, South Korea, [7]Division of Rheumatology, Department of Internal Medicine, Gyeongsang National University School of Medicine, Jinju, South Korea, [8]Department of Laboratory medicine, Chonbuk National University Medical School and Hospital, Jeonju, South Korea, [9]Division of Rhuematology, Department of Internal Medicine, Chonbuk National University Medical School and Research Institute of Clinical Medicine of Chonbuk National University Hospital-Chonbuk National University, Jeonju, South Korea

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Background/Purpose: Behcet's disease (BD) is a systemic vasculitis, whereas myelodysplastic syndrome (MDS) is a heterogeneous group of clonal hematologic disorders characterized by ineffective hematopoiesis. Some patients with BD comorbid with MDS involving trisomy 8 have intestinal lesions refractory to conventional medical therapies. We analyzed BD to evaluate the concurrence of BD and trisomy 8 and to determine whether trisomy 8 plays a role in the expression of BD associated with MDS.

Methods: Ninety-five consecutive patients were assessed for the presence of trisomy 8 in the peripheral blood. The clinical manifestation and genetic components were analyzed in patients with BD and MDS.

Results: Six of 95 patients were positive for Trisomy 8. Three of these cases were diagnosed with MDS, and they underwent bone marrow

transplantation. The prevalence of MDS was as high as 50% in BD patients with trisomy 8. Gastrointestinal (GI) involvement was more common in patients with BD involving trisomy 8 than in non-trisomy8 patients (66% vs. 25%). The mean corpuscular volume (MCV) was higher in the presence of trisomy 8 than in cases lacking trisomy 8 (100.1 fl vs. 92.64 fl, P<0.01).

Conclusion: The prevalence of MDS was more higher in BD patients with trisomy 8. GI involvement seems to be an inherent feature of BD associated with MDS involving trisomy 8. When a patient with BD has increased MCV, the presence of trisomy 8 should be evaluated. Additionally, close monitoring for the possibility of MDS is necessary.

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Abstract Number: 3037

Serum Anti-Lysozyme Is Associated with Disease Activity of Behcet's Disease

Jin Su Park[1], Mi-il Kang[2], You Jung Ha[3], Yong-Beom Park[4], Soo-Kon Lee[5] and Sang-Won Lee[6], [1]Department of Internal Medicine, NHIS Ilsan Hospital, Goyang-si Gyeounggi-do, South Korea, [2]Department of Internal Medicine, Dankook University Hospital, Cheonan-si Chungcheongnam-do, South Korea, [3]Division of Rheumatology, Department of Internal Medicine, Seoul National University Bundang Hospital, Seongnam-si, South Korea, [4]Yonsei University College of Medicine, Division of Rheumatology, Department of Internal Medicine, Seoul, South Korea, [5]Internal Medicine, Yonsei Univ College of Med, Seoul, South Korea, [6]Department of Internal Medicine, Yonsei University College of Medicine, Seoul, South Korea
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Background/Purpose: To investigate the association between autoantibodies against non- myeloperoxidase (MPO) neutrophil granule antigens and activity of Behcet's disease (BD).

Methods: We consecutively enrolled 51 BD patients without diseases requiring the differential diagnosis of BD or infection, and assessed the clinical data. We performed blood tests including antibodies against proteinase 3 (PR3), MPO, bactericidal permeability increasing protein (BPI), cathepsin G, elastase, lactoferrin and lysozyme. We evaluated the association of autoantibodies with BD activity using patients index score of Behcet's Disease Current Activity Form.

Results: The median age of patients (25 men and 36 women) was 51.0 years. The median patients index score was 2.0 (range 0, 5.0), and 56.9% of patients had active BD. In multivariate linear regression analysis of variables with significant correlations, only anti-lysozyme showed a significant correlation with BD activity (standardized $\beta = 0.417$, $p = 0.002$). In multivariate logistic regression analysis, anti-lysozyme was only predictive value of active BD, but it achieved a borderline statistical significance (OR 5.052, $p = 0.066$). When BD patients were classified into the two groups according to the optimal cutoff value of anti-lysozyme level (2.95 IU/mL), active BD was more frequent in patient having anti-lysozyme level above the cutoff value than those below (RR 12.308, $p = 0.001$).

Conclusion: Anti-lysozyme was significantly correlated with disease activity score and it was only independent value to predict active disease in patients with BD. Furthermore, patients having anti-lysozyme level ≥ 2.95 had a significantly higher risk of having active BD than those not.

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Abstract Number: 3038

Serum CXCL8, 10 and 12 Are Increased in Patients with Behcet's Disease and CXCL10 Levels Are Correlated with Number of Erythema Nodosum

Sang Jin Lee[1,2], Hyun Jung Yoo[3], Hyun Mi Kwon[4], Jin Young Moon[4], Jin Kyun Park[5], Eun Young Lee[5], Eun Bong Lee[4] and Yeong Wook Song[5], [1]Division of Rheumatology, Department of Internal Medicine, Seoul National University College of Medicine, Seoul, South Korea, [2]Department of Molecular Medicine and Biopharmaceutical Sciences, BK21 plus Graduate School of Convergence Science and Technology, and College of Medicine or College of Pharmacy, Seoul National University, Seoul, South Korea, [3]Department of Molecular Medicine and Biopharmaceutical Sciences, BK 21 plus Graduate School of Convergence Science and Technology, and College of Medicine or College of Parmarcy, Seoul National University, Seoul, South Korea, [4]Division of Rheumatology, Department of Internal Medicine, Seoul National University Hospital, Seoul, South Korea, [5]Division of Rheumatology, Department of Internal Medicine, Seoul National University, Seoul, South Korea
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Background/Purpose:

Chemokines are multifunctional mediators that control leukocyte recruitment into the inflammatory sites and enhance immune responses. It remains to be investigated which chemokines are important in Behcet's disease (BD). The objective of this study was to investigate serum levels of neutrophil and lymphocyte chemoattractants in BD patients and its association with disease activity and symptoms.

Methods:

We collected sera from patients with BD (n=64) and age-, sex matched healthy controls (n=21). Serum levels of chemokines were assayed for the neutrophil chemoattractants (CXCL1 and CXCL8) and lymphocyte chemoattractants (CXCL9, CXCL10, CXCL12, CXCL13 and CXCL16) by using a multiplex assay. Behcet's disease current activity form (BDCAF) and symptoms were evaluated at the time of blood collection.

Results:

Serum levels of CXCL8, CXCL10 and CXCL12 were significantly higher in the BD patients than in healthy controls ($p<0.001$, $p=0.050$ and $p=0.002$, respectively). Serum chemokine levels were not associated with BDCAF in BD patients. But CXCL10 levels were significantly higher in patients with erythema nodosum (EN) than in patients without EN ($p=0.008$). Additionally, CXCL10 levels were significantly correlated with number of EN ($r=0.338$, $p=0.006$). There was no difference of serum level of CXCL1, CXCL9, CXCL13 and CXCL16 between BD and healthy controls

Conclusion:

Serum levels of CXCL8, CXCL10 and CXCL12 were significantly higher in the BD patients than in healthy controls. CXCL10 levels were correlated with number of EN in BD patients.

Disclosure: S. J. Lee, None; **H. J. Yoo**, None; **H. M. Kwon**, None; **J. Y. Moon**, None; **J. K. Park**, None; **E. Y. Lee**, None; **E. B. Lee**, Pfizer Inc, 5; **Y. W. Song**, None.

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Abstract Number: 3039

Possible Contribution of HLA-A0207, B5201 and IL-23 Receptor Polymorphism in Ocular Behçet Disease

Toshikatsu Kaburaki[1], Shinji Harihara[2], Rie Tanaka[3], Hiromasa Sawamura[4], Ai Nishi[4], Atsushi Hatamochi[5], Jun Shimizu[6], Masumi Takeuchi[7], Shoji Kuwata[8], Hidetoshi Kawashima[9] and Fujio Takeuchi[10], [1]Ophthalmology, The University of Tokyo Graduate School of Medicine, Tokyo, Japan, [2]Division of Anthropology, Department of Biological Science, The University of Tokyo Graduate School of Science, Tokyo, Japan, [3]Department of Ophtalmology, The University of Tokyo Graduate School of Medicine,, Tokyo, Japan, [4]Department of Ophtalmology, The University of Tokyo Graduate School of Medicine, Tokyo, Japan, [5]Department of Dermatology, Dokkyo Medical University, Tochigi, Japan, [6]Department of Neurology, The University of Tokyo Graduate School of Medicine, Tokyo, Japan, [7]Teikyo University Support Center for Women Physicians and Researchers, Teikyo University School of Medicine, Tokyo, Japan, [8]Third Department of Internal Medicine, Teikyo University Chiba Medical Center, Teikyo University School of Medicine, Chiba, Japan, [9]Department of Ophthalmology, Jichi Medical

University, Tochigi, Japan, [10]Department of Allergy and Rheumatology, The University of Tokyo Graduate School of Medicine, Tokyo, Japan
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Background/Purpose: Behçet's disease (BD) is known to be associated with HLA-B*51:01 and HLA- A*26:01 in many different ethnic groups. Recently, HLA-A*02:07, IL-10 and IL23R-IL12RB polymorphisms have been proposed as a candidate gene for BD susceptibility. In this study, we examined the association of the HLA-A*02:07 and **single nucleotide** polymorphism (SNP) of rs1495966 located in IL23R/IL12RB region using Japanese ocular BD patients.

Methods: One hundred and thirty-six Japanese BD patients who suffered from uveitis and 213 healthy controls were enrolled for analysis of polymorphisms of HLA class Iand the SNP of rs1495966. Statistical analysis was performed mainly with odds ratio (OR) with 95% confidential interval (95%CI). Fisher's exact test was also carried out and the significance (p) was corrected by the numbers of alleles compared (pc).

Results: Twenty three and 49 alleles were observed for HLA-A and B, respectively. The phenotype frequencies (PF) of HLA-B*51:01 was significantly higher in BD patients (44.1%) than in controls (15.5%) (OR=4.31 (95%CI=2.61-7.12), pc=3.2x10E-7). The PF of HLA-A*26:01 was also significantly more frequent in BD patients (35.3%) than in controls (15.5%) (OR=2.98 (1.78-4.96), pc=6.4x10E-4). The PF of the BD patients carrying the A*26:01 or B*51:01 was extremely increased comparing to the frequency in the control (71.3% Vs 28.2%, OR=6.34 (3.94-10.22), pc=2.1x10E-12 (corrected by 23x49)). The PF of B*5201 was significantly decreased in BD (10.3% Vs 25.4%, OR=0.34 (0.18-0.63, pc=0.024). The PF of the HLA-A*02:07 tended to be increased in the BD-group without A*26:01 and B*51:01 (17.9% Vs 7.2%, OR=2.82 (1.02-7.85), pc= not significant (NS)). In addition, the PF of the HLA-B*39 was increased in the BD-group without A*26:01 and B*51:01 (17.9% Vs 3.3%, OR=6.48 (1.93-21.70), pc= NS). The allele frequency (AF) of rs1495966*A allele in IL23R/IL12RB region was significantly increased in BD patients (53.7%) than in controls (44.8%) (OR=1.43 (1.05-1.93), pc=0.024). In clinical analysis, the PF of the B*51:01 was significantly associated with complete type of BD (p=0.0416). The PF of the A*26:01 tended to be associated with posterior/panuveitis (p=0.0979). The AF of GG in IL-23R SNP tended to be associated with poor visual prognosis corresponding the best corrected-visual acuity of 0.1 or less in the worse eyes (p=0.0643).

Conclusion: Our results indicated that, (1) HLA-A*02:07 is another susceptibility gene for BD, associating independently from the B*51:01 and A*26:01, (2) HLA-B*39 is possibly associated with BD, (3) B*52:01 is a protective allele for ocular BD in Japan, (4) rs1495966*A is associated with BD and might be a disease marker for the severity of ocular disease.

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Abstract Number: 3040

Predictive Factors of Long-Term Clinical Outcome in Patients with Ocular Involvement Secondary to Behcet's Syndrome

Rosaria Talarico[1], Michele Figus[2], Anna d'Ascanio[1], Rossella Neri[1], Chiara Baldini[1], Chiara Tani[3] and Marta Mosca[1], [1]Rheumatology Unit, University of Pisa, Italy, Pisa, Italy, [2]Department of Surgical, Medical, Molecular Pathology and Emergency, University of Pisa, Pisa, Italy, [3]University of Pisa, Pisa, Italy
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Background/Purpose: Behçet's syndrome (BS) is a multisystemic, chronic relapsing inflammatory disease classified among the vasculitis. Eye involvement represent one of the most serious manifestation of BS and occurs in half of all patients. It seems more frequent and severe among young males and, unluckily, it still represents a significant cause of morbidity. The aim of the study was to identify factors able to predict long-

term outcome in patients with BS

Methods: forty-nine patients (29 males and 20 females; mean age at the onset 29±4 years) with a diagnosis of BS according the ISG criteria were studied. The probability of clinical relapse after remission of the first ocular attack was calculated using the Kaplan-Meier method. Predictors of long-term outcome were identified by univariate analysis using the log-rank test and by multivariate analysis using Cox proportional hazards regression models.

Results: The mean time between the first initial symptoms of BS and the onset of eye lesions was 3±2 years. The number of ocular attacks were the following: 32 posterior uveitis, 27 anterior uveitis, 21 retinal vasculitis, while panuveitis developed in 17 subjects. Medical treatments received at time of the study were: cyclosporine A (n=21), infliximab (n=13, azathioprine (11), adalimumab (2). The cumulative relapse rates at 1 year, 3 years, and 5 years after remission of the first ocular attack were 20%, 38.7%, and 42%, respectively. On multivariate analysis, a younger age (<30 years) at the onset of ocular involvement, male sex and medical treatments other than biological agents represent independent predictive factors for relapse in BS patients with ocular involvement.

Conclusion: As awaited, the use of anti TNF alpha agents seems to be associated with a positive effect on maintaining remission in ocular involvement due to BS. However, as literature data suggest, younger age and male sex represent predictive factors of poor long-term clinical outcome.

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Abstract Number: 3041

Long Term Biological Therapy in Uveitis Refractory Due to Behçet's Disease. Multicenter Study of 165 Patients.

Montserrat Santos-Gómez[1], Vanesa Calvo-Río[1], Ricardo Blanco[1], Emma Beltran[2], Juan Sánchez Bursón Sr.[3], Marina Mesquida[4], Alfredo Adan[4], M. Victoria Hernández[5], F.Javier López-Longo[6], Marisa Hernandez Grafella[7], Elia Valls Pascual[8], Lucía Martinez-Costa[9], Agusti Sellas-Fernandez[10], Miguel Cordero[11], Manuel Díaz-Llopis[12], Roberto Gallego[13], Jose L. García Serrano[14], JL Callejas Rubio[15], Norberto Ortego-Centeno[16], Jose M Herreras[17], Alejandro Fonollosa[18], Angel M. Garcia-Aparicio[19], Olga Maiz Alonso[20], Ana Blanco[21], Ignacio Torre[22], Cruz Fernández- Espartero[23], Vega Jovani[24], Diana Peiteado[25], David Diaz Valle[26], Esperanza Pato[26], Juan Cruz[27], Carlos Férnandez Cid[28], Elena Aurrecoechea[29], Miriam García-Arias[30], Miguel Angel Caracuel-Ruiz[31], Carlos Alberto Montilla Morales[32], Antonio Atanes-Sandoval[33], Félix Francisco[34], Santos Insua[35], Senen González-Suárez[36], Amalia Sánchez-Andrade[37], Fernando Gamero[38], Luis Francisco Linares[39], Fredeswinda Romero[40], A. Javier García-González[41], Raquel Almodóvar González[42], Enrique Minguez[43], Carmen Carrasco Cubero[44], Alejandro Olivé[45], Julio Vázquez[46], Oscar Ruiz Moreno[47], Fernando Jiménez-Zorzo[48], Javier Manero[48], Santiago MuÑoz Fernandez[49], Cristina Fernández-Carballido[50], Esteban Rubio Romero[51], Fred Antón Pagés[52], Javier Toyos-Saenz de Miera[53], Myriam Gandía[54], Carmen Gonzalez-Vela[55], Enrique Raya[56], Natalia Palmou[1], Leyre Riancho-Zarrabeitia[1] and Miguel Angel Gonzalez-Gay[1], [1]Rheumatology, Hospital Universitario Marqués de Valdecilla. IDIVAL, Santander, Spain, [2]Rheumatology, Hospital General Universitario de Valencia, Valencia, Spain, [3]Rheumatology, Hospital de Valme., Sevilla, Spain, [4]Ophthalmology, Hospital Clinic, Barcelona, Spain, [5]Arthritis Unit, Rheumatology, Hospital Clinic, Barcelona, Spain, [6]Hospital Gregorio Marañón, Madrid, Spain, [7]Ophthalmology., Hospital General Universitario de Valencia, Valencia, Spain, [8]Rheumatology, Hospital Universitario Dr Peset, Valencia, Spain, [9]Ophthalmology, Hospital Universitario Dr Peset, Valencia, Spain, [10]Rheumatology, Hospital Universitario Valle Hebron, Barcelona, Spain, [11]Ophthalmology, Hospital de León, León, Spain, [12]Hospital Universitario La Fe, Valencia, Spain, [13]Ophthalmology, Hospital Universitario La Fe, Valencia, Spain, [14]Ophthalmology, Hospital Universitario San Cecilio, Granada, Spain, [15]Hospital Universitario San Cecilio, Granada, Spain, [16]Systemic Autoimmune Diseases Unit, Hospital Universitario San Cecilio, Granada, Spain, [17]Ophthalmology, Hospital Universitario, IOBA, Valladolid, Spain, [18]Ophtalmology, Hospital de Cruces, Bilbao, Spain, [19]Rheumatology, Hospital Virgen de la Salud, Toledo, Spain, [20]Rheumatology, Donostia University Hospital, Donostia, Spain, [21]Ophthalmology, Donostia University Hospital, Donostia, Spain, [22]Rheumatology, Hospital de Basurto, Bilbao, Spain, [23]Rheumatology, Hospital La Zarzuela, Madrid, Spain, [24]Rheumatology, Hospital General de Alicante, Alicante, Spain, [25]Rheumatology, Hospital La Paz, Madrid, Spain, [26]Hospital Clínico San Carlos, Madrid, Spain, [27]Rheumatology, Hospital de Pontevedra, Pontevedra, Spain, [28]Ophthalmology, Hospital de Pontevedra, Pontevedra, Spain, [29]Rheumatology, Hospital de Sierrallana, Torrelavega, Spain, [30]Rheumatology, Hospital La Princesa, Madrid, Spain, [31]Plaza Cruz Roja, 1, Hospital Reina Sofia, Córdoba, Spain, [32]Rheumatology, Hospital Universitario de Salamanca, Salamanca, Spain, [33]Rheumatology, Complejo Hospitalario Universitario de La Coruña, La Coruña, Spain, [34]Rheumatology, Hospital Doctor Negrín, Las Palmas de Gran Canaria, Spain, [35]Rheumatology, Hospital Universitario Santiago de Compostela, La Coruña, Spain, [36]Rheumatology, Hospital de Cabueñes, Gijón, Spain, [37]Hospital Lucus Augusti, Lugo, Spain, [38]Rheumatology, Hospital San Pedro Alcántara, Cáceres, Spain, [39]Rheumatology, Hospital Virgen de la Arrixaca, Murcia, Spain, [40]Section for Autoimmune Diseases, Rheumatology, Hospital Universitario Fundación Jiménez Díaz, Madrid, Spain, [41]Rheumatology, Hospital Universitario 12 de

Octubre, Madrid, Spain, [42]Rheumatology Unit, Hospital Universitario Fundación Alcorcón, Madrid, Spain, [43]Ophthalmology., Hospital Clínico de Zaragoza, Zaragoza, Spain, [44]Rheumatology, Hospital de Mérida, Mérida, Spain, [45]Hospital Germans Trias i Pujol, Badalona, Spain, [46]Rheumatology., Hospital de Ferrol, La Coruña, Spain, [47]Ophthalmology and Rheumatology., Hospital Miguel Servet, Zaragoza, Spain, [48]Ophthalmology and Rheumatology, Hospital Miguel Servet, Zaragoza, Spain, [49]Rheumatology, Hospital Infanta Sofía, Madrid, Spain, [50]Rheumatology, Hospital General Universitario de Elda, Elda (Alicante), Spain, [51]Rheumatology Department,, Hospital Universitario Virgen del Rocío, Sevilla, Spain, [52]Rheumatology, Hospital de Palencia, Palencia, Spain, [53]Rheumatology, Hospital Virgen de la Macarena, Seville, Spain, [54]Department of Autoimmune Diseases, IDIBAPS, Hospital Clínic, Barcelona, Spain, [55]Pathology, Hospital Universitario Marqués de Valdecilla. IDIVAL, Santander, Spain, [56]Rheumatology, Hospital Universitario San Cecilio, Granada, Spain
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Background/Purpose:

Conventional management of uveitis due to Behçet's disease (UBD) consists on conventional immunosuppressive drugs. However, UBD is often refractory requiring more intensive therapy.Our aim was to assess long-term response in UBD patients refractory to conventional therapy.

Methods:

Multicenter study of 165 patients with UBD followed-up in the uveitis units of 45 hospitals. All of them had inadequate response or intolerance to traditional treatment with corticosteroids and at least 1 systemic immunosuppressive drug. The degree of ocular inflammation was assessed as "the Standardization of Uveitis Nomenclature (SUN) working Group" (Am J Ophthalmol 2005; 140: 509-516), and macular thickness was assessed by optical coherence tomography (OCT). Comparisons were made between baseline and the 1st week, 2nd week, 1st month, 6th month, 1st, 2nd, 3rd,4th and 5th year.

Results:

165 patients (89 men/76 women/297 affected eyes) with a mean age of 39.3±10.5 years (range 10-67) were studied. HLA-B51 was positive in 64.8%. Prior to biologic therapy and in addition to oral corticosteroids, patients had received the following drugs: Intravenous pulses of methylprednisolone (50 patients), cyclosporine A (CyA) (134), methotrexate (MTX) (72) and azathioprine (AZA) (87). Infliximab (IFX) was the first biologic used in 96 cases (58.2%) and adalimumab (ADA) in the remaining 69 (41.8%) patients. These agents were used as a monotherapy in 46 cases or in combination with immunosuppressive drugs::CsA (58 cases), MTX (34), AZA (24), mycophenolate (1), cyclophosphamide (1) and tacrolimus (1). The most common regimens were IFX 5 mg/kg/i.v. every 4-8 weeks and ADA 40 mg sc/2 weeks. In the course of the diseases, in cases of refractory uveitis to these drugs switching to other biologic agents was performed: golimumab (n = 6), tocilizumab (5), rituximab (2), certolizumab (1) and etanercept (1). Nevertheless, in 30 cases the biologic agents were discontinued because of maintained clinical remission. Significant improvement observed since the 1sr week was observed in the visual acuity (VA), Tyndall and vitritis. OCT improvement was observed since the 2nd week (TABLE). At baseline, 57 patients (95 eyes) had macular thickening (OCT> 250μ) and 33 patients (50 eyes) had cystoid macular edema (CME) (OCT> 300μ). The OCT improved from 344.5 ± 137.3 microns to 254.2 ± 60.8 microns ($p < 0.01$). After a mean follow-up of 38.3±22.4 months the most serious side effects were miliary TB (n=1), Mycobacterium avium pneumonia (n=1), melanoma (n=1), and fatal lymphoma (n=1).

Conclusion:

Biological treatment with IFX or ADA are effective and relatively safe in UBD refractory to conventional therapy.

	Basal (165/315)	1 week (163/310)	2 weeks (162/309)	1 month (162/302)	6 months (152/290)	1 year (145/279)	2 years (131/247)	3 years (89/161)	4 years (63/110)	5 years (44/74)
VA (mean ±SD)	0.53 ± 0.3	0.56±0.3 *	0.59±0.3 *	0.66±0.3 *	0.7±0.3 *	0.75±0.7 *	0.72±0.3 *	0.7±0.3 *	0.72±0.3 *	0.73±0.3 *
Anterior chamber cells (median [IQR])	1 [0-2]	0 [0-2] *	0 [0-1] *	0 [0-0.5] *	0 [0-0] *	0 [0-0] *	0 [0-0] *	0 [0-0] *	0 [0-0] *	0 [0-0] *
Vitritis (median [IQR])	1 [0-2]	1 [0-2] *	0 [0-1] *	0 [0-1] *	0 [0-0] *	0 [0-0] *	0 [0-0] *	0 [0-0] *	0 [0-0] *	0 [0-0] *
Retinal Vasculitis (% affected eyes)	58.4%	53.22% *	43.36% *	32.2% *	11.76% *	5% *	4.8% *	3.1%	0,9%	1.3%
OCT (µ) (mean ±SD)	344.5 ± 137.3	349±134.6	333.6±114.2 *	307.2±95 *	266.3±50.8 *	258.6±48.6 *	267.5±56.8 *	249.4±37.8 *	246.6±40.1 *	254.2±60.8 *

TABLE. Evolution of the main ophthalmological parameters

In brackets is the number of patient/number of eyes with the data available.

* p <0.05, the comparative study is done for each variable in each period compared to baseline.

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Abstract Number: 3042

Tocilizumab in Refractory Uveitis Associated with Behçet's Disease. Multicenter Study of 7 Patients.

Montserrat Santos-Gómez[1], Vanesa Calvo-Río[1], Ricardo Blanco[1], Emma Beltran[2], Antonio Atanes-Sandoval[3], Enar Pons[4], Javier Loricera[1], Carmen Gonzalez-Vela[5], Leyre Riancho-Zarrabeitia[1], Natalia Palmou[1] and Miguel Angel Gonzalez-Gay[1], [1]Rheumatology, Hospital Universitario Marqués de Valdecilla. IDIVAL, Santander, Spain, [2]Rheumatology, Hospital General Universitario de Valencia, Valencia, Spain, [3]Rheumatology, Complejo Hospitalario Universitario de La Coruña, La Coruña, Spain, [4]Hospital Universitario Marqués de Valdecilla. IDIVAL, Santander, Spain, [5]Pathology, Hospital Universitario Marqués de Valdecilla. IDIVAL, Santander, Spain
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Background/Purpose:

Treatment recommended in severe and/or refractory uveitis of Behçet disease is anti-TNF-α therapy, usually infliximab (IFX) or adalimumab (ADA) (Levy-Clarke et al Ophthalmology 2014;121:785-796). However, in some cases these biologic agents are not effective, may be contraindicated or they are not well tolerated. IL-6 is a key cytokine in the pathogenesis of uveitis, including Behçet's syndrome.

Our aim was to evaluate the response to tocilizumab (TCZ) in uveitis associated with Behçet syndrome refractory to standard systemic treatment.

Methods:

Multicenter study on 7 patients with uveitis associated to Behçet disease. Patients had previously been treated with at least one conventional immunosuppressive drug and in most cases with anti-TNF-α agents. The main parameters assessed were the visual acuity (VA) and the degree of inflammation of the anterior and posterior chamber.

Results:

4 men and 3 women were studied, with a mean age 39.1 ± 15.4 years (range 22-67). Uveitis was bilateral (n=6) and unilateral (n=1) (Table). The pattern of ocular involvement was posterior uveitis (n=1), panuveitis (n=2), panuveitis + papilitis (n=1) and panuveitis + vasculitis (n=3). The clinical course was chronic (n=3) or recurrent (n=4). Besides oral corticosteroids and before TCZ onset they had received: intraocular corticosteroids (n=7), i.v. methylprednisolone pulses (n =7), methotrexate (MTX) (n=7), cyclosporin A (CsA) (n=7), azathioprine (n=2), cyclophosphamide (n=2), daclizumab and mycophenolate (n=1), Adalimumab (n=5), inflixmab (n=2) and golimumab (n=2). In all patients TCZ was prescribed at the standard dose (8 mg/kg/i.v. month). Treatment was administered as a monotherapy in 5 cases and combined with conventional immunosuppressive drugs in 2 cases (1 MTX, 1 CsA). After a mean follow up of 5.36 ± 5.1 months from the onset of TCZ, improvement was observed in the following items: a) median VA (0.2 [0.05-0.7] to 0.95 [0,4-1]; $p<0.01$); b) Median cells in the anterior chamber (1 [0-2] to 0 [0-0]; $p=0.01$); c) average vitritis (1.4±1.1 at 0±0; $p<0.01$); d) retinal vasculitis (n=8 eyes, 57.1%) that disappeared in all cases ($p<0.01$); e) OCT mean (μ) (from 335.7±82.3 to 246.4±32.6; $p<0.01$); f) 5 patients achieved remission, g) reduction in median dose of prednisone (30 [30-30] to 3.75 [0-7.5] mg/day; $p=0.18$). TCZ was withdrawn in 1 case due to an infusion reaction. No other side effects were observed.

Conclusion:

Treatment with TCZ seems to be effective in patients with refractory uveitis due to Behçet’s disease.

TABLE

cases	Sex/age	Inmunosupressant before TCZ	Biologics before TCZ	Immunosuppressant associated with TCZ	Follow up with TCZ (months)	Anterior chamber cells (start/last visit)	Posterior involvement (start/last visit)	VA (start/last visit)
1.	Male / 27	MTX, CsA, CFM	-	MTX	4	0/0	Choroiditis, vasculitis, retinitis, EMQ / EMQ	0.1 / 0.4
2.	Female / 42	MTX, CsA, AZA, CFM	ADA, GLM	-	1	1/0	Vasculitis, EMQ / normal	0.05 / 0.7
3.	Male / 50	MTX, CsA	ADA, GLM	-	6	1/0	Vasculitis, EMQ / normal	0.05 / 0.9
4.	Male / 35	MTX, CsA, AZA, daclizumab, MMF	IFX	-	1,5	3/0	Vasculitis / normal	0.3 / 1
5.	Female / 67	MTX, CsA	ADA, IFX	-	16	2/1	Vasculitis, EMQ / normal	0.05 / 0.01
6.	Male / 31	MTX, CsA	ADA	-	6	1/0	Vasculitis, EMQ / normal	0.05 / 1
7.	Female / 22	MTX, CsA	ADA	CsA	3	2/0	EMQ / normal	0.6 / 1

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IL-17 Expression By Lymphocytes Is Higher in Behcet's Disease Compared to Takayasu Arteritis

Ali Ugur Unal[1], Rabia Deniz[2], Aysin Tulunay Virlan[3], Filiz Ture Ozdemir[3], Imren Aydin Tatli[3], Gulsen Ozen[1], Fatma Alibaz-Oner[4], Gonca Mumcu[5], Tulin Ergun[6] and Haner Direskeneli[1], [1]Department of Rheumatology, Marmara University Faculty of Medicine, Istanbul, Turkey, [2]Marmara University Faculty of Medicine, Istanbul, Turkey, [3]Department of Immunology, Marmara University Faculty of Medicine, Istanbul, Turkey, [4]Department Rheumatology, Marmara University Faculty of Medicine, Istanbul, Turkey, [5]Department of Health Management, Marmara University, Faculty of Health Sciences, Istanbul, Turkey, [6]Dermatology, Marmara University Faculty of Medicine, Dermatology, Istanbul, Turkey
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Background/Purpose: Interleukin-17 (IL-17) has been associated with the pathogenesis of various inflammatory diseases. The aim of our study was to investigate the expression of Th17-related immunity in two phenotypically different disorders: Behcet's disease (BD) with innate responses and Takayasu's arteritis (TAK) with adaptive immunity.

Methods: The study population consisted of three groups: patients with BD (n=37, age: 39.2 ±10.1 years), patients with TAK (n=25, age: 50.9

±15.5 years) and healthy controls (HC) (n=25, age 40.9± 6.9 years). Peripheral blood mononuclear cells (PBMC) from patients with BD, TAK and HC were cultured in Th17 inducing condition (IL-6, PHA, IL-1b and IL-23) for 6 days. Cultured cells were then stained with CD4, CD8, CD3, TCRgd, CD19 IFN-γ and IL-17 antibodies to determine the intracellular cytokine secretion by flow cytometry.

Results: In BD patients, IL-17 expression by CD4+ T cells was observed to be higher than both TAK patients and HC (8.9±10.6 vs 3.5±2.5 and 4.5±4.9, p=0.03 and p=0.02, respectively). IL-17 expression by gd+ (14.4±13.3 vs 6.3±4.4 and 6.1±4.1, p=0.001, p<0.001 respectively) and CD8+T cells (7.0±8.3 vs 3.6±3.8 and 2.3±2.1, p=0.007 and p<0.001, respectively) was also higher in BD compared to TAK and HC. No differences were observed between the groups in the IL-17 production by B cells. Under Th17 inducing conditions, production of IFN-γ by CD4+ T cells (4.8±5.2 vs 2.0±1.7 and 1.9±1.3, p<0.05) and CD8 +T cells (11.3±12.6 vs 4.3±4.4 and 4.0±3.6, p<0.05) were also higher in both BD and TAK patients compared to the HC. No differences were observed between the groups in IFN-γ production by B cells and gd+ T cells. IL-17 expression and IFN-γ production in patients with BD and TAK under immuno-suppressive (IS) treatments were not different compared to patients without IS and HC (Table 1).

Conclusion: Our preliminary results suggest that under Th17 stimulating conditions, T cells express higher IL-17 levels in BD. More prominent IL-17 and IFN-γ production by all lymphocyte subsets in BD might be associated with the increased innate responses and early tissue neutrophil infiltrations in BD, which is not observed in TAK.

Table 1. IL-17 expression and IFN-γ production in HC and BD and TAK patients with and without IS treatment

	HC	IS BD	Non-IS BD	IS TA	Non-IS TA
CD4+ IFN+	1.9±1.3	2.6±0.7	3.9±4.3	2.2±1.9	1.6±1.2
CD4+ IL-17+	4.5±4.9	7.8±8.5	8.9±11.3	3.3±2.3	3.5±3.1
CD8+ IFN+	4.0±3.6	6.1±2.6	10.2±12.1	5.2±5.0	3.3±3.1
CD8+ IL-17+	2.3±2.1	8.4±5.3	7.1±9.4	4.0±4.5	3.2±2.4
Gd+ IFN+	5.3±4.7	10.0±5.4	10.7±12.8	4.5±4.6	6.3±6.3
Gd+ IL17+	6.1±4.1	13.3±9.9	15.4±14.0	6.9±4.9	5.2±3.7

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Abstract Number: 3044

Microparticles (MPs) Derived from Cell Plasma Membranes Are Increased in Behcet's Syndrome (BS) and a Low Ratio of Tissue Factor Pathway Inhibitor Positive Mps to Tissue Factor Positive Mps (TFPI/TF) Is Associated with Thrombosis

Emon Khan[1], Nicola Ambrose[1], Miles Stanford[2], Michael A. Laffan[3] and Dorian O. Haskard[4], [1]Department of Vascular Sciences, National Heart and Lung Institute, Imperial College, London, United Kingdom, [2]Ophthalmology, Guy's and St. Thomas' Hospital, London, United Kingdom, [3]Department of Haemostasis and Thrombosis, Imperial College, London, United Kingdom, [4]Rheumatology, Imperial College, London, United Kingdom

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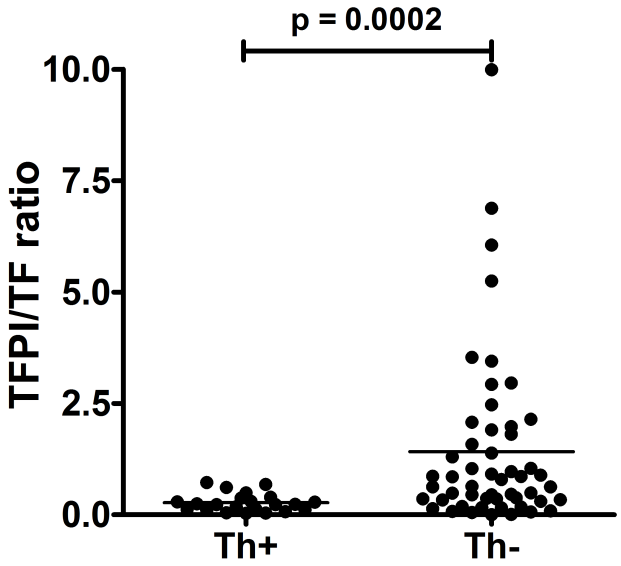
Background/Purpose: Thrombosis occurs in around 20% of Behçet's Syndrome (BS) patients and causes substantial morbidity. There is a clear need for better biomarkers of thrombotic risk in BS to inform treatment decisions. MPs are released from cells undergoing activation and/or apoptosis and express phosphatidylserine (PS) on their surface. MP that also express Tissue Factor (TF) provide a stimulus for blood coagulation, whereas Tissue Factor Pathway Inhibitor (TFPI) expressed by MP may be protective. We tested the hypothesis that imbalance between TF+ and TFPI+ MPs provides a biomarker for thrombotic risk in BS.

Methods: MPs were prepared from peripheral blood from 88 BS patients (who fulfilled International Study Group diagnostic criteria), and 72 age- and sex- matched healthy controls. The BS group was composed of 21 patients with a history of thrombosis (Th+) and 67 patients with no history of thrombosis (Th-). MPs were identified using flow cytometry by size (<1μm) and binding to Annexin V (to PS). MP were further characterized by binding of monoclonal antibodies to CD14 (a monocyte marker), TF and TFPI.

Results: Total numbers of plasma MPs and also CD14+, TF+ and CD14+TF+ MPs were increased in BS compared to HC (all $p < 0.0001$), and also in Th+ compared to Th- BS patients ($p \leq 0.0002$). TFPI+ MPs were higher in BS patients than HC (medians: 3.60 x 10^4/ml *vs.* 2.15 x 10^3/ml, $p < 0.0001$), but not between Th+ and Th- BS patients (medians: 3.09 x 10^4/ml *vs.* 3.74 x 10^4/ml, $p = 0.6660$). The TFPI/TF ratio was higher in BS patients than HCs (medians: 0.49 *vs.* 0.20, $p < 0.0001$) and in Th- compared to Th+ patients (medians: 0.85 *vs.* 0.23, $p = 0.0002$). Strikingly, a TFPI/TF ratio > 0.7 conferred freedom from thrombosis (Figure).



Conclusion: Monocyte-derived MP expressing TF were increased in BS patients and more so in those with a history of thrombosis. Discrimination between BS patients with and without a history of thrombosis was improved by also measuring TFPI+ MPs and generating a TFPI/TF ratio. The data suggest that the balance between TF+ and TFPI+ MPs is important for thrombotic risk in BS and raise the possibility that the TFPI /TF MP ratio may allow the identification and appropriate treatment of BS patients with a low risk of thrombosis.

Disclosure: E. Khan, None; **N. Ambrose**, None; **M. Stanford**, None; **M. A. Laffan**, None; **D. O. Haskard**, None.

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Abstract Number: 3045

Anti-Alpha-Enolase Antibodies in Behçet's Disease: A Marker of Articular Disease Activity?

Leandro L. Prado, Celio R. Gonçalves, Vilma S. T. Viana, Eloisa Bonfá and Carla G.S. Saad, Rheumatology Division, Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil

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Background/Purpose: Diagnosis of Behçet´s disease (BD) is challenging because is based solely on clinical features. Articular involvement in this disease may mimic other diagnosis such as enteropathic arthritis manifestations. IgM anti-alpha-enolase antibodies (AAEA) were recently described in BD, however its clinical relevance is still undefined. Therefore, this study aimed to assess IgM AAEA in systemic BD and its possible association with clinical manifestations and disease activity.

Methods: Ninety-seven BD patients were compared to 36 enteropathic arthritis patients [Crohn's disease (n=24) and ulcerative colitis (n=12)]

and healthy controls (n=87). IgM AAEA was detected by immunoblotting using human alpha-enolase transfected cells whole lysate (Santa Cruz Biotechnology Inc., USA) as antigens. Disease activity was assessed by standardized indexes, BR-BDCAF for BD, SCCI for Crohn's disease (CD) and HBI for ulcerative colitis (UC) together with c-reactive protein (CRP) levels. A longitudinal evaluation was performed in BD patients (n=56), with a minimum of two years interval, regarding IgM AAEA presence and disease activity scores.

Results: A higher IgM AAEA prevalence was found in BD compared to enteropathic arthritis and healthy controls (18.4% vs. 2.8% vs. 2.3%, p<0.001). The frequency of IgM AAEA in active BD was significantly higher than in patients with inactive disease (30.2 vs. 7.4%, p=0.006). Further longitudinal analysis after at least two years confirmed a higher IgM AAEA frequency in active BD compared to inactive BD (45.5 vs. 13.3%, p=0.02). Reinforcing these findings, the mean BR-BDCAF scores and CRP levels were higher in IgM AAEA positive group at baseline (9.11 vs. 4.95, p=0.002 and 11.9 vs. 5.0mg/L, p=0.05) and post two years (5.0 vs. 2.1, p=0.01; 9.6 vs. 3.8mg/L, p=0.008). Regarding all clinical manifestations, we observed that the subgroup with articular symptoms presented higher IgM AAEA positivity on baseline and follow-up evaluations (26.3 vs. 5%, p=0.006; 54.5 vs. 15.6%, p=0.01).

Conclusion: Taken together these data suggest that IgM AAEA may be a novel marker for BD activity, particularly related to articular involvement. Further studies are necessary to confirm their usefulness in clinical practice to distinguish BD patients with articular involvement from patients with enteropathic arthritis manifestations.

Disclosure: L. L. Prado, None; **C. R. Gonçalves**, None; **V. S. T. Viana**, None; **E. Bonfá**, None, 2; **C. G. S. Saad**, None, 2.

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Abstract Number: 3046

Venous Disease-Specific Quality-of-Life Is Impaired in Patients with Vascular Behcet's Disease

Fatma Alibaz-Oner[1], Belgin Aldag[2], Mustafa Aldag[3], Ali Ugur Unal[4], Tayfur Toptas[5], Tülin Ergun[6] and **Haner Direskeneli**[4], [1]Department Rheumatology, Marmara University Faculty of Medicine, Istanbul, Turkey, [2]Rheumatology, Marmara University, School of Medicine, Istanbul, Turkey, [3]Dr.Siyami Ersek Cardiovascular Surgery Hospital,, Istanbul, Turkey, [4]Department of Rheumatology, Marmara University Faculty of Medicine, Istanbul, Turkey, [5]Hematology, Marmara University, Istanbul, Turkey, [6]Dermatology, Marmara University Faculty of Medicine, Dermatology, Istanbul, Turkey

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Background/Purpose: Vascular involvement is seen in up to 40% of the patients with Behcet's disease (BD), with lower extremity deep vein thrombosis (DVT) as the most frequent form of vascular involvement. Chronic post-thrombotic syndrome (CPTS) develops in up to one-half of patients with DVT and is associated with varying combinations of leg pain, oedema, hyperpigmentation and varicose collateral veins. There is no data about CPTS in DVT associated with BD. In this study,we aimed to evaluate venous disease spesific quality of life (QoL) in patients with Vascular Behçet's Disease (VBD).

Methods: In this study, 62 patients (M/F: 47/15, mean age: 38.6±9.2 years) with VBD, who were regularly followed in Marmara University Behcet's Clinics and 29 patients (M/F: 20/9, mean age: 41.6±11.8 years) with DVT associated with non-BD causes, who were followed in Hematology and Vascular Surgery Departments, were assessed. Mean duration after DVT was 6.7±5 years in VBD and 1.6±1 years in non-BD group. Venous Disability Score (VDS) and Venous Clinical Severity Score (VCSS) were used to evaluate the severity of venous insufficiency. Venous disease-specific QoL (the primary outcome) was measured using the Turkish validated form of Venous Insufficiency Epidemiological and Economic Study Quality of Life/Symptom questionnaire (VEINES-QoL/Sym). After calculation, VEINES-QoL and VEINES-Sym sub-scores were identified. Higher scores shows better QoL. SF-36 and Behcet Syndrome Activity Score (BSAS) questionnaires were also fullfilled for patients.

Results: VCSS and VDS were significantly worse in non-BD group compared to VBD, similarly VEINES-QoL and VEINES-Sym were significantly better in VBD group (Table 1). There were no correlations between VEINES-QoL, VEINES-Sym score and duration after DVT, daily sitting and standing times. VEINES-QoL and VEINES-Sym negatively correlated with VCSS (r: -0.367, p<0.001 and r:-0.384, p<0.001, respectively) and VDS (r: -0.288, p=0.007 and r:-0.265, p=0.013, respectively). VEINES-Sym and VEINES-QoL also significantly correlated with BSAS (r: -0.526, p<0.001 and r:-0.496, p<0.001, respectively). Physical and mental components of SF-36 were similar between VBD and non-BD groups.

Conclusion: In VBD, we observed that venous-specific QoL and symptoms worsen together with increasing VDS and VCSS scores. These

results suggest that better control of disease activity may increase the QoL, as well as preventing the relapses in venous Behcet's disease.

Table 1: Quality of life parameters in patients with Deep Vein Thrombosis associated with Behçet's Disease and non-Behçet's Group.

	Non-Behcet's group (n=29)	Behcet's group (n=62)	p value
VCSS	6.5 ±4.5	4.2±4.6	**0.031**
VDS	1.6±0.5	0.9±0.6	**0.000**
MCS	40.8±10.2	44.9±9.5	0,071
PCS	40.3±9.3	43.1±10.5	0.222
VEINES-QoL	73.3±17.9	87.9 ±16.9	**0.000**
VEINES-Sym	32.3±9.8	39.3±9.2	**0.001**

VCSS: Venous Clinical Severity Score, VDS: Venous Disability Score, MCS:Mental component of SF-36, PCS: Physical component of SF-36, VEINES-QoL/Sym: Venous Insufficiency Epidemiological and Economic Study Quality of Life/Symptom questionnaire.

Disclosure: F. Alibaz-Oner, None; **B. Aldag**, None; **M. Aldag**, None; **A. U. Unal**, None; **T. Toptas**, None; **T. Ergun**, None; **H. Direskeneli**, None.

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Abstract Number: 3047

Association Between Red Blood Cell Distribution Width and Disease Activity in Behcet's Disease

Byung-Woo Yoo, Jason Jungsik Song, Sang-Won Lee, Yong-Beom Park, Soo-Kon Lee and Sung Soo Ahn, Division of Rheumatology, Department of Internal Medicine, Yonsei University College of Medicine, Seoul, South Korea

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Background/Purpose: Behcet's disease (BD) is a chronic systemic inflammatory disorder characterized by recurrent oral aphtae and other systemic involvement. Red blood cell distribution width (RDW) is a measurement of heterogeneity in size. RDW is commonly used in the differential diagnosis of anemia, but recently, RDW has been thought to be an inflammatory marker in many diseases. In this study, we investigated whether RDW might be a marker that reflects the disease activity of BD

Methods: 188 patients with BD were enrolled and divided into active and inactive group by Behcet's Disease Current Activity Form 2006. 100 normal healthy individuals were enrolled as control group. In addition to RDW, laboratory results including white blood cell count, hemoglobin, erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) were assessed.

Results: RDW was significantly higher in patients with active BD than both inactive BD and healthy control groups ($p < 0.05$) and also significantly higher in inactive BD group than in healthy control group ($p < 0.05$)(Figure 1). RDW was more positively correlated with disease activity index [correlation coefficient (r) = 0.299, $p < 0.05$] (Figure 2) than ESR ($r = 0.193$, $p < 0.05$) or CRP ($r = 0.221$, $p < 0.05$). Among clinical variables, RDW greater than 13.35 % was significantly associated with disease activity on univariate analysis ($p < 0.05$) and multivariate analysis revealed that the disease activity was associated with RDW only (OR 2.603 95% confidence interval 1.609, 4.214, $p < 0.05$)(Table 1).

Conclusion: RDW is independently associated with the disease activity of BD. Our findings indicated that RDW is more significant marker of the disease activity than ESR or CRP in BD.

Figure 1.

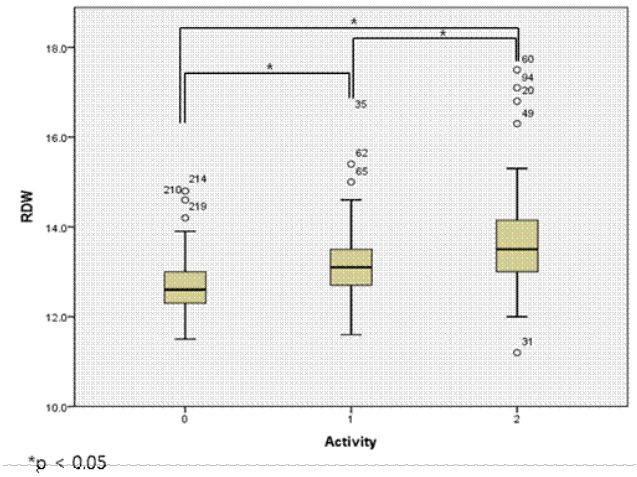

Figure 2.

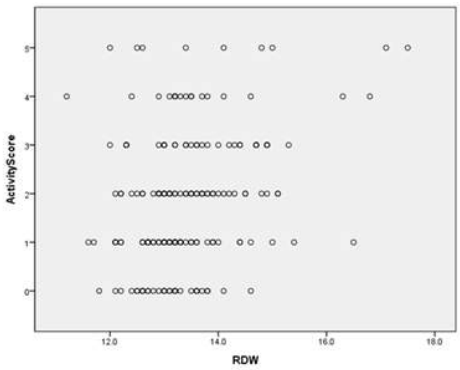

Table 1.

Variables (cut-off)	Univariate	Multivariate	
	p value	OR (95% CI)	p value
Age			0.82
Sex			0.53
WBC			0.16
Hb			0.45
RDW (13.35 %)	<0.05	2.603 (1.609,4.214)	<0.05
ESR			0.38
CRP			0.77

Disclosure: B. W. Yoo, None; **J. J. Song**, None; **S. W. Lee**, None; **Y. B. Park**, None; **S. K. Lee**, None; **S. S. Ahn**, None.

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Abstract Number: 3048

Work Disability over Time in Behcet's Syndrome

Gulen Hatemi[1], Koray Tascilar[2], Yesim Ozguler[3], Serdal Ugurlu[4] and Vedat Hamuryudan[1], [1]Rheumatology, Istanbul University, Cerrahpasa Medical School, Istanbul, Turkey, [2]Rheumatology, Istanbul University, Cerrahpasa Medical Faculty, Istanbul, Turkey, [3]Division of Rheumatology, Department of Internal Medicine, Cerrahpasa Medical Faculty, University of Istanbul, Istanbul, Turkey, [4]Rheumatology, Division of Rheumatology, Department of Internal Medicine, Cerrahpasa Medical Faculty, University of Istanbul, Istanbul, Turkey

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Background/Purpose: Behcet's syndrome (BS) is most active during young adulthood and may cause severe disability. We had previously observed a high frequency of work disability among our Behçet's patients in a cross-sectional study. This time we aimed to evaluate the sustainability of work among our patients who did have a job 5 years ago.

Methods: We had surveyed work disability among 300 consecutive Behçet's syndrome patients who attended our clinic in 2009. We had observed that after excluding students, homemakers and retired patients, among the 149 work eligible patients 29 (21%) were unemployed and 120 were employed. We now evaluated those patients who did have a job 5 years ago regarding work loss and reasons for work loss, using a standard questionnaire. We also checked their hospital charts for new types of organ involvement that developed during these 5 years, and any new medications that were started.

Results: Among the 120 patients who did have a job in 2009 (87 men, 33 women, mean age 36 ±8.6, disease duration 9.7 ±7.1 years, 48% with major organ involvement), we were able to contact 97 patients. Sixteen patients (16%) had lost their jobs during the previous 5 years. Nine of these (11%) were related with Behçet's syndrome and the rest were due to other causes (5 had retired, 1 had a baby, 1 was doing his military service). Among the 81 patients who were still working, 10 (10%) had to change their work place during the last 5 years and were unemployed for a mean of 6.7 ± 5.3 months between these jobs.

Conclusion: Work disability is an important problem among Behçet's syndrome patients. During a 5 year follow-up, 11% of patients lost their jobs due to their disease, and a further 11% had to interrupt work and change their work places. We were only able to evaluate work disability in this study, and work productivity is another important issue that needs to be studied among patients with Behçet's syndrome.

Disclosure: G. Hatemi, None; **K. Tascilar**, None; **Y. Ozguler**, None; **S. Ugurlu**, None; **V. Hamuryudan**, None.

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Abstract Number: 3049

Cognitive Dysfunction in Chronic Progressive Neuro-Behçet's Disease: Comparative Study of the Brainstem and Hippocampus Region Using Brain Magnetic Resonance Imaging

Hirotoshi Kikuchi[1], Kurumi Asako[1], Maki Takayama[1], Shoko Iga[1], Yoshitaka Kimura[1], Hajime Kono[1] and Shunsei Hirohata[2], [1]Department of Internal Medicine, Teikyo University School of Medicine, Tokyo, Japan, [2]Rheumatology and Infectious Diseases, Kitasato University School of Medicine, Kanagawa, Japan
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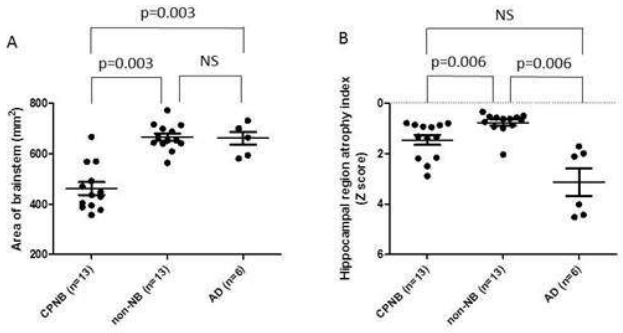
Background/Purpose: Central nervous system involvement is one of the most serious complications in Behçet's disease (BD). This condition is referred to as neuro-Behçet's disease (NB) and can be classified into acute NB (ANB) and chronic progressive NB (CPNB) based upon differences in the clinical course and response to corticosteroid treatment. Brainstem atrophy is significantly more frequently observed in CPNB than in ANB. It is also noteworthy that cognitive dysfunction, in addition to truncal ataxia, is frequently observed in CPNB, and this cannot be accounted for by brainstem atrophy. In the present study, we examined volumes of the hippocampus in order to identify the responsible lesions for neurobehavioral changes in CPNB.

Methods: The subjects were 32 patients, including 13 with CPNB (11 males and 2 females, age 51.2 ± 12.1 years old [mean ± SD]), 13 with Behçet's disease without NB (non-NB) (10 males and 3 females, age 54.4 ± 11.4 years old), and 6 with Alzheimer's Disease (AD) (5 males and 1 female, age 78.8 ± 7.5 years old). All patients with BD satisfied the international classification criteria for Behçet's disease. CPNB was defined as intractable, slowly progressive neurobehavioral changes and/or ataxia accompanied by persistent elevation of interleukin-6 of >20 pg/mL in cerebrospinal fluid on two different occasions at an interval of at least 2 weeks. All patients with AD satisfied the Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV criteria. Sagittal sections of T1-weighted images on brain magnetic resonance imaging (MRI) were obtained from each subject. The areas of the midbrain tegmentum and pons were measured on mid-sagittal sections of T1-weighted images using image analysis software (Image J ver.1.45: NIH, USA). Severity of gray matter loss in the hippocampal region and whole brain were

investigated using Voxel-Based Specific Regional Analysis System for Alzheimer's Disease (VSRAD) software (Eisai Co., Ltd) to determine the degrees of hippocampal region atrophy (Z score) and whole-brain atrophy (WBAI).

Results: The brainstem area was significantly decreased in CPNB (461.8 ± 87.3 [mean ± SD]) compared with those in AD (661.9 ± 56.1) and non-NB (666.1 ± 50.6) (Figure 1, A). VSRAD analysis showed that Z score was significantly increased in CPNB (1.46 ± 0.70) and AD (3.13 ± 1.21) compared with non-NB (0.77 ± 0.40) (Figure 1, B). All patients with CPNB showed brainstem atrophy, but there was no significant correlation between the area of brainstem atrophy and Z score. Neither Z score nor WBAI was correlated with age in CPNB.



Conclusion: These results indicate that the hippocampus, in addition to the brainstem, is a common site for lesions in CPNB, accounting for the progressive cognitive dysfunction in this disease. The lack of correlation between brainstem atrophy and hippocampal atrophy suggests that predisposing factors might determine the lesion site in CPNB.

Disclosure: H. Kikuchi, None; **K. Asako**, None; **M. Takayama**, None; **S. Iga**, None; **Y. Kimura**, None; **H. Kono**, None; **S. Hirohata**, None.

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Abstract Number: 3050

Evaluation of Olfactory Function in Behcet's Disease

Lutfi Akyol[1], Emre Gunbey[2], Rıfat Karlı[2], Metin Ozgen[1] and Mehmet Sayarlıoglu[3], [1]Department of Internal Medicine Division of Rheumatology, Ondokuz Mayıs University, Faculty of Medicine, Samsun, Turkey, [2]Otorhinolaryngology, Ondokuz Mayıs University, Samsun, Turkey, [3]İnternal Medicine Division of Rheumatology, Ondokuz MayÄ±s University, Samsun, Turkey
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Background/Purpose: Behçet's disease (BD) is a chronic, relapsing type of vasculitis of unknown etiology, characterized by oral and urogenital ulcers and ocular inflammation with cutaneous, musculoskeletal, vascular, and nervous system manifestations. Few cases involving the nasal mucosa have been reported in the literature, and the true prevalence of BD remains unknown. Neurological involvement associated with BD might play a more important role in causing olfactory dysfunction compared to mucosal involvement but sufficient clinical data is not available about the effect of BD on olfaction in adults. We evaluated the olfactory function of patients diagnosed with BD.

Methods: Patients were chosen from among a consecutive patient group population who visited our the internal medicine rheumatology polyclinic and otolaryngology departments of Ondokuz Mayıs University Hospital. A total of 50 participants (males and females), aged 18 to 60 years with a diagnosis of BD, and 46 healthy controls (matched to the study group for age and gender) were included. BD was diagnosed based on the criteria defined by the International Study Group for BD. A complete clinical history was taken, and a physical examination was performed, in all participants. Individuals with other rheumatic diseases; obstructive nasal pathologies leading to conductive-type olfactory dysfunction (e.g., septum deviation, nasal polyp); advanced systemic disease (e.g., hypertension, malignity); a history of antithyroid, antihistamine, antidepressant, or steroid medication within the past month; or who were current smokers, had an active upper respiratory infection or a history of otolaryngologic operations were excluded from the study**.** The results of the "Sniffin' Sticks" (SS) olfactory test were compared between the two groups.

Results: The mean age of the 50 BD patients was 35.3 ± 10 years, compared to 36.9 ± 11 years for the 46 control group patients. There was no significant group difference in age or gender distribution (p>0.05). Odor identification and overall scores were significantly lower in the BD group compared to the control group. There were no significant differences in odor discrimination scores between the BD and control groups (p>0.05).

Conclusion: This is the first study to evaluate olfactory function in patients diagnosed with BD using the SS test. Odor identification was impaired in patients with BD compared to healthy controls, but there was no group difference in odor discrimination. Patients with BD also should be assessed for involvement of olfactory function and may require treatment due to malfunction of the olfactory system that affects the quality of life.

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Abstract Number: 3051

Bronchial Artery Enlargement May Cause Recurring Hemoptysis in Behçet's Syndrome Patients with Pulmonary Artery Involvement Despite Response to Treatment

Vedat Hamuryudan[1], Emire Seyahi[2], Serdal Ugurlu[3], Fatih Gulsen[4], Canan Akman[4], Murat Cantasdemir[4], Furuzan Numan[4], Hasan Tuzun[5] and Hasan Yazici[6], [1]Division of Rheumatology, Department of Internal Medicine, Cerrahpasa Medical Faculty, University of Istanbul, Istanbul, Turkey, [2]Division of Rheumatology, Department of Internal Medicine, Cerrahpasa Medical Faculty, University of Istanbul, Turkey, Istanbul, Turkey, [3]Rheumatology, Division of Rheumatology, Department of Internal Medicine, Cerrahpasa Medical Faculty, University of Istanbul, Istanbul, Turkey, [4]Cerrahpasa Medical Faculty, University of Istanbul, Department of Radiology, Cerrahpasa Medical Faculty, University of Istanbul, Istanbul, Turkey, [5]Cerrahpasa Medical Faculty, University of Istanbul, Department of Vascular Surgery, Cerrahpasa Medical Faculty, University of Istanbul, Istanbul, Turkey, [6]Department of Internal Medicine, Cerrahpasa Medical Faculty, University of Istanbul, Division of Rheumatology, Department of Internal Medicine, Cerrahpasa Medical Faculty, University of Istanbul, Istanbul, Turkey

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Background/Purpose:

Hemoptysis is the most frequent and feared symptom of pulmonary artery involvement (PAI) in Behçet's syndrome (BS). Some BS patients with PAI experience recurrent hemoptysis after achieving clinical response and regression or even resolution of abnormal radiologic findings with treatment. Enlargement of bronchial arteries may be the source of recurring hemoptysis in these patients.

Methods:

Retrospective chart review of 6 BS patients (all men) having repeated hemoptysis with no overt clinical or radiologic findings for active PAI.

Results:

The mean age of the patients at the diagnosis of PAI was 28.8± 5.8 SD years and their mean disease duration was 2±1.5 SD years. Five patients had pulmonary artery aneurysms (PAA) and 1 had pulmonary artery thrombosis (PAT). Consolidation treatment consisted of monthly cyclophosphamide pulses and corticosteroids (1.7±1.2 mean±SD years) and this was followed by maintenance with azathioprine. This treatment was successful in ameliorating hemoptysis in all patients except 1 PAA patient who experienced gross hemoptysis necessitating pulmonary artery embolization 2 years later. Hemoptysis recurred in all after a mean interval of 5.8±6.2 SD years (range 1 – 17 years). Thorax CT evaluations did not show any signs for new or worsening of existing PAI. Rather, there was complete resolution of PAA in 4 patients, regression of PAA in 1 patient and regression of PAT in 1 patient. However, enlargement of bronchial arteries and enlarged collaterals were evident in 5 patients. Four of them underwent transcatheter bronchial artery embolization that was complicated by hemiparesis in 1 patient. This procedure was repeated in 1 patient 2 years later because of new enlarged epigastric arteries. This patient still continues to experience occasional and small hemoptysis 3 years after the last procedure. The other 3 patients are currently free of hemoptysis ranging for between 3 months and 8 years after the procedure. The fifth patient died of massive hemoptysis in emergency unit in another center before undergoing embolization. His last CT did not show any evidence of PAI. The source of bleeding could not be demonstrated in the last patient despite repeated bronchoscopies and pulmonary angiography who is now completely symptom free since 4 years and does not take any medications either.

Conclusion:

Enlargement of bronchial arteries and formation of collaterals can complicate the course of PAI during remission and may result in recurrent and potentially fatal hemoptysis in BS patients. Whether this enlargement is only due to the compromised pulmonary circulation or there is also accompanying vasculitis remains to be studied. Transcatheter embolization appears to be successful in controlling hemoptysis in such patients.

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Abstract Number: 3052

Budd-Chiari Syndrome in Behçet's Disease:a Retrospective Multicenter Study

Lutfi Akyol[1], Bahtiyar Toz[2], Ozun BayndÄ±r[3], Orhan Zengin[4], Dondu Uskudar Cansu[5], Murat Yigit[6], Gozde Yildirim Cetin[7], Ahmet Omma[8], Abdulsamet Erden[9], Orhan Kucuksahin[10], Senol Kobak[11], Osman Cure[1], Ali Ugur Unal[12], Ayten Yazici[13], Metin Ozgen[1], Ali Sahin[14], Emel Gonullu[15], Suleyman Serdar Koca[16], Burak Erer[2], Ahmet Gul[17], Kenan Aksu[3], Gokhan Keser[18], Ahmet Mesut Onat[4], Bunyamin Kisacik[4], Timucin Kasifoglu[5], Ayse Cefle[19], Umut Kalyoncu[9] and **Mehmet Sayarlioglu**[1], [1]Department of Internal Medicine Division of Rheumatology, Ondokuz Mayıs University, Faculty of Medicine, Samsun, Turkey, [2]Department of Internal Medicine, Division of Rheumatology, Istanbul University, Istanbul Faculty of Medicine, Istanbul, Turkey, [3]Ä°nternal Medicine Division of Rheumatology, Ege University Medical Faculty, Izmir, Turkey, [4]Ä°nternal Medicine Division of Rheumatology, Gaziantep University, Faculty of Medicine, Gaziantep, Turkey, [5]Ä°nternal Medicine Division of Rheumatology, Osmangazi University, Faculty of Medicine, Eskisehir, Turkey, [6]Ä°nternal Medicine Division of Rheumatology, Pamukkale University, Faculty of Medicine, Denizli, Turkey, [7]Rheumatology, Kahramanmaras University School of Medicine, Kahramanmaras, Turkey, [8]Department of Internal Medicine, Rheumatology Division, Ankara Numune Hospital, Ankara, Turkey, [9]Rheumatology, Hacettepe University Faculty of Medicine, Ankara, Turkey, [10]Rheumatology, Yildirim Beyazit University School of Medicine, Ankara, Turkey, [11]Rheumatology, Sifa University, Izmir, Turkey, [12]Department of Rheumatology, Marmara University Faculty of Medicine, Istanbul, Turkey, [13]Rheumatology, Kocaeli University, Faculty of Medicine, Kocaeli, Turkey, [14]Department of Rheumatology, Cumhuriyet University Faculty of Medicine, Sivas, Turkey, [15]Rheumatology, Osmangazi University, Faculty of Medicine, Eskisehir, Turkey, [16]İnternal Medicine Division of Rheumatology, Firat University, Faculty of Medicine, Elazig, Turkey, [17]Department of Internal Medicine, Rheumatology Division, Istanbul University, Istanbul Faculty of Medicine, Istanbul, Turkey, [18]Rheumatology, Ege University Medical Faculty, Izmir, Turkey, [19]Ä°nternal Medicine Division of Rheumatology, Kocaeli University, Faculty of Medicine, Kocaeli, Turkey

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Background/Purpose: Budd-Chiari syndrome (BCS), or hepatic venous outflow obstruction, is a rare and serious complication of Behçet's disease (BD). The aim of this study was to determine the demographic, clinical, laboratory and management characteristics along with the clinical course of BCS associated with BD.

Methods: Forty-four patients with BD with BCS (31 male, 13 female) were identified in 15 rheumatology centers (Group I). A total of 82 consecutive patients (51 male, 31 female) with BD who did not have clinically apparent BCS during the follow-up were evaluated as the control group (Group II). The demographic, clinical, laboratory, management characteristics, and clinical course of these two groups of patients were recorded according to predefined protocol and compared.

Results: Comparison of the demographic and clinical findings between the Group I and the Group II were as follows: Male gender was more frequent in both group I and group II but, there was no significant difference between the two groups. The mean age of disease onset was 23.1 +/- 6.7 years vs. 27.2 +/- 8.3 years ($p=0.04$), mean age at diagnosis was 26.3 +/- 6.9 vs. 31 +/- 8.2 ($p<0.01$), arthritis was 4.5% vs. 28.9% ($p=0.001$) and cardiac involvement was found to be 15.9% vs. 3.6% ($p=0.017$). Skin pathergy test positivity was observed in 40.9% vs. 21.7% of the patients ($p=0.02$), superficial thrombophlebitis was 25% vs. 7.2% ($p=0.006$), and deep vein thrombosis was 47.7% vs. 14.5% ($p<0.01$). The frequency of MTHFR mutation in BD patients with BCS was 25%. On diagnosis 46.7% of BD patients with BCS were classified as Child-Pugh A. Serum albumin level was lower (3.3 +/- 0.6 vs. 4.3 +/- 0.5, $p<0.001$) and serum AST, ALT and ALP levels were higher, and serum INR level was higher (1.4+/-0.5 vs. 1+/-0.2, $p=0.001$) in patients with BCS. Inferior vena cava obstruction was observed in 56.7% and portal vein thrombosis was seen in 6.7% of the patients with BCS. Mortality in BCS patients with BD was 18.2%. BCS related treatment after diagnosis in patients with BD were as follows: 67.4% of patients were treated with monthly cyclophosphamide intravenous pulses, 52.3% received intravenous pulse corticosteroids, 56.8% used azathioprine, 45.5% had warfarine treatment and 47.7% were treated with low

molecular weight heparin.

Conclusion: This study shows a higher frequency of cardiac involvement, skin pathergy test positivity, superficial thrombophlebitis and deep vein thrombosis in BD patients with BCS. Arthritis was observed less common in BD patients with BCS. The mean age onset was lower in patients with BCS. Medical treatment with immunosuppressive agents and anticoagulation appears to be the treatment of choice in BD patients with BCS. The majority of the *patients with BCS were Child-Pugh* class A on diagnosis. The inferior vena cava is frequently involved and, often associated with deep vein thrombosis and cardiac involvement. BCS still remains as an important mortality cause in BD patients.

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Abstract Number: 3053

Patients Treated for Behcet Syndrome in the US Have Higher Disease Activity Scores at Presentation If They Fulfill ISG Criteria and If They Are Females, However Have Less Severe Disease Overall

Yusuf Yazici, Hannah Bernstein and Christopher Swearingen, Department of Medicine, Division of Rheumatology, New York University School of Medicine, New York, NY

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Background/Purpose:

Diagnosis of Behcet's syndrome (BS) is based on clinical signs and symptoms, without the use laboratory or imaging tests and the most commonly used diagnostic criteria are the ISG criteria. Patients have also been diagnosed with BS not meeting ISBD criteria based on the clinical impression of the treating physicians.

Objective:

To determine differences in disease activity among BS patients meeting and not meeting the ISBD criteria.

Methods:

Behcet's patients seen at the NYU Behcet's Center had their demographic, clinical features and outcomes data abstracted. Confirmed BS diagnosis was determined if ISG criteria were met at any time during the course of observation. Multiple linear regression estimated any association between meeting ISG criteria and gender with the patient-reported outcomes Behcet's Syndrome Activity Score (BSAS), Pain Visual Analog Scale (VAS), Fatigue VAS, Patient Global Assessment VAS, and RAPID3 as well as Physician Global Assessment VAS.

Results:

First observation data on 832 subjects were abstracted for this analysis. 504 (63%) met ISG criteria for Behcet's, 616 (74%) were female with an average age of 35 years (+ 13.8). Mean scores for BSAS, pain, fatigue, patient global, RAPID3 and physician global were uniformly higher in those meeting criteria vs not meeting criteria. Meeting ISG criteria was significantly associated with increases in all clinical outcomes independently of gender, ranging from 5 points on the Physician Global VAS to 13 points on the Fatigue VAS (**Table**). Conversely, female gender was only associated with significant increases in BSAS, Fatigue and RAPID3 independent of meeting ISG criteria. Not surprising, meeting ISG criteria was associated with increased odds of eye involvement; CNS or vascular involvement were not associated with meeting ISG criteria, however. Notably, males [N=63 (29%)] were are significantly increased odds of having eye involvement compared to females [N=155 (25%)] [OR=1.6, 95% CI:1.11, 2.41), P=0.013] independent of meeting ISG criteria, race, age and education. No association between gender and CNS [males N=12 (10%) vs female N=45 (12%)] or vascular involvement [males N=3 (2%) vs female N=3 (1%)] was detected.

Conclusion:

Behcet's patients who fulfill ISG criteria have more active disease, based on all measures of disease activity, including patient and physician

based outcomes. Interestingly, females were also at risk for more active disease as measured by composite patient reported outcome measures, reflecting possibly the different character of Behcet's in non-endemic areas, such as the US. Males were more likely to have eye involvement, suggesting that even though females may have more activity overall, males may have more severe disease.

Table. Change in Outcomes Associated with Criteria and Gender

		Met Behcets Criteria			Gender		
Outcomes*	**N**	**Yes**	**No**	**P†**	**Female**	**Male**	**P†**
BSAS	832	47.0 (21.6)	33.6 (19.3)	**<0.001**	43.8 (21.4)	36.9 (21.9)	**0.001**
Function	784	17.8 (19.8)	8.8 (13.5)	**<0.001**	14.7 (18.2)	13.8 (18.4)	0.720
Fatigue VAS	812	55.2 (34.0)	41.1 (35.1)	**<0.001**	52.7 (34.2)	42.4 (36.6)	**<0.001**
Pt Global VAS	810	49.2 (29.2)	38.1 (29.0)	**<0.001**	46.3 (29.5)	41.7 (29.6)	0.052
MD Global VAS	781	27.5 (13.2)	22.5 (13.1)	**<0.001**	25.6 (12.4)	25.8 (15.8)	0.385
RAPID3	768	40.5 (24.0)	29.3 (22.1)	**<0.001**	37.6 (23.6)	32.5 (24.6)	**0.008**

*All outcomes are scaled [0-100].

†P-values reported from multiple linear regression modeling independent association with Criteria Status, Gender, Race, Age and Formal Education Level as covariates.

Disclosure: Y. Yazici, BMS, Celgene, 5,BMS, Celgene, 2; **H. Bernstein**, None; **C. Swearingen**, None.

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Abstract Number: 3054

Takayasu's Arteritis Associated with Behçet's Syndrome: A Case Series of 8 Patients

Sinem Nihal Esatoglu[1], **Emire Seyahi**[2], Serdal Ugurlu[2], Gulen Hatemi[2], Melike Melikoglu[2], Vedat Hamuryudan[3] and Sebahattin Yurdakul[1], [1]Rheumatology, Division of Rheumatology, Department of Internal Medicine, Cerrahpasa Medical Faculty, University of Istanbul, Turkey, Istanbul, Turkey, [2]Division of Rheumatology, Department of Internal Medicine, Cerrahpasa Medical Faculty, University of Istanbul, Turkey, Istanbul, Turkey, [3]Rheumatology, Division of Rheumatology, Department of Internal Medicine, Cerrahpasa Medical Faculty, University of Istanbul, Istanbul, Turkey

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Background/Purpose:

Takayasu's arteritis (TA) and Behçet's syndrome (BS) are both systemic vasculitis of an unknown etiology, each with unique involvement pattern. TA affects aorta and its main branches causing narrowing or occlusions. BS is characterized by recurrent skin –mucosa lesions and uveitis. Arterial involvement is rare in BS and manifests usually as aneurysms or in situ thrombosis.

We describe here 8 TA patients with concomitant BS.

Methods:

We reviewed the charts of patients diagnosed with BS and TA for information regarding patients' gender, age at diagnosis of BS and TA, BS manifestations, symptoms prior to TA diagnosis, involved vessels and the used drugs. The diagnosis of TA was based on the finding of typical homogenous arterial wall thickening.

Results:

We identified 8 (0.1%) patients among 9000 BS patients. Table summarizes demographic and clinical characteristics of these patients. Their mean age at the time of diagnosis of BS was 31.6 ± 11.5 yrs, and at the time of diagnosis of TA was 37.5 ± 10.8. F/M ratio was 3/1. TA

preceded BS in 4 cases (6, 6, 12, 15 yrs) and occurred simultaneously in the remaining 4. Skin-mucosa lesions were the most common finding, followed by uveitis (5/8), and arthritis (3/8). Initial symptoms of TA were fatigue and fever in 2 patients, absent pulse in 2, fatigue in 1, arm claudication in 1. The remaining 2 were diagnosed as TA while being evaluated for the extent of vascular disease for BS. Subclavian (5/8) and carotid arteries (5/8) were the most commonly involved arteries. In addition to prednisolone, the initial agent was methotrexate in 4 patients, azathioprine in 3 and cyclophosphamide in 1. At the end of follow-up (1, 2, 2, 3, 7, 9, 18, 21 yrs), 4 patients had a stable disease following the first treatment, 3 had to switch to infliximab and 1 had to switch to azathioprine after methotrexate. BS manifestations resolved in 6 patients while recurrent arthritis persisted in 2. Six patients were still on immunosuppressive therapy due to TA, while the other 2 were off treatment. None had died.

Conclusion:

TA may be associated with BS. Similar associations of TA have been reported with ulcerative colitis, Crohn's disease, and ankylosing spondylitis. Whether it is a true association or mere co-existence is always debated. Interestingly, in this hybrid setting, both TA and BS followed their own course: while BS abated in time, TA continued its persistent activity.

Table: Demographic and clinical characteristics of patients with TA and BS

Sex	Age at BS diagnosis (year)	Age at TA diagnosis (year)	BS Manifestations	Initial presentations of TA	Typical vessel involvement due to TA	Medical Treatment
M	27	27	O, G, PAA, STM	None	CAR, BT	AZA
F	27	39	O, G, EN, U	Fatigue	CAR, SBC, BT, ThAo	CYC, AZA
F	44	44	O, G, A	None	CAR, SBC, BT, CT	MTX, INF
F	22	22	O, G, EN, PP, U	Arm claudication	CAR, SBC, RA, CT, SMA	MTX
M	39	39	O, G, A, U	Fatigue, fever	CAR, ThAo	AZA, INF
F	51	58	O, G, PP, U	Absent pulse	SBC	AZA, MTX
F	20	35	O, G, A, U	Fatigue, fever	ThAo	MTX, AZA
F	23	36	O, G, EN	Absent pulse	SBC, SFA	MTX, CYC, INF

A: arthritis; AZA, azathioprine; BT, brachiocephalic trunk; CAR: carotid artery; CT: celiac trunk; CYC: cyclophosphamide; EN: erythema nodosum; F: female; G: genital ulcers; INF: infliximab; M: male; MTX: methotrexate; O: oral ulcers; PP: papulo-pustular lesions, PAA: pulmonary artery aneurysm; RA: renal artery; SBC: subclavian artery; SFA: superficial femoral artery, SMA: superior mesenteric artery; STM: superficial thrombophlebitis; ThAo: Thoracic aorta; U: uveitis.

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Abstract Number: 3055

Evaluation of Plasma Pentraxin-3 Level in Patients with Takayasu's Arteritis

Fatma Alibaz-Oner[1,2], Kenan Aksu[3], P.Sibel Yentür[4], Gokhan Keser[5], Guher Saruhan-Direskeneli[6] and Haner Direskeneli[7], [1]Rheumatology, Marmara University School of Medicine, Istanbul, Turkey, [2]Department Rheumatology, Marmara University Faculty of Medicine, Istanbul, Turkey, [3]Dept. Of Internal Medicine, Division of Rheumatology, Ege University, Dept. Of Internal Medicine, Division of Rheumatology, Ege University, Izmir, Turkey, [4]Physiology, Istanbul University, Istanbul Medical Faculty, Istanbul, Turkey, [5]Rheumatology, Ege University Medical Faculty, Izmir, Turkey, [6]Department of Physiology, Istanbul University Istanbul Faculty of Medicine, Istanbul, Turkey, [7]Rheumatology, Marmara University, Faculty of Medicine, Istanbul, Turkey

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Background/Purpose: Assessment of disease activity is one of the major difficulties in patients with TAK during follow-up. To date, no biomarker is universally accepted to be a surrogate for active disease in TAK. In this study, we aimed to investigate plasma Pentraxin-3(PTX-3) level and its correlation with clinical activity in patients with TAK.

Methods: The study included 94 patients (age: 43.3±13.6 years, F/M: 80/14) with TAK and 40 age and sex matched control subjects (age: 41.5±9.3 years, F/M: 28/12). All patients fulfilled the criteria of American College of Rheumatology (ACR). TAK patients were evaluated by physician's global assessment (PGA; active/inactive) and Kerr' criteria(if available). Recently, a new composite index- ITAS2010 (Indian Takayasu Clinical Activity Score) for the clinical assessment of TAK was developed and validated. We also used ITAS2010 to assess clinical

activity. Plasma samples were separated to measure PTX-3. Commercial enzyme linked immuno-sorbent assay (ELISA) kits were used for measurements of plasma PTX-3.

Results: Mean disease duration the patients was 6.8±7.2(0-42) years. Thirty-three (35.5%) patients were clinically active according to PGA. While, Kerr's activity assessment was available in 79 patients, ITAS2010 was available in 88 patients. Twenty-five(31.6%) patients were active according to the Kerr's, 28(31.8%) patients were active according the ITAS2010. Plasma Ptx3 level was significantly higher in TAK compared to healthy controls(3,5±2,5 nanogram(ng)/ml vs. 2,5±1,6 ng/ml, p=0.029). PTX-3 level was found similar between active and inactive patients according to all assessment tools(PGA, Kerr' and ITAS2010)(Table 1). PTX-3 level significantly correlated with only serum CRP level. PTX-3 level was also similar between taking corticosteroid treatment and not taking.

Conclusion: Although plasma PTX-3 levels were higher in patients with TAK compared to healthy controls, we observed no association with disease activity. PTX-3 level was similar between active and inactive patients according to all activity assessment tools such as PGA, Kerr' and ITAS2010. Our results that PTX-3 level has limited role as a biomarker for active disease in TAK.

Table 1: Plasma pentraxin-3 levels according to different activity assessment tools.

		Plasma pentraxin-3 level (ng/ml)	**P value**
PGA	Active	3.2±2.4	
	Inactive	3.6±2.4	**0.442**
Activity by *Kerr et al*	Active	3.7±2.2	
	Inactive	3.6±2.5	**0.981**
ITAS2010	Active	3.9±2.5	
	Inactive	3.3±2.3	**0.214**
ITAS-A	Active	4.2±2.6	
	Inactive	3.3±2.3	**0.147**

PGA:Physician's global assessment, ITAS: Indian Takayasu Clinical Activity Score

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Disclosure: F. Alibaz-Oner, None; **K. Aksu**, None; **P. S. Yentür**, None; **G. Keser**, None; **G. Saruhan-Direskeneli**, None; **H. Direskeneli**, None.

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Abstract Number: 3056

Increased Circulating Th17 Cells, Serum IL-17 and Serum IL-23 in Takayasu's Arteritis

Ramnath Misra, Durga Prasanna Misra and Smriti Chaurasia, Clinical Immunology, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, India

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Background/Purpose:

The immune mechanisms underlying Takayasu's arteritis (TA) are not clear. Expanded Th17 T cell subset has been demonstrated in Giant Cell Arteritis. Gamma delta T cells (γδT), natural killer cells (NK) and natural killer -T cells (NKT) are also producers of IL-17 besides Th17 cells. Studies have demonstrated an increased number of circulating γδT cells in peripheral blood and in histopathology of arterial biopsies of patients with TA. We therefore enumerated Th17, γδT , NK and NKT cells and serum levels of IL-17 and IL23 in peripheral blood of patients with TA, and looked for its correlation with disease activity and erythrocyte sedimentation rate (ESR).

Methods: 30 patients with TA fulfilling ACR 1990 criteria and 20 healthy controls were included after seeking informed consent. NK cells (CD3-CD56+), NK-T cells (CD3+CD56+) and γδ-T cells (CD3+and γδTCR+) were surface stained in whole blood. For Th17 cells, 500 µl blood+500 µl cRPMI was cultured for 6 hours in presence of 50 ng/ml PMA, 1 µg/ml ionomycin for activation and golgi plug 0.2 µM monansin was added in last 4 hours of culture. Surface staining was done with anti-CD3, CD4, and intracellular staining for IL-17. Frequencies of all cell

types were analysed by flow cytometry. Th17 cells could not be assessed in one patient due to technical difficulties.

IL-17 and IL-23 were measured in serum by ELISA according to manufacturer's instructions. The relation of studied cell populations and serum IL-17 and IL-23 was analysed with disease activity (assessed by Kerr criteria, ITAS2010 and ITASA). Non-parametric tests were used for analysis (results presented as median with inter-quartile range). This study was approved by the institute ethics committee.

Results:

Mean age of patients was 33.47±11.78 years (25 females); mean symptom duration was 7.1±5.3 years. 13 were not on immunosuppressive drugs. 12 patients had ITAS ≥ 4. Compared with normal, the percentage of Th17 cells was significantly expanded in patients with TA. No differences in other cell populations were found. Serum IL-17 and IL-23 (pg/mL) in patients were significantly higher than controls (Table 1).

Subgroup analysis showed that the increased Th17 cells, serum IL-17 and IL-23 did not correlate with ESR, disease activity or medications.

Conclusion:

There is significant expansion of Th17 cells and elevation of serum IL-17 and IL-23 levels in patients with TA as compared to healthy controls. No relationship with disease activity could be demonstrated.

Table 1 – Gamma delta T cells, NK cells, NKT cells, Th17 cells, serum IL-17 and serum IL-23 in patients and controls (median with interquartile range in brackets)

	Patients (30)	**Healthy controls (20)**	**P value**
Serum IL-17 (pg/mL)	6.2 (4.6-8.5)	3.9 (3.9-7.3)	**0.004**
Serum IL-23 (pg/mL)	15 (14.9-26.5)	14.9 (14.9-14.9)	**<0.0001**
Th17 cells (%)	2.1 (1.5-3.2) (n=29)	0.75 (0.32-1.2)	**<0.0001**
Gamma delta T cells(%)	5.5 (3.9-7.1)	6 (2.7-9.9)	0.72
NK cells(%)	5.2 (3.6-8.7)	6.9 (4.3-9.3)	0.39
NKT cells(%)	3.7 (1.9-6.5)	2.4 (1.5-4.9)	0.12

Disclosure: R. Misra, None; **D. P. Misra**, None; **S. Chaurasia**, None.

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Abstract Number: 3057

Can We Differentiate Takayasu's Arteritis from Atherosclerosis Using Carotid Artery Doppler Usg?

Serdal Ugurlu[1], Fatma Ela keskin[2], Firat Cetinkaya[3], Melike Melikoglu[1], Vedat Hamuryudan[4], Izzet Fresko[4], Pinar Kadioglu[2] and Emire Seyahi[4], [1]Division of Rheumatology, Department of Internal Medicine, Cerrahpasa Medical Faculty, University of Istanbul, Turkey, Istanbul, Turkey, [2]Division of Endocrinology and Metabolism, Department of Internal Medicine, Cerrahpasa Medical Faculty, University of Istanbul, Istanbul, Turkey, [3]Colormed Radiology Center, Istanbul, Turkey, [4]Division of Rheumatology, Department of Internal Medicine, Cerrahpasa Medical Faculty, University of Istanbul, Istanbul, Turkey

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Background/Purpose:

Clinicians can have difficulty in making differential diagnosis between Takayasu and atherosclerosis. This is especially true when laboratory evaluations and FDG PET are inconclusive. In addition o that atherosclerosis load is potentially increased in TA because of the intense vascular inflammation. About 1/3rd of the patients with TA had carotid artery plaques and almost half diffuse aortic calcifications.

We thought that TA might have unique vascular changes distinct from atherosclerosis when evaluated with Doppler ultrasonography (USG). Thus, in this study we investigated the morphologic and hemodynamic changes in the carotid arteries in TA, along with patients with diabetes mellitus and healthy controls.

Methods:

Consecutive patients with TA seen in the department of Rheumatology at Cerrahpasa Medical Faculty were studied. Healthy controls were also included. TA patients and healthy controls were aged between 18 and 50 years. Patients with diabetes mellitus (DM) who were followed by the endocrinology outpatient clinic were also studied. For the purposes of this study, no age limit was set for patients with DM. Only females were studied. Traditional atherosclerotic risk factors were also assessed.

The radiologist scanned the right and left common, internal and external carotids and carotid bulb with the help of Doppler USG. Intima media thickness (IMT) was measured and resistivity index was calculated. The presence of atherosclerotic plaques, turbulence and macaroni sign was

assessed. Macaroni sign was defined as diffuse homogenous IMT thickening of at least 0.9 mm.

Results:

We studied 58 patients with TA (mean age: 43 ±11), 42 patients with DM (mean age: 57 ± 9) and 24 healthy controls (mean age: 41 ± 4). Atherosclerotic risk factors are summarized in Table 1 and carotid artery Doppler findings in Table 2. Patients with DM were significantly older and had significantly more atherosclerotic risk factors compared to patients with TA. Only smoking was significantly more frequent among healthy controls.

Patients with DM had more plaques and had higher IMT when compared to patients with TA, however, macaroni sign and turbulence were observed almost only among patients with TA. Finally the mean resistivity index was only significantly increased in TA.

Conclusion:

This study showed that carotid artery USG may be helpful in differentiating TA from atherosclerosis. Diffuse homogenous increase in IMT, presence of turbulence and higher resistivity index can be considered as suggestive of TA rather than atherosclerosis.

Table 1. Atherosclerotic risk factors

	Takayasu arteritis n= 58	Diabetes Mellitus n= 42	Healthy controls n= 24	P
BMI	25.6 ± 4.4	30.8 ± 5.8	26.7 ± 4.9	<0.001
Smoking, n (%)	12 (22)	11 (28)	16 (76)	<0.001
Diabetes mellitus, n (%)	4 (8)	42 (100)	0	< 0.001
Hypertension, n (%)	31 (56)	30 (77)	1 (5)	< 0.001
Familial history of ischemic heart disease, n (%)	22 (41)	16 (40)	8 (38)	0.978
Post-menauposal status, n (%)	23 (42)	36 (92)	1 (5)	<0.001

Table 2. Morphologic and hemodynamic findings in the carotid artery USG

	Takayasu arteritis n= 58	Diabetes Mellitus n= 42	Healthy controls n= 24	P
Macaroni sign, n (%)	45 (78)	1 (2)	0	<0.001
Atherosclerotic plaques, n (%)	21 (36)	28 (67)	2 (8)	<0.001
Turbulence, n (%)	8 (14)	0	0	0.008
Intima-media thickness, mm	0.90 ±0.36	0.96 ± 0.25	0.40 ± 0.12	<0.001
Resistivity index	0.63 ± 0.10	0.50 ± 0.04	0.56 ± 0.04	<0.001

Disclosure: S. Ugurlu, None; **F. E. keskin**, None; **F. Cetinkaya**, None; **M. Melikoglu**, None; **V. Hamuryudan**, None; **I. Fresko**, None; **P. Kadioglu**, None; **E. Seyahi**, None.

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Abstract Number: 3058

NMR-Based Metabolomics Provides New Insights into the Inflammatory Processes in Takayasu Arteritis

Ramnath Misra[1], Anupam Guleria[2], Durga Prasanna Misra[1], Avadesh Pratap[3], Durgesh Dubey[4], Atul Rawat[4], Smriti Chaurasia[3], C L Khetrapal[4], Dinesh Kumar[4] and Paul Bacon[5], [1]Clinical Immunology, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, India, [2]Centre of Biomedical Research, Lucknow, India, [3]S.G.P.G.I.M.S, Department of Clinical Immunology, Lucknow, India, [4]Centre for Biomedical Research, Lucknow, India, [5]Rheumatology, Birmingham Universit, Birmingham, United Kingdom
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Background/Purpose:

Takayasu Arteritis (TA), a large vessel disease of unknown aetiology, is the orphan of the inflammatory vasculitides with no evidence base for therapy. It often presents with vessel occlusions and biomarkers are needed for this subclinical process. Limited knowledge of its pathogenesis has hindered finding good candidates but PET scans indicate an active metabolic process in the aortic wall. Here, we have applied NMR-based serum metabolomics to gain more basic understanding of this process. The serum metabolic profiles of TA patients, Systemic lupus erythemoatosus (SLE) patients (chosen here as a diseased control group) and normal controls (NC) were obtained and compared using multivariate statistical data analysis.

Methods:

The sera samples were collected from (a) 29 TA patients fulfilling the ACR criteria seen at first presentation in SGPGI, Lucknow and assessed for disease activity and extent using ITAS and DEI.Tak., (b) 30 SLE patients attending the OPD and (c) 30 healthy age/sex-matched normal controls (NC) from the local community. NMR experiments were performed at 298 K on Bruker Avance III 800 MHz NMR spectrometer and metabolic differences between TA, SLE and NC were identified using multivariate statistical analysis.

Results: The projection to least squares discriminant analysis (PLS-DA) showed 100% specificity and sensitivity in differentiating TA from NC regardless of TA type and disease activity. Compared to healthy controls, the TA patients had (a) increased serum levels of choline metabolites, LDL cholesterol, N-acetyl glycoproteins (NAGs), and glucose and (b) decreased serum levels of lactate, lipids, HDL cholesterol, glucogenic amino acids (such as alanine, valine, arginine, proline, histidine, glutamine, etc.). We also accessed the role of disease activity on serum metabolic profiles in 2 ways. Spectra from 12 TA clinically active at 1st visit were not significantly different from 17 inactive (r^2=0.13) but did differ clearly from 6 who had become inactive at follow-up r^2=0.98). PLS-DA model also clearly separated TA from SLE (chosen as a disease control with known vascular inflammatory components suggesting that the TA results do not simply reflect active inflammation. Compared to SLE patients, the serum levels of lipid (mainly VLDL) and choline metabolites were found to be elevated in TA patients indicating the phospholipid and choline metabolism more activated in TA.

Conclusion: NMR based serum metabonomics study revealed a distinctive signature of TA, in particular the choline metabolites were found to be significantly higher in TA as compared to NC and SLE. However, the results of this study are preliminary and need to be confirmed in a prospective study using a larger cohort of TA patients and disease control like small vessel disease (SVV) to assess the specificity and utility of the metabolomic signature.

Disclosure: R. Misra, None; **A. Guleria**, None; **D. P. Misra**, None; **A. Pratap**, None; **D. Dubey**, None; **A. Rawat**, None; **S. Chaurasia**, None; **C. L. Khetrapal**, None; **D. Kumar**, None; **P. Bacon**, None.

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Abstract Number: 3059

Abnormal Body Composition in Takayasu Arteritis Patients: Role of Inflammatory Cytokines and Adipokines

Thiago Ferreira da Silva, Mauricio Levy Neto, Valéria Caparbo, Liliam Takayama and Rosa M R Pereira, Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil
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Background/Purpose: Chronic inflammatory conditions including rheumatic diseases may alter body composition, especially lean and fat mass. In this process, adipokines and inflammatory cytokines appear to play a key role. The aim of this study is to evaluate the body composition (BC) of TA patients compared to healthy controls (HC), and correlate BC parameters of TA patients with serum adipokines (adiponectin and resistin) and inflammatory cytokines (IL-1a, IL-6 and TNF-α).

Methods: A cross-sectional study was conducted in 45 consecutive women with TA and 47 HC matched by age and body mass index (BMI). BC was measured using dual-energy X-ray absorptiometry (DXA). The fat mass parameters evaluated were: total fat mass (FM), adiposity (percentage of body fat), android and gynoid fat, visceral adipose tissue (VAT) and fat distribution ratio (FDR: FM of the trunk/(FM of arms + FM of legs). Overfat was defined to denote excess body fatness, according to the stratification by age, BMI and ethnicity. Regarding lean mass parameters, total lean mass (LM) and appendicular lean mass index (ALMI: appendicular lean mass/ht^2) were analyzed. Abnormal body composition was defined in the presence of overfat (excess body fatness from DXA), low lean mass (ALMI ≤ 5.45 kg/m^2) or combination of these two variables. Serum adipokines (adiponectin, resistin) and plasmatic cytokines (IL-1a, IL-6 e TNF-α) were determined by Luminex xMAP Technology.

Results: Abnormal body composition (35.56% vs. 6.38%; p<0.001) was more prevalent in TA patients. Adiposity (%) and android fat mass were higher in TA patients compared to HC (33.05 ± 5.39 vs. 30.43 ± 5.63 %; p=0.025 and 1.58 ± 0.73 vs. 1.27 ± 0.62 Kg; p=0.05). Decreased lean mass (ALMI) was more prevalent in TA patients than HC (24.44% vs. 4.25%; p=0.013). LM had negative correlation with IL-6 levels (r=-0.44; p=0.005). ALMI presented negative correlation with erythrocyte sedimentation rate (ESR) (r=-0.36, p=0.017), resistin (r=-0.34, p=0.035), IL-1a (r=-0.44, p=0.006) and IL-6 (r=-0.43, p=0.007) levels. Fat distribution ratio (FDR) and VAT had negative correlation with adiponectin levels (r=-0.44; p=0.004; r=-0.42; p=0.010). (table 1)_Cumulative prednisone dose was not shown any correlations with fat mass or lean mass parameters.

TABLE 1 – Correlations of body composition variables by DXA and inflammatory parameters in TA patients

	Lean Mass		ALMI		Fat Mass		FDR		VAT		Android Fat	
	r	*p*	r	*p*	r	*p*	r	*p*	r	*p*	r	*p*
Age	0.09	0.535	0.16	0.286	0.07	0.647	0.18	0.220	0.38	0.019	0.14	0.407
Disease duration	0.02	0.872	0.11	0.469	0.01	0.936	0.02	0.890	-0.02	0.887	-0.01	0.970
Cumulative prednisone	0.02	0.888	-0.05	0.731	0.01	0.945	-0.09	0.562	-0.13	0.664	-0.04	0.879
ESR	-0.20	0.178	**-0.36**	**0.017**	0.12	0.406	0.26	0.080	0.17	0.303	0.18	0.288
CRP	0.01	0.946	-0.10	0.494	0.10	0.504	0.19	0.210	0.18	0.277	0.02	0.892
Adiponectin	-0.14	0.369	-0.28	0.084	-0.01	0.933	-0.44	0.004	**-0.42**	**0.010**	-0.19	0.260
Resistin	-0.23	0.140	**-0.34**	**0.035**	0.05	0.747	0.22	0.161	-0.13	0.425	-0.05	0.766
IL-1a	-0.29	0.077	**-0.44**	**0.006**	-0,25	0.123	-0.16	0.331	-0.21	0.207	-0.20	0.225
IL-6	**-0.44**	**0.005**	**-0.43**	**0.007**	-0.26	0.113	-0.06	0.692	-0.15	0.351	-0.19	0.243
TNF-α	-0.23	0.159	-0.20	0.226	-0.25	0.115	-0.07	0.668	-0.11	0.490	-0.25	0.124

Conclusion: Abnormal BC was significantly more prevalent among TA patients compared to healthy women. Appendicular lean mass was negatively correlated with inflammation parameters and visceral adipose tissue with adiponectin serum levels, suggesting a role of inflammation on the parameters of body composition in women with TA.

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Abstract Number: 3060

The Assessment of Disease Activity in Takayasu Arteritis; Six Years Experience from a Single Center

Handan Yarkan[1], Sedanur Karaman[2], Pinar Cetin[1], Servet Akar[3], Aytac Gulcu[4], Ahmet Yigit Goktay[4], Gercek Can[1], Merih Birlik[1], Nurullah Akkoc[5] and Fatos Onen[1], [1]Rheumatology, Dokuz Eylul University Faculty of Medicine, Izmir, Turkey, [2]Dokuz Eylul University Faculty of Medicine, Izmir, Turkey, [3]Department of Internal Medicine, Division of Rheumatology, Izmir Katip Celebi University School of Medicine, Izmir, Turkey, [4]Radiology, Dokuz Eylul University Faculty of Medicine, Izmir, Turkey, [5]Department of Rheumatology, Dokuz Eylul University, Faculty of Medicine, Izmir, Turkey

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Background/Purpose: The aim of this study is to analyze the activity parameters that affect the physicians global opinion (PGO) in TA.

Methods: The data of patients with TA who were followed in the Rheumatology outpatient clinic were retrospectively evaluated. Disease activity was assessed with, National İnstitutes of Healty (NIH) criteria, disease extent index-Takayasu (DEI.Tak), the Indian Takayasu Activity Score (ITAS2010), PGO, radiological activity parameters, and acute-phase reactants. According to the TA follow-up protocol of the Rheumatology and Radiology Board of our hospital, the patients were followed using B-mode/Doppler USG examinations and magnetic resonance angiography (MRA).

Results: 52 patients (48 females; mean age:46.8±13.2 years) who fulfilled the *American College of Rheumatology*(ACR) criteria for TA were enrolled in this study. 40 (76.9%) patients were categorized as having active disease in their first visits according to PGO. In the last visit, 31 (59.6%) patients had inactive disease, 19 (36.5%) had persistent disease and two (%3.9) had active disease. All the patients used the long-term glucocorticoid therapy and DMARDs. Six (%11.5) of them were on the treatment with biologics. Six (11.5%) patients underwent vascular surgery and 26 (50%) were performed endovascular repair for arterial stenosis. In total, 360 visits of patients were evaluated. PGO was that the disease was inactive in the 181 visits, persistan in the 99 visits and active in the 80 visits. The highest aggreement was found between PGO and the results of MRA and also B-mode/Doppler USG. NIH activation, DEI.Tak and ITAS2010 scores also well correlated with PGO. There was a poor agreement between PGO and hs-CRP.

Conclusion: The results of this study suggest that imaging had a significant impact on physician's decision regarding disease activity in TA. Although disease activity scores including radiological activity parameters, NIH, DEI-Tak and ITAS2010 were well correlated with each other, there was a poor agreement between CRP and all the other activity parameters.

Table 1.Agreement rates and correlations of the disease activity parameters with each other and PGO in Takayasu arteritis

	Hs-CRP	ITAS2010 Score	DEI.Tak Score	NIH Score	Positive B mode/ Doppler US	Positive MRI	PGO
Hs-CRP		0.2**	0.19**	0.29*	0.19*	0.32*	0.32*
ITAS2010 score	0.2**		**0.93****	**0.68****	0.47**	0.43**	0.55**
DEI.Tak score	0.19**	**0.93****		**0.70****	0.47**	0.44**	0.54**
NIH score	0.29*	**0.68****	**0.70****		0.55*	0.51*	**0.64***
Positive B mode/ Doppler US	0.19*	0.47**	0.47**	0.55*		0.53*	**0.80***
Positive MRA	0.32*	0.43**	0.44**	0.51*	0.53*		**0.79***

*kappa statistic, **Spearman ro. All p values were <0.05.

Disclosure: H. Yarkan, None; **S. Karaman**, None; **P. Cetin**, None; **S. Akar**, None; **A. Gulcu**, None; **A. Y. Goktay**, None; **G. Can**, None; **M. Birlik**, None; **N. Akkoc**, None; **F. Onen**, None.

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Abstract Number: 3061

Tocilizumab in Refractory Takayasu Arteritis. a Multicenter Study

Natalia Palmou[1], Montserrat Santos-Gómez[1,2], Javier Loricera[1], Ricardo Blanco[1], Jose L. Hernández[3], Santos Castañeda[4], Alicia Humbría[5], Norberto Ortego-Centeno[6], Beatriz Bravo[7], Mercedes Freire[8,9], Sheila Melchor[10], Mauricio Minguez[11], Juan Salvatierra[12], Carmen Gonzalez-Vela[13], Vanesa Calvo-Río[1], Trinitario Pina[1] and Miguel Angel Gonzalez-Gay[1], [1]Rheumatology, Hospital Universitario Marqués de Valdecilla. IDIVAL, Santander, Spain, [2]Rheumatology, Hospital Universitario Marqués de Valdecilla. IDIVAL. Santander. Spain, Santander, Spain, [3]Internal Medicine, Hospital Universitario Marqués de Valdecilla. IDIVAL, Santander, Spain, [4]Rheumatology, H.U. La Princesa, Madrid, Spain, [5]Rheumatology, Hospital Universitario de La Princesa. IIS-Princesa, Madrid, Madrid, Spain, [6]Systemic Autoimmune Diseases Unit, Hospital Universitario San Cecilio, Granada, Spain, [7]Pediatric rheumatology, Hospital Virgen de las Nieves, Granada, Spain, [8]Rheumatology, Hospital Universitario Juan Canalejo, La Coruña, Spain, [9]Rheumatology, Complejo Hospitalario Universitario de A Coruña, La Coruna, Spain, [10]Rheumatology, Hospital Universitario 12 de Octubre, Madrid, Spain, [11]Department of Rheumatology, Hospital Universitario San Juan, Alicante, Spain, [12]Rheumatology, University Hospital San Cecilio, Granada, Spain, [13]Pathology, Hospital Universitario Marqués de Valdecilla. IDIVAL, Santander, Spain

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Background/Purpose:

Takayasu arteritis (TA) is often refractory to corticosteroids and traditional immunosuppressive agents. Interleukin (IL)-6 plays an important role in the pathogenesis of TA. Tocilizumab (TCZ) is a humanized monoclonal anti-IL6 receptor (IL-6R) antibody.

Objective: Our aim was to assess the efficacy of TCZ in patients with TA refractory to conventional treatment.

Methods:

Retrospective multicenter study of 8 patients treated with TCZ and diagnosed with TA refractory to conventional therapy. We assessed its efficacy (clinical and laboratory parameters) and the reduction in the corticosteroid dose, as well as its side effects. Comparisons were performed between baseline and 1st, 3rd, 6th and 12th months, by means of

Results:

Eight patients (all women) with a mean age of 34±16 years, median 36 years (range: 7-57) were assessed. The main clinical features at TCZ therapy onset were: constitutional symptoms (n=4), fever (n=3), headache (n=2), chest pain (n=1), abdominal pain (n=1), mesenteric ischemia (n=1), myalgia involving the lower limbs (n=1), cerebral vascular insufficiency (n=1), malaise (n=1), upper limb claudication (n=1) and nodular scleritis (n=1). Besides corticosteroids and before TCZ treatment onset, 7 of 8 patients had also received several conventional immunosuppressive and/or biologic agents. Seven patients experienced marked clinical improvement in the first 3 months after the onset of TCZ therapy. After a median follow-up of 15.5 [interquartile range-IQR: 12-24] months, 7 patients were asymptomatic. The median C-reactive protein decreased from 3.09 [IQR: 0.5-12] to 0.15 [IQR: 0.1-0.5] mg/dL (p= 0.018), and median erythrocyte sedimentation rate from 40 [IQ range: 28-72] to 3 [IQR: 2-5] mm/1st hour (p= 0.012). The median dose of prednisone was also tapered from 42.5 [IQR: 25-50] to 2.5 [IQR: 0-7.5] mg/day (p= 0.011). However, TCZ had to be discontinued in 1 patient because she developed a systemic lupus erythematosus, and in another patients due to inefficiency. TCZ dose was reduced in a patient because of mild thrombocytopenia.

Conclusion:

TCZ appears to be effective in the management of patients with TakA, in particular in patients refractory to corticosteroids and/or conventional immunosuppressive drugs.

Disclosure: N. Palmou, None; **M. Santos-Gómez**, None; **J. Loricera**, None; **R. Blanco**, None; **J. L. Hernández**, None; **S. Castañeda**, None; **A. Humbría**, None; **N. Ortego-Centeno**, None; **B. Bravo**, None; **M. Freire**, None; **S. Melchor**, None; **M. Minguez**, None; **J. Salvatierra**, None; **C. Gonzalez-Vela**, None; **V. Calvo-Río**, None; **T. Pina**, None; **M. A. Gonzalez-Gay**, None.

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Abstract Number: 3062

Frequency, Presentation and Outcome of Takayasu Arteritis in Western Australia

Krista Makin[1], Maxine Garnsey[2] and Johannes Nossent[3], [1]Rheumatology, Fiona Stanley Hospital, Murdoch, Australia, [2]Internal Medicine, Sir Charles Gairdner Hospital, Nedlands, Australia, [3]Medicine, University of Western Australia, WA, Australia
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Background/Purpose: Takayasu Arteritis (TAK) is a systemic large-vessel vasculitis that mostly affects women of childbearing age. The worldwide incidence of TAK varies due to genetic and/or environmental factors. We describe the frequency, clinical features and outcomes of TAK in Western Australia (WA).

Methods: Cohort study of TAK patients identified in the Western Australian population (2.4 million) through multiple sources including hospital discharge codes between 1-1-2000 and 30-5-2015.

Results: Sixteen patients with a clinical TAK diagnosis were identified of whom 11/16 fulfilled 1990 ACR criteria for TAK. All were female and 81% were Caucasian. The median age at diagnosis was 33 years (interquartile range, 27-44 years) with 2 patients (18%) > 40 years at time of diagnosis. The median time to diagnosis was 6 months (interquartile range 2-32 months). Limb claudication was the most common presenting symptom, present in 5/11 patients (45%), followed by fatigue in 4/11 patients (36%). ESR and/or CRP were elevated at diagnosis in only 5 patients (45%). Hata type 2a arteriographic abnormalities were the most common (55%). All patients received corticosteroids as initial treatment and all were commenced on additional immunosuppressant agents (Methotrexate in 73%). There was one death during the study period. Four patients (36%) developed cerebrovascular disease, 3 suffered more than one stroke. Two patients (18%) suffered acute myocardial infarction. Vascular intervention was performed in 3 patients (27%).

Conclusion: TAK prevalence in WA is at least 4.2/million based on ACR criteria. The high morbidity despite immunosuppressive treatment might be related to a long delay to diagnosis and indicates a need for better tools to achieve earlier diagnosis.

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Abstract Number: 3063

Ocular Findings and Ocular Blood Flow Changes in Takayasu Arteritis: A Subclinical Reduction in Blood Flow with a Milder Clinical Course of Retinopathy

Ali Ugur Unal[1], Fehim Esen[2], Fatma Alibaz-Oner[3], Gulce Celik[4], Haluk Kazokoglu[5] and Haner Direskeneli[1], [1]Department of Rheumatology, Marmara University Faculty of Medicine, Istanbul, Turkey, [2]Department of Ophthalmology, Marmara University Faculty of Medicine, Istanbul, Turkey, [3]Department Rheumatology, Marmara University Faculty of Medicine, Istanbul, Turkey, [4]Department of Internal Medicine, Marmara University Faculty of Medicine, Istanbul, Turkey, [5]Department of Ophtalmalogy, Marmara University Faculty of Medicine, Istanbul, Turkey
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Background/Purpose: Ocular involvement in Takayasu arteritis (TAK) mainly arises due to complications related with altered ocular blood flow or side effects of the treatments. In this study, we aimed to document ocular complication rates, ocular blood flow status and the association of ocular blood flow parameters with clinical outcome of the Takayasu arteritis patients followed in a tertiary rheumatology clinic.

Methods: We have included 65 Takayasu arteritis patients followed at Marmara University Medical School, Rheumatology Division (F/M:60/5

, mean age: 41.8 ±12.9 years) and 51 healthy subjects (F/M: 50/1, mean age: 37.4 ±12.9 years) in this study. All of the participants had a detailed ophthalmological examination with optical coherence tomography scan of the macula, retinal nerve fiber layer and choroid. Ocular blood flow in ophthalmic and central retinal arteries was evaluated with Color Doppler ultrasonography. The rheumatology examination data was provided from the last rheumatology visit at which the patients were referred to the ophthalmology clinic.

Results: The most common ocular complication was hypertensive retinopathy (33.9%). Only 4 patients had retinal findings related with Takayasu retinopathy (6.2%). Thirteen eyes had posterior subcapsular cataract (10%) and 7 eyes were pseudophacic (5.4%). None of the patients suffered from a reduction of visual acuity due to ischemic neovascular complications. There was no statistically significant difference between the TAK patients and healthy subjects for the central macular thickness, foveal volume, retinal nerve fiber layer thickness and subfoveal choroideal thickness. TAK patients had an increase of resistivity index in the ophthalmic artery (0.75 vs. 0.66, p=0.002) and central retinal artery (0.75 vs. 0.67, p=0.001). Patients with hypertensive retinopathy had a significantly longer disease duration compared to the group with no retinopathy (7.9 years vs. 4.7 years, p=0.016), while there was no statistically significant difference between the groups for upper extremity blood pressure values. The resistivity index of the ophthalmic artery was higher in patients with ipsilateral radial artery pulselessness compared to the patients who had no pulselessness (0.77 vs. 0.68, p=0.031). The patients with carotid artery bruits did not have a significant change in the ocular blood flow parameters compared to the patients without carotid artery bruits. There was also no significant difference for ocular blood flow parameters between the patients with long (>5 years) or short disease duration (<5 years).

Conclusion: The prevalence of Takayasu arteritis was lower in our study compared to previous series. However, while none of the patients complained about visual disturbances, Doppler findings indicate a subclinical reduction in ocular blood flow in these patients.

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Abstract Number: 3064

Cardiac Manifestation of Takayasu Arteritis

Jin Wan, rheumatology and immunology, Beijing Anzhen Hospital affiliated to Capital Medical University, Beijing, China
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SESSION INFORMATION
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Background/Purpose: To explore cardiac manifestation of Takayasu arteritis and independent risk factor.

Methods: We retrospectively analyzed manifestations and helpful tests in 55 TA patients.

Results: Fifty-five patients(55/85,64.7%)with TA complicated by cardiac involvement were seen over 10 years£®The male to female ratio was l©U5.87, and the mean age at onset of TA was 24 years. There was no statistically significant difference between TA with and without cardiac involvement groups in terms of gender,clinical type,cardiac symptoms, except confirmed diagnosis time[36(9,168)months vs 12(6,24)months, *P*=0.001], chest pain[27.3%(15/55)vs 6.7%(2/30),*P*=0.023]and blood pressure difference >10 mmHg between right-to-left sides[69.1%(38/55) vs 46.7%(14/30),*P*=0.043]. Cardiac disease included hypertensive heart disease (30 patients,54.5%),cardiomyopathy(6 patients,10.9%),valvular disease(36 patients,65.5%),coronary artery disease(9 patients,16.4%),and pulmonary hypertension (7 patients,12.7%)£®At onset age in patients renal artery involvement was significantly younger in hypertensive heart disease[(28±14)years vs(44±14)years,*P*=0.006]. LVEF[(34±8)% vs(66±7)%, *P*=0.000]and age at onset [(15±13)years vs(25±11)years, *P*=0.030] were statistically significant between patients in TA with and without cardiomyopathy. Multivariate analysis showed that higher CRP was independent risk factor for pulmonary hypertension(*OR*=0.082,*95%CI:0.007-0.965,P*=0.047),mitral valve regurgitation(*OR*=0.192,*95%CI:*0.040-0.929,*P*=0.031)and tricuspid regurgitation(*OR*=0.093,95%*CI:*0.011-0.761,*P*=0.018).

Conclusion: We should pay attention to cardiac manifestation of Takayasu's Arteritis complicated by cardiac involvement to improve its early diagnosis.

Disclosure: J. Wan, None;

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Abstract Number: 3065

Evaluation and Validation of Case-Finding Algorithms for the Identification of Patients with Takayasu's Arteritis in Large Healthcare Administrative Databases

Narender Annapureddy[1], Antoine G. Sreih[2], Kevin Byram[3], George Casey[4], Vince Frangiosa[5], Michael George[6], Rebecca Sharim[5], Sapna Sangani[7] and Peter A. Merkel[7], [1]Rheumatology and Immunology, Vanderbilt University, Nashville, TN, [2]Department of Rheumatology, University of Pennsylvania, Philadelphia, PA, [3]Internal Medicine, Vanderbilt University, Nashville, TN, [4]The Vasculitis Foundation, Kansas City, MO, [5]Rheumatology, University of Pennsylvania, Philadelphia, PA, [6]Department of Rheumatology, Hospital of the University of Pennsylvania, Philadelphia, PA, [7]Penn Vasculitis Center, Division of Rheumatology, University of Pennsylvania, Philadelphia, PA
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Background/Purpose: To facilitate clinical care and research, validated algorithms are needed to accurately identify patients with Takayasu's arteritis (TAK). This study sought to evaluate and validate case-finding algorithms for TAK in 2 large healthcare administrative databases.

Methods: All adult patients with the International Classification of Diseases version 9 (ICD9) code for TAK (446.7) were identified from 2 large healthcare systems (102 from site 1 and 85 from site 2). 26 case-finding algorithms were constructed using a combination of ICD9 code, encounter type (1 inpatient ICD9 code on 3 consecutive days or 2 outpatient ICD9 codes 3 months apart), physician specialty (Rheumatology, Cardiology, or Vascular Surgery), use of immunosuppressive medications, age, and sex. The diagnosis was confirmed by chart review using the ACR classification criteria or the Chapel Hill Consensus Conference definitions for TAK.

Results: 102 patients from the first healthcare system (site 1) and 85 patients from the second system (site 2) were included in the analysis. 47/102 (46%) patients had a confirmed diagnosis of TAK at site 1 and 35/85 (42%) patients at site 2. Table 1 shows the positive and negative predictive values of the studied algorithms in each healthcare system. An algorithm including the encounter type, physician specialty, age, and immunosuppressive medications had the highest average positive predictive value (PPV: 76.9% and 88.2 % respectively). An algorithm including only the physician specialty had the highest average negative predictive value (NPV: 90.2% and 100% respectively).

Conclusion: Case-finding algorithms can accurately identify patients with TAK using large administrative databases. A simple algorithm including the encounter type, physician specialty, age, and immunosuppressive medications had the highest positive predictive value. Similarly, an algorithm including only the physician specialty had the highest negative predictive value. These algorithms can be used to assemble a population-based cohort of patients with TAK and facilitate future research in healthcare use, outcomes, and comparative effectiveness.

Table 1. Test characteristics of Algorithms for Takayasu's Arteritis

Algorithms for Takayasu's Arteritis	Site 1 (n=102)		Site 2 (n=85)	
	PPV	NPV	PPV	NPV
ICD9+				
Sex	45.7	52.4	42.4	63.2
Age	58.5	75.7	64.3	70.2
Encounter	51.3	69.2	74.4	92.9
Specialty**	**70.5**	**90.2**	**52.2**	**100.0**
Medications	53.8	56.6	47.8	83.3
ICD9+Sex+				
Age	59.2	66.0	73.7	68.2
Encounter	50.8	61.5	72.2	81.6
Specialty	68.0	75.0	53.8	78.8
Medications	50.0	54.9	46.3	67.7
ICD9+Age+				
Encounter	60.8	68.6	83.3	70.1
Specialty	72.9	77.8	75.0	72.1
Medications	64.7	57.6	75.0	72.1
Specialty+Medications	76.9	58.4	81.8	73.0
Encounter +Sex	62.5	64.5	85.7	67.6

Disclosure: N. Annapureddy, None; **A. G. Sreih**, None; **K. Byram**, None; **G. Casey**, None; **V. Frangiosa**, None; **M. George**, None; **R. Sharim**, None; **S. Sangani**, None; **P. A. Merkel**, None.

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Specialty+Sex		71.1	68.8		77.8	68.7
Medications+Sex		66.7	56.7		82.4	69.1
ICD9+Encounter+						
Specialty+Medications		76.5	60.0		74.4	87.0
Specialty+Age		74.4	71.4		83.3	70.1
Medications+Age		64.7	57.6		88.2	70.6
Specialty+Sex		52.6	55.4		72.2	81.6
Specialty+Medications+Age*		**76.9**	**58.4**		**88.2**	**70.6**
Specialty+Medications+Sex		75.0	57.8		69.7	76.9
Specialty+Age+Sex		71.9	65.7		69.7	76.9
Medications+Age+Sex		66.7	56.7		85.7	67.6
Specialty+Medications+Age+Sex		77.8	57.0		85.7	67.6
ICD9+ Specialty+Medications+Age+Sex		77.8	57.0		82.4	69.1

* Algorithm with the highest average PPV ** Algorithm with the highest average NPV**.**

PPV: positive predictive value. **NPV**: negative predictive value. ICD9: ICD9 code 446.7.

ENCOUNTER: 1 inpatient ICD9 code on 3 consecutive days or 2 ICD9 codes 3 months apart.

SPECIALTY: a Rheumatologist, Cardiologist, or a Vascular Surgeon involved in the care of the patient.
MEDICATIONS: an immunosuppressive medication used. **AGE**: current age < 50. **Sex**: = female.

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Abstract Number: 3066

Clinical Features and Treatments of Takayasu Arteritis Complicated with Ulcerative Colitis

Toshiki Nakajima[1], Hajime Yoshifuji[1], Chikashi Terao[2], Takao Fujii[1], Koichiro Ohmura[1], Yoshitaka Imura[3], Kosaku Murakami[4], Ran Nakashima[1], Naoichiro Yukawa[1] and Tsuneyo Mimori[1], [1]Department of Rheumatology and Clinical Immunology, Kyoto University Graduate School of Medicine, Kyoto, Japan, [2]Departments of Genetics and Rheumatology, Brigham and Women's Hospital, Boston, MA, [3]Rheumatology and Clinical Immunology, Kyoto University Graduate School of Medicine, Kyoto, Japan, [4]Rheumatology & Clin Immunology, Kyoto University Graduate School of Medicine, Kyoto, Japan

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Background/Purpose: Some cases with Takayasu arteritis (TAK) complicated with ulcerative colitis (UC) have been reported. We previously performed a multi-center surveillance of TAK patients complicated with UC (Terao et al., Arthritis Rheumatol 2015) and reported that 30 of 470 TAK patients (6.4%, CI: 4.3-9.0%) were coincident with UC. We also found that the onset of TAK symptoms was approximately 6 year earlier in TAK+UC patients than in TAK-only patients (p=0.007), implying that stronger genetic backgrounds might underlie in TAK+UC patients. In this study, we investigated detailed clinical features of TAK+UC cases in a single center.

Methods: We referred to medical records of 122 Japanese TAK patients in Kyoto University Hospital, and examined their HLA-B genotypes, ages of onsets, symptoms associated with TAK or UC, and treatments.

Results: 7 of 122 TAK patients (5.7%, CI: 2.3-11.5%) had UC. HLA information was available in 6 TAK+UC patients and 77 TAK only patients. All of TAK+UC patients and 38 (49%) TAK only patients had HLA-B52 (p=0.027). In 4 TAK-preceding patients, the onset of TAK was 5.5 ± 4.5 (1-10) years earlier than that of UC, and all of them noticed bloody stool and/or diarrhea as the first symptom of UC. In 3 UC-preceding patients, the onset of UC was 4.0 ± 3.0 years (1-7) years earlier than that of TAK, and 2 of them noticed neck pain as the first symptom of TAK. We did not find particular clinical features of symptoms and signs between TAK-preceding and UC-preceding patients. Biologic agents were used in 43% (3/7) of TAK+UC, whereas in only 7.0% (8/115) of TAK-only patients. Both diseases were well controlled in the 3 TAK+UC patients when treated with biologics (2 with infliximab and 1 with ustekinumab).

Conclusion: While association of HLA-B52 had been reported both in TAK and UC, HLA-B52 was considered as a major genetic background underlying in TAK+UC patients. When stool abnormality is seen in TAK patients with HLA-B52, possible complication of UC could be considered. Biologics may be a therapeutic consideration to control both diseases.

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Microscopic Colitis in Patients with Takayasu Arteritis; A Potential Association Between the Two Disease Entities

Nilufer Alpay Kanitez[1], Bahtiyar Toz[1], Mine Gulluoglu[2], Burak Erer[1,3], Murat Inanc[4], Bilger Cavus[5], Raim Iliaz[5], Cetin Karaca[5] and Sevil Kamali[1], [1]Department of Internal Medicine, Division of Rheumatology, Istanbul University, Istanbul Faculty of Medicine, Istanbul, Turkey, [2]Pathology, Istanbul University, Istanbul Faculty of Medicine, Ä°stanbul, Turkey, [3]Department of Internal Medicine, Rheumatology Division, Istanbul University, Istanbul Faculty of Medicine, Istanbul, Turkey, [4]Department of Internal Medicine, Division of Rheumatology, Istanbul University, Istanbul Faculty of Medicine, Ä°stanbul, Turkey, [5]Department of Internal Medicine, Division of Gastroenterology, Istanbul University, Istanbul Faculty of Medicine, Ä°stanbul, Turkey

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Background/Purpose: Takayasu's arteritis (TAK) is a chronic vasculitis of large-vessels, mainly affects the aorta and its branches in the middle-aged females. There are reports regarding the concurrence of inflammatory bowel disease (IBD) and TAK. Microscopic colitis (MC) has been demonstrated in inflammatory rheumatic diseases such as spondylarthropathies which has been linked to an ethiopathogenetical association between two diseases. MC as an IBD subgroup has not been investigated in TAK, so far. We aim to assess the presence of MC in TAK patients who have no clinically overt IBD symptoms.

Methods: We cross-sectionally assessed TAK patients, between the ages of 18-65, who were diagnosed according to ACR criteria. Disease activity was evaluated by Kerr's criteria. Age and sex matched irritabl bowel syndrome (IBS) patients were selected as control group. Study subjects who have been on MC inducing medications, such as NSAIDs, PPI, anti-physchotic or anti-depressant and having co-morbidities were excluded. All patients and controls have been interviewed for IBD and IBS symptoms by the questionnaires of WHO guideline and Rome III criteria, respectively. Lower endoscopic procedure was performed with at least 5 random biopsies taken from different colonic segments and terminal ileum within the following 2 weeks after the research visit. A blinded expert pathologist evaluated the specimens for the thickness of the collagen band, the degree of inflammatory infiltration in the lamina propria, and the number of intraepithelial lymphocytes according to an algorythm proposed for MC assessment by Langner C et al.[1]. Lymphocytic and collagen colitis were defined as the subgroups of MC. Incomplete colitis has also been defined in the algorythm.

Results:

Thirty TAK patients (29 female) with the mean age of 35±11 (20-59), total disease duration of 107±79 months (3-286) and 10 female IBS controls with the mean age of 38±13 were included into the study. Type 2 vascular involvement was the most common (64%) pattern in the cohort. Nine of 30 (30%) TAK patients have active disease at the time of endoscopic procedure. MC was not demonstrated in any patients with IBS. All but one TAK patients had normal endoscopic findings. Erythema on the entire colonic mucosa as the only pathological endoscopic finding was demonstrated in one patient. The examination of terminal ileum was found normal in both TAK and control groups. Three patients (10%) were full-filled LC criteria of MC. Incomplete LC was determined in additional 6 patients (20%). LC was found significantly higher among the patients with active TAK subgroup compared with inactive patients (p= 0.03, OR= 5,7).

Conclusion: MC was found significantly high in TAK patients who had no overt IBD symptoms/diagnosis. This preliminary report from this ongoing study supports that this association might have a pathopyhsiological relevance.

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potential-association-between-the-two-disease-entities

Abstract Number: 3068

Damage Assessment in Takayasu's Arteritis

Antoine G. Sreih[1], Tanaz A. Kermani[2], David Cuthbertson[3], Simon Carette[4], Gary S. Hoffman[5], Nader A. Khalidi[6], Curry L. Koening[7], Carol A. Langford[5], Carol McAlear[8], Paul A. Monach[9], Larry W. Moreland[10], Christian Pagnoux[11], Philip Seo[12], Kenneth J. Warrington[13], Steven R. Ytterberg[14] and Peter A. Merkel[8], [1]Department of Rheumatology, University of Pennsylvania, Philadelphia, PA, [2]Rheumatology, University of California Los Angeles, Santa Monica, CA, [3]Biostatistics and Informatics, Department of Pediatrics, University of South Florida, Tampa, FL, [4]Division of Rheumatology, Mount Sinai Hospital, University of Toronto, Toronto, ON, Canada, [5]Rheumatology, Cleveland Clinic, Cleveland, OH, [6]McMaster University, Hamilton, ON, Canada, [7]Division of rheumatology, George E. Wahlen Department of Veterans Affairs Medical Center Salt Lake City and University of Utah, University of Utah School of Medicine, Salt Lake City, UT, [8]Division of Rheumatology, University of Pennsylvania, Philadelphia, PA, [9]Section of Rheumatology, Vasculitis Center, Boston University School of Medicine, Boston, MA, [10]Rheumatology & Clinical Immunology, University of Pittsburgh, Pittsburgh, PA, [11]Rheumatology, Division of Rheumatology, Mount Sinai Hospital, Toronto, ON, Canada, [12]Division of Rheumatology, Johns Hopkins, Baltimore, MD, [13]Rheumatology, Mayo Clinic, Rochester, MN, [14]Rheumatology Division, Mayo Clinic, Rochester, MN

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Background/Purpose: This study aimed to describe disease-related damage in Takayasu's arteritis (TAK) and evaluate damage assessment tools using data from a large longitudinal cohort.

Methods: Patients with TAK enrolled in a prospective, multicenter, longitudinal study were included. Measures of disease damage, including the Vasculitis Damage Index (VDI) and the Large-Vessel Vasculitis Index of Damage (LVVID), were assessed at baseline and follow-up visits. LVVID was developed specifically for large-vessel vasculitis. **Results** from patients with a diagnosis of TAK made within 6 months prior to study entry were also separately analyzed.

Results: The study included 129 patients with TAK: 94% female, 89% Caucasian with a median duration of follow-up 3.5 years (1.9, 6.2). At entry in the cohort, 113 patients (88%) had at least one damage item recorded on VDI (mean score ± SD: 2.5±1.8) and 113 (88%) on LVVID (mean score: 3.0±2.5). During follow-up 49 patients (38%) accrued at least one new damage item as measured by VDI (mean increase in score: 1.8±1.0) and 47 patients (36%) as measured by LVVID (mean increase in score: 2.0±1.9). 31/129 patients had a diagnosis of TAK made within 6 months prior to study entry, 81% of them had at least 1 item documented on VDI at entry with a mean score of 2.2±1.5 items and 81% on LVVID with a mean score of 2.7±2.1 items.

Organ systems affected by damage at baseline and follow-up are outlined in the **Table**. The cardiac, peripheral vascular, and the "other" sections, including weight gain, accounted for most of the damage captured at baseline and follow-up. The accrued damage items were mostly related to the disease (cardiac and peripheral vascular) rather than treatment (weight gain). There were 25 items never scored on VDI and 8 items never scored on LVVID. The unscored items were mostly related to the skin, ear, nose, and throat, pulmonary, and renal systems.

Conclusion: Damage from vasculitis is present in the majority (>80%) of patients with TAK even within 6 months of diagnosis. Approximately 40% of patients continue to accrue a new damage item, mostly related to disease, with a mean of 2 items per patient. The cardiac, peripheral vascular, and "other" sections capture most of the damage in TAK. LVVID appears to document more damage items overall than VDI. Revision of the VDI or adoption of the LVVID, along with data-driven approaches to item reduction and weighting, may improve damage assessment in TAK.

Major organ systems damage in 129 patients with Takayasu's arteritis as captured by VDI and LVVID					
VDI (by organ system)	Baseline N* (%)	Follow-up New** (%)	**LVVID (by organ system)**	Baseline N* (%)	Follow-up New** (%)
Cardiac	45 (35%)	14 (11%)	**Cardiac**	55 (43%)	9 (7%)
Peripheral Vascular	97 (75%)	17 (13%)	**Peripheral Vascular**	101 (82%)	9 (7%)
Musculoskeletal	10 (8%)	2 (2%)	**Musculoskeletal**	10 (8%)	3 (2%)
Skin	1 (1%)	1 (1%)	**Skin**	1 (1%)	0 (0%)
Ocular	8 (6%)	0 (0%)	**Ocular**	7 (5%)	4 (3%)
Ear, Nose, and Throat	0 (0%)	0 (0%)	**Ear, Nose, & Throat**	1 (1%)	0 (0%)
Gastrointestinal	3 (2%)	2 (2%)	**Gastrointestinal**	0 (0%)	2 (2%)
Neuropsychiatric	10 (8%)	2 (2%)	**Neuropsychiatric**	12 (9%)	1 (1%)
Endocrine	4 (3%)	1 (1%)	**Endocrine**	4 (3%)	2 (2%)
Hematology/Oncology	0 (0%)	2 (2%)	**Hematology/Oncology**	3 (2%)	3 (2%)
Pulmonary	3 (2%)	1 (1%)	**Pulmonary**	NA	NA
Renal	0 (0%)	2 (2%)	**Renal**	NA	NA
Other	9 (7%)	5 (3%)	**Other**	36 (28%)	12 (9%)
			Weight gain	24 (19%)	8 (7%)
			Damage requiring surgical intervention	12 (9%)	2 (2%)
			Other form of damage	6 (5%)	2 (2%)
Patients with ³1 damage item on VDI	**113 (88%)**	**49 (38)**	**Patients with ³1 damage item on LVVID**	**113 (88%)**	**47 (36%)**

*N = number with ³1 item captured in that category at baseline;

**New = number of new accrued damage items captured in that category during follow-up

NA = not applicable due to no items in this organ system appearing in LVVID

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Abstract Number: 3069

Long Term Follow-up Results of Endovascular Repair in the Management of Arterial Stenosis Caused By Takayasu Arteritis

Aytac Gulcu[1], Naciye Sinem Gezer[1], Pinar Cetin[2], Servet Akar[3], Nurullah Akkoc[4], Ahmet Yigit Goktay[1] and **Fatos Onen**[2], [1]Radiology, Dokuz Eylul University Faculty of Medicine, Izmir, Turkey, [2]Rheumatology, Dokuz Eylul University Faculty of Medicine, Izmir, Turkey, [3]Department of Internal Medicine, Division of Rheumatology, Izmir Katip Celebi University School of Medicine, Izmir, Turkey, [4]Department of Rheumatology, Dokuz Eylul University, Faculty of Medicine, Izmir, Turkey

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Background/Purpose: Takayasu arteritis (TA) is a chronic arteritis of the aorta and its major branches. Patients may require endovascular repair in long term follow up. The aim of this retrospective study was to report our long term follow up results of endovascular repair in the management of arterial stenosis caused by TA.

Materials and Methods: We retrospectively analyzed the outcome of endovascular interventions including angioplasty and angioplasty with stenting in patients with arterial stenosis caused by TA. The patients were followed-up in the Rheumatology out-patient clinic at 3 monthly intervals. Each visit included the evaluation of clinical symptoms, acute-phase reactants and regulation of the medical treatment including glucocorticoids and immunosuppressive drugs. For the evaluation of outcome of the interventional procedure, patients underwent Doppler ultrasonography and MR angiography routinely at every 6 months. Catheter angiography was performed if there was any suspicion of restenosis or occlusion.

Results: This study included 35 patients with TA (31 female, mean age: 42.5 years) who fulfilled the American College of Rheumatology 1990 Criteria for the diagnosis of TA. All patients had symptomatic arterial stenosis proven by catheter angiography. A total of 67 endovascular procedures were performed for 49 arterial stenotic lesions of the patients. Clinical inactivity of the disease was provided with immunosuppressive treatment before any interventions. Treatment of recurrent stenosis by a second endovascular procedure was performed in 11 (22.5%) lesions. The mean follow-up interval after endovascular procedure was 81 months (range 12-144 months). Twenty two (33%) of total 67 endovascular interventions resulted in restenosis or occlusion. Among all 49 arterial lesion, only four (8%) lesions (one common iliac, one renal, one celiac and one thoracic aortic) were occluded at the time of the final evaluation. Kaplan-Meier survival analyses of the renal arterial lesions showed that the overall 1- and 8-year restenosis-free survival rates of renal arterial interventions were 74% and 57%, respectively.

Conclusion: This study suggests that long term patency of TA lesions is related with control of the disease activity by optimal immunosuppressive therapy before and after the initial endovascular procedure. Performing reinterventions with close monitoring of the arterial lesion should not be avoided for better outcomes.

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Abstract Number: 3070

Outcome of Pregnancies in Patients with Takayasu Arteritis with Special Focus on Risk Factors and Disease Activity

Noemie Abisror[1], Arsene Mekinian[1], Marc Lambert[2], Eric Hachulla[3], Robin Dhote[4], Catherine Chapelon[5], Antoine Néel[6], Amar Smail[7], Frederic Vandergheynst[8], Nihal Martis[9], Jean Gabriel Fuzibet[10], Françoise Sarrot-Reynauld[11], Marc Andre[12], Alain Fur[13], Francois Maurier[14], Julien Haroche[15], Bertrand Godeau[16,17], Murielle Rondeau[18], Frederic Renou[19], Pauline Belenotti[20], Laure Swiader[20], Patrice Cacoub[21], Bruno Devaux[22], Luc Mouthon[23], Jean Baptiste Gaultier[24], Pascal Cathebras[25], Olivier Pourrat[26], Olivier Fain[1], Véronique Le Guern[27] and Nathalie Costedoat-Chalumeau[27], [1]Internal Medicine Department, Saint Antoine Hospital, Paris, France, [2]CHU Lille, Lille, France, [3]Department of Internal Medicine, University Lille Nord-de-France, Lille, France, [4]Internal Medicine, Hospital Avicenne, Bobigny, France, [5]Department of Internal Medicine 2. Referal center for SLE/APS, CHU Pitié-Salpêtrière, Paris, France, [6]Internal Medicine, Nantes University Hospital, Nantes, France, [7]Internal Medecine, Amiens Hospital, Amiens, France, [8]Internal Medicine, Erasme hospital, Bruxelles, Belgium, [9]Internal medicine, Nice, France, [10]Internal Medicine, Internal Medicine, Hôpital de l'Archet 1, CHU de Nice, Nice, France, [11]Internal medicine, Grenoble, France, [12]Internal medicine, Clermont Ferrand, France, [13]Internal medicine, Troyes, France, [14]HP Metz Belle Isle Hospital, Department of Internal Medicine, Metz, France, [15]Internal Medecine, Pitié-Salpêtrière hospital, Paris, France, [16]Henri Mondor, Créteil, France, [17]Internal Medicine, University of Paris, AP-HP, Hôpital Mondor Créteil, Creteil, France, [18]Internal medicine, Strasbourg, France, [19]Internal medicine, Saint Denis, France, [20]Internal medicine, Marseille, France, [21]Department of Internal Medicine, Pitié-Salpêtrière Hospital, Paris, France, [22]Internal medicine, Coulommiers, France, [23]Paris Descartes University, UPRES-EA 4058, Department of Internal Medicine, Cochin Hospital, Paris, France, [24]Internal medicine, Saint Etienne, France, [25]Internal Medicine, University Hospital St Etienne, St Etienne, France, [26]Internal medicine, Poitiers, France, [27]Internal Medicine Department, Cochin Hospital, "René-Descartes Paris V" University, Paris, France

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SESSION INFORMATION

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Background/Purpose: Takayasu arteritis (TA) is a large-vessel vasculitis that affects young women of childbearing age. We aimed to analyze the outcome of pregnancies in TA patients and to identify the factors associated with maternal and neonatal prognosis.

Methods: We conducted a French nationwide retrospective study of pregnancies occurring in patients with a TA diagnosis.

Results: Forty-one pregnancies occurred in 31 TA women between 1999 and 2015. Steroids were used in 25 pregnancies (61%), azathioprine in 9 (22%) and anti-TNF- agonist in 1 (3%). Nineteen pregnancies (46%) were complicated by at least one obstetrical adverse event: 14 gravida arterial hypertension (34%) with 3 pre-eclampsia (7%), 1 HELLP syndrome (2%), 6 intrauterine growth restriction (15%), and 2 post-partum hemorrhage (5%). Delivery was vaginal in 22 (54%) and by cesarean section in 19 pregnancies (46%).There were 40 live births (98%) with a median term of 38 [27-42] weeks of gestation with 8 premature birth (20%). The median birth weight was 2985 [1050-4310] grams with 7 neonates <2500 gr (17%). Four children required intensive care units (10%) and one died at 2 days of life. Maternal chronic arterial hypertension increased the risk of gravida arterial hypertension (p=0.01), of pre-eclampsia (p=0.04) and of cesarean delivery (p=0.01). The presence of renal artery stenosis before pregnancy increased the risk of fetal growth restriction (p=0.04). The presence of renal artery stenosis before pregnancy as well as the presence of infra-diaphragmatic vasculitis both increased the risk of low birth weight (p=0.03 and p=0.023 respectively).

TA disease activity was observed in 8 pregnancies (20%), including 2 flares in previously inactive patients. The risk of flare or of TA activity was higher if TA had been active in the 6 months before pregnancy: 6 active disease in 10 pregnancies (60%) if TA had been active before pregnancy versus 2 in 31 (6%) if TA had been inactive (p=0.0011).

Conclusion: We observed a high rate of obstetrical complications in this large series of pregnancies occurring in patients diagnosed with TA**.** The presence of chronic hypertension, infra-diaphragmatic vasculitis, renal artery stenosis or active disease before pregnancy were associated with poor pregnancy outcome. TA activity did not seem to be strongly influenced by pregnancy.

Mothers	30
Age at pregnancy, median [range]	30 [22-42]
Parity	
Primipara, n (%)	19 (61)
Multipara, n (%)	12 (39)
Treatment during pregnancy	
Aspirin 75-100 mg/day, n (%)	25 (61)
Low weight molecular heparin (end of pregnancy), n (%)	8 (20)
Curative anticoagulant therapy, n (%)	1 (3)
Prednisone, n (%)	25 (61)
Azathioprine, n (%)	9 (22)
Infliximab, n (%)	1 (3)
Antihypertensive drugs, n (%)	9 (22)
Obstetrical complications	19 (46)
Gravida arterial Hypertension, n (%)	14 (34)
Increase of preexisting hypertension, n (%)	11 (27)
De novo hypertension, n (%)	3 (7)
With preeclampsia, n (%)	3 (7)
HELLP syndrome, n (%)	1 (3)
Fetal Growth Restriction, n (%)	6 (15)
Delivery mode, n (%)	
Vaginal delivery, n (%)	21 (54)
Cesarean section, n (%)	18 (46)
Post-partum hemorraghe, n (%)	2 (5)
Children	
Premature birth, n (%)	8 (20)
Severe premature birth (<34 weeks), n (%)	2 (6)
Full-terme birth, n (%)	32 (78)
Gestational age, median weeks [range]	38 [27-42]
Birth weight, median grams [range]	2985 [1050-4310]
Birth weight < 2500gr, n (%)	7 (17)
Intrauterine death, n (%)	1 (3)
Intensive care unit transfer, n (%)	4 (10)
Perinatal mortality, n (%)	1 (3)

TABLE 2. Forty-one pregnancies: maternal and fetal outcomes

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Abstract Number: 3071

Takayasu's Arteritis and Pregnancy

Cloé Comarmond[1], Tristan Mirault[2], Lucie Biard[3], Jacky Nizard[4], Marc Lambert[5], Bertrand Wechsler[6], Eric Hachulla[5], Laurent Chiche[7], Fabien Koskas[8], Julien Gaudric[9], Philippe Cluzel[10], Emmanuel Messas[11], Mathieu Resche Regon[12], Jean-Charles Piette[13], Patrice Cacoub[13] and David Saadoun[14], [1]DHU 2iB Internal Medicine Referal Center for Autoimmune diseases Pitie Hospital, Paris, France, [2]Service de Médecine Vasculaire HEGP, Paris, France, [3]Biostatistics, Saint-Louis Hospital, Paris, France, [4]Department of obstetrics and gynaecology, Pitié-Salpêtrière Hospital, Paris, France, [5]CHU Lille, Lille, France, [6]Department of Internal Medicine 2. Referal center for SLE/APS, CHU Pitié-Salpêtrière, Paris, France, [7]Service de Chirurgie Vasculaire, Groupe Hospitalier Pitié-Salpêtrière, Paris, France, [8]Department of Internal Medicine and 2Laboratory I3 « Immunology, Immunopathology, Immunotherapy », UMR CNRS 7211, INSERM U959, Groupe Hospitalier Pitié-Salpetrière, Université Pierre et Marie Curie, Paris 6, Paris, France, Paris, France, [9]Department of Vascular surgery GHPS, Paris, France, [10]Cadiovascular Imaging and Interventional Radiology, Pitié-Salpétrière, Paris, France, [11]HEGP hospital Vascular and cardiology Department, paris, France, [12]biostatistics Saint Louis Hospital, paris, France, [13]Department of Internal Medicine, Pitié-Salpêtrière Hospital, Paris, France, [14]Department of Internal Medicine and clinical Immunology. French National Reference Center for Autoimmune Diseases. DHU I2B (Inflammation, Immunotherapy and Biotherapy), UPMC, Paris VI, Hôpital Pitié Salpétrière, AP-HP, UPMC, Univ Paris 06, Paris, France
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Background/Purpose:

To assess the relation between Takayasu's arteritis (TA) and pregnancy outcome.

Methods: This study included 240 pregnancies in 96 patients fulfilling ACR and/or Ishikawa criteria. Obstetrical and maternal outcomes in pregnant women before or concomitant with or after TA diagnosis were analyzed. Factors associated with complicated pregnancy were assessed.

Results:

One hundred and forty two pregnancies occurred in 52 patients before TA diagnosis [median age at pregnancy 26 [23-30] years] and 98 pregnancies occurred in 52 patients concomitantly or after TA diagnosis [median age at pregnancy 28 [26-31] years]. Pregnancies concomitant with or after TA diagnosis had 13 times higher rates of obstetrical complications compared to pregnancies before TA diagnosis (OR=13, 95% CI [5-33], $p<0.0001$). TA was associated with 40% obstetrical complications and include preeclampsia/eclampsia [n=24, (24%)], prematurity [n=8 (8%)] and intrauterine fetal growth restriction or death [n=5 (5%)]. Specific TA complications during pregnancy occurred in 39% and include mainly new onset or worsening hypertension [n=26, (26%)]. In multivariate analysis, smoker (OR=6.15 [1.31-28.8]) and disease activity of TA (i.e. NIH score >1) (OR=28.7 [7.89-104.7]) were independently associated with obstetrical and maternal complications.

Conclusion:

TA negatively impacts pregnancy outcomes. Disease activity increases the risk of obstetrical and maternal complications mainly due to arterial hypertension.

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Abstract Number: 3072

Childhood Takayasu Arteritis. a Single Center Experience

Florence A. Aeschlimann[1], Susanne Benseler[2], Ronald Laxer[1], Diane Hebert[3], Shehla Sheik[4] and Rae S.M. Yeung[1], [1]Division of Rheumatology, The Hospital for Sick Children, Toronto, ON, Canada, [2]Pediatrics/Alberta Children's Hospital, Department of Pediatrics/University of Calgary, Calgary, AB, Canada, [3]Division of Nephrology, The Hospital for Sick Children, Toronto, ON, Canada, [4]Research Institute, The Hospital for Sick Children, Toronto, ON, Canada
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Childhood Takayasu Arteritis – A Single Center Experience

Background/Purpose: Takayasu Arteritis is a large vessel vasculitis that rarely affects children. Data on childhood TA (cTA) are scarce.

Methods: A single-center retrospective review of all consecutive patients fulfilling the EULAR/PRINTO/PReS criteria for cTA between 1986 and 2015 was performed. Clinical, laboratory and imaging features at presentation, treatment and flares (new symptoms and/or increased inflammatory markers necessitating therapy escalation or new angiographic lesions after 2 months of inactive disease) were captured. Disease activity was retrospectively assessed by Paediatric Vasculitis Activity Score (PVAS), damage by Paediatric Vasculitis Damage Index (VDI). Active disease was defined as PVAS>1 and/or increased inflammatory markers not explained by other causes or active disease on imaging (new lesions, evidence of vessel wall inflammation); inactive disease was defined as a PVAS=0 and normal inflammatory markers or inactive disease on imaging. Outcome measurements included death, disease activity and VDI at last follow-up.

Results: Twenty-nine patients were identified; an overview and presenting features are shown in Table 1. Most frequently involved vessels were the abdominal aorta (86%), the renal (66%) and carotid arteries (55%). Data on induction treatment are presented in Table 2. Seven patients were considered in a non-inflammatory disease status at diagnosis and therefore not treated. Overall flare rate was 28%. Patients flared after a median of 12.5 months after diagnosis (range 9–73.7 months). Follow-up data were available for 27 patients with a median follow-up time of 2.1 years (range 0.2–11.7). At last follow-up median VDI was 4 (range 2–7); 48% of patients had active disease and 17% inactive disease while on treatment. Another 21% had inactive disease without treatment. Two children died within the first 6 months of diagnosis (mortality rate 7%).

Conclusion: In this cTA cohort mortality in early disease phase and relapse rate after induction treatment were high. At last follow-up half of the children had active disease. We observed a discrepancy between clinical (PVAS) and biochemical measures of disease activity, which has to be considered regarding treatment management.

Table 1: Demographic and presenting features of our cohort. Arterial hypertension = systolic/diastolic pressure >95th percentile for height. Blood pressure discrepancy >10mmHg in any of the four limbs. ESR: erythrocyte sedimentation rate, CRP: C-reactive protein, BP: blood pressure.

Patient characteristics	Patients (n = 29)
Female gender (%)	22 (75.8)
Median age at diagnosis in years (range)	12.4 (4.2 - 17.8)
Ethnicity (%)	
Caucasian	9 (31)
Asian	4 (13.7)
Black	3 (10.3)
Hispanic	2 (6.9)
East Indian / South Asian	2 (6.9)
Middle Eastern	2 (6.9)
First nation	2 (6.9)
Information not available	5 (17.2)
Co-Morbidity	
Tuberculosis	3 (10.3)
Inflammatory bowel disease	2 (6.9)
Presenting symptoms (%)	
Arterial hypertension	17 (58.6)
Malaise	14 (48.3)
Headache	11 (37.9)
Weight loss	9 (31.0)
Claudication (extremities)	6 (20.7)
Chronic nausea / vomiting	5 (17.2)
Back pain	5 (17.2)
Dizziness	7 (24.1)
Stroke / Transient ischemic attack	4 (13.8)
Abdominal pain	4 (13.8)
Shortness of breath	4 (13.8)
Findings on clinical exam (%)	
Blood pressure discrepancy	19 (65.5)
Pulseless disease	16 (55.2)
Bruits	15 (21.7)
Inflammatory markers	
Median ESR in mm/h (range)	34 (1 - 109)
Median CRP in dl/mg (range)	30.9 (0.5 - 140)
Median PVAS at diagnosis (range)	10 (4 - 35)

Table 2: Patients induced with corticosteroids and methotrexate (MTX)/cyclophosphamide/MTX+biologicals had higher biochemical disease activity at presentation, as reflected by increased ESR, CRP and platelet count. Median PVAS was similar within the groups.

Induction treatment	Number of patients (%)	Maintenance treatment (%)	Number of patients with flares after induction treatment (%)	Median PVAS at presentation (range)	Median ESR at presentation (range)	Median CRP at presentation (range)	Median platelets at presentation (range)
No treatment	7 (24)	Corticosteroids (14), no treatment (86)	0/7 (0)	10 (6 - 17)	1 (1 - 37)	0.6 (0.5 - 2.0)	289 (238 - 444)
Corticosteroids only	4 (14)	Azathioprin (25), MTX (25), Cyclo (25), no treatment (25)	2/4 (50)	16 (5 - 17)	34 (1 - 35)	3.3 (3.3)	283 (222 - 370)
Corticosteroids + MTX	9 (31)	MTX (78), Corticosteroids (11)*	3/9 (33)	11 (4 - 27)	60.5 (16 - 109)	30.9 (1 - 65)	373 (194 - 687)
Corticosteroids + Cyclophosphamide	6 (21)	MTX (33), Cyclo (17) +/- Corticosteroids (50), no therapy (17)**	3/6 (50)	10 (6 - 35)	48 (1 - 91)	69 (14.3 - 140)	536 (246 - 707)
Corticosteroids + MTX + biologicals	3 (10)	Corticosteroids, MTX + biologicals (100)	0/3 (0)	10 (6 - 25)	31 (17 - 105)	67.1 (14.5 - 111)	531 (291 - 593)

*1 patient had no 6-month follow-up.
**1 patient died during induction treatment, and 1 during the induction phase.

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Abstract Number: 3073

Patterns of Vascular Involvement in Childhood Takayasu Arteritis

Florence A. Aeschlimann[1], Simon Eng[2], Lars Grosse-Wortmann[3], Susanne Benseler[4], Ronald Laxer[1], Diane Hebert[5] and Rae S.M. Yeung[1], [1]Division of Rheumatology, The Hospital for Sick Children, Toronto, ON, Canada, [2]151 Beecroft Rd., Apt. 604, University of Toronto, Toronto, ON, Canada, [3]Divisyon of Cardiologz, The Hospital for Sick Children, Toronto, ON, Canada, [4]Pediatrics/Alberta Children's Hospital, Department of Pediatrics/University of Calgary, Calgary, AB, Canada, [5]Division of Nephrology, The Hospital for Sick Children, Toronto, ON, Canada

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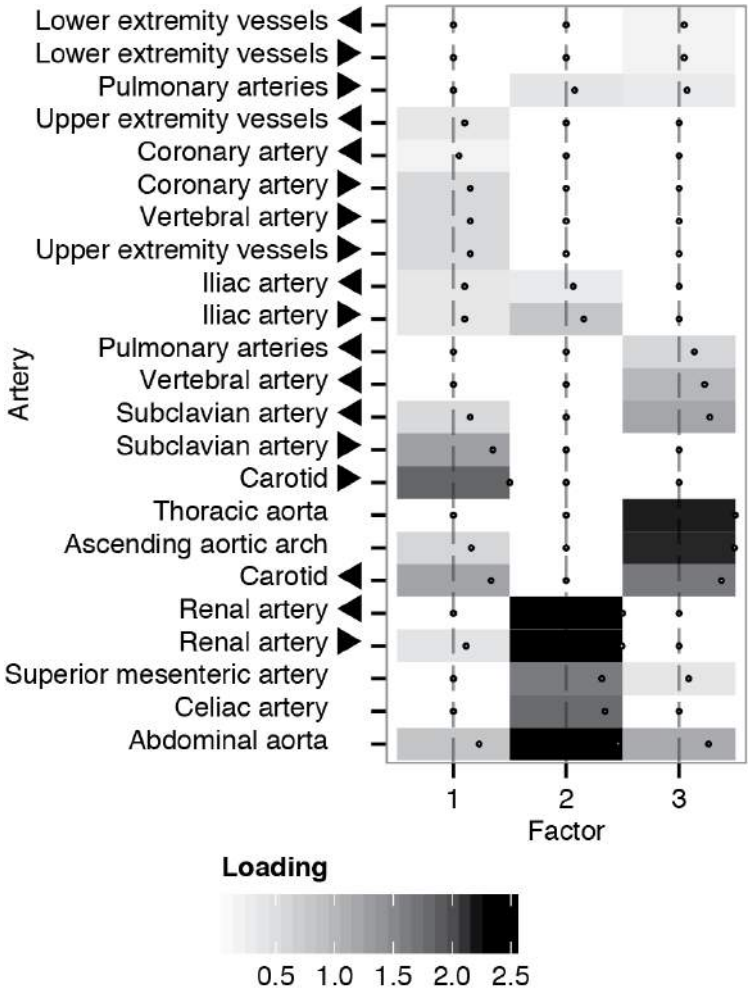
Background/Purpose: Takayasu arteritis (TA) is the most common large vessel vasculitis and may presents in childhood. Different angiographic classification systems based on adults with TA have been proposed. However, in clinical practice many children with TA do not fit into any of these classification categories. We sought to study the vascular involvement patterns in children with TA using unsupervised data-driven pattern recognition techniques to better characterize homogeneous subgroups of children with TA.

Methods: 29 children with TA were included from a single-center cohort. Non-negative matrix factorization (NMF) was conducted on baseline imaging data (MR angiography or conventional angiogram) to identify unique factors that distinguish between various types of vascular involvement in children. A feature of NMF is that the factors naturally give rise to clusters of children.

Results: NMF identified 3 factors and clusters characterized by the following distinct pattern of vessel involvement: (1) widespread vessel involvement including the aortic arch/ascending aorta, coronary artery, neck vessels, upper extremity vessels, abdominal aorta, renal and iliac arteries (7 patients); (2) the abdominal aorta its branches (coeliac trunk, superior mesenteric artery, bilateral renal) and the iliac arteries (14 patients); and (3) the entire aorta and its left-sided neck vessels (subclavian, carotid and vertebral artery), and involvement of the superior mesenteric and bilateral pulmonary arteries. The renal arteries are spared (8 patients).

Conclusion: Our data-driven, assumption-free analysis recovered unique patterns of vascular involvement that are distinct from the current adult-based angiographic classifications. These patterns may help to define homogeneous subgroups of children with TA and to guide the challenging management.

Figure 1: Contributions of individual arteries to factors. Shades of gray indicate the degrees to which individual arteries (y-axis) contribute to factors (x-axis). Shades nearer black indicate stronger contributions. Traces (lines represent 0 loadings and dots indicating absolute loadings) provide an alternative means of visualizing the loadings. Arrows indicate the side of body.



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Abstract Number: 3074

The Shared Rheumatoid Arthritis HLA-DRB1 Susceptibility Epitope Shapes the Molecular Orientation of Citrulline and the Autoreactive T Cell Receptor Repertoire

Jurgen van Heemst[1], Stephen Scally[2], Soi Cheng Law[3], Diane van der Woude[4], Carol Hitchon[5], David B. Robinson[6], T. W. J. Huizinga[7], Hugh H Reid[8], René E. M. Toes[7], Hani El-Gabalawy[9], Jamie Rossjohn[10] and **Ranjeny Thomas**[11], [1]Leiden University Medical Center, Leiden, Netherlands, [2]Monash University, Melbourne, Australia, [3]The University of Queensland Diamantina Institute, Translational Research Institute, Princess Alexandra Hospital, Brisbane, Australia, [4]Rheumatology, Leiden University Medical Center, Leiden, Netherlands, [5]University of Manitoba, Winnipeg, MB, Canada, [6]Arthritis Center, University of Manitoba, Winnipeg, MB, Canada, [7]Department of Rheumatology, Leiden University Medical Center, Leiden, Netherlands, [8]Department of Biochemistry and Molecular Biology, School of Biomedical Sciences, Monash University, Clayton, Melbourne, Australia, [9]University of Manitoba Arthritis Center, Winnipeg, MB, Canada, [10]Institute of Infection and Immunity, Cardiff University, School of Medicine, Heath Park, Cardiff, England, [11]Translational Research Institute, The University of Queensland Diamantina Institute, Brisbane, Australia

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Background/Purpose:

Large-scale genomic studies have identified many genetic associations with autoimmune diseases, but the precise pathogenetic mechanisms by which the associated genes impact disease susceptibility remain unclear in most cases. Furthermore, interpretations may be skewed by the ethnic mix of the samples. RA is linked to particular *HLA-DRB1* alleles. In the current understanding, based largely on studies of Caucasians, alleles associated with ACPA-positive RA share a conserved motif at amino acid positions 11, 13, 71 and 74 of DRβ termed the "shared susceptibility epitope (SE)". His/Phe13β is associated with ACPA-positive RA, while His13βSer polymorphisms are associated with ACPA-negative RA and RA-protection. Indigenous North American (INA) RA patients have a high prevalence of ACPA. In this population, *HLA-DRB1*04:04* and *14:02* are implicated as risk factors for RA. While *HLA-DRB1*04:04* has a typical SE His/Phe13β, *HLA-DRB1*14:02* unexpectedly has a His13βSer polymorphism. Therefore, we aimed to determine the molecular mechanism explaining the association of *HLA-DRB1*14:02*with ACPA+ RA in INA.

Methods: Competitive HLA-DR binding assays compared citrullinated and native vimentin peptide binding against HA(305-319) indicator peptide. HLA-DRB1*14:02 molecules with their class II-associated invariant peptide (CLIP) were expressed and purified, then loaded with Vimentin-64Arg(59-71) or Vimentin-64Cit(59-71), and the structure was solved using x-ray crystallography. Single CD4+ T cells were sorted from peripheral blood mononuclear cells (PBMC) of 5 HLA-DRB1*1402+ ACPA+ RA patients and 5 of their HLA-DRB1*1402+ ACPA+ non-RA first-degree relatives, based on staining with fluorescent vimentin-64Cit(59-71)-specific and vimentin(59-71)-specific pHLA tetramers. Paired TCRα/β chains were analyzed using multiplex, nested PCR and sequencing.

Results: In binding studies, HLA-DRB1*14:02 displayed no preference for citrulline residues in the P4 pocket. Structures of HLA-DRB1*14:02 complexed with Vimentin-64Arg(59-71) or Vimentin-64Cit(59-71) showed that both citrulline and arginine were accommodated in the P4-pocket of HLA-DRB1*14:02, in contrast to HLA-DRB1*0401/0404 where citrulline but not arginine was accommodated within the electro-positive P4-pocket. When bound to HLA-DRB1*04:01/04 or HLA-DRB1*14:02, citrulline was upright and TCR-exposed. In contrast, arginine was buried in the P4 pocket of HLA-DRB1*14:02. T cell receptor repertoires of citrullinated and native vimentin-sorted CD4+ T cells were distinct among PBMC of HLA-DRB1*14:02+ ACPA+ RA patients and relatives.

Conclusion:

Together, these findings based on SE alleles prevalent among Caucasians and INA suggest a new model for the *HLA-DRB1* association with ACPA+ RA, in which the SE shapes the molecular orientation of citrulline and thus the autoreactive citrulline-specific TCR repertoire required for the development of ACPA.

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Abstract Number: 3075

Salivary Gland FcRL4+ B-Cells Are a Potential Source of Progenitor Cells for MALT Lymphoma in Primary Sjögren's Syndrome

Erlin A. Haacke[1], Frans G.M. Kroese[2], Philip Kluin[3], Petra M. Meiners[4], Annie Visser[5], Fred K.L. Spijkervet[6] and Hendrika Bootsma[7], [1]Pathology, University Medical Center Groningen, Groningen, Netherlands, [2]Rheumatology and Clinical Immunology, University Medical Center Groningen, Groningen, Netherlands, [3]Department of Pathology and Medical Biology, UMCG Groningen, Groningen, Netherlands, [4]Oral and Maxillofacial Surgery, University Medical Center Groningen, University of Groningen, Groningen, Netherlands, [5]Rheumatology and Clinical Immunology, UMC Groningen, Groningen, Netherlands, [6]Oral and Maxillofacial Surgery, University Medical Center Groningen, Groningen, Netherlands, [7]Rheumatology and Clinical Immunology, University Medical Center Groningen, University of Groningen, Groningen, Netherlands
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Background/Purpose:

Patients with primary Sjögren's Syndrome (pSS) have an increased risk of non-Hodgkin's lymphoma, predominantly of the Mucosa Associated Lymphoid Tissue (MALT) type, which commonly occur in the parotid glands. MALT lymphomas in general, express Fc receptor-like 4 (FcRL4/IRTA1/CD307d)[1]. Normally FcRL4 is expressed on a very small subset of mucosa-associated B-cells. $FcRL4^+$B-cells might be closely related to the MALT lymphoma cells. Therefore, we assessed whether $FcRL4^+$B-cells are present in the inflamed salivary gland tissue of pSS patients, and whether these cells are targeted by biological therapy.

Methods:

Forty nine parotid gland MALT lymphomas, 30 parotid gland biopsies, 24 labial gland biopsies and parotid gland biopsies before and after treatment with rituximab (18 patients) or abatacept (15 patients), all obtained from pSS patients, were stained for FcRL4 expression. As control served parotid gland biopsies of 8 non-pSS sicca patients and 5 non-sicca patients. FcRL4 mRNA was isolated from 8 non-pSS sicca patients, 9 pSS patients and 11 pSS MALT lymphoma patients.

Results:

Nearly all (96%) parotid gland MALT lymphomas expressed FcRL4 (Fig. 1). Low numbers of $FcRL4^+$B-cells were detectable in parotid glands of most (90%) pSS patients. Intensely stained $FcRL4^+$B-cells were in close relation to lymphoepithelial lesions with some $FcRL4^+$B-cells within the surrounding infiltrate. Even lower numbers of $FcRL4^+$B-cells were discernible in the labial glands. Levels of FcRL4 were significantly increased in parotis gland tissue of pSS patients, compared to non-pSS sicca patients. These levels further increased significantly in pSS patients with MALT lymphomas in the parotid glands. Treatment with rituximab significantly reduced the number of $FcRL4^+$B-cells in the parotid glands, whereas abatacept treatment did not affect $FcRL4^+$B-cells in the glandular tissue (Fig. 2).

Conclusion:

$FcRL4^+$B-cells are found in the salivary glands of pSS patients and are likely the cells from which MALT lymphomas arise. The observation that $FcRL4^+$B-cells are enriched in the parotid glands may explain why MALT lymphomas preferentially develop in these glands. Our treatment studies reveal that $FcRL4^+$B-cells can be targeted by anti-CD20 therapy and that these cells are maintained in a CD28- independent manner.

References

1. Falini B. et al. IRTA1 is selectively expressed in nodal and extra nodal marginal zone lymphomas. *Histopathology*. 2012 Nov 61(5):930-41.

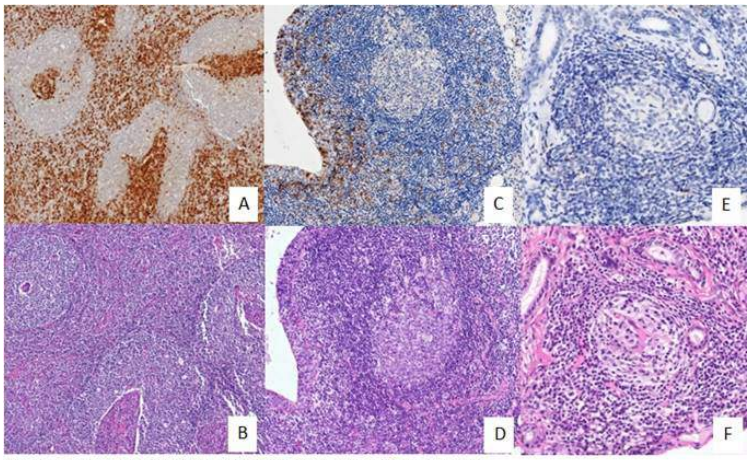

Figure 1. FcRL4⁺ cells in pSS patients: MALT lymphoma, parotid gland en labial gland.
(A) FcRL4⁺ MALT lymphoma in the parotid gland of a pSS patient. The FcRL4⁺ B-cells cluster in and around the lymphoepithelial lesions and the marginal zone. (B) Corresponding HE stain of MALT lymphoma. (C) FcRL4⁺ B-cells in the parotid gland of a pSS patient. FcRL4⁺ B-cells are in close association with the ductal epithelium. Less FcRL4⁺ B-cells are found in the infiltrate with lower intensity of the FcRL4 stain. (D) Corresponding HE stain of the parotid gland. (E) FcRL4⁺ B-cells in the labial gland of a pSS patient. Few FcRL4⁺ B-cells with low intensity are found despite inflammation. (F) Corresponding HE stain of the labial gland.

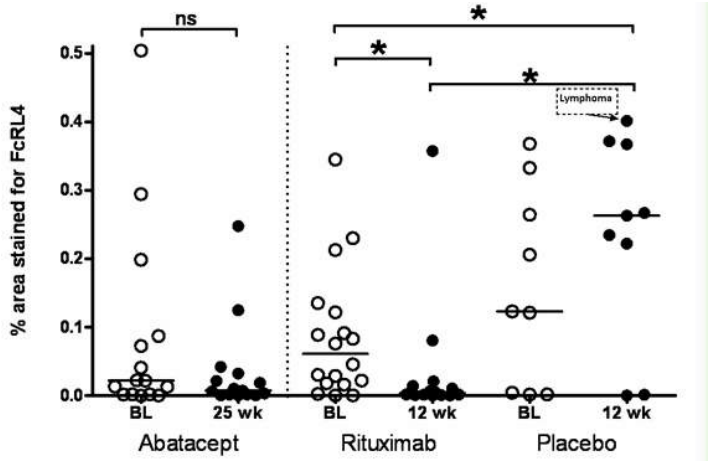

Figure 2: FcRL4 staining in pSS patient treated with abatacapt or Rituximab.
Amount of FcRL4 staining is reduced after Rituximab therapy in pSS patients. The placebo group of the rituximab study remained stable. Abatacept treatment of pSS patients did not effect the amount of FcRL4 staining. All biopsies were taken from the parotid gland. *Wilcoxon Signed Rank p<0.05

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Abstract Number: 3076

Interferon Gamma (IFNg) Is the Driving Mediator of Secondary Hemophagocytic Lymphohistiocytosis (sHLH) in TLR9-Mediated Pathogenesis in Mice and Is Correlated to Disease Parameters in Children

Cristina De Min[1], Vanessa Buatois[1], Laurence Chatel[1], Laura Cons[2], Francoise Richard[3], Claudia Bracaglia[4], Fabrizio De Benedetti[5], Marie Kosco-Vilbois[1] and Walter Ferlin[1], [1]NovImmune S.A., Geneva, Switzerland, [2]NovImmune S.A., Plan-Les-Ouates, Geneva, Switzerland, [3]NovImmune SA, Geneva, Switzerland, [4]Pediatric Medicine, Division of Rheumatology, Rome, Italy, [5]Division of Rheumatology, Department of Pediatric Medicine, IRCCS Ospedale Pediatrico Bambino Gesù, Rome, Italy

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Background/Purpose:

Life-threatening hyperinflammatory syndromes caused by severe hypercytokinemia include primary (p) and secondary (s) hemophagocytic lymphohistiocytosis (HLH). Increased circulating levels of interferon gamma (IFNg) in pHLH and sHLH patients suggest a central role for this cytokine in the development and maintenance of hypercytokinemia observed in HLH.

Methods:

C57BL/6 mice were injected i.p. on days 0, 2, 4, 7 and 9 with 50 µg of CpG-ODN 1826. Anti-mouse IFNg neutralizing mAb (XMG1.2) and rat IgG1 isotype-matched control mAb (mAb35) were injected intravenously at 100 mg/kg. Q-PCR was used to analyze inflammatory gene expression. Luminex multiplex technology was used to detect serum cytokines. Blood parameters were measured using a haematological counter. Serum concentrations of total IFNg were determined by an ELISA method developed for purpose. Serum samples were taken from 14 sHLH patients, with underlying infection demonstrated in 7 patients, (age at onset 8.6 years, interquartile range (IQR) 4.1-12.9 years; female 36%), seen at the Ospedale Pediatrico Bambino Gesù, Italy. All patients met the 2004-HLH diagnostic guidelines.

Results:

Using a model that mimics an infection-driven sHLH, TLR9 agonism resulted in a multi-phasic production of IFNg evidenced by a spike in serum cytokine levels following each CpG-ODN injection. Therapeutic blockade of IFNg reduced body weight loss, splenomegaly, normalized white blood cell counts, significantly reversed the decrease in other laboratory parameters (e.g. platelets, haemoglobin and red blood cells) and controlled hyperferritinemia. Our study reveals that total IFNg levels, originating within organs, are 500- to 2,000-fold higher than those present in blood. Expression of IFNg induced inflammatory genes demonstrated that spleen and liver are major sites of IFNg production. Furthermore, the IFNg signature gene products, CXCL9 and CXCL10, correlate with disease severity. In patients with sHLH, sampled during active full blown disease, levels of IFNg (median 34.7 pg/mL, IQR 23.9-170.1) and IFNg inducible chemokines (CXCL9: 33598 pg/mL, IQR 3083-127687; CXCL10; 4420 pg/mL, IQR 799-8226) were markedly higher than those of patients sampled during remission following effective treatment (IFNg <3.5 pg/mL, IQR <3.5-6.5; CXCL9: 745 pg/mL, IQR 469-1098; and CXCL10; 132 pg/mL, IQR 74-157). Similar to what was found in TLR9-induced sHLH in mice, IFNg levels significantly correlated with levels of CXCL9 and CXCL10. Furthermore, levels of IFNγ, as well as of CXCL9 and CXCL10, correlated with laboratory parameters of HLH including neutrophil and platelet counts, ferritin, LDH and ALT levels.

Conclusion:

IFNg production in the tissues is central to the hypercytokinemia causing the manifestations of the disease in mice following recurrent TLR9 repeated stimulation. Taken together with data in patients with sHLH, our observations demonstrate that IFNg appears to be the driving mediator of sHLH, support the role of CXCL9 and CXCL10 levels as a marker of the production of IFNg and indicate that the neutralization of IFNγ should be investigated as a therapeutic approach also in secondary forms of HLH.

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hemophagocytic-lymphohistiocytosis-shlh-in-tlr9-mediated-pathogenesis-in-mice-and-is-correlated-to-disease-parameters-in-children

Abstract Number: 3077

Anakinra in Patients with Cortico-Dependent Idiopathic Recurrent Pericarditis: A Randomised Double-Blind Placebo-Controlled Withdrawal Trial

Antonio Brucato[1], Massimo Imazio[2], Silvia Maestroni[1], Davide Faustino Cumetti[3], Anna Valenti[1], Renzo Marcolongo[4], George Lazaros[5], Mara Carraro[2], Fiorenzo Gaita[2], Gian Luca Erre[6], Martina Finetti[7], Marco Gattorno[7] and Alberto Martini[8], [1]Internal Medicine, Hospital Papa Giovanni XXIII, Bergamo, Italy, [2]Cardiology, Maria Vittoria Hospital, Torino, Italy, [3]Internal Medicine, Internal Medicine, Hospital Papa Giovanni XXIII, Bergamo, Italy, [4]Clinical Immunology, Hospital of Padova, Padova, Italy, [5]Department of Cardiology, Hippokration General Hospital, Athens, Greece, [6]Rheumatology, Hospital of Sassari, Sassari, Italy, [7]Pediatry, G. Gaslini Institute, Genova, Italy, [8]Istituto G. Gaslini, Pediatria II, PRINTO, and University of Genoa, Genoa, Italy
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Background/Purpose: Patients with recurrent pericarditis either do not respond or are intolerant to treatment with NSAIDs drugs, corticosteroids and colchicine. We aimed to assess the safety and efficacy of anakinra in patients with cortico-dependent idiopathic recurrent pericarditis.

Methods: We did a double-blind randomised controlled withdrawal trial between June2014 and June2015. We enrolled 21 patients aged 45.4 years (7 males) from 3 Italian centres, who had a history of idiopathic recurrent pericarditis with at least 2 previous recurrences, CRP elevation during recurrence (>1 mg/dL) and on therapy with corticosteroids. 20 adults patients took 100 mg of anakinra subcutaneously daily for 2 months, 1 child received 2 mg/kg/day. 11 patients were then randomly assigned to continue anakinra for additional 6 months or until a flare of the pericarditis and 10 were randomly assigned to receive placebo at the same dose and timing. Primary endpoint: time to flare of pericarditis. Flare was defined as recurrence of typical pain and CRP elevation. We analysed all patients who were treated as per protocol. The trial is registered (NCT02219828)

Results: Mean n° of recurrences in the patients before this study was 6.6 with a clinical history of recurrent pericarditis lasting 27.7 months on average. All patients completed successfully the open lead-in course with a complete response to the treatment, CRP normalization and discontinuation of all the other drugs. Flares of pericarditis occurred in all the 10 patients randomized to placebo and none of the 11 patients randomized to anakinra during the double-blind treatment ($p<0.0001$). Median time to flare of pericarditis was 48.2 days for patients given placebo; insufficient events had occurred in the anakinra group for median time to flare to be assessed ($p< 0.00001$). During study the frequency of adverse events differed in the two treatment groups. The most common side effect was a local reaction at the injection site, observed in 20 of 21 cases (95.2%) during the initial open-label phase; generally disappeared over one month, and only one patient discontinued the study for this side effect. Two serious events were reported, both in the anakinra treated patients ($p=0.47$): 1 patient developed skin herpes zoster during the open-label phase, 1 developed ischemic optic neuropathy at the fifth month of the double-blind period; she is a 70 years old woman, hypertensive and with hypercholesterolemia, but the exact mechanism of the optic neuropathy is debatable.

Conclusion: Inhibition of IL1 with anakinra is a rational alternative treatment for selected patients with severe cortico-dependent recurrent pericarditis and multiple failure of conventional therapies with colchicine.

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Abstract Number: 3078

ABCG2 rs2231142 predicts Poor Response to Allopurinol in Patients with Gout

Lisa K. Stamp[1], Mary Wallace[2], Tony R. Merriman[3], Amanda Phipps-Green[4], Ruth Topless[4,5], Jill Drake[6], Paul Tan[7], Nicola Dalbeth[8] and Rebecca Roberts[4], [1]Medicine, University of Otago, Christchurch, Christchurch, New Zealand, [2]Surgical Sciences, University of Otago, Dunedin, New Zealand, [3]Biochemistry Dept, PO Box 56, University of Otago, Dunedin, New Zealand, [4]University of Otago, Dunedin, New

Zealand, [5]Department of Biochemistry, University of Otago, Dunedin, New Zealand, [6]Rheumatology, Immunology and Allergy, Christchurch Hospital, Christchurch, New Zealand, [7]University of Auckland, Auckland, New Zealand, [8]Department of Medicine, University of Auckland, Auckland, New Zealand
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Background/Purpose: Many patients fail to reach target serum urate (SU) on allopurinol. Although the most common causes of inadequate response are non-adherence and low dosing in kidney disease, there are a group of adherent patients who fail to achieve target SU and can be considered poor responders to allopurinol. In patients who have undergone allopurinol dose escalation, poor response can be defined as failure to reach the recommended target SU of <6mg/dl on allopurinol ≤300mg/day. A recent GWAS identified the urate raising minor allele of *ABCG2 rs2231142* as a determinant of poor allopurinol response [1]. However, the definition of response used in the GWAS was allopurinol related SU change with only weak assessment of adherence. The aim of our study was to examine the association of *ABCG2 rs2231142* with allopurinol response in a well phenotyped group of patients with gout.

Methods: Patients with gout according to 1977 ARA criteria participating in clinical trials of allopurinol were recruited. Good response was defined as SU <6mg/dl on allopurinol ≤300mg/d and poor response was defined as SU ≥6mg/dl despite allopurinol >300mg/d. Adherence was assessed by plasma oxypurinol concentrations >20umol/l and in the absence of oxypurinol concentration SU reduction with allopurinol dose escalation. Genotyping for *ABCG2* (*rs2231142*) was performed using a pre-designed SNP TaqMan assay. Logistic regression analyses were used to test for an association between poor response to allopurinol and *rs2231142*. Adjustments were made for age, sex, body mass index (BMI) and ethnicity and further separate adjustments were made for eGFR, diuretic use and SU off urate lowering therapy.

Results : Of 264 patients with gout receiving allopurinol, 120 (45.4%) patients were good responders, 68 (25.8%) were poor responders and 76 (28.8%) were either non-adherent or could not be classified. Of the 188 patients included in the responder analysis, 85.6% were male, mean age was 59 years and 32% were receiving a diuretic. The mean BMI was 34.1 kg/m^2 and eGFR 55.5mls/min/1.72m^2. Mean SU prior to urate lowering therapy was 10.1 mg/dl. Mean SU was 5.2 mg/dl in good responders and 7.0mg/dl in poor responders. Mean allopurinol dose was 263 mg/d (100-300) in the good responders and 413 mg/d (350-700) in poor responders. Logistic regression found that the minor allele of *ABCG2 rs2231142* was significantly associated with poor response to allopurinol (Table; OR=2.9, P=1.5x10^{-4}). This association persisted after adjusting for eGFR, diuretic use and SU off ULT (Table).

Conclusion: This study demonstrates that *ABCG2 rs2231142* predicts poor response to allopurinol, as defined by SU ≥6mg/dl despite allopurinol >300mg/d. *ABCG2* genotyping may allow identification of people with gout for whom standard doses of allopurinol are unlikely to lead to therapeutic target serum urate levels.

1. Wen C, et al *Clin Pharm Ther* 2015, **97**(5):518-525.

Table: Association of *ABCG2* SNP rs2231142 with allopurinol response in patients with gout

	n	Genotype			MAF	Unadjusted OR (95%CI), P	OR (95%CI), P^a	OR (95%CI), P^b	OR (95%CI), P^c	OR (95%CI), P^d
		GG	GT	TT						
Poor responders	68	26 (0.38)	31 (0.46)	11 (0.16)	53 (0.38)	2.7 (1.70-4.48) $6.6x10^{-5}$	2.9 (1.70-5.17) $1.5x10^{-4}$	2.9 (1.69-5.17) $1.7x10^{-4}$	3.1 (1.77-5.59) $1.1x10^{-4}$	3.4 (1.83-6.63) $2.1x10^{-4}$
Good responders	120	81 (0.68)	34 (0.28)	5 (0.04)	44 (0.18)					

[a] P value adjusted by age, sex, BMI and ethnicity.
[b] P value adjusted by age, sex, BMI, ethnicity and eGFR.
[c] P value adjusted by age, sex, BMI, ethnicity and diuretic use.
[d] P value adjusted by age, sex, BMI, ethnicity and SU off urate lowering therapy.

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Abstract Number: 3079

Efficacy and Safety of Riociguat in Patients with Pulmonary Arterial Hypertension (PAH) Associated with Connective Tissue Disease (CTD)

Christopher P. Denton[1], J. Gerry Coghlan[2], Hossein-Ardeschir Ghofrani[3], Friedrich Grimminger[3], Jianguo He[4], Gabriela Riemekasten[5], Dario Vizza[6], Annette Boeckenhoff[7], Christian Meier[8], Janethe de Oliveira Pena[9] and Marc Humbert[10], [1]Centre for Rheumatology and Connective Tissue Disease, UCL Medical School Royal Free Campus, London, United Kingdom, [2]Royal Free London NHS Foundation Trust, London, England, [3]University of Giessen and Marburg Lung Center, Giessen, Germany, [4]Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China, [5]Clinic of Rheumatology and Clinical Immunology, Berlin, Germany, [6]La Sapienza University of Rome, Rome, Italy, [7]Bayer Pharma AG, Wuppertal, Germany, [8]Bayer Pharma AG, Berlin, Germany, [9]Bayer HealthCare Pharma, Whippany, NJ, [10]Université Paris-Sud, Laboratoire d'Excellence en Recherche sur le Médicament et Innovation Thérapeutique, and INSERM Unité 999, Le Kremlin–Bicêtre, France

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Background/Purpose:

PAH associated with CTD (PAH-CTD) has a worse prognosis than idiopathic/familial PAH. Here we report a prospective subgroup analysis of patients with PAH-CTD from the PATENT studies of the soluble guanylate cyclase stimulator, riociguat.

Methods:

PATENT-1 was a 12-week, randomized Phase III trial in which patients with PAH received either riociguat individually dose-adjusted up to 2.5 mg tid (2.5 mg–maximum group), riociguat up to 1.5 mg tid (1.5 mg–maximum group; exploratory), or placebo. The primary endpoint was change from baseline in 6-minute walking distance (6MWD). Long-term safety and survival were assessed during the PATENT-2 open-label extension.

Results:

In PATENT-1, 111 patients had PAH-CTD (systemic sclerosis [SSc; n=66, including diffuse SSc and limited SSc], non-SSc CTD [n=39], and unspecified CTD [n=6], derived post-hoc from the medical history using MedDRA preferred terms). Seventy PAH-CTD patients were pretreated with PAH-specific therapy, of whom 59 were receiving endothelin receptor antagonists. Of the overall group of PAH-CTD patients, 71, 15, and 25 were randomized to riociguat 2.5 mg–maximum, riociguat 1.5 mg–maximum, and placebo, respectively. At baseline, mean±SD 6MWD was 348±70 m in the riociguat 2.5 mg–maximum group and 361±88 m in the placebo group. At Week 12, there was an improvement in 6MWD in the 2.5 mg–maximum riociguat group (+18 m) and a deterioration in the placebo group (–8 m) (Figure 1; PAH-CTD population; intention-to-treat, imputed values). Consistent with other studies, the least-squares mean treatment difference between riociguat and placebo (+28 m) in patients with PAH-CTD was lower than that observed in the overall study population (+36 m). In the SSc subgroup the placebo-corrected mean treatment difference in change from baseline was mostly based on the deterioration in exercise capacity on placebo (Figure 1). At the March 2014 cut-off for PATENT-2, 70 patients with PAH-CTD had been receiving treatment for ≥2 years. In PATENT-2, efficacy in 6MWD was maintained over 2 years in patients with PAH-CTD receiving riociguat. Clinical worsening events were experienced by <30% of patients with PAH-CTD in the PATENT-2 study, with a higher rate of events occurring in the SSc subcategory, which was driven by patients needing to start new PAH-specific treatments. At 2 years, similar survival rates (95% CI) were observed for patients with PAH-CTD, SSc, idiopathic/familial PAH and the overall population: 93% (85–97%), 94% (82–98%), 93% (89–96%), and 93% (90–95%), respectively. Riociguat had a similar safety profile in patients with PAH-CTD as observed in the overall population.

Conclusion:

In patients with PAH-CTD, riociguat was associated with long-term improvements in exercise capacity. The 2 year survival rates in riociguat-treated patients with PAH-CTD were high and similar to patients with idiopathic/familial PAH.

Disclosure: C. P. Denton, GlaxoSmithKline, 2,Actelion Pharmaceuticals US, 5,GlaxoSmithKline, 5,Serono, 5,Inventiva, 5,CSL Behring, 2,Bayer, 5; **J. G. Coghlan**, None; **H. A. Ghofrani**, Novartis, Pfizer, 5,Novartis, Pfizer, 8; **F. Grimminger**, None; **J. He**, None; **G. Riemekasten**, None; **D. Vizza**, Bayer Pharma AG, Actelion, GSK, Utel, 5,Actelion, Novartis, GSK, Bayer Pharma AG, Gilead, 2,Bayer Pharma AG, Actelion,

GSK, Utel, 8; **A. Boeckenhoff**, Bayer Pharma AG, 3; **C. Meier**, Bayer Pharma AG, 3; **J. de Oliveira Pena**, Bayer HealthCare Pharmaceuticals Inc., 3; **M. Humbert**, Actelion, Bayer, GSK, Novartis, Pfizer, 5,Actelion, Bayer, GSK, Novartis, Pfizer, 8.

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Abstract Number: 3080

Histone H2AX Phosphorylation As a Measure of DNA Double Strand Breaks and a Marker of Environmental Stress and Disease Activity in Lupus

Rajaie Namas, Paul Renauer, Mikhail Ognenovski, Pei-Suen Tsou and Amr H. Sawalha, Division of Rheumatology, University of Michigan, Ann Arbor, MI

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Background/Purpose: Studies suggested that defective or inefficient DNA double strand break (DSB) repair results in failure to preserve genomic integrity leading to apoptotic cell death, a hallmark of lupus. Compelling evidence linked environmental factors that increase oxidative stress with lupus risk and the formation of DSBs. Histone H2AX is robustly phosphorylated in the chromatin micro-environment at DSB loci resulting in the accumulation of essential repair proteins. The aim of this study is to measure DSB levels as a marker linking the effect of environmental stressors and the chromatin micro-environment in lupus.

Methods: Peripheral-blood mononuclear cells were isolated by Ficoll-Paque density gradient centrifugation from lupus patients and age-, sex-, and ethnicity-matched healthy controls. Flow cytometry using intracellular staining was used to measure H2AX phosphorylation levels in monocytes, CD4+ T cells, and CD8+ T cells. Median fluorescence intensity of anti-phospho-H2AX represents relative accumulation of DSBs within cells. Propidium iodide DNA staining was simultaneously used to assess cell cycle phase. A dose and time-effect relationship of hydrogen peroxide (H_2O_2) exposure, as an extrinsic environmental stressor, on the formation of DSBs was studied. Statistically significant differences ($P < 0.05$) between patients and controls were determined using a two-tailed *t*-test, and correlation analysis with lupus disease activity as measured by SLEDAI was assessed by Pearson's correlation coefficient.

Results: We observed increased DSBs in monocytes, CD4+ T cells, and CD8+ T cells in lupus patients compared to healthy controls (P=0.0008, 0.001, and 0.001, respectively). This difference in DSBs between patients and controls was independent of the cell cycle phase. A significant positive correlation between DSB accumulation and SLEDAI scores was observed among lupus patients (CD4+ T cells: r^2= 0.64, P= 0.03; CD8+ T cells: r^2= 0.64, P= 0.009; Monocytes: r^2= 0.57, P= 0.01). SLEDAI also correlated positively with DSB in lupus patients during all cell cycle phases in T cells and monocytes. A time-dependent effect (0, 2, 5, 10, 30 and 60 min, n=4) of 0.5uM H_2O_2 revealed a significant increase of DSBs with time in both patients and controls in all cell types, and a significantly greater accumulation of DSBs in lupus CD4+ T cells compared to healthy controls. A similar trend was also observed in lupus CD8+T cells and monocytes.

Conclusion: Our data indicate that DSBs occur more frequently and independent of the cell cycle in lupus monocytes and T cells compared to controls, and that accumulation of DSBs in lupus correlates with disease activity. Further, lupus T cells are more sensitive and accumulate more DSBs upon exposure to extrinsic oxidative stress compared to healthy T cells.

Disclosure: R. Namas, None; **P. Renauer**, None; **M. Ognenovski**, None; **P. S. Tsou**, None; **A. H. Sawalha**, None.

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Abstract Number: 3081

IRF5 Deletion Prevents the SLE-like Disease Initiated By Dendritic Cell-Specific Loss of Caspase 8

Carla M. Cuda[1] and Harris R. Perlman[2], [1]Rheumatology, Northwestern University, Chicago, IL, [2]Feinberg School of Medicine, Northwestern University, Chicago, IL

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Background/Purpose: Previous studies implicate dendritic cells (DCs) in the initiation and persistence of systemic lupus erythematosus (SLE). While DCs from SLE patients exhibit elevated activation, the factors responsible remain unknown. Gain-of-function polymorphisms in the transcription factor IRF5 have been linked to SLE susceptibility. Moreover, mice with an underlying defect in Fas (MRL/lpr) on an IRF5-deficient background were protected from disease. We have shown that DC-specific loss of caspase 8, an enzyme in the Fas pathway classically linked to apoptosis initiation and necroptosis suppression, induces a SLE-like disease that originates from heightened DC activation. Immune complexes containing self nucleic acids activate endosomal TLRs, which require the adaptor MyD88 for subsequent up-regulation of proinflammatory gene expression, in part through the action of IRF5. The increased activation of caspase 8-deficient DCs is controlled by a MyD88-dependent mechanism, as DC-specific loss of MyD88 reduces disease, and caspase 8-deficient DCs display a hyperresponsiveness to endosomal TLR ligation with increased DNA binding activity of IRF. To this end, we have examined the interaction between DC-specific caspase 8 and IRF5 in disease development.

Methods: Mice lacking caspase 8 specifically in DCs were generated ($Cre^{CD11c}Casp8^{flox/flox}$) and crossed with $IRF5^{flox/flox}$ mice ($IRF5^{flox/flox}Cre^{CD11c}Casp8^{flox/flox}$). Flow cytometric analysis was used to characterize cell populations. ELISA and Luminex bead-based assays detected serum antibody and cytokine levels. Immunohistochemical and immunofluorescent analyses were used to evaluate spleen and kidney pathology.

Results: $Cre^{CD11c}Casp8^{flox/flox}$ develop a SLE-like disease characterized by splenomegaly, lymphadenopathy, autoantibodies, elevated serum cytokines, glomerulonephritis, immune complex deposition in the kidney and proteinuria. Further, caspase 8-deficient DCs are highly activated, leading to lymphocyte hyperactivation in a paracrine manner. Moreover, we observe a disruption of the splenic architecture in $Cre^{CD11c}Casp8^{flox/flox}$ mice, with a severe reduction in the marginal zone and metallophilic macrophage populations. Strikingly, DC-specific deletion of IRF5 in $Cre^{CD11c}Casp8^{flox/flox}$ mice prevents development of nearly all of the above inflammatory phenotypes.

Conclusion: Our previous studies showed that DC-specific loss of MyD88 reduced SLE-like disease pathogenesis associated with DC-specific deletion of caspase 8. We now reveal that deletion of IRF5 in caspase 8-deficient DCs inhibits onset of almost all SLE-like disease phenotypes observed in $Cre^{CD11c}Casp8^{flox/flox}$ mice. These data substantiate a novel DC-specific mechanism whereby caspase 8 interacts withand regulates the action of MyD88 and IRF5 to control DC activation and subsequent autoimmune disease development, thereby highlighting potentially useful targets for therapy.

Disclosure: C. M. Cuda, None; **H. R. Perlman**, None.

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Abstract Number: 3082

Nanogel Based Delivery of an Inhibitor of Calcium/ Calmodulin- Dependent Protein Kinase 4 Suppresses Experimental Autoimmune Encephalomyelitis and Lupus-like Disease in Mice

Kotaro Otomo[1], Tomohiro Koga[2], Nobuya Yoshida[3], Masayuki Mizui[4], Christina Kriegel[5], Tarek Fahmy[6] and George C. Tsokos[3], [1]Rheumatology, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, [2]Department of Rheumatology, Unit of Translational Medicine, Graduate School of Biomedical Sciences, Nagasaki University, Nagasaki, Japan, [3]Division of Rheumatology, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, [4]Department of Nephrology, Osaka University Graduate School of Medicine, Osaka, Japan, [5]Department of Biomedical Engineering, Yale University, New Heaven, CT, [6]Biomedical and Chemical Engineering, Yale University, New Heaven, CT

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Background/Purpose: Treatment of autoimmune diseases is still based on the use of general immunosuppressive drugs which invariably cause severe side effects. This fact has compelled searches for more specific or targeted delivery of drugs. Calcium/ calmodulin- dependent protein kinase IV (CaMK4) is involved in the suppression of IL-2 and enhancement of IL-17 production and its pharmacologic or genetic inhibition limits disease progression in lupus-prone mice and mice subjected to experimental allergic encephalomyelitis (EAE).

Methods: EAE and lupus prone (MRL/lpr) mice were treated with KN93 (an inhibitor of Camk4)- loaded nanolipogels (nlg) targeted into CD4+ cells, and analyzed for immunologic and clinical.

Results: KN93 delivered with nlg directly to CD4+ cells at an equivalent of one twentieth of the dose required systemically, is clinically equally effective for both lupus and EAE. Specific delivery of the CaMK4 inhibitor did not deplete T cells and did not suppress autoantibody production but it effectively blocked Th17 cell expansion in the spinal cord and the kidney of mice developing EAE or lupus respectively.

Conclusion: Inhibition of molecules proven to be involved in the expression of autoimmunity only in relevant cells is a highly promising way to advance treatment in autoimmune diseases.

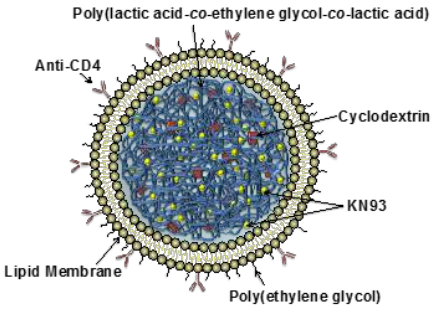

Figure 1. The schema of the structure of KN93 loaded nanolipogels (nlg) used in this work.

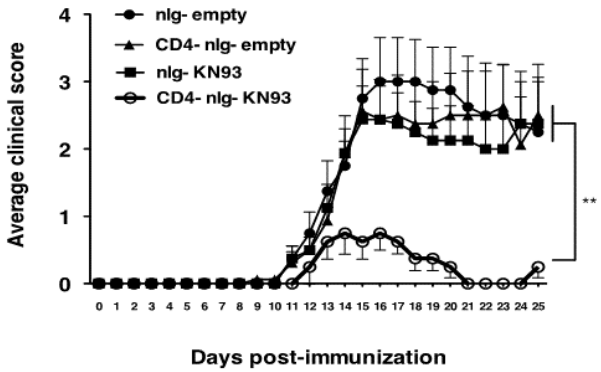

Figure 2. Average clinical score of the mice treated with nlg- empty, anti CD4 antibody coated nlg- empty (CD4- nlg- empty), nlg- KN-93 and CD4- nlg- KN-93 on EAE model (n = 8 mice in each group). The each nlg were injected weekly. Error bars represent the mean ± SEM. **P<0.01 by 2way ANOVA.

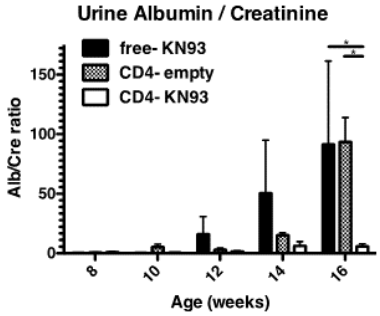

Figure 3. The mean ratio of urine albumin and creatinine from the MRL/lpr mice treated with free- KN-93, anti CD4 antibody coated nlg- empty (CD4- empty) and anti CD4 antibody coated nlg- KN93 (CD4- KN-93) (n = 4 mice in each group. Urine samples were obtained biweekly and determined by albumin and creatinine ELISA. Error bars represent the mean ± SEM. *P<0.05 by 2way ANOVA.

Disclosure: K. Otomo, None; **T. Koga**, None; **N. Yoshida**, None; **M. Mizui**, None; **C. Kriegel**, None; **T. Fahmy**, None; **G. C. Tsokos**, None.

Abstract Number: 3083

Antibody Array Based Proteomic Screening of 274 Serum Markers in Systemic Lupus Erythematosus

Tianfu Wu[1], **Huihua Ding**[2], Cristina Arriens[3], Chungwen Wei[4], Jennifer H. Anolik[5], David R. Karp[3], Nancy J. Olsen[6], Michelle Petri[7], Ignacio Sanz[4], Ramesh Saxena[8] and Chandra Mohan[2], [1]Department of Biomedical Engineering, University of Houston, Houston, TX, [2]Biomedical Engineering, University of Houston, Houston, TX, [3]Internal Medicine - Rheumatic Diseases, University of Texas Southwestern Medical Center, Dallas, TX, [4]Rheumatology, Emory University, Atlanta, GA, [5]University of Rochester Medical Center, Rochester, NY, [6]Divsion of Rheumatology, Department of Medicine, Penn State MS Hershey Medical Center, Hershey, PA, [7]Rheumatology, Johns Hopkins University Hospital, Baltimore, MD, [8]Nephrology, University of Texas Southwestern Medical Center, Dallas, TX

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Background/Purpose:

Given that early detection of renal involvement in systemic lupus erythematosus (SLE) and prompt management of the disease can have a significant impact on disease outcome, accurate diagnosis of lupus nephritis (LN) becomes absolutely critical. The current gold standard is to perform a renal biopsy in order to assess renal pathology. However, this procedure cannot be repeated serially, and is associated with untoward side-effects. Hence, there is an urgent need to identify biomarkers of LN that enable early detection of this disease.

Methods:

We have used serum samples from 22 SLE patients and matched healthy controls to hybridize to antibody-coated glass slide arrays that interrogated the level of 274 human proteins. Based on these screens, promising markers were further validated using single ELISA assays in independent cohorts of serum samples from lupus patients.

Results:

Whereas AXL, ferritin and sTNFRII were significantly elevated in patients with active LN relative to SLE patients who were quiescent, other molecules such as OPN, sTNFRI, sTNFRII, IGFBP2, SIGLEC5, FAS and MMP10 exhibited the capacity to distinguish SLE from healthy controls with ROC AUC exceeding 90%, all with $p<0.001$ significance.

These serum markers were next tested in a cohort of 45 LN patients where serum was obtained at the time of renal biopsy. In these patients, sTNFRII exhibited the strongest correlation with eGFR ($r=0.50$, $p=0.0014$) and serum creatinine ($r=0.57$, $p=0.0001$), though AXL, FAS, and IGFBP2 were also correlated with these clinical measures of concurrent nephritis. When concurrent renal biopsies from these patients were examined, serum FAS, IGFBP2 and TNFRII showed significant positive correlations with renal pathology activity index , while sTNFRII displayed the highest correlation with concurrently scored renal pathology chronicity index ($r=0.57$, $p=0.001$).

Finally, in a longitudinal cohort of 7 SLE patients examined at ~3-monthly intervals, AXL, ICAM-1, IGFBP2, SIGLEC5, sTNFRII and VCAM1 demonstrated the ability to track with concurrent disease flare, with significant subject to subject variation. To sum,

Conclusion:

Collectively, these studies suggest that serum levels of AXL, FAS, ferritin, ICAM-1, IGFBP2, SIGLEC-5 and sTNFRII are potential indicators of active LN and/or concurrent renal pathology indices or disease flares, worthy of further validation studies.

Disclosure: T. Wu, None; **H. Ding**, None; **C. Arriens**, None; **C. Wei**, None; **J. H. Anolik**, None; **D. R. Karp**, None; **N. J. Olsen**, None; **M. Petri**, None; **I. Sanz**, None; **R. Saxena**, None; **C. Mohan**, None.

Abstract Number: 3084

Progression of Lupus Pathology Is Correlative with Cardiac Magnetic Resonance Imaging Abnormalities, Diminished Function, and Inflammatory Histopathology in an Animal Model

Nicholas Young[1], Jeffrey Hampton[1], Saba Aqel[1], Jessica Pyles[2], Anna Bratasz[2], Anuradha Kalyanasundaram[3], Wael N. Jarjour[4] and Stacy P. Ardoin[5], [1]Immunology and Rheumatology, The Ohio State University Medical Center, Columbus, OH, [2]Small Animal Imaging Core, The Ohio State University Medical Center, Columbus, OH, [3]Physiology and Cell Biology, The Ohio State University Medical Center, Columbus, OH, [4]Department of Internal Medicine, Division of Immunology and Rheumatology, The Ohio State University Medical Center, Columbus, OH, [5]Pediatric & Adult Rheumatology, Ohio State University, Columbus, OH

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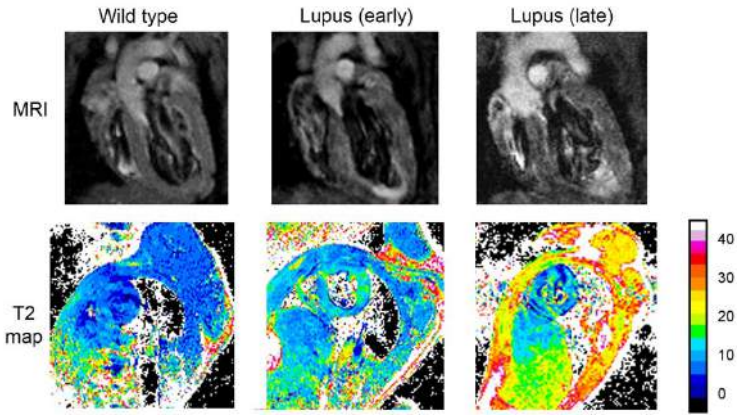
Background/Purpose: Systemic lupus erythematosus (SLE) is an autoimmune disease causing inflammation throughout the body and cardiovascular involvement is a significant contributor to morbidity and mortality in this patient population. We have previously identified data demonstrating impaired left ventricular function using cardiac magnetic resonance (CMR) with quantitative T2 mapping in patients with SLE during a flare, which is suggestive of subclinical myocardial inflammation. With the early stages of cardiac disease clinically silent, understanding the underlying pathogenic contributions of autoimmune-mediated inflammation would enable more effective therapeutic intervention. Thus, the objective of this study was to establish a T2 mapping protocol in an animal model of lupus to examine cardiac function longitudinally in order to better understand the pathobiology of SLE on cardiovascular disease.

Methods: Kidney function was assessed by weekly blood urea nitrogen (BUN) testing in NZM2410 mice, which develop severe lupus-like glomerulonephritis at 22-40 weeks of age. Quantitative analysis of *in vivo* physiological cardiac function was performed using a high-frequency ultrasound system. Myocardial edema was quantitatively measured *in vivo* with T2 CMR mapping on the BioSpec 94/30 microMRI imaging system. Heart tissue was collected for H&E and Masson's trichrome staining.

Results: For comparative analysis in this study, wild-type mice were examined along with NZM2410 mice with early-stage or late-stage lupus, as determined by weekly monitoring of BUN levels. Echocardiograms revealed differences in cardiac output, diameter, ejection fraction, fractional shortening, and stroke volume, which indicates decreased cardiac function in late-stage NZM2410 mice. CMR analysis of sagittal heart sections showed progressive thickening of the myocardium with a prominent left ventricular hypertrophy. T2 CMR mapping showed prolonged T2 signals, consistent with edema, in early and late stage lupus hearts compared to wild type mice. To examine histopathology, heart tissue was collected from early and late-stage NZM2410 mice for staining with H&E and Masson's trichrome. Evidence of myocarditis and fibrosis was observed in mice with late-stage disease.

Conclusion: Our results suggest an association of SLE disease progression with the development of cardiac abnormalities resulting from inflammation in NZM2410 mice. Therefore, this animal model could be used to further characterize the pathophysiological correlation, relationship, and interplay between lupus and cardiovascular disease in longitudinal studies. Future work will involve identification of biomarkers related to cardiac involvement and will further develop CMR with quantitative T2 mapping as a clinical tool to assess inflammation in patients with SLE.



Disclosure: N. Young, None; **J. Hampton**, None; **S. Aqel**, None; **J. Pyles**, None; **A. Bratasz**, None; **A. Kalyanasundaram**, None; **W. N. Jarjour**, None; **S. P. Ardoin**, None.

Abstract Number: 3085

Platelet Activation and Endothelial Reactivity in the Pathogenesis of Tissue Inflammation/Injury in Systemic Lupus Erythematosus

Robert Clancy[1], Sokha Nhek[2], Jonathan Newman[3], Janet Nwaukoni[1], Sara Rasmussen[4], Jill P. Buyon[1], Maya Rubin[5], Kristen Lee[1] and Jeffrey Berger[5], [1]Medicine, Division of Rheumatology, New York University School of Medicine, New York, NY, [2]New York University School of Medicine, New York, NY, [3]Medicine, New York University School of Medicine, New York, NY, [4]Department of Medicine, Division of Rheumatology, New York University School of Medicine, New York, NY, [5]Medicine, Division of Cardiology, New York University School of Medicine, New York, NY

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Background/Purpose: Patients with systemic lupus erythematosus (SLE) are at increased risk for widespread endothelial dysfunction, vascular thromboses, and premature cardiovascular disease. Enhanced platelet activation and interaction with the vascular endothelium may represent a common predisposition. This study was initiated to evaluate platelet phenotype and effect on endothelial cell function in SLE and healthy subjects.

Methods: Platelet phenotype was assessed using assays of platelet aggregation and markers of platelet activity in 50 SLE patients (mean age 41.1 ± 13.0, 81% female and 46% white) and age/sex matched healthy controls off antiplatelet therapy. SLEDAI ranged from 0 to 22 (mean 5.3 ± 4.0). Serum was collected for circulating soluble P-selectin and RANTES (chemokines from activated platelets). Agnostic (array) and candidate (qPCR) gene transcripts were identified following cotreatment of resting and thrombin-stimulated platelets from SLE patients and controls with normal endothelial cells (HUVECs).

Results: Compared to healthy controls, SLE patients had increased monocyte platelet aggregation, leukocyte platelet aggregation, light transmission platelet aggregation both with and without submaximal ADP, collagen, and arachidonic acid ($P<0.05$ for each comparison). Platelet activation did not associate with any ACR criteria or concomitant SLEDAI. However, patients with active renal disease compared to those without renal disease had significantly higher values of both sP-selectin (37.0 ± 18.6 ng/ml vs 20.6 ± 13.7, P=0.01) and RANTES (45.2 ± 13.7 ng/ml vs 29.9 ± 7.6, P=0.03) reflecting in vivo platelet activation. Predicted by serum levels, in ex vivo experiments using healthy platelets, SLE sera increased P-selectin expression (35.9%±8.6 vs. 28.0%±7.0, SLE vs control, $P<0.01$). Based on agnostic RNA array on HUVECs incubated with resting platelets from SLE vs healthy controls, endothelial adhesion molecules SELE, VCAM1, ICAM1, and cytokine IL8 and chemokine CXCR7, were among the top ten upregulated genes. KLF2 (0.69 + 0.02), a repressor of NFkB transcription factor was attenuated compared with CD146, a pan endothelial cell marker, 1.04 +0.08, p=0.034). Decreased expression of genes encoding proteins with immunomodulatory function including HMOX1, PROCR, HDAC5, and CALML4 were also noted following incubation of SLE platelets compared to controls. Validation by qPCR confirmed that cotreatment of HUVECs with resting platelets from SLE vs controls resulted in a mean fold increase in IL-8 gene expression (12.46 ± 2.55 (SE) and 4.23 ± 0.74, respectively, $P<0.01$) and ICAM-I (3.02 ± 0.5 vs. 1.31 ± 0.3, P =0.02). ICAM1 gene expression trended higher in patients with SLEDAI >4 compared to those with SLEDAI ≤4 (3.42 ± 0.7 vs 2.25 ± 0.19 , P=0.09).

Conclusion: Platelet activity measurements are increased in SLE, irrespective of accompanying disease activity which supports observations that premature atherosclerosis is not fully explained by overt clinical activity. Platelets from subjects with SLE increase pro-inflammatory gene expression by endothelial cells, suggesting a role for the platelet-endothelial interface in the pathogenesis of the more insidious vascular manifestations of disease.

Disclosure: R. Clancy, None; **S. Nhek**, None; **J. Newman**, None; **J. Nwaukoni**, None; **S. Rasmussen**, None; **J. P. Buyon**, None; **M. Rubin**, None; **K. Lee**, None; **J. Berger**, None.

Abstract Number: 3086

The Same Multidimensional Patient Health Assessment Questionnaire Used to Assess RAPID3 in Rheumatoid Arthritis, Osteoarthritis and Other Rheumatic Diseases Can Provide Quantitative Clues to Recognize and Document Comorbid Fibromyalgia

Kathryn A. Gibson[1], Annie Huang[2] and Theodore Pincus[2], [1]Liverpool Hospital, Liverpool, Australia, [2]Rheumatology, Rush University Medical Center, Chicago, IL

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SESSION INFORMATION

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Session Title: Fibromyalgia: Clinical Issues

Session Type: ACR Concurrent Abstract Session

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Background/Purpose: An MDHAQ/RAPID3 (Multidimensional Health Assessment Questionnaire/Routine Assessment of Patient Index Data) is a 2 sided, 1 page questionnaire which is completed by patients in 5-10 minutes, while waiting to see the doctor in the waiting room in routine clinical care. RAPID3 is an index which is informative in RA and other rheumatic diseases. MDHAQ also includes a 0-10 visual analog scale for fatigue and a 60 symptom checklist, which may provide clues to recognize comorbid fibromyalgia (FM) (1). Comorbid FM is seen in about 10-25% of patients with RA and may complicate assessment and management. Formal criteria for fibromyalgia are included in many research studies, but generally are not assessed in busy clinical settings, in which primary or secondary FM generally is diagnosed according to "gestalt," narrative, non-quantitative descriptions. A simple quantitative tool to recognize and document clues to comorbid FM could be of value in routine care in busy clinical settings.

Methods: MDHAQ is completed by all patients seen by a rheumatologist in routine care. MDHAQ includes scores for physical function (0-10), pain (0-10), patient global assessment (0-10), RAPID3 (0-30 sum of physical function, pain, and patient global estimate), fatigue (0-10), and total number of symptoms (0-60). Mean MDHAQ scores were compared in patients with primary diagnoses of either RA or osteoarthritis (OA) who did or did not have a secondary diagnosis of comorbid FM. Statistical significance of differences in patients with no FM vs with comorbid FM was analysed using 2-tailed t-tests, with significance at $p<0.05$.

Results: A total of 82 RA patients – 75 with no FM and 7 with FM, and 64 OA patients - 49 with no FM and 15 with FM, were studied (Table). The mean number of symptoms reported by patients with a clinical diagnosis of FM was significantly higher than reported by those who did not have secondary FM - RA 19.5 vs 7.97 P=0.0001; OA 19.5 vs 8.3 P<0.0001. The mean fatigue scores of patients with and with no secondary FM also differed significantly - RA 6.8 vs 3.86 P=0.004; OA 6.39 vs 3.82 P=0.0049. The mean physical function, pain, patient global estimate and RAPID3 scores did not differ significantly between patients with and with no secondary FM in either diagnostic group.

Conclusion: MDHAQ scales for fatigue and number of symptoms, which are found on the questionnaire to assess RAPID3 in patients with rheumatic diseases as part of routine clinical care, can provide clues to identify comorbid FM. Recognition and documentation of comorbid FM in patients with primary RA or OA may support the complexity of rheumatology visits and assist in management decisions in busy clinical settings.

Reference: **1)** DeWalt DA, et al. Clin Exp Rheumatol. 2004;22(4):453-61.

Table: Mean MDHAQ/RAPID3 scores reported by patients with rheumatoid arthritis and osteoarthritis who had or did not have secondary fibromyalgia

	N	Physical Function	Pain	Patient Global Estimate	RAPID3	Fatigue	Number of Symptoms
Rheumatoid arthritis with no comorbid fibromyalgia	75	2.02	4.79	4.05	10.00	3.86	7.97
Rheumatoid arthritis with comorbid fibromyalgia	7	3.00	5.14	5.43	14.10	6.80	19.50
p value		0.23	0.72	0.19	0.16	0.004	0.0001
Osteoarthritis with no comorbid fibromyalgia	49	3.33	5.80	5.20	14.10	3.82	11.40
Osteoarthritis with comorbid fibromyalgia	15	3.50	7.03	6.30	16.80	6.39	21.07
p value		0.75	0.09	0.17	0.07	0.005	0.0011

Disclosure: K. A. Gibson, None; **A. Huang**, None; **T. Pincus**, Health Report Services, Inc, 4.

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Abstract Number: 3087

Cell Bound Complement Activation Products in Multianalyte Assay with Algorithm Have Utility in Distinguishing Primary Fibromyalgia from Systemic Lupus Erythematosus

Daniel Wallace[1], Stuart L. Silverman[2], Derren Barken[3], John Conklin[4] and Thierry Dervieux[5], [1]Cedars-Sinai/UCLA, Los Angeles, CA, [2]OMC Clinical Research Center, Beverly Hills, CA, [3]Exagen Diagnostics, Vista, CA, [4]1261 Liberty Way Suite C, Exagen Diagnostics, Vista, CA, [5]Research and Development, Exagen Diagnostics, Vista, CA

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Background/Purpose : Our objective was to prospectively establish the performance characteristics of a cell bound complement activation products (CB-CAPS) in a multi-analyte assay with algorithm (MAAA) laboratory test currently offered in the United States as decision tool assisting rheumatologists with the differential diagnosis of systemic lupus erythematosus (SLE).

Methods : The population of subjects enrolled in this validation cohort consisted of 75 consecutive primary fibromyalgia syndrome (FMS) (96% females, mean age 48 years) and 75 consecutive adult SLE (88% females, mean age 53 years). All subjects fulfilled their respective American College of Rheumatology classification criteria of disease. The subjects were enrolled at two rheumatology practices located in Southern California, and each patient provided informed consent following appropriate Ethic Committees approval. Venous blood was collected and shipped overnight to our reference clinical laboratory conducting routine diagnostic immunology testing for CB-CAPS (erythrocyte and B-lymphocyte C4d) and other autoimmune markers including antinuclear antibodies (ANA) as determined using solid phase assay and indirect immunofluorescence (IIF), anti-dsDNA antibodies (all confirmed by Crithidia Luciliae IIF) and additional cellular autoantibodies. The CB-CAPS in MAAA combining these autoimmune markers relies on two consecutive tiers of analysis as currently approved by the Department of Health in the State of NY and reported as positive or negative. Test performances in this validation cohort were assessed using sensitivity, specificity, positive and negative likelihood ratio (LR). Post-test probability of SLE disease versus primary fibromyalgia was determined using standard 20% prior probability. All testing laboratory personnel were blinded to subject diagnosis during the pre-analytical, analytical and post-analytical phase of testing.

Results : ANA was positive in 33% FMS (67% specific) and was 80% sensitive for SLE (LR+=2.8). Anti-dsDNA was negative in all FMS (100% specific) but yielded low sensitivity in SLE (17%; LR+>13). High CB-CAPs as defined by EC4d or BC4d levels above the 95th percentile established among normal healthy individuals were infrequently detectable among FMS patients (4% positives, 96% specificity) but were detectable in 60% SLE (LR+>43)(Table). Using these performances characteristics, a positive CB-CAPS in MAAA assessment would raise the probability (post-test) for SLE compared to FMS from 20% (pre-test) to higher than 92%. Conversely, a negative CB-CAPS in MAAA test result would reduce the post-test probability of SLE from 20% to 9%.

Conclusion : Our data indicate that CB-CAPS in MAAA can distinguish FMS from SLE.

Table: Positive and negative Likelihood ratio and post-test probabilities of SLE and Fibromyalgia

	Likelihood ratio		Post-test probability (20% prior)	
	Positive	Negative	Positive result	Negative result
ANA by IIF and ELISA	2.8 (1.8 to 4.1)	0.36 (0.24 to 0.54)	41% (31% - 51%)	8% (6%-12%)
Anti-dsDNA confirmed by IIF	> 13.0 (1.8-98.2)	0.83 (0.75-0.92)	> 76% (31%-96%)	17% (16%-19%)
High CB-CAPS	11.0 (3.5-34.2)	0.59 (0.48-0.72)	73% (47%-90%)	13% (11%-15%)
CB-CAPS in MAAA	> 43.8 (6.2-310)	0.40 (0.30-0.54)	> 92% (61%-99%)	9% (7%-12%)

Disclosure: D. Wallace, Exagen, 5,Exagen, 2; **S. L. Silverman**, Exagen, 8,Exagen, 2; **D. Barken**, Exagen, 3; **J. Conklin**, Exagen, 3; **T. Dervieux**, Exagen, 3.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/cell-bound-complement-activation-products-in-multianalyte-assay-with-algorithm-have-utility-in-distinguishing-primary-fibromyalgia-from-systemic-lupus-erythematosus

Abstract Number: 3088

Genome Wide Expression Analyses Reveal Potentially Novel Drug Targets in Fibromyalgia

Kim Jones[1], Robert Bennett[2,3] and Sunil Kurian[4], [1]Rsch & Develop/Mail Code SN OR, Oregon Health Sciences Univ, Portland, OR, [2]SN-Office of Research & Development, Oregon Health & Science Univ, Portland, OR, [3]Medicine & Nursing, Oregon Health & Science Univ, Portland, OR, [4]The Scripps Research Institute, La Jolla, CA

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Background/Purpose:

Currently there are three drugs approved by the FDA for the treatment of fibromyalgia (FM), and there appears to be a paucity of drugs in development. We recently completed a study with the major aim of discovering biological disease markers that could shed light on the molecular mechanisms that drive FM. Herein we report FM associated genes that are targets of known drugs

Methods:

We analyzed gene expression from the RNA isolated from blood of 70 women with FM and 70 healthy age/gender-matched controls.

Results:

The average FM patient was aged 45.5±7.7 years and had symptoms 17.2±12.2 years. Differentially expressed genes and their known targets of available drugs are displayed below:

Symbol	Gene function	Associated Drug	Disease target
MS4A2	IgE activity	Omalizumab	Allergic asthma
IL3RA	Cytokine receptor	Gm-CSF	Bone marrow stimulation
COL4A6	Type IV subunit	Collagenase	Skin debridement
MUT	Vit B12 metabolism	Cyanocobalamin	Pernicious anemia
NPY2R	Appetite regulation	Peptide YY 3-36	Appetite regulation
CPT1A	Mitochondrial transport	Perhexiline	Angina pectoris
ITGA4	Cell surface adhesion molecule	Natalizumab	Multiple sclerosis
GGPS1	C20-prenylation of proteins	Zoledronic acid	Osteoporosis
CA3	Carbonic anhydrase gene	Thiazide diuretics	Hypertension
VWF	von Willebrand factor gene	Factor 8	Hemophilia
ALDH5A1	Aldehyde dehydrogenase gene	Valproic acid	Anticonvulsant
HRH4	Histamine receptor gene	Triprolidine	Nasal allergies
YES1	Tyrosine kinase gene	Dasatinib	Chronic myeloid leukemia

Conclusion:

Overall, genes associated with immune/inflammatory responses were up-regulated as were genes associated with neuronal development and neurotransmitters. Conversely, genes associated with allergic responses were down-regulated. There were 14 differentially expressed kinase molecules, 21 transcriptional regulators and 21 transporter molecules that have never been previously reported in FM. These represent opportunities for novel drug targets. There were 13 genes differentially expressed in FM that are known targets of already available drugs. These data contribute new targets for the further exploration of both existing drugs and development efforts to identify new candidate therapies based on molecular markers that may underlie FM disease mechanisms.

Disclosure: K. Jones, None; **R. Bennett**, None; **S. Kurian**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/genome-wide-expression-analyses-reveal-potentially-novel-drug-targets-in-fibromyalgia

Abstract Number: 3089

Evaluation of Learned Helplessness, Perceived Self-Efficacy and Functional Capacity in Patients with Fibromyalgia and Rheumatoid Arthritis

Sebastian Moyano[1], Marina Scolnik[1], Facundo Vergara[1], Maria Victoria Garcia[2], Mirtha Sabelli[3], Javier Rosa[4] and Enrique R. Soriano[5], [1]Rheumatology Unit, Internal Medicine Service, Hospital Italiano de Buenos Aires, Instituto Universitario Hospital Italiano de Buenos Aires, and Fundacion PM Catoggio, Buenos Aires, Argentina, [2]Internal Services, Rheumatology Unit, Internal Medicine Service, Hospital Italiano de Buenos Aires, Instituto Universitario Hospital Italiano de Buenos Aires, and Fundacion PM Catoggio, Buenos Aires, Argentina, [3]Cabrera 2964 Piso 6, Rheumatology Unit, Internal Medicine Service, Hospital Italiano de Buenos Aires, Instituto Universitario Hospital Italiano de Buenos Aires, and Fundacion PM Catoggio, Buenos Aires, Argentina, [4]Rheumatology, Hospital Italiano de Buenos Aires, Buenos Aires, Argentina, [5]Internal Medicine, Hospital Italiano de Buenos Aires, Buenos Aires, Argentina

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Background/Purpose: Chronic diseases involve cognitive and emotional aspects of patients. One relevant cognitive factor is the learned helplessness (LH), defined as an inadequate perception of the disease, generating feeling of defenselessness, behaviors of passivity, loss of self-esteem and belief that nothing you do can improve your situation. Another important cognitive factor is perceived self-efficacy (SE), which is defined as the individual's abilities to cope with the disease. It has been reported that patients with higher LH, have more pain and functional disability. On the other hand, patients with high levels of SE have less pain, LH and functional disability. The relationship of these cognitive aspects has not been fully studied in fibromyalgia (FM). Our purpose was to evaluate LH and SE in patients with fibromyalgia and compared them with patients with rheumatoid arthritis (RA), and to assess their association with functional disability and level of perceived pain and fatigue in both groups of patients.

Methods: Consecutive patients, older than 18 years, with diagnosis of RA (2010 ACR/EULAR criteria) and with diagnosis of fibromyalgia (1990 or 2010 ACR criteria) seen at the outpatient rheumatology unit between March 2014 and June 2015, were included. During the inclusion visit the following data were collected: HAQ-A (Health Auto Questionnaire-simplified Argentinean validation); pain (VAS); fatigue (VAS); LH measured with Rheumatology Attitudes Index (RAI) and SE measured by Arthritis Self-auto-efficacy Scale. Descriptive statistics were calculated and compared between both groups. Correlations were calculated between LH and SE and pain, fatigue and HAQ-A, using Pearson tests.

Results: One hundred and fifteen patients with RA and 57 patients with FM were included. Patient's characteristics are shown in table 1. Patients with FM had significantly more pain, more fatigue, more LH, and less SE than RA patients (table 1). There was a significant positive correlation between LH, and pain (RA: r=0.67; p<0.001; FM: 0.59; p<0.001); HAQ-A (RA: r=0.65; p<0.001; FM: r=0.52; p= 0.0004), and fatigue (RA: r=0.54; p<0.001; FM: r=0.49; p= 0.0010); and a negative correlation between SE and pain (RA: r= - 0.47; p<0.001; FM; r= -0.59; p<0.001); HAQ-A (RA: r= -0.47; p<0.001; FM: r= -0.42; p= 0.0112) in both patient's groups.

Conclusion: Patients with FM had more LH, pain and fatigue than RA, and less SE. There was a significant correlation between these psychological assessments and pain, functional capacity and fatigue. LH and SE are potentially modifiable cognitive factors that correlated with functional disability and patients related outcomes. This might have clinical implications.

Characteristics	RA (n=115)	FM (n=57)	P value
Female , n (%)	94 (82)	55 (96.5)	0.007
Age, years, mean (DS)	58 (13)	59 (14)	0.727
Time from diagnosis (years), mean (SD)	12 (10)	2 (2.8)	<0.0001
HAQ-A, mean (DS)	0.75 (0.76)	0.73 (0.59)	0.832
Pain (VAS,0-100), Mean (SD)	31 (28)	61 (25)	<0.0001
Fatigue (VAS, 0-100), Mean (SD)	26 (28)	66 (26)	<0.0001
Learned helplessness, Median (IQR)	10.4 (4.8)	14.5 (6.1)	<0.0001
Self-efficacy, Mean (SD)	61 (15.4)	48 (18.6)	<0.0001

Table 1

Disclosure: S. Moyano, None; **M. Scolnik**, None; **F. Vergara**, None; **M. V. Garcia**, None; **M. Sabelli**, None; **J. Rosa**, None; **E. R. Soriano**, Abbvie; Janssen; UCB; Roche; Bristol Myers Squibb, 2,Abbvie; UCB; Janssen; Roche; Bristol Myers Squibb; Pfizer; Novartis, 8.

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Abstract Number: 3090

Fibromyalgia Predicts Two-Year Changes in Functional Status in Rheumatoid Arthritis Patients

Hyein Kim[1], Jing Cui[2], M Frits[3], C Iannaccone[4], Jonathan S. Coblyn[3], N Shadick[5], Michael Weinblatt[4] and Yvonne C. Lee[6], [1]Western University, London, ON, Canada, [2]Division of Rheumatology, Immunology, and Allergy, Brigham & Women's Hospital, Boston, MA, [3]Brigham & Women's Hospital, Boston, MA, [4]Brigham and Women's Hospital, Boston, MA, [5]Rheumatology, Immunology and Allergy, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, [6]Rheumatology Immunology & Allergy, Brigham and Women's Hospital, Boston, MA
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SESSION INFORMATION
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Background/Purpose: The prevalence of fibromyalgia (FM) is 10-20% in rheumatoid arthritis (RA) patients, compared to 2-3% in the general population. Previous studies have shown that RA patients with FM have higher disease activity, greater medical costs and worse quality of life compared to RA patients without FM. However, these studies were limited due to their cross-sectional design. In this study, we determined the impact of FM on 2-year changes in functional status of RA patients in a prospective study.

Methods: Subjects in a single center RA registry were enrolled in a 2-year prospective observational substudy examining characteristics of FM. Subjects completed questionnaires every 6 months and underwent physical examination and laboratory tests yearly. The primary outcome was change in the Multidimensional Health Assessment Questionnaire (MDHAQ) score from baseline to 2 years. The MDHAQ was scored on a scale of 0-3, with 3 indicating the worst functional status. The primary predictor was FM status, a dichotomous variable derived from the FM survey scale, with a threshold of ≥13 indicating FM. The FM survey scale is a validated, self-report measure based on the ACR 2010 preliminary diagnostic criteria. It consists of 2 scales, assessing widespread body pain and somatic symptoms. Multivariable linear regression models were used to examine the association between FM status and change in MDHAQ score, adjusted for age, gender, race, baseline MDHAQ score, disease duration, RF/CCP seropositivity, disease activity and anxiety/depression. In secondary analyses, we also examined the association between the baseline FM survey score, as a continuous variable, and change in MDHAQ score over 2 years.

Results: Of the 156 included RA subjects, 134 (85.9%) were female, and 145 (93.6%) were Caucasian. Mean age was 58.5 ± 11.0 years. Mean disease duration was 15.4 ± 9.2 years, and 111 (72.1%) were seropositive. Twenty-six patients (16.7%) had FM, while 130 patients (83.3%) did not. Compared to RA patients without FM, RA patients with FM had significantly higher baseline MDHAQ scores (RA with FM: 0.74 ± 0.40, RA alone: 0.43 ± 0.39; $P < 0.001$) and Hospital Anxiety and Depression Scale scores (RA with FM: 13.65 ± 6.74, RA alone: 8.22 ± 5.75; $P < 0.001$). In a multivariable linear regression model adjusted for the covariates listed above, RA patients with FM had a 0.15 unit greater 2-year increase in MDHAQ score than RA patients without FM ($P = 0.012$). In secondary analyses examining the association between continuous FM survey score and change in MDHAQ, higher FM survey scores were significantly associated with greater 2-year increases in MDHAQ score (β-coefficient 0.014; $P = 0.005$).

Conclusion: RA patients with FM experience significantly greater 2-year worsening of functional status compared to RA patients without FM. The difference in the increase in MDHAQ score was 0.15 units higher over 2 years in the RA with FM group compared to those with RA alone. This difference is striking given that MDHAQ scores typically only increase 0.01-0.016 units per year in stable RA patients. Future studies are needed to determine if treatments for FM can reduce functional status decline among individuals with established RA.

Disclosure: H. Kim, None; **J. Cui**, None; **M. Frits**, None; **C. Iannaccone**, None; **J. S. Coblyn**, CVS, 5; **N. Shadick**, Amgen, Questcor, Crescendo Biosciences, UCB, Bristol-Myers Squibb, 2; **M. Weinblatt**, Amgen, Abbvie, Bristol-Myers Squibb, Lilly, Novartis, Merck, Pfizer, Roche, Crescendo, Myriad Genetics, UCB, 5,Bristol-Myers Squibb, Myriad Genetics, UCB, 2; **Y. C. Lee**, Forest Research Institute, 2.

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Abstract Number: 3091

A Randomized, Controlled Trial of Pregabalin in Adolescent Patients (12-17 years) with Fibromyalgia

Lesley Arnold[1], Lucinda Bateman[2], Kenneth N. Schikler[3], Tahira Khan[4], Lynne Pauer[4], Pritha Bhadra Brown[5], Marci L. Chew[4], Andrew Clair[5] and Joseph Scavone[4], [1]University of Cincinnati, Cincinnati, OH, [2]Bateman Horne Center, Salt Lake City, UT, [3]Pediatrics, University of Louisville, Louisville, KY, [4]Pfizer Inc, Groton, CT, [5]Pfizer Inc., New York, NY
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Background/Purpose: : Fibromyalgia (FM) is characterized by chronic widespread pain, sleep disturbance, and fatigue. Pregabalin is approved in the US in adults for the management of FM at 300-450 mg/day.

Methods: This was a 15-week, randomized, double-blind, placebo-controlled study of flexible-dose pregabalin (75-450 mg/day) in adolescents (aged 12-17 yrs) with FM. Patients met the Yunus and Masi diagnostic criteria for FM, and had a mean numeric daily pain rating scale (NRS) score of ≥4 (0–10, 24 hour recall period). Patients were randomized 1:1 to pregabalin or placebo. Pregabalin or placebo doses were optimized over 3 weeks based on efficacy and tolerability to 75, 150, 300, or 450 mg/day. Patients remained at these doses for an additional 12 weeks.. The primary outcome was change from baseline in mean pain score (NRS). Secondary outcomes included change in pain score by week, change in pain score at week 15 (with a 1 wk recall period), and Patient Global Impression of Change (PGIC). Exploratory measures were Parent Global Impression of Change (Parent GIC), a version of the PGIC completed by the patient's parent, and Fibromyalgia Impact Questionnaire-Children (FIQ-C).

Results: A total of 107 patients were randomized (54 pregabalin, 53 placebo) and 80 completed the study (44 pregabalin, 36 placebo). The percentages of pregabalin-treated patients at each optimized dose were: 25%, 19%, 15%, and 40% at 75, 150, 300, and 450 mg/day, respectively. Improvement in mean pain score at endpoint with pregabalin vs placebo was not statistically significant, treatment difference (95% CI), -0.66 (-1.51, 0.18), P=0.121. There were statistically significant improvements with pregabalin vs placebo in change in weekly mean pain score (P<0.05 for 10 of the 15 weeks); change in pain score at week 15 (1 week recall), treatment difference (95% CI), -0.87 (-1.68, -0.05), P=0.037; PGIC with 53.1% vs 29.5% very much or much improved (P=0.013); and Parent GIC with pregabalin 51.0% vs 25.0% (P=0.011). Tolerability was consistent with the known profile of pregabalin with the exception of a higher rate of mild nausea with pregabalin; 22.2% had nausea of any severity, vs 7.8% in adults with FM in previous studies. The most frequently reported adverse events with pregabalin were dizziness, nausea, headache, weight increase, and fatigue. Two serious adverse events occurred in one pregabalin treated patient (cholelithiasis, major depression). In each treatment group, 4 subjects discontinued due to adverse events.

Conclusion: In this study, pregabalin did not significantly improve the primary measure of mean pain score compared with placebo at endpoint in adolescent patients with FM. However, the treatment difference was similar to those observed in the adult FM studies. The adolescent study employed lower doses (75-450 mg/day) than are approved for adults with FM (300-450 mg/day; starting dose 150 mg/day). There were significant improvements in secondary endpoints measuring pain and global impression of change. Pregabalin was well tolerated in this study. The safety profile observed in this study was generally consistent with the known profile for pregabalin with the exception of nausea, which was mostly mild.

Disclosure: L. Arnold, Pfizer Inc, 2,Eli Lilly and Company, 2,Forest Laboratories, 2,Daiichi Pharmaceutical Co, 2,Theravance, 2,Tonix, 2,Pfizer Inc, 5,Forest Laboratories, 5,Daiichi Pharmaceutical Co., 5,Theravance, 5,Innovative Med Concepts, 5,Ironwood, 5,Zynerba, 5,Pfizer Inc, 8; **L. Bateman**, Tonix, 2,Daiichi Pharmaceutical Corporation, 2,Eli Lilly and Company, 2; **K. N. Schikler**, Novartis Pharmaceutical Corporation, 8,Abbvie, 8,Pfizer Inc, 2,Roche Pharmaceuticals, 2,Genentech and Biogen IDEC Inc., 2,UCB, 2,Forest Laboratories, 2,Novartis Pharmaceutical Corporation, 2,Abbvie, 2,Centocor, Inc., 2,Boehringer Inglelheim, 2; **T. Khan**, Pfizer stock options, 1,Pfizer Inc, 3; **L. Pauer**, Pfizer Inc., 3,Pfizer Inc., 1; **P. Bhadra Brown**, Pfizer Inc., 3,Pfizer Inc., 1; **M. L. Chew**, Pfizer stock options, 1,Pfizer Inc, 3; **A. Clair**, Pfizer Inc, 1,Pfizer Inc, 3; **J. Scavone**, Pfizer Inc., 1,Pfizer Inc., 3.

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Abstract Number: 3092

Deficiency of Adenosine Deaminase Type II – Expanding the Clinical Spectrum

Karyl Barron[1], Amanda Ombrello[2], Deborah Stone[2], Patrycja Hoffmann[2], Ivona Aksentijevich[2,3], Qing Zhou[2], Anne Jones[2] and Daniel L. Kastner[4], [1]NIAID/NIH, Bethesda, MD, [2]NHGRI/NIH, Bethesda, MD, [3]Inflammatory Disease Section, National Human Genome Research Institute, Bethesda, MD, [4]Inflammatory Disease Section, National Human Genome Research Institute, National Institutes of Health, Bethesda, MD
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SESSION INFORMATION

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Session Title: Pediatric Rheumatology - Clinical and Therapeutic Aspects III: Miscellaneous Pediatric Rheumatic Diseases

Session Type: ACR Concurrent Abstract Session

Session Time: 2:30PM-4:00PM

Background/Purpose:

The deficiency of adenosine deaminase II (DADA2), first described in 2014, is an autosomal recessive disease caused by mutations in *CECR1* and is characterized by intermittent fevers, early-onset lacunar strokes, livedoid rash, hepatosplenomegaly, immune deficiency and systemic vasculopathy. An additional report by others included patients with cutaneous polyarteritis nodosa. We now present clinical follow-up on our 5 reported patients and an additional 9 patients.

Methods:

We evaluated the 14 patients at the National Institutes of Health. We performed whole-exome sequencing in the initial 3 patients and their unaffected parents and candidate-gene sequencing in the other 11 patients. Clinical information and radiographic and laboratory testing were obtained at each visit.

Results:

All patients had 2 mutations in *CECR1*. 11/14 patients reported recurrent fevers. Ten had a history of at least one ischemic stroke. The age of onset of the first stroke ranged from 5 months to 8 years, with 8/10 before the age of 5 years. MRI of the brain showed evidence of acute or chronic small subcortical infarcts involving the deep-brain nuclei and brain stem, consistent with small-vessel occlusions (lacunar strokes). 8/10 patients with ischemic stroke had at least one occur in the thalamus; other involved areas included the midbrain (4/10), pons (4/10), internal capsule (3/10) and basal ganglia (3/10). One patient had an anterior thoracic-lumbar spinal cord infarct that resulted in the development of a neurogenic bladder. Three patients had hemorrhagic strokes in addition to their ischemic strokes. One patient developed posterior reversible encephalopathy syndrome (PRES) in relation to hypertension. Subsequent MRI revealed complete reversal of the PRES. In 10/10 patients magnetic angiography showed no evidence of cerebral vasculitis.

All 14 patients demonstrated livedo racemosa. Erythematous papules or nodules were seen in 11 of these patients. Hepato-and/or splenomegaly was observed in 10/14 with 3 patients demonstrating portal hypertension. One patient developed a perforated small bowel requiring resection.

Hypertension was noted in 2 patients. Prolonged QT was reported in 3 patients. 12/14 demonstrated hematologic abnormalities including anemia, leukopenia, and/or thrombocytopenia. Elevation of acute phase reactants was reported in 13/14. Low serum iron was noted in 8/10 patients tested. 10/13 presented with hypogammaglobulinemia, however this may reflect prior treatment with cyclophosphamide in 3 patients.

Most patients received a number of medications over the course of their disease. It was our practice to discontinue aspirin and/or anticoagulation in all DADA2 patients. We observed striking improvement in CRP, ESR, CBC, and serum iron in 10/12 patients receiving anti-TNF agents.

Conclusion:

We have expanded the clinical picture in patients with DADA2 to include multiple strokes, livedo racemosa, cutaneous PAN, portal hypertension, hematologic abnormalities, vascular pathology and mild immunodeficiency. In addition, we have demonstrated both clinical and laboratory improvement following treatment with anti-TNF agents.

Disclosure: K. Barron, None; **A. Ombrello**, None; **D. Stone**, None; **P. Hoffmann**, None; **I. Aksentijevich**, None; **Q. Zhou**, None; **A. Jones**, None; **D. L. Kastner**, None.

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Abstract Number: 3093

Development and Validation of Diagnostic Criteria for Cryopyrin Associated Periodic Syndromes

Jasmin B. Kuemmerle-Deschner[1], Seza Ozen[2], Pascal N. Tyrrell[3], Isabelle Koné-Paut[4], Raphaela Goldbach-Mansky[5], Helen Lachmann[6], Norbert Blank[7], Hal M. Hoffman[8], Elisabeth Weissbarth-Riedel[9], Boris Huegle[10], Tilmann Kallinich[11], Marco Gattorno[12], Ahmet Gul[13], Nienke M. ter Haar[14], Marlen Oswald[15], Fatma Dedeoglu[16] and Susanne M. Benseler[17], [1]Universitätsklinikum Tübingen, Klinik fuer Kinder- und Jugendmedizin, Tübingen, Germany, [2]Pediatric Nephrology and Rheumatology, Hacettepe University, Ankara, Turkey, Ankara, Turkey, [3]Department of Medical Imaging, University of Toronto, Toronto, ON, Canada, [4]Pediatrics Rheumatology, CHU Bicêtre, Le Kremlin Bicêtre,

France, [5]Bldg10 rooom 6D47-B, NIH | NIAMS, Bethesda, MD, [6]UK National Amyloidosis Centre, University College London Medical School, London, United Kingdom, [7]Med 5-Rheumatology, University of Heidelberg, Heidelberg, Germany, [8]University of California at San Diego, San Diego, CA, [9]Rheumatology, Pediatrics, Universitaetskinderklinik Hamburg, Hamburg, Germany, [10]Pediatric Rheumatology, German Center for Pediatric and Adolescent Rheumatology, Garmisch-Partenkirchen, Germany, [11]Charite, University Medicine Berlin, Berlin, Germany, [12]Pediatry, G. Gaslini Institute, Genova, Italy, [13]Department of Internal Medicine, Rheumatology Division, Istanbul University, Istanbul Faculty of Medicine, Istanbul, Turkey, [14]Laboratory for Translational Immunology, University Medical Center Utrecht, Utrecht, Netherlands, [15]University Hospital Tuebingen, Tuebingen, Germany, [16]Division of Immunology, Boston Children's Hospital, Boston, MA, [17]Rheumatology, Alberta Children's Hospital, University of Calgary, Calgary, AB, Canada
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Background/Purpose: Cryopyrin Associated Periodic Syndromes (CAPS) are a rare, clinically heterogeneous group of devastating inflammatory illnesses. *NLRP3*gene gain-of function mutations result in unceasingly raised IL1 secretion and the clinically highly variable phenotype of severe systemic and organ inflammation. Early diagnosis is crucial, since rapid start of IL1 inhibition controls inflammation and prevents organ damage in children and adults with CAPS. The aim of the study was to develop and validate diagnostic criteria for CAPS.

Methods: An innovative, rigorous model development process was followed including a) interdisciplinary, international team building including pediatric and adult subspecialists plus methods experts for rare diseases, b) item generation: systematic literature review, item review of CAPS registries, CAPS expert survey and consensus conference for item refinement and agreement, c) item reduction and weighting using 1000minds decision analysis software. The resulting CAPS criteria were validated in a large cohort CAPS cases and true CAPS controls (autoinflammatory controls – FMF, sJIA, other and inflammatory controls – Schnitzler, Kawasaki, others) from clinical registries using correspondence analysis to identify items consistently associated with CAPS. Resulting variables were used to evaluate diagnostic models using sensitivity analyses. Subanalyses were performed for all CAPS subtypes and evidence of NLRP3 mutations.

Results: The CAPS team included 18 CAPS and methods experts. Systematic literature and CAPS registry review identified 32 CAPS-typical items; the consensus conference refined these to 11 items plus “NLRP3 mutation”. The 1000minds exercise ranked these 12 variables based on importance for the diagnosis CAPS, demonstrating excellent correlations between experts. Validation: Correspondence analysis determined variables consistently associated with the diagnosis of CAPS using 284 cases and 873 controls removing infrequently observed variables such as “amyloidosis”. The remaining seven variables were found to high significantly associated with the diagnosis CAPS ($p<0.001$ for all). Different modeling approaches were explored resulting in a “coupling model” as the best fit. The best CAPS diagnosis criteria model: “Raised inflammatory markers (CRP/SAA) plus ≥ two of six CAPS typical signs/symptoms including urticara-like rash, cold/stress triggered episodes, sensorineural hearing loss, musculoskeletal symptoms of arthralgia/arthritis/myalgia, chronic aseptic meningitis, skeletal abnormalities of epiphyseal overgrowth/frontal bossing” with a sensitivity of 81% and a specificity of 94%. It performed equally well for all CAPS subtypes and in subgroups with and without evidence of germline NLRP3 mutations.

Conclusion: The CAPS diagnosis criteria model enables a rapid diagnosis and initiation of treatment for children and adults with CAPS, a rare, heterogeneous inflammatory disease. The novel approach integrated traditional methods of evidence synthesis with expert consensus, web-based decision tools and innovative statistical methods and may serve as a model for the diagnosis of other rare diseases.

Disclosure: J. B. Kuemmerle-Deschner, Novartis Pharmaceutical Corporation, 8,Novartis and Sobi, 5; **S. Ozen**, None; **P. N. Tyrrell**, None; **I. Koné-Paut**, SOBI, Novartis, Pfizer, Abbvie, CHUGAI, 5,Novartis Pharmaceutical Corporation, SOBI, Roche, 2,Novartis Pharmaceutical Corporation, SOBI, Pfizer, Roche, 8,Pfizer Inc, Novartis, SOBI, 5; **R. Goldbach-Mansky**, SOBI, Novartis, Regeneron and Lilly, 2; **H. Lachmann**, Takeda and Novartis, 5; **N. Blank**, Novartis and SOBI, 5; **H. M. Hoffman**, Novartis Pharmaceutical Corporation, 8,Novartis and Sobi, 5; **E. Weissbarth-Riedel**, None; **B. Huegle**, None; **T. Kallinich**, None; **M. Gattorno**, None; **A. Gul**, None; **N. M. ter Haar**, None; **M. Oswald**, None; **F. Dedeoglu**, None; **S. M. Benseler**, None.

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Abstract Number: 3094

Dose Adjustment of Anakinra (Kineret®) Based on Clinical Response in Patients with Severe Cryopyrin-Associated Periodic Syndromes

Bengt Hallen[1], Torbjörn Kullenberg[1], **Mika Leinonen**[2], Margareta Wiken[1], Raphaela Goldbach-Mansky[3] and Hans Olivecrona[1], [1]Swedish Orphan Biovitrum, Stockholm, Sweden, [2]4Pharma AB, Stockholm, Sweden, [3]Translational Autoinflammatory Diseases Section, NIAMS, NIH,

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Background/Purpose: Cryopyrin-Associated Periodic Syndromes (CAPS) include a group of rare inherited autoinflammatory diseases consisting of Familial Cold Autoinflammatory Syndrome (FCAS), Muckle-Wells Syndrome and the most severe form, Neonatal-Onset Multisystem Inflammatory Disease (NOMID). Anakinra is an IL-1-receptor antagonist blocking the biologic activity of naturally occurring IL-1 which has been proven effective and safe in the treatment of severe CAPS[1,2]. The objective of the present analysis was to describe anakinra dose adjustments in patients with severe CAPS.

Methods: A prospective, open-label, single arm 60-month study of anakinra was conducted at the National Institutes of Health and the main efficacy and safety findings have been reported earlier[1,2]. The patients were stratified by age at anakinra treatment initiation: infants/toddlers (<2 years), children (2-11 years), adolescents (12-18 years) and adults (>18 years). The initial starting dose of 1-2 mg/kg/day of anakinra was either maintained or adjusted during the study depending on clinical response. For patients with inadequate clinical response or a disease flare, the dose could be increased by 0.5-1 mg/kg for up to a maximum of 10 mg/kg/day. The dose increases were estimated with a Mixed Model for Repeated Measures (MMRM).. References: [1]Goldbach-Mansky et al. NEJM. 2006;355:581-92. [2]Sibley et al. Arthritis Rheum. 2012;64:2375-86.

Results: 43 patients (13 infants/toddlers, 18 children, 12 adolescents/adults) were included in the study and exposed to anakinra: 26 started on doses <1.5 mg/kg/day and 17 on ≥1.5 mg/kg/day. For 90% of the patients enrolled during the first 3 years of the study the starting dose was <1.5 mg/kg/day, while for the majority of the patients enrolled later (68%) the starting dose was ≥1.5 mg/kg/day. During the study, the treatment doses increased and the estimated mean maintenance dose at Month 60 was similar across age groups, ranging from 3.0 to 3.8 mg/kg/day (mean 3.3 mg/kg/day). On average, the dose was increased by 0.5 mg/kg/day for the first time at Month 6 and thereafter at Month 18 and 36. The actual dose range during the study was 0.9-7.6 mg/kg/day, with the highest dose maintained for 15 months followed by a decrease thereafter. The doses were not only increased for preventing disease flares e.g. rash, fever and elevated CRP but also to preserve organ function, e.g. hearing and vision. Comparable numbers of adverse events were reported for low (<3.5 mg/kg/day; total anakinra exposure 128.0 patient years) and high (≥3.5 mg/kg/day; total anakinra exposure 31.9 patient years) doses; 7.9 events per patient year for low doses and 6.8 for high doses. There was no correlation between development of anakinra anti-drug antibodies and dose adjustments.

Conclusion: Anakinra doses were adjusted based on clinical response in order to achieve systemic inflammatory remission and absence of organ inflammation. In one patient doses up to 7.6 mg/kg/day were needed to control CNS inflammation. Dose adjustments were well tolerated with adverse event reporting rates similar in patients on doses <3.5 and ≥3.5mg/kg/day.

Disclosure: B. Hallen, Swedish Orphan Biovitrum, 1,Swedish Orphan Biovitrum, 3; **T. Kullenberg**, Swedish Orphan Biovitrum, 3; **M. Leinonen**, Swedish Orphan Biovitrum, 5; **M. Wiken**, Swedish Orphan Biovitrum, 1,Swedish Orphan Biovitrum, 3; **R. Goldbach-Mansky**, SOBI, Novartis, Regeneron and Lilly, 2; **H. Olivecrona**, Swedish Orphan Biovitrum, 3.

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Abstract Number: 3095

Initial Results of a Pilot Juvenile Localized Scleroderma (jLS) Comparative Effectiveness Study

Suzanne C. Li[1], Kathryn S. Torok[2], Sandy D. Hong[3], Polly J. Ferguson[4], C. Egla Rabinovich[5], Mara L Becker[6], Fatma Dedeoglu[7], Maria F. Ibarra[8], Robert C. Fuhlbrigge[9,10], Katie G. Stewart[11], Marilynn G. Punaro[11], Thomas Mason II[12], Elena Pope[13], Ronald Laxer[14], Gloria C. Higgins[15,16] and Brian Feldman[17], [1]Pediatrics, Joseph M Sanzari Children's Hospital, Hackensack University Medical Center, Hackensack, NJ, [2]Pediatric Rheumatology, Univ of Pittsburgh Med Ctr, Pittsburgh, PA, [3]Pediatrics-Rheumatology, U of Iowa Children's Hosp, Iowa City, IA, [4]Dept of Pediatrics--Rheum, University of Iowa, Iowa City, IA, [5]Pediatric Rheumatology, Duke Univ Med Ctr, Durham, NC, [6]Rheumatology, Children's Mercy Kansas City, Kansas City, MO, [7]Rheumatology, Boston Children's Hospital, Boston, MA, [8]Pediatric Rheumatolgy, Children's Mercy Hospital, Kansas City, MO, [9]Program in Rheumatology, Division of Immunology, Boston Children's Hospital, Boston, MA, [10]Department of Dermatology, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, [11]Pediatric Rheumatology, Texas Scottish Rite Hospital, Dallas, TX, [12]Rheumatology, Mayo Clinic, Rochester, MN, [13]Dermatology, Hospital for Sick Children, Toronto, ON, Canada, [14]Rheumatology, The Hospital for Sick Children, Toronto, ON, Canada, [15]Pediatric Rheumatology OSU, Nationwide Childrens Hosp,

Columbus, OH, [16]Pediatric Rheumatology Ohio State University, Nationwide Childrens Hospital, Columbus, OH, [17]Division of Rheumatology, The Hospital for Sick Children, Toronto, ON, Canada

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SESSION INFORMATION

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Session Time: 2:30PM-4:00PM

Background/Purpose: Juvenile localized scleroderma (jLS) is a chronic inflammatory and fibrosing disease that causes severe morbidity, including growth defects, cosmetic deformities, seizures and arthropathy. Optimal therapy is not known. The LS Children's Arthritis and Rheumatology Research Alliance (CARRA) subgroup has been working towards conducting comparative effectiveness studies with the aim of improving long-term outcome. We report our initial findings from a pilot study to evaluate the feasibility of conducting such studies.

Methods:

We conducted a multi-center 12 month prospective observational cohort study of jLS subjects treated with one of 3 methotrexate (MTX)-based standardized treatment regimens (consensus treatment plans, CTPs), chosen by the treating physician. Each CTP included MTX administered for 1 year; two included corticosteroids (CS), either intravenous (IV) for 3 months or oral for 48 weeks (tapering schedule). The CTP options are based upon best available evidence and reflect the current treatment practices of CARRA members (Li et al., Arthritis Rheum 2012; 64:1175). Data were entered into a web-based registry (InForm), including activity and damage assessments, global assessments (GA), adverse events (AE), and medications.

Results:

The target enrollment (50 subjects) was reached. Median age at enrollment was 13 years, majority of subjects were Caucasian (92%), female (70%), had the linear subtype (82%) and had never been treated with MTX or CS (82%). Fourty percent of subjects had a head lesion, 72% had extracutaneous involvement.

Participating sites showed strong CTP preferences, with 50% choosing only 1 and 40% 2 CTPs. Half the subjects were enrolled into MTX + IV CS, 14 into MTX alone, and 11 into MTX + oral CS CTPs. Ninety percent of subjects were followed for at least 6 months, 80% completed the full 12 months.

Among subjects followed for at least 6 months, 49% were considered to have a major and 31% a moderate improvement in activity level compared to baseline. Subjects in the MTX + CS CTPs were more likely than those in the MTX alone CTP to be rated as having a major improvement (57% vs 22%). Thirty two percent of subjects had a major deviation from their starting CTP with the most common reasons being AE (28%) and lack of response (28%). The AEs most commonly associated with deviations were severe gastrointestinal symptoms, mood issues, and infections. There was 1 SAE: one subject required hospitalization for viral gastroenteritis. Mycophenolate mofetil and/or IV CS were the most commonly employed therapies when there was a lack of response. Subjects that deviated from initial CTP had a higher physician GA of disease activity and patient/parent GA of disease impact at baseline compared to those that did not.

Conclusion: Our pilot study shows the feasibility of conducting jLS comparative effectiveness studies across multiple centers. Despite a high rate of deviation from the CTPs, the majority of subjects were rated as having moderate or major improvement. Centers showed strong biases in their treatment preferences highlighting the need to have sufficient site variability and CTPs to enable comparative effectiveness studies.

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Abstract Number: 3096

Interferon-Gamma (IFNg) in Macrophage Activation Syndrome (MAS): CXCL9 Levels As a Biomarker for IFNg Production in MAS

Claudia Bracaglia[1], Denise Pires Marafon[2], Ivan Caiello[1], Kathy De Graaf[3], Florence Guilhot[4], Walter Ferlin[4], Sergio Davì[5], Grant Schulert[6], Angelo Ravelli[5], Alexei A. Grom[7], Robert Nelson[4], Cristina de Min[4] and Fabrizio De Benedetti[1], [1]Department of Pediatric Medicine, Division

of Rheumatology, Ospedale Pediatrico Bambino Gesù, IRCCS, Rome, Italy, [2]Pediatric Rheumatology, IRCCS Ospedale Pediatrico Bambino Gesù, Rome, Italy, [3]Novimmune S.A., Geneva, Switzerland, [4]NovImmune S.A., Geneva, Switzerland, [5]Istituto Giannina Gaslini and University of Genova, Genova, Italy, [6]Pediatric Rheumatology, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, [7]Division of Rheumatology, Cincinnati Children's Hospital Medical Center, Cincinnati, OH

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Session Type: ACR Concurrent Abstract Session

Session Time: 2:30PM-4:00PM

Background/Purpose: A vast body of evidence in animals and humans points to a pivotal pathogenic role of IFNγ, in primary HLH. The role of IFNg in HLH secondary to rheumatic diseases, usually referred to as MAS, remains to be established. We have previously reported high levels of IFNg and of the three IFNγ-related chemokines, CXCL9, CXCL10 and CXCL11 in patients with active MAS, in the context of systemic Juvenile Idiopathic Arthritis (sJIA) (1). Indirect evidence in mice suggests that IFNγ is mostly produced in peripheral tissues and blood concentrations may be relatively low.

Methods : Circulating levels of IFNγ, CXCL9, CXCL10, CXCL1, IL-1b and IL-6 in patients with sJIA (n=54) of whom 20 had MAS at time of sampling were measured by Luminex multiplexing assay. We evaluated the correlation between serum levels of IFNg and of the three IFNg related chemokines with themselves and with laboratory parameters of disease activity in active MAS.

Results: Levels of IFNγ and of the 3 IFNγ-related chemokines were significantly elevated in active MAS compared to active sJIA without MAS at sampling (all p-values <0.005). In patients with active MAS, but not in patients with active sJIA without MAS at sampling, laboratory parameters of disease severity (ferritin, neutrophils, platelets, alanine aminotransferase and lactate dehydrogenase) were significantly correlated with IFNγ and CXCL9, and to a lesser extent with CXCL10 and CXCL11 (Table1). No correlation with IL-6 levels was found. In active MAS IFNg levels were significantly correlated with levels of CXCL9 (r=0.69; r^2=0.48; p=0.001), but not with those of CXCL10 (r=0.54; r^2=0.29; p=0.015), or CXCL11 (r=-0.04; r^2=0.0016; p=0.887).

Conclusion: High levels of IFNγ and of CXCL9 during active MAS were significantly correlated with laboratory parameters of disease severity. Since CXCL9 has been shown to be induced only by IFNg and not by other interferons (2), our findings support the conclusion that CXCL9 is a potential biomarker of IFNg production in MAS.

References.

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2. Groom J.R. and Luster A.D. Immunol Cell Biol 2011, Feb; 89(2): 207-15.

Table1. Correlation of laboratory parameters of disease activity with IFNg, CXCL9, CXCL10, CXCL11 and IL-6 in patients with MAS and in patients with active sJIA.

	Macrophage Activation Syndrome	IFNg		CXCL9		CXCL10		CXCL11		IL-6	
		r*	p	r*	p	r*	p	r*	p	r*	p
Ferritin	8000 (3158.5 - 13174)	0.57	0.014	0.49	0.041	0.66	0.002	0.62	0.023	0.17	>0.1
N	6.9 (3.4 – 13.9)	-0.64	0.005	-0.61	0.010	-0.37	>0.1	-0.08	>0.1	0.09	>0.1
PLT	198 (115 - 392)	-0.53	0.017	-0.52	0.022	-0.58	0.008	-0.22	>0.1	-0.02	>0.1
ALT	46 (18 - 164)	0.49	0.045	0.49	0.044	0.51	0.038	0.06	>0.1	-0.44	0.080
LDH	1152 (722 - 2135)	0.45	0.095	0.62	0.013	0.64	0.010	0.64	0.048	0.08	>0.1
	Systemic Juvenile Arthritis	**IFNg**		**CXCL9**		**CXCL10**		**CXCL11**		**IL-6**	
		r*	p	r*	p	r*	p	r*	p	r*	p
Ferritin	215 (38 - 1669)	-0.27	>0.1	0.28	>0.1	0.27	>0.1	0.29	>0.1	-0,12	>0.1
N	8.4 (5.2 – 14.5)	0.30	>0.1	0.40	0.061	0.32	>0.1	0.40	0.067	0,28	>0.1
PLT	444 (353 - 544)	0.21	>0.1	-0.14	>0.1	-0.13	>0.1	0.27	>0.1	0,35	0.064
ALT	16 (11 - 24)	0.29	>0.1	0.42	0.049	0.50	0.011	0.44	0.039	0,04	>0.1
LDH	506 (456 - 851)	0.07	>0.1	0.49	>0.1	0	>0.1	0.26	>0.1	0	>0.1

N=neutrophils count; PLT= platelets count; ALT= alanine aminotransferase; [1]=Median (IQR); r*= Spearman r

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mas-cxcl9-levels-as-a-biomarker-for-ifng-production-in-mas

Abstract Number: 3097

Innovative Approach for the Identification of an Appropriate Dose Regimen of a Targeted Treatment, NI-0501, an Anti-Interferon Gamma (IFNg) Antibody, in Patients with Hemophagocytic Lymphohistiocytosis (HLH)

Cristina De Min[1], Philippe Jacqmin[2], Christian Laveille[3], Robert Nelson[1], Florence Guilhot[1], Maureen Deehan[1], Marie Kosco-Vilbois[1], Walter Ferlin[1] and Genevieve Lapeyre[1], [1]NovImmune S.A., Geneva, Switzerland, [2]SGS Exprimo, Mechelen, Belgium, [3]SGS Exprimo NV, Mechelen, Belgium

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Session Type: ACR Concurrent Abstract Session

Session Time: 2:30PM-4:00PM

Background/Purpose:

Based on the growing evidence that IFNg plays a pivotal role in HLH, NI-0501, an anti-IFNg monoclonal antibody, is being developed as the first targeted treatment of HLH. Since a dose-finding study could not be performed in this fragile population, an innovative, individualized-dosing approach is being investigated in a pilot study, with the objective of achieving, as quickly as possible, a complete IFNg neutralization.

Methods:

The pilot study foresees the recruitment of 10 pediatric patients receiving NI-0501 either as first or second line HLH treatment. The NI-0501 dose required for reaching and maintaining, for a defined period of time, complete IFNg neutralization depends on the amounts of cytokine produced in various body compartments.

On the basis of calculated neutralizing NI-0501 concentrations, NI-0501 PK parameters in healthy volunteers and PK information from use of recombinant IFNg in humans, we predicted, by means of PK modelling and simulation, the dose neutralizing existing and *de novo* IFNg production over 3 days. The initial interval between NI-0501 infusions was 3 days. Guided by close PK monitoring, modifications of NI-0501 dose or frequency of administration were allowed.

Results:

A dose of 1 mg/kg achieved the desired NI-0501 concentration in the 7 patients enrolled thus far in the study. NI-0501 elimination kinetics was linear at high concentrations and appeared non-linear, due to target mediated drug disposition, at lower drug concentrations. After reaching steady state, up to a 7-day administration frequency could be applied. Kinetics was not affected by the numerous therapeutic interventions (blood transfusions, hemofiltration or hemodialysis, bone marrow transplantation). IFNg neutralization in serum was confirmed *ex vivo* via the use of STAT-1 bio-assays and *in vivo* through down-modulation of IFNg-inducible proteins, such as CXCL9 and CXCL10.

Conclusion:

The adequacy of the originally planned dosing regimen was demonstrated in all patients enrolled to date in the pilot study. NI-0501 treatment has shown to be effective in improving or even abrogating all relevant clinical and laboratory features of HLH such as fever, splenomegaly, cytopenia, hyperferritinemia, hypofibrinogenemia, and also CNS disease. All infusions were well tolerated and no safety concerns emerged.

Disclosure: C. De Min, NovImmune S.A., 3; **P. Jacqmin**, NovImmune S.A., 5; **C. Laveille**, NovImmune S.A., 5; **R. Nelson**, NovImmune S.A., 3; **F. Guilhot**, NovImmune S.A., 3; **M. Deehan**, NovImmune S.A., 3; **M. Kosco-Vilbois**, NovImmune S.A., 3; **W. Ferlin**, NovImmune S.A., 3; **G. Lapeyre**, NovImmune S.A., 3.

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Abstract Number: 3098

Synovial Lymphocytic Aggregates Associate with Highly Active RA and Predict Erosive

Disease at 12 Months: Results from the Pathobiology of Early Arthritis Cohort

Maria DiCicco[1], **Frances Humby**[1], Stephen Kelly[2], Rebecca Hands[1], nora ng[3], Arti Mahto[3], Illias Lazarou[3], Vidalba Rocher[1], Lu Zou[3], Michele Bombardieri[4], Christopher Buckley[5], A.H.M. van der Helm- van Mil[6], Robert B.M. Landewé[7], Désirée van der Heijde[8], Iain B. McInnes[9], Peter C. Taylor[10] and Costantino Pitzalis[11], [1]Centre for Experimental Medicine and Rheumatology, William Harvey Research Institute, Queen Mary University of London, London, United Kingdom, [2]William Harvey Research Institute, Centre for Experimental Medicine and Rheumatology, Queen Mary University of London, London, United Kingdom, [3]William Harvey Research Institute, Centre for Experimental Medicine and Rheumatology, London, United Kingdom, [4]Experimental Medicine and Rheumatology, Queen Mary University of London, London, United Kingdom, [5]University of Birmingham, Rheumatology Research Group, Birmingham, United Kingdom, [6]Leiden University Medical Center, Leiden, Netherlands, [7]University of Amsterdam and Atrium Medical Center, Amsterdam, Netherlands, [8]Rheumatology, Leiden University Medical Center, Leiden, Netherlands, [9]Institute of Infection, Immunity and Inflammation, College of Medicine, Veterinary Medicine and Life Sciences, University of Glasgow, Glasgow, United Kingdom, [10]Kennedy Institute of Rheumatology, Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences, University of Oxford Botnar Research Centre, Oxford, United Kingdom, [11]Centre for Experimental Medicine & Rheumatology, Queen Mary's School of Medicine and Dentistry, London, United Kingdom

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SESSION INFORMATION

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Session Title: Rheumatoid Arthritis - Clinical Aspects IV: Biomarkers, Disease Progression and Treatment Response

Session Type: ACR Concurrent Abstract Session

Session Time: 2:30PM-4:00PM

Background/Purpose:

The inflammatory cell infiltrate in RA synovium has been recognised to organise into lymphocytic aggregates (Ags) with data to suggest that these structures are immunologically competent and can support chronic inflammation. However, their clinical significance has been controversial with conflicting publications reporting diverse associations with disease outcome. Therefore the aim of this study was to determine whether synovial pathotypes associate with clinical phenotype and predict radiographic damage at 12 months in early RA.

Methods:

A cohort of 119 consecutive DMARD-naïve early RA patients (<12 months duration, 2010 ACR/EULAR criteria) were recruited as part of the MRC-funded Pathobiology of Early Arthritis Cohort (PEAC) http://www.peac-mrc.mds.qmul.ac.uk/at Barts and the London Hospital and underwent a pre-treatment baseline US-guided synovial biopsy. Baseline demographics (including ESR, CRP, RF, ACPA and DAS28) and US score (0-3, synovial thickness (ST) and power doppler (PD) of biopsied joint and 12-joint total US score (10 MCP and 2 wrist joints), at baseline were determined. Furthermore, baseline and 12 month hand/feet radiographs underwent Sharp/van der Heijde scoring (SHS). All patients were treated with DMARD combination therapy +/- oral steroids with a treat to target approach (DAS<2.6). Paraffin embedded sections of synovial tissue underwent routine immunohistochemical staining for CD20+ B cells and CD68+ macrophages. Patients were then categorised as aggregate (AG) if grade 2/3 CD20+ Ags were identified and following semi-quantitative scoring (0-4) for CD68+ sublining macrophages into pauciimmune (PI) (≤ 2 CD68+) or diffuse (D) (>2 CD68+, +/- grade 1 Ags). Finally significant differences in clinical parameters at baseline and progression in SHS (≥1) score at 12 months between the 3 synovial pathotypes was determined.

Results: (Table)

At baseline a significantly higher DAS28 score (p=0.02) was seen in the AG vs D or PI pathotype. The number of patients sero + for RF and ACPA was also significantly higher (p=0.029, 0.038) in the AG group. Furthermore US-ST and US-PD scores of the biopsied joint were significantly higher and a trend for higher total US-ST and US-PD scores was also seen in the AG group. Finally a significantly higher number of radiographic progressors were seen in the AG group (p=0.02).

Conclusion:

The significant association between synovial lymphocytic Ags and high disease activity/ sero positivity in patients with early RA suggests a critical role for these structures in RA pathogenesis. Furthermore in this cohort despite a treat to target approach patients with an AG pathotype were significantly more likely to develop progressive radiographic damage. Such data suggests the potential for early patient stratification in order to target effective therapies according to clinical need.

Table 1: Clinical, US and radiographic characteristics according to synovial pathotype

N=119	Synovial pathotype			P value (Anova or Chi sq as appropriate)
Mean (SD)	**Pauciimmune (38)**	**Diffuse (39)**	**Aggregate (42)**	
Age	48.9 (14.0)	51.6 (19.0)	53.3 (17.7)	0.52
Disease duration (months)	5.3 (3.6)	4.9 (2.5)	5.6 (3.5)	0.61
ESR (mm/hr)	25.3 (28.5))	29.8 (21.2)	52.1 (29.2)	<0.0001
CRP (mg/l)	11.5 (37.1)	16.2 (21.9)	23.6 (25.3)	0.17
RF+/RF-	25/13	22/17	35/7	0.029
ACPA+/-	24/14	25/14	36/6	0.038
Swollen Joints	6.7 (6.4)	6.8 (4.7)	8.2 (5.9)	0.42
Tender Joints	11.1 (7.9)	9.8 (6.2)	12.6 (7.2)	0.20
VAS (mm)	59.6 (27.0)	59.1 (27.8)	69.1 (21.7)	0.14
DAS28	4.9 (1.7)	5.3 (1.2)	6.1 (1.5)	0.02
HAQ	1.4 (0.9)	1.4 (0.7)	1.6 (0.79)	0.47
SHS (baseline) (n=104)	1.9 (4.1)	1.8 (4.1)	4.7 (10.2)	0.14
US biopsied ST	1.9 (0.8)	2(0.77)	2.73(0.45)	<0.0001
PD	1.2 (1)	1.5 (0.98)	2.3 (0.75)	<0.0001
joint (0-3)				
US total (12 joint, 0-36)ST	14.8 (8.4)	16.1 (8.9)	16.8 (9.7)	0.67
PD	4.2 (5.3)	6.4 (5.8)	7.5 (6.6)	0.08
Mean corticosteroid dose (mg)	3.2 (3.2)	4.4 (3.6)	4.1 (2.7)	0.26
Mean MTX dose (mg)	11.2 (7.7)	13.8 (7.4)	13.8 (8.16)	0.29
SHSS progressors/non progressors (n=88)	2/26	2/27	9/22	0.021

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Abstract Number: 3099

Differential Effects of IL-6 Blockade Tocilizumab and TNF Inhibitors on the Reduced Angiogenesis and Lining Layer Degeneration in Synovial Tissues from Patients with Rheumatoid Arthritis

Hirohata Shunsei[1], Asami Abe[2,3], Akira Murasawa[3], Tetsuya Tomita[4] and Hideki Yoshikawa[4], [1]Rheumatology and infectious diseases, Kitasato University School of Medicine, Kanagawa, Japan, [2]Rheumatplogy, Niigata Rheumatic Center, Shibata, Japan, [3]Rheumatology, Niigata Rheumatic Center, Shibata, Japan, [4]Department of Orthopedics, Osaka University Graduate School of Medicine, Suita Osaka, Japan
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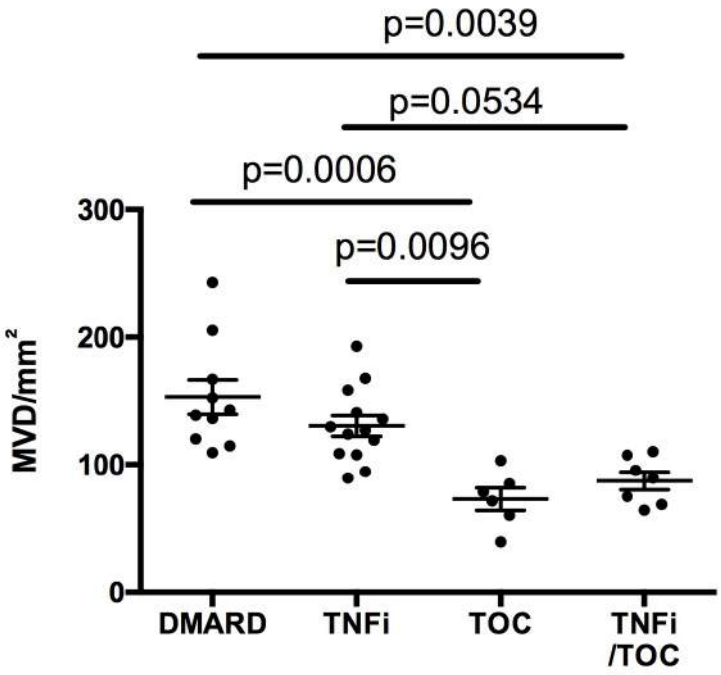
Session Type: ACR Concurrent Abstract Session
Session Time: 2:30PM-4:00PM

Background/Purpose: Rheumatoid arthritis (RA) is a chronic inflammatory disease characterized by hyperplasia of synovial tissues, leading to the destruction of joint structures. TNF inhibitors, including anti-TNF-a antibodies and soluble TNF receptors, have been shown to result in characteristic discoid fibrosis in the deep lining layer of the synovium, probably by their action on synovial cells thereof. Whereas IL-6 blockade tocilizumab has comparable beneficial effects in the treatment of RA, its detailed mechanism actions have not been fully understood. Since angiogenesis plays a pivotal role in the pathogenesis of RA, the current studies were carried out to compare the influences of tocilizumab and TNF inhibitors on the angiogenesis in synovial tissues of RA patients.

Methods: Synovial tissues were obtained during the joint surgical operations from 13 RA patients who had been treated with tocilizumab for at least 4 months (4-47months), 7 of whom had been previously received TNF inhibitors. As a control, synovial tissues were similarly obtained from 13 RA patients who had received TNF inhibitors and from 10 RA patients who had not been given only non-biological DMARDs. Synovial tissues were fixed in formaldehyde and embedded in paraffin. The sections were evaluated by hematoxylin and eosin stain as well as by immunohistological staining with anti-CD31 in which the microvessel densities (MVD) were quantitated under microscopy. Synovial histopathology was evaluated and scored for lining layer proliferation, stromal proliferation and inflammatory changes.

Results: The most remarkable change in the synovium from RA patients treated with tocilizumab was the reduced angiogenesis as well as the degeneration of lining layers in the synovium. irrespective of the previous use of TNF inhibitors. Thus, MVD in patients treated with tocilizumab with or without previous TNF inhibitors were significantly decreased compared with those in patients with TNF inhibitors alone or in patients with non-biological DMARDS (Figure). Moreover, MVD was significantly correlated with lining layer scores, but not with synovial stromal proliferation or inflammatory changes.

Conclusion: These results disclosed that inhibition of angiogenesis is a primary action of tocilizumab. Moreover, the data also suggest that the proliferation of synovial cells in the lining layers might be closely associated with angiogenesis in the sublining layers.



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Abstract Number: 3100

Anti-RA33 Citrullinated/Native Double-Reactive Antibodies Identify Patients with the Highest Risk of Radiographic Progression in Rheumatoid Arthritis

Maximilian F. Konig[1], Jon Giles[2], Peter A. Nigrovic[3] and Felipe Andrade[1], [1]Division of Rheumatology, The Johns Hopkins University School of Medicine, Baltimore, MD, [2]Rheumatology, Columbia University Medical Center, NY, NY, [3]Department of Medicine, Division of Rheumatology, Immunology and Allergy, Brigham and Women's Hospital, Harvard Medical School, Boston, MA

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Session Type: ACR Concurrent Abstract Session

Session Time: 2:30PM-4:00PM

Background/Purpose:

Antibodies against RA33 (hnRNP A2/B1) were one of the earliest antigen specificities identified in rheumatoid arthritis (RA). Unlike the erosive disease associated with anti-citrullinated proteins antibodies (ACPAs) and rheumatoid factor (RF), anti-RA33 antibodies have been uniquely associated with a milder disease phenotype. In preliminary studies, we identified that RA33 is citrullinated in RA synovial fluid (SF), and targeted as citrullinated protein in RA. Here, we define the clinical utility of antibodies against unmodified (native) and citrullinated RA33

(citRA33) in a longitudinal cohort of patients with RA.

Methods:

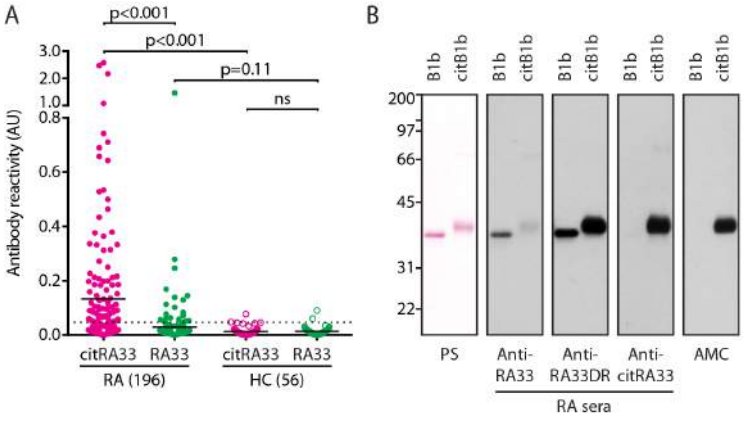
RA33 splicing variants (hnRNP A2/B1/A2b and B1b) were cloned from RA SF cDNA, and recombinant proteins citrullinated in vitro using human rPAD4. Antibody reactivity against native and citrullinated splicing variants of RA33 was compared by ELISA using ACPA-positive RA sera. Patient sera from a cohort study of subclinical cardiovascular disease in RA (n=196) and healthy control sera (n=56) were assayed for antibodies against native and citrullinated B1b by ELISA. Antibody specificities were confirmed by immunoprecipitation and immunoblotting. Antibody positivity was defined based on seroreactivity above the 95th percentile of controls, and correlated with markers of disease activity and radiographic progression.

Results:

Anti-citRA33 antibodies were identified in 86 patients (44%) with RA, while anti-native RA33 antibodies (anti-RA33) were detected in 21 patients (11%) at first visit. Analysis of the fine specificities recognized by these antibodies in patients with RA demonstrated that RA33 is targeted in three ways: (1) exclusively as a citrullinated antigen (n=75); (2) both as a native and citrullinated antigen (n=11); and (3) exclusively as a native antigen (n=10). Patients with anti-citRA33 specific antibodies had a median baseline Sharp-van der Heijde score (SHS) that was 3.4-fold higher than antibody negative patients (17 vs. 5 units, p=0.006). In contrast, anti-RA33 specific antibodies identified patients with the lowest systemic inflammatory burden as measured by CRP and IL-6 levels, and with erosion scores similar to those without either antibody (1.2-fold increase; p=0.81). Minimal longitudinal progression of erosive damage was observed among patients with anti-RA33 alone or anti-citRA33 alone (SHS change/year 0.0 and 0.6, respectively). In contrast, the subset of patients with reactivity against both RA33 and citRA33 (anti-RA33DR) demonstrated a significantly higher rate of radiographic progression (SHS change/year 2.3; p=0.035).

Conclusion:

Anti-citrullinated and anti-native RA33 antibodies identify distinct clinical subsets in RA that differ in disease duration and phenotype. Anti-RA33DR antibodies characterize a unique group of patients with markedly accelerated progression of erosive disease.



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View Abstract and Citation Information Online - http://acrabstracts.org/abstract/anti-ra33-citrullinatednative-double-reactive-antibodies-identify-patients-with-the-highest-risk-of-radiographic-progression-in-rheumatoid-arthritis

Abstract Number: 3101

Receptor Activator of Nuclear Factor Kappa-B Ligand (RANKL) and Sclerostin Are Related to Joint Destruction in Early Rheumatoid Arthritis Unrelated to Polymorphisms of the Genes

Antonia Boman[1], Heidi Kokkonen[2], Ewa Berglin[1], Lisbeth Ärlestig[1] and **Solbritt Rantapaa-Dahlqvist**[3], [1]Public Health and Clinical Medicine/Rheumatology, Umeå University, Umeå, Sweden, [2]Public Health and Clinical Medicine/ Rheumatology, Umeå University, Umeå, Sweden, [3]Department of Public Health and Clinical Medicine/ Rheumatology, Umeå University, Umeå, Sweden
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Background/Purpose: Rheumatoid arthritis (RA) is characterized by joint inflammation and destruction of cartilage and bone. The destructive process is related to autoantibodies, genetic polymorphisms involving proteins in the Wingless related MMTV integration site (Wnt) pathway and markers of inflammation, cartilage and bone. We have analysed the relationships of receptor activator of nuclear factor kappa-B ligand (RANKL) and sclerostin to radiological destruction and progression in early RA.

Methods: Patients with early RA (n=414, symptom duration <1 year) (ARA criteria) with radiological examinations at inclusion and after 24 months were consecutively included. Disease activity score, swollen (SJC) and tender (TJC) joint count, ESR, CRP and treatment were regularly registered. Concentrations of sclerostin (EIA, TECOmedical group, Sissach, Switzerland), RANKL (ELISA, BioVendor, Karasek, Czech Republic) and anti-CCP2 antibodies (ELISA, Euro-Diagnostica AB, Malmö, Sweden) were analysed at baseline. Data on gene polymorphisms were extracted from Immunochip analysis (Uppsala, Sweden).

Results: RANKL concentration was significantly higher in patients compared with controls ($p < 0.001$). Anti-CCP positive patients had significantly higher concentration of RANKL compared with anti-CCP negatives, median (Q1-Q3) 763.7 (347.3-1325.0) pmol/L and 241.5 (137.8-474.1) pmol/L. Sclerostin was significantly increased in patients 0.63 (0.49-0.78) ng/mL versus controls (0.51 (0.4-0.7) ng/mL ($p < 0.01$). After stratification for sex the difference was only significant in females, 0.59 (0.47-0.74) ng/mL compared with controls.

RANKL concentration was related to Larsen score at baseline ($p<0.01$), and after 24 months ($p<0.001$) and to radiological progression after 24 months ($p<0.001$). After adjustments (age and SJC), RANKL was only related to Larsen score at baseline. Sclerostin was significantly ($p< 0.05$) related to radiological progression after 24 months adjusted for sex, Larsen score and ESR at baseline and 24 months' treatment response.

The less frequent type of three SNPs (rs41848320, rs41887440, rs41931102) encoding RANKL was associated with increased concentrations, particularly in the RA-patients, although unrelated to radiological findings. The levels of sclerostin were not related to any of the SNPs.

Conclusion: The concentration of RANKL was related to Larsen score at baseline, whilst the concentration of sclerostin was related to radiological progression during the first 2 years. Measurement of sclerostin at baseline could be a valuable predictor of radiological progression during the first 2 years. Polymorphisms of three SNPs showed increased concentrations of RANKL but were unrelated to radiological findings.

Disclosure: A. Boman, None; **H. Kokkonen**, None; **E. Berglin**, None; **L. Ärlestig**, None; **S. Rantapaa-Dahlqvist**, None.

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Abstract Number: 3102

Increasing Circulating Adiponectin after DMARD Initiation Is Associated with Radiographic Progression in Early Aggressive RA, Regardless of Treatment Strategy

Jon T. Giles[1], S. Louis Bridges Jr.[2], James R. O'Dell[3], Stacey Cofield[4], George Howard[5], Jeffrey R. Curtis[6] and Larry W. Moreland[7], [1]Division of Rheumatology, Columbia University, College of Physicians & Surgeons, New York, NY, [2]Clinical Immunology and Rheumatology, University of Alabama at Birmingham, Birmingham, AL, [3]Rheumatology, University of Nebraska Medical Center, Omaha, NE, [4]School of Public Health, University of Alabama at Birmingham, Birmingham, AL, [5]Biostatistics, The University of Alabama at Birmingham, Birmingham, AL, [6]University of Alabama at Birmingham, Division of Clinical Immunology and Rheumatology, Birmingham, AL, [7]Rheumatology & Clinical Immunology, University of Pittsburgh, Pittsburgh, PA
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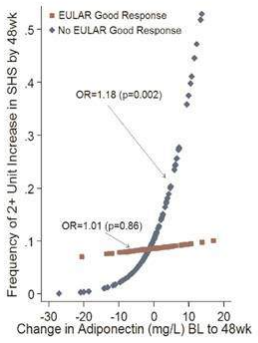
Background/Purpose: Higher levels of circulating adiponectin have been linked to radiographic progression in RA in observational studies, but never studied in the context of early RA with multiple treatment strategies.

Methods: We studied enrollees in the Treatment of Early Aggressive RA (TEAR) Trial. Participants had early, active RA, were seropositive, or had ≥2 baseline erosions. All received methotrexate and either etanercept [immediately (IE) or as step-up therapy (SE)] or sulfasalazine + hydroxychloroquine (i.e triple therapy) [immediately (IT) or as step-up therapy (ST)]. Radiographs (baseline, and wks 48 and 102) were

obtained and Sharp-van der Heijde scores (SHS) calculated blind to sequence. Available stored baseline and 48wks serum samples from patients with complete radiographic data were assayed for total adiponectin using a bead-based Luminex assay (R&D Systems). Assays were optimized, run in duplicate, and blocking for RF was used. Multivariable (MV) generalized linear modeling was used to model SHS change according to baseline and change in adiponectin level, adjusting for relevant confounders.

Results: A total of 288 patients were studied. Baseline characteristics (mean age=51 yrs; 70% female; 74% non-Hispanic White; 91% seropositive for RF or anti-CCP; median RA duration=1.2 months; mean DAS28-ESR=5.8) were similar to those of the entire trial cohort. Baseline radiographic damage was observed in 86%, with a median SHS of 2.5 units. Median baseline adiponectin was 8.6 mg/L, and higher levels at week 48 were observed in 46% of patients. Factors significantly associated with increasing adiponectin included female sex, lower baseline adiponectin, EULAR good response at 48 weeks, and randomization to the IT group. Radiographic progression (≥2 unit increase in SHS) was observed in 10% at 48 wks. MV factors significantly associated included higher age, higher baseline ESR and swollen joint count (SJC), longer RA duration, and increase in adiponectin. Seropositivity, baseline erosions, baseline adiponectin, BMI, and changes in DAS, ESR, or SJC were not associated. For adiponectin, each mg/L increase from baseline to 48wks was associated with a 10% higher odds of radiographic progression (OR=1.10; p=0.009), an effect not altered with adjustment (Figure). Interestingly, this effect was observed only in patients without a 48wk EULAR good response (Figure), and was seen regardless of randomized treatment allocation (Figure). Similar effects were observed for predicting radiographic progression at 102wks.

Conclusion: Rising adiponectin in the setting of treatment non-response was a potent factor associated with radiographic progression among RA patients at highest risk for joint damage in the early phases of disease. Additional mechanistic studies are needed to define the physiologic basis for these findings.



Odds of Radiographic Progression According to Change in Adiponectin from Baseline to Week 48

	Crude			Adjusted*		
	OR	p-value	p-interaction	OR	p-value	p-interaction
All Enrollees	**1.10**	**0.009**	---	**1.11**	**0.008**	---
No EULAR Good Response	**1.18**	**0.002**	**0.046**	**1.23**	**<0.001**	**0.009**
EULAR Good Response	1.01	0.86		1.00	0.96	
No EULAR Good/Triple Therapy	**1.38**	**0.008**	0.13	**1.43**	**0.014**	0.27
No EULAR Good/Etanercept	1.12	0.059		**1.20**	**0.012**	
EULAR Good/Triple Therapy	1.05	0.54	0.40	1.04	0.65	0.56
EULAR Good/Etanercept	0.95	0.55		0.97	0.71	
No EULAR Good/Initial Therapy	**1.27**	**0.003**	0.16	**1.31**	**0.005**	0.41
No EULAR Good/Step-up	1.10	0.20		**1.19**	**0.043**	
EULAR Good/Initial Therapy	0.99	0.93	0.70	1.01	0.89	0.78
EULAR Good/Step-up	1.04	0.68		1.04	0.67	

Odds Ratios represent the change in the odds of radiographic progression (≥2 units increase at 48 weeks) per mg/L increase in serum adiponectin between baseline and 48 weeks

* Adjusted for age, race, baseline swollen joint count, baseline ESR, disease duration

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Disclosure: J. T. Giles, None; **S. L. Bridges Jr.**, None; **J. R. O'Dell**, None; **S. Cofield**, None; **G. Howard**, None; **J. R. Curtis**, Pfizer Inc, 2,Pfizer Inc, 5; **L. W. Moreland**, None.

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Abstract Number: 3103

Carbamylated Human Albumin Is One of the Target Antigens of Anti-Carbamylated Protein Antibodies

Shuichiro Nakabo[1], Koichiro Ohmura[1], Kosaku Murakami[1], Ran Nakashima[1], Moritoshi Furu[2], Masahiro Ishikawa[2], Motomu Hashimoto[2], Yoshitaka Imura[1], Naoichiro Yukawa[1], Hajime Yoshifuji[1], Hiromu Ito[2], Takao Fujii[2] and Tsuneyo Mimori[1,2], [1]Department of Rheumatology and Clinical Immunology, Department of Rheumatology and Clinical Immunology, Graduate School of Medicine, Kyoto University, Kyoto, Japan, [2]Department of the Control for Rheumatic Diseases, Department of the Control for Rheumatic Diseases, Graduate School of Medicine, Kyoto University, Kyoto, Japan

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Background/Purpose: Anti-carbamylated protein antibody (anti-CarP) is seen in 45% of rheumatoid arthritis (RA) patients [1]. The precise target antigen (Ag) of anti-CarP had not been elucidated, since the authors of the first report used fetal calf serum (FCS) as target Ag which contains various kind of proteins. Although several proteins have been reported to be target Ags of anti-CarP, the repertoire of anti-CarP has not

been fully understood. In addition, all reported carbamylated Ags are also known as citrullinated Ags, and carbamylation-specific Ag has not been reported. Since the largest fraction of FCS is albumin, we hypothesized that human albumin (ALB) is one of target Ags of anti-CarP. The purpose of this study is to demonstrate whether anti-carbamylated ALB antibody (anti-car-ALB) is detected in RA and to evaluate its clinical importance.

Methods: ALB and FCS were carbamylated by potassium cyanate. ALB was also citrullinated by peptidyl arginine deiminase. We established in house ELISA systems of anti-carbamylated FCS antibody (anti-car-FCS), anti-car-ALB, and anti-citrullinated ALB antibody (anti-cit-ALB) as previously described [1]. Sera and clinical data of 455 RA patients were obtained from KURAMA database which was established to store clinical information and specimens from RA patients in Kyoto University. Inhibition ELISA was done by 8 representative sera, in which they were pre-incubated with increasing concentration of unmodified FCS, car-FCS, car-ALB, or cit-ALB and tested for reactivity against car-FCS.

Results: The sensitivity of anti-car-FCS, anti-car-ALB, and anti-cit-ALB were 27.0%, 44.2%, and 7.3%, respectively (Table 1). Positive result of anti-car-ALB was related to bone damage and smoking (Table 2). Inhibition ELISA showed anti-car-FCS was inhibited by car-ALB, but not by cit-ALB (Figure 1A). Strength of inhibition by car-ALB was different among sera (Figure 1B). The titer of anti-car-FCS and anti-car-ALB showed good correlation (rho=0.63), but anti-CCP did not correlate with anti-car-ALB (rho=0.28) or anti-cit-ALB (rho=0.16).

Conclusion: Anti-car-ALB was more sensitive than anti-car-FCS for diagnosing RA and correlated with bone damage and smoking. Car-ALB is one of the target Ags of anti-CarP. This is the first report of carbamylation-specific Ag.

Reference: [1] Shi J. Proc Natl Acad Sci U S A. 2011; 108: 17372.

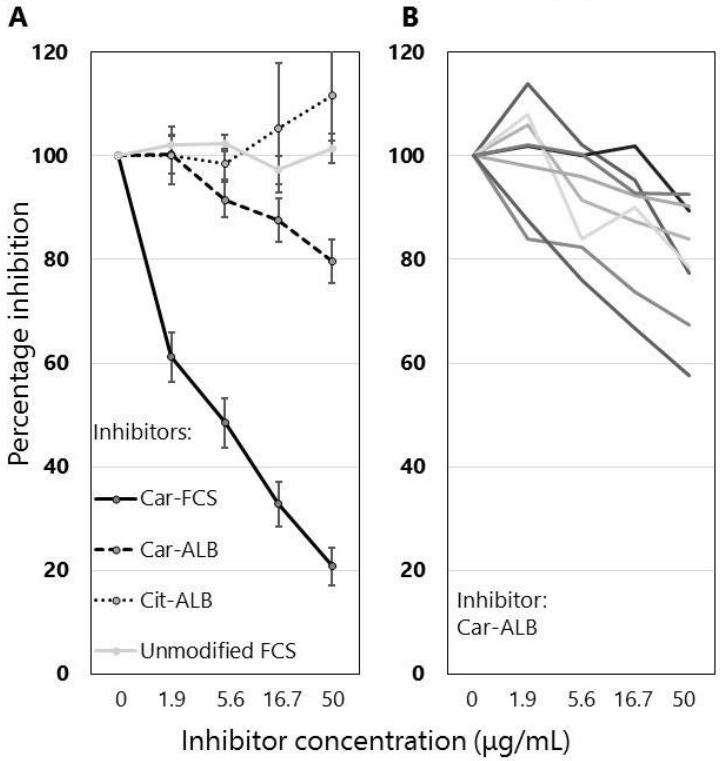
Table 1. Result of each ELISA study and their anti-CCP positivity

		Anti-car-FCS		Anti-car-ALB		Anti-cit-ALB	
		Positive N=123 (27.0%)	Negative N=332 (72.9%)	Positive N=201 (44.2%)	Negative N=254 (55.8%)	Positive N=33 (7.3%)	Negative N=422 (92.7%)
Anti-CCP	Positive N=378	122 (26.8%)	256 (56.3%)	182 (40.0%)	196 (43.1%)	31 (6.8%)	347 (76.3%)
	Negative N=77	1 (0.2%)	76 (16.7%)	19 (4.2%)	58 (12.7%)	2 (0.4%)	75 (16.5%)

Table 2. Comparison of characteristics between anti-car-ALB antibody positive and negative patients

	Anti-car-ALB antibody		
	Positive N=201	Negative N=254	p value
Disease duration, years	14.2 ± 11.6	13.8 ± 7.1	0.67
Stage **I + II** **III + IV**	 72 (29 + 43) 128 (47 + 81)	 122 (54 + 68) 131 (34 + 97)	<0.01
DAS28(CRP)	2.11 ± 0.97	1.99 ± 0.83	0.19
Smoking **Never** **Former + Current**	 108 74 (52+ 22)	 155 68 (45 + 23)	0.03

Figure 1. Inhibition of anti-car-FCS by each protein (A), and that of each serum by car-ALB (B)



Disclosure: **S. Nakabo**, None; **K. Ohmura**, None; **K. Murakami**, None; **R. Nakashima**, None; **M. Furu**, None; **M. Ishikawa**, None; **M. Hashimoto**, None; **Y. Imura**, None; **N. Yukawa**, None; **H. Yoshifuji**, None; **H. Ito**, None; **T. Fujii**, None; **T. Mimori**, None.

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Abstract Number: 3104

Abnormal DNA Methylation in a Novel PTPN11 Enhancer Increases Destructive Potential of Rheumatoid Arthritis (RA) Fibroblast-like Synoviocytes (FLS) and Joint Inflammation

Keisuke Maeshima[1], Stephanie M. Stanford[2], Deepa Hammaker[1], Cristiano Sacchetti[2], Rizi Ai[3], Vida Zhang[4], David L. Boyle[5], Lifan Zeng[6], German Muench[7], Gen-Sheng Feng[8], John Whitaker[9], Zhong-Yin Zhang[6], Wei Wang[10], Nunzio Bottini[2] and Gary S. Firestein[5], [1]Division of Rheumatology, Allergy and Immunology, UCSD School of Medicine, La Jolla, CA, [2]Cellular Biology, La Jolla Institute for Allergy and Immunology, La Jolla, CA, [3]Chemistry and Biochemistry, UC San Diego, La Jolla, CA, [4]Division of Cellular Biology, La Jolla Institute for Allergy and Immunology, La Jolla, CA, [5]Division of Rheumatology, Allergy and Immunology, University of California, San Diego, La Jolla, CA, [6]Biochemistry and Molecular Biology, Indiana University School of Medicine, Indianapolis, IN, [7]La Jolla Institute for Allergy and Immunology, La Jolla, CA, [8]Pathology and Division of Biological Sciences, UC San Diego, La Jolla, CA, [9]Janssen Pharmaceuticals, La Jolla, CA, [10]Chemistry and Biochemistry, University of California, San Diego, La Jolla, CA

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Background/Purpose: Rheumatoid arthritis (RA) fibroblast-like synoviocytes (FLS) mediate disease pathogenesis by invading the joint extracellular matrix. The *PTPN11* gene, encoding the tyrosine phosphatase SHP-2, is overexpressed in RA FLS compared to osteoarthritis (OA) FLS and promotes RA FLS invasiveness. Here we sought to elucidate the molecular basis for *PTPN11* overexpression in RA and explore

whether pharmacologic inhibition or genetic deficiency of its expressed protein, SHP-2, reduces RA FLS aggressiveness and arthritis severity.

Methods: FLS were obtained from arthroplasty RA and OA synovium. Dexamethasone (DEX)-induced DNA binding of the glucocorticoid receptor (GR) in RA FLS was assessed by chromatin immunoprecipitation (ChIP)-PCR. Arthritis severity in the K/BxN serum transfer model was assessed by measuring ankle swelling. Contribution of *PTPN11* in FLS to arthritis severity was assessed by reconstitution of irradiated wild type (WT) or *Ptpn11*$^{-/+}$mice with bone-marrow from WT mice.

Results: Potential regulatory regions of *PTPN11* were identified in the UCSC genome browser and the ENCODE database. Based on the co-localization of histone marks and transcription factor binding motifs, we identified a possible 1.4 kb enhancer in intron 1 of *PTPN11* containing a glucocorticoid receptor (GR)-binding motif. To confirm function of the enhancer, the region was subcloned into a luciferase reporter construct and transfected into FLS. The FLS were stimulated with DEX (100 nM) and ChIP-PCR showed that GR binding to the enhancer increased 5.6±0.4-fold ($p<0.01$) and increased luciferase expression by 13±5-fold ($p<0.05$). We then showed that DEX increased *PTPN11* expression 1.4-fold higher in RA than OA FLS ($p<0.05$). To determine why *PTPN11* expression is higher in RA, we pyrosequenced the 8 enhancer CpG sites near the GR-binding site. We found 2 hypermethylation sites in RA FLS compared to OA FLS: chr12 112860522 (28±4.1% in RA and 8.2±0.7% in OA; $p<0.01$) and chr12 112860601 (30%±3.6 in RA and 17%±2.4 in OA; $p<0.05$). Deletion of the two CpGs reduced enhancer activity by 40±9% ($p<0.05$), showing they are required for enhancer function. Having discovered that *PTPN11* dysregulation is associated with abnormal enhancer DNA methylation in two CpGs, we examined functional consequences of high *PTPN11*. Using a transwell assay, a small molecule SHP-2 inhibitor reduced RA FLS migration by 83±8.3% ($p<0.0001$). Furthermore, heterozygous deletion of *Ptpn11* in radioresistant cells (e.g., fibroblasts) attenuated passive K/BxN arthritis severity in mice (54±3.4% reduction, $p<0.05$). Treatment of mice daily with 7.5 mg/kg SHP-2 inhibitor reduced arthritis severity by 20±5% (AUC, $p<0.05$).

Conclusion: We identified a new intronic GR-responsive enhancer that is abnormally methylated in RA FLS, resulting in increased expression of the pathogenic gene *PTPN11*. Blocking function of its encoded protein, SHP-2, reduces RA FLS aggressiveness and arthritis severity. Our findings show how the interplay of abnormal epigenetics with a pathogenic gene determines FLS behavior and joint inflammation. SHP-2 inhibition could be an important new strategy that targets FLS invasiveness in RA.

Disclosure: K. Maeshima, None; **S. M. Stanford**, None; **D. Hammaker**, None; **C. Sacchetti**, None; **R. Ai**, None; **V. Zhang**, None; **D. L. Boyle**, None; **L. Zeng**, None; **G. Muench**, None; **G. S. Feng**, None; **J. Whitaker**, Janssen Pharmaceutica Product, L.P., 3; **Z. Y. Zhang**, None; **W. Wang**, None; **N. Bottini**, None; **G. S. Firestein**, None.

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Abstract Number: 3105

The RA Immune System Recreated in Immunodeficient Mice By Thymic Differentiation from RA Patients' Hematopoietic Stem Cells Exhibits Marked CD4 T Cell Activation and Differentiation

Robert Winchester[1], Chiara Borsotti[2], Nichole Danzl[2], Jon Giles[3], Joan M. Bathon[4] and Megan Sykes[2], [1]Dept of Pediatrics & Medicine, Columbia University, New York, NY, [2]Medicine, Columbia University, New York, NY, [3]Rheumatology, Columbia University Medical Center, NY, NY, [4]Medicine, Columbia University, College, New York, NY

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Background/Purpose: We recently reported an advance in modeling the human immune system in mice, (Kalscheuer et al. Sci Transl Med 2012) involving maturation of patient immune systems from marrow hematopoietic stem cells (HSCs) in NOD/SCID/IL-2 receptor γ chain^{null} immunodeficient mice receiving partially HLA-matched human fetal thymic tissues to recreate the adult donor's functional and diverse T and B cell repertoires. These resemble the donor repertoire in tolerance of self and non-self recognition, but predominantly consist of naïve phenotype T cells. Since HSCs contain the genetic information to recreate a replica of each individual's unique immune system, this Personalized Immune Mouse (PIM) affords a powerful and novel opportunity to recreate a functional human immune system of a patient with a systemic autoimmune disease, generated through thymic (for T cells) and bone marrow (for B cells) selection *de novo* from adult HSCs.

Methods: We explored the feasibility of creating replicas of RA patient immune systems to study early events during formation of their immune system. 120 RA patients meeting classification criteria were sequence-based typed for HLA-ABC and DRB1alleles to identify those who matched similarly HLA-typed available fetal thymic tissue by at least one HLA-A allele and one shared epitope-encoding HLA-DRB1 allele.

After informed consent, 15-25 mls of RA donor marrow was aspirated yielding ~$2x10^6$ CD34+ cells isolated by magnetic beads. ~$2.5x10^5$HSCs were injected intraosseously into each mouse in a cohort of replicates irradiated with 2Gy, that had the T cell-depleted thymic fragment implanted under the renal capsule.

Results: To date, HSC preparations from 3 RA patients, aged <34 yrs, were studied. The third donor generated an RA immune system that at 12 weeks resembled those established from healthy controls in having 12-20 % of circulating hCD45+ cells of human origin, of which 2/3 were hCD19 and 1/3 hCD3. At week 14 the thymic grafts contained 2-$9x10^6$human thymocytes, ~70% double positive. However, in marked contrast to reconstitutions with healthy control HSCs, where 80-90% of circulating CD4 T cells typically exhibit the CD45RA+CD45RO- naïve phenotype, in RA-PIM 5-25% of the CD4 T cells expressed HLA-DR and from 50 to 90% of circulating CD4 T cells had lost expression of CD45RA, reflecting activation and memory-effector differentiation. By week 14, 5-30% of bone marrow and splenic T cells were terminally differentiated to CD28-CD45RA+ and similar proportions expressed CD57, CD69, and HLA-DR, T cell phenotypes long recognized to occur in RA patients. The proportion of immature RA-PIM marrow B cells was also reduced compared to healthy controls, reflecting enhanced differentiation to naïve and transitional B cells.

Conclusion: In the initial weeks of immune cell development from HSC, replicas of RA immune systems exhibit marked CD4 T cell activation and T and B cell differentiation, suggesting their intrinsic hyperactivity compared to quiescent cell populations comparably generated from healthy controls. These results suggest that there may be genetically-predetermined defects in the selection or regulation of lymphocytes in RA that can be replicated and analyzed in PIM.

Disclosure: R. Winchester, None; **C. Borsotti**, None; **N. Danzl**, None; **J. Giles**, None; **J. M. Bathon**, None; **M. Sykes**, None.

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Abstract Number: 3106

Regulation of ASK1 Expression By microRNA-17 and Their Correlation with Rheumatoid Arthritis Pathogenesis

Nahid Akhtar and Salahuddin Ahmed, Department of Pharmaceutical Sciences, Washington State University College of Pharmacy, Spokane, WA

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Session Type: ACR Concurrent Abstract Session

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Background/Purpose: Aberrant expression of microRNAs (miRs) has shown to be critical for the pathogenesis of rheumatoid arthritis (RA). Apoptosis signal regulating kinase-1 (ASK1), a member of MAP3K family upstream of p38 and JNK MAPK has recently been associated with RA pathogenesis. Here we studied the regulation of ASK1 by miR-17 in human RA synovial fibroblasts (RA-FLS) and correlated their expressions in human RA and adjuvant induced arthritis (AIA) and collagen induced arthritis (CIA) models of RA.

Methods: Bioinformatics analysis was performed to identify miRs predicted to targets ASK1 3'UTR. ASK1 and miR-17 expressions were correlated in FLS/synovial tissue (ST) from RA (n=15), osteoarthritis (OA; n=11), or non-diseased (NL; n=8) donors using Western blotting and qRT-PCR. Effect of IL-1β (10 ng/ml) or TNF-α (20 ng/ml) with or without ASK1 inhibitor (TC-ASK-10; 12.5 μM) or ASK1 siRNA was studied on the expression of phospho-p38 (p-p38), p-JNK, IL-6, and IL-8. Luciferase assay was performed using ASK1 3'UTR construct and pre-miR-17 to verify miRNA:mRNA interaction. Effect of miR-17 overexpression and inhibition on ASK1 was evaluated by transfection of RA-FLS with pre-miR-17/anti-miR-17. Findings from human FLS were validated in AIA and CIA models. Serum miR-17 levels in RA patients, AIA and in CIA models were quantified using qRT-PCR. Effect of miR-17 overexpression on matrix metalloproteinases (MMPs) was determined in the conditioned media using MMPs protein array. $p<0.05$ was considered significant.

Results: Bioinformatics analysis predict miR-17 binding site in the 3'UTR region of ASK1 mRNA. Expression of miR-17 was down-regulated (70%) in RA-FLS compared to NL-FLS and inversely correlated with a significant increase in ASK1 mRNA (2.3-fold) and protein. Similar inverse correlation of miR-17 and ASK1 was also observed in RA-ST compared to NL-ST. No significant correlation was observed between miR-17 and ASK1 expression in OA-FLS or OA-ST. IL-1β or TNF-α stimulation further suppressed miR-17 expression, with a concomitant increase in ASK1 mRNA (2.2-12.5 fold) and protein in RA-FLS. Co-transfection of RA-FLS with the ASK1 reporter construct and pre-miR-17 significantly suppressed the luciferase activity (34%). Overexpression of miR-17 inhibited ASK1 protein, whereas its inhibition enhanced ASK1 protein in RA-FLS. Interestingly, inhibition of ASK1 using TC-ASK-10 resulted in a marked attenuation of p-p38, p-JNK MAPK, IL-6, and IL-8 expression in RA-FLS. Knockdown of ASK1 or overexpression of miR-17 inhibited TNF-α-induced IL-6 and IL-8 production in RA-FLS. Overexpression of miR-17 also inhibited MMP-1, -3, and -13 production in IL-1β stimulated RA-FLS. miR-17 levels were significantly lower in the serum of RA patients, AIA and in CIA models compared to controls with increased in arthritis score. In AIA and CIA studies,

ASK1 expression increased with the disease progression, and correlated with lower miR-17 expression and enhanced p-p38, p-JNK, IL-6, and IL-8 expression in arthritic joints.

Conclusion: This study provides evidence for the role of ASK1 in RA pathogenesis and a novel mechanism of its regulation by miR-17 in human RA-FLS and in two different models of RA.

Disclosure: N. Akhtar, None; **S. Ahmed**, None.

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Abstract Number: 3107

Investigating the Ameliorating Effect of Pregnancy on Rheumatoid Arthritis Using Whole Transcriptome Analysis

Anuradha Mittal[1], Lior Pachter[2], J. Lee Nelson[3], Hanne Kjaergaard[4], Mette Smed[4], Vibeke Zoffmann[4], Jørn Olsen[5], Merete Lund Hetland[6], Ingileif Hallgrimsdottir[2] and Damini Jawaheer[1], [1]Children's Hospital Oakland Research Institute, Oakland, CA, [2]University of California, Berkeley, Berkeley, CA, [3]Immunogenetics, Fred Hutchinson Cancer Rsch, Seattle, WA, [4]Juliane Marie Center, Copenhagen, Denmark, [5]Aarhus University, Aarhus, Denmark, [6]On behalf of all Depts of Rheumatology in Denmark, DANBIO, Glostrup Hospital, Glostrup, Denmark
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SESSION INFORMATION
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Session Type: ACR Concurrent Abstract Session
Session Time: 2:30PM-4:00PM

Background/Purpose: Pregnancy is known to induce a natural improvement of Rheumatoid Arthritis (RA) symptoms in 50-75% of patients as gestation progresses. However, the underlying mechanisms are not well understood. In this study, we aimed to identify genes that demonstrate altered expression in RA during pregnancy through analysis of transcriptome profiles before pregnancy and at the third trimester from women with RA who show pregnancy-induced improvement in Clinical Disease Activity Index (CDAI) scores, and from healthy women (controls).

Methods: Blood was drawn from 7 women fulfilling the 1987 ACR criteria for RA and from 5 healthy women, before conception and at the third trimester. Total RNA was isolated and used to prepare cDNA libraries which were sequenced on an Illumina HiSeq2500 instrument at an average depth of 60 million reads (100bp). The raw RNA sequencing (RNA-seq) data was pre-processed and aligned to the reference Human transcriptome using Bowtie2. Gene expression levels were quantified using eXpress. Genes differentially expressed between groups (between RA cases and controls or between time-points) were identified with edgeR using a fold-change cutoff of 2 and significance threshold $p<0.05$ (FDR corrected). Functional category enrichment analysis was performed using the DAVID bioinformatics resource.

Results: Before pregnancy, 1,311 genes were differentially expressed in RA cases (CDAI: 11.1 ± 8.9) vs controls. In contrast, in the third trimester of pregnancy when there was improvement in RA disease activity (CDAI: 3.0 ± 2.4), differential expression between RA cases and controls was limited to only 38 genes, showing a dilution of the pre-pregnancy RA gene expression signature. Among the genes demonstrating RA-associated expression before pregnancy, those showing differential expression among healthy women in the third trimester vs before pregnancy – i.e. genes with expression levels modulated by pregnancy in the absence of RA – were found to be enriched in biological processes such as translational elongation, inflammatory response, immune response and leukocyte activation. Interestingly, in the third trimester, a subset of these pregnancy-modulated genes no longer displayed differential expression between cases and controls, even though they were over-expressed in RA cases compared to controls before pregnancy. These included genes such as CEACAM8, OLFM4, CAMP, ELOF1 and SLPI, some of which have been implicated in RA and some in pregnancy.

Conclusion: These pre-pregnancy and third trimester transcriptional signatures in RA suggest that the set of genes that show altered expression among cases during pregnancy may have a role in the pregnancy-induced changes in RA disease activity.

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Abstract Number: 3108

Serum 14-3-3eta Are Elevated in Indigenous North Americans with Rheumatoid Arthritis and May Predict Imminent Synovitis in Their at-Risk First Degree Relatives

Carol Hitchon[1], Irene Smolik[2], Xiaobo Meng[1], David Robinson[2] and Hani S. El-Gabalawy[1], [1]University of Manitoba, Winnipeg, MB, Canada, [2]Arthritis Center, University of Manitoba, Winnipeg, MB, Canada

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SESSION INFORMATION

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Session Title: Rheumatoid Arthritis - Human Etiology and Pathogenesis III

Session Type: ACR Concurrent Abstract Session

Session Time: 2:30PM-4:00PM

Background/Purpose:

Indigenous North Americans (INA) have high prevalence rates of severe erosive rheumatoid arthritis (RA). We have established a cohort of unaffected first degree relatives (FDR) of INA RA patients who are at high risk for future RA in order to evaluate the preclinical events leading to disease. 14-3-3 eta, an extracellular ligand that activates intracellular signalling pathways associated with RA, is found in seropositive erosive RA and may predict future RA in subjects with arthralgia. In this study, we sought to evaluate 14-3-3eta in INA with RA, and in asymptomatic FDRs prior to the onset of synovitis.

Methods: FDRs are reviewed annually for the development of synovitis. Serum 14-3-3eta levels were measured by commercial ELISA in 22 INA RA subjects and in serial samples from 19 FDR (10 who developed synovitis(FDR-S)). Titers higher than 0.16 ng/ml were considered positive. Anti-citrullinated peptide antibodies (ACPA) were measured by ELISA and rheumatoid factor (RF) by nephlometry. Percent positive or median with interquartile range (IQR) are reported. Subject groups were compared using Chi square tests and odds ratios with 95% confidence limits (CL) reported and using Mann Whitney U tests. Correlations were assessed by spearman tests. Changes in titers over time were assessed by Wilcoxon signed rank tests.

Results:

INA with RA were more likely to have elevated serum levels of 14-3-3eta than their FDRs (15/20(75%) vs 3/19(16%) OR 16 CL 3.2-78.9) p<0.001). Titres ranged from 0.16-20ng/ml (median (IQR) RA 1.24(6.4))vs FDR 0.16 (0.05)ng/ml p=0.001). In RA, 14-3-3eta positivity was not associated with ACPA (4/5 (80%) without ACPA vs 12/16 (75%) with ACPA p=ns), RF (13/16 (81%) with RF vs 3/5(60%) without RF p=ns) nor with CRP or joint counts. Titers of 14-3-3 correlated modestly with RF titer (spearman rho 0.44 p=0.05) but not with other clinical activity indices. Three pre-disease serum samples were tested for each FDR-S; 2 for each non-transitioning FDR. RF and ACPA positivity generally preceded 14-3-3eta positivity. Five FDR-S initially negative for 14-3-3eta became positive up to 46 months prior to or at disease transition; one FDR-S was positive at all three visits. In FDR-S, 4 developed ACPA and 14-3-3 at the same time, 2 developed ACPA before 14-3-3eta. The two FDR initially positive for 14-3-3eta at a low titer (both <0.25) were negative on repeat testing and have not developed synovitis after 3 and 8 years. Significant changes in 14-3-3eta titer between first and last sample (taken at time of transition) were seen for FDR-S (median (IQR)0.16 (0) vs 0.37 (2.54) ng/ml p=0.04) but not for FDRs who remained arthritis-free.

Conclusion:

In this cohort of INA RA and their at risk FDRs, 10 FDR developed clinical synovitis. 14-3-3eta was found primarily in the setting of disease but did not associate with RA activity. In pre-clinical RA 14-3-3eta was usually preceded by RF and/ or ACPA and 14-3-3eta positivity generally occured at or near the time of disease onset suggesting it may be a useful predictor of imminent RA.

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Abstract Number: 3109

Single Cell Gene Expression in Classical Monocytes Correlates with Treatment Response Groups to TNF-Alpha Inhibition in Rheumatoid Arthritis

Theresa Wampler Muskardin[1], Wei Fan[2], Jessica M. Dorschner[3], Zhongbo Jin[3], Mark A. Jensen[4] and Timothy B. Niewold[3], [1]Division of Rheumatology, Mayo Clinic, Rochester, MN, [2]Department of Rheumatology, Ren Ji Hospital, School of Medicine, Shanghai Jiao Tong University, China, Shanghai, China, [3]Division of Rheumatology and Department of Immunology, Mayo Clinic, Rochester, MN, [4]Department of

Immunology and Division of Rheumatology, Mayo Clinic, Rochester, MN
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Background/Purpose: In management of rheumatoid arthritis (RA), initiating effective treatment as soon as possible within the so-called therapeutic "window of opportunity" is the strategy, and disease remission is a primary goal. Recent work from our group demonstrated that pre-treatment serum type I IFN- β/α ratio > 1.3 can predict non-response to anti-TNF-alpha therapy in RA patients. The cellular mechanisms that underlie the IFN-β/α ratio that predicts response are not known. Effects of IFN on single immune cells and uncommon cell populations may be masked in whole blood or mixed cell populations.

Methods: To better understand the underpinnings of the pre-treatment IFN-β/α ratio, we used single cell expression analysis to investigate whether monocyte gene expression differs significantly between RA patients according to their pre-TNF-α inhibitor serum IFN-β/α ratio. Single classical (CL) and single non-classical (NCL) blood-derived monocytes were isolated from 15 seropositive RA subjects prior to biologic therapy. An IFNα gene score was calculated from the expression level of 10 genes induced in healthy control blood-derived monocytes after in vitro stimulation by IFNα. An IFNβ gene score was calculated from the expression level of 10 genes found to be induced by IFNβ while excluding the possibility of influence of IFNα. Subjects were grouped by pre-TNF-α inhibitor serum IFN-β/α ratio into two groups, IFN-β/α > 1.3 (n=6) and IFN-β/α < 1.3 (n=9). Comparisons between groups were by Mann-Whitney. Hierarchical clustering of 87 target genes was done to determine if there were functional gene expression differences between groups.

Results: Hierarchical clustering revealed striking differences of expression of gene sets in CL monocytes between patients with IFN-β/α < 1.3 and IFN-β/α > 1.3, the groups which correspond to response/non-response to anti-TNF-α agents. This same clustering was not observed in NCL monocytes, and the differentiation between anti-TNF-α response patient groups was lost when hierarchical clustering was done on total monocytes (CL and NCL). Two major gene sets which differentiated subjects with IFN-β/α > 1.3 (non-response to anti-TNF-α group) in CL monocytes included TLR and IFN pathway genes, cell surface markers and cytokines as follows: cluster 1 (GMCSF, TLR7, STAT2, ILT7, MYD88) and cluster 2 (TLR2, CD16, JAK1, IFI27, IL1A, and MAVS).

Conclusion: These within-cell expression patterns demonstrate biological differences in CL monocytes of RA patients with an IFN-β/α > 1.3, the ratio of type I IFNs previously found to be predictive of non-response to anti-TNF-α therapy. Differentiation by gene expression among the response/non-response patient groups is lost when comparing gene expression in single NCL monocytes and single mixed population monocytes (CL and NCL), suggesting that further study of CL monocytes will likely illuminate molecular differences that determine treatment response to TNF-α inhibition in RA. This work will help to develop a more individualized approach to therapy in RA based upon the underlying biology of disease in a given patient.

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Abstract Number: 3110

In the Multicenter Randomized Controlled Rotation or Change Trial, a Non-TNF Targeted Therapy Has a Higher Efficacy Than a Second Anti-TNF at 3, 6 and 12 Months

Jacques Gottenberg[1], Olivier Brocq[2], Aleth Perdriger[3], Slim Lassoued[4], Jean-Marie Berthelot[5], Daniel Wendling[6], Liana Euller-Ziegler[7], Martin Soubrier[8], Christophe Richez[9], Bruno Fautrel[10], Arnaud Constantin[11], Xavier Mariette[12], Jacques Morel[13], Mélanie Gilson[14], Gregoire Cormier[15], Jean Hugues Salmon[16], Stephanie Rist Bouillon[17], Frederic Lioté[18], Hubert Marotte[19], Christine Bonnet[20], Christian Marcelli[21], Jeremie Sellam[22], Olivier Meyer[23], Elisabeth Solau-Gervais[24], Sandrine Guis[25], Jean Marc Ziza[26], Charles Zarnitsky[27], Isabelle Chary-Valckenaere[28], O Vittecoq[29], Alain Saraux[30], Yves-Marie Pers[31], Martine Gayraud[32], Gilles Bolla[33], Pascal Claudepierre[34], Marc Ardizzone[35], Emmanuelle Dernis Labous[36], Maxime A. Breban[37], Olivier Fain[38], Jean Charles Balblanc[39], Ouafaa Aberkane[40], Marion Vazel[40], Christelle Back[40], Elodie Perrodeau[41], Jean Sibilia[42] and Philippe Ravaud[32], [1]Hautepierre, Strasbourg, France, [2]Hospital Center Princesse Grâce, Monaco, Monaco, [3]Service de Rhumatologie, CHU de Rennes, Rennes, France, [4]Rheumatology, Cahors, France, [5]Rheumatology, University Hospital, Nantes, France, [6]Université de Franche-Comté, Besançon, France, [7]Rheumatology, Nice, France, [8]Rheumatology department CHU Clermont-Ferrand, Clermont-Ferrand, France, [9]Rheumatology, Bordeaux, France, [10]Rheumatology, AP-HP Pitié-Salpêtrière Hospital / Pierre and Marie Curie University Paris 6 GRC-08 (EEMOIS), Paris, France, [11]Rheumatology, CHU Purpan - Hopital Pierre-Paul Riquet, Toulouse, France, [12]Université Paris-Sud, AP-HP, Hôpitaux Universitaires Paris-Sud, Paris, France, [13]Department

of rheumatology, Lapeyronie Hospital and Montpellier University, Montpellier, France, [14]Hospital Center, Grenoble, France, [15]Rheumatology, La Roche Sur Yon, France, [16]Hôpital Maison Blanche, Rheumatology, REIMS, France, [17]Rhumatologie, Hopital La Source, La Source, France, [18]Rheumatology, Lariboisière, France, [19]INSERM 1059 / LBTO, Université de Lyon, Saint-Etienne; Rheumatology Department, Saint-Etienne, France, [20]Rheumatology, CHU Dupuytren, Limoges, France, [21]Rheumatology, Caen, France, [22]Rheumatology, PARIS, France, [23]Rheumatology, Hopital Bichat, Paris, France, [24]Rhumatologie, University Hospital, Poitiers, France, [25]Rheumatology, Marseille, France, [26]Hopital Croix-Saint-Simon, Paris Cedex 20, France, [27]Rheumatology, Le Havre, France, [28]Rheumatology, Nancy, France, [29]University Hospital, Rouen, France, [30]Rheumatology, Brest, France, [31]Rheumatology, Montpellier, France, [32]Rheumatology, Paris, France, [33]Rheumatology, Cannes, France, [34]Rheumatology, Université Paris Est Créteil, Créteil, France, [35]Rheumatology, Centre Hospitalier de Mulhouse, Mulhouse, France, [36]Réseau Hôpital et Ville en Rhumatologie (RHEVER) Network, Paris, France, [37]Rheumatology, A. Paré University Hospital, Boulogne-Billancourt, France, [38]Internal Medicine Department, Saint Antoine Hospital, Paris, France, [39]Rheumatology, Belffort, France, [40]Rheumatology, Strasbourg, France, [41]Epidemiologist, Paris, France, [42]Department of Rheumatology, Strasbourg University Hospital, Strasbourg, France
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SESSION INFORMATION

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Session Title: Rheumatoid Arthritis-Small Molecules, Biologics and Gene Therapy V: Immunogenecity
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Session Time: 2:30PM-4:00PM

Background/Purpose:

As many as one third of patients show insufficient response to their first TNF inhibitor (TNF-insufficient response, TNF-IR). The lack of efficacy of one anti-TNF drug does not preclude the potential efficacy of another anti-TNF drug. Alternatively, switching to a non-TNF-targeted therapy is also a rationale strategy. These 2 strategies (a second anti-TNF agent or a non-TNF targeted therapy) have only been compared in scarce observational studies in TNF-IR patients. However, no randomized controlled trial has compared the efficacy of a non-TNF-targeted biologic and a second anti-TNF drug in TNF-IR patients. We previously presented the preliminary results at 6 months. We now present the final 12 month-results of the trial.

Methods:

The “Rotation of anti-TNF Or Change of class of biologic” (ROC) trial (NCT01000441) is a multicenter,investigator-initiated, open, parallel-group, randomized controlled trial. Patients with inadequate response to a first anti-TNF were randomly assigned in a 1:1 ratio to receive a non-TNF-targeted biologic or a second anti-TNF agent. The choice of the biologic prescribed within each randomized group (ie, non-TNF-targeted biologic or a second anti-TNF agent) was left to the treating clinician. The study duration was 48 weeks.

Results:

- Week 12

At week 12 (W12), for patients randomized to a non-TNF-targeted biologic (n=146) or a second anti-TNF agent (n=146), 64.2% and 47.8%, respectively, achieved a good or moderate EULAR response (good response: 27.7% and 13.2%, respectively; moderate response: 36.5% and 34.6%, respectively) (OR 2.01, 95% CI [1.23; 3.32], p = 0.005).

- Week 24

At W24 (primary outcome), 69.7% and 52.1%, respectively, achieved a good or moderate EULAR response (good response: 39.4% and 21.1%, respectively; moderate response: 30.3% and 31.0%) (OR 2.12, 95%confidence interval [95% CI] [1.31; 3.46], p=0.003). At W24, DAS28-ESR was lower for patients with the non-TNF-targeted biologic than second anti-TNF drug (difference adjusted to baseline value -0.43, 95% CI [-0.72; 0.14], p= 0.004). The proportion with low disease activity was 44.6% and 27.9%, respectively (OR 2.09, 95%CI [1.27; 3.43], p= 0.004).

- Week 48

At W48, 60.0% of patients treated with a non TNF-targeted biologic and 43.2% of those treated with a second anti-TNF were EULAR responders (good response: 37.7% and 21.2%, respectively; moderate response: 22.3 and 22.0%, respectively) (OR 1.97 (95%CI [1.21; 3.24], p = 0.007). DAS28-ESR was lower for patients with the non-TNF-targeted biologic than second anti-TNF drug (difference adjusted to baseline value -0.38, 95% CI [-0.69; 0.08], p= 0.013). The proportion with low disease activity was 40.8% and 23.5%, respectively (OR 2.24, 95%CI [1.32; 3.82], p= 0.003). The proportion with DAS28-ESR remission was 26.9% and 13.6%, respectively (OR 2.34, 95% CI [1.24; 4.39], p= 0.009. Ongoing comparison of radiographic progression and safety will be also presented at ACR.

Conclusion: This randomized controlled trial demonstrated a better efficacy of a non-TNF-targeted biologic than a second anti-TNF agent for TNF-IR patients. This superiority was consistent over time and across numerous outcome criteria.

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Abstract Number: 3111

Long-term Safety and Efficacy of Mavrilimumab, a Fully Human Granulocyte-Macrophage Colony-Stimulating Factor Receptor-α (GM–CSFR-α) Monoclonal Antibody, in Patients with Rheumatoid Arthritis (RA)

Gerd Burmester[1], IB McInnes[2], JM Kremer[3], P Miranda[4], J Vencovský[5], A Godwood[6], M Albulescu[6], D Close[6] and Michael Weinblatt[7], [1]Department of Rheumatology and Clinical Immunology, Charité - Universitätsmedizin Berlin, Berlin, Germany, [2]Glasgow Biomedical Research Centre, Glasgow, United Kingdom, [3]The Albany Medical College, Albany, NY, [4]Centro De Estudios Reumatológicos, Santiago, Chile, [5]Institute of Rheumatology and Department of Rheumatology, Charles University, Prague, Czech Republic, [6]MedImmune, Cambridge, United Kingdom, [7]Division of Rheumatology, Immunology and Allergy, Brigham and Women's Hospital, Boston, MA
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Background/Purpose: Modulating macrophage function through GM–CSF is a novel therapeutic approach for RA. Mavrilimumab, a fully human monoclonal antibody, which targets GM–CSFR-α, has demonstrated efficacy and an acceptable safety profile in prior 12- and 24 week studies.[1,2]This analysis evaluated the long term (LT) safety and efficacy of mavrilimumab through 74 weeks of treatment.

Methods: This open-label extension (OLE) study (NCT01712399) enrolled adult RA patients (pts) who had completed the EARTH EXPLORER 1[2] and 2 (NCT01715896) Phase IIb studies or were rescued as inadequate responders at a predefined time point. Pts received subcutaneous mavrilimumab 100 mg every other week (eow), consistent with the highest dosage in the Phase IIa study.[1]The primary objective was to assess the LT risk:benefit ratio of mavrilimumab via evaluation of i) Treatment emergent adverse events (TEAEs), TE serious AEs (TESAEs), and pulmonary function tests (PFTs), and ii) Exploratory LT efficacy endpoints (DAS28–CRP/ACR responses). AEs with onset date after mavrilimumab had been started are presented. Change from baseline (BL) in modified Total Sharp Score (mTSS) was used to explore radiographic progression in pts previously included in EARTH EXPLORER 1.

Results: At the 74 week (includes original study) cutoff, 391 pts had been enrolled in the OLE study. Of these, 329 (84.1%) continued on treatment and 62 (15.9%) discontinued (due to withdrawal of consent, 9/391 [2.3%]; death [cardiopulmonary failure], 1/391 [0.3%]; adverse event, 7/391 [1.8%]; non study-related site closure, 20/391 [5.1%]; other, 24/391 [6.1%]; lost-to-follow-up, 1/391 [0.3%]). Between the Phase IIb and OLE studies, 440 pts received mavrilimumab, with a safety exposure of 603 pt years (yr) and median (min–max) duration of 1.6 (0.1–2.4) yr. Most common TEAEs (n [/100 pt yr]) were nasopharyngitis (51 [8.45]), bronchitis (36 [5.97]) and hypertension (32 [5.30]); the serious infection rate was 1.82/100 pt yr. PFT demonstrated a generally transient 20% reduction to < 80% of predicted in a few pts (Table). Mavrilimumab demonstrated sustained efficacy with DAS28–CRP <3.2 and <2.6 rates of 57.3% and 38.5%, respectively (Table). After 74 weeks of treatment, 68% of pts showed no radiographic progression (<0.5 change in mTSS vs. BL) (Table).

Conclusion: Mavrilimumab continues to demonstrate a sustained efficacy and safety profile in pts with moderate to severe RA, over the 74 week treatment duration reported. No significant pulmonary signals were observed. Although mavrilimumab 100 mg eow is suboptimal compared with 150 mg eow in DMARD-IR pts,[2] efficacy results are comparable with those of previous studies,[1,2]further validating the use of mavrilimumab to target the GM–CSFR-α.

Table: Long term safety data and efficacy data at 74 weeks (48 weeks in OLE)

Previous treatment, n (%)				
Placebo/mavrilimumab 30 mg/100 mg/150 mg/ golimumab 50 mg	81/81/155/79/68			
	Mavrilimumab eow (N=440)[a]			
Baseline characteristics				
Mean (SD) age, years	51.3 (11.4)			
Mean (SD) RA duration, years	7.9 (6.9)			
Mean (SD) DAS28–CRP	5.8 (0.8)			
Long-term safety results				
Duration of mavrilimumab exposure (patient years)	603			
Patients reporting ≥1 TEAE, n (rate/100 pt years)	296 (49.1)			
Patients reporting ≥1 TESAE, n (rate/100 pt years)	47 (7.8)			
TESAEs, n (%)[b,c]				
Osteoarthritis	4 (0.7)			
Bronchitis	3 (0.5)			
Rheumatoid arthritis	2 (0.3)			
Pulmonary tuberculosis	2 (0.3)			
Gastroenteritis	2 (0.3)			
Anemia	2 (0.3)			
Patients reporting ≥1 TEAE of special interest, n (rate/100 pt years)	89 (14.8)			
TEAEs of special interest, n (%)[b,d]				
Bronchitis	29 (4.8)			
Respiratory tract infection	12 (2.0)			
Cholelithiasis	6 (1.0)			
Cough	5 (0.8)			
Neutropenia	5 (0.8)			
PFTs				
	Week 12	Week 24	Week 50	Week 74
FEV_1, n	419	372	175[e]	216
>20% reduction from baseline to <80% predicted (%)	7 (1.7)	13 (3.5)	15 (8.6)	13 (6.0)
FVC ,n	419	372	175	216
>20% reduction from baseline to <80% predicted (%)	7 (1.7)	8 (2.2)	10 (5.7)	11 (5.1)
Long term efficacy results				
Response rates at Week 74 (Week 48 in OLE), n=239				
DAS28-CRP <3.2 (%)	137 (57.3)			
DAS28–CRP <2.6 (%)	92 (38.5)			
ACR20 responders (%)	180 (75.3)			
ACR50 responders (%)	109 (45.6)			
ACR70 responders (%)	61 (25.5)			
Radiographic progression				
Mean (SD) mTSS at baseline, n=321	36.2 (2.7)			
Mean (SD) mTSS change from baseline at Week 74, n=305	1.3 (6.8)			
Patients with no radiographic progression at Week 74 (%)[f], n=305	207 (67.9)			

[a]440 patients had received mavrilimumab treatment in EARTH EXPLORER 1 or 2 and/or in the OLE study; [b]Adverse events with onset after the first dose of mavrilimumab; [c]TESAEs included ≥n=2; [d]TEAEs of special interest included ≥n=5; [e]The number of patients with PFT data available at Week 50 (n=175) is lower than that at Week 74 (n=216), because 43 patients were assessed close to Week 36 and their PFT data were reported under the Week 36 visit; [f]Defined as <0.5 change in mTSS vs. baseline
ACR20/50/70, American College of Rheumatology rating scale (20/50/70% or more improvement); DAS28–CRP, 28-joint Disease Activity Score C-reactive protein; eow, every other week; FEV_1; forced expiratory volume in 1 second, FVC, forced vital capacity; mTSS, modified Total Sharp Score; OLE, open-label extension; PFTs, pulmonary function tests; RA, rheumatoid arthritis; SD, standard deviation; TEAEs, treatment-emergent adverse events; TESAEs, treatment-emergent serious adverse events

References:
[1]Burmester G, et al. *Ann Rheum Dis* 2013;72:1445–1452
[2]Burmester G, et al. *Arthritis Rheum* 2014;66:S1231

^Joint senior authors

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Abstract Number: 3112

Incidence of Anti-Drug Antibodies in Rheumatoid Arthritis Patients Treated with Adalimumab, Etanercept, or Infliximab in a Real-World Setting

RJ Moots[1], Ricardo Xavier[2], Chi Chiu Mok[3], Mahboob U Rahman[4], Wen-Chan Tsai[5], Mustafa Al Maini[6], Karel Pavelka[7], Ehab Mahgoub[8], Sameer Kotak[9], Joan Korth-Bradley[10], Ronald Pedersen[11], Linda Mele[8], Qi Shen[8] and Bonnie Vlahos[8], [1]Department of Musculoskeletal Biology, University of Liverpool, Liverpool, United Kingdom, [2]Hospital de Clínicas de Porto Alegre, Porto Alegre, Brazil, [3]Medicine, Tuen Mun Hospital, Hong Kong, Hong Kong, [4]Perelman School of Medicine, University of Pennsylvania, Philadephia, PA, [5]Kaohsiung Medical University, Kaohsiung, Taiwan, [6]Rheumatology, Allergy and Clinical Immunology Division, Mafraq Hospital, Abu Dhabi, United Arab Emirates, [7]Charles University, Prague, Czech Republic, [8]GIPB - Clinical Sciences, Pfizer, Collegeville, PA, [9]Global Health and Value, Pfizer,

New York, NY, [10]GIPB- Clinical Sciences, Pfizer, Collegeville, PA, [11]Department of Biostatistics, Pfizer, Collegeville, PA
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Session Time: 2:30PM-4:00PM

Background/Purpose: Treatment with biologics can elicit unwanted immune responses such as antidrug antibodies (ADA), which may decrease their clinical efficacy and increase adverse events. However, use of different assay methods and inconsistent sample collection times has made direct comparison difficult.

To assess incidence of ADA for etanercept (ETN), adalimumab (ADL), and infliximab (IFX), and to correlate it with trough drug concentration, efficacy, and patient health outcomes in a real world setting.

Methods: This non-interventional, cross-sectional study was conducted in 57 centers across Argentina, Australia, Bulgaria, Turkey and the United States. Adult patients with rheumatoid arthritis, treated with ETN, ADL, or IFX continuously for 6–24 months were eligible. ADA, using RIA, and trough drug concentrations, using ELISA, were measured in samples collected on one occasion ≤2 days prior to the next scheduled dose. All assays were performed at the same laboratory. Efficacy was measured as Disease Activity Score 28-joint count (DAS28), Clinical Disease Activity Index (CDAI), Simplified Disease Activity Index (SDAI), C-reactive protein (CRP) levels, erythrocyte sedimentation rate (ESR) and health outcomes measures, eg, HAQ-DI, EQ-5D, SF-36. History of injection site or infusion reactions, serum sickness, and thromboembolic events while on the current biologic were also assessed.

Results: A total of 595 eligible patients (ETN: n=200; ADL: n=199; IFX: n=196) were enrolled in the study. Baseline demographics were similar across all groups. The mean duration of treatment was 14.6, 13.5, and 13.1 months for ETN, ADL, and IFX, respectively. None of the patients receiving ETN tested positive for ADA, whereas 62 (31.2%) and 34 (17.4%) of patients treated with ADL and IFX, respectively, tested positive for ADA ($p<0.0001$). In ADL- or IFX-treated patients, those with ADA had significantly lower trough drug levels. Efficacy and health outcomes are summarized in the table. DSR28-ESR LDA and remission rates are higher in patients without ADA. There was a correlation noted in objective measurements of inflammation in patients with ADA. All 3 treatments were well tolerated with regard to reporting targeted medical events.

Conclusion: ADA were not detected in ETN-treated patients. Statistically significant higher proportion of patients in the ADL/IFX treatment groups was positive for ADA. Patients with ADA had lower serum concentration of the drug and showed a higher value for CRP and ESR. Patients without ADA showed statistical differences in clinical and health outcomes between groups compared with patients with ADA. This is a cross-sectional study recruiting patients currently on continuous treatment of tumor necrosis factor α inhibitors. A prospective longitudinal study may be needed to further evaluate the impact of ADA on efficacy.

Table

	Etanercept		Adalimumab		Infliximab		Overall	
	ADA +ve	ADA –ve	ADA +ve	ADA –ve	ADA +ve	ADA –ve	ADA +ve	ADA -ve
CRP, mean (SD)	NA	9.0 (20.4)	12.3 (20.5)	5.5 (8.9)	13.4 (14.3)	6.5 (8.2)	12.7 (18.4)	7.2 (14.6)
ESR, mean (SD)	NA	23.3 (18.7)	31.2 (24.5)	22.5 (19.4)	41.5 (25.2)	24.5 (19.6)	34.7 (25.1)	23.5 (19.2)
DAS28-CRP, mean (SD)	NA	2.9 (1.2)	3.4 (1.2)	3.1 (1.4)	3.7 (1.3)	3.4 (1.3)	3.5 (1.3)	3.1 (1.3)
DAS28-ESR, mean (SD)	NA	2.5 (1.2)	3.1 (1.2)	2.8 (1.4)	3.5 (1.3)	3.1 (1.3)	3.2 (1.3)	2.8 (1.3)
CDAI, mean (SD)	NA	12.6 (10.6)	17.3 (13.6)	16.3 (14.8)	21.7 (16.1)	18.5 (13.8)	18.8 (14.6)	15.5 (13.2)
SDAI, mean (SD)	NA	13.5 (11.0)	18.5 (14.5)	16.8 (14.9)	23.1 (16.3)	19.2 (13.9)	20.1 (15.3)	16.3 (13.3)
DAS28-ESR LDA, n/N (%)	NA	131/197 (66.5)	39/62 (62.9)	88/135 (65.2)	14/32 (43.8)	81/152 (53.3)	53/94 (56.4)	300/484 (62.0)
DAS28-ESR Remission, n/N (%)	NA	106/197 (53.8)	22/62 (35.5)	64/135 (47.4)	7/32 (21.9)	56/152 (36.8)	29/94 (30.9)	226/484 (46.7)
HAQ-DI, mean (SD)	NA	0.8 (0.7)	1.0 (0.8)	0.9 (0.7)	1.2 (0.7)	1.0 (0.6)	1.1 (0.7)	0.9 (0.7)
EQ-5D Utility Score, mean (SD)	NA	0.7 (0.2)	0.6 (0.3)	0.7 (0.2)	0.5 (0.4)	0.6 (0.3)	0.5 (0.3)	0.7 (0.3)
EQ-5D VAS Score, mean (SD)	NA	70.3 (21.6)	61.9 (22.1)	69.4 (20.6)	62.8 (23.5)	65.6 (21.0)	62.2 (22.5)	68.5 (21.2)
SF-36 MCS, mean (SD)	NA	47.8 (11.1)	43.4 (11.3)	45.9 (11.8)	44.8 (11.8)	46.6 (11.6)	43.9 (11.4)	46.9 (11.5)
SF-36 PCS, mean (SD)	NA	41.4 (9.9)	38.5 (9.7)	40.0 (9.2)	35.1 (8.9)	36.5 (8.8)	37.3 (9.5)	39.4 (9.6)

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Abstract Number: 3113

Interest of Assessing Anti-Drug Antibodies for the Choice Between a Second Anti-TNF and a Non-TNF-Targeted Biologic in Patients with Inadequate Response to a First Anti-TNF : Results from the Randomized Controlled Trial « Rotation or Change »

Sophie Candon[1], Lucienne Chatenoud[1], Olivier Brocq[2], Aleth Perdriger[3], Slim Lassoued[4], Jean-Marie Berthelot[5], Daniel Wendling[6], Liana Euller-Ziegler[7], Martin Soubrier[8], Christophe Richez[9], Bruno Fautrel[10], Arnaud Constantin[11], Xavier Mariette[12], Jacques Morel[13], Mélanie Gilson[14], Gregoire Cormier[15], Jean Hugues Salmon[16], Stephanie Rist Bouillon[17], Frederic Liote[18], Hubert Marotte[19], Christine Bonnet[20], Christian Marcelli[21], Jeremie Sellam[1], Olivier Meyer[22], Elisabeth Solau-Gervais[23], Sandrine Guis[24], Jean Marc Ziza[25], Charles Zarnitsky[26], Isabelle Chary-Valckenaere[27], O Vittecoq[28], Alain Saraux[29], Yves-Marie Pers[30], Martine Gayraud[31], Gilles Bolla[32], Pascal Claudepierre[33], Marc Ardizzone[34], Emmanuelle Dernis Labous[35], Maxime A. Breban[36], Olivier Fain[37], Jean Charles Balblanc[38], Elodie Perrodeau[39], Jean Sibilia[40], Philippe Ravaud[31] and **Jacques Gottenberg**[41], [1]Rheumatology, PARIS, France, [2]Hospital Center Princesse Grâce, Monaco, Monaco, [3]Service de Rhumatologie, CHU de Rennes, Rennes, France, [4]Rheumatology, Cahors, France, [5]Rheumatology, University Hospital, Nantes, France, [6]Université de Franche-Comté, Besançon, France, [7]Rheumatology, Nice, France, [8]Rheumatology department CHU Clermont-Ferrand, Clermont-Ferrand, France, [9]Rheumatology, Bordeaux, France, [10]Rheumatology, AP-HP Pitié-Salpêtrière Hospital / Pierre and Marie Curie University Paris 6 GRC-08 (EEMOIS), Paris, France, [11]Rheumatology, CHU Purpan - Hopital Pierre-Paul Riquet, Toulouse, France, [12]Université Paris-Sud, AP-HP, Hôpitaux Universitaires Paris-Sud, Paris, France, [13]Department of rheumatology, Lapeyronie Hospital and

Montpellier University, Montpellier, France, [14]Hospital Center, Grenoble, France, [15]Rheumatology, La Roche Sur Yon, France, [16]Hôpital Maison Blanche, Rheumatology, REIMS, France, [17]Rhumatologie, Hopital La Source, La Source, France, [18]Rheumatology, Lariboisière, France, [19]INSERM 1059 / LBTO, Université de Lyon, Saint-Etienne; Rheumatology Department, Saint-Etienne, France, [20]Rheumatology, CHU Dupuytren, Limoges, France, [21]Rheumatology, Caen, France, [22]Rheumatology, Hopital Bichat, Paris, France, [23]Rhumatologie, University Hospital, Poitiers, France, [24]Rheumatology, Marseille, France, [25]Hopital Croix-Saint-Simon, Paris Cedex 20, France, [26]Rheumatology, Le Havre, France, [27]CHU de Nancy, Rheumatology, Nancy, France, [28]University Hospital, Rouen, France, [29]Rheumatology, Brest, France, [30]Rheumatology, Montpellier, France, [31]Rheumatology, Paris, France, [32]Rheumatology, Cannes, France, [33]Rheumatology, Université Paris Est Créteil, Créteil, France, [34]Rheumatology, Centre Hospitalier de Mulhouse, Mulhouse, France, [35]Réseau Hôpital et Ville en Rhumatologie (RHEVER) Network, Paris, France, [36]Rheumatology, A. Paré University Hospital, Boulogne-Billancourt, France, [37]Internal Medicine Department, Saint Antoine Hospital, Paris, France, [38]Rheumatology, Belffort, France, [39]Epidemiologist, Paris, France, [40]Department of Rheumatology, Strasbourg University Hospital, Strasbourg, France, [41]Hautepierre, Strasbourg, France
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Background/Purpose: Anti-drug antibodies (ADAs) might result in loss of efficacy to anti-TNF. The impact of ADAs to a 1st anti-TNF on subsequent response to a second biologic has never been assessed in the setting of a randomized controlled trial. The "Rotation of anti-TNF Or Change of class of biologic" (ROC) trial showed a better efficacy at 6 months of a non-TNF-targeted biologic than a second anti-TNF. In a post-hoc analysis, we investigated the potential usefulness of assessing anti-drug antibodies to guide the choice of the second biologic in TNF-IR patients.

Methods: The ROC trial (NCT01000441) is a multicenter,investigator-initiated, open, parallel-group, randomized controlled trial. Patients with inadequate response to a first anti-TNF were randomly assigned in a 1:1 ratio to receive a non-TNF-targeted biologic (abatacept, rituximab or tocilizumab) or a second anti-TNF agent. Anti-TNF drug concentration in serum was measured using solid phase ELISA assays based on the capture of infliximab, adalimumab, golimumab, certolizumab with plate-bound recombinant TNF-a. For infliximab and adalimumab, the detection of anti-drug antibodies (ADAb) was performed by a homemade assay based on the ability of anti-idiotypic antibodies to neutralize anti-TNF drug activity and inhibit its capture by TNF-alpha (Candon S, et al. 2006). For the other anti-TNF, commercial tests were used. (Shikari, Eurobio for anti-etanercept ADAs, Lisa-Tracker kits (Theradiag, France) for anti-golimumab and anti-certolizumab ADAs).

Results: ADAs were assessed in 278 patients. In 19 (6.8%) patients, ADAs could not be detected because of persistent levels of the 1st anti-TNF. No ADA was detected in 227 (81.7%) patients. Presence of ADAs was detected in 32 (11.5%) of patients (anti-adalimumab: 20 patients ; anti-certolizumab : 2 patients ; anti-golimumab : 1 patient ; anti-infliximab: 9 patients). In all these patients with ADAs, blood levels of the 1st anti-TNF were very low or indetectable. Among the 120 patients randomized to a 2d anti-TNF and assessed for ADAs, 12 had ADAs and 108 had no ADA. Among the 139 patients randomized to a non-TNF targeted biologic and assessed for ADAs, 20 had ADAs and 119 had no ADA. In patients with ADAs, change in DAS28-ESR at 6 months adjusted on baseline DAS28-ESR was similar between patients randomized to a second anti-TNF and those randomized to a non-TNF-targeted biologic (median change of 0.45 and 0.45, respectively, P=0.96). In patients without ADA, change in DAS28-ESR at 6 months adjusted on baseline DAS28-ESR was lower in patients randomized to a second anti-TNF than in those randomized to a non-TNF targeted biologic (median change -0.22 and -0.36, respectively, P= 0.003).

Conclusion:

In the ROC trial, only a minority (~ 10%) of TNF-IR patients had ADAs. Interestingly, in TNF-IR patients with an immunogenic response against TNF inhibitors, the response to a second TNF inhibitor did not differ from response to a non-TNF-targeted drug. Therefore, the assessment of ADAs might contribute to guide the choice of a second biologic in TNF-IR patients.

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Immunogenicity of Subcutaneous and Intravenous Tocilizumab As Monotherapy or in Combination with Dmards

Mark C. Genovese[1], Atsushi Ogata[2], Akira Nomura[3], Min Bao[4], Elena Hitraya[4], Stuart Lacey[5] and Gerd Burmester[6], [1]Division of Rheumatology, Stanford University Medical Center, Palo Alto, CA, [2]Osaka University Graduate School of Medicine and NTT West Osaka Hospital, Osaka, Japan, [3]Chugai Pharmaceutical Co Ltd, Tokyo, Japan, [4]Genentech, South San Francisco, CA, [5]Roche, Welwyn Garden City, United Kingdom, [6]Department of Rheumatology and Clinical Immunology, Charité - Universitätsmedizin Berlin, Berlin, Germany
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Background/Purpose: Intravenous (IV) and subcutaneous (SC) formulations of tocilizumab (TCZ) are available for treatment of adult RA based upon the efficacy and safety outcomes of the Phase III and IV trials and their open-label, long-term extensions. The objective of this study was to provide an overview of the immunogenicity profile of TCZ-SC and TCZ-IV as monotherapy or in combination with DMARDs, including the incidence of anti-TCZ antibodies and their impact on safety and efficacy in patients with RA.

Methods: In the TCZ-IV (4 or 8 mg/kg every 4 weeks) studies, patients were monitored for up to 5 years, and for TCZ-SC (162 mg weekly or every other week), up to 2 years. Blood samples were taken at baseline and regularly prior to TCZ dosing throughout the studies for anti-drug antibody (ADA) assessment. All samples were screened using a bridging enzyme-linked immunosorbent assay method for ADAs, and samples that tested positive were analyzed by a confirmation assay for specificity. Those samples that were confirmation assay positive were further characterized for neutralizing potential and the immunoglobulin E (IgE) isotype (SC studies only). Safety and efficacy measures were evaluated in association with ADA development.

Results: For patients who received TCZ-SC, the proportion that developed ADAs postbaseline was low and comparable to that for TCZ-IV (2.0% vs 1.2%; Table). Overall, the incidence of ADA development was ≤2.0% and similar between patients who received TCZ monotherapy (1.3%) or TCZ+DMARDs (1.4%), regardless of formulation. No anaphylaxis or serious hypersensitivity reactions were observed in patients who received TCZ-SC monotherapy, TCZ-SC+DMARDs or TCZ-IV monotherapy and developed ADAs. Of the patients who had anaphylaxis, serious hypersensitivity or clinically significant hypersensitivity (n=131), 7.6% developed ADAs. Of the 63 patients who received TCZ-IV+DMARDs and developed ADAs, 5 had anaphylaxis; 1 additional patient had a serious hypersensitivity reaction and 4 additional had clinically significant hypersensitivity reactions. One patient who received TCZ-IV monotherapy and developed ADAs had a clinically significant hypersensitivity reaction. Three patients who received TCZ-SC+DMARDs and developed ADAs had injection site reactions (ISRs), and no ISRs occurred in patients who received TCZ-SC monotherapy and developed ADAs. Among patients who developed ADAs with neutralizing potential, none experienced loss of efficacy, regardless of formulation or concomitant DMARDs.

Conclusion: TCZ-SC and TCZ-IV have a low risk of immunogenicity potential, with no impact on safety or efficacy. For patients who received TCZ-SC, the proportion that developed anti-TCZ antibodies was comparable to that for TCZ-IV. TCZ had low and comparable immunogenicity to that of monotherapy or in combination with DMARDs.

TCZ-SC vs TCZ-IV				
	TCZ-SC all exposure (N = 1638)	**TCZ-IV all exposure (N = 5875)**		
Total pts screened, n (%)[a]	1636	5806		
Anaphylaxis[b]	0	9 (0.2)		
Clinically significant hypersensitivity[c]	13 (0.8)	89 (1.5)		
Serious hypersensitivity[d]	6 (0.4)	48 (0.8)		
Injection site reactions[e]	171 (10.4)	N/A		
Total pts who developed ADAs, n (%)[a]	33 (2.0)	69 (1.2)		
Neutralization assay +[f]	25 (1.7)	54 (0.9)		
IgE assay +[g]	11 (0.7)	N/A		
Anaphylaxis[b]	0	5 (0.1)		
Clinically significant hypersensitivity[c]	0	10 (0.2)		
Serious hypersensitivity[d]	0	6 (0.1)		
Injection site reactions[e]	3 (0.2)	N/A		
TCZ monotherapy vs TCZ + DMARDs				
	TCZ-SC mono (N = 173)	**TCZ-SC + DMARDs (N = 1465)**	**TCZ-IV mono (N = 753)**	**TCZ-IV + DMARDs (N = 5122)**
Total pts screened, n (%)[a]	173	1463	745	5061
Anaphylaxis[b]	0	0	1 (0.1)	8 (0.2)
Clinically significant hypersensitivity[c]	1 (0.6)	12 (0.8)	12 (1.6)	77 (1.5)
Serious hypersensitivity[d]	0	6 (0.4)	7 (0.9)	41 (0.8)
Injection site reactions[e]	30 (17.3)	141 (9.6)	N/A	N/A
Total pts who developed ADAs, n (%)[a]	6 (3.5)	27 (1.8)	6 (0.8)	63 (1.2)
Neutralization assay +[f]	N/A	25 (1.7)	4 (0.5)	50 (1.0)
IgE assay +[g]	5 (2.9)	6 (0.4)	N/A	N/A
Anaphylaxis[b]	0	0	0	5 (0.1)
Clinically significant hypersensitivity[c]	0	0	1 (0.1)	9 (0.2)
Serious hypersensitivity[d]	0	0	0	6 (0.1)
Injection site reactions[e]	0	3 (0.2)	N/A	N/A

ADA, anti-drug antibody; DMARD, disease-modifying antirheumatic drugs; IV, intravenous; mono, monotherapy; SC, subcutaneous; TCZ, tocilizumab.

TCZ-SC was dosed at 162 mg weekly or every other week. TCZ-IV was dosed at 4 or 8 mg/kg every 4 weeks.

[a] Denominator is total patients screened.

[b] Anaphylactic reactions were defined using Sampson criteria (Sampson HA, *J Allergy Clin Immunol,* 2006).

[c] In the MUSASHI study, hypersensitivity events were defined as adverse events (AEs), excluding ISRs, that occurred during or within 24 hours of an infusion or injection and were judged as a hypersensitivity event by the clinical expert. In all other studies, hypersensitivity events were defined as all AEs, excluding injection site reactions, that occurred during or within 24 hours of an infusion or injection and were not judged "unrelated"' to treatment by the investigator; those events may or may not be consistent with hypersensitivity clinically. Clinically significant hypersensitivity events were hypersensitivity events that also led to withdrawal from treatment.

[d] Serious hypersensitivity events were defined as hypersensitivity events that were reported as serious AEs.

[e] Injection site reactions were AEs occurring at the local injection site.

[f] The neutralization assay was not performed in MUSASHI. The denominator used for this does not include the MUSASHI population.

[g] IgE assay was not performed in the TCZ-IV studies.

Disclosure: M. C. Genovese, Roche Pharmaceuticals, 5; **A. Ogata**, Chugai Pharmaceutical, 5,Chugai Pharmaceutical, 8; **A. Nomura**, Chugai Pharmaceutical, 3; **M. Bao**, Genentech, Inc, 3; **E. Hitraya**, Genentech, Inc, 3; **S. Lacey**, Roche Products Ltd, 3; **G. Burmester**, Roche, Abbott, Pfizer, UCB, Merck Sharp & Dohme, and Bristol-Myers Squibb, 2,Roche, Chugai, Pfizer, UCB, and Bristol-Myers Squibb, 5,Roche, Pfizer, Merck Sharp & Dohme, Abbott, and Bristol-Myers Squibb, 8.

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Abstract Number: 3115

Autoantibodies of the IgA Type a Link Between the Gut and the Anti-TNF Therapy Response in Rheumatoid Arthritis Patients Analysed in Two Clinical Trials

Zoltan Konthur[1], Ute Nonhof[2], Melvin Michael Wiemkes[3], Jacqueline Detert[3], Tanja Braun[4], Jörg Hollidt[2], Gerd Burmester[5] and **Karl Skriner**[5], [1]Department of Vertebrate Genomics, Max Planck Institute for Molecular Genetics, Berlin, Germany, [2]Drug Response DX GmbH, Berlin, Germany, [3]Department of Rheumatology and Clinical Immunology, Germany, Charité - Universitätsmedizin Berlin, Berlin, Germany, [4]Charité - Universitätsmedizin Berlin, Berlin, Germany, [5]Department of Rheumatology and Clinical Immunology, Charité - Universitätsmedizin Berlin, Berlin, Germany

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SESSION INFORMATION

Session Date: Tuesday, November 10, 2015

Session Title: Rheumatoid Arthritis-Small Molecules, Biologics and Gene Therapy V: Immunogenecity

Session Type: ACR Concurrent Abstract Session

Session Time: 2:30PM-4:00PM

Background/Purpose: So far no mechanism for non response to biologicals targeting TNFα has been described despite one third of rheumatoid arthritis patients treated are non-responders. A link to the gut mirobiota its ability to drive an autoimmune disease. Immunity. 2010 Jun 25;32(6):815-27 can be made vie segmented filamentous bacteria (SFB) that cooperate to generate potent IgA and Th17 cell responses. Immunity. 2014 Apr 17;40(4):608-20. We investigated the differences in seroreactivity of patients responding and not responding to TNF therapies prior and after therapy and identified diagnostically applicable IgA autoantigenicity set to identify non response

Methods: Screening with patient sera were conducted with 5 different roteins candidates which were identified by protein maroarray screening (Anal Biochem. 1999 May 15;270(1):103-11.9) expressed recombinantly in *E. coli*, purified and further stratified with a large well defined patient cohort by ELISA. Baseline sera form PREDICT trial treated with Enbrel) and patients treated with Humira in the HIT HARD (Ann Rheum Dis. 2013 Jun;72(6):844-509 trial and 66 baseline sera from Charite in addition treated with (Cimzia ,Infiximab) were ivestigated by Pre. mark TNF ELISA from DRDx GmbH.

Results: Pretreatment sera from patients with diagnosis of RA based on the ACR classification criteria who were initiated on therapy with TNFalpha inhibitors were analyzed with five markers from the biomarker set of highest priority (RAB11B, PPP2R1A, KPNB1,Cog 4, FTFT1) using an ELISAs assay. . In total, analyses of 203 patients were carried out, of which 162 were clearly defined as Responder and 41 were clearly defined as non-Responder after 6 month treatment. 81% of Non-responder could be clearly identified with the pre.markTNF Test. The assay has currently a specificity 94%. Moreover, 80 baseline serum samples from the PREDICT study with Enbrel and 57 baseline sera from an early intervention trial Hit Hard (Ann Rheum Dis. 2013 Jun;72(6):844-509) with Humira were analysed. In early subset, all 3 non-responder were identified and the specificity of the assay was 98 %. In the PREDICT study Enbrel non responders were identified with 68.8 % sensitivity and a specificity of 92.5 %. The amount of IgA produceing B cell in the synovia differs significantly between the patients which is not seen with IgG produceing B cells. Moreover the potent IgA response is linked to Th17 cell response. A dual pathomechnism of local TNF produceing IgA B cells in RA synovial tissue and TNF produceing macrophages is proposed

Conclusion: These data suggest that non-response to anti-TNFα biologicals might be predicted based on frequency and magnitude of autoantibodies to specific IgA autoantigens. SFB can stimulate multiple intestinal homeostatic IgA and Th17 cell responses and specific IgA and TNF producing B cells might be important for disease persistence in TNFα non responders

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Disclosure: Z. Konthur, None; **U. Nonhof**, None; **M. M. Wiemkes**, None; **J. Detert**, None; **T. Braun**, None; **J. Hollidt**, None; **G. Burmester**, None; **K. Skriner**, None.

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Abstract Number: 3116

High Level of Inflammation Predicts the Development of Diabetes Mellitus in Patients with Psoriatic Arthritis

Lihi Eder[1], Vinod Chandran[1], Richard J. Cook[2] and Dafna D. Gladman[1], [1]Rheumatology, University of Toronto, Toronto Western Hospital, Toronto, ON, Canada, [2]Statistics and Actuarial Science, University of Waterloo, Waterloo, ON, Canada

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SESSION INFORMATION

Session Date: Tuesday, November 10, 2015
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Session Type: ACR Concurrent Abstract Session
Session Time: 2:30PM-4:00PM

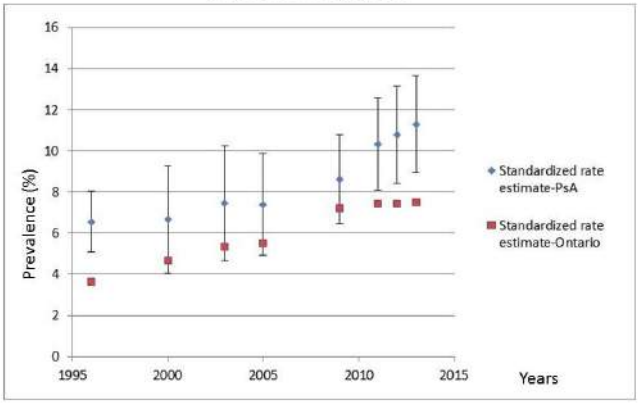
Background/Purpose: To estimate trends in the prevalence of diabetes mellitus (DM) in patients with psoriatic arthritis (PsA) in comparison to the general population in Ontario, Canada and to assess whether the levels of disease activity and inflammation over time predicts the development of DM in these patients.

Methods: A cohort analysis was conducted in patients followed in a large PsA clinic from 1978 to 2013. The collected information included demographics, lifestyle habits, medical history and disease-related outcomes. DM was defined as the use of medications for DM or elevated blood glucose or HbA1C levels. The prevalence of DM in patients followed up in the cohort was compared with data obtained from the Canadian Community Health Survey (CCHS), a cross sectional examination of health status conducted from 1995 to 2013 in Ontario. Age-standardized morbidity ratio (SMR) of DM was calculated for years with available CCHS data. For the assessment of risk factors for DM, patients with an existing diagnosis of the disease at clinic entry were excluded. The following time-weighted arithmetic mean (AM-) levels were assessed as predictors of incident DM: tender and swollen joint counts, number of dactylitic digits, psoriasis area and severity index (PASI) and erythrocyte sedimentation rate (ESR). Cox proportional hazard models stratified by age-group at clinic entry and controlled for sex, cumulative steroid dose, duration of PsA and body mass index were used to compute the multivariate relative risk (RR) for incident DM.

Results: A total of 1305 patients were included in the analysis. The standardized prevalence of DM in 2013 was 11.3% (95% Confidence Interval (CI) 8.9%, 13.7%) and the SMR compared to the general population was 1.43 (95% CI 1.2, 1.7, p=0.002). An increase in the point-prevalence of DM over the past two decades was observed (Figure 1). Of the 1065 patients who were included in the time to event analysis, 73 patients developed incident DM. This cohort had a total of 11006 person-years of follow-up, with a mean of 10.3± 8.9 years per person. On multivariate analysis AM- tender joint count (RR 1.68, 95% CI 1.2-2.36, p=0.003) and AM-ESR (RR 1.21, 95% CI 1.04-1.41, p=0.01) predicted the development of DM.

Conclusion: The prevalence of DM is increased in patients with PsA compared to the general population with a gradual increase in the prevalence over the past decades. The risk of developing PsA is predicted by exposure to elevated levels of inflammation over time.

Figure 1 - Standardized prevalence of diabetes in PsA and in Ontario population by years



Age-standardized prevalence of DM in PsA (95% CI in blue) and in the general population in Ontario (in red) by years

Disclosure: L. Eder, None; **V. Chandran**, None; **R. J. Cook**, None; **D. D. Gladman**, None.

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Abstract Number: 3117

Under-Treatment of Cardiovascular Risk Factors in Patients with Psoriatic Disease – an International Multicentre Study

Lihi Eder[1], Vinod Chandran[1], Cheryl Rosen[2], Jan Dutz[3], James T. Elder[4], Proton Rahman[5], Christopher T. Ritchlin[6], Francisco A. Tausk[7], Sherry Rohekar[8], Richard Hayday[9], Snezana Barac[10], Devy Zisman[11], Joy Feld[12] and Dafna D. Gladman[1], [1]Rheumatology, University of Toronto, Toronto Western Hospital, Toronto, ON, Canada, [2]Dermatology, University of Toronto, Toronto Western Hospital, Toronto, ON, Canada, [3]University of British Columbia, Vancouver, BC, Canada, [4]University of Michigan Medical School, Ann Arbor, MI, [5]Computer Sciences, Memorial University of Newfoundland, St. John's, NF, Canada, [6]Allergy, Immunology and Rheumatololgy Division, University of Rochester Medical Center, Rochester, NY, [7]University of Rochester Medical Center, Rochester, NY, [8]Western University, London, ON, Canada, [9]University of Manitoba, Winnipeg, MB, Canada, [10]Winnipeg Clinic, Winnipeg, MB, Canada, [11]Rheumatology Unit, Carmel Medical Center, Haifa, Israel, [12]Carmel Medical Center, Haifa, Israel
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Session Time: 2:30PM-4:00PM

Background/Purpose: Cardiovascular risk in patients with psoriatic disease is partly attributed to the high prevalence of traditional cardiovascular risk factors in these patients. This study aimed to estimate the proportion of under-treatment of cardiovascular risk factors in an international multicentre cohort of patients with psoriasis and psoriatic arthritis (PsA).

Methods: A cross-sectional analysis of patients with psoriatic disease from the International Psoriasis and Arthritis Research Team (IPART) cohort was conducted. The presence of traditional modifiable cardiovascular risk factors (diabetes, hypertension, dyslipidemia, smoking and central obesity) and the use of appropriate therapies were determined based on patients' report, physical examination and laboratory tests. The 10-year cardiovascular risk was calculated according to the Framingham Risk Score (FRS). Adherence with guidelines for the treatment of dyslipidemia (Stone et al. Circulation 2014;129:S1-45) and hypertension (James et al. JAMA 2014;311:507-20) was assessed. Chi-square and Cochran-Armitage trend test were used to compare categorical variables across groups.

Results: A total of 2254 patients (58.9% PsA, 41.1% psoriasis alone) from 8 centres in Canada, US and Israel were included. Their mean age was 52±13.8 years and 53% were males. 83.2% of the patients had at least one modifiable cardiovascular risk factor. Based on the FRS classification 30% of patients were in a high risk and 18% were in a moderate risk category. 6.1% of the patients had ischemic heart disease, 45.1% hypertension, 71.1% dyslipidemia, 12.6% diabetes, 54.3% central obesity and 17.3% were current smokers. A significant proportion of under-treatment of hypertension and dyslipidemia was found. 455 (20.4%) patients had uncontrolled blood pressure (43% of them were not on antihypertensive medications). Uncontrolled hypertension was associated with low level of education ($p<0.001$) and severe psoriasis (PASI≥10, $p<0.001$). 850 (37.9%) patients had an indication for statin therapy but were not using these medications. Under-treatment of dyslipidemia was more frequent in patients with PsA ($p=0.005$), those with low-level of education ($p<0.001$) and patients with severe psoriasis ($p=0.03$).

Conclusion: In a real-world setting, a large proportion of patients with psoriasis and PsA were undertreated for hypertension and hyperlipidaemia.

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Abstract Number: 3118

Clinical Characteristics and Disease Outcomes in Psoriatic Arthritis Patients By Extent of Body Surface Area Affected By Psoriasis: Results from Corrona Registry

Philip J. Mease[1,2,3,4], Chitra Karki[5], Carol J. Etzel[5,6], Arthur Kavanaugh[7], Christopher T. Ritchlin[8], Wendi Malley[5], Vivian Herrera[9], Jacqueline B. Palmer[9] and Jeffrey D. Greenberg[5,10], [1]Swedish Medical Center and University of Washington School of Medicine, Seattle, WA, [2]Seattle Rheumatology Associates, Seattle, WA, [3]Rheumatology Research, Swedish Medical Center, Seattle, WA, [4]Clinical Professor, University of Washington School of Medicine, Seattle, WA, [5]Corrona, LLC, Southborough, MA, [6]University of Texas M.D. Anderson Cancer Center, Houston, TX, [7]University of California San Diego, La Jolla, CA, [8]Allergy, Immunology and Rheumatololgy Division, University of Rochester Medical Center, Rochester, NY, [9]Novartis Pharmaceuticals Corporation, East Hanover, NJ, [10]NYU School of Medicine, New York, NY

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Session Time: 2:30PM-4:00PM

Background/Purpose: Psoriatic arthritis (PsA) is a type of inflammatory arthritis that is commonly comorbid with the skin condition, psoriasis. A major contributor to the severity and burden of psoriatic disease is the extent of skin lesions. The objective of this study was to characterize the demographic and clinical characteristics of PsA patients with >3% versus ≤3% of body surface area (BSA) affected by psoriasis and evaluate the association with outcomes such as minimal disease activity (MDA) and disability, measured by health assessment questionnaire (HAQ) in a large national observational cohort of patients with PsA and spondyloarthritis (Corrona).

Methods: All PsA patients ≥18 years enrolled in the Corrona registry and had data on BSA were included in this study. Descriptive analyses of patient characteristics, disease activity, and functionality measures at registry enrollment were assessed for patients with >3% versus ≤3% BSA. Regression models were used to evaluate the associations of BSA level with the outcome measures MDA and HAQ (0-3); adjusted for age, gender, race, BMI, disease duration, history of csDMARD use, history of biologic use and history of prednisone use at enrollment.

Results: Of the 1,240 PsA patients that were included in the analysis, 451 (36.4%) had >3% and 789 (63.6%) had ≤3% BSA. Patients with BSA>3% were younger with a mean (SD) age of 52.2 (13.4) years [vs 54.4 (13.2)], with 49.4% women [vs 52.1%], 89.1% Caucasian [vs 91.5%], with mean (SD) BMI 32 (7.5) [vs. 31.2 (7)] and mean (SD) disease duration of 9 (9.4) years [vs 8.7 (8.6)]. There were slightly higher rates of cardiovascular disease (61.25% vs. 59.4%), cancer (9.1% vs. 6.6%), and serious infections (5.1% vs. 4.4%) in the patients with BSA >3% vs. those with BSA ≤ 3% respectively. About 60% of patients in both groups used a biologic therapy and approximately 21% of patients with BSA>3% were in MDA vs. 30 % of patients with BSA ≤3%. Adjusted models showed that patients with BSA >3% were 1.79 times (OR=1.79, 95% CI=1.30, 2.47) more likely to not be in MDA relative to those with BSA ≤3%. Sensitivity analysis evaluating the associations between BSA >3% and ≤ 3% and a modified MDA (5/6 criteria excluding BSA) showed consistent results (OR=1.71, 95% CI=1.21, 2.41). Similarly, adjusted models showed a significant difference in mean HAQ in patients with >3% BSA (mean difference=0.21 units higher; 95% CI=0.13, 0.29) compared to patients with BSA≤3%.

Conclusion: Data from the Corrona registry showed that PsA patients with >3% of BSA affected by psoriasis were significantly more likely to not be in MDA and more likely to be disabled than patients with ≤3% BSA at enrollment. Even at the low cutoff of >3% BSA affected used in this analysis, the extent of psoriasis lesions confers a significantly greater burden of disease in PsA. These findings underscore the importance of assessing and effectively managing psoriasis in patients with PsA.

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Abstract Number: 3119

The Risk of Venous Thromboembolism in Psoriatic Arthritis, Psoriasis and Rheumatoid Arthritis

Alexis Ogdie-Beatty[1], Daniel Shin[2], Junko Takeshita[2], Zelma ChiesaFuxench[2] and Joel Gelfand[3], [1]Medicine/Rheumatology, University of Pennsylvania, Philadelphia, PA, [2]University of Pennsylvania, Philadelphia, PA, [3]University of Pennsylvania Health System , Philadelphia, PA
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Session Type: ACR Concurrent Abstract Session
Session Time: 2:30PM-4:00PM

Background/Purpose: Venous thromboembolism (VTE), the combined endpoint of deep venous thrombosis (DVT) and pulmonary embolism (PE), is a common and potentially deadly medical problem with an annual incidence between 1-3/1,000. While rheumatoid arthritis (RA) has been linked to an increased incidence of VTE, few studies have examined the risk associated with psoriasis and psoriatic arthritis (PsA). The objective of this study was to determine the risk of VTE among patients with PsA, psoriasis and RA compared with the general population.

Methods: A longitudinal cohort study was conducted in The Health Improvement Network (THIN), a primary care medical record database in the United Kingdom, to determine the risk of VTE, DVT only and PE only using data from 1994-2014. Patients aged 18-89 were selected if they had a diagnosis of PsA, RA, or psoriasis. Diagnosis codes for PsA, RA, psoriasis, DVT and PE have been validated in THIN. Up to 5 unexposed controls matched on practice and start date within the practice were selected for each exposed patient. Cox proportional hazards models were used to calculate the relative hazards for each outcome. Multivariable models were constructed to include confounders which changed the main effects by >10% (e.g., hospitalization, cancer, hypertension, hyperlipidemia, liver disease, oral glucocorticoid use, NSAID use, body mass index, smoking, and alcohol use). An interaction with disease modifying anti-rheumatic drug (DMARD) was hypothesized a priori and was significant. Adjusted hazard ratios (aHR) stratified by DMARD are presented. Severe psoriasis was defined as a prescription for a DMARD specific to psoriasis or phototherapy.

Results: Patients with PsA (N=12,447), RA (N=51,949), psoriasis (N=194,639) and unexposed controls (N=1,247,933) were identified. Patients with RA (with and without a DMARD) and patients with psoriasis without a DMARD prescription had a significantly elevated risk of VTE (See Table: aHR 1.50, 1.40, and 1.19 respectively). This risk was elevated but not statistically significant among patients with severe psoriasis and PsA with a DMARD (aHR 1.16 and 1.22 respectively) and not elevated in patients with PsA without a DMARD. While the findings were similar for DVT, the aHR were different for PE. Patients with RA (with and without DMARD) and patients with PsA prescribed a DMARD had a significantly higher risk of PE than controls. Adjusted HR for patients with psoriasis were not statistically significant. These results were robust to several sensitivity analyses.

Conclusion: Patients with RA had a significantly increased risk of VTE compared with the general population even after accounting for risk factors for VTE. VTE and DVT were not significantly elevated in PsA. However, patients with PsA on a DMARD had a substantially increased risk of PE. Further investigation of the increased risk for PE in patients with PsA on a DMARD is needed.

Table. Incidence and Hazard Ratios for Venous Thromboembolism, Deep Venous Thrombosis, and Pulmonary Embolus

		N	VTE Incidence (per 10,000 PY)	VTE HR (95% CI)	DVT HR (95% CI)	PE HR (95% CI)
Controls		1,247,933	29.43*	Ref	Ref	Ref
Psoriatic Arthritis	No DMARD	8,989	23.52	0.81 (0.62-1.07)	0.83 (0.61-1.12)	0.78 (0.41-1.51)
	DMARD	3,458	27.38	1.22 (0.86-1.74)	1.06 (0.71-1.60)	2.16 (1.16-4.02)
Rheumatoid Arthritis	No DMARD	25,183	67.41	1.40 (1.29-1.51)	1.35 (1.24-1.47)	1.64 (1.39-1.92)
	DMARD	26,766	77.32	1.50 (1.40-1.61)	1.44 (1.34-1.56)	1.91 (1.66-2.19)
Psoriasis	No DMARD	188,506	34.98	1.19 (1.14-1.24)	1.21 (1.16-1.26)	1.05 (0.96-1.16)
	DMARD	6,133	35.99	1.16 (0.93-1.44)	1.10 (0.86-1.40)	1.51 (0.98-2.32)

*The incidence of VTE in the UK is 30/10,000 person years. Incidence as shown is unadjusted.

Models were adjusted for age, sex, history of malignancy, hypertension, hospitalization in the baseline period, liver disease, oral steroid and NSAID use in the baseline period, body mass index category, smoking and alcohol intake, joint replacement surgery.

Patients could be included in more than one category (e.g. patients with both psoriasis and PsA were included in both analyses)

Disclosure: A. Ogdie-Beatty, None; **D. Shin**, None; **J. Takeshita**, Pfizer Inc, 2; **Z. ChiesaFuxench**, None; **J. Gelfand**, Abbvie, Novartis, Pfizer, Janssen, 2,Abbvie, Amgen, Novartis, Pfizer, Janssen, Merck, Coherus, 5.

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Abstract Number: 3120

The Prevalence, Incidence and Management of Hypertension, Diabetes and Hyperlipidemia in Psoriatic Arthritis, Psoriasis and Rheumatoid Arthritis

Kashif Jafri[1], Christie M. Bartels[2], Daniel Shin[3] and Alexis Ogdie-Beatty[4], [1]Department of Medicine, University of Pennsylvania, Philadelphia, PA, [2]Medicine, Rheumatology, University of Wisconsin School of Medicine and Public Health, Madison, WI, [3]University of Pennsylvania, Philadelphia, PA, [4]Medicine/Rheumatology, University of Pennsylvania, Philadelphia, PA

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Session Time: 2:30PM-4:00PM

Background/Purpose: Psoriasis, psoriatic arthritis (PsA), and rheumatoid arthritis (RA) are associated with an increased risk for cardiovascular disease (CVD). While management of traditional CVD risk factors improves outcomes, it is unclear to what degree CVD risk factors are recognized and managed in patients with these inflammatory diseases. The objectives of this study were the following: 1) to determine the prevalence and incidence of hypertension (HTN), hyperlipidemia (HL), and diabetes mellitus (DM) among patients with PsA, psoriasis and RA compared to the general population, and 2) to examine the treatment of incident HTN, HL, and DM among patients with RA, PsA, and psoriasis compared to the general population.

Methods: A retrospective cohort study was performed in The Health Improvement Network (THIN), a medical record database in the United Kingdom, among patients with PsA, psoriasis, RA and controls from the general population matched on general practice and start date (1994-2014). Logistic regression analysis was used to examine the relative prevalence of HTN, HL, and DM (defined by diagnosis codes) in RA, PsA, and psoriasis compared to controls after adjusting for age and sex. Cohort studies were performed to determine the incidence of HTN, HL, DM, the hazard ratios for each outcome adjusting for potential confounders, and the receipt of appropriate therapy within one year following these diagnoses.

Results: Study subjects included 12,666 patients with PsA, 193,053 with psoriasis, 54,890 with RA and 1,319,542 matched controls. In patients with PsA, the age/sex-adjusted prevalence of HTN (OR 1.43; 95% CI 1.37-1.49), HL (OR 1.30; 95% CI 1.23-1.36), and DM (OR 1.42; 95% CI 1.35-1.51) were significantly increased compared to controls (see Table). In contrast, in patients with RA, only the age/sex-adjusted prevalence of DM (OR 1.03; 95% CI 1.01-1.06) was significantly increased. The age/sex-adjusted prevalence of HTN, HL, and DM was significantly increased in both mild and severe psoriasis, although higher among patients with severe psoriasis compared to mild psoriasis. The frequency of receipt of therapy among patients with incident diagnoses of HTN, HL, and DM was not significantly different between the disease groups and controls; approximately 80%, 50%, and 60% of patients received prescriptions for HTN, DM, and HL respectively.

Conclusion: In this study, the age-and-sex adjusted prevalence of diagnosed HTN, HL, and DM was higher in psoriasis and PsA compared to RA and controls. Treatment of HTN, DM, and HL was similar between those with inflammatory diseases and controls. This study examined only "diagnosed" HTN, HL and DM and did not examine lifestyle modification or potential under-diagnosis of CVD risk factors. Future work should investigate strategies to manage CVD risk factors in these inflammatory conditions.

	Prevalence	Age/Sex Adj OR (95%CI)	Incidence[2] /10,000 PY	Adjusted-HR[3] HR (95%CI)	Treatment
HYPERTENSION					
Control	399,604 (30.3%)	REF	343	REF	79.2%
PsA	4,214 (33.3%)	1.43 (1.37-1.49)	444	1.36 (1.25-1.48)	82.2%
RA	22,750 (41.5%)	1.00 (0.98-1.02)	923	1.22 (1.18-1.26)	82.6%
Mild Psoriasis	50,944 (26.4%)	1.03 (1.02-1.05)	285	1.08 (1.06-1.10)	79.2%
Severe Psoriasis[1]	1,955 (30.8%)	1.37 (1.29-1.45)	501	1.31 (1.19-1.44)	82.0%
DIABETES					
Control	124,422 (9.4%)	REF	64	REF	47.5%
PsA	1,498 (11.8%)	1.42 (1.35-1.51)	88	1.36 (1.20-1.53)	53.3%
RA	6,728 (12.3%)	1.03 (1.01-1.06)	76	1.10 (1.05-1.15)	49.7%
Mild Psoriasis	17,657 (9.2%)	1.11 (1.10-1.13)	72	1.14 (1.11-1.17)	48.7%
Severe Psoriasis	759 (12.0%)	1.52 (1.41-1.65)	76	1.34 (1.16-1.54)	53.9%
HYPERLIPIDEMIA					
Control	182557 (13.8%)	REF	118	REF	57.1%
PsA	1996 (15.8%)	1.30 (1.23-1.36)	152	1.34 (1.21-1.48)	57.2%
RA	8924 (16.3%)	0.86 (0.84-0.88)	157	1.08 (1.04-1.12)	63.2%
Mild Psoriasis	24,553 (12.7%)	1.05 (1.04-1.07)	117	1.10 (1.08-1.13)	57.6%
Severe Psoriasis	961 (15.2%)	1.31 (1.22-1.41)	143	1.19 (1.05-1.35)	64.7%

1) Severe psoriasis was defined as patients with psoriasis and a code for either a disease modifying drug or phototherapy.
2) Incidence was specified per 10,000 person years. Incident diagnoses were defined as cases in which the first diagnosis for HTN, HL, or DM occurred after registration with the practice, software implementation ("Vision") date, and diagnosis of the disease (which was assigned for controls).
3) Hazard ratios are adjusted for age, sex, and baseline covariates including charlson comorbidity index, number of visits in the baseline period, body mass index category, smoking status, cardiovascular disease, and the remaining two of hypertension, hyperlipidemia, and diabetes (those with a previous diagnosis of the primary outcome were excluded).

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Abstract Number: 3121

Gender Differences in Patient Reported Outcomes (PROs) in Psoriatic Arthritis

Tawnie Braaten[1], Brian Breviu[1], Jessica Walsh[2], Angela Presson[3], Chong Zhang[3] and Daniel Clegg[4], [1]Department of Internal Medicine, Salt Lake City Veteran Affairs and University of Utah Medical Centers, Salt Lake City, UT, [2]Division of Rheumatology, Salt Lake City Veteran Affairs and University of Utah Medical Centers, Salt Lake City, UT, [3]Department of Epidemiology, University of Utah Hospitals and Clinics, Salt Lake City, UT, [4]Rheumatology, Salt Lake City Veteran Affairs and University of Utah Medical Centers, Salt Lake City, UT
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SESSION INFORMATION

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Session Type: ACR Concurrent Abstract Session
Session Time: 2:30PM-4:00PM

Background/Purpose: Gender is an important patient characteristic that may potentially be used to predict clinical presentation, disease progression and therapeutic response. In recent studies, women with psoriatic arthritis (PsA) have reported less favorable function, increased fatigue, and decreased quality of life compared to men. Less is known about gender differences with other patient reported outcomes (PROs) such as pain, joint counts, and work limitations. Our purpose was to characterize gender differences in PROs, in participants of the Utah Psoriasis Initiative Arthritis Registry.

Methods: Baseline demographics, PsA characteristics, and PROs were compared between men and women enrolled between January 2010 and November 2014, using student's t-test, Wilcoxon rank sum test, or Chi-square test. Work limitations were assessed in participants working for pay at the time of enrollment. Multivariate logistic regression was used to adjust for age, erythrocyte sedimentation rate (ESR) and PsA severity, as measured by the number of lifetime disease modifying anti-rheumatic drugs (DMARDs).

Results: Participants included 115 men and 138 women. Compared to men, women were older, had higher mean ESR, and were exposed to more DMARDs (Table 1). Women had less favorable unadjusted PROs for pain, fatigue, joint count, physical demands at work, work output, and function as measured by both Health Assessment Questionnaire (HAQ) and the Psoriatic Arthritis Screening and Evaluation (PASE) function subscale (Table 2). After adjustment for age, ESR, and number of lifetime DMARDs, these differences persisted for fatigue and HAQ.

Conclusion: Women experienced PsA differently than men, with higher fatigue and more functional limitations. The etiology of the gender differences in PsA are unclear, and further research is indicated to better understand the role of hormones, gene expression, and other potential pathophysiologic differences between men and women.

Table 1. Demographics, PsA characteristics, and therapies

	n	Male No. (%) or Mean (SD)	n	Female No. (%) or Mean (SD)	p
Age	115	47.0 (12.3)	138	51.4 (14.1)	0.01
White race	115	107 (93%)	138	126 (91%)	0.61
Working for pay	97	71 (73%)	121	62 (50%)	0.001
PsA duration (years)	115	5.6 (8.8)	136	5.2 (10.2)	0.44
Psoriasis duration (years)	105	16.2 (13.4)	123	18.3 (16.9)	0.69
Tender joint count (0-68)	115	7.9 (10.8)	138	7.7 (9.1)	0.45
Swollen joint count (0-66)	115	3.7 (6.8)	138	3.5 (4.7)	0.33
Dactylitis count (0-20)	114	0.4 (1.2)	137	0.3 (1.0)	0.68
Enthesitis count (Leeds) (0-6)	115	0.4 (0.8)	137	0.5 (1.0)	0.25
Inflammatory back pain	115	47 (41%)	138	49 (36%)	0.38
PGAxBSA	115	10.7 (37.9)	138	5.4 (10.9)	0.07
Global Provider Assessment (0-10)	115	3.7 (1.8)	136	4.0 (1.7)	0.06
Psoriatic fingernails	113	67 (59%)	125	51 (41%)	0.004
ESR (mm/hr)	89	9.6 (14.7)	111	14.2 (15.1)	<0.001
CRP (mg/dL)	93	1.1 (2.3)	115	1.3 (2.4)	0.57
Axial PsA changes on imaging	74	23 (31%)	103	24 (23%)	0.25
Peripheral PsA changes on imaging	98	44 (45%)	121	68 (56%)	0.10
Nonbiological DMARD(s), current	115	30 (26%)	138	48 (35%)	0.14
Biological DMARD(s), current	115	29 (25%)	138	54 (39%)	0.02
# lifetime DMARDs (biologic & nonbiologic)	115	1.4 (1.3)	138	1.9 (1.7)	0.02

PGAxBSA = psoriasis Physician Global Assessment x Body Surface Area. Table 2. Patient reported outcomes

Table 2: Patient reported outcomes

	Male n	(N=115)	Female n	(N=138)	Unadjusted p	Adjusted p*
Pain (0-10)	96	4.9 (2.7)	120	5.8 (2.8)	0.02	0.23
Patient global assessment (0-10)	96	5.3 (2.7)	120	5.9 (2.7)	0.15	0.73
Fatigue [BASDAI#1] (0-10)	97	5.4 (2.7)	121	6.6 (2.4)	<0.001	0.05
Joint count [PEST mannequin] (0-21)	84	10.1 (4.8)	112	11.6 (5.3)	0.04	0.20
Psoriatic Arthritis Quality of Life	88	7.1 (5.7)	101	7.9 (5.6)	0.28	0.59
Dermatology Life Quality Index	95	5.0 (5.7)	116	4.7 (5.2)	0.91	0.93
WLQ Work Productivity Loss (%)	63	5.9 (5.4)	54	7.8 (5.7)	0.06	0.16
WLQ Time Management (%)	65	30.2 (27.6)	60	33.5 (30.3)	0.61	0.29
WLQ Physical Demands (%)	70	26.2 (26.8)	62	37.9 (28.3)	0.01	0.06
WLQ Mental Interpersonal (%)	70	19.1 (19.8)	60	23.5 (23.7)	0.35	0.27
WLQ Output (%)	68	20.0 (27.2)	56	29.9 (29.6)	0.04	0.72
PASE Symptom subscale	85	24.4 (5.3)	111	25.3 (5.5)	0.20	0.37
PASE Function subscale	85	26.2 (7.0)	111	28.4 (6.6)	0.05	0.23
Health Assessment Questionnaire	94	0.6 (0.5)	117	0.9 (0.6)	<0.001	0.01

*Adjusted for age, ESR, and number of lifetime biologic and non-biologic DMARD therapies. BASDAI#1 = question 1 from Bath Ankylosing Spondylitis Disease Activity Index. PASE = Psoriatic Arthritis Screening and Evaluation. WLQ = Work Limitations Questionnaire

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A Longitudinal Analysis of Change in Lupus Nephritis in an International Inception Cohort Using a Multistate Markov Model Approach

John G. Hanly[1], Li Su[2], Murray Urowitz[3,4], Juanita Romero-Diaz[5], C. Gordon[6], Sang-Cheol Bae[7], Sasha R Bernatsky[8], Ann Clarke[9], Daniel J Wallace[10], Joan T. Merrill[11], David A. Isenberg[12], Anisur Rahman[13], Ellen M. Ginzler[14], Paul Fortin[15], Dafna D. Gladman[16], Jorge Sanchez-Guerrero[17], Michelle Petri[18], Ian N. Bruce[19], Mary Anne Dooley[20], Rosalind Ramsey-Goldman[21], Cynthia Aranow[22], Graciela S. Alarcon[23], Barri J. Fessler[24], Kristján Steinsson[25], Ola Nived[26], Gunnar K. Sturfelt[27], Susan Manzi[28], Munther Khamashta[29], Ronald F. van Vollenhoven[30], Asad Zoma[31], Guillermo Ruiz-Irastorza[32], Manuel Ramos-Casals[33], S. Sam Lim[34], Thomas Stoll[35], Murat Inanc[36], Kenneth C. Kalunian[37], Diane L. Kamen[38], Peter Maddison[39], Christine A. Peschken[40], Søren Jacobsen[41], Anca Askanase[42], Chris Theriault[43], Kara Thompson[43] and Vernon Farewell[44], [1]Rheumatology, Division of Rheumatology, Capital Health and Dalhousie University, Halifax, NS, Canada, [2]Nova Scotia Rehab Site, Division of Rheumatology, Capital Health and Dalhousie University, Halifax, NS, Canada, [3]Rheumatology, TWH, Toronto, ON, Canada, [4]Rheumatology, U of Toronto, Toronto Western Hospital, Toronto, ON, Canada, [5]Immunology and Rheumatology, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico city, Mexico, [6]School of Immunity and Infection, College of Medical and Dental Sciences, University of Birmingham, Birmingham, United Kingdom, [7]Rheumatology, Hanyang University Hospital for Rheumatic Diseases, Seoul, South Korea, [8]Division of Rheumatolog, McGill Unversity Health Cener, Montreal, QC, Canada, [9]Division of Rheumatology, Department of Medicine, University of Calgary, Calgary, AB, Canada, [10]Cedars-Sinai Medical Center, West Hollywood, CA, [11]Clinical Pharmacology, Oklahoma Medical Research Foundation, Oklahoma City, OK, [12]Rayne Institute, Centre for Rheumatology Research,

UCL Division of Medicine, London, United Kingdom, [13]Centre for Rheumatology Research, U College of London, London, United Kingdom, [14]Medicine/Box 42, SUNY-Downstate, Brooklyn, NY, [15]Medicine, Division of Rheumatology, Centre Hospitalier Universitaire de Quebec et Universite Laval, Quebec, QC, Canada, [16]Department of Medicine, Division of Rheumatology, University of Toronto, Toronto, ON, Canada, [17]Rheumatology, Toronto Western Hospital, Toronto, ON, Canada, [18]Rheumatology, Johns Hopkins University Hospital, Baltimore, MD, [19]Stopford Building, Arthritis Research UK Centre for Epidemiology, Centre for Musculoskeletal Research, Institute of Inflammation and Repair, Manchester Academic Health Science Centre, The University of Manchester, Manchester, United Kingdom, [20]UNC Kidney Centre, Chapel Hill, NC, [21]Northwestern University Feinberg School of Medicine, Chicago, IL, [22]Feinstein Institute for Medical Research, Manhasset, NY, [23]Medicine, University of Alabama at Birmingham, Birmingham, AL, [24]UAB, Birmingham, AL, [25]Rheumatology, Univ. Hospital, Reykjavik, Iceland, [26]Rheumatology, Inst of Clinical sciences, Lund, Sweden, [27]Department of Rheumatology, Univ Hospital Lund, Lund, Sweden, [28]Rheumatology, Allegheny Health Network, Pittsburgh, PA, [29]Graham Hughes Lupus Research Laboratory, The Rayne Institute, St Thomas' Hospital, London, United Kingdom, [30]Department of Medicine, Unit for Clinical Therapy Research, Inflammatory Diseases (ClinTRID), The Karolinska Institute, Stockholm, Sweden, [31]Rheumatology, Hairmyres Hospital, East Kilbride, United Kingdom, [32]Universidad del Pais Vasco, Servicio de Medicina Interna, Hospital de Cruces, Bizkaia, Spain, [33]Autoimmune Diseases, IDIBAPS, Hospital Clinic, Barcelona, Spain, [34]Emory University School of Medicine, Atlanta, GA, [35]Abteilung Rheumatologie/Rehab, Kantonsspital Schaffhausen, Schaffhausen, Switzerland, [36]Department of Internal Medicine, Division of Rheumatology, Istanbul University, Istanbul Faculty of Medicine, Istanbul, Turkey, [37]Center for Innovative Therapy, UCSD School of Medicine, La Jolla, CA, [38]Medicine, Medical University of South Carolina, Charleston, SC, [39]School of Sport, Health and Exercise Sciences, Bangor University, George Building, Bangor, Gwynedd, LL57 2PZ, UK., Bangor, United Kingdom, [40]Rheumatology, Univ of Manitoba, Winnipeg, MB, Canada, [41]Rheumatology, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark, [42]NYU School of Medicine, New York, NY, [43]Dept of Medicine, Queen Elizabeth II Health Sciences Centre and Dalhousie University, Halifax, NS, Canada, [44]Medicine, Division of Rheumatology, Capital Health and Dalhousie University, Halifax, NS, Canada
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SESSION INFORMATION

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Session Time: 2:30PM-4:00PM

Background/Purpose: Patients with lupus nephritis (LN) may have improvement or deterioration in renal status over time. To capture bidirectional change we used a reversible multistate Markov model to study transitions in glomerular filtration rate (GFR) and proteinuria (PrU) in a prospective, international, inception cohort of SLE patients receiving standard of care.

Methods: Patients were evaluated at enrollment and annually. LN was identified from the ACR classification criteria and/or renal biopsy. Data included medications, estimated GFR (eGFR) and PrU (ePrU), disease activity (SLEDAI-2K), organ damage [(SLICC)/ACR damage index (SDI)] and lupus autoantibodies including IgG anticardiolipin (aCL) and lupus anticoagulant (LAC). GFR states were defined: state 1 (eGFR: >60 ml/min); state 2 (eGFR: 30–60 mL/min); and state 3 (eGFR: <30 ml/min). Similarly, PrU states were defined: state 1 (ePrU: <0.25 gr/day); state 2 (ePrU: 0.25–3.0 gr/day); and state 3 (ePrU: >3.0 gr/day). Multistate models were used to provide estimates of relative transition rates and state occupancy probabilities for various time periods.

Results: Of 1,826 SLE patients, 89% were female, 49.2% Caucasian with mean±SD age 35.1±13.3 years. The mean disease duration at enrollment was 0.5±0.3 years and follow-up was 4.6±3.4 years. LN occurred in 700/1,826 (38.3%) patients. There was no observed change in eGRF state for 2303/2430 (94.8%), 136/255 (53.3%) and 26/55 (47.3%) visits when the previous eGFR state was 1, 2 and 3 respectively. The corresponding values for ePrU states were 1167/1460 (79.9%), 547/983 (55.6%) and 59/205 (28.8%). For both outcomes the likelihood of improvement (states 2 to 1 and 3 to 2) was greater than deterioration (states 1 to 2 and 2 to 3). The transition from state 3 to ESRD was more likely with eGFR (54%) than ePrU (9%). Probability estimates of transitioning between eGFR and ePrU states, ESRD and death at 1, 2 and 5 years were determined. At year one the highest probability was for patients to remain in the initial eGFR (95%, 55%, 42%) or ePrU (81%, 56%, 31%) state. Following 2 and 5 years, the estimated probability for improvement in either eGFR or ePrU was higher than deterioration. Multivariate analysis identified older age ($p<0.001$), race/ethnicity (Hispanic, Asian and African ancestry) ($p<0.001$), higher ePrU state ($p<0.001$), higher renal biopsy chronicity score ($p=0.013$) and baseline aCL antibodies ($p=0.039$) as predictors for deterioration in eGFR states and male sex ($p=0.04$) for improvement. For ePrU, multivariate analysis identified race/ethnicity (Hispanic, Asian and African ancestry) ($p=0.009$), corticosteroid use ($p=0.031$), higher eGFR state ($p=0.011$) and higher renal biopsy chronicity score ($p=0.015$) as predictors for deterioration. Positive LAC ($p=0.006$) and ISN/RPN class V nephritis ($p=0.013$) were associated with lower improvement rate.

Conclusion: Multistate modeling in patients with LN generates probability estimates of transitions between disease states that reflect improvement or deterioration in renal outcomes. This approach can identify predictors of change in renal status and can inform clinical trial design by providing minimum expectations for benefit from new therapeutic interventions for LN.

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Abstract Number: 3123

Evidence of Altered Blood Brain Barrier Permeability in Systemic Lupus Erythematosus Using Magnetic Resonance Imaging

Gaurav Gulati[1], Jordan T. Jones[2], Mekibib Altaye[3], Jamie Meyers Eaton[4], Kasha Wiley[2], Mark DiFrancesco[5] and Hermine I. Brunner[6], [1]Division of Immunology, Allergy and Rheumatology, University of Cincinnati College of Medicine, Cincinnati, OH, [2]Division of Rheumatology, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, [3]Biostatistics and Epidemiology, Cincinnati Children's Hospital and Medical Center, Cincinnati, OH, [4]Division of Pediatric Rheumatology, Cincinnati Children's Hospital and Medical Center, Cincinnati, OH, [5]Radiology, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, [6]Pediatric Rheumatology Collaborative Study Group, Cincinnati Children's Hospital Medical Center, Cincinnati, OH

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Session Title: Systemic Lupus Erythematosus - Clinical Aspects and Treatment V: Neuropsychiatric Lupus

Session Type: ACR Concurrent Abstract Session

Session Time: 2:30PM-4:00PM

Background/Purpose:

Neurocognitive dysfunction is a common manifestation of childhood-onset Systemic Lupus Erythematosus (cSLE). Murine models suggest that loss of the blood-brain barrier (BBB) integrity allows brain-reactive proteins to enter the CNS and contribute to SLE-associated pathology. Contrast magnetic resonance imaging (MRI) can provide a measure of BBB integrity, but has risk associated with gadolinium use. We have previously identified multiple areas of gray matter (GM) loss on structural MRI in cSLE patients with neurocognitive deficits. Our aim was to evaluate safe, non-invasive MRI-methods of measuring regional BBB permeability and its relationship with neurocognitive function and regional GM volume in cSLE.

Methods:

Twelve cSLE patients and 12 healthy controls (age, gender, race and socioeconomic status matched) were enrolled. Those with diseases or medications (except prednisone) affecting neurocognitive function were excluded. Cognitive performance was assessed using the *cSLE Neurocognitive Battery*, which probes four cognitive domains: working memory, psychomotor speed, attention, and visuoconstructional ability. Performance in each of these was standardized and expressed as a Z-score. We almost concurrently performed arterial spin labeling (ASL) and diffusion-weighted imaging to measure regional BBB permeability. Voxel-based morphometric analysis was done to measure regional GM volume. Voxel-wise comparisons of capillary permeability were made between the cSLE and control groups. Correlation analysis was performed between regional BBB permeability and cognitive performance Z-scores, as well as local GM volume for the cSLE group.

Results:

Among the cSLE patients (11 females, 7 African American, mean age 18 ± 6.8 years), 9 were treated with prednisone (median dose 5 mg/d). None was diagnosed with active neuropsychiatric SLE. Group comparison revealed clusters of voxels with significantly greater BBB permeability for cSLE patients than controls, in three regions as shown in **Figure 1**. Correlations between BBB permeability and regional GM volume or overall and individual domain Z-scores for neurocognitive performance were not statistically significant, although locations of significant increases in permeability for cSLE closely match our previously identified areas of GM loss and functional changes associated with clinically overt neurocognitive impairment.

Conclusion:

We present imaging evidence of altered regional BBB permeability in cSLE, using a novel non-invasive MRI technique. The absence of correlation with GM volume or cognitive performance Z-scores, yet similar location to GM loss in previous work in our cSLE cohort suggests that BBB breakdown may precede clinically overt neurocognitive impairment and brain tissue loss. Longitudinal studies are needed to confirm the change in GM volume in relation to BBB permeability over time.

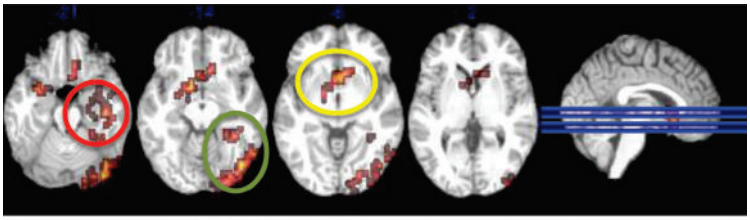

Figure 1: Select slices of a group difference T map for Blood-Brain Barrier permeability (SLE>controls). The three identified significant clusters (< 0.05 family-wise error corrected) are shown with legend.
[Red indicates decreased Blood-Brain Barrier integrity]

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Abstract Number: 3124

Associations of Circulating Cell-Free Micro-RNA with Vasculopathy and Vascular Events in SLE Patients

Susan Due Kay[1], Anting L. Carlsen[2], Anne Voss[1], Mikael Kjær Poulsen[3], Axel Cosmus Pyndt Diederichsen[4] and Niels H. H. Heegaard[5], [1]Department of Rheumatology, Odense University Hospital, Odense C, Denmark, [2]Department of Congenital Disorders, Statens Serum Institut, Copenhagen, Denmark, [3]Department of Cardiology, Odense University Hospital, Odense C, Denmark, [4]Department of Cardiology,, Odense University Hospital, Odense C, Denmark, [5]Department of Clinical Biochemistry & Pharmacology, Odense University Hospital, Odense C, Denmark

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Session Type: ACR Concurrent Abstract Session

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Background/Purpose:

MicroRNAs (miRNAs) are small noncoding RNAs that modulate protein translation and regulate numerous immunologic and inflammatory pathways. Certain miRNA profiles have been associated with several diseases, including atherosclerosis. Patients with systemic lupus erythematosus (SLE) are known to have a high prevalence of atherosclerosis and a recent study has shown that circulating miRNAs are systematically altered in SLE.

Therefore, our objective was to investigate the association between markers of atherosclerosis and cell-free circulating microRNAs in patients with systemic lupus erythematosus.

Methods:

120 SLE patients were screened for atherosclerosis by means of cardiac CT demonstrating coronary artery calcification (CAC) and carotid ultrasound visualizing intima-media thickness (IMT) and plaque. Atherosclerosis was defined as either CAC > 99U, carotid IMT>1.00mm and/or carotid plaque. Total RNA was purified from plasma, and 46 specific miRNAs were determined using quantitative real time PCR on a dynamic microfluidic array. Patients with atherosclerosis were compared to those without in terms of expression of cell-free circulating miRNAs.

Results:

Six miRNAs were expressed differently in plasma from SLE patients with atherosclerosis compared to those without. The expression of miR-125b, miR-29b-3p, miR-375, miR-101, miR- 122-5p and miR-20a were all decreased in SLE patients with atherosclerosis.

Unsupervised hierarchical clustering identified miRNA profiles (an 8-miRNA signature) that differentiated a group of SLE patients from the rest. This patient group (n=16) had significantly increased frequencies of recorded venous thrombotic events (p=0.045), a higher prevalence of β_2-glycoprotein 1 IgG antibodies (p=0.029), and significantly lower platelet counts (p=0.024).

Conclusion: Six circulating miRNAs are for the first time shown to be associated with atherosclerosis in a cross-sectional SLE cohort. Furthermore, an 8-miRNA signature was associated with the phenotype of the antiphospholipid syndrome with the patients having a history of venous thrombotic events, β2-glycoprotein 1 antibodies and lower platelet counts. The findings warrant further prospective studies of the putative association between specific circulating miRNAs and vasculopathy in SLE patients.

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View Abstract and Citation Information Online - http://acrabstracts.org/abstract/associations-of-circulating-cell-free-micro-rna-with-vasculopathy-and-vascular-events-in-sle-patients

Abstract Number: 3125

White Matter Magnetization Transfer Ratio Histogram Peak Height Helps Identifying Inflammatory Neuropsychiatric Systemic Lupus Erythematosus

César Magro Checa[1], Ece Ercan[2], Bart J Emmer[3], Ron Wolterbeek[4], Itamar Ronen[2], Mark A. Van Buchem[2], T. W. J. Huizinga[5] and **Gerda M. Steup-Beekman**[5], [1]Department of Rheumatology, Leiden University Medical Center, Leiden, Netherlands, [2]Radiology, C.J. Gorter Center for High Field MRI, Department of Radiology, Leiden University Medical Center, Leiden, Netherlands, [3]Department of Radiology, Erasmus Medical Center, Rotterdam, Netherlands, [4]Department of Medical Statistics and Bioinformatics, Leiden University Medical Center, Leiden, Netherlands, [5]Rheumatology, Department of Rheumatology, Leiden University Medical Center, Leiden, Netherlands
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SESSION INFORMATION
Session Date: Tuesday, November 10, 2015
Session Title: Systemic Lupus Erythematosus - Clinical Aspects and Treatment V: Neuropsychiatric Lupus
Session Type: ACR Concurrent Abstract Session
Session Time: 2:30PM-4:00PM

Background/Purpose: Magnetization transfer ratio (MTR) can be used to detect microstructural cerebral changes in normal-appearing brain tissue of neuropsychiatric systemic lupus erythematosus (NPSLE) patients. Our aim was to assess white matter (WM) and grey matter (GM) magnetization transfer ratio histogram peak heights (MTR-HPHs) in different subsets of NPSLE patients with a non-remarkable 3T-brain-MRI and to evaluate whether these values could highlight different clinically suspected underlying pathogenic processes, recognize the clinical NPSLE status or be associated with a specific NPSLE syndrome.

Methods: Sixty-four SLE-patients with neuropsychiatric symptoms were included. The initial NPSLE diagnosis and suspected pathogenic underlying process were established by multidisciplinary evaluation. Furthermore, we performed a re-evaluation of the disease course and confirmation of the diagnosis 6-18 months later. Thirty-three patients with central nervous system (CNS) NPSLE and 31 SLE patients with neuropsychiatric complaints non-related to SLE (NP-non-SLE) were included. Twenty SLE patients without neuropsychiatric complaints and 36 healthy controls were included for comparison. Differences of mean WM and GM MTR-HPH values between different NPSLE subgroups (inflammatory or ischemic NPSLE phenotype), the clinical changes after treatment and the relation with NPSLE syndromes were evaluated.

Results: The mean and standard deviation of the WM and GM MTR-HPHs are presented in Table 1. Inflammatory NPSLE patients have significantly lower WM MTR-HPH than healthy controls ($P < 0.001$), SLE ($P < 0.001$) and NP-non-SLE patients ($P < 0.05$) (Figure 1). Cognitive disorder, mood disorder and psychosis were related to lower values and cerebrovascular symptoms to higher values of WM MTR-HPH ($P < 0.05$). Furthermore, we show how the mean WM MTR-HPHs increased when the clinical status of the NPSLE patients improved ($P < 0.001$) (Figure 1).

Conclusion: WM MTR-HPH has potential to identify inflammatory NPSLE with CNS involvement corroborating the usefulness of this technique to detect cerebral changes in NPSLE patients and to assess clinical changes after treatment.

Table 1. Comparison of white matter and grey matter MTR-HPHs in the study groups					
	Healthy controls (n=36)	SLE (n = 20)	NP-non-SLE (n = 31)		
				Phenotype	
				Inflammatory NPSLE (n=22)	Ischemic NPSLE (n = 11)
WM MTR-HPH µ	43.37 ± 5.11†	42.74 ± 6.22†	38.35 ± 4.64‡	32.22 ± 7.76	39.42 ± 4.21†
GM MTR-HPH µ	10.01 ± 2.51	10.02 ± 1.92‡	9.81 ± 3.68	7.71 ± 3.25	10.25 ± 2.85

CNS: central nervous system; GM: grey matter; MTR-HPH: magnetization transfer ratio histogram peak height; NP-non-SLE: SLE patients with neuropsychiatric complaints non associated with CNS involvement due to SLE; NPSLE: neuropsychiatric SLE; SLE: systemic lupus erythematosus; WM: white matter.

* Values are the mean ± standard deviation.

† Indicates significance level at $P < 0.001$ when compared with inflammatory NPSLE

‡ Indicates significance level at $P < 0.05$ when compared with inflammatory NPSLE

µ Peak height values were multiplied by 10,000 for readability.

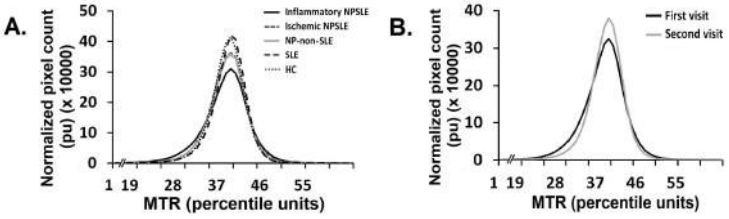

Figure 1. Average magnetization transfer ratio histograms of white matter from **(A)** subjects with inflammatory and ischemic neuropsychiatric systemic lupus erythematosus (NPSLE), systemic lupus erythematosus patients with neuropsychiatric complaints non-related to SLE (NP-non-SLE), systemic lupus erythematosus patients without neuropsychiatric complaints (SLE) and healthy controls and **(B)** active NPSLE patients on the first visit and after treatment on the second visit.

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Abstract Number: 3126

Biomarkers Associated with Hyperintense White Matter Lesions in Systemic Lupus Erythematosus

Mariana Postal, Aline Tamires Lapa, Karina O. Peliçari, Nailu A. Sinicato, Fernando A. Peres, Angela C. Gomes, Lilian TL Costallat, Fernando Cendes and **Simone Appenzeller**, Medicine, State University of Campinas, Campinas, Brazil

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Session Time: 2:30PM-4:00PM

Background/Purpose: Cytokines and neuronal injury markers act as crucial mediators in the bidirectional signaling between the immune system and the brain and may be biomarkers for brain damage. The aim of this study was to determine the prevalence of hyperintense white matter (WM) lesions and to elucidate the possible relationship between biomarkers such as Th1 (IL-12, IFN-γ, TNF-α), Th2 (IL-4,6,10) cytokines and S100β, subunit of high molecular weight neurofilament (NF-H) and antiribosomal P protein antibodies (anti-P) and WM lesions in systemic lupus erythemathosus (SLE) patients.

Methods: Consecutive SLE patients followed at the Rheumatology unit of the State University of Campinas were enrolled in this study. Healthy volunteers, matched by age and sex, were included as control group. A complete clinical, laboratory and neurological evaluation was performed in all subjects. Neurological manifestations were analyzed according to the ACR classification criteria. SLE patients were further assessed for clinical and laboratory SLE manifestations, disease activity [SLE Disease Activity Index (SLEDAI)], damage [Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index (SDI)] and current therapy. WM lesions were analyzed in T2-weighted images (3T Phillips®scanner) using a semiautomated computer program (Neuroline®). Th1, Th2 cytokines and S100β, NF-H and anti-P were measured by ELISA using commercial kits. Data were compared by non-parametric tests.

Results: One hundred fifty SLE patients (138 women; mean age of 42.03±11.37; range 24-73) and 56 (50 women; mean age of 41.35±12.44; range 18-69) healthy controls were included. WM lesions were identified in 121 (80.67%) SLE patients and in 4 (7.4%) healthy controls (p=0.001). In SLE patients, we observed, predominantly, subcortical lesions (74.67%), followed by periventricular (65.33%), deep WM (59.33%) and cortical (26.67%) lesions. Both the number (N=6549 *vs* N=27; p=0.001) and the volume of lesions (244109.94cm^3 *vs* 994.65cm^3; p<0.001) were significantly increased in SLE patients compared to controls. Significantly increased sera levels of Th1 [IL-12 (p=0.026), IFN-γ (p=0.021), TNF-α (p<0.001)], Th2 [IL-4 (p=0.006), IL-6 (p=0.008) and IL-10 (p<0.001)], S100β (p=0.006), NF-H (p<0.001) and anti-P (p<0.001) were observed in SLE patients compared to controls. We observed an association between the presence of subcortical lesions and IL-10 (p=0.018) and TNF-α (p=0.014). The presence of deep WM lesion was associated with IFN-γ (p=0.04). We also identified an indirect correlation between the volume of subcortical lesions and IL-10 (r=-0.26; p=0.027). We did not observe an association between WM lesions and neuronal injury markers, current corticosteroid dose or any other clinical or laboratory manifestations.

Conclusion:

TNF-α, IFN-γ and IL-10 levels are associated with WM lesion in SLE, suggesting that peripheral inflammation contributes to WM by triggering an inflammatory response in the microglia. Both Th1 and Th2 cytokines may be useful as biomarkers for brain damage in SLE, once they play a critical role in the interface between the systemic circulation and the brain.

Disclosure: M. Postal, None; **A. T. Lapa**, None; **K. O. Peliçari**, None; **N. A. Sinicato**, None; **F. A. Peres**, None; **A. C. Gomes**, None; **L. T. Costallat**, None; **F. Cendes**, None; **S. Appenzeller**, None.

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Abstract Number: 3127

Serologic Diagnosis of Human Neuropsychiatric Lupus Using the Immunarray ICHIP®

Chaim Putterman[1], D. Scott Batty[2], I.R. Cohen[3], Nicole Jordan[4], Debbie Rybak[1], Tamar Rubinstein[1], Keren Jakobi[5], Rachel Sorek[5], Anat Reiner-Benaim[5], Yakov Blumenstein[5] and Pennina Safer[5], [1]Division of Rheumatology, Albert Einstein College of Medicine, Bronx, NY, [2]ImmunArray Inc., Richmond, VA, [3]Weizmann Institute of Science, Rehovot, Israel, [4]Montefiore Medical Center, New York, NY, [5]ImmunArray LTD, Rehovot, Israel

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Session Type: ACR Concurrent Abstract Session

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Background/Purpose:

Peripheral neurologic syndromes and central nervous system (CNS) manifestations are recognized as primary disease manifestations in systemic lupus erythematosus (SLE). Neuropsychiatric SLE (NPSLE) involves a wide range of nervous system disorders, and can affect 50% or more of SLE patients(1). There is no single diagnostic test specific for NPSLE; rather, the diagnosis is currently based on the combined use of serological testing, functional and/or structural neuroimaging, and standardized neurological and neuropsychological assessments(1). A sensitive and specific serological biomarker for NPSLE would be very helpful in the management of lupus patients. Using a novel antigen microarray platform, unique multivariate classification models were developed to distinguish between patients with NPSLE and SLE patients without active neuropsychiatric manifestations (non-NPSLE).

Methods:

Thirty-eight SLE serum samples were obtained from the Einstein Lupus Cohort at the Albert Einstein College of Medicine (Bronx, NY) and tested using the ImmunArray iCHIP®(2), printed with a set of 225 antigens associated with SLE and/or brain injury. All SLE samples satisfied the ACR classification criteria. Twelve of the 38 patients were diagnosed as positive for NPSLE based on the use of a validated questionnaire

(3). Two independent classification methods were developed. Classifier training and testing were performed based on 5-fold cross validation on all samples.

Results:

Both classification methods differentiated between the lupus patients with and without neuropsychiatric symptoms. The support vector machine (SVM) classification model performed with sensitivity greater than 99% and specificity of 88%. The logistic regression method separated the populations with 83% sensitivity and 96% specificity. Several auto-antigens were shared between the two models, increasing the confidence in the selected antigen lists.

Conclusion:

In a proof of concept study, classification methods based on autoantibody profiles from the ImmunArray iCHIP® were able to successfully distinguish between lupus patients with and without neuropsychiatric symptoms. Our preliminary results based on 38 patients are very promising and warrant additional validation in a larger cohort of NPSLE patients.

References:

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(3) M Mosca et at.; Lupus (2011) 20, 485–492

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View Abstract and Citation Information Online - http://acrabstracts.org/abstract/serologic-diagnosis-of-human-neuropsychiatric-lupus-using-the-immunarray-ichip

Abstract Number: 3128

Genome-Wide DNA Methylation Analysis in Blood and Dermal Fibroblasts from Twin Pairs Discordant for Systemic Sclerosis

Paula S. Ramos[1], Thomas A. Medsger Jr.[2] and Carol A. Feghali-Bostwick[1], [1]Medicine, Medical University of South Carolina, Charleston, SC, [2]Medicine/Rheumatology, University of Pittsburgh, Pittsburgh, PA

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Session Title: Systemic Sclerosis, Fibrosing Syndromes and Raynaud's - Pathogenesis, Animal Models and Genetics II

Session Type: ACR Concurrent Abstract Session

Session Time: 2:30PM-4:00PM

Background/Purpose: The etiology and mechanisms underlying the wide variation in disease heterogeneity and severity in systemic sclerosis (SSc) remain unknown. To assess the role of DNA methylation in SSc risk and clinical heterogeneity while controlling for genetic background, we performed a genome-wide DNA methylation analysis in whole blood and skin fibroblasts of twin pairs discordant for SSc. We also performed gene expression analysis from the same fibroblasts to investigate the relationship between the DNA methylation changes and mRNA expression levels.

Methods: Genome-wide methylation was assessed on approximately 480,000 CpG sites using genomic DNA isolated from 1) whole blood from 20 twin pairs discordant for limited cutaneous SSc (lcSSc) and 10 twin pairs discordant for diffuse cutaneous SSc (dcSSc), and 2) skin fibroblasts cultured from dermal punch biopsies of 7 twin pairs discordant for dcSSc and 5 twin pairs discordant for lcSSc. Total RNA was extracted from fibroblasts in passage 3 for gene expression profiling of 47,000 transcripts. An efficiency analysis was performed with caGEDA to determine best normalization and feature selection methods and to identify differentially methylated probes and differential gene expression between unaffected and affected twins. Ingenuity Pathway Analysis was used for pathway analysis.

Results: A total of 68 CpGs were differentially methylated in whole blood from patients with SSc compared with their healthy twin. In the disease subsets, 206 and 409 CpGs were differentially methylated in the twin pairs discordant for lcSSc and dcSSc, respectively. Only 1% of

differentially methylated genes were common between both subsets. In the dermal fibroblasts, 103 CpGs were differentially methylated in patients with SSc compared with their healthy twin. In the disease subsets, 110 and 220 CpGs were differentially methylated in lcSSc and dcSSc, respectively. 7% of differentially methylated genes were common between both subsets. In each disease subset, less than 2% of differentially methylated genes were observed in blood and fibroblasts. Despite the enrichment of different pathways and biological functions in each cell type and disease subset, most of these pathways can be placed into broader categories implicating an overall involvement of cancer functions. On the other hand, gene expression data from fibroblasts revealed 20% of genes shared between disease subsets. There were common and unique pathways enriched in disease subsets, also implicating an involvement of cancer functions. There were no genes simultaneously differentially methylated and expressed in either disease subset.

Conclusion: The distinct methylation patterns observed in blood and fibroblasts between lcSSc and dcSSc corroborate a similar observation reported in skin fibroblasts and suggest that subset-specific epigenetic signatures may be, at least in part, responsible for the clinical heterogeneity of the disease. These data also support a role for DNA methylation differences in mediating susceptibility to SSc.

Disclosure: P. S. Ramos, None; **T. A. Medsger Jr.**, None; **C. A. Feghali-Bostwick**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/genome-wide-dna-methylation-analysis-in-blood-and-dermal-fibroblasts-from-twin-pairs-discordant-for-systemic-sclerosis

Abstract Number: 3129

Integrative Analysis of the Colonic Microbiota in Systemic Sclerosis

Elizabeth R. Volkmann[1], Yu-Ling Chang[2], Nashla Barroso[3], Daniel E. Furst[3], Philip J. Clements[1], Alan Gorn[4], Bennett Roth[3], Jeffrey Conklin[3], Terri Getzug[3], Maomeng Tong[2], Jonathan Jacobs[3] and Jonathan Braun[2], [1]Medicine, University of California Los Angeles, David Geffen School of Medicine, Los Angeles, CA, [2]Pathology and Laboratory Medicine, University of California, Los Angeles, David Geffen School of Medicine, Los Angeles, CA, [3]Medicine, University of California, Los Angeles, David Geffen School of Medicine, Los Angeles, CA, [4]Medicine, UCLA David Geffen School of Medicine, Division of Rheumatology, Los Angeles, CA

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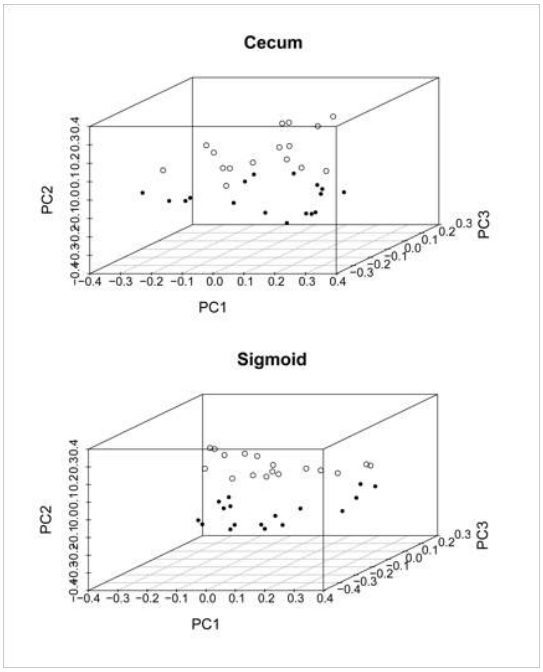
Background/Purpose: Gastrointestinal tract (GIT) dysfunction is a leading cause of morbidity in patients with systemic sclerosis (SSc). However, the etiology of SSc-related lower GIT dysfunction remains elusive. The purpose of the present study was to compare colonic microbial composition of SSc patients and healthy controls and to determine whether certain microbial genera are associated with SSc-GIT symptoms.

Methods: Adults SSc patients who had no contraindication to colonoscopy were eligible to participate. Patients were excluded if they were on chronic antibiotic therapy. Healthy controls were age- and gender-matched to SSc patients (1:1). Cecum and sigmoid mucosal lavage samples were obtained during colonoscopy. SSc patients completed the GIT 2.0 questionnaire to assess GIT symptom severity at the time of colonoscopy. The microbiota from these samples were determined by Illumina HiSeq 2000 16S sequencing, and operational taxonomic units (OTU) were selected using the Greengenes database at 97% identity. Linear Discriminant Analysis (LDA) Effect Size was used to identify the genera that showed differential expression in SSc versus controls. Multivariate Association with Linear Models (MaAsLn) was used to identify specific genera associated with GIT symptoms.

Results: Among 17 patients with SSc (88% Female; Median age 52.1 years), the mean (SD) total GIT 2.0 score was 0.7 (0.6). Principal coordinate analysis illustrated significant microbial community differences in SSc versus healthy controls in the cecum ($p=0.001$) and sigmoid ($p=0.001$) regions (Figure 1). Similar to inflammatory disease states, SSc patients had decreased commensal genera, such as *Faecalibacterium* and *Clostridium* and increased pathogenic genera, such as *Fusobacterium*, *Erwinia* and *Trabsulsiella* compared with healthy controls. However, SSc patients had increased *Bifidobacterium* and *Lactobacillus*, which are typically reduced in inflammation. Increased *Erwinia* and *Trabsulsiella* levels were associated with increased scores on the constipation and diarrhea domains of the GIT 2.0.

Conclusion: This study demonstrates a distinct colonic microbial signature in SSc patients compared with healthy controls. This unique ecological change may perpetuate immunological aberrations and contribute to clinical manifestations of SSc.

Figure 1. Significant differences in the beta diversity of the SSc and healthy samples as demonstrated by principal coordinate analysis plots of the unweighted UniFrac distance for the cecum (top panel) and sigmoid (bottom panel) samples. Each dot represents a sample from a SSc patient (closed circle) or a healthy control (open circle).



Disclosure: **E. R. Volkmann**, None; **Y. L. Chang**, None; **N. Barroso**, None; **D. E. Furst**, Gilead, 2,GlaxoSmithKline, 2,NIH, 2,Novartis Pharmaceutical Corporation, 2,Pfizer Inc, 2,Roche Pharmaceuticals, 2,Genentech and Biogen IDEC Inc., 2,UCB, 2,Abbvie, 5,Actelion Pharmaceuticals US, 5,Amgen, 5,Bristol-Myers Squibb, 5,Cytori, 5,Janssen Pharmaceutica Product, L.P., 5,Gilead, 5,GlaxoSmithKline, 5,NIH, 5,Novartis Pharmaceutical Corporation, 5,Pfizer Inc, 5,Roche Pharmaceuticals, 5,Genentech and Biogen IDEC Inc., 5,UCB, 5,Abbvie, 8,Actelion Pharmaceuticals US, 8,Bristol-Myers Squibb, 2,Amgen, 2,Actelion Pharmaceuticals US, 2,Abbvie, 2,UCB, 8; **P. J. Clements**, None; **A. Gorn**, None; **B. Roth**, None; **J. Conklin**, None; **T. Getzug**, None; **M. Tong**, None; **J. Jacobs**, None; **J. Braun**, None.

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Abstract Number: 3130

Epstein-Barr Virus Induces Activation of Infammatory Markers Via the TLR8 Transduction Pathway in Infected Scleroderma Monocytes

Antonella Farina[1], Giovanna Peruzzi[2,3], Valentina Lacconi[4], Edoardo Rosato[5], Silvia Quarta[6], Stefania Morrone[1], Alberto Faggioni[1], Maria Trojanowska[4] and **Giuseppina Alessandra Farina**[4], [1]Department of Experimental Medicine, Sapienza University, Department of Experimental Medicine, Rome, Italy, [2]Istituto Italiano di Tecnologia (IIT), CLNS@Sapienza, Rome, Italy, [3]Istituto Italiano di Tecnologia (IIT), CLNS@Sapienza, Viale Regina Elena 291, 00161, Rome, Italy, Rome, Italy, [4]Arthritis Center, Boston University, Arthritis Center, Boston, MA, [5]Department of Clinical Medicine, Clinical Immunology Unit,, Sapienza University,Department of Clinical Medicine, Rome, Italy, [6]Department of Clinical Medicine, Clinical Immunology Unit., Sapienza University,Department of Clinical Medicine, Rome, Italy

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Background/Purpose:

Monocytes from patients with systemic sclerosis (Scleroderma, SSc), are characterized by the increased expression of IFN-regulatory genes, implicating dysregulation of the innate immune response in activation of these cells. However, what triggers and sustains monocyte activation in SSc remains unclear. Since Epstein-Barr virus (EBV) mRNA and proteins were found in fibroblasts and endothelial cells in SSc skin, we sought to determine whether EBV might also infect monocytes and contribute to their activation in SSc.

Methods:

Monocytes were isolated from peripheral blood mononuclear cells (PBMCs) depleted of CD19+ cell fraction, using CD14/CD16 negative depletion (CD14-) (Human Monocyte Enrichment Kit without CD16 Depletion,EasySep, StemCell). Circulating monocytes from diffuse cutaneous SSc (dcSSc) (n=8) and healthy donors (HDs) (n=6), were examined for the presence of EBV lytic proteins using Immunofluorescence (IF). EBV-p2089 recombinant virus was used to infect dcSSc and HDs monocytes. Gene expression of IFNs, TLRs (TLR7/8/9) and innate immune mediators (IRF5/7) was evaluated in EBV-p2089 infected dcSSc and HD monocytes using real-time PCR, and proteins examined by IF staining and Western Blot. Flow cytometry was performed on dcSSc and HD PBMCs labeled with phycoerythrin (PE), allophycocyanin (APC), fluorescein isothiocynate (FITC) and PE-cyanine7 (PE-Cy7) conjugated mouse monoclonal antibodies (mAb) against human CD14, CD16, CD163, CD206, CD169/siglec1, CD4, CD8, CD20, CD19, CD23. THP1 monocytes were stimulated with TLR7 (R837) and TLR8 synthetic ligands (cpd14b, R848).

Results:

We found that EBV lytic proteins (Zebra, BFRF1 and gp-350/220), were expressed in skin macrophages and in circulating monocytes from SSc patients, while no expression of lytic EBV was detected in monocytes/macrophages from HDs. Infection of SSc monocytes by EBV-p2089 strongly induced TLR8 expression, while no induction of TLR7 and TLR9 was observed in the infected cells. EBV also significantly induced markers of activated monocytes, such as IRF7, IRF5, Siglec1 and IL-6. Further supporting the importance of TLR8 activation in SSc, expression of TLR8 was significantly increased in freshly isolated monocytes from dcSSc patients compared to HDs. Furthermore, distinct monocyte subsets (CD14+/CD16++) and activation markers were identified in dcSSc PBMCs compared to HDs by FACS analysis. Activation of TLR8 by synthetic ligands mimicked EBV effects on TLR8, inducing IRF7 and inflammatory cytokines, whereas the TLR7 agonist did not induce monocyte inflammation markers on THP1 cells.

Conclusion: These data suggest that dcSSc monocytes are carrying an EBV lytic infection. Activation of TLR8 by EBV RNA might represent a novel mechanism in mediating monocyte inflammation in SSc by which EBV triggers the innate immune response in infected cells.

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View Abstract and Citation Information Online - http://acrabstracts.org/abstract/epstein-barr-virus-induces-activation-of-infammatory-markers-via-the-tlr8-transduction-pathway-in-infected-scleroderma-monocytes

Abstract Number: 3131

Interferon Regulatory Factor 7 (IRF7): The Possible Link Between Inflammation and Fibrosis in SSc Pathogenesis

Minghua Wu[1], Gloria Salazar[1], Xiaodong Zhou[2], Xinjian Guo[2], John D. Reveille[3], Sandeep K. Agarwal[4], Michael R. Blackburn[5], Maureen D Mayes[1] and Shervin Assassi[1], [1]Rheumatology, University of Texas Medical School at Houston, Houston, TX, [2]Internal Medicine, University of Texas Medical School at Houston, Houston, TX, [3]Internal Medicine/Rheumatology, University of Texas Medical School at Houston, Houston, TX, [4]Internal Med, Rheumatology, Baylor College of Medicine, Houston, TX, [5]Biochemistry and Molecular Biology, The University of Texas Medical School at Houston, Houston, TX

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Background/Purpose: A recent global gene expression profile study in a large early SSc patient samples revealed a type I interferon (IFN) signature. Type I IFN and associated genes might serve as biomarkers of more severe disease. Interferon regulatory factors (IRFs) are transcriptional regulators of type I IFN and IFN-inducible genes. Furthermore, IRF7 gene polymorphisms are associated with SSc susceptibility. In our most recent global gene expression study, IRF7 was the most prominent transcription factor in SSc skin (manuscript in press). However, the specific role of IRF7 in SSc pathogenesis has not been identified.

Methods: Early passage SSc fibroblasts (n=20) and age-, gender-, and ethnicity- matched control fibroblasts (n=20) were investigated. SSc and healthy control skin biopsies (14 SSc patients and 14 healthy controls) were used to quantify IRF7 expression by qPCR and protein expression by immunohistochemistry (IHC) analyses. IRF7 expression and activation were also determined in bleomycin induced SSc mouse model. Lesional murine skin tissues were examined by IHC analysis. To better understand the role of IRF7 in SSc pathogenesis, we utilized the bleomycin animal model with a loss-of-function approach. IRF7 KO (n=10) and wild-type mice (n=10) received daily subcutaneous bleomycin injection for 7 or 28 days. The lesional skin was harvested and processed for analysis. For *in vitro* experiments, we used IRF7 KO and wild-type fibroblasts to further investigate the role of IRF7 in fibroblast biology.

Results: IRF7 mRNA and protein levels were significantly up-regulated in SSc skin biopsies compared to control subjects. Furthermore,

compared to control subjects, IRF7 activation was prominent in fibroblasts and macrophages in SSc skin. Explanted skin fibroblast results further confirmed IRF7 mRNA up-regulation (SSc vs control; fold change = 2.37; p=0.024) and protein activation (IRF7 phosphorylation) in SSc. Interestingly, IRF7 showed complex dimerization with SMAD3 in vitro which is a major transcription factor of the TGF-b driven fibrosis signaling. In the bleomycin animal model studies, IRF7 KO mice demonstrated attenuated dermal thickness (IRF7 KO vs wild-type: 162.8 ± 13.6 µm vs 251.3 ± 24.5 µm; p=0.004) as well as inflammatory response and other fibrosis features compared to C57BL/6 wild-type mice after receiving bleomycin for 7 or 28 days. TGF-β1 (IRF7 KO vs wild-type: 1.98 ± 0.76 vs 3.09 ± 0.14 fold changes; p=0.025) and IL6 mRNA expression were significantly abrogated in IRF7 KO mice skin tissue compared to wild-type mice exposed to bleomycin for 7 days. Interestingly, Col1a2 (IRF7 KO vs wild-type: 1.23 ± 0.13 vs 2.36 ± 0.68 fold changes; p=0.008), α-SMA (p=0.035) and CTGF (p=0.046) mRNA expression were also significantly abrogated in IRF7 KO mice skin tissue compared to wild-type mice of 28 days bleomycin injection. Furthermore, IRF7 KO dermal fibroblasts showed reduced collagen and a-SMA protein levels compared to wild-type mice fibroblasts.

Conclusion: Up-regulation and activation of IRF7 in SSc might play a pivotal role in the IFN driven inflammatory response as well as the TGF-ß-driven fibrotic process. IRF7 may therefore represent as a promising novel therapeutic target in SSc.

Disclosure: M. Wu, None; **G. Salazar**, None; **X. Zhou**, None; **X. Guo**, None; **J. D. Reveille**, None; **S. K. Agarwal**, None; **M. R. Blackburn**, None; **M. D. Mayes**, None; **S. Assassi**, None.

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Abstract Number: 3132

Histone Deacetylase 5 Is Overexpressed in Scleroderma Endothelial Cells and Impairs Angiogenesis Via Repressing Pro-Angiogenic Factors

Pei-Suen Tsou[1,2], M. Asif Amin[3], Elena Schiopu[2,4], David A. Fox[3], Dinesh Khanna[1,2] and Amr H. Sawalha[1], [1]Division of Rheumatology, University of Michigan, Ann Arbor, MI, [2]University of Michigan Scleroderma Program, Ann Arbor, MI, [3]Internal Medicine, Division of Rheumatology, University of Michigan Medical Center, Ann Arbor, MI, [4]Internal Medicine, Division of Rheumatology, University of Michigan, Ann Arbor, MI

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SESSION INFORMATION

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Session Type: ACR Concurrent Abstract Session

Session Time: 2:30PM-4:00PM

Background/Purpose:

Scleroderma (SSc) is a complex disease characterized by inflammation, vascular complications, and excessive deposition of extracellular matrix. Vascular dysfunction represents a disease initiating event in SSc. Indeed, endothelial cell (EC) damage is thought to trigger a self-fueling process that results in tissue fibrosis. Recent data suggest that epigenetic dysregulation impairs normal angiogenesis and can result in abnormal blood vessel growth patterns in various disease conditions. Studies have shown that histone deacetylases (HDACs) control EC proliferation and participate in EC migration. Specifically, HDAC5 appears to be anti-angiogenic through the repression of pro-angiogenic factors such as basic fibroblasts growth factors (bFGF), vascular endothelial growth factor (VEGF), and epherin B2. The phenotypic and functional abnormalities of SSc ECs are stable *in vitro*over multiple generations of tissue culture, suggesting that persistent epigenetic changes might play a role in EC dysfunction in SSc. We hypothesized that HDAC5 contributes to impaired angiogenesis in SSc by repressing pro-angiogenic factors in ECs.

Methods:

Dermal ECs were isolated from biopsies from patients with diffuse cutaneous SSc. HDAC5, VEGF, and ephrin B2 expression were determined by qPCR. HDAC5 was knocked down using HDAC5 siRNA. Angiogenesis was assessed by an *in vitro*Matrigel tube formation assay. bFGF and VEGF in culture media were measured using ELISA. A paired t-test was used to compare differences between groups, and a p-value of <0.05 was considered significant. An assay for transposase-accessible chromatin using sequencing (ATAC-seq) was performed to assess and localize genome-wide effects of HDAC5 knockdown on chromatin accessibility.

Results:

The expression of HDAC5 was significantly increased in SSc ECs compared to normal ECs (0.0058 ± 0.0017 vs. 0.0028 ± 0.0003, $p<0.05$) while pro-angiogenic ephrin B2 was down regulated (0.0021 ± 0.0011 vs. 0.0096 ± 0.0005, $p<0.05$). Cells transfected with HDAC5 siRNA showed 87% knockdown in SSc ECs. Silencing of HDAC5 in SSc ECs restored normal angiogenesis, as reflected by a significant increase in tube formation on Matrigel compared to sham-transfected cells. After HDAC5 knockdown, ephrin B2 mRNA decreased 50% compared to sham-transfected group in SSc ECs. In contrast, SSc ECs released increased amounts of VEGF and bFGF into the cell culture media (2 and 1.2 fold for

VEGF and bFGF). In addition, VEGF mRNA increased significantly after HDAC5 knockdown (2.9 fold, $p<0.05$). ATAC-seq was used to identify additional HDAC5-regulated targets in EC, which will help to further mechanistically understand the anti-angiogenic effects of HDAC5.

Conclusion:

By knocking down HDAC5 in SSc ECs, we were able to restore the tube-forming ability of these cells. Our data indicate that overexpression of HDAC5 in SSc gears ECs to an anti-angiogenic state via repressing pro-angiogenic factors such as VEGF and bFGF. This appears to be a complicated process, as HDAC5 knockdown decreased pro-angiogenic ephrin B2. We provided a link between epigenetic regulation and impaired angiogenesis in SSc, and present a novel mechanism for the dysregulated angiogenesis that characterizes this disease.

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Abstract Number: 3133

The Anti-Fibrotic Effect of Endostatin-Derived Peptide Is Mediated By the Urokinase Pathway Via Binding to Enolase-1 and Urokinase Plasminogen Activator Receptor

Tetsuya Nishimoto[1], Takahisa Takihara[2], Logan Mlakar[3], Yunyun Su[4], Roger Chambers[3] and Carol Feghali-Bostwick[3], [1]Department of Medicine, Medical University of South Carolina, Charleston, SC, [2]Tokai University School of Medicine, Kanagawa, Japan, [3]Medical University of South Carolina, Charleston, SC, [4]Medicine, Medical University of South Carolina, Charleston, SC

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Session Time: 2:30PM-4:00PM

Background/Purpose: Fibroproliferative disorders such as systemic sclerosis (SSc) have no effective therapies and result in significant morbidity and mortality. We recently demonstrated that the C-terminal domain of endostatin known as E4 prevented and reversed both dermal and pulmonary fibrosis. Our goal was to identify the E4 receptor and the mechanism by which E4 abrogates fibrosis.

Methods: To identify E4 binding, we conducted a pull down assay using biotinylated-E4 and neutravidin-beads. Proteins that bound E4 in fibroblasts were identified by mass spectrometry. Binding was confirmed using immunoblotting. To assess the mechanism by which E4 exerts anti-fibrotic effects *in vitro*, lung fibroblasts were treated with TGF-b with vehicle or E4. The expression levels and activity of urokinase plasminogen activator (uPA) and plasminogen activator inhibitor-1 (PAI-1), an inhibitor of uPA, were evaluated by immunoblotting and activity assays, respectively. Since MMP-1 and MMP-3 are downstream effectors of plasminogen activation, we assessed MMP-1 and -3 activity using collagen and casein zymography, respectively. *In vivo*, bleomycin with vehicle or E4 was administered intratracheally to C57BL/6J male mice to induce lung fibrosis. Bronchoalveolar lavage fluid (BALF) was collected on days 3, 5, 7, and 14 post treatment, and the levels and activity of uPA and PAI-1 were measured. Furthermore, the mRNA levels of uPA and PAI-1 in human whole lung tissue and primary lung fibroblasts from 9 healthy controls (HC) and 32 SSc patients were measured using real-time PCR.

Results: Proteins bound to biotinylated-E4 were identified as enolase-1, known as a plasminogen receptor, and urokinase plasminogen activator receptor (uPAR). TGF-b reduced uPA levels and increased PAI-1 levels in primary fibroblasts. E4 abrogated these effects and increased the uPA/PAI-1 ratio. Moreover, E4 increased MMP-1 and MMP-3 expression and activity. Knockdown of uPAR abolished the anti-fibrotic activity of E4. Plasminogen exerted anti-fibrotic activity similarly to E4 treatment. *In vivo*, bleomycin reduced uPA levels and activity, and increased PAI-1 levels and activity in BALF. E4 reduction of PAI-1 preceded the increase in uPA activity, suggesting that a release from inhibition may explain in part the increase in uPA activity. Finally, the uPA:PAI-1 ratio was decreased in both SSc patient lung tissues and fibroblasts, compared to HC. The lowest uPA:PAI-1 ratio was detected in SSc patients with pulmonary fibrosis.

Conclusion: Our findings show that E4 binds enolase-1 and uPAR, suggesting that E4 bridges enolase-1 and uPAR, likely to facilitate activation of enolase-bound plasminogen by uPAR-bound uPA. The anti-fibrotic effect of E4 is mediated, in part, by its increase uPA and activation of plasminogen. Further, E4 induces MMP-1 and MMP-3 levels and activity, thus promoting extracellular matrix degradation. In SSc patients, the uPA/PAI-1 balance shifted toward PAI-1. Taken together, our findings suggest that E4 exerts its anti-fibrotic effects via regulation of the urokinase pathway. Thus, E4 is a promising therapeutic agent for SSc.

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Abstract Number: 3134

Safety and Tolerability of Pirfenidone in Patients with Systemic Sclerosis Interstitial Lung Disease

Dinesh Khanna[1], Carlo Albera[2], Aryeh Fischer[3], James R. Seibold[4], Nader A. Khalidi[5], Ganesh Raghu[6], Lorinda Chung[7], Elena Schiopu[1], Dan Chen[8] and Eduard Gorina[9], [1]University of Michigan, Ann Arbor, MI, [2]University of Turin, Turin, Italy, [3]National Jewish Health and University of Colorado, Denver, CO, [4]Scleroderma Research Consultants LLC, Litchfield, CT, [5]McMaster University, Hamilton, ON, Canada, [6]University of Washington, Seattle, WA, [7]Division of Immunology and Rheumatology, Stanford University School of Medicine, Stanford, CA, [8]Jazz Pharmaceuticals (formerly of InterMune), Palo Alto, CA, [9]Formerly of InterMune, Brisbane, CA

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Background/Purpose: Interstitial lung disease (ILD) is a common and serious complication of systemic sclerosis (SSc). Pirfenidone, a novel antifibrotic agent, has been shown to be safe and effective in the treatment of idiopathic pulmonary fibrosis (IPF). The LOTUSS study was designed to assess the safety and tolerability of pirfenidone in patients with SSc-ILD.

Methods: This is an open-label, 16-week study. Patients were randomized to a 2- or 4-week titration to the target dose of 2403 mg/day. Eligibility required a diagnosis of SSc ≤7 years from first non-Raynaud's symptom, HRCT-confirmed ILD, FVC ≥50% and DL_{co} ≥40%, absence of clinically significant pulmonary hypertension or severe GERD. Stable treatment with mycophenolate mofetil (MMF) or oral cyclophosphamide was permitted. Safety assessments included collection of treatment emergent adverse events (TEAEs), vital signs, ECGs and laboratory tests. Though the study was not designed or powered to evaluate efficacy, FVC %-predicted, DL_{co} %-predicted, modified Rodnan skin score (mRSS), Mahler BDI/TDI, and UCLA SCTC GIT 2.0 were recorded at baseline and 4 months.

Results: Of the 63 patients enrolled, the mean (SD) age was 50.6 (12.3) years; the majority were female (82.5%) and white (76.2%). The mean (SD) SSc duration was 38.3 (26.0) months. Forty patients (63.5%) were on MMF and the rest (36.5%) were not receiving any immunosuppressants. The mean (SD) mRSS, %FVC and $\%DL_{co}$ at baseline were 11.4 (9.6), 76.0 (14.2) and 59.7 (16.5), respectively.

The frequency and type of TEAEs were similar for both titration groups. The safety results are summarized below. No clinically significant changes in vital signs, ECGs, or laboratory tests were observed.

At week 16, the median change from baseline in %FVC was -0.5% (range -42% to 12%); 10 patients (16.7%) had an increase ≥5% whereas 5 (8.3%) had a decrease >5% at week 16. Median change from baseline in $\%DL_{co}$ was 1.5% (range -24.0% to 40.0%); 19 subjects (31.7%) had an increase ≥5% vs. 10 (16.7%) had a decrease >5% at week 16. Minor changes (mean±SD) were observed in Mahler TDI (1.0±3.41) and mRSS (-0.4±3.71). No change was noted in the GI symptoms on UCLA SCTC GIT 2.0.

Conclusion: In the 16-week, open-label trial of pirfenidone in SSc-ILD, pirfenidone was safe and generally well-tolerated in SSc-ILD patients, despite pre-existing co-morbidities, including underlying GI disease, and concomitant use of MMF. The AEs were expected and consistent with those previously seen in IPF trials. The data support further investigation of pirfenidone in SSc-ILD.

Safety Summary	
	All Patients (N=63)
Total Number of TEAEs	521
No. of Patients with Any TEAEs	61 (96.8%)
No. of Patients with TEAEs by Maximum Intensity	
Mild TEAEs	19 (30.2%)
Moderate TEAEs	30 (47.6%)
Severe TEAEs	12 (19.0%)
Most Common TEAEs (>=10% of Patients)	
NAUSEA	31 (49.2%)
HEADACHE	28 (44.4%)
FATIGUE	23 (36.5%)
DIARRHEA	19(30.2%)
VOMITING	18(28.6%)
COUGH	14(22.2%)
GASTROESOPHAGEAL REFLUX DISEASE (GERD)	13(20.6%)
RASH	13(20.6%)
DIZZINESS	10(15.9%)
ARTHRALGIA	9(14.3%)
BACK PAIN	8(12.7%)
DYSPEPSIA	8(12.7%)
PRURITUS	8(12.7%)
ANOREXIA	7(11.1%)
ASTHENIA	7(11.1%)
CONSTIPATION	7(11.1%)
DYSPNEA	7(11.1%)
INSOMNIA	7(11.1%)
STOMACH DISCOMFORT	7(11.1%)
No. of Patients with Serious TEAEs	3 (4.8%)
Serious TEAEs	
SMALL INTESTINAL OBSTRUCTION	1 (1.6%)
BRONCHITIS	1 (1.6%)
PULMONARY HYPERTENSION	1 (1.6%)
WORSENING ILD	1 (1.6%)
No. of Patients Who Discontinued Study Due to TEAEs	6 (9.5%)
TEAEs Leading to Study Discontinuation	
DRUG HYPERSENSITIVITY	1 (1.6%)
WORSENING FIBROMYALGIA PAIN	1 (1.6%)
PULMONARY HYPERTENSION	1 (1.6%)
PHOTOSENSITIVITY REACTION	1 (1.6%)
RASH	2 (3.2%)

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Abstract Number: 3135

Incidences and Predictors of Organ Manifestations in the Early Course of Systemic Sclerosis: A Longitudinal Study

Veronika K. Jaeger[1], Elina G. Wirz[2,3], Yannick Allanore[4], Gabriela Riemekasten[5], Eric Hachulla[6], Oliver Distler[7], Paolo Airo[8], Patricia E. Carreira[9], Alexandra Balbir-Gurman[10], Mohammed Tikly[11], Serena Vettori[12], Nemanja Damjanov[13], Ulf Müller-Ladner[14], Jorg HW. Distler[15], Mangtao Li[16], **Ulrich A. Walker**[17] and EUSTAR collaborators, [1]Department of Rheumatology, University Hospital Basel, Basel, Switzerland, [2]Department of Rheumatology, University Hospital Basel, Basel, Switzerland, Basel, Switzerland, [3]Department of Dermatology, University Hospital Basel, Basel, Switzerland, [4]Department of Rheumatology A, Paris Descartes University, Cochin Hospital, Paris, France, [5]Clinic of Rheumatology, University of Luebeck, Lübeck, Germany, [6]Service de Médecine Interne, Hôpital Huriez, Université de Lille, Lille, France, [7]Department of Rheumatology, University Hospital Zurich, Zurich, Switzerland, [8]UO Reumatologia ed Immunologia Clinica, Spedali Civili, Brescia, Italy, [9]Servicio de Reumatologia, Hospital Universitario 12 de Octubre, Madrid, Spain, [10]B. Shine Rheumatology Unit,

Rambam Health Care Campus, Rappaport Faculty of Medicine, Technion - Institute of Technology, Haifa, Israel, [11]Division of Rheumatology, Chris Hani Baragwanath Academic Hospital, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa, [12]Department of Internal and Experimental Medicine, Rheumatology Unit, Second University of Naples, Naples, Italy, [13]Institute of Rheumatology, University of Belgrade Medical School, Belgrade, Serbia, [14]Internal Medicine and Rheumatology, Justus-Liebig-University of Giessen, Kerckhoff-Klinik, Bad Nauheim, Germany, [15]Department of Internal Medicine 3, University of Erlangen-Nuremberg, Erlangen, Germany, [16]Department of Rheumatology, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences, Beijing, China, [17]Rheumatology, University Hospital, Basel, Basel, Switzerland
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Background/Purpose:

Systemic sclerosis (SSc) is a rare and clinically heterogeneous autoimmune disorder characterised by fibrosis and microvascular obliteration of the skin and internal organs, particularly the heart, lungs, kidneys and the digestive tract. Organ involvement mostly manifests after a variable period of the onset of Raynaud's phenomenon (RP). Using data from the large, multinational EUSTAR cohort, we aimed to map the incidence and predictors of pulmonary, cardiac, gastrointestinal (GI) and renal involvement in the early course of SSc.

Methods:

Patients from the EUSTAR cohort with early SSc, defined as those who had a visit within the first year of RP onset were studied. Outcome measures were analysed as a function of time after RP onset using Kaplan-Meier methods, and Cox regression analysis was used to evaluate predictors of incident organ manifestations.

Results:

Of the 695 SSc patients in the EUSTAR database who had a baseline visit within one year after RP onset, the incident non-RP manifestations (in order of frequency) were: skin sclerosis (75%), GI symptoms (71%), impaired diffusing capacity for carbon monoxide of <80% predicted (65%), digital ulcers (34%), cardiac involvement (32%), impaired forced vital capacity (FVC) of <80% predicted (31%), increased resting systolic pulmonary artery pressure estimated by echocardiography (PAPsys)>40mmHg (14%), and renal crisis (3%; Figure 1).

Diffuse skin involvement was a significant predictor of incident FVC impairment (Figure 2; Table 1), older age and male sex were predictors of incident PAPsys>40mmHg (Figure 2; Table 1), and anti-topoisomerase positivity and older age were predictors of incident cardiac manifestations (Table 1). Incidence rates were highest for diastolic dysfunction, followed by conduction blocks and pericardial effusion. Male sex, anti-RNA-polymerase-III positivity and older age were predictors of renal crisis (Table 1).

Conclusion:

In SSc patients presenting early after RP onset, approximately half of all incident organ manifestations occur within 2 years. These findings may have implications for the design of new diagnostic and therapeutic strategies aimed to ‘widen' the still very narrow ‘window of opportunity'. They may also enable physicians to counsel and manage patients presenting early in the course of SSc more accurately.

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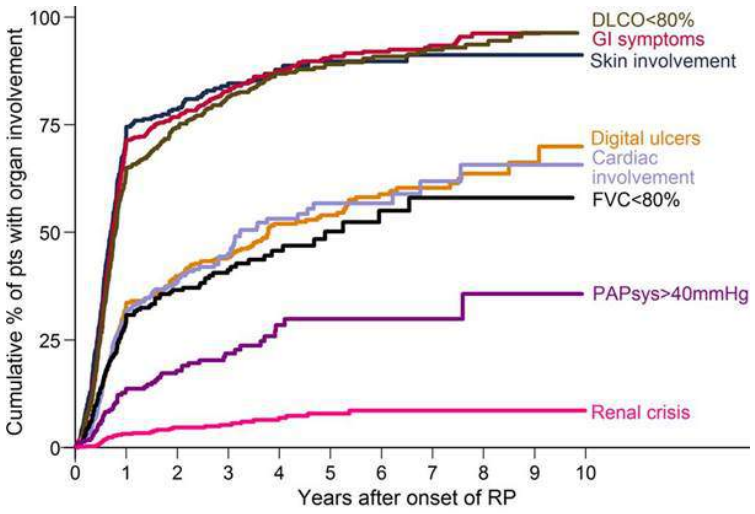

Figure 1 Kaplan-Meier curves of incident organ involvement in SSc patients after RP onset.

RP - Raynaud's phenomenon; Pts - patients; DLCO - single breath diffusing capacity for monoxide; GI symptoms - gastrointestinal symptoms - defined as a history of either dysphagia, reflux, early satiety, vomiting, diarrhoea, bloating or constipation; Skin involvement - defined as a modified Rodnan skin score of ≥2 at any part of the body; Cardiac involvement - defined as either the presence of diastolic dysfunction, conduction blocks, a left ventricular ejection fraction (LVEF) < 50%, or a pericardial effusion; FVC - forced vital capacity; PAPsys - systolic pulmonary artery pressure as estimated by echocardiography.

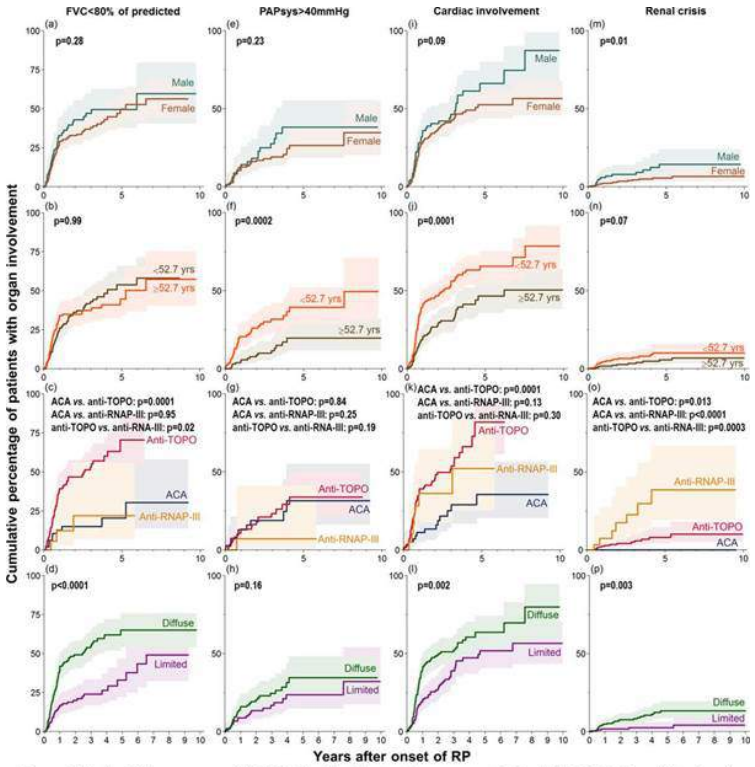

Figure 2 Kaplan-Meier curves with 95% CI of incident pulmonary restriction (FVC<80% of predicted; a-d), suspected pulmonary hypertension (PAPsys>40 mmHg; e-h), cardiac involvement (i-l) and renal crisis (m-p) after RP onset in SSc patients; stratified by sex (a/e/i/m), the median age at RP onset (b/f/j/n), autoantibody status (c/g/k/o) and extent of skin involvement within the first year after RP onset (d/h/l/p).

CI - confidence interval; FVC - forced vital capacity; PAPsys - systolic pulmonary artery pressure as estimated by echocardiography; cardiac involvement - defined as either the presence of diastolic dysfunction, conduction blocks, a left ventricular ejection fraction (LVEF)<50%, or a pericardial effusion; RP - Raynaud's phenomenon; yrs – years; ACA - anti-centromere autoantibodies; Anti-TOPO - Anti-topoisomerase-I autoantibodies; Anti-RNAP-III - anti-RNA-polymerase-III autoantibodies.

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	FVC<80% of predicted		PAPsys >40mmHg		Any cardiac involvement		Diastolic dysfunction		Conduction block		Pericardial effusion		Renal Crisis	
	HR	95%CI	HR	95%CI	HR	95%CI	HR	95%CI	HR	95%CI	HR	95%CI	HR	95%CI
Sex														
Male	1		1		1		1		1		1		1	
Female	1.30	0.75-2.25	0.40	0.17-0.93	0.85	0.52-1.38	1.09	0.54-2.22	2.12	0.85-5.28	0.46	0.19-1.13	0.39	0.15-0.97
Age at onset of RP (in years)	1.01	0.99-1.03	1.09	1.05-1.13	1.04	1.02-1.06	1.08	1.04-1.11	1.01	0.99-1.04	1.02	0.98-1.06	1.04	1.00-1.08
Autoantibody status														
ACA	1		1		1		1		1		-*	-	-*	-
Anti-TOPO	2.37	0.80-7.03	2.04	0.61-6.80	3.90	1.82-8.35	1.78	0.61-5.20	17.59	3.81-81.33	1		1	
Anti-RNAP-III	0.62	0.13-2.91	0.49	0.05-4.76	2.56	0.91-7.19	2.09	0.55-8.00	6.62	0.88-49.95	0.31	0.04-2.31	5.18	2.03-13.22
Extent of skin involvement														
Limited	1		1		1		1		1		1		1	
Diffuse	3.08	1.43-6.62	0.91	0.33-2.50	0.93	0.52-1.64	1.78	0.72-4.38	0.45	0.21-0.95	2.86	0.65-12.51	2.96	0.68-12.81

Table 1 Cox multivariable regression analysis of risk factors for the time to incident FVC<80% of predicted, PAPsys>40 mmHg, any cardiac dysfunction, diastolic dysfunction, conduction block, pericardial effusion and renal crisis.

FVC - forced vital capacity; PAPsys - systolic pulmonary artery pressure as estimated by echocardiography; cardiac involvement - defined as either the presence of diastolic dysfunction, conduction blocks, left ventricular ejection fraction (LVEF)<50%, or pericardial effusion; HR - hazard ratio; CI - confidence interval; RP - Raynaud's phenomenon; ACA - anti-centromere autoantibodies; Anti-TOPO - anti-topoisomerase-I autoantibodies; Anti-RNAP-III - anti-RNA-polymerase-III autoantibodies. * no patient with ACA developed a renal crisis or pericardial effusion.

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Abstract Number: 3136

Impact of Prokinetic Agents on Systemic Sclerosis-Associated Gastrointestinal Disease: A Systematic Review

Annaliese Tisseverasinghe[1], Ahmad Kadhim[2], Ambica Parmar[2], Louis Liu[2] and Sindhu R. Johnson[1], [1]Toronto Scleroderma Program, Division of Rheumatology, Toronto Western Hospital, Mount Sinai Hospital, Institue of Health Policy, Management and Evaluation, University of Toronto, Toronto, ON, Canada, [2]Division of Gastroenterology, Toronto Western Hospital, University of Toronto, Toronto, ON, Canada

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SESSION INFORMATION

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Session Title: Systemic Sclerosis, Fibrosing Syndromes, and Raynaud's - Clinical Aspects and Therapeutics II

Session Type: ACR Concurrent Abstract Session

Session Time: 2:30PM-4:00PM

Background/Purpose: More than 90% of patients with Systemic Sclerosis (SSc) have gastroinstestinal (GI) involvement, commonly dysmotility causing complications such as gastroesophageal reflux and constipation. Treatment with prokinetic drugs is mostly modelled on their use in the general population, despite pathophysiological differences between GI disease in SSc and other etiology. Thus, our goal is to identify and appraise all studies evaluating the impact of prokinetics on GI outcomes in patients with SSc.

Methods: Three databases (Cochrane Central Register of Controlled Trials, Ovid MEDLINE, and Embase) were searched until November 27, 2013 using permutations of the terms “scleroderma” and “systemic sclerosis” combined with “prokinetic”, “anti-emetic”, and generic and trade names of individual drugs. Studies were included if they evaluated the impact of a prokinetic on any GI outcome in at least 5 adults (age > 18 years) with SSc, regardless of language or study type. Two reviewers independently evaluated all studies, and conflicts were resolved by a third.

Results: Of 492 search results, 21 studies from 12 countries met our criteria (Figure 1). The sample sizes ranged from 5 to 64, with 362 participants in all (83% women), ranging in age from 30 to 80 years. Using Cochrane guidelines, 7 studies had high risk of bias in at least one domain for at least one outcome measure (Table 1). Six prokinetics were evaluated: cisapride in 9 studies, metoclopramide in 6, octreotide in 2, erythromycin in 2, and mosapride and clebopride in 1 study each. Only 2 studies evaluated >1 prokinetic. Outcomes included GI motility as evaluated by manometry (ex. esophageal sphincter pressure), scintigraphy (ex. gastric emptying time), and hydrogen breath tests; serum levels of motility-altering peptides (ex. motilin); and symptoms (ex. Index of Gastrointestinal Status). Each prokinetic was associated with a favourable

outcome in at least half the studies that evaluated it, without serious adverse effects, except diarrhea with octreotide in one study. The heterogeneity in treatment administration, outcomes, and comparator groups precluded any meta-analyses.

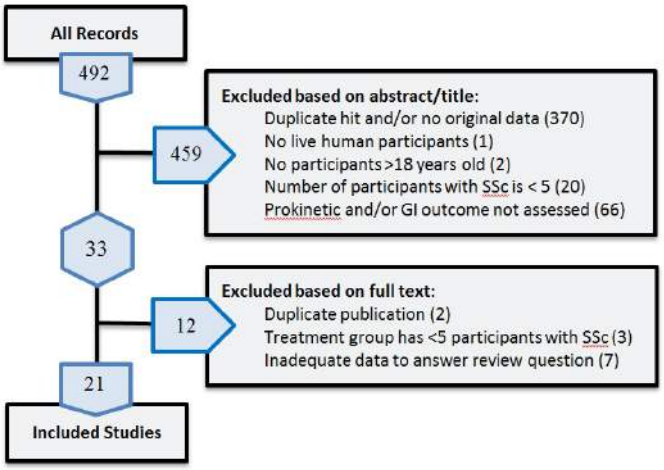

Figure 1: Study Selection

Study Reference (primary author, year)	Study Type	N (with SSc)	Prokinetic(s) evaluated	GI site(s) studied	Outcome(s) evaluated (significant improvement: † = from baseline, ‡ = vs. placebo/ comparator)	Risk of Bias
Grossi L, 2012	B&A	7	Clebopride	E	LESP†. PW amplitude. Sx†	M
Ostojic P, 2008	Cohort	60	Metochlopramide	.	IGS score (SAQ subset)†	H
Nikou GC, 2007	B&A	7	Octreotide	.	Sx†	H
Guo G, 2005	RCT	64	Cisapride, SZM	E	Sx†. QOL. Transit time†. Emptying time. Esophageal diameter‡	L
Sjolund K, 2005	B&A	10	Octreotide	SB	Phase 3 PW duration, amplitude, & frequency. Motility index. Motilin & CCK levels	L
Mercado U, 2005	B&A	27	Metochlopramide	E	LESP†. Residual pressure†. PW amplitude†, duration, & velocity	L
Linke R, 2005	B&A	9	Cisapride	G	Emptying time†. PW amplitude†, duration, & velocity	L
Wang SJ, 2002	RCT*	12	Cisapride	E	Transit time	L
Folwaczny C, 1997	B&A	9	Cisapride, Erythromycin, Octreotide	G, SB, LB	Emptying time for G†, SB, LB. Transit time for G, SB, LB	H
Fiorucci S, 1994	B&A	12	Erythromycin	G, GB	Emptying time†. Sx†	H
Suzuki T, 1993	RCT	10	Mosapride	.	Global rating of Δ in Sx	H
Bost R, 1992	RCT	31	Cisapride	E	LESP†. PW amplitude, duration, & velocity	L
Soudah HC, 1991	B&A	5	Octreotide	SB, G	Motility index†. Motilin level†. H2 breath test†. Sx†	M
Limburg AJ, 1991	RCT*	8	Cisapride	E	LESP. PW amplitude	L
Kahan A, 1991	RCT*	20	Cisapride	E, G	LESP†. PW amplitude, duration, & velocity. Number of fundic contractions/30 min‡	L
Wehrmann T, 1990	RCT*	12	Cisapride	E	LESP. UESP†. PW amplitude† & velocity	L
Drane WE, 1987	B&A	14	Metochlopramide	E	Mid & end expiration LESP†. Proximal & distal contracture amplitude. Transit time. Percent emptying†	L
Horowitz M, 1987	RCT*	8	Cisapride	E, G	G† & E emptying time. Upper GI Sx†	L
Johnson DA, 1987	B&A	12	Metochlopramide	E	LESP†. PW amplitude. Reflux score†	L
Rees WDW, 1982	B&A	15	Metochlopramide, Bethanechol	SB	Motility index†. Time to motor activity. Motilin & PP levels	L
Battle WM, 1981	B&A	10	Metochlopramide	LB	Spike potential/10 min	L

Table 1: Summary of Included Studies
Legend: RCT = randomized controlled trial, NRCT = non-randomized controlled trial, B&A = before & after study, * = cross-over design, E = esophagus, G = gastrum, SB = small bowel, LB = large bowel, GB = gall-bladder, SZM = Shenzhe Zhuyun mixture, LESP/UESP = lower/ upper esophageal sphincter pressure, QOL = quality of life, PW = peristaltic wave, Sx = symptoms, PP = pancreatic polypeptide, L = low, H = high, M = mixed, with high risk of bias for patient reported outcomes (i.e. Sx), and low risk of bias for all other outcomes

Conclusion: Available studies suggest a favourable side-effect profile and impact of prokinetics on SSc-associated GI disease, but are limited by small numbers, lack of uniform outcome measures, and risk of bias. Evaluation of prokinetics in larger SSc cohorts using validated and standardized outcome measures are needed to assess the generalizability of these findings, and to determine the ideal type, dose, and duration of prokinetics for a given GI dysfunction in SSc.

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Scleroderma Hand Contracture Study

Joyce Joseph, Rheumatology, Univeristy of Teas Health Science Center at Houston, Houston, TX
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Background/Purpose: To investigate the progression of hand contractures in patients with systemic sclerosis and to identify disease features predictive of contractures. A sub-group analysis was also performed on patients with less than or equal to 2 years since disease onset.

Methods: Patients enrolled in the GENISOS cohort were assessed for disease features predictive of hand contractures. Such variables are included in Table 1.

Linear mixed model was used to analyze longitudinal measurements of each hand separately given the potential for variation in the extent of contracture development. The time variable is the date of first non-Raynaud's symptom.

A subgroup analysis was also performed with the same disease variables to assess for predictive features and to assess if the rate of decline was faster earlier in disease.

Results: 1108 sets of hand measurements were evaluated over a median follow-up period of 8.8 years. 219 patients were included in the analysis and 62 patients in the subgroup analysis. In the right hand, ATA and MRSS scores were predictive of a decrease in hand extension. ATA positive patients showed a decrease in right hand extension by 0.24 cm/year while ATA negative patients showed a decrease in hand extension by 0.075 cm/year. A similar decrease in hand extension was observed in the left hand for ATA positive patients.

A unit increase in the MRSS score was predictive of faster decline in right hand extension by 0.006 cm/yr.

In the subgroup analysis, disease type and ACA were predictive of contracture development in the right hand. Patients with diffuse disease were found to have a decrease in right hand extension by 0.64 cm/year. ACA negative patients were found to have a decrease in hand extension by 0.21 cm/yr in the right hand.

In the left hand, ATA, ACA and digital ulcers were predictive of contracture development. ATA positive patients showed a decrease in left hand extension by 1.54 cm/year while ATA negative patients showed a decrease in hand extension by 0.08 cm/year. Further, the absence of digital ulcers was also predictive of decrease in hand extension in the left hand.

Conclusion: This is the largest and longest reported prospective study assessing disease features predictive of hand contractures in patients with systemic sclerosis.

ATA and MRSS scores were predictive of hand contracture development in the right hand. ATA was also predictive of hand contracture development in the left hand. Discrepancy in skin score as a predictor between the two hands may be related to hand dominance.

Disease Variable	Right hand rate of change	p-value	Left hand rate of change	p-value
Topo positive	-0.2354	0.037	-0.2791	0.0025
Topo negative	-0.0751		-0.0523	
ACA positive	-0.0312	0.4399	-0.0293	0.4799
ACA negative	-0.1166		-0.1072	
RNA pol 3 positive	-0.112	0.964	-0.0848	0.7469
RNA pol 3 negative	-0.109		-0.1075	
Diffuse disease	-0.1153	0.8127	-0.118	0.5288
Limited disease	-0.1001		-0.0781	
Digital ulcers present	-0.1327	0.6714	-0.0783	0.6581
Digital ulcers absent	-0.1017		-0.1102	
Small joint arthritis present	-0.1233	0.7401	-0.1418	0.368
Small joint arthritis absent	-0.1009		-0.0819	
Baseline MRSS	-0.0056	0.0407	-0.0048	0.076
FVC percent predicted	0.0004	0.784	0.0009	0.547

Subgroup Analysis

Disease Variable	Right hand rate of change	p-value	Left hand rate of change	p-value
Topo positive	-0.495	0.41	-1.5363	0.015
Topo negative	-0.0123		-0.0822	
ACA positive	1.287	0.038	1.206	0.027
ACA negative	-0.210		-0.446	
RNA pol 3 positive	0.5276	0.19	-0.343	0.76
RNA pol 3 negative	0.0773		-0.195	
Diffuse disease	-0.637	0.003	-0.6271	0.092
Limited disease	0.524		0.0737	
Digital ulcers present	0.066	0.67	0.456	0.046
Digital ulcers absent	-0.142		-0.524	
Small joint arthritis present	-0.4235	0.37	-0.745	0.24
Small joint arthritis absent	0.0112		-0.156	
Baseline MRSS	-0.0291	0.099	-0.0138	0.45
FVC percent predicted	-0.0141	0.169	0.00897	0.41

Disclosure: J. Joseph, None;

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Prognostic Role of Ventricular Ectopic Beats in Systemic Sclerosis

Giacomo De Luca[1], Silvia Laura Bosello[1], Francesca Gabrielli[2], Giorgia Berardi[1], Federico parisi[1], Manuela Rucco[1], Giovanni Canestrari[1], Leonarda Galiuto[3], Filippo Crea[3], Francesco Loperfido[2] and Gianfranco Ferraccioli[1], [1]Division of Rheumatology, Catholic University of the Sacred Heart, Rome, Italy, [2]Division of Heart Failure and Cardiac Rehabilitation, Catholic University - Rome, Rome, Italy, [3]Institute of Cardiology, Catholic University of the Sacred Heart, Rome, Italy

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Background/Purpose:

Heart involvement is common during Systemic Sclerosis (SSc), even if often clinically silent, and represents the leading cause of death in about one third of patients. Arrhythmias, in particular, are a frequent event and portend a bad prognosis, accounting alone for 6% of SSc total deaths.

We performed a prospective cohort study to define the role of 24h-ECG-Holter in the identification of patients at high risk of life-threatening arrhythmias and sudden cardiac death(SCD) in Systemic Sclerosis.

Methods:

100 SSc-patients with symptoms and/or signs suggestive of cardiac involvement underwent 24h-ECG-Holter. The primary end-point was a composite of SCD or the need for implantable cardioverter defibrillator(ICD). A mean follow-up of 23.1±16.0 months was reached.

Results:

Fifty-six patients(56%) had 24h-ECG-Holter alterations and 24(24%) presented frequent ventricular ectopic beats(VEBs), classified as polymorphic in 11 (26.2%). The mean number of VEBs was strikingly high (2046.1 ± 6027.8//24h), with a maximum of 33615/24h. Supraventricular ectopic beats (SVEBs)>1000/24h were also frequent (19%), with a mean number of 798.9±1835.6 per day; seventeen patients (17%) presented runs of SVEBs. Fourteen patients (14%) presented episodes of supraventricular paroxysmal tachycardia (SVPT), with a maximum of 36 beats, while 11 patients (11%) exhibited runs of NS-VT, the longest of 34 beats. The number of VEBs correlated with cardiac troponin T(cTnT) levels (R=0.4,p<0.001) and inversely correlated with left ventricular ejection fraction(LV-EF) on echocardiography (R=-0.4,p<0.001). Furthermore, the number of VEBs directly correlated with severity index and with the extension of skin involvement evaluated by the mRSS (p=0.3 for both correlations).

During the follow-up, 5 patients died of SCD and two required ICD-implantation for life-threatening arrhythmias. The 7 patients who met the composite end-point had a higher number of VEBs, higher levels of cTnT and NT-proBNP and lower LV-EF(p=0.001 for all correlations), while in all of them a pulmonary arterial hypertension was ruled out by right heart catheterization. All 7 patients had frequent ventricular ectopy at baseline ECG-Holter, while LV-EF range in patients who met the primary end-point was wide and LV-EF was not reduced in all. At ROC curve, VEBs>1190/24h showed 100% of sensitivity and 83% of specificity to predict the primary end-point (AUROC=0.92,p<0.0001). Patients with VEBS>1190/24h had lower LV-EF and higher cTnT levels compared to patients with VEBs<1190/24h.

Conclusion:

VEBs are frequent in SSc and correlate with cardiac damage; VEBS>1190/24h identify patients at high risk of major arrhythmic complications. 24h-ECG-Holter need to be considered as a part of routine evaluation in SSc-patients with suspicious cardiac involvement and it could be an additional risk-stratification technique for selection of SSc-patients at high-risk of SCD, in whom an ICD-implantation could represent a potential life-saving intervention.

Disclosure: G. De Luca, None; **S. L. Bosello**, None; **F. Gabrielli**, None; **G. Berardi**, None; **F. parisi**, None; **M. Rucco**, None; **G. Canestrari**, None; **L. Galiuto**, None; **F. Crea**, None; **F. Loperfido**, None; **G. Ferraccioli**, None.

Abstract Number: 3139

Screening Algorithm for Pulmonary Hypertension in Systemic Sclerosis – Comparison of Predictive Accuracy of Three Algorithms

Vivek Nagaraja[1], Scott H. Visovatti[2], Heather Gladue[3], Veronica J. Berrocal[4], Jennifer Serrano[5], Vallerie McLaughlin[2] and Dinesh Khanna[6], [1]Department of Medicine [Division of Rheumatology], University of Toledo, Toledo, OH, [2]Internal Medicine, Division of Cardiology, University of Michigan, Ann Arbor, MI, [3]Rheumatology, Emory University, Atlanta, GA, [4]Div of Rheumatology, University of Michigan, Ann Arbor, MI, [5]University of Michigan, Ann Arbor, MI, [6]Division of Rheumatology, University of Michigan, Ann Arbor, MI
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Background/Purpose: Pulmonary arterial hypertension (PAH) is the leading cause of mortality in systemic sclerosis (SSc), and is associated with a 3-year survival of approximately 50%. Early screening for SSc-PAH may improve survival. We compared the predictive accuracy of three recently published screening algorithms - DETECT 2013, Australian Scleroderma Interest Group (ASIG) 2012, Cochin risk prediction score (RPS) 2011 - for SSc-PAH.

Methods: We included consecutive SSc patients with suspected PAH undergoing right heart catheterization (RHC). The inclusion criteria were based on 2013 recommendations for screening PAH (Khanna D. Arthritis Rheum. 2013). The three screening models were applied to each

patient. For each model, contingency table analysis was used to determine sensitivity, specificity, and positive (PPV) and negative (NPV) predictive values for PAH [defined as mean pulmonary artery pressure (mPAP) > or = 25, pulmonary capillary wedge pressure (PCWP) < or = 15, and no/mild interstitial lung disease (ILD) on high-resolution CT scan of chest (HRCT), or FVC > or = 70%], WHO group 2 pulmonary hypertension (PH defined as mPAP > or = 25, PCWP >15, and no / Mild ILD on HRCT, or FVC > or = 70%), and WHO group 3 PH (defined as mPAP > or = 25, PCWP < or = 15, and moderate / severe ILD on HRCT, or FVC <70%).

Results: Of the 108 patients screened for PAH, 77 met the recommendations, and 60 patients had the RHC. The prevalence of PAH was 18%. Figure 1 provides a flowchart of patients screened for PAH. There were no significant differences in the baseline clinical characteristics between the PH and non-PH patients. Majority of the patients were females (60% vs 57%), had telangiectasia (70% vs 78%) and about a third of the patients had anticentromere antibody (35% vs 38%). DETECT and ASIG algorithms performed similarly in detecting PAH with sensitivities and NPV of 100 % (Table 1). Approximately 1/3 of patients who met the criteria had PAH (PPV 32-38%). In detecting group-2 PH, DETECT and RPS algorithms had sensitivities and NPV of 100% (Table 1).

Conclusion: In this cohort, the DETECT and ASIG algorithms were comparable in detecting PAH in the SSc patients.

Figure 1: Flowchart of patients screened for PAH

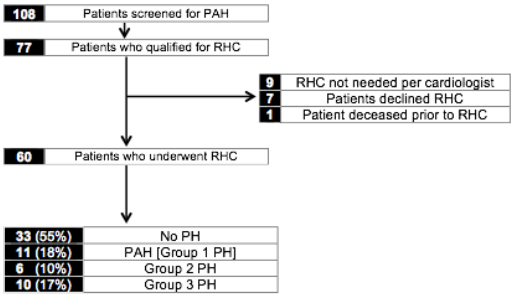

Table 1: Summary of the predictive accuracies (in percentage) of the screening models for PAH in SSc patients

	ASIG			DETECT			RPS		
	PAH	Group-2 PH	Group-3 PH	PAH	Group-2 PH	Group-3 PH	PAH	Group-2 PH	Group-3 PH
Positive	58	47	50	66	60	58	74	73	71
Negative	42	53	50	34	40	42	26	27	29
Sensitivity	100	50	62	100	100	70	91	100	75
Specificity	53	53	53	45	45	45	32	36	30
PPV	37	12	25	38	22	28	32	22	50
NPV	100	89	85	100	100	83	91	100	83

PPV positive predictive value; NPV negative predictive value; PAH pulmonary arterial hypertension; PH pulmonary hypertension

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Abstract Number: 3140

A Meta-Immunochip Analysis Suggests IL12B As a Common Susceptibility Factor for Large-Vessel Vasculitides

Francisco David Carmona[1], Patrick Coit[2], Güher Saruhan-Direskeneli[3], Maria C. Cid[4], Roser Solans[5], Santos Castañeda[6], Augusto Vaglio (on behalf of the Italian GCA Study Group)[7], Haner Direskeneli (on behalf of the Turkish Takayasu Study Group)[8], Peter A. Merkel[9], Carlo Salvarani[10], Miguel A. Gonzalez-Gay[11], Javier Martín[12], Amr H. Sawalha[2] and Spanish GCA consortium, [1]Instituto de Parasitología y Biomedicina López-Neyra, IPBLN-CSIC, PTS-Granada, Granada, Spain, [2]Division of Rheumatology, University of Michigan, Ann Arbor, MI, [3]Department of Physiology, Istanbul University, Istanbul Faculty of Medicine, Istanbul, Turkey, [4]Autoimmune and Systemic Diseases, Hospital Clínic. IDIBAPS. University of Barcelona, Barcelona, Spain, [5]Department of Internal Medicine, Hospital Vall d'Hebron, Barcelona, Spain, [6]Rheumatology, H.U. La Princesa, Madrid, Spain, [7]Medicina Clinica e Nefrologia, Università di Parma, Parma, Italy, [8]Department of Rheumatology, Marmara University, School of Medicine, Istanbul, Turkey, [9]Penn Vasculitis Center, Division of Rheumatology, University of Pennsylvania, Philadelphia, PA, [10]Azienda Ospedaliera ASMN, Istituto di Ricovero e Cura a Carattere Scientifico, Reggio Emilia, Italy,

[11]Reumatologia, Hospital Universitario Marqués de Valdecilla, IDIVAL, University of Cantabria, Santander, Spain, [12]Immunology, Instituto de Parasitología y Biomedicina López-Neyra, IPBLN-CSIC, Armilla (Granada), Spain
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Background/Purpose: Large-vessel vasculitides (LVV) comprise giant cell arteritis (GCA) and Takayasu arteritis (TAK). They are characterized by self-sustaining inflammatory damage of the wall of large-sized vessels such as the aorta. Using previously published Immunochip data, we carried out an inter-disease meta-analysis of these two disorders in order to identify common susceptibility genetic factors predisposing to LVV development.

Methods: Two cohorts from Spain (759 cases/1,505 controls) and Italy (238 cases/1,270 controls) included in an Immunochip study on GCA, were combined with two additional cohorts from Turkey (327 cases/481 controls) and USA (110 cases/558 controls) included in an Immunochip study on TAK. In total, 1,434 LVV cases and 3,814 unaffected controls were analysed. We compared in every cohort the variation frequencies of cases and controls by logistic regression under a fixed-effects model using the ten first principal components as covariates. We then used the inverse variance weighted meta-analysis method to test for common association signals. Only those variants showing a nominally significant association with both diseases separately ($P<0.05$), as well as no significant heterogeneity in the overall meta-analysis ($Q>0.05$), were considered as putative shared risk variants.

Results: Strong association signals were observed within the HLA class II region (lead SNP rs9268923, P=6.50E-16, OR=1.49), although associations at the genome-wide level of significance were also detected in HLA class I (rs10947210, P=2.25E-08, OR=1.66). The highest non-HLA peak corresponded to a genetic variant nearby the *IL12B* gene (rs6871626, P=4.67E-07, OR=1.28), which is in complete linkage disequilibrium ($r^2=1$) with the reported TAK-associated *IL12B* SNP rs56167332. Other suggestive signals were observed within *GRIN2A* (rs1448258, P=2.69E-06, OR=1.24), a member of the glutamate-gated ion channel protein family, and *GPSM1* (rs28489139, P=1.38E-05, OR=1.45), a receptor-independent activator of G protein signaling.

Conclusion: A strong contribution of HLA class I and II variants to LVV predisposition was evident. Outside the HLA region, our data indicated that *IL12B* may be a common susceptibility factor for both GCA and TAK, and suggested other putative shared loci between these vasculitides including *GRIN2A* and *GPSM1*.

Abstract Number: 3141

Endothelial Cells Regulate Proinflammatory T Cell Responses in Large Vessel Vasculitis Via NOTCH-NOTCH Ligand Interactions

Zhenke Wen[1], Hui Zhang[1], Joyce Liao[2], Gerald Berry[3], Lindsy J. Forbess[4], Michael Weissman[5], Jorg Goronzy[1] and Cornelia M. Weyand[6], [1]Medicine: Immunology and Rheumatology, Stanford University School of Medicine, Stanford, CA, [2]Byers Eye Institute at Stanford, Stanford University, Palo Alto, CA, [3]Pathology, Stanford University School of Medicine, Stanford, CA, [4]Rheumatology, Cedars-Sinai Medical Center, Los Angeles, CA, [5]Division of Rheumatology, Cedars-Sinai Medical Center, Los Angeles, CA, [6]Medicine, Stanford University School of Medicine, Stanford, CA
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Background/Purpose: In large vessel vasculitis (LVV), inflammatory infiltrates typically accumulate within the mural layers of the aorta and its

major branches and are composed of macrophages, T cells and dendritic cells. Before T cells can reach the site of inflammation, they have to extravagate from the circulation and interact with endothelial cells (EC). How this interaction shapes disease-relevant T cell functions is not understood.

Methods: Peripheral blood T cells were isolated from healthy donors and patients with aortitis who had a positive biopsy for GCA and cultured on EC monolayers that had previously been treated with the patient's serum for 24 hours. Four days later CD4 T cells were analyzed for the expression of the lineage-determining transcription factors RORγt, T-bet, GATA-3 and FoxP3 and for intracellular cytokine stores.

Results: Serum pretreated EC changed the differentiation program of the interacting T cells and upregulated RORγt (P=0.03) and T-bet (P<0.001), while suppressing GATA-3 (P<0.001) and FoxP3 (P<0.001). The shift in transcription factor expression was associated with the expansion of Th1 and Th17 cells and the loss of Th2 and Treg cells. This effect required serum pretreatment and was not observed if the serum derived from patients with the inflammatory disease rheumatoid arthritis (P>0.1). To identify underlying molecular pathways, the T cell-EC cocultures were treated with small molecule inhibitors to block intracellular signaling networks. The γ-secretase inhibitor DAPT, which disrupts the NOTCH signaling pathway, was able to abrogate the shift in T cell differentiation (P<0.001). Flow cytometry confirmed that GCA T cells express the NOTCH receptor NOTCH1 and GCA serum-treated EC express the NOTCH ligand Jagged1 (P=0.003).

Conclusion: In patients with GCA, EC acquire expression of Jagged1, which enables such cells to actively communicate with T cells and interfere with their differentiation program. Signal-sending Jagged1$^+$ EC bias T cell differentiation towards proinflammatory effector functions, including the production of IFN-γ and IL-17 and loss of anti-inflammatory Tregs. In LVV, EC not only facilitate the entrance into the arterial wall, they actively participate in swaying T cell immunity.

Disclosure: Z. Wen, None; **H. Zhang**, None; **J. Liao**, None; **G. Berry**, None; **L. J. Forbess**, None; **M. Weissman**, None; **J. Goronzy**, None; **C. M. Weyand**, None.

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Abstract Number: 3142

Tocilizumab Enhances Regulatory T-Cell Activation and Proliferation in Giant Cell Arteritis

Chie Miyabe[1], Klemen Strle[2], Yoshishige Miyabe[1], John H. Stone[1,3], Andrew D. Luster[1,4] and **Sebastian Unizony**[1,5], [1]Rheumatology, Allergy and Immunology, Massachusetts General Hospital, Harvard Medical School, Boston, MA, [2]Division of Rheumatology, Allergy & Immunology, Massachusetts General Hospital, Harvard Medical School, Boston, MA, [3]Rheumatology, Massachusetts General Hospital, Harvard Medical School, Boston, MA, [4]Massachusetts General Hospital, Charlestown, MA, [5]Rheumatology, Massachusetts General Hospital, Boston, MA
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Background/Purpose : CD4+ T helper (Th) 17 cells, Th1 cells, and regulatory T-cells (Treg) contribute to the pathogenesis of giant cell arteritis (GCA). Interleukin (IL)-6, a key mediator in the differentiation of both Th17 and Treg cells, is up-regulated in this disease. Preliminary use of the IL-6 receptor antagonist tocilizumab (TCZ) has shown encouraging results in patients with GCA. However, the mechanism of action of TCZ in this disorder is unknown. We aimed to characterize the effector and regulatory CD4+ T-cell compartments in the peripheral blood of patients with GCA treated with TCZ

Methods: We evaluated 39 patients with GCA classified into one of three categories (**Table 1**): 1) active disease (aGCA, n=11); 2) disease remission on corticosteroid (CS) monotherapy (rGCA-CS, n=17); and 3) disease remission on TCZ therapy (rGCA-TCZ, n=11). Thirteen healthy controls (HC) were also included. Using flow cytometry, we determined the percentages (%) of IFNg+IL-17- (Th1), IL-17+IFNg- (Th17), IL21+, CD25high (Treg), and CD45RA-Foxp3high (activated Treg, aTreg) cells within the CD4+ T-cell population. In addition, we determined the % of Foxp3+ cells expressing the proliferation marker Ki67, and the activation markers CCR4 and CTLA4. We assessed Treg function in suppression assays. Serum levels of IL-12, IFNg, IL-6, IL-1β, IL-23, IL-21, TNF-α, CCL20, IL-17A, and IL-10 were measured by Luminex. Univariate and multivariate analyses were completed.

Results: The frequency (mean %) of Treg cells was equivalent across groups. However, the frequency of aTregs was significantly higher in rGCA-TCZ patients (1.3%) compared to rGCA-CS patients (0.6%; p<0.01) (**Figure 1**). The significant difference in aTregs persisted in age-, sex-, and CS-dose-adjusted analysis. Moreover, the number of Ki67+ Tregs was significantly higher in rGCA-TCZ patients (31.7%) as opposed to rGCA-CS patients (16.4%; p<0.01) and aGCA patients (15.5%; p<0.01). Multivariate analyses demonstrated that compared to rGCA-CS

patients, Tregs from rGCA-TCZ patients expressed CCR4 and CTLA4 significantly more often (**Figure 1**). Tregs were functional in all groups. The frequency of Th1 cells was equivalent across groups. The frequency of CD21+CD4+ T-cells was significantly higher in aGCA patients compared to patients with GCA in remission. The frequency of Th17 cells was significantly higher in GCA patients compared to HC. IL-10 levels were significantly increased in the serum of aGCA patients

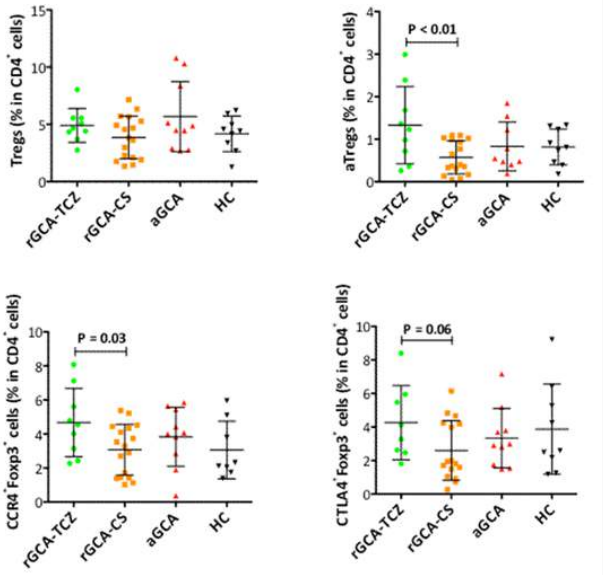
Conclusion: The therapeutic effects of TCZ in GCA could be mediated by changes in the activation and proliferative potential of Tregs

Table 1. Baseline characteristics of GCA patients and healthy controls

	rGCA-CS (n= 17)	rGCA-TCZ (n = 11)	aGCA (n =11)	P-value	Controls* (n = 13)	P-value
Age, years: mean (SD)	74 (10)	69 (8)	72 (10)	0.77	50 (14)	<0.01
Sex: % females	65	82	82	0.48	46	0.09
Ethnicity/Race: % White	88	91	100	0.26	77	0.16
Relapsing disease: number (%)	10 (59)	11 (100)	8 (73)	0.05	-	-
Biopsy-proven GCA: number (%)	10 (59)	5 (45.5)	7 (63.5)	0.77	-	-
Positive vascular imaging¥: number (%)	1 (6)	4 (36)	3 (27)	0.14		
Disease duration, months: median (IQR)	27 (6; 54)	29.5 (19.5; 67)	24 (0; 54)	0.40	-	-
Duration of CS treatment, months: median (IQR)	33 (9; 56)	28 (10; 68)	26 (4; 57)	0.61	-	-
Duration of TCZ treatment, months: median (IQR)	-	21 (14; 29)	-	-	-	-
Prior MTX use: number (%)	6 (35)	4 (36.4)	3 (30)	0.95	-	-
CS dose at time of sampling, mg/day: mean (SD)	15.5 (19.4)	0.2 (0.4)	8.0 (6.8)	<0.01#	-	-

GCA = giant cell arteritis; CS = corticosteroids (prednisone); TCZ = tocilizumab; MTX = methotrexate; rGCA-CS = GCA in remission on CS; rGCA-TCZ = GCA in remission on TCZ without or without CS; aGCA = active GCA; SD = standard deviation; IQR = interquartile range; ¥ MRA, CTA or PET/CT; Analysis: ANOVA, Student's t-test, and Fisher's exact test; *compared to all GCA patients; # rGCA-CS versus rGCA-TCZ

Figure 1. Regulatory T-cell frequencies and phenotypes



rGCA-CS = GCA in remission on CS; rGCA-TCZ = GCA in remission on TCZ without or without CS; aGCA = active GCA.
Analysis: Student st-test. All P-values displayed were < 0.05 after adjusting for age, sex, and CS dose at the time of blood sampling

Disclosure: **C. Miyabe**, None; **K. Strle**, NIH K (K01AR062098), 2,Arthritis Foundation, 2; **Y. Miyabe**, None; **J. H. Stone**, None; **A. D. Luster**, None; **S. Unizony**, None.

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Abstract Number: 3143

Mapping the Back-Door Routes into the Vascular Wall: 3D Microscopic Reconstruction of Microvasculature in the Normal Temporal Artery and in Giant Cell Arteritis

Daniel Drayton[1], Aruna Chakrabarty[2], Ann Morgan[3], Darren Treanor[4] and Sarah Mackie[5], [1]School of Medicine, University of Leeds, Leeds, United Kingdom, [2]Department of Cellular Pathology, Leeds Teaching Hospitals NHS Trust, Leeds, United Kingdom, [3]Leeds Institute of Rheumatic and Musculoskeletal Medicine and NIHR-Leeds Musculoskeletal Biomedical Research Unit, University of Leeds, Leeds, United Kingdom, [4]Leeds Institute of Cancer and Pathology, Leeds Teaching Hospitals NHS Trust, Leeds, United Kingdom, [5]NIHR-Leeds Musculoskeletal Biomedical Research Unit and Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds, University of Leeds, Leeds, United Kingdom

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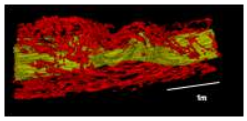
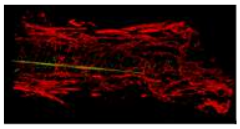
Background/Purpose: The arterial wall is nourished by microvessels (vasa vasorum), which are a potential route of entry for inflammatory cells in vasculitis. Little is known about the anatomy of temporal artery vasa vasorum or their relationship to the inflammatory neovessels in giant cell arteritis.

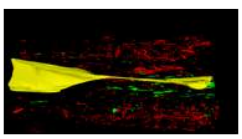
Methods: Temporal arteries from consenting patients were serially sectioned (5µm) and stained with haematoxylin and eosin (H&E). Slides were scanned at 0.5µm/pixel generating 'virtual copies'. Virtual slides were registered (aligned) and segmented (annotated). Area and circularity (isoperimetric quotient) were calculated for microvessels (vasa vasorum and neovessels). 2D segmentations were connected throughout the virtual case using Medical Image Manager (Heterogenius Ltd, Leeds), creating 3D iso-surfaced images.

Results: Vasa vasorum (red) formed a dense plexus within the adventitia of the normal temporal artery (lumen in yellow), becoming smaller and more numerous towards the internal elastic lamina. In a completely-occluded temporal artery with panarteritis, microvessels penetrated all layers of the vascular wall. Leukocyte aggregates surrounded some of the adventitial vasa vasorum. In a temporal artery with partial luminal occlusion, the segment with greater occlusion had a greater number of neovessels (innermost neovessels shown in green). In GCA, median microvessel area (834 (IQR 421-1881)um^2 and 150 (90-289)um^2 in the first and second GCA specimens respectively) was smaller than that of the normal vasa vasorum (1177 (555-2822)um^2); $p<0.001$. Median microvessel circularity (0.62 (IQR 0.37-0.84) and 0.45 (0.46-0.87)) was also reduced in each GCA specimen compared to normal vasa vasorum (0.69 (0.46-0.87)); $p<0.001$.

Conclusion: The vasa vasorum of the temporal artery form a dense plexus. Inflammatory neovessels are smaller and have reduced circularity compared to vasa vasorum. This method could be used to visualise 3D relationships of microvessels and skip lesions in vasculitis.







Disclosure: D. Drayton, None; **A. Chakrabarty**, None; **A. Morgan**, None; **D. Treanor**, None; **S. Mackie**, None.

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Abstract Number: 3144

Efficacy and Safety of Tocilizumab for Polymyalgia Rheumatica

Lindsay Lally[1], Lindsy J. Forbess[2], Chris Hatzis[1] and Robert F. Spiera[3], [1]Rheumatology, Hospital for Special Surgery, New York, NY, [2]Rheumatology, Cedars-Sinai Medical Center, Los Angeles, CA, [3]Rheumatology, HSS, New York, NY

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Background/Purpose: IL-6 is a pivotal cytokine in PMR pathogenesis, yet the efficacy of IL-6 blockade with tocilizumab (TCZ) for treatment of PMR is unknown. The aim of this study was to assess the efficacy and safety of TCZ for treatment of newly diagnosed PMR.

Methods: In a single-center open-label study, subjects with newly diagnosed PMR (Healey criteria) and prior treatment with <1 month (mo) of corticosteroids (CS) were treated with TCZ 8mg/kg IV monthly for 12 mos plus a rapid CS taper. Subjects were followed for 15 mos. Those with concurrent GCA or those treated with >30mg prednisone were excluded. Primary endpoint was the proportion of subjects in relapse-free remission off CS at 6 mos. A cohort of consecutively evaluated patients with newly diagnosed PMR who declined participation in the trial or failed to meet inclusion criteria served as a control group. These patients were treated contemporaneously by a single rheumatologist with expertise in PMR and received CS alone, tapered at the treating physician's discretion.

Results:

Primary endpoint: Ten subjects were enrolled. All 10 also met ACR/EULAR 2012 Provisional Classification Criteria for PMR. One subject withdrew after 2 mos due to a mild infusion reaction, leaving 9 subjects in whom primary endpoint was assessed. 9/9 subjects achieved the primary endpoint of relapse-free remission off CS at 6 mos. Of the 7 subjects who have reached 12 mos in the study to date, all remained in remission without relapse, as did all 4 of those who have thus far completed their 15 mos of follow-up. No flares in subjects treated with TCZ were observed throughout the study.

Ten controls were identified who had been seen consecutively with newly diagnosed PMR. Controls did not differ from study subjects with regard to age, gender, acute phase reactants, or mean baseline CS dose [Table 1]. No controls were in remission off of CS at 6 mos. At 12 mos, a 60% relapse rate was observed in controls.

Steroid-sparing effects: 8/9 TCZ-treated subjects were able to discontinue CS following the third TCZ dose; one subject tapered off CS following the fourth TCZ dose. No subjects receiving TCZ required resumption of CS once they had been tapered off. Cumulative prednisone dose in subjects was 1085±301mg compared to 2562±1356mg in controls (p-value 0.01). Total duration of steroid exposure was significantly less in subjects (3.9±0.9 mos) compared to the controls (14.1±6.0 mos), p-value 0.002 [Table 1].

Safety: 22 adverse events were observed in subjects on TCZ (1 infusion reaction, 5 URIs, 5 episodes of mild neutropenia); only one SAE observed (subject hospitalized after motor vehicle accident).

Conclusion: In this study**,** TCZ was an effective, safe and well-tolerated treatment for newly diagnosed PMR with a robust steroid-sparing effect compared to contemporaneously-treated controls. Subjects treated with TCZ received on average <4 mos of CS and enjoyed relapse-free remission out to 15 mos.

Table 1

Baseline Demographics			
	Subjects	Controls	P-value
Female (%)	50	50	
Age (yrs), mean±SD	68±8.5	72±10.7	0.44
Mean ESR at diagnosis, range	63.2 (13-116)	62.5 (30-123)	0.91
Mean CRP at diagnosis (xULN), range	3.8 (1.3-6.0)	9.7 (1.1-22.2)	0.14
Percent meeting ACR/EULAR 2012 Provisional Classification Criteria for PMR (%)	100	100	
Initial Prednisone Dose (mg), mean ±SD	16.5±6.7	16.5±4.1	0.87
Results			
	Subjects	Controls	P-value
Steroid-free Remission Rate at 6 months (n)	100 % (9/9)	0 % (0/10)	<0.0001
Relapse Rate at 12 months (n)*	0 % (0/7)	60% (6/10)	0.03
Cumulative Prednisone dose (mg), mean±SD	1085.3 ± 301.3	2562.0 ± 1355.9	0.01
Duration of Prednisone Exposure (months), mean±SD	3.9 ± .0.9	14.1 ± 6.0	0.002

*The remaining 2 subjects have yet to reach 12 months follow-up and continue on study protocol.

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Efficacy and Safety of Modified-Release Prednisone in Patients with Polymyalgia Rheumatica: Results of a Multicenter, Randomized, Active-Controlled Phase 3 Study

Maurizio Cutolo[1], Michael Hopp[2], Stefan Liebscher[2], Bhaskar Dasgupta[3] and Frank Buttgereit[4], [1]Research Laboratory and Academic Division of Clinical Rheumatology, Department of Internal Medicine, University of Genova, Genova, Italy, [2]Medical Science, Mundipharma Research GmbH & Co. KG, Limburg, Germany, [3]Rheumatology, Southend University Hospital, Essex, United Kingdom, [4]Department of Rheumatology and Clinical Immunology, Charité – Universitätsmedizin Berlin, Berlin, Germany

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Background/Purpose: Polymyalgia rheumatica (PMR) is characterized by persisting proximal pain and morning stiffness of the neck, shoulder and hip girdles of 2 weeks' duration, an acute-phase response, and a rapid clinical response to glucocorticoids. Modified release (MR) prednisone improves oral prednisone treatment strategies, at least in RA, by adapting glucocorticoid release to endogenous cortisol rhythms and symptom severity, both of which have their peaks during the early morning hours. We assessed the efficacy and safety of MR prednisone compared to immediate release (IR) prednisone in patients with newly diagnosed PMR previously untreated with glucocorticoids.

Methods: Patients meeting the 2012 EULAR/ACR classification criteria for PMR (excluding US) were randomized to double-blind MR prednisone or IR prednisone 15 mg/day for 4 weeks. MR prednisone/placebo was taken at approx. 10pm and IR prednisone/placebo was taken between 5am and 9am. Patients recorded duration of morning stiffness and symptoms of PMR, global pain, shoulder pain and fatigue on visual analog scales (VAS) in a daily diary. CRP, ESR and IL-6 were measured at study visits. The primary efficacy endpoint was the percentage of complete responders (CRs, defined as ≥70% reduction in PMR VAS, duration of morning stiffness and CRP [or CRP <2 x ULN]) at Week 4,

analyzed using a logistic regression model. Non-inferiority was concluded if the lower limit of the 95% CI for the treatment comparison (MR vs. IR prednisone) was above -15%.

Results: The study randomized 62 patients; 66% female, mean age 69 years. The percentage of CRs at Week 4 was 54% for MR prednisone and 41% for IR prednisone in the per protocol population (PPP) (53% and 33%, respectively, in the full analysis population [FAP]). Non inferiority of MR vs. IR prednisone was not proved in the primary analysis on the PPP (N=48; treatment difference: 12.22% in favour of MR prednisone; 95% CI: -15.82%, 40.25%) as the lower 95% CI was less than 15%, but sensitivity analysis on the FAP showed a trend in favour of MR prednisone (N=62; treatment difference: 15.56%; 95% CI: -9.16%, 40.28%). There was a clear consistent trend for a stronger effect of MR compared with IR prednisone across most secondary efficacy endpoints at Week 4 (Table 1), with a discernible treatment difference observed as early as Week 1. MR prednisone showed a larger efficacy in reducing IL 6 levels. The incidence of treatment-related adverse events was relatively low and the events reported were generally consistent with the known safety profiles of used doses of MR and IR prednisone.

Conclusion: Although the primary analysis of non-inferiority was not met, the consistently positive and clinically meaningful results for MR prednisone compared with IR prednisone observed in this study provide an indication of a beneficial clinical effect of MR over IR prednisone in patients with PMR, with improvements observed as early as Week 1.

Table 1 Secondary Efficacy Results (Double-Blind Core Phase, Full Analysis Population)

Parameter	Modified Release Prednisone (N=32)		Immediate Release Prednisone (N=30)		p-value for Treatment Difference
	Mean (SD) at Baseline	Mean (SD) Change from Baseline at Week 4	Mean (SD) at Baseline	Mean (SD) Change from Baseline at Week 4	
PMR VAS	80.71 (12.884)	-70.37 (20.814)	80.95 (11.700)	-59.77 (24.016)	0.011
PMR VAS at awakening	81.73 (17.260)	-70.74 (18.722)	85.92 (9.676)	-63.72 (23.252)	0.021
Duration of MST (min)	529.94 (530.990)	-456.94 (517.912)	615.57 (590.990)	-417.32 (574.652)	0.592
Global pain VAS	79.99 (13.142)	-68.70 (21.729)	78.15 (13.958)	-55.47 (25.552)	0.011
Global pain VAS at awakening	80.59 (18.943)	-69.34 (20.665)	83.36 (13.132)	-60.92 (28.282)	0.028
Shoulder pain VAS	81.00 (13.308)	-68.38 (21.463)	79.90 (13.011)	-57.71 (25.916)	0.033
Fatigue VAS	72.86 (19.309)	-59.40 (27.338)	75.67 (14.313)	-57.60 (23.162)	0.225
CRP (mg/L)	50.58 (32.341)	-44.04 (32.238)	69.59 (49.384)	-52.88 (48.333)	0.060
ESR (mm/hr)	66.53 (21.618)	-38.77 (24.137)	68.33 (22.842)	-40.12 (23.651)	Not estimable*
IL-6 (pg/mL)	41.40 (34.967)	-37.41 (41.272)	40.86 (35.183)	-29.84 (32.613)	0.017

Decreases from baseline represent a favourable treatment effect.
* Convergence criteria not met.
CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; IL-6 = interleukin-6; MST = morning stiffness; PMR = polymyalgia rheumatica; SD = standard deviation; VAS = visual analog scale.

Disclosure: M. Cutolo, Horizon Pharma, 2,Mundipharma International Ltd, 5,Mundipharma International Ltd, 8; **M. Hopp**, Mundipharma Research GmbH Co. KG, 3; **S. Liebscher**, Mundipharma Research GmbH Co. KG, 3; **B. Dasgupta**, Servier, Roche, Merck, GSK & Mundipharma, 5,NAPP Pharmaceuticals Ltd., 2; **F. Buttgereit**, Horizon Pharma, 2,Mundipharma International Ltd, 5,Horizon Pharma, Mundipharma International Ltd, 8.

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Health Related Quality of Life in Adults with JIA – a 30 Year Longitudinal Study

Anita Tollisen[1,2,3], Anne Marit Selvaag[1], Hanne A. Aulie[1], Anners Lerdal[4,5] and Berit Flato[1,2], [1]Department of Rheumatology, Oslo University Hospital, Rikshospitalet, Oslo, Norway, [2]Faculty of Medicine, Institute of Clinical Medicine, University of Oslo, Oslo, Norway, [3]Department of Medicine, Lovisenberg Diakonale Hospital, Oslo, Oslo, Norway, [4]Faculty of Medicine, Institute of Health and Society, University of Oslo, Oslo, Norway, [5]Lovisenberg Diakonale Hospital, Oslo, Oslo, Norway
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Background/Purpose: Improvement of health-related quality of life (HRQOL) is a central aim in treatment of patients with JIA. The primary

aim of the study is to acquire knowledge about HRQOL in JIA patients, 30 years after disease onset.

Methods: From a total of 336 JIA patients, first time referred to Oslo University Hospital between 1980-85 and reassessed after 15 years, 176 participated in a study mean 29.7 (± 2.3) years after disease onset. HRQOL was assessed by SF-36, physical disability by Health Assessment Questionnaire Disability Index (HAQ-DI) and pain by Visual Analogue Scale (VAS pain). Patients, mean age 37.8 (± 4.5), male 27%, were matched to 90 controls selected randomly from the Norwegian population register.

Results: At 30 year follow-up 102 patients (58%) were in remission off medication (table 1). Differences in PCS, HAQ-DI and VAS pain between JIA subtypes were found.

Compared to controls, patients had reduced HRQOL according to the SF-36 physical component summary score (PCS) including all subscales of SF-36 except mental health after 30 years (table 2). Between patients with active disease and patients in remission a difference was found in PCS and HAQ-DI, but both groups had reduced PCS compared to controls.

From 15 to 30 year follow-up PCS decreased and HAQ-DI increased (Δ 1.5, p-value 0.046, & Δ 0.08, p-value 0.024, respectively). All disease activity variables (core set recommended by ACR) assessed at 15-year, except ESR, correlated with PCS at 30-year follow-up (table 3). In a multiple linear analysis, HAQ-DI and VAS pain after 15 years predicted PSC after 30 years.

Conclusion: JIA has a detrimental effect on HRQOL 30 years after disease onset; also in patients in clinical remission. HRQOL worsened from 15 to 30 year follow-up. Physical disability (HAQ-DI) and pain (VAS) after 15 years predicted physical health assessed by PCS after 30 years. However, substantial unexplained variance in HRQOL exists in adults with JIA.

Tabl.1 Thirty year follow-up, subtypes, gender, SF-36 (PCS and MCS), HAQ-DI, VAS pain and remission status.

Values are medians and ranges if not indicated otherwise.

Disease subtype	N(%)	Female/Male (% girls)	PCS	MCP	HAQ-DI	VAS pain	Remission* yes/no (% yes)
Systemic arthritis	12(7)	8/4 (67)	54.8 (28.5-63.7)	54.2 (24.2-61.4)	0.0 (0.0-0.7)	2 (1-46)	9/3 (75)
Polyarticular RF neg	26(15)	20/6 (95)	45.9 (27.5-64.4)	51.5 (32.4-62.6)	0.3 # (0.0-1.6)	5□ (1-87)	13/13 (50)
Polyarticular RF pos	6(3)	6/0 (100)	48.8 (32.1-51.7)	56.9 (42.9-61.7)	0.9 □#¤ (0.0-1.6)	14 (2-56)	1/5 (17)
Oligoarticular persistent	52(30)	41/11 (79)	54.6 (26.6-65.4)	54.3 (22.3-62.1)	0.0 (0.0-1.6)	6 (1-72)	38/14 (73)
Oligoarticular extended	23(13)	18/5 (78)	49.4 (26.5-65.4)	51.2 (29.6-66.9)	0.0 (0.0-1.3)	11 (1-76)	11/12 (48)
Enthesitis-related arthritis	27(15)	10/17(37)	49.5# (22.1-61.8)	54.6 (21.3-62.4)	0.06 (0.0-1.5)	11 (1-100)	12/15 (44)
Psoriatic articular	21(12)	18/3 (86)	49.0 (25.5-60.2)	54.4 (25.8-61.8)	0.4 (0.0-1.4)	5 (1-84)	12/9 (57)
Undifferentiated arthritis	9(5)	8/1 (89)	47.1 (27.3-62.3)	54.3 (29.5-62.6)	0.0 (0.0-1.6)	1 (1-47)	6/3 (67)
Total	176						102/74

* 12 months of inactive disease off medication.

□ P<0.05 vs systemic arthritis, # P<0.05 vs oligoarticular persistent, ¤ P<0.05 vs enthesitis related arthritis.

Tabl.2 Mean (SD) HRQOL scores after 30 years in JIA patients.

Variabler	Patients N=176	Controls N=90	Patients active disease N= 74	Patients in remission, off medication N= 102
Physical functioning	83.4 (19.3)*	95.3 (9.6)	79.1 (20.2)*#	86.5 (18.2)*
Role physical	69.7 (40.0)*	91.1 (21.6)	62.7 (40.9)*	74.8 (38.8)*
Bodily pain	72.7 (23.6)*	83.3 (19.3)	70.6 (21.6)*	74.2 (24.9)*
General health	66.7 (25.2)*	78.2 (17.7)	61.8 (23.7)*	70.2 (25.7)*
SF-36 PCS	48.5 (10.8)*	55.2 (6.4)	46.1 (10.2)*#	50.2(11.0)*
Vitality	52.6(25.0)*	61.8 (23.0)	49.5 (22.7)*	54.8 (26.5)
Social functioning	83.6(21.9)*	92.4 (14.8)	82.6 (21.5)*	84.4 (22.3)*
Role emotional	78.6 (35.3)*	90.0 (26.2)	79.4 (33.4)*	78.1 (36.8)*
Mental health	80.5 (15.7)	83.8 (14.6)	80.5 (15.6)	80.6 (15.9)
SF-36 MCS	50.5 (10.3)	52.6 (8.9)	51.0 (10.1)	50.2(10.4)
VAS Pain	16.2 (22.8)	NA	20.4 (20.4)	14.7(22.8)
HAQ-DI	0.35 (0.49)	NA	0.47(0.54)#	0.26 (0.43)

P-values were determined by Independent Sample T-test. * Patients vs controls p-value ² 0.01,

Patients active disease vs patients in remission p-value ² 0.01.

Tabl.3 Association between PCS at 30-year follow-up

Disclosure: **A. Tollisen**, None; **A. M. Selvaag**, None; **H. A. Aulie**, None; **A. Lerdal**, None; **B. Flato**, None.

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and disease variables at 15 years (n= 160).

	Univariat Analysis		Multiple Regression Analysis[1]		
	Pearsons correlation coefficient	P-value	R^2	Standardized B	P-value
Gender	-0.106	0.160			
Age	-0.158	0.036			
HAQ 15yrs	-0.474	< 0.001*		-2.045	< 0.001
Pain VAS 15 yrs	-0.398	< 0.001*		-0.040	0.050
SR 15 yrs	-0.118	0.129			
Patients global assessment of overall well-being	-0.239	< 0.002#			
Physicians global assessment of overall disease activity	-0.275	< 0.001*			
Number of joints with active arthritis	-0.259	0.001#			
Number of joints with limited range of motion	-0.202	0.008*			
			0.225		

[1] Results from the final model of multiple linear regression analysis (backward regression methods).

* Variables entered in the multiple regression model, # Highly intercorrelated variables.

http://acrabstracts.org/abstract/health-related-quality-of-life-in-adults-with-jia-a-30-year-longitudinal-study

Abstract Number: 3147

Inter-Provider Reliability in Scoring the Physician Global Assessment of Disease Activity Among Patients with Juvenile Idiopathic Arthritis Patients Who Met the ACR Provisional Criteria for Clinical Inactive Disease

Janalee Taylor[1], Edward H. Giannini[1], Daniel Lovell[2] and Esi M. Morgan DeWitt[1], [1]Division of Rheumatology, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, [2]PRCSG, Cincinnati Children's Hospital Medical Center, Cincinnati, OH
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Background/Purpose: With the advent and implementation of advanced drug therapy clinical inactive disease (CID) has become an attainable

target in the treatment of juvenile idiopathic arthritis (JIA). As a result CID is becoming an endpoint in clinical trials and a goal of quality improvement efforts. The ACR Provisional Criteria that describe CID include the physician/provider's global assessment (PGA), which must be scored as zero on a scale of 0 (indicating no disease activity) to 10 (most disease activity) or ≤ 1 when using the Juvenile Arthritis Disease Activity Score. Scoring of the PGA is not standardized and considerable inter-provider variation is known to exist. Our goal was to measure the degree of this variation when scoring patients who were known to meet the ACR provisional criteria of CID, (intended for systemic, oligo- and polyarthritis) and determine clinical and/or laboratory parameters that contribute most to the non-uniformity in the assessment of the PGA in clinical practice.

Methods: Twenty patient profiles from the JIA registry at Cincinnati Children's Hospital Medical Center (CCHMC) who met the ACR provisional criteria for CID were given to a total of 51 providers who were members of the clinical faculty of the Rheumatology division of CCHMC, the Childhood Arthritis and Rheumatology Research Alliance (CARRA), or of the Pediatric Rheumatology ─ Care and Outcomes Improvement Network (PR-COIN). Using Delphi questionnaire and nominal group techniques for consensus building we determined the intra-class correlation (ICC) for the entire provider group, and asked what variables most strongly influenced their scoring of the PGA.

Results: The twenty cases included systemic 0, oligoarthritis 6, polyarthritis 7, psoriatic 3, ERA 3, arthritis associated with IBD 1. Two patients had uveitis. A total of 51 providers participated in the exercise with a total of 1022 PGA scores. The ICC was 0.15. The standard deviation (SD) due to patient differences was 0.127, and SD due to different raters of the patients was 0.697, suggesting that differences in physician-ratings accounted for most of the variability. Variables that influenced scoring were presence of pain, questionable TMJ involvement, joint loss of motion, morning stiffness, psoriasis, and past history of uveitis.

Conclusion: Combined data from 3 groups of experienced pediatric rheumatologists reveal that substantial variation in scoring the PGA continues to exist when scoring JIA patients with very low disease activity. JIA is a heterogeneous collection of conditions, with various extra-articular manifestations that providers consider in making assessments. Due to the complexity of the conceptual framework of the PGA, standardization is likely not feasible. This implies that other disease states, other than CID, that do not require the PGA to equal zero may be more suitable for clinical trial endpoints and when setting goals of quality improvement efforts.

Disclosure: J. Taylor, None; **E. H. Giannini**, AbbVie, 5; **D. Lovell**, AbbVie Inc., AstraZeneca, Centocor, Bristol-Myers Squibb, Pfizer, Regeneron, Hoffman La-Roche, Novartis, UBC, Xoma, and Genentech, 9; **E. M. Morgan DeWitt**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/inter-provider-reliability-in-scoring-the-physician-global-assessment-of-disease-activity-among-patients-with-juvenile-idiopathic-arthritis-patients-who-met-the-acr-provisional-criteria-for-clinical-i

Abstract Number: 3148

Physical Activity in Children and Adolescents with Juvenile Idiopathic Arthritis and Associated Factors

Sabrina Cavallo[1], Marie-Ève Mathieu[2], Annette Majnemer[3], Désirée B. Maltais[4], Ciarán M. Duffy[5], Mélanie Henderson[6] and Debbie Ehrmann Feldman[7], [1]École de Santé Publique, Université de Montréal, Montreal, QC, Canada, [2]Département de Kinésiologie, Université de Montréal, Montréal, QC, Canada, [3]School of Physical and Occupational therapy, McGill University, Montreal, QC, Canada, [4]Département de Réadaptation, Université de Laval, Québec, QC, Canada, [5]Children's Hospital of Eastern Ontario and University of Ottawa, Ottawa, ON, Canada, [6]Centre de recherche du Centre Hospitalier Universitaire Sainte-Justine, Montréal, QC, Canada, [7]School of Rehabilitation, Université de Montréal, Montreal, QC, Canada

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Background/Purpose: Physical activity has health benefits for all children and adolescents, including those with juvenile idiopathic arthritis (JIA). Our study aimed 1) to determine whether the physical activity level of children and adolescents with JIA met Canadian health guidelines, 2) to compare the physical activity levels of children and adolescents with JIA to those without JIA, and 3) to identify disease-related, personal and environmental factors associated with time spent in moderate to vigorous physical activity (MVPA).

Methods: We analysed data on physical activity obtained objectively through accelerometry for 76 children and adolescents with JIA between the ages of 8 to 17 years followed at the Montreal Children's Hospital, McGill University Health Center. Data obtained from a study of healthy children and adolescents devoid of JIA or other joint problems (ages 8 to 14 years) was used as a control group. All participants were asked to wear an accelerometer for 7 consecutive days. The disease characteristics related to JIA were abstracted from the child's medical file (JIA sub-type, active joint count, age of diagnosis), pain perception and functional status were obtained through self-report. Participants with JIA and their parents completed a series of questionnaires to gather information on the child's socio-demographic characteristics, mastery motivation,

self-concept, activity preference, and perceived social support. Hierarchical regression analysis was used to explore factors associated with MVPA in children and adolescents with JIA.

Results: Mean daily MVPA for all participants with JIA was 24.0 minutes (SD = 14.6). Only 2.9% of those with JIA met international recommendations of 60 minutes of daily MVPA. Having JIA was associated with significantly less time (minutes/day) spent in MVPA (β=-12.25, 95% CI= -17.70, -6.81), p<0.0001) compared with controls. Only younger age, being a boy and identifying as Canadian (versus other cultural backgrounds) were identified as predictors of increased MVPA.

Conclusion: Most children and adolescents with JIA did not meet international health recommendations of engaging in 60 minutes of daily MVPA and were less active than those without JIA. In light of the known health benefits of physical activity, it should be encouraged in children and adolescents with JIA to potentially improve disease symptoms, as well as limit development of comorbidities. The identification of personal and environmental factors associated with physical activity may help guide the development of strategies to promote physical activity in JIA.

Disclosure: S. Cavallo, None; **M. Mathieu**, None; **A. Majnemer**, None; **D. B. Maltais**, None; **C. M. Duffy**, None; **M. Henderson**, None; **D. Ehrmann Feldman**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/physical-activity-in-children-and-adolescents-with-juvenile-idiopathic-arthritis-and-associated-factors

Abstract Number: 3149

Predictors of Longitudinal Quality of Life Impact in Pediatric Localized Scleroderma

Kaveh Ardalan, Christina Kelsey and Kathryn S. Torok, Pediatric Rheumatology, Children's Hospital of Pittsburgh of UPMC, Pittsburgh, PA
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Background/Purpose: Localized scleroderma (LS) is an autoimmune disease characterized by inflammation and fibrosis of the skin and a wide range of extracutaneous manifestations (ECMs). The longitudinal impact of this disease on children's quality of life (QoL) is not currently known. The aim of this study was to longitudinally assess predictors of QoL impact in a cohort of pediatric LS patients.

Methods: Subjects who were 4-16 years old at the time of enrollment into the National Registry for Childhood Onset Scleroderma were included in analysis. Children's Dermatology Life Quality Index (CDLQI) scores at baseline and follow-up clinic visits were dichotomized; scores of 0 or 1 indicated minimal QoL impact, and a score of >1 was considered significant impact.

Hierarchical generalized linear modeling was used to determine predictors of QoL impact, first assessing univariably (alpha = 0.10) and then including all univariably significant variables in the final model (alpha = 0.05). Variables included initially were gender, age at diagnosis, time from initial visit, presence of disease flare, the activity and damage portions of the physician-scored Localized Scleroderma Cutaneous Assessment Tool (i.e. the modified Localized Scleroderma Skin Severity Index (mLoSSI) and the Localized Scleroderma Damage Index (LoSDI) respectively), presence of facial lesion(s), use of systemic immunosuppressive medications, total number of body sites affected, medication side effects, and number of ECMs.

Results: Eighty subjects with a total of 616 visits were included for analysis, with median follow-up of 29.5 months (IQR: 14.0-50.3 months) per subject. Demographics were representative of typical LS populations (see Table 1). Five univariably significant variables were included in the final model: time from initial visit, mLoSSI, LoSDI, gender, and number of ECMs. Males were less likely to have QoL impact than females (*OR*: 0.12, $p = 0.002$). Each month after the initial visit yielded 5% lower odds of QoL impact (*OR*: 0.95, $p < 0.001$). Two thirds of participants reported at least one ECM, with musculoskeletal, orofacial and neurologic ECMs being the most common. Each additional ECM increased the likelihood of QoL impact by 37% (*OR*: 1.37, $p = 0.019$). mLoSSI and LoSDI did not reach significance in the final model. Unit-specific and population-average models were found to be similar; the addition of an over-dispersion factor to the final model did not meaningfully alter the results.

Table 1: Demographic and Visit Descriptive Statistics	
Female Sex, n (%)	58 (73%)
Race - White, n (%)	74 (93%)
Median Age at Disease Onset (years), (IQR)	7.8 (4.9-10.3)
Median Age at Diagnosis (years), (IQR)	9.5 (7.2-11.9)
Median Age at Initial Study Visit (years), (IQR)	10.4 (8.0-13.2)
LS Subtype, n (%)	
Linear (limb/trunk)	27 (33.8%)
Linear (Head/Face)	14 (17.5%)
Generalized Morphea	11 (13.8%)
Superficial Circumscribed	8 (10%)
Deep Circumscribed	4 (5%)
Mixed Subtype	16 (20%)
Lesion Location, n (%)	
Face/Neck	28 (35%)
Trunk	43 (54%)
Limb	50 (63%)
Extracutaneous Manifestations	
ECM(s) Present, n (%)	53 (66%)
Median # ECMs (IQR)	1.5 (0-3)
Treatment, n (%)	
# Visits on Immunosuppressive Treatment	420 (68%)
# Visits with Med Side Effects	337 (55%)
Disease Activity, n (%)	
# Visits with "Inactive Disease"*	480 (78%)
# Visits with "Active Disease"*	106 (17%)
"Active Disease Visits" Considered "Flare"	26 (25%)
# Visits with QoL Impact (CDLQI Score > 1), n (%)	299 (49%)

*30 visits (5%) missing disease activity status

Conclusion: This study is the first longitudinal assessment of predictors of QoL impact in pediatric LS. Female sex and presence of ECMs significantly increase the likelihood of negative QoL impact. In addition, the odds of QoL impact decrease with time from initial visit, suggesting that factors such as effective immunosuppressive treatment, physical/occupational therapy, and patient/family coping mechanisms may mitigate the QoL impact.

Disclosure: K. Ardalan, None; **C. Kelsey**, None; **K. S. Torok**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/predictors-of-longitudinal-quality-of-life-impact-in-pediatric-localized-scleroderma

Abstract Number: 3150

Virtual Peer-to-Peer Mentoring Support for Adolescents with Juvenile Idiopathic Arthritis: The Virtual Peer-to-Peer Program

Jennifer N. Stinson[1], Sara Ahola Kohut[2,3], Khush Amaria[2], Mary J. Bell[4], Paula Forgeron[5], Miriam Kaufman[6], Nadia Luca[7] and Lynn R. Spiegel[8], [1]Anesthesia and Pain Medicine, The Hospital for Sick Children, Toronto, ON, Canada, [2]Hospital for Sick Children, Toronto, ON, Canada, [3]University of Toronto, Toronto, ON, Canada, [4]Rheum Div/Univ of Toronto, University of Toronto, Toronto, ON, Canada, [5]University of Ottawa, Ottawa, ON, Canada, [6]Adolescent Medicine, The Hospital for Sick Children, Toronto, ON, Canada, [7]Division of Rheumatology, The Hospital for Sick Children, Toronto, ON, Canada, [8]Rheumatology/Pediatrics, The Hospital for Sick Children, Toronto, ON, Canada

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Background/Purpose:

Juvenile Idiopathic Arthritis (JIA) is a common chronic disease that results in physical and emotional symptoms as well as difficulties in social and role functioning that negatively impact health-related quality of life (HRQL). Many youth with JIA are isolated, having never met another person with JIA and most do not receive comprehensive support to develop self-management skills. The Virtual Peer-to-Peer (VP2P) Program aims to fill this gap by providing peer mentoring via the Internet to improve the *accessibility* and *acceptability* of self-management programs while providing essential peer support for adolescents with JIA.

Methods:

The VP2P program was developed in a phased approach. First, a needs assessment was completed in youth with JIA. Second, a systematic review of peer support programs for adolescents with chronic disease was conducted in order to highlight essential components of successful peer interventions. Third, the VP2P program was developed for adolescents with JIA, informed by results of the systematic review, and included a 2.5-day peer mentor training session. Fourth, using a waitlist pilot randomized control trial (RCT) design, young adult peer mentors (16-25 years; successfully managing their JIA) were matched to adolescent participants (12-18 years; diagnosed with JIA, English speaking, access to a computer with Internet) to provide peer support (emotional, informational, and appraisal) and education for effective self-management of JIA. All mentors and adolescents met American College of Rheumatology criteria for JIA. Mentors and adolescents connected 10 times over the 8-week study period using Skype video calls. Primary outcomes focused on implementation of the VP2P program and included measures of feasibility and acceptability. Secondary outcomes focused on effectiveness of the VP2P program and included measures of self-management, self-efficacy, pain, social support and HRQL.

Results:

Thirty adolescents (mean age 14.3±1.7 years, range = 12-17 years, 97% female) completed participation in the pilot RCT (intervention n = 16, control n = 14). *Primary outcomes:* Over half (64%) of adolescents who were approached agreed and consented to participate; 13% dropped out prior to beginning the intervention or did not complete the 10 full sessions; and 70% of participant-mentor pairings completed the program within 2 months. Median program length was 63.5 days. Average call length was twice the required amount with median call lengths of 45.2±17.2 minutes. Participants reported satisfaction with the program and all reported that they would recommend it to a friend. Participants reported median engagement levels of 8/10 (range = 7.5-10). *Secondary outcomes:* Participants who completed the VP2P program demonstrated significant improvements in their perceived ability to manage JIA ($p = 0.04$), improvements in social support ($p = 0.03$) and disease knowledge ($p = 0.01$) compared to controls.

Conclusion:

The VP2P program is a promising intervention that improves accessibility and acceptability of self-management and peer support treatments for adolescents with JIA. Findings were used to inform a full-scale multi-site RCT of the VP2P program for adolescents with JIA.

Disclosure: J. N. Stinson, None; **S. Ahola Kohut**, None; **K. Amaria**, None; **M. J. Bell**, Janssen Inc., 5; **P. Forgeron**, None; **M. Kaufman**, None; **N. Luca**, None; **L. R. Spiegel**, None.

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Abstract Number: 3151

Validation of Patient-Reported Outcomes Measurement Information System (PROMIS®) Modules for Use in Childhood-Onset Lupus

Jordan T. Jones[1], Janet Wootton[2], Jun Ying[3], Brianna Liberio[4], Jiha Lee[5], Adam Carle[6], Laura Schanberg[2] and Hermine I. Brunner[6], [1]Division of Rheumatology, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, [2]Pediatrics, Duke Medical Center, Durham, NC, [3]University of Cincinnati, Cincinnati, OH, [4]University of Cincinnati College of Medicine, Cincinnati, OH, [5]Rheumatology, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, [6]Cincinnati Children's Hospital Medical Center, Cincinnati, OH
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Background/Purpose: Childhood-onset lupus (cSLE) has a substantial negative impact on health-related quality of life (HRQoL). Patient-reported outcomes (PROs) that accurately assess HRQoL and are responsive to change can contribute to improvements in clinical care, and treatment decisions. The PRO Measurement Information System (PROMIS®, http://nihpromis.org) is a publicly available system, supported by the National Institute of Health that measures PROs. Although several accepted legacy HRQoL measures exist for cSLE, the goals of PROMIS are to decrease respondent burden, increase comparison diseases, and increase responsiveness of measured domains. Our objectives were to investigate the validity and responsiveness of the pediatric PROMIS short forms in cSLE in a clinical setting.

Methods: In a longitudinal study 100 cSLE patients completed pediatric PROMIS short forms (anger, anxiety, depressive, fatigue, mobility, upper extremity function, pain interference, peer relations) and legacy HRQoL measures (Pediatric Quality of Life Inventory™ Generic Core [GC] & Rheumatology Modules [RM], Childhood Health Assessment Questionnaire [CHAQ], Functional Disability Inventory [FDI], and parents completed Child Health Questionnaire [CHQ]) at three study visits approximately three to six months apart. We used legacy measures, physician reported health status change, cross-sectional correlations, and path analyses to evaluate construct validity and responsiveness to change for PROMIS scores.

Results: Participants (80% female; 33% White, 48% Black, 8% other) had a mean age of 15.8 years (SD 2.2) and SLEDAI score of 6.0 (SD 5.9). Completion of the PROMIS short forms averaged seven minutes in total (legacy measures 5 to15 minutes each). Validity of the pediatric PROMIS short forms is supported by moderate to high correlations (Pearson's $r \geq 0.5$) with the scores of various legacy measures (Table 1), and with similar PROMIS domains, respectively, and dissimilar PROMIS domains having low correlations (Pearson's $r \leq 0.4$). Path analyses showed that physician reported changes (e.g., improvement from visit 1 to visit 2) corresponded to parallel change in PROMIS scores (see Table 2). Moreover, the changes were largest for HRQoL scores more closely aligned with clinical change.

Conclusion: The pediatric PROMIS short form measures of HRQoL demonstrated construct validity, and responsiveness to change in a sample of children with cSLE. PROMIS measures can be utilized by clinicians treating cSLE for a more efficient, responsive measure of HRQoL while reducing respondent and clinician time burden.

Table 1. Bivariate correlations between pediatric PROMIS® short forms and legacy measures

Pediatric PROMIS Short Forms Domains	Anger	Anxiety	Depression	Fatigue	Mobility	Upper Extremity Function	Pain Interference	Peer Relationships
SLEDAI*	0.12	0.06	0.03	0.11	-0.23	-0.12	0.16	0.11
CHQ – Psychosocial Summary Score (PsS)	-0.37	-0.32†	-0.33†	-0.35†	0.43†	0.21	-0.36†	0.32†
CHQ – Physical Summary Score (PhS)	-0.15	-0.24	-0.20	-0.36†	0.55†	0.31†	-0.40†	0.03
CHAQ	0.23	0.29	0.27	0.42†	-0.67†	-0.71†	0.46†	-0.11
PedsQL – GC	-0.58†	-0.66†	-0.64†	-0.78†	0.70†	0.39†	-0.74†	0.30†
PedsQL – RM	-0.53†	-0.65†	-0.60†	-0.72†	0.61†	0.42†	-0.72†	0.24
SMILEY	0.27	0.25	0.25	0.27	-0.19	-0.06	0.30†	0.03
Functional Disability Inventory (FDI)	0.37†	0.47†	0.42†	0.62†	-0.73†	-0.49†	0.62†	-0.18

Values are correlation coefficients

† Represent p-value < 0.05

* Systemic Lupus Erythematosus Disease Activity Index 2000

Table 2. Change in PROMIS® short form domain score† between visits

Variable	Category	Anger	Anxiety	Depression	Fatigue	Mobility	Upper Extremity Function	Pain	Peer Relationships
Visit 2	Better	-0.73 (0.26)*	-0.34 (0.22)	-0.36 (0.26)	-0.65 (0.28)*	0.39 (0.24)	0.66 (0.28)*	-0.55 (0.25)*	-0.19 (0.29)
	Worse	-0.17 (0.38)	-0.18 (0.35)	0.03 (0.33)	-0.31 (0.46)	0.28 (0.29)	0.57 (0.30)	-0.32 (0.33)	0.43 (0.38)
Visit 3	Better	0.05 (0.15)	-0.10 (0.13)	0.03 (0.16)	0.01 (0.15)	0.26 (0.14)	0.14 (0.14)	-0.12 (0.13)	0.07 (0.17)
	Worse	0.18 (0.17)	0.09 (0.15)	0.05 (0.17)	0.01 (0.15)	-0.44 (0.14)*	-0.16 (0.14)	0.30 (0.18)	-0.12 (0.18)

† Values are standardized coefficients (Standard Error)

* Represents p-value < 0.05

Disclosure: J. T. Jones, None; **J. Wootton**, None; **J. Ying**, None; **B. Liberio**, None; **J. Lee**, None; **A. Carle**, None; **L. Schanberg**, None; **H. I. Brunner**, None.

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Abstract Number: 3152

The IL-21 Signaling Pathway Is Enhanced in RA B Cells and Has the Potential to Alter Development and Cytokine Production in RA B Cells

Jane H. Buckner[1] and **Elizabeth Samuelson**[2], [1]Benaroya Research Institute at Virginia Mason, Seattle, WA, [2]Translational Research, Benaroya Research Institute at Virginia Mason, Seattle, WA

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Session Title: B cell Biology and Targets in Autoimmune Disease: Novel B cell roles in RA and SLE

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Background/Purpose: B cells have been implicated in the development of rheumatoid arthritis (RA) based on their production of autoantibodies and cytokines as well as the therapeutic response to B cell depletion therapy. The maturation of B cells occurs in the germinal center and is influenced by multiple factors including T cell dependent CD40-CD40L signals, toll-like receptor signals and cytokines including BAFF and IL-21. Each of these is a potential therapeutic target in RA. In this study we examined the response to IL-21 as measured by phosphorylation of STAT3 (pSTAT3), to better understand its potential role in RA.

Methods: We utilized frozen PBMC from a cohort of RA subjects and healthy controls obtained from the BRI Rheumatic disease Registry. Samples were thawed, rested for 1 hour and were stimulated with cytokine; IL-21 (50 ng/mL and 15 pg/mL) for 15 and 45 minutes (n=20 per group); IL-10 for 10 min at 10 ng/mL (n=20 per group); or IL-4 at 100 ng/mL for 15 min (RA n=10, Control n=12). Response to IL-21 and IL-10 was measured as mean fold change in phosphorylation of STAT3 (pSTAT3) and for IL-4 pSTAT6. IL-21R, the common gamma chain and total STAT3 expression were determined through flow cytometric analysis.

Results: We determined that RA subjects exhibit enhanced IL-21 signaling in total B cells ($p = 0.02$), memory B cells ($p = 0.0096$), IgM+ memory B cells (0.01), naïve B cells ($p = 0.02$) and transitional B cells (0.005) but not in the more mature switched memory B cells as compared to controls. We observed no significant differences in IL-10 or IL-4 stimulations. Further, IL-21 signaling in total B cells of RA subjects as measured by pSTAT3 positively correlated with the expression of IL-21R ($p = 0.0004$, $r = 0.70$). Similarly we found a significant correlation with the common gamma chain level of expression ($p = 0.01$, $r = 0.55$). When we measured total STAT3 we observed no significant differences between RA and control subjects.

Conclusion: We found that the response to IL-21 is enhanced in the B cells of subjects with RA in comparison to healthy age and gender matched controls. This is unique to IL-21 and not other cytokines; IL-4 which signal through the common gamma chain nor IL-10 which signaling via STAT3, suggesting a link with the IL-21R specifically. Consistent with this we found an increase in the expression of the IL-21R on the cell surface. This heightened response has the potential to enhance or alter the maturation of B cells leading to alterations in antibody and cytokine production in RA. Characterizing the response to IL-21 in RA B cells is important as it relates to disease pathogenesis but also is vital as therapeutics that target this cytokine and its signaling pathway are currently under development. Thus this work may have implications with respect to how best to use such drugs in the setting of RA.

Disclosure: J. H. Buckner, None; **E. Samuelson**, None.

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Abstract Number: 3153

Microrna-155/PU.1 Axis As an Epigenetic Regulator of B-Cells in Rheumatoid Arthritis

Stefano Alivernini[1], Barbara Tolusso[1], Mariola Kurowska-Stolarska[2], Roberta Benvenuto[3], Antonella Mangoni[3], Silvia Canestri[1], Luca Petricca[1], Anna Laura Fedele[1], Maria Rita Gigante[1], Clara Di Mario[1], Elisa Gremese[1], Iain B. McInnes[2] and Gianfranco Ferraccioli[1], [1]Division of Rheumatology, Institute of Rheumatology, Catholic University of the Sacred Heart, Rome, Italy, [2]Institute of Infection, Immunity and Inflammation, College of Medicine, Veterinary Medicine and Life Sciences, University of Glasgow, Glasgow, United Kingdom, [3]Division of Pathology - Catholic University of the Sacred Heart, Rome, Italy

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SESSION INFORMATION

Session Date: Tuesday, November 10, 2015

Session Title: B cell Biology and Targets in Autoimmune Disease: Novel B cell roles in RA and SLE

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Session Time: 4:30PM-6:00PM

Background/Purpose: MicroRNA-155(miR-155) has been shown to be a key regulator of B cell biology by PU.1 regulation. However, the role of miR-155 in the activation of B cells in Rheumatoid Arthritis(RA) has not been explored. This study aimed to investigate miR-155 expression in RA B cells and its association with B cell driven pathologies such as levels of antibodies against citrullinated peptides(ACPA) and follicular structures in the synovial tissues(ST).

Methods: 60 RA patients underwent ST biopsy. Based on immunostaining for CD68, CD21, CD3 and CD20 cells, ST samples were categorized as diffuse or with follicular pattern. MiR-155 expression in RA ST and synovial B cells was evaluated by in situ hybridization(ISH). B cells from peripheral blood(PB) and matched synovial fluid(SF) of RA and PB of healthy controls(HC) were isolated by $CD19^{+}$micro-beads. IL-6 and BAFF levels in PB and SF were measured by ELISA. MiR-155 and PU.1 expression in B cells from PB and SF of RA; and in ST samples of osteoarthritis(OA) and RA patients was determined by qPCR. Finally, PB-derived B cells were cultured with or without IL-6(30ng/ml) or BAFF(20ng/ml) and miR-155 and PU.1 expression was assessed by qPCR.

Results: 29 out of 60 RA patients(49.2%) had follicular pattern in the ST biopsy. These patients were more likely ACPA positive compared to RA with a diffuse pattern(p=0.04). Moreover, ACPA plasma levels directly correlated with the synovial aggregate grade(r=0.39;p=0.01). IL-6 and BAFF levels were higher in SF than in PB of RA regardless of the synovial infiltrate pattern(p=0.001 for both). PB B-cells from ACPA positive RA showed higher miR-155 expression compared to ACPA negative RA(p=0.02) and HC(p=0.001). Furthermore, ISH showed that miR-155 was highly expressed in ST of follicular RA compared to diffuse RA(p=0.03). Double staining revealed that the majority of B cells within synovial follicular structures were miR-155 positive. qPCR further confirmed that miR-155 was significantly increased in ST of follicular RA compared to diffuse RA(p=0.03) and OA(p=0.03), respectively. Consistently, the expression of miR-155 target in B cells, PU.1 was found to be lower within synovial aggregates in RA. At the cellular level, miR-155 was highly expressed in PB-derived B-cells of RA compared to HC(p=0.0002). In addition, miR-155 was over-expressed in SF B-cells compared to matched PB B-cells(p=0.05) in RA. This was associated with reciprocal lower expression of PU.1 in SF-derived B-cells and within ST follicular structures compared to matched PB B-cells(p=0.001) and ST with a diffuse pattern, respectively. Finally, *in vitro*stimulation of HC B-cells with IL-6 and BAFF induced miR-155(p=0.04 and p=0.03) and decreased PU.1(p=0.01 and p=0.03) expression.

Conclusion: B-cells of RA show high expression of miR-155 that is associated with ACPA positivity, follicular synovial pattern and low expression of PU.1. IL-6 and BAFF that are significantly increased in the SF environment and induce miR-155 expression in B-cells *in vitro* are likely candidates for maintaining high levels of miR-155 in the synovial B cells. Thus, miR-155 may represent a key regulator of B-cells in RA patients.

Disclosure: S. Alivernini, None; **B. Tolusso**, None; **M. Kurowska-Stolarska**, None; **R. Benvenuto**, None; **A. Mangoni**, None; **S. Canestri**, None; **L. Petricca**, None; **A. L. Fedele**, None; **M. R. Gigante**, None; **C. Di Mario**, None; **E. Gremese**, None; **I. B. McInnes**, None; **G. Ferraccioli**, None.

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Abstract Number: 3154

The Importance of Somatic Hypermutation for the Immunoreactivity Towards Neutrophil Extracellular Traps (NETs)-Citrullinated Autoantigens of RA Synovial Monoclonal Antibodies

Elisa Corsiero[1], Emanuela Carlotti[2], Costantino Pitzalis[3] and Michele Bombardieri[4], [1]WHRI - EMR, London, United Kingdom, [2]Centre for Experimental Medicine and Rheumatology, William Harvey Research Institute, QMUL, London, United Kingdom, [3]Centre for Experimental Medicine & Rheumatology, Queen Mary's School of Medicine and Dentistry, London, United Kingdom, [4]Experimental Medicine and Rheumatology, Queen Mary University of London, London, United Kingdom

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Background/Purpose:

We previously showed that anti-citrullinated peptide/protein antibodies (ACPA) targeting citrullinated antigens contained in neutrophils extracellular traps (NETs) can be manufactured within ectopic germinal center-like structure (GC-LS) in the rheumatoid arthritis (RA) synovium. Here, we aimed to characterise **a)** whether the RA synovial anti-NETs antibodies had undergone antigen-driven affinity maturation, **b)** the importance of somatic hypermutations (SHM) within the V_H and V_L chain for their binding and **c)** whether the presence of N-glycosylation sites in the variable domains introduced by SHM can modulate the reactivity towards NETs.

Methods:

82 full recombinant monoclonal antibodies (RA-syn-rmAbs) were generated from single CD19+ B cells FACS-sorted from fresh GC-LS+ synovial cell suspensions following IgV_H+V_L genes cloning. RA-syn-rmAbs for reversion experiments (n=9) were chosen according to their level of reactivity towards NETs. Reversion of the IgV genes into germ-line (GL) and generation of hybrid clones (where V_H, V_L or selected CDRs/FRs were reverted into GL, n=5) was performed by overlap-PCR. Further characterization of the mature vs GL RA-syn-rmAbs sequence was performed by structural alignment via an *in silico*prediction model using the root-mean-square-deviation (RMSD) score to measure the similarity between the mature and GL structures (1). Anti-NETs immunoreactivity was detected using cell-based immunoassays with activated peripheral blood or RA synovial fluid neutrophils.

Results:

Structural alignment showed some differences in the 3D structure between mature vs GL sequences in 3 RA-syn-rmAbs suggesting that SHM is critical for antigen binding. Accordingly, the anti-NETs immunoreactivity of the RA-syn-rmAbs was dependent on affinity maturation within GC-LS and was completely abrogated when the full IgV_H+V_L genes were reverted to GL. Conversely, when only the IgV_L gene was reverted to GL, 2 out of 5 RA-syn-rmAbs displayed a residual reactivity toward NETs suggesting that in some clones the V_H chain plays a dominant role in conferring the reactivity towards NETs. Preliminary data also showed that the increased molecular weight observed in selected anti-NET antibodies, likely due to the presence of Fab-linked N-glycans sites (2), was lost in the GL counterpart.

Conclusion:

Importantly, our data showed that SHM is necessary for the development of high-affinity NETs-binding antibodies in synovial GC-LS. The importance of defining the contribution of individual CDRs and FRs to the affinity of antigen-binding sites may help to engineer new therapeutic Abs and design of CDRs/FRs-specific peptides for tolerogenic strategy.

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Abstract Number: 3155

Bob1 Expression Is Elevated in Rheumatoid Synovium and Its Expression in B Cells Is Required for Development of Collagen-Induced Arthritis

Maartje Levels[1,2,3], Melissa van Tok[2,3,4], Tineke Cantaert[2,3], Frans G.M. Kroese[5], Hergen Spits[6], Dominique Baeten[2,3,4] and Nataliya Yeremenko[1,2,3], [1]Amsterdam Rheumatology and immunology Center, Amsterdam, Netherlands, [2]Clinical Immunology and Rheumatology, Academic Medical Center/University of Amsterdam, Amsterdam, Netherlands, [3]Laboratory of Experimental Immunology, Academic Medical Center/University of Amsterdam, Amsterdam, Netherlands, [4]Amsterdam Rheumatology and Immunology Center, Amsterdam, Netherlands, [5]Rheumatology and Clinical Immunology, University Medical Center Groningen, University of Groningen, Groningen, Netherlands, [6]Department of Cell Biology and Histology, Academic Medical Center/University of Amsterdam, Amsterdam, Netherlands

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Background/Purpose: Rheumatoid arthritis (RA) is a prototypic autoimmune disease characterized by a prominent humoral autoimmunity. Of particular relevance is the local production of autoantibodies and the presence of ectopic lymphoid neogenesis (ELN) in the rheumatoid synovium. However, the mechanisms underlying break of B cell tolerance and local autoantibody production remain poorly understood. In this study we aimed to identify cellular and molecular pathways implicated in RA-specific humoral autoimmunity.

Methods: Gene expression profiling was performed on synovial tissue from individuals with RA and inflammation-matched non-RA controls without known autoantibodies. Expression of Bob1 was validated on three independent cohorts of synovium by qPCR and immunohistochemistry. Bob1-positive cells were analysed by triple-color immunofluorescence. B and T cell subsets were FACS-sorted from tonsils. Effects of Bob1-deficiency on collagen-induced arthritis (CIA) model were examined using Bob1-deficient mice ($Bob1^{-/-}$) and RAG-1-*null* mice after adoptive transfer of WT and $Bob1^{-/-}$B and T cells. Anti-collagen type II (CII) antibodies (Abs) were assessed by ELISA. Germinal center (GC) formation was analysed in the inguinal lymph nodes of immunized mice by FACS.

Results: Transcriptional profiling in RA synovium revealed a prominent B cell signature with the B cell-specific transcriptional co-activator Bob1 and its transcriptional target BCMA among the most upregulated genes. Further validation by qPCR and immunohistochemistry confirmed the microarray data and demonstrated elevated expression of Bob1 in RA synovium at the early phase of the disease. Triple immunofluorescence analysis of RA synovium revealed expression of Bob1 in B cells and in a subset of T cells. Subsequent Western blot analysis of tonsillar T cell subsets confirmed expression of Bob1 in T follicular helper (T_{FH}) cells. Interestingly, expression of Bob1 in RA synovium was strongly correlated ($r=0.91$; $p<0.0001$) with expression of CD21L, a molecular marker of ELN, linking highest levels of Bob1 to the presence of GCs. In addition, functional analysis in mice showed that $Bob1^{-/-}$mice failed to produce pathogenic anti-CII Abs and were completely protected from CIA. Adoptive transfer of different combination Bob1-deficient and sufficient B and T cells to RAG-1-*null* mice demonstrated that only mice which received Bob1-sufficient B cells developed CIA. The susceptibility to CIA was mirrored by the presence of anti-CII Abs in serum and GC B cells in lymph nodes of animals. Mice which received Bob1-deficient B cells were resistant to CIA, did not develop anti-CII Abs and did not have GC B cells despite the ability of transferred Bob1-deficient T cells differentiate into T_{FH}cells and produce IL-21. Finally, increased expression of Bob1 and its correlation with CD21L in salivary glands of patients with Sjögren's Syndrome, but not in Sicca controls, suggest a general role for Bob1 in B cell-driven autoimmunity.

Conclusion: Aberrant high Bob1 expression in RA synovium and failure of Bob1-deficient B cells to form GCs and produce autoantibodies indicate that Bob1 may contribute to humoral autoimmunity in RA.

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Abstract Number: 3156

IL17 Promotes Development of Autoreactive Early Stage B Cells in Distinct Regions of the Spleen Follicle

Jennie Hamilton[1], Qi Wu[2], PingAr Yang[3], Jun Li[4], Yanna Ding[1], Bao Luo[5], John Mountz[6] and Hui-Chen Hsu[2], [1]University of Alabama at

Birmingham, Birmingham, AL, [2]Department of Medicine, University of Alabama at Birmingham, Birmingham, AL, [3]Department of Medicine, Clinical Immunology & Rheumatology, University of Alabama at Birmingham, Birmingham, AL, [4]Medicine, University of Alabama at Birmingham, Birmingham, AL, [5]Division of Clinical Immunology and Rheumatology, Department of Medicine, University of Alabama at Birmingham, Birmingham, AL, [6]Dept of Med/Rheumatology Div, University of Alabama at Birmingham, Birmingham, AL
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Background/Purpose: The early stage transitional B cell has been shown to be the key peripheral B-cell tolerance control point defect in SLE patients. Anti-RNP Abs can occur before the onset of SLE, but the mechanism underlying tolerance loss to RNPs is unclear. Our previous B cell RNP Ag tetramer analysis indicates abnormal maturation of La_{13-27} epitope reactive transitional T1 B cells in autoimmune BXD2 mice. As B-cell signaling strength and NF-kB p-p65 signaling play an important role in T1 B cell maturation, the purpose of this study was to determine the contribution of elevated IL-17R mediated NF-kp-p65 signaling in autoreactive transitional B cell development.

Methods: Using a La-peptide specific tetramer, La_{13-27} autoreactive B cells from the spleens of B6, autoimmune WT BXD2, and BXD2-*Il17r*$^{-/-}$ mice were analyzed by FACS for the development of $CD93^+$ transitional B cell subsets. T1 B cells were co-transferred into WT vs. BXD2-*Il17r*$^{-/-}$. B cell proliferative responses to anti-IgM and PMA/Ionomycin were determined by the Dojindo assay, and NF-kB p-p65 and p-Tyr levels were determined by phospho-flow.

Results: Tetramer analysis of $CD93^+$ transitional B cells revealed a 2-fold accelerated development of $La_{13-27}{}^+$ T3 transitional spleen B cells ($CD23^-IgM^{hi}$) in BXD2 (38%±5%) compared to that in B6 (18%±3%) mice (n=8, p≤0.01). Interestingly, we have identified that there was mislocalization of $IgM^{hi}CD93^+$ T1 B cells in the follicles of BXD2 mice. However, in normal B6 mice, T1 B cells are located in the peri-follicular region. IL-17R signaling was previously shown to stabilize B-cell retention in the germinal center light zone. Follicular mislocation of T1 B cells was normalized in BXD2-*Il17r*$^{-/-}$ mice. Interestingly, a deficiency in IL17R signaling in BXD2-*Il17r*$^{-/-}$ mice prevented the abnormal maturation of T1 to T3 $La_{13-27}{}^+$ B cells (T3=14±2% vs 38±5%, n=8, p≤0.01). *In vivo* co-transfer of WT and BXD2-*Il17r*$^{-/-}$ into WT or BXD2-*Il17r*$^{-/-}$recipients support a role for IL-17R signaling in transitional B cell development in BXD2 mice. Phospho-flow experiments suggest IL-17R mediated elevated NF-kB p-p65 activation at the T1 stage in BXD2 compared to B6 mice. This elevation was associated with increased protein kinase C (PKC) activation and proliferation in BXD2 B cells stimulated *in vitro* with anti-IgM and PMA/ionomycin (p≤0.01). A deficiency of IL-17R normalized these responses in BXD2-*Il17r*$^{-/-}$ mice.

Conclusion: The present data suggest that follicular exclusion of T1 B cells promotes peripheral tolerance, whereas follicular translocation and retention of T1 B cells promotes maturation. Furthermore, IL-17 can promote NF-kB signaling in T1 B cells that have entered the follicle, bypassing tolerance checkpoint two in BXD2 mice. This provides a mechanistic basis for checkpoint two defects. As anti-La autoAbs can occur before the onset of SLE, these mechanisms may play a key role in initiation of disease.

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Disclosure: J. Hamilton, None; **Q. Wu**, None; **P. Yang**, None; **J. Li**, None; **Y. Ding**, None; **B. Luo**, None; **J. Mountz**, None; **H. C. Hsu**, None.

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Abstract Number: 3157

B Cell Profile As a Biomarker of Disease Segmentation and Flare Prognosis in SLE

Chungwen Wei[1], Bridget Neary[2], Jamie Biear[3], Jennifer Barnard[3,4], Michelle Petri[5], Alex Rosenberg[6], Jennifer H. Anolik[7] and Ignacio Sanz[1], [1]Rheumatology, Emory University, Atlanta, GA, [2]Emory University, Atlanta, GA, [3]Rheumatology, University of Rochester, Rochester, NY, [4]Allergy, Immunology and Rheumatology, University of Rochester, Rochester, NY, [5]Rheumatology, Johns Hopkins University Hospital, Baltimore, MD, [6]University of Rochester, Rochester, NY, [7]University of Rochester Medical Center, Rochester, NY
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Background/Purpose: B cell abnormalities in SLE are well-established contributors to disease pathogenesis. Perturbation of B cell homeostasis in SLE is often described separately for each affected B cell subset independent of others. Such univariate approaches fail to reveal how collections of subsets and their relative distribution might contribute to patient segmentation. Hence, we sought a global B cell profiling approach in conjunction with comprehensive clinical parameters to identify distinct B cell signatures in SLE.

Methods: PBMCs were analyzed by flow cytometry from healthy controls (HC) (n=25) and SLE patients (n=135). B cell subsets were identified using the following markers: IgD, CD19, CD27, CD38, CD24, CXCR3, CD21, CD24, CD95, MitoTracker Green, CD10, IgM, CD23. Patients met ACR criteria for the classification of SLE. Disease activity and flares were measured by SELENA-SLEDAI and PGA. All clinical and experimental data were imported into a database where multivariate clustering methods were used to seek natural divisions based on the B cell profiles and relationship to clinical parameters. Flare incidence was followed in a subset of patients with no active disease at baseline (n=52).

Results: High dimensional multiparameter analysis identifies three major clusters of SLE patients based on the B cell profiles. Cluster 1 is characterized by expansions of $IgD^{-}CD27^{+}$ switched memory (SM), $IgD^{-}CD27^{-}$ double negative (DN) cells and plasmablasts, with a concomitant reduction of $IgD^{+}CD27^{-}$ naïve and transitional (N+T) B cells. Of the expanded SM and DN subsets, cells that exhibit the activated phenotype ($CD21^{-}$, $CD24^{-}$ or $CD95^{+}$) are particularly in abundance. A fine subset analysis of the contracted N+T population further reveals that, in contrary to the reduction of resting naïve B cells, there is a pronounced increase in activated naïve B cells ($IgD^{+}CD27^{-}MTG^{+}CD24^{-}$). This cluster with an activated B cell profile is significantly enriched with patients who present high SLEDAI, multiple autoantibodies and elevated serum IFNa activity, and who are of African descent. In contrast, patients in cluster 3 exhibit a B cell profile that is similar to that of HC and are least likely to present high disease activity. Cluster 2 is exemplified by a greatly expanded N+T subset with moderate expansions of activated SM and DN. To evaluate the application of B cell profiling in predicting future lupus flare, low-SLEDAI, non-flaring patients from each cluster at baseline were followed for flare incidences over a period of two years. Preliminary results show that such patients in clusters 1 and 2 experience shorter time lag to first flare and higher incidence of flares than the counterparts from cluster 3.

Conclusion: A system-wide view of B cell populations provides a means to segment the lupus patients. Significantly, inactive patients with an activated B cell profile appear to have a higher propensity to develop a flare sooner. Our results provide a proof of concept that, when combined with other informative clinical parameters, B cell profiling offers a systems biology approach to identifying potential biomarkers to estimate risk of disease progression and to initiate early treatment that might halt disease progression or improve long-term outcome.

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Abstract Number: 3158

Impact of Family History of Systemic Lupus Erythematosus on Risk of Autoimmune Diseases: National Cohort Study in Denmark 1977-2012

Constance Jensina Ulff-Møller[1], Jacob Simonsen[2], Søren Jacobsen[1] and Morten Frisch[2], [1]Department of Rheumatology, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark, [2]Department of Epidemiology Research, Statens Serum Institut, Copenhagen, Denmark
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Background/Purpose: Systemic lupus erythematosus (SLE) is a complex autoimmune disease (AID), which develops through the interplay of genetic, epigenetic and environmental factors and may cluster within families with other AIDs. Previous studies suggest that 4-12% of SLE patients have a first-degree relative with SLE and 14-27% have a first-, second- or third-degree relative with some AID. However, the relative risk of SLE or other AIDs once a relative has been diagnosed with SLE has so far remained unexamined.

Methods: All Danish citizens born after 1950 and identified through the Civil Registration System were coupled to their relatives through the parental link. Information regarding SLE and other AIDs was obtained through linkage to the National Patient registry. Cohort members were

followed for SLE and other AIDs from 1997-2012 and hazard ratios (HRs) with 95% confidence intervals (CI) were calculated through Cox proportional hazards regression analyses.

Results: The cohort was followed for more than 100 million person-years of follow-up. In that time, 3,612 persons were hospitalized with an SLE diagnosis. During follow-up, 80 first-degree relatives of individuals with SLE developed SLE themselves (HR 10.0, 95% CI 8.0-12.5), while 17 second- or third-degree relatives developed SLE (HR 3.4, 95% CI 2.1-5.5). Overall, first-degree relatives had a slightly increased risk of any AID (HR 1.43, 95% CI 1.30-1.56), which was still significant among second- and third-degree relatives (HR 1.18, 95% CI 1.04-1.34). For rheumatoid arthritis there was a 64% increased risk among first-degree relatives (95% CI 1.35-1.99), but not among second- or third-degree relatives (HR 1.16, 95% CI 0.81-1.65). Furthermore, there was a slightly increased risk of inflammatory bowel disease (HR 1.21, 95% CI 1.02-1.43) and type 1 diabetes mellitus (HR 1.65, 95% CI 1.12-2.42) among first-degree relatives and multiple sclerosis among second- or third-degree relatives (HR 1.62, 95% CI 1.09-2.43).

Conclusion: There is a clearly increased risk of SLE among relatives of SLE patients and to a lesser degree of other AIDs.

Table 1. Hazard ratios with corresponding 95% CIs for delevoping a given AID when a relative has SLE†

		First-degree relatives			Second- and third-degree relatives		
Disease	Family history of SLE	Cases*	HR	95% CI	Cases*	HR	95% CI
Any AID	No	146,176	1	Reference	146,400	1	Reference
	Yes	461	1.43	1.30-1.56	245	1.18	1.04-1.34
SLE	No	3,532	1	Reference	3,595	1	Reference
	Yes	80	10.0	8.04-12.5	17	3.39	2.10-5.48
RA	No	24,803	1	Reference	24,875	1	Reference
	Yes	103	1.64	1.35-1.99	31	1.16	0.81-1.65
AITD	No	28,909	1	Reference	28,951	1	Reference
	Yes	84	1.15	0.93-1.43	42	1.21	0.89-1.64
MS	No	13,946	1	Reference	13,956	1	Reference
	Yes	34	0.98	0.70-1.37	24	1.62	1.09-2.43
IBD	No	49,455	1	Reference	49,493	1	Reference
	Yes	130	1.21	1.02-1.43	92	1.04	0.85-1.27
Psoriasis	No	19,237	1	Reference	19,267	1	Reference
	Yes	57	1.27	0.98-1.64	27	0.97	0.66-1.41
T1DM	No	12,732	1	Reference	12,739	1	Reference
	Yes	26	1.65	1.12-2.42	19	1.08	0.69-1.70

†Analysis restricted to index persons born after January 1, 1950. Adjusted for age, sex, birth cohort and number of relatives in each relation category. First-degree: children, parents, siblings; Second-degree: half-siblings, aunts/uncles, nieces/nephews, grandparents; Third-degree: cousins.

* Based on more than 100 million person-years of follow-up.

Abbreviations: CI, confidence interval; AID, autoimmune disease; SLE, systemic lupus erythematosus; AITD, autoimmune thyroid disease; RA, rheumatoid arthritis; MS, multiple sclerosis; IBD, inflammatory bowel disease; T1DM, type 1 diabetes mellitus.

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Abstract Number: 3159

Systemic Lupus Erythematosus Is a Risk Factor for Young Stroke: A Population-Based Cohort Study

Elizabeth V Arkema[1], Elisabet Svenungsson[2], Christopher Sjöwall[3] and Julia F Simard[4,5], [1]Department of Medicine, Clinical Epidemiology Unit, Karolinska Institutet, Stockholm, Sweden, [2]Department of Medicine, Karolinska Insitutet, Rheumatology Unit, Karolinska University Hospital, Stockholm, Sweden, [3]Department of Clinical and Experimental Medicine, Rheumatology/AIR, Linköping, Sweden, [4]Division of Epidemiology, Health Research and Policy Department, and Division of Immunology & Rheumatology, Department of Medicine, Stanford School of Medicine, Stanford, CA, [5]Clinical Epidemiology Unit, Dept of Medicine, Karolinska Institutet, Stockholm, Sweden

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Background/Purpose: Previous studies indicate that individuals with SLE have a high risk of stroke but have not investigated when the highest risk occurs. We aimed to estimate the risk of ischemic stroke (IS) and hemorrhagic stroke (HS) in SLE compared to the general population by

age, sex, and time since diagnosis.

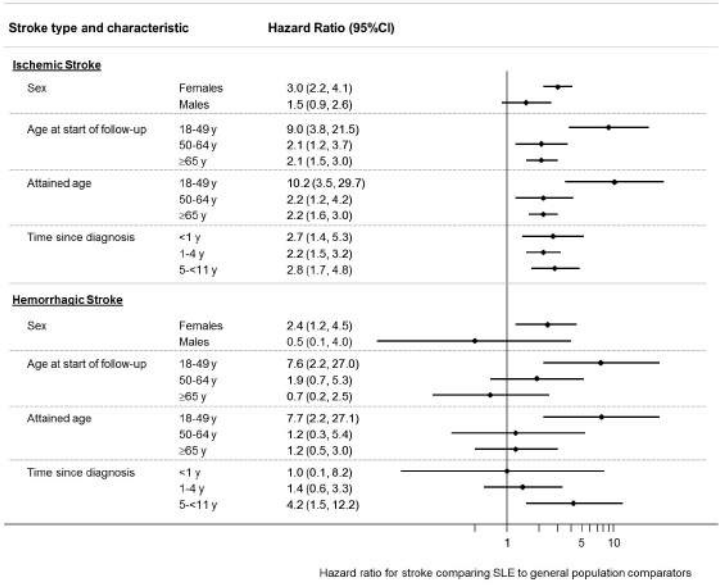
Methods: Adult patients (≥18y) with SLE were identified from the National Patient Register (NPR) to create a population-based and nationwide cohort of individuals with SLE. SLE was defined as ≥2 SLE ICD codes in the inpatient (1969-2013) or outpatient (2001-2013) registers with ≥1 code in a specialist clinic and ≥1 in outpatient care. We included only those who received their first observed SLE ICD code Jan 2003 or later as a proxy for incident SLE. General population comparators were selected from the Total Population Register alive at the SLE patient's estimated diagnosis date (index date) and were matched 5:1 to the SLE population on age, sex, and county. Stroke was identified from the NPR and those with a history of stroke at baseline were excluded. Follow-up was from index date through first of death, stroke, emigration or end of study (Dec 2013). Age- and sex-adjusted Cox models were used to estimate the hazard ratio (HR) for stroke comparing SLE to non-SLE. Models were additionally stratified by sex, age at diagnosis, attained age and time since diagnosis. Effect modification by stratification variables was tested using the likelihood ratio test (LRT). In secondary analyses, we estimated the HR for stroke among individuals with confirmed SLE from two clinical cohorts.

Results: We identified 3 133 individuals with SLE and 15 504 general population comparators. The average age at SLE diagnosis was 49 and 85% were female. We observed 90 strokes in SLE (76 IS, 14 HS) and 198 in the general population (160 IS, 38 HS). The HR for IS comparing SLE to the general population was 2.4 (95%CI 1.9, 3.2) and the HR for HS was 1.9 (95%CI 1.0, 3.5). HRs were higher in analyses using confirmed SLE only (IS 4.2 (95%CI 2.2, 8.0), HS 4.4 (95%CI 1.2, 16.5).

The HR for IS was significantly higher in females than in males (females HR 3.0 (95%CI 2.2, 4.1), males HR 1.5 (95%CI 0.9, 2.6); LRT p=0.01; **Figure**). Younger individuals (18-49y) had the highest risk of stroke (IS HR 10.2 (95%CI 3.5, 29.7), LRT p=0.003; HS HR 7.7 (95%CI 2.2, 27.1), LRT p=0.008). The HR for IS was similar over time since diagnosis whereas the HR for HS was higher the further from diagnosis (LRT p=0.05), although this was based on small numbers.

Conclusion: Individuals with SLE are at high risk of both ischemic and hemorrhagic stroke. The relative risk was especially high in females and below the age of 50. Notably, the risk for IS was high already within the first year of diagnosis and remained constant during the following decade.

Figure. Hazard ratios and 95% confidence intervals for ischemic and hemorrhagic stroke stratified by sex, age and time since diagnosis comparing individuals with SLE to the general population.



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Abstract Number: 3160

Comparative Rates of Serious Infections and All-Cause Mortality Among Systemic Lupus Erythematosus Patients Receiving Mycophenolate Mofetil Versus Azathioprine

Candace H. Feldman[1], Francisco M. Marty[2], Wolfgang C. Winkelmayer[3], Hongshu Guan[4], Jessica M. Franklin[5], Daniel H. Solomon[1],

Seoyoung C. Kim[6] and Karen H. Costenbader[7], [1]Division of Rheumatology, Immunology and Allergy, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, [2]Department of Medicine, Division of Infectious Disease, Brigham and Women's Hospital, Boston, MA, [3]Medicine-Nephrology, Baylor College of Medicine, Houston, TX, [4]Rheumatology, Immunology and Allergy, Brigham and Women's Hospital, Boston, MA, [5]Division of Pharmacoepidemiology and Pharmacoeconomics, Brigham and Women's Hospital, Boston, MA, [6]Div. of Pharmacoepidemiology and Pharmacoeconomics, Div. of Rheumatology, Immunology and Allergy, Brigham and Women's Hospital, Boston, MA, [7]Rheumatology, Immunology and Allergy, Brigham and Women's Hospital, Harvard Medical School, Boston, MA
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SESSION INFORMATION

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Background/Purpose: Patients with systemic lupus erythematosus (SLE) are at high risk of infections partly from use of immunosuppressives (IS). Clinical trials are powered to detect differences in treatment efficacy and therefore the comparative risks of infections are understudied. We compared the rates of hospitalized infection and all-cause mortality among SLE patients receiving mycophenolate mofetil (MMF) vs. azathioprine (AZA), two commonly and often interchangeably used IS. We hypothesized based on prior small studies that MMF users may be at increased risk of infection and death.

Methods: We used Medicaid data from 47 states and Washington, DC, 2000-2006, to identify adults (18-65 years) with ≥2 SLE ICD-9 codes separated by ≥30 days, who were new users of MMF or AZA with no use of either drug in the prior 183 days of continuous Medicaid enrollment. The index date was the first MMF or AZA prescription fill date. We excluded patients with HIV/AIDS or prior organ transplant. We used multivariable logistic regression to calculate propensity scores (PS) for receipt of MMF vs. AZA. Covariates included sociodemographics, year, comorbidities, lupus nephritis, vaccines, healthcare utilization, hydroxychloroquine and other IS use during the 183 days prior to the index date, and cumulative corticosteroid dose during the 60 days prior to the index date. We matched new users of MMF and AZA by PS (1:1) and conducted as-treated (AT) analyses, censoring at drug discontinuation, gaps >30 days, switch to the comparator drug, death, disenrollment or end of follow-up. In secondary intention-to-treat (ITT) analyses, patients were censored at death, disenrollment or end of follow-up. We identified hospitalized infections using a validated algorithm (PPV 80%) and used Cox proportional hazard regression models to estimate hazard ratios (HR) of first infection and death comparing PS-matched new users of MMF and AZA (referent).

Results: We identified 926 PS-matched pairs of MMF and AZA new users with SLE. Characteristics were well balanced: mean age was 34 (SD 11) years, 92% were female, 45% were Black, 25% White and 20% Hispanic. In AT analyses, the incidence rate (IR) of first hospitalized infection per 100 person-years was 13.95 among MMF users and 11.91 among AZA users (**Table**). The hazard ratio of first infection was similar for new MMF vs. AZA users (HR 1.18, 95% CI 0.80-1.75). Mortality rates per 100 person-years were 2.39 among MMF users and 1.74 among AZA users (HR 1.39, 95% CI 0.53-3.65). Findings of secondary ITT analyses were similar to the AT analyses with no significant differences between groups.

Conclusion: In this large, diverse cohort of SLE patients, while the rates of hospitalized infection and all-cause mortality were marginally higher among MMF vs. AZA new users, there were no significant differences. Further studies are needed to determine whether there are differences in other relevant safety outcomes.

Table. Propensity Score-Matched* Analyses of First Hospitalized Infection and All-Cause Mortality among SLE New Users of Mycophenolate mofetil (MMF) vs. Azathioprine (AZA)									
		Mycophenolate Mofetil (N=926)				Azathioprine (N=926)			
Analysis**	Outcome	Events	Person-years	IR+ (95% CI)	HR++ (95% CI)	Events	Person-years	IR+ (95% CI)	HR++
As treated (AT)	First infection	56	401.5	13.95 (13.83-14.07)	1.18 (0.80-1.75)	46	386.3	11.91 (11.80-12.02)	Ref
	Death	10	417.8	2.39 (2.35-2.44)	1.39 (0.53-3.65)	7	402.8	1.74 (1.70-1.78)	Ref
Intention-to-treat (ITT, 183 days)	First infection	79	401.7	19.67 (19.52-19.81)	1.13 (0.82-1.56)	70	402.1	17.41 (17.27-17.54)	Ref
	Death	15	421.6	3.56 (3.50-3.62)	1.06 (0.51-2.2)	14	418.9	3.34 (3.29-3.40)	Ref
Intention-to-treat (ITT, 365 days)	First infection	116	690.8	16.79 (16.69-16.89)	1.25 (0.96-1.64)	93	694.8	13.39 (13.30-13.48)	Ref
	Death	18	748.3	2.41 (2.37-2.44)	0.94 (0.49-1.79)	19	742.6	2.56 (2.52-2.60)	Ref

*Propensity scores included age, sex, race/ethnicity, US region, SLE comorbidity index (Ward MM, 2000), comorbidities, lupus nephritis, number of SLE and renal-related laboratory tests, number of medications, immunosuppressive use, 60-day cumulative corticosteroid dose, NSAID use, healthcare utilization, vaccinations, and calendar year

**Mean follow-up for AT infection analysis was 0.43 (SD 0.53) person-years, for ITT (183 days) 0.43 (SD 0.13) person-years and for ITT (365 days) 0.75 (SD 0.33) person-years

+ IR is the incidence rate per 100 for first hospitalized infection and for all-cause death

++ HR is the hazard ratio calculated using Cox proportional hazard regression models of propensity score-matched MMF vs. AZA new users

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Abstract Number: 3161

Rates of Hospitalization for Infection and Related Mortality By Race/Ethnicity and Sex Among Patients with End-Stage Renal Disease Due to Systemic Lupus Erythematosus

Candace H. Feldman[1], Francisco M. Marty[2], Wolfgang C. Winkelmayer[3], Hongshu Guan[4], Jessica M. Franklin[5], Seoyoung C. Kim[6], Daniel H. Solomon[7] and Karen H. Costenbader[8,9], [1]Division of Rheumatology, Immunology and Allergy, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, [2]Department of Medicine, Division of Infectious Disease, Brigham and Women's Hospital, Boston, MA, [3]Medicine-Nephrology, Baylor College of Medicine, Houston, TX, [4]Rheumatology, Immunology and Allergy, Brigham and Women's Hospital, Boston, MA, [5]Division of Pharmacoepidemiology and Pharmacoeconomics, Brigham and Women's Hospital, Boston, MA, [6]Medicine, Division of Rheumatology, Division of Pharmacoepidemiology, Brigham & Women's Hospital, Boston, MA, [7]Division of Pharmacoepidemiology, Harvard Medical School, Brigham and Women's Hospital, Division of Rheumatology, Division of Pharmacoepidemiology, Boston, MA, [8]Rheumatology, Brigham & Women's Hospital, Boston, MA, [9]Rheumatology, Immunology and Allergy, Brigham and Women's Hospital,

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Background/Purpose: Infections are a significant cause of morbidity and mortality in SLE patients. Recent studies show that lupus nephritis patients have more than two-fold higher incidence of serious infections than the overall SLE population. We investigated the burden of hospitalized infections and related mortality among patients with SLE-related end-stage renal disease (ESRD).

Methods: We used the US Renal Data System, the national registry of ESRD patients, 1995-2008, to identify adults ≥18 years with ESRD due to SLE as recorded by nephrologists on the Medical Evidence Report. We ascertained age, sex, race/ethnicity, region, comorbidities, prior insurance, and dialysis type at ESRD onset. For patients with Medicare Parts A and B coverage beginning 90 days following ESRD onset, we used linked claims to determine hospitalizations for infection from primary discharge diagnosis ICD-9 codes. We calculated mortality due to infection, as documented on the ESRD Death Notification Form, among patients with SLE-related ESRD regardless of Medicare coverage. We calculated incidence rates (IR) of first hospitalization for infection after ESRD onset, and mortality due to infection. We used multivariable Cox proportional hazard regression to determine the hazard ratio (HR) of first hospitalized infection and mortality from infection by race/ethnicity and sex, adjusting for demographics, comorbidities, and dialysis type.

Results: We identified 12,533 patients with SLE-related ESRD and 6,064 with linked Medicare claims. The mean age for the linked cohort was 41.8 years (SD 16.5), 81% were female, 52.4% Black, 42.3% White, and 4.2% Asian, and 15.2% were Hispanic. Mean follow-up was 4.0 years (SD 3.3). The majority (84%) received hemodialysis. The IR of first hospitalization for infection after ESRD onset was 25.9 per 100 person-years. In adjusted models, the risk was lower among males compared to females (HR 0.83, 95% CI 0.76-0.91) and higher among Blacks (HR 1.16, 95% CI 1.11-1.27) and Native Americans (HR 1.40, 95% CI 1.04-1.88) compared to Whites. The risk of infection was higher among patients receiving peritoneal dialysis compared to hemodialysis (HR 1.19, 95% CI 1.07-1.32). Among all patients with SLE-related ESRD, there were 4,428 deaths; 865 (19.5%) were from infection, the majority from septicemia (79.9%). Infection-related mortality was 1.77 per 100 person-years, significantly higher among Blacks compared to Whites (HR 1.20, 95% CI 1.02-1.42), and not statistically different for other racial/ethnic groups or by sex.

Conclusion: In this cohort of patients with SLE-related ESRD, we observed a high burden of hospitalization for infection and related mortality with similar infection rates to pre-ESRD lupus nephritis patients. Female, Black and Native American patients were at increased risk of infection. Further studies are needed to compare these rates to non-SLE patients with ESRD.

Table. Incidence Rates and Adjusted Hazard Ratios of First Hospitalized Infection* among patients with SLE-Related End-stage Renal Disease and Medicare Parts A and B				
	Events	**Person-years**	**IR** ** **(95% CI)**	**HR**+ **(95% CI)**
Overall (N=6064)	3496	13498.1	25.9 (25.1-26.7)	--
Sex				
Female	2913	10762.3	27.1 (26.1-28.1)	Ref.
Male	583	2735.8	21.3 (19.6-23.1)	**0.83 (0.76-0.91)**
Race/Ethnicity				
White	1344	5710.0	23.5 (22.3-24.8)	Ref.
Black	1982	6964.9	28.4 (27.2-29.7)	**1.16 (1.11-1.27)**
Asian	123	694.3	17.7 (14.8-21.1)	0.88 (0.72-1.07)
Native American	47	129.0	36.4 (27.4-48.5)	**1.40 (1.04-1.88)**
Hispanic Ethnicity				
Hispanic	531	2299.0	23.1 (21.2-25.1)	1.01 (0.90-1.13)
Non-Hispanic	2965	11199.1	26.4 (25.5-27.4)	Ref.

*Primary discharge diagnosis with ICD-9 code for bacterial, viral, fungal or opportunistic infection (Schneeweiss et al. J Clin Epidemiol. 2007)

**Incidence rate of first hospitalized infection per 100 person-years

+Hazard ratios from Cox proportional hazard regression models adjusted for age group, sex, race/ethnicity, US region, insurance status prior to ESRD, baseline comorbidities including hypertension, smoking, diabetes, coronary artery disease, cerebrovascular disease, cancer, and COPD, renal replacement therapy, and calendar year

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Disclosure: C. H. Feldman, None; **F. M. Marty**, None; **W. C. Winkelmayer**, None; **H. Guan**, None; **J. M. Franklin**, None; **S. C. Kim**, Pfizer Inc, 2,AstraZeneca, 2,Lilly, 2,Genentech and Biogen IDEC Inc., 2; **D. H. Solomon**, None; **K. H. Costenbader**, None.

Abstract Number: 3162

Prevalence of Chronic Comorbidities in Patients with Rheumatoid Arthritis, Psoriatic Arthritis, Ankylosing Spondylitis and Systemic Lupus Erythematosus: An Analysis of UK Biobank Data

Eftychia Bellou[1], Michael Cook[2], John Bowes[1], Jamie C Sergeant[3], Anne Barton[4], Terence W. O'Neill[2] and Suzanne M.M. Verstappen[2], [1]Arthritis Research UK Centre for Genetics and Genomics, The University of Manchester, Centre for Musculoskeletal Research, Manchester,

United Kingdom, [2]Arthritis Research UK Centre for Epidemiology, The University of Manchester, Centre for Musculoskeletal Research, Manchester, United Kingdom, [3]Arthritis Research UK Centre for Epidemiology, Centre for Musculoskeletal Research, Manchester Academic Health Science Centre, University of Manchester, Manchester, United Kingdom, [4]The Kellgren Centre for Rheumatology, Central Manchester Foundation Trust, NIHR Manchester Biomedical Research Centre, Manchester, United Kingdom

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Background/Purpose: Rheumatoid arthritis (RA), psoriatic arthritis (PsA), ankylosing spondylitis (AS) and systemic lupus erythematosus (SLE) are immune-mediated disorders and are associated with a number of comorbidities, including cardiovascular disease. However, reported rates may depend on study design, control population and exposure data. The aim of this study was to assess the rate of comorbidities in patients with RA, PsA, AS and SLE compared to the general population without these rheumatological conditions using data from a large national study.

Methods: This study was conducted using UK Biobank data from over 500,000 people aged 40-70 years in the UK. At entry, participants completed a touchscreen questionnaire on lifestyle, sociodemographics, and health and medical history, followed by a verbal interview with a research nurse. Health history questions captured the occurrence of cardiovascular, pulmonary, allergic and metabolic comorbidities (Table 2). Patients reporting non-specific arthritis were excluded from the total population. Indirect standardization was used to adjust the comorbidity prevalence rates in each of the four rheumatological populations separately (i.e. RA, PsA, AS, SLE) using the age and gender rates in the population without these conditions. The Standardized Incidence Ratios (SIR) were estimated by dividing the observed number of comorbidity events by the "expected" number of events.

Results: 498,611 participants were included in this study, cohort characteristics are summarised in Table 1. The incidence rates of all cardiovascular diseases were significantly higher in the RA and SLE population compared to the general population. Although not significant, similar trends were observed for the AS and PsA population. Rates of allergies were similar between the populations with rheumatological conditions and those observed in the general population without these conditions. Moreover, the incidence rate of emphysema was significantly higher in all populations with rheumatological compared to the general population. Finally, the rate of diabetes in RA patients was higher compared to the general population. However, this was not observed in the other rheumatological conditions (Table 2).

Conclusion: In this cross-sectional study, prevalence rates of cardiovascular diseases and lung disorders are especially increased in people with RA, AS and SLE. This study is unique in that it captures morbidities in a similar way across several rheumatic conditions in a large national-based study.

Table 1

	PsA	AS	RA	SLE	General Population
n	892/498,611	1,314/498,611	5,533/498,611	587/498,611	490,285/498,611
(%)	0.18	0.26	1.11	0.12	98.33
Age, mean(sd)	56.2 (7.4)	57.5 (7.5)	59.3 (7.1)	55.4 (8.1)	56.5 (8.1)
males (%)	48.5	62.8	30.2	10.7	45.8
Ethnicity (white background) (%)	97.2	96.6	94.3	86.2	94.1
Current smokers (%)	10.3	14.7	12.7	12.4	10.5

Table 2

Comorbidities	PsA			AS			RA			SLE		
	crude rate (%)	SIR	C.I. (95%)	crude rate (%)	SIR	C.I. (95%)	crude rate (%)	SIR	C.I. (95%)	crude rate (%)	SIR	C.I. (95%)
Cardiovascular:												
Heart attack	2.9	1.27	0.83-1.87	4.0	1.34	1.00-1.75	4	1.86	1.63-2.13	3.6	3.35	2.07-5.11
Angina	4.7	1.50	1.08-2.03	3.2	1.34	1.04-1.69	6.3	1.87	1.68-2.08	6.0	2.94	2.05-4.09
Stroke	1.5	0.97	0.52-1.67	2.6	1.47	1.02-2.05	2.9	1.78	1.51-2.07	6.0	5.21	3.63-7.25
Hypertension	38.6	1.43	1.28-1.59	34.4	1.17	1.06-1.28	36.1	1.24	1.19-1.30	33.4	1.42	1.23-1.63
Pulmonary:												
Emphysema/ chronic bronchitis	2.5	1.54	0.97-2.34	4.2	2.37	1.78-3.08	4.4	2.48	2.18-2.81	3.2	2.28	1.37-3.56
Asthma	10.7	0.91	0.74-1.11	10.8	0.96	0.80-1.13	15.5	1.33	1.24-1.42	13.6	1.10	0.87-1.37
Allergies:												
Hay fever, eczema or allergic rhinitis	28.8	1.19	1.05-1.34	24	1.04	0.93-1.16	23.1	0.98	0.93-1.04	27.9	1.07	0.91-1.24
Metabolic:												
Diabetes	6.4	1.22	0.93-1.58	6.2	1.04	0.83-1.29	7.8	1.49	1.35-1.63	5.3	1.35	0.92-1.92

Verstappen, None.

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Abstract Number: 3163

The Smoking Paradox in the Development of Psoriatic Arthritis Among Psoriasis Patients

Uyen Sa D.T. Nguyen[1], Yuqing Zhang[2], Na Lu[3], Qiong Louie-Gao[4], Jingbo Niu[5], David T. Felson[5], Michael P. Lavalley[6], Thorvardur Love[7,8], Maureen Dubreuil[4], Jeffrey A. Sparks[9], Elizabeth W. Karlson[10] and Hyon K. Choi[3], [1]Orthopedics & Physical Rehabilation, Univerity of Massachusetts Medical School, Worcester, MA, [2]Clinical Epidemilogy and Training Unit, Boston University School of Medicine, Boston, MA, [3]Rheumatology, Allergy and Immunology, Massachusetts General Hospital, Harvard Medical School, Boston, MA, [4]Boston University School of Medicine, Boston, MA, [5]Clinical Epidemiology Research and Training Unit, Boston University School of Medicine, Boston, MA, [6]Biostatistics, Boston University, Boston, MA, [7]Rheumatology, Immunology and Allergy, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, [8]Faculty of Medicine, University of Iceland, Reykjavik, Iceland, [9]Division of Rheumatology, Immunology, and Allergy, Brigham & Women's Hospital, Boston, MA, [10]Rheumatology, Brigham & Women's Hospital, Boston, MA

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Background/Purpose: Smoking is a strong risk factor of psoriasis, but a previous study has suggested that smoking protects against the development of psoriatic arthritis (PsA) among psoriasis (PsO) patients. These paradoxical findings occur because of two possibilities. First, a type of selection bias called index event bias arises from selecting a group of patients (e.g. PsO) on the causal pathway (e.g., between smoking and PsA). Second, the causal net effect (**i.e.,** *total effect*) of smoking cannot be validly estimated using conventional methods **(Figure a)**. We sought to evaluate the impact of smoking on the risk of PsA among PsO patients (index population), and clarify the paradox using a counterfactual mediation analysis.

Methods: We used 1995-2015 data from The Health Improvement Network (THIN), an electronic medical records database representative of the UK general population. We analyzed data from adults (age ≥ 20 years), free of PsO and PsA after at least 1 year of enrollment into the THIN database, and with available data on factors of interest. Follow-up began with first record of smoking status (exposure) after the 1-year enrollment period and ended at time of PsA diagnosis, death, disenrollment in THIN, or the end of the study period, whichever came first. Using Cox regression, we assessed the effect of smoking on incident PsA in the general population, and restricting on incident PsO patients. We then clarified the paradox using marginal structural models (MSM) for mediation analysis to partition the total effect of smoking on PsA into its *indirect effect* (via its effect on PsO) and its *direct effect* not through PsO. All analyses were adjusted for known confounders.

Results: There were ~3.7 million subjects without PsO and PsA at baseline (mean age 47 years; 54% females; 27% current smokers, and 20% ex-smokers). Of those, 46,372 developed incident PsO of which 715 developed incident PsA. The adjusted hazard ratio (HR) for smoking and the risk of PsA among PsO patients was 0.85 (95%CI: 0.70, 1.04), but the corresponding HR for PsA in the general THIN population was 1.19 (95%CI: 1.06, 1.33) (**Table**). Using MSM, the *indirect effect* of current smoking compared with non-smoking on risk of PsA was 1.20 (95%CI: 1.12, 1.28); the *direct effect* was 0.99 (95%CI: 0.92, 1.06) and the *total effect* was 1.19 (95%CI: 1.06, 1.33) (**Table**).

Conclusion: We showed that conditioning on PsO can reverse the association between smoking and PsA, and that the effect of smoking on the risk of PsA may be mediated almost entirely through smoking's effect on PsO. Conditioning on an index event may bias conclusions about the contribution of modifiable risk factors; therefore investigators should consider study designs that are free of such bias **(Figure b,** analysis assessing the impact of exposure status change or analogous randomized trials in the index population).

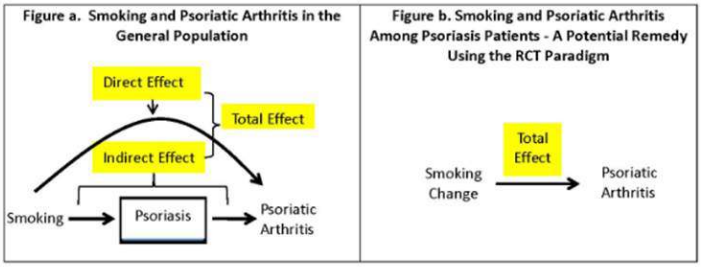

Table 1. Association between SMOKING and Psoriatic Arthritis in the General Population and Among PsO Patients

	Non-Smokers	Ex-smokers	Current Smokers
General THIN Population	**N=1,992,303**	**N=738,128**	**N=1,031,399**
Number of PsA	1047	460	657
Total Follow-up Years	12,437,166	4,453,108	6,470,374
PsA Incidence Rate (1/1000 person-yr)	0.08	0.10	0.10
Crude HR	1.0	1.24 (1.10, 1.40)	1.21 (1.09, 1.35)
*Adjusted HR**	*1.0*	*1.27 (1.12, 1.44)*	*1.19 (1.06, 1.33)*
Among PsO Patients	**N=19,417**	**N=10,126**	**N=16,829**
Number of PsA	312	159	244
Total Followup Years	92,160	48,228	81,236
PsA Incidence Rate (1/1000 person-yr)	3.39	3.30	3.00
Crude HR	1.0	0.98 (0.80, 1.21)	0.89 (0.74, 1.06)
*Adjusted HR**	*1.0*	*1.04 (0.83, 1.29)*	*0.85 (0.70, 1.04)*

Partitioning of the Total Effect of Smoking on the Risk of Psoriatic Arthritis (Counterfactual Mediation Analysis)

	Non-Smokers	Ex-smokers	Current Smokers
*Total Effect**	*1.00 (Ref)*	*1.27 (1.12 to 1.44)*	*1.19 (1.06 to 1.33)*
*Indirect Effect**	*1.00 (Ref)*	*1.09 (1.02 to 1.17)*	*1.20 (1.12 to 1.28)*
*Direct Effect**	*1.00 (Ref)*	*1.16 (1.07 to 1.25)*	*0.99 (0.92 to 1.06)*

*Adjusting for age, sex, baseline body mass index , baseline alcohol intake, history of trauma

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Abstract Number: 3164

Calcium Pyrophosphate Deposition Disease and Associated Medical Co-Morbidities in the Veteran Population

Crystal Kleiber Balderrama[1], Daniel S. Lans[2], Ann K. Rosenthal[1,3] and Christie M. Bartels[4], [1]Division of Rheumatology, Medical College of Wisconsin, Milwaukee, WI, [2]Clement J. Zablocki Veterans Affairs Medical Center, Milwaukee, WI, [3]Division of Rheumatology, Clement J. Zablocki Veterans Affairs Medical Center, Milwaukee, WI, [4]Medicine, Rheumatology, University of Wisconsin School of Medicine and Public Health, Madison, WI

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SESSION INFORMATION

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Session Title: Metabolic and Crystal Arthropathies II: Mechanisms and Associations

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Title: Calcium Pyrophosphate Deposition Disease and Associated Medical Co-Morbidities in the Veteran Population.

Background/Purpose: Precipitation of calcium pyrophosphate dihydrate (CPP) crystals in articular tissues results in a variety of clinical presentations collectively called CPP crystal deposition disease (CPPD). The cause of CPPD remains unknown and no evidence-based treatments are available. Some risk factors for CPPD have been identified including aging, prior joint trauma, and various metabolic conditions. The objective of this study was to identify patient characteristics and medical conditions associated with CPPD in the veteran population using

data from the Veteran Affairs' (VA) Corporate Data Warehouse using previously validated ICD-9 codes.

Methods: This cross-sectional case control study included patients seen at any VA medical center from 2010 through 2014 with ICD-9 codes for CPPD. Cases were age-matched with a control population that also received care at a VA facility in the same time frame and lacked ICD-9 codes for CPPD. Prevalences of various co-morbidities were examined in each cohort. Univariate odds ratios were computed to examine the association between CPPD and each condition.

Results: A total of 54,564 (27,282 CPPD cases; 27,282 Controls) patients were included (Table 1). The conditions having the strongest associations with CPPD included osteoarthritis (OR, 3.71; CI, 3.58 to 3.85), gout (OR, 3.11; CI, 2.97 to 3.26), hyperparathyroidism (OR, 4.31; CI, 3.76 to 4.94), rheumatoid arthritis (OR, 3.43; CI, 3.13 to 3.75), and hemochromatosis (OR, 2.29; CI, 1.86 to 2.81). Hypothyroidism, hypomagnesemia, diabetes, and chronic kidney disease did not appear to be associated with the disease. Knee, shoulder, and hip arthroplasties were more common in the CPPD cohort.

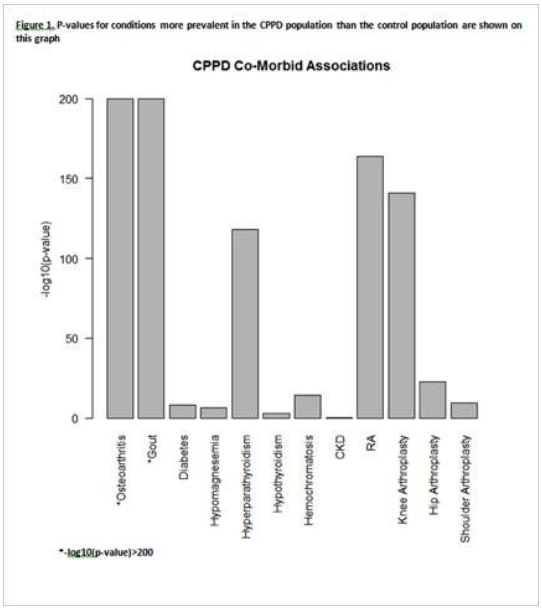
Conclusion: This data set contains the largest study population of CPPD patients examined to date. We confirm known disease associations with conditions such as osteoarthritis, gout, hemochromatosis, and hyperparathyroidism. Interestingly, there was not a significant association between CPPD and hypothyroidism, chronic kidney disease, or diabetes, and the difference in rates of hypomagnesemia was not statistically significant. In contrast, an interesting association with rheumatoid arthritis was noted which could reflect diagnostic mimicry or concomitant disease. CPPD patients also had higher rates of total joint replacements, particularly for knee arthroplasty. We anticipate that this data set could shed additional light on this understudied disease.

Table 1. CPPD Co-Morbid Conditions and Odds Ratios

Condition	Prevalence in CPPD patients n=27,282	Prevalence in Controls n=27,282	Odds Ratio (95% CI)
Osteoarthritis	20,146 (73.8%)	11,785 (43.2%)	3.71 (3.58 to 3.85)**
Gout	7,265 (26.6%)	2,849 (10.4%)	3.11 (2.97 to 3.26)**
Diabetes	10,065 (36.9%)	10,518 (38.6%)	0.93 (0.90 to 0.96)
Hypomagnesemia	1,078 (3.9%)	877 (3.2%)	1.24 (1.13 to 1.36)
Hyperparathyroidism	1,090 (4%)	261 (1.0%)	4.31 (3.76 to 4.94)**
Hypothyroidism	3,671 (13.5%)	3,522 (12.9%)	1.05 (1.00 to 1.10)
Hemochromatosis	300 (1.1%)	132 (0.48%)	2.29 (1.86 to 2.81)*
CKD/ESRD	1,898 (7.0%)	1,852 (6.8%)	1.03 (0.96 to 1.10)
RA	2,025 (7.4%)	624 (2.3%)	3.43 (3.13 to 3.75)**
Knee Arthroplasty	2,440 (8.9%)	944 (3.5%)	2.74 (2.54 to 2.96)**
Hip Arthroplasty	979 (3.6%)	559 (2.1%)	1.78 (1.60 to 1.98)*
Shoulder Arthroplasty	202 (0.7%)	77 (0.3%)	2.64 (2.03 to 3.43)*

*P<$1x10^{-10}$
**P < $1x10^{-100}$

Figure 1. P-values for conditions more prevalent in the CPPD population than the control population are shown on this graph



Disclosure: C. Kleiber Balderrama, None; **D. S. Lans**, None; **A. K. Rosenthal**, None; **C. M. Bartels**, Pfizer Inc, 2.

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Abstract Number: 3165

Do Omega-3 Fatty Acids Reduce Risk of Recurrent Gout Attacks?

MaryAnn Zhang[1], Yuqing Zhang[2], Robert Terkeltaub[3], Clara Chen[4] and Tuhina Neogi[2], [1]Internal Medicine, Boston University School of Medicine, Boston, MA, [2]Boston University School of Medicine, Boston, MA, [3]Medicine-Rheumatology, VA Medical Ctr/University of California San Diego, San Diego, CA, [4]Boston University School of Public Health, Boston, MA
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Background/Purpose:

Current guidelines for gout management, based in part on epidemiologic data for development of incident gout, recommend limiting intake of high-purine fish. However, fatty fish also contain omega-3 polyunsaturated fatty acids (ω-3 FA), which have been shown to have multiple anti-inflammatory effects including reduction of NSAID consumption, morning stiffness, and tender joint counts in rheumatoid arthritis, particularly in early disease. ω-3 FA are known to suppress activation of the NLRP3 inflammasome in vitro in macrophages, and limit experimental IL-1beta mediated inflammatory responses in vivo. Since gouty inflammation is driven by NLRP3 inflammasome-mediated IL-1beta release, we assessed whether ω-3 FA intake is associated with reduction of acute flares in gout.

Methods:

We used data from the Boston University Online Gout Study, an internet-based, case-crossover study conducted from 2003-2012. Each subject acted as his or her own control, allowing for elimination of between-person differences. All subjects were recruited online and had to report at least one gout attack in the prior year, with diagnosis confirmed by medical record review. Participants logged on to the study website at times of gout attacks (hazard periods) and every 3 months for 1 year during gout flare-free periods (control periods) to complete questionnaires regarding exposures (including over-the-counter medications, supplements, and diet) during the 24 and 48 hours preceding the attack or control period. We examined the relation of self-reported ω-3 FA-rich supplements and fish intake in the prior 48 hours to the risk of recurrent gout attacks using conditional logistic regression, adjusting for alcohol and total purine intake, and urate-lowering or flare prophylactic medications (allopurinol, NSAIDs, colchicine).

Results:

Of the 724 participants who experienced ≥ 1 gout attack during the study period and completed ≥1 control period questionnaire, 85% met the 1977 Preliminary ACR classification criteria for acute gout. In the 48 hours prior to attack, 22% of participants reported some form of FA consumption. Of those, 4.6% reported use of supplements (i.e., “fish oil” supplements, “ω-3 FA” supplements, or “cod liver oil” supplements) and 19% was from dietary fish. The adjusted odds ratios (aOR) were 1.01 (95% CI, 0.63-1.60) for all three supplement types combined and 0.77 (95% CI, 0.61-0.96; p=0.02) for ≥1 ω-3 FA-rich fish servings, respectively (**Table**). For any ω-3 FA-rich supplements or fish combined, the aOR was 0.78 (95% CI, 0.63-0.97; p=0.02).

Conclusion:

Dietary ω-3 FA-rich fish consumption had a protective effect for recurrent gout attacks in the community, whereas ω-3 FA supplementation alone, as taken in a self-directed manner, did not. Consumption of specific sources of ω-3 FA for gout flare prevention warrants further study in an adequately powered clinical trial.

Table 1. Association of ω-3 FA-rich Supplements and Fish with Risk of Recurrent Gout Attacks.

Exposure over 48 hours	Control Periods	Case Periods	Adjusted OR* (95% CI)	p-value
ω-3 FA-rich Supplements (any of the three):**				
Not consumed	1830	1362	1.0 (ref)	0.98
Consumed	117	72	1.01 (0.63-1.60)	
ω-3 FA-rich Fish:				
0 servings	1564	1123	1.0 (ref)	
≥1 servings	383	311	0.77 (0.61-0.96)	0.02

*adjusted for alcohol and total purine intake, and urate-lowering or flare prophylactic medications (allopurinol, NSAIDs, colchicine)

**supplements: “fish oil”, “cod liver oil”, “omega-3 fatty acids”

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Abstract Number: 3166

Epistatic Interaction of Functional Inflammasome Genetic Variants in Determining the Risk of Gout

Tony R. Merriman[1], Lisa K. Stamp[2], Nicola Dalbeth[3], Ruth Topless[4], Richard Day[5], Diluk Kannangara[5], Kenneth Williams[5], Matthijs Janssen[6], Tim Jansen[7], Leo A. Joosten[8], Timothy Radstake[9], Philip L. Riches[10], Anne-Kathrin Tausche[11], Frederic Lioté[12], Alex So[13,14] and Cushla McKinney[4], [1]Biochemistry Dept, PO Box 56, University of Otago, Dunedin, New Zealand, [2]Medicine, University of Otago, Christchurch, Christchurch, New Zealand, [3]Department of Medicine, University of Auckland, Auckland, New Zealand, [4]University of Otago, Dunedin, New Zealand, [5]University of New South Wales, Sydney, Australia, [6]Rheumatology Dept, Ziekenhuis Rijnstate, Arnhem, Netherlands, [7]P O Box 581, Haarlem, Netherlands, [8]Department of Medicine, Radboud University Nijmegen Medical Centre, Nijmegen, Netherlands, [9]Radboud University Nijmegen Medical Centre, Nijmegen, Netherlands, [10]Centre for Genomic and Experimental Medicine, Western General Hospital, Edinburgh, United Kingdom, [11]Medizinische Klinik und Poliklinik III, Universitätsklinikum Carl Gustav Carus an der Technischen Universität Dresden, Dresden, Germany, [12]Rheumatology Department; Inserm UMR-S606; Paris-Diderot University, hôpital Lariboisiere, Paris, France, [13]Service De Rhumatologie, CHUV, Lausanne, Switzerland, [14]Department of Rheumatology, CHUV, Lausanne, Switzerland
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Background/Purpose: The acute gout flare results from a localised self-limiting innate immune response to monosodium urate (MSU) crystals deposited in joints in hyperuricaemic individuals. Activation of the inflammasome and secretion of IL-1b by immune cells plays a key role in triggering clinical inflammation. Genome-wide association studies have yielded insights into genetic control of the cause of hyperuricaemia. However very little is known about genetic control of the innate immune response involved in acute gouty arthritis. Therefore our aim was to test functional single nucleotide polymorphism (SNP) variants in the toll-like receptor (TLR)-inflammasome-IL1b axis for association with gout.

Methods: 1,494 cases of European ancestry and 863 cases of New Zealand (NZ) Polynesian (Māori and Pacific Island) ancestry. All people with gout fulfilled the 1977 ARA gout classification criteria. There were 1,030 Polynesian controls and 10,942 European controls from the publically-available Atherosclerosis Risk in Communities (ARIC) and Framingham Heart (FHS) studies. The eleven SNPs were genotyped by Sequenom MassArray in the gout cases and either genotyped by Affymetrix SNP array or imputed in the ARIC and FHS datasets. Allelic association was done by logistic regression adjusting by age and sex with European and Polynesian data combined by meta-analysis. Sample sets were pooled for epistatic interaction analysis, which was also adjusted by sample set.

Results: Eleven SNPs were tested in the *TLR2*, *CD14*, *IL1B*, *CARD8*, *NLRP3*, *MYD88*, *P2RX7*, *DAPK1* and *TNXIP* genes. Nominally significant ($P<0.05$) associations with gout were detected at *CARD8 rs2043211* (OR=1.12, $P=0.007$, risk allele T) *IL1B rs1143623* (OR=1.10, $P=0.020$, risk allele G) and *CD14 rs2569190* (OR=1.08; $P=0.036$, risk allele A). There was significant epistatic interaction between *CARD8* and *IL1B* ($P=0.005$) (Table), with the *IL1B* risk genotype amplifying the risk effect of *CARD8*.

Conclusion: There is evidence for association of gout with functional immune system variants in *CARD8, IL1B* and *CD14*. The gout-associated allele of *IL1B* increases expression of IL1-b – the epistatic interaction with *CARD8* would be consistent with a biological scenario of the amount of pro-IL1-b limiting the amount of mature IL1-b generated in stimulatory conditions.

Table Genotype combinations of *IL1B rs1143623* and *CARD8 rs2043211*

Combination	Cases (n, %)	Controls (n,%)	OR [95% CI]	*P*
CC/AA	430 (0.174)	2,821 (0.236)	1.00	
CC/AT	488 (0.197)	2,740 (0.229)	1.13 [0.96-1.32]	0.16
CC/TT	136 (0.055)	644 (0.054)	1.26 [0.99-1.62]	0.066
CG/AA	390 (0.157)	2,182 (0.182)	1.10 [0.92-1.31]	0.28
CG/AT	495 (0.200)	1,979 (0.165)	1.48 [1.25-1.75]	$4.3x10^{-6}$
CG/TT	162 (0.065)	575 (0.048)	1.74 [1.36-2.22]	$8.7x10^{-6}$
GG/AA	112 (0.045)	425 (0.036)	1.33 [1.00-1.77]	0.049
GG/AT	166 (0.067)	465 (0.039)	1.61 [1.25-2.07]	$2.0x10^{-4}$
GG/TT	100 (0.040)	147 (0.012)	3.77 [2.65-5.34]	$<1.0x10^{-6}$

Disclosure: T. R. Merriman, None; **L. K. Stamp**, None; **N. Dalbeth**, None; **R. Topless**, None; **R. Day**, None; **D. Kannangara**, None; **K. Williams**, None; **M. Janssen**, None; **T. Jansen**, None; **L. A. Joosten**, None; **T. Radstake**, None; **P. L. Riches**, Menarini, 2; **A. K. Tausche**, None; **F. Lioté**, None; **A. So**, None; **C. McKinney**, None.

Abstract Number: 3167

Association of the Apolipoprotein A1-C3-A4 Gene Cluster with the Risk of Gout: Evidence for a Causal Role in Gout

Tony R. Merriman[1], Amanda Phipps-Green[2], Ruth Topless[2], Malcolm D. Smith[3], Catherine Hill[4], Susan Lester[4], Maureen Rischmueller[5], Matthijs Janssen[6], Tim Jansen[7], Leo A. Joosten[8], Timothy Radstake[9], Philip L. Riches[10], Anne-Kathrin Tausche[11], Frederic Lioté[12], Alex So[13,14], Andre M. van Rij[2], Gregory T. Jones[15], Sally McCormick[16], Andrew Harrison[2], Lisa K. Stamp[17], Nicola Dalbeth[18] and Humaira Rasheed[16], [1]Biochemistry Dept, PO Box 56, University of Otago, Dunedin, New Zealand, [2]University of Otago, Dunedin, New Zealand, [3]Rheumatology, Repatriation General Hospital, Adelaide, Australia, [4]Rheumatology Unit, The Queen Elizabeth Hospital, Woodville, Australia, [5]Rheumatology, Queen Elizabeth Hospital, Adelaide, Australia, [6]Rheumatology Dept, Ziekenhuis Rijnstate, Arnhem, Netherlands, [7]P O Box 581, Haarlem, Netherlands, [8]Department of Medicine, Radboud University Nijmegen Medical Centre, Nijmegen, Netherlands, [9]Radboud University Nijmegen Medical Centre, Nijmegen, Netherlands, [10]Centre for Genomic and Experimental Medicine, Western General Hospital, Edinburgh, United Kingdom, [11]Medizinische Klinik und Poliklinik III, Universitätsklinikum Carl Gustav Carus an der Technischen Universität Dresden, Dresden, Germany, [12]Rheumatology Department; Inserm UMR-S606; Paris-Diderot University, hôpital Lariboisiere, Paris, France, [13]Service De Rhumatologie, CHUV, Lausanne, Switzerland, [14]Department of Rheumatology, CHUV, Lausanne, Switzerland, [15]Surgery, University of Otago, Dunedin, New Zealand, [16]Department of Biochemistry, University of Otago, Dunedin, New Zealand, [17]Medicine, University of Otago, Christchurch, Christchurch, New Zealand, [18]Department of Medicine, University of Auckland, Auckland, New Zealand
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Background/Purpose: Gout is caused by an inflammatory response to monosodium urate (MSU) crystals and is associated with elevated triglyceride and very low density lipoprotein levels. There is evidence that suggests apolipoprotein coating of MSU crytsals modulates the inflammatory response. Association of the apolipoprotein A1-C3-A4 gene cluster with gout has previously been reported. To investigate a possible causal role for this locus in gout we tested the association of genetic variants from *APOA1* and *APOC3* with gout.

Methods: Testing of rs670 (*APOA1)* and *rs5128 (APOC3*) was undertaken in 2452 controls and 2690 clinically-ascertained gout cases of European and of New Zealand Polynesian (Māori and Pacific) ancestry. Data from the publically-available Atherosclerosis Risk in Communities (n=5367) study and the Framingham Heart Study (n=2984) were also analyzed. Multivariate adjusted logistic and linear regression was used to test the association of SNPs with gout risk, serum urate, triglyceride and high-density lipoprotein cholesterol (HDL-C).

Results: In Europeans and Polynesians, consistent with previous studies, both SNPs were associated with HDL-C ($P \leq 0.027$) and *rs5128* was associated with triglyceride levels ($P \leq 0.006$). There was no evidence for association of *rs670* or *rs5128* with the risk of gout in Europeans ($OR_{T\ allele}=1.11$, $P=0.059$; $OR=1.01_{G\ allele}$, $P=0.91$ respectively). In contrast, in Polynesians the T-allele of *rs670* (*APOA1*) increased the risk of gout (OR=1.53, $P=4.88\times10^{-6}$) and the G-allele of *rs5128* (*APOC3*) decreased the risk of gout (OR=0.86, $P=0.026$). Association in Polynesians was independent of any effect of *rs670* and *rs5128* on triglyceride and HDL-C levels. There was no evidence for association of either SNP with serum urate levels in Europeans or Polynesians ($P \geq 0.10$).

Conclusion: The data supports the hypothesis that the apolipoprotein A1-C3-A4 gene cluster plays a causal role in the inflammatory response in gout. The effect was specific to Polynesians in this study and could indicate a pathogenic process, outside of the inherent hyperuricaemia present in Polynesians, that contributes to the increased prevalence of gout in this population group.

Disclosure: T. R. Merriman, None; **A. Phipps-Green**, None; **R. Topless**, None; **M. D. Smith**, None; **C. Hill**, None; **S. Lester**, None; **M. Rischmueller**, None; **M. Janssen**, None; **T. Jansen**, None; **L. A. Joosten**, None; **T. Radstake**, None; **P. L. Riches**, Menarini, 2; **A. K. Tausche**, None; **F. Lioté**, None; **A. So**, None; **A. M. van Rij**, None; **G. T. Jones**, None; **S. McCormick**, None; **A. Harrison**, None; **L. K. Stamp**, None; **N. Dalbeth**, None; **H. Rasheed**, None.

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Abstract Number: 3168

How Strong Cardiovascular Risk Factor Are Gouty Tophi?

Rada Gancheva[1], Atanas Kundurdjiev[2], Mariana Ivanova[1], Todor Kundurzhiev[3] and Zlatimir Kolarov[4], [1]University Hospital "St. Iv. Rilski", Clinic of Rheumatology, Sofia, Bulgaria, [2]University Hospital "Alexandrovska", Clinic of Nephrology, Sofia, Bulgaria, [3]Medical University, Faculty of Public Health, Sofia, Bulgaria, [4]Clinic of Rheumatology, University Hospital "St. Iv. Rilski", Clinic of Rheumatology, Sofia, Bulgaria
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Background/Purpose: We have not found a study determining cardiovascular (CV) risk in the different stages of gout. This led us to use a complex multimodal ultrasonography in order to assess the independent influence of the different stages of gout on parameters associated with CV risk: renal resistive index (RRI), left ventricular mass index (LVMI), Em - reflecting diastolic function of the heart, intima-media thickness (IMT) and common carotid artery resistive index (CCARI).

Methods: A total of 170 patients (pts) were examined cross-sectionally, divided into four groups. Control group - pts with osteoarthritis who were with conventional CV risk factors (arterial hypertension, diabetes mellitus, obesity, dyslipidemia, reduced eGFR, smokers), normal level of serum uric acid and no history of gouty crisis (n=35), 15 males and 20 females aged 61±9.7 years. The other three groups of pts were asymptomatic hyperuricemia (n=41), 23 males and 18 females aged 54.6±15.6 years, gout pts without tophi (n=52), 45 males and 7 females aged 55.9±11.6 years and gouty tophi pts (n=42), 41 males and 1 female aged 58.8±11.4 years. All pts underwent a complex multimodal ultrasonography done by one researcher unaware with clinical and laboratory data. RRI was measured in both kidneys with 3.5 MHz transducer. Echocardiography was done by 2.5 MHz transducer. Carotid arteries were examined with 10 MHz linear transducer. Statistical analyses were performed by ANOVA, Kruskal-Wallis, chi-square tests. We conducted a multiple logistic regression to pts with osteoarthritis. In this way we assessed the independent influence of the three stages of gout and CV risk factors on measured parameters. The cutoff for RRI was >0.70; for LVMI>125 g/m² in males and >110 g/m² in females; for Em<0.08 m/s; for IMT>0.90 mm; for CCARI>0.70.

Results: Of conventional CV risk factors we revealed an association between smoking (p=0.044), dyslipidemia (p=0.006) and the examined groups of diseases. There was no significant difference in the incidence of arterial hypertension (p=0.148), diabetes mellitus (p=0.343), obesity (p=0.539) and reduced eGFR (p=0.145) between the four groups. We established that gout without tophi raised the risk of having thicker intima-media with an OR=6.245 (95% CI; 1.371 - 28.443, p=0.018), gouty tophi markedly raised the risk with an OR=11.509 (95% CI; 2.315 - 57.213, p=0.003), but asymptomatic hyperuricemia did not significantly modify the odds of having abnormal IMT. Arterial hypertension increased the risk of having abnormally high CCARI with an OR=3.217 (95% CI; 1.105 - 9.363, p=0.032), the presence of tophi raised the risk with an OR=11.179 (95% CI; 2.613 - 47.825, p=0.001), while asymptomatic hyperuricemia and gout without tophi did not significantly change the risk of having higher CCARI. The different stages of gout had no independent impact on LVMI, Em and RRI.

Conclusion: Tophi raised the likelihood of having abnormal CCARI three times more than arterial hypertension. CCARI is a well known independent predictor of higher CV risk. We suggest that tophi in gout are independent, commensurable and even stronger risk factor than arterial hypertension.

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Abstract Number: 3169

Diagnostic Value of Ultrasound for the Diagnosis of Gout in a Prospective Cross-Sectional Study

Alexis Ogdie-Beatty[1], William J. Taylor[2], Tuhina Neogi[3], Jaap Fransen[4], Tim Jansen[5], H. Ralph Schumacher Jr.[6] and Nicola Dalbeth[7], [1]Medicine/Rheumatology, University of Pennsylvania, Philadelphia, PA, [2]Department of Medicine, University of Otago Wellington, Wellington, New Zealand, [3]Clinical Epidemiology, BUSM, Boston, MA, [4]Rheumatology, Radboud University Medical Centre, Nijmegen, Netherlands, [5]P O Box 581, Haarlem, Netherlands, [6]Medicine, Rheumatology, U Penn & VA Med Ctr, Philadelphia, PA, [7]Department of Medicine, University of Auckland, Auckland, New Zealand

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Background/Purpose: Musculoskeletal ultrasound (US) is a non-invasive option for diagnosing gout. However, little is known about the test characteristics of US for the diagnosis of gout in clinical practice. The objective of this study was to determine the diagnostic performance of ultrasound for the diagnosis of gout using presence of monosodium urate (MSU) crystals as the gold standard.

Methods: A sub study was performed within the Study for Updated Gout Classification Criteria (SUGAR), a large, multi-center observational cross-sectional study in consecutive subjects with at least one swollen joint who conceivably may have gout. Cases were subjects with MSU crystal confirmation and controls had an arthrocentesis negative for MSU crystals. Rheumatologists or radiologists, blinded to the results of the MSU crystal analysis, performed US on an involved joint. US findings of interest were: double contour sign (DCS), tophus, and snowstorm appearance. Sensitivity and specificity were calculated for these features. Multivariable logistic regression models were used to examine factors associated with true positive US results.

Results: Among 982 subjects enrolled in SUGAR, ultrasound was performed in 824 subjects (416 cases and 408 controls). Sensitivity and specificity for DCS, tophi, snowstorm, and any US feature for all subjects, those with early (<2 years since symptom onset) versus late disease (³2 years since symptom onset), and the presence or absence of suspected clinical tophi on examination are shown in the Table. Among subjects with gout, 249 (60%) subjects had a DCS, 189 (46%) had US evidence of tophus, and 125 (30%) had a "snowstorm" appearance on ultrasound. Associations with a true positive DCS result included highest ever serum uric acid (SUA; OR 1.31; 95%CI: 1.13-1.53), tender joint proximal to the ankle (2.02; 1.34-3.04) and any xray feature of gout (3.04; 1.95-4.75). Associations with a true positive US tophus included suspected clinical tophus on exam (7.47; 4.72-11.84), current SUA (1.22; 1.05-1.41), and asymmetrical swelling on joint xray (6.14; 3.93-9.60). Finally, associations with a true positive "snowstorm" included suspected clinical tophus on exam (2.29; 1.40-3.76), cystic changes on X-ray (1.70; 1.06-2.72), and the number of episodes (compared to 1 as the reference, 2-5 episodes OR 0.20; 0.06-0.51 and >5 episodes OR 0.34; 0.15-0.76).

Conclusion: In this study, US features of gout have high specificity (but more limited sensitivity) for gout. This was also true in subjects with early disease and in those without suspected clinical tophi on clinical examination. However, sensitivity of DCS and US tophus was better for subjects with long standing disease compared to those with early disease. The presence of other features of gout (e.g. suspected clinical tophus, elevated SUA or xray features) increased the likelihood of achieving a true positive result.

Table. Sensitivity and Specificity of US Features of Gout				
	Cases	**Controls**	**Sensitivity**	**Specificity**
Ultrasound: DCS				
All subjects	249/414 (60%)	35/408 (9%)	60.1%	91.4%
Early disease (<2 yrs)	55/108 (51%)	15/195 (8%)	50.9%	92.3%
Late disease (³2 yrs)	192/303 (63%)	18/209 (9%)	63.4%	91.4%
No suspected clinical tophus*	141/264 (53%)	27/389 (7%)	53.4%	93.1%
Suspected clinical tophus*	107/149 (72%)	8/19 (42%)	71.8%	57.9%
Ultrasound: Tophus				
All subjects	189/411 (46%)	21/408 (5%)	46.0%	94.9%
Early disease (<2 yrs)	36/107 (34%)	9/195 (5%)	33.6%	95.4%
Late disease (³2 yrs)	152/301 (51%)	10/209 (5%)	50.5%	95.2%
No suspected clinical tophus*	77/262 (29%)	13/389 (3%)	29.4%	96.7%
Suspected clinical tophus*	112/148 (76%)	8/19 (42%)	75.7%	57.9%
Ultrasound: Snowstorm				
All subjects	125/412 (30%)	37/407 (9%)	30.3%	90.9%
Early disease (<2 yrs)	35/108 (32%)	15/195 (8%)	32.4%	92.3%
Late disease (³2 yrs)	89/301 (30%)	20/208 (10%)	29.7%	90.4%
No suspected clinical tophus*	63/262 (24%)	29/388 (7%)	24.1%	92.5%
Suspected clinical tophus*	62/142 (42%)	8/19 (42%)	41.6%	57.9%
Ultrasound: Any feature				
All subjects	320/416 (77%)	64/408 (16%)	76.9%	84.3%
Early disease (<2 yrs)	78/109 (72%)	31/195 (16%)	71.6%	84.1%
Late disease (³2 yrs)	239/304 (79%)	31/209 (15%)	78.6%	85.2%
No suspected clinical tophus*	182/265 (69%)	55/389 (14%)	68.7%	85.9%
Suspected clinical tophus*	137/150 (91%)	9/19 (48%)	91.3%	52.6%
The number of available test results for each imaging feature may differ as some features were not reported for all subjects. *Suspected clinical tophus refers to clinically apparent tophus on physical examination				

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Abstract Number: 3170

Peripheral Osteoblastogenesis in Rheumatoid Arthritis Is Enhanced after TNF Blocker

Treatment, Irrespective of Systemic Inflammation

Mie Jin Lim[1], Won Park[2], Seong-Ryul Kwon[2], Kyong-Hee Jung[2] and Min Jung Son[3], [1]Division of Rheumatology, Department of Internal Medicine,, Inha University Hospital, Incheon, South Korea, [2]Division of Rheumatology, Department of Internal Medicine, Inha University Hospital, Incheon, South Korea, [3]Inha University Hospital, Incheon, South Korea

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Background/Purpose:

We investigated osteoclastogenesis and osteoblastogenesis in peripheral blood before and 6 months after TNF blocker treatment in seropositive RA patients.

Methods:

Seventeen seropositive RA patients who received TNF blocker treatment including infliximab, adalimumab and etanercept were enrolled. Peripheral blood mononuclear cells (PBMCs) were collected at baseline and 6 months after TNF blocker treatment. For osteoblast culture, PBMCs were cultured and stained with alizarin S to detect calcified nodules. The optical density (OD) of alizarin S was measured for quantitative analysis. We also evaluated serum level of bone formation markers including osteocalcin, bone specific alkaline phosphatase (BSALP) using enzyme linked immunosorbent assay (ELISA). For osteoclast culture, PBMCs (1×10^6 cells/well) were cultured and stained with tartrate resistant acid phosphatase (TRAP). TRAP positive cells with more than 3 nuclei were regarded as osteoclasts. To assess resorption potential of osteoclasts, PBMCs were cultured on bone slices and resorption pits were visualized with 0.1% toluidine blue. The areas of pits were quantified using our own devised computerized image analysis program (Fig. 1). Inflammatory markers including erythrocyte sedimentation rate (ESR), c-reactive protein (CRP) and IL-6 were measured.

Results:

The OD of calcified nodules and bone formation markers including osteocalcin and BSALP all increased after TNF blocker treatment (Table 1). There was a positive correlation between differences of osteocalcin and that of BSALP ($p = 0.002$, $r = 0.696$). The number of cultured osteoclasts and the area of resorption pit by osteoclasts decreased after treatment. The difference of numbers of circulating monocytes showed negative correlation with difference of BSALP ($p = 0.008$, $r = -0.617$) and that of osteocalcin ($p = 0.005$, $r = -0.651$). Inflammatory markers did not respond to the treatment.

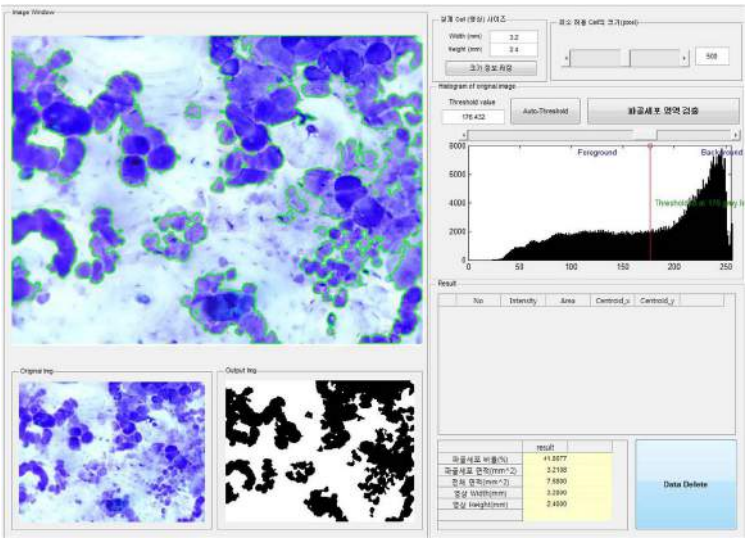
Conclusion:

Increase both in bone formation markers and optical density of calcified nodules by cultured osteoblasts showed improved peripheral osteoblastogenesis after TNF blocker treatment. The tendency of peripheral osteoclastogenesis which is responsible for osteoporosis and bone erosion in RA was in downstream after treatment. Although inflammatory markers did not respond to TNF blocker, the peripheral osteoblastogenesis was markedly enhanced. There was a negative correlation between changes of circulating monocytes, the osteoclast progenitor cells and that of bone formation markers, suggesting a strong tie between bone formation and resorption.

Table 1.

	At Baseline	6 months after treatment	*p*
Bone formation markers in serum			
osteocalcin	**5.81 ± 1.94**	**8.6 ± 3.23**	**< 0.001**
BSALP	**22.17 ± 6.99**	**25.82 ± 8.89**	**0.007**
ex vivo culture			
OD of calcified nodule (mmol/well)	**205.7 ± 196.27**	**752.5 ± 671.93**	**0.024**
Number of osteoclasts (per well)	**565 ± 294.5**	**304 ± 120.9**	**0.007**
Bone resorption pit by osteoclasts (μ±)	**0.18 ± 0.113**	**0.08 ± 0.076**	**0.007**
Inflammatory markers			
ESR (mm/hr)	33 ± 19.9	25 ± 26.6	0.06
CRP (mg/dL)	1.67 ± 1.48	0.67 ± 1.54	0.05
IL-6	4 ± 2.83	0.9 ± 0.36	0.072
Circulating blood cells			
circulating monocytes (/μ°)	465 ± 135.7	417.8 ± 130.3	0.07

Figure 1



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Abstract Number: 3171

Combination Therapy with Denosumab and Biologic DMARD Associated with Higher Risk of Serious Infections Compared to Denosumab Alone and Biologic DMARD Alone

Ivana Parody[1], Luis Arias-Urdaneta[2], Ricardo Garcia Alemany[2] and Carlos Sesin[2], [1]Internal Medicine, Mount Sinai Medical Center, Miami Beach, FL, [2]Vanguard Rheumatology Partners, Miami Beach, FL
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Background/Purpose:

Patients with RA and other rheumatologic disorders are at increased risk for osteoporotic fractures. Biologic DMARDs are an important treatment option for these patients. However, they are associated with increased infection risk. It is well known that combining biologic DMARDs increases the risk of serious adverse effects, including infections. Considering its mechanism of action, there has been concern that denosumab (Dmab) may increase infection risk when combined with biologic DMARDs. Here we report the results of a retrospective chart review in an outpatient rheumatology practice that evaluated and compared the rates of serious infections in patients receiving Dmab alone, biologic DMARDs alone, Dmab with biologic DMARDs, and bisphosphonates with biologic DMARDs.

Methods:

We performed a retrospective chart review of 389 patients, of whom 159 received Dmab alone, 193 biologic DMARD alone, 10 Dmab + biologic DMARD, and 27 bisphosphonate + biologic DMARD. Data were collected from Jan 2010 through May 2015. The primary endpoint was to compare the rate of serious infections in the Dmab + biologic DMARD group to the biologic DMARD alone group. Rates were calculated for each group and then compared. Chi-square test and relative risk estimates were used for statistical analysis. 95% CI and P values were calculated for each group.

Results:

The Dmab + biologic DMARD group had a higher rate of serious infections compared to the biologic DMARD alone group (RR=12, 95%CI 2.41-68.52, P=0.002). The rate of serious infections for the Dmab + biologic DMARD group was also significantly higher compared to the

Dmab alone group (RR=10.60; 95% CI:1.99-56. P=0.005). No difference in serious infections was observed between the Dmab + biologic DMARD and bisphosphonate + biologic DMARD groups (RR 1.80, 95% CI 0.35-9.2 P=0.48). The Dmab + biologic DMARD group was older (76; SD 7.7) than the biologic DMARD alone group (56; SD 16), and bisphosphonate + biologic DMARD group (63; SD 10), but similar to the Dmab alone group (77; SD 9.9). Gender was female predominant in all 4 groups, 94% in Dmab alone, 100% in Dmab + biologic DMARD, 68% in biologic DMARD alone, and 88% in bisphosphonate + biologic DMARD. The types of serious infections requiring hospitalization were not significantly different between the 4 groups. These included community acquired pneumonia (n=3), post surgical wound infection (n=1), infectious bursitis (n=1), skin and soft tissue infections (SSTI) (n=2), Lyme disease (n=1), and Chikungunya (n=1).

Conclusion:

We observed a greater rate of serious infections in patients receiving combination treatment with Dmab + biologic DMARD compared to biologic DMARD alone and to Dmab alone. The Dmab + biologic DMARD group was older compared to biologic DMARD alone group, which may contribute to the higher rate of serious infections observed. No other significant differences were observed among the 4 treatment groups, including duration of exposure. In summary, the findings of this retrospective study suggest that combination treatment with denosumab and biologic DMARD may increase the risk of serious infections, particularly in an older patient population. Caution should be exercised when considering combination therapy.

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Abstract Number: 3172

Effect of Anti Citrullinated Protein Antibodies on Periarticular and Systemic Bone Mass in Early Arthritis Patients

Irene Llorente Cubas*[1], Leticia Merino-Meléndez[2], Ana M. Ortiz Garcia[2], Eugenio Escolano[3], Teresa Velasco[1], Elena García[2], Esther Vicente-Rabaneda[2], Alberto Garcia-Vadillo[4], Rosario Garcia-Vicuña[4], Isidoro González-Alvaro*[2] and Santos Castañeda*[2], [1]Rheumatology, H.U La Princesa, Madrid, Spain, [2]Rheumatology, H.U. La Princesa, Madrid, Spain, [3]Radiology Department, H.U La Princesa, Madrid, Spain, [4]Rheumatology, Hospital Universitario de La Princesa. IIS La Princesa, Madrid, Spain

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Background/Purpose: Recently it has been described that anti citrullinated protein antibodies (ACPA) can induce differentatiomn and activation of osteoclasts even before arthritis onset (1,2). The aim of this study was to analyze the effect of ACPA on periarticular and systemic bone mineral density (BMD) in a large population from an early arthritis (EA) clinic.

Methods: We analyzed data from patients belonging to PEARL (Princesa Early Arthritis Longitudinal) study. Demographic, clinical, laboratory and treatment data were collected per protocol. BMD was meaasured at the first visit of the following up through dual X-ray absorptiometry (DXA) (Hologic ©QDR-4500) at lumbar spine (LS), hip, forearm and hand. ACPAs were determined by ELISA. Multivariable analysis was performed adjusting for coufinding variables such as sex, age and body mass index (BMI) was performed using generalized linear models with the command glm of STATA 12.

Results: We analyzed data from 474 patients (39.6% ACPA positive, 80% women). 56.1% of patients fullfiled the Rheumatoid Arthritis (RA) 2010 Criteria at start of follow up. The other patients were undifferentiated arthritis, spondyloarthritis , connective tissue disease and other diagnostics. Median age at disease onset was 54 years [43 - 66 (p25 - p50)]. Symptom duration until BMD measurement was 5 months [6-8 (p25-p50)]. Median DAS28 in patients who fullfilled RA criteria was 4.98 [4-6 (p25-p50)] and 3.6 [3-4 (p25-p50)] in remaning patients. Likewise, HAQ score was higher in RA patients (median 0.750 vs 1.125 in non-RA group). However, neither of these two variables was significantly associated with baseline bone mass. We found ACPA positive patients had lower BMD in LS (beta coefficient - 0.025; p=0.051), femoral neck (coef. beta: -0.02; p=0.053) and total hip (coef. beta. - 0.017; p=0.1). This association was not observed in the nondominant hand or forearm.

Conclusion: Our data provide further support Schett at al suggesting that ACPA may induce systemic osteoporosis even at very early stages of the disease in absence of a long term inflammatory state. Subsequently, bone loss mass would extend to more localized areas in relation to the persistence of inflammatory activity.

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Abstract Number: 3173

Premature Mortality Due to Fractures in a Population-Based Prospective Cohort Study of 238,673 Older Women and Men

Lyn March[1], Weiwen Chen[2], Judy M Simpson[3], Fiona Blyth[4] and Jacqueline Center[2], [1]Department of Rheumatology, Northern Clinical School, Institute of Bone and Joint Research, Kolling Institute, University of Sydney & Department of Rheumatology, Royal North Shore Hospital, St Leonards, Sydney, Australia, [2]Endocrinology, Osteoporosis & Bone Biology Garvan Institute of Medical Research, St Vincent's Clinical School, UNSW, Darlinghurst, Australia, [3]Statistics, University of Sydney School of Public Health, Sydney, Australia, [4]Concord Clinical School University of Sydney and Sax Institute, Sydney, Australia

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Background/Purpose: Osteoporotic (OP) fractures and falls are a growing global problem as the population ages. One third of all falls related deaths are attributable to low bone density. Yet OP is poorly managed despite effective treatments being available. A potential reason for not prioritizing OP treatment may be the lack of awareness of the increased mortality due to OP fractures. The aim of this analysis was to determine mortality risk with all fragility fractures in community-dwelling older women and men in New South Wales, Australia.

Methods: Baseline questionnaire data from the 45 & Up Study, a prospective population-based cohort of 238,673 older women (125,174) and men (113,499), were linked to the Emergency Department Data Collection (EDDC), Admitted Patient Data Collection (ADPC- including all hospital admissions, procedures and diagnoses within NSW), Registry of Births, Marriages and Death (RBDM). Fractures were identified from the EDDC and ADPC using the ICD 9, 10, SNOMED and procedure codes. Participants were followed from recruitment (2006-2008) till either death or 31 December 2013. Cox proportional hazards models calculated mortality hazard ratios (HR) (adjusted for age, gender, Charlson comorbidity index, prior fracture history) between those who did and did not fracture.

Results: A total of 14,827 fractures (9,145 females (F) and 5,682 males (M)) and 15,621 deaths (5,604 F and 10,017 M) were available for analysis. The mean age of the cohort was 63 yrs with mean follow-up of 5.7 yrs (sd:1.0). In the whole cohort, absolute mortality rate was higher in men (15.7/1000 person yrs) than women (7.9/1000 person yrs). Having an incident fracture increased mortality rates by ~ two-fold in both men: (33/ 1000 person yrs) and women (19/1000 person yrs). This differed by fracture type as demonstrated by adjusted HRs. Mortality was increased for all proximal site but not distal fractures (See Table).

Conclusion: In a large sample of community dwelling older women and men premature mortality risk is significantly increased following all proximal but not distal fractures. The cause of this increased mortality needs to be explored.

Table 1: Adjusted hazard Ratios (HR) and 95% confidence interval (CI) for mortality risk and all fracture types for females and males

	FEMALES				MALES			
Site	**N**	**HR**	**95% CI**		**N**	**HR**	**95% CI**	
Hip	1477	**2.58**	2.30	2.89	977	**3.21**	2.85	3.60
Pelvis	564	**2.33**	1.94	2.79	295	**3.28**	2.63	4.07
Vertebral	599	**2.32**	1.88	2.87	508	**2.72**	2.25	3.30
Femur	259	**1.91**	1.40	2.60	181	**2.86**	2.12	3.85
Humerus	904	**1.90**	1.55	2.35	354	**1.80**	1.39	2.34
Clavicle	142	**2.32**	1.37	3.90	252	**2.11**	1.44	3.09
Tibia	279	**2.81**	1.51	5.22	131	**3.12**	2.04	4.78
Elbow	109	**2.03**	1.39	2.96	89	**1.92**	1.00	3.69
Knee	*223*	*1.28*	*0.78*	*2.12*	106	**1.81**	1.07	3.05
Forearm	*137*	*1.28*	*0.67*	*2.47*	*44*	*1.30*	*0.91*	*1.88*
Wrist	*178*	*1.15*	*0.91*	*1.44*	*489*	*1.30*	*0.91*	*1.88*
Hand	*204*	*1.3*	*0.68*	*2.51*	*198*	*1.25*	*0.73*	*2.16*
Finger	*266*	*1.49*	*0.80*	*2.77*	*318*	*0.99*	*0.57*	*1.70*
Ankle	*108*	*1.00*	*0.68*	*1.47*	*472*	*1.29*	*0.89*	*1.87*
Foot	*628*	*0.96*	*0.59*	*1.57*	*236*	*1.17*	*0.64*	*2.14*
Toe	*285*	*0.78*	*0.29*	*2.08*	*157*	*0.95*	*0.36*	*2.53*

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Abstract Number: 3174

Vitamin D Binding Protein and Tenofovir-Associated Bone Loss Among Individuals with HIV

Evelyn Hsieh[1,2], Liana Fraenkel[1], Weibo Xia[3], Yang Han[2], Michael Yin[4], Karl Insogna[5], Ting Zhu[2] and Taisheng Li[2], [1]Section of Rheumatology, Yale School of Medicine, New Haven, CT, [2]Department of Infectious Diseases, Peking Union Medical College Hospital, Beijing, China, [3]Department of Endocrinology, Peking Union Medical College Hospital, Beijing, China, [4]Division of Infectious Diseases, Columbia University Medical Center, New York, NY, [5]Section of Endocrinology, Yale School of Medicine, New Haven, CT

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Background/Purpose:

Antiretroviral regimens containing tenofovir disoproxil fumarate (TDF) have been associated with decreases in bone mineral density, and elevations in bone turnover markers (BTM) and intact parathyroid hormone (iPTH) in patients with HIV. Prior cross-sectional studies suggested that a functional vitamin D deficiency may in part explain these changes. To explore this hypothesis further, we measured change in plasma vitamin D binding protein (DBP) levels from baseline to 48 weeks among a cohort of patients treated with TDF/lamivudine(3TC)/efavirenz(EFV) in the context of other serologic markers of vitamin D and bone metabolism.

Methods:

We performed a secondary analysis using plasma samples collected at 0, 24, and 48 weeks after initiation of TDF/3TC/EFV from 140 adult participants enrolled in a multi-center randomized trial. Women over 45 years were excluded to avoid confounding due to menopausal status. Data regarding socio-demographic characteristics, BMI, $CD4^+$ counts, and HIV viral load were obtained as part of the parent study. Laboratory tests included plasma DBP, iPTH, total 25-hydroxyvitamin D (25OHD), the bone resorption marker collagen type 1 cross-linked C-telopeptide (CTX), and the bone formation marker total procollagen type 1 N-terminal propeptide (P1NP). Differences between time points were compared using the paired t-test and Wilcoxin signed-rank test.

Results:

Our sample included 108 men and 26 women with a mean age of 33.6±9.6 years and BMI of 22.3±2.9 kg/m^2. Mean BMI remained stable from 0 to 48 weeks (p=0.47), however median CD4$^+$ count increased significantly from 290.5 (IQR: 201-362) to 424 (IQR: 294-555) cells/mm^3 (p<0.001) and median viral load decreased from 53767 (IQR: 19802 to 136493) to 0 (IQR:0 to 10) copies/mL (p<0.001). Significant increases were observed in DBP levels from 0 to 24 weeks followed by smaller increases from 24 to 48 weeks (see Table). Similar increases were detected in iPTH levels, however 25OHD levels remained stable. BTM levels increased significantly from 0 to 24 weeks followed by a slight decline (CTX) or stabilization (P1NP), however remained significantly higher compared with baseline at 48 weeks.

Conclusion:

Plasma levels of DBP rose significantly in the first 24 weeks after initiation of TDF/3TC/EFV, followed by a more modest increase from 24 to 48 weeks. This change was observed in concert with elevations iPTH and BTMs, despite stable 25OHD levels, supporting a potential role for DBP in bone loss associated with TDF therapy.

Table. Markers of vitamin D and bone metabolism at 0, 24 and 48 weeks after initiation of tenofovir/lamivudine/efavirenz therapy (N=134)

	0 weeks Median (IQR)	24 weeks Median (IQR)	48 weeks Median (IQR)	p 0 to 24 wks	p 24 to 48 wks	p 0 to 48 wks
DBP *mg/mL*	154 (91.8-257.4)	182.9 (108.5-317.2)	198.3 (119.6-351.9)	<0.001	<0.001	<0.001
iPTH *pg/mL*	32.3 (24.4-40.9)	39.8 (31.4-51.4)	45.2 (35.1-60.4)	<0.001	<0.001	<0.001
25OHD *ng/mL*	22.7 (17.2-31.6)	24.4 (18.1-33.9)	23.5 (17.8-30.3)	0.12	0.12	0.997
CTX *ng/L*	255 (177-363)	481 (327-592)	411(321-488)	<0.001	<0.001	<0.001
P1NP *ng/mL*	39.9 (31.0-52.1)	65.1 (50.3-79.2)	66.4 (52.3-79.9)	<0.001	0.049	<0.001

Disclosure: E. Hsieh, None; **L. Fraenkel**, None; **W. Xia**, None; **Y. Han**, None; **M. Yin**, None; **K. Insogna**, None; **T. Zhu**, None; **T. Li**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/vitamin-d-binding-protein-and-tenofovir-associated-bone-loss-among-individuals-with-hiv

Abstract Number: 3175

Strength at the Lumbar Spine and Hip Improves with Romosozumab Compared with Teriparatide in Postmenopausal Women with Low Bone Mass

TM Keaveny[1], DB Crittenden[2], MA Bolognese[3], HK Genant[4], K Engelke[5], B Oliveri[6], JP Brown[7], BL Langdahl[8], YC Yang[2], A Grauer[2] and C Libanati[9], [1]UC Berkeley, Berkeley and O.N. Diagnostics, Berkeley, CA, [2]Amgen Inc., Thousand Oaks, CA, [3]The Bethesda Health Research Center, Bethesda, MD, [4]UCSF & Synarc Inc., San Francisco, CA, [5]Synarc Germany, Hamburg, Germany, [6]Hospital de Clínicas, INIGEM, Buenos Aires, Argentina, [7]Laval University and CHU de Québec (CHUL) Research Centre, Québec City, QC, Canada, [8]Aarhus University Hospital, Aarhus, Denmark, [9]UCB Pharma, Brussels, Belgium

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Background/Purpose: Romosozumab is a bone-forming agent that inhibits sclerostin. In a phase 2 study (NCT00896532), 12 months of romosozumab increased DXA bone mineral density (BMD) in postmenopausal women with low bone mass (McClung et al. *NEJM* 2014). A subset of these women underwent spine and hip quantitative computed tomography (QCT) imaging, confirming the BMD gains (romosozumab vs teriparatide integral volumetric BMD gains of 17.7% vs 12.9% at the spine and 4.1% vs 1.2% at the hip). To investigate the effects of romosozumab on bone strength, we performed a finite element analysis (FEA) on these QCT scans.

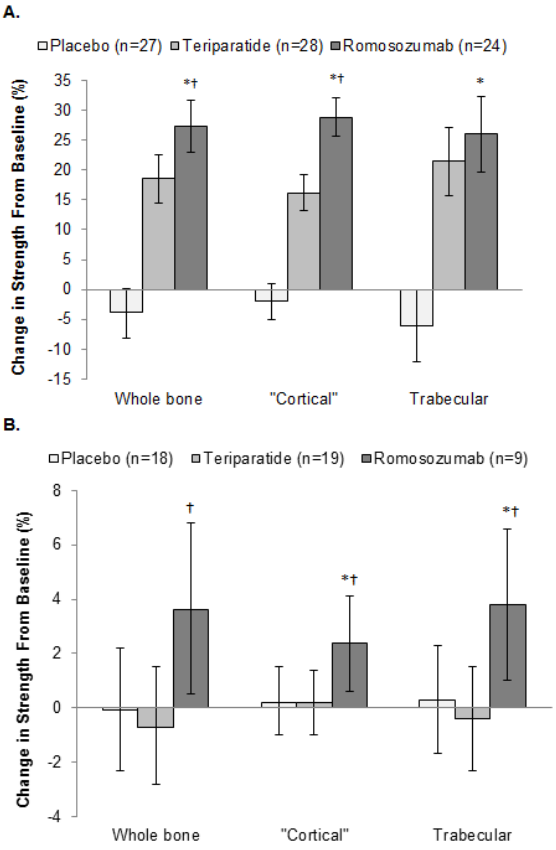
Methods: This international randomized study enrolled postmenopausal women with lumbar spine, total hip, or femoral neck T scores ≤–2.0 and ≥–3.5. In this analysis, subjects received blinded subcutaneous romosozumab 210 mg monthly, placebo, or open-label teriparatide (20 mcg daily). QCT scans were performed at the L1 and L2 lumbar vertebrae and proximal femur at baseline and month 12. Subject-specific vertebral strength for a simulated compression overload and femoral strength for a simulated sideways fall were estimated blinded-to-treatment using a FDA-approved non-linear 3D FEA (VirtuOst, O.N. Diagnostics). Whole-bone and compartment strength changes were estimated. The "cortical" compartment was defined as all bone within 2 mm and 3 mm of the periosteal surface for the spine and hip, respectively, plus any high-density bone (>1.0 g/cm^3 of apparent density); the trabecular compartment was defined as all other bone.

Results: At the spine, romosozumab increased strength from baseline by 27.3% at month 12, which was substantially higher than placebo (–3.9%) and teriparatide (18.5%; Figure A). This strengthening effect was due to contributions from both the "cortical" and trabecular

compartments. At the hip, despite a small sample size for the romosozumab group, strength increased compared with baseline for romosozumab (3.6%), but did not change for placebo or teriparatide (Figure B). Again, both "cortical" and trabecular compartment changes contributed to the overall strengthening observed with romosozumab.

Conclusion: Romosozumab increased strength at the spine and hip over 12 months, with strength improving in the "cortical" and trabecular compartments at both sites. These strength improvements, documented using a validated method for assessing fracture risk and monitoring treatment, confirm and extend existing data and support romosozumab evaluation in the ongoing phase 3 clinical program.

Figure. Percentage Change (95% CI) in FEA-Estimated Strength at Month 12 for the Lumbar Spine (A) and Hip (B)



*P<0.05 compared with placebo; †P<0.05 compared with teriparatide.
ANCOVA model compared the treatment arms from baseline to month 12 adjusting for baseline quantitative computed tomography FEA value and geographic region.
FEA, finite element analysis.

Disclosure: T. Keaveny, O.N. Diagnostics, 4,Amgen, Agnovos Healthcare, 5; **D. Crittenden**, Amgen, 3,Amgen, 1; **M. Bolognese**, Amgen, 5,Amgen, Lilly, 8; **H. Genant**, Amgen, Lilly, Merck, Novartis, Pfizer, Janssen, Daiichi, Medtronic, Agnovos, Biomarin, Clementia, BioClinica, 5; **K. Engelke**, Synarc-Bioclinica, 3,Amgen, 5,German and EU research grants, 2; **B. Oliveri**, Shire HGT, GSK, Servier, 8; **J. Brown**, Abbvie, Amgen, Eli Lilly, Novartis, Takeda, 2,Amgen, Eli Lilly, Radius, 5,Amgen, Eli Lilly, 8; **B. Langdahl**, Eli Lilly, Novo Nordisk, Orkla, 2,Amgen, Merck, Eli Lilly, UCB, 5,Amgen, Merck, Eli Lilly, 8; **Y. Yang**, Amgen, 3,Amgen, 1; **A. Grauer**, Amgen, 3,Amgen, 1; **C. Libanati**, Ex employee - Amgen, 3,Amgen, 1,UCB Pharma, 3.

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Abstract Number: 3176

New Prospects for Interpreting Bony Depressions in Juvenile Idiopathic Arthritis: A Novel MRI Computer-Assisted Technique for Detection of Erosive Progression

Pieter van Dijkhuizen[1,2], Carlotta Covizzi[1], Andrea Schiappacasse[3], Michela Moraldo[4], Matteo Santoro[5], Francesca Magnaguagno[6], Gianmichele Magnano[7], Alberto Martini[1,4] and Clara Malattia[1,4], [1]Istituto G Gaslini, Pediatria II, Reumatologia, Genova, Italy, [2]UMC Utrecht, Wilhelmina Children's Hospital, Pediatric rheumatology, Utrecht, Netherlands, [3]DIBRIS Università degli studi di Genova, Genova, Italy, [4]DINOGMI Università degli studi di Genova, Genova, Italy, [5]Camelot Biomedical Systems, Genova, Italy, [6]Istituto G Gaslini, UO Radiologia

Pediatrica, Genoa, Italy, [7]Istituto G Gaslini, UO Radiologia Pediatrica, Genova, Italy
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Background/Purpose: Structural damage is the main disease outcome to be avoided in JIA. The gold standard to assess joint damage in JIA is X-ray, which is however limited by its late detection of erosions. Alternatively, MRI is sensitive, but distinction between normal variants and bone erosions secondary to the disease is a real challenge. We posit that only bony depressions whose size increases over time should be considered true bone erosions. To test this hypothesis, we developed software to co-register and compare baseline and follow-up MRIs. The aim of this study was to assess the performance of this novel method in detecting bone erosion progression.

Methods: 66 JIA patients with active wrist arthritis who participated in a prospective trial, were enrolled. The baseline and 1 year follow-up MRI of the wrists were assessed separately according to the OMERACT RAMRIS score. Erosive progression was defined as a change between the baseline and 1-year follow-up MRI bone erosion score of at least two points. The novel computer-assisted MRI technique allows to visualize simultaneously two consecutive MRIs and to overlap each of the carpal bones, distal radius, distal ulna and metacarpal bones. Two independent readers assigned 0 or 1 points to each bone indicating absence or presence of progression, respectively. Structural damage progression was defined as progression in at least one bone. The baseline and last X-ray available for each patient were scored according to the Sharp-Van der Heijde method with a difference of at least 2 points indicating joint damage progression. This score served as reference standard for the MRI scores. Inter-reader reliability of the new method was assessed by Cohen's kappa. Of both MRI scores, the diagnostic properties and correlation with clinical variables were evaluated.

Results: Median disease duration at baseline was 4.9 years. The last X-ray was available in 43 patients after a median time of 4.2 years from baseline. 23 (35%) patients showed radiographic progression of joint damage, while 14 (21%) and 32 (48%) patients showed progression of bone erosions using the RAMRIS score and computer-assisted technique, respectively. Inter-reader agreement for detecting erosive progression using the novel software was substantial, with Cohen's kappa ranging from 0.63-1 for the individual bones and equaling 0.79 for the total score. The novel method was accurate with a sensitivity of 0.83, specificity of 0.78, positive predictive value (PPV) of 0.83 and negative predictive value (NPV) of 0.78, whereas the RAMRIS bone erosion score performed poorly with a sensitivity of 0.17, specificity of 0.74, PPV of 0.44 and NPV of 0.42. As expected, the novel method did not correlate with traditional measurements of disease activity, while it was correlated with validated measurements of damage such as conventional radiography (Spearman's rho = 0.60).

Conclusion: The novel method outperformed the RAMRIS bone erosion score and allowed a reliable and accurate evaluation of structural damage progression in JIA, with the potential to select patients who are eligible for a more aggressive treatment.

Disclosure: P. van Dijkhuizen, None; **C. Covizzi**, None; **A. Schiappacasse**, None; **M. Moraldo**, None; **M. Santoro**, None; **F. Magnaguagno**, None; **G. Magnano**, None; **A. Martini**, AbbVie Inc., AstraZeneca, Bristol-Myers Squibb, Janssen Biologics B.V., Eli Lilly and Co., "Francesco Angelini", GlaxoSmithKline, Italfarmaco, Novartis, Pfizer, Roche, Sanofi Aventis, Schwarz Biosciences GmbH, Xoma, Astellas, medImmune and Wyeth Pharmaceu, 9; **C. Malattia**, None.

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Abstract Number: 3177

Whole-Body MRI: A Valuable Diagnostic Tool for the Assessment of Disease Damage in Juvenile Dermatomyositis

Clara Malattia[1], Agnese Beltramo[1], Isabella Buffoni[1], Annalisa Madeo[1], Francesca Magnaguagno[2], Stefania Viola[1] and Alberto Martini[1,3], [1]Istituto G Gaslini, Pediatria II, Reumatologia, Genova, Italy, [2]Istituto G Gaslini, UO Radiologia Pediatrica, Genoa, Italy, [3]Pediatria, Istituto G Gaslini, Pediatria II, Reumatologia, Genova, Italy
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Background/Purpose:

Although the prognosis of JDM has significantly improved during the past decade, some patients still experience persistent active disease, which potentially leads to irreversible damage and permanent disability. In patients with longstanding disease muscle weakness may be due to a combination of ongoing muscle inflammation, muscle atrophy, fatty replacement and steroid-induced myopathy; MRI allows to define the role of each of these components in the patients' weakness and to overcome the limits of the clinical evaluation. The aim of this study is to estimate the frequency and distribution of muscle damage in JDM, using Whole-Body MRI (WB-MRI) and to investigate its feasibility and validity in the assessment of damage.

Methods:

WB-MRIs were obtained from 50 JDM patients (22M;28F, mean age 10.88 years, mean disease duration 3.86 years) and 50 age and sex-matched controls, using a 1.5 T MRI scanner. Muscular atrophy and fatty replacement were assessed on T1 W sequences and scored in 39 muscular groups using a 0-2 and a 0-1 point scales respectively. WB-MRI and clinical assessments were performed concurrently and the results compared. Validation procedures included analysis of reliability, construct validity and discriminative validity.

Results:

WB-MRI revealed muscle atrophy in 43/50 patients (86%) and fatty replacement in 17/50 patients (34%). Quadriceps and ileopsoas muscles were more frequently affected. The inter-reader agreement for WB-MRI scores ranged from moderate to excellent (with Cohen's kappa ranging from 0.556-1 for the individual muscular group and intra-class correlation coefficient 0.96 for the total muscular damage score). Correlations between MDI and muscle atrophy ($rs=0.4$, $p< 0.01$) and fatty replacement ($rs=0.51$, $p= 0.0007$) were moderate and, as expected, MRI muscular damage score did not correlate with traditional measurements of disease activity. Unexpectedly, MRI damage scores did not correlate with disease duration or steroid therapy. None of controls showed signal changes in muscle revealing an excellent discriminant validity of the WB-MRI score.

WB imaging allowed to detect abnormalities in other organ and systems, including osteonecrosis (6/50 patients, 12%), vertebral fractures (7/50, 14%) and calcinosis (14/50, 28%). Other incidental findings detected by WB MRI were a renal cyst and a thyroidal lesion which resulted to be a papillary thyroid carcinoma.

Conclusion:

WB-MRI represents a promising tool to estimate the overall spectrum of damage in JDM. An accurate discrimination between the persistent disease activity and the disease damage burden is crucial to guide treatment decision.

Disclosure: C. Malattia, None; **A. Beltramo**, None; **I. Buffoni**, None; **A. Madeo**, None; **F. Magnaguagno**, None; **S. Viola**, None; **A. Martini**, None.

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Abstract Number: 3178

Tocilizumab in Refractory Uveitis Associated to Juvenile Idiopathic Arthritis. Multicenter Study of 13 Cases

Montserrat Santos-Gómez[1], Vanesa Calvo-Río[1], Ricardo Blanco[1], Inmaculada Calvo[2], Marina Mesquida[3], Alfredo Adan[3], M. Victoria Hernández[4], Olga Maiz Alonso[5], Antonio Atanes-Sandoval[6], Beatriz Bravo[7], Consuelo Modesto[8], Gisela Diaz Soriano[9], Javier Loricera[1], Leyre Riancho-Zarrabeitia[1], Natalia Palmou[1] and Miguel Angel Gonzalez-Gay[1], [1]Rheumatology, Hospital Universitario Marqués de Valdecilla. IDIVAL, Santander, Spain, [2]Rheumatology, Hospital La Fe, Valencia, Spain, [3]Ophthalmology, Hospital Clinic, Barcelona, Spain, [4]Arthritis Unit, Rheumatology, Hospital Clinic, Barcelona, Spain, [5]Rheumatology, Donostia University Hospital, Donostia, Spain, [6]Rheumatology, Complejo Hospitalario Universitario de La Coruña, La Coruña, Spain, [7]Rheumatology, Hospital Universitario HUVN, Granada, Spain, [8]Rheumatology, Hospital HSLL, Palma de Mallorca, Spain, [9]Rheumatology, Hospital Regional Universitario de Málaga, Málaga, Spain
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Background/Purpose:

To assess the efficacy of Tocilizumab (TCZ) in refractory uveitis associated to juvenile idiopathic arthritis (JiA).

Methods:

Multicenter study of uveitis related to JiA and refractory to at least **a)** one standard synthetic immunosuppressive drug and, **b)** one anti-TNFα drug**.**

Results:

We studied 13 patients/24 eyes (11 women/2 men) with a mean age of 20.38±9 years (range 8-38). The most frequent ocular pattern was anterior uveitis (n=11), bilateral (n=11), and chronic (n=13).

Besides corticosteroids and before TCZ onset, they had received methotrexate (n=11), cyclosporine A (n=5), mycophenolate (n=1) and leflunomide (n=1). The first biological treatment was: adalimumab (ADA) (n=6) (40 mg/sc/2 weeks), infliximab (IFX) (n=3) (5 mg/kg/i.v./every 6-8 weeks) and etanercept (ETN) (n=4). Before TCZ onset they were switched to other biologic drug (n=11) (most of them due to inefficacy), a third (n=5), fourth (n=3) and a fifth biologic therapy (n=1). TCZ was used at a conventional dose (8 mg/kg/4 weeks) in most cases and combined in all cases (MTX=7, LFN=4, CsA=1, MMF=1). Improvement from baseline to 1 year was observed in: a) Visual acuity: from 0.46±0.35 to 0.52±0.37 (p=0.007); b) Anterior chamber cells from a median [IQR] of 1 [0.5-2] to 0 [0-0] (p=0.001), c) vitritis from 0 [0-1] to 0 [0-0] (p=0.06) and d) Macular thickness from a mean of 277±127 to 234±32 microns (p=0.04). After a mean follow-up of 15.2±8.3 months, ocular remission was achieved in 9 of 13 patients and adverse events were severe thrombocytopenia (n=1), pneumonia (n=1), viral conjunctivitis and bullous impetigo (n=1).

Conclusion:

Tocilizumab seems to be effective and relatively safe in refractory uveitis related to JiA.

Disclosure: M. Santos-Gómez, None; **V. Calvo-Río**, None; **R. Blanco**, None; **I. Calvo**, None; **M. Mesquida**, None; **A. Adan**, None; **M. V. Hernández**, None; **O. Maiz Alonso**, None; **A. Atanes-Sandoval**, None; **B. Bravo**, None; **C. Modesto**, None; **G. Diaz Soriano**, None; **J. Loricera**, None; **L. Riancho-Zarrabeitia**, None; **N. Palmou**, None; **M. A. Gonzalez-Gay**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/tocilizumab-in-refractory-uveitis-associated-to-juvenile-idiopathic-arthritis-multicenter-study-of-13-cases

Abstract Number: 3179

Diagnosing Childhood Small Vessel CNS Vasculitis

Marinka Twilt[1], Maryam Nabavi Nouri[2], Pascal N. Tyrrell[3], Anastasia Dropol[1], Shehla Sheikh[4], Cynthia Hawkins[5] and Susanne Benseler[6,7], [1]Rheumatology, Alberta Children's Hospital, Calgary, AB, Canada, [2]Neurology, The Hospital for Sick Childern, Toronto, ON, Canada, [3]Department of Medical Imaging, University of Toronto, Toronto, ON, Canada, [4]Rheumatology, The Hospital for Sick Children, Toronto, ON, Canada, [5]Paediatric Laboratory Medicine, The Hospital for Sick Children, Toronto, ON, Canada, [6]Alberta Children's Hospital Research Institute/University of Calgary, Calgary, AB, Canada, [7]Pediatrics/Alberta Children's Hospital, Department of Pediatrics/University of Calgary, Calgary, AB, Canada

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Background/Purpose:

Childhood primary small vessel CNS vasculitis (SVcPACNS) is an increasingly recognized inflammatory brain disease with high morbidity and mortality mandating an elective brain biopsy to confirm the diagnosis. The aim of the study was to systematically review biopsies of SVcPACNS patients and inflammatory and epilepsy controls and to determine characteristic features defining the diagnosis of SVcPACNS.

Methods:

A previously developed, standardized brain biopsy review instrument was applied to consecutive full thickness brain biopsies of pediatric cases and controls collected at a single center. Standardized stains including Hematoxyllin & Eosin, histochemistry of immune cell subsets plus electron microscopy. Nine North American expert neuropathologists were blinded reviewed to the patient’s presentation, diagnosis and therapy. All biopsies were de-identified and scored independently by two reviewers. Univariate analyses compared variable between groups;

correspondence analysis determined the multi-dimensional relationship of histological variables and patient diagnoses.

Results:

A total of 31 brain biopsy specimens of children with SVcPACNS, 12 with epilepsy and 11 with non-vasculitic inflammatory brain disease controls were included. Correspondence analyses revealed distinct clusters of the three diagnoses based on dimensions of location of infiltrate and subtype/ severity of inflammation. Significant histological characteristics found to set apart SVcPACNS from controls included angiocentric ($p<0.01$) and/or perivascular infiltrates ($p=0.04$), evidence of endothelial cell activation ($p<0.01$) and inflammation in both grey and white matter ($p<0.01$). The infiltrate was found to be primarily T-cell mediated (CD3+ 86%, CD8+ 90%) only 27% of SVcPACNS biopsies had evidence of B cells. Features reported in adult PACNS including granulomas, necrosis or fibrin deposits were absent in all biopsies. Leptomeningeal inflammation was non-diagnostic.

Conclusion:

Distinct histological features were identified on brain biopsies of SVcPACNS and may help defining the disease. These were absent in biopsies of children with epilepsy and non-vasculitic inflammatory brain diseases and allow for the development of diagnostic criteria.

Disclosure: M. Twilt, None; **M. Nabavi Nouri**, None; **P. N. Tyrrell**, None; **A. Dropol**, None; **S. Sheikh**, None; **C. Hawkins**, None; **S. Benseler**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/diagnosing-childhood-small-vessel-cns-vasculitis

Abstract Number: 3180

Mesenchymal Stromal Cell Treatment in Juvenile Idiopathic Arthritis: A Pilot Study

Joost Swart[1], Nico Wulffraat[2], Berent J. Prakken[3], Ineke Slaper-Cortenbach[4] and Caroline Lindemans[5], [1]PO Box 85090, UMC Utrecht, Utrecht, Netherlands, [2]University Medical Center Utrecht, Utrecht, Netherlands, [3]University Medical Center, Utrecht, Netherlands, [4]Cell Therapy Facility, University Medical Center Utrecht, Utrecht, Netherlands, [5]Pediatric Immunology, Wilhelmina Children's Hospital/ UMC Utrecht, Utrecht, Netherlands

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Background/Purpose: Juvenile Idiopathic Arthritis (JIA) is a frequent childhood disease with a prevalence of 1 per 1000 children. The introduction of the biological agents including have greatly improved the outcome. However a proportion of these children remains refractory to all of these drugs. We were the first to show earlier that using another form of cellular therapy, autologous SCT, was effective in some 50% of such children, even after 8 years of follow up. Given the immunosuppressive effects of Mesenchymal Stromal Cells (MSC) and clinical responses observed in animal models and human studies show that MSC could be an attractive and safe option for this group with the poorest clinical outcome. Infusion of MSC is quite simple compared to haemopoietic stem cell transplantation. It can be performed as a short-stay procedure and does not require hazardous treatment with myelo-ablative drugs. We believe that intravenous injection of MSC in therapy refractory JIA will be tolerated and will enable us to estimate the effect to plan for further studies.

Methods: Phase 2 pilot safety study in 6 therapy-refractory JIA patients with a maximum of 3 MSC-infusions according to the scheme (figure 1). Visit 1 starts at week 0, the next visit (visit 2) will be after 4 weeks, visit 3 at 8 weeks and so on. The main objective is to offer a safe alternative for therapy-resistant JIA patients as measured by the total number of adverse events in the 3 months after MSC infusion compared to 3 months before. Secondary aims: Effectiveness as measured by the active joint count, by the Juvenile Arthritis Disease Activity Score (JADAS) an by the erythrocyte sedimentation rate (ESR). Does infusion of MSC induce remission of inflammation as seen on MRI?

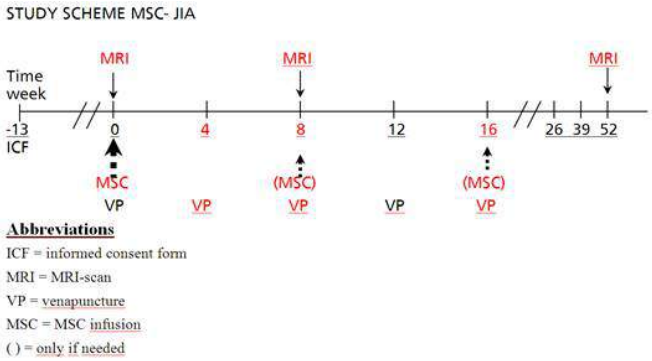

Figure 1.

Results: Currently, 3 of the 6 patients have been enrolled with now 4 MSC administrations given. Patient 1 is now at week 16 of the study (visit 4); patient 2 in week 12 (visit 3) and patient 3 in week 4 (visit 2). No new adverse events were yet observed during or after administration MSC. In all 3 patients, there was a decline in the number of active joints at final follow-up compared with study start. The same improvement was seen in JADAS (figure 2) with the ESR coming down after each MSC-infusion. The second follow-up MRI's of the first two patients had shown (slight) improvement in inflammation, but the pre-existing cartilage-damage did not improve.

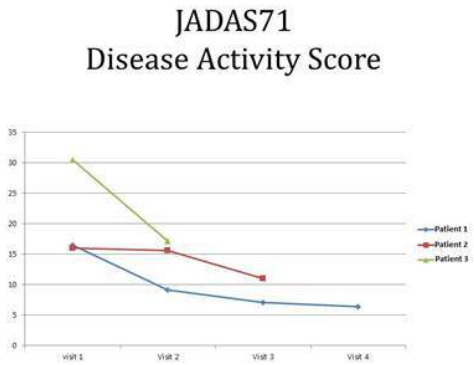

Figure 2.

Conclusion: The preliminary results of a Phase 2 pilot safety study show that MSC infusion in 3 therapy refractory JIA patients was safe. Furthermore there was a trend to improvement of the JIA in active joint count, disease activity score, ESR and improvement as seen on the MRI of an active joint.

Disclosure: J. Swart, None; **N. Wulffraat**, None; **B. J. Prakken**, None; **I. Slaper-Cortenbach**, None; **C. Lindemans**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/mesenchymal-stromal-cell-treatment-in-juvenile-idiopathic-arthritis-a-pilot-study

Abstract Number: 3181

How Common Is Inactive Disease in a Prospective Cohort of Patients with Juvenile Idiopathic Arthritis? the Importance of Definition

Stephanie Shoop[1], Suzanne M. Verstappen[2], Eileen Baildam[3], Alice Chieng[4], Joyce Davidson[5,6], Helen Foster[7], Yiannis Ioannou[8], Flora McErlane[7], Lucy R Wedderburn[9], Wendy Thomson[10] and Kimme L. Hyrich[10], [1]ARC Epidemiology, Stopford Building, ARC Epidemiology Unit, The University of Manchester, M13 9PT, United Kingdom, [2]ARC Epidemiology, Stopford Building, ARC Epidemiology Unit, the University of Manchester, Manchester, United Kingdom, [3]Paediatric Rheumatology, Alder Hey Children's NHS Foundation Trust, Liverpool, United Kingdom, [4]Royal Manchester Children's Hospital, Manchester, United Kingdom, [5]The Royal Hospital for Sick Children, Glasgow, Glasgow, United Kingdom, [6]The Royal Hospital for Sick Children, Edinburgh, Edinburgh, United Kingdom, [7]Royal Victoria Hospital, Newcastle, United Kingdom, [8]Rayne Institute, University College London, London, UK, London, United Kingdom, [9]Great Ormond Street Hospital NHS Foundation Trust, Paediatric Rheumatology, London, United Kingdom, [10]arc Epidemiology Unit, Manchester, United Kingdom
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Background/Purpose: Patients with JIA are at risk of disability, pain and joint damage in the longer-term. Treating toward clinically inactive disease (ID) has the potential to improve outcomes and standardise the quality of care provided across different clinical settings. A number of ID definitions have been developed for JIA. Few studies have compared the frequency of achieving ID across definitions in a single patient population.

Methods: Children were recruited to the Childhood Arthritis Prospective Study (CAPS), a JIA prospective inception cohort established in 2001. Single and composite definitions of ID and composite definitions of minimal disease activity (MDA) were applied to the cohort at one year following first presentation (Table 1). Composite definitions included Wallace's preliminary criteria and cut-offs on Juvenile Arthritis Disease Activity Score (JADAS) measures. Multiple imputation was used to account for missing variables at baseline and at one year.

Results: A total of 1415 children were included. At baseline, the median age was 7.7 years and 65% were female. The most common ILAR subtypes were oligoarticular (50%) and RF-negative polyarticular (21%) at one year. Median baseline JADAS71 score was 11.

At one year, 1331 patients remained in the study. Sixteen (1.1%) patients had been discharged due to low disease activity and a further 68 had been discharged for other reasons or lost-to-follow-up. At least one state of ID was achieved by 69% of patients (Table 1). Estimates of ID ranged from 20% using Wallace's preliminary criteria to 48% using parental remission on JADAS71. Physician, parent and child-driven JADAS cut-offs resulted in similar remission frequencies, with between 45% (Physician JADAS10) and 48% (Parental JADAS71) of patients achieving these states. There was very little difference between the frequency of remission using JADAS10 and JADAS71 tools, with a 1% maximum discrepancy using corresponding cut-offs.

MDA was achieved slightly more frequently than ID, with 51% patients achieving MDA on JADAS71. Other MDA definitions could only be applied to specific ILAR subtypes. In persistent oligoarticular JIA, 66% achieved MDA although the frequency in patients with extended oligoarticular, polyarticular or systemic JIA was lower at 50%. However, only 47% achieved MDA using cJADAS which excludes the systemic disease course.

Conclusion: The frequencies of patients achieving MDA and ID varied greatly between definitions, although a large proportion of children still had active disease one year following diagnosis. Estimates from the JADAS71, JADAS10 and cJADAS10 were similar supporting the use of the more clinically feasible JADAS tools. However the disparity in rates between the majority of measures has implications for research and clinical practice, where distinctly different disease states are being used as treatment targets in patients with JIA.

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Table 1. The frequency of Inactive Disease (ID) after one year of disease in patients recruited to the CAPS cohort

ID measure	Applied to which ILAR subtypes	Percent in ID (%; 95% CI) (n=1415)
Single measures of ID		
Discharge from rheumatology due to low disease activity	All	1.1 (0.6 to 1.7)
Active joint count = 0	All	64 (61 to 67)
Physician global assessment = 0	All	32 (29 to 35)
Parental global assessment = 0	All	23 (21 to 26)
Composite measures of ID		
Wallace's preliminary criteria for ID	All	20 (17 to 23)
ID using JADAS10	All	35 (31 to 39)
ID using JADAS71	All	35 (31 to 39)
Physician-assessed remission using JADAS10	All	45 (41 to 49)
Physician-assessed remission using JADAS71	All	45 (41 to 49)
Parent-assessed remission using JADAS10	All	47 (44 to 51)
Parent-assessed remission using JADAS71	All	48 (44 to 51)
Child-assessed remission using JADAS10	All	47 (43 to 51)
Child-assessed remission using JADAS71	All	47 (43 to 51)
ID using cJADAS10	Not systemic	37 (34 to 40)
Composite measures of MDA		
MDA using JADAS71	All	51 (47 to 55)
MDA using cJADAS10	Not systemic	47 (43 to 50)
MDA criteria in persistent oligoarticular JIA	Persistent oligoarticular	66 (62 to 71)
MDA criteria in other JIA subtypes	Extended oligoarticular RF negative polyarticular RF positive polyarticular Systemic	50 (45 to 55)

ID: Inactive disease, MDA: Minimal disease activity, JADAS: Juvenile Arthritis Disease Activity Score, cJADAS: JADAS excluding erythrocyte sedimentation rate, CI: Confidence Interval. 1. Wallace et al., 2004, 2. Consolaro et al., 2012, 3. Consolaro et al., 2014, 4. Magni-Manzoni et al., 2008.

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Abstract Number: 3182

High Body Mass Index Negatively Impacts Time to Achieving Sustained Remission in Early Rheumatoid Arthritis: Results from a Multicenter Early Arthritis Cohort Study

Elizabeth Schulman[1], Kathleen Andersen[2], Meng Zhang[3], Susan M. Goodman[4], Daming Lin[5], Gilles Boire[6], Boulos Haraoui[7], Carol Hitchon[8], Shahin Jamal[9], Edward C. Keystone[10], Janet E. Pope[11], Diane Tin[12], Carter Thorne[13], VP Bykerk[2] and CATCH Investigators, [1]Rheumatology, Hospital for Special Surgey, New York, NY, [2]Hospital for Special Surgery, New York, NY, [3]Epidemiology and Biostatistics, Hospital for Special Surgery, New York, NY, [4]Rheumatology, Hospital for Special Surgery, New York, NY, [5]Rheumatology, Mount Sinai Hospital, University of Toronto, Toronto, ON, Canada, [6]Department of Medicine/Division of Rheumatology, University of Sherbrooke, Sherbrooke, QC, Canada, [7]Institut de Rhumatologie de Montréal, Montréal, QC, Canada, [8]University of Manitoba, Winnipeg, MB, Canada, [9]Vancouver Coastal Health, Vancouver, BC, Canada, [10]Mount Sinai Hospital, University of Toronto, Toronto, ON, Canada, [11]University of Western Ontario, London, ON, Canada, [12]The Arthritis Program, Southlake Regional Health Centre, Newmarket, ON, Canada, [13]Southlake Regional Health Centre, Newmarket, ON, Canada

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Background/Purpose: High BMI has been associated with worse disease severity and lower rates of sustained remission (susREM) in early rheumatoid arthritis (ERA). In this study, we examined the relationship of increased BMI on time to susREM in patients with ERA.

Methods: Patients from the multicenter, prospective cohort study, CATCH (Canadian Early Arthritis Cohort) were analyzed. Patients with ERA (symptoms ≤12-months and fulfilling American College of Rheumatology 1987 and/or 2010 RA criteria), available BMI data, and at least 2 consecutive DAS-28 measurements met inclusion criteria. Underweight patients (BMI ≤18.5) were excluded due to small sample size (n=24). Patients were stratified into 3 BMI groups: normal (18.5-24.9), overweight (25-29.9), and obese (≥30), and time to sustained remission (time from 1st visit to DAS28≤2.6 at two consecutive visits) was assessed. A Kaplan Meier survival plot was generated along with the log-rank test to compare the time to susREM among the three BMI groups. Cox proportional hazard regression was performed to quantify the relationship between BMI groups and the hazard ratio for achieving susREM, after adjusting for statistically significant variables from univariate analysis and other identified potential confounders.

Results: Of 1066/2626 patients with available BMI, 348 (33%) had a normal BMI, 369 (35%) were overweight, and 348 (33%) were obese. Both Kaplan Meier curves (Figure 1) and log-rank test ($p<0.001$) showed the difference in the survival functions among the 3 BMI groups. The difference remained significant in the multivariate cox regression analysis. Specifically, patients in obese and overweight groups were less likely to achieve susREM quickly compared to those with normal BMI (HR=0.63, p=0.0008 and HR=0.75, p=0.03 respectively). Additionally, achieving DAS28≤3.2 by 6 months (HR 4.209, $p<0.01$), higher education (1.608, p=0.05), and use of methotrexate in the1st 3 months (1.401, p=0.02) were more likely to achieve susREM, while higher BMI, number of comorbidities (0.911, $p<0.01$), and use of steroids in 1st 3 months (0.761, p=0.01) were less likely to achieve susREM.

Conclusion: Overweight and obesity impact time and ability to achieve sustained remission. In addition to lower rates, patients with high BMI take longer to achieve sustained remission in ERA. Early methotrexate use is associated with shortened time whereas early steroid use is associated with prolonged time to sustained remission, independent of BMI. These findings support a growing body of evidence to include weight management interventions in ERA treatment plans.

FIGURE 1:

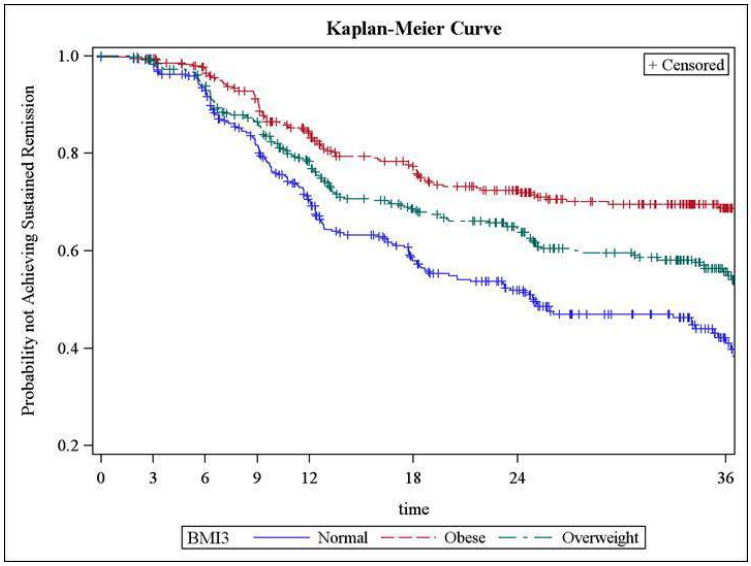

TABLE 1: Multivariate Analysis about the Relationship between Time to Sustained Remission and the Variables of Interest using Cox Regression*

Hazard ratio Estimate				
Parameter	Point Estimate	95% Confidence Interval		p-value
BMI Overweight vs Normal	0.75	0.59	0.97	**0.03**
BMI Obese vs Normal	0.63	0.48	0.82	**0.0008**
HAQ-DI	0.81	0.65	1.01	0.06
Pain (0-10)	0.99	0.94	1.04	0.74
DAS28<3.2 by 6 months (Yes vs No)	4.21	3.33	5.32	**<0.0001**
Age	1.00	0.99	1.00	0.22
Gender (Female vs Male)	0.80	0.63	1.00	0.07
Ethnicity (Non-Caucasian vs Caucasian)	0.72	0.51	1.02	0.06
Education >high school	1.61	1.00	2.58	**0.05**
Never/Ex smoker	1.35	0.99	1.84	0.06
Symptom Duration	1.00	1.00	1.00	0.88
CRP	1.01	1.00	1.01	0.14
Number of co-morbidities	0.91	0.09	0.98	**0.007**
MTX 1st 3 months	1.40	1.05	1.87	**0.02**
Steroids 1st 3 months	0.76	0.61	0.95	**0.01**

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Abstract Number: 3183

The Clinical and Economic Costs of Not Achieving Remission in Rheumatoid Arthritis

Jeffrey R. Curtis[1], Lang Chen[1,2], Meredith Kilgore[3], Huifeng Yun[4] and Jeffrey D. Greenberg[5], [1]University of Alabama at Birmingham, Birmingham, AL, [2]University of Alabama at Bimingham, Birmingham, AL, [3]Health Care Organization & Policy, University of Alabama at Birmingham, Birmingham, AL, [4]Epidemiology, University of Alabama at Birmingham, Birmingham, AL, [5]Corrona, LLC, Southborough, MA
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Background/Purpose: Treat to target guidelines recommend achieving a state of remission or low disease activity for rheumatoid arthritis (RA) patients. However, the benefit of lower disease activity for reduction of adverse events and costs is not clear. Our objective was to evaluate clinical outcomes and economic costs associated with RA disease activity states.

Methods: We used CORRONA data linked to national Medicare data to identify RA patients and their disease activity, measured using the Clinical Disease Activity Index (CDAI) captured at each registry visit. CDAI was modeled using a time-varying, area under the curve approach. Follow-up began at the date of the 2nd registry visit and the analysis was censored at time of the first event, 12/31/2012. Outcomes included all cause hospitalization, a composite of hospitalization or ED visits, mortality, and paid monthly healthcare costs. Outcome-specific Cox proportional hazards models evaluated the adjusted hazard ratios (aHR) between disease activity and outcomes, controlling for potential confounders. Costs were analyzed with mixed models using a Gaussian distribution with log transformation.

Results: Slightly depending on outcome, 4593 RA patients contributed up to 14,756 person years. Mean (SD) age was 69.8 (9.3) years, 75% women. At baseline, 59% of patients were in remission or low disease activity (LDA); 43.8% were on biologics. There was a strong dose-response relationship between the four categories of RA disease activity (remission, low, moderate, high) and incidence rate for hospitalization (13.7, 19.0, 23.1, 29.9 per 100py). For hospitalization, all aHR were significant: 0.65 (remission), 0.81 (low), and 1.16 (high) referent to

moderate. Similar crude and adjusted trends were observed for other outcomes. The crude difference in monthly costs between remission ($956/mo) and moderate disease activity ($1607/mo) was $651; the adjusted difference was -441.60 (-563.96, -319.24) per month.

Conclusion: Lower disease activity states in RA were associated with incrementally reduced risks of all-cause hospitalization, ED visits, mortality, and healthcare costs in a dose-dependent fashion.

Table 2a: Crude Rates* of Outcomes, by RA Disease Activity Associated with Cumulative, Time-Averaged CDAI

Disease Activity Category by CDAI	Hospitalization	ED Visit or Hospitalization	Death	Costs, $ per 30 days
Events, n Person-time, years	1,833 9,084.81	2,353 7,151.41	315 13,290.4	
Remission (<=2.8)	13.7 (12.0, 15.5)	26.3 (23.7, 29.3)	1.5 (1.1 2.1)	956.39 (895.08,1017.71)
Low (2.8-10)	19.0 (17.7, 20.4)	30.4 (28.6, 32.4)	2.3 (1.9, 2.7)	1269.27 (1228.46,1310.07)
Moderate (10-22)	23.1 (21.3, 25.1)	36.9(34.3, 39.6)	2.8 (2.3, 3.4)	1607.08 (1549.70,1664.46)
High (>22)	29.9 (26.4, 33.9)	46.3 (41.4, 51.8)	2.8 (2.0, 3.9)	1791.28 (1696.58,1885.97)

*Rate per 100py

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Is Treat-to-Target Really Working? a Longitudinal Analysis in Biodam

Sofia Ramiro[1], Robert B.M. Landewé[2], Désirée van der Heijde[1], Oliver FitzGerald[3], Mikkel Østergaard[4,5], Joanne Homik[6], Ori Elkayam[7], J Carter Thorne[8], Margaret Larche[9], Gianfranco Ferraccioli[10], Marina Backhaus[11], Gilles Boire[12], Bernard Combe[13], Thierry Schaeverbeke[14], Alain Saraux[15], Maxime Dougados[16], Silvano Adami[17], Marcello Govoni[18], Luigi Sinigaglia[19], Alain G. Cantagrel[20], Cornelia F. Allaart[1], Cheryl Barnabe[21], Clifton O. Bingham III[22], Paul P. Tak[23], Dirkjan van Schaardenburg[24], Hilde Berner Hammer[25], Rana Dadashova[26], Edna Hutchings[26], Joel Paschke[26] and Walter Maksymowych[27], [1]Rheumatology, Leiden University Medical Center, Leiden, Netherlands, [2]Department of Rheumatology, Amsterdam Rheumatology Center, Amsterdam, Netherlands, [3]Rheumatology, St Vincent's University Hospital, Dublin, Ireland, [4]Copenhagen Center for Arthritis Research, Copenhagen University Hospital at Glostrup, Glostrup, Denmark, [5]Rigshospitalet-Glostrup, Copenhagen Center for Arthritis Research, Center for Rheumatology and Spine Diseases, Rigshospitalet - Glostrup, Glostrup, Denmark, [6]Rheumatology, University of Alberta, Edmonton, AB, Canada, [7]Rheumatology, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel, [8]University of Toronto, Toronto, ON, Canada, [9]Rheumatology, McMaster University, Hamilton, ON, Canada, [10]Rheumatology and Internal Medicine, Catholic University of the Sacred Heart, Rome, Italy, [11]Rheumatology/Immunology, Charite University Hospital, Berlin, Germany, [12]Department of Medicine/Division of Rheumatology, University of Sherbrooke, Sherbrooke, QC, Canada, [13]Department of rheumatology, Lapeyronie Hospital and Montpellier University, Montpellier, France, [14]Rheumatology, Pellegrin University Hospital, Bordeaux, France, [15]Rheumatology Department, CHU de la Cavale Blanche, Brest Cedex, France, [16]Cochin Hospital, Paris Descartes University, Paris, France, [17]University of Verona, Verona, Italy, [18]University of Ferrara, Ferrara, Italy, [19]Department of Rheumatology, Gaetano Pini Institute, Milan,

Italy, [20]Dept of Rheumatology, Centre Hospitalier Universitaire de Toulouse, Toulouse, France, [21]Cumming School of Medicine, University of Calgary, Calgary, AB, Canada, [22]Rheumatology, Johns Hopkins University, Baltimore, MD, [23]Division of Clinical Immunology and Rheumatology, Amsterdam Rheumatology Center, Amsterdam, Netherlands, [24]Rheumatology, Amsterdam Rheumatology and immunology Center, Reade, Amsterdam, Netherlands, [25]Department of Rheumatology, Diakonhjemmet Hospital, Oslo, Norway, [26]CaRE Arthritis, Edmonton, AB, Canada, [27]Department of Medicine, University of Alberta, Edmonton, AB, Canada
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Background/Purpose: A Treat-to-Target approach (T2T), treating patients with RA towards a target, either remission or low disease activity (T2T-REM or T2T-LDA), is nowadays recommended. However it has never been assessed whether such a strategy in daily clinical practice really leads to more patients meeting that target.

Methods: Two-year data from BIODAM were used. BIODAM is a prospective cohort including RA patients in daily practice from 10 countries, who were started or changed on DMARD and/or anti-TNF treatment and were followed-up every 3 months. Participating physicians were required to practice treat-to-target per protocol. Per visit was decided whether a patient was treated according to T2T-REM or not. The T2T-REM principle was considered met: i) if a patient had already a disease activity score below the target (DAS28-CRP≤2.6) at a certain time point; or ii) if treatment was intensified (by increasing dosage or adding drugs) upon a DAS28>2.6. T2T-LDA was computed using the benchmark for low disease activity (DAS28≤3.2). The main outcome was the presence or absence of ACR/EULAR-boolean remission 3 months after T2T-REM or T2T-LDA. The relationship between T2T and ACR/EULAR Boolean remission 3 months later was investigated using generalized estimating equations with auto-regression.

Results: In total 3084 visits of 539 patients were included (mean (SD) age: 56 (13) years, 76% female, disease duration 6 (8) years, 49% DMARD-naive). In 68% of the visits, T2T-REM was applied (in 79% of the visits T2T-LDA was applied). ACR/EULAR-boolean remission was reached in 15% of the visits, DAS28 remission in 39%, DAS28-LDA in 53%, CDAI remission in 16% and SDAI in 18%. Appropriate application of T2T-REM led to a 52% higher likelihood of ACR/EULAR-boolean remission 3 months later than not applying T2T-REM (OR (95%CI): 1.52 (1.20; 1.93)). Both T2T-REM and T2T-LDA strategies led to lower disease activity (with an exception of DAS28 remission or DAS28-LDA)(see table). Only 9% of the treatment intensifications followed upon a DAS28 between 2.6 and 3.2, and 79% of the intensifications were applied upon a DAS28>3.2. The effect of T2T-REM on ACR/EULAR-boolean remission was stronger in DMARD-naive patients (OR: 2.10 (1.45; 3.03) than in DMARD-experienced patients (OR 1.20 (0.86; 1.66))(P-value for the interaction:<0.05).

Table - Effect of treat-to-target approach on disease activity outcomes 3 months later

		ACR/EULAR boolean remission (OR (95% CI))	DAS28 remission (OR (95% CI))	DAS28-LDA (OR (95% CI))	CDAI remission (OR (95% CI))	SDAI remission (OR (95% CI))
T2T-REM	Unadjusted	**1.49 (1.19; 1.86)**	0.99 (0.85; 1.15)	1.10 (0.94; 1.29)	**1.47 (1.18; 1.83)**	**1.62 (1.32; 2.00)**
	Adjusted*	**1.52 (1.20; 1.93)**	0.96 (0.82; 1.13)	1.09 (0.93; 1.27)	**1.49 (1.18; 1.88)**	**1.62 (1.30; 2.02)**
T2T-LDA	Unadjusted	**1.95 (1.46; 2.61)**	**1.37 (1.14; 1.64)**	**1.30 (1.09; 1.56)**	**2.24 (1.66; 3.01)**	**2.53 (1.90; 3.38)**
	Adjusted*	**2.14 (1.56; 2.95)**	**1.36 (1.12; 1.64)**	**1.30 (1.08; 1.56)**	**2.46 (1.77; 3.43)**	**2.74 (2.00; 3.76)**

* Adjusted for age, gender and disease duration

T2T-REM: treat-to-target with remission (DAS28≤2.6) as benchmark; T2T-LDA: treat-to-target with low disease activity (DAS28≤3.2) as benchmark

Conclusion: A treat-to-target approach, even with a modest benchmark (DAS28=3.2), works instantaneously and leads to higher ACR/EULAR-remission rates. T2T is more effective in DMARD-naïve than in DMARD-experienced patients. Rheumatologists should be encouraged to follow a treat-to-target approach in order to improve the outcome of their patients.

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Abstract Number: 3185

A Cluster-Randomized Trial of a Behavioral Intervention to Incorporate a Treat-to-Target Approach in the Clinical Care of Rheumatoid Arthritis Patients in the United States

Leslie Harrold[1,2], George W. Reed[1,2], J. Timothy Harrington[3], Christine J. Barr[1], Katherine C. Saunders[1], Allan Gibofsky[4], Eric M. Ruderman[5], Tmirah Haselkorn[6], Jeffrey D. Greenberg[1,7], Ani John[6] and Joel M. Kremer[8], [1]Corrona, LLC, Southborough, MA, [2]University of Massachusetts Medical School, Worcester, MA, [3]Joiner Associates, LLC, Madison, WI, [4]Hospital for Special Surgery, New York, NY, [5]Medicine, Division of Rheumatology, Northwestern University Feinberg School of Medicine, Chicago, IL, [6]Genentech, Inc, South San Francisco, CA, [7]NYU School of Medicine, New York, NY, [8]Albany Medical College and The Center for Rheumatology, Albany, NY

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Background/Purpose: We report the results of a cluster-randomized behavioral intervention trial designed to assess the impact of implementing a treat-to-target (T2T) approach vs usual care (UC) in a large, US-based, observational cohort of rheumatoid arthritis (RA) patients.

Methods: Thirty-one rheumatology practices from the Corrona network were randomly assigned to either T2T (n=16) or UC (n=15) between July 29, 2011 and July 30, 2013. Eligible RA patients with moderate or high disease activity (Clinical Disease Activity Index [CDAI>10]) were followed for 12 months. In the T2T group, encounters associated with a CDAI>10 were to result in treatment acceleration (e.g., a new initiation or dose increase of a prescribed biologic or nonbiologic DMARD) when deemed appropriate, with a follow-up appointment in 4 weeks. In contrast, UC patients were seen at least every 3 months with treatment changes and follow-up visits decided by the treating provider. Co-primary endpoints were achievement of low disease activity (LDA; CDAI≤10) and measures of feasibility, most importantly treatment acceleration conditional on CDAI>10. Baseline characteristics of the T2T and UC groups were compared using standardized differences. An intent-to-treat analysis was performed adjusting for clustering by site and covariates associated with standardized differences >0.10.

Results: There were 246 patients in the T2T practices and 286 from UC practices enrolled. The 2 groups were similar in terms of mean age, gender and race, but not Hispanic ethnicity (**Table 1**). Patients had similar clinical features (disease duration, rheumatoid factor seropositivity, prior medications and current medications) at baseline. During the 12-month study period, 19.9% of the T2T group and 16.4% of the UC group dropped out (p=0.457). Median (IQR) number of visits in the T2T group was 7.0 (5.2-9.7) compared to 4.6 (3.8-6.7) in the UC group, adjusting for clustering and varied person time (p<0.001). Rates of treatment acceleration and achievement of LDA were similar in the 2 groups (**Table 2**). There were no differences between the 2 arms in terms of trends in LDA over time (p=0.20).

Conclusion: This first US-based T2T behavioral intervention in RA patients was not associated with an increased likelihood of achievement of LDA, and acceleration occurred only ≈50% of the time, despite providers being instructed to have more frequent visits and accelerate therapy based upon disease activity in the T2T arm. Further analysis is ongoing to better understand patient, provider and healthcare factors associated with T2T implementation.

Table 1. Baseline Demographic and Clinical Characteristics of the T2T and UC Study Populations

Characteristic	Population Comparisons		Standardized Differences
	T2T Population N=246	UC Population N=286	
Age, mean (SD), years	57.0 (12.8)	58.0 (13.1)	0.08
Female, n (%)	196 (79.7)	224 (79.4)	0.01
White, n (%) [Total][a]	181 (87.9) [n=206]	224 (89.6) [n=250]	0.06
Hispanic, n (%) [Total][a]	47 (22.4) [n=210]	18 (8.2) [n=219]	0.40
Medicare, n (%)	60 (26.8)	86 (32.6)	0.13
Not working, n (%)	23 (9.5)	15 (5.4)	0.16
Working part time, n (%)	19 (7.8)	33 (11.8)	0.13
RF seropositivity, n (%) [Total][b]	124 (67.4) [n=184]	153 (73.9) [n=207]	0.14
Disease duration, mean (SD), years	7.3 (9.5)	8.4 (9.4)	0.12
Clinical Disease Activity Index, mean (SD)	26.7 (13.4)	25.5 (11.8)	0.09
No. of prior biologics/small molecules (including current), n (%)			
0	105 (42.7)	115 (40.2)	0.05
1	88 (35.8)	88 (30.8)	0.11
≥2	53 (21.5)	83 (29.0)	0.17
Current biologic/small molecule use, n (%)	118 (48.0)	146 (51.1)	0.06
Current conventional synthetic DMARDs use, n (%)	201 (81.7)	231 (80.8)	0.02
Current corticosteroid use, n (%)	92 (37.4)	103 (36.0)	0.03

DMARD, disease-modifying antirheumatic drug; RF, rheumatoid factor; SD, standard deviation; T2T, treat-to-target; UC, usual care.
[a]Patient self-reported.
[b]Seropositivity status was not required.

Table 2. Outcomes at 12 Months in the T2T and UC Study Populations

	T2T	UC	Adjusted OR (95% CI)[a]	Multivariable Adjusted OR (95% CI)[b]
Primary Feasibility Outcome				
Probability of acceleration conditional on CDAI>10, %	46.6	46.9	0.96 (0.61-1.50)	0.92 (0.64-1.34)
Primary Efficacy Outcome				
Overall achievement of LDA, %	56.5	54.6	0.90 (0.50-1.62)	1.05 (0.60-1.84)
Secondary Efficacy Outcomes				
Achievement of LDA among those who completed the study, %	61.4	57.3	0.94 (0.51-1.73)	1.09 (0.62-1.91)

CDAI, Clinical Disease Activity Index; DMARD, disease-modifying antirheumatic drug; LDA, low disease activity; RF, rheumatoid factor; T2T, treat-to-target; UC, usual care.
[a]T2T vs UC adjusted for clustering by patient, physician and practice site for the feasibility outcomes and for the efficacy outcomes adjusted for physician only.
[b]Adjusted for age, Hispanic ethnicity, Medicare insurance, RF seropositivity, disease duration, number of prior biologics, number of prior conventional synthetic DMARDs, current biologic/small molecule use and clustering.

Disclosure: **L. Harrold**, Corrona, LLC, 3; **G. W. Reed**, Corrona, LLC, 3; **J. T. Harrington**, Crescendo Bioscience, 5; **C. J. Barr**, Corrona, LLC, 3; **K. C. Saunders**, Corrona, LLC, 3; **A. Gibofsky**, AbbVie, Amgen, BMS, GlaxoSmithKline, Johnson & Johnson and Pfizer, 1,AbbVie, Celgene, Drais, Horizon, Iroko, Medac, Pfizer, Relburn, Samumed and Takeda, 5,AbbVie, Amgen, Celgene, Iroko and Pfizer, 8; **E. M. Ruderman**, Amgen, AbbVie, Corrona, Eli Lilly, Janssen, Novartis and Pfizer, 5; **T. Haselkorn**, Genentech, Inc, 3; **J. D. Greenberg**, Corrona, LLC, 1,Corrona, LLC, 3,AstraZeneca, Celgene, Novartis and Pfizer, 5; **A. John**, Genentech, Inc, 3; **J. M. Kremer**, Corrona, LLC, 1,Corrona, LLC, 3,Genentech, Inc, 5,Genentech, Inc, 2.

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Abstract Number: 3186

Foot Synovitis in Patients with Rheumatoid Arthritis in Apparent Remission Is Associated with Unstable Remission Status, Radiographic Progression and Worse Long-Term Functional Outcomes

Mihir D. Wechalekar[1,2,3], Susan Lester[4,5], Maureen Rischmueller[6,7], Catherine Hill[8,9] and Susanna Proudman[1,8], [1]Rheumatology Unit, Royal Adelaide Hospital, Adelaide, Australia, [2]School of Medicine, Flinders University School of Medicine, Adelaide, Australia, [3]Repatriation General Hospital, Rheumatology Research Unit, Daw Park, Australia, [4]Rheumatology, Basil Hetzel Institute, QEH, Woodville South, Australia, [5]Rheumatology Unit, The Queen Elizabeth Hospital, Woodville, Australia, [6]Rheumatology, The Queen Elizabeth Hospital, Adelaide, Australia, [7]University of Adelaide, Adelaide, Australia, [8]Discipline of Medicine, University of Adelaide, Adelaide, Australia, [9]The Queen Elizabeth Hospital, Woodville South, South Australia, Australia

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Background/Purpose: Previous cross-sectional data revealed disease activity (DA) measures that omit foot joint assessment inadequately capture foot synovitis in in apparent remission at 6 months[1]. We sought to determine whether foot synovitis is associated with adverse radiographic and functional outcomes after 3 years in an inception cohort receiving treat-to-target combination DMARD therapy.

Methods: Patients with early RA (<1 year; fulfilling ACR 1987 and/or 2010 classification criteria) were included. Remission was assessed using DAS28, clinical disease activity index (CDAI) and simplified disease activity index (SDAI); radiographic outcomes by annual hand and feet radiographs scored by the van der Heijde modified Sharp score and quality of life by SF-36. The prevalence of remission by different DA criteria and presence of foot synovitis was estimated using marginal binomial generalised estimating equations and transition between disease remission and non-remission states using a multi-state Markov model. Changes in radiographic scores were analysed using negative binomial mixed regression log-link model. SF-36 data were transformed to a norm-based scale (NBS) using population matched data and analysed by mixed effects linear regression.

Results: Baseline DA in 266 patients was 5.43 (SD 1.27). Dynamic correlation revealed DA scores that omit foot joint scores were modest in their ability to capture foot synovitis over time. Despite relative stringency of SDAI and CDAI as remission criteria, a significant proportion of patients in remission had foot synovitis, ranging from 25-36% (Table 1). In patients in apparent remission, foot synovitis predicted transition from remission into relapse by up to 2-fold (Table 2), and the sustainability of remission markedly influenced progression of erosion scores (p=0.006) After adjustment for DA, foot synovitis was associated with significantly worse SF-36 physical functioning subscale (p=0.025).

Table 1. Proportion of patients in remission

	DAS28 (CRP)	DAS28 (ESR)	SDAI	CDAI
Patients in remission, with or without foot synovitis (95%CI)	0.47 (0.11, 0.51)	0.43 (0.10, 0.47)	0.28 (0.05, 0.32)	0.27 (0.05, 0.31)
Patients in remission with foot synovitis (95% CI)	0.35 (0.29, 0.41)	0.36 (0.30, 0.42)	0.24 (0.18, 0.30)	0.25 (0.19, 0.32)

Table 2. The effect of foot synovitis on transition from remission to non-remission and vice versa

Transition Hazard Ratio (95% CI)	**DAS28(CRP)**	**DAS28(ESR)**	**SDAI**	**CDAI**
Non-remission to Remission	0.68 (0.42, 1.10)	0.70 (0.45, 1.10)	0.70 (0.40, 1.24)	0.68 (0.39, 1.17)
Remission to Non-remission	1.47 (0.84, 2.57)	1.81 (1.03, 3.17)	2.06 (1.00, 4.26)	2.08 (1.03, 4.18)
Likelihood Ratio test p-value	0.015	0.002	0.0004	0.0002

Conclusion:

DA measures that omit foot joints capture foot synovitis poorly. When used to define remission, a substantial proportion have foot synovitis which predicts relapse into non-remission and worse physical function. Foot synovitis influences sustainability of remission which in turn markedly influences radiographic progression. Presence of foot synovitis regardless of remission status should warrant consideration of escalation of therapy to improve long-term outcomes.

[1] Wechalekar MD *et al.* Arthritis Rheum 2012;64:1316-22.

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Abstract Number: 3187

Predictors of Disease Relapse and Recapture of Remission Following Relapse in an Ontario Rheumatoid Arthritis Population

Bindee Kuriya[1], Xiuying Li[2], George A. Tomlinson[3], Edward C. Keystone[4], Claire Bombardier[2] and OBRI Investigators, [1]Rheumatology, Mount Sinai Hospital, University of Toronto, Toronto, ON, Canada, [2]Toronto General Hospital Research Institute, University Health Network, Toronto, ON, Canada, [3]Medicine, Mount Sinai Hospital, Toronto, ON, Canada, [4]Mount Sinai Hospital, University of Toronto, Toronto, ON, Canada

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Background/Purpose: The timing and severity of relapse and likelihood of "recapturing" remission following a relapse in RA is not well known. We aimed to describe time-to-relapse, as well as factors associated with relapse and subsequent remission after disease relapse.

Methods: We performed a longitudinal analysis of patients enrolled in the Ontario Best Practices Research Initiative (OBRI), a clinical registry of RA patients in routine care. First clinical remission according to DAS28-ESR <2.6 following cohort entry was determined. Patients achieving remission with >/= 1 follow-up visit were observed for the average time until relapse (DAS28 >2.6). Disease activity at relapse as well as the prevalence and timing of subsequent remission was examined. Cox proportional hazards models calculated the hazard of remission and relapse adjusted for baseline variables and time-varying disease activity and medication changes.

Results: The total cohort (N=2591) was 78% female with mean age 57 (13) years. Remission was achieved in 1258 patients (60%) with median time-to-first-remission of 314 days (IQR 153,552). Early RA was the only positive predictor of remission (Table). Among the remission group, 1117 had follow-up and 776 (69%) went on to experience a relapse. Median time-to-relapse was 204 days (IQR 129-390) and the majority switched from a state of remission to mild or moderate disease activity, in contrast to moderate or severe levels of disease activity they experienced at baseline. In the multivariable analysis, relapse was significantly associated with female sex, higher DAS28 preceding relapse and use of biologic DMARD (bioDMARD) monotherapy and/or corticosteroids in the interval between remission and relapse; combination conventional synthetic DMARD (csDMARD) appeared to protect against the risk of relapse (Table). 452 (58%) patients regained remission after spending a median of 209 days (IQR 126-386) in a state of relapse. Similar variables associated with first remission, including disease duration and receipt of combination csDMARD or bioDMARD after relapse, were negatively associated with regaining remission (Table).

Conclusion: Clinical remission in routine care is achievable but relapses to states of low or moderate disease activity are common and may last several months. High disease activity and need for biologics or corticosteroids may predict those at highest risk for relapse. Recapturing remission after a relapse appears possible but occurs at a lower frequency than initial remission. Additional investigation about the optimal timing, dosing and sequence of DMARD therapy needed to maintain and recapture remission will inform how to best manage and prevent disease flares.

Table. Multivariable analysis with hazard ratios and 95% confidence intervals of time-to-remission and time-to-relapse.

	Time-to-First Remission	Time-to-Relapse	Time-to-Recapture-Remission
Variable	**HR (95%CI)**	**HR (95%CI)**	**HR (95%CI)**
Female	**0.68 (0.58-0.81)**	**1.23 (1.01-1.52)**	1.07 (0.84-1.37)
Age, years	**0.99 (0.98-0.99)**	0.99 (0.98-1.00)	1.00 (0.99-1.01)
Private Insurance	0.98 (0.85-1.13)	**0.76 (0.63-0.91)**	--
College Education	0.98 (0.85-1.12)	**0.83 (0.70-0.98)**	**1.26 (1.02-1.55)**
Early RA	**1.52 (1.32-1.75)**	1.01 (1.00-1.01)	--
RA > 5 years duration	--	--	**0.62 (0.47-0.81)**
HAQ (0-3)	**0.59 (0.52-0.68)**	1.09 (0.93-1.29)	0.96 (0.79-1.15)
DAS28-ESR	**0.83 (0.79-0.88)**	**1.12 (1.04-1.20)**	0.94 (0.76-1.15)
Pain Score (0-10)	**0.82 (0.74-0.92)**	0.95 (0.83-1.09)	0.93 (0.80-1.08)
Combination Therapy (csDMARD + bDMARD)	**0.19 (0.11-0.35)**	0.83 (0.66-1.05)	**0.45 (0.34-0.59)**
Combination Therapy (csDMARD)	**0.39 (0.23-0.69)**	**0.72 (0.57-0.89)**	**0.42 (0.33-0.54)**
Monotherapy (csDMARD)	0.82 (0.47-1.46)	--	--
Monotherapy (bDMARD)	0.54 (0.29-1.01)	**1.76 (1.22-2.54)**	0.97 (0.62-1.52)
Corticosteroids	1.02 (0.75-1.37)	**2.42 (1.96-3.47)**	--

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Pharmaceuticals, 5,Pfizer Pharmaceuticals, 5; **C. Bombardier**, None.

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Abstract Number: 3188

Inhibition of Lymphatic Muscle Contraction By Lymphatic Endothelial iNOS Impairs Lymph Drainage from Arthritic Joints in TNF-Tg Mice and Is Prevented By Herbal Drugs

Qianqian Liang[1], Yan Chen[1], Jinlong Li[1], Wensheng Wang[2], Li Zhang[1], Hao Xu[1], Ronald Wood[2], Brendan Boyce[2], Edward Schwarz[3], Yongjun Wang[1] and Lianping Xing[4], [1]Longhua Hospital, Shanghai University of Traditional Chinese Medicine, Shanghai, China, [2]University of Rochester, Rochester, NY, [3]Orthopedeatrics, University of Rochester, Rochester, NY, [4]University of Rochester Medical Center, Rochester, NY
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Background/Purpose: We reported previously that inflammation in TNF-Tg mice, a model of rheumatoid arthritis (RA), inhibits lymphatic vessel maturation, resulting in decreased lymphatic smooth muscle cell (LSMC) coverage and lymph leakage, thereby reduced draining function. Here, we investigatedthe mechanisms responsible for LSMCdysfunction in TNF-Tg mice and if existing drugs could be used asnew lymphatic-based therapy for RA.Wetestedthe hypotheses:1) chronic jointinflammation stimulateslymphatic endothelial cells(LECs) to produce iNOS, leading to reduced draining functionvia inhibition of LSMC contraction; and 2)Ferulic acid (FLA) andPanaxNotoginsengSaponins(PNS), herbal drugs that have been used to treat patients with vascular diseases, reduce LEC iNOSand restoreLSMC/lymphatic vessel function toattenuate RA.

Methods: TNF-Tg mice and WT littermates were used. 1)iNOS expression was examined by qPCR in synovial LECs that were purified with anti-Podoplanin Ab-conjugated beads, and by immunostaining in the collecting lymphatic vessels. (2) The effect of LECs on LSMCs that were isolated from rat mesenteric lymphatic vessels were assessed by pre-treating LECs with TNF on glass coverslips, transferring LECs to LSMC cultures, and measuring expression of functional muscle genes in LSMCs by qPCR and Western blot. 3)TNF-Tg mice were treated with the herbal drugs,FLA orPNS, or vehicle for 3 months. Lymphatic draining function, including clearance and pulse,was measured by indocyanine green near-infrared lymphatic imaging, and tissue damage was determined by histology. 4) The effects of FLA and PNS on LEC inhibition of LSMCs were tested in co-cultures, as in (3).

Results: 1) Synovial LECs from TNF-Tg mice expressed higher levels of *nos2*thanWT LECs (8.4+2.7 vs. 1+0.4) and these were greater than those observed for*nos1*and *tnf*(*nos1*: 2.4+SD,*tnf*: 3.8+0.7). Low levels of TNF (0.1ng/mL) stimulated the expression of *nos2*,but not *nos1*and *tnf*, in LECs (*nos2:* 40+11, *nos1*: 6.5+2.5, *tnf:*2.4+0.9). Immunostainingrevealedthat LECs in the collecting lymphatic vessels from TNF-Tg mouse leg stained strongly positively for iNOS.2) TNF pre-treated LECssignificantly decreased expression of multiple functional muscle genes (*h1-calponin, sMYH11, SMα2* and *SMα22*)in LMSCs at mRNA and protein levels, which was blocked by a NO inhibitor. 3) FLA and PNS significantly improved lymph clearance of ankle tissues, restored lymphatic pulses, and markedly reduced joint inflammation, bone erosion and cartilage loss inTNF-Tg mice in comparison with vehicle-treated TNF-Tg mice. 4) FLA and PNS blocked the inhibitory effects on expression of LSMC functional genes in LECs withpre-treated TNF.

Conclusion: In the setting ofchronic inflammation in TNF-Tg mice, LECs express high levels of iNOS and produce NO, which negatively affects the structure and contractile function of LSMCs, leading to impaired lymphatic drainagefrom collecting lymphatic vessels, and exacerbates inflammation and tissue damage in afferent joints.Herbal drugscommonly used to treat patients with vascular diseases have potential as anti-RA agents based on theirinhibition of NO production and preservation of lymphatic function.

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Abstract Number: 3189

Enhancement of Mitochondrial Biogenesis Inhibits Cell Proliferation and MMP-

3/RANKL Secretion in Rheumatoid Arthritis Fibroblast-like Synovial Cells and Joint Destruction in Arthritis Model Mice

Takeshi Ueha[1], Yoshitada Sakai[1], Masayuki Morishita[2], Toshihisa Maeda[2], Koji Fukuda[2], Miho Inoue[2], Risa Harada[2], Masaya Minoda[2], Yasushi Miura[3,4,5], Akira Hashiramoto[6] and Masahiro Kurosaka[1,4], [1]Division of Rehabilitation Medicine, Kobe University Graduate School of Medicine, Kobe, Japan, [2]Department of Orthopaedic Surgery, Kobe University Graduate School of Medicine, Kobe, Japan, [3]Orthopaedic Surgery, Kobe University Graduate School of Medicine, Kobe, Japan, [4]Orthpaedic Surgery, Kobe University Graduate School of Medicine, Kobe, Japan, [5]Department of Rehabilitation Science, Kobe University Graduate School of Health Sciences, Kobe, Japan, [6]Department of Biophysics, Kobe University Graduate School of Health Sciences, Kobe, Japan

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Background/Purpose: Joint destruction in rheumatoid arthritis (RA) progresses via the hyperproliferation of the synovium and secretion of MMP-3/RANKL from fibroblast-like synoviocytes (FLS). In tumors, we previously reported that the expression of mitochondria-related genes is low and increased numbers of mitochondria enhance cell apoptosis. However, the relationship between mitochondrial biogenesis and joint destruction in RA remains unclear. To elucidate this relationship, we measured the expression levels of mitochondria-related genes and mitochondrial DNA in RA-FLS and osteoarthritic (OA)-FLS. We then tested the effects of AICAR (5-Aminoimidazole-4-carboxamide ribonucleotide), an enhancer of mitochondrial biogenesis, on MMP-3/RANKL secretion in RA-FLS and on joint destruction in collagen-induced arthritis (CIA) mice.

Methods: Quantitative PCR was used to assess the expression levels of mitochondria-related mRNA (PGC-1a, NRF-1, and TFAM) and number of mitochondrial DNA (mtDNA) in RA- and OA-FLS. The effect of AICAR (2 mM) on mitochondrial biogenesis in RA-FLS was assessed in the same way. Cell viability was assessed using WST assay, and MMP-3/RANKL secretion was measured using an immunoassay (immunoblot and ELISA) with/without IL-1b or TNFa stimulation. For evaluating the effect of AICAR (500 mg/kg) on joint destruction in CIA mice, micro-CT was used.

Results: The expression of NRF-1 and TFAM and the levels of mtDNA were lower in RA-FLS than in OA-FLS (Fig. 1). In RA-FLS, the levels of mtDNA and mRNA expression of mitochondria-related genes were enhanced by AICAR (Fig. 2a, 2b). AICAR inhibited cell viability and IL-1b- or TNFa-induced MMP-3/RANKL secretion in inflammation-induced RA-FLS (Fig. 2c, 2d). Moreover, AICAR reduced the arthritis score and joint destruction in CIA mice (Fig. 3).

Conclusion: Downregulation of mitochondrial biogenesis is related to the disease state of RA, and enhancement of mitochondrial biogenesis resulted in the suppression of disease activities of RA, such as reducing RA-FLS viability, secretion of MMP-3/RANKL from RA-FLS, and joint destruction in CIA mice. A novel therapeutic approach by changing mitochondrial biogenesis is proposed.

Fig.1 Clinical data (RA-FLS VS OA-FLS)

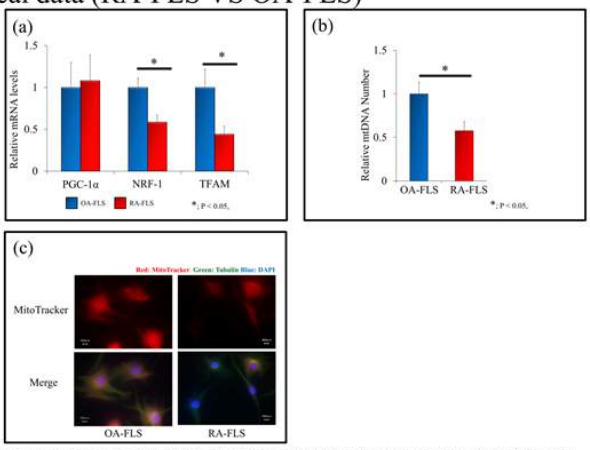

Fig.1 **Downregulation of mitochondrial biogenesis in RA-FLS** (a) mRNA expression of mitochondria-related genes (PGC-1α, NRF-1, TFAM) in RA-FLS and OA-FLS (b) Numbers of mitochondrial DNA in RA-FLS and OA-FLS (c) Immunostaining for mitochondria in RA-FLS and OA-FLS.

Fig.2 Mitochondria-activated drug in human RA-FLS

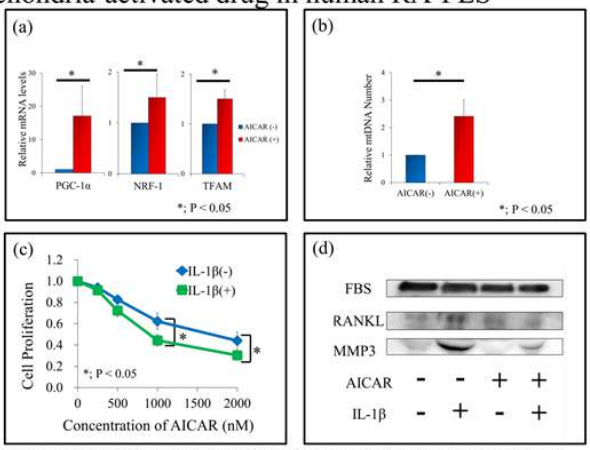

Fig.2 **Activated mitochondrial biogenesis in RA-FLS inhibited cell proliferation and secretion of MMP-3/RANKL.** (a) mRNA expression of mitochondria-related genes with/without AICAR (b) Numbers of mitochondrial DNA with/without AICAR (c) Cell proliferation at different concentrations of AICAR with/without IL-1β (d) Immunoblot from RA-FLS with/without IL-1β and with/without AICAR.

Fig.3 Mitochondria-activated drug in CIA mice

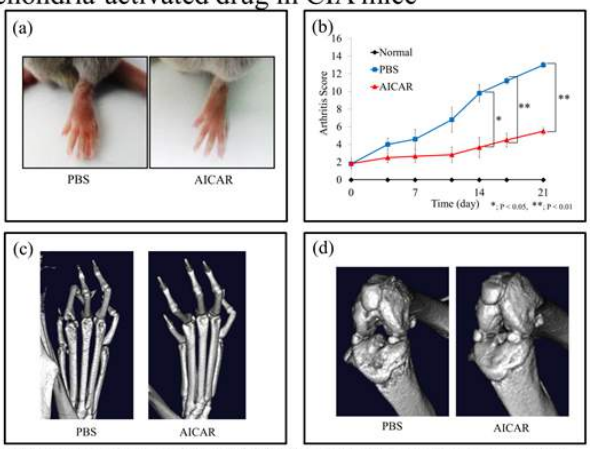

Fig.3 **Activated mitochondrial biogenesis in CIA mice decreased the arthritis score and inhibited joint destruction.** (a) Effects of AICAR on the severity and progression of arthritis in CIA mice 21 days after treatment. (b) Arthritis scores. (c, d) Micro-CT scans of AICAR treatment in CIA mice, showing the 3-D reconstructed bones of ankle (c) and knee joints (d).

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Abstract Number: 3190

Netrin-1 and Its Receptor Unc5b Are Novel Targets for the Treatment of Inflammatory Arthritis

Aranzazu Mediero[1], Tuere Wilder[2] and Bruce Cronstein[3], [1]Medicine, Divison of Translational Medicine, NYU School of Medicine, New York City, NY, [2]Dept of Med, Div of Rheum, NYU School of Medicine, New York, NY, [3]Medicine, Division of Rheumatology, NYU School of Medicine, NEW YORK, NY

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Background/Purpose: Rheumatoid arthritis (RA) is an autoimmune disease that causes chronic inflammation and destruction of the joints and some extra-articular tissues. Netrin-1 is a laminin-like matrix protein that acts as a chemorepulsant and which is expressed during and required for osteoclast differentiation. In other settings Netrin1 has been reported to play a pathogenic role during inflammation by preventing macrophage egress from inflamed sites. Therefore, we asked whether blockade of Netrin-1 or its receptors Unc5b and DCC may be useful therapeutic targets in the treatment of inflammatory arthritis.

Methods: The K/BxN serum transfer model was used. 8wk old C57Bl/6 mice were injected ip with 0.2ml K/BxN serum at day 0 and 2, and at the same time murine monoclonal antibodies against Netrin-1, Unc5b or DCC (10μg/mice) were injected ip (n=10 each). Antibodies were administered weekly for up to 4 weeks. Clinical signs like paw swelling and thickness were measured daily using a caliper. The scores of all four paws were added for a composite score. Animals were sacrificed 2 and 4 weeks after serum transfer, and legs were prepared for microCT and histology.

Results: Serum transfer induced an increase in paw inflammation that was maximal 2 weeks after injection, and weekly ip injection of anti-Netrin-1 or anti-Unc5b antibodies significantly reduced paw inflammation (clinical score of 9.8±0.8 and 10.4±0.9 respectively vs. 16±0 for control, $p<0.001$, n=10) whereas anti-DCC antibodies had no effect (13.5±0.5 vs. 16±0 for control, p=ns, n=10). The same results were observed for changes in paw thickness; weekly ip injection of anti-Netrin-1 or anti-Unc5b antibodies significantly reduced the change in paw thickness from baseline 2 weeks after serum transfer (0.4±0.05mm and 0.3±0.4mm respectively vs. 0.7±0.02mm for control, $p<0.001$, n=10) and anti-DCC antibodies had no effect (0.6±0.04 vs. 0.7±0.02 for control, p=ns, n=10). microCT analysis showed bony erosions in untreated or anti-DCC treated mice whereas there were no erosions in anti-Netrin-1 and anti-Unc5b treated animals. TRAP staining demonstrated a marked decrease in osteoclasts in anti-Netrin-1 and anti-Unc5b treated animals but not in anti-DCC treated or control mice (4±1 3±1 and 9±2 cells/hpf respectively vs.12±1 cells/hpf for control, $p<0.001$ and p=ns, n=5). Immunofluorescence staining revealed decrease Cathepsin K and CD68-positive cells in bones and joints of anti-Netrin-1 and anti-Unc5b treated animals but not in anti-DCC treated or control mice but Alkaline Phosphatase immunostaining for osteoblasts was not affected by any of the treatments.

Conclusion: Blockade of Netrin-1 and its receptor Unc5b by treatment, *in vivo*, with murine monoclonal antibodies prevents bone destruction and K/BxN serum transfer-induced arthritis. Netrin-1 may be a novel therapeutic target for inflammatory bone destruction and other forms of osteoclast-mediated bone resorption.

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Abstract Number: 3191

Siglec9 Suppresses Arthritis in Collagen-Induced Mice Model and Inhibits M1 Activation of RAW264.7 Macrophages

Takuya Matsumoto[1], Nobunori Takahashi[1], Toshihisa Kojima[1] and Naoki Ishiguro[2], [1]Department of Orthopedic Surgery, Nagoya University Hospital, Nagoya, Japan, [2]Department of Orthopedic Suregery, Nagoya University Hospital, Nagoya, Japan

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Background/Purpose: Siglecs (Sialic acid-binding immunoglobulin-type lectins) are type1 transmembrane proteins and expressed on cell surface of various immunocytes. Siglec9 is a member of CD33 related Siglecs which down-regulate both innate and acquired immune response. In our earlier studies, soluble Siglec9 was identified in the culture supernatant fluid of pulpal cells as a powerful anti-inflammatory element and has been found to be effective in several inflammatory diseases. The aim of this study is to investigate the efficacy of Siglec9 on murine collagen induced arthritis (CIA) model *in vivo* and the activation of cultured murine macrophage *in vitro*.

Methods: To initiate CIA model, DBA/1J mice were immunized subcutaneously with bovine type II collagen emulsified with adjuvant. Recombinant Siglec9 (5 or 50ng/gm body weight) was administered intravenously to the mice with CIA weekly from day 23 (primary immunization in day 0) to day 42. The arthritis score and the histologic score were evaluated using the parameters described in a previous report. The serum concentration of TNFα was measured using an ELISA assay. In vitro, murine macrophage cell-line RAW264.7 was cultured in monolayers, stimulated with 10 ng/ml of IFNγ, and concurrently treated with Siglec9 (0–10ng/ml) for 12 hours. Total RNA was extracted and subjected to real-time polymerase chain reaction (PCR) analysis to determine the mRNA expression of TNFα, IL-6, iNOS, as M1 markers, and CD206, Arginage-1, as M2 markers and GAPDH for RAW264.7. The effect of Siglec9 on the expression levels of TNFα, IL-6, and iNOS

protein in RAW264.7 was evaluated by ELISA and Western blot analysis. To clarify whether sialic acid are necessary for Siglec9 to demonstrate inhibitory effect, we used sialidase to remove sialic acid. RAW264.7 was pre-incubated with sialidase for 1 h before stimulation protocols were administered.

Results: Treatment with Siglec9 in CIA mice significantly suppressed the incidence rate and severity of arthritis (based on the arthritis score) in a dose-dependent manner. The beneficial effect was maximal in mice treated with 50ng/gm of Siglec9. Serum TNFα level was significantly inhibited in groups treated with Siglec9 compared with control group. Treatment with Siglec9 significantly reduced the histologic score in both knee and ankle joints. RT–PCR analysis revealed that treatment with Siglec9 decreased the mRNA expression of TFNα, IL-6, and iNOS in RAW264.7 stimulated with IFNγ in a dose-dependent manner. However, we could not find significant increase in mRNA expression of M2 marker such as CD206, arginaze-1, fizz1 by treatment with Siglec9. The protein expression of each M1 markers were also suppressed by treatment with Siglec9. Sialidase treatment canceled the inhibitory effect which was seen in treatment group with Siglec9.

Conclusion: Siglec9 reduced disease activity of arthritis and suppressed histological inflammation and joint destruction, and in vitro, M1 markers (TNFα, IL-6, iNOS) were remarkably suppressed by treatment with Siglec9 in dose dependent manner. The inhibitory effect of Siglec9 was canceled by removing sialic acid with sialidase.

Disclosure: T. Matsumoto, None; **N. Takahashi**, None; **T. Kojima**, Takeda Pharma Corporation, 2,Janssen Pharmaceutical, 2,Astellas Pharma Corporation, 2,Mitsubishi Tanabe Pharma Corporation, 8,Takeda Pharma Corporation, 8,Eisai Pharma Corporation, 8; **N. Ishiguro**, Takeda, Mitsubishi-Tanabe, Astellas, Chugai, Abbott, Bristol-Myers Squibb, Eisai, Janssen, Kaken, Pfizer, 2,Takeda, Mitsubishi-Tanabe, Astellas, Chugai, Abbott, Bristol-Myers Squibb, Eisai, Janssen, Kaken, Pfizer, Taisho-Toyama, Otsuka, 8.

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Abstract Number: 3192

KCa3.1 Ion Channel in the Pathogenesis of Rheumatoid Arthritis: KCa3.1-/- Mice Do Not Develop CIA

Siba Raychaudhuri[1], Smriti K. Raychaudhuri[2] and Heike Wulff[3], [1]Med/Rheumatology, Univ California Davis/VA Sacramento, Davis, CA, [2]Rheumatology/Immunology, VA Sacramento Medical Center, Davis, CA, [3]Pharmacology, UC Davis School of Medicine, Davis, CA
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SESSION INFORMATION
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Session Time: 4:30PM-6:00PM

Background/Purpose: KCa3.1 is a Ca^{2+}-activated K^+ channel that modulates Ca^{2+}-dependent signaling processes such as activation and cellular proliferation. KCa3.1 is expressed in $CCR7^+$ naïve and central memory T cells, in mast cells, macrophages, fibroblasts and endothelium. Given this expression pattern, KCa3.1 is likely to play a critical role in the pathogenesis of rheumatoid arthritis (RA). Here using KCa3.1 knockout mice ($KCa3.1^{-/-}$) we are reporting that functional KCa3.1 channels are critical for induction of collagen induced arthritis (CIA).

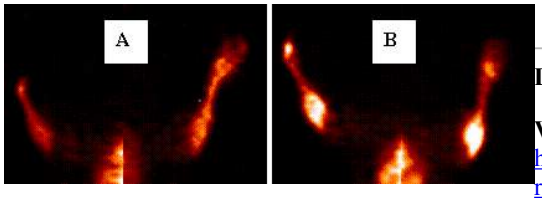
Methods: CIA mouse model is a well established tool to study the pathogenesis of RA and mostly DBA/1 mice are used for this model. $KCa3.1^{-/-}$ mice are on the C57BL/6 background so we used C57BL/6 mice to induce CIA as per the protocol of Inglis et al (*Arthritis Research & Therapy* 2007, **9**:R113). CIA was induced in $KCa3.1^{-/-}$ mice (n=10) and in C57BL/6 wild mice (n=10). Mice were observed for development of arthritis for 60 days. Arthritis was evaluated by clinical score (weekly); histopathological score and PET imaging of the joints was performed before sacrificing the mice on day-60.

Results: $KCa3.1^{-/-}$ mice did not develop any clinical evidence of arthritis and did not have histological evidence of joint inflammation. Whereas, about 60% of the wild-type C57BL/6 mice developed clinical and histological evidence of arthritis. Both clinical scores and histopathological scores for arthritis on day-60 was zero in the $KCa3.1^{-/-}$ mice; in wild-type mice the respective scores were 2.5 ±0.5 and 6±1.5. Further evidence of arthritis was confirmed by micro-PET imaging (Fig 1). CD3+ T cell proliferation in response to mouse collagen type II by CFSE dilution FACS study was significantly higher in the C57BL/6 wild mice compared to $KCa3.1^{-/-}$ mice .

Conclusion: Using the CIA model here we have demonstrated that wild-type C57BL/6 mice developed clinical, histopathological, immunological and radiological evidence of inflammatory arthritis whereas $KCa3.1^{-/-}$ mice did not. These results substantiate a critical role of the KCa3.1 potassium channel in the pathogenesis of RA. Since small molecule-based interference with KCa3.1 such as TRAM-34 is well tolerated, further evaluation of KCa3.1 channel blockers in models of RA may be a promising approach to identify new pharmacological targets

and develop new therapeutic strategies for this debilitating disease.

Fig 1. PET imaging showing increased ^{18}F-FDG uptake in the elbow joints and hands (front paws) in the C57BL/6 wild mice (B) compared to the KCa3.1$^{-/-}$ mouse (A).



Disclosure: S. Raychaudhuri, None; **S. K. Raychaudhuri**, None; **H. Wulff**, None.

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Abstract Number: 3193

Immunomodulatory and Antiviral Therapies in a Mouse Model of Chikungunya Viral Arthritis

Jonathan Miner[1], Lindsey Cook[1], Raeann Shimak[2], Julie Fox[1], Alissa Young[1], Kristen Monte[2], Subhajit Poddar[2], Michael Diamond[1] and Deborah Lenschow[1], [1]Department of Medicine, Washington University in Saint Louis School of Medicine, Saint Louis, MO, [2]Washington University in Saint Louis School of Medicine, Saint Louis, MO

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SESSION INFORMATION

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Session Time: 4:30PM-6:00PM

Background/Purpose: Chikungunya virus (CHIKV) is a rapidly emerging arthritogenic mosquito-borne alphavirus that has infected more than 1 million individuals in the Western Hemisphere since 2014. CHIKV arthritis can persist for months to years, but little is known about potential therapies for this epidemic polyarthritis. We previously reported that CHIKV arthritis and rheumatoid arthritis (RA) exhibit similar clinical features as well as peripheral T cell phenotypes, suggesting immunological overlap in the pathogenesis of CHIKV arthritis and RA. However, the effects of immunosuppression during CHIKV arthritis are unknown. Here, we describe the clinical and virological effects of immunosuppressive and antiviral therapies in a mouse model of CHIKV arthritis.

Methods: Two hundred and eighty C57BL6/J mice were infected with the La Reunion strain of CHIKV, followed by treatment on day 3 after infection with either neutralizing anti-CHIKV monoclonal antibodies or with one of seven immunomodulatory therapies: CTLA4-Ig, tofacitinib, anti-CD20, etanercept, methylprednisolone, naproxen, and methotrexate. Clinical disease was assessed by measuring footpad thickness over time. Viral titers at day 7 were measured by qRT-PCR.

Results: Treatment with CTLA4-Ig, tofacitinib, or with anti-CHIKV monoclonal antibodies effectively reduced arthritic swelling at day 7 after infection without major effects on viral titers in the affected joints. Administration of anti-CD20 or etanercept exacerbated CHIKV arthritis, distinguishing CHIKV arthritis from RA.

Conclusion: CHIKV arthritis is clinically ameliorated by tofacitinib, CTLA4-Ig or neutralizing monoclonal antibodies directed against the CHIKV E2 envelope protein. By contrast, blockade of TNF-alpha and depletion of CD20+ B cells had deleterious effects. Our results demonstrate novel potential therapies for CHIKV arthritis in a preclinical model. Additional studies are required to determine the safety and efficacy of these therapies in human patients with CHIKV arthritis since immunosuppression may still pose serious risks, especially during the acute phase of infection.

Disclosure: J. Miner, None; **L. Cook**, None; **R. Shimak**, None; **J. Fox**, None; **A. Young**, None; **K. Monte**, None; **S. Poddar**, None; **M. Diamond**, None; **D. Lenschow**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/immunomodulatory-and-antiviral-therapies-in-a-mouse-model-of-chikungunya-viral-arthritis

Abstract Number: 3194

Oral to Subcutaneous Methotrexate Dose-Conversion Strategies in the Treatment of

Rheumatoid Arthritis

Michael Schiff[1] and Peter Sadowski[2], [1]Division of Rheumatology, University of Colorado, Denver, CO, [2]Antares Pharma Inc., Minneapolis, MN

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Background/Purpose:

Methotrexate (MTX) is the cornerstone of rheumatoid arthritis (RA) therapy[1] but absorption saturation limitations compromise oral MTX bioavailability (BA). Subcutaneous (SC) MTX has a dose-proportional, linear absorption profile compared to oral MTX, which plateaus at doses >15 mg.[2] Differences in the relative BA of oral vs SC MTX demonstrate the need for guidance on successful dose-conversion strategies.

Methods:

In a phase 2, 12-week, open-label, crossover study, 49 adults with RA already receiving MTX for ≥3 months were given 10, 15, 20, or 25 mg MTX based on their current MTX dose and disease control, and then randomized 1:1:1 to oral MTX, SC MTX (abdomen; $MTXAI_{ab}$), or SC MTX (thigh; $MTXAI_{th}$). Blood samples for pharmacokinetic (PK) analysis were collected pre-dose and at 13 time points 0.25 to 12 h post-dose; samples were analyzed by liquid chromatography–mass spectrometry. Mixed model analysis derived area under the curve (AUC), maximum observed concentration (C_{max}), and time to maximum concentration (T_{max}) PK parameters. Dose-normalized parameter ratios were calculated.

Results:

Mean age was 61 y, mean body mass index was 30.7 kg/m^2, and mean disease duration was 13 y; 63% of patients were female. PK analysis of $MTXAI_{th}$ vs oral MTX showed that BA of $MTXAI_{th}$ was consistently greater at all dose levels (Figure 1). $MTXAI_{th}$ and $MTXAI_{ab}$ PK measures were similar. Although oral MTX plateaued at 15 mg, MTXAI had no plateau, resulting in higher exposure than comparable oral doses. Relative BA (AUC of $MTXAI_{th}$ vs AUC of oral MTX) at 10, 15, 20 and 25 mg were 121%, 114%, 131%, and 141% respectively (Table 1). Ratios of the dose-normalized AUC_{0-24} [90% CI] and C_{max} [90% CI] of MTXAI vs oral MTX were 127.61 [122.30, 133.15] and 94.88 [87.95, 102.37]. Equivalence between oral and SC MTX doses was determined based on BA (Table 2). SC MTX was safe and well-tolerated in subjects with RA.

Conclusion:

A dose conversion method was established based on the BA of MTX from oral and SC administration. SC administration provided higher exposure of MTX than the same dose given orally.

1. Singh JA, *et al*. *Arthritis Care Res*. 2012; 64:625–39

2. Schiff MH, *et al*. *Ann Rheum Dis*. 2014; 73:1549–1551

Figure 1. Bioavailability of SC Methotrexate ($MTXAI_{th}$) vs Oral Methotrexate[2]

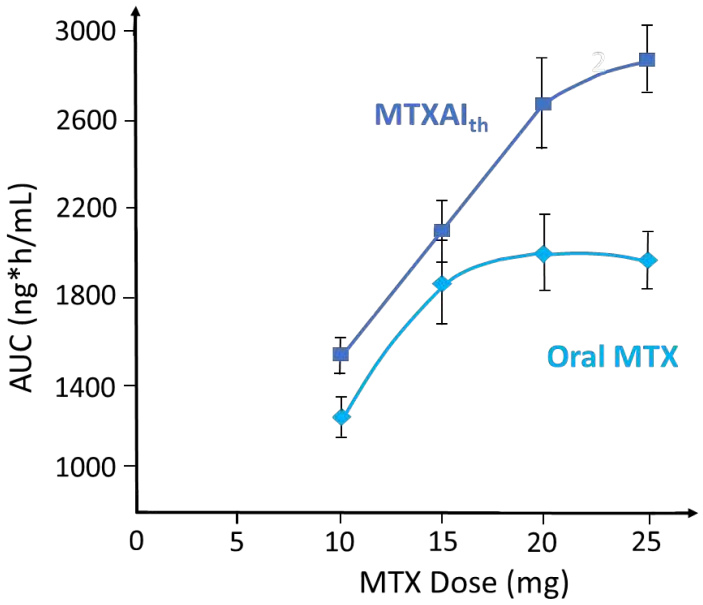

Table 1: Analysis of Dose-normalized PK parameters[†]

Dose-normalized PK Parameters: SC vs Oral			
MTX 10 mg	**MTXAI[‡] (n=25)**	**Oral (n= 12)**	**Ratio [90% CI]**
$AUC_{0\text{-}24}$/Dose (ng*hr/mL/mg)	1477.1	1225.5	120.53 [114.01, 127.43]
$AUC_{0\text{-}inf}$/Dose (ng*hr/mL/mg)	1506.4	1248.8	120.63 [114.13, 127.50]
C_{max}/Dose (ng/mL/mg)	211.1	250.2	84.36 [72.12, 98.68]
MTX 15 mg	**MTXAI[‡] (n=24)**	**Oral (n=12)**	**Ratio [90% CI]**
$AUC_{0\text{-}24}$/Dose (ng*hr/mL/mg)	1993.4	1752.0	113.78 [107.26, 120.69]
$AUC_{0\text{-}inf}$/Dose (ng*hr/mL/mg)	2040.1	1786.6	114.19 [107.50, 121.30]
C_{max}/Dose (ng/mL/mg)	263.3	349.4	75.36 [70.00, 81.12]
MTX 20 mg	**MTXAI[‡] (n=24)**	**Oral (n=12)**	**Ratio [90% CI]**
$AUC_{0\text{-}24}$/Dose (ng*hr/mL/mg)	2521.9	1927.2	130.85 [121.05, 141.45]
$AUC_{0\text{-}inf}$/Dose (ng*hr/mL/mg)	2560.7	1949.7	131.34 [121.46, 142.02]
C_{max}/Dose (ng/mL/mg)	397.8	440.4	90.33 [8.22, 104.32]
MTX 25 mg	**MTXAI[‡] (n=23)**	**Oral (n=11)**	**Ratio [90% CI]**
$AUC_{0\text{-}24}$/Dose (ng*hr/mL/mg)	2804.4	1991.2	140.84 [128.22, 154.70]
$AUC_{0\text{-}inf}$/Dose (ng*hr/mL/mg)	2846.3	2016.1	141.18 [128.63, 154.96]
C_{max}/Dose (ng/mL/mg)	444.2	423.6	104.87 [89.48, 122.92]

[†]A mixed model was performed on log-transformed PK parameters of each dose. The model contains sequence, period, and treatment effects as fixed effects, and subject as random effect. Geometric LS means were derived from the mixed model presented after back transformation to the original scale. The 90% CIs were presented after back transformation to the original scale.

[‡]Combined SC abdomen and thigh.

Abbreviations used: AUC=area under the curve; $AUC_{0\text{-}24}$/Dose=dose-normalized AUC from time zero to 24 h; $AUC_{0\text{-}inf}$=AUC from time zero to infinity; CI=confidence interval; C_{max}=maximum observed concentration; LS=least squares; MTX=methotrexate; MTXAI=subcutaneous MTX; PK=pharmacokinetic; SC=subcutaneous

Table 2: Methotrexate Oral to Subcutaneous Dose Conversion

Oral Dose (mg)	Equivalent SC* Dose (mg) [90% CI]	Recommended SC Dose (mg)
10	8.3 [8.8, 7.9]	10
15	13.2 [14.0, 12.4]	15
20	15.3 [16.5, 14.2]	15
25	17.7 [19.5, 16.1]	20

Note: The SC dose recommendation is based on systemic MTX levels equivalent to or higher than what was achieved by oral MTX.

*Combined abdomen and thigh

Abbreviations used: CI=confidence interval; SC=subcutaneous

Disclosure: M. Schiff, AbbVie, Amgen, Antares, BMS, Janssen, Eli Lilly, 5,AbbVie, 8; **P. Sadowski**, Antares Pharma, Inc., 1,Antares Pharma, Inc., 3,Member, Dean's Advisory Council, College of Letters and Sciences, Montana State University, 6.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/oral-to-subcutaneous-methotrexate-dose-conversion-strategies-in-the-treatment-of-rheumatoid-arthritis

Abstract Number: 3195

Circulating Micro-RNA Profiles in Responders to Adalimumab Plus Methotrexate Versus Methotrexate Alone: A Placebo-Controlled Clinical Trial

Jacob Sode[1,2,3], Sophine B. Krintel[4], Anting L. Carlsen[5], Merete Lund Hetland[6], Julia Johansen[7,8], Kim Hørslev-Petersen[9], Kristian Stengaard-Pedersen[10], Peter Junker[11], Mikkel Østergaard[12,13], Niels H. H. Heegaard[14,15] and OPERA study group, [1]Department of Autoimmunology and Biomarkers, Statens Serum Institut, Copenhagen, Denmark, [2]Institute of Regional Health Research, University of Southern Denmark, Odense, Denmark, [3]Department of Rheumatology, Frederiksberg Hospital, Frederiksberg, Denmark, [4]Department of Rheumatology, Copenhagen University Hospital at Glostrup, Copenhagen, Denmark, [5]Department of Congenital Disorders, Statens Serum Institut, Copenhagen, Denmark, [6]The DANBIO Registry, Copenhagen Center for Arthritis Research, Center for Rheumatology and Spine Diseases, Rigshospitalet, Glostrup, Denmark, [7]Faculty of Health Sciences, University of Copenhagen, Copenhagen, Denmark, [8]Departments of Medicine and Oncology, Copenhagen University Hospital at Herlev, Copenhagen, Denmark, [9]Rheumatology, Research Unit at King Christian X Hospital for Rheumatic Diseases, Graasten, Graasten, Denmark, [10]Department of Rheumatology, Aarhus University Hospital, Aarhus, Denmark, [11]Department of Rheumatology, Odense University Hospital, Odense, Denmark, [12]Rigshospitalet-Glostrup, Copenhagen Center for Arthritis Research, Center for Rheumatology and Spine Diseases, Rigshospitalet - Glostrup, Glostrup, Denmark, [13]Department of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark, [14]Department of Autoimmunology & Biomarkers, Statens Serum Institut, Copenhagen, Denmark, [15]Department of Clinical Biochemistry & Pharmacology, Odense University Hospital, Odense C, Denmark

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Background/Purpose:

The variable response to anti-TNF therapy in patients with rheumatoid arthritis (RA) remains largely unexplained, and biomarkers for treatment response are scarce. We previously investigated whole blood micro-RNA (miRNA) as predictors of anti-TNF response. In this study we aimed to investigate association between plasma miRNAs and treatment response in 180 DMARD naïve early RA patients enrolled in the OPERA Study, a prospective, double-blinded, placebo-controlled study.

Methods:

Patients were randomized to methotrexate, intra-articular glucocorticoids plus either adalimumab or placebo. All patients had RA (ACR 1987 criteria). Plasma samples for total RNA purification were collected pre-treatment and at 3-month. 91 specific miRNAs were investigated by quantitative RT-PCR on a microfluidic dynamic array. Cq values were normalized with spiked-in synthetic miRNAs and further normalized using means of all endogenous expressed miRNAs. Means were compared (Welch's *t*-test) of pre-treatment miRNAs and of the 3-month change in miRNA expression for the groups of responding and non-responding patients. Response was defined by 12-month ACR/EULAR Boolean remission.

Results:

We successfully profiled 76/91 miRNAs in 180 pre-treatment samples and in 170 (94%) 3-month samples. Pre-treatment expression of six miRNAs (Table 1), and altered change in expression of eight miRNAs (Table 2) were associated ($p<0.05$) with remission to adalimumab treatment. In the placebo group, pre-treatment expression of 12 miRNAs, and altered change in expression of four miRNAs were associated with remission. Adalimumab treated responders had increased pre-treatment miR-27a-3p ($p=0.004$), which decreased after 3 months compared to non-responders ($p=0.0001$). Placebo treated responders had increased miR-27a-3p compared to adalimumab responders ($p=0.03$). miR-146a decreased ($p=0.01$) in adalimumab responders vs. non-responders consistent with previous data on miR-146a as a putative marker of disease activity. Placebo responders vs. non-responders did not differ with respect to miR-146a changes. In our previous study of whole blood, miR-23a was also associated with remission in the adalimumab group.

Conclusion:

In this well-characterized cohort we have identified miRNAs predictive of treatment response. Our results suggest miR-27a-3p as particular promising as both predictor and biomarker of response to adalimumab treatment. The results should be interpreted with some reservation due to the large number of associations investigated, and need validation in independent prospective studies.

Table 1. Pre-treatment expression in remitting RA patients

miRNA	Adalimumab + DMARD Remission (n=43) vs no-remission (n=43)	p-value	Placebo + DMARD Remission (n=29) vs no-remission (n=54)	p-value
hsa-miR-27a-3p	↑	**0.004**	-	0.17
hsa-miR-10b-5p	↓	**0.006**	-	0.11
hsa-miR-23a-3p	↑	**0.01**	-	0.42
hsa-miR-142-3p	↓	**0.01**	-	0.52
hsa-miR-27b-3p	↓	**0.03**	-	0.25
hsa-miR-19b-3p	↑	**0.05**	-	0.17
hsa-miR-28-3p	-	0.31	↑	**0.01**
hsa-miR-223-3p	-	0.14	↓	**0.01**
hsa-miR-145-5p	-	0.50	↓	**0.02**
hsa-miR-378-3p	-	0.53	↑	**0.02**
hsa-miR-7-5p	-	0.34	↑	**0.03**
hsa-miR-15b-5p	-	0.89	↓	**0.03**
hsa-miR-106a-5p	-	0.18	↓	**0.03**
hsa-miR-342-3p	-	0.24	↑	**0.03**
hsa-miR-199a/b-3p	-	0.11	↓	**0.03**
hsa-miR-208a-3p	-	0.29	↑	**0.03**
hsa-miR-29c-3p	-	0.11	↓	**0.05**
hsa-miR-106b-5p	-	0.39	↓	**0.05**

Table 2. Change in expression in remitting RA patients

miRNA	Adalimumab + DMARD Remission (n=43) vs. no-remission (n=43)	p-value	Placebo + DMARD Remission (n=29) vs. no- remission (n=54)	p-value
hsa-miR-27a-3p	↓	**0.0001**	-	0.25
hsa-miR-146a-5p	↓	**0.01**	-	0.38
hsa-miR-29c-3p	↑	**0.02**	-	0.90
hsa-miR-24-3p	↓	**0.03**	-	0.19
hsa-miR-423-5p	↓	**0.04**	↑	**0.01**
hsa-miR-21-5p	↓	**0.04**	-	0.16
hsa-miR-122-5p	↑	**0.04**	-	0.72
hsa-miR-19b-3p	↓	**0.05**	-	0.09
hsa-miR-659-3p	-	0.33	↓	**0.03**
hsa-miR-10b-5p	-	0.08	↑	**0.04**
hsa-miR-28-3p	-	0.09	↓	**0.05**

Disclosure: J. Sode, None; **S. B. Krintel**, None; **A. L. Carlsen**, None; **M. Lund Hetland**, None; **J. Johansen**, None; **K. Hørslev-Petersen**, None; **K. Stengaard-Pedersen**, None; **P. Junker**, None; **M. Østergaard**, None; **N. H. H. Heegaard**, None.

Abstract Number: 3196

Predictive Biomarkers for Response or Non-Response to MTX Monotherapy in Early RA

Karen Hambardzumyan[1], Rebecca J. Bolce[2], Saedis Saevarsdottir[3], Kristina Forslind[4,5], Johan A Karlsson[6] and Ronald F. van Vollenhoven[1], [1]Department of Medicine, Unit for Clinical Therapy Research, Inflammatory Diseases (ClinTRID), The Karolinska Institute, Stockholm, Sweden, [2]Crescendo Bioscience Inc., South San Francisco, CA, [3]Department of Medicine, Rheumatology Unit, The Karolinska Institute and Karolinska University Hospital, Stockholm, Sweden, [4]Departments of Rheumatology, Helsingborgs Hospital and University of Lund, Helsingborg and Lund, Sweden, [5]Department of Medicine, Helsingborgs Lasarett, Section of Rheumatology, Helsingborg, Sweden, [6]Section of Rheumatology, Department of Clinical Sciences Lund, Lund University, Lund, Sweden

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Background/Purpose: In early rheumatoid arthritis (eRA), a clinically significant proportion of patients may respond to first-line treatment with methotrexate (MTX). A priori identification of patients with high or low likelihood of response to MTX would enhance therapy strategies. Previously, we have presented data on the multi-biomarker disease activity (MBDA) score, based on twelve biomarkers, from the Swedish Farmacotherapy (SWEFOT) trial. The objective of this study was to investigate these biomarkers at baseline (BL) separately and in simple combinations as predictors of response to MTX monotherapy.

Methods: Analyses were done on a subset of 298 patients with eRA from the SWEFOT population (104 responders [DAS28≤3.2] and 194 non-

responders [DAS28>3.2] to MTX) who had complete data on the 12 biomarkers from the MBDA score at BL and DAS28 at Month 3. The categories of these biomarkers (low, moderate and high) were defined using tertiles with the exception of CRP, where the following cutoffs (mg/L) were applied: ≤10 for low, >10-30 for moderate and >30 for high. For the comparison of proportions of responders and non-responders between patients with different categories of the biomarkers, the χ^2 test was used. Each individual biomarker was analyzed as a predictor (without correcting for multiple comparisons), followed by a study of combinations of the most strongly predictive biomarkers.

Results: In MTX-responders versus non-responders, out of the 12 biomarkers at BL, the medians of CRP and IL-6 were significantly lower (15 vs 20, p=0.038, and 49 vs. 67, p=0.049), and TNF-RI and VCAM-1 were significantly higher (1.9 vs 1.7, p=0.005, and 0.70 vs. 0.64, p=0.006), respectively. Of patients with both low CRP AND high TNF-RI at BL (n=19), or low IL-6 AND high TNF-RI (n=27) higher proportions were responders compared with the rest (79% vs 32%, p<0.001, and 74% vs 31%, p<0.001, Figures 1A and B respectively). In contrast, patients with low/moderate VCAM-1 AND high CRP (n=61) or low VCAM-1 AND moderate/high IL-6 (n=55) were more likely not to respond to MTX than the others (85% vs 60%, p<0.001; Figures 1C and D). All 19 patients with low VCAM-1 AND high CRP AND moderate/high IL-6 were MTX-non-responders.

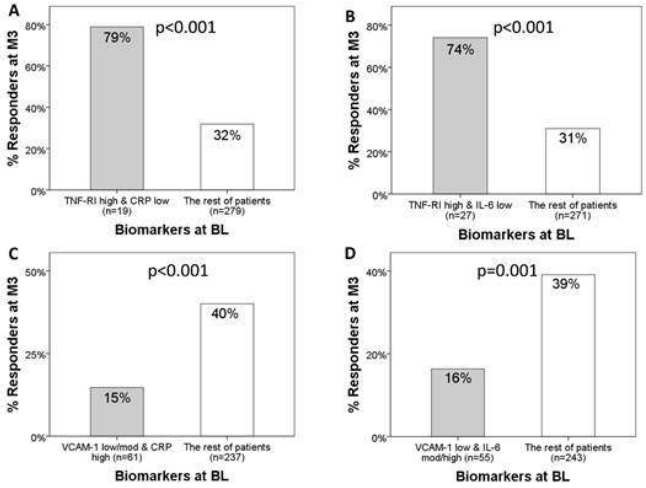

Figure 1. Association of different biomarkers with response to MTX therapy. Patients grouped using combination of TNF-RI with CRP **(A)**, TNF-RI with IL-6 **(B)**, VCAM-1 with CRP **(C)** and VCAM-1 with IL-6 **(D)**. M3 – Month 3, BL – baseline.

Conclusion: We identified individual biomarkers and 2-biomarker combinations that were associated, positively or negatively, with the clinical response to MTX monotherapy. If reproduced in other study populations, these results suggest that biomarkers and their combinations might be helpful in decision-making on the initial therapy of patients with early RA.

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Abstract Number: 3197

Clinical Practice Experience in Rheumatoid Arthritis Patients Treated with Triple Therapy and Methotrexate-Tumor Necrosis Factor Inhibition Differs from That of Randomized Controlled Trials

Daniel Erhardt[1], Brian Sauer[2], Chia-Chen Teng[3], Ted R. Mikuls[4], Jeffrey R. Curtis[5], Derek Tang[6], Bradley S. Stolshek[6] and Grant W. Cannon[1], [1]Division of Rheumatology, Salt Lake City VA Medical Center and University of Utah, Salt Lake City, UT, [2]Salt Lake City VA Medical Center and University of Utah, Salt Lake City, UT, [3]HSR&D SLC VA Medical Center and University of Utah, Salt Lake City, UT, [4]University of Nebraska Medical Center, Omaha, NE, [5]University of Alabama at Birmingham, Birmingham, AL, [6]Amgen, Inc., Thousand Oaks, CA

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SESSION INFORMATION

Session Date: Tuesday, November 10, 2015

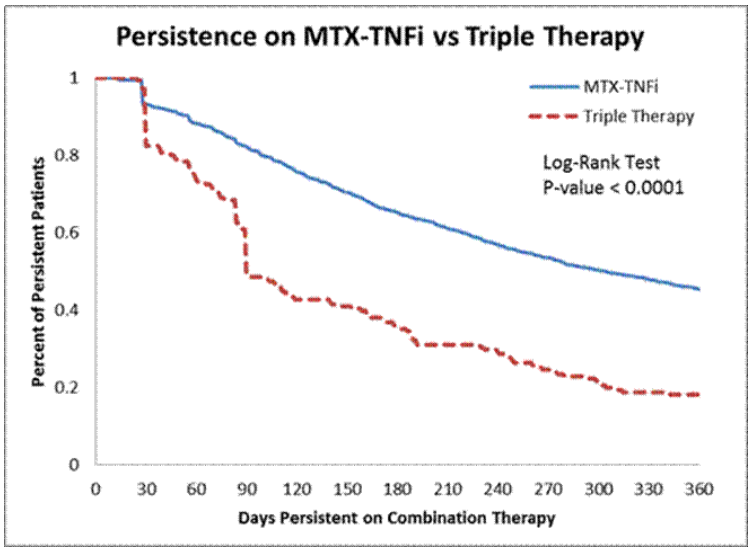
Session Title: Rheumatoid Arthritis-Small Molecules, Biologics and Gene Therapy VI: Strategies

Session Type: ACR Concurrent Abstract Session
Session Time: 4:30PM-6:00PM

Background/Purpose: Recently published randomized controlled trials (RCTs) have demonstrated similar outcomes in rheumatoid arthritis (RA) patients treated with triple therapy [methotrexate (MTX), sulfasalazine (SUL) and hydroxychloroquine (HCQ)] in comparison to patients receiving MTX plus etanercept, a tumor necrosis factor inhibitor (TNFi). Competing strategies examined in RCTs have included the addition of TNFi or concomitant SUL/HCQ to MTX in patients experiencing suboptimal improvement in MTX alone. This study aims to compare adherence and persistence rates between combination treatments in US Veterans who added TNFi or concomitant SUL/HCQ to MTX.

Methods: Veteran's Affairs clinical and administrative data from January 1, 2006 to December 31, 2012 was used for this retrospective cohort study. Veterans with ICD-9-CM codes for RA transitioning from MTX monotherapy to MTX-TNFi or triple therapy, the latter characterized by simultaneous addition of HCQ/SUL, were examined for the 12-month period following combination initiation. For the primary outcome, persistence required that all drugs in each treatment be continued over the 12-month period without a ≥90 day gap in refilling of any drug. Two alternative outcomes were examined: 1) allowed discontinuation of any one DMARD in triple therapy or MTX in the MTX-TNFi group, provided no new DMARDs were initiated or 2) permitted switching between drugs within the TNFi class and non-biologic DMARD. Adherence was calculated using proportion of days covered (PDC), defined as PDC ≥ 80% at 12 months.

Results: The MTX-TNFi patients (n=2,125) had higher adherence and persistence compared to triple therapy patients (n=171) (p<0.001 for all outcomes). The primary persistence outcome demonstrated that 45% were persistent on MTX-TNFi and 18% were persistent on triple therapy (p<0.001) (Figure, Table). 12 month adherence (PDC) was higher for the MTX-TNFi group (26%) than the triple therapy group (11%). While the relatively small sample size of the triple therapy group made controlling for all potential confounders difficult, adjustment for observed covariates did not significantly alter persistence and adherence.



	Crude Model				Matching Weights Adjusted Model			
Outcomes (% of patients)	MTX-TNFi N=2,125	Triple Rx N=171	P Value	Relative Risk (95% CI)	MTX-TNFi N=170	Triple Rx N=171	P Value	Relative Risk (95% CI)
Primary Outcome	960 (45.2%)	30 (17.5%)	<0.0001	2.6 (1.8, 3.6)	73.4 (43.1%)	30.0 (17.6%)	<0.0001	2.5 (1.7, 3.6)
Persistent Alternative #1	1115 (52.5%)	56 (32.8%)	<0.0001	1.6 (1.3, 2.0)	85.6 (50.3%)	56.0 (32.8%)	0.0022	1.5 (1.2, 2.0)
Persistent Alternative #2	1235 (58.1%)	58 (33.9%)	<0.0001	1.7 (1.4, 2.1)	97.2 (42.9%)	58.0 (33.9%)	<0.0001	1.7 (1.3, 2.2)
Adherence Outcome	547 (25.7%)	18 (10.5%)	<0.0001	2.4 (0.1, 3.8)	43.0 (25.3%)	18.0 (10.5%)	<0.0001	2.4 (1.4, 4.0)

Conclusion: Real-world persistence and adherence in VA patients were higher in RA patients receiving MTX-TNFi therapy compared to triple therapy. Findings were robust to varying outcome definitions and controlling for potential confounders. While potential effects of channeling bias cannot be excluded, these findings suggest that the patterns and benefits of use of triple therapy in clinical practice may be different than that seen in RCTs.

Disclosure: D. Erhardt, None; **B. Sauer**, Amgen, 2,Pfizer Inc, 5; **C. C. Teng**, Amgen, 2; **T. R. Mikuls**, Roche/Genetech, 2,Pfizer Inc, 5; **J. R. Curtis**, Roche, Genentech, UCB Pharma, Janssen, CORRONA, Amgen, Pfizer, BMS, Crescendo, AbbVie, 2,Roche, Genentech, UCB Pharma, Janssen, CORRONA, Amgen, Pfizer, BMS, Crescendo, AbbVie, 5; **D. Tang**, Amgen, 1,Amgen, 3; **B. S. Stolshek**, Amgen, 1,Amgen, 3; **G. W. Cannon**, Amgen, 2.

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Abstract Number: 3198

Treatment of Rheumatoid Arthritis with an Anti-Tumor Necrosis Factor Agent or Tocilizumab As First Biologic Therapy in a Global Comparative Observational Study

Ernest H. Choy[1], Corrado Bernasconi[2], Maher Aassi[2], Jose F. Molina[3] and Oscar M. Epis[4], [1]Cardiff University, Institute of Infection and Immunity, Tenovus Building, University Hospital of Wales, Cardiff, United Kingdom, [2]F. Hoffmann-La Roche, Basel, Switzerland, [3]Centro Integral de Reumatologia Reumalab, Medellin, Colombia, [4]Rheumatology Unit, A.O. Ospedale Niguarda Ca' Granda, Milan, Italy
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Session Type: ACR Concurrent Abstract Session
Session Time: 4:30PM-6:00PM

Background/Purpose: ACT-iON was a global, multicenter, observational, 52-wk, clinical practice study of the effectiveness of tocilizumab (TCZ) vs anti–tumor necrosis factor (aTNF) agents prescribed as first biologic therapy after inadequate response to DMARDs (DMARD-IR).

Methods: Eligible patients were DMARD-IR with moderate to severe RA (1987 ACR criteria) for ≥24 wks who were prescribed TCZ or aTNF as their first biologic, in accordance with local label, within 6 weeks of enrollment. The study comprised a 52-wk observation period. No study-specific medication or dosing regimen was stipulated. The primary effectiveness measure was change in $DAS28_{ESR}$ from baseline to wk 24. Data were analyzed by treatment group based on the first administered biologic. Safety was assessed in patients receiving ≥1 dose of biologic. Effectiveness was assessed in patients with a disease activity assessment <60 days before first biologic dose (effectiveness population). Missing data were not imputed, and no correction for multiple testing was applied.

Results: Of 1250 patients screened, 1225 were enrolled; 1216 received ≥1 dose of biologic (safety population: TCZ, 423 [34.8%]; aTNF, 793 [65.2%]), and 1083 were included in the effectiveness population (TCZ, 390 [36.0%]; aTNF, 693 [64.0%]). Overall, 158/1216 (13.0%) patients discontinued the study (lack of efficacy: TCZ, 0.9%; aTNF, 2.0%; adverse events [AEs]: TCZ, 2.1%; aTNF, 1.6%). Drug survival was higher with TCZ than aTNFs (p<0.001; Table). TCZ vs aTNF patients had shorter disease duration and started their biologic more often as monotherapy (28.1% vs 16.0%; Table). Oral corticosteroids were used in a higher proportion of TCZ patients. Although baseline $DAS28_{ESR}$ was similar between groups, TCZ patients had a significantly larger change from baseline in $DAS28_{ESR}$ than aTNF patients (difference in adjusted means [95% CI]: wk 24, –0.9 [–1.1, –0.6]; wk 52, –0.9 [–1.2, –0.6]; p<0.001 at wks 24 and 52). Changes from baseline at wks 24 and 52 for other effectiveness parameters were also significantly better with TCZ (Table). Sensitivity analysis restricting validated baseline assessments to 2 weeks before first biologic dose confirmed these results. AEs and serious AEs (SAEs) occurred in 49.2% and 5.2% of TCZ patients and 56.6% and 8.1% of aTNF patients. Infections were the most common AEs (TCZ, 20.8%; aTNF, 25.9%) and SAEs (TCZ, 1.9%; aTNF, 3.3%). Three (0.7%) TCZ patients and 6 (0.8%) aTNF patients died; 1 death in each group (both due to pneumonia) was deemed treatment related.

Table. Demographics and Baseline, Wk 24, and Wk 52 Effectiveness Parameters

	TCZ	aTNF	Difference
Baseline Demographics and RA Disease Characteristics[a]	**n = 423**	**n = 793**	
Age, years, mean (SD)[b]	54.3 (12.8)	55.2 (13.1)	p=0.171
Disease duration, years, mean (SD)[b]	7.8 (7.3)	9.4 (9.0)	p=0.014
Initiated biologic as monotherapy, n (%)	119 (28.1)	127 (16.0)	p<0.001[g]
MTX, n (%)[c] [median dose in mg/wk][d]	219 (72.0) [15.0]	537 (80.6) [15.0]	—
Hydroxychloroquine, n (%)[c]	71 (23.4)	167 (25.1)	—
Leflunomide, n (%)[c]	63 (20.7)	111 (16.7)	—
Sulfasalazine, n (%)[c]	38 (12.5)	121 (18.2)	—
Oral corticosteroid use, n (%) [mean dose in mg/day prednisone equiv.]	256 (60.5) [8.3]	369 (46.5) [7.3]	—
Drug survival at wks 24/52 (KM estimate), %	91/85	85/73	p<0.001
Baseline Disease Activity and Effectiveness at 24 and 52 Wks[e]	**n = 390**	**n = 693**	—
$DAS28_{ESR}$, baseline, mean (SD)	5.8 (1.1)	5.5 (1.2)	—
$DAS28_{ESR}$, change from baseline to wk 24, adjusted mean (95% CI)[f]	−2.8 (−3.1, −2.5)	−1.9 (−2.2, −1.6)	−0.9 (−1.1, −0.6) p<0.001
$DAS28_{ESR}$, change from baseline to wk 52, adjusted mean (95% CI)[f]	−3.0 (−3.3, −2.8)	−2.1 (−2.3, −1.9)	−0.9 (−1.2, −0.6) p<0.001
$DAS28_{ESR}$ remission rates at wk 24, %	44.7	29.7	p<0.001
CDAI, baseline, mean (SD)	33.0 (13.5)	31.2 (13.2)	—
CDAI, change from baseline to wk 24, adjusted mean (95% CI)[f]	−20.3 (−21.9, −18.6)	−16.8 (−18.3, −15.3)	−3.5 (−5.5, −1.5) p<0.001
CDAI, change from baseline to wk 52, adjusted mean (95% CI)[f]	−22.8 (−24.6, −21.1)	−18.2 (−19.8, −16.7)	−4.6 (−6.7, −2.5) p<0.001
HAQ-DI, baseline, mean (SD)	1.5 (0.7)	1.5 (0.7)	—
HAQ-DI change from baseline to wk 24, adjusted mean (95% CI)[f]	−0.6 (−0.7, −0.5)	−0.4 (−0.5, −0.4)	−0.1 (−0.3, −0.0) p=0.020
HAQ-DI change from baseline to wk 52, adjusted mean (95% CI)[f]	−0.6 (−0.7, −0.5)	−0.4 (−0.5, −0.3)	−0.2 (−0.3, −0.0) p=0.020

[a]Safety population.
[b]p value based on Wilcoxon rank-sum test.
[c]Percentages based on number of patients who initiated biologic in combination with DMARDs.
[d]For MTX dose: TCZ, n = 233; aTNF, n = 541.
[e]Primary effectiveness population (N for specific analyses are lower).
[f]p value based on analysis of covariance with change from baseline as dependent variable; therapy (monotherapy/combination), site country, and treatment as fixed effects; and baseline value as covariates.
[g]p value based on Chi-square test for comparison of monotherapy and combination therapy between both treatment groups.

Conclusion: In DMARD-IR patients starting a biologic for the first time in real-life settings, TCZ was initiated as monotherapy more often than aTNFs. Safety profiles of TCZ and aTNFs were comparable and similar to the safety profiles from clinical trials. TCZ was associated with better drug survival and was possibly associated with better improvements in DAS28, CDAI, and HAQ-DI than aTNFs.

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Abstract Number: 3199

In Rheumatoid Arthritis (RA) Patients, Retreatment with Rituximab (RTX) at Half Dose Does Not Alter Maintenance on Drug and Allows One Third Reduction of Cumulative

Dose of Drug/Year: Data from the Autoimmunity and Rituximab (AIR) Registry

julien henry[1], stéphane pavy[2], Jacques Gottenberg[3], rakiba belkhir[4], Stéphanie Rouanet[5], Jérémie Sellam[6], Xavier Mariette[7] and raphaèle seror[4], [1]departement of rheumatology, Assistance Publique-Hôpitaux de Paris (APHP), Hôpitaux universitaires Paris Sud, Université Paris Sud, kremlin bicetre, France, [2]rheumatology, Assistance Publique-Hôpitaux de Paris (APHP), Hôpitaux universitaires Paris Sud, Université Paris Sud, kremlin bicetre, France, [3]Hautepierre, Strasbourg, France, [4]Assistance Publique-Hôpitaux de Paris (APHP), Hôpitaux universitaires Paris Sud, Université Paris Sud, kremlin bicetre, France, [5]Biostatistics, Roche France, Boulogne-Billancourt, France, [6]Rheumatology and Inserm UMRS_938, AP-HP, St Antoine Hospital, Univ Paris 06, DHU i2B, Paris, France, [7]Université Paris-Sud, AP-HP, Hôpitaux Universitaires Paris-Sud, Paris, France

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Session Type: ACR Concurrent Abstract Session

Session Time: 4:30PM-6:00PM

Background/Purpose:

In RA patients, different randomized clinical trials have showed that the efficacy of reduced dose of RTX either initially and for subsequent courses (DANCER, SERENE MIRROR trials), or for retreatment after an initial full dose (SMART trial) did not differ from standard dose, with the advantage of a lower cost and a possible better safety.

Objective

To investigate the maintenance of RTX in patients retreated with reduced doses after an initial full-dose compared with RTX to standard doses at each infusion in real life setting.

Methods:

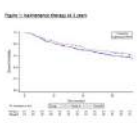
Patients of AIR registry (a nationwide prospective study investigating the long-term safety and efficacy of RTX in real life) were included in this specific study if they were retreated at least once with RTX for RA and had at least 6 months of follow-up. According to RTX retreatment regimen, three groups were defined. Group A: patients treated with 2 infusions of 1000 mg for all courses, group B: patients treated by 2 infusions of 1000 mg for the first course and reduced dose from the second course of RTX and thereafter and group C: patients treated by 2 infusions of 1000 mg for more than 1 course and reduced dose at a later course of RTX. Regimen of RTX was very variable in group C and will need specific analyses. Thus, this work focus on comparison of group A and B. Non maintenance was defined by the scientific committee of the registry as either death, lack of efficacy defined by introduction of a DMARD, switch to another biologic agent, increase in corticosteroid dose (≥10 mg at 2 times during follow-up), or according to physician judgment, or for side effect. Patient follow-up was censored at 3 years. Maintenance of group B was compared to that of group A using Kaplan Meier analyses and Hazard Ratio were calculated using Cox proportional Hazard model.

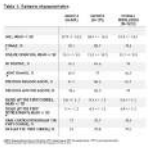
Results:

In total, 1233/1986 patients from the registry fulfilled inclusion criteria: group A (n=841), group B (n=175) and group C (n=217). Comparison of patient characteristics between groups did not revealed major difference. However, the patients of the group B were more likely to have erosive disease and a lower DAS28 at time of retreatment compared to group A. Maintenance of Rituximab did not significantly differ between groups A and B (median= 38 vs 40 months; hazard ratio [HR]= 0.79 [0.62-1.02], p= 0.0972). Overall, the mean time between 2 courses was lower in group B compared to group A (6.5 months vs 7.5, $p< 0.001$), but the cumulative RTX dose for retreatment measured in mg/year were decreased by 36% in group B compared to group A (1400 vs 2500 mg, $p< 0.001$).

Conclusion:

Maintenance therapy at 3 years in RA patients treated with RTX did not differ between patients treated with full-dose at each course or with reduced dose since the second course. Also the total dose of RTX / year may be decreased by 36% leading to economic and possibly safety benefits without interfering with effectiveness.





Disclosure: J. henry, None; **S. pavy**, None; **J. Gottenberg**, None; **R. belkhir**, None; **S. Rouanet**, None; **J. Sellam**, None; **X. Mariette**, None; **R. seror**, None.

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Abstract Number: 3200

Characterization of Early and Progressive Autoimmunity in Sjogrens Syndrome: The Incomplete Sjogrens Syndrome Model

Astrid Rasmussen[1], Christopher J Lessard[2], Indra Adrianto[1], Graham B. Wiley[1], Donald U Stone[3,4], C. Erick Kaufman[5], Lida Radfar[6], David M. Lewis[7], Stephen K Young[8], Michael H. Weisman[9], Daniel J Wallace[10], Swamy Venuturupalli[11], Barbara M. Segal[12], John A. Ice[1], Juan-Manuel Anaya[13], Michael D. Rohrer[14], Raj Gopalakrishnan[15], Glen D Houston[16], James Chodosh[17], Pamela J Hughes[18], Nelson L. Rhodus[19], Jennifer A. Kelly[20], Kiely Grundahl[21], Kimberly Hefner[22], R. Hal Scofield[1,23,24] and Kathy L. Sivils[1], [1]Arthritis and Clinical Immunology Research Program, Oklahoma Medical Research Foundation, Oklahoma City, OK, [2]Arthritis and Clinical Immunology, Oklahoma Medical Research Foundation, Oklahoma City, OK, [3]Research Department, King Khaled Eye Specialist Hospital, Riyadh, Saudi Arabia, [4]Department of Ophthalmology, Johns Hopkins University, Riyadh, Saudi Arabia, [5]College of Medicine, University of Oklahoma Health Sciences Center, Oklahoma City, OK, [6]Oral Diagnosis and Radiology Department, University of Oklahoma Health Sciences Center College of Dentistry, Oklahoma City, OK, [7]College of Dentistry, Department of Oral and Maxillofacial Pathology, University of Oklahoma Health Sciences Center, Oklahoma City, OK, [8]College of Dentistry, University of Oklahoma Health Sciences Center, Oklahoma City, OK, [9]Rheumatology, Cedars-Sinai Medical Center, Los Angeles, CA, [10]Division of Rheumatology, Cedars-Sinai Medical Center, Los Angeles, CA, [11]Cedars-Sinai Medical Center, West Hollywood, CA, [12]Rheumatology, Hennepin County Medical Center, Minneapolis, MN, [13]Center for Autoimmune Diseases Research (CREA), Universidad del Rosario., Bogota, Colombia, [14]Diagnostic and Biological Sciences, University of Minnesota, Minneapolis, MN, [15]Diagnostic and Biological Sciences, Division of Oral Pathology, University of Minnesota, Minneapolis, MN, [16]Heartland Pathology, Oklahoma City, OK, [17]Ophthalmology, Massachusetts Eye and Ear Infirmary, Harvard Medical School, Boston, MA, [18]Division of Oral and Maxillofacial Surgery, University of Minnesota, Minneapolis, MN, [19]Department of Oral Surgery, University of Minnesota School of Dentistry, Minneapolis, MN, [20]Arthritis & Clinical Immunology Research Program, Oklahoma Medical Research Foundation, Oklahoma City, OK, [21]Arthritis and Clinical Immunology Research Program, Oklahoma Medical Research Foundation, Oklahoma CIty, OK, [22]Hefner Eye Care and Optical Center, Oklahoma City, OK, [23]Department of Medicine, University of Oklahoma Health Sciences Center, Oklahoma City, OK, [24]US Department of Veterans Affairs Medical Center, Oklahoma City, OK

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SESSION INFORMATION

Session Title: Sjögren's Syndrome II: Clinical Discoveries

Session Type: ACR Concurrent Abstract Session

Background/Purpose: Autoimmune diseases are often preceded by subclinical serologic and functional abnormalities that predate diagnosis by several years. The insidious and progressive nature of these incomplete syndromes results in a lag in diagnosis, preventive and therapeutic strategies, and likely contributes to damage accrual.

Methods: : To explore possible markers of transition from incomplete Sjögren's Syndrome (iSS) to complete Sjögren's Syndrome (SS), 467 iSS patients were compared to 364 SS (SS) meeting AECG classification criteria in a multi-disciplinary sicca clinic. All subjects were evaluated for AECG classification measures, clinical and serological features (25 autoantibodies), and gene expression profiling of 64 interferon (IFN)-inducible genes. We developed an IFN-score based on the most informative 14 genes, which were differentially expressed ($p<0.05$, fold-change>2, and log2[SD(expression)]<1.75 for each group) in nine controls from previous microarray and RNASeq experiments

with known high (n=4) and low (n=5) IFN-signature expression. A logistic regression model was created to calculate the probability of having a high interferon level for each iSS case; the resulting probability output is the IFN score.

Results: Nineteen iSS subjects had anti-Ro antibodies (4.1%), and 33 (7.1%) were biopsy (+); the remaining 415 had nonSS-sicca. Ro (+) iSS constituted a distinct subgroup from all Ro (-) iSS: they were younger (*p=0.001*), less white (*p=1.95E10-7*), more anti-La (+) (*p=8.8E10-6*), and had more hypergammaglobulinemia (*p=0.02)* and lymphopenia (*p=0.009)*; 14/19 had extraglandular manifestations. These same statistically significant clinical differences were also observed when Ro (+) iSS to biopsy (+) iSS and Ro (-)/biopsy (-) iSS. Subsets of Ro (-) iSS subjects were (+) for other autoantibodies associated with SLE or Scleroderma: 14 had anti-Cenp-B and 10 had anti-dsDNA. Quantitatively, IFN-inducible gene expression occurs in a gradient: non-SS sicca patients have low IFN scores, biopsy (+)/Ro (-) have intermediate scores, and Ro (+) have high IFN scores, which are similar to those identified in autoantibody (+) pSS patients. High IFN-scores correlated with presence of any autoantibodies (*p=1.08E-08*), Ro (+) iSS (*p=4.53E-06*), and biopsy (+) iSS (*p=6E-03)*, but only marginally with reduced salivary flow (*p=0.018*). There was no significant difference in IFN scores between SS and Ro (+) iSS, but SS had higher IFN scores than both biopsy (+) iSS and non-SS sicca (*p=8.6E-3* and *1.95E-30*, respectively).

Conclusion: Patients with iSS may represent a *forme frustre* of SS, but it is plausible that some subsets, in particular Ro (+) iSS and dsDNA(+) iSS, will progress to SS, SLE, or overlap syndromes, respectively. The fact that they present similar IFN-signatures as those observed in SS further supports this notion, and therefore, iSS patients warrant careful follow up to characterize the transition to full-blown SS. Understanding the early events of disease has the strongest potential to lead to improvements in prevention, early diagnosis, and therapeutics.

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Abstract Number: 3201

IL-7 Drives Cytokine Secretion of IL-7Rabright CCR9-Expressing T-Follicular Helper-like Cells: Potential New Axis in Lymphoid Neogenesis in Salivary Glands of Primary Sjogren s Syndrome Patients

S.L.M. Blokland[1,2], M.R. Hillen[1,2], A.A. Kruize[1], A. Kislat[3], S. Meller[3], B. Homey[3], G.M. Smithson[4], J. Zalevsky[5], T.R.D.J. Radstake[1,2] and J.A.G. van Roon[1,6], [1]Department of Rheumatology & Clinical Immunology, University Medical Center Utrecht, Utrecht, Netherlands, [2]Laboratory for Translational Immunology, University Medical Center Utrecht, Utrecht, Netherlands, [3]Department of Dermatology, University of Düsseldorf, Medical Faculty, Düsseldorf, Germany, [4]Takeda Pharmaceuticals International, Chicago, IL, [5]Takeda California, San Diego, CA, [6]Laboratory for Translational immunology, University Medical Center Utrecht, Utrecht, Netherlands

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SESSION INFORMATION

Session Title: Sjögren's Syndrome II: Clinical Discoveries

Session Type: ACR Concurrent Abstract Session

Background/Purpose:

In primary Sjögren's syndrome (pSS) B cell hyperactivity including autoantibody secretion and lymphoma development are hallmark immunopathological features. Specific lymphoid organization (including germinal centers) is associated with increased risk for development of extraglandular manifestations and lymphoma. Thus better understanding of the cellular and molecular pathways that underlie formation of ectopic lymphoid structures is of pivotal importance. T follicular helper (Tfh) cells, expressing ICOS and cytokines like IL-21 play a critical role in the formation of such structures and in activation of B cells. Recently, a novel subset of CD4+ T cells found to have Tfh-like characteristics was found to be specifically attracted to mucosal sites by CCL25, the ligand for CCR9. Our objective was to investigate the role of CCR9+ T cells and CCL25 in pSS.

Methods:

Levels of CCL25 and 103 other soluble targets were measured in serum and washouts from labial salivary gland (LSG) biopsies by Luminex. CCL25 mRNA in LSG was quantified by qPCR. CCR9-expressing cells were assessed in the LSG by immunohistochemistry. Circulating CCR9-expressing cells were assessed by flow cytometry and cultured to assess functional properties (cytokine production).

Results:

Increased CCL25 was measured in serum of pSS and nSS patients as compared to HC (median pSS, nSS, HC 2.75, 2.61 and 1.99 ng/mL, sicca

patients vs HC: p=0.04, nSS vs pSS: ns). CCL25 serum levels in pSS correlated with chemokines involved in formation of ectopic lymphoid structures CXCL13 and CCL19, and proinflammatory cytokines IL-12 and TWEAK. In addition, pSS patients displayed around an increase in CCL25 mRNA levels in LSG (p=0.04) and increased CCL25 protein levels in LSG washouts as compared to nSS patients (median 1.24 vs 0.97 ng/mL, p=0.04). pSS patients showed enhanced numbers of CCR9-expressing cells in the salivary gland (mean pSS 9.2, nSS 3.8 cells/mm2, p=0.006). Interestingly, CCR9+ Th cells from pSS patients express increased levels of PD-1 and ICOS (both $p<0.05$). In addition, CCR9+ T cells expressed significantly higher levels of IL-7Rα as compared to CXCR5 Tfh precursor cells ($p<0.01$) and secreted strongly increased levels of IFN-y, IL-10, IL- 17, IL-6, IL-21 but not CXCL13 upon stimulation with IL-7 as compared to CXCR5+ Tfh cells.

Conclusion:

Enhanced expression of CCL25 could significantly contribute to the increased numbers of CCR9+ cells in particular CCR9-expressing Tfh-like cells in labial salivary glands from pSS patients. Considering the increased expression of ICOS and IL-7Rα on CCR9+ Th cells and the capacity of IL-7 to induce pro-inflammatory and Tfh-like cytokine secretion this suggests that the CCL25/CCR9-axis might play a significant role in lymphoid neogenesis and immunopathology of pSS, representing a novel therapeutic target in this disease.

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Abstract Number: 3202

Functional Anti-Muscarinic Receptor-3 Monoclonal Antibodies Derived from Salivary Gland in Patients of Sjögren's Syndrome

Syed M.S. Quadri[1,2], Kristi A. Koelsch[3], Valerie Harris[4], Biji T Kurien[5] and R. Hal Scofield[6], [1]Medicine, University of Oklahoma Health Sciences Center, Oklahoma City, OK, [2]Arthritis and Clinical Immunology, Oklahoma Medical Research Foundation, Oklahoma City, OK, [3]Arthritis and Clinical Immunology, Oklahoma Medical Research Foundation, Okalahoma City, OK, [4]University of Oklahoma Health Sciences Center, Oklahoma City, OK, [5]Arthritis and Immunology, Oklahoma Medical Research Foundation, Oklahoma City, OK, [6]Department of Pathology, University of Oklahoma Health Sciences Center, Oklahoma City, OK

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SESSION INFORMATION

Session Title: Sjögren's Syndrome II: Clinical Discoveries

Session Type: ACR Concurrent Abstract Session

Background/Purpose:

Sjögren's syndrome (SS) is a chronic autoimmune inflammatory disease characterized by bilateral hypofunction of lacrimal and salivary glands leading to keratoconjuctivitis and xerostomia. The hallmark of SS is presence of antibodies against Ro (SS-A) and La (SS-B). Recent studies showed the presence of antibodies against M3 muscarinic acetylcholine receptor (M3R), a receptor found in endocrine and exocrine glands including salivary and lacrimal glands. M3R is a seven transmembrane GPCR having 3 extracellular and 3 intracellular domains/loops, responsible for smooth muscle contraction and glandular secretion. We hypothesized that antibodies derived from salivary gland against extracellular domains of M3R are functional and are responsible for decrease in salivary and lacrimal flow observed in Sjögren's syndrome.

Methods:

Production of monoclonal antibodies (MAbs): Patients meeting the American College of Rheumatology (ACR) classification criteria for primary Sjögren's syndrome (pSS) were evaluated at OMRF Sjögren's Research Clinic (OSRC). Control patients do not meet the criteria (DNMCs). A single cell suspension was prepared from labial salivary gland tissue obtained following biopsy. Antibody secreting cells (ASCs) having CD3- CD4- CD8- CD19+ $CD27^{high}$ $CD38^{high}$ IgG+ were sorted by fluorescence-activated single cell sorting. Recombinant MAbs were produced from ASCs by sequencing the V, D, J and CDR of the heavy and light chains amplified by RT-PCR and nested PCR, cloned into an expression vector, transfected to human cell line, expressed and purified. MAbs derived from pSS and DNMCs were 51 and 18 respectively.

M3R experiments: Peptides encoding the 2^{nd} (a.a. 213-228) and 3^{rd}(a.a. 514-527) ECL of M3R were employed in an ELISA to detect antibodies against these domains. FRET agonist/antagonist functional assays for MAbs using chimeric CHO-K1 NFAT bla cells, engineered to express human M3R along with beta lactamase reporter gene under control of NFAT response element, were carried out. CHO-K1 cells were incubated with 100 µg/ml mAb following incubation with either assay media or with carbachol at EC80 followed by substrate and fluorescence detection.

Results:

MAbs from pSS patients were highly reactive to 2nd as well as 3rd ECL as compared to DNMCs. We found significantly high O.D. values (> 4) in MAbs derived from pSS as compared to DNMCs. In MAbs from pSS, 9/51 were positive for 2nd ECL and 5/51 were positive for 3rd ECL. Where as in DNMCs none of the MAbs were positive for 2nd ECL however two of the MAbs were found positive for 3rdECL (cut-off 2 S.D. above DNMCs average O.D.). From the functional assays we have tested eight MAbs so far and found significant inhibition ranging from 14-66 % of the total stimulated response. None of these antibodies were found to be stimulatory.

Conclusion:

Anti-M3R antibodies have become a center of interest in rheumatology because of its possible pathogenesis and detection in SS as well as borderline SS patients. This data suggests inhibitory role of anti-M3R antibodies in producing SS symptoms. Second extracellular loop could play an antigenic role for anti-M3R antibodies. Our further studies will test whether passive transfer of MAbs into mice could induce Sjögren's like disease.

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Abstract Number: 3203

The Clinical Efficacy and Safety of Baminercept, a Lymphotoxin-Beta Receptor Fusion Protein, in Primary Sjögren's Syndrome: Results from a Randomized, Double-Blind, Placebo-Controlled Phase II Trial

E. William St.Clair[1], Alan N. Baer[2], Ghaith Noaiseh[3], Anne Parke[4], Andreea Coca[5], Tammy Utset[6], Mark C. Genovese[7], Daniel J Wallace[8], James McNamara[9], Karen Boyle[10], Lynette Keyes-Elstein[10], Nathalie Franchimont[11], Judith A James[12] and for the Autoimmunity Centers of Excellence supported by a grant from NIAID 5U19-AI056363, [1]Medicine, Duke University, Durham, NC, [2]Division of Rheumatology, Johns Hopkins University School of Medicine, Baltimore, MD, [3]University of Pittsburgh Medical Center, Pittsburgh, PA, [4]University of Connecticut, Farmington, CT, [5]University of Rochester Medical Center, Rochester, NY, [6]University of Chicago, Chicago, IL, [7]Division of Rheumatology, Stanford University Medical Center, Palo Alto, CA, [8]Cedars-Sinai Medical Center, West Hollywood, CA, [9]NIAID/NIH, Bethesda, MD, [10]Rho Federal Systems, Inc., Chapel Hill, NC, [11]Biogen, Cambridge, MA, [12]OMRF, OU, Oklahoma City, OK
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SESSION INFORMATION
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Background/Purpose: Primary Sjögren's syndrome (pSjS) is characterized by chronic inflammation of the lacrimal and salivary glands, as well as frequent extraglandular involvement and increased risk of B cell lymphoma. Several lines of evidence implicate the lymphotoxin (LT) pathway in the pathogenesis of this disease. Baminercept inhibits the LT pathway, which is important in lymphoid tissue organization and chronic inflammation. This study tests the clinical efficacy and safety of baminercept in pSjS.

Methods: We randomized subjects in a 2:1 ratio to receive 24 weekly subcutaneous injections of baminercept 100 mg or placebo. Eligible subjects met the 2002 American-European Consensus Group classification criteria for pSjS, had a pilocarpine-stimulated whole salivary flow (SWSF) of ≥ 0.1 mL/min, and had ≥ 1 systemic manifestations. The primary endpoint was the change in SWSF between baseline and week 24. Secondary endpoints included the safety of baminercept and the changes in unstimulated whole salivary flow (UWSF), Schirmer-I-test, ocular staining, fatigue, joint pain, overall dryness, and the EULAR SjS Disease Activity Index (ESSDAI). Subjects that received at least one dose of study medication constituted the modified intent-to-treat (mITT) population. Subjects were followed for 48 weeks.

Results: Only 52 of the planned 72 subjects were enrolled due to study drug expiration. Of the 52 eligible subjects, 33 and 19 subjects were randomized to the baminercept and placebo treatment groups, respectively. Ten of the 52 (19%) participants withdrew from treatment (adverse event, 4; subject decision 3; > 4 missed doses, 1; investigator decision, 1; other, 1). In the mITT population (n=52), we found no difference between the baminercept and placebo groups in the change in SWSF (adjusted mean: -0.01 vs. 0.06 mL/min; p=0.37). However, the ESSDAI improved significantly more in the baminercept than the placebo group (adjusted mean change: -1.6 vs. -0.25; p=0.043). In addition, there were no significant differences between treatment groups in the change in UWSF, Schirmer-I-test, ocular staining, fatigue, joint pain, and overall dryness. Lymphocyte numbers increased during baminercept treatment compared to the placebo group (p < 0.0001), an expected effect of baminercept on cellular trafficking. Baminercept treatment was not associated with any significant changes in the serum levels of CXCL13, LIGHT, IP10, and BAFF. Seven subjects had a serious adverse event (SAE), including 2 subjects (baminercept group) with grade 3 hepatic injury who recovered without sequela. Transaminase abnormalities (>ULN) occurred more frequently in the baminercept group (10 subjects [30%], 15 events) than the placebo group (3 subjects [16%], 5 events), including the 2 subjects with SAEs who had grade 3 abnormalities; the

remainder had grade 1 elevations.

Conclusion: Baminercept therapy was no more effective than placebo for increasing salivary flow or reducing ocular dryness, and was accompanied by an imbalance in transaminase elevations and 2 cases of reversible grade 3 hepatic injury. The finding that baminercept therapy was associated with improvement in the ESSDAI warrants further study.

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Abstract Number: 3204

Hypoechoic Lesions on Parotid Gland Ultrasound Are a Surrogate Marker of Focal Lymphocytic Sialadenitis on Minor Salivary Gland Biopsy in Sjögren's Syndrome

Thomas Grader-Beck[1], Joel Fradin[2], Jean Kim[3], Esen Akpek[4], Brendan Antiochos[5], Julius Birnbaum[6] and Alan N. Baer[7], [1]Medicine Div of Rheumatology, Johns Hopkins University School of Medicine, Baltimore, MD, [2]Department of Radiology and Radiological Science, Johns Hopkins University School of Medicine, Baltimore, MD, [3]Otolaryngology, Head & Neck Surgery, Johns Hopkins University, Baltimore, MD, [4]Ophthalmology, Johns Hopkins University School of Medicine, Baltimore, MD, [5]Medicine-Division of Rheumatology, Johns Hopkins University, Baltimore, MD, [6]Medicine (Rheumatology), Johns Hopkins University School of Medicine, Baltimore, MD, [7]Division of Rheumatology, Johns Hopkins University School of Medicine, Baltimore, MD

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SESSION INFORMATION

Session Title: Sjögren's Syndrome II: Clinical Discoveries

Session Type: ACR Concurrent Abstract Session

Background/Purpose: To determine whether hypoechoic lesions on parotid gland ultrasound can serve as a surrogate marker for a focus score ≥1 on minor salivary gland biopsy in patients with suspected Sjogren's syndrome (SS)**.**

Methods: We analyzed 220 parotid gland salivary gland ultrasounds that were obtained on 220 patients being evaluated for possible or known SS at the Johns Hopkins Sjogren's Center between 2012 and 2015. All scans were performed and interpreted by a radiologist (JF) with expertise in ultrasonography. The presence of hypoechoic lesions within the parotid gland parenchyma was determined in each scan. Sjogren's syndrome (SS) was diagnosed according to AECG or preliminary ACR criteria. Statistical analyses were performed using Fisher's exact and Student's t-test.

Results: Among the 220 patients, 116 fulfilled classification criteria for SS. The remaining patients were labeled as "sicca controls". Hypoechoic lesions were significantly more frequent in SS patients versus controls (55/116 versus 3/104; $p < 0.0001$) resulting in a sensitivity of 47% and specificity of 97% for SS. A minor salivary gland biopsy was performed in 64 patients with SS and showed a focus score ≥ 1 in 51 (80%). The presence of hypoechoic lesions on ultrasound was highly associated with FLS ≥1 (23/24 versus 28/40, OR 9.9; 95% CI 1.2-81.5). The mean focus score was not significantly different in SS patients with hypoechoic lesions compared to SS patients without hypoechoic lesions (3.22 versus 2.39, p=*ns*). Positive autoantibody status (anti-SSA/SSB/rheumatoid factor, hypergammaglobulinemia) as well as leukopenia, monoclonal gammopathy and salivary gland swelling were significantly more frequent in SS patients with hypoechoic lesions, whereas there was no difference in frequency of C3 and C4 hypocomplementemia or symptom duration. Other features on parotid gland ultrasound, including heterogeneity, calcifications and presence of cysts did not predict FLS ≥ 1 as accurately as hypoechoic lesions. Moreover, addition of submandibular gland ultrasound data did not add additional predictive value.

Conclusion: Hypoechoic lesions on parotid gland ultrasound strongly correlate with the presence of a focus score ≥1 on minor salivary gland biopsy. Larger studies are needed to determine whether ultrasound imaging may replace a diagnostic lip biopsy in subsets of patients evaluated for SS.

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Abstract Number: 3205

Treatment with Abatacept or Rituximab Targets T Follicular Helper Cells in Patients with Primary Sjogren s Syndrome

Gwenny M. Verstappen[1], Petra M. Meiners[2], Odilia B.J. Corneth[3], Rudi W. Hendriks[3], Arjan Vissink[4], Frans G.M. Kroese[5] and Hendrika Bootsma[5], [1]Rheumatology & Clinical Immunology, University Medical Center Groningen, University of Groningen, Groningen, Netherlands, [2]Oral and Maxillofacial Surgery, University Medical Center Groningen, University of Groningen, Groningen, Netherlands, [3]Pulmonary Medicine, Erasmus MC, Rotterdam, Netherlands, [4]Department of Oral and Maxillofacial Surgery, University Medical Center Groningen, University of Groningen, Groningen, Netherlands, [5]Rheumatology and Clinical Immunology, University Medical Center Groningen, University of Groningen, Groningen, Netherlands

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SESSION INFORMATION

Session Title: Sjögren's Syndrome II: Clinical Discoveries

Session Type: ACR Concurrent Abstract Session

Background/Purpose: T cell-dependent B cell hyperactivity is a characteristic pathogenetic feature of primary Sjögren's syndrome (pSS). This is illustrated by the finding that treatment of pSS patients with either abatacept or rituximab improves disease activity [1-2]. However, the mode of action of both treatment modalities in pSS remains elusive. The current study assessed the impact of abatacept or rituximab treatment on circulating $CD4^+$memory T cell subsets in pSS patients.

Methods: Fifteen pSS patients treated with abatacept and twenty-four pSS patients treated with rituximab were included in this study [1-2]. Percentages of $CD4^+$memory T cell subsets were assessed by flow cytometry analysis of peripheral blood mononuclear cells from patients at baseline, during treatment and after treatment. Expression patterns of CD45RA, CXCR3, CCR6, CCR4, CXCR5, programmed death-1 (PD-1), inducible costimulator (ICOS) and FoxP3 were used for distinction of Th1, Th2, Th17, T follicular helper (Tfh) and T regulatory (Treg) subsets. Generalized estimating equations were used to analyze the presence of different subsets over time within patients, viz. on treatment (week 0-24) and off treatment (week 24-48).

Results: Treatment with abatacept or rituximab results in a decrease in absolute numbers of Tfh cells ($CXCR5^+PD\text{-}1^+$) ($p<0.001$ for both treatments). Furthermore, expression levels of the activation marker ICOS by Tfh cells became concomitantly lower ($p<0.001$ for both treatments). Absolute numbers of Treg cells ($FoxP3^+$) were only reduced by abatacept ($p<0.001$). In contrast, other $CD4^+$memory T cell subsets (Th1, Th2, Th17 cells) were unaffected. Off treatment (week 24-48), changes in Tfh cells, ICOS expression and Treg cells reversed to baseline levels.

Conclusion: Treatment of pSS patients with abatacept or rituximab primarily affects Tfh cells. The lower numbers of Tfh cells may lead to reduced T cell-dependent B cell hyperactivity and contribute to the beneficial clinical effects of both treatment modalities in pSS patients. These findings indicate that Tfh cells may play a central role in the pathogenesis of pSS.

1. Meiners PM, et al. Abatacept treatment reduces disease activity in early primary Sjogren's syndrome (open-label proof of concept ASAP study). Ann Rheum Dis 2014;73:1393-6
2. Meiners PM, et al. Responsiveness of disease activity indices ESSPRI and ESSDAI in patients with primary Sjögren's syndrome treated with rituximab. Ann Rheum Dis 2012;71:1297-302

Disclosure: G. M. Verstappen, None; **P. M. Meiners**, None; **O. B. J. Corneth**, None; **R. W. Hendriks**, None; **A. Vissink**, None; **F. G. M. Kroese**, None; **H. Bootsma**, Roche Pharmaceuticals, 2,Bristol-Myers Squibb, 2.

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Abstract Number: 3206

Inflammation on MRI in Sacroiliac-Joints and Spine Is Longitudinally Related to Disease Activity in Male but Not in Female Patients with Axial Spondyloarthritis: 2-Year Data from the DESIR Cohort

Victoria Navarro-Compán[1], Sofia Ramiro[2], Robert B. M. Landewé[3], Maxime Dougados[4], Corinne Miceli-Richard[5], Pascal Richette[6] and Désirée van der Heijde[7], [1]Rheumatology, University Hospital La Paz, Madrid, Spain, [2]Rheumatology, Leiden University Medical Center,

Leiden, Netherlands, [3]Amsterdam Rheumatology & Immunology Center, Academic Medical Center, Amsterdam, Netherlands, [4]Université Paris René Descartes and Hôpital Cochin, Paris, France, [5]Rheumatology, Université Paris Sud, Le Kremlin Bicêtre, France, [6]Université Paris Diderot, UFR médicale, Paris, France; APHP Hôpital Lariboisière, Fédération de Rhumatologie and Inserm U1132, Hôpital Lariboisière, Paris, France, [7]Department of Rheumatology, Leiden University Medical Center, Leiden, Netherlands

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SESSION INFORMATION

Session Date: Tuesday, November 10, 2015

Session Title: Spondylarthropathies and Psoriatic Arthritis - Clinical Aspects and Treatment: Clinical Aspects, Imaging and Biomarkers

Session Type: ACR Concurrent Abstract Session

Session Time: 4:30PM-6:00PM

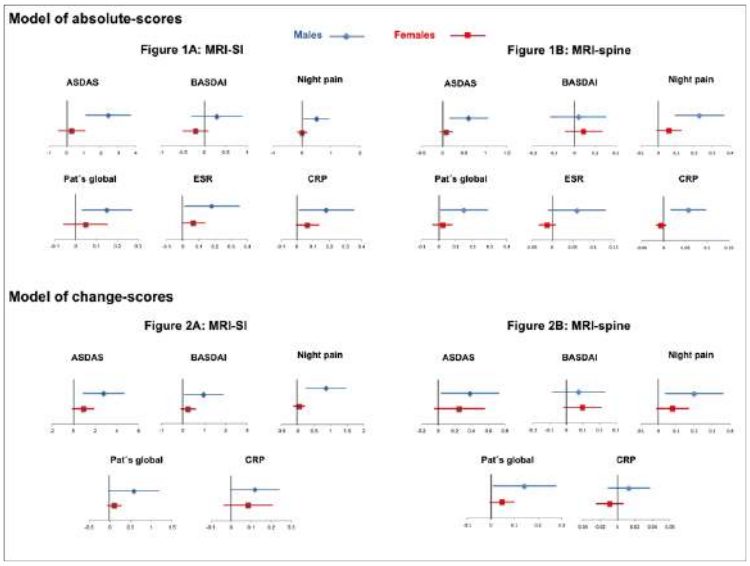
Background/Purpose: In patients with axial spondyloarthritis (axSpA), clinical disease activity measures (DA) have been longitudinally related to radiographic progression. Interestingly, a gender disparity has been observed in this relationship, but the reason for this is unclear. Here, we investigate whether such a gender disparity also exists with respect to the relationship between DA and inflammatory lesions on magnetic resonance imaging (MRI) of the sacroiliac joints (SI) and the spine.

Methods: Two-year follow-up data from 167 patients fulfilling ASAS axSpA criteria in the DESIR cohort with at least two MRIs of SI and/or spine available during this period were analyzed. Baseline characteristics of patients included were: 50% males, mean (SD) age: 33 (9) years, 81% HLA-27 positive and symptom duration: 18 (11) months. The association between inflammatory lesions on MRI of SI/spine (measured by SPARCC/Berlin score, respectively) and DA (ASDAS, BASDAI, patient«s global disease activity, night pain, CRP and ESR) was investigated using generalized estimating equation (GEE) models: i) a model of absolute-scores; and ii) a model of change-scores. All models were adjusted for age, symptom duration and HLA-B27.

Results: The relationship between inflammatory lesions on MRI and DA was different in males than in females. MRI-scores of SI/spine (i) were statistically significantly associated to most of the DA in males, but not in females (Figure 1A&1B). In the model of changes (ii), ASDAS was significantly associated with inflammatory lesions on MRI of either SI (Fig 2A) or spine (Fig 2B) in males, but not in females. Similar effects were seen with different DA measures.

Conclusion: In male, but not in female patients with axSpA, clinical disease activity is longitudinally associated with inflammatory lesions on MRI. This observation supports the hypothesis that some aspects of axSpA are different in males compared to females.

Figure: Longitudinal relationship between clinical disease activity measures and inflammation degree (SPARCC/Berlin) on MRI-SI/spine stratified for gender. Markers and surrounding lines represent beta values and 95%CI, respectively.



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Abstract Number: 3207

Axial Disease in Psoriatic Arthritis: A Clinical and Radiographic Comparison with Ankylosing Spondylitis

Deepak R. Jadon[1], Raj Sengupta[1], Alison L Nightingale[2], Mark Lindsay[3], Eleanor Korendowych[1], Graham Robinson[4], Amelia Jobling[5], Gavin Shaddick[6], Anne Barton[7] and Neil J. McHugh[8], [1]Rheumatology, Royal National Hospital for Rheumatic Diseases, Bath, United Kingdom, [2]Pharmacy and Pharmacology, University of Bath, Bath, United Kingdom, [3]Pharmacy & Pharmacology, University of Bath, Bath, United Kingdom, [4]Royal United Hospital, Bath, United Kingdom, [5]Mathematical Sciences, University of Bath, Bath, United Kingdom, [6]Department of Mathematics, University of Bath, Bath, United Kingdom, [7]Arthritis Research UK Centre for Genetics and Genomics, Centre for Musculoskeletal Research, Manchester Academic Health Science Centre, The University Of Manchester, Manchester, United Kingdom, [8]Rheumatology, Royal National Hospital for Rheumatic Diseases, Upper Borough Walls, United Kingdom

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Session Type: ACR Concurrent Abstract Session

Session Time: 4:30PM-6:00PM

Background/Purpose:

Little is known of the characteristics of psoriatic spondyloarthritis (PsSpA). A study was conducted to determine the: (i) prevalence of PsSpA in a psoriatic arthritis (PsA) cohort; (ii) clinical and radiographic characteristics of PsSpA.

Methods:

A prospective single-centre cross-sectional observational study was conducted, recruiting consecutive patients: 201 PsA (CASPAR+) and 201 ankylosing spondylitis (AS; modified New York, mNY+). Participants were examined clinically, completed patient reported outcome measures, and their axial radiographs (cervical, lumbar, pelvis) were scored. Multivariate Poisson regression analyses are presented.

Results:

The 402 enrolled cases were reclassified on the basis of radiographic axial disease and psoriasis: 118 PsSpA, 127 peripheral-only PsA (pPsA), and 157 AS cases (40, 7, and 89% were *HLA-B27*+, respectively). The prevalence of PsSpA in this SpA cohort was 118/245 (48%).

CASPAR criteria were fulfilled by 49/201 (24%) AS cases, and mNY criteria by 48/201 (24%) PsA cases.

Symptomatically-silent PsSpA (radiographic but no recall of symptoms) was present in 30/118 (25%) of PsSpA cases. Of 118 PsSpA cases: 45/118 (38.14%) had sacroiliitis and spondylitis; 34/118 (28.81%) had sacroiliitis alone; and 39/118 (33%) had spondylitis without sacroiliitis.

Younger age at arthritis symptom onset (p=0.01) and psoriatic nail crumbling (adjusted incidence risk ratio, aIRR 2.86; 95%CI 1.67, 5.00; p<0.001) predicted the occurrence of PsSpA.

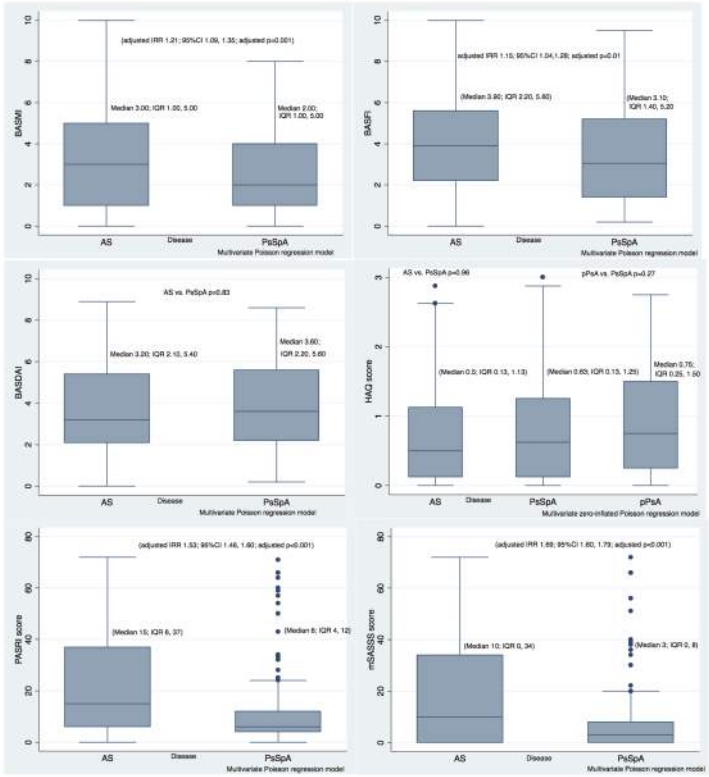
PsSpA cases had similarly high disease activity (ASDAS, BASDAI) to that seen in the AS cases (*Figure 1)*. Disability (HAQ) was no different across the three groups. Function (BASFI, aIRR 1.15; 95%CI 1.05, 1.28; p=0.01) and axial metrology (BASMI, aIRR 1.21; 95%CI 1.09, 1.35; p=0.001) were poorer in AS than PsSpA cases.

Both AS and PsSpA cases predominantly have bilateral symmetrical-grade sacroiliitis, and both cervical vertebral and facet spondylitis. Complete SIJ ankylosis (aOR 4.35; 95%CI 2.26, 8.36; p<0.001) and bridging syndesmophytes (aOR 2.78; 95%CI 1.49, 5.18; p<0.001) were more likely in AS than PsSpA cases. Radiographic severity was higher in AS compared with PsSpA cases (mSASSS score, aIRR 1.69; 95%CI 1.60, 1.79; p<0.001; PASRI score, aIRR 1.53; 95%CI 1.46, 1.60; p<0.001).

Conclusion:

PsSpA was more prevalent than expected. Symptomatically-silent PsSpA, and spondylitis without sacroiliitis are important considerations when classifying PsSpA. PsSpA has as severe a clinical impact as AS, but is radiographically less severe. Bridging syndesmophytes and complete SIJ fusion appear to best radiographically differentiate PsSpA from AS.

Figure 1. **Clinical and radiographic composite indices in PsSpA, AS and pPsA cases**



Multivariate modelling, adjusted as required for: sex, age at clinical / radiographic assessment, disease duration at clinical / radiographic assessment, synthetic and biological DMARD use, smoking, and body mass index.

PsSpA: psoriatic spondyloarthritis
aIRR: adjusted incidence risk ratio
BASMI: Bath Ankylosing Spondylitis Metrology Index
BASDAI: Bath Ankylosing Spondylitis Disease Activity Index
PASRI: Psoriatic Arthritis Spondylitis Radiology Index
pPsA: peripheral-only psoriatic arthritis
95% CI: 95% confidence interval
BASFI: Bath Ankylosing Spondylitis Functional Index
HAQ: Health Assessment Questionnaire
mSASSS: modified Stoke Ankylosing Spondylitis Spinal Score
AS: ankylosing spondylitis
IQR: interquartile range

Table 1. **Pattern of radiographic disease in PsSpA and AS cases**

Domain	Radiographic Parameter	Disease	Yes (%)	Adjusted OR	Adjusted 95% CI	Adjusted p-value
Radiographic pattern	Sacroiliitis	PsSpA	79/118 (66.95)	-	-	-
		AS	157/157 (100.00)			
	Spondylitis (cervical and / or lumbar)	PsSpA	84/118 (71.19)	0.94	0.52, 1.70	0.85
		AS	109/157 (69.43)			
Spondylitis pattern	Cervical vertebrae	PsSpA	52/116 (44.83)	1.51	0.87, 2.63	0.15
		AS	85/157 (54.14)			
	Cervical facet joint	PsSpA	29/118 (24.58)	1.50	0.83, 2.72	0.18
		AS	60/157 (38.22)			
	Lumbar vertebrae	PsSpA	50/117 (42.74)	1.79	1.04, 3.06	0.03
		AS	85/157 (54.14)			
Sacroiliitis pattern	Bilateral	PsSpA	65/79 (82.28)	6.10	2.08, 17.98	0.001
		AS	142/147 (96.60)			
	Symmetrical grade	PsSpA	60/79 (75.95)	1.16	0.59, 2.31	0.66
		AS	119/147 (80.95)			
Sacroiliac joint morphology	Simple sclerosis bilaterally (Grade 2)	PsSpA	6/118 (5.08)	1.75	0.56, 5.48	0.34
		AS	9/157 (5.73)			
	Erosion (Grade 3)	PsSpA	42/118 (35.59)	1.00	0.60, 1.68	0.99
		AS	53/157 (33.76)			
	Partial ankylosis (Grade 3)	PsSpA	25/118 (21.19)	1.69	0.96, 3.00	0.07
		AS	46/157 (29.30)			
	Complete ankylosis (Grade 4)	PsSpA	18/118 (15.25)	4.35	2.26, 8.36	<0.001
		AS	68/157 (43.31)			
Vertebral morphology	Erosion	PsSpA	3/118 (2.54)	1.58	0.38, 6.57	0.53
		AS	6/157 (3.82)			
	Non-bridging syndesmophyte	PsSpA	47/118 (39.83)	0.95	0.57, 1.58	0.84
		AS	58/157 (36.94)			
	Bridging syndesmophytes	PsSpA	12/118 (10.17)	2.78	1.49, 5.18	0.001
		AS	36/157 (22.93)			

PsSpA: psoriatic spondyloarthritis AS: ankylosing spondylitis OR: odds ratio 95% CI: 95% confidence interval
* Multivariate reverse-stepwise logistic regression model adjusted as required for: sex, age at radiographic assessment, disease duration at radiographic assessment, anti-TNF use ever, synthetic DMARD use ever, and smoking ever.

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Abstract Number: 3208

Spinal Radiographic Progression in Early Axial Spondyloarthritis: Data from the DESIR Cohort

Sofia Ramiro[1], Désirée van der Heijde[1], Rosaline van den Berg[2], Victoria Navarro-Compán[3], Antoine Feydy[4], Maria-Antonietta d'Agostino[5], Damien Loeuille[6], Maxime Dougados[7], Monique Reijnierse[8] and Pascal Claudepierre[9], [1]Rheumatology, Leiden University Medical Center, Leiden, Netherlands, [2]Leiden University Medical Center, Leiden, Netherlands, [3]Rheumatology, University Hospital La Paz, Madrid, Spain, [4]Paris Descartes University, Radiology B department, Cochin Hospital, Paris, France, [5]Rheumatology, Versailles-Saint Quentin en Yvelines University, Boulogne-Billancourt, France, [6]Rheumatology, Nancy University Hospital, Nancy, France, [7]Rheumatology Department, Cochin hospital, Paris-Descartes University, Paris, France, [8]Radiology, Leiden University Medical Center, Leiden, Netherlands, [9]Rheumatology, Université Paris Est Créteil, Créteil, France
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Background/Purpose: The development of radiographic damage over time has been investigated in patients with AS, but not yet in early axial spondyloarthritis (axSpA). We have recently shown that the modified Stoke in Ankylosing Spondylitis Spine Score (mSASSS) is the most sensitive and adequate scoring method in (early) axSpA. Our aim was to analyse the development and progression of radiographic damage in the spine in patients with IBP and early axSpA.

Methods: Patients with IBP for <3 years and with a clinical suspicion for axSpA were included in DESIR. Yearly cervical and lumbar radiographs from the first 2 years of follow-up were used in this analysis. Patients with radiographs available allowing the estimation of at least one (1-year or 2-year) progression interval were included in this analysis. Two trained readers independently scored the radiographs according to the mSASSS (0-72). Scores per vertebral corner were averaged between the readers. One-year (M0-M12) and two-year (M0-M24) progression scores were computed. Progression was assessed in each of the different subgroups of patients defined at baseline according to the fulfillment of the ASAS axSpA criteria, imaging arm (modified New York Criteria (mNYC) +/- and MRI positivity (according to the ASAS definition)), clinical arm only (+/- positive CRP). In addition, patients were grouped according to presence of baseline syndesmophytes.

Results: In total, 608 patients (mean age 36.0 (SD 8.8) years, 47% males, 74% fulfilling ASAS axSpA criteria) were included. At baseline, the average mSASSS was 0.36 (1.49). From these patients, 571 one-year mSASSS progression intervals could be obtained and 441 two-year progression intervals. Patients fulfilling the ASAS axSpA criteria had on average 0.29 (1.73) mSASSS-units progression in 2 years, whereas those not fulfilling the criteria showed a progression of 0.06 (1.00) units. Patients fulfilling the imaging arm had a progression of 0.42 (2.21) mSASSS-units per 2 years. Within this subgroup of patients, patients fulfilling the mNYC and with a negative MRI had the highest progression, followed by those mNYC+ and MRI+ and lastly those mNYC- but with MRI+ (Table). Patients fulfilling only the clinical arm of the ASAS criteria had a progression of 0.11 (0.60) mSASSS-units per 2 years. Patients with baseline syndesmophytes (across all subgroups) had a 2-year progression of 1.16 (4.31) mSASSS-units.

Table - Progression of spinal radiographic damage over 2 years (1-year and 2-year intervals)

	Subgroup	1-year mSASSS progression (M0-M12) n=517 mean (SD)	2-year mSASSS progression (M0-M24) n=441 mean (SD)
ASAS criteria	ASAS +	0.11 (1.15), n=366	0.29 (1.73), n=322
	ASAS -	0.08 (0.69), n=147	0.06 (1.00), n=116
ASAS criteria Imaging arm	MRI+ mNYC+	0.20 (2.11), n=96	0.36 (2.38), n=88
	MRI+ mNYC-	-0.02 (0.26), n=76	0.18 (0.93), n=63
	MRI- mNYC+	0.17 (0.47), n=41	1.02 (3.21), n=34
ASAS criteria Clinical arm	Clinical arm only CRP+	0.05 (0.22), n=20	0.14 (0.50), n=21
	Clinical arm only CRP-	0.10 (0.59), n=130	0.10 (0.62), n=112
Baseline syndesmophytes	Baseline syndesmophytes +	0.38 (3.15), n=34	1.16 (4.31), n=30
	Baseline syndesmophytes -	0.08 (0.68), n=483	0.16 (1.12), n=411

Conclusion: Development of spinal radiographic progression can be captured in a cohort of patients with early axSpA within a 2-year follow-up. Progression is higher in patients fulfilling the mNYC and also in patients with baseline syndesmophytes.

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Abstract Number: 3209

Utility of Power Doppler Ultrasound-Detected Synovitis for the Prediction of Short Term Flare in Psoriatic Arthritis Patients in Clinical Remission

Josefina Marin[1,2], M Laura Acosta-Felquer[2], Leandro Ferreyra-Garrot[3], Erika Catay[4], Javier Rosa[5], Santiago Ruta[2], Mirtha Sabelli[2], Ricardo Garcia-Monaco Sr.[6] and Enrique R. Soriano[7], [1]Internal Medicine, Rheumatology Unit, Internal Medical Services, Hospital Italiano de Buenos Aires, Buenos Aires, Argentina, [2]Rheumatology Unit, Internal Medicine Service, Hospital Italiano de Buenos Aires, Buenos Aires, Argentina, [3]Rheumatology Section, Internal Medicine Service, Hospital Italiano de Buenos Aires, Instituto Universitario Hospital Italiano de Buenos Aires, and Fundacion PM Catoggio, Internal Medicine, Argentina, Buenos Aires, Argentina, [4]Salguero 569 7 35, Hospital Italiano de Buenos Aires, Buenos Aires, Argentina, [5]Rheumatology, Hospital Italiano de Buenos Aires, Buenos Aires, Argentina, [6]Hospital Italiano de Buenos Aires, Buenos Aires, Argentina, [7]Internal Medicine, Hospital Italiano de Buenos Aires, Buenos Aires, Argentina

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Background/Purpose: Ultrasound has been shown to detect subclinical synovitis in in rheumatoid arthritis and psoriatic arthritis (PsA in clinical remission.). The value of power Doppler ultrasound (PDUS) to predict flares in patients with PsA in remission or minimal disease activity has not been fully studied.

Objective: To determine whether PDUS assessment of synovitis predicts short term relapse in patients with PsA in clinical remission or minimal disease activity.

Methods: consecutive PsA patients in clinical minimal disease activity (MDA) and/or remission (fulfillment MDA criteria or Disease Activity Score in 28 joints [DAS28] <2.6, respectively) underwent PDUS examination of 18 joints (second and third metacarpophalangeal joints, second and third proximal interphalangeal joints, wrist, knee, ankle and second and fifth metatarsophalangeal joints). US assessment were performed by the same rheumatologist, blinded to clinical data, usig a MyLab 70 machine (Esaote) provided with a 6-18 MHz multifrequency broad band linear transducer. PD signal was graded on a semi-quantitative scale from 0 to 3. PD synovitis was defined as the presence of intraarticular PD signal ≥1, and was treated as a dichotomous variable. On the same day a complete clinical assessment was performed by another rheumatologist. All patients were followed-up for 6 months. Flare was defined as the requirement of a change in disease modifying antirheumatic drugs (DMARDs) (increasing dose, adding or changing DMARDs or biologics therapy) by the treating rheumatologist, who was blinded to the US findings. Relative risks (RR) with their 95% CI for flare among patients with and without PD signal were calculated. Multivariable analysis using logistic regression with flare as the outcome variable, and PD signal, demographic characteristics, and baseline disease activity as independent variables were also calculated.

Results: Fifty four patients were included: 47 patients fulfilling MDA criteria, 36 DAS28 remission criteria (DAS28<2.6) (29 patients fulfilled both criteria). Baseline patients' characteristics are shown in the table. Among the 54 patients on MDA or DAS28 remission, 15 (28 %) experienced a flare within the next 6 months,15/47 (32%) of patients in MDA, 10/36 (28%) of patients in DAS28 remission, and 10/29 (35%) patients fulfilling both criteria. Thirteen (87%) of the 15 patients with flares had baseline PD synovitis, compared with 7/39 (35%) patients without flares (RR= 11; 95% CI: 2.8-44; p<0.0001).). On logistic regression analysis the only variables associated with short term flares were baseline positive PD signal (OR: 119;p=0.001), and baseline use of non-biologics DMARDs (OR: 5.9; p=0.038).

Conclusion: Among PsA patients on clinical remission and/or MDA, synovial inflammation determined by the presence of a positive PD signal, was a strong predictor of short term flare.

Table: Patients' characteristics.

Feature	Patients on remission (n=54)
Male, no. (%)	33 (61)
Mean age (SD) years	54.5 (14)
Median disease duration (IQR) months	36 (10-60)
DMARDs use, no. (%)	35(65)
TNFi use, no. (%)	12 (22)
erythrocyte sedimentation rate, median (IQR)	14 (7-22)
Swollen joint count 66, mean (SD)	0.3 (0.65)
Tender joint count 68, mean (SD)	0.3 (0.68)
DAS28 remission, no. (%)	36 (67)
Mean DAS28 (SD)	2.26 (0.7)
Minimal disease activity, no. (%)	47 (87)
MDA + DAS28 remision	29 (54)
Synovial PD>=1, no. (%)	20 (37)
Patients with flare, no. (%)	15 (28)

Disclosure: J. Marin, None; **M. L. Acosta-Felquer**, None; **L. Ferreyra-Garrot**, None; **E. Catay**, None; **J. Rosa**, None; **S. Ruta**, None; **M. Sabelli**, None; **R. Garcia-Monaco Sr.**, None; **E. R. Soriano**, Abbvie; Janssen; UCB; Roche; Bristol Myers Squibb, 2,Abbvie; UCB; Janssen; Roche; Bristol Myers Squibb; Pfizer; Novartis, 8.

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Abstract Number: 3210

Evaluation of Sacroiliac Joint Radiographs in Patients with Chronic Low Back Pain: Is Erosion the Main Driver of Interreader Disagreement?

Alice Ashouri Christiansen[1,2], Oliver Hendricks[1,2], Dorota Kuettel[1], Kim Hørslev-Petersen[1,2], Anne Grethe Jurik[2,3,4], Steen Nielsen[1], Kaspar Rufibach[5], Anne Gitte Loft[6,7], Susanne Juhl Pedersen[8,9], Louise Thuesen Hermansen[1,2], Mikkel Østergaard[8,10], Bodil Arnbak[2,4], Claus Manniche[2,4] and Ulrich Weber[1,2], [1]Department of Research, King Christian 10th Hospital for Rheumatic Diseases, Graasten, Denmark, [2]Institute of Regional Health Research, University of Southern Denmark, Odense, Denmark, [3]Department of Radiology, Aarhus University Hospital, Aarhus, Denmark, [4]Hospital Lillebaelt, Spine Centre of Southern Denmark, Middelfart, Denmark, [5]rePROstat, Basel, Switzerland, [6]Department of Rheumatology, Aarhus University Hospital, Aarhus, Denmark, [7]Department of Rheumatology, Vejle Hospital, Vejle, Denmark, [8]Department of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark, [9]Rigshospitalet-Glostrup, Copenhagen Center for Arthritis Research, Center for Rheumatology and Spine Diseases, Copenhagen, Denmark, [10]Rigshospitalet-Glostrup, Copenhagen Center for Arthritis Research, Center for Rheumatology and Spine Diseases, Rigshospitalet - Glostrup, Glostrup, Denmark

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Background/Purpose: Evaluation of sacroiliac joints (SIJ) on pelvic radiographs according to the modified New York criteria (mNYc) is considered the gold standard for classification of axial spondyloarthritis (SpA). However, agreement among trained readers was consistently limited with kappa values around 0.5 [1-4]. The goals of this study in chronic back pain patients suspected of having SpA were: to determine the reproducibility of radiographic SIJ evaluation among 7 readers with varying levels of experience; to identify potential drivers to disagreement in classification among 5 predefined radiographic lesion types.

Methods: The study sample comprised 104 (38% male) consecutive patients aged 18-40 years with low back pain ≥3 months' duration, who met the Assessment of Spondyloarthritis International Society (ASAS) definition for a positive SIJ MRI (n=92) or were HLA B27 positive (n=12) and had ≥1 SpA related clinical/laboratory feature according to the ASAS classification criteria for axial SpA. All readers (2 musculoskeletal (MSK) radiologists; 2 junior and 3 senior rheumatologists) were calibrated by reference images covering all mNYc grades. The rheumatologists additionally had 3 training sessions comprising independent evaluation of unrelated pelvic radiographs. 7 blinded readers classified pelvic radiographs according to the mNYc and then recorded 5 lesion types in both SIJ: erosion, sclerosis, ankylosis, joint space widening and narrowing. Reproducibility of the mNYc classification among 21 reader pairs was assessed by Cohen's kappas and percent agreement. Potential drivers of disagreement were identified as proportions of concordant lesion types among patients with discordant classification. Finally, a generalized linear mixed logistic regression model was computed to explore to which extent discordance in lesion type was associated to discrepant mNYc classification.

Results: Kappas (percent concordance) for classification by mNYc were: 0.39 over 7 readers; 0.46 (79.8%) between 2 MSK radiologists; 0.55 (86.5%) and 0.36 (77.9%) among the most experienced rheumatologist and the 2 MSK radiologists.

Figure 1 Proportion of concordant lesion types among patients with discordant classification among 21 reader pairs

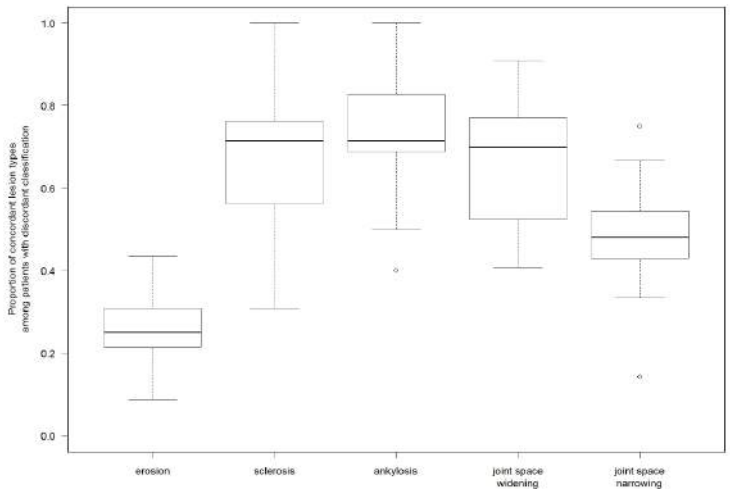

Table 1 Odds ratio for disagreement in classification in relation to lesion type among 21 reader pairs

Discordance in lesion type	Odds ratio for disagreement in mNYc	95% confidence interval	P-value
Erosion	13.5	9.1 to 20.1	<0.0001
Sclerosis	0.9	0.6 to 1.3	0.49
Ankylosis	4.8	2.7 to 8.3	<0.0001
Joint space widening	5.6	3.4 to 9.2	<0.0001
Joint space narrowing	3.0	2.0 to 4.6	<0.0001

Conclusion: Reproducibility of SIJ classification by mNYc was fair to moderate among 7 readers with varying experience in assessing pelvic X-rays. Erosion was the main driver of discordant classification.

References: ARD 1987;46:139. ARD 2003;62:519. A&R 2012;64:1412. A&R 2014;66:2403.

Disclosure: A. Ashouri Christiansen, None; **O. Hendricks**, None; **D. Kuettel**, None; **K. Hørslev-Petersen**, None; **A. G. Jurik**, None; **S. Nielsen**, None; **K. Rufibach**, None; **A. G. Loft**, None; **S. Juhl Pedersen**, None; **L. Thuesen Hermansen**, None; **M. Østergaard**, None; **B. Arnbak**, None; **C. Manniche**, None; **U. Weber**, None.

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Abstract Number: 3211

Current Smoking, Its Intensity and Duration, Is Associated with Fat Metaplasia on MRI in Patients with Spondyloarthritis

Walter Maksymowych[1], Stephanie Wichuk[1], Praveena Chiowchanwisawakit[2], Zheng Zhao[3], Donald Spady[1], Barbara Conner-Spady[1], Robert G Lambert[4] and Susanne Juhl Pedersen[5], [1]Medicine, Medicine, University of Alberta, Edmonton, AB, Canada, [2]Rheumatology, Medicine, Siriraj Hospital, Mahidol University, Bangkok, Thailand, [3]Rheumatology, Chinese PLA General Hospital, Beijing, China, [4]Radiology, Radiology, University of Alberta, Edmonton, AB, Canada, [5]Copenhagen Center for Arthritis Research, Glostrup Hospital, University of Copenhagen, Copenhagen, Denmark

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Background/Purpose: Smoking has been associated with radiographic severity and progression in SpA although there is little understanding of the mechanism. Prospective MRI data indicates that ankylosis develops following an intermediary phase of fat metaplasia, which follows resolution of inflammation in subchondral bone and at sites of erosion, when it is termed backfill[1]. We aimed to determine whether smoking influences the propensity to develop fat metaplasia as a potential mechanism for its association with progression in SpA.

Methods: In the FOllow-up Research Cohort in AS (FORCAST), AS patients from Northern Alberta attending community and academic practices are assessed for clinical and laboratory outcomes every 6 months, MRI is performed at baseline, at 3-6 months for patients starting anti-tumor necrosis factor alpha (anti-TNFα), and annually. MRI scans are scored independently by 2 readers and adjudicated by a third reader according to pre-specified rules. MRI inflammation is assessed on short tau inversion recovery (STIR) scans using the Spondyloarthritis Research Consortium of Canada (SPARCC) Sacroiliac Joint (SIJ) and 23-DVU Spine scores while structural change is assessed independently on T1-weighted (T1W) scans using the SPARCC SIJ Structural Score (SSS) score for fat metaplasia, erosion, backfill, ankylosis, and the Fat AS Spine Score (FASSS). We used univariate and multivariate regression to assess associations between smoking (current (yes/no, <10/ ³10 years), past, never, pack per day, pack year) and MRI parameters.

Results: The cohort includes 730 patients: mean age 41.3 years, 72.7% males, 78.6% B27 positive, mean disease duration of 17.5 years. Of 517 patients reporting smoking history, 105 (20.2%) were current smokers, 148 (29.0%) past smokers, and 264 (51.8%) never smoked. MRI scans were available on 250 cases in the cohort. In univariate analyses, current but not previous smoking, especially intensity (from 0.25 to 1 pack/day) and duration of current smoking (³10 years vs <10), was associated with spinal (FASSS: β=11.1, p=0.03)) and SIJ fat metaplasia (SSS backfill: β=2.4, p=0.01; SSS fat ³2: OR 2.4, p=0.03), SIJ ankylosis (β=4.5, p=0.01), and spinal inflammation (SPARCC 23-DVU (β=8.3, p=0.02). In multivariate models that included age, sex, B27, smoking, ASDAS, and selected according to the best goodness of fit Akaike Information Criterion (AIC), current smoking (intensity and/or duration) was independently associated with several MRI parameters (Table).

Conclusion: Current, but not past smoking, and its intensity and duration is associated with the degree of fat metaplasia and ankylosis on MRI of the SIJ suggesting that it may influence the tissue response to inflammation.

1. Maksymowych et al. Arthritis Rheum 2014; 66: 2958-67.

MRI feature	Smoking variable	β or OR [95%CI]	P value	R squared
SSS ankylosis score	Current, 1 pack/day	4.6 [0.5-8.7]	0.03	0.23
SSS ankylosis score	Current, >10 pack years	4.6 [0.4-8.8]	0.03	0.21
SSS backfill score	Current, 1 pack/day	2.4 [0.6-4.1]	0.01	0.06
SSS backfill score	Current, 10.1-20 pack years	2.7 [0.8-4.7]	0.01	0.07
SSS fat metaplasia ³2	Current	2.8 [0.9-8.7]	0.07	0.18
SPARCC 23-DVU score	Current, 0.5 pack/day	10.8 [1.2-20.3]	0.03	0.14

Disclosure: W. Maksymowych, None; **S. Wichuk**, None; **P. Chiowchanwisawakit**, None; **Z. Zhao**, None; **D. Spady**, None; **B. Conner-Spady**, None; **R. G. Lambert**, None; **S. J. Pedersen**, None.

Abstract Number: 3212

Characterizing the Effects of the G-CSF-R Coding rs13377964 SNP Located within Murine Lupus Susceptibility Locus Sle2c2

Ramya Sivakumar[1] and Laurence Morel[2], [1]Pathology, University of Florida, Gainesville, FL, [2]Pathology, Immunology, and Laboratory Medicine, University of Florida, Gainesville, FL

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SESSION INFORMATION

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Background/Purpose:

The genetic analysis of the lupus prone NZM2410 mouse has identified a suppressor locus, *Sle2c2,* which confers resistance to both spontaneous and chronic graft-vs.-host disease (cGVHD) induced lupus. We hypothesized that a non-synonymous polymorphism in the granulocyte colony stimulating factor (G-CSF) receptor 3 (*Csf3r)* gene in *Sle2c2* is responsible for providing protection. G-CSF acts as a pleiotropic growth factor and mediates its biological functions including granulopoiesis by binding specifically to G-CSF-R. Exogenous G-CSF restored cGVHD susceptibility in *Sle2c2*, suggesting that the *Csf3r* rs13377964 coding SNP results in a loss-of-function in signaling modulating the expression of targets in myeloid cells expressing G-CSF-R, including neutrophils and dendritic cells, and thus mediating lupus resistance.

Methods:

We investigated the functional differences between the wild type B6 and congenic *Sle2c2* alleles of *Csf3r* transduced in the murine Csf3r-negative myeloblast- like 32d.cl3 cell line with a lentiviral vector. G-CSF-R signaling was measured using phospho-flow staining and gene expression assays in transduced 32d.cl3 cells stimulated with mouse G-CSF. Furthermore, the assays were repeated using primary bone-marrow derived dendritic cells, splenocytes and peripheral blood leukocytes of B6 and congenic B6.*Sle2c2*mice. In addition, the progression and activation of G-CSF-R expressing myeloid cells throughout the entire course of cGVHD was compared between B6 and congenic mice by flow cytometry.

Results:

32d.cl3 cells expressing the *Sle2c2* allele of G-CSF-R showed a reduced expression of Jak and Src targets in response to G-CSF with both phospho-flow and gene expression assays. The *Sle2c2* allele of G-CSF-R induced a reduced phosphorylation of STAT3, ERK and p38 and lowered the expression of genes such as SOCS3, cFOS, Fcgr3, IRF1 compared to B6 allele. The effects of phospho signaling associated with Jak-STAT and ERK pathways were recapitulated with ex-vivo experiments using primary BM derived DCs as well as total splenic and blood

neutrophils. Differences in frequency of G-CSF-R positive neutrophils and splenic dendritic cell subsets as well as levels of G-CSF-R expression during the course of cGVHD further suggest the functional relevance of the G-CSF-R SNP in lupus.

Conclusion: Our results show that the coding rs13377964 SNP affects G-CSFR signaling, supporting the hypothesis that it could confer resistance to lupus. The defective signaling observed downstream of G-CSF-R primarily within the Jak and Src pathways in both primary cells and cell lines transduced with *Csf3r* alleles suggest the functional relevance of the polymorphism. Both Jak and Src kinase pathways are involved in differentiation, proliferation and survival of myeloid progenitor cells and activation of neutrophils. Future experiments aimed at elucidating the differences in functions of these pathways using cell lines and myeloid cells such as neutrophils and dendritic cells will enhance our understanding of the GCSFR axis in lupus pathogenesis.

Disclosure: R. Sivakumar, None; **L. Morel**, None.

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Abstract Number: 3214

Impaired Phagocytosis of Apoptotic Cells in Pristane-Induced Lupus Simulates the Clearance Defect in Human SLE

Shuhong Han[1], Haoyang Zuang[1], Ravil Khaybullin[2], Stepan Shumyak[3], Anan Afaneh[4], Xin Qi[5], Lijun yang[6] and Westley H. Reeves[7], [1]Division of Rheumatology and Clinical Immunology, University of Florida, Gainesville, FL, [2]medicinal chemistry, University of Flordia, gainesville, FL, [3]division of Rheumatology & Clinical Immunology, university of florida, gainesville, FL, [4]Division of Rheumatology & Clinical Immunology, university of florida, gainesville, FL, [5]medicinal chemistry, University of Florida, gainesville, FL, [6]Pathology, Immunology & Laboratory Medicine, University of Florida, Gainesville, FL, [7]Medicine, University of Florida, Gainesville, FL
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Background/Purpose: Defective phagocytosis of dead cells is seen in SLE patients' monocytes. Pristane-induced lupus causes accumulation of dead cells in tissues resembling that in SLE patients. However, the extent to which this reflects increased cell death vs. impaired removal of dead cells is unclear. The present studies addressed the clearance of dead cells in pristane-lupus

Methods: Clearance of dead cells from human bone marrow (BM) was examined by immunohistochemistry. The distribution of pristane in mouse tissues was detected by oil red staining and mass spectrometry. Murine macrophage (Mϕ) subsets were identified by flow cytometry ($F4/80^+CD11b^+Ly6G^-$). Gene expression in sorted cells was determined by real-time PCR. Phagocytosis of pHrodo red-labeled thymocytes by Mϕ from pristane-treated (develop lupus) vs. mineral oil (MO)-treated (do not develop lupus) mice was assessed in vitro and in vivo by flow cytometry. Autophagy was quantified by Cyto-ID green staining.

Results:

Tissues from SLE patients and pristane-treated mice contained numerous dead cells (activated caspase-3^+). In non-SLE patients undergoing BM ablation and massive cell death prior to stem cell transplantation, dead cells were found only within resident BM Mϕ, not free as in lupus BM, consistent with a high capacity to clear dead cells. After i.p. injection in mice, pristane was transported to the lung and BM and could be detected by oil red staining and mass spectrometry along with numerous dead cells. We hypothesized that exposure of Mϕ to pristane causes a phagocytosis defect that predisposes to lupus. Consistent with that model, resident $Tim4^+$ peritoneal Mϕ disappeared within hours of either pristane or MO injection and were replaced by BM-derived neutrophils and Mϕ. Peritoneal Mϕ from pristane-treated mice were poorly phagocytic vs. those from MO-treated controls and cells from pristane-treated mice were deficient in the class A scavenger receptor Marco. Marco is known to mediate phagocytosis of apoptotic cells, and the $Marco^+$ Mϕ subset from control mice efficiently took up dead cells. The uptake of dead cells by peritoneal Mϕ from MO-treated mice was inhibited by anti-Marco antibodies. Expression of *Marco* mRNA is regulated by the transcription factor Nrf2 and was low in pristane- vs. MO- treated mice. Autophagy, which has been found to regulate phagocytosis by modulating Nrf2-mediated Marco expression, was increased in pristane-treated mice.

Conclusion:

Pristane may cause lupus by inducing a phagocytosis defect. The mechanism appears to involve modulation of phagocytosis due to increased autophagy, resulting in decreased activation of Nrf2, decreased scavenger receptor expression, and impaired clearance of dead cells.

Disclosure: S. Han, None; **H. Zuang**, None; **R. Khaybullin**, None; **S. Shumyak**, None; **A. Afaneh**, None; **X. Qi**, None; **L. yang**, None; **W. H. Reeves**, None.

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Abstract Number: 3215

Bim Suppresses the Development of SLE By Limiting Macrophage Inflammatory Responses

Fu-Nien Tsai[1] and Harris R. Perlman[2], [1]Medicine, Rhuematology, Northwestern University, Chicago, IL, [2]Feinberg School of Medicine, Northwestern University, Chicago, IL

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Background/Purpose: The Bcl-2 family guards the mitochondrial apoptotic pathway. Among numerous Bcl-2 antagonists, only the loss of Bim in mice leads to the development of SLE-like disease, suggesting Bim's unique state that exerts dominance in several pathways that are vital for the development of SLE. We have shown that reduction of Bim alters macrophage function thereby preventing the break in tolerance. We hypothesize that Bim limits inflammatory responses in macrophages and therefore prevents SLE-like disease development independent of its role in apoptosis.

Methods: We generated mice lacking Bim specifically in myeloid cells ($Cre^{LysM}Bim^{fl/fl}$) and assessed mice at 8 months of age for characterization of SLE-like disease. Macrophage turnover/proliferation and activation were examined *in vivo* using flow cytometric analyses and luminex based assays.

Results: $Cre^{LysM}Bim^{fl/fl}$ mice displayed splenomegaly, lymphadenopathy, hypergammaglobulinemia, IC deposition in the kidney, proteinuria, GN, and early mortality as compared to $Bim^{fl/fl}$ and mice lacking Bim in either lymphocyte compartments. Bim functions independently of its role in apoptosis in macrophages and monocytes, because we did not detect any differences in the rate of EdU incorporation in tissue-resident macrophages and monocyte-derived populations from $Bim^{fl/fl}$ and $Cre^{LysM}Bim^{fl/fl}$ mice. $Cre^{LysM}Bim^{fl/fl}$ splenic macrophages also displayed an enhanced activated phenotype that may not be due to an endogenous TLR that requires MyD88, as loss of MyD88 in $Cre^{LysM}Bim^{fl/fl}$ mice did not reverse disease phenotype. Mixed bone marrow chimera mice showed reduced disease activities, indicating that macrophages from the wild type mice are sufficient to suppress autoimmunity caused by loss of Bim in macrophages. Loss of Bim in macrophages is sufficient to induce SLE-like disease, as adoptively transferring wild type lymphocytes to $Cre^{LysM}Bim^{fl/fl}Rag^{-/-}$ mice increased glomeruli size and leukocyte infiltrates in the kidneys compared to $Rag^{-/-}$ mice receiving wild type lymphocytes. The BH3 domain and JNK phosphorylation site of Bim, which are essential for apoptotic functions, are necessary for the disease development, because replacing BH3 domain or mutating the phosphorylation sites resulted in the development of SLE-like disease. Lastly, kidney macrophages can be accurately identified by multi-parameter flow cytometry, which increased in number in $Cre^{LysM}Bim^{fl/fl}$ mice. Gene expression profiling revealed that kidney macrophages from $Cre^{LysM}Bim^{fl/fl}$ exhibited M2 phenotype that is associated with collagen deposition and fibrosis in the kidney.

Conclusion: The expression of Bim in macrophages is sufficient to inhibit SLE-like pathogenesis. These data suggest that Bim acts as a molecular rheostat controlling macrophage functions through its BH3 domain and JNK phosphorylation site, which is independent of its role in apoptosis. Bim mediates macrophage inflammatory responses not only in secondary lymphoid organs (spleen), but also in end-organs (kidney). These studies are crucial for understanding the development SLE, and for translational studies leading to the development of new targets for SLE.

Disclosure: F. N. Tsai, None; **H. R. Perlman**, None.

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Abstract Number: 3216

T Cell Restricted Deletion of Serine/Arginine-Rich Splicing Factor 1 (SRSF1) in Mice

Causes Immune Cell Dysfunction and Contributes to Lupus-like Nephritis

Vaishali R. Moulton[1], Michael W. Mosho[2], Hao Li[2], Andrew R. Gillooly[2] and George C. Tsokos[3], [1]Medicine/Rheumatology, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, [2]Medicine/ Rheumatology, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, [3]Division of Rheumatology, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA
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Background/Purpose: T cells from patients with systemic lupus erythematosus (SLE) express reduced amounts of the critical CD3 zeta signaling chain, and are poor producers of the vital cytokine interleukin (IL)-2. Using a discovery approach (mass spectrometry analysis of proteins "pulled-down" by a CD3 zeta mRNA-defined oligonucleotide), we identified the splicing regulator serine arginine-rich splicing factor 1 (SRSF1). We showed that SRSF1 promotes generation of a full-length CD3 zeta transcript over a short spliced unstable isoform to promote normal expression of CD3 zeta chain in human T cells. Recently we showed that overexpression of SRSF1 into SLE T cells rescues IL-2 production. SRSF1 expression levels are decreased in SLE T cells, more so in patients with worse disease. Although these findings suggest that SRSF1 deficiency is important in the expression of SLE T cell dysfunction, it remains unknown whether SRSF1 contributes to immune-mediated disease. To this end, we generated mice with a T cell-restricted deletion of SRSF1 to evaluate the mechanistic role of SRSF1 in T cell dysfunction and the development of immune-mediated disease *in vivo*.

Methods: We used the Cre-lox recombination strategy to cross *Srsf1* "floxed" B6/129 mice with *Lck.Cre* (distal promoter) transgenic mice to delete SRSF1 specifically in mature T cells and generate the T cell Srsf1 conditional knockout (*Srsf1*-cko) mice. Mice were euthanized at 10-16 weeks of age, or aged to >1 year. Central (thymus) and peripheral (spleen, lymph nodes) lymphoid organs were analyzed for immune cell phenotype and function by flow cytometry, enzyme-linked immunosorbent assay (ELISA) and intracellular staining. Serum and urine were collected at monthly intervals to assess autoantibody levels and proteinuria respectively. Lymphoid tissues from aged mice were analyzed for immune cell phenotype and function by flow cytometry. Non-lymphoid (lung, liver, kidney) tissues were fixed, sectioned and stained with hematoxylin and eosin to evaluate histopathology.

Results: The *Srsf1*-cko mice exhibit T cell lymphopenia, with a striking reduction in the CD8 compartment. The CD4 T cells exhibit increased proportions of activated (CD69hi) cells, and produce increased amounts of IFN-γ and IL-17 upon *ex vivo* stimulation. The *Srsf1*-cko mice develop increased levels of anti nuclear autoantibodies (ANA), and exhibit increased proteinuria compared to control mice. Tissue histopathology displays glomerular capillary hyperplasia, glomerular hyperproliferation and interstitial infiltration of mononuclear cells in the kidneys. These results indicate that lack of SRSF1 leads to a reduction of CD8 T cells, aberrantly increased inflammatory cytokine production, autoantibody development and renal pathology.

Conclusion: Our results reveal that the splicing factor SRSF1 is a novel regulator of T cell homeostasis and function, and its deficiency leads to autoimmunity and kidney damage. Therefore, deficiency of SRSF1 may represent a molecular defect that contributes to the pathogenesis of systemic autoimmune disease.

Disclosure: V. R. Moulton, None; **M. W. Mosho**, None; **H. Li**, None; **A. R. Gillooly**, None; **G. C. Tsokos**, None.

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Abstract Number: 3217

Macrophage Depletion Using a Specific CSF-1R Kinase Inhibitor Ameliorates Kidney and Skin Disease in a Mouse Model of Systemic Lupus Erythematosus

Jessica Doerner[1], Samantha Chalmers[2] and **Chaim Putterman**[3], [1]Albert Einstein College of Medicine, Bronx, NY, [2]Microbiology and Immunology, Albert Einstein College of Medicine, Bronx, NY, [3]The Division of Rheumatology, Albert Einstein College of Medicine, Bronx, NY
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Background/Purpose: Kidney and skin involvement are common in systemic lupus erythematosus (SLE). Nephritis is seen in up to 60% of patients, and contributes significantly to morbidity and mortality. Approximately 80% of patients manifest some form of cutaneous lupus erythematosus (CLE), and there is a strong correlation between rash and ultraviolet light-B (UVB) exposure. Macrophages contribute to the pathogenesis of nephritis and are correlated with poor outcomes. Furthermore, following UVB exposure, macrophages are increased in the skin where they contribute to keratinocyte apoptosis.

Methods: To evaluate the role of macrophages in the pathogenesis of kidney and skin disease in murine SLE, we depleted macrophages using GW2580, a kinase inhibitor specific for colony stimulating-factor 1 receptor (CSF-1R). CSF-1R is found almost exclusively on macrophages and is important for their survival, recruitment, and activation. Lupus-prone female MRL/lpr mice (10 weeks of age) were treated with GW2580 (n=9) (or control, n=10) for 6 weeks via oral gavage. We tracked the development of kidney disease by measuring proteinuria, and assessed kidney function at 17 weeks of age by measuring serum BUN levels. In a separate cohort, female MRL/lpr mice (10 weeks of age) were exposed to two doses of UVB irradiation (50 mJ/cm^{2}each), 24 hours apart, following 2 weeks of GW2580 or control treatment (GW2580, n=5; PBS, n=6). Histology was blindly scored to assess skin damage.

Results: Macrophage depletion in MRL/lpr mice ameliorated kidney disease. Proteinuria in GW2580-treated mice was significantly lower, at multiple time points, than that seen in PBS-treated mice (13 weeks, GW2580=18±9.6 mg/dl, PBS=82±22 mg/dl, p-value=0.02; 15 weeks, GW2580=40±11.1 mg/dl, PBS=168±39.3 mg/dl, p-value=0.006). Macrophage depletion treatment also led to improved kidney function, with lower BUN levels in GW2580 as compared to control-treated mice at 17 weeks of age (GW2580=90±4.5 mg/dl, PBS=110±6.6 mg/dl, p-value=0.02). Anti-double stranded DNA antibody levels did not differ between the two groups of mice. Following macrophage depletion and subsequent UVB irradiation, MRL/lpr mice treated with GW2580 developed less severe skin lesions than those treated with PBS (mean skin scores: GW2580=2.3±0.12, PBS=4.6±0.2, p-value=0.0001). Classic characteristics of lupus-associated cutaneous disease such as hyperkeratosis and acanthosis were less prevalent in GW-treated mice.

Conclusion: Our studies support a role for macrophages in the pathogenesis of both kidney and skin disease in SLE. As current therapies are largely immunosuppressive and non-specific, these cells may represent a promising therapeutic target for LN and CLE treatment.

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Abstract Number: 3218

A Randomized, Double-Blind, Placebo-Controlled, 52-Week Study of the Efficacy and Safety of Belimumab Administered Subcutaneously Plus Standard Care to Patients with Systemic Lupus Erythematosus (SLE)

William Stohl[1], Andreas Schwarting[2], Masato Okada[3], Morton Scheinberg[4], Andrea Doria[5], Anne Hammer[6], Christi Kleoudis[7], Damon Bass[8], James Groark[9], Norma Lynn Fox[10], David Roth[11] and David Gordon[11], [1]Division of Rheumatology, University of Southern California Keck School of Medicine, Los Angeles, CA, [2]ACURA Kliniken, Bad Kreuznach, Germany, [3]Immuno-Rheumatology Center, St. Luke's International Hospital, Tokyo, Japan, [4]Rheumatology Hospital Abreu Sodre Pesquisa Clínica, São Paulo, Brazil, [5]Division of Rheumatology, University of Padova, Padova, Italy, [6]GlaxoSmithKline, Research Triangle Park, NC, [7]Parexel, Durham, NC, [8]Immuno-Inflammation, GlaxoSmithKline, King of Prussia, PA, [9]GlaxoSmithKline, Philadelphia, NC, [10]GlaxoSmithKline, Washington, MD, [11]GlaxoSmithKline, Philadelphia, PA
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Background/Purpose: To assess the efficacy and safety of belimumab (BEL) administered subcutaneously plus standard SLE care (SoC) in patients with active SLE.

Methods:

BLISS-SC (BEL112341; NCT01484496) is a randomized, double-blind, placebo-controlled trial.

Patients with SLE with SELENA-SLEDAI (SS) score ≥8, receiving stable SLE therapy for ≥30 days were randomized (2:1) to receive weekly BEL 200 mg or placebo (PBO), administered subcutaneously (using a prefilled syringe), plus SoC. The primary endpoint was SLE Responder Index 4 (SRI4; ≥4 point reduction in SS, increase of <0.3 in Physician's Global Assessment and no new BILAG A organ domain score or 2 new BILAG B organ domain scores, all compared with baseline) response rate at week 52. Secondary endpoints included time to severe flare and reduction in corticosteroid dose. Safety was assessed using adverse events (AEs).

Results:

839 adults enrolled; 3 patients were randomized but did not receive study drug and were removed from the intent-to-treat population. Baseline disease characteristics were similar between groups: mean (standard deviation [SD]) age was PBO 39.6 (12.61), BEL 38.1 (12.10) years; median (range) SLE disease duration was PBO 4.6 (0–38), BEL 4.3 (0–35) years; mean (SD) SS was PBO 10.3 (3.0), BEL 10.5 (3.2). SRI4 response at week 52 was: PBO 48.7% vs BEL 61.4%, odds ratio 1.65, p=0.0009 (95% CI 1.23, 2.22), with each individual component achieving statistical significance (all p≤0.0247). SRI4 response was significantly greater with BEL compared with PBO as early as week 16 and was sustained for 52 weeks. SRI5 response was significantly greater with BEL compared with PBO from week 12 and SRI6, 7 and 8 responses were significantly greater from week 8; all were sustained for 52 weeks (p≤0.0002, week 52). The BEL group was 50% less likely to experience a severe flare (hazard ratio = 0.50, p=0.0003) relative to the PBO group; time to severe flare for subjects experiencing a flare was PBO 116.5 vs BEL 170.0 days. More BEL patients were able to reduce steroid dose by ≥25% to ≤7.5 mg/day during weeks 40–52, but this did not achieve statistical significance: PBO 11.9% vs BEL 18.2%, odds ratio 1.65, p=0.0732 (95% CI 0.95, 2.84). Treatment compliance with the subcutaneous injections according to patient diaries was ≥96% in both groups.

Overall study withdrawals (PBO 23.6%, BEL 16.7%) included: AEs PBO 8.9%, BEL 7.2%; subject request PBO 5.4%, BEL 2.2%; lack of efficacy PBO 3.6%, 2.7% BEL. Serious AEs (PBO 15.7%, BEL 10.8%) included: infections/infestations PBO 5.4%, BEL 4.1%; renal/urinary PBO 2.5%, BEL 1.4%; nervous system PBO 2.1%, BEL 1.4%. The incidence of depression/suicide/self-injury was PBO 3.6%, BEL 3.1%. Five deaths occurred: PBO 0.7% (one each of hematologic and vascular), BEL 0.5% (three infections).

Conclusion:

BEL 200 mg administered weekly via subcutaneous injection plus SoC significantly improved SRI response and decreased time to severe flare compared with PBO plus SoC, and safety with BEL plus SoC was similar to that with PBO plus SoC.

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Abstract Number: 3219

Efficacy and Safety of 4 Weeks Administration of Arsenic Trioxide in Moderate Active Systemic Lupus Erythematosus. a Phase I/II Proof-of-Concept Sequential Dose Escalation Multicenter Study

Mohamed Hamidou[1], Benjamin Gaborit[2], Eric Hachulla[3], Zahir Amoura[4], Mikael Ebbo[5], Emmanuel Chatelus[6], Jean Sibilia[7], Jean-Francois Viallard[8,9], Julie Graveleau[1], Melanie Saint Jean[10], Sandrine Gardes[11], Yohann Foucher[11], Christelle Volteau[12], Joel Poupon[13], Antoine Neel[14] and François Rieger[15], [1]Internal Medicine Department, Nantes University Hospital, Nantes, France, [2]Internal Medicine, Department of Internal Medicine, Nantes University Hospital, Nantes, France, [3]Department of Internal Medicine, University Lille Nord-de-France, Lille, France, [4]Internal Medecine - Centre de Référence National pour les Lupus et et le Syndrome des Antiphospholipides, Pitié-Salpêtrière hospital, Paris, France, [5]Internal Medicine, Aix-Marseille Université, AP-HM, Marseille, France, [6]Department of Rheumatology, Strasbourg University Hospital, Strasbourg, France, [7]Department of Rheumatology, Strasbourg University Hospital, Strasbourg, France, [8]Internal Medecine, Haut Lévèque Hospital, Bordeaux, France, [9]Hôpital Haut-Lévêque, Bordeaux, CHU Bordeaux, France, [10]Department of Dermatology, Nantes University Hospital, Nantes, France, [11]Nantes Universitary Hospital, Nantes, France, [12]Clinical Research Department, Nantes University Hospital, Nantes, France, [13]Paris University, Paris, France, [14]Department of Internal Medicine, Nantes University Hospital, Nantes, France, [15]MEDSENIC, Hôpital Cochin, Paris Descartes University, Paris, France

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Background/Purpose: Arsenic Trioxide (ATO) is approved for the treatment of acute promyelocytic leukemia, increasing oxidative stress with selective apoptosis of leukemia cells. In *MLR/lpr* model of SLE, ATO demonstrated a dramatic improvement. Given the promising results of experimental models, we conducted this study in patients with SLE

Methods: The primary objective of this phase I/IIa proof-of-concept study was to evaluate the safety and tolerability of IV ATO in patients with SLE. Efficacy and pharmacokinetics were also evaluated. Patients with mild-to-moderate SLE, defining as SELENA-SLEDAI score of ≥ 4 at baseline and corticosteroid dosage > 10 mg/day with active disease despite standard-of-care treatment, including hydroxychloroquine (HCQ) were enrolled. Concomitant therapy with methotrexate (MTX), mycophenolate (MMF), and azathioprine (AZA) were allowed at constant doses during the study. Patients with severe active renal or CNS disease were excluded. Patients received 10 IV infusions of ATO from day1 to day 4 than at day 8, 11, 14, 17, 21 and 25, with escalading dose from 0.10 mg/kg to 0.20 mg/kg, and follow-up for 20 weeks. The primary outcome measure was safety assessment with recording of adverse events (AEs) according to NCI Common Terminology Criteria for Adverse Events. Major secondary endpoint included disease activity measures, assessed by SLE Responder Index (SLEDAI, Physician's Global Assessment (PGA) and BILAG : combination of SLEDAI response ≥ 4 points, no BILAG A or 2 x B flares and no PGA score worsening, corticosteroid sparing.

Results: 11 patients (all on HCQ) are included to date in this ongoing study, and were evaluated for safety and toxicity. Five among 11 received MTX, 1 AZA, 1 thalidomide and 2 MMF. Dose of ATO was 0.10mg/kg/day in 4 patients, 0.15mg/kg/day in 4 and 0.2 mg/kg/day in 3. Two severe AEs occurred in 2 patients (0.15 and 0.2 mg/kg, receiving also MMF) with transient (<5 days) asymptomatic grade 3 neutropenia (at day 15). ATO was discontinued in these patients without MMF interruption. Mean SLEDAI at baseline was 8 and decreased to 4 at Month 2 and 3 at Month 4, with steroid sparing (Figures). Six patients among 8 had SRI response, generally without improvement of anti-dsDNA antibodies and C3/C4.

Conclusion: In this proof-of-concept phase 1/IIa study, 4 weeks IV ATO treatment with 20 weeks follow-up, demonstrated an acceptable safety and tolerability profile (except in patients treated by MMF) with a clinical efficacy, supporting further evaluation in larger clinical trials.

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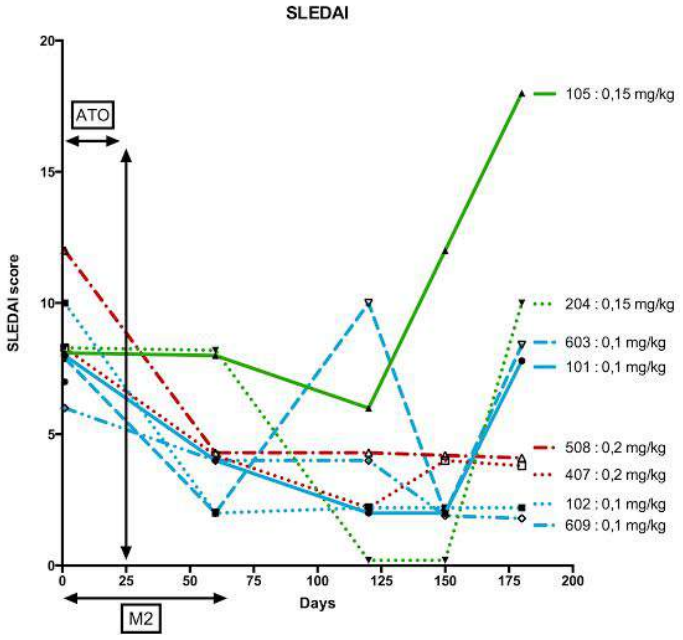

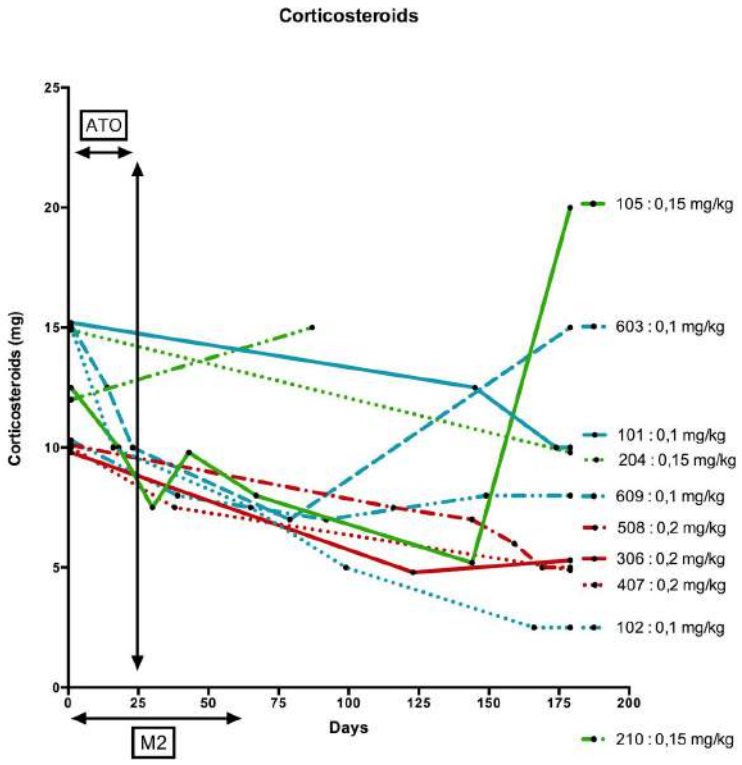

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Abstract Number: 3220

Anifrolumab Differentially Suppresses Peripheral Biomarkers of Systemic Lupus Erythematosus Compared with Placebo in a Phase IIb Trial

Xiang Guo[1], L Wang[2], G Illei[3], P Brohawn[1], Brandon Higgs[1] and **Wendy White**[1], [1]Translational Sciences, MedImmune, LLC, Gaithersburg, MD, [2]MedImmune, Gaithersburg, MD, [3]Clinical Development, MedImmune, LLC, Gaithersburg, MD

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SESSION INFORMATION

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Session Title: Systemic Lupus Erythematosus - Clinical Aspects and Treatment VI: Novel Therapies

Session Type: ACR Concurrent Abstract Session

Session Time: 4:30PM-6:00PM

Background/Purpose: Anifrolumab is a fully human IgG_1 κ monoclonal antibody directed against subunit 1 of the type I interferon receptor (IFNAR1). A Phase IIb randomized, double-blinded, placebo-controlled, multicenter clinical trial of adult patients with systemic lupus erythematosus (SLE) has been conducted for anifrolumab. Our project aimed to provide an initial assessment of downstream effects of anifrolumab on serum protein markers and pathophysiologic pathways in SLE patients.

Methods: A total of 305 patients with moderate to severe SLE were randomized in a 1:1:1 ratio to receive a fixed intravenous dosage of placebo or anifrolumab (300 or 1000 mg) in addition to standard of care every 28 days for 1 year. Type I IFN status was assessed by a 4-gene type I IFN signature. Sera were procured at baseline, Day 85, and 169 days post-administrations of placebo, 300- or 1000-mg anifrolumab. Samples were tested for 138 selected proteins using a multiplex luminex immunoassay. Protein concentrations in different patient groups were compared using Student's *t*-test with multiple testing adjustments.

Results: Serum proteomics results were obtained for 304 SLE patients at baseline: 229 had an elevated type I IFN gene signature (IFN-high) and 75 did not (IFN-low). Forty-five proteins were significantly greater in sera of IFN-high vs. IFN-low patients ($p<0.05$), of which 27 are type I

and/or II IFN-inducible. Effects of anifrolumab on serum protein concentrations were assessed by paired comparison between patient-matched pre- and post-treatment sera concentrations, as well as comparisons between anifrolumab and placebo. Anifrolumab administration was associated with significant suppression of 15 serum proteins at Days 85 and/or 169 compared with placebo ($p<0.05$), of which 10 are type I and/or II IFN-inducible. Fourteen of these proteins had greater serum concentrations in IFN-high vs. IFN-low patients at baseline. Of these 15 proteins, CCL2, CCL8, and CCL19 are involved in the recruitment of T cells, monocytes, dendritic cells, and other immune cells to inflammation sites. CXCL10 and CXCL11 are ligands of CXCR3 that recruit activated CD4+ and CD8+ T cells, while CXCL13 is a chemoattractant for B cells. IL-18 is a Th1 cytokine and CD163 is a marker for monocyte/macrophage activation. Anifrolumab-driven suppression of these proteins indicates reduction in T-cell, B-cell, and monocyte activation and movement, compared with placebo. Further, decreased concentration of FCN3, an initiator of the lectin pathway of complement, indicates inhibition of complement system activation by anifrolumab.

Conclusion: This preliminary data set indicates that anifrolumab elicits a potent effect on multiple serum biomarkers in SLE compared with placebo. Suppression of both immune cell dysregulation and complement system may be key contributors to the mechanism of action of anifrolumab in SLE.

Disclosure: X. Guo, AstraZeneca, 1,MedImmune, 3; **L. Wang**, AstraZeneca, 1,MedImmune, 3; **G. Illei**, AstraZeneca, 1,MedImmune, 3; **P. Brohawn**, AstraZeneca, 1; **B. Higgs**, AstraZeneca, 1,MedImmune, 3; **W. White**, AstraZeneca, 1,MedImmune, 3.

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Abstract Number: 3221

Safety and Efficiency of Low-Dose Interleukin-2 Treatment in Systemic Lupus Erythematosus

Jing He[1], Xia Zhang[2], Yunbo Wei[3], Xiaolin Sun[4], Jianping Guo[5], Yuebo JIn[6], Rulin Jia[6], Lei Zhu[6], Zhaohua Hou[7], Yaping Chen[8], Yuan An[6], Yuan Jia[6], Xu Liu[6], Limin Ren[6], Ru Li[6], HUA YE[9], Shi Chen[6], Xuewu Zhang[10], Yin Su[11], Eric Morand[12], Yu Di[13] and Zhanguo Li[6], [1]Peking Univerisity People's Hospital, Beijing, China, [2]Department of Rheumatology & immunology, Peking University People's Hospital, Beijing, China, [3]Immunology for Environment and Health, Shandong Analysis and Test Center, Shandong Academy of Science, Shandong, China, [4]People's hospital,Peking University, Beijing, China, [5]Department of Rheumatology and Immunology, Peking University People's Hospital, Beijing, China, [6]Peking University People's Hospital, Beijing, China, [7]Shandong Analysis and Test Center, Beijing, China, [8]Monash University, Clayton, Austria, [9]No.11 XIZHIMENG SOUTH STREET,, Peking University People's Hospital, Beijing, China, [10]Rheumatology, Peking University People's Hospital, Beijing, China, [11]Department of Rheumatology and Immunology,Clinical Immunology Center, Peking University People's Hospital, Beijing, China, [12]Medicine, Monash University, Clayton, Australia, [13]Molecular Immunomodulation Laboratory, Monash University, Clayton, Austria

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Session Time: 4:30PM-6:00PM

Background/Purpose:

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease with multi-system involvement, associated with an imbalance between effector and regulatory CD4+ T cells. The development and activation of these T cell subsetsis critically regulated by interleukin-2 (IL-2) which is impaired in SLE patients. Using animal models and human samples, we characterised precursor Tfh cells in blood with a $CXCR5^{+}CCR7^{low}PD1^{high}$ phenotype. The increase of the early memory Tfh cells in blood represents the active Tfh cell differentiation and correlates with the disease activities of systemic lupus erythematosus (SLE). We hypothesized that low-doseIL-2 treatment of SLE would result in selective expansion of regulatory CD4+ T (Treg) cells, while suppressing follicular helper T (Tfh) cells and IL-17-producing helper T (Th17) cells. Our study was to assess the safety and efficacy of low-dose IL-2 therapy in active SLE.

Methods:

Forty patients with active SLE were recruited to a prospective open label study; 38 patients completed three cycles of 1 million IU recombinant human IL-2 (rhIL-2), administered subcutaneously every other day for 2 weeks, followed by a 2-week break. Both clinical and immunological responses were assessed. The primary end points were the SLE Responder Index (SRI) and safety at week 12. Secondary end points were the effects of the therapy on Treg, Tfh and Th17 cells.

Results:

An SRI response was seen in 34/38 patients (89.5%) at week 12. Disease activity measured using the Safety of Estrogens in Lupus Erythematosus National Assessment version of the SLE Disease Activity Index (SELENA-SLEDAI) improved significantly, from a median (range) of 11 (8 - 23) to 4 (0 – 12) ($p<0.001$). At week 12, resolution of clinical activity present at baseline was observed in multiple domains, including rash (20/24 patients), alopecia (13/14), arthritis (10/11), fever (3/3), leukopenia (18/19) and thrombocytopenia (4/4).No severe adverse events were observed. Significant reductions of anti-dsDNAtitres ($p<0.001$) and proteinuria ($p=0.005$), and increased levels of C3 ($p<0.001$) and C4 ($p<0.001$), were observed at week 12. Immunological analysis revealed that low-dose rhIL-2 administration was associated with selective expansion of Treg cells ($p<0.001$) and conversely with reductions of Tfh andTh17cells ($p=<0.001$), but had not effect on Th1 and Th2 cells.

Conclusion:

Low-dose IL-2 was efficient and well tolerated in active SLE. The improvements in disease activity were associated with selective modulation of $CD4^+$ T cell subsets.

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Abstract Number: 3222

Repeated Administration of Dapirolizumab Pegol (DZP) Appears Safe and Well Tolerated in Patients with Systemic Lupus Erythematosus (SLE) and Is Accompanied By an Improvement in Disease Activity: Results from a Phase 1 Study

Chris Chamberlain[1], Murray Urowitz[2,3], Julie Soranson[1], Mark Watling[1], Peter Colman[1], Olivier Harari[1], Thomas Dorner[4] and Falk Hiepe[4], [1]UCB Pharma, Slough, United Kingdom, [2]University of Toronto, Toronto, ON, Canada, [3]Rheumatology, U of Toronto, Toronto Western Hospital, Toronto, ON, Canada, [4]Charité – Universitätsmedizin, Berlin, Germany

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Session Time: 4:30PM-6:00PM

Background/Purpose:

CD40 ligand (CD40L) regulates interactions between T cells, B cells, and antigen presenting cells. Considerable evidence suggests CD40L blockade might provide an effective treatment for systemic autoimmune disorders.

In previous studies, some evidence of efficacy was seen using monoclonal antibodies (hu5c8) to CD40L; however, the program was halted due to thromboembolic events, possibly mediated by Fc interaction with platelet Fc gamma RIIA receptor. DZP (formerly CDP7657) is a PEGylated anti-CD40L Fab' fragment with no Fc.

Methods:

This 32-week randomized, double-blind, multicenter study (NCT01764594) evaluated the efficacy of repeat IV administration of DZP in patients with SLE with a SELENA SLEDAI score ≥4. Patients were documented as positive for anti-dsDNA antibodies or antinuclear antibodies and, if taking immunomodulatory therapies, were on a stable dose throughout the study. Patients with active severe glomerulonephritis or renal flare in the last 6 months, or history of thromboembolism within a year were excluded from the study.

After screening (up to 4 weeks), patients (n=24) were randomized 2:1 to DZP (loading dose 30 mg/kg then 5 doses of 15 mg/kg every 2 weeks) or placebo (PBO), stratified by presence or absence of antiphospholipid antibodies. Patients were subsequently followed for 18 weeks.

The primary objective was to evaluate DZP safety and tolerability; disease activity measures were exploratory variables. Two composite measurements for SLE disease activity: BILAG-based Composite Lupus Assessment (BICLA) and Systemic Lupus Responder Index (SRI-4) were analyzed separately. These responses were determined on a subset of patients with ≥1 BILAG A or B (BICLA) or SLEDAI ≥6 (SRI-4) at baseline.

Results:

DZP and PBO groups had similar demography and SLE disease status at baseline.

Variable	Statistics	PBO N=8	DZP N=16	Total N=24
Gender (female, male)	n (%)	8 (100), 0 (0)	13 (81), 3 (19)	21 (87.5), 3 (13.5)
Age (years)	Mean (SD)	40.55 (15.19)	42.41 (9.5)	41.79 (11.4)
BMI (kg/m^2)	Mean (SD)	25.67 (5.08)	24.07 (6.06)	24.61 (5.69)
Duration of disease (years)	Median (Min, Max)	7.08 (1.0, 31.6)	8.88 (0.6, 24.7)	8.30 (0.6, 31.6)
SELENA SLEDAI total score	Median (Min, Max)	8.0 (4, 14)	9.0 (2, 14)	8.0 (2, 14)
Physician's Global Assessment of Disease	Median (Min, Max)	31.0 (0, 68)	28.5 (0, 67)	29.0 (0, 68)
BILAG total score	Median (Min, Max)	10.0 (2, 21)	13.0 (2, 21)	12.0 (2, 21)
At least 1 BILAG Grade A or B at baseline	n (%)	7 (87.5)	14 (87.5)	21 (87.5)

There were no serious treatment emergent adverse events (TEAEs) and no deaths occurred. There were no thromboembolic events and no laboratory findings suggestive of such. Nasopharyngitis was the most common TEAE, reported for 6 patients in the DZP group and none in the PBO group. The majority of TEAEs observed were mild or moderate in intensity, transient, and resolved without intervention. There was 1 withdrawal due to a TEAE of infection in the DZP group.

Preliminary evidence of clinical activity was seen in the DZP group.

		Week 12		Week 28	
		Treatment group			
		PBO	DZP	PBO	DZP
BICLA	N	7	11	6	10
	Responders, n (%)	1 (14.3)	5 (45.5)	1 (16.7)	3 (30.0)
	Non-responders, n (%)	6 (85.7)	6 (54.5)	5 (83.3)	7 (70.0)
SRI-4	N	7	12	6	11
	Responders, n (%)	1 (14.3)	5 (41.7)	1 (16.7)	4 (36.4)
	Non-responders, n (%)	6 (85.7)	7 (58.3)	5 (83.3)	7 (63.6)

Conclusion:

Multiple administrations of DZP over 12 weeks in patients with mild to moderate SLE were well tolerated and the safety profile supports further development. Exploratory analyses show greater improvement in clinical measures of disease activity in the DZP group vs PBO.

Disclosure: C. Chamberlain, UCB Pharma, 3; **M. Urowitz**, member of the DZP Data and Safety Monitoring Committee, 6,The Systemic Lupus International Collaborating Clinics has received research funds from UCB (epratuzumab), 2; **J. Soranson**, UCB Pharma, 3; **M. Watling**, UCB Pharma, 3; **P. Colman**, UCB Pharma, 3; **O. Harari**, UCB Pharma, 3; **T. Dorner**, Deutsche Forschungsgemeinschaft, Johnson & Johnson, Sanofi, and UCB, 2,Eli Lilly, Roche/Chugai, Sanofi, and UCB, 5,Eli Lilly, Pfizer, Roche, and UCB, 8; **F. Hiepe**, Deutsche Forschungsgemeinschaft and IMI (PRECISESADS), 2,Eli Lilly, Sanofi, and UCB, 5,GSK and Pfizer, 8.

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Abstract Number: 3223

Anifrolumab, an Anti-Interferon Alpha Receptor Monoclonal Antibody, in Moderate to Severe Systemic Lupus Erythematosus (SLE)

Richard Furie[1], JT Merrill[2], VP Werth[3,4], M Khamashta[5], K Kalunian[6], P Brohawn[7], G Illei[7], J Drappa[7], L Wang[7] and S Yoo[8], [1]North Shore-LIJ Health System, New York, NY, [2]Oklahoma Medical Research Foundation, Oklahoma City, OK, [3]Philadelphia V.A. Medical Center, Philidelphia, PA, [4]University of Pennsylvania, Philadelphia, PA, [5]Graham Hughes Lupus Research Laboratory, The Rayne Institute, St Thomas' Hospital, London, United Kingdom, [6]UCSD School of Medicine, La Jolla, CA, [7]MedImmune, Gaithersburg, MD, [8]Regenx Bio, Rockville, MD
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Background/Purpose: The efficacy and safety of anifrolumab (ANIFR), a type I IFN receptor antagonist, were assessed in a Phase II, randomized, double-blind, placebo-controlled study in SLE (NCT01438489).

Methods: Three hundred and five adults with seropositive moderate to severe SLE despite standard of care medication were randomized and received intravenous (iv) ANIFR (300 mg, 1000 mg) or placebo (PBO) every 4 weeks for 48 weeks. Patients were stratified by SLEDAI score, oral corticosteroid (OCS) dose, and IFN gene signature (IFN high vs. IFN low) based on a 4-gene expression assay. Disease activity was assessed by SLEDAI-2K, BILAG 2004, Physician's Global Assessment, CLASI, BICLA, and 28-joint count. The primary endpoint was a composite of SRI(4) response at Day 169 with sustained reduction of OCS (<10 mg/day and ≤Day 1 dose maintained between Days 85 and 169). Two secondary efficacy endpoints were assessed at Day 365: A) Composite of SRI(4) response at Day 365 with sustained reduction of OCS maintained between Days 281 and 365; B) Reduction of OCS to ≤7.5 mg/day by Day 365 in those taking ≥10 mg/day at baseline. Other efficacy measures of systemic and organ-specific disease activity and safety were also assessed at Day 365.

Results: The primary endpoint at Day 169 was met by a greater proportion of ANIFR-treated patients vs. PBO (PBO: 17.6%; 300 mg: 34.3%, p=0.014; 1000 mg: 28.8%, p=0.063). At Day 365, the secondary SRI endpoint was met by 25.5% of PBO, 51.5% of 300 mg (p<0.001) and 38.5% of 1000 mg (p=0.048) patients. OCS reduction to ≤7.5 mg/day at Day 365 was achieved by 26.6% of PBO, 56.4% of 300 mg (p=0.001) and 31.7% of 1000 mg (p=0.595) patients. ANIFR demonstrated consistent benefit across multiple global and organ-specific measures at Day 365 (Table), as well as lower rates of BILAG moderate/severe flares/patient-year (PBO: 0.611; 300 mg: 0.266; 1000 mg: 0.391). 75% of patients were IFN high at baseline. The ANIFR efficacy observed in the entire cohort was similar or more pronounced in IFN high patients. Median suppression of 21 IFN-regulated genes was ~90% for both doses of ANIFR. Serious adverse events were reported in 18.8% of patients on PBO and 16.7% of patients in the pooled ANIFR groups. A higher frequency of influenza (most unconfirmed) (PBO: 1.0%; 300 mg: 6.1%; 1000 mg: 7.6%) and a dosage-dependent increase in *Herpes zoster* (PBO: 2.0%; 300 mg: 5.1%; 1000 mg: 9.5%) occurred in the ANIFR arms.

Conclusion: Anifrolumab significantly reduced disease activity compared with PBO across multiple clinical endpoints. Enhanced effects in IFN high patients support the pathobiology of this treatment strategy. The lack of dose response can be explained by the nearly similar degrees of IFN gene signature inhibition achieved with the two anifrolumab doses. These data strongly support further development of anifrolumab.

Efficacy Assessments								
Outcome variable	**N**	**Placebo**	**Anifrolumab 300 mg**			**Anifrolumab 1000 mg**		
		N (%)	**N (%)**	**Odds ratio (90% CI)**	***P*-value**	**N (%)**	**Odds ratio (90% CI)**	***P*-value**
Primary endpoints								
SRI(4) with OCS taper at Day 169	305	18 (17.6)	34 (34.3)	2.38 (1.33, 4.26)	0.014	30 (28.8)	1.94 (1.08, 3.49)	0.063
IFNGS high	229	10 (13.2)	27 (36.0)	3.55 (1.72, 7.32)	0·004	22 (28.2)	2.65 (1.27, 5.53)	0.029
IFNGS low	76	8 (30.8)	7 (29.2)	0.96 (0.34, 2.74)	0·946	8 (30.8)	1.04 (0.37, 2.88)	0.953
Secondary endpoints								
SRI(4) with OCS taper at Day 365	305	26 (25.5)	51 (51.5)	3.08 (1.86, 5.09)	<0.001	40 (38.5)	1.84 (1.11, 3.04)	0.048
OCS reduction at Day 365[a]	182	17 (26.6)	31 (56.4)	3.59 (1.87, 6.89)	0.001	20 (31.7)	1.23 (0.64, 2.37)	0.595
Exploratory endpoints at Day 365								
SRI(4)	305	41 (40.2)	62 (62.6)	2.66 (1.64, 4.31)	<0.001	56 (53.8)	1.78 (1.11, 2.85)	0.043
IFNGS high	229	27 (35.5)	45 (60.0)	2.98 (1.69, 5.24)	0.001	43 (55.1)	2.33 (1.34, 4.04)	0.012
SRI(5)	304	30 (29.4)	49 (49.5)	2.47 (1.51, 4.06)	0.003	48 (46.6)	2.14 (1.31, 3.49)	0.010
IFNGS high	228	20 (26.3)	38 (50.7)	3.27 (1.81, 5.90)	<0.001	38 (49.4)	2.93 (1.64, 5.24)	0.002
SRI(7)	278	16 (17.2)	33 (36.7)	2.83 (1.58, 5.07)	0.003	26 (27.4)	1.83 (1.01, 3.32)	0.094
IFNGS high	205	10 (14.7)	28 (41.8)	4.59 (2.26, 9.33)	<0.001	21 (30.0)	2.65 (1.29, 5.43)	0.026
BICLA	302	26 (25.7)	54 (54.5)	3.57 (2.15, 5.92)	<0.001	42 (41.2)	2.06 (1.25, 3.41)	0.018
IFNGS high	227	18 (23.7)	40 (53.3)	3.87 (2.14, 7.01)	<0.001	32 (42.1)	2.41 (1.34, 4.35)	0.014

CLASI, 50% reduction[b]	77	8 (30.8)	17 (63.0)	4.49 (1.67, 12.12)	0.013	14 (58.3)	2.97 (1.08, 8.19)	0.077
28-joint count, 50% reduction[c]	131	18 (48.6)	32 (69.6)	2.67 (1.23, 5.82)	0.038	31 (64.6)	1.92 (0.90, 4.09)	0.156

[a]Patients with a baseline OCS ≥10 mg/day

[b]Patients with a baseline CLASI activity score ≥10

[c]Patients with a baseline joint count of >8 swollen and >8 tender joints

BICLA, BILAG-based Composite Lupus Assessment; CI, confidence interval; CLASI, Cutaneous Lupus Erythematosus Disease Area and Severity Index; IFNGS, IFN gene signature; OCS, oral corticosteroid; SRI, SLE responder index

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Abstract Number: 3224

Salivary IL-1 Alpha and IL-1 Beta Levels Are Associated with Oral Mucosal Activity in Behcet's Disease

Nilufer Alpay Kanitez[1], Bahtiyar Toz[1], Feyza Berktas[1], Sertan Ergun[2], Meltem Koray[2], Nuray Gurel Polat[3], Burak Erer[1] and **Ahmet Gül**[1], [1]Department of Internal Medicine, Division of Rheumatology, Istanbul University, Istanbul Faculty of Medicine, Istanbul, Turkey, [2]Department of Oral Medicine, Istanbul University, Faculty of Dentistry, Istanbul, Turkey, [3]Department of Microbiology, Istanbul University, Istanbul Faculty of Medicine, Istanbul, Turkey

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SESSION INFORMATION

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Session Title: Vasculitis IV

Session Type: ACR Concurrent Abstract Session

Session Time: 4:30PM-6:00PM

Background/Purpose: Recurrent oral aphthous ulcers are the common manifestation of the Behçet's disease (BD), and they are indistinguishable from ulcers of recurrent aphthous stomatitis (RAS). There is no reliable biomarker reflecting disease activity in BD, and systemic acute phase reactants are not helpful in evaluation of active disease, especially in patients with predominantly mucocutaneous activity. We aimed to assess the potential of salivary interleukin-1 alpha and beta (IL-1α and IL-1β) concentrations as well as two S100 proteins, namely S100A12 (calprotectin) and S100A13 in comparison to their serum levels in BD, RAS, and healthy controls.

Methods: A total of 67 patients with BD, 43 patients with RAS, and 22 healthy controls with no history of aphthous ulcers or other oral mucosal disorders (NA) comprised the study group. BD patients fulfilled the ISG criteria for the diagnosis, and patients with active systemic disease were excluded. Patients with BD and RAS were classified as active and inactive according to the presence or absence of aphthous ulcers at the time of sample collection. Unstimulated saliva and serum samples were collected after overnight fasting. IL-1α, IL-1β, S100A13 and calprotectin levels were measured by ELISA, and concomitant measurements of ESR and serum CRP levels of BD patients were recorded.

Results: At the time of sample collection, 38 BD patients (18 male, mean age: 39,1±10,3) were classified as active and 29 patients (18 male, mean age: 38,9±10,5) as inactive. Similarly, 19 patients with RAS (11 male, mean age: 36,6±8,7) were active and 24 patients (7 male, mean age: 36,7±10,1) were inactive state. Mean values of salivary and serum ELISA measurements are given in Table 1. Salivary IL-1α and IL-1β, levels were higher in BD patients compared to RAS and NA even during inactive state (IL-1α $p<0.001$ for RAS and $p<0.001$ for NA, IL-1β $p<0.001$ for RAS and $p=0.003$ for NA). There was a correlation between IL-1α and IL-1β levels, but IL-1α increase was more prominent in

active BD patients. No correlation was detected between salivary IL-1α and S100A13 levels. Serum CRP and ESR were within normal range in BD patients, and they showed no correlation with salivary measurements.

	SALIVA				SERUM			
	IL-1α (pg/ml)	IL-1β (pg/ml)	S100A12 (ng/ml)	S100A13 (ng/ml)	IL-1α (pg/ml)	IL-1β (pg/ml)	S100A12 (ng/ml)	S100A13 (ng/ml)
BD active (n=38)	2147	5.1	49.1	1.8	13.9	17.8	57.7	0.6
BD inactive (n=29)	1492	4.7	48.4	1.5	12.4	18.3	67.1	0.9
RAS active (n=19)	1324	2.3	60.1	1.8	35.2	22.8	110.0	1.9
RAS inactive (n=24)	282	0.7	37.0	1.9	28.5	23.2	146.0	1.7
Healthy controls (n=22)	361	1.8	30.3	1.3	31.4	23.3	188.0	1.2

Conclusion: These results suggest a role for IL-1α and IL-1β in the development of oral aphthous ulcers. S100A13 is known to be involved in controlled secretion of IL-1α. Increased IL-1a levels without an increase in S100A13 levels may suggest that pyroptosis or other causes of cellular damage is the main source of salivary IL-1α. Further studies are necessary both to improve saliva collection and analysis methods and to search the biomarker potential of salivary IL-1α and IL-1β concentrations in the management of mucocutaneous and systemic manifestations of BD.

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Abstract Number: 3225

Whole Exome Sequencing Identifies Rare Protein-Coding Variants in Behcet's Disease

Mikhail Ognenovski[1], Paul Renauer[1], Ina Koetter[2], Joerg C. Henes[3], Bruno Casali[4], Carlo Salvarani[5], Haner Direskeneli[6], Kenneth M. Kaufman[7] and Amr H. Sawalha[1], [1]Division of Rheumatology, University of Michigan, Ann Arbor, MI, [2]Internal Medicine IV Rheumatology, Asklepios Klinik Altona, Hamburg, Germany, [3]Department of Internal Medicine II, Rheumatology Division, University Hospital Tuebingen, Tuebingen, Germany, [4]Divisione di Biologia Molecolare, Arcispedale Santa Maria Nuova, Reggio Emilia, Italy, [5]Rheumatology, Arcispedale S.Maria Nuova, Reggio Emilia, Italy, [6]Department of Rheumatology, Marmara University Faculty of Medicine, Istanbul, Turkey, [7]Center for Autoimmune Genomics and Etiology, Cincinnati Children's Hospital Medical Center, Cincinnati, OH

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Background/Purpose: Behcet's disease (BD) is a systemic inflammatory disease characterized by recurrent oral and genital ulcers, skin lesions, uveitis, and other organ complications such as vascular, central nervous system, and gastrointestinal involvement. The etiology and pathogenesis of BD are poorly understood. Despite the identification of multiple common genetic variants associated with BD, rare genetic variants have been less explored. We performed whole exome sequencing (WES) in a European-derived cohort of BD patients to investigate the role of rare protein-coding variants in this disease.

Methods: Whole exome sequencing was initially performed in 14 BD patients of European descent. Exome enrichment was performed using the TrueSeq Exome Enrichment Kit (Illumina), then paired-end 100bp reads were sequenced on an Illumina HiSeq 2000 instrument. Sequence alignment, quality assurance measures, and data analysis were performed using the DNA-Seq Analysis Package (SVS 7) implemented in Golden Helix. Sanger sequencing and Sequenom technology genotyping were performed in the original patient set and two additional independent European-derived sets for validation and replication. Protein damaging potential for non-synonymous coding variants was assessed using SIFT, Polyphen, Mutation Taser, Mutation Assessor, and FATHMM.

Results: We identified 77 protein-coding non-synonymous variants in 74 genes detected in at least 2 out of 14 re-sequenced BD patients, with a minor allele frequency (MAF)<0.01 in 6,500 control individuals included in the NHLBI Exome Sequencing Project, and predicted to have

protein damaging effect. Sanger sequencing in selected variants confirmed our exome sequencing results. Genotyping was successfully performed and passed quality control measures in 61 variants in two additional sets of 49 and 129 European-derived BD patients from Germany and Italy, respectively. Genetic analysis was performed in BD cases compared to 503 European-derived controls included in the 1000 Genomes Project. Two rare protein-coding non-synonymous genetic variants were significantly associated with BD with a Bonferroni-corrected *P* value of $<8X10^{-4}$. We detected an association with non-synonymous potentially damaging variants in *LIMK2* which is involved in actin cytoskeleton organization, and the DNA repair gene *NEIL1*.

Conclusion: We used whole exome sequencing in BD for the first time, and identified rare non-synonymous protein-coding variants associated with this disease.

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Abstract Number: 3226

Increased Serum Levels of IgG Antibodies Against to Alpha-Enolase Are Associated with Severity of Oral Ulcers in Patients with Behcet's Disease

Shin Eui Kang[1], Sang Jin Lee[2,3], Jin Kyun Park[2,4], Joo Youn Lee[2], Eun Young Lee[3], Eun Bong Lee[3] and Yeong Wook Song[3,5], [1]Department of Molecular Medicine and Biopharmaceutical Sciences, BK 21 plus Graduate School of Convergence Science and Technology, and College of Medicine or College of Parmarcy, Seoul National University, Seoul, South Korea, [2]Department of Molecular Medicine and Biopharmaceutical Sciences, BK21 plus Graduate School of Convergence Science and Technology, and College of Medicine or College of Pharmacy, Seoul National University, Seoul, South Korea, [3]Division of Rheumatology, Department of Internal Medicine, Seoul National University College of Medicine, Seoul, South Korea, [4]Department of Molecular Medicine and Biopharmaceutical Sciences Graduate School of Convergence Science and Technology, and College of Medicine or College of Pharmacy Seoul National University, Seoul, South Korea, [5]Department of Molecular Medicine and Biopharmaceutical Sciences, Graduate School of Convergence Science and Technology and College of Medicine Seoul National University, Seoul, South Korea

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Background/Purpose:

Behcet's Disease (BD) is a chronic inflammatory disease characterized by recurrent oral and genital ulcers, skin lesions, uveitis, and arthritis. Although the etiology of BD still remains to be elucidated, several autoantibodies including anti-alpha-enolase (ENO1) antibodies (AEA) have been associated with BD. AEA are directed against endothelial cells and might contribute to vasculitis leading to subsequent oral ulcer formation. This study was aimed to investigate the association between AEA and clinical manifestations of BD.

Methods:

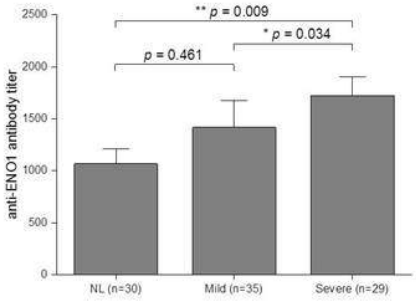
In this study 64 BD patients and 30 age/sex matched healthy controls (HCs) were enrolled. Western blot with recombinant ENO1 proteins were performed to detect the presence of AEA in serum from BD patients and HCs. Subsequently, enzyme-linked immunosorbent assay (ELISA) was performed to determine the serum levels of AEA. The association between BD manifestation and AEA levels were examined.

Results:

AEA were present in 14 (82.4%) of 17 BD patients as compared to 6 (66.7%) of 9 HCs on Western blot. Serum levels of AEA tended to be increased in BD patients compared to HCs. (Mean ± SE : 1543 ± 160 vs. 1067 ± 144, p= 0.06). Number of oral ulcers tended to correlate with serum levels of AEA (r = 0.238, p = 0.06 by Spearmann). BD patients with oral ulcers were grouped into a mild (number of oral ulcer is less than or equal to 2) and a severe (number of oral ulcer is greater than 2) disease based on the cumulative number of oral ulcers in the preceding 4 weeks prior to blood sampling. AEA levels differed between HCs, the BD patients mild and those with extensive oral ulcers (p = 0.04 Kruskal-Wallis). Patients with extensive oral ulcers exhibited significantly higher levels of AEA than those with mild oral ulcers (1722 ± 178 vs. 1416 ± 257, p = 0.03), and HCs (1722 ± 178 vs. 1067 ±144, p < 0.01). Skin lesions, uveitis, and arthritis had no association with serum AEA levels.

Conclusion:

BD patients with severe oral ulcers have increased serum levels of AEA than those with mild oral ulcers and HCs, suggesting a possible pathogenic role of AEA in the oral ulcer formation. A treatment targeting AEA might offer a new therapeutic option for BD associated severe oral ulcer.



Disclosure: S. E. Kang, None; **S. J. Lee**, None; **J. K. Park**, None; **J. Y. Lee**, None; **E. Y. Lee**, None; **E. B. Lee**, None; **Y. W. Song**, None.

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Abstract Number: 3227

Identification of Novel Protein-Coding Genetic Variants Associated with Takayasu Arteritis

Paul Renauer[1], Patrick Coit[1], Peter A. Merkel[2] and Amr H. Sawalha[1], [1]Division of Rheumatology, University of Michigan, Ann Arbor, MI, [2]Penn Vasculitis Center, Division of Rheumatology, University of Pennsylvania, Philadelphia, PA

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Background/Purpose: Takayasu arteritis is a rare large vessel vasculitis of unclear etiology. Previous studies identified associations between Takayasu arteritis and genetic variants within HLA class I and II, *FCGR2A*/*FCGR3A*, *IL12B*, *RPS9*/*LILRB3*, *IL6*, and chromosome 21q22. The purpose of this study was to uncover protein-coding genetic risk variants in Takayasu arteritis.

Methods: We analyzed 230,050 exonic protein-coding genetic variants included on the Illumina Human Exome BeadChip array in a European-American cohort consisting of 134 patients with Takayasu arteritis and 1051 healthy controls. Genotyping data were subjected to rigorous quality control assessment and filtering prior to genetic analysis.

Results: Outside of the HLA region, 4 nonsynonymous protein-coding variants associated with increased risk for Takayasu arteritis were identified ($P<5X10^{-5}$). The most significant genetic associations were with missense genetic variants in *TXK* (OR= 1.95, $P= 7.75X10^{-6}$) and *CCDC91* (OR= 3.69, $P= 2.11X10^{-5}$). *TXK* encodes a non-receptor tyrosine kinase that plays an important role in T cell function and differentiation. *CCDC91* encodes P56 which interacts with the trans-Golgi network and is involved in regulating protein trafficking. Evidence for gene-gene epistatic interaction was detected between the two genetic variants in *TXK* and *CCDC91* and the risk for Takayasu arteritis (interaction OR= 3.09, $P= 2.38X10^{-2}$). Two additional missense variants within the collagen gene *COL11A2* and the acyl-coenzyme A synthetase gene *ACSM5* were also associated with Takayasu arteritis ($P= 3.27X10^{-5}$ and $3.41X10^{-5}$, respectively).

Conclusion: Missense protein-coding variants associated with increased risk for Takayasu arteritis were identified. A larger cohort will be necessary to confirm these associations with a genome-wide level of significance.

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Abstract Number: 3228

Sofosbuvir Plus Ribavirin for Hepatitis C Virus Associated Cryoglobulinemia Vasculitis: Vascuvaldic Study

David Saadoun[1], V Thibault[2], L Alric[3], C Guillaud[4], H Izzedine[2], M Costopoulos[2], L Musset[2], H Fontaine[5], C Hezode[4], S Pol[5], T Poynard[2], P Cacoub[2] and SN SI Ahmed[6], [1]Department of Internal Medicine and clinical Immunology. French National Reference Center for Autoimmune Diseases. DHU I2B (Inflammation, Immunotherapy and Biotherapy), UPMC, Paris VI, Hôpital Pitié Salpétrière, AP-HP, UPMC, Univ Paris 06, Paris, France, [2]CHU Pitie Salpetriere, Paris, France, [3]CHU Toulouse, Toulouse, France, [4]CHU H Mondor, Creteil, France, [5]CHU Cochin, Paris, France, [6]CH Orleans, Orleans, France

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Background/Purpose: Hepatitis C virus (HCV) is the etiologic agent for most cases of cryoglobulinemia vasculitis (Cryovas). Interferon–containing regimens are associated with important side effects and may exacerbate the vasculitis. We evaluated the safety and efficacy of an oral interferon-free regimen, sofosbuvir plus ribavirin, in patients with HCV-Cryovas.

Methods: We enrolled 24 patients [median age of 56.5 years and 46% of women] with HCV-Cryovas. Sofosbuvir (400mg/day) was associated to ribavirin (200-1,400mg/day), for 24 weeks. Selection of the initial ribavirin dose and subsequent dose modification for anemia were at the investigator's discretion. The primary efficacy end point was a complete clinical response of the Cryovas at the end of treatment (week 24).

Results : Main clinical features of Cryovas included purpura and peripheral neuropathy (67%), arthralgia (58%), glomerulonephritis (21%), and skin ulcers (12%).Twenty one participants (87.5%) had a complete clinical response at week 24. Complete clinical response was achieved in 6 (25%) patients at week 4, 4 (16.6%) at week 8, 7 (29.2%) at week 12, 3 (12.5%) at week 16 and 1 (4.2%) at week 20. Purpura, skin ulcers and arthralgia disappeared in all cases. Kidney involvement improved in four out of five (80%) patients. Peripheral neuropathy improved in 16 out of 17 (94%) cases. The cryoglobulin level decreased from 0.35 (0.16-0.83) at baseline to 0.15 (0.05-0.45) g/l at week 24. The C4 serum level increased from 0.10 (0.07-0.19) to 0.17 (0.09-0.23) g/l at week 24. Seventy four percent of patients had a sustained virological response at week 12 post treatment. The most common side effects were fatigue, insomnia and anemia. Two serious adverse events were observed leading to treatment discontinuation. Thirteen patients (54%) received erythropoietin and three required blood transfusion.

Conclusion: Treatment with sofosbuvir plus ribavirin for 24 weeks was associated with a high rate of complete clinical response and a low rate of serious adverse events among HCV-Cryovas patients.

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Abstract Number: 3229

Using Exome Sequencing to Identify Novel Genetic Associations with Granulomatosis with Polyangiitis Susceptibility

Angel C.Y. Mak[1], Paul L.F. Tang[2], Gang Xie[3], Pui-Yan Kwok[2], Paul A. Monach[4], Simon Carette[3], David Cuthbertson[5], Gary S. Hoffman[6], Nader A. Khalidi[7], Curry L. Koening[8], Carol A. Langford[6], Carol A. McAlear[9], Larry W. Moreland[10], Christian Pagnoux[3], Philip Seo[11], Ulrich Specks[12], Antoine G. Sreih[13], Steven R. Ytterberg[14], Peter A. Merkel[15], Katherine A. Siminovitch[3], **Sharon A. Chung**[16] and Vasculitis Clinical Research Consortium, [1]Cardiovascular Research Institute, University of California, San Francisco, San Francisco, CA, [2]Institute for Human Genetics, University of California, San Francisco, San Francisco, CA, [3]Mount Sinai Hospital, Toronto, ON, Canada, [4]Rheumatology, Boston University School of Medicine, Boston, MA, [5]Biostatistics and Informatics, Department of Pediatrics, University of South Florida, Tampa, FL, [6]Rheumatology, Cleveland Clinic, Cleveland, OH, [7]McMaster University, Hamilton, ON, Canada, [8]Rheumatology, University of Utah, Salt Lake City, UT, [9]University of Pennsylvania, Philadelphia, PA, [10]Rheumatology & Clinical Immunology, University of Pittsburgh, Pittsburgh, PA, [11]Division of Rheumatology, Johns Hopkins University, Baltimore, MD, [12]Division of Pulmonary and Critical Care Medicine,

Mayo Clinic College of Medicine, Rochester, MN, [13]Department of Rheumatology, University of Pennsylvania, Philadelphia, PA, [14]Rheumatology Division, Mayo Clinic, Rochester, MN, [15]Division of Rheumatology, University of Pennsylvania, Philadelphia, PA, [16]Russell/Englemen Rheumatology Research Center, Rosalind Russell / Ephraim P. Engleman Rheumatology Research Center, University of California, San Francisco, San Francisco, CA
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Background/Purpose: Previous genome-wide association studies of granulomatosis with polyangiitis (Wegener's, GPA) identified common genetic variants associated with susceptibility to GPA. However, since GPA is a rare disease, we hypothesize that rare genetic variants may be more strongly associated with disease susceptibility. Therefore, we conducted an exome-sequencing study to identify rare, deleterious exonic variants associated with GPA.

Methods: Seventy-seven individuals with GPA underwent exome sequencing using the Illumina HiSeq platform and the Nimblegen SeqCap EZ exome enrichment protocol. All cases of GPA were of European descent, c-ANCA/anti-PR3 positive, and fulfilled either the ACR Classification Criteria or the Chapel Hill Consensus Conference definition of GPA. Exome sequencing reads were processed according to the Genome Analysis Toolkit Best Practices for DNA sequencing. Variants were annotated and filtered with ANNOVAR and Variant Tools. Functional effects of the variant were assessed using *in silico* bioinformatics algorithms and databases of known pathogenic variants. We applied a gene burden test to identify genes that were enriched with deleterious variants in patients with GPA when compared to publicly available data from the 1000 Genomes and the National Institutes of Health-funded Exome Sequencing Projects. Pathway analysis was performed using the Gene Set Enrichment Analysis Molecular Signatures database.

Results: After quality control filtering and bioinformatics analysis, we identified 4,306 exonic, non-synonymous, deleterious variants in the 77 cases of GPA, of which 3,812 were rare (minor allele frequency <1%). After applying gene burden tests, we identified 153 genes not previously associated with GPA that were enriched with deleterious variants in GPA cases compared to controls. These genes fell into the following 3 groups (with overlap): 1) 98 genes were enriched with rare deleterious variants, 2) 35 genes with homozygous rare deleterious variants not present in controls, and 3) 42 genes enriched with common deleterious variants. Genes with the strongest evidence of enrichment for rare, deleterious variants include *FOXD4L1*, *UMODL1*, and *PNKP*. Pathways over-represented by the 153 genes include the metabolism of lipoproteins and extracellular matrix organization. Lastly, we found enrichment for 6 variants in 3 genes previously associated with GPA (*ITGB2, RXRB, SERPINA1*).

Conclusion: Our initial results indicate that exome sequencing can identify novel genetic associations with GPA beyond what has been previously observed in genome-wide association studies. These associations implicate new biologic pathways that may contribute to the pathogenesis of disease. To our knowledge, this is the first study to utilize next-generation sequencing to assess for genetic variants associated with GPA susceptibility. The results from this study can be used to inform future genomic and translational investigations of this and other systemic vasculitides.

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Abstract Number: 3230

Perceived Barriers in Care for Arthritis

Elizabeth M. Badley[1], Lynn Moore[2] and Monique A.M. Gignac[3], [1]Toronto Western Research Institute, Toronto, ON, Canada, [2]The Arthritis Society, Toronto, ON, Canada, [3]Instititue for Work and Health, Toronto, ON, Canada
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Background/Purpose: To examine current arthritis treatments, barriers to treatment, and perceptions of health care decision making, especially preferences for patient-physician shared input.

Methods: A poll of people with arthritis was commissioned to gather data on patient perceptions with the purpose of improving information on the web site of The Arthritis Society of Canada. Respondents were asked for their disease diagnosis; impact of arthritis (e.g., pain, fatigue, disability with activities and social roles); challenges in getting care; and preferences for physician involvement in care decisions. Most questions were on a 1 to 5 scale ranging from 1 = no impact/importance to 5 = extreme impact/importance. Scores are reported as means or percentages unless otherwise stated.

Results:

Of the 1514 respondents, 558 reported only osteoarthritis (OA) and 1043 reported inflammatory arthritis (IA) (rheumatoid arthritis 499, psoriatic arthritis 235, ankylosing spondylitis 227, lupus 156). 69% were female; 69% were aged <65 years; 65% were married and 46% had completed post-secondary education. Mean disease duration was 12.9 years. There were few differences in findings by disease. Mean pain intensity was 6.0 (95% CI: 5.9-6.1) (1 to 10 scale). Mean number of joints (out of 13) was 4.3 (95% CI: 3.9-4.8), slightly less for OA (mean 3.8; 95% CI:3.6-4.0). The impact on daily activities was moderate with mean scores in the range of 2.6 to 4.0. The greatest impact was for intimate relations (4.0) and exercise (3.4). Respondents reported controlling pain, mobility and fatigue as being of high importance (mean score range 4.1-4.4). 52% reported taking medication orally; 15% by injection or infusion (mainly respondents with IA). Overall, 75% of respondents reported at least one challenge in getting treatment. The top 3 challenges were lack of affordable treatment (27.5%), long wait times for appointments (28.8%), and a perceived absence of beneficial treatments (e.g., "don't think anything can be done") (21.2%). Costs for treatments like physiotherapy and medication were noted in particular. Younger respondents tended to report more challenges. A sizable minority reported that nothing could be done for their arthritis (range 16.2 % to 26.3 % by disease). Respondents rated highly the importance of physician input when making decisions related to prescription medication (mean = 4.4) and surgery or physiotherapy (mean = 4.4). They expressed lower importance of seeking physician input on treatments like diet and exercise (mean = 3.7) and over-the counter-medications (mean = 3.8).

Conclusion: Despite pain, a moderate impact on valued roles and activities, and a high importance of controlling a range of symptoms, most respondents reported challenges with getting treatment, including costs not covered by the health care system. Of concern is the perception of some that little was available in the way of efficacious care. There is a need for better patient information on what can be done to control arthritis and for interventions to minimize barriers in accessing appropriate treatments. Additional research on decision-making preferences would be beneficial in addressing a patient-centered approach to care.

Disclosure: E. M. Badley, None; **L. Moore**, None; **M. A. M. Gignac**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/perceived-barriers-in-care-for-arthritis

Abstract Number: 3231

A Systematic Review of the Persuasive Design Principles Used in Health Apps for Arthritis

Jonas Geuens[1], Vero Vanden Abeele[2], Thijs Swinnen[3], R Westhovens[4], Kurt L. de Vlam[4] and Luc Geurts[5], [1]Faculty of Engineering Technology, KU Leuven, Leuven, Belgium, [2]Technology Cluster Computerscience, KU Leuven, Leuven, Belgium, [3]Rheumatology, UZ Leuven, Leuven, Belgium, [4]Rheumatology, University Hospitals Leuven, Leuven, Belgium, [5]Electrical Engineering (ESAT), KU Leuven, Leuven, Belgium

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Background/Purpose: Recently, we witnessed a steep increase in the amount of mobile applications (apps) in the category of "Health & Fitness". Most popular examples of such apps are RunKeeper GPS Track Run Walk, HealthTap, Sworkit Workout Trainer and iTriage Health. These apps all have between 1 and 50 million downloads and a rating of 4.4 or more out of 5, significantly higher than the average 3.9 rating for this category of apps. Possibly, this above average rating can be explained by their usage of so-called persuasive design techniques to engage users in using the app. The same principles can be employed for apps that target a specific disease. The aim of this study is to investigate which of these persuasive design principles are prevalent in apps that aid in the management of arthritis. It is our aspiration that these insights may help experts and app developers to build more effective patient support and may result in increasing the use of apps in arthritis management.

Methods: A systematic search was conducted in all three major app stores (Google Play, iTunes App Store and Windows Phone Store) using keywords related to arthritis. Criteria for inclusion were that the app (1) should target one or more arthritis related diseases, (2) provides tracking or monitoring of arthritis related disease factors or provides information about arthritis, (3) targeted adult patients. Exclusion criteria were (1) apps intended for medical personnel, (2) magazines, general pain trackers or food guides in app format. There were no language restrictions. Apps were coded by two independent raters using an adapted version of the Persuasive System Design (PSD) model by Harjumaa and Oinas-Kukkonen (2009) and the taxonomy of behavior change by Abraham and Michie (2008).

Results: Twenty-eight apps met the inclusion criteria. The most used task support principle (n=15) was to solely provide information to patients. Other common task support principles were reduction (reducing complex behavior into simple tasks) and self-monitoring (being able to (re)view your own data); many apps (n=11) offer reduction as the calculation of the Disease Activity Score (DAS) and visualized to evolution as self-monitoring. Goal setting and ways to support self-efficacy beliefs (e.g. recognition, rewards) were less prevalent (n=2). In addition, principles to influence system credibility were limited to offering a level of surface credibility and perceived expertise in the information provided but lacked other system credibility measures such as figures of authority and third-party endorsements. Surprisingly, techniques to influence normative beliefs or to include social support were lacking.

Conclusion: The results of this study are an indication that current apps for arthritis patients are mostly designed to calculate DAS scores and convey information on the disease. There is a remarkable lack of other persuasive principles to engage patients in digital management of their disease. Although these persuasive principles such as social support and dialogue support contribute to the success of other fitness and health apps, apps for arthritis patients rarely use them.

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Abstract Number: 3232

The Comparative Efficacy of Kinesio Taping and Local Steroid Injection in Patients with Subacromial Impingement Syndrome

Hamit Goksu[1], **Pinar Borman**[2], Figen Gokoglu[3] and Seher Kocaoglu[2], [1]Clinic of Physical Medicine and Rehabilitation, Ankara Training and Research Hospital, Ankara, Turkey, [2]Department of 1st Physical Medicine and Rehabilitation, Ministry of Health Ankara Education and Research Hospital, Ankara, Turkey, [3]Dept of Physical Medicine and Rehabilitation, Ahi Evran University, Medical Faculty, Kýrþehir, Turkey
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Background/Purpose: There are several approaches in the treatment of subacromial impingement syndrome (SIS). The aim of this study was to compare the therapeutic effects of kinesio taping (KT) and local subacromial injection in patients with SIS, in regard to pain, range of motion (ROM) and disability.

Methods:

Sixty-one patients with subacromial impingement syndrome were enrolled into the study. Demographic and clinical characteristics including age, sex, duration of disease were recorded. The patients were randomized into two treatment groups receiving either a single corticosteroid and local anesthetic (LA) injection, or kinesio taping performed three times by intervals of 3 day. Visual analog scale (VAS) was used to assess pain intensity, shoulder abduction, flexion and rotation range of motion (ROM) degrees were recorded and Shoulder Pain and Disability Index (SPADI) was performed to evaluate functional disability, before treatment, at the first and fourth weeks after therapies. Both groups were educated for home exercise programme.

Results:

Forty-eight female and 13 male patients (mean age, 42.4+6.48 years; mean disease duration, 2.35+0.79 months) were included in the study. There were no differences between the groups regarding demographic variables on entry to the study. Pain, functional outcome measures were determined to have improved significantly in both groups at the end of therapies at first and fourth weeks, but these improvements were more significant in the injection group than in kinesio taping group ($p>0.05$). The improvements in pain at rest, shoulder abduction degrees, and SPADI scores at first and fourth weeks were statistically higher in injection group than in kinesio taping group.

Conclusion:

We imply that single dose subacromial injection and three times of kinesio taping by 3 day intervals, in addition to exercise programme have favorable effects on pain and functional status in the early period (up to one month) of subacromial impingment syndrome. Although the improvement in pain intensity at rest, abduction ROM measures and disability were better with local injection, KT may be an alternative non-invasive method for patients suffering from subacromial impingement syndrome in the early period.

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Abstract Number: 3233

A Comparison of Interobserver Agreement Between Advanced Practice Physiotherapists and Rheumatologists in the Detection of Axial Spondyloarthritis

Laura Passalent[1,2], Christopher Hawke[3], Ahmed Omar[4], Khalid Alnaqbi[5], Dinny Wallis[6], Nigil Haroon[4] and Robert D Inman[7], [1]Allied Health, Toronto Western Hospital, Toronto, ON, Canada, [2]Physical Therapy, University of Toronto, Toronto, ON, Canada, [3]Toronto Western Hospital, University of Toronto, Toronto, ON, Canada, [4]Rheumatology, Toronto Western Hospital, University of Toronto, Toronto, ON, Canada, [5]Rheumatology, Al Ain Hospital, Al Ain, United Arab Emirates, [6]University Hospital Southampton NHS Foundation Trust, Southampton, United Kingdom, [7]Immunlogy and Institute of Medical Science, Toronto Western Hospital, University of Toronto, Toronto, ON, Canada
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Background/Purpose: Emerging models of care in rheumatology are using non-physician health care professionals to assess patients with suspected inflammatory arthritis with the aim to improve early detection and access to care. Such models of care have been recently implemented for early identification of axial spondyloarthritis (SpA). The primary objective of this study was to compare the clinical impression and confidence of advanced practice physiotherapists (APP), having specialized training in inflammatory arthritis, with rheumatologists experienced in axial SpA according to: 1) the evaluation of patients with chronic back pain being assessed for axial SpA and 2) MRI recommendation for further investigation of the above patients.

Methods: Patients with more than 3 months of back pain with onset prior to the age of 45 years and attending community primary care or high risk clinics (e.g. gastroenterology or ophthalmology) were referred for axial SpA evaluation. Two APPs and three rheumatologists evaluated each patient's history, physical examination, laboratory studies and plain radiographs. Patients were classified as either axial SpA or mechanical back pain (MBP) based on the above clinical and investigative findings. Level of confidence in the clinical impression and recommendation for obtaining an MRI for further investigation were noted. Agreement between assessors was evaluated using percent agreement and Cohen's Kappa coefficient.

Results: Of 57 patients assessed, 56% were referred through community care pathways. The majority (56.1%) of patients was male and the mean (±SD) age was 38.5 years (±12.2). Overall interobserver agreement of clinical impression for all raters was moderate (K=0.52). Agreement of clinical impression between the APPs and rheumatologists ranged between 71.2% (K=0.41; 95% CI: 0.17-0.67) and 79.7% (K=0.57; 95% CI: 0.35-0.79). Agreement of clinical impression amongst rheumatologists ranged from 74.1% (K=0.49; 95% CI: 0.26-0.71) and 79.7% (K=0.58; 95% CI: 0.37-0.8). All rater agreement for recommendation of MRI showed fair agreement (K=0.37). The APP agreement with rheumatologist for MRI recommendation ranged from 64.2% (K-0.31, 95% CI: 0.13-0.55) and 75% (K=0.48, 95% CI: 0.23-0.72). Agreement to recommend MRI amongst rheumatologists ranged from 62.9% (K=0.27, 95% CI: 0.02-0.52) and 74% (K=0.47, 95% CI: 0.24-0.71). Confidence in clinical impression was similar amongst all practitioners (APPs median score 7/10; rheumatologists median score 6/10).

Conclusion: APPs with specialty training in inflammatory arthritis demonstrate comparable case ascertainment as rheumatologists in the assessment of axial SpA. Utilization of such advanced practice roles may assist in improving the early detection of axial SpA, thereby facilitating early treatment and improving overall outcomes in this patient population.

Table 1: Interobserver agreement between advanced practice physiotherapists and rheumatologists			
	Percent Agreement	Cohen's Kappa	95% Confidence Interval
CLINICAL IMPRESSION			
APP and Rheumatologist consensus	75.5	0.5	(0.26-0.73)
APP and Sr Rheum	79.7	0.57	(0.35-0.79)
APP and Jr Rheum	77.7	0.56	(0.33-0.77)
APP and Fellow	71.2	0.41	(0.17-0.67)
Sr Rheum and Jr Rheum	76.8	0.55	(0.35-0.75)
Sr Rheum and Fellow	79.7	0.58	(0.37-0.8)
Jr Rheum and Fellow	74.1	0.49	(0.26-0.71)
MRI RECOMMENDATION			
APP and Rheumatologist consensus	71.1	0.43	(0.2-0.66)
APP and Sr Rheum	75	0.48	(0.23-0.72)
APP and Jr Rheum	64.2	0.32	(0.1-0.5)
APP and Fellow	64.7	0.31	(0.13-0.55)
Sr Rheum and Jr Rheum	63.7	0.29	(0.06-0.53)
Sr Rheum and Fellow	62.9	0.27	(0.02-0.52)
Jr Rheum and Fellow	74	0.47	(0.24-0.71)
APP=Advanced Practice Physiotherapist; Sr Rheum=senior staff rheumatologist; Jr Rheum=junior staff rheumatologist; Fellow=visiting rheumatology fellow			

Disclosure: L. Passalent, None; **C. Hawke**, None; **A. Omar**, None; **K. Alnaqbi**, None; **D. Wallis**, None; **N. Haroon**, None; **R. D. Inman**, None.

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Abstract Number: 3234

Roadblocks Perceived By Canadian Dermatologists for Referring Patients with Suspected Psoriatic Arthritis

Renise Ayearst[1], Daniel Pereira[1], Charles Lynde[2], Holly Etchegary[3] and Vinod Chandran[1], [1]Rheumatology, University of Toronto, Toronto Western Hospital, Toronto, ON, Canada, [2]University of Toronto, Toronto, ON, Canada, [3]Memorial University of Newfoundland, St.John's, NF, Canada

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Background/Purpose: The current system of referral by Canadian dermatologists of patients who may have psoriatic arthritis (PsA) to rheumatologists is suboptimal. Hypothesizing that knowledge level, attitude and confidence in being able to refer appropriately impacts the ability of dermatologists to refer patients who may have PsA to a rheumatologist, we aimed to define their current awareness of, and practices relating to, the diagnosis and referral of PsA.

Methods: Based on recommendations from our advisory group comprising rheumatologists, dermatologists, methodologists and patient-partners, questions for structured interviews and focus groups with practicing dermatologists were developed. Dermatologists from across Canada at different stages of their career were recruited via electronic mail. Telephone or face-to-face interviews and focus groups were conducted by

trained research associates. The interviews and focus groups were recorded, transcribed, and analyzed by 2 experts and key themes identified.

Results: 8 interviews and 2 focus groups involving a total of 20 dermatologists in community practice (10 males, mean years in practice 18.4) were conducted and data saturation reached. The following themes were identified- (1) **Self-perceived knowledge** of psoriasis and associated co-morbidities was fairly high [mean of 8.5 (out of 10) across the interviews and 7.1 across focus groups]. (2) The **number of patients** with psoriasis seen was quite variable, 30-50 weekly on average. Of these, the percentage with PsA or suspected PsA ranged from 5%-50%. (3) **Co-morbidities**, including PsA, diabetes, obesity, heart disease, depression, metabolic syndrome, and hypertension were consistently mentioned. (4) **Red flags** noted for PsA included morning stiffness and joint pain**.** Fewer mentioned nail lesions and joint swelling. (5) All dermatologists recognized the **importance of identifying PsA early**, both for the patient and for the broader healthcare system. (6) There was a notable divide between their **perceived role in screening for PsA and in making the diagnosis**. A minority of respondents felt comfortable managing PsA if it was mild without confirmation by a rheumatologist. (7) If arthritis is perceived to be mild, dermatologists perceive an ongoing **role in patient management**. Other aspects of the healthcare system that affected dermatologists' perception included the nature of the local healthcare context, access to rheumatologists, and the role of primary care.

Conclusion: This qualitative study shows that dermatologists have high self-perceived knowledge of psoriasis, PsA and its associated comorbidities, and recognize the importance of identifying PsA early. However, the nature of the local healthcare context and access to rheumatologists are significant road blocks to appropriate referral.

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Abstract Number: 3235

Factors Associated with Nonadherence to Recently Initiated Disease-Modifying Antirheumatic Drugs

Candace H. Feldman[1], Elena Massarotti[2], Alyssa Wohlfahrt[3], Anarosa Campos[3], Yuanyu Lo[3], Zhi Zhang[3], Maura D. Iversen[4] and Daniel H. Solomon[1], [1]Division of Rheumatology, Immunology and Allergy, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, [2]Rheumatology, Immunology and Allergy, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, [3]Rheumatology, Immunology and Allergy, Brigham and Women's Hospital, Boston, MA, [4]Northeastern University, Department of Physical Therapy, and Brigham & Women's Hospital, Harvard Medical School, Boston, MA

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Background/Purpose: Medication nonadherence accounts for more than $100 billion in preventable healthcare costs annually in the US. Nonadherence to disease-modifying antirheumatic drugs (DMARDs) among patients with rheumatic diseases likely results in significant morbidity. We investigated the association between demographic, disease-related and psychosocial factors and nonadherence to recently initiated DMARDs; the long-term goal is to better tailor interventions to target patients at highest risk for nonadherence.

Methods: English or Spanish-speaking patients ≥18 years old who recently started an oral DMARD for a systemic rheumatic disease were invited to participate. The study took place between 2013 and 2015 at an academic medical center. We identified patients using electronic medical record review and obtained permission to contact the patients from the treating rheumatologist. Medications and demographic factors were ascertained using electronic medical record queries. Trained bilingual research assistants administered baseline surveys by phone or in person. We measured self-reported adherence to oral DMARDs using the eight-item Morisky Medication Adherence Scale (MMAS). We determined disease activity for rheumatoid arthritis (RA) and other inflammatory arthritis with the Rheumatoid Arthritis Disease Activity Index (RADAI). Anxiety and depression were assessed with the Mental Health Inventory (MHI-5) and perceived illness severity using the Brief Illness Perception Questionnaire. We used descriptive statistics to compare demographics and survey findings by degree of adherence.

Results: We administered surveys to 92 patients. The mean age was 56.1 years (SD 16.2), 95% were female, 72.8% were White, 5.4% Black, 2.2% Asian and 19.6% not reported;17.4% identified as Hispanic. 80.4% had RA or other inflammatory arthritis, 7.6% lupus, and 4.3% other systemic rheumatic diseases. In terms of medication use, 52.2% recently started methotrexate, 20.7% hydroxychloroquine, 10.9% sulfasalazine, 6.5% leflunomide, 3.3% azathioprine, and 3.3% tofacitinib. The mean RADAI was 14.7 (SD 9.1). 89.8% of patients had depressive symptoms (MHI-5<70). The mean adherence score was 6.6 (SD 1.4); 23.9% reported poor adherence to their prescribed DMARD (MMAS <6), 53.3% borderline (MMAS 6 to <8) and 22.8% high (MMAS=8). Patients with poor adherence were more likely to be younger (p=0.01), have more active RA (p=0.05), and more depressive symptoms (p=0.02) (**Table**).

Conclusion: In this cross-sectional analysis, the majority of patients who recently started an oral DMARD had borderline or poor adherence and a significant burden of depressive symptoms. Increased disease activity, depression and younger age were associated with poorer adherence. Interventions that target these individuals at high risk for nonadherence are being tested to determine whether clinical outcomes improve.

Table. Association of demographic, disease-related and psychosocial factors with degree of adherence as measured by the eight-item Morisky Medication Adherence Scale (MMAS)

	Overall*	Poor Adherence (MMAS<6)	Borderline Adherence (MMAS 6-<8)	High Adherence (MMAS=8)	p-value**
Age –mean years (SD)	56.1 (16)	48 (14.6)	57.1 (15.7)	62.4 (16.1)	**0.01**
Gender – N (%)					
Female	87 (95)	19 (21.8)	47 (54)	21 (22.8)	0.71
Male	5 (5)	2 (40)	2 (40)	1 (20)	
Ethnicity					
Hispanic- N (%)	N=16 (17.4)	6 (37.5)	9 (56.3)	1 (6.3)	
Non-Hispanic – N (%)	N=72 (78.2)	15 (20.8)	39 (42.4)	18 (25)	0.17
Not reported	N=4 (4.3)	1 (25)	1 (25)	2 (50)	
Insurance Status (N=86)- N (%)					
Medicaid	N=11 (12.8)	5 (45.5)	4 (36.4)	2 (18.2)	
Medicare	N=28 (32.6)	6 (21.4)	13 (46.4)	9 (32.1)	0.14
Private	N=46 (53.5)	10 (21.7)	29 (63)	7 (15.2)	
Self-pay	N=1 (1)	0 (0)	0 (0)	1 (100)	
Rheumatic disease – N (%)					
RA/psoriatic arthritis/JIA	N=74 (80.4)	16 (21.6)	42 (56.8)	16 (21.6)	0.37
Lupus and other rheumatic diseases+	N=18 (19.6)	6 (33.3)	7 (38.9)	5 (27.8)	
RA Disease Activity (RADAI, N=73) – Mean (SD)	14.7 (9.1)	16.2 (10.7)	16.1 (9.1)	9.8 (5.8)	**0.05**
Depression/Anxiety (MHI-5, N=88)- Mean (SD)++	61.1 (9.7)	57.5 (10.4)	62.3 (9.6)	62.2 (8.6)	**0.02**
Illness Perception (N=91) - Mean (SD)	44.6 (9.9)	42.3 (12)	45.1 (9)	45.8 (9.6)	0.46

*N=92 unless otherwise specified

**p-values calculated with ANOVA (continuous variables) or Fisher's exact tests (categorical variables)

+Other rheumatic diseases include: mixed connective tissue disease, systemic sclerosis, systemic vasculitis, sarcoidosis, polymyositis, polymyalgia rheumatica, immune-mediated necrotizing myopathy, Behcet's disease

++Lower MHI-5 scores reflect increased depressive symptoms

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Abstract Number: 3236

Circulating Cytokine/Chemokine Concentrations Predict Cancer Mortality in Men with Rheumatoid Arthritis

Bryant R. England[1], Jeremy Sokolove[2], William H. Robinson[3], Geoffrey M. Thiele[4], Apar K. Ganti[5], Harlan Sayles[6], Kaleb Michaud[7], Liron Caplan[8], Lisa A. Davis[8], Grant W. Cannon[9], Brian Sauer[10], E. Blair Solow[11], Andreas Reimold[12], Gail S. Kerr[13], Pascale Schwab[14], Joshua F. Baker[15] and Ted R. Mikuls[16], [1]Division of Rheumatology, Department of Internal Medicine, University of Nebraska Medical Center, Omaha, NE, [2]Division of Immunology and Rheumatology, Stanford University Medical Center, Mountain View, CA, [3]Division of Immunology and Rheumatology, Stanford University School of Medicine, Stanford, CA, [4]Research Services 151, Omaha VA Medical Center, Omaha, NE, [5]Internal Medicine, Division of Oncology, University of Nebraska Medical Center, Omaha, NE, [6]University of Nebraska Medical Center, Omaha, NE, [7]Rheumatology & Immunology, University of Nebraska Medical Center and National Data Base for Rheumatic Diseases, Omaha, NE, [8]Div of Rheumatology, Univ of CO Denver School of Med, Aurora, CO, [9]Division of Rheumatology, Salt Lake City VA Medical Center and University of Utah, Salt Lake City, UT, [10]Salt Lake City VA Medical Center and University of Utah, Salt Lake City, UT, [11]Rheumatology, UT Southwestern Medical Center, Dallas, TX, [12]Rheumatology, VAMC, University of Texas Southwestern Medical Center, Dallas, TX, [13]VAMC, Georgetown University, Washington, DC, [14]Div Arth & Rheum Dis, Oregon Health & Sci Univ OP09, Portland, OR, [15]Rheumatology, University of Pennsylvania, Philadelphia, PA, [16]Medicine, University of Nebraska Medical Center, Omaha, NE

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Session Type: ACR Concurrent Abstract Session

Session Time: 9:00AM-10:30AM

Background/Purpose: Rheumatoid arthritis (RA) is characterized by chronic inflammation and the dysregulated expression of pro-inflammatory cytokines / chemokines (CK). Chronic inflammation has also been implicated in cancer pathogenesis, particularly through the intercommunication of immune and cancer cells mediated by CK signaling. In this study we sought to test the hypothesis that circulating CKs predict cancer mortality in RA.

Methods: Male participants in the Veterans Affairs RA registry were followed from enrollment until death or December 2013. Using banked serum from enrollment, CKs were measured using a bead-based multiplex assay. CK scores were calculated from individual CKs. Both CK scores and individual CKs were examined in quartiles and as log transformed values. Vital status and cause of death were determined through the National Death Index. Associations of CK score and individual CKs with cancer mortality were examined using multivariable competing-risks regression adjusting for age, race, smoking status, body mass index, comorbidity, visit frequency, nodules, RF concentration, enrollment DAS-28, baseline DMARDs and prednisone use.

Results: There were 1,294 RA patients included with 71 cancer deaths occurring over 5,585 patient-years of follow-up. Patients were older (mean 65 ± 11 years), had established disease (mean 12 ± 12 years), were seropositive for RF (80%) or anti-CCP antibody (77%), and had frequent smoking history (82% current or former). Lung cancer was the most common cause of cancer deaths (n = 30, 42%), followed by leukemia (n = 7) and lymphoma (n = 6). Adjusted associations of CK score with overall and lung cancer mortality are shown in Table 1. After MV adjustment, log-transformed CK score was associated with mortality from all cancers (HR 1.65, 95% CI 1.40 to 1.94, P < 0.001) and lung cancer (HR 1.81, 95% CI 1.47 to 2.22, P < 0.001). Fifteen of the 17 CK analytes examined were associated with cancer mortality after multivariable adjustment. In sub-analyses, excluding those with prevalent cancer at enrollment (n=190), CK score remained associated with overall cancer mortality (HR 3.82, 95% CI 2.19-6.65, P < 0.001 for highest quartile vs. lowest; P trend < 0.001) and lung cancer mortality (HR 9.47, 95% CI 0.85-105.90, P = 0.068 for highest quartile vs. lowest; P trend = 0.001).

Table 1. Multivariable Associations of CK Score with Overall and Lung Cancer Mortality in RA.

CK Score Quartile	Overall Cancer Mortality	Lung Cancer Mortality
	Hazard Ratio (95% Confidence Interval)	
Quartile 1 (Lowest)	1.00	1.00
Quartile 2	1.34 (0.39-4.61)	1.83 (0.35-9.58)
Quartile 3	1.83 (0.50-6.71)	2.85 (0.43-18.88)
Quartile 4 (Highest)	3.29 (1.63-6.67)	4.44 (0.83-23.77)
	P-trend < 0.001	P-trend = 0.018

Conclusion: Circulating CK concentrations are strongly associated with future cancer mortality in men with RA, an association that is independent of multiple factors including RA disease activity and medications. In addition to highlighting the potential value of CK as a predictive biomarker, these findings suggest that CK expression could act as a crucial link between RA and cancer. Further studies are needed to investigate the role of specific CKs in cancer development and the impact that therapies targeting CKs could yield in reducing cancer burden in RA.

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Abstract Number: 3237

Decreased Cardiovascular Mortality in Patients with Incident Rheumatoid Arthritis (RA) in Recent Years: Dawn of a New Era in Cardiovascular Disease in RA?

Elena Myasoedova[1], Cynthia S. Crowson[2], Eric L. Matteson[3], John M. Davis III[4], Terry M. Therneau[5] and Sherine E. Gabriel[6], [1]Internal Medicine and Rheumatology, Mayo Clinic, Rochester, MN, [2]Health Sciences Research, Mayo Clinic, Rochester, MN, [3]Rheumatology, Mayo Clinic, Rochester, MN, [4]Division of Rheumatology, Mayo Clinic, Rochester, MN, [5]Department of Health Sciences Research, Mayo Clinic, Rochester, MN, [6]Rutgers Robert Wood Johnson Medical School, New Brunswick, NJ

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Session Time: 9:00AM-10:30AM

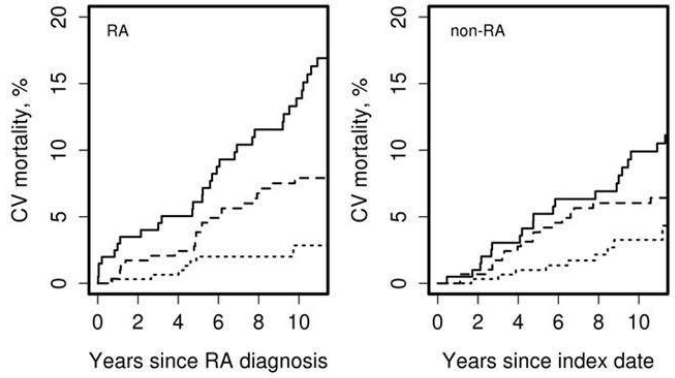
Background/Purpose: Rheumatoid arthritis (RA) is associated with increased cardiovascular (CV) morbidity and mortality as compared to the general population. Recent prospective studies with limited follow-up suggest a trend towards decreasing CV fatality in RA. Longitudinal studies of CV mortality trends in RA patients diagnosed in the recent years are lacking, and the trends in the relative CV mortality in RA versus the general population are not fully understood. We aimed to assess trends in CV mortality in patients with incident RA in 2000-2007 compared to the previous decades, and to evaluate trends in relative CV mortality in RA compared to non-RA subjects.

Methods: The study population comprised a retrospectively identified population-based incidence cohort of patients with RA (age≥18 years, 1987 ACR criteria met in 1980-2007). A comparison cohort included non-RA subjects from the same underlying population with similar age, sex and calendar year of index. All subjects were followed until death, migration, or Jan. 1, 2014. Underlying causes of death were obtained from state and local death certificates as well as the National Death Index Plus and grouped according to ICD-9 and ICD-10 chapters. Kaplan-Meier methods were used to estimate CV mortality rates. Cox proportional hazards models, adjusting for age and sex, were used to compare CV mortality by decade.

Results: The study included a total of 813 RA patients (mean age 55.9 years; 68% female; 66% rheumatoid factor [RF] positive) and 813 non-RA subjects (mean age 55.9 years; 68% female). Figure shows CV mortality by decade of RA incidence/index date and the table summarizes these data. In patients with incident RA during the 2000–2007 period, the 10-year overall CV mortality was 2.8% (95% confidence interval [CI]: 0.4%, 5.2%); coronary heart disease (CHD) mortality was 1.2% (95% CI: 1.0, 1.4%), suggesting significant improvement compared to those diagnosed in 1990–1999 (hazard ratio [HR] for overall CV death: 0.43; 95% CI: 0.19, 0.94; p=0.035; CHD death: HR 0.21; 95% CI: 0.05, 0.95; p=0.042). Furthermore, 10-year overall CV mortality and CHD mortality in 2000-2007 RA incidence cohort did not differ from non-RA subjects (p=0.95 and p=0.79, respectively), which has not been observed in RA patients diagnosed in the prior decades.

Conclusion: Our findings suggest significant improvement in overall CV mortality, particularly CHD mortality, among patients with incident RA in 2000-2007 versus patients with incident RA in the previous decades. Furthermore, we have shown significant improvement in the relative 10-year CV mortality, including CHD mortality, in patients with incident RA in 2000-2007 versus the general population. These findings represent an important milestone in CV disease management in RA with significant implications for understanding determinants of improvement of CV disease in RA and in the general population.

Figure. Cardiovascular (CV) mortality in patients with Rheumatoid Arthritis (RA) (left panel) and subjects without RA (right panel) with incidence/index date in 1980-89 (solid line) 1990-99 (dashed line), 2000-07 (dotted line).



Incidence/index year	1980-1989		1990-1999		2000-2007	
	RA	Non-RA	RA	Non-RA	RA	Non-RA
Number of patients	202	202	296	296	315	315
Mean follow-up, years	17.6	19.6	14.5	15.7	8.6	9.1
Cardiovascular deaths	58	45	32	27	8	9
- Coronary heart disease (CHD) deaths	28	21	16	12	2	3
10-year CV mortality, %	13.9±2.5	9.9±2.2	7.9±1.6	6.0±1.4	2.8±1.2	3.3±1.2
10-year CHD mortality, %	7.8±2.0	5.0±1.6	4.7±1.3	2.5±0.9	1.2±0.9	1.3±0.7

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Abstract Number: 3238

The Impact of Biologic DMARD Treatment on Sepsis and Mortality after Serious Infection

Adrian Richter[1], Anja Strangfeld[2], Prof. Dr. Matthias Schneider[3], Thomas Klopsch[4], Andreas Kapelle[5], Jörg Kaufmann[6], Angela Zink[7] and Joachim Listing[8], [1]German Rheumatism Research Center, Berlin, Germany, [2]Epidemiology, German Rheumatism Research Center, Berlin, Germany, [3]Rheumatology, Heinrich-Heine-University, Duesseldorf, Germany, [4]Rheumatologist in private practice, Neubrandenburg, Germany, [5]Rheumatologist, Hoyerswerda, Germany, [6]Medical practice specialising, Ludwigsfelde, Germany, [7]Epidemiologie, Deutsches Rheuma-Forschungszentrum, Berlin, Germany, [8]Epidemiology, DRFZ, Berlin, Germany
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SESSION INFORMATION

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Session Type: ACR Concurrent Abstract Session

Session Time: 9:00AM-10:30AM

Background/Purpose: Tumor-necrosis-factor-α inhibition (TNFi) was assumed to be a relevant mechanism for the treatment of sepsis[1]. However, randomized controlled trials failed to show a survival benefit caused by TNFi in patients with diagnosed sepsis[2].

Methods: We investigated the outcomes of serious infection (SI, N=1,170) reported in 947 patients in the German biologics register RABBIT (**R**heumatoid **a**rthritis: o**b**servation of **bi**ologic **t**herapy) as: (i) no complication of SI, (ii) sepsis following SI (≤30d), and (iii) death after SI (≤90d). We applied a GEE model for multinomial responses in longitudinal data [3] to evaluate the risks of sepsis and death (accounting for age at SI, sex, physical function, comorbid heart failure or renal disease, glucocorticoid (GC) dose and the disease-modifying anti-rheumatic drug (DMARD)). Biologic (b)DMARDs were grouped as TNFi or other classes of bDMARDs. Sensitivity analyses were applied: [a] in a subset of

patients with pneumonia (N=298), [b] by restricting the conventional synthetic (cs)DMARD group to biologic naive patients and [c] by incorporating patients with incomplete data.

Results: 135 of 947 patients with an SI developed sepsis 137 times, 85 of 135 patients died due to sepsis. 53 patients died without known sepsis within 90 days after SI. The adjusted risk (odds ratio (OR)) of sepsis was significantly higher in older patients and in patients with chronic renal disease (Table). Patients with an SI who were exposed to bDMARDs and those with better physical function had a significantly lower risk to develop sepsis (Table). Risk factors of death after SI were higher age, glucocorticoids in high doses and heart failure, patients treated with bDMARDs and those with better physical function had a significantly lower risk of death after SI. Results remained consistent in sensitivity analyses [a-c].

Table: Results of multinomial regression. Adjusted odds ratios (OR) show increase or decrease of the risks of sepsis or death. Reference group: patients with SI but no further complication.

	Sepsis		Death	
	OR	95% CI	OR	95% CI
Age (by 10 years)	1.41	[1.15; 1.74]	2.47	[1.61; 3.79]
Sex (male vs female)	0.99	[0.63; 1.55]	1.45	[0.74; 2.83]
% of physical function (10% improvement)	0.92	[0.84; 1.00]	0.86	[0.76; 0.98]
Glucocorticoids (<5 mg/d=Referenz)				
Glucocorticoids (5- <10 mg/d vs. Ref.)	1.26	[0.82; 1.93]	0.93	[0.47; 1.83]
Glucocorticoids (≥10 mg/d vs. Ref.)	1.66	[0.96; 2.88]	2.40	[1.04; 5.55]
csDMARDs (reference)				
TNFi	0.64	[0.42; 0.97]	0.48	[0.24; 0.95]
Other bDMARDs	0.45	[0.25; 0.80]	0.16	[0.05; 0.54]
Heart failure (yes vs. no)	1.38	[0.74; 2.56]	3.56	[1.73; 7.33]
Chronic renal disease (yes vs. no)	1.93	[1.19; 3.14]	1.51	[0.72; 3.17]

Conclusion: Our results suggest a protective effect of bDMARDs in terms of lowering the risk of sepsis after SI if patients were already exposed to bDMARDs at the SI. Further investigation is needed for each class of bDMARDs and separately for bacterial and viral SI.

[1] Waage A, et al. Association between tumour necrosis factor in serum and fatal outcome in patients with meningococcal disease. The Lancet 1987.

[2] Remick DG. Cytokine therapeutics for the treatment of sepsis: why has nothing worked? Current parmaceutical design 2003.

[3] Touloumis A, et al. GEE for Multinomial Responses Using a Local Odds Ratios Parameterization. Biom 2013.

Disclosure: A. Richter, None; **A. Strangfeld**, AbbVie, Celltrion, Hospira, Bristol-Myers Squibb, MSD Sharp&Dohme, Pfizer, Roche, and UCB., 2,BMS, Merck-Sharp & Dohme, Pfizer, Roche, Sanofi-Aventis, 9; **P. D. M. Schneider**, Abbvie, Actelion, Merck Serono, Pfizer, Roche, 2,Abbvie, Roche, UCB, 5,Abbvie, Chugai, Roche, Pfizer, UCB, 8; **T. Klopsch**, None; **A. Kapelle**, MSD, UCB, Chugai Roche,, 5,Abbvie, Chugai, Roche, MSD, Pfizer, UCB,, 2,Amgen, Pfizer, Abbvie, Chugai, Roche., 9; **J. Kaufmann**, None; **A. Zink**, AbbVie, Celltrion, Hospira, Bristol-Myers Squibb, MSD Sharp&Dohme, Pfizer, Roche, and UCB., 2,BMS, Merck-Sharp & Dohme, Pfizer, Roche, UCB., 9; **J. Listing**, AbbVie, Celltrion, Hospira, Bristol-Myers Squibb, MSD Sharp&Dohme, Pfizer, Roche, and UCB., 2,Pfizer Inc, 5.

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Abstract Number: 3239

Response to Methotrexate Predicts Mortality in Rheumatoid Arthritis up to 30 Years

Carolin Krause[1], Siegfried Wassenberg[2], Rolf Rau[3], Gertraud Herborn[4], Juergen Braun[5] and Dietmar Krause[6], [1]University Munster, Munster, Germany, [2]Rheumaklinik, Themistocles Gluck hospital - Rheumazentrum Ratingen, Ratingen, Germany, [3]Expert in Rheumatology, Düsseldorf, Germany, [4]Evangelisches Fachkrankenhaus Ratingen, Ratingen, Greece, [5]Rheumazentrum Ruhrgebiet, Herne, Germany, [6]Dept. for Medical Informatics, Biometry and Epidemiology, Ruhr University, Bochum, Germany

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Session Type: ACR Concurrent Abstract Session

Session Time: 9:00AM-10:30AM

Background/Purpose:

Methotrexate (MTX) is considered as the anchor drug for the treatment of patients with rheumatoid arthritis (RA). MTX has been shown to reduce disease activity and decrease radiographic progression and mortality. Response to MTX treatment is known to predict long term outcomes over some years. However, it is not clear whether this effect becomes weaker in the long-term.

Methods:

We analysed data of one of the earliest MTX-cohorts in Europe (Evangelisches Fachkrankenhaus Ratingen, Germany)[1]. From 1980 to 1987, all patients starting treatment with MTX (n=271) were enrolled in a prospective observational study. One year after baseline, response to MTX-treatment was determined (improvement or no improvement of at least 20%). Re-evaluations were performed 10, 18, and 30 years after baseline. In 2015, outcomes of 192 patients (71%) could be assessed. Cox regression was applied to estimate risks for increased mortality. The Cox model included age, gender, rheumatoid factor, signs of disease activity at baseline (number of swollen joints, ESR), patient global assessment at baseline, and response to MTX treatment after one year.

Results:

30 years after baseline, 167 patients were deceased. A positive effect on mortality was seen for the response to MTX treatment after one year (hazard ratio (HR) 0.60; 95%-confidence interval (CI): 0.42-0.89, p = 0.007) (Table 1). Furthermore, in the group of patients still alive ten years after baseline continued MTX-treatment was associated with lower mortality (HR 0.95 per mg; 95%-CI: 0.91-0.98, p = 0.003) in the next 20 years.

Table 1. Predictors of all-cause mortality for the entire observation period

Variable	Hazard ratio	95% confidence interval	Chi-Square	p-value
Improvement ≥20% after the first year of MTX treatment	0.60	0.42 to 0.87	7.37	0.007
Age	1.09	1.07 to 1.11	76.3	<0.001
Female gender	0.76	0.52 to 1.10	2.11	0.146
RF positivity	1.20	0.71 to 2.02	0.44	0.507
No. of swollen joints at baseline (0 – 32)	1.01	0.99 to 1.03	0.77	0.379
ESR at baseline	1.00	0.99 to 1.01	2.40	0.121
Patient global assessment at baseline	1.20	0.80 to 1.81	0.80	0.370

RF: rheumatoid factor; MTX: methotrexate; ESR: erythrocyte sedimentation rate.

Conclusion:

In this cohort, response to MTX after one year of treatment was a predictor of lower mortality during the next 30 years. Continued MTX treatment after ten years was positively associated with lower mortality in the following 20 years.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/response-to-methotrexate-predicts-mortality-in-rheumatoid-

Abstract Number: 3240

Improved Survival in Rheumatoid Arthritis: A General Population-Based Study

Na Lu[1,2], Hyon K. Choi[3], Sara R. Schoenfeld[3], Christine Peloquin[4], Maureen Dubreuil[5], Sharan K. Rai[6], J Antonio Avina-Zubieta[7] and Yuqing Zhang[8], [1]Division of Rheumatology, Allergy & Immunology, Massachusetts General Hospital, Harvard Medical School, Boston, MA, [2]Boston University School of Medicine, Boston, MA, [3]Rheumatology, Allergy and Immunology, Massachusetts General Hospital, Harvard Medical School, Boston, MA, [4]Clinical Epidemiology Unit, Boston University School of Medicine, Boston, MA, [5]Rheumatology, Boston VA HealthCare System, Boston, MA, [6]Experimental Medicine, University of British Columbia, Vancouver, BC, Canada, [7]Arthritis Research Canada / University of British Columbia, Vancouver, BC, Canada, [8]BUSM, Boston, MA

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Session Type: ACR Concurrent Abstract Session

Session Time: 9:00AM-10:30AM

Background/Purpose: All-cause mortality in UK has been decline by almost 20% over the past two decades. While rheumatoid arthritis (RA) is associated with an increased risk of mortality [1], it is unknown whether RA patients has experienced similar trend of reduced mortality or even a greater reduction of mortality owing to the improvement of clinical management of RA (e.g., biologics use since middle of 2000's). To address this knowledge gap, we evaluated mortality trends among RA patients between January 1, 1999 and December 31, 2012 in a general population context.

Methods: Using The Health Improvement Network, an electronic medical record database representative of the UK general population, we identified individuals with incident cases of RA and up to 5 non-RA controls matched on sex, age, and year of RA diagnosis, between 1999 and 2012 (i.e., ≥ 1 year before the end of our dataset to allow for follow-up). The RA cohort was then divided in two cohorts based on the year of RA diagnosis (i.e., 1999-2005 and 2006-2012) to evaluate changes in mortality. The follow-up time of early cohort ended at the end of 2005 and late cohort ended at the end of 2012. We calculated hazard ratios for death using a Cox-proportional hazards model and the rate differences using an additive hazard model, adjusting for potential confounders (i.e., number of GP visits, body mass index, smoking, alcohol and Charlson Comorbidity Index). We tested if the effect of RA mortality varied according to time period by adding an interaction term (i.e., RA*period) into regression model.

Results: Among the early cohort (1999-2005) RA patients had considerably higher mortality rates than the late cohort (2006-2012) (i.e., 23.8 vs. 15.7 cases per 1000 person-years), as compared with only a moderate improvement in the general population between the two periods (14.1 vs. 11.1 cases per 1000 person-years). The adjusted mortality rate differences between two comparison cohorts was 9.7 (95% CI, 7.2-12.2) cases per 1000 person-years in the early cohort and 4.7 (95% CI, 2.9-6.4) cases per 1000 person-years in the late cohort (p for interaction <0.01). The corresponding HRs for all-cause mortality were 1.51 (95% CI, 1.33-1.72) in the early cohort and 1.21 (95% CI, 1.05-1.39) in the late cohort, respectively (p for interaction=0.027), suggesting that mortality reduction over time is more apparent among RA patients than that in the general population.

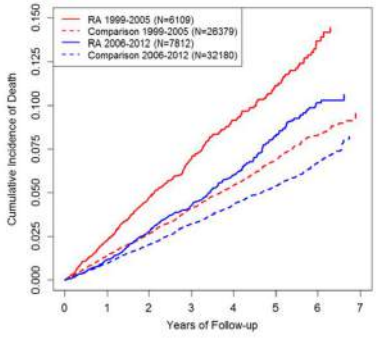
Conclusion: This study shows that survival of RA patients has improved over the past decade, suggesting that new treatments and improved management of complications and associated comorbidities may be providing substantial benefits.

References: 1. Annals of the Rheumatic Diseases 2014 Jan;73(1):149-153.

Table 1. Incidence Rates and Hazard Ratios (HR) for Associations between RA and Death According to cohort period

	RA Status	N	Deaths	Follow-up Time (person-years)	Mean Follow-up (years)	Incidence Rate (cases per 1000 person-years)	Age, Sex and Entry-time Matched HR (95%CI)	+ GPs visits, BMI, Smoking, Alcohol and Charlson index Adjusted HR (95%CI)
1999-2005	Yes	6109	400	16841.7	2.8	23.75 (21.48 to 26.20)	1.60 (1.41 to 1.81)	1.51 (1.33 to 1.72)
	No	26379	1045	74291.4	2.8	14.07 (13.23 to 14.95)	1.0 (reference)	1.0 (reference)
2006-2012	Yes	7812	351	22311.5	2.9	15.73 (14.13 to 17.47)	1.38 (1.22 to 1.58)	1.21 (1.05 to 1.39)
	No	32180	1026	92572.7	2.9	11.08 (10.42 to 11.78)	1.0 (reference)	1.0 (reference)
Female 1999-2005	Yes	4394	246	12085.3	2.8	20.36 (17.89 to 23.06)	1.62 (1.39 to 1.90)	1.59 (1.35 to 1.87)
	No	18925	632	53200.9	2.8	11.88 (10.97 to 12.84)	1.0 (reference)	1.0 (reference)
Female 2006-2012	Yes	5338	213	15632.7	2.9	13.63 (11.86 to 15.58)	1.38 (1.17 to 1.63)	1.25 (1.05 to 1.50)
	No	21931	604	64597.8	2.9	9.35 (8.62 to 10.13)	1.0 (reference)	1.0 (reference)
Male 1999-2005	Yes	1715	154	4756.4	2.8	32.38 (27.47 to 37.91)	1.56 (1.28 to 1.90)	1.37 (1.12 to 1.68)
	No	7454	413	21090.6	2.8	19.58 (17.74 to 21.56)	1.0 (reference)	1.0 (reference)
Male 1999-2005	Yes	2474	138	6678.9	2.7	20.66 (17.36 to 24.41)	1.39 (1.13 to 1.70)	1.15 (0.93 to 1.43)
	No	10249	422	27974.9	2.7	15.08 (13.68 to 16.60)	1.0 (reference)	1.0 (reference)

Figure 1. Cumulative Mortality of Rheumatoid Arthritis Patients and Comparisons in early and late cohorts (1999-2005 vs. 2006-2012, respectively)



Disclosure: N. Lu, None; **H. K. Choi**, None; **S. R. Schoenfeld**, None; **C. Peloquin**, None; **M. Dubreuil**, None; **S. K. Rai**, None; **J. A. Avina-Zubieta**, None; **Y. Zhang**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/improved-survival-in-rheumatoid-arthritis-a-general-population-based-study

Abstract Number: 3241

Do Boosters Support Long-Term Physical Activity Maintenance after an Intervention? a Systematic Review

Kathryn Remmes Martin[1], Chloé Charlotte Schröder[1,2] and Daniel Whibley[1], [1]Musculoskeletal Research Collaboration (Epidemiology Group), University of Aberdeen, Aberdeen, United Kingdom, [2]Faculty For Human and Health Sciences, University of Bremen, Bremen, Germany
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SESSION INFORMATION
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Session Type: ARHP Concurrent Abstract Session
Session Time: 9:00AM-10:30AM

Background/Purpose: Physical activity (PA) is an important health behaviour, particularly for individuals with rheumatic and musculoskeletal disease (RMD). While PA interventions can successfully increase PA levels, they often reduce over time post-intervention. One strategy for supporting PA maintenance is the introduction of a booster after an initial intervention, though this is less studied. This current review aims to identify whether evidence exists that supports the efficacy of booster components to support PA maintenance.

Methods: A systematic review was undertaken and used a search strategy designed to broadly detect articles focused on PA interventions and long-term maintenance. Eligibility criteria: randomized control trials including healthy community dwelling adults or those with RMD aged 25 years or older. Trials had to include a PA intervention at baseline for all subjects with subsequent randomization to either a booster or non-booster arm, and a PA outcome measure. Cohorts comprised exclusively of non-RMD clinically defined populations (e.g., cancer, diabetes) were excluded. Six electronic bibliographic databases were searched, including Medline and Cochrane Library, with no date restrictions (date of last search December 2014). Study quality and risk of bias were assessed in accordance with the *Scottish Intercollegiate Guidelines Network*. All stages were independently undertaken by reviewer pairs and consensus was reached after discussion for any discrepancy. A

narrative synthesis of results was undertaken.

Results: 16,664 unique studies were identified. After screening by journal, title and abstract, 47 full-text articles were assessed for eligibility, with eight included in the final synthesis. Of these, two were in the workplace, three focused on older adults, and one consisted of individuals with lower-extremity OA. Study duration ranged from 2 to 18 months and employed diverse PA outcome measures, including self-report questionnaires and/or objective markers (e.g., accelerometry). PA interventions included website, mail, in-person counselling, and exercise training sessions. Booster components included mail, email, telephone counselling calls. No identified studies reported significant differences between PA levels between booster and non-booster groups at long-term follow-up. Issues of low sample size/power and sources of bias found in quality assessment suggest definitive conclusions cannot be made.

Conclusion: A limited number of studies have compared boosters to a control group after a cohort has received the same PA intervention. There is a particular paucity of research focused on those with RMD and what is available is heterogeneous and of questionable quality. Evidence strongly supports PA as beneficial to those with RMD, however further research is required to elucidate the role of boosters in the role of supporting long-term maintenance. Attention should be given to the development and rigorous testing of boosters following intervention to support long-term maintenance of PA in RMD populations for sustained health and symptom benefit.

Disclosure: K. R. Martin, None; **C. C. Schröder**, None; **D. Whibley**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/do-boosters-support-long-term-physical-activity-maintenance-after-an-intervention-a-systematic-review

Abstract Number: 3242

A Comprehensive Method for Using Sensewear MiniTM Monitors to Explore Differences in Ambulatory Activities in People Living with and without Early Rheumatoid Arthritis: Moving Beyond Measuring Total Steps

Lynne Feehan[1,2,3], Jake McIvor[4], Ju Young Yoo[3] and Linda Li[3,5], [1]University of British Columbia, Vancouver, BC, Canada, [2]Rehabilitation Program, Fraser Health Authority, Surrey, BC, Canada, [3]Arthritis Research Canada, Richmond, BC, Canada, [4]Consultant, Arthritis Research Canada, Richmond, BC, Canada, [5]Physical Therapy, University of British Columbia, Vancouver, BC, Canada

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Background/Purpose: Measures of daily steps does not allow for examination of how steps are accumulated from different type or intensity of ambulatory activity, which is important information for designing physical activity interventions to support people living with arthritis to be more physically active. Our study aimed to: 1) introduce an approach for more comprehensive evaluation of ambulatory activities using Sensewear Mini ^{TM} (SW) monitor data, and 2) demonstrate how this analytical approach could be used to explore differences in intensity of ambulation across 1-year in people living with and without early rheumatoid arthritis (RA).

Methods: RA participants had a physician diagnosis of RA within the last year and were matched with age and gender peers living without RA. All participants wore the SW monitor for 7-days at baseline and 12 months later. Off body and non-ambulatory minutes are excluded to allow for evaluation of minutes of ambulatory activity, including: 1) daily ambulation, 2) intensity of ambulation, 3) type of ambulation, and 4) time of ambulation (Figure 1). To demonstrate how this analytical approach could be used we explored difference in daily ambulation and intensity of ambulation with Paired T-tests at baseline and 12 month follow up.

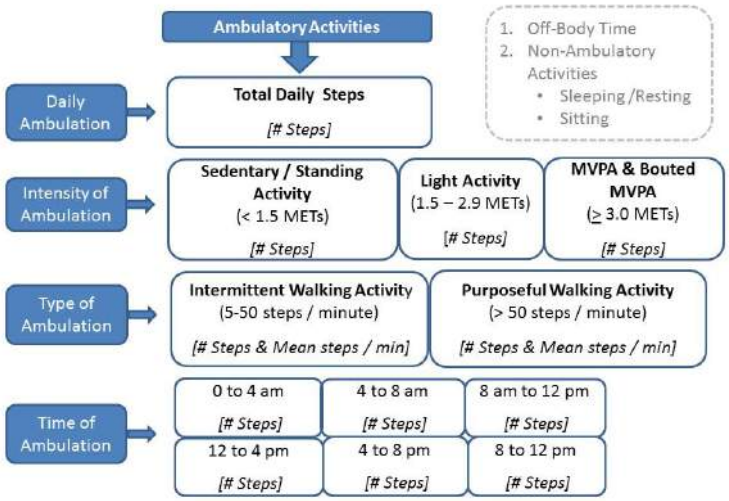

Figure 1: Ambulatory Activity Evaluation Framework (SenseWearMini™ Monitor)

Results: At baseline RA participants [n=27, Age: mean 53 y (21-73 y). Female: 22] acquired significantly fewer total daily steps than their peers (n=27). However, when examined across intensity of activity RA participants actually had markedly more steps acquired from sedentary and light ambulatory activity and significantly fewer steps from moderate to vigorous intensity ambulatory activity. One year later differences in total daily steps between RA and Non-RA participants (n=46, 23 pairs) was no longer significant. However, when examined across intensity of activity similar trends for differences in ambulatory activity seen at baseline remained (e.g. RA more sedentary / light vs less MVPA steps), with the most notable difference being RA acquiring significantly more steps from light intensity ambulatory activity (Table 1).

Table 1: Summary of Selected Comparisons of Ambulatory Activity (Paired T-Test, two tailed) in People Living With and Without Early Rheumatoid Arthritis (RA) [Baseline and 12-month follow up]

Ambulatory Activity Examined	Non-RA [Mean (SEM)]	RA [Mean (SEM)]	* Difference (Non-RA-RA). [Mean (SEM)]	P value
Selected Ambulatory Activity Comparison: (n=54, 27 Pairs) - Baseline				
Total Daily Steps (#)	9819 (744.9)	6855 (598.2)	2964 (893.5)	<0.001
Sedentary - Standing Steps (#)	741 (88.7)	1186 (185.1)	- 445 (230.5)	0.07
Light – Steps (#)	2441 (137.5)	3073 (312.4)	-632 (358.0)	0.09
MVPA 3+ METs – Steps (#)	6581 (783.0)	2509 (437.5)	4072 (891.5)	<0.001
MVPA 3+ METs Bouted (>=10 min,±2) – Steps (#)	5540 (737.9)	1805 (399.3)	3735 (826.7)	<0.001
Selected Ambulatory Activity Comparison: (n=46, 23 Pairs) – 12 Month Follow-up				
Total Daily Steps (#)	8716 (698.4)	8075 (794.7)	641 (1039.2)	0.54
Sedentary - Standing Steps (#)	833 (119.1)	1080 (170.9)	-247 (213.0)	0.26
Light – Steps (#)	2313 (131.2)	3511 (400.1)	-1198 (428.6)	0.01
MVPA 3+ METs – Steps (#)	5444 (723.1)	3592 (729.3)	1852 (1030.0)	0.09
MVPA 3+ METs Bouted (>=10 min,±2) – Steps (#)	4607 (672.3)	2633 (683.5)	1974 (939.9)	0.05

* Negative value indicates Non-RA less than RA. No correction for multiple comparisons

Conclusion: A more comprehensive evaluation of ambulatory activities allows for examination of differences (or change) in ambulatory activities that would not otherwise be detected with measures of total daily steps. Moving beyond measuring daily steps to evaluations of intensity, type and timing of ambulatory activities can inform clinical and research initiatives aimed at supporting individuals living with arthritis to move more and sit less.

Disclosure: L. Feehan, None; **J. McIvor**, None; **J. Y. Yoo**, None; **L. Li**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/a-comprehensive-method-for-using-sensewear-minitm-monitors-to-explore-differences-in-ambulatory-activities-in-people-living-with-and-without-early-rheumatoid-arthritis-moving-beyond-measuring-total-s

Abstract Number: 3243

A Randomized Controlled Trial for a Physical Activity Intervention for RA Fatigue

Patricia P. Katz[1], Mary Margaretten[2], Steven Gregorich[1], Sandi Kaplan[3], Stephanie Rush[4] and Laura Trupin[1], [1]Medicine, University of California San Francisco, San Francisco, CA, [2]Medicine, University of California, San Francisco, San Francisco, CA, [3]Arthritis Research Group, University of California, San Francisco, CA, [4]University of California, San Francisco, San Francisco, CA
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Background/Purpose: Fatigue is a major problem for people with RA. Physical inactivity is an indirect risk factor for fatigue[1]. We tested the effect of a simple pedometer-based physical activity intervention to reduce fatigue in people with RA.

Methods: Individuals with rheumatologist-diagnosed RA were recruited from previous studies or rheumatology clinics. Eligibility criteria were: English- or Spanish-speaking, able to walk, able to return for study visits, at least moderate level of fatigue, and not currently engaged in regular exercise. Eligible individuals completed baseline questionnaires and received activity-monitoring devices for a one-week baseline step count. After one week, subjects returned and were randomized into one of three groups: (1) Education only (control), (2) Pedometer and step diary, or (3) Pedometer, step diary, and step targets. Step targets were based on the baseline step counts with the goal of increasing steps by 10% every two weeks. Groups 2 and 3 received phone calls every two weeks to collect step diary information and, for Group 3, to assign new step targets. Follow-up assessments were made at Week 10 (by phone) and Week 21 (in person). The primary outcome was fatigue measured with the PROMIS Fatigue short-form. Changes in the number of steps and in fatigue were tested within each group using paired t-tests and across groups with linear regression using Group 1 (education only) as the reference group.

Results: 359 individuals were approached to participate; 91 refused before screening, 150 were ineligible, and 22 were eligible but refused, leaving 96 participants. Mean ±SD age of participants was 54 ±13 years, 88% were female, and 21% were Spanish-speaking. Mean RA duration was 14 ±13 years. At baseline, mean RA Disease Activity Index (RADAI) was 4.1 ±1.9, mean HAQ was 1.34 ± 0.65, 59% were currently using glucocorticoids, and 60% were currently receiving biologics. Overall, the median of the average number of daily steps at baseline was 3710 (<5000 is considered “sedentary”) and mean fatigue score was 59.0 ±6.9. At 21 weeks, both intervention groups had significant increases in mean daily steps compared to the control group ($p<.05$; table). Only Group 3 achieved a significant increase in steps as a proportion of baseline. Both intervention groups had significant and meaningful decreases in fatigue ($p<.05$, table). Across all groups, decreases in fatigue were correlated with the percentage increase in average daily steps ($r = -0.37$, $p = .005$).

Conclusion: A low-resource, pedometer-based physical activity intervention yielded significant increases in physical activity and significant decreases in fatigue among individuals with RA. Results suggest that increasing physical activity by prescribing a pedometer can be effective for reducing fatigue, particularly among individuals with very low activity levels initially.

[1]Katz et al. Arthritis Care Res [epub 2015 Mar 16]

	Group 1: Education	Group 2: Pedometer	Group 3: Pedometer + step targets
N (at baseline)	28	34	34
Baseline steps			
Median (IQR)	5055 (3162, 7842)	2956 (1847, 5189)	3417 (1988, 6693)
Mean ± SD	5653 ± 3823*	3653 ± 2484	5418 ± 5214
Baseline fatigue†	57.6 ± 7.6	59.7 ± 6.5	60.0 ± 6.4
Changes, baseline to 21 weeks			
Δ steps (number)	-327 ± 2429 (p = .53)§	2132 ± 2698 (p = .002)	1299 ± 2389 (p = .02)
Δ steps (% increase from baseline)	3% ± 56	92% ± 125	188% ± 506
Δ fatigue	-2.3 ± 8.4 (p = .23)	-3.8 ± 7.6 (p = .04)	-5.1 ± 9.2 (p = .02)

* All values are mean ± SD except median (IQR) of baseline steps

† PROMIS Fatigue scores have a population mean of 50 and standard deviation of 10. Higher scores reflect greater fatigue.

§ p-values obtained from paired t-test comparing baseline and 21-week follow-up within each group.

Disclosure: P. P. Katz, None; **M. Margaretten**, None; **S. Gregorich**, None; **S. Kaplan**, None; **S. Rush**, None; **L. Trupin**, None.

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Abstract Number: 3244

Evaluation of a Self-Directed Walking Program in Hispanics with Arthritis

Leigh F. Callahan[1], Alfredo Rivadeneira[2], Mary Altpeter[3], Rebecca J. Cleveland[4], Betsy Hackney[1], Leigha Vilen[2], Victoria Sepulveda[4], Daniel S Reuland[5] and Claudia Rojas[4], [1]Thurston Arthritis Research Center, University of North Carolina, Chapel Hill, NC, [2]Thurston Arthritis Research Center, University of North Carolina at Chapel Hill, Chapel Hill, NC, [3]Institute on Aging, University of North Carolina at Chapel Hill, Chapel Hill, NC, [4]University of North Carolina at Chapel Hill, Chapel Hill, NC, [5]Department of Internal Medicine, University of North Carolina at Chapel Hill, Chapel Hill, NC

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Background/Purpose: *Walk with Ease* (*WWE*) is the Arthritis Foundation's (AF) 6-week evidence-based walking program for adults with arthritis that can be offered in 2 formats: 1) a group led by a trained instructor; 2) or self-directed using only the workbook. Both formats have been shown to improve physical function, pain, stiffness, fatigue and self-efficacy in non-Hispanic (NH) white and black individuals with arthritis. The AF translated and modified the workbook for Hispanics, *Camine con Gusto* (*CCG*). The purpose of this study was to examine

feasibility (recruitment), tolerability (retention, adherence), safety (adverse events), acceptability (satisfaction), and efficacy (effect sizes [ES]) of the self-directed version of *CCG*.

Methods: A simple pre and post 6-week evaluation with no usual care comparison group was conducted in 285 Hispanics in North Carolina (NC). Self-reported outcomes including symptoms (pain, stiffness, and fatigue visual analog scales [VAS]), performance of activities of daily living (HAQ), perceived helplessness (RAI), and self-efficacy in arthritis management (ASE) were evaluated. Means and effect sizes (ES) with 95% confidence intervals were computed for changes in symptoms between baseline and 6 weeks, adjusted for gender, age, education, body mass index (BMI), comorbidities, and baseline outcome. Multiple imputation was carried out for covariates due to a large amount of missing data for BMI (22%).

Results: The mean age of the participants was 46.9 years, 44% had less than a high school degree, 2% were born in the USA, 60.1% spoke only Spanish, 74.7% were female, 44.6% had a BMI ≥ 30. Feasibility was demonstrated by recruitment and retention of 255 (84% completed 6 week questionnaires) participants, safety established with no adverse events, acceptability with 98% of participants reporting program satisfaction, and promise with moderate ES of 0.50 for pain, 0.75 for fatigue, 0.49 for stiffness, 0.33 for the HAQ, 0.26 for RAI, and 0.24 for ASE (see Table). Efficacy was greatest for individuals who reported walking at least 5 days per week (data not shown).

Conclusion: The self-directed CCG showed promise of self-reported outcomes in Hispanics comparable to those noted in NH white and black individuals with self-reported arthritis.

Table 1. *CCG* baseline characteristics of participants who completed the 6-week follow-up*

Characteristic	Statistic
Age, mean ± SD	46.9 ± 11.0
Education, % < HS	44.4
Born in USA, %	2.5
Only Speak Spanish, %	60.1
Female, %	74.7
Body mass index, % ≥ 30 kg/m^2	45.4
Number of comorbidities, mean ± SD	1.23 ± 1.54
Self-reported function	
General Health, % fair-poor	47.3
HAQ (range 0-3), mean ± SD	0.41 ± 0.44
Symptoms VAS (range 0-100), mean ± SD	
Pain	54.2 ± 25.7
Fatigue	45.2 ± 30.2
Stiffness	44.6 ± 29.1
Psychosocial	
Rheumatology Attitudes Index (range 0-4), mean ± SD	1.43 ± 0.92
Arthritis Self Efficacy (range 1-10), mean ± SD	7.31 ± 2.14

HAQ: Health Assessment Questionnaire
VAS: visual analog scale
*Analysis includes only participants who completed follow-up measures at 6 weeks (n=255)

Table 2. *CCG* covariate-adjusted† means (SD) for baseline and follow-up measures¥

Health Status Outcomes	Difference from Baseline (95% Confidence Interval)	Effect Size (95% Confidence Interval)
Symptoms		
VAS (range 0-100)		
Pain	n=227	
Baseline Mean (±SD)	57.45 (18.86)	
Follow-up Mean (±SD)	40.93 (43.03)	
Change (95% CI)	-16.6 (-22.2,-11.0)‡	0.50 (0.35,0.65)
Fatigue	n=222	
Baseline Mean (±SD)	49.73 (11.93)	
Follow-up Mean (±SD)	33.42 (28.14)	
Change (95% CI)	-15.5 (-19.2,-11.8)‡	0.75 (0.56,0.95)
Stiffness	n=219	
Baseline Mean (±SD)	47.56 (27.60)	
Follow-up Mean (±SD)	31.71 (36.45)	
Change (95% CI)	-15.8 (-20.7,-11.0)‡	0.49 (0.31,0.67)
Self-reported Function		
HAQ (range 0-3)	n=222	
Baseline Mean (±SD)	0.46 (0.54)	
Follow-up Mean (±SD)	0.30 (0.39)	
Change (95% CI)	-0.16 (-0.21,-0.11)‡	0.33 (0.14,0.51)
Psychosocial		
Rheumatology Attitudes Index (range 0-4)	n=214	
Baseline Mean (±SD)	1.47 (0.56)	
Follow-up Mean (±SD)	1.22 (1.19)	
Change (95% CI)	-0.22 (-0.38,-0.06)‡	0.26 (0.08,0.45)
Arthritis Self Efficacy (range 1-10)	n=222	
Baseline Mean (±SD)	7.18 (2.54)	
Follow-up Mean (±SD)	7.79 (2.55)	
Change (95% CI)	0.66 (0.33,1.00)‡	0.24 (0.07,0.42)

†Adjusted for gender, age, education, BMI, comorbidities, and baseline outcome
study site adjusted for as a random effect

¥Sample restricted to those who completed the 6-week follow-up (n=255)

‡ $p < 0.01$ difference from baseline to 6 weeks

Missing values for covariates multiply imputed

HAQ: Health Assessment Questionnaire; VAS: visual analog scale

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Disclosure: L. F. Callahan, None; **A. Rivadeneira**, None; **M. Altpeter**, None; **R. J. Cleveland**, None; **B. Hackney**, None; **L. Vilen**, None; **V. Sepulveda**, None; **D. S. Reuland**, None; **C. Rojas**, None.

Abstract Number: 3245

Factors Associated with Physical Activity in Older Children with Juvenile Idiopathic Arthritis

Jennifer R. Horonjeff[1], Shira Weiner[2], Susan Klepper[3], Ali Sheikhzadeh[2], Philip Kahn[4] and Sherri Weiser[2], [1]Ergonomics and Biomechanics, New York University, New York, NY, [2]Orthopedics, New York University, New York, NY, [3]Physical Therapy Program, Columbia University,

New York, NY, [4]Pediatric Rheumatology, New York University, New York, NY
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Background/Purpose: The purpose of this study was to examine factors associated with physical activity (PA) in children with JIA. PA is important for the physical, psychological and social development of all children. In children with JIA, PA can also improve disease sequelae, yet previous literature has reported that this population has lower PA levels than their healthy peers. There is little research regarding what keeps children with JIA from being active outside of disease-related physical impairments, such as pain and stiffness. There is a large body of research on healthy children that supports a biopsychosocial analysis of PA and suggests the importance of physical, psychological and social factors. The present study examined the relationship between PA in children with JIA and three modifiable factors—gross motor proficiency (GMP), perceived physical competence and parent-perceived physical competence of the child—which were derived from a biopsychosocial model reported in the literature on healthy children.

Methods: This cross-sectional study sampled 40 children with JIA between 8-12 years old. Demographic and clinical variables were collected through self-reports. GMP was collected using the Bruininks-Oseretsky Test of Motor Proficiency, 2nd edition. The results were compared to a normative sample using a one-sample t-test. The revised 38-question Child Health Assessment Questionnaire was used as a measure of perceived physical competence using a self-report for the child and a proxy-report for the parent. PA level was collected using the Intensity Score of the Children's Assessment of Participation and Enjoyment. Spearman's rho correlations examined associations between variables and logistic regression examined the associations of the independent variables with PA level. The relationships of weight percentile, pain level and disease duration with PA in the sample were examined for use as covariates.

Results: The study subjects had significantly impaired GMP compared to a normative sample ($p<0.001$). Of the three independent variables, only GMP was associated with PA levels in the sample ($p=0.01$). GMP was also related to the parent's perception of the child's physical competence ($p=0.04$), but not related to the child's self-perceived competence. The perception of physical competence of the parent and the child were related to each other ($p=0.001$), but significantly different ($p=0.04$). Weight percentile, disease duration and pain level were not associated with PA.

Conclusion: This study found GMP was both significantly impaired as well as strongly associated with PA levels. These findings may have developmental and safety implications in this population. Although the perception of physical competence of the parent and the child were not directly related to the outcome, significant associations among the independent variables suggest that they may still influence PA in this population. Future researchers should continue to build upon these results and explore what other variables may influence PA in children with JIA using a biopsychosocial approach, which may be different from what affects the healthy population.

Disclosure: J. R. Horonjeff, None; **S. Weiner**, None; **S. Klepper**, None; **A. Sheikhzadeh**, None; **P. Kahn**, None; **S. Weiser**, None.

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Abstract Number: 3246

Does Loss of a Community Walking Speed Lead to More Symptoms of Depression in Knee OA? a Trajectory Analysis from the Osteoarthritis Initiative

Daniel White[1], Tuhina Neogi[2], Yuqing Zhang[3], Jingbo Niu[4] and Patricia P. Katz[5], [1]Department of Physical Therapy, University of Delaware, Newark, DE, [2]Clinical Epidemiology, BUSM, Boston, MA, [3]BUSM, Boston, MA, [4]Clinical Epidemiology Research and Training Unit, Boston University School of Medicine, Boston, MA, [5]Rheumatology, UCSF, SF, CA
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Background/Purpose: Knee osteoarthritis (OA) is a well-known risk factor for major depression. While major limitations, e.g., inability to walk, are thought to mediate this relationship, it is not known to what extent minor limitations, i.e., not walking at a community speed, may

contribute to depressive symptoms. The purpose of this study was to investigate the association of minor and major limitations in walking speed with trajectories of depressive symptoms among people with or at high risk of knee OA.

Methods: We utilized data from the Osteoarthritis Initiative (OAI) to describe trajectories of depressive symptoms over 84-months. Depressive symptoms were measured annually with the Center for Epidemiologic Studies Depression Scale (CES-D) which ranges from 0 to 60, with higher scores representing more depressive symptoms. We included only participants with CES-D < 16, which represents those without major depression. Gait speed was measured from the 20-meter walk test at baseline. We categorized 'No limitation' as ≥ 1.2 meters/second (m/s) which represents the minimum time needed to walk across a timed crosswalk, i.e., a community walking speed; 'Minor limitation' as < 1.2 m/s and ≥ 1.0 m/s; and 'Major limitation' as < 1.0 m/s which is associated with persistent functional limitation, hospitalization, and death. To describe trajectories of depressive symptoms, we used a group-based method (PROC TRAJ) to agnostically identify homogeneous clusters of developmental trajectories in OAI. We then examined the relation of gait speed categories with depressive symptom trajectories using multinomial logistic regression adjusting for age, sex, BMI, race, education, radiographic knee OA, and intensity of knee pain.

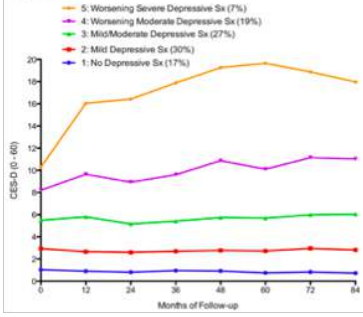
Results: From the 3801 participants included (age 61.4 ± 9.1, BMI 28.4 ± 4.7, 57.5% women, 64% college degree), we identified five depressive symptom trajectories. The first three trajectories were stable over time and had baseline values < 6, on average, and included 74% of the sample. The 4th and 5th trajectories had worsening scores, increasing 0.4 and 1.0 points/year on the CES-D and included 19% and 7% of the sample, respectively. Study participants with minor limitation had 1.7 and 1.9 times the adjusted risk of being in the 4th and 5th trajectory groups, respectively. Compared with those without limitation, those with major limitation had 2.7 and 3.6 times the adjusted risk of being in the 4th and 5th trajectory groups, respectively. (Table)

Conclusion: Loss of the ability to walk a community speed appears to signal risk for worsening worsening depressive symptoms over time in people with or at high risk of knee OA. Maintaining walking speeds adequate to cross the street safely in the community may be important to consider in order to maintain psychological well-being among people with knee OA.

Association of gait speed with depressive symptoms trajectory groups among those with with CES-D < 16 at baseline. Adjusted* Odds Ratio (OR) and 95% Confidence Interval (CI). Gait speed was categorized as no limitation >1.2 m/s; minor limitation 1.0 m/s to 1.2 m/s; and major limitation < 1.0 m/s.

Trajectory Group (n=3810)	No limitation[%]	Minor limitation[%]	Major limitation[%]	Adjusted* OR [95% CI] Minor vs No limitation	Major vs No limitation
1: 17%	84.6	13.2	2.2	1.0 Ref	1.0 Ref
2: 30%	78.1	17.9	4.1	1.3 [1.0, 1.7]	1.6 [0.8, 2.9]
3: 27%	74.0	21.2	4.8	1.4 [1.1, 1.9]	1.7 [0.9, 3.1]
4: 19%	67.6	24.7	7.8	1.7 [1.2, 2.3]	2.7 [1.4, 5.0]
5: 7%	65.0	25.7	9.3	1.9 [1.3, 2.9]	3.6 [1.8, 7.2]

*Adjusted for age, sex, BMI, race, education, radiographic knee OA, and intensity of knee pain.



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Abstract Number: 3247

Dietary Intake of Omega-3 Fatty Acids and Vitamin C and D Associate with Decreased Pain, Independent of Inflammation, in MTX Treated Early RA Patients

Cecilia Lourdudoss[1], Alicja Wolk[2], Lars Alfredsson[3], Lars Klareskog[4], Ronald F. van Vollenhoven[5] and Jon Lampa[6], [1]Dept. of Medicine, ClinTRID, Karolinska institutet, Stockholm, Sweden, [2]Institute of Environmental Medicine (IMM), Karolinska institutet, Stockholm, Sweden, [3]The Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden, [4]Department of Medicine, Karolinska University Hospital, Stockholm, Sweden, [5]Department of Medicine, Unit for Clinical Therapy Research, Inflammatory Diseases (ClinTRID), The Karolinska Institute, Stockholm, Sweden, [6]Dep of Medicine, Rheumatology unit, Karolinska Institute, Karolinska Institute, Stockholm, Sweden
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Background/Purpose:

Chronic pain is common in RA and considered as the major disease burden from the patients' perspective. Earlier data suggest that omega-3 fatty acids, vitamin D and vitamin C are anti-inflammatory and can decrease disease activity in RA. Also, excessive intake of omega-6 fatty acids has been linked with inflammation. However, little is known how these dietary factors may affect pain in RA. Our aim was to study the association between diet and pain, in spite of inflammation, after three months of MTX treatment in early RA patients.

Methods:

We included newly diagnosed RA patients with MTX monotherapy from Epidemiological Investigation of Rheumatoid Arthritis (EIRA) linked to clinical data in the Swedish Rheumatology Quality register (SRQ). Dietary data based on food frequency questionnaires were linked with data on pain after three months of MTX treatment. Pain in spite of inflammatory control (remaining pain) was defined based on the patient acceptance of symptoms scale (PASS) (1) together with low systemic inflammation (VAS>40 + CRP<10) at the three months follow-up. Associations between dietary nutrient intake and remaining pain were analyzed with logistic regression, adjusted for age, sex and BMI.

Results:

This study included 628 RA patients. 70.1% were females and the median age was 55 years. 68.0% were ACPA positive. Mean values for clinical measures: DAS28 5.1, VAS pain 53.8 and HAQ 1.0. All patients received MTX monotherapy and the mean BMI was 25.8 kg/m^2.

After three months of MTX treatment, 103 patients (16.4%) had remaining pain. Higher intake of omega-3, vitamin D and vitamin C were inversely associated with remaining pain (OR=0.4[95% CI: 0.2-0.7], OR=0.5[95% CI: 0.3-0.8] and OR=0.5[95% CI: 0.3-0.9], respectively), whereas a higher omega-6:3 ratio was associated with increased risk of remaining pain (OR=2.7[95% CI: 1.6-4.7]). Adjustment for ACPA status did not change the ORs markedly.

Conclusion:

Intake of anti-inflammatory fatty acids and antioxidants are known to affect disease activity, and here we show that also pain may be affected, regardless of inflammation. Our findings reflect an inverse association between increased intake of omega-3, vitamin D and vitamin C, respectively and remaining pain. In addition, higher omega-6:3 ratio was found to associate with increased pain. These effects were independent of inflammation. Altogether, our data indicate that omega-3, vitamin D and vitamin C may dampen the development of chronic pain in early RA.

Reference:

1. Tubach F et al, Arthritis Care Res (Hoboken). 2012;64(11):1699-707.

Disclosure: C. Lourdudoss, None; **A. Wolk**, None; **L. Alfredsson**, None; **L. Klareskog**, None; **R. F. van Vollenhoven**, None; **J. Lampa**, None.

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Abstract Number: 3248

Which Factors Explain Multi-Site Pain Caused By Obesity: A 5-Year Follow-up Study in Older Adults?

Feng Pan[1], Laura Laslett[2], Russell Thomson[2], Tania Winzenberg[3], Flavia Cicuttini[4], Changhai Ding[5] and Graeme Jones[5], [1]Musculoskeletal Unit, Menzies Institute for Medical Research, University of Tasmania, Hobart,7000, Australia, [2]Menzies Institute for Medical Research, University of Tasmania, Hobart, Australia, [3]Menzies Institute for Medical Research, University of Tasmania, Hobart,7000, Australia, [4]Department of Epidemiology and Preventive Medicine, Monash University, Melbourne, Australia, [5]Musculoskeletal Unit, Menzies Institute for Medical Research, University of Tasmania, Hobart, Australia
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Background/Purpose: Joint pain is common in older adults; typically multiple joints are involved. Obesity is an important risk factor in pathogenesis of multi-site joint pain (MSJP). Potential mechanisms include increased physical loading and systemic inflammation, but may also include genetic factors. However, whether the effects of fat mass on pain are related to loading or to systemic inflammation is unclear. There may also be other underlying mechanisms involved in the association between obesity and pain. Therefore, this study aimed to determine longitudinal associations between fat mass and MSJP; and to determine genetic correlation between heritability of body mass index (BMI) and knee pain.

Methods: Longitudinal population-based Tasmanian Older Adult Cohort study of older adults (n=1099). Presence of pain (yes/no) at the neck, back, hands, shoulders, hips, knees and feet was assessed by questionnaire at baseline and after 2.6 and 5.1 years. Fat mass was assessed at baseline using dual energy x-ray absorptiometry. Longitudinal data was analysed using mixed effect models, adjusting for age, sex, physical activity, educational and occupational status, and quality of life. 748 samples typed on the exome chip yielded 266,163 single nucleotide polymorphisms (SNPs). The genetic correlation between BMI and knee pain measured by WOMAC was estimated using genome-wide complex trait analysis software.

Results: Study participants were older adults (average age 63 years; range 51 to 81 years). 58% of participants reported pain at >2 sites. Participants reporting greater number of painful sites had higher baseline fat mass and BMI. Greater fat mass was associated with greater odds of MSJP (odds ratio [OR] 1.007; 95% confidence interval [CI] 1.002, 1.011), pain in lower limbs (knee, hip and feet) (OR= 1.042 to 1.077, all P≤0.002), and hand pain (OR 1.027; 95% CI 1.000 to 1.055), after adjustment for confounders. Results were similar with BMI as the outcome. Estimates of heritability (h2) accounted for by the SNPs were 83% for BMI and 72% for knee pain. The genetic correlation between BMI and knee pain was 8% independent of age, sex and principal components (P=0.003).

Conclusion: High fat mass and high BMI independently predict MSJP, lower limb pain and hand pain, suggesting that systemic inflammatory factors are more important than loading in the pathogenesis of pain at multiple sites. Genetic correlation between BMI and knee pain support the importance of genetic factors in pain pathogenesis.

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Abstract Number: 3249

Pooled Efficacy and Safety from Phase 3 Controlled Studies of Tanezumab in Patients with Osteoarthritis

Leslie Tive[1], David Radin[2], Alfonso Bello[3], Ha Nguyen[1], Mark T. Brown[4], Christine R. West[4] and Kenneth M. Verburg[4], [1]Pfizer, Inc, New York, NY, [2]Stamford Therapeutics Consortium, Stamford, CT, [3]Illinois Bone & Joint Inst, Glenview, IL, [4]Pfizer Inc., Groton, CT

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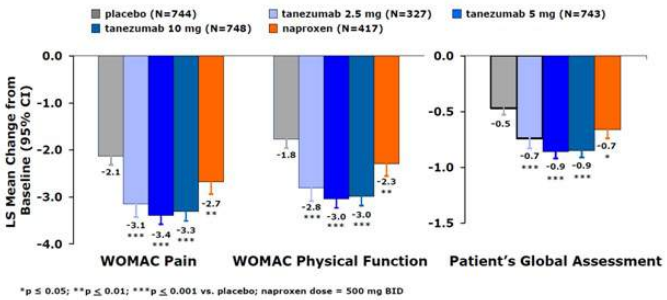
Session Time: 11:00AM-12:30PM

Background/Purpose: Tanezumab (TNZ) significantly reduces pain and improves physical function and Patient's Global Assessment (PGA) in patients with chronic pain. From June 2010 to August 2012 the US FDA imposed a partial clinical hold on noncancer pain-related studies due to unexpected adverse events initially reported as osteonecrosis that required total joint replacement. **Methods:** Four, phase 3 placebo (PBO)-controlled clinical trials of TNZ in patients with moderate-to-severe OA of the knee or hip completed before the clinical hold were pooled to evaluate efficacy and 9 phase 3 controlled OA studies were pooled to evaluate safety. Patients received 1 to 3 injections of intravenous TNZ 2.5, 5, or 10 mg every 8 weeks, naproxen 500 mg twice daily (BID), celecoxib 100 mg BID, oxycodone controlled release 10-40 mg BID, or PBO. Efficacy was assessed using WOMAC pain and WOMAC physical function subscales and PGA of OA as co-primary endpoints; ≥30%, ≥50%, ≥70%, and ≥90% improvement on WOMAC Pain subscale were secondary endpoints. Safety assessments included adverse event documentation and physical and neurologic examinations. Patients who reported abnormal peripheral sensation and/or had clinically significant neurologic exam findings underwent neurologic consultation. Subgroup analyses were also conducted on the pooled populations. **Results:** In the overall population, TNZ 2.5-10 mg provided significant improvement in all efficacy endpoints (p≤0.05; Figure). More patients treated with TNZ 5 or 10 mg reported pain improvement ≥30%, ≥50%, ≥70%, and ≥90% (p≤0.05 for all). Substantial increases in efficacy were not noted for TNZ 10 mg over TNZ 5 mg. Incidence of adverse events in TNZ-treated patients was similar to patients receiving active comparator and increased over PBO-treated patients; rates with TNZ 5 and 10 mg were similar and elevated vs TNZ 2.5 mg. Adverse events of abnormal peripheral sensation were reported more frequently by patients receiving TNZ vs PBO or active comparator. Most TNZ-treated patients whose final neurologic consultations were categorized as having a new or worsening peripheral neuropathy based on clinically significant signs or

diagnostic tests were diagnosed with some form of mononeuropathy, predominantly carpal tunnel syndrome or radiculopathy; few patients were diagnosed with a polyneuropathy. TNZ 10 mg but not 2.5 or 5 mg was associated with a higher rate of rapidly progressive OA than active comparator. **Conclusion:** TNZ provides significant improvement of pain, physical function, and PGA of OA. Non-joint-related safety was similar in patients treated with TNZ 2.5-10 mg versus active comparator but increased versus PBO-treated patients.

Figure. Changes in the primary endpoints for the overall population in 4 pooled studies.



Disclosure: L. Tive, Pfizer Inc, 3,Pfizer Inc, 1; **D. Radin**, None; **A. Bello**, None; **H. Nguyen**, Pfizer Inc, 1,Pfizer Inc, 3; **M. T. Brown**, Pfizer Inc, 1,Pfizer Inc, 3; **C. R. West**, Pfizer Inc, 1,Pfizer Inc, 3; **K. M. Verburg**, Pfizer Inc, 1,Pfizer Inc, 3.

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Abstract Number: 3250

Systemic Inflammation and Pain Sensitization in Knee Osteoarthritis: The Multicenter Osteoarthritis Study

Tuhina Neogi[1], Laura Frey-Law[2], Devyani Misra[1], Michael C. Nevitt[3], Lars Arendt-Nielsen[4], Emily K. Quinn[5] and Cora E. Lewis[6], [1]Clinical Epidemiology Research and Training Unit, Boston University School of Medicine, Boston, MA, [2]UIowa, Iowa City, IA, [3]Epidemiology and Biostatistics, UCSF, San Francisco, CA, [4]Aalborg University, Aalborg, Denmark, [5]Data Coordinating Center, Boston University School of Public Health, Boston, MA, [6]Preventive Medicine, University of Alabama at Birmingham, Birmingham, AL
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SESSION INFORMATION
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Background/Purpose: Pain sensitization is associated with pain severity in knee osteoarthritis (OA), but its cause in humans is not well-understood. We recently demonstrated that local inflammation at the joint could lead to pain sensitization. Whether inflammation systemically could do the same is not known, and data from animal models are sparse. Knee OA, considered to be a state of potentially low-grade inflammation, is also associated with obesity, which itself can contribute to systemic inflammation through elaboration of adipokines such as leptin and adiponectin, which are expected to have opposite effects to one another. We therefore evaluated whether systemically measured inflammatory cytokines and/or adipokines may be related to pain sensitization in knee OA.

Methods: Participants from the Multicenter Osteoarthritis (MOST) Study, a NIH-funded longitudinal prospective cohort of persons with or at risk of knee OA, had plasma stored and standardized pressure pain threshold (PPT) at the wrist and patellae assessed at the 60-month visit. PPT was assessed with an algometer (1 cm^2 tip, 0.5 Kg/sec) as the point at which the subject felt the pressure change to slight pain. Lower PPT indicates more sensitivity. We measured TNF-α (Linco multiplex), leptin and total adiponectin (R&D ELISA for both) from a random sample of participants who were free of knee replacement. We evaluated the sex-specific cross-sectional relation of each inflammatory marker to PPT using linear regression (PPT was normally distributed) with GEE to adjust for correlations between two knees within a person, adjusting for relevant potential confounders (age, race, BMI, pain medications, depressive symptoms, radiographic knee OA (ROA) in either knee). We repeated analyses stratified by ROA status.

Results: There were 750 subjects randomly selected from the 60-month MOST study visit among those who had bilateral native knees (mean age (SD) 66.8 (7.6), mean BMI 30.3 (5.8), 58% female, 44.8% knees with radiographic knee OA). Plasma levels of TNF-α were not associated with PPT at either site (**Table**). Leptin and total adiponectin were both associated with lower PPT at the patella (more sensitized), while there was no association at the wrist. The results were similar among those with and without ROA.

Conclusion: Although a general marker of systemic inflammation (TNF-α) does not appear to be associated with pain sensitization, adipokines

may be associated with increased pain sensitization and/or sensitivity at the knee. While we expected adiponectin to have an association opposite to that of leptin, total adiponectin may not be an accurate reflection of adiponectin's biologically active form. Nonetheless, the finding of similar effects of these two adipokines on pain sensitization requires further study.

Table: Relation of inflammatory markers to PPT				
Inflammatory Marker	PPT: Adjusted standardized beta (95% CI)			
	Men		Women	
	Patella	Wrist	Patella	Wrist
TNF-α	-0.02 (-0.16, 0.11)	-0.05 (-0.20, 0.10)	-0.14 (-0.31, 0.02)	-0.14 (-0.29, 0.01)
Leptin	-0.76 (-1.14, -0.39)	-0.21 (-0.62, 0.20)	-0.21 (-0.38, -0.05)	-0.01 (-0.16, 0.14)
Total Adiponectin	-0.32 (-0.56, -0.09)	-0.06 (-0.31, 0.19)	-0.14 (-0.27, -0.01)	-0.05 (-0.17, 0.07)
*adjusted for age, BMI, race, pain medications, depressive symptoms, radiographic knee OA				

Disclosure: T. Neogi, None; **L. Frey-Law**, None; **D. Misra**, None; **M. C. Nevitt**, None; **L. Arendt-Nielsen**, None; **E. K. Quinn**, None; **C. E. Lewis**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/systemic-inflammation-and-pain-sensitization-in-knee-osteoarthritis-the-multicenter-osteoarthritis-study

Abstract Number: 3251

The Relation of Massive Weight Loss to Changes in Knee Pain and Sensitization

Joshua Stefanik[1,2], David T. Felson[3], Jingbo Niu[3], Anyu Hu[4], Caroline Apovian[5], Michael P. Lavalley[6] and Tuhina Neogi[7], [1]Northeastern University, Boston, MA, [2]Clinical Epidemiology, Boston University, Boston, MA, [3]Clinical Epidemiology Research and Training Unit, Boston University School of Medicine, Boston, MA, [4]Clinical Epidemiology Research Unit, Boston University School of Medicine, Boston, MA, [5]Boston University School of Medicine, Boston, MA, [6]Biostatistics, Boston University School of Public Health, Boston, MA, [7]Clinical Epidemiology, Boston University School of Medicine, Boston, MA

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Background/Purpose: Individuals with chronic knee pain often develop central and/or peripheral sensitization (altered pain processing of the nervous system). Whether improvements in knee pain are accompanied by resolution of pain sensitization is not clear. For example, obesity is related to knee pain, and musculoskeletal pain improves after massive weight loss. As obesity is also associated with systemic low-grade inflammation, which itself may contribute to pain sensitization, weight loss may theoretically lead to a reduction in pain sensitization. However, whether this actually occurs is not known. We sought to determine if knee pain and sensitization improve after massive weight loss in individuals undergoing bariatric surgery.

Methods: Individuals for the current study were part of the Osteoarthritis Before and After Bariatric Surgery (OABS) Study. Individuals aged 25-60 were included if they had BMI ≥35, knee pain on most days of the month and were approved for bariatric surgery (laparoscopic gastric bypass surgery or laparoscopic sleeve gastrectomy). Subjects had knee pain assessed at baseline and one year later in the knee that was more painful at baseline (index knee) using the WOMAC (0-20; 0=no pain) and VAS (0-100; 0=no pain). A pressure algometer applied at 0.5kg/s was used to assess pressure pain threshold (PPT) at the index patella (indicator of peripheral and/or central sensitization) and the right wrist (indicator of central sensitization) as the point at which the pressure first changed to slight pain. Three PPT trials at each anatomical site were averaged. Higher PPTs represent less sensitization or decreased pain sensitivity. To determine the mean change in measures of pain and pain sensitization before and after surgery, we performed a paired t-test.

Results: To date 23 individuals completed baseline and follow-up visits (mean (SD) age 45.7 (8.2), mean BMI 41.6 (3.4), 86% female). The

mean (SD) weight loss was 31.1 (10.3) kilograms (% weight loss 28.1). There were significant mean improvements after surgery for all pain and sensitization measures (see Table).

Conclusion: Similar to previous findings, we found a reduction in knee pain severity after weight loss. For the first time, we report that persons who had bariatric surgery and experienced a major reduction in weight experienced a reduction in pain sensitivity, as evidenced by significant improvements in PPT.

Table. Mean difference in measures of knee pain and sensitization (post-pre) surgery

Outcome	Difference	p-value
VAS Pain	-27.8	<0.01
WOMAC Pain	-5.1	<0.01
PPT Wrist	+105.7	0.04
PPT Patella	+124.5	0.03

Disclosure: J. Stefanik, None; **D. T. Felson**, None; **J. Niu**, None; **A. Hu**, None; **C. Apovian**, None; **M. P. Lavalley**, None; **T. Neogi**, None.

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Abstract Number: 3252

Impact of Knee Pain Frequency on Physical Function in the Osteoarthritis Initiative

Jin Zhou[1], Erin Ashbeck[2], Lynn Hamilton[2] and C. Kent Kwoh[3], [1]Epidemiology & Biostatistics, University of Arizona, Tucson, AZ, [2]Arthritis Center, University of Arizona, Tucson, AZ, [3]Rheumatology, University of Arizona, Tucson, AZ

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Background/Purpose: Knee pain is a prominent symptom among patients with knee osteoarthritis (OA), but the impact of knee pain frequency on physical function has been understudied. The purpose of this study was to evaluate whether knee pain frequency at baseline and its trajectory over 72 months were associated with baseline-to-72-month physical function outcome.

Methods: This analysis was based on data from the Osteoarthritis Initiative (OAI). Knee pain frequency was assessed using an item from the Knee Injury and Osteoarthritis Outcome Score (KOOS). Physical function was assessed using self-report measures including the WOMAC function score and the Short Form 12 physical component scale (SF-12). Longitudinal models and mixed effects regression were used to evaluate the relationship between baseline knee pain frequency level and the trajectory of physical function, adjusting for potential body mass index (BMI), sex, and race. KOOS knee pain frequency was aggregated to the following categories: Never/Monthly, Weekly, and Daily/Always. Knee pain trajectory over 72 months was defined based on its changes over this time period as: 1) Maintain Never/Monthly knee pain (reference group); 2) Maintain Weekly knee pain; 3) Maintain Daily/Always knee pain; 4) Monotonic worsening of knee pain frequency; 5) Monotonic improvement of knee pain frequency; and 6) Fluctuating knee pain. We used a random effects model to account for the clustering of two knees within a person.

Results *:* The sample included 4,796 men and women with or at high risk of developing knee osteoarthritis. At baseline, the "Daily/Always" knee pain group had the lowest SF-12 throughout 72 months, with a mean (95% CI) ranging from 41.6 (40.6, 43.8) at baseline to 38.39 (37.4, 39.3) at 72 months; whereas, the group who maintained "Never/Monthly" had the highest SF-12 throughout 72 months, ranging from 53.2 (52.6, 53.8) at baseline to 51.7 (50.9, 52.4) at 72 months. Interestingly, in the "monotone improvement" group, the SF-12 increased significantly over time, while in all other groups SF-12 decreased significantly compared to the "maintain Never/Monthly" group ($P<0.001$). Comparing the knee pain trajectory groups that had worsening SF-12, the SF-12 for the "monotone worsening" group decreased three times more compared to the "maintain Never/Monthly", "maintain Daily/Always", and "fluctuating KP" groups. The results are similar for the knee pain trajectory groups and changes in WOMAC over 72 months.

Conclusion: These findings indicate that higher knee pain frequency at baseline is associated with worsening function over time. In addition, worsening knee pain frequency trajectory is associated worsening function over time, while improving knee pain trajectory is associated with improvement in function.

Disclosure: J. Zhou, None; **E. Ashbeck**, None; **L. Hamilton**, None; **C. K. Kwoh**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/impact-of-knee-pain-frequency-on-physical-function-in-the-osteoarthritis-initiative

Abstract Number: 3253

The Predictive Value of Antibodies to Cyclic Citrullinated Peptide in Two Prospective Early Rheumatoid Arthritis Cohorts 10 Years Apart

Alf Kastbom[1], Michael Ziegelasch[1], Ingrid Thyberg[1], Birgir Arge[2], Klara Martinsson[1], Olle Svernell[3], Åsa Häggström[4], Per Salomonsson[5], Britt-Marie Nyhäll-Wåhlin[6], Sören Transö[7], Claudia Jacobs[8] and Thomas Skogh[1], [1]IKE/Rheumatology, Linköping University, Linköping, Sweden, [2]Rheumatology clinic, Eskilstuna Hospital, Eskilstuna, Sweden, [3]Rheumatology Dpt, Västervik Hospital, Västervik, Sweden, [4]Rheumatology clinic, Kalmar Hospital, Kalmar, Sweden, [5]Rheumatology Clinic, Örebro University Hospital, Örebro, Sweden, [6]Department of Rheumatology, Falun Hospital, Falun, Sweden, [7]Rheumatology Clinic, Ryhov Hospital, Jönköping, Sweden, [8]Rheumatology Dept, Oskarshamn Hospital, Oskarshamn, Sweden

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Background/Purpose:

Antibodies to cyclic citrullinated peptides (anti-CCP) associate with a more severe rheumatoid arthritis (RA) disease course, and therefore have influence on therapeutic decisions. By comparing two early RA cohorts enrolled 10 years apart, we wished to determine whether the predictive value of anti-CCP has changed in contemporary early RA.

Methods:

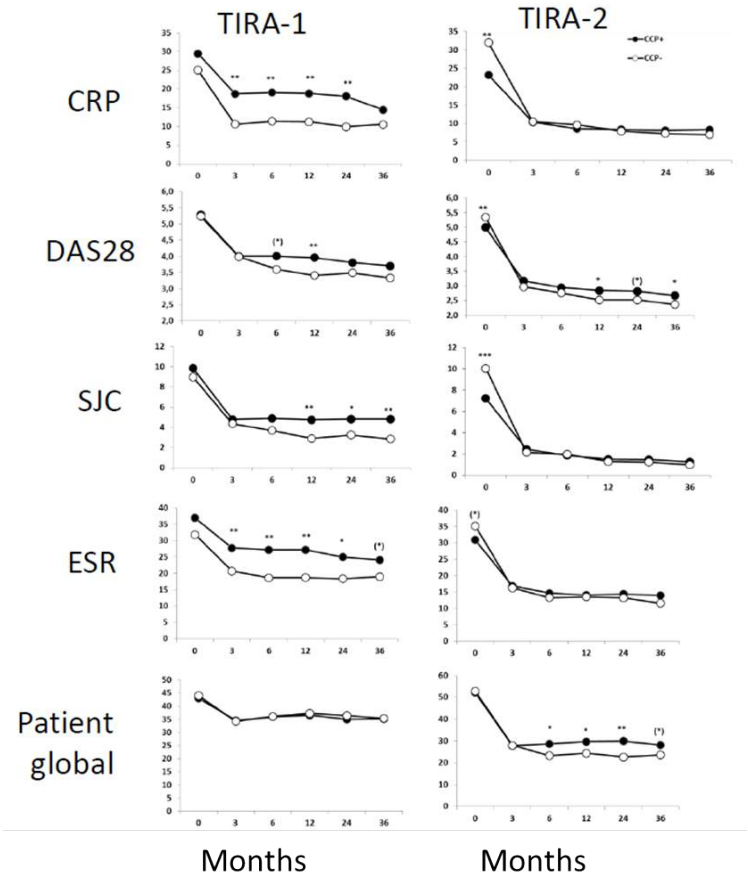
Two Swedish multicenter prospective observational early RA cohorts (denoted 'TIRA') enrolled patients with symptom duration <12 months and fulfilling either the 1987 American College of Rheumatology criteria or suffering from morning stiffness >60 min, symmetrical arthritis, and small-joint engagement. TIRA-1 enrolled patients 1996-1999, i.e. when neither anti-CCP tests nor biological therapy were used in clinical routine. TIRA-2 enrolled patients 2006-2009 using the same inclusion criteria as TIRA-1. Both cohorts were followed prospectively over 3 years. Anti-CCP tests (CCP2, EuroDiagnostica AB, Sweden) were performed on baseline serum samples. In TIRA-2, radiological damage was determined by Larsen score.

Results:

Baseline anti-CCP occurrence was similar in TIRA-1 (156/239, 65%) and TIRA-2 (303/444, 68%). In TIRA-1, follow-up disease activity measures related to inflammation (ESR, CRP, swollen joint count (SJC)) were higher among anti-CCP positive patients compared with anti-CCP negative patients (fig 1). In TIRA-2, anti-CCP positive patients had significantly lower 28-joint disease activity score (DAS28), CRP, and SJC at baseline compared with anti-CCP negative patients, while the 3-year follow-up revealed no significant differences regarding ESR, CRP or SJC (fig 1). In both cohorts, anti-CCP positive patients were treated more aggressively. In TIRA-2, baseline anti-CCP occurrence associated with more radiological damage over time ($p = 0.001$ regarding 3-year Larsen score; $p=0.006$ regarding progression). Anti-CCP remained associated with radiological progression also after adjusting for age, sex, baseline DAS28, and baseline Larsen score ($p=0.024$).

Conclusion:

Modern management of early RA attenuates the association between baseline anti-CCP status and disease activity over time, but the radiological progression remains increased. Thus, despite early aggressive therapy, anti-CCP occurrence remains predictive of erosive disease. This supports pathogenetic properties of antibodies to citrullinated proteins with regard to bone destruction, regardless of inflammatory responses reflected by swollen joints or raised CRP/ESR levels.



Disclosure: **A. Kastbom**, None; **M. Ziegelasch**, Abbvie, 5; **I. Thyberg**, None; **B. Arge**, None; **K. Martinsson**, None; **O. Svernell**, None; **Häggström**, None; **P. Salomonsson**, None; **B. M. Nyhäll-Wåhlin**, None; **S. Transö**, None; **C. Jacobs**, None; **T. Skogh**, None.

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Abstract Number: 3254

A Clinical Risk Score to Predict Functional Disability at 1 Year in an Early Rheumatoid Arthritis Inception Cohort

Caroline Kronisch[1,2], David Mclernon[3], James Dale[4], Caron Paterson[4], Stuart H. Ralston[5], David M. Reid[6], Ann Tierney[4], John Harvie[7], Neil McKay[8], Hilary E. Wilson[9], Robin Munro[10], Sarah Saunders[11], Ruth Richmond[12], Derek Baxter[13], Mike McMahon[14], Vinod Kumar[15], John McLaren[16], Stefan Siebert[4], Iain B. McInnes[17], Duncan Porter[4], Gary J. Macfarlane[2] and Neil Basu[2], [1]Department of Rheumatology, Cantonal Hospital Fribourg, Fribourg, Switzerland, [2]Musculoskeletal Research Collaboration (Epidemiology Group), University of Aberdeen, Aberdeen, United Kingdom, [3]Musculoskeletal Research Collaboration (Medical Statistics Team), University of Aberdeen, Aberdeen, United Kingdom, [4]Institute of Infection, Immunity and Inflammation, University of Glasgow, Glasgow, United Kingdom, [5]Centre for Genomic and Experimental Medicine, Western General Hospital, Edinburgh, United Kingdom, [6]Musculoskeletal Research Collaboration (Medicine & Therapeutics), University of Aberdeen, Aberdeen, United Kingdom, [7]Department of Rheumatology, Raigmore Hospital, Inverness, United Kingdom, [8]Department of Rheumatology, Western General Hospital, Edinburgh, United Kingdom, [9]Department of Rheumatology, Stobhill General Hospital, Glasgow, United Kingdom, [10]Department of Rheumatology, Wishaw General Hospital, Lanarkshire, United Kingdom, [11]Centre of Rheumatic Diseases, Glasgow Royal Infirmary, Glasgow, United Kingdom, [12]Department of Rheumatology, Borders General Hospital, Melrose, United Kingdom, [13]Department of Rheumatology, University Hospital Ayr, Ayr, United Kingdom, [14]Department of Rheumatology, Dumfries & Galloway Royal Infirmary, Dumfries, United Kingdom, [15]Department of Rheumatology, Ninewells Hospital, Dundee, United Kingdom, [16]Department of Rheumatology, Whyteman Brae Hospital, Fife, United Kingdom, [17]Immunology, Infection and Inflammation, University of Glasgow, Glasgow, United Kingdom

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Background/Purpose: When diagnosed with rheumatoid arthritis (RA), patients are especially concerned by the prospect of disability. Predictors of future disability may inform early decision making. Previous studies have sought to identify such predictors, but have been limited to the evaluation of traditional biomedical measures within historical cohorts. This study aimed to evaluate both psychosocial and biomedical factors, within a contemporary RA cohort, in order to identify baseline predictors of significant disability at 1 year. Subsequently, we aimed to develop a clinically useful tool which may support early patient education and decision making.

Methods: Analysis used data from the Scottish Early Rheumatoid Arthritis (SERA) inception cohort, an ongoing prospective multicentre study which began recruitment in September 2011. A forward stepwise multivariable logistic regression model was developed. Exposures were putative psychosocial (e.g. work ability, depression, and anxiety) and biomedical (e.g. DAS28-CRP score, neutrophil count and morning stiffness) baseline predictor variables. The outcome was high functional disability (defined as a Health Assessment Questionnaire [HAQ] score >1) at 1 year. The ability of the model to correctly discriminate between patients at low and high risk of the outcome was assessed using the c-statistic. Finally, a clinical prediction score was created based on the coefficients of the predictors determined by the logistic regression model. Each score was translated into a probability of reporting a high HAQ score at 1 year. As a method of external validation, the score was tested using SERA patient data which had been newly acquired since the initial analysis.

Results: Of 578 participants (64.5% female), 80.6% (466/578) fulfilled the 2010 ACR/EULAR classification criteria and 36.7% (212) exhibited high functional disability at 1 year with a HAQ >1. Independent predictors were baseline high HAQ score (OR 2.67; 95%CI 1.98 – 3.59), depression (2.52; 1.18 – 5.37), anxiety (2.37; 1.33 – 4.21), being in paid employment with absenteeism during the last seven days (1.19; 0.63 – 2.23), not in paid employment (2.36; 1.38 – 4.03) and obesity (1.61; 1.04 – 2.50). The good discriminative performance of the model was evidenced by a c-statistic of 0.78. The clinical prediction score (Table 1) ranged from 0 – 26 and had a good discriminative performance in both the original (c-statistic 0.78) and validation data sets (c-statistic 0.78).

Conclusion: In the context of modern treatment paradigms, predictors of 1 year disability appear to be dominated by psychosocial rather than more traditional biomedical measures. Such information may aid both patients and physicians during initial management planning and alludes to the potential benefit of early non-pharmacological interventions targeting key psychosocial factors such as mental health and work disability.

Table 1 Clinical Risk Score for estimation of functional disability (HAQ-DI score >=1) at one year in RA:

Predictors	Categories and corresponding score					Score
HAQ[1]	<1	>=1	>=1.5	>=2	>=2.5	
	0	**4**	**6**	**9**	**11**	
HADS[2] depression score	Low <11	High >=11				
	0	**5**				
HADS[2] anxiety score	Low <11	High >=11				
	0	**4**				
Employment & Absenteeism	In paid employment without absenteeism during the last seven days	In paid employment with absenteeism during the last seven days	Not in paid employment			
	0	**1**	**4**			
BMI	High <25 kg/m^2	High >=25 kg/m^2				
	0	**2**				
					Total score	

[1]HAQ: Health Assessment Questionnaire. [2]HADS: Hospital anxiety and depression scale.
Score ranges between 0 and 26 points.

Disclosure: C. Kronisch, None; **D. Mclernon**, None; **J. Dale**, Pfizer Inc, 2,BMS, 2,Pfizer Inc, 8,Abbvie, 8,Janssen Pharmaceutica Product, L.P., 8; **C. Paterson**, None; **S. H. Ralston**, None; **D. M. Reid**, None; **A. Tierney**, None; **J. Harvie**, None; **N. McKay**, None; **H. E. Wilson**, None; **R. Munro**, None; **S. Saunders**, None; **R. Richmond**, None; **D. Baxter**, None; **M. McMahon**, None; **V. Kumar**, None; **J. McLaren**, None; **S. Siebert**, None; **I. B. McInnes**, Pfizer Inc, 2,Pfizer Inc, 5; **D. Porter**, Pfizer Inc, 2,Pfizer Inc, 5; **G. J. Macfarlane**, Pfizer Inc;, 2,Pfizer Inc, 9,AbbVie, 2; **N. Basu**, Pfizer Inc, 2,Pfizer Inc, 5,Roche Pharmaceuticals, 8.

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Abstract Number: 3255

Brain White Matter Integrity: A Future Biomarker for Rheumatoid Arthritis Related Fatigue?

Neil Basu[1], Marayam Alsyedalhashem[2], Mariella D'Allesandro[3], Alison D. Murray[2], Daniel J. Clauw[4] and Gordon D. Waiter[2], [1]Musculoskeletal Research Collaboration (Epidemiology Group), University of Aberdeen, Aberdeen, United Kingdom, [2]Aberdeen Biomedical Imaging Centre, University of Aberdeen, Aberdeen, United Kingdom, [3]Muscloskeletal Collaboration (Epidemiology Group), University of Aberdeen, Aberdeen, United Kingdom, [4]Anesthesiology, University of Michigan, Ann Arbor, MI

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Background/Purpose: Fatigue is a major burden among patients with rheumatoid arthritis (RA). The identification of reliable biomarkers would greatly enhance research in this challenging field. Diffusion tensor magnetic resonance imaging (DTI) brain studies have previously reported fatigue specific abnormalities in the white matter integrity of patients with other autoimmune conditions. These studies were however cross-sectional and underpowered. We present the first study to evaluate brain white matter integrity in RA. We specifically aimed to evaluate the responsiveness of this putative biomarker to changing fatigue levels over time in a large sample.

Methods: Consecutive clinic attending RA patients fulfilling ACR/EULAR 2012 criteria were recruited if they reported problems with fatigue >3 months and scored >3 on the Chalder Fatigue Scale (CFS, binary scoring). All participants underwent DTI scanning on 2 occasions, 6 months apart, during which time they received standard care. At both visits they were clinically characterised. This included an evaluation of disease activity (DAS28), depressive symptoms (Hospital Anxiety & Depression Scale), pain (numerical rating scale) and sleep disturbance (Jenkin's scale).

DTI data was acquired by a 3 Tesla, 8 channel phased array head coil and presented as fractional anisotropy (FA) values, where decreased FA reflects reduced white matter structural integrity and raised FA reflects the opposite. Participants were split into 2 groups: those who reported a clinically significant improvement in their fatigue levels (2 point reduction in CFS) and those who did not. Within-group differences between the time-points were analysed using paired Tract-Based Spatial Statistics and corrected for multiple comparisons.

Results: Of the 54 participants who attended both visits (76% female, mean age 55.2 years, mean disease duration 11.35 months at baseline), 22 (40.7%) reported a clinical improvement in fatigue at 6 months (mean 2.64 point reduction in CFS) and 32 (60.3%) reported unchanged fatigue (-0.13 change in CFS). Within the fatigue improver group, statistically significantly reduced FA levels were observed at visit 2 compared to visit 1. The regions of change were diffuse, but much greater in the right hemisphere and specifically the periventricular, internal capsule, thalamus, inferior frontal and parietal areas (figure). The regions were unchanged after adjusting individually for disease activity or sleep, although became focalised following adjustment of depression or pain.

In contrast, no significant differences in FA levels were observed between visits within the fatigue non-improver group.

Conclusion: The striking disparity in white matter integrity changes between the fatigue improver and non-improver groups provides preliminary evidence to support the role of DTI as a future biomarker of RA related fatigue.

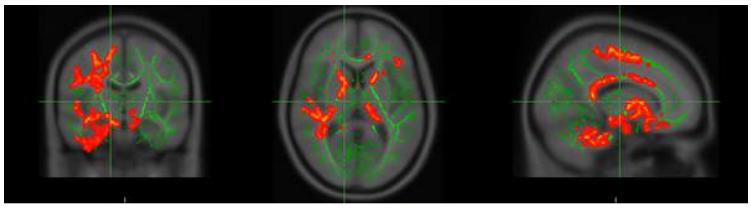

Figure: Significant differences in white matter structural integrity among fatigue improvers.

RED: Regions of the brain where FA reduced at visit 2 compared to visit 1. GREEN: Standardised skeleton of white matter tracts

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Disclosure: **N. Basu**, Pfizer Inc, 2,Pfizer Inc, 5,Roche Pharmaceuticals, 8; **M. Alsyedalhashem**, None; **M. D'Allesandro**, None; **A. D. Murray**, Pfizer Inc, 2; **D. J. Clauw**, Pfizer Inc, 2,Pfizer Inc, 5,Pfizer Inc, 9; **G. D. Waiter**, Pfizer Inc, 2.

Abstract Number: 3256

Epigenetic Chromosome Conformations Predict MTX Responsiveness in Early Rheumatoid Arthritis Patients

Claudio Carini[1], Aroul Ramadass[2], Philip Jordan[2], Ewan Hunter[2], Alexandre Akoulitchev[2], Iain. B. McInnes[3], **Carl. S. Goodyear**[3] and Scottish Early Rheumatoid Arthritis Inception Cohort Investigators, [1]35 Cambridgepark Drive, Pfizer, Cambridge, MA, [2]Oxford Biodynamics, Oxford, United Kingdom, [3]Institute of Infection, Immunity and Inflammation, College of Medicine, Veterinary Medicine and Life Sciences, University of Glasgow, Glasgow, United Kingdom

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SESSION INFORMATION

Session Date: Wednesday, November 11, 2015

Session Title: Rheumatoid Arthritis - Clinical Aspects VII: Disease Activity and Updates in Measurement

Session Type: ACR Concurrent Abstract Session

Session Time: 11:00AM-12:30PM

Background/Purpose: In early rheumatoid arthritis (RA), it is not possible to predict response to first line DMARDs (e.g. methotrexate (MTX)) and as such treatment decisions rely primarily on clinical algorithms. The capacity to classify drug naïve patients into those that will not respond to first line DMARDs would be an invaluable tool for patient stratification. Here we report that chromosome conformational signatures (highly informative and stable epigenetic modifications that have not previously been described in RA) in blood leukocytes of early RA patients can predict non-responsiveness to MTX treatment.

Methods: Peripheral blood mononuclear cells were obtained from DMARD naïve early RA patients recruited in the Scottish early rheumatoid arthritis inception cohort. Inclusion in this study was based on diagnosis of RA (fulfilling the 2010 ACR/EULAR Criteria) with moderate to high disease activity (DAS28 $\geq$ 3.2) and subsequent monotherapy with MTX. MTX responsiveness was defined at 6 months using the following criteria: Responders - DAS28 remission (DAS28 <2.6) or a good response (DAS28 improvement of >1.2 and DAS28 $\leq$3.2). Non-responders - no improvement in DAS28 ($\leq$0.6). Initial analysis of chromosome conformational signatures (CCS) in 4 MTX responders, 4 MTX non-responders and 4 healthy controls was undertaken using an EpiSwitch™ array containing 13,322 unique probes covering 309 RA-related genetic loci. Differentiating CCS were defined by LIMMA linear modeling, subsequent binary filtering and cluster analysis. A validation cohort of 30 MTX responders and 30 non-responders were screened for the differentiating CCS using the EpiSwitch™ PCR platform. The differentiating signature was further refined using binary scores and logistical regression modeling, and the accuracy and robustness of the model determined by ROC analysis.

Results: CCS EpiSwitch™ array analysis identified 30 CCS markers with the potential to stratify early RA patients into responders and non-responders. Subsequent evaluation of this signature in our validation cohort refined this to a CCS signature that was able to discriminate responders and non-responders. Prediction modeling provided a probability score for responders and non-responders, ranging from 0.0098 to 0.99 (0 = responder, 1 = non-responder). There was a true positive rate of 92% (95% confidence interval [95% CI] 75-99%) for responders and a true negative rate of 93% (95% CI 76-99%) for non-responders. Importantly, ROC analysis to validate this stratification model demonstrated that the signature had a predictive power of sensitivity at 92% for non-responders to MTX.

Conclusion: We have identified a highly informative systemic epigenetic state in the peripheral blood of DMARD naïve early RA patients that has the power to stratify patients at the time of diagnosis. The capacity to differentiate patients *a priori* into non-responders, using a blood-based clinical test, would be an invaluable clinical tool; paving the way towards stratified medicine and justifying more aggressive treatment regimes in early RA clinics.

Disclosure: C. Carini, Pfizer Inc, 3; **A. Ramadass**, Oxford Biodynamics Limited, 3; **P. Jordan**, Oxford Biodynamic Limited, 3; **E. Hunter**, Oxford Biodynamics, 3; **A. Akoulitchev**, Oxford Biodynamics, 3; **I. B. McInnes**, Pfizer Inc, 5,Pfizer Inc, 2; **C. S. Goodyear**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/epigenetic-chromosome-conformations-predict-mtx-responsiveness-in-early-rheumatoid-arthritis-patients

Abstract Number: 3257

The Link Between DAS28 and the Short-Term Risk of Acute Coronary Syndrome in RA, and Its Driving Factors

Lotta Ljung[1,2], Thomas Frisell[3] and Johan Askling[3,4], [1]Department of Medicine, Solna, Clinical epidemiology unit, Karolinska Institutet, Stockholm, Sweden, [2]Department for Public Health and Clinical Medicine/Rheumatology, Umeå University, Umeå, Sweden, [3]Clinical Epidemiology Unit, Department of Medicine, Karolinska Institutet, Stockholm, Sweden, [4]Rheumatology Unit, Rheumatology Unit, Karolinska

University Hospital, Stockholm, Sweden
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SESSION INFORMATION

Session Date: Wednesday, November 11, 2015
Session Title: Rheumatoid Arthritis - Clinical Aspects VII: Disease Activity and Updates in Measurement
Session Type: ACR Concurrent Abstract Session
Session Time: 11:00AM-12:30PM

Background/Purpose:

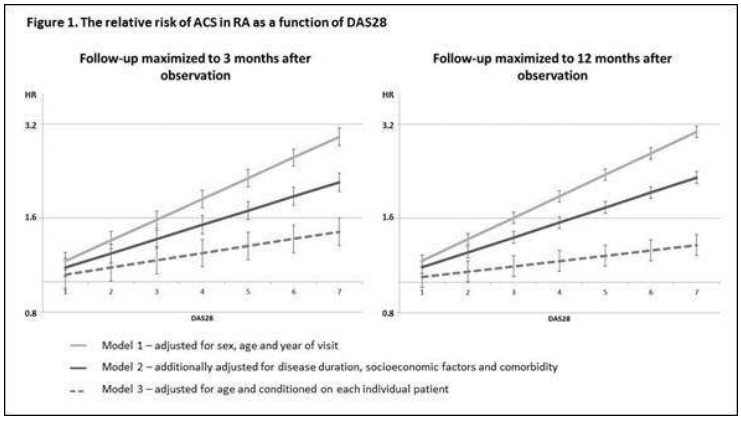
The extent to which a short-term effect of the disease activity adds to the over-risk of coronary events in patients with Rheumatoid Arthritis (RA) is largely unknown. Theoretically, inflammation might affect the vasculature in the long-term by accelerated atherosclerosis, but there have also been indications of effects on shorter-term risks. For instance, inflammatory cytokines and inflammation-driven hypercoagulability could affect the vulnerability of plaques and thrombus formation in the coronaries, i.e., processes underlying unstable ischemic heart disease and myocardial infarctions. In this study we evaluated the risk of acute coronary syndrome (ACS) shortly after disease activity assessment in a large population of patients with RA.

Methods:

We assembled all registrations, Jan 1st 2001 to Dec 31st 2012 from doctor's visits for patients with a diagnosis of RA in the Swedish Rheumatology Quality Register (SRQ). The observations were linked to the Patient Register, the Population Register, and the Cause-of-Death Register to add information on the outcome (ACS; unstable angina and myocardial infarction), vital status, emigration, comorbidity (chronic and acute ischemic heart disease, congestive heart disease, cerebrovascular disease, other atherosclerotic disease, diabetes, and/or hypertension) antedating the observation, and socioeconomic factors (educational level, unemployment, sick leave from work, disability pension). We evaluated the association between DAS28 and ACS risk in three risk windows (0 to 3, 0 to 6, 0 to 12 months after each visit, respectively), using three Cox regression models: 1) adjusted for age, sex and year of visit, 2) additionally adjusted for disease duration, comorbidity and socioeconomic factors, and 3) adjusted for age and conditioned on each individual patient, implicitly adjusting for all factors that are constant within a patient.

Results:

There were 215,135 visits (n patients=31,460, 72.0% women, mean of age at first visit 59.4 SD 14.5 years) during the study period. The crude incidence rates were 9.9 (96% CI 9.1-10.9), 10.0 (9.3-10.7), and 10.2 (9.7-10.8) per 1,000 person-years for the 3, 6 and 12 months follow-up, respectively, with 493, 836, and 1203 ACS events occurring during follow-up. Disease activity score 28-joints (DAS28) was available from 187,659 (87.2%) visits. DAS28 was associated with the risk of ACS in all risk windows in Models 1 and 2, but the association was weakened in Model 3 (Figure 1). The 12 months follow-up provided similar results (Figure 1).



Conclusion:

There is a strong link between clinical disease activity and short-term risk of ACS. Whilst useful for clinical prediction, the association is, however, only partially likely to be causal, since it was attenuated by adjustment for socioeconomic factors and comorbidities, in particular when DAS28 values were compared within each individual.

Disclosure: L. Ljung, None; **T. Frisell**, None; **J. Askling**, AstraZeneca, Pfizer, UCB, Roche, Merck, BMS, Abbvie., 9.

Abstract Number: 3258

Different Perception of Disease Activity in Multimorbid Rheumatoid Arthritis Patients

Helga Radner[1,2], Kazuki Yoshida[1,3], Sara K. Tedeschi[4], M Frits[5], C Iannaccone[6], N Shadick[7], Michael Weinblatt[1], Daniel Aletaha[8], Josef S. Smolen[9] and Daniel H. Solomon[10], [1]Division of Rheumatology, Immunology and Allergy, Brigham and Women's Hospital, Boston, MA, [2]Department of Internal Medicine III; Division of Rheumatology, Medical University of Vienna, Vienna, Austria, [3]Department of Epidemiology, Harvard School of Public Health, Boston, MA, [4]Rheumatology, Brigham & Women's Hospital, Boston, MA, [5]Division of Rheumatology, Brigham and Women's Hospital, Boston, MA, [6]Division of Rheumatology, Immunology and Allergy, Brigham and Women's Hospital, Boston, MA, [7]Division of Rheumatology, Immunology & Allergy, Brigham and Women's Hosp, Boston, MA, [8]Rheumatology, Medical University Vienna, Vienna, Austria, [9]Dept of Medicine 3, Division of Rheumatology, Medical Univ Vienna, Vienna, Austria, [10]Rheumatology, Brigham and Women's Hospital, Boston, MA

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Session Time: 11:00AM-12:30PM

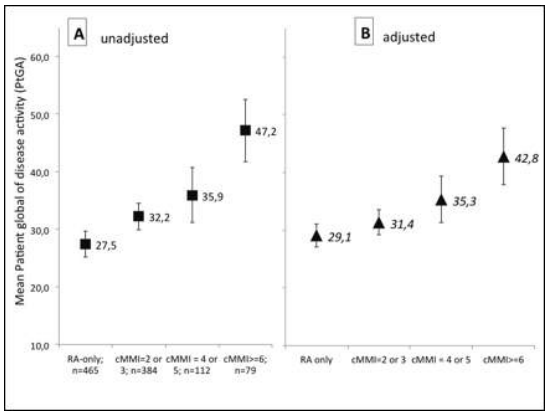
Background/Purpose: The patient rating of global rheumatoid arthritis (RA) disease activity (PtGA) is a key variable in composite measures of disease activity as well as definition of remission (REM). In multimorbid RA patients (RA-MM) the perception of RA disease activity as measured by the PtGA might be impacted by the burden of multiple diseases, leading to higher levels of PtGA. In this study, we aimed to quantify the difference in PtGA between RA-MM and RA-only patients and to determine the factors contributing to this difference.

Methods: We compared mean levels of PtGA between RA-MM and RA-only patients followed in a longitudinal RA cohort at an academic medical center. Multimorbidity was defined as having at least one chronic condition in addition to RA and assessed by the counted multimorbidity index (cMMI ³ 2) [1]. The mean difference in PtGA (ΔPtGA) between RA-MM and a cohort of RA-only patients, matched on swollen and tender joint count (SJC, TJC), evaluator global of disease activity, and disease duration, was assessed. The unique contribution of specific components to the explained variation of ΔPtGA in the matched cohort was calculated as semi-partial R^2 in linear regression models and summarized as the percentage of the total R^2.

Results: Out of a total of 1,040 RA patients, 575 (55.5%) were multimorbid; RA-MM reported higher (worse) PtGA, with a positive linear relationship between number of morbidities and PtGA (linear trend $p<0.01$). This relationship remained significant after adjusting for disease activity, age and disease duration (**Figure 1**). In the matched cohort of 294 RA-MM patients and 294 RA-only patients, the mean PtGA (in mm) was significantly higher for RA-MM (30.5±24.3) versus RA-only patients (25.6±22.9), with a mean difference of 4.9±26.7 ($p<0.01$, paired t-test). Variables contributing to this difference were fatigue (18.2% of total R^2), pain (16.8% of total R^2) and modified health assessment questionnaire (mHAQ; 8.7% of total R^2). Age, gender and level of education were not significantly contributing to the difference in PtGA between RA-MM and RA-only.

Conclusion: RA-MM patients had higher levels of PtGA compared to RA-only patients. The most relevant determinants of this difference in PtGA between RA-MM and RA-only patients are differences in fatigue and pain.

Figure 1. This figure demonstrates higher mean values of patient global of disease activity (PtGA) in groups of patients with higher number of morbidities assessed by the counted multimorbidity index (cMMI). Panel **A** shows unadjusted analyses of variance (ANOVA) testing for linear trend $p<0.001$. Panel **B** shows adjusted estimated marginal means generated by a general linear model considering all covariates set to the cohort's mean (tender joint count= 7.9; swollen joint count = 7.1; evaluator global = 32.2; Age = 56.8; Disease duration = 13.7years).



Disclosure: H. Radner, None; **K. Yoshida**, None; **S. K. Tedeschi**, None; **M. Frits**, None; **C. Iannaccone**, None; **N. Shadick**, Amgen, Questcor, Crescendo Biosciences, UCB, Bristol-Myers Squibb, 2; **M. Weinblatt**, Amgen, Abbvie, Bristol-Myers Squibb, Lilly, Novartis, Merck, Pfizer, Roche, Crescendo, Myriad Genetics, UCB, 5,Bristol-Myers Squibb, Myriad Genetics, UCB, 2; **D. Aletaha**, None; **J. S. Smolen**, Abbvie, Janssen, MSD, Pfizer, Roche, UCB, 2,Abbvie, Amgen, Astra-Zeneca, Astro, Celgene, Glaxo, ILTOO, Janssen, Lilly, Medimmune, MSD, Novartis-Sandoz, Novo-Nordisk, Pfizer, Roche, Samsung, Sanofi, UCB, 5; **D. H. Solomon**, None.

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Abstract Number: 3259

Immunoablation Followed By Autologous Stem Cell Transplantation in Systemic Sclerosis Patients Decreases Significantly the Interferon Signatrue

Shervin Assassi[1], Maureen D Mayes[1], Claudia Pedroza[2], Jeffrey T. Chang[2], Daniel E. Furst[3], Leslie J. Crofford[4], Richard Nash[5], Peter McSweeney[5], Mary Ellen Csuka[6], Ellen Goldmuntz[7], Lynette Keyes-Elstein[8], Paul Wallace[9] and Keith Sullivan[10], [1]Rheumatology, University of Texas Medical School at Houston, Houston, TX, [2]University of Texas Medical School at Houston, Houston, TX, [3]Medicine, University of California, Los Angeles, David Geffen School of Medicine, Los Angeles, CA, [4]Medicine, Vanderbilt University, Nashville, TN, [5]Colorado Blood Cancer Institute, Denver, CO, [6]Rheum/Med Coll of Wisconsin, Med Coll of Wisconsin, Milwaukee, WI, [7]NIAID, National Institutes of Health, Bethesda, MD, [8]Rho Federal Systems, Inc., Chapel Hill, NC, [9]Roswell Park, Buffalo, NY, [10]Duke University, Durham, NC
First publication: September 29, 2015

SESSION INFORMATION

Session Date: Wednesday, November 11, 2015

Session Title: Systemic Sclerosis, Fibrosing Syndromes, and Raynaud's - Clinical Aspects and Therapeutics III

Session Type: ACR Concurrent Abstract Session

Session Time: 11:00AM-12:30PM

Background/Purpose: Previous clinical trials have suggested that immunoablation followed by autologous hematopoietic cell transplantation (HCT) can lead to clinical improvements in systemic sclerosis (SSc). However, global gene expression studies for understanding the molecular basis of these effects were not performed. We aimed at investigating changes in the peripheral blood gene expression patterns ensuing after HCT in the randomized SCOT trial.

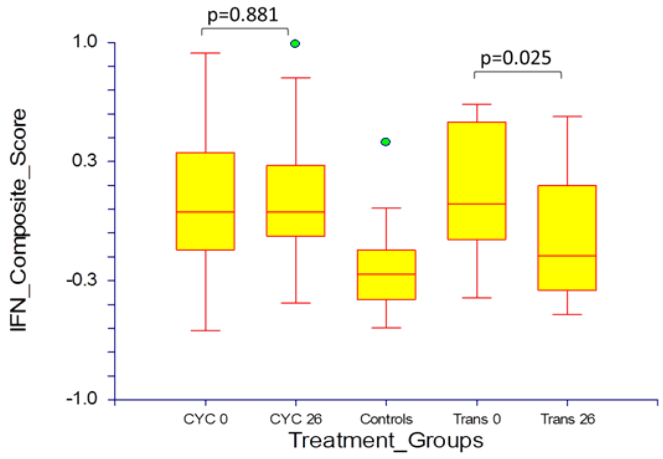
Methods: Global transcript studies on Illumina HT-12 arrays were performed in whole blood samples collected at pretreatment baseline and 26 months post-randomization. Sixty-two SSc patients undergoing HCT or receiving 12-month of IV cyclophosphamide (CYC) were investigated . The immune reconstitution after immunoablation is generally completed at 26-months and patients in CYC arm were off treatment for 14 months at that time point. Healthy controls (age, race and gender matched) were also studied (n=62). A false discovery rate < 5% in the multivariable analysis was utilized to identify the differentially expressed genes (DEG). Clinical correlations with long-term outcomes could not be performed as this awaits maturation of follow-up until all subjects have reached the 54 month SCOT primary endpoint.

Results: Compared to controls, the baseline SSc samples showed 3168 DEGs. In agreement with our previous studies, the top three over-represented pathways belonged to interferon (IFN) alpha (p=0.00001), IL22 soluble receptor (p=0.0009), and IFN gamma (p=0.00038) signaling pathways. Restricting the comparison (healthy controls vs. SSc) to 312 IFN inducible genes revealed 160 DEGs (51.2%). A composite score of these IFN inducible genes correlated with the baseline modified Rodnan Skin Score (r=0.28, p=0.027) while there was no significant correlation with the baseline fibrosis score on CT imaging.

Gene expression data on 36 SCOT patients were available at 26 months. In 18 HCT recipients, 2805 DEGs belonging mainly to immune pathways were identified when comparing 26-month to baseline samples. In contrast, no DEGs were detected in a similar comparison in 18 CYC recipients. Restricting the analysis to IFN inducible transcripts revealed 135 DEGs 26-months after HCT while no differentially expressed IFN inducible genes were detected in CYC group. As shown in Figure 1, HCT was associated with a significant decline in the IFN transcript sore compared to baseline (p=0.025), while there was no apparent effect on this composite score 14 months after completion of CYC (p=0.881).

Conclusion: Unique differential gene expression including a decrease in immune regulation anomalies were observed at 26 months after HCT. The IFN signature, which is the most prominent peripheral blood transcript profile, declined significantly after HCT supporting the notion this treatment has the potential of “resetting” SSc patient's immune system.

Figure 1: IFN Composite Transcript Scores in SCOT Trial



Disclosure: S. Assassi, Biogen Idec, 5,Boehringer Ingelheim, 5; **M. D. Mayes**, None; **C. Pedroza**, None; **J. T. Chang**, None; **D. E. Furst**, Gilead, 2,GlaxoSmithKline, 2,NIH, 2,Novartis Pharmaceutical Corporation, 2,Pfizer Inc, 2,Roche Pharmaceuticals, 2,Genentech and Biogen IDEC Inc., 2,UCB, 2,Abbvie, 5,Actelion Pharmaceuticals US, 5,Amgen, 5,Bristol-Myers Squibb, 5,Cytori, 5,Janssen Pharmaceutica Product, L.P., 5,Gilead, 5,GlaxoSmithKline, 5,NIH, 5,Novartis Pharmaceutical Corporation, 5,Pfizer Inc, 5,Roche Pharmaceuticals, 5,Genentech and Biogen IDEC Inc., 5,UCB, 5,Abbvie, 8,Actelion Pharmaceuticals US, 8,Bristol-Myers Squibb, 2,Amgen, 2,Actelion Pharmaceuticals US, 2,Abbvie, 2,UCB, 8; **L. J. Crofford**, None; **R. Nash**, None; **P. McSweeney**, None; **M. E. Csuka**, None; **E. Goldmuntz**, None; **L. Keyes-Elstein**, None; **P. Wallace**, None; **K. Sullivan**, None.

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Abstract Number: 3260

Increased Frequency of Malignancies Synchronous to the Onset of Systemic Sclerosis in Anti-RNA Polymerase III Antibodies Positive Patients: A Eustar Multicentre Study

Maria Grazia Lazzaroni[1], Enrico Colombo[2], Ilaria Cavazzana[1], Oliver Distler[3], Rucsandra Dobrota[3], Jasmin Eisenring[3], Roger Hesselstrand[4], Lazlo Czirjak[5], Cecilia Varju[5], Gabriella Nagy[5], Vanessa Smith[6], Paola Caramaschi[7], Valeria Riccieri[8], Eric Hachulla[9], Katarzyna Romanowska-Próchnicka[10], Alexandra Balbir-Gurman[11], Emmanuel Chatelus[12], Ana Carolina Araújo[13], Yannick Allanore[14], Paolo Airò[15] and EUSTAR , [1]Rheumatology and Clinical Immunology, Spedali Civili and University of Brescia, Brescia, Italy, [2]Rheumatology and Clinical Immunology Unit, University and Spedali Civili of Brescia, Brescia, Italy, [3]Division of Rheumatology, University Hospital Zurich, Zurich, Switzerland, [4]Department of Clinical Sciences, Section of Rheumatology, Lund University, Lund, Sweden, [5]University of Pécs Medical Center, Pécs, Hungary, [6]Rheumatology, Ghent University Hospital, Ghent, Belgium, [7]Rheumatology Unit, Azienda Ospedaliera Universitaria Integrata, Verona, Italy, [8]Department of Internal Medicine and Medical Specialities, University Sapienza, Rome, Italy, [9]Department of Internal Medicine, University Lille Nord-de-France, Lille, France, [10]Department of Pathophysiology, Medical University of Warsaw and Department of Connective Tissue Diseases, Institute of Rheumatology, Warsaw, Poland, [11]B. Shine Rheumatology Unit, Rambam Health Care Campus, Rappaport Faculty of Medicine, Technion - Institute of Technology, Haifa, Israel, [12]Department of Rheumatology, Strasbourg University Hospital, Strasbourg, France, [13]Serviço de Medicina 2, Hospital de Curry Cabral, Centro Hospitalar Lisboa Central, Lisbon, Portugal, [14]Department of Rheumatology, University Paris Descartes and Cochin Hospital, Paris, France, [15]Rheumatology and Clinical Immunology Unit, Spedali Civili of Brescia, Brescia, Italy

First publication: September 29, 2015

SESSION INFORMATION

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Session Title: Systemic Sclerosis, Fibrosing Syndromes, and Raynaud's - Clinical Aspects and Therapeutics III

Session Type: ACR Concurrent Abstract Session

Session Time: 11:00AM-12:30PM

Increased Frequency of Malignancies Synchronous to the Onset of Systemic Sclerosis in Anti-RNA Polymerase III Antibodies Positive Patients: a EUSTAR Multicentre Study

Background/Purpose:

Several clinical issues have been associated with anti-RNA polymerase III (RNAP) antibodies in patients with systemic sclerosis (SSc), but most data derive from single-centre studies or relatively small positive case numbers. Recently, a temporal relationship between the onset of SSc and malignancy has been described in anti-RNAP+ patients. The analysis of the large EUSTAR cohort may provide further information on the clinical associations of this autoantibody.

Methods:

Patients from the EUSTAR database were included when the item anti-RNAP was fulfilled in at least one visit; data were collected from the last visit available.

In a second phase, 13 EUSTAR centers participated to a case-control study, fulfilling a supplementary form. Anti-RNAP-negative SSc controls were matched for sex, cutaneous subset and disease duration.

Results:

Anti-RNAP status was available in 4,986 of 11,399 patients from EUSTAR database: 223 were anti-RNAP+. After exclusion of 47 patients with multiple autoantibody positivity, 176 anti-RNAP+ patients were compared with 4,763 anti-RNAP-negative patients: multivariate analysis confirmed the association of anti-RNAP with scleroderma renal crisis (SRC) and diffuse cutaneous involvement (Table 1). A multivariate analysis was also performed to compare patients with (n=80) and without SRC (n=4697) (Table 2).

In the case-control study 158 anti-RNAP+ and 199 anti-RNAP-negative patients were collected. We found an association of anti-RNAP with SRC (p:0.0005), arterial hypertension (p:0.006), gastric antral vascular ectasia (p:0.0009), and a shorter time to reach the peak of mRSS (p:0.013, log-rank test). An increased rate of malignancies in anti-RNAP+ patients was accounted for by the increased rate of malignancies synchronous to the onset of SSc (Table 3). Moreover, an increased rate of solid tumors, in particular breast cancer synchronous to the onset of SSc was observed.

Conclusion:

Anti-RNAP antibodies are an important and not always routinely used marker in SSc. They are associated with severe clinical manifestations and cancer, with relevant prognostic implications which should guide the monitoring and follow-up of the patients.

	Univariate analysis			Multivariate analysis		
Characteristics	**anti-RNAP+ (n=4763)**	**anti-RNAP- (n=176)**	**p Value**	**N available data (%)**	**OR, 95% CI**	**p Value***
Age at disease onset (years, mean, SD), (n=available)	46.5 (14.2) (n=3946)	46.4 (13.1) (n=140)	0.981	4086 (82.7)		0.461
Disease duration (months, mean, SD), (n=available)	138.6 (102.6) (n=3943)	131.0 (125.0) (n=140)	0.391	4083 (82.7)		0.843
Male sex (%)	684/4763 (14.4)	45/176 (25.6)	**<0.0001**	4939 (100.0)		0.306
Caucasian ethnicity (%)	3425/3605 (95.0)	134/176 (76.1)	0.220	3781 (76.6)		
Arterial hypertension (%)	1040/4600 (22.6)	50/168 (29.8)	**0.030**	4768 (96.5)		0.508
Scleroderma renal crisis (%)	59/4608 (1.3)	21/169 (12.4)	**<0.0001**	4777 (96.7)	**7.06 (3.77 to 12.2)**	**<0.0001**
Diffuse cutaneous SSc (%)	1289/4573 (28.2)	98/169 (58.0)	**<0.0001**	4742 (96.0)	**2.35 (1.58 to 3.49)**	**<0.0001**
Joint contractures (%)	1346/4489 (30.0)	74/160 (46.3)	**<0.0001**	4659 (94.3)		0.104

Table 1: Results of the univariate and multivariate analysis (adjusted on sex. age at disease onset and disease duration) comparing RNAPIII-patients and RNAPIII+ patients at the last visit (n=4939 patients).
*p Value after Bonferroni correction <0.007.

	Univariate analysis			Multivariate analysis		
Characteristics	**Patients with SRC (n=80)**	**Patients without SRC (n=4697)**	**p Value**	**N available data (%)**	**OR, 95% CI**	**p Value**
Age at disease onset (years, mean, SD), (n=available)	46.4 (13.7) (n=71)	46.5 (14.1) (n=3884)	0.937	3955 (82.8)		0.601
Male sex (%)	31/80 (38.8)	660/4697 (14.1)	**<0.0001**	4777 (100.0)	**3.22 (1.69 to 6.15)**	**0.0004**
Caucasian ethnicity (%)	67/80 (83.8)	3406/4697 (72.5)	**0.025**	4777 (100.0)		0.135
RNAPIII +	21/80 (26.3)	148/4697 (3.2)	**<0.0001**	4777 (100.0)	**6.50 (2.63 to 16.1)**	**<0.0001**
Diffuse cutaneous SSc (%)	50/80 (67.5)	1318/4611 (28.6)	**<0.0001**	4778 (98.2)	**4.44 (2.14 to 9.19)**	**<0.0001**
Joint contractures (%)	42/80 (52.5)	1370/4546 (30.1)	**<0.0001**	4626 (96.8)		0.429
Tendon friction rubs (%)	9/79 (11.4)	262/4536 (5.8)	**0.004**	4615 (96.6)		0.909
Pericardial effusion (ECHO, %)	12/60 (20.0)	188/3471 (5.4)	**<0.0001**	3531 (73.9)	**5.06 (2.33 to 11.0)**	**<0.0001**
Elevated PAPs (ECHO, %)	17/67 (25.4)	623/3912 (15.9)	**0.037**	3979 (83.3)		0.112
Lung fibrosis on chest x-rays (%)	26/60 (43.3)	1054/3379 (31.2)	**0.045**	3439 (72.0)		0.679

Table 2: Results of the univariate and multivariate analysis comparing patients with and without renal crisis at the last visit (n=4,777 patients) *p Value after Bonferroni correction <0.005

	anti-RNAP+	**anti-RNAP-**	**P Value**	**OR (95% CI)**
Malignancies	28/158 (18%)	18/199 (9%)	**0.015**	**2.17** (1.15-4.08)
Malignancies synchronous (-6/+12 months,%)	11/158 (7%)	2/199 (1%)	**0.004**	**7.38** (1.61-33.8)
Malignancies non synchronous (%)	17/158 (11%)	16/199 (8%)	0.486	
Malignancies synchronous (±2 years, %)*	14/155 (9%)	5/199 (3%)	**0.007**	**3.85** (1.36-10.9)
Solid tumors (%)	22/158 (14%)	12/199 (6%)	**0.012**	**2.52** (1.21-5.27)
Breast cancers (%)	**11/158 (7%)**	**4/199 (2%)**	**0.030**	**3.65** (1.14-11.7)
Breast cancers synchronous (±2 years,%)*	**7/155 (5%)**	**0/199 (0%)**	**0.003**	**20.2** (1.41-355)
Hematologic malignancies (%)	1/158 (1%)	2/199 (1%)	0.702	
Non melanoma skin cancer (%)	3/158 (2%)	4/199 (2%)	0.940	
Melanoma (%)	2/158 (1%)	0/199 (0%)	0.195	

Table 3: Results of the univariate analysis comparing patients anti-RNAP+ patients vs. anti-RNAP- patients about malignancies. *patients with <2 years of follow up were excluded.

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Abstract Number: 3261

Examining the Impact of Radiation Therapy on Scleroderma and Cancer Outcomes in Scleroderma Patients with Breast Cancer

Dhaval Shah[1], Ram Hirpara[1], Laura K. Hummers[1], Fredrick M. Wigley[2], Virginia D. Steen[3], Robyn T. Domsic[4] and Ami A. Shah[5], [1]Johns Hopkins University School of Medicine, Baltimore, MD, [2]Rheum Div/Mason F Lord, Johns Hopkins University School of Medicine, Baltimore, MD, [3]Rheumatology, Georgetown University Medical Center, Washington, DC, [4]Medicine - Rheumatology, University of Pittsburgh, Pittsburgh, PA, [5]Rheumatology, Johns Hopkins University School of Medicine, Baltimore, MD

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Session Type: ACR Concurrent Abstract Session

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Background/Purpose:

Radiation oncologists are hesitant to treat scleroderma (SSc) patients with cancer due to concerns about triggering exaggerated fibrosis. In this study, we examined SSc patients with breast cancer to 1) identify the prevalence of radiation complications and 2) examine whether SSc and cancer outcomes differed between SSc patients who received or did not receive radiation therapy (RT) as part of their cancer treatment regimen.

Methods:

Patients with SSc and breast cancer were identified from the Johns Hopkins Scleroderma Center database. Demographics, SSc phenotypic data, cancer treatments and RT outcomes were abstracted from the database and medical record review. Among women exposed to RT, we examined whether erythema, blistering, ulceration, or thickening of the skin developed in the RT port. The following outcomes were compared between patients who did and did not receive RT: 1) changes in mRSS and FVC at 2 years post cancer diagnosis by the Student's t test and 2) percentage of patients cancer free at 1, 2 and 5 years by a chi square test.

Results:

116 female SSc patients with a breast cancer diagnosis were identified. Most patients had limited disease (65.4% vs. 34.6% diffuse) and were white (90.5%). The mean age at SSc onset and cancer diagnosis was 53.4±12.2 and 55.7±10.6 years, respectively. 43 women (37.1%) received RT as part of their cancer treatment regimen: 4/31 with available data developed erythema, 0/31 had blistering, 1/31 developed ulceration, and 16/33 had skin thickening in the RT port. There was not a statistically significant association between skin thickening in the RT port and cutaneous subtype (OR 1.89 for diffuse vs. limited, 95% CI 0.44, 7.85). 3/30 patients with available data developed pulmonary fibrosis that was restricted to the lung fields in the radiation port. While 48.5% of women treated with RT developed localized cutaneous fibrosis, patients treated with RT required less extensive surgery for their breast cancers (66% with lumpectomy in RT group vs 34% in no RT group, $p<0.001$). When comparing patients with and without exposure to RT, there were no statistically significant differences in change in mRSS (mean change 0.6 in RT group (N=5) vs. 0.26 in no RT group (N=19), $p= 0.32$) or change in FVC at 2 years (mean change 5.6% in RT group (N=6) vs. -1.8% in no RT group (N=24), $p= 0.15$). There were no statistically significant differences in the proportion of patients who were cancer free 1, 2, and 5 years post breast cancer diagnosis in patients who received RT versus those who did not. Similarly, there were no significant differences in mortality (34.3% no RT, 34.9% RT).

Conclusion:

While <50% SSc patients with breast cancer developed localized radiation induced cutaneous fibrosis, patients treated with RT were able to avoid more extensive surgery. Cutaneous subtype was not associated with the risk of developing localized radiation fibrosis. While our sample size was limited, SSc and cancer outcomes were similar between the two groups, suggesting that exposure to RT did not exacerbate SSc. These data suggest that among SSc patients with breast cancer, the decision about whether or not to proceed with RT should be an individualized decision based on patient preferences.

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Abstract Number: 3262

The Influence of Immunosuppressive Therapy on Microangiopathy in Systemic Sclerosis As Measured with Nailfoldcapillaroscopy

Jessica Meijs[1], B. de Boer[1], Anne Schouffoer[1,2], T. W. J. Huizinga[3], Hein Putter[4] and **Jeska K. de Vries-Bouwstra**[1], [1]Rheumatology, Leiden University Medical Center, Leiden, Netherlands, [2]Rheumatology, Haga Hospital, The Hague, Netherlands, [3]Department of Rheumatology, Leiden University Medical Center, Leiden, Netherlands, [4]Medical Statitics and Bioinformatics, professor in medical statistics, Leiden, Netherlands

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Background/Purpose:

Microangiopathy in systemic sclerosis (SSc), as visualized by nailfold videocapillaroscopy (NVC) is a dynamic and sequential process[1]. In time, NVC patterns progress from early, to active and finally late SSc pattern. A relation between improvement of NVC pattern and treatment with immunosuppressive drugs has been suggested[2,3]. We aimed to evaluate 1. change of NVC patterns in SSc patients, and 2. influence of

treatment with cyclophosphamide (CYC) and autologous hemopoetic stem cell transplantation (HSCT) on change of NVC patterns.

Methods:

NVC was performed annually in SSc patients participating in a care program. For the current analysis, patients were included if at least two NVCs were performed and qualitatively assessed (normal, borderline changes, or SSc pattern [early, active or late]). Change of NVC pattern was classified as: 1. stable (same pattern at all evaluations), 2. progressive (change from early to active/ late or from active to late) or 3. reverse transition (change from late to early/active, or from active to early) . In order to asses the association between CYC and HSCT with relative rates of transition of NVC patterns a maximum likelihood estimation in a multistate model was used, which, additionally to correction for age, gender and disease duration, corrects for time to transition in relation to drug exposure time.

Results: NVC was performed twice in n=98 patients, 3 times in n= 35 patients and 4 times in n=5 patients. Of these 138 patients, 82% was female, mean age was 51 years, and median disease duration was 3 years. At baseline 6 patients had a normal pattern, n=4 borderline changes, n=13 an early pattern, n=54 an active pattern, and n=61 a late pattern. Over time, NVC pattern was stable in 53%, progressive in 21% and 26% showed reverse transition (table 1). Treatment with HSCT was significantly associated with higher rate of reverse transition (relative transition rates [95% CI] 5.4 [1.0-28.8]). No association between CYC and rate and direction of change of NVC pattern was found.

Conclusion:

Change of NVC pattern was observed in 47% of SSc patients; 26% showed reverse transition. Rapid reverse transition was associated with treatment with HSCT but not with CYC, indicating that more aggressive immunosuppressive treatment can influence microangiopathy in SSc.

(1) Arthritis Rheum 2012;64:821.

(2) Ann Rheum Dis 2008 ;67:1057.

(3) PLoS One 2008;3:e1452.

Table 1. Baseline characteristics of SSc patients stratified according to change of NVC pattern
*

	Total N =138	Stable N=65	Progressive N=31	Reverse N=42
Sociodemographics				
Age, years, mean (SD)	51 (13.6)	50.7 (12.6)	48.4 (17.5)	53.6 (11.6)
Female, N (%)	113 (82)	55 (84.6)	29 (93.5)	29 (69)
Caucasian origin, N (%)	98 (71)	44 (67.7)	23 (74.2)	31 (73.8)
Disease characteristics				
Disease duration, years, median (IQR)	3 (1-10.3)	3 (1-11)	1 (0-8)	4 (1-10)
Onset of RP, years, median (IQR)§	11.5 (4.8-19.3)	13 (5-21.3)	8 (3-15)	10 (5-17)
Onset of non-RP, years, median (IQR)†	6 (3-12)	8 (3-13)	3 (1.3-9.5)	5 (3-10)
DU	38 (27.5)	20 (30.8)	10 (32.3)	8 (19)
Pitting scars	64 (46.4)	37 (56.9)	13 (41.9)	14 (33.3)
Synovitis	16 (11.6)	8 (12.3)	5 (16.1)	3 (7.1)
Friction rubs	3 (2.2)	1 (1.5)	2 (6.5)	0 (0)
Proximal muscular weakness	6 (4.3)	3 (4.6)	1 (3.2)	2 (4.9)
Renal crisis	3 (2.2)	2 (3.1)	0 (0)	1 (2.4)
MRSS, median (IQR)	4 (0-6)	4 (0-6)	4 (2-6)	2 (0-6)
Autoantibodies, N (%)				
ANA§	120 (87)	58 (89.2)	28 (90.3)	34 (81)
Anti-Scl-70†	35 (25)	15 (23.1)	10 (32.3)	10 (23.8)
Anti-centromere†	46 (33)	22 (33.8)	8 (25.8)	16 (38.1)
Cardiopulmonary investigations				
FVC % of predicted, mean (SD)§	101.5 (22.1)	101.1 (23)	103.8 (21.7)	100.4 (21.5)
DLCO % of predicted, mean (SD)§	63.8 (16.2)	62.8 (16.9)	66.5 (16.7)	63.2 (15)
ILD, N (%)	77 (55.8)	36 (55.4)	15 (48.4)	26 (61.9)
SPAP≥35mmHg, N (%)	10 (7.2)	6 (9.2)	0 (0)	4 (9.5)
LVEF %, mean (SD)	59.6 (7.6)	58.7 (7.3)	62.8 (7.9)	58.5 (7.5)
Pericardial fluid, N (%)	4 (2.9)	2 (3.1)	1 (3.2)	1 (2.4)
Nailfold videocapillaroscopy, N (%)				
Normal	6 (4.3)	1 (1.5)	5 (16.1)	NA
Borderline changes	4 (2.9)	1 (1.5)	2 (6.5)	1 (2.4)
SSc pattern				
Early	13 (9.4)	1 (1.5)	7 (22.6)	5 (11.9)
Active	54 (39.1)	27 (41.5)	17 (54.8)	10 (23.8)
Late	61 (44.2)	35 (53.8)	NA	26 (61.9)
Immunosuppressive treatmentD				
Previous	52 (37.7)	21 (32.3)	12 (38.7)	19 (45.2)
Current	38 (27.5)	19 (29.2)	10 (32.3)	9 (21.4)

DcSSc: diffuse cutaneous SSc; LcSS: limited cutaneous SSc; LSSc: limited non cutaneous SSc; RP: Raynaud's Phenomenon; MRSS: modified Rodnan Skin Score;
ANA: antinuclear antibody; Anti-Scl-70: anti-topoisomerase; FVC: forced vital capacity;
DLCO: diffusing capacity for carbon monooxide; ILD: interstitial lung disease; SPAP:
systolic pulmonary arterial pressure; LVEF: left ventricle ejection fraction; IQR: interquartile
range; NA: not applicable.
*According to the last available NVC
D Any of the following: autologous hematopoeitic stem cell transplantation, cyclophosphamide,
mycophenolate mofetil, methotrexate, corticosteroids or rituximab.
§ <5% missing
† 20% missing

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Abstract Number: 3263

The Promis-29 in Systemic Sclerosis: Associations with Clinical Characteristics in the Scleroderma Patient-Centered Intervention Network (SPIN) Cohort

Linda Kwakkenbos[1,2], Brett D. Thombs[1], Susan J. Bartlett[3,4], Marie-Eve Carrier[2], Marie Hudson[1], Luc Mouthon[5], Vanessa L. Malcarne[6], Maureen Sauvé[7], **Dinesh Khanna**[8] and SPIN investigators, [1]McGill University, Montreal, QC, Canada, [2]Lady Davis Institute for Medical Research, Jewish General Hospital, Montreal, QC, Canada, [3]Medicine , Divisions of Clinical Epidemiology, Rheumatology, Respirology, McGill University, Montreal, QC, Canada, [4]Division of Rheumatology, Johns Hopkins School of Medicine, Baltimore, MD, [5]Paris Descartes University, UPRES-EA 4058, Department of Internal Medicine, Cochin Hospital, Paris, France, [6]SDSU/UC San Diego Joint Doctoral Program in Clinical Psychology, San Diego, CA, [7]Scleroderma Societies of Canada and Ontario, Hamilton, QC, Canada, [8]Division of Rheumatology, University of Michigan, Ann Arbor, MI

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Background/Purpose: Systemic sclerosis (SSc) has far-reaching physical consequences and impacts health-related quality of life. The Patient-Reported Outcomes Measurement Information System (PROMIS)-29 measure includes four items each for domains reflecting physical function, anxiety, depression, fatigue, sleep disturbance, pain interference, and ability to perform social roles, plus a single item on pain intensity (range 0-10). The objective was to explore associations of PROMIS-29 domains with clinical variables in subjects with SSc.

Methods: Adult SSc subjects were enrolled in the Scleroderma Patient-centered Intervention Network (SPIN) Cohort from 19 centers across Canada, the USA and the UK between July 2014 and May 2015. Baseline medical data are provided by the enrolling physician, and SPIN Cohort participants completed the PROMIS-29 at baseline. For all PROMIS-29 domains, t-tests were conducted for gender and dichotomous clinical variables. The standardized mean effect size [95% CI] was calculated to assess the magnitude of the difference between groups. Correlations and effect sizes were interpreted as small (²0.3), moderate (between 0.3 and 0.5), or large (³0.5).

Results: In total, 473 subjects were included in the analyses. Mean age was 55 years (SD=11.9) and mean time since onset of the first non-Raynaud symptom was 11.8 years (SD=8.7). Most subjects were female (n=411, 86.9%) with lcSSc (n=277, 59.1%). The PROMIS-29 domains were 0.1-0.8 SD below general population. The involvement of the gastrointestinal tract was consistently associated with worse outcomes across PROMIS-29 domains (lower scores for function and roles, higher scores for fatigue, pain interference, pain intensity, anxiety and depression), with moderate to large effect sizes in 7 of 8 domains. Other clinical variables with decrements in at least 5 domains included: more skin thickening, diffuse disease, and presence of contractures (Tables 1 and 2). **Conclusion:** SSc is associated with significant impairment in PROMIS-29 domains, with certain disease characteristics more commonly associated than others. These data inform priorities for future patient-centered research.

Table 1. Mean differences of PROMIS-29v2 function, fatigue, and pain domains between subjects with different disease characteristics

	N	Function M (SD)	Effect size [95% CI]	Fatigue M (SD)	Fatigue effect size [95%CI]	Pain interference M (SD)	Effect size [95% CI]	Pain intensity M (SD)	Effect size [95% CI]
Sex:									
Female	411	43.01 (8.73)	0.16	56.08 (11.24)	0.10	55.74 (9.97)	-0.16	3.68 (2.72)	-0.04
Male	62	41.58 (8.72)	[-0.10, 0.43]	55.00 (10.77)	[-0.17, 0.36]	57.3 (8.22)	[-0.43, 0.11]	3.79 (2.45)	[-0.31, 0.23]
Disease subtype:									
Limited/Sine	277	43.93 (8.74)	**0.30**	55.55 (11.47)	-0.08	54.93 (9.59)	**-0.24**	3.54 (2.63)	-0.13
Diffuse	192	41.36 (8.5)	**[0.11, 0.48]**	56.41 (10.76)	[-0.26, 0.11]	57.24 (9.68)	**[-0.42, -0.06]**	3.88 (2.71)	[-0.31, 0.06]
Raynauds:									
No	4	39.98 (11.66)	-0.32	61.78 (12.31)	0.52	61.28 (7.47)	0.55	6.00 (2.94)	0.87
Yes	463	42.80 (8.71)	[-1.31, 0.66]	55.91 (11.2)	[-0.46, 1.51]	55.94 (9.76)	[-0.44, 1.53]	3.68 (2.68)	[-0.12, 1.85]
Puffy fingers:									
No	172	42.03 (8.91)	-0.10	56.86 (10.65)	0.06	56.47 (9.8)	0.05	3.73 (2.69)	-0.03
Yes	273	42.87 (8.47)	[-0.29, 0.09]	56.19 (11.07)	[-0.13, 0.25]	56 (9.73)	[-0.14, 0.24]	3.80 (2.69)	[-0.22, 0.16]
Sclerodactyly:									
No	74	42.68 (8.32)	-0.02	56.82 (11.81)	0.10	56.47 (9.56)	0.07	3.86 (2.64)	0.08
Yes	395	42.90 (8.85)	[-0.27, 0.22]	55.74 (11.1)	[-0.15, 0.34]	55.83 (9.84)	[-0.18, 0.31]	3.66 (2.70)	[-0.17, 0.33]
Skin thickening:									
No	218	43.73 (8.58)	**0.19**	55.13 (11.88)	-0.13	54.19 (9.85)	**-0.34**	3.39 (2.68)	**-0.21**
Yes	253	42.09 (8.82)	**[0.01, 0.37]**	56.57 (10.53)	[-0.31, 0.05]	57.45 (9.48)	**[-0.52, -0.16]**	3.96 (2.68)	**[-0.39, -0.03]**
Digital ulcers:									
No	302	43.38 (8.57)	0.17	55.71 (11.16)	-0.06	55.33 (9.82)	-0.18	3.48 (2.63)	**-0.22**
Yes	167	41.86 (9.06)	[-0.02, 0.36]	56.39 (11.17)	[-0.25, 0.13]	57.11 (9.61)	[-0.37, 0.01]	4.07 (2.74)	**[-0.41, -0.03]**
Joint contractures:									
No	333	43.88 (8.67)	**0.49**	55.54 (11.04)	-0.16	54.75 (9.66)	**-0.46**	3.39 (2.59)	**-0.42**
Yes	115	39.66 (8.20)	**[0.28, 0.71]**	57.33 (10.60)	[-0.38, 0.05]	59.16 (9.29)	**[-0.67, -0.25]**	4.50 (2.70)	**[-0.64, -0.21]**
Telangiactasias:									
No	116	43.37 (7.78)	0.07	55.65 (10.7)	-0.03	54.94 (8.77)	-0.13	3.59 (2.49)	-0.05
Yes	354	42.72 (9.02)	[-0.14, 0.28]	55.99 (11.36)	[-0.24, 0.18]	56.21 (10.04)	[-0.34, 0.08]	3.73 (2.75)	[-0.26, 0.16]
Overlap syndrome:									
No	371	42.74 (8.52)	0.10	55.95 (11.00)	-0.17	56.06 (9.36)	-0.07	3.70 (2.61)	-0.12
Yes	91	41.9 (9.09)	[-0.13, 0.33]	57.84 (10.58)	[-0.40, 0.06]	56.75 (10.97)	[-0.30, 0.16]	4.03 (2.89)	[-0.35, 0.10]
GI involvement:									
		47.19		49.4				3.02	**0.29**

No	60	47.19 (7.92)	**0.58**	49.4 (9.79)	**-0.69**	52.37 (9.93)	**-0.42**	3.02 (2.67)	**-0.29**
Yes	413	42.19 (8.67)	**[0.31, 0.86]**	56.88 (11.06)	**[-0.96, -0.41]**	56.47 (9.64)	**[-0.7, -0.15]**	3.8 (2.67)	**[-0.56, -0.02]**
Lung disease:									
No	287	43.73 (8.82)	**0.30**	55.41 (11.12)	-0.09	55.41 (9.83)	-0.15	3.63 (2.71)	-0.05
Yes	172	41.14 (8.42)	**[0.11, 0.49]**	56.48 (11.36)	[-0.28, 0.09]	56.9 (9.57)	[-0.34, 0.04]	3.77 (2.62)	[-0.24, 0.13]
Pulmonary hypertension:									
No	358	43.18 (8.9)	**0.51**	55.71 (11.41)	-0.17	55.59 (9.86)	-0.29	3.64 (2.70)	-0.15
Yes	48	38.67 (8.65)	**[0.20, 0.81]**	57.60 (10.92)	[-0.47, 0.13]	58.41 (9.90)	[-0.59, 0.02]	4.04 (2.59)	[-0.45, 0.15]

Table 2. Mean differences of PROMIS-29v2 anxiety, depression, sleep, and role domains between subjects with different disease characteristics

	N	Anxiety M (SD)	Effect size [95% CI]	Depression M (SD)	Effect size [95% CI]	Sleep M (SD)	Effect size [95% CI]	Roles M (SD)	Effect size [95% CI]
Sex:									
Female	411	51.63 (9.71)	0.07	50.78 (9.19)	-0.09	51.75 (5.04)	-0.05	47.75 (9.55)	0.17
Male	62	50.99 (9.27)	[-0.2, 0.33]	51.57 (8.95)	[-0.35, 0.18]	52.03 (4.78)	[-0.32, 0.21]	46.13 (10.22)	[-0.1, 0.44]
Disease subtype:									
Limited/Sine	277	50.66 (9.48)	-0.21	50.15 (8.77)	**-0.18**	51.57 (4.99)	-0.09	48.62 (9.58)	**0.27**
Diffuse	192	52.71 (9.71)	[-0.40, -0.03]	51.84 (9.57)	**[-0.37, 0.00]**	52.01 (5.02)	[-0.27, 0.1]	46.1 (9.43)	**[0.08, 0.45]**
Raynauds:									
No	4	60.05 (13.58)	0.00	58.75 (4.7)	0.87	55.1 (5.88)	0.66	39.2 (9.23)	-0.87
Yes	463	51.48 (9.57)	[-0.98, 0.98]	50.83 (9.15)	[-0.12, 1.85]	51.78 (5.01)	[-0.32, 1.65]	47.57 (9.59)	[-1.86, 0.11]
Puffy fingers:									
No	172	51.99 (9.19)	0.03	50.85 (8.92)	-0.05	51.38 (4.98)	-0.16	47.35 (9.58)	0.03
Yes	273	51.72 (9.92)	[-0.16, 0.22]	51.29 (9.3)	[-0.24, 0.14]	52.17 (5.01)	[-0.35, 0.03]	47.11 (9.49)	[-0.17, 0.22]
Sclerodactyly:									
No	74	51.64 (11.05)	0.01	51.22 (9.39)	0.04	51.84 (5.18)	0.01	47.23 (9.25)	-0.04
Yes	395	51.51 (9.42)	[-0.23, 0.26]	50.83 (9.13)	[-0.21, 0.29]	51.8 (4.98)	[-0.24, 0.25]	47.63 (9.75)	[-0.29, 0.21]
Skin thickening:									
No	218	49.86 (9.84)	**-0.32**	49.43 (8.99)	**-0.29**	51.42 (4.99)	-0.14	48.89 (9.9)	**0.26**
Yes	253	52.95 (9.28)	**[-0.51, -0.14]**	52.07 (9.14)	**[-0.47, -0.11]**	52.12 (5.01)	[-0.32, 0.04]	46.4 (9.32)	**[0.08, 0.44]**
Digital ulcers:									
No	302	51.2 (9.6)	-0.10	50.31 (8.75)	-0.18	51.71 (4.92)	-0.04	47.71 (9.56)	0.05
Yes	167	52.19 (9.78)	[-0.29, 0.09]	51.95 (9.81)	[-0.37, 0.01]	51.91 (5.20)	[-0.23, 0.15]	47.24 (9.89)	[-0.14, 0.24]
Joint contractures:									
No	333	51.14 (9.77)	-0.16	50.42 (8.89)	**-0.22**	51.29 (4.82)	**-0.35**	48.26 (9.46)	**0.32**
Yes	115	52.73 (9.25)	[-0.38, 0.05]	52.43 (9.58)	**[-0.43, -0.01]**	53.08 (5.89)	**[-0.56, -0.14]**	45.23 (9.68)	**[0.11, 0.53]**
Telangiactasias:									
No	116	52.90 (9.61)	0.19	51.52 (8.95)	0.09	51.65 (4.65)	-0.04	47.34 (8.29)	-0.04
Yes	354	51.09 (9.64)	[-0.02, 0.40]	50.66 (9.23)	[-0.12, 0.3]	51.83 (5.14)	[-0.24, 0.17]	47.69 (10.03)	[-0.25, 0.17]
Overlap syndrome:									
No	371	51.94 (9.41)	0.09	51.11 (9.16)	0.02	51.87 (4.99)	0.04	47.53 (9.38)	0.16
Yes	91	51.06 (10.53)	[-0.14, 0.32]	50.95 (9.2)	[-0.21, 0.25]	51.67 (5.2)	[-0.19, 0.27]	46.05 (9.96)	[-0.07, 0.39]
GI involvement:									
No	60	49.03 (9.15)	**-0.30**	47.95 (8.13)	**-0.37**	51.45 (4.95)	-0.08	51.7 (8.62)	**0.50**
Yes	413	51.91 (9.68)	**[-0.57, -0.03**]	51.31 (9.23)	**[-0.64, -0.10]**	51.84 (5.02)	[-0.35, 0.19]	46.94 (9.64)	**[0.23, 0.77]**
Lung disease:									
No	287	51.22 (9.44)	-0.08	50.1 (8.56)	**-0.20**	51.67 (4.94)	-0.04	48.22 (9.83)	**0.21**
Yes	172	51.99 (9.96)	[-0.27, 0.11]	51.87 (9.87)	**[-0.38, -0.01]**	51.87 (5.05)	[-0.23, 0.15]	46.22 (9.11)	**[0.02, 0.40]**

Pulmonary hypertension:								
No	358	51.63 (9.82)	-0.03 [-0.33, 0.27]	50.86 (9.22)	-0.08 [-0.38, 0.22]	51.75 (4.89)	0.06 [-0.24, 0.36]	47.79 (9.71)	**0.39** **[0.09, 0.70]**
Yes	48	51.88 (8.47)		51.58 (7.88)		51.45 (5.09)		43.96 (9.66)	

Disclosure: L. Kwakkenbos, None; **B. D. Thombs**, None; **S. J. Bartlett**, None; **M. E. Carrier**, None; **M. Hudson**, None; **L. Mouthon**, None; **V. L. Malcarne**, None; **M. Sauvé**, None; **D. Khanna**, None.

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Abstract Number: 3264

Multiplex Serum Protein Analysis in Systemic Sclerosis Defines Potential Anti-Fibrotic Mechanisms and Markers of Response to Hyperimmune Caprine Serum

Niamh Quillinan[1], Kristina E.N. Clark[1], Deirdre McIntosh[2], Jeffrey Vernes[2] and **Christopher P. Denton**[3], [1]Rheumatology, UCL Division of Medicine, London, United Kingdom, [2]Daval International, London, United Kingdom, [3]Rheumatology and Connective Tissue Diseases, University College London, London, United Kingdom

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Background/Purpose: Hyperimmune caprine serum (HICS) administered by subcutaneous injection over 26 weeks has shown benefit for modified Rodnan skin score in diffuse systemic sclerosis (SSc) in a recent phase II placebo controlled trial[1]. We report multiplex protein analysis of serum samples from the trial to explore mechanisms of action of this novel biological agent and identify potential biomarkers in SSc.

Methods: In a parallel group placebo controlled trial patients were treated with HICS (n=10) or placebo (n=10) over 26 weeks, with a follow up open label treatment for 26 weeks. Serum samples at baseline, 6 weeks, 26 and 52 weeks were analysed using a multiplex assay for 40 cytokines and growth factors (Luminex®) and additional individual solid phase immunoassays for procollagen III N-terminal propeptide (PIIINP), serum IL-2R, cartilage oligomeric matrix protein (COMP), TGF-beta1 and von Willebrand factor (vWF). To explore patterns of change over multiple analytes heat maps were constructed using CIMminer NIH software. Clustering was performed using correlation, and Pearson coefficient and significance analysis of microarrays (SAM) correction.

Results*:* Cluster analysis defined factors that were increased or decreased from baseline after 26 weeks treatment with HICS. **Results** for key analytes are summarised in **Table 1**. Consistent with previous preclinical studies there was evidence for marked upregulation of the hypothalmo-pituitary-adrenal axis from 6 weeks after HCS treatment and this effect was maintained at 26 weeks. This was evidenced by increase in alpha-MSH and ACTH in cases treated with HICS. There were changes in markers of fibroblast biology including changes in bFGF, PIIINP and COMP. Novel findings include consistent increase in PIIINP associated with improved MRSS suggesting that this may be a marker of ECM turnover rather than fibrogenesis. Other factors that were frequently reduced, though not reaching statistical significance, included TIMP2, fractalkine and TGFbeta1 levels.

Conclusion: This study illustrates the feasibility of conducting relatively short term parallel group placebo controlled trials in established dcSSc to target skin fibrosis. The benefit of including multiplex analysis of serum proteins in early phase trials to better understand treatment mechanisms and disease biology is confirmed. This study suggests possible mechanisms of action for HICS, including upregulation of alpha-MSH, that has been shown to be antifibrotic in preclinical studies, and suggests possible serum markers to be included in future trials.

Table 1 Change in serum protein level (mean [sd]) after 26 weeks HICS or placebo treatment

	Serum protein	HICS Change during study		t-test (p)	Placebo Change during study		t-test (p)	SAM analysis HICS versus placebo		HICS change versus placebo
Direction of change		Basal	26 wk	26 wk versus basal	basal	26 wk	26 wk versus basal	Fold change	q-value	p-value
UP										
	alpha-MSH pg/ml	3.7 [3.6]	31.1 [35.8]	**0.0035**	1.8 [0.9]	2.2 [1.9]	0.75	299.6	0	**0.039**
	ACTH pg/ml	1.9 [2.4]	27.6 [42.3]	**0.0099**	1.1 [1.1]	1.0 [0.7]	0.97	176.6	0	**0.05**
	bFGF pg/ml	3.4 [6.5]	21.5 [21.9]	**0.0185**	21.3 [43.3]	23.6 [51.6]	0.62	65.0	0	0.15
	PIIINP ug/ml	6.9 [3.8]	15.4 [10.1]	**0.0002**	5.3 [2.7]	5.9 [2.7]	0.62	14.6	20	**0.012**
DOWN										
	COMP ng/ml	1.8 [1.1]	1.4 [0.3]	**0.055**	1.3 [0.5]	1.4 [0.6]	0.70	-3.38	36	0.265
	FRACT ng/ml	3.7 [6.4	3.3 [6.1]	0.108	1.1 [0.7]	1.0 [0.6]	0.79	-6.1	43	0.318

Reference: [1] Ann Rheum Dis. 2014, 73:56-61

Disclosure: N. Quillinan, None; **K. E. N. Clark**, None; **D. McIntosh**, Daval International, 3; **J. Vernes**, Daval International, 3; **C. P. Denton**, GlaxoSmithKline, 2,Actelion Pharmaceuticals US, 5,GlaxoSmithKline, 5,Serono, 5,Inventiva, 5,CSL Behring, 2,Bayer, 5.

Abstract Number: 3265

Sustaining Employment with Arthritis: Can Existing Workplace Policies and Accommodations Make a Difference?

Monique A.M. Gignac[1,2], Elizabeth M. Badley[3], Dorcas Beaton[4], Vicki Kristman[5], Cameron Mustard[6], Peter Smith[6] and Selahadin Ibrahim[6], [1]Instititue for Work and Health, Toronto, ON, Canada, [2]Dalla Lana School of Public Health, University of Toronto, Toronto, ON, Canada, [3]Toronto Western Research Institute, Toronto, ON, Canada, [4]St. Michael's Hospital, Toronto, ON, Canada, [5]Lakehead University, Toronto, ON, Canada, [6]Institute for Work and Health, Toronto, ON, Canada

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Background/Purpose: Despite improved treatment, many individuals with inflammatory arthritis (IA) and osteoarthritis (OA) report difficulties working, reduced productivity and elevated absenteeism. Lacking is research on workplace policies and whether they are associated with better health and employment outcomes. This research: 1) examined the availability, need and use of diverse workplace policies, comparing those with arthritis to healthy controls; and 2) contrasted health and work outcomes of participants who reported accommodation needs were unmet to those whose needs were met or whose needs were exceeded (i.e., used more accommodations than needed).

Methods: Participants had osteoarthritis (OA) or inflammatory arthritis (IA) or no disabling health conditions. They were recruited from a

national panel of 80,000 Canadians. Invitations were sent to a sub-sample of individuals aged ≥ 50 yrs to reach a quota of 500 arthritis and 500 healthy respondents. Eligibility included current employment; absence of disabling conditions other than arthritis; and fluency in English/French. A cross-sectional survey was administered on-line or by telephone and assessed demographic (age, gender, education); health (pain, fatigue, workplace activity limitations); work context (job sector, hours, physical work); workplace practices (health benefits, flexible hours, special equipment/adaptations, modified duties, altered work schedules, work-at-home arrangements) and job outcomes (absenteeism, productivity loss, job disruptions). Descriptive statistics and analyses of variance compared groups.

Results: There was a 59% response rate to study invitations and final sample of 631 participants with arthritis (OA>70%; women=53.6%) and 538 with no disabling conditions (healthy controls, 44% women). Groups were similar in demographics, work context and availability of policies to manage work and health. Those with arthritis reported significantly poorer health (pain, fatigue, workplace activity limitations). Yet, there were few differences in their reports of needing or using workplace policies compared to healthy controls. Exceptions were that more individuals with arthritis reported needing and using modified job duties and needing special equipment/adaptations. Comparing the groups revealed similar associations of policy use and job outcomes. Healthy controls and those with arthritis who had unmet accommodation needs reported greater work stress, health variability, productivity loss and job disruptions. Unmet need in those with arthritis also was related to greater fatigue and workplace activity limitations. Respondents whose needs were exceeded had the lowest levels of fatigue, activity limitations, productivity loss and job disruptions.

Conclusion: Despite poorer health, respondents with arthritis often did not take advantage of available workplace policies. Yet using accommodations, even when not needed, was associated with better health and work outcomes. These results need to be replicated with longitudinal data. However, they point to potential benefits of more proactive use of work policies to manage arthritis and employment.

Disclosure: M. A. M. Gignac, None; **E. M. Badley**, None; **D. Beaton**, None; **V. Kristman**, None; **C. Mustard**, None; **P. Smith**, None; **S. Ibrahim**, None.

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Abstract Number: 3266

Keeping Baby Boomers in the Labour Force Longer: What Does It Mean for Workers with Arthritis?

Monique A.M. Gignac[1], Elizabeth M. Badley[2], Dorcas Beaton[3], Vicki Kristman[4], Cameron Mustard[5], Peter Smith[5] and Selahadin Ibrahim[5], [1]Instititue for Work and Health, Toronto, ON, Canada, [2]Toronto Western Research Institute, Toronto, ON, Canada, [3]St. Michael's Hospital, Toronto, ON, Canada, [4]Lakehead University, Toronto, ON, Canada, [5]Institute for Work and Health, Toronto, ON, Canada

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Background/Purpose: There is concern that an aging workforce results in lost skills and high burden on pension programs. This has resulted in the dissolution of mandatory retirement in many countries and an expectation that older adults will work longer, including in bridge employment (retiring from a main career but continuing to work in a new job/capacity). Previous research finds that many individuals with arthritis leave employment prematurely, but information about retirement plans and sustaining work is scarce. This study examined older workers with arthritis and healthy controls in terms of: 1) retirement plans and bridge employment; and 2) factors associated with bridge employment.

Methods: Participants had osteoarthritis (OA) or inflammatory arthritis (IA) or no disabling health conditions. They were recruited from a national panel of 80,000 Canadians. Invitations were sent to a sub-sample of individuals aged ≥ 50 yrs to reach a quota of 500 arthritis and 500 healthy respondents. Eligibility included current employment; absence of disabling conditions other than arthritis; and fluency in English/French. A cross-sectional survey was administered on-line or by telephone and assessed demographic (age, gender, education); health (pain, fatigue); planned retirement age and expectations, returning to work after retirement (bridge employment) and work context (job sector, hours, physical work, self employment). Analyses of variance and logistic regression examined differences between groups and factors related to retirement.

Results: There was a 59% response rate to study invitations and final sample of 631 arthritis participants (OA >70%; women=53.6%) and 538 healthy controls (44% women) who were on average 59 yrs old. Groups were similar in many demographic and work context factors. Respondents with arthritis reported significantly poorer health (pain, fatigue, workplace activity limitations). Yet, healthy controls and respondents with arthritis were not significantly different in planned retirement age (~65 yrs) or in desiring to remain working full- or part-time after retirement (healthy FT=7.1%, PT=52.4%; arthritis FT=7.6%, PT=50.6%). Arthritis respondents were more likely to believe they might retire sooner than planned (22.1%; healthy 6.8%) and to have retired previously and returned to work (20.3%; healthy 13.0%). Health factors (pain, fatigue, co-morbidities, workplace activity limitations) were significantly associated with expectations of retiring sooner than planned.

Healthy controls working in bridge employment were more likely to be self-employed and working for smaller organizations (<50 people); arthritis respondents were more likely to be in contract or part-time work and to report financial need as a reason for bridge employment.

Conclusion: Previous research has focused on giving up work among those with arthritis. This study highlights that many with arthritis return to bridge employment after retiring and have similar expectations and plans as their healthy counterparts. Research is needed examining types of work that might sustain the employment of those with arthritis.

Disclosure: M. A. M. Gignac, None; **E. M. Badley**, None; **D. Beaton**, None; **V. Kristman**, None; **C. Mustard**, None; **P. Smith**, None; **S. Ibrahim**, None.

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Abstract Number: 3267

Functional Disability in Adolescents Is Predicted By Self-Report of Sleep Problems, Depressive Symptoms, Low Physical Activity and Worst Pain Intensity Levels

Kari Firestone[1], **Kim Jones**[2] and Anna Wilson[3], [1]School of Nursing, Oregon Health & Science University, Portland, OR, [2]Rsch & Develop/Mail Code SN OR, Oregon Health Sciences Univ, Portland, OR, [3]OHSU Institute on Development and Disability, Oregon Health & Science University, Portland, OR

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Background/Purpose: Pain intensity has been shown to be important in understanding pain related functional disability in adolescents. Additional factors may affect other critical outcomes including functional disability and quality of life. Findings from adult-based studies indicate that contextual factors (e.g. demographics and other patient centered characteristics) may contribute to functional disability beyond that of pain intensity but are less documented in pediatric populations. The purpose of this study was to describe pain distribution and characteristics in adolescents with chronic pain and to explore predictors of functional disability.

Methods: Data were collected from electronic medical records review in a consecutive series of 314 new pediatric pain patients in an academic pain clinic. Available variables included demographics, pain intensity, location, history and frequency, child optimism, anxiety and depression, and the Children's Activity Limitations Interview (CALI) a 21-item measure designed to assess pain-related activity limitations and is a proxy for functional disability in children and adolescents.

Results: The mean (±SD) age at presentation was 15.9±3.27. Participants reported high levels of pain with a typical pain intensity of 5.82 ± 1.98 and worst pain intensity of 8.95 ± 1.33. 42.3% of participants reported experiencing pain in three or greater locations. The most commonly reported pain location included the head (28.5%), abdomen (23.4%), leg (13.6%) and lower back (11.2%) with 78.5% of participants reported experiencing pain at least daily within the last month. 87.6% of participants reported difficulty sleeping related to their pain. The CALI sum scores had a mean of 43.86 ± 17.89. Child/adolescent perception of their ability to cope or deal with their pain was a mean of 4.86. Regression analysis conducted with CALI as independent variable. Stage 1, pain characteristics, contributed significantly to the model and accounted for 18.3% of variance in functional disability. Stage 2, psychological function, explained an additional 10% of variation in functional disability. Stage 3, physical variables, accounted for an additional 3.2% of variance. Stage 4, sleep problems, explained an additional 1.5% of the variance in functional disability. Significant predictors of functional disability included "worst" pain intensity levels, depressive symptoms, physical activity and sleep problems. Together, all independent variables accounted for 32.8% of the variance in functional disability.

Conclusion: In line with previous research, pain characteristics were found to be a significant predictor of functional disability. Novel factors (depressive symptoms, engagement in physical activity and sleep problems) also significantly predicted functional disability after controlling for pain characteristics. Understanding a more comprehensive set of variables that contribute to adolescents' functional disability is an important step in tailoring interventions in adolescents with chronic pain.

Disclosure: K. Firestone, None; **K. Jones**, None; **A. Wilson**, None.

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Abstract Number: 3268

Foot and Ankle Characteristics Associated with Falls in People with Rheumatoid Arthritis: A Prospective Longitudinal Study

Angela Brenton-Rule[1], Nicola Dalbeth[2], Hylton B. Menz[3], Sandra Bassett[4] and Keith Rome[5], [1]Podiatry, AUT University, Auckland, New Zealand, [2]Department of Medicine, University of Auckland, Auckland, New Zealand, [3]Musculoskeletal Research Centre, La Trobe University, Bundoora, VIC, Australia, [4]AUT University, Auckland, New Zealand, [5]Health & Research Rehabilitation Centre, AUT University, Auckland, AR, New Zealand

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Background/Purpose: People with rheumatoid arthritis (RA) have an increased risk of falls. The consequences of falls include loss of confidence and independence, injury and death. The foot is a common site of pathology in RA and foot problems are reported in up to 90% of people with established disease. Previous studies in non-RA populations have identified that foot and ankle problems are associated with falls in older adults. The aim of this prospective observational study was to determine whether foot and ankle characteristics are associated with falls in people with RA.

Methods: Adults with RA according to the 2010 ACR/EULAR classification criteria were recruited from rheumatology outpatient clinics. RA characteristics, common fall risk factors, and foot and ankle variables were measured at baseline. Foot and ankle measures included deformity, joint swelling and tenderness, sensation, muscle strength, range of motion, gait speed, plantar pressures, postural stability, foot pain and self-reported foot impairment. Participants were then followed for 12 months, to record the occurrence of falls, using monthly falls calendars and telephone calls. The Prevention of Falls Network Europe (ProFaNE) definition of, "an event that results in a person coming to rest unintentionally on the ground or other lower level", was used to identify falls. Univariate parametric and non-parametric analysis compared fallers and non-fallers on all baseline variables to determine significant differences. Logistic regression analysis identified baseline variables which were independent predictors of falls over the 12 month period.

Results: Two hundred and one participants completed the baseline assessment and 196 (98%) completed follow-up to 12 months. Eighty-four (42%) participants fell at least once and 39 (19%) experienced multiple (>1) falls over the 12 month follow-up period. Significant baseline factors associated with falls in univariate analysis are presented in Table 1. Fallers had significantly higher tender joint count, took more medications, were more likely to take psychotropic medication or use an assistive device. Fallers also had increased postural sway with eyes closed, were more likely to have tender joints in the feet or ankles and a 12-month history of falls. In logistic regression analysis, including age and all baseline variables at a level of $p<0.15$ in the univariate analysis, but excluding 12-month fall history, psychotropic medication (odds ratio 2.4, $p=0.03$) and presence of foot or ankle tender joints (odds ratio 2.0, $p=0.03$) were independent predictors of falls.

Conclusion: Psychotropic medications and tender joints in the feet and ankles are independent predictors of falls in people with RA. Clinical assessment of synovitis in the feet and review of psychotropic medications may be of benefit when considering falls prevention in people with RA.

Table 1: Significant factors associated with falls in univariate analysis.
Data are presented as mean (SD) unless specified.

	Non-fallers n=116	Fallers n=84	*P* value
Clinical features			
Number of medications	3.8 (2.1)	4.5 (2.3)	0.039
Psychotropic medication, n (%)	15 (13)	22 (26)	0.028
Tender joint count	9 (11)	14 (14)	0.005
Uses an assistive device, n (%)	24 (21)	33 (39)	0.007
History ≥1 falls in preceding 12 months, n (%)	59 (51)	59 (70)	0.009
Foot and ankle features			
Presence foot or ankle tender joints, n (%)	65 (56)	60 (72)	0.028
Eyes-closed anteroposterior postural sway, mm	27.7 (10.6)	31.8 (15.5)	0.040
Eyes-closed mediolateral postural sway, mm	16.1 (7.6)	19.2 (11.9)	0.042

Disclosure: **A. Brenton-Rule**, None; **N. Dalbeth**, None; **H. B. Menz**, None; **S. Bassett**, None; **K. Rome**, None.

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Abstract Number: 3269

Trends in Prevalence of Knee Pain Among US Adults, National Health Interview Survey, 2002-2010

Jennifer M. Hootman[1], Charles G. Helmick[2] and Yvonne M. Golightly[3], [1]Division of Population Health, Centers for Disease Control and Prevention, Atlanta, GA, [2]Arthritis Program, Centers for Disease Control and Prevention, Atlanta, GA, [3]Epidemiology, University of North Carolina, Chapel Hill, NC

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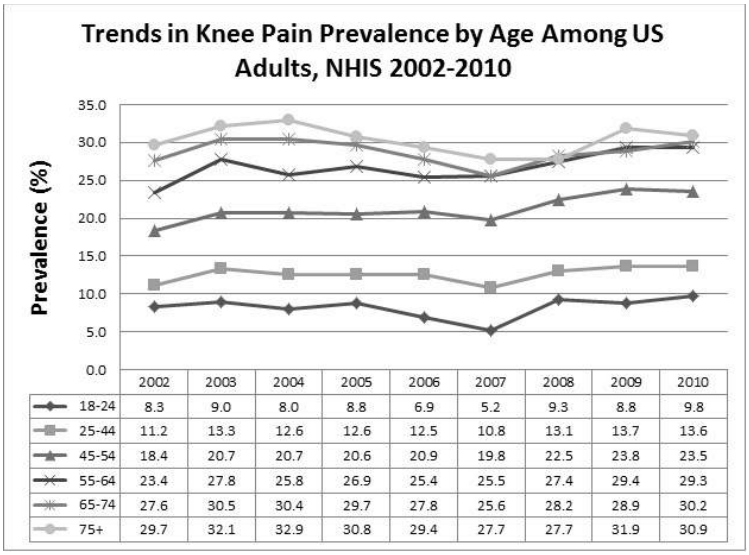
Trends in prevalence of knee pain among US adults, National Health Interview Survey, 2002-2010

Background/Purpose : Aging of the population as well as the obesity epidemic will play a significant role in future cases of arthritis and other lower extremity orthopedic conditions. The purpose of this study is to examine trends in the prevalence of knee pain among adults age 18 and older, overall and by age and sex.

Methods : The National Health Interview Survey, conducted annually, targets the civilian, non-institutionalized population and gathers data on a variety of health topics. From 2002 – 2010 the adult sample size ranged from 21,781 to 31,428. Adults were asked if they had joint pain in the past 30 days not including the back or neck. For those responding "yes", respondents were then asked what joints were affected. Prevalence (%) and 95% confidence intervals (CI) of knee pain were calculated using design variables and sampling weights to account for the complex survey design. Prevalence was also stratified by age group (18-24, 25-44, 45-64, 65-74, 75+) and sex, and graphed by age to show trends over time. Percent increase was calculated using the formula: (prevalence 2010 – prevalence 2002)/prevalence 2002*100. Statistical significance was determined by non-overlapping 95% CIs.

Results : The overall age-adjusted prevalence of knee pain increased significantly from 16.5% (CI 15.6-17.4) in 2002 to 19.6% (CI 18.5-20.7) in 2010. With a few exceptions, in each year, knee pain prevalence was higher with increasing age and highest for the 75+ age group. (Figure) For most years more than 1 in 4 adults aged 55-64 and 65-74 and 75+ reported having knee painr. Knee pain prevalence increased significantly over the 9 years in all age groups. The age groups with the largest percent increase were 25-44 (+21.4%), 45-64 (+27.7%), and 55-64 (+25.2%). Women had higher prevalence of knee pain than men for all years, but prevalence increased more in men (+23.0%) versus women (+15.3%).

Conclusion : Knee pain prevalence is high and has increased over time for all age groups with adults aged 45-54and 55-64 showing the largest increases. The findings suggest a large burden of knee pain among working age adults. Public health and worksite wellness efforts should consider implementing evidence-based interventions aimed at reducing knee pain such as physical therapy, aerobic and muscle strengthening exercises, and weight loss. The data also support the need for increasing the number of primary care, rheumatology and orthopedic health professionals in the workforce to address the growing burden of knee pain in the population.



	2002	2003	2004	2005	2006	2007	2008	2009	2010
18-24	8.3	9.0	8.0	8.8	6.9	5.2	9.3	8.8	9.8
25-44	11.2	13.3	12.6	12.6	12.5	10.8	13.1	13.7	13.6
45-54	18.4	20.7	20.7	20.6	20.9	19.8	22.5	23.8	23.5
55-64	23.4	27.8	25.8	26.9	25.4	25.5	27.4	29.4	29.3
65-74	27.6	30.5	30.4	29.7	27.8	25.6	28.2	28.9	30.2
75+	29.7	32.1	32.9	30.8	29.4	27.7	27.7	31.9	30.9

Disclosure: J. M. Hootman, None; **C. G. Helmick**, None; **Y. M. Golightly**, None.

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Abstract Number: 3270

Correction of Limb Length Inequality in Adults with Knee or Hip Symptoms: A Pilot Study

Yvonne M. Golightly[1], Michael T. Gross[2], Amanda Nelson[3], Leigh F. Callahan[4] and Joanne M. Jordan[4], [1]Epidemiology, University of North Carolina, Chapel Hill, NC, [2]University of North Carolina, Chapel Hill, NC, [3]Division of Rheumatology, Allergy, and Immunology and Thurston Arthritis Research Center, University of North Carolina, Chapel Hill, NC, [4]Thurston Arthritis Research Center, University of North Carolina, Chapel Hill, NC

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SESSION INFORMATION

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Session Title: ARHP VI: Physical Function and Disability

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Session Time: 11:00AM-12:30PM

Background/Purpose: Limb length inequality (LLI; paired lower extremities of unequal length) is associated with knee and hip osteoarthritis (OA) and symptoms consistent with OA (pain, aching, stiffness on most days) in adults. Shoe lifts are effective for treating LLI and low back pain, but evidence is lacking for their influence on knee or hip symptoms. This study examined shoe lift therapy as an intervention for LLI and knee or hip symptoms.

Methods: Thirty participants from a large cohort study of OA with current knee or hip symptoms, a minimum score of 6 out of 20 on the Western Ontario and McMasters Universities Osteoarthritis Index (WOMAC) pain subscale, and a LLI $\geq$ 3.2 mm on radiograph were invited to participate in a 3-month trial of shoe lift therapy. Anteroposterior pelvic radiographs were acquired for participants as they stood with equal weight bearing on each limb with knees extended. The difference in height between the most superior aspects of the femoral heads was measured in mm to determine the magnitude of LLI and identify the longer limb. Per protocol, participants began with the minimum amount of lift material (3.2mm) applied to the shoe of the shorter limb, and those with a LLI $\geq$ 6.4 mm had the option of adding lifts in 3.2 mm increments to their shoes every 7-10 days. The magnitude of lift correction did not exceed the magnitude of the LLI; otherwise, participants self-selected their lift based on symptom relief. Participants were randomized to Group 1 (lift therapy for 3 months) and Group 2 (usual care and brochures on joint pain management with the option to begin lift therapy after the study period). Participants completed baseline and 3-month assessments, and the primary outcome was change in WOMAC score. Secondary outcomes were change in time for the 8-foot walk, time for 5 repeated chair stands, and single leg stance time. Means and standard deviations for change in outcomes were calculated and compared using t-tests.

Results: Participant characteristics and study results are summarized in the Table. Characteristics and baseline outcomes were similar between groups, except a greater proportion of participants were African-American in Group 1 than Group 2. All participants completed the 3-month study, and no adverse events related to lift therapy were reported. WOMAC total scores declined meaningfully and significantly more in Group 1 than Group 2 (-13.1 vs. -2.9, $p<0.01$), most notably driven by a decrease in the function subscale score (an improvement in function). The mean 5 repeated chair stand times became faster in Group 1 over 3 months, but slowed on average in Group 2 ($p=0.08$). All participants with 3.2 mm LLI accepted lift correction. Participants with LLI ≥ 6.4 mm self-selected 25-67% lift correction.

Conclusion: This preliminary study suggests that 3 months of shoe lift therapy with self-selected lift height improves function among older adults with knee or hip symptoms of OA and LLI.

Table. Participant Characteristics and Study Results.

Participant Characteristics	Group 1 (N=15) Shoe Lift Intervention	Group 2 (N=15) No Shoe Lift
Age, mean (SD*)	70 (8)	73 (8)
Body mass index, mean (SD)	30 (4)	29 (2)
Women, n (%)	12 (80%)	12 (80%)
African American, n (%)	7 (47%)	2 (13%)
Left longer limb, n (%)	5 (33%)	5 (33%)
Leg length inequality*, n (%)		
3.2 mm	6 (40%)	6 (40%)
6.4 mm	4 (27%)	6 (40%)
9.6 mm	2 (13%)	2 (13%)
12.8 mm	2 (13%)	0
16.0 mm	0	1 (7%)
31.8 mm	1 (7%)	0
Use of pain medication, n (%)	12 (80%)	12 (80%)

Change, Baseline to 3 months*	Group 1 mean (SD)	Group 2 mean (SD)	p-value
WOMAC Total, 0-96	-13.1 (9.2)	-2.9 (8.2)	<0.01
WOMAC Pain, 0-20	-2.9 (3.4)	-1.6 (2.4)	0.23
WOMAC Stiffness, 0-8	-0.7 (1.3)	+0.13 (1.0)	0.05
WOMAC Function, 0-68	-9.5 (6.5)	-1.5 (6.4)	<0.01
8 foot walk time, seconds	-0.5 (0.9)	-0.1 (0.4)	0.18
5 chair stand time, seconds	-4.6 (6.7)	+5.5 (18.4)	0.08
Single leg stance time, seconds	+0.6 (3.5)	-0.3 (2.5)	0.45

*SD =standard deviation; WOMAC = Western Ontario and McMasters Universities Osteoarthritis Index; Leg length inequality categories are based on height of shoe lift material; WOMAC score "-" improving, "+" worsening; walk & chair times "-" faster/improving, "+" slower/worsening; single leg stance times "-" shorter/worsening, "+" longer/improving

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Late-breaking Abstract Number: 1L

Tocilizumab for the Treatment of Giant Cell Arteritis – a Randomized Placebo-Controlled Trial

Sabine Adler[1], Stephan Reichenbach[2], Stefan Kuchen[3], Felix Wermelinger[2], Diana Dan[2], Peter M. Villiger[2] and Michael Seitz[2], [1]Rheumatology, Immunology, Allergology, University Hospital Bern, Bern, Switzerland, [2]Department of Rheumatology, Immunology and Allergology, University Hospital Bern, Bern, Switzerland, [3]Department of Rheumatology, Immunology and Allergology, University Hospital Bern, Bern, MD, Switzerland

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SESSION INFORMATION

Session Date: Tuesday, November 10, 2015
Session Title: ACR Late-breaking Abstract Session
Session Type: ACR Late-breaking Abstract Session
Session Time: 4:30PM-6:00PM

Background/Purpose: Giant cell arteritis (GCA) is characterized by a destructive, granulomatous inflammation in the walls of medium and large-sized arteries. Glucocorticoid (GC) treatment controls symptoms and reduces the risk of vascular complications such as vessel occlusion with blindness or rupture with fatal bleeding. Unfortunately, the duration of treatment and frequent relapses lead to high cumulative GC doses with substantial toxicity and morbidity. Tocilizumab (TCZ) is a humanized IgG1k monoclonal antibody directed against the human interleukin-6 receptor, it has been shown to rapidly induce remission in case series. This RCT was designed to evaluate the efficacy and safety of TCZ in the induction and maintenance of disease remission in patients with newly diagnosed or recurrent GCA.

Methods: Single center, randomized, placebo-controlled trial. Participants satisfying the 1990 ACR criteria were randomly assigned between 2011 and 2014 in a 2:1 ratio to receive TCZ (8 mg/kg IV of body weight) + GC (PO) or placebo (IV) + GC (PO). Infusions were given every 4 weeks for 1 year. GC was started at 1mg/kg/d and tapered by 0.1mg/kg/d weekly until week 8, then by 0.05mg/kg/d weekly until week 12 (0.1mg/kg/d). Thereafter, the dosage was decreased by 1mg/d monthly to 0mg.

The primary outcome was the number of patients with complete remission at week 12 (GC dose of 0.1mg/kg/d), reported as crude risk difference and corresponding 95% confidence intervals (CI). *P*-values were derived by Fisher's exact test. The secondary outcome was the number of patients who remained relapse-free at week 52 while the GC dosage was being tapered, plotted as a Kaplan-Meier curve for relapse-free survival for each group. Groups were compared with a Cox proportional hazard model.

Results: Thirty patients, 70% of whom were female were randomized (20 assigned to TCZ + GC, and 10 to Placebo +GC). Sixteen (80%) patients in the TCZ group and 7 (70%) in the placebo group were newly diagnosed. After 12 weeks, 17 patients in the TCZ group and 4 in the placebo group were in complete remission, (85% vs. 40%, respectively; difference, 45 percentage points [95% CI = 11 to 79 percentage points]; $P = 0.030$). At the end of the trial, 17 in the TCZ group and 2 patients in the placebo group had experienced no relapse (85% vs. 20%, respectively; difference, 65 percentage points), with a corresponding hazard ratio = 0.05 (95% CI 0.01 to 0.47), $P = 0.008$ (Figure).

Conclusion: This trial demonstrates the efficacy of TCZ for induction and maintenance therapy in patients with newly diagnosed or relapsed GCA in the context of rapidly tapered glucocorticoids.

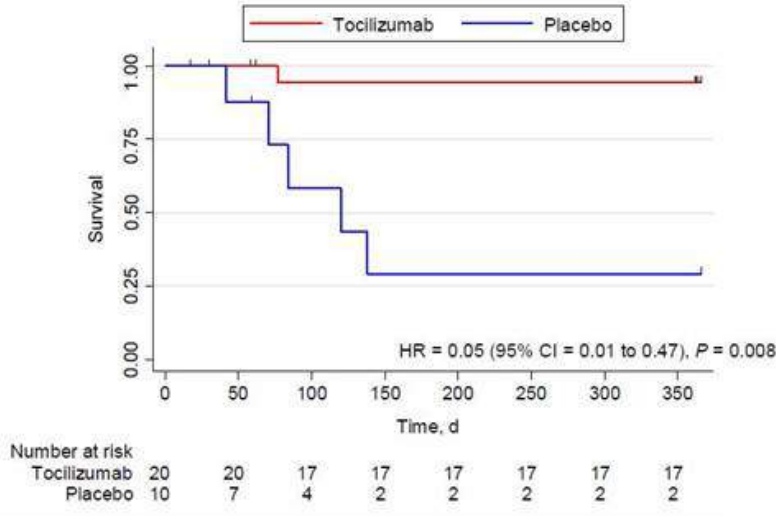

Figure: Kaplan Meier estimate of the time to first relapse after induction of remission.

Disclosure: S. Adler, None; **S. Reichenbach**, None; **S. Kuchen**, Abbvie, GSK, Roche, 5; **F. Wermelinger**, None; **D. Dan**, None; **P. M. Villiger**, None; **M. Seitz**, None.

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Late-breaking Abstract Number: 2L

Baricitinib Versus Placebo or Adalimumab in Patients with Active Rheumatoid Arthritis (RA) and an Inadequate Response to Background Methotrexate Therapy: Results of a Phase 3 Study

Peter C. Taylor[1], Edward C. Keystone[2,3], D. van der Heijde[4], Yoshiya Tanaka[5], Taeko Ishii[6], Kahaku Emoto[6], Lili Yang[6], Vipin Arora[6], Carol L. Gaich[6], Terence Rooney[6], Douglas E. Schlichting[6], William Macias[6], Stephanie de Bono[6] and Michael E. Weinblatt[7], [1]Nuffield Dept. of Orthopaedics, Rheumatology and Musculoskeletal, Sciences, Kennedy Institute of Rheumatology, University of Oxford,, Oxford, United Kingdom, [2]University of Toronto, Toronto, ON, Canada, [3]Rebecca MacDonald Centre, Mount Sinai Hospital, University of Toronto, Toronto, ON, Canada, [4]Leiden University Medical Center, Leiden, Netherlands, [5]The First Dept. of Internal Medicine, University of Occupational & Environmental Health, Kitakyusyu, Japan, [6]Eli Lilly and Company, Indianapolis, IN, [7]Brigham and Women's Hospital, Boston, MA

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Background/Purpose: In phase 3 studies, baricitinib (bari) improved disease activity in patients (pts) with active RA and an inadequate response (IR) to conventional synthetic DMARDs[1] or biologic DMARDs[2]. This abstract reports the 24-wk results from a 52-wk, global, phase 3, double-blind, placebo (PBO) and active-controlled study of bari in MTX-IR RA pts.

Methods: Pts with active RA (TJC≥6 & SJC≥6 & hsCRP≥6 mg/L) despite stable background MTX were randomized 3:3:2 to PBO, bari 4 mg once daily (QD), or adalimumab (ADA) 40 mg biweekly (Q2W), stratified by region and baseline joint erosion status. Non-responders were rescued from Wk 16. At Wk 24, pts on PBO switched to bari 4 mg QD. The primary endpoint was ACR20 response at Wk 12 for bari vs. PBO. Major secondary endpoints included comparisons of bari vs. ADA for ACR20 and change in DAS28-CRP at Wk 12.

Results: Of 1305 randomized pts, 89%, 94% and 93% completed Wk 24 in PBO, bari and ADA groups, respectively. Rescue rates were 26%, 7% and 12% for PBO, bari and ADA, respectively. ACR20 response at Wk 12 was higher for bari vs. PBO (70% vs. 40%, p≤.001 – Table 1). At Wks 12 and 24, statistically significant improvements in ACR 20/50/70 & HAQ-DI response rates, and DAS28, CDAI, and SDAI low disease activity and remission rates were seen for bari vs. PBO, many as early as Wk 1. Compared to ADA, bari was superior with respect to measures including ACR20 response and improvement in DAS28-CRP at Wk 12. Compared to PBO, daily diary measures of morning joint stiffness (MJS) duration and severity, worst tiredness, and worst joint pain were significantly improved in pts receiving bari, from as early as Wk 1. Rates of treatment-emergent adverse events (TEAEs), including infections, were higher for bari and ADA compared to PBO (Table 2). Compared to PBO, serious adverse events (SAE) rates were similar for bari and lower for ADA; serious infection rates were similar across groups. Two deaths occurred (bari), 1 pneumonia and 1 duodenal ulcer haemorrhage. Five malignancies were reported, 2 bari and 3 PBO. Three potential opportunistic infections occurred, 2 bari and 1 PBO; none were SAEs. One case of tuberculosis occurred (ADA). There were no GI perforations. Lab abnormalities were consistent with other phase 3 studies[1,2]; few led to discontinuation.

Conclusion: In pts with active RA despite background MTX, once-daily oral bari was associated with significant clinical improvements compared to PBO and to ADA, with an acceptable safety and tolerability profile.

References: [1]Dougados M et al. *Ann Rheum Dis* 2015;74(S2):79; [2]Genovese M et al. *Ann Rheum Dis* 2015;74(S2):75-76.

	Wk 12			Wk 24		
Table 1: Efficacy Measures	**PBO (N=488)**	**Bari (N=487)**	**ADA (N=330)**	**PBO (N=488)**	**Bari (N=487)**	**ADA (N=330)**
ACR20	40	70*** $^{+}$	61***	37	74*** $^{+}$	66***
ACR50	17	45*** $^{++}$	35***	19	50***	46***
ACR70	5	19*** $^{+}$	13***	8	30*** $^{+}$	22***
DAS28-CRP ≤3.2	14	44*** $^{++}$	35***	19	52***	48***
DAS28-CRP <2.6	4	24***	19***	8	35***	32***
DAS28-ESR ≤3.2	7	24***	21***	10	32***	34***
DAS28-ESR <2.6	2	11***	12***	5	18***	18***
CDAI ≤10	17	40*** $^{+}$	33***	20	50***	48***
CDAI ≤2.8	2	8***	7**	4	16***	12***
SDAI ≤11	16	42*** $^{+}$	35***	20	51***	49***
SDAI ≤3.3	2	8***	8***	3	16***	14***
HAQ-DI MCID ≥0.22	58	75***	71***	45	73*** $^{+}$	64***
LS mean D DAS28-CRP[#]	-1.0	-2.2*** $^{+++}$	-1.9***	-1.1	-2.4*** $^{+}$	-2.2***
Duration of MJS, median (minutes)	60	27*** $^{+}$	37***	Not applicable		
Severity of MJS, LS mean[‡]	4.1	3.0*** $^{++}$	3.5***			
Worst tiredness, LS mean[‡]	4.3	3.6*** $^{+}$	3.9***			
Worst joint pain, LS mean[‡]	4.6	3.4*** $^{+++}$	4.0***			

Patients received stable background MTX throughout the study. Data are % pts (NRI), unless otherwise stated; [#]Data are least squares (LS) mean change from baseline; Data for duration and severity of MJS, worst tiredness, and worst joint pain were collected in a daily diary until week 12; [‡]Pts recorded these measures using a numeric rating scale (0-10), higher score indicates worse state; *p≤.05, **p≤.01, ***p≤.001 vs. PBO; $^{+}$p≤.05, $^{++}$p≤.01, $^{+++}$p≤.001 vs. ADA

	Wks 0-12			Wks 0-24		
Table 2: Safety Measures	**PBO (N=488)**	**Bari (N=487)**	**ADA (N=330)**	**PBO (N=488)**	**Bari (N=487)**	**ADA (N=330)**
TEAEs	231 (47.3)	257 (52.8)	168 (50.9)	293 (60.0)	345 (70.8)	221 (67.0)
Infections	87 (17.8)	106 (21.8)	66 (20.0)	132 (27.0)	174 (35.7)	110 (33.3)
Herpes zoster	2 (0.4)	3 (0.6)	3 (0.9)	2 (0.4)	7 (1.4)	4 (1.2)
Tuberculosis	0	0	1 (0.3)	0	0	1 (0.3)
SAEs‡	13 (2.7)	11 (2.3)	4 (1.2)	21 (4.3)	22 (4.5)	6 (1.8)
Serious infections	5 (1.0)	4 (0.8)	0	7 (1.4)	5 (1.0)	2 (0.6)
Malignancy	1 (0.2)	0	0	3 (0.6)	2 (0.4)	0
Breast cancer	0	0	0	1 (0.2)	1 (0.2)	0
Lung squamous cell	0	0	0	0	1 (0.2)	0
Non-melanoma skin cancer	1 (0.2)	0	0	1 (0.2)	0	0
Ovarian cancer	0	0	0	1 (0.2)	0	0
Lymphoproliferative disorder	0	0	1 (0.3)¥	0	0	1 (0.3)¥
Deaths	0	0	0	0	2 (0.4)	0
CTCAE Grade Shift (≥1 increase in grade from baseline)§						
Hemoglobin	97 (19.9)	92 (19.0)	43 (13.0)	117 (24.0)	127 (26.2)	56 (17.0)
Lymphocyte	82 (16.8)	51 (10.5)	29 (8.8)	108 (22.2)	90 (18.6)	41 (12.4)

ALT	53 (10.9)	84 (17.4)	56 (17.0)	80 (16.4)	121 (25.0)	77 (23.3)

Patients received stable background MTX throughout the study. Data are n (%) pts up to the time of rescue; ‡ SAEs defined by International Conference on Harmonization criteria; ¥Lymphoproliferative disorder was a transient neck adenopathy with no evidence of neoplasia; CTCAE = Common Terminology Criteria for Adverse Events; § % of pts with laboratory grade shifts are based on n-observed for analyte

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Late-breaking Abstract Number: 3L

A Randomised Controlled Trial of the Clinical Effectiveness, Safety and Cost-Effectiveness of Adalimumab in Combination with Methotrexate for the Treatment of Juvenile Idiopathic Arthritis Associated Uveitis

Athimalaipet V Ramanan[1], Andrew D. Dick[2], Andrew McKay[3], Ashley Jones[4], Paula Williamson[4], Sandrine Compeyrot-Lacassagne[5], Ben Hardwick[4], Helen Hickey[4], Dyfrig Hughes[6], Patricia Woo[5], Diana Benton[1], Clive Edelsten[5] and Michael W. Beresford[7], [1]University Hospitals Bristol NHS Foundation Trust, Bristol, United Kingdom, [2]University of Bristol, Bristol Eye Hospital, Bristol, United Kingdom, [3]Biostatistics, Clinical Trials Research Centre, University of Liverpool, Liverpool, United Kingdom, [4]Clinical Trials Research Centre, University of Liverpool, Liverpool, United Kingdom, [5]Great Ormond Street Hospital, London, United Kingdom, [6]Bangor University, Bangor, United Kingdom, [7]University of Liverpool, Liverpool, United Kingdom

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Background/Purpose: Uveitis associated with Juvenile Idiopathic Arthritis (JIA) is a major cause of morbidity with potentially sight-threatening complications. Despite current screening and (pre-biologic) therapeutic options, 10-15% of children develop bilateral visual impairment. Tumour necrosis factor alpha plays a pathogenic role in JIA-uveitis. No controlled trials have determined the impact of biologic therapy in JIA-associated uveitis. This double blind, randomised placebo-controlled trial assessed the efficacy, safety and cost-effectiveness of adalimumab in JIA-associated uveitis.

Methods: Patients aged 2 to 18 years with active JIA-associated uveitis, despite stable methotrexate (MTX) treatment for at least 12 weeks, were randomly assigned to adalimumab or placebo in a ratio of 2:1. All patients were treated up to a maximum period of 18 months, with follow up of 2 years from randomisation. All patients received a stable dose of MTX and in addition either adalimumab (20 mg for patients weighing <30 kg or 40 mg for patients weighing ≥30 kg, subcutaneous injection every 2 weeks) or placebo.

Primary endpoint was "time to treatment failure" defined by the "Standardisation of the Uveitis Nomenclature" criteria. Ten secondary efficacy endpoints were assessed including quality of life variables and arthritis disease activity measures. Adverse events from both arms were collected. Statistical analysis of the primary outcome used the log rank test to compare treatment groups with a hazard ratio and 95% confidence interval also being reported.

Results: The trial was stopped early for efficacy after 90 patients had been randomised as interim analysis met the pre-specified statistical stopping guidelines. The final analysis of the primary outcome showed positive treatment effect in favour of adalimumab: hazard ratio (HR) 0.27 (95% CI 0.13-0.52); $p<0.0001$. Adverse events were experienced by 88.3% (53/60, 687 events) of patients in the adalimumab group and 90% (27/30, 144 events) of patients in the placebo group. Events were consistent with the known adalimumab profile. 15 serious adverse events (SAEs) most commonly infection (10 events) occurred in 21.7% (n=13) of the patients in the adalimumab group, 3 of these resulted in the patient being withdrawn from treatment and there were 2 SAEs (flare of uveitis) reported in 6.7% (n=2) patients in the placebo group (both patients were withdrawn from the trial).

Conclusion: This trial, the largest of its kind to be conducted in JIA-associated uveitis, provides evidence of efficacy of adalimumab treatment used in addition to methotrexate in this population. The safety profile of adalimumab was consistent with that previously reported for adalimumab.

University Hospitals Bristol NHS Foundation Trust was contracted to receive a sum under data sharing agreement.

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Adalimumab was provided by Abbvie which reviewed this abstract and provided comments for author consideration. Trial protocol design and analyses were undertaken independent of AbbVie.

Disclosure: **A. V. Ramanan**, AbbVie, 5; **A. D. Dick**, AbbVie, 5,Novartis Pharmaceutical Corporation, 2,Novartis Pharmaceutical Corporation, 5,Genentech and Biogen IDEC Inc., 5; **A. McKay**, None; **A. Jones**, None; **P. Williamson**, None; **S. Compeyrot-Lacassagne**, None; **B. Hardwick**, None; **H. Hickey**, None; **D. Hughes**, None; **P. Woo**, None; **D. Benton**, None; **C. Edelsten**, None; **M. W. Beresford**, None.

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Late-breaking Abstract Number: 4L

Efficacy and Safety of Epratuzumab in Patients with Moderate-to-Severe Systemic Lupus Erythematosus: Results from Two Phase 3 Randomized, Placebo-Controlled Trials

Megan E. B. Clowse[1], Daniel J Wallace[2], Richard Furie[3], Michelle Petri[4], Marilyn Pike[5], Piotr Leszczynski[6], C Michael Neuwelt[7], Kathryn Hobbs[8], Mauro Keiserman[9], Liliana Duca[10], Kenneth Kalunian[11], Sabine Bongardt[12], Christian Stach[12], Carolyn Beaudot[13], Brian Kilgallen[13], Catrinel Galateanu[14] and **Caroline Gordon**[15,16], [1]Rheumatology, Duke University, Durham, NC, [2]Division of Rheumatology, Cedars-Sinai Medical Center, Los Angeles, CA, [3]North Shore LIJ Health System, Manhasset, NY, [4]Division of Rheumatology, Johns Hopkins University School of Medicine, Baltimore, MD, [5]Med Pharm Consulting Inc, Cambridge, MA, [6]Dept. of Rheumatology and Clinical Immunology, J. Strus Poznan Municipal Hospital, Poznan University of Medical Sciences, Poznan, Poland, [7]Division of Rheumatology, Alameda County Medical Center, Oakland, CA, [8]Denver Arthritis Clinic, Denver, CO, [9]School of Medicine, Pontifical Catholic University, Porto Alegre, Brazil, [10]Clinica Neomed, Brasov, Romania, [11]UCSD School of Medicine, La Jolla, CA, [12]UCB Pharma, Monheim, Germany, [13]UCB Pharma, Raleigh, NC, [14]UCB Pharma, Brussels, Belgium, [15]Rheumatology Research Group, School of Immunity and Infection, College of Medical and Dental Sciences, University of Birmingham, Birmingham, United Kingdom, [16]NIHR/Wellcome Trust Clinical Research Facility, University Hospital Birmingham NHS Foundation Trust, Birmingham, United Kingdom

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Background/Purpose:

In phase 2b trials, epratuzumab, a humanized anti-CD22 mAb that modulates B cell signaling without total B cell depletion, significantly improved disease activity in patients (pts) with moderate-to-severe SLE.[1] We report the first data from two phase 3, randomized, double-blind, placebo (PBO)-controlled, multicenter

studies of epratuzumab in active, moderate-to-severe SLE: EMBODY 1™ (SL0009, NCT01262365) and EMBODY 2™ (SL0010, NCT01261793). **Methods:**

Pts were ≥18 years of age from North and South America, Europe, Australia, Asia and Africa. Entry requirements included ANA ≥1:80 and/or anti-dsDNA positivity, ≥4 ACR revised criteria, SLEDAI-2K score ≥6, BILAG-2004 ≥1 A or ≥2 Bs in mucocutaneous, musculoskeletal or cardiorespiratory domains and receipt of stable dose CS (5–60 mg/day prednisone equivalent) for ≥5±1 days prior to baseline (BL). Temporary CS dose increases ≤25% of BL dose were permitted until Week (Wk) 8. Pts with BILAG A grade renal or central nervous system domain scores were excluded.

Pts were randomized 1:1:1 to PBO, IV epratuzumab 600 mg every wk (QW) or 1200 mg every other wk (QOW) in addition to their standard of care (SOC) therapies, stratified by region and BL disease severity. Drug or PBO was administered for a 4-wk period at the beginning of each 12-wk treatment cycle for 4 cycles (48 wks total).

The primary endpoint was the Wk48 responder rate according to the BILAG-based Combined Lupus Assessment (BICLA) definition, requiring all of the following: BILAG improvement and no worsening (all BILAG As at entry improved to B/C/D; all Bs improved to C/D; no new BILAG As and ≤1 new BILAG B), no worsening in SLEDAI score, no worsening in physician's global assessment of disease activity, no disallowed changes in concomitant medications. Secondary efficacy variables included BICLA response at Wks 36/24/12. CS use was evaluated.

Efficacy data are presented for the full analysis set. Missing values were imputed using modified non-responder imputation with missing data incorporated as the worst possible outcome. Safety data were comprehensively assessed.

Results:

In EMBODY™ 1, 793 pts were randomized, 786 (99.1%) received study medication, and 528 (66.6%) completed the study. In EMBODY™ 2, 791 pts were randomized, 788 (99.6%) received study medication, and 533 (67.4%) completed the study. BL characteristics were similar across groups (Table A).

Neither study met the primary endpoint: Wk48 BICLA response rates in epratuzumab+SOC groups were not statistically different from PBO+SOC groups (Table B). No significant differences were seen in other efficacy measures.

No new safety signals were identified (Table B).

Conclusion:

BICLA response rates at Wk48 were no different in SLE patients treated with epratuzumab+SOC compared to PBO+SOC. The safety profile of epratuzumab was similar to previous studies.

1. Wallace D. Ann Rheum Dis 2014;73:183–90

Table A: Patient Disposition, Demographics and Disease Characteristics

	EMBODY™ 1			EMBODY™ 2		
	PBO+SOC	Emab 1200mg QOW+SOC	Emab 600mg QW+SOC	PBO+SOC	Emab 1200mg QOW+SOC	Emab 600mg QW+SOC
Patient Disposition and Reasons for Discontinuation						

Patient Disposition and Reasons for Discontinuation						
Randomized Set	**N=266**	**N=262**	**N=265**	**N=263**	**N=262**	**N=266**
Received study medication	264 (99.2)	259 (98.9)	263 (99.2)	263 (100)	261 (99.6)	264 (99.2)
Completed study	176 (66.2)	181 (69.1)	171 (64.5)	178 (67.7)	171 (65.3)	184 (69.2)
Discontinued	90 (33.8)	81 (30.9)	94 (35.5)	85 (32.3)	91 (34.7)	82 (30.8)
Adverse event	27 (10.2)	18 (6.9)	12 (4.5)	12 (4.6)	25 (9.5)	19 (7.1)
Lack of efficacy	35 (13.2)	30 (11.5)	47 (17.7)	44 (16.7)	37 (14.1)	32 (12.0)
Protocol violation	3 (1.1)	1 (0.4)	1 (0.4)	3 (1.1)	5 (1.9)	6 (2.3)
Lost to follow-up	3 (1.1)	7 (2.7)	6 (2.3)	10 (3.8)	3 (1.1)	7 (2.6)
Consent withdrawn	17 (6.4)	22 (8.4)	22 (8.3)	12 (4.6)	14 (5.3)	14 (5.3)
Other	5 (1.9)	3 (1.1)	6 (2.3)	4 (1.5)	7 (2.7)	4 (1.5)
Patient Demographics and Disease Characteristics						
Full Analysis Set	**N=249**	**N=244**	**N=248**	**N=263**	**N=261**	**N=264**
Age, mean years, (SD)	41.2 (12.8)	42.2 (11.7)	42.2 (11.4)	41.1 (11.8)	40.8 (11.5)	41.2 (12.7)
Female, n (%)	237 (95.2)	228 (93.4)	226 (91.1)	245 (93.2)	247 (94.6)	245 (92.8)
Years since Dx, median (min, max)	5.8 (0, 36)	7.3 (0, 34)	6.1 (0, 43)	5.7 (0, 37)	5.0 (0, 29)	4.8 (0, 42)
Racial group, n (%)						
Asian	26 (10.4)	22 (9.0)	18 (7.3)	7 (2.7)	7 (2.7)	12 (4.5)
Black/African American	26 (10.4)	32 (13.1)	33 (13.3)	25 (9.5)	29 (11.1)	34 (12.9)
BILAG 2004						
Total score, mean (SD) [a]	20.0 (5.5)	19.8 (5.9)	19.6 (5.6)	21.0 (6.7)	21.3 (6.6)	21.0 (6.7)
≥1 BILAG A, n (%)	139 (55.8)	142 (58.2)	147 (59.3)	157 (59.7)	148 (56.7)	161 (61.0)
≥2 BILAG Bs, n (%)	129 (51.8)	118 (48.4)	124 (50.0)	136 (51.7)	139 (53.3)	136 (51.5)
SLEDAI-2K total score, mean (SD)	10.7 (4.1)	9.9 (3.7)	10.2 (3.6)	10.1 (3.6)	10.1 (3.8)	10.2 (3.6)
PGA, mm, mean (SD) [b]	55.5 (12.9)	55.7 (14.3)	56.5 (14.9)	56.2 (14.4)	57.2 (14.0)	57.3 (15.6)
Daily CS dose, mg/day, mean (SD) [c]	10.8 (7.4)	11.3 (9.5)	11.1 (8.2)	12.1 (9.6)	13.3 (10.2)	12.7 (9.1)
Laboratory parameters, n (%)						
ANA >1:80	216 (86.7)	212 (86.9)	218 (87.9)	231 (87.8)	232 (88.9)	233 (83.3)
Anti-dsDNA positive	133 (53.4)	126 (51.6)	131 (52.8)	143 (54.4)	126 (48.3)	134 (50.8)
Concomitant SLE medications, n (%)						
Immunosuppressant	116 (46.6)	123 (50.4)	112 (45.2)	121 (46.0)	113 (43.3)	129 (48.9)
Antimalarial	175 (70.3)	181 (74.2)	181 (73.0)	162 (61.6)	160 (61.3)	179 (67.8)

[a] BILAG total scores calculated using A=12, B=8, C=1, D=0, E=0; [b] 0–100 mm visual analog scale, higher scores indicate greater disease activity; [c] prednisone equivalent

BILAG: British Isles Lupus Assessment Group; CS: corticosteroid; Dx: diagnosis; Emab: epratuzumab; PBO: placebo; PGA: Physician's Global Assessment of Disease; QOW: every other week; QW: every week; SLEDAI-2K: Systemic Lupus Erythematosus Disease Activity Index 2000

Table B: Efficacy outcomes and safety events

	EMBODY™ 1			EMBODY™ 2		
	PBO+SOC	Emab 1200mg QOW+SOC	Emab 600mg QW+SOC	PBO+SOC	Emab 1200mg QOW+SOC	Emab 600mg QW+SOC
Week 48 Outcomes Full Analysis Set	**N=249**	**N=244**	**N=248**	**N=263**	**N=261**	**N=264**
BICLA responders, n (%) [NRI]	**85 (34.1)**	**97 (39.8)**	**93 (37.5)**	**88 (33.5)**	**89 (34.1)**	**93 (35.2)**
Odds ratio [a] (95% CI) [p-value]		1.307 (0.89, 1.92) [0.175]	1.164 (0.79, 1.71) [0.442]		1.024 (0.71, 1.48) [0.899]	1.070 (0.74, 1.54) [0.716]
BILAG improvement and no worsening, n (%) [b]	103 (41.4)	126 (51.6)	120 (48.4)	115 (43.7)	104 (39.8)	110 (41.7)
Change from Baseline LS mean (SD) [LOCF]						

SLEDAI-2K total score	-3.6 (4.8)	-3.8 (4.2)	-3.6 (4.5)	-3.3 (4.2)	-3.5 (4.6)	-3.9 (4.3)
PGA, mm [c]	-23.8 (22.2)	-25.6 (22.4)	-21.9 (24.2)	-22.3 (23.9)	-23.7 (22.6)	-26.0 (23.2)
Daily CS dose, mg/day [d]	-1.13 (9.0)	-1.26 (8.6)	-0.85 (7.7)	-1.54 (8.9)	-1.98 (12.2)	-1.79 (9.8)
Safety Events, n (%) Safety Set	**N=263**	**N=259**	**N=264**	**N=263**	**N=261**	**N=264**
All TEAEs	222 (84.4)	228 (88.0)	211 (79.9)	255 (85.6)	220 (84.3)	230 (87.1)
Serious TEAEs	48 (18.3)	44 (17.0)	45 (17.0)	45 (17.1)	45 (17.2)	50 (18.9)
Discontinuation due to TEAEs	27 (10.3)	16 (6.2)	11 (4.2)	12 (4.6)	24 (9.2)	18 (6.8)
Deaths	1 (0.4)	2 (0.8)	2 (0.8)	3 (1.1)	1 (0.4)	0

[a] Odds ratios (Emab/PBO) and p-values calculated using logistic regression with factors for treatment, region, and baseline disease status; [b] BILAG total scores calculated using A=12, B=8, C=1, D=0, E=0; [c] 0–100 mm visual analog scale, higher scores indicate greater disease activity; [d] prednisone equivalent
BILAG: British Isles Lupus Assessment Group; CS: corticosteroid; Emab: epratuzumab; LOCF: last observation carried forward; NRI: Non-responder imputation; PBO: placebo; PGA: Physician's Global Assessment of Disease Activity; QOW: every other week; QW: every week; SLEDAI-2K: Systemic Lupus Erythematosus Disease Activity Index 2000; TEAE: Treatment-emergent adverse event

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Late-breaking Abstract Number: 5L

Tofacitinib in Patients with Ankylosing Spondylitis: A Phase 2, 16-Week, Randomized, Placebo-Controlled, Dose-Ranging Study

Désirée van der Heijde[1], Atul A Deodhar[2], James C Wei[3], Edit Drescher[4], Dona Fleishaker[5], Thijs Hendrikx[6], David Li[6], Sujatha Menon[5] and Keith S Kanik[5], [1]Dept. of Rheumatology, Leiden University Medical Center, Leiden, Netherlands, [2]Division of Arthritis & Rheumatic Diseases, Oregon Health & Science University, Portland, OR, [3]Division of Allergy, Immunology and Rheumatology, Chung Shan Medical University Hospital, Taichung, Taiwan, [4]Csolnoky Ferenc Hospital, Veszprém, Hungary, [5]Pfizer Inc, Groton, CT, [6]Pfizer Inc, Collegeville, PA
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SESSION INFORMATION

Session Date: Tuesday, November 10, 2015

Session Title: ACR Late-breaking Abstract Session

Session Type: ACR Late-breaking Abstract Session

Session Time: 4:30PM-6:00PM

Background/Purpose: This was the first investigation of the effects of tofacitinib (TOFA) in adult patients (pts) with active ankylosing spondylitis (AS). TOFA is an oral Janus kinase inhibitor under investigation for the treatment of AS.

Methods: This was a 16-week (wk), Phase 2, multicenter, randomized, double-blind, placebo (PBO)-controlled, dose-ranging study (NCT01786668) to investigate efficacy, safety, and dose-response of TOFA in pts with AS. Pts fulfilling the modified New York criteria (central read) were randomized 1:1:1:1 to PBO or TOFA 2, 5, or 10 mg twice daily (BID) for 12 wks plus 4 wks follow-up. The primary efficacy endpoint was ASAS20 response rate at Wk 12 using a 3-parameter Bayesian E_{max} model by assuming a monotonic response. Secondary endpoints included ASAS40 response rate, AS disease activity score using C-reactive protein (ASDAS), Bath AS disease activity index 50% (BASDAI50) response rate, Bath AS functional index, Bath AS metrology index (linear method), Spondyloarthritis Research Consortium of Canada (SPARCC) score of sacroiliac (SI) joints and spine. Safety endpoints included adverse event (AE), and laboratory outcomes.

Results: 208 pts were randomized and 207 treated; 196 pts completed the study. 51 pts in the PBO group and 52 in each TOFA group were included in analyses. Baseline demographics and disease characteristics were balanced in general between groups and typical of AS populations (87.4% HLA-B27 positive; 81.2% white; 69.1% male; mean age 42 years; mean disease duration 6.3 years; mean BASDAI 6.7).

The Table summarizes efficacy results. The ASAS20 E_{max} model showed TOFA 10 mg BID had a high response rate and its confidence bounds met a pre-specified efficacy decision rule. Observed ASAS20 response rates were significantly greater with TOFA 5 mg BID vs PBO, compared with 2 or 10 mg BID. All TOFA groups had ASAS40, ASDAS, and BASDAI50 improvements of similar magnitude vs PBO. TOFA 2 mg BID did not differ vs PBO in remaining clinical efficacy measures or SPARCC scores. TOFA 5 and 10 mg BID had greater clinical efficacy vs PBO, with minimal differences between doses, and significantly improved SPARCC SI joint and spine scores vs PBO.

The Table summarizes safety results. No TOFA-related safety issues unique to the AS population or new safety concerns were identified. Two treatment-related herpes zoster cases were reported (1 each with TOFA 2 and 10 mg BID). No cases of tuberculosis, malignancy, gastrointestinal perforation, or death were reported. Dose-dependent changes in laboratory outcomes commonly reported in other TOFA studies were observed and returned to approximately baseline values by Wk 16.

Conclusion: TOFA 5 and 10 mg BID demonstrated greater clinical and imaging efficacy vs PBO in reducing the signs and symptoms of AS in adults with active AS. Safety was similar to that reported for TOFA studies in other indication

Table. Summary of efficacy and safety endpoints				
	Placebo (n=51)	**TOFA 2 mg BID**	**TOFA 5 mg BID**	**TOFA 10 mg BID**

		(n=52)	(n=52)	(n=52)
Primary endpoint ASAS20 E_{max} model estimates[a]				
ASAS20 response rate, %	40.1	56.0	63.0	67.4
ASAS20 response rate vs placebo, %	N/A	15.8	22.9	27.3
50% credible interval		(11.1, 19.9)	(17.8, 28.0)	(21.8, 33.0)
60% credible interval		(10.2, 21.2)	(16.5, 29.3)	(20.3, 34.4)
95% credible interval		(5.0, 30.3)	(8.4, 37.7)	(10.7, 43.4)
Secondary efficacy endpoints at Wk 12				
ASAS20 response rate (%), observed[a]	41.2	51.9	80.8***	55.8
ASAS40 response rate (%), observed[a]	19.6	42.3*	46.2**	38.5*
CBL in ASDAS, LS mean (SE)	-0.7 (0.1)	-1.2 (0.1)**	-1.4 (0.1)***	-1.4 (0.1)***
BASDAI50 response rate (%), observed[a]	23.5	46.2*	42.3*	42.3*
CBL in BASFI, LS mean (SE)	-1.4 (0.3)	-1.9 (0.3)	-2.4 (0.3)*	-2.2 (0.3)*
CBL in BASMI, LS mean (SE)	-0.2 (0.1)	-0.3 (0.1)	-0.4 (0.1)	-0.6 (0.1)*
CBL in SPARCC MRI of the SI joints, LS mean (SE)	-0.8 (0.8)	-1.7 (0.8)	-3.2 (0.8)*	-3.6 (0.8)*
CBL in SPARCC MRI of the spine, LS mean (SE)	-0.1 (1.1)	-3.1 (1.1)	-5.5 (1.1)***	-6.6 (1.1)***
Safety endpoints				
TEAEs, n (%)	22 (43.1)	23 (44.2)	28 (53.8)	27 (51.9)
Treatment related	14 (27.5)	14 (26.9)	12 (23.1)	14 (26.9)
Serious AEs, n (%)	2 (3.9)	0	1 (1.9)	1 (1.9)
Treatment related	1 (2.0)[b]	0	0	0
Discontinuations due to AEs, n (%)	3 (5.9)	0	1 (1.9)	1 (1.9)
Treatment related	2 (3.9)[c]	0	1 (1.9)[c]	1 (1.9)[c]
AST >3x ULN, n (%)	1 (2.0)	0	3 (5.8)	0
ALT >3x ULN, n (%)	1 (2.0)	0	2 (3.8)	1 (2.0)
Wk 12 CBL in serum creatinine, g/dL, mean (SD)	0.0 (0.1)	0.0 (0.1)	0.0 (0.1)	0.1 (0.1)
Wk 12% CBL in LDL-C, mean (SD)	-1.2 (15.8)	7.2 (13.5)	9.6 (21.0)	23.5 (28.3)
Wk 12% CBL in HDL-C, mean (SD)	1.0 (17.4)	10.0 (15.1)	11.0 (18.6)	18.5 (17.0)
Wk 12 CBL in ANC, cells $10^3/mm^3$, mean (SD)	-0.3 (1.2)	-0.3 (1.6)	-0.3 (1.4)	-0.9 (1.6)
Wk 12 CBL in ALC, cells $10^3/mm^3$, mean (SD)	0.0 (0.4)	0.1 (0.4)	-0.1 (0.4)	0.0 (0.4)
Wk 12 CBL in Hb, g/dL, mean (SD)	-0.2 (0.6)	0.1 (0.6)	0.3 (0.7)	0.1 (0.9)

*p<0.05, **p<0.01, ***p<0.001

[a]NRI/LOCF

[b]vertigo

[c]spinal pain (placebo), hypertransaminasemia (placebo), peripheral swelling (TOFA 5 mg BID), herpes zoster (TOFA 10 mg BID)

[d]50, 51, 52, and 50 patients receiving PBO, and TOFA 2, 5, and 10 mg BID, respectively were included in this analysis.

AE, adverse event; ALC, absolute lymphocyte count; ALT, alanine aminotransferase; ANC, absolute neutrophil count; ASAS, assessments in ankylosing spondylitis improvement; ASDAS, ankylosing spondylitis disease activity score using C-reactive protein; AST, aspartate aminotransferase; BASDAI, Bath ankylosing spondylitis disease activity index; BASFI, Bath ankylosing spondylitis functional index; BASMI, Bath ankylosing spondylitis metrology index (linear method); BID, twice daily; CBL, change from baseline; Hb, hemoglobin; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; LOCF, last observation carried forward; LS, least squares; N/A, not applicable; NRI, non-responder imputation; SD, standard deviation; SE, standard error; SPARCC, spondyloarthritis research consortium of Canada; TEAE, treatment-emergent AE; TOFA, tofacitinib; ULN, upper limit of normal; Wk, week.

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Late-breaking Abstract Number: 6L

Effect of Interleukin-17A Inhibition on Spinal Radiographic Changes through 2 Years in Patients with Active Ankylosing Spondylitis: Results of a Phase 3 Study with Secukinumab

Xenofon Baraliakos[1], Atul A. Deodhar[2], Jürgen Braun[1], Dominique Baeten[3], Maxime Dougados[4], Joachim Sieper[5], Paul Emery[6], Aimee Readie[7], Ruvie Martin[7], Shephard Mpofu[8] and Hanno Richards[8], [1]Rheumazentrum Ruhrgebiet, Herne, Germany, [2]Division of Arthritis & Rheumatic Diseases, Oregon Health & Science University, Portland, OR, [3]Clinical Immunology and Rheumatology, Academic Medical Center, Amsterdam, Netherlands, [4]Hospital Cochin, Descartes Univ, Paris, France, [5]University Hospital Charité, Berlin, Germany, [6]NIHR-Leeds Musculoskeletal Biomedical Research Unit, University of Leeds, Leeds, United Kingdom, [7]Novartis Pharmaceuticals Corporation, East Hanover, NJ, [8]Novartis Pharma AG, Basel,

Switzerland

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Background/Purpose: In the MEASURE 1 trial (NCT01358175), secukinumab significantly improved the signs and symptoms of patients (pts) with active ankylosing spondylitis (AS) over 52 weeks (wks).[1] Here, we report the effects of secukinumab on radiographic progression up to 104 wks.

Methods: In MEASURE 1, 371 pts with active AS were randomized to secukinumab or placebo (pbo). Pts on secukinumab received a 10 mg/kg i.v. loading dose at baseline (BL), Wks 2 and 4, and then 150 mg s.c. (IV→150 mg) or 75 mg s.c. (IV→75 mg) every 4 wks from Wk 8. Pbo was given on the same schedule. Pbo pts were re-randomized to secukinumab 150 or 75 mg s.c. based on ASAS20 response at Wk 16 (non-responders switched at Wk 16 and responders at Wk 24). Lateral radiographs of the cervical and lumbar spine performed at BL and Wk 104 were read centrally applying the modified Stoke Ankylosing Spondylitis Spinal Score (mSASSS). Two independent readers, blinded to treatment arm and radiograph sequence, scored the digitized images. Pts initially randomized to secukinumab, who had x-rays available at BL and Wk 104 (n=168), were included in this analysis. Only observed data are shown.

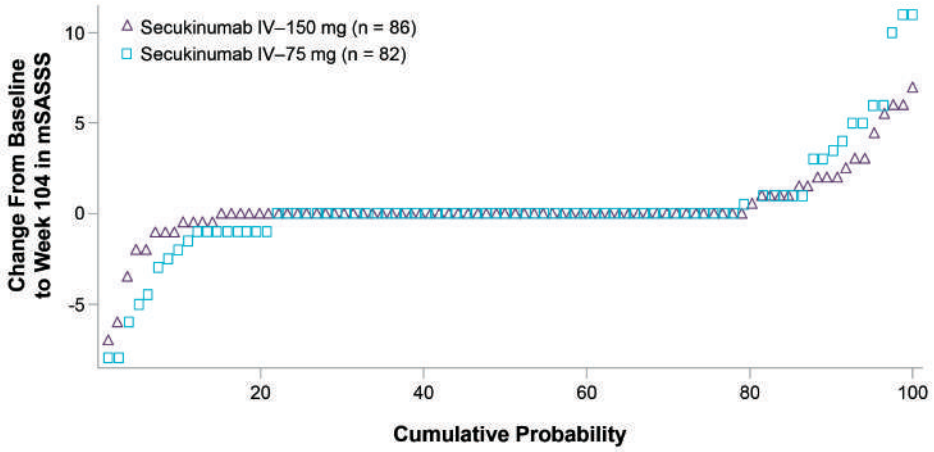
Results: Secukinumab data were pooled as there were no major differences between the two doses. Data from pts randomized to secukinumab at BL and those who switched from pbo were analyzed separately. At BL in the secukinumab only group, 104/168 (62%) pts had syndesmophytes, 105/168 (63%) had elevated (>5 mg/L) C-reactive protein (CRP) levels, 42/168 (25%) were smokers, and 123/168 (73%) were men. The mean (±SD) mSASSS at BL was 10.22±16.62; mean change from BL at Wk 104 was 0.30±2.53. There were no major differences between the secukinumab only and pbo→secukinumab groups in terms of mSASSS change through Wk 104. Approximately 80% of pts randomized to secukinumab at BL showed no radiographic progression (mSASSS change ≤0) (Figure). At Wk 104 in the secukinumab only group, new syndesmophytes were found in 3/64 (5%) pts who were without syndesmophytes at BL. Overall, BL mSASSS and mean mSASSS change at Wk 104 in the secukinumab only group were higher in males (mean change 0.38±2.79 vs 0.08±1.58 in females), those with BL syndesmophytes (0.47±3.20 vs 0.02±0.26 in pts with no BL syndesmophytes), or elevated CRP levels at BL (0.47±2.66 vs 0.02±2.27 in pts with normal CRP levels).

Conclusion: The mean change in mSASSS was only 0.30±2.53 in the secukinumab only group, with no major difference between doses. Changes were higher in pts who were male, had BL syndesmophytes, or elevated BL CRP. No radiographic progression was observed in ~80% of the pts receiving secukinumab over 104 wks. This is the first report of interleukin-17A inhibition on structural changes in patients with AS. The changes in mSASSS through 2 years reported here may be lower than those reported in earlier observational and interventional studies in AS.

Reference

1. Baeten et al. *Arthritis Rheumatol* 2014; 66 (11Suppl):S360

Figure: Cumulative probability plot of change from baseline to Week 104 in mSASSS



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Late-breaking Abstract Number: 7L

Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA): Treatment Recommendations for Psoriatic

Arthritis 2015

Laura C Coates[1,2], Arthur Kavanaugh[3], Philip J. Mease[4], Enrique R. Soriano[5], M Laura Acosta-Felquer[6], April W Armstrong[7], Wilson Bautista-Molano[8], Wolf-Henning Boehncke[9], Willemina Campbell[10], Alberto Cauli[11], Luis Espinoza[12], Oliver FitzGerald[13], Dafna D. Gladman[14], Alice B. Gottlieb[15], Philip S. Helliwell[2], M. Elaine Husni[16], Thorvardur Love[17,18], Ennio Lubrano[19], Neil J McHugh[20], Peter Nash[21], Alexis Ogdie-Beatty[22], Ana-Maria Orbai[23], Andrew Parkinson[24], Denis O'Sullivan[25], Cheryl F Rosen[26], Sergio Schwartzman[27], Evan Siegel[28], Sergio Toloza[29], William Tuong[30] and Christopher T. Ritchlin[31], [1]Medicine, University of Rochester, Rochester, NY, [2]Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds, Leeds, United Kingdom, [3]University of California San Diego, La Jolla, CA, [4]Rheumatology Research, Swedish Medical Center, Seattle, WA, [5]Rheumatology, Hospital Italiano de Buenos Aires, Buenos Aires, Argentina, [6]Rheumatology Unit, Internal Medicine Service, Hospital Italiano de Buenos Aires, Buenos Aires, Argentina, [7]Keck School of Medicine, University of Southern California, Los Angeles, CA, [8]Department of Rheumatology, Faculty of Medicine HMC/UMNG, Bogota, Colombia, Bogotá, Colombia, [9]Department of Dermatology,, Geneva University Hospital, Geneva, Switzerland, [10]Toronto Western Hospital, Toronto, ON, Canada, [11]University of Cagliari, Cagliari, Italy, [12]Medicine-Section of Rheumatology, LSU Medical Center, New Orleans, LA, [13]Department of Rheumatology, St. Vincent's University Hospital, UCD School of Medicine and Medical Sciences and Conway Institute of Biomolecular and Biomedical Research, University College Dublin, Dublin, Ireland, [14]Division of Rheumatology, Toronto Western Hospital and University of Toronto, Toronto, ON, Canada, [15]Tufts Medical Center, Boston, MA, [16]Rheumatology Dept A50, Cleveland Clinic, Cleveland, OH, [17]Faculty of Medicine, University of Iceland, Reykjavik, Iceland, [18]Landspitali University Hospital, Reykjavík, Iceland, [19]Cattedra di Reumatologia, Università del Molise, Campobasso, Italy, [20]Royal National Hospital for Rheumatic Diseases, Bath, United Kingdom, [21]Department of Medicine, University of Queensland, Brisbane, Australia, [22]Medicine/Rheumatology, Epidemiology and Biostatistics, University of Pennsylvania, Philadelphia, PA, [23]Rheumatology, Johns Hopkins University, Baltimore, MD, [24]Chapel Allerton Hospital, Leeds, United Kingdom, [25]St. Vincent's University Hospital, Dublin, Ireland, [26]Division of Dermatology, Toronto Western Hospital, University of Toronto, Toronto, ON, Canada, [27]Rheumatology, Hospital for Special Surgery, New York, NY, [28]Arthritis & Rheumatism Assoc, Wheaton, MD, [29]Rheumatology, Ministry of Health, San Fernando del Valle de Catamarca, Argentina, [30]Department of Dermatology, University of California David, Davis, CA, [31]Allergy, Immunology and Rheumatololgy Division, University of Rochester Medical Center, Rochester, NY

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Background/Purpose: Since the 2009 GRAPPA treatment recommendations were published, therapeutic options and management strategies for psoriatic arthritis (PsA) have advanced considerably. We updated

and improved these recommendations through development of overarching management principles and evidence based guidance for treatment of the different manifestations of PsA including associated comorbidities.

Methods: GRAPPA rheumatologists, dermatologists, and patient research partners (PRPs) drafted overarching principles for the management of adult PsA patients by consensus. We updated systematic literature reviews based on data publicly available through November 2014. Six separate literature reviews were performed covering treatment for the key clinical manifestations of PsA (arthritis, spondylitis, enthesitis, dactylitis, skin, and nail disease), and we reviewed a new topic (PsA related comorbidities). Evidence was assessed, and the GRADE system was applied to generate strong or conditional recommendations for therapies within the domain groups and for the management of comorbidities. These recommendations were then incorporated into an overall treatment schema. Consensus for the overarching principles and treatment recommendations was obtained among GRAPPA members with an online questionnaire.

Results: GRAPPA members voted on six overarching principles developed through multiple iterations with significant agreement among both health care professionals (HCPs; n=135, agreement 83.7-92.6% for individual principles) and PRPs (n=10, agreement 80-100%). Evidence was assessed from the published literature reviews and formally evaluated with the GRADE system to provide treatment recommendations (table 1). Based on the evidence, individual groups developed treatment recommendations which were incorporated into an overall schema including principles for management of arthritis, spondylitis, enthesitis, dactylitis, skin, and nail disease, and comorbidities in PsA (figure 1). Consensus amongst the GRAPPA members was 87.2% agreement (n=176) for the treatment recommendations and 87.9% (n=176) for the schema.

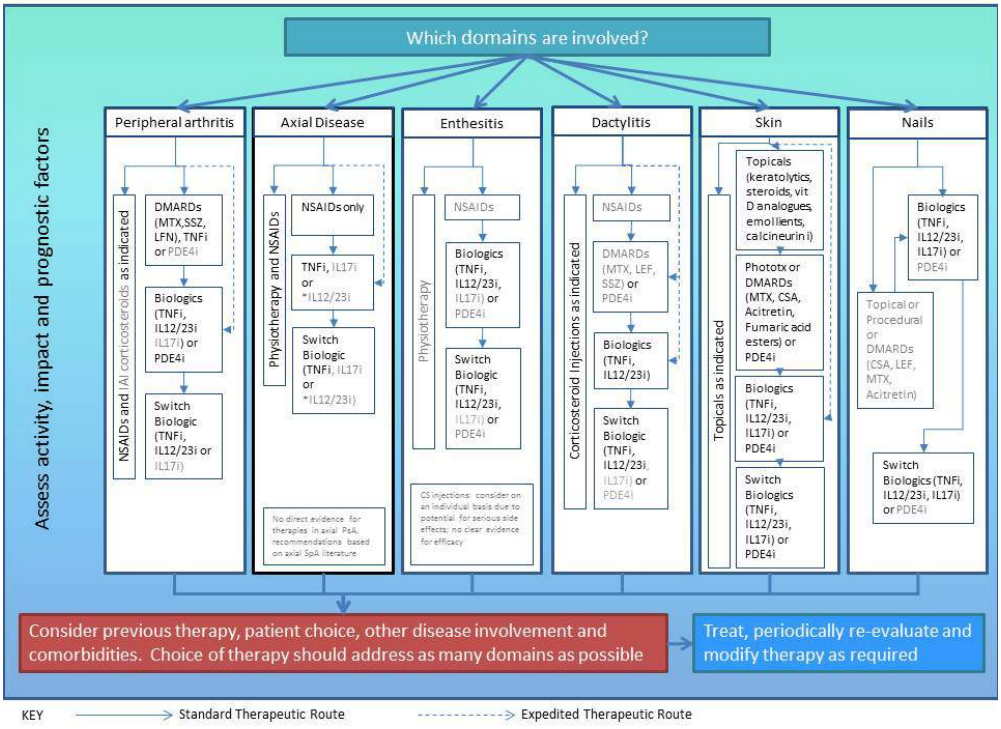
Conclusion: Based on the results of the literature review and GRADE assessment of the evidence, we developed updated comprehensive treatment recommendations for the key manifestations of PsA, including related comorbidities. These recommendations are supplemented by overarching principles developed by consensus of GRAPPA members (rheumatologists, dermatologists, other HCPs, and PRPs).

Indication	Recommended Strong	Recommended Weak	Not recommended Strong	No recommendations as lack of evidence
Peripheral Arthritis DMARD Naïve	DMARDs (MTX, SSZ, LEF), TNFi	NSAIDs, oral CS, IA CS, *PDE4i*		IL12/23i, IL17i
Peripheral Arthritis DMARD Inadequately Responsive	TNFi, ustekinumab, PDE4i	NSAIDs, oral CS, IA CS, *IL17i*		
Peripheral Arthritis Biologic Inadequately Responsive	TNFi	NSAIDs, oral CS, IA CS, IL12/23i, *IL17i*, PDE4i		
Axial PsA, Biologic Naïve (based on AS literature)	NSAIDs, Physiotherapy, simple analgesia, TNFi	*IL17i*, CS SIJ injections, bisphosphonates *(IL12/23i)*	DMARDs, IL6i, CD20i	
Axial PsA, Biologic Inadequately Responsive (based on AS literature)	NSAIDs, Physiotherapy, simple analgesia	TNFi, *IL12/23i, IL17i*		
Enthesitis	TNFi, IL12/23i,	NSAIDs, physiotherapy, CS injections (with extreme caution since injecting CS in weight-bearing entheseal sites can lead to rupture of entheses), *PDE4i*, *IL17i*		DMARDs
Dactylitis	TNFi (INF, ADM, GOL, CZP)	CS injections, DMARDs (MTX, LEF, SSZ), TNFi (ETN), IL12/23i, *IL17i (SEC)*, *PDE4i*		
Psoriasis (plaque)	Topical therapies, phototherapy, DMARDs (MTX, LEF, CyA), TNFi, IL12/23i, IL17i, PDE4i			
Nail psoriasis	TNFi, IL12/23i	Topical therapies, procedural therapies, DMARDs (CyA, LEF, Acitretin, MTX), IL17i, *PDE4i*		

Italicized text identifies conditional recommendations for drugs without current regulatory approvals or where recommendations are based on abstract data only.

Italicized text in brackets identifies a conditional recommendation based only on abstract data from a small open-label proof-of-concept trial.

ADM = adalimumab, AS = ankylosing spondylitis, CD20i = CD20 inhibitor, CS = corticosteroids, CyA = cyclosporin, CZP = certolizumab, DMARDs = disease modifying anti-rheumatic drugs, GOL = golimumab, IA = intra articular, IL6i = interleukin 6 inhibitor, IL17i = interleukin 17 inhibitor, IL12/23i = interleukin 12/23 inhibitor, INF = infliximab, LEF = leflunomide, MTX = methotrexate, NSAIDs = nonsteroidal anti-inflammatory drugs, PDE4i = phosphodiesterase 4 inhibitor (apremilast), SEC = secukinumab, SIJ = sacroiliac injections, SSZ = sulfasalazine, TNFi = tumor necrosis factor inhibitor



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5,Abbvie, 5,Celgene, 5,Lilly, 5,Janssen Pharmaceutica Product, L.P., 5,UCB, 5; **D. D. Gladman**, Abbvie, 5,Amgen, 5,Celgene, 5,BMS, 5,Janssen Pharmaceutica Product, L.P., 5,Novartis Pharmaceutical Corporation, 5,Pfizer Inc, 5,UCB, 5; **A. B. Gottlieb**, Amgen, AbbVie, Celgene, Coronado, Eli Lilly, Janssen, Levia, Merck, Pfizer, 2,AbbVie, Actelion, Akros, Amgen, Astellas, Bristol Myers Squibb, Canfite, Catabasis, Celgene, Coronado, CSL Behring Biotherapies for Life, Dermipsor, Eli Lilly, GlaxoSmithKline, Incyte, Janssen, Karyopharm, Novartis, Novo Nordisk, Pfizer, Sanofi Aventix, 5,UCB Pharma, Vertex, Xenoport, 5; **P. S. Helliwell**, Abbvie, 5,Pfizer Inc, 5,Amgen, 5,Novartis Pharmaceutical Corporation, 5,Janssen Pharmaceutica Product, L.P., 5; **M. E. Husni**, Abbvie, 5,Amgen, 5,BMS, 5,Celgene, 5,Janssen Pharmaceutica Product, L.P., 5,Lilly, 5,Novartis Pharmaceutical Corporation, 5,Genentech and Biogen IDEC Inc., 5,UCB, 5; **T. Love**, None; **E. Lubrano**, None; **N. J. McHugh**, Abbvie, 5,Pfizer Inc, 5,Celgene, 5,Novartis Pharmaceutical Corporation, 5; **P. Nash**, Amgen, 5,BMS, 5,Abbvie, 5,Pfizer Inc, 5,Roche Pharmaceuticals, 5,UCB, 5,Janssen Pharmaceutica Product, L.P., 5,Novartis Pharmaceutical Corporation, 5,Lilly, 5; **A. Ogdie-Beatty**, None; **A. M. Orbai**, None; **A. Parkinson**, None; **D. O'Sullivan**, None; **C. F. Rosen**, Abbvie, 5,Janssen Pharmaceutica Product, L.P., 5,Celgene, 5,Amgen, 5; **S. Schwartzman**, Genentech and Biogen IDEC Inc., 5,Janssen Pharmaceutica Product, L.P., 5,Abbvie, 5,Pfizer Inc, 5,UCB, 5,Antares, 5,Medac, 5,Hospira, 5,Novartis Pharmaceutical Corporation, 5,AP Pharma, 5,Pfizer Inc, 1; **E. Siegel**, Amgen, 5,Janssen Pharmaceutica Product, L.P., 5,Celgene, 5,Abbvie, 5; **S. Toloza**, None; **W. Tuong**, None; **C. T. Ritchlin**, Amgen, 2,UCB, 2,Abbvie, 2,Abbvie, 5,Amgen, 5,Boehringer Ingelheim, 5,Janssen Pharmaceutica Product, L.P., 5,Novartis Pharmaceutical Corporation, 5,Regeneron, 5.

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Late-breaking Abstract Number: 8L

A Phase III, Randomized, Double-Blind Clinical Study Comparing SB5, an Adalimumab Biosimilar, with Adalimumab Reference Product (Humira®) in Patients with Moderate to Severe Rheumatoid Arthritis Despite Methotrexate Therapy (24-week Results)

Michael E. Weinblatt[1], Asta Baranauskaite[2], Jaroslaw Niebrzydowski[3], Eva Dokoupilova[4], Agnieszka Zielinska[5], Karina Sitek-Ziolkowska[6], Janusz Jaworski[7], Artur Racewicz[8], Margarita Pileckyte[2], Krystyna Jedrychowicz-Rosiak[9], Vyacheslav Zhdan[10], Soo Yeon Cheong[11] and Jeehoon Ghil[11], [1]Brigham and Women's Hospital, Boston, MA, [2]Lithuanian University of Health Sciences, Kaunas, Lithuania, [3]Medica Pro Familia, Gdynia, Poland, [4]Medical Plus s.r.o., Uherske Hradiste, Czech Republic, [5]Medica pro Familia, Warszawa, Poland, [6]Medica pro Familia, Katowice, Poland, [7]Reumatika Centrum Reumatologi, Warszawa, Poland, [8]Zdrowie Osteo- Medic s.c, Bialystok, Poland, [9]Mazowieckie Centrum Badañ Klinicznych, Grodzisk Mazowiecki, Poland, [10]M.V.Sklifosovskyi Poltava Regional Clinical Hospital, Poltava, Ukraine, [11]Samsung Bioepis Co., Ltd., Incheon, South Korea

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Background/Purpose:

SB5 is a biologic agent developed as a biosimilar of the adalimumab reference product (ADL). Equivalence in pharmacokinetics (PK) between SB5 and ADL in healthy subjects has been demonstrated[1] in a phase I study. This phase III study was a randomized, double-blind, multicenter study to compare the efficacy, safety, PK, and immunogenicity of SB5 with ADL in patients with moderate to severe rheumatoid arthritis (RA) despite methotrexate (MTX) treatment up to 52 weeks. **Results** up to 24 weeks are presented in this abstract.

Methods:

Patients with moderate to severe RA despite MTX treatment were randomly assigned to receive 40 mg of either SB5 or ADL administered subcutaneously every other week for 24 weeks. At Week 24, patients in ADL group were randomized again to receive 40 mg of either SB5 or ADL for additional 28 weeks. Patients in SB5 group continued to receive SB5. The primary endpoint was the ACR20 response rate at Week 24. Other secondary efficacy endpoints and safety were measured.

Results:

A total of 544 patients were randomized to either SB5 (N=271) or ADL (N=273). Baseline demographic and disease characteristic were comparable between two treatment groups. The ACR20 response rate at Week 24 in the per-protocol set (PPS) was 72.5% (174/240) in SB5 and 72.0% (170/236) in ADL. The 95% confidence interval (CI) of the treatment difference adjusted by region and baseline C-reactive protein was –7.66% to 8.30%, which was within the pre-defined equivalence margin of [–15%, 15%]. The ACR20 response rate at Week 24 was shown to be equivalent in the full analysis set as well (95% CI: -7.03%, 8.56%) when non-responder analysis was applied. The 95% CI of the estimated difference between the time-response curves of SB5 and ADL in the PPS met the pre-defined equivalence margin (Figure). The ACR50 response rates at Week 24 in the PPS were 38.3% vs. 39.8% and the ACR70 response rates were 19.2% vs. 20.3% in SB5 and ADL, respectively. The safety profile of SB5 was generally similar to that of ADL (Table). The overall incidence of anti-drug antibody up to Week 24 was 32.8% in SB5 vs. 31.7% in ADL. The PK profile was also comparable between the two treatment groups.

Conclusion:

SB5 was shown to be equivalent in terms of clinical efficacy when compared with ADL. SB5 was well tolerated with similar safety profile, PK, and immunogenicity to ADL.

Table. Safety Results

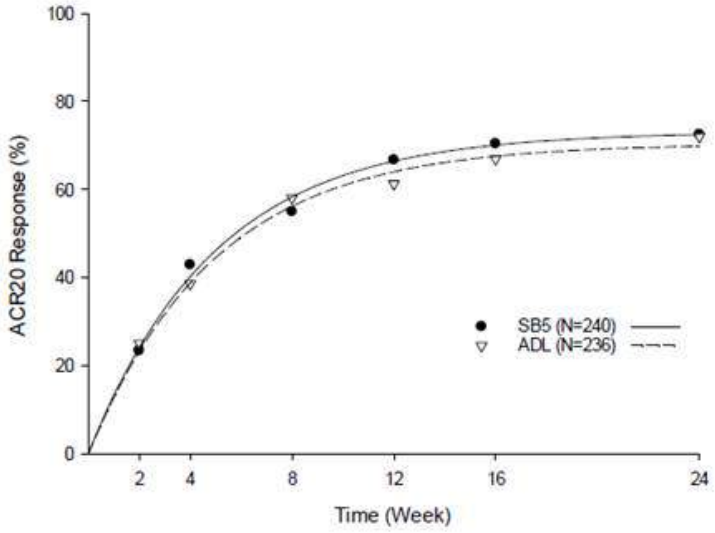
Patients with	SB5 (N=268*)		ADL (N=273)	
	n	(%)	n	(%)
At least 1 TEAE	96	(35.8)	110	(40.3)
At least 1 serious TEAE	3	(1.1)	7	(2.6)
Serious infection	1	(0.3)	2	(0.7)
Tuberculosis	0	(0.0)	0	(0.0)
Injection site reactions**	8	(3.0)	8	(2.9)
Malignancy	0	(0.0)	2	(0.7)
Death	0	(0.0)	2	(0.7)

TEAE: treatment-emergent adverse event

*Three patients withdrew before receiving at least one dose of the study drug.

**Numbers are based on high-level group term of administration site reactions.

Figure. Estimated Time-response Curves of ACR20 Response Rate up to Week 24 (PPS)



Reference

1. Shin DH et al. EULAR 2015, FRI0110.

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Bioepis, 2; **V. Zhdan**, Samsung Bioepis, 2; **S. Y. Cheong**, Samsung Bioepis, 3; **J. Ghil**, Samsung Bioepis, 3.

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Late-breaking Abstract Number: 9L

A Randomized Double-Blind Trial of Abatacept and Glucocorticoids for the Treatment of Giant Cell Arteritis

Carol A. Langford[1], David Cuthbertson[2], Steven R. Ytterberg[3], Nader A. Khalidi[4], Paul A. Monach[5], Simon Carette[6], Philip Seo[7], Larry W. Moreland[8], Michael Weisman[9], Curry L. Koening[10], Antoine G. Sreih[11], Robert F. Spiera[12], Carol McAlear[13], Kenneth J. Warrington[14], Christian Pagnoux[6], Kathleen Maksimowicz-McKinnon[15], Lindsy J. Forbess[16], Gary S. Hoffman[1], Renee Borchin[17], Jeffrey Krischer[17] and Peter A. Merkel[18], [1]Rheumatology, Cleveland Clinic, Cleveland, OH, [2]Biostatistics and Informatics, Department of Pediatrics, University of South Florida, Tampa, FL, [3]Rheumatology Division, Mayo Clinic, Rochester, MN, [4]McMaster University, St Joseph's Healthcare Hamilton, Hamilton, ON, Canada, [5]Rheumatology, Boston University School of Medicine, Boston, MA, [6]Division of Rheumatology, Mount Sinai Hospital, University of Toronto, Toronto, ON, Canada, [7]Division of Rheumatology, Johns Hopkins, Baltimore, MD, [8]Rheumatology & Clinical Immunology, University of Pittsburgh, Pittsburgh, PA, [9]Cedars-Sinai Medical Center, Los Angeles, CA, [10]Division of rheumatology, George E. Wahlen Department of Veterans Affairs Medical Center Salt Lake City and University of Utah, University of Utah School of Medicine, Salt Lake City, UT, [11]Department of Rheumatology, University of Pennsylvania, Philadelphia, PA, [12]Rheumatology, Hospital for Special Surgery, New York, NY, [13]Penn Vasculitis Center, Division of Rheumatology, University of Pennsylvania, Philadelphia, PA, [14]Rheumatology, Mayo Clinic, Rochester, MN, [15]Rheumatology, University of Pittsburgh, Pittsburgh, PA, [16]Rheumatology, Cedars-Sinai Medical Center, Los Angeles, CA, [17]University of South Florida, Tampa, FL, [18]Division of Rheumatology, University of Pennsylvania, Philadelphia, PA

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Background/Purpose: Giant cell arteritis (GCA) is a large-vessel primary systemic vasculitis. Although glucocorticoids are effective in treating GCA, they are associated with substantial toxicity and relapse of vasculitis occurs in a high percentage of patients. T-cell activation has been implicated in the pathophysiology of GCA. A multi-center, randomized, double-blind, placebo-controlled, withdrawal design trial was conducted to examine the efficacy and safety of treatment with abatacept (CTLA4-Ig) combined

with prednisone in patients with GCA.

Methods: Patients with newly diagnosed or relapsing GCA were eligible for the trial. All patients were treated with abatacept 10 mg/kg IV on days 1, 15, 29, and week 8, together with prednisone. At week 12 patients in remission underwent a double-blinded randomization to continue monthly abatacept or be switched to placebo. Patients in both study arms received prednisone according to a standardized taper schedule that reached discontinuation of prednisone at week 28. Patients remained on their randomized assignment until meeting criteria for early termination or until the common closeout date, 12 months after enrollment of the last patient. The primary endpoint was duration of remission (relapse-free survival, RFS). A planned sample size of 30 or more patients was based on detecting a 30% improvement in RFS utilizing a one-sided alpha = 0.1. Kaplan-Meier curves were constructed and differences in treatment arms compared using the log-rank test in an intent-to-treat analysis.

Results: 49 eligible patients with GCA received study drug with 41 reaching the week 12 randomization. Disease characteristics of the 41 randomized patients are outlined in Table 1.

The RFS at 12 months was estimated to be 48% for those receiving abatacept and 31% for those receiving placebo (p=0.049), Figure 1. A longer median duration of remission was seen with abatacept compared to placebo (abatacept 9.9 months, placebo 3.9 months). Covariate analysis examining those variables that differed between study arms did not impact the results.

129 adverse events occurred in 35 patients, including 23 serious adverse events in 15 patients. There was no difference in the frequency or severity of adverse events between treatment arms, including the rate of infection.

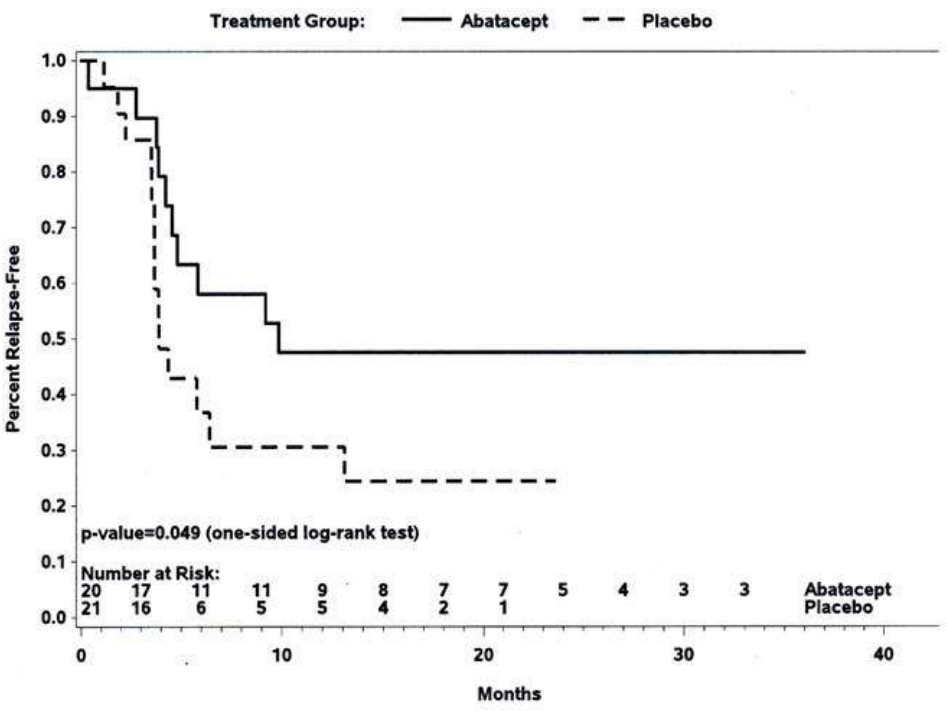
Conclusion: In patients with GCA the addition of abatacept to a standard treatment regimen with prednisone reduced the risk of relapse of vasculitis and was not associated with a higher rate of toxicity compared to prednisone alone. This study provides the first trial-level evidence of a targeted immunomodulatory therapy that has demonstrated efficacy for the treatment of GCA.

Table 1. Baseline characteristics of the study population of patients with giant cell arteritis

		Abatacept N=20	Placebo N=21	
		N (%)	N (%)	p-value
Patient demographics				
Age at enrollment (years), median (range)		63.5 (57.3-80.1)	71.5 (54.3-86.6)	0.052
Age at diagnosis (years), median (range)		62.4 (53.6-80.1)	70.5 (52.4-86.6)	0.043
Sex	Female	16 (80%)	21 (100%)	0.048
	Male	4 (20%)	0 (0%)	-
Diagnosis category at enrollment	Newly-diagnosed	12 (60%)	11 (52.4%)	0.62
	Relapsing	8 (40%)	10 (47.6%)	-
Disease duration (years), median (range)		0.15 (0-13.3)	0.31 (0-6.9)	0.77
Race	Asian	0 (0%)	1 (4.8%)	1.00
	Black or African-American	1 (5%)	1 (4.8%)	-
	Caucasian	19 (95%)	19 (90.5%)	-
TA biopsy performed		15 (75%)	17 (81.0%)	0.72
TA biopsy positive (of those performed)		12 (80%)	13 (76.5%)	1.00
Active disease characteristics at enrollment				
Vascular pain or tenderness		8 (40%)	10 (47.6%)	0.62
Headache		12 (60%)	13 (61.9%)	0.90
Ischemic retinopathy or visual loss		1 (5%)	1 (4.8%)	1.00
Tongue/jaw pain or claudication		10 (50%)	9 (42.9%)	0.65
Extremity claudication		3 (15%)	6 (28.6%)	0.45
Musculoskeletal symptoms		6 (30%)	5 (23.8%)	0.65
Malaise/fatigue + ESR > 40 mm/hour		7 (35%)	10 (47.6%)	0.41
New vascular stenosis or aneurysm		2 (10%)	3 (14.3%)	1.00
Other features attributed to GCA		5 (25%)	3 (14.3%)	0.45

ESR: erythrocyte sedimentation rate; GCA: giant cell arteritis; TA: temporal artery

Figure 1. Relapse-free survival comparing treatment with abatacept to placebo in patients with giant cell arteritis.



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Late-breaking Abstract Number: 10L

Aiming for Remission in Rheumatoid Arthritis: Clinical and

Radiographic Outcomes from a Randomized Controlled Strategy Trial Investigating the Added Value of Ultrasonography in a Treat-to-Target Regimen

Espen A. Haavardsholm[1], Anna-Birgitte Aga[1], Inge C Olsen[2], Hilde B. Hammer[3], Till Uhlig[4], Hallvard Fremstad[5], Tor Magne Madland[6], Åse S. Lexberg[7], Hilde Haukeland[8], Erik Rødevand[9], Christian Høili[10], Hilde Stray[11], Anne Noraas Bendvold[12], Inger Johanne Widding Hansen[13], Gunnstein Bakland[14,15], Lena B. Nordberg[1], Siri Lillegraven[1], Désirée van der Heijde[1,16] and Tore K. Kvien[1], [1]Dept. of Rheumatology, Diakonhjemmet Hospital, Oslo, Norway, [2]Department of Rheumatology, Diakonhjemmet Hospital, Oslo, Norway, [3]Postboks 23 Vinderen, Diakonhjemmet Hospital, Oslo, Norway, [4]Diakonhjemmet Hospital, Oslo, Norway, [5]Dept. of Rheumatology, Ålesund Hospital, Helse Møre og Romsdal HF, Ålesund, Norway, [6]Dept. of Rheumatology, Haukeland University Hospital, Bergen, Norway, [7]Dept. of Rheumatology, Vestre Viken Hospital, Drammen, Norway, [8]Dept. of Rheumatology, Martina Hansens Hospital, Bærum, Norway, [9]Dept. of Rheumatology, St. Olavs Hospital, Trondheim, Norway, [10]Dept. of Rheumatology, Hospital Østfold HF, Moss, Norway, [11]Haugesund Rheumatism Hospital, Haugesund, Norway, [12]The Rheumatology Clinic Dovland/Bendvold, Kristiansand, Norway, [13]Dept. of Rheumatology, Sørlandet Hospital, Kristiansand, Norway, [14]Dept. of Rheumatology, University Hospital Northern Norway, Tromsø, Norway, [15]Institute of Clinical Medicine, University Hospital of North Norway, Tromsø, Norway, [16]Dept. of Rheumatology, Leiden University Medical Center, Leiden, Netherlands

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Background/Purpose: The application of ultrasonography (US) in rheumatology clinical practice is growing. The ARCTIC trial (NCT01205854) was designed to examine if the use of a treatment strategy including information from a structured US assessment would lead to better clinical and radiographic outcomes for patients with rheumatoid arthritis (RA), compared to a conventional strategy based on clinical and laboratory assessments alone.

Methods: The study population consisted of disease-modifying antirheumatic drug (DMARD) naïve early RA patients with <2 years symptom duration, fulfilling the 2010 ACR/EULAR classification criteria and with indication for DMARD therapy. Patients were followed in a tight control regimen with 13 visits over the 2-year follow-up period and randomized 1:1 to A) an US tight control (UTC) strategy targeting DAS < 1.6, no swollen joints and no power-Doppler (PD) signal in any joint or B) a conventional tight control (CTC) strategy targeting DAS<1.6 and no swollen joints. US was performed by experienced sonographers at every visit in the UTC arm, using a validated semi-quantitative scoring system with scores 0-3 for grey scale (GS) and PD in 32 joints (1). Patients in both arms were treated according to the same treat-to-target strategy with a step-up DMARD escalation approach starting with MTX, then triple combination therapy MTX/SSZ/HCQ, then biologic DMARD if target was not reached.

The primary endpoint was the proportion of patients meeting all the 3 following criteria: 1) Sustained clinical remission, defined as DAS<1.6 at 16, 20 and 24 months 2) No swollen joints at 16, 20 and 24 months (44 SJC) and 3) No progression (<0.5 units) in van der Heijde-modified total Sharp Score (vdHSS) between 16 and 24 months. Secondary efficacy endpoints included various measures of disease activity/remission and vdHSS.

Results: A total of 238 patients were randomized, and all patients with at least one follow-up visit were included in the full analysis set (UTC n=118, CTC n=112). 105 patients in the UTC arm and 99 patients in the CTC arm completed the study. The primary endpoint was reached by 26 patients (22.0%) in the UTC and 21 patients (18.8%) in the CTC (p=0.54, mean difference 3.3%; 95%CI -7.1% to 13.7%). Secondary efficacy outcomes are shown in Table 1.

Conclusion: There was no difference in the probability of achieving sustained clinical remission and halt of radiographic progression between the two strategies. Both the strategy adding ultrasonography and the conventional strategy led to early and sustained improvements in clinical outcomes, providing excellent disease control and minimal radiographic progression. The implementation and systematic use of US in the follow-up of early RA patients treated with an aggressive treat-to-target strategy is not justified based on the results of the ARCTIC trial.

References: 1 Hammer HB, et al, Ann Rheum Dis 2011

Table 1. Clinical and radiographic outcomes

Variable	Ultrasonography tight control (n=118)	Conventional tight control (n=112)	Difference (95% CI)	*p*-value
Primary endpoint, n (%)				
DAS<1.6, SJC44<1, ΔvdHSS<0.5 between 16 and 24 months[1,2]	26 (22.0)	21 (18.8)	3.3 (-7.1 to 13.7)	0.54
Components of primary endpoint, n (%)				
No swollen joints (SJC44<1) at 16, 20 and 24 months[1,2]	62 (52.5)	61 (54.5)	1.9 (-14.8 to 11.1)	0.77
DAS remission (DAS<1.6) at 16, 20 and 24 months[1,2]	64 (54.2)	58 (51.8)	2.45 (-10.4 to 15.4)	0.71
No radiographic progression (ΔvdHSS<0.5) 16-24 months[1,2]	49 (41.5)	39 (34.8)	6.7 (-19.2 to 5.8)	0.30
Secondary outcomes at 24 months (end of study), n (%)				
DAS remission (DAS<1.6)[1]	80 (67.8)	75 (67.0)	0.8 (-11.3 to 13.0)	0.89
CDAI remission (CDAI≤2.8)[1]	70 (59.3)	59 (52.7)	6.6 (-6.2 to 19.5)	0.31
SDAI remission (SDAI≤3.3)[1]	71 (60.2)	56 (50.0)	10.2 (-2.6 to 23.0)	0.12
EULAR good/moderate response[1]	98 (83.1)	90 (80.4)	2.7 (-7.3 to 12.7)	0.60
Radiographic outcomes, median (25^{th}; 75^{th} percentile)				
Change in vdHSS total score 0-24 months[3]	1 (0; 2.5)	1.5 (0.5; 3)	-0.43 (-0.93 to 0.07)	0.09
Change in vdHSS erosion	0.5	1	-0.39	0.04

score 0-24 months[3]	(0; 1.5)	(0.5; 2)	(-0.77 to -0.02)	
Change in vdHSS JSN score 0-24 months[3]	0 (0; 0.5)	0 (0; 0.5)	0 (-0.06 to 0.06)	1
Treatment at end of study, n (%)				
MTX monotherapy	63 (53.4)	80 (71.4)	-18.0 (-30.3 to -5.8)	0.03
MTX/SSZ/HCQ	21 (17.8)	13 (11.6)	6.2 (-2.9 to 15.3)	0.18
Biologic treatment	34 (28.8)	19 (17.0)	11.8 (1.1 to 22.6)	0.03

[1] *Missing observations at 24 months imputed with worst outcome*

[2] *Missing observations before 24 months imputed with last observation carried forward*

[3] *Missing observations imputed using linear intra- and extrapolation*

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Late-breaking Abstract Number: 11L

Preliminary Results of a Double-Blind Randomised Trial of Rituximab Anti-B-Cell Therapy in Patients with Primary Sjogrens Syndrome

Simon Bowman[1], Colin Everett[2], Michele Bombardieri[3], Robert Busch[4], Paul Emery[5], Frances Hall[6], Colin T. Pease[7], Costantino Pitzalis[8], Elizabeth Price[9], Luke Dawson[10], Peter Smith[11], Nurhan Sutcliffe[3], Wan-Fai Ng[12], Catherine Fernandez[13], Sharon Ruddock[13], Linda Sharples[13], Catherine Reynolds[13] and Sue Pavitt[14], [1]Rheumatology Dept, University Hospital Birmingham, Birmingham, United Kingdom, [2]Leeds Institute for Clinical Trials Research, University of Leeds, LEEDS, United Kingdom, [3]Experimental Medicine and Rheumatology, Queen Mary University of London, London, United Kingdom, [4]Department of Life Sciences, University of Roehampton, London, United Kingdom, [5]Leeds Institute of Rheumatic and Musculoskeletal Medicine, Leeds Gen Infirmary, Leeds, United Kingdom, [6]School of Clinical Medicine, University of Cambridge, Cambridge, United Kingdom, [7]Rheumatology, Leeds Teaching Hospitals NHS Trust, Leeds, United Kingdom, [8]Centre for Experimental Medicine & Rheumatology, Queen Mary's School of Medicine and Dentistry, London, United Kingdom, [9]Rheumatology Department, Great Western Hospital, Swindon, United Kingdom, [10]School of Dental Sciences, University of Liverpool,, Liverpool, United Kingdom, [11]School of Dental Sciences,, University of Liverpool, Liverpool, United Kingdom, [12]NIHR Newcastle Biomedical Research Centre, Newcastle University, Newcastle upon Tyne, United Kingdom, [13]Leeds Institute for Clinical Trials Research, University of Leeds, Leeds, United Kingdom, [14]Division of Applied Health & Clinical Translation , School of Dentistry, University of Leeds, Leeds, United Kingdom
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Background/Purpose: Evidence from open-label and observational studies support anti-B-cell therapy in patients with primary Sjogren's Syndrome (PSS). The TRACTISS trial aimed to determine the extent to which rituximab improves symptoms of fatigue and oral dryness in patients with PSS.

Methods: Multicentre, randomised, parallel group, double-blind, placebo-controlled trial. Patients with PSS, and symptomatic fatigue and oral dryness were recruited from 25 rheumatology clinics in the UK from June 2012 to January 2014. At weeks 0, 2, 24 and 26, patients received pre- and post-infusion corticosteroids and either placebo (P) IV or rituximab (R) IV (1000mg in 250mL). Intervention was decided by 24hr central telephone minimisation service. Primary endpoint was the proportion of patients achieving 30% reduction in either fatigue or oral dryness at 48 weeks, measured by Visual Analogue Scale (VAS). Other outcomes included VAS scales for fatigue or oral dryness separately, global assessment of PSS activity, pain, ocular and overall dryness, as well as salivary and lachrymal flow rates, quality of life, EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI) and Patient Reported Index (ESSPRI). Patients and physicians were blinded to the patient's allocation. ISRCTN 65360827

Results:

All patients (n=133) randomised to P (n=66) and to R (n=67) were included in the primary analysis. 55 P and 54 R patients received all 4 infusions in full. Mean age was 54 years, 93% of patients were female, mean ESSDAI was 5.7 and mean time since diagnosis was 5.7 years. Among complete cases at 48 weeks, 21/56 P and 24/61 R patients achieved the primary endpoint. After multiple imputation of missing outcomes, response rates were 36.8% (P) and 39.8% (R) (adjusted odds ratio 1.13, 95% confidence interval 0.50-

2.55). There were no significant differences in any outcome measure, except unstimulated salivary flow: P patients deteriorated compared to R patients with a significant relative difference seen after Week 24. There were more adverse events reported in total for R (275 P vs 325 R), but no difference in serious adverse events. (10 vs 10) One serious infusion reaction (R) and one serious anaphylaxis (P) occurred in one patient each.

Conclusion: TRACTISS is the largest randomised trial of biologic therapy in PSS. No improvement in symptoms was seen in the Rituximab arm (unlike the TEARS study) but modest benefit for Rituximab in salivary flow was observed.

Funding: Funded by Arthritis Research UK.

Table 1: Summary of results (* denotes values were log-transformed before analysis, and results back-transformed for presentation, ** denotes effects as a ratio, rather than a difference)

	24 Weeks			48 Weeks		
	Placebo	Rituximab	Difference	Placebo	Rituximab	Difference
Unadjusted Complete Case analyses (95% Confidence Intervals)						
Fatigue VAS Response rates (%)	30.5 (19.2, 43.9)	29.5 (18.5, 42.6)	-1.0 (-18.6, 17.0)	26.8 (15.8, 40.3)	29.5 (18.5, 42.6)	2.7 (-15.5, 20.7)
Oral Dryness VAS Response rates (%)	22.0 (12.3, 34.7)	21.3 (11.9, 33.7)	-0.7 (-18.6, 17.0)	17.9 (8.9, 30.4)	31.1 (19.9, 44.3)	13.3 (-4.9, 30.9)
Primary Endpoint (Either fatigue or oral dryness) response rates (%)	37.3 (25.0, 50.9)	34.4 (22.7, 47.7)	-2.9 (-20.2, 15.3)	37.5 (24.9, 51.5)	39.3 (27.1, 52.7)	1.8 (-16.3, 19.9)
Mixed Model Estimates – adjusted for baseline values (95% Confidence Intervals)						
Fatigue VAS (0-100mm, 100=Severe)	64.5 (58.2, 71.5)	69.5 (63.7, 75.4)	4.7 (-2.9, 12.2)	65.8 (59.3, 72.2)	67.9 (61.3, 74.4)	2.1 (-5.9, 10.1)
Oral Dryness VAS (0-100mm, 100=Severe)	70.1 (63.9, 76.4)	70.2 (63.7, 76.7)	0.1 (-7.5, 7.6)	70.5 (64.5, 76.4)	66.4 (59.2, 73.7)	-4.1 (-12.0, 3.9)
Unstimulated Salivary Flow (mL/15min)*	0.66 (0.51, 0.87)	0.83 (0.64, 1.08)	1.25** (0.91, 1.72)	0.59 (0.45, 0.77)	1.00 (0.76, 1.31)	1.71** (1.23, 2.37)
ESSPRI (0-10, 10=Severe)	5.8 (5.3, 6.2)	6.3 (5.8, 6.8)	0.6 (0.01, 1.09)	5.7 (5.2, 6.2)	6.3 (5.7, 6.9)	0.5 (-0.1, 1.2)
ESSDAI (0-123, 123=Maximal activity)*	4.4 (3.6, 5.4)	4.1 (3.3, 5.2)	0.9** (0.7, 1.2)	4.5 (3.5, 5.8)	3.4 (2.7, 4.4)	0.8** (0.6, 1.0)

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Late-breaking Abstract Number: 12L

Assessment of Immunogenicity of Live Zoster Vaccination (Zostavax®) in Rheumatoid Arthritis Patients on Background Methotrexate before and after Initiating Tofacitinib or Placebo

Kevin Winthrop IV[1], Ann Wouters[2], Ernest H. Choy[3], Koshika Soma[2], Jennifer Hodge[2], Chudy Nduaka[2], Pinaki Biswas[2], Lisa K. McNeil[2], Sherry Passador[2], Christopher F. Mojcik[2] and William F.C. Rigby[4], [1]Oregon Health and Sciences University, Portland, OR, [2]Pfizer Inc, New York, NY, [3]CREATE Center, Institute of Infection and Immunity, Cardiff University School of Medicine, Cardiff, United Kingdom, [4]Geisel School of Medicine at Dartmouth, Lebanon, NH

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Background/Purpose: Tofacitinib is an oral Janus kinase inhibitor for the treatment of rheumatoid arthritis (RA). Clinical guidelines recommend using live zoster vaccine (LZV) to prevent shingles in RA, but this vaccine has not been previously studied in RA patients (pts) and the effect of tofacitinib on humoral or cell-mediated live vaccine responses is unknown.

Methods: To evaluate the effect of tofacitinib upon the immune response and safety of LZV, we recruited pts aged ≥50 years with active RA (≥4 tender/painful joints and ≥4 swollen joints) despite methotrexate (MTX) therapy (≥4 months of treatment with 15–25 mg/week [wk] before screening) (study NCT02147587). Pts with prior history of zoster vaccination were excluded, as were those receiving any vaccine in the 6 wks prior to randomization. After screening, eligible pts were given LZV and then randomized to either tofacitinib 5 mg BID or placebo (PBO) to start 2–3 wks post-vaccination with continuation of background MTX. We measured both humoral (varicella-zoster virus [VZV]-specific IgG via gpELISA) and cell-mediated responses (VZV-specific T cell enumeration via ELISPOT) prior to vaccination (baseline, day of vaccination), and then at 2, 6, and 14 wks post-vaccination. The primary endpoint was an assessment of the geometric mean fold rise (GMFR) in VZV-specific IgG titer at 6 wks post-vaccination. Secondary endpoints included the proportion of patients achieving a ≥1.5 fold rise in VZV-specific IgG titer 6 wks post-vaccination. Exploratory endpoints included the GMFR in VZV-specific T cells (spot-forming cells/10^6 peripheral blood mononuclear cells [PBMCs]) by ELISPOT between baseline and 6 wks post-vaccination. Pts were followed for 12 wks after randomization for safety.

Results: 112 pts were randomized into PBO (n=57) and tofacitinib arms (n=55). Most PBO (93%) and tofacitinib (98%) pts were evaluable for immune response endpoints. Pts were similar with regard to sex, age, baseline disease activity, and baseline VZV immune measures (i.e. IgG, ELISPOT). The GMFR in VZV-specific IgG titer at 6 wks was 2.11 for tofacitinib pts and 1.74 for PBO pts. The GMFRs both in tofacitinib and PBO pts were comparable with the GMFRs in healthy people ≥50 years as indicated in the LZV labels. The proportion of patients developing a 1.5 fold post-vaccination rise in IgG titer at 6 wks trended higher for tofacitinib (57.4%) versus PBO (43.4%). For cell-mediated immune responses, the VZV-

specific T cell GMFR at 6 wks increased similarly for tofacitinib pts (1.50) and PBO pts (1.29). SAEs occurred in 0 (0%) and 3 (5.5%) of PBO and tofacitinib arms respectively. One pt in the study developed cutaneous dissemination with vaccine-strain VZV (Oka strain virus) that occurred 2 days after starting tofacitinib (16 days post-vaccination). Subsequently, this pt was found to lack pre-existing immunity to VZV, consistent with vaccine-induced disease. This event resolved after tofacitinib discontinuation and antiviral therapy.

Conclusion: Pts starting tofacitinib had similar VZV-specific humoral and cell-mediated immune responses to LZV as compared to PBO-treated pts. Vaccination appeared safe in all pts but one who lacked pre-existing VZV immunity.

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Late-breaking Abstract Number: 13L

Safety and Efficacy of E6011, an Anti-Fractalkine Monoclonal Antibody, in a First-in-Patient Phase 1/2 Study in Rheumatoid Arthritis

Yoshiya Tanaka[1], Tsutomu Takeuchi[2], Hisanori Umehara[3], Toshihiro Nanki[4], Hideto Akama[5], Nobuyuki Yasuda[5], Fumitoshi Tago[5], Makoto Kawakubo[5], Seiichiro Hojo[5], Tetsu Kawano[6] and Toshio Imai[6], [1]The First Department of Internal Medicine, University of Occupational and Environmental Health, Japan, Kitakyushu, Japan, [2]Dept. of Internal Medicine, School of Medicine Keio University, Tokyo, Japan, [3]Kyoto University Graduate School of Medicine, Kyoto, Japan, [4]School of Medicine, Faculty of Medicine, Toho University, Tokyo, Japan, [5]EISAI Co. Ltd., Tokyo, Japan, [6]KAN Research Institute, Inc., Kobe, Japan

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Background/Purpose: Fractalkine (CX3CL1, designated as FKN hereafter) is the sole member of the CX3C-chemokine which leads to dual actions, chemotaxis and cell adhesion for leukocytes expressing the cognate receptor, CX3CR1, during their migration. Accumulating evidence is telling that FKN-CX3CR1 axis plays a pivotal role in leukocyte/lymphocyte accumulation in inflamed tissues in RA[1]. We developed E6011, a novel humanized anti-FKN monoclonal antibody, and its safety and tolerability was assessed in a Phase 1/2, open-label, multiple ascending dose study in RA patients for the first time (NCT02196558).

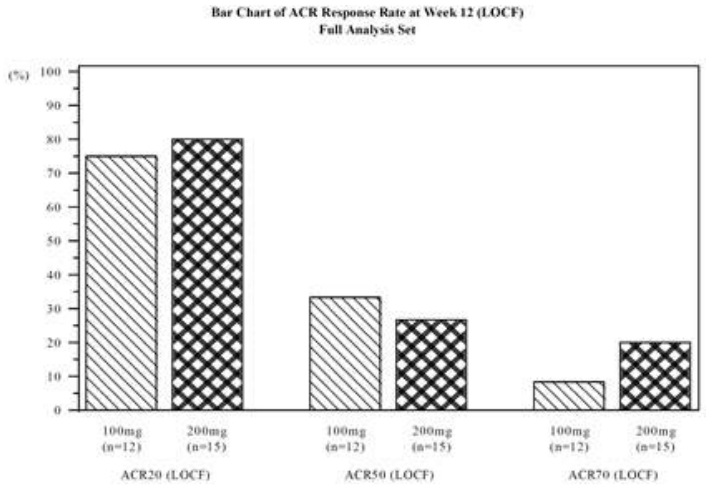
Methods: Active RA patients with inadequate response to MTX or TNF inhibitors were received 7 consecutive doses (subcutaneous) of E6011 at week 0, 1, 2 and thereafter every 2 weeks up to week 10. A hundred and 200 mg of E6011 were chosen for the study as putatively appropriate doses for patients by the PK/PD modeling previously obtained in the Ph1 healthy volunteer study of E6011. The primary objective was safety and tolerability of E6011 in Japanese RA patients while the efficacy of E6011 was also explored.

Results: Twelve subjects were enrolled in the cohort of 100 mg and subsequently 15 subjects were enrolled in the 200 mg cohort, in total, 27 subjects received repeated subcutaneous administrations of E6011. As a result, repeated dose of E6011 was found safe and well tolerated. The incidence of AE, treatment related AE and SAE was 59.3%, 29.6% and 7.4%, respectively. There were no severe AE or deaths, and no significant differences were observed in the incidence or severity of AE between the 100 mg and 200 mg cohorts.

Clinical outcome was also available in the study in which response rates of ACR20, 50 and 70 at week 12 were 75.0%, 33.3%, 8.3% and 80.0%, 26.7%, 20.0% in the cohort of 100 and 200 mg, respectively. At week 12, 33.3% of subjects achieved DAS28-CRP remission in both cohorts, 16.7% and 20.0% for SDAI remission and 8.3% and 26.7% for Boolean remission were observed in the 100 and 200 mg cohorts, respectively.

Category	E6011		
	100 mg (N=12) n (%)	200 mg (N=15) n (%)	Total (N=27) n (%)
All AEs	6 (50.0)	10 (66.7)	16 (59.3)
Treatment-related AEs	3 (25.0)	5 (33.3)	8 (29.6)
Severe AEs	0	0	0
Serious AEs	1 (8.3)	1 (6.7)	2 (7.4)
Death	0	0	0
AEs leading to study drug withdrawal	0	2 (13.3)	2 (7.4)

For each row category, a subject with 2 or more AEs in that category was counted only once.



Conclusion: E6011 was safe and well tolerated, and demonstrated a promising efficacy in active RA patients with MTX or TNFi-IR. While further clinical studies are required, the results obtained indicate that a novel biological DMARD targeting FKN/CX3CR1 interaction will be clinically beneficial for active RA patients.

Reference:

1. Nanki T. Arthritis Rheum. 2002; 46(11):2878-83.

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Late-breaking Abstract Number: 14L

Safety and Efficacy of ABT-494, a Novel Selective JAK1 Inhibitor, in Patients with Active Rheumatoid Arthritis and Inadequate Response or Intolerance to Anti-TNF Biologic Therapy

Joel M. Kremer[1], Edward C. Keystone[2], Paul Emery[3], Heidi S. Camp[4], Alan Friedman[4], Li Wang[4], Ahmed A. Othman[4], Nasser Khan[4] and Steven Jungerwirth[4], [1]Albany Medical College, Albany, NY,

[2]Mount Sinai Hospital, University of Toronto, Toronto, ON, Canada, [3]NIHR-Leeds Musculoskeletal Biomedical Research Unit, University of Leeds, Leeds, United Kingdom, [4]AbbVie Inc., North Chicago, IL
First publication: October 27, 2015

SESSION INFORMATION

Session Date: Tuesday, November 10, 2015

Session Title: ACR Late-breaking Abstract Poster Presentations

Session Type: ACR Late-breaking Abstract Session

Session Time: 9:00AM-11:00AM

Background/Purpose: The safety, efficacy, and dose response of ABT-494, a novel selective JAK1 inhibitor, were characterized vs placebo (PBO) in patients (pts) with moderately to severely active RA and an inadequate response to ≥1 anti-TNF biologic therapy (TNF-IR). **Methods:** This was a phase 2b, 12-week, double-blind PBO-controlled study; TNF-IR pts receiving stable background methotrexate (MTX) were randomized 1:1:1:1:1 to ABT-494 3, 6, 12, and 18 mg twice daily (BID) or matching PBO. The primary efficacy endpoint was the proportion of pts who achieved an ACR20 response at week 12. **Results:** All 276 pts had failed ≥1 anti-TNF therapy prior to enrollment; 28% had received ≥2 anti-TNF biologics and 20% had also received non–anti-TNF biologics. Baseline (BL) characteristics were similar in all treatment groups. The proportion of pts achieving ACR20 at week 12 was significantly higher for all ABT-494 groups vs PBO **(Table 1)**. There was a significant (P<0.01) dose response between PBO and all ABT-494 treatment groups for ACR20 response rates (non-responder imputation) at week 12. ACR50 and ACR70 responses were statistically significantly higher at doses of ≥6 mg BID. Changes in DAS28(CRP) from BL were significantly greater for all doses of ABT-494 vs PBO. Onset of action was rapid, with significant differences in ACR20 and change in DAS28(CRP) from BL at week 2 (P≤0.007) for 6, 12, and 18 mg BID vs PBO. Low disease activity and clinical remission per DAS28(CRP) criteria were achieved statistically significantly more often in the 12-mg BID dose group vs PBO. The incidences of AEs were numerically higher in ABT-494 dose groups, with some trend towards dose dependency **(Table 2)**. The majority of infections were mild. There was one serious infection ("bronchiectasis") in the PBO group and none in the ABT-494 treatment groups were reported. Five pts had non-serious events of herpes zoster: 1 pt each in the ABT-494 3 mg, 12 mg, and 18 mg BID treatment groups, and 2 pts in the PBO group. One pt in the 6-mg BID dose group reported 2 events of non-melanoma skin cancer (basal cell and squamous cell carcinomas). There was 1 report of anemia in the 18-mg BID dose group. No deaths were reported during the study. **Conclusion:** This phase 2b study demonstrated the clinical efficacy of ABT-494 vs PBO when dosed in combination with MTX in TNF-IR pts with active RA. ABT-494 had an acceptable safety and tolerability profile.

Table 1. Efficacy Endpoints at Week 12					
		ABT-494			
	PBO (n=56)	3 mg BID (n=55)	6 mg BID (n=55)	12 mg BID (n=55)	18 mg BID (n=55)
ACR20, %	34	53*	58**	71***	67***
ACR50, %	16	24	35*	42**	38**
ACR70, %	4	13	26**	22**	22**
DAS28(CRP), mean change from baseline†	-1.1	-1.9**	-2.2***	-2.5***	-2.3***
CR DAS28 <2.6, %	13	24	26	33*	27
LDA DAS28 <3.2, %	25	33	36	49**	42
LDA CDAI ≤10, %	25	27	31	40	40
ACR20/50/70, 20%/50%/70% improvement in American College of Rheumatology score; BID, twice daily; CDAI, Clinical Disease Activity Index; CR, clinical remission; CRP, C-reactive protein; DAS28, 28-joint Disease Activity Score; LDA, low disease activity. Non-responder imputation (NRI) unless otherwise noted. ***, **, *: statistically significant at the 0.001, 0.01, and 0.05 levels. †Last observation carried forward.					

Table 2. Adverse Events Summary					
		ABT-494			
Number of pts, n (%)	PBO (n=56)	3 mg BID (n=55)	6 mg BID (n=55)	12 mg BID (n=55)	18 mg BID (n=55)
Any AE	25 (45)	26 (47)	31 (56)	37 (67)	39 (71)
Serious AE	1 (2)	2 (4)	2 (4)	0	1 (2)
Severe AE	2 (4)	1 (2)	2 (4)	2 (4)	1 (2)
AE leading to discontinuation	2 (4)	0	6 (11)	2 (4)	3 (6)
Infections	13 (23)	11 (20)	12 (22)	22 (40)	21 (38)
Serious infection	1 (2)	0	0	0	0
Anemia	0	0	0	0	1 (2)
Herpes zoster	2 (4)	1 (2)	0	1 (2)	1 (2)
Hepatic disorder	1 (2)	0	0	0	2 (4)
Neutropenia	0	0	0	1 (2)	1 (2)
Malignancy	0	0	1 (2)	0	0
AE, adverse event; BID, twice daily.					

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Samsung, and Lilly, 5; **H. S. Camp**, AbbVie Inc., 3,AbbVie Inc., 1; **A. Friedman**, AbbVie Inc., 3,AbbVie Inc., 1; **L. Wang**, AbbVie Inc., 3,AbbVie Inc., 1; **A. A. Othman**, AbbVie Inc., 3,AbbVie Inc., 1; **N. Khan**, AbbVie Inc., 3,AbbVie Inc., 1; **S. Jungerwirth**, AbbVie Inc., 3,AbbVie Inc., 1.

Late-breaking Abstract Number: 15L

Identification of Four-and-a-Half-LIM Domain 1 (FHL1) As a New Autoantibody Target in Idiopathic Inflammatory Myopathies

Inka Albrecht[1], Cecilia Wick[1], Åsa Hallgren[2], Anna Tjärnlund[1], Kanneboyina Nagaraju[3], Felipe Andrade[4], Kathryn Thompson[5], William Coley[5], Aditi Phadke[6], Lina-Marcela Diaz-Gallo[1], Matteo Bottai[7], Inger Nennesmo[8], Karine Chemin[9], Jessica Herrath[10], Karin Johansson[1], Anders Wikberg[1], Jimmy Ytterberg[1], Roman Zubarev[1], Olof Danielsson[11], Olga Krystufkova[12], Jiri Vencovsky[13], Nils Landegren[2], Marie Wahren-Herlenius[14], Leonid Padyukov[15], Olle Kämpe[2] and Ingrid E. Lundberg[16], [1]Rheumatology Unit, Department of Medicine, Solna, Karolinska Institutet, Stockholm, Sweden, [2]Experimental Endocrinology, Department of Medicine, Solna, Karolinska Institutet, Stockholm, Sweden, [3]The George Washington University Medical Center, Children's National Medical Center, Washington, DC, [4]Division of Rheumatology, The Johns Hopkins University School of Medicine, Baltimore, MD, [5]Children's National Medical Center, Washington, DC, [6]Research Center for Genetic Medicine, Children's National Medical Center, Washington, DC, [7]Institute for Environmental Medicine, Karolinska Institutet, Stockholm, Sweden, [8]Department of Laboratory Medicine, Karolinska Institutet, Stockholm, Sweden, [9]Medicine, Rheumatology Unit, Department of Medicine, Solna, Karolinska Institutet, Stockholm, Sweden, [10]Department of Medicine,, Rheumatology Unit, Department of Medicine, Solna, Karolinska Institutet, Stockholm, Sweden, [11]Department of Clinical and Experimental Medicine, Division of Neurology, Faculty of Health Sciences, Linköping University, Linköping, Sweden, [12]Institute of Rheumatology and Department of Rheumatology, 1st Faculty of Medicine, Charles University, Prague, Czech Republic, [13]Rheumatology, Institute of Rheumatology and Department of Rheumatology, 1st Faculty of Medicine, Charles University, Prague, Czech Republic, [14]Department of Medicine, Experimental Rheumatology Unit, Solna, Sweden, [15]Department of medicine, Rheumatology Unit, Department of Medicine, Solna, Karolinska Institutet, Stockholm, Sweden, [16]Karolinska University Hospital, Rheumatology Unit, Department of Medicine, Solna, Karolinska Institutet, Stockholm, Sweden

First publication: October 27, 2015

SESSION INFORMATION

Session Date: Tuesday, November 10, 2015

Session Title: ACR Late-breaking Abstract Poster Presentations

Session Type: ACR Late-breaking Abstract Session

Session Time: 9:00AM-11:00AM

Background/Purpose:

Idiopathic inflammatory myopathies (IIMs) are a heterogeneous group of rare systemic autoimmune diseases collectively called myositis causing progressive muscle weakness. Interestingly, myositis-specific autoantibodies described in different subsets of IIM are directed against ubiquitously expressed, intracellular proteins and show a lack of muscle specificity. Here we show for the first time that patients with IIM develop autoimmunity to the muscle-specific protein Four-and-a-half-LIM-domain 1 (FHL1). Strikingly, FHL1 is the causative factor for several X-linked hereditary myopathies, collectively called FHL1-related myopathies.

Methods:

Sera from IIM patients (n=141), followed at the Rheumatology Unit, Karolinska University Hospital, were compared to gender- and age-matched healthy controls (n=126) as well as patients diagnosed with other autoimmune disorders (n=186) and patients with non-inflammatory neuromuscular diseases (n=9) by ELISA and immunoblot. For 132/141 patients detailed clinical and laboratory data from patient records were available and the significance of differences between anti-FHL^+ and anti-FHL^- patients was calculated by the Wilcoxon's rank-sum test for continuous variables, and by Pearson's Chi-square test or by the Fischer's exact test for categorical variables. Expression pattern of FHL1 in muscle tissue of affected patients was analysed by confocal microscopy. Functional aspects of an anti-FHL1 autoimmune response was investigated in IIM-susptible MHC class I-overexpressing HT mice.

Results:

Anti-FHL1 autoantibodies were detected in 25% of IIM patients, while patients with other autoimmune diseases including rheumatoid arthritis (RA), systemic sclerosis (SSc) and systemic lupus erythematosus (SLE) or non-inflammatory neuromuscular diseases were largely anti-FHL1-negative. A comprehensive analysis of clinical data on muscular and extra-muscular involvement as well as biopsy characteristics revealed that anti-FHL1 reactivity was predictive for muscle atrophy, dysphagia, pronounced muscle fiber damage characterized by necrosis and connective tissue/fat replacement of muscle tissue, and vasculitis. The targeted autoantigen FHL1 showed an altered expression pattern with focal accumulation in muscle fibers of autoantibody-positive patients compared to a homogeneous expression in anti-FHL1-negative patients and healthy controls. By addressing the question how FHL1-autoimmunity might be initiated, we found that FHL1 is a target of granzyme B. To investigate if FHL1-autoimmunity contributes to muscle damage, we immunized myositis-prone mice with FHL1 and found aggravated muscle weakness, pronounced muscle damage, evidence for T cell infiltrates and increased mortality.

Conclusion:

Our findings provide the first evidence that FHL1 may be involved in the pathogenesis not only of genetic FHL1-related myopathies but also of autoimmune IIM. Importantly, detection of anti-FHL1 autoantibodies in peripheral blood represents a potential biomarker able to identify a subset of severe IIM characterized by a progressive, therapy-resistant disease and poor prognosis.

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